SYNTHETIC STUDIES TOWARDS BIOLOGICALLY ACTIVE COMPOUNDS CONTAINING 1,2-/1,3-AMINOALCOHOLS AND 1,3-DIAMINES EMPLOYING ASYMMETRIC DIHYDROXYLATION AND PROLINE CATALYSED REACTIONS

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(IN CHEMISTRY)

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UNDER THE GUIDANCE OF
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CERTIFICATE

This is to certify that the research work presented in the thesis entitled "**Synthetic Studies towards biologically active compounds containing 1,2-/1,3-aminoalcohols and 1,3-diamines employing asymmetric dihydroxylation and proline catalysed reactions**" has been carried out under my supervision and is a bonafide work **Mr. Vishwajeet Jha**. 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

October 2013

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Synthetic Studies towards biologically active compounds containing 1,2-/1,3-aminoalcohols and 1,3-diamines employing asymmetric dihydroxylation and proline catalysed reactions**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or Institution. This work was carried out at CSIR-National Chemical Laboratory, Pune, India.

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October 2013

Dedicated to…..

Maa & Papa

When I started doing chemistry, I did it the way I fished – for the excitement, the discovery, the adventure, for going after the most elusive catch imaginable in uncharted seas.

K. Barry Sharpless

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Rahul

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Abbreviations

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	-	*par*a-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 by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on 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.

The thesis entitled "**Synthetic Studies towards biologically active compounds containing 1,2-/1,3-aminoalcohols and 1,3-diamines employing asymmetric dihydroxylation and proline catalyzed reactions"** has been divided into five chapters.

Chapter 1: Introduction to the Sharpless asymmetric dihydroxylation (AD) and proline catalysed reactions.

Chapter 2: Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols using proline catalysed reactions and is divided into two sections.

Chapter 3: Application of 1,3-amino alcohols towards synthesis of naturally occurring piperidine and pyrrolidine alkaloids and is divided into two sections.

Chapter 4: An organocatalytic approach to asymmetric synthesis of *syn*- and *anti*-1,3-diamines.

Chapter 5: Enantioselective syntheses of 1,2-amino alcohols using Sharpless asymmetric dihydroxylation (AD) and proline catalysed reactions and is divided into two sections.

Chapter 1: Introduction to the Sharpless asymmetric dihydroxylation (AD) and proline catalysed 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 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 acts 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.

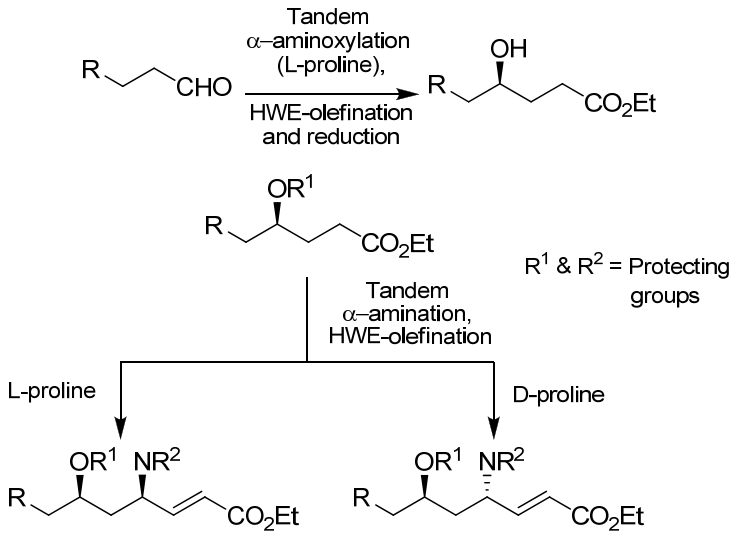
Chapter 2: Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols using proline catalysed reactions and is divided into two sections

Section A: Iterative Approach to Enantiopure *syn*/*anti*-1,3-Aminoalcohols via Proline Catalyzed Organic Transformations

1,3-Amino alcohols are key structural components in many natural products, potent drugs and numerous bioactive compounds viz. HIV-protease inhibitors, μ-opioid receptors antagonists, potent antibiotic negamycin, serotonin reuptake inhibitor and antidepressants. Additionally 1,3-amino alcohols have also been used as ligands for asymmetric catalysis, as chiral auxiliaries, as resolving agents and as phase transfer catalysts.[4]

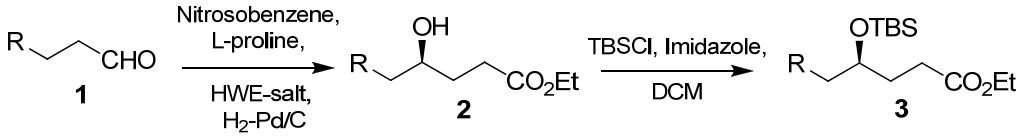
Proline in the recent past has been defined as 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom economical access to enantiomerically pure products.[5] Recently, we reported a concise synthesis of γ-hydroxy ester by proline catalysed sequential α-aminoxylation and HWE olefination of an aldehyde and successfully used this reaction in iterative fashion for the enantiopure synthesis of *syn*-/*anti*-1,3-polyols.[6] Similarly List *et al*. have developed a proline-catalysed direct α-amination of aldehyde protocol for the synthesis of α-amino aldehydes from readily available achiral aldehyde.[2a] We envisioned that the proline-catalysed α-aminoxylation and α-amination could be utilized to incorporate both hydroxy and amine functionality respectively in a desired *syn/anti* fashion and this sequential reaction could easily give us

stereocontrolled synthetic access to 1,3-amino alcohols as shown by the representative synthesis of 1,3-amino alcohols.



Toward the synthesis of 1,3-amino alcohols, our first goal was to synthesize various protected γ-hydroxy esters by the protocol developed recently by us.[6] Thus commercially available aldehydes **1** 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 triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **2** in good yields and excellent enantioselectivities. The free hydroxy group of γ-hydroxy esters **2** was protected as TBS ether using TBSCl to furnish compounds **3** in excellent yields (Scheme **1**).

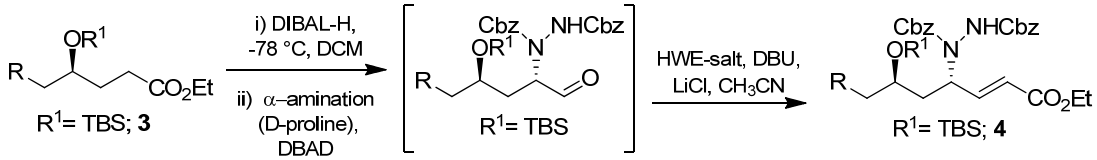
Scheme 1. Synthesis of γ-hydroxy esters



With TBS protected γ-hydroxy esters **3** in hand, the stage was set for the introduction of amine functionality at the 3-position with respect to hydroxy group. As illustrated in Scheme **2**, the DIBAL-H reduction of ester **3** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the

α-amino aldehyde, which on in situ trapping by triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *anti*-1,3-amino alcohol **4** in 64% yield and 97:3 diastereomeric ratio as determined from HPLC analysis (Scheme **2**).

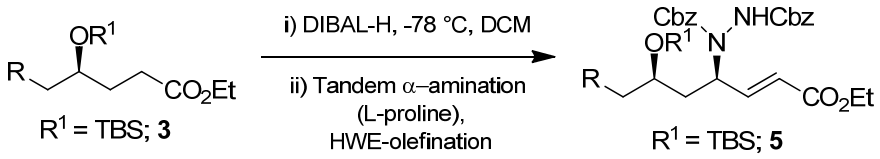
Scheme 2. Synthesis of *anti*-1,3-Amino Alcohol



We examined the scope of this reaction using various aldehydes bearing different functional groups. It was observed that the reaction sequence displayed a wide substrate scope and was compatible with functionalities such as alkyl, aryl and substituted aryl group. Excellent diastereomeric ratio (dr 97:3 to 99:1) and good yields (63 to 68%) were obtained for all the substrates.

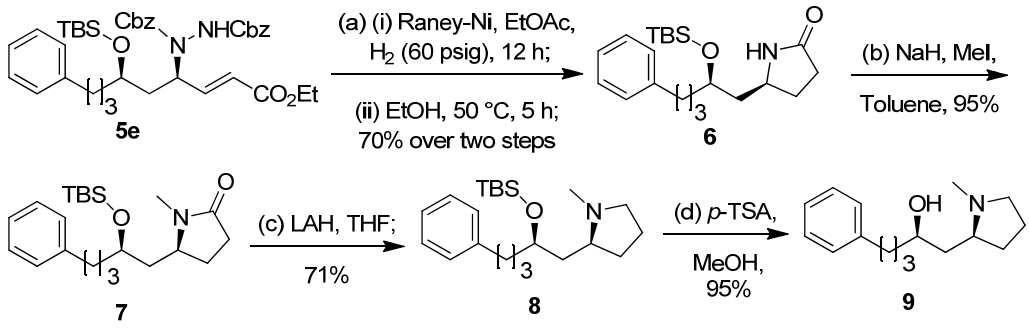
Encouraged by the excellent *anti*-selectivities achieved, we next turned our attention toward the synthesis of *syn*-1,3-amino alcohols. Following similar sequence of reaction as described for the preparation of *anti*-1,3-amino alcohols, we attempted (at) the synthesis of *syn*-1,3-amino alcohols using L-proline as a catalyst in the α-amination step (Scheme **3**). We examined the scope of this reaction using the same set of aldehydes. The results were more or less comparable with 1,3-*anti* amino alcohol with regard to the substrate scope and functional group compatibility. However selectivity in the case of *syn*-isomer was generally less as compared to the corresponding *anti*-isomer.

Scheme 3: Synthesis of *syn*-1,3-Amino alcohol.



In order to further demonstrate the utility of this approach we have developed a short synthesis of (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**9**)**,** a cyclic amino alcohol derivative. Compound **9** and its analogues have recently been found to be useful for the treatment of various neurological disorders such as Parkinson's disease, Alzhemier's disease, ALS, Huntington's diseases, strokes and spinal cord injuries etc.[7]

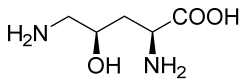
Scheme 4: Synthesis of (*R*)-1-((*S*)-1-Methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**9**)



As illustrated in Scheme **4**, the diastereomerically pure *syn*-amino alcohol **5e** prepared above was subjected to synthetic manipulation in order to achieve the synthesis of target compound **9**. Toward this end, the reduction of the double bond and cleavage of the *N*-*N* bond in **5e** was achieved in one-pot using freshly prepared Raney nickel. Subsequent filtration and reflux in ethanol afforded the lactam **6**. Monoalkylation of **6** using MeI and NaH furnished the *N*-methylated compound **7**. Finally LAH reduction of amide to amine and TBS deprotection using *p*-TSA in methanol afforded the target compound **9**.

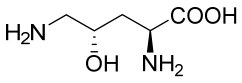
<u>Section B:</u> An efficient and organocatalytic route towards synthesis of protected (2*S*,4*R*)-4-hydroxyornithine

4-Hydroxyornithine **1a-b** is a nonproteinogenic amino acid found abundantly in nature. It is a component of marine organism and plants, as well as a constituent of a number of peptide natural products, such as the antifungal lipopeptides echinocandin and pneumocandin,[8] the K 582 type antibiotics,[9] macrocyclic antibiotic such as biphenomycin A and B **2a-b**,[10] polyoxin M and anticancer agent clavalanine **3**.[11] The related 4-hydroxylated α-amino acids such as (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinylnorvaline **4** has also been identified as a key component of ustiloxin A and B, a family of cyclic peptides with potent antimitotic activity.



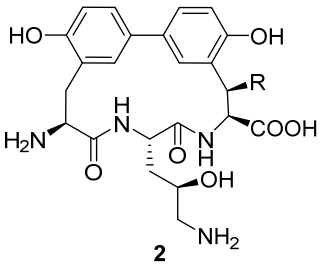
1a

(2S,4R)-4-Hydroxyornithine



1b

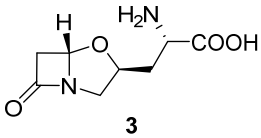
(2S,4S)-4-Hydroxyornithine



2

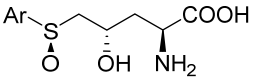
Biphenomycin A R = OH

Biphenomycin B R = H



3

Clavalanine

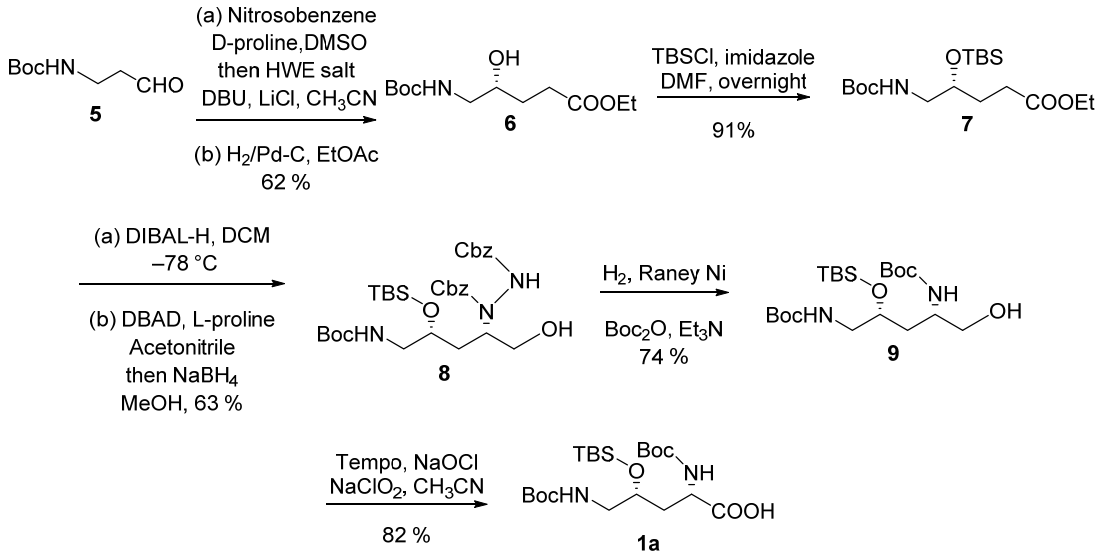


4

(2S,4S,6R)-4-Hydroxy-5-phenylsulfinylnorvaline

Our synthetic strategy for the synthesis of protected (2*S*,4*R*)-4-hydroxyornithine **1a** started from the commercially available aldehyde **5**. 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 triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **6.** The free hydroxy group of γ-hydroxy esters **6** was protected as TBS ether using TBSCl to furnish compound **7**. The DIBAL-H reduction of ester **7** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on treatment with $NaBH_4$ in ethanol afforded the substituted hydrazine **8** in 63% yield (over three steps). The *N*-*N*-bond of substituted hydrazine **8** was easily cleaved using freshly prepared Raney-Ni and subsequently free amine was converted into its Boc derivative using Boc_2O to furnish 1,3-aminoalcohol **9** in 74% yield. Amino-alcohol **9** was oxidized with TEMPO/NaOCl/$NaClO_2$ to furnish the desired protected amino acid **1a** in 82% yield (scheme **1**).

Scheme 1. Synthetic strategy for the synthesis of protected (2*S*,4*R*)-4-hydroxyornithine



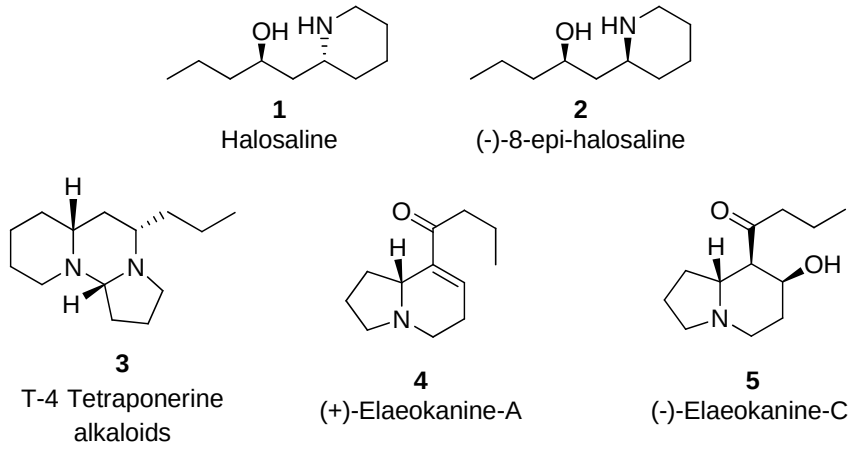
<u>Chapter 3:</u> Application of 1,3-amino alcohols towards synthesis of naturally occurring piperidine and pyrrolidine alkaloids and is divided into two sections.

<u>Section A:</u> Total synthesis of (-)-Halosaline and formal synthesis of Tetraponerine alkaloids T-4 and Elaeocarpus Alkaloid (+)-Elaeokanine-A and (±)-Elaeokanine-C

Piperidine ring system is frequently found as a key structural component in a variety of naturally occurring alkaloids,, which display a wide range of biological and pharmacological activity.[12] Considering their potent biological activity and less abundance, substituted piperidines ring system always remains an area of considerable synthetic interest[13] in the field of asymmetric synthesis and still it is highly desirable to devise diverse synthetic route for the asymmetric approach to these classes of compounds.

(-)-Halosaline (**1**), a 2-(2-hydroxy substituted)-piperidine was isolated from *Haloxylon salicornicum*.[14] (-)-8-epi-halosaline (**2**), a diastereomer of (-)-halosaline, was isolated from *Andrachne aspera spreng*,[15] a small perennial under shrub commonly found in Karachi. Tetraponerines T-4 (**3**) were isolated from the venom of a New Guinean ant

Tetraponera sp.[16] Elaeocarpus alkaloids elaeokanine A (**4**) and C (**5)** were isolated from *Ekaeocarous kaniensis Schltr*.,[17] a large rain-forest tree found in New Guinea.



1 Halosaline

2 (-)-8-epi-halosaline

3 T-4 Tetraponerine alkaloids

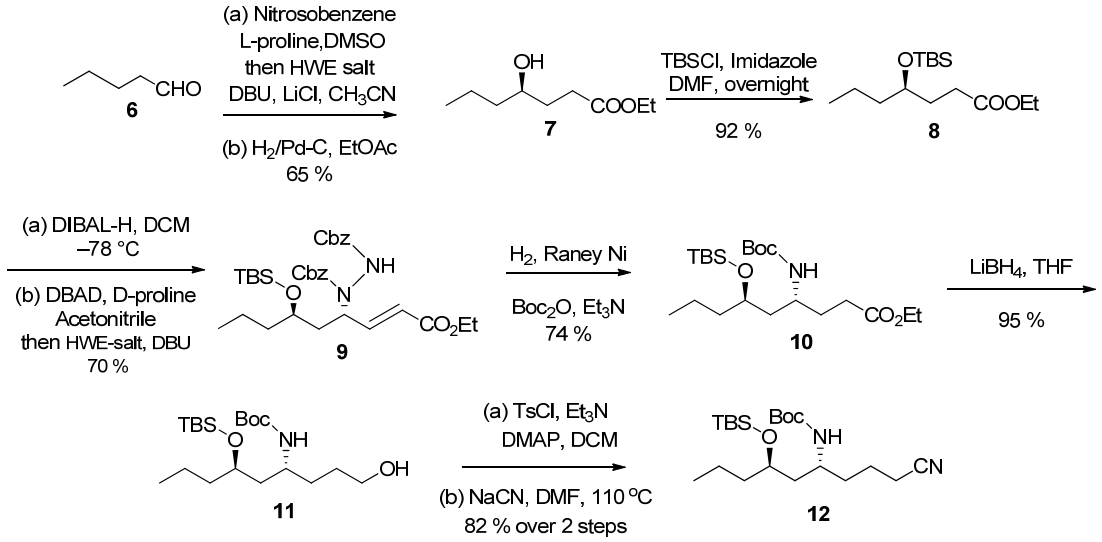
4 (+)-Elaeokanine-A

5 (-)-Elaeokanine-C

In continuation of our interest in organocatalysis and asymmetric synthesis of 1,3-aminoalcohol,[18] we consider extending the protocol of the sequential α-aminoxylation, HWE olefination and α-amination, HWE olefination as the key steps for the synthesis all these alkaloids.

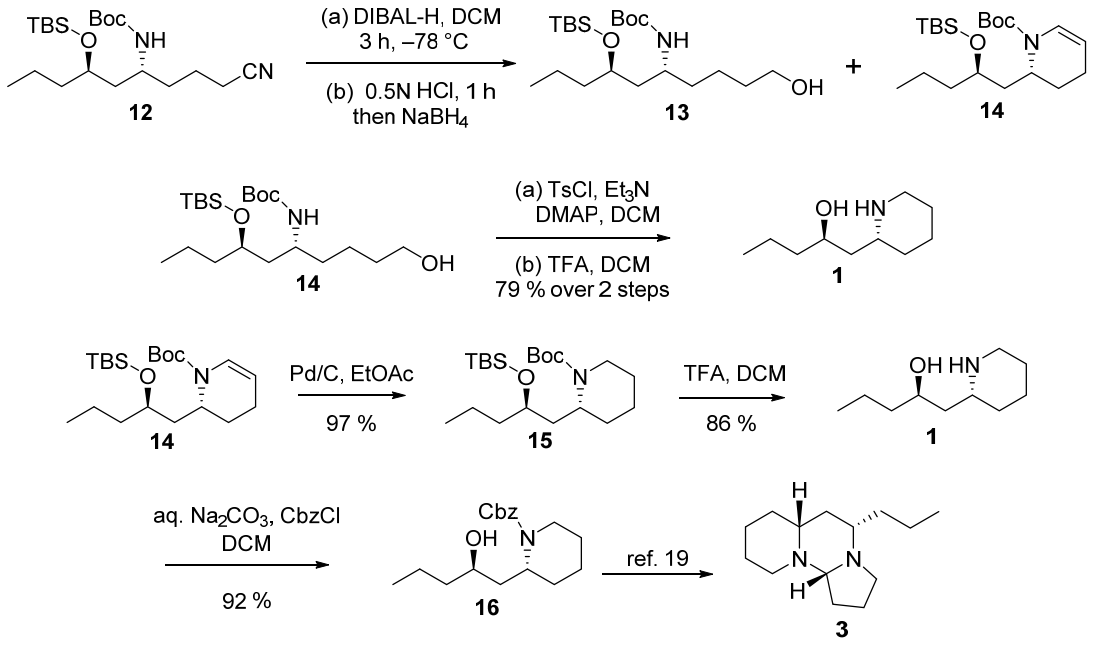
The synthesis started with commercially available aldehyde **6**, which on sequential α-aminoxylation using nitroso benzene as oxygen source and L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **7**. The free hydroxy group of γ-hydroxy esters **7** was protected as TBS ether using TBSCl to furnish compounds **8**. The DIBAL-H reduction of ester **8** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on treatment with triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *anti*-1,3-amino alcohol **9**. The *N*-*N*-bond of substituted hydrazine **9** was easily cleaved using freshly prepared Raney-Ni and subsequently free amine was converted into its Boc derivative using Boc_2O to furnish 1,3-aminoalcohol **10**. The $LiBH_4$ reduction of aminoalcohol **10** furnished alcohol **11**, which on subsequent treatment with TsCl followed by reaction with NaCN gave cyano compound **12** (Scheme **1**).

Scheme 1: Synthesis of cyano compound



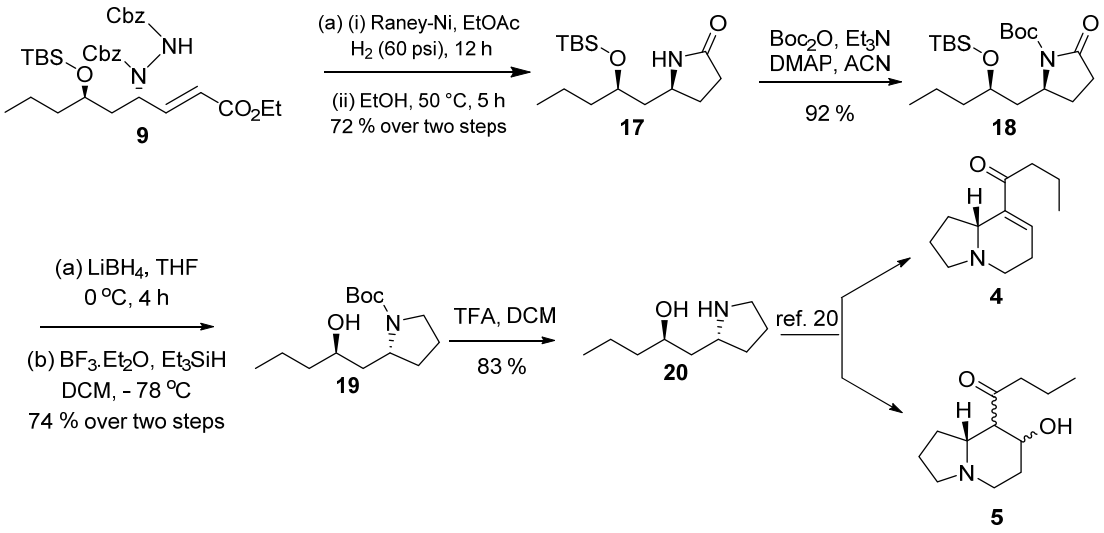
The DIBAL-H reduction of cyano compound **12** gave aldehyde which on treatment with $NaBH_4$ gave alcohol **13** as well as cyclized product **14**. Alcohol **13** on was subjected to tosylation followed by treatment with TFA to give (-)-halosaline **1**. Alternatively cyclized product **14** on treatment with 10% Pd-C under hydrogenation condition gave protected halosaline **15**, which on global deprotection gave (-)-halosaline **1**. Benzyl carbamate protection of (-)-halosaline **1** gave compound **16** which can be converted to the target compound **3** by known procedure [19] (Scheme **2**).

Scheme 2: Synthesis of (-) Halosaline



Similarly the synthesis of **(+)**-elaeokanine-A and (±)-elaeokanine-C was achived from *anti*-1,3-amino alcohol **9**. The reduction of the double bond and cleavage of the *N*-*N* bond of substituted hydrazine **9** was easily carried out using freshly prepared Raney-Ni. Subsequent filtration and reflux in ethanol afforded the lactam **17**, which was converted into its Boc derivative **18** using Boc_2O. The $LiBH_4$ reduction followed by treatment with Et_3SiH furnished cyclic amine **19**. Compound **19** on Boc deprotection under TFA condition gave compound **20** which can be converted to the target compound **4** and **5** by known procedure [20] (Scheme **3**).

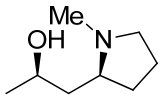
Scheme 3: Synthesis of **(+)**-Elaeokanine-A and (±)-Elaeokanine-C



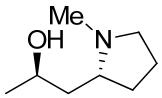
SectionB: Synthesis of (-)-hygrine and (-)-pseudohygroline via proline catalysed functanalization

The pyrrolidine ring is ubiquitous structural component in many naturally occurring alkaloids which shows a wide range of biological and pharmacological activity. Due to this, the development of methods for the asymmetric synthesis of 2-substituted pyrrolidine ring systems remains an area of considerable synthetic efforts.[21]

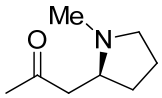
(+)-Pseudohygroline (**1**) and (+)-hygroline (**2**) were isolated from Carallia brachiata,[22a] Erythroxylon coca[22b] and Schizanthus hookeri.[22c] Norhygrine (**4**) was isolated from *Nierembergia hippomanica,*[22d] a toxic plant native to Argentina along with hygrine (**3**).



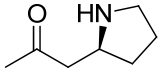
1
(-)-pseudohygroline



1
(-)-hygroline



3
(-)-hygrine,

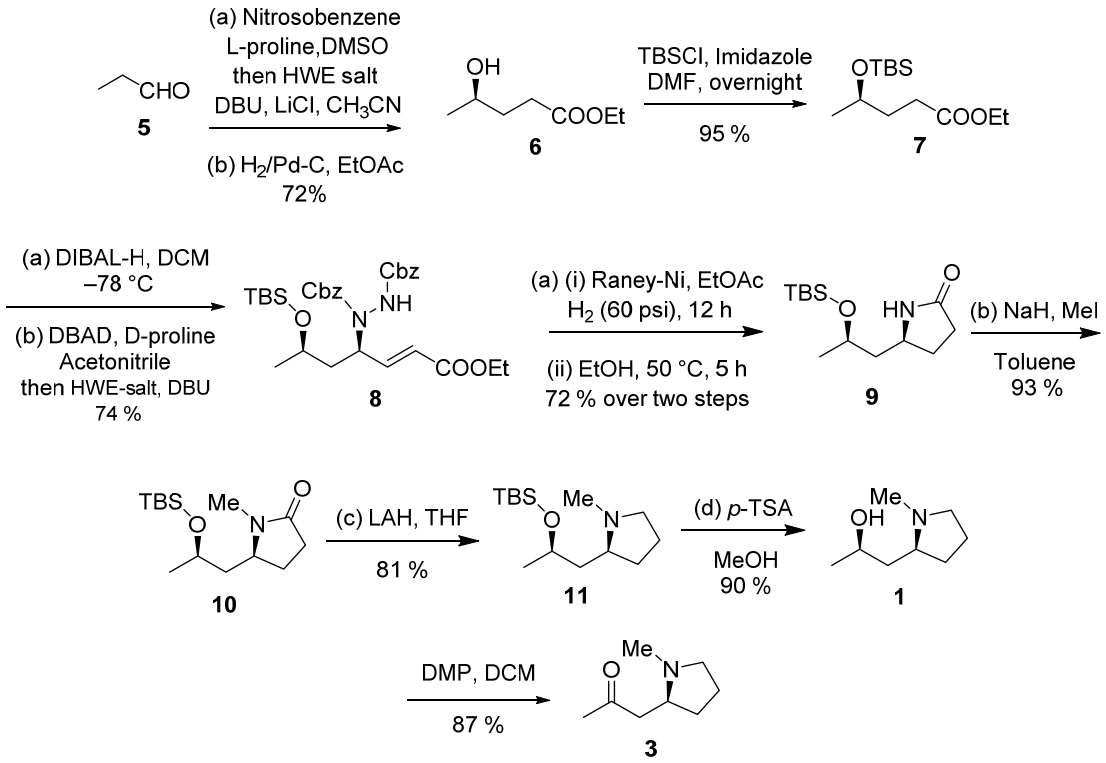


4
(-)-norhygrine

In continuation of our interest in organocatalysis and asymmetric synthesis of 1,3-aminoalcohol,[18] we have further extended the application of our protocol for the synthesis these alkaloids.

The synthesis started with commercially available aldehyde **5**, which on sequential α-aminoxylation using nitrosobenzene as oxygen source and L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **6**. The free hydroxy group of γ-hydroxy esters **6** was protected as TBS ether using TBSCl to furnish compounds **7**. The DIBAL-H reduction of ester **7** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to furnish the α-amino

Scheme 1: Synthesis of (+)-Pseudohygroline and hygrine.

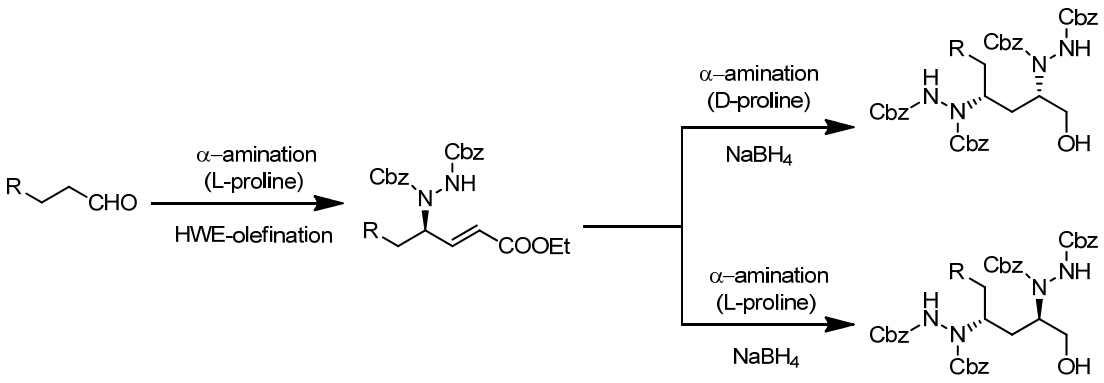


aldehyde, which on treatment with triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *syn*-1,3-amino alcohol **8**. The reduction of the double bond and cleavage of the *N*-*N* bond in **8** was achieved in one-pot using freshly prepared Raney nickel. Subsequent filtration and reflux in ethanol afforded the lactam **9**. Monoalkylation of **9** using MeI and NaH furnished the *N*-methylated compound **10**. Finally LAH reduction of amide to amine and TBS deprotection using *p*-TSA in methanol afforded the target compound **1**. DMP oxidation of **1** gave another target compound **3** (Scheme **1**).

Chapter 4: An organocatalytic approach to asymmetric synthesis of *syn*- and *anti*-1,3-diamines.

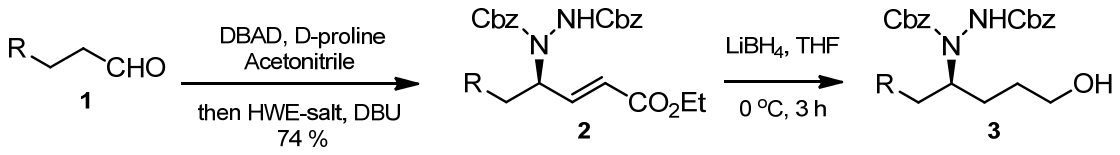
The chiral 1,3-diamine motif constitutes an important structural element in various bioactive natural products and medicinal compounds. Prominent examples include the marine alkaloids batzelladines or HIV-1 protease inhibitors, such as A-74704. It is also present in the chiral core of ligands and synthetic reagents.[23]

Proline has been found to be an excellent asymmetric catalyst for α-functionalization of carbonyl compounds. Recently, Sudalai *et. al.*[24] have reported the sequential amination and HWE olefination reaction of aldehyde to generate γ -amino-α,*β*-unsaturated esters. We have devised a general iterative strategy for the synthesis of 1,3-*syn*/*anti*- diamines using Sudalai sequential amination, HWE olefination reaction as shown by the representative synthesis. Depending upon the catalyst used (L/D)-proline in each iteration we can synthesize both (s*yn*/*anti*) isomer.



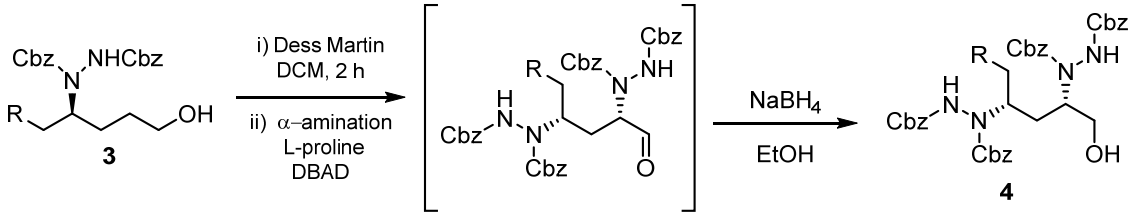
Toward the synthesis of 1,3-amino alcohols, our first goal was to synthesize various enantiomerically pure protected γ- amino- α,β-unsaturated esters. Thus commercially available aldehydes **1** on sequential α-amination using DBAD as nitrogen source and L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate furnished the protected γ-amino-α,β-unsaturated esters **2** in good yields and excellent enantioselectivities. The reduction of the double bond with $LiBH_4$ with concomitant reduction of ester gave alcohol **3** (Scheme **1**).

Scheme 1: Synthesis of γ-amino-α,β-unsaturated esters



With protected γ-amino alcohol **3** in hand, the stage was set for the introduction of another amine functionality at the 3-position. As illustrated in Scheme **2**, the DMP oxidation of alcohol **3** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to furnish the α-amino aldehyde, which on in situ reduction with $NaBH_4$ furnished the *syn*-1,3-diamine **4** (scheme **2**).

Scheme 2: Synthesis of *syn*-1,3-diamine

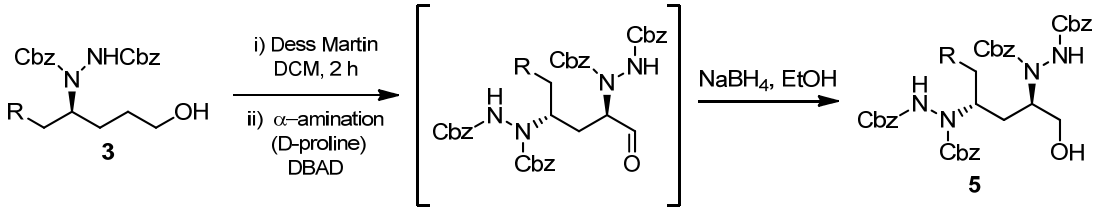


We examined the scope of this reaction using various aldehydes bearing different functional groups. It was observed that the reaction sequence displayed a wide substrate scope and was compatible with functionalities such as alkyl, aryl and substituted aryl group. Excellent diastereomeric ratio (dr 98:2 to ~100) and good yields (62 to 67 %) were obtained for all the substrates.

Encouraged by the excellent *syn*-selectivities achieved, we next turned our attention toward the synthesis of *anti*-1,3-diamine. Following similar sequence of reaction as

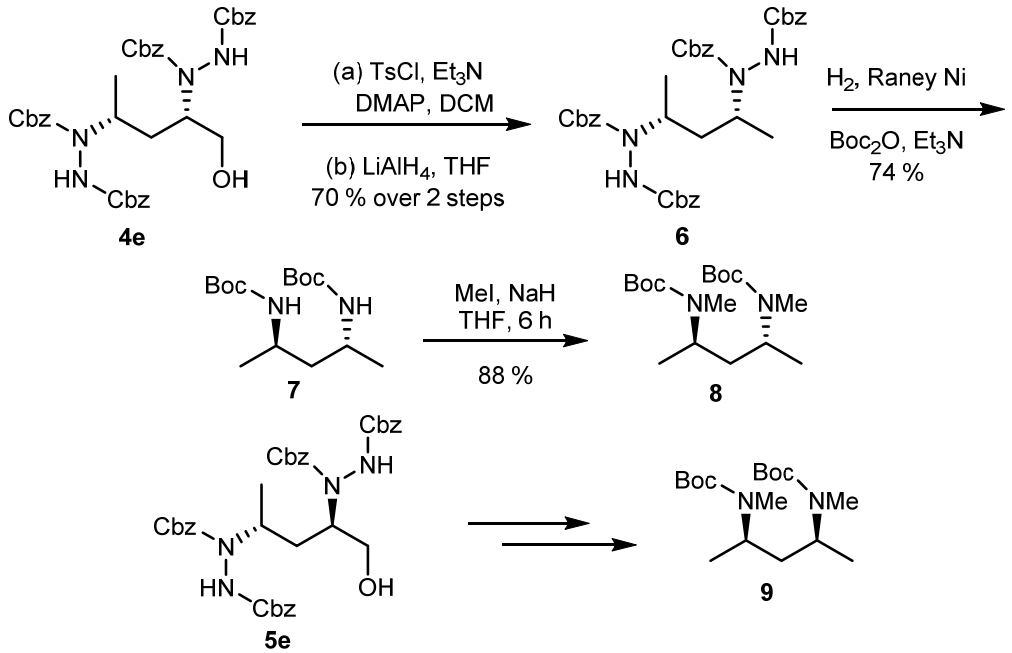
described for the preparation of *syn*-1,3-diamine, we attempted (at) the synthesis of *anti*-1,3-diamine using L-proline as a catalyst in the α-amination step (Scheme **3**). We examined the scope of this reaction using the same set of aldehydes. The results were more or less comparable with 1,3-*syn*-diamine with regard to the substrate scope and functional group compatibility. However selectivity in the case of *anti*-isomer was generally less as compared to the corresponding *syn*-isomer (scheme **3**).

Scheme 3: Synthesis of *syn*-1,3-diamine



In order to further demonstrate the utility of this approach we have developed a short synthesis of both diasteriomers of N-protected N^2,N^4-dimethylpentane-2,4-diamine. The Chiral diamine ligand forms complex with Pt which interact stereospecifically with DNA and even with mononucleotides, and acts as antitumor.[25] As illustrated in Scheme **4**, the diastereomerically pure *anti*-diamine **4e** and *syn*-diamine **5e** prepared above was subjected to synthetic manipulation in order to achieve the synthesis of target compounds **8** and **9** (scheme **4**).

Scheme 4: Synthesis of N^2,N^4-dimethylpentane-2,4-diamine

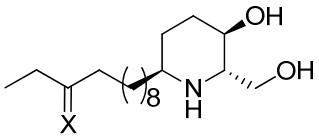


Toward this end, the free alcohol of protected *anti*-diamine **4e** was tosylated followed by treatment with $LiAlH_4$ to furnish compound **6**. The N-N bond of compound **6** was cleaved and free amine was protected as its Boc derivative **7**. Methylation of Boc derivative gave target compound **8**. Same set of reactions were done on 1,3-syn-diamine to get other diasteremer **9**.

<u>Chapter 5:</u> Enantioselective syntheses of 1,2-amino alcohols using Sharpless asymmetric dihydroxylation (AD) and proline catalysed reactions and is divided into two sections.

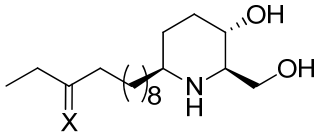
<u>Section A:</u> Total synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline

Naturally occurring alkaloids containing multi-functionalised piperidine rings are found abundantly in nature and many of them exhibit biological activity of medicinal interest.[26] Prosopis alkaloids, one of the sub group of these piperidine alkaloids, were isolated from the leaves of *Prosopis afrikana* Tab, contains 2,6-disubstituted piperidin-3-ol piperidine framework such as prosopinine **1**, prosophylline **2** and their deoxo analogues deoxoprosopinine **3**, deoxoprosophylline **4**, respectively (Figure 1). [27] These alkaloids exhibit antibiotic, anaesthetic, analgesic and CNS stimulating properties.



(-)-Prosopinine (**1**, X = O)

(-)-Deoxoprosopinine (**3**, X = H_2)



(+)-Prosophylline (**2**, X = O)

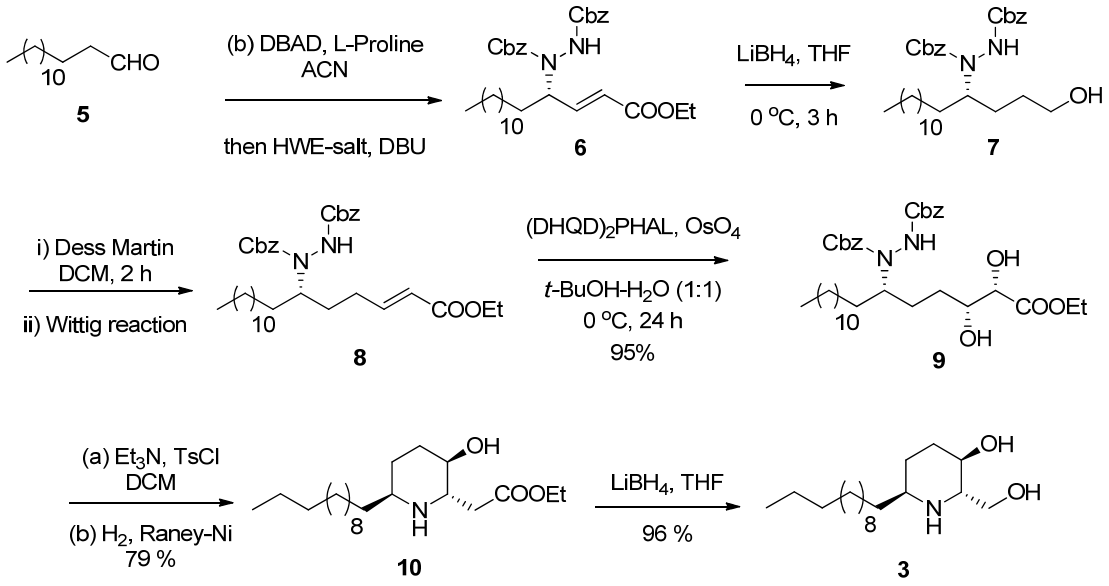
(+)-Deoxoprosophylline (**4**, X = H_2)

In continuation of our interest in organocatalysis and asymmetric synthesis of aminoalcohol, we further wanted to study the scope of our protocol for the synthesis of deoxoprosopinine **3** and deoxoprosophylline **4** using proline catalyzed organic transformation followed by asymmetric dihydroxylation.[3]

As illustrated in scheme **1**, the synthesis started with commercially available aldehyde **5**, which on sequential α-amination using DBAD as nitrogen source and L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide

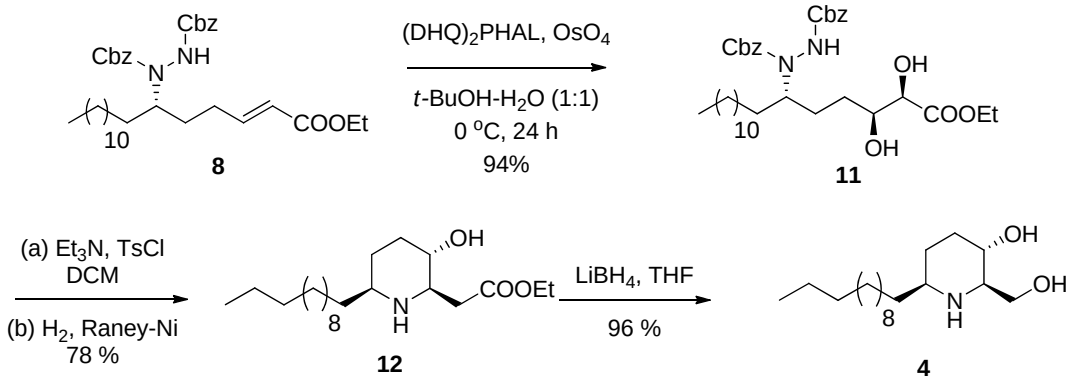
generated from triethyl phosphonoacetate furnished the protected γ-amino-α,β-unsaturated esters **6** in good yield and excellent enantioselectivity. $LiBH_4$ Reduction of ester gave alcohol **7** with concomitant reduction of double bond. DMP oxidation of alcohol **7** gave aldehyde which on Wittig reaction furnished α,β-unsaturated ester **8**. Asymmetric dihydroxylation of double bond using $(DHQD)_2PHAL$ gave diol **9**. Mono tosylation of diol **9** followed by N-N bond cleavage using Raney-Ni gave cyclized product **10**, which on $LiBH_4$ reduction gave (-)-deoxoprosopinine **3** (scheme **1**).

Scheme 1: Synthesis of (-)-deoxoprosopinine



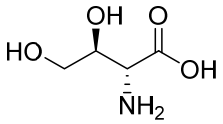
For the synthesis of deoxoprosophylline **4**, α,β-unsaturated esters **8** was subjected to asymmetric dihydroxylation using $(DHQ)_2PHAL$ to give diol **11**. Mono tosylation of diol **11** followed by N-N bond cleavage using Raney-Ni gave cyclized product **12**, which on $LiBH_4$ reduction gave (+)-deoxoprosophylline **4** (scheme **2**).

Scheme 2: Synthesis of (+)-deoxoprosophylline



Section B: Total synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid

α-Hydroxy-β-amino acids serve as intermediates in the synthesis of important class of compounds as naturally occurring amino acids (threonine, serine, and 3-hydroxyproline) and as components of many complex natural products possessing a wide range of biological activities such as antibiotics and immunosuppressants (e.g., vancomycin, echinocardin D, cyclosporin, katanosin, polyoxin D, empedopeptin, and other peptide conjugates).[28]



1

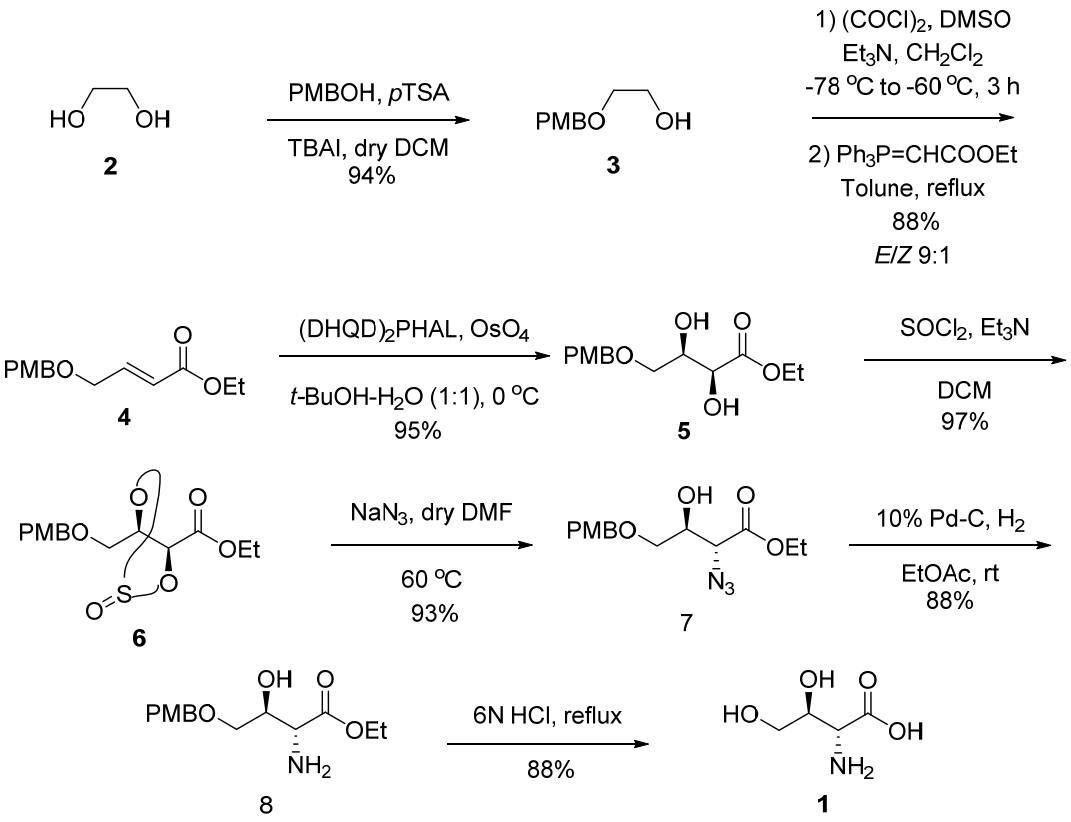
(2R,3S)-2-amino-3,4-dihydroxybutyric acid

As part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols, we herein describe the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid using Sharpless asymmetric dihydroxylation procedure as the source of chirality.

As illustrated in scheme **1**, the synthesis started with commercially available 2-butene-1,4-diol **2**. PMB protection of both the alcohol gave di-PMB protected product **3**. $NaIO_4$ mediated chopping of double bond gave aldehyde which was subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF to furnish the Wittig product **4**. Subsequent treatment of olefin **4** with osmium tetroxide and potassium ferricyanide as co-oxidant, in the presence of $(DHQD)_2PHAL$ under Sharpless asymmetric conditions,[3] gave diol **5**.

Diol **5** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **6**. Cyclic sulfite **6** reacted with NaN_3 with apparent complete selectivity for attack at C-2 to furnish azido alcohol **7**. The carbonyl group must be responsible for the increased reactivity of the α-position.[29] Hydrogenation of azido alcohol **7** with 10% Pd–C led to amino alcohol **8**. Finally, concomitant deprotection of the PMB group and ester hydrolysis were carried out with 6 N HCl to furnish **1** in excellent yield (scheme **1**).

Scheme 1: Synthesis of (2*R*,3*S*)-2-Amino-3,4-Dihydroxybutyric acid



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Chapter-2

Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols using proline-catalyzed reactions

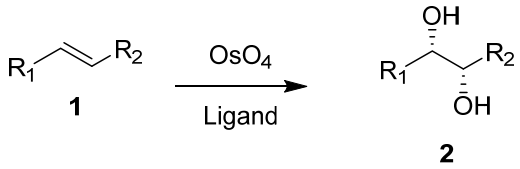
1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies. The goal of asymmetric synthesis-whether it is done in an academic or an industrial setting-is to prepare stereochemically-enriched compounds in the most efficient and practical manner possible.

In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in last decade. A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand.

The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry.

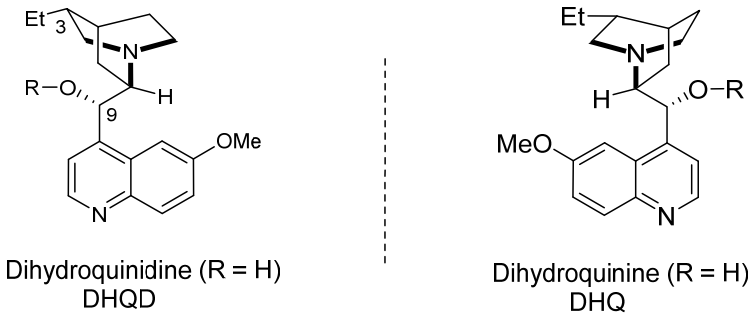


Scheme 1: Dihydroxylation of olefin

In the pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of

the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Much better results were obtained with *N*-methylmorpholine *N*-oxide (NMO).[9a,b] Tsuji *et al*. demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.[9c]

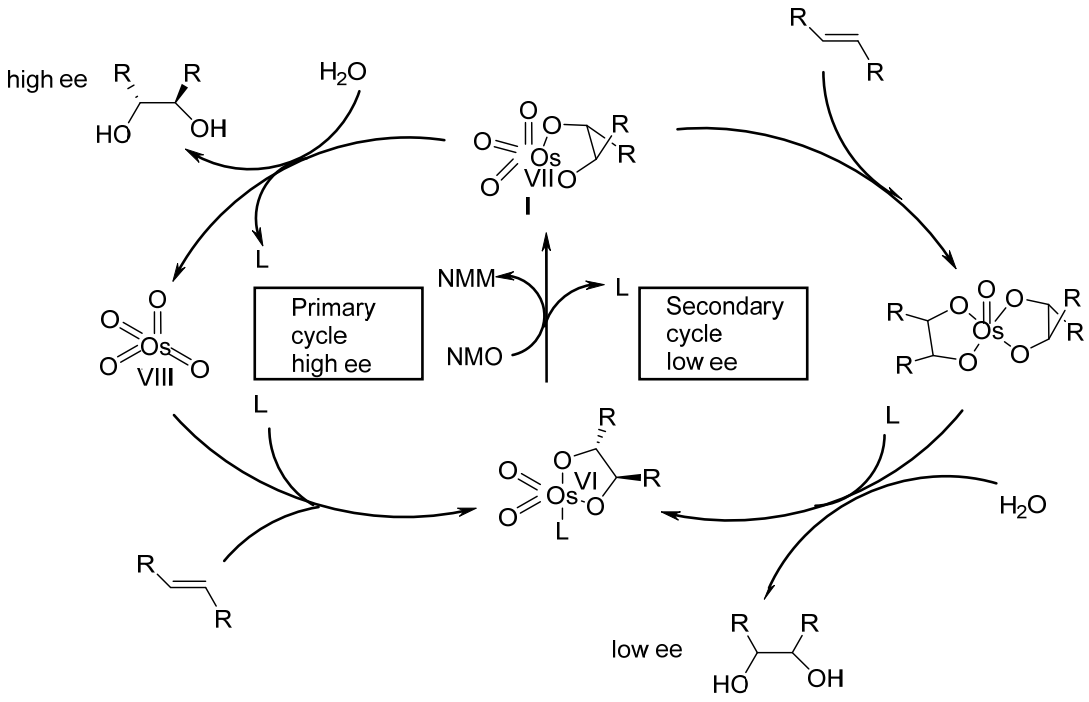
Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[10] Quinuclidine derivatives were used instead of pyridines for further investigations and moderate to good enantiomeric excess were obtained using acetate esters of cinchona alkaloids (Figure **1**) in stoichiometric ammount as chiral ligands. Marko and Sharpless found that the process became catalytic when NMO was employed as the co-oxidant.[11] However, the enantiomeric excess was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[12] (Scheme **2**) which exhibited only low or no enantioselectivity. Kwong found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ 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.



Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

Figure 1. Cinchona Alkaloid Ligands for AD under Catalytic Conditions.[22,25]



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

Sharpless *et al.*[14] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial influence on the selectivity.[15]

The discovery of ligands with two independent cinchona alkaloid units by Hartung[14] (phthalazine core) and Crispino[16] (diphenylpyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (Figure **2**).

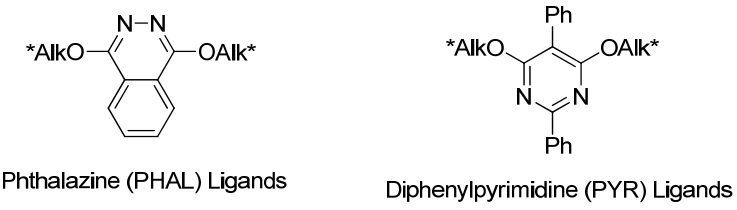


Figure 2. The latest generation of "dimeric" PHAL and PYR ligands

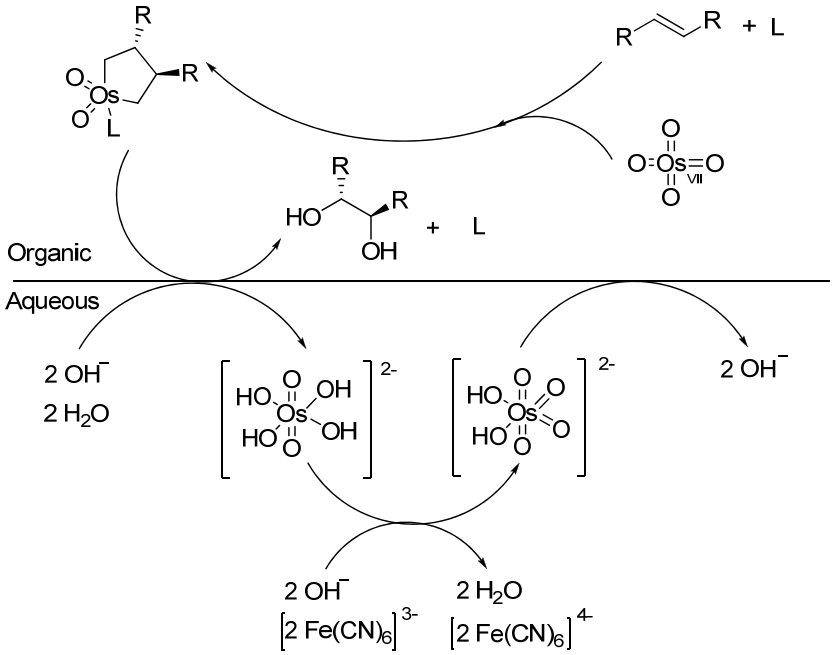
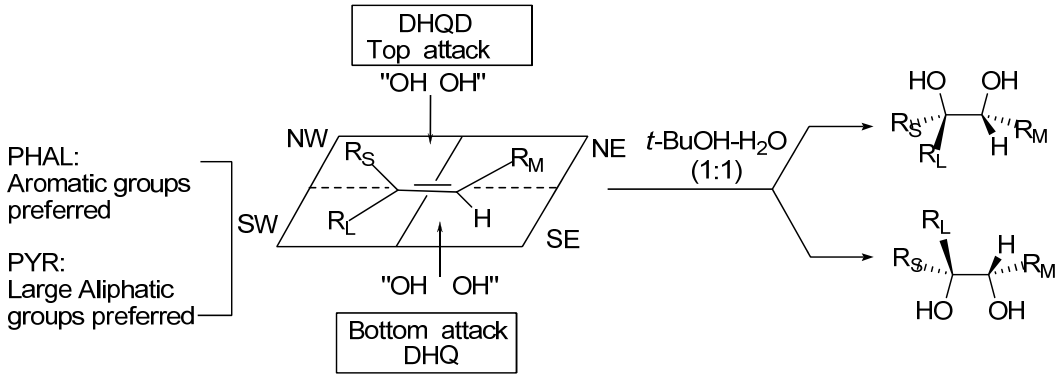


Figure 3. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the Co-oxidant

1.1.2. Empirical rules for predicting the face selectivity

The face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (Scheme **3**).[17] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. 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 (Scheme **3**).



Scheme 3. The mnemonic device for predicting the face selectivity

1.1.3. Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[18] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the 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 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

1.1.4. The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[19] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[20] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[21] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[22] and diols derived from allyl halides or allyl alcohols can be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

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

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

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PYR ligands.[24] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[25] However, in certain cases better results are obtained with the new second generation ligands.[26]

1.2 PROLINE-CATALYZED ASYMMETRIC ORGANIC TRANSFORMATIONS

1.2.1. Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyze organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born'.[27] It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metal. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researchers attention. Tremendous efforts will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[28] introduced a system of classification based on the mechanism of catalysis (Figure **4**). The four categories are Lewis base, Lewis acid, Brönsted base and Brönsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

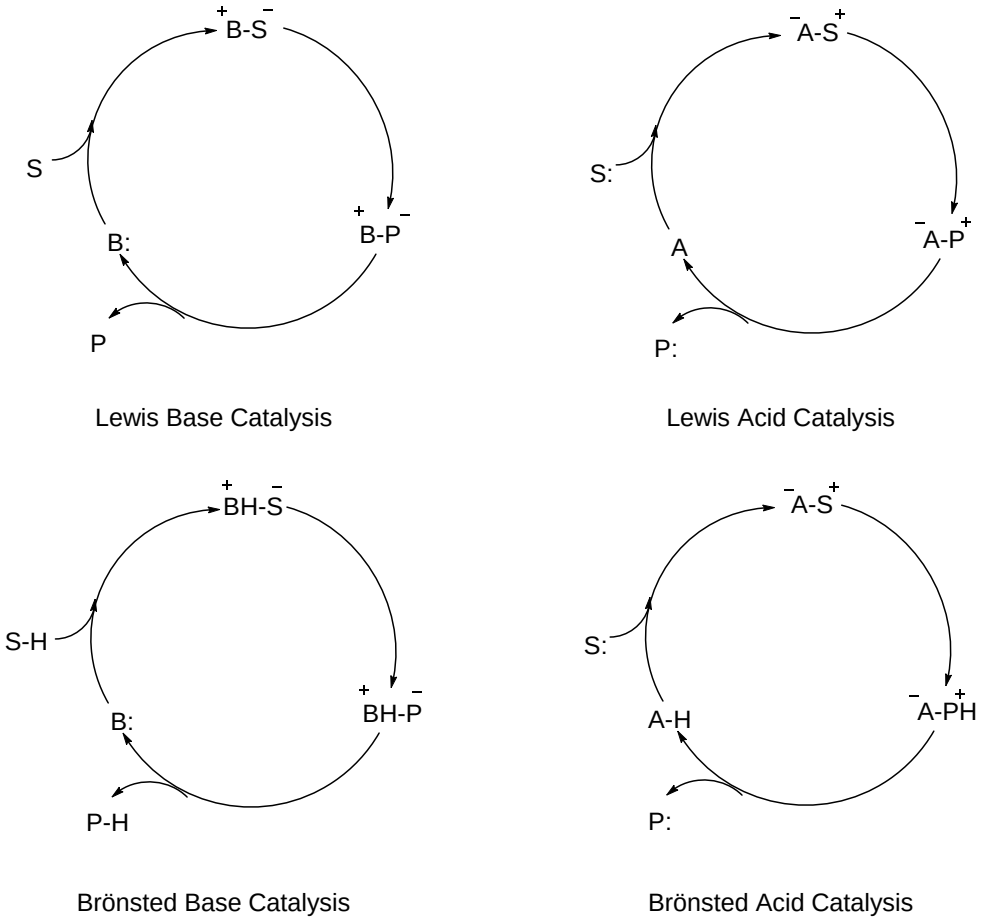


Figure 4. Organocatalytic cycles

1.2.2. Proline a "Universal catalyst"

Proline has been defined as a "universal catalyst" because of its high utility in 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 acts as Brönsted acid (Figure **5**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations.

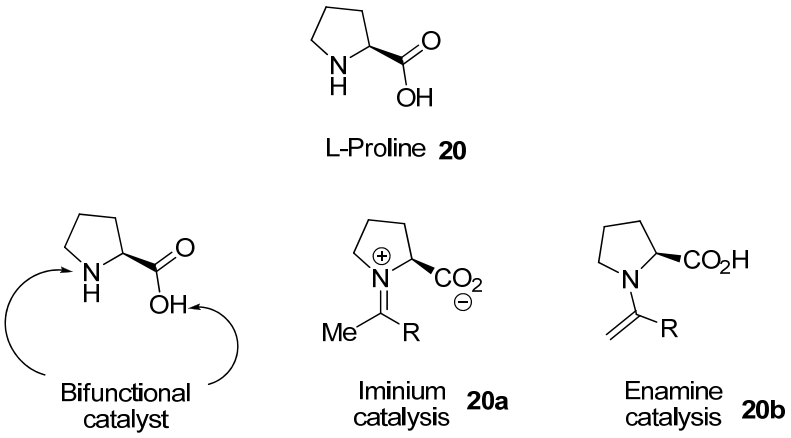


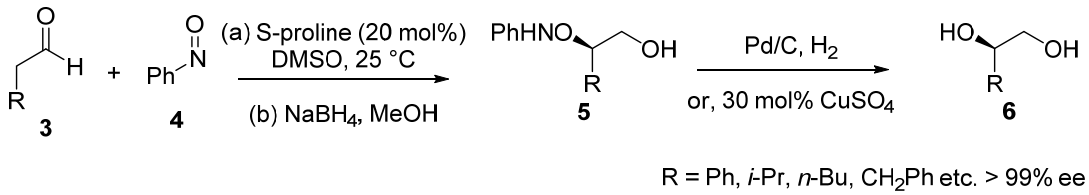
Figure 5. Modes of proline catalysis

It is known to catalyze aldol,[29] Diels-Alder,[30] Michael addition[31] and α-functionalization[32] among many other organic transformations.[33] Particularly proline-catalyzed α-aminoxylation[34] and α-amination[35] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

1.2.3. Proline-catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[36a] Sharpless dihydroxylation of enol ethers,[36b] manganese–salen epoxidation of enol ethers,[36c] and Shi epoxidation of enol ethers.[36d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[37] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[34] of carbonyl

compounds. When an aldehyde **3** without substitution at α-position was reacted with nitrosobenzene **4** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **6** in very high enantioselectivities (Scheme **4**).



Scheme 4. Proline-catalyzed α-aminoxylation

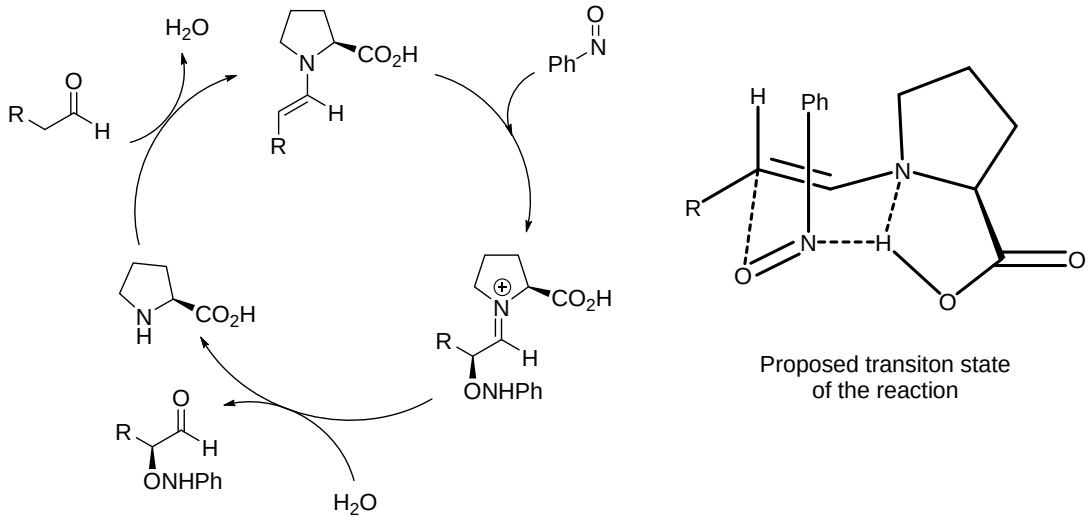


Figure 6. Proposed mechanism of the α-aminoxylation reaction

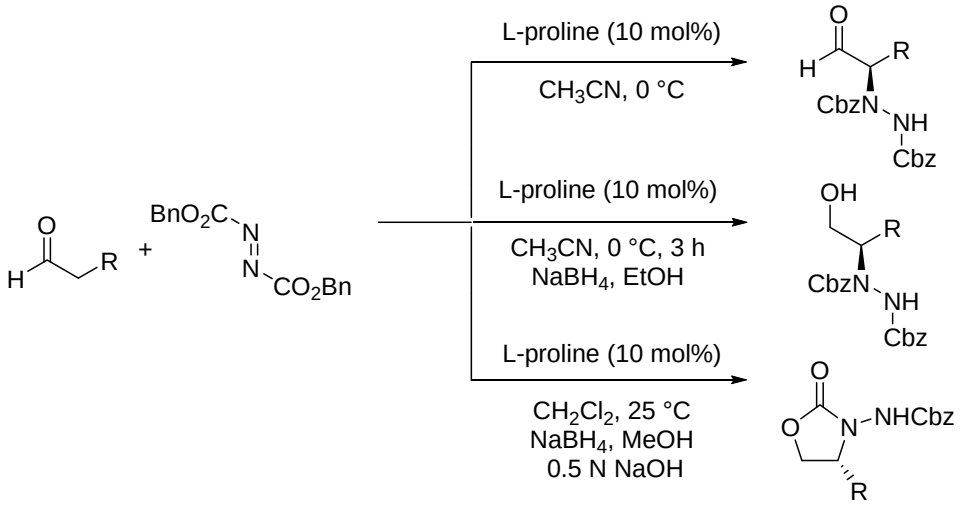
The mechanism of the α-aminoxylation reaction is shown in figure **6**. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with

$NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

1.2.4. Proline-catalyzed α-amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the *C-C* and the *C-N* bond-forming reactions.

Asymmetric α-amination[35] of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[35a] and Jørgensen[35b] disclosed the asymmetric α-amination of aldehydes (Scheme **5**) using catalytic quantities of proline.



Scheme 5. Proline-catalyzed α-amination

While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

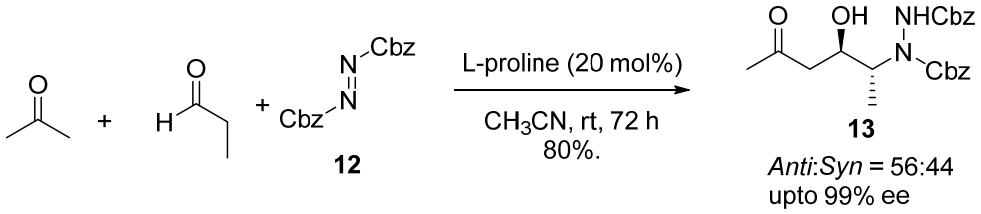
1.2.5. Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[38] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot

procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

1.2.5.1. Sequential amination-aldol[38a]

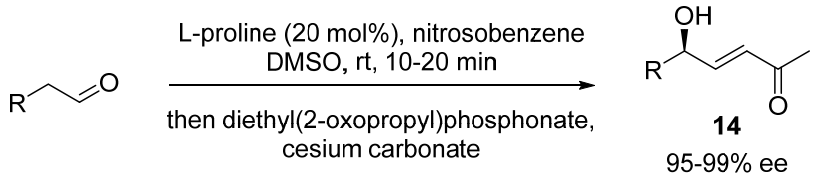
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **13** from aldehydes, ketones and azodicarboxylates (Scheme **6**).



Scheme 6. Sequential amination-aldol

1.2.5.2. Sequential aminoxylation-olefination[38b]

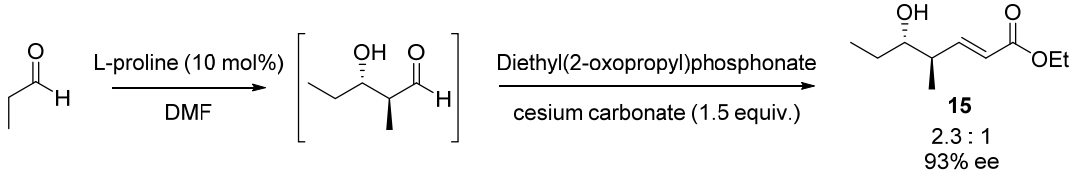
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substitutedallylic alcohols **14** in good enantioselectivities using cesium carbonate as base (Scheme **7**).



Scheme 7. Sequential aminoxylation-olefination

1.2.5.3. Sequential aldol-olefination[38c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide (Scheme **8**).

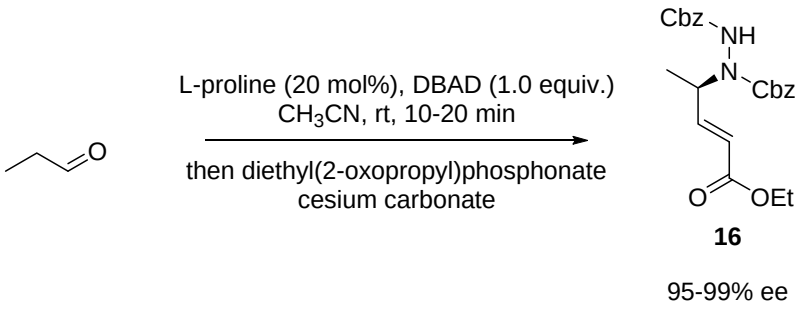


Scheme 8. Sequential aldol-olefination

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[38d]

1.2.5.4. Sequential α-amination-olefination[38e]

Sudalai *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme **9**).



Scheme 9. Sequential α-amination-olefination

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Chapter-2

Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols using proline-catalyzed reactions

2.1. SECTION A

Iterative Approach to Enantiopure *syn*/*anti*-1,3-Aminoalcohols via Proline-Catalyzed Organic Transformations

2.1.1. Introduction

1,3-Amino alcohols are key structural components in many natural products,[1] potent drugs[2] and numerous bioactive compounds viz. HIV-protease inhibitors,[3] μ-opioid receptors antagonists,[4] potent antibiotic negamycin,[5] serotonin reuptake inhibitor and antidepressants.[6] Additionally 1,3-amino alcohols have also been used as ligands for asymmetric catalysis, as chiral auxiliaries, as resolving agents and as phase transfer catalysts.[7] Despite the importance of 1,3-amino alcohol, there are relatively fewer methods for their stereoselective synthesis.[8,9] Currently the most common strategy for their synthesis is based on the diastereoselective reduction of an enantiomerically pure substrate, whereby the chirality of the substrate controls the formation of the new stereogenic center.[9a-d] Recently there has been a report of a reagent-controlled synthesis of *anti*-1,3-amino alcohol using rhodium as a catalyst.[9e] However all these reports suffer from one or more disadvantages such as (a) They give predominantly one of the two isomers *syn* or *anti* (b) Require specially modified starting materials (β-keto alcohols, β-amino ketones) (c) Use of toxic metal catalysts like Rh((COD)dunphos)BF_4, SmI_2, $Ti(^iOPr)_4$ and $Pd(OAc)_2$ etc. In view of the above considerations, there is still need for a versatile synthetic method that addresses the following issues: mild reaction conditions, cheap and readily available catalysts, flexible construction of all possible isomers, large substrate scope, minimum steps and simple (unmodified) starting materials.

In recent years the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[10] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[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.[12] Similarly organocatalytic tandem reactions are characterized by high efficiencies and are in a way biomimetic. They avoid time consuming and costly protection/deprotection processes as well as the purification of intermediates. They often proceed with excellent stereocontrol and are environmentally friendly.[13]

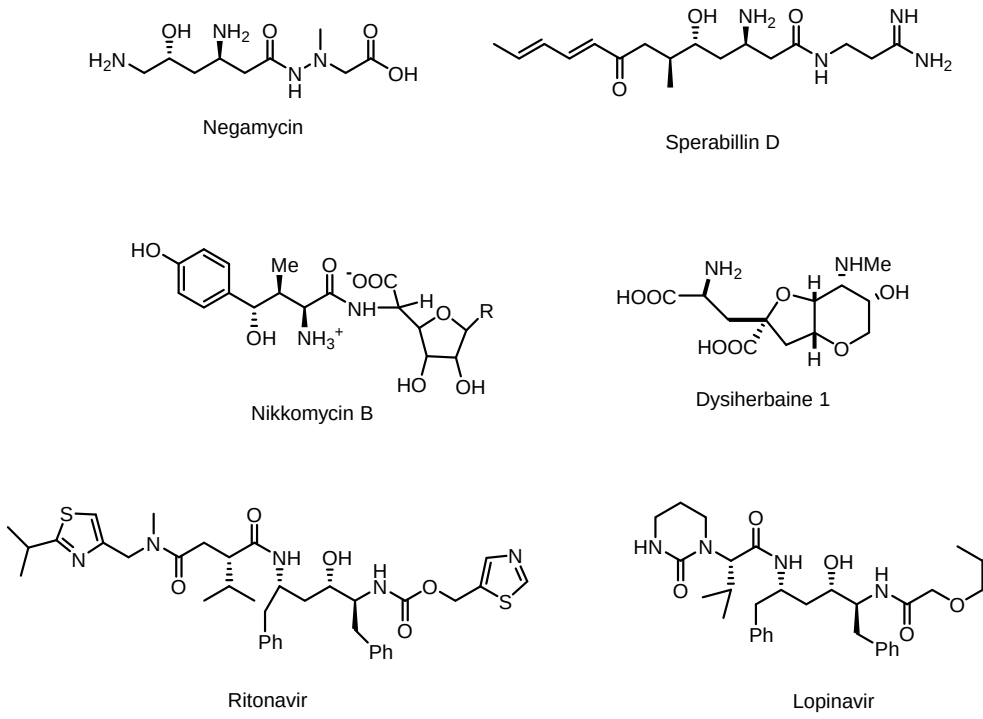
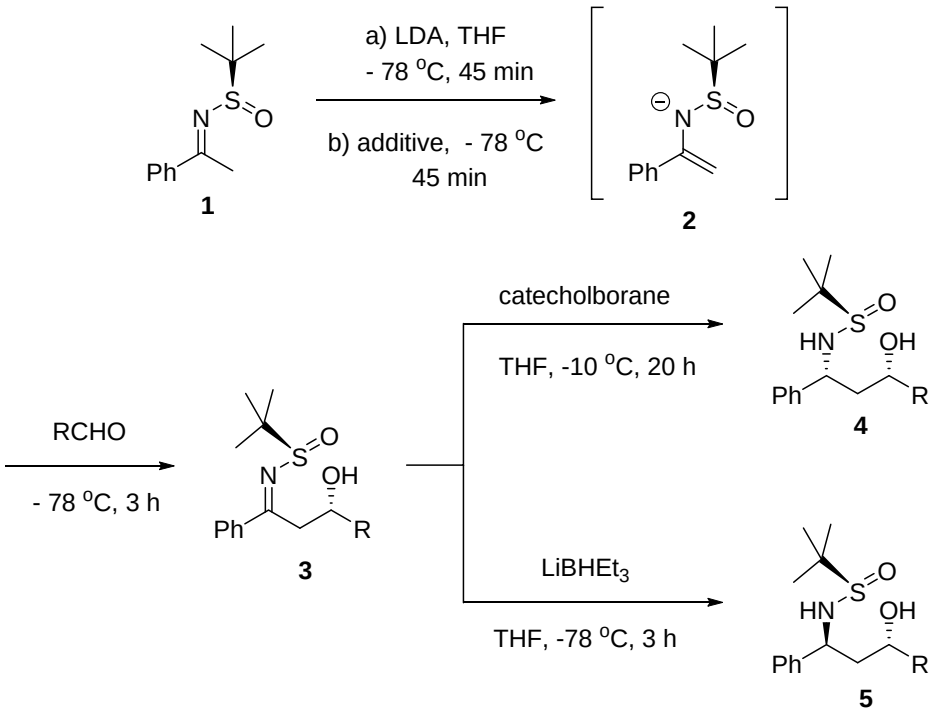


Figure 1. Representative examples of bioactive molecules containing 1,3-aminoalcohol moiety.

2.1.2. Review of Literature

Ellman *et al.* (2002)[9a]

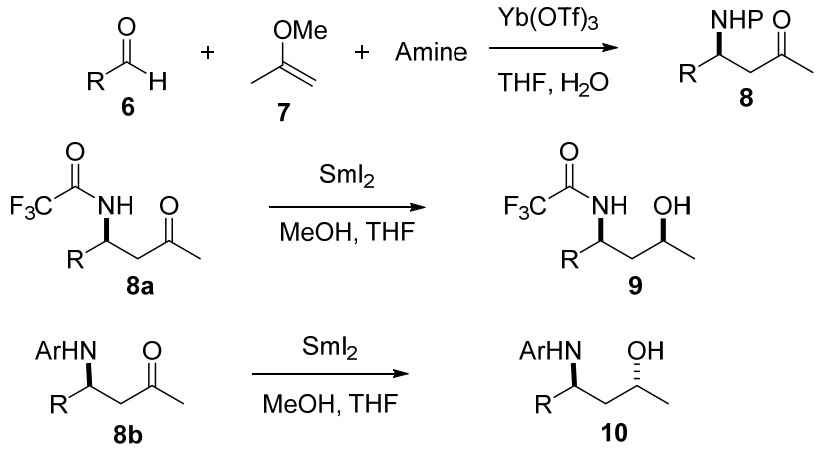
Ellman and co-workers developed an asymmetric synthesis of both *syn*- and *anti*-1,3-amino alcohols *via* diastereoselective addition of *N*-sulfinyl imines to aldehydes. Thus phenyl *N*-sulfinyl imines **1** was deprotonated using LDA in THF to get metaloenamine **2**, which on further treatment with aldehyde afforded β-hydroxy sulfinyl imine **3** in 80-88% yield and with 86:14 diastereomeric ratio. However, the addition of metal salts resulted in a dramatic increase in diastereoselectivity. Specifically, addition of $MgBr_2$ and $ZnBr_2$ afforded **3** with ratios of 96:4 and 93:7, respectively. Then β-hydroxy sulfinyl imine **3** was reduced with catecholborane at -10 °C to give *syn*-1,3-amino alcohols **4** in 84% yield and 95:5 diastereomeric ratio after chromatography. Alternatively, reduction of **3** with $LiBHEt_3$ at -78 °C provided the *anti*-1,3-amino alcohols **5** in 83% yield and 99:1 diastereomeric ratio.



Scheme 1. Synthesis of 1,3-amino alcohol (Ellman's method)

Keck *et al.* (2002)[9b]

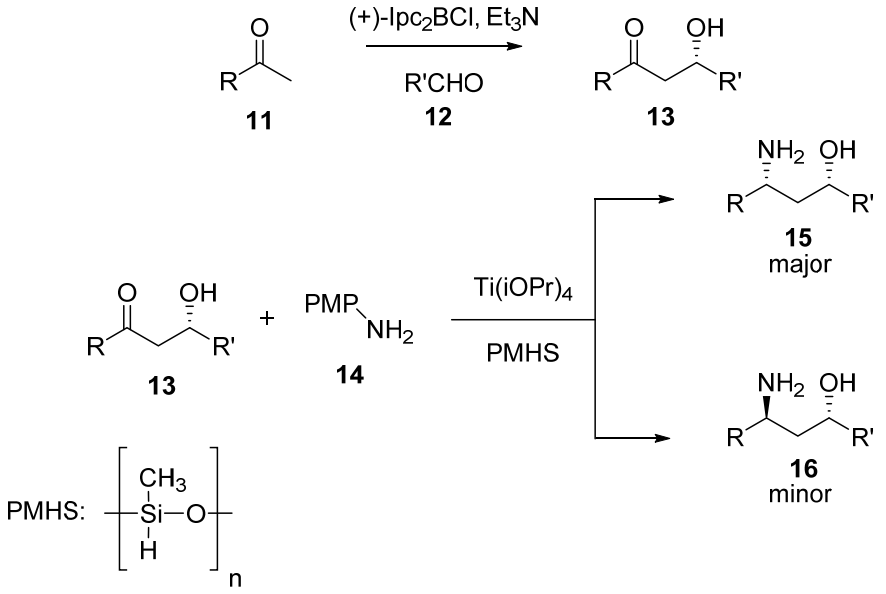
Keck and co-workers developed an enantioselective synthesis of both *syn*- and *anti*-1,3-amino alcohols *via* reduction of β-amino ketones with samarium(II) iodide. Thus, different protected *β*-amino ketones **8** were synthesized using treatment of aldehydes **6** with different amine and enol-ethers **7** in the presence of $Yb(OTf)_3$. Then *N*-acyl-*β*-amino ketones **8a** were dissolved in THF and freshly prepared solution (0.1-0.5 M) of SmI_2 in THF was added at 0 °C to get *syn*-1,3-amino alcohols **9** in 86% yield and 9:1 diastereomeric ratio. When *N*-aryl-*β*-amino ketones were subjected to same reaction condition it gave *anti*-1,3-amino alcohols **10** in 98% yield and 97:3 diastereomeric ratio. Thus, it was found that a complete reversal of stereoselectivity for the reduction occurs between the two classes of substrates: whereas the N-acyl derivatives reduced to afford the 1,3-*syn* diastereomer as the major product, the N-aryl derivatives afforded the 1,3-*anti* diastereomer as the major product.



Scheme 2. Synthesis of 1,3-amino alcohol (Keck method)

Menche *et al.* (2007)[9d]

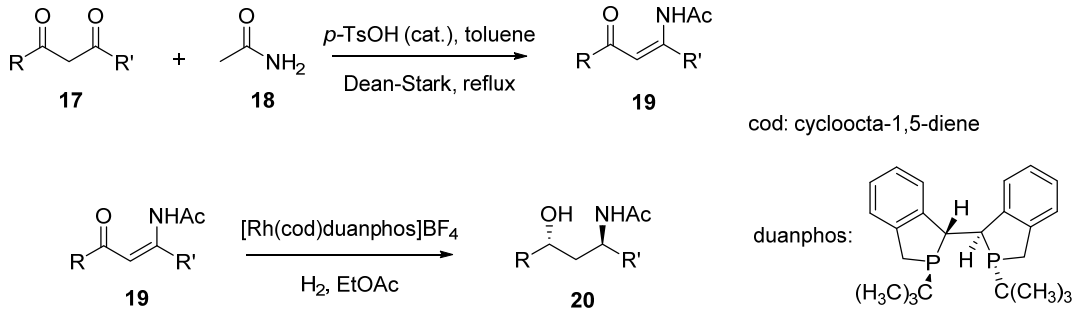
Menche and co-workers developed an enantioselective synthesis of *syn*-1,3-amino alcohols *via* directed reductive amination of chiral *β*-hydroxy-ketones. Thus, chiral *β*-hydroxyketones **13** are easily prepared by well-established asymmetric aldol reaction of ketone **11** and aldehyde **12** using Ipc-boron as a chiral catalyst. Then **13** was subjected to amination reaction with *para*-anisidine **14** as nitrogen source in the presence of various Lewis acids and hydride reagents. Best results were obtained with the reagent combination of Ti(*i*OPr)$_4$ as Lewis acid and polymethylhydrosiloxane as the hydride source to give *syn*-1,3-amino alcohols **15** in 81% yield and 9:1 diastereomeric ratio.



Scheme 3. Synthesis of 1,3-amino alcohol (Menche method)

Zhang *et al.* (2009)[9e]

Zhang and co-workers developed an enantioselective synthesis of *anti*-1,3-amino alcohols *via* highly efficient rhodium catalyzed asymmetric hydrogenation of β-ketoenamides. Two stereogenic centers are generated simultaneously with excellent enantioselectivity and diastereoselectivity in this atom-economical process. β-Ketoenamides **19** were prepared in one step from readily accessible 1,3-diketones **17** and acetamide **18** using Dean–Stark conditions. Now β-Ketoenamides were subjected to asymmetric hydrogenation conditions with the Rh/duanphos catalytic system in EtOAc to give *anti*-1,3-amino alcohols **20** in 100% yield and 98% ee and 95:5 diastereomeric ratio. The hydrogen pressure was found to be critical for the formation of the desired product in good yield and good enantio and diastereomeric ratio.



Scheme 4. Synthesis of 1,3-amino alcohol (Zhang method)

2.1.3. Present work

Objective

Recently, we reported an iterative approach to enantiopure synthesis of *syn*/*anti*-1,3-polyols *via* proline catalyzed sequential α-aminoxylation and HWE olefination of aldehydes.[14a]As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds,[14b] we envisioned that the proline-catalyzed α-aminoxylation[15a] and α-amination[15b] could easily give us stereocontrolled synthetic access to 1,3-amino alcohols. 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.[15b,16] 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*.[16a] 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 1,3-amino alcohol is outlined in Figure **2**.

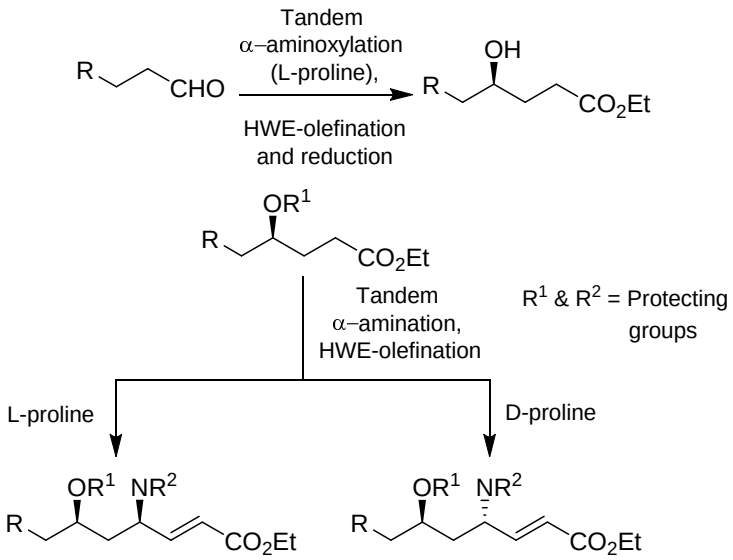
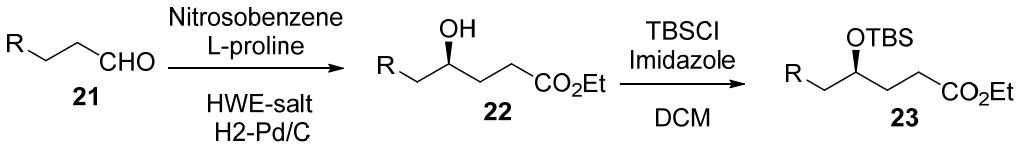


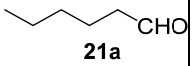
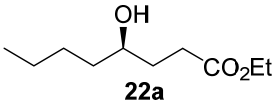
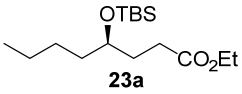
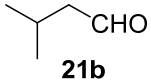
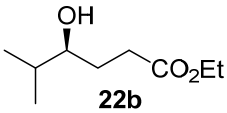
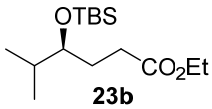
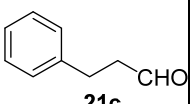
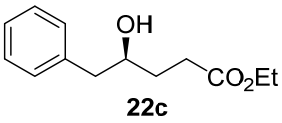
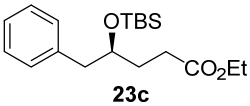
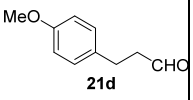
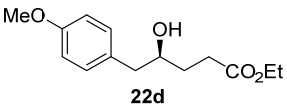
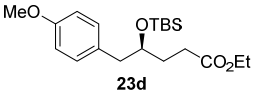
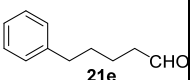
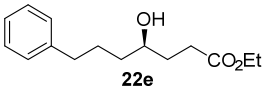
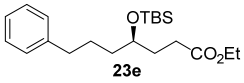
Figure 2. General strategy for the synthesis of 1,3-amino alcohol

2.1.4. Results and discussion

Toward the synthesis of 1,3-amino alcohols, our first goal was to synthesize various protected γ-hydroxy esters by the protocol developed recently by us.[14a] Thus commercially available aldehydes **21a-e** on sequential α-aminoxylation using nitroso benzene as oxygen source, L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using triethyl phosphonoacetate, followed by hydrogenation using catalytic amount of Pd/C furnished the γ-hydroxy esters **22a-e** in good yields (65-73%) and excellent enantioselectivities (94 to >99%). The appearance of ester proton at δ 1.25 as triplet and 4.11 as quartet confirmed the formation of product **22a**. The free hydroxy group of γ-hydroxy esters **22a-e** was protected as TBS ether using TBSCl to furnish compounds **23a-e** in excellent yields. Disappearance of peak at 3430 cm^{-1} in IR spectrum confirmed the formation of **23a**. (Scheme **5**, Table **1**).



Scheme 5. Synthesis of TBS protected γ-hydroxy esters

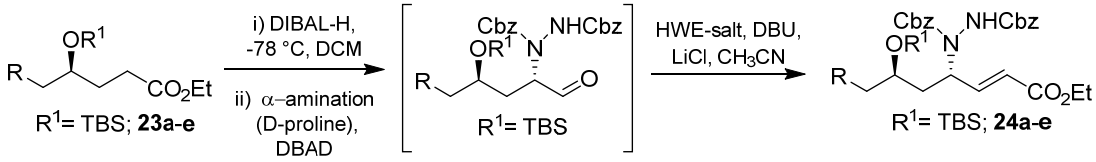
Entry	Substrates **1 a-e**	γ-Hydroxy esters **2a-e**	Yield	ee[a] (%)	TBS Protected γ-hydroxy ester **3a-e**	Yield (%)
1	 **21a**	 **22a**	65	94	 **23a**	92
2	 **21b**	 **22b**	69	98[b]	 **23b**	89
3	 **21c**	 **22c**	71	98	 **23c**	91
4	 **21d**	 **22d**	73	98.6	 **23d**	92
5	 **21e**	 **22e**	68	98.6	 **23e**	90

[a] ee was determined by chiral HPLC/ chiral GC analysis.

[b] ee was determined by optical rotation

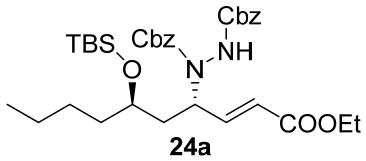
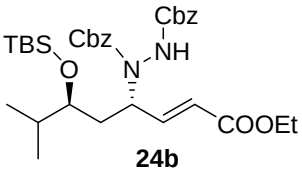
Table 1. Synthesis of TBS Protected γ-Hydroxy Esters (**23a-e**)

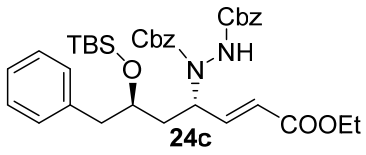
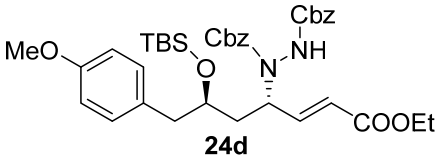
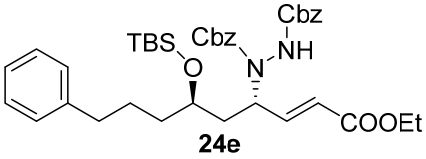
With TBS protected γ-hydroxy esters **23a-e** in hand, the stage was set for the introduction of amine functionality at the 3-position with respect to hydroxy group. As illustrated in Scheme **6**, the DIBAL-H reduction of ester **23a** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on in situ trapping by triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *anti*-1,3-amino alcohol **24a**[17] in 64% yield and 97:3 diastereomeric ratio as determined from HPLC analysis. The appearance of olefinic proton in the range 5.92 as multiplate and 6.86 as dd in 1H NMR spectrum confirmed the formation of product (Scheme **6**).



Scheme 6. Synthesis of *anti*-1,3-Amino Alcohol

We examined the scope of this reaction using various aldehydes bearing different functional groups. It was observed that the reaction sequence displayed a wide substrate scope and was compatible with functionalities such as alkyl, aryl and substituted aryl group. Excellent diastereomeric ratio (dr 97:3 to 99:1) and good yields (63 to 68%) were obtained for all the substrates (Table **2**).

Entry	Substrates **23a-e**	*anti*-1,3-Amino alcohol **24a-e**	Yield[a] (%)	dr[b] (%)
1	**23a**	 **24a**	64	97: 3
2	**23b**	 **24b**	68	99: 1

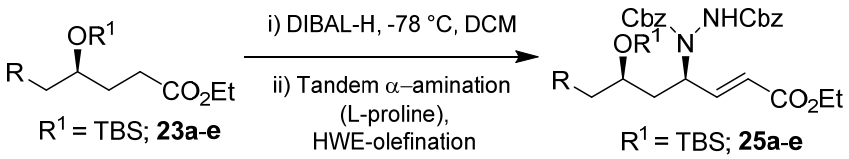
3	**23c**	 **24c**	63	99:1
4	**23d**	 **24d**	64	98: 2
5	**23e**	 **24e**	63	99:1

[a] Isolated yield of diastereomerically pure material

[b] Diastereomeric ratio was determined by HPLC analysis.

Table 2: D-Proline Catalyzed Asymmetric Tandem α-Amination/HWE-Olefination: Synthesis of *anti*-1,3-Amino Alcohol

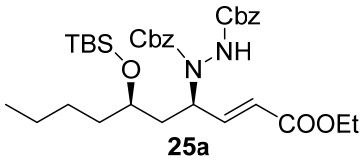
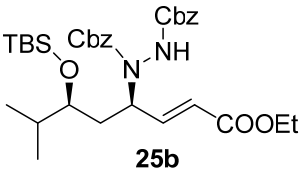
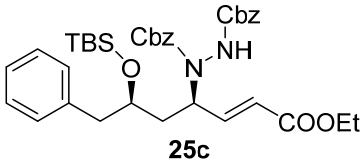
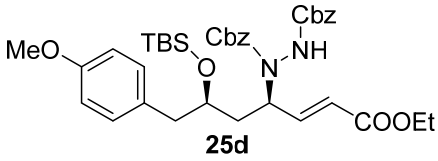
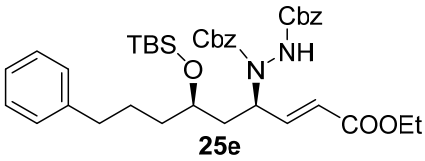
Encouraged by the excellent *anti*-selectivities achieved, we next turned our attention toward the synthesis of *syn*-1,3-amino alcohol following similar sequence of reaction as described for the preparation of *anti*-1,3-amino alcohols, and using L-proline as a catalyst in the α-amination step. As illustrated in Scheme **7**, the DIBAL-H reduction of TBS protected γ-hydroxy ester **23a** furnished the corresponding aldehyde which was then subjected to α-amination using DBAD and L-proline as catalyst followed by HWE-olefination to give *syn*-1,3-amino alcohol **5a** in 65% yield and 9:1 diastereomeric ratio as determined from HPLC analysis. We were able to separate the major diastereomerically pure *syn*-1,3-amino alcohol by silica gel column chromatography.



Scheme 7. Synthesis of *syn*-1,3-Amino alcohol

We further examined the scope of this reaction using the same set of aldehydes and the results obtained are summarized in Table **3**. The results were more or less comparable

with 1,3-*anti* amino alcohol with regard to the substrate scope and functional group compatibility. However selectivity in the case of *syn*-isomer was less as compared to the corresponding *anti*-isomer.

Entry	Substrates **23a-e**	*syn* -1,3- Amino alcohol **25a-e**	Yield[a] (%)	dr[b] (%)
1	**23a**	 **25a**	65	90:10
2	**23b**	 **25b**	62	81:19
3	**23c**	 **25c**	68	91:9
4	**23d**	 **25d**	66	89:11
5	**23e**	 **25e**	64	86:14

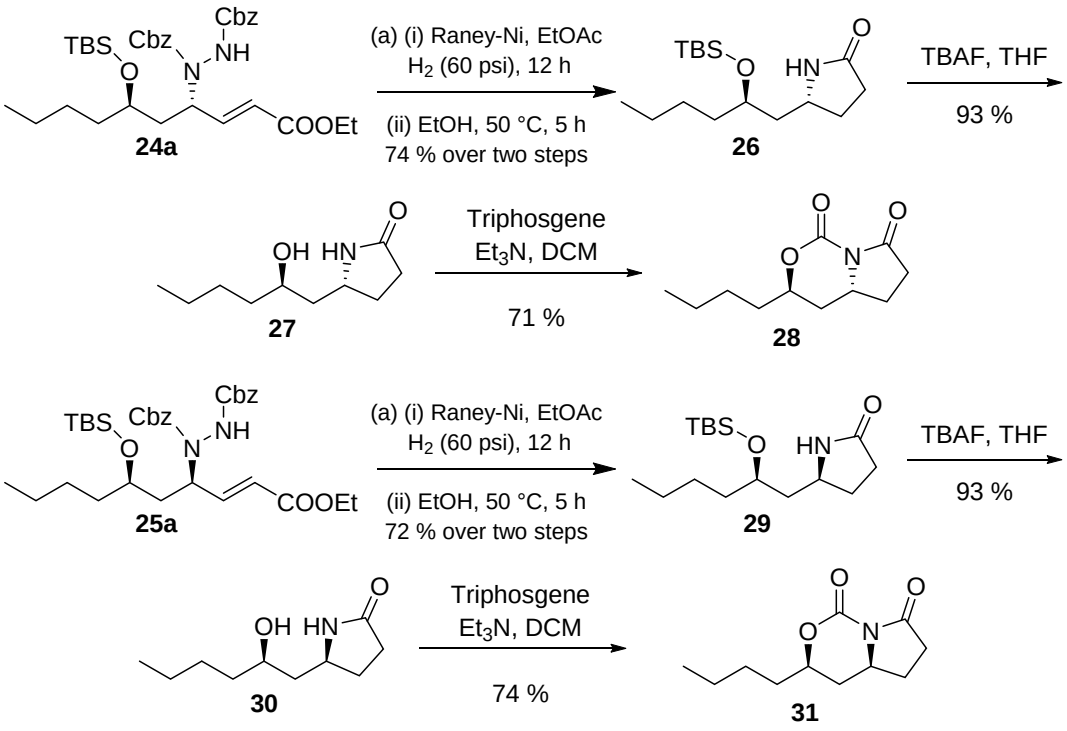
[a] Isolated yield of diastereomerically pure material
[b] Diastereomeric ratio was determined by HPLC analysis.

Table 3: L-Proline Catalyzed Asymmetric Tandem α-Amination/HWE Olefination : Synthesis of *syn*-1,3-Amino Alcohol

Overall these findings are in co-relation with those observed for the synthesis of *syn*/*anti*-1,3-diols from γ-hydroxy esters[14a] where the asymmetric induction for *anti*-isomer was greater as compared to s*yn*-isomer. Presumably the considerable steric bulk on the

incoming nitrogen source coupled with the steric bulk of silyl protecting group on hydroxy group might be the possible cause for lowering the selectivities.

The relative stereochemistry of 1,3-aminoalcohols **24a-e** and **25a-e** was determined using 2D NOSEY NMR spectrum analysis and further confirmed by *J*-based configurational analysis. For this purpose, the *N*-*N*-bond of diastereomerically pure 1,3-*anti*-aminoalcohol **24a** was easily cleaved with concomitant reduction of double bond under hydrogenation condition using freshly prepared Raney-Ni at 60 psi of H_2 to give free amine, which was subsequently converted into lactam **26** and in 72% yield. The disappearance of olefinic protons in the range of δ 5.93 as multiplate and 6.81-6.92 as dd in ^{1}H NMR spectrum confirmed the formation of the product. TBS group of compound **26** was deprotected using TBAF in THF to give free alcohol **27** in 93% yield which was subsequently treated with triphosgene to give carbamate **28** in 74% yield. Disappearance of peak at 3402 cm^{-1} in IR spectrum confirmed the formation of **28**. Same set of reaction was repeated with 1,3-*syn*-aminoalcohol **25a** to get carbamate **31** (scheme **8**).



Scheme 8. Synthesis of *anti*/*syn*-carbamate

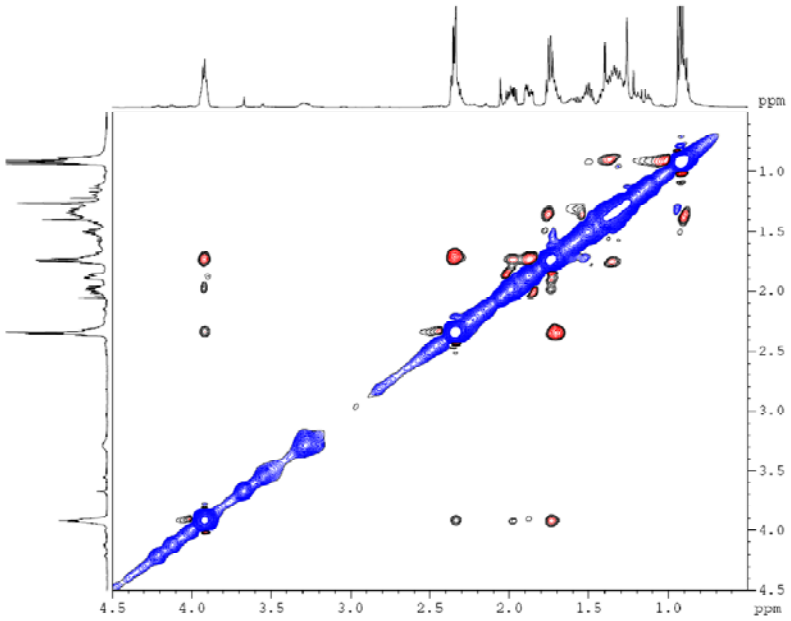


Fig. 3. NOESY of *anti*-compound **28**

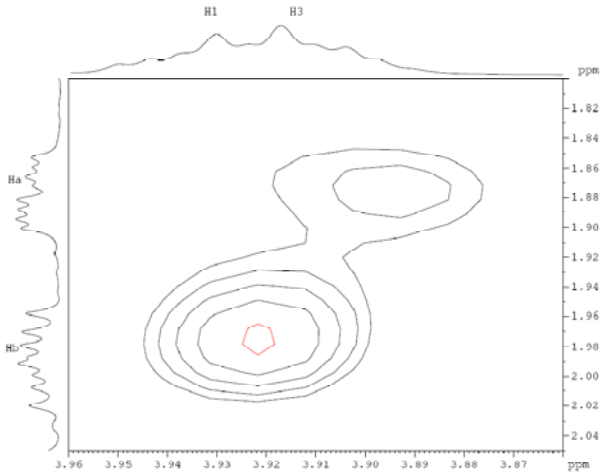


Fig. 4. NOESY of *anti*-compound **28**

In *anti*-compound **28**, methylene -C**H**$_2$ (H_a H_b) proton appears at δ 1.88 (H_a) and δ 1.99 (H_b) ppm respectively. The H_a peak at δ 1.88 shows NOESY correlation with H^3 appearing at δ 3.90 ppm. Similarly H_b peak at δ 1.99 ppm shows NOESY correlation with H^1 at δ 3.92 ppm. As there is no NOESY correlation of either H_a and H_b with both H^1 and H^3 clearly showing the *anti*-stereochemistry at 1,3- position (figure **3** and **4**).

To further confirm our observation of 1,3-*anti*–relationship, we have done *J*-based configurational analysis. It was observed that H_a couples with H^1 with coupling constant 14.3 Hz which indicates *anti*-coupling, where as it couples with H^3 with coupling constant 3.1 Hz which indicates *syn*-coupling. In the same way, H_b couples with H^1 with coupling constant 4.2 Hz which shows *syn*-coupling where as it couples with H^3 with coupling constant 16.4 Hz which indicates *anti*-coupling. Hence it further proves the *anti*-stereochemistry at 1,3- position (figure **5**)

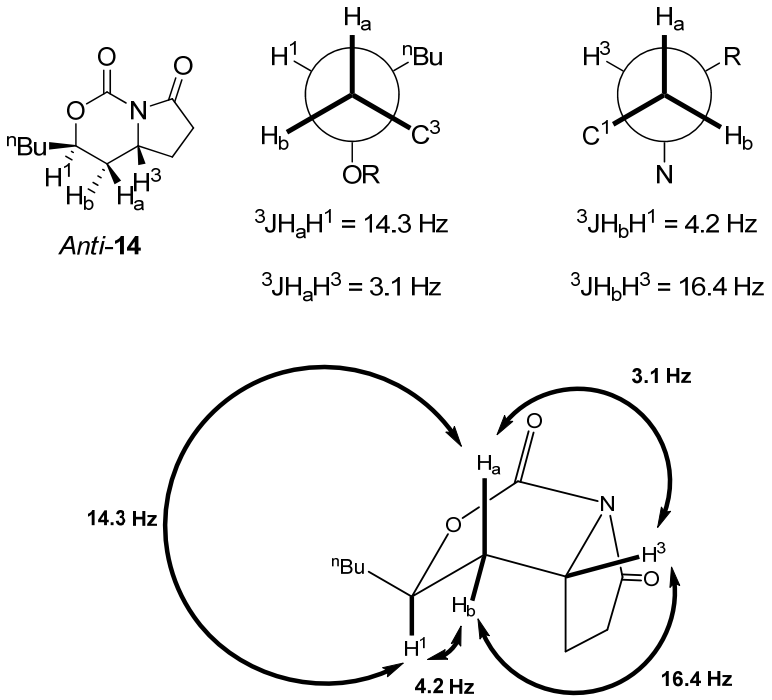


Fig. 5. *J*-based configurational analysis of *anti*-compound **28**

In *syn*-compound **31**, methylene -C**H**$_2$ (H_a H_b) proton appears at δ 1.84 (H_b) and δ 1.85 (H_a) ppm respectively. The H_b peak at δ 1.84 ppm shows NOESY correlation with both H^1 and H^3 protons appearing at δ 3.98 and δ 3.88 ppm respectively, where as H_a proton at δ 1.85 ppm shows no correlation with any of the H^1(δ 3.98) and H^3(δ 3.88) protons. This clearly establishes the relative *syn*-stereochemistry (figure **6** and **7**).

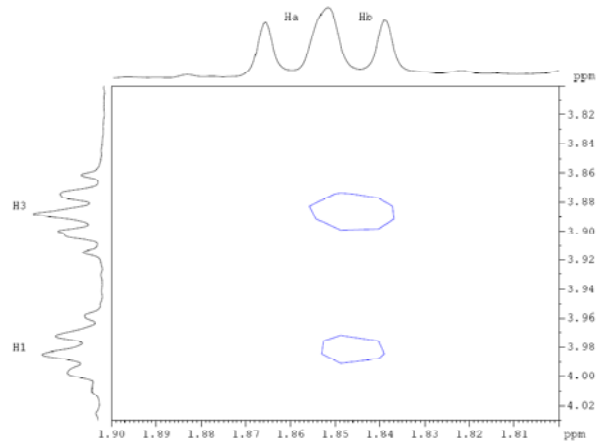


Fig. 6. NOESY of *syn*-compound **31**

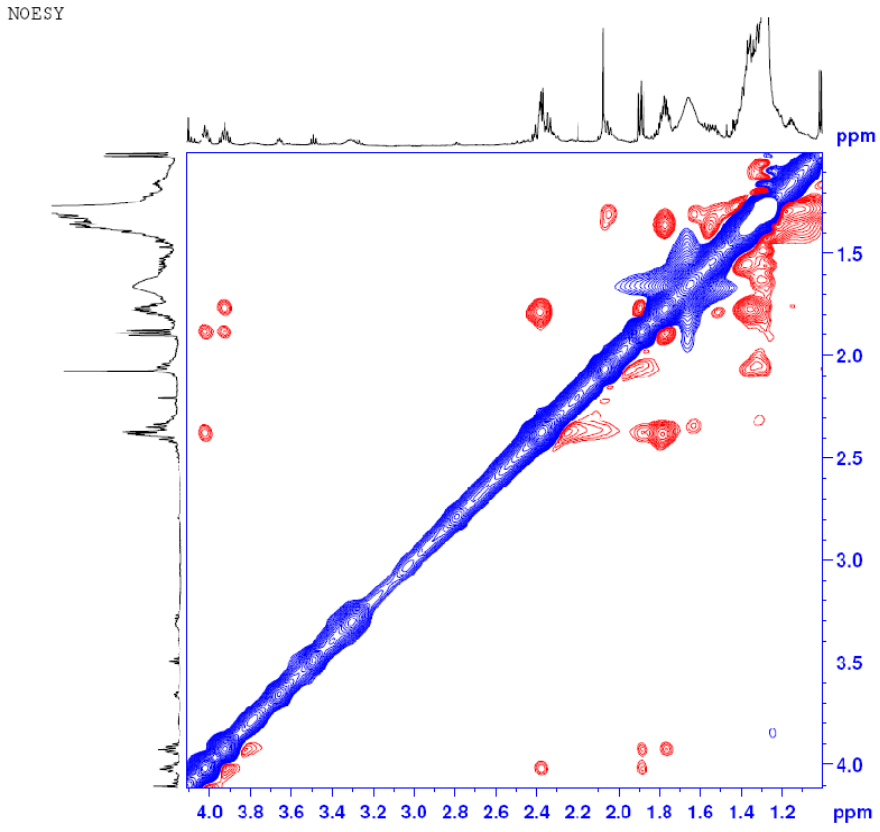


Fig. 7. NOESY of *syn*-compound **31**

To further confirm our observation of 1,3-*syn*–relationship, we have done *J*-based configurational analysis. It was observed that H_a couples with H^1 with coupling constant

12.4 Hz which indicates *anti*-coupling, where as it couples with H^3 with coupling constant 14.3 Hz which also indicates *anti*-coupling. In the same way, H_b couples with H^1 with coupling constant 4.2 Hz which shows *syn*-coupling where as it couples with H^3 with coupling constant 3.5 Hz which also indicates *syn*-coupling. Hence it further proves the *syn*-stereochemistry at 1,3- position (Figure **8**)

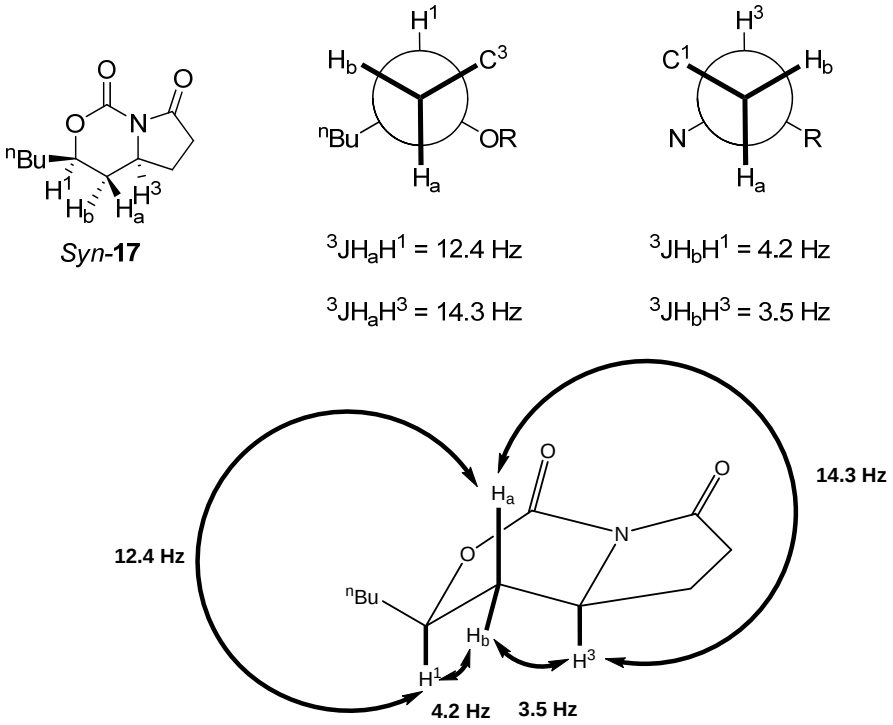
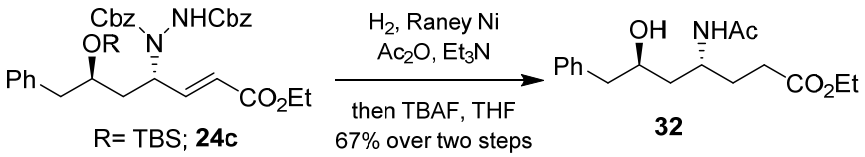


Fig. 8. *J*-based configurational analysis of *syn*-compound **31**

This sequence of reaction for the synthesis of 1,3-amino alcohol is particularly attractive because of the mild reaction conditions, use of easily available aldehydes as starting materials and cheap and commercially available proline as catalyst. Since the stereochemical outcome of the reaction can be predicted on the basis of catalyst used, this method gives an easy access to *syn*/*anti*-1,3-amino alcohols with predictable and useful stereocontrol in good yield.

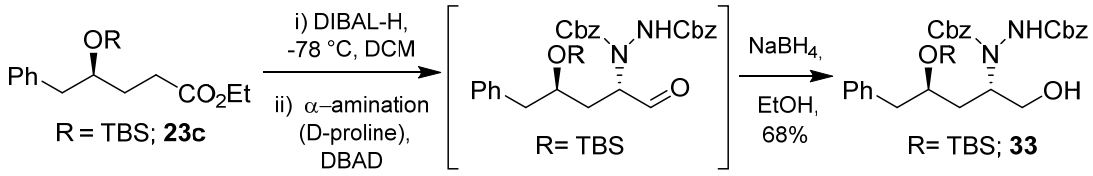
For further synthetic manipulation, the *N*-*N*-bond of substituted hydrazine **24c** was easily cleaved with concomitant reduction of double bond using freshly prepared Raney-Ni and free amine was converted into its acetate derivative using Ac_2O. Subsequent silyl deprotection using TBAF furnished compound **32** in 67% yield. The disappearance of protons in the range of δ -0.02 as multiplate and 0.86 as a singlet and appearance of Ac

proton at 1.96 as singlet in ^{1}H NMR spectrum confirmed the formation of compound **32** (Scheme **9**).



Scheme 9. Cleavage of *N*-*N*-bond by reductive hydrogenation

In yet another synthetic manipulation, the α-amino aldehyde formed in the reaction can easily be reduced in situ by sodium borohydride in ethanol to furnish the 2-hydrazino alcohol. Thus, the DIBAL-H reduction of TBS protected γ-hydroxy ester **23c** at -78 ^oC gave the corresponding aldehyde which was then subjected to α-amination using DBAD as a nitrogen source and D-proline as catalyst to furnish the α-amino aldehyde, which on treatment with $NaBH_4$ in ethanol afforded the *anti*-1,3-amino alcohol **33** in 68% yield (over three steps) thus offering considerable opportunities for further synthetic manipulations[17] (Scheme **10**).

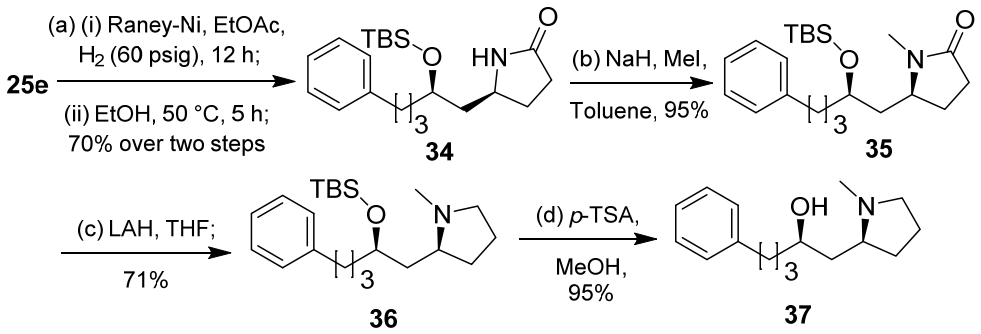


Scheme 10. Synthesis of 2-hydrazino alcohol

In order to further demonstrate the utility of this approach we have developed a short synthesis of (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**37**), a cyclic amino alcohol derivative. Compound **37** and its analogues have recently been found to be useful for the treatment of various neurological disorders such as Parkinson's disease, Alzhemier's disease, Huntington's diseases, strokes and spinal cord injuries etc.[18]

As illustrated in Scheme **11**, the reduction of the double bond and cleavage of the *N*-*N* bond in **25e** was achieved in one-pot using freshly prepared Raney nickel. Subsequent filtration and reflux in ethanol afforded the lactam **34** in 70% yield (over two steps). Monoalkylation of **34** using MeI and NaH furnished the *N*-methylated compound

35 in 95% yield. The disappearance of -NH protons in the range of δ 6.06 as brs and appearance of $-CH_3$ proton at 2.85 as singlet in ^1H NMR spectrum confirmed the formation of the *N*-methylated compound product **35**. LAH reduction of amide **35** furnished amine **36** in 71% yield. Disappearance of peak at 1678 cm^{-1} in IR spectrum confirmed the reduction of amide **35**. Finally TBS deprotection using *p*-TSA in methanol afforded the target compound **31** in 95% yield.



Scheme 11. Synthesis of (*R*)-1-((*S*)-1-Methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**37**)

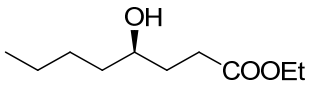
2.1.5. Conclusion

In conclusion, we have demonstrated a practical, efficient and organocatalytic approach to the stereocontrolled synthesis of 1,3-amino alcohols from commercially available and inexpensive starting material using modified α-aminoxylation and α-amination reactions of an aldehyde. To the best of our knowledge this is the first organocatalytic approach to the enantiopure *syn* or *anti*-1,3-amino alcohols from readily available aldehydes. The advantages of using this process are as follows. (a) The reaction uses mild reaction conditions (b) The reaction employs cheap and easily available proline as catalyst (available in both forms) and thus in principle all the possible isomers of 1,3-amino alcohol can be accessed. (c) The γ-hydroxy-α-amino aldehydes can easily be trapped by different reactions and converted into various useful building blocks.

The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol.

2.1.6. Experimental Section

(*R*)-Ethyl 4-hydroxyoctanoate (22a):



General Procedure:

To a solution of hexanal (2.0 g, 19.9 mmol) and nitroso benzene (2.13 g, 19.9 mmol) in anhydrous DMSO (40 mL) was added L-proline (0.92 g, 7.96 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to orange red during this time), then cooled to 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (11.9 mL, 59.9 mmol), DBU (8.94 mL, 59.9 mmol) and LiCl (2.535 g, 59.9 mmol) in CH_3CN (40 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 ^{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 γ-hydroxy ester **22a**. The crude product was then purified by using silica gel flash column chromatography using pet ether: EtOAc (85:15) as eluent to give (*R*)-ethyl 4-hydroxyoctanoate **22a** as a colorless liquid.

Yield: 1.77g, 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

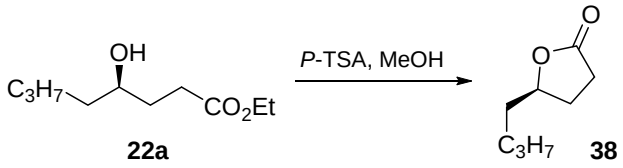
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.93 (m, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.32-1.36 (m, 3H), 1.41-1.45 (m, 2H), 1.62-1.93 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 3.55-3.67 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H) ppm.

^{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 $(M+Na)^+$

The analytical data are identical to those reported elsewhere.[2]

In order to determine the chiral purity of (*R*)-ethyl 4-hydroxyoctanoate **22a** formed it was converted into known lactone on treatment with *p*-TSA in methanol.

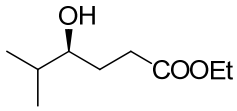


22a **38**

Chiral GC using Cyclodextrin TA column (70 kPa pressure, 140 °C isotherm for 30 min, major enantiomer 17 min, minor enantiomer 15 min).[2] The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 94%.

Using the same procedure as described for the synthesis of **22a**, compounds **22b**-**22e** were prepared.

(*S*)-Ethyl 4-hydroxy-5-methylhexanoate (22b):



Physical State: colorless liquid

Yield: 69%

Mol. Formula: $C_9H_{18}O_3$

$[\alpha]_D^{25}$: - 9.86 (*c* 1.05, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3446, 2963, 1724, 1216, 1053

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, J = 1.0 Hz, 3H), 0.93 (d, J = 1.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.56-1.72 (m, 2H), 1.75-1.86 (m,1H), 2.06 (brs, 1H), 2.41-2.50 (m, 2H), 3.30-3.39 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H) ppm.

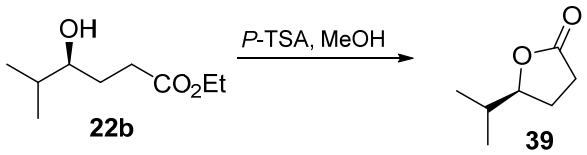
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 17.3, 18.4, 28.8, 30.9, 33.6, 60.1, 75.7, 174.2 ppm.

MS (ESI): m/z 197.1611 $(M + Na)^+$

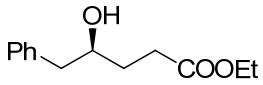
Elemental analysis: Calcd. C, 62.04; H, 10.41; Found C, 62.18; H, 10.29.

The chiral purity of the (*S*)-ethyl 4-hydroxy-5-methylhexanoate (**22b**) was determined by converting it into known lactone with *P*-TSA treatment and comparing the optical

rotation with the literature value. $[\alpha]_D^{25}$: +34.66 (*c* =1.1, $CHCl_3$). Lit.[3] $[\alpha]_D^{25}$: +34.9 (*c* =1.1, $CHCl_3$). ee is 98%.



(*S*)-Ethyl 4-hydroxy-5-phenylpentanoate (22c):



Physical State: colorless liquid

Yield: 71%

Mol. Formula: $C_{13}H_{18}O_3$

$[\alpha]_D^{25}$: + 14.54 (*c* 1, $CHCl_3$).

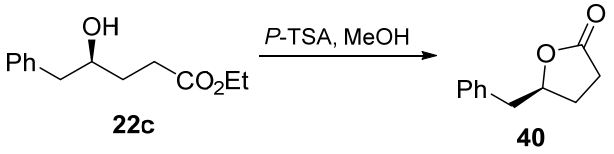
IR ($CHCl_3$, cm^{-1}): ν^{max} 3488, 1731, 1602, 1494, 1022.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.71-2.01 (m, 3H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.66-2.88 (m, 2H), 3.80-3.93 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 7.20-7.34 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): *δ* 13.9, 30.5, 31.3, 43.8, 60.1, 71.5, 126.1, 128.2, 129.1, 138.2, 173.8 ppm.

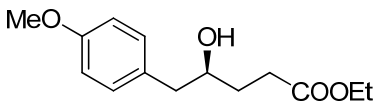
The analytical data are identical to those reported elsewhere.[2a]

In order to determine the chiral purity of (*S*)-ethyl 4-hydroxy-5-phenylpentanoate **22c** formed, it was converted into known lactone **40** by treatment with *p*-TSA in methanol.



HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 10:90, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 17.17 (major) and 20.67 (minor). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 98%.

(*S*)-Ethyl 4-hydroxy-5-(4-methoxyphenyl)pentanoate (22d):



Physical State: slight yellow liquid

Yield: 73%

Mol. Formula: $C_{14}H_{20}O_4$

$[\alpha]_D^{25}$: - 1.14 (*c* 0.28, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3422, 2934, 1727, 1611, 1584, 1035

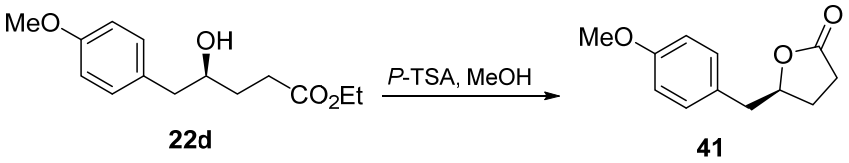
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.75-1.91 (m, 3H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.65 (dd, *J* = 8.0, 13.6 Hz, 1H) 2.75 (dd, *J* = 8.0, 13.6 Hz, 1H), 3.67-3.77 (m, 1H), 3.80 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 30.6, 31.2, 43.0, 55.0, 60.3, 71.8, 113.7, 130.1, 130.2, 158.0, 174.0 ppm.

MS (ESI): m/z 275.2150 $(M+Na)^+$

Elemental analysis: Calcd. C, 66.65; H, 7.99; Found C, 66.44; H, 7.85.

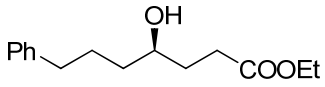
In order to determine the chiral purity of (*S*)-ethyl 4-hydroxy-5-(4-methoxyphenyl) pentanoate **22d** formed, it was converted into known lactone **41** by treatement with *p*-TSA in methanol.



22d **41**

HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 10:90, flow rate 0.5 mL/min, λ = 214 nm). Retention time (min): 35.28 (major) and 42.44 (minor). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 99%.

(*R*)-Ethyl 4-hydroxy-7-phenylheptanoate (22e):



Physical State: colorless liquid

yield: 68%

Mol. Formula: $C_{15}H_{22}O_3$

$[\alpha]_D^{25}$: + 14.96 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3368, 3022, 1728, 1602, 1496, 1454, 1217.

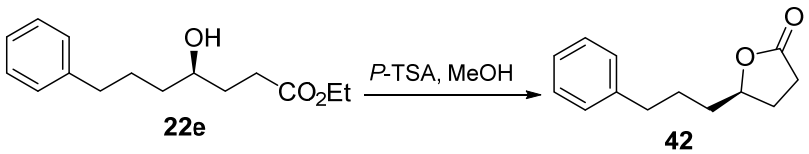
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 1.51-1.62 (m, 2H), 1.70-1.81 (m, 2H), 1.83-1.92 (m, 2H), 2.12 (brs, 1H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.7 Hz, 2H), 3.68-3.78 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 7.23-7.28 (m, 3H), 7.32-7.36 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.05, 27.3, 30.7, 32.0, 35.6, 36.9, 60.4, 70.8, 125.6, 128.2, 128.3, 142.1, 174.2 ppm.

MS (ESI): m/z 273.1910 $(M+Na)^+$

Elemental analysis: Calcd. C, 71.97; H, 8.86; Found C, 71.7; H, 8.66.

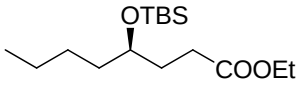
In order to determine the chiral purity of (*R*)-Ethyl 4-hydroxy-7-phenylheptanoate **22e** formed, it was converted into known lactone **42** by treatement with *p*-TSA in methnol.



22e **42**

HPLC: Kromasil 5-Amycoat column (EtOH: n-Hexane = 25:75, flow rate 0.7 mL/min, λ = 214 nm). Retention time (min): 8.82 (major) and 10.1 (minor). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 99%.

(*R*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate (23a):



General Procedure:

To an ice-cold stirred solution of **22a** (1.0 g, 5.31 mmol) in DMF (12 mL) were added imidazole (0.452 g, 6.64 mmol) and TBSCl (1.00 g, 6.64 mmol) at room temperature. The resulting mixture was stirred for 6 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 25 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: 99:1) of the crude product gave (*R*)-ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate **23a** as a colorless liquid.

Yield: 1.48 g, 92%

$[\alpha]_D^{25}$: - 9.96 (*c* 1.78, $CHCl_3$)

Mol. Formula: $C_{16}H_{34}O_3Si$

IR ($CHCl_3$, cm^{-1}): ν^{max} 2856, 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.

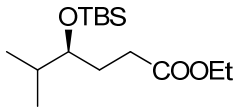
^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.7, 13.9, 14.0, 17.8, 22.6, 25.7, 27.2, 29.8, 31.5, 36.6, 59.9, 70.9, 173.5 ppm.

MS (ESI): m/z 325.4028 $(M+Na)^+$

Elemental analysis: Calcd. C, 63.52; H, 11.33; Found C, 63.64; H, 11.19.

Using the same procedure as described for the synthesis of **23a**, Compounds **23b**-**23e** were prepared.

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-methylhexanoate (23b):



Physical State: colorless liquid

Yield: 89%

Mol. Formula: $C_{15}H_{32}O_3Si$

$[\alpha]_D^{25}$: - 14.73 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3019, 1725, 1215, 1081.

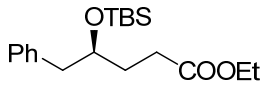
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (d, J = 6.8 Hz, 6H), 0.89 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 1.65-1.76 (m, 3H), 2.29-2.39 (m, 2H), 3.43-3.51 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, 14.2, 17.3, 18.1, 25.9, 27.6, 30.3, 32.9, 60.2, 75.7, 174.0 ppm.

MS (ESI): m/z 289.2407 $(M+H)^+$, 311.1563 $(M+Na)^+$

Elemental analysis: Calcd. C, 62.45; H, 11.18; Found: C, 62.66; H, 11.10.

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-phenylpentanoate (23c):



Physical State: colorless liquid

Yield: 91%

Mol. Formula: $C_{19}H_{32}O_3Si$

$[\alpha]_D^{25}$: - 2.08 (*c* 1.1, $CHCl_3$)

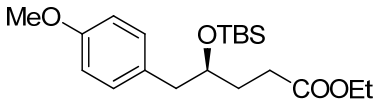
IR ($CHCl_3$, cm^{-1}): ν^{max} 2955, 1736, 1684, 1454, 1088.

^{1}H NMR (400 MHz, $CDCl_3$): δ -0.12 (s, 3H), 0.03(s, 3H), 0.91 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.69-1.78 (m, 1H), 1.80-1.89 (m, 1H), 2.37-2.47 (m, 2H), 2.73 (dd, *J* = 6.3, 13.2 Hz, 1H), 2.79 (dd, *J* = 6.3, 13.2 Hz, 1H), 3.92-3.98 (m, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 7.18-7.23 (m, 3H), 7.27-7.31 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.0, -4.9, 14.1, 17.9, 25.8, 29.8, 31.5, 43.8, 60.1, 72.4, 126.1, 128.1, 129.6, 138.6, 173.6 ppm.

The analytical data are identical to those reported elsewhere.[2a]

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-(4-methoxyphenyl)pentanoate (23d):



Physical State: colorless liquid

Yield: 92%

Mol. Formula: $C_{20}H_{34}O_4Si$

$[\alpha]_D^{25}$: - 4.46 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3019, 1726, 1512, 1473, 1215, 1083.

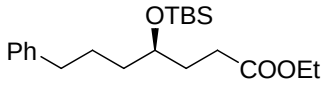
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.12 (s, 3H), 0.00 (s, 3H), 0.88 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.65-1.81 (m, 2H), 2.33-2.43 (m, 2H), 2.58-2.78 (m, 2H), 3.79 (s, 3H), 3.83-3.89 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.8, 14.2, 18.0, 25.8, 30.0, 31.4, 42.9, 55.2, 60.2, 72.5, 113.6, 130.5, 130.7, 158.0, 173.8 ppm.

MS (ESI): m/z 389.2971 $(M+Na)^+$, 405.3299 $(M+K)^+$

Elemental analysis: Calcd. C, 65.53; H, 9.35; Found: C, 65.71; H, 9.23.

(*R*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-7-phenylheptanoate (23e):



Physical State: colorless liquid

Yield: 90%

Mol. Formula: $C_{21}H_{36}O_3Si$

$[\alpha]_D^{25}$: - 7.32 (*c* 1.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2929, 1735, 1456, 1256, 1094.

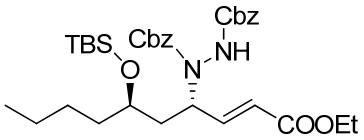
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.47-1.55 (m, 2H), 1.65-1.81 (m, 4H), 2.36 (t, *J* = 7.7 Hz, 2H) 2.63 (t, *J* = 7.7 Hz, 2H), 3.66-3.80 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H) 7.18-7.23 (m, 3H), 7.27-7.30 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.5, 14.2, 18.0, 25.8, 26.7, 30.0, 31.7, 35.9, 36.5, 60.2, 70.9, 125.6, 128.2, 128.3, 142.3, 173.6 ppm.

MS (ESI): m/z 365.3719 $(M+H)^+$, 387.3083 $(M+Na)^+$, 403.3958 $(M+K)^+$

Elemental analysis: Calcd. C, 69.18; H, 9.95; Found: C, 69.43; H, 9.79.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate (24a):



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

To a solution of ethyl ester **23a** (1.0 g, 3.31 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (1.6 mL 2.25 M solution in toluene, 3.62 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (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 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced

pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.96 g, 3.22 mmol) and D-proline (0.036 g, 8 mol%) in CH_3CN (32 mL) at 0 °C was added above aldehyde (1.0 g, 3.87 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 (0.21 g, 4.84 mmol), triethyl phosphonoacetate (0.97 mL, 4.84 mmol) and DBU (0.48 mL, 3.22 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 (diastereomeric ratio/ 97:3). Silica gel column chromatography (petroleum ether: ethyl acetate: 90:10) of the crude product gave dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate **24a** as a colorless syrupy liquid.

Yield: 1.33 g, 64%

Mol. Formula: $C_{34}H_{50}N_2O_7Si$

$[\alpha]_D^{25}$: - 20.39 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3392, 3019, 1742, 1717, 1554, 1498, 1215, 1027.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.85 (m, 12H), 1.23-1.32 (m, 8H), 1.39-1.52 (m, 2H), 1.92-2.04 (m, 1H), 3.75-3.89 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.96-5.07 (m, 1H), 5.14 (s, 4H), 5.92 (m, 1H), 6.59 (m, 1H), 6.86 (dd, *J* = 6.2, 15.2 Hz, 1H), 7.32 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.3, 14.0, 14.1, 18.0, 22.8, 25.8, 26.8, 37.0, 60.5, 67.7, 68.2, 122.0, 122.1, 128.0, 128.1, 128.2, 128.4, 135.6, 145.9, 156.2, 156.3, 166.2 ppm.

MS (ESI): m/z 627.5165 $(M+H)^+$, 649.5575 $(M+Na)^+$, 665.559 $(M+K)^+$

Elemental analysis: Calcd. C, 65.14; H, 8.04; N, 4.47; Found: C, 65.31; H, 8.17; N, 4.51.

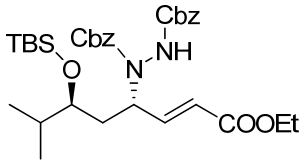
Diastereomeric ratio was determined by HPLC analysis; 97:3 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 6.43 min and t_R for (*syn*)- isomer = 5.76 min.

Using the same procedure as described for synthesis of **24a**, compounds **24b**-**24e** were prepared.

Dibenzyl 1-((4*S*,6*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-methyl-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (24b):



Physical State: colorless syrupy liquid

Yield: 68%

Mol. Formula: $C_{33}H_{48}N_2O_7Si$

$[\alpha]_D^{25}$: - 8.44 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3292, 2955, 1757, 1718, 1610, 1512, 1406, 1249.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.06 (s, 3H), 0.85-0.91 (m, 15H), 1.26-1.29 (m, 4H), 1.74-1.93 (m, 2H), 3.65-3.77 (m, 1H), 4.19 (q, J = 7.0 Hz, 2H), 4.92 (m, 1H), 5.13 (s, 4H), 5.83 (m, 1H), 6.40 (m, 1H), 6.73 (d, J = 17.4 Hz, 1H), 7.32 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.3, 14.1, 16.2, 17.9, 18.0, 25.9, 29.6, 33.3, 60.5, 63.2, 67.8, 68.3, 72.6, 122.0, 128.1, 128.3, 128.5, 135.5, 145.9, 156.4, 166.2 ppm.

MS (ESI): m/z 635.5057 $(M+Na)^+$, 651.5379 $(M+K)^+$

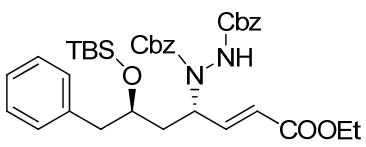
Elemental analysis: Calcd. C, 64.68; H, 7.89; N, 4.57; Found: C, 64.82; H, 7.74; N, 4.45.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 5.89 min and t_R for (*syn*)- isomer = 5.14 min.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-7-phenylhept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24c):



Physical State: colorless syrupy liquid

Yield: 63%

Mol. Formula: $C_{37}H_{48}N_2O_7Si$

$[\alpha]_D^{25}$: - 11.08 (*c* 0.84, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3390, 3030, 2953, 2928, 1754, 1718, 1496, 1456, 1255, 1082.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.02 (m, 6H), 0.86 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.42-1.53 (m, 1H), 1.93 (m, 1H), 2.62-2.89 (m, 2H), 3.89-4.08 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.86-5.19 (m, 5H), 5.84 (m, 1H), 6.24 (m, 1H), 6.78 (dd, *J* = 6.1, 15.0 Hz, 1H), 7.21-7.37 (m, 15H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.5, 14.0, 17.9, 25.8, 37.2, 43.9, 60.4, 64.9, 67.4, 68.0, 68.5, 121.9, 126.1, 126.8, 127.3, 127.9, 128.1, 128.3, 129.5, 135.5, 138.0, 140.9, 145.6, 155.3, 156.1, 166.2 ppm.

MS (ESI): m/z 683.4795 $(M+Na)^+$, 699.7712 $(M+K)^+$

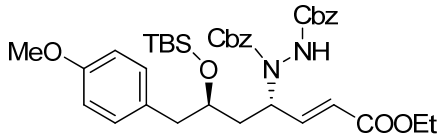
Elemental analysis: Calcd. C, 67.24; H, 7.32; N, 4.24; Found: C, 67.37; H, 7.23; N, 4.13.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 95:5; t_R for (*anti*)-isomer = 7.67 min and t_R for (*syn*)- isomer = 6.84 min.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-(4-methoxyphenyl)-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24d):



Physical State: colorless syrupy liquid

Yield: 64%

Mol. Formula: $C_{38}H_{50}N_2O_8Si$

$[\alpha]_D^{25}$: - 4.60 (*c* 0.536, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3296, 2955, 2929, 1755, 1718, 1610, 1512, 1462, 1249, 1039.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (m, 6H), 0.86 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.43-1.48 (m, 1H), 1.85-1.97 (m, 1H), 2.63-2.82 (m, 2H), 3.71 (s, 3H), 4.08-4.19 (m, 3H),

4.81-4.97 (m, 1H), 5.08-5.21 (m, 4H), 5.85 (m, 1H), 6.23 (m, 1H), 6.76-6.80 (m, 3H), 7.02 (m, 2H), 7.32 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.0, -4.4, 14.1, 17.9, 19.1, 25.8, 42.9, 55.1, 60.4, 67.6, 68.2, 71.7, 113.7, 122.0, 128.0, 128.2, 128.4, 128.5, 130.4, 135.5, 145.6, 156.0, 158.0, 166.1 ppm.

MS (ESI): m/z 713.5326 $(M+Na)^+$, 729.5472 $(M+K)^+$.

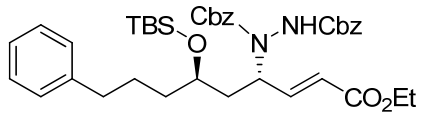
Elemental analysis: Calcd. C, 66.06; H, 7.29; N, 4.05; Found: C, 66.29; H, 7.14; N, 4.13.

Diastereomeric ratio was determined by HPLC analysis; 97:3 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 5.15 min and t_R for (*syn*)- isomer = 5.76 min.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-9-phenylnon-2-en-4-yl)hydrazine-1,2-dicarboxylate (24e):



Physical State: colorless syrupy liquid

Yield: 63%

Mol. Formula: $C_{39}H_{52}N_2O_7Si$

$[\alpha]_D^{25}$: - 14.3 (*c* 0.96, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3298, 2953, 2929, 1757, 1718, 1560, 1458, 1404, 1253, 1041.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.02 (s, 6H), 0.84 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.44-1.58 (m, 5H), 1.88-2.02 (m, 1H), 2.49-2.62 (m, 2H), 3.76-3.94 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.97-5.19 (m, 5H), 5.89 (m, 1H), 6.55 (m, 1H), 6.84 (dd, J = 5.6, 14.3 Hz, 1H), 7.14-7.31 (m, 15H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.4, 14.0, 17.8, 19.0, 25.7, 35.8, 36.8, 37.6, 60.4, 64.8, 67.4, 68.4, 71.6, 121.8, 125.6, 126.7, 127.2, 127.9, 128.1, 128.2, 128.3, 135.5, 142.1, 146.0, 155.5, 156.4, 166.2 ppm.

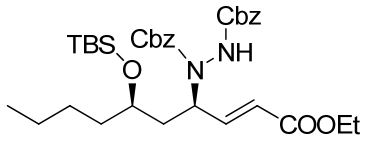
MS (ESI): m/z 711.5634 $(M+Na)^+$, 727.5909 $(M+K)^+$

Elemental analysis: Calcd. C, 67.99; H, 7.61; N, 4.07; Found: C, 68.12; H, 7.53; N, 4.15.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr
UV detector: Merck-HITACHI L-7400 series
Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 6.41 min and t_R for (*syn*)- isomer = 5.9 min.

Using the same procedure as described for the synthesis of 2**4a** and using L-proline as a catalyst in α-amination step compounds **25a**-**25e** were prepared.

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate (25a):

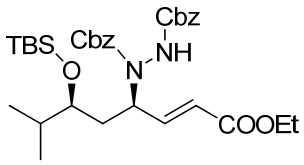


Physical State: colorless syrupy liquid
Yield: 65%
Mol. Formula: $C_{34}H_{50}N_2O_7Si$
$[\alpha]_D^{25}$: - 6.61 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$, cm^{-1}): ν^{max} 3392, 3019, 1754, 1717, 1215, 1027.
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.04 (s, 3H), 0.87 (m, 12H), 1.26-1.30 (m, 7H), 1.47 (m, 2H), 1.74-1.76 (m, 1H), 1.98 (m, 1H), 3.73 (m, 1H), 4.18-4.20 (m, 2H), 4.84-5.02 (m, 1H), 5.16 (s, 4H), 5.96 (m, 1H), 6.67-6.73 (m, 1H), 6.87 (m, 1H), 7.32 (m, 10H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ -4.6, -4.2, 14.0, 14.1, 17.9, 22.8, 25.8, 26.7, 37.0, 37.8, 56.6, 60.5, 67.8, 68.4, 69.2, 122.9, 128.1, 128.2, 128.3, 128.5, 135.5, 144.8, 155.4, 156.2, 166.0 ppm.
MS (ESI): m/z 627.5165 $(M+H)^+$, 649.5575 $(M+Na)^+$, 665.559 $(M+K)^+$
Elemental analysis: Calcd. C, 65.14; H, 8.04; N, 4.47; Found: C, 65.29; H, 8.15; N, 4.37.

Diastereomeric ratio was determined by HPLC analysis; 9:1 dr
UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 6.56 min and t_R for (*syn*)-isomer = 5.82 min.

Dibenzyl 1-((4*R*,6*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-methyl-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):



Physical State: colorless syrupy liquid

Yield: 62%

Mol. Formula: $C_{33}H_{48}N_2O_7Si$

$[\alpha]_D^{25}$: - 4.01 (*c* 0.87, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3387, 3020, 2958, 2929, 1757, 1718, 1462, 1217, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.02 (s, 3H), 0.02 (s, 3H), 0.86 (m, 15H), 1.26-1.33 (m, 3H), 1.65-1.71 (m, 1H), 1.76-1.95 (m, 2H), 3.47-3.65 (m, 1H), 4.20 (q, *J* = 6.8 Hz, 2H), 4.90 (m, 1H), 5.16 (s, 4H), 5.94 (brs, 1H), 6.40-6.51 (m, 1H), 6.77-6.88 (m, 1H), 7.32 (s, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, -4.3, 14.1, 18.0, 25.8, 29.6, 33.2, 33.4, 60.5, 67.7, 68.3, 73.2, 122.9, 128.0, 128.1, 128.2, 128.3, 128.4, 135.5, 155.2, 156.3, 166.1 ppm.

MS (ESI): m/z 635.5057 $(M+Na)^+$, 651.5379 $(M+K)^+$

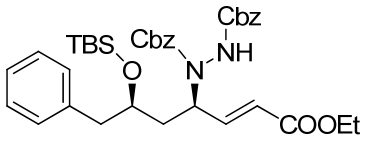
Elemental analysis: Calcd. C, 64.68; H, 7.89; N, 4.57; Found: C, 64.82; H, 7.74; N, 4.43.

Diastereomeric ratio was determined by HPLC analysis; 81: 19 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 5.98 min and t_R for (*syn*)-isomer = 5.2 min.

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-7-phenylhept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25c):



Physical State: colorless syrupy liquid;

Yield: 68%

Mol. Formula: $C_{37}H_{48}N_2O_7Si$

$[\alpha]_D^{25}$: + 2.21 (*c* 0.62, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3392, 3030, 2953, 2928, 1756, 1720, 1456, 1255, 1082, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.08 (s, 3H), 0.00 (s, 3H), 0.90 (s, 9H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.78-1.91 (m, 2H), 2.75-2.93 (m, 2H), 3.94-4.08 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 5.05- 5.22 (m, 5H), 5.89 (brs, 1H), 6.37-6.59 (m, 1H), 6.80-6.86 (m, 1H), 7.37 (m, 15H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, 14.0, 17.8, 25.8, 37.6, 43.7, 56.1, 60.4, 65.0, 67.6, 70.7, 122.7, 126.2, 126.8, 127.3, 128.0, 128.2, 128.3, 128.4, 129.5, 135.4, 138.1, 140.9, 144.6, 155.3, 156.4, 166.0 ppm.

MS (ESI): m/z 683.4795 $(M+Na)^+$, 699.7712 $(M+K)^+$

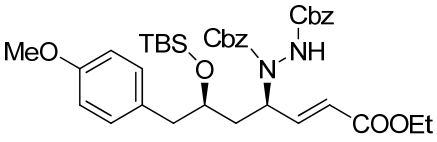
Elemental analysis: Calcd. C, 67.24; H, 7.32; N, 4.24; Found: C, 67.37; H, 7.23; N, 4.31.

Diastereomeric ratio was determined by HPLC analysis; 91:9 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 95:5; t_R for (*anti*)-isomer = 7.66 min and t_R for (*syn*)- isomer = 6.81 min.

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-(4-methoxyphenyl)-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25d):



Physical State: colorless syrupy liquid

Yield: 66%

Mol. Formula: $C_{38}H_{50}N_2O_8Si$

$[\alpha]_D^{25}$: + 2.09 (*c* 0.66, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3294, 2955, 2929, 1757, 1718, 1512, 1458, 1249, 1084, 1039.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.09 (s, 3H), -0.04 (s, 3H), 0.85 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.67-1.74 (m, 1H), 1.84-1.98 (m, 1H), 2.72-2.75 (m, 2H), 3.79 (s, 3H), 3.85-3.96 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.93-5.02 (m, 1H), 5.14-5.16 (m, 4H), 5.81 (brs, 1H), 6.44 (m, 1H), 6.70-6.81 (m, 3H), 7.01 (m, 2H), 7.33 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.6, 14.0, 17.8, 25.8, 37.4, 42.8, 55.0, 60.4, 67.6, 68.2, 70.8, 113.6, 122.7, 128.0, 128.2, 128.4, 130.4, 135.5, 144.6, 155.3, 156.2, 158.0, 166.0 ppm.

MS (ESI): m/z 713.5326 $(M+Na)^+$, 729.5472 $(M+K)^+$

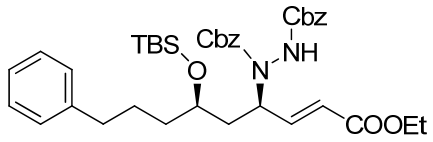
Elemental analysis: Calcd. C, 66.06; H, 7.29; N, 4.05; Found: C, 66.21; H, 7.14; N, 3.96.

Diastereomeric ratio was determined by HPLC analysis; 88:12 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 5.22 min and t_R for (*syn*)- isomer = 5.86 min.

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-9-phenylnon-2-en-4-yl)hydrazine-1,2-dicarboxylate (25e):



Physical State: colorless syrupy liquid

Yield: 64%

Mol. Formula: $C_{39}H_{52}N_2O_7Si$

$[\alpha]_D^{25}$: - 6.04 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3298, 2953, 2929, 1757, 1718, 1462, 1400, 1253, 1041.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.86 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H), 1.44-1.65 (m, 5H), 1.91-2.03 (m, 1H), 2.56-2.65 (m, 2H), 3.68-3.99 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.94-5.27 (m, 5H), 5.93 (brs, 1H), 6.55 (m, 1H), 6.81-6.90 (m, 1H), 7.16-7.23 (m, 3H), 7.27-7.40 (m, 12H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, -4.3, 14.1, 17.9, 25.8, 26.1, 35.8, 35.9, 36.7, 60.5, 65.0, 67.7, 68.3, 69.0, 122.0, 122.9, 125.7, 126.8, 127.4, 128.0, 128.2, 128.3, 128.4, 135.5, 140.9, 142.2, 155.2, 156.4, 166.1 ppm.

MS (ESI): m/z 711.5643 $(M+Na)^+$, 727.5909 $(M+K)^+$

Elemental analysis: Calcd. C, 67.99; H, 7.61; N, 4.07; Found: C, 68.12; H, 7.53; N, 4.15.

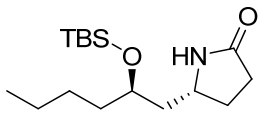
Diastereomeric ratio was determined by HPLC analysis; 86:14 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH: H_2O = 97:3; t_R for (*anti*)-isomer = 6.18 min and t_R for (*syn*)-isomer = 5.53 min.

Determination of relative configuration:

(*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)hexyl)pyrrolidin-2-one (26):



General experimental Procedure

The solution of dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate **24a** (0.2 g, 0.32 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (0.6 g, excess) under H_2 (60 psig) atmosphere for 12 h. The reaction mixture was filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 55 ^oC for 5h. The reaction mixture was then concentrated in vacuo to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 40:60) of the crude product gave cyclic lactam (*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)hexyl)pyrrolidin-2-one **26** as a colorless liquid.

Yield: 0.08 g, 74%

Mol. Formula: $C_{16}H_{33}NO_2Si$

$[\alpha]_D^{25}$: - 22.77 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3437, 3019, 1692, 1215.

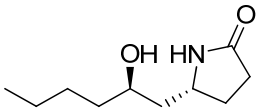
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.87-0.94 (m, 12H), 1.20-1.38 (m, 6H), 1.44-1.54 (m, 2H), 1.59-1.67 (m, 2H), 2.28-2.29 (m, 1H), 2.32-2.36 (m, 1H), 3.74-3.87 (m, 2H), 6.29 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.6, 13.9, 17.9, 22.6, 25.7, 27.4, 28.3, 30.0, 36.4, 42.7, 50.8, 70.4, 177.9 ppm.

MS (ESI): m/z 300.4293 $(M+H)^+$, 322.4282 $(M+Na)^+$

Elemental analysis: Calcd. C, 64.16; H, 11.10; N, 4.68; Found: C, 64.30; H, 11.19; N, 4.54.

(*R*)-5-((*R*)-2-Hydroxyhexyl)pyrrolidin-2-one (27):



To a stirred solution of compound **26** (0.056 g, 0.187 mmol) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture was stirred overnight at the same temperature. Solid $NaHCO_3$ (0.1 g) was added to the reaction mixture and stirred for 30 min. The reaction mixture was then filtered through a celite pad, washed with MeOH, concentrated and column purified using ethyl acetate to give (*S*)-5-((*R*)-2-hydroxyhexyl)pyrrolidin-2-one **27** as a colorless liquid.

Yield: 0.031 g, 93%

Mol. Formula: $C_{10}H_{19}NO_2$

$[\alpha]_D^{25}$: - 29.40 (*c* 1.15, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3402, 3019, 1681, 1217, 1020.

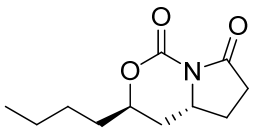
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.27-1.37 (m, 4H), 1.43-1.52 (m, 3H), 1.61 (t, *J* = 6.1 Hz, 2H), 1.68-1.73 (m, 1H), 2.25-2.29 (m, 1H), 2.31-2.33 (m, 1H), 3.75 (quint, *J* = 6.3 Hz, 1H), 3.94 (quint, *J* = 6.6 Hz, 1H), 7.01 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 27.6, 27.8, 30.1, 37.3, 43.5, 51.3, 68.3, 179.0 ppm.

MS (ESI): m/z 186.2229 $(M+H)^+$, 208.2148 $(M+Na)^+$

Elemental analysis: Calcd. C, 64.83; H, 10.34; N, 7.56; Found: C, 64.67; H, 10.47; N, 7.49

(3*R*,4a*R*)-3-Butyltetrahydro-1*H*-pyrrolo[1,2-c][1,3]oxazine-1,7(3*H*)-dione (28):



To a stirred solution of compound **27** (0.03 g, 0.164 mmol) in dry CH_2Cl_2 (1 mL) was added triethyl amine (0.115 mL, 0.818 mmol) and triphosgene (58.6 mg, 0.196 mmol) at 0 ^oC and the reaction mixture was stirred for 3 h at the same temperature before H_2O (0.25 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 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: 60:40) of the crude product gave (3*R*,4a*R*)-3-butyltetrahydro-1*H*-pyrrolo[1,2-c][1,3]oxazine-1,7(3*H*)-dione **28** as pale yellow liquid

Yield: 0.02 g, 71%

Mol. Formula: $C_{11}H_{17}NO_3$

$[\alpha]_D^{25}$: -0.21 (*c* 2.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2944, 2833, 1668, 1115, 1027.

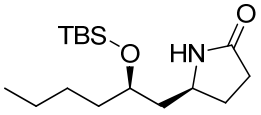
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.27-1.39 (m, 4H), 1.43-1.63 (m, 2H), 1.72-1.76 (m, 2H), 1.84-1.89 (m, 1H), 1.95-2.02 (m, 1H), 2.31-2.35 (m, 2H), 3.83-4.01 (m, 2H), 6.51 (brs, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.1, 27.4, 28.3, 29.9, 38.7, 45.0, 53.0, 60.9, 178.0 ppm.

MS (ESI): m/z 234.3252 $(M+Na)^+$

Elemental analysis: Calcd. C, 62.54; H, 8.11; N, 6.63; Found: C, 62.67; H, 8.02; N, 6.51.

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)hexyl)pyrrolidin-2-one (29):



Compound **29** was prepared from **25a** using same procedure as described for preparation of compound **26**.

Physical State: colorless liquid

Yield: 72%

Mol. Formula: $C_{16}H_{33}NO_2Si$

$[\alpha]_D^{25}$: - 5.42 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3437, 3019, 2932, 1692, 1215, 1044.

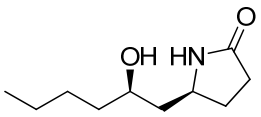
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.87-0.93 (m, 12H), 1.25-1.30 (m, 5H), 1.42-1.52 (m, 2H), 1.59-1.74 (m, 3H), 2.27-2.29 (m, 1H), 2.31-2.34 (m, 1H), 3.66-3.73 (m, 1H), 3.75-3.82 (m, 1H) 5.97 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.4, 13.9, 17.9, 22.7, 25.8, 26.8, 27.8, 30.0, 37.4, 43.2, 52.4, 70.7, 177.8 ppm.

MS (ESI): m/z 300.4293 $(M+H)^+$, 322.4282 $(M+Na)^+$

Elemental analysis: Calcd. C, 64.16; H, 11.10; N, 4.68; Found: C, 64.30; H, 11.19; N, 4.54.

(*S*)-5-((*R*)-2-Hydroxyhexyl)pyrrolidin-2-one (30):



Compound **30** was prepared from **29** using same procedure as described for preparation of compound **27**.

Physical State: colorless liquid;

Yield: 93%

Mol. Formula: $C_{10}H_{19}NO_2$

$[\alpha]_D^{25}$: + 10.14 (*c* 1.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3402, 3019, 2931, 1681, 1420, 1215, 1042, 1217, 1020.

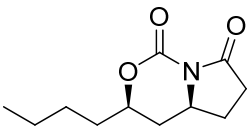
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.22-1.31 (m, 6H), 1.38-1.48 (m, 2H), 1.55-1.65 (m, 2H), 2.25 (m, 2H), 3.68-3.75 (m, 2H), 7.03 (brs, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 27.5, 28.2, 29.6, 38.2, 43.3, 54.8, 71.7, 178.2 ppm.

MS (ESI): m/z 186.2229 $(M+H)^+$, 208.214 $(M+Na)^+$

Elemental analysis: Calcd. C, 64.83; H, 10.34; N, 7.56; Found: C, 64.71; H, 10.47; N, 7.49.

(3*R*,4a*S*)-3-Butyltetrahydro-1*H*-pyrrolo[1,2-c][1,3]oxazine-1,7(3*H*)-dione (31):



Compound **31** was prepared from **30** using same procedure as described for preparation of compound **28**.

Physical State: Pale yellow liquid

Yield: 74%

Mol. Formula: $C_{11}H_{17}NO_3$

$[\alpha]_D^{25}$: + 16.4 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2944, 2833, 1668, 1115, 1027.

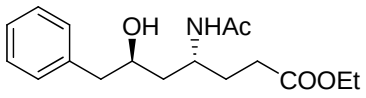
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.32-1.42 (m, 4H), 1.48-1.55 (m, 1H), 1.57-1.62 (m, 1H), 1.72-1.75 (m, 2H), 1.83-1.90 (m, 2H), 2.31-2.35 (m, 2H), 3.92-3.95 (m, 1H), 3.97-4.05 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.1, 27.5, 28.4, 29.7, 38.6, 45.1, 51.7, 60.6 ppm.

MS (ESI): m/z 234.3252 $(M+Na)^+$

Elemental analysis: Calcd. C, 62.54; H, 8.11; N, 6.63; Found: C, 62.67; H, 8.02; N, 6.51.

(4*R*,6*R*)-Ethyl 4-acetamido-6-hydroxy-7-phenylheptanoate (32):



The solution of dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-7-phenylhept-2-en-4-yl)hydrazine-1,2-dicarboxylate **24c** (0.15 g, 0.23mmol) in MeOH (12 mL) and acetic acid (6 drops) was treated with Raney nickel (0.4 g, excess) under H_2 (80 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 (0.14 mL, 0.91 mmol), acetic anhydride (0.095 mL, 0.91 mmol) and cat. DMAP in dry DCM (2 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*-acetate derivative. This *N*-acetate

derivative was further treated with TBAF (0.12 mL, 0.43 mmol) in THF (2 mL) at 0 ^{o}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 (petroleum ether: ethyl acetate: 25:75) of the crude product gave (4*R*,6*R*)-ethyl 4-acetamido-6-hydroxy-7-phenylheptanoate **32** as a syrupy liquid.

Yield: 0.047 g, 67% over 2 steps

Mol. Formula: $C_{17}H_{25}NO_4$

$[\alpha]_D^{25}$: - 20.23 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3287, 2925, 1732, 1654, 1550, 1250, 1030.

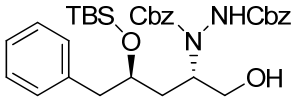
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.37-1.44 (m, 1H), 1.53-1.60 (m, 1H), 174-1.81 (m, 2H), 1.96 (s, 3H), 2.29-2.46 (m, 2H), 2.67 (dd, *J* = 6.0, 13.5 Hz, 1H), 2.87 (dd, *J* = 6.0, 13.5 Hz, 1H), 3.76-3.81 (m, 1H), 4.07-4.17 (m, 3H), 5.96 (d, *J* = 8.5 Hz, 1H), 7.20-7.23 (m, 3H), 7.27-7.31(m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.1, 29.5, 31.3, 43.1, 43.4, 47.1, 60.7, 68.5, 126.2, 128.3, 129.4, 138.8, 171.5, 173.9 ppm.

MS (ESI): m/z 308.4499 $(M+H)^+$, 330.4310 $(M+Na)^+$

Elemental analysis: Calcd. C, 66.43; H, 8.20; N, 4.56; Found: C, 66.57; H, 8.05; N, 4.68.

Dibenzyl 1-((2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (33):



To a solution of ethyl ester **23c** (0.5 g, 1.49 mmol) in CH_2Cl_2 (20 mL), was added DIBAL-H (0.8 mL 2.25 M solution in toluene, 0.16 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (0.5 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 colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.43 g, 1.43 mmol) and D-proline (0.016 g, 8 mol%) in CH_3CN (15 mL) at 0 °C was added above aldehyde (0.5 g, 1.49 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. Then reaction mixture was cooled to 0 ^oC, treated with ethanol 12 ml and $NaBH_4$ (0.05 g) and was stirred for 5 min at 0 ^oC. 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 (diastereomeric ratio/ 97:3). Silica gel column chromatography (petroleum ether: ethyl acetate: 60:40) of the crude product gave dibenzyl 1-((2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate **33** as a colorless syrupy liquid

Yield: 0.68 g, 68%

Mol. Formula: $C_{33}H_{44}N_2O_6Si$

$[\alpha]_D^{25}$: - 2.97 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3386, 2928, 1720, 1603, 1497, 1257, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.02-0.09 (m, 6H), 0.87 (s, 9H), 1.23-1.35 (m, 2H), 1.56 (brs, 1H), 2.67-2.84 (m, 2H), 3.21-3.40 (m, 2H), 3.88-4.04 (m, 1H), 4.51-4.71 (m, 1H), 5.09-5.28 (m, 4H), 6.12 (d, J = 16.2 Hz, 1H), 7.12-7.36 (m, 15H) ppm.

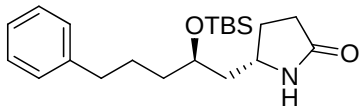
^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ - 4.9, - 4.7, 17.6, 25.8, 36.0, 43.9, 57.2, 62.0, 66.4, 67.0, 70.4, 125.8, 127.3, 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 129.5, 136.3, 138.6, 155.8, 156.9 ppm.

MS (ESI): m/z 593.9030$(M+H)^+$, 615.8833 $(M+Na)^+$

Elemental analysis: Calcd. C, 66.86; H, 7.48; N, 4.73; Found: C, 66.71; H, 7.39; N, 4.81.

Application:

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)pyrrolidin-2-one (34):



The solution of Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-9-phenylnon-2-en-4-yl)hydrazine-1,2-dicarboxylate **25e** (0.26 g, 0.377 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (0.6 g, excess) under

H_2 (60 psig) atmosphere for 12 h. The reaction mixture was then filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 50 ^oC 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 cyclic lactam (*S*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)-5-phenylpentyl)pyrrolidin-2-one **34** as a colorless liquid.

Yield: 0.096 g, 70% (over two steps)

Mol. Formula: $C_{21}H_{35}NO_2Si$

$[\alpha]_D^{25}$: -10.29 (*c* 1.36, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3428, 2951, 1692, 1255, 1095.

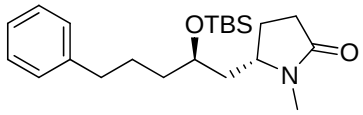
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 1.53-1.72 (m, 7H), 2.27-2.35 (m, 3H), 2.61 (t, J = 7.5 Hz, 2H), 3.66-3.80 (m, 2H), 6.06 (brs, 1H), 7.15-7.22 (m, 3H), 7.26-7.29 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.5, 14.0, 17.8, 25.7, 26.3, 27.7, 30.0, 35.8, 37.0, 43.2, 52.2, 70.3, 125.7, 128.2, 142.0, 177.9 ppm.

MS (ESI): m/z 384.3512 $(M+Na)^+$, 400.3469 $(M+K)^+$

Elemental analysis: Calcd. C, 69.75; H, 9.76; N, 3.87; Found: C, 69.87; H, 9,84; N, 3.73.

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidin-2-one (35):



To a stirred solution of **34** (0.09 g, 0.25 mmol) in dry toluene (8 mL) was added NaH (0.024 g, 1.00 mmol), CH_3I (0.16 mL, 2.5 mmol) and the reaction mixture was heated at 85 ^oC for 5 h. The reaction mixture was then diluted with EtOH (40 mL) and H_2O (2 mL), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 8 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: 70:30) of the crude product gave (*S*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidin-2-one **35** as a colorless liquid.

Yield: 0.088 g, 95%

Mol. Formula: $C_{22}H_{37}NO_2Si$

$[\alpha]_D^{25}$: - 26.64 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2928, 1678, 1462, 1402, 1253, 1280, 1028.

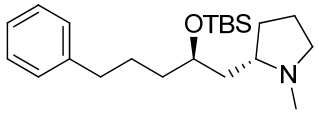
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.96 (s, 9H), 1.63-1.73 (m, 4H), 1.91-2.02 (m, 3H), 2.13-2.24 (m, 1H), 2.38-2.49 (m, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.85 (s, 3H), 3.64-3.75 (m, 1H), 3.77-3.90 (m, 1H), 7.23-7.30 (m, 3H), 7.34-7.38 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.1, 17.9, 24.2, 25.7, 26.5, 27.6, 29.7, 35.9, 37.5, 39.8, 57.2, 68.7, 125.8, 128.3, 142.0, 174.7 ppm.

MS (ESI): m/z 376.5161 $(M+H)^+$, 398.4931 $(M+Na)^+$, 414.4659 $(M+K)^+$

Elemental analysis: Calcd. C, 70.35; H, 9.93; N, 3.73; Found: C, 70.49; H, 10.05; N, 3.63.

(*S*)-2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidine (36):



To a stirred suspension of $LiAlH_4$ (0.013 g, 0.33 mmol) in dry THF (1 mL) was added a solution of **35** (0.05 g, 0.13 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 sulphate (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 (petroleum ether: ethyl acetate: 50:50) of the crude product gave (*S*)-2-((*R*)-2-(*tert*-butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidine **36** as a colorless liquid

Yield: 0.034 g, 71%

Mol. Formula: $C_{22}H_{39}NOSi$

$[\alpha]_D^{25}$: - 28.3 (*c* 0.96, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2953, 1596, 1452, 1255, 1047.

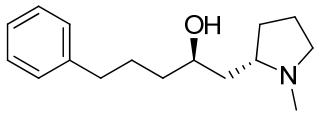
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01-0.05 (m, 6H), 0.88 (s, 9H), 1.42-1.49 (m, 2H), 1.62-1.75 (m, 3H), 1.80-1.96 (m, 5H), 2.02-2.08 (m, 1H), 2.13-2.18 (m, 1H), 2.32 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 3.03-3.15 (m, 1H), 3.64-3.74 (m, 1H), 7.15-7.20 (m, 3H), 7.25-7.28 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.1, 18.0, 21.6, 25.8, 26.4, 30.4, 35.9, 37.5, 38.8, 39.4, 56.0, 64.3, 70.1, 125.7, 128.2, 128.3, 142.2 ppm.

MS (ESI): m/z 362.0878 $(M+H)^+$

Elemental analysis: Calcd. C, 73.07; H, 10.87; N, 3.87; Found: C, 73.21; H, 10.76; N, 3.74

(*R*)-1-((*S*)-1-Methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (37):



To a stirred solution of compound **36** (0.03g, 0.083 mmol) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture was stirred overnight at the same temperature. Solid $NaHCO_3$ (0.06 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated and column purified using ethyl acetate to give (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol **37** as a colorless liquid.

Yield: 0.02 g, yield 95%

Mol. Formula: $C_{16}H_{25}NO$

$[\alpha]_D^{25}$: - 9.3 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3391, 2924, 1602, 1455, 1222, 1010.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-1.75 (m, 8H), 1.99-2.06 (m, 4H), 2.34 (s, 3H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.86 (brs, 1H), 3.34-3.45 (m, 1H), 3.59-3.67 (m, 1H), 7.13-7.17 (m, 3H), 7.23-7.27 (m, 2H).

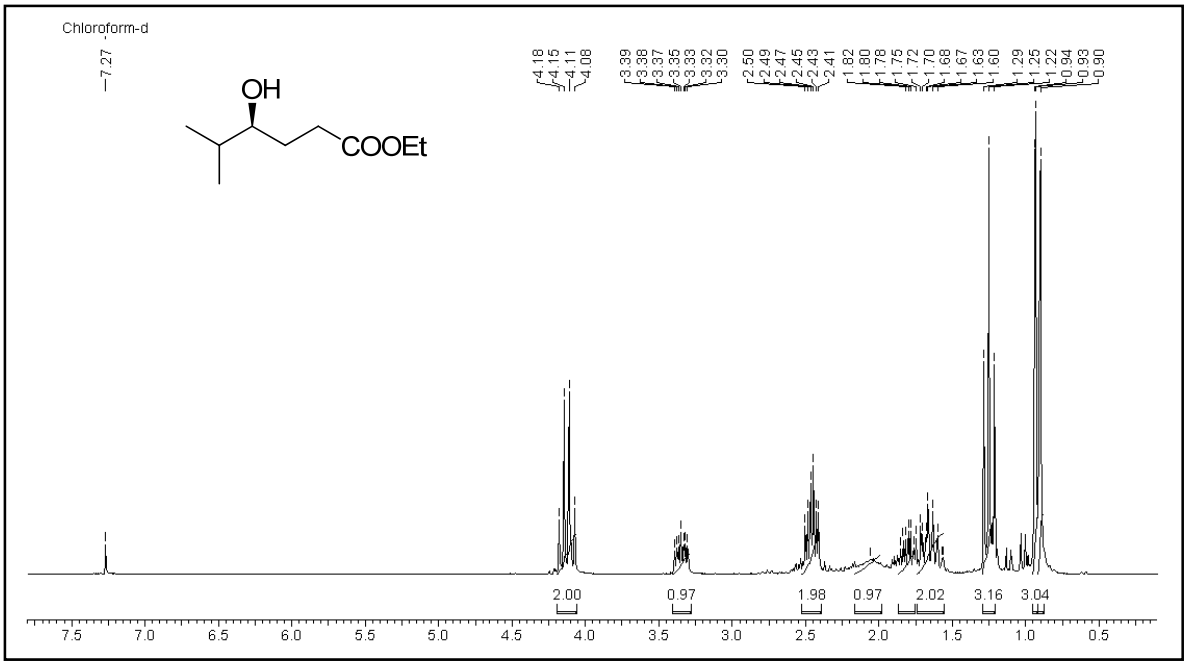
^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6, 27.3, 31.9, 33.8, 35.6, 37.6, 40.5, 56.2, 68.2, 69.3, 125.8, 128.2, 128.8, 139.2 ppm.

MS (ESI): m/z 248.2361 $(M+H)^+$

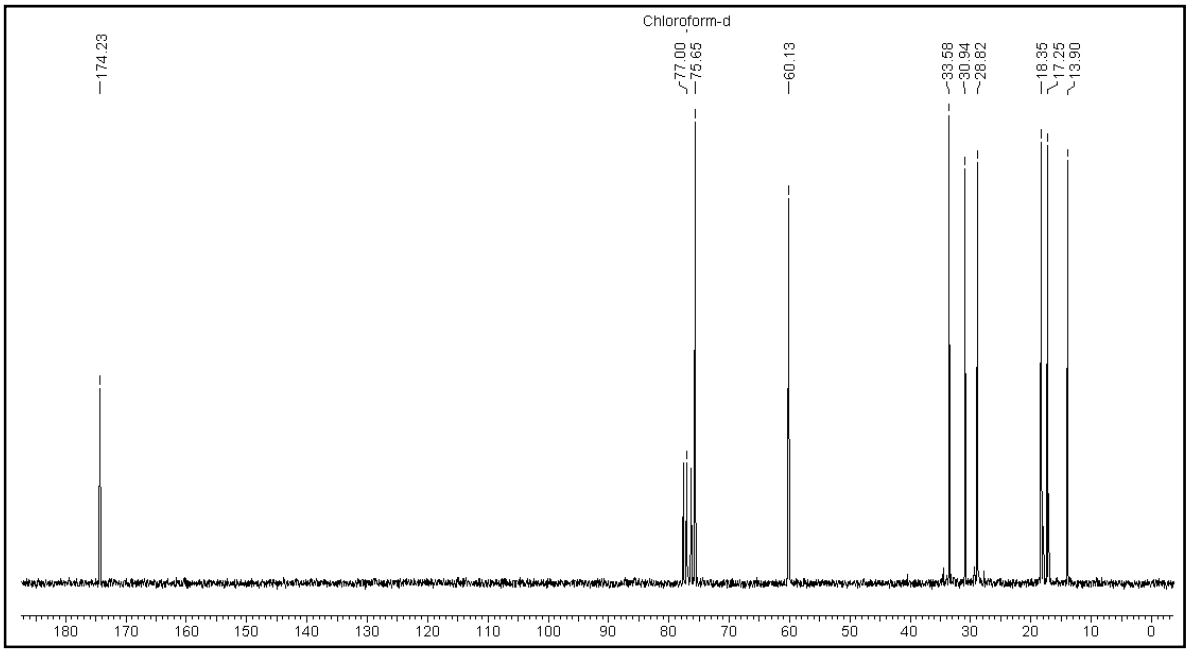
Elemental analysis: Calcd. C, 77.68; H, 10.19; N, 5.66; Found: C, 77.56; H, 10.28; N, 5.74.

2.1.7. Spectra

(*S*)-Ethyl 4-hydroxy-5-methylhexanoate (22b):

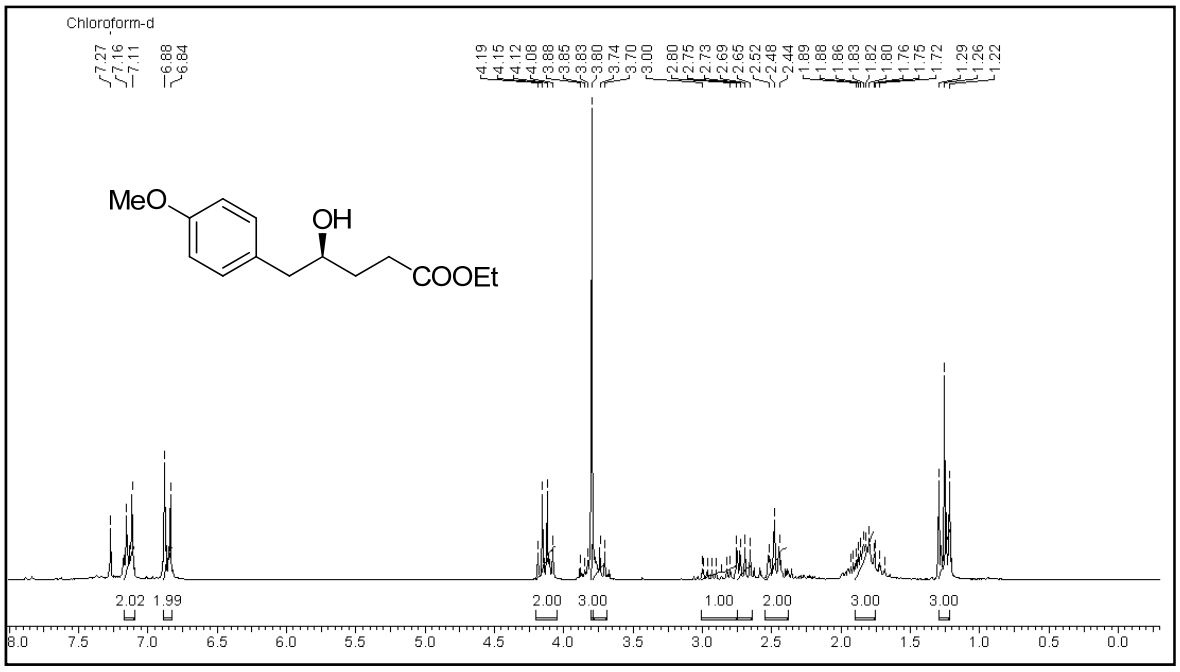


- **^{1}H NMR of the compound 22b in $CDCl_3$**

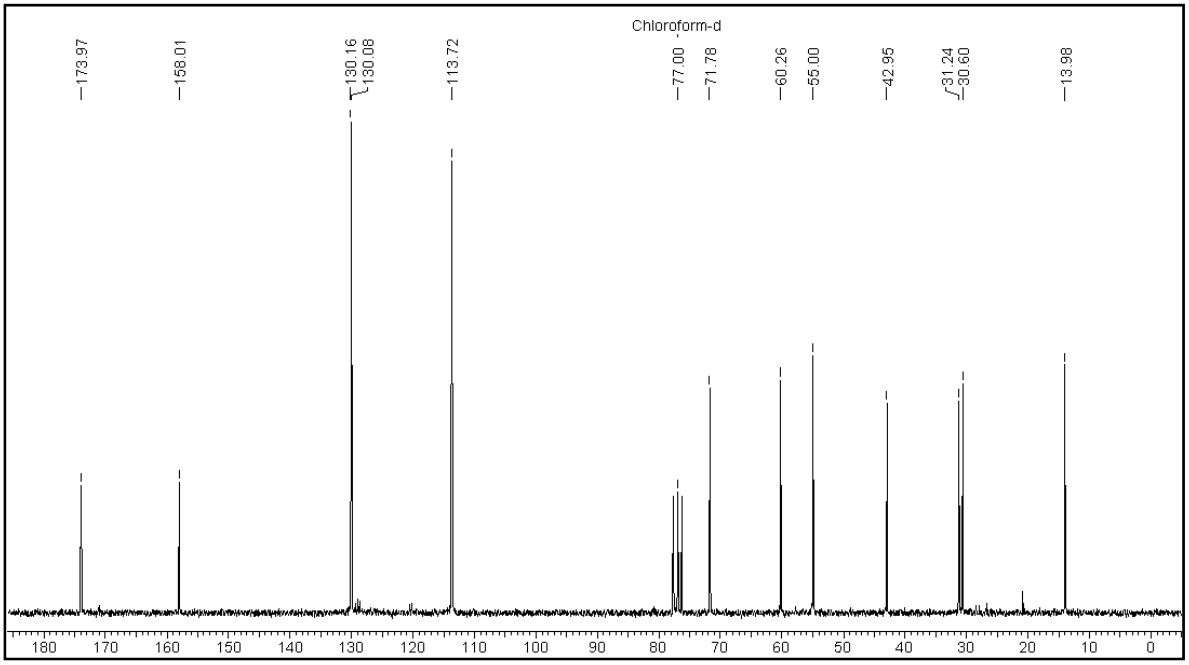


- **^{13}C NMR of the compound 22b in $CDCl_3$**

(*S*)-Ethyl 4-hydroxy-5-(4-methoxyphenyl)pentanoate (22d):

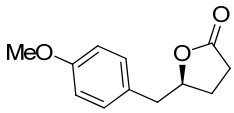


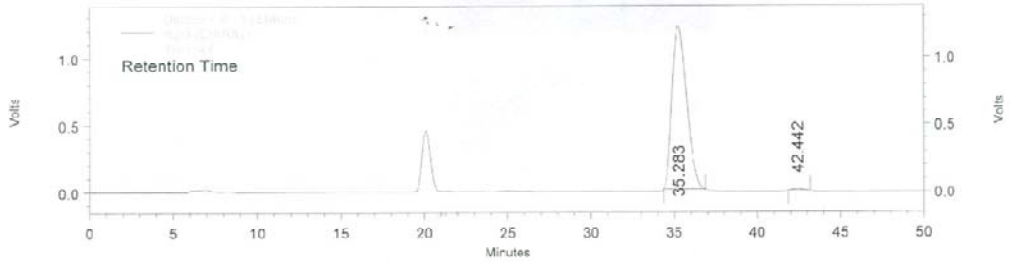
- **^{1}H NMR of the compound 22d in $CDCl_3$**



- **^{13}C NMR of the compound 22d in $CDCl_3$**

Enantiomeric excess:

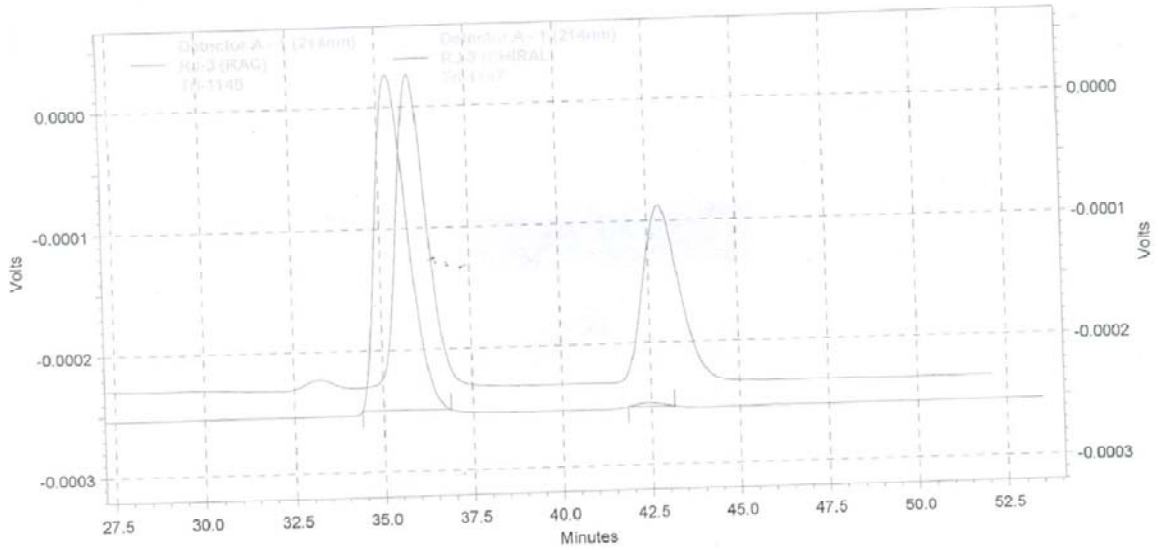




Detector A - 1 (214nm)

Pk #	Retention Time	Area	Area %
1	35.283	75476840	99.289
2	42.442	540350	0.711
Totals		76017190	100.000

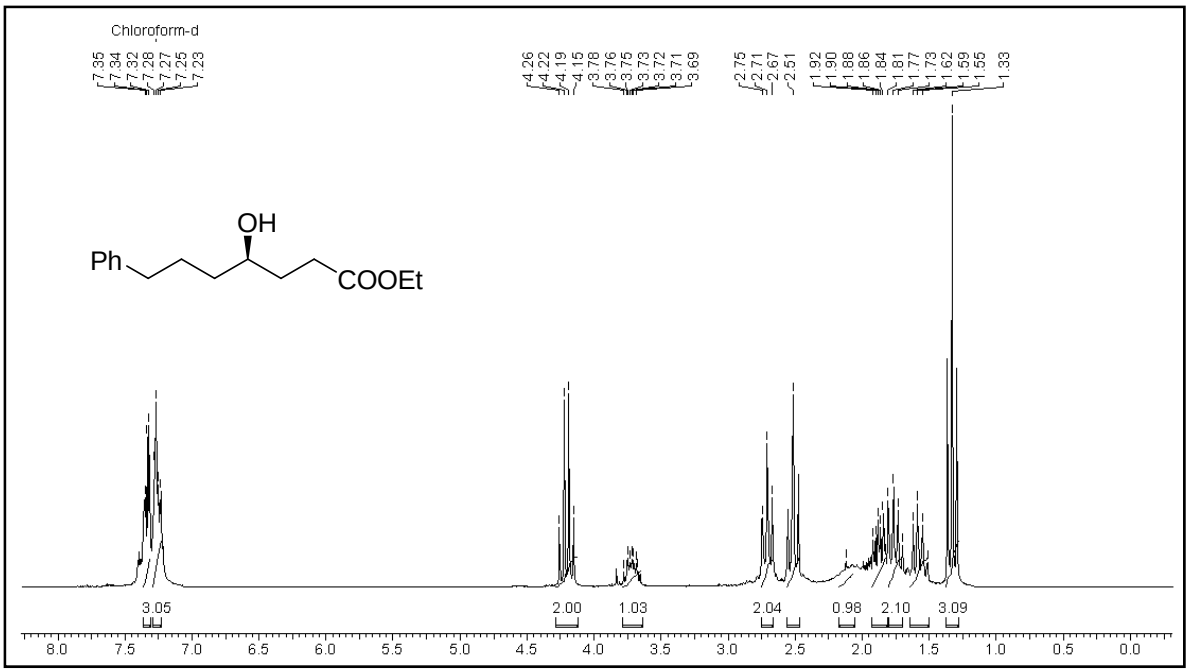
Grp Leader :Dr Pradeep Kumar
Column :Chiralcel OD-H (250x4.6mm)
Mobile Phase : IPA: PE: (10:90)
Wavelength : 214 nm
Flow Rate : 0.5mL/min(21Kgf)
Sample Con :0.55mg/ 1mL



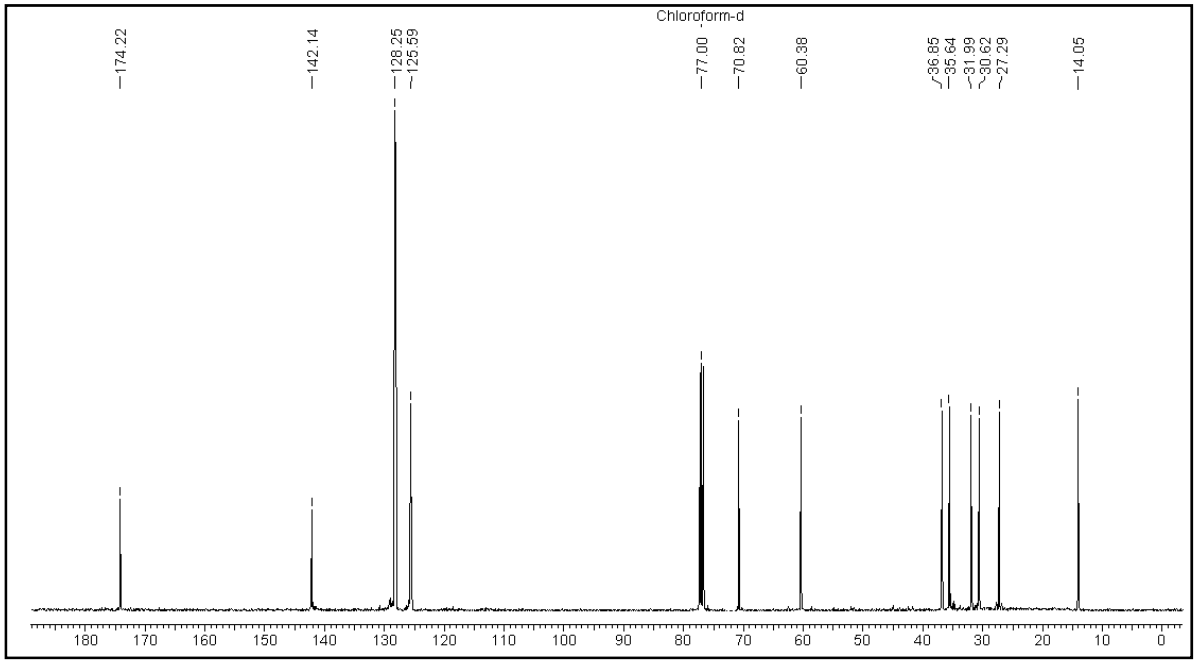
C:\CLASS-VP\Data\Dr Tripathi\Tri-1146, Detector A - 1 (214nm)

C:\CLASS-VP\Data\Dr Tripathi\Tri-1147, Detector A - 1 (214nm)

(*R*)-Ethyl 4-hydroxy-7-phenylheptanoate (22e):

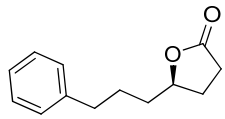


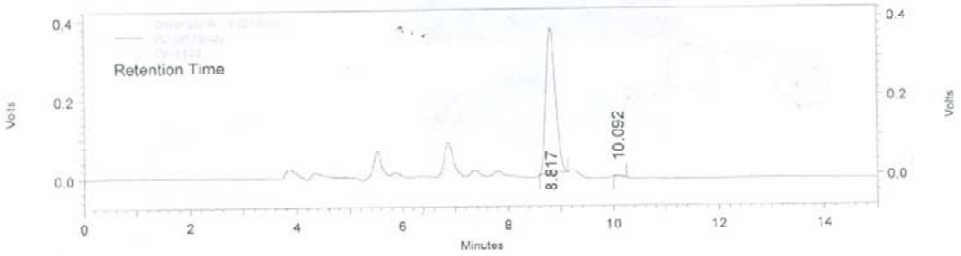
- **^{1}H NMR of the compound 22e in $CDCl_3$**



- **^{13}C NMR of the compound 22e in $CDCl_3$**

Enantiomeric excess:



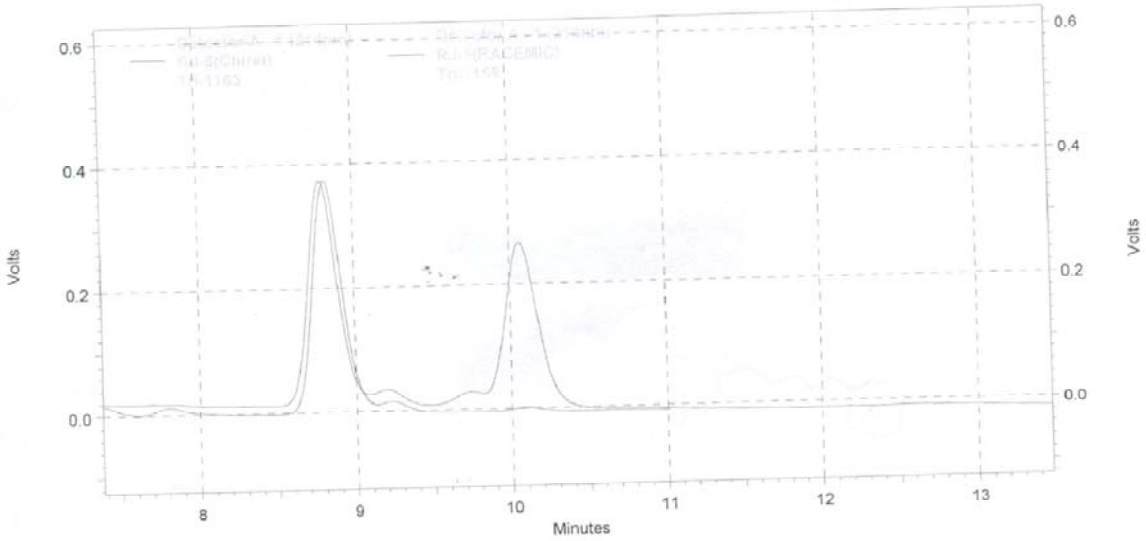


Detector A - 1 (214nm)

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

Grp Leader :Dr Pradeep Kumar
Column :Kromasil 5-Amycoat (250x4.6mm)
Mobile Phase :EtOH:n-Hexane (25:75)
Wavelength : 214nm
Flow Rate : 0.7mL/min(47Kgf)
Sample Con Xmg/ 4mL

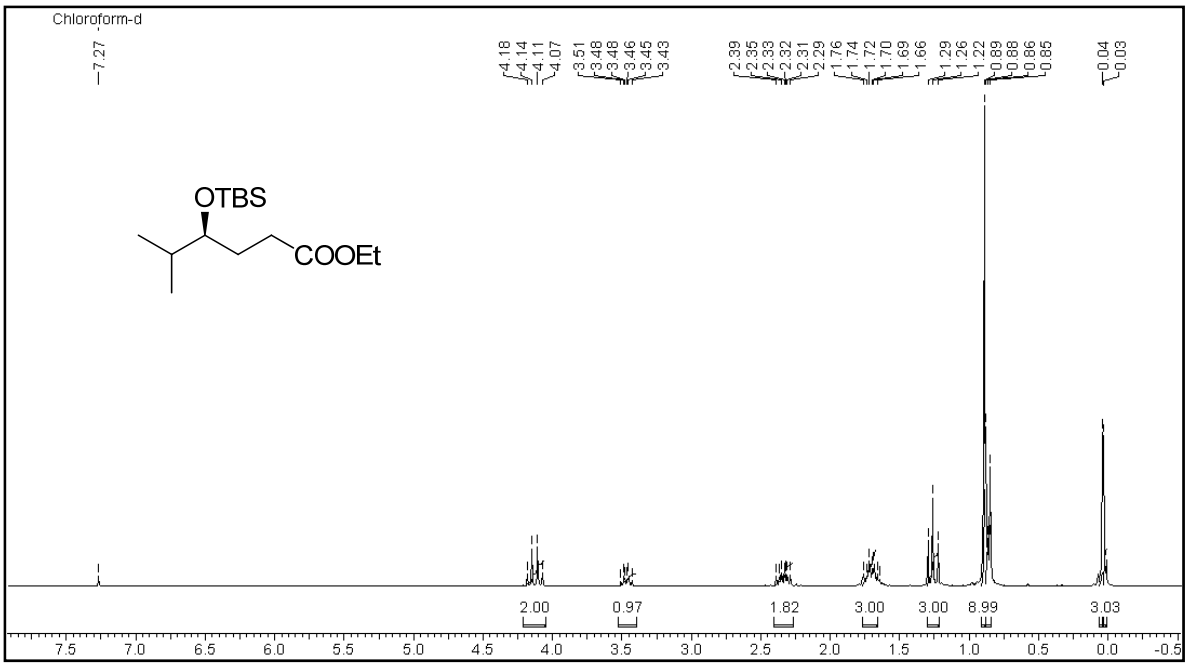
Kunte



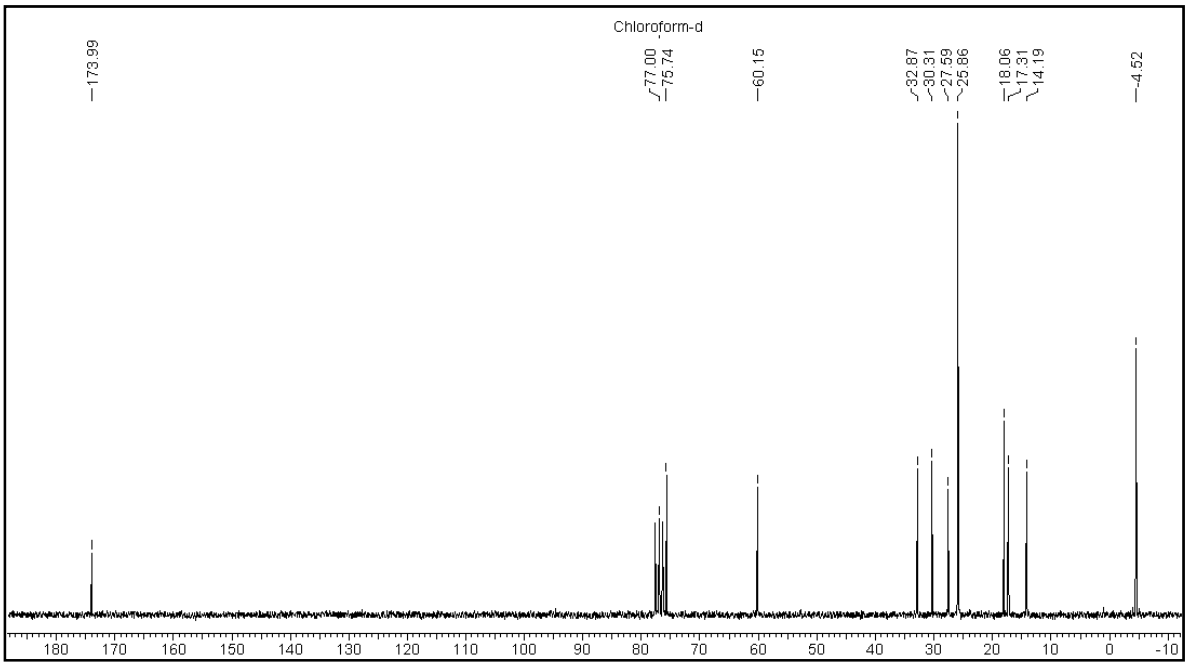
C:\CLASS-VP\Data\Dr Tripathi\Tri-1163, Detector A - 1 (214nm)

C:\CLASS-VP\Data\Dr Tripathi\Tri-1159, Detector A - 1 (214nm)

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-methylhexanoate (23b):

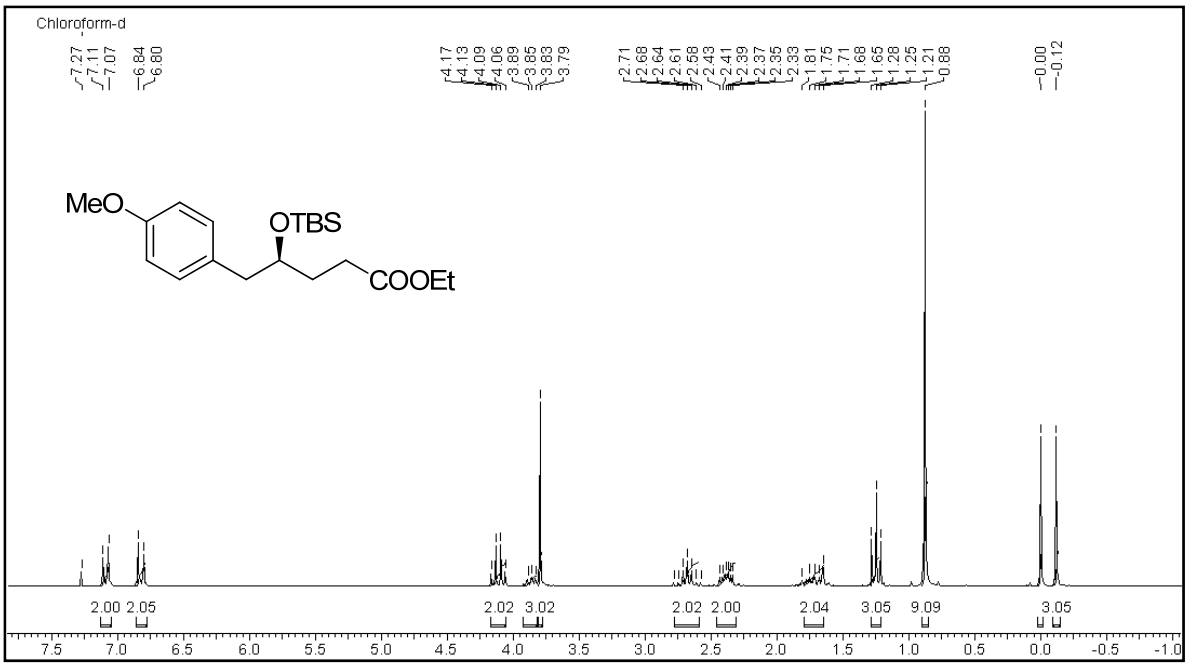


- **^{1}H NMR of the compound 23b in $CDCl_3$**

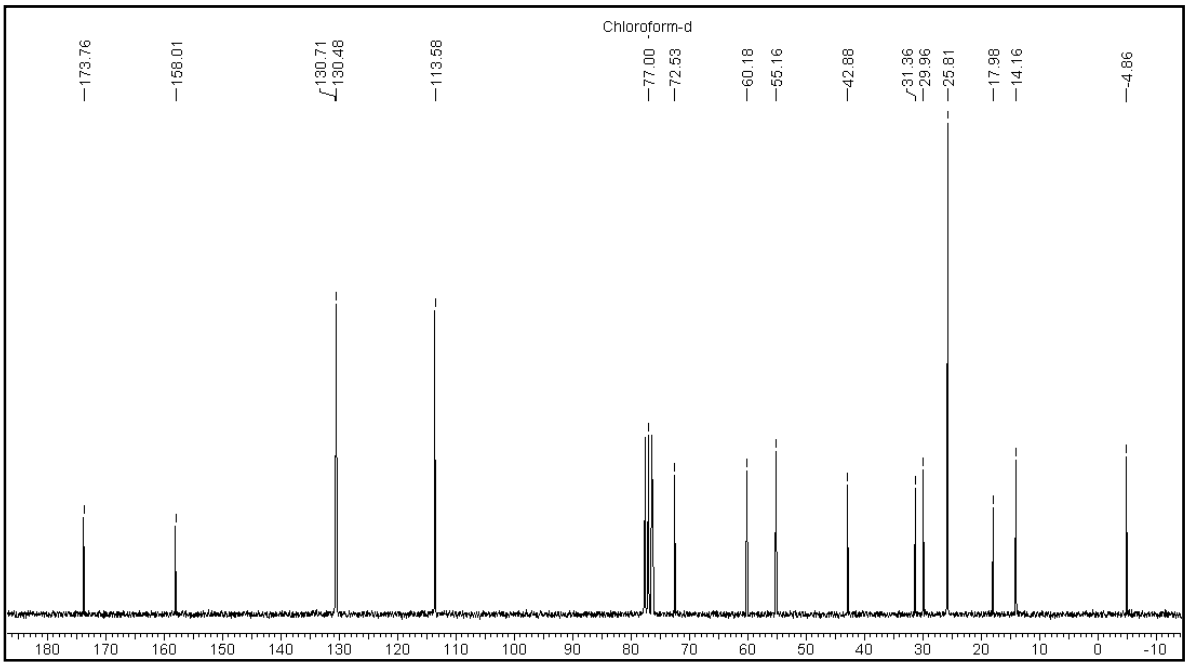


- **^{13}C NMR of the compound 23b in $CDCl_3$**

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-(4-methoxyphenyl)pentanoate (23d):

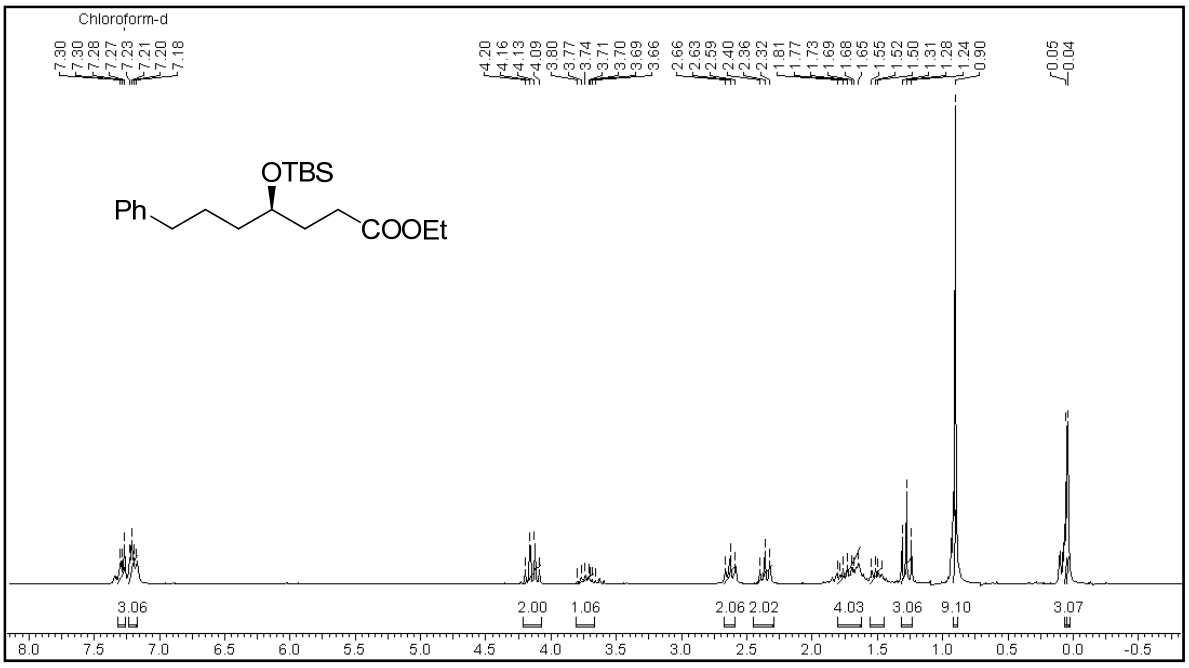


- **^{1}H NMR of the compound 23d in $CDCl_3$**

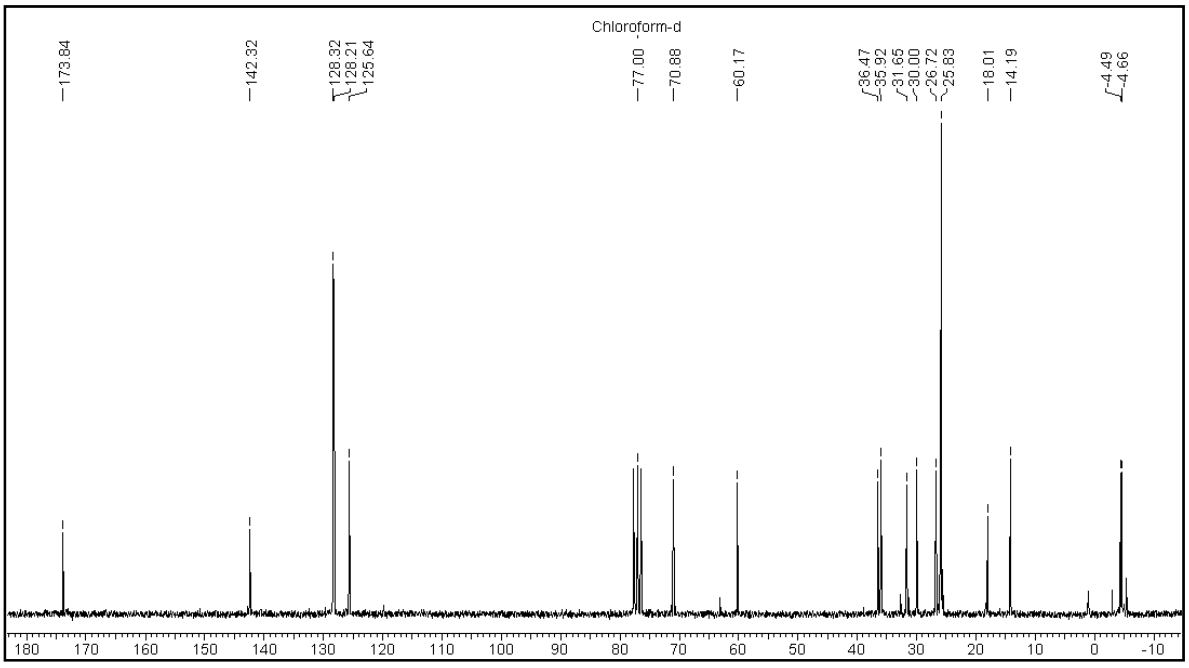


- **^{13}C NMR of the compound 23d in $CDCl_3$**

(*R*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-7-phenylheptanoate (23e):

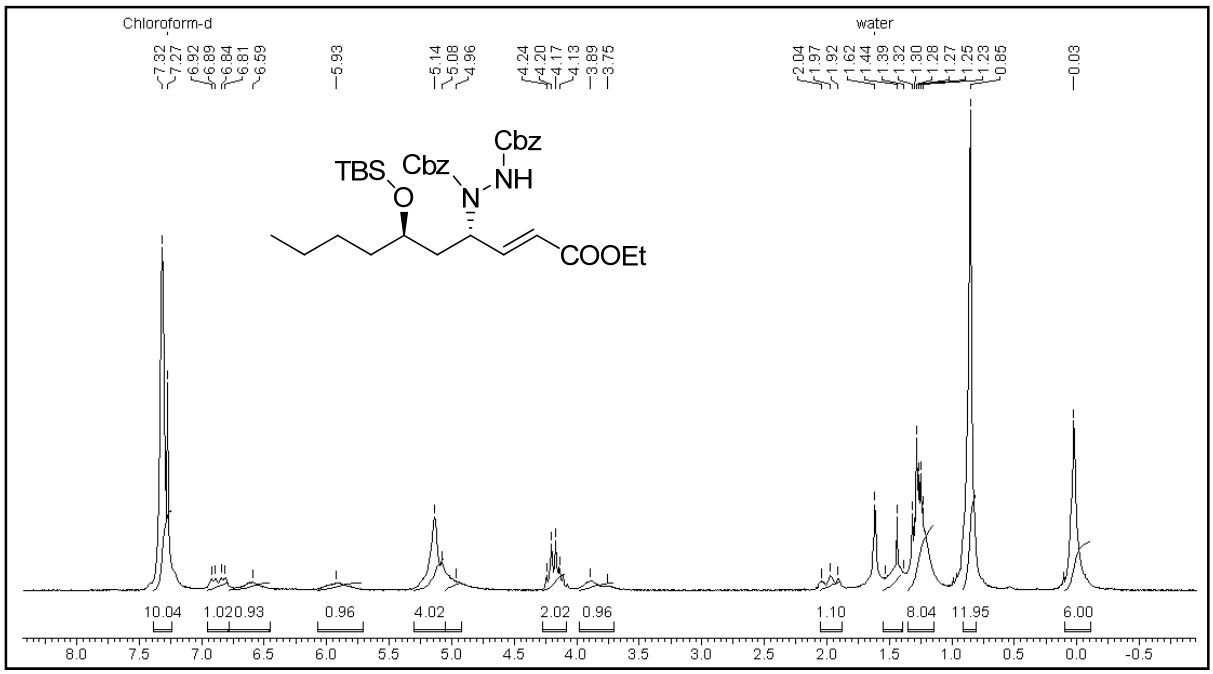


- **^{1}H NMR of the compound 23e in $CDCl_3$**

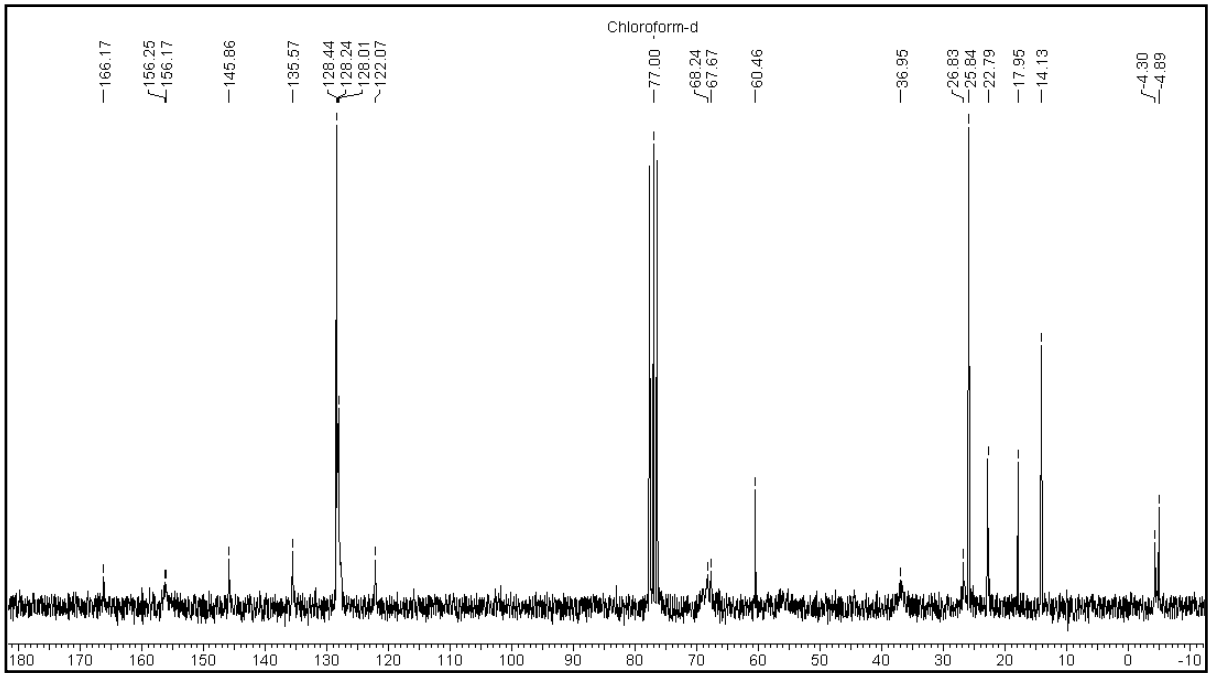


- **^{13}C NMR of the compound 23e in $CDCl_3$**

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate (24a):

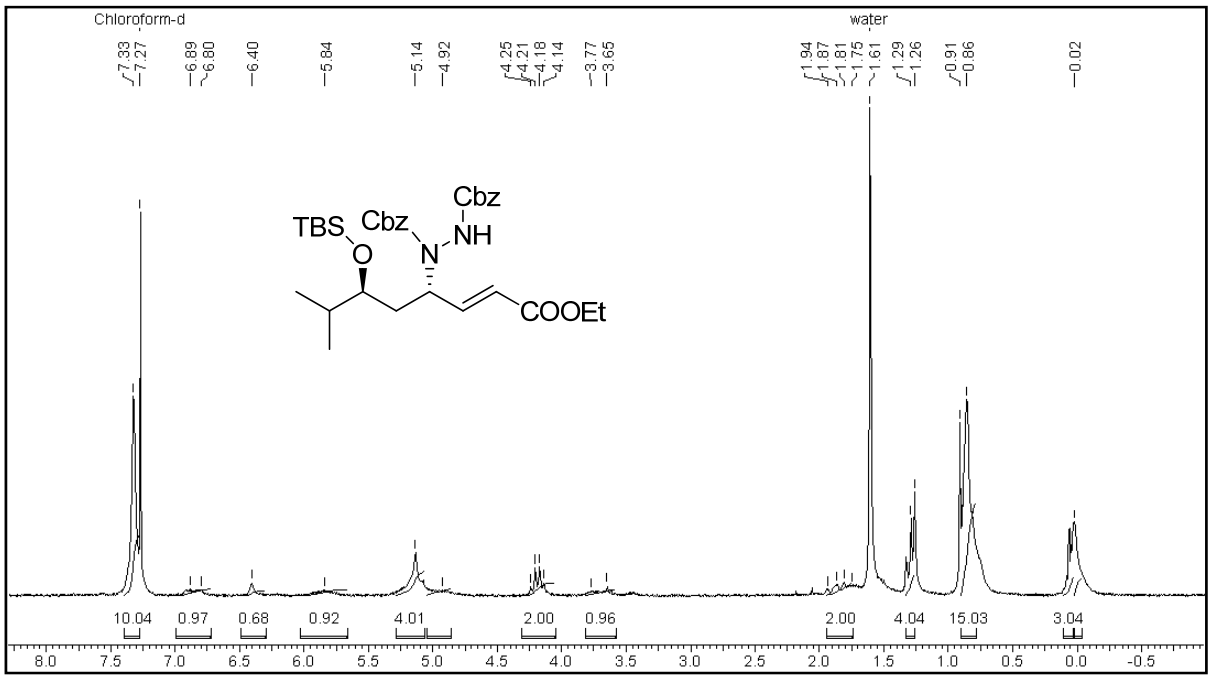


➢ **^{1}H NMR of the compound 24a in $CDCl_3$**

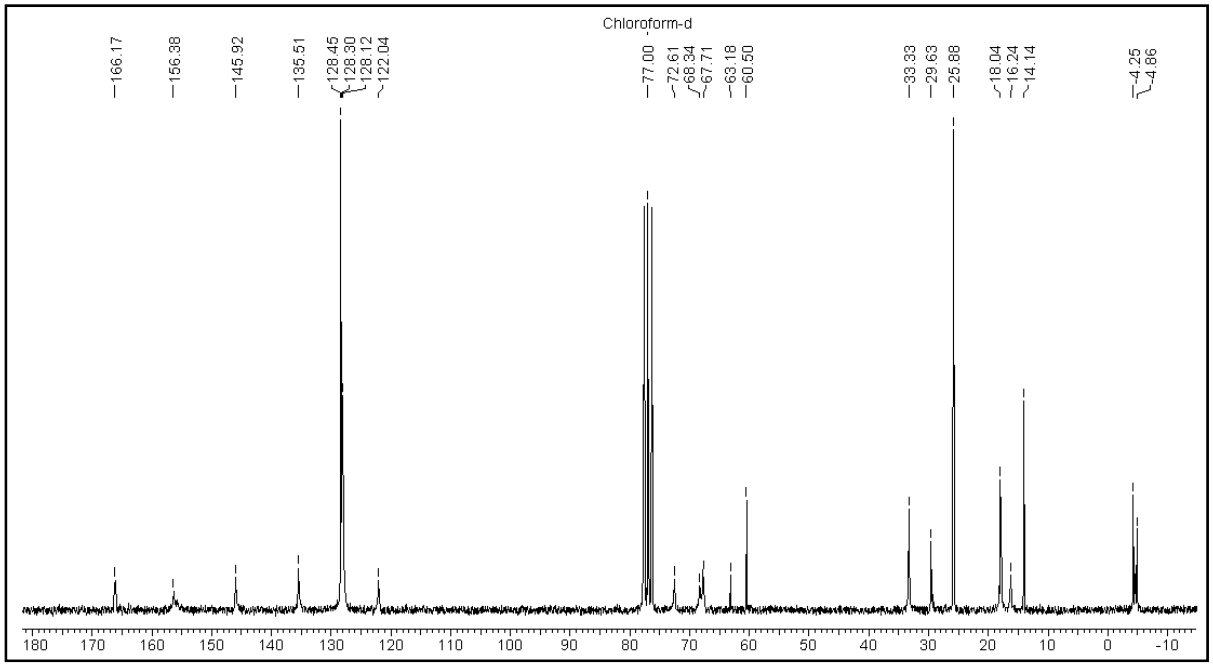


➢ **^{13}C NMR of the compound 24a in $CDCl_3$**

Dibenzyl 1-((4*S*,6*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-methyl-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (24b):

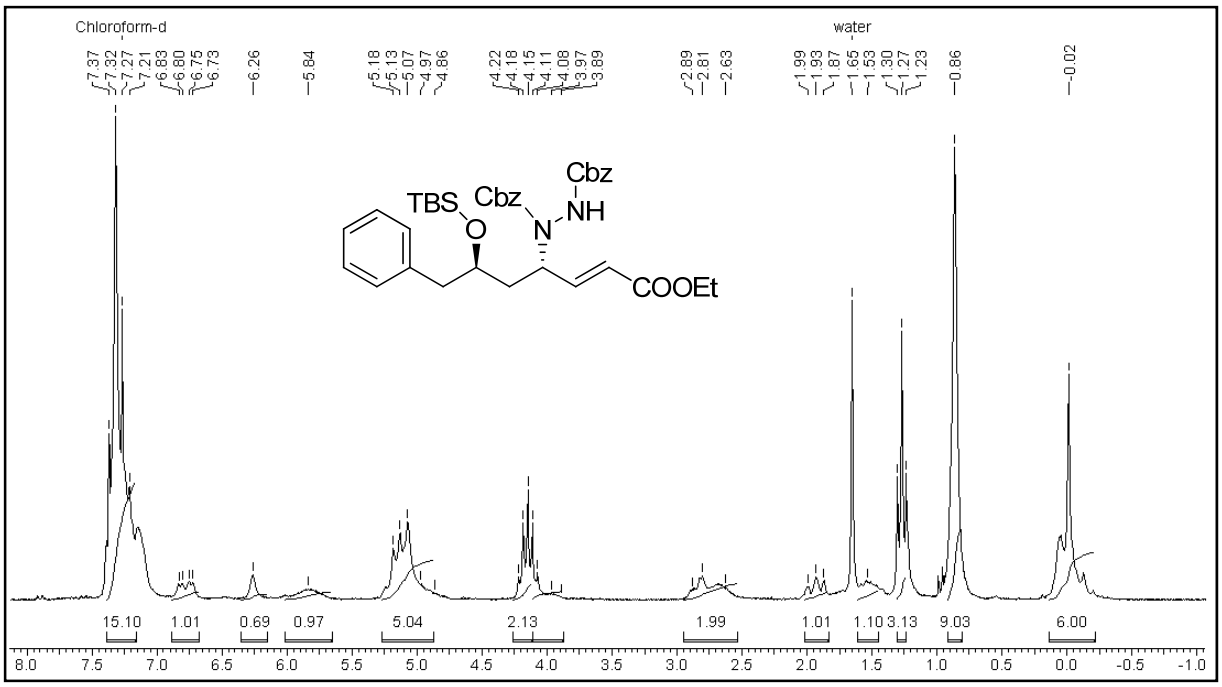


- **^{1}H NMR of the compound 24b in $CDCl_3$**

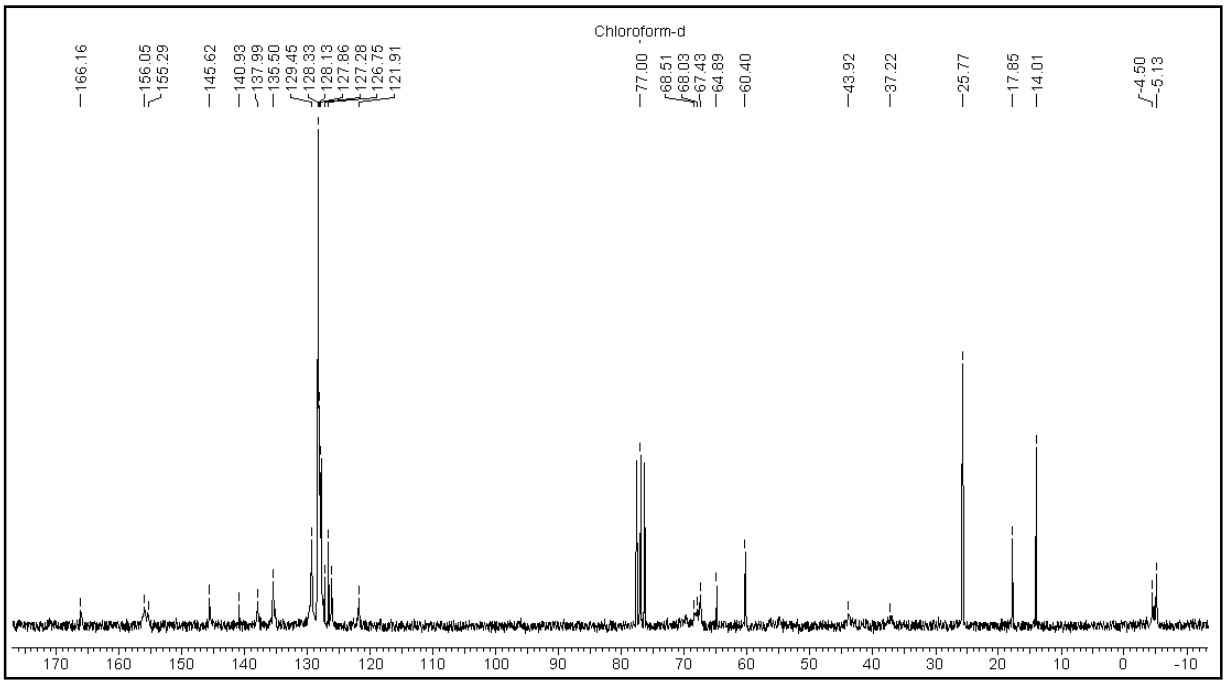


- **^{13}C NMR of the compound 24b in $CDCl_3$**

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-7-phenylhept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24c):

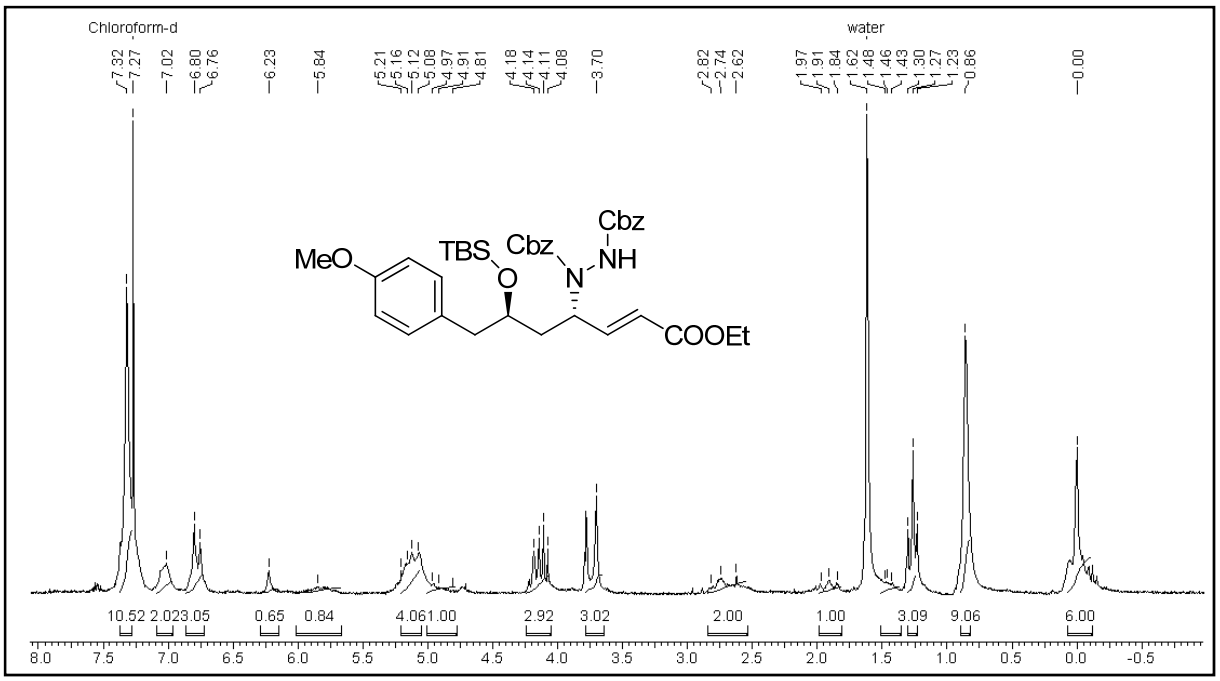


➢ **^{1}H NMR of the compound 24c in $CDCl_3$**

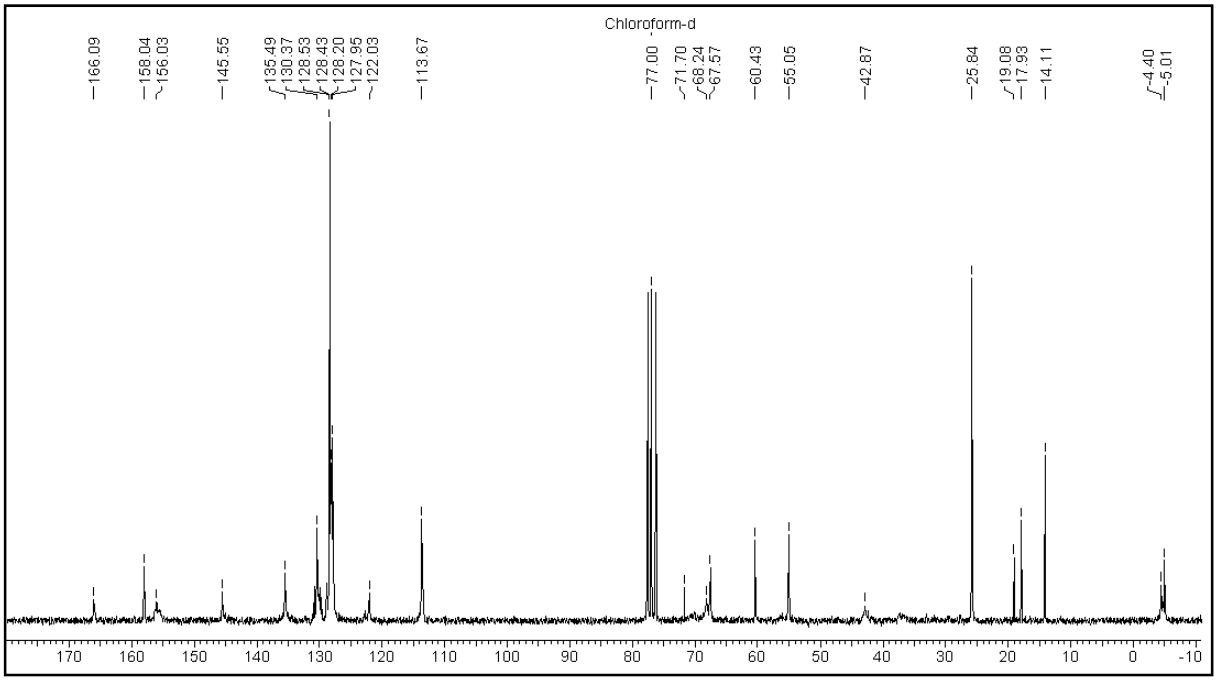


➢ **^{13}C NMR of the compound 24c in $CDCl_3$**

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-(4-methoxyphenyl)-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24d):

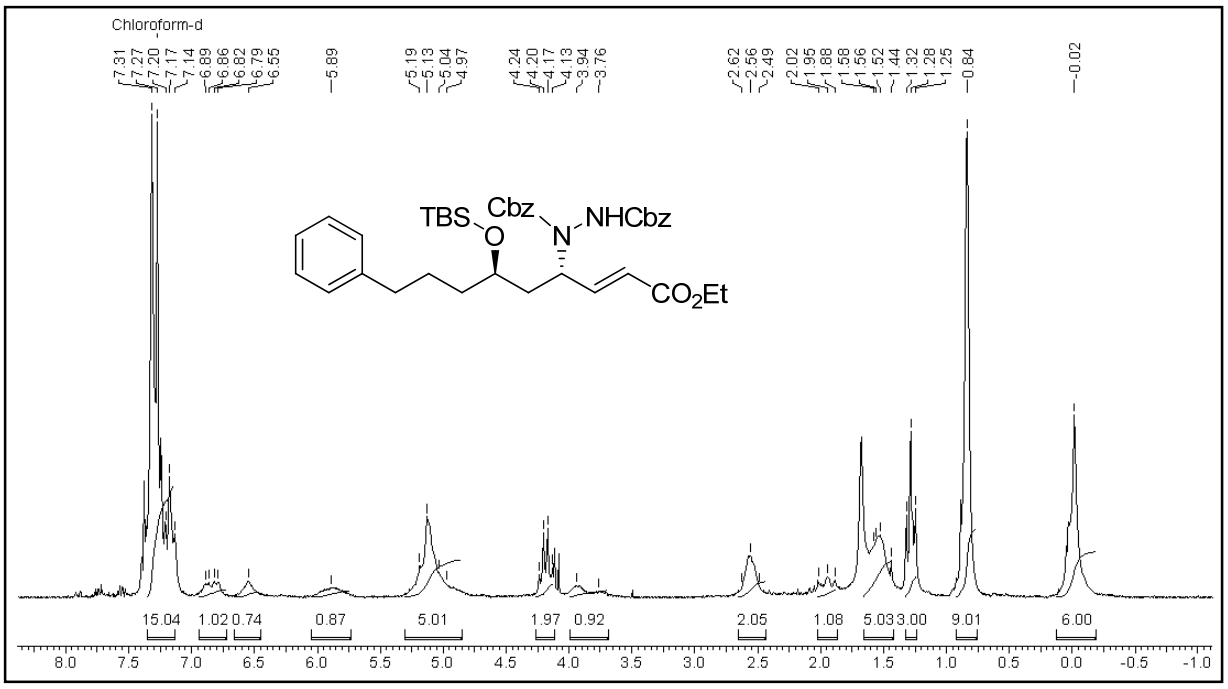


➢ **^{1}H NMR of the compound 24d in $CDCl_3$**

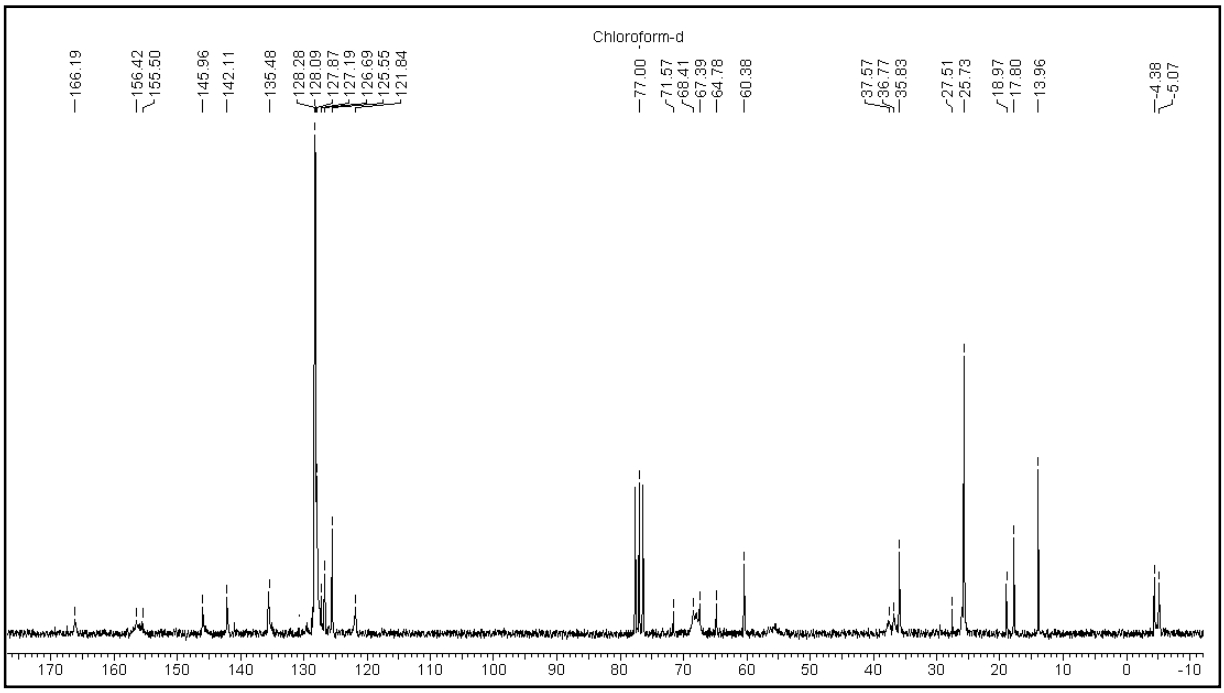


➢ **^{13}C NMR of the compound 24d in $CDCl_3$**

Dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-9-phenylnon-2-en-4-yl)hydrazine-1,2-dicarboxylate (24e):

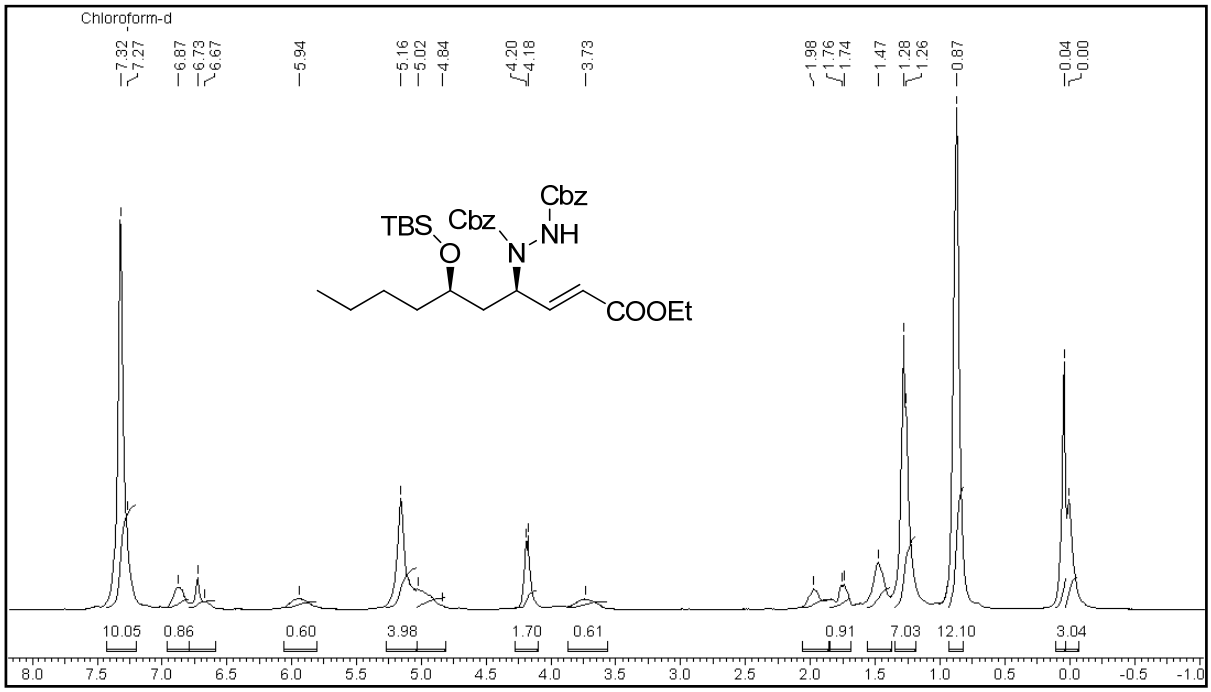


- **^{1}H NMR of the compound 24e in $CDCl_3$**

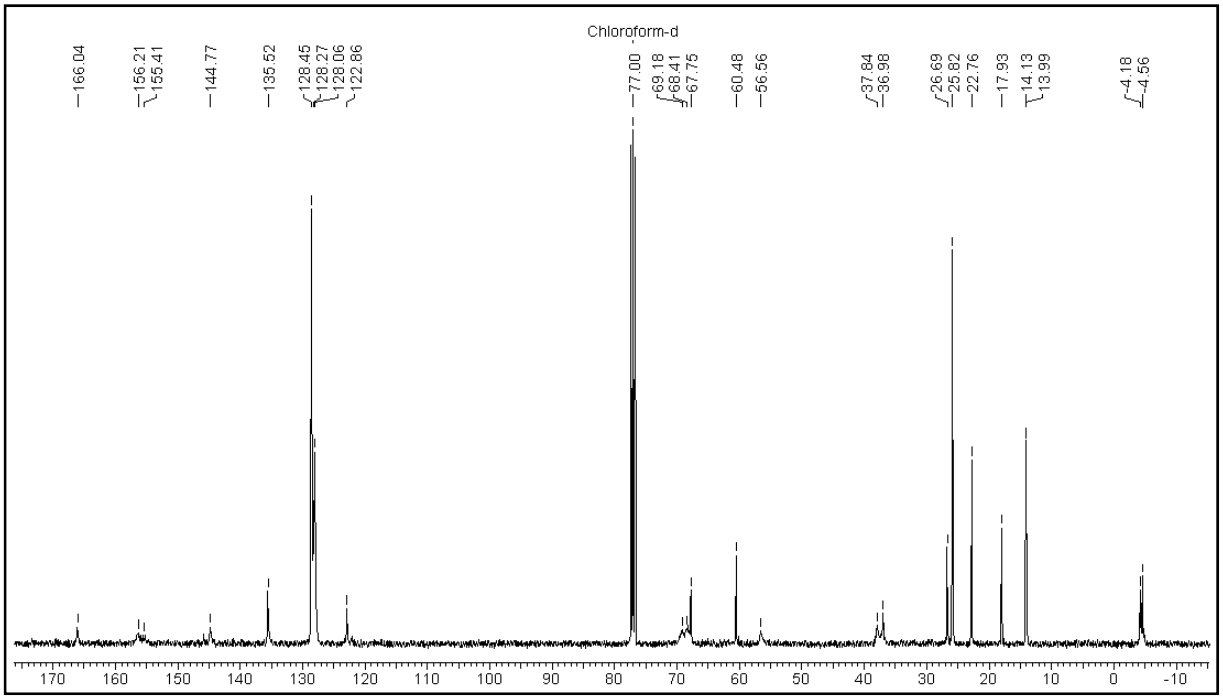


- **^{13}C NMR of the compound 24e in $CDCl_3$**

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxodec-2-en-4-yl)hydrazine-1,2-dicarboxylate (25a):

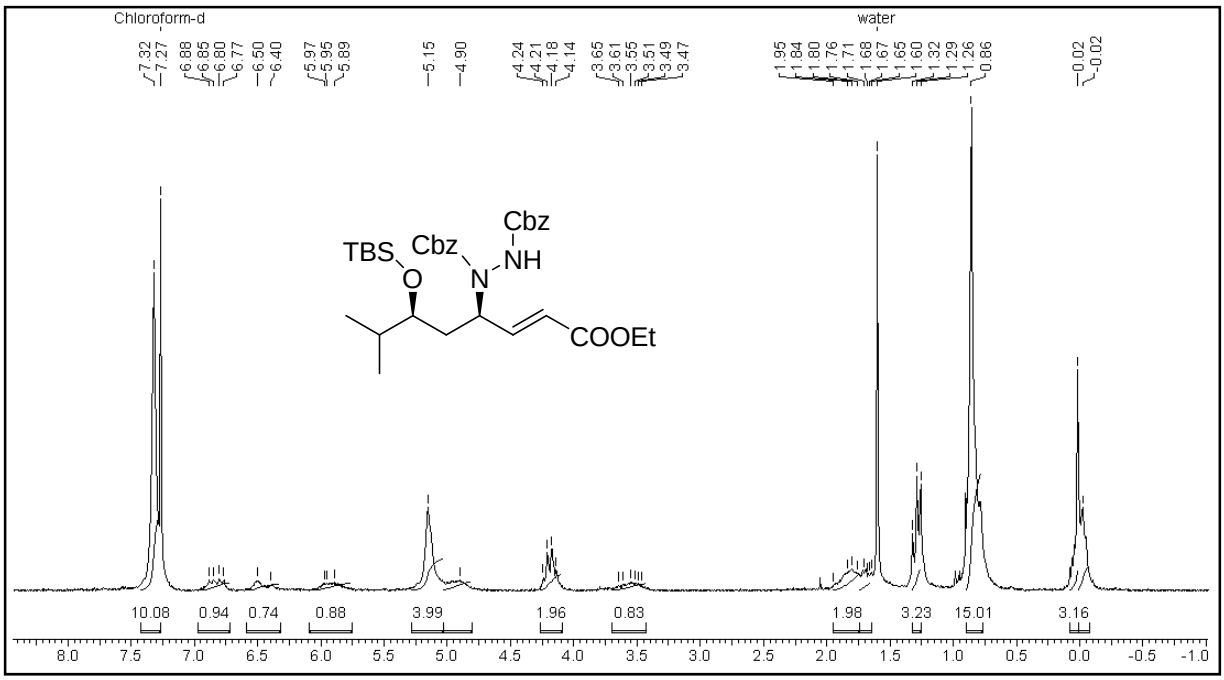


➢ **^{1}H NMR of the compound 25a in $CDCl_3$**

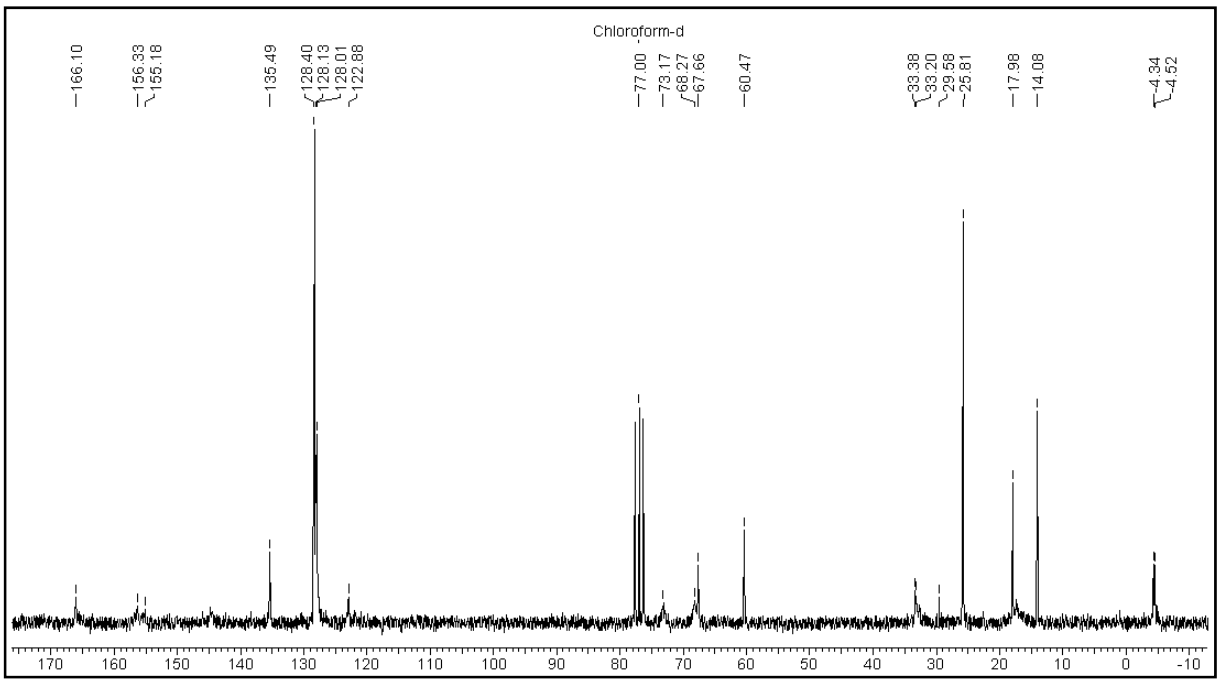


➢ **^{13}C NMR of the compound 25a in $CDCl_3$**

Dibenzyl 1-((4*R*,6*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-methyl-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):

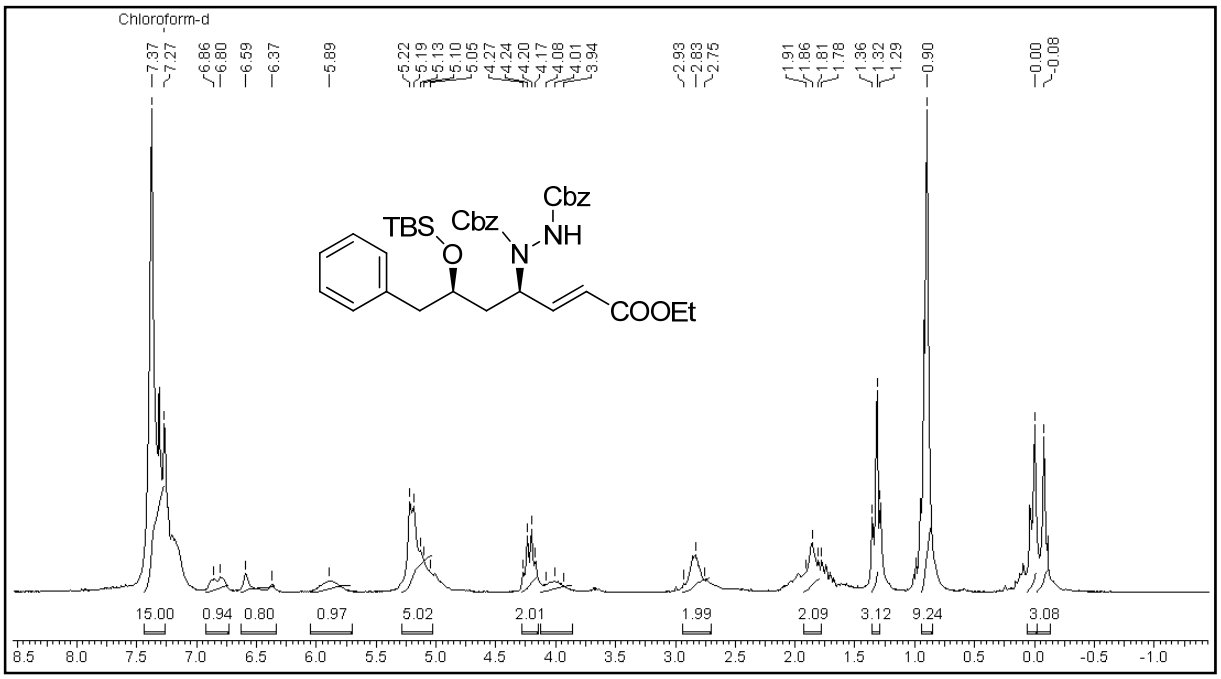


➢ **^{1}H NMR of the compound 25b in $CDCl_3$**

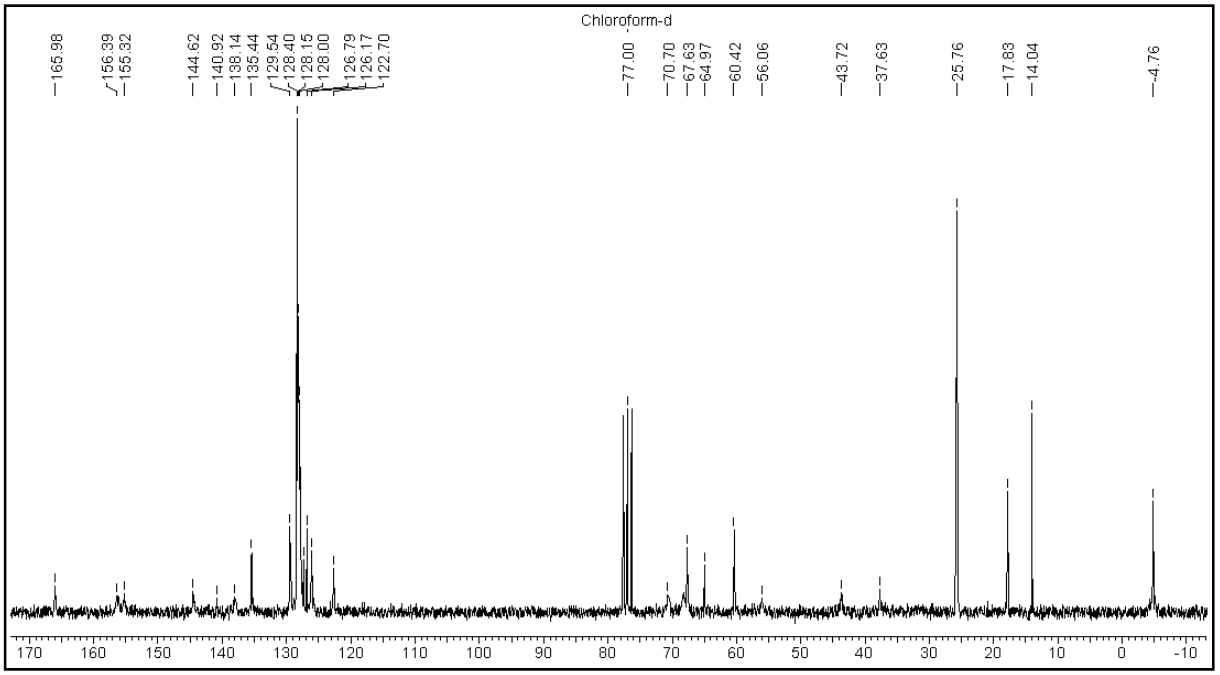


➢ **^{13}C NMR of the compound 25b in $CDCl_3$**

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-7-phenylhept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25c):

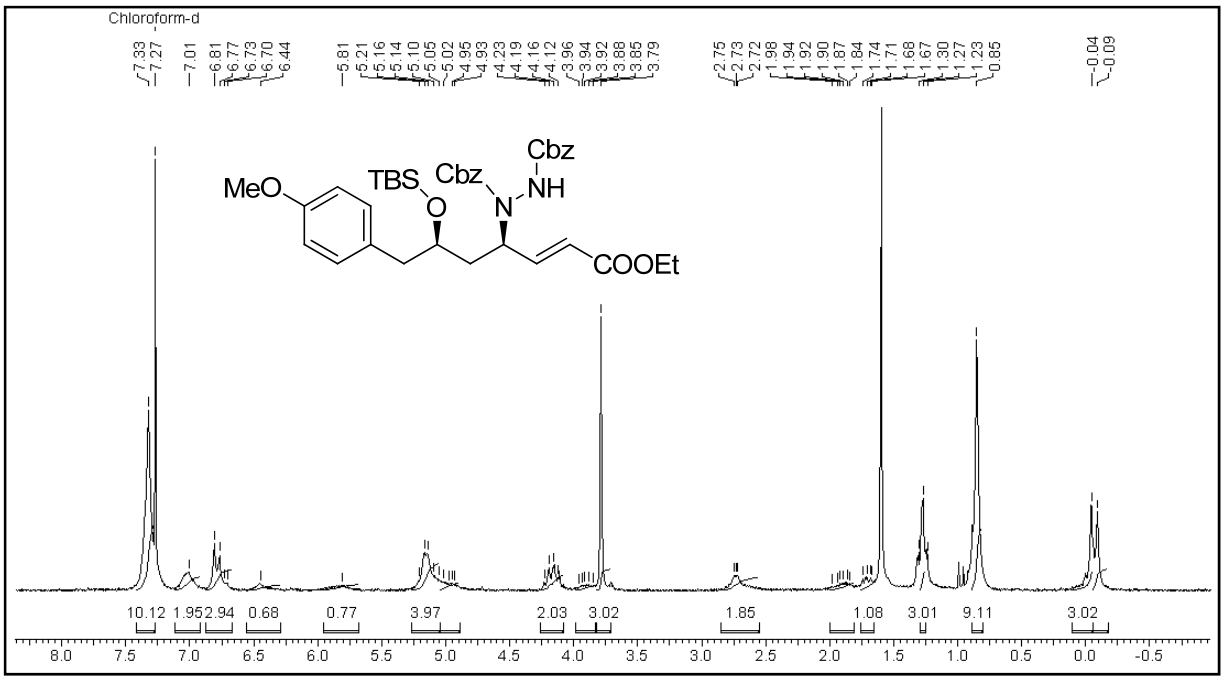


- **^{1}H NMR of the compound 25c in $CDCl_3$**

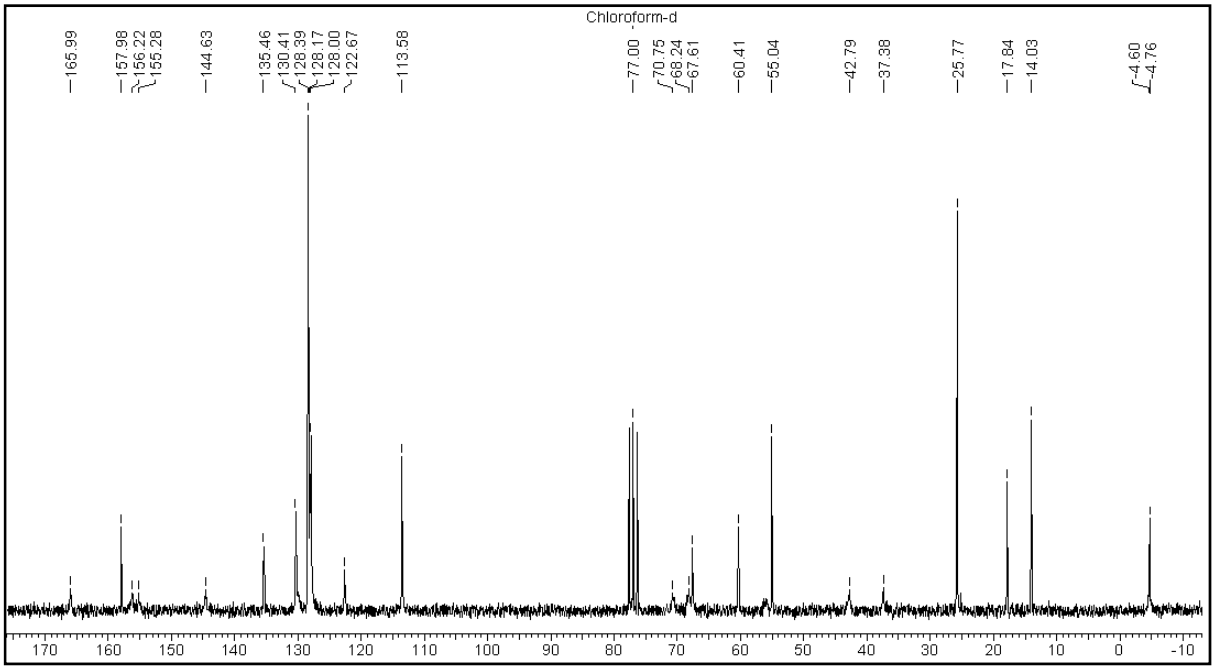


- **^{13}C NMR of the compound 25c in $CDCl_3$**

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-7-(4-methoxyphenyl)-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25d):

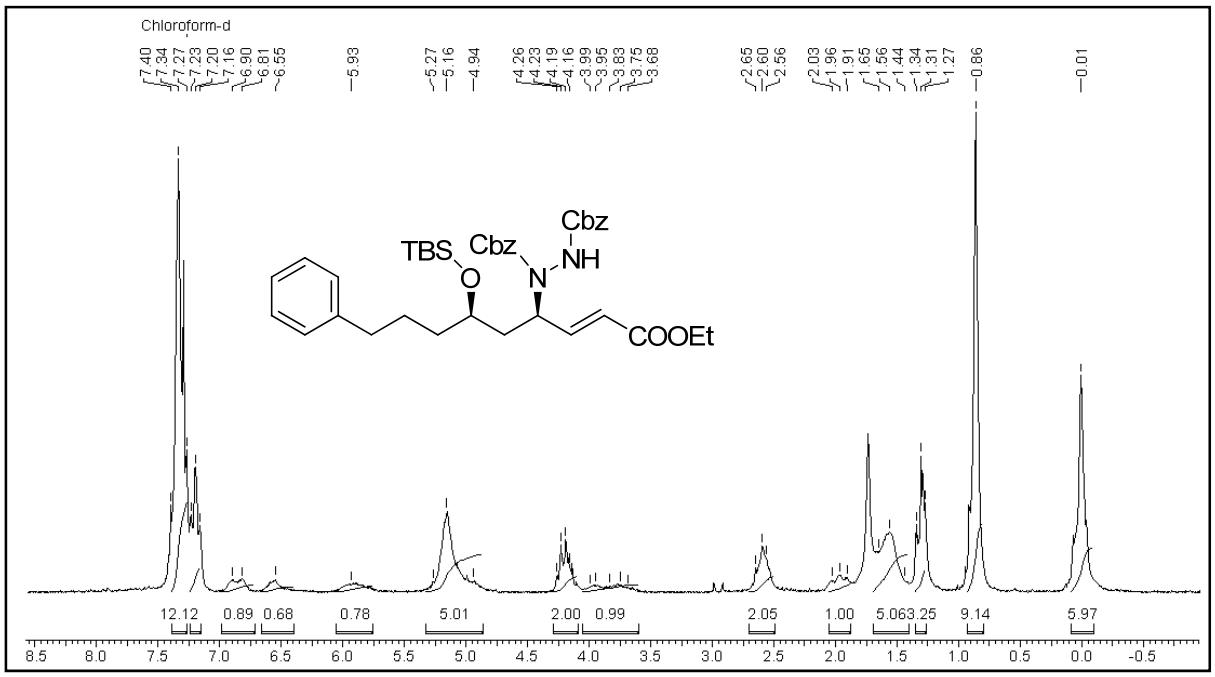


➢ **^{1}H NMR of the compound 25d in $CDCl_3$**

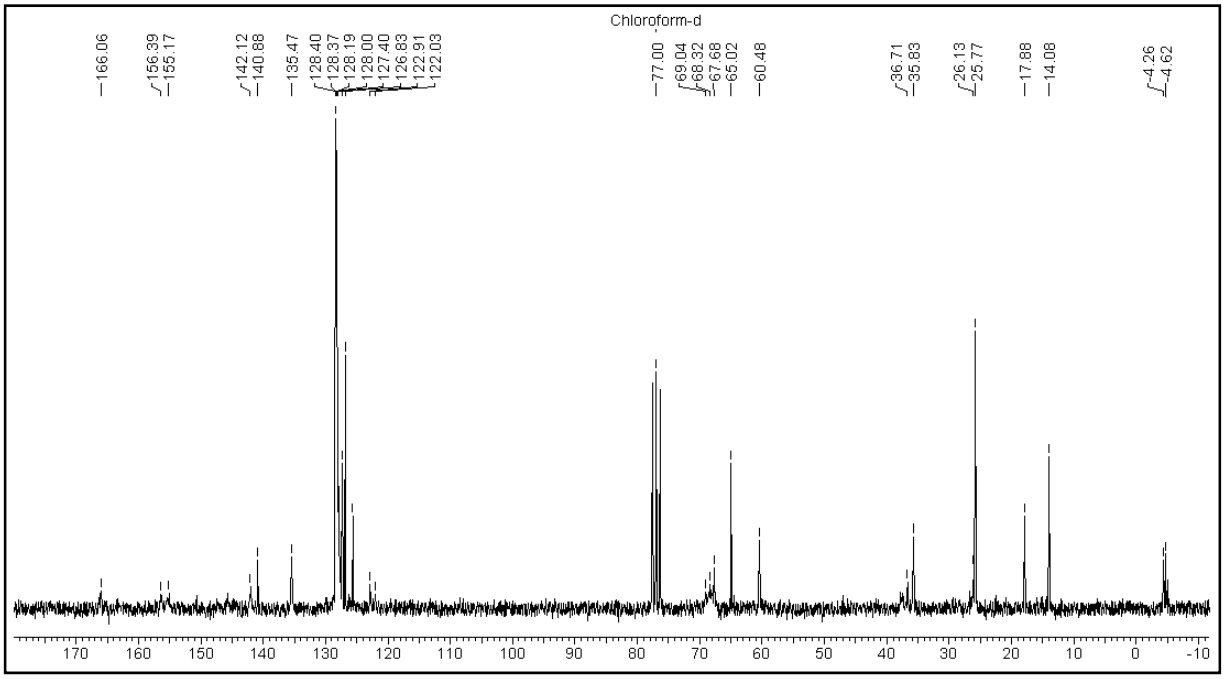


➢ **^{13}C NMR of the compound 25d in $CDCl_3$**

Dibenzyl 1-((4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxo-9-phenylnon-2-en-4-yl)hydrazine-1,2-dicarboxylate (25e):

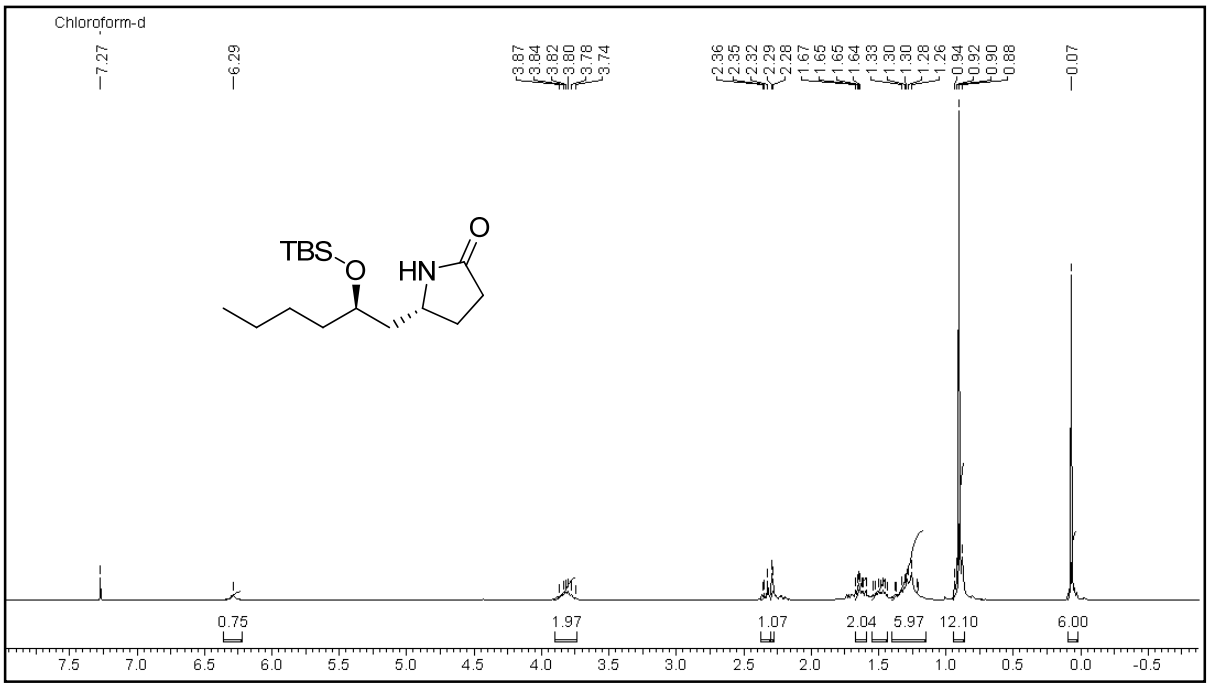


- **^{1}H NMR of the compound 25e in $CDCl_3$**

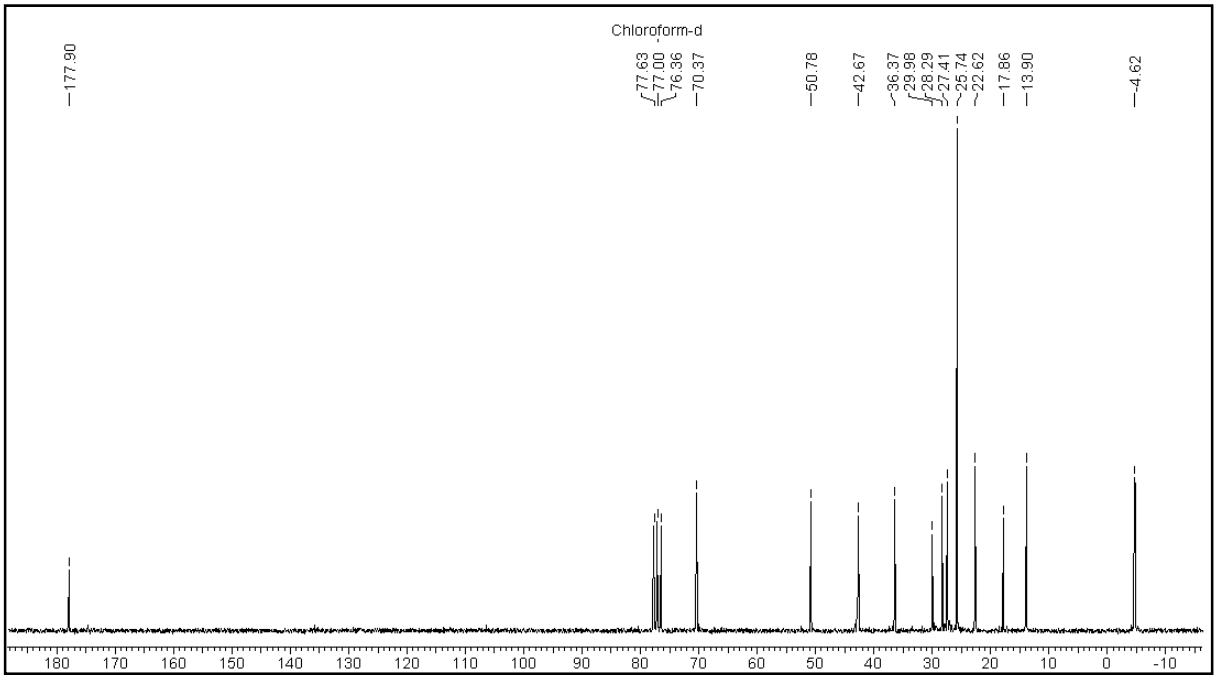


- **^{13}C NMR of the compound 25e in $CDCl_3$**

(*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)hexyl)pyrrolidin-2-one (26):

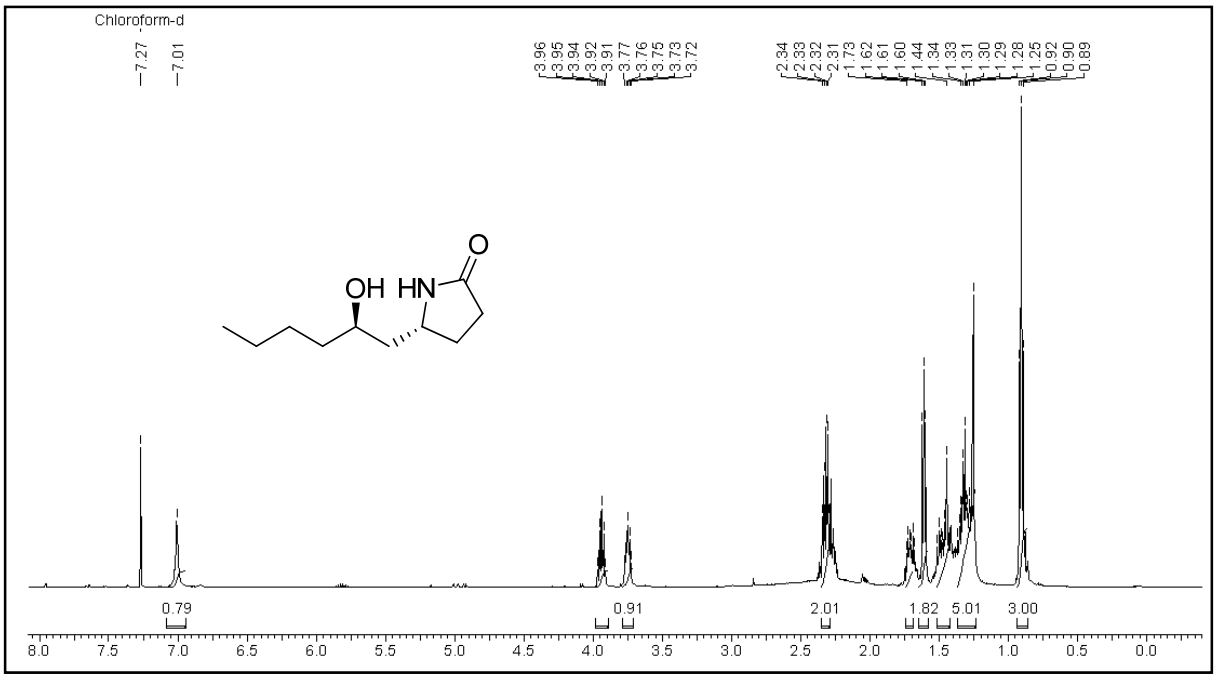


- **^{1}H NMR of the compound 26 in $CDCl_3$**

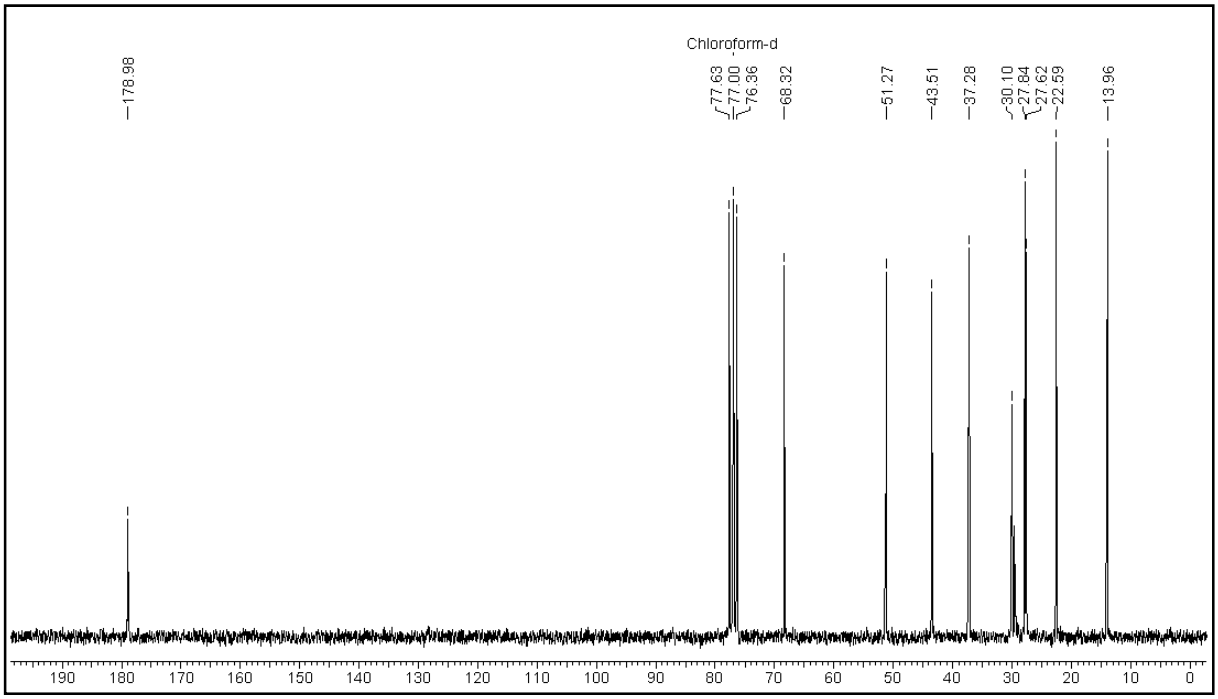


- **^{13}C NMR of the compound 26 in $CDCl_3$**

(*R*)-5-((*R*)-2-Hydroxyhexyl)pyrrolidin-2-one (27):

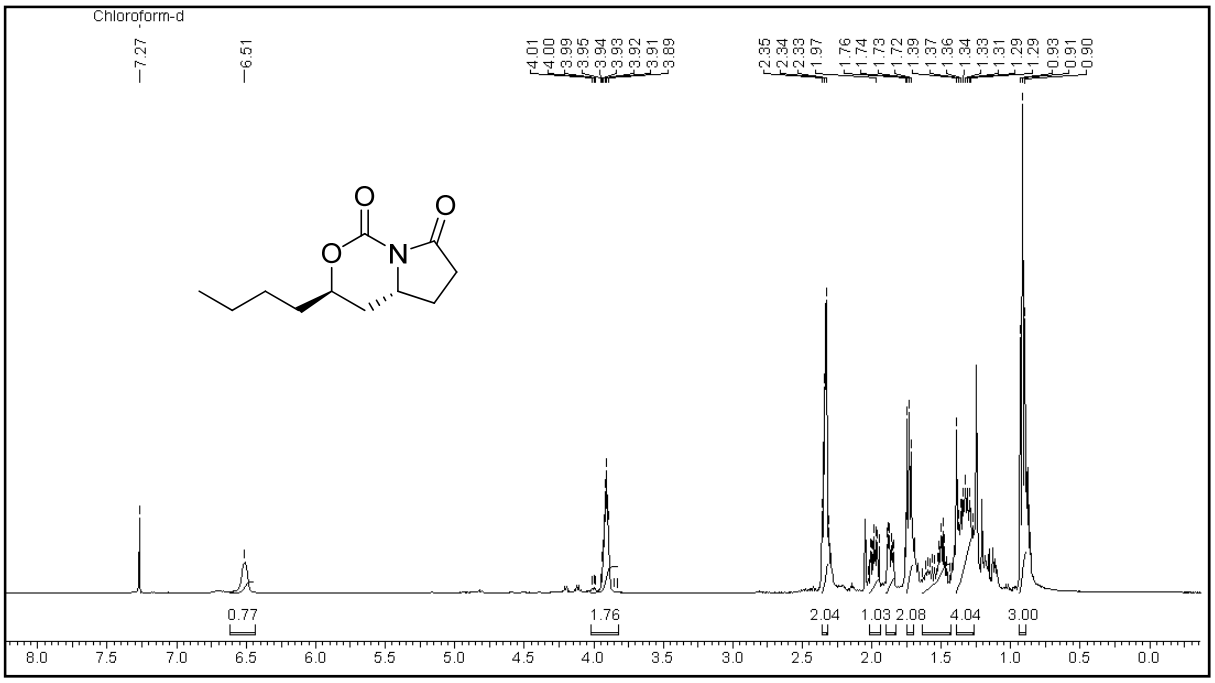


- **^{1}H NMR of the compound 27 in $CDCl_3$**

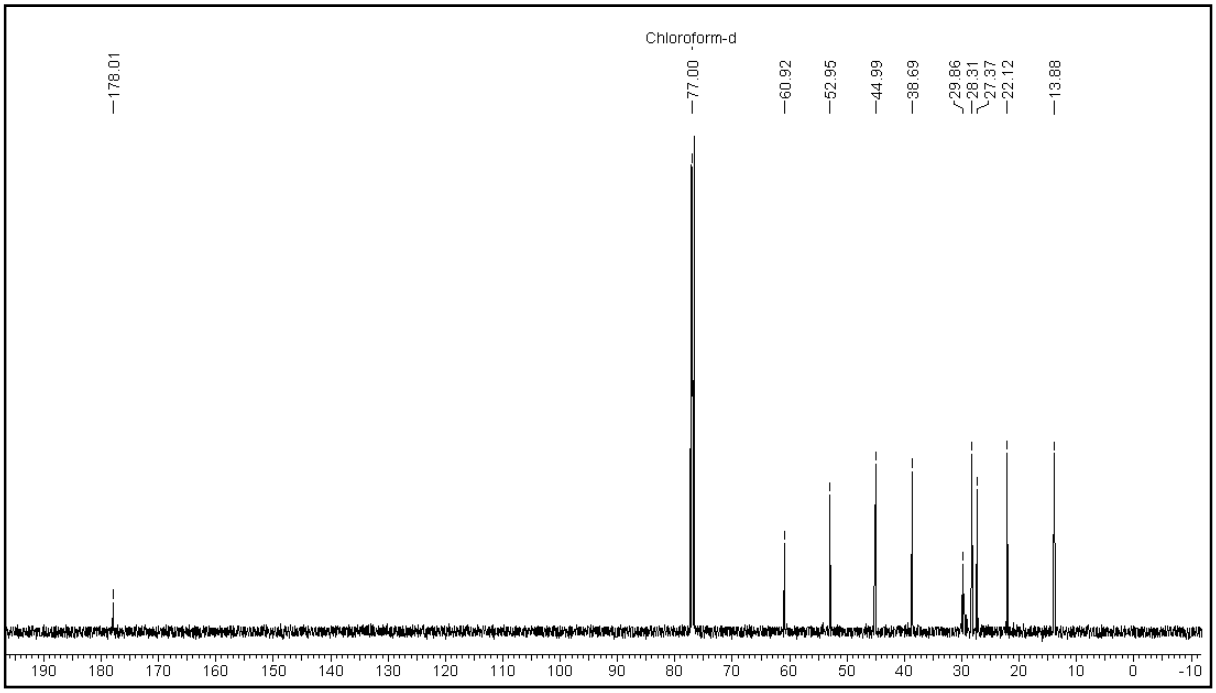


- **^{13}C NMR of the compound 27 in $CDCl_3$**

(3*R*,4a*R*)-3-Butyltetrahydro-1H-pyrrolo[1,2-c][1,3]oxazine-1,7(3H)-dione (28):

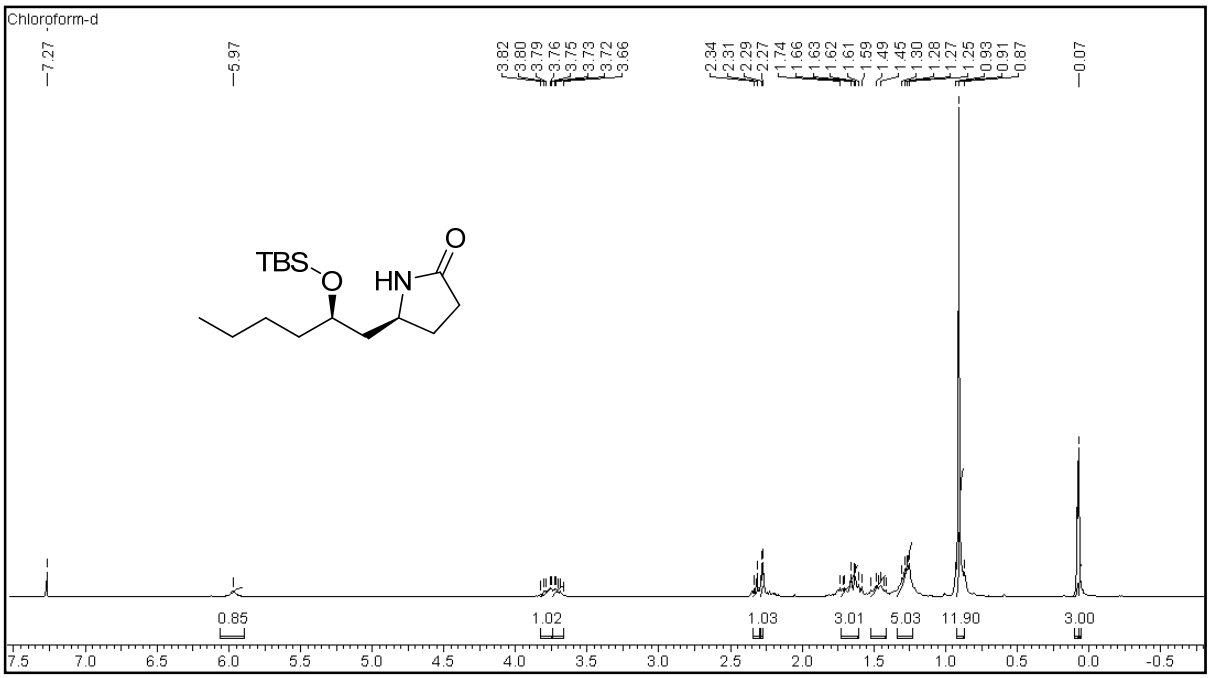


- **^{1}H NMR of the compound 28 in $CDCl_3$**

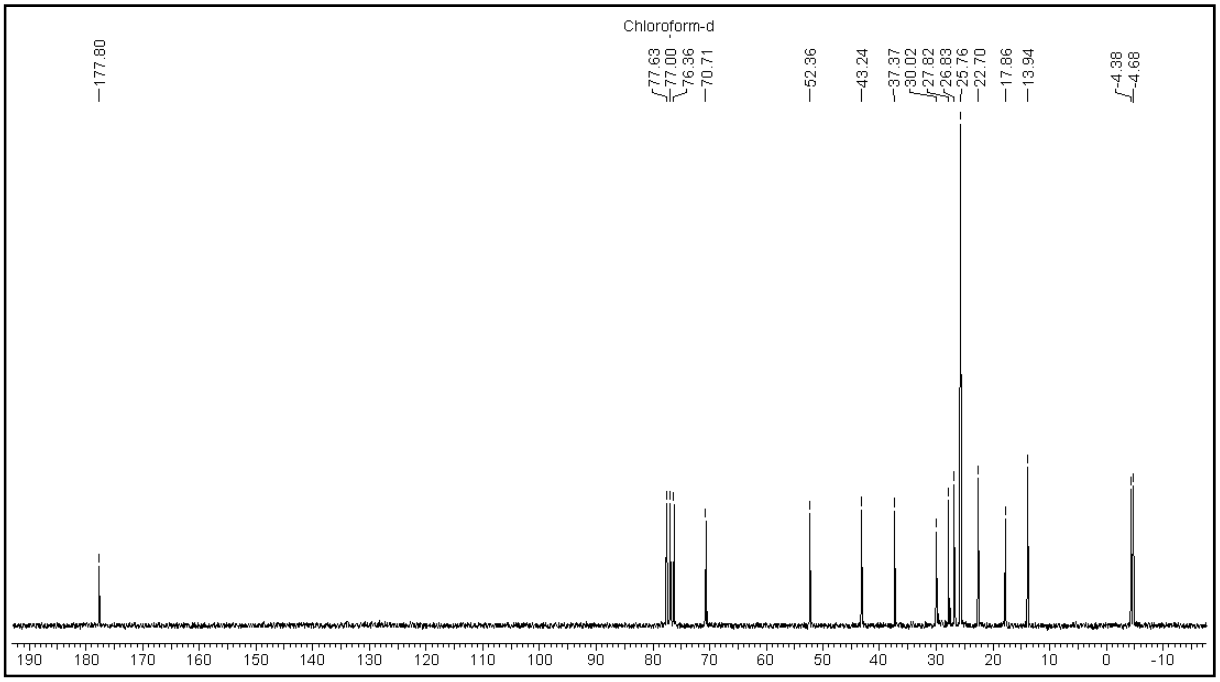


- **^{13}C NMR of the compound 28 in $CDCl_3$**

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)hexyl)pyrrolidin-2-one (29):

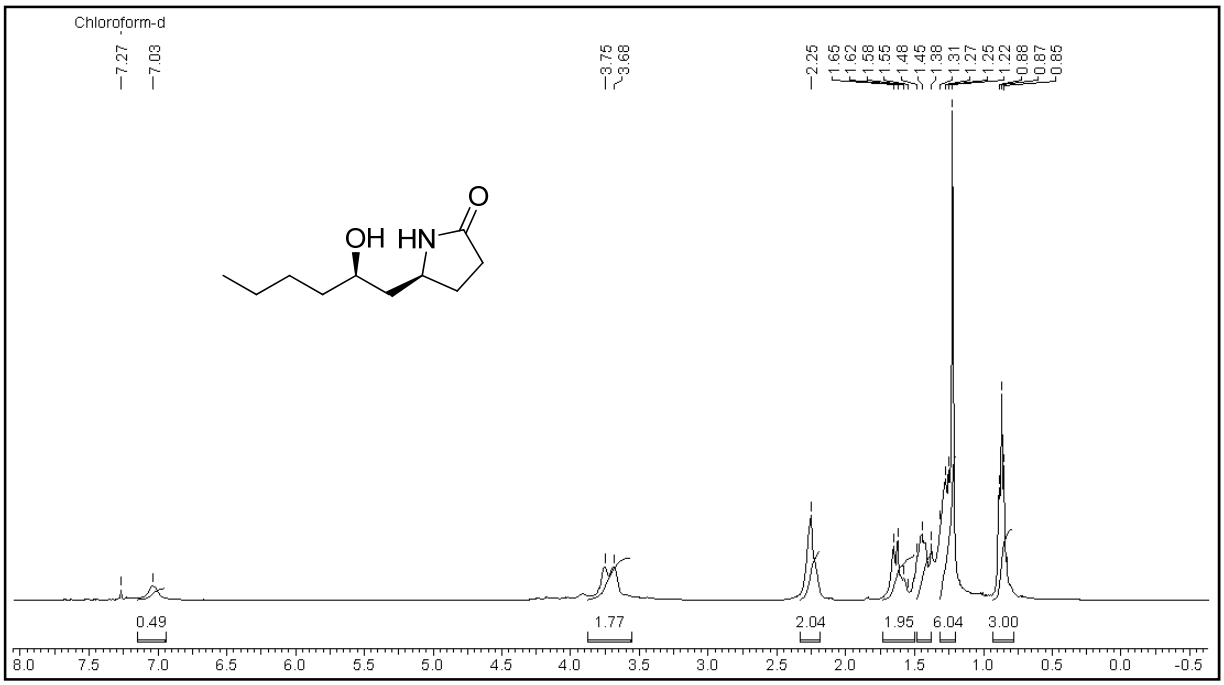


➢ **^{1}H NMR of the compound 29 in $CDCl_3$**

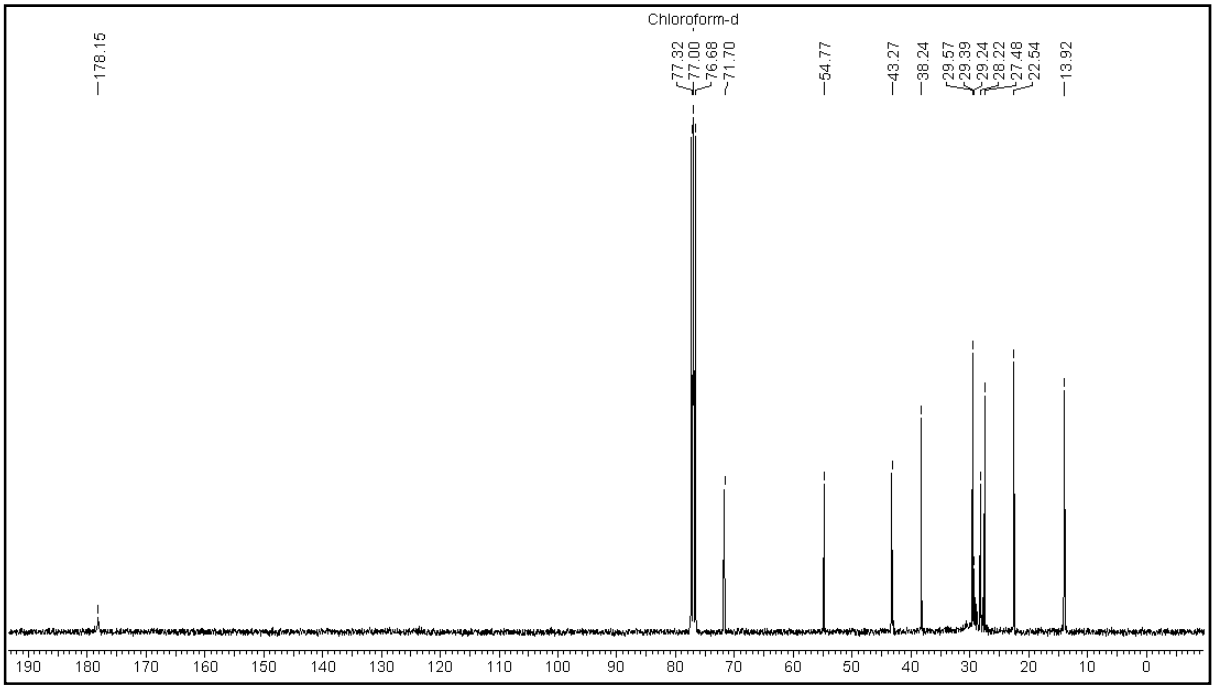


➢ **^{13}C NMR of the compound 29 in $CDCl_3$**

(*S*)-5-((*R*)-2-Hydroxyhexyl)pyrrolidin-2-one (30):

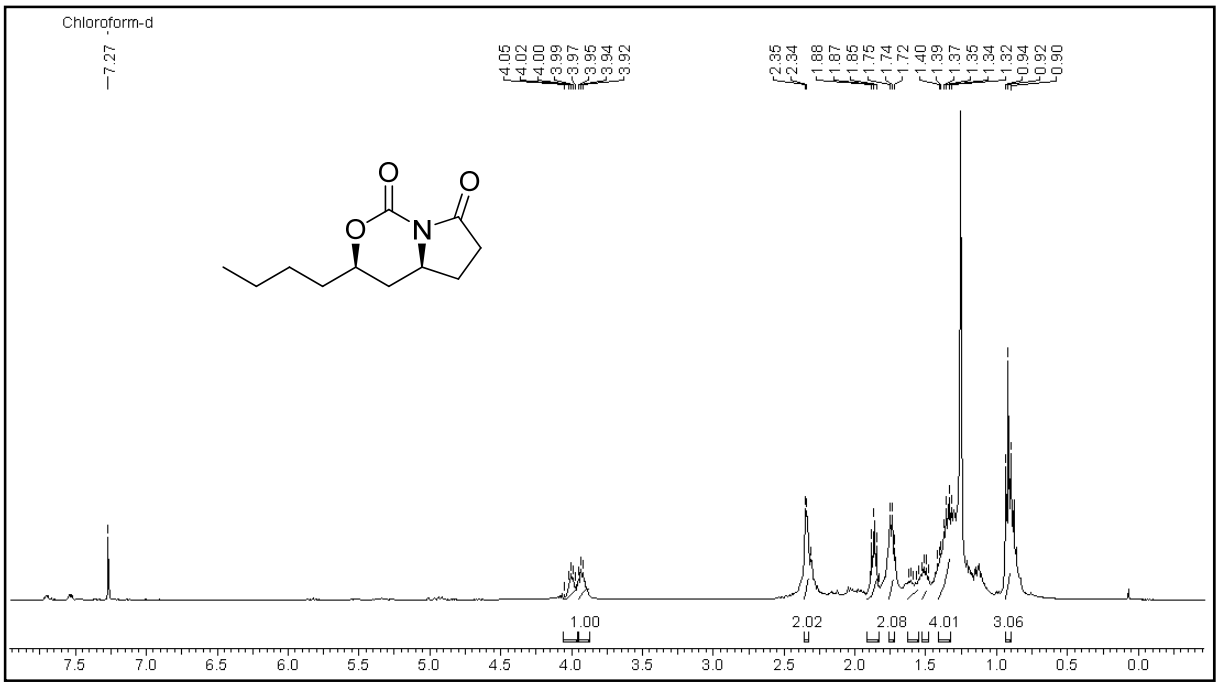


- **^{1}H NMR of the compound 30 in $CDCl_3$**

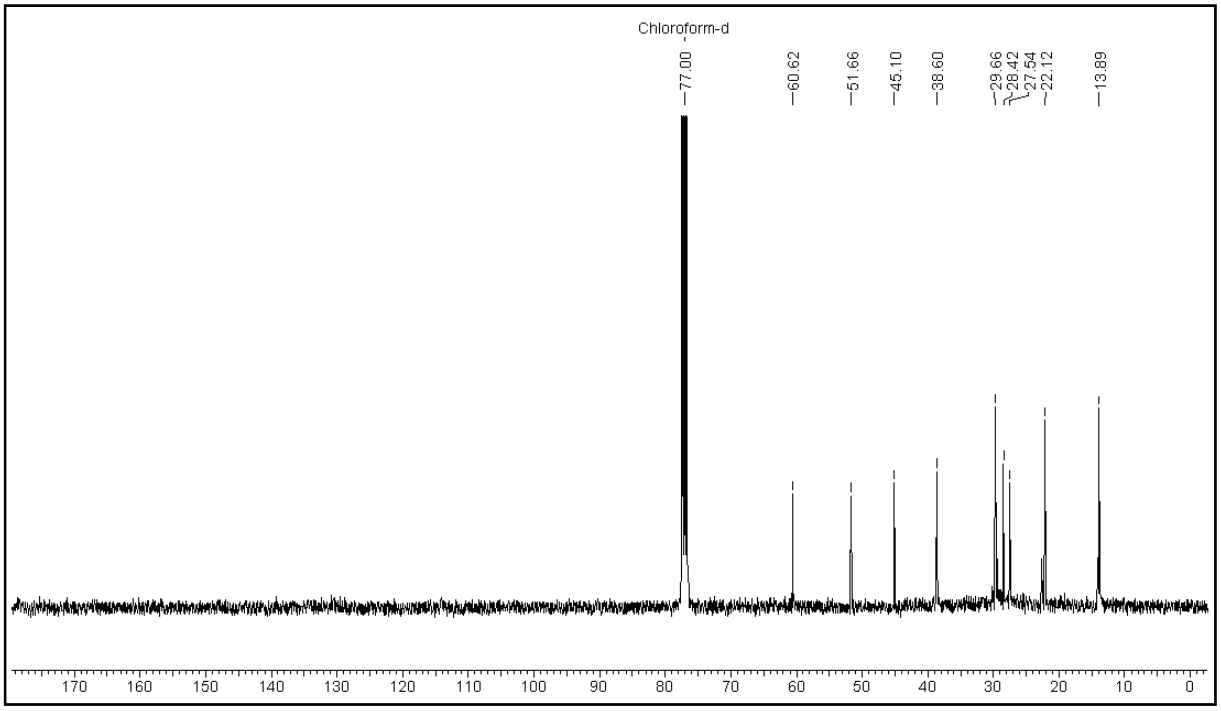


- **^{13}C NMR of the compound 30 in $CDCl_3$**

(3*R*,4a*S*)-3-Butyltetrahydro-1H-pyrrolo[1,2-c][1,3]oxazine-1,7(3H)-dione (31):

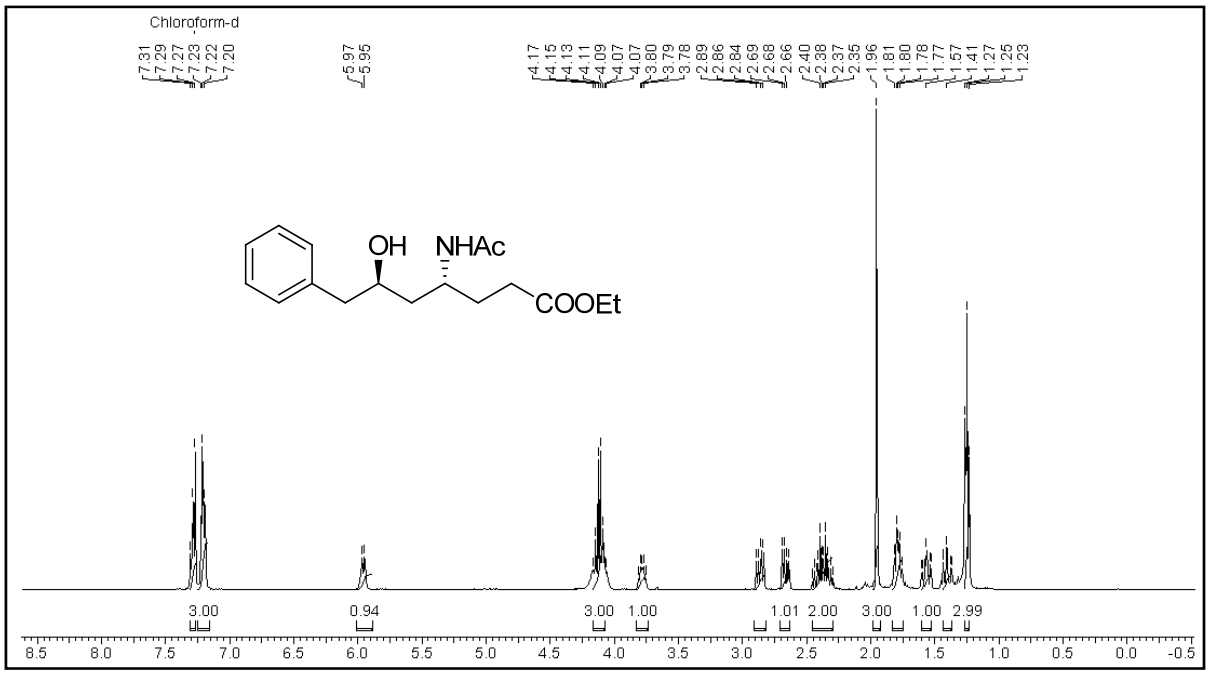


- **^{1}H NMR of the compound 31 in $CDCl_3$**

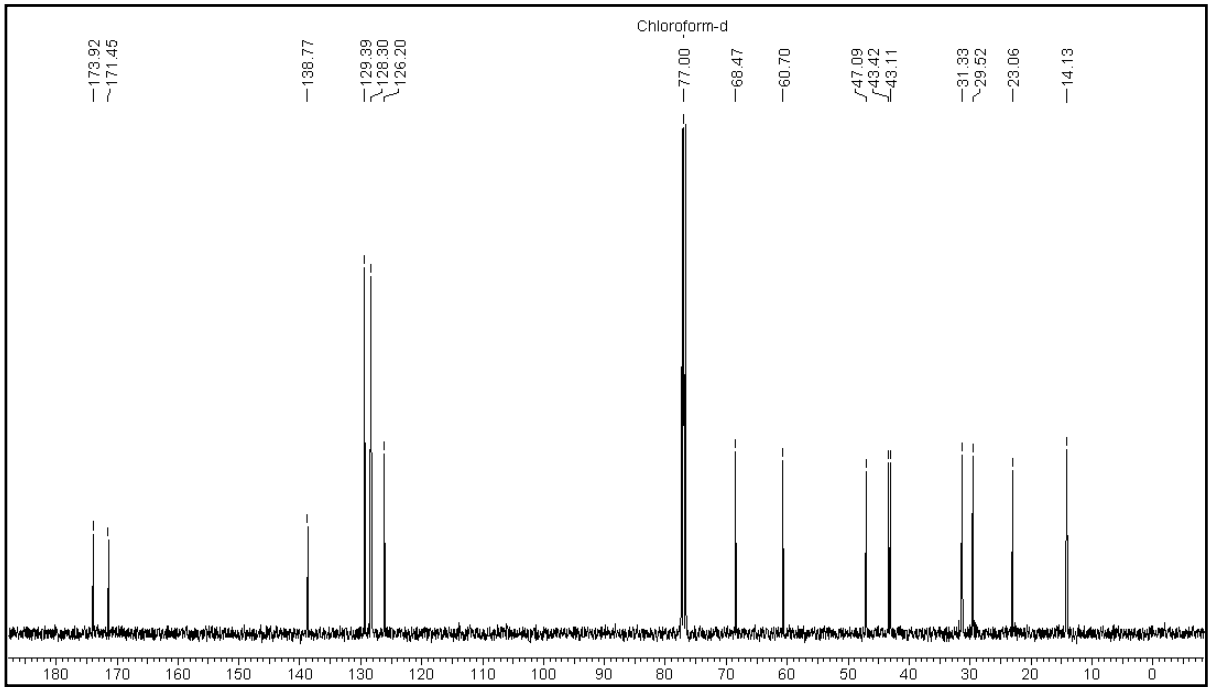


- **^{13}C NMR of the compound 31 in $CDCl_3$**

(4*R*,6*R*)-Ethyl 4-acetamido-6-hydroxy-7-phenylheptanoate (32):

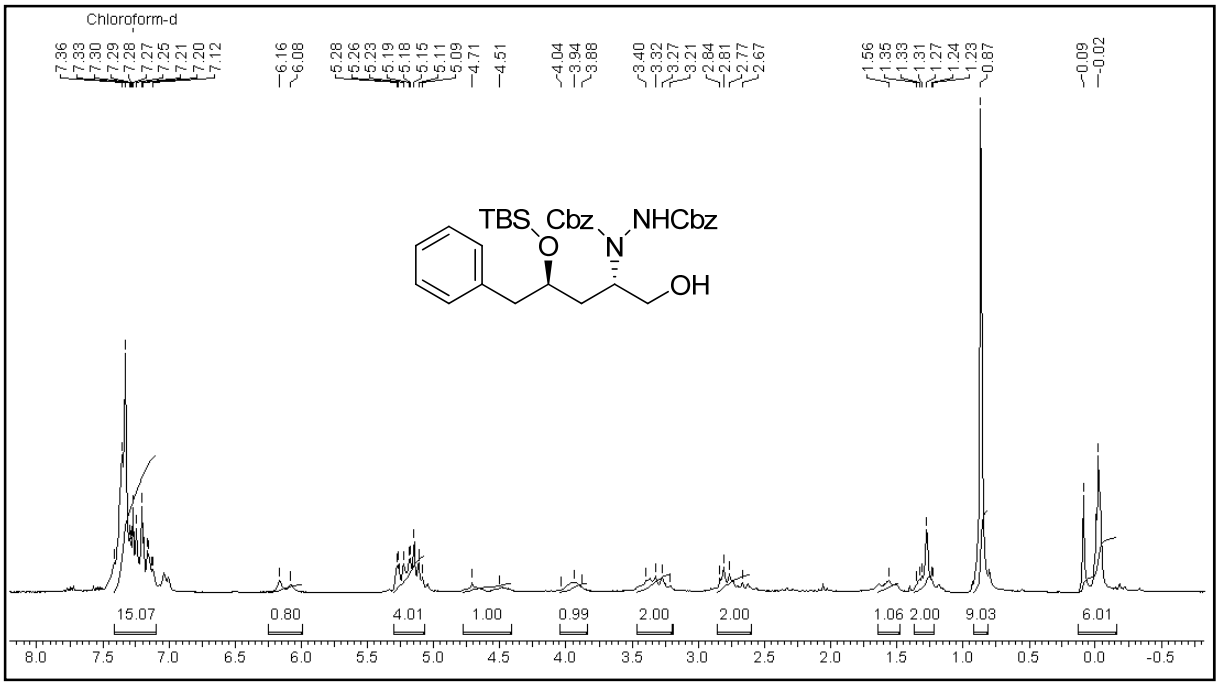


- **^{1}H NMR of the compound 32 in $CDCl_3$**

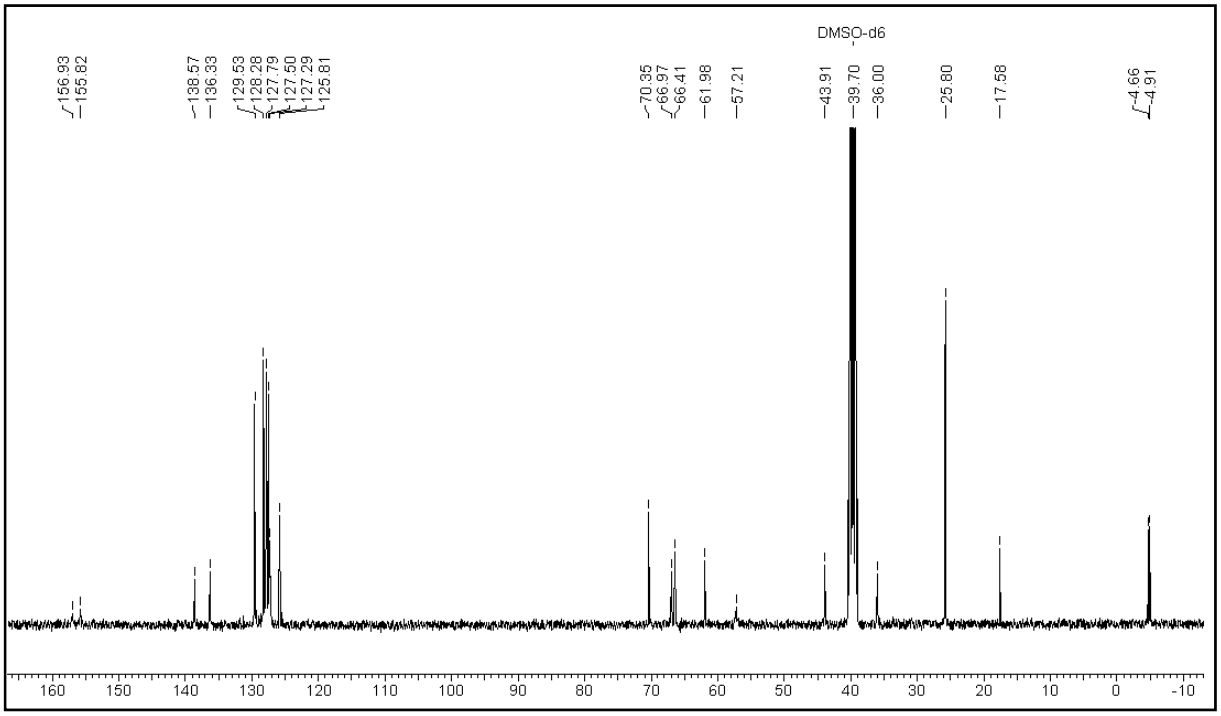


- **^{13}C NMR of the compound 32 in $CDCl_3$**

Dibenzyl 1-((2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (33):

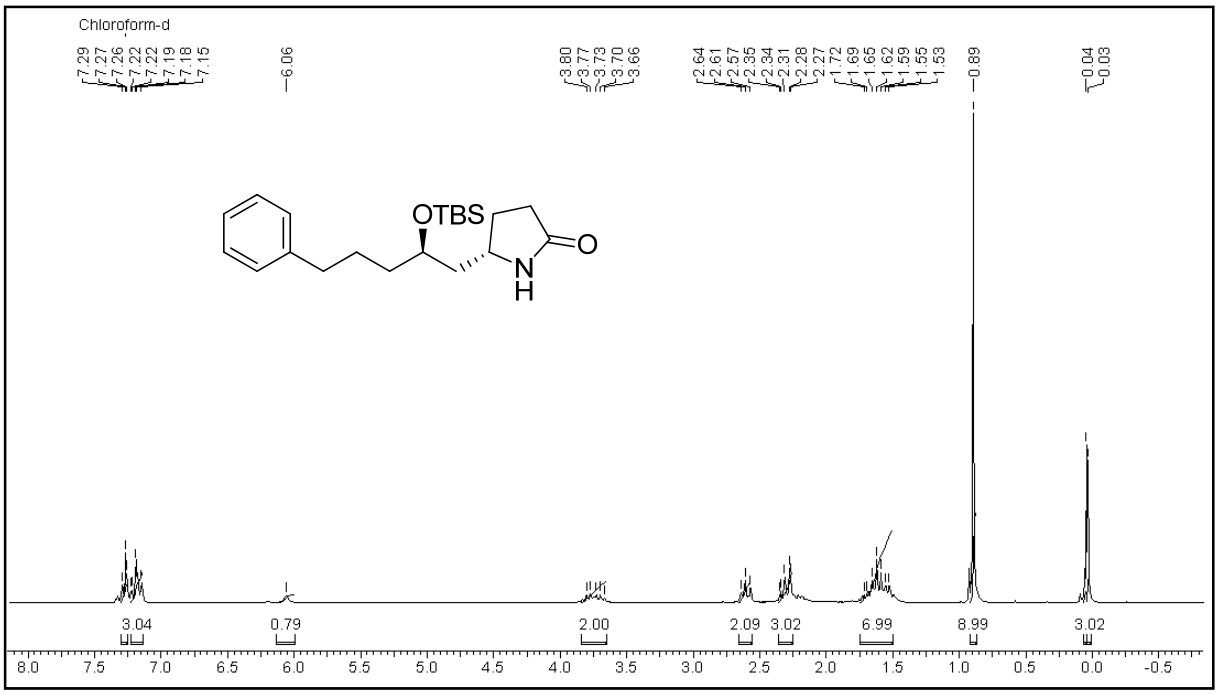


➢ **^{1}H NMR of the compound 33 in $CDCl_3$**

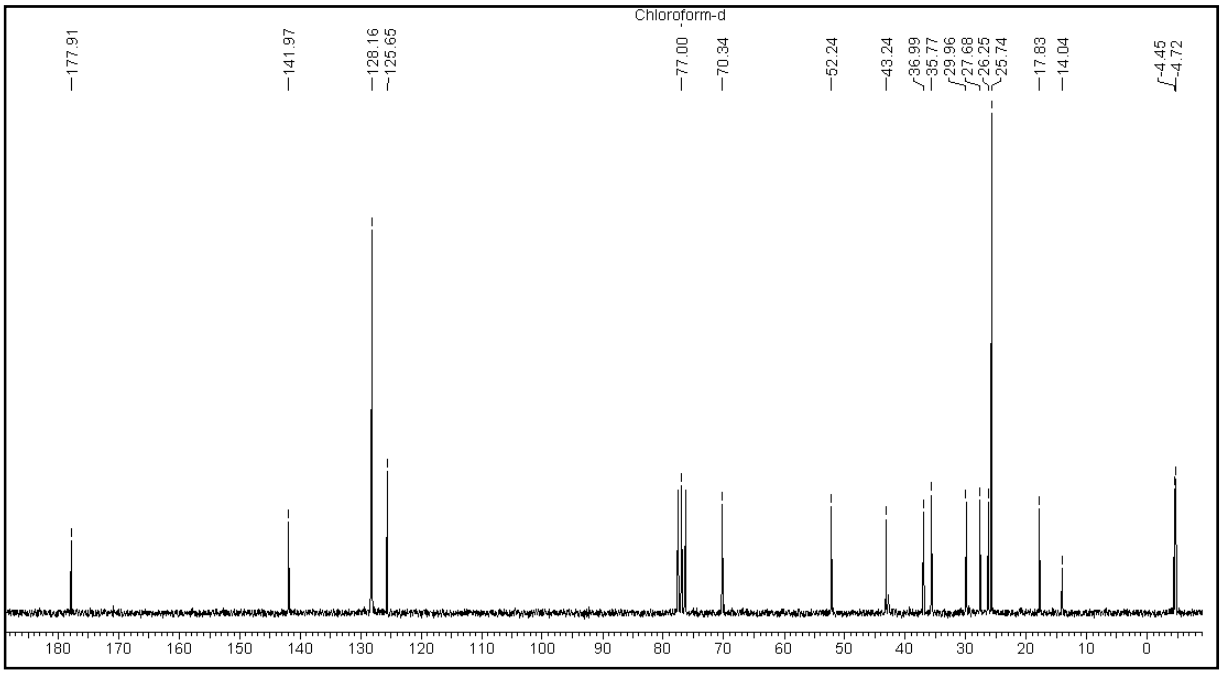


➢ **^{13}C NMR of the compound 33 in DMSO-d_6**

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)pyrrolidin-2-one (34):

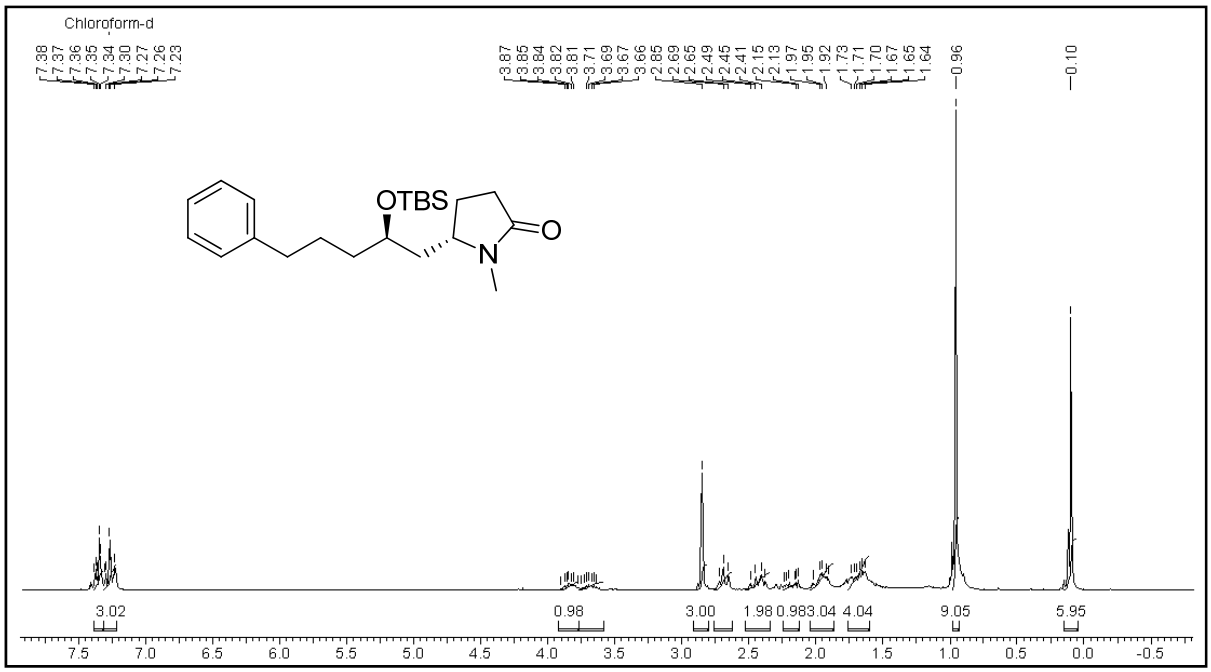


- **^{1}H NMR of the compound 34 in $CDCl_3$**

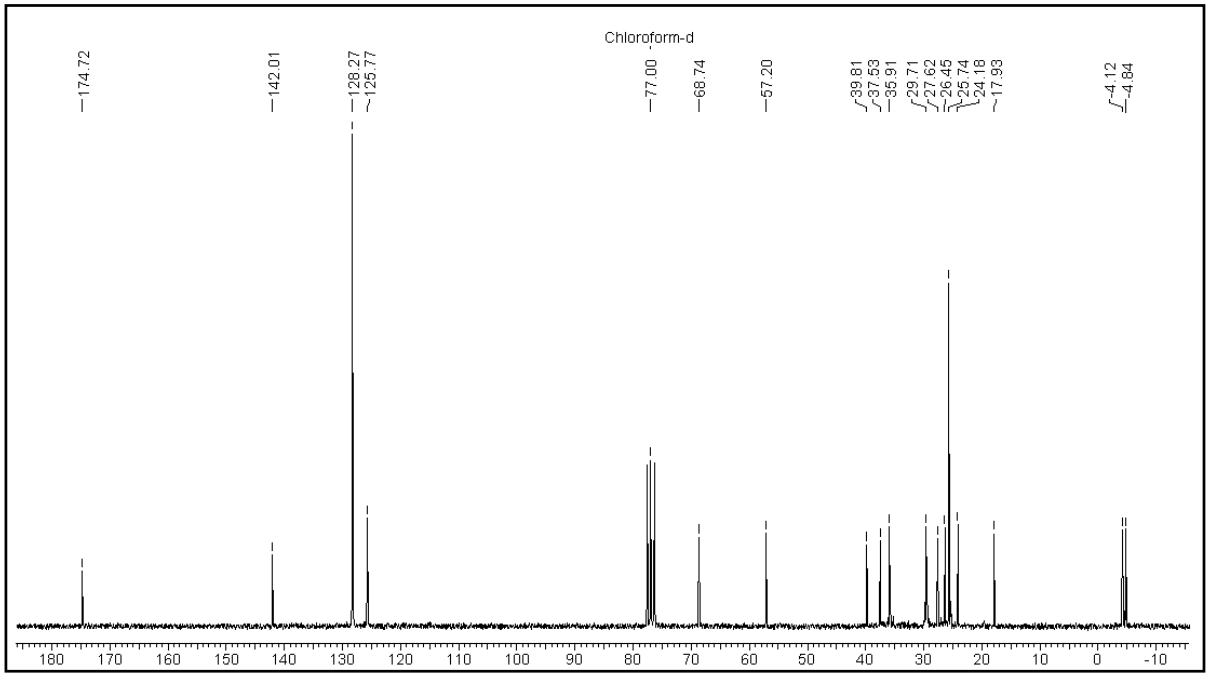


- **^{13}C NMR of the compound 34 in $CDCl_3$**

(*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidin-2-one (35):

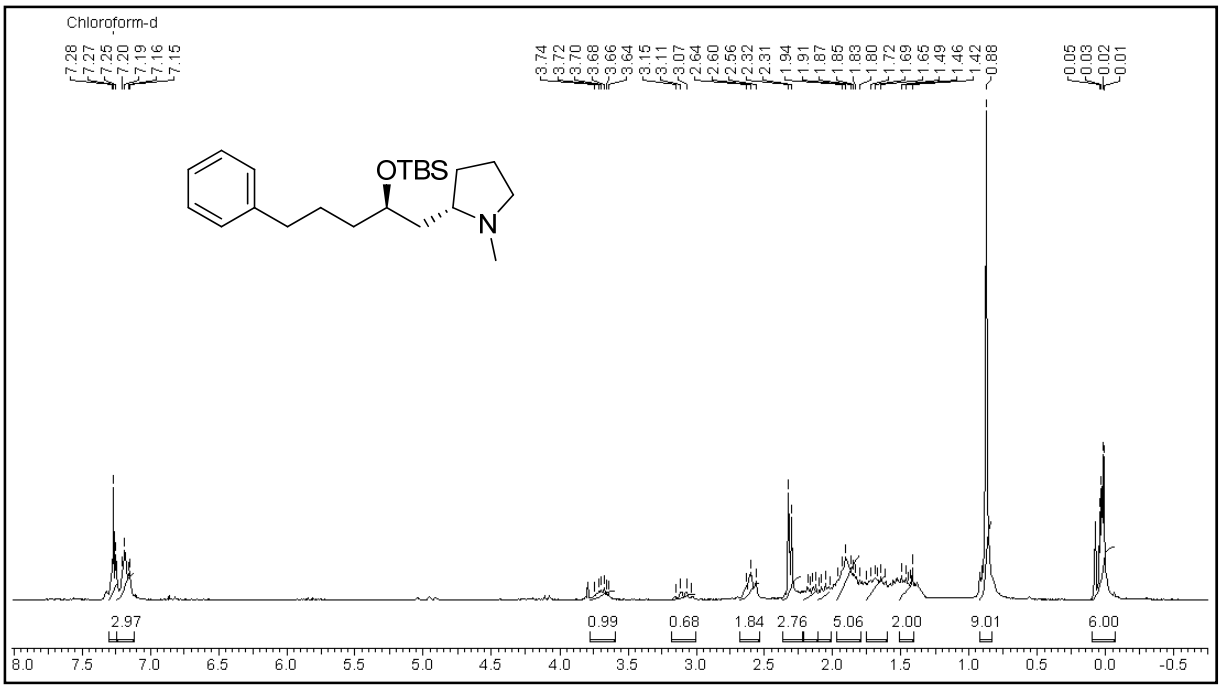


- **^{1}H NMR of the compound 35 in $CDCl_3$**

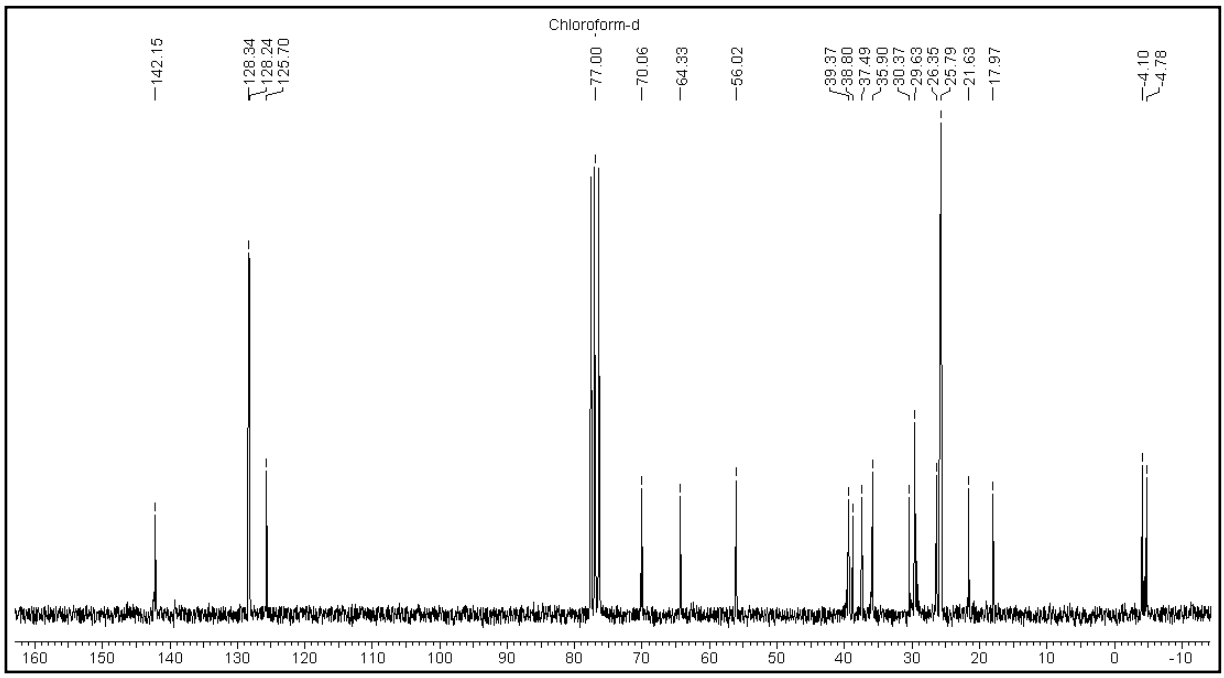


- **^{13}C NMR of the compound 35 in $CDCl_3$**

(*S*)-2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-phenylpentyl)-1-methylpyrrolidine (36):

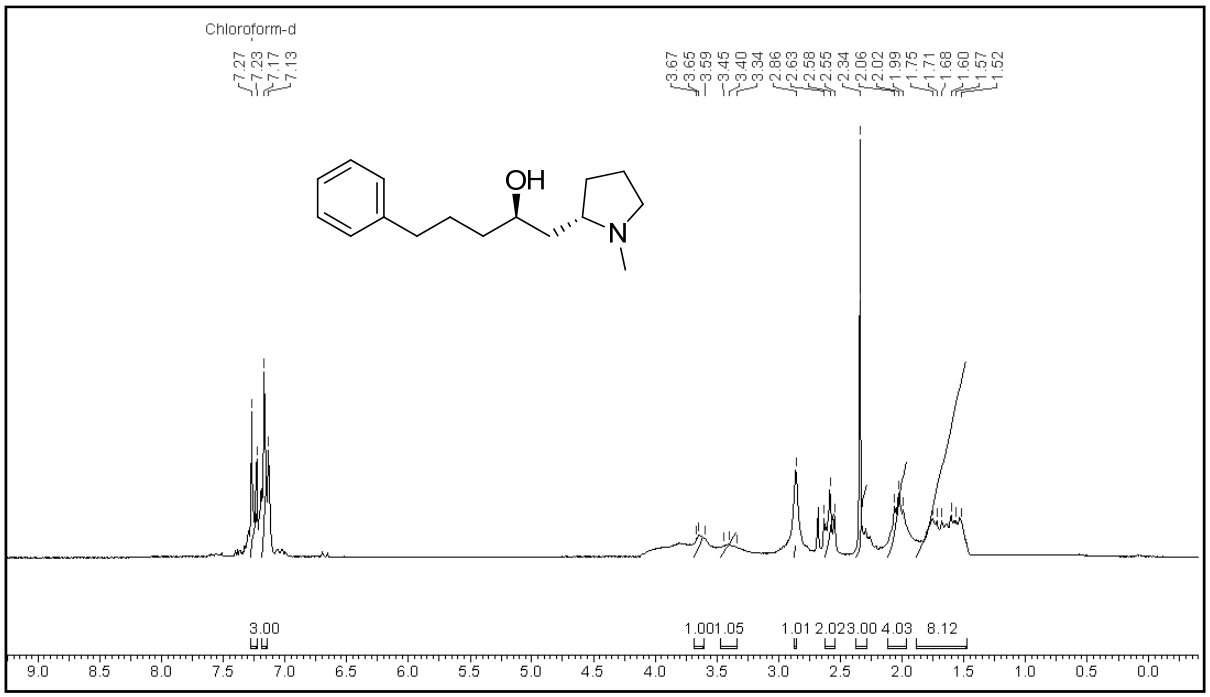


- **^{1}H NMR of the compound 36 in $CDCl_3$**

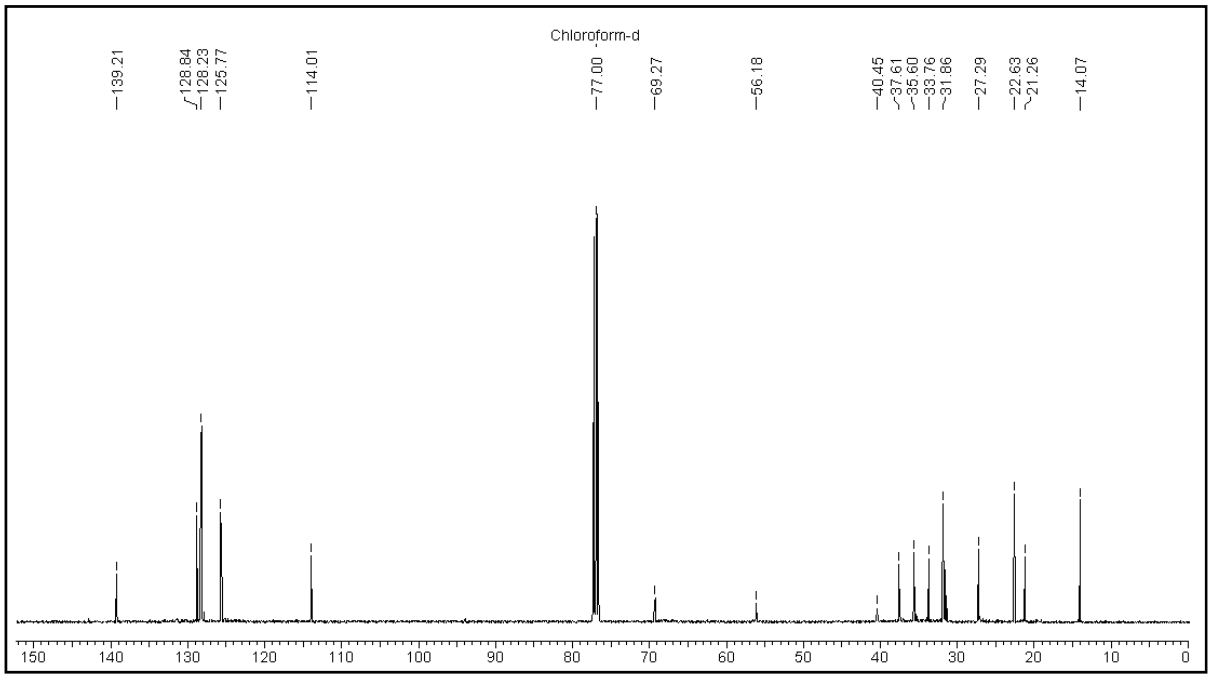


- **^{13}C NMR of the compound 36 in $CDCl_3$**

(*R*)-1-((*S*)-1-Methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (37):

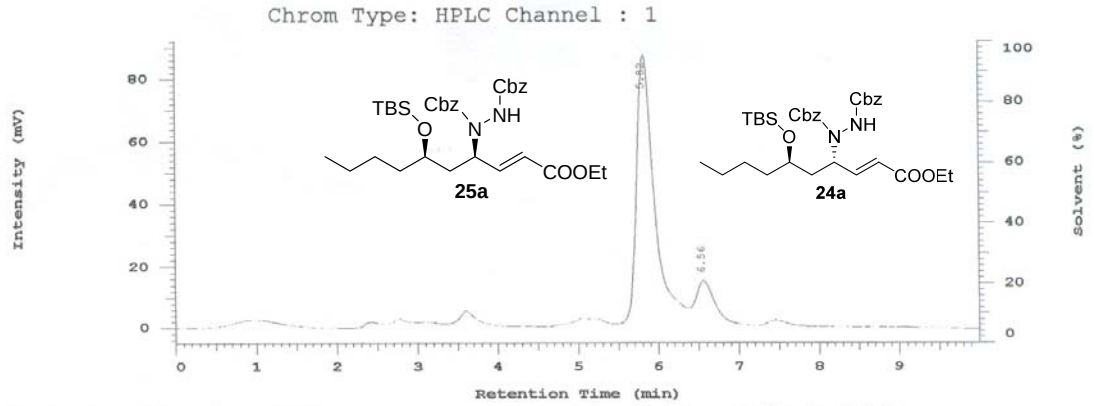


- **^{1}H NMR of the compound 37 in $CDCl_3$**



- **^{13}C NMR of the compound 37 in $CDCl_3$**

Diastereomeric ratio of *syn*-compounds 25a-e



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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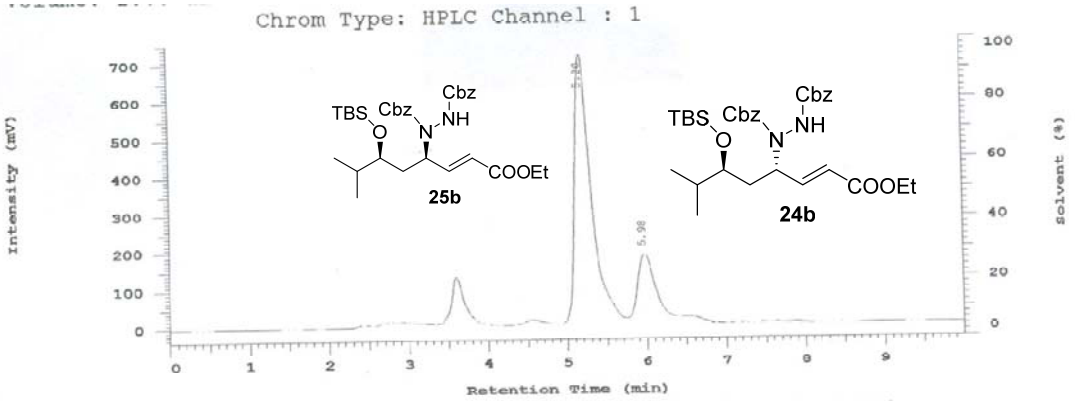
2	6.56	10795	139471	10.251
		96157	1360574	100.000



Peak Quantitation: AREA Calculation Method: AREA%

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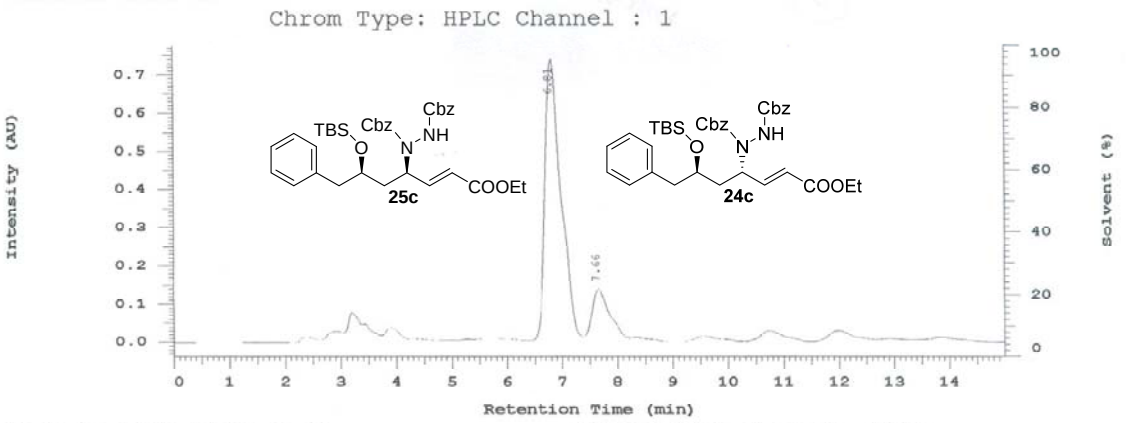

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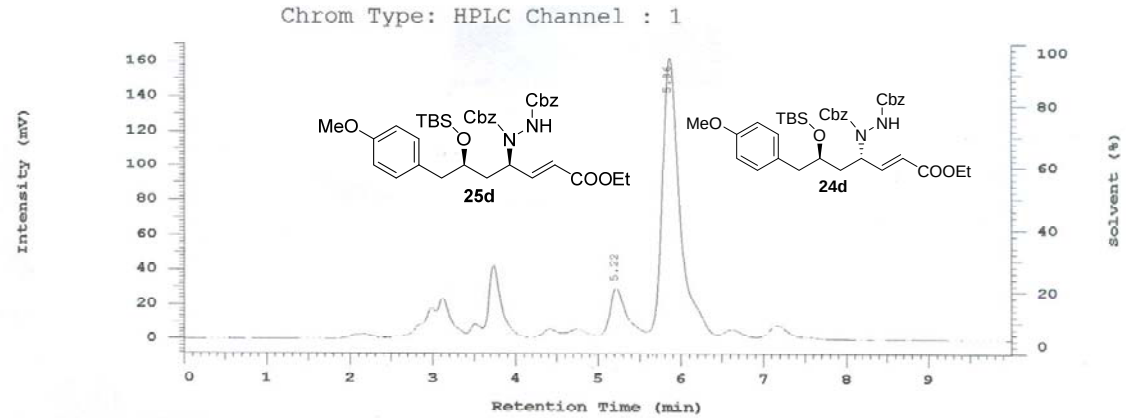

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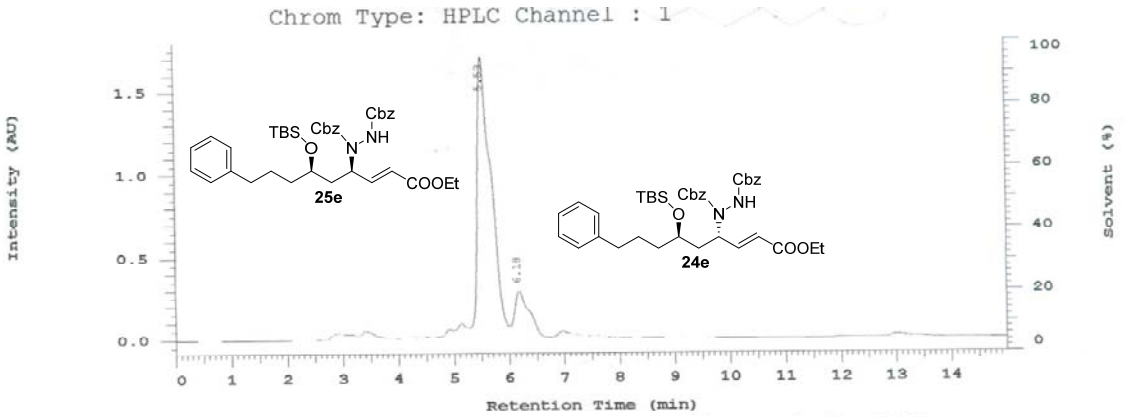

Peak Quantitation: AREA Calculation Method: AREA%

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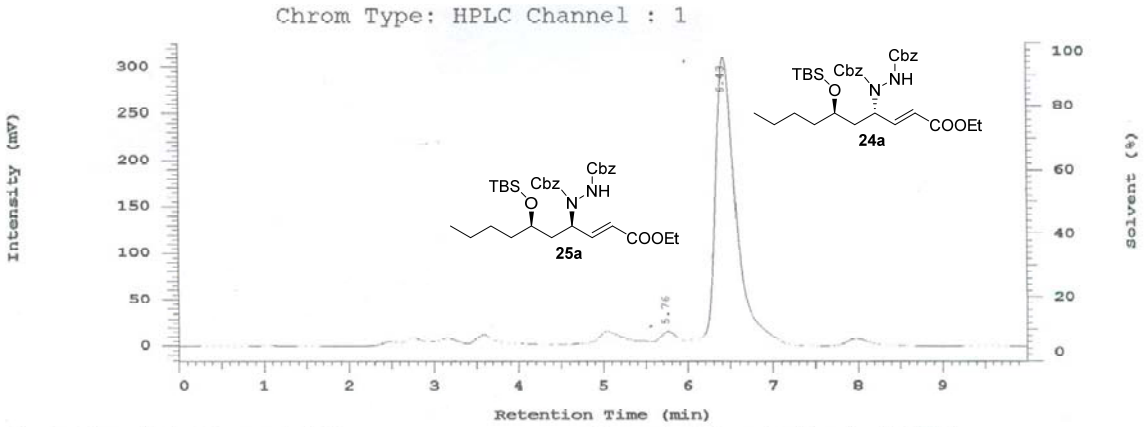
2	6.18	130969	2272423	13.948
		959302	16291751	100.000

Diastereomeric ratio of *anti*-compounds 24a-e:



Peak Quantitation: AREA Calculation Method: AREA%

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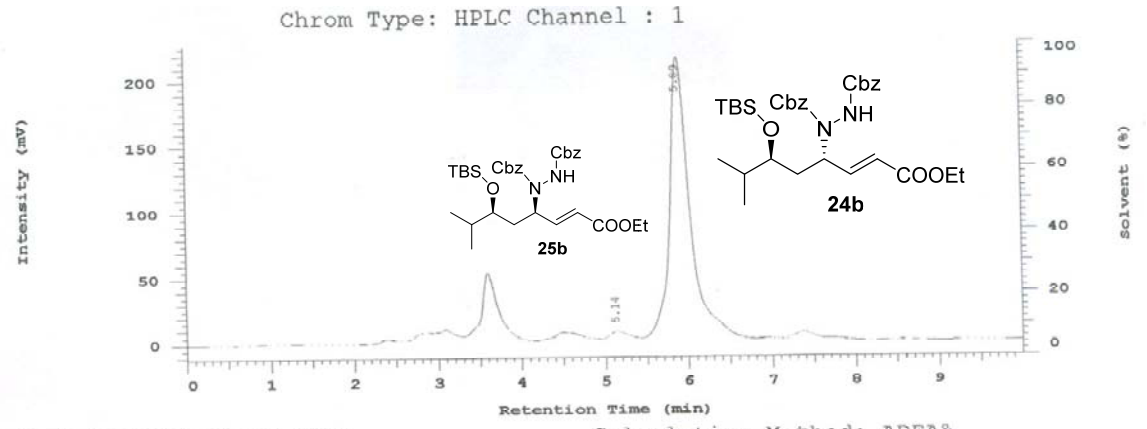
2	6.43	305328	4984500	97.414
		316785	5116840	100.000



Peak Quantitation: AREA Calculation Method: AREA%

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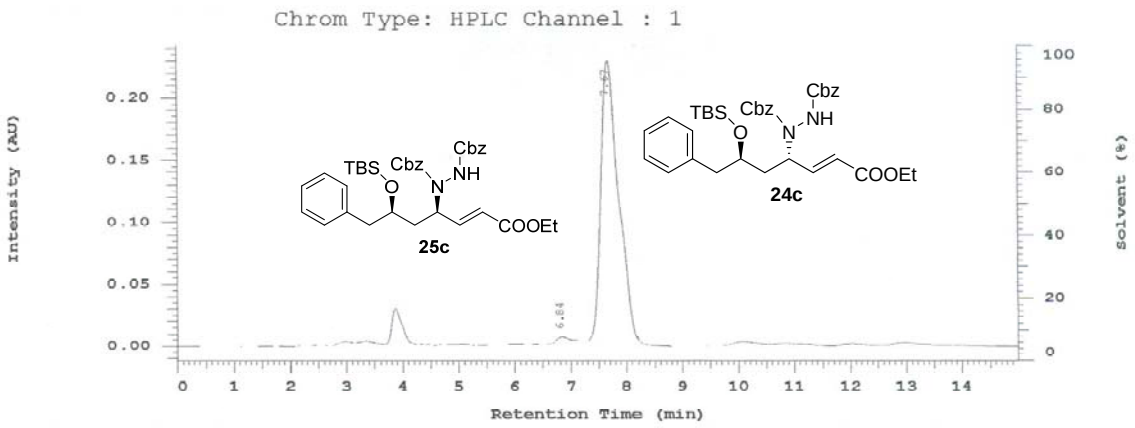
		214305	3438225	100.000



Peak Quantitation: AREA Calculation Method: AREA%

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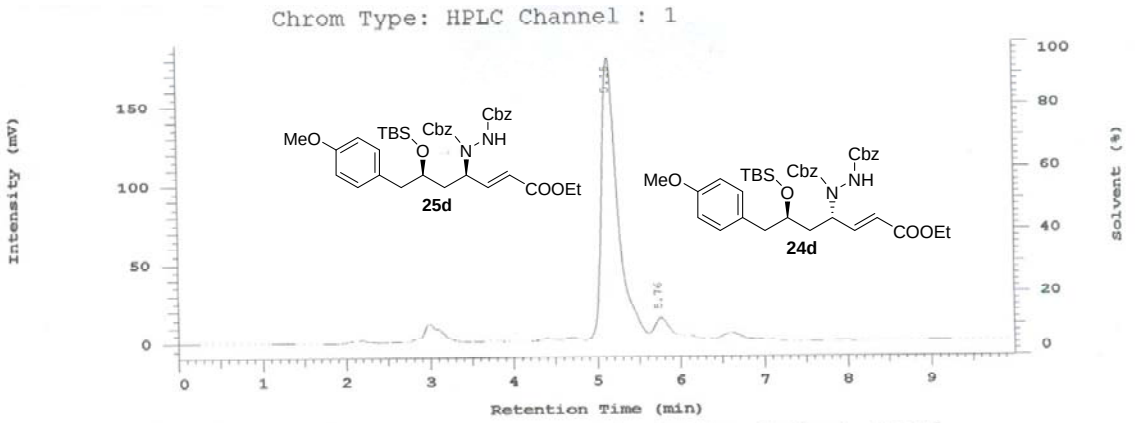
		115013	2501672	100.000



Peak Quantitation: AREA Calculation Method: AREA%

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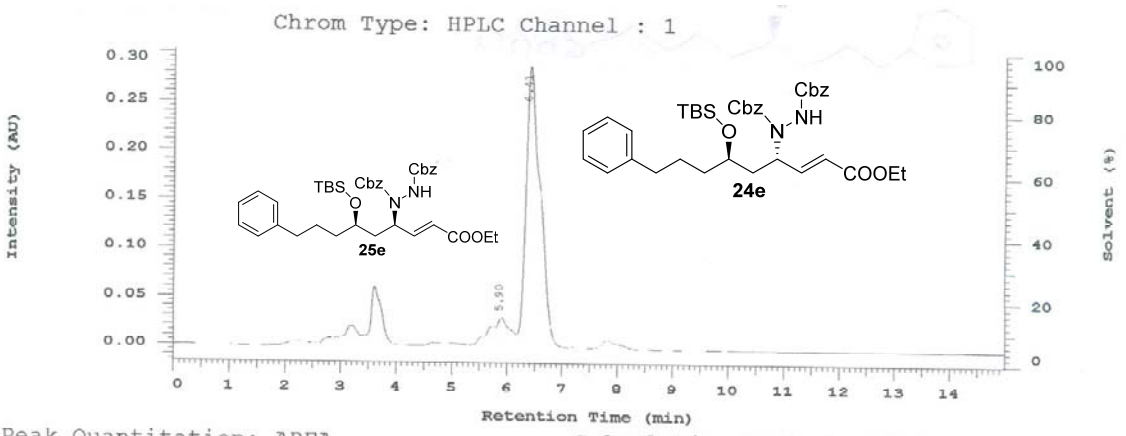
1	5.15	177423	2312876	96.670
2	5.76	8862	79680	3.330
		186285	2392556	100.000



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	5.90	2747	13687	0.599
2	6.41	135878	2270284	99.401
		138625	2283971	100.000

2.1.8. Reference

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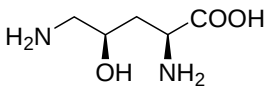
2.2. SECTION B

An efficient and organocatalytic route towards synthesis of protected (2*S*,4*R*)-4-hydroxyornithine

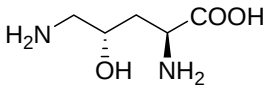
2.2.1. Introduction

4-Hydroxyornithine is a rare nonproteinogenic amino acid found in lentils[1] (e.g., *Lens culinaris* Medik.) and some members of the genus *Vicia*[2] (e.g., *V. unijuga* A. Br.). It is a component of marine organism[3] and plants,[4] as well as a constituent of a number of peptide natural products, such as the antifungal lipopeptides echinocandin and pneumocandin,[5] the K 582 type antibiotics,[6] the β-lactam antibiotic clavalanine **3**[7a-c] and polyoxin M,[7d] and macrocyclic antibiotic such as biphenomycin A and B 2,[8] which has high in vitro and in vivo antibacterial activity against multiresistant gram-positive pathogens.[9] The related 4-hydroxylated α-amino acids such as (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinylnorvaline **4** has also been identified as a key component of ustiloxin A and B,[10] a family of cyclic peptides with potent antimitotic activity.[11]



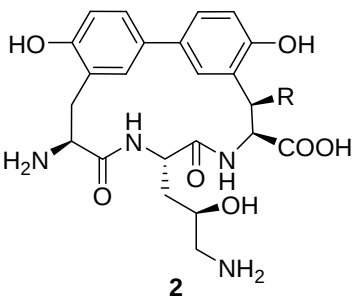
1a

(2*S*,4*R*)-4-Hydroxyornithine



1b

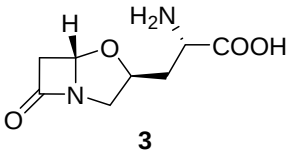
(2*S*,4*S*)-4-Hydroxyornithine



2

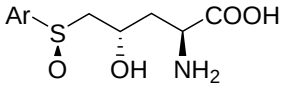
Biphenomycin A R = OH

Biphenomycin B R = H



3

Clavalanine



4

(2*S*,4*S*,6*R*)-4-Hydroxy-5-phenylsulfinylnorvaline

Figure 1.

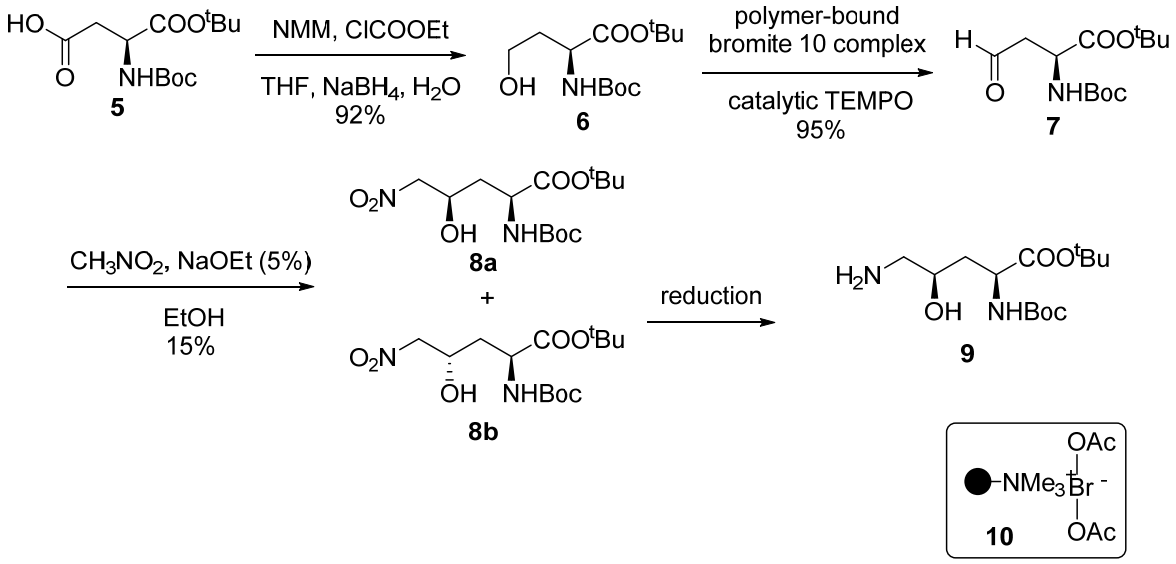
2.2.2. Review of Literature

Various methods for the synthesis of 4-hydroxyornithine including stereoselective approaches have been reported in the literature.[12] So far only six asymmetric synthesis of 4-hydroxyornithine is reported. A detailed report of recent syntheses is described below.

Rudolph *et al.* (2001)[13a]

Rudolph and co-workers synthesized (2*S*,4*R*)-4-hydroxyornithine **1a** starting from diprotected L-aspartic acid, the scaffold of the target compound is constructed in a three-step approach: an efficient α-nitroketone formation through acylation of nitromethane is followed by a diastereoselective reduction of the resulting ketone. In the last step, the nitro group is reduced to furnish the (2*S*,4*R*)-4-hydroxyornithine.

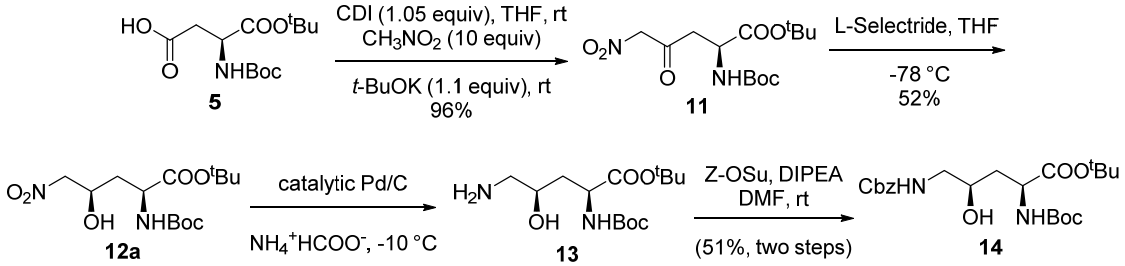
The synthesis started from commercially available (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **5** which was reduced to the homoserine derivative **6** followed by oxidation to the semialdehyde **7**. Henry reaction of compound **7** gave the (2*S*,4*R*)-diastereomer (erythro) (**8a**) and (2*S*,4*S*)-diastereomer (threo) (**8b**) in a 2:3 ratio (Scheme **1**).



Scheme 1. Synthesis of 4-hydroxyornithine (Rudolf method)

Because of the unfavorable diastereoselectivity and yield of the nitroaldol reaction, they turned to a different strategy for C-C-coupling which would involve the generation of an α-nitroketone. (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **5** was transformed to the nitroketone **11** and reduction of the keto group with L-Selectride gave rise to a 85:15

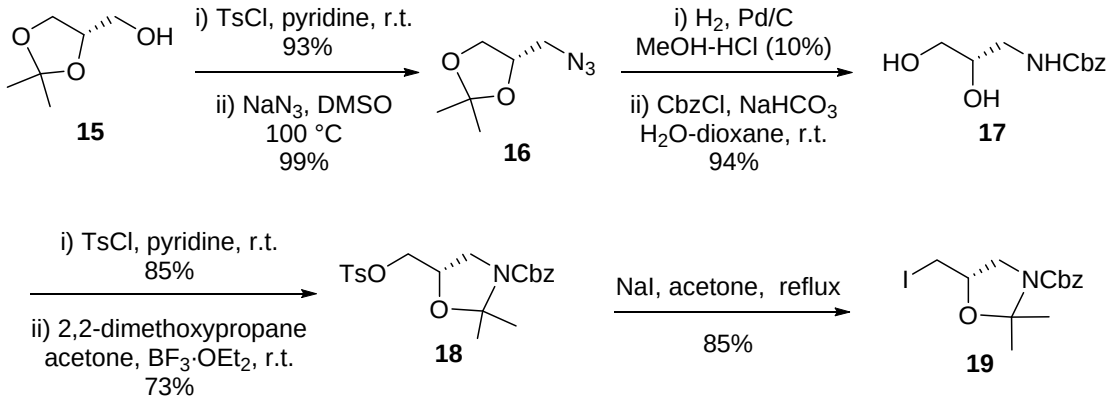
mixture in favor of the desired erythro compound **12a** (= (2*S*,4*R*)-diastereomer). In the last step of the sequence, the nitro group was reduced to furnish the vicinal amino alcohol function of the *tert*-butyl (2*S*,4*R*)-*N*-Boc-4-hydroxyornithinate **13** (Scheme **2**).



Scheme 2. Revised synthesis of 4-hydroxyornithine (Rudolf method)

Zhu *et al.* (2003)[13b]

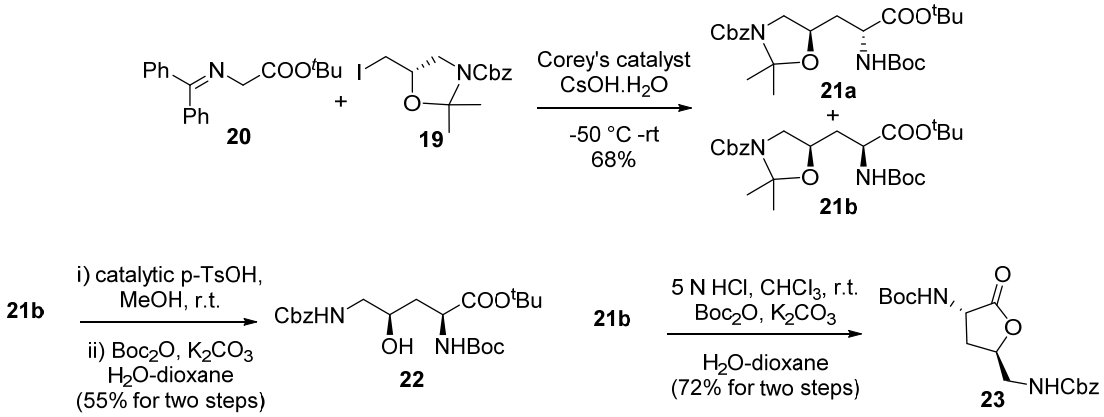
Zhu and co-workers synthesized orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine starting from (*S*)-1,2-*O*-isopropylidene glycerol **15,** which on tosylation followed by nucleophilic displacement of tosylate with sodium azide provided azido derivative **16.** Hydrogenolysis under acidic conditions provided an amino diol that was chemoselectively *N*-acylated to give carbamate **17**. Regioselective tosylation of the primary hydroxy group afforded **18**, which was subsequently converted into iodide **19** *via* two-step sequence (Scheme **3**).



Scheme 3. Synthesis of 4-hydroxyornithine (Zhu method)

Alkylation of **20** with iodide **19** was carried out using *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide as catalyst under Corey's conditions (CsOH,

0.56 M in CH_2Cl_2) to give two diastereomers **21a** and **21b.** Selective hydrolysis of oxazolidine function of **21b** with *p*-TsOH followed by *N*-Boc formation led to ester **22**. On the other hand, treatment of **21b** with 5 N HCl provided the γ-lactone that was *N*-protected to afford **23** in 72% yield (Scheme **4**).

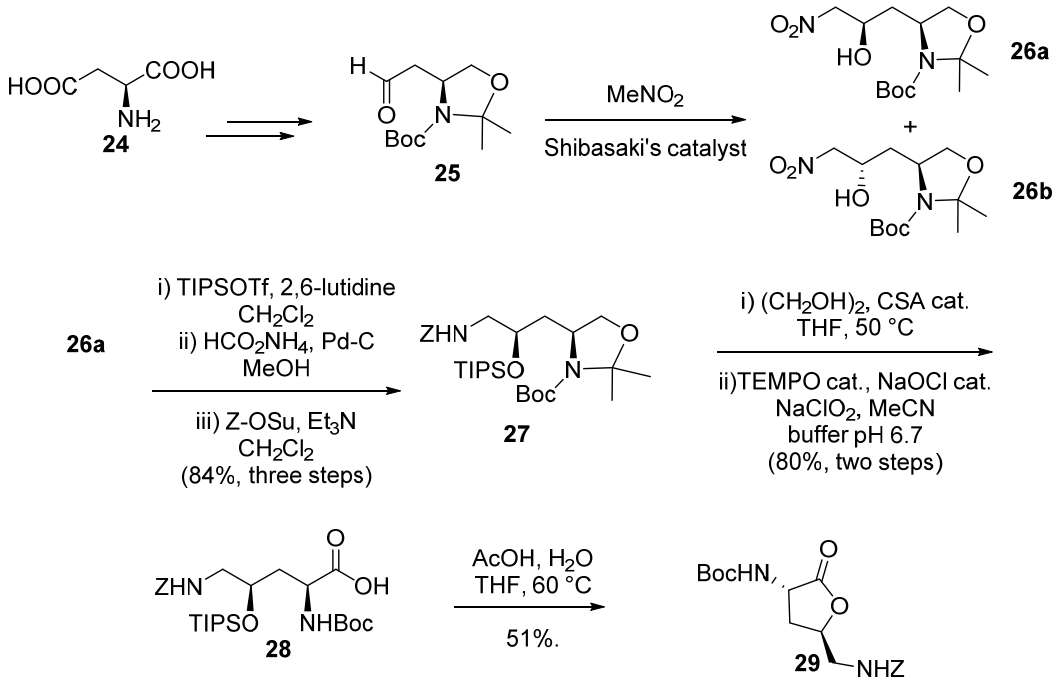


Scheme 4. Completion of Synthesis of 4-hydroxyornithine (Zhu method)

Paintner *et al.* (2005)[13c]

Paintner and co-workers synthesized both orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine **1a-b**. The approach is based on bis(oxazoline) copper(II)-complex-catalyzed diastereoselective Henry reactions of nitromethane with the homoserine-derived aldehyde. The synthesis started from aldehyde **25** prepared from known literature procedure, which was subjected to nitroaldol (Henry) reaction with nitromethane using Shibasaki's well-established heterobimetallic (*S*)-BINOL catalyst to give nitro alcohols **26a** and **26b**.

Protection of the hydroxyl group as a TIPS ether and reduction of the nitro group was accomplished using ammonium formate as a hydrogen source and palladium on carbon as catalyst to afford the corresponding amine, which was transformed with (*Z*)-OSu/NEt_3) to compound **27** in 84% overall yield (three steps). Selective hydrolysis of the *N*,*O*-acetal using ethylene glycol/CSA (THF, 50 °C, 2 days) and final oxidation of the amino alcohol was best accomplished with TEMPO/NaOCl/$NaClO_2$ to give the desired carboxylic acid **28**. The absolute configuration of product **1a** was established to be (2*S*,4*R*) by subsequent transformation into the known *γ*-lactone **29** (Scheme **5**).

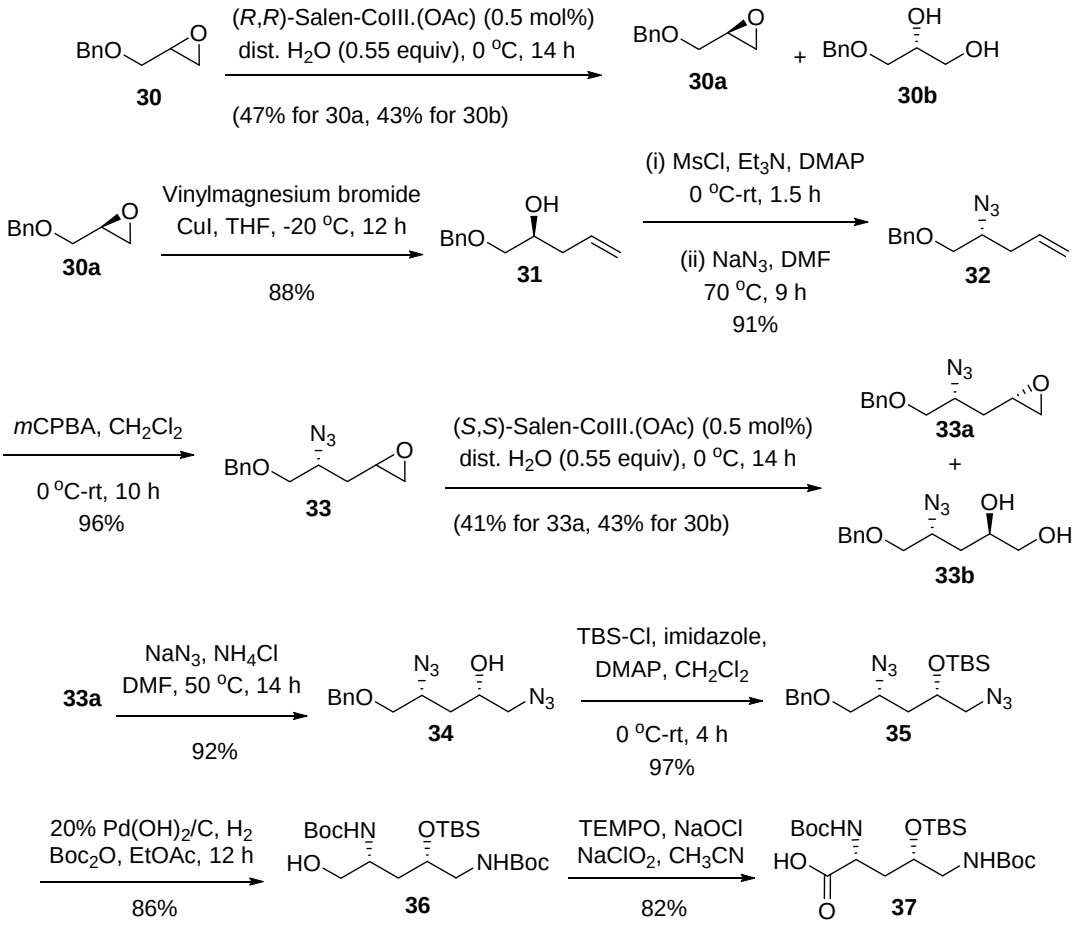


Scheme 5. Synthesis of 4-hydroxyornithine (Painter method)

Kumar *et al.* (2005)[13d]

Our own group synthesized protected (2*S*,4*R*)-4-Hydroxyornithine **1a** starting from racemic epoxide **30**. Racemic benzyl glycidol **30** was subjected to Jacobsen's HKR using (*R*,*R*)-Salen-Co^{III}.OAc as the catalyst to give enantiomerically pure epoxide **30a** which was was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **31**. Compound **31** was then converted into its *O*-mesyl derivative, which on treatment with sodium azide in dry DMF furnished azide **32** with the desired inverted stereochemistry. Compound **32** was then subjected to *m*-CPBA epoxidation, and racemic epoxide was again subjected to Jacobsen's HKR to afford chiral epoxide **33a** and diol **33b**.

The ring opening of epoxide **33a** was carried out with NaN_3 to give the diazido alcohol **34** in (Scheme **7**). Hydroxyl protection of **34** with *tert*-butyldimethylsilyl chloride afforded the silyl ether **35** and Concomitant one-pot deprotection of benzyl group, reduction of both the azide groups and Boc protection of the resulting diamine was carried out with $H_2/Pd(OH)_2$, Boc_2O to give the alcohol **36**. Finally, amino alcohol **36** was oxidized with TEMPO/NaOCl/$NaClO_2$ to furnish the desired protected amino acid **37**.



Scheme 6. Synthesis of protected 4-hydroxyornithine (Kumar method)

2.2.3. Present work

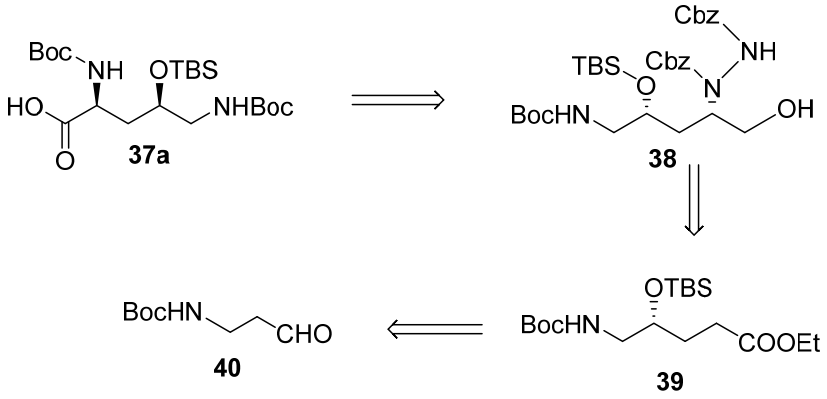
Objective

The stereoselective synthesis of 1,3-amino alcohol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-amino alcohol in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. Recently, we have developed an efficient approach to the asymmetric synthesis of 1,3-amino alcohols using sequential α-aminoxylation/α-amination and HWE olefination reaction catalysed by proline,[14] we further considered extrapolating the above knowledge to the synthesis of 4-hydroxyornithine. Herein we describe our efforts towards the synthesis of target molecule, 4-hydroxyornithine.

2.2.4. Results and discussion

In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis.[15] 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,[16] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[17] Proline is among the most successful secondary amine based organocatalysts which have 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 and asymmetric synthesis of 1,3-amino alcohol[14] we have accomplished the synthesis of (2*S*,4*R*)-4-hydroxyornithine, employing sequential α-aminoxylation HWE olefination reaction and α-amination reaction catalyzed by proline.

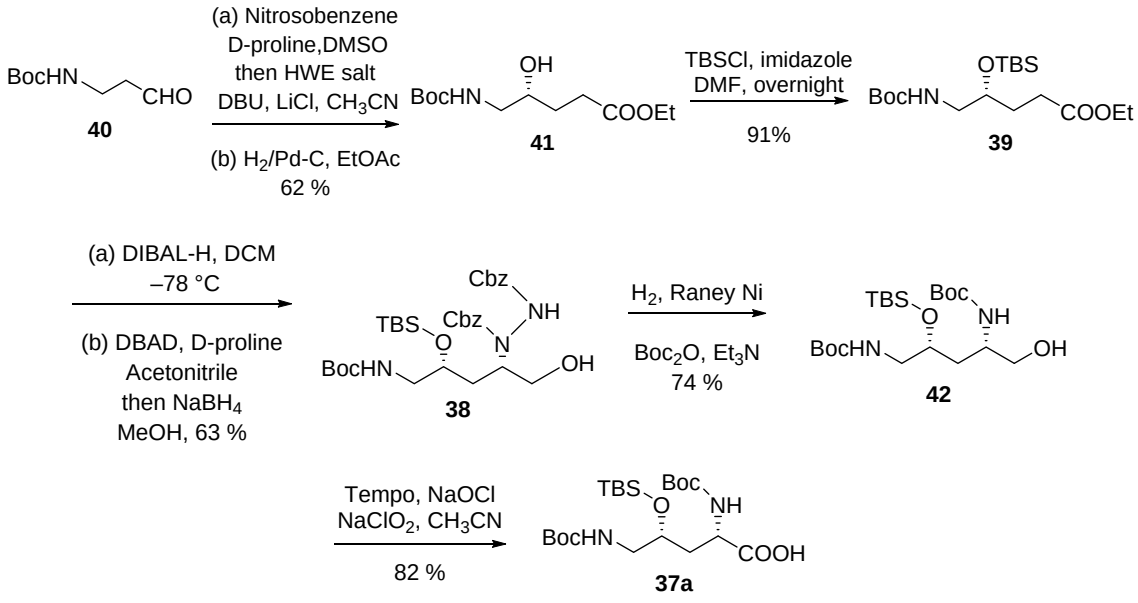


Scheme 7. Retrosynthetic route for the synthesis of (2*S*,4*R*)-4-hydroxyornithine

Our synthetic approach for the synthesis of (2*S*,4*R*)-4-hydroxyornithine is envisioned via the retrosynthetic route shown in the Scheme **7**. Protected (2*S*,4*R*)-4-Hydroxyornithine **37a** was thought to be synthesized from alcohol **38**, which in turn could be synthesized from γ-hydroxy ester **39** by α-amination. γ-hydroxy ester **39** could be easily obtained by the sequential α-aminoxylation and HWE olefination of the corresponding aldehyde **40**.

Thus our synthetic strategy for the synthesis of protected (2*S*,4*R*)-4-hydroxyornithine **37a** started from the commercially available aldehyde **40**. 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 triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **41** in 62% yield and >95% ee.[18] The free hydroxy group of γ-hydroxy esters **41** was protected as TBS ether using TBSCl in DMF to furnish compound **39** in 91% yield. Disappearance of peak at 3446 cm^{-1} in IR spectrum confirmed the formation of **39**. The DIBAL-H reduction of ester **39** at –78 ^oC furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on treatment with $NaBH_4$ in ethanol afforded the substituted hydrazine **38** in 63% yield (over three steps) and 88:12 diastereomeric ratio which was determined by HPLC analysis. Both the diastereomers can be separated using flash column chromatography. The *N*-*N*-bond of diastereomerically pure substituted hydrazine **38** was easily cleaved under hydrogenation condition using freshly prepared Raney-Ni at 60 psi of H_2 and free amine was subsequently converted into its Boc derivative using Boc_2O to furnish 1,3-aminoalcohol **42** in 74% yield. Disappearance of Cbz peak at δ 7.22 as multiplate in ^1H NMR spectrum confirmed the formation of product. Finally amino-alcohol **42** was oxidized with TEMPO/NaOCl/$NaClO_2$ to furnish the desired protected amino acid **37a** in 82% yield (scheme **8**).



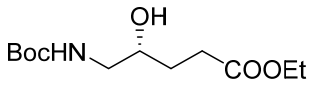
Scheme 8. Synthesis of (2*S*,4*R*)-4-hydroxyornithine

2.2.5. Conclusion

In conclusion, we have developed a short approach to protected (2*S*,4*R*)-4-hydroxyornithine in high enantio- and diastereomeric excess using proline catalysed sequential α-aminoxylation and HWE olefination reaction and α-amination reaction of an aldehydes as the key step. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the proline in the α-aminoxylation/α-amination step. The target compound **37a** has been synthesized from **40** in 5 steps and in 21.57% overall yield. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other stereoisomers.

2.2.6. Experimental Section

Ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-hydroxypentanoate (41):



To a solution of aldehyde **40** (2.0 g, 11.6 mmol) and nitroso benzene (1.236 g, 11.6 mmol) in anhydrous DMSO (25 mL) was added D-proline (0.532 g, 4.62 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to orange red during this time), then cooled to 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (4.60 mL, 23.2 mmol), DBU (3.45 mL, 23.2 mmol) and LiCl (0.978 g, 23.2 mmol) in CH_3CN (25 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 (50 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 crude γ-hydroxy ester **3**. The crude product was then purified by using silica gel flash column chromatography using pet ether: EtOAc

(3:1) as eluent to give ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-hydroxypentanoate **41** as a colorless liquid.

Yield: 1.871 g, 62%

Mol. Formula: $C_{12}H_{23}NO_5$

$[\alpha]_D^{25}$: - 12.50 (*c* 1.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 2981, 1708, 1513, 1168.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.7 Hz, 3H), 1.42 (s, 9H), 1.71-1.84 (m, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 3.00-3.10 (m, 1H), 3.22-3.32 (m, 1H), 3.64-3.74 (m, 1H), 4.12 (q, *J* = 7.7 Hz, 2H), 5.03 (brs, 1H) ppm.

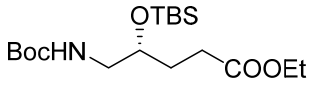
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 28.2, 29.3, 30.4, 46.4, 60.5, 70.6, 79.5, 156.8, 174.1 ppm.

MS (ESI): m/z 284.09 $(M+Na)^+$

Elemental analysis: Calcd. C, 55.16; H, 8.87; N, 5.36; Found C, 55.31; H, 8.75; N, 5.28.

The enantiomeric excess (ee) was determined by converting alcohol **41** into the Mosher ester and analyzing the ^{19}F NMR spectrum. The ee was found to be > 96%.

Ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)pentanoate (39):



To an ice-cold stirred solution of **41** (1.0 g, 3.83 mmol) in DMF (8 mL) were added imidazole (0.326 g, 4.79 mmol) and TBSCl (0.718 g, 4.79 mmol) at room temperature. The resulting mixture was stirred for 6 h at 0 °C before H_2O (15 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 25 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: 9:1) of the crude product gave ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy) pentanoate **39** as a colorless liquid.

Yield: 1.31 g, 91%

Mol. Formula: $C_{18}H_{37}NO_5Si$

$[\alpha]_D^{25}$: + 3.44 (*c* 1.16, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2956, 1712, 1505, 1216.

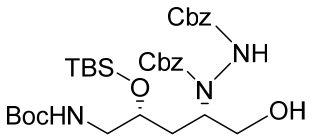
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.24 (t, J = 7.4 Hz, 3H), 1.43 (s, 9H), 1.71-1.81 (m, 2H), 2.35 (t, J = 8.2 Hz, 2H), 3.02-3.14 (m, 2H), 3.74-3.85 (m, 1H), 4.11 (q, J = 7.4 Hz, 2H), 4.75 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -3.8, 13.98, 17.8, 25.6, 28.2, 29.4, 30.4, 45.4, 60.1, 69.9, 78.9, 155.8, 173.3 ppm.

MS (ESI): m/z 398.17 $(M+Na)^+$

Elemental analysis: Calcd. C, 57.56; H, 9.93; N, 3.73; Found C, 57.34; H, 9.98; N, 3.81.

Dibenzyl 1-((2*S*,4*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (38):



To a solution of ethyl ester **39** (2.0 g, 5.33 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (6.65 mL 2.25 M solution in toluene, 6.66 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (10 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 25 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (1.323 g, 4.44 mmol) and D-proline (0.049 g, 8 mol%) in CH_3CN (44 mL) at 0 °C was added above aldehyde (2.0 g, 5.33 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. Then reaction mixture was cooled to 0 ^oC, treated with ethanol (10 ml) and $NaBH_4$ (0.25 g) and was stirred for 5 min at 0 ^oC. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product (diastereomeric ratio/ 88:12). Silica gel column chromatography (petroleum ether: ethyl acetate: 60:40) of the crude product gave dibenzyl 1-((2*S*,4*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate **38** as a colorless syrupy liquid.

Yield: 2.122 g, 63%

Mol. Formula: $C_{32}H_{49}N_3O_8Si$

$[\alpha]_D^{25}$: - 9.56 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2956, 1712, 1505, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.91 (s, 9H), 1.45 (s, 9H), 1.58-1.61 (m, 2H), 2.79 (brs, 1H), 3.06-3.29 (m, 2H), 3.59-3.69 (m, 2H), 3.76-3.85 (m, 1H), 4.65-4.84 (m,1H), 4.93-5.24 (m, 4H), 7.20-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.7, 17.9, 25.8, 28.6, 31.8, 32.6, 53.3, 62.3, 62.5, 67.9, 71.8, 71.9, 79.7, 126.4, 127.8, 128.1, 128.5, 129.3, 135.3, 135.5, 135.9, 138.1, 138.3, 155.9, 156.5, 158.1, 158.6 ppm.

MS (ESI): m/z 654.43 $(M+Na)^+$

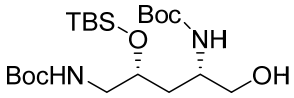
Elemental analysis: Calcd. C, 60.83; H, 7.82; N, 6.65; Found C, 60.70; H, 7.91; N, 6.57.

Diastereomeric ratio was determined by HPLC analysis; 88: 12 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 90:10; t_R for (*anti*)-isomer = 12.46 min and t_R for (*syn*)-isomer = 14.55 min.

Di-*tert*-butyl ((2*R*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-5-hydroxypentane-1,4-diyl)dicarbamate (42):



The solution of dibenzyl 1-((2*S*,4*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate **38** (2.0 g, 3.17 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 (0.87 mL, 6.3 mmol) and Boc anhydride (1.1 mL, 4.76 mmol) 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 10 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 di-*tert*-

butyl ((2*R*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-5-hydroxypentane-1,4-diyl)dicarbamate **42** as a viscous liquid.

Yield: 1.04 g, 74%

Mol. Formula: $C_{21}H_{44}N_2O_6Si$

[α]$^{25}_{D}$: - 20.3 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3390, 3020, 2958, 2931, 2858, 1737, 1643, 1521, 1394, 1216.

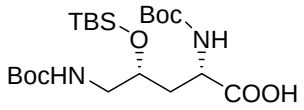
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6 H), 0.91 (s, 9 H), 1.43 (s, 18 H), 1.59-1.71 (m, 2 H), 3.17 (t, J = 5.6 Hz, 2 H), 3.60-3.96 (m, 4 H), 4.78 (brs, 1 H), 5.24 (brs, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.6, 17.9, 25.8, 28.3, 35.6, 50.0, 63.4, 68.7, 79.5, 156.1 ppm.

MS (ESI): m/z 471.18 $(M+Na)^+$

Elemental analysis: Calcd. C, 56.22; H, 9.88; N, 6.24%; Found: C, 56.35; H, 9.69; N, 6.28%.

(2*S*,4*R*)-2,5-Bis((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)pentanoic acid (37a):



A catalytic amount of TEMPO (4 mg, 0.02 mmol) was added to a solution of alcohol **42** (100 mg, 0.22 mmol) in MeCN (2 mL) and sodium phosphate buffer pH 6.7 (1 mL). The mixture was heated to 35 ^oC, 2.0 M $NaClO_2$ (0.5 mL) and diluted bleach (100 μl, 0.006 mmol free chlorine) were added simultaneously over 1 h (**Caution** ! Do not mix bleach and $NaClO_2$ before being added to the reaction mixture). The reaction mixture was stirred at 35 ^oC for another 4.5 h then cooled to room temperature, H_2O (5 mL) was added and the pH was adjusted to 8-9 with 4M NaOH. Then the mixture was poured into cold 0.5 Na_2SO_3 (10 mL). After 30 min the mixture was extracted with EtOAc (3 x 10). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude reaction product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 6:4 + 0.5 % HOAc) to afford **37a** as a thick syrup liquid.

Yield: 84 mg, 82%

Mol. Formula: $C_{21}H_{42}N_2O_7Si$

[α]$^{25}_{D}$: - 38.36 (*c* 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3346, 2910, 1716, 1453.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.45 (s, 18H), 1.73-1.79 (m, 2H), 3.07-3.28 (m, 1H), 3.55-3.80 (m, 1H), 3.90-4.11 (m, 2H), 5.59 (brs, 1H), 5.74 (brs, 1H) ppm.

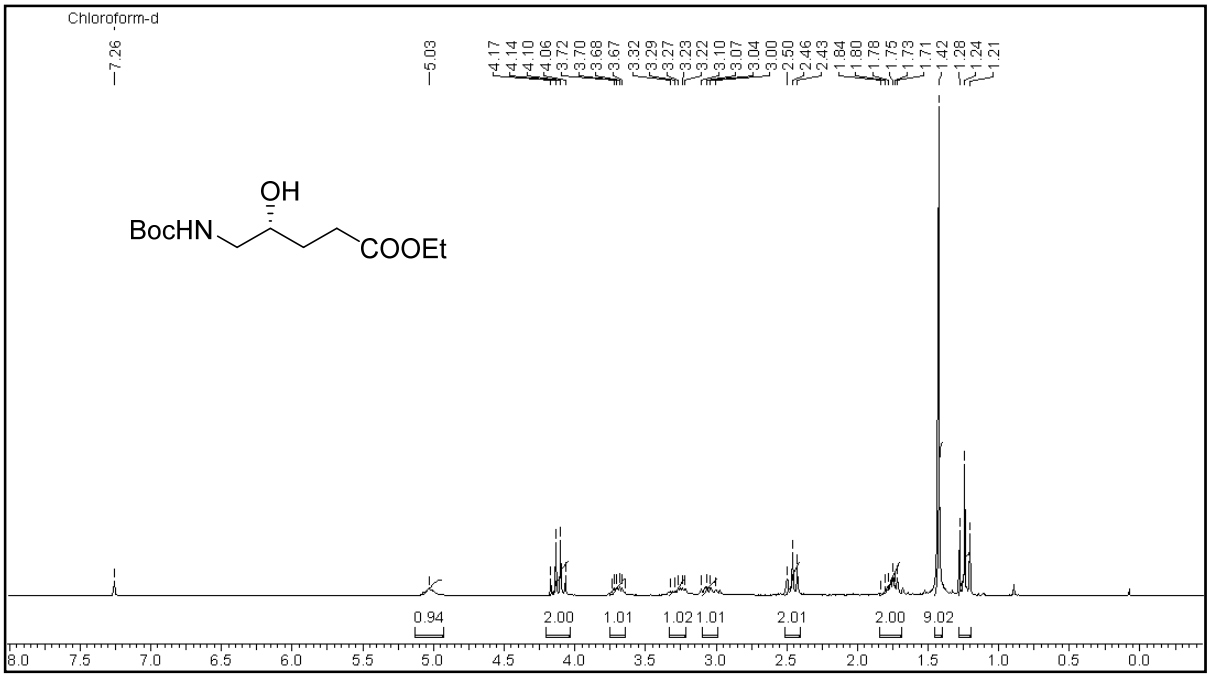
^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.7, 14.1, 18.0, 22.7, 25.7, 28.3, 31.9, 42.5, 65.2, 66.4, 80.4, 163.3 ppm.

MS (ESI): m/z 485.21 $(M+Na)^+$

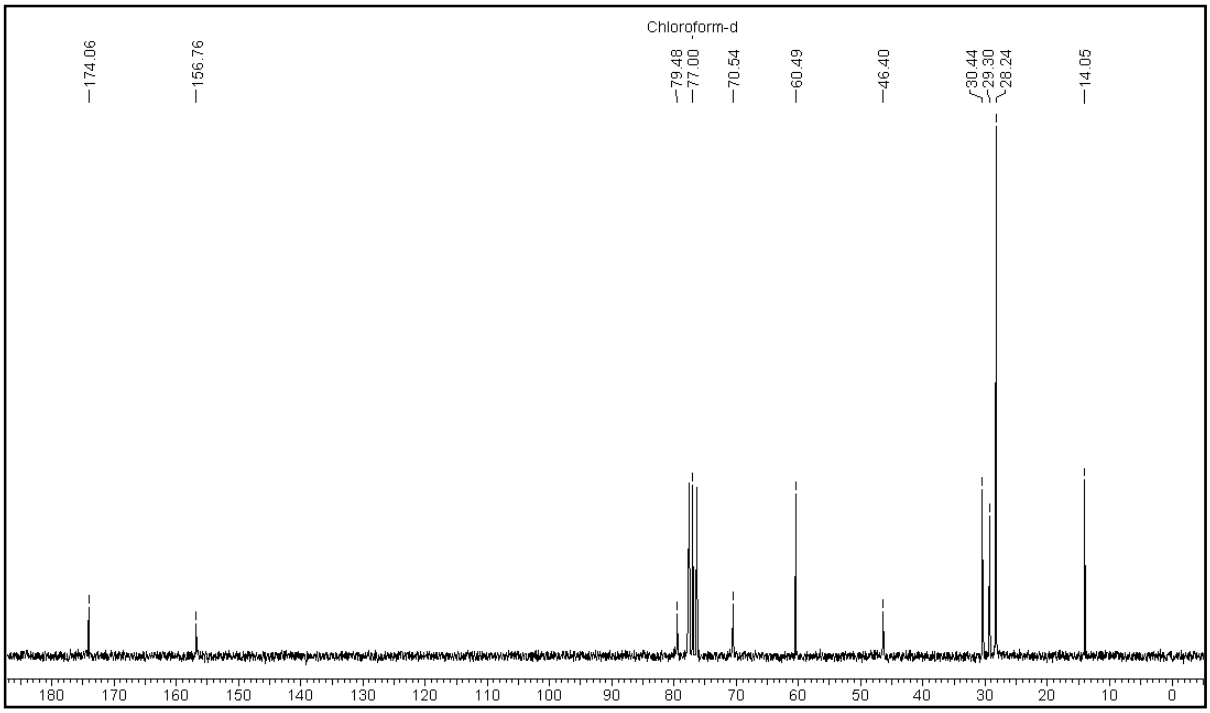
Elemental analysis: Calcd. C, 54.52; H, 9.15; N, 6.05%; Found: 54.25; H, 9.37; N, 5.75%.

2.2.7. Spectra

Ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-hydroxypentanoate (41):

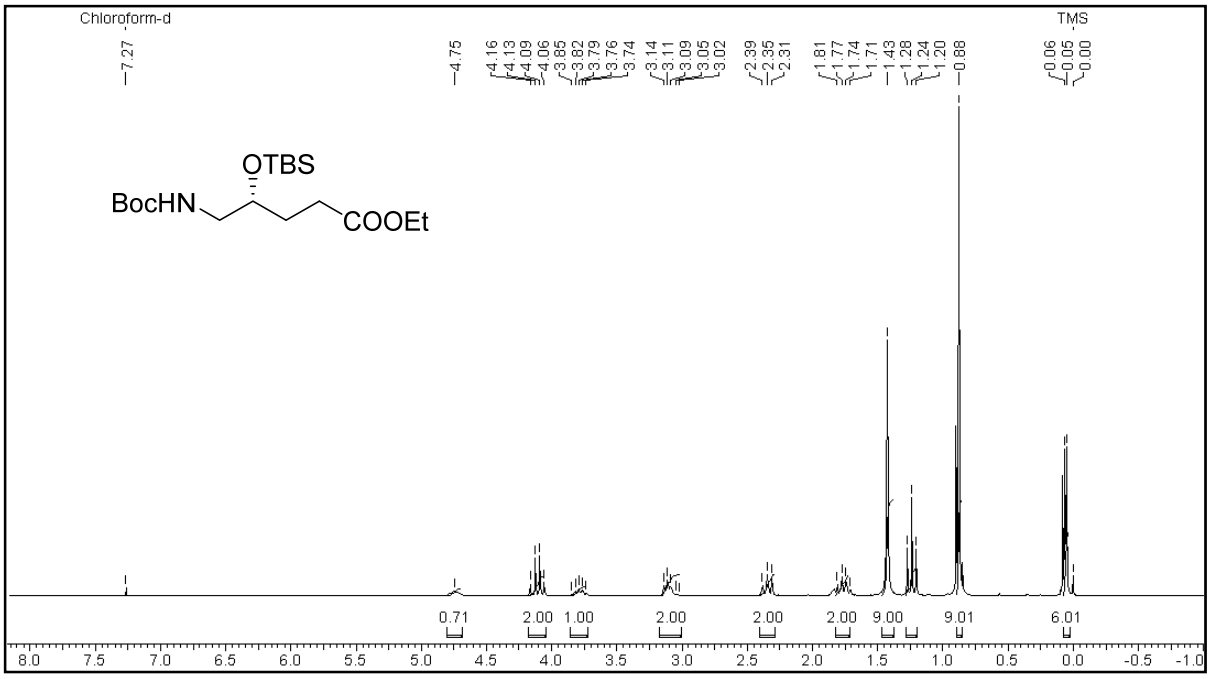


➢ **^{1}H NMR of the compound 41 in $CDCl_3$**

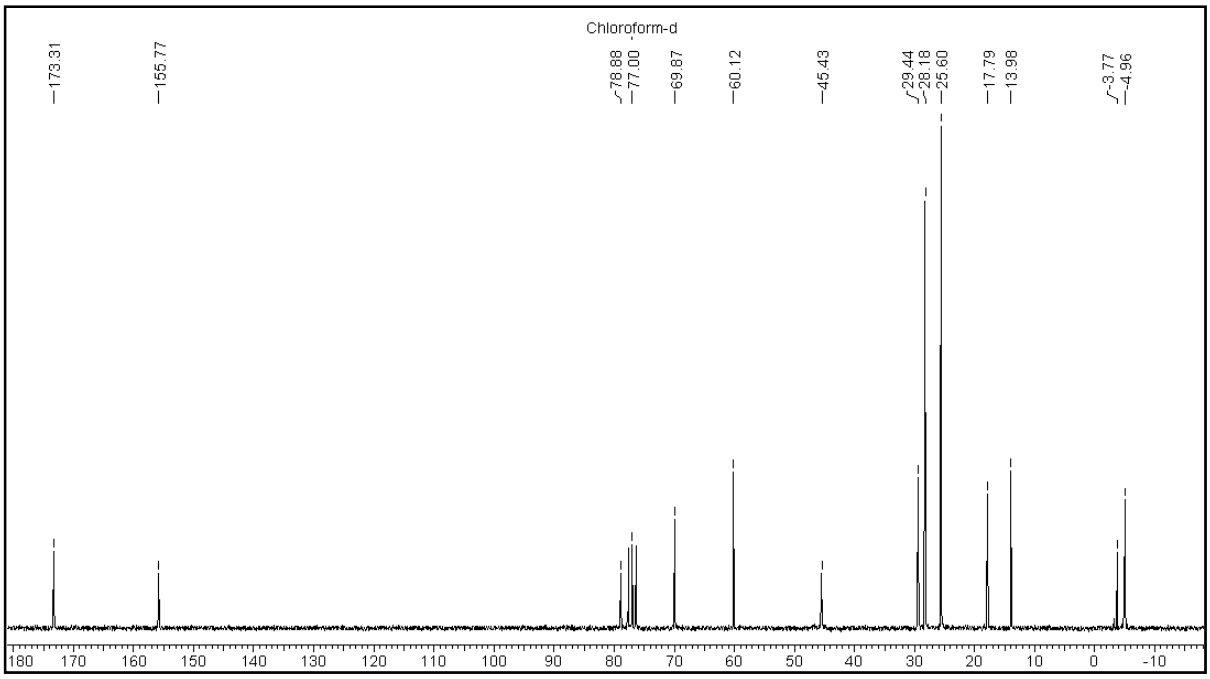


➢ **^{13}C NMR of the compound 41 in $CDCl_3$**

Ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)pentanoate (39):

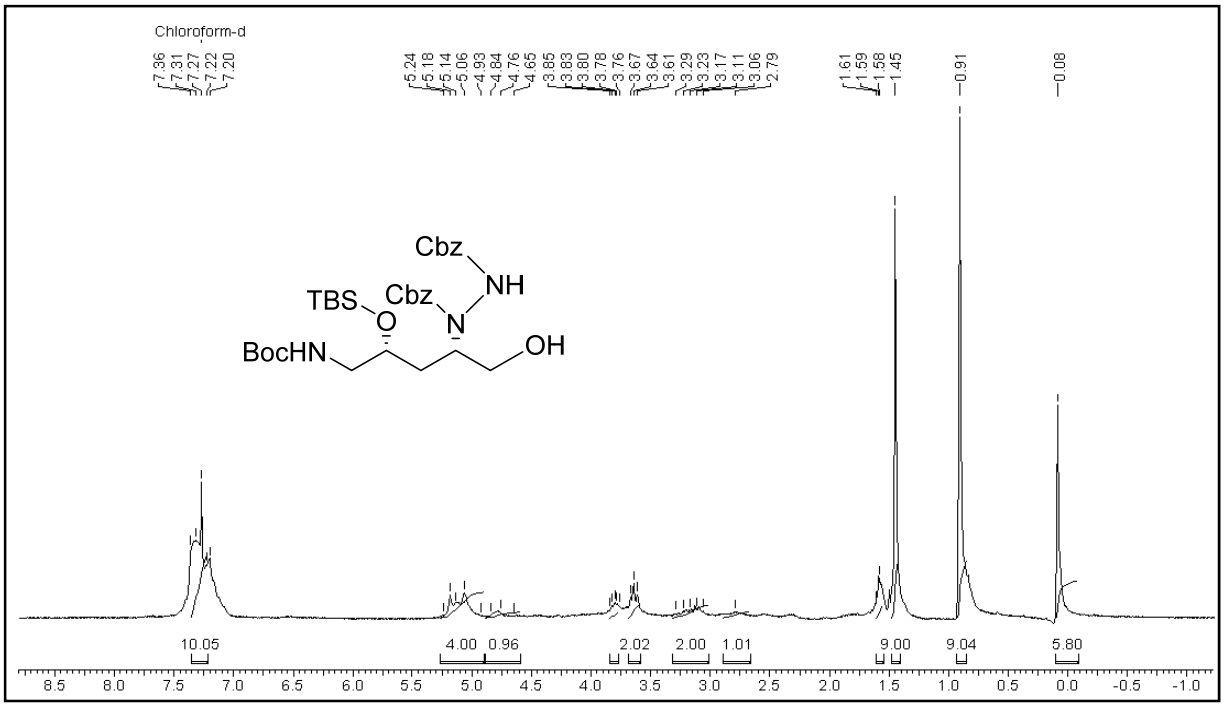


➢ **^{1}H NMR of the compound 39 in $CDCl_3$**

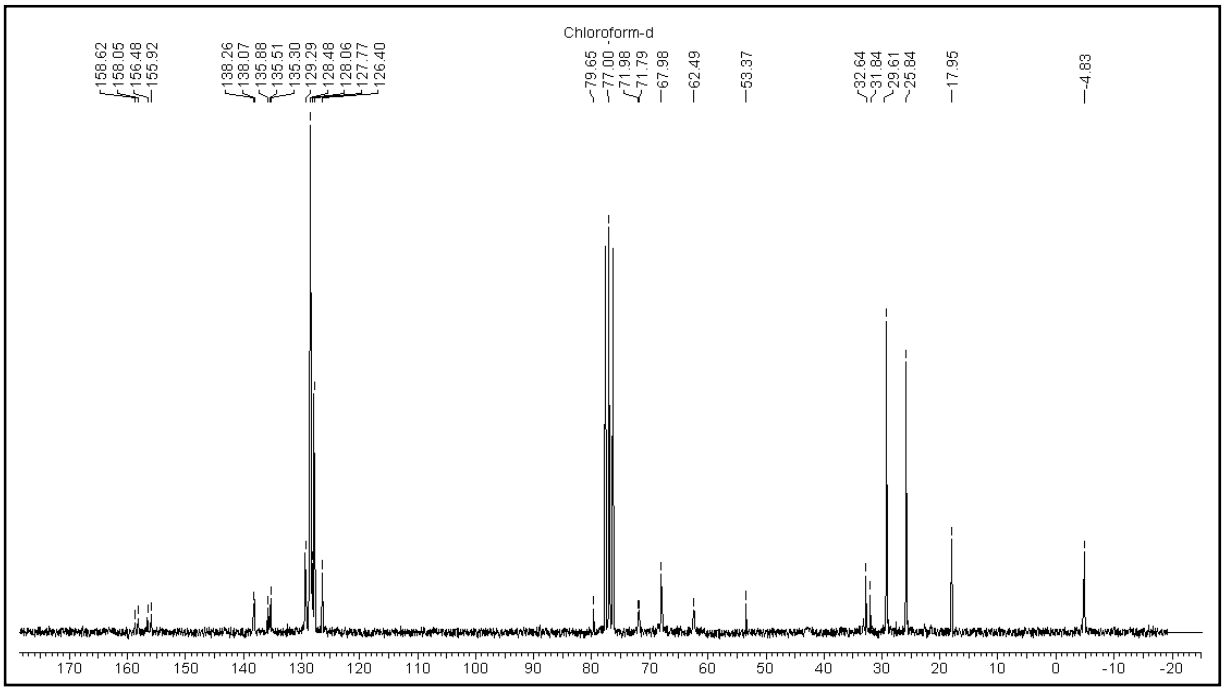


➢ **^{13}C NMR of the compound 39 in $CDCl_3$**

Dibenzyl 1-((2*S*,4*R*)-5-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (38):

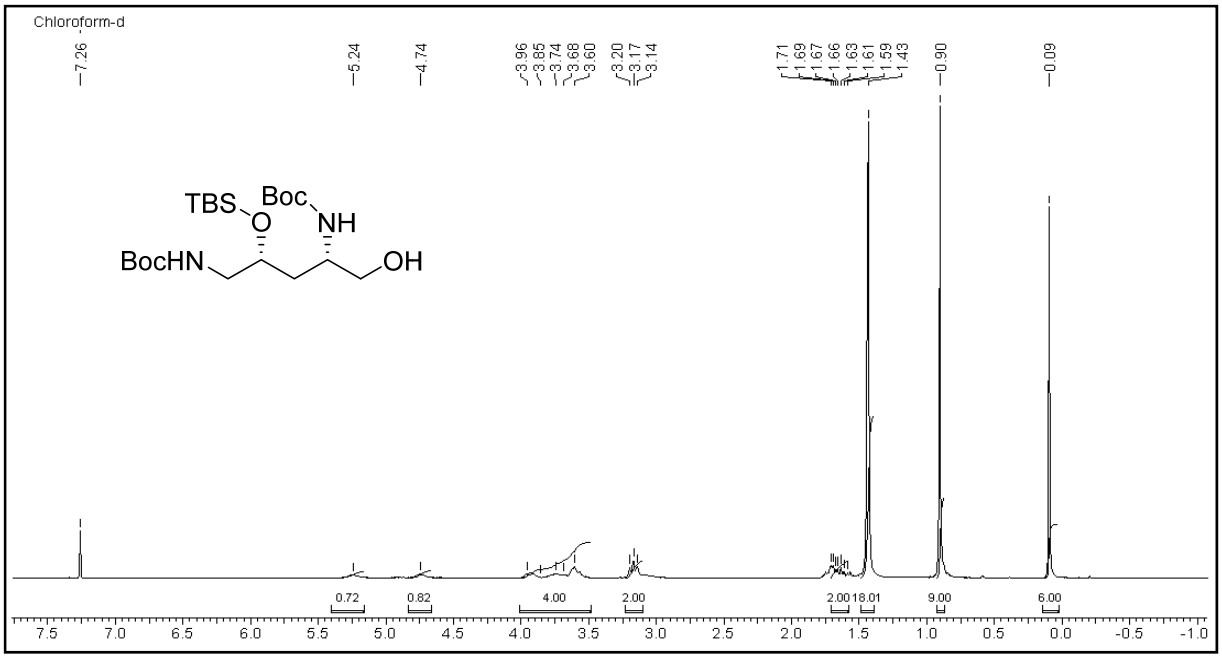


➢ **^{1}H NMR of the compound 38 in $CDCl_3$**

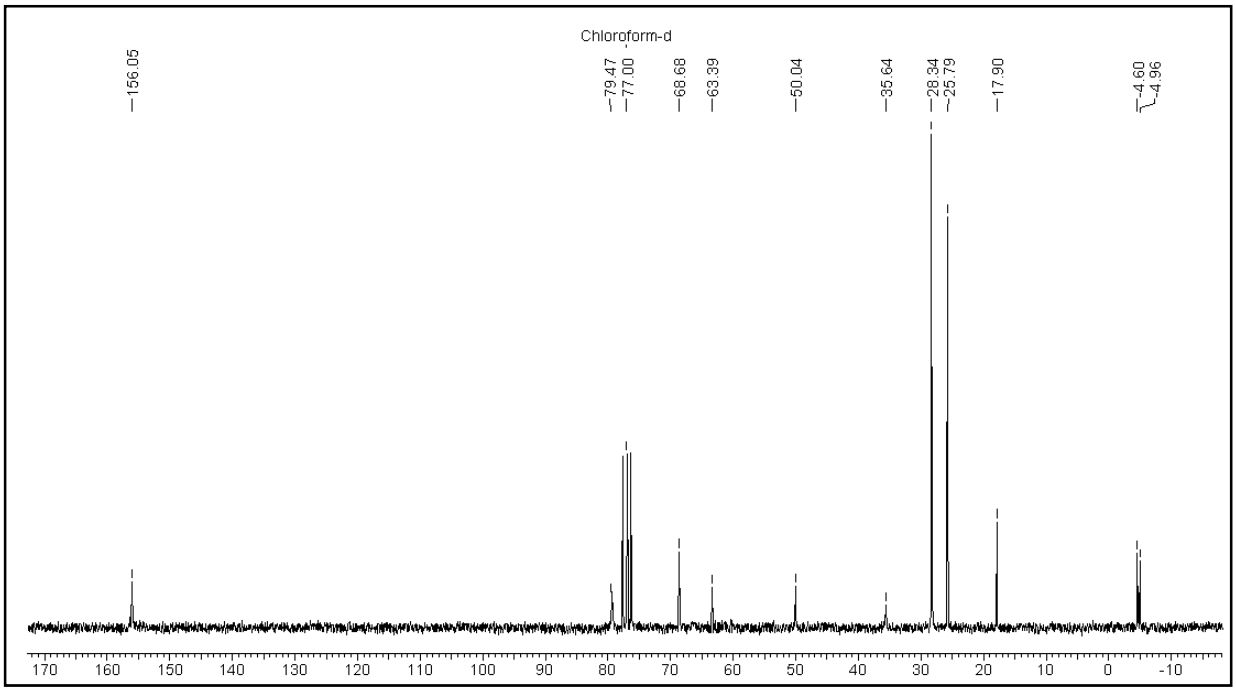


➢ **^{13}C NMR of the compound 38 in $CDCl_3$**

Di-*tert*-butyl ((2*R*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-5-hydroxypentane-1,4-diyl)dicarbamate (42):

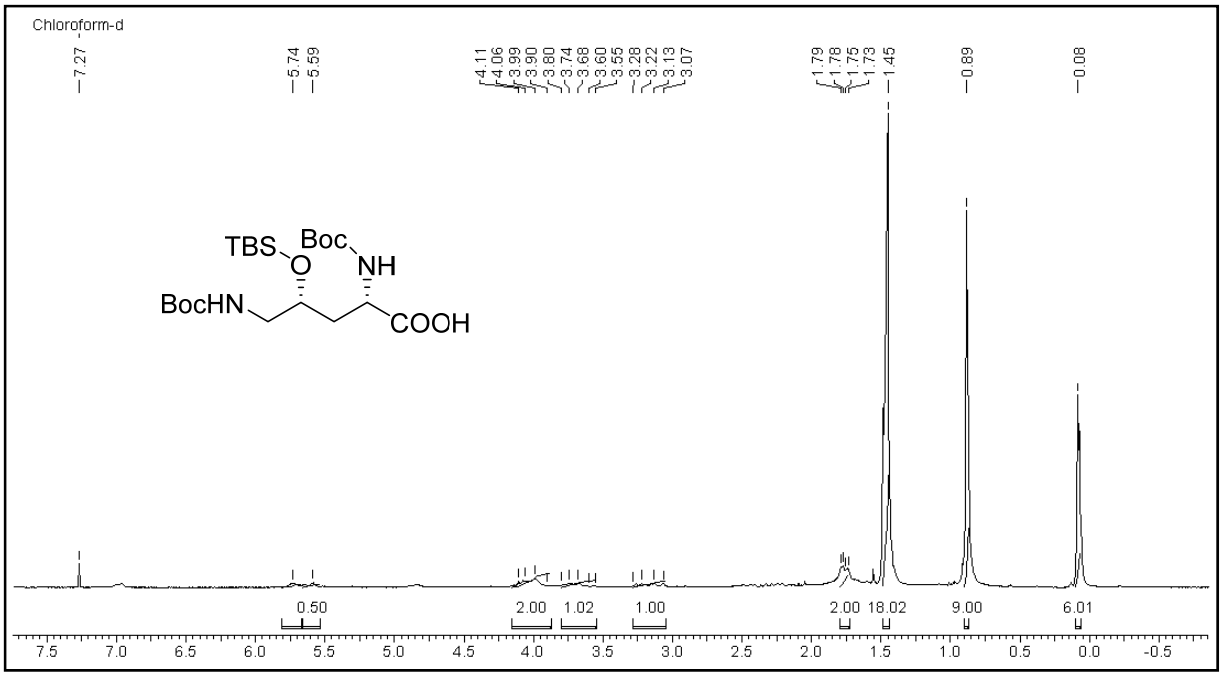


- **^{1}H NMR of the compound 42 in $CDCl_3$**

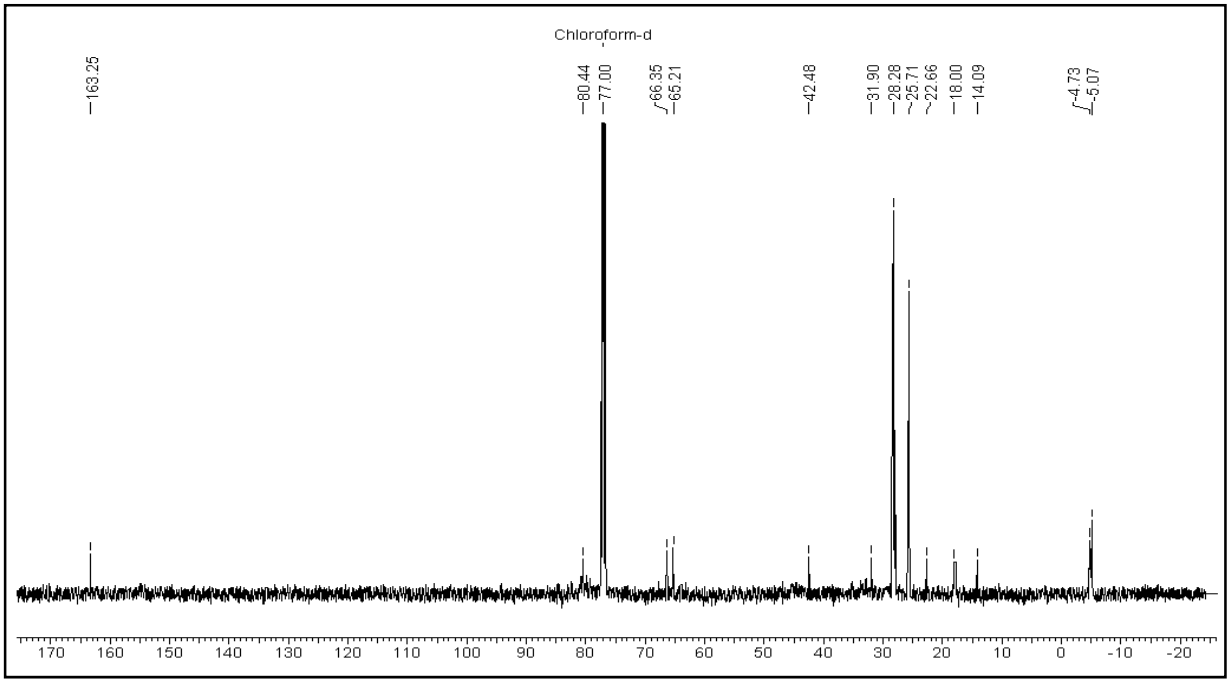


- **^{13}C NMR of the compound 42 in $CDCl_3$**

(2*S*,4*R*)-2,5-Bis((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)pentanoic acid (37a):

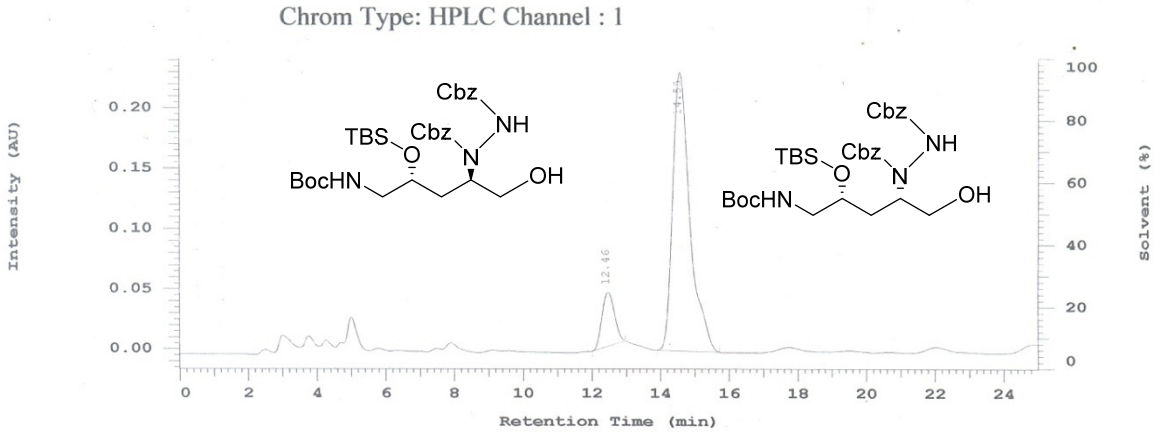


➢ **^{1}H NMR of the compound 37a in $CDCl_3$**



➢ **^{13}C NMR of the compound 37a in $CDCl_3$**

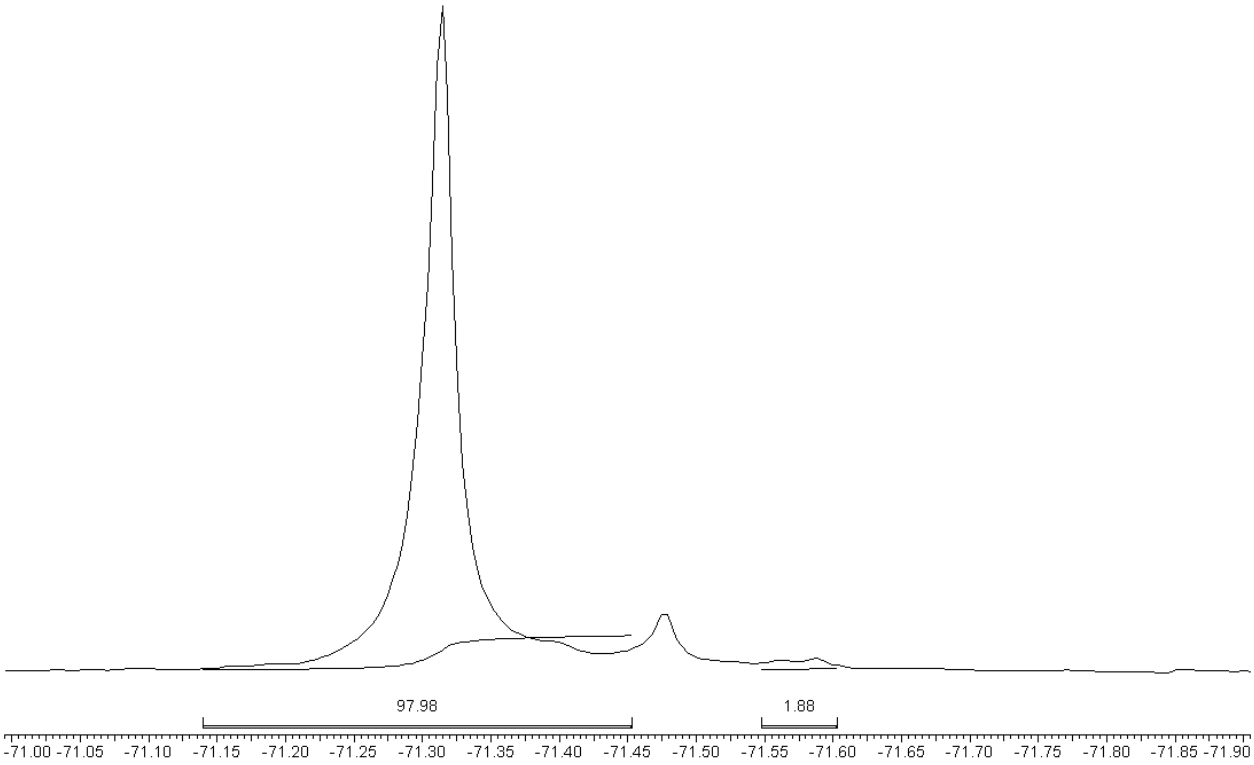
Diastereomeric ratio of *syn*-compounds 38



No.	RT	Height	Area	Area %
1	12.46	22534	564580	12.289
2	14.55	115471	4029770	87.711
		138005	4594350	100.000

Peak rejection level: 0

^{19}F spectrum of Mosher ester 43:



2.2.8. References

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18. The enantiomeric excess (ee) was determined by derivatizing its precursor α,β-unsaturated-γ-hydroxy ester with Mosher's acid and analyzing the ^{19}F NMR spectrum. The ee was found to be > 96%.

Chapter-3

Application of 1,3-amino alcohols towards synthesis of natural occurring piperidine and pyrrolidine alkaloids

3.1. SECTION A

Total synthesis of (-)-Halosaline and Formal synthesis of Tetraponerine alkaloids T-4 and Elaeocarpus Alkaloid (+)-Elaeokanine-A and (±)-Elaeokanine-C using Proline-Catalyzed Organic Transformations

3.1.1. Introduction

Piperidine ring system is frequently found as a key structural component in a variety of naturally occurring alkaloids, which display a wide range of biologically and pharmacological activity.[1] Considering their potent biological activity and less abundance, substituted piperidine ring system always remains an area of considerable synthetic interest[2] in the field of asymmetric synthesis and still it is highly desirable to devise diverse and efficient synthetic route for the asymmetric approach to these classes of compounds.

(-)-Halosaline **1**, a 2-(2-hydroxy substituted)-piperidine was isolated from *Haloxylon salicornicum*.[3] (-)-8-Epi-halosaline **2**, a diastereomer of (-)-halosaline, was isolated from *Andrachne aspera spreng*,[4] a small perennial under shrub commonly found in Karachi. Tetraponerines T-4 **3** were isolated from the venom of a New Guinean ant *Tetraponera sp.*[5] Elaeocarpus alkaloids elaeokanine A **4** and C **5** were isolated from *Ekaeocarous kaniensis Schltr*.,[6] a large rain-forest tree found in New Guinea (Fig **1**).

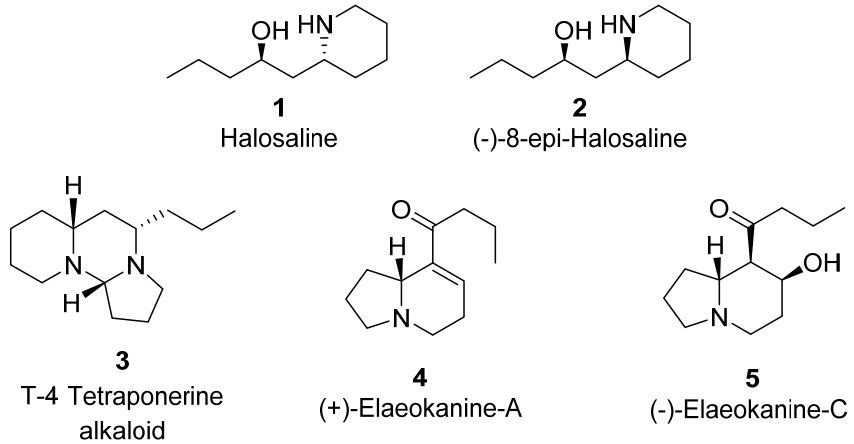


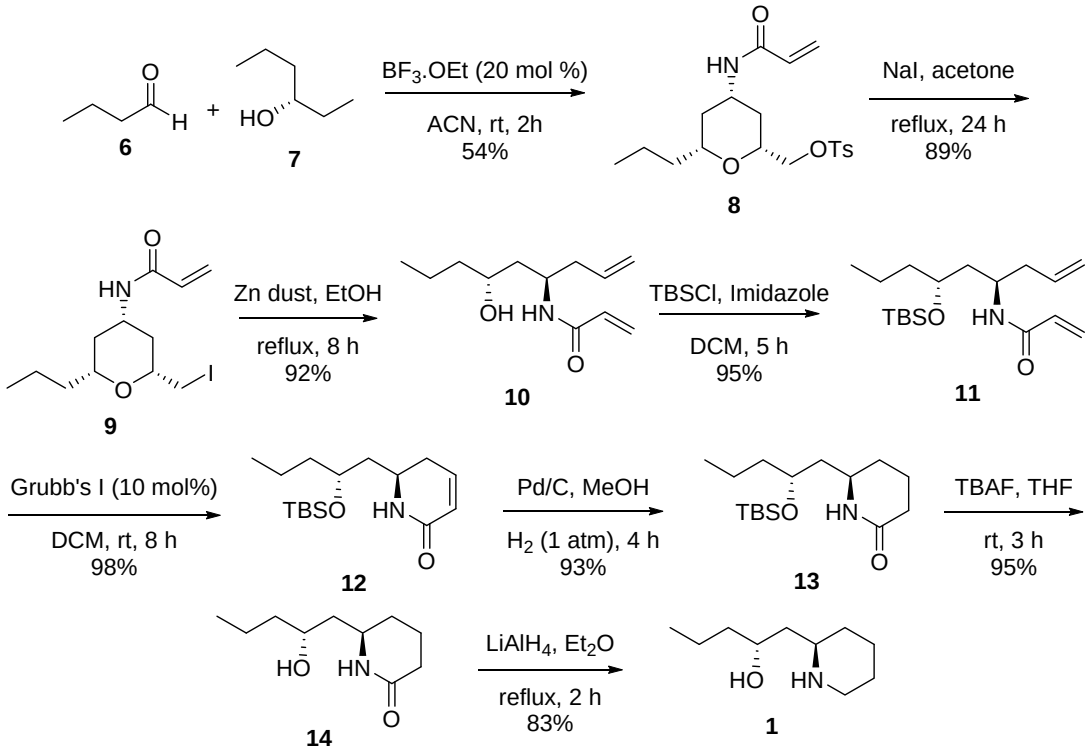
Figure 1.

3.1.2. Review of Literature

There are several reports on the synthesis of (-)-halosaline, in the literature.[7] So far nine asymmetric synthesis of (-)-Halosaline is reported. A detailed report of recent syntheses is described below.

Yadav *et al.* (2013)[7a]

J. S. Yadav and co-workers synthesized (-)-halosaline starting from chiral homoallylic alcohol **7** which on treatment with butyraldehyde **6** under Prins-Ritter conditions afforded the trisubstituted tetrahydropyran **8**. Treatment of compound **8** with NaI in refluxing acetone gave the corresponding iodide **9** which on reductive ring opening using Zn in refluxing ethanol afforded the *anti*-1,3-aminoalcohol **10**. The hydroxyl group of **10** was then protected as its TBS



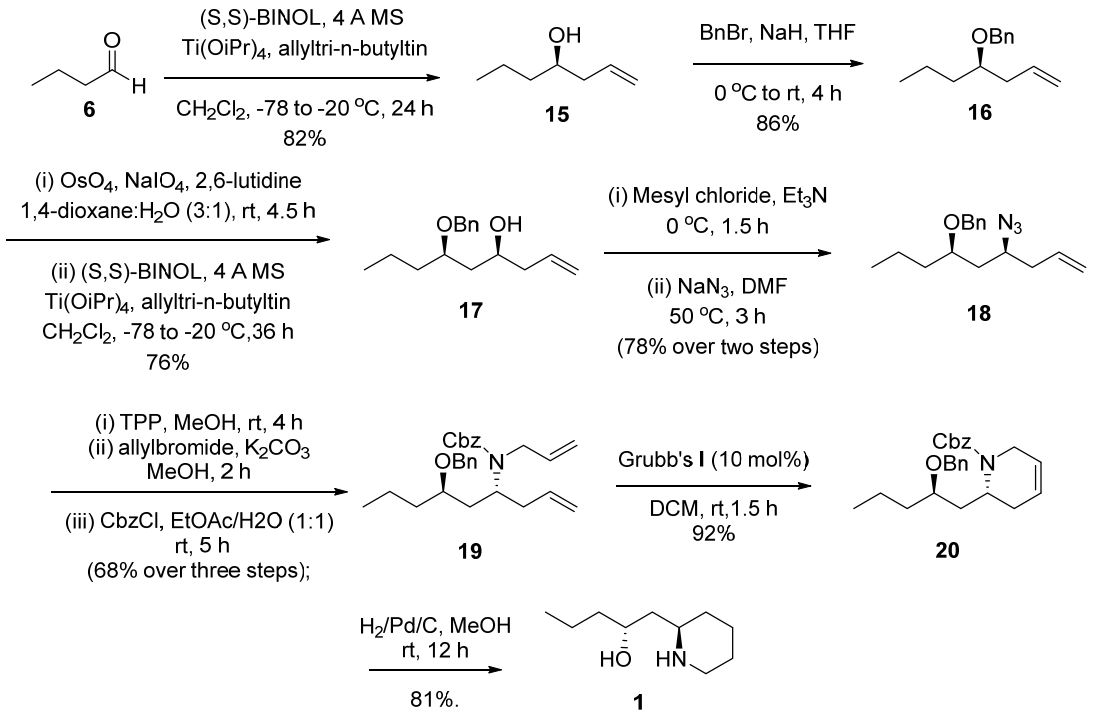
Scheme 1. Synthesis of (-)-halosaline (Yadav method)

ether **11**. Compound **11** was then subjected to ring-closing metathesis using Grubb's I catalyst (10 mol %) in DCM to furnish the α,β-unsaturated-δ-lactam **12** which on hydrogenation using palladium on carbon in methanol gave the δ-lactam **13**.

Deprotection of silyl ether **13** with TBAF in THF gave the desilylated δ-lactam **14** which on reduction with $LiAlH_4$ in refluxing Et_2O gave the target molecule (-)-halosaline **1** (Scheme **1**).

Radha Krishna *et al.* (2012)[7b]

Radha Krishna and co-workers synthesized (-)-halosaline starting from *n*-butyraldehyde **6** which on asymmetric Keck allylation reaction afforded homoallylic alcohol **15**. Alcohol **15** was protected as its benzyl ether **16** and subsequently subjected to one-pot dihydroxylation followed by oxidative cleavage of diol to furnish the corresponding aldehyde, which on second asymmetric Keck allylation gave the homoallylic alcohols **17**. Alcohol 17 was protected as



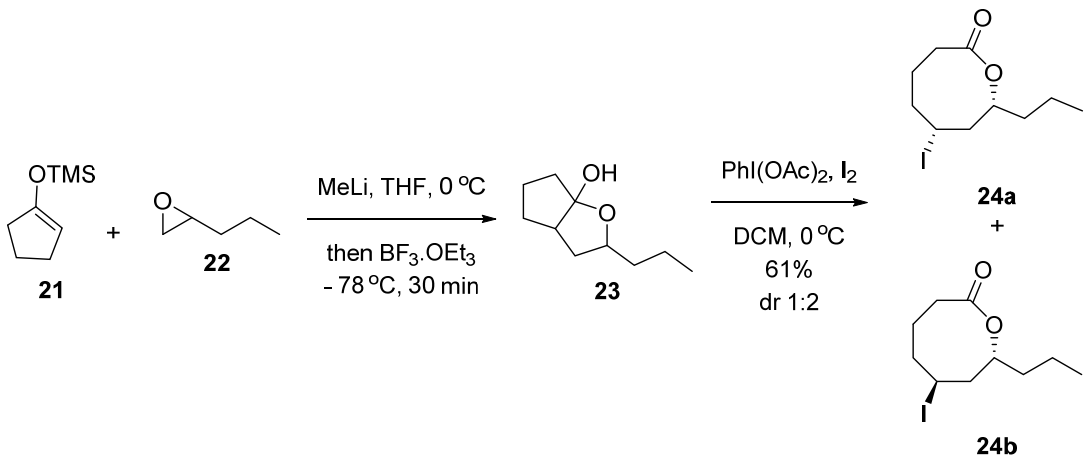
Scheme 2. Synthesis of (-)-halosaline (Radha Krishna method)

mesylate under conventional conditions which was subjected to azidation to afford homoallyl azide **18**. The azide **18** was converted to the corresponding N-allyl benzylcarbamate **19** via a two-step process; firstly to their amines using TPP in MeOH followed by allylation and later the second derivatization to afford **19** that was subsequently cyclized via ring-closing metathesis using Grubbs I catalyst (10 mol %) in

CH_2Cl_2 to furnish unsaturated piperidine carbamate **20**. Finally, natural products (-)-halosaline **1** was obtained by global deprotection of the protecting groups like benzyl ether and benzylcarbamate with simultaneous saturation of the double bond of unsaturated piperidine carbamates **20** (Scheme **2**).

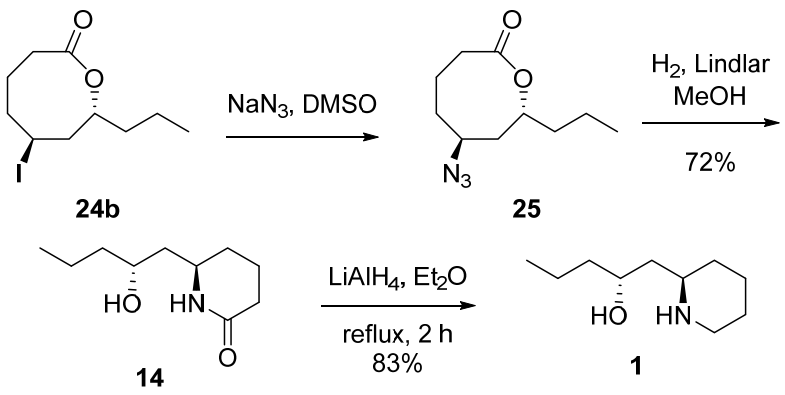
Posner *et al.* (2007)[7d]

Posner and co-workers synthesized (-)-halosaline using oxidative ring expansion reaction as key step. Thus synthesis starts with (cyclopentenyloxy)-trimethylsilane **21** which on treatment with MeLi and (*R*)-1,2-epoxypentane **22** gave hemi-ketal **23**. Hemi-ketal **23** on homologous Baeyer-Villiger ring expansion furnished iodolactone pairs of diastereomers **24a** and **24b**, which were easily separable by column chromatography (Scheme **3**).



Scheme 3. Cyclopentanone ring expansion reaction

Nucleophilic displacement of iodide **24b** with excess sodium azide in DMSO provided compound **25** with complete stereochemical inversion. Hydrogenation of azide **25** over Lindlar's catalyst results in O-to-N ring contraction to form regiospecifically monosubstituted δ-lactam **14**, which on reduction with $LiAlH_4$ in refluxing Et_2O gave the target molecule (-)-halosaline **1 (Scheme 4)**.



Scheme 4. Completion of synthesis of (-)-halosaline (Posner method)

3.1.3. Present work

Objective

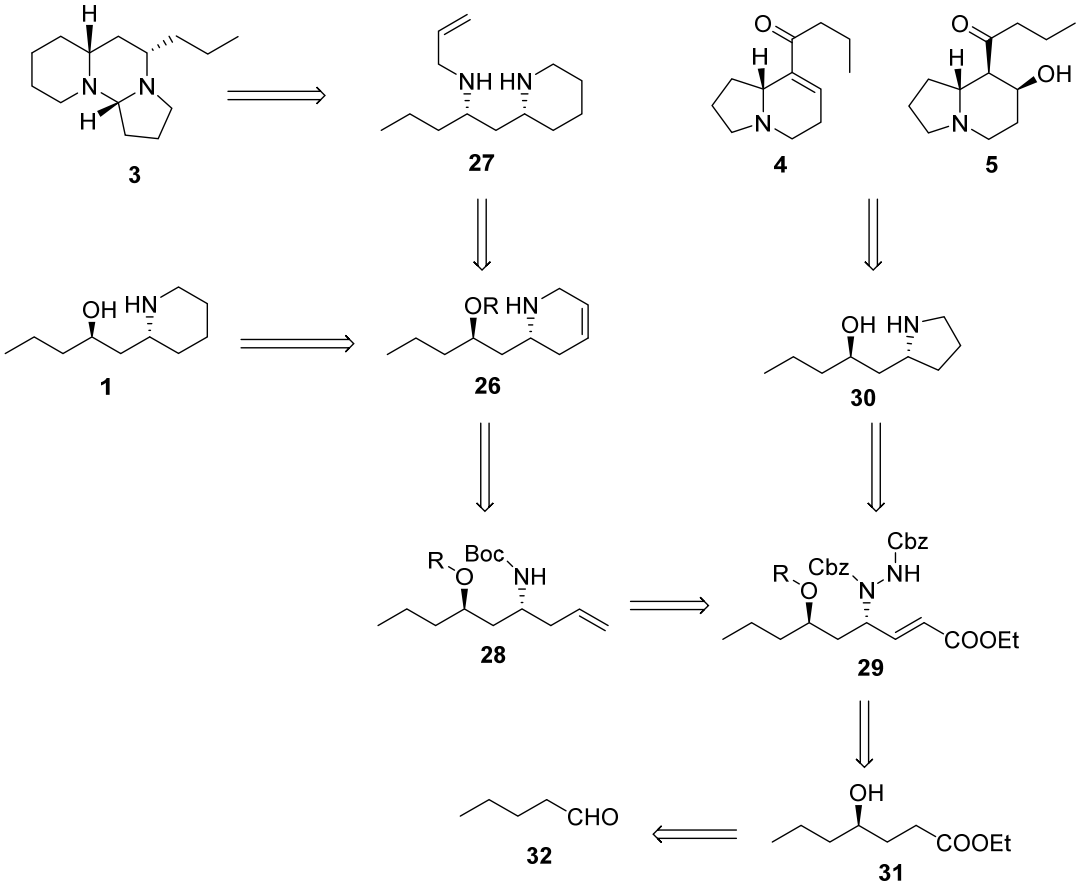
The stereoselective synthesis of 1,3-amino alcohol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-amino alcohol in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. Recently, we have developed an efficient approach to the asymmetric synthesis of 1,3-amino alcohols using sequential α-aminoxylation/α-amination and HWE olefination reaction catalyzed by proline.[8] In continuation of our interest on synthesis of biologically active natural products, we further considered extrapolating the above knowledge to the synthesis of alkaloids containing substituted piperidine ring.

3.1.4. Results and discussion

In recent years, there has been growing interest in the use of small organic molecules to catalyze organic reactions. As a result, the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[9] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[10] 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.[11] Similarly organocatalytic tandem reactions are characterized by high efficiencies and are in a way biomimetic. They avoid time consuming and costly protection/deprotection processes as well as the purification of

intermediates. They often proceed with excellent stereocontrol and are environmentally friendly.[12]

In continuation of our interest in organocatalysis and asymmetric synthesis of 1,3-amino alcohol, we have accomplished the syntheses of different alkaloids which contain substituted piperidine ring, employing sequential α-aminoxylation[13a-b]/α-amination[13c-d] reaction and HWE olefination reaction catalyzed by proline.

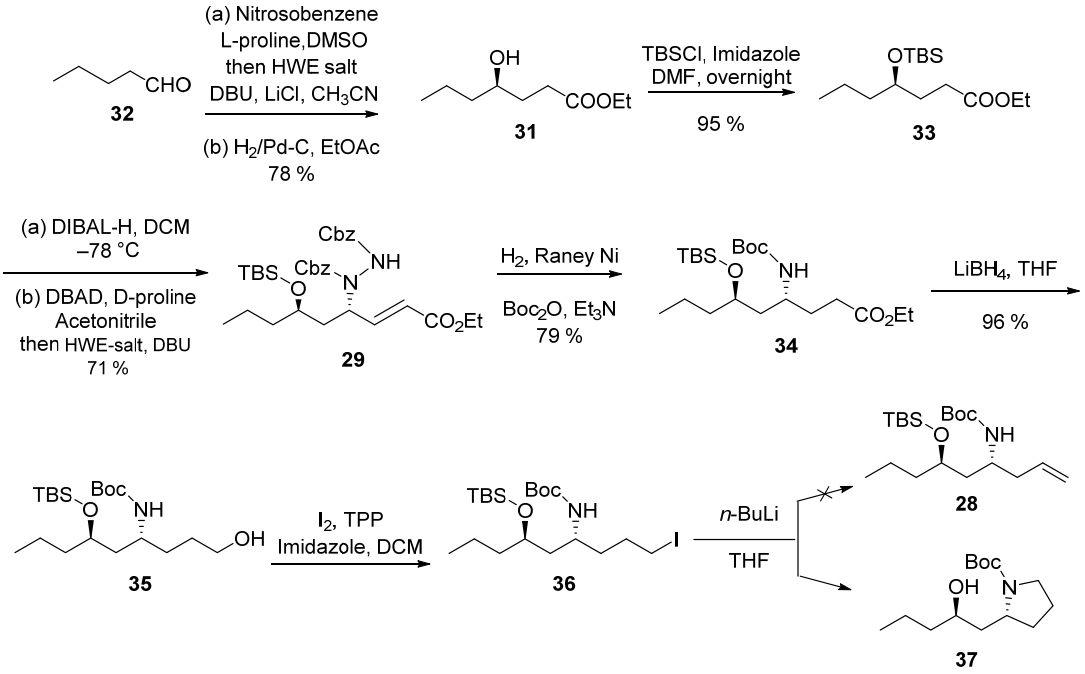


Scheme 5. Retrosynthetic route for synthesis of alkaloids containing substituted piperidine ring

Our synthetic approach was envisioned via the retrosynthetic route shown in the Scheme **5**. Cyclic aminoalcohol **26** was thought to be common intermediate for the synthesis of compound **1** and **3**. The piperidine ring in cyclic aminoalcohol **26** could be constructed by the allylation followed by ring closing metathesis of homoallylic amine **28**. Homoallylic amine **28** could be synthesized from 1,3-aminoalcohol **29** using standard protocol, which is also thought to be a precursor for the synthesis of alkaloids **4** and **5**. 1,3-Aminoalcohol **29** could be obtained from γ-hydroxy ester **31** by α-amination. γ-

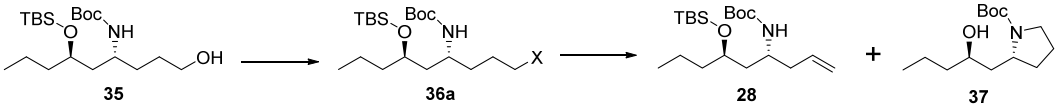
Hydroxy ester **31** could be easily obtained by the sequential α-aminoxylation and HWE olefination of the corresponding aldehyde **32**.

Thus synthesis starts with valeraldehyde **32** which 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 triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **31** in 78% yield and 94% ee. The free hydroxy group of γ-hydroxy esters **31** was protected as TBS ether using TBSCl in DMF to furnish compound **33** in 95% yield. Disappearance of peak at 3430 cm^{-1} in IR spectrum confirmed the formation of **33**. The DIBAL-H reduction of ester **33** at –78 ^oC furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on in situ trapping by triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *anti*-1,3-amino alcohol **29** in 71% yield and 98:2 diastereomeric ratio as determined from HPLC analysis. The *N*-*N*-bond of diastereomerically pure 1,3-*anti*-aminoalcohol **29** was easily cleaved with concomitant reduction of double bond under hydrogenation conditions using freshly prepared Raney-Ni at 60 psi to give free amine, which was subsequently converted into its Boc derivative using Boc_2O to furnish ester compound **34** in 79% yield. The disappearance of olefinic protons in the range of δ 5.92 as doublet and 6.85 as dd in ^1H NMR spectrum confirmed the formation of the product. Ester **34** was reduced using $LiBH_4$ to give alcohol **35** in 96% yield which was confirmed by the disappearance of ester protons in the range of δ 4.12 as quartet and 1.25 as triplet in ^1H NMR spectrum of the product. Alcohol **35** was converted to its iodo derivative **36** using Appel reaction condition and was subsequently treated with *n*-BuLi to undergo dehydrohalogenation to get allylic amine **28**, but to our disappointment we got cylic aminoalcohol **37** instead of our expected compound **28**. The formation of **37** was confirmed using ^1H NMR spectrum and HRMS (Scheme **6**).



Scheme 6. Attempted synthesis of homoallylic amine

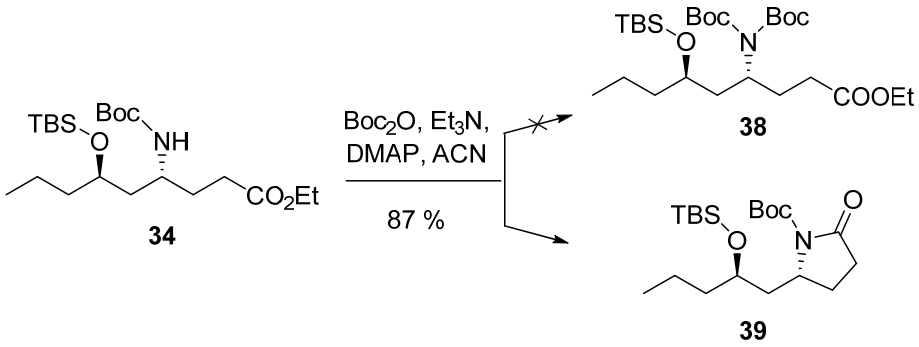
We then tried various other reaction conditions of dehydrohalogenation to achieve the target compound **28** and results are summarized in Table **1**. However none of the reaction conditions led to the formation of **28**.



X	Base	Yield of 28(%)	Yield of 37(%)
I	*n*-BuLi	-	82
	KO^tBu	-	76
	DBU	-	80
OMs	*n*-BuLi	-	74
	KO^tBu	-	52
Br	*n*-BuLi	-	43
	KO^tBu	-	31

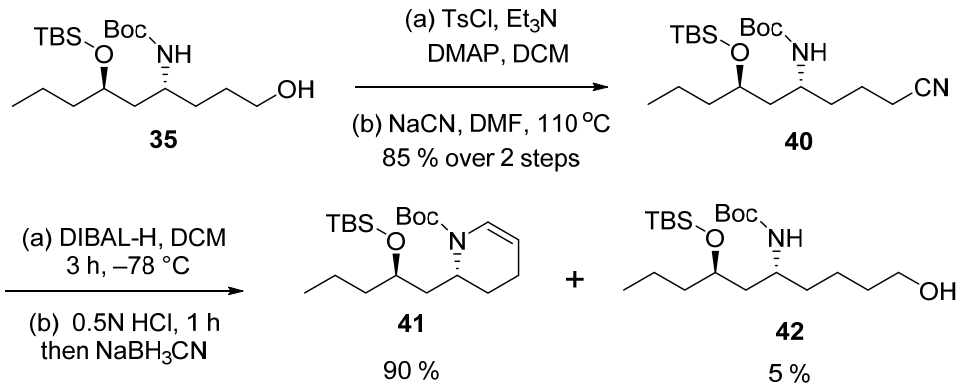
Table 1: Standardization of dehydrohalogination reaction

By analyzing the result, we concluded that due to presence of NH proton, nucleophilic displacement was the predominant reaction instead of dehydrohalogenation leading to exclusive formation of **37**. Therefore, further attempts were made to functionalize the amine group of ester compound **34**. For this purpose, compound **34** was treated with Boc_2O in presence of catalytic DMAP, but to our disappointment once again we obtained cyclic amide **39** as the only product instead of di-boc compound **38**. The disappearance of ester protons in the range of δ 1.25 as triplet and 4.12 as quartet in ^{1}H NMR spectrum confirmed the formation of compound **39** (Scheme **7**).



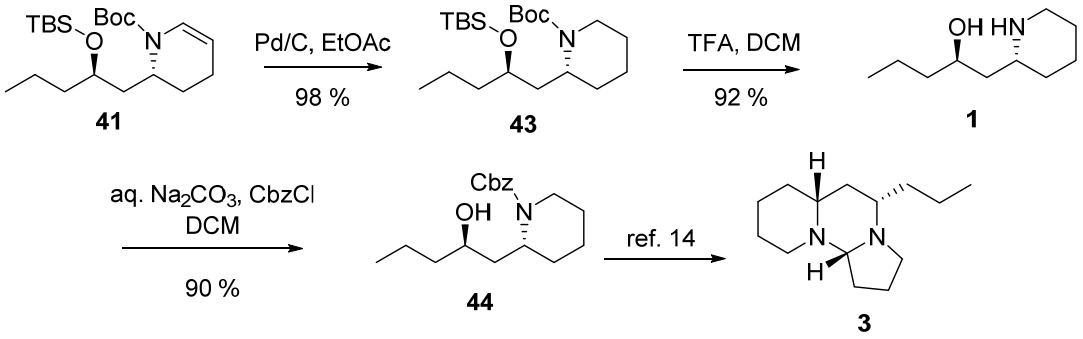
Scheme 7. Attempted functionalization of aminoester compound

We then switched over to different strategy to construct the piperidine ring via one carbon homologation and further cyclization of alcohol **35**. Towards this end, the free hydroxy group of **35** was converted into its toluenesulfonate derivative, which on subsequent treatment with NaCN in dry DMF at 100 ^oC furnished the cyano compound **40** in 85% yield. Disappearance of peak at 3525 cm^{-1} and appearance of peak at 2247 cm^{-1} in IR spectrum confirmed the formation of cyano compound **40**. Cyano compound **40** on treatment with DIBAL-H at -78 ^oC followed by acid hydrolysis gave the aldehyde which was subjected to reductive amination using $NaBH_3CN$ to get the cyclized product **41**, along with small amount of open chain product **42** (Scheme **8**). The formation of product **41** was confirmed by ^{1}H NMR spectrum and HRMS. We have used both the products, **41** and **42** for the synthesis of the target molecule (-)-halosaline.



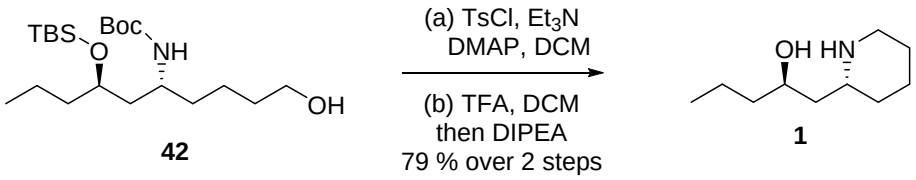
Scheme 8. Revised synthetic strategy

Towards this end, compound **41** was subjected to the double bond reduction under hydrogenation conditions using 10% Pd-C in EtOAc to give protected piperidine **43**. The disappearance of olefinic protons in the range of δ 5.92 as doublet and 6.85 as dd in ^{1}H NMR spectrum confirmed the formation of compound **43**. Piperidine **43** on global deprotection of both the TBS and Boc group with TFA afforded the final compound (-)-halosaline **1** (Scheme **9**). Compound **1** on treatment with CbzCl and sodium carbonate gave Cbz protected halosaline **44**. The conversion of compound **44** into target molecule **3** is already documented in literature.[14]



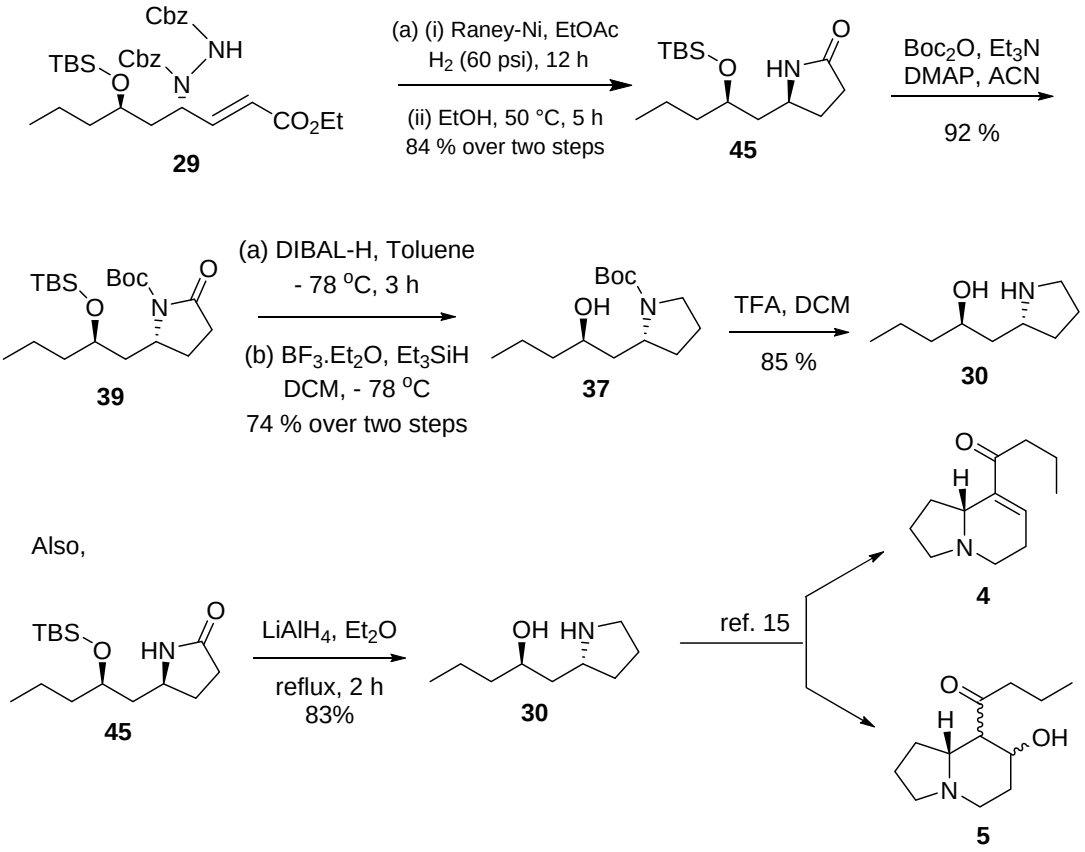
Scheme 9. Completion of synthesis

Similarly, the open chain compound **42** obtained as minor product, was converted into (-)-halosaline **1** by two step process. As shown in the Scheme **10**, compound **42** was first converted into its *p*-toluene sulfonate derivative. Subsequent global deprotection of both the TBS and Boc group with TFA followed by nucleophilic displacement of tosyl with the resultant amine in the presence of diisopropylethyl amine afforded the (-)-halosaline **1** in 79% yield.



Scheme 10. Alternative route to (-)-halosaline

Having successfully achieved the synthesis of target molecule **1**, our next aim was to synthesize compound **30** in order to achieve the formal synthesis of **4** and **5**. Cyclic aminoalcohol **37** (derived from Scheme **6**), was visualized as an ultimate precursor to achieve the synthesis of compound **30**. In an alternative route, **37** was also synthesized from 1,3-aminoalcohol **29** in a fewer steps (Scheme **11**). For this purpose, the *N*-*N*-bond of 1,3-*anti*-aminoalcohol **29** was easily cleaved with concomitant reduction of double bond under hydrogenation conditions using freshly prepared Raney-Ni at 60 psi to give free amine, which was subsequently converted into lactam **45** in 84% yield. The disappearance of olefinic protons in the range of δ 5.92 as doublet and 6.85 as dd in ^{1}H NMR spectrum confirmed the formation of compound **45**. The lactam **45** was converted into its Boc derivative **39** using Boc_2O in 92% yield. The disappearance of NH protons in the range of δ 6.12 as multiplate in ^{1}H NMR spectrum confirmed the formation of compound **39**. Amide group present in compound **39** was reduced using two step process with simultaneous deprotection of TBS; it was first treated with DIBAL-H in toluene, followed by treatment with $BF_3.OEt_2$ in DCM to get the cyclic aminoalcohol **37** which on deprotection of Boc group using TFA furnished the expected compound **30**. In another direct approach to the synthesis of **30**, the lactam **45** was subjected to reduction with $LiAlH_4$ in refluxing Et_2O followed by quenching with dil. HCl to furnish **30** in 83% yield. Since the conversion of compound **30** to target molecule **4** and **5** is already reported in the literature,[15] this constitutes the formal synthesis of target molecules **4** and **5**.



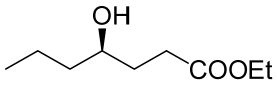
Scheme 11. Formal synthesis of elaeokanine A and C

3.1.5. Conclusion

In conclusion, we have developed a practical, efficient and organocatalytic approach to the synthesis of various substituted piperidine alkaloids in high enantio- and diastereomeric excess using proline catalyzed sequential α-aminoxylation/α-amination reaction and HWE olefination reaction of an aldehyde as the key step. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the proline in the α-aminoxylation/α-amination step. The synthetic strategy described here has significant potential for stereochemical variations and further access to other stereoisomers as well as various other substituted piperidine alkaloids.

3.1.6. Experimental Section

Ethyl (*R*)-4-hydroxyheptanoate (31):



To a solution of valeraldehyde **32** (2.0 g, 23.2 mmol) and nitroso benzene (0.83 g, 7.74 mmol) in anhydrous CH_3CN (50 mL) was added L-proline (0.27 g, 2.32 mmol) at 0 °C. The mixture was vigorously stirred for 24 h under argon (the color of the reaction changed from green to orange red during this time) at 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (9.25 mL, 46.4 mmol), DBU (6.95 mL, 46.4 mmol) and LiCl (1.969 g, 46.4 mmol) in CH_3CN (40 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 ^{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 γ-hydroxy ester **31**. The crude product was then purified by using silica gel flash column chromatography using pet ether: EtOAc (85:15) as eluent to give (*R*)-ethyl 4-hydroxyheptanoate **31** as a colorless liquid.

Yield: 1.05g, 78%

Mol. Formula: $C_9H_{18}O_3$

$[\alpha]_D^{25}$: + 11.66 (*c* 2.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2934, 1719, 1466, 1177.

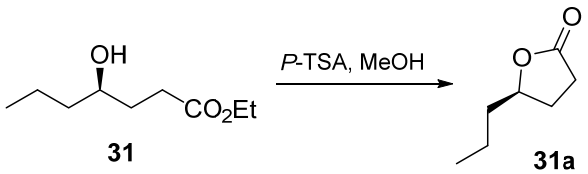
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91-0.96 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.38-1.49 (m, 3H), 1.61-2.05 (m, 4H), 2.46 (t, J = 7.2 Hz, 2H), 3.58-3.78 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 18.7, 30.7, 32.1, 39.6, 60.4, 70.8, 174.3 ppm.

MS (ESI): m/z 197.1862 $(M+Na)^+$

HRMS: 197.1173 $(M+Na)^+$ Calcd. 197.1148

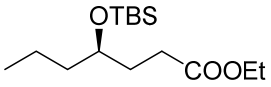
In order to determine the chiral purity of (*R*)-ethyl 4-hydroxyoctanoate **31** formed it was converted into known lactone **31a** on treatment with *p*-TSA in methanol.



31 **31a**

Chiral GC using Cyclodextrin TA column (70 kPa pressure, 140 °C isotherm for 35 min, major enantiomer 19.9 min, minor enantiomer 20.6 min). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 94%.

Ethyl (*R*)-4-((*tert*-butyldimethylsilyl)oxy)heptanoate (33):



To an ice-cold stirred solution of **31** (1.0 g, 5.75 mmol) in DMF (12 mL) were added imidazole (0.452 g, 6.64 mmol) and TBSCl (1.00 g, 6.64 mmol) at room temperature. The resulting mixture was stirred for 6 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 25 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/ 99:1) of the crude product gave ethyl (*R*)-4-((tert-butyldimethylsilyl)oxy)-heptanoate **33** as a colorless liquid

Yield: 1.57 g, 95%

Mol. Formula: $C_{15}H_{32}O_3Si$

$[\alpha]_D^{25}$: - 7.98 (*c* 1.34, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν^{max} 2958, 1727, 1463, 1256, 908.

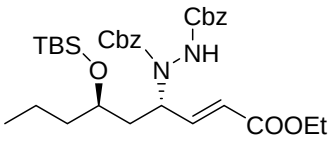
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.87-0.93 (m, 3H), 0.89 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 1.29-1.46 (m, 4H), 1.63-1.83 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 3.68-3.73 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, -4.5, 14.2, 18.0, 18.4, 25.8, 25.9, 31.7, 39.3, 60.2, 70.9, 173.9 ppm.

MS (ESI): m/z 311.3840 $(M+Na)^+$

Elemental analysis: Calcd. C, 62.45; H, 11.18; Found: C, 62.64; H, 11.12.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate (29):



To a solution of ethyl ester **33** (1.0 g, 3.5 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (1.7 mL 2.25 M solution in toluene, 3.85 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (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 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (1.02 g, 2.9 mmol) and D-proline (0.038 g, 8 mol%) in CH_3CN (40 mL) at 0 °C was added above aldehyde (1.0 g, 3.5 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 (0.22 g, 4.3 mmol), triethyl phosphonoacetate (1.02 mL, 4.3 mmol) and DBU (0.5 mL, 2.9 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 (diastereomeric ratio/ 98:2). Silica gel column chromatography (petroleum ether: ethyl acetate: 90:10) of the crude product gave dibenzyl 1-((4S,6R,E)-6-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate **29** as a colorless syrupy liquid.

Yield: 1.52 g, 71%

Mol. Formula: $C_{33}H_{48}N_2O_7Si$

$[\alpha]_D^{25}$: - 1.56 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν^{max} 3428, 2950, , 1717, 1652, 1399, 1084.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.84 (m, 12H), 1.24-1.31 (m, 5H), 1.40-1.53 (m, 2H), 1.72-1.81 (m, 1H), 1.89-2.02 (m, 1H), 3.58-3.90 (m, 1H), 4.17 (q, J = 7.0

Hz, 2H), 4.84-5.25 (m, 5H), 5.92 (d, *J*= 17.5 Hz, 1H), 6.51 (m, 1H), 6.85 (dd, *J* = 6.4, 15.1 Hz, 1H), 7.31 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.4, 14.0, 14.2, 17.9, 25.8, 39.4, 60.4, 67.5, 68.1, 121.9, 122.7, 127.9, 128.1, 128.3, 135.6, 146.0, 155.5, 156.3, 166.2 ppm.

MS (ESI): m/z 635.5057$(M+Na)^+$, 651.5379 $(M+K)^+$

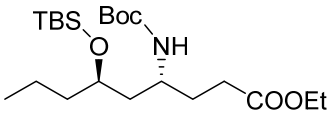
HRMS: 635.3116 $(M+Na)^+$ Calcd.635.3123

Diastereomeric ratio was determined by HPLC analysis; 98:2 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O = 97:3; t_R for (*anti*)-isomer = 6.90 min and t_R for (*syn*)- isomer = 6.31 min.

Ethyl (4*R*,6*R*)-4-((*tert*-butoxycarbonyl)amino)-6-((tert-butyldimethylsilyl)oxy) nonanoate (34):



The solution of dibenzyl 1-((4*S*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate **29** (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 (60 psi) 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) and Boc anhydride (1.2 mL, 5.1 mmol) 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 ethyl *(R)*-4-((*tert*-butoxycarbonyl)amino)-8-((tert-butyldimethylsilyl)oxy)octanoate **34** as a viscous liquid

Yield: 0.111 g, 79%

Mol. Formula: $C_{22}H_{45}NO_5Si$

$[\alpha]_D^{25}$: - 10.37 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3382, 2956, 1722, 1703, 1173

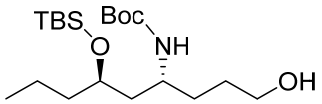
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (m, 12H), 1.25 (t, *J*= 7.0 Hz, 3H), 1.31-1.35 (m, 2H), 1.43 (s, 9H), 1.47-1.60 (m, 4H), 1.76-1.86 (m, 2H), 2.35 (t, *J*= 7.5 Hz, 2H), 3.59-3.87 (m, 2H), 4.12 (q, *J*= 7.0 Hz, 2H), 4.92-4.95 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.3, 14.2, 17.9, 18.2, 25.9, 28.3, 30.9, 39.4, 40.7, 47.8, 60.3, 69.7, 78.7, 155.6, 173.6 ppm.

MS(ESI): m/z 454.21 $(M+Na)^+$

Elemental analysis: Calcd. C, 61.21; H, 10.51; N, 3.24; Found: C, 61.29; H, 10.44; N, 3.29.

***tert*-Butyl ((4R,6R)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynonan-4-yl)carbamate (35):**



To a stirred suspension of $LiBH_4$ (0.60 g, 2.2mmol) in dry THF (1 mL) was added a solution of **34** (0.60 g, 1.4mmol) in THF (5 mL) at 0 ^oC and the mixture was stirred at room temperature for 3 hrs. 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 *tert*-butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynonan-4-yl)carbamate **35** as a colorless liquid

Yield: 0.51 g, 96%

$[\alpha]_D^{25}$: - 8.29 (*c* 0.9, $CHCl_3$)

Mol. Formula: $C_{22}H_{45}NO_5Si$

IR ($CHCl_3$, cm^{-1}): ν^{max} 3525, 3365, 2929, 1691, 1100.

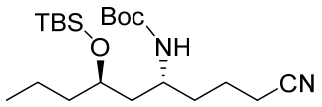
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.20-1.38 (m, 4H), 1.43 (s, 9H), 1.54-1.66 (m, 6H), 3.60-3.91 (m, 4H), 5.12 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.4, 14.2, 17.9, 18.2, 25.9, 28.3, 28.6, 32.1, 39.9, 40.3, 47.6, 62.3, 69.7, 78.8, 155.9 ppm.

MS(ESI): m/z 412.20 $(M+Na)^+$

HRMS: 390.3032 $(M+ H)^+$ Calcd. 390.3034.

***tert*-Butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-cyanononan-4-yl)carbamate (40):**



To an ice-cold stirred solution of **35** (0.50 g, 1.33 mmol) and triethylamine (0.27 mL, 1.99 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise toluenesulfonyl chloride (0.5 mL, 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 CH_2Cl_2 (10 mL), 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 ^{0}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 (15mL) dried ($NaSO_4$) and concentrated in vacuo. Silica gel colum chromatography of the crude product using (petroleum ether: ethyl acetate 90:10) gave *tert*-butyl *tert*-butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-cyanononan-4-yl)carbamate **40** as yellow syrupy liquid.

Yield: 0.44 g, 85%

Mol. Formula: $C_{21}H_{42}N_2O_3Si$

$[\alpha]_D^{25}$: - 18.34 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3369, 2957, 2931, 2247, 1704, 1505, 1253, 1056.

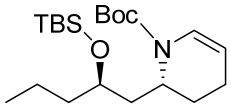
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.19-1.35 (m, 4H), 1.43 (s, 9H), 1.56-1.74 (m, 6H), 2.41 (t, *J*= 6.7 Hz, 2H), 3.59-3.89 (m, 2H), 5.04 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.4, 14.9, 16.8, 17.8, 18.0, 21.8, 25.7, 28.2, 29.5, 34.9, 39.3, 46.9, 69.4, 78.6, 119.5, 155.6 ppm.

MS(ESI): m/z 421.20 $(M+Na)^+$

HRMS: 421.2856 $(M+Na)^+$, Calcd. 421.2857

***tert*-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-3,4-dihydropyridine-1(2H)-carboxylate (41):**



To a solution of **40** (0.250 g, 0.65mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (0.715 mL 1M solution in toluene, 0.71mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 2 hrs. 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 as a colorless liquid, which was directly used in the next step without further purification.

To the cooled solution of anhydrous THF and a drop of MeOH was added $NaBH_4$ (0.098g, 2.6mmol) over 20 mins followed by addition of aldehyde. The reaction mixture was allowed to warm to room temperature and was stirred for 8 hrs. 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 crude product. The crude product was then purified by silica gel flash column chromatography using pet ether: EtOAc: 19:1 to give **41** (0.216 g, 90%) as yellow oil. Continued chromatography with pet ether: EtOAc/ 4:1 provided **42** as a colorless liquid.

Mol. Formula: $C_{21}H_{41}NO_3Si$

$[\alpha]_D^{25}$: + 42.97 (*c* 0.6, $CHCl_3$**)**

IR ($CHCl_3$,cm^{-1}): ν^{max} 2929, 2857, 1702, 1649, 1254

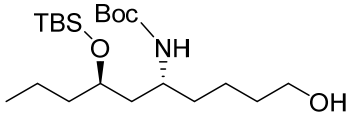
^{1}H NMR (500 MHz, $CDCl_3$): Spectra showed 1:1 mixture of amide rotamers δ 0.06 (s, 6H), 0.88(m, 12H), 1.26-1.44 (m, 4H), 1.48 (s, 9H), 1.53-1.63 (m, 2H), 1.69-1.73 (m, 1H), 1.80-1.82 (m, 1H), 1.94-1.98 (m, 1H), 2.06-2.12 (m, 1H), 3.70-3.79 (m, 1H), 4.07-4.15 (m, 0.5H), 4.30-4.33 (m, 0.5H), 4.77-4.88 (m, 1H), 6.65 (d, *J*= 7.3 Hz, 0.5H), 6.79 (d, *J*= 7.4 Hz, 0.5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.4, 14.3, 18.0, 23.9, 24.5, 25.9, 28.3, 30.3, 38.3, 38.5, 39.0, 39.3, 47.6, 48.8, 69.9, 80.3, 80.5, 104.5, 104.8, 124.0, 124.4, 151.9, 152.3 ppm.

MS(ESI): m/z 406.24 $(M+Na)^+$

HRMS: 384.2929 $(M+H)^+$ Calcd. 384.2928.

***tert*-Butyl ((5*R*,7*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-hydroxydecan-5-yl)carbamate (42):**



Physical State: colorless liquid

Mol. Formula: $C_{21}H_{45}NO_4Si$

$[\alpha]_D^{25}$: - 8.29 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3365, 2930, 1692, 1366, 1100.

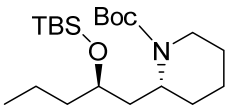
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.29-1.35 (m, 4H), 1.43 (s, 9H), 1.47-1.57 (m, 4H), 1.58-1.68 (m, 2H), 1.76-1.88 (m, 2H), 3.58-3.73 (m, 3H), 3.78-3.91 (m, 1H), 5.02 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.3, 14.3, 17.9, 18.3, 21.8, 25.9, 28.4, 29.7, 32.5, 35.5, 39.5, 47.6, 62.7, 69.8, 78.7, 155.8 ppm..

MS(ESI): m/z 426.26 $(M+Na)^+$

Elemental analysis: Calcd. C, 61.21; H, 10.51; N, 3.24; Found: C, 61.29; H, 10.44; N, 3.29.

***tert*-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)piperidine-1-carboxylate (43):**



To the solution of **41** (0.1g, 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 **43** as a colorless liquid.

Yield: 0.098 g, 98%

Mol. Formula: $C_{21}H_{43}NO_3Si$

$[\alpha]_D^{25}$: + 23.91 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2931, 2858, 1693, 1416, 1253, 1167.

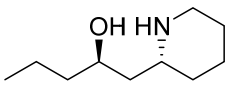
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (m, 12H), 1.26-1.41 (m, 4H), 1.46 (s, 9H), 1.57-1.62 (m, 6H), 1.70-1.83 (m, 2H), 2.69-2.82 (m. 1H), 3.59-3.71 (m, 1H), 3.91-3.97 (m, 1H), 4.11-4.35 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): Spectra showed amide rotamers δ -4.5, -4.4, 14.0, 14.3, 18.0, 18.3, 19.0, 19.2, 25.6, 25.9, 28.4, 28.5, 29.7, 30.3, 37.8, 39.3, 48.5, 70.8, 79.1, 154.9 ppm.

MS(ESI): m/z 408.18 $(M+Na)^+$

HRMS: 386.3085 $(M+ H)^+$ Calcd. 386.3085

(-)-Halosaline (1):



To the solution of **43** (0.1g, 0.27 mmol) in dry CH_2Cl_2 (1 mL) was added TFA (0.075 mL, 0.78 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 colum chromatography of the crude product using (MeOH: CH_2Cl_2: NH_4OH/ 8:90:2) gave (-)-Halosaline as product.

Yield: 0.042 g, 92%

Mol. Formula: $C_{10}H_{21}NO$

MP: 80-82 ^oC

$[\alpha]_D^{25}$: - 18.9 (*c* 0.9, EtOH) [lit.[3] $[\alpha]_D^{25}$: - 19.5 (*c* 0.6, EtOH)]

IR ($CHCl_3$, cm^{-1}): ν^{max} 3445, 3373, 2928, 1399, 1125.

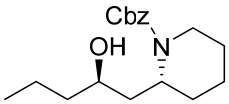
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, J = 7.1 Hz, 3H), 1.25-1.95 (m, 12H), 2.84 (dt, J = 4.5, 12.1 Hz, 1H), 3.19-3.34 (m, 1H), 3.41 (d, J = 12.7 Hz, 1H), 3.87-4.00 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 18.7, 22.1, 22.6, 28.6, 39.2, 39.4, 45.0, 55.0, 66.8 ppm.

MS(ESI): m/z 194.06 $(M+Na)^+$

HRMS: 172.1696 $(M+ H)^+$ Calcd. 172.1696

Benzyl (*R*)-2-((*R*)-2-hydroxypentyl)piperidine-1-carboxylate (44):



To an ice-cold stirred solution of **1** (0.030 g, 0.17 mmol) and triethylamine (0.03 mL, 0.2 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise CbzCl (0.05 mL, 0.2 mmol) at 0 ^oC. The resulting mixture was allowed to warm up to room temperature and stirred for 4 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*-Cbz derivative. Silica gel column chromatography (petroleum ether: ethyl acetate/ 1:1) of the crude product gave **44** as a colorless liquid

Yield: 0.047 g, 90%

Mol. Formula: $C_{18}H_{27}NO_3$

$[\alpha]_D^{25}$: + 19.84 (*c* 0.5, $CHCl_3$) [lit.[14] **$[\alpha]_D^{25}$** : + 21.6 (*c* 0.09, $CDCl_3$)]

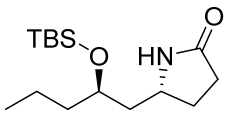
IR ($CHCl_3$, cm^{-1}): ν^{max} 3430, 2925, 1695, 1536, 1252, 1174

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.95 (m, 3H), 1.19-1.96 (m, 12H), 2.57-2.77 (m, 1H), 2.98-3.15 (m, 2H), 4.07-4.17 (m. 1H), 4.22-4.43 (m, 1H), 5.11 (s, 2H), 7.35 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 17.9, 27.1, 29.7, 31.1, 37.1, 40.5, 57.3, 68.0, 70.9, 128.3, 128.4, 128.6, 135.2, 155.5 ppm.

MS(ESI): m/z 328.21 $(M+Na)^+$

(*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pentyl)pyrrolidin-2-one (45):



The solution of dibenzyl 1-((4*S*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate **29** (0.5 g, 0.32 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (0.6 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 55 ^oC for 5h. The reaction mixture was then concentrated in vacuo to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate/ 40:60) of the crude product gave cyclic lactam (*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)pentyl)pyrrolidin-2-one **45** as a colorless liquid.

Yield: 0.2 g, yield 84%

Mol. Formula: $C_{15}H_{31}NO_2Si$

$[\alpha]_D^{25}$: - 13.59 (*c* 2.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3432, 2930, 1695, 1256.

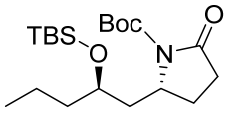
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (m, 12H), 1.26-1.52 (m, 5H), 1.59-1.66 (m, 2H), 2.18-2.35 (m, 3H), 3.69-3.90 (m, 2H), 6.12-6.25 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.6, 14.1, 17.9, 18.6, 25.8, 28.4, 29.9, 38.9, 42.6, 50.6, 70.3, 177.7 ppm.

MS (ESI): m/z 308.15 $(M+Na)^+$

HRMS: 286.2196 $(M+ H)^+$ Calcd. 286.2197.

***tert*-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-oxopyrrolidine-1-carboxylate (39):**



To an ice-cold stirred solution of **45** (0.060 g, 0.15 mmol) and triethylamine (0.03 mL, 0.2 mmol) in anhydrous CH_3CN (2 mL) was added dropwise Boc anhydride (0.05 mL, 0.2 mmol) and DMAP (catalytic) at 0 ^oC. The resulting mixture was allowed to warm up to room temperature and stirred for 6 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/ 9:1) of the crude product gave **39** as a colorless liquid

Yield: 0.073 g, 92%

Mol. Formula: $C_{20}H_{39}NO_4Si$

$[\alpha]_D^{25}$: + 17.34 (*c* 1.7, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν^{max} 3019, 1777, 1728, 1215.

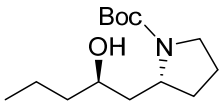
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (m, 12H), 1.31-1.47 (m, 4H), 1.53 (s, 9H), 1.60-1.67 (m, 1H), 1.85-2.11 (m, 3H), 2.38-2.45 (m, 1H), 2.52-2.62 (m, 1H), 3.74-3.80 (m, 1H), 4.04-4.09 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.5, 14.2, 18.1, 23.9, 25.8, 28.0, 31.1, 39.9, 40.7, 57.1, 70.9, 82.7, 149.7, 174.4 ppm.

MS (ESI): m/z 408.20 $(M+Na)^+$.

HRMS: 408.2541 $(M+ H)^+$ Calcd. 408.2541

***tert*-Butyl (*R*)-2-((*R*)-2-hydroxypentyl)pyrrolidine-1-carboxylate (37):**



To a cooled (0 °C), stirred solution of Ph_3P (0.35 g, 1.46 mmol) in THF–MeCN (1:1, 5 mL) were added imidazole (0.10 g, 1.45 mmol) and I_2 (0.34 g, 1.46 mmol). The mixture was stirred for 2 h and then a solution of alcohol **35** (0.50 g, 1.33 mmol) in THF (10 mL) was added at 0 °C. The mixture was stirred for 2 h, then diluted with 10% aq $Na_2S_2O_3$ (6 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, to give iodo product **36** which was used without purification for the next step.

To the crude iodo compound dissolved in benzene (5 mL) was added ^{t}BuOK (0.3 g, 2.66 mmol) and the mixture was stirred at r.t. for 1 h. Then, the mixture was poured into H_2O and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (2 × 10 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography (petroleum ether: ethyl acetate/ 9:1) afforded **37** as a colorless liquid

Yield: 0.23 g, 76%

$[\alpha]_D^{25}$: + 21.56 (*c* 1.7, $CHCl_3$)

Mol. Formula: $C_{14}H_{27}NO_3$

IR ($CHCl_3$, cm^{-1}): ν^{max} 3419, 2928, 1690, 1415, 1163

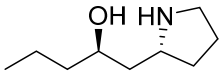
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H),1.24-1.37 (m, 5H), 1.44 (s, 9H), 1.51-1.60 (m, 2H), 1.83-2.00 (m, 3H), 3.28-3.35 (m, 2H), 3.39-3.49 (m, 1H), 4.11-4.21 (m, 1H), 4.94 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.1, 23.5, 28.3, 31.1, 38.9, 43.9, 46.4, 53.6, 67.0, 79.7, 156.6 ppm.

MS (ESI): m/z 280.20 $(M+Na)^+$

HRMS: 280.1878 $(M+ Na)^+$ Calcd. 280.1883

(*R*)-1-((*R*)-Pyrrolidin-2-yl)pentan-2-ol (30):



To the solution of **37** (0.1 g, 0.39 mmol) in dry CH_2Cl_2 (1 mL) was added TFA (0.075 mL, 0.78 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 colum chromatography of the crude product using (MeOH: CH_2Cl_2: NH_4OH/ 8:95:2) gave **30** as product.

Yield: 0.052 g, 85%

Mol. Formula: $C_9H_{19}NO$

$[\alpha]_D^{25}$: - 3.06 (*c* 1.0, MeOH)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3456, 3377, 2924, 1455, 1215, 1124.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 6.8 Hz, 3H), 1.11-1.77 (m, 8H), 1.80-1.92 (m, 2H), 2.00-2.32 (m, 2H), 3.32-3.39 (m, 1H), 3.64-3.91 (m, 2H) ppm.

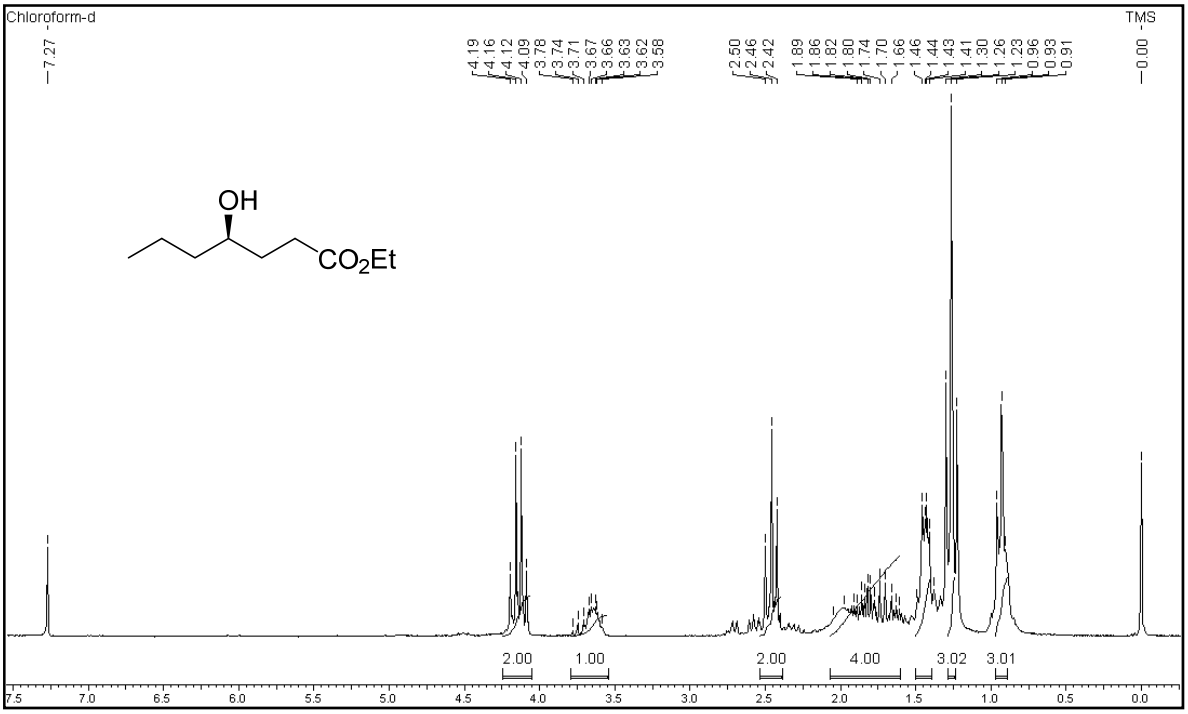
^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 18.8, 23.4, 30.3, 37.4, 38.7, 45.6, 57.7, 68.1 ppm.

MS(ESI): m/z 180.24 $(M+Na)^+$

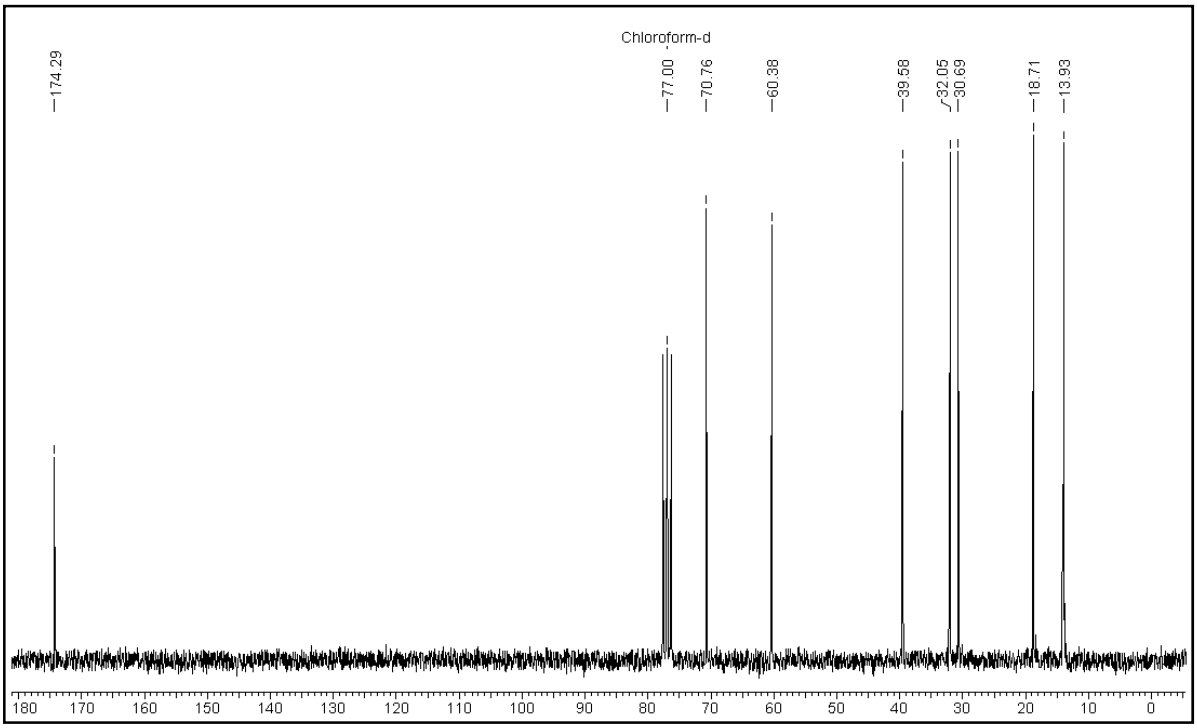
HRMS: 158.1537 $(M+ H)^+$ Calcd. 158.1539.

3.1.7. Spectra

Ethyl (*R*)-4-hydroxyheptanoate (31):

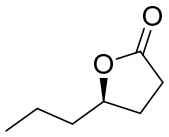


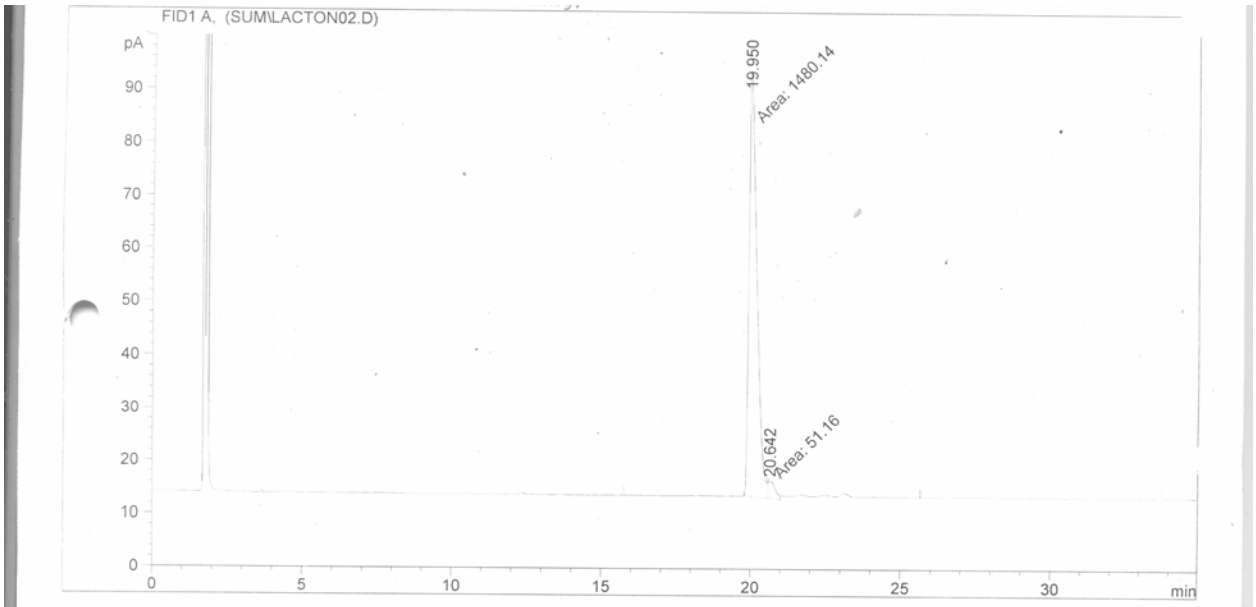
➢ **^{1}H NMR of the compound 31 in $CDCl_3$**



➢ **^{13}C NMR of the compound 31 in $CDCl_3$**

Enantiomeric excess:



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================================================================================
                              Area Percent Report
================================================================================

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Dilution              :      1.0000
Sample Amount         :      2.00000  [ng/ul]    (not used in calc.)

Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
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   2  20.642 FM    0.2582   51.16001    3.30218  3.34095
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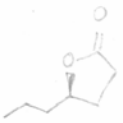
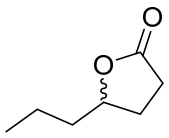
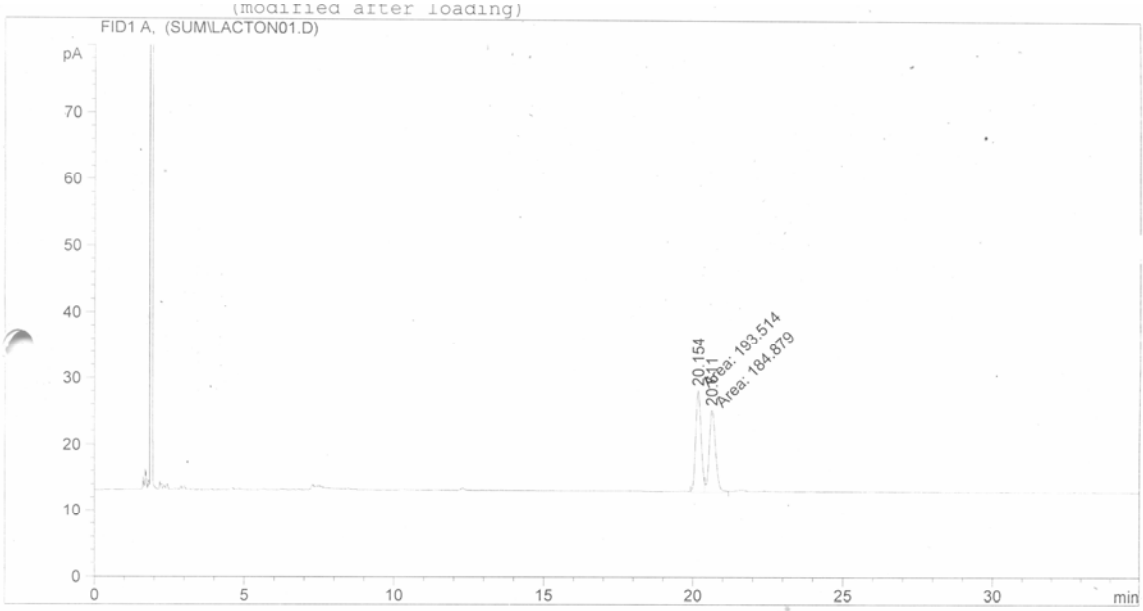




(modified after loading)



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 2.00000 [ng/ul] (not used in calc.)

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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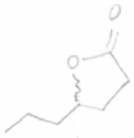
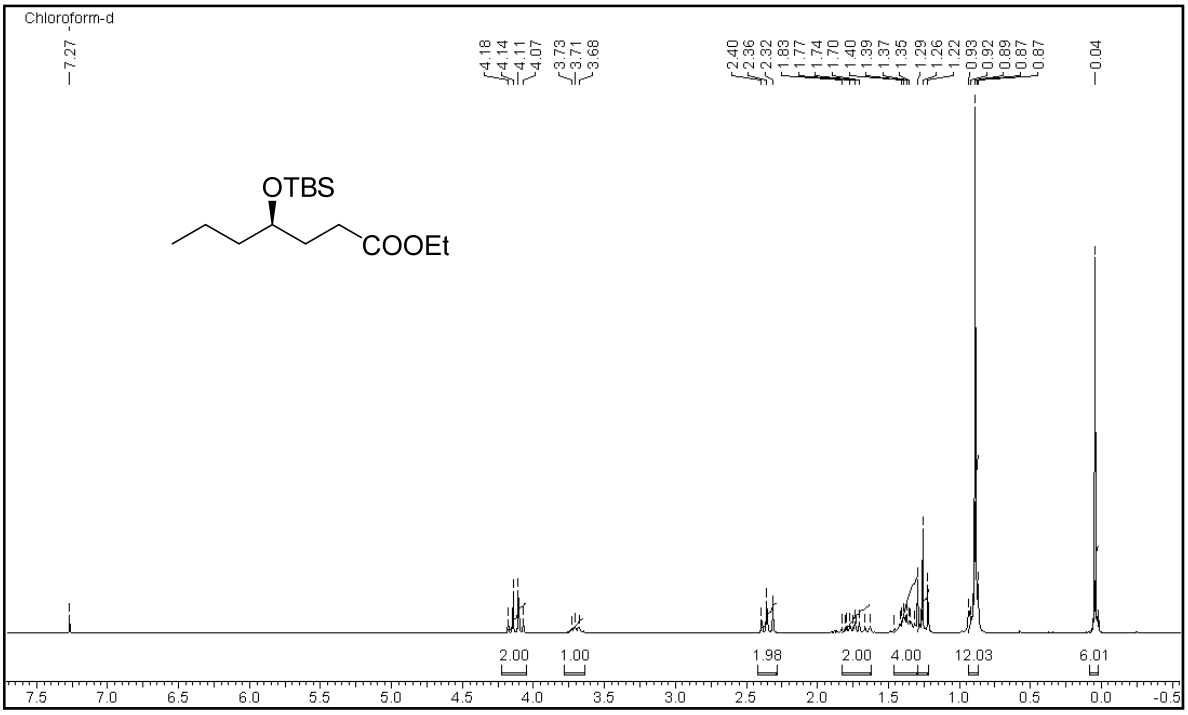
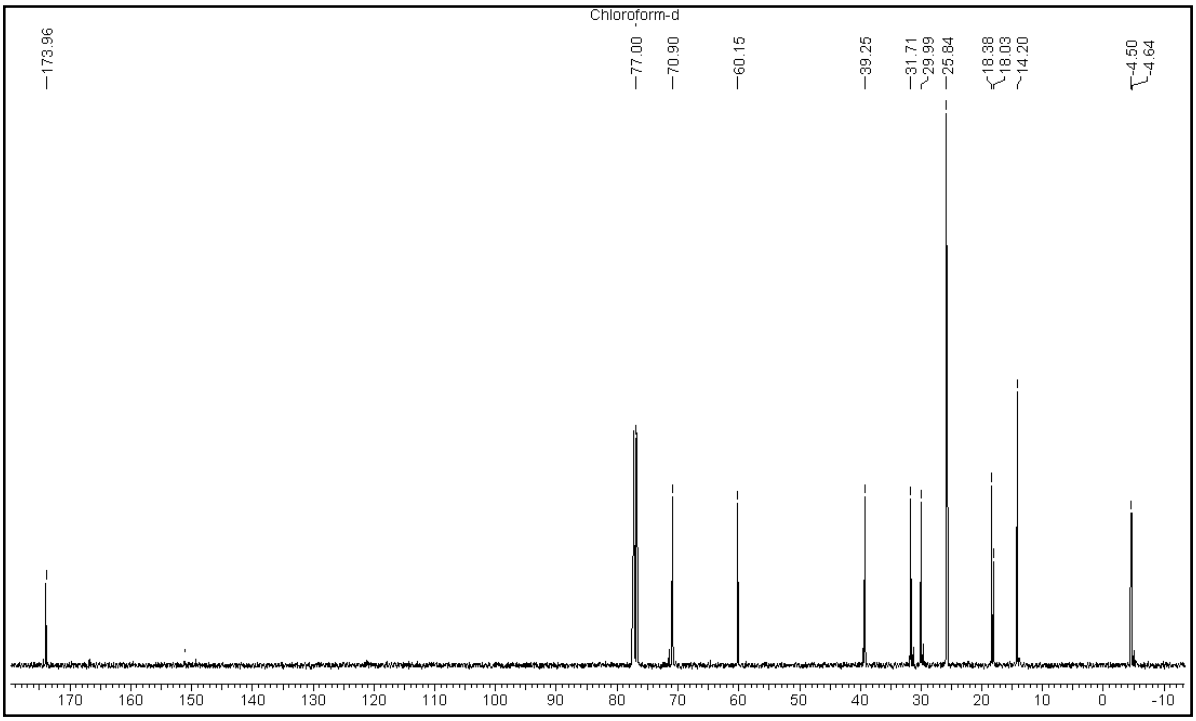
2	20.611	FM	0.2495	184.87860	12.35137	48.85898



Ethyl (*R*)-4-((*tert*-butyldimethylsilyl)oxy)heptanoate (33):

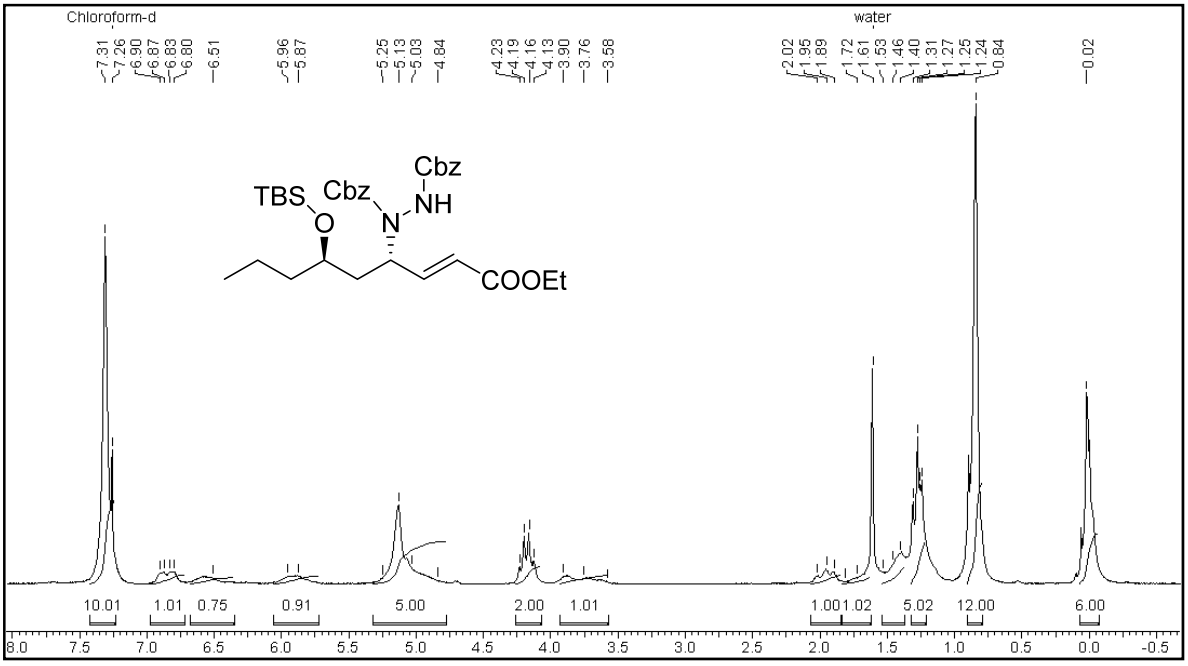


- **^{1}H NMR of the compound 33 in $CDCl_3$**

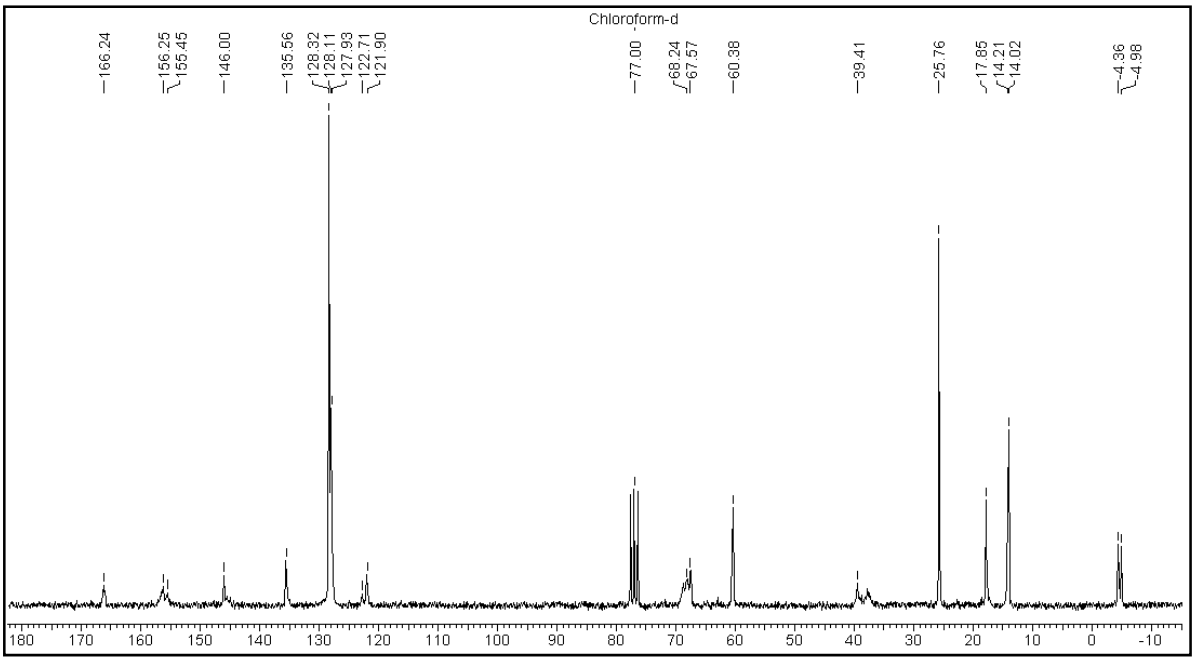


- **^{13}C NMR of the compound 33 in $CDCl_3$**

Dibenzyl 1-((4S,6R,E)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate (29):



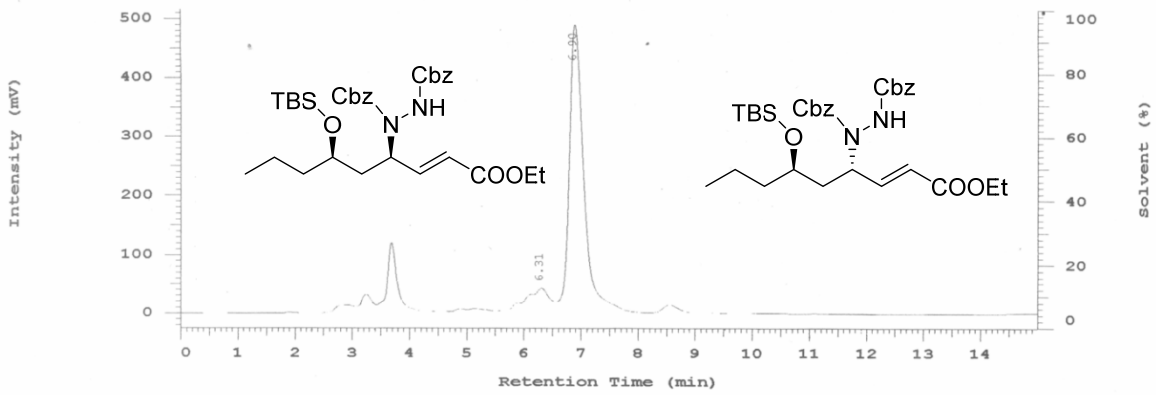
➢ **^{1}H NMR of the compound 29 in $CDCl_3$**



➢ **^{13}C NMR of the compound 29 in $CDCl_3$**

Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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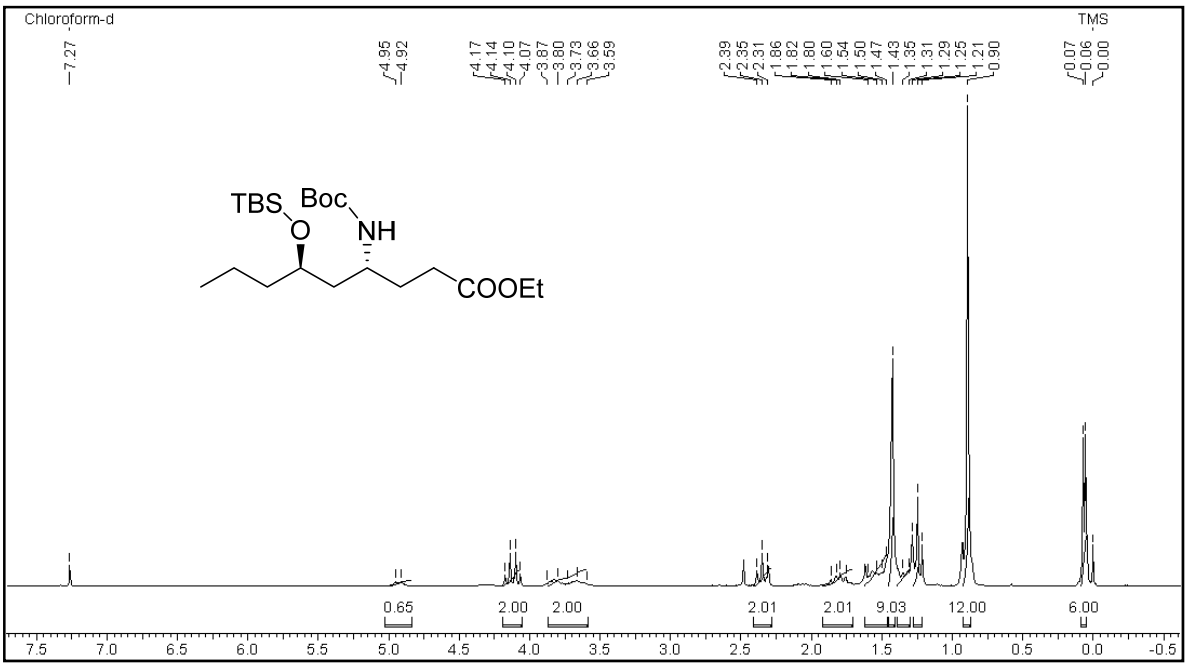
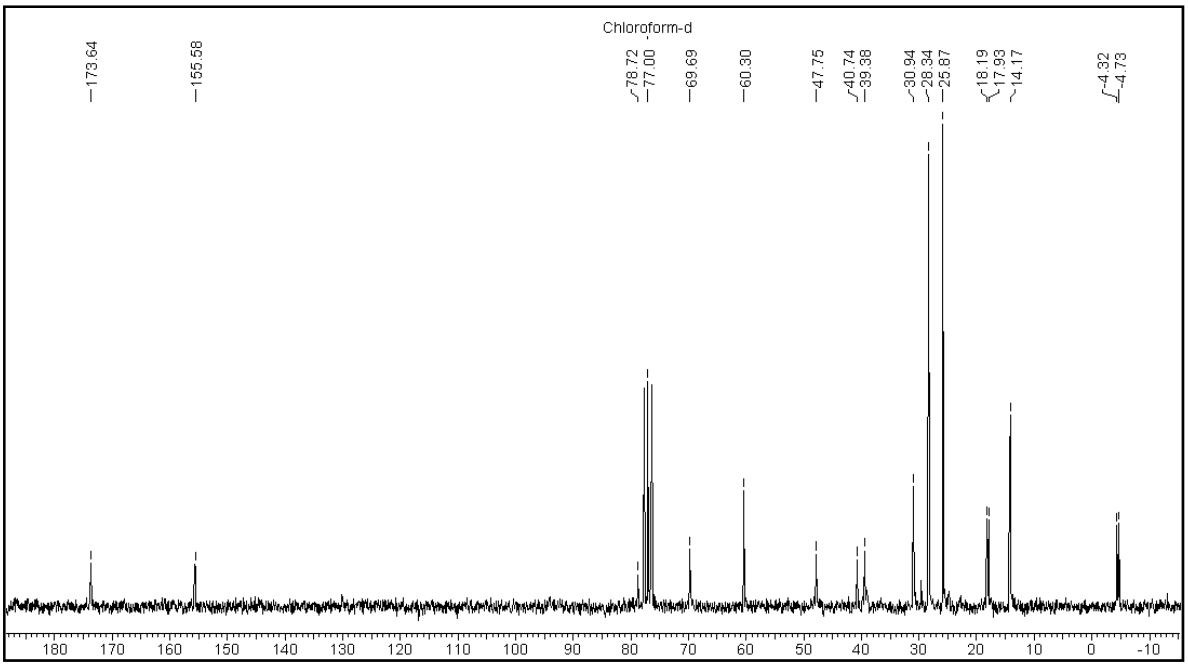
Ethyl(4*R*,6*R*)-4-((*tert*-butoxycarbonyl)amino)-6-((tert-butyldimethylsilyl)oxy)nonanoate (34):

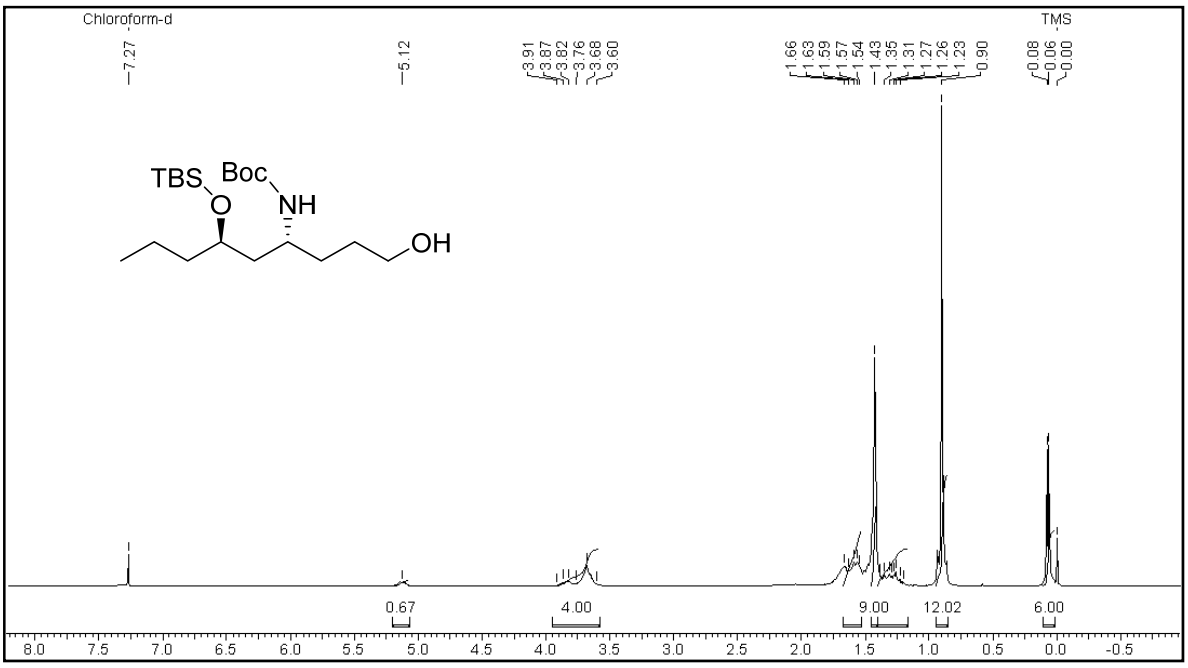


- **^{1}H NMR of the compound 34 in $CDCl_3$**

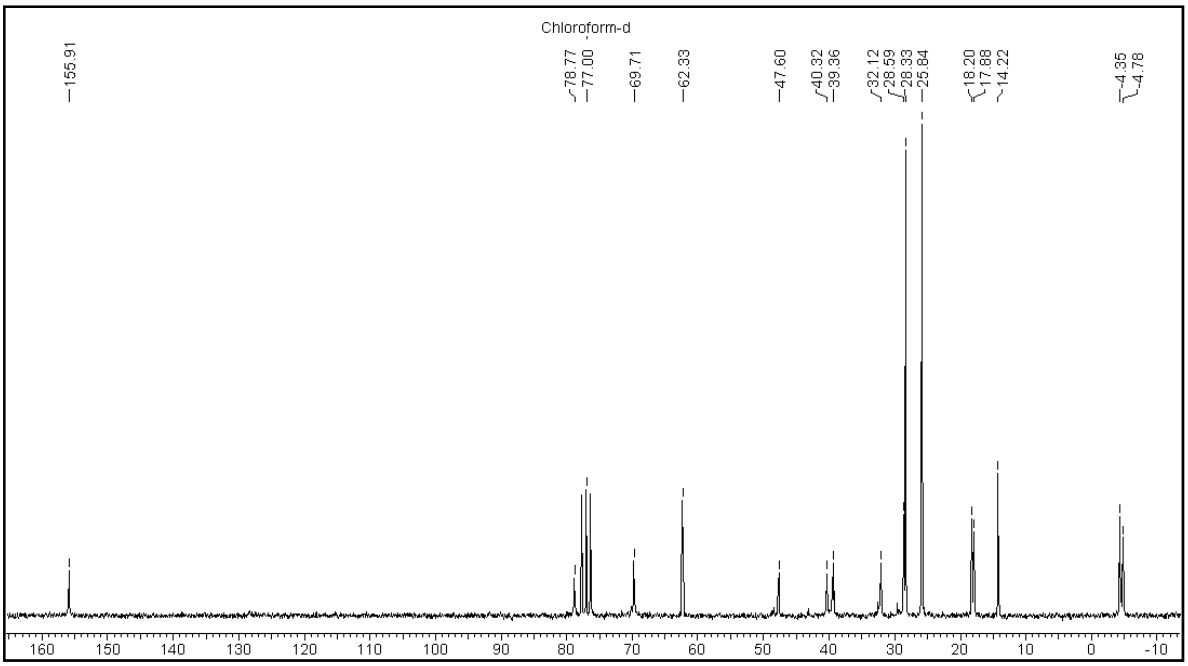


- **^{13}C NMR of the compound 34 in $CDCl_3$**

***tert*-Butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynonan-4-yl)carbamate (35):**

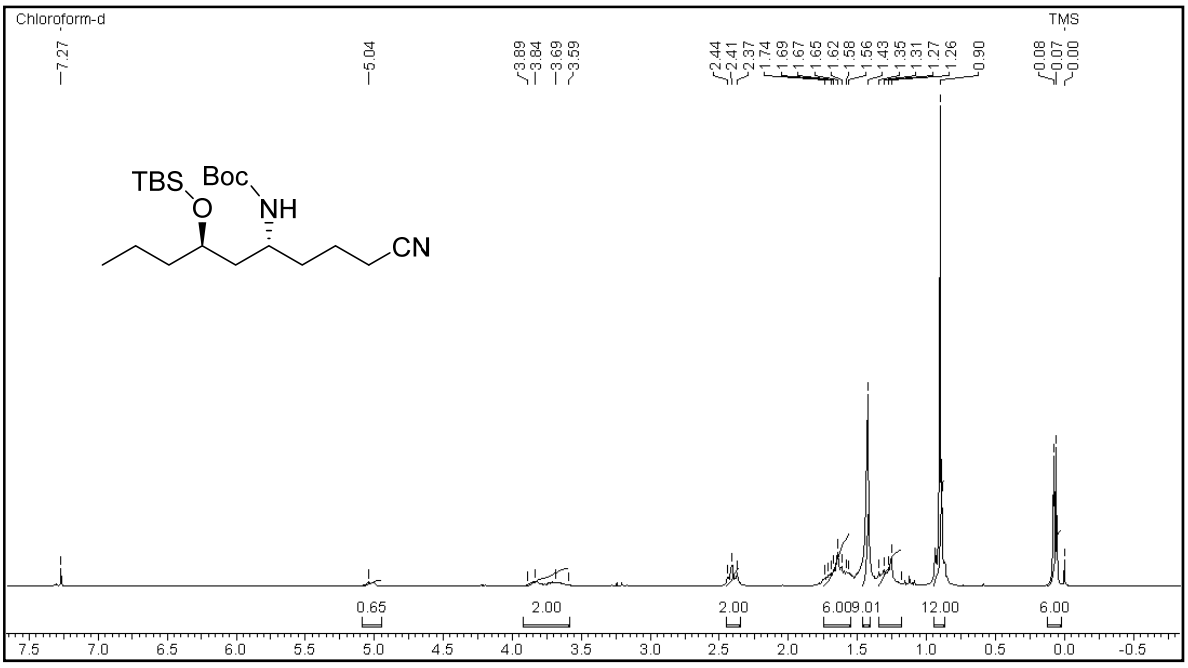


- **^{1}H NMR of the compound 35 in $CDCl_3$**

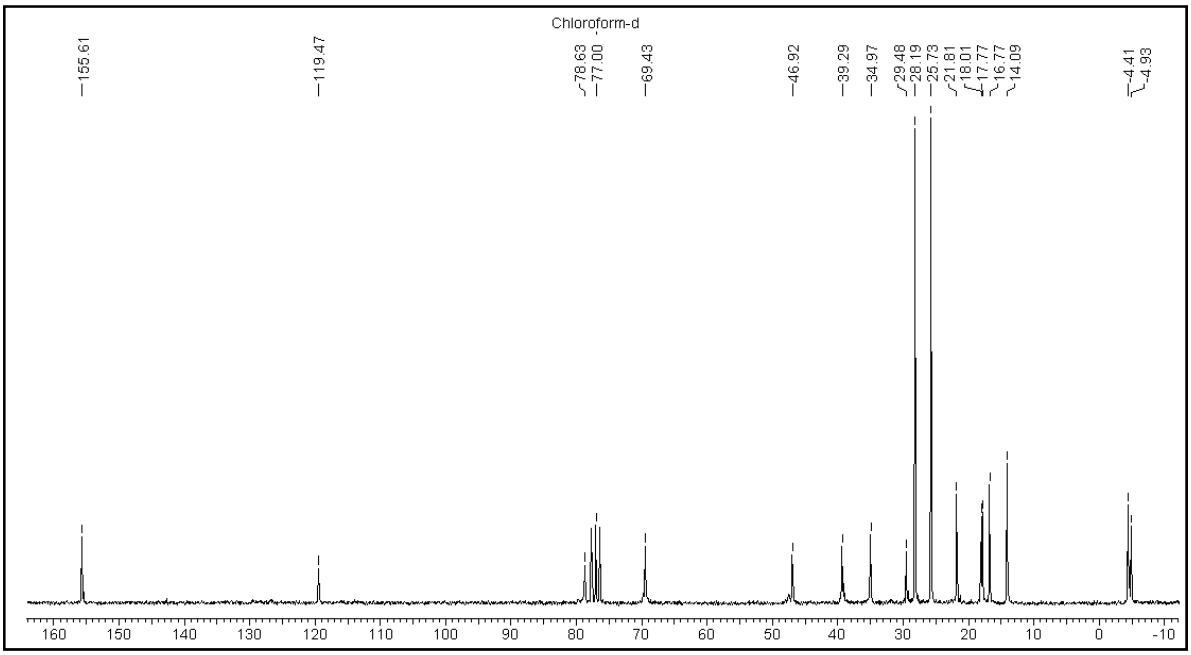


- **^{13}C NMR of the compound 35 in $CDCl_3$**

tert-Butyl ((4_R_,6_R_)-6-((_tert_-butyldimethylsilyl)oxy)-1-cyanononan-4-yl)carbamate (40):

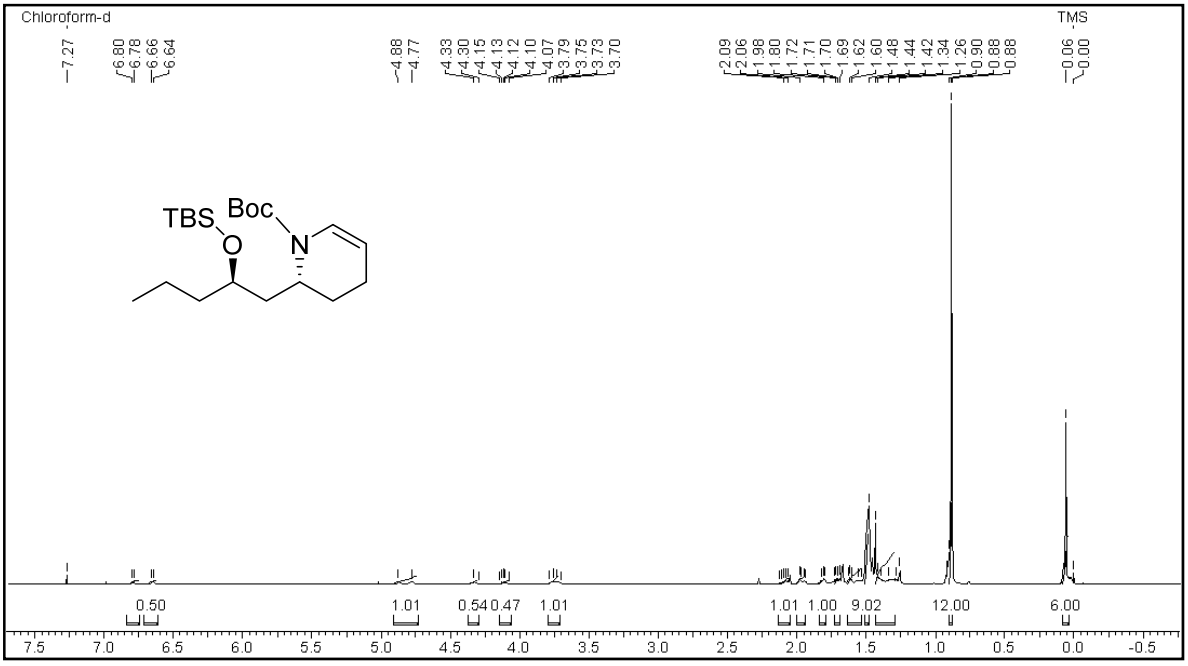


- **^{1}H NMR of the compound 40 in $CDCl_3$**

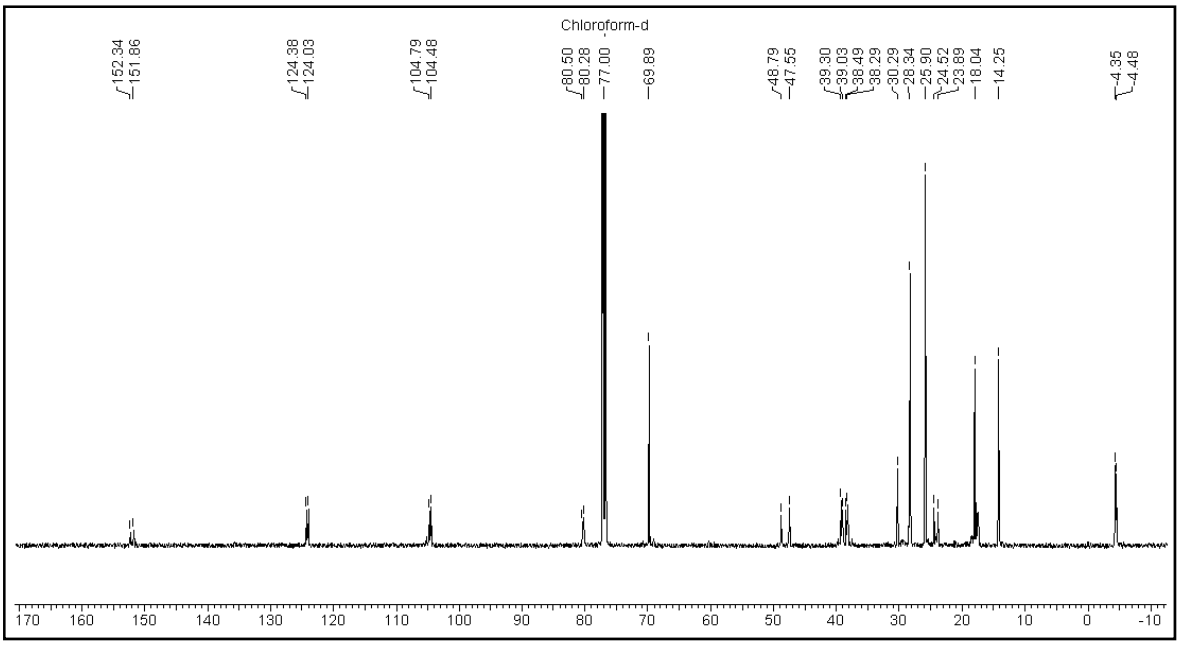


- **^{13}C NMR of the compound 40 in $CDCl_3$**

***tert*-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-3,4-dihydropyridine-1(2H)-carboxylate (41):**

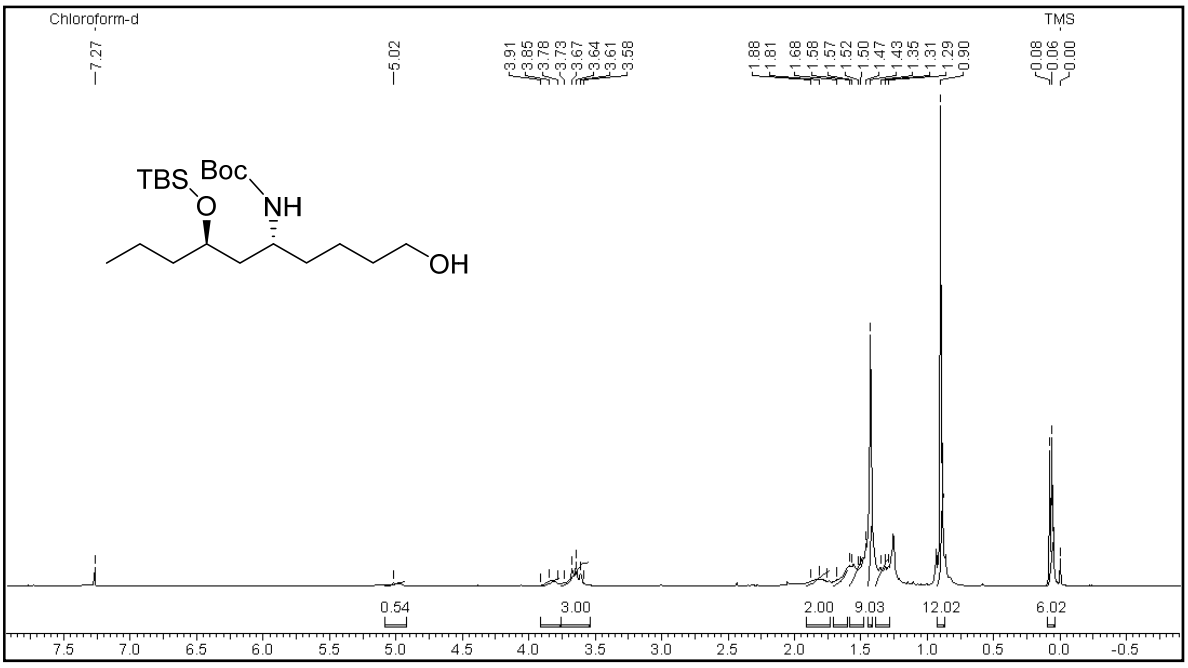


- **^{1}H NMR of the compound 41 in $CDCl_3$**

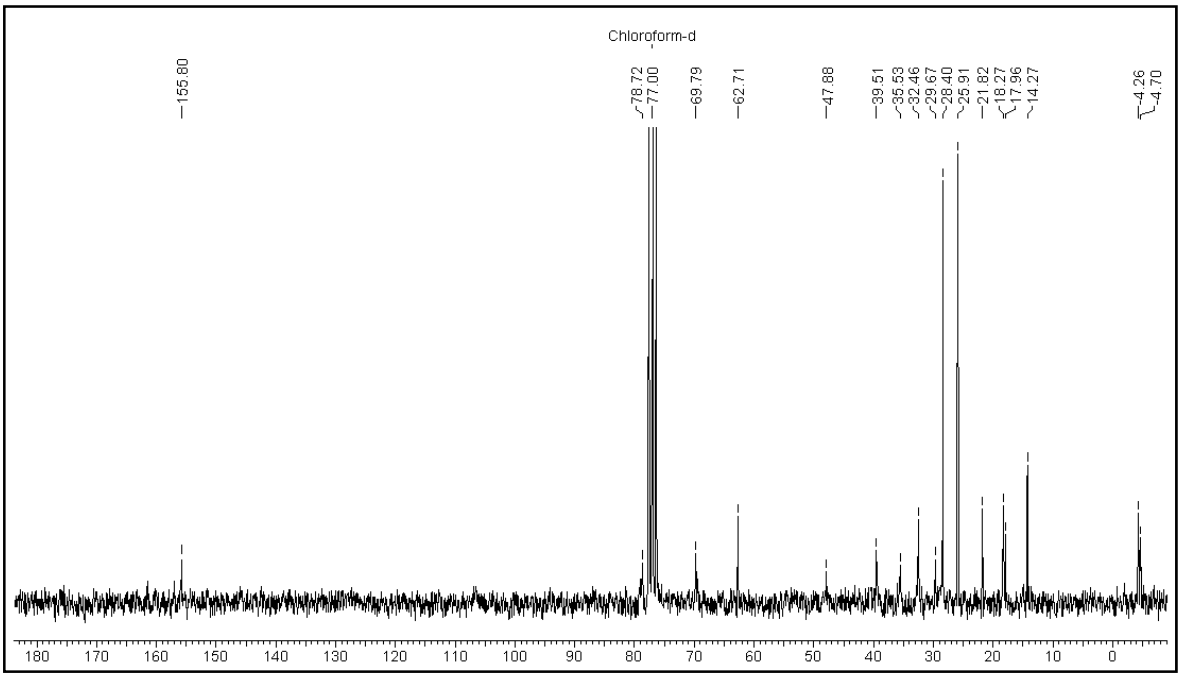


- **^{13}C NMR of the compound 41 in $CDCl_3$**

tert-Butyl((5_R_,7_R_)-7-((_tert_-butyldimethylsilyl)oxy)-1-hydroxydecan-5-yl)carbamate (42):

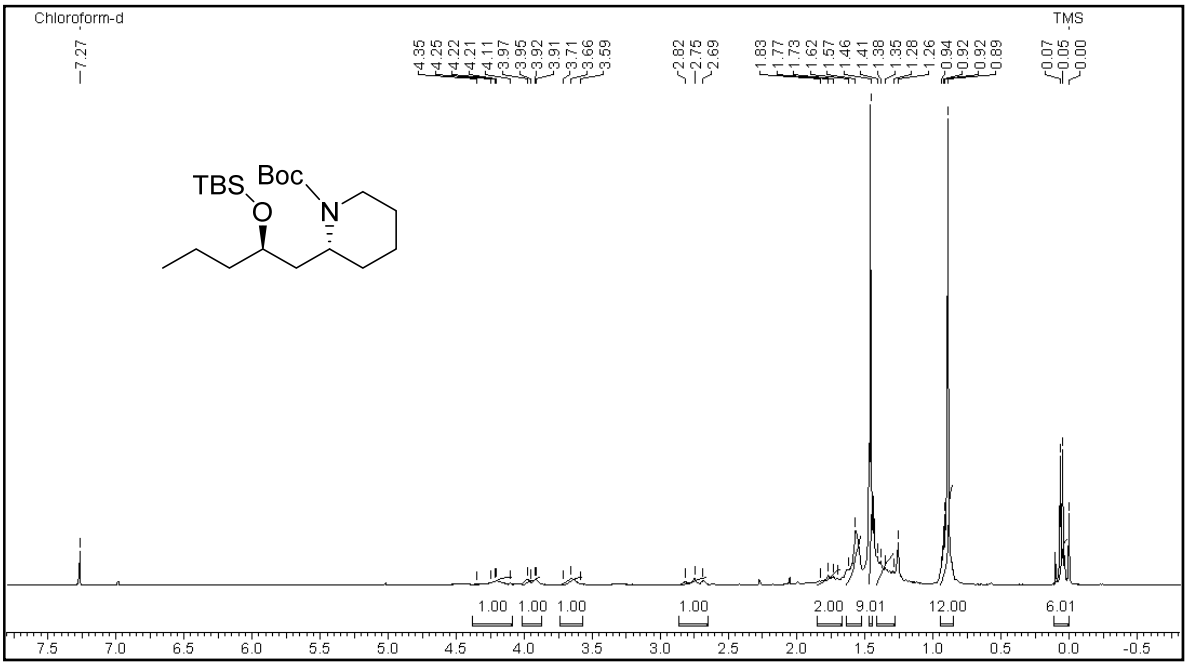


- **^{1}H NMR of the compound 42 in $CDCl_3$**

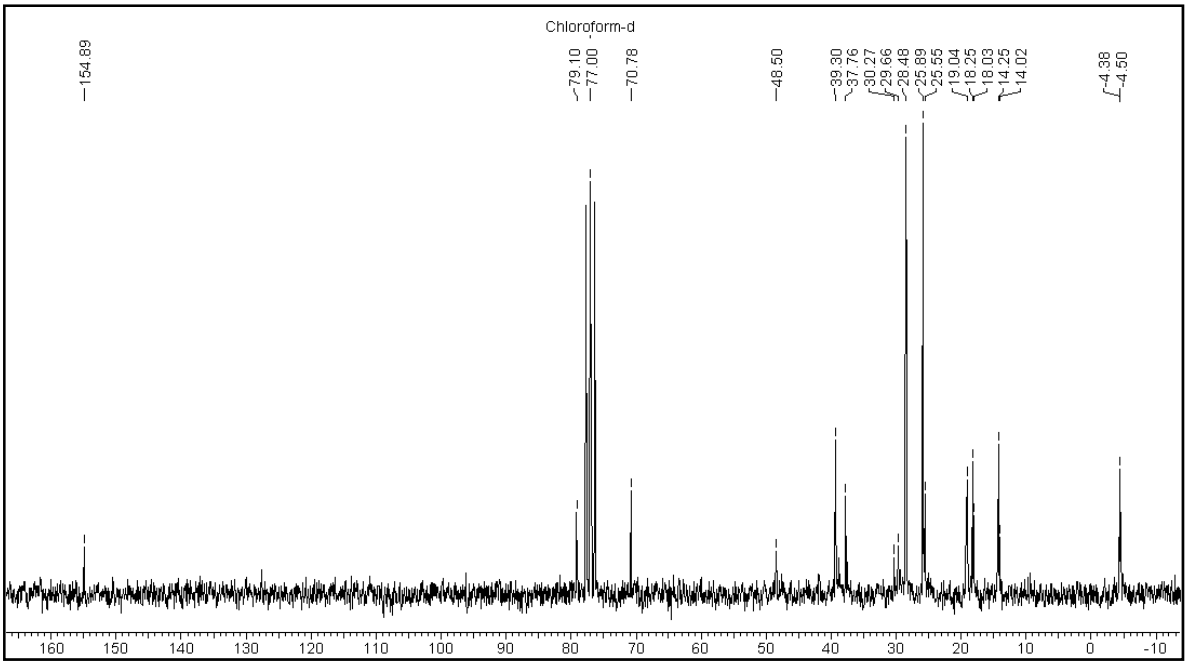


- **^{13}C NMR of the compound 42 in $CDCl_3$**

tert-Butyl(_R_)-2-((_R_)-2-((_tert_-butyldimethylsilyl)oxy)pentyl)piperidine-1-carboxylate (43):

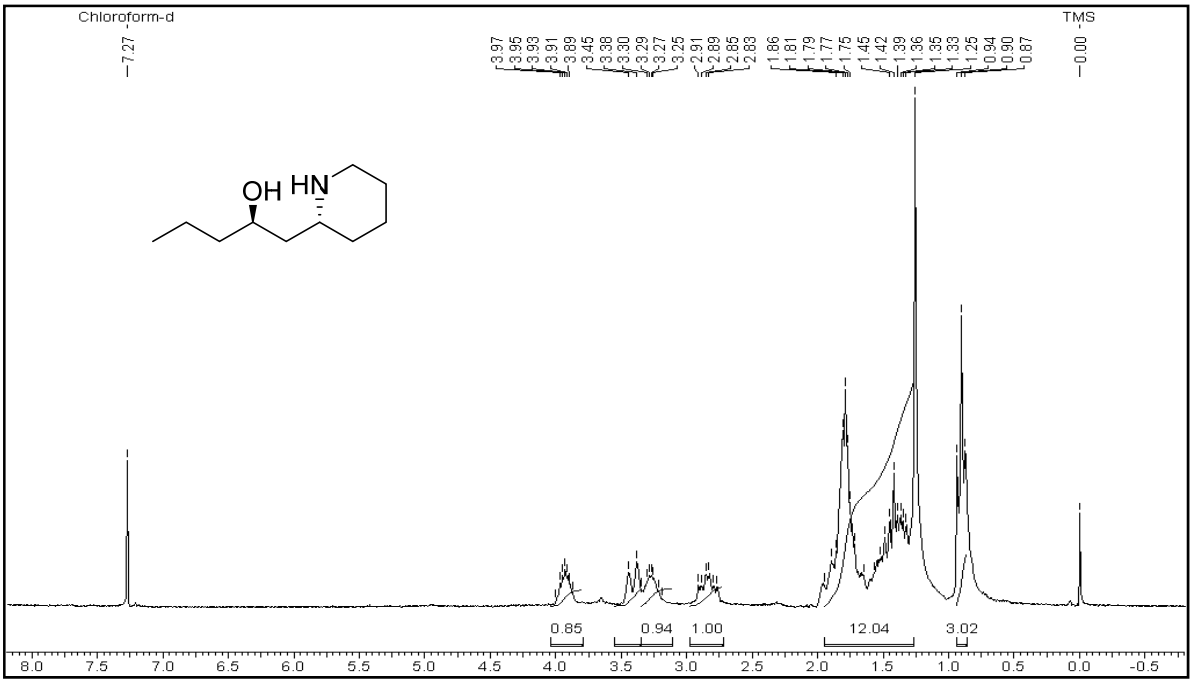


- **^{1}H NMR of the compound 43 in $CDCl_3$**

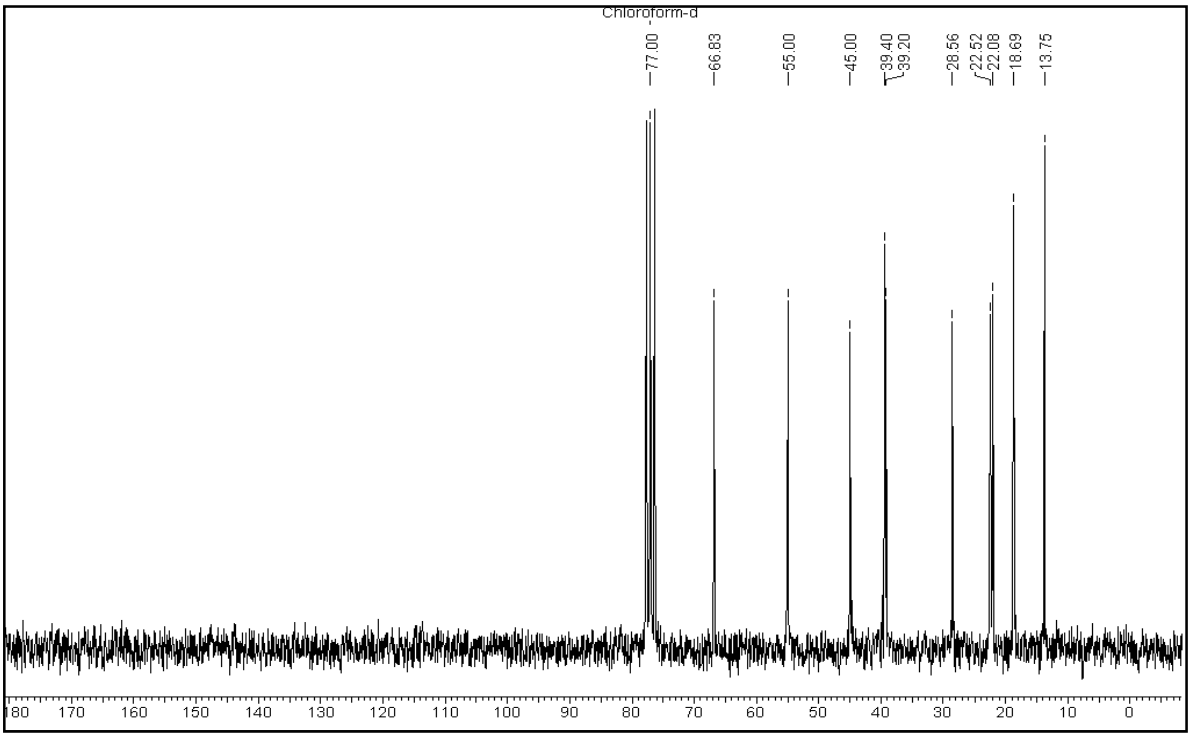


- **^{13}C NMR of the compound 43 in $CDCl_3$**

(-)-Halosaline (1):

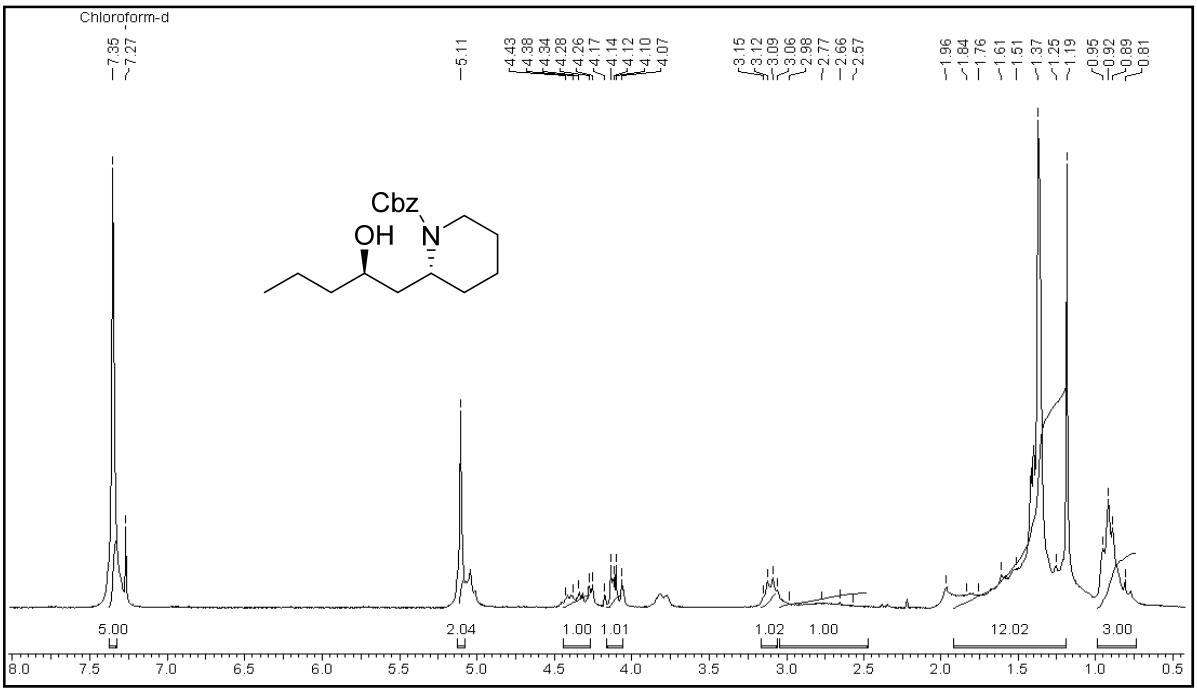


- **^{1}H NMR of the compound 1 in $CDCl_3$**

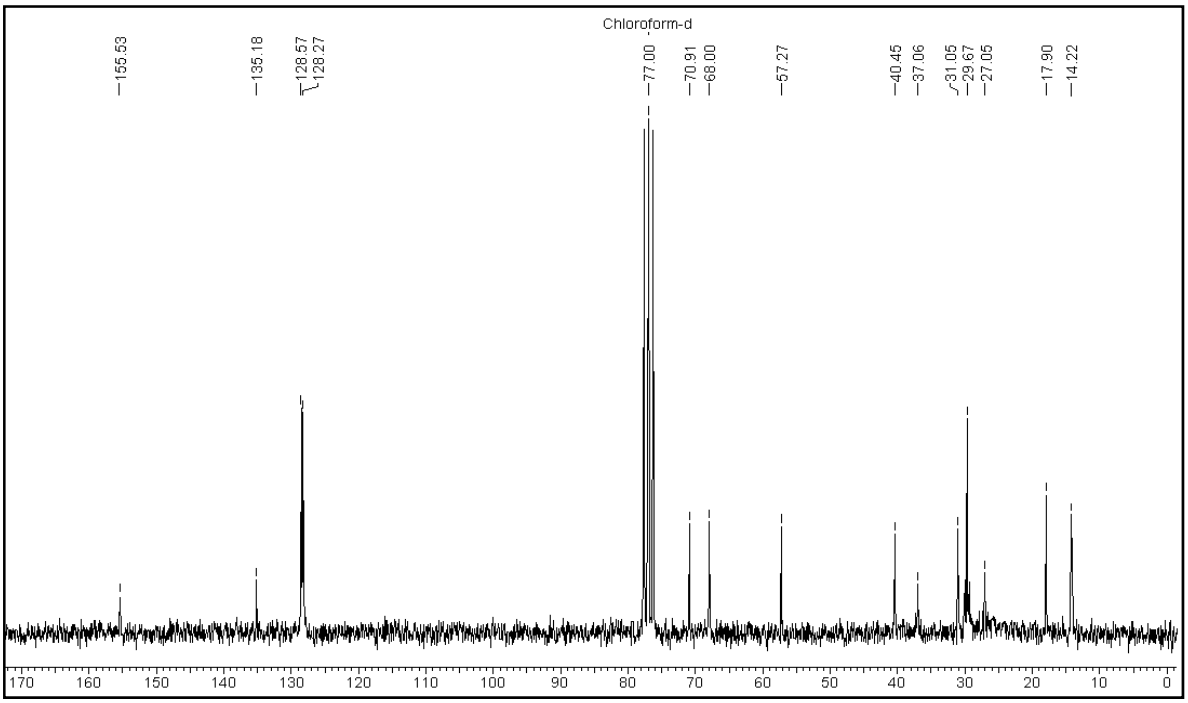


- **^{13}C NMR of the compound 1 in $CDCl_3$**

Benzyl (*R*)-2-((*R*)-2-hydroxypentyl)piperidine-1-carboxylate (44):

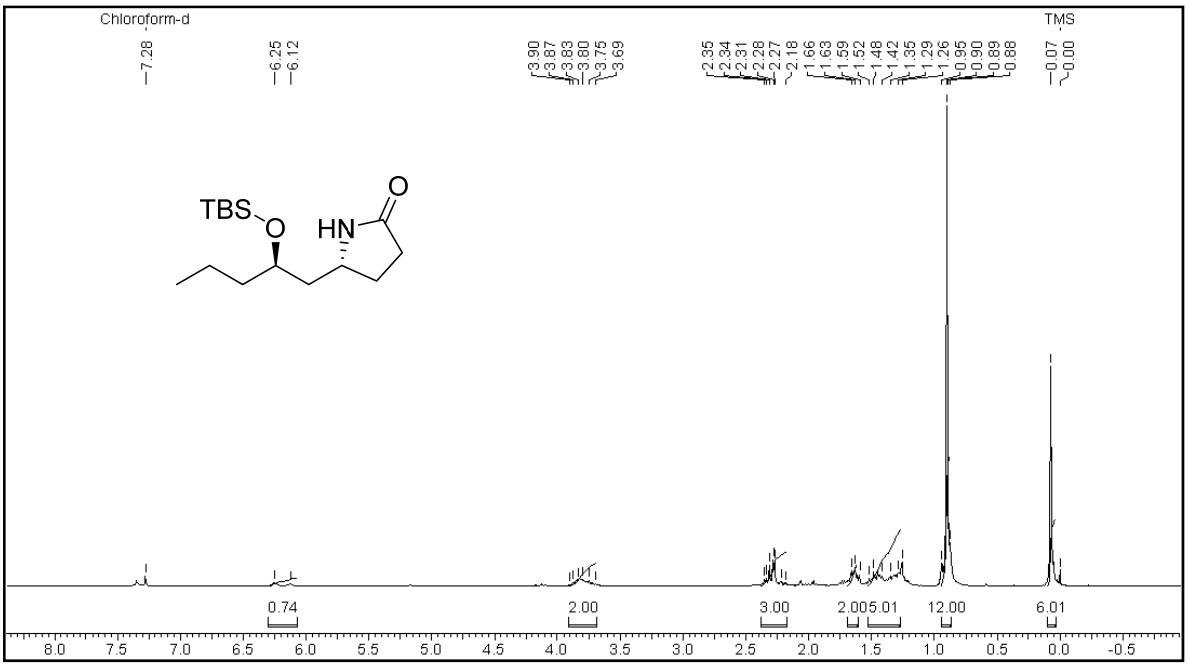


- **^{1}H NMR of the compound 44 in $CDCl_3$**

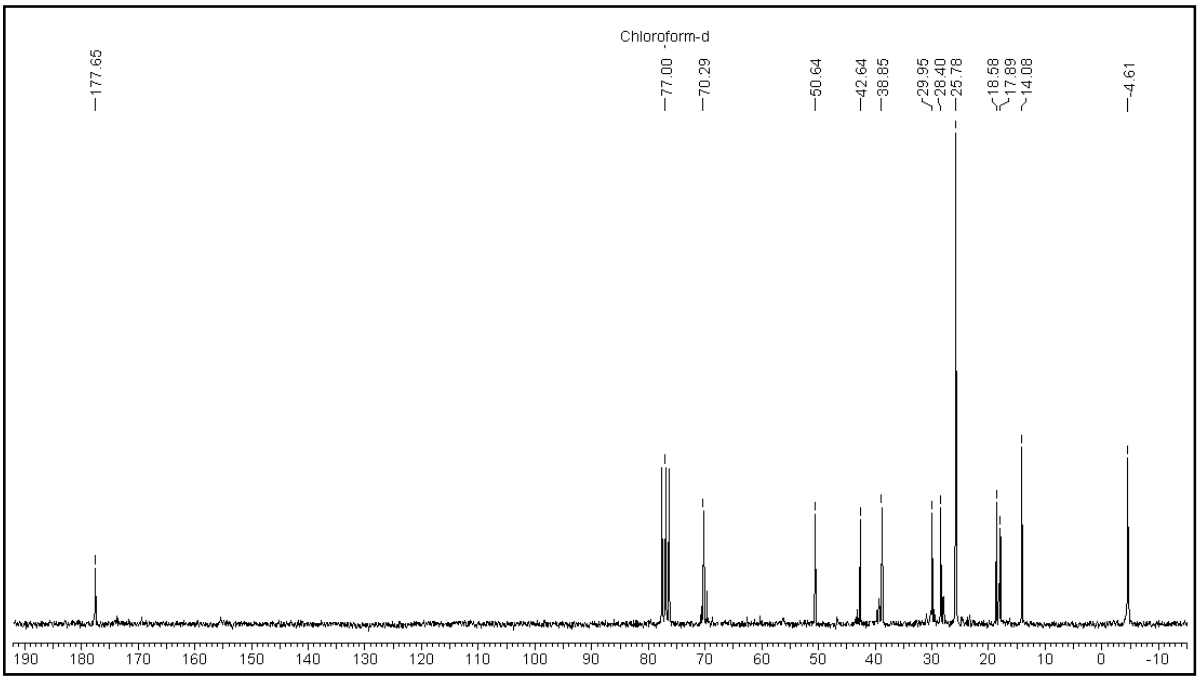


- **^{13}C NMR of the compound 44 in $CDCl_3$**

(*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pentyl)pyrrolidin-2-one (45):

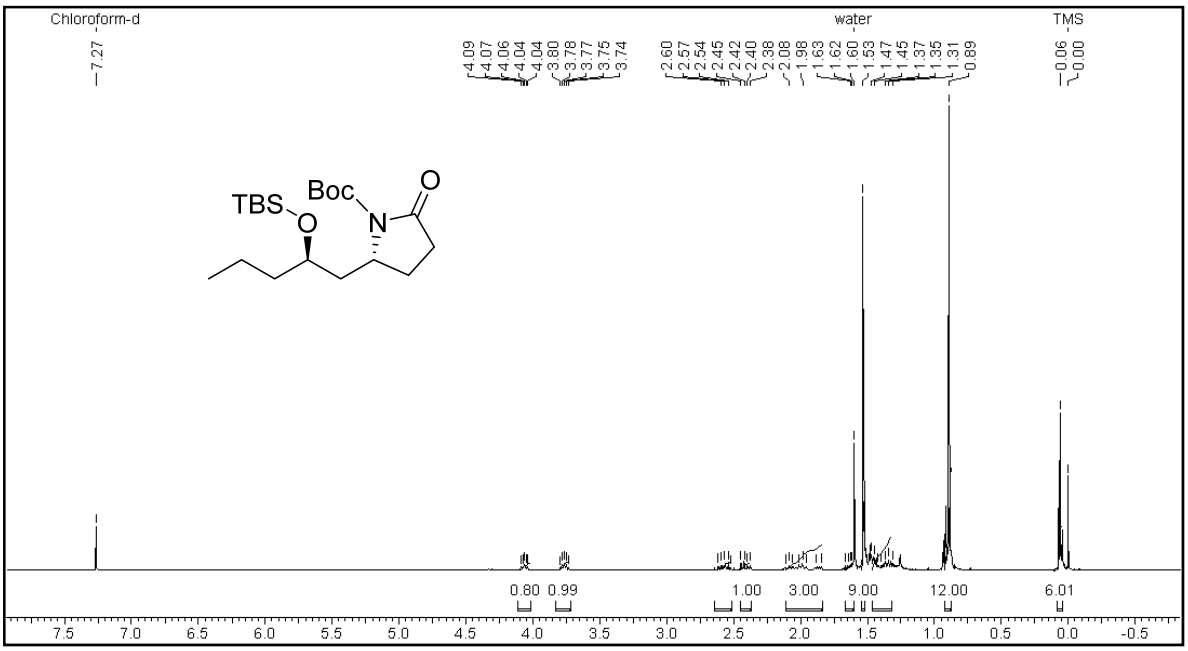


- **^{1}H NMR of the compound 45 in $CDCl_3$**

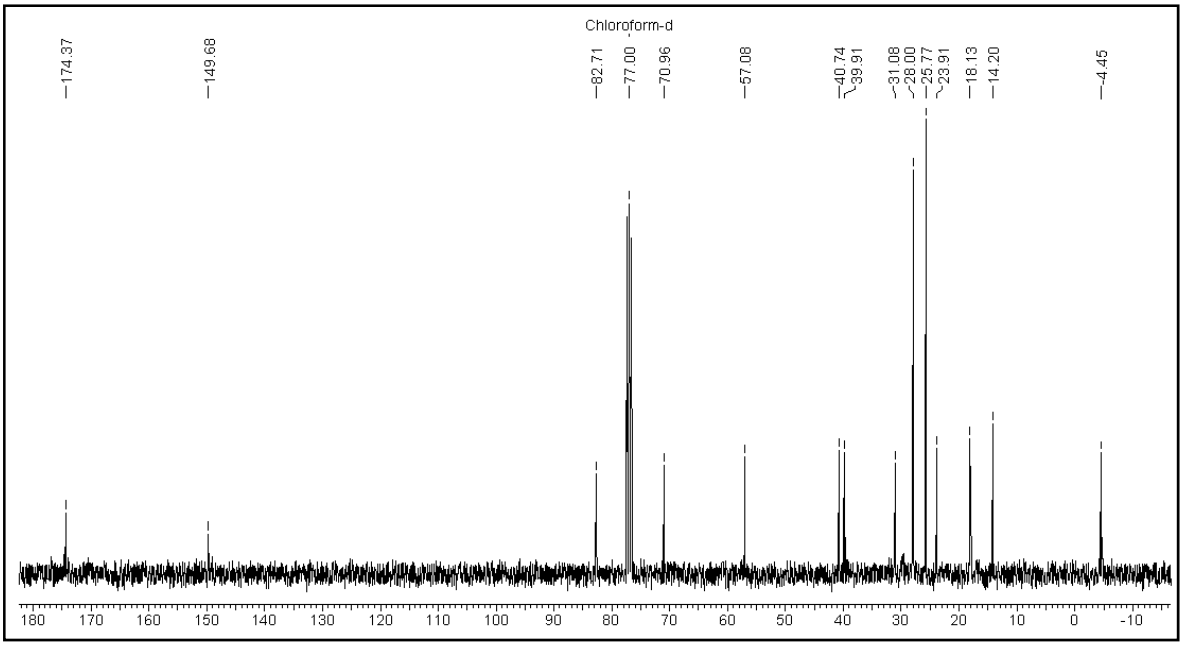


- **^{13}C NMR of the compound 45 in $CDCl_3$**

***tert*-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-oxopyrrolidine-1-carboxylate (39):**

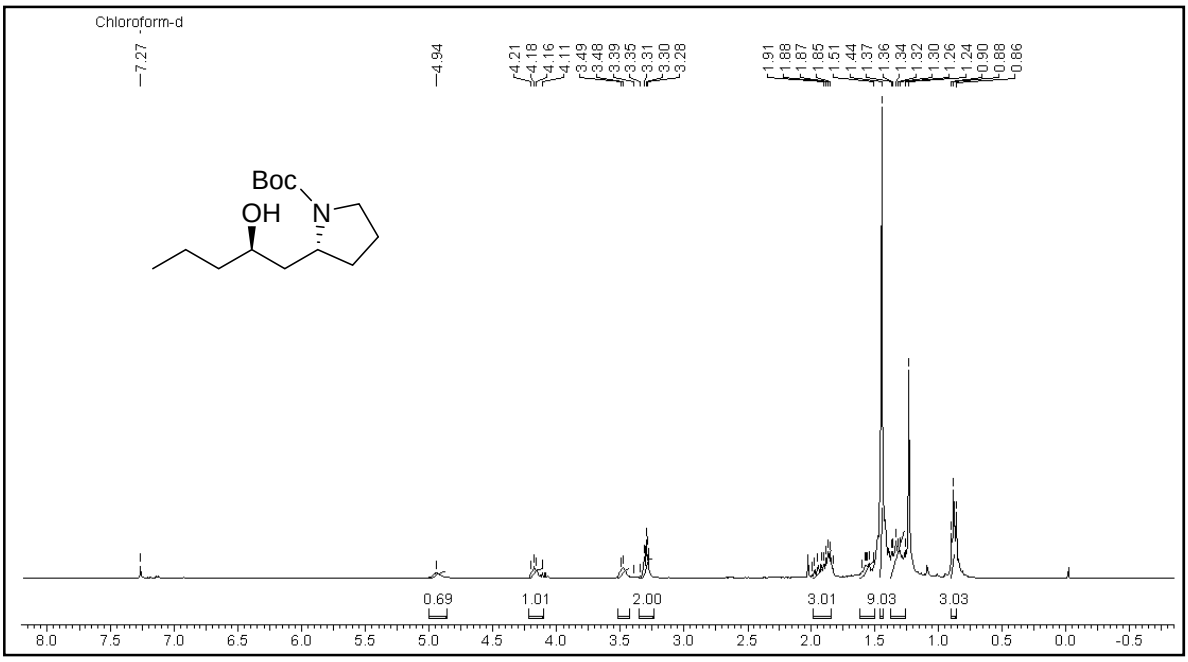


- **^{1}H NMR of the compound 39 in $CDCl_3$**

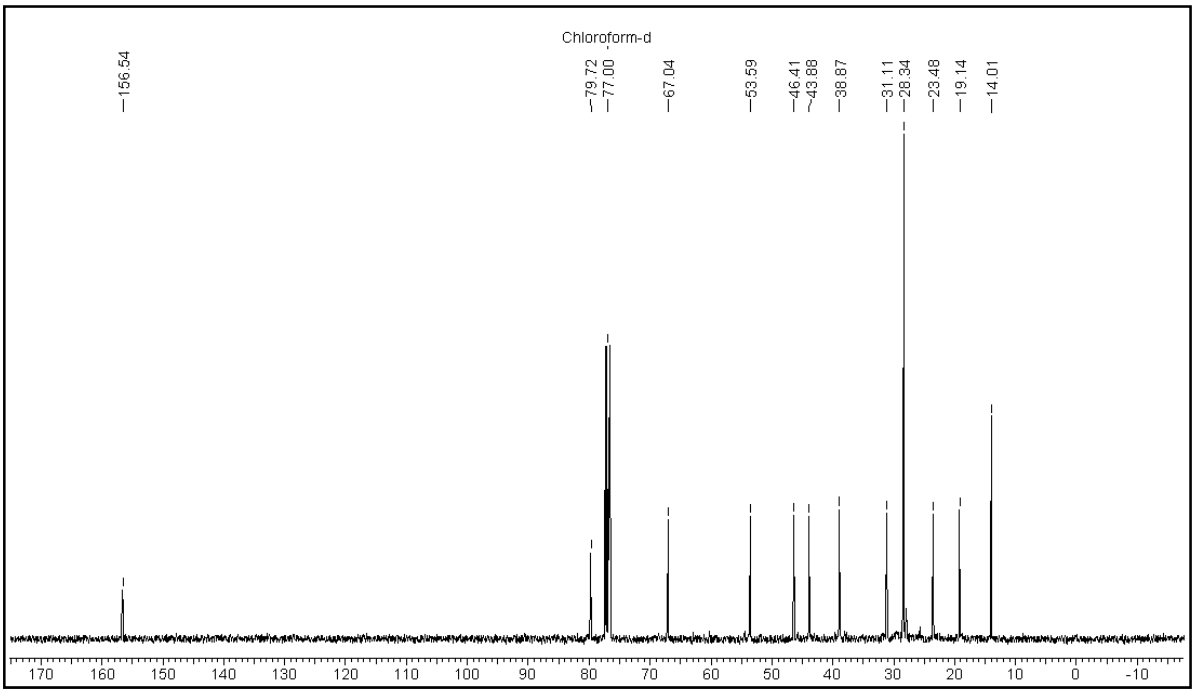


- **^{13}C NMR of the compound 39 in $CDCl_3$**

***tert*-Butyl (*R*)-2-((*R*)-2-hydroxypentyl)pyrrolidine-1-carboxylate (37):**

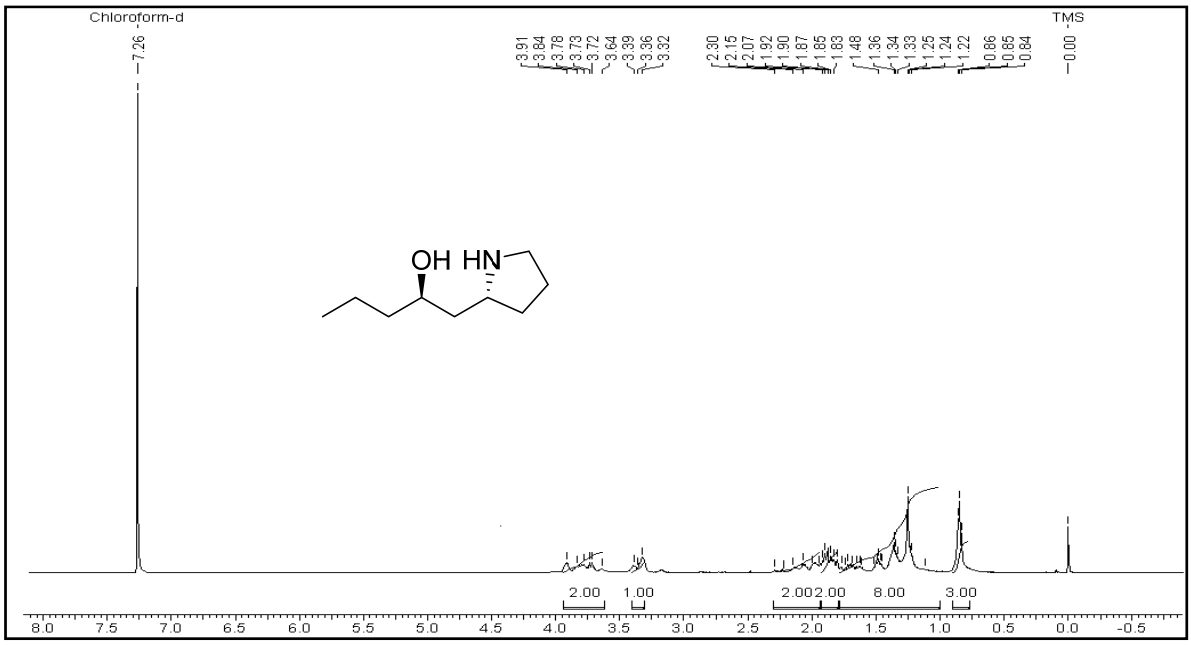


- **^{1}H NMR of the compound 37 in $CDCl_3$**

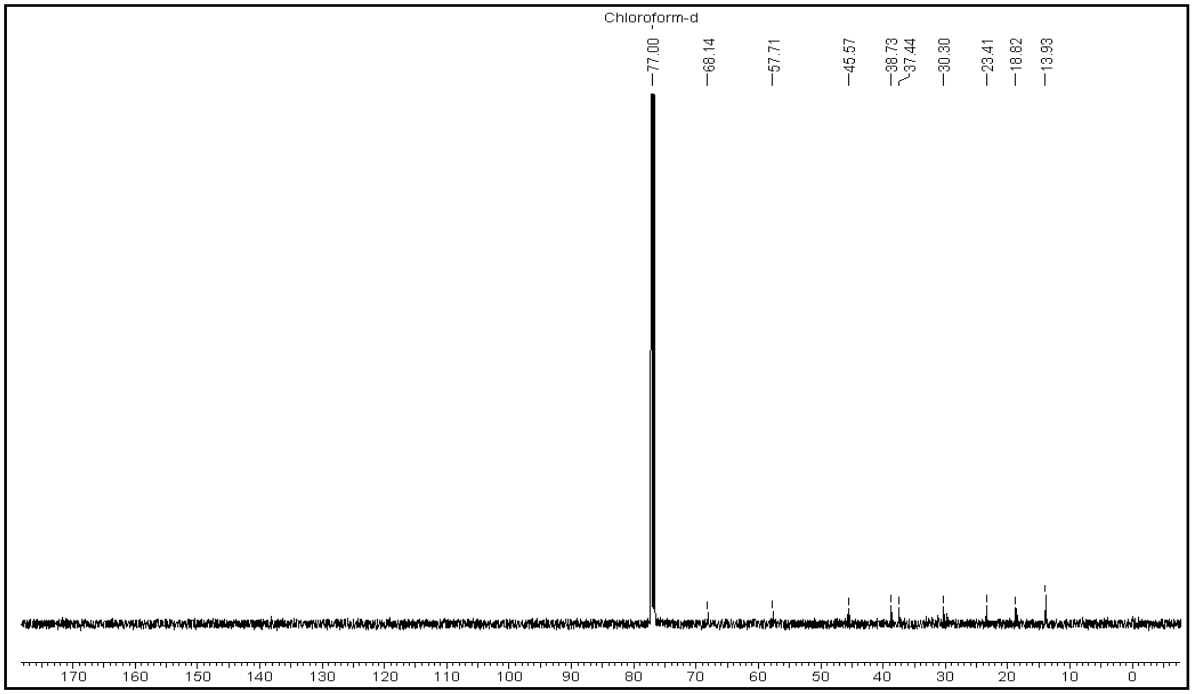


- **^{13}C NMR of the compound 37 in $CDCl_3$**

(R)-1-((R)-Pyrrolidin-2-yl)pentan-2-ol (30):



- **^{1}H NMR of the compound 30 in $CDCl_3$**



- **^{13}C NMR of the compound 30 in $CDCl_3$**

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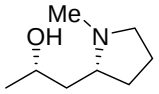
3.2. SECTION B

Synthesis of (+)-hygrine and (+)-pseudohygroline via Proline catalyzed α-functionalization

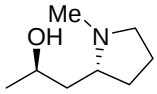
3.2.1. Introduction

The pyrrolidine ring is ubiquitous structural component in many naturally occurring alkaloids which shows a wide range of biologically and pharmacological activity.[1] Due to this, the development of methods for the asymmetric synthesis of 2-substituted pyrrolidine ring systems remains an area of considerable synthetic efforts.[2]

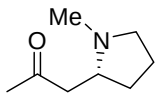
(+)-Pseudohygroline **1** and (+)-hygroline **2** were isolated from *Carallia brachiata*,[3a] *Erythroxylon coca*[2b] and *Schizanthus hookeri*.[3c] Norhygrine **4** was isolated from *Nierembergia hippomanica,*[3d] a toxic plant native to Argentina along with hygrine **3**. Considering their potent biological activity[4] and interesting structural features, several syntheses have been reported for (+)-pseudohygroline.[5]



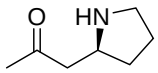
1
(+)-Pseudohygroline



2
(-)-Hygroline



3
(+)-Hygrine,



4
(-)-Norhygrine

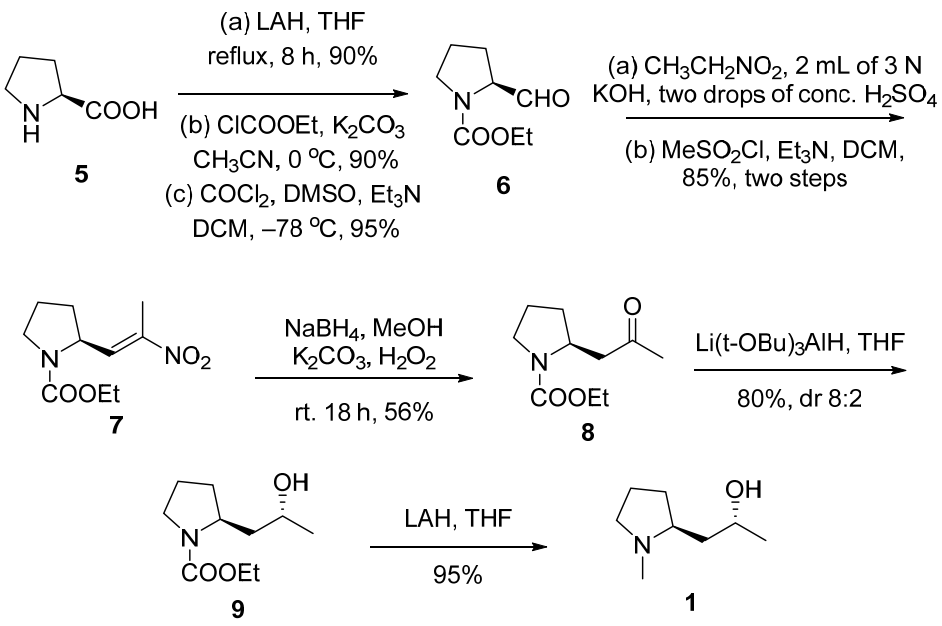
Figure 1.

3.2.2. Review of Literature

Tilve *et al.* (2011)[5a]

Tilve and co-workers synthesized (-)-pseudohygroline **1** starting from L-proline via Henry and Nef reactions. Thus, synthesis started from the cheaply available L-proline **5** which was reduced with LAH followed by protection of nitrogen to give N-protected prolinol. The Swern oxidation of the prolinol gave N-protected prolinal **6** which on Henry reaction with nitroethane gave the corresponding nitro alcohol as diastereomeric mixtures which as such were converted to unsaturated nitro compound **7**. Compound **7** on Nef reaction using $NaBH_4/MeOH/H_2O_2$ gave moderate yields of the keto pyrrolidines

8. The keto group was reduced using Li(t-OBu)$_3$AlH to give hydroxylated pyrrolidines **9** which again on reduction with LAH gave (-)-pseudohygroline **1** (Scheme **1**).

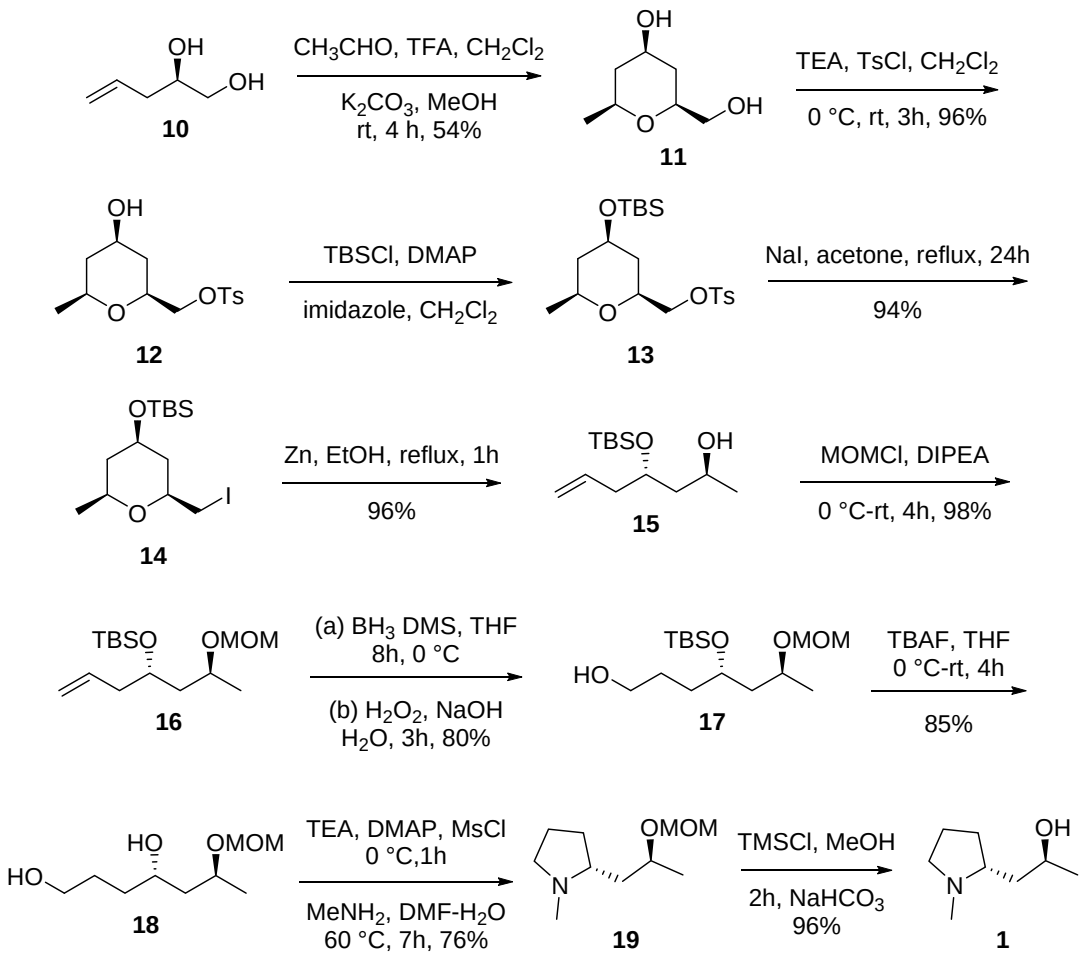


Scheme 1. Synthesis of (-)-pseudohygroline (Tilve method)

Yadav *et al.* (2010)[5b]

Yadav and co-workers synthesized (-)-pseudohygroline **1** starting from chiral homoallylic alcohol **10** which was subjected to Prins cyclisation with acetaldehyde in the presence of TFA (10 equiv), followed by hydrolysis of the resulting trifluoroacetate to give the tetrahydropyranol **11**. The chemoselective tosylation of primary alcohol **11** with 1.1 equiv of tosyl chloride in the presence of TEA in DCM gave the corresponding tosylate **12**, which on protection of secondary alcohol with TBSCl, DMAP and imidazole gave the TBS ether **13**. Treatment of tosylate **13** with NaI in refluxing acetone afforded iodo compound **14**, which on exposure to activated zinc in refluxing ethanol furnished the intermediate **15** with a required anti-1,3-diol system. The newly created secondary alcohol **15** was protected as its MOM ether **16** in the presence of DIPEA and MOM chloride in dichloromethane followed by hydroboration using BH_3-DMS in THF to furnish the primary alcohol **17**. Treatment of compound **17** with TBAF in THF produced the diol **18** in 85% yield. Mesylation of diol **18** with mesyl chloride in the presence of TEA gave the dimesylate, which was subsequently treated with 40% aqueous methylamine in DMF at 60 ^oC to afford the *N*-methyl pyrrolidine **19**. Deprotection of

MOM ether using TMS chloride in methanol gave the pure (+)-pseudohygroline **1** (Scheme **2**).

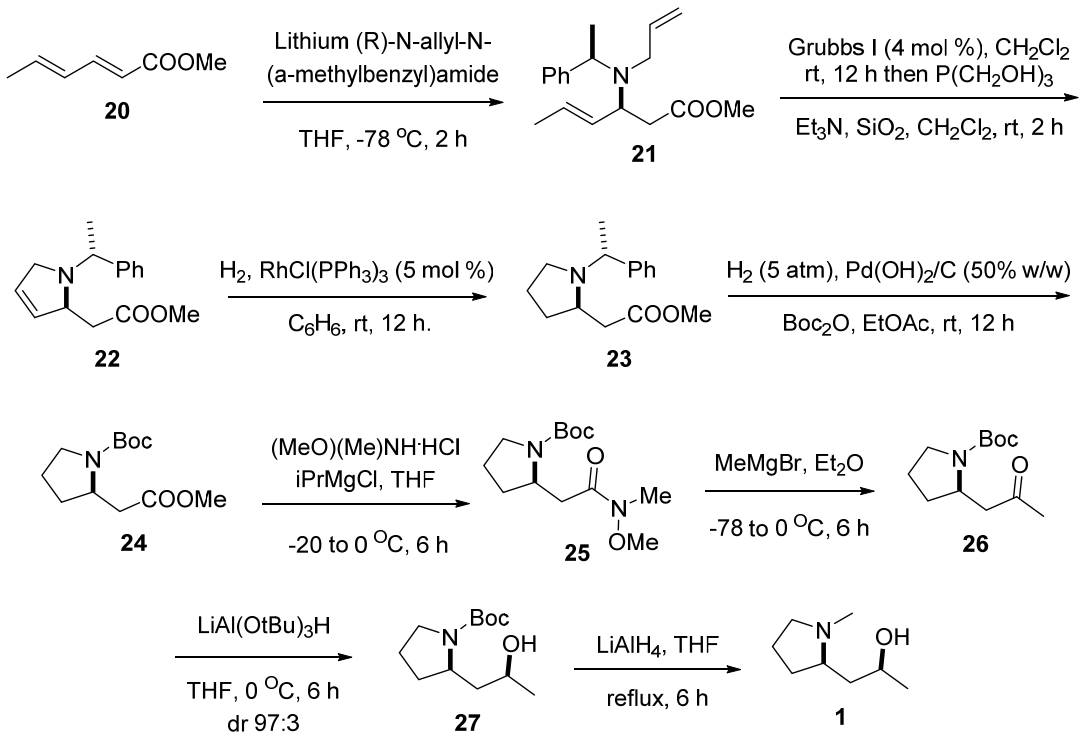


Scheme 2. Synthesis of (+)-pseudohygroline (Yadav method)

Davis *et al.* (2009)[5c]

Davis and co-workers synthesized (+)-pseudohygroline **1** starting from α,β-unsaturated ester **20** which on conjugate addition with lithium (*R*)-N-allyl-N-(a-methylbenzyl)amide furnished β-amino ester (3S,αR) **21** in 83% yield and 97:3 dr after purification. Subsequent ring closing metathesis with Grubbs I furnished dihydropyrrole **22** which on hydrogenation in benzene furnished pyrrolidine **23**. Hydrogenolysis of **23** in the presence of Boc_2O gave N-Boc pyrrolidine **24**, with subsequent treatment with (MeO)(Me)NH·HCl and iPrMgCl giving Weinreb amide **25**. Conversion to the methyl ketones **26** was achieved upon reaction with the methyl Grignard reagent. Reduction of ketones with $LiAl(OtBu)_3H$ proceeded to give the corresponding *syn*-diastereoisomer **27**

as the major product (*syn*:*anti* >99:1), which on further reduction with $LiAlH_4$ gave (+)-pseudohygroline **1**.



Scheme 3. Synthesis of (+)-pseudohygroline (Davis method)

3.2.3. Present work

Objective

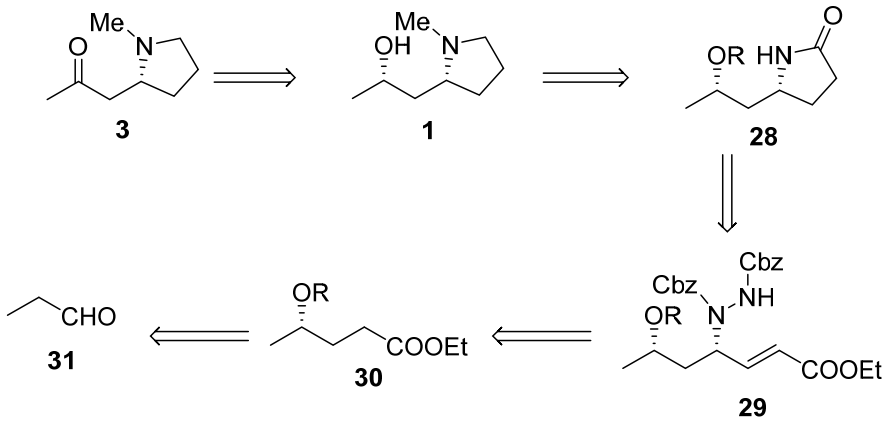
The stereoselective synthesis of 1,3-amino alcohol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-amino alcohol in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. Recently, we have developed an efficient approach to the asymmetric synthesis of 1,3-amino alcohols using sequential α-aminoxylation/α-amination and HWE olefination reaction catalyzed by proline. In continuation of our interest on the application of protocol developed for 1,3-aminoalcohol, we further considered extrapolating the above knowledge to the synthesis of alkaloids containing substituted pyrrolidine ring.

3.2.4. Results and discussion

In recent years, there has been growing interest in the use of small organic molecules to catalyze organic reactions. As a result, the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[7] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[8] 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.[9] Similarly organocatalytic tandem reactions are characterized by high efficiencies and are in a way biomimetic. They avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates. They often proceed with excellent stereocontrol and are environmentally friendly.[10]

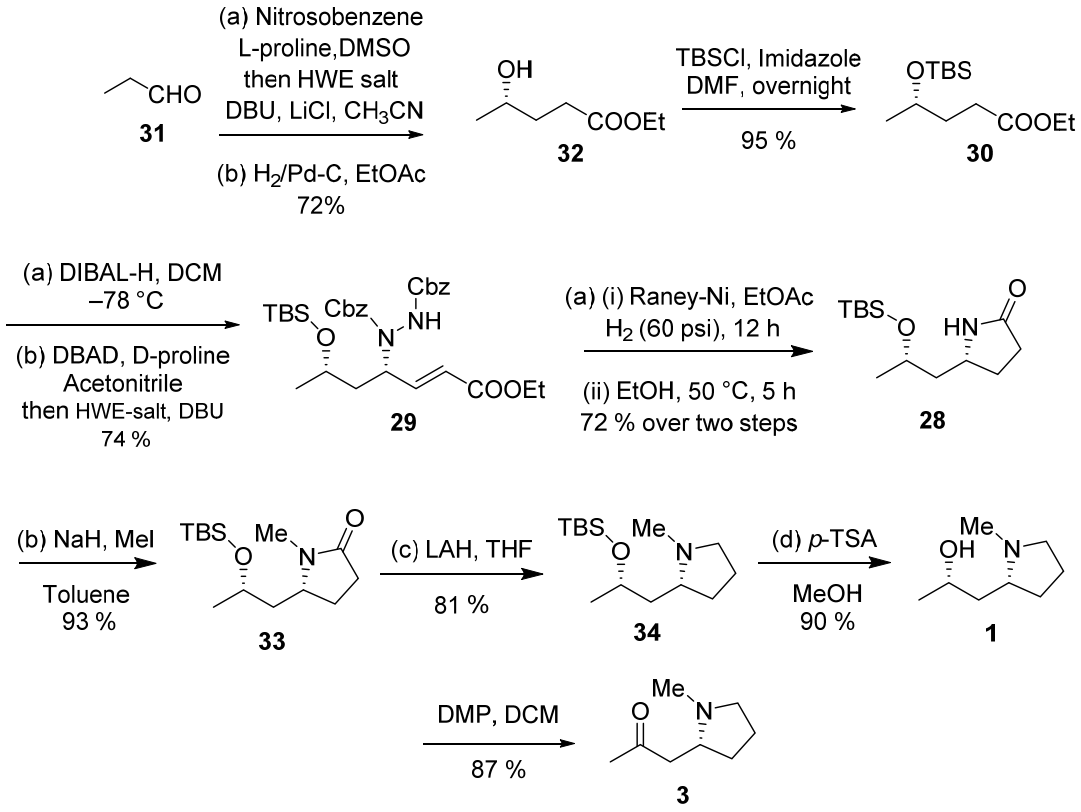
In continuation of our interest in organocatalysis[11] and asymmetric synthesis of 1,3-amino alcohol, we have accomplished the syntheses of substituted pyrrolidine alkaloids, employing proline catalyzed sequential α-aminoxylation[12a-b]/α-amination[12c-d] reaction and HWE olefination reaction.

Our synthetic approach was envisioned via the retrosynthetic route shown in the Scheme **4**. Hygrine **3** could be obtained from pseudohygroline **1**, which in turn could be synthesized from lactam **28**. Lactam **28** could be achieved from 1,3-aminoalcohol **29**, which could be obtained from γ-hydroxy ester **30** by α-amination. γ-Hydroxy ester **30** could be easily obtained by the sequential α-aminoxylation and HWE olefination of the corresponding aldehyde **31**.



Scheme 4. Retrosynthetic route for the synthesis of substituted pyrrolidine alkaloids

Thus synthesis starts with propanaldehyde **31** which on sequential α-aminoxylation using nitroso benzene as oxygen source and D-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy esters **32** in 72% yield and 95% ee. The free hydroxy group of γ-hydroxy esters **32** was protected as TBS ether using TBSCl in DMF to furnish compound **30** in 95% yield. Disappearance of peak at 3425 cm^{-1} in IR spectrum confirmed the formation of **30**. The DIBAL-H reduction of ester **30** at –78 ^oC furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to furnish the α-amino aldehyde, which on in situ trapping by triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *syn*-1,3-amino alcohol **29** in 74% yield and 9:1 diastereomeric ratio as determined from HPLC analysis. The *N*-*N*-bond of diastereomerically pure 1,3-*syn*-aminoalcohol **29** was easily cleaved with concomitant reduction of double bond under hydrogenation condition using freshly prepared Raney-Ni at 60 psi of H_2 to give free amine, which was refluxed in ethanol to afford the lactam **28** in 72% yield (over two steps). Monoalkylation of **28** using MeI and NaH furnished the *N*-methylated compound **33** in 95% yield. The disappearance of -NH protons in the range of δ 6.26 as brs and appearance of $–CH_3$ proton at 2.79 as singlet in ^1H NMR spectrum confirmed the formation of the *N*-methylated product **33**. LAH reduction of amide **33** furnished amine **34** in 81% yield. Disappearance of peak at 1676 cm^{-1} in IR spectrum confirmed the reduction of amide **34**. Finally TBS deprotection using *p*-TSA in methanol afforded the target compound **1** in 90% yield. DMP oxidation of **1** gave another target compound **3** (Scheme **5**).



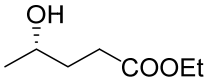
Scheme 5: Synthesis of substituted pyrrolidine alkaloids

3.2.5. Conclusion

In conclusion, we have developed an organocatalytic approach to (+)-pseudohygroline and (+)-hygrine in high enantio- and diastereomeric excess using proline catalyzed sequential α-aminoxylation/α-amination and HWE olefination reaction of an aldehydes as the key step. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the proline in the α-aminoxylation/α-amination step. The target compound **1** has been synthesized from **31** in 8 steps and in 21.49% overall yield. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other substituted pyrrolidine alkaloids.

3.2.6. Experimental Section

Ethyl (*S*)-4-hydroxypentanoate (32):



To a solution of propanal **31** (2.0 g, 34.5 mmol) and nitroso benzene (3.69 g, 34.5 mmol) in anhydrous DMSO (70 mL) was added D-proline (1.59 g, 13.8 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to orange red during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (20.6 mL, 103.5 mmol), DBU (15.5 mL, 103.5 mmol) and LiCl (4.395 g, 103.5 mmol) in CH_3CN (70 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 ^{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 crude γ-hydroxy ester **32**. The crude product was then purified by using silica gel flash column chromatography using pet ether: EtOAc (85:15) as eluent to give (*S*)-ethyl 4- hydroxypentanoate **32** as a colorless liquid

Yield: 3.62 g, 72 %

Mol. Formula: $C_7H_{14}O_3$

$[\alpha]_D^{25}$: + 12.36 (*c* 2.0, $CHCl_3$) {lit.[13a] **$[\alpha]_D^{25}$:** + 12.8 (c 2.37, $CHCl_3$)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3425, 2930, 1718, 1191.

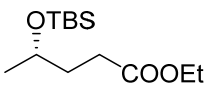
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19-1.29 (m, 6H), 1.32-1.36 (m, 3H), 1.66-1.83 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 3.72-3.88 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 23.1, 30.6, 33.6, 60.3, 66.9, 174.1 ppm.

MS (ESI): m/z 169.06 $(M+Na)^+$

The enantiomeric excess (ee) was determined by comparing the optical rotation with the literature value. The ee was found to be > 94%.

Ethyl (*S*)-4-((*tert*-butyldimethylsilyl)oxy)pentanoate (30):



To an ice-cold stirred solution of **32** (1.0 g, 6.85 mmol) in DMF (12 mL) were added imidazole (0.560 g, 8.21 mmol) and TBSCl (1.237 g, 8.21 mmol) at room temperature. The resulting mixture was stirred for 6 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 25 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/ 99:1) of the crude product gave (*S*)-ethyl 4-(*tert*-butyldimethylsilyloxy)pentanoate **30** as a colorless liquid

Yield: 1.53 g, 95%

$[\alpha]_D^{25}$: + 14.36 (*c* 2.0, $CHCl_3$) {lit.[13b] for *R*-isomer $[\alpha]_D^{25}$: -15.2 (*c* = 0.5, CHCl3)}.

Mol. Formula: $C_{13}H_{28}O_3Si$

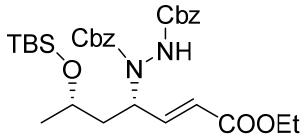
IR ($CHCl_3$, cm^{-1}): ν_{max} 2934, 1718, 1462, 1256, 1174.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (d, *J* = 1.2 Hz, 6 H), 0.87 (s, 9H), 1.13 (d, *J* = 6.1 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.64–1.77 (m, 2H), 2.35 (td, *J* = 7.2, 2.1 Hz, 2 H), 3.75–3.89 (m, 1 H), 4.11 (q, *J* = 7.1 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.5, 14.2, 17.9, 23.6, 25.8, 30.4, 34.3, 60.1, 67.4.5, 173.8 ppm.

MS (ESI): m/z 283.14 $(M+Na)^+$

Dibenzyl 1-((4*S*,6*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (29):



To a solution of ethyl ester **30** (1.0 g, 3.84 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (1.9 mL 2.25 M solution in toluene, 4.23 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (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 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.96 g, 3.22 mmol) and D-proline (0.036 g, 8 mol%) in CH_3CN (32 mL) at 0 °C was added above aldehyde (1.0 g,

3.84 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 (0.21 g, 4.84 mmol), triethyl phosphonoacetate (0.97 mL, 4.84 mmol) and DBU (0.48 mL, 3.22 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 (diastereomeric ratio/ 97:3). Silica gel column chromatography (petroleum ether: ethyl acetate/ 89:11) of the crude product gave dibenzyl 1-((4*S*,6*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate **29** as a colorless syrupy liquid

Yield: 1.51 g, 74 %

Mol. Formula: $C_{31}H_{44}N_2O_7Si$

$[\alpha]_D^{25}$: + 2.32 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3295, 2956, 1755, 1719, 1406, 1043.

^{1}H NMR (200 MHz, $CDCl_3$): δ - 0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 2H), 1.64-1.72 (m, 2H), 3.76-3.93 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.91-5.15 (m, 5H), 5.94 (m, 1H), 6.57 (brs, 1H), 6.83 (dd, *J* = 6.8, 15.6 Hz, 1H), 7.31 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.1, 14.1, 17.9, 24.1, 29.9, 40.6, 56.5, 60.5, 67.4, 67.7, 68.3, 122.9, 128.0, 128.1, 128.3, 128.4, 135.5, 144.6, 155.3, 156.3, 166.1 ppm.

MS (ESI): m/z 607.32 $(M+Na)^+$

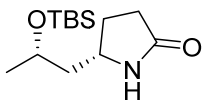
HRMS: 585.2991 $(M+H)^+$ Calcd. 585.2991

Diastereomeric ratio was determined by HPLC analysis; 19:1 dr

UV detector: Merck-HITACHI L-7400 series

Column: Kromasil RP-18, Flow rate: 1.0 mL/min, MeOH = 100; t_R for (*anti*)-isomer = 6.96 min and t_R for (*syn*)-isomer = 5.78 min.

(*S*)-5-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (28):



The solution of dibenzyl 1-((4*S*,6*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate **29** (1.0 g, 1.71 mmol) in MeOH (10 mL)

and acetic acid (8 drops) was treated with Raney nickel (0.9 g, excess) under H_2 (80 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 ^oC for 5h. 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 cyclic lactam (*S*)-5-((*S*)-2-((*tert*-butyldimethylsilyl)oxy) propyl)pyrrolidin-2-one **28** as a colorless liquid.

Yield: 0.318 g, 72 % (over two steps)

Mol. Formula: $C_{13}H_{27}NO_2Si$

$[\alpha]_D^{25}$: - 0.46 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3205, 2957, 1698, 1462, 1093.

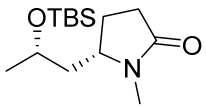
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.59-1.77 (m, 3H), 2.19-2.36 (m, 3H), 3.70-3.80 (m, 1H), 3.88-4.00 (m, 1H), 6.26 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.0, -4.5, 17.7, 23.9, 25.6, 27.4, 29.9, 45.9, 52.3, 66.6, 178.2 ppm.

MS (ESI): m/z 280.13 $(M+Na)^+$

HRMS: 258.1884 $(M+H)^+$ Calcd. 258.1884

(*S*)-5-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidin-2-one (33):



To a stirred solution of **28** (0.1 g, 0.389 mmol) in dry toluene (8 mL) was added NaH (0.038 g, 1.56 mmol), CH_3I (0.25 mL, 4 mmol) and the reaction mixture was heated at 85 ^oC for 5 h. The reaction mixture was then diluted with EtOH (20 mL) and H_2O (2 mL), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 8 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/ 70:30) of the crude product gave (*S*)-5-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidin-2-one **33** as a colorless liquid

Yield: 0.102 g, 93%

Mol. Formula: $C_{14}H_{29}NO_2Si$

$[\alpha]_D^{25}$: + 57.54 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2957, 1676, 1425, 1090.

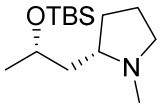
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.69-1.76 (m, 2H), 1.85-1.98 (m, 1H), 2.11-2.16 (m, 1H), 2.31-2.42 (m, 2H), 2.79 (s, 3H), 3.58-3.71 (m, 1H), 3.84-3.97 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.0, -4.0, 17.9, 24.1, 24.6, 25.7, 27.6, 29.8, 42.7, 57.2, 65.1, 174.8 ppm.

MS (ESI): m/z 294.12 $(M+Na)^+$

HRMS: 272.2040 $(M+H)^+$ Calcd. 272.2040

(*S*)-2-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidine (34):



To a stirred suspension of $LiAlH_4$ (0.036 g, 0.93 mmol) in dry THF (1 mL) was added a solution of **33** (0.10 g, 0.369 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 sulphate (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 (petroleum ether: ethyl acetate/ 50:50) of the crude product gave (*S*)-2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidine **34** as a colorless liquid.

Yield: 0.034 g, 81%

Mol. Formula: $C_{14}H_{31}NOSi$

$[\alpha]_D^{25}$: + 18.25 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2960, 1445, 1261, 1088.

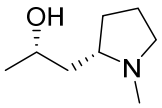
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.95-2.08 (m, 4H), 2.15-2.36 (m, 3H), 2.74-2.85 (m, 1H), 2.79 (s, 3H), 3.10-3.21 (m, 1H), 3.84-3.89 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.0, -3.9, 17.8, 21.3, 24.4, 25.7, 29.2, 38.6, 39.2, 55.5, 65.9, 66.6 ppm.

MS (ESI): m/z 258.09 $(M+H)^+$.

HRMS: 258.2249 $(M+H)^+$ Calcd. 258.2248

(+)-Psuedohygroline (1):



To a stirred solution of compound **34** (0.03g, 0.083 mmol) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture was stirred overnight at the same temperature. Solid $NaHCO_3$ (0.06 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated and column purified using ethyl acetate to give (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol **1** as a colorless liquid.

Yield: 0.02 g, 90%

Mol. Formula: $C_8H_{17}NO$

IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 1454, 1215, 1190.

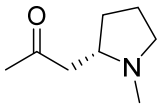
$[\alpha]_D^{25}$: - 48.12 (*c* 0.5, EtOH)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (d, J = 6.2 Hz, 3H), 1.31-1.45 (m, 3H), 1.71-1.78 (m, 2H), 1.98-2.04 (m, 1H), 2.31-2.40 (m, 1H), 2.37 (s, 3H), 2.69-2.77 (m, 1H), 3.00-3.08 (m, 1H), 3.87-3.96 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 22.8, 29.1, 38.1, 40.6, 56.5, 67.1, 68.2 ppm.

MS (ESI): m/z 144.22 $(M+H)^+$

(+)-Hygrine (3):



To a stirred solution of **1** (0.020 g, 0.142 mmol) in CH_2Cl_2 (1 mL) was added DMP (0.010 g, 0.213 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 1 hr. It was then quenched with a 1:1 mixture of (10 %) aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and extracted with diethyl ether (3 X 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude aldehyde Silica gel column chromatography ($CHCl_3$: MeOH/ 8.5:1.5) of the crude product gave (+)-hygrine **3** as a colorless syrupy liquid.

Yield: 0.016 g, 87%

Mol. Formula: $C_8H_{15}NO$

IR ($CHCl_3$, cm^{-1}): ν_{max} 2925, 2853, 1718, 1583, 1459, 1376.

$[\alpha]_D^{25}$: + 35.78 (*c* 0.5, H_2O)

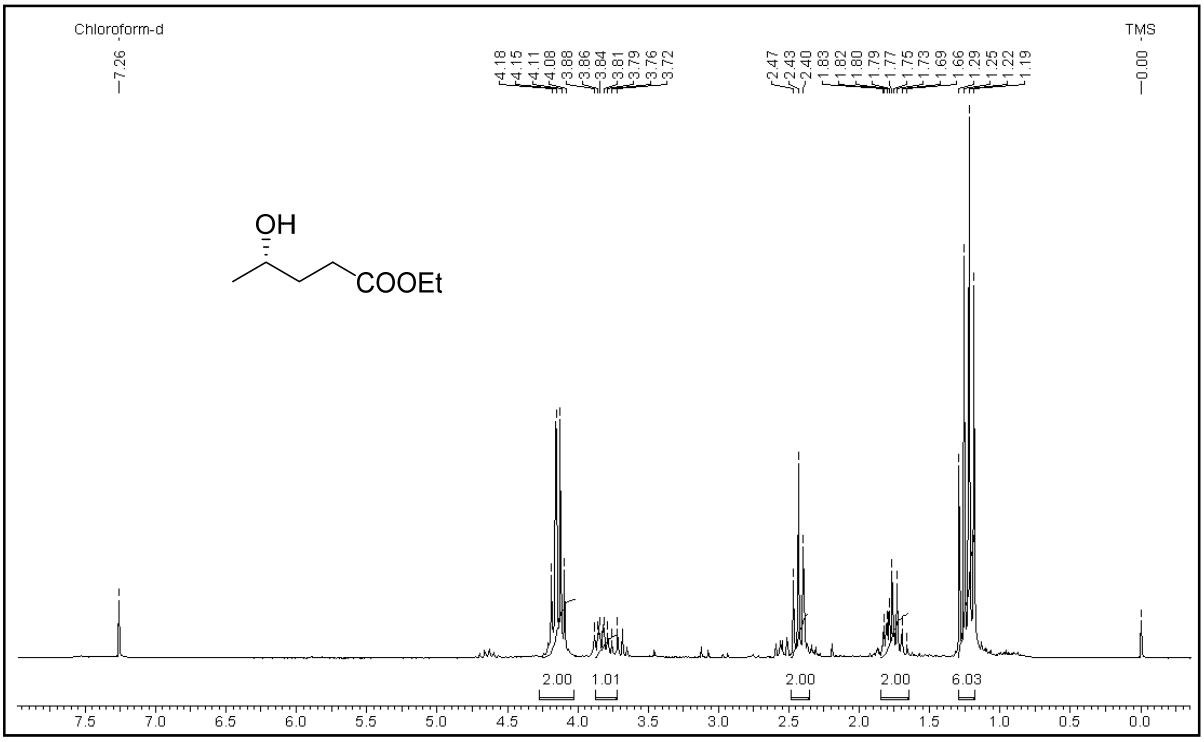
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73-2.16 (m, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.99-3.21 (m, 3H), 3.42 (dd, J = 5.9, 18.8 Hz, 1H), 3.53-3.65 (m, 1H), 3.90-4.02 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 30.0, 30.1, 40.7, 44.0, 56.4, 64.6, 205.3 ppm.

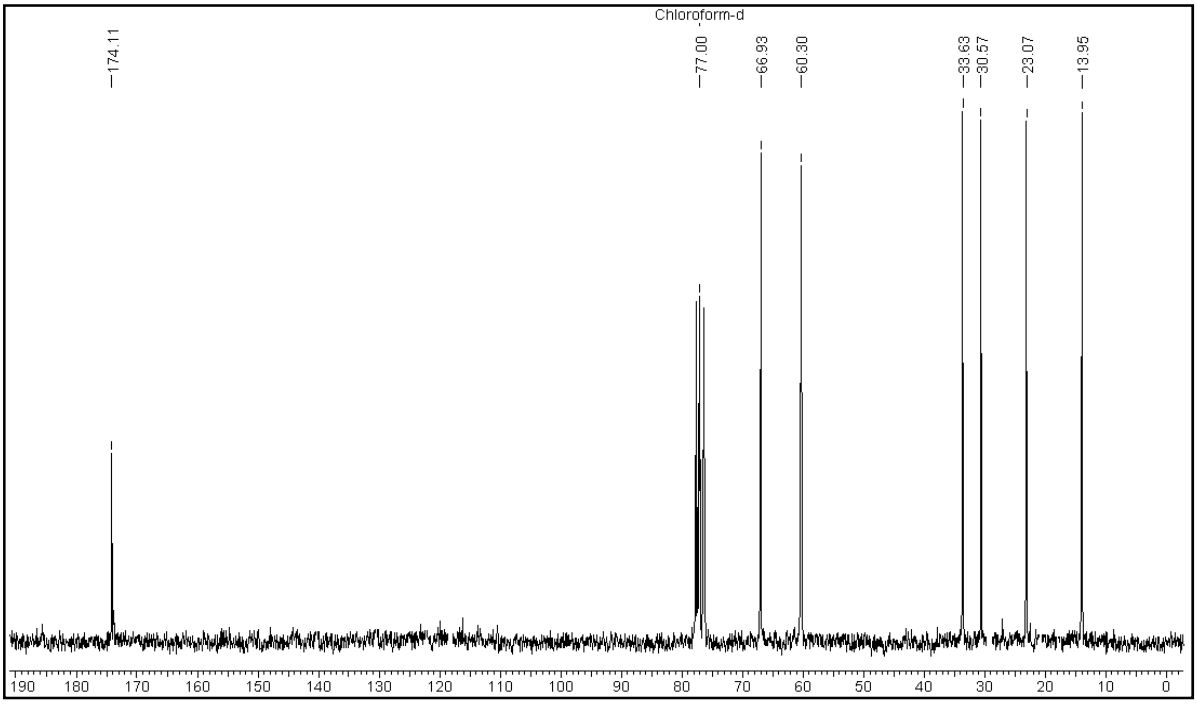
MS (ESI): m/z 142.16 $(M+H)^+$

3.2.7. Spectra

Ethyl (*S*)-4-hydroxypentanoate (32):

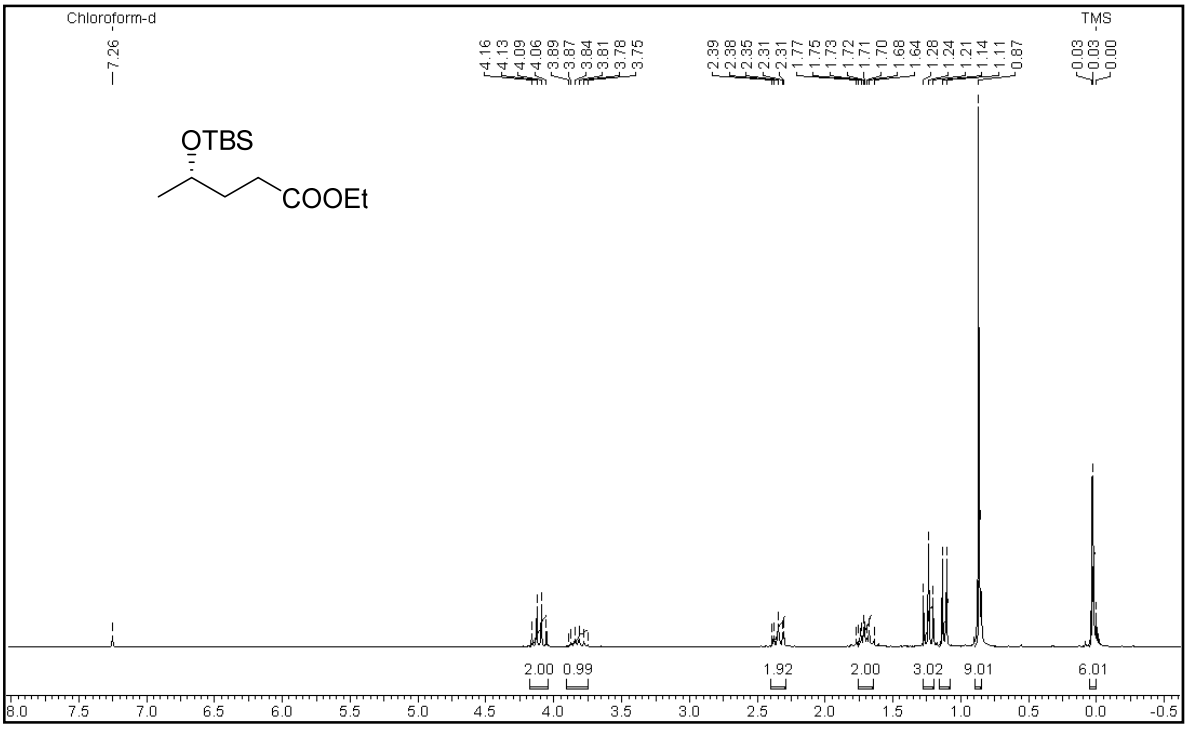


- **^{1}H NMR of the compound 32 in $CDCl_3$**

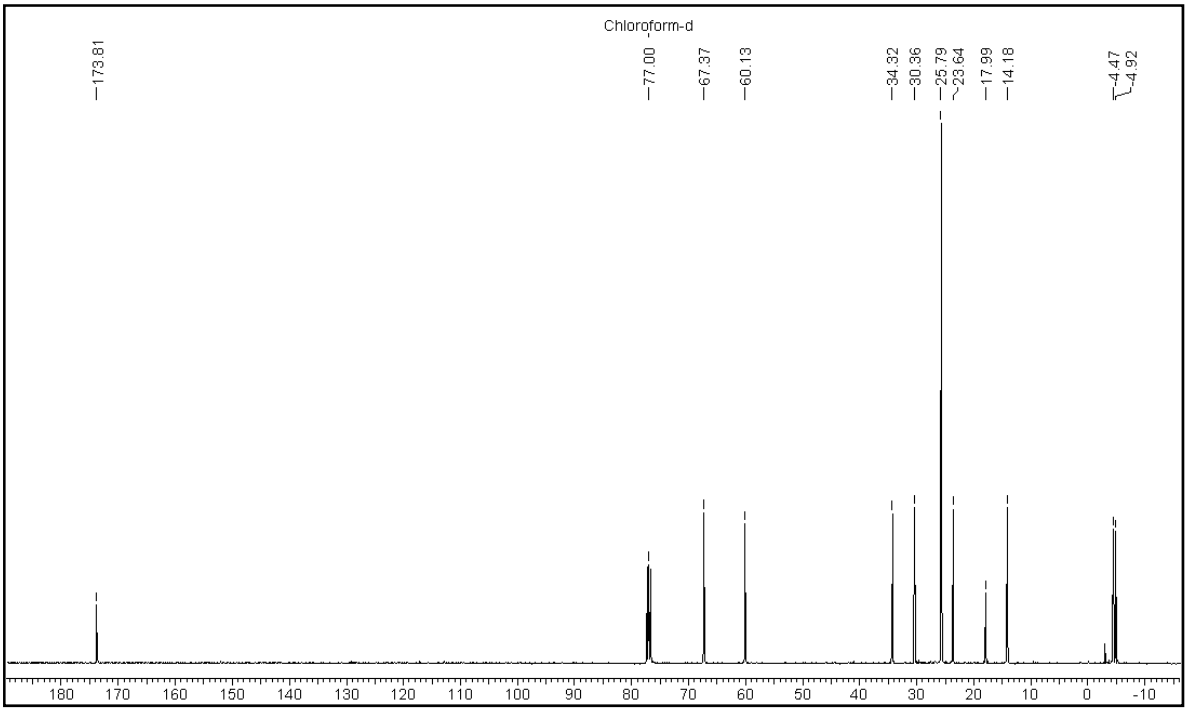


- **^{13}C NMR of the compound 32 in $CDCl_3$**

Ethyl (*S*)-4-((*tert*-butyldimethylsilyl)oxy)pentanoate (30):

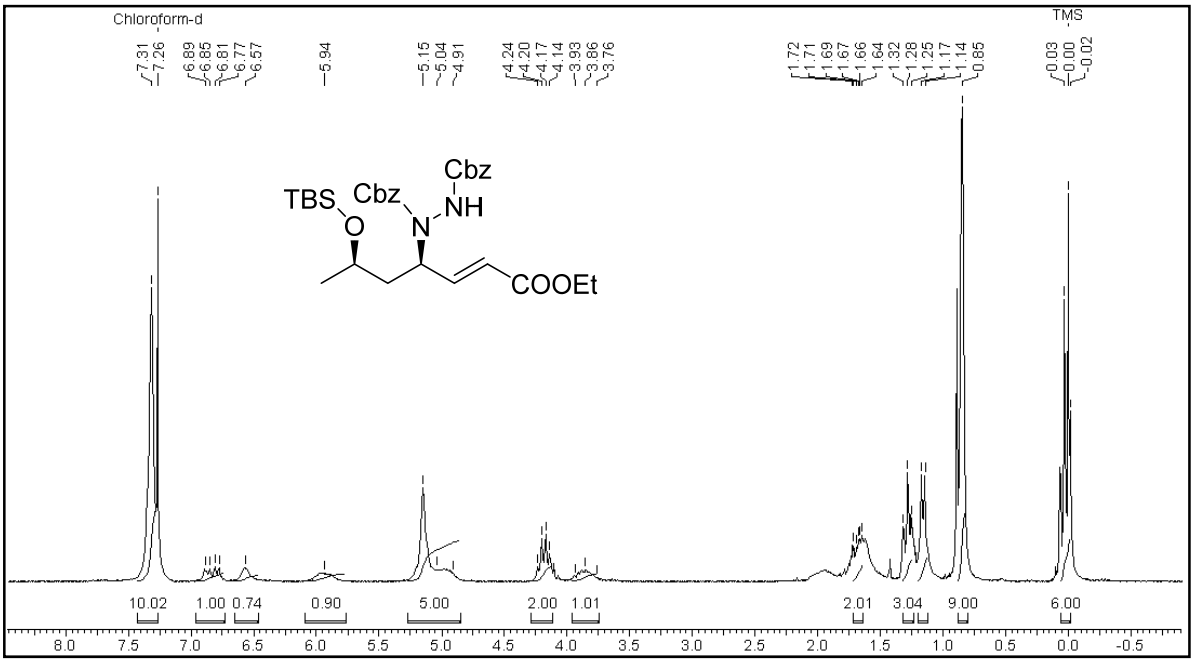


- **^{1}H NMR of the compound 30 in $CDCl_3$**

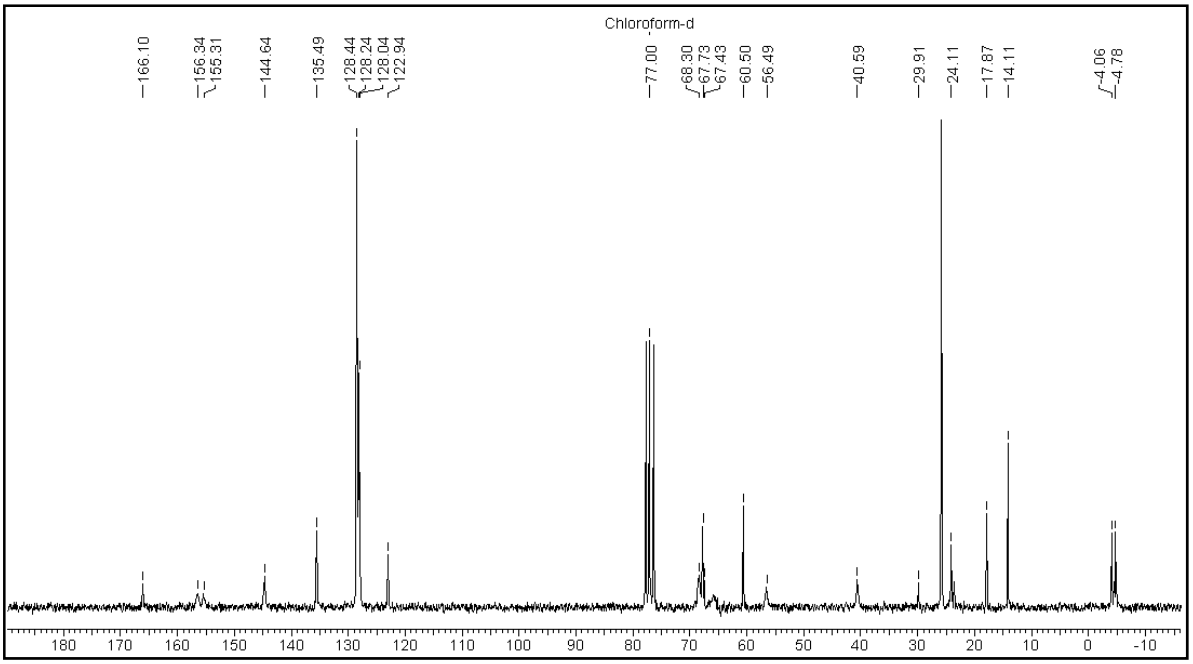


- **^{13}C NMR of the compound 30 in $CDCl_3$**

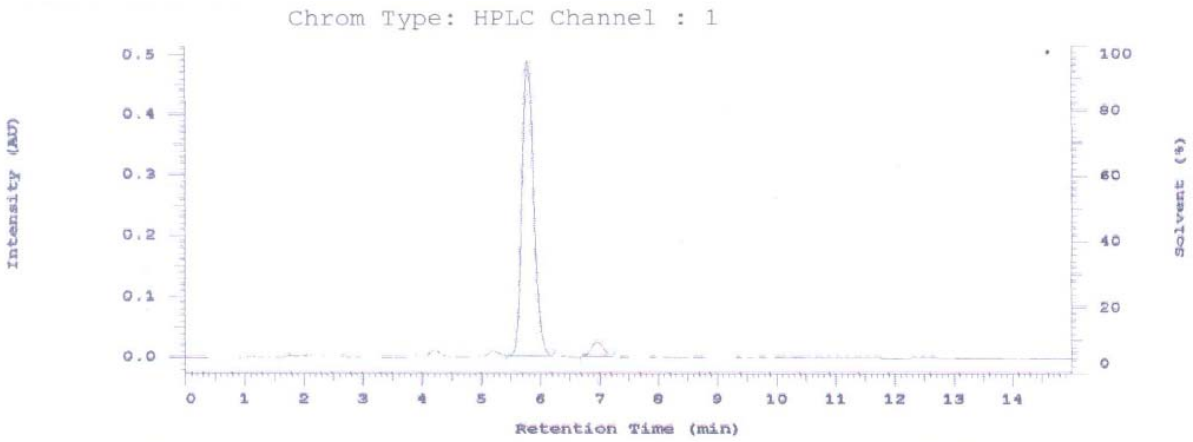
Dibenzyl 1-((4R,6R,E)-6-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (29):



- **^{1}H NMR of the compound 29 in $CDCl_3$**



- **^{13}C NMR of the compound 29 in $CDCl_3$**

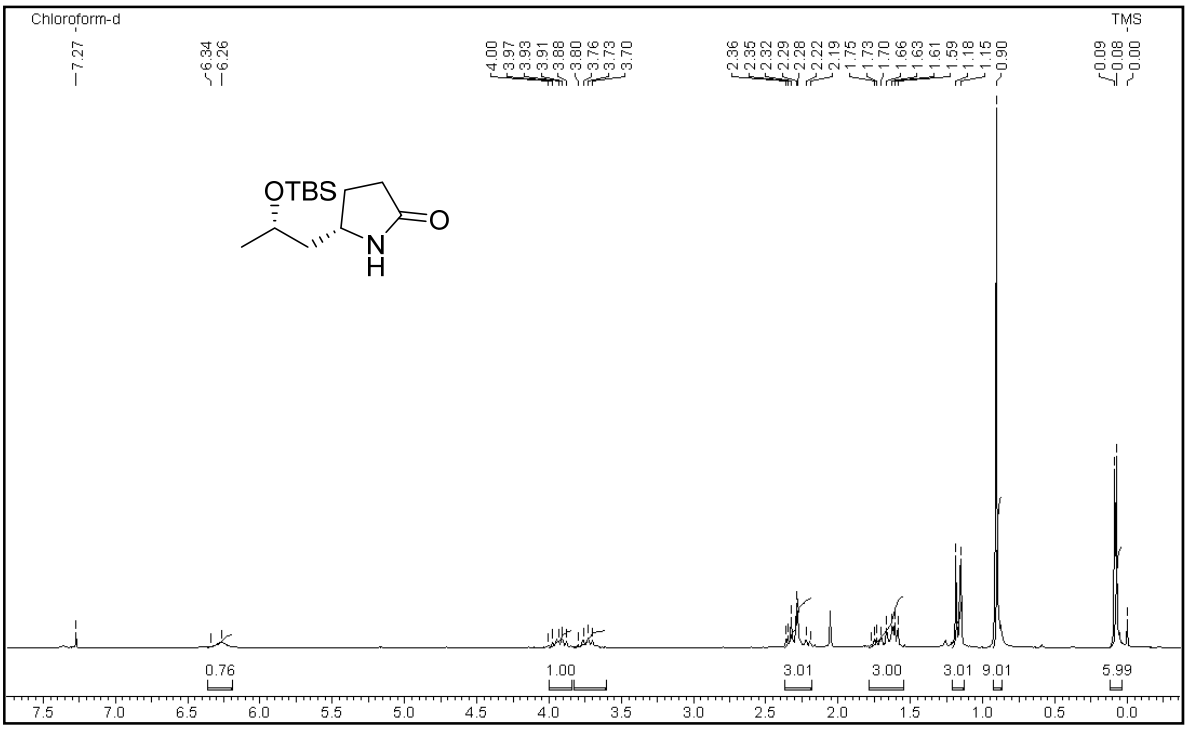


Peak Quantitation: AREA Calculation Method: AREA%

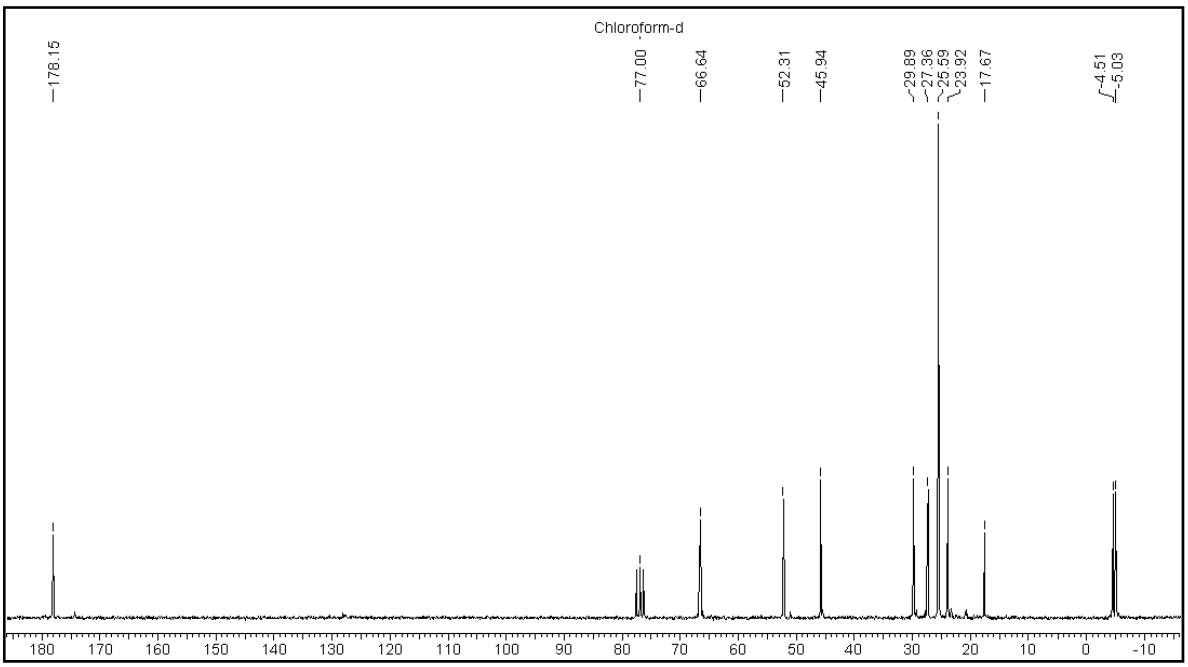
No.	RT	Height	Area	Area %
1	5.78	242760	3339591	94.833
2	6.96	12203	181957	5.167
		254963	3521548	100.000

Peak rejection level: 0

(*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (28):

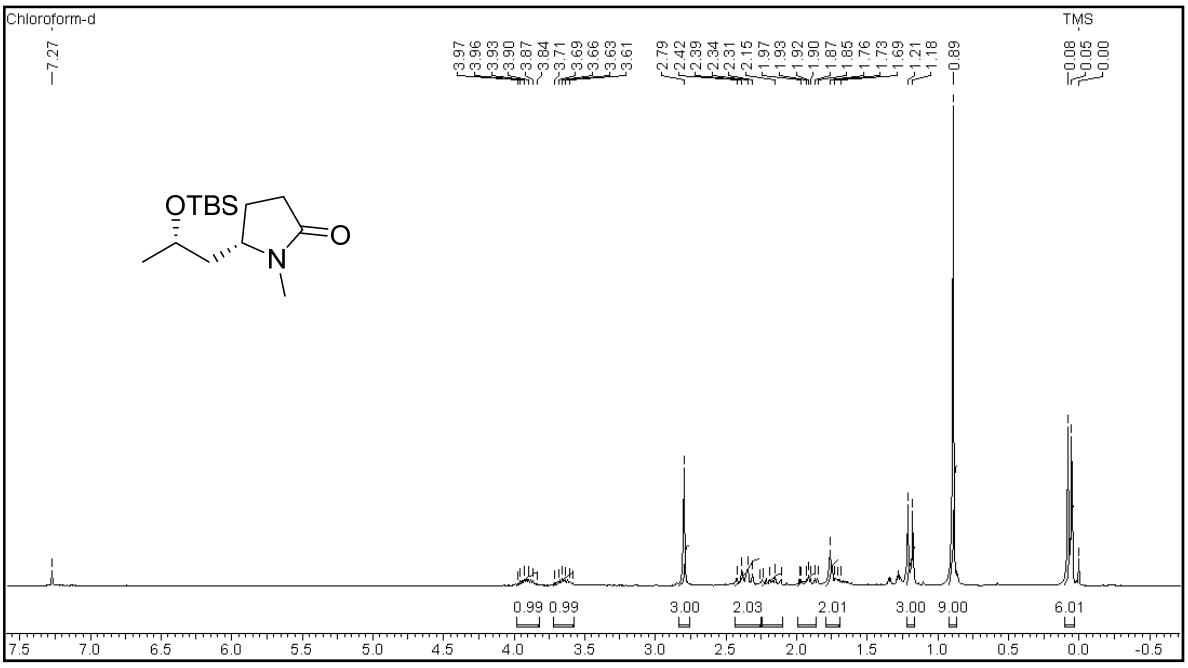


- **^{1}H NMR of the compound 28 in $CDCl_3$**

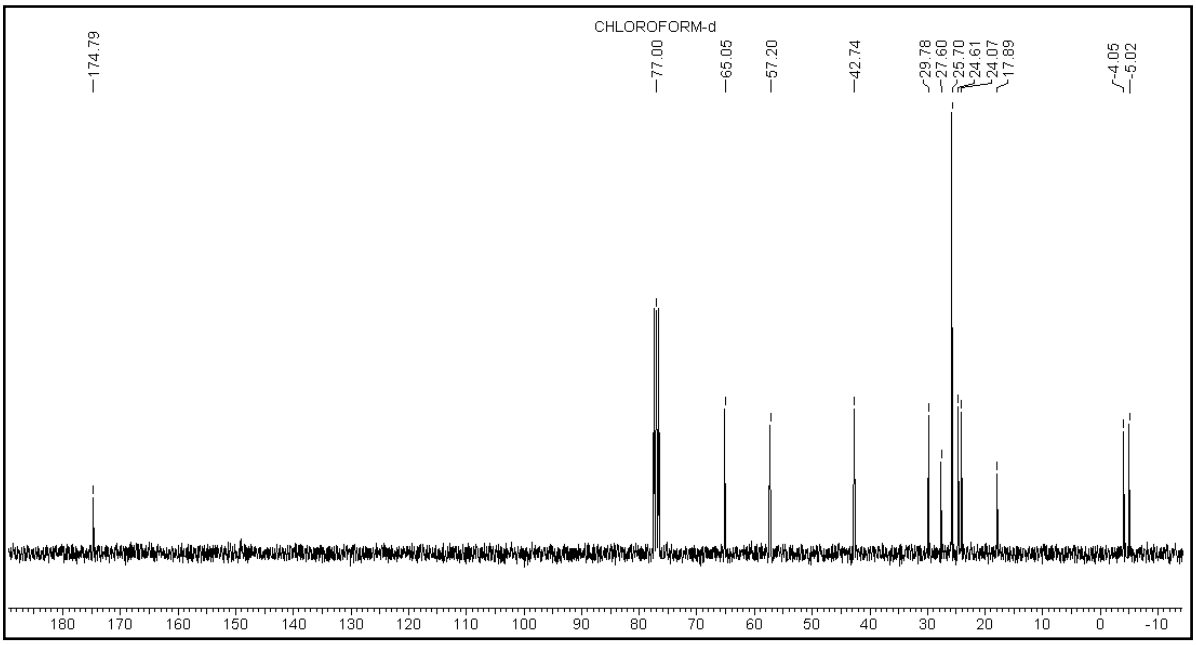


- **^{13}C NMR of the compound 28 in $CDCl_3$**

(*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidin-2-one (33):

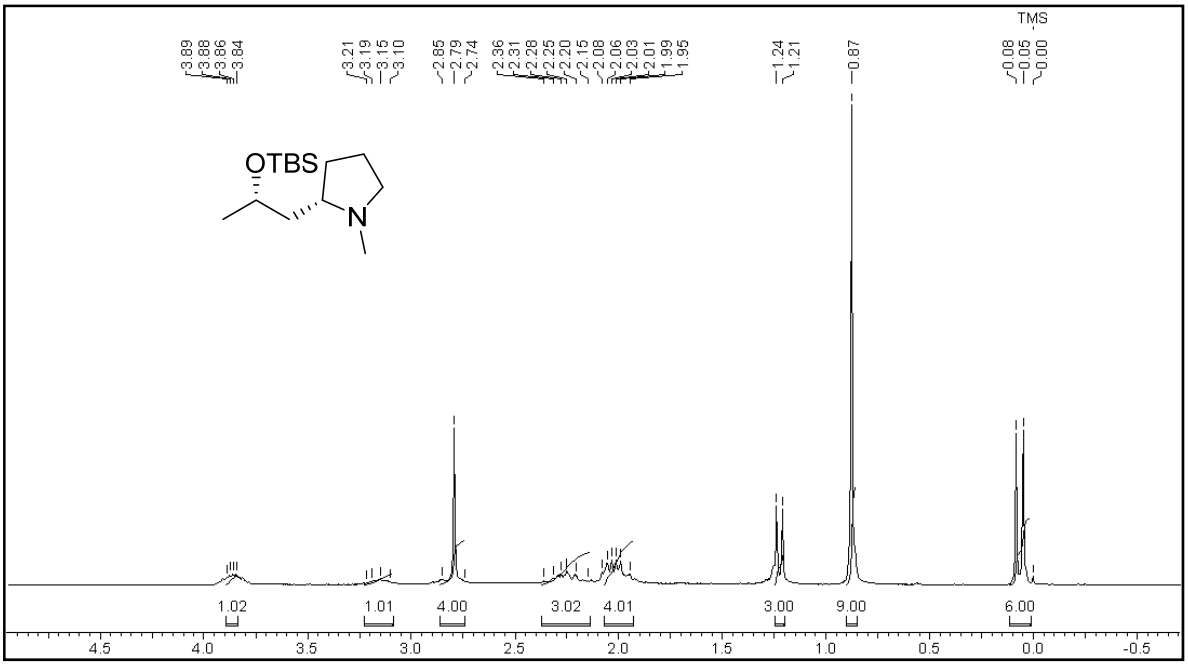


- **^{1}H NMR of the compound 33 in $CDCl_3$**

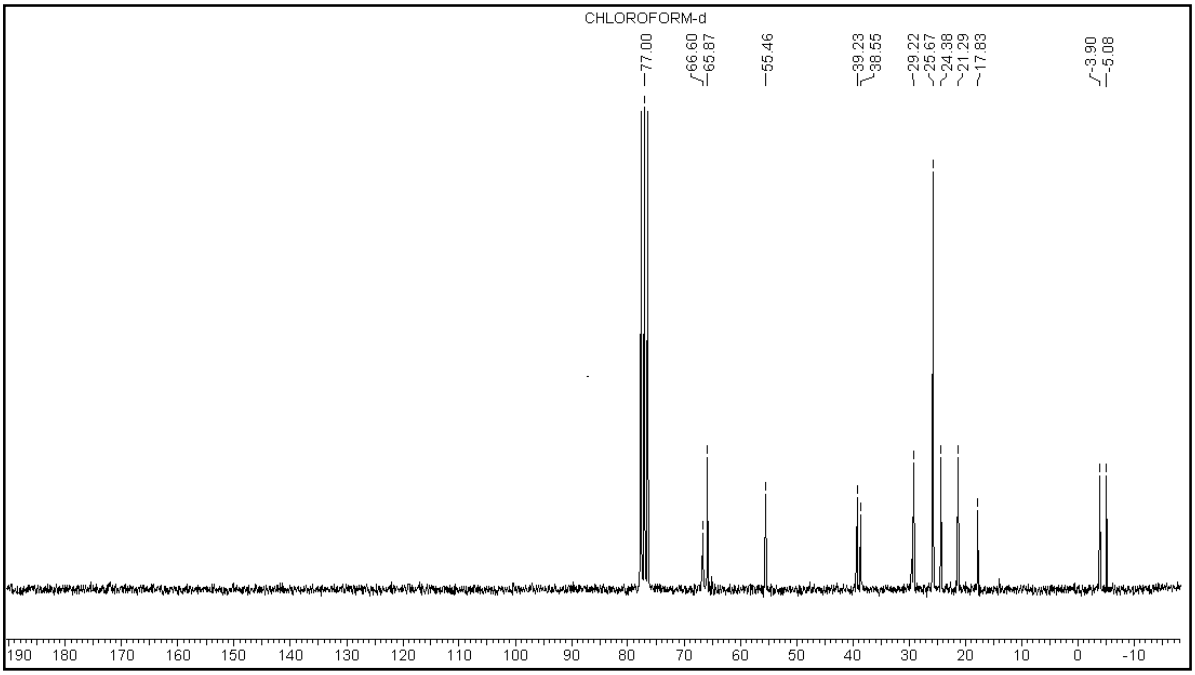


- **^{13}C NMR of the compound 33 in $CDCl_3$**

(*R*)-2-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-methylpyrrolidine (34):

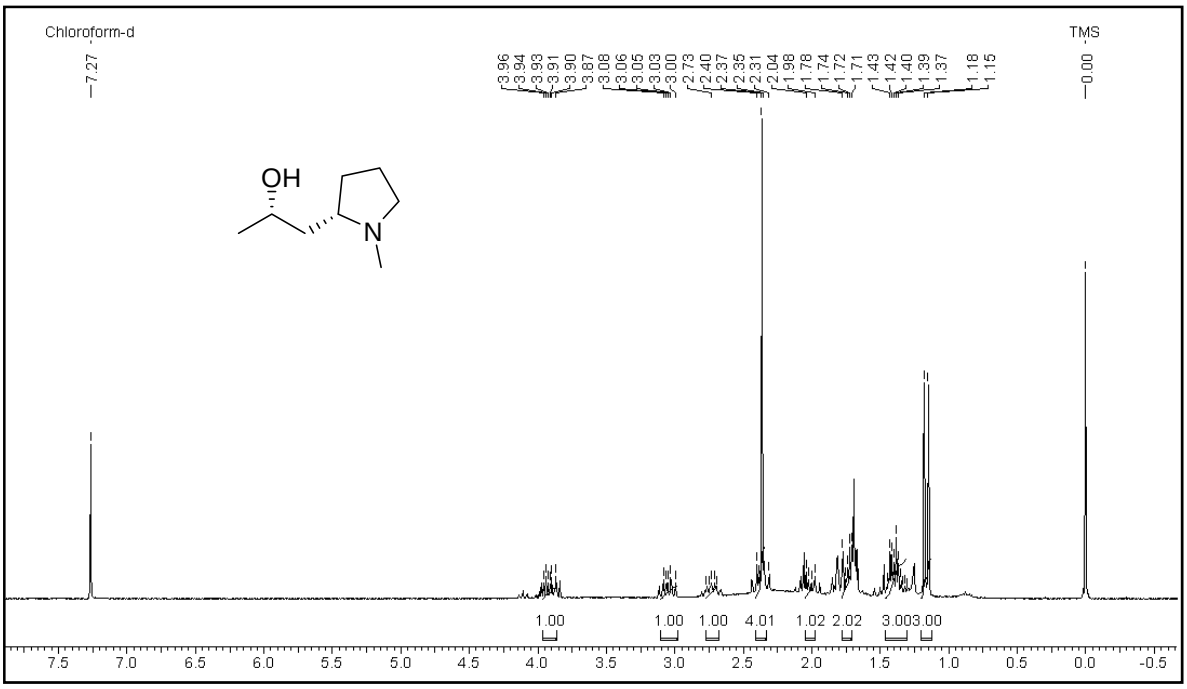


- **^{1}H NMR of the compound 34 in $CDCl_3$**

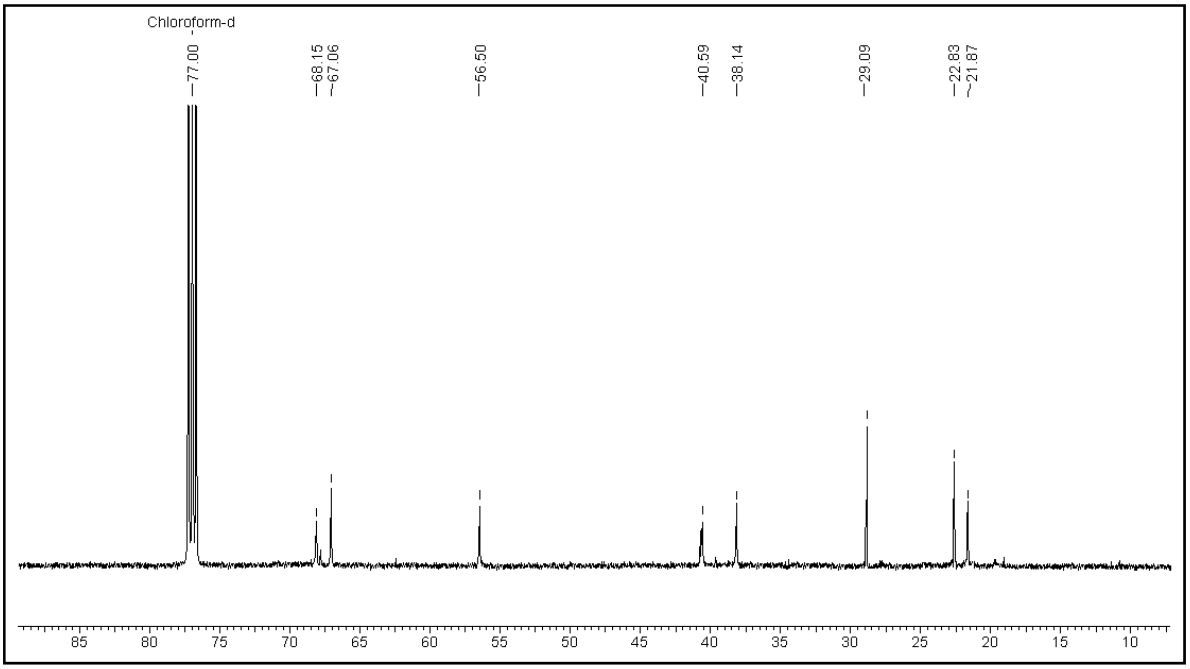


- **^{13}C NMR of the compound 34 in $CDCl_3$**

(+)-Psuedohygroline (1):

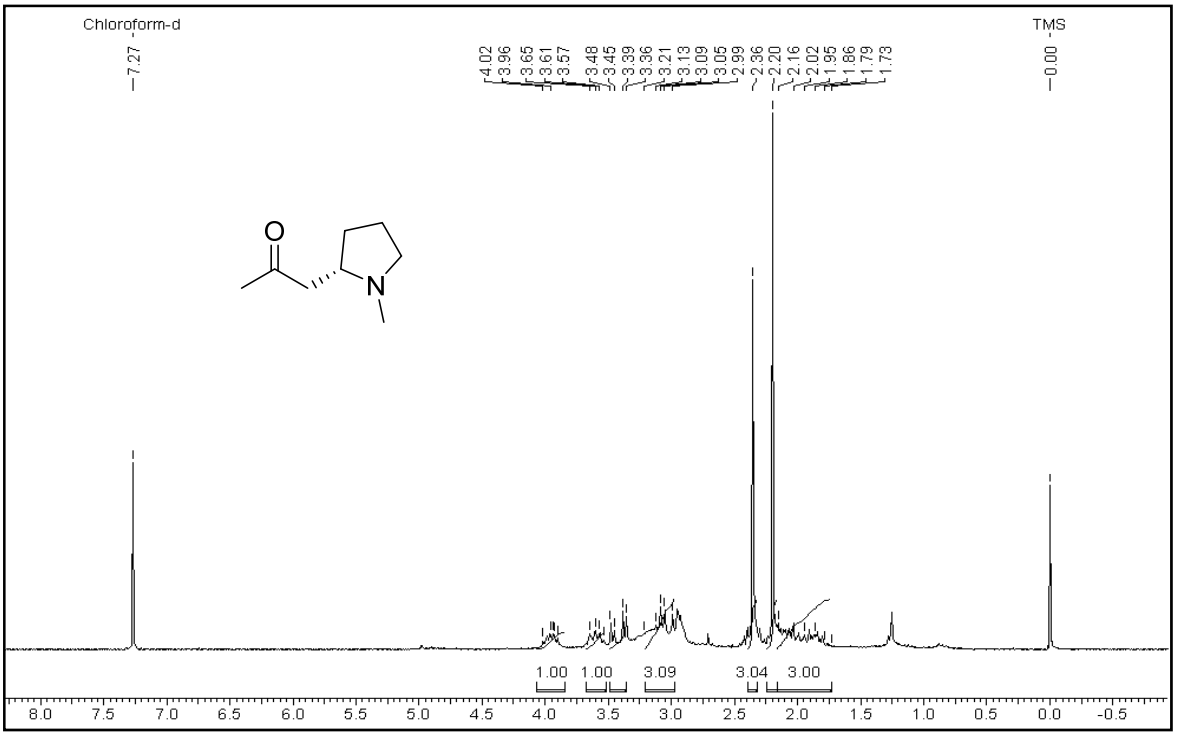


- **^{1}H NMR of the compound 1 in $CDCl_3$**

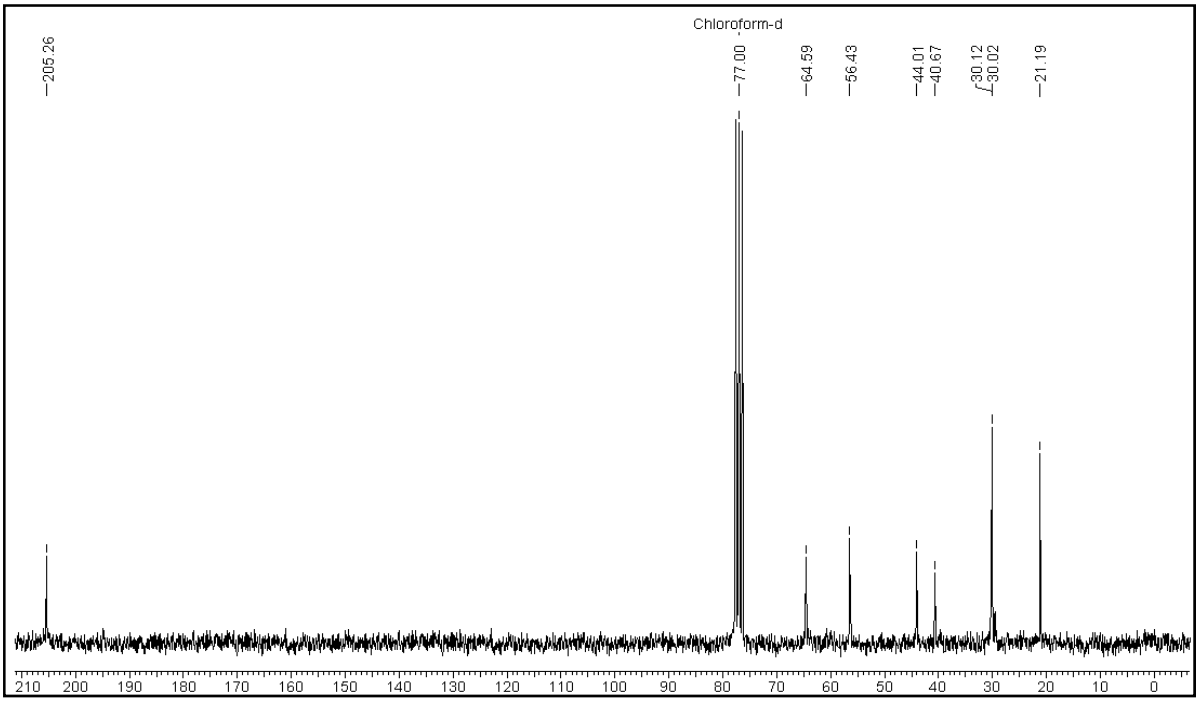


- **^{13}C NMR of the compound 1 in $CDCl_3$**

(+)-Hygrine (3):



➢ **^{1}H NMR of the compound 3 in $CDCl_3$**



➢ **^{13}C NMR of the compound 3 in $CDCl_3$**

3.2.8. Reference

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Chapter-4

An organocatalytic approach to asymmetric synthesis of *syn*- and *anti*-1,3-diamines

An organocatalytic approach to asymmetric synthesis of *syn*- and *anti*-1,3-diamines

4.1. Introduction

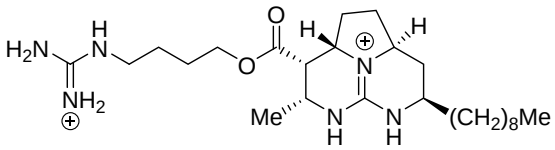
The 1,3-diamine functionality with *syn*- or *anti*-configuration are key structural components in wide range of natural products and various bioactive compounds,[1] viz., marine alkaloids batzelladines,[2] α-adrenoreceptor blockers manzacidin,[3] antibiotic glycocinnamoylspermidines,[4] or HIV-1 protease inhibitors, such as A-74704.[5]Additionally 1,3-diamines have also been used as ligands for asymmetric catalysis and chiral core of numerous synthetic reagents.[6]

Increasingly synthetic organic chemists are merging discrete organic reactions in one pot (Referred to by various names viz domino reactions, sequential addition reactions, one pot multicomponent reactions, multicatalysis)[7] to generate complex organic molecules from simple starting material in order to increase efficiencies and reduce the environmental impact in terms of reduction in by-products.[8]

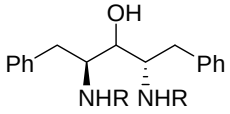
Recently we and others have developed one-pot sequential addition reaction sequence to synthesize γ-hydroxy esters,[9a,10a] γ-amino-α,β-unsaturated ester[10b] from proline-catalyzed α-amination,[11a-d] α-aminoxylation[11e-f] of aldehydes. We have further used these reactions in a iterative or sequential manner to develop synthetic protocols for *syn*/*anti*-1,3-polyols[9a-b] and *syn*/*anti*-1,3-amino alcohols[9c] in good to useful level of stereo induction. Herein we have used the catalyst control to determine the stereochemistry of the final product. In case of both 1,3-polyols and 1,3-aminoalcohol we were able to get good selectivity for *anti* isomer as compared to *syn* isomer, wherein steric factors interfere in the catalyst control to give lower level of selectivity. Given the importance of 1,3-diamines, it would be worthwhile to develop short reaction sequence for enantioselective and diastereoselective synthesis of 1,3-diamines.

Despite the importance of 1,3-diamine, there are relatively fewer methods for their stereoselective synthesis.[12,13] Currently the most common strategy for their synthesis includes reduction of diimines,[13b] pyrazolidines,[13c,d] pyrimidines,[13e] azides,[13f] quaternary immonium salts generated in situ by aminoalkylation of enamines[13g] or β-amino imines.[13i] Recently Trost *et al.* have reported sequential process which involves an asymmetric allylic amination and subsequent formation and opening of amino

aziridines[13h] while, Menche *et al.* have reported stereodivergent cyclization of urea-type substrates by intramolecular allylic substitution.[13j] However, These methods involve specially modified starting materials such as pyrimidines, diimines, amino imines, being catalyzed by toxic metal catalysts like $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Rh_2(esp)_2$, etc.

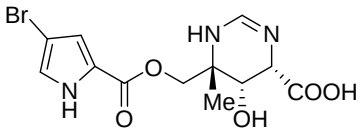


Betzelladiene D

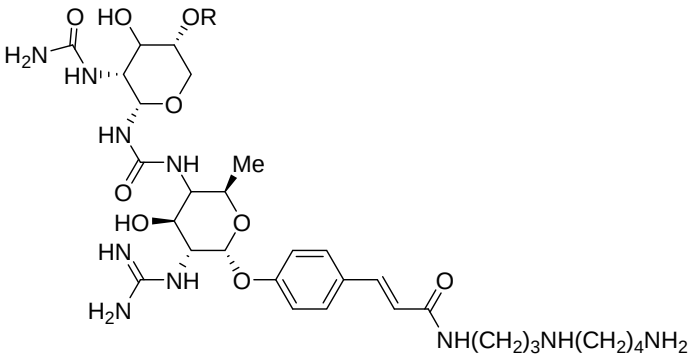


R = ValCbz

A-74704



Manzacidin B



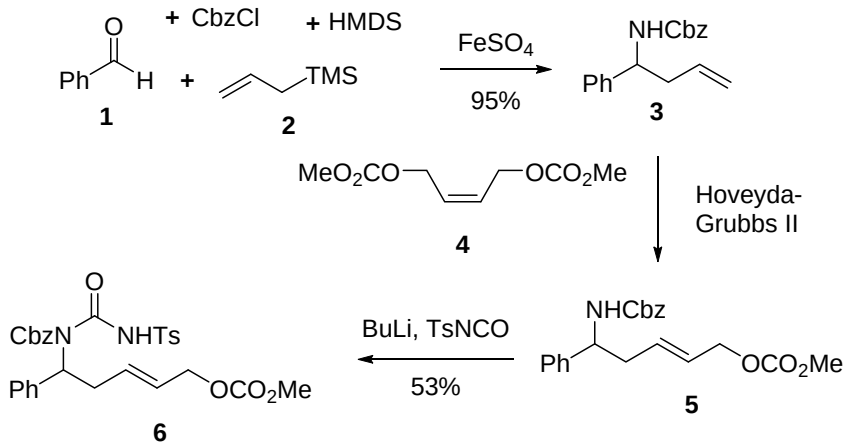
Glycocinnamoylspermidines

Figure 1. Representative examples of bioactive molecules containing 1,3-diamine moiety.

4.2. Review of Literature

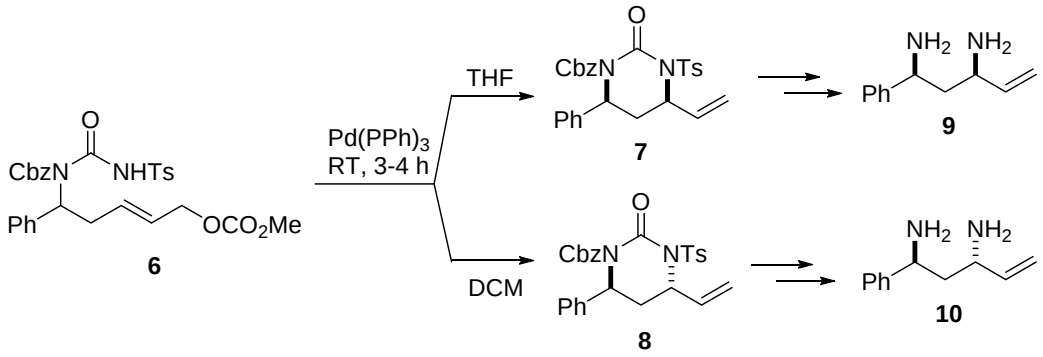
Menche *et al.* (2010)[13j]

Menche and co-workers developed a stereoselective synthesis of *syn*- and *anti*-1,3-diamine *via* stereodivergent cyclization of urea-type substrates by intramolecular allylic substitution. Thus condensation of aldehyde **1** with benzyl chloroformate (CbzCl), hexamethyldisilazide (HMDS), and allyltrimethylsilane **2** in the presence of catalytic amounts of iron(II) sulfate accessed homoallylic amines **3** in high yields. Subsequent homologation with allylcarbonate **4** by cross metathesis proceeded smoothly in the presence of Hoveyda-Grubbs catalyst II to give compound **5** which on attachment of tosylisocyanate to NH functional group gave urea type substrate **6**.



Scheme 1. Preparation of urea type substrate

Pd catalyzed stereoselective intramolecular allylic substitution reaction was carried out on urea type substrate **6** to give *syn*- and *anti*-tetrahydropyrimidinones. Here stereoselectivity depends upon the solvent *i.e.* THF gave *syn* compound **7** whereas *anti* compound **8** was observed when DCM was used as solvent. *syn*- and *anti*-Tetrahydropyrimidinones was readily converted to the respective *syn*- and *anti*-diamines **9** and **10** using standard protocol.

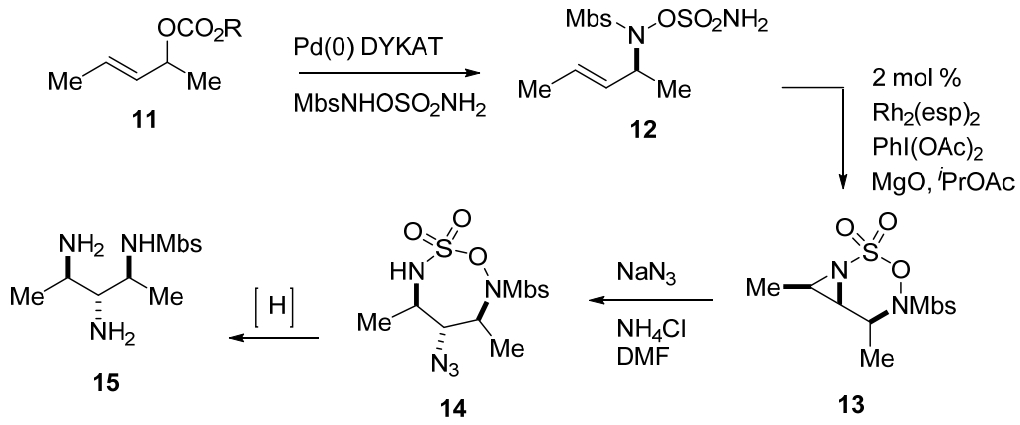


Scheme 2. Diastereodivergent synthesis of 1,3-*syn*- and -*anti*-amines (Menche method)

Trost *et al.* (2009)[13h]

Trost and co-workers developed an asymmetric synthesis of *syn*-1,3-diamine *via* sequential Pd- and Rh-catalyzed transformations. Palladium-catalyzed allylic amination was carried out on compound **11** to prepare allylic hydroxylamine-derived sulfamate esters **12** in enantioenriched form. Diastereoselective oxidative cyclization of **12** under rhodium catalysis afforded aziridine product **13**. Subsequent S_N2 ring opening of the resultant aziridine **13** occurred with modest levels of regioselectively to yield the seven-

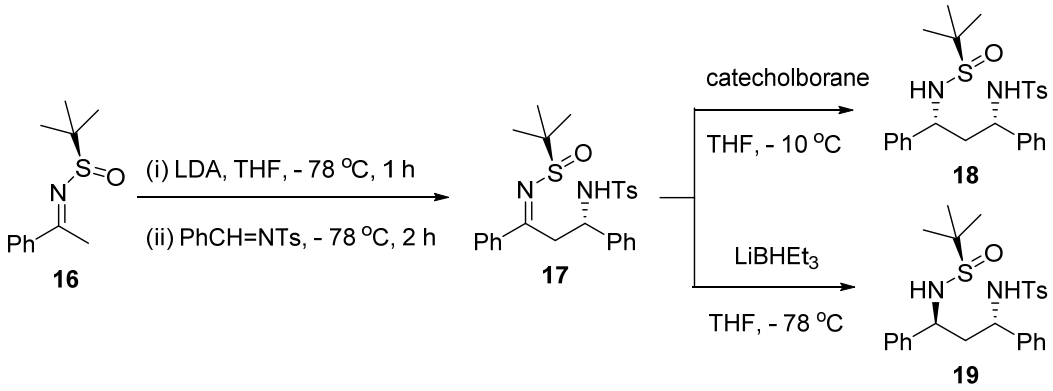
membered-ring heterocycle **14**. Reduction of the heterocycle and the azido group in **14** unveiled the singly protected triamino compound **15**.



Scheme 3. Asymmetric synthesis of polyfunctionalized diamines (Trost method)

Chen *et al.* (2006)[13i]

Chen and co-workers developed an asymmetric synthesis of *syn*-1,3-diamine *via* asymmetric Mannich-Type reaction of a chiral *N*-(*tert*-butylsulfinyl) ketimine with imines. Deprotonation of the chiral *N*-(*tert*-butylsulfinyl) ketimine **16** using LDA followed by trapping with imines afforded the β-amino imines **17** as the Mannich-type products in high diastereoselectivities (99:1 *dr*). Chiral β-amino imines **17** on reduction with catecholborane gave *syn*-1,3-diamines **18** whereas *anti*-1,3-diamines **19** was obtained when β-amino imines **17** was reduced with $LiBHEt_3$.



Scheme 4. Asymmetric synthesis of 1,3-diamine (Chen method)

4.3. Present work

Objective

As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds,[9] we envisioned that the proline-catalyzed α-amination[11a-b] could easily give us stereocontrolled synthetic access to 1,3-diamines. However, it would be interesting to see the catalyst as well as substrate role in determining the ratio of *syn*/*anti*-1,3- diamine since in this case we have bulky protected amine in place of relatively smaller OTBS group as used in the previous two cases. It may be pertinent to mention here that the N-N-Cbz group of the already established γ-amino-α,β-unsaturated esters makes the stereoselective chain elongation a challenging process. Our strategy for the synthesis of di-amines is outlined in Figure **2**.

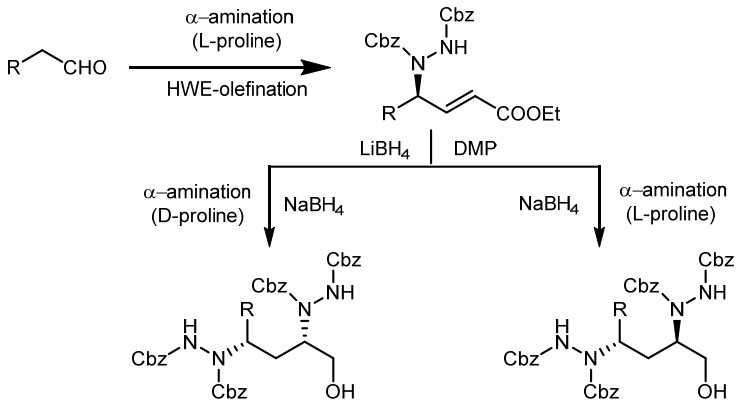
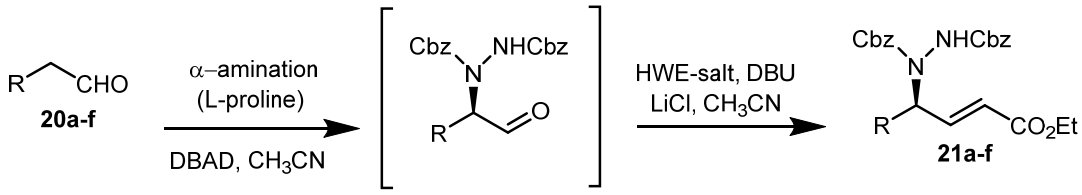


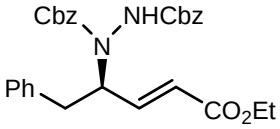
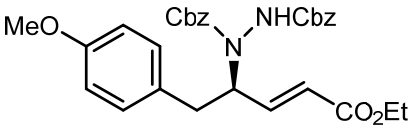
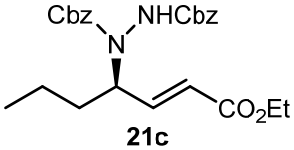
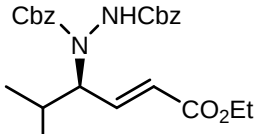
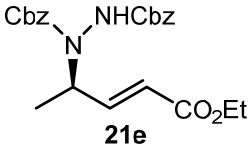
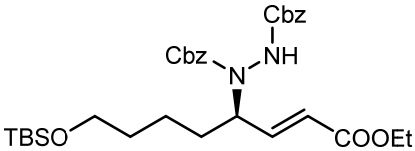
Figure 2. General strategy for the synthesis of 1,3-diamines

4.4. Results and discussion

Toward the synthesis of 1,3-diamine, our first goal was to synthesize various protected γ-amino esters. Thus, commercially available aldehydes **20a-f** on sequential α-amination using commercially available dibenzylazodicarboxylate (DBAD) as the nitrogen source, L-proline as catalyst and subsequent HWE olefination using triethylphosphonoacetate furnished the γ-amino-α,β-unsaturated esters **21a-f** in good yields (78-87%) and excellent enantioselectivities (91 to 95%) (Scheme **5,** Table **1**).[10b] The appearance of olefinic protons in the range δ 5.90 as doublet and at 6.96 as dd in ^{1}H NMR spectrum confirmed the formation of product.

Scheme 5. Synthesis of γ-amino-α,β-unsaturated esters



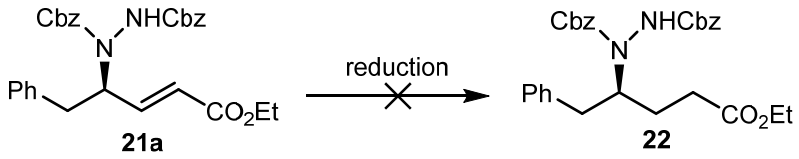
Entry	R **(20a-f)**	Hydrazino Ester **21**	Yield (%)	***ee**** (%)
1	Bn	 **21a**	87	95
2	*p*-$MeOC_6H_4CH_2$	 **21b**	84	91
3	Pr	 **21c**	84	94
4	*i*-Pr	 **21d**	83	92
5	CH_3	 **21e**	80	93
6	$(CH_2)_3CH_2OTBS$	 **21f**	78	91

***** ee was determined by chiral HPLC

Table 1. Synthesis of γ-amino-α,β-unsaturated esters

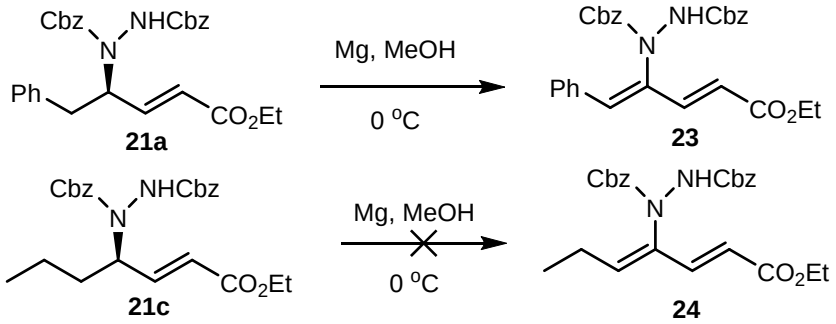
With protected γ-amino-α,β-unsaturated esters **21a-f** in hand, our next target was selective reduction of double bond in presence of Cbz group. For this purpose, ester **21a** was subjected to hydrogenation conditions using different catalyst such as Pd/C, PtO_2,

Pt, Lindlar's catalyst etc but the formation of reduced product **22** could not be observed (Scheme **6**).



Scheme 6. Attempted reduction of double bond by hydrogenation conditions

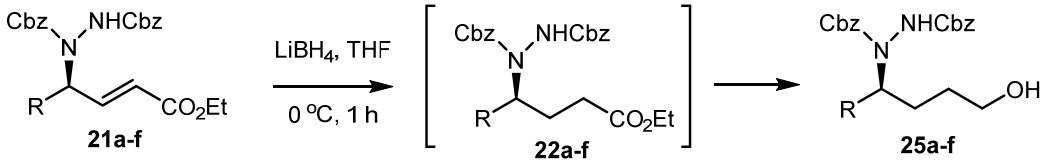
The unsaturated ester **21a** was subjected to Mg/MeOH condition,[14] but interestingly we could obtain **23** as the only product. The disappearance of benzylic protons in the range of δ 2.87-3.19 as multiplate in ^{1}H NMR spectrum confirmed the formation of the product. Extension of conjugation may be possible cause for the formation of **23**, as the same reaction when repeated with acyclic substrate **21c**, did not afford the product **24**, instead the starting material was recovered back (Scheme **7**).



Scheme 7. Attempted selective reduction of double bond

We resorted next to reduce the ester group. For this purpose, ester **21a** was treated with $LiBH_4$ in THF but, to our surprise double bond also got reduced with concomitant reduction of the ester group to give alcohol **25a**. The disappearance of ester and olefinic protons in the range of δ 1.26 as triplet, 4.16 as doblet, 5.90 as doublet and 6.96 as dd in ^{1}H NMR spectrum confirmed the formation of the product. To check the sequence of reaction, ester **21a** was treated with $NaBH_4$ in MeOH and we found that reaction proceeds first via reduction of double bond followed by reduction of ester as determined by isolating the intermediate product **22** (Scheme **8**). The disappearance of olefinic protons in the range of δ 5.90 as doublet and 6.96 as dd in ^{1}H NMR spectrum confirmed the formation of the product. To assess the generality of this procedure for reduction of ester group as well as double bond, various γ-amino-α,β-unsaturated esters **21a-f** were

subjected to reduction conditions using $LiBH_4$ and similar results were obtained in all the cases (Scheme **8,** Table **2**).



Scheme 8. Reduction of ester group

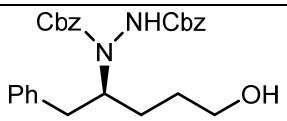
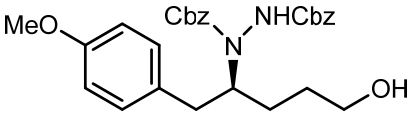
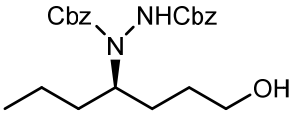
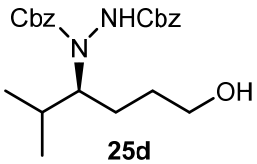
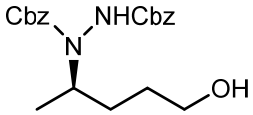
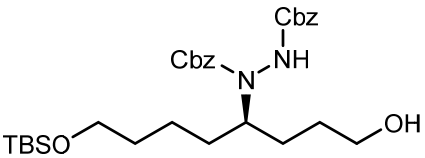
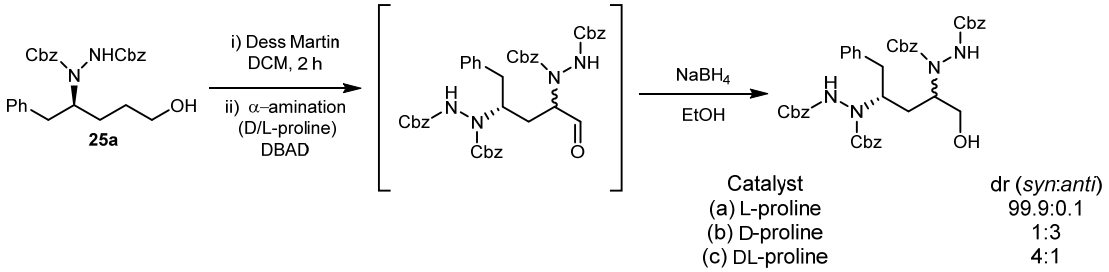
Entry	R **(21a-f)**	Hydrazino Alcohol **25**	Yield (%)
1	Bn	 **25a**	92
2	*p*-$MeOC_6H_4CH_2$	 **25b**	92
3	Pr	 **25c**	89
4	*i*-Pr	 **25d**	88
5	CH_3	 **25e**	89
6	$(CH_2)_3CH_2OTBS$	 **25f**	90

Table 2. Reduction of ester group

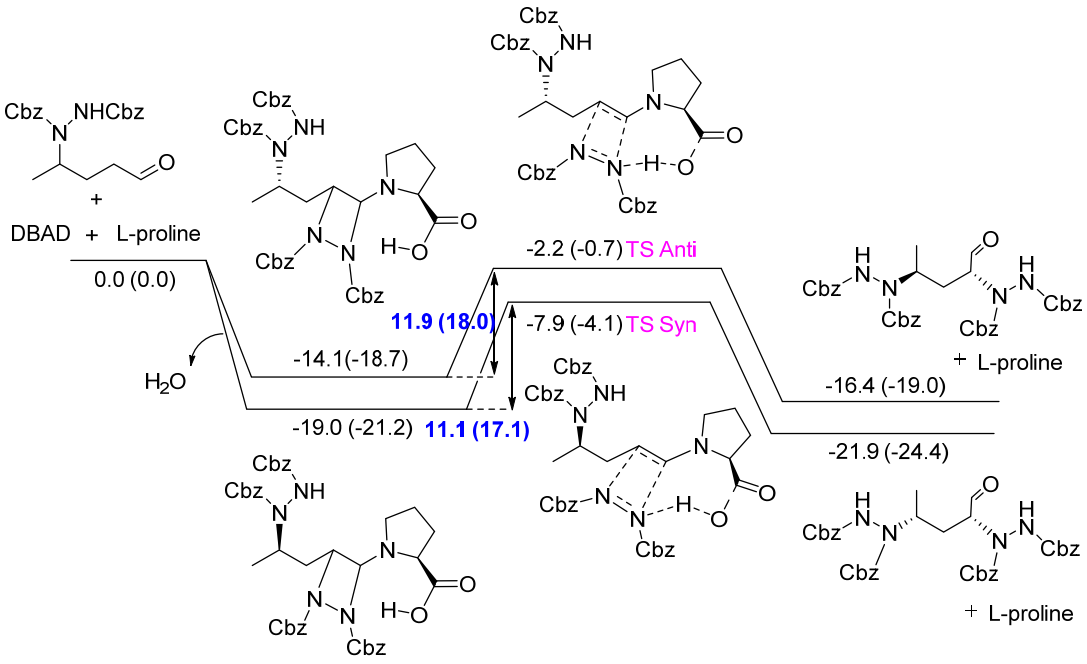
With substantial amount of various hydrazine alcohols **25a-f** in hand, the stage was set for the introduction of another amine functionality at the 3-position. As illustrated in Scheme **9**, the DMP oxidation of alcohol **25a** furnished the corresponding aldehyde which was then again subjected to α-amination using commercially available dibenzylazodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to furnish α-aminoaldehyde, which on treatment with $NaBH_4$ in ethanol afforded the *syn*-1,3-diamine **26a** in 68% yield and 99.9:0.1 diastereomeric ratio. Surprisingly, when the same sequence of reaction was repeated using D-proline as a catalyst, we got *anti*-1,3-diamine **27a** in 64% yield and 3:1 diastereomeric ratio. We were able to separate the major diastereomerically pure *anti*-1,3-diamine by flash silica gel column chromatography. By analyzing the diastereomeric ratio of both *syn* as well as *anti* product, we concluded that not only the catalyst but also the existing stereochemistry of the substrate plays a major role in asymmetric induction of new chiral centre and favours the formation of *syn* product. To further prove this hypothesis, we repeated the same sequence of reaction using D/L-proline as a catalyst and got diastereomeric ratio 4:1 in favour of *syn* isomer (Scheme **9**). Overall these findings are in contrast with those observed for the synthesis of *syn*/*anti*-1,3-diol[9a] and *syn*/*anti*-1,3-amino alcohols,[9b] where the asymmetric induction for the *anti*-isomer is greater as compared to the s*yn*-isomer. However a detailed literature survey revealed the observed selectivity for the N-N-Cbz group,[10b,15] as reported by Sudalai *et al*. for the synthesis of *syn* aminodiol.



Scheme 9. Synthesis of 1,3-diamine

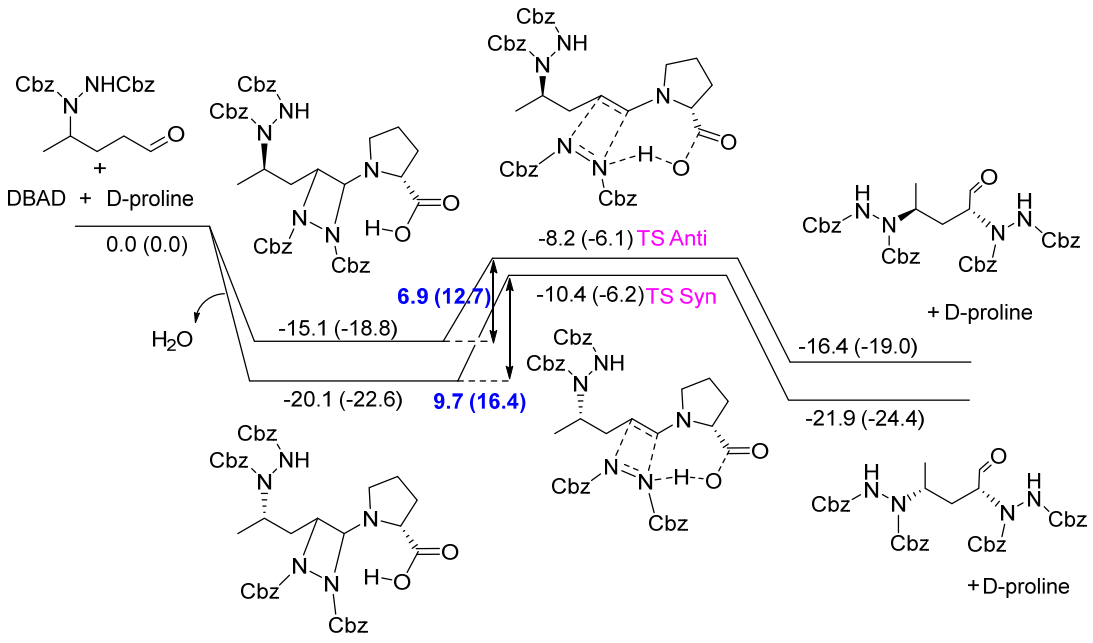
In order to further probe into the interesting selectivity results when using L-proline and D-proline as the catalysts, full quantum chemical calculations were done with density functional theory (DFT). All calculations were done with the Turbomole suite of programs. The focus of the calculations was on determining the nature of the stereoselectivity at the catalyst addition step. The reaction of the aldehyde analogue of **25a** with DBAD and L-proline is shown in Scheme **10** below. The three moieties react to give rise to a diastereomeric complex, which is seen to lie 14.1 kcal/mol lower in energy

on the free energy surface for the *anti* addition case and 19.0 kcal/mol lower in energy for the *syn* addition case. The high exothermicity in either case, even though the reaction of three molecules to yield one complex is entropically unfavourable, indicates the high favourability of the interaction. From this point on, both the *syn* and *anti* addition cases undergo the conversion to the final *syn* and *anti* addition products, releasing the catalyst L-proline in the process. This conversion entails overcoming a barrier in each case. The barrier heights, determined by the evaluation of exact transition states in each case, were found to be 11.1 kcal/mol for the *syn* case and 11.9 kcal/mol for the *anti* addition case (see Scheme **10**).



Scheme 10. The free energy profile for the L-proline catalyzed 1,3-diamine synthesis; the values in parenthesis are the gas phase values, and the values outside the parenthesis are the solvent phase values; all values are in kcal/mol.

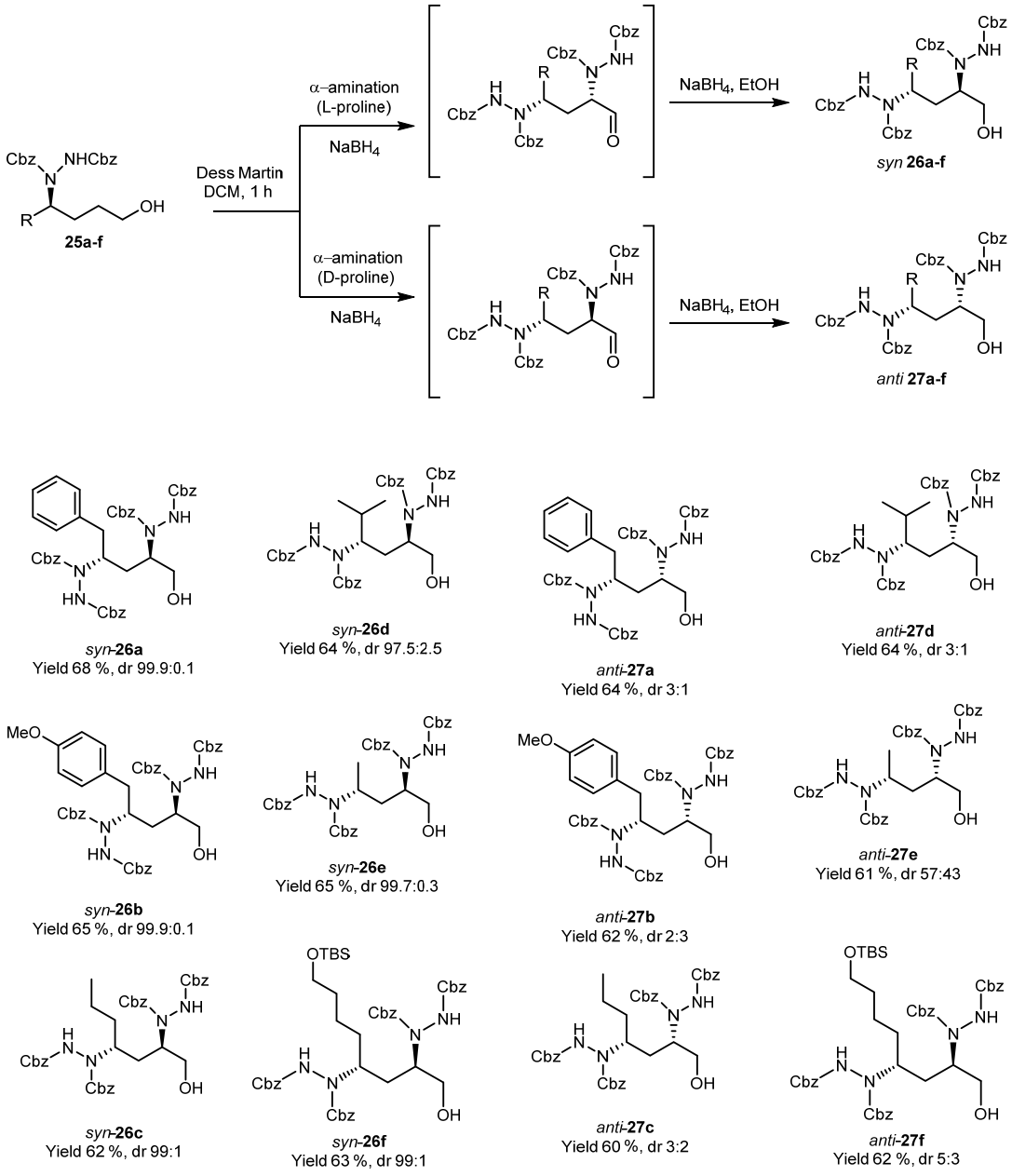
This indicates that the probability of obtaining either product would be comparable from a kinetic point of view. However, the calculations indicate that the *syn* addition final product is 5.5 kcal/mol more stable than the *anti* addition product, i.e. the *syn* addition product is significantly favoured from a thermodynamic point of view. This result suggests that if the reaction were to be allowed to proceed for a sufficient length of time, the *syn* addition product would be almost exclusively obtained as the major product, corroborating the experimental results.



Scheme 11. The free energy profile for the D-proline catalyzed 1,3-diamine synthesis; the values in parenthesis are the gas phase values, and the values outside the parenthesis are the solvent phase values; all values are in kcal/mol.

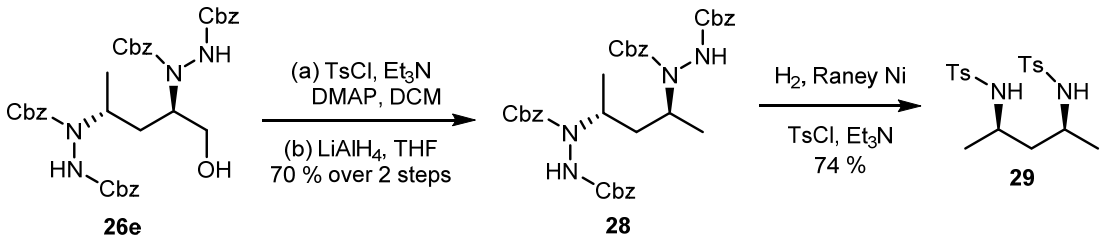
The corresponding reactions of the aldehyde analogue of **25a** with DBAD and D-proline are shown below in Scheme **11**. The essential nature of the reaction: (i) the favourable formation of the complex from the three separate moieties: the aldehyde analogue of **25a**, DBAD and the D-proline catalyst, and (ii) the overcoming of a barrier in order to obtain the final *syn* or *anti* addition product, is the same as in the case of the L-proline catalyst. What is different is that the barrier for the *anti* addition case (6.9 kcal/mol) is significantly lower than the corresponding barrier for the *syn* addition case (9.7 kcal/mol) (see Scheme **11**). This high kinetic favourability of the reaction suggests that the *anti* addition product would be formed almost exclusively at the initial stages of the reaction. However, since the *anti* addition product is 5.5 kcal/mol higher in energy than the corresponding *syn* addition product, this also means that if the reaction is allowed to continue for a long length of the time, the amount of the *syn* addition product in the reaction vessel would increase. Hence, the combination of the kinetic and thermodynamic factors in this case would lead to the *anti* product being the major product, but not by a significant amount, again corroborating experimental evidence.

We examined the scope of this reaction using various aldehydes bearing different functional groups. It was observed that the reaction sequence displayed a wide substrate scope and was compatible with functionalities such as the alkyl, aryl, and substituted aryl groups. Excellent diastereomeric ratio (dr 98:2 to ~100) and good yields (62 to 68%) were obtained for all the substrates in case of *syn* product whereas moderate to low diastereomeric ratio (dr 3:1 to 2:3) and good yields (60 to 64%) were obtained for all the substrates in case of *anti* product (scheme **12**).



Scheme 12. Synthesis of *syn*/*anti*-1,3-diamine

The relative stereochemistry of 1,3-diamines **26a-e** and **27a-e** was determined using X-ray analysis of di N-tosyl compound **29** and **31** derived from *syn*-**26e** and *anti*-**27e**. For this purpose, the free alcohol of protected *syn*-diamine **26e** was tosylated followed by treatment with $LiAlH_4$ to furnish compound **28**. The N-N bond of compound **28** was cleaved under hydrogenation conditions using freshly prepared Raney-Ni at 60 psi of H_2 to give free amine which was subsequently protected as its Ts- derivative **29** (Scheme **13**). Delightfully the isolated compound **29** was found to be nice crystal. Recrystallistion was done by slow evaporation of the solution mixture of pet ether and ethyl acetate to give clear crystalline solid. The ORTEP diagram (Fig. **3**) clearly established the *syn* stereochemistry of 1,3-diamine.



Scheme 13. Synthesis of ditosyl-*syn*-1,3-diamine

X-ray Crystal Structure Analysis For *syn*-1,3-Diamine 29

Crystal Data: $C_{19}H_{26}N_2O_4S_2$,0.5(H_2O),0.25(H_2O),0.25(H_2O), M=428.56, colorless plate, 0.46 x 0.45 x 0.09 mm^3, monoclinic, space group *C*2/*c*, a = 28.3830(10), b = 11.6353(4), c = 15.9062(5)Å, β = 107.593(2)°, V= 5007.2(3) $Å^3$, Z = 8, T = 296(2) K, $2\theta_{max}$ = 50.0°, D_{calc} (g cm^{-3}) = 1.132, $F(000)$ = 1808, μ (mm^{-1}) = 0.240, 18629 reflections collected, 4417 unique reflections (R_{int} = 0.0396), 2903 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.8977, T_{max} = 0.9787, 256 refined parameters, S = 1.080, $R1$ = 0.0700, $wR2$ = 0.2094 (all data R = 0.1003, $wR2$ = 0.2417), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.82, $\Delta\rho_{min}$ = -0.36 ($eÅ^{-3}$).

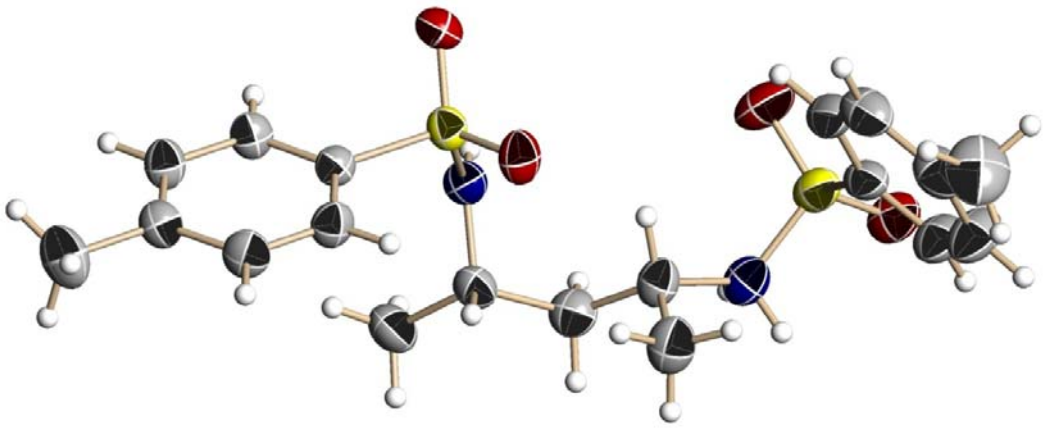
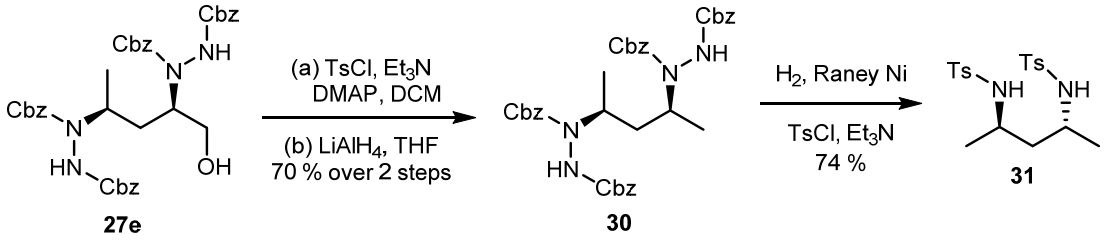


Figure 3. ORTEP of *syn*-compound **29**

As illustrated in Scheme **14**, Same set of reactions were repeated with 1,3-*anti*-diamine 27**e** to obtain the *anti* ditosyl diastereomers **31** (Scheme **14**), which also appeared to be nice crystal. Recrystallistion was done by slow evaporation of the solution mixture of pet ether and ethyl acetate to give clear crystalline solid. The ORTEP diagram (Fig. **4**) clearly established the *anti* stereochemistry of 1,3-diamine.



Scheme 14. Synthesis of ditosyl-*anti*-1,3-diamine

X-ray Crystal Structure Analysis For *anti*-1,3-Diamine

Crystal Data: $C_{19}H_{26}N_2O_4S_2$, M=410.54, colorless plate, 0.43 x 0.35x 0.17 mm^3, tetragonal, space group $P4_12_12$, a = 10.666(10), b = 10.666(10), c = 18.087(17) Å, V= 2058(3) $Å^3$, Z = 4, T = 293(2) K, $2\theta_{max}$ = 53.76°, D_{calc} (g cm^{-3}) = 1.325, $F(000)$ = 872, μ (mm^{-1}) = 0.285, 18655 reflections collected, 2208 unique reflections (R_{int}=0.0499), 1996 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.8871, T_{max} = 0.9531, 126 refined parameters, S = 1.048, $R1$ = 0.0359, $wR2$ = 0.0932 (all data R = 0.0418, $wR2$ = 0.0978), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.24, $\Delta\rho_{min}$= -0.32 ($eÅ^{-3}$).

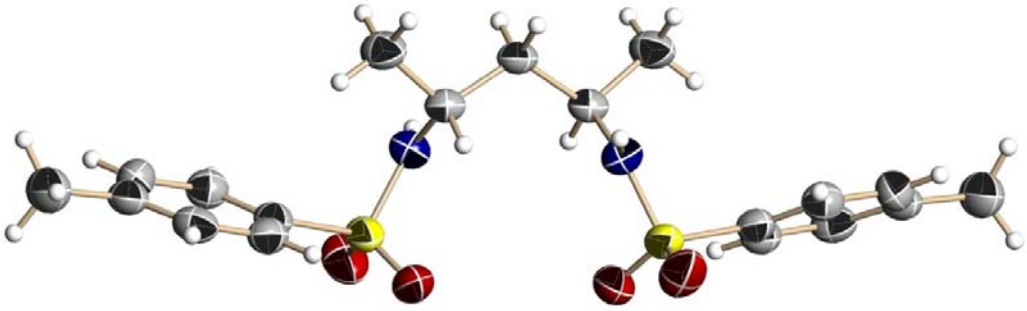
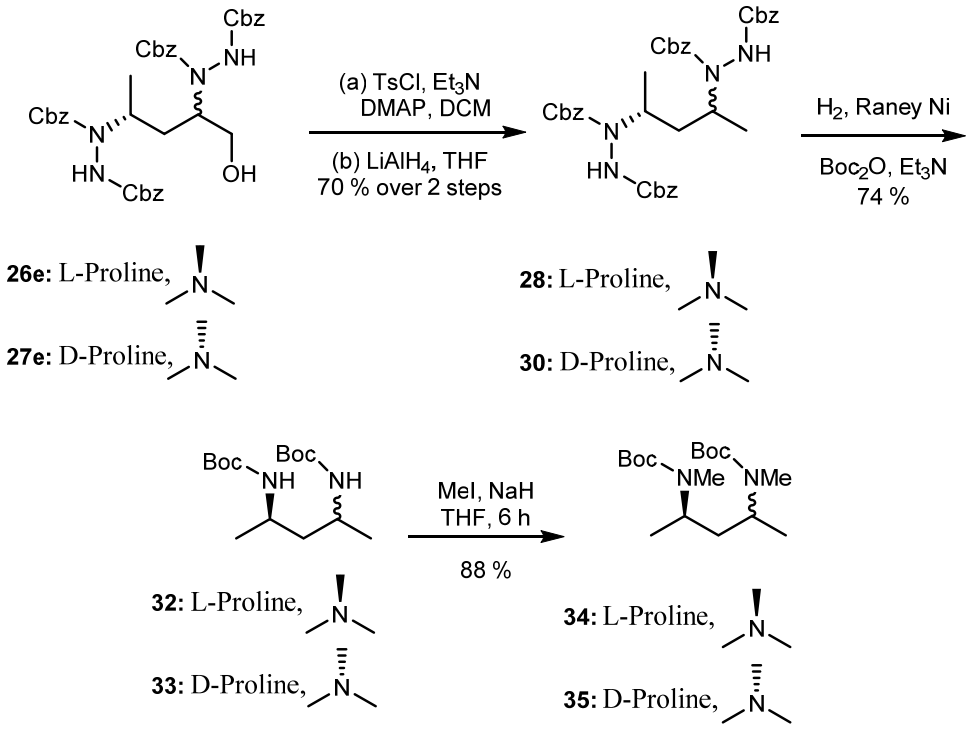


Figure 4. ORTEP of *anti*-compound **31**

In order to further demonstrate the utility of this approach we have developed a short synthesis of both diastereomers of N-protected N^2,N^4-dimethylpentane-2,4-diamine **34** & **35**. The chiral diamine ligand forms complex with Pt which interact stereospecifically with DNA and even with mononucleotides, and acts as antitumor.[16] As illustrated in Scheme **15**, the diastereomerically pure *syn*-diamine **26e** was subjected to synthetic manipulation in order to achieve the synthesis of target compound **34**.



Scheme 15. Synthesis of N^2,N^4-dimethylpentane-2,4-diamine

Toward this end, the free alcohol of protected *syn*-diamine **26e** was tosylated followed by treatment with $LiAlH_4$ to furnish compound **28**. The N-N bond of compound **28** was

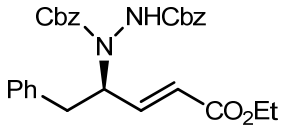
cleaved under hydrogenation conditions using freshly prepared Raney-Ni at 60 psi of H_2 to give free amine which was subsequently protected as its Boc derivative **32**. Methylation of Boc derivative gave the target compound **34**. The disappearance of NH protons in the range of δ 3.62-3.76 as multiplate and appearance of Me protons in the range of δ 2.70 as singlet in ^{1}H NMR spectrum confirmed the formation of the product. Same set of reactions were repeated with 1,3-*anti*-diamine 2**7e** to obtain the other diastereomers **35**.

4.5. Conclusion

In conclusion, we have developed for the first time a practical, efficient, and organocatalytic approach to the stereocontrolled synthesis of both *syn*- and *anti*-1,3-diamine from commercially available and inexpensive starting material using modified α-amination reactions of an aldehyde where the asymmetric induction for the *syn*-isomer is greater as compared to the *anti*-isomer. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of both the diastereomers of N-protected N^2,N^4-dimethylpentane-2,4-diamine.

4.6. Experimental Section

(*R,E*)-Dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21a):



General Procedure:

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.19 g, 0.62 mmol) and L-proline (0.007 g, 8 mol%) in CH_3CN (4 mL) at 0 °C was added aldehydes **20a** (0.1 g, 0.74 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 (0.040 g, 0.78 mmol), triethyl phosphonoacetate (0.2 mL, 0.78 mmol) and DBU (0.1 mL, 0.62 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: 90:10) of the crude product gave (*R,E*)-dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpent-3-en-2-yl)hydrazine-1,2-dicarboxylate **21a** as a colorless solid

Yield: 0.33g, 87%

Mol. Formula: $C_{29}H_{30}N_2O_6$

$[\alpha]_D^{25}$: + 8.44 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3292, 3031, 1717, 1455, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.87-3.19 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.91-5.25 (m, 5H), 5.90 (d, *J* = 15.6 Hz, 1H), 6.29 (s, 1H), 6.96 (dd, *J* = 6.7, 15.8 Hz, 1H), 7.16-7.32 (m, 15H) ppm.

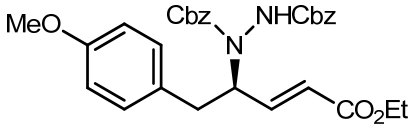
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 37.5, 60.5, 61.1, 67.9, 68.2, 123.2, 126.8, 127.9, 128.2, 128.5, 128.9, 135.5, 136.7, 143.9, 155.2, 156.6, 165.9 ppm.

MS (ESI): m/z 525.20 $(M+Na)^+$

HPLC: Chiralcel OD-H (250 X 4.6mm) (2-propanol : Petroleum ether = 3:97, flow rate 1.0 ml/min, (λ = 254 nm). Retention time (min):67.692 (major) and 75.817 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 95%

Using the same procedure as described for synthesis of **21a**, compounds **21b-21f** were prepared.

(*R,E*)-Dibenzyl 1-(5-ethoxy-1-(4-methoxyphenyl)-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21b):



Physical State: colorless solid

Yield: 84%

Mol. Formula: $C_{30}H_{32}N_2O_7$

$[\alpha]_D^{25}$: + 4.02 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3293, 3019, 1717, 1513, 1215.

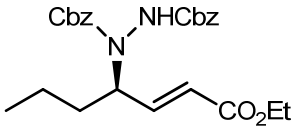
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3H), 2.80-3.13 (m, 2H), 3.77 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 4.92-5.24 (m, 5H), 5.88 (d, J = 16 Hz, 1H), 6.30 (s, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.92 (dd, J = 6.8, 16.3 Hz, 1H), 7.01-7.09 (m, 2H), 7.26-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 36.8, 55.2, 60.5, 68.0, 68.4, 114.1, 123.2, 126.9, 127.6, 127.9, 128.2, 128.5, 128.6, 128.9, 136.3, 135.5, 144.1, 155.3, 156.4, 158.4, 165.9 ppm.

MS (ESI): m/z 555.20 $(M+Na)^+$

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2- propanol : Petroleum ether = 10:90, flow rate 0.7 ml/min, (λ = 254 nm). Retention time (min):57.192 (major) and 63.683 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 91%

(*R*,*E*)-Dibenzyl 1-(1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (21c):



Physical State: colorless solid

Yield: 84%

Mol. Formula: $C_{25}H_{30}N_2O_6$

$[\alpha]_D^{25}$: + 8.01 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3296, 2960, 1715, 1658, 1456, 1041.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88-0.93 (m, 3H), 1.28 (t, J = 6.9 Hz, 3H), 1.31-1.52 (m, 2H), 1.63-1.81 (m, 2H), 4.18 (q, J = 6.9 Hz, 2H), 4.68-4.90 (m, 1H), 5.04-5.20 (m, 4H), 5.90 (d, J = 16.1 Hz, 1H), 6.39 (s, 1H), 6.84 (dd, J = 7.3, 15.7 Hz, 1H), 7.26-7.39 (m, 10H) ppm.

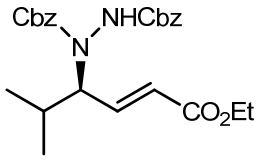
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 14.1, 22.3, 28.0, 58.8, 60.5, 67.8, 68.3, 122.9, 127.8, 128.2, 128.4, 135.6, 144.9, 155.5, 156.5, 166.1 ppm.

MS (ESI): m/z 477.17 $(M+Na)^+$

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : Petroleum ether = 10:90, flow rate 0.5 ml/min, (λ = 254 nm). Retention time (min):26.100 (major) and 36.575

(minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 94%

(*R,E*)-Dibenzyl 1-(6-ethoxy-2-methyl-6-oxohex-4-en-3-yl)hydrazine-1,2-dicarboxylate (21d):



Physical State: colorless solid

Yield: 83%

Mol. Formula: $C_{25}H_{30}N_2O_6$

$[\alpha]_D^{25}$: + 1.98 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3297, 2962, 1716, 1657, 1456, 1043.

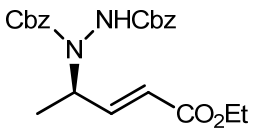
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz 3H), 0.92-1.09 (m, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.87-2.05 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.26-4.50 (m, 1H), 5.04-5.22 (m, 4H), 5.95 (d, *J* = 15.2 Hz, 1H), 6.43 (s, 1H), 6.83 (dd, *J* = 9.1, 15.8 Hz, 1H), 7.26-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.3, 19.8, 29.0, 60.3, 64.8, 67.6, 68.1, 124.0, 126.7, 127.2, 127.6, 128.0, 128.3, 135.4, 135.5, 143.4, 155.7, 156.4, 165.9 ppm.

MS (ESI): m/z 477.17 $(M+Na)^+$

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : Petroleum ether = 10:90, flow rate 0.7 ml/min, (λ = 254 nm). Retention time (min):19.250 (major) and 28.650 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 92%

(*R,E*)-Dibenzyl 1-(5-ethoxy-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21e):



Physical State: colorless solid

Yield: 80%

Mol. Formula: $C_{23}H_{26}N_2O_6$

$[\alpha]_D^{25}$: + 5.04 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 2981, 1717, 1498, 1219.

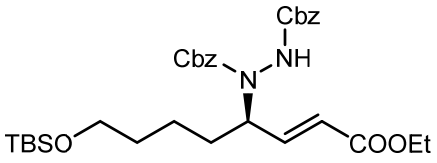
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.31 (dd, *J* = 6.9, 13.9 Hz, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 5.05-5.15 (m, 5H), 5.88 (d, *J* = 16.0 Hz, 1H), 6.53 (s, 1H), 6.90 (dd, *J* = 5.3, 15.8 Hz, 1H), 7.27-7.37 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 58.8, 60.3, 67.3, 67.9, 121.5, 126.5, 127.5, 127.7, 127.9, 135.4, 146.6, 155.1, 156.6, 166.1 ppm.

MS (ESI): m/z 449.13 $(M+Na)^+$

HPLC: Chiralcel OD-H (250 X 4.6mm) (2-propanol : n-Hexane = 6:94, flow rate 1.0 ml/min, (λ = 254 nm). Retention time (min): 27.042 (minor) and 34.208 (major). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 93%

Dibenzyl (*R,E*)-1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (21f):



Physical State: Colorless oil

Yield: 78%

Mol. Formula: $C_{32}H_{46}N_2O_7Si$

$[\alpha]_D^{25}$: + 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, $CDCl_3$): δ -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.

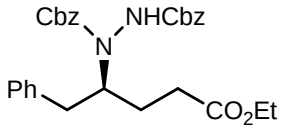
MS(ESI) : m/z 621.24 $(M+Na)^+$

HRMS : 621.2963 $(M+Na)^+$ Calcd. 621.2966

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%

(*S*)-Dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (22):



To a solution of ethyl ester **21a** (0.1 g, 0.2 mmol) in THF (2 ml) and MeOH (0.5 ml), was added $NaBH_4$ (0.028 g, 0.9 mmol) at 0 ^oC. The reaction was mixture was stirred at rt for 8 h. It was then quenched with aq. ammonium chloride solution (1.5 mL) 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 crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 9:1) of the crude product gave (*S*)-dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate **22** as a colorless solid

Mp: 94 °C

Yield: 0.09 g, 90%

Mol. Formula: $C_{29}H_{32}N_2O_6$

$[\alpha]_D^{25}$: + 7.49 (*c* 1.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3293, 3031, 2943, 1718, 1497, 1215.

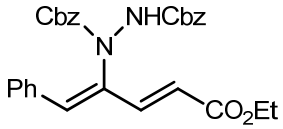
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15-1.26 (m, 3H), 1.72-1.95 (m, 2H), 2.29-2.57 (m, 2H), 2.67-2.99 (m, 2H), 3.94-4.13 (m, 2H), 4.34-4.64 (m, 1H), 5.05-5.19 (m, 4H), 6.16-6.46 (m, 1H), 7.22-7.36 (m, 15H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 29.6, 31.2, 38.9, 51.5, 60.4, 67.8, 68.2, 125.7, 126.5, 127.5, 127.9, 128.2, 128.3, 128.5, 135.5, 135.6, 135.8, 137.9, 155.8, 156.4, 157.0, 174.2.

MS (ESI): m/z 527.18 $(M+Na)^+$

HRMS 505.2332 $(M+H)^+$, calcd 505.2333.

Dibenzyl 1-((1*Z*,3*E*)-5-ethoxy-5-oxo-1-phenylpenta-1,3-dien-2-yl)hydrazine-1,2-dicarboxylate (23):



To a solution of acttivated Mg (0.02 g, 0.8 mmol) under argon in dry MeOH (5 ml) was added ethyl ester **21a** (0.1 g, 0.2 mmol). The reaction mixture was stirred for 3 h at 10 ^{o}C in an ice bath. The reaction mixture was poured into 10 ml of ice cooled 1 N HCl solution. The reaction mixture was then treated with 1 N ammonium hydroxide solution to adjust p^{H} to 8 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 crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 9:1) of the crude product gave dibenzyl 1-((1*Z*,3*E*)-5-ethoxy-5-oxo-1-phenylpenta-1,3-dien-2-yl)hydrazine-1,2-dicarboxylate **23** as a colorless solid

Mp: 88 °C

Yield: 0.05 g, 50%

Mol. Formula: $C_{29}H_{28}N_2O_6$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 3030, 1715, 1497, 1218.

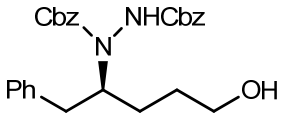
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.14-5.24 (m, 4H), 6.07 (d, *J* = 15.8 Hz, 1H), 7.25-7.36 (m, 17H), 7.61 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 60.6, 6.9, 68.5, 120.8, 127.7, 128.2, 128.4, 128.5, 128.9, 129.7, 134.1, 135.3, 135.5, 136.2, 137.1, 138.6, 155.3, 156.1, 166.7 ppm.

MS (ESI): m/z 523.18 $(M+Na)^+$

HRMS 501.2019 $(M+H)^+$, calcd 501.2020; 518.2287 $(M+NH_4^+)^+$, calcd 518.2286

(*S*)-Dibenzyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (25a):



General Procedure:

To a solution of ethyl ester **21a** (0.1 g, 0.2 mmol) in THF (2 ml), was added $LiBH_4$ (0.01 g, 0.6 mmol) at 0 ^{o}C. The reaction was mixture was stirred at rt for 1 h. It was then

quenched with aq. ammonium chloride solution (1 mL) 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 crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 7:3) of the crude product gave **(***S***)**-dibenzyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate **25a** as a colorless solid

Mp: 97 °C

Yield: 0.09 g, 92%

Mol. Formula: $C_{27}H_{30}N_2O_5$

$[\alpha]_D^{25}$: + 13.08 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 3285, 2927, 1709, 1454, 1221, 1057.

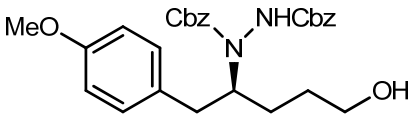
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45-1.58 (m, 2H), 1.71-1.76 (m, 2H), 2.72-2.86 (m, 2H), 3.26 (brs, 1H), 3.49-3.73 (m, 2H), 4.37-4.63 (m, 1H), 5.05-5.18 (m, 4H), 6.34 (s, 1H), 7.12-7.22 (m, 5H), 7.29-7.44 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.9, 38.8, 60.3, 61.7, 67.3, 67.8, 126.0, 127.1, 127.8, 128.2, 128.6, 136.3, 135.7, 138.2, 155.8, 156.7 ppm.

MS (ESI): m/z 485.19 $(M+Na)^+$

HRMS 463.2226 $(M+H)^+$, calcd 463.2227; 485.2044 $(M+Na)^+$, calcd 485.2044

(*S*)-Dibenzyl 1-(5-hydroxy-1-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (25b):



Physical State: colorless solid

Mp: 120 °C

Yield: 92%

Mol. Formula: $C_{28}H_{32}N_2O_6$

$[\alpha]_D^{25}$: + 20.08 (*c* 0.75, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3420, 2925, 1711, 1456, 1127.

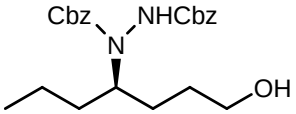
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39-1.54 (m, 2H), 1.69-1.93 (m, 2H), 2.62-2.84 (m, 2H), 3.48-3.73 (m, 2H), 3.76 (s, 3H), 4.29-4.62 (m, 1H), 5.00-5.18 (m, 4H), 6.25 (brs, 1H), 6.78 (d, J = 8.5 Hz, 2H), 6.98-7.16 (m, 3H), 7.27-7.42 (m, 9H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 29.4, 38.1, 55.1, 60.5, 62.2, 67.8, 68.2, 113.9, 127.4, 127.9, 128.2, 128.4, 128.5, 129.6, 129.8, 130.1, 135.4, 135.7, 135.9, 155.9, 156.9, 158.1 ppm.

MS (ESI): m/z 515.21 $(M+Na)^+$

HRMS 493.2335 $(M+H)^+$, calcd 493.2333; 515.2155 $(M+Na)^+$, calcd 515.2153

(*R*)-Dibenzyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (25c):



Physical State: colorless solid

Mp: 95 °C

Yield: 89%

Mol. Formula: $C_{23}H_{30}N_2O_5$

$[\alpha]_D^{25}$: + 4.14 (c 1.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3461, 3274, 2961, 1711, 1692, 1457, 1042.

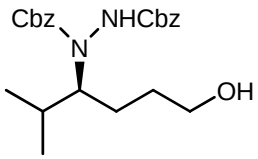
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.10-1.56 (m, 8H), 3.30-3.61 (m, 2H), 4.06-4.23 (m, 1H), 5.04-5.24 (m, 4H), 6.47 (brs, 1H), 7.26-7.43 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 19.6, 28.6, 29.3, 34.7, 57.8, 62.3, 67.8, 68.2, 127.6, 127.8, 128.0, 128.2, 128.4, 128.5, 135.5, 135.8, 135.9, 156.3, 156.9 ppm.

MS (ESI): m/z 437.12 $(M+Na)^+$

HRMS 415.2224 $(M+H)^+$ calcd 415.2227; 437.2042 $(M+Na)^+$, calcd 437.2047

(*S*)-Dibenzyl 1-(6-hydroxy-2-methylhexan-3-yl)hydrazine-1,2-dicarboxylate (25d):



Physical State: colorless solid

Mp: 97 °C

Yield: 88%

Mol. Formula: $C_{23}H_{30}N_2O_5$

$[\alpha]_D^{25}$: + 0.96 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3284, 2960, 1711, 1657, 1410, 1049.

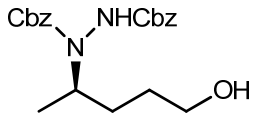
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-0.97 (m, 6H), 1.52-1.80 (m, 5H), 3.26-3.69 (m, 2H), 3.87-4.12 (m, 1H), 5.10-5.19 (m, 4H), 6.49 (brs, 1H), 7.26-7.35 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 20.2, 25.2, 29.4, 30.4, 62.1, 64.1, 67.6, 68.2, 127.5, 127.7, 127.9, 128.1, 128.4, 135.5, 135.8, 135.9, 156.5, 157.2 ppm.

MS (ESI): m/z 437.12 $(M+Na)^+$.

HRMS 415.2224 $(M+H)^+$, calcd 415.2227; 437.2042 $(M+Na)^+$, calcd 437.2047

(*R*)-Dibenzyl 1-(5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (25e):



Physical State: colorless solid

Mp: 81 °C

Yield: 89%

Mol. Formula: $C_{21}H_{26}N_2O_5$

$[\alpha]_D^{25}$: - 2.75 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3292, 2941, 1711, 1658, 1455, 1221.

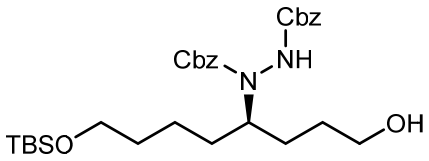
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (d, J = 6.5 Hz, 3H), 1.37-1.50 (m, 2H), 1.63-1.73 (m, 2H) 3.51-3.73 (m, 2H), 4.21-4.44 (m, 1H), 5.08-5.21 (m, 4H), 6.49 (brs, 1H), 7.27-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9, 29.1, 29.9, 53.5, 62.0, 67.5, 67.8, 127.6, 127.9, 128.2, 128.4, 135.6, 135.8, 155.8, 156.9 ppm.

MS (ESI): m/z 409.14 $(M+Na)^+$.

HRMS 387.1913 $(M+H)^+$, calcd 387.1914; 409.1732 $(M+Na)^+$, calcd 409.1734

(*R*)-Dibenzyl 1-(8-((tert-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (25f):



Physical State: waxy solid

Yield: 90%

Mol. Formula: $C_{30}H_{46}N_2O_6Si$

$[\alpha]_D^{25}$: + 11.51 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 295, 1705, 1658, 1224.

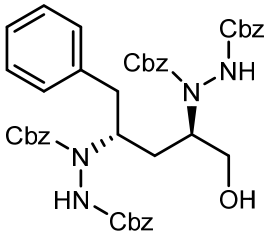
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.16-1.73 (m, 10H), 2.48 (brs, 1H), 3.27-3.55 (m, 4H), 3.90-4.26 (m, 1H), 4.85-5.20 (m, 4H), 7.11-7.42 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 18.1, 21.9, 22.2, 25.7, 28.4, 28.9, 32.1, 57.9, 61.8, 62.6, 67.3, 67.5, 127.3, 127.8, 127.9, 128.2, 135.5, 135.9, 156.2, 156.7 ppm.

MS (ESI): m/z 581.24 $(M+Na)^+$.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{47}N_2O_6Si$ 559.3198; Found 559.3189; $[M+Na]^+$ Calcd for $C_{30}H_{46}N_2O_6NaSi$ 581.3017; Found 581.3010.

1,1'-((2*R*,4*R*)- Tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26a):



General Procedure:

To a solution of alcohol **25a** (0.1g, 0.216 mmol) in DCM (2 ml) was added DMP (0.137g, 3.25 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 1 hr. It was then quenched with a 1:1 mixture of (10 %) aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and extracted with diethyl ether (3 X 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.065 g, 0.216 mmol) and L-proline (0.003 g, 10 mol%) in CH_3CN (2 mL) at 0 °C was added above aldehyde (0.1 g, 0.216 mmol) and the mixture was stirred for 4 h at 0 °C and further for 1 h at 10 °C. Then reaction mixture was cooled to 0 ^oC, treated with ethanol 1 ml and $NaBH_4$ (0.02 g) and was stirred for 5 min at 0 ^oC. It was then quenched with aq. ammonium chloride solution (3 mL) 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 crude product (diastereomeric ratio/ 3:1). Silica gel column chromatography (petroleum ether: ethyl acetate: 70:30) of the crude product gave 1,1'-((2*R*,4*R*)- tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) **26a** as a waxy solid.

Yield: 0.11 g, 68%

Mol. Formula: $C_{43}H_{44}N_4O_9$

$\mathbf{[\alpha]_D^{25}}$: + 37.41 (*c* 1.05, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3292, , 2925, 1718, 1455, 1219, 1060.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41-1.70 (m, 1H), 1.75-2.12 (m, 1H), 2.72-3.14 (m, 2H), 3.39-3.61 (m, 2H), 3.66-3.93 (m, 1H), 4.23-4.52 (m, 1H), 4.85-5.35 (m, 8H), 6.19-6.33 (m, 1H), 7.12-7.44 (m, 25H), 7.94-8.16 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 37.7, 57.9, 61.7, 61.8, 67.9, 68.2, 68.4, 68.6, 126.6, 127.2, 127.5, 127.8, 128.0, 128.4, 128., 128.7, 135.1, 135.5, 156.7, 156.8, 158.6, 159.0 ppm.

MS (ESI): m/z 783.33 $(M+Na)^+$, 799.30 $(M+K)^+$.

HRMS 761.3182 $(M+H)^+$, calcd 761.3181

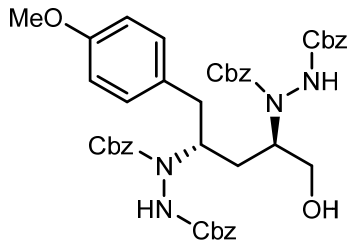
Diastereomeric ratio was determined by HPLC analysis; 99.9:0.1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.4 mL/min, IPA:Pet Ether = 6:4; t_R for (*anti*)-isomer = 25.800 min and t_R for (*syn*)- isomer = 19.667 min.

Using the same procedure as described for synthesis of **26a**, compounds **26b-26f** were prepared.

1,1'-((2*R*,4*R*)- Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26b):



Physical State: waxy solid

Yield: 65%

Mol. Formula: $C_{44}H_{46}N_4O_{10}$

$[\alpha]_D^{25}$: + 12.08 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 2927, 1718, 1512, 1455, 1247, 1059.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45-1.74 (m, 2H), 2.61-2.88 (m, 2H), 3.33-3.70 (m, 3H), 3.77 (s, 3H), 4.15-4.69 (m, 2H), 4.88-5.37 (m, 8H), 6.21-6.49 (m, 1H), 6.73-6.82 (m, 2H), 7.00-7.09 (m, 2H), 7.19-7.48 (m, 20H), 8.03-8.21 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 38.1, 55.0, 60.3, 61.6, 62.2, 67.6, 67.9, 68.2, 68.5, 113.9, 114.0, 127.1, 127.4, 127.9, 128.2, 128.3, 128.5, 129.5, 129.6, 129.9, 135.1, 135.4, 135.7, 135.9, 155.9, 156.4, 156.8, 157.3, 158.1 ppm.

MS (ESI): m/z 813.37 $(M+Na)^+$

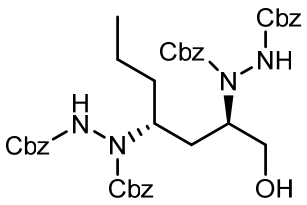
HRMS 791.3288 $(M+H)^+$, calcd 791.3287; 813.3095 $(M+Na)^+$, calcd 813.3106

Diastereomeric ratio was determined by HPLC analysis; 99.9:0.1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 37.550 min and t_R for (*syn*)- isomer = 29.225 min.

1,1'-((2*R*,4*R*)- Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26c):



Physical State: waxy solid

Yield: 62%

Mol. Formula: $C_{39}H_{44}N_4O_9$

$[\alpha]_D^{25}$: - 5.32 (*c* 1.85, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3293, 2925, 1714, 1498, 1456, 1259, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.72-0.88 (m, 3H), 1.26-1.34 (m, 3H), 1.48-1.80 (m, 3H), 3.40-3.72 (m, 2H), 3.88-4.02 (m, 1H), 4.21-4.54 (m, 2H), 4.83-5.33 (m, 8H), 6.64-6.96 (m, 1H), 7.22-7.48 (m, 20H), 7.56-7.83 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 19.5, 31.6, 34.7, 57.7, 61.6, 62.0, 67.5, 67.8, 68.1, 68.4, 127.2, 127.4, 127.7, 127.9, 128.1, 128.3, 128.4, 129.8, 132.9, 135.4, 135.5, 135.8, 156.2, 156.5, 156.7, 156.9 ppm.

MS (ESI): m/z 735.34 $(M+Na)^+$

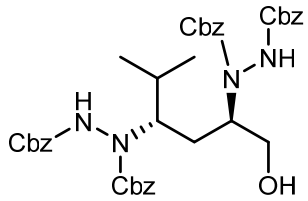
HRMS 713.3182 $(M+H)^+$, calcd 71.3181; 735.2983 $(M+Na)^+$, calcd 735.3001.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 22.283 min and t_R for (*syn*)- isomer = 14.792 min.

1,1'-((2*R*,4*S*)- Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26d):



Physical State: waxy solid

Yield: 64%

Mol. Formula: $C_{39}H_{44}N_4O_9$

$[\alpha]_D^{25}$: - 8.29 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3280, 2960, 1715, 1498, 1456, 1260, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-0.94 (m, 6H), 1.55-1.84 (m, 3H), 3.42-3.66 (m, 2H), 3.75-4.16 (m, 3H), 5.08-5.14 (m, 8H), 5.65-5.78 (m, 1H), 6.72-6.91 (m, 1H), 7.26-7.39 (m, 20H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 19.7, 29.4, 30.4, 61.4, 62.5, 64.2, 67.6, 67.9, 68.3, 127.2, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 129.9, 130.7, 131.9, 135.5, 135.8, 156.5, 156.7, 157.2 ppm.

MS (ESI): m/z 735.34 $(M+Na)^+$

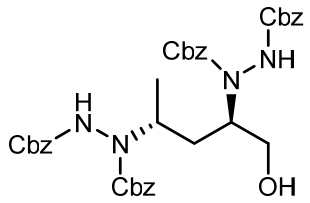
HRMS 713.3182 $(M+H)^+$ calcd 71.3181; 735.2983 $(M+Na)^+$ calcd 735.3001.

Diastereomeric ratio was determined by HPLC analysis; 97.5:2.5 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 25.542 min and t_R for (*syn*)- isomer = 17.342 min.

1,1'-((2*R*,4*R*)- Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26e):



Physical State: waxy solid

Yield: 65%

Mol. Formula: $C_{37}H_{40}N_4O_9$

$[\alpha]_D^{25}$: - 10.17 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3290, 2936, 1712, 1498, 1455, 1223, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): *δ* 1.08-1.23 (m, 3H), 1.28-1.53 (m, 2H), 3.30-3.66 (m, 3H), 4.02-4.47 (m, 2H), 4.91-5.53 (m, 8H), 6.84-6.98 (m, 1H), 7.19-7.41 (m, 20H), 7.64-7.75 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 22.6, 29.6, 61.8, 61.9, 62.3, 67.7, 67.9, 68.1, 68.5, 127.4, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 135.3, 135.5, 156.4, 156.6, 156.7, 156.8 ppm.

MS (ESI): m/z 707.40 $(M+Na)^+$

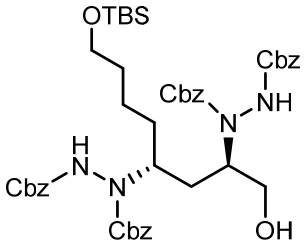
HRMS 685.2869 $(M+H)^+$ calcd 685.2868; 707.2675 $(M+Na)^+$, calcd 707.2687.

Diastereomeric ratio was determined by HPLC analysis; 99.7:0.3 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 26.558 min and t_R for (*syn*)- isomer = 22.017 min.

1,1'-((2*R*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26f):



Physical State: waxy solid

Yield: 63%

Mol. Formula: $C_{46}H_{60}N_4O_{10}Si$

$[\alpha]_D^{25}$: + 4.45 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3295, 2932, 1712, 1496, 1261, 1051.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.93 (s, 9H), 1.31-1.89 (m, 8H), 3.46-3.73 (m, 4H), 3.83-4.61 (m, 3H), 4.83-5.39 (m, 8H), 6.88-6.99 (m, 1H), 7.12-7.34 (m, 20H), 7.91-8.28 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, 18.2, 22.6, 25.8, 29.5, 31.8, 61.6, 61.9, 62.7, 67.9, 68.1, 68.4, 127.2, 127.7, 127.9, 128.2, 128.4, 131.3, 132.4, 135.4, 141.3, 156.3, 156.7, 156.8 ppm.

MS (ESI): m/z 879.24 $(M+Na)^+$.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{46}H_{60}N_4O_{10}NaSi$ 879.3971; Found 879.3964.

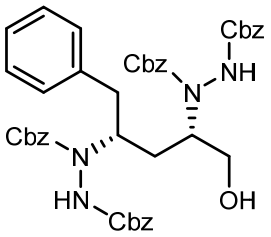
Diastereomeric ratio was determined by HPLC analysis; 99:1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 27.542 min and t_R for (*syn*)- isomer = 23.642 min.

Using the same procedure as described for the synthesis of **26a** and using D-proline as a catalyst in α-amination step compounds **27a**-**27f** were prepared.

1,1'-((2*S*,4*R*)- Tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27a):



Physical State: waxy solid

Yield: 64%

Mol. Formula: $C_{43}H_{44}N_4O_9$

$[\alpha]_D^{25}$: + 2.74 (*c* 1.7, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3292, 2925, 1718, 1455, 1219, 1060.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.82 (m, 2H), 2.49-2.99 (m, 2H), 3.11-3.71 (m, 2H), 4.18-4.73 (m, 2H), 4.88-5.18 (m, 8H), 6.42-6.57 (m, 1H), 7.32 (m, 25H), 7.92-8.21 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 29.1, 38.9, 52.6, 60.4, 61.9, 67.3, 67.5, 67.7, 67.9, 127.2, 127.7, 127.9, 128.3, 128.7, 128.8, 129.7, 132.8, 134.9, 135.4, 135.8, 138.2, 155.8, 156.3, 156.7, 157.2 ppm.

MS (ESI): m/z 783.33 $(M+Na)^+$

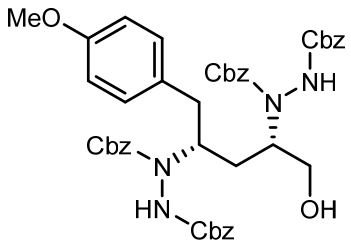
HRMS 761.3182 $(M+H)^+$, calcd 761.3181

Diastereomeric ratio was determined by HPLC analysis; 3:1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.4 mL/min, IPA:Pet Ether = 6:4; t_R for (*anti*)-isomer = 22.825 min and t_R for (*syn*)- isomer = 20.317 min.

1,1'-((2*S*,4*R*)-Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27b):



Physical State: waxy solid

Yield: 62%

Mol. Formula: $C_{44}H_{46}N_4O_{10}$

$[\alpha]_D^{25}$: + 13.24 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 2927, 1718, 1512, 1455, 1247, 1059.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30-1.49 (m, 2H), 2.46-2.71 (m, 2H), 3.40-3.61 (m, 3H), 3.66 (s, 3H), 3.90-4.58 (m, 2H), 4.67-5.17 (m, 8H), 6.27-6.43 (m, 1H), 6.69 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 2H), 7.02-7.23 (m, 20H), 7.45-7.73 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 38.1, 55.1, 60.4, 62.2, 62.3, 67.8, 67.9, 68.2, 113.9, 127.5, 127.9, 128.2, 128.4, 128.5, 129.4, 129.6, 129.8, 129.9, 135.2, 135.4, 135.7, 135.9, 155.9, 156.5, 156.8, 157.4, 158.1 ppm.

MS (ESI): m/z 813.37 (M^++Na).

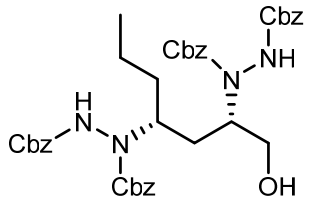
HRMS 791.3288 $(M+H)^+$, calcd 791.3287; 813.3095 $(M+Na)^+$, calcd 813.3106

Diastereomeric ratio was determined by HPLC analysis; 2:3 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 37.185 min and t_R for (*syn*)- isomer = 31.017 min.

1,1'-((2*S*,4*R*)-Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27c):



Physical State: waxy solid

Yield: 60%

Mol. Formula: $C_{39}H_{44}N_4O_9$

$[\alpha]_D^{25}$: - 2.27 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3293, 2925, 1714, 1498, 1456, 1259, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75-0.93 (m, 3H), 1.09-1.32 (m, 3H), 1.37-1.81 (m, 3H), 3.42-3.76 (m, 3H), 3.90-4.37 (m, 2H), 4.86-5.30 (m, 8H), 6.68 (m, 1H), 7.14-7.45 (m, 20H), 7.56-7.73 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.6, 29.7, 34.8, 57.7, 58.8, 62.3, 67.8, 67.9, 68.1, 68.3, 126.9, 127.6, 127.7, 128.0, 128.2, 128.5, 135.5, 135.8, 135.9, 156.3, 156.6, 156.9, 157.2 ppm.

MS (ESI): m/z 735.34 $(M+Na)^+$

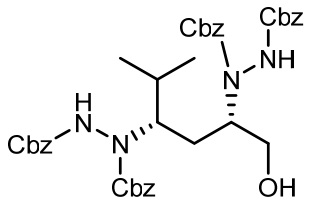
HRMS 713.3182 $(M+H)^+$, calcd 71.3181; 735.2983 $(M+Na)^+$, calcd 735.3001

Diastereomeric ratio was determined by HPLC analysis; 3:2 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 22.533 min and t_R for (*syn*)- isomer = 15.575 min.

1,1'-((2*S*,4*S*)- Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27d):



Physical State: waxy solid

Yield: 64%

Mol. Formula: $C_{39}H_{44}N_4O_9$

$[\alpha]_D^{25}$: - 10.14 (*c* 1.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3280, 2960, 1715, 1498, 1456, 1260, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-0.95 (m, 6H), 1.47-1.84 (m, 3H), 3.34-3.93 (m, 4H), 4.05-4.24 (m, 1H), 4.77-5.28 (m, 8H), 5.65-5.78 (m, 1H), 6.77-7.03 (m, 1H), 7.25-7.39 (m, 20H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 19.9, 29.4, 30.4, 62.3, 62.6, 64.2, 67.7, 67.8, 68.0, 68.3, 127.3, 127.5, 127.6, 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 129.9, 135.4, 135.8, 156.4, 156.7, 156.9, 157.2 ppm.

MS (ESI): m/z 735.34 $(M+Na)^+$

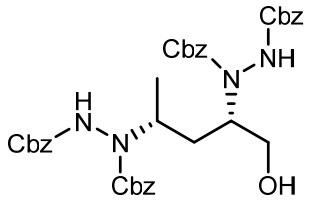
HRMS 713.3182 $(M+H)^+$, calcd 71.3181; 735.2983 $(M+Na)^+$, calcd 735.3001

Diastereomeric ratio was determined by HPLC analysis; 3:1 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 24.817 min and t_R for (*syn*)- isomer = 17.308 min.

1,1'-((2*S*,4*R*)- Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27e):



Physical State: waxy solid

Yield: 61%

Mol. Formula: $C_{37}H_{40}N_4O_9$

$[\alpha]_D^{25}$: - 3.08 (*c* 2.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3290, 2936, 1712, 1498, 1455, 1223, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (d, J = 6.4Hz, 3H), 1.28-1.48 (m, 2H), 3.03-3.22 (s, 1H), 3.36-3.57 (m, 2H), 4.02-4.41 (m, 2H), 4.75-5.29 (m, 4H), 6.79-7.03 (m, 1H), 7.12-7.46 (m, 20H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.9, 29.2, 53.5, 54.5, 62.2, 67.6, 67.8, 68.1, 127.3, 127.6, 128.0, 128.2, 135.6, 135.8, 155.7, 155.8, 156.6, 156.8 ppm.

MS (ESI): m/z 707.40 $(M+Na)^+$

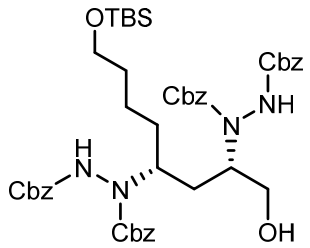
HRMS 685.2869 $(M+H)^+$, calcd 685.2868; 707.2675 $(M+Na)^+$, calcd 707.2687.

Diastereomeric ratio was determined by HPLC analysis; 57:43 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 26.092 min and t_R for (*syn*)- isomer = 21.625 min.

1,1'-((2*S*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27f):



Physical State: waxy solid

Yield: 62%

Mol. Formula: $C_{46}H_{60}N_4O_{10}Si$

$[\alpha]_D^{25}$: - 5.59 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3295, 2932, 1712, 1496, 1261, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.26-1.32 (m, 3H), 1.38-1.67 (m, 5H), 2.51 (brs, 1H), 3.40-4.27 (m, 6H), 4.79-5.34 (m, 8H), 6.79-6.97 (m, 1H), 7.27 (m, 20H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, 18.3, 22.2, 25.9, 29.6, 32.3, 62.2, 62.4, 62.7, 67.7, 67.9, 68.1, 127.5, 128.1, 128.2, 128.4, 128.5, 135.5, 135.7, 156.3, 156.5, 156.8 ppm.

MS (ESI): m/z 879.24 $(M+Na)^+$.

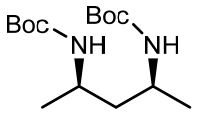
HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{46}H_{60}N_4O_{10}NaSi$ 879.3971; Found 879.3964.

Diastereomeric ratio was determined by HPLC analysis; 5:3 dr

UV detector: Shimadzu Class-VP V6.12 SP5

Column: Kromasil 5-AmyCoat, Flow rate: 0.5 mL/min, IPA:Pet Ether = 3:7; t_R for (*anti*)-isomer = 26.200 min and t_R for (*syn*)- isomer = 21.050 min.

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)dicarbamate (32):



The solution of 1,1'-((2*S*,4*R*)- tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate **26e** (0.5g, 0.73 mmol) in DCM was treated with triethylamine (0.148g, 1.46 mmol) and TsCl (0.21g, 1.1 mmol) was added at 0 ^oC followed by addition of catalytic DMAP. The reaction mixture was stirred at rt for 2 h. After completion of reaction, the reaction mixture was quenched with addition of water and extracted with DCM (3 X 15 ml). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude tosyl compound. This crude tosyl compound was then treated with $LiAlH_4$ (0.03 g, 0.8 mmol) in THF for 1 h. The reaction was quenched by addition of saturated Na_2SO_4 solution. The mixture was filtered with pad of celite, and washed with EtOAc. The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude diamine product **28** which was directly used in the next step without further purification.

The solution of crude diamine product **28** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (80 psig) atmosphere for 24 h.

The reaction mixture was then filtered over celite and concentrated to give crude free diamine which was further treated with triethylamine (0.3g, 2.92 mmol), $(Boc)_2O$ (0.65 mL, 2.92 mmol) in dry DCM (2 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 di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)dicarbamate **32** as a waxy solid

Yield: 0.113 g, 51%

Mol. Formula: $C_{15}H_{30}N_2O_4$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3363, 2976, 1690, 1523, 1170.

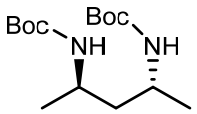
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (d, *J*= 6.4 Hz, 6H), 1.43 (s, 18H), 1.67 (m, 2H), 3.62-3.76 (m, 2H), 4.38-4.59 (brs, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 28.4, 29.7, 44.1, 79.1, 155.3 ppm.

MS (ESI): m/z 325.15 $(M+Na)^+$

HRMS 325.2098 $(M+Na)^+$, calcd 325.2096

Di-*tert*-butyl ((2*R*,4*R*)-pentane-2,4-diyl)dicarbamate (33):



Compound **33** was prepared from **27e** using same procedure as described for preparation of compound **32**.

Physical State: waxy solid

Yield: 51%

Mol. Formula: $C_{15}H_{30}N_2O_4$

$[\alpha]_D^{25}$: + 5.92 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3363, 2976, 1690, 1523, 1170.

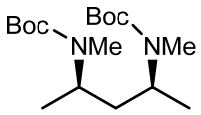
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (d, *J*= 6.7 Hz, 6H), 1.44 (s, 18H), 1.53-1.55 (m, 2H), 3.62-3.76 (m, 2H), 4.41-4.52 (brs, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0, 28.4, 29.6, 43.9, 79.0, 156.2 ppm.

MS (ESI): m/z 325.15 $(M+Na)^+$.

HRMS 325.2098 $(M+Na)^+$, calcd 325.2096

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)bis(methylcarbamate) (34):



To a stirred solution of **32** (0.03 g, 0.116 mmol) in dry toluene (3 mL) was added NaH (0.010 g, 0.464 mmol), CH_3I (0.1 mL, 1.55 mmol) and the reaction mixture was heated at 85 ^oC for 5 h. The reaction mixture was then diluted with EtOH (5 mL) and H_2O (2 mL), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 4 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: 85:15) of the crude product gave di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)bis(methylcarbamate) **34** as a colorless liquid.

Yield: 0.029 g, 88%

Mol. Formula: $C_{17}H_{34}N_2O_4$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3445, 2926, 1695, 1456, 1158.

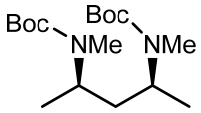
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (d, *J*= 6.7 Hz, 6H), 1.46 (s, 18H), 1.54-1.69 (m, 2H), 2.70 (s, 6H), 3.87-4.26 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.7, 28.5, 29.7, 31.9, 47.2, 79.1, 155.52 ppm.

MS (ESI): m/z 353.21 (M^++Na).

HRMS 331.2591 (M^++H), calcd 331.2591; 353.2409 (M^++Na), calcd 353.2411.

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)bis(methylcarbamate) (35):



Compound **35** was prepared from **33** using same procedure as described for preparation of compound **34**.

Physical State: colorless liquid

Yield: 88%

Mol. Formula: $C_{17}H_{34}N_2O_4$

$[\alpha]_D^{25}$: + 2.10 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3445, 2926, 1695, 1456, 1158.

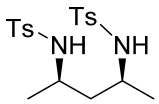
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, J= 6.8 Hz, 6H), 1.46 (s, 18H), 1.61-1.66 (m, 2H), 2.68 (s, 3H), 2.71 (s, 3H), 3.88-4.07 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.7, 28.5, 29.7, 31.9, 49.5, 79.0, 79.4, 155.4, 155.6 ppm.

MS (ESI): m/z 353.21 $(M+Na)^+$

HRMS 331.2591 $(M+H)^+$, calcd 331.2591; 353.2409 $(M+Na)^+$, calcd 353.2411

N,N'-((2*R*,4*S*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) (29):



The solution of 1,1'-((2*S*,4*R*)- tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate **26e** (0.5 g, 0.73 mmol) in DCM was treated with triethylamine (0.148 g, 1.46 mmol) and TsCl (0.21 g, 1.1 mmol) was added at 0 ^oC followed by addition of catalytic DMAP. The reaction mixture was stirred at rt for 2 h. After completion of reaction, the reaction mixture was quenched with addition of water and extracted with DCM (3 X 15 ml). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude tosyl compound. This crude tosyl compound was then treated with $LiAlH_4$ (0.03 g, 0.8 mmol) in THF for 1 h. The reaction was quenched by addition of saturated Na_2SO_4 solution. The mixture was filtered with pad of celite, and washed with EtOAc. The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude diamine product **28** which was directly used in the next step without further purification.

The solution of crude diamine product **28** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free diamine which was further treated with triethylamine (0.3 g, 2.92 mmol), TsCl (0.555 g, 2.92 mmol) in dry DCM (2 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: 80:20) of the crude product gave N,N'-((2*R*,4*S*)-pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) **29** as a crystalline solid (0.148 g, 50%).

mp: 115 °C

Yield: 0.118 g, 50%

Mol. Formula: $C_{19}H_{26}N_2O_4S_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3275, 2928, 1328, 1161.

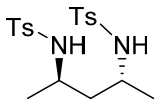
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, *J*= 6.5 Hz, 6H), 1.39-1.50 (m, 1H), 1.69-1.79 (m, 1H), 2.42 (s, 6H), 3.21-3.47 (m, 2H), 4.46 (d, *J*= 8.6 Hz, 2H), 7.29 (d, *J*= 8.4 Hz, 4H), 7.74 (d, *J*= 8.4 Hz, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 21.5, 45.7, 47.2, 127.0, 129.7, 137.9, 143.3 ppm.

MS (ESI): m/z 433.04 $(M+Na)^+$

HRMS 433.1224 $(M+Na)^+$, calcd 433.1226

N,N'-((2*R*,4*S*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) (31):



Compound **31** was prepared from **27e** using same procedure as described for preparation of compound **29**.

Physical State: Crystalline solid

mp: 113 °C

Yield: 50%

Mol. Formula: $C_{19}H_{26}N_2O_4S_2$

$[\alpha]_D^{25}$: + 0.15 (*c* 0.75, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3275, 2928, 1328, 1161.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (d, *J*= 6.7 Hz, 6H), 1.59-1.63 (m, 2H), 2.44 (s, 6H), 3.43-3.57 (m, 2H), 4.61 (d, *J*= 7.8 Hz, 2H), 7.32 (d, *J*= 8.3 Hz, 4H), 7.78 (d, *J*= 8.3 Hz, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 21.5, 44.6, 47.4, 127.0, 129.7, 138.3, 143.3 ppm.

MS (ESI): m/z 433.04 $(M+Na)^+$

HRMS 433.1224 $(M+Na)^+$, calcd 433.1226

4.7. X-ray Crystal Structure Analysis

X-ray intensity data measurements of compound **29** and **31** was carried out on a Bruker SMART Apex2 CCD diffractometer with graphite-monochromatized (MoK_α=

0.71073Å) radiation at 296 (2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from 125 and 109 reflections respectively harvested from three sets of 36 frames. The optimized strategy used for data collection consisted of three φ scan for 15 and three ω scan and one φ scan sets for 16, with 0.5° steps in φ or ω. Data were collected with a frame time of 10 sec for 15 and 15sec for 16 keeping the sample-to-detector distance fixed at 5.00 cm. A total of 1638 and 1177 frames were collected for 15 and 16 respectively. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] Final unit cell parameters were obtained from 6451 and 4474 reflections for 29 and 31 respectively after integration.

Table 3. Crystal data and structure refinement for compound **29**

Empirical formula	$C_{19}\ H_{26}\ N_2\ O_4\ S_2$
Formula weight	410.54
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P4(1)2(1)2
Unit cell dimensions	a = 10.666(10) Å α= 90°. b = 10.666(10) Å β= 90°. c = 18.087(17) Å γ = 90°.
Volume	2058(3) $Å^3$
Density (calculated)	1.325 Mg/m^3
Absorption coefficient	0.285 mm^{-1}
F(000)	872
Crystal size	0.43 x 0.35 x 0.17 mm^3
Theta range for data collection	2.22 to 26.88°.
Index ranges	-13<=h<=13, -13<=k<=13, -22<=l<=22
Reflections collected	18655
Independent reflections	2208 [R(int) = 0.0499]
Completeness to theta = 26.88°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9531 and 0.8871
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2208 / 0 / 126

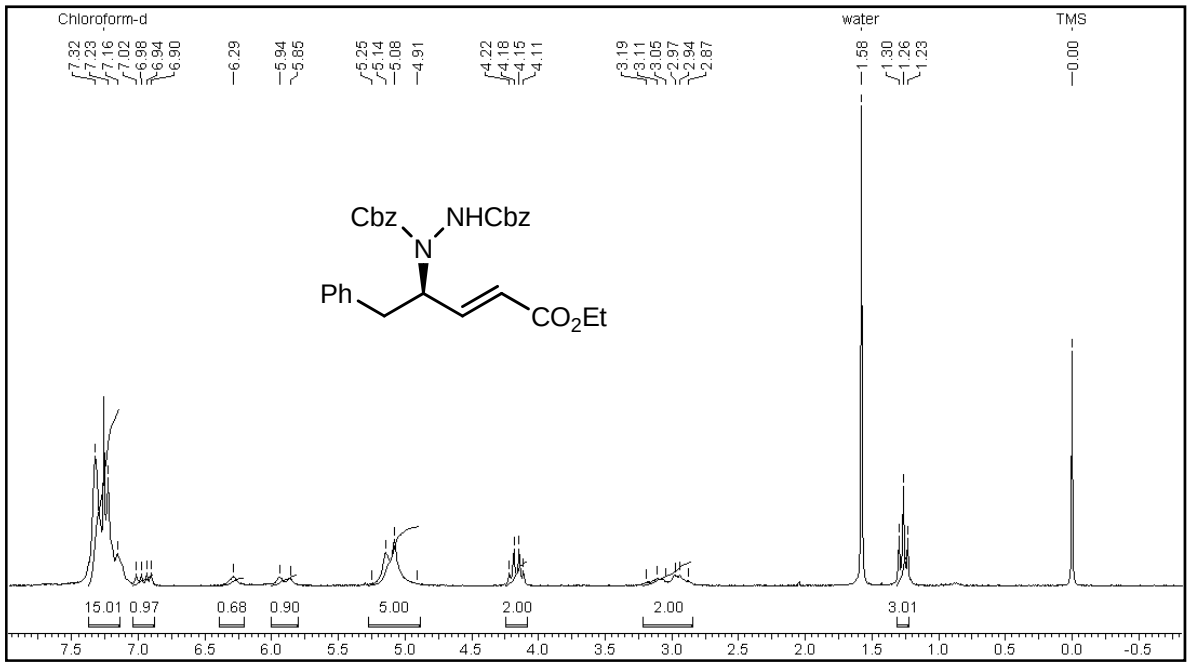
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.0932
R indices (all data)	R1 = 0.0418, wR2 = 0.0978
Absolute structure parameter	0.12(11)
Largest diff. peak and hole	0.237 and -0.322 e.Å^{-3}

Table 4. Crystal data and structure refinement for compound **31**

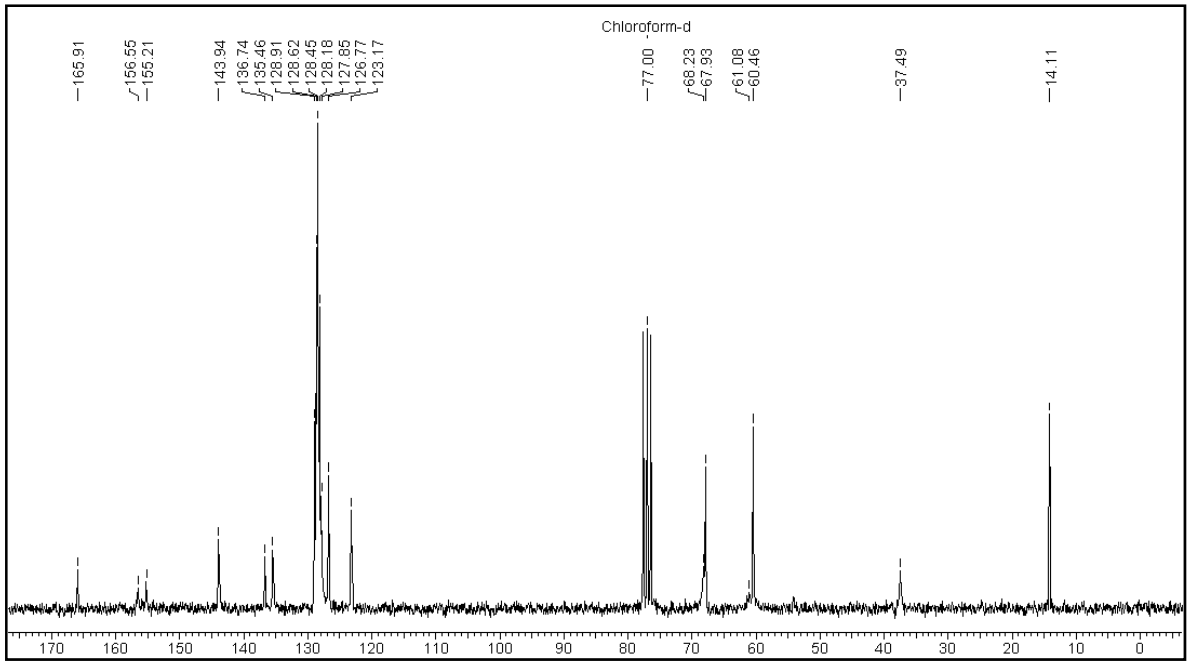
Empirical formula	C_{19} H_{26} N_2 O_5 S_2
Formula weight	428.56
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	MONOCLINIC
Space group	C2/C
Unit cell dimensions	a = 28.3830(10) Å α= 90°. b = 11.6353(4) Å β= 107.593(2)° c = 15.9062(5) Å γ = 90°.
Volume	5007.2(3) Å3
Density (calculated)	1.132 Mg/m^3
Absorption coefficient	0.240 mm^{-1}
F(000)	1808
Crystal size	0.46 x 0.45 x 0.09 mm^3
Theta range for data collection	2.20 to 25.00°.
Index ranges	-31<=h<=33, -13<=k<=13, -18<=l<=18
Reflections collected	18629
Independent reflections	4417 [R(int) = 0.0396]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9787 and 0.8977
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4417 / 0 / 256
Goodness-of-fit on F2	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0700, wR2 = 0.2094
R indices (all data)	R1 = 0.1003, wR2 = 0.2417
Largest diff. peak and hole	0.819 and -0.359 e.Å^{-3}

4.8. Spectra

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21a):

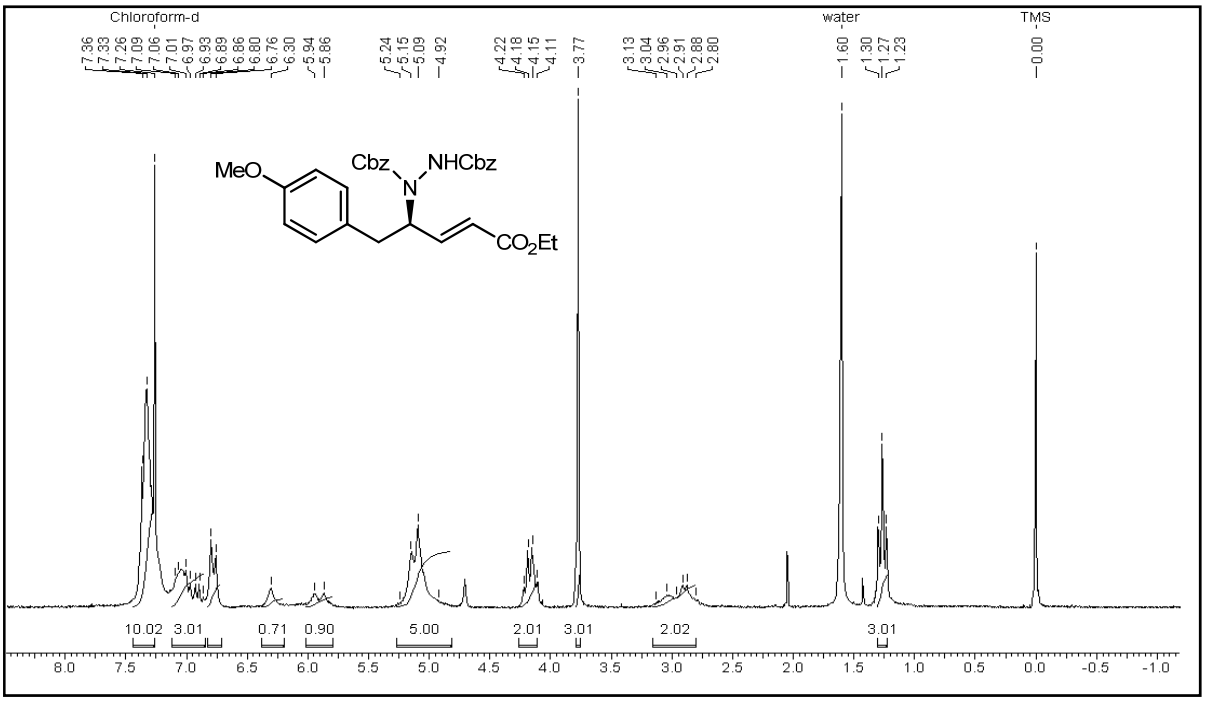


➢ **^{1}H NMR of the compound 21a in $CDCl_3$**

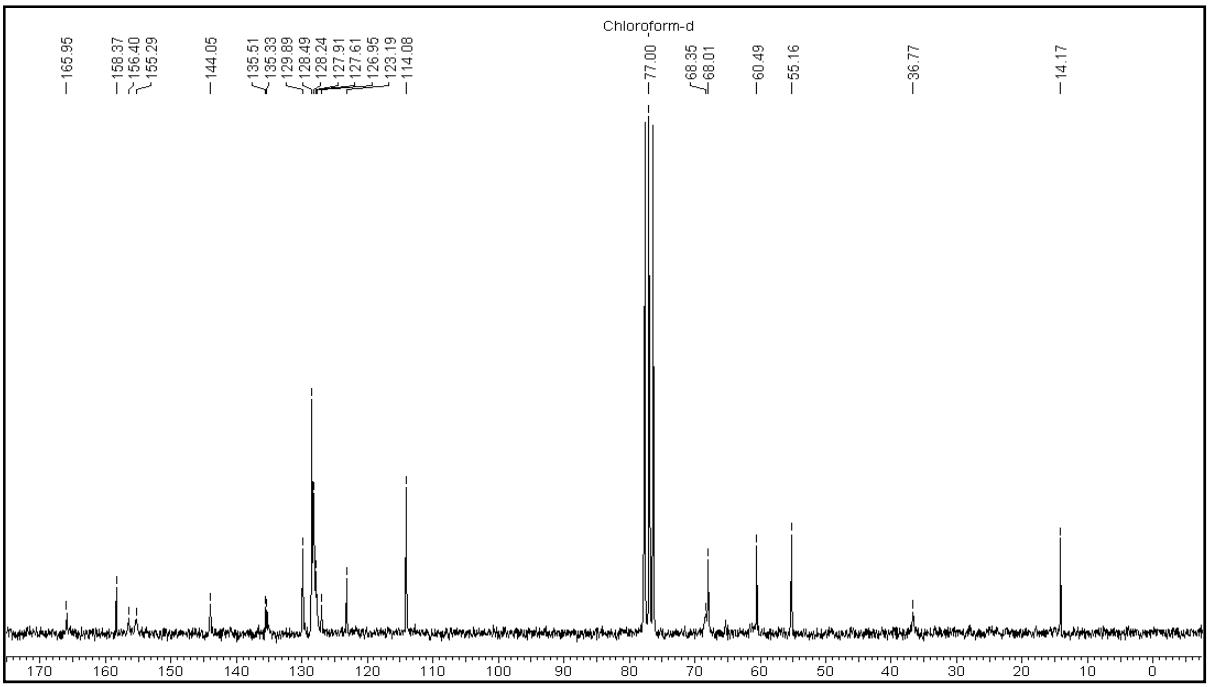


➢ **^{13}C NMR of the compound 21a in $CDCl_3$**

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-1-(4-methoxyphenyl)-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21b):

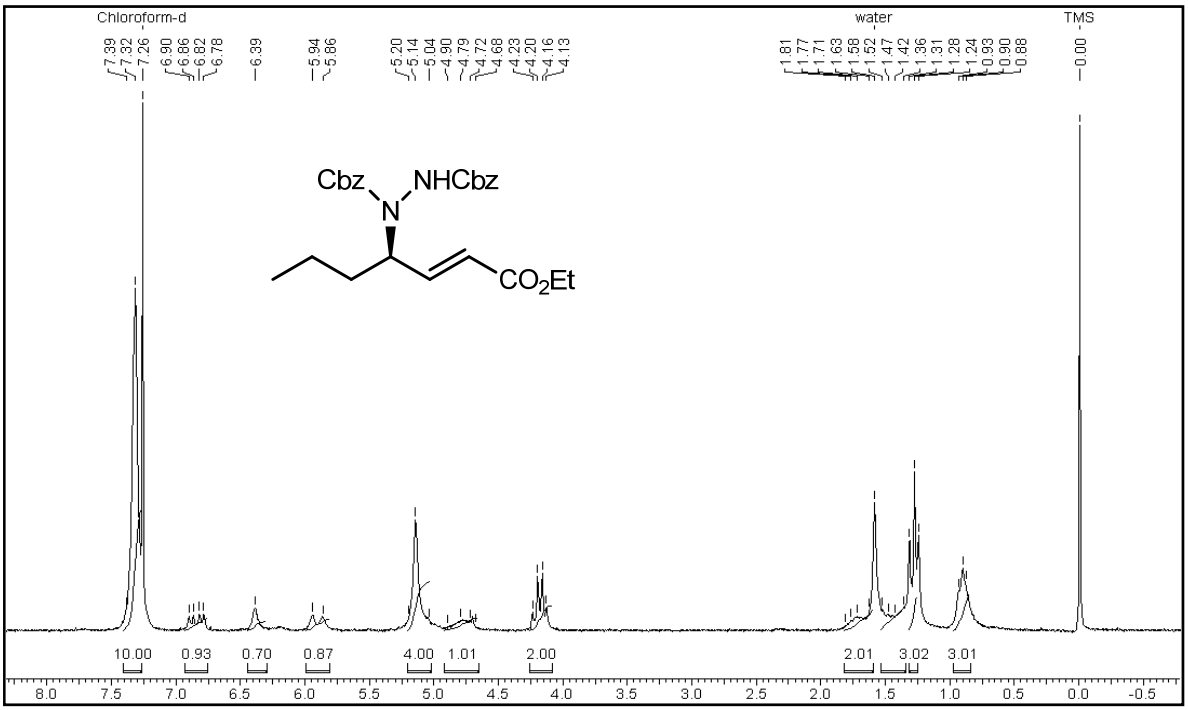


➢ **^{1}H NMR of the compound 21b in $CDCl_3$**

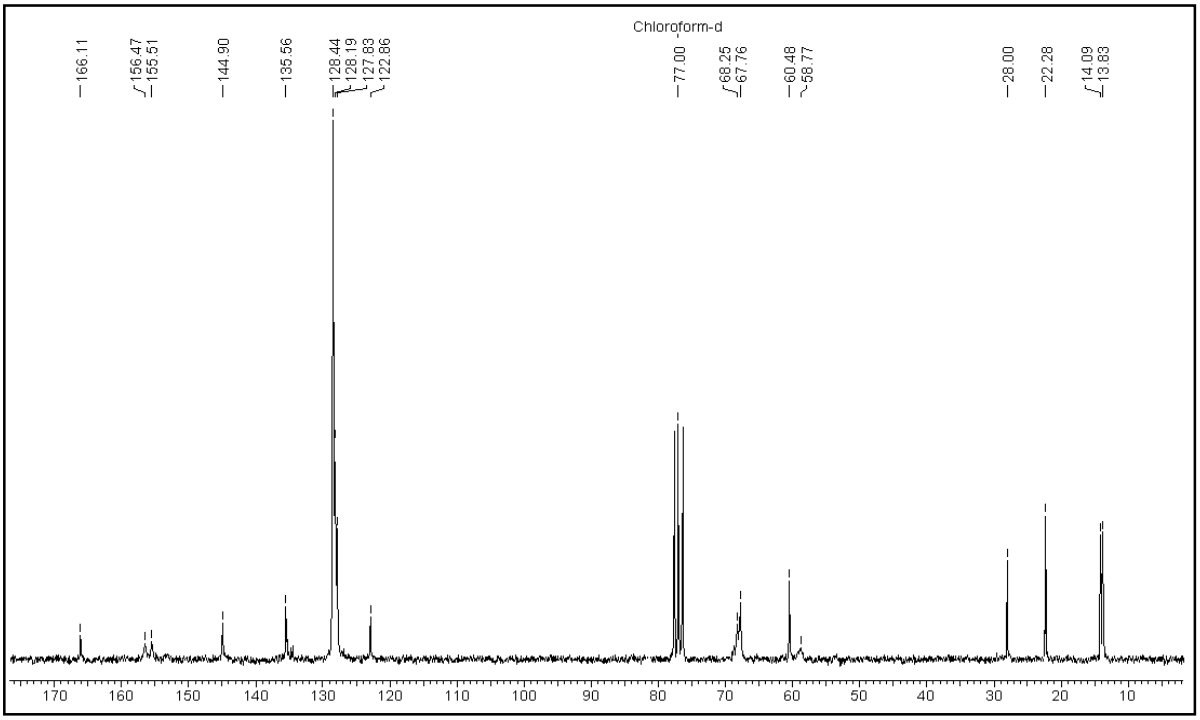


➢ **^{13}C NMR of the compound 21b in $CDCl_3$**

(*R*,*E*)-Dibenzyl 1-(1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (21c):

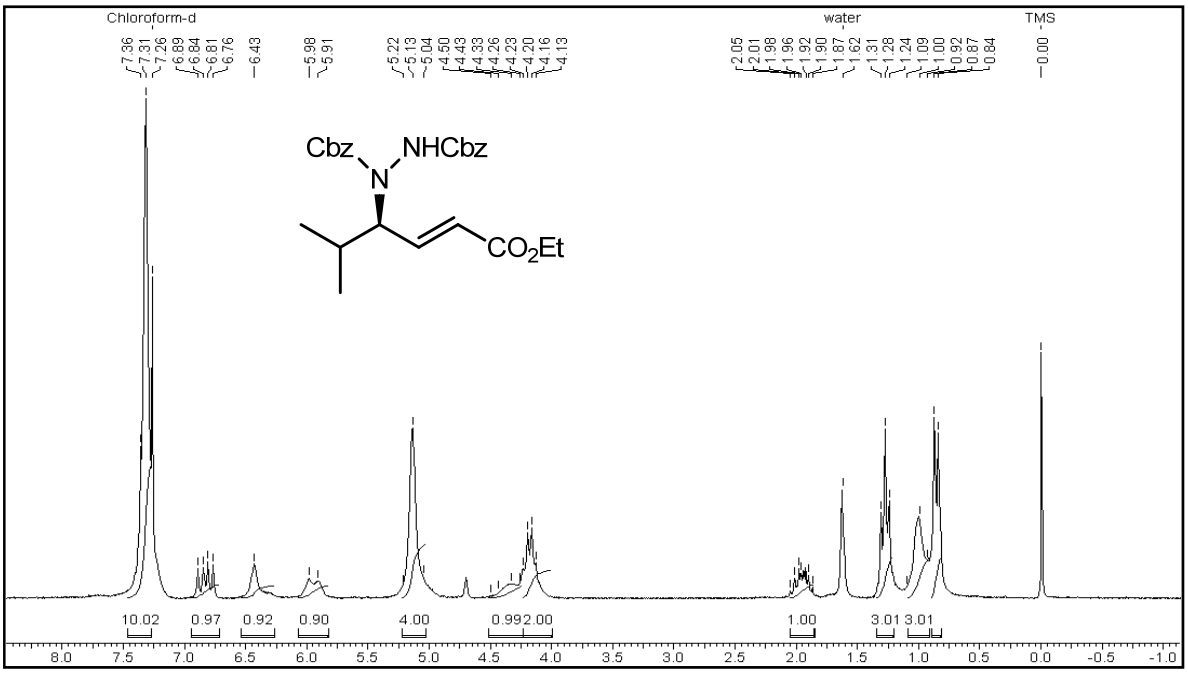


➢ **^{1}H NMR of the compound 21c in $CDCl_3$**

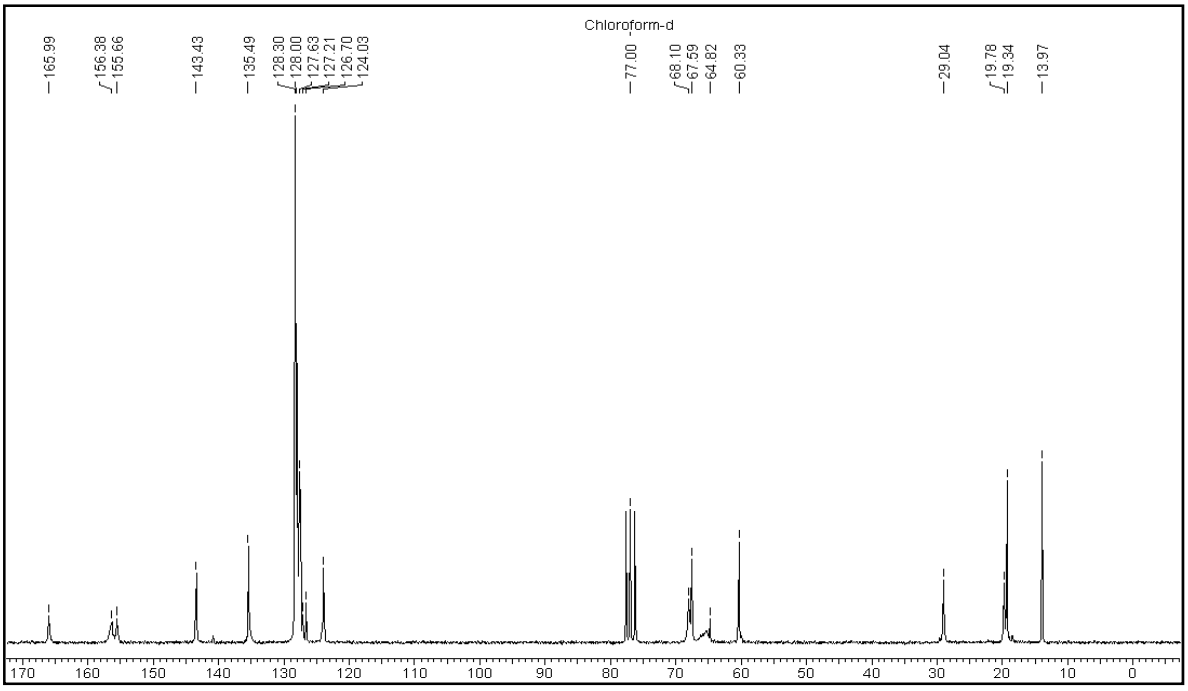


➢ **^{13}C NMR of the compound 21c in $CDCl_3$**

(*R*,*E*)-Dibenzyl 1-(6-ethoxy-2-methyl-6-oxohex-4-en-3-yl)hydrazine-1,2-dicarboxylate (21d):

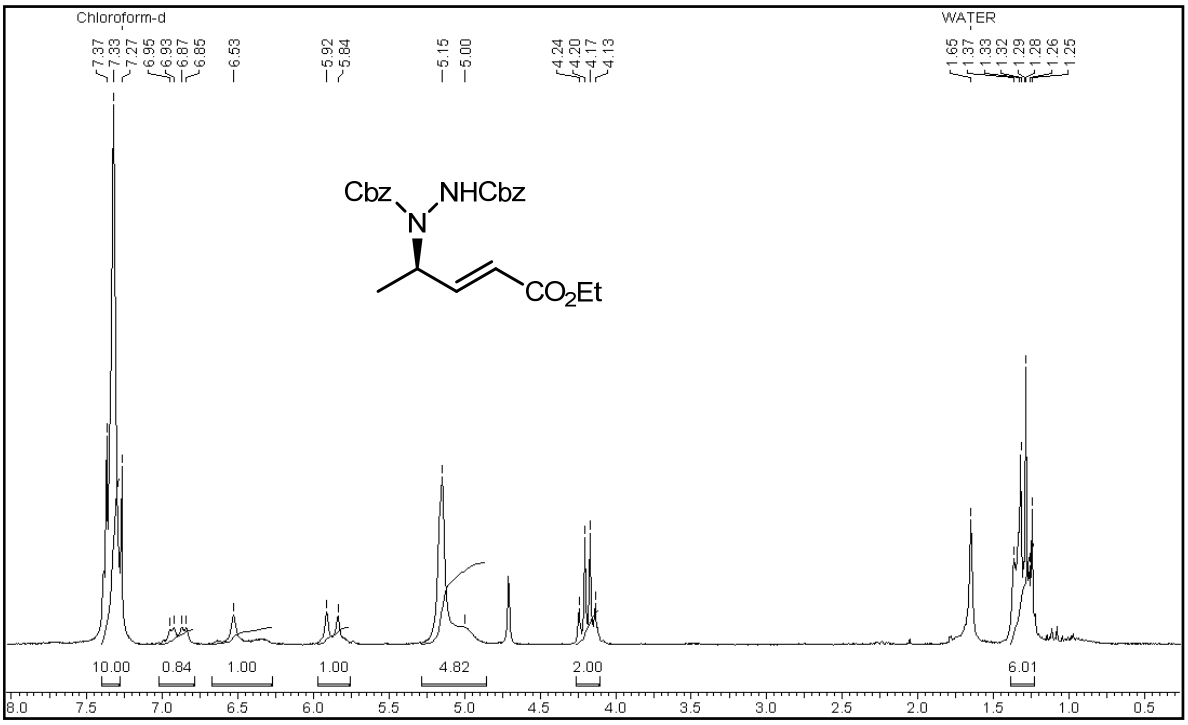


➢ **^{1}H NMR of the compound 21d in $CDCl_3$**

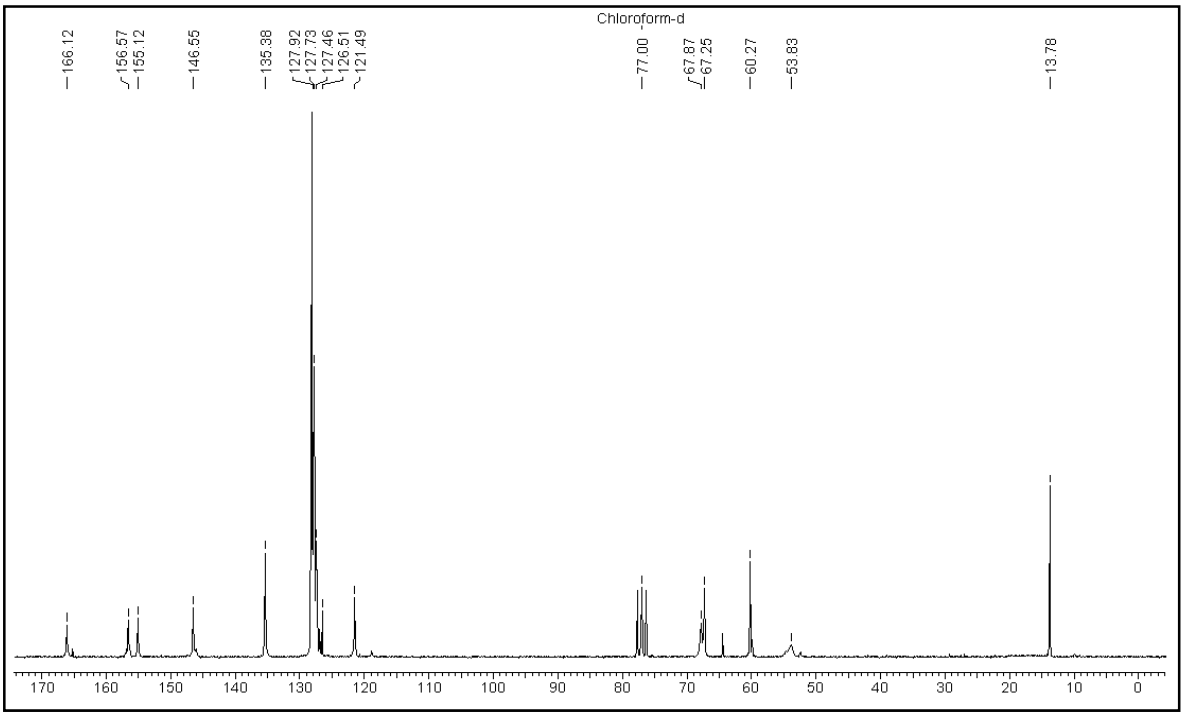


➢ **^{13}C NMR of the compound 21d in $CDCl_3$**

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (21e):

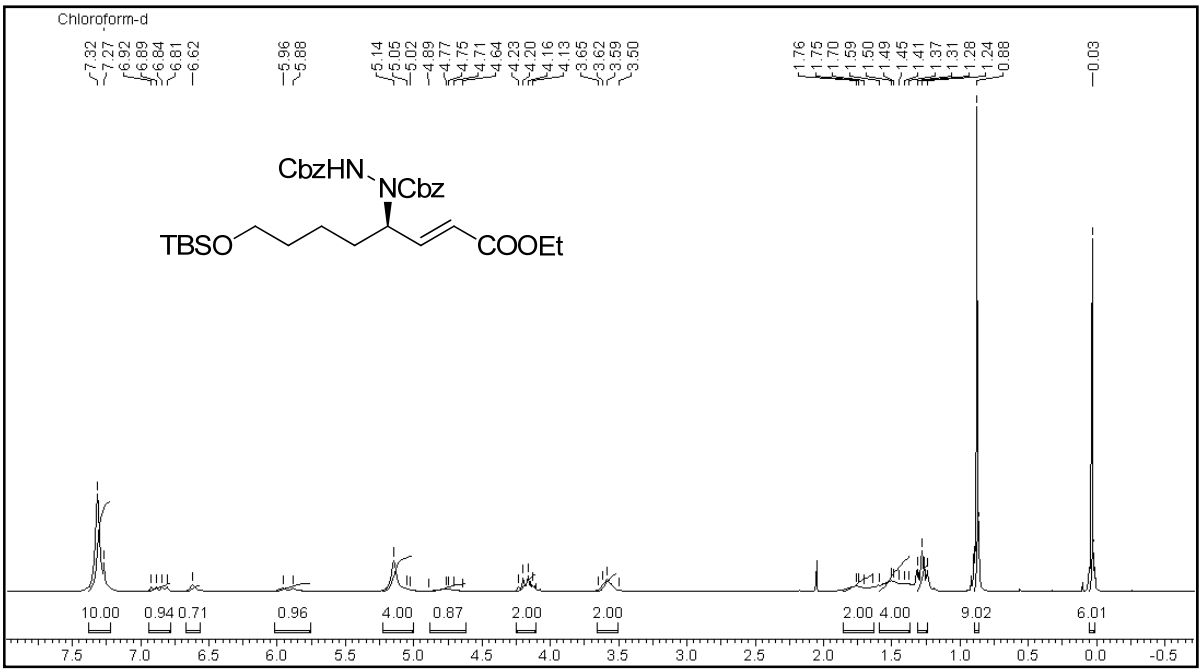


- **^{1}H NMR of the compound 21e in $CDCl_3$**

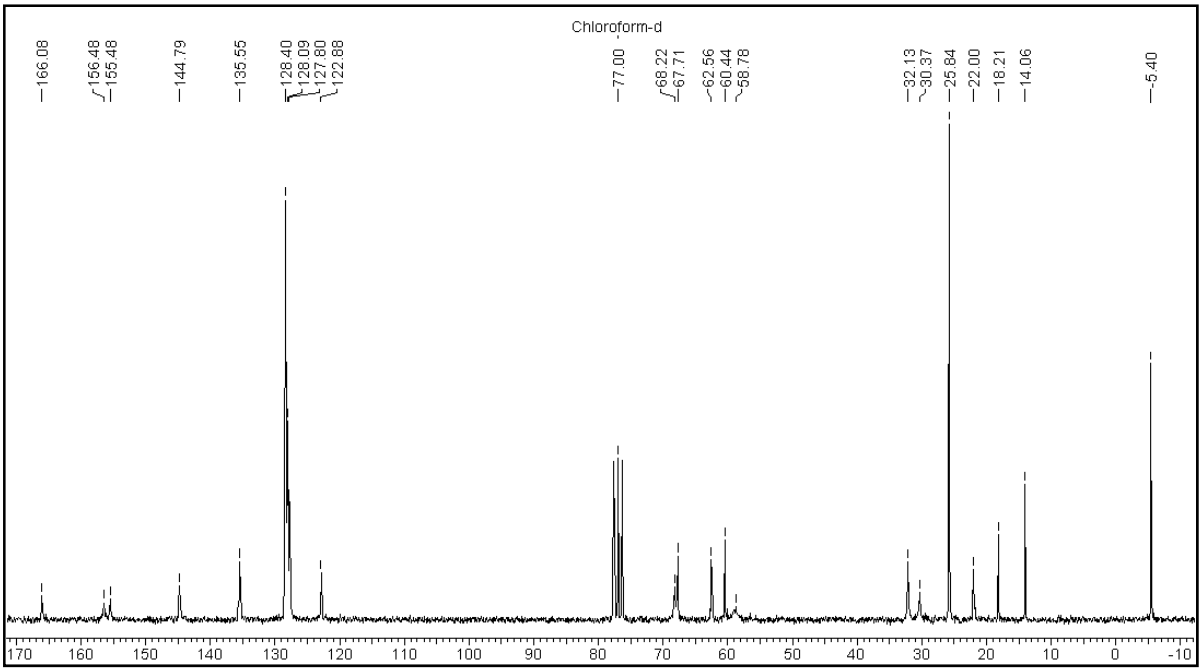


- **^{13}C NMR of the compound 21e in $CDCl_3$**

(*R*,*E*)-Dibenzyl1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (21f):

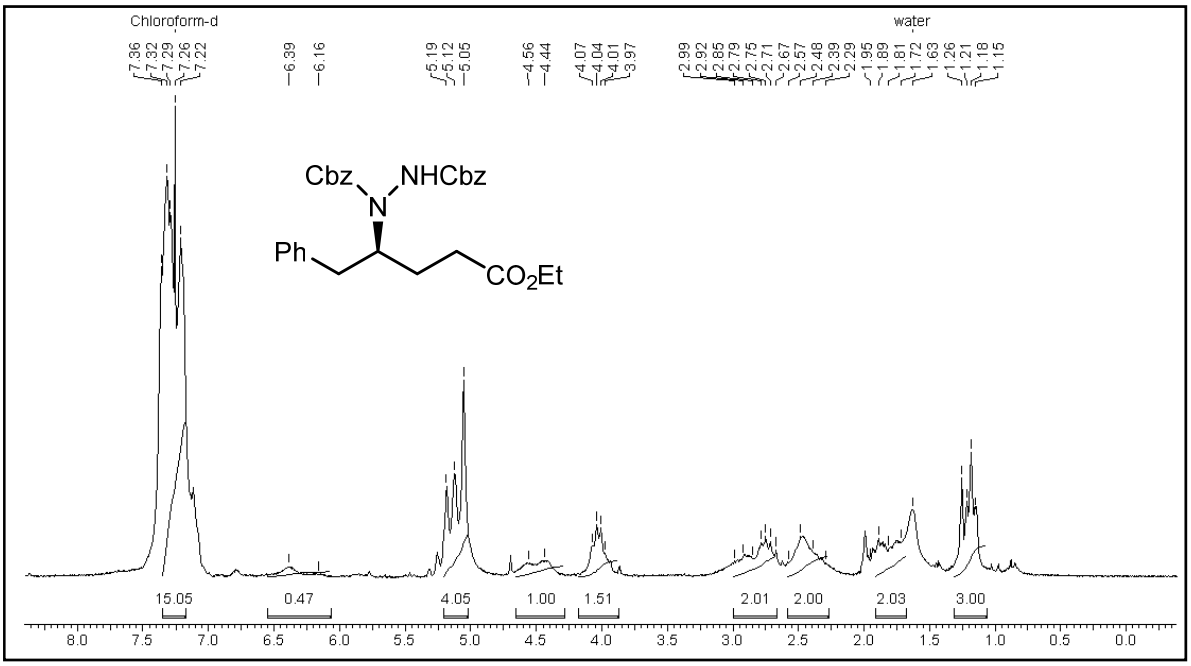


- **^{1}H NMR of the compound 21f in $CDCl_3$**

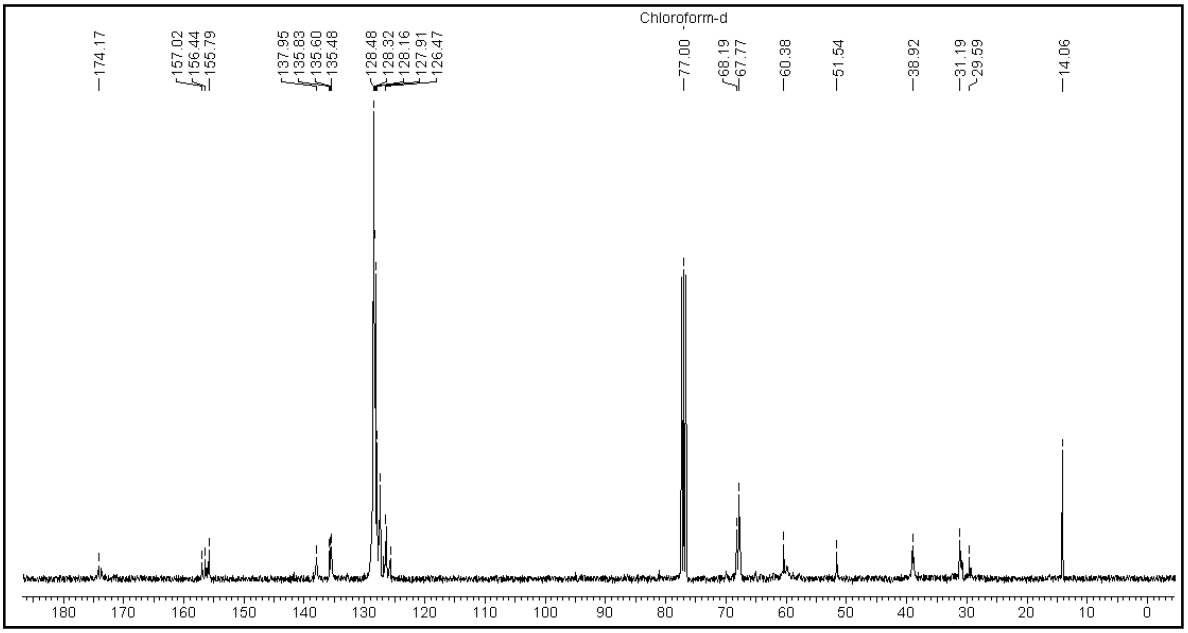


- **^{13}C NMR of the compound 21f in $CDCl_3$**

(*S*)-Dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (22):

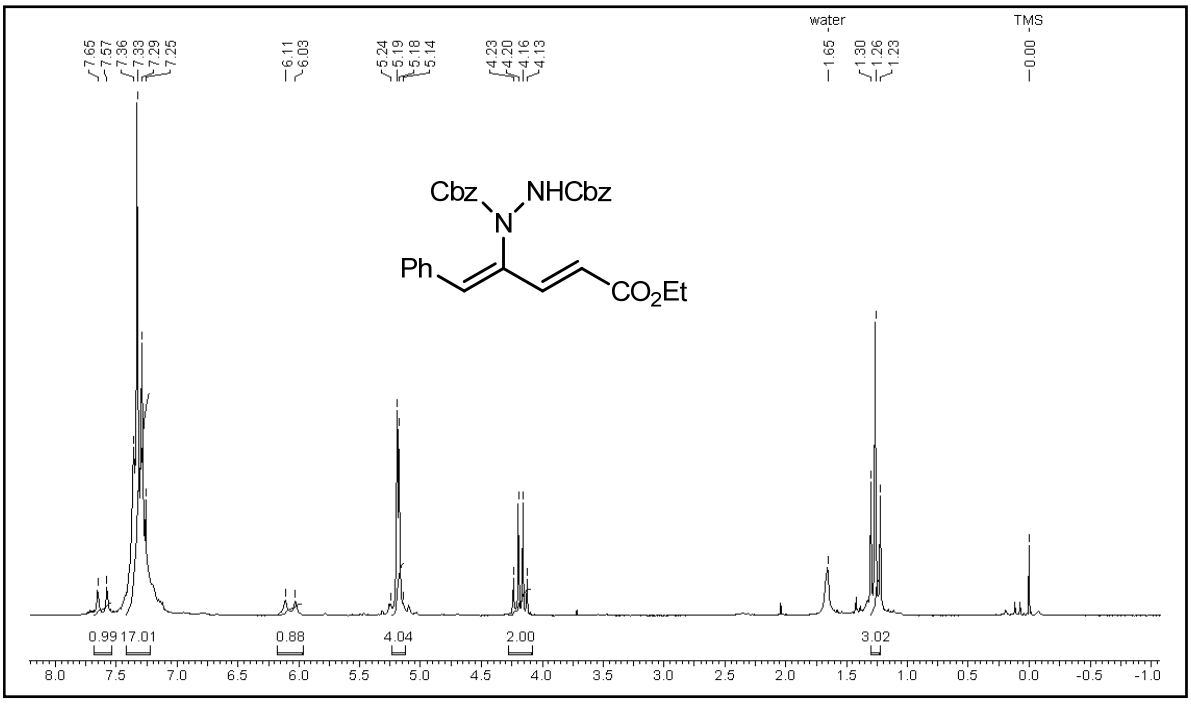


➢ **^{1}H NMR of the compound 22 in $CDCl_3$**

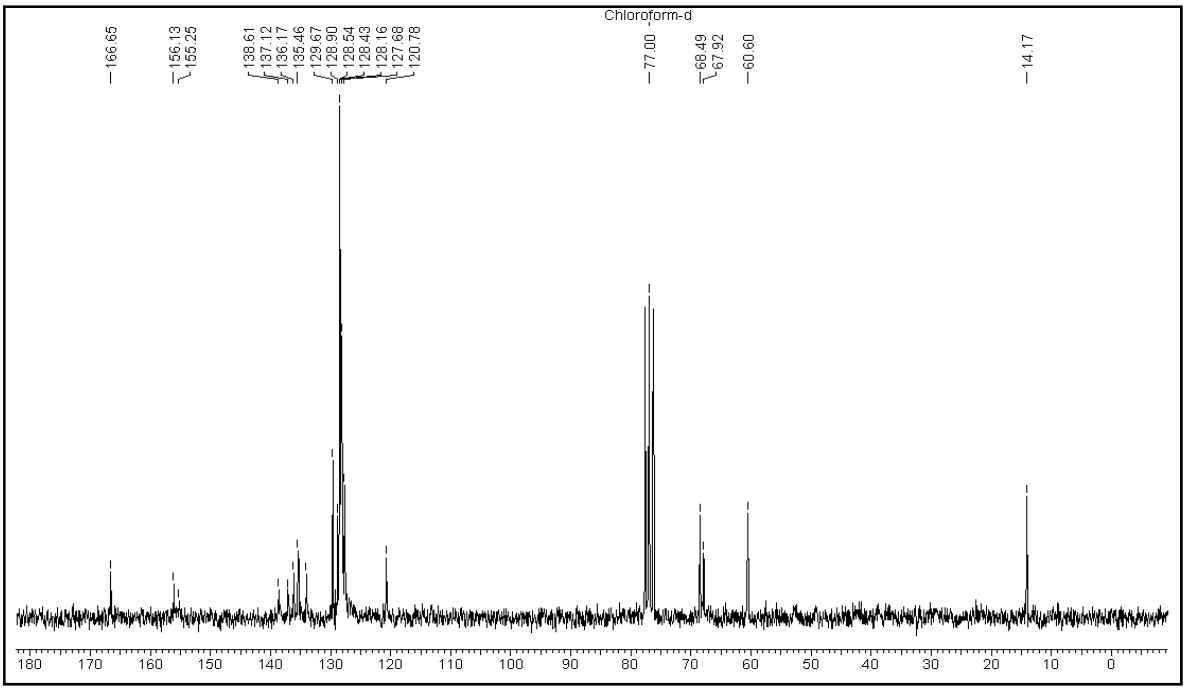


➢ **^{13}C NMR of the compound 22 in $CDCl_3$**

Dibenzyl 1-((1*Z*,3*E*)-5-ethoxy-5-oxo-1-phenylpenta-1,3-dien-2-yl)hydrazine-1,2-dicarboxylate 23:

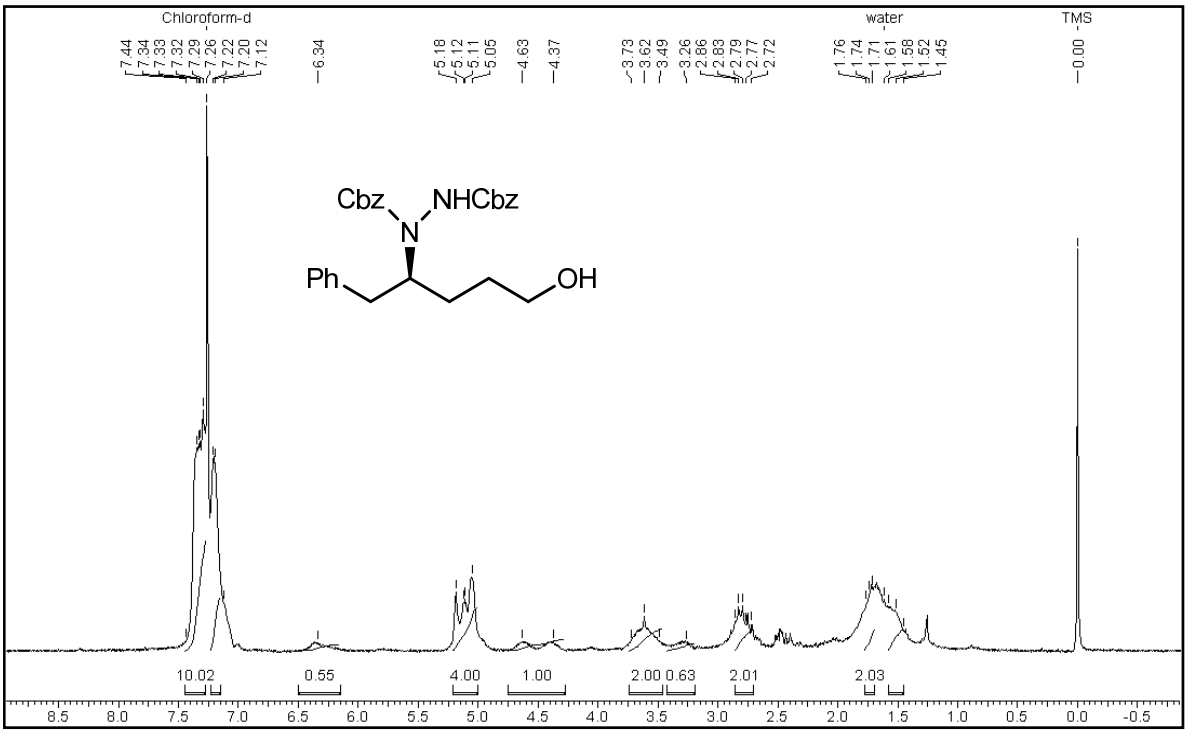


➢ **^{1}H NMR of the compound 23 in $CDCl_3$**

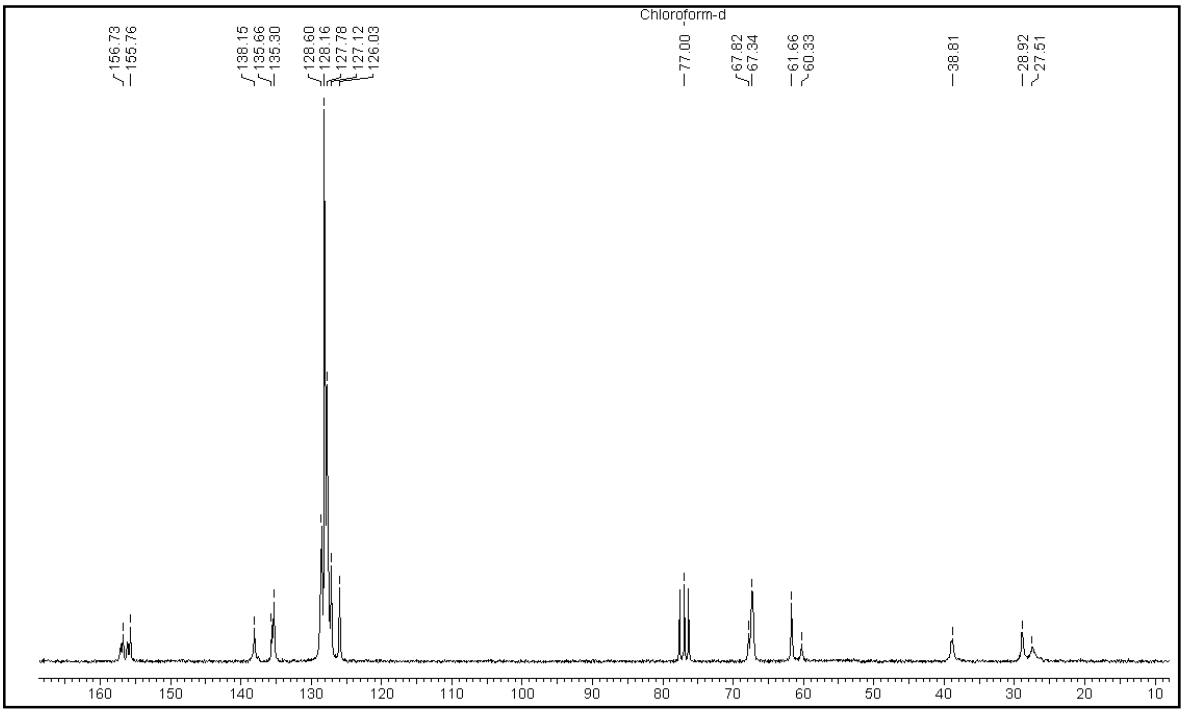


➢ **^{13}C NMR of the compound 23 in $CDCl_3$**

(*S*)-Dibenzyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (25a):

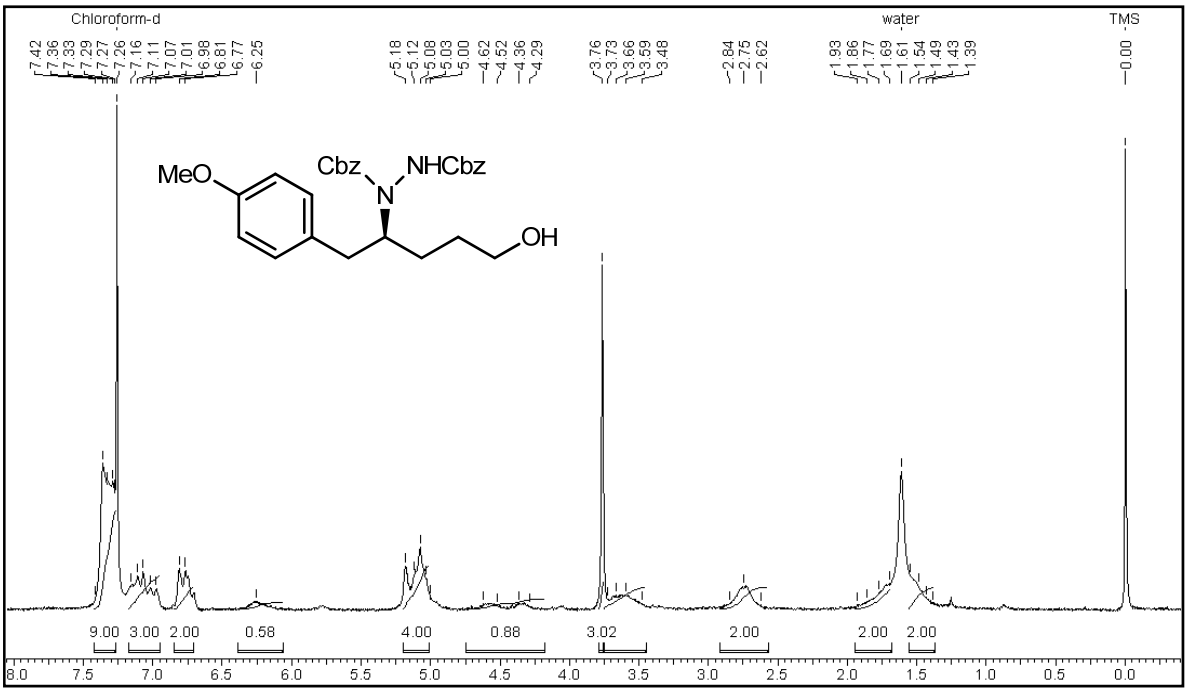


- **^{1}H NMR of the compound 25a in $CDCl_3$**

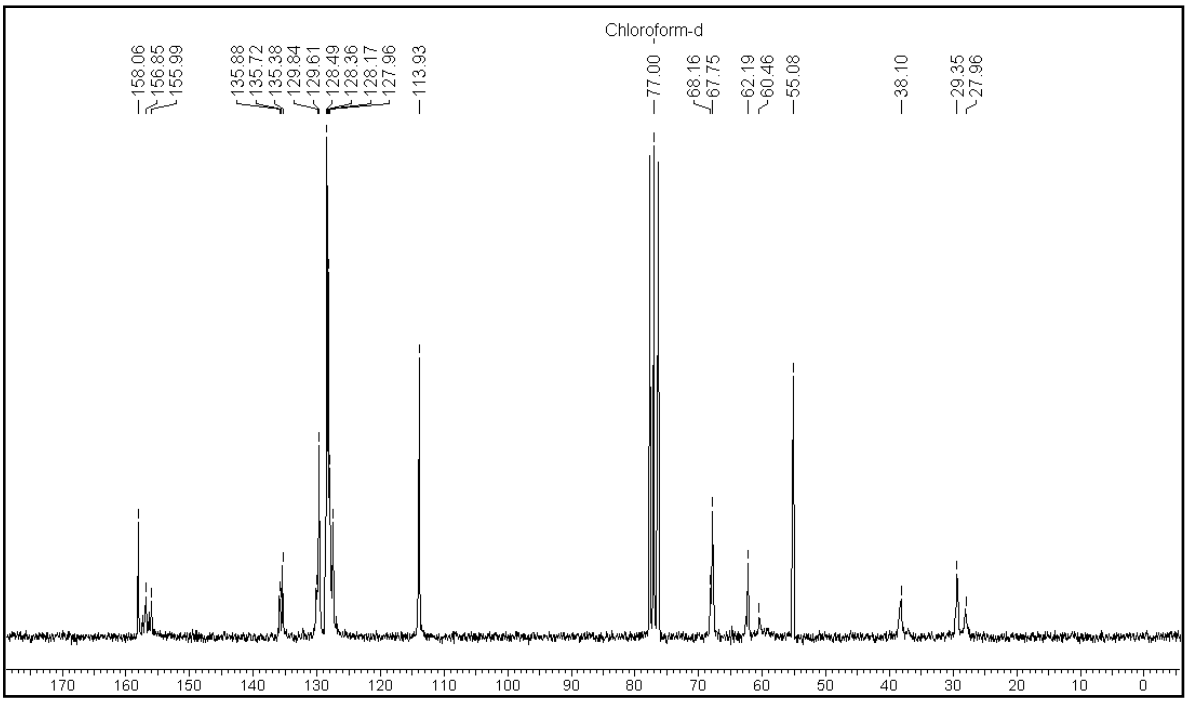


- **^{13}C NMR of the compound 25a in $CDCl_3$**

(*S*)-Dibenzyl 1-(5-hydroxy-1-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (25b):

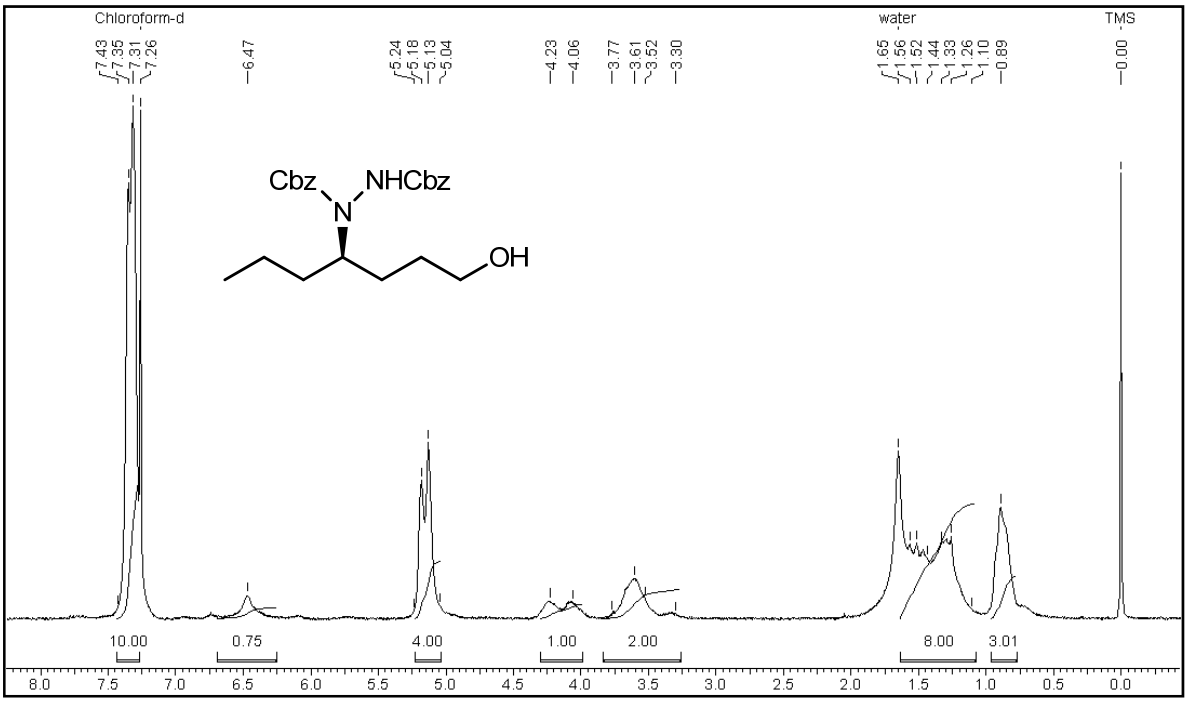


➢ **^{1}H NMR of the compound 25b in $CDCl_3$**

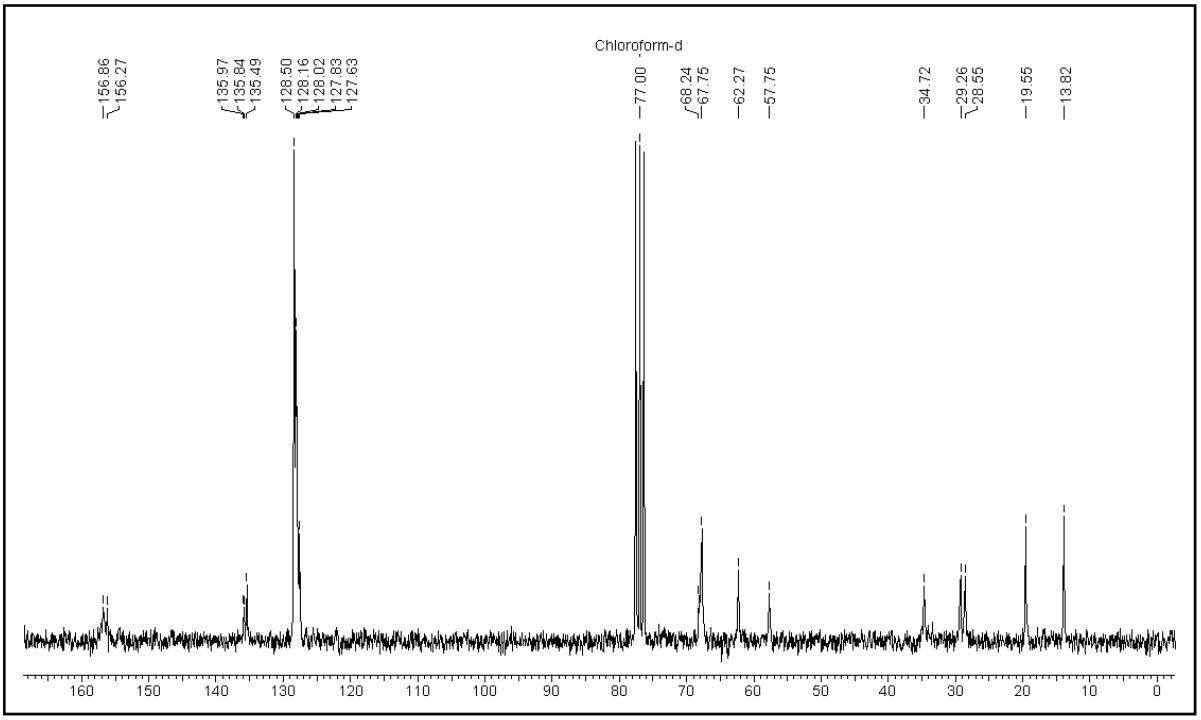


➢ **^{13}C NMR of the compound 25b in $CDCl_3$**

(*R*)-Dibenzyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (25c):

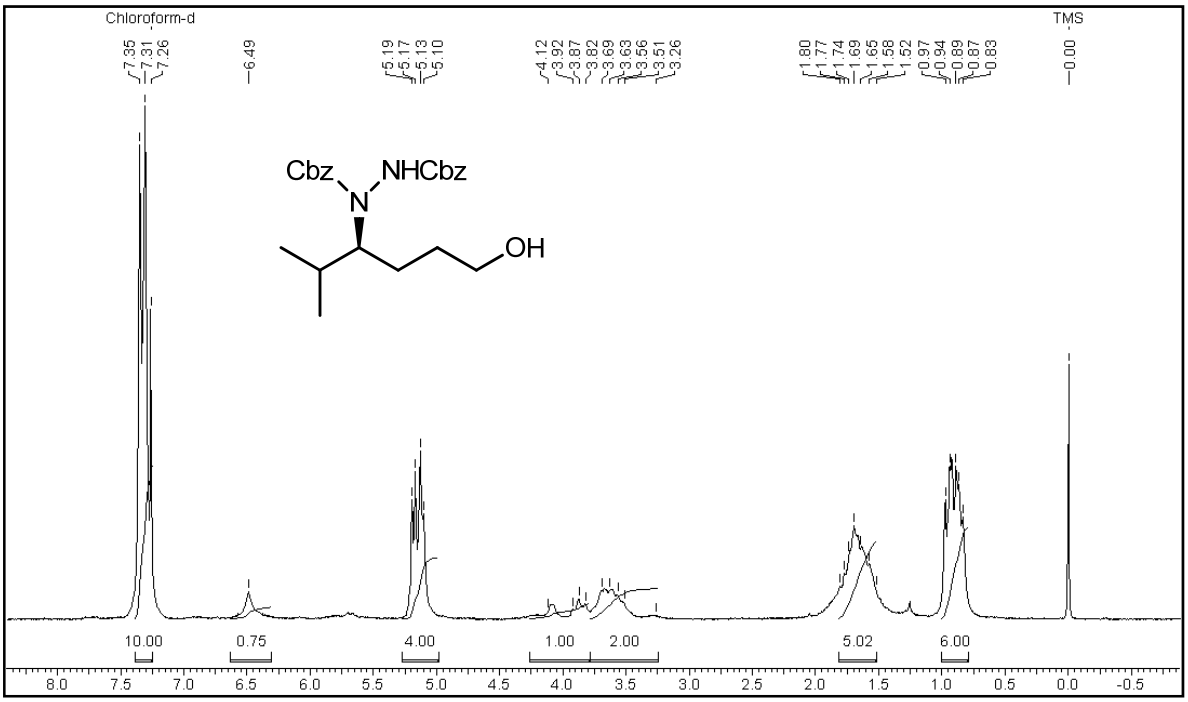


➢ **^{1}H NMR of the compound 25c in $CDCl_3$**

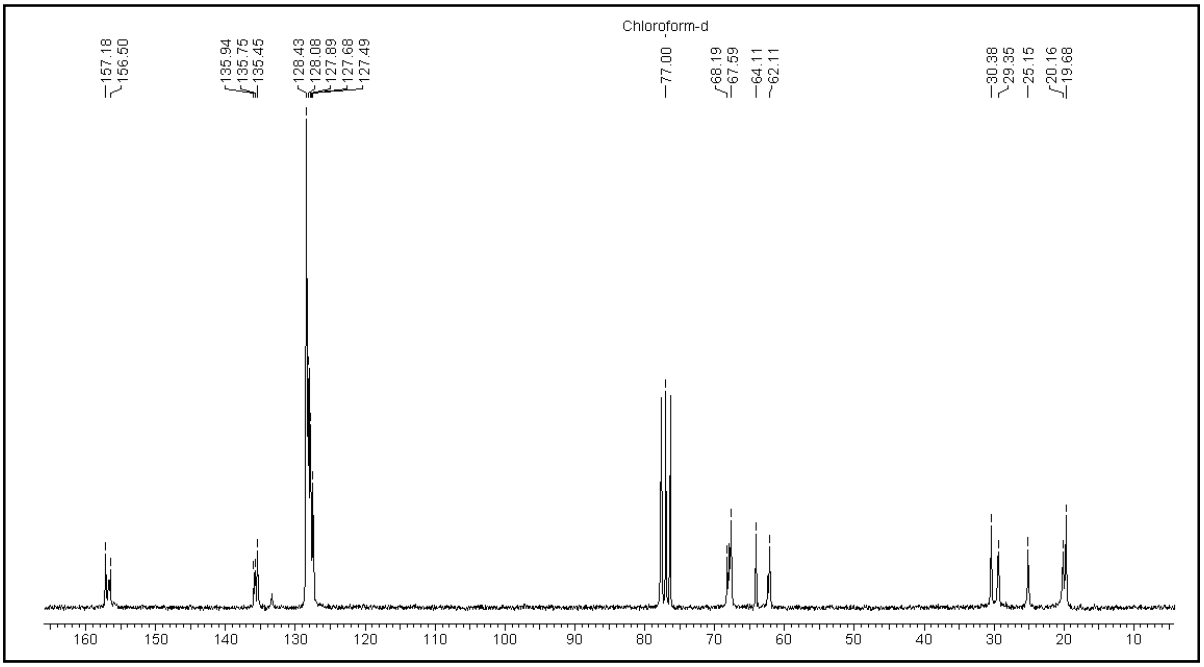


➢ **^{13}C NMR of the compound 25c in $CDCl_3$**

(*S*)-Dibenzyl 1-(6-hydroxy-2-methylhexan-3-yl)hydrazine-1,2-dicarboxylate (25d):

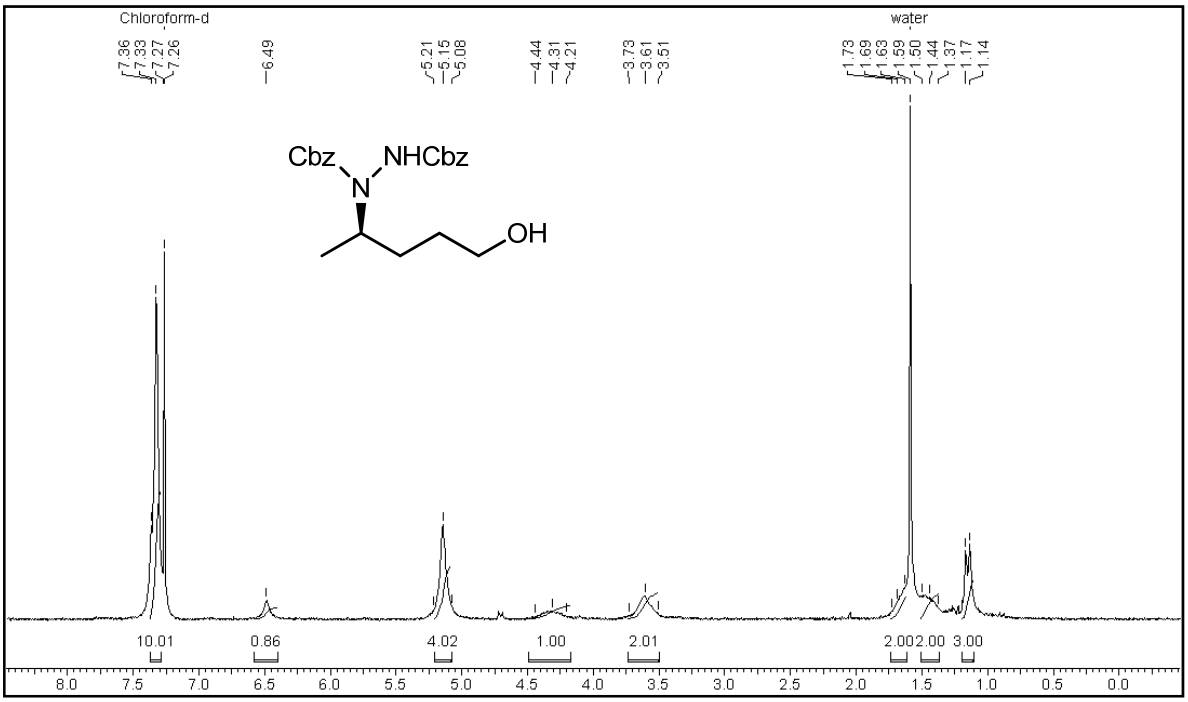


➢ **^{1}H NMR of the compound 25d in $CDCl_3$**

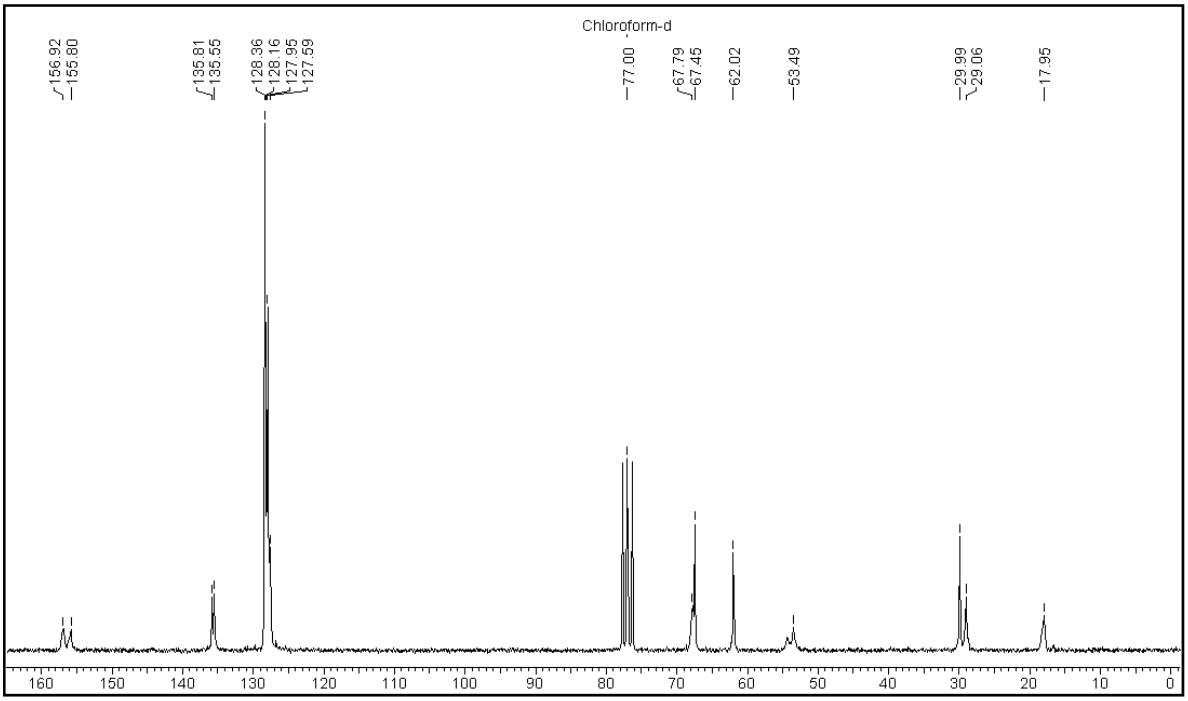


➢ **^{13}C NMR of the compound 25d in $CDCl_3$**

(*R*)-Dibenzyl 1-(5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (25e):

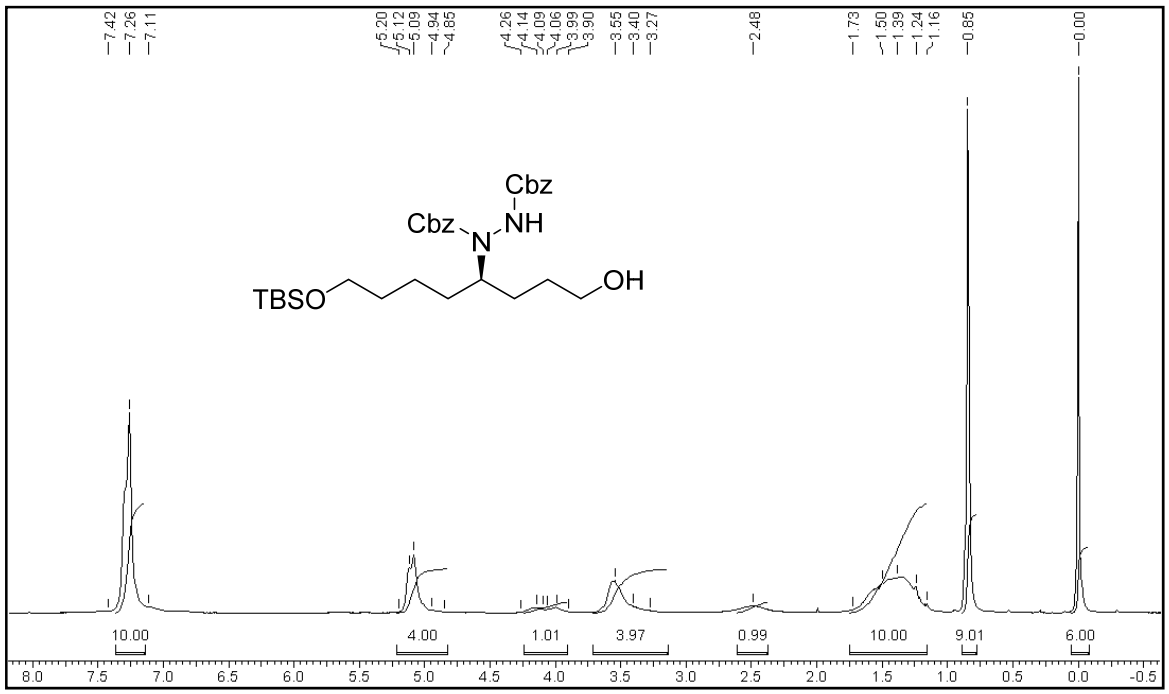


- **^{1}H NMR of the compound 25e in $CDCl_3$**

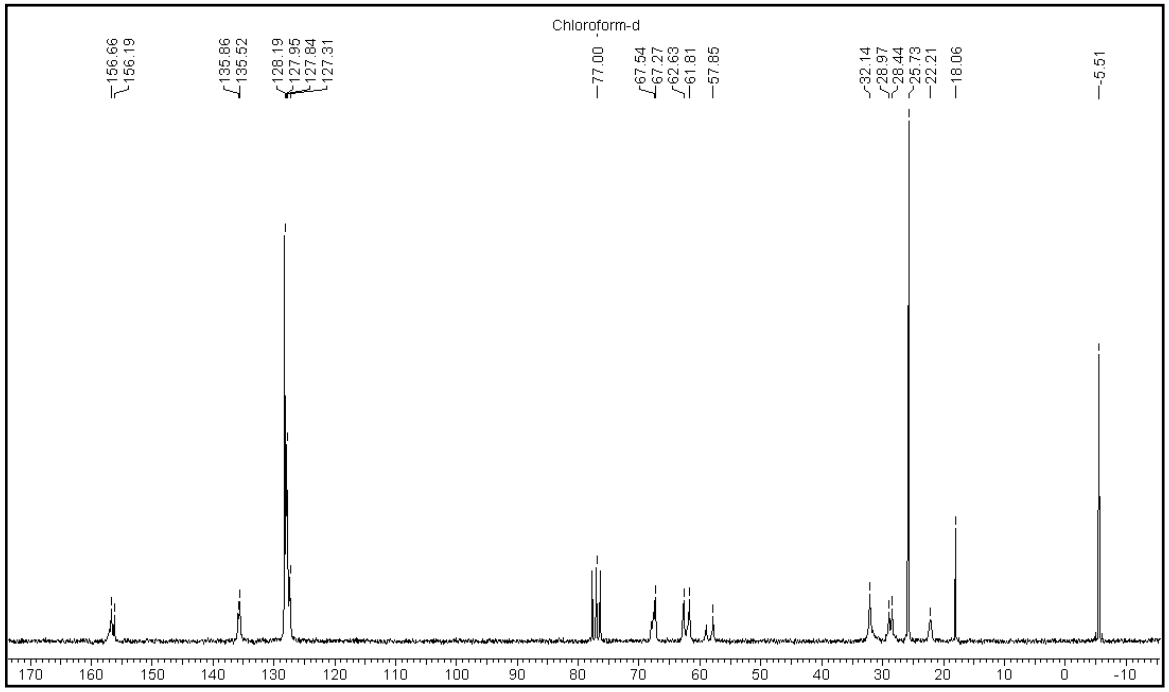


- **^{13}C NMR of the compound 25e in $CDCl_3$**

(*R*)-Dibenzyl 1-(8-((tert-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (25f):

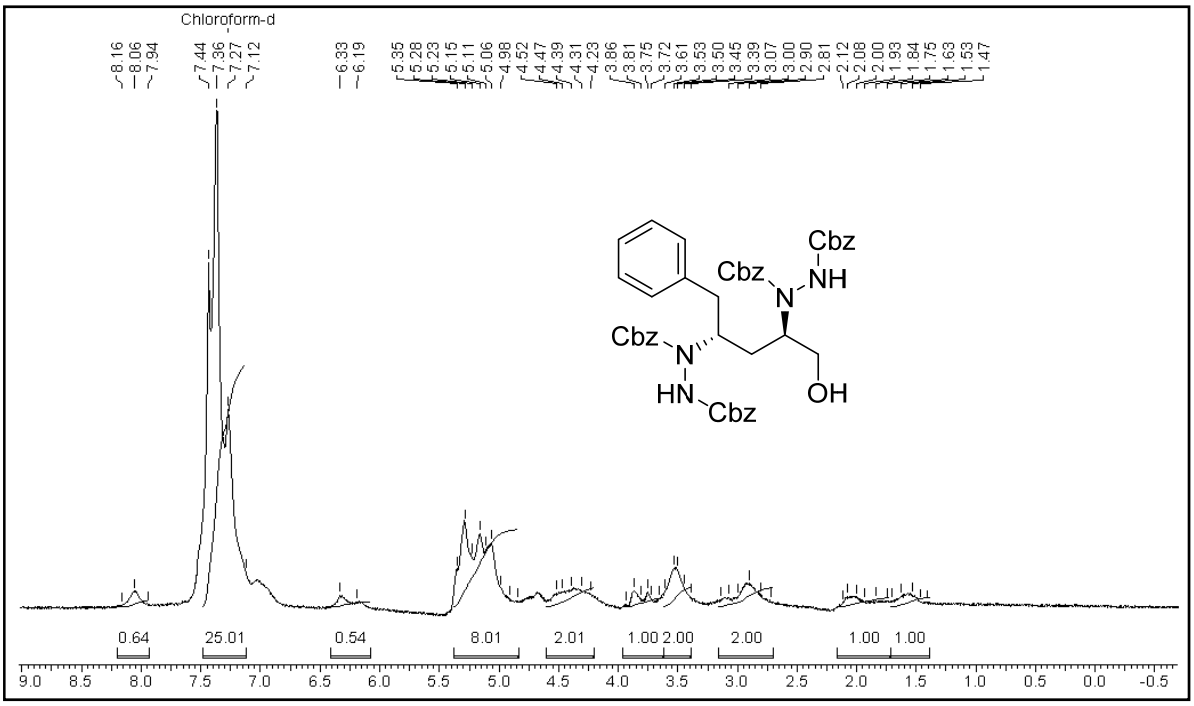


➢ **^{1}H NMR of the compound 25f in $CDCl_3$**

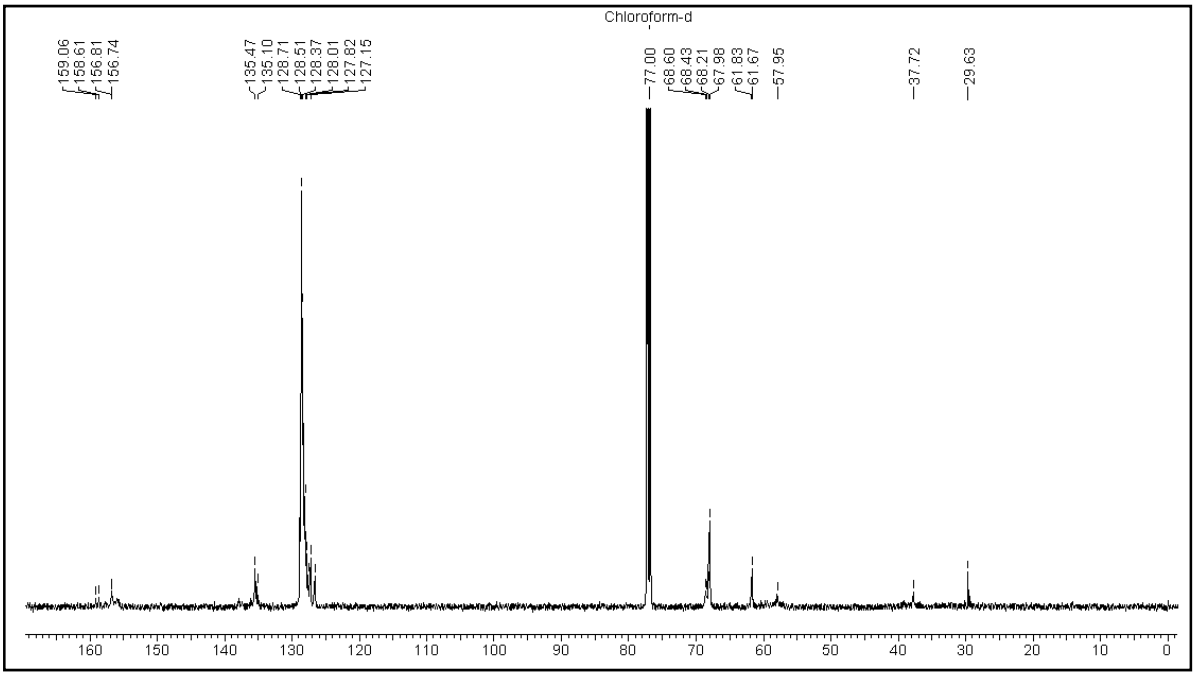


➢ **^{13}C NMR of the compound 25f in $CDCl_3$**

1,1'-((2*R*,4*R*)- Tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26a):

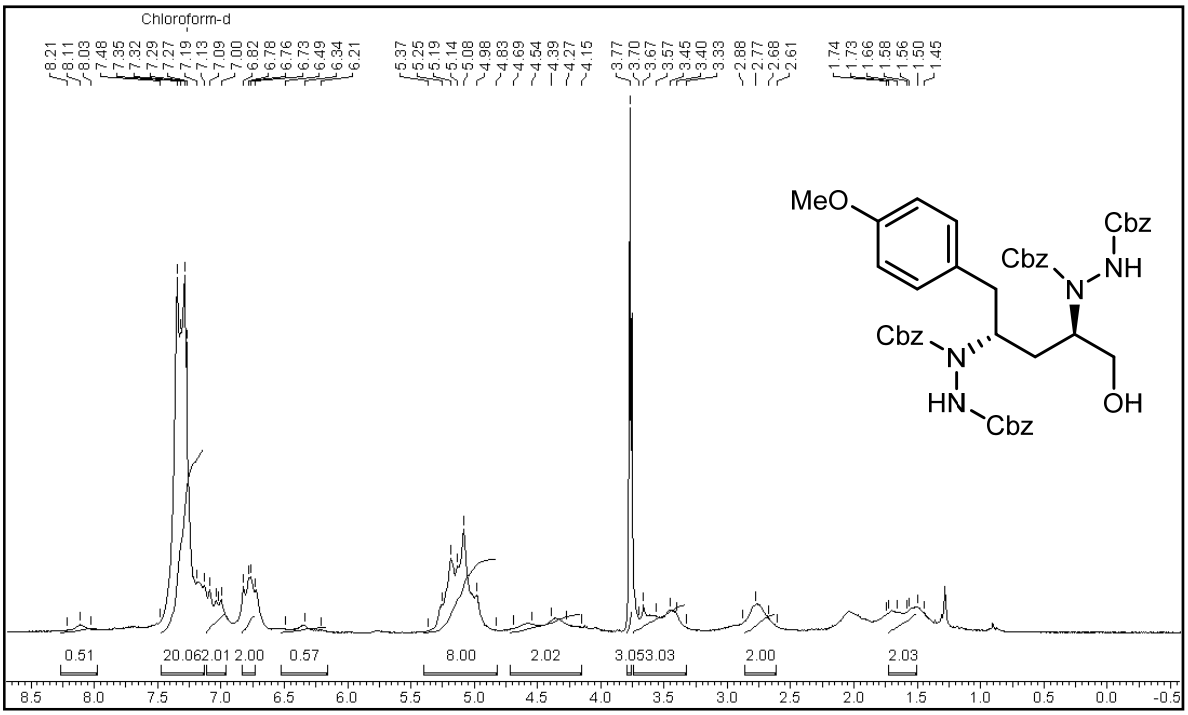


- **^{1}H NMR of the compound 26a in $CDCl_3$**

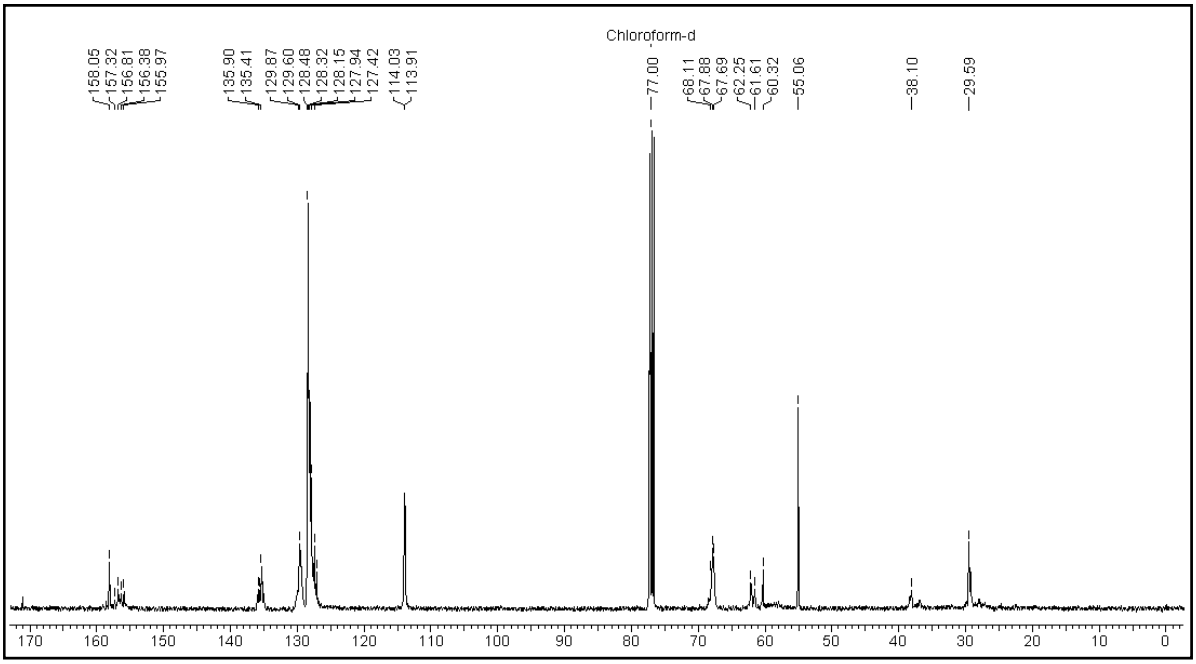


- **^{13}C NMR of the compound 26a in $CDCl_3$**

1,1'-((2*R*,4*R*)-Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26b):

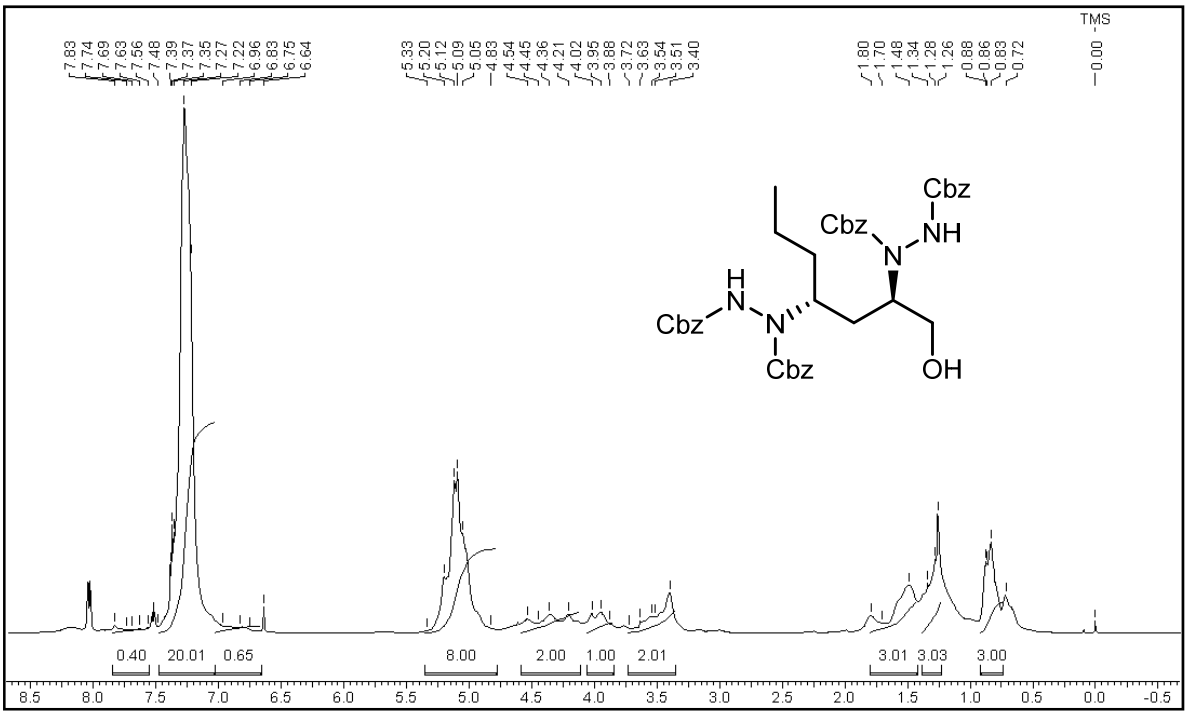


- **^{1}H NMR of the compound 26b in $CDCl_3$**

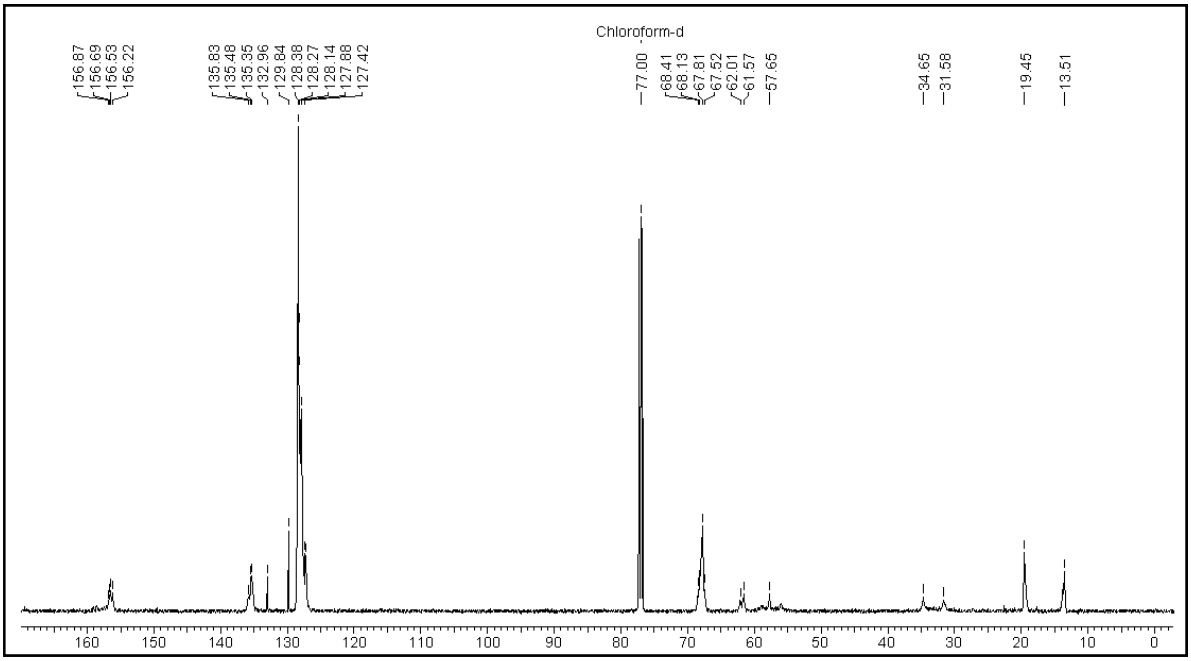


- **^{13}C NMR of the compound 26b in $CDCl_3$**

1,1'-((2*R*,4*R*)-Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26c):

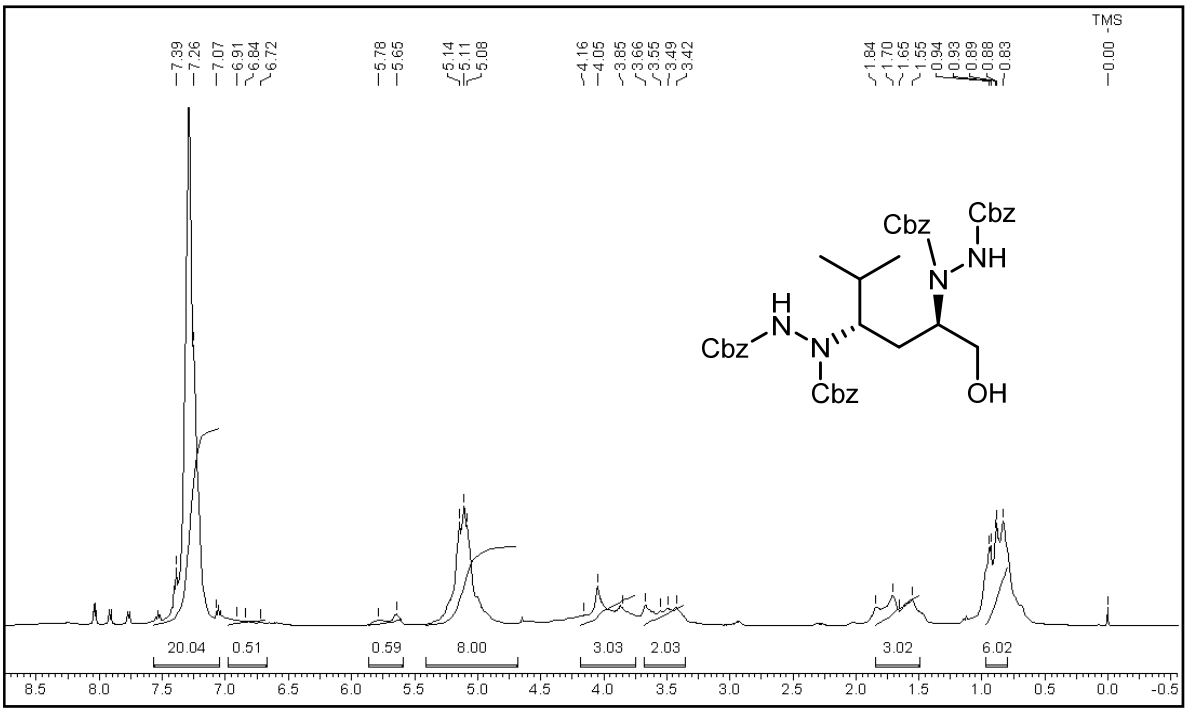


- **^{1}H NMR of the compound 26c in $CDCl_3$**

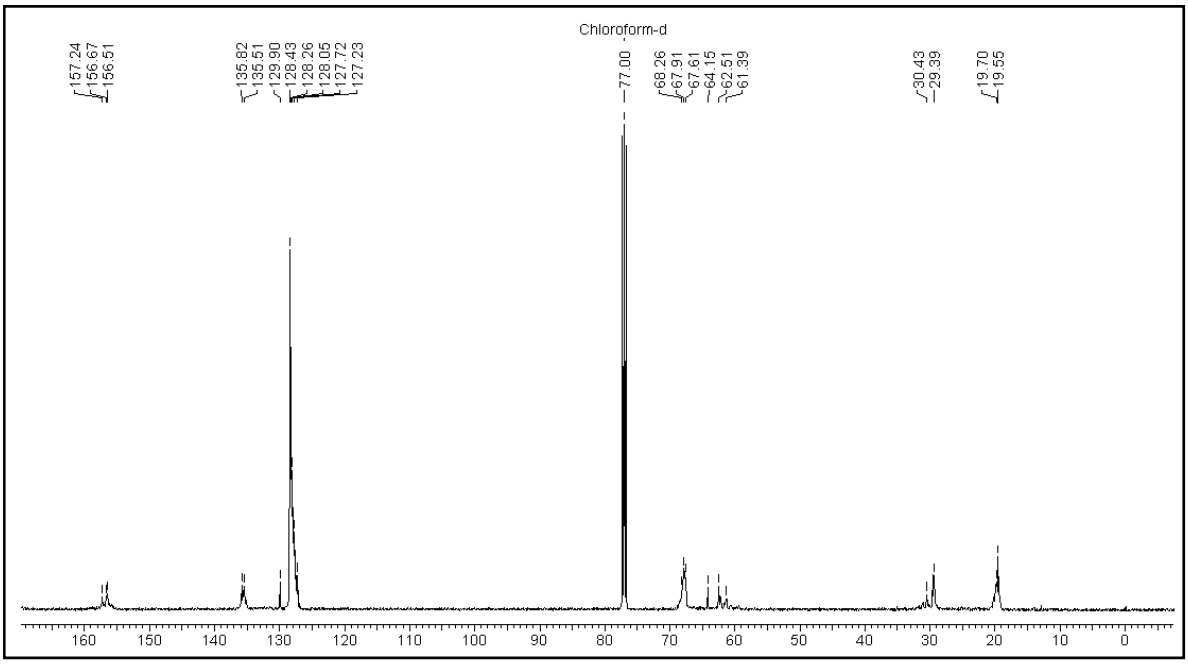


- **^{13}C NMR of the compound 26c in $CDCl_3$**

1,1'-((2*R*,4*S*)- Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26d):

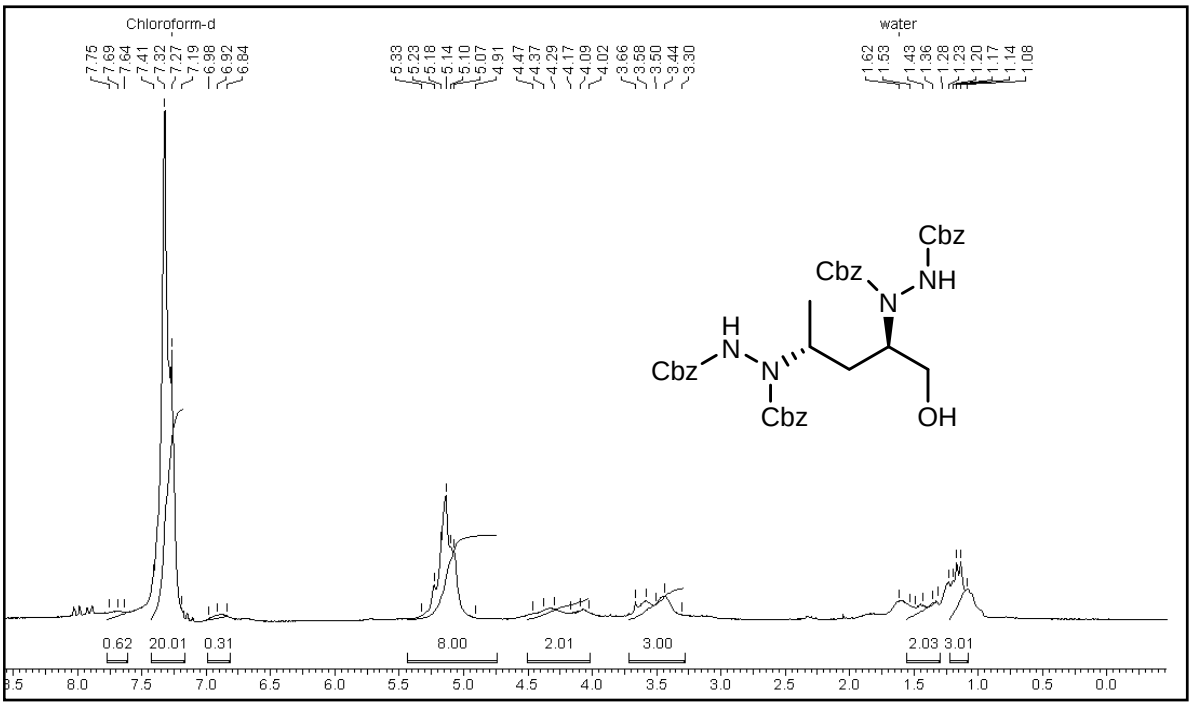


- **^{1}H NMR of the compound 26d in $CDCl_3$**

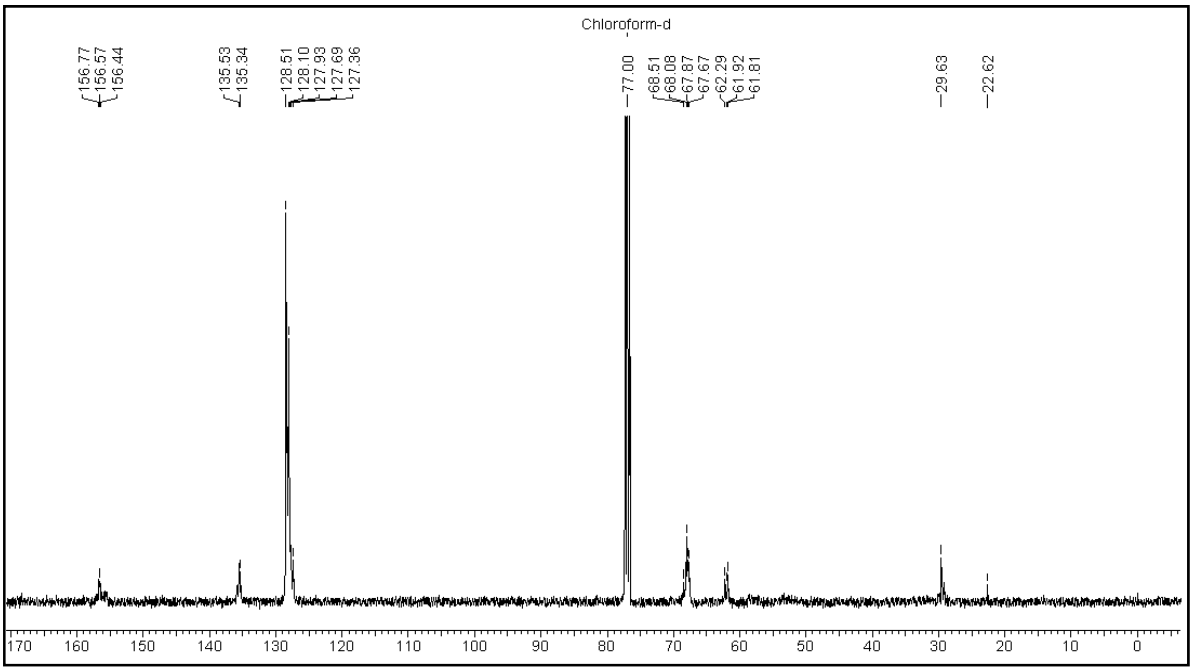


- **^{13}C NMR of the compound 26d in $CDCl_3$**

1,1'-((2*R*,4*R*)-Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26e):

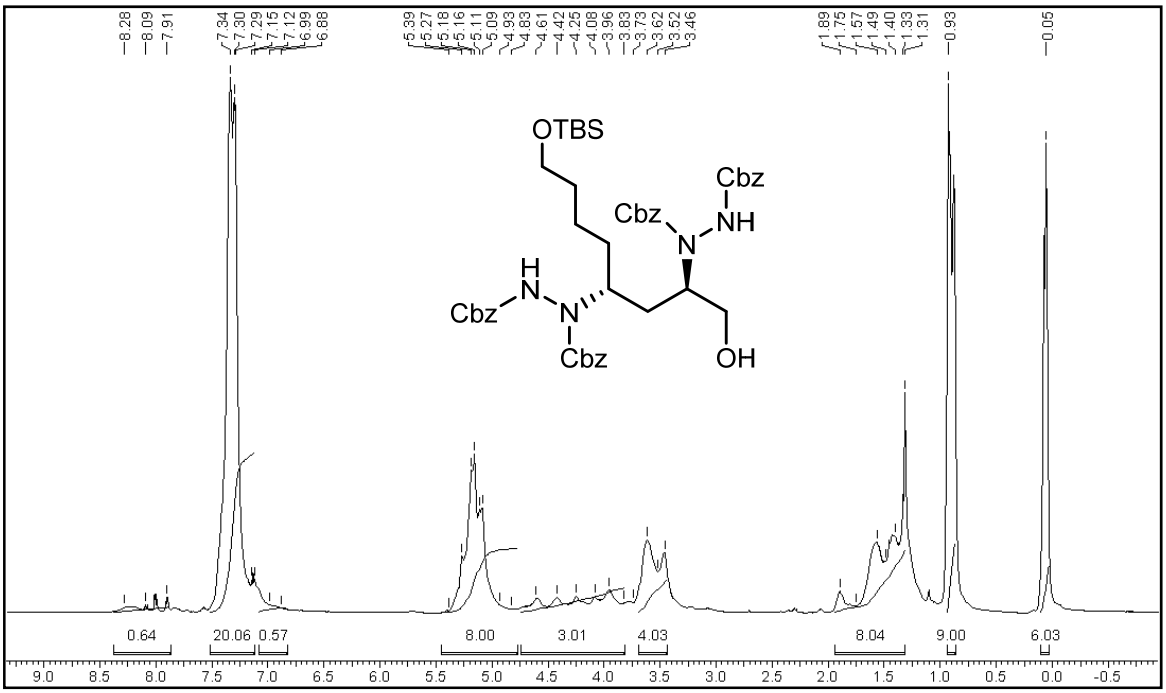


- **^{1}H NMR of the compound 26e in $CDCl_3$**

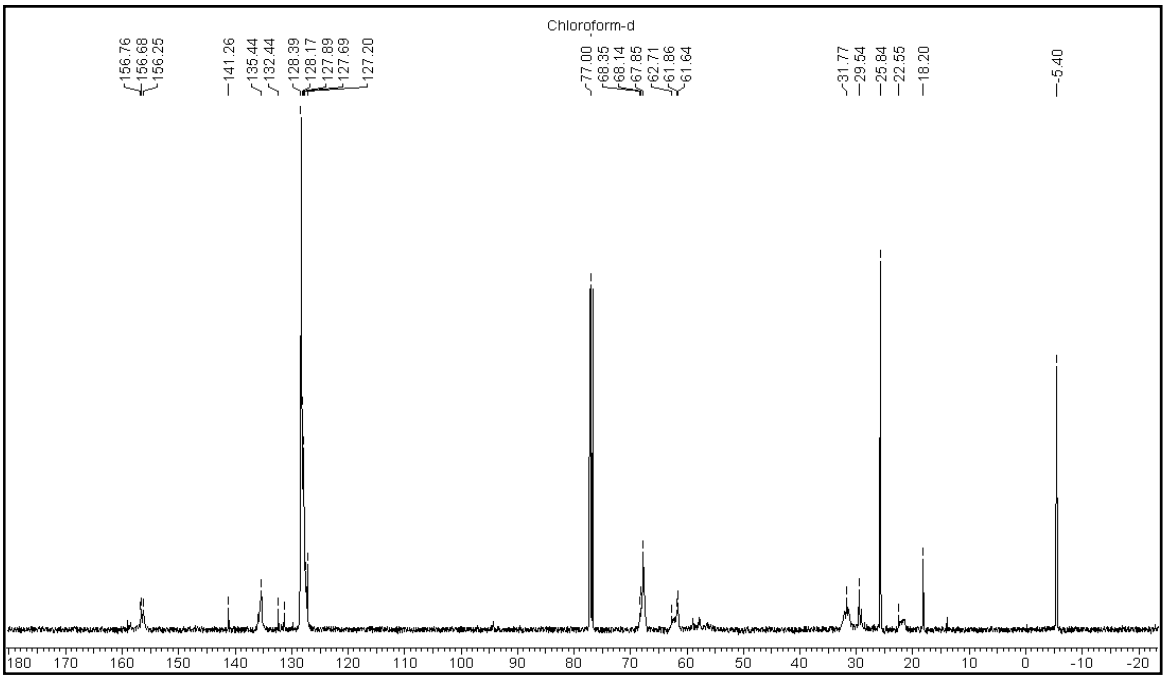


- **^{13}C NMR of the compound 26e in $CDCl_3$**

1,1'-((2*R*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (26f):

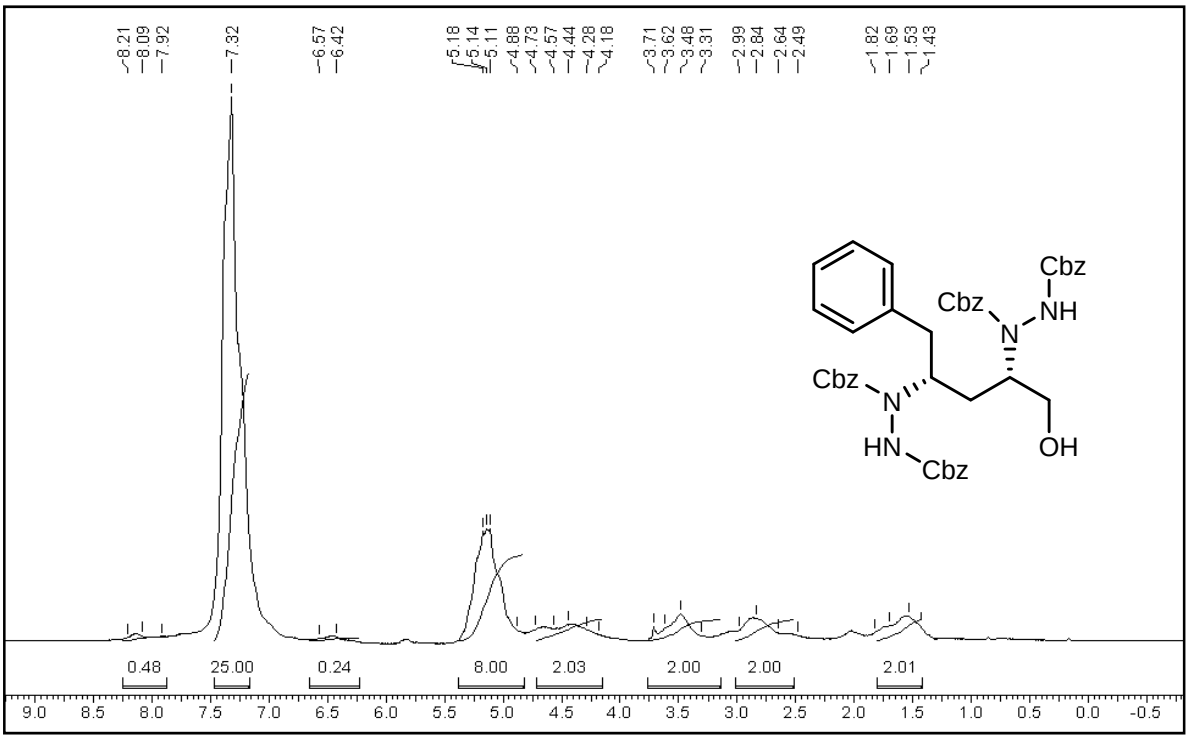


- **^{1}H NMR of the compound 26f in $CDCl_3$**

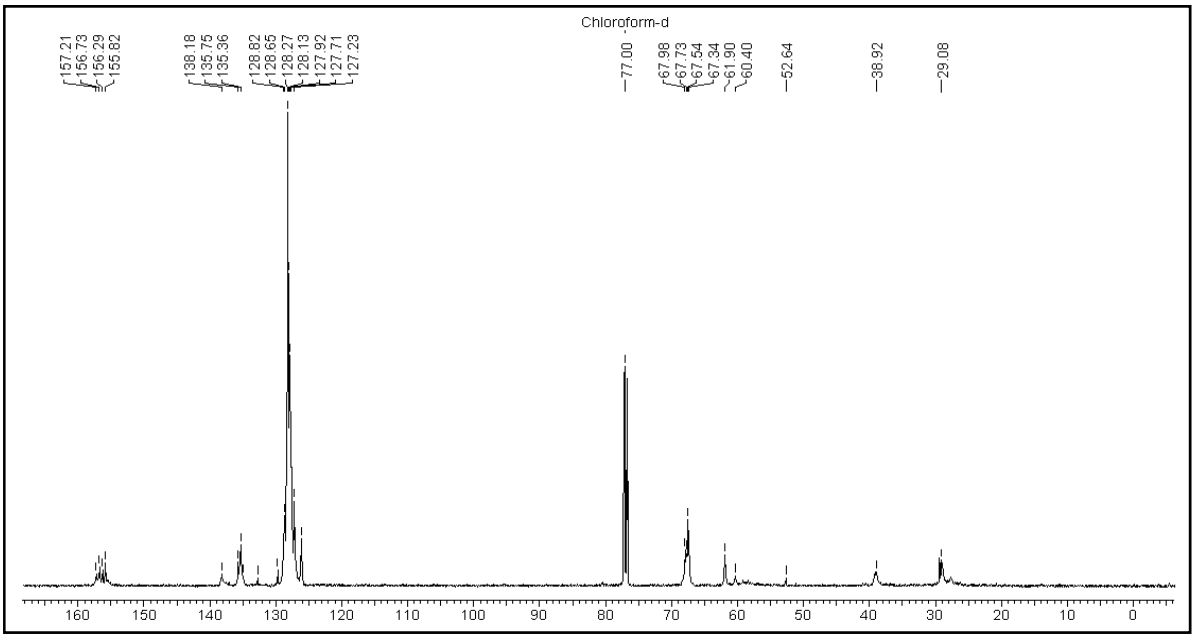


- **^{13}C NMR of the compound 26f in $CDCl_3$**

1,1'-((2*S*,4*R*)-Tetrabenzyl ` 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27a):

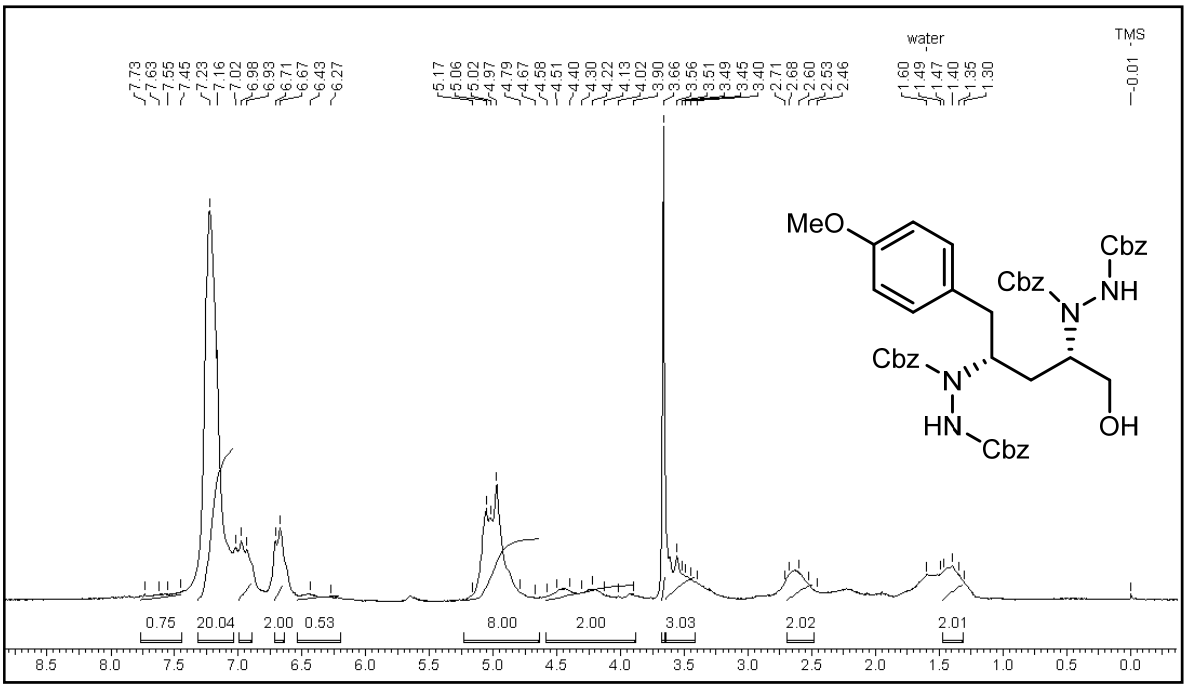


- **^{1}H NMR of the compound 27a in $CDCl_3$**

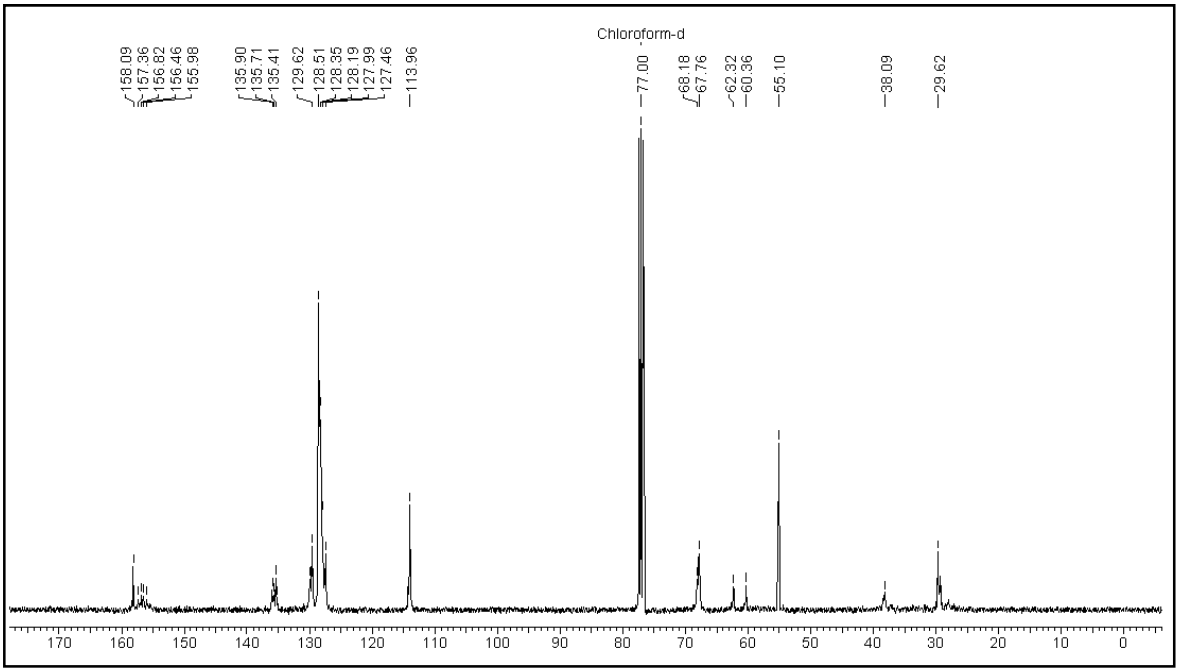


- **^{13}C NMR of the compound 27a in $CDCl_3$**

1,1'-((2*S*,4*R*)- Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27b):

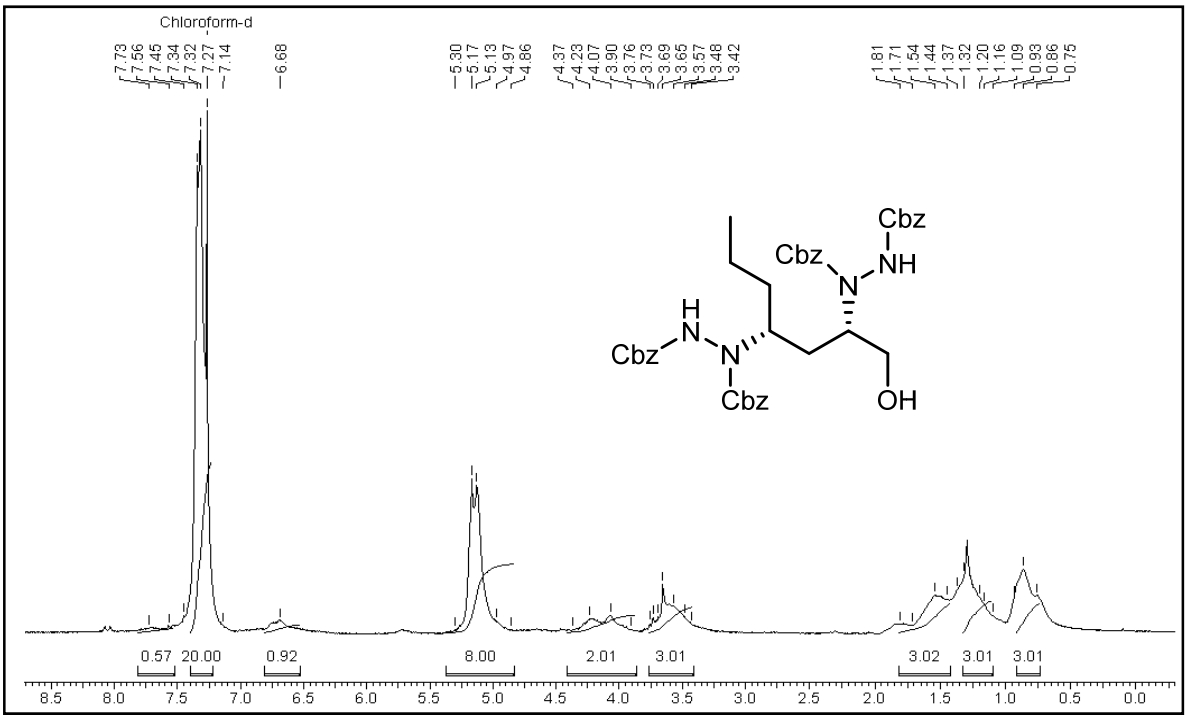


➢ **^{1}H NMR of the compound 27b in $CDCl_3$**

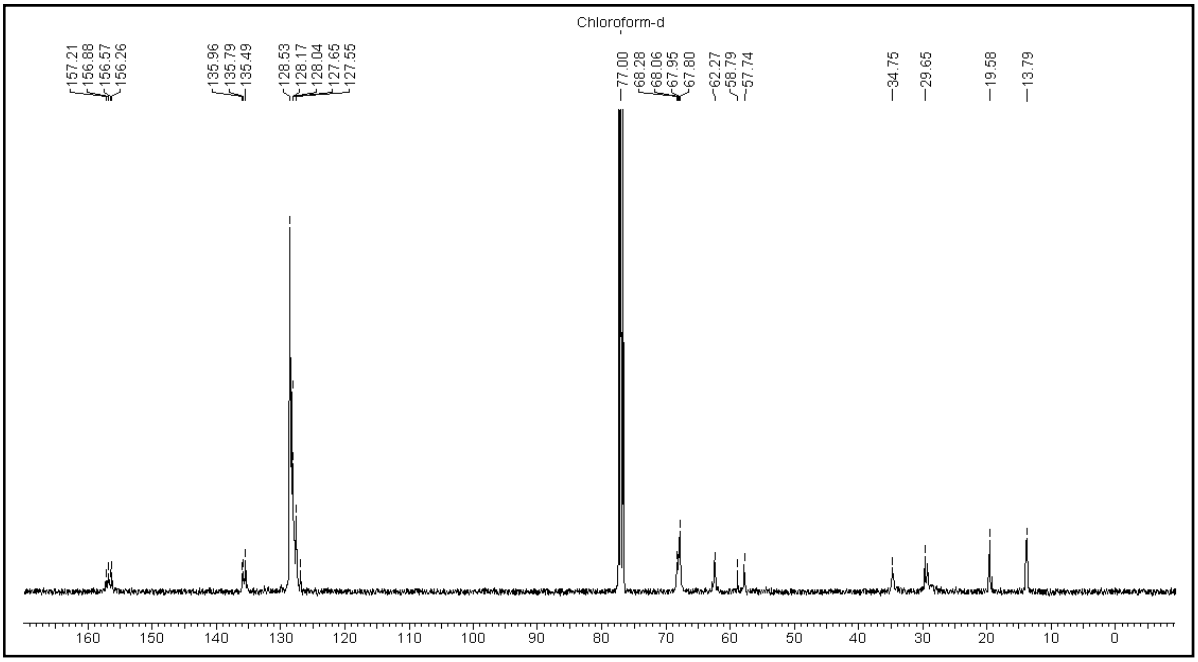


➢ **^{13}C NMR of the compound 27b in $CDCl_3$**

1,1'-((2*S*,4*R*)-Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27c):

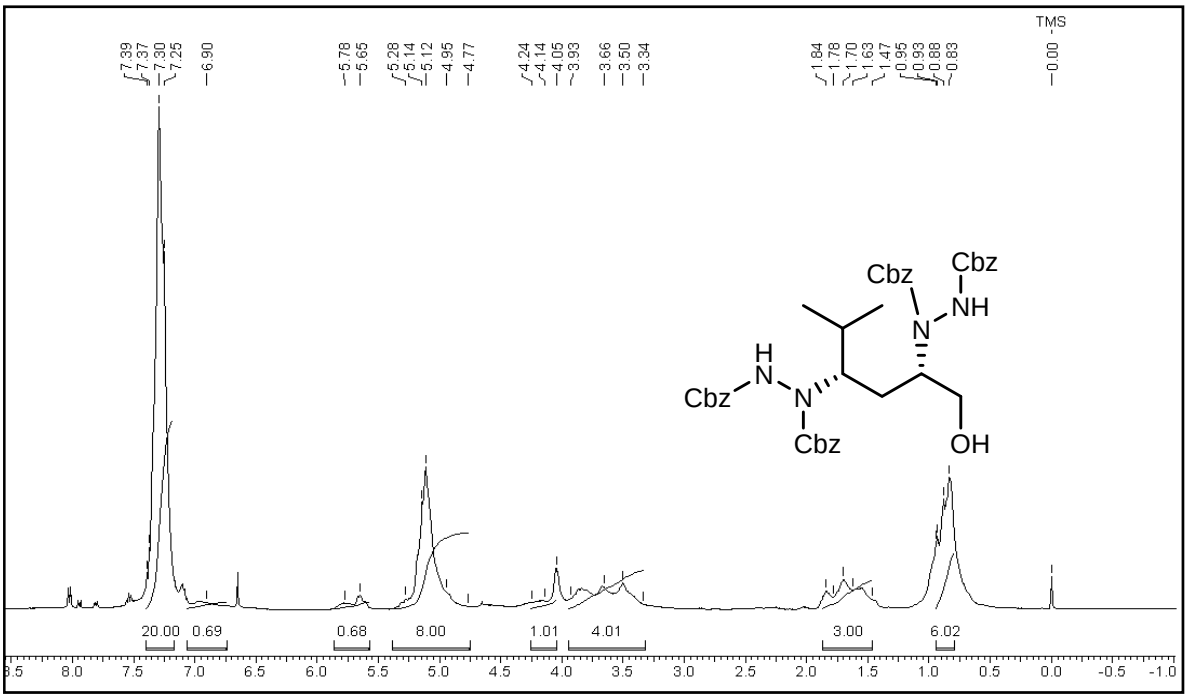


- **^{1}H NMR of the compound 27c in $CDCl_3$**

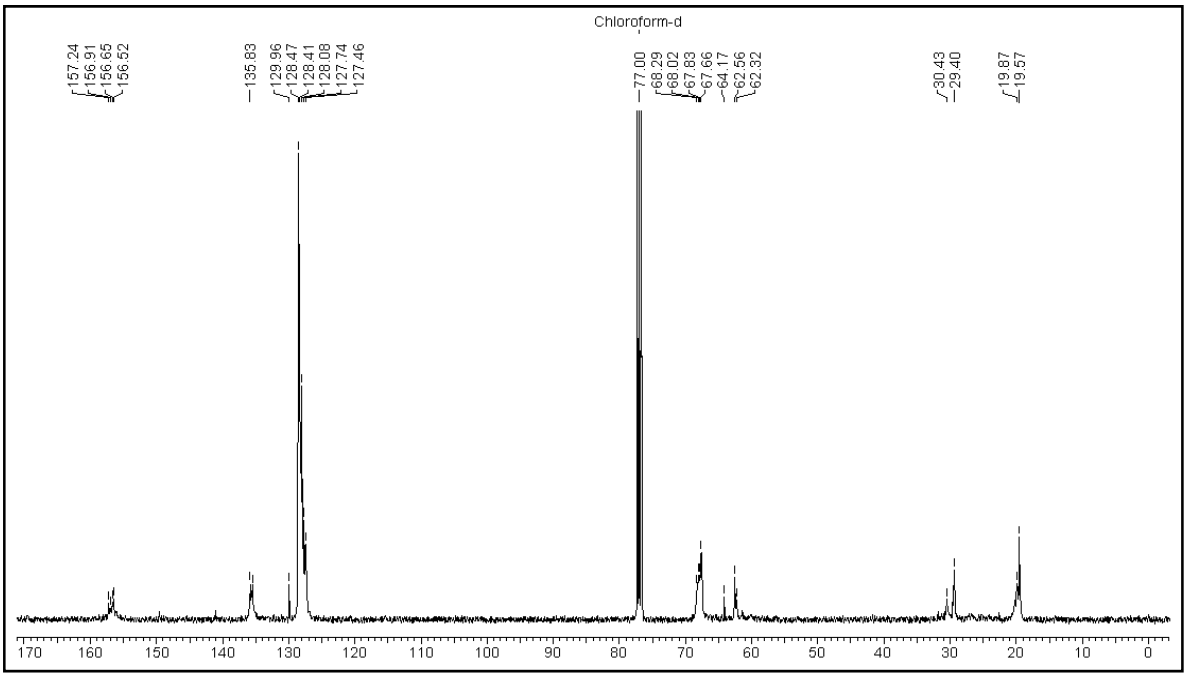


- **^{13}C NMR of the compound 27c in $CDCl_3$**

1,1'-((2*S*,4*S*)- Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27d):

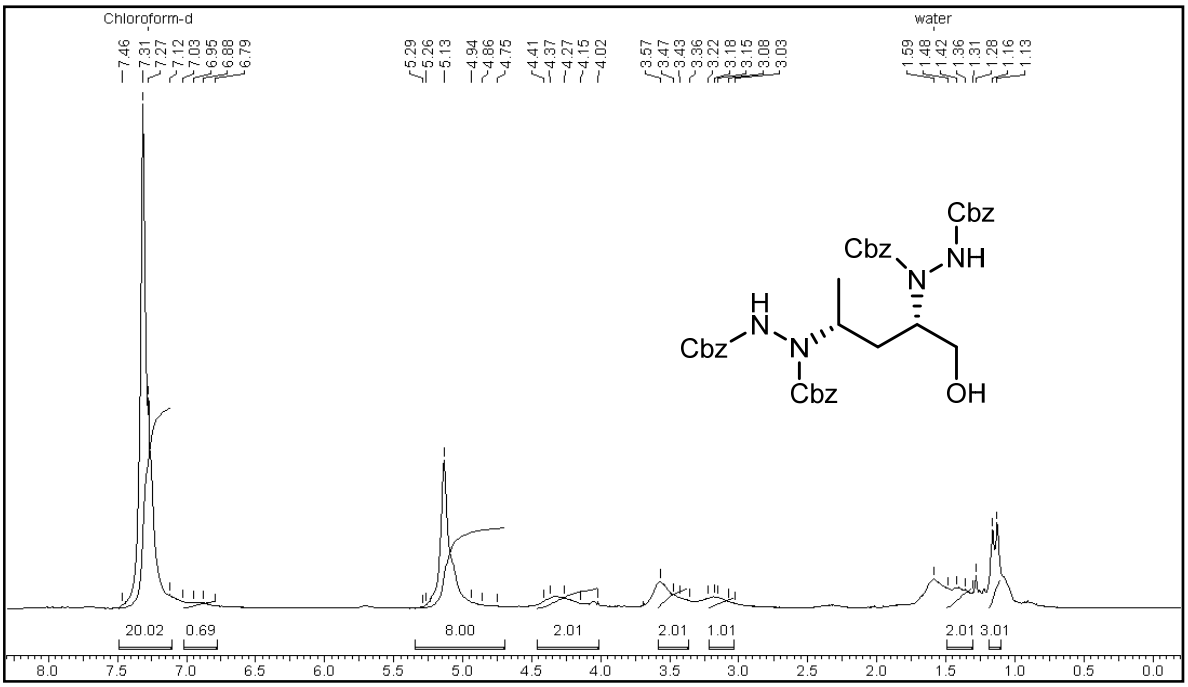


➢ **^{1}H NMR of the compound 27d in $CDCl_3$**

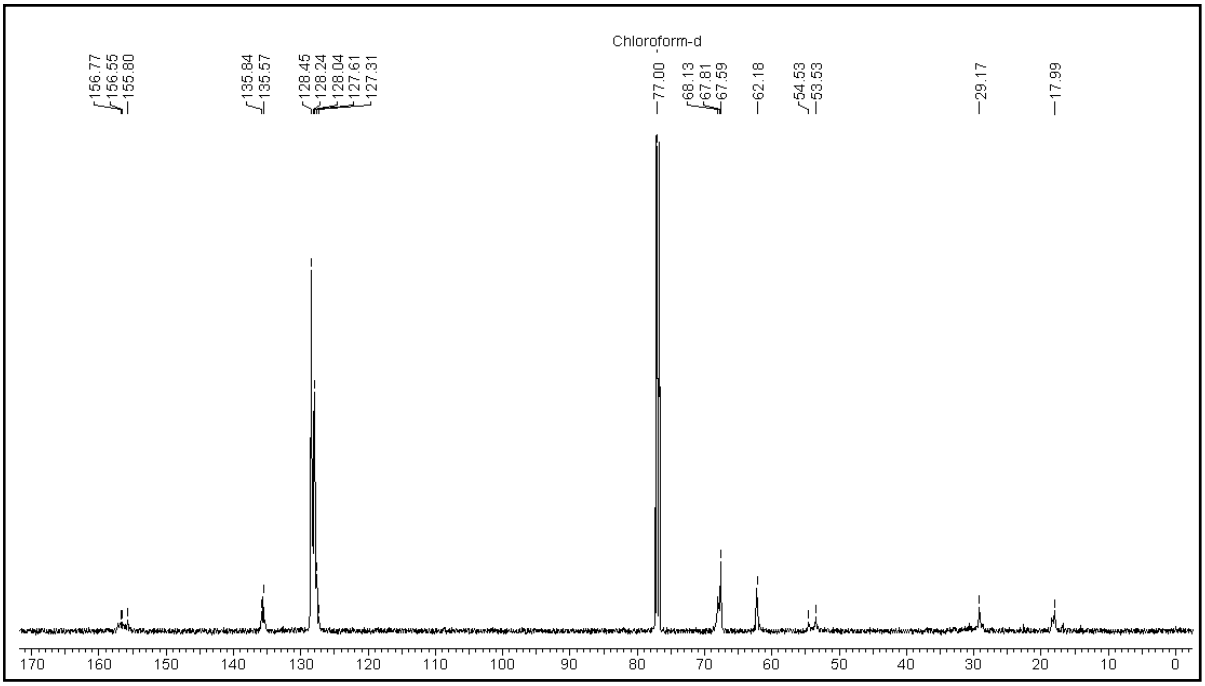


➢ **^{13}C NMR of the compound 27d in $CDCl_3$**

1,1'-((2*S*,4*R*)-Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27e):

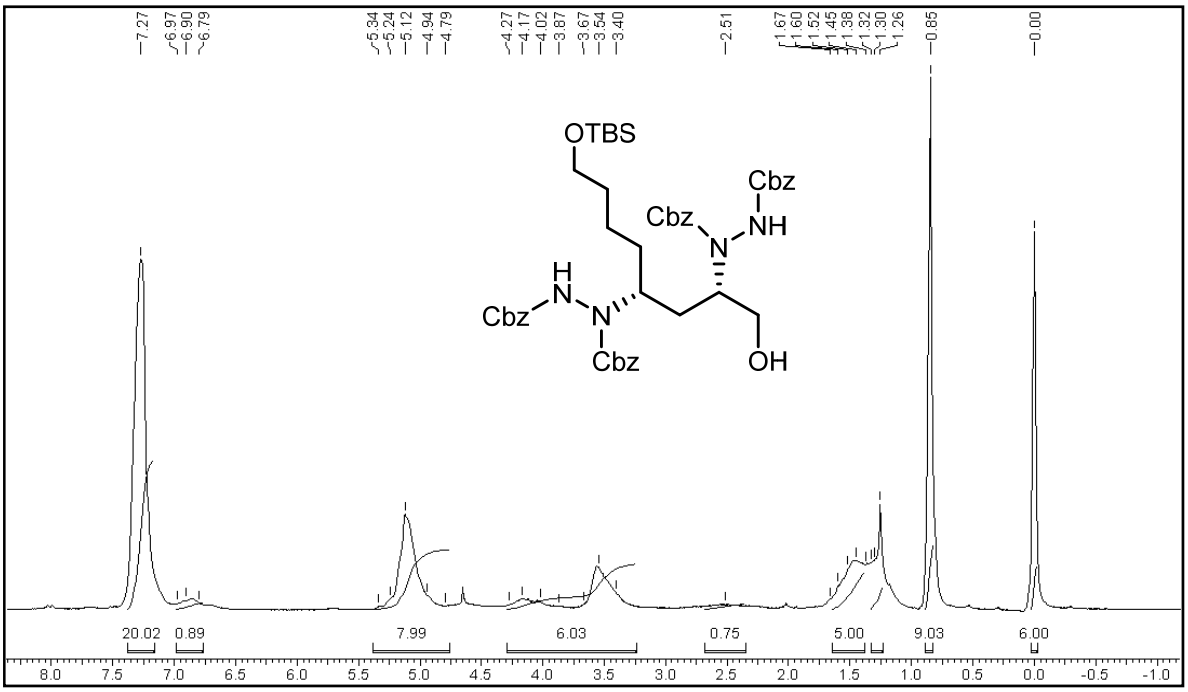


- **^{1}H NMR of the compound 27e in $CDCl_3$**

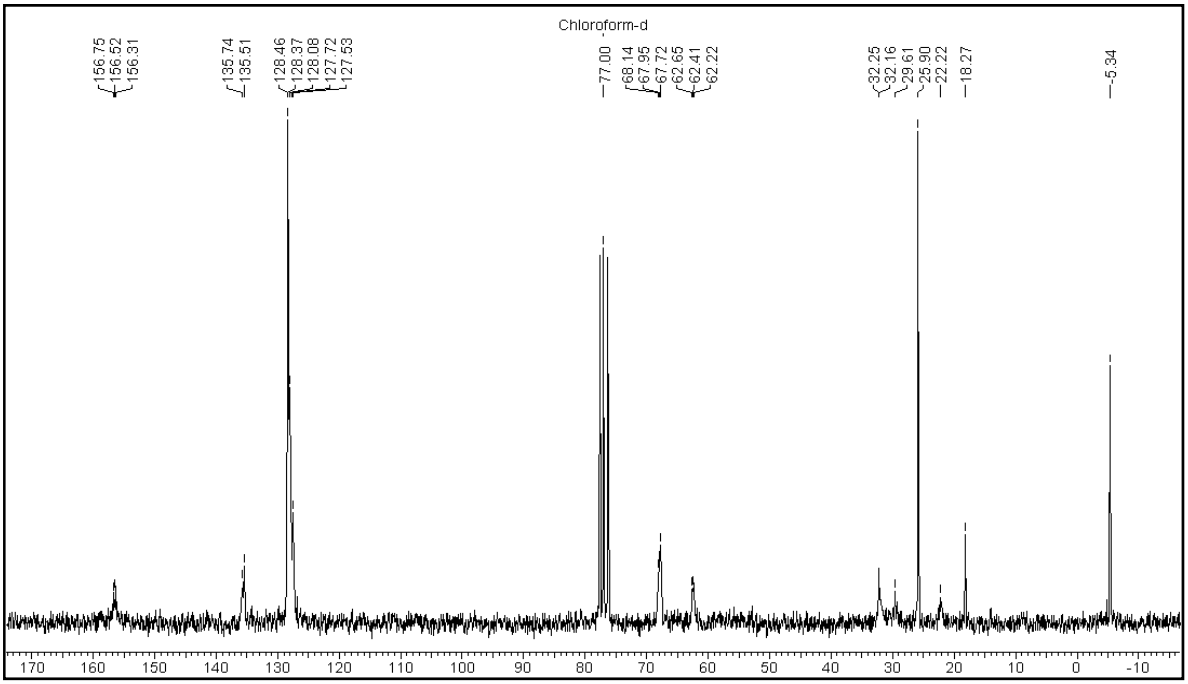


- **^{13}C NMR of the compound 27e in $CDCl_3$**

1,1'-((2*S*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (27f):

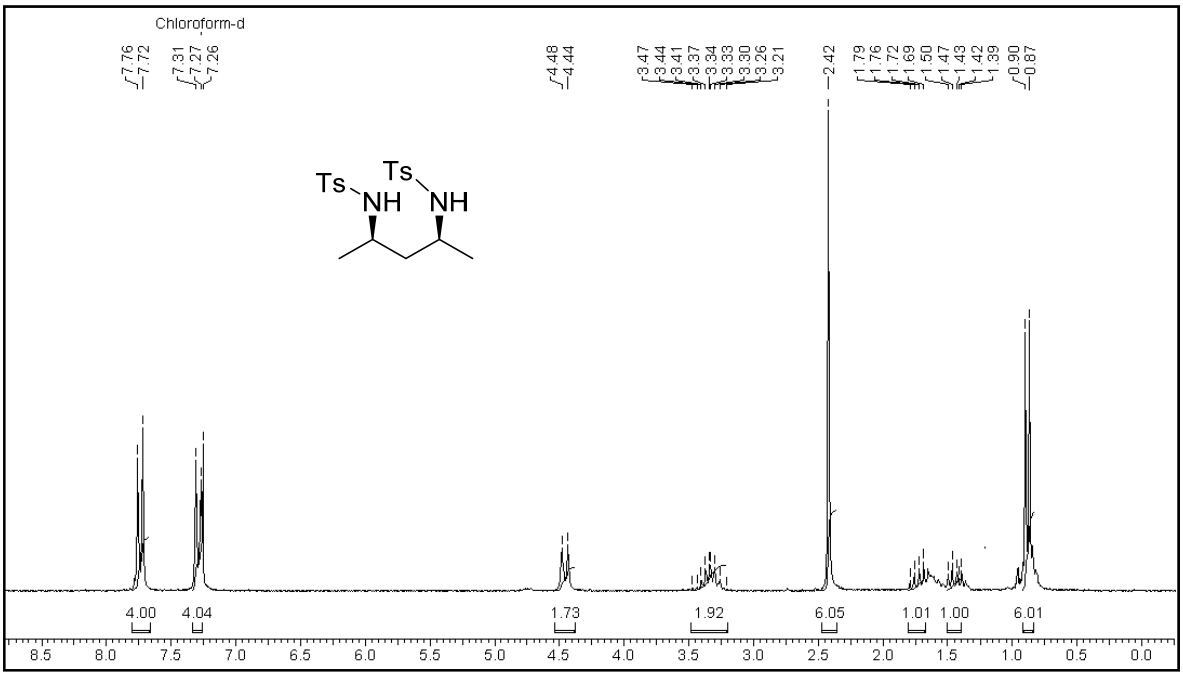


➢ **^{1}H NMR of the compound 27f in $CDCl_3$**

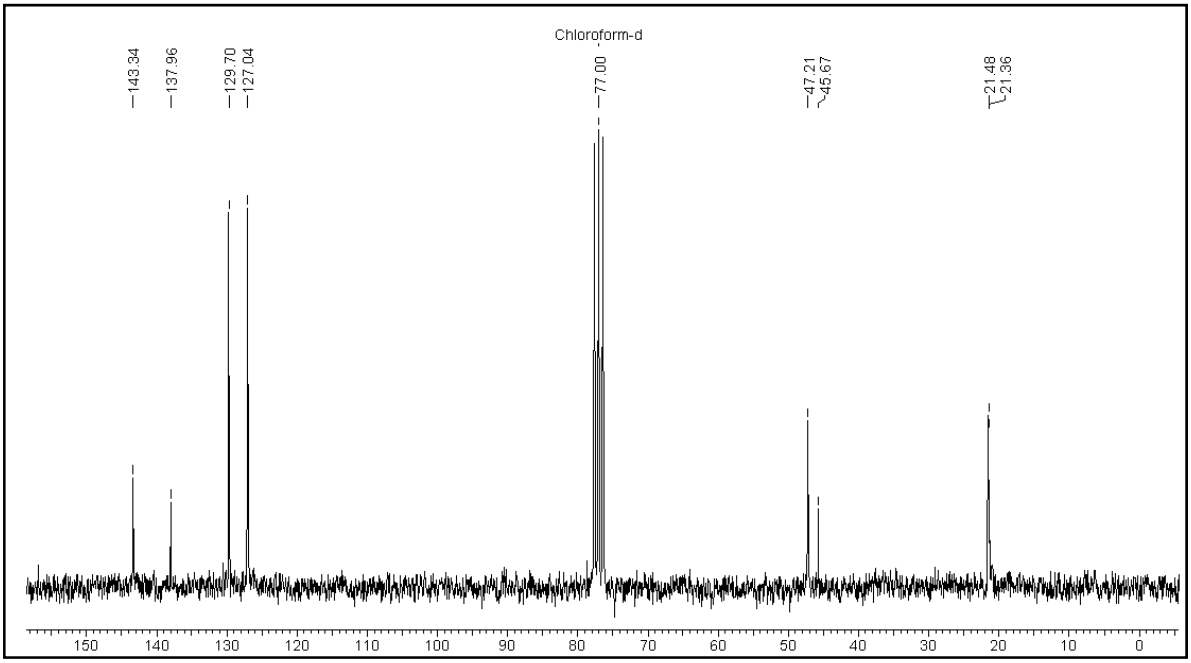


➢ **^{13}C NMR of the compound 27f in $CDCl_3$**

N,N'-((2*R*,4*S*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) (29):

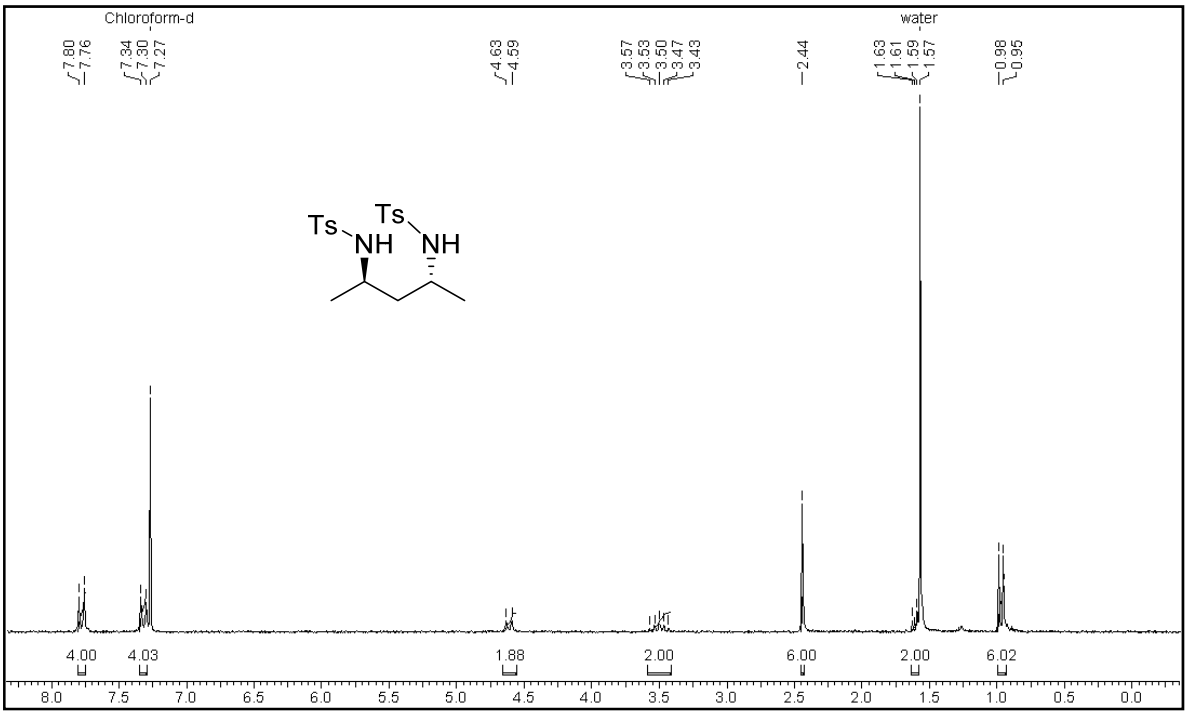


- **^{1}H NMR of the compound 29 in $CDCl_3$**

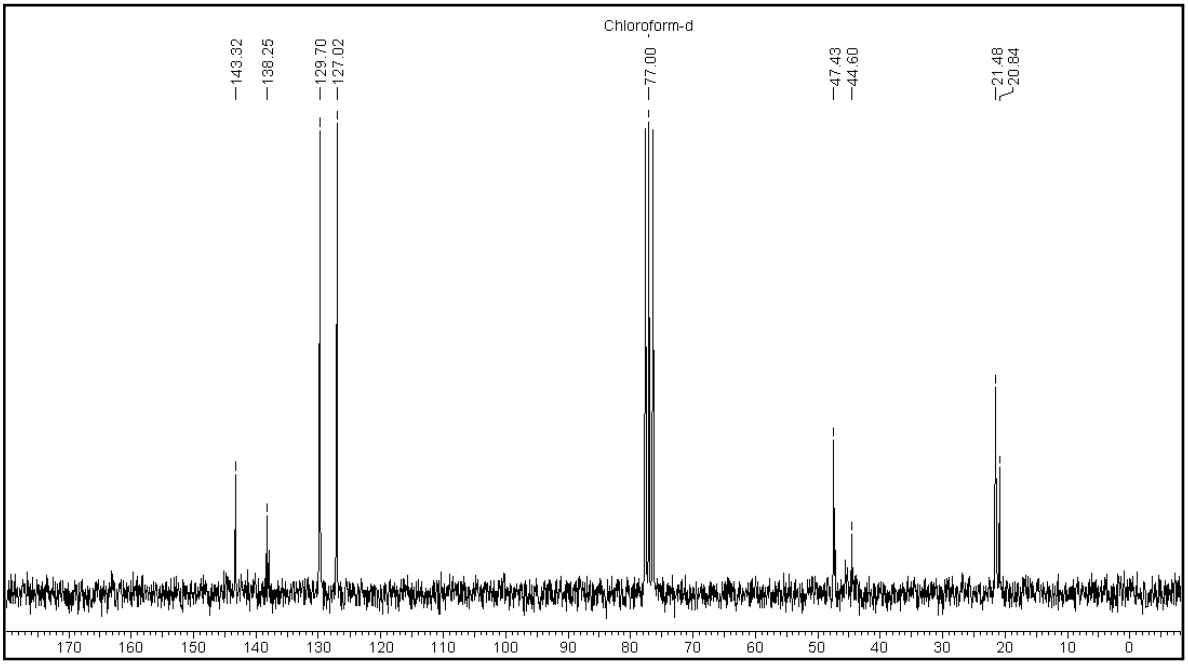


- **^{13}C NMR of the compound 29 in $CDCl_3$**

N,N'-((2*R*,4*R*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) (31):

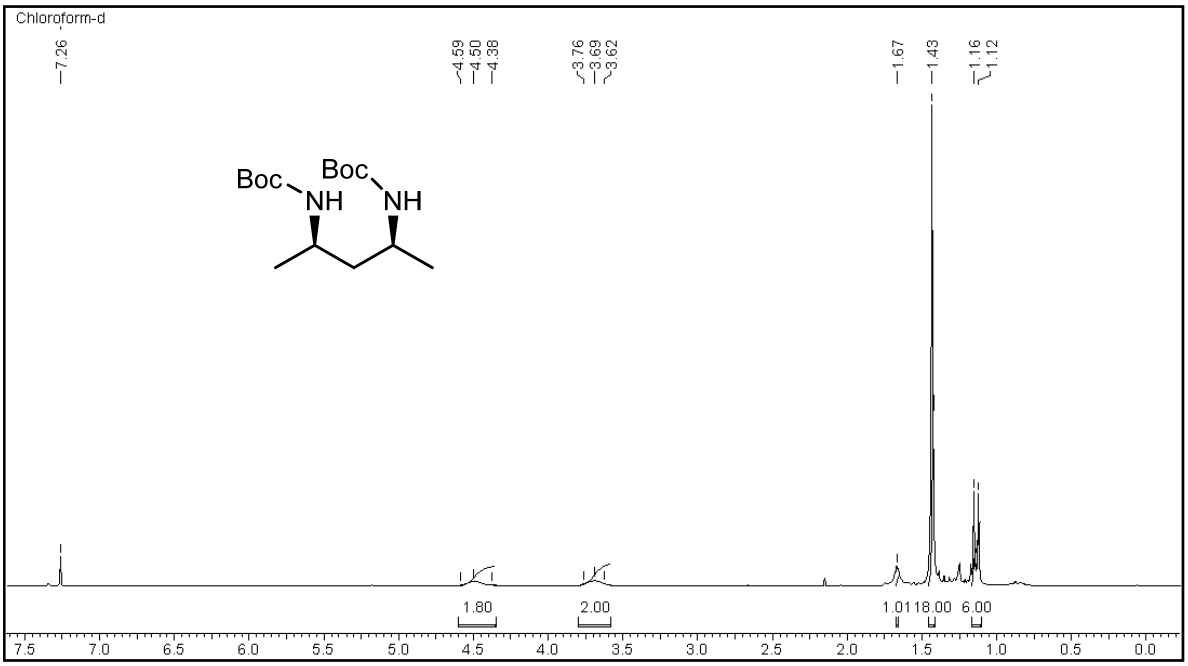


➢ **^{1}H NMR of the compound 31 in $CDCl_3$**

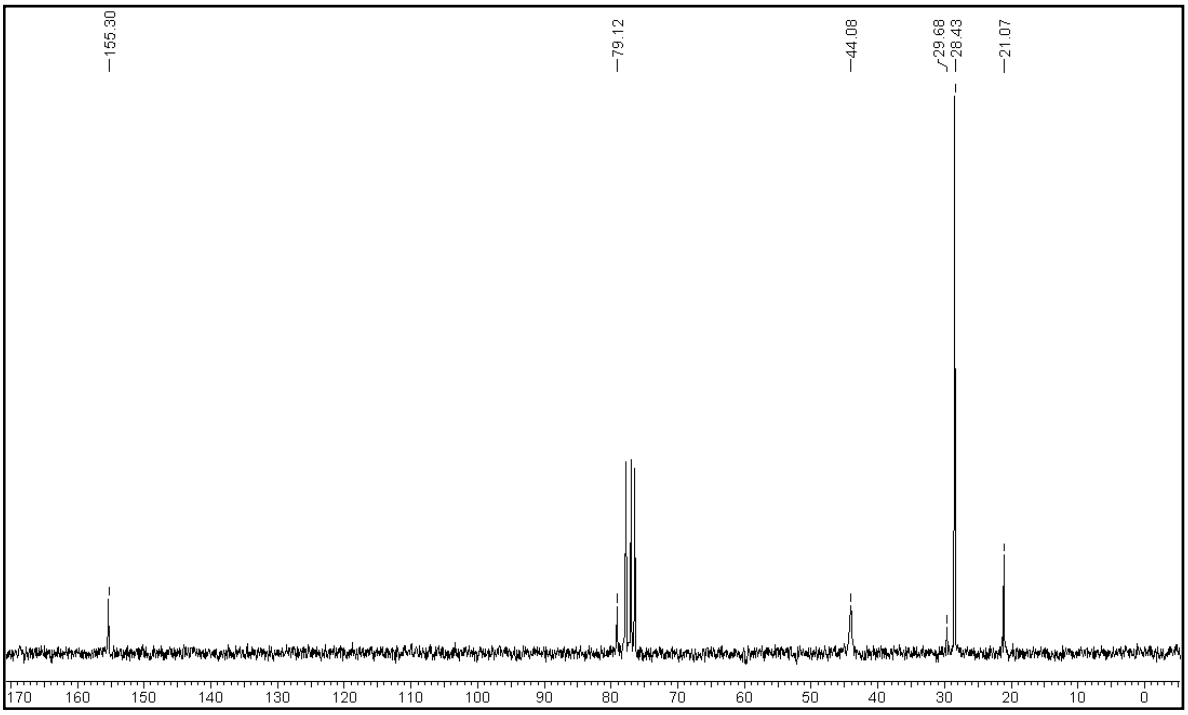


➢ **^{13}C NMR of the compound 31 in $CDCl_3$**

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)dicarbamate (32):

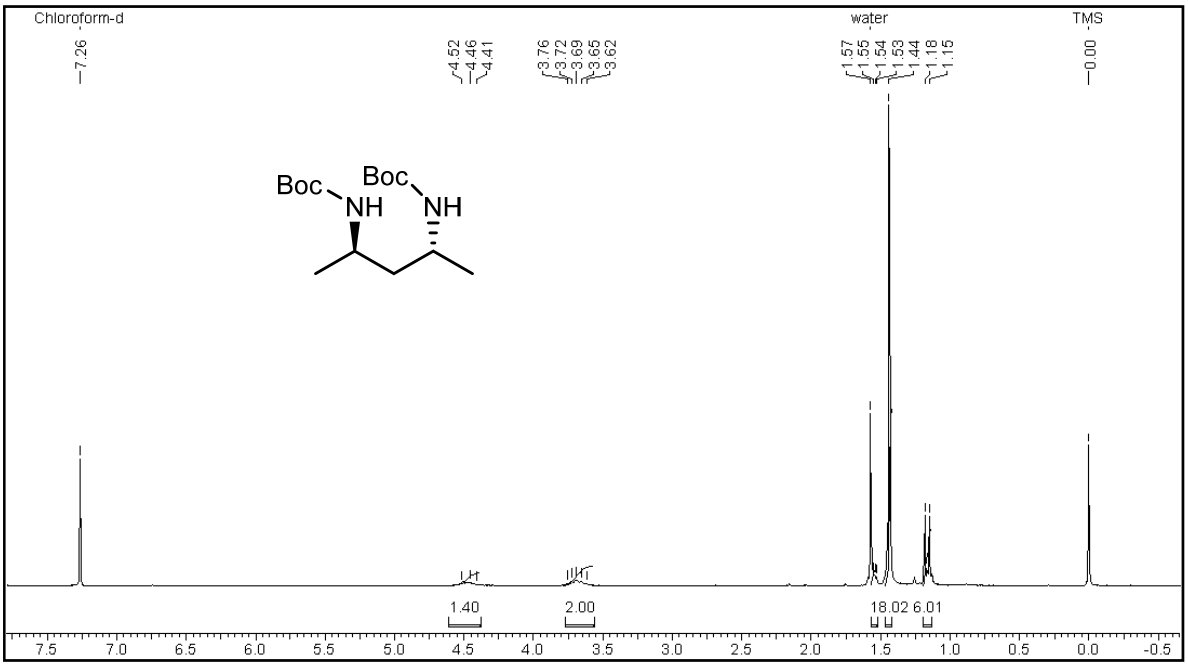


- **^{1}H NMR of the compound 32 in $CDCl_3$**

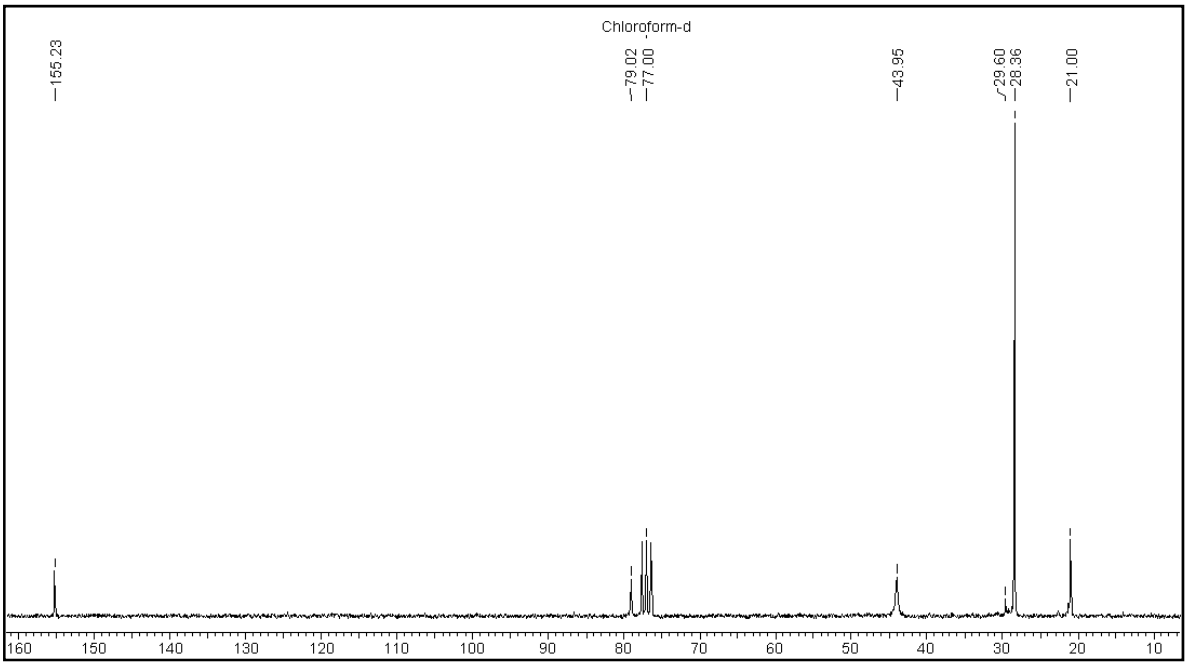


- **^{13}C NMR of the compound 32 in $CDCl_3$**

Di-*tert*-butyl ((2*R*,4*R*)-pentane-2,4-diyl)dicarbamate (33):

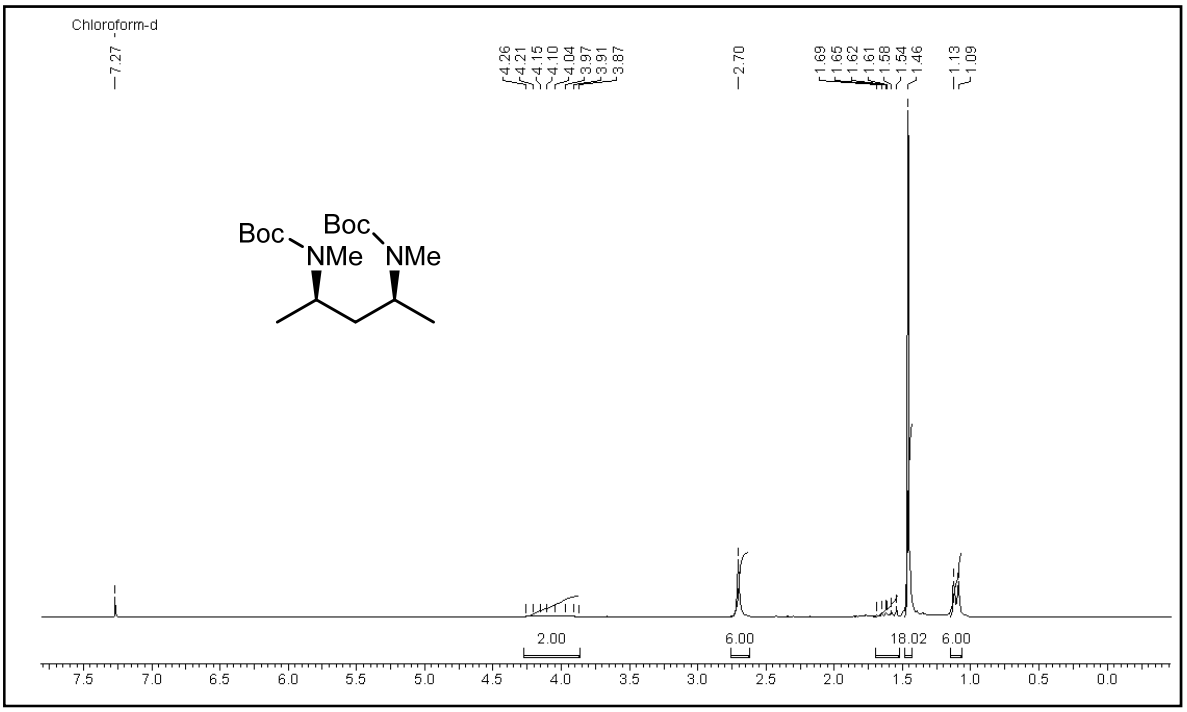


- **^{1}H NMR of the compound 33 in $CDCl_3$**

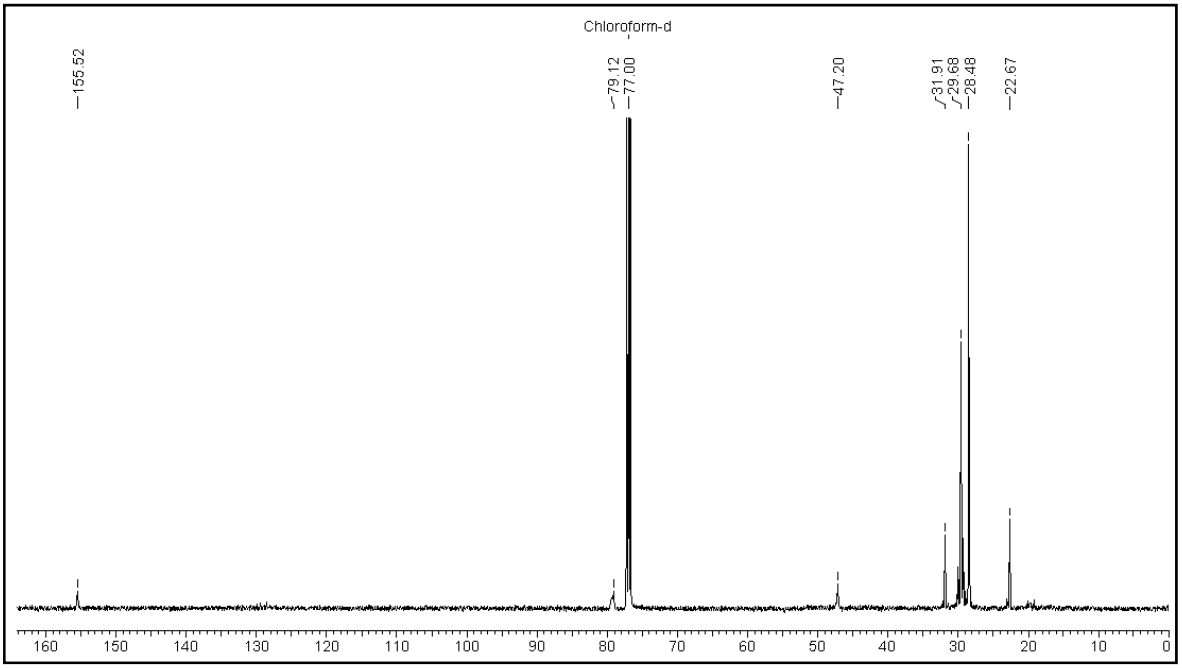


- **^{13}C NMR of the compound 33 in $CDCl_3$**

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)bis(methylcarbamate) (34):

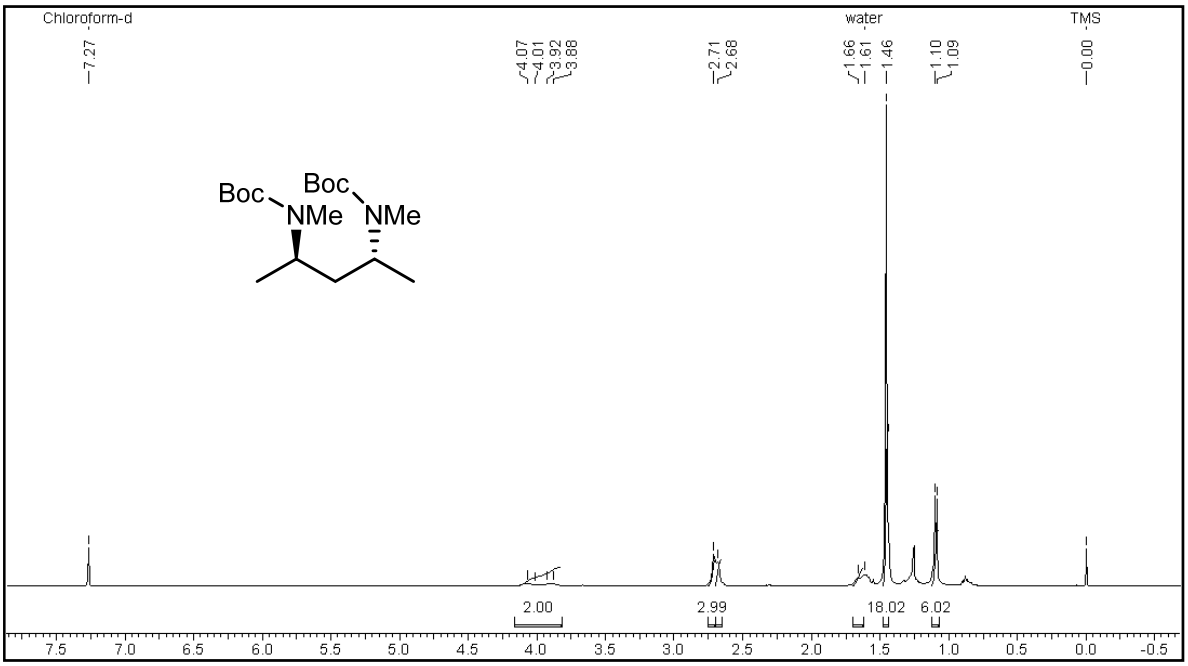


- **^{1}H NMR of the compound 34 in $CDCl_3$**

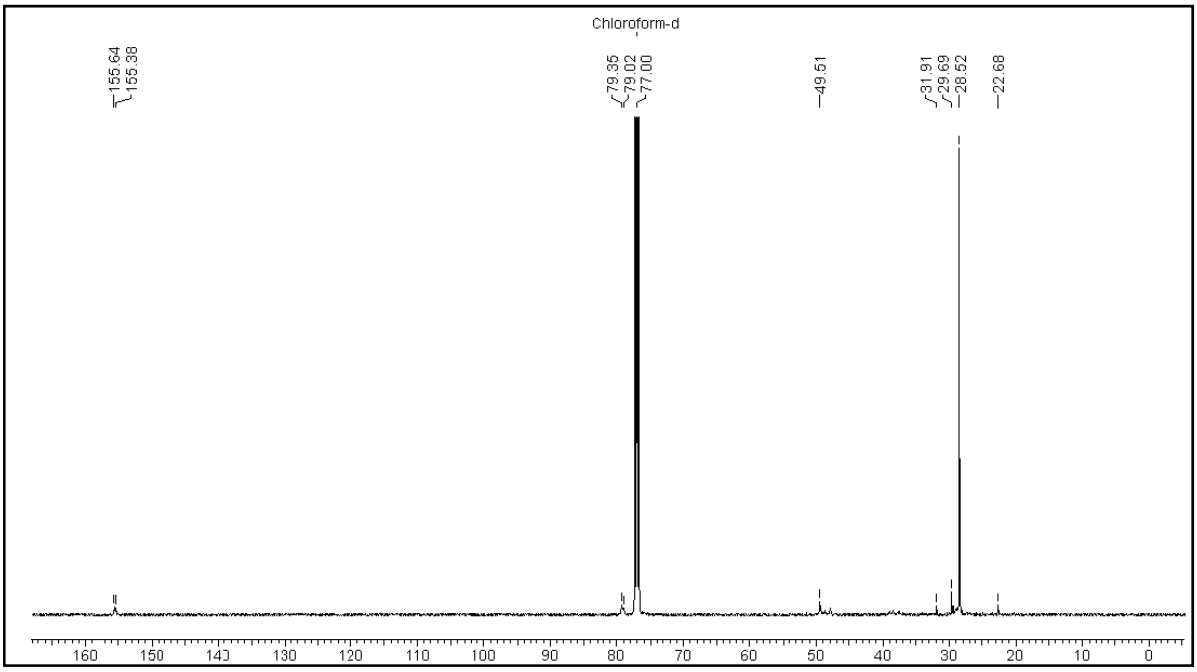


- **^{13}C NMR of the compound 34 in $CDCl_3$**

Di-*tert*-butyl ((2*R*,4*R*)-pentane-2,4-diyl)bis(methylcarbamate) (35):

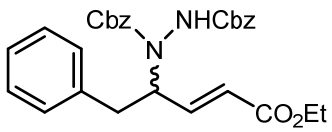


- **^{1}H NMR of the compound 35 in $CDCl_3$**

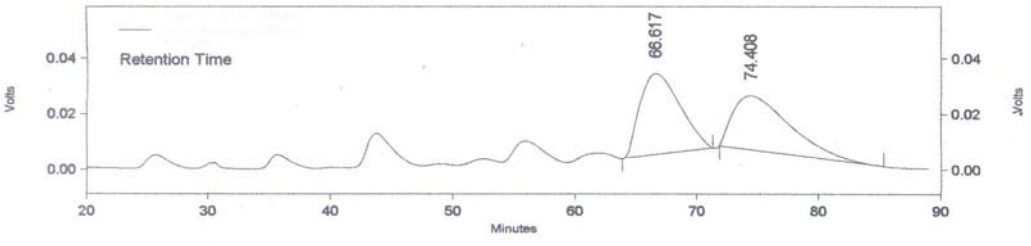


- **^{13}C NMR of the compound 35 in $CDCl_3$**

Enantiomeric excess of compound 21a-f :

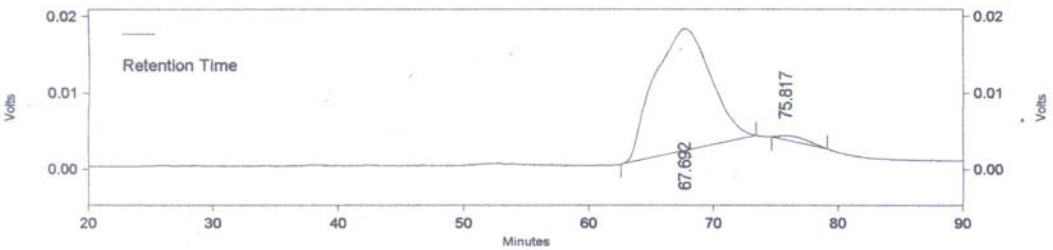


21a



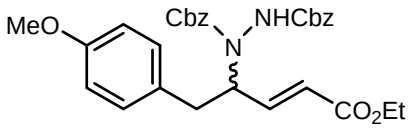
Detector A - 1 (254nm)

Retention Time	C Area	Area %
66.617	6690611	51.161
74.408	6387063	48.839
Totals	13077674	100.000

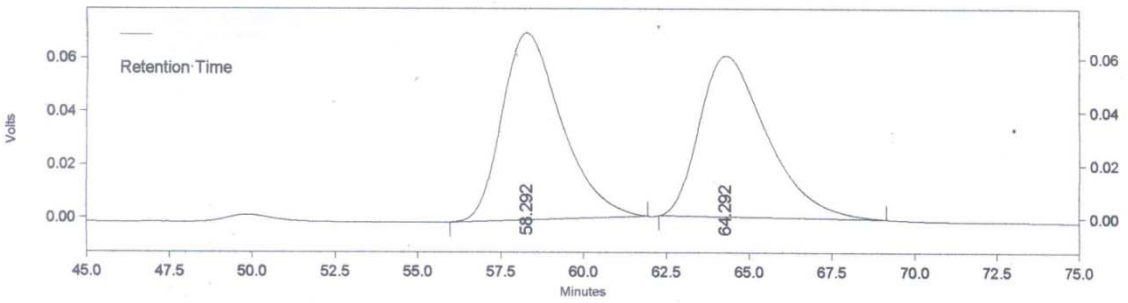


Detector A - 1 (254nm)

Retention Time	C Area	Area %
67.692	5029320	97.980
75.817	103685	2.020
Totals	5133005	100.000

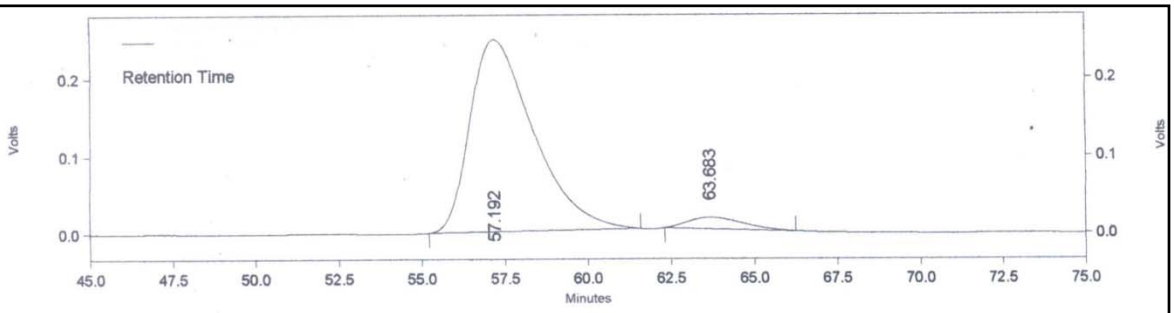


21b



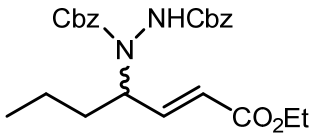
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	58.292	8788443	50.480
2	64.292	8621277	49.520
Totals		17409720	100.000

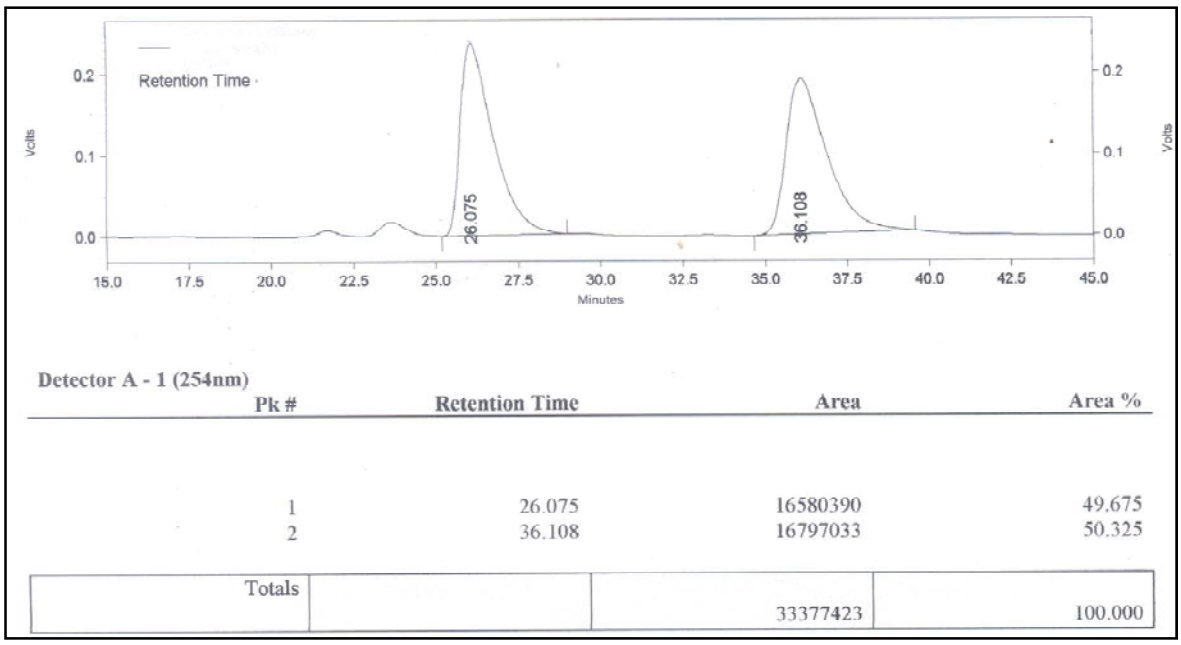


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	57.192	32938698	95.129
2	63.683	1686441	4.871
Totals		34625139	100.000

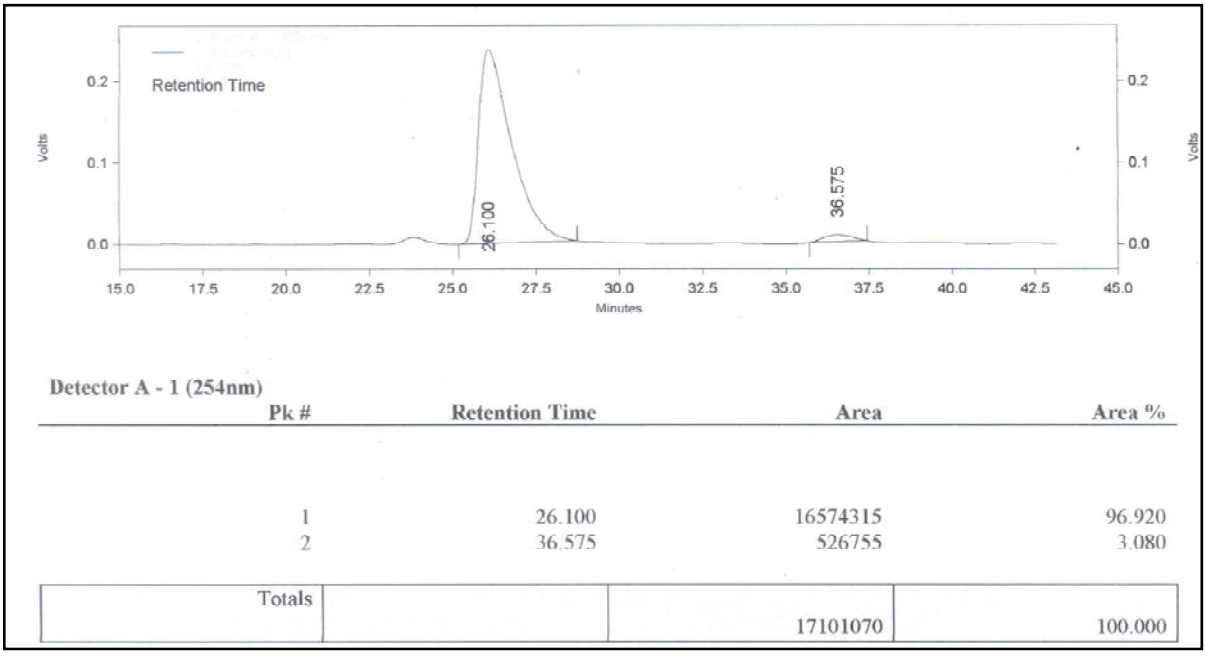


21c



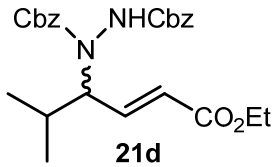
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	26.075	16580390	49.675
2	36.108	16797033	50.325
Totals		33377423	100.000

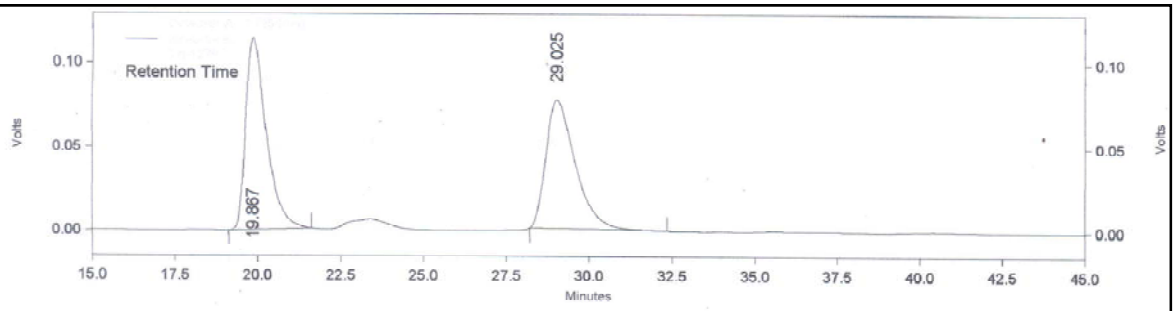


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	26.100	16574315	96.920
2	36.575	526755	3.080
Totals		17101070	100.000

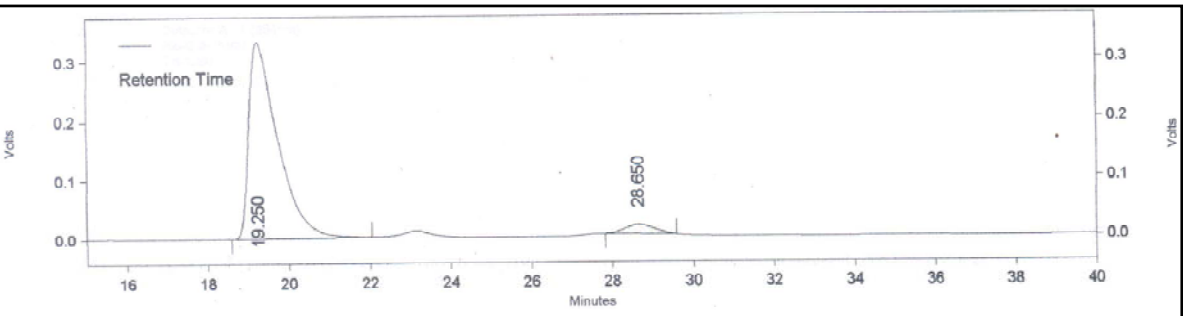


21d



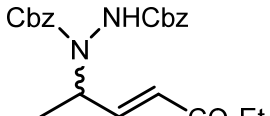
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	19.867	4958174	50.999
2	29.025	4764017	49.001
Totals		9722191	100.000

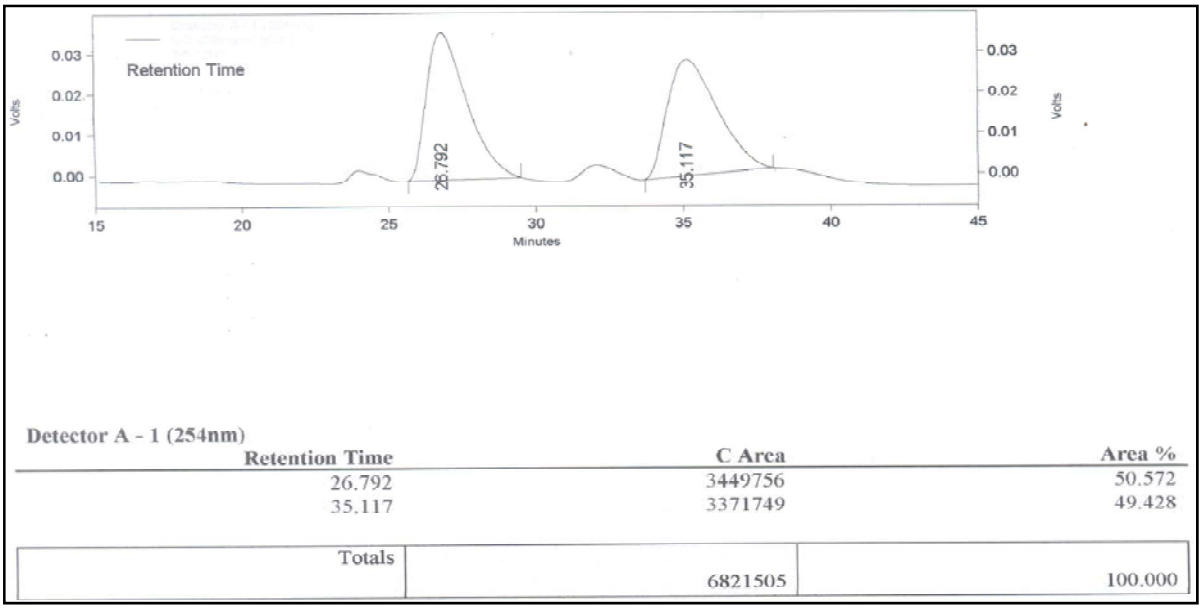


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	19.250	16501382	95.690
2	28.650	743229	4.310
Totals		17244611	100.000

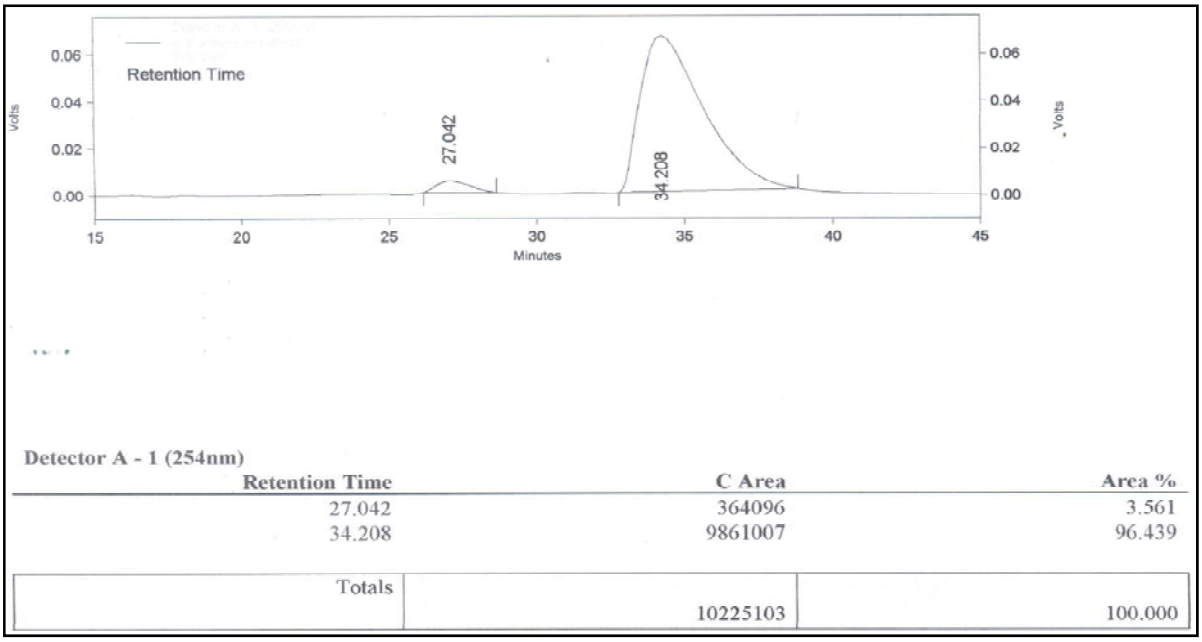


21e



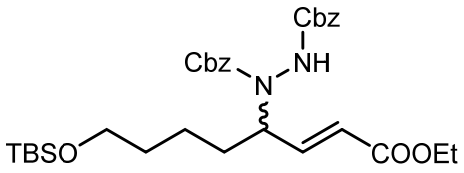
Detector A - 1 (254nm)

Retention Time	C Area	Area %
26.792	3449756	50.572
35.117	3371749	49.428
Totals	6821505	100.000

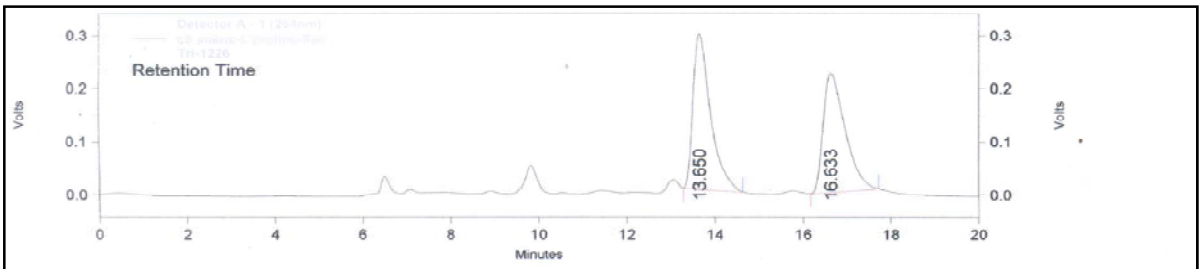


Detector A - 1 (254nm)

Retention Time	C Area	Area %
27.042	364096	3.561
34.208	9861007	96.439
Totals	10225103	100.000

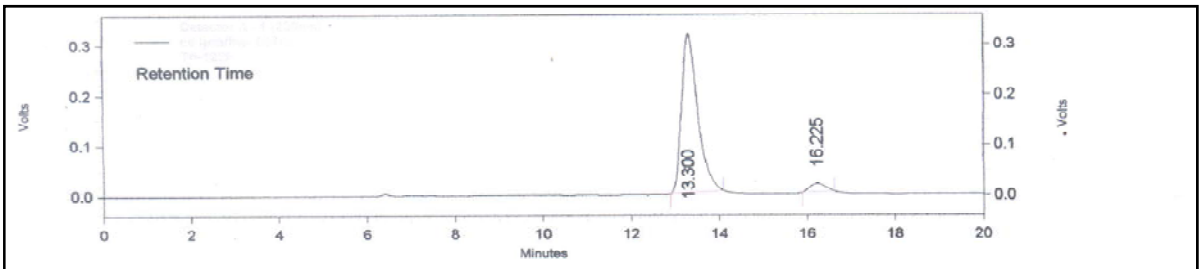


21f



Detector A - 1 (254nm)

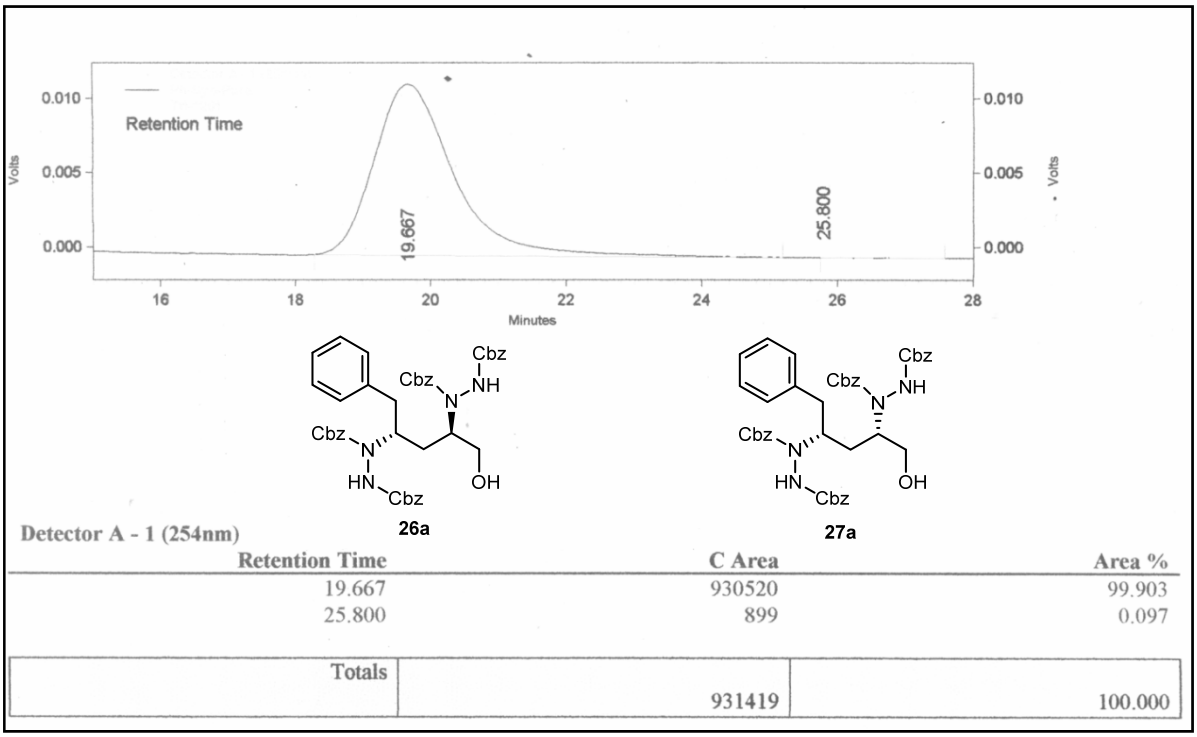
Retention Time	C Area	Area %
13.650	8063940	51.217
16.633	7680650	48.783
Totals	15744590	100.000



Detector A - 1 (230nm)

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

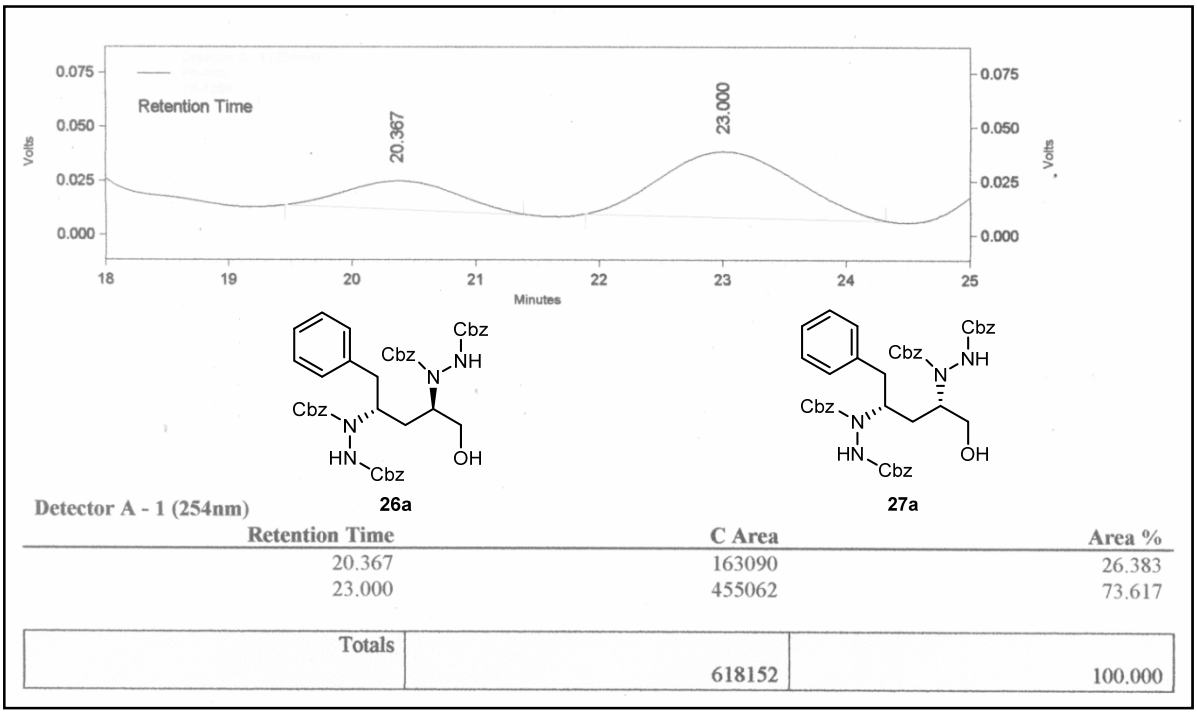
Diastereomeric ratio of *syn*-compound 26a-f and *anti*-compounds 27a-f



26a **27a**

Detector A - 1 (254nm)

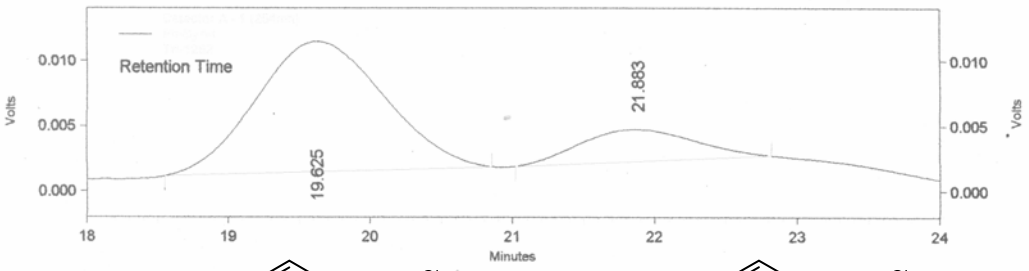
Retention Time	C Area	Area %
19.667	930520	99.903
25.800	899	0.097
Totals	931419	100.000

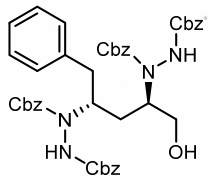


26a **27a**

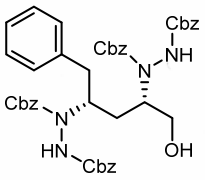
Detector A - 1 (254nm)

Retention Time	C Area	Area %
20.367	163090	26.383
23.000	455062	73.617
Totals	618152	100.000





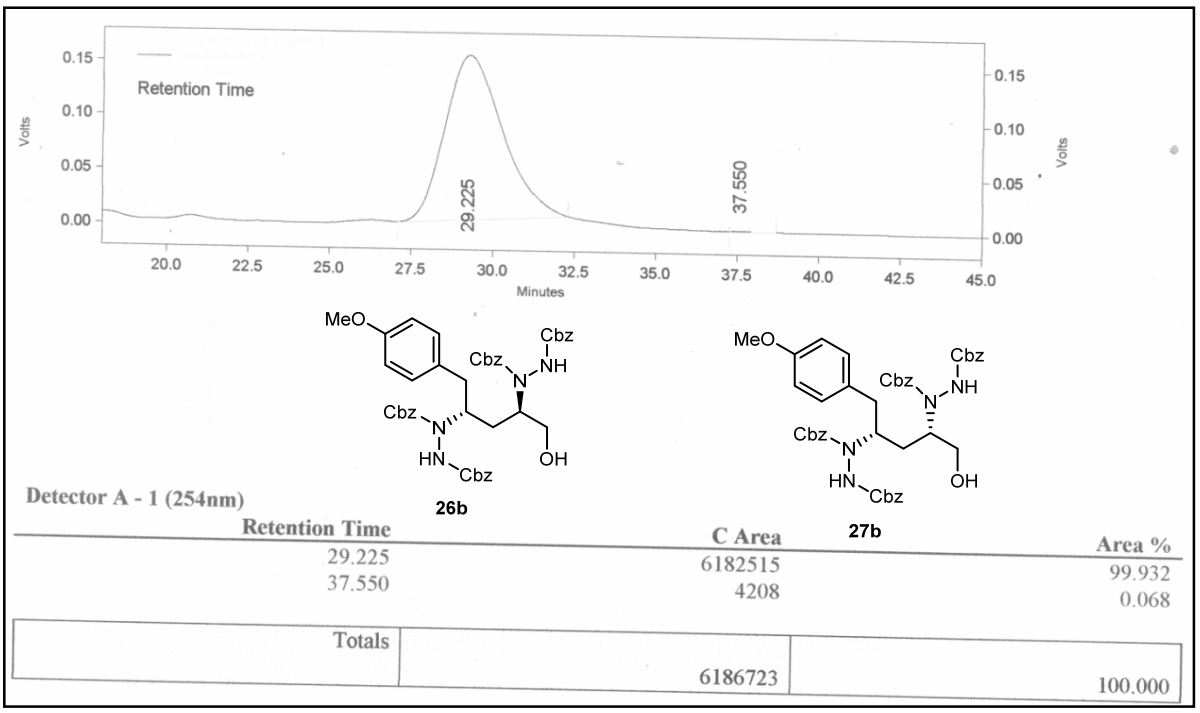
26a



27a

Detector A - 1 (254nm)

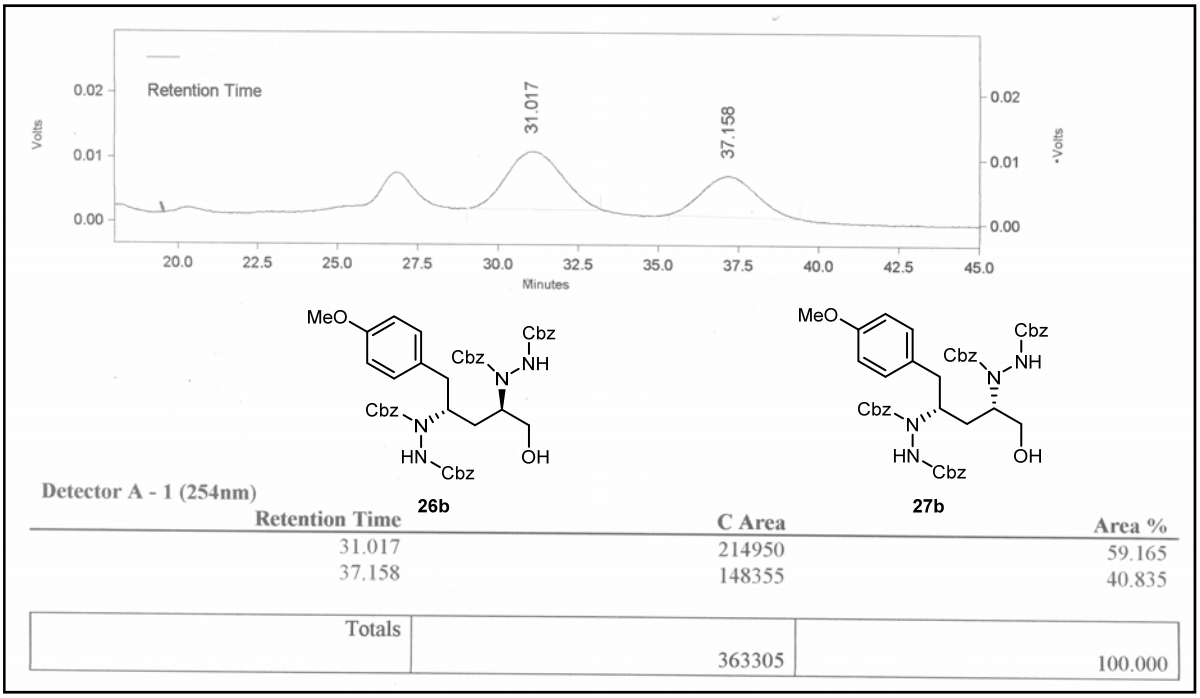
Retention Time	C Area	Area %
19.625	416931	81.903
21.883	92122	18.097
Totals	509053	100.000



26b 27b

Detector A - 1 (254nm)

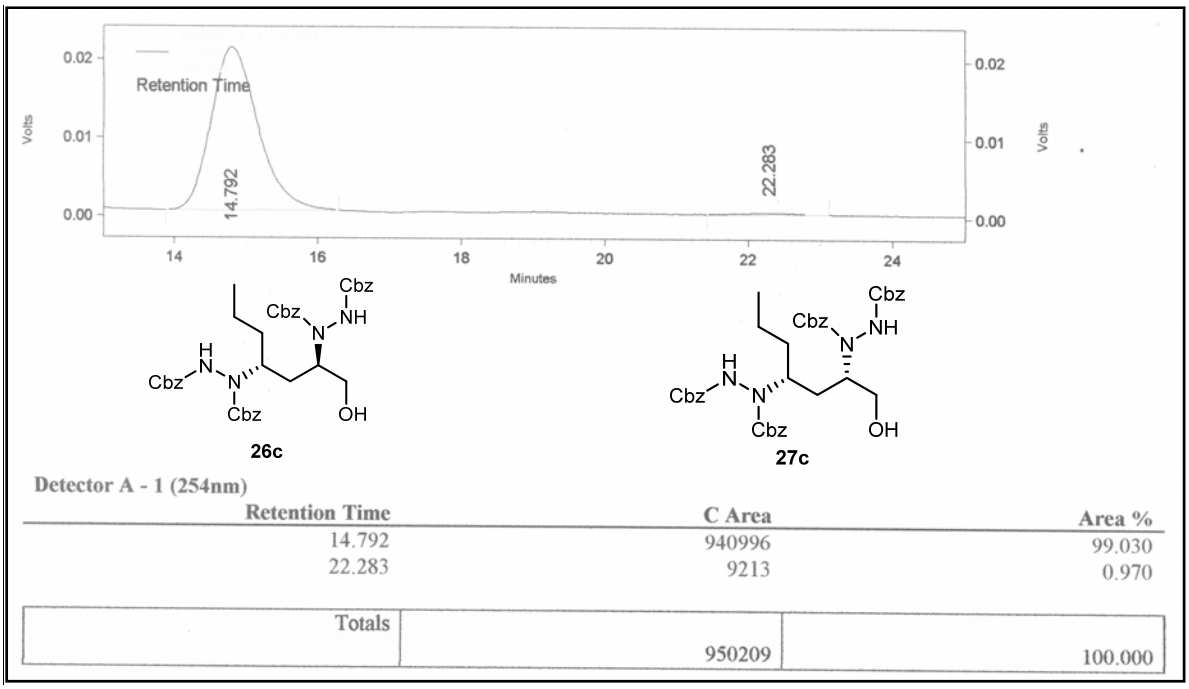
Retention Time	C Area	Area %
29.225	6182515	99.932
37.550	4208	0.068
Totals	6186723	100.000



26b 27b

Detector A - 1 (254nm)

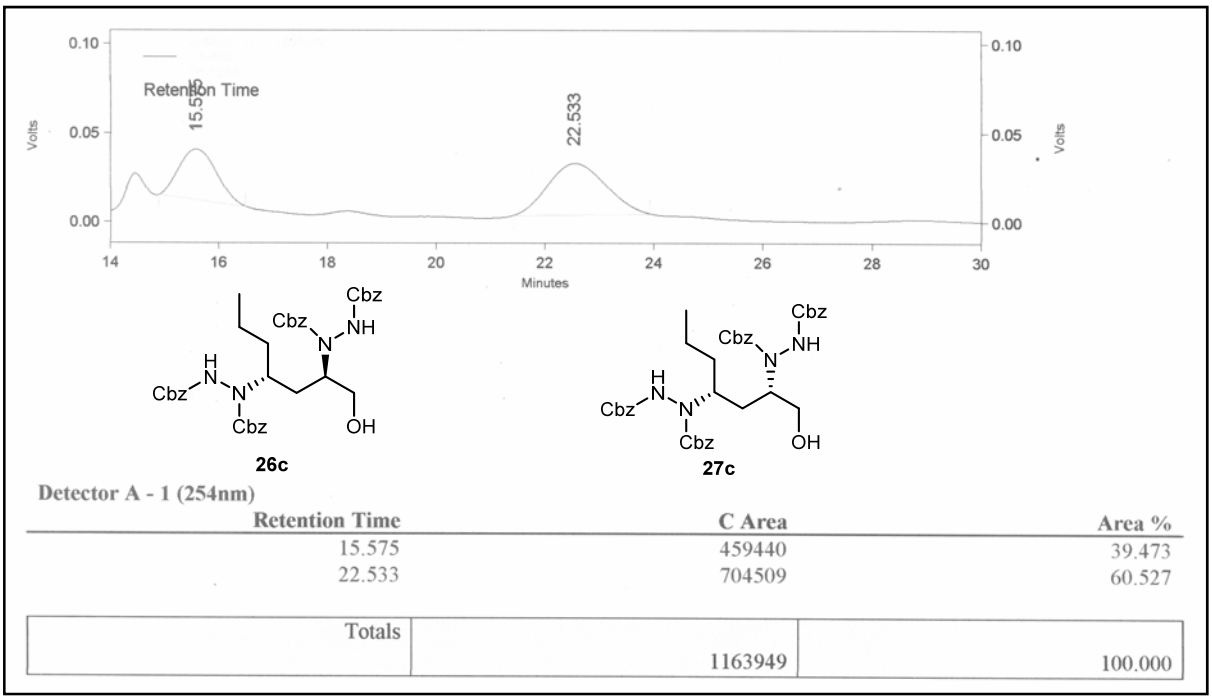
Retention Time	C Area	Area %
31.017	214950	59.165
37.158	148355	40.835
Totals	363305	100.000



26c **27c**

Detector A - 1 (254nm)

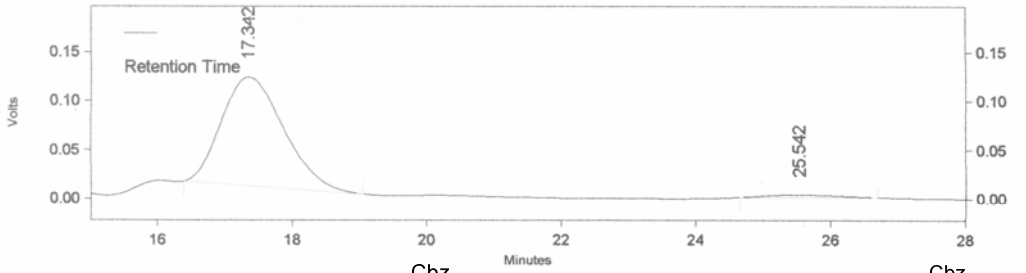
Retention Time	C Area	Area %
14.792	940996	99.030
22.283	9213	0.970
Totals	950209	100.000

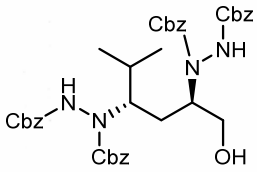


26c **27c**

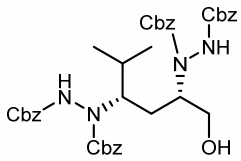
Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.575	459440	39.473
22.533	704509	60.527
Totals	1163949	100.000





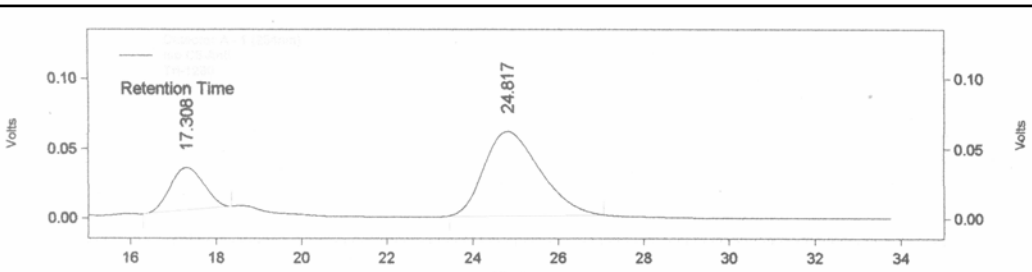
26d

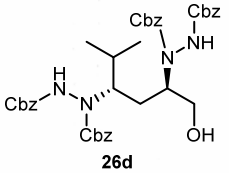


27d

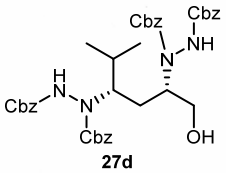
Detector A - 1 (254nm)

Retention Time	C Area	Area %
17.342	7150295	97.422
25.542	189201	2.578
Totals	7339496	100.000





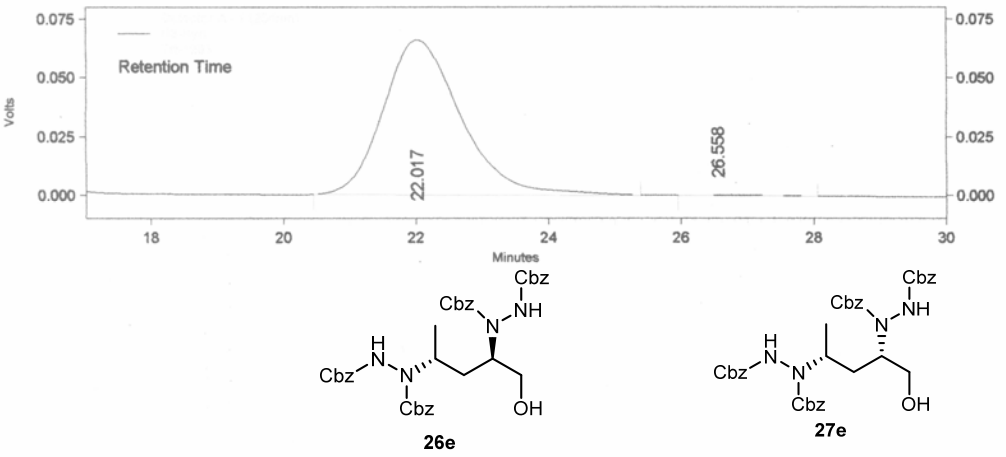
26d



27d

Detector A - 1 (254nm)

Retention Time	C Area	Area %
17.308	1664035	23.347
24.817	5463477	76.653
Totals	7127512	100.000

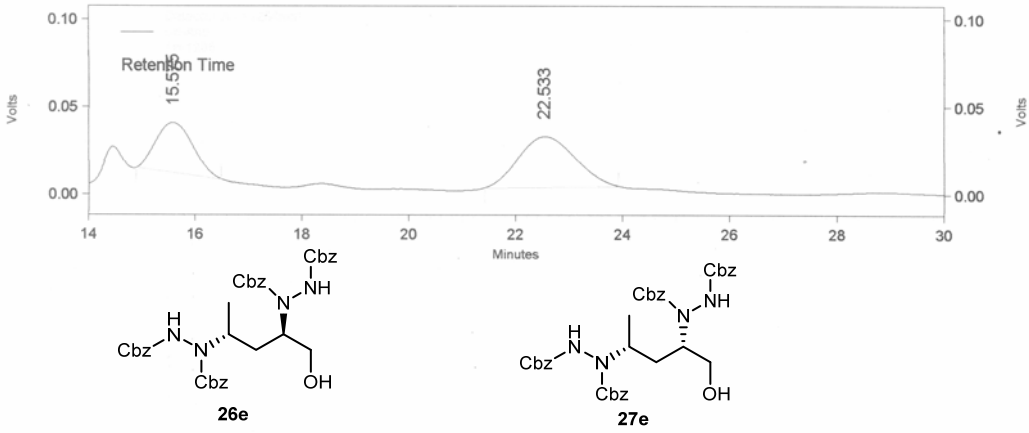


26e

27e

Detector A - 1 (254nm)

Retention Time	C Area	Area %
22.017	5335709	99.687
26.558	16727	0.313
Totals	5352436	100.000

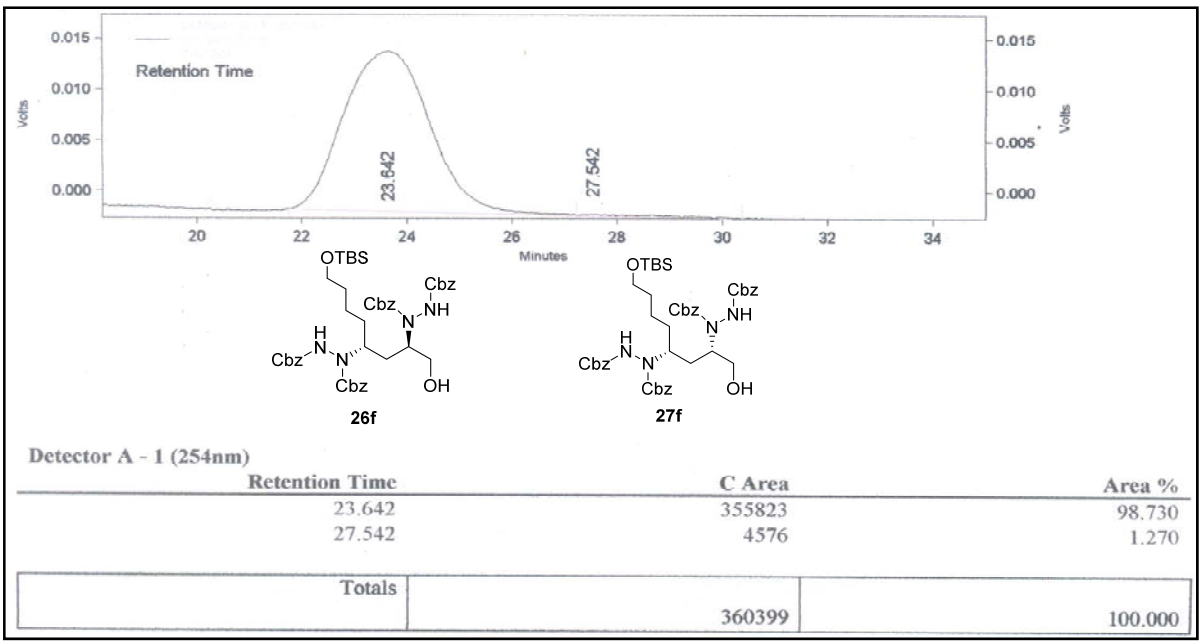


26e

27e

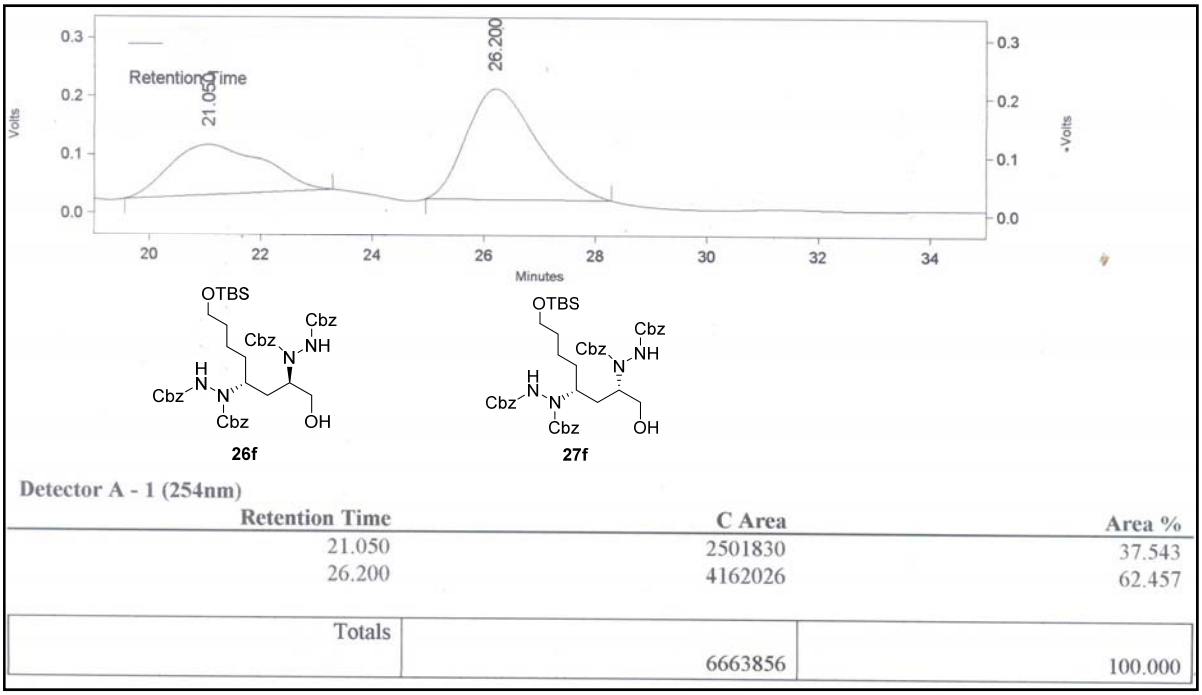
Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.575	459440	39.473
22.533	704509	60.527
Totals	1163949	100.000



Detector A - 1 (254nm)

Retention Time	C Area	Area %
23.642	355823	98.730
27.542	4576	1.270
Totals	360399	100.000



Detector A - 1 (254nm)

Retention Time	C Area	Area %
21.050	2501830	37.543
26.200	4162026	62.457
Totals	6663856	100.000

4.9. Reference

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Chapter-5

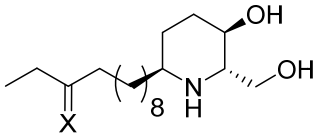
Enantioselective syntheses of 1,2-amino alcohols using Sharpless asymmetric dihydroxylation (AD) and proline-catalyzed reactions

5.1. SECTION A

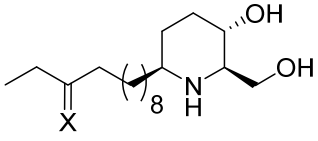
Stereoselective organocatalytic approach to 2,6-disubstituted piperidin-3-ol: A concise and protecting group free synthesis of (-)-Deoxoprosopinine and (+)-Deoxoprosophylline

5.1.1. Introduction

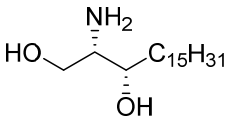
Naturally occurring alkaloids that contain multi-functionalized piperidine ring system as a key constituent are found abundantly in nature. Most of them exhibit potent biological activity and are of medicinal and pharmachological interest.[1] Among them, Prosopis alkaloids that were isolated from the leaves of *Prosopis afrikana* Taub,[2] exhibit antibiotic, anaesthetic, analgesic and CNS stimulating properties. Typical representatives include prosopinine **1**, prosophylline **2** and their deoxo analogues deoxoprosopinine **3**, deoxoprosophylline **4**, all containing 2,6-disubstituted piperidin-3-ol framework (Figure 1). The unique structural features of these alkaloids are known to resemble the cyclic structure of sphingolipids such as, safingol **5** and sphingosine **6** which contain a hydrophobic aliphatic tail and a hydrophilic headgroup.[3] The polar headgroup is required for glycosidase inhibition,[4] while the hydrophobic tail facilitates transfer across the lipid membrane thus, enhancing their therapeutic potential for the treatment of diseases such as diabetes, viral infection, and cancer.



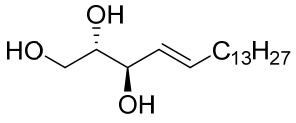
(-)-Prosopinine (**1**, X = O)
(-)-Deoxoprosopinine (**3**, X = H_2)



(+)-Prosophylline (**2**, X = O)
(+)-Deoxoprosophylline (**4**, X = H_2)



5
Safingol



6
Sphingosine

Figure **1**

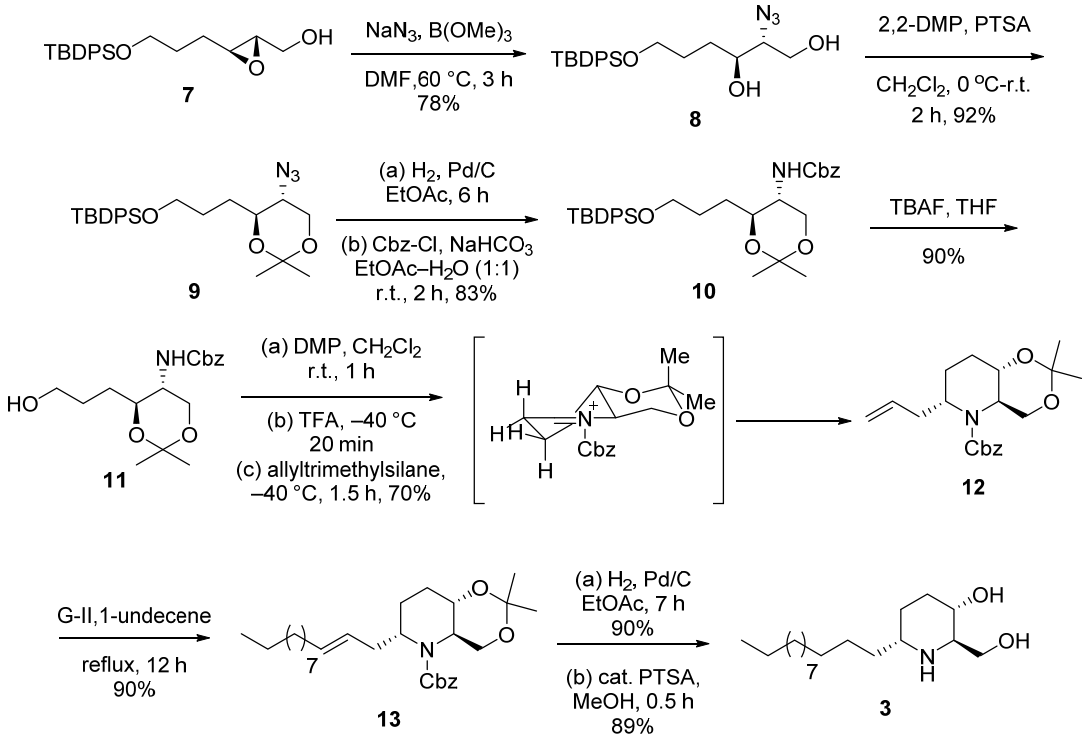
5.1.2. Review of Literature

The asymmetric synthesis of these alkaloids has aroused interest among synthetic organic chemists mainly due to their promising biological activities. This led to the designing of several synthetic strategies by various groups.[5,6] A detailed report of recent syntheses is described below.

A. Synthesis of deoxoprosopinine

Radha Krishna, P. *et al.* (2012)[5q]

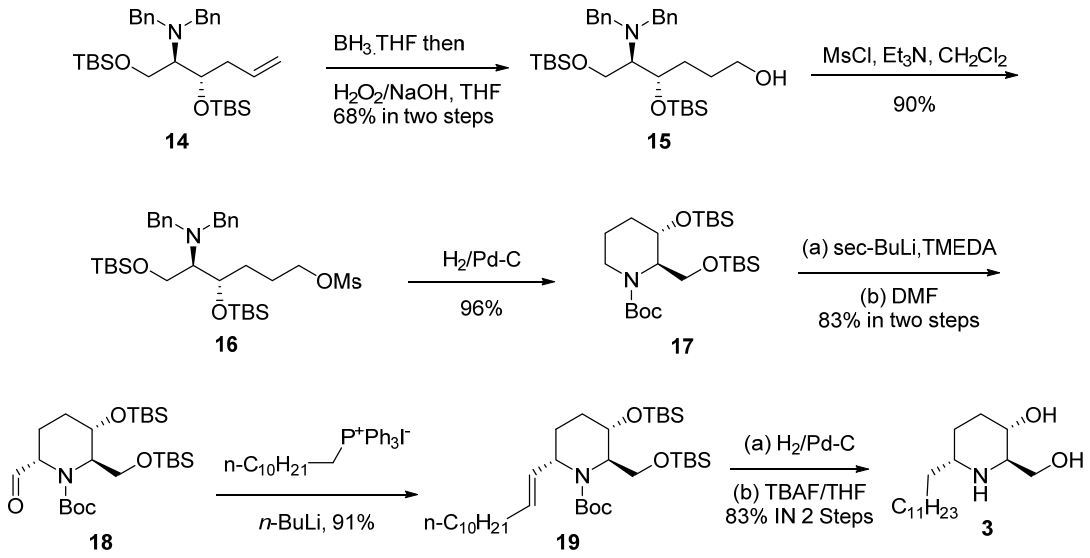
Radha Krishna and co-workers synthesized (+)-deoxoprosopinine starting from chiral epoxy alcohol **7**, which on regioselective ring-opening reaction from the C-2 position by the azide nucleophile, afforded **8** as the major isomer (C2/C3, 9:1). Diol **8** was protected as its acetonide derivative **9** by using 2,2-dimethoxypropane and catalytic PTSA in anhydrous CH_2Cl_2 and azide functionality was subsequently converted into its benzyl carbamate **10** by catalytic hydrogenation (H_2-Pd/C), followed by treatment of the resulting amine with benzyl chloroformate. The TBDPS group was then deprotected to afford the primary alcohol **11**, which was oxidized under Dess–Martin conditions to afford an aldehyde that, without further purification, on exposure to trifluoroacetic acid (TFA) at –40 °C for 20 min, was converted into the bicyclic *N*-acyl iminium ion in situ. The iminium ion thus formed was diastereoselectively trapped by a π-type nucleophile (allyltrimethylsilane) to afford allyl piperidine **12** as an exclusive *trans* adduct. The terminal olefin **11** was subjected to olefin cross-metathesis with 1-undecene under standard conditions [G-II catalyst (10 mol%), anhydrous CH_2Cl_2, reflux, 12 h] to afford **13**. Deprotection of the Cbz group and saturation of the double bond took place in one-pot through catalytic hydrogenation of **13**, to furnish acetonide-protected (+)-deoxoprosopinine which on treatment with catalytic amount of PTSA in methanol afforded (+)-deoxoprosopinine **3**.



Scheme 1. Synthesis of (+)-deoxoprosopinine (Radha Krishna method)

Arévalo-García, E. B. *et al.* (2008)[5p]

Arévalo-García and co-workers synthesized (+)-deoxoprosopinine starting from *N*-benzyl-*N*-Boc serine derivative **14**, which on hydroboration afforded alcohol **15**. Mesylation of alcohol **15** generated compound **16**, which on catalytic hydrogenation of the benzyl group in **16** produced an amine that displaced the mesyl group to yield **17**. Side chain at C-6 of **17** was introduced in two steps: first it was treated with *sec*-BuLi/TMEDA at -30 ^{o}C to generate carbanion followed by reaction of the carbanion with DMF at -78 ^{o}C to afford a mixture of aldehydes **18** in a 92:8 dr ratio. Aldehyde **18** was then rapidly reacted with the ylide generated in situ from undecyltriphenylphosphonium iodide and n-BuLi/THF at -78 ^{o}C to give compound **19**. Catalytic hydrogenation of product **19** followed by the cleavage of all protecting groups by TBAF/THF and HCl/MeOH gave (+)-deoxoprosopinine **3**.

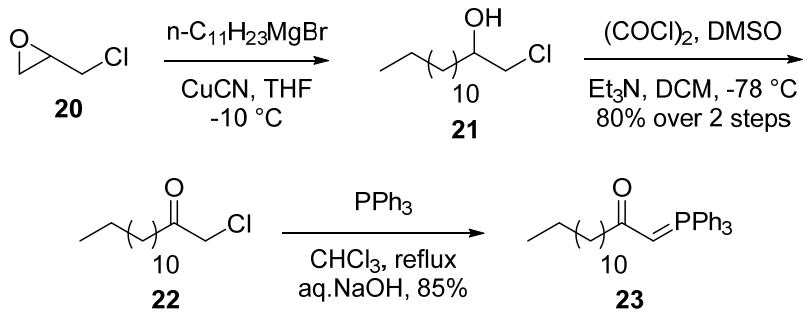


Scheme 2. Synthesis of (+)-deoxoprosopinine (Arévalo-García method)

B. Synthesis of deoxoprosophylline

Subba Reddy, B. V. *et al.* (2012)[6r]

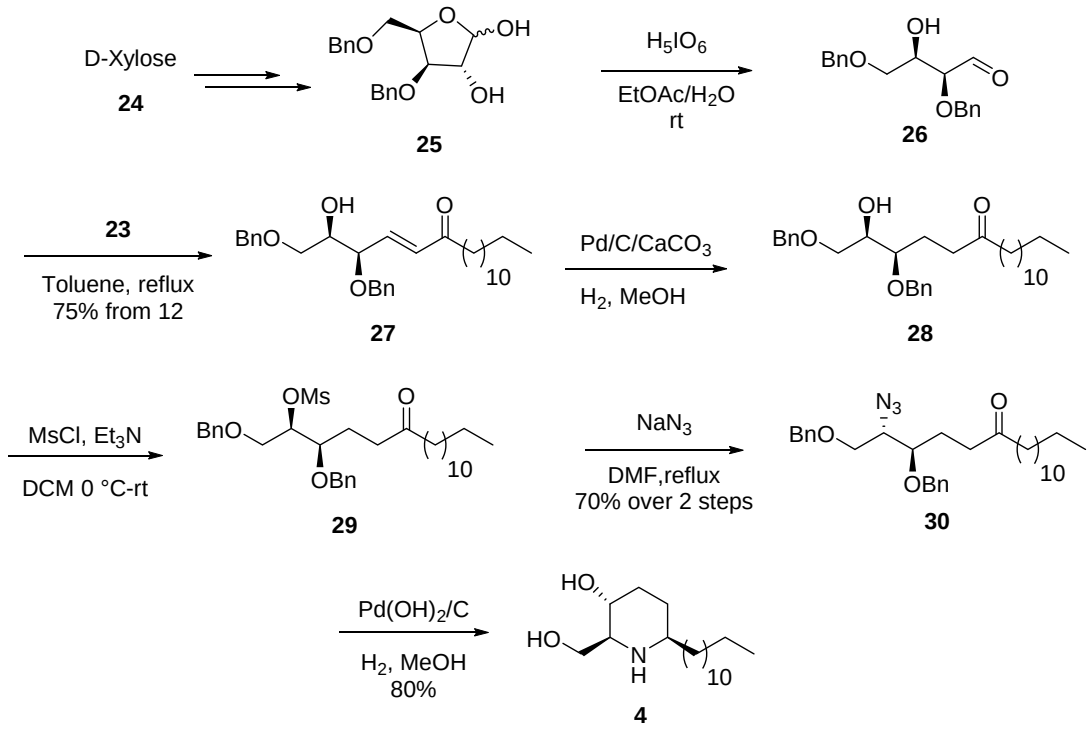
Subba Reddy and co-workers synthesized deoxoprosophylline starting from epichlorohydrin **20**, which on Grignard reaction with undecylmagnesium bromide provided 2-halo-1-terdecanol **21**. Swern oxidation of **21** gave chloroketone **22**, which on treatment with one equivalent of triphenylphosphine in chloroform under reflux conditions gave the Wittig salt which was then converted into a stable ylide **23** by treating with 20% NaOH solution (Scheme **3**).



Scheme 3. Preparation of a stable ylide **23**

The synthesis of other fragment began from D-xylose **24** which was converted into compound **25** using known procedures reported in the literature. Oxidative cleavage of **25** gave the hydroxy aldehydes **26**, which on Wittig olefination with ylide **23** in toluene

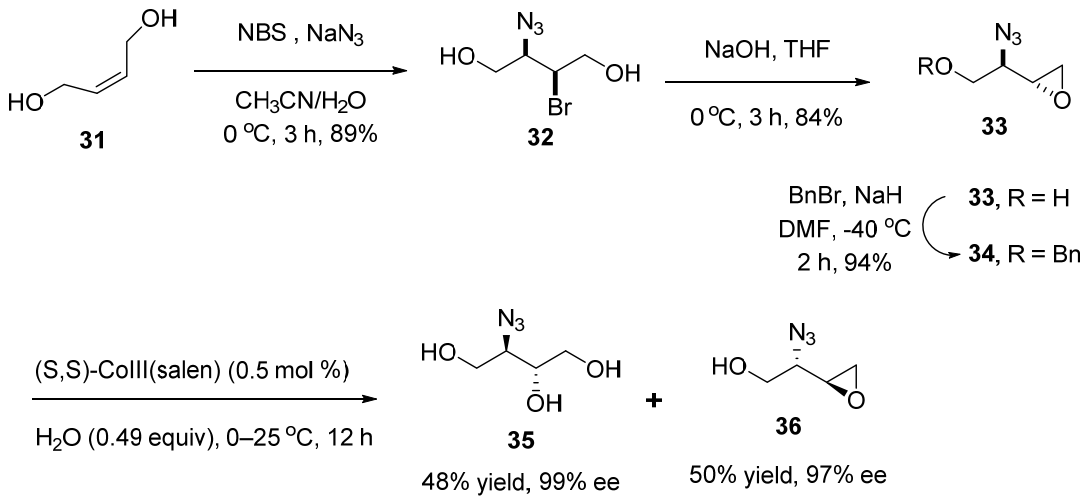
under reflux conditions gave the α,β-unsaturated ketone **27** with *trans*-selectivity. Reduction of olefin **27** with 10% $Pd/CaCO_3/C$ under hydrogen atmosphere in methanol gave the saturated ketone **28**. Mesylation of hydroxyl group of **28** with methanesulfonyl chloride in the presence of triethylamine followed by treatment with sodium azide under reflux conditions gave the corresponding azide **30**. Treatment of azide **30** with 10% $Pd(OH)_2/C$ under hydrogen atmosphere gave the enantiopure deoxoprosophylline **4**.



Scheme 4. Synthesis of (+)-deoxoprosophylline (Subba Reddy method)

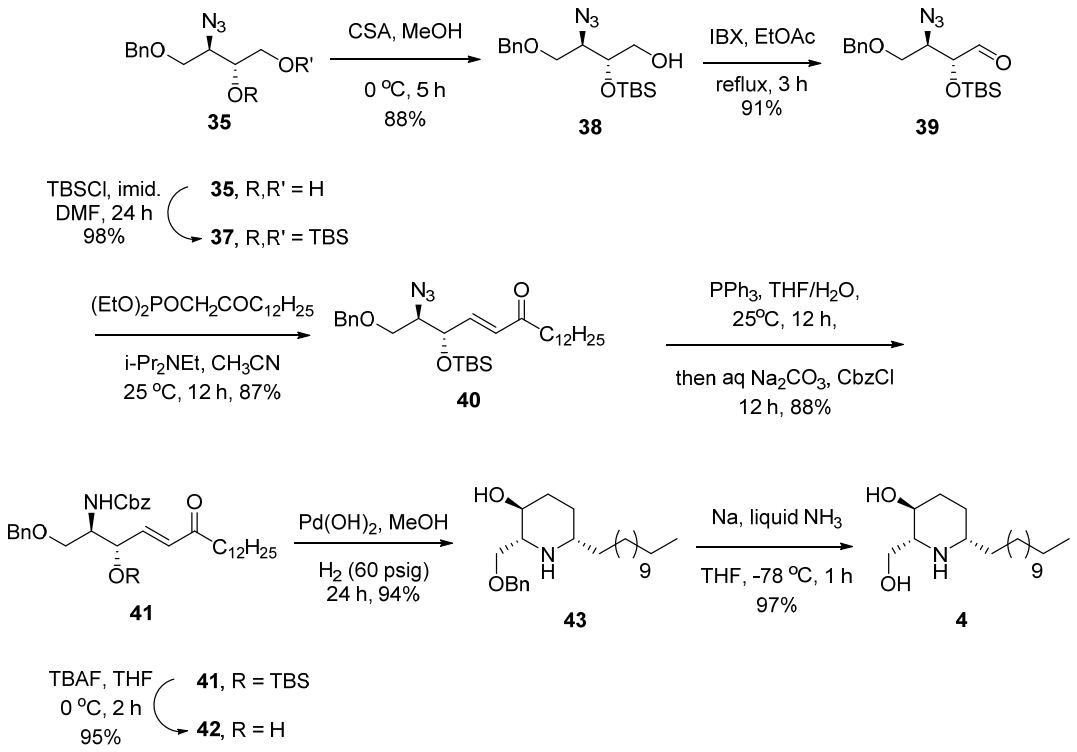
Sudalai, A. *et al.* (2012)[6q]

Sudalai and co-workers synthesized deoxoprosophylline starting from cis-2-butene-1,4-diol **31**, which on treatment with NBS in the presence of sodium azide, gave bromo azide **32**. The bromo azide **32** was readily transformed into racemic *anti*-azido epoxide **33** under basic conditions (NaOH, dry THF). The primary hydroxyl group in azido epoxide **33** was protected as benzyl ether **34** which on HKR with (*S*,*S*)-salen Co(OAc)complex (0.5 mol %) and H_2O (0.49 equiv), produced the corresponding diol **35** (48%, 99% ee) and chiral epoxide **36** (50%, 97% ee) in high optical purity (Scheme **5**). The diol **35** was, however, readily separated from epoxide **36** by a simple flash column chromatographic purification over silica gel.



Scheme 5. Synthesis of azido alcohol

Both the free hydroxyl groups in diol **35** was protected as its disilyl ether derivative **37**, followed by selective deprotection of primary silyl ether using CSA to afford monosilyl ether **38**. The primary hydroxyl group in **38** was oxidized using IBX to produce the corresponding aldehyde **39** which was then subjected to Wittig reaction with $(EtO)_2POCH_2COC_{12}H_{25}$ to give the corresponding (*E*)-unsaturated keto azide **40** with exclusive *trans* selectivity. Azide functionality in **40** was reduced using Staudinger conditions (PPh_3, THF/H_2O) and resulting free amine was in situ protected as its carbamate derivative **41**. Deprotection of silyl group in **41** gave amino ketone **42** which was subjected to intramolecular diastereoselective cyclization under catalytic hydrogenation conditions [$Pd(OH)_2$, MeOH, H_2 (60 psig)] to give **43** as a single diastereomer, without affecting the OBn group. Finally, O-debenzylation in **43** was carried out by Birch reduction to furnish (+)-deoxoprosophylline **4** (Scheme **6**).



Scheme 6. Synthesis of (+)-deoxoprosophylline (Sudalai method)

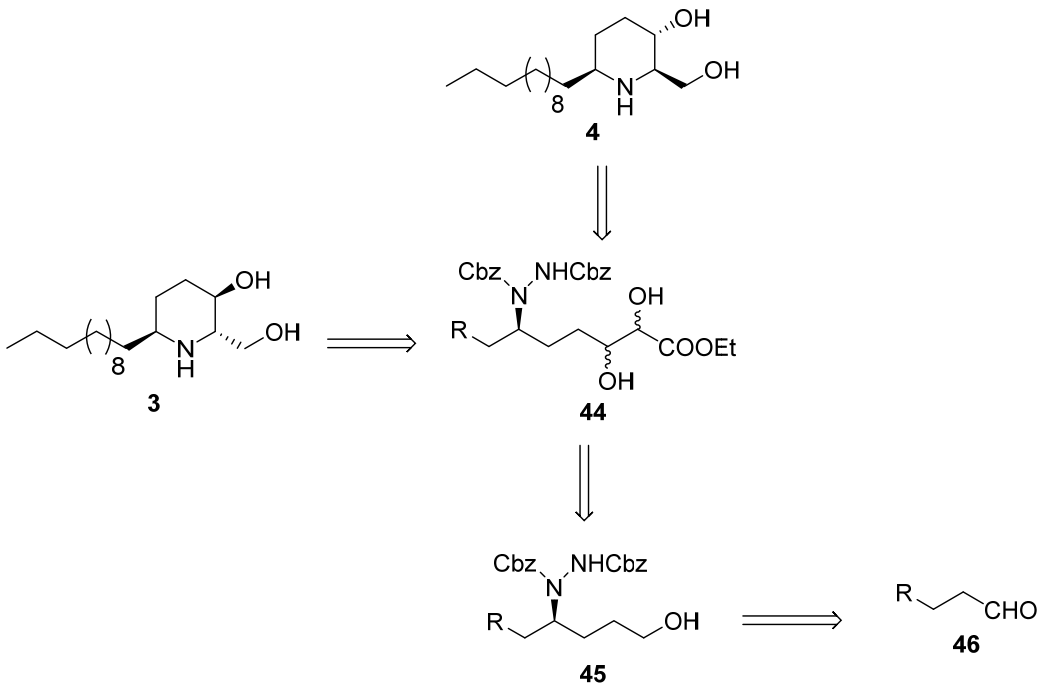
5.1.3. Present work

Objective

2,6-Disubstituted piperidin-3-ol piperidine framework has received considerable interest as synthetic target. Various syntheses of this class of compounds have been reported, the literature describing a general synthetic strategy to construct the 2,6-disubstituted piperidin-3-ols framework is rather scarce.[5m,p,7] Also majority of the syntheses of deoxoprosopinine and deoxoprosophylline employ chiral pool starting materials such as sugars and amino acids which involve large number of steps, protection-deprotection strategies resulting in lower overall yields. Therefore, it is highly desirable to develop a consise and general synthetic route that provides a common pivotal intermediate from which piperidin-3-ol derivatives with desired stereochemical variations can be synthesized.

5.1.4. Results and discussion

In continuation of our interest in organocatalysis and asymmetric synthesis of natural products, we herein describe a general, stereoselective and protecting group free synthetic strategy to 2,6-disubstituted piperidin-3-ols framework that has led to the total syntheses of (-)-deoxoprosopinine **3** and (+)-deoxoprosophylline **4** using sequential α-amination and HWE olefination reaction catalyzed by proline[8] and asymmetric dihydroxylation[9] as the key steps.

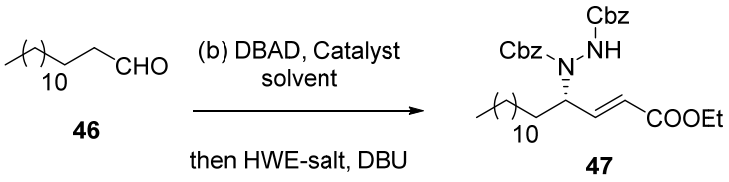


Scheme 7. Retrosynthetic route to the synthesis of 2,6-disubstituted piperidin-3-ols framework

Our synthetic approach was envisioned via the retrosynthetic route shown in the Scheme **7**. Amino diol **44** was thought to be common intermediate for the synthesis of compound **3** and **4**, which could be synthesized from alcohol **45**. Alcohol **45** could in turn be obtained from sequential α-aminoxylation and HWE olefination followed by reduction of aldehyde **46**.

Thus synthesis starts with long chain aldehyde **46**, which on sequential α-amination using DBAD as nitrogen source and D-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate furnished the γ-amino-α,β-unsaturated ester **47** (Scheme **8**). The α,β-

unsaturated ester **47** was obtained only in 7% yield presumably because of low solubility of long chain aldehydes in acetonitrile. To overcome the problem of low yield, we performed the reaction by varying the reaction conditions using different solvent and time; the results obtained are summarized in Table **1**. When the reaction was prolonged for 7 h, the yield increased slightly to 17%. There was slight change in the yield (19%), on further increasing the reaction time to 24 h. The use of DMF as solvent lowered the yield (Entry **4**). When $CHCl_3$ was used as co-solvent along with acetonitrile, the yield increased drastically to 53% (Entry **5**). The yield increased further to 72% by using $CHCl_3$ as solvent. However the best result was obtained when CH_2Cl_2 was used as solvent and desired product **47** was obtained in 81% yield (Entry **7**).



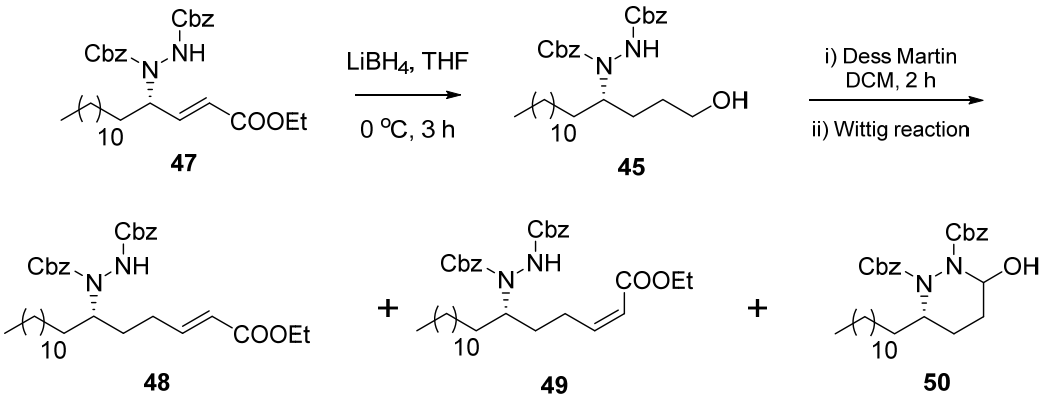
Scheme 8. Synthesis of γ-amino-α,β-unsaturated ester

Entry	Catalyst	Solvent	Time	Yield (%)
1	D-Proline	ACN	3 h	7
2			7 h	17
3			24 h	19
4		DMF	24 h	13
5		ACN + $CHCl_3$	7 h	53
6		$CHCl_3$	24 h	72
7		**CH_2Cl_2**	**24 h**	**81**

Table 1: Optimization of reaction conditions for α-amination of aldehyde **46**

Having obtained γ-amino-α,β-unsaturated esters **47** in hand, we next resorted to reduced the ester group. For this purpose ester **47** was treated with $LiBH_4$. However the ester group was reduced with concomitant rduction of double bond to get alcohol **45** in 92% yield (Scheme **9**). The disappearance of olefinic protons in the range of δ 5.90 as doublet

and 6.85 as dd in ^{1}H NMR spectrum confirmed the formation of the compound **45**. Alcohol **45** was oxidized using DMP to furnish aldehyde which was then subjected to HWE olefination (ylide generated from triethyl phosphonoacetate using *n*-BuLi as a base) in order to prepare *trans*-olefin **48**, but to our disappointment we got cyclized compound **50** as major product with desired *trans*-olefin **48** in only 18% yield. The disappearance of NH protons in the range of δ 6.41 as multiplate in ^{1}H NMR spectrum confirmed the formation of cyclized compound **50**. We then tried various other conditions for Wittig olefination and the results are summarized in Table **2**. There was no substantial increase in yield when different bases (such as NaH, DBU, Cs_2CO_3) were used to generate the ylide from triethyl phosphonoacetate. When (ethoxycarbonylmethylene)triphenylphosphorane was used as Wittig reagent in THF solvent, we got *trans*-olefin **48** in 46% yield alongwith *cis*-olefin **49** in 24% yield and cyclized product **50** in 14% yield (Entry **5**). To reduce the formation of *cis*-olefin **49**, reaction was carried out in toluene under reflux condition to get *trans*-olefin **48** in 67% yield with small amount of *cis*-olefin **49**.



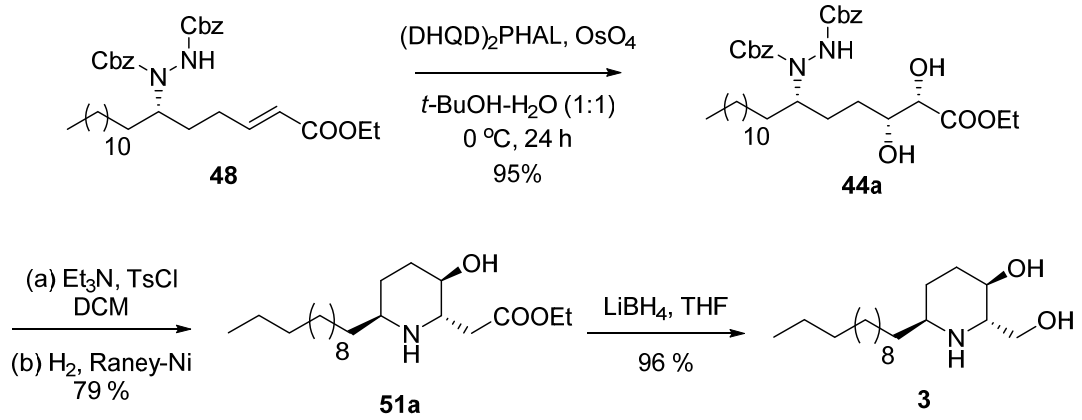
Scheme 9. Synthesis of α,β-unsaturated ester **48**

Entry	Wittig Reagent	Base	Solvent	48 (%)	49 (%)	50 (%)
1	HWE	n-BuLi	THF	18		65
2		NaH	THF	17		65
3		DBU	ACN	32		54
4		Cs_2CO_3	ACN	34		53

5	2-C Wittig	-	THF	46	24	14
6	**2-C Wittig**	**-**	**Toluene (reflux)**	**67**	**7**	**18**

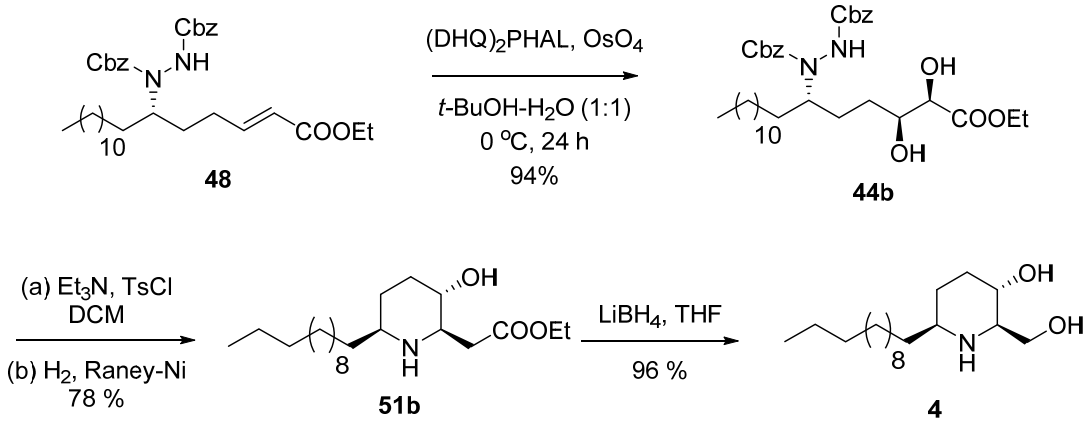
Table 2: Optimization Wittig reaction condition

With the desired *trans* olefin **48** in hand, the stage was set to functionalize the double bond. For this purpose, olefin **48** was subjected to Sharpless asymmetric dihydroxylation[12] condition using $(DHQD)_2PHAL$ as a ligand to get the diol **44a** in 95% yield and 98:2 dr ratio. The disappearance of olefinic protons in the range of δ 5.82 as multiplet and 6.94 as multiplet in ^1H NMR spectrum confirmed the formation of the compound **44a**. Regioselective monotosylation[10] of this diol **44a** with tosyl chloride (TsCl) resulted in the α-tosylate which on concomitant cleavage of N-N bond and nucleophilic displacement of α-tosylate on hydrogenation with Raney-Ni led to the cyclized product **51a** in 79% yield. Finally, reduction of **51a** with $LiBH_4$ produced (-)-deoxoprosopinine **3** in 96% yield (Scheme **10**).



Scheme 10. Synthesis of (-)-deoxoprosopinine

In a similar way, as illustrated in Scheme **11**, (+)-deoxoprosophylline **4** was synthesized using $(DHQ)_2PHAL$ as a ligand in the Sharpless asymmetric dihydroxylation step and following series of reactions analogous to those shown in Scheme **10**.



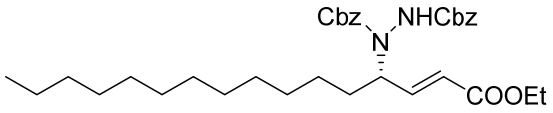
Scheme 11. Synthesis of (+)-deoxoprosophylline

5.1.5. Conclusion

In conclusion, a simple, highly efficient and protecting group free strategy to 2,6-disubstituted piperidin-3-ol has been developed employing α-amination and Sharpless asymmetric dihydroxylation as the key steps. Its usage is illustrated by the total synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for stereochemical variations at C-2, C-3 and C-6 positions and further extension to other stereoisomers, and analogues.

5.1.6. Experimental Section

Dibenzyl (*R*,*E*)-1-(1-ethoxy-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate (47):



To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.588 g, 1.97 mmol) and D-proline (0.028 g, 10 mol%) in CH_2Cl_2 (30 mL) at 0 °C was added aldehyde **46** (0.5 g, 2.4 mmol) and the mixture was stirred for 24 h at 0 °C and further for 6 h at 10 °C. This was followed by addition of lithium chloride (0.125 g, 2.95 mmol), triethyl phosphonoacetate (0.7 mL, 2.95 mmol) and DBU (0.3 mL, 1.97 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/ 90:10) of the crude product gave compound **47** (enantiomeric excess 99 %) as a colorless solid.

Yield: 1.108 g, 81%

Mol. Formula: $C_{34}H_{48}O_6N_2$

$[\alpha]_D^{25}$: - 11.93 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3294, 2981, 1717, 1498, 1219.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (m, 23H), 1.64-1.69 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.68-4.75 (m, 1H), 5.05-5.22 (m, 4H), 5.90 (d, *J* = 15.6 Hz, 1H), 6.39 (s, 1H), 6.85 (dd, *J* = 6.9, 15.8 Hz, 1H), 7.26-7.38 (m, 10H) ppm.

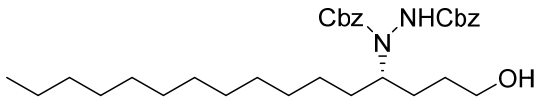
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.1, 22.6, 25.9, 29.3, 29.4, 29.6, 30.9, 31.9, 58.9, 60.5., 67.8, 68.3, 122.9, 127.9, 128.1, 128.2, 128.3, 128.5, 135.6, 144.9, 155.6, 156.7, 166.2 ppm.

MS (ESI): m/z 603.42 $(M+Na)^+$

HRMS 581.3586 $(M+H)^+$, calcd 581.3585; 603.3405 $(M+Na)^+$, calcd 603.3405

HPLC: Chiralcel OD-H (250 X 4.6mm) (2-propanol: Pet ether = 4:96, flow rate 0.5ml/min, λ= 220 nm). Retention time (min):18.592 (major) and 19.400 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 99%.

Dibenzyl (*S*)-1-(1-hydroxyhexadecan-4-yl)hydrazine-1,2-dicarboxylate (45):



To a solution of ethyl ester **47** (0.600 g, 1.04 mmol) in THF (8 ml), was added $LiBH_4$ (0.045 g, 2.08 mmol) at 0 ^oC. The reaction was mixture was stirred at 0 ^oC for 3 h. It was then quenched with aq. ammonium chloride solution (1 mL) 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 crude product. Silica gel column chromatography (petroleum ether: ethyl acetate/ 7:3) of the crude product gave **45** as a colorless solid.

Yield: 0.514 g, 92%

Mol. Formula: $C_{32}H_{48}O_5N_2$

$[\alpha]_D^{25}$: - 17.46 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 3285, 2927, 1709, 1454, 1221, 1057.

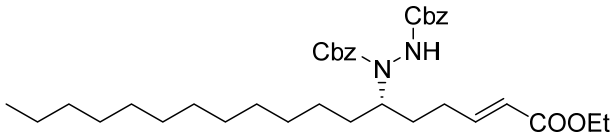
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.25 (m, 22H), 1.30-1.53 (m, 4H), 3.31-3.74 (m, 2H), 3.96-4.24 (m, 1H), 5.13-5.18 (m, 4H), 6.41 (s, 1H), 7.26-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 26.5, 28.6, 29.3, 29.4, 29.6, 31.9, 32.7, 62.4, 64.7, 67.9, 127.7, 128.2, 128.5, 128.6, 135.5, 156.2, 157.3 ppm.

MS (ESI): m/z 563.18 $(M+Na)^+$

HRMS 541.3638 $(M+H)^+$, calcd 541.3636; 563.3452 $(M+Na)^+$, calcd 563.3455

Dibenzyl (*S*,*E*)-1-(1-ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (48):



To a solution of alcohol **45** (0.5 g, 0.93 mmol) in DCM (8 ml) was added DMP (0.780 g, 1.9 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 2 hr. It was then quenched with a 1:1 mixture of (10 %) aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and extracted with diethyl ether (3 X 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (0.860 g, 2.47 mmol) in dry toluene (10 mL) was added a solution of the above aldehyde in dry toluene (5 mL). The reaction mixture was stirred at 110 ^oC (under reflux) for 12 h. It was then concentrated and purified by flash silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **49** as a waxy white solid (0.040 g, 7%). Continued chromatography with (EtOAc/petroleum ether, 1:9) gave olefin **48** as a waxy white solid (0.407 g, 67%). Further chromatography with (EtOAc/petroleum ether, 1:8) gave cyclized product **50** as waxy solid (0.090 g, 18%).

Mol. Formula: $C_{36}H_{52}O_6N_2$

$[\alpha]_D^{25}$: + 1.96 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3311, 2923, 1717, 1464, 1263.

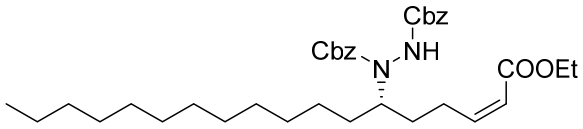
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H), 1.26 (m, 23H), 1.42-1.67 (m, 4H), 2.02-2.45 (m, 2H), 4.04-4.22 (m, 3H), 5.02-5.22 (m, 4H), 5.82-5.85 (m, 1H), 6.33-6.47 (m, 1H), 6.94 (m, 1H), 7.26-7.32 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 26.4, 29.1, 29.2, 29.3, 29.5, 29.6, 30.9, 31.9, 32.3, 32.5, 33.7, 58.5, 60.1., 67.8, 68.3, 121.4, 127.9, 128.1, 128.2, 128.5, 128.6, 135.5, 135.7, 135.9, 148.5, 156.5, 156.8, 166.6 ppm.

MS (ESI): m/z 631.15 $(M+Na)^+$

HRMS 609.3896 $(M+H)^+$, calcd 609.3898; 631.3712 $(M+Na)^+$, calcd 631.3718

Dibenzyl (*S*,*Z*)-1-(1-ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (49):



Mol. Formula: $C_{36}H_{52}O_6N_2$

$[\alpha]_D^{25}$: + 2.85 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3311, 2923, 1717, 1464, 1263.

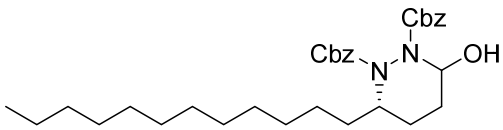
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H), 1.26 (m, 23H), 1.42-1.67 (m, 4H), 2.02-2.45 (m, 2H), 4.04-4.22 (m, 3H), 5.02-5.22 (m, 4H), 5.82-5.85 (m, 1H), 6.33-6.47 (m, 1H), 6.94 (m, 1H), 7.26-7.32 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 26.4, 29.1, 29.2, 29.3, 29.5, 29.6, 30.9, 31.9, 32.3, 32.5, 33.7, 58.5, 60.1., 67.8, 68.3, 121.4, 127.9, 128.1, 128.2, 128.5, 128.6, 135.5, 135.7, 135.9, 148.5, 156.5, 156.8, 166.6 ppm.

MS (ESI): m/z 631.15 $(M+Na)^+$

HRMS 609.3896 $(M+H)^+$, calcd 609.3898; 631.3712 $(M+Na)^+$, calcd 631.3718

Dibenzyl (3*S*)-3-dodecyl-6-hydroxytetrahydropyridazine-1,2-dicarboxylate (50):



Mol. Formula: $C_{32}H_{46}O_5N_2$

$[\alpha]_D^{25}$: - 6.18 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3448, 2932, 1719, 1450, 1232, 1054.

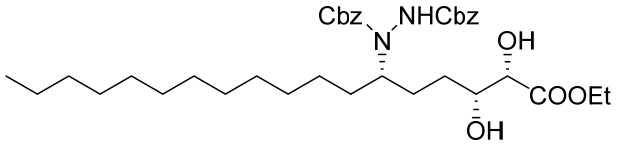
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6.6 Hz, 3H), 1.16-1.26 (m, 19H), 1.49-1.69 (m, 5H), 1.90-2.11 (m, 2H), 4.12-4.28 (m, 1H), 4.98-5.28 (m, 4H), 5.53-5.56 (m, 1H), 7.27-7.37 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 23.3, 25.7, 26.2, 29.3, 29.5, 29.6, 31.9, 32.7, 54.6, 67.7, 67.8, 68.1, 127.6, 127.9, 128.0, 128.2, 128.5, 128.6, 135.6, 135.8, 136.1, 156.4, 156.6 ppm.

MS (ESI): m/z 561.01 $(M+Na)^+$.

HRMS: 561.3299 $(M+Na)^+$, calcd 561.3299

Dibenzyl 1-((2*S*,3*R*,6*S*)-1-ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl)hydrazine-1,2-dicarboxylate (44a):



To a mixture of $K_3Fe(CN)_6$ (1.10 g, 3.28 mmol), K_2CO_3 (0.455 g, 3.28 mmol), $(DHQD)_2PHAL$ (10 mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 20 mL) at 0 °C was added osmium tetroxide (0.05 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (0.104 g, 1.09 mmol). After stirring for 5 min at 0 °C, the olefin **48** (0.660 g, 1.09 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2.0 g). The 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 (petroleum ether: EtOAc / 4:6) of the crude product gave **44a** as a white solid.

Yield: 0.63 g, 95%

Mol. Formula: $C_{36}H_{54}N_2O_8$

$[\alpha]_D^{25}$: + 9.78 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3018, 1717, 1452, 1218.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6.4 Hz, 3H), 1.26-1.43 (m, 25H), 1.53-1.72 (m, 4H), 2.28 (brs, 2H), 3.57-3.71 (m, 1H), 3.85-3.96 (m, 1H), 4.28 (q, J = 6.4 Hz, 2H), 4.52-4.64 (m, 1H), 5.12-5.26 (m, 4H), 6.68-6.96 (m, 1H), 7.30-7.37 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.8, 29.2, 29.5, 29.6, 29.8, 31.4, 31.8, 35.5, 51.1, 61.8., 66.4, 72.3, 73.4, 74.3, 127.9, 128.3, 128.5 128.6, 130.9, 134.9, 135.4, 135.7, 156.0, 156.2, 173.4 ppm.

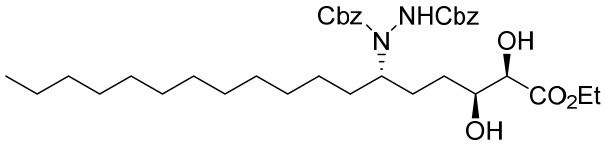
MS (ESI): m/z 665.07 $(M+Na)^+$

Diastereomeric ratio was determined by HPLC analysis; 98:2 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH = 100; t_R for (*anti*)-isomer = 4.63 min and t_R for (*syn*)- isomer = 4.25 min.

Dibenzyl 1-((2*R*,3*S*,6*S*)-1-ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl)hydrazine-1,2-dicarboxylate (44b):



Yield: 0.63 g, 95%

Mol. Formula: $C_{36}H_{54}N_2O_8$

$[\alpha]_D^{25}$: - 12.38 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3018, 1717, 1452, 1218.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6.8 Hz, 3H), 1.26-1.42 (m, 26H), 1.59-1.78 (m, 3H), 2.42 (brs, 2H), 3.62-3.91 (m, 2H), 4.28 (q, J = 6.8 Hz, 2H), 4.52-4.66 (m, 1H), 5.11-5.18 (m, 4H), 6.72-6.82 (m, 1H), 7.26-7.36 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.8, 29.2, 29.5, 29.6, 31.8, 35.4, 51.2, 61.7., 66.5, 72.7, 73.4, 74.4, 127.9, 128.3, 128.5 128.6, 130.8, 134.8, 135.3, 135.5, 156.7, 157.1, 173.3 ppm.

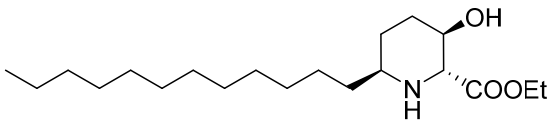
MS (ESI): m/z 665.07 $(M+Na)^+$.

Diastereomeric ratio was determined by HPLC analysis; 9:1 dr

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL/min, MeOH = 100; t_R for (*anti*)-isomer = 4.63 min and t_R for (*syn*)- isomer = 4.24 min.

(2*S*,3*S*,6*S*)-Ethyl 6-dodecyl-3-hydroxypiperidine-2-carboxylate (51a):



To a one-neck round-bottomed flask were added the diol ester **44a** (780 mg, 1.18 mmol), dry CH_2Cl_2 (10 mL) and Et_3N (178 mg, 0.25 mL, 1.76 mmol). The flask was placed in an ice water bath and allowed to equilibrate for 10-30 min, at which time the *p*-toluene sulfonyl chloride (224 mg, 1.18 mmol) was added in one portion using a solid addition funnel. The flask was fitted with a serum cap and placed in a refrigerator (5 ^oC) for 72 h. The mixture was then concentrated to afford a paste, which was dissolved in Et_2O. The organic phase was washed three times with a 1 N aqueous HCl solution, once with a saturated aqueous $NaHCO_3$ solution, and once with brine, dried over Na_2SO_4, and concentrated to afford the crude tosyl compound which was directly used in the next step without further purification.

The solution of crude tosyl compound in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated. The residue was purified by flash column chromatography on silica gel (MeOH: CH_2Cl_2/ 1:9) to give compound **51a**.

Yield: 235 mg, 79%

Mol. Formula: $C_{20}H_{39}NO_3$

M.P. : 96 ^oC

$[\alpha]_D^{25}$: + 5.65 (*c* 0.60, $CHCl_3$).

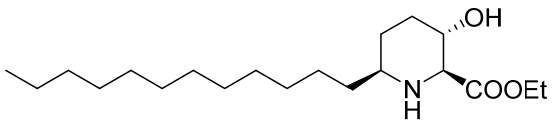
IR ($CHCl_3$, cm^{-1}): ν_{max} 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.26-1.33 (m, 26H), 1.43-1.56 (m, 2H), 1.60-1.70 (m, 1H), 1.72-1.81 (m, 1H), 2.13 (brs, 1H), 2.68-2.76 (m, 1H), 3.58 (d, *J* = 4.0 Hz, 1H), 4.15-4.16 (m, 1H), 4.22 (q, *J* = 6.6 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.2, 22.6, 25.7, 26.1, 28.0, 29.3, 29.5, 29.6, 31.8, 35.8, 51.6, 60.8, 61.5, 65.5, 172.2 ppm.

MS (ESI): m/z 342.21 $(M+H)^+$

Ethyl (2S,3S,6S)-6-dodecyl-3-hydroxypiperidine-2-carboxylate (51b):



Yield: 232 mg, 78%

M.P. : 92 ^{o}C

Mol. Formula: $C_{20}H_{39}NO_3$

$[\alpha]_D^{25}$: +2.47 (*c* 0.60, $CHCl_3$)

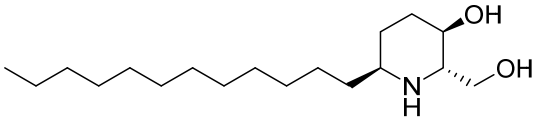
IR ($CHCl_3$, cm^{-1}): ν_{max} 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.26-1.36 (m, 27H), 1.68-1.79 (td, *J* = 3.27 Hz, 12.79 Hz, 1H), 1.99-2.24 (m, 2H), 2.45-2.65 (m, 2H), 3.17 (d, *J* = 9.0 Hz, 1H), 3.63-3.75 (m, 1H), 4.26 (dq, *J* = 3.3 Hz, 7.2 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.9, 29.2, 29.4, 29.5, 29.6, 30.6, 31.8, 32.3, 36.3, 55.9, 61.3, 64.6, 69.2, 172.6 ppm.

MS (ESI): m/z 342.21 $(M+H)^+$

(-)-Deoxoprosopinine (3):



A suspension of $LiBH_4$ (10 mg, 1.10 mmol) in anhydrous THF (10 mL) was stirred for 5 min at 0 °C, and a solution of **51a** (65 mg, 0.73 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 1 h at room temperature. Excess $LiBH_4$ was destroyed by slow addition of aq. NH_4Cl solution and EtOAc (5 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 x 15 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (MeOH: CH_2Cl_2/ 2:8) to give **3** as a colourless solid

Yield: 55 mg, 96%

Mol. Formula: $C_{18}H_{37}NO_2$

M.P. : 90 ^{o}C, [Lit.[5a] 89.5-90 ^{o}C]

$[\alpha]_D^{25}$: -15. 81 (*c* 0.30, $CHCl_3$), [Lit[5a] $[\alpha]_D^{25}$: -14.7 (*c* 0.30, $CHCl_3$).]

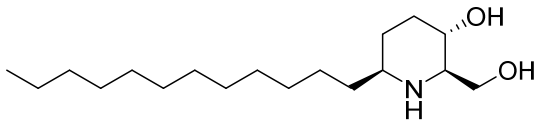
IR ($CHCl_3$, cm^{-1}): ν_{max} 3267, 2922, 2852, 1639, 1465, 1376.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 (m, 24H), 1.38-1.50 (m, 2H), 1.53-1.60 (m, 2H), 1.66-1.77 (m, 2H), 2.66 (brs, 3 H), 2.79-2.92 (m, 1H), 2.86 (q, *J* = 5.59 Hz, 12.73 Hz, 1H), 3.51-3.59 (m, 1H), 3.61-3.73 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.4, 27.0, 28.3, 29.3, 29.6, 29.7, 31.9, 33.3, 50.2, 57.9, 62.1, 67.8 ppm.

MS (ESI): m/z 300 $(M+H)^+$

(+)-Deoxosoprosophylline (4):



Yield: 55 mg, 96%

Mol. Formula: $C_{18}H_{37}NO_2$

M.P. : 84 ^oC, [Lit.[6g] 85-86 ^oC]

$[\alpha]_D^{25}$: + 13.86 (*c* 0.22, $CHCl_3$), [Lit.[6g] $[\alpha]_D^{25}$: + 12.50 (*c* 0.22, $CHCl_3$)].

IR ($CHCl_3$, cm^{-1}): ν_{max} 3267, 2922, 2852, 1639, 1465, 1376.

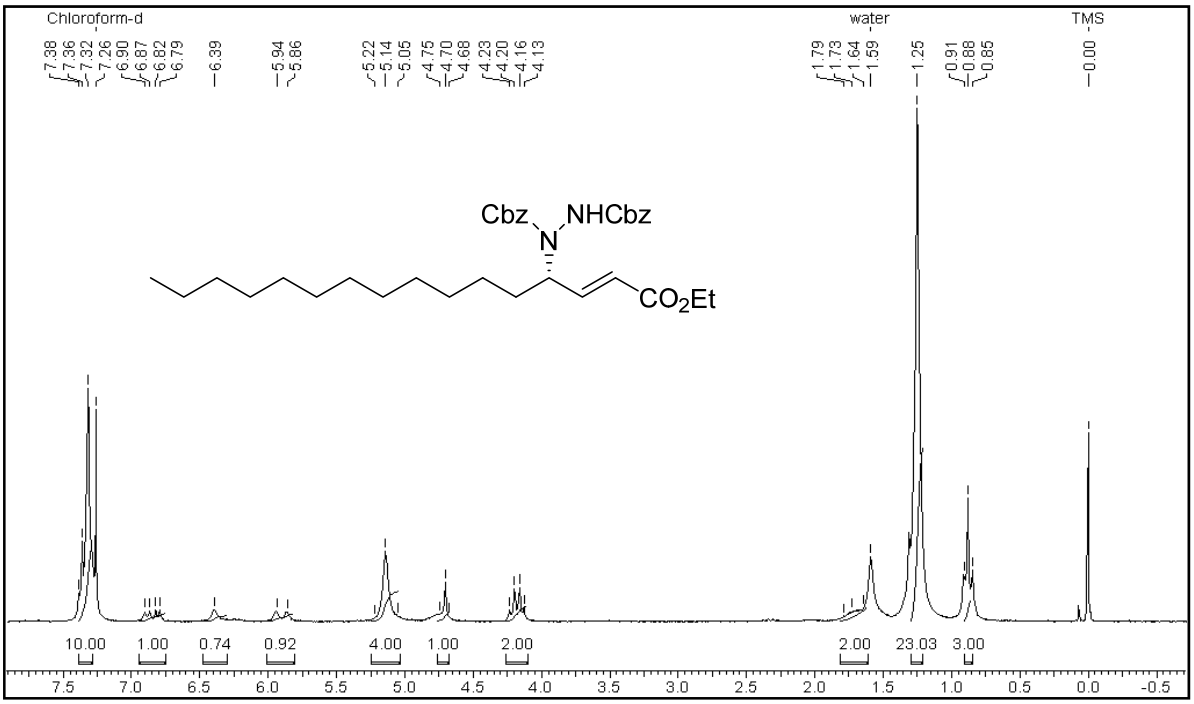
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.23-1.30 (m, 22H), 1.39-1.51 (m, 2H), 1.77-1.85 (m, 1H), 2.03-2.09 (m, 1H), 2.58-2.66 (m, 2H), 3.33 (brs, 3H), 3.54-3.63 (m, 1H), 3.84-3.85 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.1, 29.3, 29.6, 29.7, 29.9, 31.9, 33.3, 35.5, 56.4, 62.2, 63.4, 68.2 ppm.

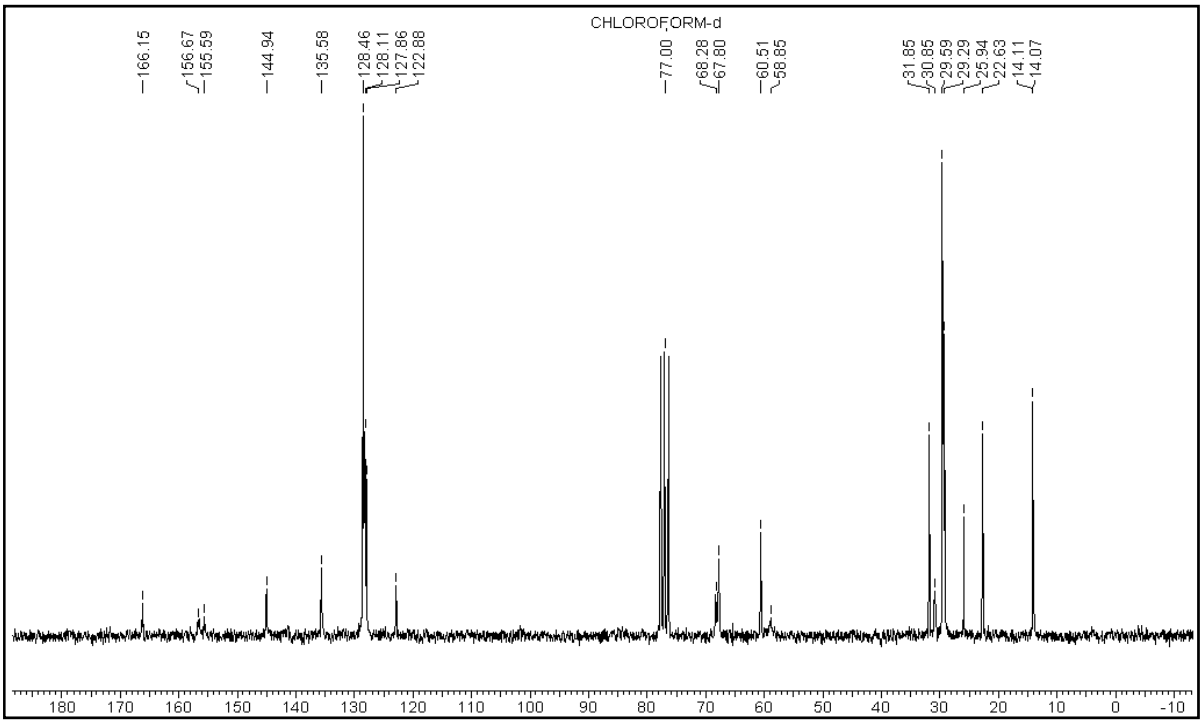
MS (ESI): m/z 300 $(M+H)^+$

5.1.7. Spectra

Dibenzyl (R,E)-1-(1-ethoxy-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate (47):

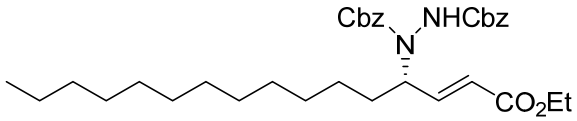


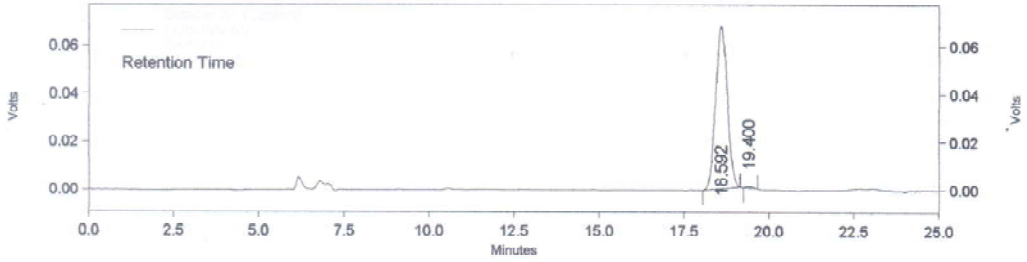
➢ **^{1}H NMR of the compound 47 in $CDCl_3$**



➢ **^{13}C NMR of the compound 47 in $CDCl_3$**

Enantiomeric excess:

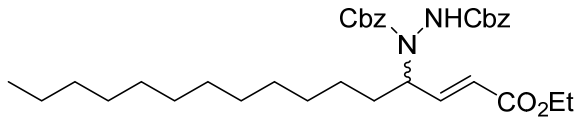


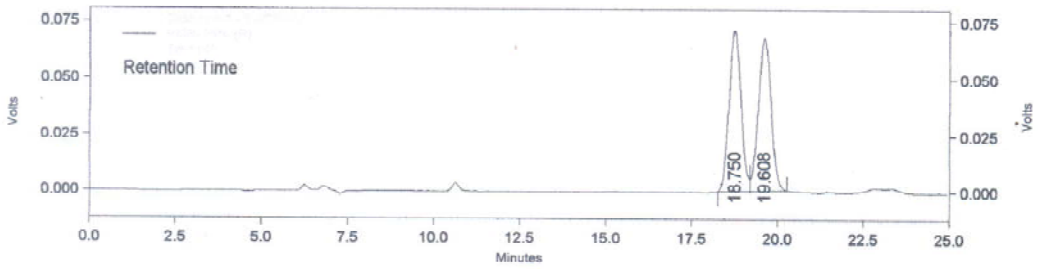


Detector A - 1 (220nm)

Retention Time	C Area	Area %
18.592	1625161	99.404
19.400	9749	0.596
Totals	1634910	100.000

Project Leader : Dr. P. K. Tripathi
Column :Chiralcel OD-H (250 x4.6mm)
Mobile Phase :IPA:Petether (04:96)
Wavelength : 220 nm
Flow Rate :0.5 ml/min
Conc. :1 mg/ 2.0 ml
Inj vol- :5ul.



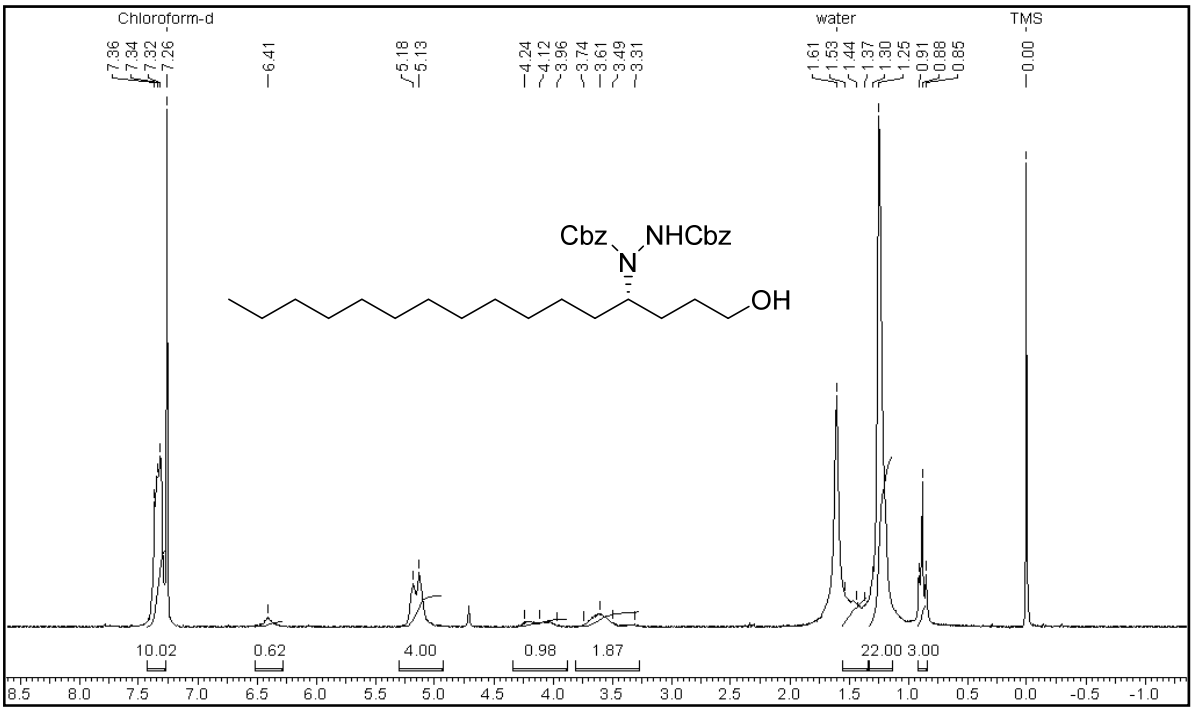


Detector A - 1 (220nm)

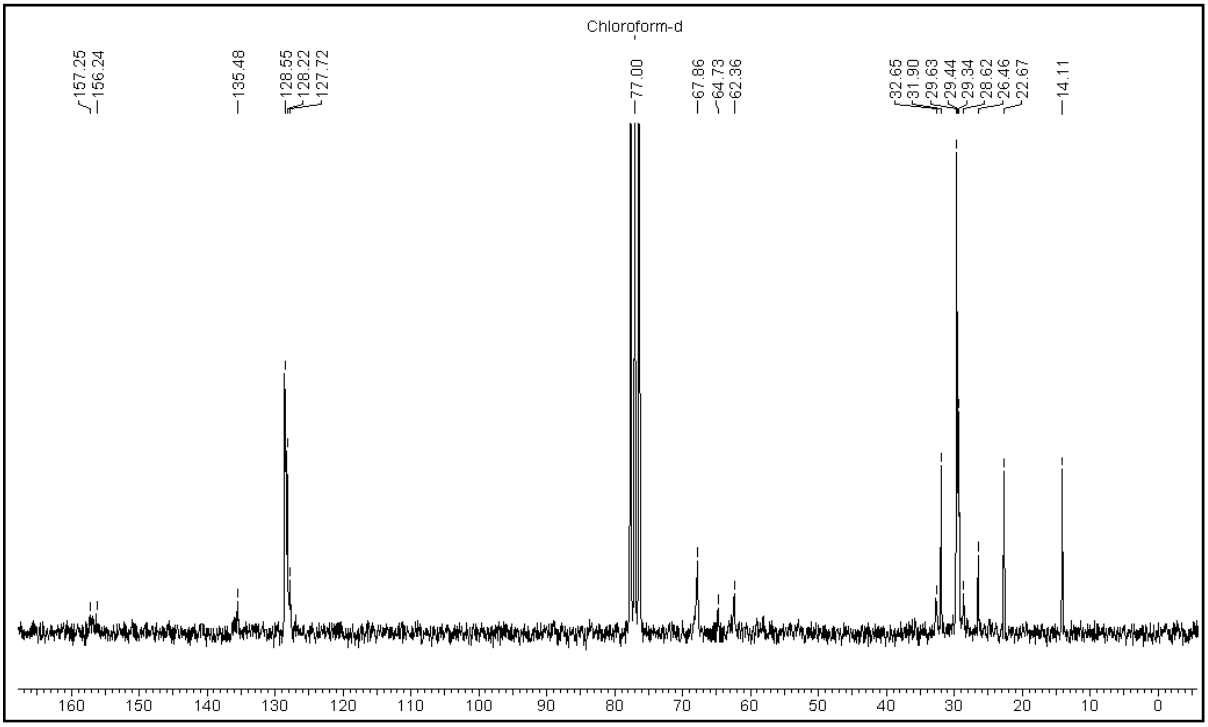
Retention Time	C Area	Area %
18.750	1739438	49.910
19.608	1745728	50.090
Totals	3485166	100.000

Project Leader : Dr. P. K. Tripathi
Column :Chiralcel OD-H (250 x4.6mm)
Mobile Phase :IPA:Petether (04:96)
Wavelength : 220 nm
Flow Rate :0.5 ml/min
Conc. :1 mg/ 2.0 ml
Inj vol- :5ul.

Dibenzyl (S)-1-(1-hydroxyhexadecan-4-yl)hydrazine-1,2-dicarboxylate (45):

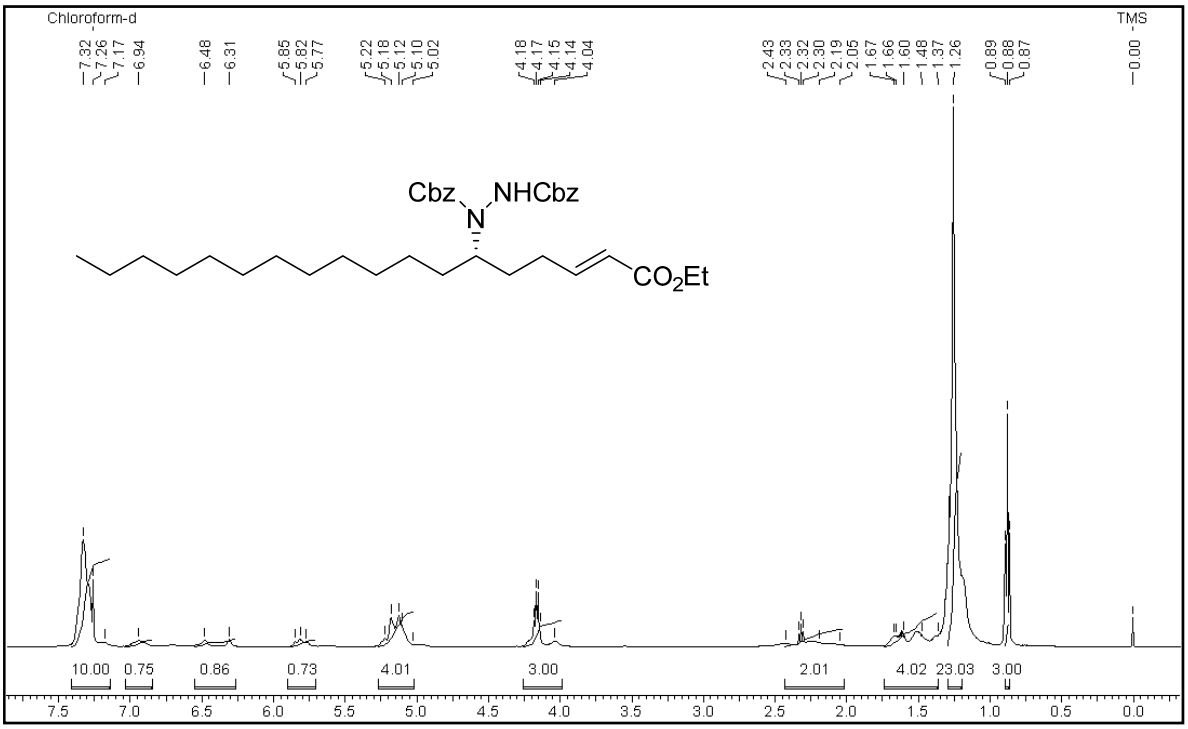


➢ **^{1}H NMR of the compound 45 in $CDCl_3$**

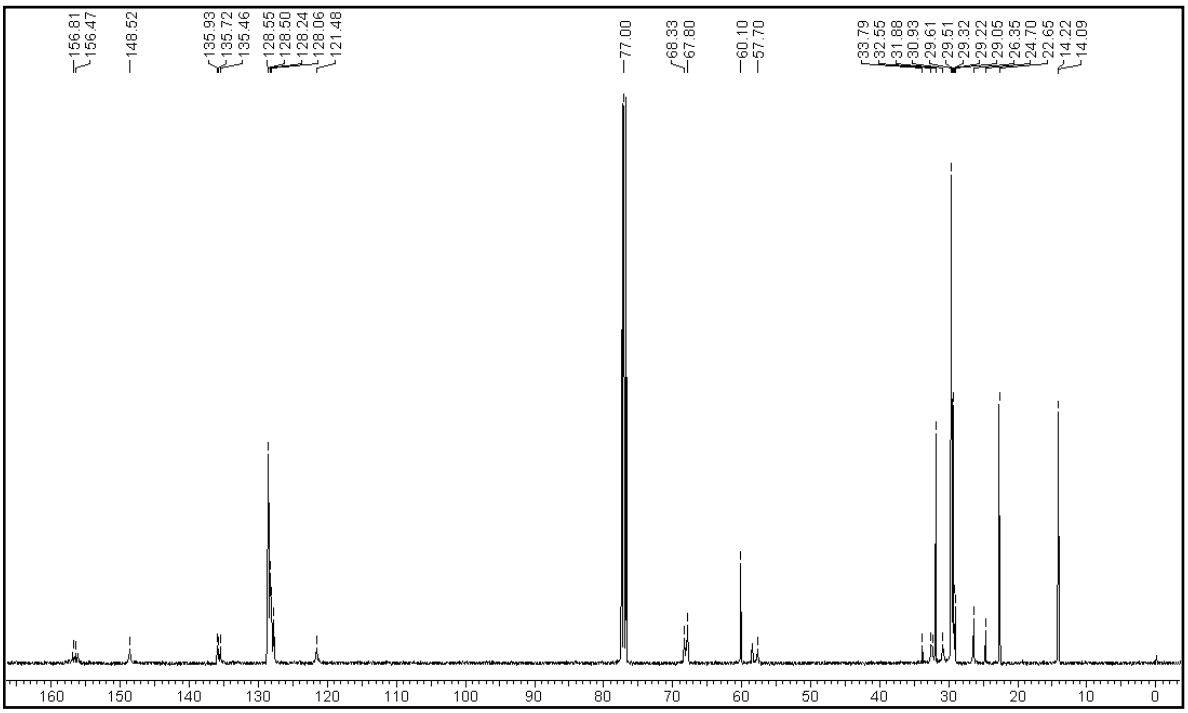


➢ **^{13}C NMR of the compound 45 in $CDCl_3$**

Dibenzyl (S,E)-1-(1-ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (48):

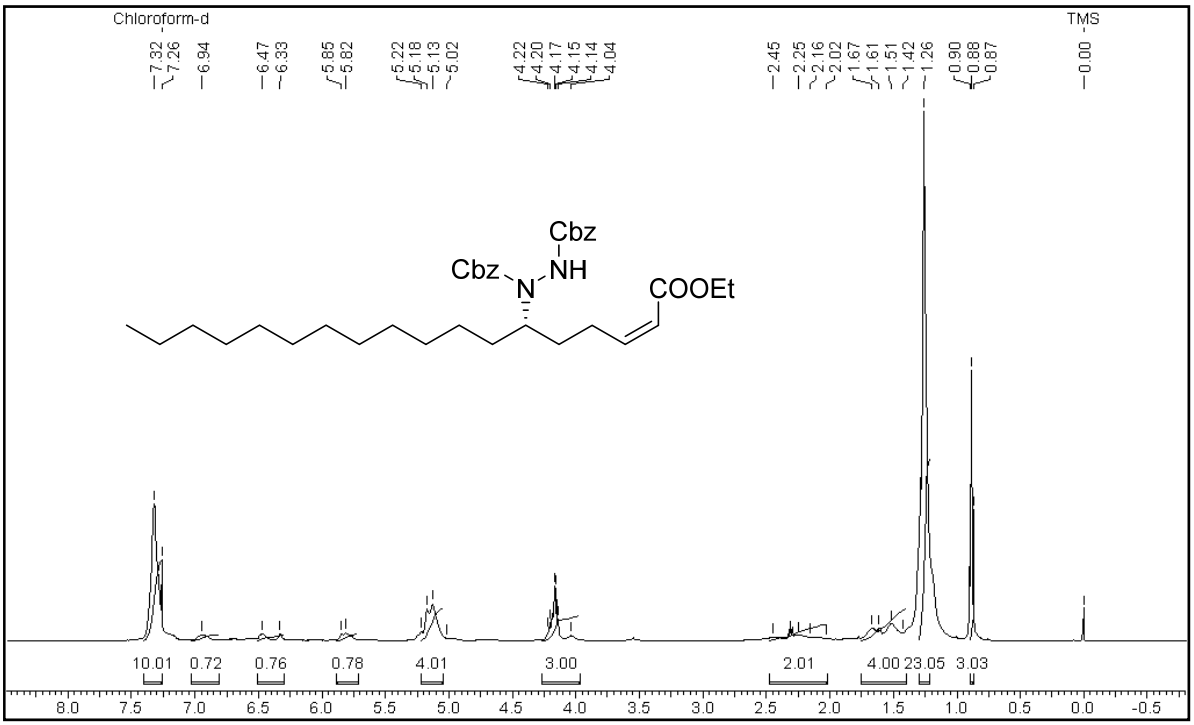


- **^{1}H NMR of the compound 48 in $CDCl_3$**

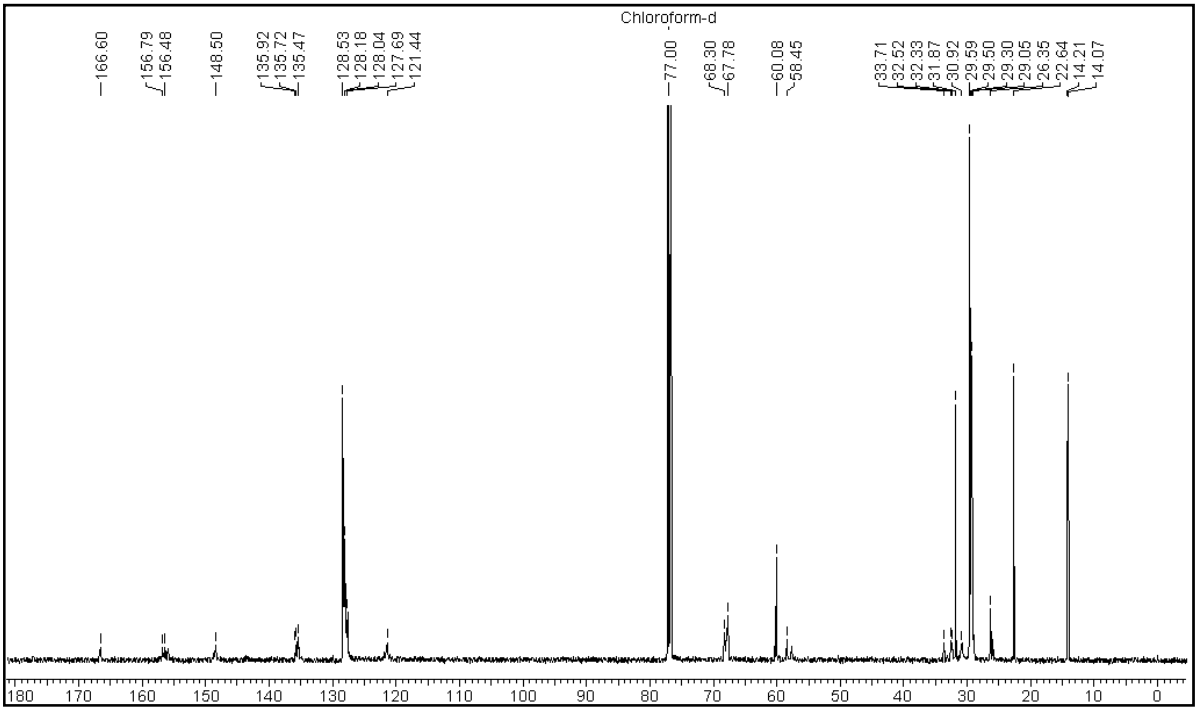


- **^{13}C NMR of the compound 48 in $CDCl_3$**

Dibenzyl (S,Z)-1-(1-ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (49):

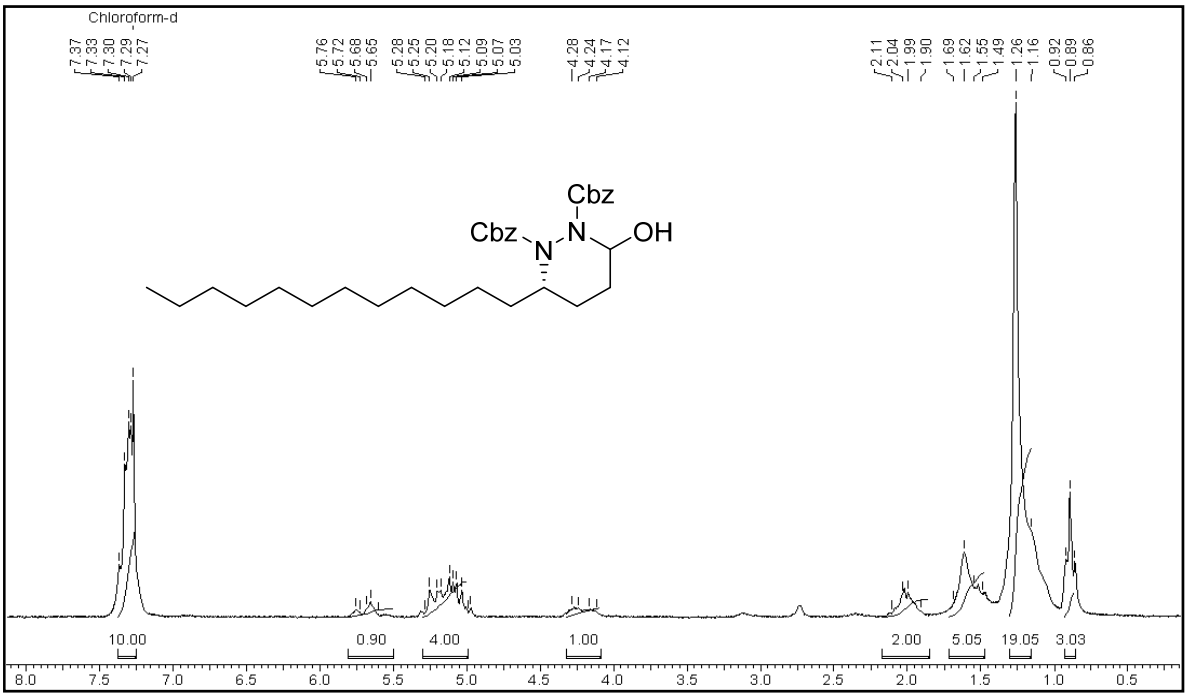


- **^{1}H NMR of the compound 49 in $CDCl_3$**

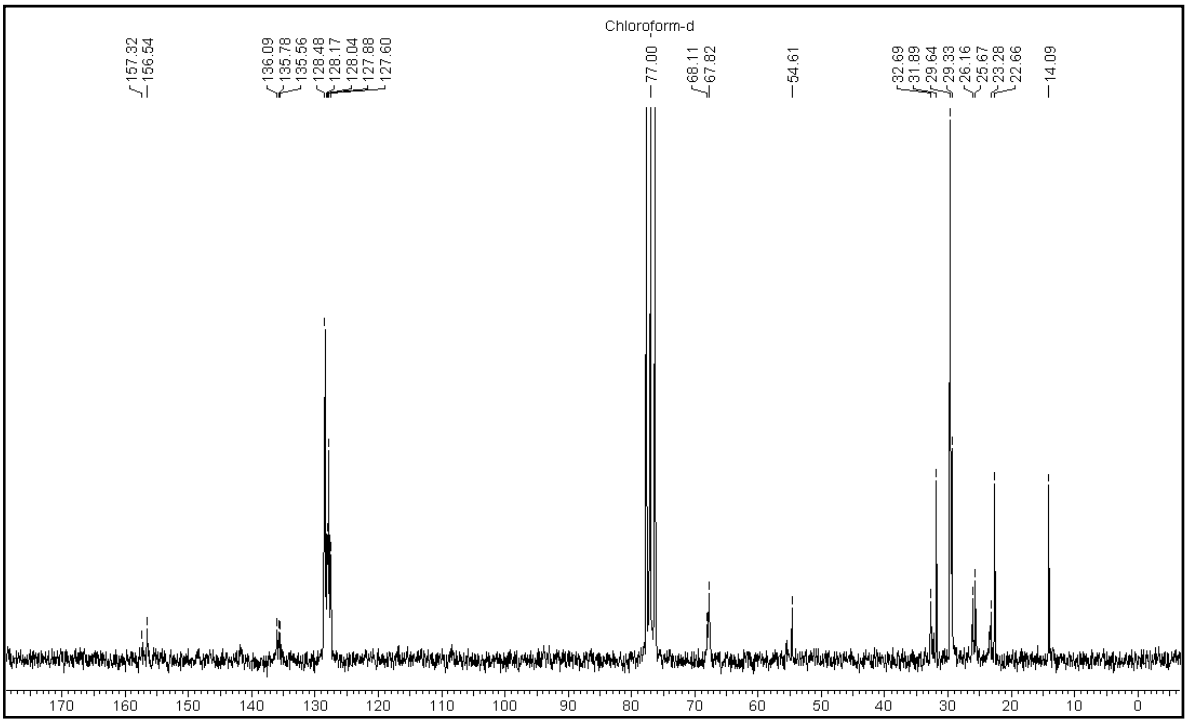


- **^{13}C NMR of the compound 49 in $CDCl_3$**

Dibenzyl (3S)-3-dodecyl-6-hydroxytetrahydropyridazine-1,2-dicarboxylate (50):

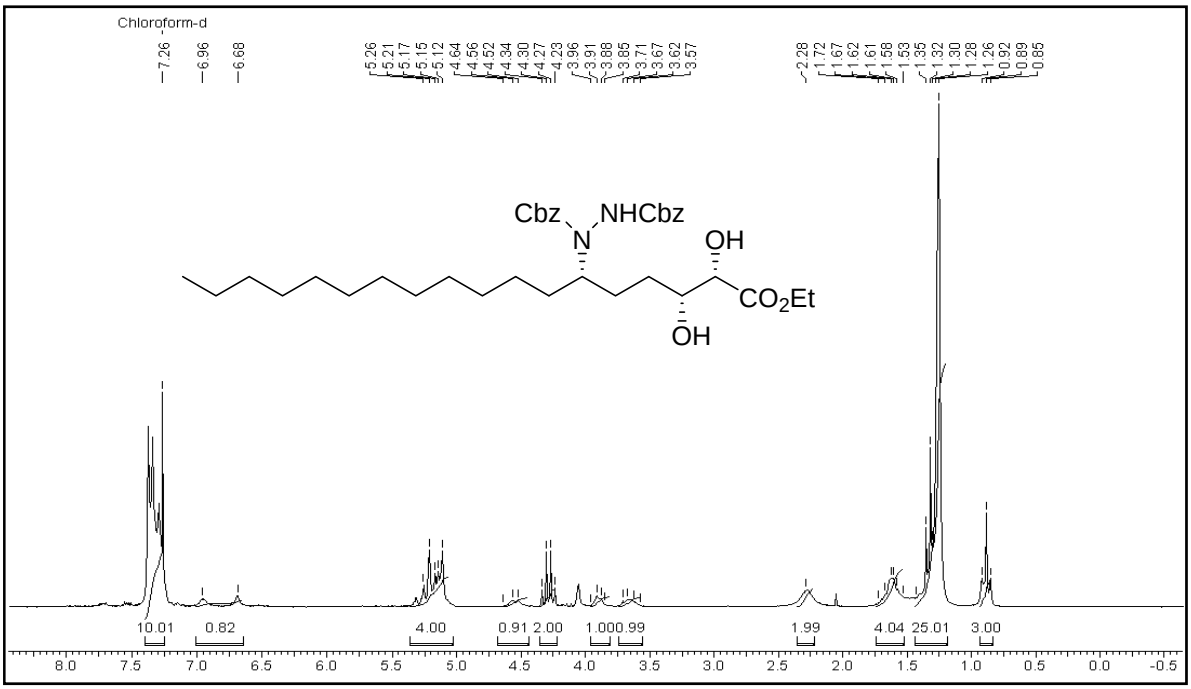


➢ **^{1}H NMR of the compound 50 in $CDCl_3$**

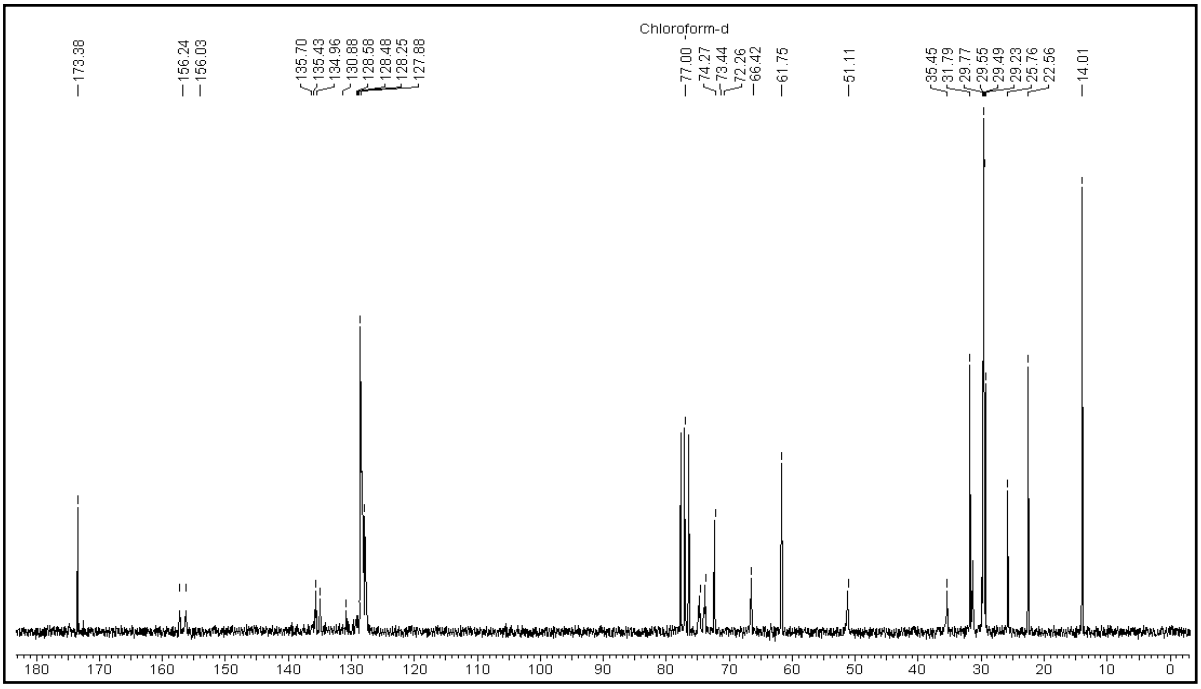


➢ **^{13}C NMR of the compound 50 in $CDCl_3$**

Dibenzyl 1-((2*S*,3*R*,6*S*)-1-ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl)hydrazine-1,2-dicarboxylate (44a):

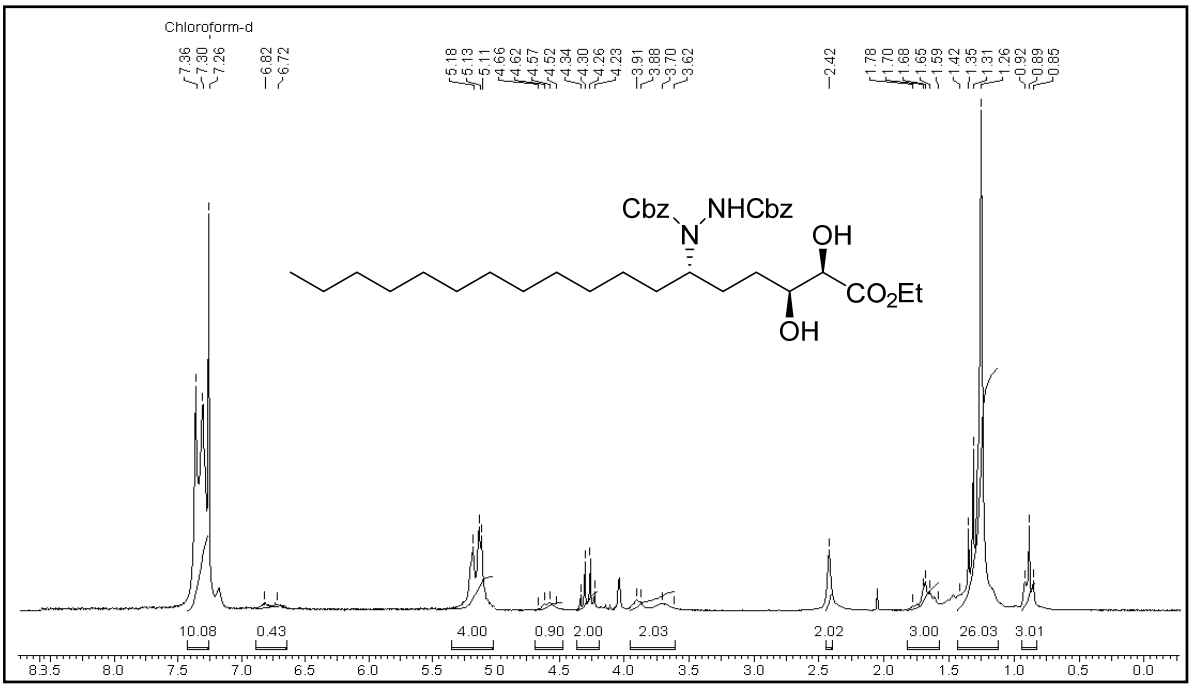


- **^{1}H NMR of the compound 44a in $CDCl_3$**

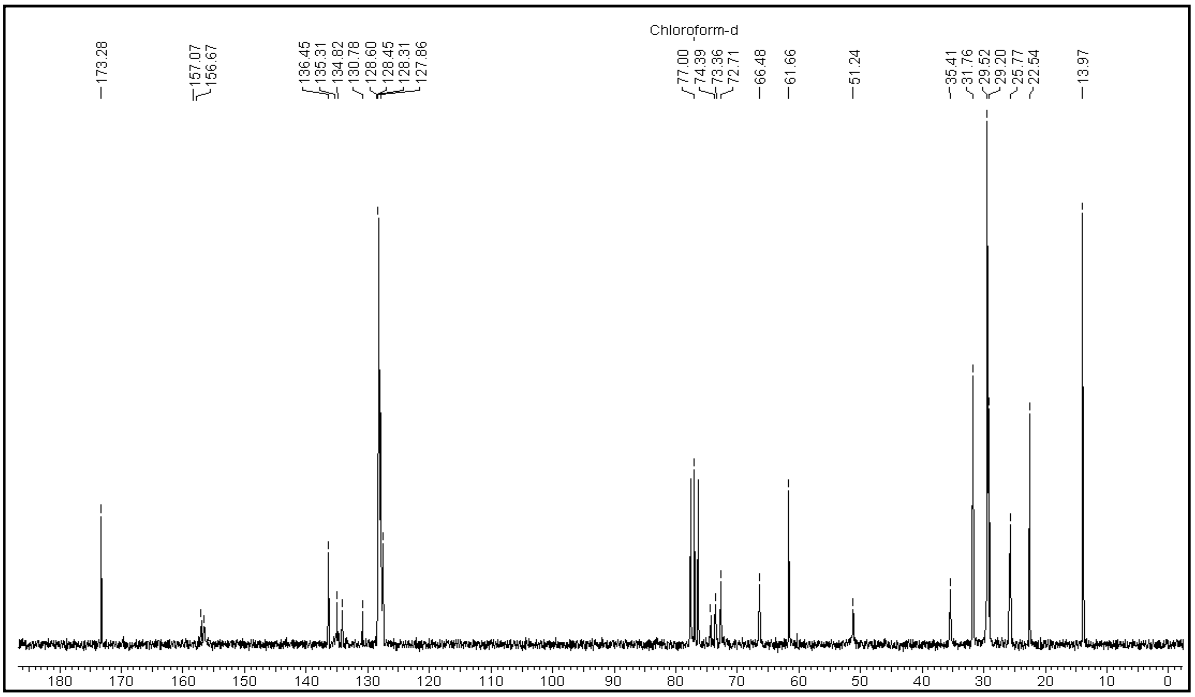


- **^{13}C NMR of the compound 44a in $CDCl_3$**

Dibenzyl 1-((2*R*,3*S*,6*S*)-1-ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl)hydrazine-1,2-dicarboxylate (44b):



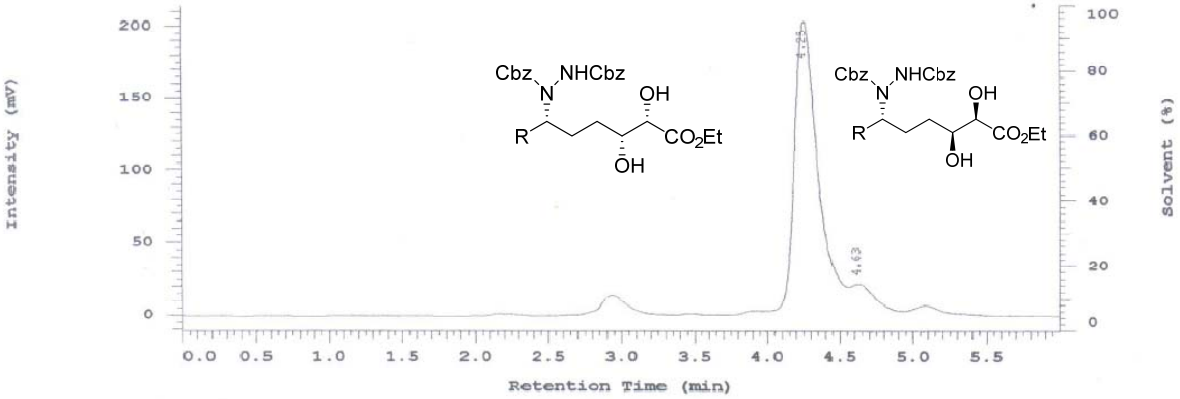
- **^{1}H NMR of the compound 44b in $CDCl_3$**



- **^{13}C NMR of the compound 44b in $CDCl_3$**

Diastereomeric ratio:

Chrom Type: HPLC Channel : 1



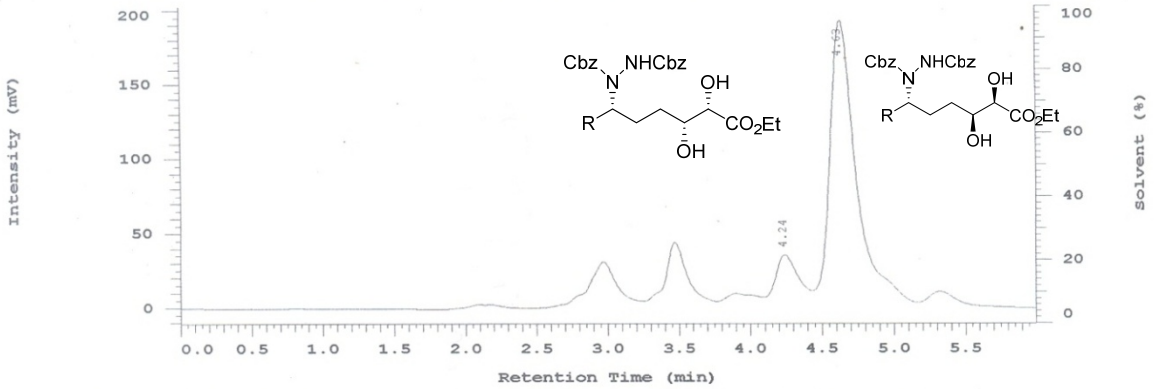
Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	4.25	198953	2314758	97.903
2	4.63	5722	49577	2.097
		204675	2364335	100.000

Peak rejection level: 0

Volume: 10.0 ul

Chrom Type: HPLC Channel : 1

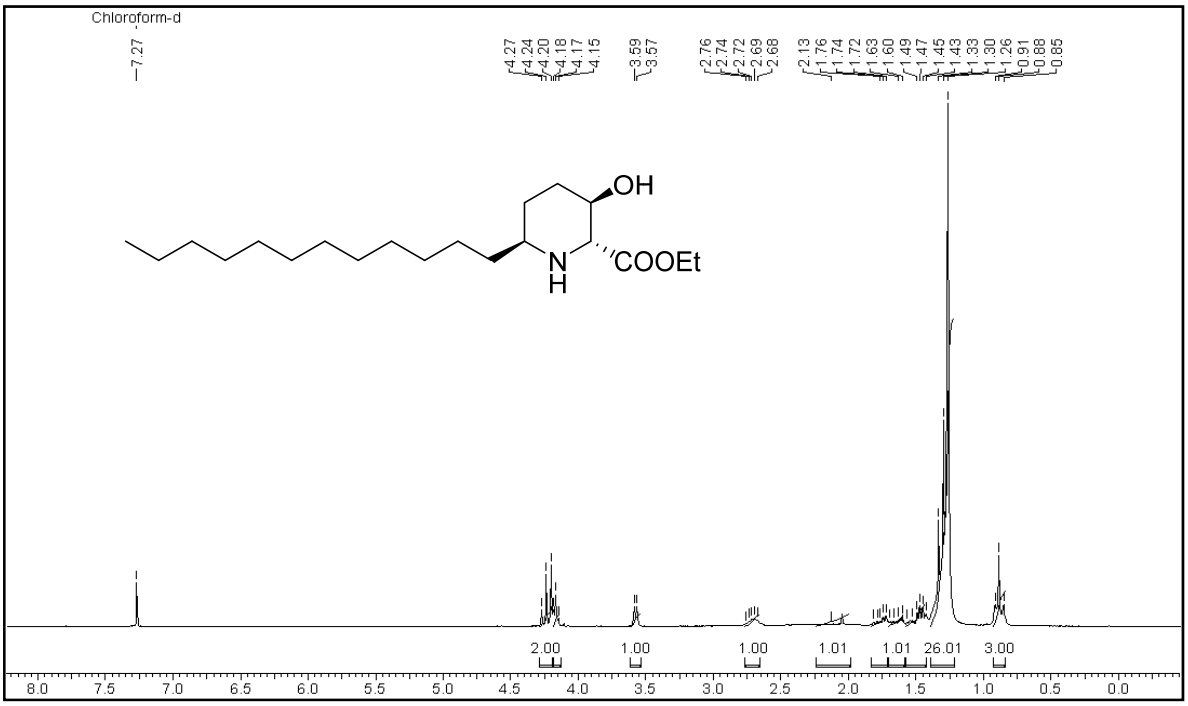


Peak Quantitation: AREA Calculation Method: AREA%

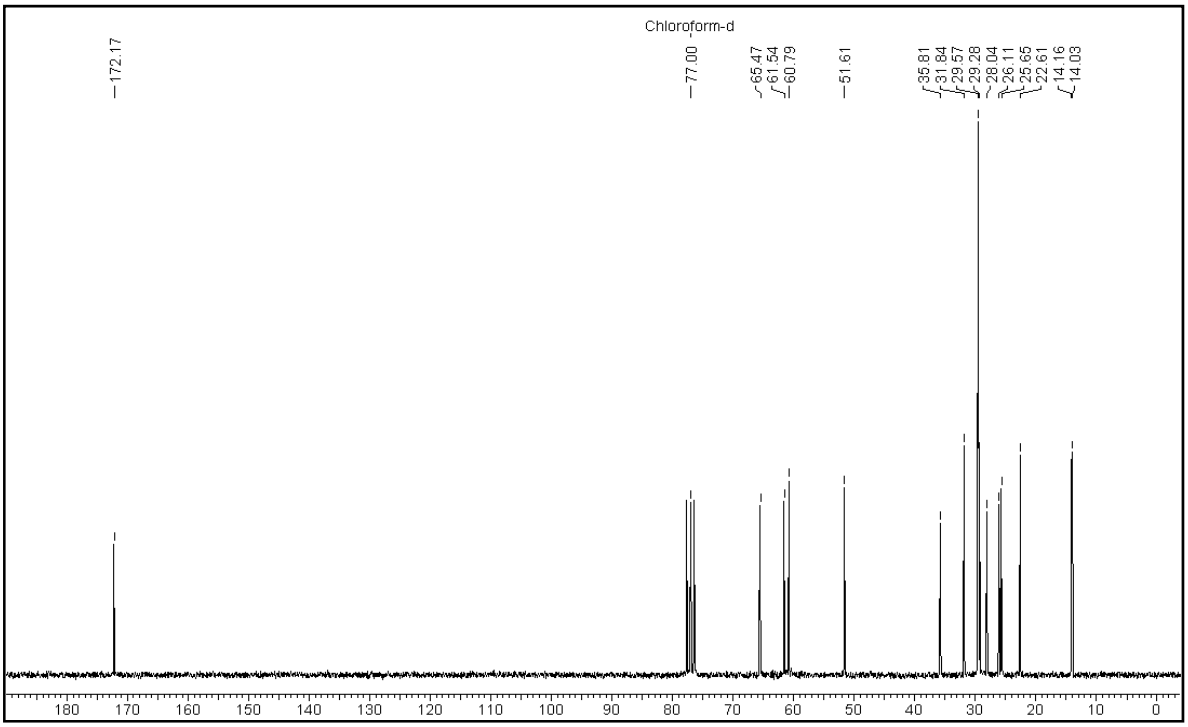
No.	RT	Height	Area	Area %
1	4.24	27302	254721	11.094
2	4.63	181087	2041209	88.906
		208389	2295930	100.000

Peak rejection level: 0

(2*S*,3*S*,6*S*)-Ethyl 6-dodecyl-3-hydroxypiperidine-2-carboxylate (51a):

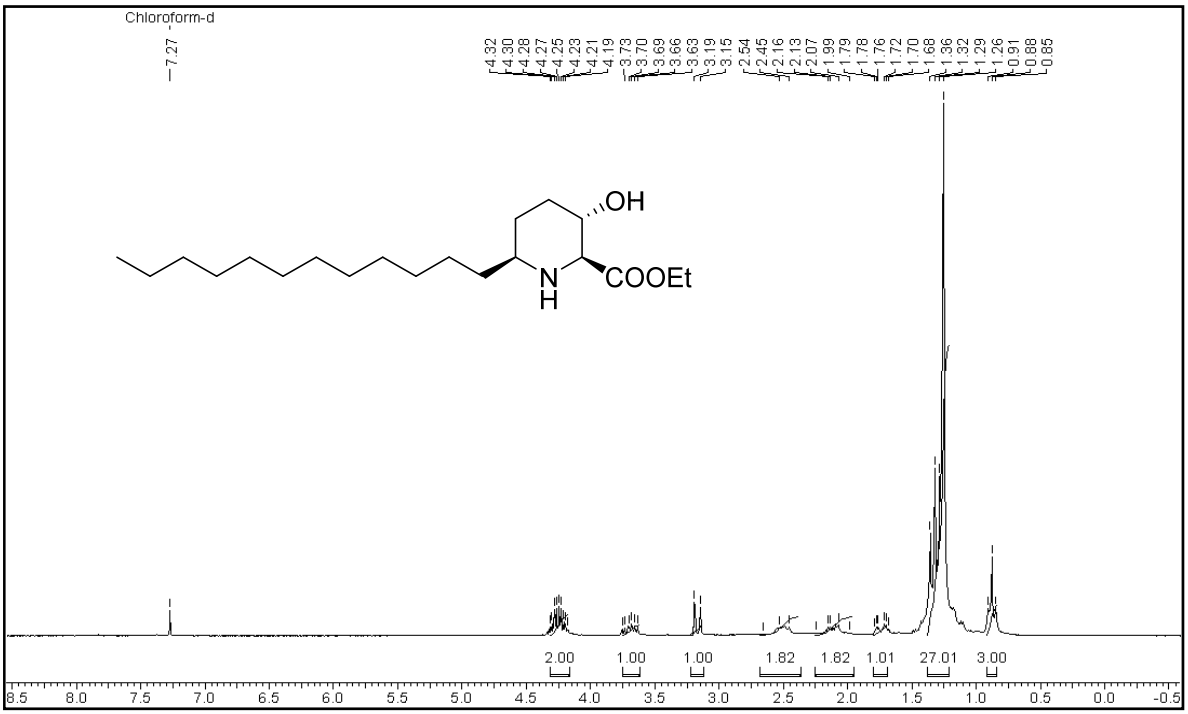


- **^{1}H NMR of the compound 51a in $CDCl_3$**

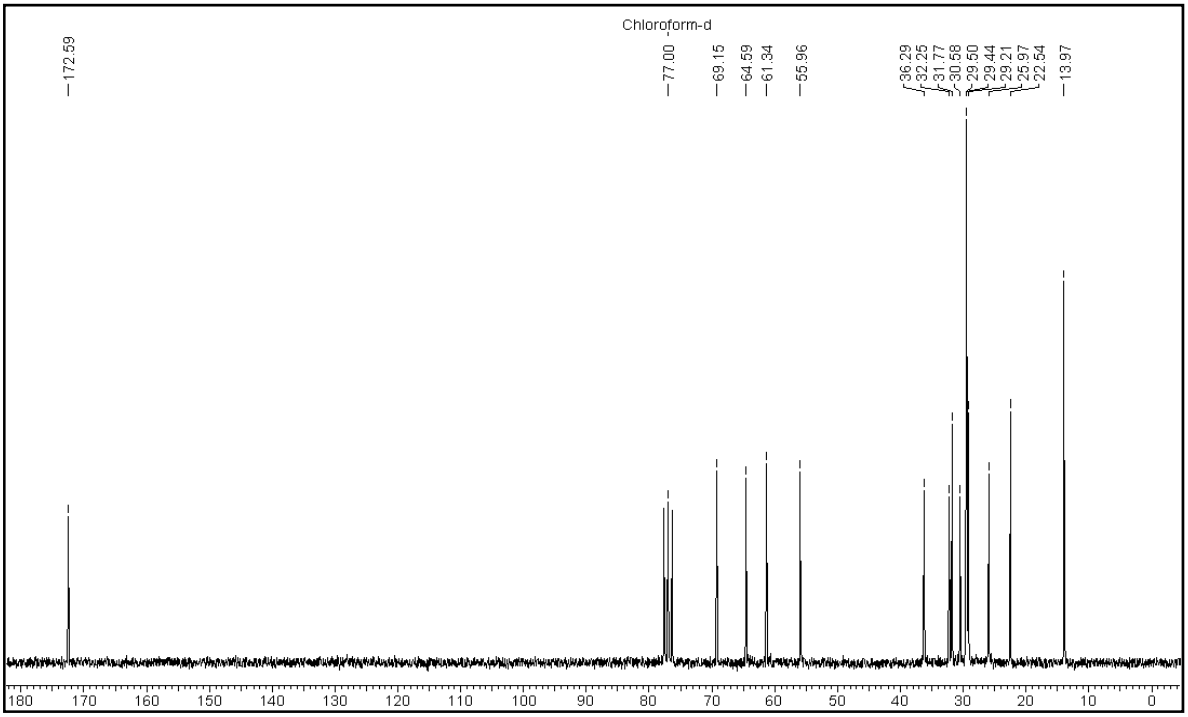


- **^{13}C NMR of the compound 51a in $CDCl_3$**

Ethyl (2S,3S,6S)-6-dodecyl-3-hydroxypiperidine-2-carboxylate (51b):

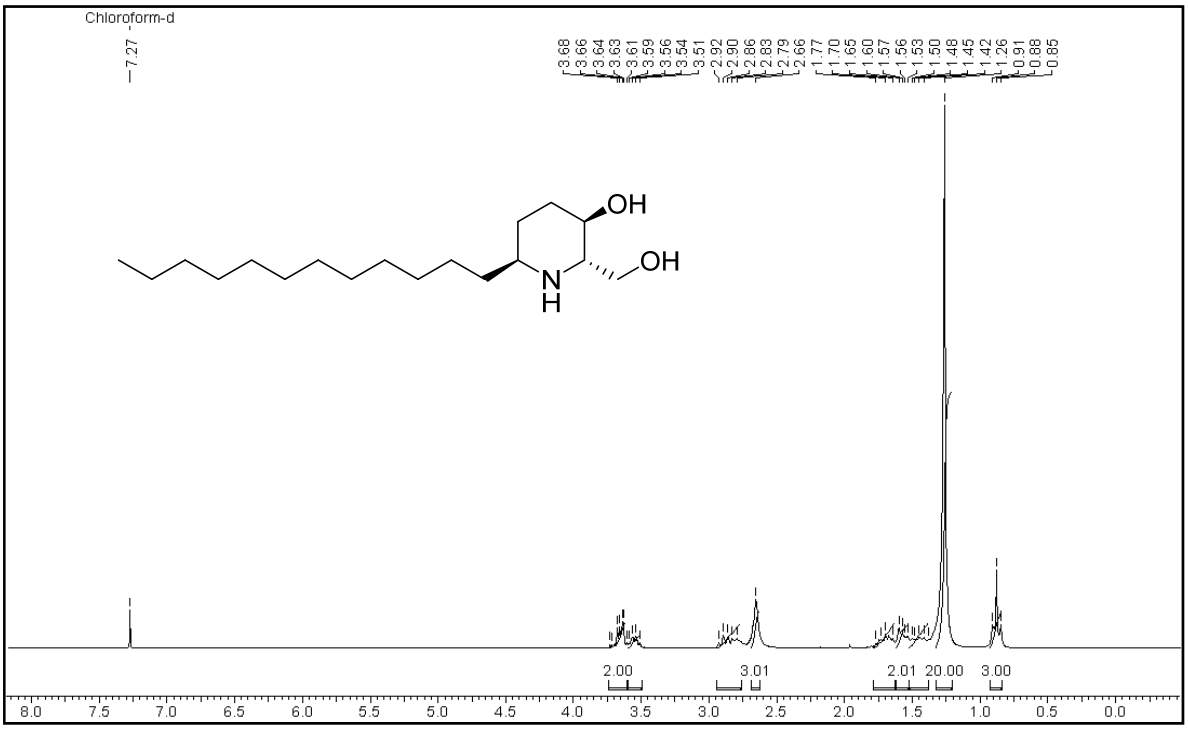


- **^{1}H NMR of the compound 51b in $CDCl_3$**

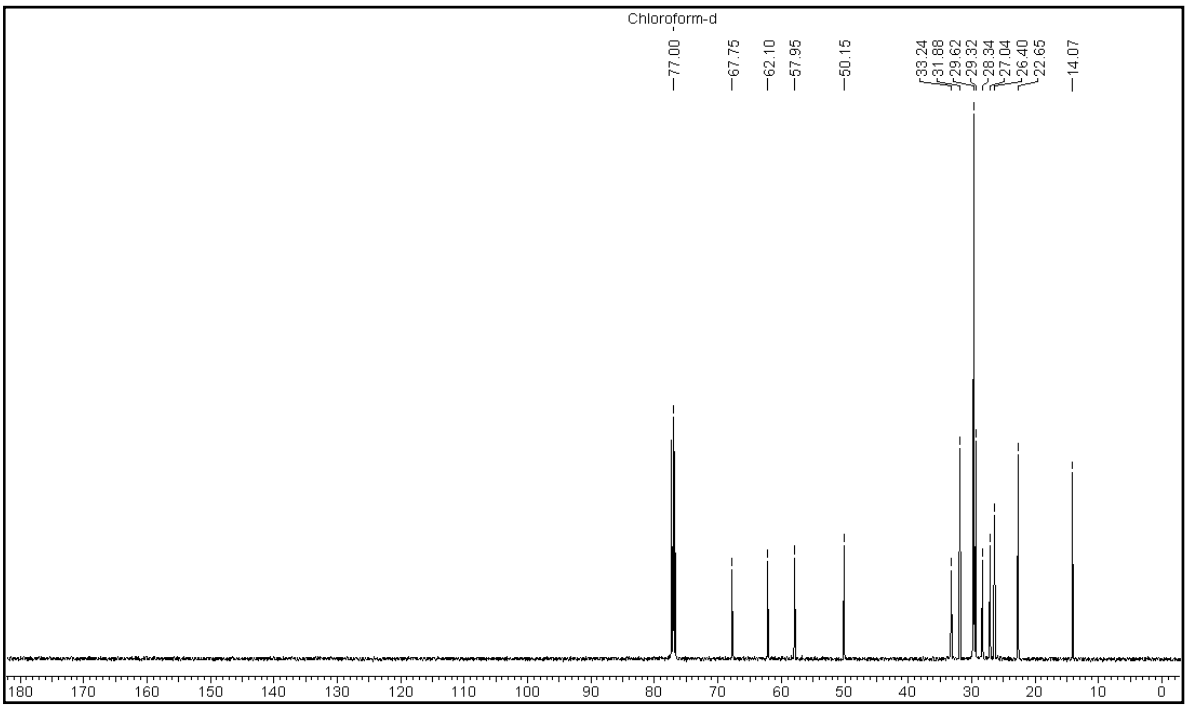


- **^{13}C NMR of the compound 51b in $CDCl_3$**

(-)-Deoxoprosopinine (3):

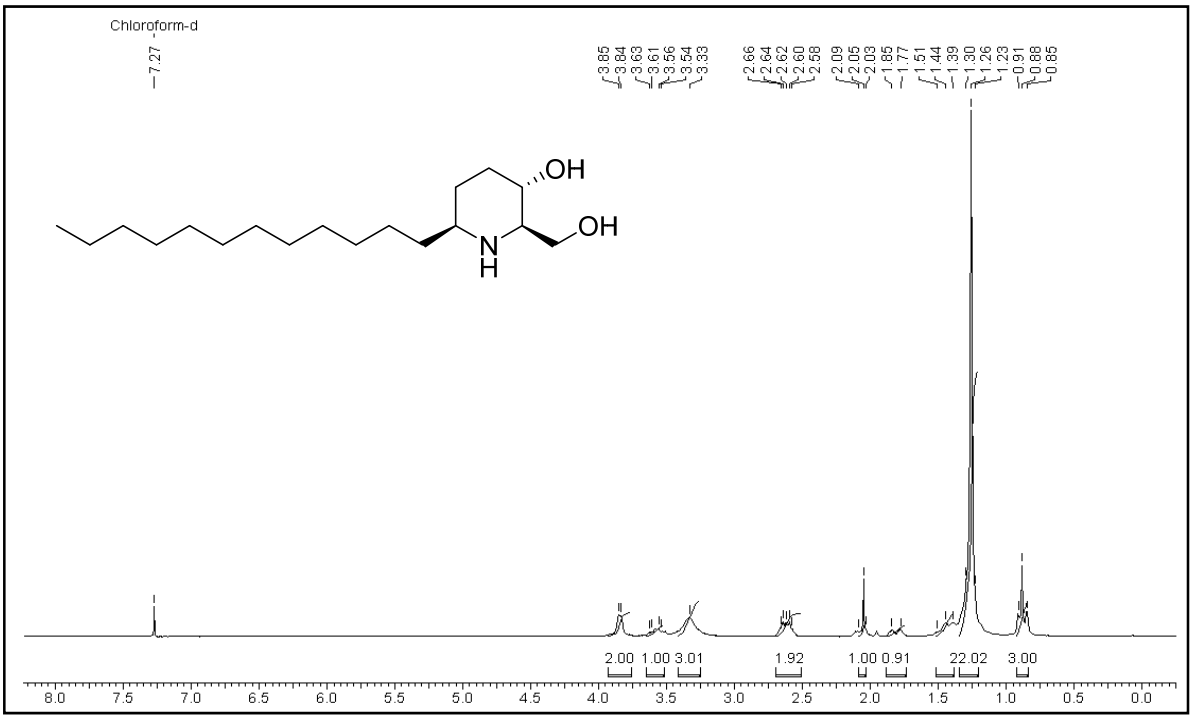


- **^{1}H NMR of the compound 3 in $CDCl_3$**

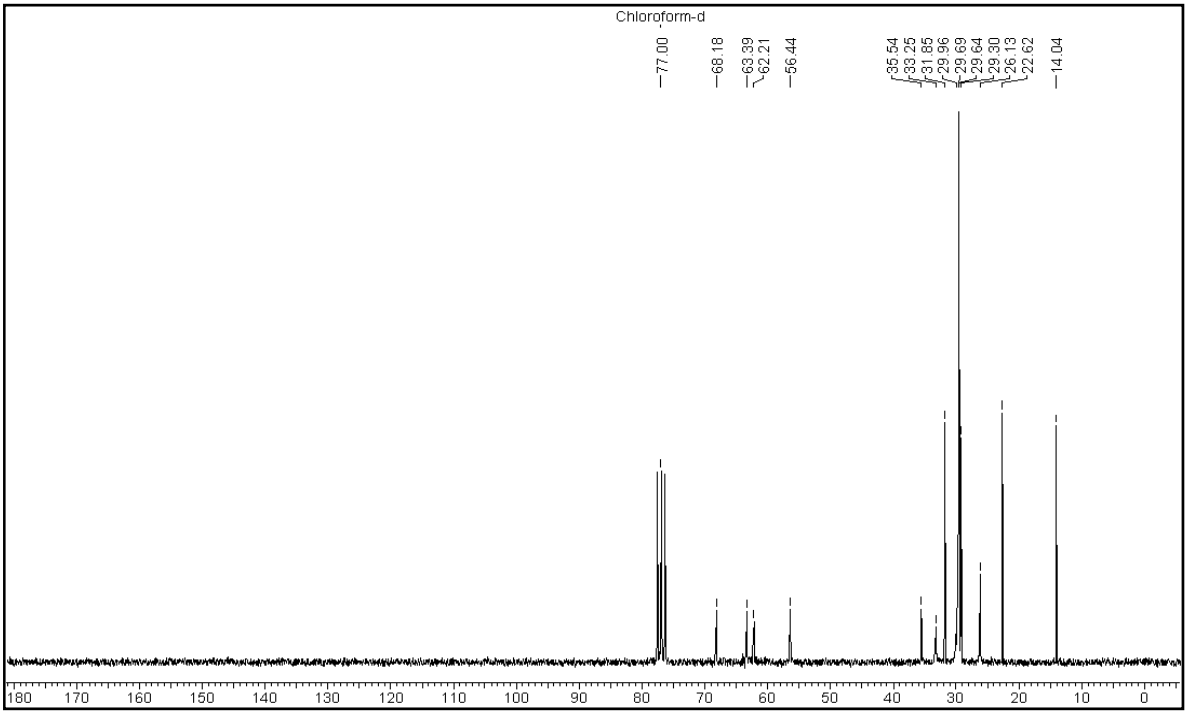


- **^{13}C NMR of the compound 3 in $CDCl_3$**

(+)-Deoxosoprosophylline (4):



- **^{1}H NMR of the compound 4 in $CDCl_3$**



- **^{13}C NMR of the compound 4 in $CDCl_3$**

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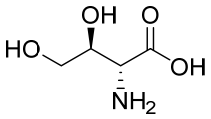
5.2. SECTION B

Total synthesis of (2*R*,3*S*)-2-Amino-3,4-Dihydroxybutyric acid

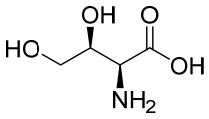
5.2.1. Introduction

β-Hydroxy-α-amino acids serve as key intermediates in the synthesis of important class of compounds as naturally occurring amino acids (threonine, serine, and 3-hydroxyproline) and as components of many complex natural products possessing a wide range of biological activities such as antibiotics and immunosuppressants (e.g., vancomycin, echinocardin D, cyclosporin, katanosin, polyoxin D, empedopeptin, and other peptide conjugates).[1]



1a

(2*R*,3*S*)-2-amino-3,4-dihydroxybutyricacid



1b

(2*S*,3*S*)-2-amino-3,4-dihydroxybutanoic acid

Figure 1.

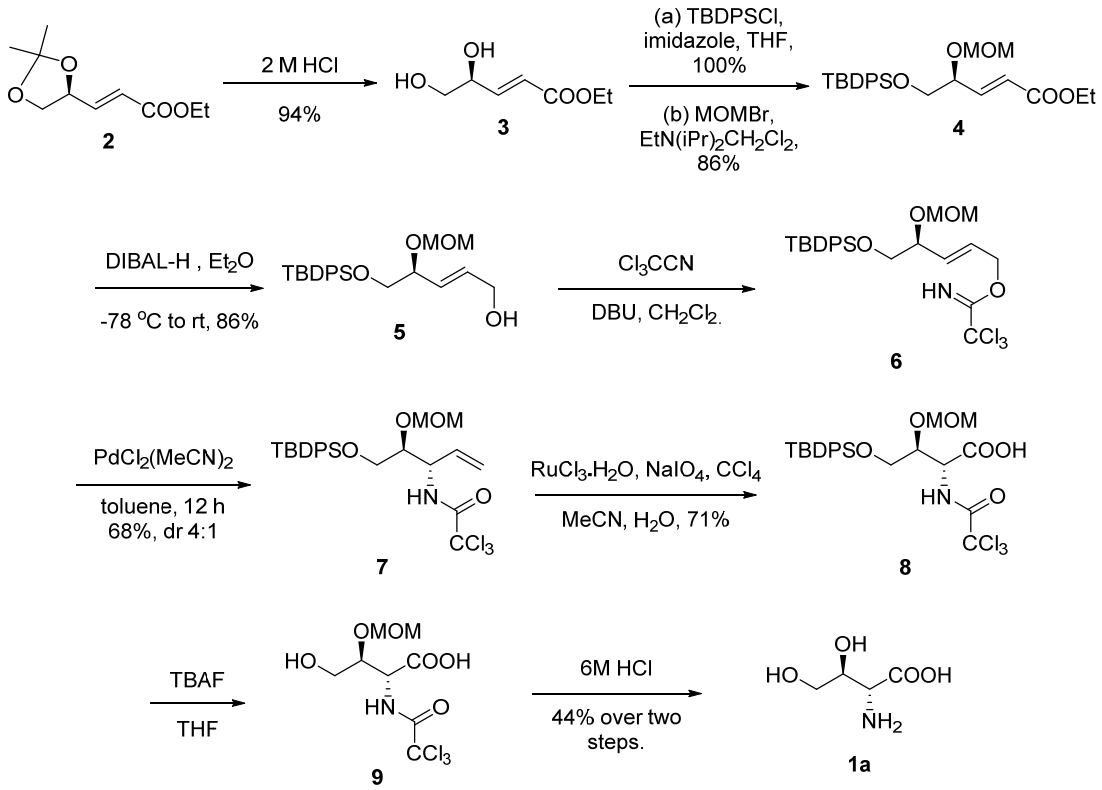
5.2.2. Review of Literature

Due to their importance, various methods for the synthesis of β-hydroxy-α-amino acids in its different stereoisomeric forms have been documented in the literature.[2] A detailed report of recent syntheses is described below.

Sutherland, A. *et al.* (2007)[2a]

Sutherland and co-workers synthesized (2*R*,3*S*)-2-amino-3,4-dihydroxybutyricacid **1a** starting from α,β-unsaturated ester **2**, which on acid mediated hydrolysis gave the corresponding diol **3**. Subsequent protection of the primary alcohol as the *tert*-butyldiphenylsilyl ether and the secondary alcohol as MOM-ether under standard conditions gave compound **4**, which undergoes reduction with 2.2 equiv of DIBAL-H to give allylic alcohol **5**. Alcohol **5** on reaction with DBU and trichloroacetonitrile gave allylic trichloroacetimidate **6** in hand, which on aza-Claisen rearrangement gave allylic amides **7**. Ruthenium (III) trichloride catalyzed oxidation of allylic amide **7** gave the

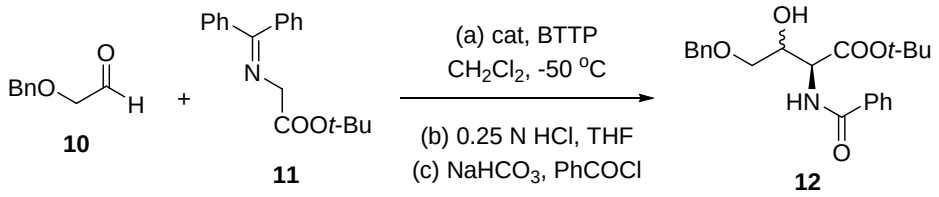
corresponding carboxylic acid **8**. Removal of the silyl ether with TBAF provided **9** which on acid mediated deprotection of the other functional groups gave (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1a** (Scheme **1**).



Scheme 1. Synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid (Sutherland method)

Castle, S. L. *et al.* (2004)[2b]

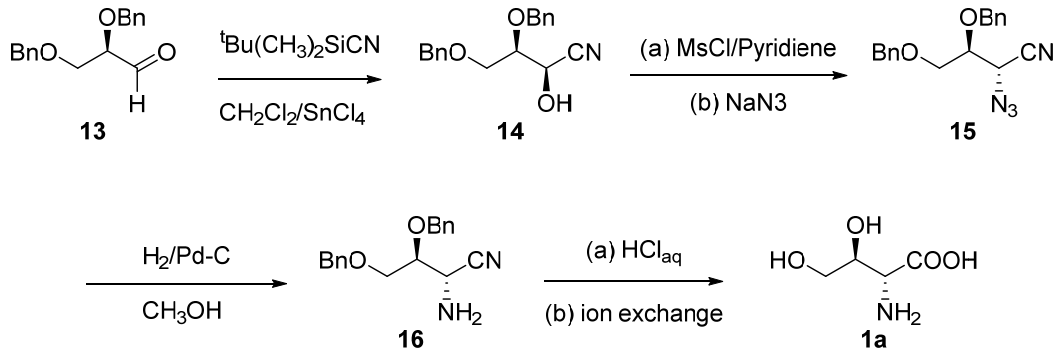
Castle and co-workers synthesized (2*R*,3*S*)-2-amino-3,4-dihydroxybutyricacid **1a** starting from benzyloxyacetaldehyde **10**, which on asymmetric aldol reaction with *tert*-butyl glycinate benzophenone imine **11** provided protected 2-amino-3,4-dihydroxybutyric acid **12** as a mixture of diastereomers.



Scheme 2. Synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid (Castle method)

Catieviela, C. *et al.* (1996)[2c]

Catieviela and co-workers synthesized (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1a** starting from protected D-glyceraldehyde **13**, which on treatment with $^{t}Bu(CH_3)_2SiCN$ in methylene chloride in the presence of $SnCl_4$ at room temperature furnished corresponding cyanohydrin **14** in 85/15 dr ratio. Treatment of the diastereoisomeric mixture of cyanohydrins **14** with trifluoromethanesulfonic chloride in the presence of pyridine, followed by nucleophilic replacement of the OMs group by reaction with sodium azide gave 2-azido-3,4- dibenzyloxybutyronitrile **15** as an oily, inseparable mixture of diastereoisomers. The catalytic hydrogenolysis of the azido group of **15** with 10 % Pd/C afforded the corresponding amino nitrile **16** as a mixture of diastereoisomers from which the major diastereoisomer could be easily isolated by column chromatography. Consequent acid hydrolysis of **16** followed by ion exchange chromatography afforded the desired (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1a** (Scheme **3**).



Scheme 3. Synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid (Catieviela method)

5.2.3. Present work

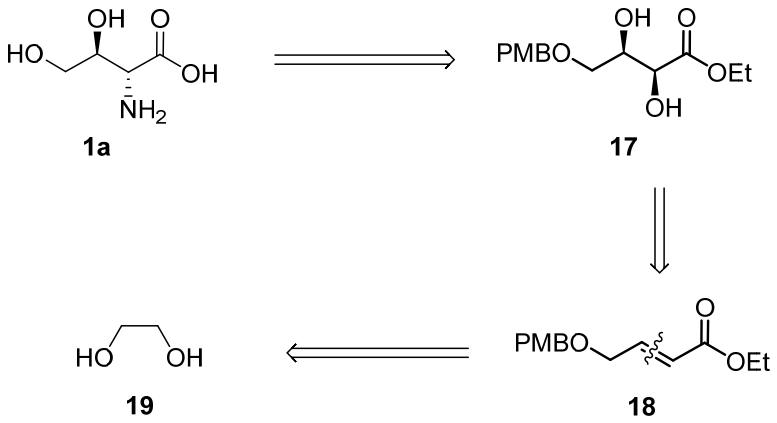
Objective

The advent of Sharpless asymmetric dihydroxylation (AD)[3] greatly facilitated the synthesis of optically active dihydroxy compounds that serve as important synthons to a vast array of natural products. In continuation of our ongoing research towards syntheses of naturally occurring bioactive compounds employing asymmetric dihydroxylation approach,[4] we further aimed towards developing a concise and general protocol for the synthesis of various enantiomers of 2-amino-3,4-dihydroxybutyric acid using Sharpless

asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps.

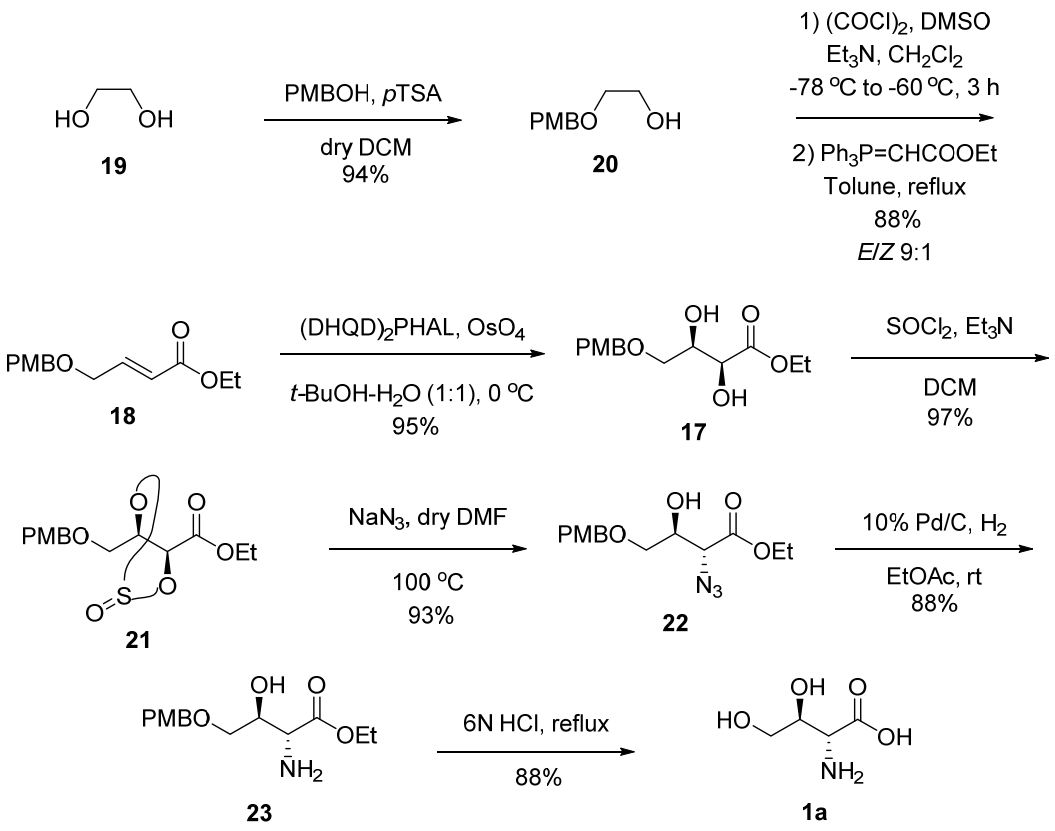
5.2.4. Results and discussion

Our synthetic approach for the synthesis of 2-amino-3,4-dihydroxybutyric acid **1a** is envisioned via the retrosynthetic route shown in the Scheme **4**. Target molecule **1a** was thought to be synthesized from diol **17**, which in turn could be synthesized from α,β-unsaturated ester **18** by asymmetric dihydroxylation. Ester **18** could be easily obtained from ethylene glycol **19**.



Scheme 4. Retrosynthetic route to the synthesis of 2-amino-3,4-dihydroxybutyric acid

As illustrated in Scheme **5**, synthesis of 2-amino-3,4-dihydroxy butyric acid **1a** started from the commercially and cheaply available ethylene glycol **19**. Hydroxy group protection of **19** with PMBOH led to compound **20** in 94% yield, which was oxidized to the aldehyde under Swern conditions[5] and subsequently refluxed with (ethoxycarbonylmethylene)triphenylphosphorane in dry toluene to furnish the Wittig product **18** in 88% yield and 9:1 *E*/*Z* ratio. Appearence of olefinic proton at δ 6.15 as td and 7.01 again as td in ^{1}H NMR spectrum confirmed the formation of product **18**. Subsequent treatment of olefin **18** with osmium tetroxide and potassium ferricyanide as co-oxidant, in the presence of $(DHQD)_2PHAL$ under Sharpless asymmetric conditions, gave diol **17** in 95% yield with 98% ee.[6] Disappearance of olefinic proton at δ 6.15 as td and 7.01 again as td in ^{1}H NMR spectrum confirmed the formation of product **17**.



Scheme 5. Synthesis of 2-amino-3,4-dihydroxybutyric acid

Diol **17** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **21** in 97% yield. Disappearance of peak at 3444 cm^{-1} in IR spectrum confirmed the formation of **21**. The synthetic strategy shown in Scheme **5** was based on the presumption that the nucleophilic opening of cyclic sulfite **21** would occur in a region specific manner at the α-carbon atom. Indeed, the cyclic sulfite reacted with NaN_3 with apparent complete selectivity for attack at C-2 to furnish azido alcohol **22** in 93% yield. Appearance of peak at 2112 cm^{-1} in IR spectrum confirmed the formation of **22**. The carbonyl group must be responsible for the increased reactivity of the α-position.[7] Hydrogenation of azido alcohol **22** with 10% Pd/C led to 1,2-amino alcohol **23** in 88% yield. Finally, concomitant deprotection of the PMB group and ester hydrolysis were carried out with 6 N HCl to furnish **1a** in 88% yield.

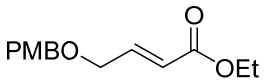
5.2.5. Conclusion

In conclusion, a practical, short and highly enantioselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxy butyric acid has been achieved employing Sharpless asymmetric

dihydroxylation and cyclic sulfite methodology as the key steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for further extension to other stereoisomers via double inversion at the α-carbon.

5.2.6. Experimental Section

Ethyl (E)-4-((4-methoxybenzyl)oxy)but-2-enoate (18):



To a solution of oxalyl chloride (4.37 g, 3.00 mL, 34.44 mmol) in dry CH_2Cl_2 (50 mL) at -78 ^oC was added dropwise dry DMSO (5.56 g, 5.02 mL, 71.17 mmol) in CH_2Cl_2 (10 mL). After 30 min, alcohol **20** (4.2 g, 22.95 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 3 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (10.22 g, 14.08 mL, 101.02 mmol) was added slowly and dry DCM was added dropwise and stirred for 1 hour (30 minutes at -60 ^oC and 30 minutes at room temperature). The reaction mixture was poured into saturated solution of $NaHCO_3$ and the organic layer was extracted with diethyl ether (3 X 60 ml). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude aldehyde. This was used for next step without further purification.

The solution of above aldehyde in dry THF was added (ethoxycarbonylmethylene) triphenylphosphorane in dry toluene. The reaction mixture was refluxed at 110 ^oC for 12 hours. It was then concentrated and purified by column chromatography over silica gel using petroleum ether/EtOAc (19:1) to give **18** as colourless oil.

Yield: 0.604 g, 88%, *E*/*Z* ratio 9:1

Mol. Formula: $C_{14}H_{18}O_4$

IR ($CHCl_3$, cm^{-1})**:** ν_{max} 3436, 3019, 2839, 1715, 1662, 1613, 1514, 1216, 823, 757, 668.

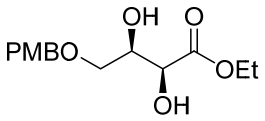
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J*= 7.2 Hz, 3H), 3.85 (s, 3H), 4.17-4.29 (m, 4H), 4.53 (s, 2H), 6.10-6.20 (td, *J* = 2 Hz, *J*= 15.8 Hz, 1H), 6.92 (d, *J*= 8.8 Hz, 2H), 6.97- 7.05 (td, *J*= 4.3 Hz, *J*= 15.8 Hz, 1H), 7.31 (d, *J*= 8.8 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 55.1, 60.2, 68.2, 72.3, 113.7, 121.2, 129.2, 129.6, 144.3, 159.2, 166.2 ppm.

MS (ESI): m/z 273.2767 $(M+Na)^+$

Elemental analysis: required C, 67.18, H, 7.25. Found C, 67.29, H, 7.12.

Ethyl (2*S*,3*R*)-2,3-dihydroxy-4-((4-methoxybenzyl)oxy)butanoate (17):



0.1 M Solution of osmiumtetraoxide (0.48 mL, 48 μmol) in toluene was added to mixture of $K_3Fe(CN)_6$ (11.84 g, 36 mmol), K_2CO_3 (4.97 g, 36 mmol), $(DHQD)_2PHAL$ (0.0935 g, 1 mol%) in t-BuOH/H_20 (1:1) at 0^oC followed by addition of methanesulfonamide (1.14 g, 12 mmol). After stirring for 5 minutes at 0^oC, the olefin **18** (3.0 g, 12 mmol) was added in one portion. The reaction mixture was stirred at 0^oC for 24 hour and then quenched with solid sodium sulfite solution. The stirring was continued for additional 15 minutes and then the solution was extracted with EtOAc (3 X 50 ml). The combine organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude diol which was purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **17** as colourless oil.

Yield: 3.239 g, 95%

Mol. Formula: $C_{14}H_{20}O_6$

$[\alpha]_D^{25}$: + 7.27 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3444, 3014, 2869, 2062, 1737, 1613, 1514, 1466, 1302, 1249, 1131

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, *J*= 7.2 Hz, 3H), 3.64 (dd, *J*= 1.2 Hz, *J*= 5.9 Hz, 2H), 3.84 (s, 3H), 4.14-4.34 (m, 4H), 4.53 (s, 3H), 6.92 (d, *J*= 8.6 Hz, 2H), 7.30 (d, *J*= 8.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 55.1, 61.8, 70.3, 70.8, 70.9, 72.9, 113.6, 129.4, 129.7, 159.1, 173.1 ppm.

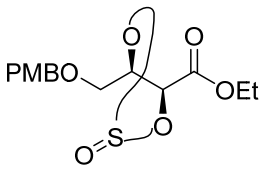
MS (ESI): m/z 307.3992 $(M+Na)^+$

Elemental analysis: required C, 59.14, H, 7.09. Found C, 59.36, H, 7.01.

The enantiomeric purity of the diol was determined to be 98% by chiral HPLC analysis.

HPLC: Chiracel OJ-H column (2-Propanol: petroleum ether = 10:90, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 78.483 (minor) and 80.708 (major). The racemic standard was prepared in the same way without using $(DHQD)_2PHAL$ ligand, >ee 98%.

Ethyl (2*R*,4*S*,5*R*)-5-(((4-methoxybenzyl)oxy)methyl)-1,3,2-dioxathiolane-4-carboxylate 2-oxide (21):



To a solution of diol **17** (1.5 g, 5 mmol) in dry CH_2Cl_2 was added Et_3N (1.47 mL, 10 mmol) at 0^o C. After being stirred for 10 minutes, thionyl chloride (0.5 mL, 6 mmol) was added dropwise at 0 ^{o}C. The reaction mixture was stirred for 2 h at room temperature and carefully quenched with water. The reaction mixture was extracted with diethyl ether (3 X 25 ml). The combine organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give crude cyclic sulfite which was purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **21** as colourless oil.

Yield: 1.69 g, 97%

Mol. Formula: $C_{14}H_{18}O_7S$

$[\alpha]_D^{25}$: + 116.08 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): 3020, 1742, 1613, 1514, 1466, 1216, 1034.

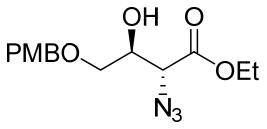
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, *J*= 7.2 Hz, 3h), 3.81-3.92 (m, 2H), 3.85 (s, 3H), 4.26-4.39 (m, 2H), 4.58-4.61 (m, 2H), 4.80-4.98 (m, 1H), 5.28-5.35 (m, 1H), 6.93 (d, *J*= 8.7 Hz, 2H), 7.29 (d, *J*= 8.7 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 55.2, 62.5, 66.9, 73.2, 77.9, 81.3, 113.8, 129.4, 159.4, 166.8, 167.4 ppm.

MS (ESI): m/z 353.3236 $(M+Na)^+$

Elemental analysis: required C, 50.90, H, 5.49. Found C, 50.69, H, 5.45.

Ethyl (2*R*,3*S*)-2-azido-3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (22):



To a solution of cyclic sulfite **21** (1 g, 3 mmol) in dry DMF was added NaN_3 (0.787 g, 12 mmol) at 0 ^{o}C and the reaction mixture was refluxed at 100 ^{o}C for 8 h. The reaction mixture was quenched using ice at 0 ^{o}C and extracted with EtOAc (3 X 25 ml). The

combine organic layer was washed using brine, dried over anhydrous Na_2SO_4 and concentrated to give crude azido alcohol which was purified by column chromatography over silica gel using petroleum ether/EtOAc (4:1) to give **22** as colourless oil.

Yield: 0.842 g, 93%

Mol. Formula: $C_{14}H_{19}N_30_5$

$[\alpha]_D^{25}$: + 11.08 (*c* 0.84, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): 3455, 2935, 2112, 1740, 1612, 1514, 1249.

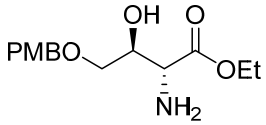
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J*= 7.2 Hz, 3H), 2.84 (d, *J*= 5.7 Hz, 1H), 3.63 (d, *J*= 4.3 Hz, 2H), 3.85 (s, 3H), 4.04-4.35 (m, 4H), 4.52 (s, 2H), 6.92 (d, *J*= 8.8 Hz, 2H), 7.29 (d, *J*= 8.8 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 55.1, 61.9, 63.1, 69.5, 70.7, 73.1, 113.7, 128.5, 129.4, 159.3, 168.6 ppm.

MS (ESI): m/z 332.3965 $(M+Na)^+$

Elemental analysis: required C, 54.36, H, 6.19, N, 13.58. Found: C 54.50, H, 6.29, N, 13.39.

Ethyl (2*R*,3*S*)-2-amino-3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (23):



To a solution of azido alcohol **22** (600 mg, 2 mmol) in dry EtOAc (25 ml) was added catalytic amount of 10% Pd/C and the resulting heterogeneous mixture was stirred for 10 h at room temperature under hydrogen condition (2 atm.). The reaction mixture was then filtered through a pad of celite and the solvent was removed under reduced pressure to give crude amino alcohol, which was purified by column chromatography over silica gel using petroleum ether/EtOAc (1:1) to give **23** as pale yellow oil.

Yield: 0.482 g, 88%

Mol. Formula: $C_{14}H_{21}NO_5$

$[\alpha]_D^{25}$: + 6.22 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): 3492, 2979, 1745, 1576, 1244.

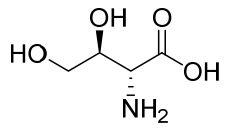
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, *J*= 7.1 Hz, 3H), 3.41-3.58 (m, 2H), 3.63-3.75 (m, 1H), 3.81 (s, 3H), 3.95-4.20 (m, 3H), 4.44 (s, 2H), 6.88 (d, *J*= 8.8 Hz, 2H), 7.25 (d, *J*= 8.8 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 55.2, 56.6, 61.1, 70.4, 70.9, 73.1, 113.7, 129.4, 129.8, 159.3, 171.2 ppm.

MS (ESI): m/z 306.2962 $(M+Na)^+$

Elemental analysis: required C, 59.35, H, 7.47, N, 4.94. Found: C 59.47, H, 7.39, N, 4.66.

(2*R*,3*S*)-2-amino-3,4-dihydroxybutanoic acid (1a):



To the above amino alcohol **23** (0.100 g, 0.35 mmol) was added 6N HCl and the resulting mixture was refluxed for 10 hours. After the reaction was over, the hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in water (5 ml), washed with ether. The water was evaporated under reduced pressure to get pale yellow solid. Further purification was performed by silica gel column chromatography using acetonitrile/water 2:1 to get **1a** as a colorless solid.

Yield: 0.040 g, 88%

Mol. Formula: $C_4H_9NO_4$

$[\alpha]_D^{25}$: + 10.9 (*c* 1.0, H_2O) [Lit.[2c] $[\alpha]_D^{25}$: + 11.3 (*c* 7.0, H_2O)].

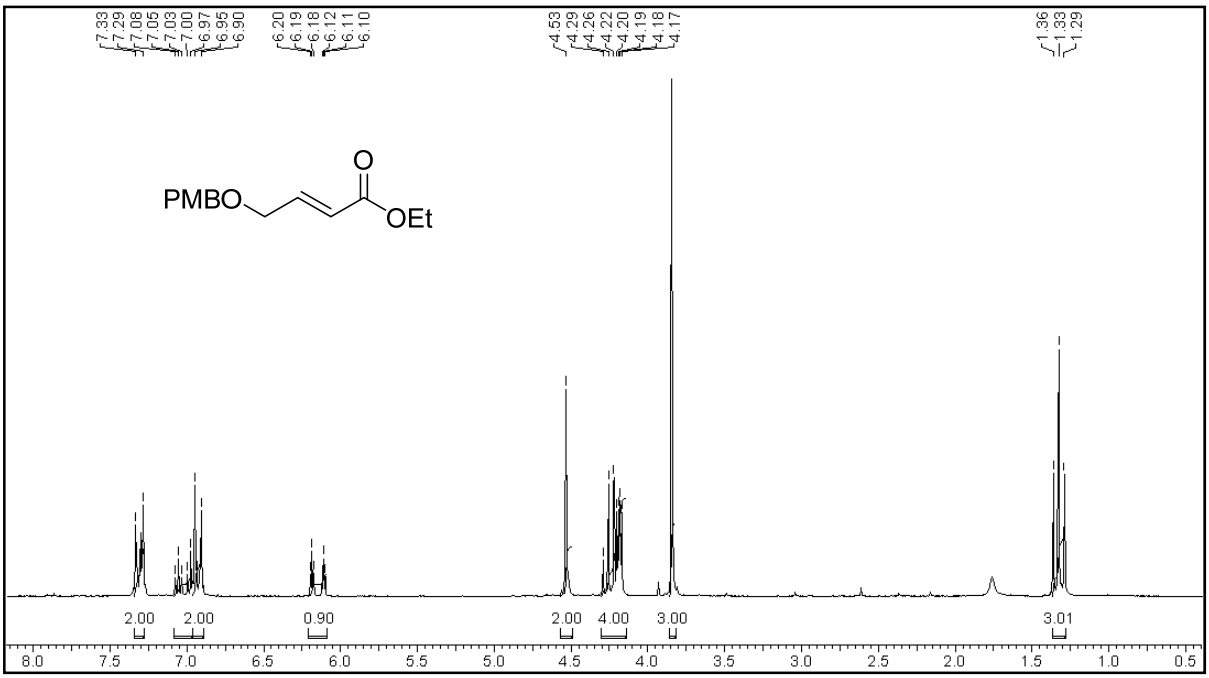
^{1}H NMR (500 MHz, D_2O): δ 3.75-3.82 (m, 2H), 3.95 (d, *J*= 3.7 Hz, 1H), 4.16-4.24 (m, 1H) ppm.

^{13}C NMR (125 MHz, D_2O): δ 57.7, 62.7, 69.4, 171.5 ppm.

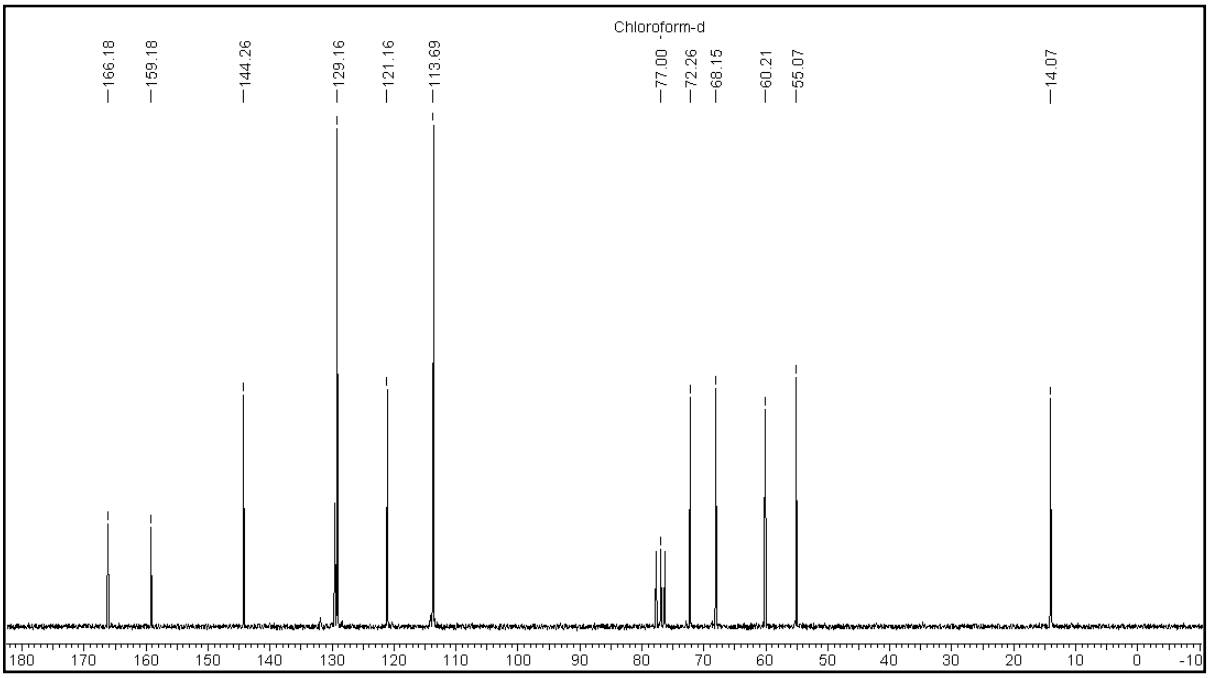
(ESI): m/z 136.1084 $(M+H)^+$

5.2.7. Spectra

Ethyl (E)-4-((4-methoxybenzyl)oxy)but-2-enoate (18):

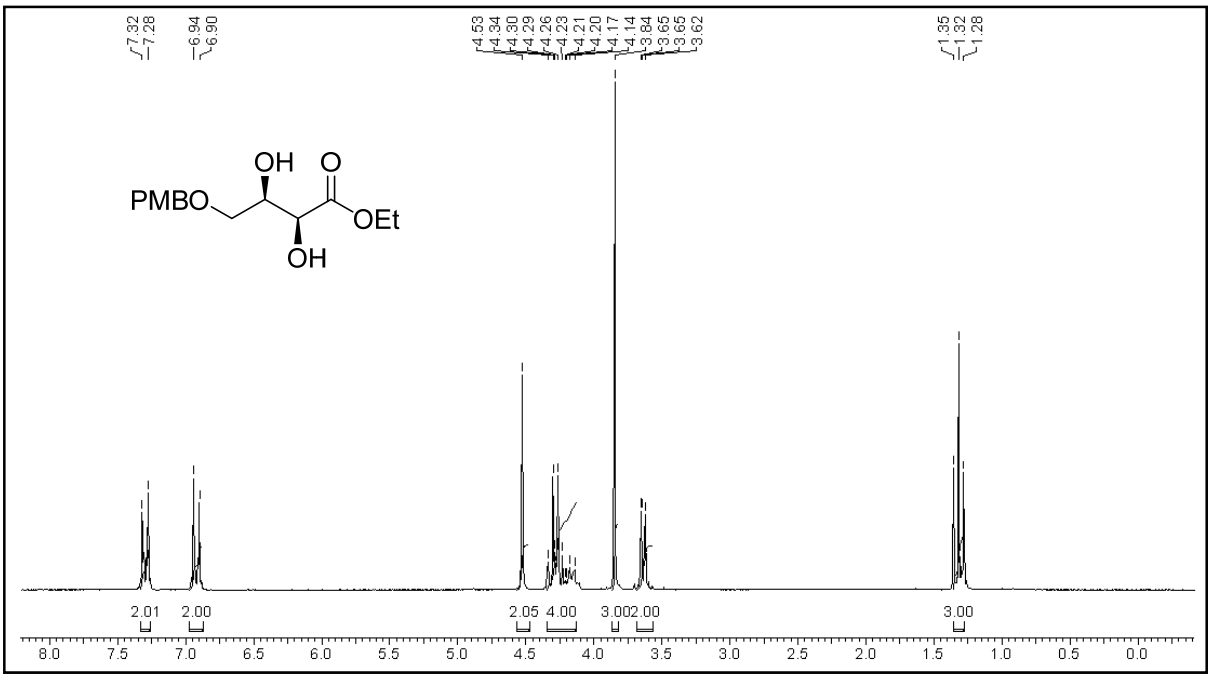


- **^{1}H NMR of the compound 18 in $CDCl_3$**

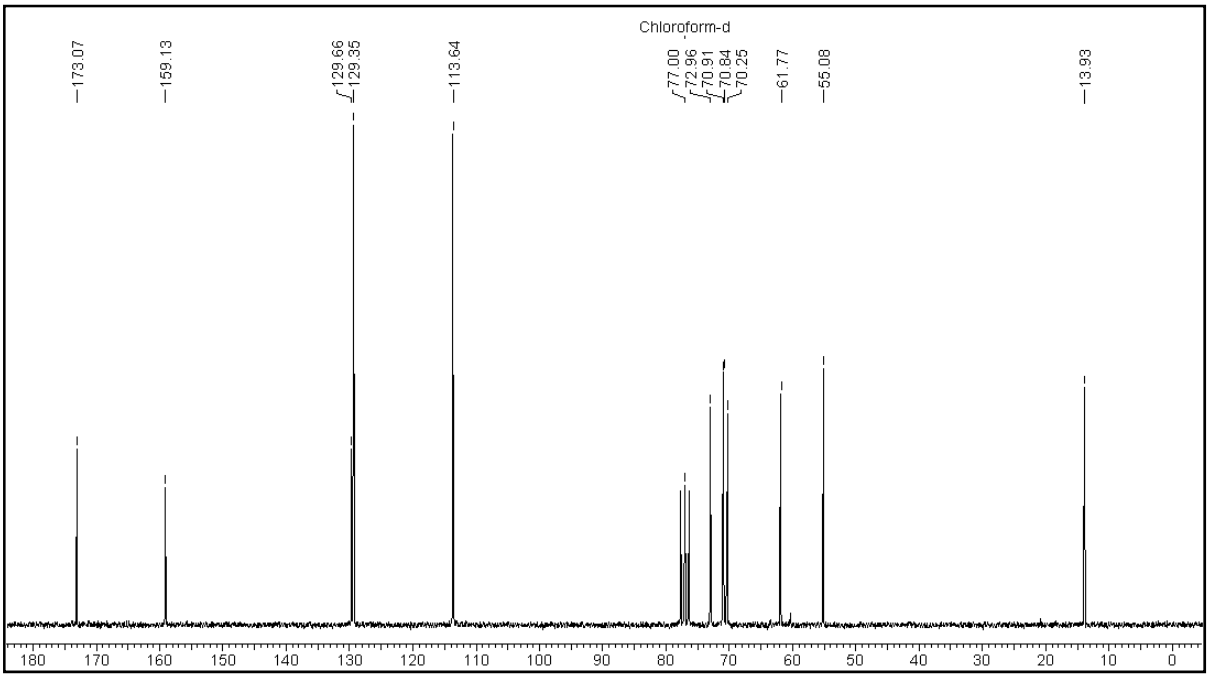


- **^{13}C NMR of the compound 18 in $CDCl_3$**

Ethyl (2*S*,3*R*)-2,3-dihydroxy-4-((4-methoxybenzyl)oxy)butanoate (17):

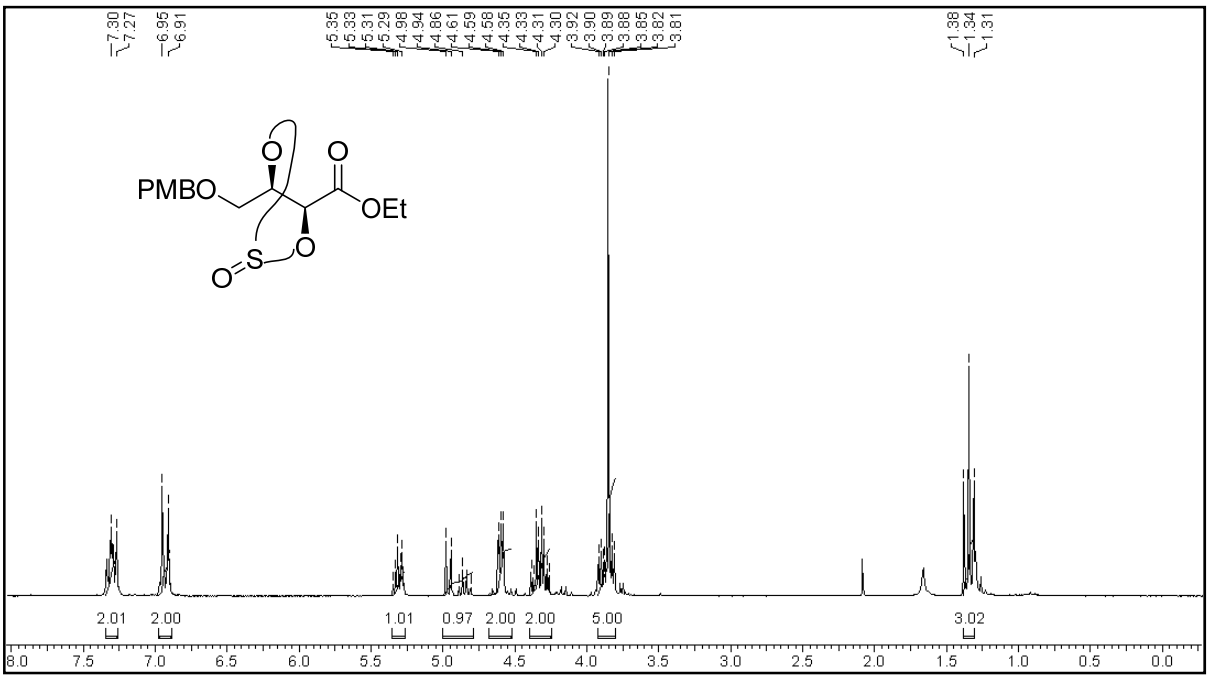


➢ **^{1}H NMR of the compound 17 in $CDCl_3$**

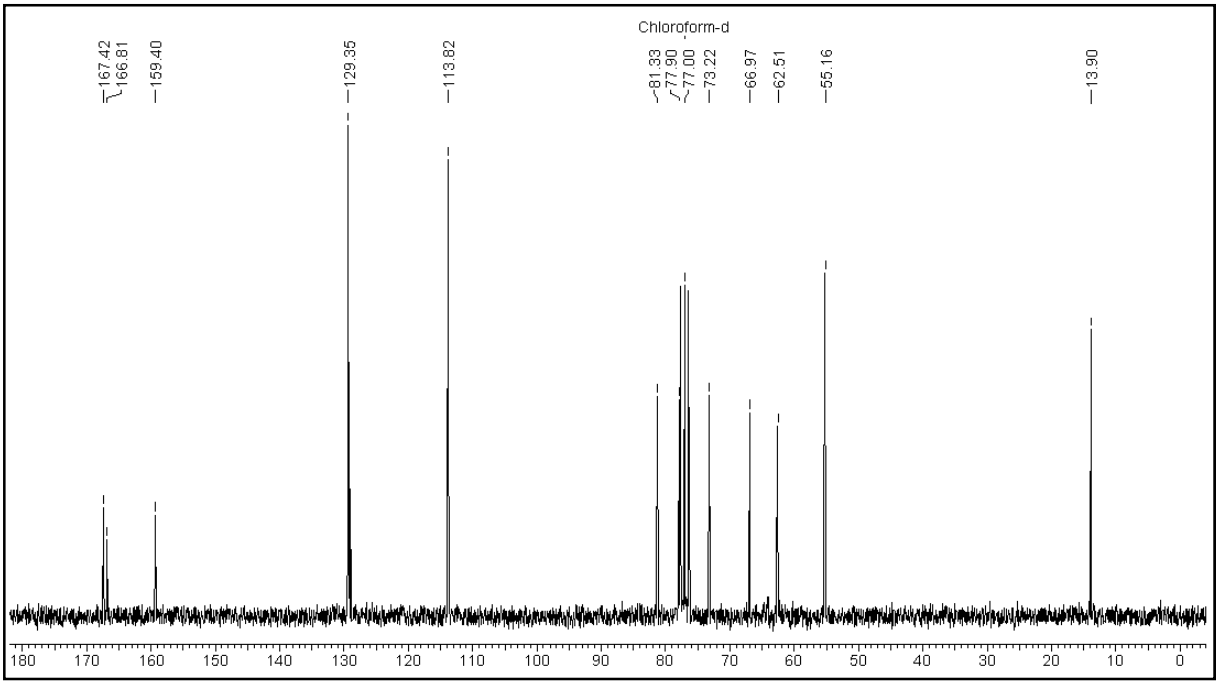


➢ **^{13}C NMR of the compound 17 in $CDCl_3$**

Ethyl (2R,4S,5R)-5-(((4-methoxybenzyl)oxy)methyl)-1,3,2-dioxathiolane-4-carboxylate 2-oxide (21):

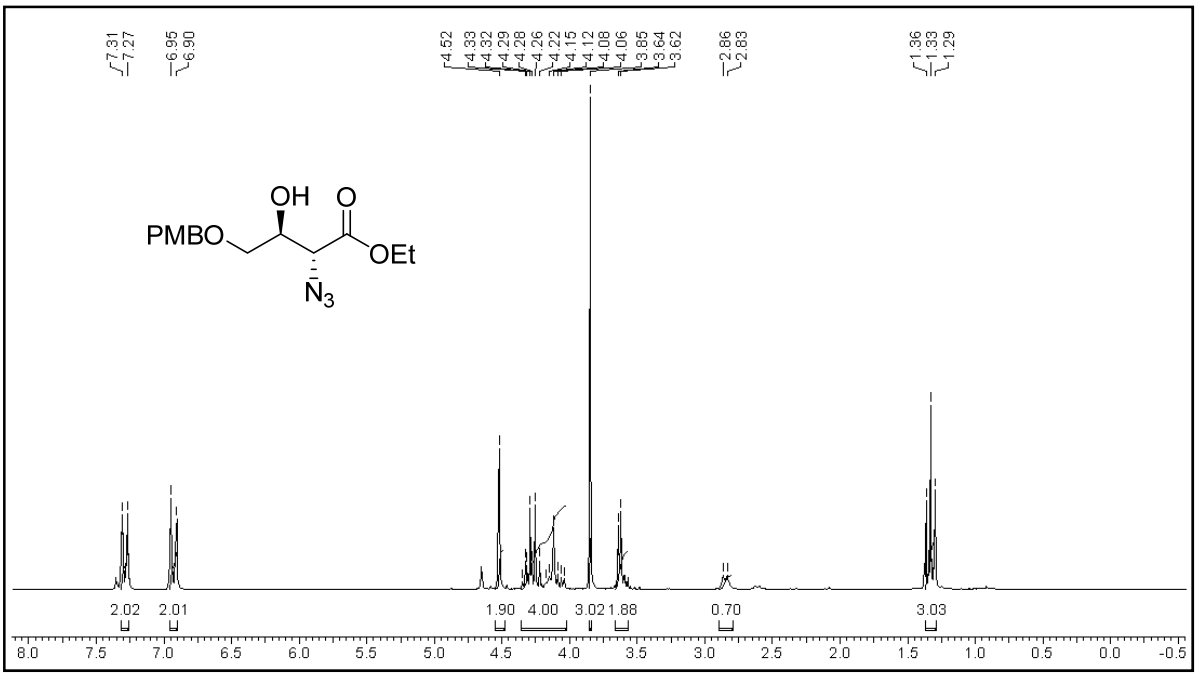


➢ **^{1}H NMR of the compound 21 in $CDCl_3$**

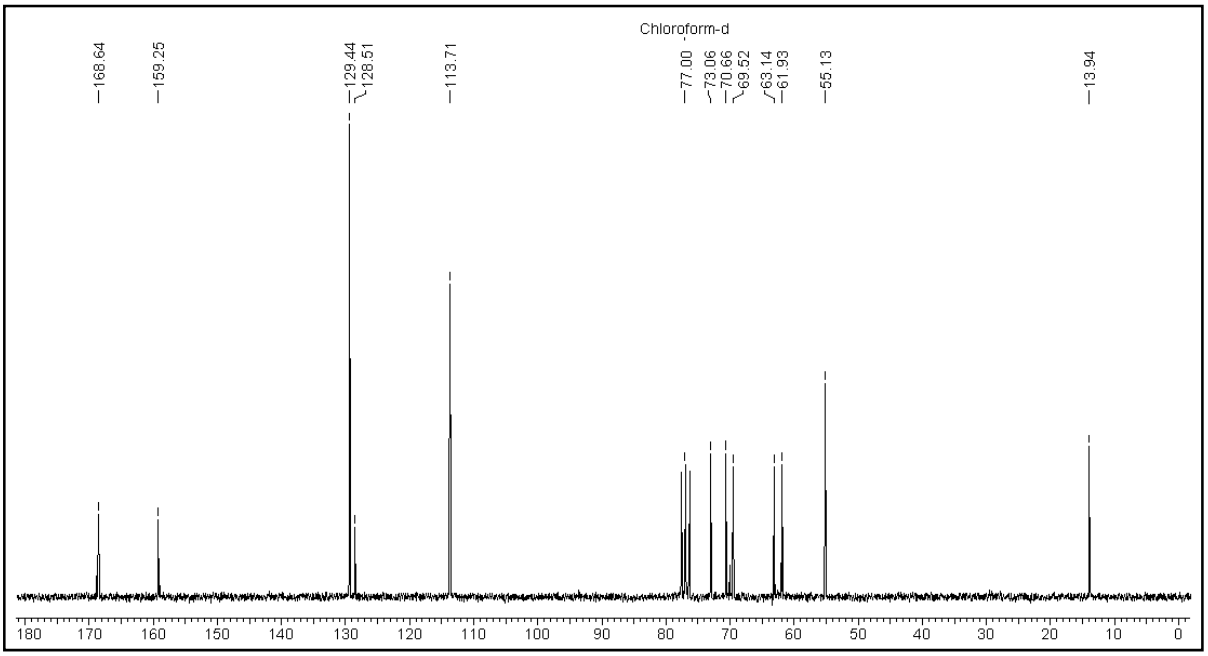


➢ **^{13}C NMR of the compound 21 in $CDCl_3$**

Ethyl (2*R*,3*S*)-2-azido-3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (22):

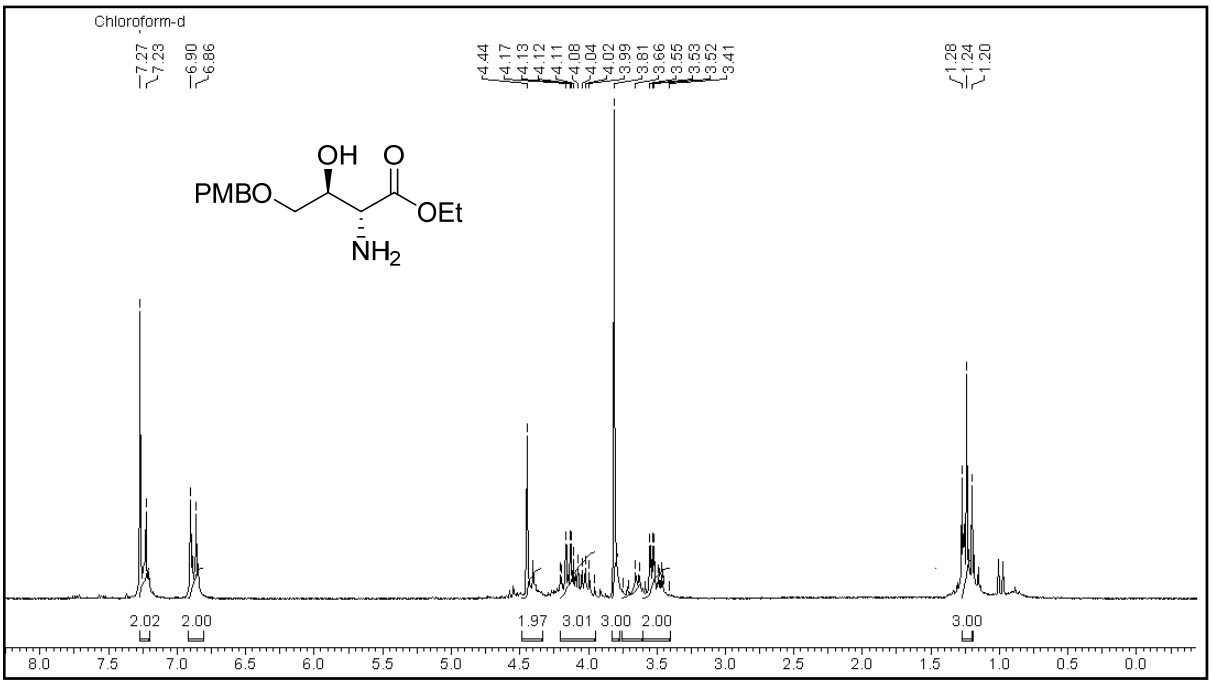


➢ **^{1}H NMR of the compound 22 in $CDCl_3$**

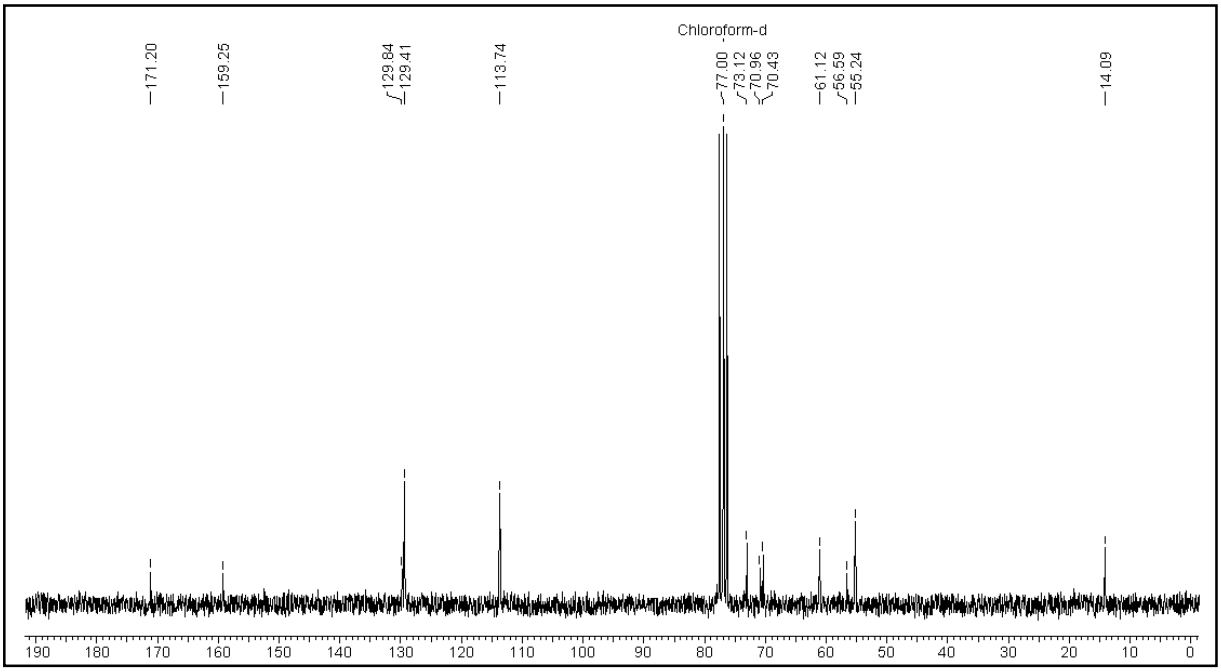


➢ **^{13}C NMR of the compound 22 in $CDCl_3$**

Ethyl (2R,3S)-2-amino-3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (23):

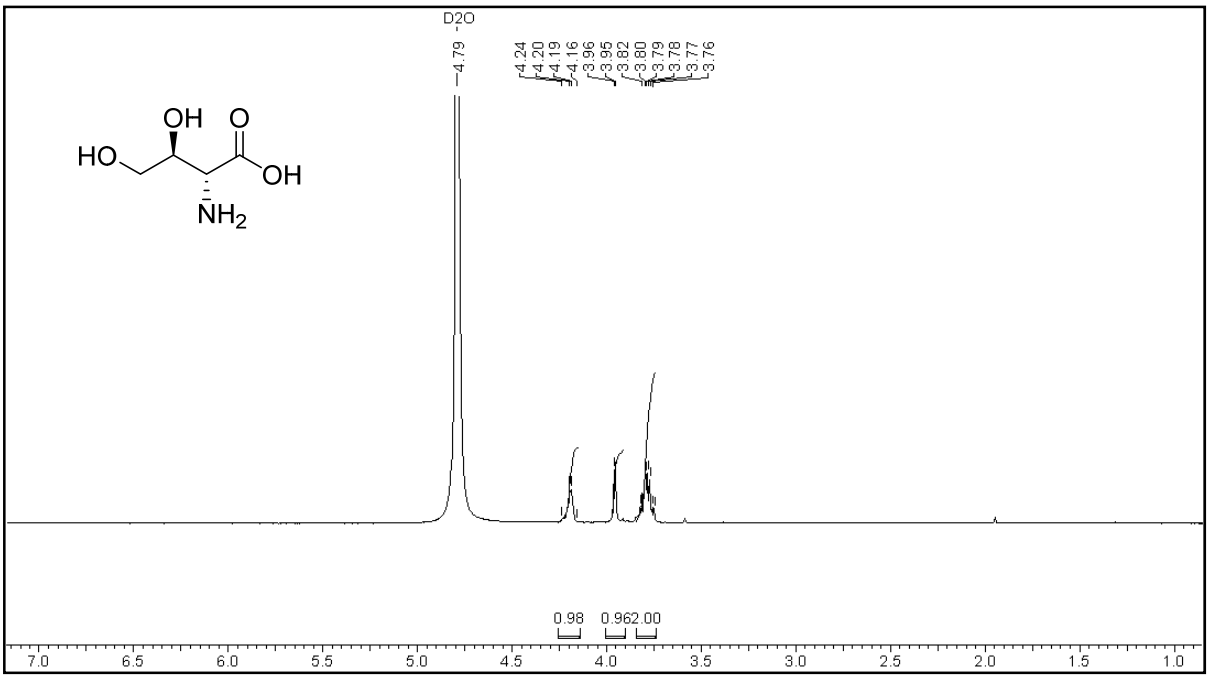


➢ **^{1}H NMR of the compound 23 in $CDCl_3$**

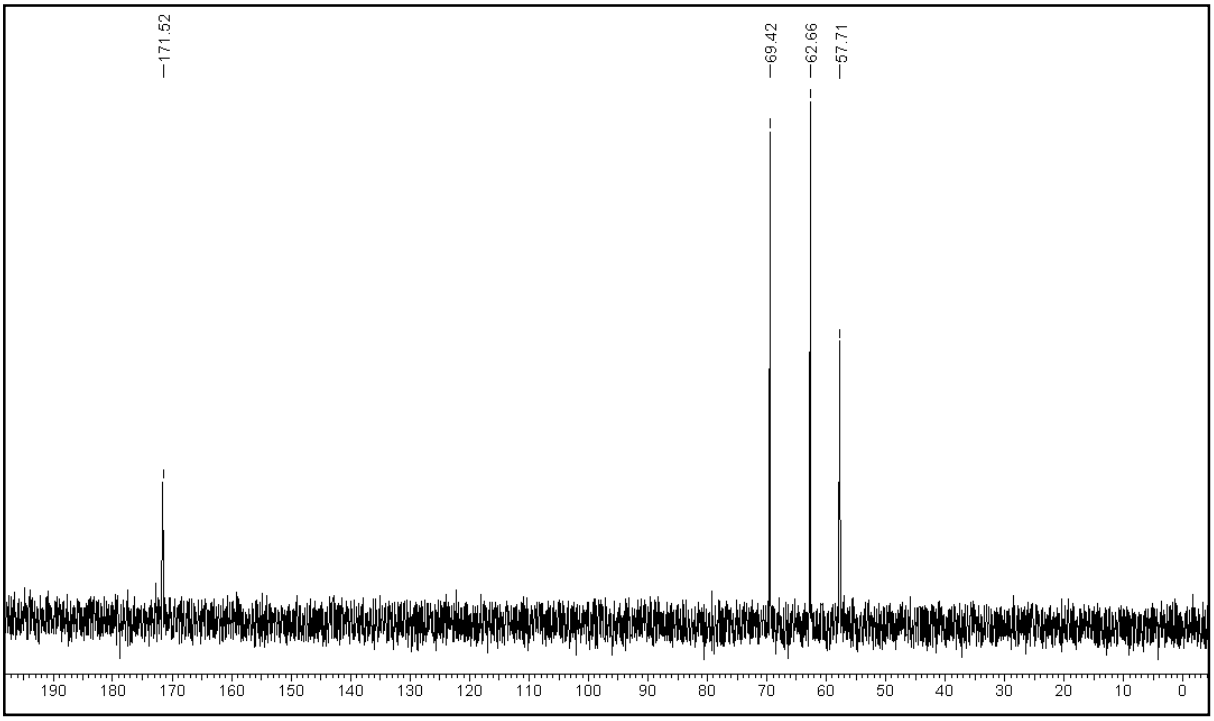


➢ **^{13}C NMR of the compound 23 in $CDCl_3$**

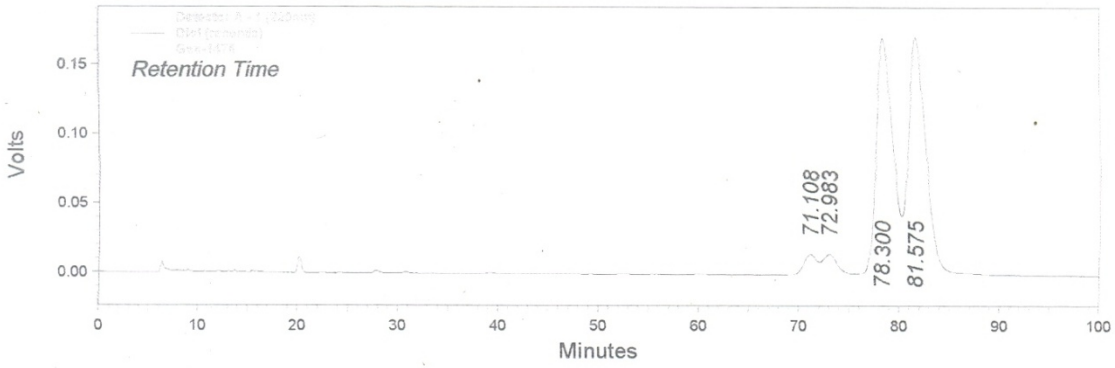
(2*R*,3*S*)-2-Amino-3,4-dihydroxybutanoic acid (1a):



- **^{1}H NMR of the compound 1a in D_2O**



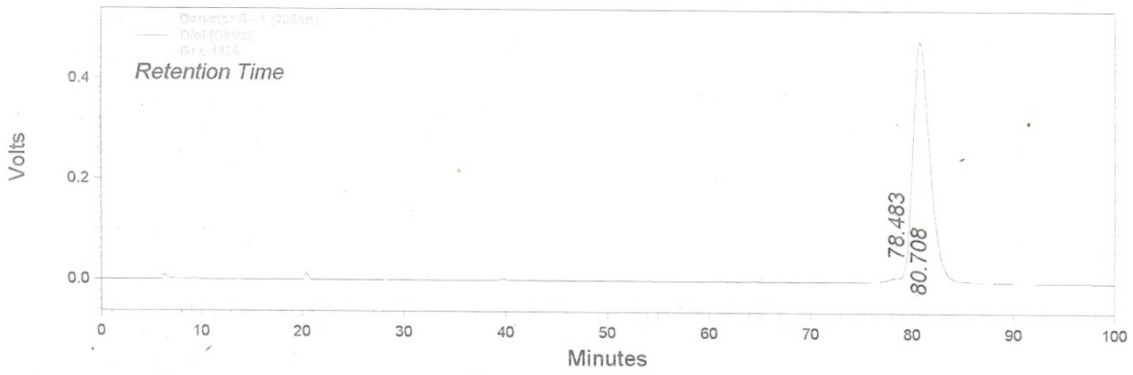
- **^{13}C NMR of the compound 1a in D_2O**



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

5.2.8. References:

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