DEVELOPMENT OF NEW METHODOLOGY USING PHOSPHORUS YLIDES AND ENANTIOSELECTIVE SYNTHESIS OF PYRROLIDINE AND PIPERIDINE ALKALOIDS

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IN

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Development of new methodology using phosphorus ylides and enantioselective synthesis of pyrrolidine and piperidine alkaloids**" submitted by **Puspesh K. Upadhyay** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Development of new methodology using phosphorus ylides and enantioselective syntheis of pyrrolidine and piperidine alkaloids**" 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 the National Chemical Laboratory, Pune, India.

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November 2009

Dedicated to

My Beloved Parents
&
My Family

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ABBREVIATIONS

Ac	-	Actyl
AcCl	-	Acetyl chloride
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobis-isobutyric acid
Bn	-	Benzyl
BnOH	-	Benzyl alcohol
BnBr	-	Benzyl bromide
$BF_3.OEt_2$	-	Boron trifluoride etherate
$BF_3.2AcOH$	-	Boron trifluoride acetic acid
$BH_3.SMe_2$	-	Boron dimethyl sulfide
$BH_3.THF$	-	Boron tetrahydrofuran
BHT	-	2,6-Di-*tert*-butyl-4-methyl phenol
Boc	-	*tert*-Butoxy carbonyl
Boc_2O	-	Di-*tert*-butyl dicarbonate
Bz	-	Benzoyl
n-BuLi	-	*n*-Butyl lithium
CAN	-	Ceric ammonium nitrate
Cat	-	Catalytic
Cbz	-	Benzyloxy carbonyl
Cbzcl	-	Benzyloxy carbonyl chloride
$CDCl_3$	-	Deuterated chloroform
CDI	-	Carbonyl diimidazole
CNS	-	Central nervous system
Cl-PNB	-	Chloro-*p*-nitro benzoic acid
CSA	-	Camphor sulfonic acid
CSI	-	Chloro sulfonyl isocyanate
DCM	-	Dichloromethane
D_2O	-	Deuterium oxide
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	-	Diastereomeric excess

DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis (dihydroquinin-9-O-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis (dihydroquinidin-9-O-yl)phthalazine
$(DHQD)_2AQN$	-	1,4-Bis (dihydroquinidin-9-O-yl)anthraquinone
DIBAL-H	-	Diisobutyl aluminium hydride
Dioxane	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	-	Diisopropyl ethylamine
DMF	-	*N*, *N*-Dimethyl formamide
2,2'-DMP	-	2,2'-Dimethoxy propane
DMP	-	Dess-Martin periodinane
DMAP	-	*N*,*N*-Dimethyl aminopyridine
DMSO	-	Dimethyl sulfoxide
dr	-	Diastereomeric ratio
ds	-	Diastereoselectivity
ee	-	Enantiomeric excess
ent	-	Enantiomer
eq. or equiv.	-	Equivalent
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
Et_3N	-	Triethyl amine
g	-	Gram
h	-	Hour
HMPA	-	Hexamethyl phosphoramide
HPLC	-	High Pressure Liquid Chromatography
HQ	-	2-Hydroxy quinolinone
H_Z	-	Hertz
IBX	-	2-Iodoxy benzoic acid
Im	-	Imidazole
^{i}Pr	-	Isopropyl
IR	-	Infrared
KHMDS	-	Potassium hexamethyl disilazide

KH	-	Potassium hydride
$LiBH_4$	-	Lithium borohydride
LDA	-	Lithium diisopropylamide
LiHMDS	-	Lithium hexamethyl disilazide
m-CPBA	-	*meta*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Miligram
min	-	Minutes
ml	-	Mililitre
mmol	-	Milimole
M.P.	-	Melting point
MQ	-	Methyl quinolinone
Ms	-	Methane sulfonyl
MsCl	-	Methane sulfonyl chloride
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodium borohydride
NaH	-	Sodium hydride
NBS	-	*N*-Bromosuccinamide
NMNO	-	4-Methyl morpholin-*N*-oxide. monohydrate
$Pb(OAc)_2$	-	Lead diacetate
PCC	-	Pyridinium chlorochromate
Pd/C	-	Palladium on charcoal
Ph	-	Phenyl
PhMe	-	Toluene
PhSeSePh	-	Diphenyldiselenide
PMB	-	*para*-Methoxybenzyl
KF	-	Potassium fluoride
PPTS	-	Pyridinium *para*-toluenesulfonate
p-TsOH	-	*para*-Toluene sulfonic acid
py	-	Pyridine
Q	-	Quinolinone
RCM	-	Ring-closing metathesis

rt	-	Room temperature
sec-BuLi	-	*secondary*-Butyl lithium
TEA	-	Triethyl amine
TBAI	-	Tetra-*n*-butyl ammonium iodide
TBAF	-	Tetra-*n*-butyl ammonium fluoride
TBDMSCl	-	*tert*-Butyldimethylsilylchloride
TBS	-	*tert*-Butyldimethylsilyl
TBSOTf	-	*tert*-Butyldimethylsilyltrifluromethane sulfonate
TBDPS	-	*tert*-Butyldiphenylsilyl
TBDPSCl	-	*tert*-Butyldiphenylsilylchloride
^{t}Bu	-	*tert*-Butyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
THP	-	Tetrahydropyran
TLC	-	Thin Layer Chromatography
TMEDA	-	Tetramethyl ethylenediamine
TMSOTf	-	Trimethylsilyltrifluoromethane sulfonate
TPP	-	Triphenyl phosphine
TPS	-	*tert*-Butyl diphenylsilyl
Ts	-	*para*-Toluene sulfonyl
p-TsCl	-	*para*-Toluene sulfonyl chloride
$Zn(BH_4)_2$	-	Zinc borohydride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 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, MSL-75 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 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, 100-200 and 230-400 mesh) 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 are given in each section of chapter refers to that particular section of the chapter only.

ABSTRACT

The thesis entitled **"Development of new methodology using phosphorus ylides and enantioselective synthesis of pyrrolidine and piperidine alkaloids"** consists of five chapters.

Chapter 1. Introduction to Sharpless asymmetric dihydroxylation, Jacobsen's hydrolytic kinetic resolution and Wittig reaction.

Chapter 2. Synthesis of coumarin derivatives using phosphorus ylide.

Chapter 3. Asymmetric synthesis of hydroxylated piperidine alkaloids using Sharpless asymmetric dihydroxylation and hydroxylated pyridone derived alkaloids.

Chapter 4. Asymmetric dihydroxylation route towards the diastereoselective synthesis of polyhydroxylated pyrrolidine and indolizidine alkaloids.

Chapter 5. An easy access to enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone: a building block for pyrrolidine alkaloids.

Chapter 1:

Introduction to Sharpless asymmetric dihydroxylation, Jacobsen's hydrolytic kinetic resolution and Wittig reaction

This chapter gives a brief introduction to the Sharpless asymmetric dihydroxylation (AD),[1] Jacobsen's hydrolytic kinetic resolution (HKR)[2] and Wittig reaction.[3]

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to varied applications in drug and pharmaceutical industries. A large number of enantiomerically pure compounds have been obtained from nature, but quite a few of them are either not easily isolated or not available in useful amounts. However, an organic chemist can provide multi-gram biologically active compounds.

The ultimate goal of an organic chemist is, how to assemble a given target molecule from readily available starting materials and reagents in highly efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes.

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The pioneering work of K. B. Sharpless[1] on "Chirally catalyzed oxidation reactions" viz. the asymmetric epoxidation (AE) developed in early 1980 and the asymmetric dihydroxylation (AD) in early 1990 and newly developed asymmetric aminohydroxylation (AA) in 1995, bagged him the 'Nobel Prize' in chemistry in the year 2001.
The hydrolytic kinetic resolution (HKR) of terminal epoxides[2] catalyzed by chiral (salen)-Co(III)OAc complex affords both recovered epoxide and 1,2-diol products in highly enantioenriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

The conventional Wittig reaction[3] entails the reaction of a phosphonium ylide with an aldehyde or a ketone. This olefination method has enjoyed wide-spread prominence and recognition because of its simplicity, convenience, and efficiency. Yet, despite such venerable attributes, the attractiveness of the Wittig reaction in synthesis may often hinge on effective stereocontrol. High selectivity for (*Z*)-or *(E)*- alkenes is available, depending on the particular circumstances, such as the type of ylide, type of carbonyl compound, or reaction conditions. Phosphorus ylides have been loosely classified according to their general reactivity. "Stabilized" ylides have strongly conjugating substituents (e.g. COOMe, CN, or SO_2,Ph) on the ylidic carbon and usually favor the production of *E*-alkenes, "semistabilized" (or "moderated") ylides bear mildly conjugating substituents (e.g. Ph or allyl) and often give no great preference one way or the other, and "nonstabilized" ylides lack such functionalities and usually favor (*Z*)-alkenes.

In this chapter, we describe the development of Sharpless AD, development of HKR and Wittig reaction.

Chapter 2:

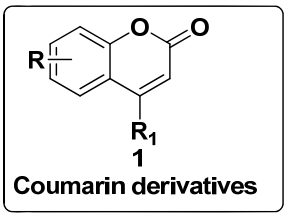
Synthesis of coumarin derivatives using phosphorus ylide

This chapter is further divided into two sections.

Section A:

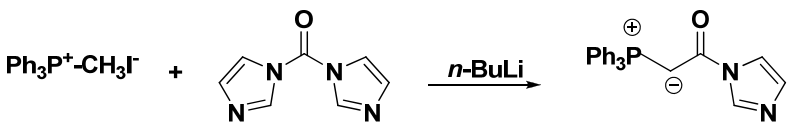
Synthesis of coumarin derivatives using triphenyl(α-carboxymethylene)phosphorane imidazolide as C-2 synthon

The intramolecular Wittig reaction has been extensively used as an excellent method for the C-C bond-forming process in the synthesis of natural products.[4] As part of our ongoing programme for developing a methodology employing phosphacumulene and (trimethylsilyl) methylene triphenyl phosphorane and their subsequent application to the biologically useful compounds,[5] triphenyl (α-carboxymethylene)phosphorane imidazolide **4**[6] is envisaged as a versatile reagent offering considerable opportunity for synthetic manipulation.



1
Coumarin derivatives

Ylide **4** was prepared by the reaction of carbonyl diimidazole (CDI) **3** and methylenetriphenyl phosphorane generated from the corresponding phosphonium salt **2** as depicted in Scheme 1.



2 **3** **4**

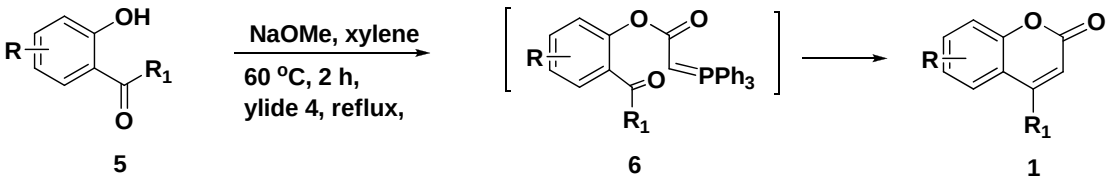
Wittig salt **CDI** **ylide**

Scheme 1. Synthesis of phosphorus ylide **4**

Coumarins **1** constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[7] They also represent the core structure of several molecules of pharmaceutical importance. The synthetic utility of **4** is hitherto unknown in the literature, and herein we report for the first time the application of triphenyl (*α*-carboxymethylene) phosphorane imidazolide as a C-2 synthon for the one-pot synthesis of biologically relevant coumarins.

Thus, the hydroxy carbonyl compounds **5** was first heated with NaOMe in xylene at 60 ^{o}C for 2 h and then reacted with ylide **4** under reflux conditions to afford phosphorane **6** which underwent intramolecular Wittig cyclization to furnish the desired coumarin derivatives **1** in good yields (Scheme 2).

Synthesis of coumarin derivatives



5 6 1

Scheme 2. Synthesis of coumarin derivatives

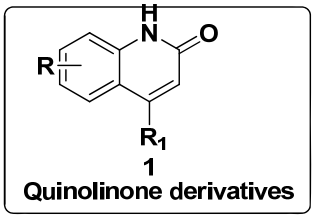
The generality of this concept has been established with several examples.

Based on the above results we have studied 10 different examples for the synthesis of coumarin derivatives.

Section B:

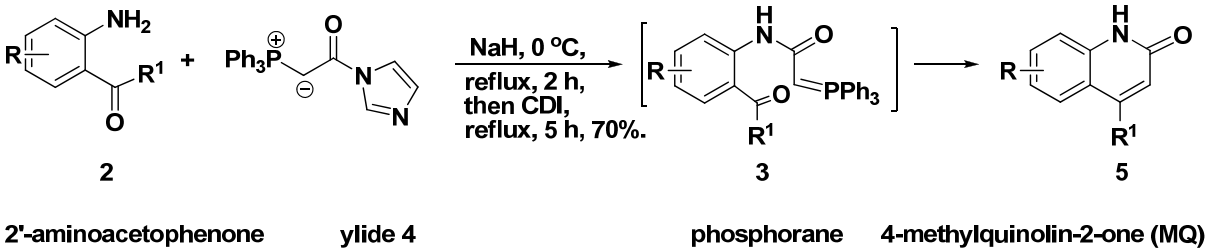
Synthesis of quinolinone derivatives using triphenyl(α-carboxymethylene)phosphorane imidazolide as C-2 synthon

Similarly, we have also synthesized the *N*-analogoues of coumarin, i.e. quinolinone derivatives from *O*-aminocarbonyl compound using above phosphorus ylide **4** as C-2 synthon (as described in Sec A). Nitrogen-containing heterocycles play a privileged role in medicinal chemistry. Quinolinones are an interesting class of molecules present in a number of biologically active natural products. This core is present in the antibiotics nybomycin and deoxynybomycin isolated from streptomycete cultures.[8]



Synthesis of quinolinone derivatives

When 2-amino acetophenone **2** was treated with phosphorus ylide in presence of NaH under reflux condition, it gave the desired quinolinone derivative **5** via intramolecular Wittig cyclisation of phosphorane **3** (Scheme 1).



Scheme 1. Synthesis of quinolinone derivatives **5**

On the basis of the above reaction we have also studied 4 different substituted *O*-aminocarbonyl compound that gave quinolinone derivatives in reasonably good yield.

Chapter 3:

Asymmetric synthesis of hydroxylated piperidine alkaloid using Sharpless asymmetric dihydroxylation and hydroxylated pyridone derived alkaloids

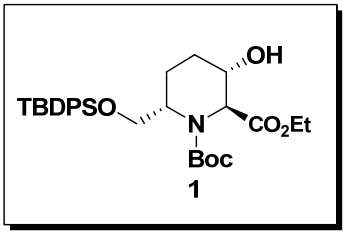
Alkaloids were known in ancient times because they could be easily extracted from plants and some of them have powerful and deadly effects. Any plant contains a millions of chemical compounds, but some plants like deadly nightshade, can be mashed up and extracted with aqueous acid to give a few compounds soluble in that

medium which precipitate on neutralization. These compounds were seen to "like-alkali" and Meissner, the apothecary from halle, in 1819, named them "alkaloids".
This chapter is further divided into three sections.

Section A:

Studies toward stereoselective synthesis of hydroxylated (2*S*,3*S*,6*S*)-1-*tert*-butyl-2-ethyl, 6-(*tert*-butyldiphenylsilyloxy)methyl)-3-hydroxypiperidine-1,2-dicarboxylate

Among the multifunctionalized piperidine alkaloids widely found in nature, 3-hydroxy-2,6-disubstituted prosopis alkaloids, have attracted much attention because of their interesting biological properties and stereochemical variations at the C-2, C-3, and C-6 position.[9a] Target molecule **1** is an important building block for the synthesis of (+)-prosopinine and (+)-deoxoprosopinine. To synthesize the target molecule **1**, we have chosen L-glutamic acid as a chiral pool starting material. To date there is no report about its synthesis using Sharpless asymmetric dihydroxylation (AD) as a key step.

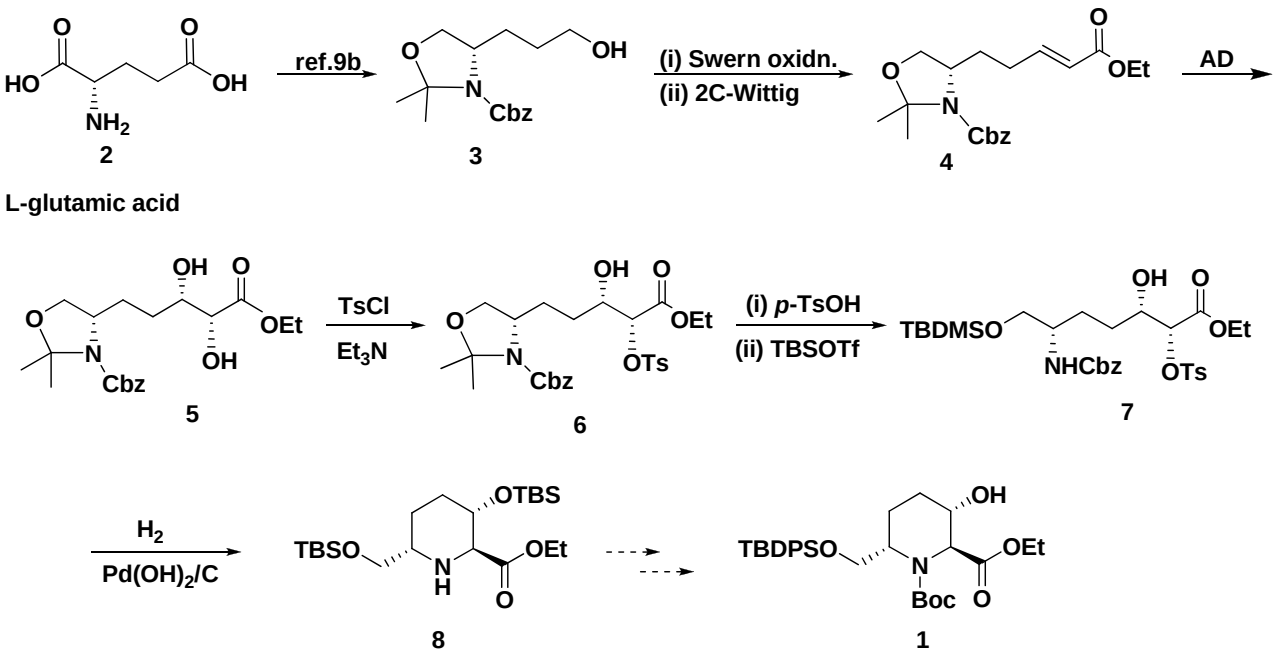


1

As illustrated in Scheme 1, compound **3** was prepared in four steps from commercially available L-glutamic acid following a literature procedure.[9b] Compound **3** was oxidised to the corresponding aldehyde under the Swern conditions[10] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF at room temperature to furnish the *trans*-olefin **4**. Dihydroxylation of olefin **4** under the Sharpless asymmetric dihydroxylation conditions[1] using $(DHQ)_2PHAL$ ligand gave the diol **5** as a single diastereomer. The diastereoselectivity was confirmed by ^1H and ^{13}C-NMR spectroscopy. The regioselective α-tosylation[11] of hydroxyl group of **5** was carried out using tosyl chloride in the presence of triethyl amine to give **6**. The deprotection of isopropylidene under acidic conditions and subsequent protection of both the resulting hydroxy groups with TBS-OTf /2,6-lutidine afforded compound **7** in excellent yield. Finally Cbz group was cleaved with H_2, $Pd(OH)_2$ /C followed by in situ intramolecular

cyclisation with the inversion of configuration at C2 centre to furnish the desired molecule **8** in 40% yield.

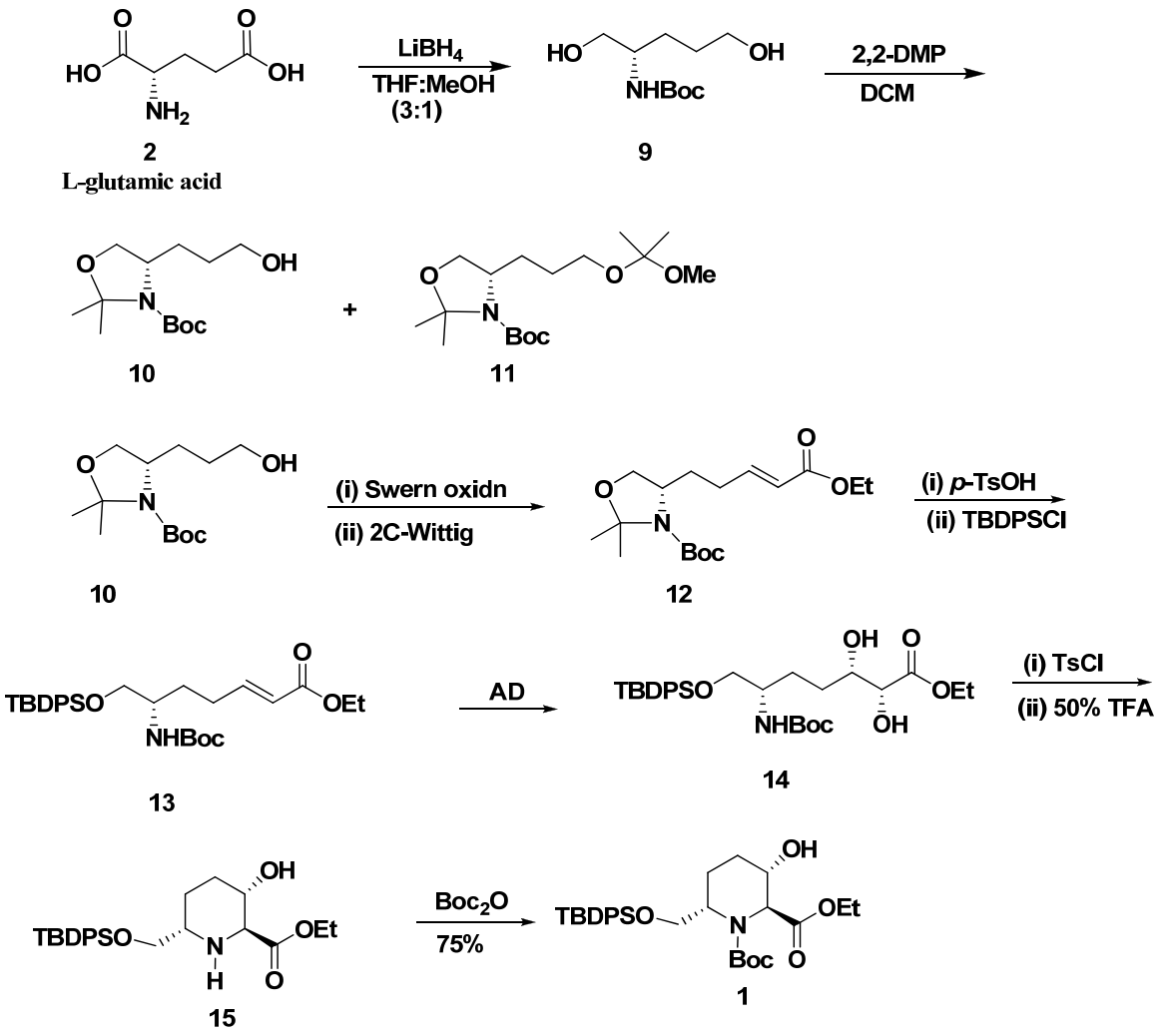
Scheme 1



Strategy II: Since during Cbz deprotection and intramolecular cyclisation under S_N2 conditions, we got only 40% of 2,6-disubstituted piperidin-3-ol derivative along with the recovery of starting material (as shown above in Scheme 1), therefore, we thought to change the amino protecting group from Cbz to Boc and try the sequence of reaction as shown in Scheme 2.

The substrate α,β-diol ester **14** was prepared from olefinic ester **13** by Sharpless asymmetric dihydroxylation condition[1] in reasonably good yield. The subsequent regioselective α-tosylation[11] of hydroxyl group of **14** and subsequent Boc group deprotection with 50% TFA followed by cyclisation in the presence of diisopropyl ethylamine afforded the piperidinol derivative **15** in 70% yield. Finally, amino group was protected with Boc_2O to give the target molecule **1** in 75% yield.

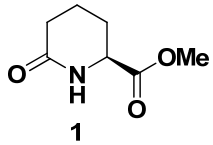
Scheme 2



Section B:

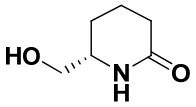
Enantioselective synthesis of (*S*)-(+)-2-(hydroxymethyl)-6-piperidin-2-one

The title compound **2** is an important class of antitumor agent and useful for the synthesis of pipecolic acid derivatives. There has been considerable interest in the development of synthetic routes to substituted piperidines, piperidinones and indolizidines due to their wide spread occurrence in nature and important biological activity.[12] We have synthesized the target molecule **2**[13] from L-aspartic acid using 2-C Wittig olefination as a key step.



1

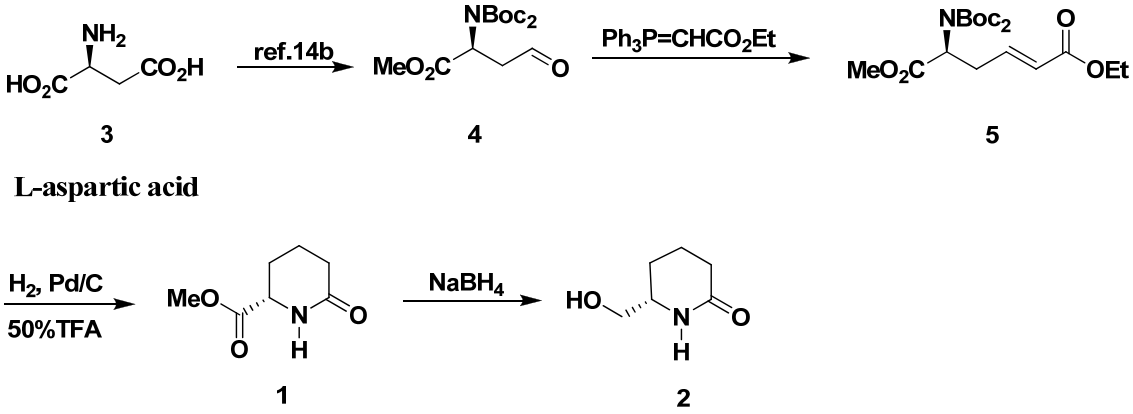
Methyl-6-oxopipecolate



2

(*S*)-2-Hydroxymethyl-6-piperidinone

Scheme 1



3 4 5

L-aspartic acid

1 2

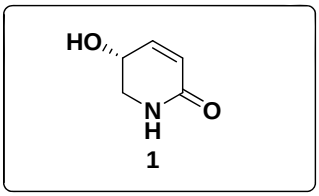
The L-aspartic semialdehyde **4**[14] on treatment with 2C-Wittig reagent afforded unsaturated ester **5**. Hydrogenolysis of compound **5** and finally deprotection of Boc group with 50% TFA followed by neutralization with sat. $NaHCO_3$ gave the desired product **1**[13] in 80% yield. Finally, compound **1** was reduced to the target molecule **2** using known procedure.[13]

Section C:

A facile synthesis of 5,6-dihydro-5-hydroxy-2(1*H*)pyridone

The title compound **1** has been isolated from whole plant of *Piper sentenense* and is known to exhibit interesting biological activities such as anti HIV, antifungal, antibacterial and cytotoxicity against P-388, H-T-29 or A-549 cell lines in vitro.[15a] It is an important building block for the synthesis of (*R*)-pipermethystine [15b] and several other polyhydroxylated pyridones.[15c] As a part of our research on the asymmetric synthesis of hydroxylated piperidines, we became interested in developing a route to 2-

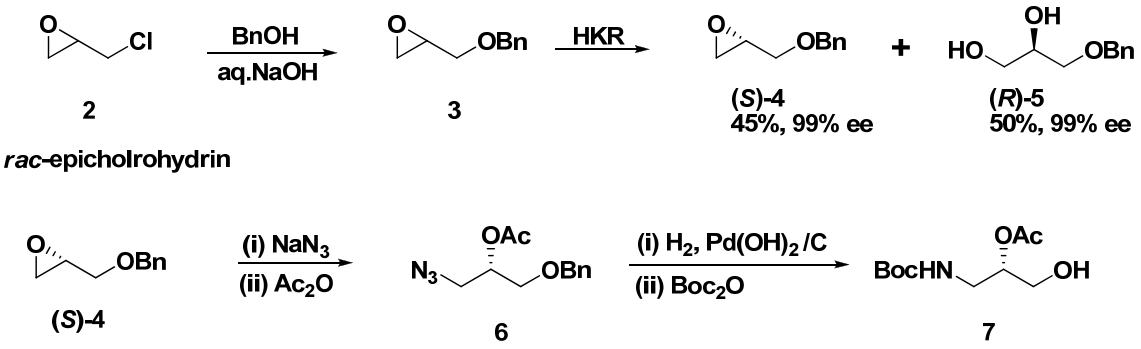
pyridone derivatives. Herein we describe our successful endeavors towards a new approach to 5,6-dihydro-5-hydroxy-2(1*H*)-pyridone from L-serine using Horner–Emmons olefination as the key step.



1

As illustrated in Scheme 1, the synthesis of **1** commenced with commercially available *rac*.epichlorohydrin **2** which was transformed into benzyl protected glycidol[16] **3** in presence of benzyl alcohol and sodium hydroxide.

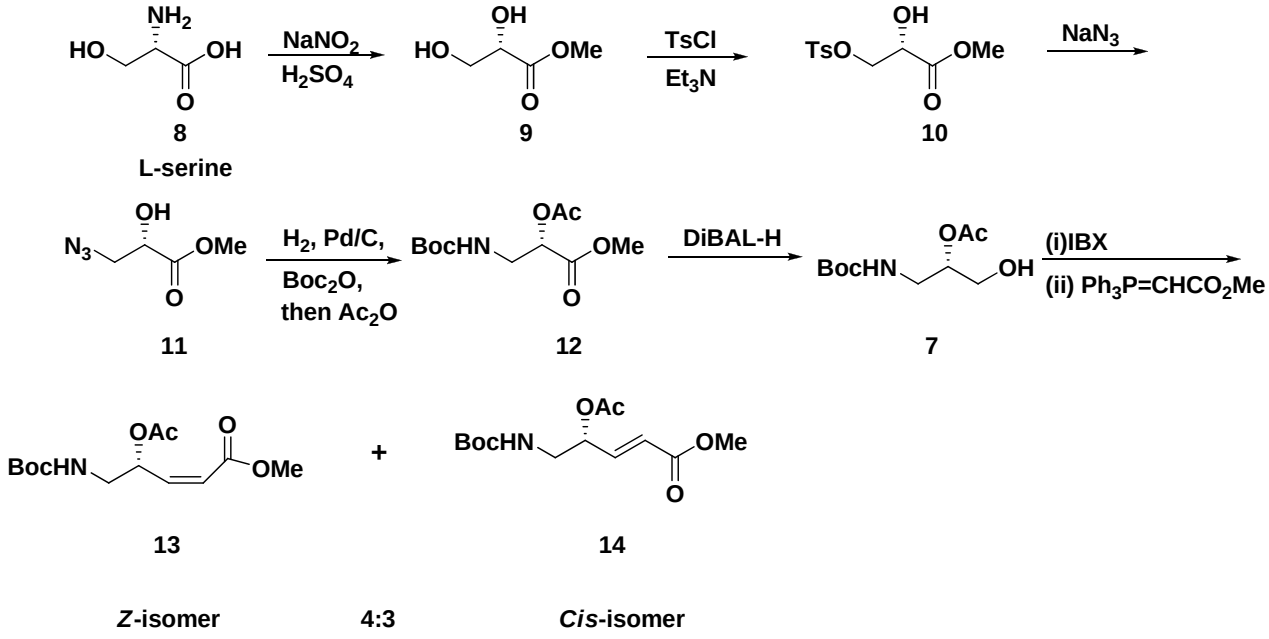
Scheme 1



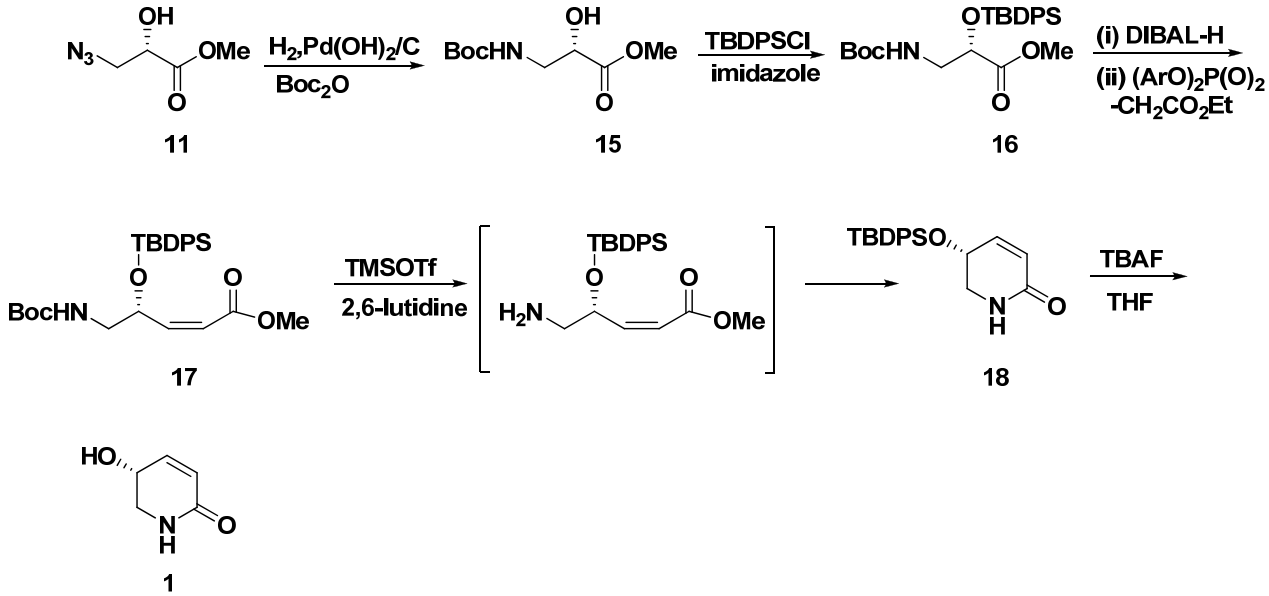
2 — *rac*-epicholrohydrin; 3; (*S*)-4 45%, 99% ee; (*R*)-5 50%, 99% ee; (*S*)-4; 6; 7

The glycidol **3** was then resolved using (*S,S*)-Co-salen catalyst (Jacobsen resolution)[2,17] to give (*S*)-epoxide **4** and (*R*)-diol **5** with 99% *ee*. Regioselective opening of (*S*)-epoxide **4** was carried out using NaN_3 and subsequent acylation of resulting azide gave azido acetate **6**. Concomitant benzyl deprotection, reduction of azide to amine and in situ Boc protection afforded the amino alcohol **7**. Since we lose 50% of diol as side product, we thought to prepare the intermediate **7** from L-serine in five steps (Scheme 2). Oxidation of alcohol **7** with IBX followed by 2C-Wittig olefination in MeOH at 0 ^{o}C resulted in a mixture of both *cis* and *trans*-isomers in the ratio **4:3**. The ratio of desired *cis-isomer* could not be improved even after performing the reaction at lower temperature (Scheme 2).

Scheme 2



Scheme 3



To circumvent the problem of low yield, we thought of masking the hydroxyl group preferably with a bulky protecting group. Towards this end, the azido compound **11** was converted into compound **16** under routine transformation (Scheme 3). The compound **16** was reduced with 1.2 equiv of DIBAL-H at -78 ^{o}C to the corresponding aldehyde and subsequently subjected to 2C-Wittig olefination in MeOH at -78 ^{o}C.

However, we could not observe much improvement in the ratio of *cis-isomer*. With an aim to prepare the required cis-compound, we then employed the new Horner-Emmons reagent, diarylphosphonoacetate for the highly selective synthesis of *Z*-unsaturated ester as reported by Ando.[18]

Thus, the aldehyde obtained from **16** was treated with Horner-Emmons reagent, methyl (ditolylphosphono)acetate to produce the *cis-olefin* **17** as the major isomer (98:2).

Finally, cleavage of Boc group with TBSOTf and subsequent deprotection of TBDPS group with TBAF afforded pyridone **1**[15a] in good yield (Scheme 3).

Chapter 4:

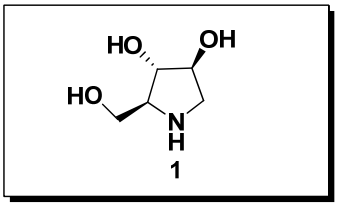
Asymmetric dihydroxylation route towards the diastereoselective synthesis of polyhydroxylated pyrrolidine and indolizidine alkaloids

This chapter is further divided into two sections.

Section A:

Asymmetric dihydroxylation route towards stereoselective synthesis of polyhydroxylated (2*S*,3*S*,4*S*)-2-(hydroxymethyl)pyrrolidin-3,4-diol (LAB 1)

The synthesis of polyhydroxylated pyrrolidine alkaloids/azasugars has attracted a great deal of attention, and a number of methods have been developed in recent times. In view of the presence of α-hydroxymethyl-dihydroxypyrrolidine as the common structural feature in many azasugars, an attractive approach to these compounds would be by installation of the α-hydroxymethyl group in a straight forward manner.[19]

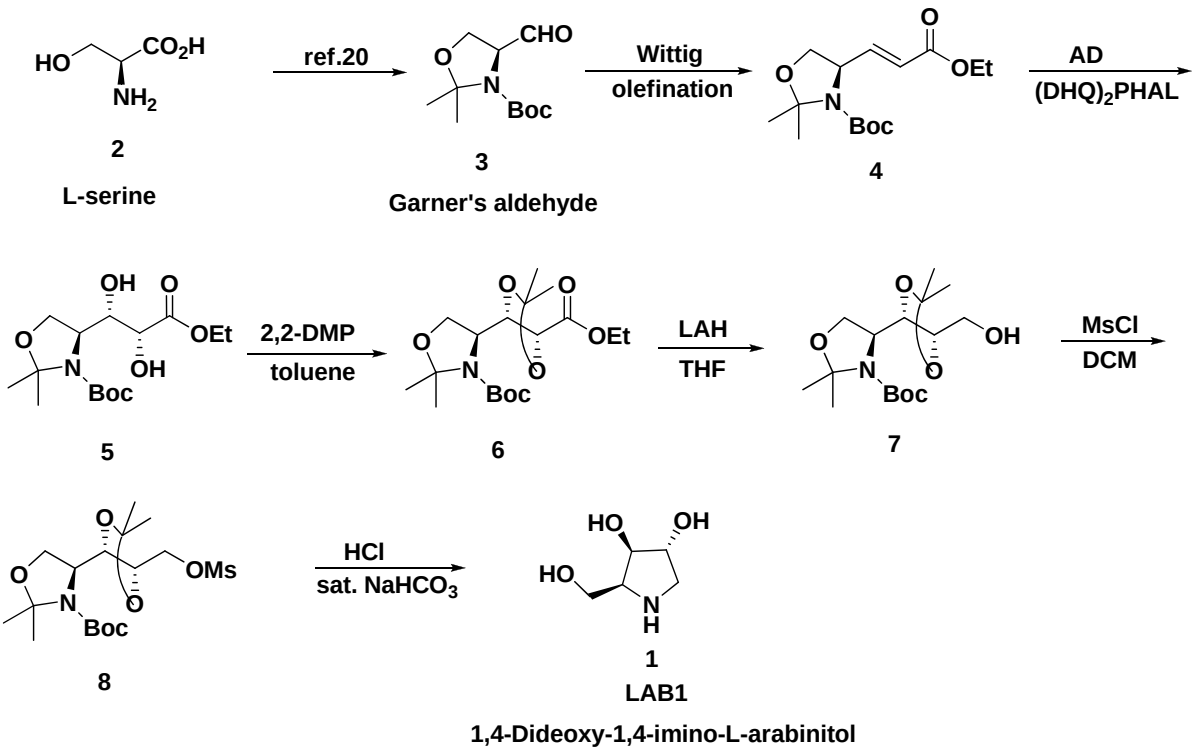


1

Various synthetic methods for the synthesis of hydroxyprolines and pyrrolidines have been reported from carbohydrates and from non-carbohydrates out of which there are very few synthesis of hydroxylated pyrrolidine derivatives with the use of α-amino

aldehydes as the synthetic precursor. The synthesis of **1** started from Garner's aldehyde which in turn was synthesized from L-serine using known procedure.[20] After preparation of Garner's aldehyde we subjected this for 2C-Wittig olefination and subsequent Sharpless asymmetric dihydroxylation of resulting olefin **4** afforded diol ester **5** in a ratio of 9:1 diastereoselectivity.[21,22] The diol **5** was treated with 2,2-DMP in presence of *p*-toluenesulphonic acid to give the ester **6** in 90% yield. Reduction of ester group of **6** with LAH and subsequent mesylation followed by global deprotection with 2N HCl gave the desired molecule **1** (LAB **1**)[23] in a reasonably good yield.

Scheme 1

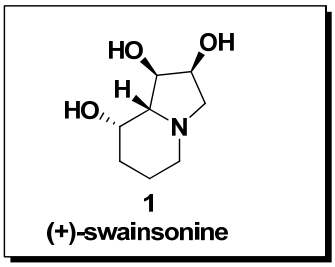


Section B:

Attempted synthesis of (+)-1,2,8-tri-*epi*-swainsonine

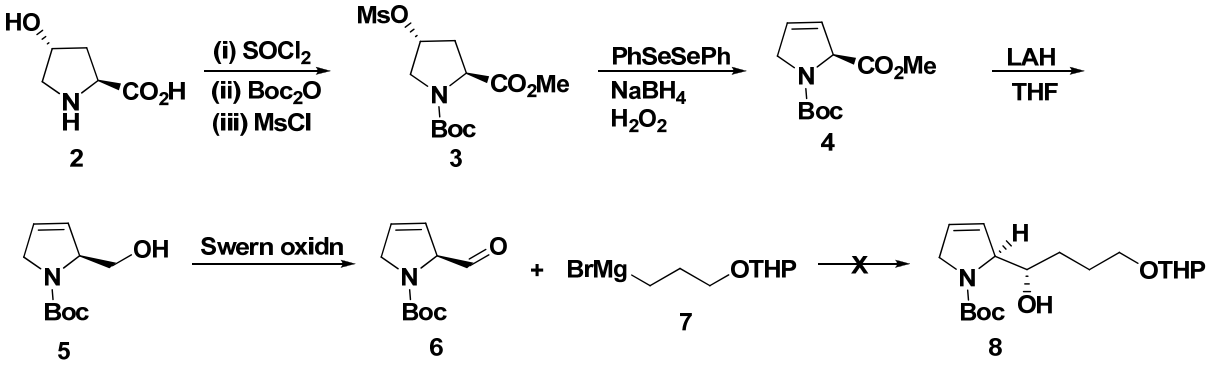
Polyhydroxy indolizidine alkaloids possess a wide range of biological activities such as immunoregulatory activity, anti-HIV activity and anticancer activity.[24,25] For the synthesis of (+)-swainsonine, 4-hydroxy-L-proline was chosen as the chiral pool starting material and dihydroxylation and Grignard reaction was employed as the key

steps. Thus, the substrate **5** is prepared from 4-hydroxy-L-proline under known procedure.[26]



1
(+)-swainsonine

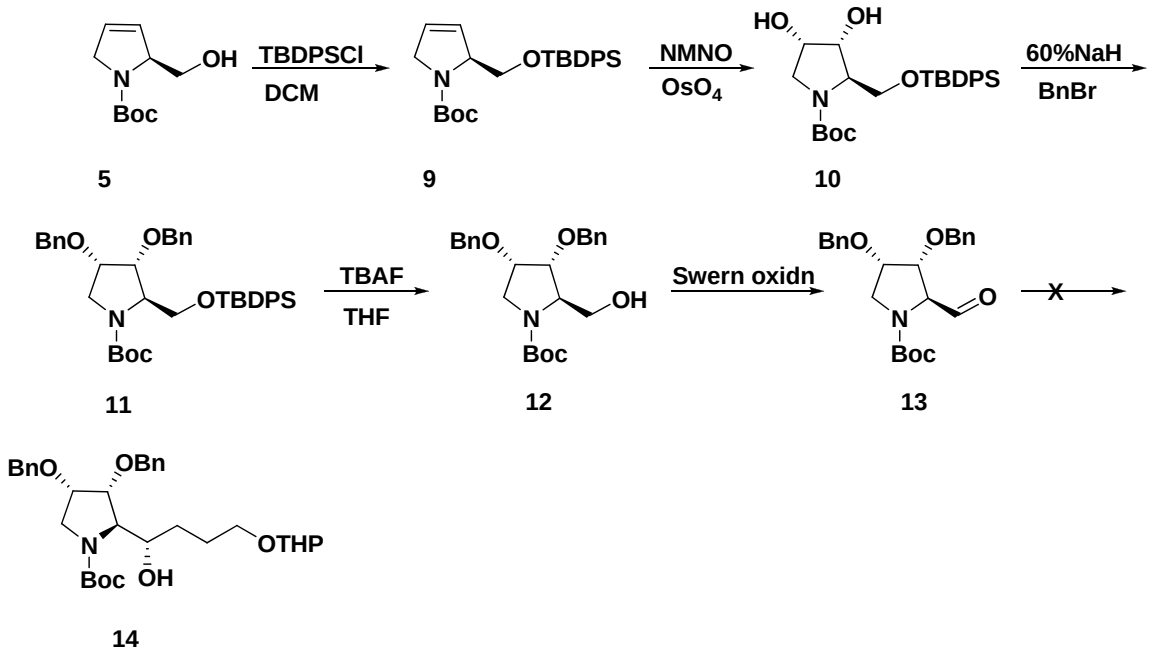
Scheme 1



Alcohol **5** was oxidized under Swern oxidation to give the aldehyde **6** in good yield. The crude aldehyde **6** was then treated with Grignard reagent **7**, ($THPO(CH_2)_3MgBr$), that led to the formation of only mixture of compounds and decomposed product (Scheme 1).

The failure of reaction may be attributed to the isomerisation of doule bond present in the ring. To avoid this problem we carried out dihydroxylation of compound **9** to give the diol **10** in ratio of 99:1 of diastereoselectivity.[26] Benzyl protection of diol **10** and subsequent deprotection of TBDPS group with TBAF gave the amino alcohol **12** in 75% yield. Oxidation of alcohol under Swern conditions[10] gave the aldehyde **13** which was immediately used for Grignard reaction. However we could not get the expected product **14**. Therefore, this route was not further pursued and eventually abandoned (Scheme 2).

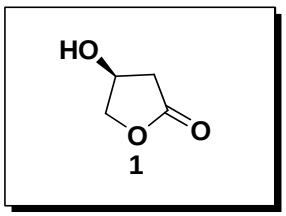
Scheme 2



Chapter 5:

An easy access to enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone: a building block for pyrrolidine alkaloids

(*S*)-3-Hydroxy-γ-butyrolactone is an important synthetic intermediate for a variety of chiral compounds. It serves as key intermediate for the preparation of neuromediator (*R*)-GABOB, L-carnitine,[27] and HMG-CoA reductase inhibitor, CI-981.[28]

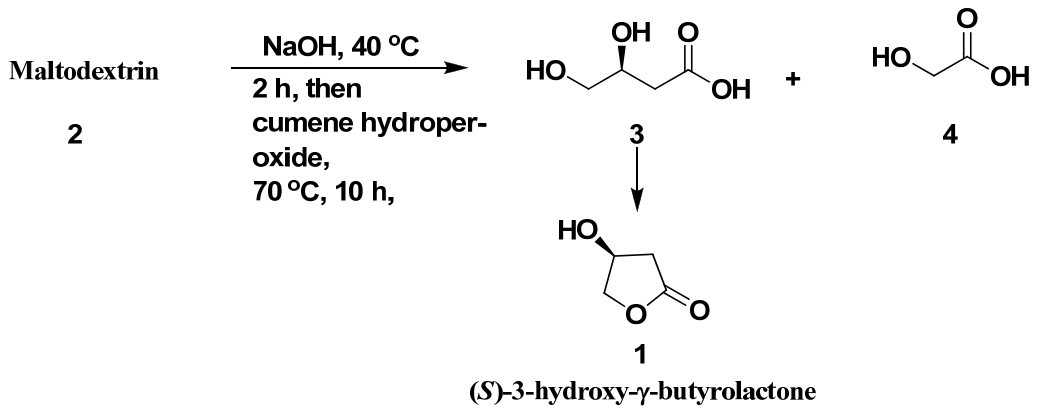


1

(*S*)-3-Tetrahydrofuran derived from 3-hydroxy-γ-butyrolactone is an intermediate for an AIDS drug.[29] (*S*)-3-Hydroxy-γ-butyrolactone is important building block for the synthesis of hydroxylated pyrrolidine and pyrrolidinone derivatives. [30] It possesses

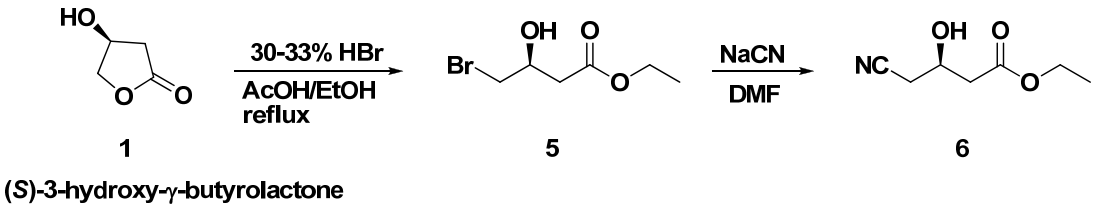
interesting biological activities and it serves as useful building block for statin based cholesterol lowering drugs.

Scheme 1



The synthesis of (*S*)-3-hydroxy-γ-butyrolactone started from the readily available carbohydrate source as depicted in Scheme 1. Thus, a 1,4-linked $_D$-hexose sugar, such as maltose/maltodextrin/lactose was treated with cumene hydroperoxide under basic conditions at 70 ^oC to give 3,4-dihydroxybutyric acid **3**, which was cyclized in the presence of an acid to afford the desired butyrolactone **1** in reasonably good yield.[30,31]
Our next aim was to convert lactone compound **1** into useful chiral intermediate such as cyanoester **6** in two steps (Scheme 3).

Scheme 2



When hydroxy lactone **1** was first treated with 30-33% HBr in AcOH/EtOH, it gave the corresponding bromo ester **5** in 85% yield. The subsequent treatment with sodium cyanide furnished the cyano compound **6** (by direct displacement of bromo with cyano) in about 50% yield. Cyano ester **6** is a chiral intermediate in the preparation of statin based drugs (cholesterol lowering drugs), such as mevacor, atorvastatin, lipitor, etc.

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1. Enantioselective Synthesis of (*R*)-phenylephrine hydrochloride.

   Rajesh Kumar Pandey, **Puspesh Kumar Upadhyay** and Pradeep Kumar *Tetrahedron Lett*. **2003**, *44*, 6245-6346.

2. An efficient enantioselective synthesis of (2*S*,3*S*)-3-hydroxy-2-phenyl piperidine.

   Mandar S. Bodas, **Puspesh K. Upadhyay** and Pradeep Kumar *Tetrahedron Lett*. **2004**, *45*, 987-988.

3. Process for preparing enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone.

   M. K. Gurjar, Pradeep Kumar, A. N. Deshmukh, R. K. Upadhyay and **Puspesh K. Upadhyay**, US patent no. 6, 713, 639. (5th May, **2005**).

4. A novel synthesis of coumarin employing triphenyl (α-carboxymethylene)phosphorane imidazolide as C-2 synthon. **Puspesh K. Upadhyay** and Pradeep Kumar *Tetrahedron Lett.* **2009**, *50*, 236-238.

5. A facile synthesis of 5,6-dihydro-5-hydroxy-2(1*H*) pyridone. **Puspesh K. Upadhyay**, Rajendra Prasad, Menaka Pandey and Pradeep Kumar *Tetrahedron Lett*. **2009**, *50*, 2440-2442.

6. Asymmetric dihydroxylation route towards stereoselective synthesis of hydroxylated (2*S*,3*S*,6*S*)-1-*tert*-butyl-2-ethyl-6-((*tert*-butyldiphenylsilyloxy)methyl)-3-hydroxypiperidine- 2-dicarboxylate. **Puspesh K. Upadhyay** and Pradeep Kumar (manuscript under preparation).

7. Diastereoselective synthesis of (2*S*,3*S*,6*S*)-2-(hydroxymethyl)pyrrolidin-3,4-diol.

   Puspesh K. Upadhyay and Pradeep Kumar (manuscript under preparation).

8. Enantioselective synthesis of (*S*)-6-(hydroxymethyl)-piperidin-2-one.

   Puspesh K. Upadhyay and Pradeep Kumar (manuscript under preparation).

9. Synthesis of quinolinone from *O*-aminocarbonyl compound using triphenyl(α-carboxymethylene)phosphorane imidazolide as C-2 synthon. **Puspesh K. Upadhyay** and Pradeep Kumar (manuscript under preparation).

Symposia/ Conferences Attended

1. A novel one-pot synthesis of coumarin employing triphenyl (α-carboxymethylene) phosphorane imidazolide as C-2 synthon. Presented at NSC-5 in CLRI Chennai, India in Feb **2003**.
2. Stereoselective synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine: Application to the synthesis of NK1 receptors. IUPAC symposium on Biodiversity and Natural Products, New Delhi, January 27-31, **2004**.
3. Asymmetric dihydroxylation route to (2*R*,3*S*,6*S*)2,6-bis (hydroxymethyl) piperidin-3-ol. Presented at NSC-10 in IISc, Bangalore, India in Feb **2008**.
4. Attended 4th INSA- KOSEF Symposia in Organic chemistry, NCL, India in **2009**.

CHAPTER 1

Introduction to Sharpless asymmetric dihydroxylation, Jacobsen's hydrolytic kinetic resolution and Wittig reaction

1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

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 (Figure 1).

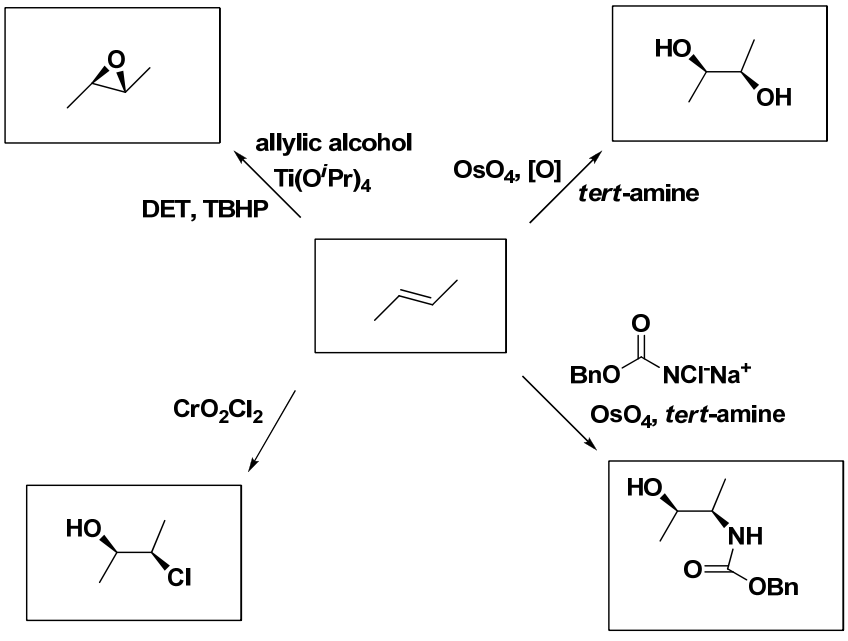


Figure 1. Transition metal mediated suprafacial 1,2-difunctionalisation of olefins

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.

A series of discoveries[5] gave a best reaction condition for dihydroxylation to be a biphasic reaction carried out in 1:1 mixture of water: *t*-BuOH, using catalytic OsO_4, and $K_3Fe(CN)_6$ as the stoichiometric re-oxidant along with K_2CO_3, methane sulphonamide in the presence of "dimeric" PHAL or PYR ligands (Figure 2 and 3).

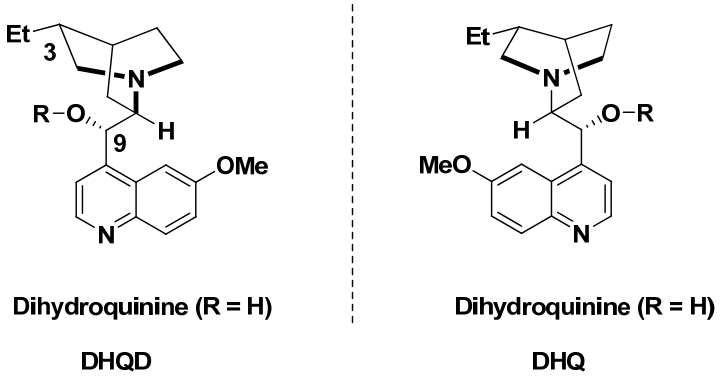


Figure 2. Cinchona alkaloid ligand for AD under catalytic conditions

The two independent cinchona alkaloid units (phthalazine core)[8] and (diphenylpyrimidine core)[9] attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (Figure 3).

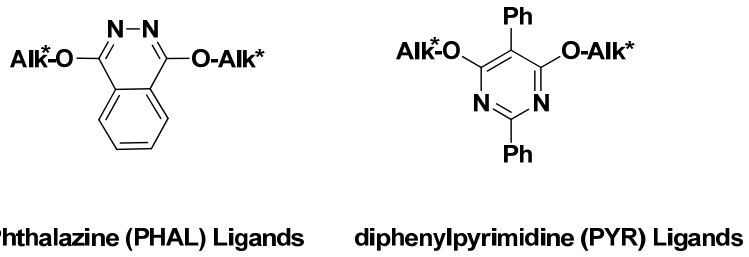


Figure 3. Latest generation of "dimeric" PHAL and PYR ligands

The resulting osmium (VI) monoglycolate ester undergoes hydrolysis and releases the diol and ligand to the organic layer and Os (VI) to the aqueous layer (Figure 4). Hydrolysis of Os (VI) glycolate ester can be accelerated by $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in presence of this additive. Due to this

sulphonamide effect, most AD reaction can be carried out at 0 ^{o}C rather than room temperature which normally has beneficial influence on the selectivity.[10] We routinely add 1.0 equiv of $MeSO_2NH_2$ to the reaction mixture[8] except for terminal olefins.

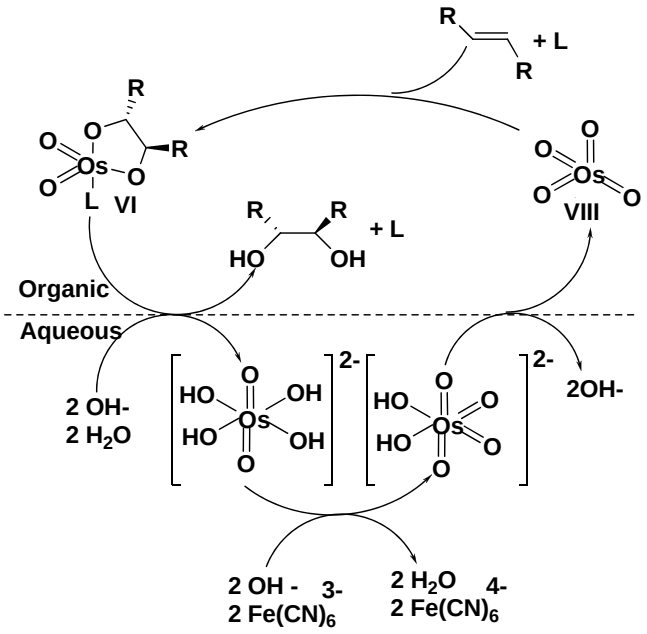


Figure 4. Catalytic Cycle of the AD reaction with $K_3Fe(CN)_6$ as the cooxidant[11]

1.1.2. Empirical rules for predicting the face selectivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device'.[12a] 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.[12c] An olefin which is placed into this olefin according to the constraints received the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (Figure 5).

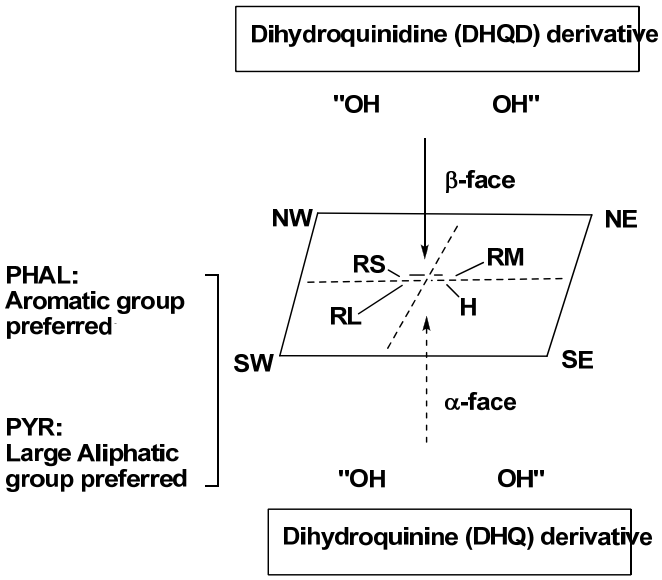


Figure 5. The mnemonic device for predicting the face selectivity

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.[12b] The key reagents are 3.0 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3.0 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[13] (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[14] like in trans-stilbene for which the enantioselectivity is as high as 99.8%.[9] 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[15] 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.[16]

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.[17] 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.[18] However, in certain cases better results are obtained with the new second generation ligands.[19]

1.2. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.2.1. Introduction

The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis. Amongst various syntheses, the enantioselective syntheses of complex natural products containing multiple stereocenters are often the most challenging. The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[20] Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis. As a consequence, the preparation of enantioenriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantioenriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantioenriched epoxyalcohols.[21] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)MnIII complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides. A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantioenriched form to a significant extent.[22] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[23]

Despite these considerable advances in asymmetric catalytic synthesis of epoxides, to date no general methods have been identified for the direct preparation of highly enantioenriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis. The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology[24] or by enzymatic kinetic resolution methods,[25] and these compounds have become widely used starting materials for target-oriented synthesis.[26] Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of *rac*-2,3-dichloro-1-propanol,[27] and it, too, has found widespread application.

The asymmetric catalysis provides a practical, cost effective and efficient synthesis of such molecules. Furthermore, the enantioselective synthesis of natural products by a catalytic process assumes significance since isolation from natural sources can only be accomplished in minute quantities. The use of catalytic methods not only provides an easy access to an enantiomerically pure product but also permits maximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogs required for biological activity. While tremendous advances have been made in asymmetric synthesis, substrate driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. In a kinetic resolution process, one of the enantiomers of the racemic mixture is transformed to the desired product while the other is recovered unchanged.

Epoxides are versatile building blocks that have been extensively used in the synthesis of complex organic compounds. Their utility as valuable intermediates has further expanded with the advent of asymmetric catalytic methods for their synthesis.[28] The terminal epoxides are a most important sub class of these compounds, but no general and practical methods were available for their synthesis in enantiomerically pure form.

Hydrolytic kinetic resolution (HKR) developed by Jacobsen has emerged in recent times as a powerful tool to synthesize both terminal epoxides and their corresponding diols in highly enantiomerically pure form.[29,30] The process uses water as the only

reagent, no added solvent, and low loading of recyclable chiral cobalt-based salen complexes to afford the terminal epoxides and 1,2-diol in high yield and high enantiomeric excess (Scheme 1). With the advent of the HKR method, synthetic organic chemists have gradually adopted this as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form. Since its discovery in the year 1997, HKR has got tremendous application for the synthesis of variety of compounds of biological interest.[33]

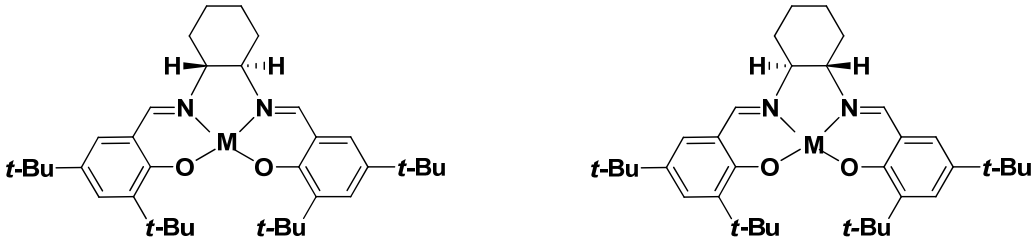
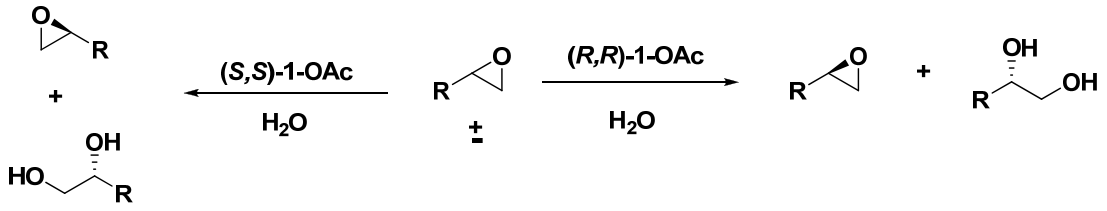


Figure 6. Jacobsen's catalyst

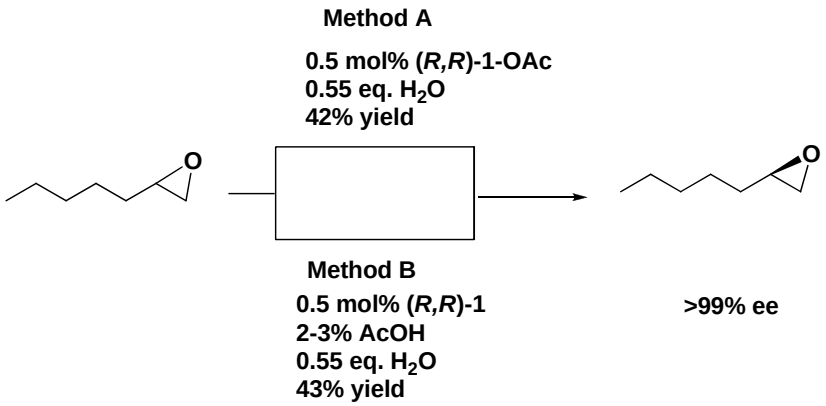


Scheme 1. Hydrolytic kinetic resolution (HKR) reaction[30,31,32]

Our group has recently compiled all the literature reports pertaining to the HKR application and published it in the form of a review article.[34] Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes.

1.2.2. Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen) CoII complex **1** are available commercially on research or commercial scale, or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **1** (Figure 6) is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen) CoIIIX complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc (Figure 6) is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **1**.OAc have been developed (Scheme 2). Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution and acetic acid (2.0 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**.OAc under HKR conditions by suspension of the Co (II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study.



Scheme 2. Resolution of epoxide

For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed. Aside from the method of generation of **1**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol% or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol%) to attain complete resolution. Reactions were initiated at 0°C and then allowed to warm to room temperature with continued stirring for 12-18 h.

[(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-1)

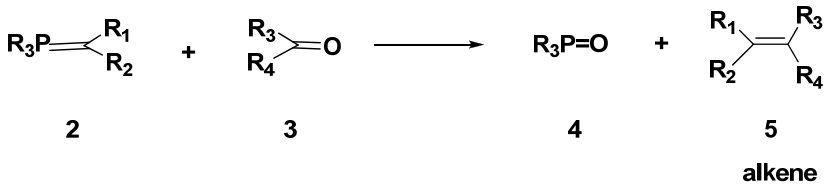
A solution of cobalt (II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL was added to a solution of ligand [(*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL) and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R,R*)-*N,N'*- bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-1) (11.6 g, 19.2 mmol, 96%).

1.3. WITTIG REACTION

1.3.1. Introduction

There was a time in organic chemistry when the olefination of ketones and aldehydes was faced with some trepidation. Because of limited synthetic methods, as recently as 50 years ago, the chemist had to contend with two isomer problems, that of double-bond position and that of double-bond geometry. Landmark papers published by Wittig and co-workers in the early 1950s disclosed a means for the preparation of alkenes with unambiguous positioning of the double bond, based on the reaction of aldehydes or ketones with phosphonium ylides. Because of its effectiveness and generality, the Wittig reaction became widely used and thereby changed the course of olefin synthesis for all time. Indeed, the development of the Wittig reaction helped to user in the modern era of organic synthesis, wherein positional selectivity, stereoselectivity, and chemoselectivity are of paramount importance to, and under the sensitive and responsive control of, the synthetic practitioner. The 1960s witnessed major advances in the Wittig reaction and in Wittig-style olefinations.[35a] The stereochemistry and mechanism of the Wittig reaction were investigated, and a complementary reaction involving phosphoryl-stabilized carbanions was developed. Several reviews have documented the state of the Wittig and related reactions.

In 1953, Wittig and Geissler discovered that the reaction of triphenylmethylenetriphenyl- phosphorane with benzophenone resulted in an almost quantitative yield of 1,1-diphenylethene and triphenylphosphine oxide (Scheme 3).[35b]



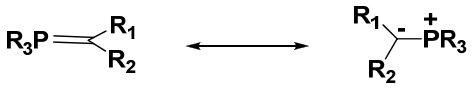
Scheme 3. Wittig reaction

Thus the reaction between a phosphorane or phosphonium ylide, and an aldehyde or ketone to form a phosphine oxide and an alkene is known as the Wittig reaction after

the German chemist George Wittig, who first showed the value of this procedure in the synthesis of alkenes. This unusual reaction leading to carbon-carbon bonds in one synthetic step was quickly applied to a large variety of different triphenylalkylidene phosphoranes and carbonyl compounds to give alkenes.

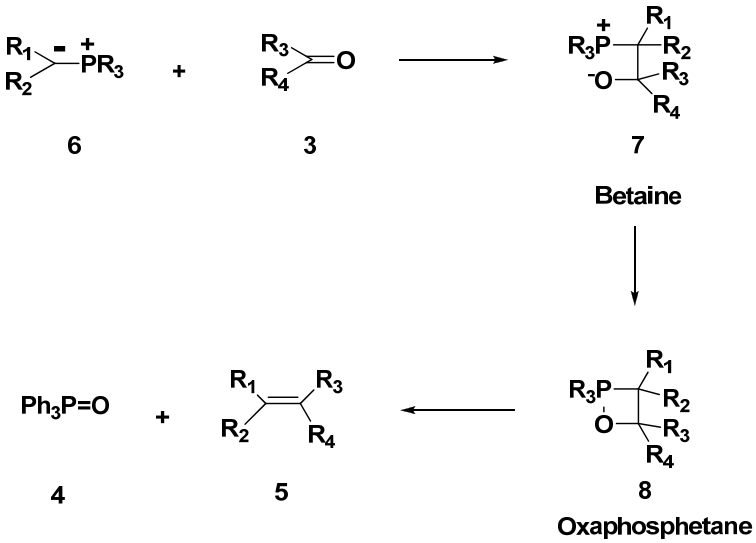
1.3.2. Phosphonium Ylides

Phosphoranes (phosphonium ylide) are resonance stabilized structure in which there is some overlap between the carbon *p*-orbital and one of the d-orbitals of phosphorus as shown in Scheme 4.



2 6

Scheme 4. Resonance stabilized ylide



6 3 7

4 5 8

Oxaphosphetane

Scheme 5. Mechanism of Wittig reaction

Reaction with a carbonyl compound takes place by attack of the carbanionoid carbon of the ylide form on the electrophilic carbon of the carbonyl group with the formation of a betaine which collapses to the products by way of a four-membered cyclic transition state, the driving force being provided by formation of the very strong phosphorus oxygen bonds. The reactivity of phosphorane **6** depends on the nature of the groups $\mathbf{R_1}$, $\mathbf{R_1}$ & $\mathbf{R_2}$. In practice, **R** is nearly always phenyl. Alkylidenetrialkylphosphoranes, in

which the formal positive charge on the phosphorus is lessened by the inductive effect of the alkyl groups, are more reactive than alkylidene triphenylphosphoranes in the initial addition to a carbonyl group to form a betaine (Scheme 5). In the alkylidene part of the phosphorane, if $\mathbf{R_1}$ or $\mathbf{R_2}$ is an electron withdrawing group (eg. CO or CO_2R), the negative charge in the ylide becomes delocalised into $\mathbf{R_1}$ or $\mathbf{R_2}$ and the nucleophilic character, and reactivity towards carbonyl groups is decreased. Reagents of this type are much more stable and less reactive than those in which $\mathbf{R_1}$ **or** $\mathbf{R_2}$ are alkyl groups and with them the rate determining step in reaction with carbonyl groups is the initial addition to form the betaine. The more electrophilic the carbonyl group the more readily does the reaction proceed. In the reaction of phosphonate anions and resonance stabilized ylides with aldehydes, the *E*-alkene generally predominates. Non-stabilized ylides, on the other hand, usually give more of the *Z*-alkene.

1.3.3. Stereochemistry of the Wittig reaction

The general rule is:

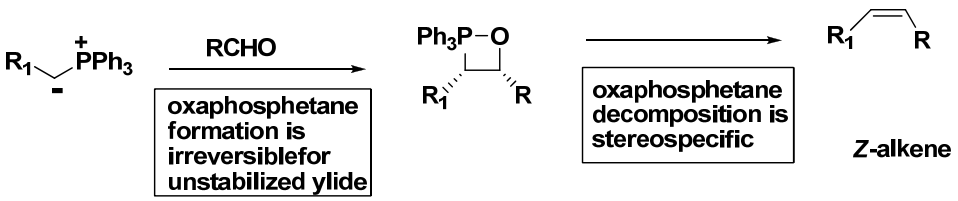
1. With stabilized ylides the Wittig reaction is *E* selective.
2. With unstabilized ylides the Wittig reaction is *Z* selective.

The Z-selective Wittig reaction

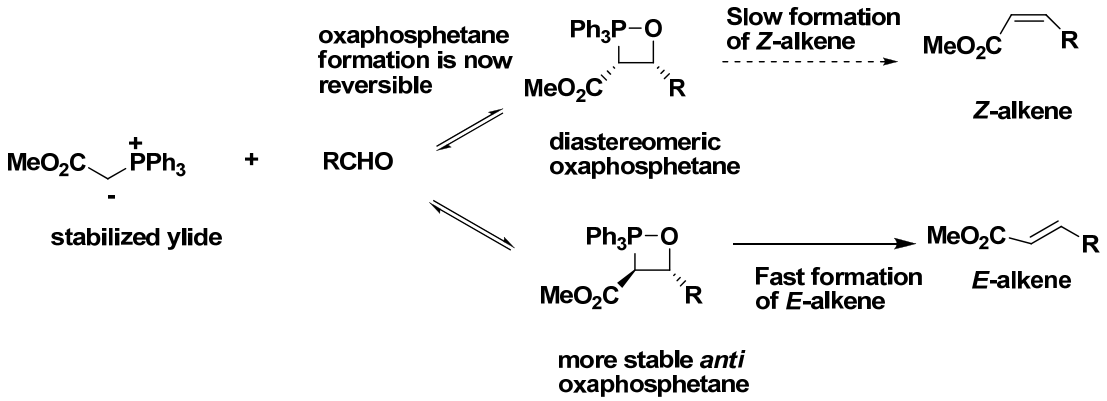
Stereoselectivity in Wittig reaction depends on the nature of ylide. When **R** is not conjugating or anion satbilizing; *syn* diastereomer of the oxaphosphetane is formed preferentially and predominantly *Z*-alkene was formed. The *Z*-selective Wittig reaction therefore consists of a kinetically controlled stereoselective first step followed by stereospecific elimination from this intermediate (Scheme 6).

The *E*-selectivity Wittig reaction

Stabilized ylides, that is ylide whose anion is stabilized by further conjugation usually within a carbonyl group to give *E*-alkenes on reaction with aldehydes (Scheme 7). These ylides are also enolates.



Scheme 6. Reaction of stabilized ylide with aldehyde



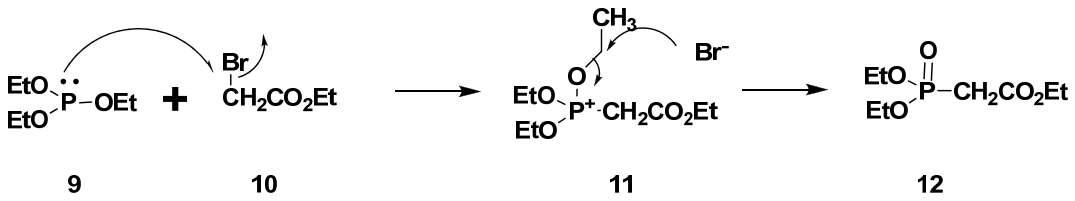
Scheme 7. Reaction of unstabilized ylide with aldehyde

The *anti* diastereomer is therefore 'siphoned off' to give *E*-alkene more rapidly than the *syn* distereomer. Meanwhile equlilibration of the two oxaphosphetane diastereomer via starting material replenishes the supply of *anti* diastereomer and virtually only *E*-alkene is produced (Scheme 7).

1.3.4. Modified Wittig-Horner reaction

Horner-Emmons, Wadsworth-Emmons, or Wittig-Horner reaction.

These ylides are more reactive than the corresponding phosphoranes, these compound often reacts with ketone that are inert to phosphoranes. In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike triphenyl phosphine oxide which makes it is easy to separate from the olefin product.



9 10 11 12

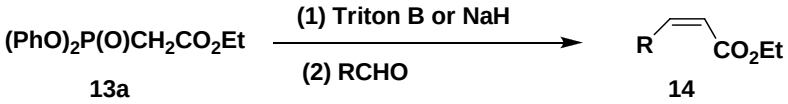
Scheme 8. Arbuzove reaction

The phosphonates are also cheaper than phosphonium salt and can easily be prepared by the arbuzov reaction (Scheme 8).

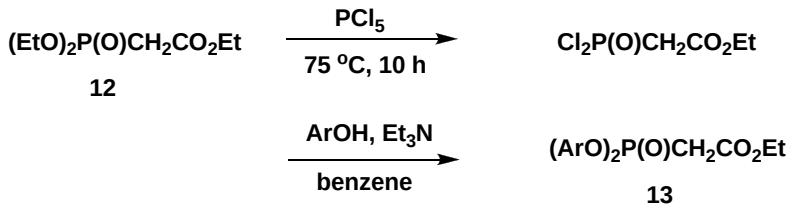
The Horner-Emmons modification of the Wittig reaction is a widely used method for the preparation of unsaturated esters. The phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form an olefin and a water soluble phosphate ester in good yields. However, in general, this reaction preferentially gives more stable *E*-disubstituted olefins. In order to prepare *Z*-olefins, several attempts have been made by the choice of cation, temperature, solvent, and phosphonate reagents, but they were with a limited success.[36,37] Some other reports on the preferential formation of *Z*-olefins involve the five membered cyclic phosphonate,[38] five-membered cyclic phosphonamide,[39] and bis(trifluoroethyl)phosphonate.[40] Among them, Still's method using methyl [bis(trifluoroethyl) phosphono]acetate in the presence of KHMDS/18- crown-6 in THF has been shown to be the most selective and versatile. Although this method has attained widespread recognition in synthesis,[35,41,] the use of 5 equiv of expensive and hygroscopic 18-crown-6 is a considerable drawback. Recently, Ando reported the preparation of ethyl (diphenylphosphono)acetate **13a** and the reaction of **13a** with some aldehydes in the presence of an inexpensive base, such as Triton B or NaH in THF to give Z-unsaturated esters **14** in 89-93% selectivity (Scheme 9).[42] Furthermore, when Still's conditions (KHMDS/18-crown-6) were applied to this reaction, selectivity for *Z*-isomers was increased up to 99%. Although **13a** is as Z-selective as Still's reagent, it still leaves some room for improvement.

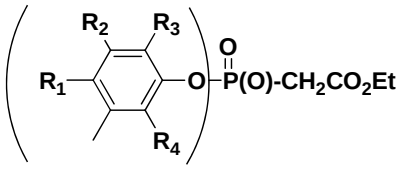
New Horner-Emmons reagents, ethyl (diarylphosphono)acetates **13**, were prepared from triethyl phosphonoacetate **12**, PCl_5, and the corresponding phenols (Scheme 10).

Scheme 9



Scheme 10





13a: $R_1 = R_2 = R_3 = R_4 = H$

13b: $R_1 = R_2 = R_4 = H$, $R_3 = Cl$

13c: $R_1 = R_2 = R_4 = H$, $R_3 = OMe$

13d: $R_1 = R_2 = R_4 = H$, $R_3 = Me$

13e: $R_1 = R_2 = R_4 = H$, $R_3 = Et$

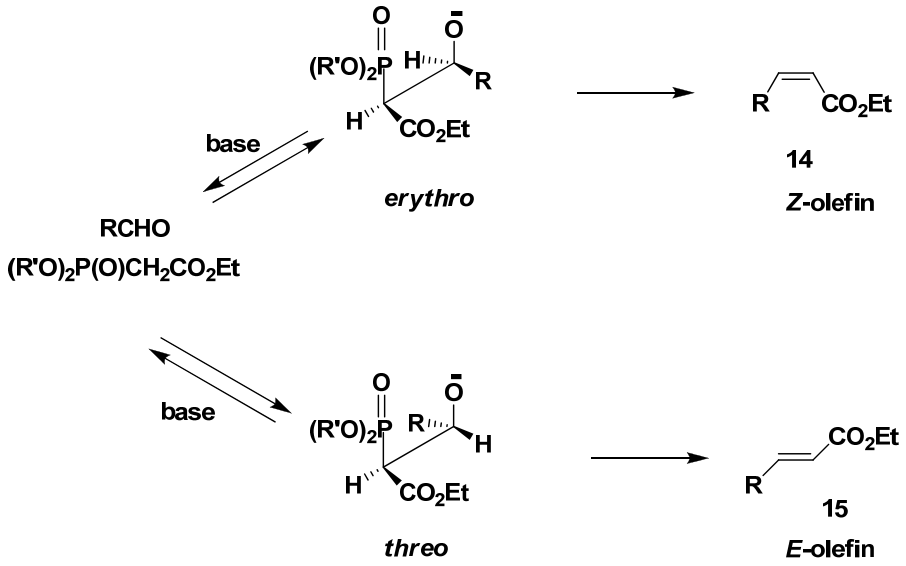
13f: $R_1 = R_2 = R_4 = H$, $R_3 = i\text{Pr}$

The reaction of **13** with several kinds of aldehydes in the presence of Triton B or NaH in THF solvent revealed that these reagents are useful for the synthesis of Z-unsaturated esters. Among these reagents, ethyl(di-*O*-tolylphosphono)-, [bis(*O*-ethylphenyl)phosphono]-, and [bis(*O*-isopropylphenyl)phosphono]acetates (**13d-f**) were found to be the most effective, giving *Z*-unsaturated esters with 93-99% selectivity.[43]

Stereoselectivity

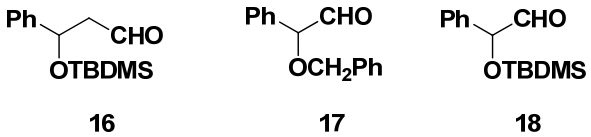
It is generally accepted that the stereoselectivity in Horner-Emmons reactions is a result of both kinetic and thermodynamic control upon the reversible formation of the *erythro* and *threo* adducts and their decomposition to olefins (Scheme 11).[42] That is, the stereochemistry is determined by a combination of the stereoselectivity in the initial carbon-carbon bond-forming step and reversibility of the intermediate adducts. The predominant formation of the *E*-olefins in the case of (dialkylphosphono) acetate reagents can be explained by the formation of thermodynamically more stable *threo*

adducts. On the other hand, the *Z*-stereoselectivities of the (diarylphosphono) acetate reagents **13** can be interpreted by the predominant formation



Scheme 11. Stereochemistry of Modified Wittig-Horner reaction[42,43]

of the erythro adducts which irreversibly collapse to the *Z*-olefins. Due to the electron-withdrawing character of the aryloxy group (p*K*a(PhOH)) 10.0 vs p*K*a(CF_3CH_2OH)) 12.4 vs p*K*a(CH_3CH_2OH)) 16), the electrophilicity of the phosphorus of the intermediate adducts derived from the reagents **13** is enhanced. Increased reactivity of the intermediate adducts to olefins would result in lower rates of decomposition to the starting materials; consequently formation of considerable amounts of Z-olefins could be expected. One possible explanation for the substituent effects of the aryl group is enhanced kinetic selectivity for the erythro adducts due to the steric hindrance rather than the electronic effects (Scheme 11).

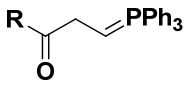


Scheme 12. Strucure of silylated aldehyde

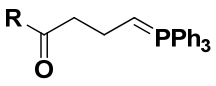
Furthermore, the reaction of **13a** with aldehydes **16-18** (Scheme 12), containing an oxygen functionality at the α or β-position gave the highest selectivity (97%). These results suggest that the oxygen functionality does not affect the *Z*/*E* ratio but that the steric hindrance at the α position favors *Z*-isomers.

1.3.5. Intramolecular Wittig reaction

In an intramolecular Wittig reaction, a bicyclic oxaphosphetane must be formed. It is therefore no surprise that cyclopropenes and cyclobutenes are not accessible by this reaction. The corresponding oxaphosphabicyclo[2.1.0]pentanes and [2.2.0]hexanes would be excessively strained, although the P-O bond is much longer than a C-C single bond.[44] The β-carbonyl alkylidenephosphoranes (a) hypothetical precursors of cyclopropenes, are hard to come by, because the corresponding acylethyltriphenyl phosphonium salts undergo Hofmann type elimination of triphenylphosphine on base treatment.[45,46]



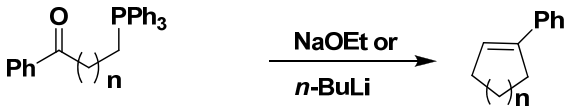
a



b

γ-Carbonyl alkylidenephosphoranes (b) rather give cyclooctadienes by double condensation than cyclobutanes.[47] Triphenylphosphine elimination and formation of a cyclopropyl ketones can also occur.[46]

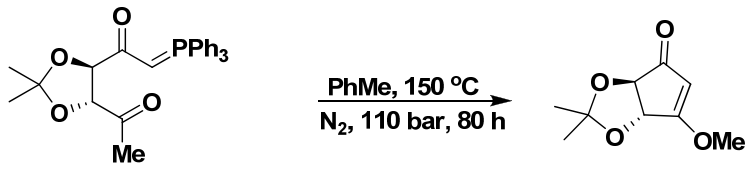
The first example of an intramolecular Wittig reaction with a carbonyl alkyltriphenylphosphonium salt was reported in 1962 and 1964 by two independent groups[46,48] who described the synthesis of 1-phenyl cyclohexene and cyclopentene (Scheme 13).



19 **20**

Scheme 13.

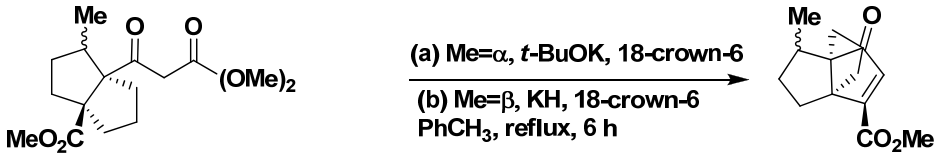
Simple esters show better reactivity when used in intramolecular reactions, for example Bestmann and co-workers have reported the interesting cyclisation of the tartrate-derived phosphorane, which proceeds in 60% yield to give cyclopentenone, the starting material in his synthesis of the carbocyclic nucleoside (-)-neplanocin A. It is however worthy of note that the reaction, which proceeds with epimerisation at C-3, requires highly forcing conditions (Scheme 14).[49]



21 22

Scheme 14.

In a related process Kraus and Shir reported the synthesis of the tricycles by cyclisation of the phosphonates in modest yield (Scheme 15).[50]

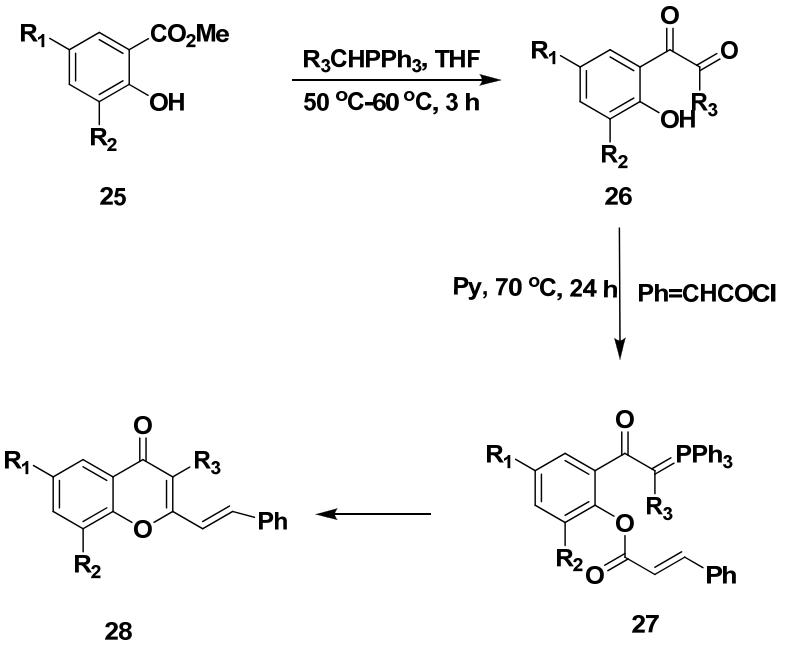


23 24

Scheme 15.

Intramolecular reaction of ester have found considerable application in the synthesis of heterocycles and several examples detailing the formation of benzofurans, chromones, isochromones, dihydrofurans and dihydropyrans have been reported.[51,52]

An example of the synthesis of 2-styryl-4H-[1]benzopyran-4-ones involve the commonly used strategy[53] of reacting the ester function of aromatic ester with non-stabilized ylides leading to the *O*-ketophosphoranes followed by acylation of the free hydroxy group with an excess of cinnamyl chloride in pyridine to give the intermediate which undergo cyclisation on heating to give the benzopyran-4-one (Scheme 16).[54]

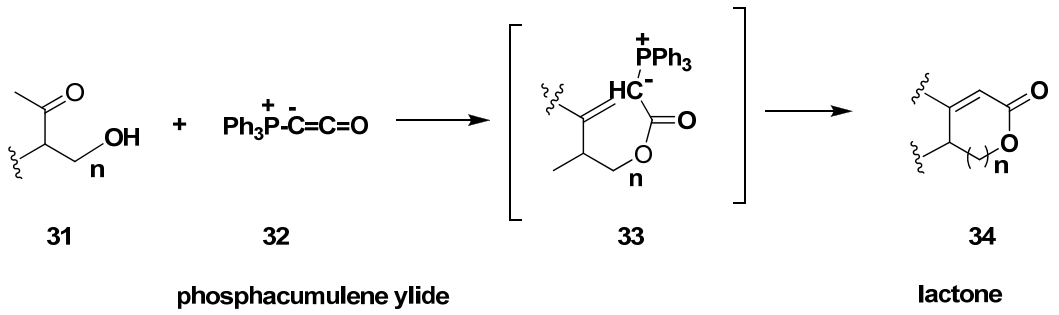


Scheme 16.

Phosphacumulene ylide

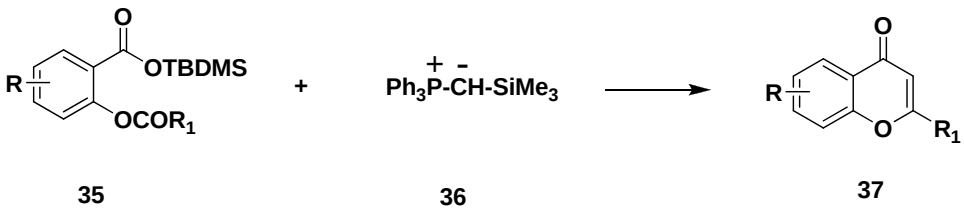
The intramolecular Wittig reaction has been extensively employed as an excellent method for the C-C bond forming process in the synthesis of natural products.' In this connection the phosphacumulene ylides, one of the recent arrivals in the series of organophosphorus reagents, are of special interest.

Kumar *et al.* (1998)[55] reported an efficient methodology for the conversion of hydroxy ketones into the corresponding lactones **34** employing intramolecular Wittig reaction as the key step. The generality of this concept has been established with several models. The annulation protocol is depicted in Scheme 17.



Scheme 17. Synthesis of lactone

Kumar *et al.* (2000)[56] reported the novel synthesis of 4*H*-chromen-4-ones from the reaction of the silyl ester of *O*-acyl(aroyl)salicylic acids and (trimethylsilyl)-methylenetriphenylphosphorane via intramolecular Wittig cyclisation as the key step (Scheme 18).



35 36 37

Scheme 18. Synthesis of chromones

1.3.6. References

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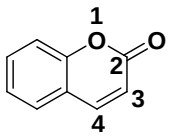
CHAPTER 2

Synthesis of coumarin derivatives using phosphorus ylide

2.1. SECTION A
SYNTHESIS OF COUMARIN DERIVATIVES USING TRIPHENYL (α-CARBOXYMETHYLENE)PHOSPHORANE IMIDAZOLIDE AS C-2 SYNTHON

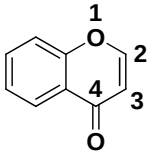
2.1.1. Introduction

The fusion of a pyrone ring with a benzene nucleus gives rise to a class of heterocyclic compounds known as benzopyrones, of which two distinct types are recognized : (i) benzo-α-pyrones, commonly called coumarins **1**, and (ii) benzo-γ-pyrones, called chromones **2**, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring.



1

Benzo-α-pyrone



2

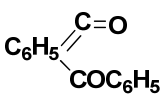
Benzo-γ-pyrone

Representatives of these groups of compounds are found to occur in the vegetable kingdom, either in the free or in the combined state. Coumarin **1**, the parent substance of the benzo-α-pyrone group, was first isolated from tonka beans in 1820. Several coumarin derivatives have been found to be widely distributed in the plant kingdom. Particularly the plants belonging to the natural orders of *Orchidaceae*, *Leguminoceae*, *Rutaceae*, Umbelliferae and *Labiatae* are rich sources of naturally occurring coumarins.

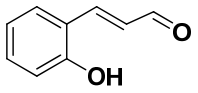
Coumarin **1** was initially considered to be a benzoic acid derivative, but its synthesis by W. H. Perkin Sr. from salicylaldehyde by means of his classical reaction established its relation to *O*-hydroxycinnamic acid, which loses a molecule of water in forming the lactone ring.

However, different constitutional formulae have been suggested from time to time. Of the various formulae proposed by Perkin (**I**), Basecke (**II**), Strecker, Fittig, and Tiemann (**III**), Salkowski (**IV**), and Morgan and Micklethwait (**V**), formula **III** has

been found to be in complete accord with the known reactions of the coumarin derivatives and has been universally accepted as correct (vide Hugo Schiff).[1]



I



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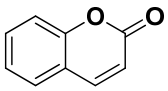
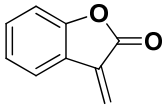
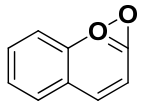


III (1)



IV



V

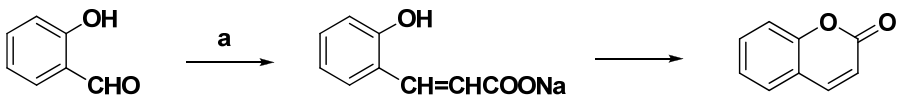
Coumarins **1** constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[2] They also represent the core structure of several molecules of pharmaceutical importance. A number of coumarin derivatives have been isolated from natural sources and their pharmacological and biochemical properties depend upon the pattern of substitutions. Coumarins have been reported to exhibit antibacterial, anticarcinogenic and analgesic activity.[3] In addition, they also serve as anti-oxidant, anti-inflammatory agents and HIV protease inhibitors.[3]

2.1.2. Review of Literature

Of the number of synthetic methods, there are a few which have yielded important results; there are several others whose applications are less general. All these methods center round the possibility of building up the pyrone ring on a suitable benzene derivative.

Perkin *et al.* (1868)[4]

First synthesis of coumarin was reported by Perkin *et al.*[4] from salicylaldehyde **3** by heating with acetic anhydride and anhydrous sodium acetate. This reaction occurs with



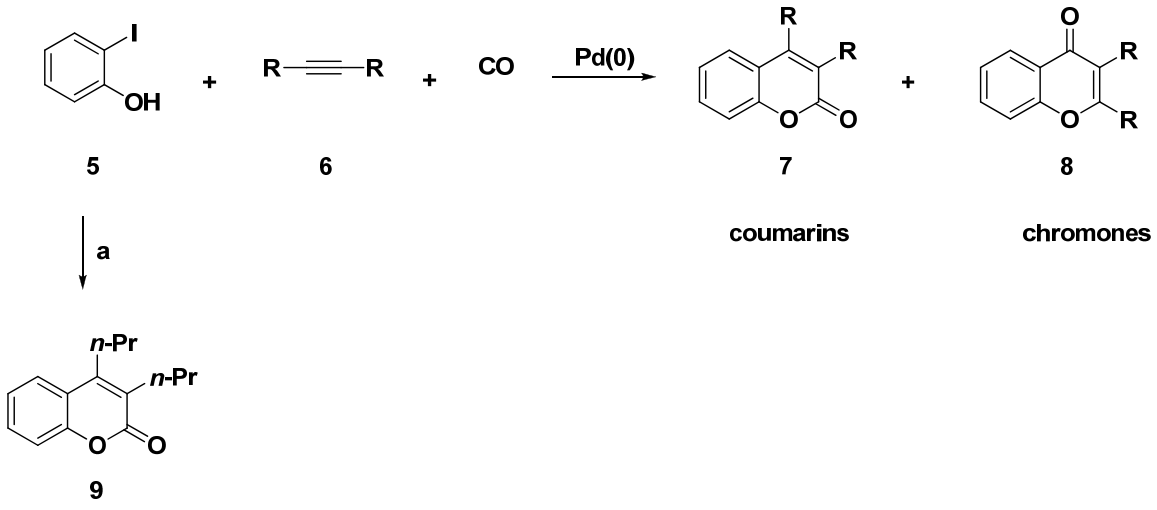
3 **4** **1**

Scheme 1. *Reagents and conditions:* (a) $(CH_3CO)_2O$, anhyd. CH_3COONa, Δ

the formation of an intermediate *O*-hydroxycinnamic acid derivative which passes spontaneously into the lactone when liberated from its sodium salt **4** (Scheme 1).

Larock *et al.* (2000)[5]

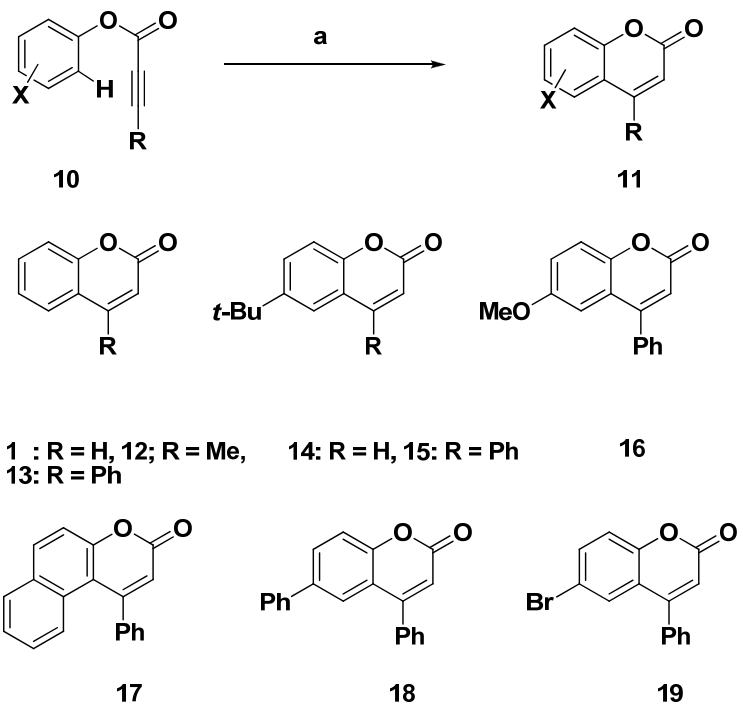
Larock and his co-workers[5] reported the synthesis of 3,4-disubstituted coumarin bearing a variety of functional groups via the palladium catalysed coupling of *o*-iodophenols **5** with internal alkynes **6** and 1 atm of carbon monoxide. The reaction of *o*-iodophenol and 4-octyne in presence of 1 atm of carbon monoxide under similar reaction conditions gave exclusively 3,4-di-*n*-propyl coumarin **9** (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) 4-octyne, 5 mol % $Pd(Ac)_2$, 10 mol % PPh_3, NaOAc, *n*-Bu_4NCl, DMF, 120 ^oC, 24 h.

He *et al.* (2004)[6]

He *et al.*[6] reported the synthesis of various substituted coumarins via gold catalysed intramolecular addition of aryl alkynoates (Scheme 3).

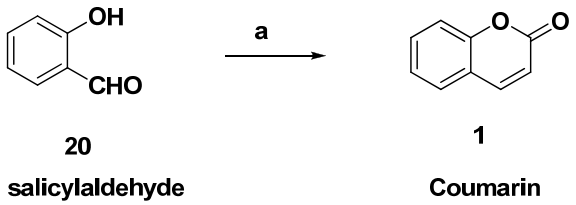


Scheme 3. *Reagents and conditions:* (a) 5 mol% $AuCl_3$/3AgOTf, 0.5 mmol of ester in 2 mL of CH_2Cl_2, 50°C.

Dittmer *et al.* (2005)[7]

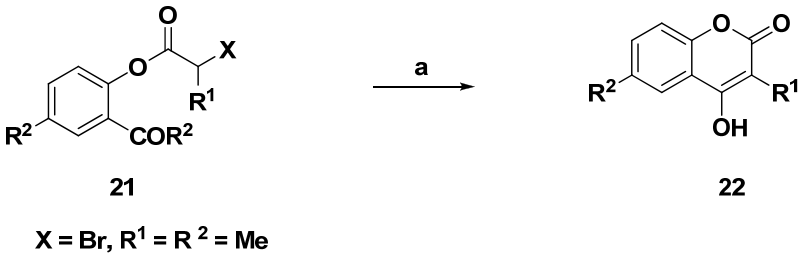
Dittmer *et al.*[7] reported the synthesis of coumarin **1**, 4-hydroxycoumarin **22** and 4-hydroxyquinolin-2(1*H*)-ones **24** by treatment of *α*-halocarboxylic acid ester of salicylaldehyde, *O*-hydroxyacetophenone, methyl salicylate and methyl *N*-methyl- or *N*-phenylanthranilates with sodium or lithium telluride (Scheme 4, 5 & 6).

One-pot synthesis of coumarin (1)



Scheme 4. *Reagents and conditions:* (a) (i) NaH, THF, 0 °C - rt; (ii) $BrCH_2COBr$, 0 °C - rt; (iii) Li_2Te, THF, -78 °C - rt, 1.5 h, -Te.

Synthesis of 4-hydroxy coumarin (22)



21

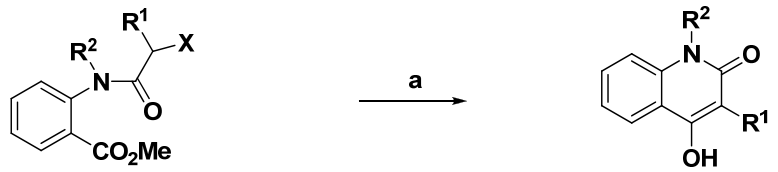
22

X = Br, R^1 = R^2 = Me

Scheme 5. *Reagents and conditions:* (a) Na_2Te, THF, -Te, -20 ^oC.

Synthesis of 4-hydroxyquinolinone (24)

4-Hydroxyquinolin-2(1*H*)-ones **24** can be efficiently synthesized from the corresponding methyl *N*-(*R*-haloacyl)-anthranilates under similar cyclization conditions in the presence of sodium telluride (Scheme 6).



23

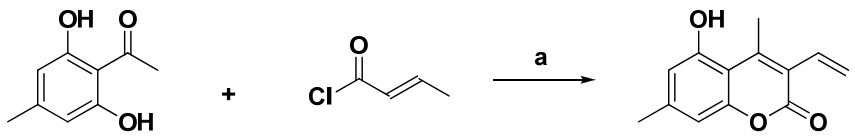
24

X = Cl, R^1 = Ph, R^2 = Me

Scheme 6. *Reagents and conditions:* (a) Na_2Te, THF, rt, -Te.

Waldvogel *et al.* (2008)[8]

Waldvogel *et al.*[8] reported the one-pot synthesis of a variety of 3-vinyl coumarins from 2-acyl-, 2-aroyl- and 2-formyl-substituted phenols and α,β-unsaturated carboxylic acid chlorides (Scheme 7).



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26

27

Scheme 7. *Reagents and conditions:* (a) K_2CO_3, acetone, 38%.

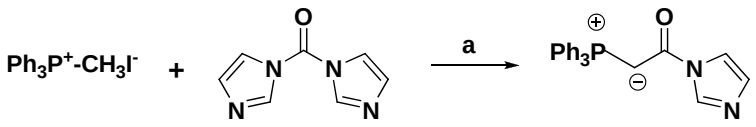
2.1.3. Present Work

Objective

Because of the utmost significance of this heterocyclic system and their diverse pharmacological properties, many strategies for the synthesis of substituted coumarins have been developed.[8,9] Classical routes[10] to coumarins incorporate Pechmann, Knoevenagel, Perkin, Reformatsky and Wittig condensation reactions. However, most of these methods suffer from expensive catalyst, harsh reaction conditions, multistep synthesis or low chemical yield. The intramolecular Wittig reaction has been extensively used as an excellent method for the C-C bond forming process in the synthesis of natural products.[11] As part of our ongoing programme for developing a methodology employing phosphacumulene and (trimethylsilyl)methylene triphenyl phosphorane and their subsequent application to the biologically useful compounds,[12] triphenyl (α-carboxymethylene)phosphorane imidazolide **30**[13] is envisaged as a versatile reagent offering considerable opportunity for synthetic manipulation. The synthetic utility of **30** is hitherto unknown in the literature, and we considered to investigate the application of triphenyl (α-carboxymethylene)phosphorane imidazolide as a C-2 synthon for the one-pot synthesis of biologically relevant coumarins. The generality of this concept has been established with several examples.

2.1.4. Results and Discussion

Ylide **30** was prepared by the reaction of carbonyl diimidazole (CDI) **29** and methylenetriphenyl phosphorane generated from the corresponding phosphonium salt **28** as depicted in Scheme 8.

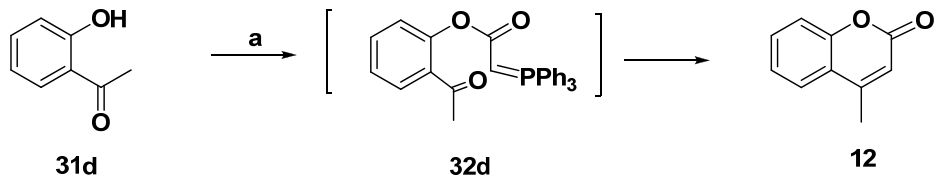


Scheme 8. *Reagents and conditions:* (a) (i) *n*-BuLi, dry THF, rt, 2h; (ii) CDI, dry THF, rt, 24 h, 80%.

The m.p. of ylide **30** was in accordance with the literature precedence.[13] The ^{1}H NMR spectrum of ylide **30** showed the presence of -CH proton at δ 3.12 (d, 1H) and aromatic

protons at δ 7.66-7.84 (m, 18H) confirming the formation of ylide **30**. Since the carbanion in ylide **30** is stabilized by the amide carbonyl, one would expect low reactivity of this ylide in a nucleophilic reaction. At the same time, imidazole being a good leaving group would facilitate reaction at the carbonyl centre. Thus, the hydroxy carbonyl compound **31d** was first heated with NaOMe in xylene at 60 ^{o}C for 2 h and then reacted with ylide **30** under reflux conditions to afford phosphoranes **32d** which underwent intramolecular Wittig cyclization to furnish the desired coumarin **12** in good yields (Scheme 9). The ^{1}H NMR spectrum of compound **12** showed the presence of olefinic proton at δ 6.4 (d, 1H).

Taking into consideration the low nucleophilicity of ylide **30**, it was necessary to use an equimolar amount of an additional base such as sodium methoxide to generate an alkoxy anion from hydroxy carbonyl compound **31**. The reaction is then followed by a nucleophilic attack of the alkoxy anion on the carbonyl of ylide **30**, ultimately leading to the formation of the intermediate **32d** with the extrusion of imidazole as a by-product. The phosphorane **32d** thus formed immediately undergoes ring closure via an intramolecular Wittig reaction to afford the desired coumarin **12** in good yields.

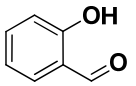
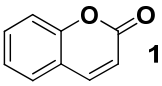
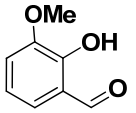
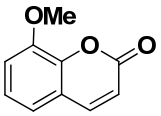
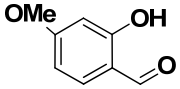
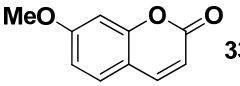
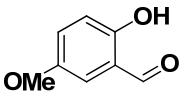
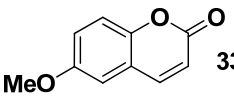
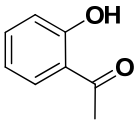
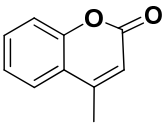
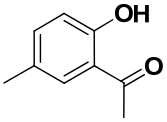
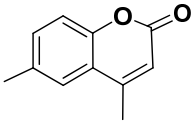
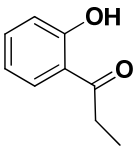
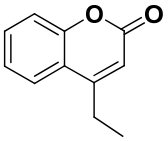
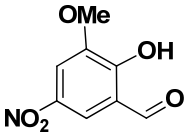
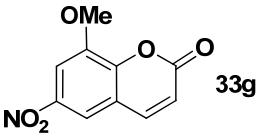
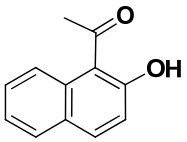
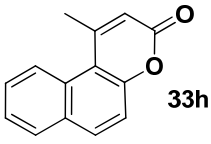
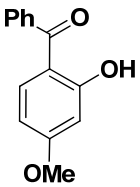
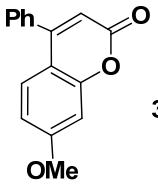


31d **32d** **12**

Scheme 9. *Reagents and conditions:* (a) (i) NaOMe, xylene, 60 ^{o}C, 2 h, then ylide **30**, reflux, 48 h.

To support our mechanism, the intermediacy of **32d** has been established by spectroscopic means. Appearance of CH protons at δ 3.10 (d, 1H) and aromatic protons at δ 7.36-7.76 (m, 19H) in ^{1}H NMR spectrum confirmed the formation of phosphorane **32d**. Although the treatment of **32d** with **30** in xylene in the presence of NaOMe at room temperature did not show any progress in the reaction, the extrusion of imidazole and the formation of phosphorane **32d** could be observed when the reaction was performed at reflux temperature. Interestingly, compound **32d** was found to be stable enough to be isolated after 3 h of the reaction and was further identified by its spectral data.

Table 1. One-pot synthesis of substituted coumarin derivatives.

Entry No	Hydroxy carbonyl comp.		Products		%Yield
1.		20		1	85
2.		31a		33a	70
3.		31b		33b	72
4.		31c		33c	70
5.		31d		12	75
6.		31e		33e	72
7.		31f		33f	62
8.		31g		33g	70
9.		31h		33h	75
10.		31i		33i	60

Compound **32d** on subsequent heating in refluxing xylene for 48 h gave the desired coumarin **12**. Thus, the above finding indicates that compound **32d** which results from

the extrusion of imidazole is an intermediate that undergoes subsequent intramolecular Wittig cyclization at reflux temperature to furnish the desired product **12**. As is apparent from Table 1, the intramolecular Wittig cyclization involving phosphorus ylide and carbonyl is general for the preparation of a variety of coumarin derivatives. While the electron-donating or electron-withdrawing substituents in the aromatic rings (entries 2-4 and 8, respectively) do not have any considerable effect in terms of the yields of the products obtained, the steric effect during Wittig cyclization resulting from substitution in aromatic rings appears to be significant. Thus, propionyl and benzoyl groups (entries **7** and **10**) have pronounced steric hindrance due to their close proximity to the carbonyl group, and hence a longer time (55 h) is required for completion of the reaction affording relatively low yields of the products, **33f** and **33 i**, respectively. It may be pertinent to mention here that a few applications of transition-metal catalyzed reactions for coumarin synthesis have been reported, but most of these are of limited scope.[14,15] For example, palladium-catalyzed carbonylative annulations of internal alkynes by *O*-iodophenols is known to give varying proportions of two regioisomers of substituted coumarins.[5,16] In this connection the present methodology for the synthesis of coumarins is noteworthy.

2.1.5. Conclusion

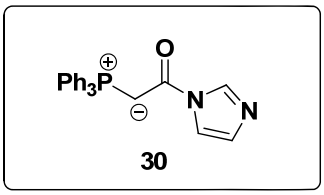
In conclusion, an efficient annulation protocol for a variety of coumarins has been developed. To the best of our knowledge, this is the first report of coumarin synthesis via intramolecular Wittig carbonyl olefination using triphenyl (α-carboxymethylene) phosphorane as a C-2 synthon.

2.1.6. Experimental Section

General Information

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and 500 MHz spectrometer. In the ^{13}C NMR data, peaks of only the major diastereomer (in Mass spectra were obtained with a TSQ70, Finningen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNSO analyzer.

Synthesis of triphenyl (α-carboxymethylene)phosphorane imidazolide (30).[13]



30

To a solution of Wittig salt **28** (10.0 g, 24.75 mmol) in dry THF, *n*-BuLi (15% in hexane) (10.55 mL, 24.75 mmol) was added under argon atmosphere and stirred for 2 h, and then carbonyldiimidazole **29** (2.0 g, 12.4 mmol) was added at rt and stirred for 24 h. After completion of the reaction, the solvent was removed and the crude product was purified by recrystallization from dry CH_2Cl_2-THF (1:1.5) to give the ylide **30** as a white solid.

Yield: 14.7 g (80%).

M.P. 185 ^oC-187 ^oC [lit. (M.P.185 ^oC)].[13]

Mol. Formula: $C_{23}H_{19}N_2OP$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3063, 2934, 2365, 1613.

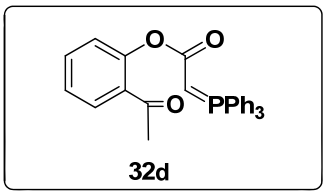
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.12 (d, J = 13 Hz, 1H), 7.66-7.84 (m, 18H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 67.3, 117.6, 118.8, 128.8, 129.9, 130.0, 132.3, 132.6, 132.7, 134.7, 190.1.

Mass (ESI): 371 (277 + CH_3COONH_4 + H_2O).

Analysis Calcd.: C, 74.58; H, 5.17%; Found: C, 74.45.; H, 5.53%.

Synthesis of phosphorane (32d).[13c]



32d

To a solution of 2-hydroxy acetophenone **31d** (500 mg, 3.68 mmol) in dry xylene, NaOMe (0.2 g, 3.68 mmol) was added under argon atmosphere. After being stirred under heating for 2 h, ylide **30** (2.72 g, 3.68 mmol) was added and refluxed for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was removed under rotavapour and the crude solid residue was purified by

silica gel column chromatography using EtOAc/pet ether as eluent (98:2) to give the phosphorane **32d** as a red colour solid.

Yield: 1.45 g (90%).

M.P. 180 ^{o}C-182 ^{o}C

Mol. Formula: $C_{28}H_{23}O_3P$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3073, 1736,1683.

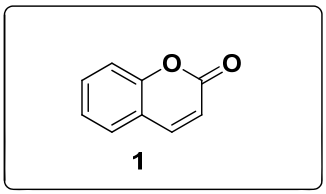
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.0 (s, 3H), 3.10 (d, J = 13 Hz, 1H), 7.36-7.76 (m, 19H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 60.3, 117.6, 119.3, 128.6, 128.9, 130.3, 130.6, 131.7, 132.0, 132.3, 132.5, 133.0, 133.2, 135.2, 176.2.

Mass (LCMS): 438 (M^{+1}), 301, 277, 267, 245, 239, 229, 223.

Analysis Calcd.: C, 76.70; H, 5.29%; Found: C, 76.48.; H, 5.58%.

Synthesis of Coumarin (1).[6,7,17,18,19c,20a]



1

Yield: (85%).

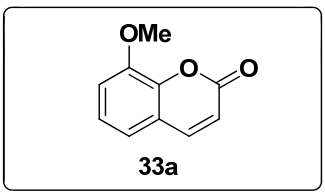
M.P. 70 ^{o}C-71 ^{o}C; [(lit. M.P. 69 ^{o}C-70 ^{o}C)].[17c]

Mol. Formula: $C_9H_6O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1724, 1622.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.44 (d, J = 9.8 Hz, 1H), 7.29 (m, 2H), 7.48 (m, 2H), 7.50 (m, 1H), 7.73 (d, J = 9.3 Hz, 1H).

Synthesis of 8-methoxy-2*H*-chromen-2-one (33a).[18]



33a

Yield: (70%).

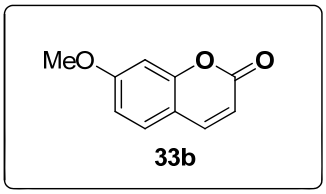
M.P. 91 ^{o}C-92 ^{o}C; [(lit. M.P.90 ^{o}C-91 ^{o}C)].[18a]

Mol. Formula: $C_{10}H_8O_3$

^{1}H NMR (200MHz, $CDCl_3$): δ 3.96 (s, 3H), 6.44 (d, J = 9.3 Hz, 1H), 7.04 (m, 2H), 7.17 (m, 1H), 7.67 (d, J = 9.3 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 56.3, 113.9, 116.9,119.3, 119.5, 124.2, 143.5, 143.9, 147.3, 160.8.

Synthesis of 7-methoxy-2*H*-chromen-2-one (33b).[17a,18b,18c,19c]



33b

Yield: (72%).

M.P.117 ^{o}C-118 ^{o}C; [(lit. M.P.119 ^{o}C)].[17a]

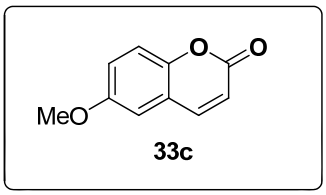
Mol. Formula: $C_{10}H_8O_3$

IR ($CHCl_3$, cm^{-1}): ν_{max}, 1729, 1614.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.27 (d, J = 9.3 Hz, 1H), 6.83 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 9.8 Hz, 1H).

Mass (GCMS):176 (M^+), 161, 148, 133, 120.

Synthesis of 6-methoxy-2*H*-chromen-2-one (33c).[17a,18a,18b,19c]



33c

Yield: (70%).

M.P.103 ^{o}C-104 ^{o}C; [(lit. M.P.102 ^{o}C-103 ^{o}C)].[17a]

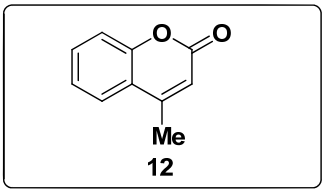
Mol. Formula: $C_{10}H_8O_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1722, 1571.

^{1}H NMR (200 MHz, $CDCl_3$): δ3.86 (s, 3H), 6.44 (d, J = 9.3 Hz, 1H), 6.93 (d, J = 2.9, 1H), 7.09 (m, 1H), 7.31 (m, 1H), 7.67 (d, J = 9.3, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ55.8, 100.9, 112.6, 113.2, 128.7, 143.4, 156.0, 162.90.

Synthesis of 4-methyl-2*H*-chromen-2-one (12).[6,19a,19b]



12

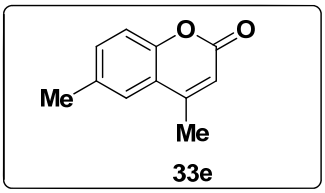
Yield: (75%).

M.P. 87 °C; [(lit. M.P. 88 °C)].[6,22]

Mol. Formula: $C_{10}H_8O_2$

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.52 (s, 3H), 6.4 (d, J = 2 Hz, 1H), 7.39 (m, 4H).

Synthesis of 4,6-dimethyl-2*H*-chromen-2-one (33e).[20]



33e

Yield: (72%).

M.P. 149 °C-150 °C

Mol. Formula: $C_{11}H_{10}O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1643,1618.

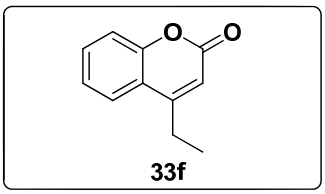
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.63 (s, 3H), 5.39-5.54 (m, 1H), 6.88 (m, 1H), 7.28 (m, 1H), 7.52 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.5, 26.6, 115.4, 118.2, 119.5, 128.0, 129.1, 130.4, 137.5, 160.4.

Mass (ESI): 202 (M^{+2}+CH_3CN), 165, 161, 151.

Analysis Calcd.: C, 75.84; H, 5.79%; Found: C, 75.63; H, 5.58%.

Synthesis of 4-ethyl-2*H*-chromen-2-one (33f).[21]



33f

Yield: (62%).

Mol. Formula: $C_{11}H_{10}O_2$

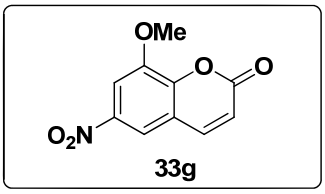
IR ($CHCl_3$, cm^{-1}): ν_{max} 1721.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, J = 7.32, 3H), 3.02 (q, J = 7.39, 14.53, 2H), 6.38 (s, 1H), 7.43-7.65 (m, 2H), 7.90-7.99 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.0, 29.4, 114.5, 116.3, 117.8, 125.0, 125.4, 127.8, 129.7, 130.2, 131.4, 133.6, 154.0, 154.7, 160.3.

Mass (ESI): 211 ($M^+ + NH_4^+ + H_2O$).

Synthesis of 8-methoxy-6-nitro-2*H*-chromen-2-one (33g).[22]



33g

Yield: (70%).

M.P. 184 ^{o}C-185 ^{o}C; [(lit. M.P. 185 ^{o}C)].[22]

Mol. Formula: $C_{10}H_7NO_5$

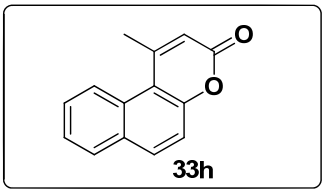
I.R. ($CHCl_3$, cm^{-1}): ν_{max} 1738.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.08 (s, 3H), 6.62 (d, J = 15 Hz, 1H), 7.78 (d, J = 9Hz, 1H), 7.94 (d, J = 3 Hz, 1H), 8.05 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 56.34, 118.0, 118.84, 11.0, 119.5, 124.0, 126.5, 129.7, 131.6, 166.1.

Mass (ESI): 279 ($M^+ + NH_4^+ + CH_3CN$).

Synthesis of 1-methyl-*3H*-benzo[*f*]chromene-3-one (33h).[23]



33h

Yield: (75%).

M.P. 167 ^{o}C-168 ^{o}C; [(lit. M.P.169 ^{o}C-170 ^{o}C)].[23b]

Mol. Formula: $C_{14}H_{10}O_2$

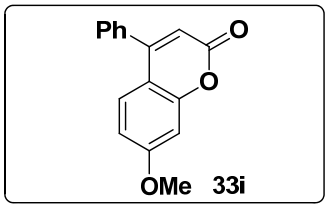
IR ($CHCl_3$, cm^{-1}): ν_{max} 1722.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.93 (s, 3H), 6.39 (s, 1H), 7.56-7.66 (m, 3H), 7.76-8.00 (m, 2H), 8.6 (d, J = 8.79 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 114.3, 116.3, 117.6, 124.8, 125.3, 127.7, 129.5, 130.0, 131.2, 133.5, 154.1, 154.4, 159.6, 160.3.

Mass (ESI): 210 (M^+ +1), 183, 165, 149, 121.

Synthesis of 7-methoxy-4-phenylcoumarin (33i).[19c,19d]



33i

Yield: (60%).

M.P.112 ^{o}C-113 ^{o}C; [(lit. M.P. 111 ^{o}C-115 ^{o}C)].[19c]

Mol. Formula: $C_{16}H_{12}O_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1622.

^{1}H NMR (50 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.81(s, 1H), 6.48-6.53 (m, 2H), 7.02-7.07 (m, 1H), 7.32-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ55.2, 101.3, 106.7, 115.9, 120.2, 127.2, 128.5, 131.0, 140.0, 145.3, 154.3, 160.8.

Mass (ESI): 253 (M+1), 239, 227, 213.

2.1.7. Spectra

1] ^{1}H NMR spectrum of **30**

2] ^{1}H NMR spectrum of **32d**

3] ^{13}C NMR spectrum of **32d**

4] ^{1}H NMR spectrum of **33c**

5] ^{13}C NMR spectrum of **33c**

6] ^{1}H NMR spectrum of **33e**

7] ^{13}C NMR spectrum of **33e**

8] ^{1}H NMR spectrum of **33f**

9] ^{13}C NMR spectrum of **33f**

10] ^{1}H NMR spectrum of **33g**

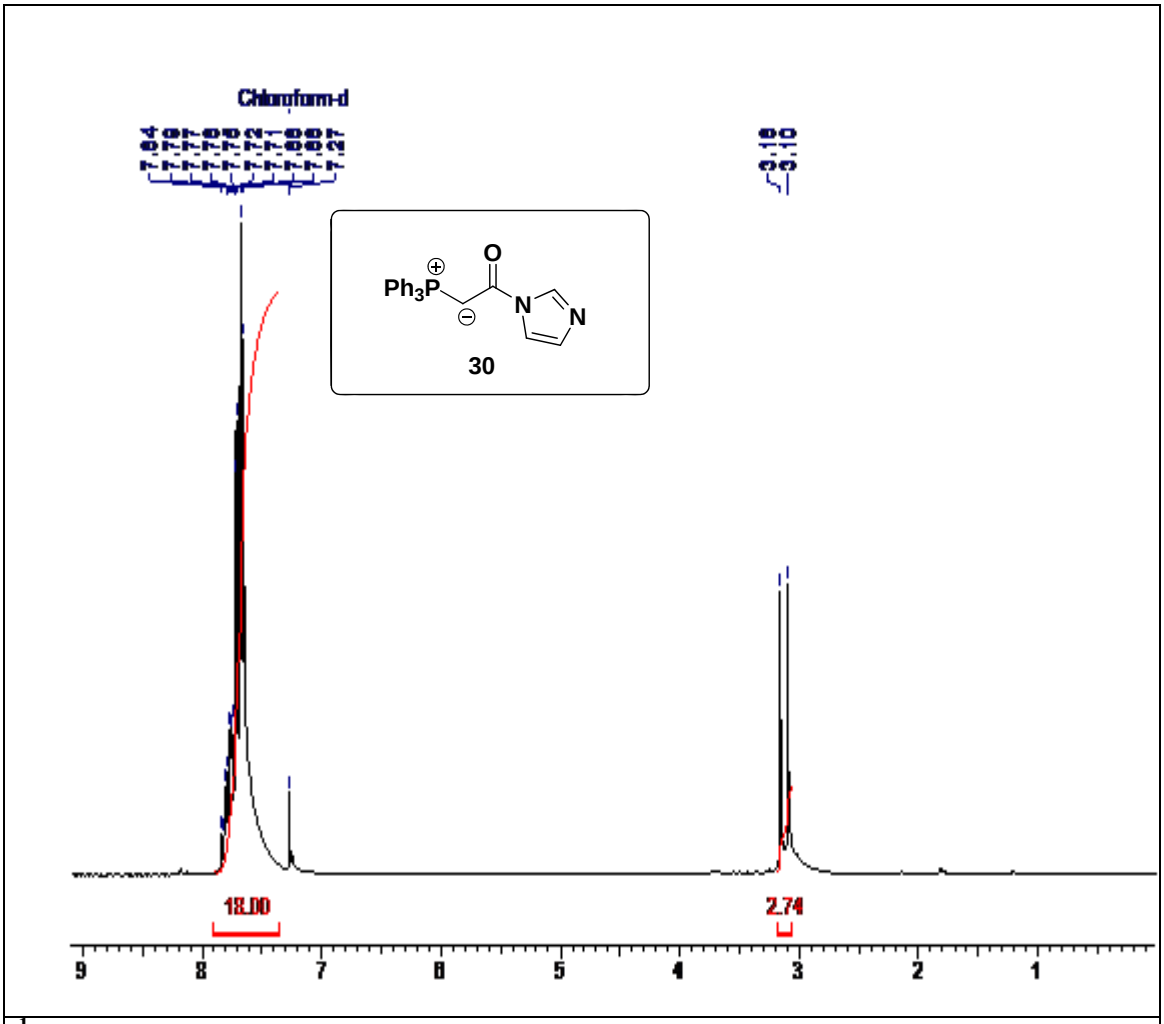
11] ^{13}C NMR spectrum of **33g**

12] ^{1}H NMR spectrum of **33h**

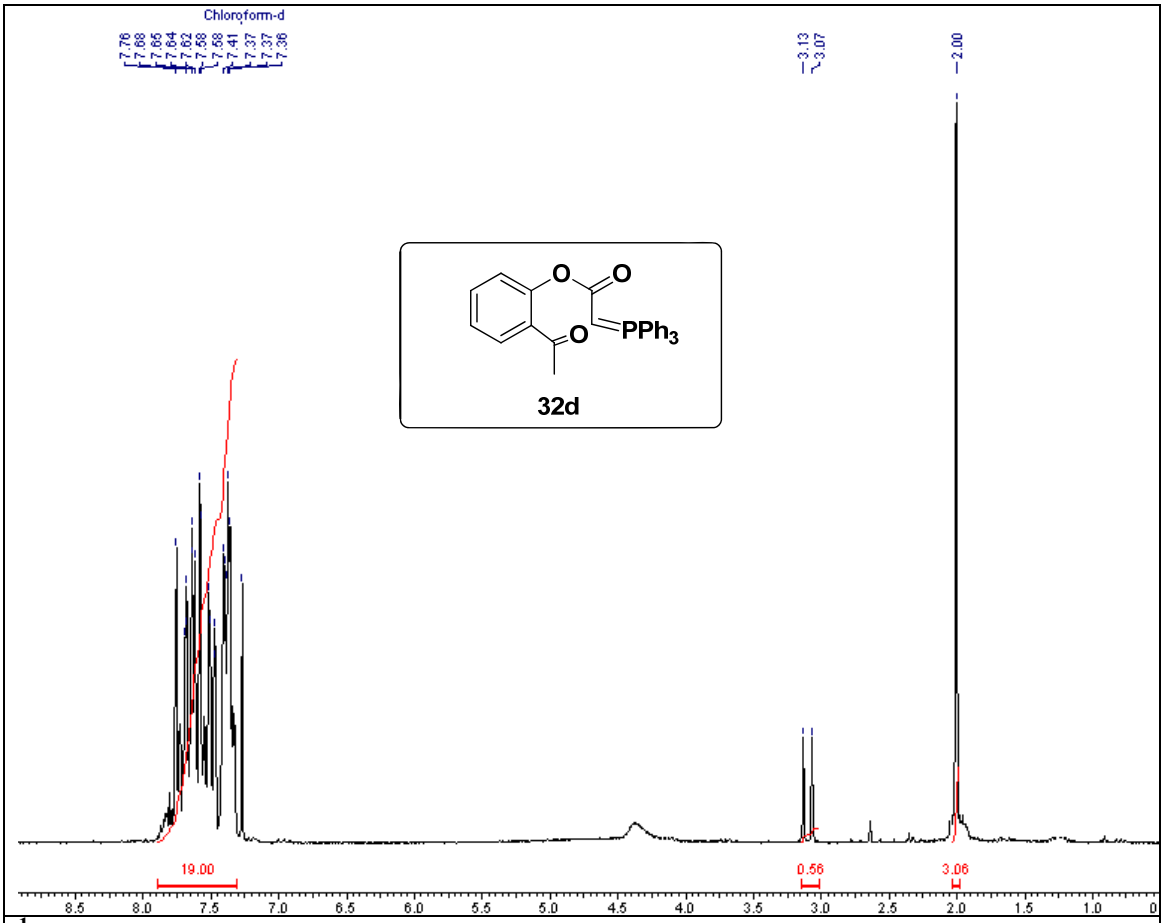
13]^{13}CNMR spectrum of **33h**

14]^{1}H NMR spectrum of **33i**

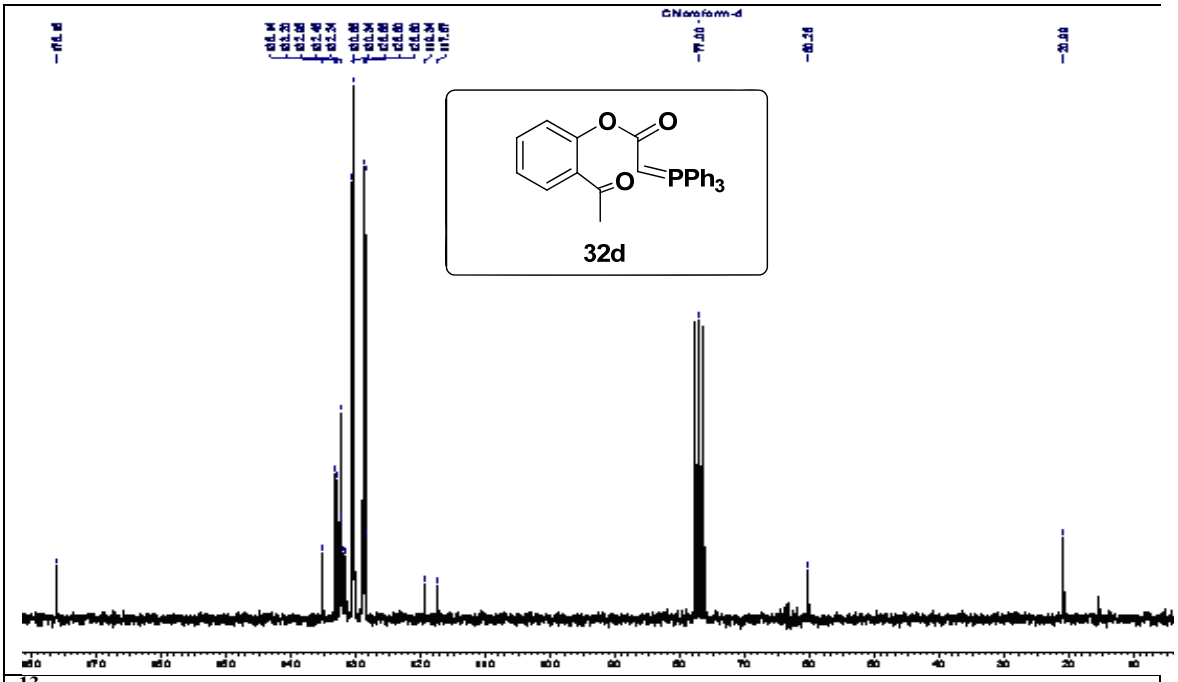
15] ^{13}C NMR spectrum of **33i**



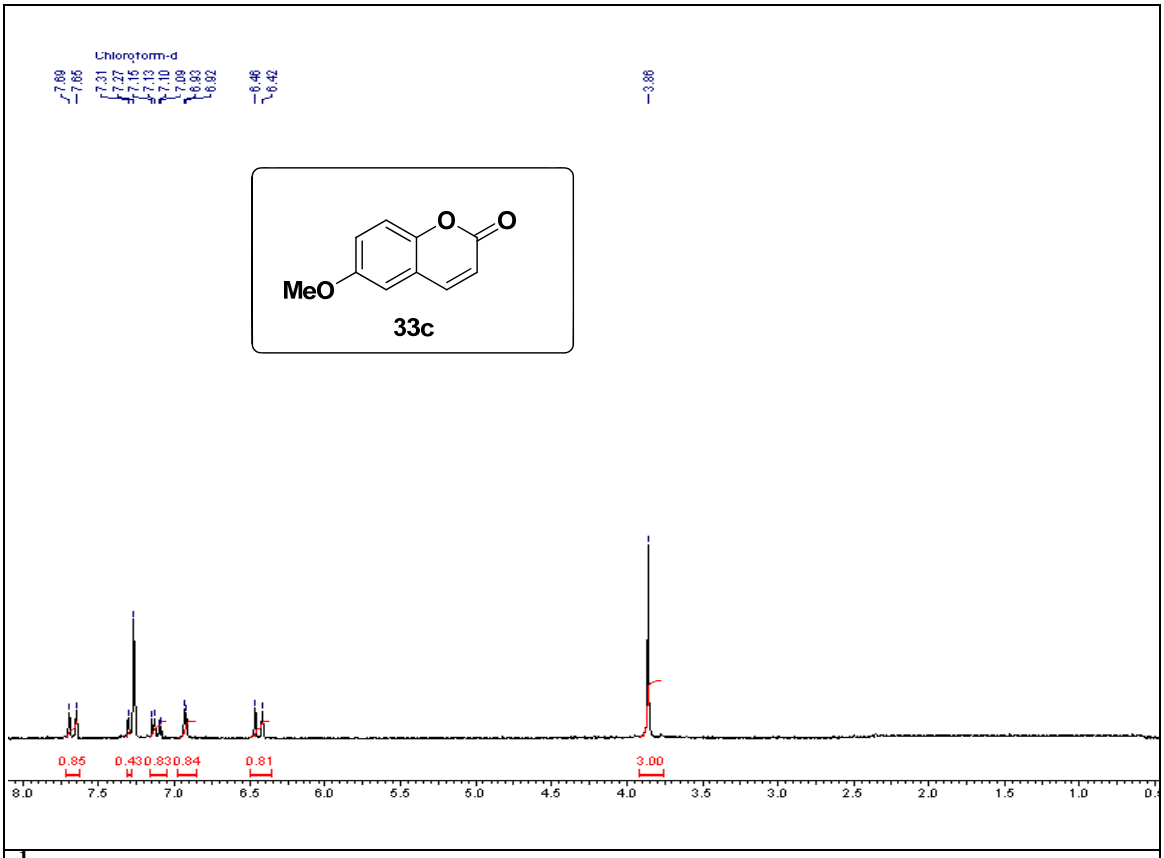
^{1}H NMR spectrum of ylide 30 in $CDCl_3$



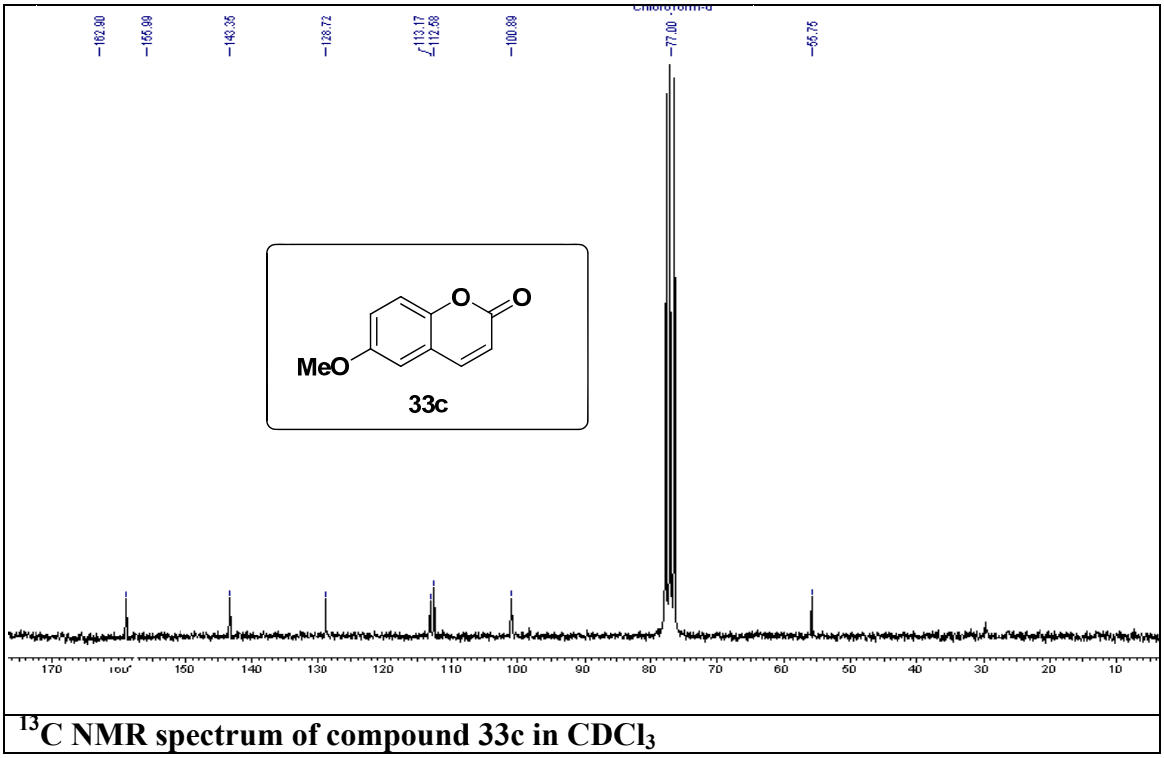
^{1}H NMR spectrum of phosphorane 32d in $CDCl_3$



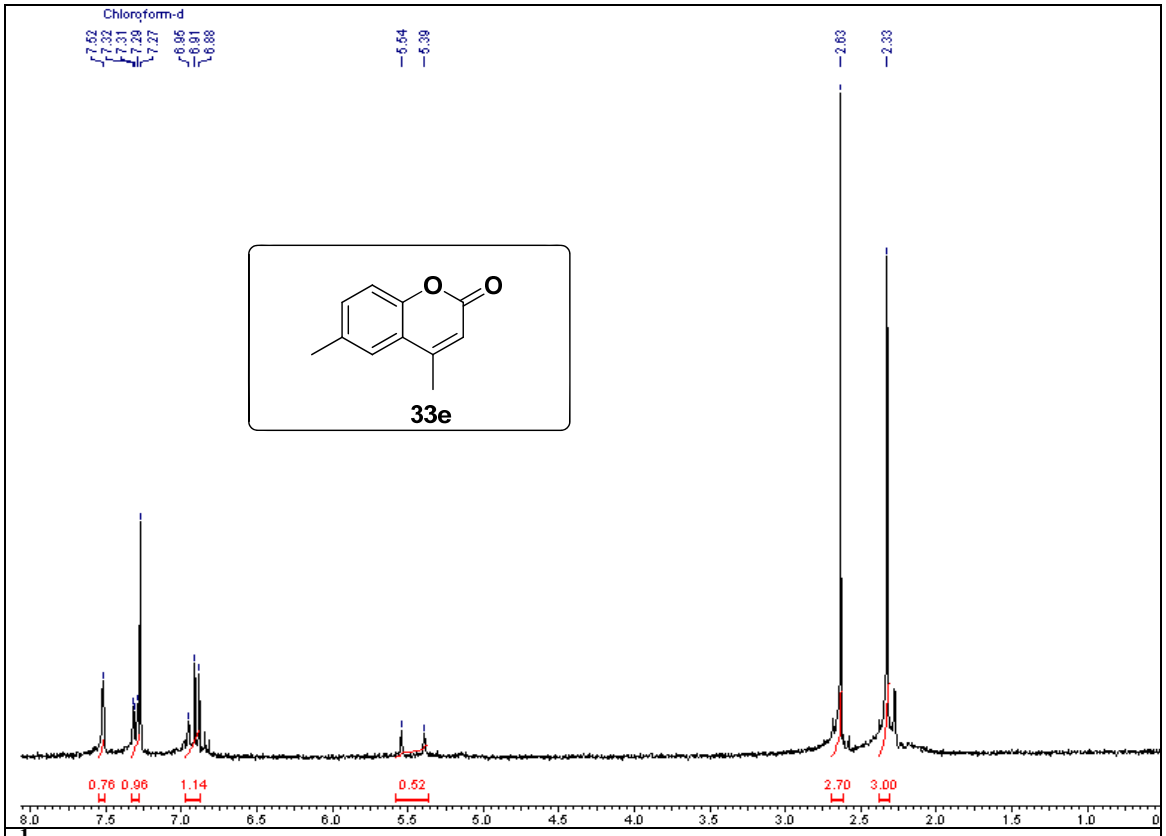
^{13}C NMR spectrum of phosphorane 32d in $CDCl_3$



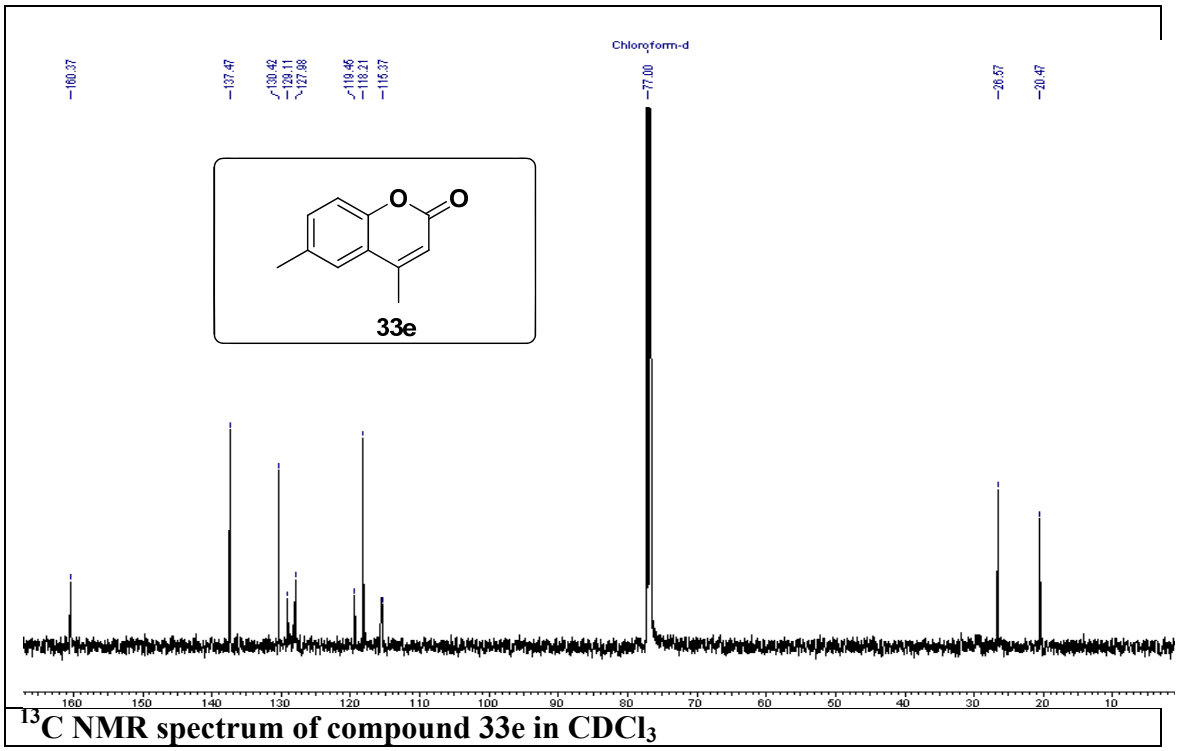
^{1}H NMR spectrum of compound 33c in $CDCl_3$



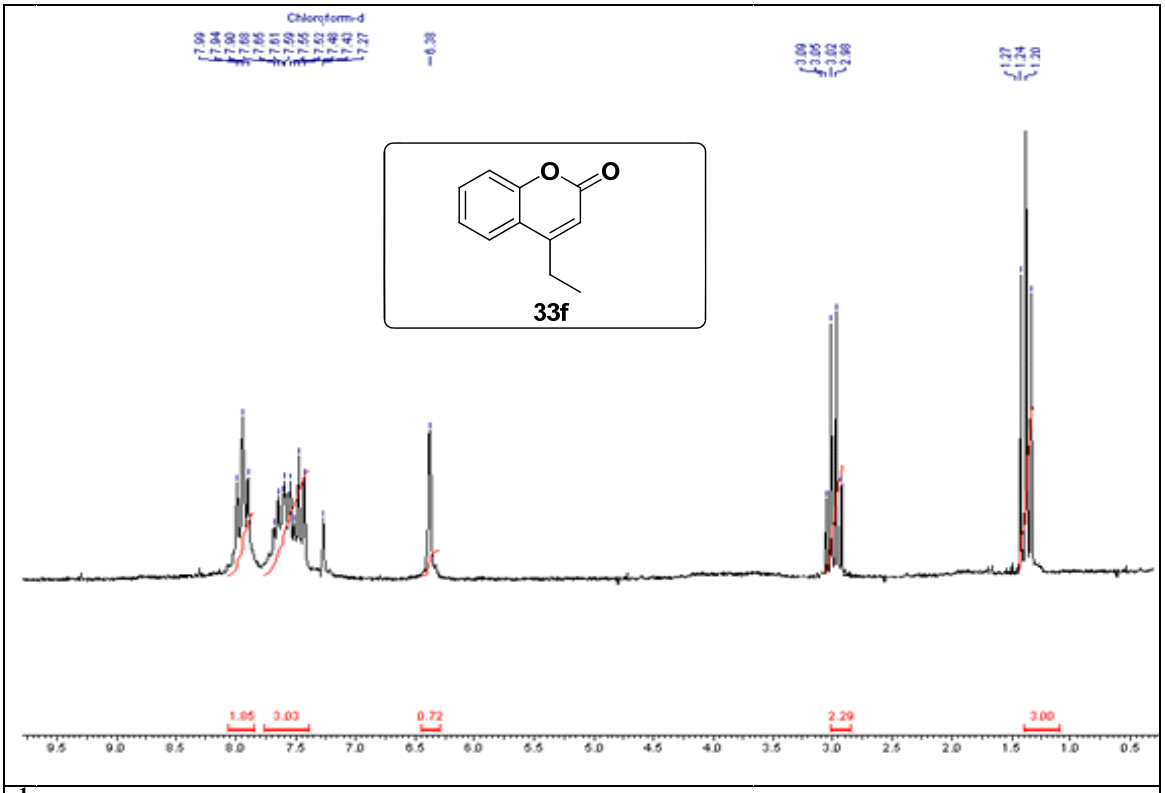
^{13}C NMR spectrum of compound 33c in $CDCl_3$



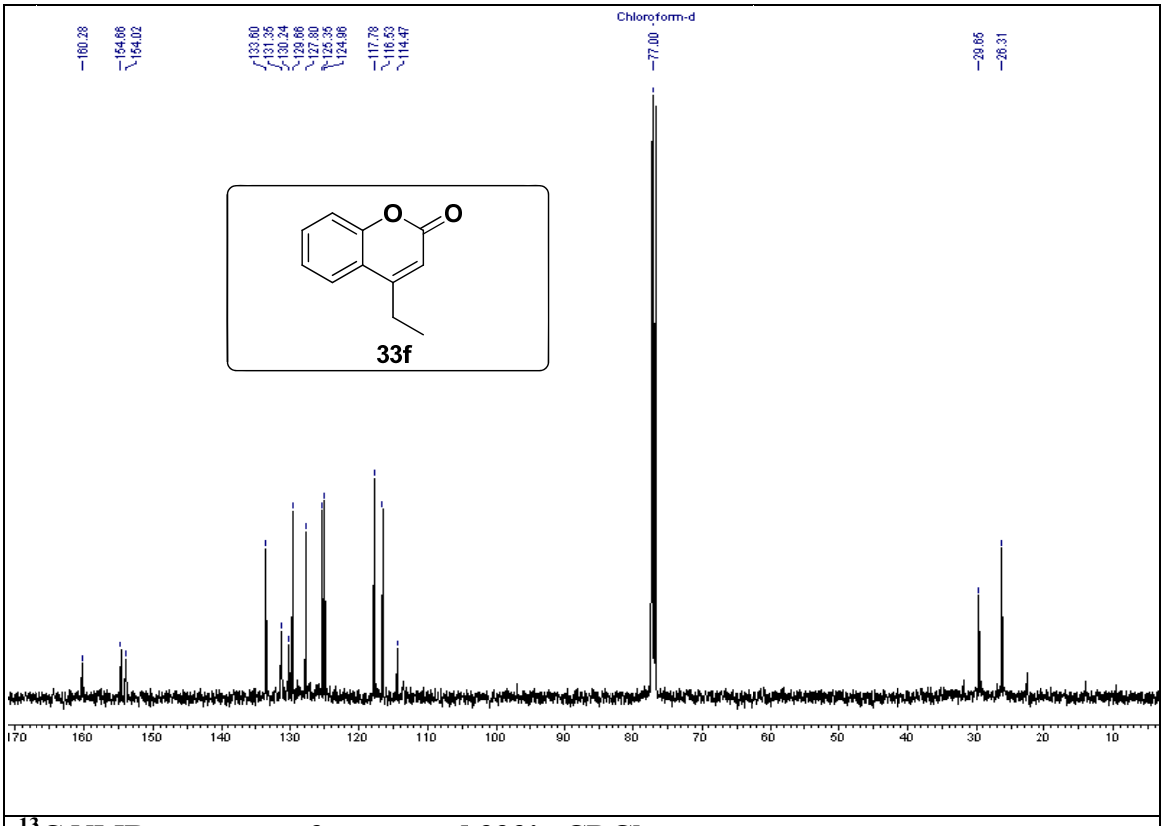
^{1}H NMR spectrum of compound 33e in $CDCl_3$



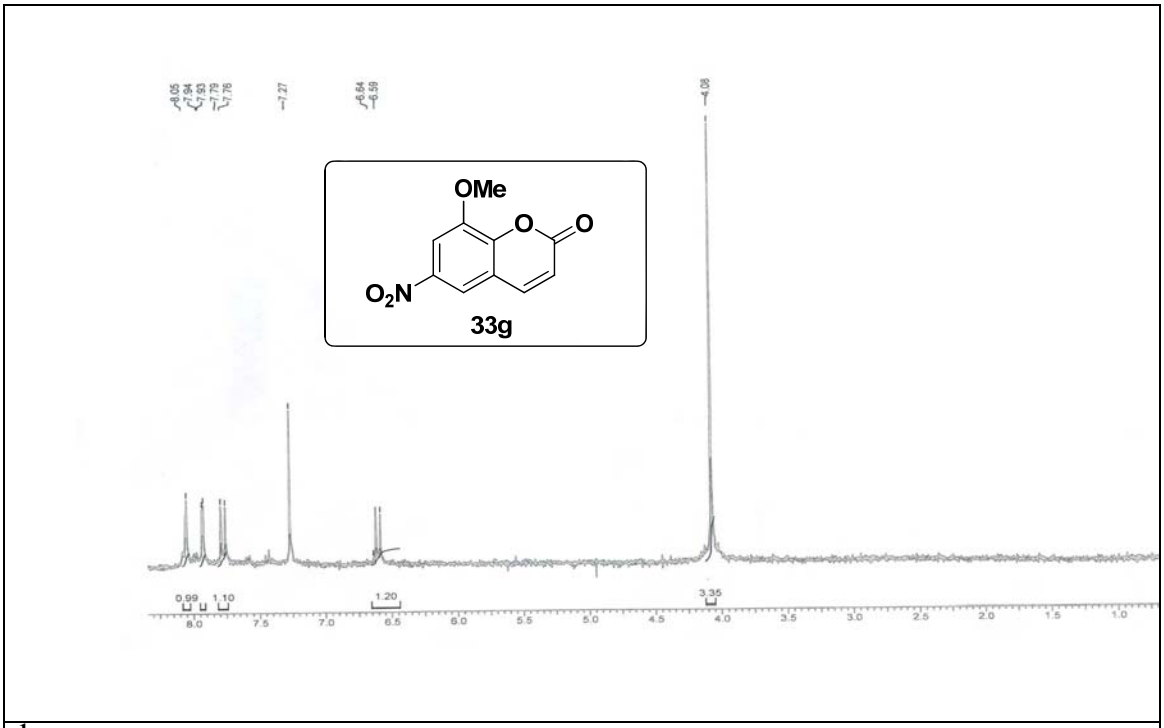
^{13}C NMR spectrum of compound 33e in $CDCl_3$



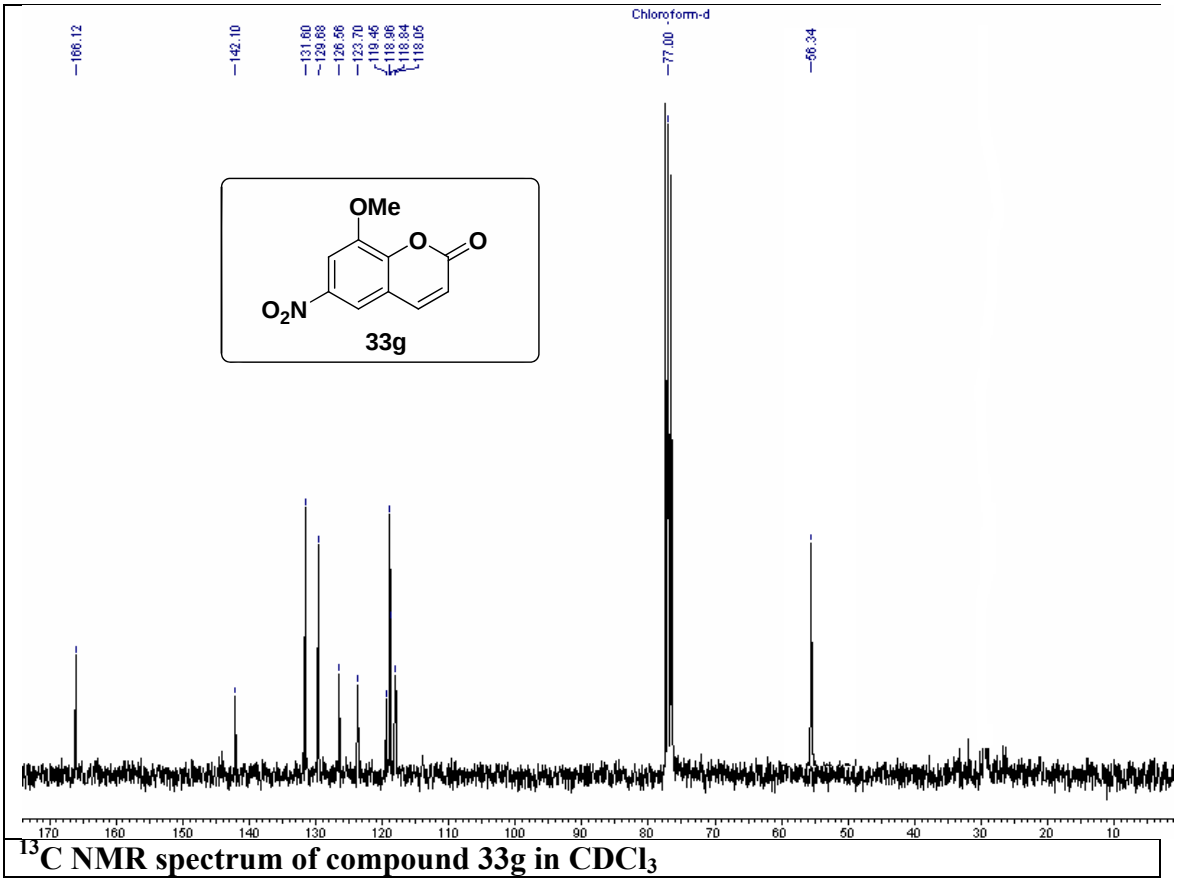
^{1}H NMR spectrum of compound 33f in $CDCl_3$



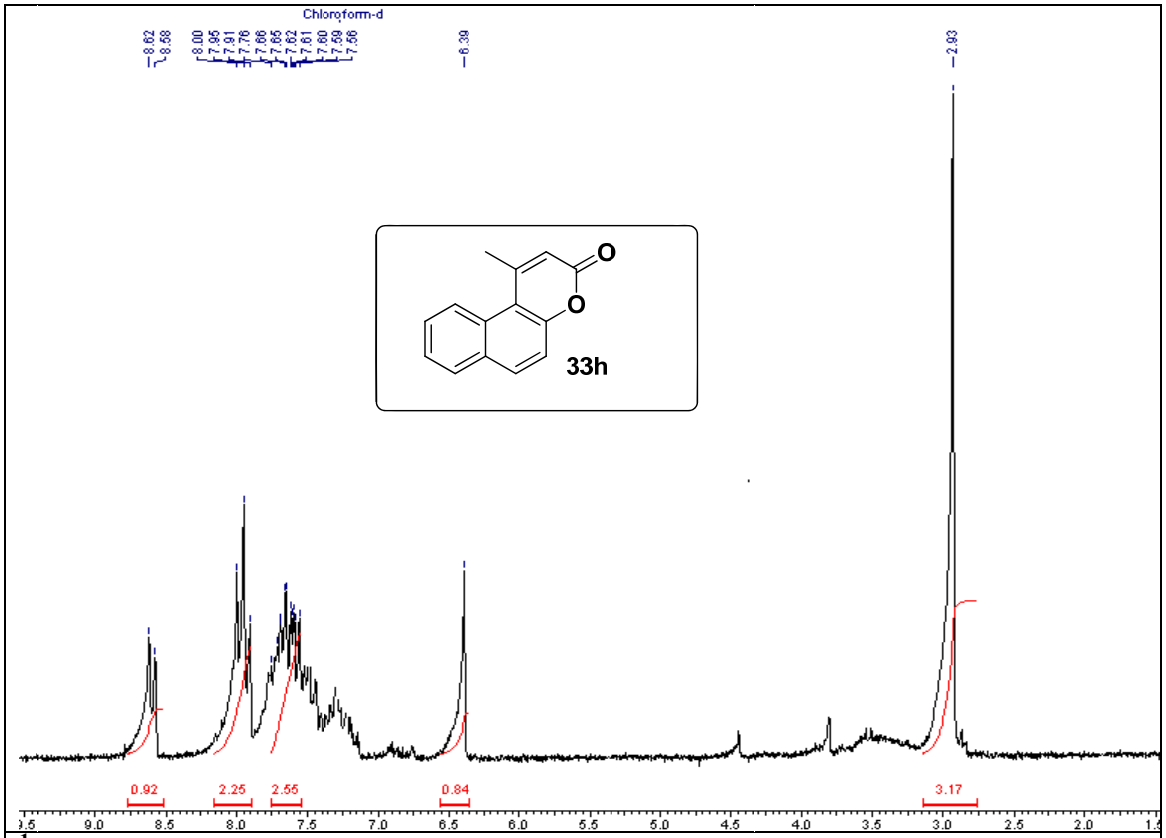
^{13}C NMR spectrum of compound 33f in $CDCl_3$



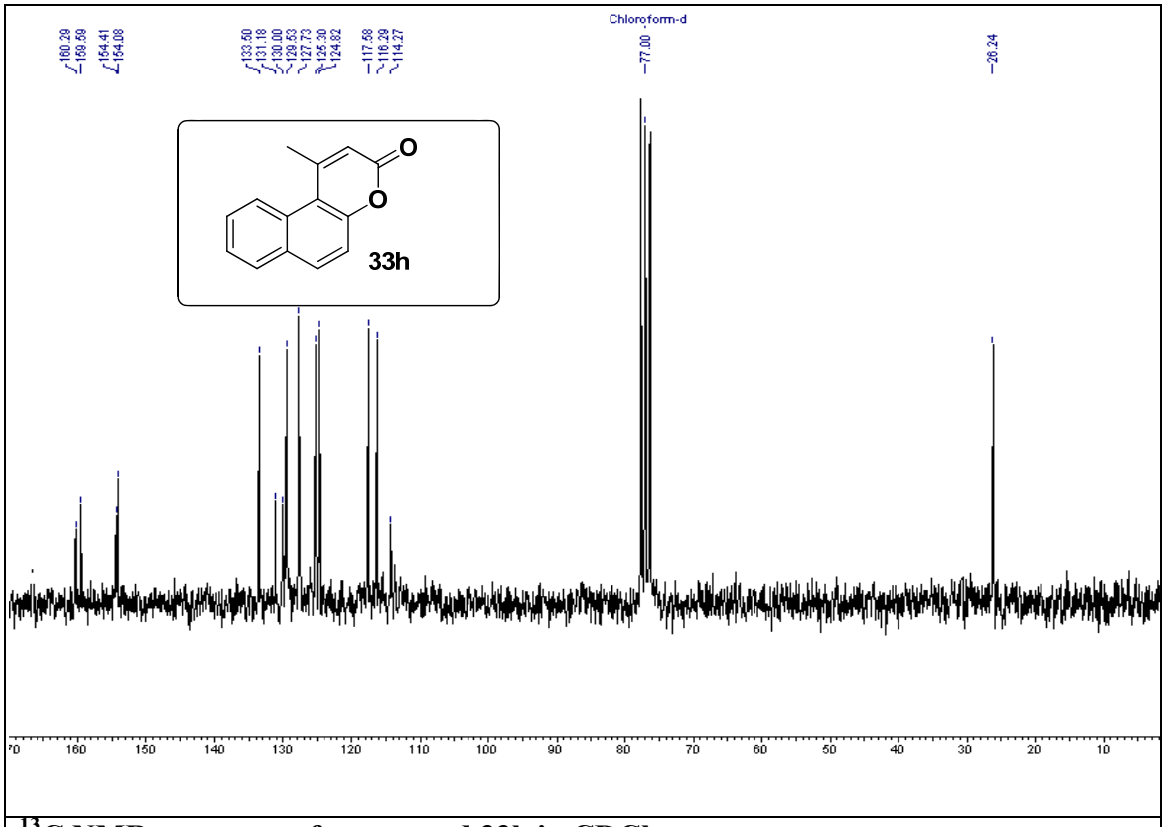
^{1}H NMR spectrum of compound 33g in $CDCl_3$



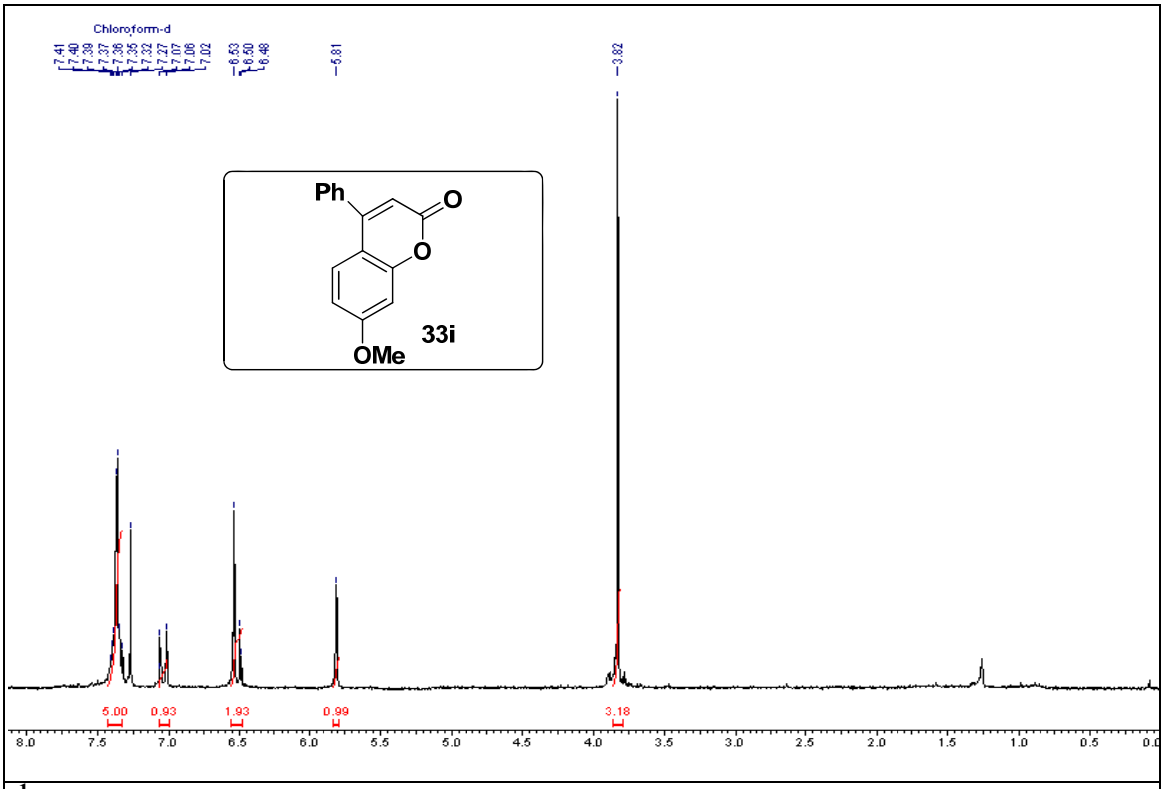
^{13}C NMR spectrum of compound 33g in $CDCl_3$



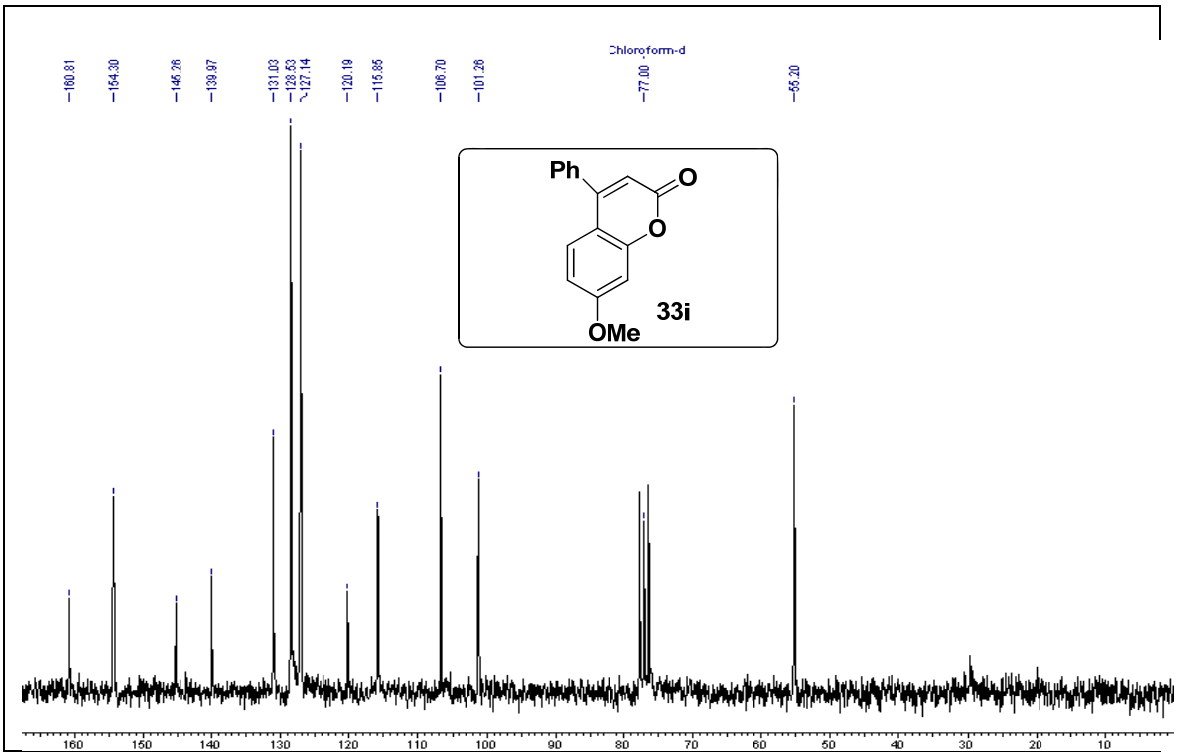
^{1}H NMR spectrum of compound 33h in $CDCl_3$



^{13}C NMR spectrum of compound 33h in $CDCl_3$



^{1}H NMR spectrum of compound 33i in $CDCl_3$



^{13}C NMR spectrum of compound 33i in $CDCl_3$

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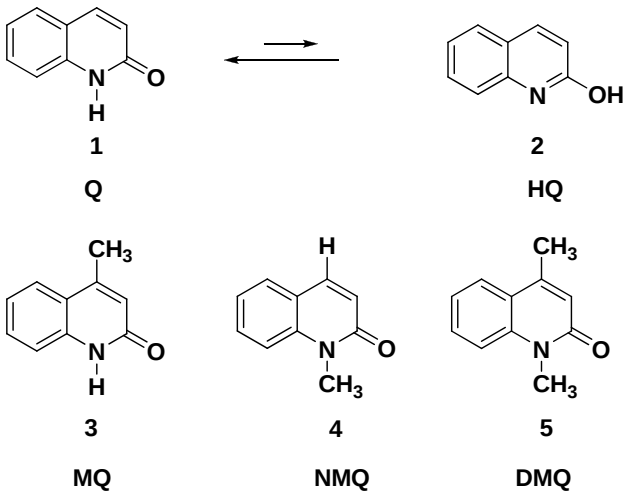
2.2. SECTION B

SYNTHESIS OF QUINOLINONE DERIVATIVES USING TRIPHENYL(α-CARBOXYMETHYLENE)PHOSPHORANE IMIDAZOLIDE AS C-2 SYNTHON

2.2.1. Introduction

Nitrogen-containing heterocycles play a privileged role in medicinal chemistry. Therefore, considerable efforts have been deployed to elucidate their tautomeric profiles. In solution, as opposed to the gas phase, pyridines and quinolines carrying oxygen at the 2- or 4-position were found to exist as 2- or 4-pyridinones and 2- or 4-quinolinones rather than as 2- or 4-hydroxypyridines and 2- or 4-hydroxyquinolines.[1]



The spectroscopy and structure of 2-quinolone (Q), **1** are of continuing interest because of the possible existence of its tautomer, 2-hydroxyquinoline (HQ), **2** the observation of fluorescence from the neutral and its conjugate base and acid and the utility of some of its derivatives as laser dyes. In nonaqueous solution and in the solid state' Q, **1** exists in the form of the hydrogen-bonded dimer. A very large free energy of association (-8.8 kcal mol) accounts for its limited solubility in most solvents. HQ, **2** has been identified as a minor tautomer in the vapor phase but there is no evidence for its formation upon irradiation of Q, **1** in the vapor phase or in solution. Protonation of Q, **1** occurs on the carbonyl oxygen, resulting in a significant increase in the fluorescence quantum yield and lifetime. The ground state and lowest singlet are of roughly comparable basicity.[2]

Quinolinones **1** are an interesting class of molecules present in a number of biologically active natural products. This core is present in the antibiotics nybomycin and deoxynybomycin isolated from streptomycete cultures.

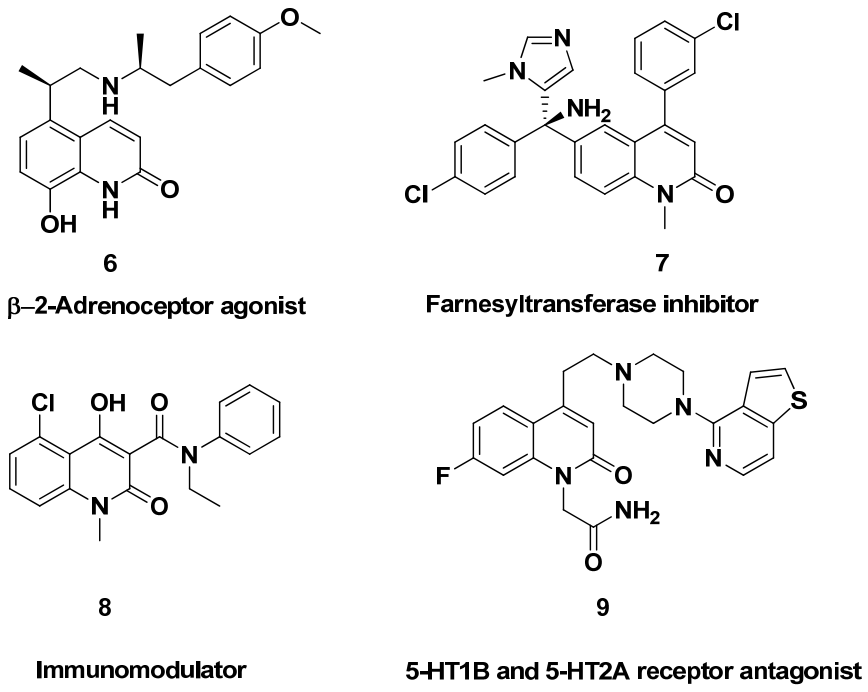


Figure 1. Biologically active quinolinones

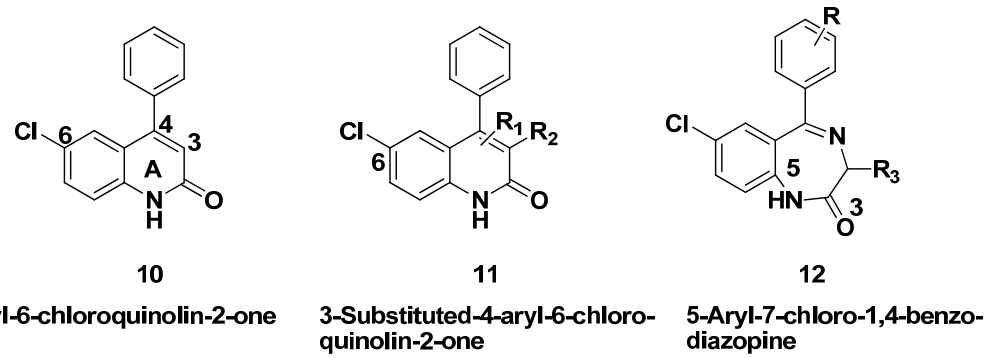


Figure 2. Structure of 6-chloro-4-arylquinolin-2-one (**10**), 3-substituted-4-aryl-6-chloroquinolin-2-one (**11**) and 5-aryl-7-choloro-1,4-benzodiazopine (**12**)

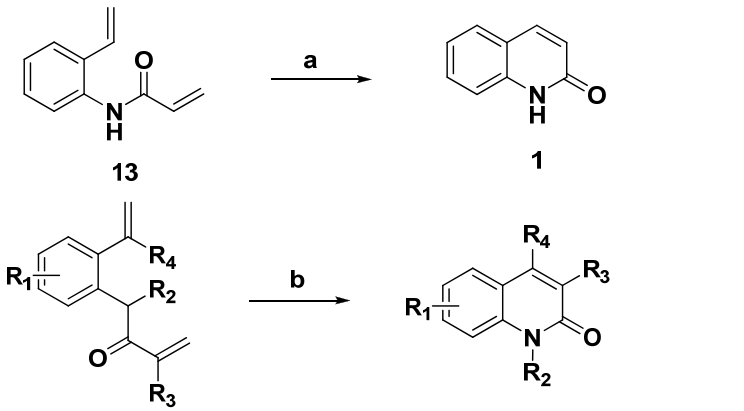
This structural core is also employed in medicinal chemistry and is present in a number of medicinally valuable compounds and also serves to illustrate the variety of substitution patterns incorporated in these molecules (Figure 1).[3] 4-Aryl-quinolin-2(1*H*)-ones[4] are inhibitors of acyl coenzyme A and cholesterol acyltransferase and are potent openers of the high conductance, calcium-activated K^+ channels. These compounds are useful as hypolipidemic, antiatherosclerosis agents and in afflictions arising from dysfunction of cellular membrane polarization and conductance (Figure 2).

2.2.2. Review of Literature

Quinolin-2(1*H*)-one derivatives have been of use in organic synthesis. Moreover, some compounds having this skeleton have interesting biological profile, angiotensin II receptor and oxytocin antagonist activities. Therefore, a number of new methods for the synthesis of this class of molecules have recently appeared.[5]

Sturino *et al.* (2008)[3]

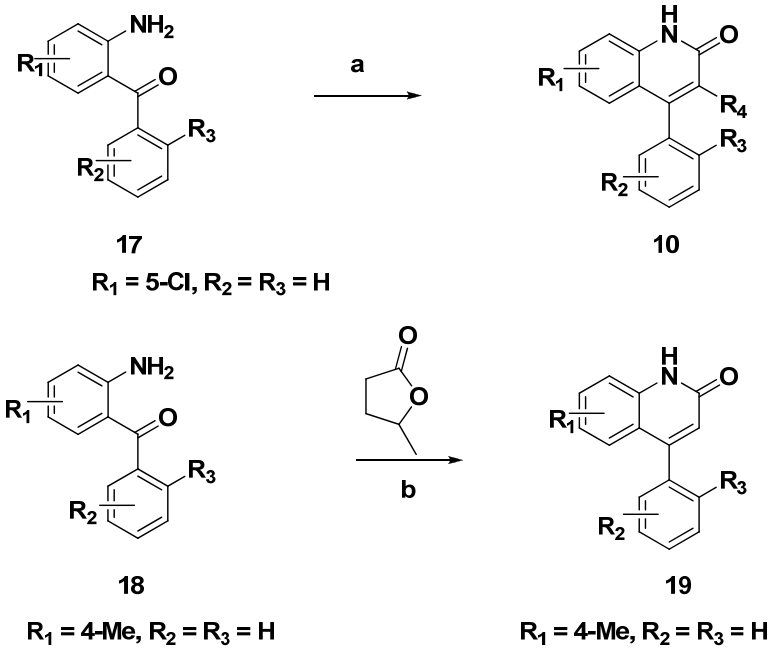
Sturino *et al.*[3] reported the efficient synthesis of quinolinones derivative from substituted *N*-phenylacrylamides **13** using ring closing metathesis (RCM) as the key step.



Scheme 1. *Reagents and conditions*: (a) 10 mol% Grubbs 2nd gen. catalyst, CH_2Cl_2, 0.01 mol%, 40 °C; (b) 5 mol% Grubbs 2nd, CH_2Cl_2, 0.01 M, 40 °C.

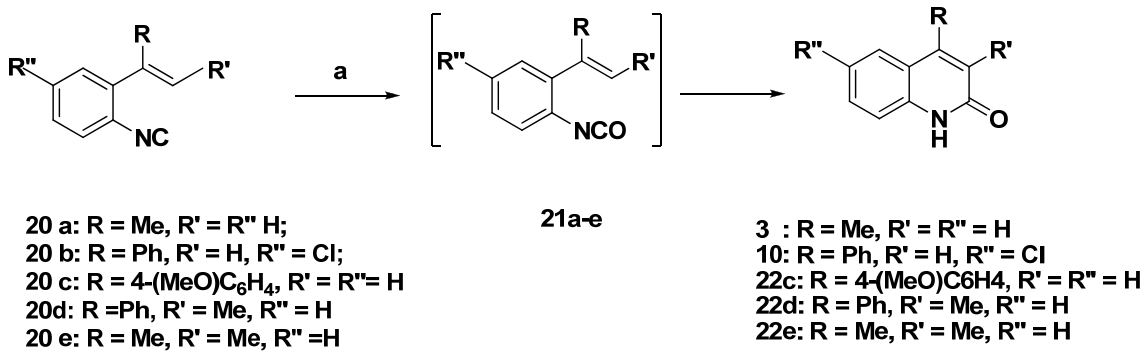
Wang *et al.* (2003)[6]

Wang *et al.*[6] reported a mild and efficient synthesis of 4-aryl-quinolin-2(1*H*)-one via a *tandem* amidation/Knoevenagel condensation of 2-amino acetophenones with esters or lactones.



Scheme 2. *Reagents and conditions:* (a) CH_3CO_2Et, LiHMDS 1M in THF, 0 ^oC-rt, 1 h, then H_2O, 2-3 h, 96%; (b) LiHMDS 1M in THF, 0 ^oC-rt, 1 h, then H_2O, 2-3 h, 96%;

Kobayashi *et al.* (2000)[5]



Scheme 3. *Reagents and conditions: m*CPBA, CH_2Cl_2, 0 ^oC.

Kobayashi *et al*.[5] described the one-pot synthesis of 4-substituted or 3,4-disubstituted quinolin-2(1*H*)-ones from 2-isocyanostyrene derivatives which involves *m*-*C*PBA oxidation to the corresponding isocyanate intermediates followed by electrocyclisation (Scheme 3).

2.2.3. Present Work

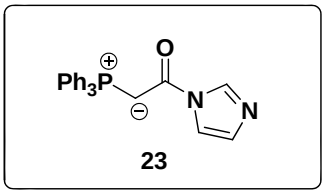
Objective

As part of our ongoing programme for developing a methodology employing phosphacumulene and (trimethylsilyl) methylene triphenyl phosphorane and their subsequent application to the biologically useful compounds,[7] triphenyl (α-carboxymethylene) phosphorane imidazolide **23**[8] is envisaged as a versatile reagent offering considerable opportunity for synthetic manipulation. The synthetic utility of **23** is hitherto unknown in the literature, and therefore we considered investigating the application of triphenyl (α-carboxymethylene) phosphorane imidazolide as a C-2 synthon for the one-pot synthesis of biologically relevant quinolin-2(1*H*)-ones. The generality of this concept has been established with several examples. Several procedures have been reported for the synthesis of quinolinones.[3] The intermolecular Wittig reaction has been extensively used as an excellent method for the C-C bond-forming process in the synthesis of natural products.[9]

2.2.4. Results and Discussion

Synthesis of phosphorus ylide (23)

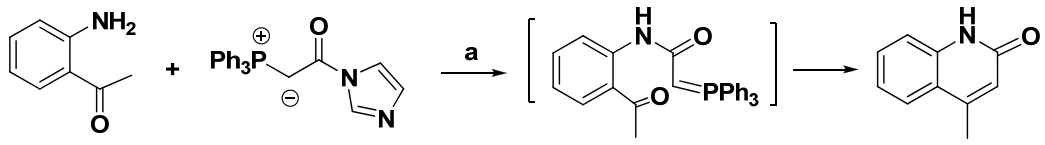
The phosphorus ylide **23** was synthesized in sufficient amount following the procedure as described in Sec. A of this chapter.



23

Synthesis of quinolinone derivative (3)

When 2'-amino acetophenone **24** was treated with ylide **23** in presence of NaH under reflux condition, it gave the desired quinolinone derivative **3** via intramolecular Wittig cyclisation of phosphorane **25** (Scheme 4).

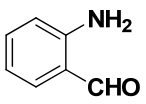
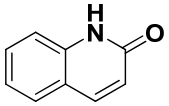
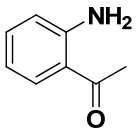
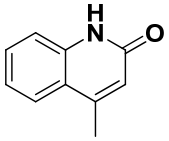
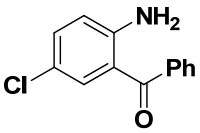
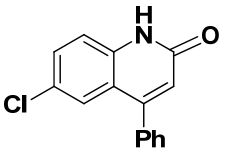
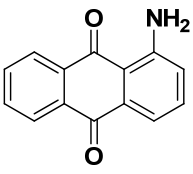
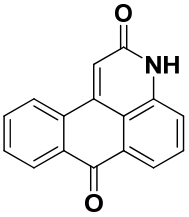


24 **23** **25** **3**

2'-aminoacetophenone **ylide** **phosphorane** **4-methylquinolin-2-one (MQ)**

Scheme 4. *Reagents and conditions:* (a) NaH, 0 ^{o}C, reflux, 2 h, then CDI, reflux, 5 h, 70%.

Table 1. One-pot synthesis of substituted quinolinone derivatives

Entry No.	*O*-Amino carbonyl compound	Product	% yield
1.	 **26**	 **1**	76
2.	 **24**	 **3**	70
3.	 **27**	 **10**	64
4.	 **28**	 **29**	60

Appearance of CH_3 protons at δ 2.01 (s, 3H) and CH proton at δ 2.05 (s, 1H) and aromatic protons at δ 7.47-7.53 (m, 11H) and at δ 7.69-7.76 (m, 8H) in the ^{1}H NMR spectrum confirming the formation of phosphorane **25**. On the basis of results of the above reaction we have studied additional three different substituted *O*-aminocarbonyl compounds that gave quinolinone derivatives in reasonably good yields as shown in the table 1. The spectroscopic data of all compound were in accordance with the literature precedence. A slight lower yield obtained in case of anthraquinone derivative (entry 4) could be attributed to the steric hindrance of aryl group.

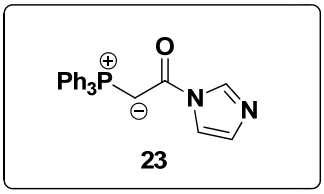
2.2.5. Conclusion

In summary, We have achieved one-pot synthesis of quinolinones derivatives using triphenyl (α-carboxymethylene) phosphorane imidazolide as a C-2 synthon.

2.2.6. Experimental Section

General Information: As described in Sec. A.

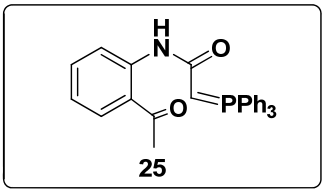
Synthesis of triphenyl (α-carboxymethylene)phosphorane imidazolide (23).[8]



23

Pl. see the experimental procedure in sec. A of this chapter.

Synthesis of phosphorane (25).



25

To a solution of 2'-amino acetophenone **24** (0.5 g, 3.70 mmol) in xylene was added 60% NaH (0.3 g, 7.41 mmol) under argon atmosphere at 0 ^oC and mixture refluxed for 2 h and to this was added ylide **23** (1.37 g, 3.70 mmol) in one portion. The reaction

mixture was further refluxed for 5 h. As the reaction showed the consumption of the starting material, solvent was evaporated in vacuo and quenched with ice piece and extracted with EtOAc (20 x 3 mL). The solvent was evaporated to dryness and crude residue was purified by silica gel column chromatography using EtOAc/pet ether (1.5:8.5) as eluent to give phosphorane **25** as a colorless solid.

Yield: 1.2 g (74%).

M.P. 112 ^{o}C-114 ^{o}C

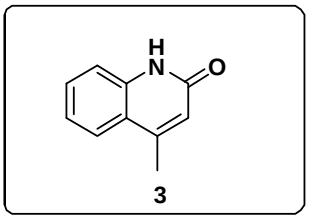
Mol. Formula: $C_{28}H_{24}NO_2P$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3384, 3060, 2981, 1713, 1592, 1484, 1438, 1310, 12951070.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.05 (s, 1H), 7.47-7.53 (m, 11H), 7.69-7.76 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 17.1, 128.4, 128.6, 130.2, 130.4, 131.6, 160.4, 185.4.

Synthesis of 4-methylquinolin-2(1*H*)-one (3) [2,3,5,11]



3

To a solution of 2'-amino acetophenone **24** (0.5 g, 3.70 mmol) was added 60% NaH (0.3 g, 7.41 mmol) under argon atmosphere at 0 ^{o}C in dry xylene and mixture refluxed for 2 h and to this reaction mixture was added ylide **23** (1.37 g, 3.70 mmol) in one portion. The reaction mixture was further refluxed for 5 h. As the reaction showed the consumption of the starting material, solvent was evaporated in vacuo and quenched with ice piece and extracted with EtOAc (20 x 3 mL). The solvent was evaporated to dryness and crude residue was purified by silica gel column chromatography using EtOAc/pet ether (1.5:8.5) as eluent to give 4-methyl quinolinone **3** as colorless solid.

Yield: 0.41 g (70%).

M.P. 215 ^{o}C-217 ^{o}C; [lit.(M.P. 217 ^{o}C-220 ^{o}C)].[5]

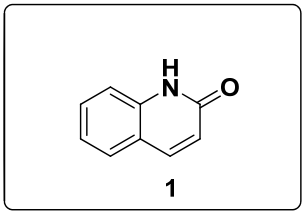
Mol. Formula: $C_{10}H_9NO$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3013, 2925, 1676, 1216, 1023.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 5.31 (s, 1H), 6.76 (t, J =8.3 Hz, 2H), 7.04-7.12 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 120.3, 127.4, 127.7, 128.5, 129.4, 131.9, 132.1, 148.2, 160.5.

Synthesis of Quinolin-2(1*H*)-one (1).[2,3,10,11d]



1

Yield: 76%.

M.P. 197 ^{o}C-199 ^{o}C; [lit. (M.P. 199 ^{o}C-200 ^{o}C)].[2b]

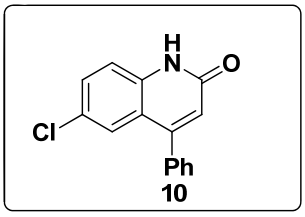
Mol. Formula: C_9H_7NO

IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2925, 1730, 1614, 1215, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47-7.49 (m, 2H), 7.63-7.70 (m, 3H), 8.30 (m, 1H), 8.92 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 115.7, 118.4, 119.8, 122.3, 127.9, 128.7, 137.5, 140.8, 163.8.

Synthesis of 6-chloro-4-phenylquinolin-2(1*H*)-one (10).[5,6]



10

Yield: 64%.

M.P. 265 ^{o}C-266 ^{o}C [lit. (M.P. 261 ^{o}C-264 ^{o}C)][5]

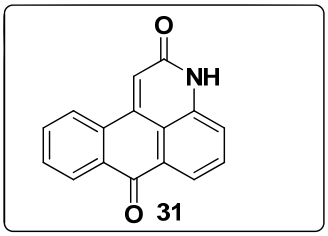
Mol. Formula: $C_{15}H_{10}ClNO$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 1616, 1589, 1471, 1357, 1215, 1110, 1078.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.97-7.0 (m, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.46 (t, J =7.2 Hz, 1H), 7.50-7.59 (m, 2H), 7.70-7.75 (m, 2H), 7.87-7.89 (brs, 1H), 8.22 (brs,1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 110.8, 122.5, 127.2, 128.4, 128.9, 129.1, 129.4, 130.0, 131.5, 137.2, 150.2, 168.8.

Synthesis of 2*H*-naphtho[1,2,3-de]quinoline-2,7(3*H*)-dione (31).[12]



31

Yield: 60%.

M.P. 316 ^{o}C-318 ^{o}C [lit. (M.P.> 316 ^{o}C)][12a]

Mol. Formula: $C_{16}H_9NO_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1683, 1736, 3073.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 (d, J = 8.3 Hz, 1H), 6.83 (s, 1H), 7.02 (t, J = 7.8 Hz, 1H), 7.21 (d, J =7.4 Hz, 1H), 7.28-7.35 (m, 2H), 7.81-7.86 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 108.8, 113.8, 117.3, 123.1, 126.8, 133.2, 133.9, 134.7, 151.1, 161.7, 185.3.

2.2.7. Spectra

1] ^{1}H NMR Spectrum of **3**

2] ^{1}H NMR Spectrum of **25**

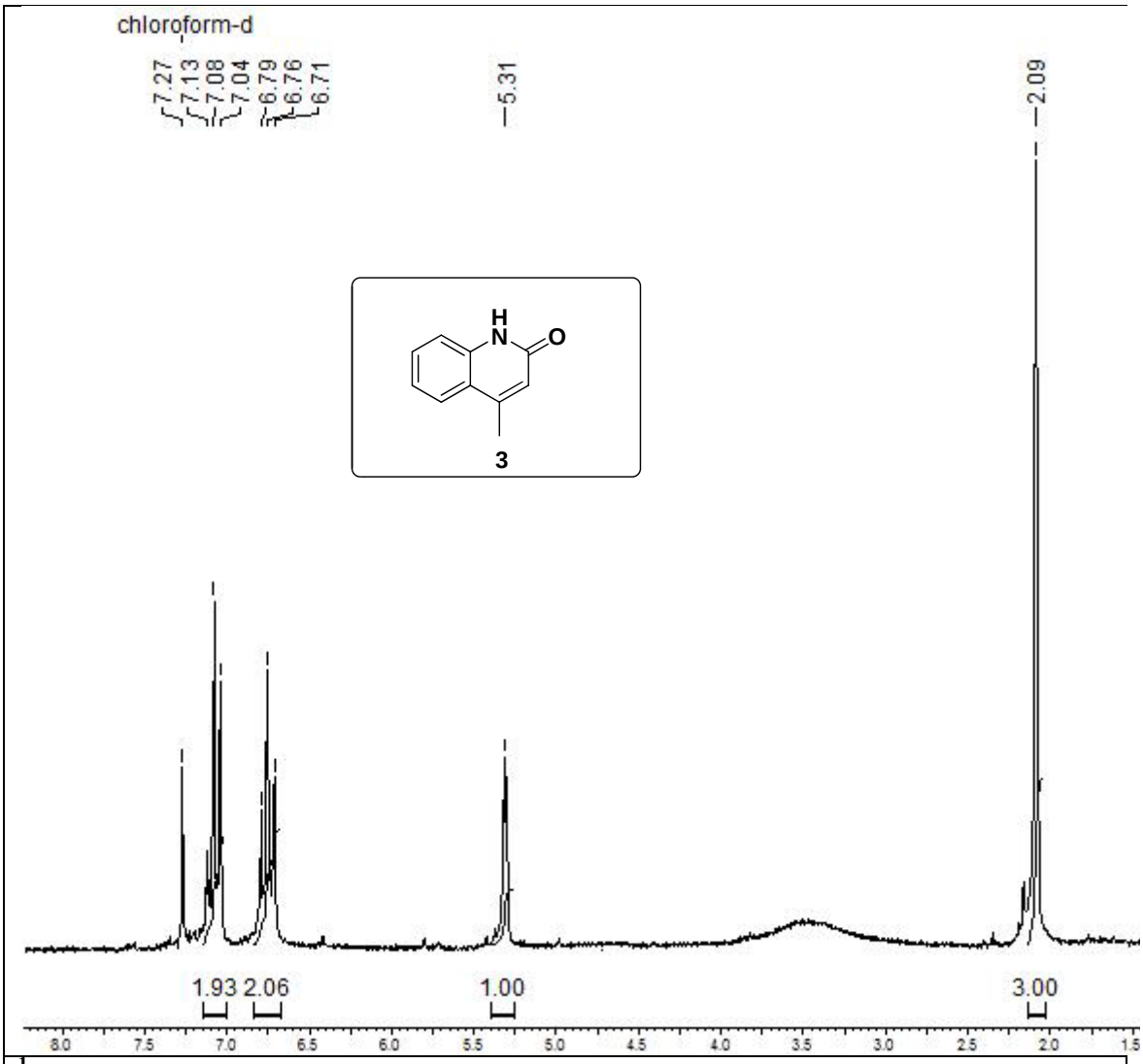
3] ^{13}C NMR spectrum of **25**

4] ^{1}H NMR Spectrum of **10**

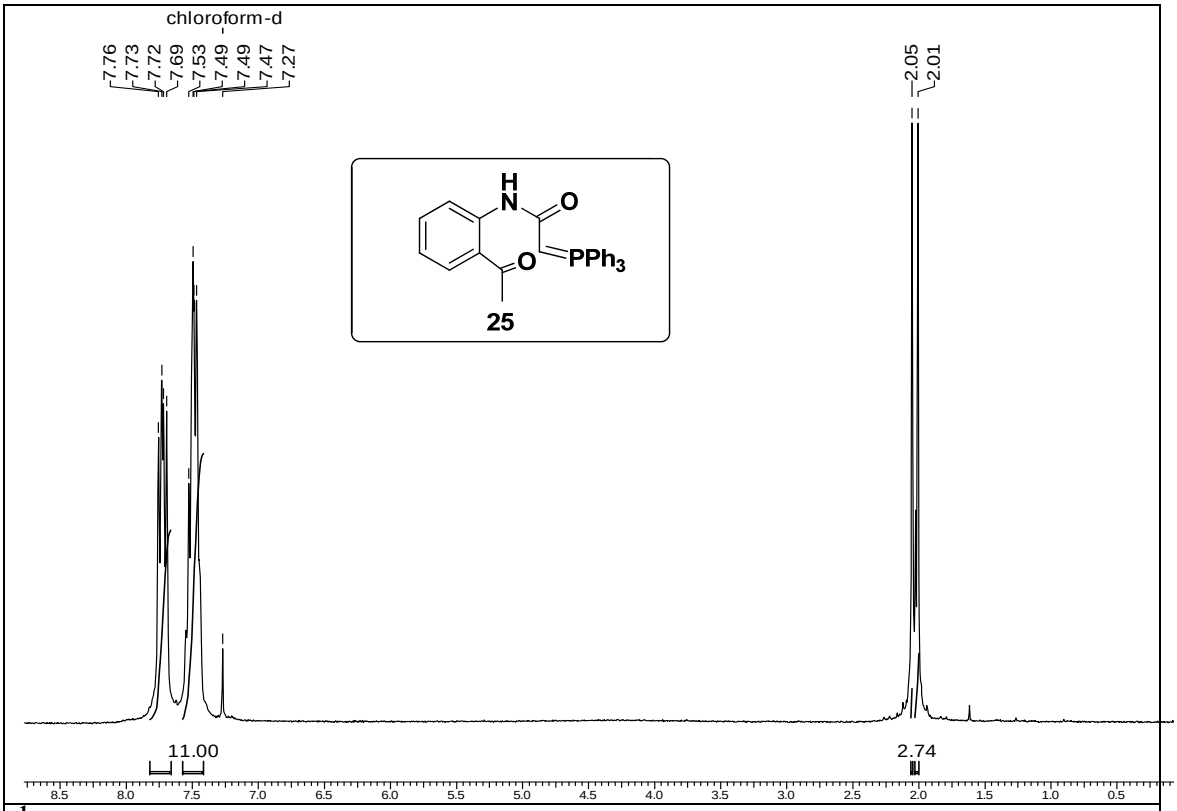
5] ^{13}C NMR Spectrum of **10**

6] ^{1}H NMR Spectrum of **29**

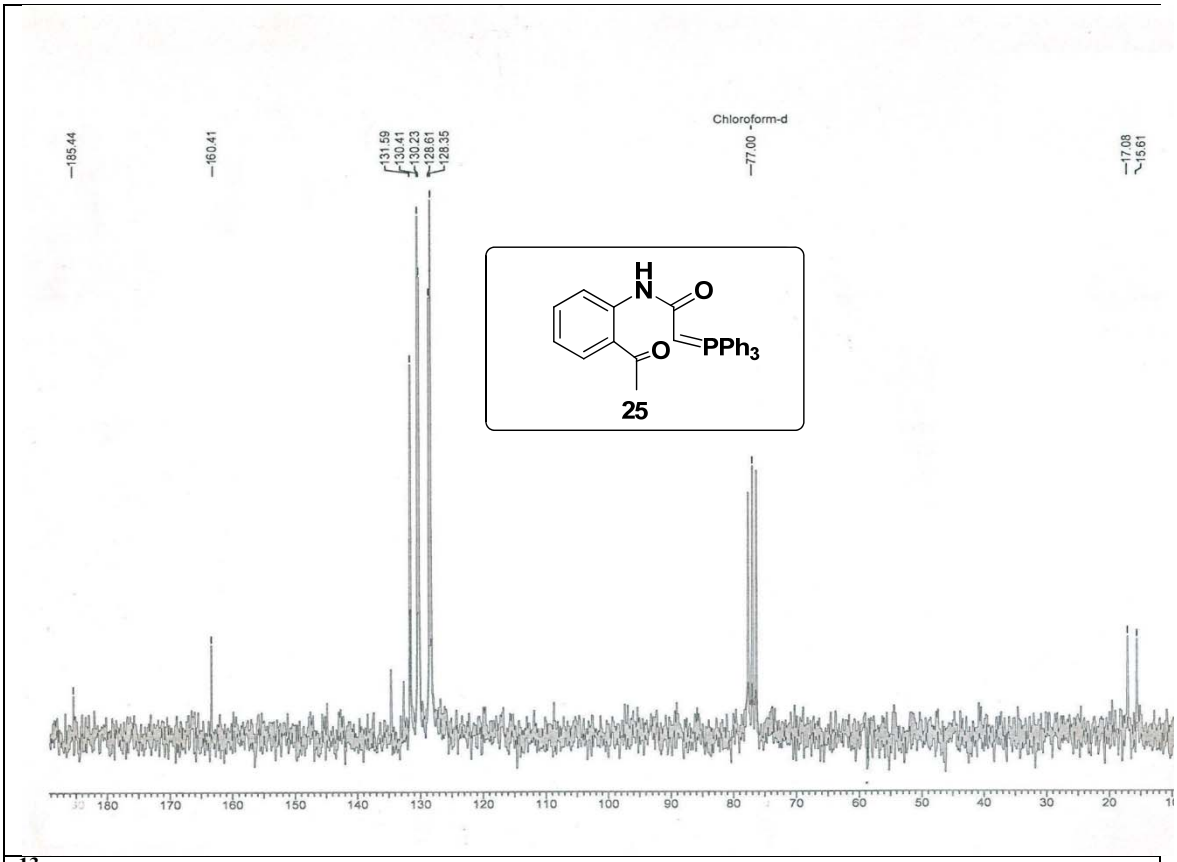
7]^{13}C NMR spectrum of **29**



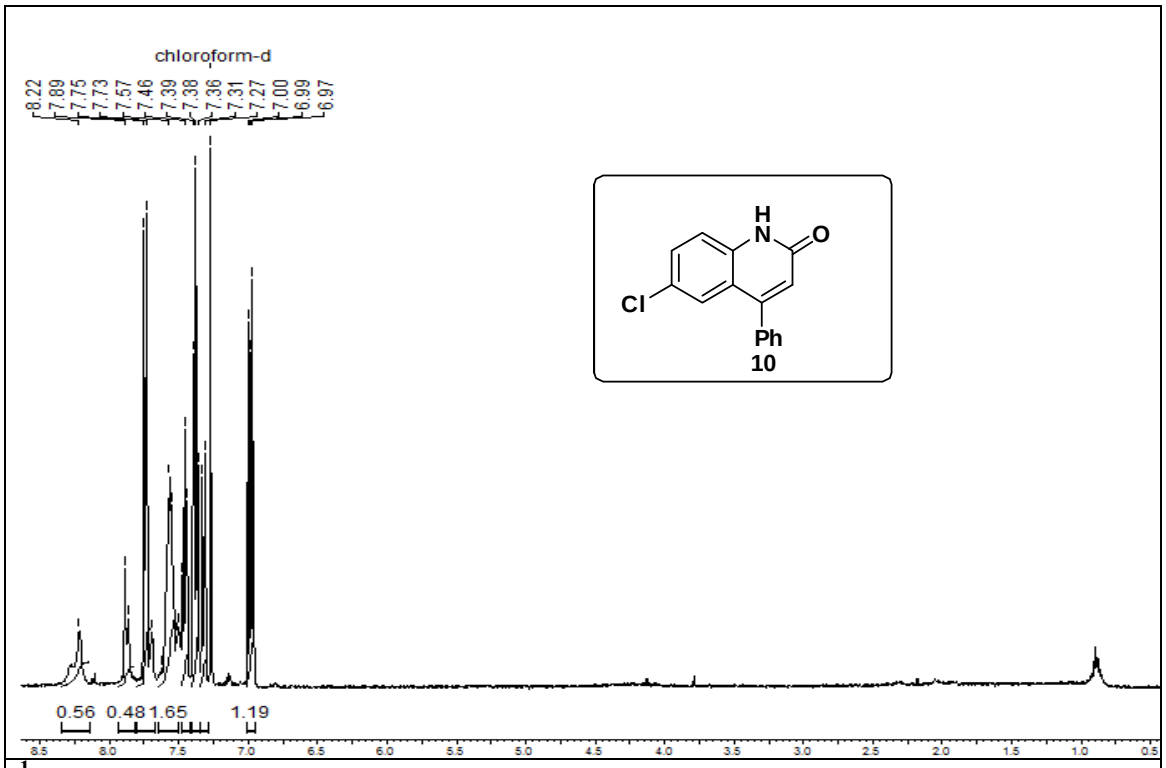
^{1}H NMR spectrum of compound 3 in $CDCl_3$



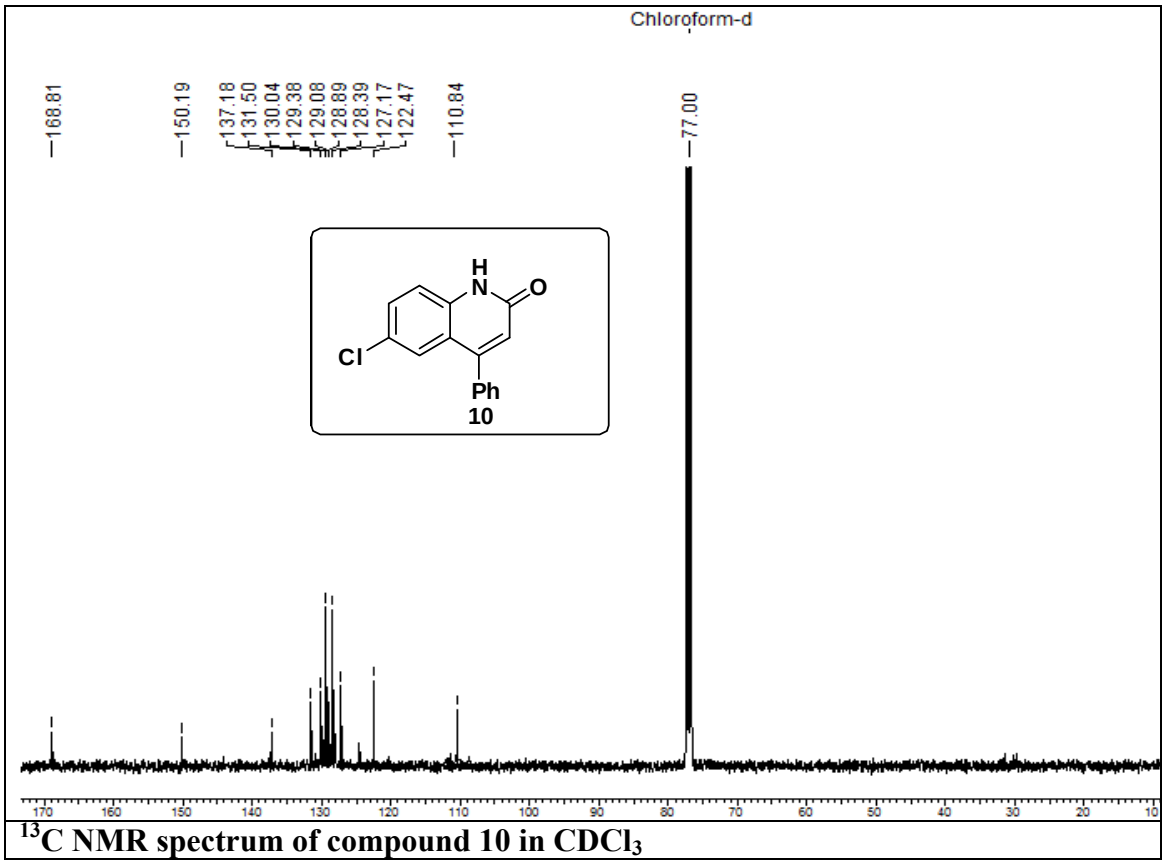
^{1}H NMR spectrum of phosphorane 25 in $CDCl_3$



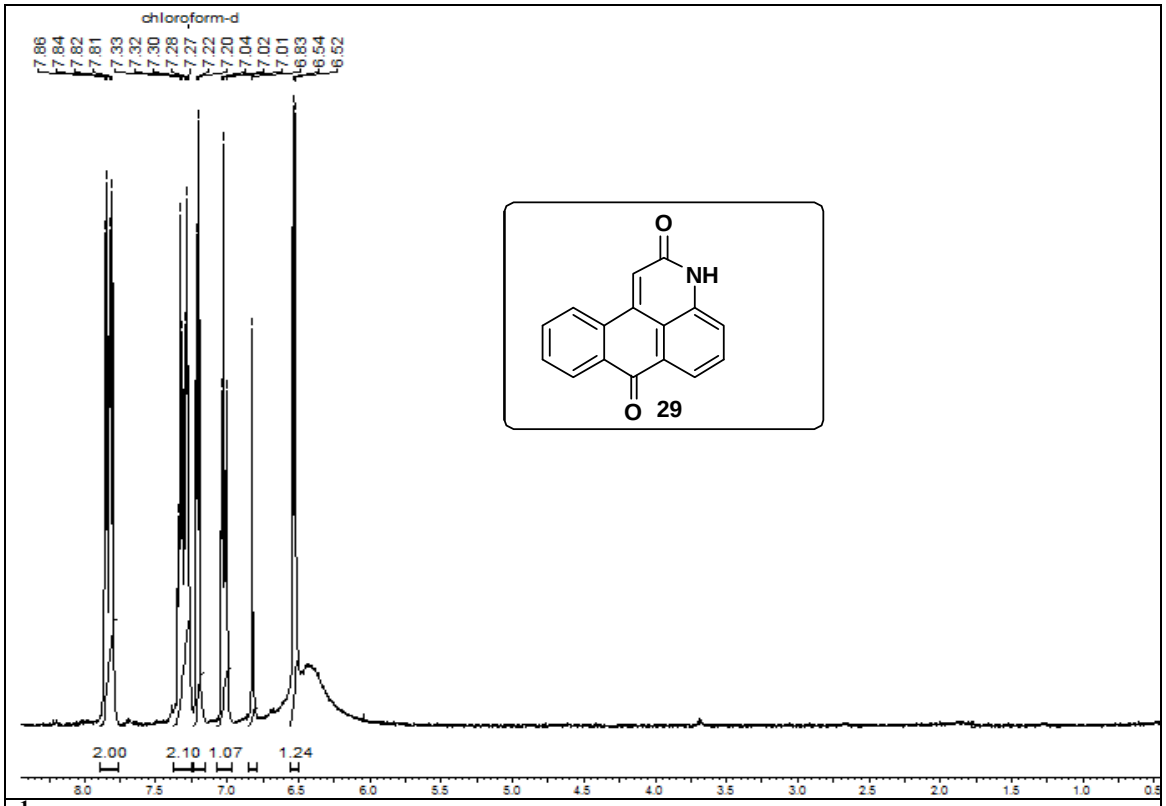
^{13}C NMR spectrum of phosphorane 25 in $CDCl_3$



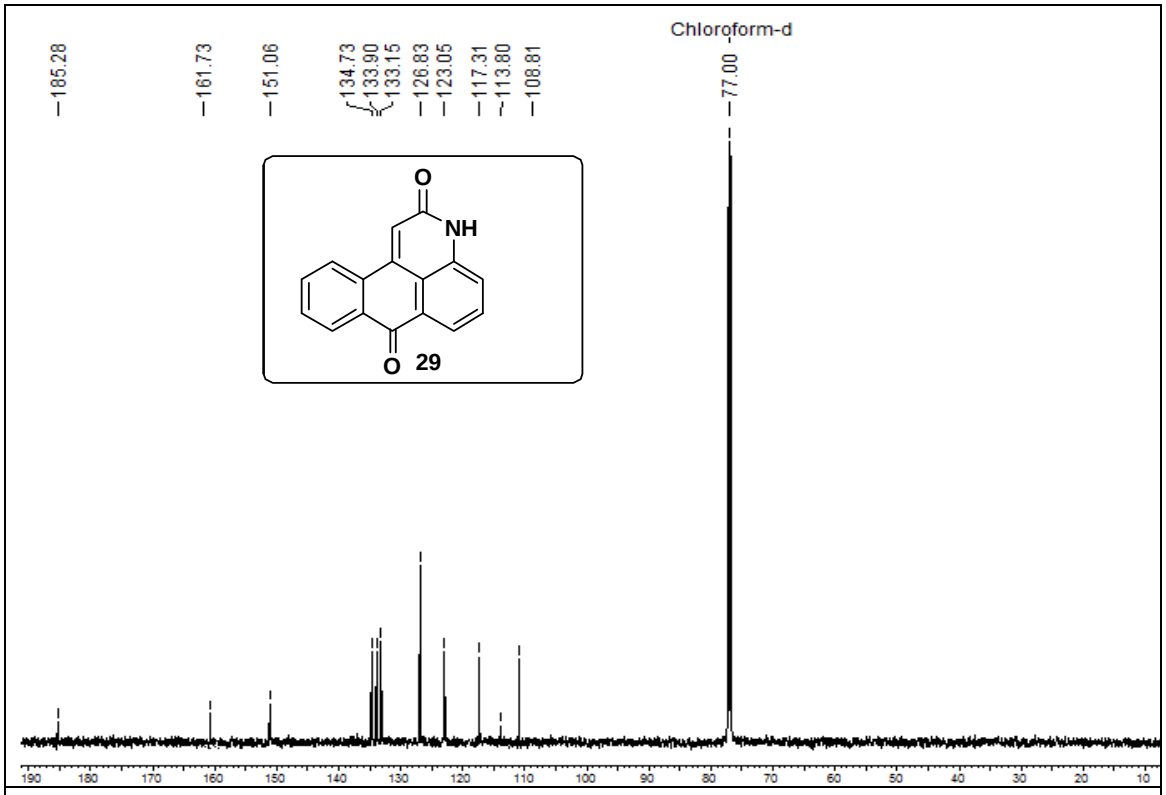
^{1}H NMR spectrum of compound10 in $CDCl_3$



^{13}C NMR spectrum of compound 10 in $CDCl_3$



^{1}H NMR spectrum of compound 29 in $CDCl_3$



13 NMR spectrum of compound 29 in $CDCl_3$

2.2.8. References

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CHAPTER 3

Asymmetric synthesis of hydroxylated piperidine alkaloid using Sharpless asymmetric dihydroxylation and hydroxylated pyridone derived alkaloids

3.1. SECTION A

STUDIES TOWARD STEREOSELECTIVE SYNTHESIS OF HYDROXYLATED (2*S*,3*S*,6*S*)-1-*TERT*-BUTYL-2-ETHYL-6-(*TERT*-BUTYLDIPHENYLSILYLOXY)METHYL)-3-HYDROXYPIPERIDINE-1,2-DICARBOXYLATE

3.1.1. Introduction

Alkaloids were known in ancient times because they are easy to extract from plants and some of them have powerful and deadly effects. Any plant contains a millions of chemical compounds, but some plants like deadly nightshade, can be mashed up and extracted with aqueous acid to give a few compounds soluble in that medium which precipitate on neutralization. These compounds were seen to "like-alkali" and Meissner, the apothecary from halle, in 1819, named them "alkaloids".

Polyhydroxylated piperidine alkaloids are frequently found in living system and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.

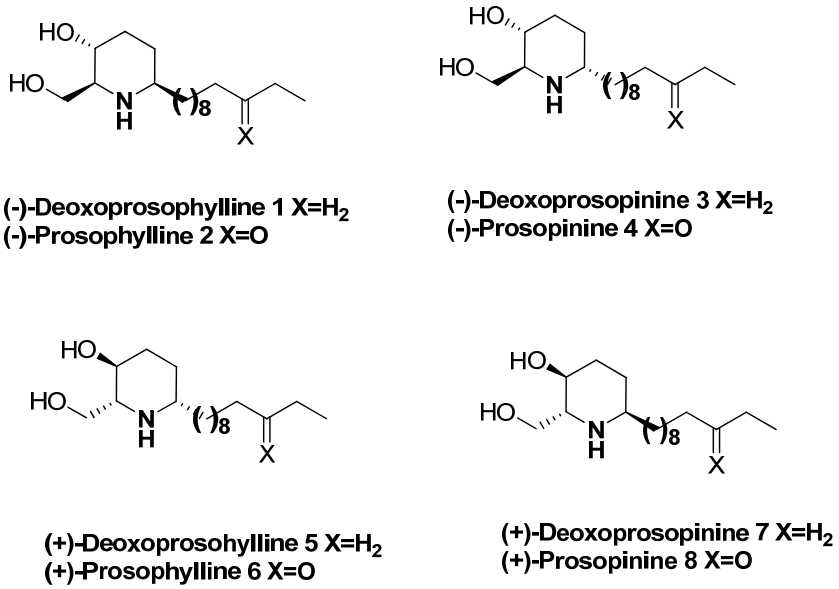


Figure 1. Structure of various prosopis alkaloids and its synthetic analogues

Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids an important tools in the study of biochemical pathways. A number of piperidines and indolizidines alkaloids bearing

carbonaceous substituents at both α and α' position have been isolated from natural sources, many of them have received much attention due to a variety of biological activities. Piperidin-3-ol alkaloids having appendages at α and α' position have also been isolated from plants. These piperidinol alkaloids also exhibit a variety of pharmacological properties such as anaesthetic, analgesic and antibiotic activities. Recently, alkaloids containing this ring system were isolated from marine species and all of them showed substantial cytotoxic activity against human solid tumor cell lines. These 2,6-dialkylated piperidine alkaloids have been found frequently in nature and are key structural units in medicinally important compounds.

Alkaloids containing multifunctionalized piperidine rings exist abundantly in nature.[1] Several 2,3,6-trisubstituted piperidines such as prosophyllines **2** and **6**, and prosopinines **4** and **8** have been isolated from the leaves of the West African savanna tree *Prosopis Africana Taub*[2] and the leaves of *Microcos philippinenis* (Perk) Burrentt (Tiliaceae).[3] These trisubstituted piperidine alkaloids and their deoxygenated analogues, especially 2-hydroxymethyl-6-alkylated 3-hydroxypiperidines and their deoxygenated derivatives (Fig. 1), have shown anaesthetic, analgesic, antibiotic, and CNS stimulating biological properties, and are of considerable pharmacological interest.[4] Structurally, these compounds possess a polar head group and a hydrophobic aliphatic tail, and can be considered as cyclic analogues of the lipid sphingosine membrane.[5] These interesting structural features and therapeutic potential make them attractive synthetic targets. For example, various synthetic strategies for deoxoprosophylline **1** have been reported.[6–8]

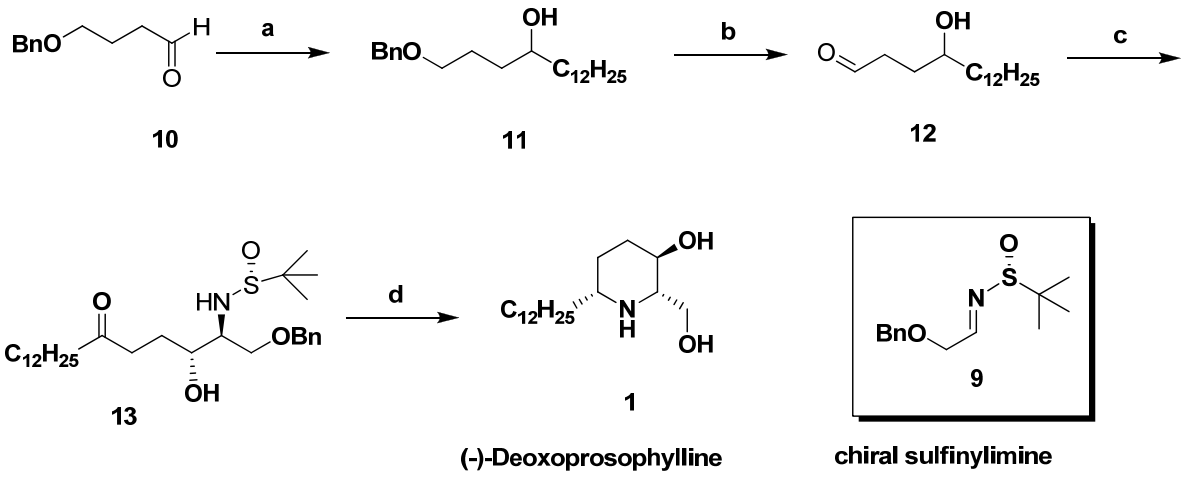
Although it could be conveniently synthesized based on chiral building blocks from natural amino acids and carbohydrates, there is still a need to develop a general strategy for the asymmetric preparation with desired stereochemistry.

3.1.2. Review of Literature

Due to biological activities possessed by 3-piperidinol alkaloids, they have gained huge attention by the chemist to synthesize these kind of alkaloids. There are various synthetic methods in the literature for the synthesis of α,α'-3-piperidinol alkaloids as discussed below.

Lin *et al.* (2008)[9a]

Lin and his co-workers[9a] accomplished the synthesis of (-)-deoxoprosophylline by SmI_2- mediated cross-coupling of chiral *N-tert*-butanesulfinyl imine **9**[9b] with aldehyde **12** to construct hydroxymethyl-β-amino alcohol **13** in 83% yield and high diastereoselectivity (>99% de) (Scheme1).

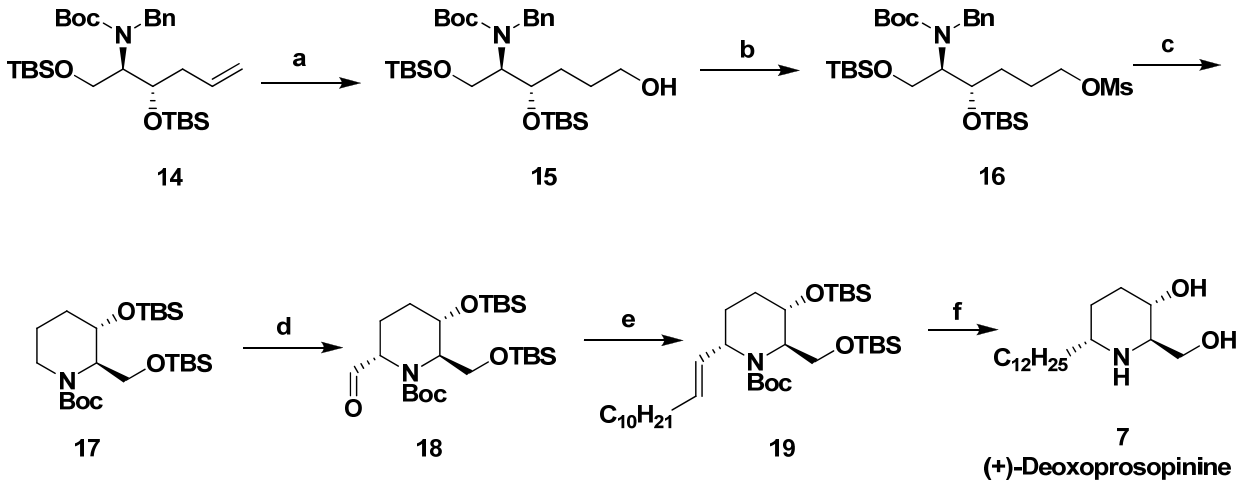


Scheme 1. *Reagents and conditions*: (a) $C_{12}H_{25}MgBr$, THF, 88%; (b) (i) Pd/C, H_2, MeOH, rt, 12 h; (ii) PCC, CH_2Cl_2, 5 h, two steps, 81%; (c) **9**, SmI_2, *t*-BuOH, THF, 83%; (d) (i) HCl/MeOH, MeOH; (ii) $Pd(OH)_2/C$, H_2, EtOH, 4 h, then conc. HCl, 33 h, two steps, 58%.

Removal of the chiral auxiliary of **13** with HCl/MeOH, followed by treatment with saturated aqueous $NaHCO_3$ solution led to the cyclic imine, which, without further purification, was hydrogenated under acidic conditions and basified with an aqueous solution of 1M sodium hydroxide to give (-)-deoxoprosophylline **1** as a white solid.

Garcia *et al.* (2008)[10]

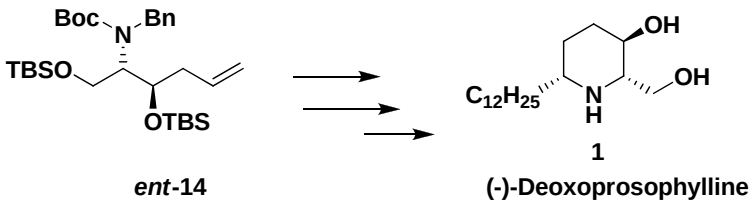
Garcia *et al.*[10] reported the versatile synthesis of (+)-deoxoprosopinine **7** and (-)-deoxoprosophylline **1** by using allyl derivatives of *N*-protected amino aldehydes. As outlined in Scheme 2, *N*-benzyl-*N*-Boc serine derivative **14**[11] was subjected to hydroboration (BH_3.THF) and subsequently treated with $NaOH/H_2O_2$ to afford alcohol **15** with good regioselectivity (8:1).



Scheme 2. *Reagents and conditions*: (a) BH_3.THF, $NaOH/H_2O_2$, THF, 68%; (b) MsCl, Et_3N, CH_2Cl_2, 90%; (c) H_2, Pd/C, 96%; (d) (i) *sec*-BuLi, TMEDA; (ii) DMF, 83%; (e) *n*-BuLi, $nC_{11}H_{23}Ph_3P^+I^-$, 91%; (f) (i) H_2, Pd/C; (ii) Bu_4NF/THF; (iii) HCl/MeOH.

Mesylation of alcohol **15** furnished compound **16** which on catalytic hydrogenation afforded compound **17.** Employing Beak's methodology,[12] the side chain at C-6 of **17** was introduced by treatment with *sec*-BuLi/TMEDA at -30 ^oC and reaction of the carbanion formed with DMF (-78 ^oC) afforded a mixture of aldehydes **18** which was treated immediately with the ylide generated in situ from undecyltriphenylphosphonium iodide and *n*-BuLi/THF at -78 ^oC to give compound **19** as single diastereoisomer. Finally, catalytic hydrogenation of compound **19** followed by the cleavage of all protecting groups by Bu_4NF/THF and HCl/MeOH gave product (+)-deoxoprosopinine **7** in 38% overall yield.

Similarly, synthesis of (-)-deoxoprosophylline was achieved in a similar manner starting from *ent*-**14**[13] as shown in Scheme 3.

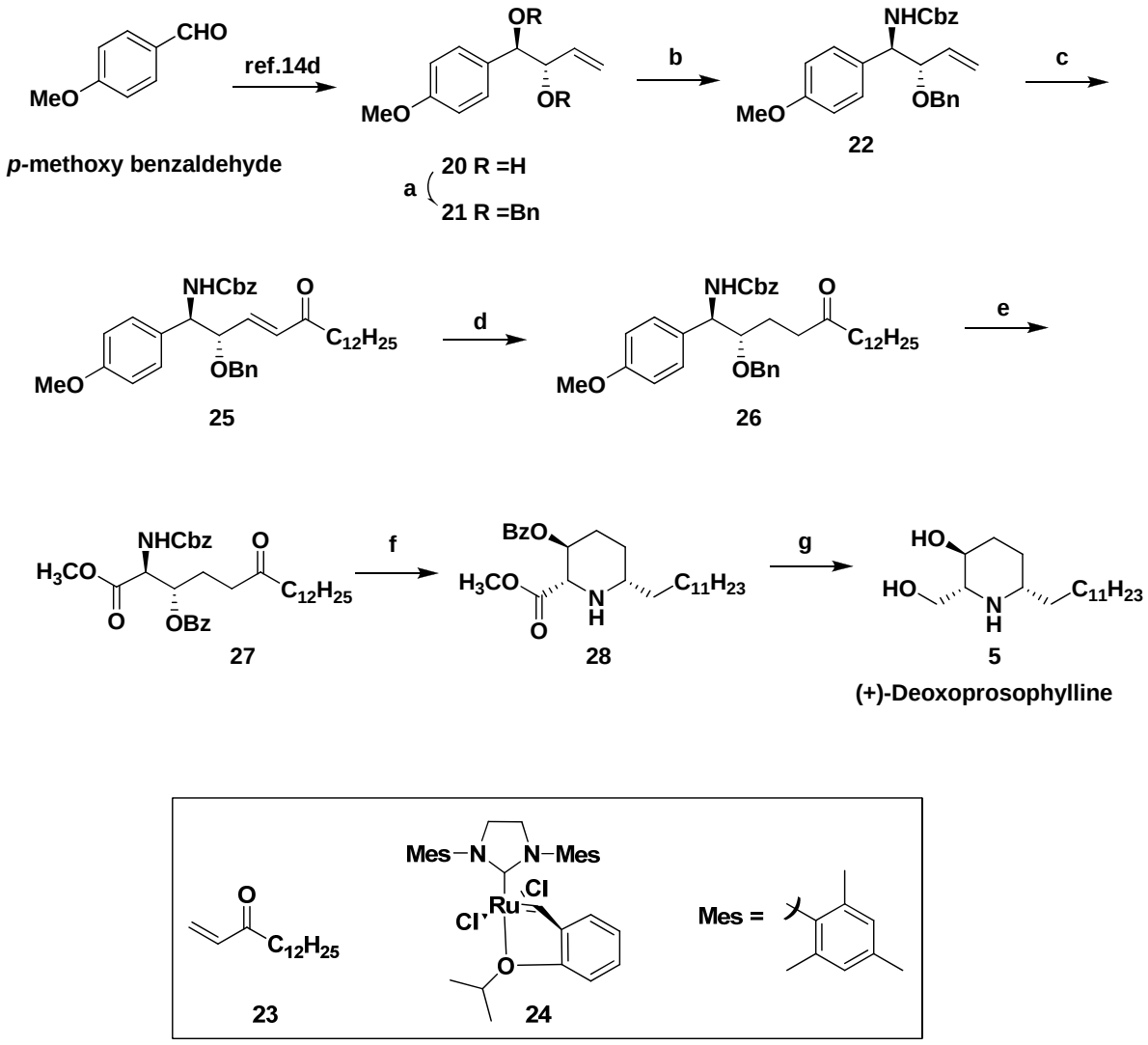


Scheme 3. Synthesis of (-)-Deoxoprosophylline

Jung *et al.* (2007) [14a]

Jung and his coworkers[14a] reported the asymmetric synthesis of (+)-deoxoprosophylline **5** via the stereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulphonyl isocyanate (**CSI**), intermolecular olefination, and Pd-catalyzed intramolecular cyclization. Thus synthesis of **1** began with the commercially available *p*-anisaldehyde, which was converted into *anti*-1,2-diol **20** with high enantioselectivity (95% *ee*). According to the literature[14b,c] (Scheme 4), treatment of diol **20** with benzyl bromide and sodium hydride in the presence of DMF and THF gave *anti*-1,2-dibenzyl ether **21** in quantitative yield. The regioselective and diastereoselective chlorosulphonyl isocyanate (CSI) reaction of **21** was carried out in toluene solution at -78 ^{o}C for 24 h, followed by desulfonylation with aqueous 25% sodium sulfite solution to give the desired *anti*-1,2-amino alcohol **22** with high diastereoselectivity (*anti:syn* = 49:1, 98% **de**).[14a,b] Cross-metathesis of **22** with pentadec-1-en-3-one **23**[15] using Hoveyda catalyst **24** in toluene at 80 ^{o}C provided (*E*)-α,β-unsaturated ketone **25**[16] which was then hydrogenated using PtO_2 for 2 h to afford **26**.

Oxidation of **26** with $RuCl_3$ and $NaIO_4$[17] gave the intermediate carboxylic acid, in which the benzyl group had been oxidized to benzoate.[18] Treatment of the crude carboxylic acid with diazomethane gave the desired methyl ester **27**. Removal of the Cbz group by palladium-catalyzed hydrogenolysis and simultaneous intramolecular cyclization afforded piperidine **28**.[19ab] Finally, reduction of ester **28** with $LiAlH_4$ and removal of the benzoate group using potassium hydroxide gave (+)-deoxoprosophylline **5**.

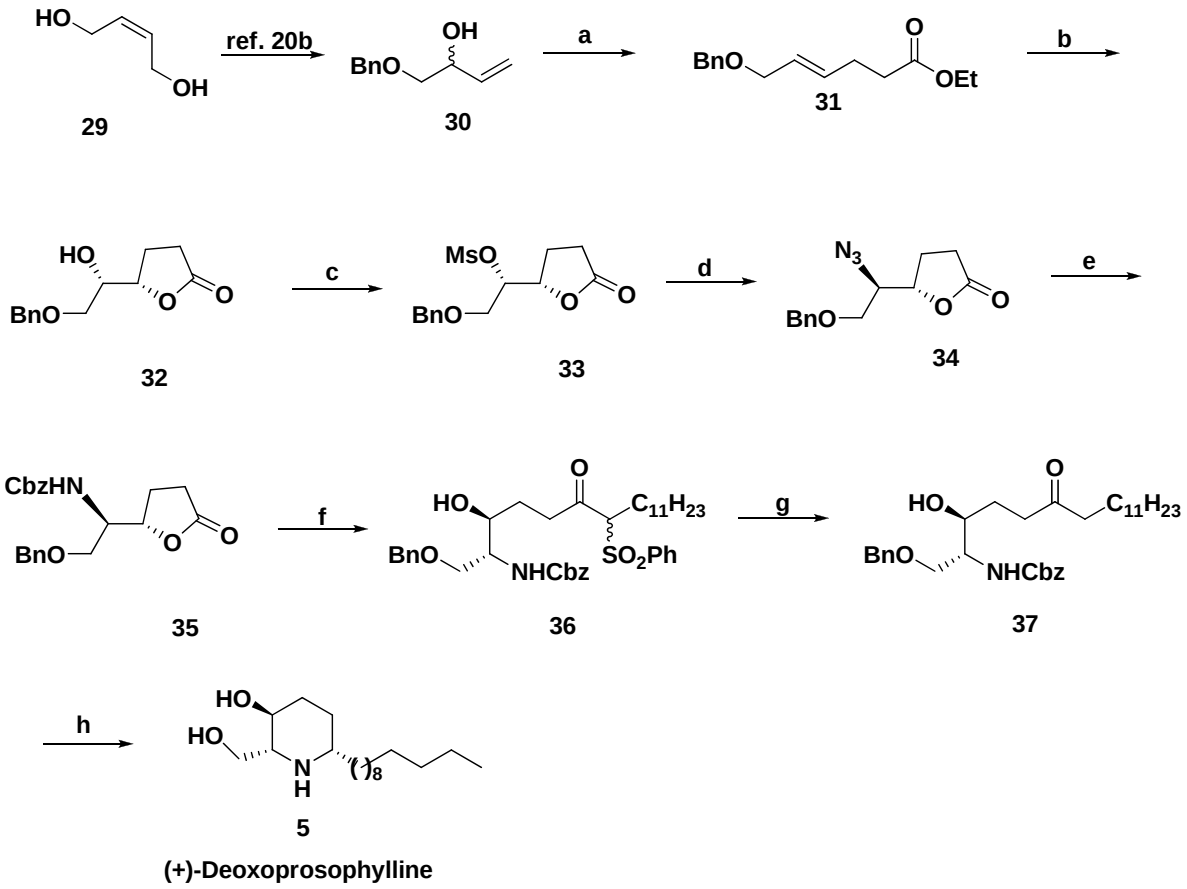


Scheme 4. *Reagents and conditions*: (a) NaH, BnBr, THF/DMF (1:1), 11 h; (b) (i) $ClS(O)_2$-N=C=O (CSI), Na_2CO_3, toluene, -78 ^oC, 24 h; (ii) 25% Na_2SO_3, 24 h; (c) **23**, **24**, toluene, 80 ^oC, 48 h; (d) PtO_2, H_2, EtOAc, 2 h; (e) (i) cat. $RuCl_3$, $NaIO_4$, H_2O/CH_3CN/EtOAc (2:1:1), 4 h; (ii) CH_2N_2, Et_2O, 0 ^oC, 1 h; (f) 10% Pd/C, H_2, MeOH, 24 h; (g) (i) LAH, THF, 12 h; (ii) 8 N KOH, MeOH, reflux, 10 h.

Chavan *et al.* (2004) [20]

Chavan *et al.*[20] reported the efficient synthesis of (+)- and (-)-deoxoprosophylline from the readily available *cis*-2-butene-1,4-diol **29** using Sharpless asymmetric dihydroxylation as the key step. Thus Sharpless asymmetric dihydroxylation[21] of α,β-

unsaturated ester **31** employing AD-mix-α and followed by in situ cyclization of the resulting diol ester furnished the hydroxy lactone **32**.



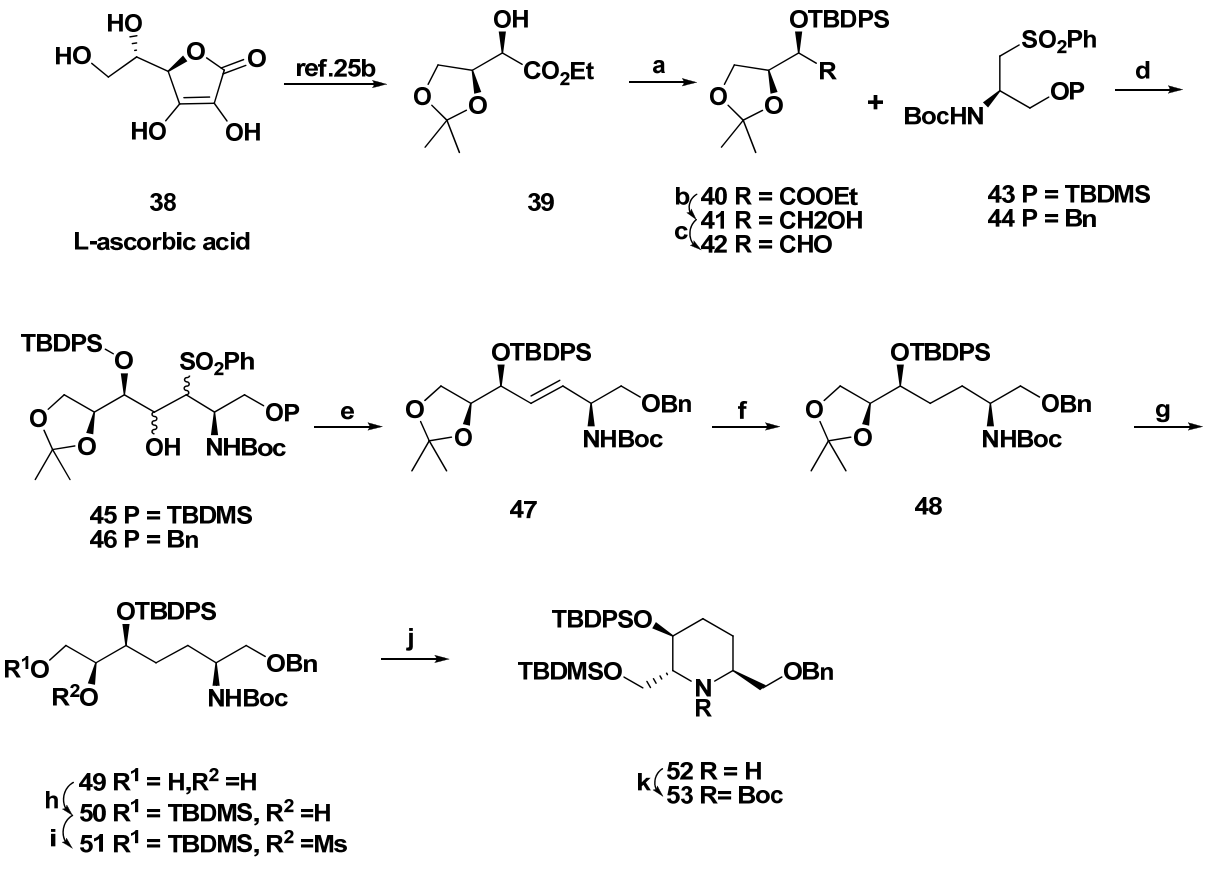
Scheme 5. *Reagents and conditions*: (a) $CH_3(OEt)_3$, cat. Propionic acid, 140 ^oC, 2 h, 94%; (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 0 ^oC, 24 h, 95%, 93% ee; (c) CH_3SO_2Cl, Et_3N, DCM, 92%; (d) NaN_3, DMF, 90 ^oC, 89%; (e) (i) TPP, H_2O, C_6H_6, 8 h; (ii) CbzCl, Et_3N, cat.DMAP, DCM, 75%; (f) $C_{12}H_{25}SO_2Ph$, *n*-BuLi, THF, -78 ^oC, 2 h, 94%; (g) 6% Na-Hg, Na_2HPO_4, CH_3OH, -10 ^oC, 95%; (h) 20% $Pd(OH)_2/C$, H_2, CH_3OH, rt, 24 h, 76%.

Mesylation of the hydroxy lactone **32** and displacement of the mesylate with NaN_3 in DMF gave the azidolactone **34**. The azide was reduced to the amine by using triphenylphosphine and water and the resulting amine was protected as its Cbz derivative by using Cbz-Cl. Opening of the lactone of **35** was achieved using $C_{12}H_{25}SO_2Ph$ and *n*-BuLi.[22,23] to get **36** which on desulfonylation with 6% Na–Hg and Na_2HPO_4 at -10 ^oC gave the ketone **37**.[24] Removal of the protecting groups and

cyclization of the ketone **37** using catalytic $Pd(OH)_2$ and H_2 afforded (+)-deoxoprosophylline **5** in 76% yield (Scheme 5). Similarly, **(**-)-deoxoprosophylline **1** was synthesized from α,β-unsaturated ester **31** in a similar fashion following a similar sequence.

Sasaki *et al.* (2004)[25]

Sasaki *et al.*[25] developed a versatile methodology for the synthesis of an enantiopure 2,6-disubstituted piperidin-3-ol framework starting from chiral building blocks, γ-sulfonyl-β-amino alcohol derivative **44**[26] and aldehyde **42**[27] using Julia olefination followed by cyclisation as the key steps (Scheme 6).

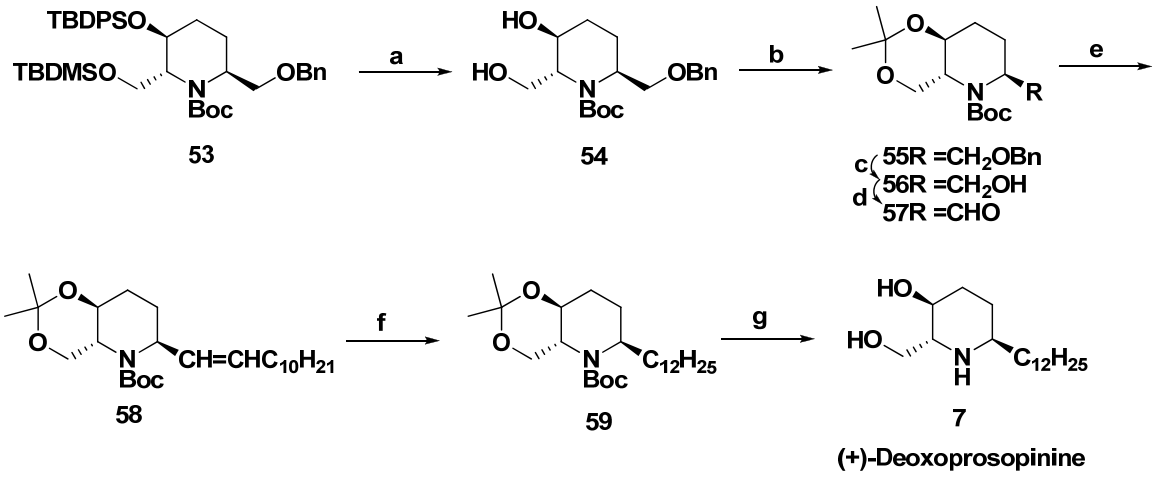


Scheme 6. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMF, 0 °C, 15 min; rt, 3 h; (b) $LiBH_4$, MeOH, Et_2O, 0 °C, 3 h, 95%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, -70 °C, 20 min; Et_3N, -70 °C, 1 h, 100%; (d) *n*-BuLi (2.2 equiv), THF, -70 °C, 30 min; **42**, -70 °C, 4 h, 83%; (e) 6% Na-Hg, Na_2HPO_4, MeOH, 0 °C, 2 h, 72%; (f) H_2, 10% Pd-C, NH_4OAc, MeOH, rt, 24 h, 100%; (g) HOAc-H_2O (4/1), rt, overnight, 93%; (h)

TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 100%; (i) MsCl, Et_3N, DMAP, CH_2Cl_2, -20 to 0 °C, 2 h, 99%; (j) (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h; 1% citric acid in MeOH, rt, overnight, 99%; (ii) $^iPr_2NEt$, MeOH, reflux, 48 h, 92%; (k) Boc_2O, Et_3N, DMF, rt, overnight, 99%.

Synthesis of (+)-Deoxoprosopinine

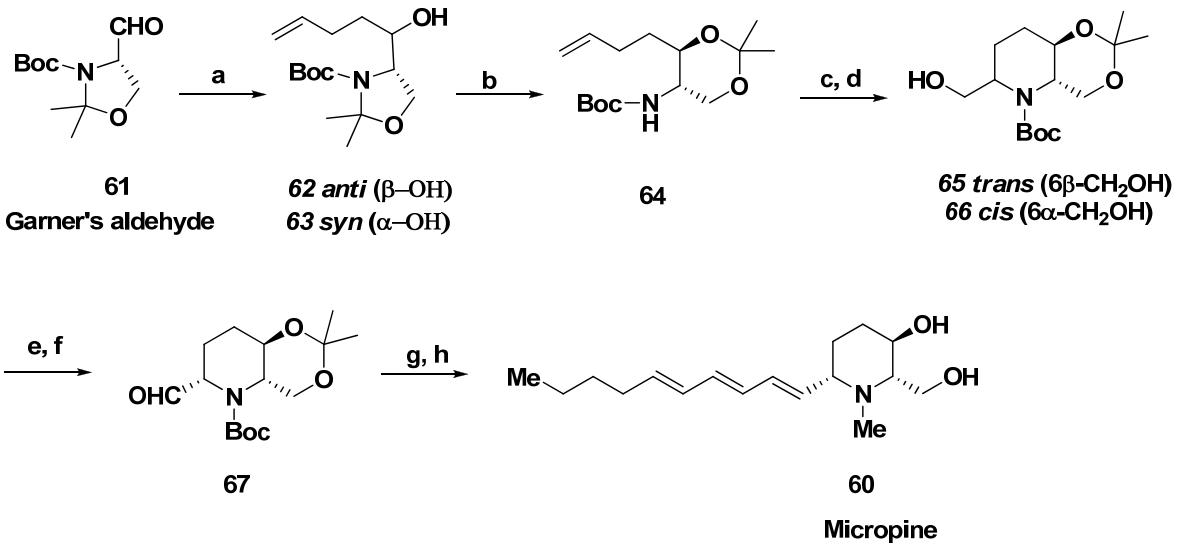
Compound **53** was converted into (+)-deoxoprosopinine **7** via routine transformations as depicted in Scheme 7.



Scheme 7. *Reagents and conditions*: (a) Bu_4NF, THF, 0 °C, 10 min; rt, 1 h, 100%; (b) 2,2-dimethoxypropane, TsOH, acetone, rt, 2 h, 93%; (c) H_2 (1 atm), 20% $Pd(OH)_2/C$, EtOAc, rt, 2 h, 96%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 15 min; Et_3N, 0 °C, 1 h, 100%; (e) $Ph_3PC_{11}H_{23}Br$, KHMDS, THF, -78 °C, 10 min; 0 °C, 1 h; compound **57**, -78 °C, 20 min; 0 °C, 5 h, 87%; (f) H_2 (1 atm), 20% $Pd(OH)_2/C$, EtOAc, rt, overnight, 99%; (g) 1 N HCl/MeOH, rt, 24 h, 79%.

Read *et al.* (1996)[28]

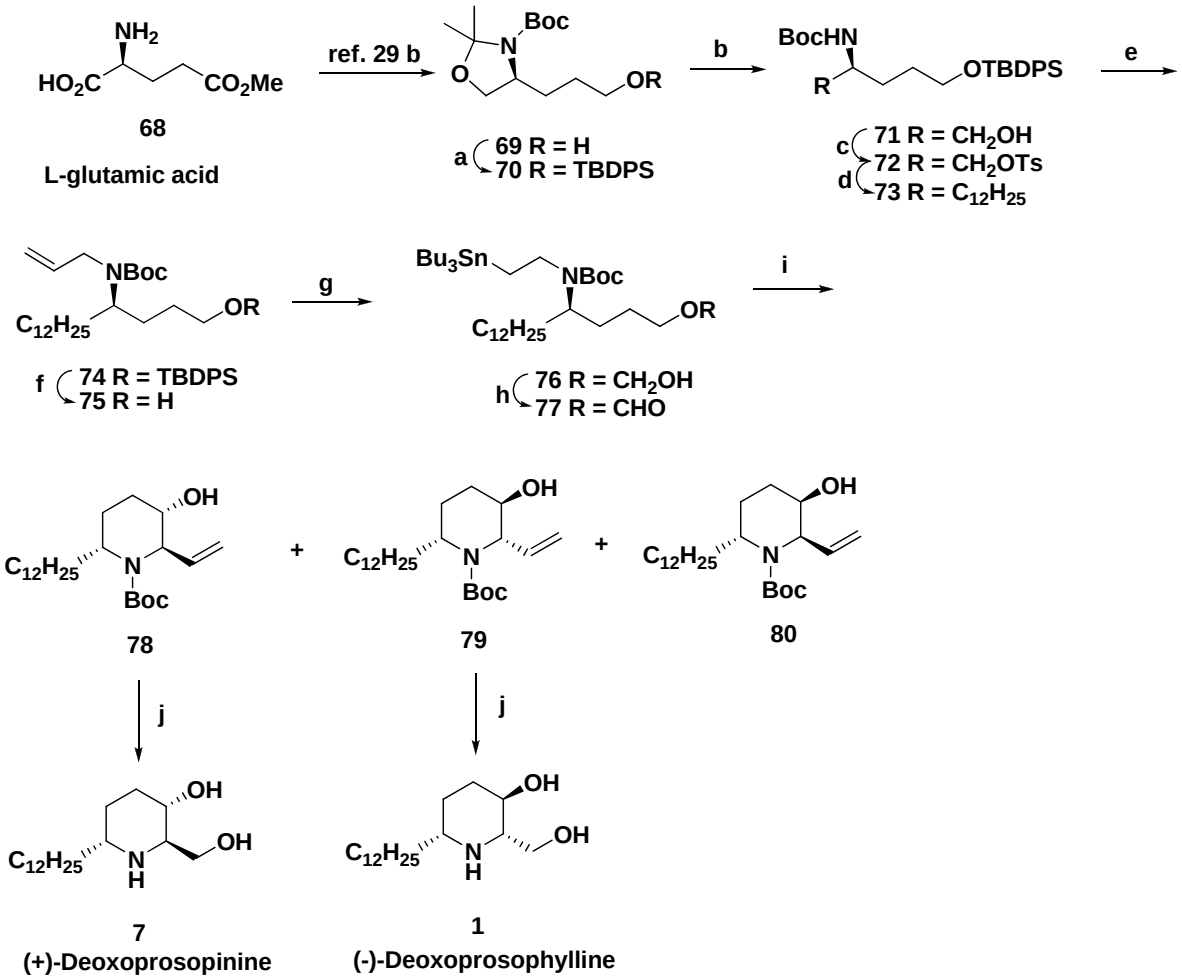
Read *et al.* [28] reported the enantioselective total synthesis of micropine **60**, an unusual 2,6-disubstituted piperidine alkaloid, using mercuric trifluoroacetate-catalysed intramolecular alkenylamide cyclisation as the key step. The synthesis proceeded from L-serine derived Garner's aldehyde and afforded material of the same positive sign of optical rotation as the natural product thereby confirming the absolute stereochemistry of micropine **60** (Scheme 8).



Scheme 8. *Reagents and conditions*: (a) CH_2=$CHCH_2CH_2MgBr$, THF; (b) (i) Amberlyst 15, MeOH; (ii) $Me_2C(OMe)_2$, PPTS, CH_2C1_2; (c) (i) $Hg(OCOCF_3)_2$, THF; (ii) $NaHCO_3$, KBr; (d) O_2, $NaBH_4$, DMF; (e) $LiA1H_4$, ether; (f) $(COCI)_2$, DMSO, Et_3N; (g) $CH_3(CH_2)_3(CH)_4CH_2P(O)(OEt)_2$, KH, THF; (h) H_2SO_4, MeOH.

Yamamoto *et al.* (1997)[29a]

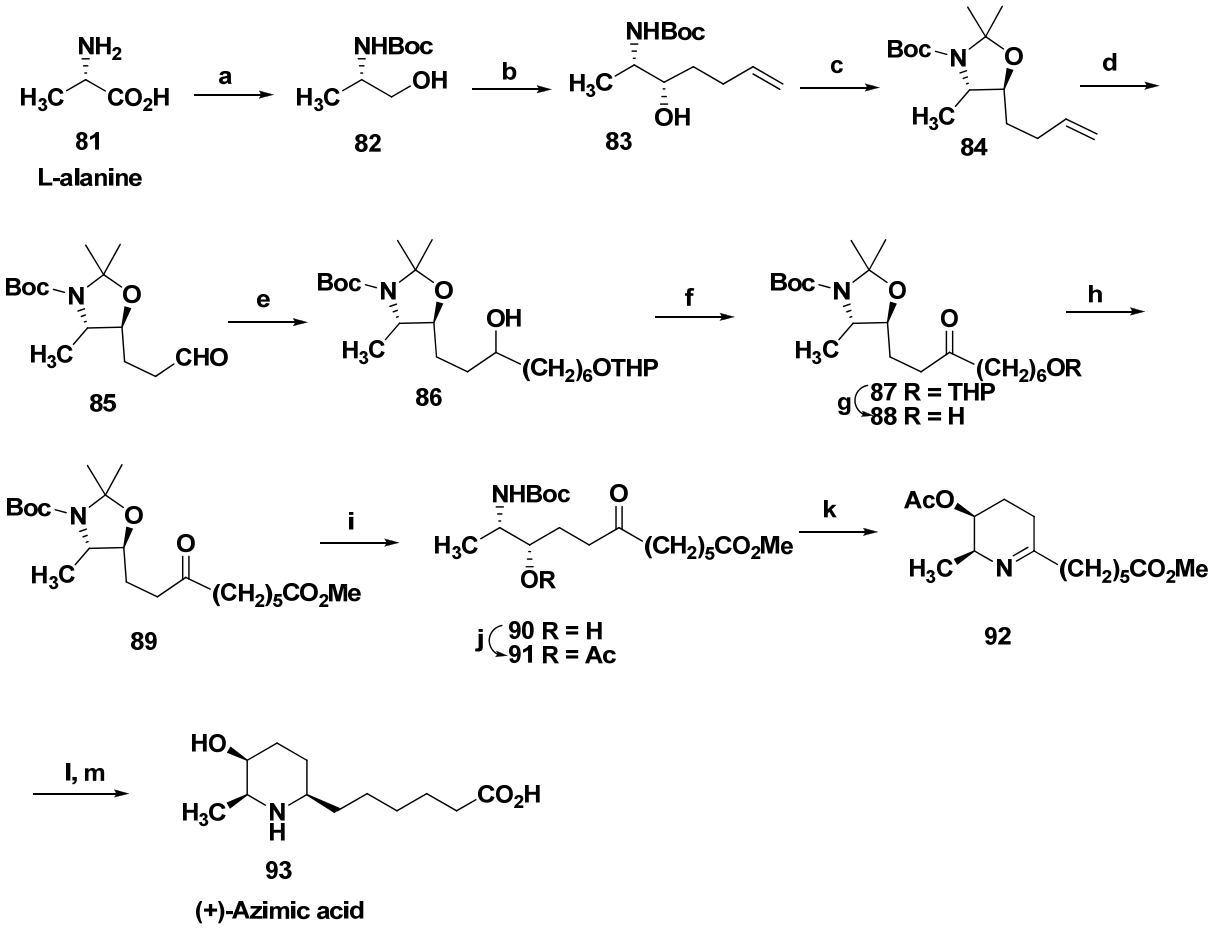
Asymmetric total syntheses of (+)-deoxoprosopinine **7** and (-)-deoxoprosophylline **1** were accomplished using L-glutamic acid as the chiral source by Yamamoto *et al.*[29a] in which the intramolecular reaction of a γ-aminoallylstannane with an aldehyde was used as a key step (Scheme 9).



Scheme 9. *Reagents and conditions:* (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 100%; (b) $PdCl_2(CH_3CN)_2$, CH_3CN, reflux, 98%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 98%; (d) $C_{11}H_{23}Li$, CuI, Et_2O, -35 ^oC, 82%; (e) allylbromide, KH, THF, 0 ^oC-rt, 92%; (f) TBAF, THF, rt, 74%; (g) *sec*-BuLi, TMEDA, THF, -78 ^oC, then *n*-Bu_3SnCl, -78 ^oC-rt, 61%; (h) SO_3·Py DMSO, Et_3N, CH_2Cl_2, 0 ^oC, 92%; (i) $BF_3.Et_2O$ or $TiCl_4$ or $ZrCl_2$ or $SnCl_4$, $MgBr_2$·OEt_2 or HCl or CF_3CO_2H, -78 ^oC or 0 ^oC 58%-98%; (j) O_3, MeOH, -78 ^oC; then $NaBH_4$, -78 ^oC-rt, 53% for **7** and 43% for **1**.

Datta *et al.* (1999)[30]

Asymmetric total syntheses of enantiopure (+)-azimic acid **93** was developed using L-alanine as the chiral source by Datta *et al.*[30] (Scheme 10).

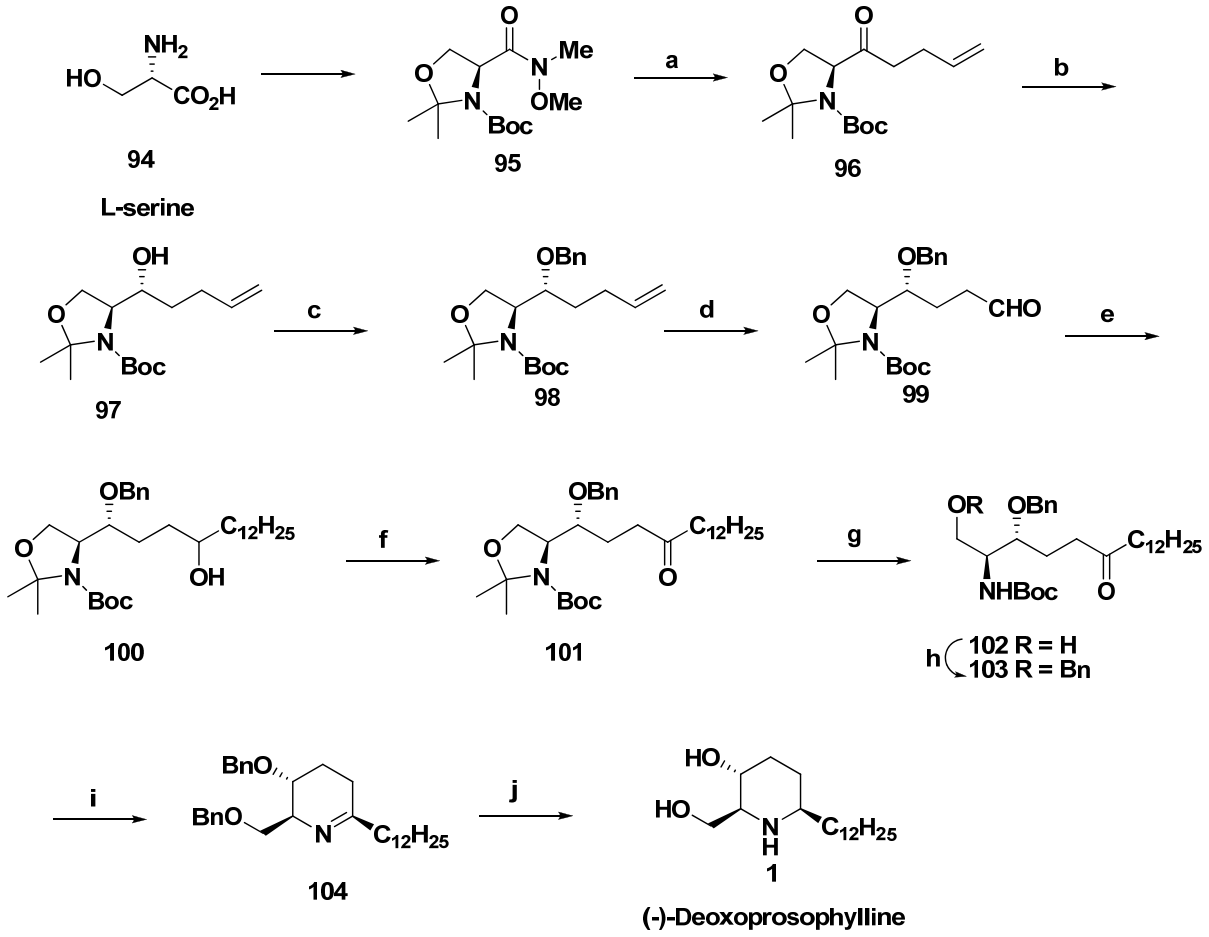


Scheme 10. *Reagents and conditions*: (a) $LiAlH_4$, THF; then Boc_2O, 70% ; (b) Swern oxidn., then $H_2C{=}CH(CH_2)_2MgBr$; (c) $Me_2C(OMe)_2$, PPTS; (d) OsO_4, NMO; then $NaIO_4$ (impregnated on silica gel), 93%; (e) $BrMg(CH_2)_6OTHP$, 79%; (f) 2-iodoxybenzoic acid, 88%; (g) *p*-TsOH, EtOH, 80%; (h) $RuCl_3{\cdot}H_2O$, $NaIO_4$; then CH_2N_2, Et_2O, 78%; (i) 80% $AcOH{\cdot}H_2O$, 84%; (j) Ac_2O, DMAP, 92%; (k) HCO_2H, CH_2Cl_2, 72%; (l) H_2, Pd/C, 77%; (m) $N_2H_4{\cdot}H_2O$, MeOH, 68%.

The, strategy envisages initial building-up of the functionalized *syn*-1,2-amino alcohol fragment **83** with required stereochemistry, *via* chelation controlled addition of a suitable Grignard reagent to *N*-Boc-alaninal. The strategically placed terminal alkene group of **83** can then be utilized towards formation of the pivotal ketoester intermediate **90**. Finally, intramolecular cyclodehydration involving the amine and the ketone functionalities followed by stereoselective hydrogenation of the resulting piperidine completed the synthesis.

Datta *et al.* (2001)[31]

Datta *et al.*[31] reported the asymmetric syntheses of prosopis alkaloid (-)-deoxoprosophylline **1** from easily available amino acid, L-serine as a chiral pool starting material (Scheme 11).



Scheme 11. *Reagents and conditions*: (a) $BrMgCH_2CH_2CH{=}CH_2$, THF, 0 ^oC, 76%; (b) $Zn(BH_4)_2$, Et_2O-C_6H_6, 76%; (c) NaH, BnBr, 70%; (d) (i) OsO_4; (ii) $NaIO_4$ (on silica gel), 92%; (e) $C_{12}H_{25}MgBr$, 80%; (f) 2-Iodoxybenzoic acid, 91%; (g) 80% AcOH in H_2O, 83%; (h) BnBr, Ag_2O, 85%; (i) HCO_2H, 78%; (j) Palladium hydroxide, H_2, EtOH·HCl, 72%.

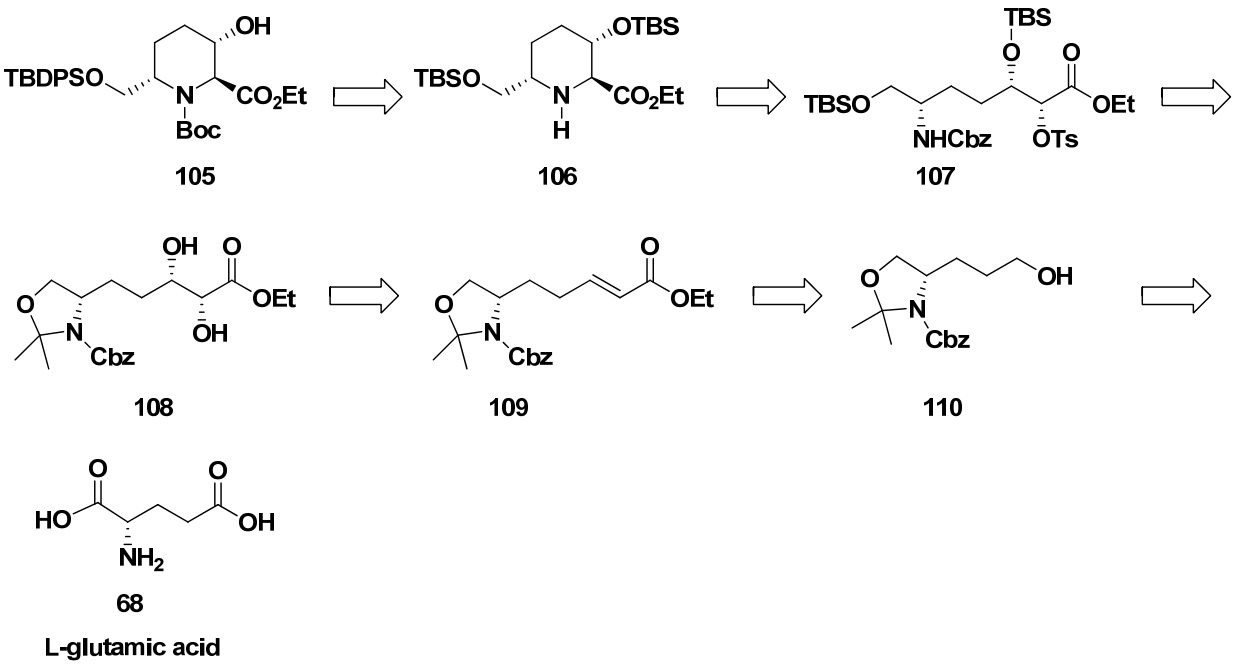
3.1.3. Present Work

Objective

As seen from the literature, there are very few synthesis of hydroxylated piperidine derivatives with the use of α-amino aldehydes as the synthetic precursor which mostly

suffers from harsh reaction conditions, poor selectivity and low yields of the desired products. Also on the other hand, they are designed to obtain exclusively one desired derivative of hydroxylated piperidine alkaloids without any generalization to obtain a number of derivatives from a single starting amino acid. On the basis of the application of hydroxylated piperidine alkaloids, and the exceptional usage of α-amino aldehydes as a building block, we thought of synthesizing such an intermediate which can be useful to prepare a variety of derivatives of biological interest.

Retrosynthetic analysis



Scheme 12. Retrosynthetic analysis for 2,6-disubstituted piperidinol derivative (**105**)

Though numerous syntheses of this class of compounds have been reported, however, it is still desirable to develop a general synthetic strategy that provides a common pivotal intermediate from which 2,3,6-trisubstituted piperidines with desired stereochemistry can be derived. With this in mind, we have developed an efficient strategy for the synthesis of an enantiopure 2,6-disubstituted piperidin-3-ol framework using L-glutamic acid as the chiral pool material. As shown in Scheme 12, the target molecule **105** could easily be obtained from piperidine derivative **106** which could be accessed from tosylate **107.** The compound **107** could be synthesized from α,β-diol ester **108**. The unsaturated compound **109** could be accessed from amino alcohol **110** that could

be obtained from commercially available L-glutamic acid **68** using known procedure.[32] The synthetic utility and versatility of this building block **105** is such that it can easily be transformed into various hydroxylated piperidine alkaloids of biological importance (Fig. 2).

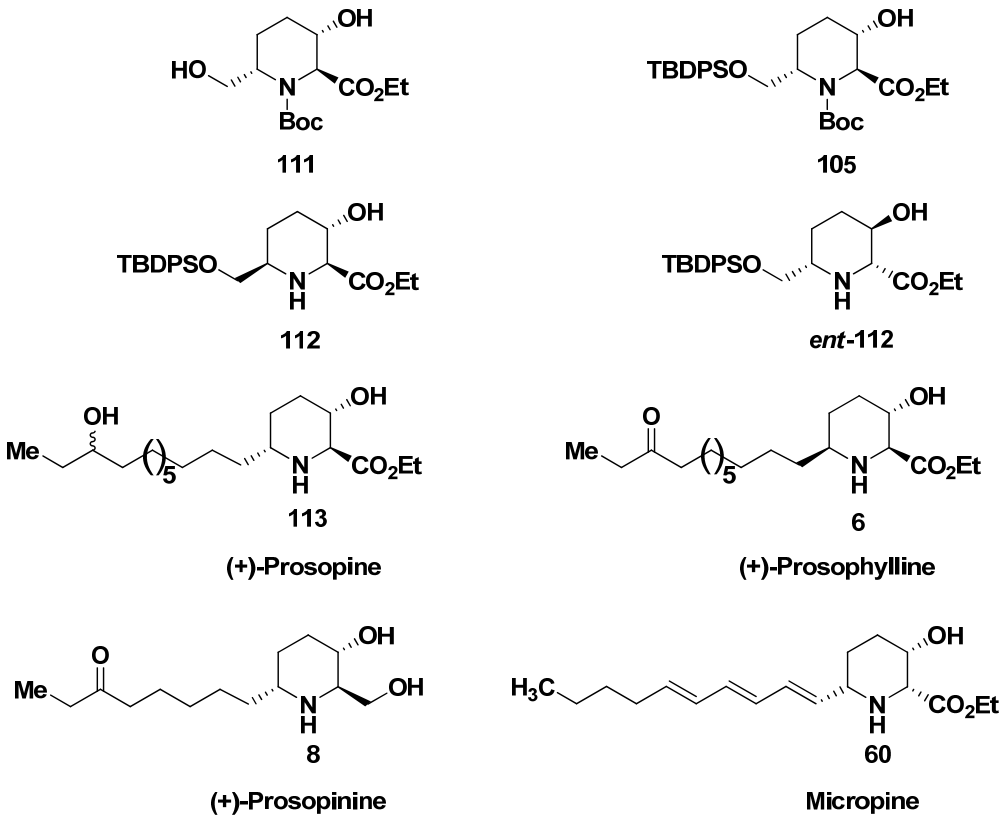


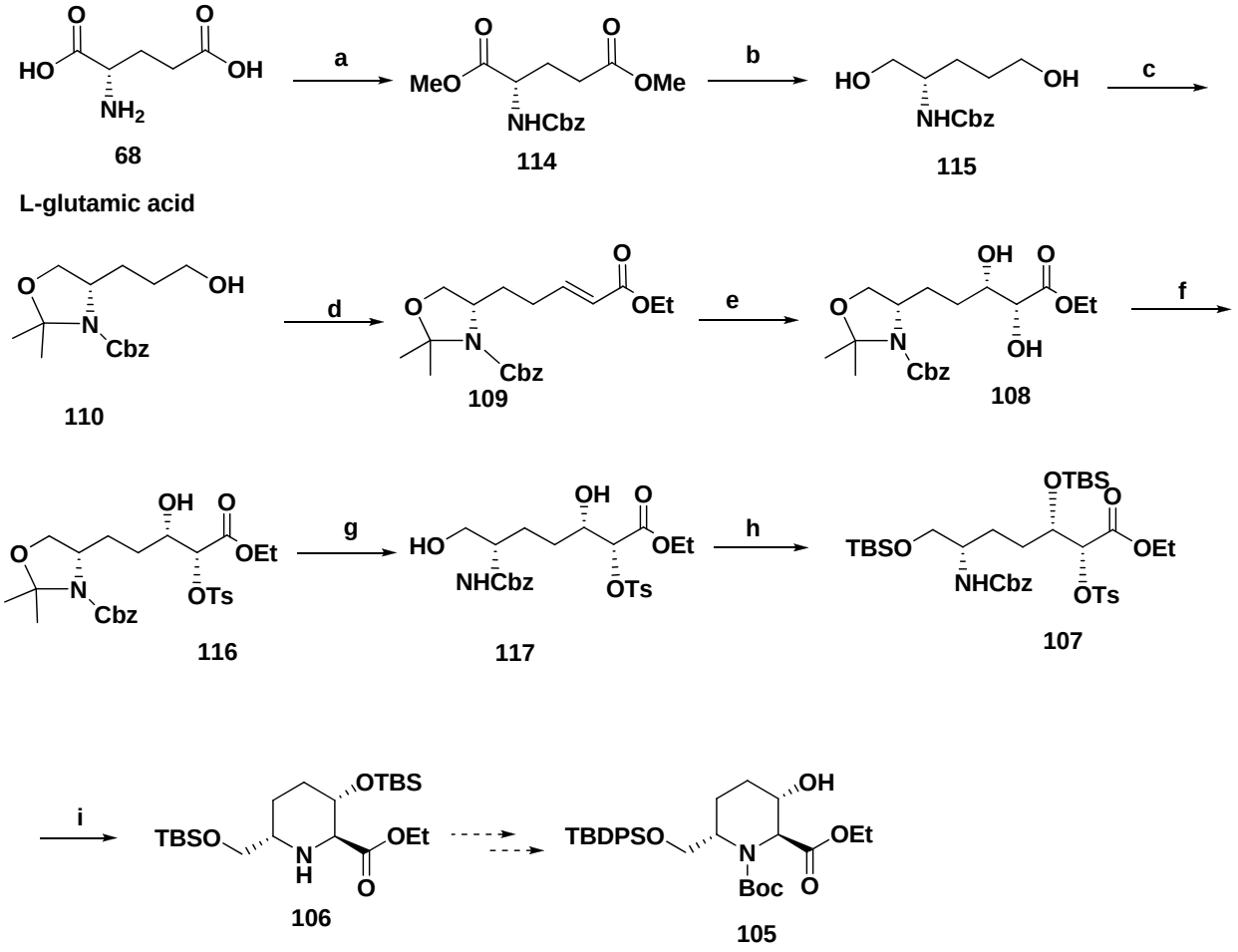
Figure 2. Structure of various hydroxylated piperidine alkaloids

3.1.4. Results and Discussion

Strategy I

As illustrated in Scheme 13, compound **110** was prepared in four steps from commercially available L-glutamic acid following a literature procedure.[32] The spectroscopic data of compound **110** was in accordance with the literature precedence. Thus, L-glutamic acid **68** was treated with CbzCl followed by esterification of resultant amino acid with MeOH in presence of BF_3.OEt to give the compound **114** in 96% yield.

The spectroscopic data of compound **114** was in accordance with the literature precedence.[33 a, d]



Scheme 13. *Reagents and conditions:* (a) (i) CbzCl, $NaHCO_3$, H_2O, dioxane, 0 ^oC - rt, o/n, 94%; (ii) $BF_3.OEt_2$, MeOH, 60 ^oC, 5 h, 96%; (b) $LiBH_4$, THF, MeOH, 0 ^oC, 4 h, 78%; (c) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt, 24 h, 86%; (d) (i) $(COCl)_2$, DMSO, dry CH_2Cl_2, -78 ^oC, 15 min, then compound **110** , -60 ^oC, 45 min., Et_3N, 2 h; (ii) $Ph_3P{=}CHCO_2Et$, dry THF, rt, 6 h, 83%; (e) $(DHQ)_2PHAL$, OsO_4, K_2CO_3, $K_3Fe(CN)_6$, ^{t}BuOH:H_2O (1:1), 0 ^oC, 24 h, 92%; (f) *p*-TsCl, Et_3N, CH_2Cl_2, 5 ^oC, 72 h, 71%; (g) *p*-TsOH, MeOH, rt, 5 h, 80%; (h) TBSOTf, 2,6-lutidine, dry CH_2Cl_2, 0 ^oC, 2 h, 87%; (i) H_2, Pd $(OH)_2$ /C, EtOAc, rt, 24 h, 40%.

The ^{1}H NMR spectrum of compound **114** showed the presence of two CH_3 group at δ 3.64 (s) and δ 3.72 (s) and -CH_2Ph proton of benzylic group at δ 5.08 (s, 2H). The IR spectum also showed the presence of >C=O group at 1736 cm^{-1}. The diester compound

114 was reduced with $LiBH_4$ to give the corresponding diol **115**[32] which was further subjected to oxazolidine formation by 2,2-dimethoxypropane to afford the oxazolidine derivative **110** in 86% yield. The spectroscopic data of compound **110** was in accordance with the literature precedence.[32] Compound **110** was oxidised under the Swern conditions[34] to give the aldehyde which on 2C-Wittig olefination with (ethoxycarbonymethylene)triphenyl phosphorane in dry THF at room temperature furnished the *trans*-olefin **109** in 83% yield. The ^{1}H NMR spectrum of **109** showed the two sets of olefinic protons at δ 5.13 (d,1H) and δ 6.83-7.01 (m, 1H). The IR spectrum showed the absence of hydroxy group at 3450 cm^{-1} and the presence of peaks at 1704 cm^{-1} confirming the presence of α, β-unsaturated ester **109**.

In the asymmetric dihydroxylation of olefin, the stereoselective outcome of the reaction gets affected by the presence of pre-existing chiral information in the substrate.[21] In order to explore the concept of double diastereoselection,[35a,b] the olefinic ester **109** was subjected to AD reaction using different ligands. Thus, the dihydroxylation of olefin **109** under the Sharpless asymmetric dihydroxylation conditions[21] using $(DHQ)_2PHAL$ ligand gave the diol **108** in 92% yield and >99% de.

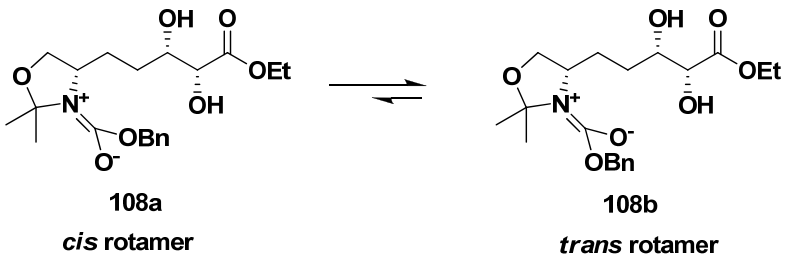


Figure 3. Structure of *cis* and *trans* rotamer

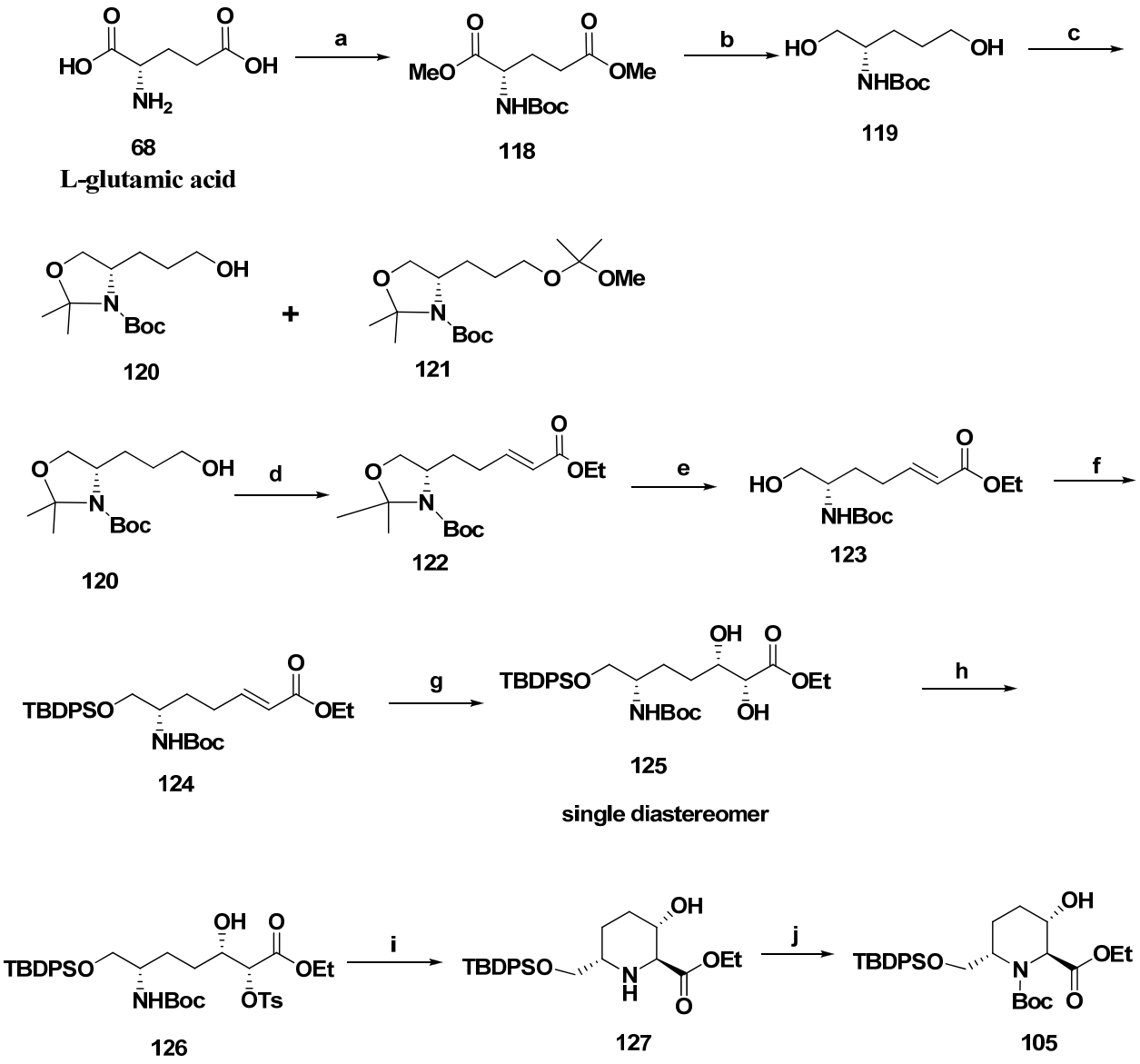
The diastereomeric excess was confirmed by ^{13}C-NMR spectroscopy. Interestingly, when sample was scanned below 24 ^oC, ^{13}C spectra showed two rotamers, i.e. *cis* and *trans* isomers, owing to restricted rotation about the *N*-CO bond of carbamate (Figure 3).

To confirm the diastereoselectivity of **108** we placed the sample for the NMR scanning at high temperature (70 ^oC), the spectroscopic measurement showed only one diastereomer and d.e. was estimated to be >99%. Comparable results of diastereoselectivity was obtained even with the use of other ligand $(DHQD)_2PHAL$

under the similar conditions employed. This finding showed that the chirality present in the substrate **109** has no influence on the diastereoselectivity of the reaction and this could probably be attributed to the presence of chiral centre at reasonable distance, being two carbons away from the olefinic bond. The ^{1}H NMR spectrum of diol **108** showed the absence of the olefinic protons at δ 5.13 (doublet) and at δ 6.83-7.01 (multiplet). The IR spectrum showed the presence of hydroxyl function at ν 3461 cm^{-1}. The subsequent regioselective α-tosylation of hydroxyl group of **108** was carried out using tosyl chloride in the presence of triethyl amine to give **116** in 71% yield.[21d] The ^{1}H NMR spectrum of the tosyl derivative **116** showed the CH_3 proton of toluyl group at δ 2.40 (s, 3H). The deprotection of isopropylidene under acidic condition using *p*-TsOH/ MeOH gave the amino alcohol **117** in 80% yield which on subsequent protection of both the hydroxy groups with TBS-OTf /2,6-lutidine afforded compound **107** in excellent yield (87%). Disappearance of peak at 3395 cm^{-1} in the IR spectrum confirmed the formation of **107**. Finally Cbz group was cleaved with H_2, $Pd(OH)_2$/C followed by intramolecular cyclisation of resulting amine with the inversion of configuration at C2 centre to furnish the piperidine derivative **106** in 40% yield. The ^{1}H NMR spectrum of compound **106** showed the absence of tosyl group at δ 2.44 (s, 3H), and Cbz group by the absence of benzylic protons at δ 5.10 (s, 2H) and phenolic protons at δ 7.36 (m, 7H) and δ 7.82 (2H) confirming the cyclisation process.

Strategy II Since during Cbz deprotection and intramolecular cyclisation under S_N2 conditions, we got only 40% yield of 2,6-disubstituted piperidin-3-ol derivative along with the recovered starting material (as shown above in Scheme 13), therefore, we thought to change the amino protecting group from Cbz to Boc and try the sequence of reaction as shown in Scheme 14.

Hence, L-glutamic acid **68** was converted into the *N*-Boc-(*S*)-glutamic acid dimethylester **118** in 90% yield by first treating it with Boc_2O and then followed by esterification of the resultant product with CH_3I.



Scheme 14. *Reagent and conditions*: (a) (i) Boc_2O, 1N NaOH, dioxane, H_2O, 0 ^oC, 3.5 h; (ii) MeI, K_2CO_3, 0 ^oC - rt, 1 h, 90%; (b) $LiBH_4$, MeOH, THF, 0 ^oC, 4 h, 80%; (c) 2,2-DMP, *p*-TsOH, CH_2Cl_2, 24 h, 67% for **120** and 26% for **121**; (d) (i) $(COCl)_2$, DMSO, dry CH_2Cl_2, -78 ^oC, 15 min. then compound **120**, 45 min. -78 ^oC, Et_3N, 1 h; (ii) $Ph_3P{=}CHCO_2Et$, dry THF, reflux, 6 h, 83%; (e) (i) *p*-TsOH, MeOH, 2 h, 70%; (f) TBDPSCl, imidazole, DMAP, dry CH_2Cl_2, 0 ^oC, 4 h, 80%; (g) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^{t}BuOH:H_2O (1:1), 0 ^oC, 24 h, 92%; (h) TsCl, Et_3N, dry CH_2Cl_2, 5 ^oC, 72 h, 72%; (i) (i) 50% TFA in dry CH_2Cl_2, 0 ^oC - rt, 2.5 h; (ii) $^i Pr_2EtN$, dry CH_2Cl_2, 0 ^oC, 3 h, , 71%; (j) Boc_2O, Et_3N, 0 ^oC, CH_2Cl_2, 2 h, 75%.

The ^{1}H NMR spectrum of compound **118** showed the *tert*-butyl protons at δ 1.40 (s, 9H) and the dimethyl ester protons at δ 3.64 (s, 3H) and δ 3.71 (s, 3H). The spectroscopic data of compound **118** was in accordance with the literature precedence.[33a,b,c,d] The diester of **118** was then reduced by $LiBH_4$ to give the corresponding alcohol **119** in 80% yield, which was further subjected to oxazolidine formation by 2,2-dimethoxypropane to afford **120** in 67% yield and **121** in 26% yield. The spectroscopic data of compound **120** was in accordance with the literature precedence.[29,32] Compound **120** was then subjected to Swern oxidation[34] followed by Wittig olefination with the two carbon Wittig ylide to afford the α,β-unsaturated olefinic ester **122** in 83% yield. The ^{1}H NMR spectrum of **122** showed the two set of olefinic protons at δ 5.84 (d, 1H) and at δ 6.88-7.03 (m, 1H). The IR spectrum showed the absence of hydroxyl absorption at ν 3437 cm^{-1} confirming the transformation of compound **120** and the presence of peak at ν 1689 cm^{-1} corresponding to the α,β-unsaturated olefinic ester. The deprotection of isopropylidene group in **122** under acidic conditions using *p*-TsOH/ MeOH gave the amino alcohol **123** which on subsequent protection of the hydroxy group with TBDPSCl afforded **124** in excellent yield. The presence of *tert*-butyl proton at δ 1.08 (s, 9H) and phenyl proton at δ 7.38-7.46 (m, 6H) and δ 7.63-7.65 (m, 4H) of TBDPS group in ^{1}H NMR confirmed the formation of compound **124**. Compound **124** was then transformed into its dihydroxy derivative **125** by Sharpless asymmetric dihydroxylation (AD) using $(DHQ)_2PHAL$ ligand in 92% yield and >99% de. Here the diastereomeric excess of the resultant diol **125** was measured by its ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of diol **125** showed the absence of the olefinic protons at δ 5.84 (d, 1H) and at δ 6.88-7.03 (m, 1H). The IR spectrum showed the presence of hydroxyl function at ν 3400 cm^{-1}. The diol **125** was then regioselectively tosylated at α-position to the ester with the help of *p*-toluenesulfonyl chloride to afford the tosyl derivative **126** in 72% yield. The ^{1}H NMR spectrum of the tosyl derivative **126** showed the presence of methyl (CH_3) portons of toluyl group at δ 2.41 (s, 3H) and *ortho*-coupled protons at δ 7.32 (d, 2H) and at δ 7.82 (d, 2H) for benzene ring of *p*-toluyl group. Cleavage of Boc group with 50% TFA in CH_2Cl_2 followed by intramolecular cyclisation of resultant amine in S_N2 fashion in presence of diisopropylethyl amine ($^iPr_2EtN$) gave the piperidinol derivative **127** in 71% yield. The ^{1}H NMR spectrum of compound **127** showed that the disappearance of methyl (CH_3) proton of toluyl group at δ 2.41 (s, 3H) and *ortho*-coupled protons at δ

7.32 (d, 2H) and δ 7.82 (d, 2H) for benzene ring of toluyl group. Finally, compound **127** was protected with Boc_2O to furnish the target molecule **105** in 75% yield. Presence of *tert*-butyl protons at δ 1.07 (s, 9H) confirmed the formation of compound **105**.

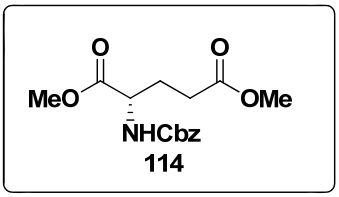
3.1.5. Conclusion

In summary, we have developed a simple and concise route to 2,6-disubstituted 3-piperidinol derivative **105** using Sharpless asymmetric dihydroxylation as the key step.

3.1.6. Experimental Section

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Mass spectra were obtained with TSQ 70, Finningen MAT spectrometer. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Elemental analysis were carried out on a Carlo Erba CHNSO analyzer.

(*S*)-Dimethyl-2-(benzyloxycarbonylamino)pentanedioate (114).



114

To a solution of L-glutamic acid **68** (10.0 g, 68.03 mmol) and $NaHCO_3$ (29.4 g, 340.2 mmol) in H_2O was added a solution of 50% CbzCl (36 mL, 105.0 mmol) at 0 ^oC and reaction was stirred at rt for overnight. After completion, the reaction mixture was washed with ether and aqueous layer was acidified with 1N $KHSO_4$ (*pH* =2) and then extracted with EtOAc (200 mL) and solvent was evaporated to dryness to give crude product as a colorless sticky compound (18 g, 94%).

To a mixture of *N*-Cbz protected-L-glutamic acid (5.0 g, 17.8 mmol) in dry MeOH (100 mL) was added $BF_3.OEt_2$ (4.6 mL, 40.0 mmol) at 0 ^oC and allowed to reflux at 60 ^oC for 5 h. After completion of the reaction solvent was evaporated and crude residue was purified by silica gel column chromatography using 15% EtOAc in pet ether as eluent to give **114** as yellow color liquid.

Yield: 5.3 g (96%).

Mol. Formula: $C_{15}H_{19}NO_6$

$[\alpha]_D^{25}$: +8.1 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]_D^{25}$: +8.0 (*c* 1.0 $CHCl_3$)].[33a]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3353, 2954, 1736, 1527. 1214, 1052.

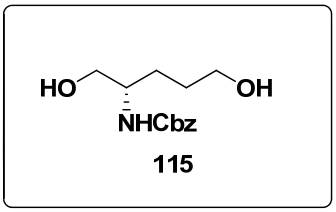
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94-2.17 (m, 1H), 2.20-2.27 (m, 1H), 2.35-2.43 (m, 2H),

3.64 (s, 3H), 3.72 (s, 3H), 4.33-4.44 (m, 1H), 5.08 (s, 2H), 5.64 (d, *J* = 11.3 Hz, 1H), 7.32 (s, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 27.2, 51.6, 52.3, 54.6, 66.7, 127.3, 128.4, 136.4, 155.8, 172.2, 172.8.

Mass (LCMS): 331.9774 (M^+ + Na), 310.0049 (M^+ +1), 266.0265.

(*S*)-Benzyl 1,5-dihydroxypentan-2-ylcarbamate (115).



115

$LiBH_4$ (130 mg, 4.9 mmol) and MeOH (0.243 mL, 4.9 mmol) were added successively at 0 °C, to a solution of **114** (0.5 g, 1.62 mmol) in THF (9 mL). The reaction mixture was stirred for 4 h at 0 °C and then quenched by addition of 1 M HCl. The reaction mixture was stirred for 20 min and then extracted with dichloromethane. The organic extracts were dried with Na_2SO_4 and filtered through celite. The solvents were removed in vacuo to afford the crude diol which was purified by flash chromatography on silica gel (dichloromethane/ MeOH, 95:5) to yield pure **115** as a white solid.

Yield: 320 mg (78%).

Mol. Formula: $C_{13}H_{19}NO_4$

$[\alpha]_D^{25}$: -18.5 (*c* 1.0, MeOH); [lit. $[\alpha]_D^{25}$: -16 (*c* 1.0 MeOH)].[32]

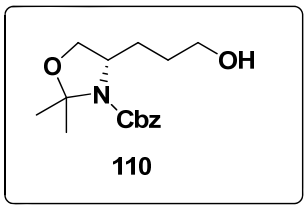
IR ($CHCl_3$, cm^{-1}): ν_{max} 3314, 2953, 1684.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54-1.70 (m, 4H), 2.28 (brs, 1H), 3.60-374 (m, 5H), 5.11 (s, 2H), 7.31-7.36 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.7, 31.0, 55.3, 63.6, 66.4, 68.4, 129.8, 130, 130.5, 139.4, 159.8.

Mass (ESI): 276 (M^+ + Na), 292 (M^+ + K).

(*S*)-Benzyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (110).



110

p-TsOH (75 mg, 0.4 mmol) and dimethoxypropane (4.86 mL, 39.5 mmol) were added at room temp. to a solution of **115** (1.0 g, 3.95 mmol) in dichloromethane (17 mL). The reaction mixture was stirred for 24 h at room temp. Et_3N (0.10 mL) was then added and the solvents were evaporated in vacuo. Ethyl acetate and 1 M HCl were added to the residue, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed successively with 1 M HCl, water, saturated aqueous $NaHCO_3$, water, and brine. The solvents were removed in vacuo to afford the crude alcohol which was purified by flash chromatography on silica gel (heptane/EtOAc, 1:1) to yield pure **110.**

Yield: 1.0 g (86%).

Mol. Formula: $C_{16}H_{23}NO_4$

$[\alpha]^{25}_D$: +26.4 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]^{25}_D$: +27 (*c* 1.0 $CHCl_3$)].[32]

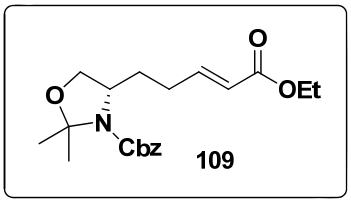
IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 2984, 2939, 1704.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45-1.63 (m, 10H), 3.54-3.79 (m, 3H), 3.93-4.06 (m, 2H), 5.15 (s, 2H), 7.36-7.40 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.4, 28.8, 29.0, 29.3, 29.9, 57.6, 62.2, 67.1, 66.4, 99.0, 127.8, 128.4, 136.1, 136.5, 152.2, 160.0.

Mass: 316.15 (M^+ + Na), 294.17 (M^+ +1).

(*S*,*E*)-Benzyl 4-(5-ethoxy-5-oxopent-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (109).



109

(a) Swern oxidation. A solution of DMSO (3.57 mL, 46.2 mmol) in dry dichloromethane (13 mL) was added at -78 °C to a solution of oxalyl chloride (1.83 mL, 20.0 mmol) in dry dichloromethane (50 mL). The reaction mixture was stirred for 15 min at -78 °C, and a solution of **110** (4.1 g, 14.0 mmol) in dichloromethane (30 mL) was added. The reaction mixture was stirred for 45 min at -60 °C. Et_3N (13.3 mL, 95.2 mmol) was then added at -78 °C, the cooling bath removed, and the reaction mixture was stirred for 1 h at room temp. The reaction was quenched by addition of water, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed successively with 1 M HCl, water, aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, filtered through celite, and the solvent was removed in vacuo to give crude aldehyde as pale yellow oil. This aldehyde was used without any purification for the next step.

(b) Wittig olefination. To a solution of (ethoxycarbonylmethylene) triphenylphosphorane (6.5 g, 18.6 mmol) in dry THF (30 mL) was added a solution of the above aldehyde (3.6 g, 12.4 mmol) in dry THF (25 mL). The reaction mixture was refluxed for 6 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **109** as a pale yellow liquid.

Yield: 4.2 g (83%); (after two step).

Mol. Formula: $C_{20}H_{27}NO_5$

$[\alpha]_D^{25}$: +25.13 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 1704, 1654.

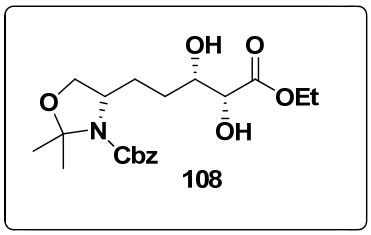
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 1.45-1.81 (m, 6H), 2.17-2.39 (m, 4H), 3.61-3.78 (m, 2H), 3.92-399 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 5.13 (d, J = 9.2 Hz, 2H), 5.76-5.87 (m, 1H), 6.83-7.01(m, 1H), 7.35-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 28.4, 31.5, 56.2, 59.9, 66.7, 93.9, 121.6, 127.7, 127.8, 128.3, 136.3, 147.3,151.9, 166.1.

Mss (LCMS): 384.1917 (M^++ Na), 379 (M^+ + H_2O), 362.2265 (M^+ + 1).

Analysis: Calcd.: C, 66.46; H, 7.53; N, 3.88%; **Found:** C, 66.35; H, 7.70%; N, 3.72%.

(*S*)-Benzyl 4-((3*S*,4*R*)-5-ethoxy-3,4-dihydroxy-5-oxopentyl)-2,2-dimethyloxazolidine-3-carboxylate (108).



108

To a mixture of $K_3Fe(CN)_6$ (12.03 g, 36.6 mmol), K_2CO_3 (5.1 g, 36.6 mmol) and $(DHQ)_2PHAL$ (95 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 120 mL) cooled at 0 ^oC was added OsO_4 (0.5 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.2 g, 12.2 mmol). After being stirred for 5 min at 0 ^oC, the olefin **109** (4.4 g, 12.2 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (18.0 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **108** as a colorless syrupy liquid.

Yield: 4.4 g (92%).

Mol. Formula: $C_{20}H_{29}NO_7$

$[\alpha]_D^{25}$: +15.56 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3461, 2984, 1738, 1695.

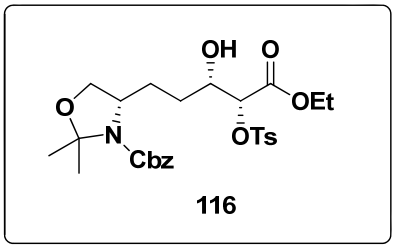
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7 Hz, 3H), 1.40 (s, 5H), 1.49 (s, 5H), 2.51 (brs, 2H), 3.64-3.66 (m, 1H), 3.71(d, J = 8.3 Hz, 1H), 3.90-3.93 (m, 3H), 4.09 (q, J =7.3 Hz, 2H), 5.08 (s, 2H), 7.35 (s, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 29.5, 60.6, 67.1, 72.3, 74.0, 93.7, 127.9, 128.3, 128.9, 137.2, 152.4, 173.2.

Mass (LCMS): 418.038 (M^+ + Na), 434.0017 (M^+ + K).

Analysis: Calcd.: C, 60.74; H, 7.39; N, 3.54%; **Found:** C, 60.64; H, 7.42%; 3.49%.

(*S*)-Benzyl-4-((3*S*,4*R*)-5-ethoxy-3-hydroxy-5-oxo-4-(tosyloxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (116).



116

To a solution of diol **108** (2.0 g, 5.1 mmol) and Et_3N (1.1 mL, 7.6 mmol) in CH_2Cl_2 (25.3 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.97 g, 5.1 mmol). The reaction mixture was stirred at 5 °C for 72 h. After the reaction was complete, water (30 mL) was added and the solution was extracted in CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (4:1) as eluent gave **116** as a colorless sticky compound.

Yield: 2.0 g (71%).

Mol. Formula: $C_{27}H_{35}NO_9S$

$[\alpha]_D^{25}$: 19.03 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3405, 2983, 1731, 1703, 1661.

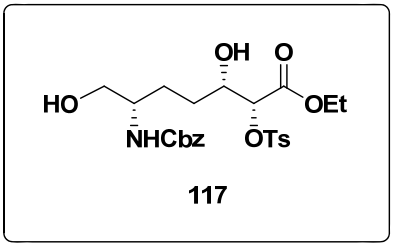
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (t, J = 7 Hz, 3H), 1.43-1.59 (m, 10H), 2.43 (s, 3H), 3.7 (d, J = 7.6 Hz, 1H), 3.90-3.3.94 (m, 3H), 4.09 (q, J =7.0 Hz, 2H), 4.81 (d, J = 15.3 Hz, 1H), 5.12 (s, 2H), 7.35 (m, 7H), 7.8 (d, J = 7.8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 21.4, 22.6, 24.0, 26.0, 28.8, 60.0, 61.5, 66.0, 66.7, 71.0, 79.6, 93.6, 127.7, 128.1, 129.3, 132.6, 136.2, 144.9, 151.8, 166.8.

Mass (LCMS): 571.918 (M^+ + Na), 549.914 (M^+ + 1), 491.9.

Analysis: Calcd.: C, 59.00; H, 6.42; N, 2.55%; **Found:** C, 59.4; H, 6.50%; N, 2.48%.

(2*R*,3*S*,6*S*)-Ethyl-6-(benzyloxycarbonylamino)-3,7-dihydroxy-2-(tosyloxy)heptanoate (117).



117

To a solution of the tosylate **116** (0.5 g, 0.91 mmol) in dry CH_2Cl_2 (3 mL) *p*-TSA (0.09 mg, 0.45 mmol) was added and reaction mixture stirred for 5 h at room temperature. Solid $NaHCO_3$ (0.2 g) was added and mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and filtrate concentrated. Silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent gave **117** as a colorless liquid.

Yield: 0.37 g (80%).

Mol. Formula: $C_{24}H_{31}NO_9S$

$[\alpha]_D^{25}$: -4.5 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3395, 3019, 1707, 1598.

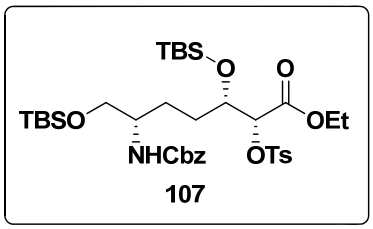
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7 Hz, 3H), 1.46-1.64 (m, 4H), 2.04 (s, 1H), 2.40 (s, 3H), 3.53-3.59 (m, 4H), 3.74 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 4.77 (t, *J* = 3.2 Hz, 1H), 5.07 (s, 2H), 5.5 (d, *J* = 7.6 Hz, 1H), 7.33 (br s, 7H), 7.78 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 21.4, 26.6, 28.6, 52.5, 60.3, 61.8, 64.2, 66.5, 70.6, 71.0, 80.2, 127.7, 128.0, 128.3, 129.6, 132.5, 136.3, 145.2, 156.7, 167.2.

Mass (LCMS): 532.02 (M^+ + Na), 518.03, 510.034.

Analysis: Calcd.: C, 56.57; H, 6.13; N, 2.75%; **Found:** C, 56.55; H, 6.19; N, 2.81%.

(2*R*,3*S*,6*S*)-Ethyl-6-(benzyloxycarbonylamino)-7-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilylperoxy)-2-(tosyloxy)heptanoate (107).



107

To a solution of the amino alcohol **117** (425 mg, 0.84 mmol) and 2,6-lutidine (0.3 mL, 2.50 mmol), in dry CH_2Cl_2 (5 mL), TBS-OTf (0.5 mL, 2.09 mmol) was added at 0 ^oC and After 2 h reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 20 mL). The solvent was evaporated. Crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to give **107** as a yellow color liquid.

Yield: 0.54 g (87%).

Mol. Formula: $C_{36}H_{59}NO_9SSi_2$

$[\alpha]_D^{25}$: -9.02 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 1715, 1599, 1506.

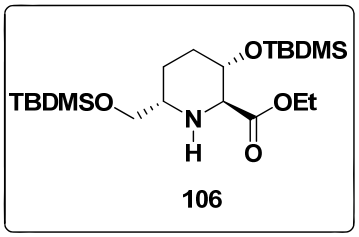
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.02-0.04 (s, 12H), 0.83 (s, 9H), 0.88 (s, 9H), 1.12-1.16 (m, 1H), 1.49-1.67 (m, 6H), 2.44 (s, 3H), 3.58 (s, 5H), 3.97-4.06 (m, 1H), 4.71-4.87 (m, 2H), 5.10 (s, 2H), 7.36 (m, 7H), 7.82 (d, J = 8.2 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.6, -4.6, 18.2, 21.6, 25.8, 29.3, 52.3, 66.6, 71.8, 79.5, 128.0, 128.5, 129.7, 133.1, 145.0, 156.0, 167.6.

Mass (LCMS): 760.05 (M + Na), 746.04, 724.06.

Analysis: Calcd.: C, 58.58; H, 8.06; N, 1.90%; **Found:** C, 58.61; H, 8.10; N, 1.82%.

(2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldimethylsilyloxy)methylpiperidine-2-carboxylic acid ethyl ester (106).



106

To a solution of the amino alcohol **107** (100 mg, 0.12 mmol) in EtOAc (4 mL), $Pd(OH)_2/C$ (20 mg) was added and after 24 h, the reaction mixture was filtered through a short pad of celite and solvent was evaporated and crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **106** as a light yellow color liquid.

Yield: 23 mg (40%).

Mol. Formula: $C_{21}H_{45}NO_4Si_2$

$[\alpha]_D^{25}$: 15.6 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 1735.

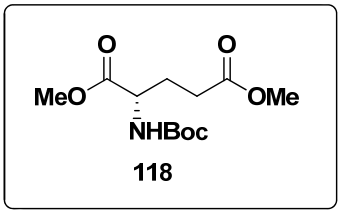
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.05 (s, 12H), 0.90 (s, 18H), 1.23-1.32 (m, 4H), 1.63-170 (m, 2H), 2.05 (brs, 2H), 2.86-2.93 (m, 1H), 3.51-3.61 (m, 3H), 4.11-4.22 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.5, -5.0, -4.7, 14.2, 18.2, 22.1, 25.8, 28.9, 52.6, 60.7, 62.2, 65.7, 66.8, 172.3.

Mss (LCMS): 432.1262 (M + 1), 454.0719 (M + Na).

Analysis: Calcd.: C, 58.42; H, 10.51; N, 3.24%; **Found:** C, 58.40; H, 10.63, N, 3.19%.

(*S*)-2-(*tert*-Butoxycarbonylamino)pentanedioic acid dimethyl ester (118).



118

A solution of di-*tert*-butyldicarbonate (17.81 g, 81.63 mmol) in dioxane (90 mL) is added to an ice cold solution of L-glutamic acid **68** (10.0 g, 68.0 mmol) in 1N NaOH

(5.4 g in 135 mL H_2O) by means of an addition funnel. The two phase mixture is stirred at 5 ^oC for 30 min, then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35 ^oC, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 ml). The combined extracts were dried over Na_2SO_4, filtered and concentrated to give *N*-Boc-L-glutamic acid as colorless, sticky foam which is used without further purification.

To an ice cold solution of *N*-Boc- L-glutamic acid (16.0 g, 64.8 mmol) in DMF (160 mL) is added solid K_2CO_3 (19.7 g, 145.5 mmol). After stirring for 10 min in an ice bath, methyl iodide (36.8 g, 259.2 mmol) is added to the white suspension and stirring continued at 0 ^oC for 30 min. where upon the mixture solidifies. The reaction was warmed to room temperature and stirred for additional 1 h or at point when TLC analysis indicates complete formation of the methyl ester. The reaction mixture was filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase was washed with brine, dried, filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (9:1) as eluent gave *N*-Boc-L-glutamic acid methyl ester **118** as a yellow colour thick liquid.

Yield: 17 g (90%); (after two step).

Mol. Formula: $C_{12}H_{21}NO_6$

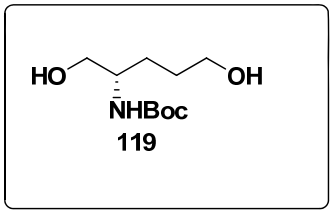
$[\alpha]_D^{25}$: +15.6 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]_D^{25}$: +12.5 (*c* 2.0 $CHCl_3$)].[33e]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 1735.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.86-2.00 (m, 1H), 2.06-2.33 (m, 1H), 2.34-2.42 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H), 4.28 (m, 1H), 5.16 (brs 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.3, 28.0, 29.8, 51.4, 52.1, 52.6, 79.5, 155.2, 172.4, 172.9.

***(S)*-*tert*-Butyl-1,5-dihydroxypentan-2-ylcarbamate (119).**



119

$LiBH_4$ (240 mg, 10.90 mmol) and MeOH (0.4 mL, 10.92 mmol) were added successively, at 0 °C, to a solution of **118** (1.0 g, 3.64 mmol) in dry THF (20 mL). The reaction mixture was stirred for 4 h at 0 °C and was then quenched by addition of 1 M HCl. The reaction mixture was stirred for 20 min and then extracted with dichloromethane. The organic extracts were dried with Na_2SO_4 and filtered through celite. The solvents were removed in vacuo to afford the crude diol which was purified by flash chromatography on silica gel (dichloromethane/ MeOH, 95:5) to yield pure **119** as a colorless sticky compound.

Yield: 0.64 g (80%).

Mol. Formula: $C_{10}H_{21}NO_4$

$[\alpha]_D^{25}$: -15.6 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]_D^{25}$: -14.9 (c 0.9, MeOH)].[33f]

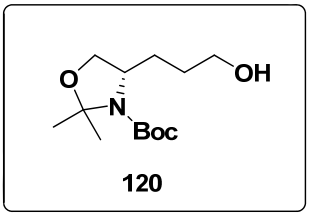
IR ($CHCl_3$, cm^{-1}): ν_{max} 3437, 3018, 2980, 2937,1693.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41(s, 9H), 1.51-1.73 (m, 4H), 3.58 (d, J = 10 Hz, 5H), 3.80 (brs, 2H), 5.19 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ27.7, 28.4, 28.5, 52.0, 61.7, 64.4, 79.3, 156.4.

Mass (ESI): 242.11 (M^+ + Na), 228.05, 200.09.

(*S*)-*tert*-Butyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (120).



120

p-TsOH (55 mg, 0.3 mmol) and dimethoxypropane (4.86 mL, 29.22 mmol) were added at room temp. to a solution of **119** (0.64 g, 2.92 mmol) in dichloromethane (15 mL). The reaction mixture was stirred for 24 h at room temp. Et_3N (0.10 mL) was then added and the solvents were evaporated in vacuo. Ethyl acetate and 1 M HCl were added to the residue, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed successively with 1 M HCl, water, saturated aqueous $NaHCO_3$ and brine. The solvents were removed in vacuo to afford the crude alcohol which was purified by flash chromatography on silica gel (heptanes/EtOAc,1:1) to yield pure **120** and **121** as yellow colorless oil.

Yield: 0.4 g (67%).

Mol. Formula: $C_{13}H_{25}NO_4$

$[\alpha]_D^{25}$: +29.6 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]_D^{25}$: +31 (*c* 1.0, $CHCl_3$)].[32]

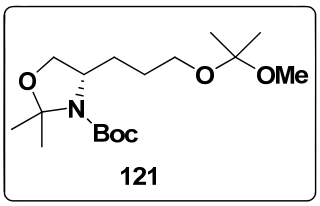
IR ($CHCl_3$, cm^{-1}): ν_{max} 3437, 3019, 1685.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.69 (m, 19H), 2.41 (br s, 1H), 3.58-3.75 (m, 4H), 3.90-3.96 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.2, 27.3, 27.7, 28.2, 29.2, 30.7, 57.0, 61.8, 66.6, 80.0, 93.0. 152.2.

Mss (ESI): 282.12 (M^+ + Na), 258.09, 250.10.

(*S*)-*tert*-Butyl-4-(3-(2-methoxypropan-2-yloxy)propyl-2,2-dimethyloxazolidine-3-carboxylate (121).



121

Yield: 0.25 g (26%).

Mol. Formula: $C_{17}H_{33}NO_5$

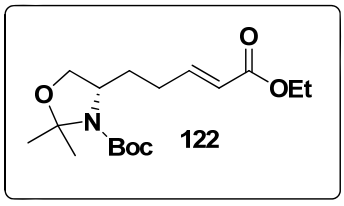
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 5H), 1.47-1.58 (m, 19H), 1.72-1.85 (m, 1H), 3.19 (s, 3H), 3.36-3.42 (m, 1H), 3.66-3.77 (m, 2H), 3.90-3.97 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.1, 24.3, 27.4, 28.3, 30.8, 57.1, 62.1, 66.8, 79.4, 80.1, 93.1, 99.5, 152.3.

Mass (ESI): 354.14 (M^+ + Na), 350.14, 294.06.

Analysis: Calcd.: C, 61.60; H, 10.04; N, 4.23%; **Found:** C, 61.64; H,10.11; N, 4.17%.

(*S,E*)-*tert*-Butyl-4-(5-ethoxy-5-oxopent-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (122).



122

(a) Swern oxidation. A solution of DMSO (0.2 mL, 2.54 mmol) in dry dichloromethane (5 mL) was added at –78 °C to a solution of oxalyl chloride (0.1 mL, 1.2 mmol) in dry dichloromethane (50 mL). The reaction mixture was stirred for 15 min at –78 °C, and a solution of **120** (0.2 g, 0.77 mmol) in dichloromethane (5 mL) was added. The reaction mixture was stirred for 45 min at –78 °C. Et_3N (0.73 mL, 5.24 mmol) was then added at –78 °C, the cooling bath removed, and the reaction mixture was stirred for 1 h at room temp. The reaction was quenched by addition of water, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed successively with 1 M HCl, water, aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, filtered through Celite, and the solvent was removed in vacuo to give crude aldehyde (0.18 g) as pale yellow oil. This aldehyde was used without any purification for the next step.

(b) Wittig olefination. To a solution of (ethoxycarbonylmethylene) triphenylphosphorane (0.4 g, 1.05 mmol) in dry THF (30 mL) was added a solution of the above aldehyde (0.18 g, 0.7 mmol in dry THF (5 mL). The reaction mixture was refluxed for 6 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **122** as a pale yellow liquid.

Yield: 0.21 mg (83%), (after two step).

Mol. Formula: $C_{17}H_{29}NO_5$

$[\alpha]_D^{25}$: +20 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 1742, 1689.

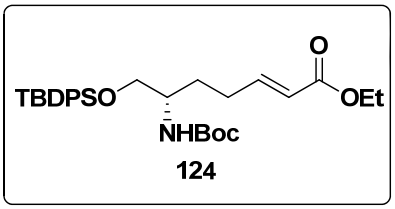
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7 Hz, 3H), 1.47-159 (m, 14H), 1.69-1.79 (m, 2H), 1.89-2.05 (m, 1H), 2.17-2.27 (m, 2H), 3.73 (d, *J* = 7.5 Hz, 1H), 3.80-3.84 (m, 1H), 3.90-3.97 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.84 (d, *J* =15.7 Hz, 1H), 6.88-7.03 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 24.1, 26.5, 27.3, 28.1, 31.6, 56.2, 59.8, 66.4, 79.8, 93.5, 121.7, 147.5, 151.4, 166.0.

Mass (ESI): 350.13 (M^+ + Na), 294.06, 250.11.

Analysis: Calcd.: C, 62.42; H, 8.93; N, 4.28%; **Found:** C, 62.40; H, 8.90; N, 4.21%.

(*S*,*E*)-Ethyl-6-(*tert*-butoxycarbonylamino)-7-(*tert*-butyldiphenylsilyloxy)hept-2-enoate (124).



124

To a solution of the unsaturated ester **122** (0.5 g, 1.53 mmol), *p*-TSA (0.03 mg, 0.153 mmol) in dry MeOH (3 mL) was added and reaction mixture was stirred at room temperature for 2 h. Solid $NaHCO_3$ (0.2 g) was added and mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and filtrate concentrated. Silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent gave **123** as a colorless liquid.

To a solution of the amino alcohol **123** (350 mg, 1.22 mmol) and imidazole (0.125 mg, 1.83 mmol), in dry CH_2Cl_2 (10 mL), TBDPSCl (0.4 mL, 1.34 mmol) was added at 0 ^oC. After 4 h. the reaction mixture was quenched with water and extracted with CH_2Cl_2 (10 x 3 mL). The solvent was evaporated in vacuo and crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to give **124** as a yellow color liquid.

Yield: 500 mg (80%).

Mol. Formula: $C_{30}H_{43}NO_5Si$

$[\alpha]_D^{25}$: -3.6 (*c* 1.0, $CHCl_3$).

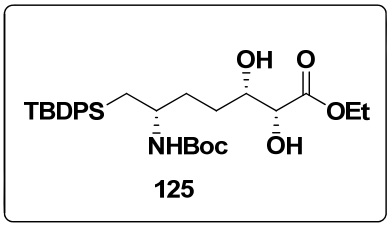
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 3018, 1745, 1590.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.30 (t, *J* = 7 Hz, 3H), 1.45 (s, 9H), 1.67-175 (m, 2H), 2.17-2.24 (m, 2H), 3.60-3.71 (m, 3H), 4.19 (q, *J* = 7 Hz, 2H), 4.69 (brs, 1H), 5.8 (d, *J* = 15.7 Hz, 1H), 6.93-6.97 (m, 1H), 7.38-7.46 (m, 6H), 7.63-7.65 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.1, 26.7, 28.2, 28.6, 30.2, 51.4, 59.9, 65.4, 78.9, 121.4, 127.6, 129.6, 132.9, 135.3. 148.1, 155.3, 166.3.

Analysis: Calcd.: C, 68.53; H, 8.24; N, 2.66%; **Found:** C, 68.51; H, 8.31; N, 2.59%.

(2*R*,3*S*,6*S*)-Ethyl-6-(*tert*-butoxycarbonylamino)-7-(*tert*-butyldiphenylsilyl)-2,3-dihydroxyheptanoate (125).



125

To a mixture of $K_3Fe(CN)_6$ (10.34 g, 31.43 mmol), K_2CO_3 (4.34 g, 31.43 mmol) and $(DHQ)_2PHAL$ (82 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 106 mL) cooled at 0 ^oC was added OsO_4 (0.4 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.0 g, 10.5 mmol). After being stirred for 5 min at 0 ^oC, the olefin **124** (5.5 g, 10.5 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (15.8 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **125** as a colorless syrupy liquid.

Yield: 5.3 g (92%).

Mol. Formula: $C_{30}H_{45}NO_7Si$

$[\alpha]_D^{25}$: -19.5 (*c* 1.0, $CHCl_3$).

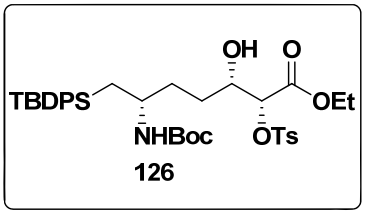
IR ($CHCl_3$, cm^{-1}): ν_{max} . 3400, 3012, 1740

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 1.57-1.75 (m, 4H), 3.05 (brs, 2H), 3.59-3.73 (m, 3H), 3.88-3.91 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 1H), 7.34-7.44 (m, 6H), 7.63-7.69 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 20.3, 27.6, 28.8, 29.1, 30.8, 53.5, 62.3, 67.5, 73.5, 75.2, 80.0, 129.0, 131.0, 134.7, 136.8, 158.2, 174.7.

Analysis: Calcd.: C, 64.37; H, 8.10; N, 2.58%; **Found:** C, 64.40; H, 8.22; N, 2.63%.

(2*R*,3*S*,6*S*)-Ethyl-6-(*tert*-butoxycarbonylamino)-7-(*tert*-butyldiphenylsilyl)-3-hydroxy-2-(tosyloxy)heptanoate (126).



126

To a solution of diol **125** (1.0 g, 1.79 mmol) and Et_3N (0.4 mL, 2.68 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.34 g, 1.79 mmol). The reaction mixture was stirred at 5 °C for 72 h. After the reaction was complete, water (30 mL) was added and the solution was extracted in CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (4:1) as eluent gave **126** as a colorless sticky compound.

Yield: 0.94 g (72%).

Mol. Formula: $C_{37}H_{51}NO_9SSi$

$[\alpha]_D^{25}$: - 8.5 (*c* 1.86, $CHCl_3$).

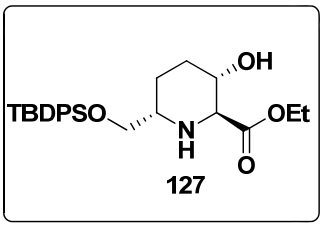
IR ($CHCl_3$, cm^{-1}): ν_{max} 3416, 3020, 1735.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.21 (t, *J* =7.1 Hz, 3H), 1.45 (s, 9H), 1.54-1.72 (m, 4H), 2.41 (s, 3H), 3.50-3.70 (m, 3H), 3.97-4.03 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.75 (d, *J* =3.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.40-7.46 (m, 6H), 7.62-7.66 (m, 4H), 7.81 (d, *J* =8.3 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 19.2, 21.5, 24.6, 26.8, 27.5, 28.3, 29.1, 36.5, 51.3, 61.9, 65.5, 71.2, 79.2, 80.0, 127.7, 128.1, 129.7, 132.9, 133.1, 135.5, 145.1, 155.7, 167.2.

Analysis: Calcd.: C, 62.24; H, 7.20; N, 2.01%; **Found:** C, 62.30; H, 7.23; N, 2.11%.

(2*S*,3*S*,6*S*)-Ethyl-6-(*tert*-butyldiphenylsilyloxy)methyl)-3-hydroxypiperidine-2-carboxylate (127).



127

To an ice cold solution of **126** (0.5 g, 0.70 mmol) in dry CH_2Cl_2 (5 ml) was added TFA (0.1 mL, 1.40 mmol). The reaction was stirred for 2.5 h at room temperature after which the solvent was evaporated in vacuo. The resultant residue was dissolved in dry CH_2Cl_2 (5 mL) and the reaction mixture cooled at 0 ^oC, diisopropylethyl amine (0.14 ml, 0.77 mmol) was added and the reaction stirred for 3 h at 0 ^oC. After the reaction was complete, ice piece was added and the solution was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to yield the cyclized compound which was purified by silica gel column chromatography using EtOAc/ pet ether (1:9) as a eluent to give piperidinol derivative **127** as a yellow color oil.

Yield: 220 mg (71%).

Mol. Formula: $C_{25}H_{35}NO_4Si$

$[\alpha]_D^{25}$: -0.87 (*c* 0.8, MeOH).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3420, 3010, 1737.

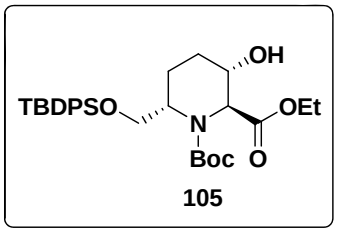
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.32 (t, *J* =7.3 Hz, 3H), 1.35-1.38 (m, 2H), 1.64-1.72 (m, 2H), 3.01-3.06 (m, 1H), 3.56 (d, *J* = 6.5 Hz, 2H), 3.6 (d, *J* = 4 Hz, 1H), 4.20-4.21 (m, 1H), 4.25 (q, *J* = 5.5 Hz, 2H), 7.38-7.47 (m, 6H), 7.68-7.70 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.2, 21.8, 26.8, 27.5, 53.0, 60.8, 60.9, 65.7, 66.7, 127.7, 129.7, 133.3, 135.5, 172.1.

Mass (LCMS): 442.4062 (M^++ 1).

Analysis: Calcd.: C, 67.99; H, 7.99; N, 3.17%; **Found:** C, 67.94; H, 7.97; N, 3.13%.

(2*S*,3*S*,6*S*)-1-*t*ert-Butyl-2-ethyl-6-(*tert*-butyldiphenylsilyloxy)methyl)-3-hydroxypiperidine-1,2-dicarboxylate (105).



105

To a cold solution of piperidinol derivative **126** (0.05 g, 0.12 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.02 ml, 0.12 mmol) and Boc_2O (0.03 g, 0.13 mmol) respectively. The reaction was stirred at 0 ^oC for 2 h. Water (2 mL) was added, after the completion of reaction, the solution extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (9:6) as eluent gave product **105** as a yellow colour oil.

Yield: 46 mg (75%).

Mol. Formula: $C_{30}H_{43}NO_6Si$

$[\alpha]_D^{25}$: +7.15 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3018, 1735.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.31 (t, *J* = 7.3 Hz, 3H), 1.50 (s, 9H), 1.58-1.81 (m, 2H), 1.92-2.06 (m, 1H), 2.18-2.50 (m, 1H), 2.91-3.02 (m, 1H), 3.58 (d, *J* = 6.1 Hz, 2H), 3.92 (br s, 1H), 4.23 (q, *J* = 7 Hz, 2H), 5.17 (m, 1H), 7.34-744 (m, 6H), 7.66-7.71 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 19.2, 22.3, 25.5, 26.7, 27.7, 53.1, 58.8, 61.1, 67.3, 70.6, 82.1, 127.6, 129.6, 133.3, 135.5, 153.1, 171.3.

Analysis: Calcd.: C, 66.51; H, 8.00, N, 2.59%; **Found:** C, 66.56; H, 8.09; N, 2.51%

3.1.7. Spectra

1] ^{1}H NMR Spectrum of **109**

2] ^{13}C NMR Spectrum of **109**

3] ^{1}H NMR Spectrum of **108**

4] ^{13}C NMR Spectrum of **108**

5] ^{1}H NMR Spectrum of **116**

6] ^{13}C NMR Spectrum of **116**

7] ^{1}H NMR Spectrum of **107**

8] ^{13}C NMR Spectrum of **107**

9] ^{1}H NMR Spectrum of **106**

10] ^{13}C NMR Spectrum of **106**

11] ^{1}H NMR Spectrum of **120**

12] ^{13}C NMR Spectrum of **120**

13] ^{1}H NMR Spectrum of **121**

14] ^{13}C NMR Spectrum of **121**

15] ^{1}H NMR Spectrum of **122**

16] ^{13}C NMR Spectrum of **122**

17] ^{1}H NMR Spectrum of **124**

18] ^{13}C NMR Spectrum of **124**

19] ^{1}H NMR Spectrum of **125**

20] ^{13}C NMR Spectrum of **125**

21] ^{1}H NMR Spectrum of **126**

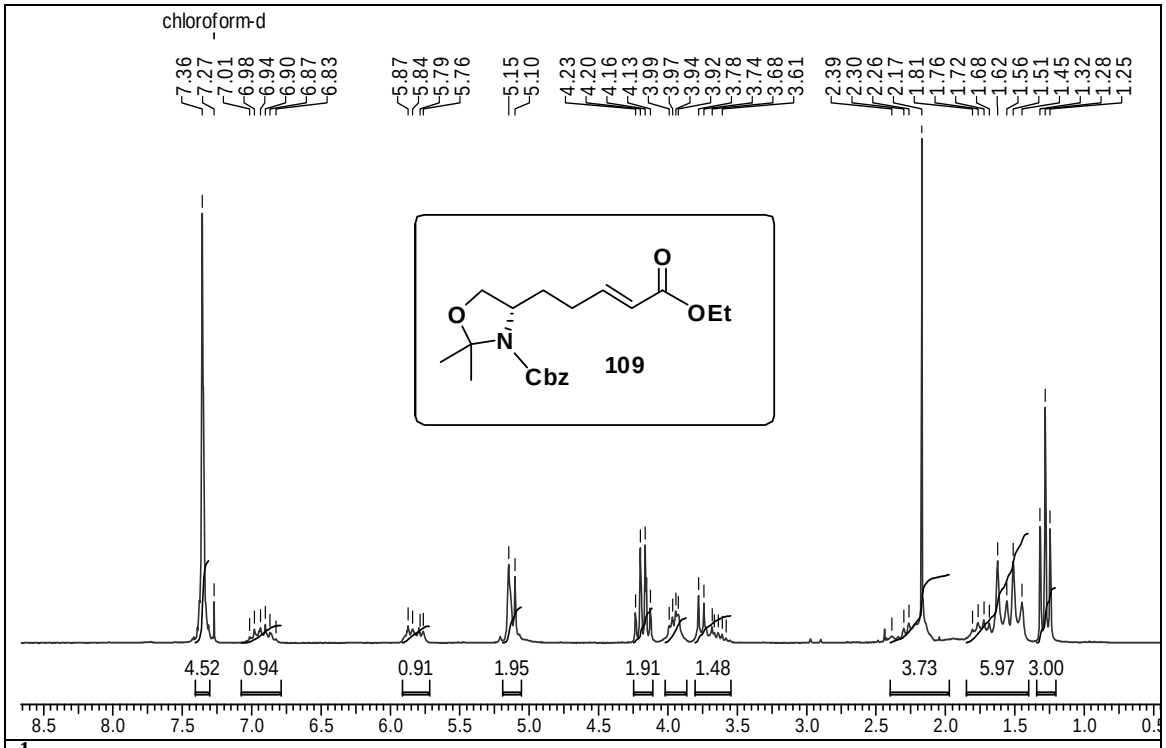
22] ^{13}C NMR Spectrum of **126**

23] ^{1}H NMR Spectrum of **127**

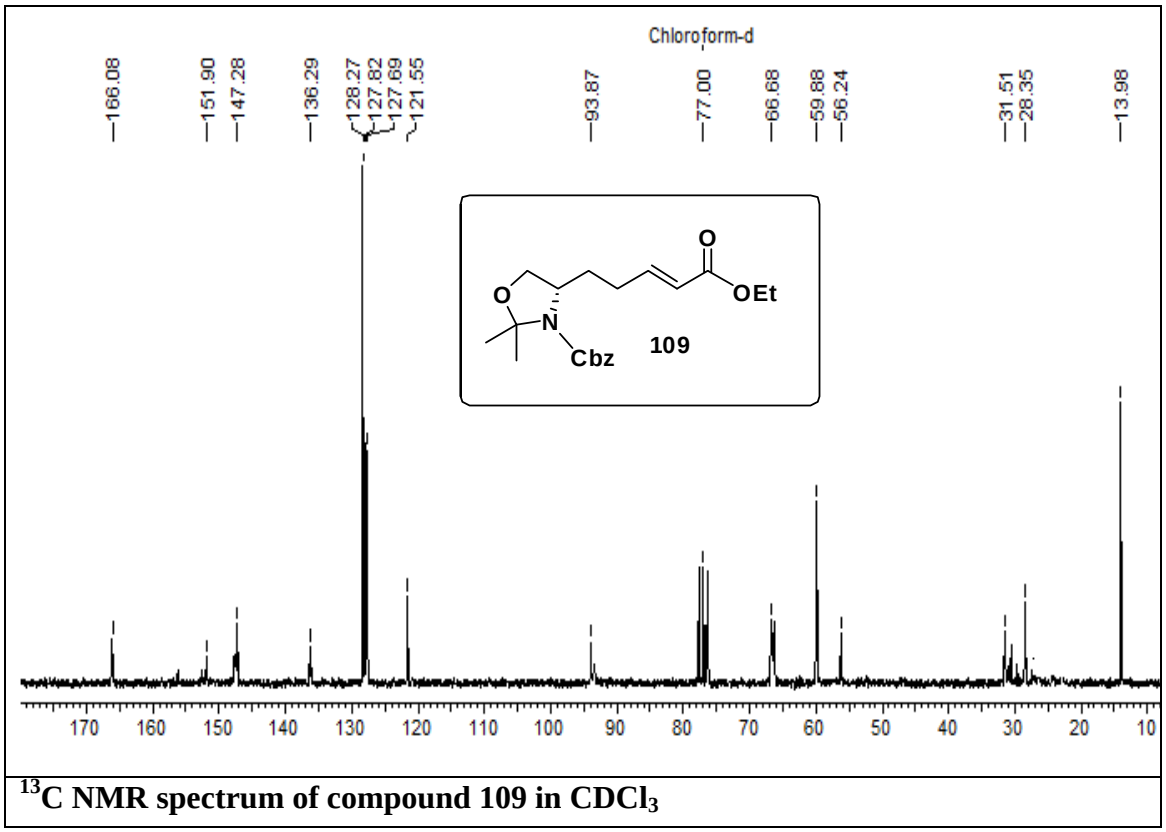
24]] ^{13}C NMR Spectrum of **127**

25] ^{1}H NMR Spectrum of **105**

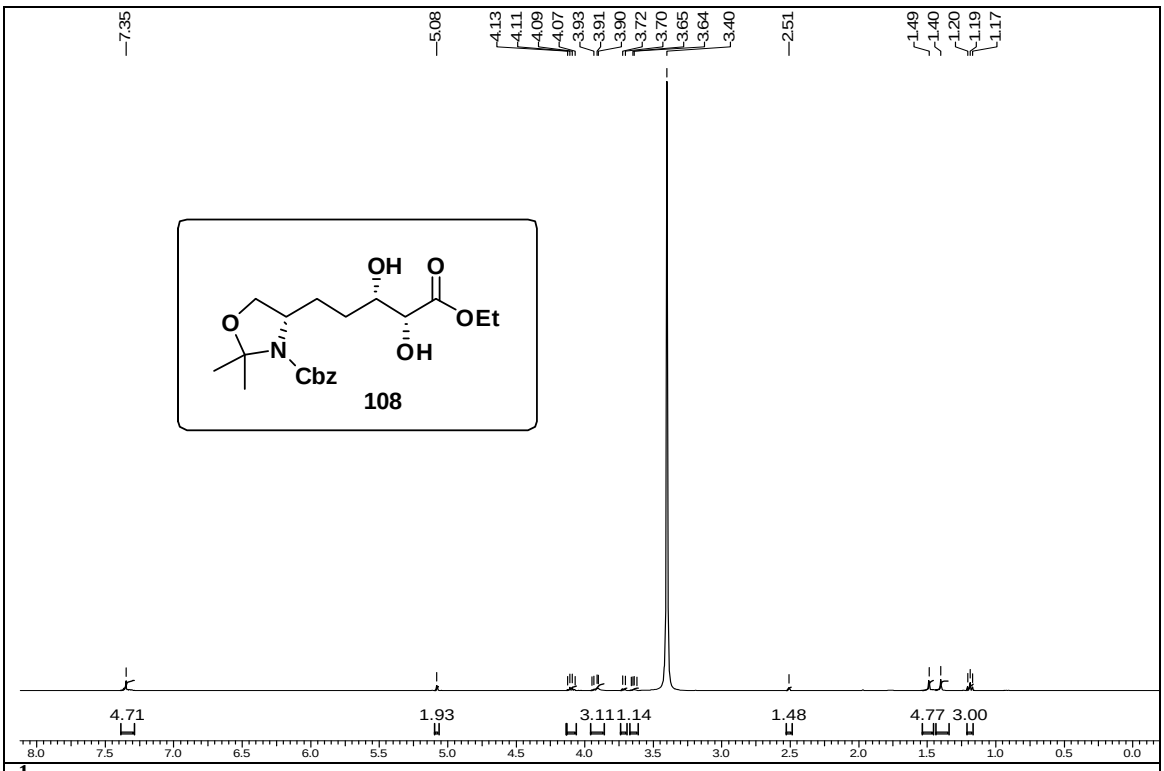
26] ^{13}C NMR Spectrum of **105**



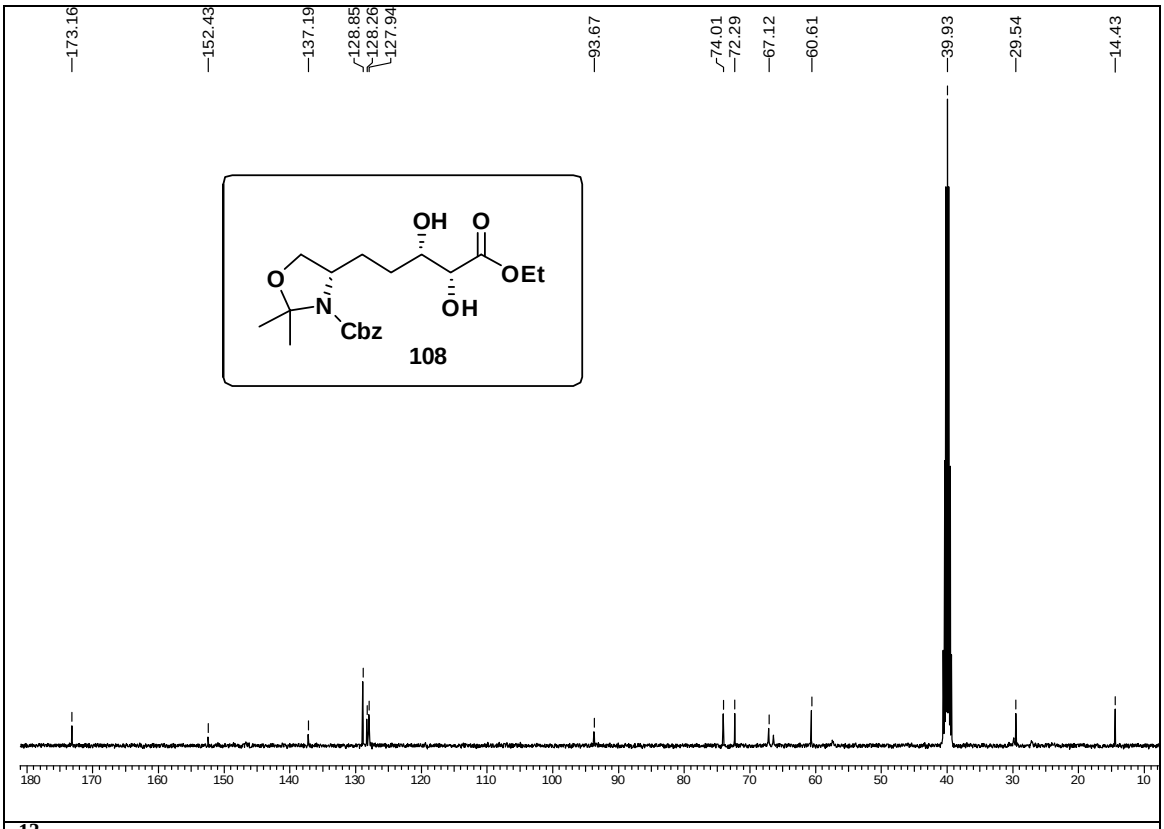
^{1}H NMR spectrum of compound 109 in $CDCl_3$



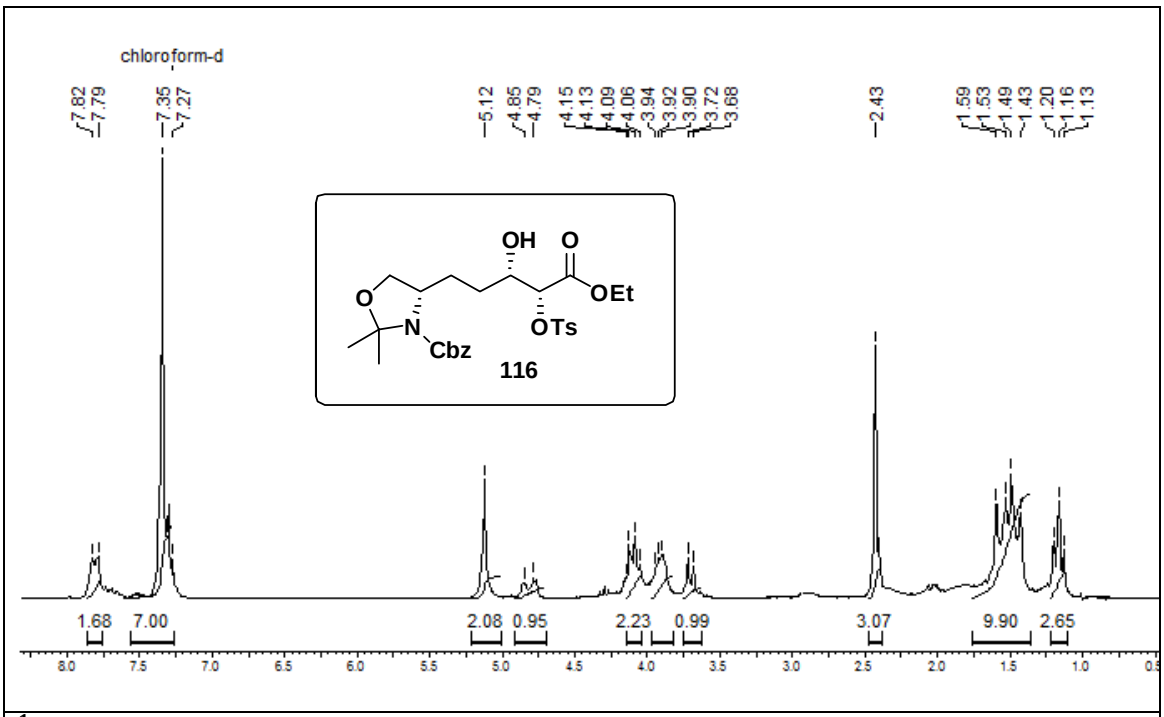
^{13}C NMR spectrum of compound 109 in $CDCl_3$



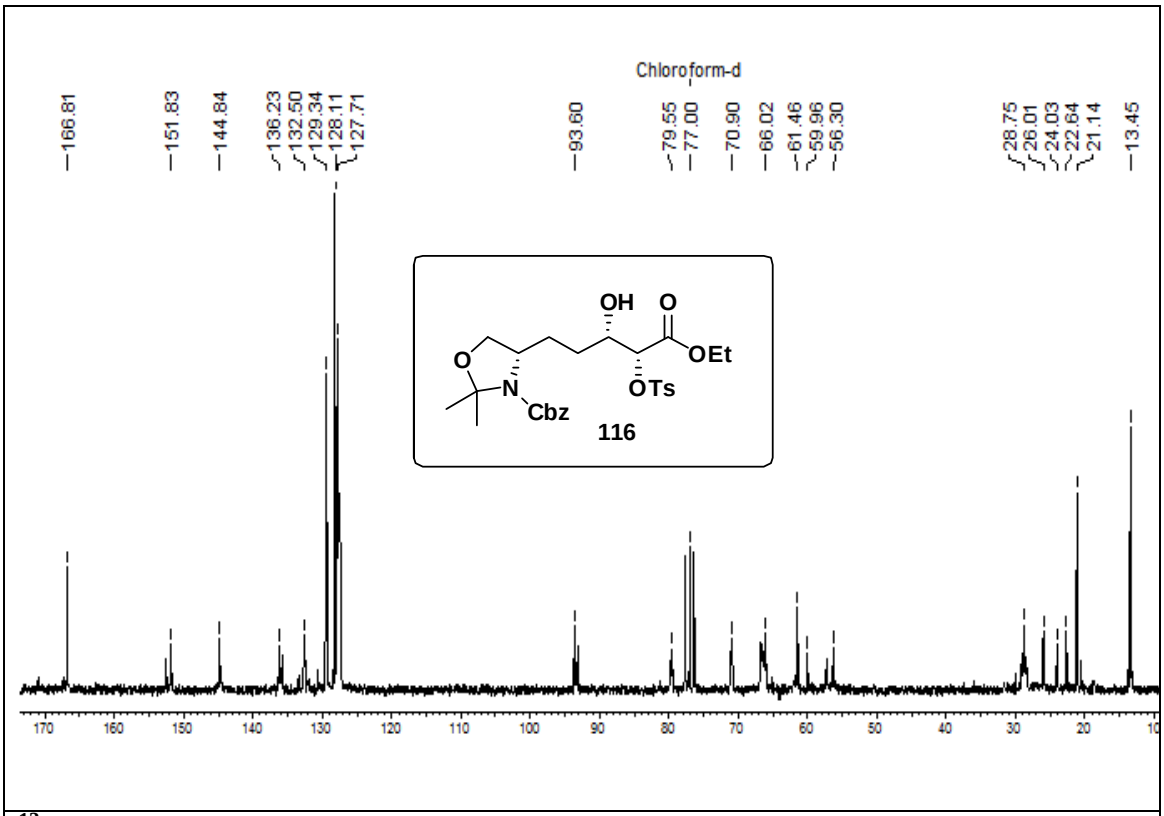
^{1}H NMR spectrum of compound 108 in $CDCl_3$



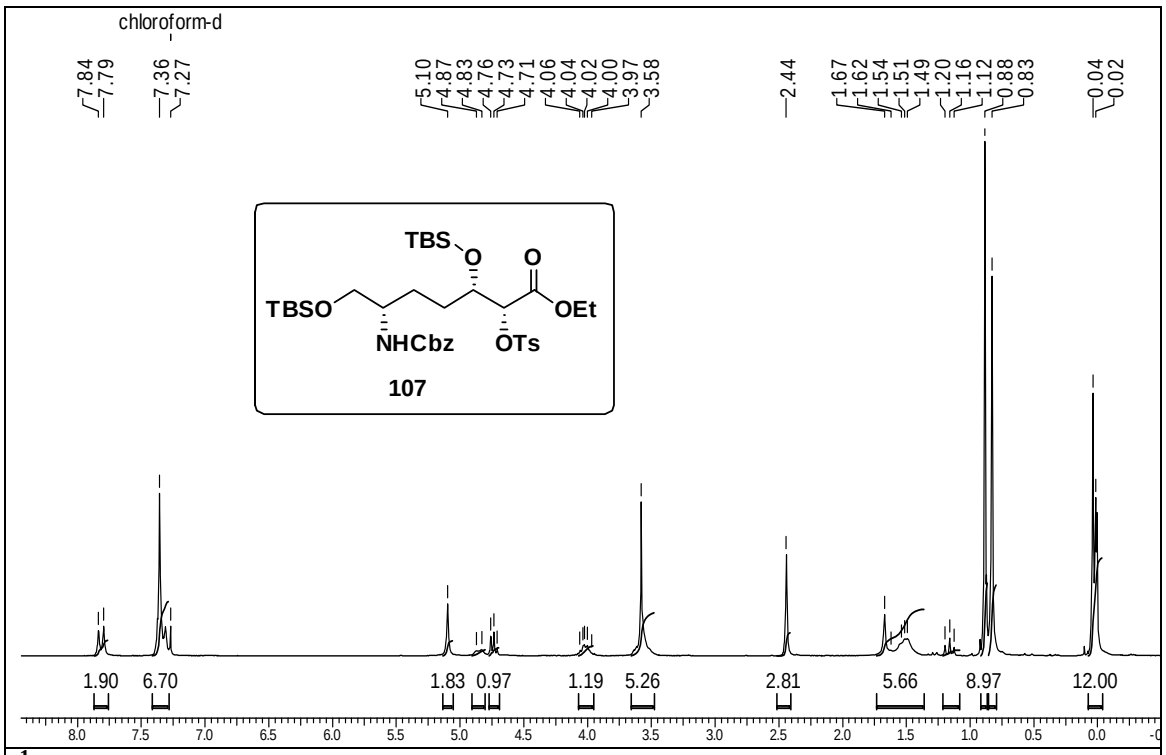
^{13}C NMR spectrum of compound 108 in $CDCl_3$



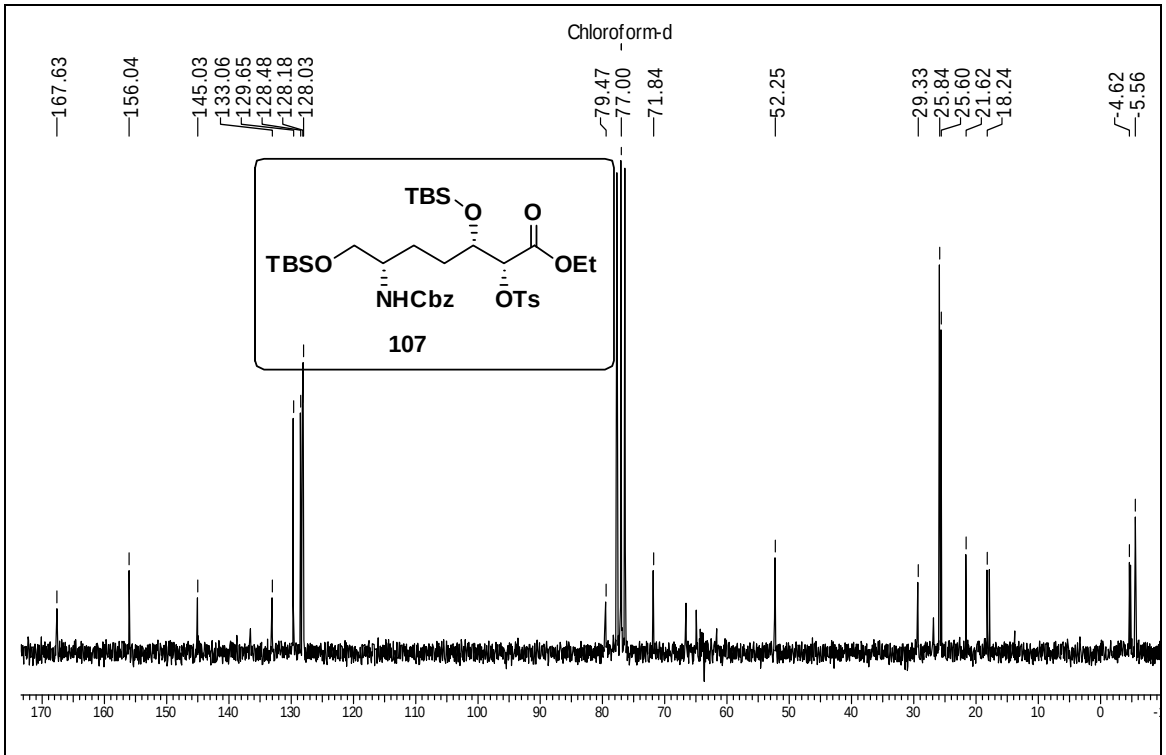
^{1}H NMR spectrum of compound 116 in $CDCl_3$



^{13}C NMR spectrum of compound 116 in $CDCl_3$



^{1}H NMR spectrum of compound 107 in $CDCl_3$



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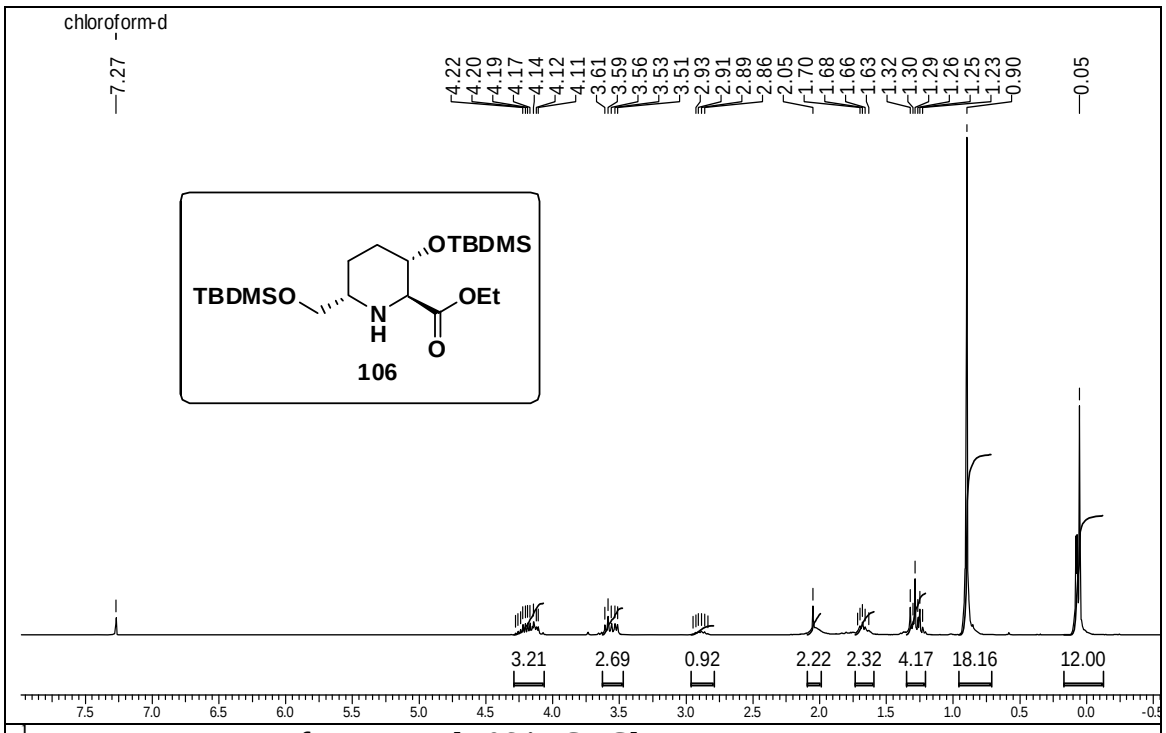
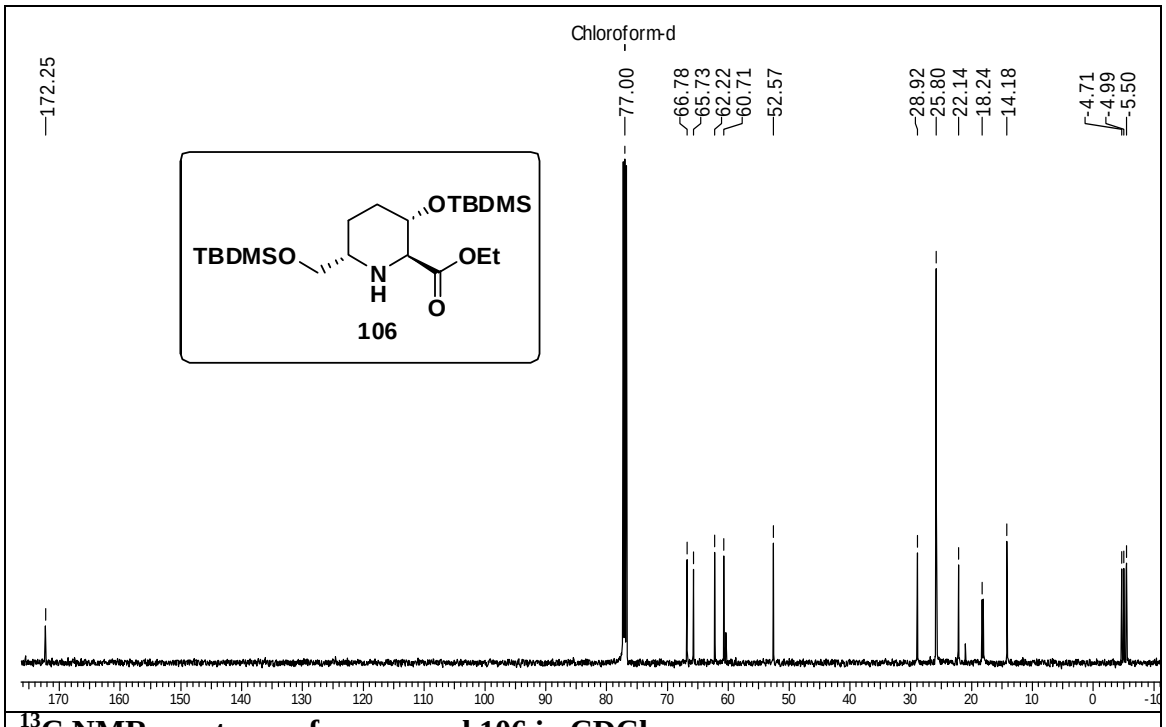
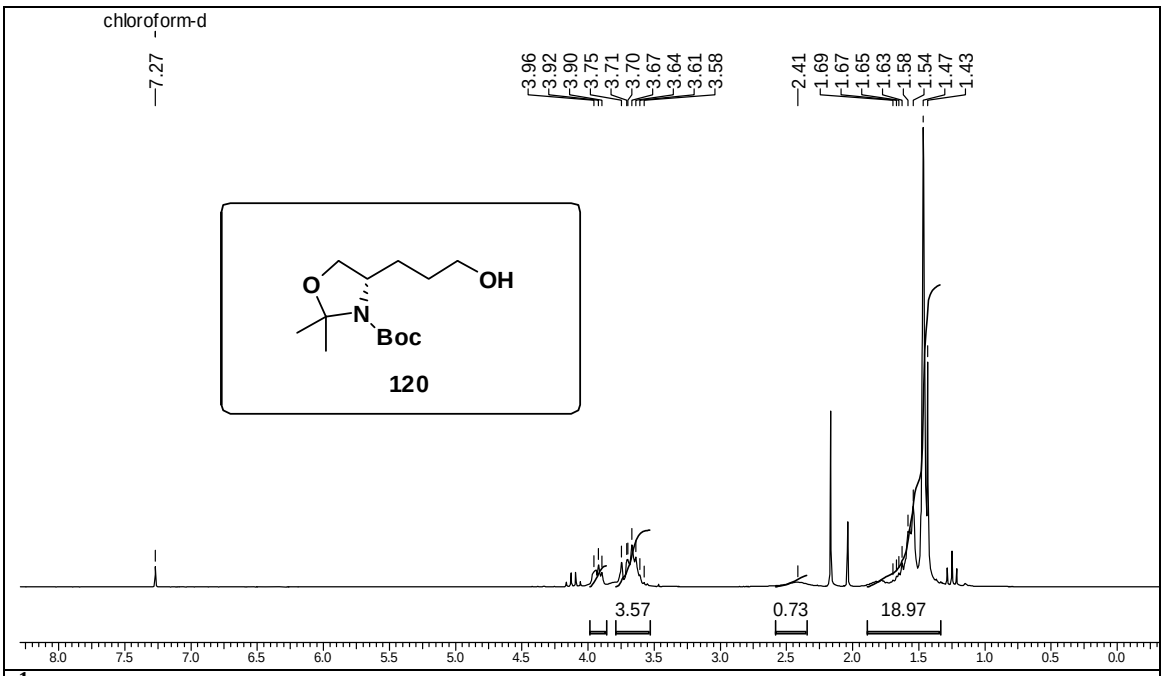


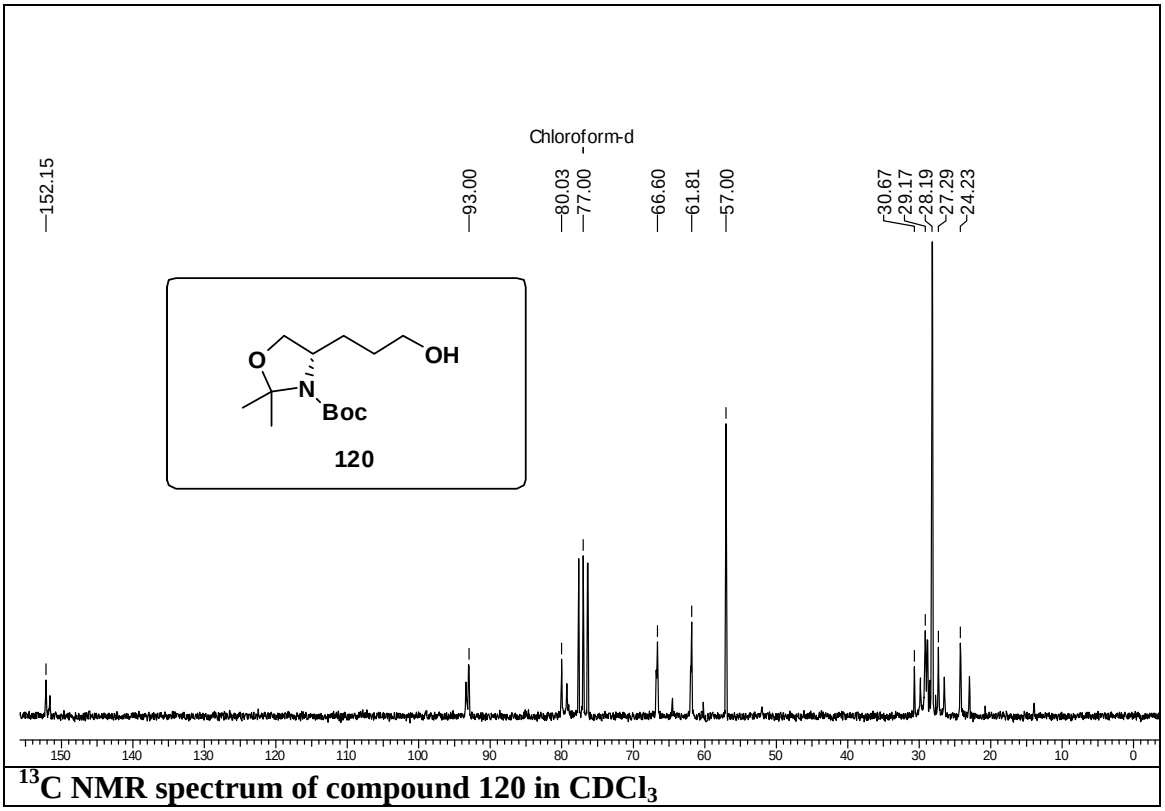
^{1}H NMR spectrum of compound 106 in $CDCl_3$



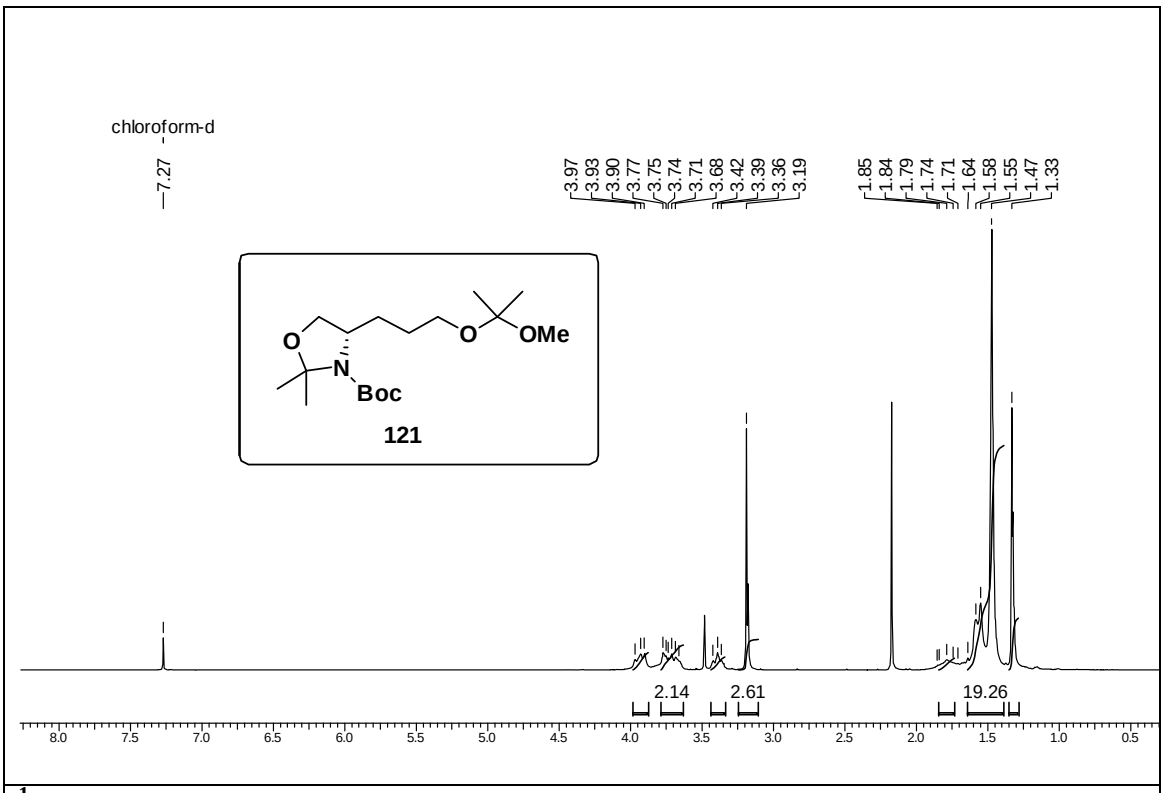
^{13}C NMR spectrum of compound 106 in $CDCl_3$



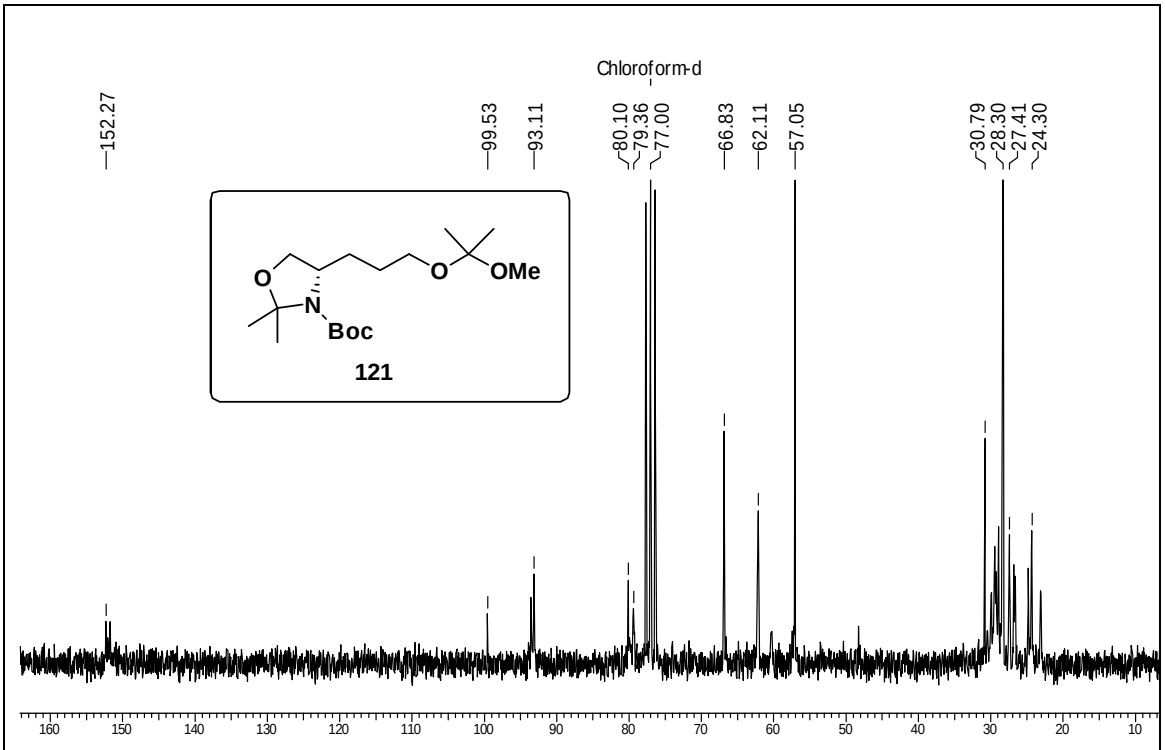
^{1}H NMR spectrum of compound 120 in $CDCl_3$



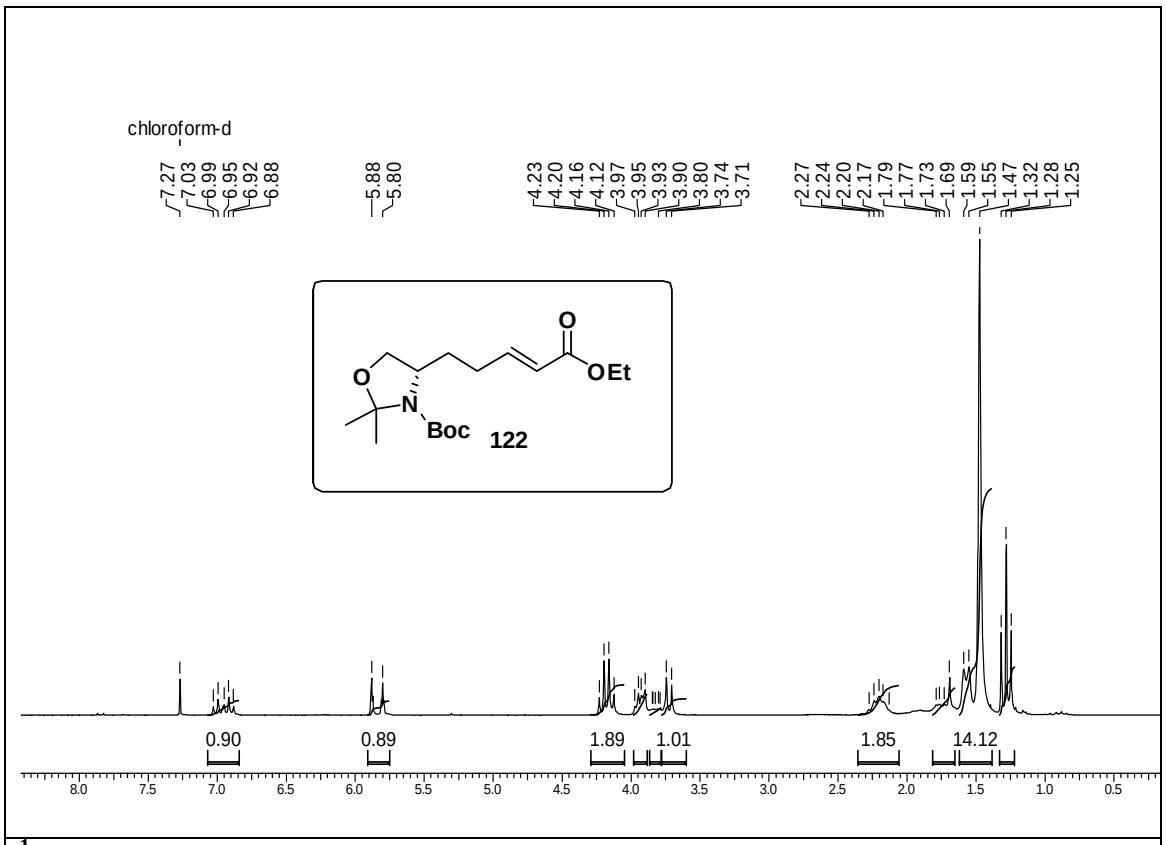
^{13}C NMR spectrum of compound 120 in $CDCl_3$



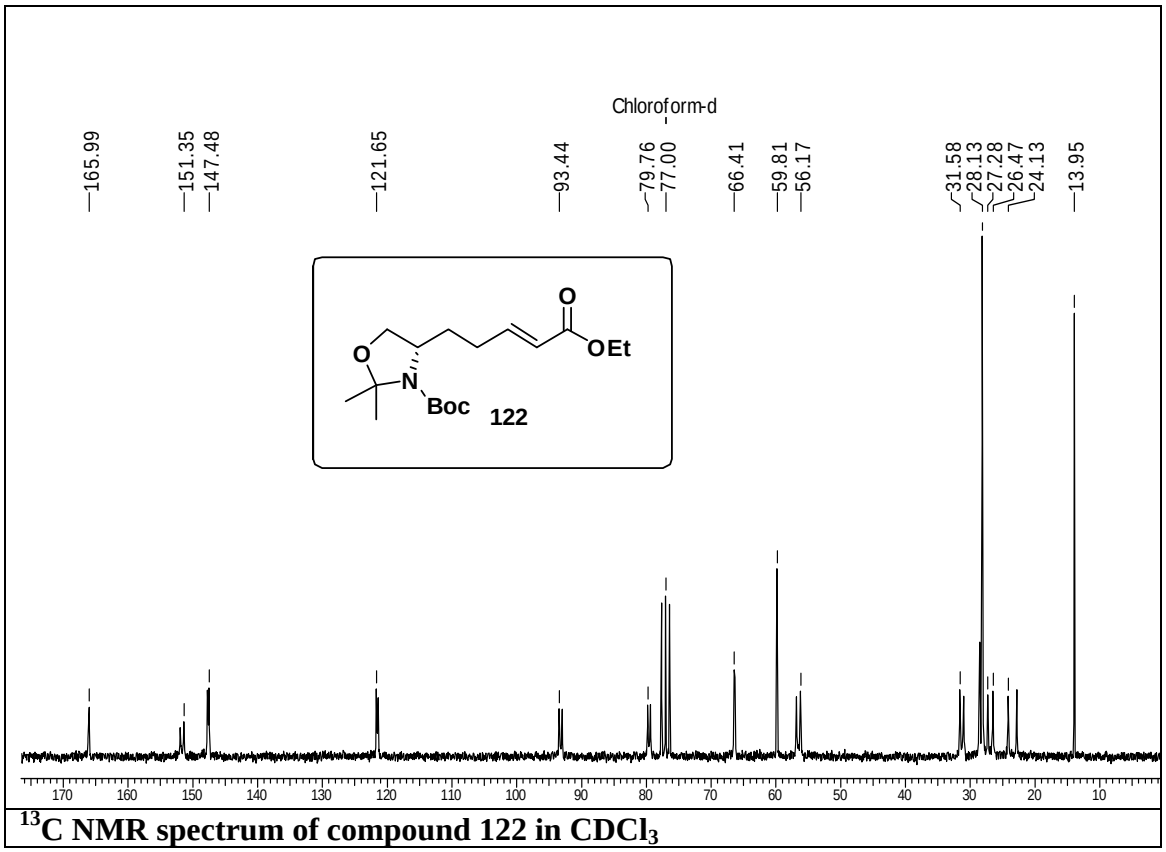
^{1}H NMR spectrum of compound 121 in $CDCl_3$



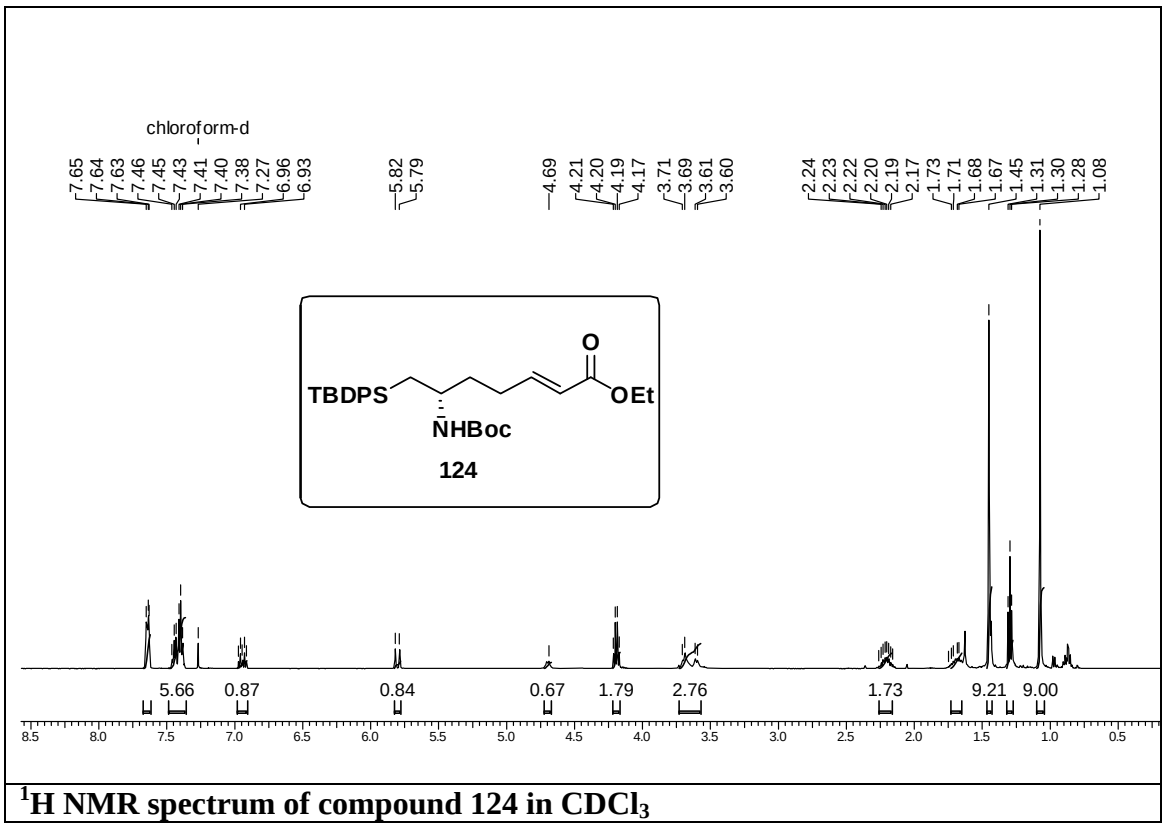
^{13}C NMR spectrum of compound 121 in $CDCl_3$



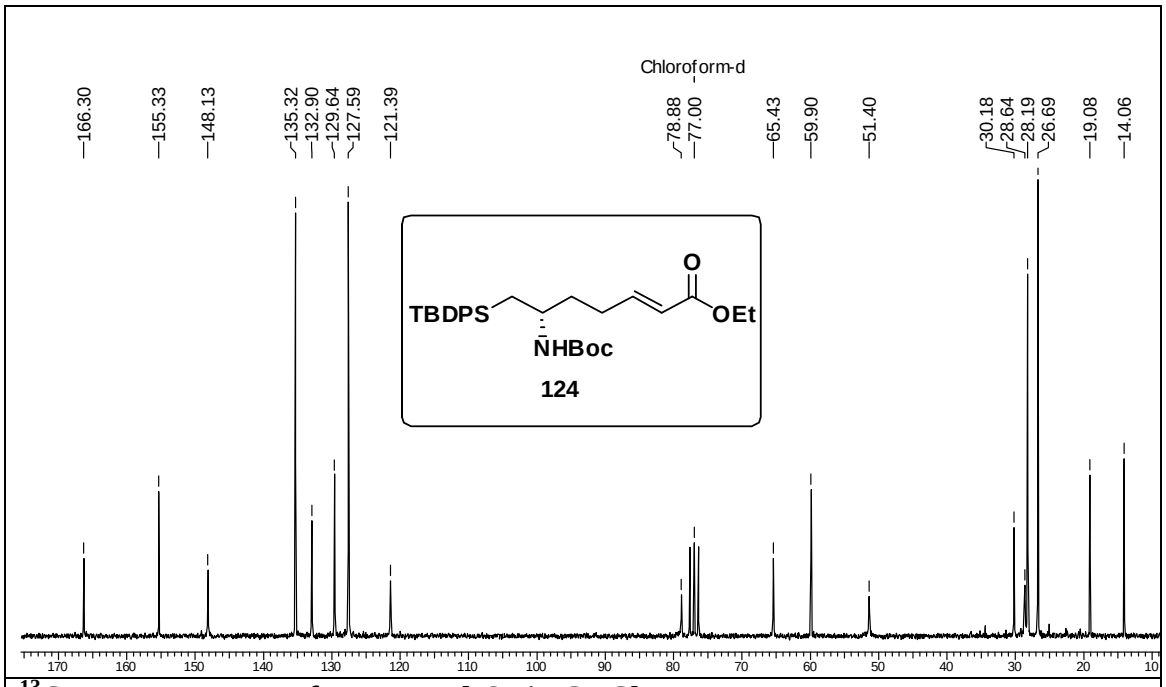
^{1}H NMR spectrum of compound 122 in $CDCl_3$



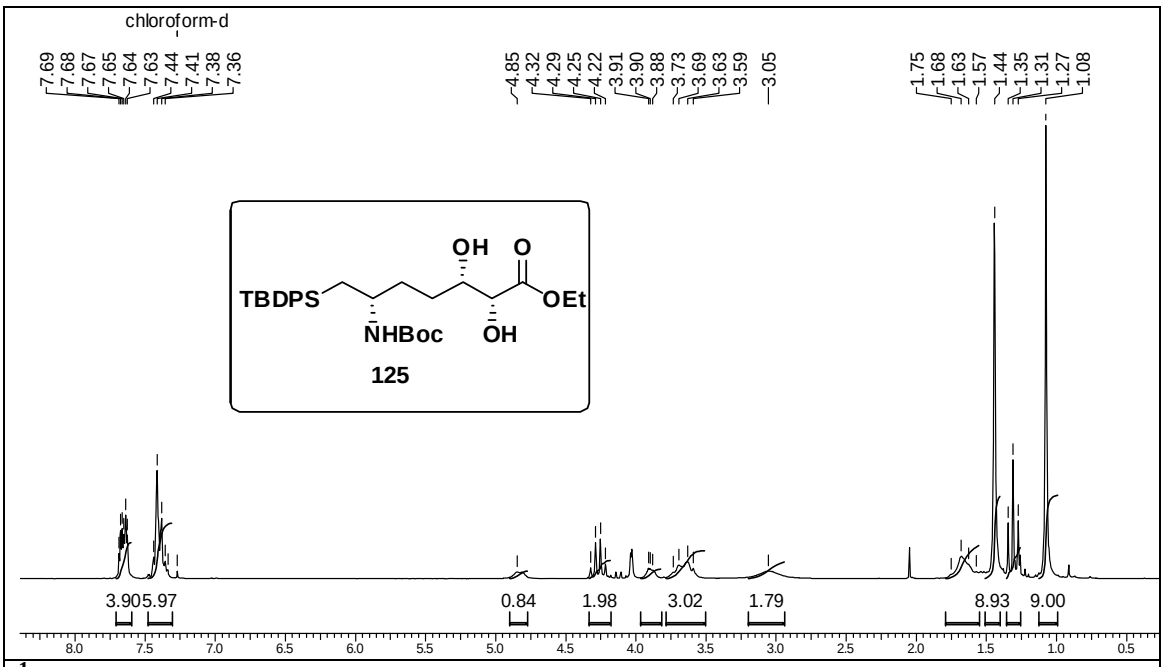
^{13}C NMR spectrum of compound 122 in $CDCl_3$



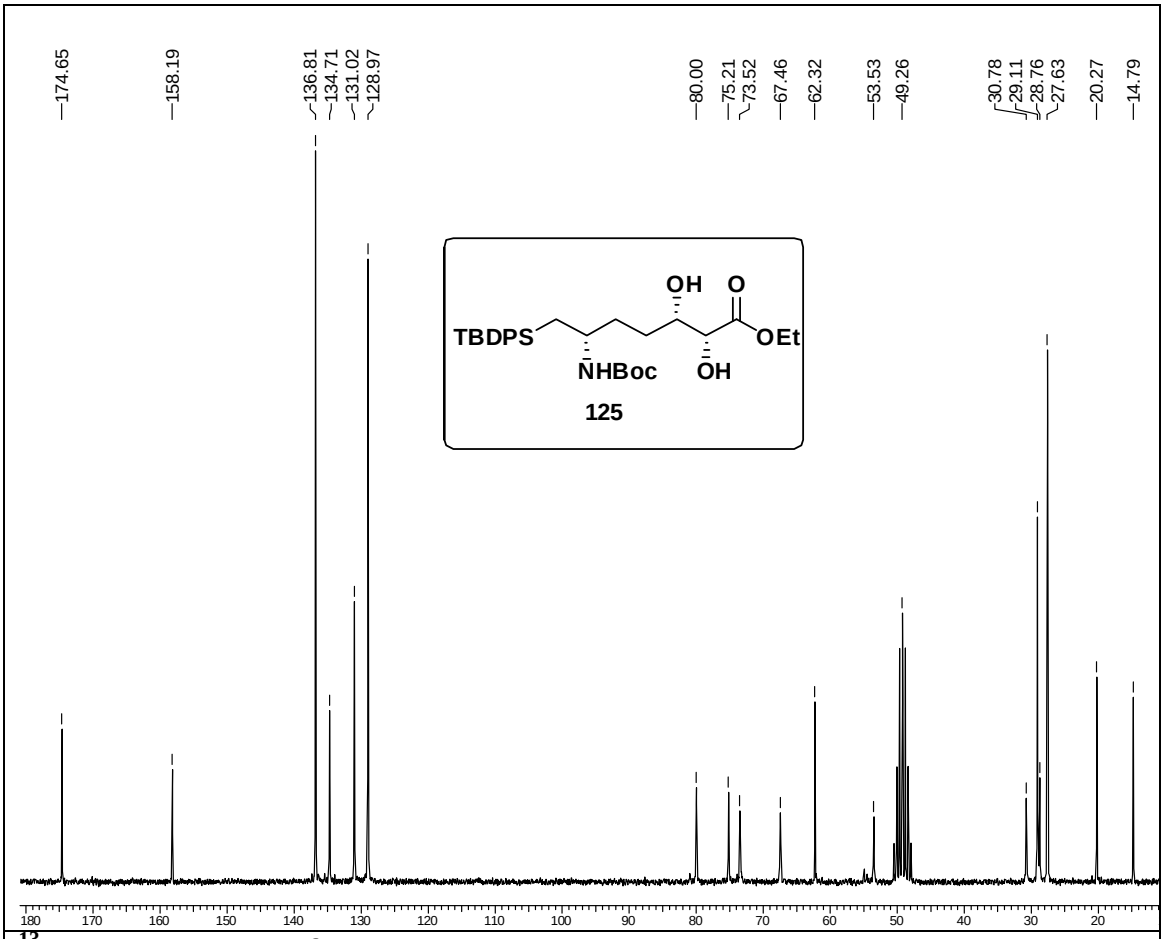
^{1}H NMR spectrum of compound 124 in $CDCl_3$



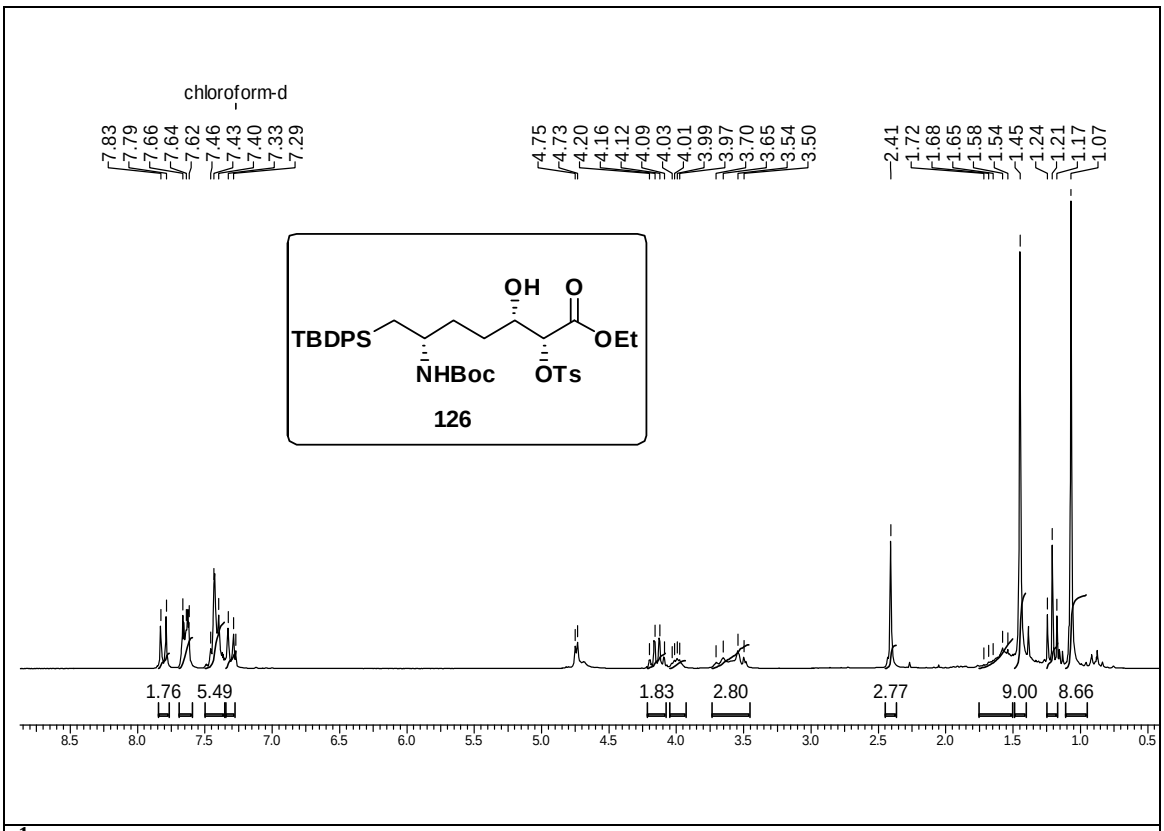
^{13}C NMR spectrum of compound124 in $CDCl_3$



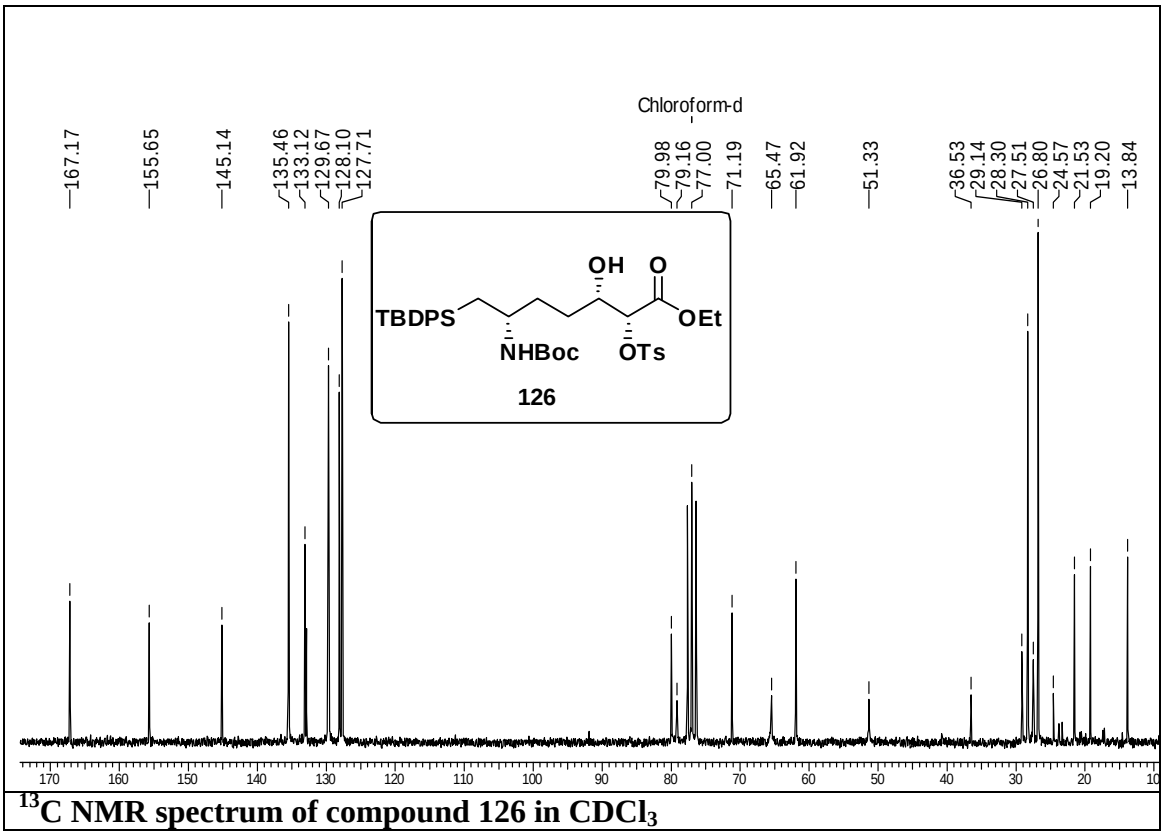
^{1}H NMR spectrum of compound 125 in $CDCl_3$



^{13}C NMR spectrum of compound 125 in $CDCl_3$



^{1}H NMR spectrum of compound 126 in $CDCl_3$



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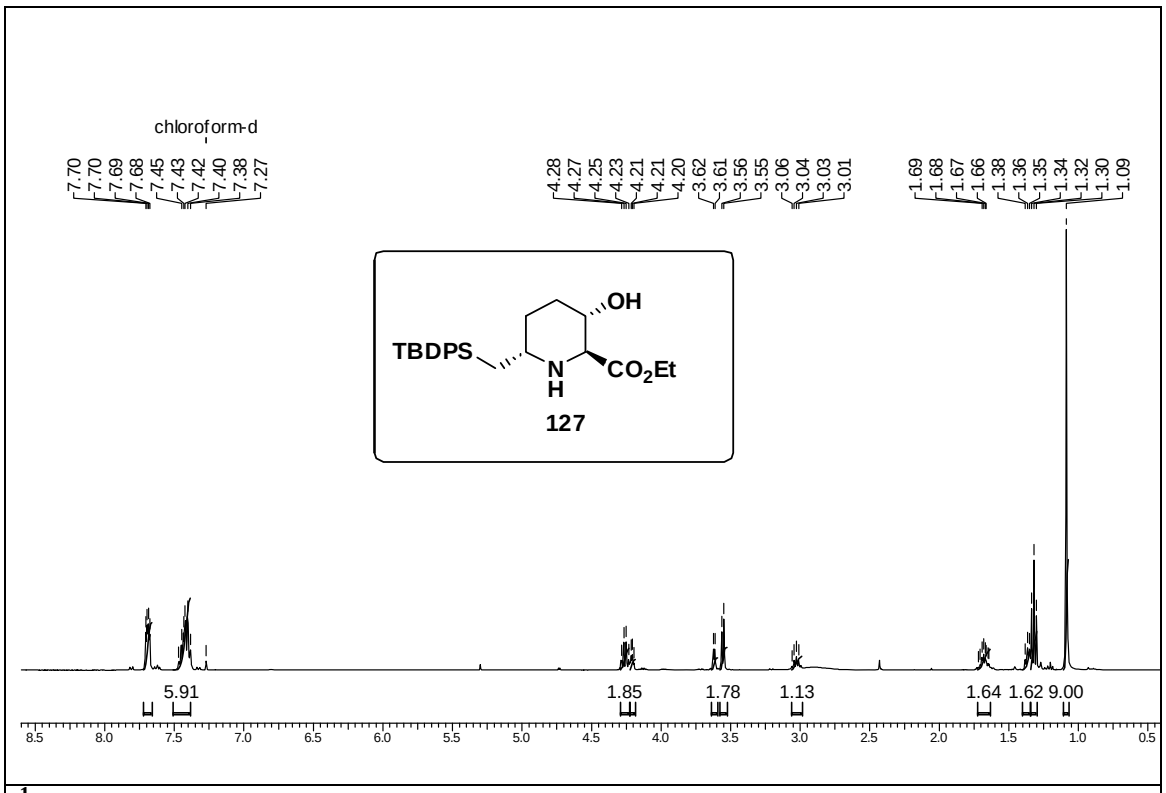

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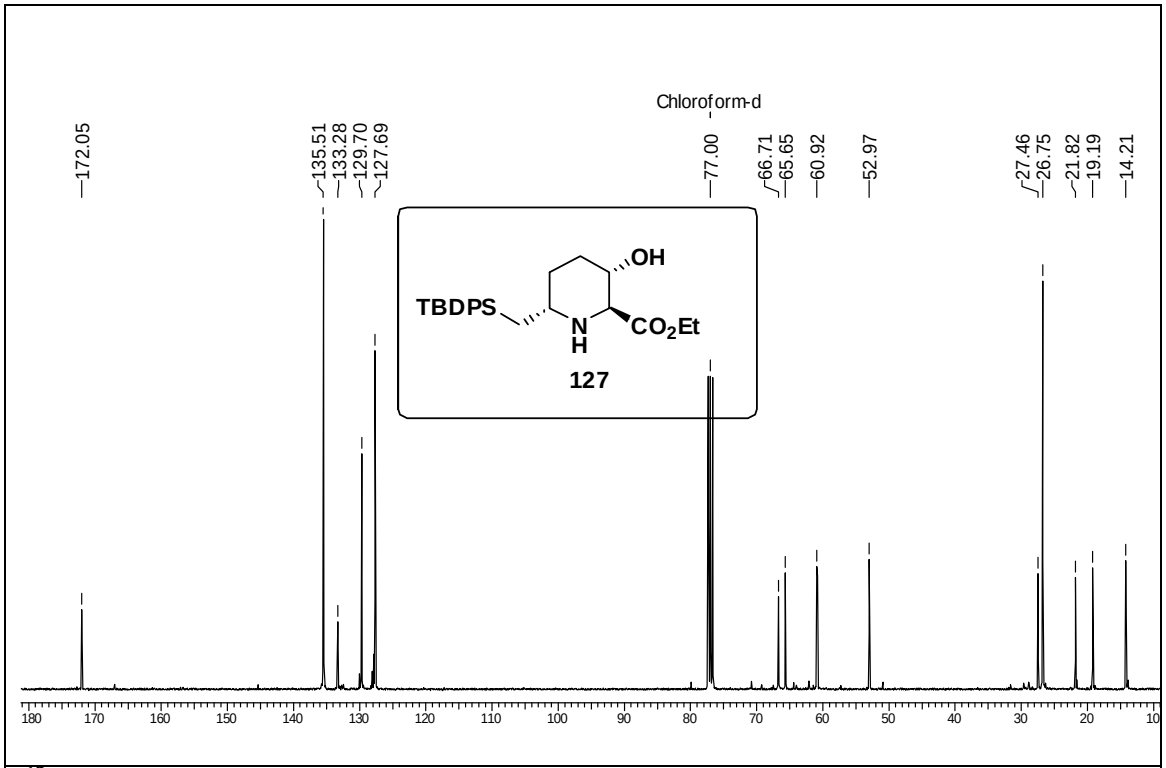
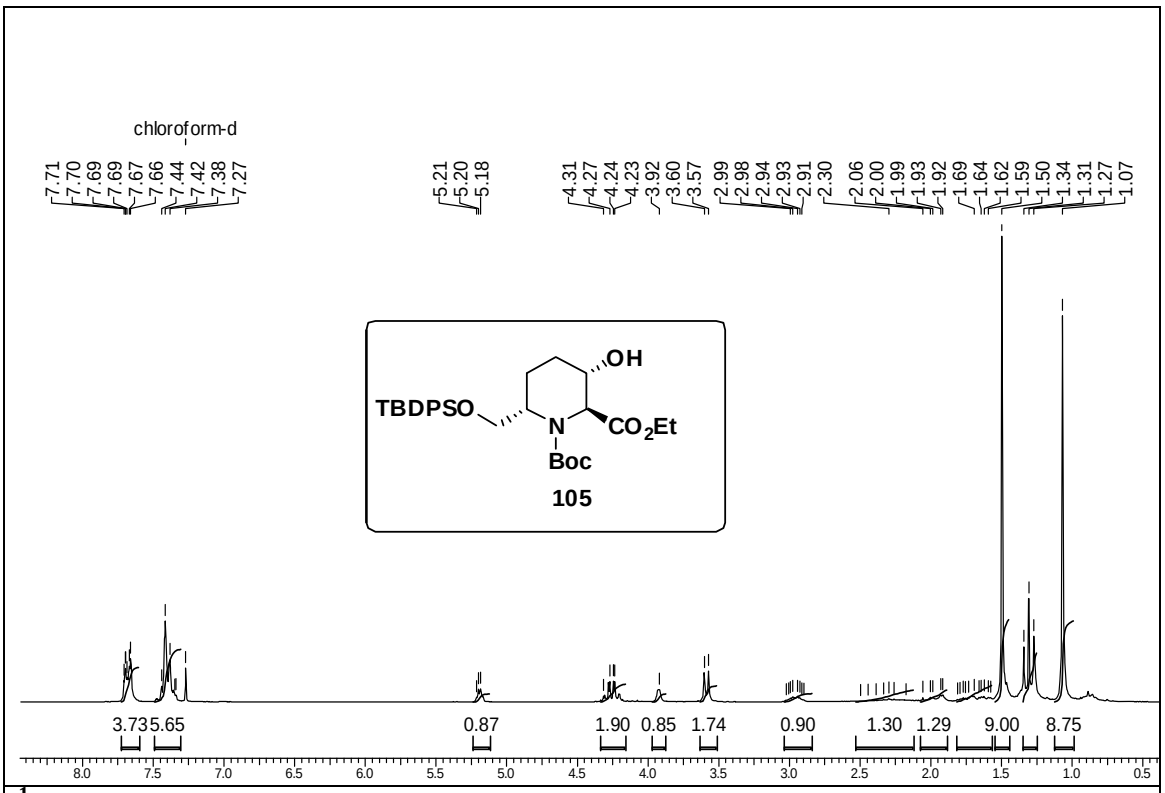
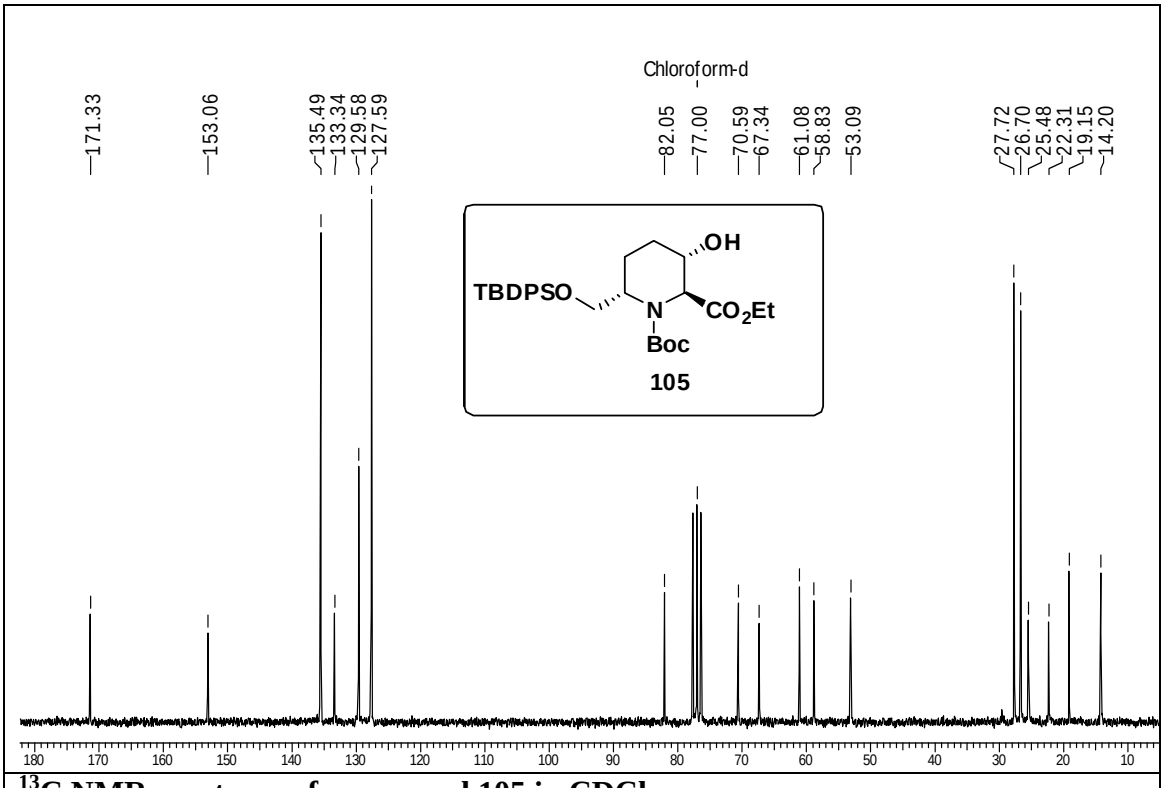


^{13}C NMR spectrum of compound 127 in $CDCl_3$



^{1}H NMR spectrum of compound 105 in $CDCl_3$



^{13}C NMR spectrum of compound 105 in $CDCl_3$

3.1.8. References

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13. The *ent*-**14** is obtained in following way: (L)-serine methyl ester hydrochloride is reacted with 1 equiv of benzaldehyde and 1 equiv of Et_3N/CH_3OH, followed by reduction of the resulting imine with $NaBH_4$. The resultant *N*-monoprotected methyl ester is reacted with $(Boc)_2O/Et_3N$/THF and then with TBSCl/imidazole to give *N*-diprotected serine derivative. This product is then treated with DIBAL-H at - 40 ^oC to obtain the desired amino aldehyde. To a suspension of this aldehyde, zinc powder and aqueous solution of NH_4Cl in THF is added followed by allyl bromide at -10 ^oC, after stirring at room temperature, until the substrate disappeared, the reaction mixture was extracted with Et_2O; then the combined extracts were dried and evaporated in vacuo. The final product is obtained as a mixture of *syn* (minor) and *anti* (major) adducts that can be separated by column chromatography after protection of the hydroxyl moiety with the TBS group.
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3.2. SECTION B

ENANTIOSELECTIVE SYNTHESIS OF (*S*)-(+)-2-(HYDROXYMETHYL)-6-PIPERIDIN-2-ONE

3.2.1. Introduction

There has been considerable interest in the development of synthetic routes to substituted piperidines, piperidinones and indolizidines due to their widespread occurrence in nature and important biological activity.[1]

In particular, the development of general methodology for the preparation of piperidines, substituted or any or all of the ring carbons in a diastereoselective and enantioselective manner, has attracted considerable attention.[2,3] Moloney *et al*.[1] have described that 6-oxopipecolic acid derivative can readily be converted into substrate which are amenable to further ring functionalisation (Fig. 1).

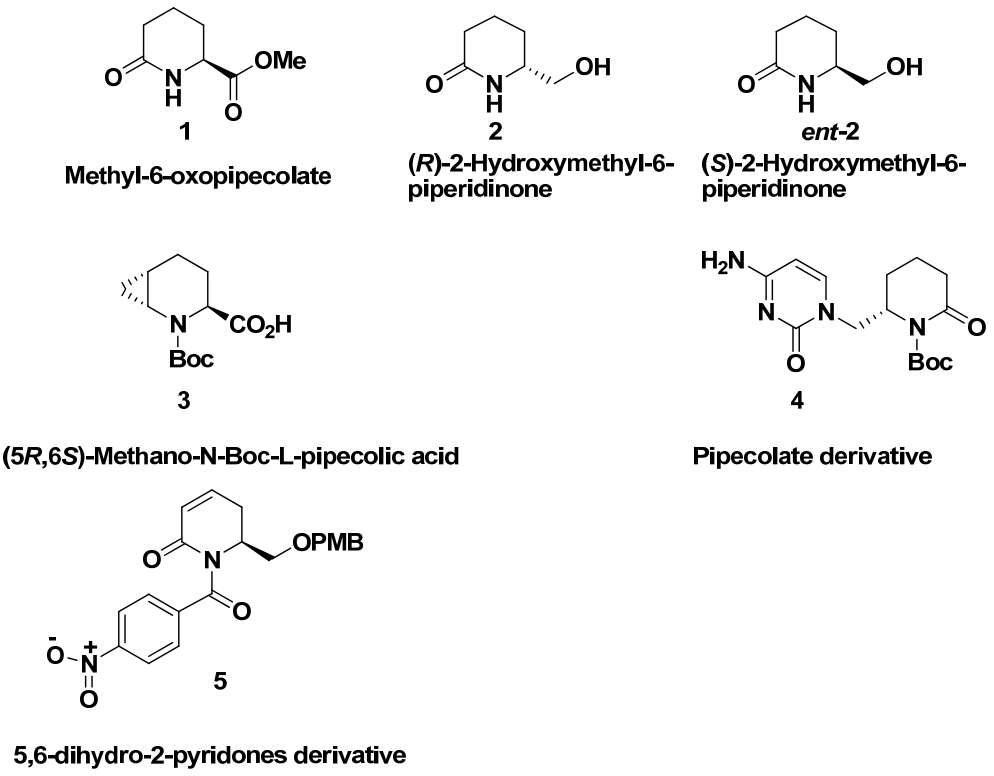


Figure 1. Structure of various pyridone and its derivatives

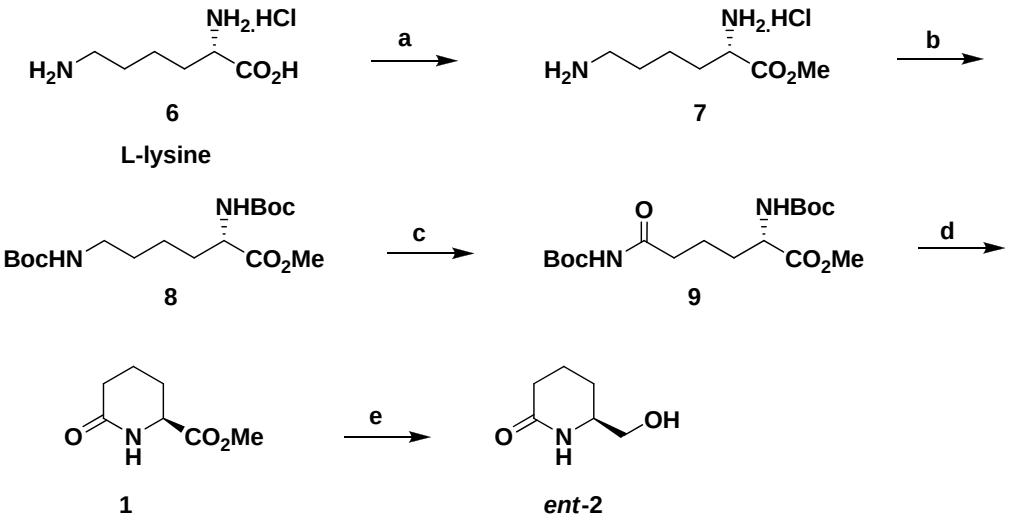
3.2.2. Review of Literature

From a synthetic point of view, there are three synthesis (two chiral and one racemic) reported in literature. The (*S*)-enantiomer **1** is a useful synthon for conformationally constrained pipecolic acid derivatives,[4] 5,6-dihydro-2-pyridinones derivatives and few novel acyclic nucleic acid analogues.[5] Furthermore, this lactam can also be employed to make a chiral bicyclic lactam template which can be used to make other functionalised piperidines in a stereoselective fashion[6] (Figure **1**).

Moloney *et al.* (1996)[1b]

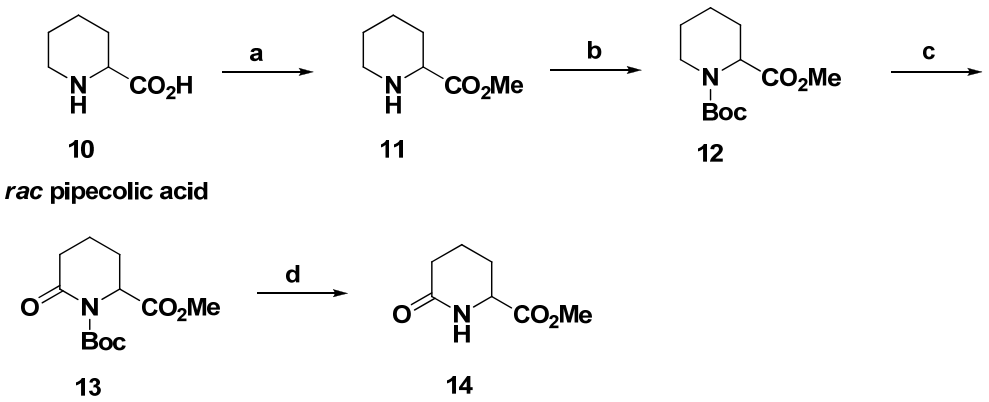
Moloney *et al.*[1b] developed a method for the preparation of both racemic and enantiopure 6-oxopipecolic acid derivatives from readily available and inexpensive (*S*)-lysine and racemic pipecolic acid as starting materials (Scheme 1 & 2).

Chiral synthesis



Scheme 1. *Reagents and conditions*: (a) $(MeO)_2CMe_2$, HCl, MeOH, 93%; (b) Boc_2O, $NaHCO_3$, MeOH, sonicate, 82%; (c) $RuCl_3$, $NaIO_4$, EtOAc, H_2O, pH 4.5, 96%; (d) TFA, 86%; (e) $NaBH_4$, EtOH, 86%.

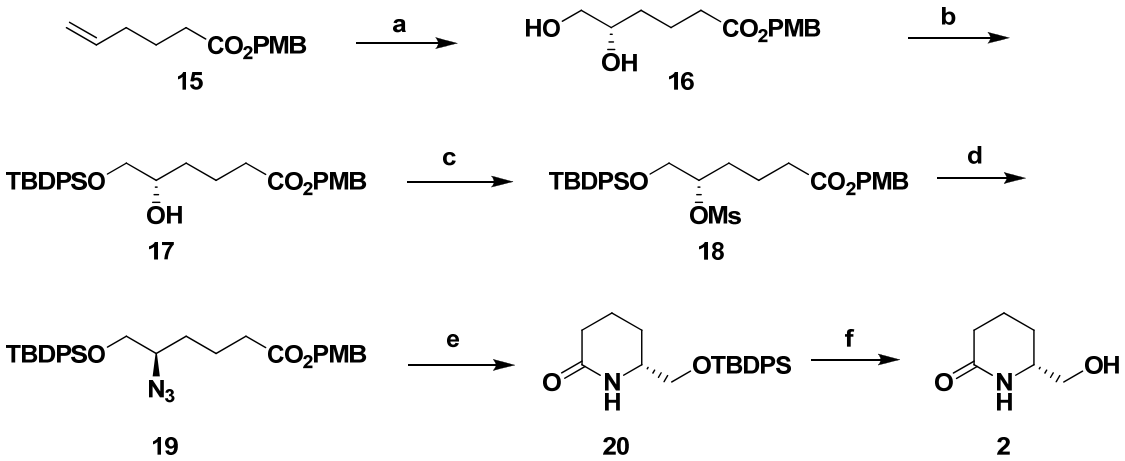
Racemic synthesis



Scheme 2. *Reagents and conditions*: (a) MeOH, HCl, 100%; (b) Boc_2O, Et_3N/H_2O/dioxane, 99%; (c) $RuO_2/NaIO_4/H_2O/CH_3CN$, 95%; (d) CF_3CO_2H/room temperature, 84%.

Shipman *et al.* (1998)[6]

Shipman *et al.*[6] has reported asymmmetric synthesis of both the enantiomer of **2** from *p*-methoxybenzyl ester of hex-5-enoic acid using Sharpless asymmetric dihydroxylation[7] as a key step (Scheme 3).

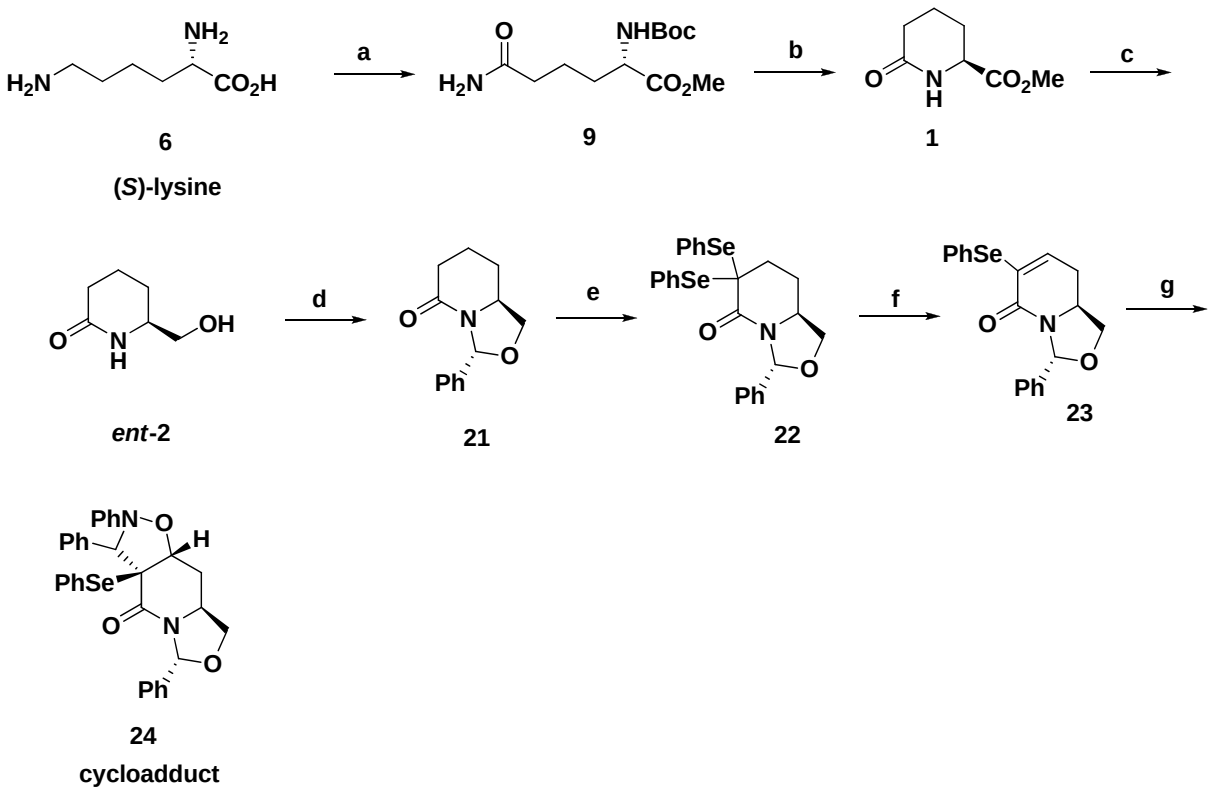


Scheme 3. *Reagents and conditions*: (a) $(DHQ)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, 0 ^oC, $^tBuOH:H_2O$, 99% ee, 56%; (b) TBDPSCl, imidazole, DMF, 91%. (c) MsCl, Et_3N,

CH_2Cl_2, 0 ^oC, 94%; (d) NaN_3, DMF, 80 ^oC, 82%; (e) H_2, Pd/C, EtOH, 84%; (f) TBAF, THF, 89%.

Moloney *et al.* (1994)[1a]

Moloney *et al.*[1a] has also developed a short approach towards the synthesis of highly substituted piperidinones with excellent diastereoselectivity using a chiral tempelate **21** derived from commercially available (*S*)-lysine (Scheme 4).

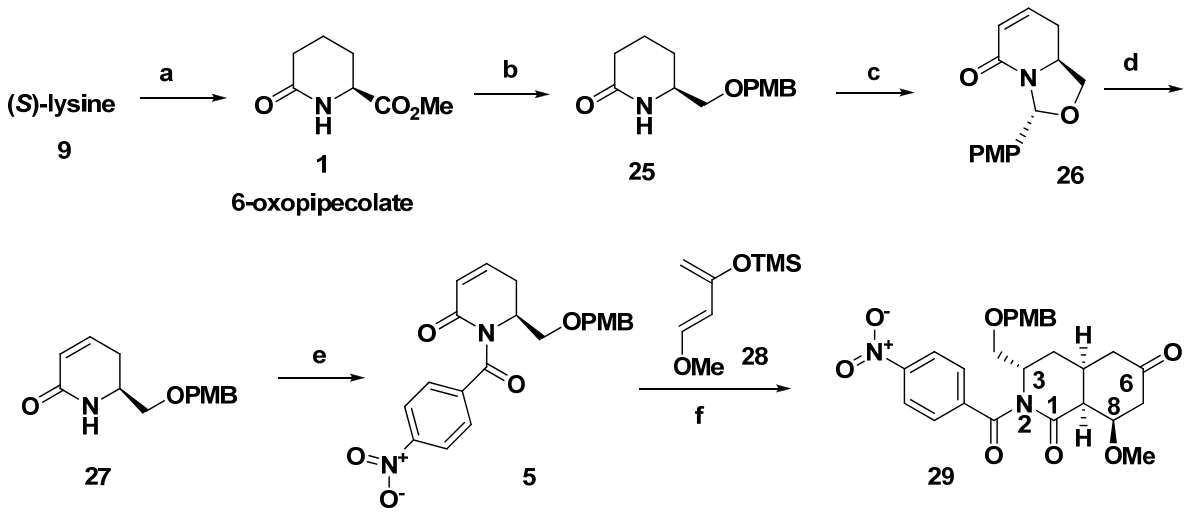


Scheme 4. *Reagents and conditions*: (a) (i) $(MeO)_2CMe_2$, HCl, MeOH, 93%; (ii) Boc_2O, $NaHCO_3$, MeOH, sonicate, 82%; (iii) $RuCl_3$, $NaIO_4$, EtOAc, H_2O, pH 4.5, 96%; (b) TFA, 86%; (c) $NaBH_4$, EtOH, 86%; (d) $PhCH(OMe)_2$, TsOH, 80 ^oC, 72 h; (e) (i) LiHMDS, THF; (ii) 2PhSeCl, THF; (f) *m*-CPBA, CH_2Cl_2; (g) $PhCH{=}N^+(Ph)O^-$.

Dias *et al.* (2002)[8]

Dias *et al.*[8] used 6-oxopipecolate derived from (*S*)-lysine as a starting material for the synthesis of *cis*-hydroisoquinoline moieties from Danishefsky's diene reagent using Diels-Alder reaction as the key step. Hence, compound **25** derived from (*S*)-lysine, was

treated with benzaldehyde dimethyl acetal and subsequent introduction of double bond with LDA afforded the compound **26**. Removal of protecting group was achieved using complex BF_3-2AcOH and protection of primary alcohol as its PMB ether gave lactam **27**. Treatment of **27** with MeLi and *p*-nitrobenzoyl chloride provided (*S*)-(-)-**5** which on heating with an excess of Danishefsky's diene **28** under reflux in degassed dry xylene in the presence of catalytic amount of 2,6-di-*tertbutyl*- 4-methylphenol (BHT) followed by treatment of the intermediate adduct with KF in aqueous THF gave the expected product **29** (Scheme 5).



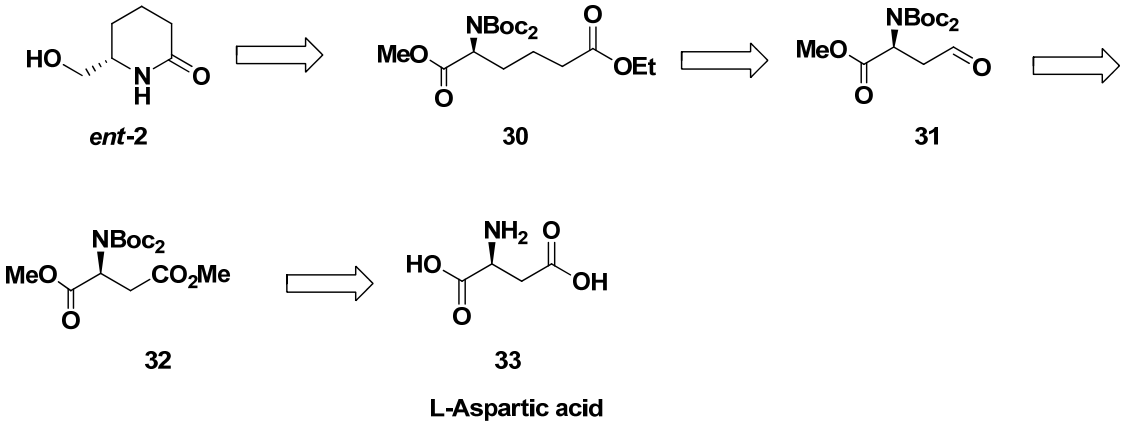
Scheme 5. *Reagents and conditions*: (a) (i) $(MeO)_2CMe_2$, HCl, MeOH, 93%; (ii) Boc_2O, $NaHCO_3$, MeOH, sonicate, 82%; (iii) RuO_2, $NaIO_4$, EtOAc, H_2O, pH 4.5, 96%; (iv) TFA, 86%; (b) (i) $NaBH_4$, EtOH, 86%; (ii) PMB-acetimidate, CH_2Cl_2, CSA; (c) (i) $MeOPhCH(OMe)_2$, CSA, CH_2Cl_2, 79%; (ii) LDA, THF, -78 ^oC, PhSeBr, then H_2O_2, pyridine, rt, 60%; (d) (i) BF_3-2AcOH, MeOH, rt; (ii) PMB-acetimidate, CH_2Cl_2, CSA, 70% (2 steps); (e) MeLi, ClPNB, THF, -78 ^oC, 70%; (f) **28**, BHT, KF, dry THF.

3.2.3. Present Work

Objective

Because of the wide spread occurrence of the piperidine ring skeleton in naturally occurring compounds and their importance in pharmacologically active compounds, the preparation of such saturated heterocyclic has attracted considerable attention. The title compound is an important class of antitumor agent and useful for the synthesis of

pipecolic acid derivatives.[5] There has been considerable interest in the development of synthetic routes to substituted piperidines, piperidinones and indolizidines due to their wide spread occurrence in nature and important biological activity.[1] We have synthesized the target molecule **2**[1a,b,6] from L-aspartic acid using 2-C Wittig olefination as a key step. The reterosynthetic analysis of target molecule **2** is based on convergent approach as outlined in Scheme 6.



Scheme 6. Retrosynthetic analysis of 2

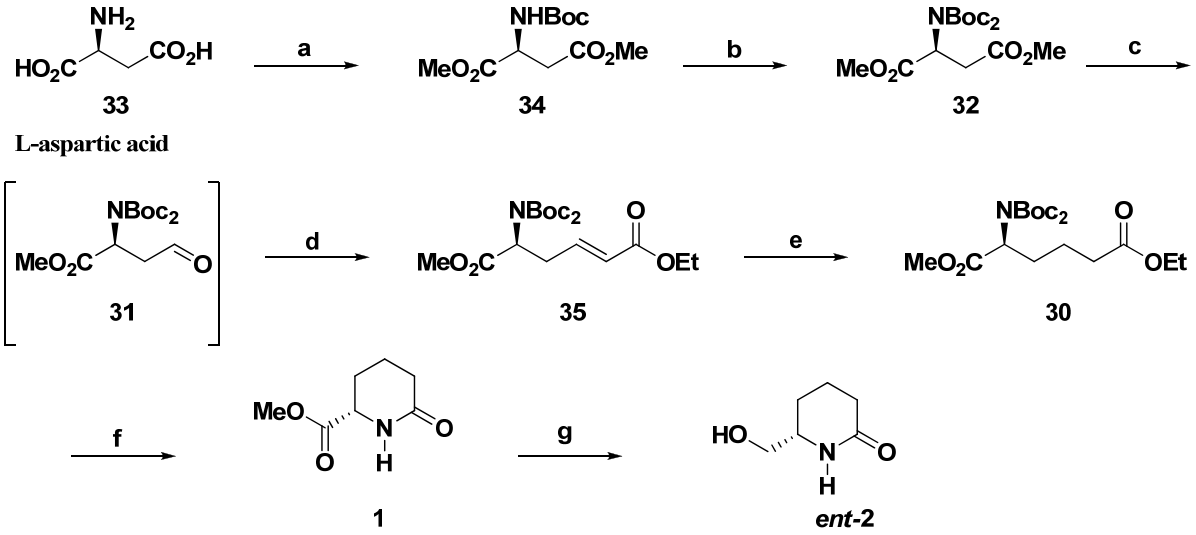
From the synthetic analysis we observed that ***ent*-2** could be obtained from substrate **30** which in turn could be obtained from aldehyde **31** through 2C-Wittig olefination reaction. The aldehyde **31** could be obtained by DIBAL-H reduction of compound **32** which could be accessed from commercially available L-aspartic acid **33**.

3.2.4. Results and Discussion

The synthesis of target molecule *ent*-**2** began from commercially available L-aspartic acid. Thus, amino group of L-aspartic acid was protected with Boc_2O in presence of NaOH and subsequently both carboxylic group was esterified with MeI to give the diester **34** in 90% yield. The spectroscopic data of compound **34** was in accordance with the literature precedence.[9a,b] Carbamate **34** was again protected with Boc_2O in presence of DMAP to give the desired bis carbamate **32** in 93% yield.[9a,b]

The ^{1}H NMR spectrum of compound **32** showed the di *tert*-butyl protons at δ 1.43 (s, 18H) and dimethyl ester protons at δ 3.69 (s, 3H) and δ 3.72 (s, 3H). Regioselective reduction of β-methyl ester **32**[9a,b] with DIBAL-H at -78 ^{o}C afforded the L-aspartic acid

semi-aldehyde **31**[9a,b] which on subsequent treatment with 2C-Wittig reagent gave unsaturated ester **35** with 86% yield.



Scheme1. *Reagents and conditions*: (a) (i) Boc_2O, 1N NaOH, dioxane, H_2O, 5 ^oC- rt, 3.5 h; (ii) MeI, K_2CO_3, DMF, 0 ^oC - rt, 1 h, 87%; (b) Boc_2O, DMAP, CH_3CN, rt, o/n, 93%; (c) DIBAL-H, dry ether, -78 ^oC, 5 min; (d) $Ph_3P{=}CHCO_2Et$, dry THF, rt, o/n, 60 ^oC, 86%; (e) H_2, Pd/C, EtOAc, 2 h, 87%; (e) TFA, CH_2Cl_2, 0 ^oC-rt, 2 h, $NaHCO_3$, 81%; (g) $NaBH_4$, EtOH.

The ^1H NMR spectrum of compound **35** showed the two sets of olefinic protons at δ 5.86 (d, 1H) and δ 6.81-6.96 (m, 1H) and also the appearance of ethyl ester functionality as the combination of triplet and quartet at δ 1.26 (t, 3H) and δ 4.14 (q, 2H) confirmed the formation of compound **35**. Hydrogenolysis of compound **35** with Pd/C in the presence of H_2 gas afforded the saturated ester **30** in 87% yields. Disappearance of olefin peak at δ 5.86 (d, 1H) and δ 6.81-6.96 (m, 1H) confirmed the formation of compound **30**. Finally, deprotection of BOC group with 50% TFA followed by neutralization with sat.$NaHCO_3$ gave the pipecolate **1**[1a,b] in 81% yield. The spectroscopic data of compound **1** was in accordance with the literature precedence.[1a,b] Finally, ester group was reduced to the corresponding lactol **2**[1a,b] using known conditions.

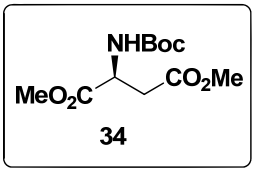
3.2.5. Conclusion

In summary, a short synthesis of (*S*)-2-(hydroxymethyl)-6-piperidin-2-one was achieved from L-aspartic acid using 2C-Wittig olefination reaction as a key step.

3.2.6. Experimental Section

General information: As described in Section A.

(*S*)-Dimethyl-2-(*tert*-butoxycarbonylamino)succinate (34).



34

A solution of di-*tert*-butyldicarbonate (Boc_2O) (9.03 g, 41.2 mmol) in dioxane (45 mL) was added to an ice cold magnetically stirred solution of L-aspartic acid **33** (5.0 g, 37.6 mmol) in 1N NaOH (3.0 g in 75.2 mL H_2O) by means of additional funnel. The two phase mixture is stirred at 5 ^oC for 30 min., then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The reaction mixture is concentrated to its half of the original volume at 45 ^oC, cooled in ice bath, acidified to *pH* 2-3 by the slow addition of 1N $KHSO_4$ (13.6 g in 100 mL) and then extracted with EtOAc (3x150 mL). The combined extract were washed with brine, dried over Na_2SO_4, filtered and concentrated to give *N*-Boc-L-aspartic acid as colourless sticky foam which was used without further purification.

To an ice cold solution of *N*-Boc-L-aspartic acid (8.2 g, 31.42 mmol) in DMF (50 mL) was added solid K_2CO_3 (9.54 g, 69.12 mmol). After stirring for 10 min in an ice bath, methyl iodide (7.8 mL, 125.7 mmol) is added to the white suspension and stirring continued at 0 ^oC for 30 min. whereupon the mixture solidifies. The reaction mixture is warmed to room temperature and stirred for additional 1 h at which point TLC analysis indicates complete formation of the methyl ester. The reaction mixture is filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase is washed with brine, dried, filtered and concentrated. Silica gel column chromatography

of the crude product using petroleum ether / EtOAc (8.5: 1.5) as eluent gave *N*-Boc-L-aspartic acid methyl ester **34** as a white solid.

Yield: 8.5 g (87%); (after two step).

Mol. Formula: $C_{11}H_{19}NO_6$

M.P.: 61 ^oC [lit.(M.P. 60 ^oC)]. [9b]

$[\alpha]^{25}_D$: +30.4 (*c* 2.1, $CHCl_3$); [lit.$[\alpha]^{25}_D$: +30.8 (*c* 2.1, $CHCl_3$)].[9b]

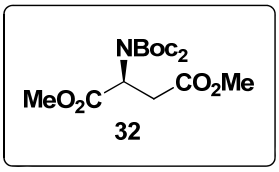
IR (neat, cm^{-1}): ν_{max} 3445, 3032, 1731, 1720.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.76-3.06 (m, 2H), 3.69 (s, 3H), 3.76 (s, 3H), 4.53-4.62 (m, 1H). 5.5 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ27.5, 35.3, 51.5, 52.1, 54.5, 83.1, 151.2, 169.8, 170.6.

Mass [LCMS] : 284.32 [M^+ + Na], 228.2, 206.

(*S*)-Dimethyl-2-(bis(*tert*-butoxycarbonyl)amino)succinate (32).



32

To a mixture of *N*-Boc amino ester **34** (1.0 g, 3.83 mmol) and DMAP (0.094 g, 0.8 mmole) in dry CH_3CN (10 mL) was added Boc_2O (1.3 g, 5.75 mmol) at r.t. The reaction mixtures become slightly red color with gas evolution. After stirring for 2 h, TLC showed some starting material. Excess Boc_2O (0.42 g, 1.92 mmol) was added and mixture was stirred for overnight. After completion of reaction, solvent was evaporated in *vacuo* and crude residue was purified by silica gel column chromatography using EtOAc/ pet ether (1:9) as eluent to give bis carbamate **32** as an oily compound.

Yield: 1.3 g (93%).

Mol. Formula: $C_{16}H_{27}NO_8$

$[\alpha]_D^{25}$: - 60.5 (*c* 2.0, $CHCl_3$); [lit. $[\alpha]_D^{25}$]: - 61 (*c* 2.0, $CHCl_3$).[9b]

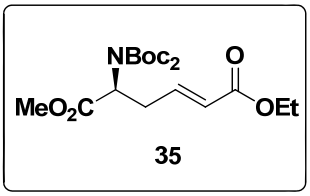
IR (neat, cm^{-1}): ν_{max} 3032, 1731, 1720.

^{1}H NMR (50 MHz, $CDCl_3$): δ 1.43 (s, 18H), 2.66-2.77 (m, 1H), 3.18-3.30 (m, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 5.41-5.47 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ27.5, 35.2, 51.4, 52.0, 54.4, 83.0, 151.1, 169.7, 170.5.

Mass [LCMS] : 381.5 [M^++K], 359.68, 304.01, 282.16.

(*S*,*E*)-1-Ethyl-6-methyl 5-(bis(*tert*-butoxycarbonyl)amino)hex-2-enedioate (35).



35

To a solution of the dimethyl ester **32** (1.0 g, 2.77 mmol) in dry ether (27.7 mL) was added dropwise DIBAL (1.32 mL, 2.3 M in toluene, 2.77 mmol) at -78 ^{o}C and reaction mixture was stirred for 5 min. and quenched with H_2O (0.35 mL, 19.4 mmol). After stirring for 30 min. the reaction mixture was dried over Na_2SO_4 and filtered through a pad of celite. The solvent was evaporated to give aldehyde **31** as colorless oil.

To a solution of aldehyde (0.92 g, 2.78 mmol) in dry THF (15 mL) was added ethyl (triphenylphosphoranylidene)acetate (1.5 g, 4.2 mmol) at rt and reaction mixture was stirred for overnight. After completion of the reaction, solvent was evaporated and cude residue was purified by silica gel column chromatography using EtOAc/pet ether as a eluent to furnish compound **35** as colorless oil.

Yield: 0.96 g (86%); (after two step).

Mol. Formula: $C_{19}H_{31}NO_8$

$[\alpha]_D^{25}$: - 50.3 (*c* 1.0, $CHCl_3$).

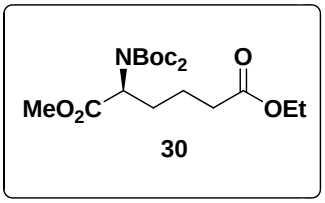
IR (neat, cm^{-1}): ν_{max} 1790, 1743, 1654.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.48 (s, 18H), 2.73-3.06 (m, 2H), 3.73 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.0-5.07 (m, 1H), 5.86 (d, *J* = 14.3 Hz, 1H), 6.81-6.96 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 27.9, 33.0, 52.4, 56.9, 60.2, 83.5, 124.3, 144.0, 151.7, 166.0, 170.3.

Analysis: Calcd.: C, 56.84, H, 7.78; N, 3.49%; **Found:** C, 56.88, H, 7.80; N, 3.44%.

(*S*)-6-Ethyl-1-methyl-2-(bis(*tert*-butoxycarbonyl)amino)hexanedioate (30).



30

To a solution of olefin **35** (0.4 g) in dry EtOAc (10 mL) was added 10% Pd/C (25 mg) in the presence of hydrogen atmosphere. After 2 h stirring, the reaction mixture was filtered on celite and filtrate was evaporated in vacuo and crude compound was purified by silca gel column chromatography to afford **30** as an oil.

Yield: 0.35 g (87%).

Mol. Formula: $C_{19}H_{33}NO_8$

$[\alpha]_D^{25}$: - 43.8 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 1788, 1740.

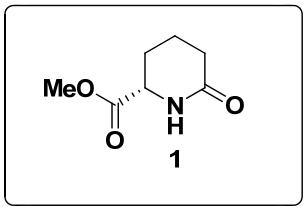
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.49 (s, 18H), 1.63-1.73 (m, 2H), 1.98-2.11 (m, 2H), 2.29-2.37 (m, 2H), 3.70 (s, 3H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.83-4.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 21.5, 27.7, 29.1, 33.6, 51.9, 57.5, 60.0, 82.9, 151.8, 170.9, 172.8.

Mass[LCMS]: 204.48 (M^{+1}), 166.18, 158.33.

Analysis: Calcd.: C, 56.56, H, 8.24; N, 3.47%; **Found:** C, 56.60, H, 8.30; N, 3.41%.

(*S*)-(-)-Methyl-6-oxo-2-piperidine carboxylate (1).



1

To a solution of compound **30** (0.2 g, 0.5 mmol) in dry CH_2Cl_2 (1.0 mL), TFA (0.1 mL, 1.0 mmol) was added at 0 ^oC and reaction mixture stirred at rt for 2 h, solvent was evaporated and neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (20 x 30 mL) and solvent was evaporated in vacuo and crude residue was purified by silica gel column chromatography using ethylacetate/pet ether as eluent to give pipecolate derivative **1** as a pale yellow color liquid.

Yield: 65 mg (81%).

Mol. Formula: $C_7H_{11}NO_3$

$[\alpha]_D^{25}$: - 9.4 (*c* 1.06, $CHCl_3$); [lit.$[\alpha]_D^{25}$: -9.6 (*c* 1.06, $CHCl_3$)].[1b]

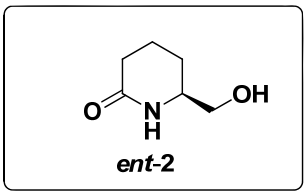
IR (neat, cm^{-1}): ν_{max} 3019, 1743, 1666.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78-1.93 (m, 3H), 2.10-2.22 (m, 1H), 2.31-2.38 (m, 2H), 3.76 (s, 3H), 4.06-4.12 (m, 1H), 6.68 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 25.3, 30.9, 52.6, 54.6, 171.6.

Mass [LCMS]: 180.21(M^++Na), 166.18, 158.33.

(*S*)-(+)-2-(hydroxymethyl)-6-piperidin-2-one (*ent*-2).[1b,d]



***ent*-2**

The compound **1** was reduced to the corresponding ***ent*-2** using known procedure.[1b,d] The spectroscopic data obtained for ***ent*-2** was found to be same as reported by Moloney *et al*.[1b,d]

3.2.7. Speactra

1] ^{1}H NMR spectrum of **34**

2] ^{13}C NMR spectrum of **34**

3] ^{1}H NMR spectrum of **32**

4] ^{13}C NMR spectrum of **32**

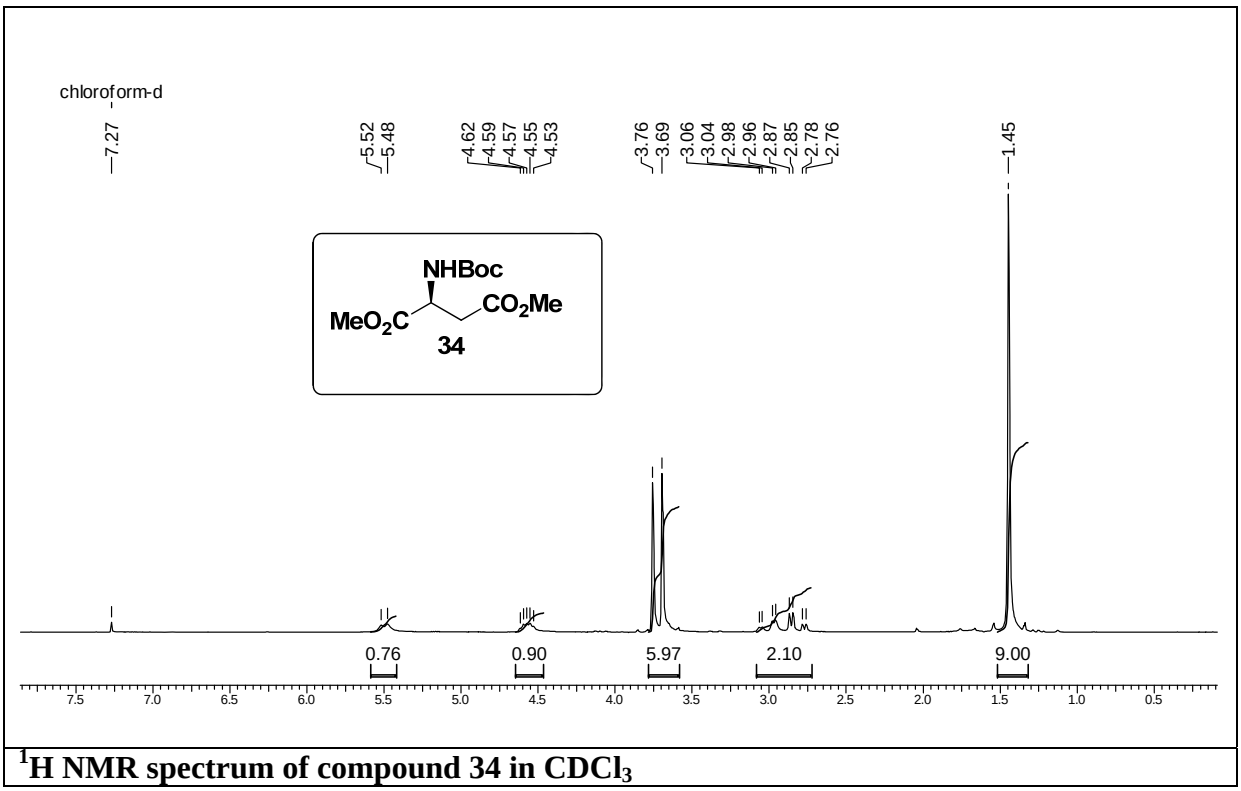
5] ^{1}H NMR spectrum of **35**

6] ^{13}C NMR spectrum of **35**

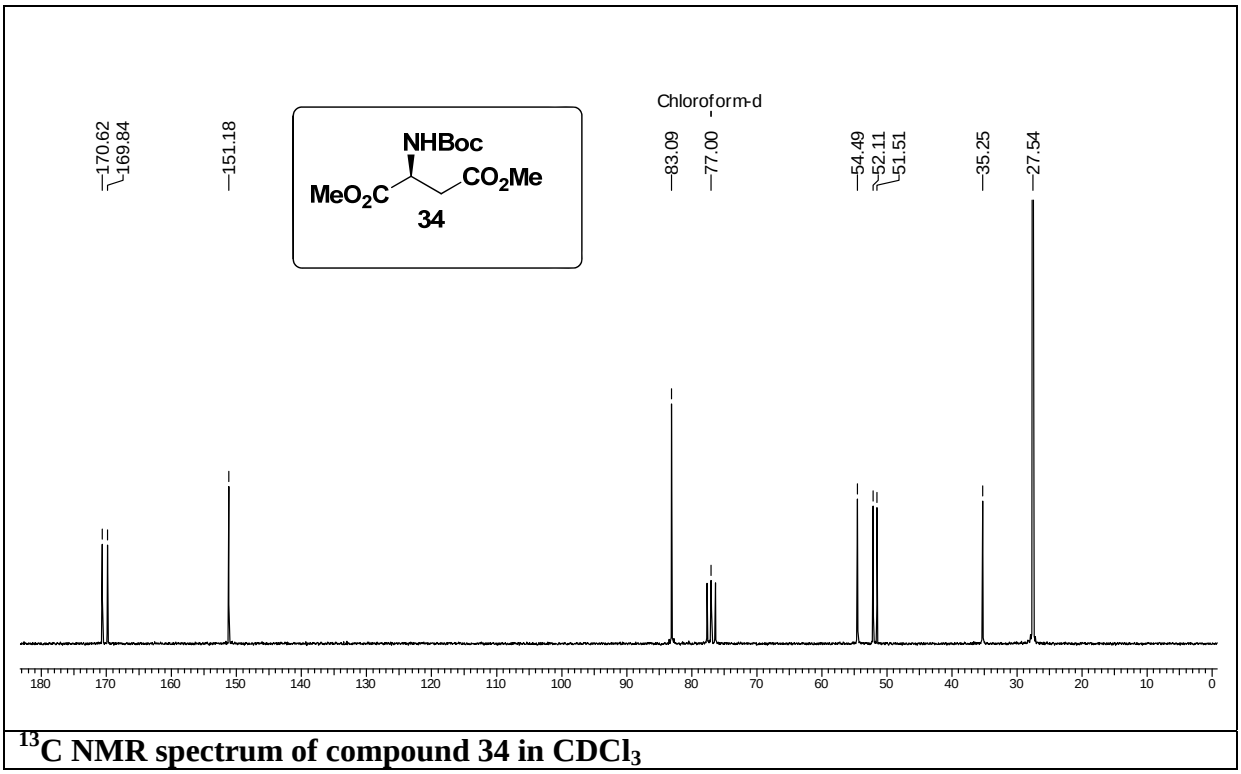
7] ^{1}H NMR spectrum of **30**

8] ^{13}C NMR spectrum of **30**

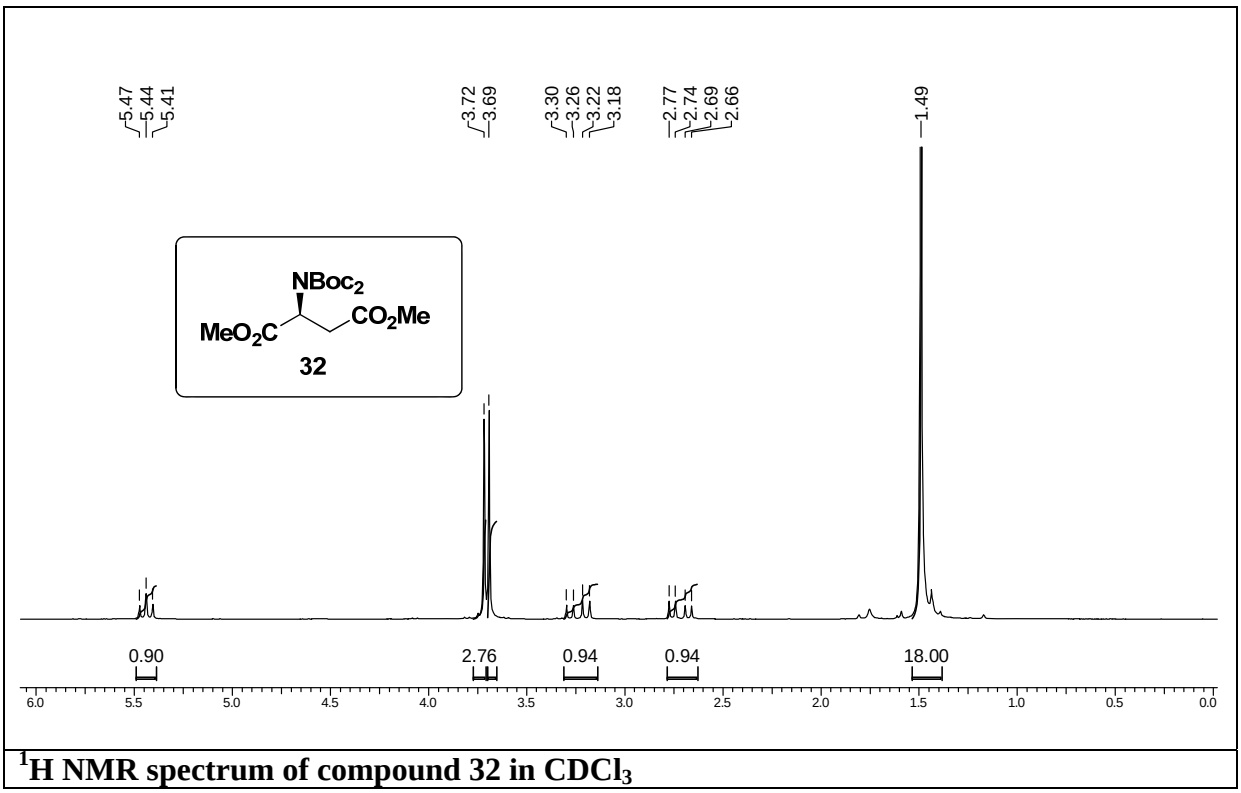
9] ^{1}H NMR spectrum of **1**



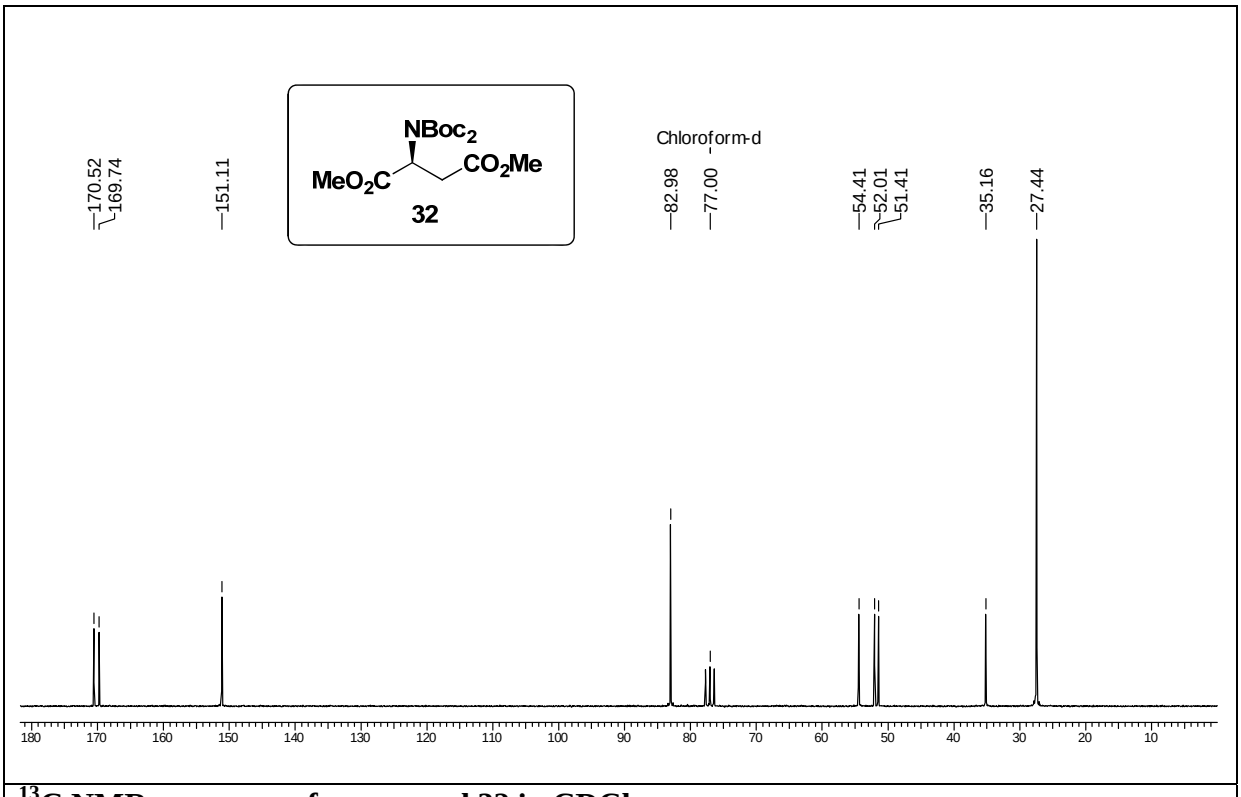
^{1}H NMR spectrum of compound 34 in $CDCl_3$



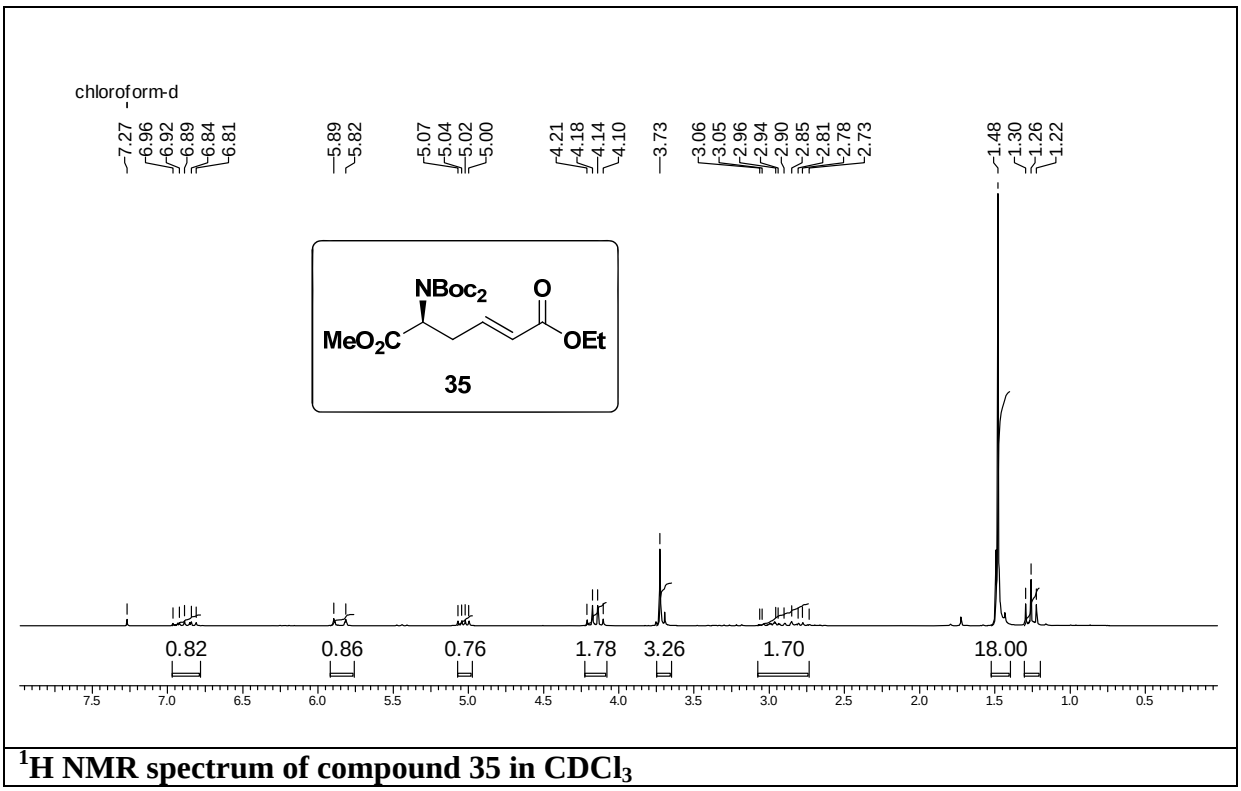
^{13}C NMR spectrum of compound 34 in $CDCl_3$



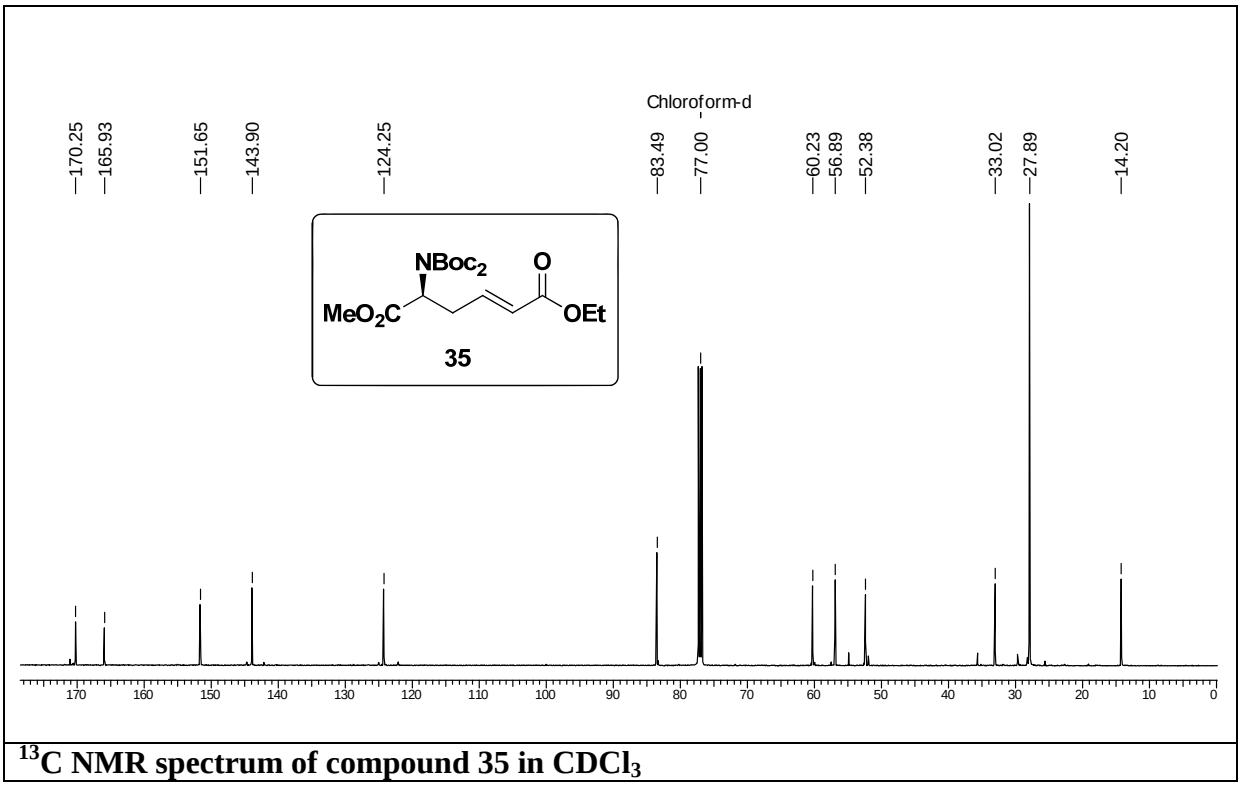
^{1}H NMR spectrum of compound 32 in $CDCl_3$



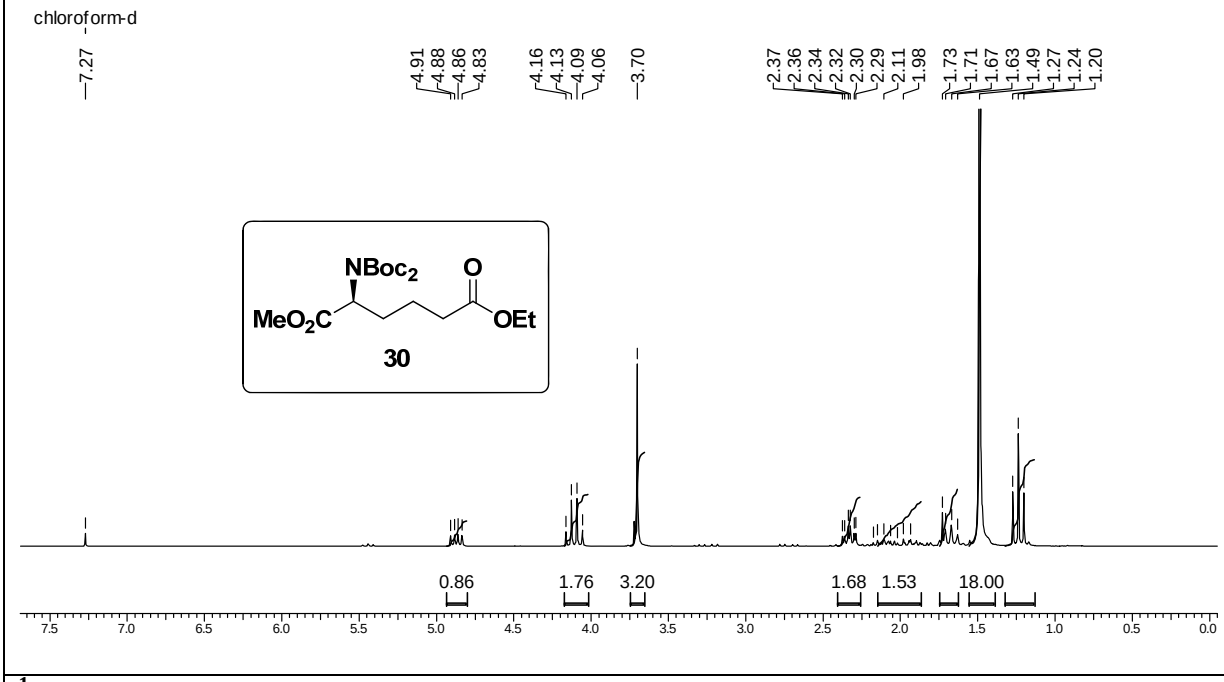
^{13}C NMR spectrum of compound 32 in $CDCl_3$



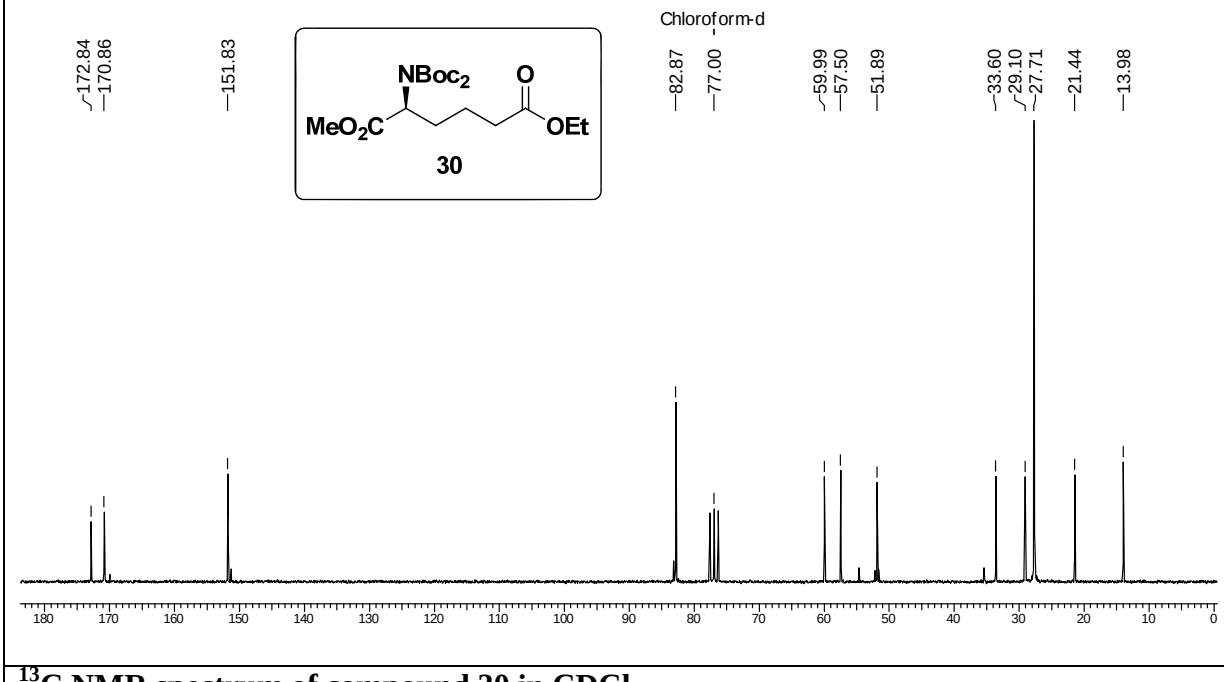
^{1}H NMR spectrum of compound 35 in $CDCl_3$



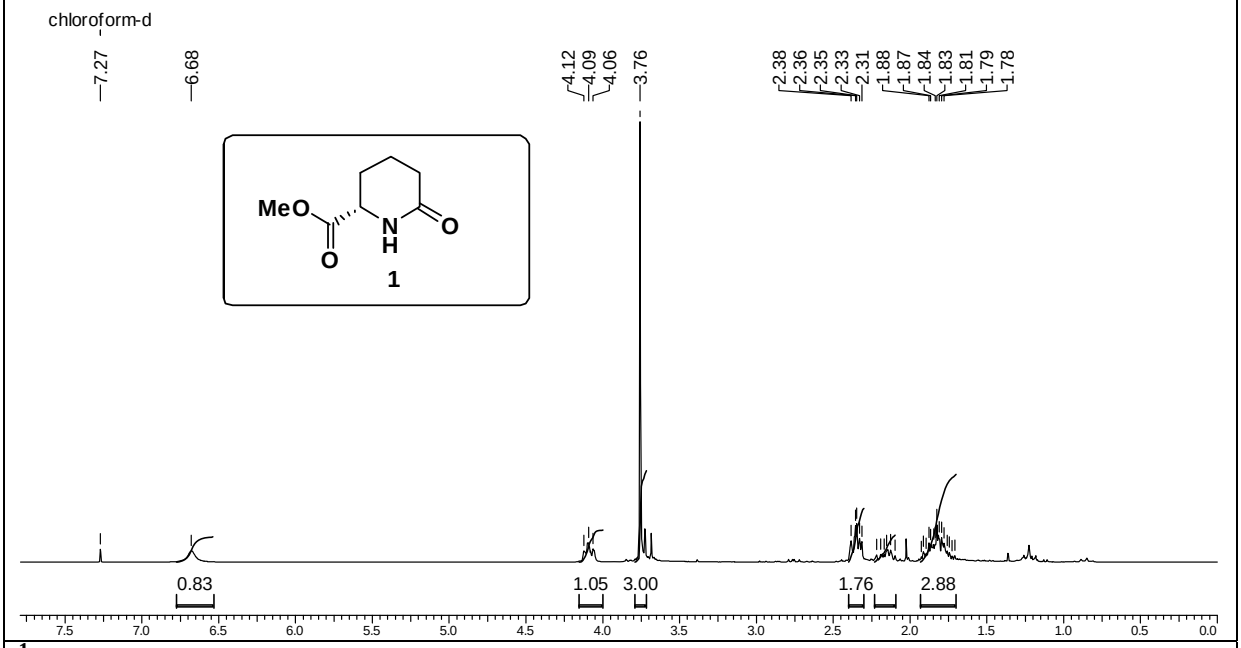
^{13}C NMR spectrum of compound 35 in $CDCl_3$



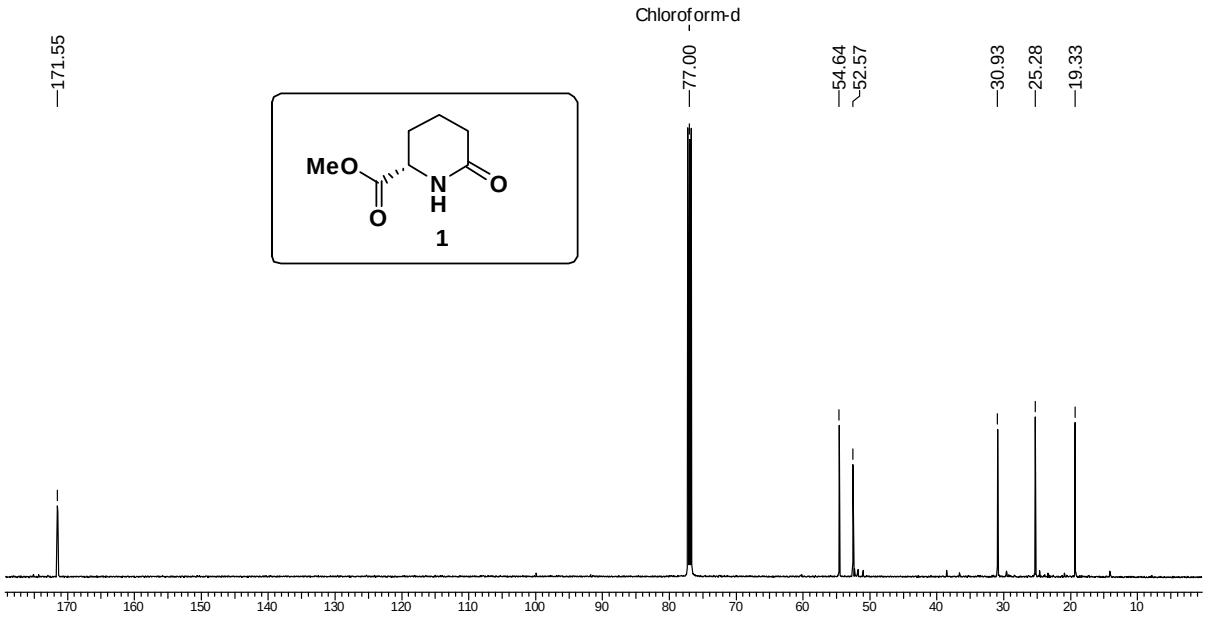
^{1}H NMR spectrum of compound 30 in $CDCl_3$



^{13}C NMR spectrum of compound 30 in $CDCl_3$



^{1}H NMR spectrum of compound 1 in $CDCl_3$



^{13}C NMR spectrum of compound 1 in $CDCl_3$

3.2.8. References

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9. (a) Fanning, K. N.; Sutherland, A. *Tetrahedron Lett.* **2007**, *48*, 8479; (b) Padron, J. M.; Kokotos, G.; Martin, T.; Markidis, T.; Gibbons, W. A.; Martin, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381; (c) Hernandez, J. N.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2003**, *68*, 743.

3.3. SECTION C
A FACILE SYNTHESIS OF 5,6-DIHYDRO-5-HYDROXY-2(1*H*)PYRIDONE

3.3.1. Introduction

The 2(1*H*)pyridone ring system and the corresponding dihydro and tetrahydro derivatives are found abundantly in a wide variety of naturally occurring alkaloids and novel synthetic biologically active molecules.[1]

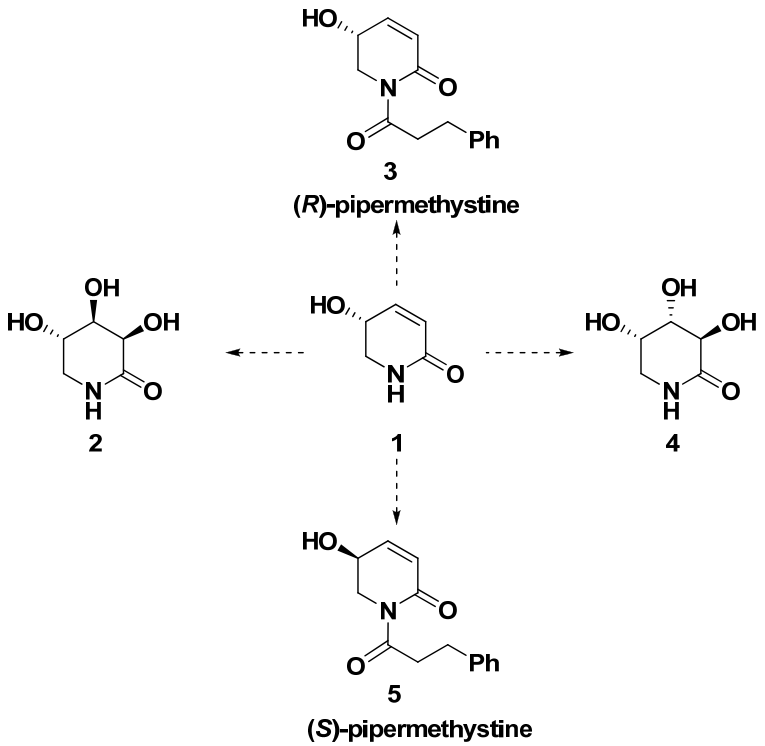


Fig. 1. Structure of 2-pyridone derived alkaloids

Heterocycles incorporating a 2(1*H*)pyridone framework constitute an extensively studied class of compounds owing to their diverse biological activities ranging from anti-HIV, antibacterial and antifungal to free radical scavengers. Several 3-amino-2-pyridinone acetamides act as thrombin inhibitors. Some non-nucleoside-3-aminopyridin-2(1*H*)-ones have been reported to exhibit HIV-1-specific reverse transcriptase inhibitory properties.[2] In addition, dihydro and tetrahydro derivatives of 2(1*H*)-pyridone have been applied as scaffold for the construction of constrained

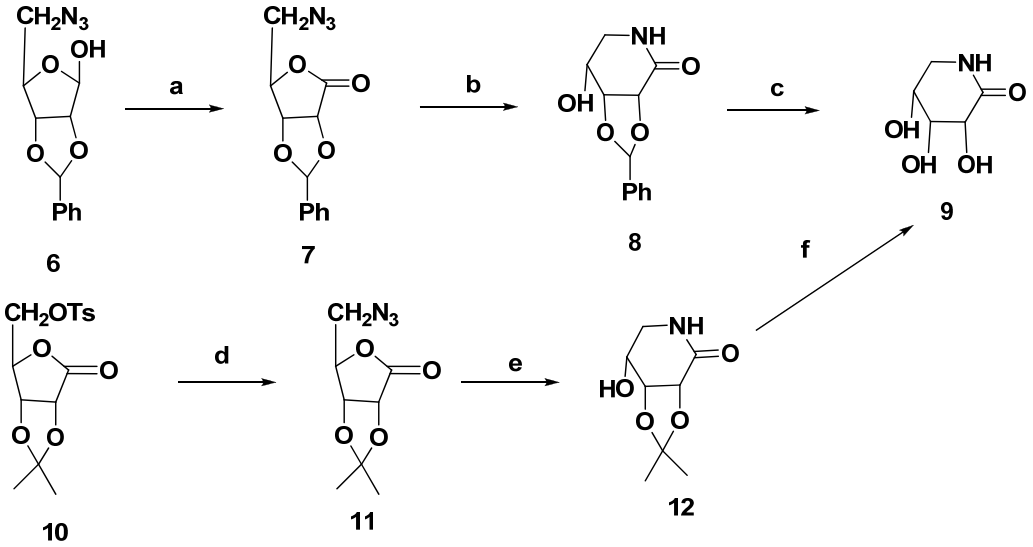
aminoacids,[3] quinoline[4a] and isoquinoline[4b] derivatives, indolizidine,[4c] quinolizidine alkaloids and polyhydroxylated piperidines[5,7] with important pharmaceutical activity.

The title compound has been isolated from whole plant of *Piper sentenense* and is known to exhibit interesting biological activities such as anti HIV, antifungal, antibacterial and cytotoxicity against P-388, H-T-29 or A-549 cell lines in vitro.[6] It is an important building block for the synthesis of (*R*)-pipermethystine[1b] and several other polyhydroxylated pyridones[7] (Fig.1).

3.3.2. Review of Literature

Hannessian *et al.*(1969)[8]

Hannessian *et al*.[8] reported the synthesis of sugar lactam of various ring sizes using azido ribono lactone as the starting material.

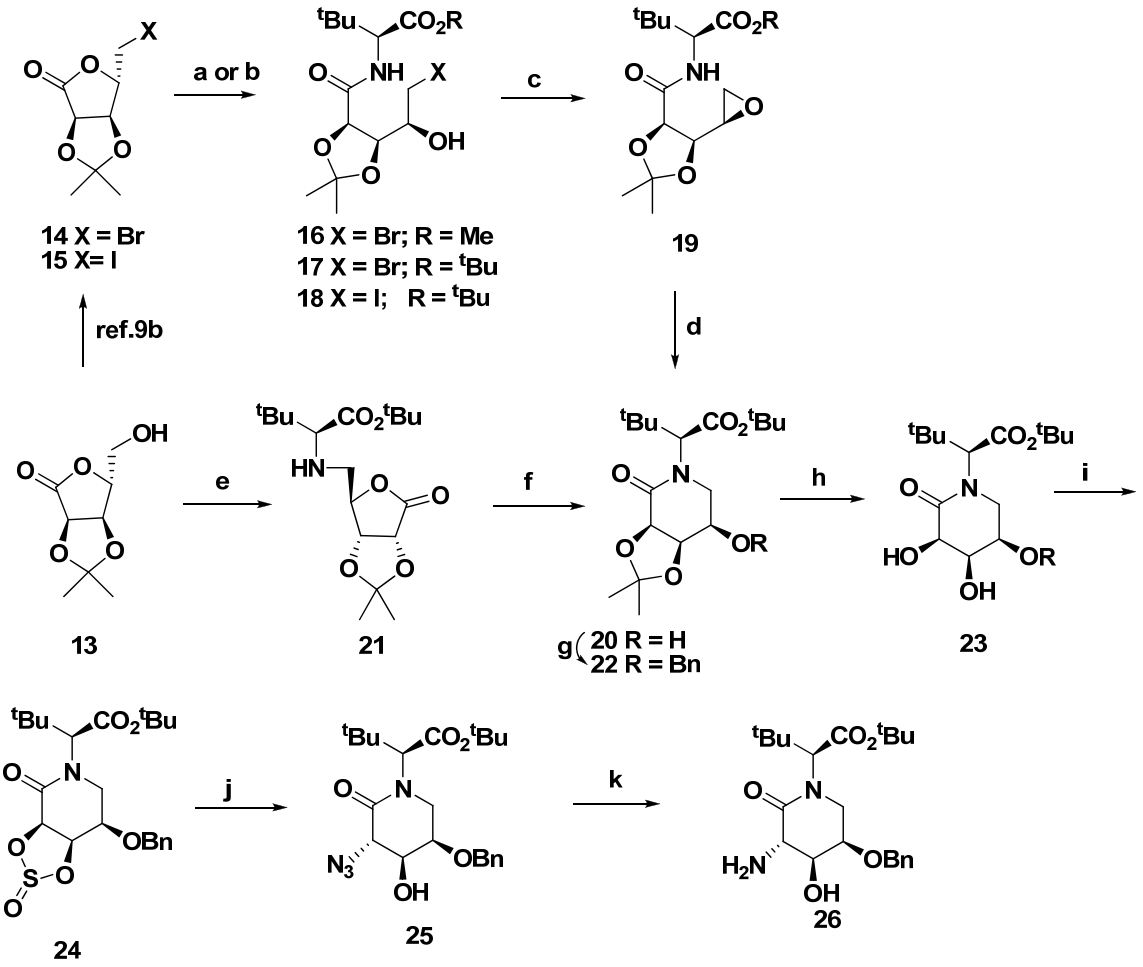


Scheme 1. *Reagents and conditions:* (a) PCC, pyridine, 82%; (b) H_2, Pd/C or PtO_2, EtOAc or MeOH, 1-2 h, 92%; (c) H_2, Pd/C, 95% EtOH containing 5% glacial acetic acid, at 50 psi, 2 h, 80%; (d) NaN_3, DMF, 100 ^oC, 90%; (e) H_2, Pd/C, MeOH, 1 h, 80%; (f) H_2, Pd/C, 95% EtOH in 5% glacial acetic acid, 50 psi, 1 h, 75%.

Thus, oxidation of 5-azido-2,3-*O*-benzylidene-5-deoxy-β-ribofuranose **6** with pyridine-chromium trioxide (PCC) and subsequent hydrogenation of the resulting lactone

afforded 5-amino-2,3-*O*-benzylidene-5-deoxy-$_D$-ribonolactam **8** which on hydrogenolysis over palladium on carbon afforded 5-amino-5-deoxy-D-ribonolactam **9**. Alternatively, sugar lactam **9** can also be prepared from 2,3-*O*-isopropylidene-5-*O*-*p*-tolyl-sulfonyl-D-ribonolactone in three step as shown in Scheme 1.

Diez *et al*. (1990)[9a]

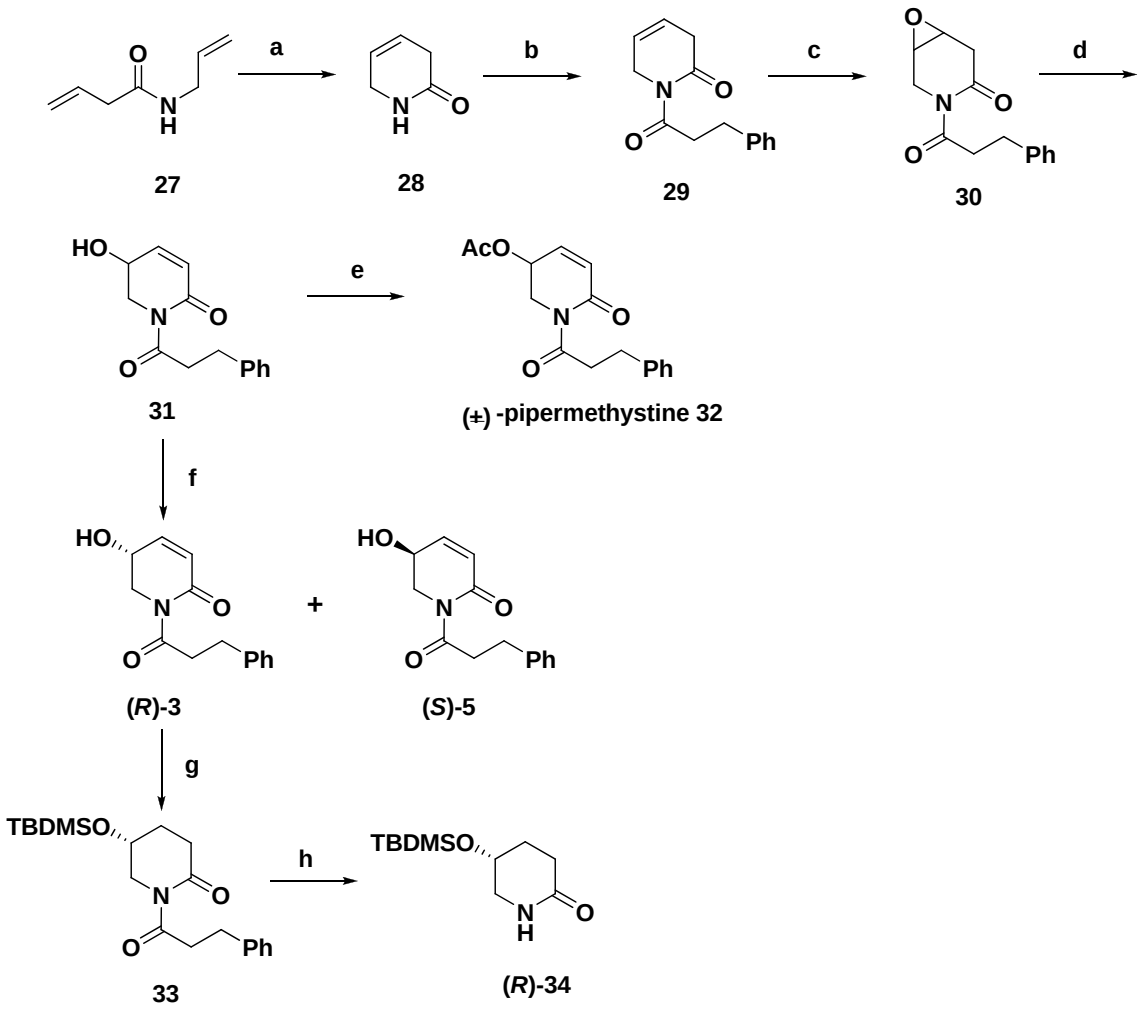


Scheme 2. *Reagents and conditions*: (a) EtN_3,THF; (b) 2,6-lutidine, CH_2CI_2, (8: 95%: 9: 70%); (c) K_2CO_3, CH_3CN, quantitative; (d) NaH, THF; (e) (i) Tf_2O, CH_2CI_2, 2,6-lutidine, 15 min, 0 °C, (ii) Leu-O^{t}Bu, 12 h, rt, 73%; (f) NaOAc, MeOH, Δ, 48 h, 90%; (g) K_2CO_3, BnBr, KI, CH_3CN, Δ, 32 h,70%; (h) PPTs, MeOH, Δ, 24 h; (i) Et_3N, THF, 0 ^oC, $SOCl_2$, 1 h, 2a+2b (1:1); (j) NaN_3, HMPA, rt, 15 h, 90%; (k) H_2, Pd/C/, $PbAcO_2$, EtOH, 24 h.

Diez *et al*.[9a] reported the stereoselective synthesis of 3-amino-2-piperidinone **26** using readily available D-ribonolactone as the source of desired chirality.

Hence, key precursor 2-piperidinone **20** was synthesized through two routes as shown in Scheme 2. Benzylation of the hydroxy group with BnBr in substrate **20** and hydrolysis of the acetal and and subsequent reaction of dihydroxy lactam **23** with $SOCl_2$ in the presence of Et_3N afforded the sulfites **24** which on treatment with NaN_3 in HMPA yielded azide **25** as a single isomer by an *anti* attack of the azide on the 3-position. The azide was then hydrogenated using Lindlar's catalyst to obtain the target Ser-Leu surrogate **26**.

Liebeskind *et al*. (2001)[1b]



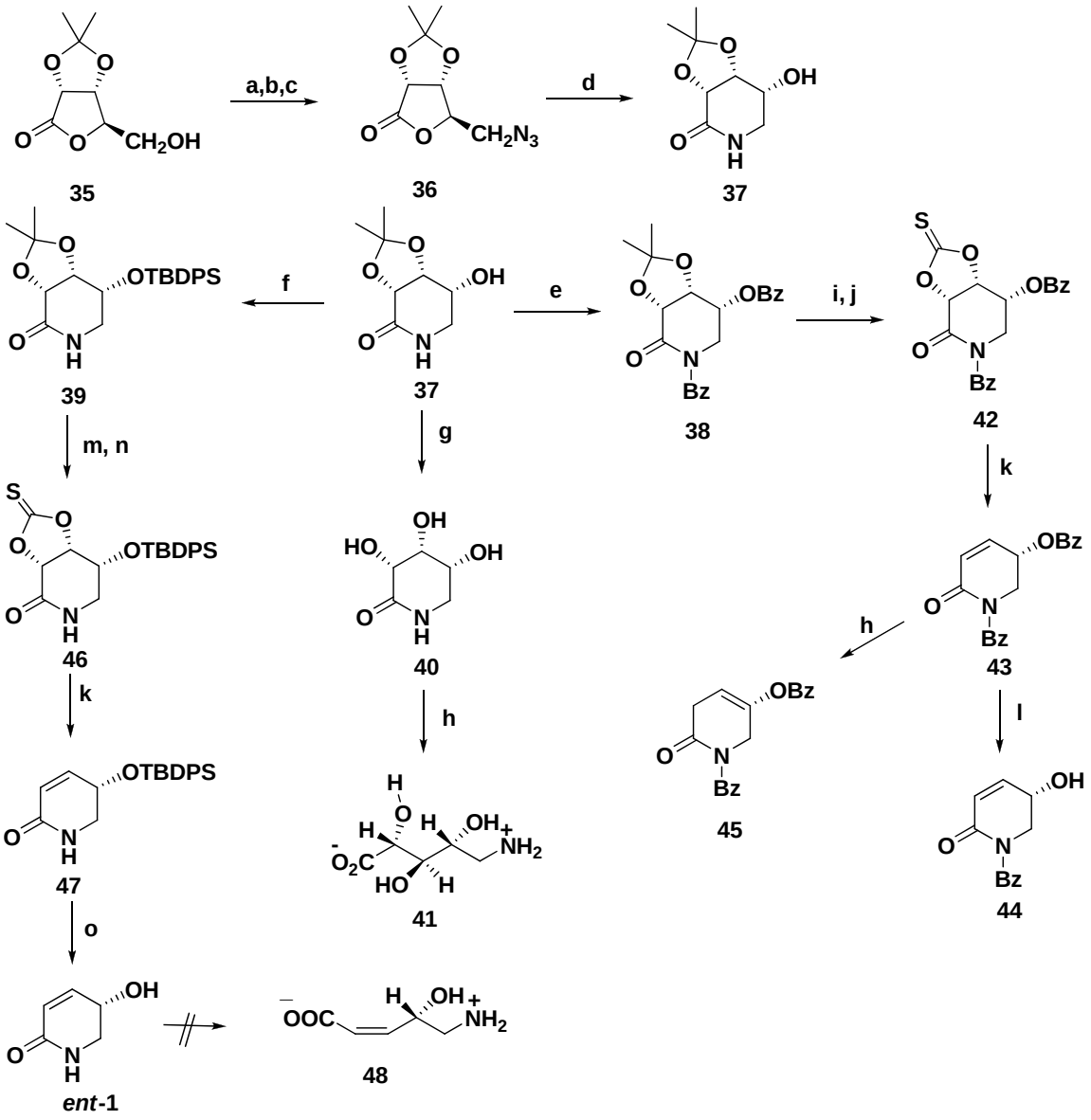
Scheme 3. *Reagents and conditions*: (a) $RuCl_2$ $(PCy_3)_2CHPh$ (4 mol%), CH_2Cl_2, reflux, 12 h, 80%; (b) (i) *n*-BuLi, THF, -78 ^oC; (ii) $Ph(CH_2)COCl$, 94%; (c) *m*-CPBA,

CH_2Cl_2, r.t. 91%; (d) KO^{t}Bu (cat), ^{t}BuOH, 99%; (e) Ac_2O, TMSOTf (cat), CH_2Cl_2, 0 ^oC, 98%; (f) Lipase PPL, 4 d, 47%, (*R*)-7, >99.5 *ee* and (*S*)-2, 48%, 99.5% *ee*.; (g) (i) H_2, Pd/C, EtOAc, r. t.; (ii) TBDMSCl, imidazole, CH_2Cl_2, r.t., 84%; (h) K_2CO_3, MeOH, r.t. 95%.

Liebeskind *et al.*[1b] reported a novel enantiodivergent approach to 5-hydroxy-5,6-dihydro-2(1*H*)-pyridones using a ring closing metathesis and a lipase-mediated kinetic resolution as key steps. The synthesis of this molecule commenced from acyclic *N*-allyl-3-butenamide (**27**). The 3,5-dihydro-2(1*H*)-pyridone **28** was prepared by ring closing metathesis of **27** which on treatment with hydrocinnamoyl chloride afforded the corresponding imide **29**. The allylic alcohol **31** was prepared by epoxidation of **29** with *m*-CPBA followed by treatment of the resulting epoxide **30** with a catalytic amount of KO^{t}Bu. Standard acetylation of **31** was achieved under acidic conditions to give the racemic pipermethystine **32** which was resolved with lipase, PPL to furnish both the isomers of pipermethystin, (*R*)-**3** and (*S*)-**5** with 99.5 *ee* (Scheme 3).

Herdeis *et al.*(1991)[6b]

Herdeis *et al.*[6b] reported the synthesis of homochiral 2-piperidinone using D-Ribonolactone **35** as a starting material (Scheme 4).



Scheme 4. *Reagents and conditions:* (a) Acetone/Nafion NR 50, RT; (b) MsCl, Et_3N; (c) NaN_3, CH_3CN; (d) Pd/C, H_2, MeOH; (e) DMSO, KOH, (plv.), BzCl; (f) TBDPSCl, Imidazole, DMF; (g) $LiBH_4$, 20% H_2O/CH_3CN; (h) $Ba(OH)_2/H_2O$; (i) $AcOH/H_2O$, 80/20; (j) Thiocarnbonyldiimidazole/THF; (k) Raney-Ni, THF, Δ; (l) $BF_3.OEt_2(CH_3)_2S$; (m) $AcOH/H_2O$, 80:20, Δ; (n) Thiophosgene, DMAP, CH_2Cl_2; (o) CF_3COOH/H_2O, 50/50, RT.

3.3.3. Present Work

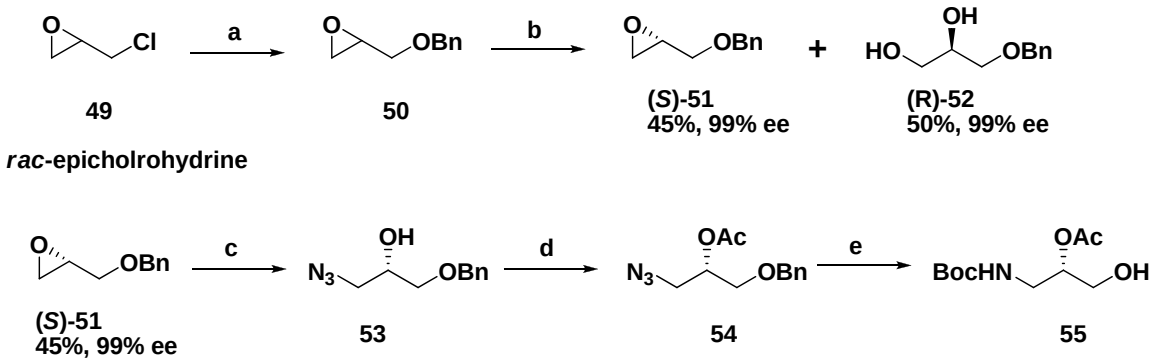
Objective

Despite its apparent simple structure, surprisingly there has been no report on the synthesis of *N*-unsubstituted pyridone **1** except for a sole publication of its *S*-enantiomer which has been synthesized by Herdeis *et al*. starting from D-ribonolactone.[6b] There are few methods available in the literature for preparing the chiral, nonracemic *N*-substituted pyridone derivatives which utilise either achiral or chiral pool starting materials and typically requiring a large number of synthetic steps.[1]

As a part of our research on the asymmetric synthesis of hydroxylated piperidines[10] we became interested in developing a route to 2-pyridone derivatives. Herein we describe our successful endeavors towards a new approach to 5,6-dihydro-5-hydroxy-2(1*H*)-pyridone from L-serine using Horner–Emmons olefination as the key step.

3.3.4. Results and Discussion

As illustrated in Scheme 5, the synthesis of **1** commenced with commercially available *rac*.epichlorohydrin **49** which was transformed into benzyl protected glycidol **50** in presence of benzyl alcohol and sodium hydroxide.



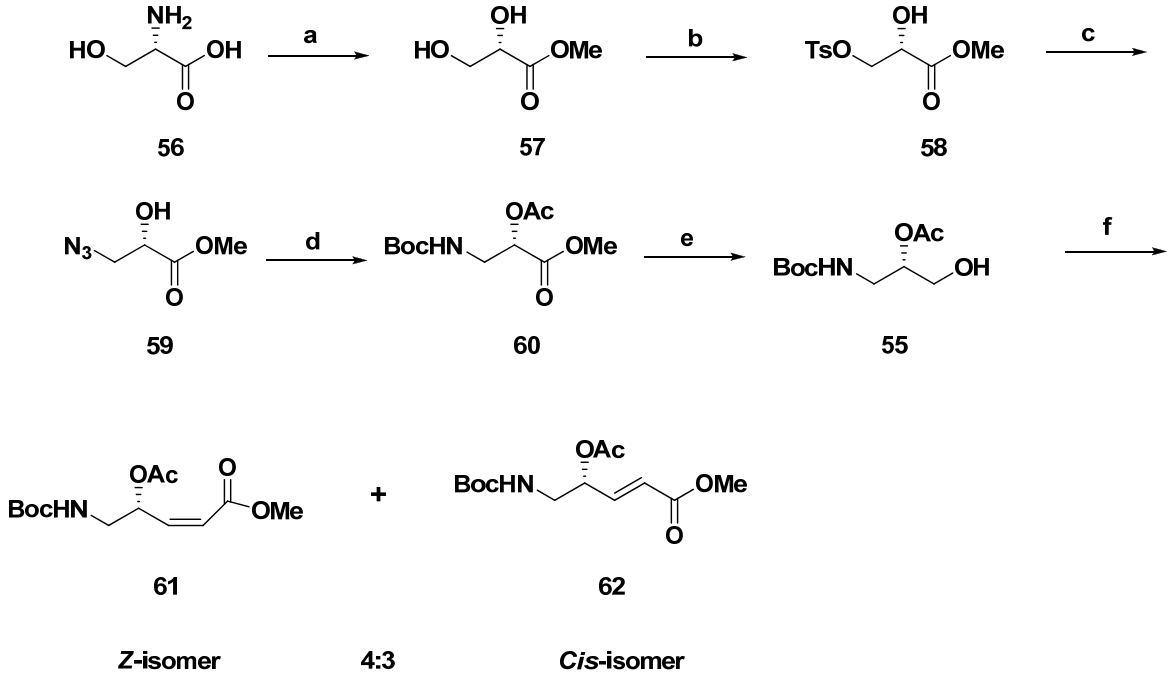
Scheme 5. *Reagents and conditions:* (a) BnOH, Bu_4NHSO_4, aq.NaOH, rt, 3.5 h, 80%; (b) (*S*,*S*)-Salen-OAc catalyst, THF:H_2O (1:1); 0 ^oC - rt, 16 h, 45% (*S*)-epoxide, and

48% (*R*)-diol; (c) NaN_3, NH_4Cl, 15-crown-5, DMF, 55 ^oC, 10 h, 71%; (d) Ac_2O, Et_3N, DMAP, 0 ^oC - rt, 6 h, 71%; (e) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 2 h, 89%.

The spectroscopic data of compound was in accordance with literature precedence.[11] The glycidol **50** was resolved by Jacobsen resolution using (*S,S*)-Co-salen catalyst to give (***S***)-epoxide **51** and (***R***)-diol **52** with 99% ***ee***.[12,13] Regioselective opening of epoxide[14] **51** was carried out using NaN_3 and subsequent acylation of hydroxyl group of **53** gave azido acetate **54** in 71% yield. Appearance of $-CH_3$ protons at δ 2.11 (s, 3H) in the ^1H NMR spectrum and peak at 2105 confirmed the formation of compound **54**. Concomitant benzyl deprotection, reduction of azide to amine and in situ Boc protection afforded the amino alcohol **55** in 89% yield.[15] Appearance of *tert*-butyl protons at δ 1.43 (s, 9H) and disappearance of $-CH_2Ph$ protons at δ 4.55 (s, 2H) and aromatic protons at δ 7.30-7.34 (m, 5H) in the ^1H NMR spectrum confirmed the formation of compound **55**. IR spectrum also showed the absence of azide peak at 2105 and presence of hydroxyl group at 3457. Hence, compound **54** was successfully transformed into the substrate **55**. Since we lose 50% of diol as side product, we thought to prepare the intermediate **6** from L-serine in five steps.

Thus, L-serine 5**6** was initially transformed into the diol ester **57** by the reported procedure.[16] Selective primary hydroxy protection of diol was performed with tosyl chloride in the presence of catalytic amount of dibutyltin oxide[17] followed by the nucleophilic displacement of resulting tosylate with sodium azide to afford compound **59** in 75% yield. Appearance of peak at 2104 in IR spectrum confirmed the formation of compound **59**.The acylation of hydroxyl group followed by azide reduction in the presence of Boc_2O under hydrogenation conditions[15] using $Pd(OH)_2/C$ furnished the desired amino alcohol **60** in 75% yield. Appearance of Boc group at δ 1.48 (s, 9H) and acetyl group at δ 2.10 (s, 3H) confirmed the formation of compound **60**. IR spectrum also showed the absence of N_3 peak at 2104. Subsequent reduction using 2 equiv of DIBAL-H at -78 °C produced alcohol **55** in 70% yield. It may be noted that we did not observe any cleavage of acetoxy group during DIBAL-H reduction. The spectroscopic data of compound **55** was in accordance with the compound derived from (***S***)-glycidol. Oxidation of alcohol **55** with IBX followed by two carbon Wittig olefination in MeOH[18] at 0 °C resulted in a mixture of both *cis*- and *trans*-isomers in the ratio 4:3. The ^1H NMR spectrum of compound **61** and **62** showed the presence of ester proton at δ 3.74 (s, 3H), olefin protons at δ 6.04-6.14 (m, 1H) and at δ 6.23-6.26 (m,1H)

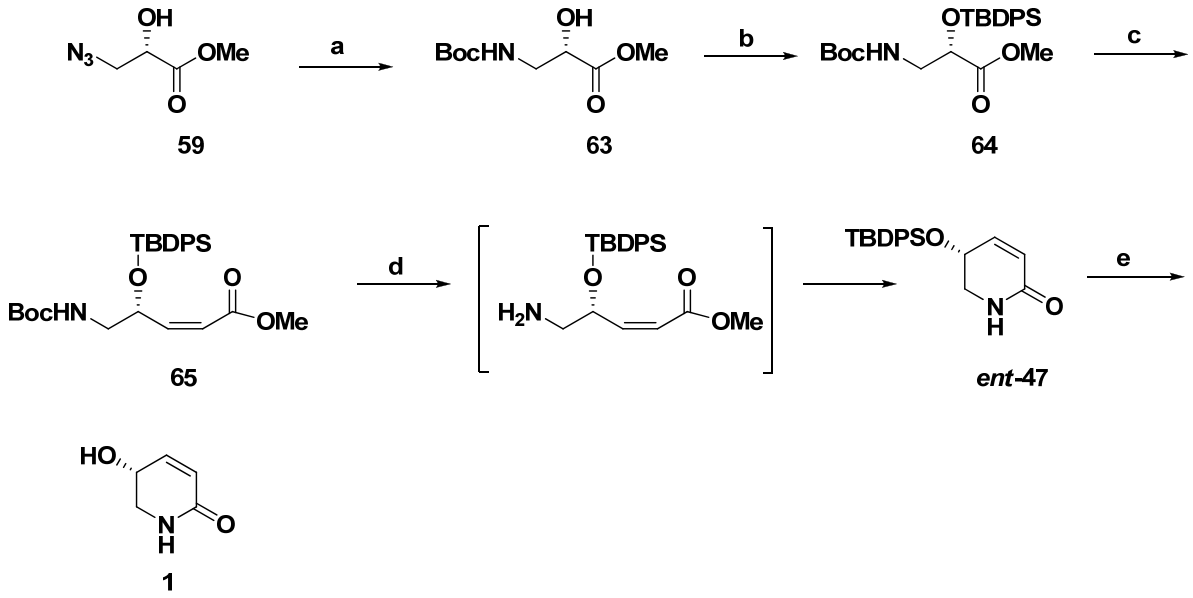
confirmed the formation of *cis* and *trans* olefin.The ratio of desired *cis*-isomer could not be improved even after performing the reaction at lower temperature (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) $NaNO_2$, aq. H_2SO_4, 3 days, 100%; (b) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 ^oC, 2 h, 75%; (c) NaN_3, DMF, 80 ^oC, 10 h, 70%; (d) (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 ^oC - rt, 3 h, 70%; (ii) H_2, $Pd(OH)_2/C$, Boc_2O, MeOH, 5 h, 75%; (e) DIBAL-H, CH_2Cl_2, -78 ^oC, 2 h, 70%; (f) (i) IBX, EtOAc, reflux, 2 h; (ii) $Ph_3P{=}CHCO_2Me$, MeOH, -78 ^oC, 24 h, *cis*- and *trans*-isomer (4:3), 70%.

The poor yield obtained for *cis*-isomer **61** could probably be attributed to the electron-withdrawing effect of acetoxy group. To circumvent the problem of low yield, we thought of masking the hydroxyl group preferably with a bulky protecting group. Towards this end, the azido compound **59** was first reduced to amine in the presence of Boc_2O under hydrogenation conditions using ($Pd(OH)_2/C$) (**59→63**) followed by the hydroxyl group protection with *tert*-butyldiphenylsilyl chloride in the presence of imidazole to furnish compound **64** in 80% yield (Scheme 7). Appearance of Boc at δ1.43 (s, 9H) and *tert*-butyl protons at δ 1.12 (s, 9H) and phenyl protons at δ 7.37-7.45 (m, 6H) and at δ 7.62-7.70 (m, 4H) of TBDPS confirmed the formation of product **64**. IR spectrum also showed the absence of hydroxyl peak at 3019 that confirms the

protection of hydroxy group. The ester group was reduced with 1.2 equiv of DIBAL-H at -78 °C to the corresponding aldehyde and subsequently subjected to two carbon Wittig olefination in MeOH at -78 °C. However, we could not observe much improvement in the ratio of *cis*-isomer. With an aim to prepare the required *cis*-compound, we then employed the new Horner–Emmons reagent, diarylphosphonoacetate for the highly selective synthesis of *Z*-unsaturated ester as reported by Ando.[19] Thus, the aldehyde obtained from **64** was treated with Horner–Emmons reagent, methyl (ditolylphosphono) acetate to produce the *cis*-olefin **65** as the major isomer (98:2) as confirmed from the ^{1}H NMR spectroscopy of the crude product.



Scheme 7. *Reagents and conditions*: (a) H_2, $Pd(OH)_2/C$, Boc_2O, MeOH, 5 h, 75%; (b) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2, 0 ^oC, 4 h, 80%; (c) (i) DIBAL-H, toluene, -78 ^oC, 2 h, (ii) $(CH_3\text{-}C6H_4O)_2\text{-}P(O)CH_2CO_2Me$, NaH, -78 ^oC, THF, 5 h, 72%; (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 5 h, then sat. $NaHCO_3$, 24 h, 55%; (e) TBAF, THF, 0 ^oC - rt, 12 h, 40%.

The *Z*-selectivity of the (diarylphosphono) acetate reagent is a result of kinetic control and can be interpreted by the predominant formation of *erythro* adduct which irreversibly collapses to the *Z*-olefin. This could probably be attributed to the enhanced kinetic selectivity for the *erythro* adduct due to the steric hindrance of the aryl group and also silyloxy group at α-position rather than the electronic effect.[19] Apperance of olefin protons at δ 5.6 (d, J = 11.6 Hz, 1H) and at δ 6.12-6.62 (m, 1H), ester proton at δ

3.55 (s, 3H) in the ^{1}H NMR spectrum and also the presence of peak at 1742 in IR confirmed the formation of compound **65**. The Boc group of **65** was deprotected under standard conditions using TMS-OTf and 2,6-lutidine as base[20] and subsequently neutralized with saturated sodium bicarbonate solution to produce the pyridone derivative *ent*-**47** in 55% yield.[6b] Disappearance of *tert*-butyl protons of Boc at δ 1.42 (s, 9H) and CH_3 proton of ester at δ 3.55 (s, 3H) confirmed the formation of *ent*-47. Finally,TBDPS group was deprotected with tetrabutyl ammonium fluoride to furnish the desired pyridone **1** as an oily compound in 40% yield, $[\alpha]^{25}$ +53.4 (c 0.23, MeOH); [lit.[6a] $[\alpha]^{26}$ +55.7 (c 0.2, MeOH)]. The spectral data of pyridone **1** were in accord with those described in the literature.[6a]

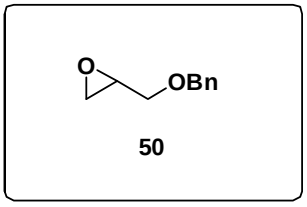
3.3.5. Conclusion

In conclusion, we have achieved a concise synthesis of 5,6-dihydro-5-hydroxy-2(1*H*)pyridone from L-serine in overall 5% yield using Horner-Emmons olefination as the key step.

3.3.6. Experimental Section

General information: As described in section A.

***Rac*-2-(Benzyloxymethyl)oxirane (50).**



50

A mixture of 50% w/w aq. NaOH (32 mL), epichlorohydrin (20 mL) and tetrabutyl ammonium hydrogen sulphate (8.4 g), was vigorously stiired at r.t. in a 250 mL round bottom flask, benzyl alcohol (8.0 g, 0.6 mol) was gradually added during 30 min with cooling in ice, so that tempetrature does not exceed 25 ^{o}C. The progress of reaction was monitored by GLC after 3.5 h, the reaction was complete and reaction mixture was poured on ice/water (150 mL). The aquous phase was extracted with diethyl ether (3 x 50 mL). The organic phase was washed with brine, dried on Na_2SO_4, filtered, evaporated in vacuo, rectified under vaccum to give benzyl protected glycidol **50** in 80% yield.

Yield: 28.7 g (80 %).

B.P. 130-132 ^{o}C,[lit(b.p. 130-133 ^{o}C)].[11]

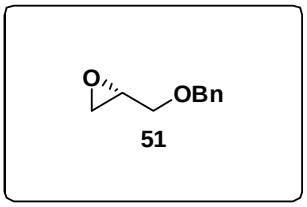
Mol. Formula: $C_{10}H_{12}O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1610, 1115, 875.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.58-2.62 (m, 1H), 2.78 (t, J = 4.2 Hz, 1H), 3.14-3.21 (m, 1H), 3.38-3.46 (m, 1H), 3.72-3.80 (m, 1H), 4.58 (d, J = 3.7 Hz, 2H), 7.31-7.38 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ43.6, 50.3, 70.4, 72.7, 127.2, 127.9, 137.6.

(*S*)-2-(Benzyloxymethyl)oxirane (51).



51

The catalyst ((*S*, *S*)-**1**, 202 mg, 0.30 mmol) was dissolved in *rac*-benzyl glycidyl ether (10.0 g, 70.0 mmol), AcOH (70 micro litre , 1.0 mmol) and 0.7 mL THF and the solution was cooled to 0 ^{o}C and treated with H_2O (495 micro lit, 27.5 mmol) and 0.7 mL THF. After 16 h, (*S*)- benzyl glycidyl ether **51** (3.0 g. 23.3 mmol) was isolated from more polar diol (**52**) by vacuum distillation into a cooled (0 ^{o}C) receiving flask.

Yield: 4.5 g (45%).

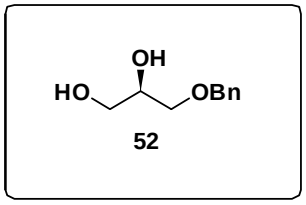
Mol. Formula: $C_{10}H_{12}O_2$

$[\alpha]_D^{25}$: -9.5 (*c* 5.2, MeOH); [lit.$[\alpha]_D^{32}$ +9.8 (*c* 5.13, MeOH) for *ent*-**51**].[12]

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.61-2.65 (m, 1H), 2.81 (t, J = 4.3 Hz, 1H), 3.16-3.24 (m, 1H), 3.40-3.49 (m, 1H), 3.75-3.82 (m, 1H), 4.6 (d, J = 3.7 Hz, 2H), 7.29-7.38 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ43.6, 50.3, 70.4, 72.7, 127.2, 127.9, 137.6.

***(R)*-3-(Benzyloxy)propane-1,2-diol (52).**



Yield: 5.0 g (50%).

Mol. Formula: $C_{10}H_{14}O_3$

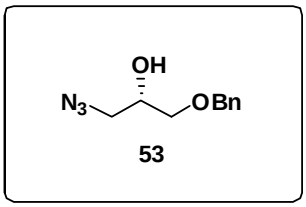
$[\alpha]_D^{25}$: +2.27 (*c* 3.32 EtOH)

IR ($CHCl_3$, cm^{-1}): ν_{max} .3401, 3018, 1634, 1454, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.49-3.72 (m, 7H), 3.84-3.98 (m, 1H), 4.52 (s, 2H), 7.29-7.32-7.39 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ62.5, 70.4, 71.5, 73.4, 127.2, 127.8, 128.2, 138.2.

***(S)*-1-Azido-3-(benzyloxy)propan-2-ol (53).**



To a solution of epoxide **51**(3.0 g, 18.3 mmol) in dry DMF (20 mL) was added portion wise NaN_3 (3.6 g, 54.9 mmol), NH_4Cl (3.0 g, 55.3 mmol) amd 15-crown-5 (0.4 mL, 1.83 mmol) at r.t. under an argon atmosphere and mixture was stirred at 55 ^oC for 10 h. The suspension was diluted with ethyl acetate and added to the water. The aqueous layer was extracted with ethyl acetate. The combined organic layer were washed with brine, dried over MgSO4 and conc in vacuo. The residue was chromatographed by silica gel column (5% EtOAc in pet ether) to give azido alcohol **53**.

Yield: 2.7 g (71%).

Mol. Formula: $C_{10}H_{13}N_3O_2$

$[\alpha]_D^{25}$: +14.26 (*c* 1.2, $CHCl_3$).

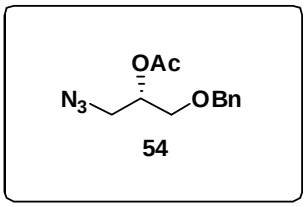
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 2922, 2865, 2102, 1664, 1453, 1280, 1095.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.85 (br s, 1H), 3.35-3.38 (m, 2H), 3.44-3.53 (m, 2H), 3.90-4.02 (m, 1H), 4.56 (s, 2H), 7.32-7.42 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 53.1, 69.2, 71.1, 73.1, 127.5, 128.1, 137.3.

Analysis: Calcd.: C, 57.96; H, 6.32; N, 20.28%; **Found:** C, 58.05; H, 6.44; N, 20.35%.

(*S*)-1-Azido-3-(benzyloxy)propan-2-yl-acetate (54).



54

To a solution of compound **53** (1.0 g, 4.83 mmol) in dry CH_2Cl_2 (15 mL) was added Ac_2O (0.9 mL, 9.7 mmol), Et_3N (0.8 mL, 5.8 mmol) and DMAP (20 mg) at 0 ^oC. The reaction mixture was stirred for 6 h. After completion of the reaction, solvent was evaporated and to this water was added and aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer were washed with brine, dried over $MgSO_4$ and conc. in vacuo and crude residue was purified by silica gel column chromatography using ethylacetate and pet ether (0.5:9.5) as eluent to give the desired compound **54**.

Yield: 0.85 g (71%).

Mol. Formula: $C_{12}H_{15}N_3O_3$

$[\alpha]_D^{25}$: +13.93 (*c* 1.04, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2105, 1737, 1582, 1454, 1278, 1216.

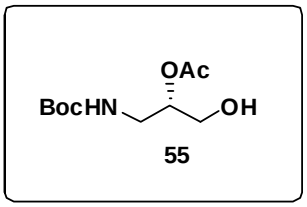
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11 (s, 3H), 3.52 (d, *J* = 5.2 Hz, 2H), 3.61 (d, *J* =5.1 Hz, 2H), 4.55 (s, 2H), 5.08-5.19 (m, 1H), 7.30-7.40 (m,5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 50.5, 67.9, 70.8, 72.9, 127.2, 128.0, 137.3, 169.6.

Mass [LCMS]: 270.87 (M^+ + Na), 265.94, 248.98.

Analysis: Calcd.: C, 57.82; H, 6.07; N, 16.86%; **Found:** C, 57.89; H, 6.15, N, 16.78%.

(*S*)-1-(*tert*-Butoxycarbonylamino)-3-hydroxypropan-2-yl-acetate (55).



55

To a solution of compound **54** (0.2 g, 0.8 mmol) in EtOAc (10 mL) was added 20% $Pd(OH)_2/C$ (15 mg) and Boc_2O (0.2 g, 0.9 mmol) and resulting solution was stirred under hydrogen atmosphere for 2 h at r.t. and then reaction mixture was filtered through celite pad to remove the catalyst and filtrate was concentrated in vacuo. Silica gel column chromatography of crude product using EtOAc/Pet ether (3:7) as eluent to give **55** as colorless liquid.

Yield: 0.17g (89%).

Mol. Formula: $C_{10}H_{19}NO_5$

$[\alpha]_D^{25}$: -19.60 (*c* 1.0, $CHCl_3$).

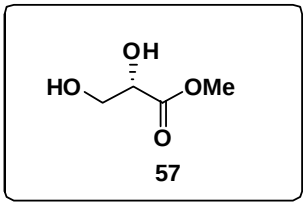
IR ($CHCl_3$, cm^{-1}): ν_{max} 3457, 3019, 1731.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.08 (s, 3H), 3.11-3.21 (m,1H), 3.29-3.42 (m, 2H), 3.63 (brs, 1H), 3.87-3.97 (m, 1H), 4.03-4.11 (m, 1H), 5.08 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ20.8, 28.0, 39.6, 60.5, 73.3, 79.8, 157.0, 170.6.

Analysis: Calcd.: C, 51.49; H, 8.21; N, 6.00%; **Found:** C, 51.58; H, 8.34; N, 6.09%.

(*S*)-Methyl-2,3-dihydroxypropanoate (57).



57

The compound **57** was prepared from commercially available L-serine using known procedure.[16]

Yield: 5.4 g (92%).

Mol. Formula: $C_4H_8O_4$

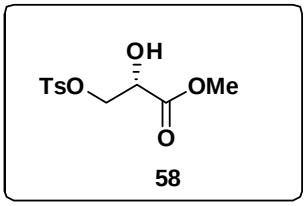
$[\alpha]_D^{25}$: -11.5 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3457, 3019, 1731.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (brs, 2H), 3.80 (s, 3H), 3.84-3.88 (m, 2H), 4.29 (t, J = 3.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.0, 63.6, 71.6, 173.0.

(*S*)-Methyl-2-hydroxy-3-(tosyloxy)propanoate (58).



58

To a solution of diol ester **57** (3.0 g, 25.0 mmol) in CH_2Cl_2 (20 mL) were added Bu_2SnO (0.124 g, 0.5 mmol), *p*-toluenesulphonyl chloride (4.77 g, 25.0 mmol) and Et_3N (4.21 mL, 30.0 mmol) was added at 0 ^oC. The reaction mixture was stirred until TLC indicated complete consumption of starting material. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 25 mL) and combined organic layer was washed sequentially with water, brine, dried (Na_2SO_4), filtered and filtrate was concentrated in vacuo. The residue was crystallised to afford the desired mono tosylate **58**.

Yield: 5.14 g (75%).

Mol. Formula: $C_{11}H_{14}O_6S$

$[\alpha]_D^{25}$: -6.41 (*c* 1.0, $CHCl_3$).

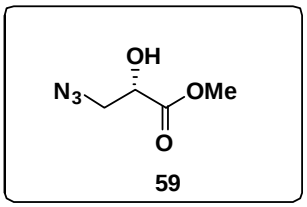
IR ($CHCl_3$, cm^{-1}): ν_{max} 3507, 1748, 1598, 1363, 1177.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.0 (s, 1H), 3.74 (s, 3H), 4.27-4.38 (m, 3H), 7.32-7.36 (m, 2H), 7.75-7.79 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0, 52.3, 68.6, 70.5, 127.4, 129.5, 131.7, 144.8, 170.8.

Analysis: Calcd.: C, 48.17; H, 5.14%; **Found:** C, 48.30; H, 5.28%.

(*S*)-Methyl-3-azido-2-hydroxypropanoate (59).



59

To a solution of tosylate **58** (3.6 g, 13.14 mmol) in dry DMF (25.0 mL) was added portion wise NaN_3 (8.53 g, 131.4 mmol), at r.t. under an argon atmosphere and mixture was stirred at 80 ^oC for 10 h. The suspension was diluted with ethyl acetate and added to the water. The aqueous layer was extracted with ethyl acetate. The combined organic layer were washed with brine, dried over MgSO4 and conc. in vacuo. The residue was chromatographed by silica gel column (15% EtOAc in pet ether) to give azido alcohol **59**.

Yield: 1.34 g (70%).

Mol. Formula: $C_4H_7N_3O_3$

$[\alpha]_D^{25}$: -9.23 (*c* 1.03, $CHCl_3$).

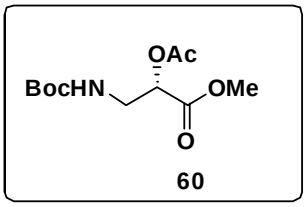
IR ($CHCl_3$, cm^{-1}): ν_{max} 3404, 2104, 1746.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.19 (brs, 1H), 3.47-3.71 (m, 1H), 3.85 (s, 3H), 3.93-3.95 (m, 1H), 4.12 (t, J = 4.3 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 53.3, 77.6, 169.8.

Analysis: Calcd.: C, 33.11; H, 4.86; N, 28.96%; **Found:** C, 33.20; H, 4.94; N, 28.90%.

(*S*)-Methyl-2-acetoxy-3-(*tert*-butoxycarbonylamino)propanoate (60).



60

To a solution of compound **59** (0.5 g, 3.5 mmol) in dry CH_2Cl_2 (10 mL) was added Ac_2O (0.7 mL, 7.0 mmol), Et_3N (0.6 mL, 4.2 mmol) and DMAP (15 mg) at 0 ^oC. The reaction mixture was stirred at for 6 h. After completion of the reaction, solvent was evaporated and to this water was added and aquous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer were washed with brine, dried over $MgSO_4$ and conc. in vacuo to give the crude acylated compound as yellow color oil which was used further without purification.

The crude azido compound (0.4 5 g, 2.41 mmol) was dissolved in EtOAc (5 mL) and to this was added 20% $Pd(OH)_2/C$ (40 mg) and Boc_2O (0.6 g, 2.65 mmol) and resulting solution was stirred under hydrogen atmoshphere for 5 h at r.t. until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through celite pad to remove the catalyst and filtrate was concentrated in vacuo. Silica gel column chromatography of crude product using EtOAc/Pet ether (1:9) as eluent to give **60** as a yellow color oil.

Yield: 0.61 g (75%). (after two step)

Mol. Formula: $C_{11}H_{19}NO_6$

$[\alpha]_D^{25}$: -12.23 (*c* 1.02, $CHCl_3$).

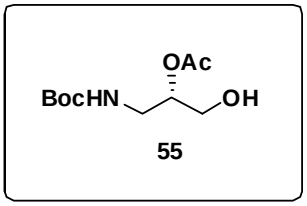
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1742, 1696.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.10 (s, 3H), 3.43-3.52 (m, 1H), 3.65 (s, 3H), 3.69-3.75 (m, 1H), 4.05 (t, J = 4.3 Hz, 1H), 5.02 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 28.2, 40.4, 52.3, 80.2, 82.5, 156.3, 170.2, 171.1.

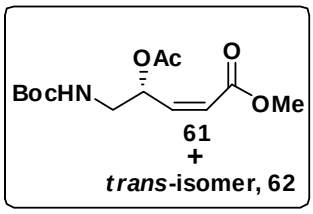
Analysis: Calcd.: C, 50.57; H, 7.33; N, 5.36%; **Found:** C, 50.68; H, 7.48; N, 5.29%.

(*S*)-1-(*tert*-Butoxycarbonylamino)-3-hydroxypropan-2-yl-acetate (55).



To a solution of the compound **60** (1.0 g, 3.83 mmol) in dry CH_2Cl_2 (10.0 mL) was added DIBAL-H (1.92 M, 4.0 mL,7.66 mmol) at -78 ^oC and reaction mixture was stirred for 2 h. After completion, the reaction mixture was quenched with H_2O (0.2 mL) at -78 ^oC and allowed to warm at rt for 1 h and then diluted with CH_2Cl_2, filtered through celite pad and filtrate was concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/pet ether (2:8) as eluent to give compound **55** in 70 % yield as yellow color oil. The spectroscopic data obtained are the same as described earlier.

(*R*,*Z*)-Methyl-4-acetoxy-5-(*tert*-butoxycarbonylamino)-pent-2-enoate (61&62).



2-Iodobenzoic acid IBX (0.55 g, 1.95 mmol) was added to a solution of alcohol **55** (0.3 g, 1.3 mmol) in DMSO (10 mL). After stirring at r.t. for 2 h, the reaction mxture was diluted with water, filtered and extracted with Et_2O. The combined organic layer was washed with sat. $NaHCO_3$, brine and dried (Na_2SO_4) and evaporated in vacuo. The crude aldehyde was pure enough to be used in a next step without further purification.

To a solution of aldehyde (0.28 g) in dry MeOH (20 ml) was added Wittig ylide and stirred for 24 h at -78 ^oC. After completion of the reaction solvent was evaporated in vacuo to give *cis*- and *trans*-isomer in ratio of 4:3.

Mol. Formula: $C_{13}H_{21}NO_6$

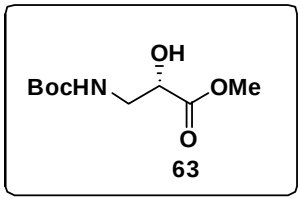
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1731, 1646.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.07 (s, 3H), 3.39-3.48 (m, 2H), 3.74 (s, 3H), 4.83 (brs, 1H), 5.88-5.97 (m, 1H), 6.05-6.14 (m, 1H), 6.23-6.26 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 28.1, 43.0, 51.5, 70.7, 71.6, 79.2, 79.6, 121.6, 122.4, 142.6, 144.6, 155.6, 155.7, 165.6, 165.9, 169.6, 170.0.

Analysis: Calcd.: C, 51.49; H, 8.21; N, 4.88%; **Found:** C, 51.58; H, 8.34; N, 4.81%.

(*S*)-Methyl-3-(*tert*-butoxycarbonylamino)-2-hydroxypropanoate (63).



63

To a solution of compound **59** (1.3 g, 8.97 mmol) in EtOAc (20 mL) was added 20% $Pd(OH)_2/C$ (50 mg) and Boc_2O (2.15 g, 9.86 mmol) and resulting solution was stirred under hydrogen atmosphere for 5 h at r.t. until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through celite pad to remove the catalyst and filtrate was concentrated in vacuo. Silica gel column chromatography of crude product using EtOAc/pet ether (1:9) as eluent to gave **63** as colorless liquid.

Yield: 1.47 g (75%).

Mol. Formula: $C_9H_{17}NO_5$

$[\alpha]_D^{25}$: +20.39 (*c* 1.0, $CHCl_3$).

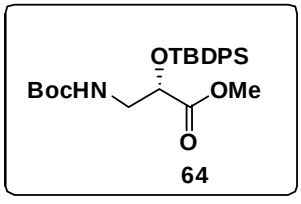
IR ($CHCl_3$, cm^{-1}): ν_{max} 3452, 3019, 1738, 1509.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 3.45-3.50 (m, 2H), 3.77 (s, 3H), 4.24-4.28 (m, 1H), 5.07 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1, 43.9, 52.3, 70.3, 79.4, 156.3, 173.4.

Analysis: Calcd.: C, 49.31; H, 7.82; N, 6.39%; **Found:** C, 49.24; H, 7.91; N, 6.45%.

(*S*)-Methyl-2,2,10,10-tetramethyl-8-oxo-3,3-diphenyl-4,9-dioxa-7-aza-3-silaundecane-5 carboxylate (64).



64

To a solution of the amino alcohol **63** (1.14 g, 5.21 mmol) and imidazole (0.53 g, 7.82 mmol), in dry CH_2Cl_2 (10 mL), TBDPSCl (1.5 mL, 5.73 mmol) was added at 0 ^oC.

After 4 h the reaction mixture was quenched with water and extracted with CH_2Cl_2 (10 x 3 mL). The solvent was evaporated in vacuo and crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **64** as a yellow color oil.
Yield: 1.9 g (80%).

Mol. Formula: $C_{25}H_{35}NO_5Si$

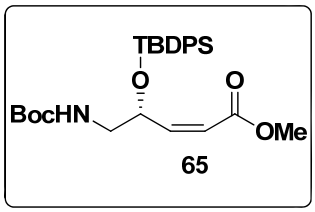
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1742, 1696.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (s, 9H), 1.43 (s, 9H), 3.41-3.49 (m, 2H), 3.50 (s, 3H), 4.28 (t, J = 4.7 Hz, 1H), 4.86 (brs, 1H), 7.37-7.45 (m, 6H), 7.62-7.70 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 28.2, 44.4, 51.5, 71.7, 79.2, 127.5, 127.6, 129.8, 132.5, 132.7, 135.6, 135.8, 155.5, 171.5.

Analysis: Calcd.: C, 65.61; H, 7.71; N, 3.06%; **Found:** C, 50.70; H, 7.84; N, 3.15%.

(*R,Z*)-Methyl-5-(*tert*-butoxycarbonylamino)-4-(*tert*-butyldiphenylsilyloxy)pent-2-enoate (65).



65

To a solution of ester **64** (1.0 g, 2.19 mmol) in dry toluene (20.0 mL) was added dropwise DIBAL (1.3 mL, 1.92 M in toluene, 2.41 mmol) at -78 ^oC and reaction mixture was stirred for 2 h at -78 ^oC and then MeOH and sat.phosphorus buffur (pH = 7.0, 25 ml) were added. After the reaction mixture has been stirred for 30 min., the mixture was treated with brine and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give a crude aldehyde which was used for next step without purification.

A solution of methyl (di-*o*-tolylphosphono) acetate (0.54 g, 2.32 mmol) in THF (25 mL) was treated with NaH (0.070 g, 2.74 mmol) at -78 ^oC for 15 min. To the above reaction mixture was added a freshly prepared aldehyde (0.90 g, 2.11 mmol) in THF (10 mL) and the resulting mixture was stirred at -78 ^oC for 5 h. After TLC showed

completion of the starting material, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 x 20 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **65** as a colourless oil.

Yield: 0.72 g (72%).

Mol. Formula: $C_{27}H_{37}NO_5Si$

$[\alpha]_D^{25}$: +1.4 (*c* 1.0, $CHCl_3$).

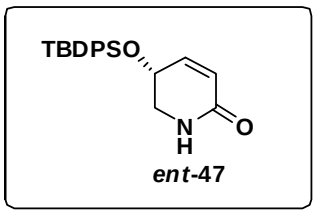
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1742, 1696.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.42 (s, 9H), 3.30-3.47 (m, 2H), 3.55 (s, 3H), 4.85 (br s, 1H), 5.32-5.41 (m, 1H), 5.6 (d, *J* =11.6 Hz, 1H), 6.12-6.62 (m, 1H), 7.31-7.45 (m, 6H), 7.60-7.70 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 28.2, 45.9, 51.6, 71.7, 79.2, 119.3, 127.4, 127.5, 127.6, 127.7, 129.7, 129.8, 129.9, 132.6, 132.8, 133.3, 133.4, 135.6, 135.6, 135.7, 135.8, 149.5, 155.7, 165.7

Analysis: Calcd.: C, 67.05; H, 7.71; N, 2.90%; **Found:** C, 67.18; H, 7.82; N, 2.83%.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-5,6-dihydropyridin-2(1*H*)-one (*ent*-47).



ent-47

To a solution of the olefinic compound **65** (0.1 g, 0.21 mmol) and 2,6-lutidine (0.05 mL, 0.41 mmol), in dry CH_2Cl_2 (5.0 mL) was added TMSOTf (0.042 mL, 0.32 mmol) dropwise at 0 ^oC. After stirring for 5 h, the reaction mixture was quenched by addition of sat. $NaHCO_3$ (10 mL) solution and stirred the reaction for additional 24 h. After completion, the reaction mixture was extracted with CH_2Cl_2 (10 x 3 mL) and combined organic layer were separated and washed with brine, dried over Na_2SO_4. After evaporation of the solvent crude residue was purified by silica gel column

chromatography using EtOAc/pether (1:9) as eluent to give the pyridone compound *ent*-**47** as pale yellow color oil.

Yield: 40 mg (55%).

Mol. Formula: $C_{21}H_{25}NO_2Si$

$[\alpha]_D^{25}$: -62.4 (*c* 1.9, $CHCl_3$); [lit.$[\alpha]^{20}_D$: +62 (c 1.9, $CHCl_3$)].[6b]

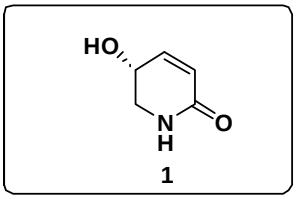
IR ($CHCl_3$, cm^{-1}): ν_{max} 3290,1728,1628, 1614.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 3.32 (dd, J = 12.5, J = 2.7 Hz, 1H), 3.42 (dd, J = 12.6 Hz, J = 2.2 Hz, 1H), 4.43-4.50 (m, 1H), 5.83 (d, J = 10 Hz, 1H), 6.43 (dd, J = 9.9 Hz, J = 3.2 Hz, 1H), 6.20 (s, -NH, 1H), 7.38-7.48 (m, 6H), 7.64-7.67 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 28.2, 45.9, 51.6, 71.7, 79.2, 119.3, 127.4, 127.5, 127.6, 127.7, 129.7, 129.8, 129.9, 132.6, 132.8, 133.3, 133.4, 135.6, 135.6, 135.7, 135.8, 149.5, 155.7, 165.7.

Analysis: Calcd.: C, 71.75; H, 7.17; N, 3.98%; **Found:** C, 71.60; H, 7.24; N, 3.91%.

(*R*)-5-Hydroxy-5,6-dihydropyridin-2(1*H*)-one (1).



1

To a solution of ***ent*-47** (40 mg, 0.11mmol) in dry THF was added 1M TBAF(0.1 mL, 0.17 mmol) at 0 ^oC and reaction mixture was stirred at r.t. for 12 h. Afterwards solvent was evaporated in vacuo and crude residue was purified by silica gel colum chromatography using EtOAc/pet ether (6:4) as eluent to give **1** as an oily compound.

Yield: 5.2 mg (40%).

Mol. Formula: $C_5H_7NO_2$

$[\alpha]_D^{25}$: +53.4 (c 0.23, MeOH); [lit. $[\alpha]^{26}$ +55.7 (*c* 0.2, MeOH)].[6a]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3290, 1740, 1682.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (brs, 1H), 4.08 (d, *J* = 6.03 Hz, 1H), 4.19 (d, *J* = 6.0 Hz, 1H), 5.74-5.76 (m, 1H), 5.81-5.86 (m, 1H), 6.89 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 72.2, 128.5, 132.2, 159.3.

3.3.7. Spectra

1] ^{1}H NMR Spectrum of **51**

2] ^{13}C NMR Spectrum of **51**

3] ^{1}H NMR Spectrum of **53**

4] ^{13}C NMR Spectrum of **53**

5] ^{1} H NMR Spectrum of **54**

6] ^{13}C NMR Spectrum of **54**

7] ^{1}H NMR spectrum of **55**

8] ^{13}C NMR Spectrum of **55**

9] ^{1}H NMR Spectrum of **61 & 62**

10] ^{13}C NMR Spectrum of **61 & 62**

11] ^{1}H NMR Spectrum of **57**

12] ^{13}C NMR Spectrum of **57**

13] ^{1}H NMR Spectrum of **58**

14] ^{13}C NMR Spectrum of **58**

15] ^{1}H NMR Spectrum of **59**

16] ^{13}C NMR Spectrum of **59**

17] ^{1}H NMR Spectrum of **63**

18] ^{13}C NMR Spectrum of **63**

19] ^{1}H NMR Spectrum of **64**

20] ^{13}C NMR Spectrum of **64**

21] ^{1}H NMR Spectrum of **65**

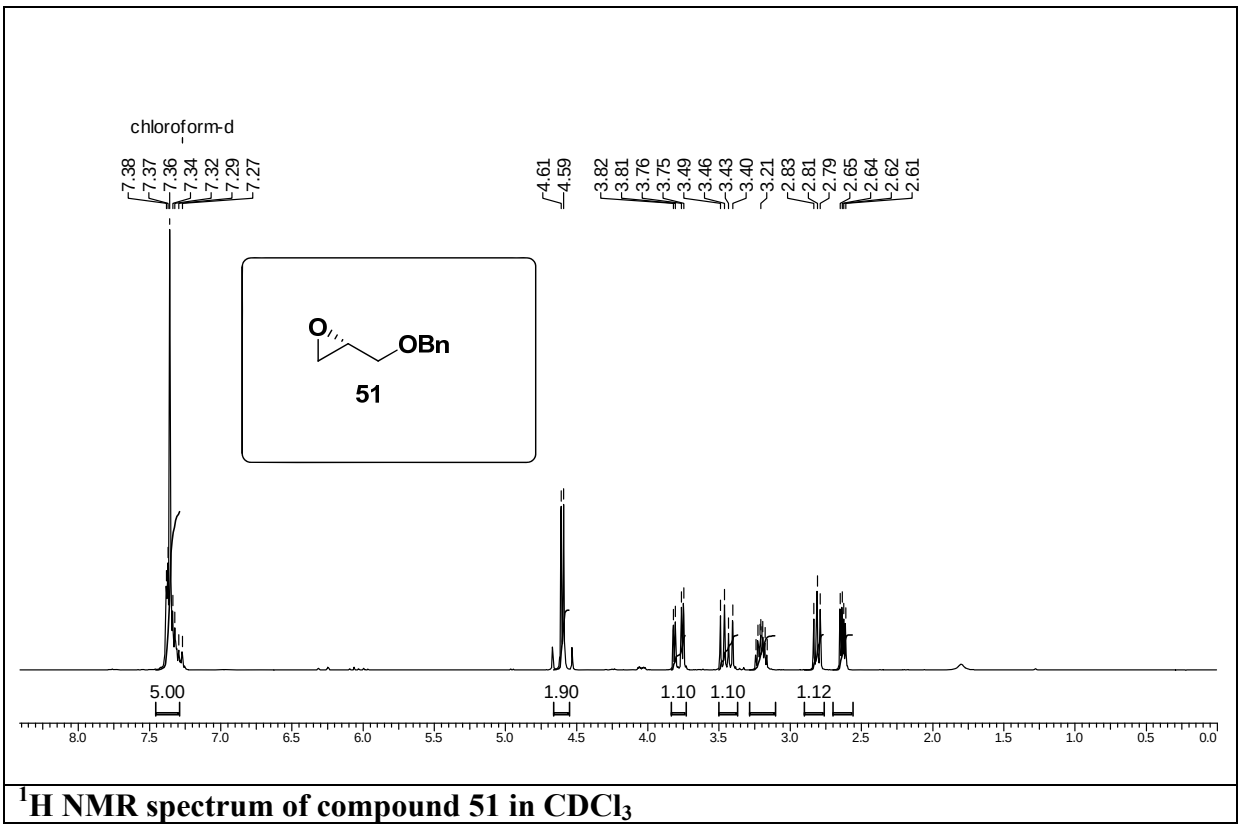
22] ^{13}C NMR Spectrum of **65**

23] ^{1}H NMR spectrum of *ent*-**47**

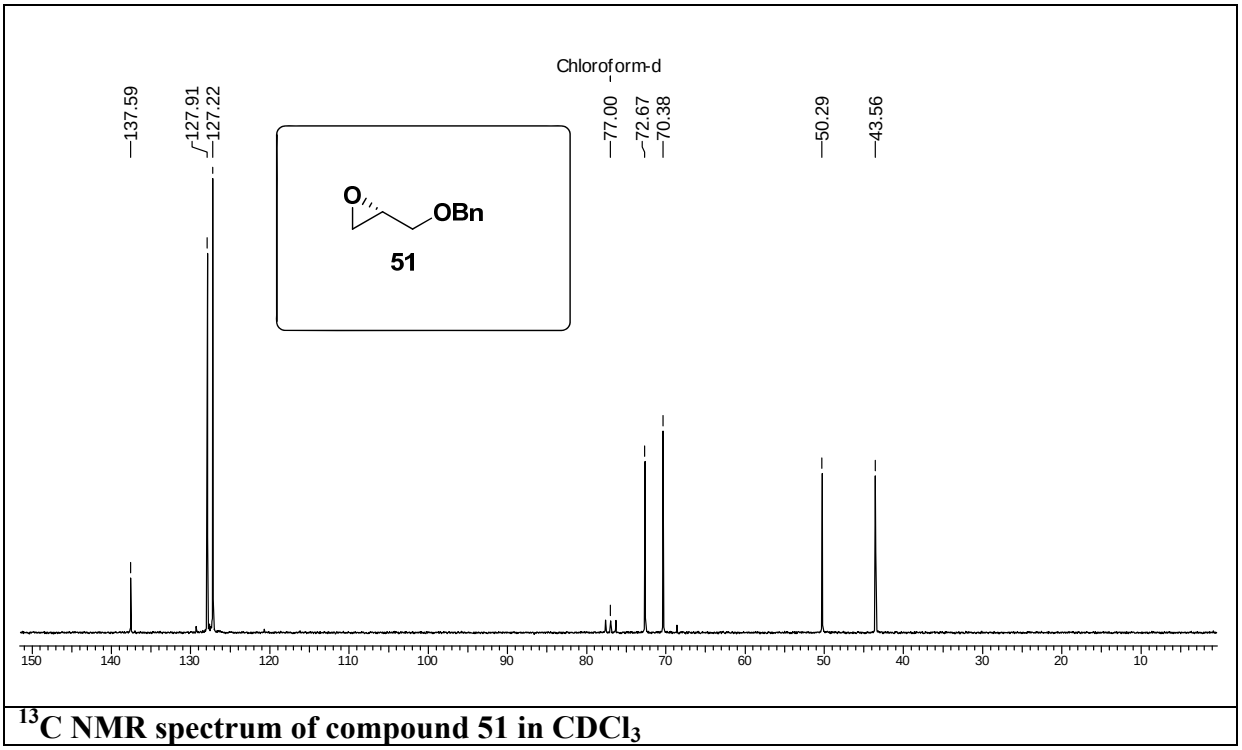
24] ^{13}C NMR spectrum of *ent*-**47**

25] ^{1}H NMR spectrum of **1**

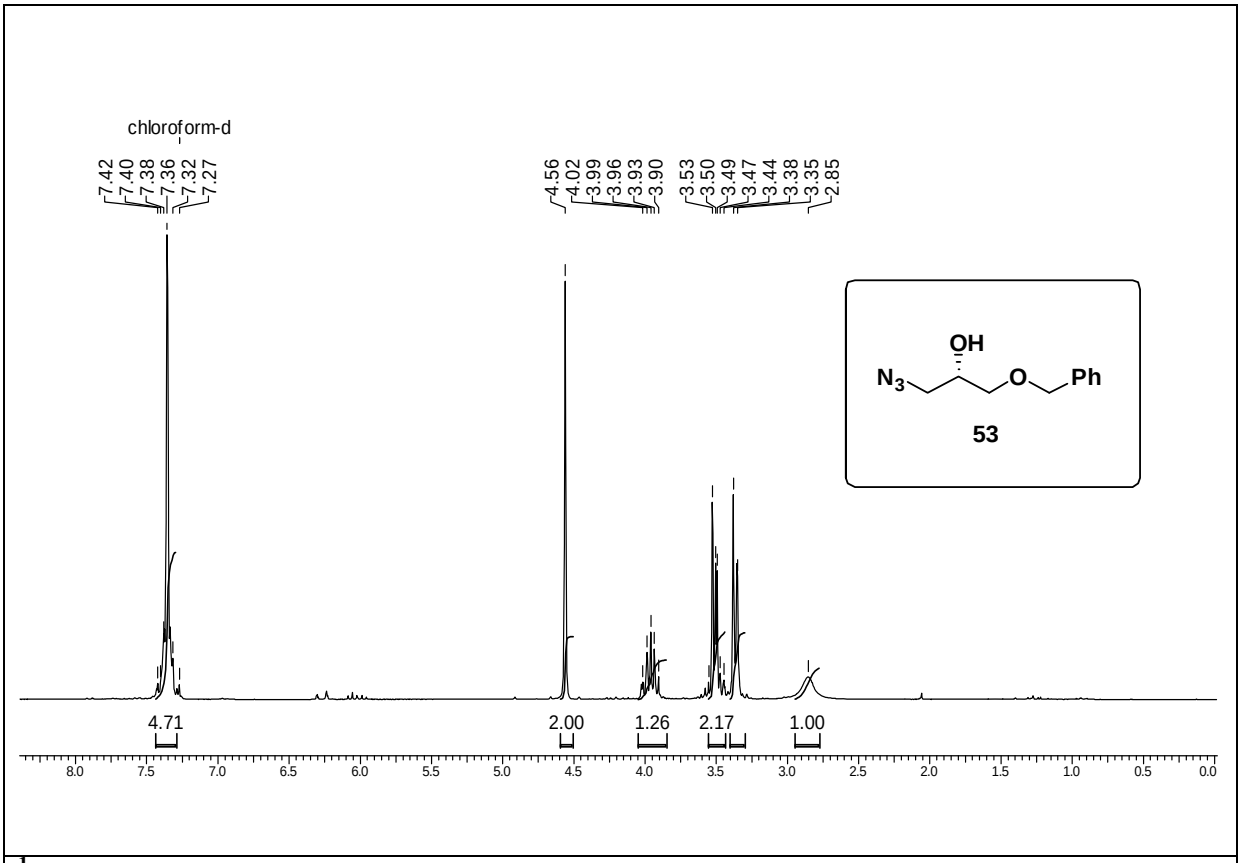
26] ^{13}C NMR spectrum of **1**



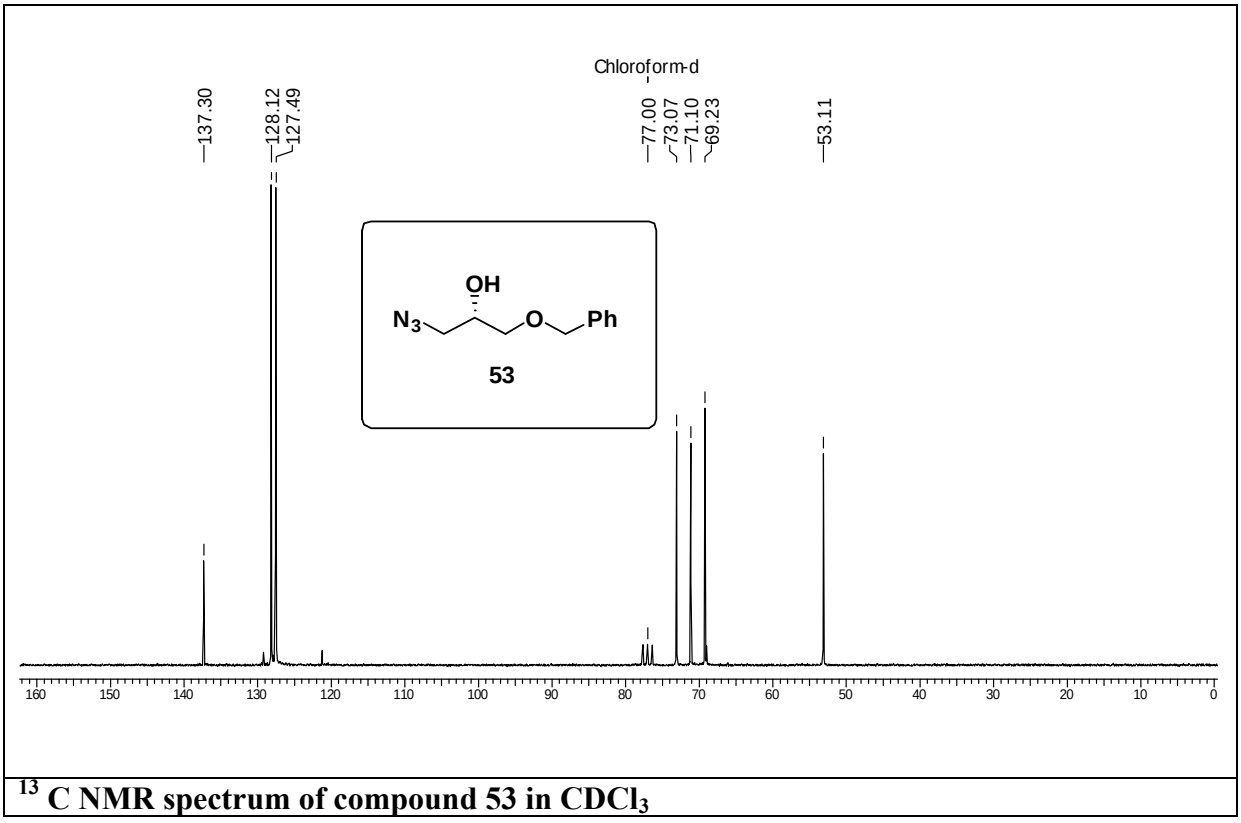
^{1}H NMR spectrum of compound 51 in $CDCl_3$



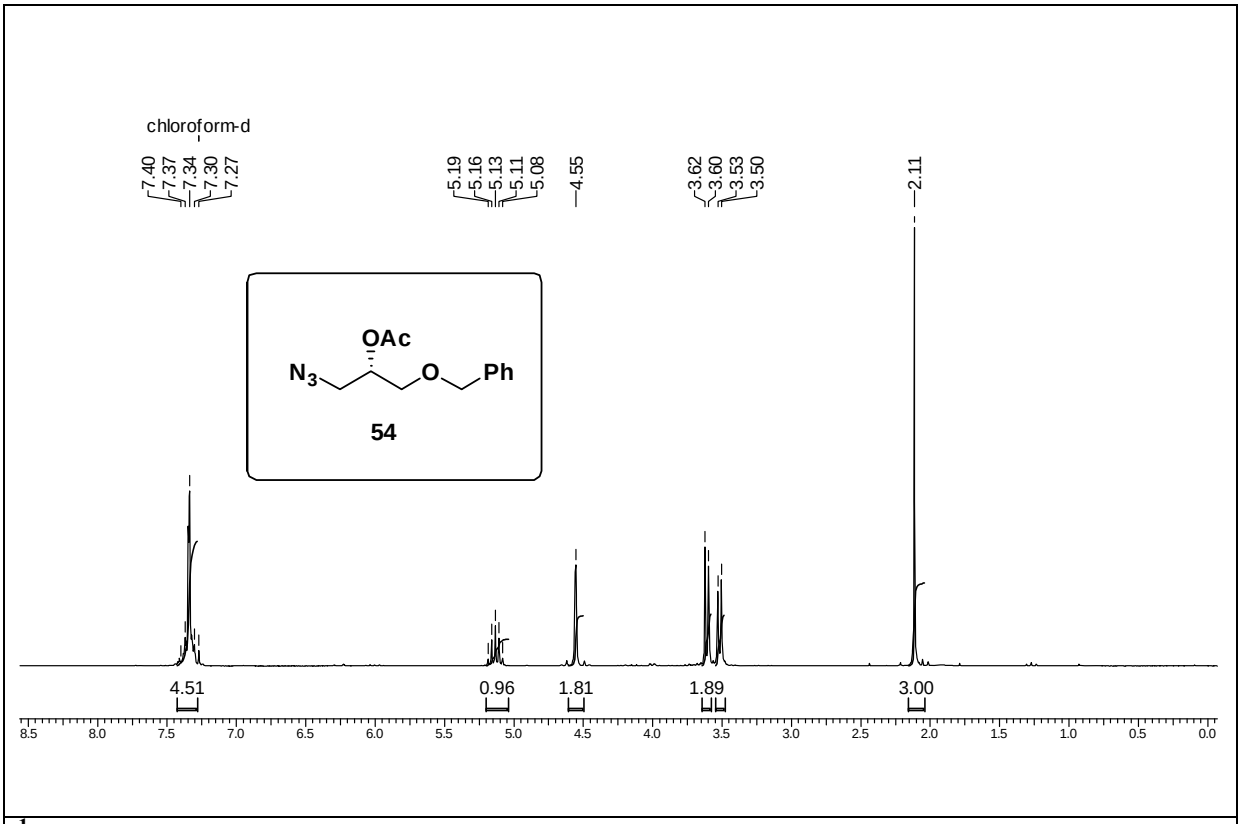
^{13}C NMR spectrum of compound 51 in $CDCl_3$



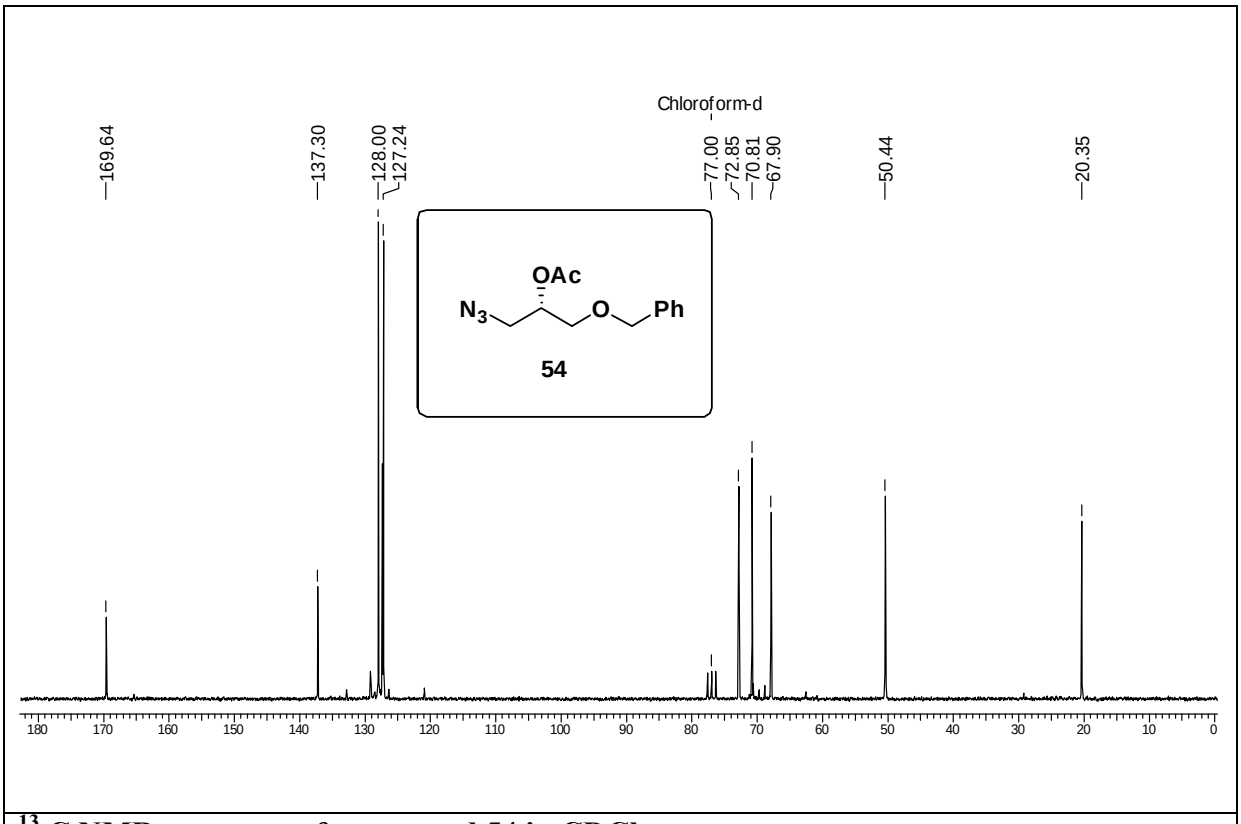
^{1}H NMR spectrum of compound 53 in $CDCl_3$



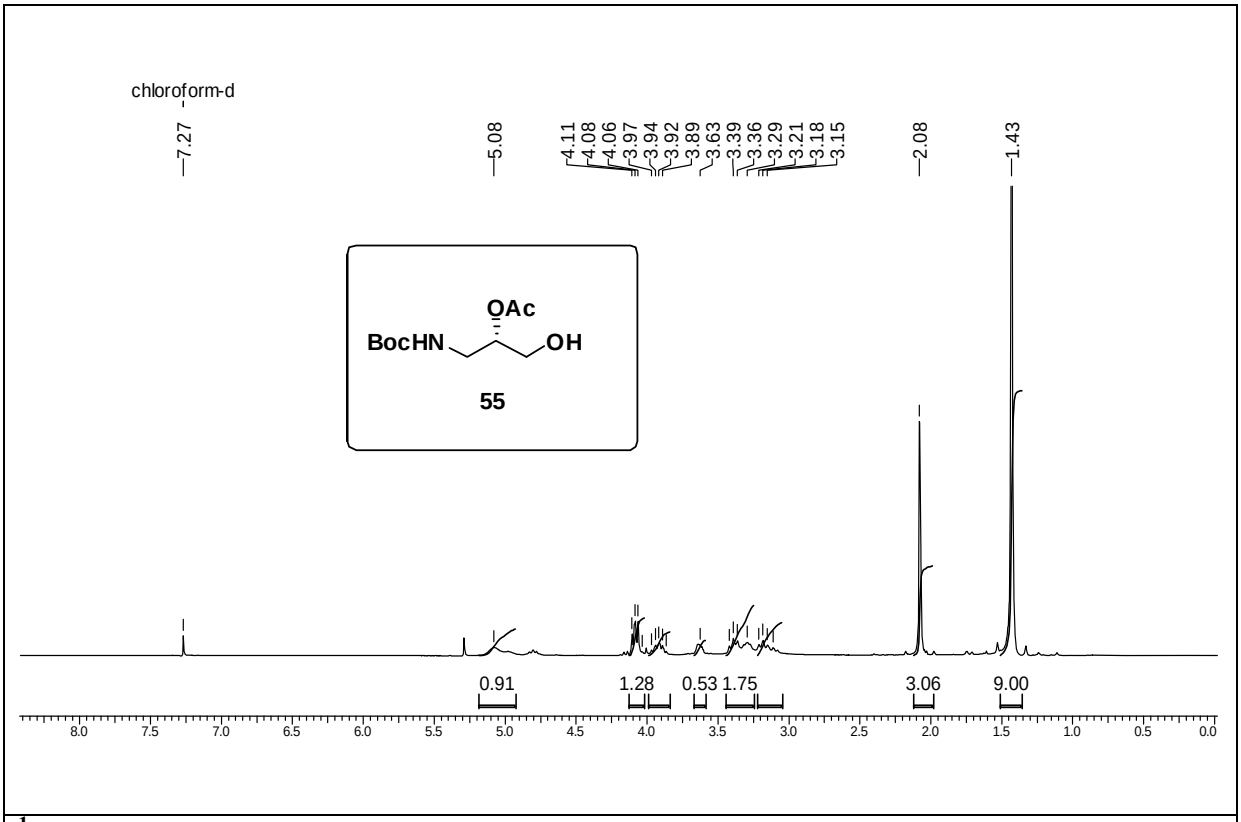
^{13}C NMR spectrum of compound 53 in $CDCl_3$



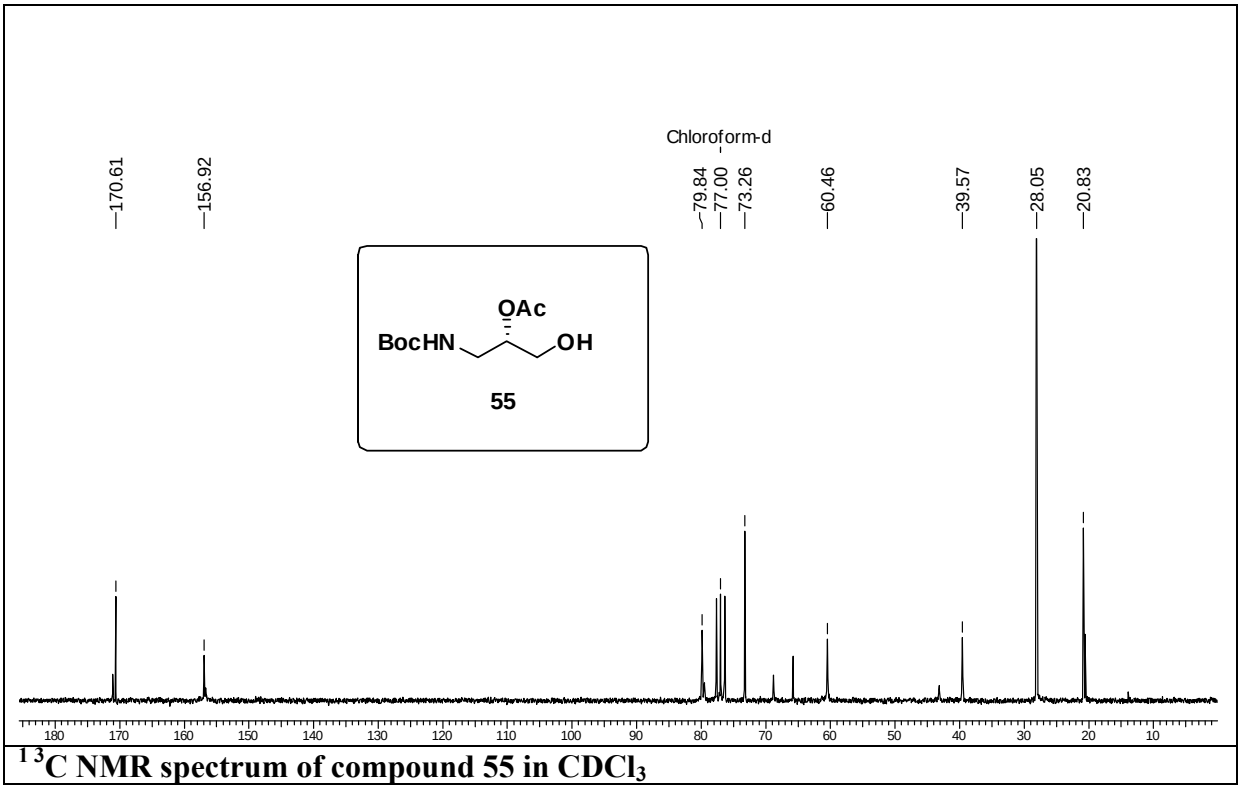
^{1}H NMR spectrum of compound 54 in $CDCl_3$



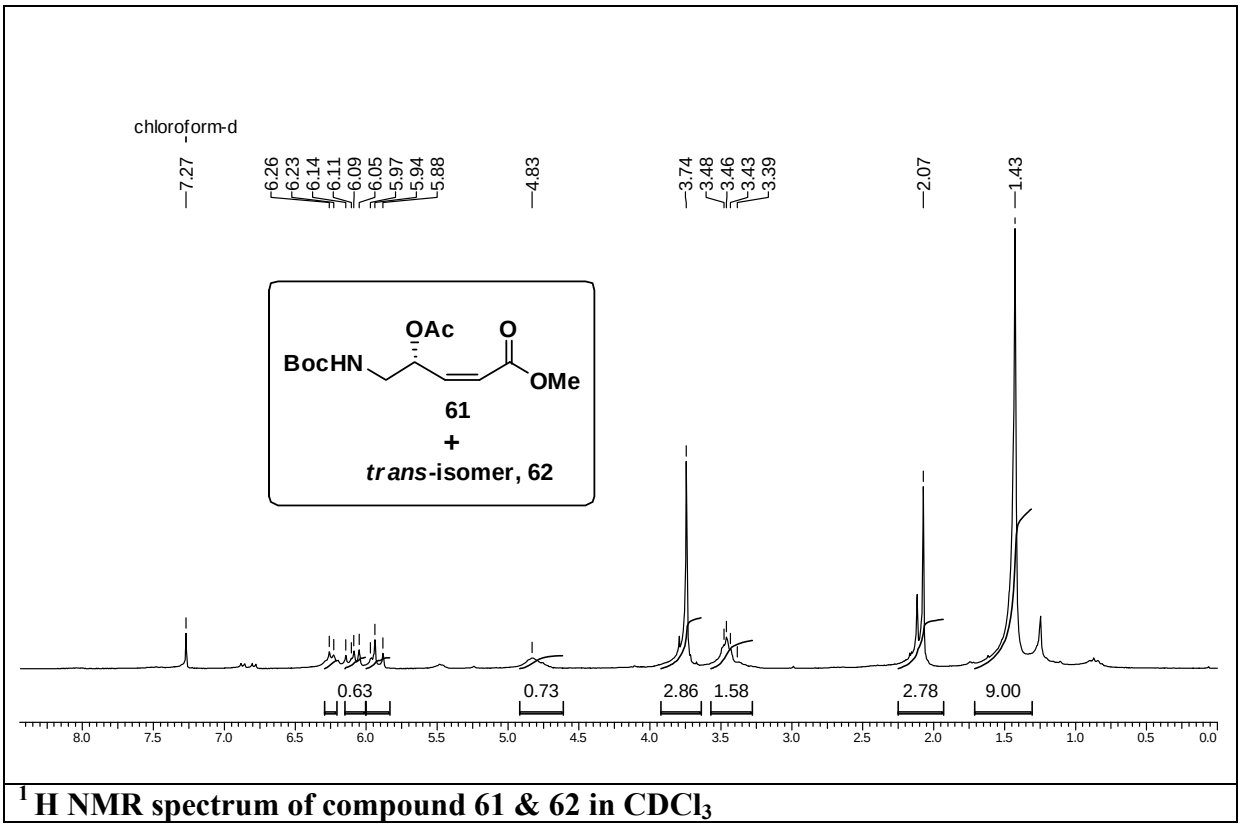
^{13}C NMR spectrum of compound 54 in $CDCl_3$



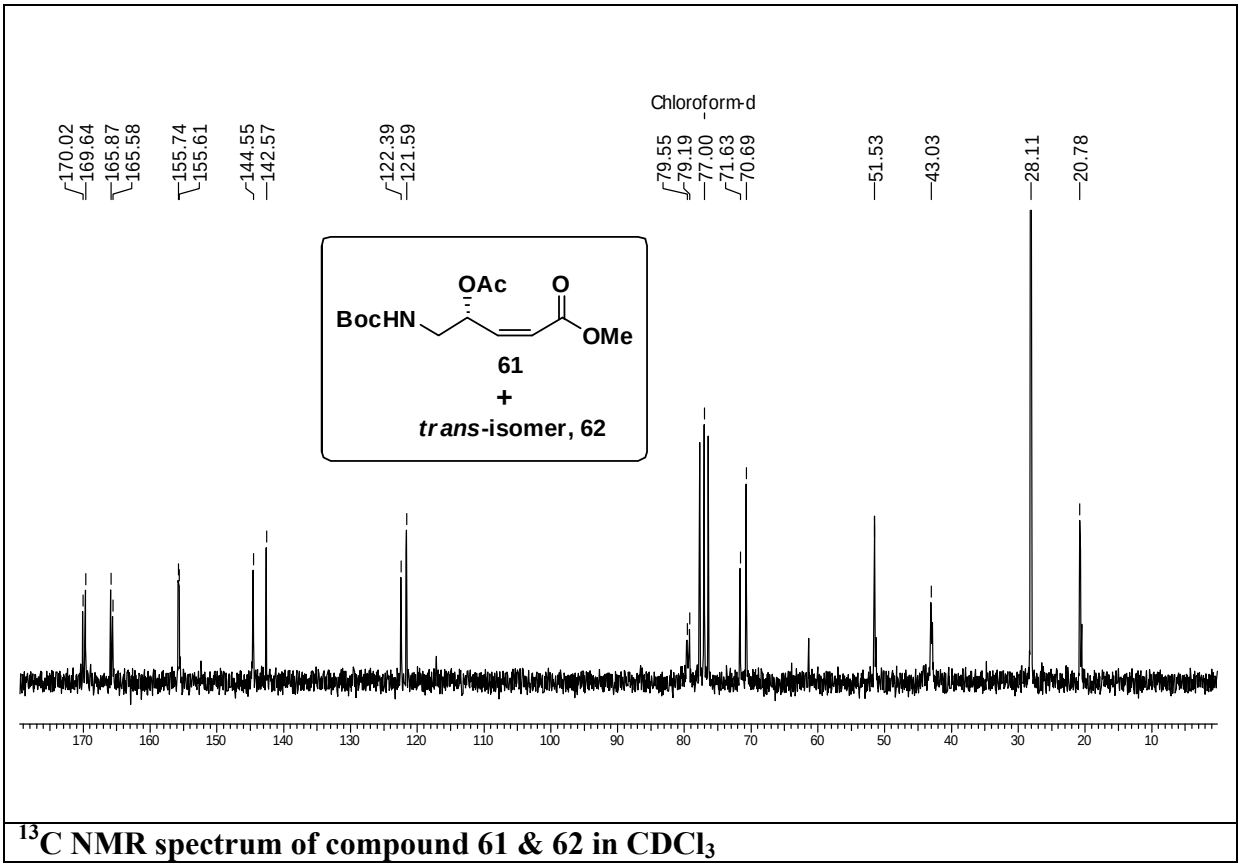
^{1}H NMR spectrum of compound 55 in $CDCl_3$



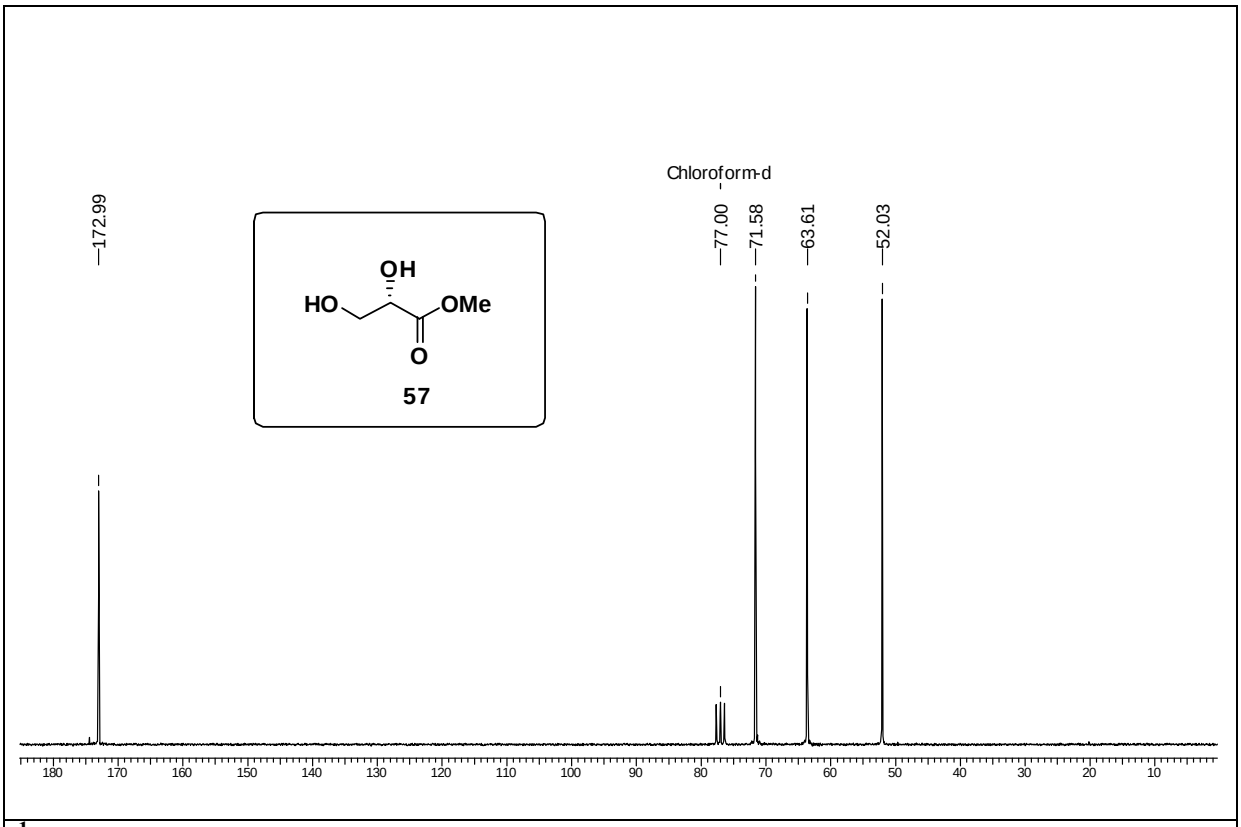
^{13}C NMR spectrum of compound 55 in $CDCl_3$



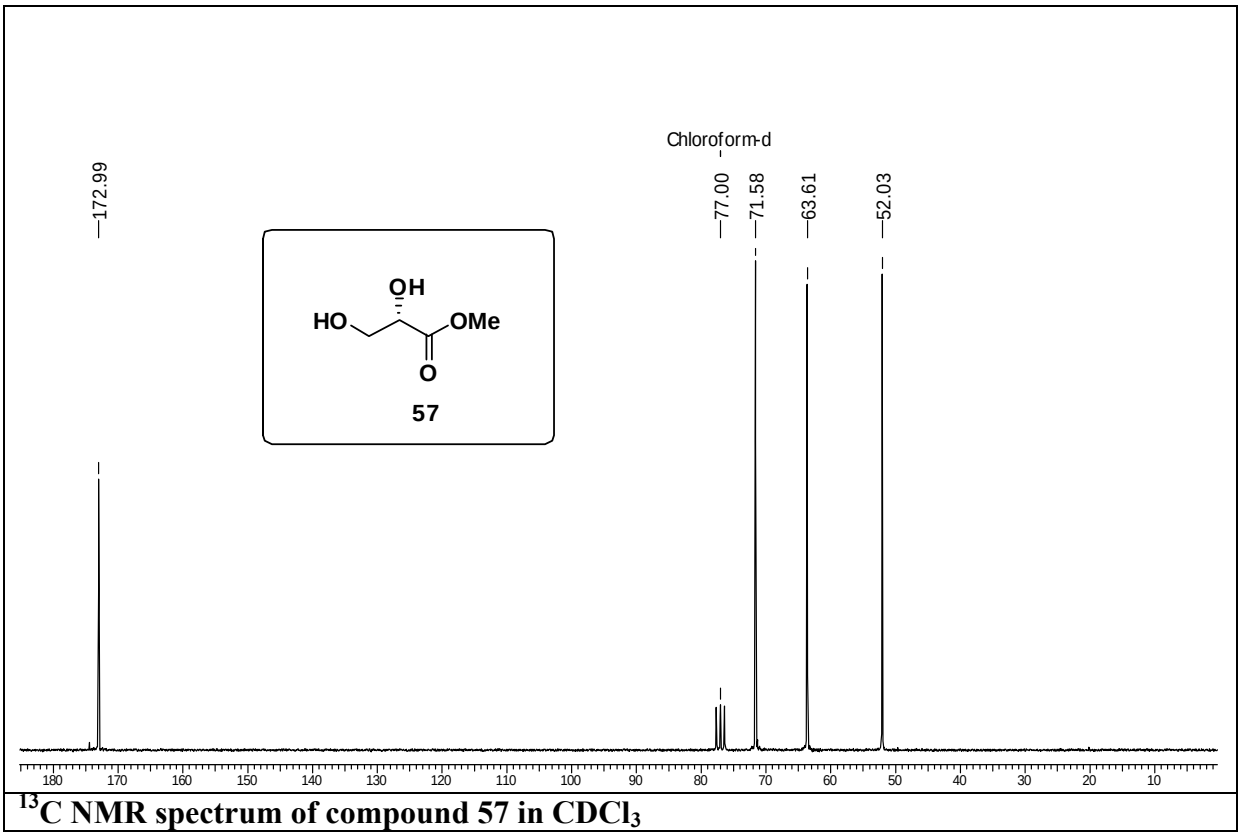
^{1}H NMR spectrum of compound 61 & 62 in $CDCl_3$



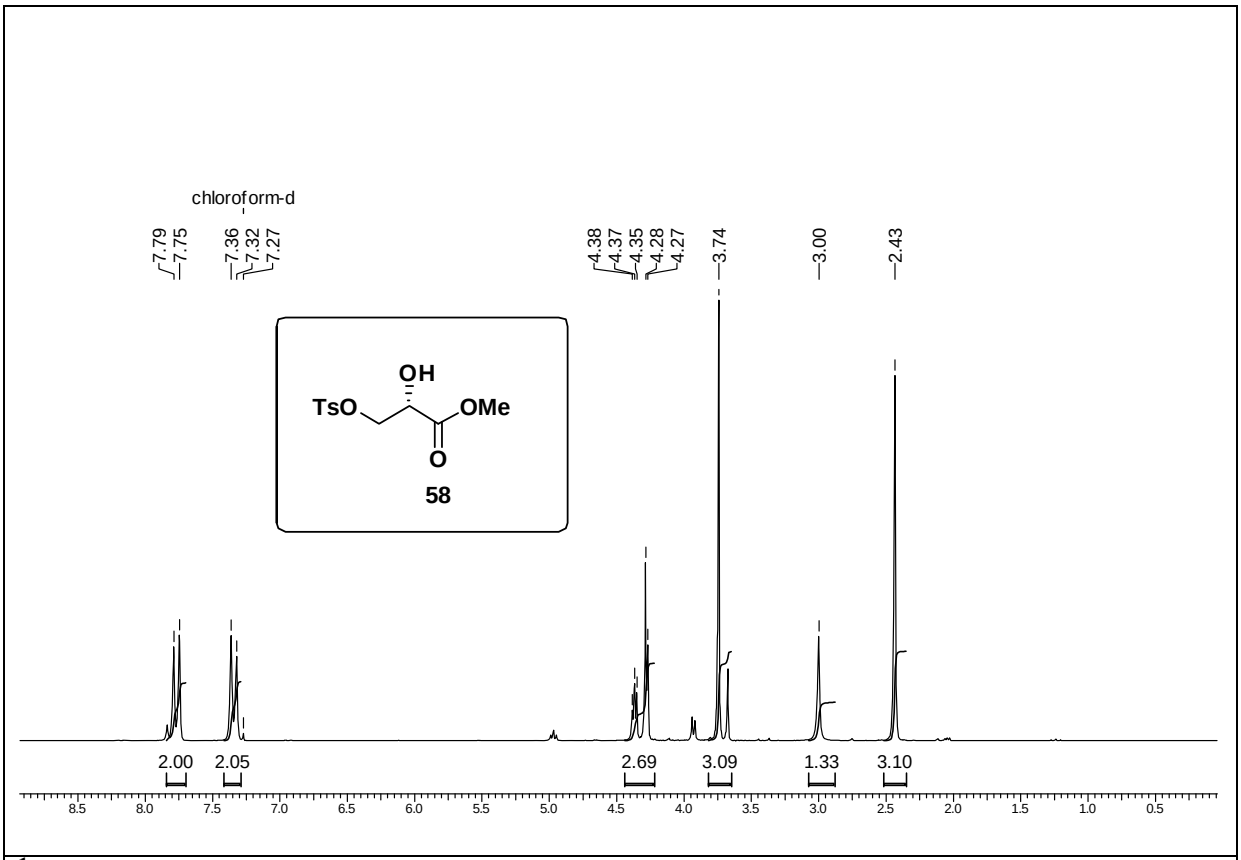
^{13}C NMR spectrum of compound 61 & 62 in $CDCl_3$



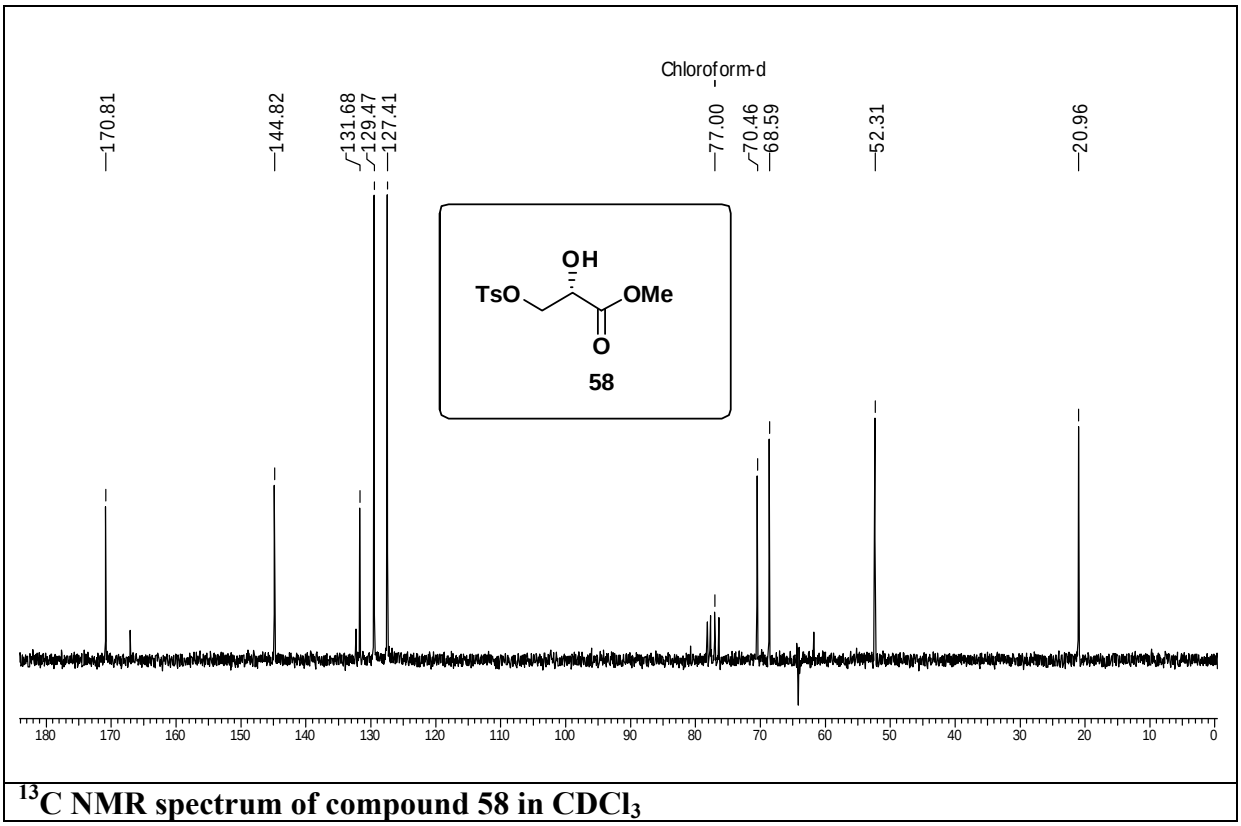
^{1}H NMR spectrum of compound 57 in $CDCl_3$



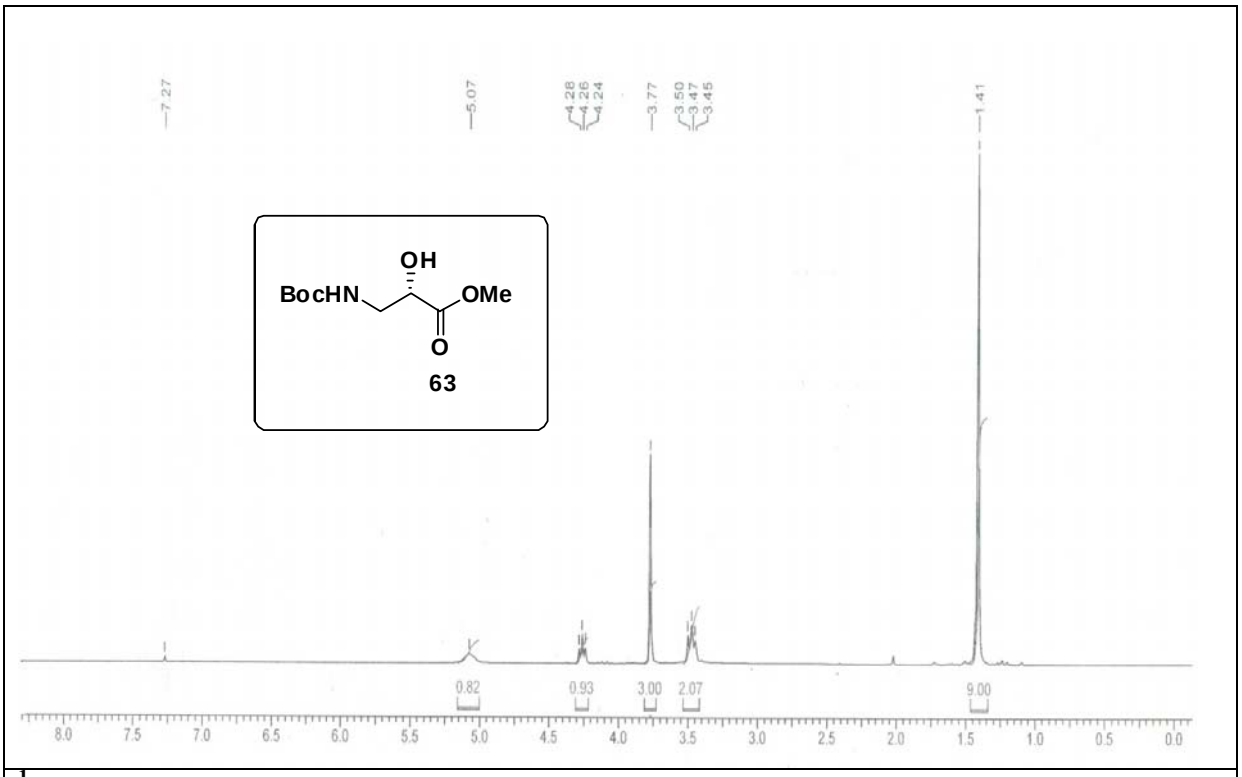
^{13}C NMR spectrum of compound 57 in $CDCl_3$



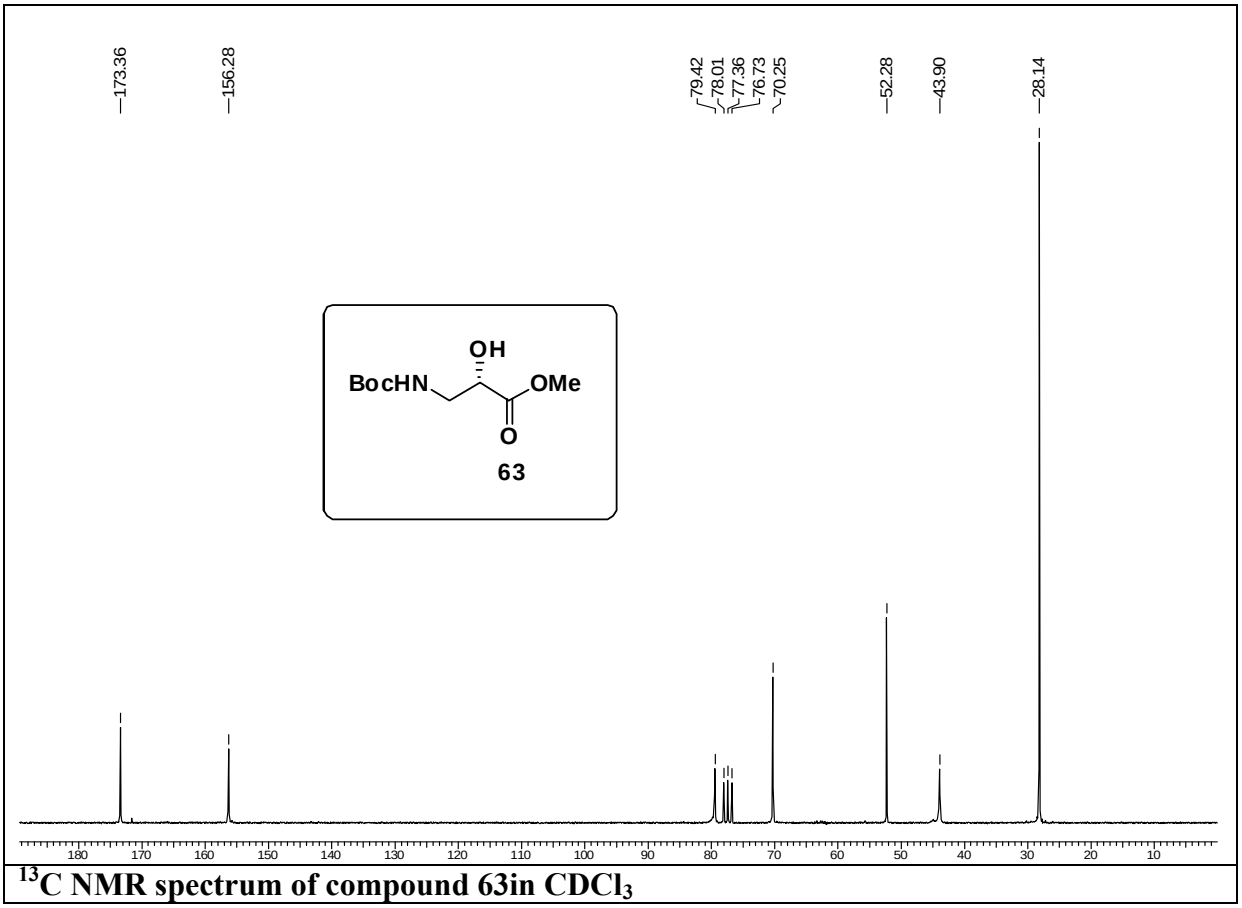
^{1}H NMR spectrum of compound 58 in $CDCl_3$



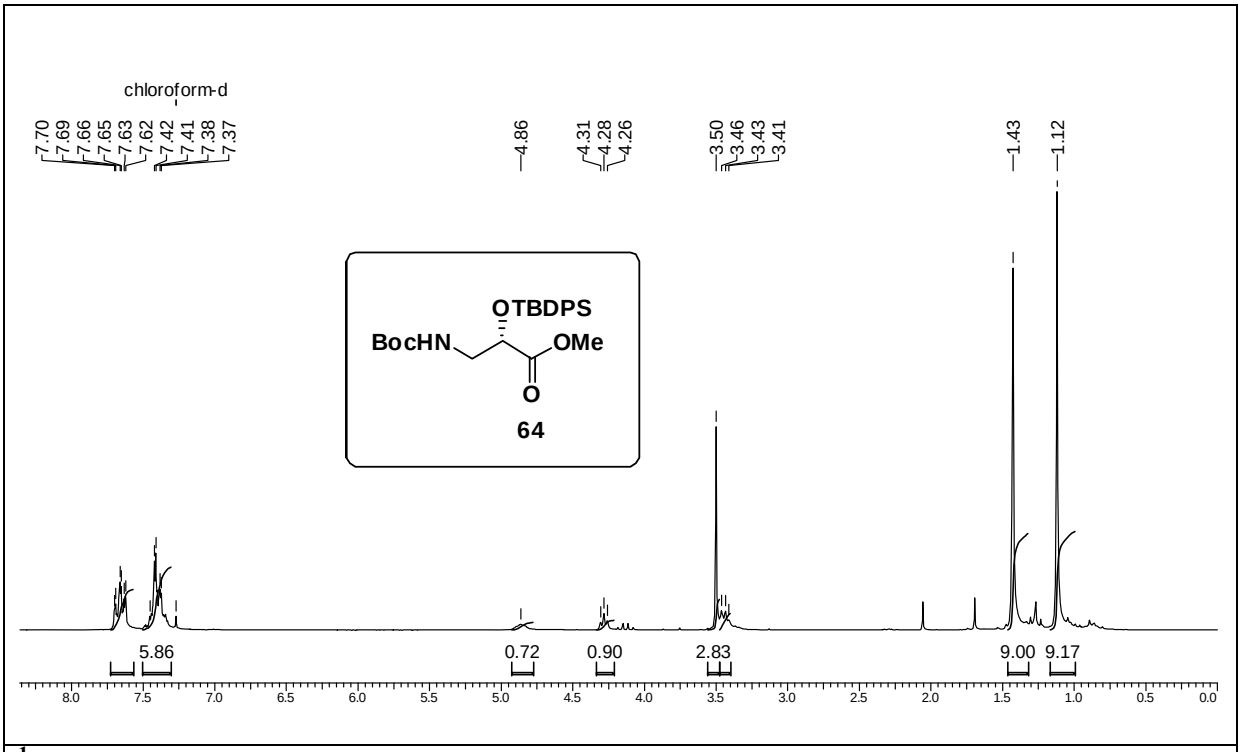
^{13}C NMR spectrum of compound 58 in $CDCl_3$



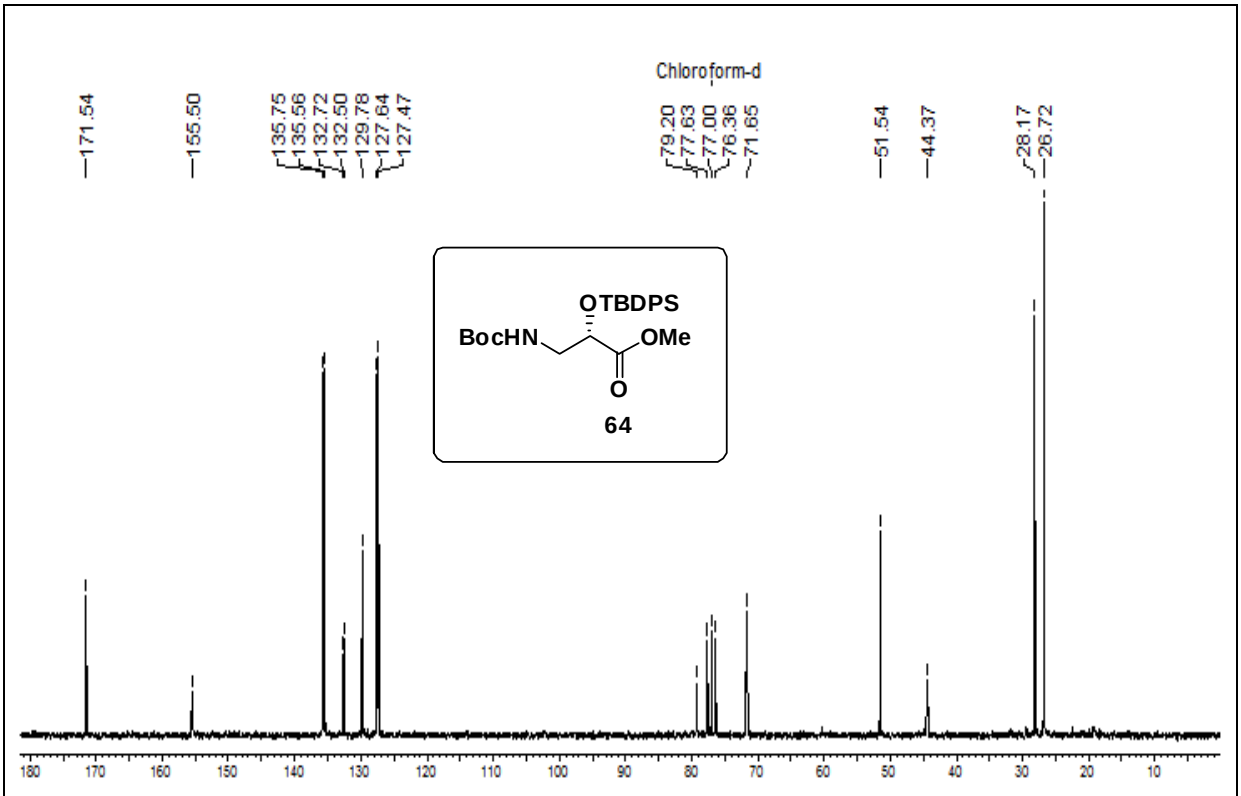
^{1}H NMR spectrum of compound 63in $CDCl_3$



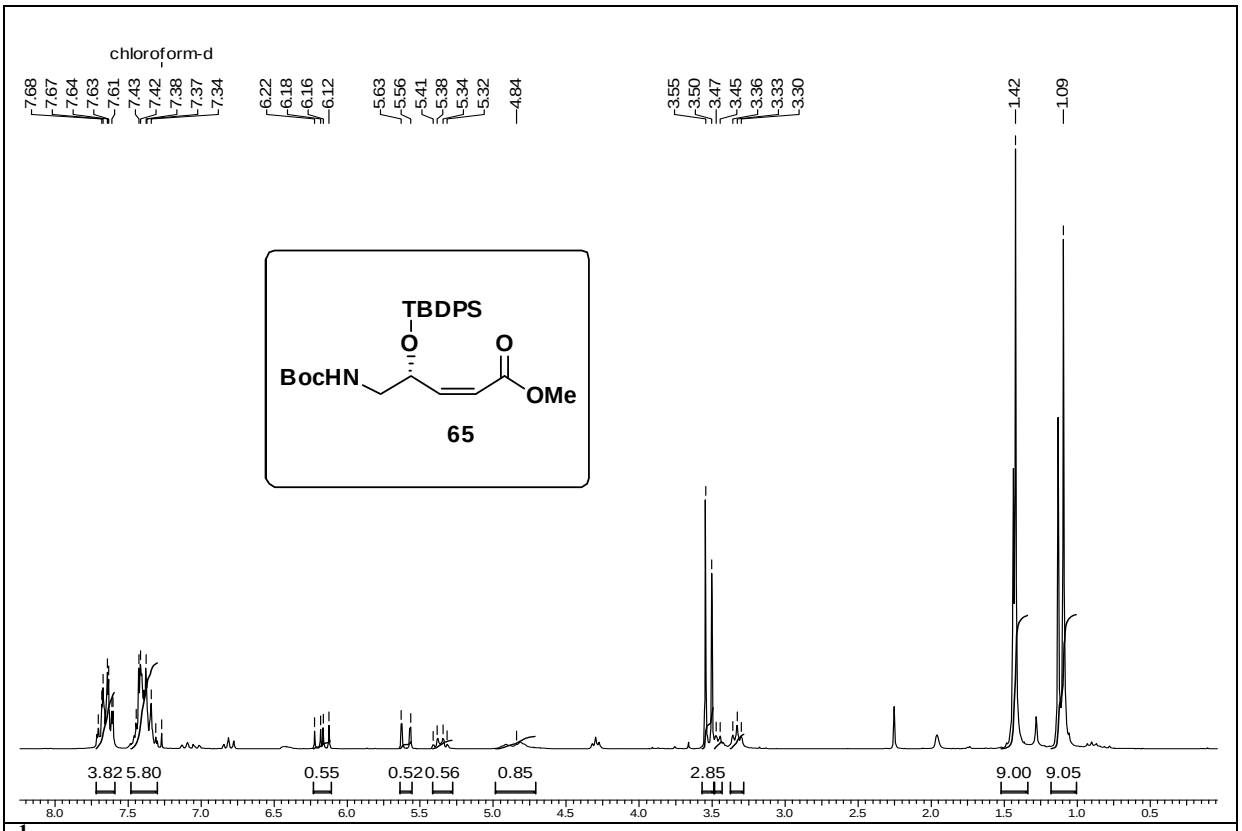
^{13}C NMR spectrum of compound 63in $CDCl_3$



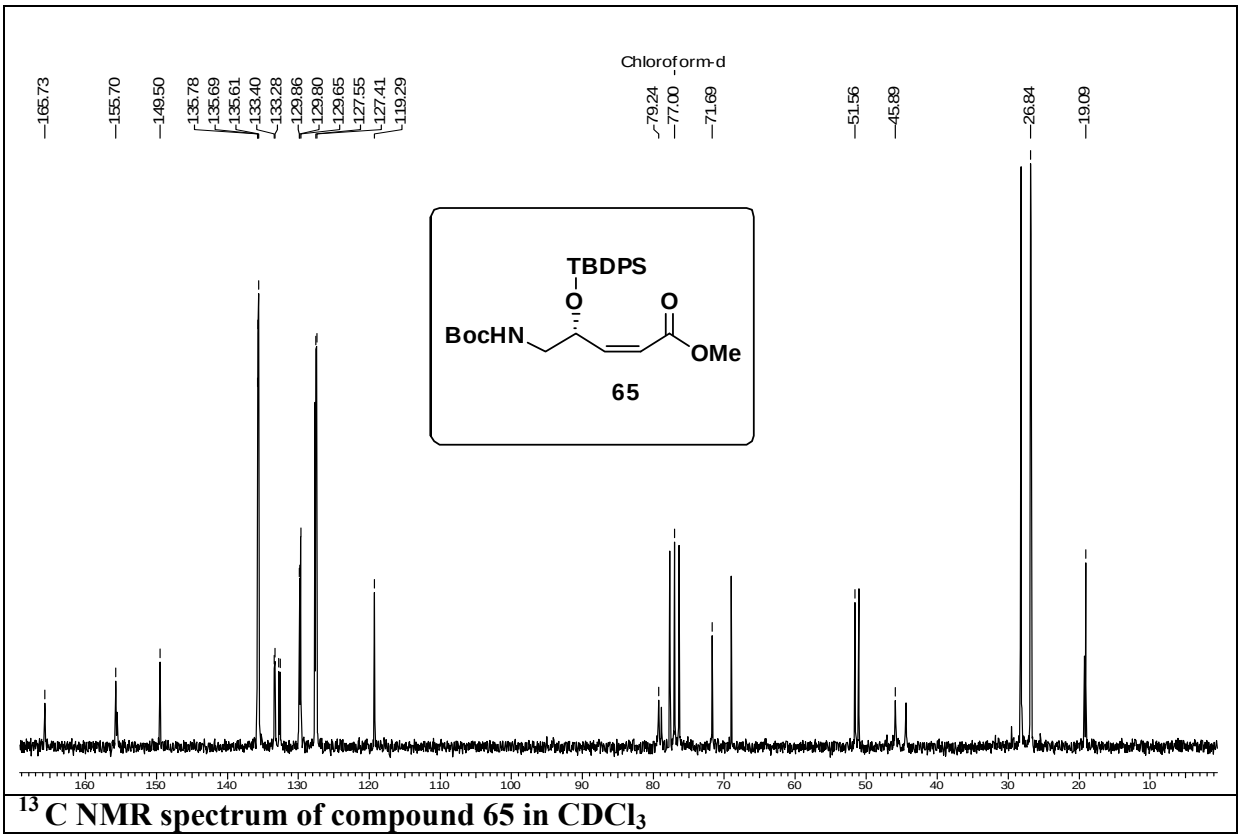
^{1}H NMR spectrum of compound 64 in $CDCl_3$



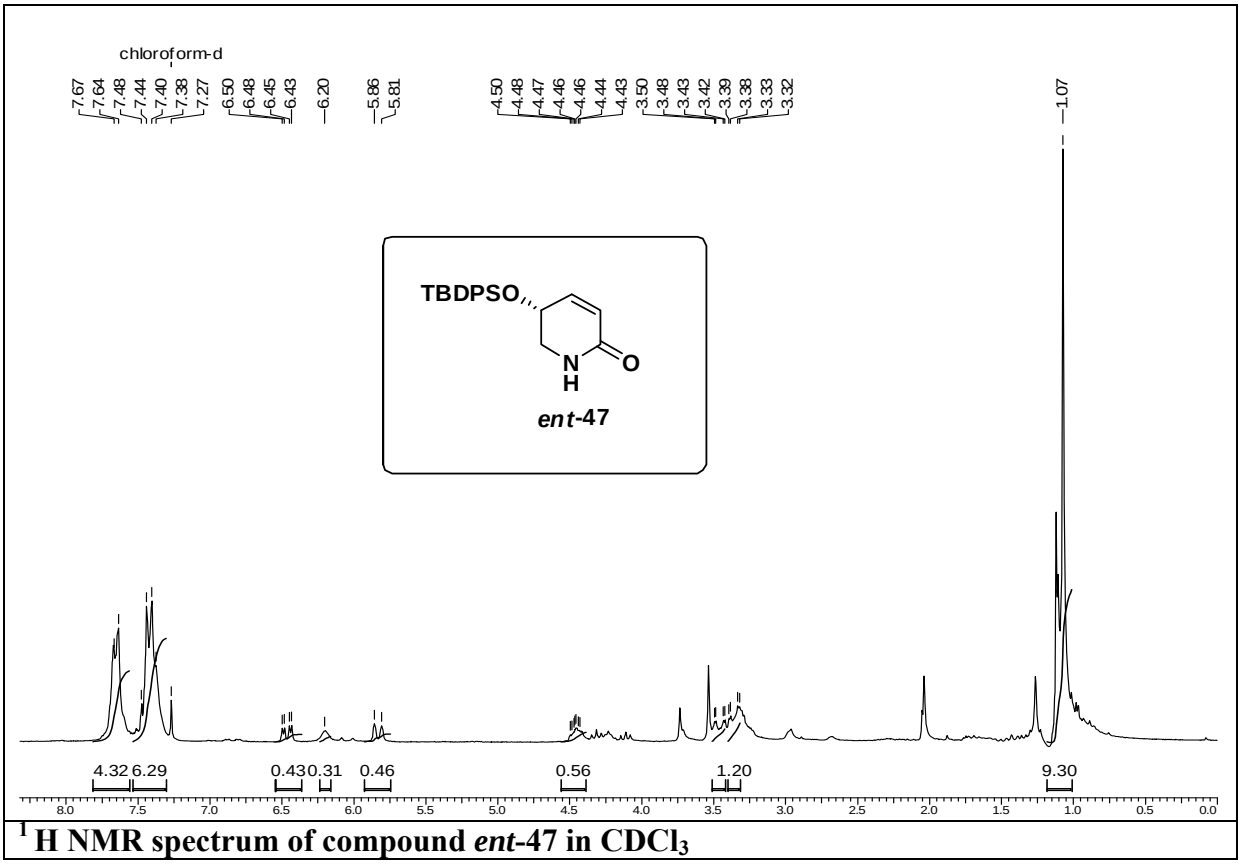
^{13}C NMR spectrum of compound 64 in $CDCl_3$



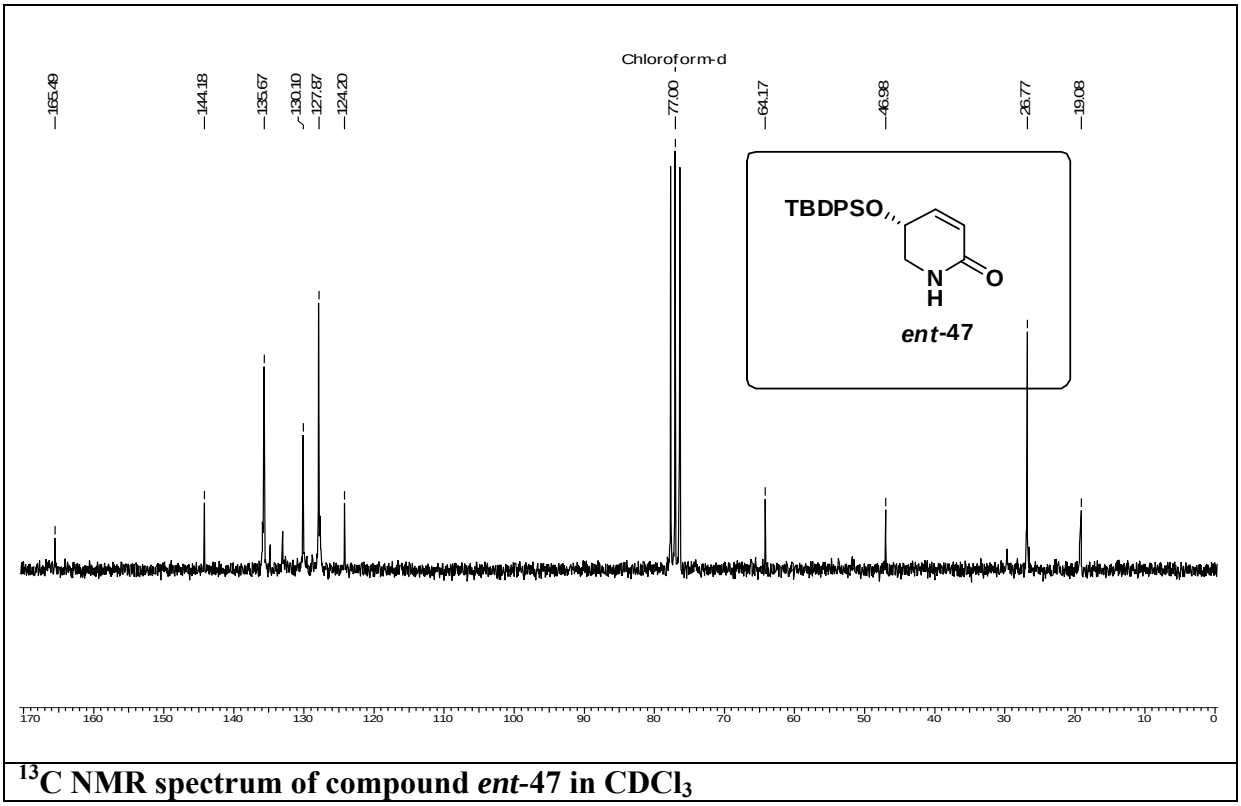
^{1}H NMR spectrum of compound 65 in $CDCl_3$



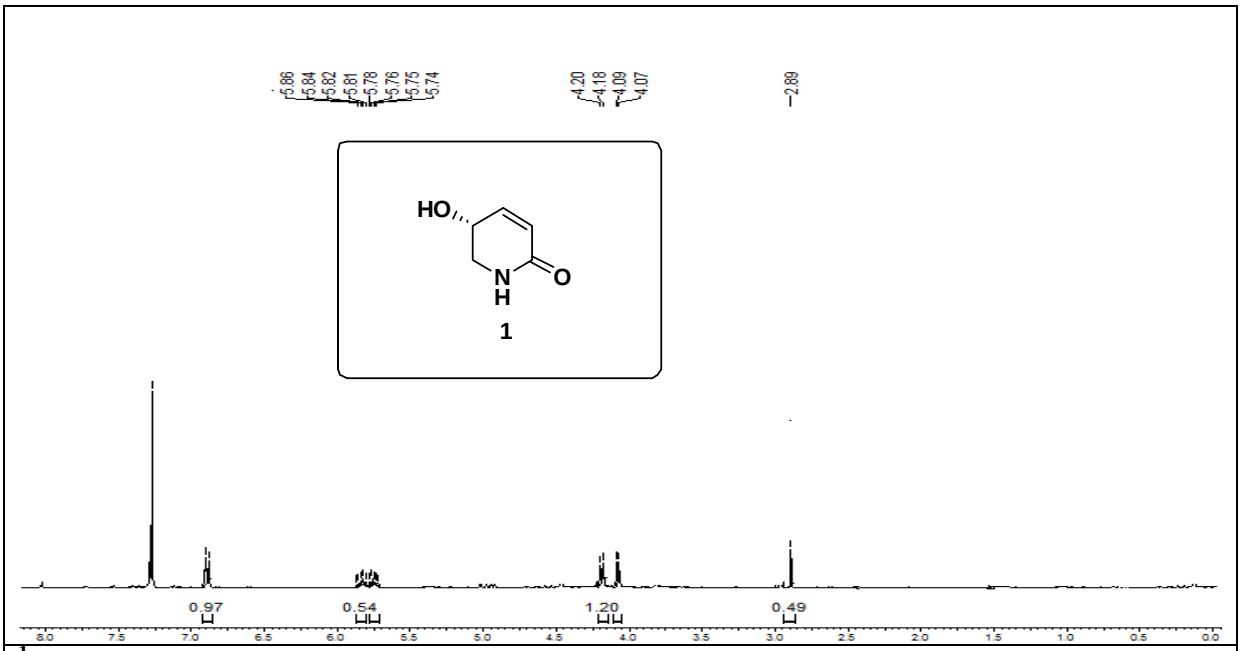
^{13}C NMR spectrum of compound 65 in $CDCl_3$



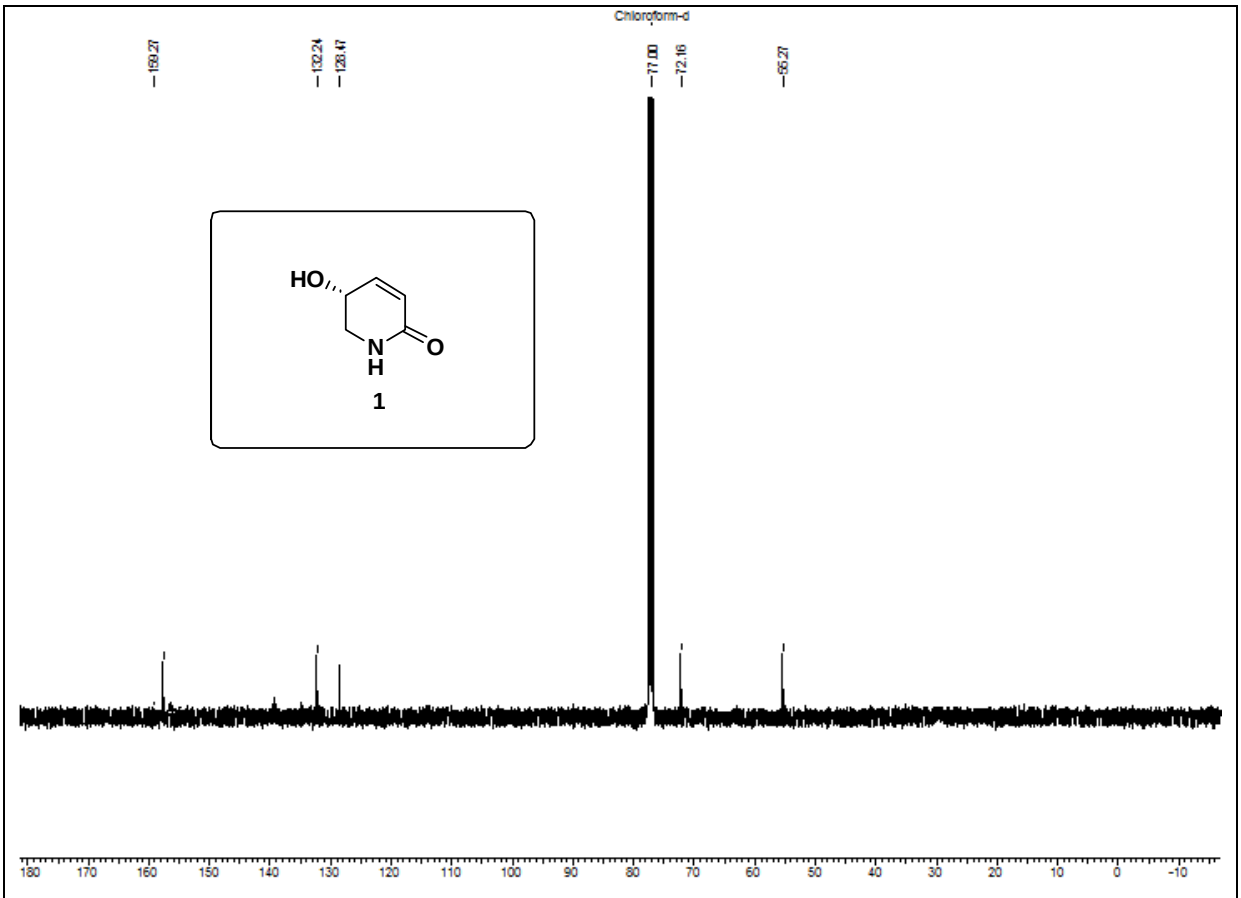
^{1}H NMR spectrum of compound *ent*-47 in $CDCl_3$



^{13}C NMR spectrum of compound *ent*-47 in $CDCl_3$



^{1}HNMR spectrum of compound 1 in $CDCl_3$



13 C NMR spectrum of compound 1 in $CDCl_3$

3.3.8. References

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CHAPTER 4

Asymmetric dihydroxylation route towards the diastereoselective synthesis of polyhydroxylated pyrrolidine and indolizidine alkaloids

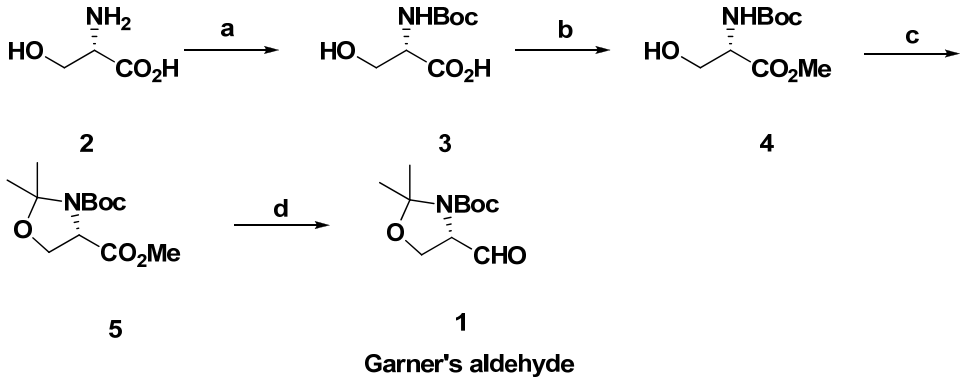
4.1. SECTION A
ASYMMETRIC DIHYDROXYLATION ROUTE TOWARDS STEREOSELECTIVE SYNTHESIS OF POLYHYDROXYLATED (2*S*,3*S*,4*S*)-2-(HYDROXYMETHYL)PYRROLIDINE-3,4-DIOL (LAB 1)

4.1.1. Garner aldehyde

In 1984 Garner published[1] a method for preparing the configurationally stable 1,1-dimethylethyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (**1**), today called Garner's aldehyde. Since that time both enantiomers of **1** have been used extensively as chiral building blocks in asymmetric synthesis. Garner's aldehyde (**1**) is perhaps one of the most valuable chiral building blocks in recent times as it has been employed in more than 200 reported studies since its discovery.

Garner (1984)[1]

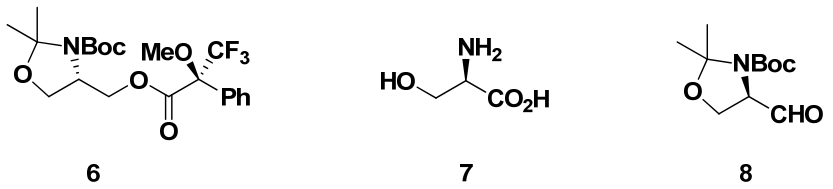
The first synthesis of Garner's aldehyde was, as the compound's name implies, reported by Philip Garner.[1]



Scheme1. *Reagents and conditions:* (a) Boc_2O, NaOH; (b) MeI, K_2CO_3; (c) 2,2-DMP, TsOH; (d) DIBAL, PhMe.

Synthesis started with Boc protection of serine (**2**) using di-*tert*-butyl dicarbonate [$(Boc)_2O$] at pH ≥ 10 to form *N*-Boc-serine **3** which was converted to the methyl ester **4** either by diazomethane[2] or, more conveniently, with MeI and K_2CO_3 (Scheme 1).[3] Compound **4** was then treated with $Me_2C(OMe)_2$ and TsOH to give the oxazolidine

ester **5** in 70-89% yield. Direct reduction of ester **5** with DIBAL in toluene afforded the title aldehyde **1** in 76% yield.[3] The optical purity of **1** was determined by reducing it to the corresponding alcohol and converting that into the Mosher ester **6** (Fig. 1).[3] NMR analysis of **6** revealed that **1** had an optical purity of 93-95% *ee*.

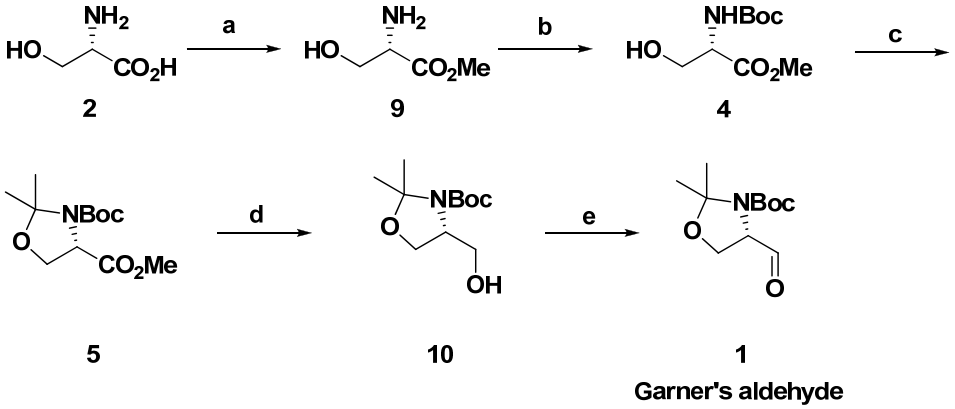


6 7 8

Figure 1. Mosher ester **6**, D-serine **7** and the (*R*)-Garner's aldehyde **8**

McKillop *et al.* (1994)[4]

The first two steps i.e. Boc protection and esterification, have advantageously been reversed by McKillop *et al*.[4]



2 9 4 5 10 1

Garner's aldehyde

Scheme 2. *Reagents and conditions:* (a) HCl, MeOH, quantitative yield; (b) Boc_2O, Et_3N, 90%; (c) 2,2-DMP, $BF_3.OEt$; (d) $LiAlH_4$; (e) $(COCl)_2$, DMSO, -78 ^oC, $^iPr_2EtN$, CH_2Cl_2.

Thus, treatment of **2** with HCl in MeOH gave the methyl serinate **9** in essentially quantitative yield (Scheme 2). Compound **9** was reacted with $(Boc)_2O$ and Et_3N to give **4** in 90% yield from **2**.[5] The transformation of **4** to oxazolidine **5** has been improved by Moriwake *et al*.[6] who used $BF_3.OEt_2$ as catalyst in place of TsOH. Many workers noted

that the reduction of **5** could be difficult to reproduce and was very dependent on the quality of the DIBAL used. A more reliable procedure was to reduce the ester **5** to the alcohol **10** and then oxidise it back to **1** under Swern conditions (Scheme 2).[7-12]

Roush *et al.* (1995)[9]

Roush *et al.*[9] reported that not only was the DIBAL reduction tricky, but the enantiomeric excess was also only 86–87% in their hands.[9]

Marshall *et al.* (1994)[8]

Marshall *et al.*[8] reported the reliability and yield of the synthesis can be improved by replacing the DIBAL with the $LiAlH_4$-Swern protocol (Scheme 2), but not the enantiomeric purity of **1** (who also obtained a product with 90% *ee* after the Swern oxidation).[8]

Dondoni *et al.* (1995)[10]

Dondoni *et al*.[10] solved the above problem by changing the base used in the Swern oxidation from Et_3N to Hünig's base.[11] Hünig's base is more hindered and therefore less likely to facilitate enolisation of **1**. With this modification the enantiomeric purity of the product **1** was more than 97% *ee*. The oxidation of **10** to **1** can also be performed via a TEMPO-catalysed oxidation which proceeds in 90% yield and with 100% *ee* optical purity[13] or with DMSO-triphosgene which gives an 81% yield of a product with an optical purity similar to that reported by Garner.[14]

In conclusion, Garner's aldehyde **1** has proven an extremely useful chiral building block in organic synthesis. Its value is due to its simple structure that allows it to be used for many targets and because good methods exist for diastereoselective elaboration of aldehydes.

4.1.2. Introduction

Imino sugars are well known as glycosidase inhibitors and many of them are naturally occurring.[15,16] 1,4-Dideoxy-1,4-imino-*D*-arabinose and *D*-ribose are naturally occurring imino sugars exhibiting activity as glycosidase inhibitors and hydroxylated pyrrolidines constituted one of the main classes of naturally occurring sugar mimics having nitrogen in the ring.

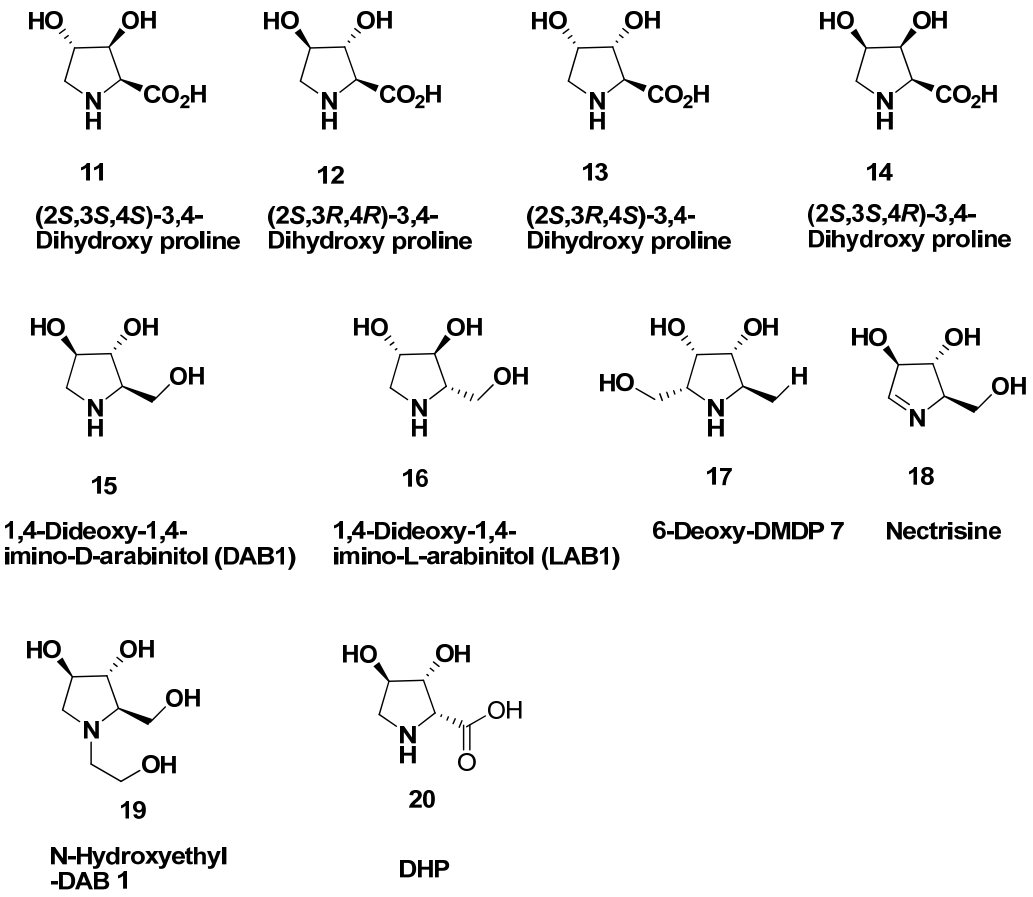


Figure 2. Naturally occurring hydroxylated prolines and pyrrolidines alkaloids

Much attention has been focused on this class of compounds because of their potential for cell-biological and therapeutic applications as a consequence of their role as glycosidase inhibitors.[15,16] A wide range of analogues have been synthesized because of their sugar-like structures.[15-18]

Many pyranoses and furanoses with the ring oxygen replaced by an amino group, known as imino sugars or azasugars are sugar mimics, which have been found to inhibit specific enzymes such as glycosidases.[19] Because glycosidases are involved in several important biological processes, these polyhydroxylated alkaloids have stimulated interest in the development of specific glycosidase inhibitors for studying and treating metabolic disorders such as diabetes, or as antiviral, antibacterial, and anticancer agents or as immunomodulators and are providing biochemists with molecular tools for probing several important processes such as the metastasis of some cancers, the

immune response, and virus replication. In particular, α-glucosidase inhibitors have shown potential as therapeutic agents for type II diabetes and HIV-1 infection.

1,4-Dideoxy-1,4-imino-$_D$-arabinitol (**15**, known as DAB **1**) was isolated from two types of leguminose plants *Arachniodes standishii* and *Angylocalyx boutiqueanus*. The antipode of DAB **1** is a synthetic product. LAB **1** (**16**)[20] was shown to be a potent inhibitor of the α-L-arabinofuranosidase III of *Monilinia fructigena* and a much more powerful inhibitor of sucrose and some mouse gut α-glucosidases than DAB **1**. It is also a promising candidate for treatment of type II diabetes and was one of the most powerful anti-HIV agents among **47** aminosugar derivatives screened. Structurally related nectrisine (FR 900483) (**18**) is a fungal metabolite isolated from *Nectria lucida*. DAB **1** and nectrisine exhibit extremely potent yeast *α*-glucosidase inhibitory activities [IC_{50} = 1.8 x 10^{-7} M and 4.8 x 10^{-8} M, respectively]. The *N*-hydroxyethylated derivative of DAB **1**, namely, *N*-hydroxyethyl-DAB 1 (**19**) was isolated from the seeds of African legume *Angylocalyx pynaertii*, while the oxidation product of DAB **1**, $_L$-2,3-*trans*-3,4-*trans*-dihydroxyproline (DHP) (**20**), was isolated from the acid hydrolyzates of the toxic mushroom *Amanita virosa*.

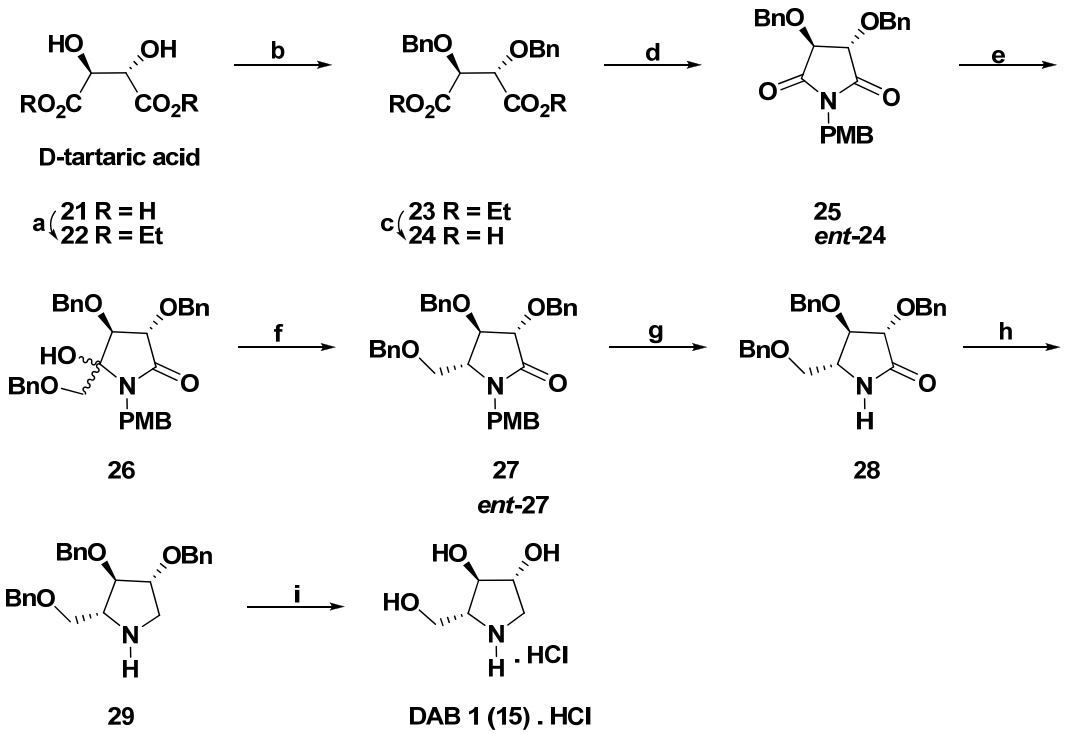
4.1.3. Review of Literature

Consequently, the synthesis of polyhydroxylated pyrrolidine alkaloids/azasugars has attracted much attention and a number of methods have been developed in recent times. In view of the presence of α-hydroxymethyl-dihydroxypyrrolidine **15** (DAB **1**) as the common structural feature in many azasugars, an attractive approach to these compounds would be that allowing installation of the *α*-hydroxymethyl group in a straight forward manner. Although, optically active tartaric acid has been used to synthesize this class of compounds such as DAB **1** (**15**), LAB **1** (**16**), nectrisine (**18**) and broussonetine C, methods for the introduction of the hydroxymethyl group into the *α*-position of a pyrrolidine or a piperidine ring have generally been accomplished by indirect and multistep procedures. In some of these approaches, low diastereoselectivities have been observed.

Huang *et al.* (2007)[21]

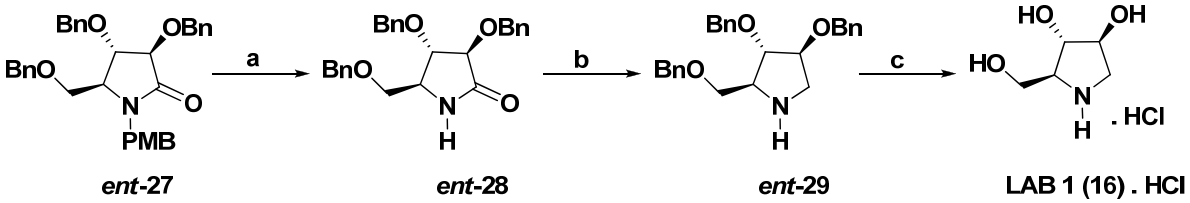
Huang *et al*.[21] reported the synthesis of 1,4-Dideoxy-1,4-imino-$_D$-arabinitol (DAB **1**) and 1,4-Dideoxy-1,4-imino-L-arabinitol (LAB **1**) using D and L-tartaric acid as the starting material (Scheme 3&4).

Synthesis of DAB 1 from D-tartaric acid



Scheme 3. *Reagents and conditions*: (a) EtOH, $SOCl_2$, rt, quantitative; (b) NaH, BnBr, DMF, -20 ^oC - 0 ^oC, 88%; (c) LiOH, aq. EtOH, 0 ^oC - 5 ^oC, quantitative; (d) AcCl, reflux, $PMBNH_2$, CH_2Cl_2, 90%; (e) $BnOCH_2Cl$, THF, 0.1 M SmI_2 in THF, 0.01 equiv. $FeCl_3$, 0 ^oC - rt, 61%; (f) Et_3SiH, BF_3.OEt, CH_2Cl_2, -78 ^oC - rt; (g) CAN, $CH_3CN:H_2O$ = 9:1, 0 ^oC, 4 h, rt, 1.5 h, 84%; (h) $LiAlH_4$, THF, 60 ^oC, 12 h, 92%; (i) 10% Pd/C, HCOOH, MeOH, rt, 24 h, HCl, 100%.

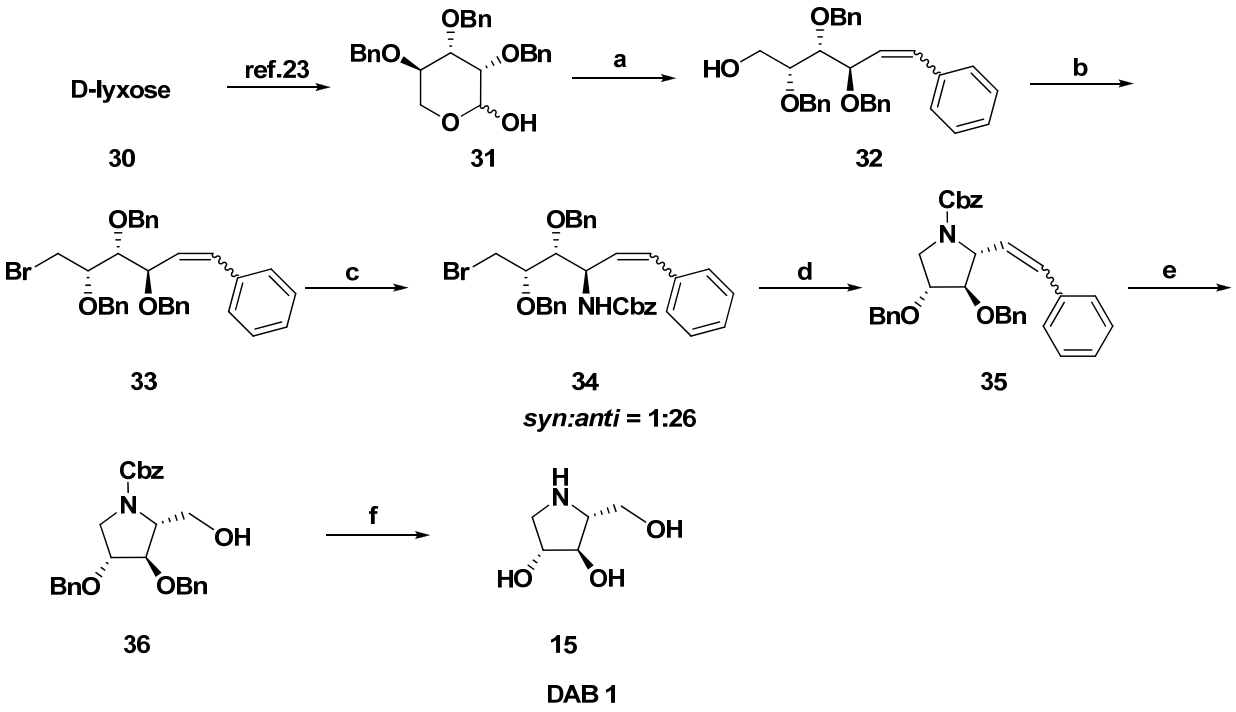
Synthesis of LAB 1 from L-tartaric acid



Scheme 4. *Reagents and conditions*: (a) CAN, $CH_3:CN:H_2O$ = 9:1, 0 ^oC, 4 h, rt, 1.5 h, 84%; (b) $LiAlH_4$, THF, 60 ^oC, 12 h, 92%; (c) 10% Pd/C, HCOOH, MeOH, rt, 24 h, HCl, 100%.

Jung *et al.* (2006)[22]

Jung *et al*.[22] reported the diastereoselective synthesis of 1,4-dideoxy-1,4-imino-$_D$-arabinitol from D-lyxose using chlorosulphonyl isocyanate as the key step (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) NaH, DMSO, $BnPPh_3Cl$, THF, 45 ^oC, 94%; (b) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 ^oC, 89%; (c) (i) CSI (chlorosulfonyl isocyanate), Na_2CO_3, toluene, 0 ^oC; (ii) 25% Na_2SO_3, 84%; (d) KO^{t}Bu, THF, 0 ^oC, 95%; (e) O_3, MeOH:CH_2Cl_2 (1:1), -78 ^oC, then $NaBH_4$, 0 ^oC, 85%; (f) 10% Pd/C, H_2, 6N HCl, EtOH, 98%.

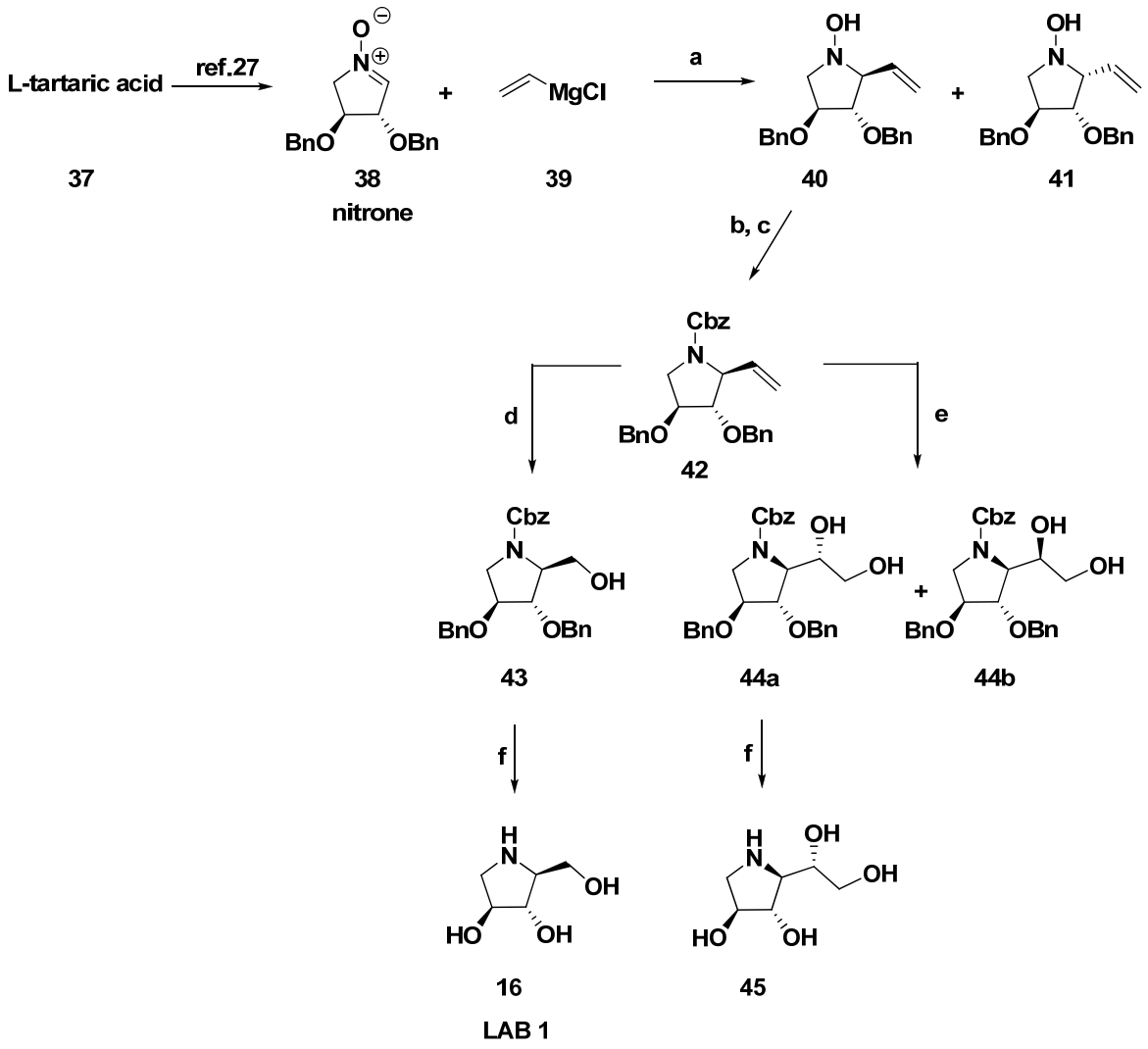
Hence, synthesis of DAB **1** started with the Wittig olefination of **31** with DMSO anion[24] in THF at 45 °C afforded **32** as a 3.1:1 mixture of *cis*/*trans* isomer. The hydroxyl moiety of **32** was then converted into bromide **33**[25] with CBr_4 and subsequent CSI (chlorosulfonyl isocyanate) reaction on cinnamyl tribenzyl ether **33** in toluene solution followed by desulfonylation with 25% sodium sulfite to give the allylic amine product **34** with a high diastereoselectivity (*syn*/*anti* = 1:26, 96% ds). Treatment of **34** with potassium *tert*-butoxide provided the pyrrolidine **35** which on ozonolysis and subsequent reduction of the resulting aldehyde gave the alcohol **36**.[26] Finally, the

benzyl and *N*-Cbz protecting groups of **36** were removed by palladium-catalyzed hydrogenolysis to give DAB**1** (**15**) in 98% yield.

Trombini *et al.* (2001)[26]

Trombini *et al*.[26] reported a short synthesis of enantiopure 1,4-Dideoxy-1,4-imino-$_L$-arabinitol (LAB **1**) and 1,4-Dideoxy-1,4-imino-$_D$-galactitol from nitrone derived from L-tartaric acid **37**. Thus, addition of vinylmagnesium chloride **39** to nitrone **38** in THF at 20 °C gave the *trans* adduct (2*S*,3*S*,4*S*)-1-hydroxy-2-ethenyl-3,4- bis(benzyloxy) pyrrolidine **40** in 90% yield and in a *dr* = 93/7. Cleavage of the *N*-O bond of **40** is carried out with Zn/Cu couple in aq. AcOH at 70 °C followed by Cbz protection of resulting amine produced **42**. Ozonolysis of terminal olefin followed by reductive quenching with $BH_3.SMe_2$ led to the Cbz protected pyrrolidine **43**.

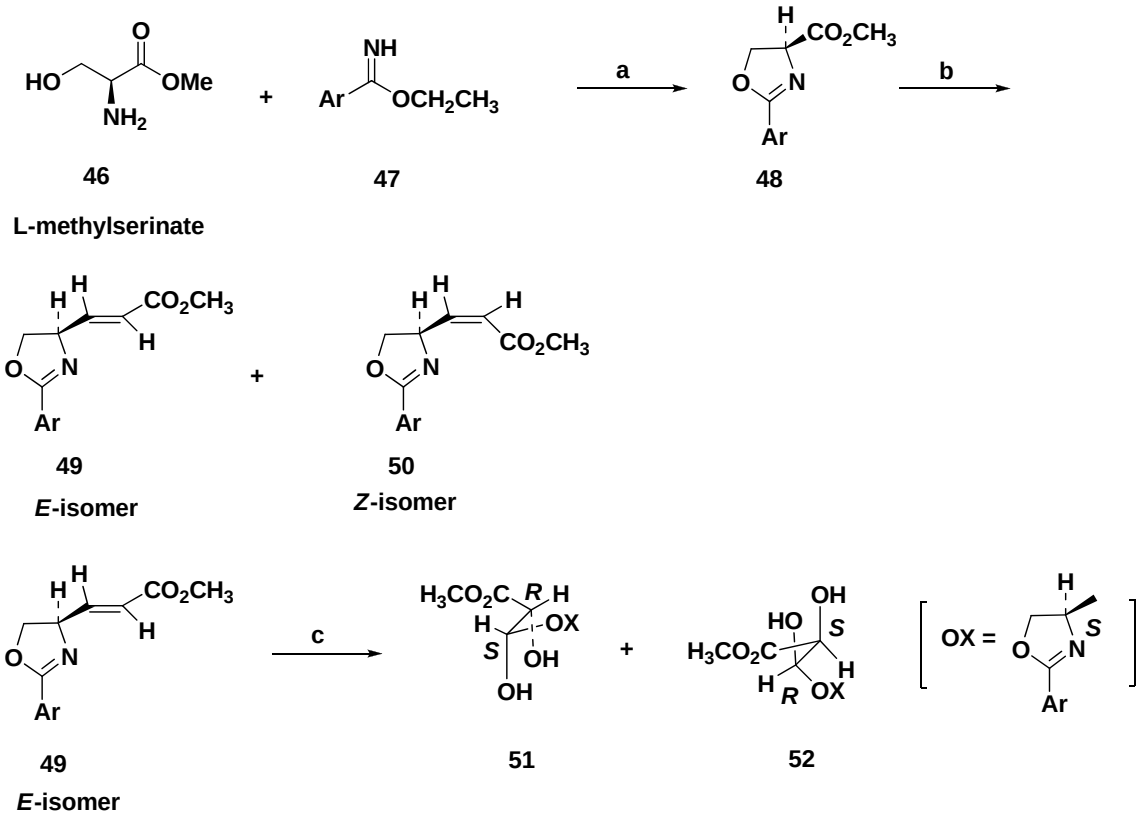
The target 1,4-dideoxy-1,4-imino-$_L$-arabinitol **16** may be freed by hydrogenolysis of **43** on Pd/carbon at atmospheric pressure in acidic ethanol. Finally, dihydroxylation of terminal olefin followed by cleavage of benzyl group led to the formation of requisite D-galactitol **45** (Scheme 6).



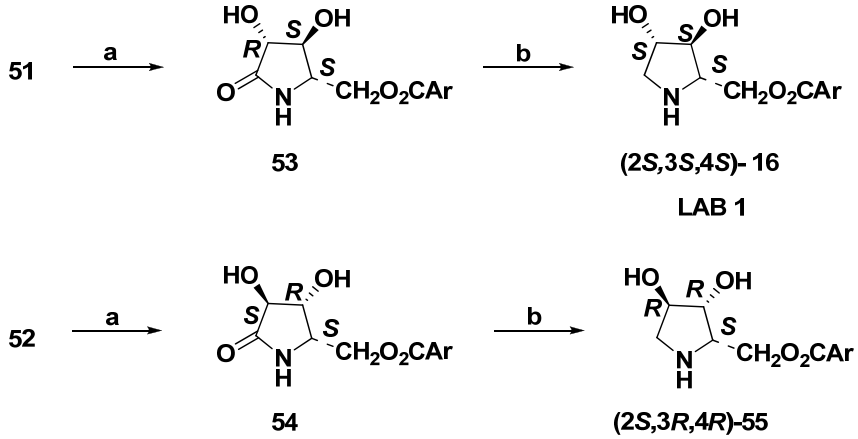
Scheme 6. *Reagents and condition*s: (a) THF, 20 ^{o}C, 1 h, 90%, dr = 93:7; (b) Zn/Cu, AcOH, H_2O, 70 ^{o}C, 30 min; (c) Cbz-Cl, Et_3N, CH_2Cl_2, 12 h, 89%; (d) (i) O_3, CH_2Cl_2, -78 ^{o}C, 30 min; (ii) $BH_3.SMe_2$, -78 ^{o}C→20 ^{o}C, 1 h, 67%; (e) AD-mix α, *t*-BuOH/H_2O, 24 h, 86%, dr = 83:17; (f) H_2, Pd/C, 2N HCl in EtOH, 1 atm, 12 h, 85-90%.

Dalton *et al.* (1997)[28]

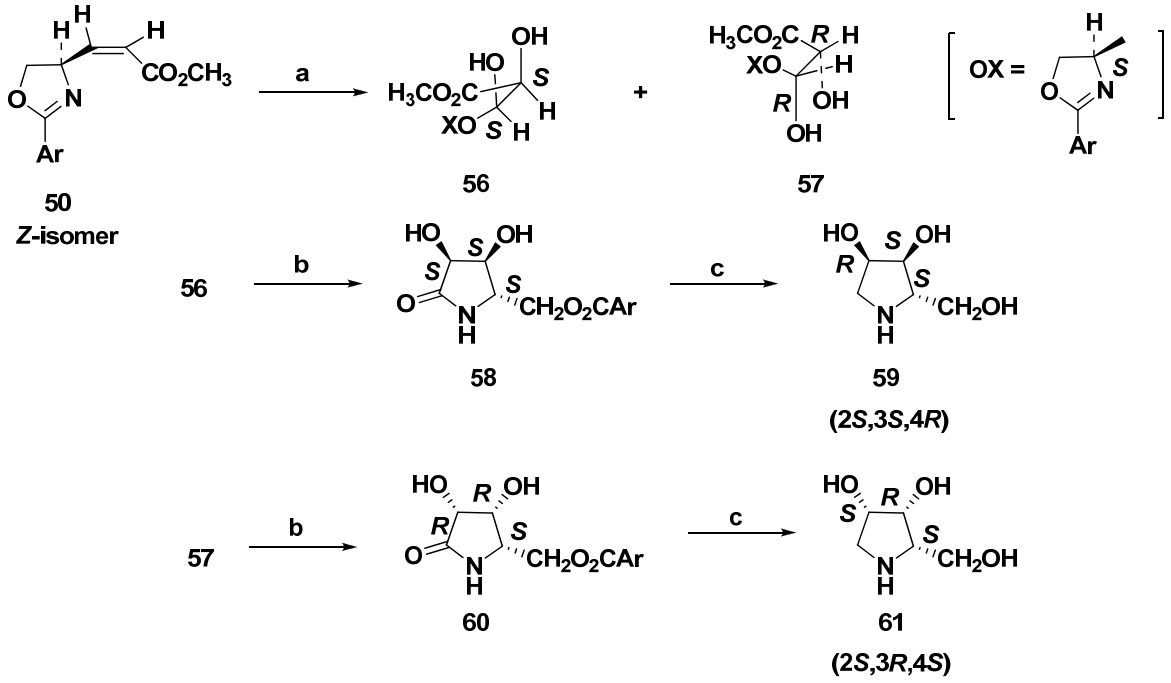
Dalton *et al.*[28] reported a short, stereoselective synthesis of all eight stereoisomeric 2-hydroxymethyl-3,4-dihydroxypyrrolidines (the enantiomeric pairs of iminorbitol, -arabinitol, -xylitol and -lyxitol) (Scheme 7, 8 & 9).



Scheme 7. *Reagents and conditions*: (a) DIBALH, ROH quench; (b) $(C_6H_5)_3P{=}CHCO_2Et$; (c) OsO_4 and NMO or $(DHQ)_2PHAL$ [$(DHQD)_2PHAL$].

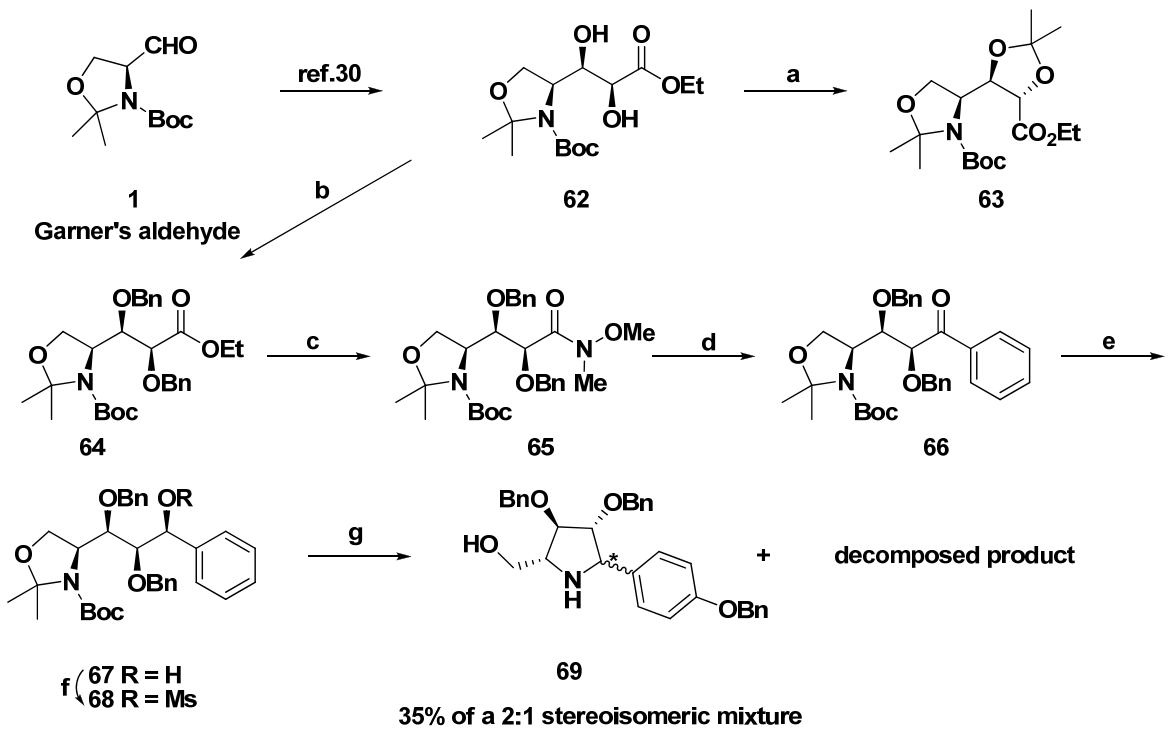


Scheme 8. *Reagents and conditions*: (a) aquous HCl; (b) B_2H_6/THF.



Scheme 9. *Reagents and conditions*: (a) OsO_4 and NMO or $(DHQ)_2PHAL$ [$(DHQD)_2PHAL$]; (b) aquous HCl; (c) B_2H_6/THF.

Falomir *et al.* (2008)[29]



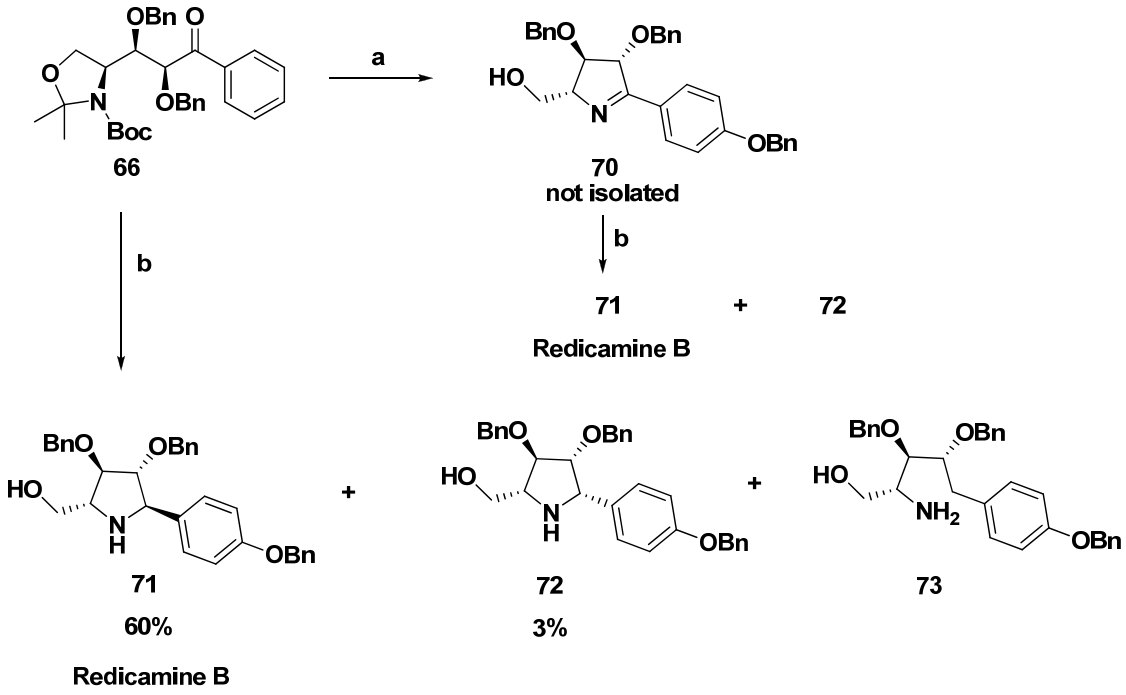
Scheme 10. *Reagents and conditions*: (a) DMP, TsOH, toluene, Δ; (b) Ag_2O, BnBr, Et_2O, 24 h, rt, 89%; (c) MeONH(Me).HCl, ^{i}PrMgCl, THF, 96%; (d) THF, 0 ^{o}C, 89%; (e) L-selectride, THF, -78 ^{o}C; (f) MsCl, Et_3N, CH_2Cl_2, 0 ^{o}C; (g) TFA, CH_2Cl_2, 0 ^{o}C, 35%, (2:1).

Falomir *et al.*[29] reported a short stereoselective synthesis of the naturally occurring pyrrolidine radicamine **B** and a formal synthesis of nectrisine from Garner's aldehyde **1** using Sharpless asymmetric dihydroxylation as the key step (Scheme 10, 11 & 12).

Attempted stereoselective synthesis of radicamine B

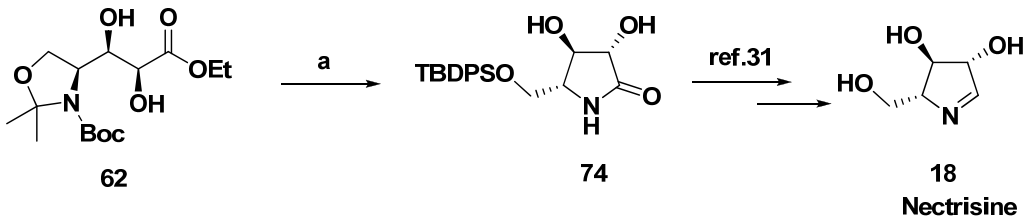
The absolute configuration of **62** was determined by converting it into its diacetonide derivative **63** (Scheme 10).

Stereoselective synthesis of radicamine B (71)



Scheme 11. *Reagents and conditions*: (a) $ZnBr_2$ (10 eq.), CH_2Cl_2, rt; (b) H_2, 10% Pd/C, 6 M HCl/MeOH, 1:10.

Formal synthesis of nectrisine (18)



Scheme 12. *Reagents and conditions*: (a) (i) TFA, 0 ^{o}C, 2 h; (ii) TPSCl, imidazole, DMF, rt, 16 h (67%).

4.1.4. Present Work

Much attention has been focused on this class of compounds because of their potential for cell-biological and therapeutic applications as a consequence of their role as glycosidase and glycosyltransferase inhibitors[15,16] due to their mimicry of the transition state of the enzymatic reactions.

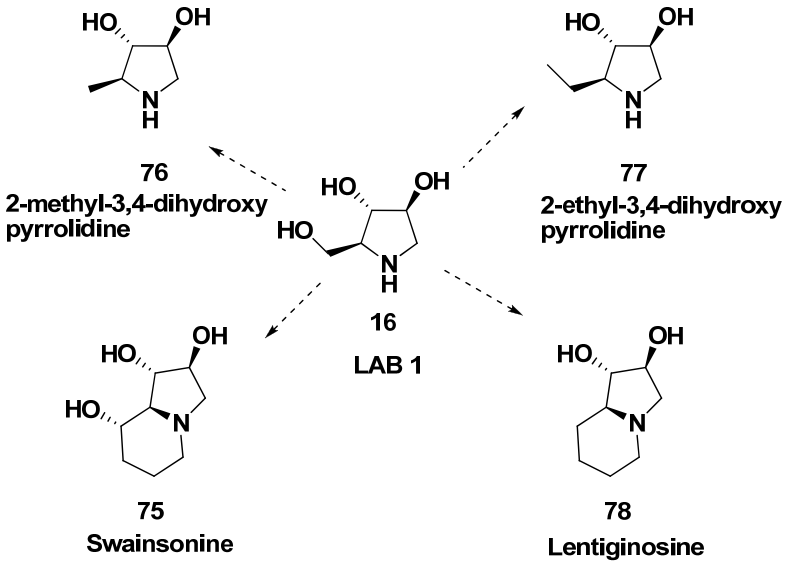


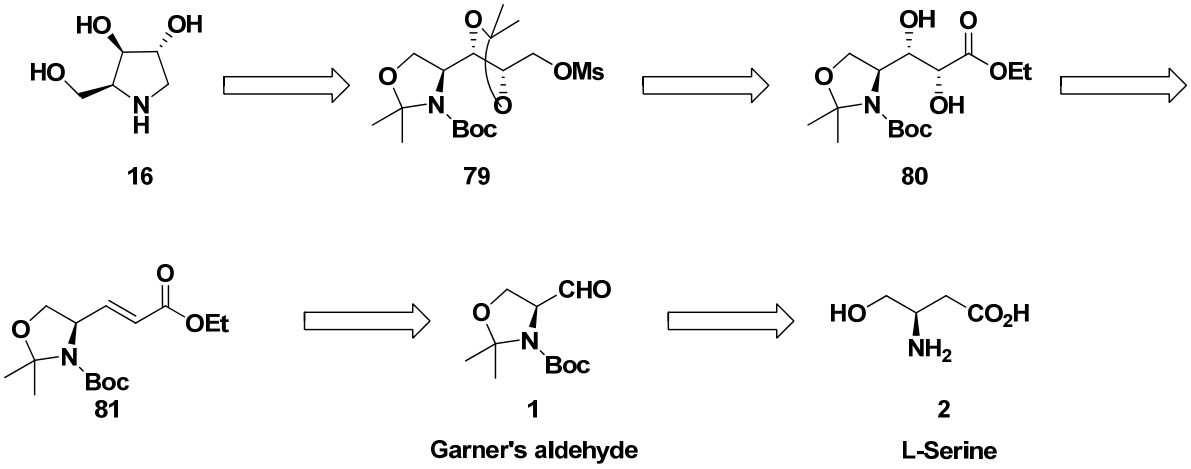
Figure 3. Structure of various polyhydroxylated pyrrolidine and indolizidine alkaloids

As a result, iminocyclitols have been attractive as target drug candidates for a number of diseases such as cancer, viral infection, lysosomal storage disorders, and diabetes.[32] Various synthetic methods for the synthesis of hydroxyprolines and pyrrolidines have

been reported from carbohydrates[33] and from non-carbohydrates,[34] out of which there are very few synthesis[34b-f] of hydroxylated pyrrolidine derivatives with the use of α-amino aldehydes as the synthetic precursor. As part of our research program aimed at developing enantioselective synthesis of naturally occurring amino alcohols[35] and on the above basis of the application of pyrrolidine alkaloids (Fig. 2) and the exceptional usage of α-amino aldehydes as a building block, we became interested for the synthesis of such an intermediate **16** which can be useful in the synthesis of variety of compounds of biological interest.

Retrosynthetic analysis of LAB 1 (16)

Our synthetic approach for the synthesis of 1,4-Dideoxy-1,4-imino-$_L$-arabinitol (LAB **1**) was envisioned via the synthetic route as shown below.



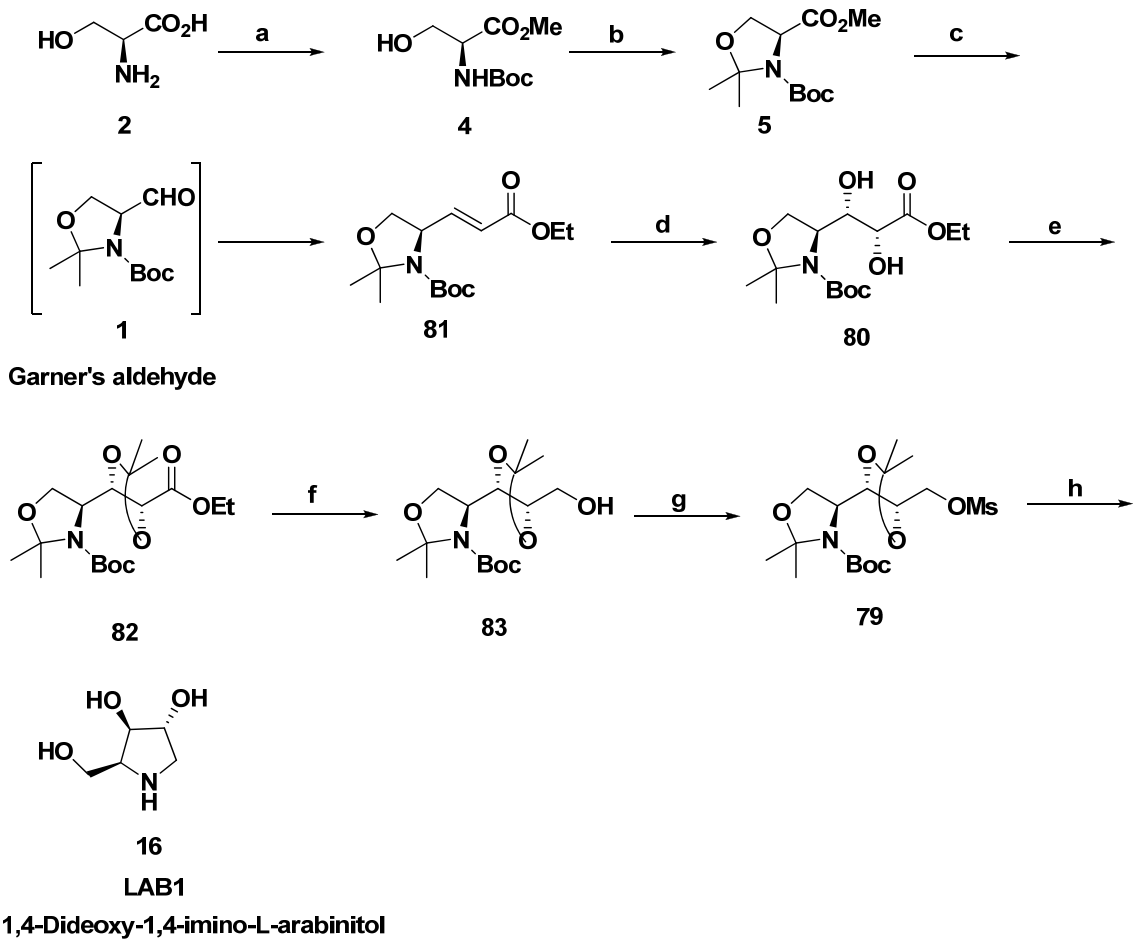
Scheme 13. Retrosynthetic analysis of LAB **1**

From the above synthetic analysis we observed that target molecule LAB **1** (**16**) could be obtained from mesylate **79** which in turn could be accessed from α,β-diol ester **80** that would be produced by dihydroxylation of olefin **81** which in turn could be synthesized from Garner's aldehyde **1** using L-serine **2** as the starting material.

4.1.5. Results and Discussion

The synthesis of molecule **16** (LAB 1) started from chiral pool material L-serine **2**. Following the literature precedence,[1-14] Garner's aldehyde was prepared in five step

from L-serine **2** under known conditions (Scheme 1).[2,3] The freshly prepared Garner's aldehyde was immediately subjected for 2C-Wittig olefination to give the compound **81** in 90% yield. The ^{1}H NMR spectrum of **81** showed the presence of olefinic proton at δ 5.87 (d, 1H) and at δ 6.75-6.86 (m, 1H) and also the presence of peak at ν 1712 cm^{-1}confirmed the presence of C=O group (Scheme 14).



Scheme 14. *Reagents and condition*s: (a) (i) Boc_2O, 1N NaOH, dioxane, H_2O, 0 ^oC - rt, 3.5 h; (ii) MeI, K_2CO_3, DMF, 0 ^oC - rt, 1.5 h, 86%; (b) 2,2-DMP, $BF_3.OEt_2$, dry acetone, rt, 2 h, 90%; (c) (i) DIBAL-H, -78 ^oC, dry toluene, 1-2 h; (ii) $Ph_3P{=}CHCO_2Et$, dry THF, 60 ^oC, 5 h, 80%; (d) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH:H_2O, 0 ^oC, 24 h, 92%; (e) 2,2-DMP, TsOH, dry toluene, reflux, 30 min, 96%; (f) $LiAlH_4$, dry THF, 0 ^oC - rt, 1 h, 75%; (g) CH_3SO_2Cl, Et_3N, DMAP, dry CH_2Cl_2, 0 ^oC, 2 h, 80%; (h) 2N HCl, EtOAc, 0 ^oC, 3 h, then sat.$NaHCO_3$, pH = 8, 67%.

By modifying Dondoni method,[30] we carried out dihydroxylation of **81** under Sharpless condition using $(DHQ)_2PHAL$ ligand to give dihydroxy ester **80** in 92% yield.[50] The ^1H NMR spectrum of compound **80** showed the absence of olefinic protons at δ 5.87 (d, 1H) and at δ 6.75-6.86 (m, 1H) and also the presence of peak at ν 3435 cm^{-1} in IR confirmed the formation of compound **80**. Acetonide protection of compound **80** with 2, 2-DMP in presence of catalytic amount of *p*-TsOH furnished the diacetonide **82** in 96% yield. The spectroscopic data of **82** was in accordance with the literature precedence.[30] Reduction of compound **82** was carried out with 1.2 equivalent of $LiAlH_4$ and subsequent mesylation of resulting amino alcohol **83** gave the mesylate **79** in 80% yield. The ^1H NMR spectrum of compound **79** showed the presence of methyl proton of mesylate at δ 3.03 (s, 3H) and and absence of -OH peak at 3500 cm^{-1} in IR confirmed the formation of compound **79**. Finally, global deprotection of **79** with 2N HCl gave the target molecule **16** in 67% yield. The spectral properties (^1H and ^{13}C NMR) of target molecule **16** (LAB 1) were in full agreement with the reported literature values.[26]

4.1.6. Conclusion

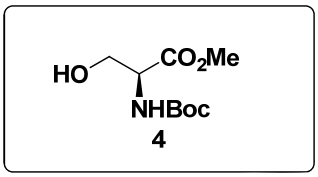
In summary, we have achieved a short synthesis of polyhydroxylated (2*S*,3*S*,4*S*)-2-(hydroxymethyl)pyrrolidine-3,4-diol using dihydroxylation as key step.

4.1.7. Experimental Section

General information

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature using sodium D line on JASCO-181. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (4).



4

A solution of di-*tert*-butyldicarbonate (Boc_2O) (24.94 g, 114.29 mmol) in dioxane (90 mL) is added to an ice cold solution of L-serine **2** (10.0 g, 95.24 mmol) in 1N NaOH (7.62 g in 190.5 mL H_2O) by means of an addition funnel. The two phase mixture is stirred at 5°C for 30 min, then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35°C, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 mL). The combined extracts are dried over Na_2SO_4, filtered and concentrated to give 18.5 g (95% crude yield) of *N*-Boc-L-serine as colorless, sticky foam which is used without further purification.

To a ice cold solution of *N*-Boc-L-serine (18.5 g, 90.24 mmol) in DMF (160 mL) was added solid K_2CO_3 (13.70 g, 99.26 mmol). After stirring for 10 min in an ice bath, methyl iodide (25.62 g, 180.48 mmol) is added to the white suspension and stirring continued at 0°C for 30 min where upon the mixture solidifies. The reaction is warmed to room temperature and stirred for additional 1 h or so at which point TLC analysis indicates complete formation of the methyl ester. The reaction mixture is filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase is washed with brine, dried, filtered and filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (3: 7) as eluent gave *N*-Boc-L-serine methyl ester **4** as a thick liquid.

Yield: 18 g (86%, after two step).

Mol. Formula: $C_9H_{17}NO_5$

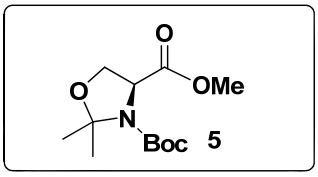
$[\alpha]^{25}_D$: -18.4 (*c* 5.0 MeOH); [lit. $[\alpha]^{20}_D$: -18.9 (*c* 5.0 MeOH)].[4]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3464, 3350, 1740, 1652.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 3.76 (s, 3H), 3.87-3.95 (m, 2H), 4.35 (m, 1H), 5.56 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 52.1, 55.4, 62.4, 79.8, 155.6, 171.4.

(*S*)-3-*tert*-Butyl-4-methyl-2,2-dimethyloxazolidine-3,4-dicarboxylate (5).



5

To a solution of ester **4** (1.0 g, 4.57 mmol) in dry acetone (19.0 mL) was added 2,2-DMP (5.0 mL) and $BF_3.OEt_2$ (0.033 mL) at rt and solution was stirred for 2 h, after which time TLC showed no remaining starting material, solvent was evaporated in vacuo and residual oil was dissolved in CH_2Cl_2 (15 mL) and washed with sat. $NaHCO_3$ and H_2O (1:1), then brine (20 mL), dreid over Na_2SO_4 and evaporated in vacuo to give compound **5** as a pale yellow color oil.

Yield: 1.07 g (90%).

Mol. Formula: $C_{12}H_{21}NO_5$

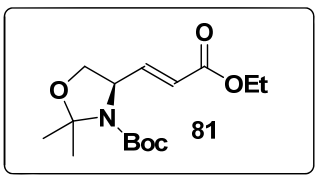
$[\alpha]^{25}_D$: -56.9 (*c* 1.3 $CHCl_3$); [lit $[\alpha]^{20}_D$: -57 (*c* 1.3 $CHCl_3$)].[2,3]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2981, 1752, 1685, 1538, 1438, 1395.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.37-3.40 (m, 5H), 3.43-3.49 (m, 7H), 3.59-3.62 (m, 3H), 5.71 (s, 3H), 5.95-6.15 (m, 2H), 6.32-6.47 (m,1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 28.0, 52.1, 62.5, 68.4, 79.5, 105.4, 152.4, 171.2.

(*R, E*)-*tert*-Butyl-4-(3-ethoxy-3-oxoprop-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate (81).



81

To a solution of ester **5** (1.0 g, 3.86 mmol) in dry toluene (10 mL) was added a solution of 1.923 M DIBAL (2.21 mL, 4.25 mmol) at -78 ^oC. The rate of addition is adjusted so as to keep the internal temperature below -65 ^oC and takes approximately 1 h to complete. The reaction mixture is stirred for an additional 2 h at -78^oC. The reaction was quenched by slow addition of 10 mL of cold (-78^oC) methanol (evolution of

hydrogen occurs) so as to keep the internal temperature below -65 ^{o}C. The resulting white emulsion is slowly poured into 5 mL of ice cold 1N HCl with swirling over 15 min. and the aqueous mixture is then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated to give Garner's aldehyde **1** (0.8 g) as a colorless oil which was used immediately without further purification.

To a solution of (ethoxycarbonylmethylene) triphenyl phosphorane (1.83 g, 5.24 mmol) in dry THF (15 mL) was added a solution of above aldehyde **1** (0.8 g, 3.45 mmol) in dry THF (5 mL). The reaction mixture was stirred at rt for 5 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether / EtOAc (9.5:0.5) as eluent to give the α,β-unsaturated olefin **81** as an yellow color oil.

Yield: 0.94 g (80%); (after two step).

Mol. Formula: $C_{15}H_{25}NO_5$

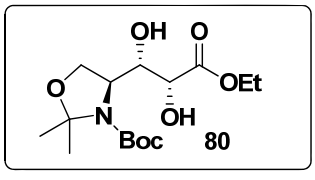
$[\alpha]^{25}_D$: -44.02 (*c* 1.09, $CHCl_3$); [lit. $[\alpha]^{20}_D$: -44.3 (*c* 1.09, $CHCl_3$)].[30]

IR ($CHCl_3$, cm^{-1}): ν_{max} 1712,

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.08 Hz, 3H), 1.40-1.61 (m, 15H), 3.74-3.80 (m, 1H), 4.03-4.11 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.39-4.52 (m, 1H), 5.87 (d, *J* = 15.4 Hz, 1H), 6.75-6.86 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 25.1, 28.2, 60.5, 65.7, 72.3, 80.2, 105.5, 121.2, 137.1, 150.5, 165.8.

(*S*)-*tert*-Butyl-4-(1*S*,2*R*)-3-ethoxy-1,2-dihydroxy-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (80).



To a mixture of $K_3Fe(CN)_6$ (6.94 g, 21.1 mmol), K_2CO_3 (2.91 g, 21.1 mmol) and $(DHQ)_2PHAL$ (60 mg, 1 mol%) in *t*-BuOH:H_2O (1:1, 35 mL) cooled at 0 ^{o}C was added OsO_4 (0.3 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (0.7 g, 7.02 mmol). After being stirred for 5 min at 0 ^{o}C, the olefin **81** (2.10 g, 7.02

mmol) was added in one portion. The reaction mixture was stirred at 0 ^{o}C for 24 h and then quenched with solid sodium sulfite (10.5 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (80:20) as eluent to give the diol **80** as a colorless syrupy liquid.
Yield: 2.15 g (92%).

Mol. Formula: $C_{15}H_{27}NO_7$

$[\alpha]^{25}_{D}$: -22.03 (*c* 0.82, $CHCl_3$); [lit. $[\alpha]^{20}_{D}$: -21.2 (*c* 0.82, $CHCl_3$)].[30]

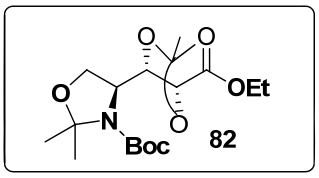
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3019, 1719, 1693, 1599, 1369.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.20 Hz, 3H), 1.48-1.56 (m, 15H), 3.86-3.94 (m, 2H), 3.99-4.05 (m, 1H), 4.14-4.20 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.73 (brs, 1H),

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 23.8, 28.1, 58.6, 61.3, 65.2, 70.4, 72.8, 81.7, 94.0, 154.3, 171.4.

Mass [LCMS]: 334 (M+1), 356 (M^+ + Na), 372.3 (M^+ + K).

Ethyl(2*R*,3*S*,4*S*)-2,3,5-trihydroxy-2,3-*O*-isopropylidene-4,5-*N*,*O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanoate (82).



82

To a solution of the diol **80** (0.5 g, 1.51 mmol) in dry toluene (16 mL), 2,2-dimethoxypropane (5 mL) and *p*-toluensulfonic acid monohydrate (6.3 mg, 0.03 mmol) were added. After refluxing for 30 min, the solution was treated with saturated aqueous $NaHCO_3$. The separated organic layer was dried (Na_2SO_4) and the solvent was concentrated in vacuo. The crude residue was chromatographed on silica gel using EtOAc/petether (0.5:95) as eluent to give compound **82** as a white solid.
Yield: 0.54 g (96%).

Mol. Formula: $C_{18}H_{31}NO_7$

M.P: 52 ^{o}C-54 ^{o}C; [lit.(M.P.54 ^{o}C-56 ^{o}C)].[30]

$[\alpha]^{25}_{D}$: -15.21 (*c* 1.04, $CHCl_3$); [lit.$[\alpha]^{20}_{D}$: -15.4 (*c* 1.04, $CHCl_3$)].[30]

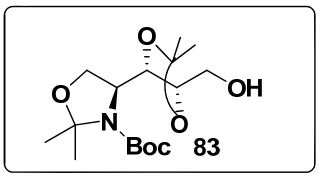
IR ($CHCl_3$, cm^{-1}): ν_{max} 2984, 1746, 1692, 1459, 1377, 1210.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.39-1.56 (m, 21H), 3.89-3.97 (m, 1H), 4.04-4.20 (m, 4H), 4.9 (d, *J* = 6.2 Hz, 1H), 4.27-4.32 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 25.8, 27.0, 28.2, 59.4, 61.1, 65.2, 78.7, 80.5, 93.9, 94.5, 110.5, 111.2, 153.1, 170.8.

Mass [LCMS]: 371 (M^{+3}), 396 (M^{+2} + Na), 411.9 (M^{+1} + K).

(2*R*,3*S*,4*S*)-1,2,3,5-Tetrahydroxy-2,3-*O*-isopropylidene-4,5-*N*,*O*-isopropylidene-4-(*tert*butoxycarbonylamino)pentanol (83).



To a solution of LAH (0.23 g, 6.1 mmol) in anhydrous THF (20 mL) was added a solution of ester **82** (1.5 g, 4.04 mmol) in anhydrous THF at 0 ^{o}C through syringe and resulting mixture was stirred for 1 h at rt. As the TLC showed the complete consumption of starting material, the reaction mixture was quenched with sat. Na_2SO_4 at 0 ^{o}C, then filtered through celite pad and filtrate was concentrated. The crude residue was purified by silica gel column chromatography using EtOAc/pet ether (2:8) as eluent to give the amino alcohol **83** as a colorless oil.
Yield: 1.0 g (75%).

Mol. Formula: $C_{16}H_{29}NO_6$

$[\alpha]^{25}_{D}$: -22 (*c* 0.8, $CHCl_3$).

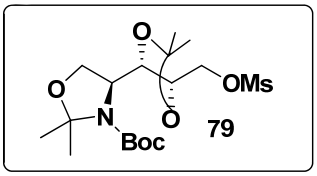
IR ($CHCl_3$, cm^{-1}): ν_{max} 3500, 2938, 1694, 1456, 1378, 1251, 1060.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37-153 (m, 21H), 2.38 (brs, 1H), 3.52 (m, 1H), 3.73-3.92 (m, 3H), 4.06-4.26 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 26.8, 28.1, 58.9, 62.0, 65.2, 79.2, 80.6, 93.7, 108.2, 153.0.

Analysis: Calcd.: C, 57.99; H, 8.82; N, 4.23%; **Found:** C, 58.10; H, 8.93; N 4.37%.

Mesylate-(2*R*,3*S*,4*S*)-1,2,3,5-tetrahydroxy-2,3-*O*-isopropylidene-4,5-*N*,*O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanol (79).



To a solution of alcohol **83** (0.6 g, 1.81 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Et_3N (0.4 mL, 2.72 mmol) at 0 ^oC. After stirring for 10 min mesyl chloride (0.2 mL, 2.17 mmol) and DMAP (0.27 g, 2.72 mmol) was added respectively and resulting mixture was stirred for 2 h at 0 ^oC. As the TLC showed the complete consumption of starting material, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (3 x 15 mL), then washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified with silica gel column chromatography using EtOAc/pet ether (10:90) as eluent to give compound **79** as a white sticky compound.

Yield: 0.6 g (80%).

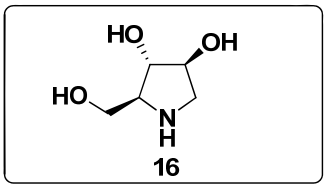
Mol. Formula: $C_{17}H_{31}NO_8S$

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 6H), 1.47-1.53 (m, 15H), 3.03 (s, 3H), 3.84 (t, J = 8.5 Hz, 1H), 3.90-3.93 (m, 1H), 4.06-4.15 (m, 3H), 4.32 (d, J = 11.3 Hz, 1H), 4.52 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.9, 27.0, 28.3, 37.7, 62.3, 69.1, 75.6, 80.3, 110.1, 120.0, 155.8

Analysis: Calcd.: C, 49.86; H, 7.63; N, 3.42%; **Found:** C, 49.94; H, 7.73; N, 3.58%.

(2*S*,3*S*,4*S*)-2-(hydroxymethyl)pyrrolidine-3,4-diol, LAB 1 (16).[26]



16

To a solution of mesylate **79** (0.1 g, 0.24 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added TFA (0.05 mL, 0.61 mmol) at 0 ^oC and after having stirred for 3 h, solvent was evaporated and crude residue washed with CH_2Cl_2 (3 x 5 mL) to remove excess TFA then neutralized with sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (5 x 10 mL), then dried over Na_2SO_4 and concentrated. The crude compound was purified by flash silica gel column chromatography using CH_2Cl_2/MeOH (1:1) as eluent to give the target molecule **16** as a pale yellow color oil.

Yield: 22 mg (67%).

Mol. Formula: $C_5H_{11}NO_3$

$[\alpha]^{25}_D$:-11.4 (*c* 0.2 MeOH); [lit $[\alpha]^{25}_D$: -12 (*c* 0.21 MeOH)].[26]

IR ($CHCl_3$, cm^{-1}): ν_{max} 2995, 2488, 1671.

^{1}H NMR (500 MHz, MeOH-d_4): δ 5.17-5.52 (m, 3H), 5.67-5.72 (m, 4H), 6.87 (s, 4H)

^{13}C NMR (125 MHz, MeOH-d_4): δ 54.4, 66.8, 77.7, 78.0, 78.2.

4.1.8. Spectra

1] ^{1}H NMR Spectrum of **4**

2] ^{13}C NMR spectrum of **4**

3] ^{1}H NMR spectrum of **80**

4] ^{13}C NMR spectrum of **80**

5] ^{1}H NMR spectrum of **82**

6] ^{13}C NMR spectrum of **82**

7] ^{1}H NMR spectrum of **83**

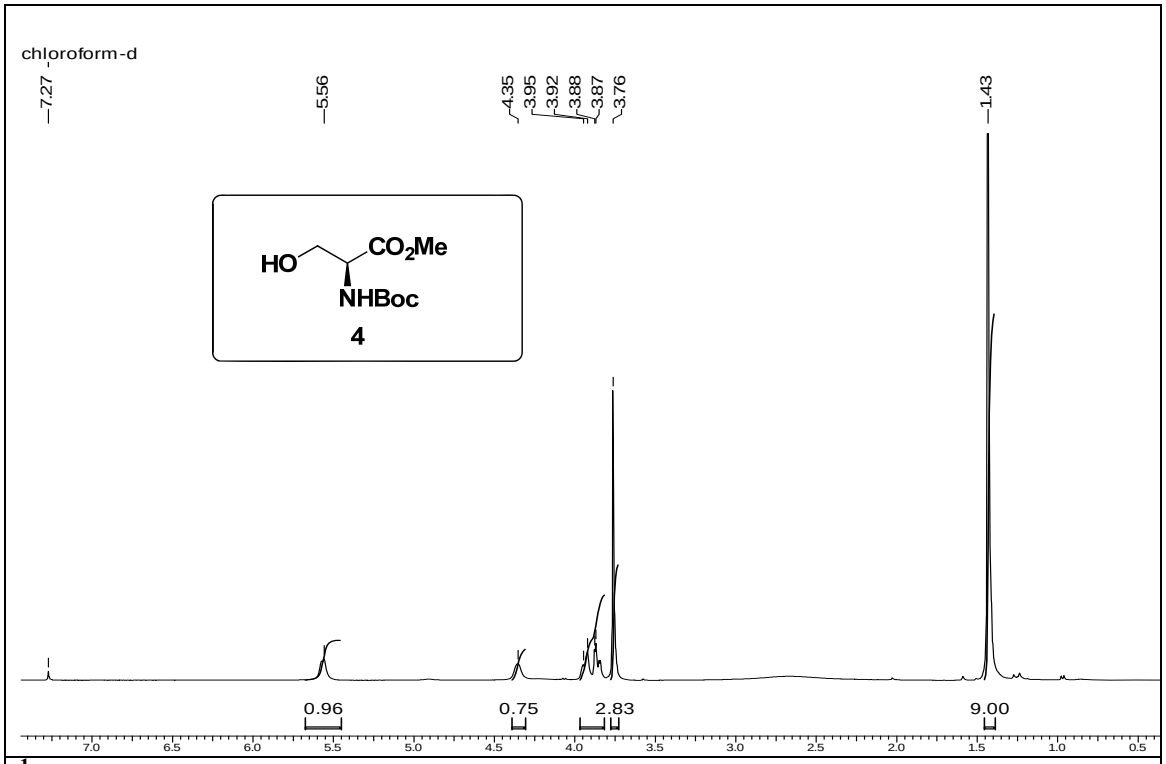
8] ^{13}C NMR spectrum of **83**

9] ^{1}HNMR spectrum of **79**

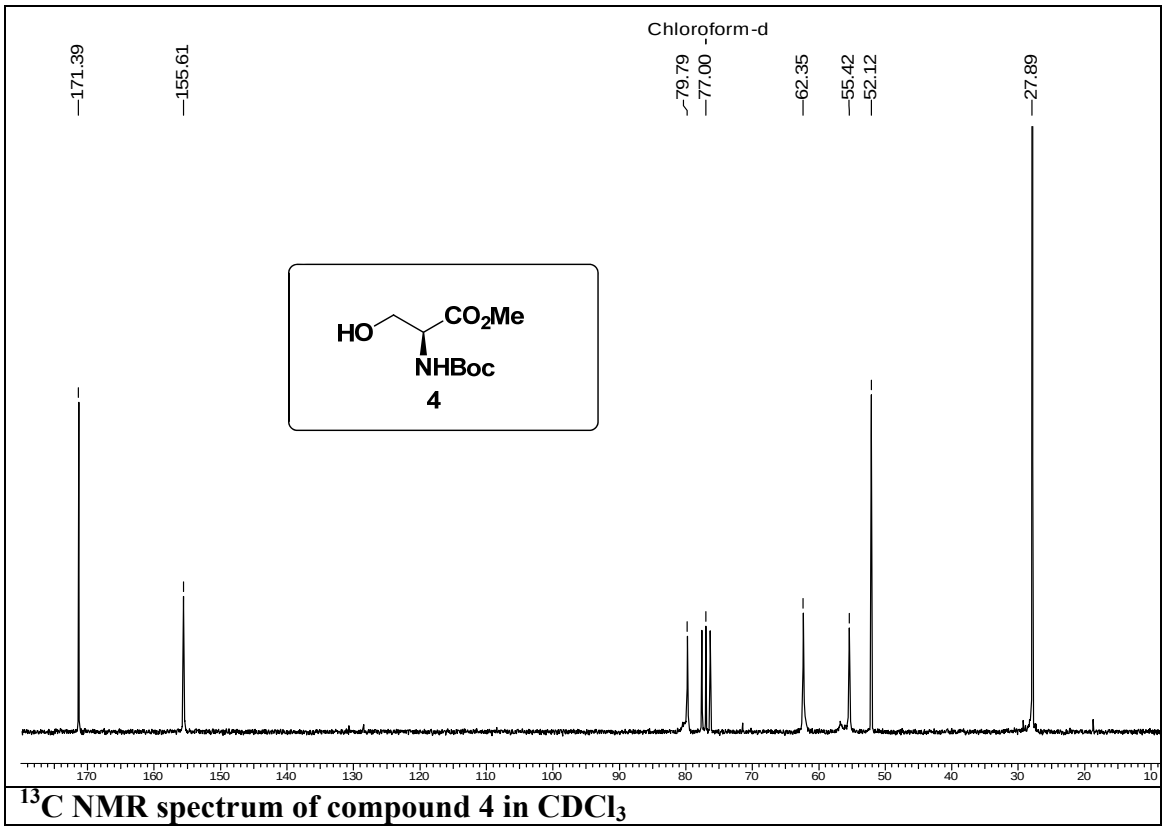
10]^{13}C NMR spectrum of **79**

11] ^{1}HNMR spectrum of **16**

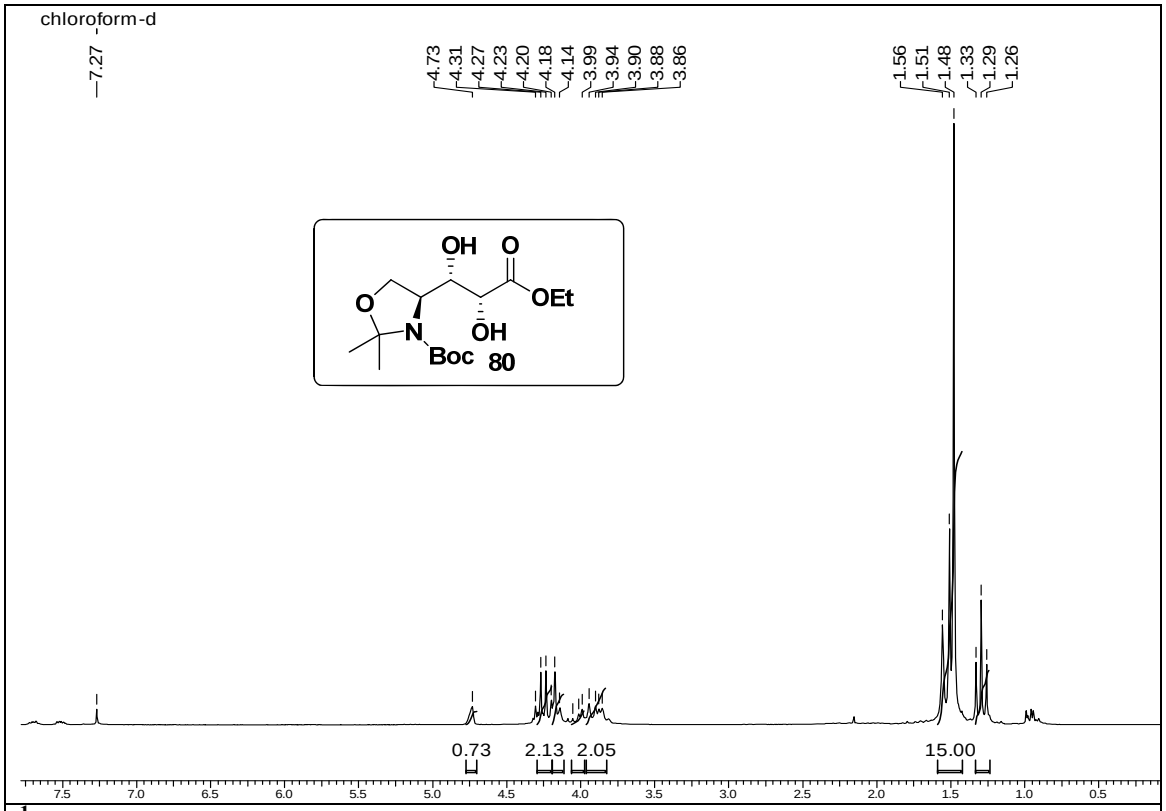
12] ^{13}C NMR spectrum of **16**



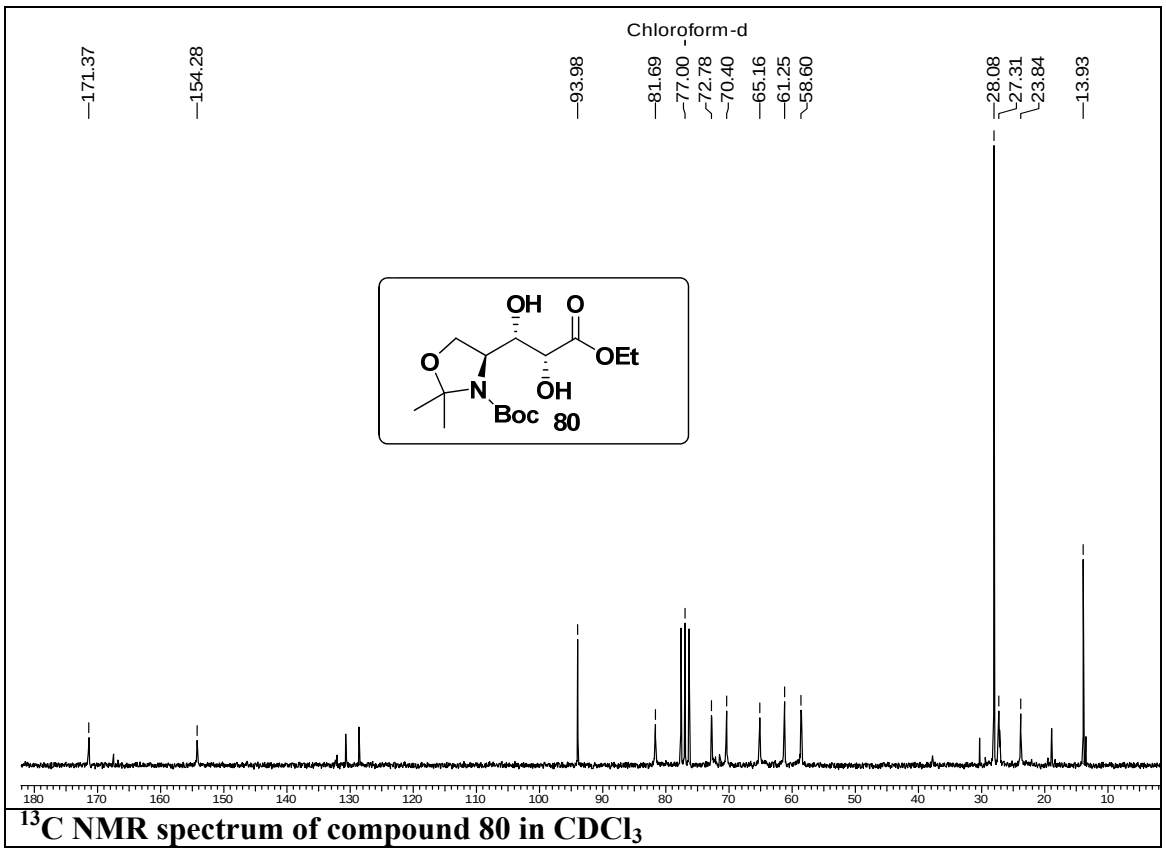
^{1}H NMR spectrum of compound 4 in $CDCl_3$



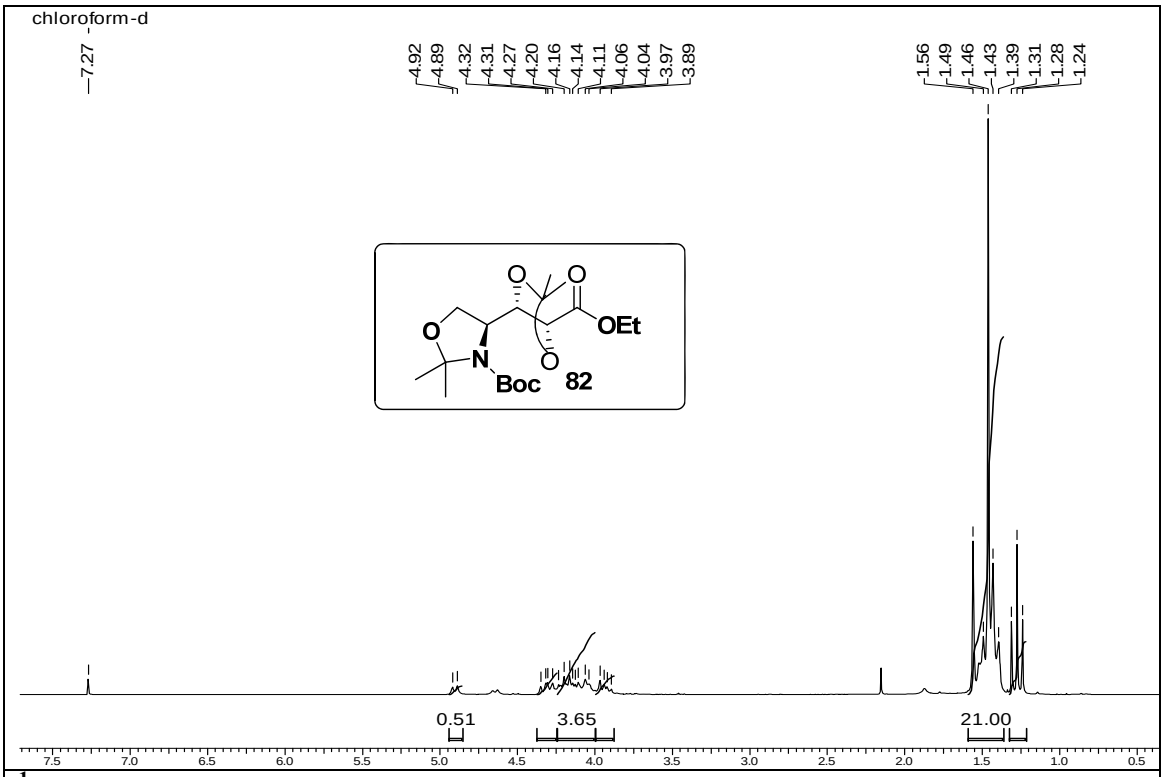
^{13}C NMR spectrum of compound 4 in $CDCl_3$



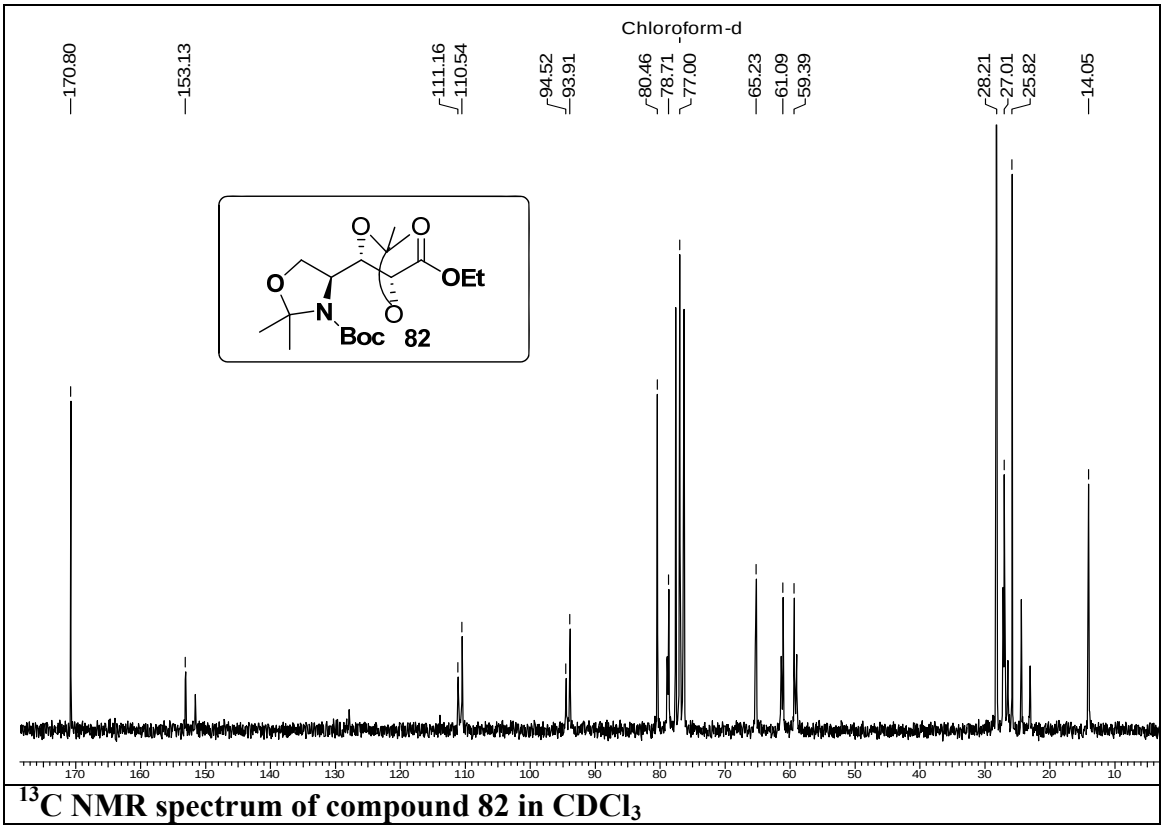
^{1}H NMR spectrum of compound 80 in $CDCl_3$



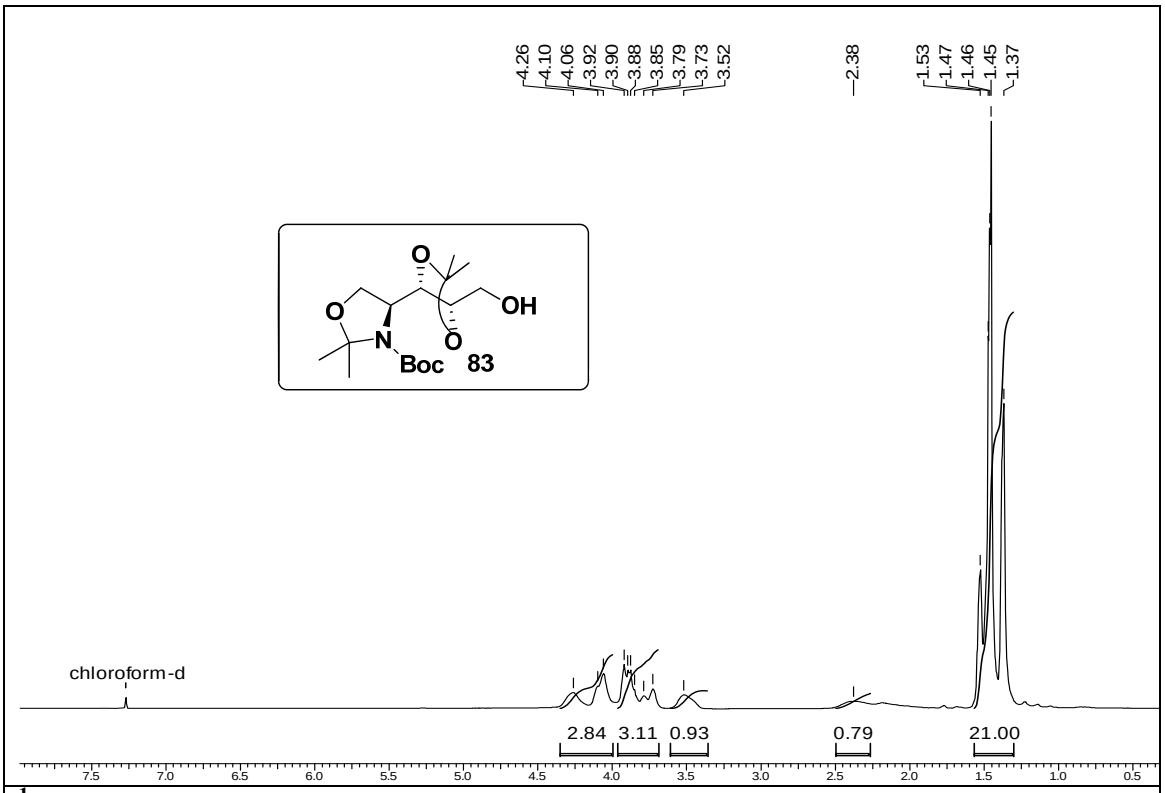
^{13}C NMR spectrum of compound 80 in $CDCl_3$



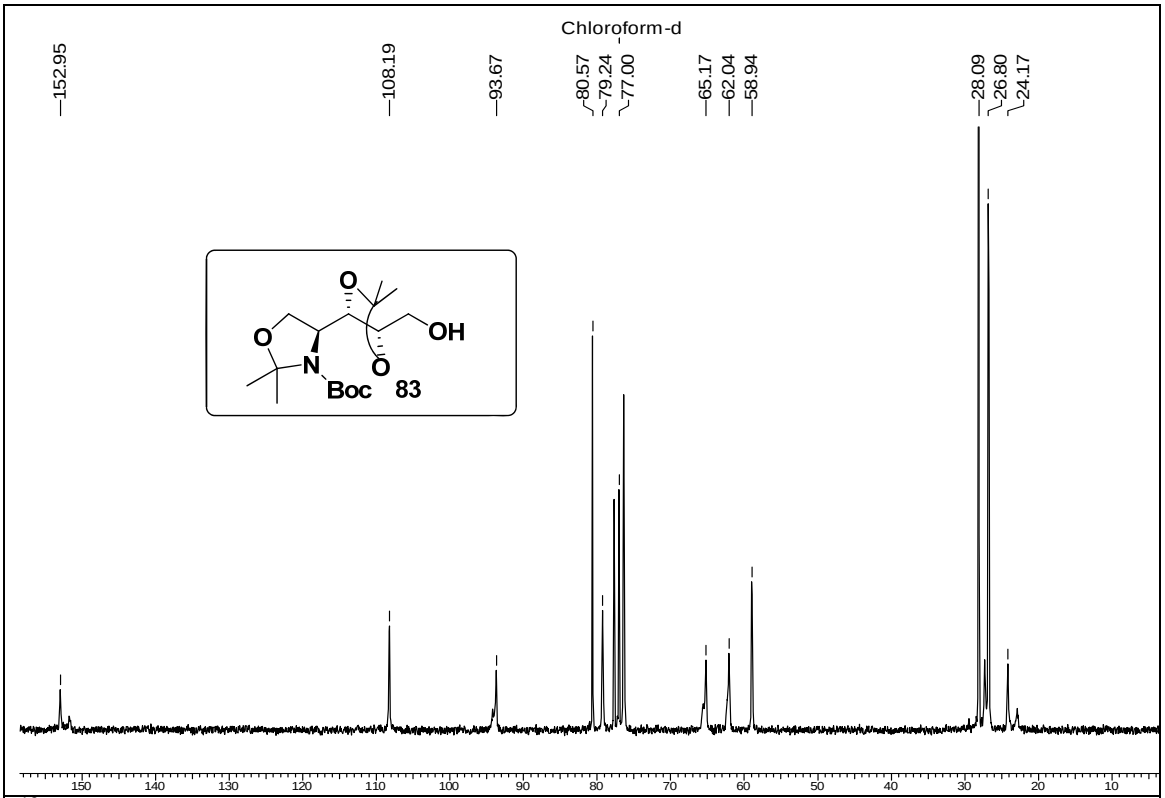
^{1}H NMR spectrum of compound 82 in $CDCl_3$



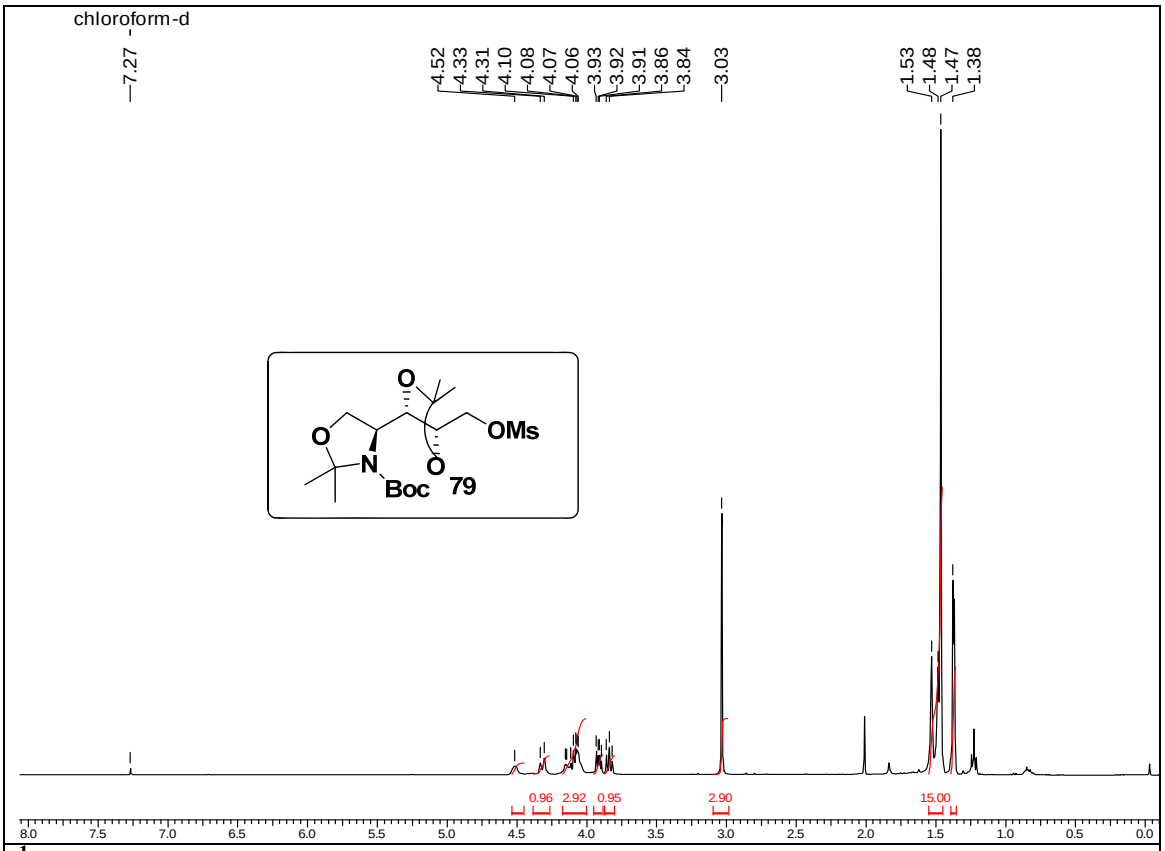
^{13}C NMR spectrum of compound 82 in $CDCl_3$



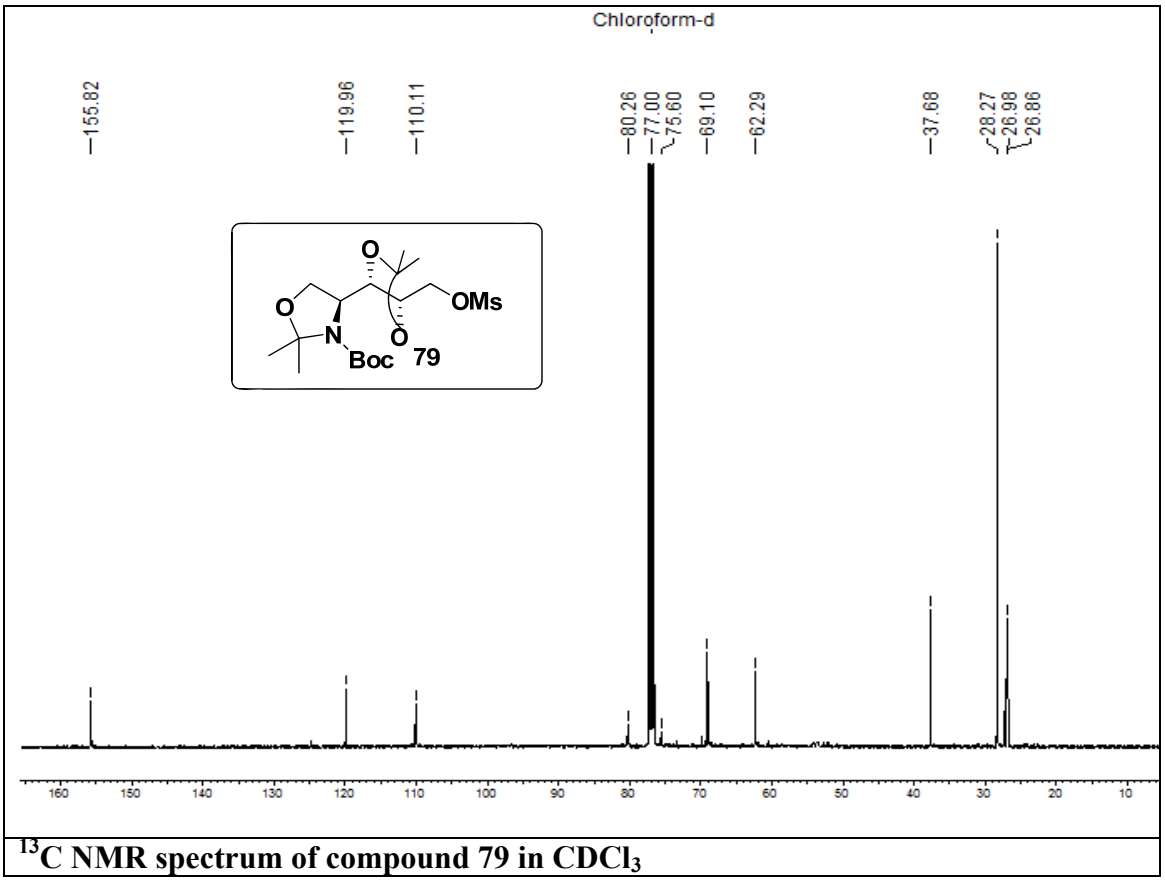
^{1}H NMR spectrum of compound 83 in $CDCl_3$



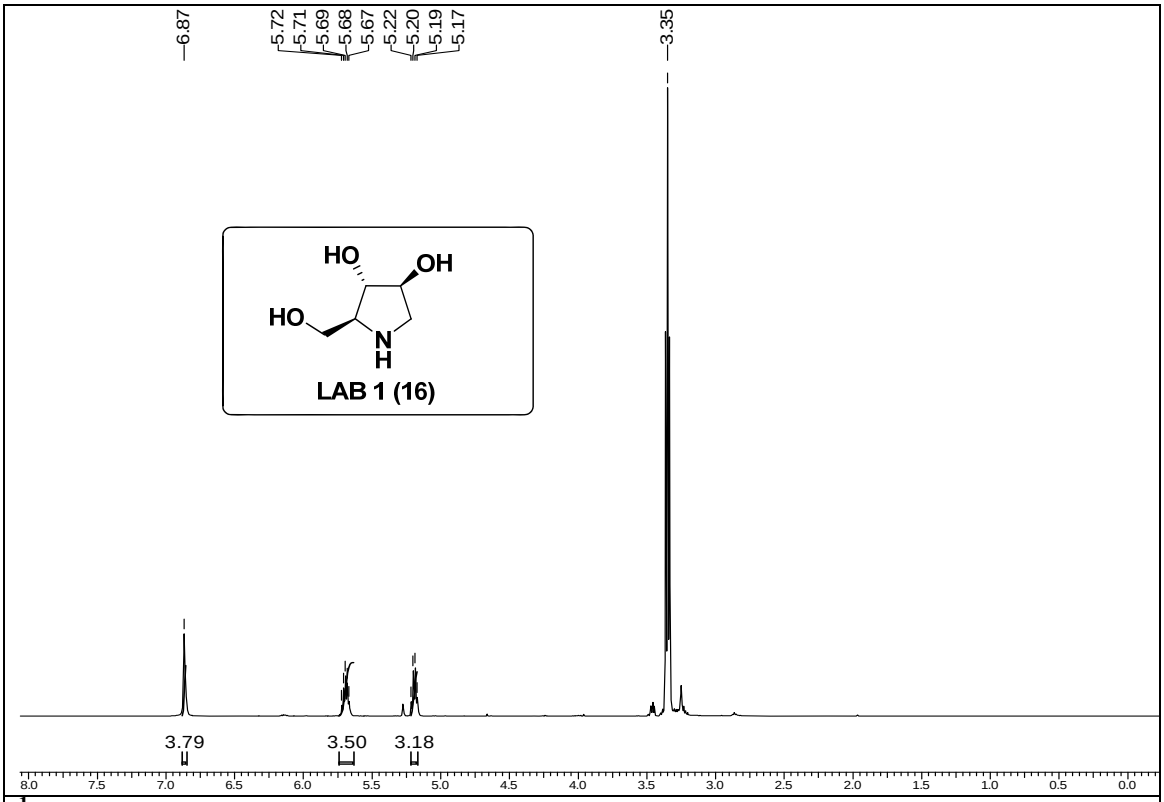
^{13}C NMR spectrum of compound 83 in $CDCl_3$



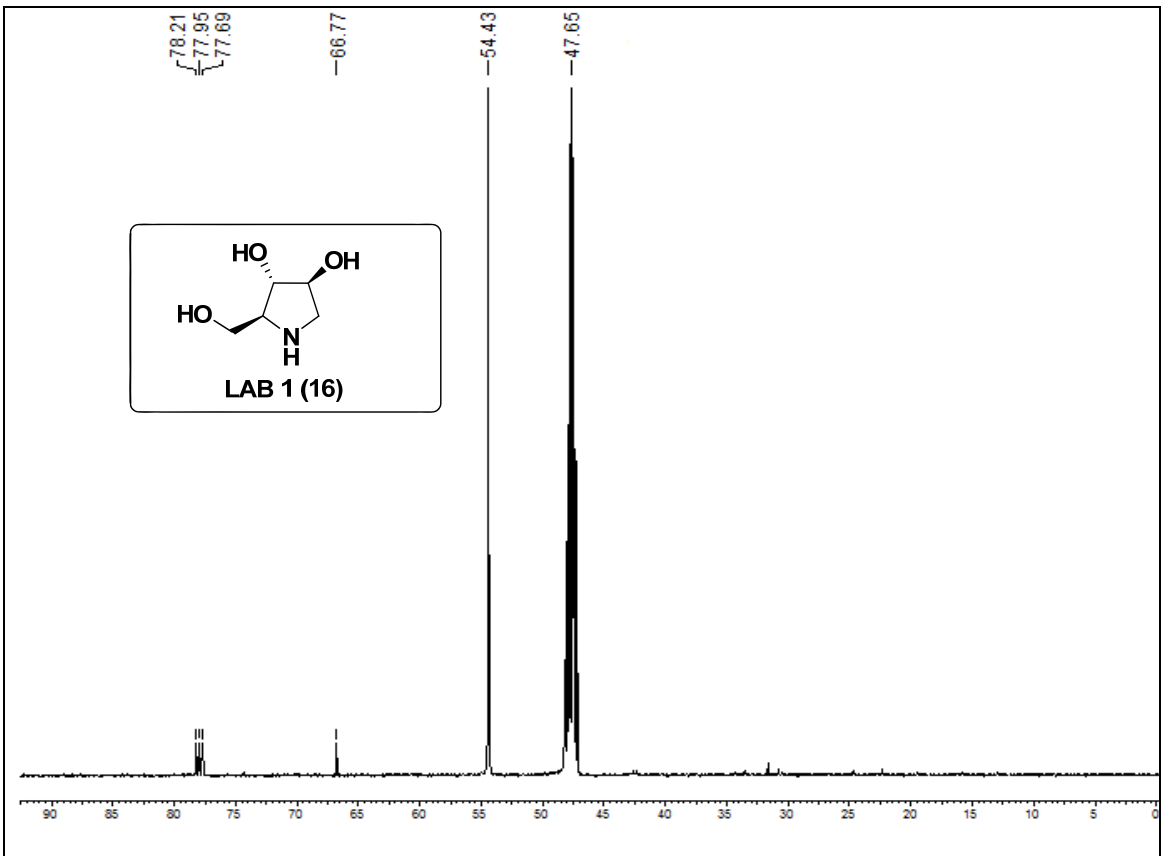
^{1}H NMR spectrum of compound 79 in $CDCl_3$



^{13}C NMR spectrum of compound 79 in $CDCl_3$



^{1}H NMR spectrum of LAB 1 (16) in MeOH-d_4



^{13}C NMR spectrum of LAB 1 (16) in MeOH-d_4

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4.2. SECTION B
ATTEMPTED SYNTHESIS OF (+)-1,2,8-TRI-*EPI*-SWAINSONINE

4.2.1. Introduction

(-)-Swainsonine[1] (**1**), which was first isolated from the fungus *Rhizoctonia leguminicola* and later found in the Australian plant *Swainsona canescens* (and has been produced from cultures of normal and transformed roots of Swainsona galegifolia), the North American spotted locoweed plant *Astragalus lentiginosus* and the fungus *Metarhizium anisopline* F-3622, is found to be an effective inhibitor of both lysosomal α-mannosidase and mannosidase II (lysosomal α-mannosidase is involved in the cellular degradation of polysaccharides and mannosidase II is a key enzyme in the processing of asparagine-linked glycoproteins). It also has antimetastic, antitumor-proliferative, anticancer (swainsonine is the first glycoprotein processing inhibitor to be selected for clinical testing as an anticancer drug, but its high cost has hindered clinical trials) and immunoregulating activity.

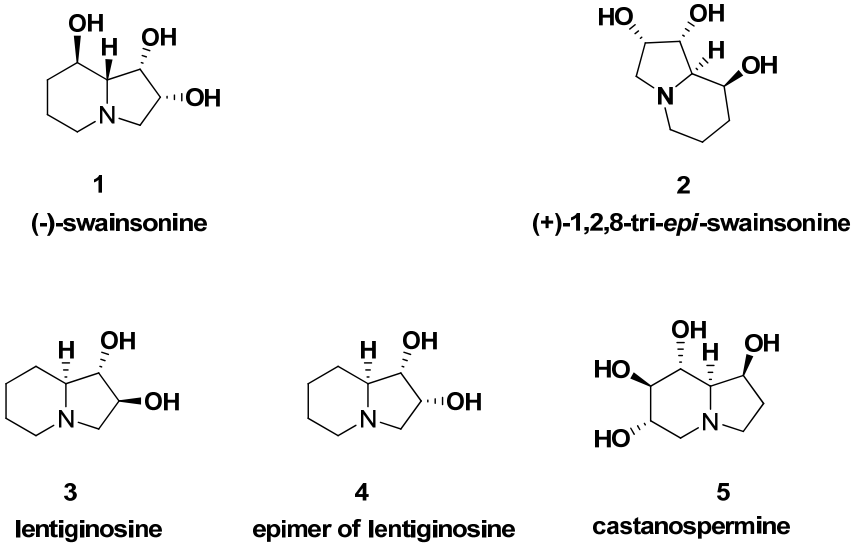


Figure 1. Structure of (-) swainsonine **1, (+)**-1,2,8-tri-*epi*-swainsonine **2**, lentiginosine **3**, 2-*epi*-lentiginosine **4** and castanospermine **5**

Swainsonine has been the subject of many other biological investigations, e.g. its effects on murine survival and bone marrow proliferation, modification of glycan structure, activity of intestinal sucrase, rats appetite, aspartate transaminase activity, insulin and lectin binding, inhibition of tyrosinase activity, rat epididymal glycosidases, inhibition of the formation of the normal oligosaccharide chain of the G-protein of

vesicular stomatitis virus and modulation of ricin toxicity, its biochemical and pathological effects in the pig, toxicity and lesion production, rate of clearance from animal tissues, effect on neuronal lysosomal mannoside storage disease on inhibition of mammalian digestive disaccharidases increasing the high-mannose glycoproteins in cultured mammalian cells inducing a high mountain disease in calves, fucose incorporation in soy bean cells normal human fibroblasts in culture, recycling of the transferrin receptor and inhibition of root length elongation have been investigated, and swainsonine is the principal toxin responsible for the induction of locoism. The absolute configuration of **1** was deduced on the basis of biosynthetic, asymmetric induction studies, and unambiguous nuclear magnetic resonance alignments, although the relative stereochemistry of swainsonine was determined by X-ray crystallography. Other polyhydroxyindolizidines isolated from natural sources are lentiginosine (**3**) (8-deoxy-2,8a-di-*epi*-swainsonine), isolated from the leaves of spotted locoweed, *Astragalus lentiginosus* var. *diphysus*,[2] 2-*epi*-lentiginosine (**4**) (8-deoxy-8a-*epi*-swainsonine), isolated from *Rhizoctonia lenguminicola* (this alkaloid has been demonstrated to be a biosynthetic precursor to swainsonine) and castanospermine (**5**), isolated from the seeds of the Australian legume *Castanospermum australe*[3] and the dried pod of *Alexa leiopetala*[4] (Fig. 1). There is no clear knowledge of the particular glycosidases mechanism (s), although there are two generally accepted pathways which involve acid-catalysed cleavage of the exocyclic (anomeric) carbon-oxygen bond giving a cyclic oxonium ion and the endocyclic (ring) carbon-oxygen bond resulting in an acyclic oxonium ion. For mannosidase inhibitors, it has been suggested that correlation with mannofuranose is important but other calculations indicate that structures similar to the mannopyranosyl cation, not mannose itself, exhibit the more potent activity. The high potential for using these alkaloids in a wide range of biological applications makes them attractive targets for synthesis.[5] In particular, the preparation of unnatural epimers and other structural analogues of (-)-swainsonine (**1**) has created much interest since the biological activity of these compounds varies substantially with the number, position and stereochemistry of the hydroxy groups in the indolizidine skeleton.

4.2.2. Review of Literature

Due to their ‘sugar-like’ structure it is not surprising that many syntheses of 1,2,8-trihydroxyindolizidines utilise carbohydrate starting materials. Hexoses and their

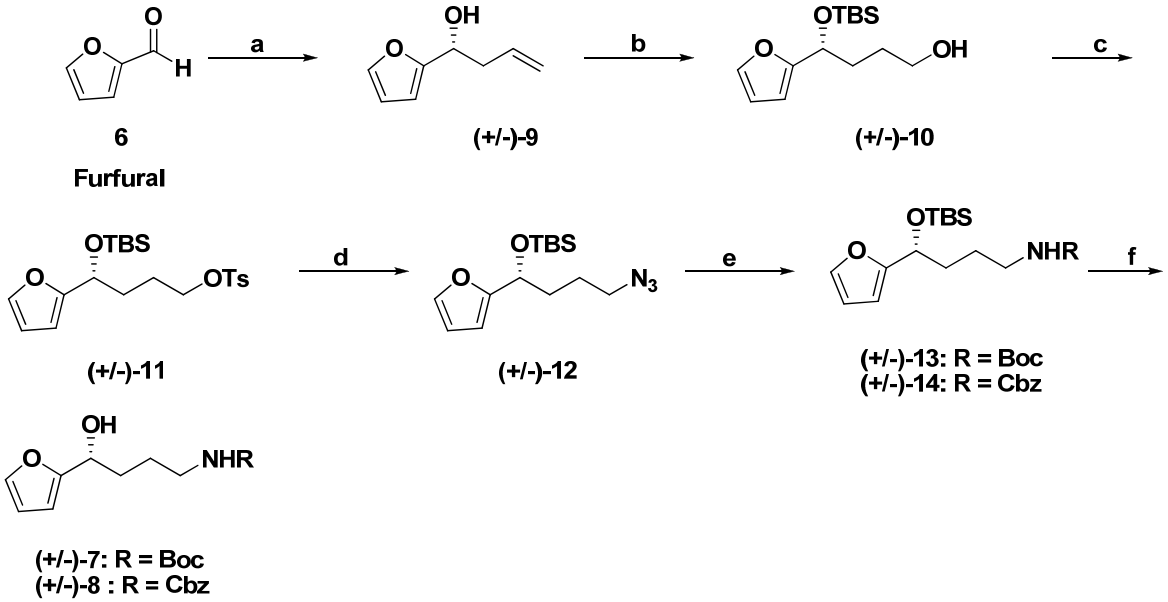
derivatives are often used with four chiral centres required in the product. There is also a strategy based on the utilisation of pentoses. Many syntheses of 1,2,8-trihydroxyindolizidines also employ non-carbohydrate starting materials. A few interesting synthesis of swainsonine were described below.

Doherty *et al.* (2008)[6]

Doherty *et al.*[6] reported the enantioselective and diastereocontrolled approach towards the synthesis of (-)-8a-*epi*-swainsonine using commercially available furfural as a starting material.

Synthesis of *rac*-furfuryl alcohol

The synthesis of racemic furfuryl alcohol (+/-) **7** and (+/-)-**8** are shown below.

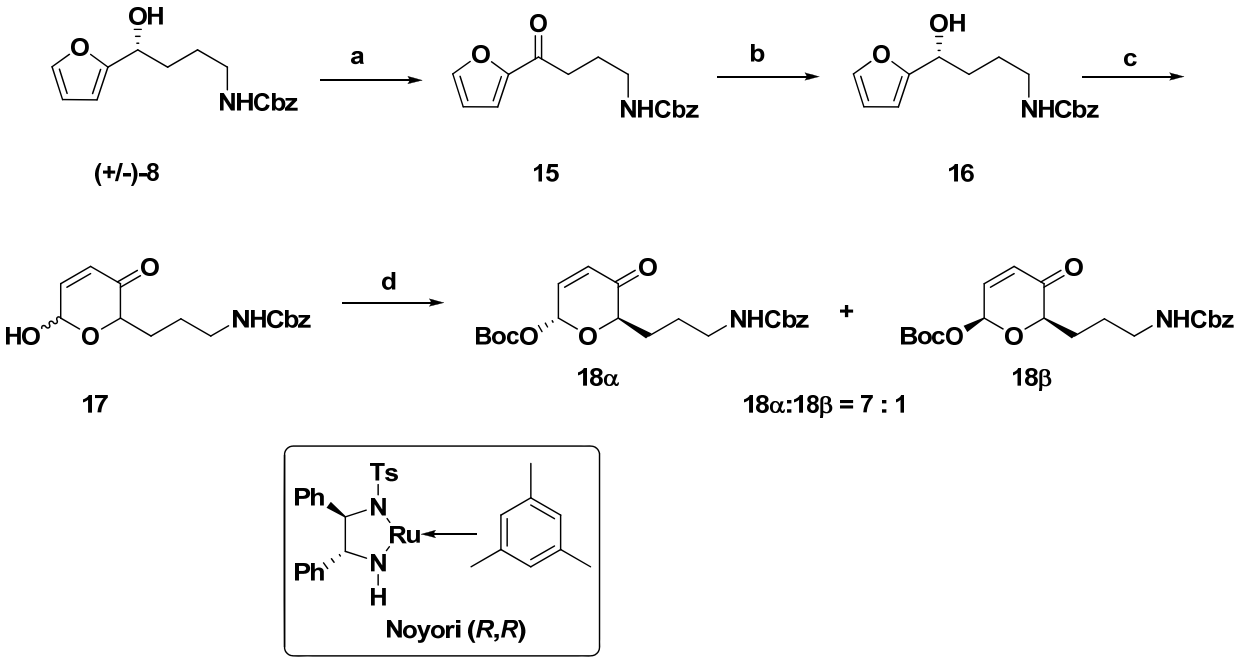


Scheme 1. *Reagents and conditions:* (a) CH_2=CH-CH_2Cl, THF, 0 ^oC - rt; (b) (i) TBSCl, 74%; (ii) $BH_3.SMe_2$, then H_2O_2, NaOH, 70%; (c) TsCl, DMAP, pyridine, CH_2Cl_2, 0 ^oC, 70%; (d) NaN_3, TBABr, acetone, H_2O, 60 ^oC, 75%; (e) Ph_3P, K_2CO_3, then $(Boc)_2O$ or CbzCl, THF/H_2O; (f) TBAF, THF.

Racemic furfuryl alcohol (+/-)-**8** was oxidized to give furfuryl ketone **15** with MnO_2. Exposure of the furfuryl ketone **15** to the Noyori conditions afforded **16** in high enantiomeric excess (>96% *ee*). Achmatowicz reaction of **16** provided the ring-

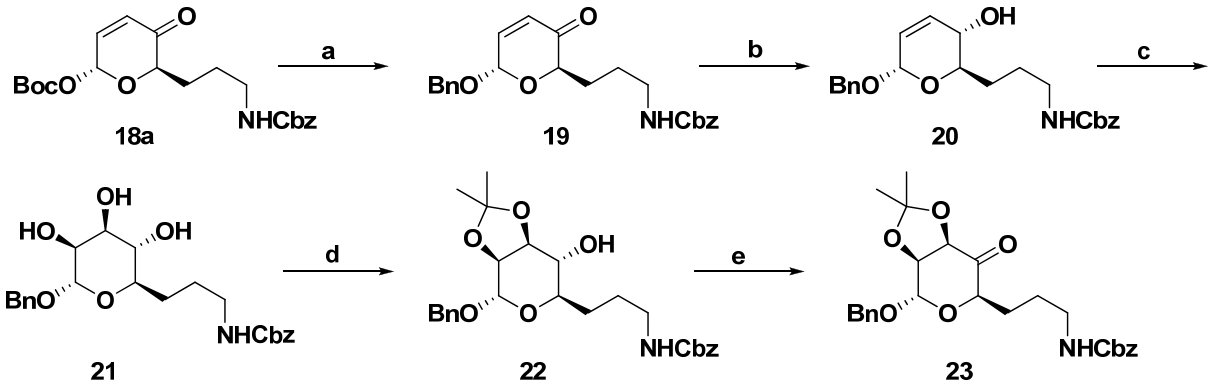
expanded pyranone product **17** which on acylation with Boc_2O furnished the Boc-protected pyranones **18**α and **18**β with a diastereoselectivity of 7:1 (Scheme 2).

Enantioselective synthesis of pyranone



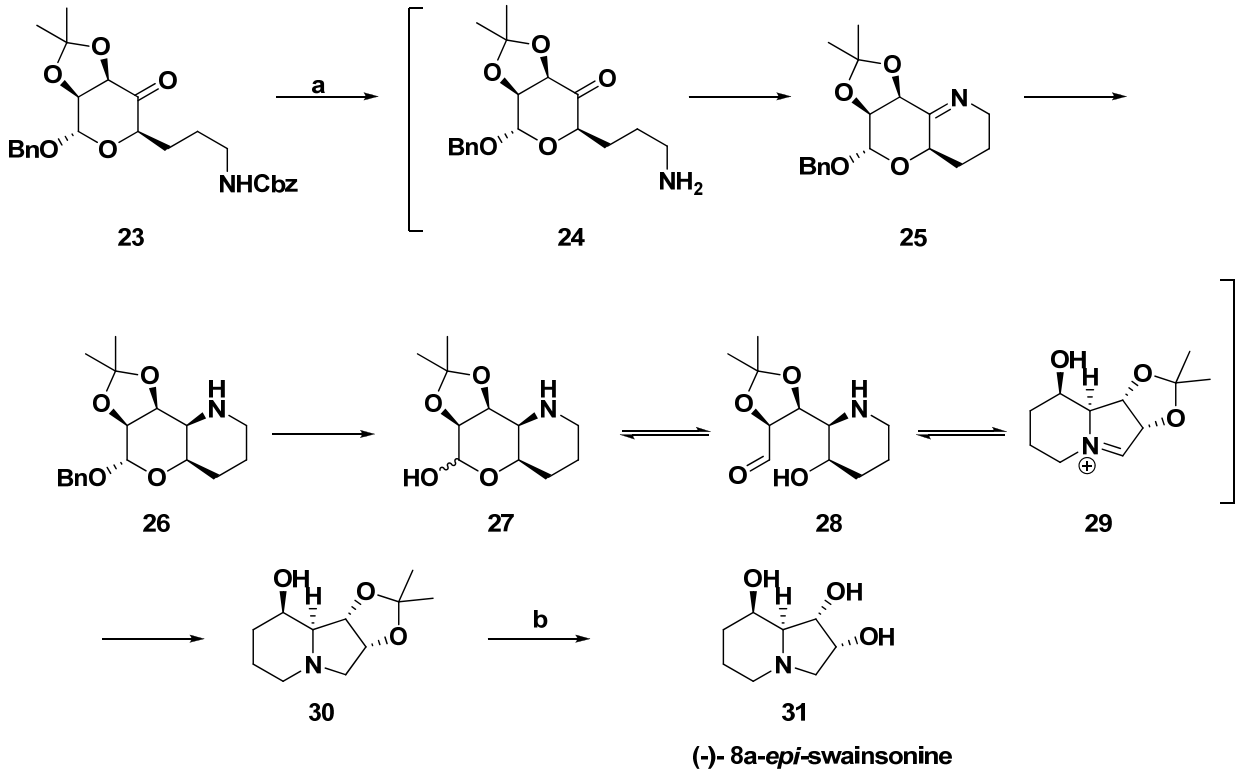
Scheme 2. *Reagents and conditions:* (a) MnO_2, 90%; (b) Noyori (*R*,*R*), HCO_2H/Et_3N, 91%; (c) NBS, NaOAc, THF/H_2O, 92%; (d) $(Boc)_2O$/ DMAP, -78 ^oC, 80%.

Synthesis of acetonide ketone 23



Scheme 3. *Reagents and conditions:* (a) $Pd(0)/PPh_3$, BnOH, 88%; (b) $NaBH_4$, $CeCl_3$, -78 ^oC, 87%; (c) OsO_4, NMO, 89%; (d) 2,2-DMP, *p*-TsOH, 87%; (e) $(COCl)_2$/DMSO, Et_3N, -78 ^oC, 92%.

Diastereoselective palladium catalyzed glycosylation of Boc-pyranone **18**α with benzyl alcohol in the presence of palladium(0) and triphenylphosphine provided an *O*-benzyl ether **19** which on Luche reduction produced the equatorial allylic alcohol **20** in excellent yield. The dihydroxylation of allylic alcohol **20** under Upjohn conditions[7] followed by acetonide protection afforded acetonide **22** which in turn was oxidized under Swern condition to give acetonide ketone **23** in good yield (Scheme 3).

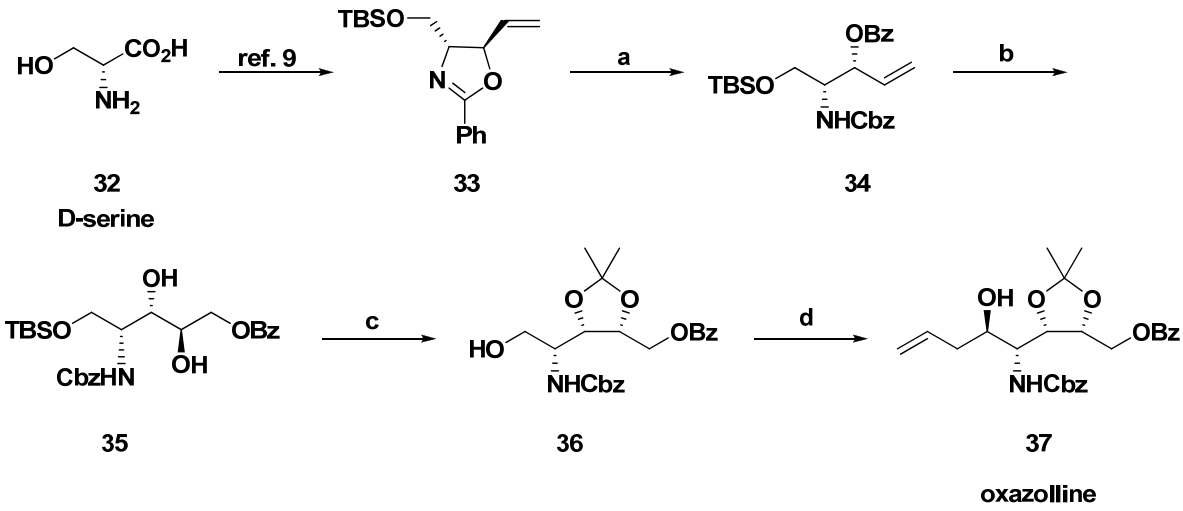


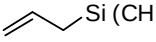
Scheme 4. *Reagents and conditions:* (a) H_2, $Pd(OH)_2/C$, 76%; (b) HCl/THF, 92%.

Thus, compound **23** was converted into Schiff base **25** via compound **24** after deprotection of Cbz group under hydrogenation condition. Amino sugar **26** were formed by hydrogenation of imine **25**. Hydrogenolytic deprotection of the Bn group in **26** gave hemiacetal **27**, which can equilibrate to intermediate hydroxy aldehyde **28**. An intramolecular reductive amination of **28** afforded the protected (-) 8a-*epi*-swainsonine **30** via a bicyclic iminium ion intermediate **29**. Finally, (-)-8a-*epi*-swainsonine **31** was obtained by acidic hydrolysis of the acetonide **30** in excellent yield after ion-exchange chromatography (Scheme 4).

Ham *et al*. (2009)[8]

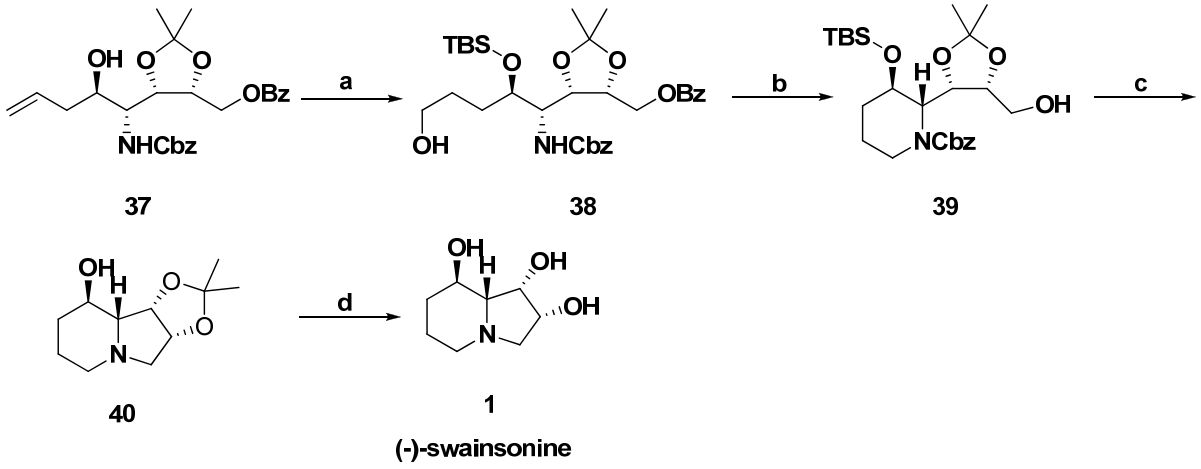
Ham *et al*.[8] reported a new asymmetric method for the synthesis of (-)-swainsonine using a diastereoselective chiral oxazoline formation by Pd(0) catalyst, diastereoselective dihydroxylation and the stereocontrolled allylation with $TiCl_4$.



Scheme 5. *Reagents and conditions:* (a) CbzCl, $NaHCO_3$, CH_2Cl_2, H_2O, 0 ^oC-rt, 3 h, 96%; (b) OsO_4, NMO, acetone:H_2O, then Na_2SO_3, 0 ^oC, 10 h, 99% (dr = 9 :1); (c) (i) DMP, PPTS, acetone, 40 ^oC, 8 h; (ii) HF, pyridine, THF, 0 ^oC-rt, 3 h, 78% (2 step); (d) (i) Dess-Martin periodinane; (ii) $TiCl_4$, CH_2Cl_2, -78 ^oC,  .

Hence, the synthesis of (-)-swainsonine started with *trans*-oxazoline which was prepared from D-serine according to known procedures.[9] The *trans*-oxazoline **33** was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate,[10] to afford the carbamate **34** in 96% yields. The dihydroxylation of **34**[11] followed by acetonide protection of resulting diol **35** gave the compound **36**. Oxidation of alcohol **36** with Dess-Martin periodinane gave the corresponding aldehyde which was subsequently reacted with allyltrimethylsilane in the presence of $TiCl_4$ to give the adduct of amino alcohol **37** with high *anti*-selectivity (15:1) (Scheme 5). The protection of the alcohol **37** by TBS-OTf and subsequent oxidation of the alkene with borane-methyl sulphide gave the corresponding alcohol **38** in 70% yield. Mesylation of compound **38** and then exposure of the corresponding mesylate to NaH and then to 2 *N*

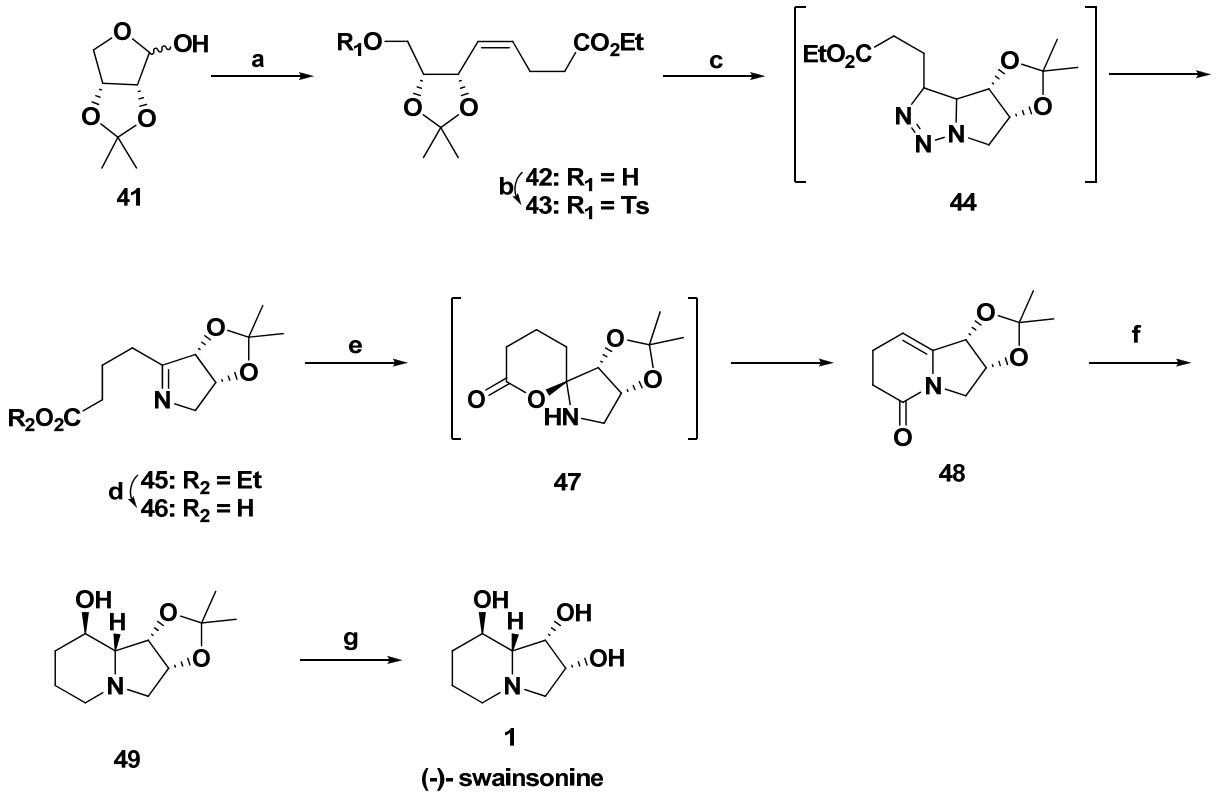
NaOH led to intramolecular cyclization and then benzoate hydrolysis provided **39** in 76% yield. Again mesylation of compound **39** followed by hydrogenolysis of mesylate afforded the protected (-)- swainsonine **40**. Finally, acidic hydrolysis of the acetonide groups gave (-)-swainsonine **1** in 82% yield (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2; (ii) $BH_3.SMe_2$, THF, 0 ^oC - rt, 70% (2 steps); (b) (i) MsCl, TEA, CH_2Cl_2; (ii) NaH, THF, then 2N NaOH, 76% (2 steps); (c) (i) MsCl, TEA, CH_2Cl_2; (ii) $Pd(OH)_2/C$, H_2, MeOH, 84% (2 steps); (d) 6N HCl, Dowex-50WX8-100, 82%.

Sharma *et al*. (2008)[12]

Sharma *et al*.[12] reported large scale synthesis of (-)-swainsonine **1** from lactol **41** using Wittig olefination, Mitsunobu reaction and 1,3-dipolar cycloaddition reaction as a key step (Scheme 7).

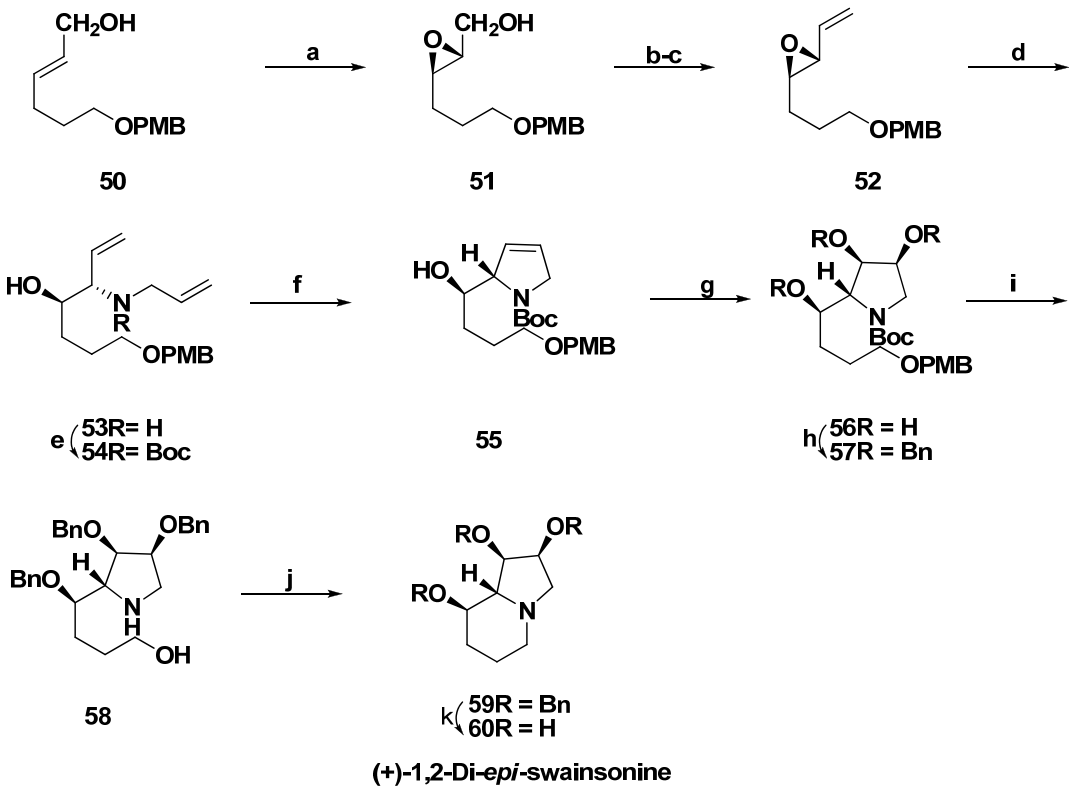


Scheme 7. *Reagents and conditions*: (a) $BrPh_3P(CH_2)_3CO_2Et$, $KN(TMS)_2$, THF, -78 ^oC; (b) TsCl, Et_3N, CH_2Cl_2; (c) NaN_3, DMF; (d) NaOH, H_2O, CH_2Cl_2; (e) toluene; (f) BH_3.THF, H_2O_2, H_2O, NaOH; (g) HCl, Dowex, OH^- resin.

Pyne *et al.* (2002)[13]

Pyne *et al.*[13] reported the asymmetric synthesis of (-)-swainsonine, (+)-1,2-di-*epi*-swainsonine and (+)-1,2,8-tri-*epi*-swainsonine involving vinyl epoxide aminolysis, ring-closing metathesis and intramolecular *N*-alkylation and *cis*-dihydroxylation using AD-mix-α as the key step. Synthesis of (+)-1,2-di-*epi*-swainsonine was shown below (Scheme 8).

Synthesis of (+)-1,2-di-*epi*-swainsonine



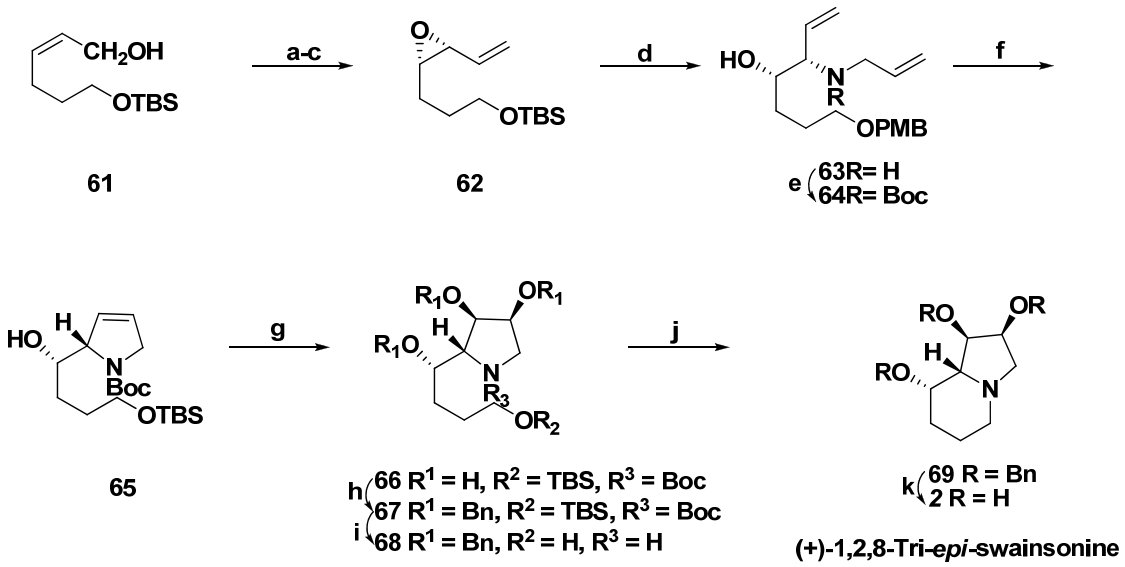
Scheme 8. *Reagents and conditions*: (a) D-(-)-DIPT, $Ti(OPr^i)_4$, TBHP, CH_2Cl_2, 4A^0 MS, -20 ^oC; (b) (i) DMSO, $(COCl)_2$, CH_2Cl_2, -60 ^oC; (ii) Et_3N; (c) $MePPh_3Br$, KHMDS, toluene; (d) allylamine, *p*-TsOH.H_2O (0.1 equiv); (e) Boc_2O, Et_3N, CH_2Cl_2; (f) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, reflux; (g) OsO4, NMO, acetone/water; (h) NaH, BnBr, Bu_4NI, THF; (i) TFA/anisole, CH_2Cl_2, rt; (j) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 ^oC; (k) Pd/C, H_2, EtOH, rt, 3d.

Commercially available 4-pentyne-1-ol was converted into the *trans*-allylic alcohol **50**[14] in three steps. Epoxidation of **50** under Sharpless condition[15] gave the epoxy alcohol **51** which on Swern oxidation followed by 1C-Wittig olefination provided the vinyl epoxide **52.** Aminolysis of **52** afforded the compound **53** as a single diastereomer. Protection of amino group of **53** as its *N*-Boc derivative **54** followed by ring closing metathesis reaction at high dilution gave the 2,5-dihydropyrrole derivative **55** in excellent yield. Cis-dihydroxylation of **55** followed by perbenzylation of the resulting triol **56** gave the tri-*O*-benzyl ether **57**. Deprotection of PMB group with TFA/anisole gave the amino alcohol **58** which was cyclised to indolizidine **59.**

Hydrogenolysis of **59** over palladium on carbon gave (+)-1,2-di-*epi*-swainsonine **60** as desired product (Scheme 8).

Similarly, (+)-1,2,8-tri-*epi*-swainsonine was also synthesized under similar condition using *E*-allylic alcohol[14b] as the starting material (Scheme 9).

Synthesis of (+)-1,2,8-tri-*epi*-swainsonine 2



Scheme 9. *Reagents and conditions*: (a) D-(-)-DIPT, $Ti(OPr^i)_4$, TBHP, CH_2Cl_2, $4A^0$ MS, -20 ^oC; (b) (i) DMSO, $(COCl)_2$, CH_2Cl_2, -60 ^oC; (ii) Et_3N; (c) $MePPh_3Br$, KHMDS, toluene; (d) allylamine, *p*-TsOH.H_2O (0.1 equiv); (e) Boc_2O, Et_3N, CH_2Cl_2; (f) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, reflux; (g) $K_2OsO_4.H_2O$, NMO, acetone, water; (h) NaH, BnBr, Bu_4NI, THF; (i) TFA, CH_2Cl_2, rt, 2.5 h; (j) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 ^oC; (k) $PdCl_2$, H_2, rt, 1 h.

4.2.3. Present Work

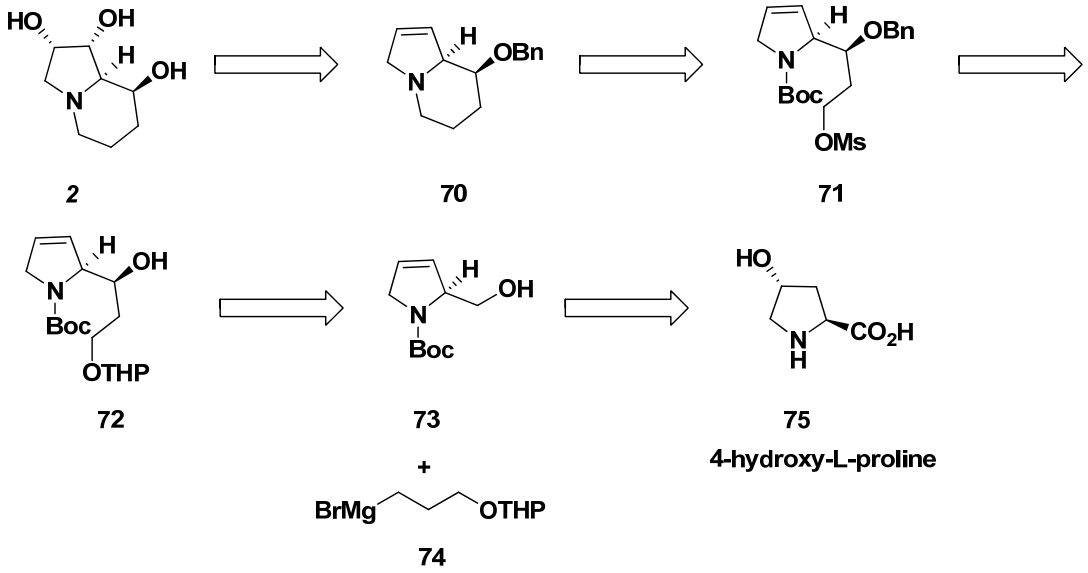
Objective

Swainsonine **1**[16] is a potent inhibitor of certain-mannosidases and has proven useful as a biochemical tool for the study of glycoprotein processing, since it inhibits a key late-stage enzyme in the biosynthesis of glycoproteins. That enzyme, Golgi-mannosidase II (GM II), is necessary for the formation of so-called complex glycoproteins. The altered distribution of such glycoproteins on the surface of cancer cells is associated with

metastasis and disease progression, hence inhibitors of GM II are potentially useful for cancer treatment. Unfortunately, human GM II has proven difficult to isolate and characterize. More selective inhibition of GM II over other mannosidases is a desirable goal for cancer drug development, and makes the synthesis of analogs of swainsonine a significant undertaking. Many analogs of swainsonine have been reported, e.g. those where the oxygenation pattern, ring size, or configuration has been modified but these changes usually result in a diminution of potency.

As a part of our research interest on the asymmetric synthesis of hydroxylated piperidines[17] we became interested in developing a route towards the synthesis of (+)-swainsonine **2** using dihydroxylation and Grignard reaction as the key steps.

Retrosynthetic analysis of (+)-1,2,8-tri-*epi*-swainsonine

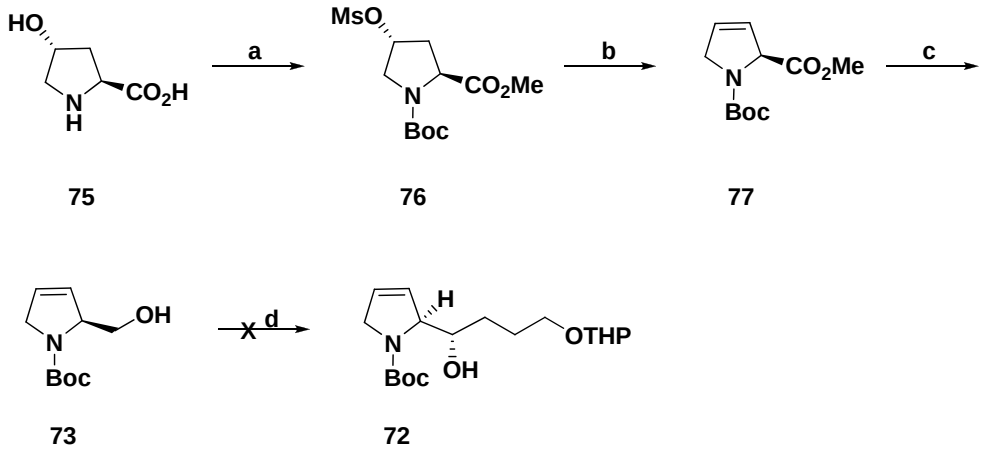


Scheme 10. Retrosynthetic analysis for (+)- swainsonine

As shown in Scheme 10, our retrosynthetic analysis suggested that (+)-swainsonine **2** could be synthesized from compound **70** that in turn would be synthesized from mesylate **71**. Amino alcohol **72** could be obtained by the Grignard reaction of aldehyde obtained from compound **73** and Grignard reagent **74**. The compound **73** could be accessed from commercially available 4-hydroxy-L-proline **75**.

4.2.4. Results and Discussion

To achieve the synthesis of (+)-swainsonine **2**, we used 4-hydroxy-L-proline **75** as the starting material. Thus, 4-hydroxy-L-proline **75** was transformed into dihydroprolinol **73** using known procedure.[18] The spectroscopic data of all compound (**76**→**73**) were in accordance with literature precedence.[18]

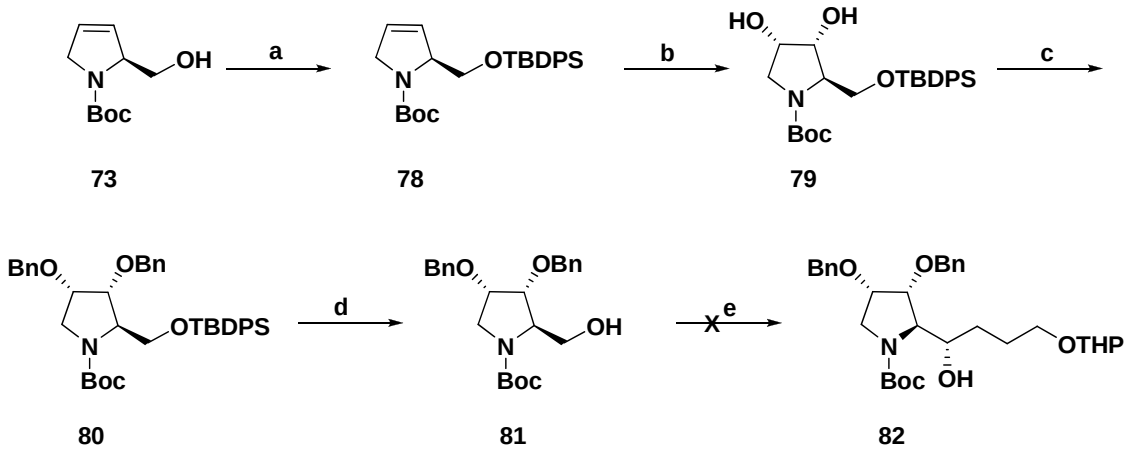


Scheme 11. *Reagents and conditions*: (a) (i) $SOCl_2$, MeOH, 0 ^oC to rt; (ii) Boc_2, CH_2Cl_2, Et_3N, DMAP, rt; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 77%; (b) (i) PhSeSePh, MeOH, reflux; (ii) H_2O_2, pyridine, rt, 60%; (c) $LiAlH_4$, Et_2O, 0 ^oC - rt, 1 h, 80%; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, 2 h, Et_3N, then **74** ($BrMg(CH_2)_3$-OTHP), THF, 2 h, 0 ^oC - rt.

Compound **73** was oxidized under Swern oxidation[19] to give aldehyde in good yield. The crude aldehyde was then treated with Grignard reagent (3-(tetrahydropyran-2-yloxy)propyl magnesium bromide **74)**, unfortunately we got only mixture of compound and decomposed product **72** (Scheme 11). The failure of reaction may be attributed to the isomerisation of doule bond present in the ring.

Thus, we have decided to carry out dihydroxylation of olefin **73** (Scheme 12). Hence, diol **79** was prepared from substrate **73** in two steps using known procedure.[18] The spectroscopic data of **79** was in accordance with the literature precedence.[18] Protection of diol **79** with BnBr and subsequent deprotection of TBDPS group in **80** with TBAF gave the amino alcohol **81** in 87% yield. The ^1H NMR spectrum of **81** showed the absence of *tert*-butyl proton of TBDPS group at δ 1.01 (s, 9H) and presence of two

benzyl proton at δ 4.57-4.68 (m, 4H) and at δ 7.35-7.37 (m, 10H) and presence of -OH peak at ν 3410 cm^{-1} in IR spectrum confirming the formation of compound **81**. Oxidation of alcohol **81** under Swern conditions gave the aldehyde which was used immediately without purification for Grignard reaction. Thus, crude aldehyde was treated with 3-(tetrahydropyran-2-yloxy)propyl magnesium bromide **74** at -78 ^{o}C, however we did not get the expected compound **82** which was difficult to characterize through NMR spectroscopy. Therefore, this route was not further pursued and eventually abandoned.



Scheme 12. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 0 ^{o}C - rt., o/n, 80%; (b) OsO_4, 4-methylmorpholine-*N*-oxide monohydrate (NMNO), acetone-H_2O, rt, 5 h, 91%; (c) BnBr, 60% NaH, TBAI, dry THF, 0 ^{o}C - rt, 4 h, 91%; (d) 1M TBAF, THF, 0 ^{o}C - rt, 4.5 h, 87%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^{o}C, Et_3N, 2 h, then **74** ($BrMg(CH_2)_3OTHP$), dry ether, -78 ^{o}C, 5 h.

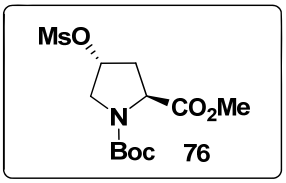
4.2.5. Conclusion

In conclusion, we attempted the synthesis of (+)- 1,2,8-tri-*epi*-swainsonine from 4-hydroxy-L-proline using dihydroxylation and Grignard reaction as the key step.

4.2.6. Experimental Section

General Information: See Sec. A of this chapter.

(2*S*,4*R*)-1-*tert*-Butyl 2-methyl 4-(methylsulfonyloxy)pyrrolidine-1,2-dicarboxylate (76).



To a cooled solution of *trans*-4-hydroxy-L-proline **75** (10.00 g, 76.34 mmol) in anhydrous MeOH (100 mL) was added $SOCl_2$ (6.5 mL, 89.06 mmol) dropwise. After the mixture was refluxed for 2 h it was cooled to room temperature and stirred overnight. After the solvent was removed in vacuo, the residue was washed twice with anhydrous Et_2O to provide white solid (14.00 g). Then, to a cooled solution of the above white solid (14.00 g) and DMAP (2.00 g, 16.39 mmol) in anhydrous CH_2Cl_2 (150 mL) was added Et_3N (25 mL) followed by a solution of Boc_2O (19.0 mL, 88.79 mmol) in CH_2Cl_2 (50 mL) dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 1M citric acid and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to afford a white solid (15.529 g), which was then dissolved in CH_2Cl_2 (250 mL). After the mixture was cooled to 0 °C, DMAP (2.00 g, 16.39 mmol) and Et_3N (13 mL) were added, followed by MsCl (7.3 mL, 94.32 mmol) dropwise. The mixture was stirred for 2 h and H_2O (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2. Then, the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 2:1) to afford **76** as a white solid

Yield: 19.0 g (77%).

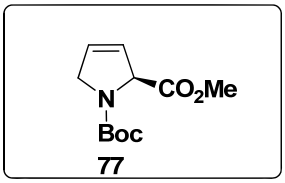
Mol. Formula: $C_{12}H_{21}NO_7S$

$[\alpha]_D^{25}$: -48.02 (*c* 1.58, $CHCl_3$); [lit. $[\alpha]_D^{25}$ **:** -48.4 (*c* 1.58, $CHCl_3$)].[18]

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.18-2.31 (m, 1H), 2.56-2.70 (m, 1H), 3.05 (s, 3H), 3.74 (s, 3H), 3.78-3.82 (m, 2H), 4.35-4.49 (m, 1H), 5.22-5.27 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 37.1, 38.3, 52.0, 56.8, 57.1, 78.1, 80.5, 153.0, 153.6, 172.2, 172.4, (rotamer).

(*S*)-1-*tert*-Butyl 2-methyl 1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate (77).



77

To a 0 °C solution of **76** (19.0 g, 58.82 mmol) and PhSeSePh (11.04 g, 35.29 mmol) in MeOH (450 mL) was added $NaBH_4$ (2.93 g, 77.65 mmol) in several portions. Then, the mixture was refluxed about 11 h and the solution was removed in vacuo. H_2O (60 mL) was added and the mixture was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 2:1) to afford an oil (19.88 g), which was then resolved in CH_2Cl_2 (320 mL) and pyridine (6.5 mL) and 30% aqueous H_2O_2 (15 mL) were added. After about 2 h, H_2O (100 mL) was added. The organic layer was then washed with 1M citric acid, saturated aqueous Na_2SO_3, and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ ethyl acetate, 10:1) to afford **77** as a clear oil.

Yield: 8.2 g (60%).

Mol. Formula: $C_{11}H_{17}NO_4$

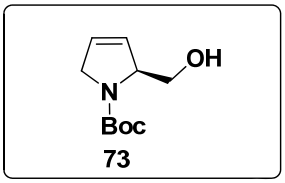
$[\alpha]_D^{25}$: -260.2 (*c* 1.11, $CHCl_3$); [lit.$[\alpha]^{20}_D$: -261.0 (c 1.11, $CHCl_3$)].[18]

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 3.71 (s, 3H), 4.17-4.32 (m, 2H), 4.91-5.02 (m, 1H), 5.66-5.74 (m, 1H), 5.90-5.99 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 51.8, 53.0, 53.2, 65.9, 66.2, 79.8, 124.3, 129.1, 153.0, 153.5, 170.4, 170.7, (rotamer).

Mass [LCMS]: 228 (M^{+1}), 250.35 (M^+ + Na), 266.34 (M^+ + K).

(*S*)-*tert*-Butyl 2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (73).



73

To a 0 °C solution of **77** (5.0 g, 22.02 mmol) in anhydrous Et_2O (100 mL) was added $LiAlH_4$ (920 mg, 24.22 mmol). The mixture was then warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. Na_2SO_4 and filtered through celite pad and filtrate was extracted with Et_2O (3 x 50 mL). The combined organic phases

were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:1 then 2:1) to afford **73** as a clear oil.

Yield: 3.5 g (80%).

Mol. Formula: $C_{10}H_{17}NO_3$

$[\alpha]_D^{25}$: -106.7 (c 1.23, $CHCl_3$); [lit.$[\alpha]^{20}_D$: -107.8 (c 1.23, $CHCl_3$)].[18]

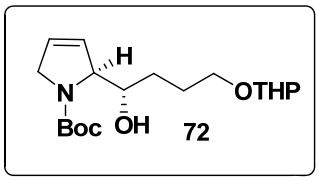
IR (neat, cm^{-1}): ν_{max} 3362, 3019, 1667, 1407, 1161.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.51-3.60 (m, 1H), 3.73-3.82 (m, 1H), 4.08-4.15 (m, 2H), 4.69-4.72 (m, 1H), 5.58-5.64 (m, 1H), 5.79-5.83 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 54.02, 66.7, 67.4, 80.4, 126.6, 156.3.

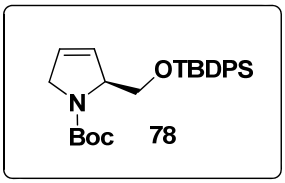
Mass [LCMS]: 200.42 (M^{+1}), 222.45 (M^+ + Na), 238.53 (M^+ + K).

(2*S*)-*tert*-Butyl2-(1-hydroxy-3-(tetrahydro-2*H*-pyran-2-yloxy) propyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (72).



To a stirred solution of oxalyl chloride (0.66 mL, 7.55 mmol) in CH_2Cl_2 (25 mL) at -78 ^oC under nitrogen atmosphere was added DMSO (1.17 mL, 15.09 mmol) in dropwise manner. After stirring for 30 min, a solution of amino alcohol **73** (1 g, 5.03 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture over 30 min. The mixture was warmed to -60 ^oC and stirred for 2 h at this temperature followed by dropwise addition of triethylamine (3.50 mL, 25.15 mmol) over 5 min. The reaction mixture was then warmed to 0 ^oC in 15 min and transferred through a cannula to a room temperature solution of **74** [$MgBr(CH_2)_3OTHP$] prepared from Mg (1.7 g, 70.42 mmol) and tetrahydropyranyl protected 1-bromo-3-propanol (7.85 g, 35.21 mmol) in ether (20 mL over 30 min) after stirring for 2 h at room temperature. The reaction mixture was poured into aq. NH_4Cl solution (30 mL) and acidified to *pH* 4 by adding 10% aqueous HCl solution. The organic layer was separated, aqueous layer extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4, solvent was removed under vacuo and the crude residue purified by silica gel column chromatography using petroleum ether / EtOAc (8.5:1.5) to yield the complex mixture of desired compound **72**.

(*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy) methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (78).



To a 0 °C solution solution of **73** (6.0 g, 30.15 mmol) and imidazole (6.16 g, 90.45 mmol) in dry CH_2Cl_2 (100 mL) was added DMAP (368 mg, 3.02 mmol) followed by TBDPSCl (13.3 g, 48.24 mmol) dropwise. The mixture was then stirred overnight and the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 15:1) to afford **78** as a white foam.

Yield: 10.56 g (80%).

Mol. Formula: $C_{26}H_{35}NO_3Si$

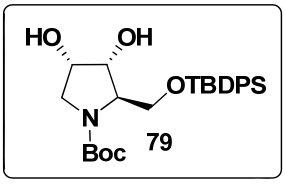
$[\alpha]_D^{25}$: -90.22 (*c* 1.06, $CHCl_3$); [lit.$[\alpha]^{20}_D$: -90.1 (*c* 1.06, $CHCl_3$)].[18]

IR (neat, cm^{-1}): ν_{max} 2930, 1676, 1427, 1366, 1172, 1113, 1008.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (s, 18H), 3.65-3.72 (m, 1H), 3.79-3.93 (m, 1H), 3.98-4.17 (m, 2H), 4.51-4.65 (m, 1H), 5.83-5.91 (m, 2H), 7.36-7.43 (m, 6H), 7.63-7.76 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.9, 26.5, 28.3, 53.9, 54.2, 64.9, 65.3, 79.6, 126.2, 127.5, 128.5, 129.3, 134.4, 134.8, 150.1(rotamer).

(2*R*,3*R*,4*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-3,4-dihydroxypyrrolidine-1-carboxylate (79).



To a 0 °C solution of **78** (2.0 g, 4.57 mmol) and 4-methylmorpholine-*N*-oxide monohydrate (NMNO) (1.82 g, 13.43 mmol) in acetone (250 mL) and H_2O (60 mL) was added OsO_4 (5.0 mL, 0.1 M in toluene, 0.5 mmol). The resulting mixture was warmed to room temperature and stirred for 5 h. Then, Na_2SO_3 (5.0 g) was added and

after 30 min of stirring, the mixture was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to afford **79** as a white foam.

Yield: 1.96 g (91%).

Mol. Formula: $C_{26}H_{37}NO_5Si$

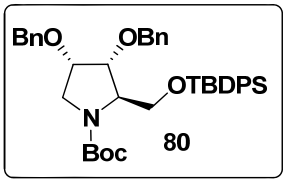
$[\alpha]_D^{25}$: -29.5 (*c* = 1.01, MeOH); [lit.$[\alpha]^{20}{}_D$: -30.5 (*c* = 1.01, MeOH)].[18]

IR (neat, cm^{-1}): ν_{max} 3398, 2932, 1672, 1589, 1473, 1427, 1172, 1143, 1113, 1007.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.30 (2s, 9H), 3.39-3.48 (m, 1H), 3.56-3.66 (m, 2H), 3.73-3.88 (m, 3H), 4.31-4.45 (m, 2H), 7.39-7.49 (m, 6H), 7.62-7.67 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 28.2, 28.4, 51.1, 51.7, 62.3, 63.1, 64.3, 69.5, 70.2, 73.5, 74.3, 79.6, 80.0, 127.7, 129.7, 132.9, 135.4, 154.8 (rotamer).

(2*R*,3*R*,4*S*)-*tert*-Butyl3,4-bis(benzyloxy)-2-((*tert* butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (80).



To a solution of diol **79** (2.0 g, 4.24 mmol) in dry THF (40 mL) was added 60% NaH (340 mg, 8.49 mmol) at 0 ^oC, after stirring for 10 min benzyl bromide (1.5 mL, 12.72 mmol) and TBAI (156 mg, 0.424 mmol) was added to the reaction mixture. After stirring for 4 h at rt, the reaction was quenched with ice-piece and extracted with EtOAc (20 x 3 mL), washed with brine and dried over Na_2SO_4. After removal of solvent, the resulting residue was purified by silica gel column chromatography using EtOAc/ pet ether (5:95) as eluent to give the compound **80** as pale yellow color.

Yield: 2.5 g (91%).

Mol. Formula: $C_{40}H_{49}NO_5Si$.

$[\alpha]_D^{25}$: -14.4 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3010, 2930, 1685, 1405, 1216, 1112, 1027.

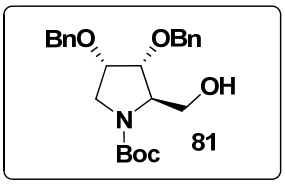
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.33 (2s, 9H), 3.44-3.58 (m, 1H), 3.73-391 (m, 3H), 4.05-4.16 (m, 2H), 4.25 (t, *J* = 3.8 Hz, 1H), 4.46-4.65 (m, 4H), 7.32-7.44 (m, 16H), 7.57-7.62 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 28.2, 33.4, 48.5, 49.1, 62.7, 71.4, 71.8, 75.1, 78.9, 79.3, 79.5, 127.7, 128.3, 128.6, 128.9, 129.7, 133.1, 135.4, 137.9, 154.5.

Mass [LCMS]: 652.68 (M^{+1}), 674.60 (M^+ + Na), 690.67 (M^+ + K).

Analysis Calcd.: C, 73.70; H, 7.58; N, 2.15%; **Found:** C, 73.80; H, 7.63; N, 2.23%.

(2*R*,3*R*,4*S*)-*tert*-Butyl3,4-bis(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (81).



To a solution of compound **80** (2.0 g, 3.07 mmol) in dry THF (15 mL) was added 1M TBAF (4.6 mL, 4.60 mmol) at rt and reaction mixture was stirred for 4.5 h. Afterwards solvent was evaporated in vacuo and crude residue was purified by silica gel colum chromatography using EtOAc/pet ether (6:4) as eluent to give required compound **81** as yellow color compound.

Yield: 1.1 g (87%).

Mol. Formula: $C_{24}H_{31}NO_5$.

$[\alpha]_D^{25}$: +10.15 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3410, 2400, 1681, 1455, 1412, 1215, 1120.

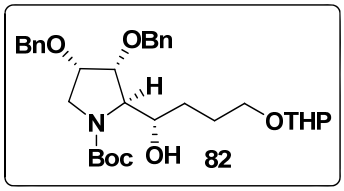
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.37-3.46 (m, 1H), 3.52-3.71 (m, 2H), 3.75-3.83 (m, 1H), 3.94-4.11 (m, 2H), 4.28-4.35 (m, 1H), 4.57-4.68 (m, 4H), 7.35-7.37 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 49.4, 63.1, 64.3, 71.5, 71.7, 74.9, 78.5, 80.4, 127.7, 127.8, 128.3, 137.7, 156.3.

Mass [LCMS]: 414.71 (M^{+1}), 436.69 (M^+ + Na), 452.70 (M^+ + K).

Analysis Calcd: C, 69.71; H, 7.56; N, 3.39%; **Found:** C, 69.80; H, 7.63; N, 3.46%.

(2*R*,3*R*,4*S*)-*tert*-Butyl 3,4-bis(benzyloxy)-2-(1-hydroxy-3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)pyrrolidine-1-carboxylate (82).



To a stirred solution of oxalyl chloride (0.16 mL, 1.82 mmol) in CH_2Cl_2 (10 mL) at -78 ^oC under nitrogen atmosphere was added DMSO (0.28 mL, 3.63 mmol) in dropwise manner. After stirring for 30 min, a solution of amino alcohol **81** (0.5 g, 1.21 mmol) in CH_2Cl_2 (15 mL) was added to the reaction mixture over 30 min. Afte stirring for 2 h, the reaction mixture was quenched by dropwise addition of Et_3N (0.84 mL, 6.05 mmol) over 5 min. After work up, the resulting aldehyde was dissolved in dry ether and was added to a solution of Grignard reagent ([$MgBr(CH_2)_3OTHP$] prepared from Mg (0.41 g, 8.47 mmol) and tetrahydropyranyl protected 1-bromo-3-propanol (1.89 g, 35.21 mmol)) in ether (10 mL over 15 min) at -78 ^oC. After stirring for 2 h at the same temperature, the reaction mixture was poured into aq. NH_4Cl solution (10 mL). The organic layer was separated, aqueous layer extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4, solvent was removed under vacuo and the crude residue was purified by silica gel column chromatography using petroleum ether / EtOAc (8.5:1.5) to give complex mixture of compound **82**.

4.2.7. Spectra

1] ^1H NMR spectrum of **76**

2] ^{13}C NMR spectrum of **76**

3] ^1H NMR spectrum of **77**

4] ^{13}C NMR spectrum of **77**

5] ^1H NMR spectrum of **73**

6] ^{13}C NMR spectrum of **73**

7] ^1H NMR spectrum of **78**

8] ^{13}C NMR spectrum of **78**

9] ^1H NMR spectrum of **79**

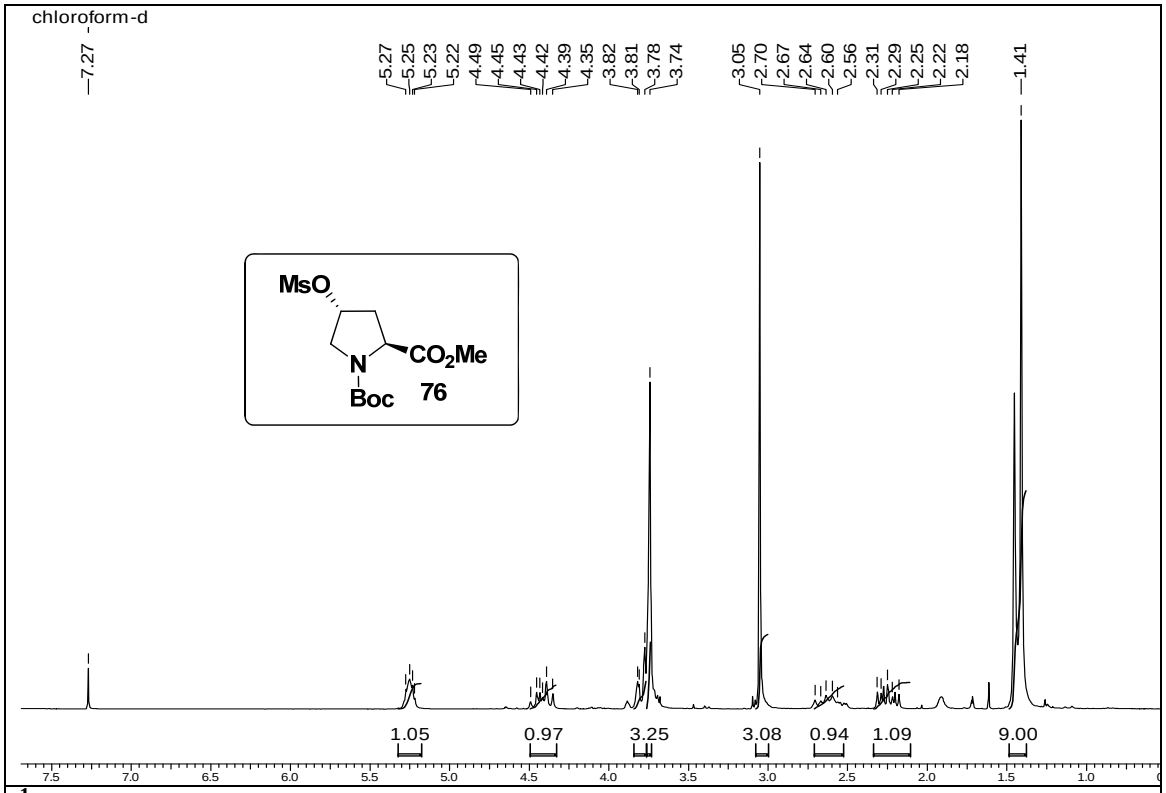
10] ^{13}C NMR spectrum of **79**

11] ^1H NMR spectrum of **80**

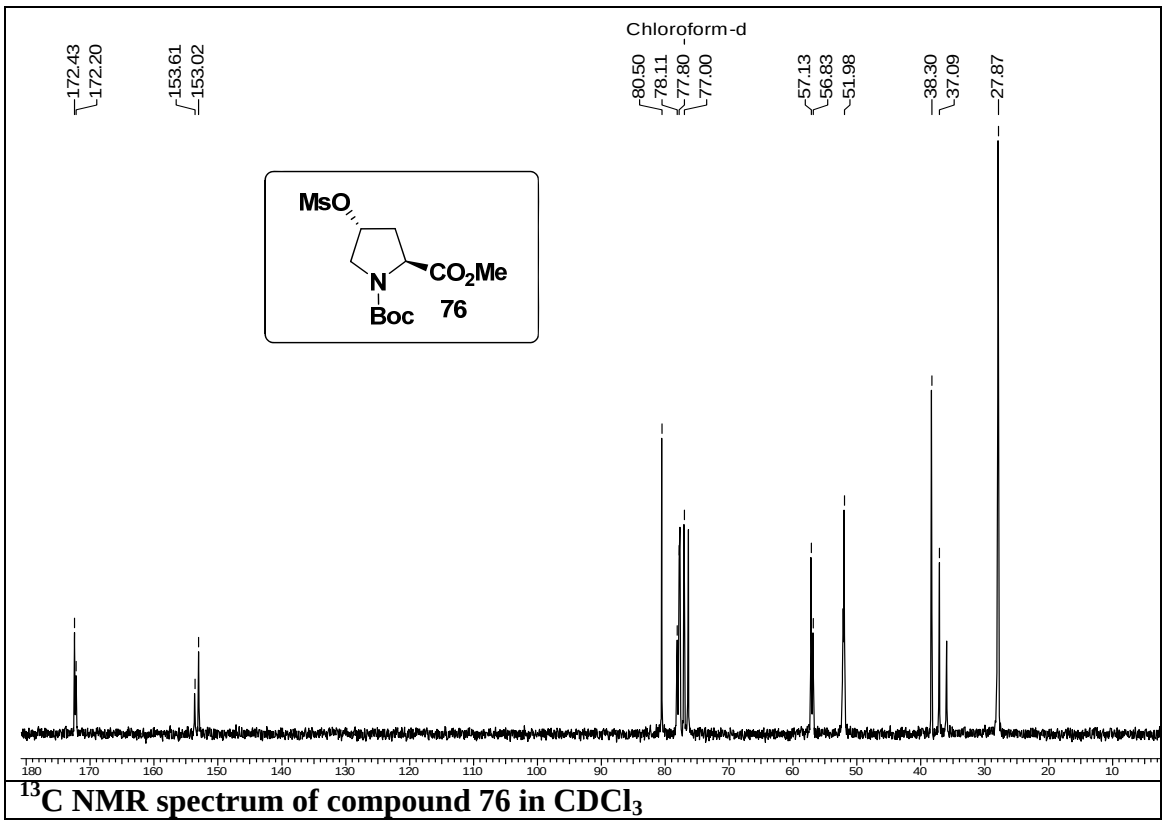
12] ^{13}C NMR spectrum of **80**

13] ^1H NMR spectrum of **81**

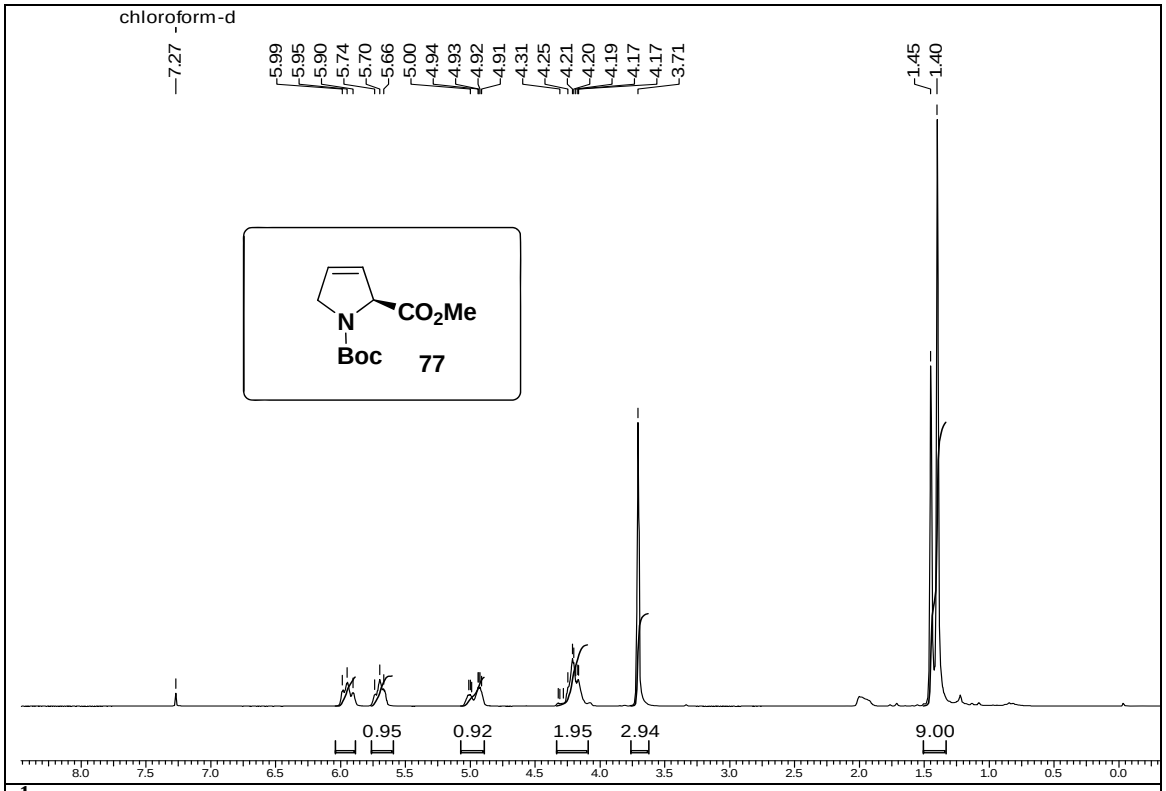
14] ^{13}C NMR spectrum of **81**



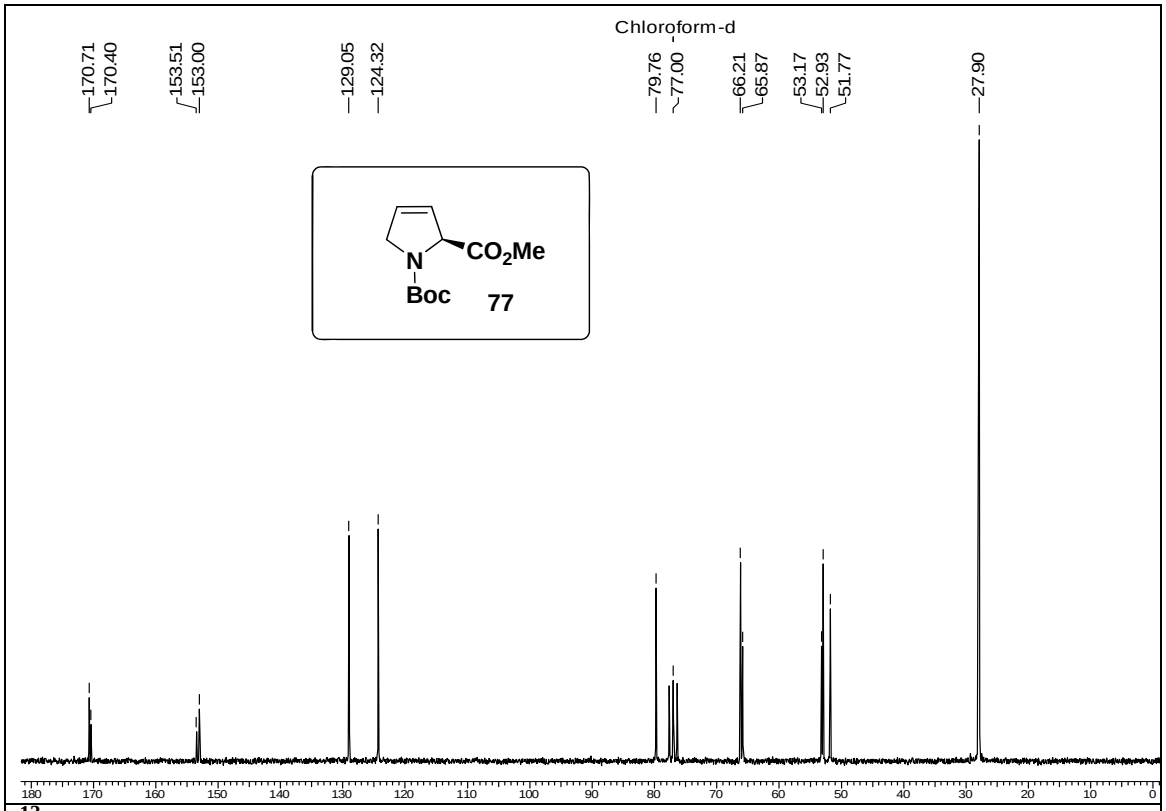
^{1}H NMR spectrum of compound 76 in $CDCl_3$



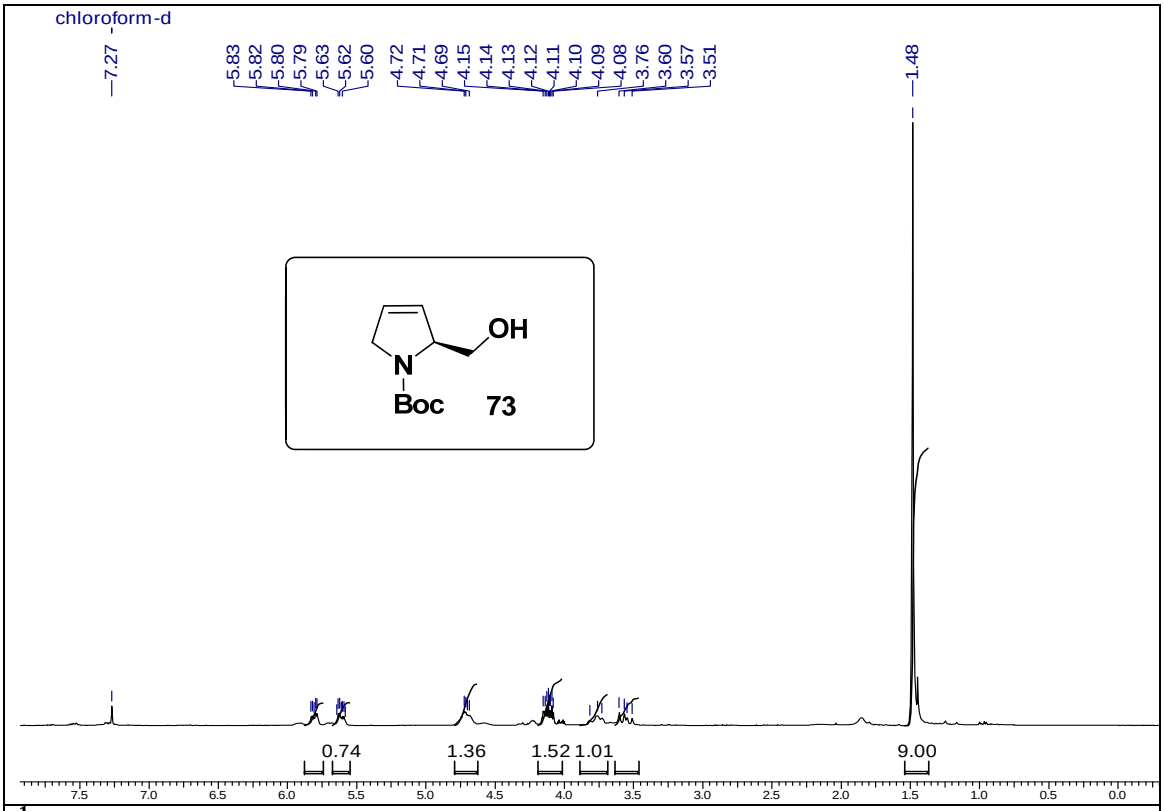
^{13}C NMR spectrum of compound 76 in $CDCl_3$



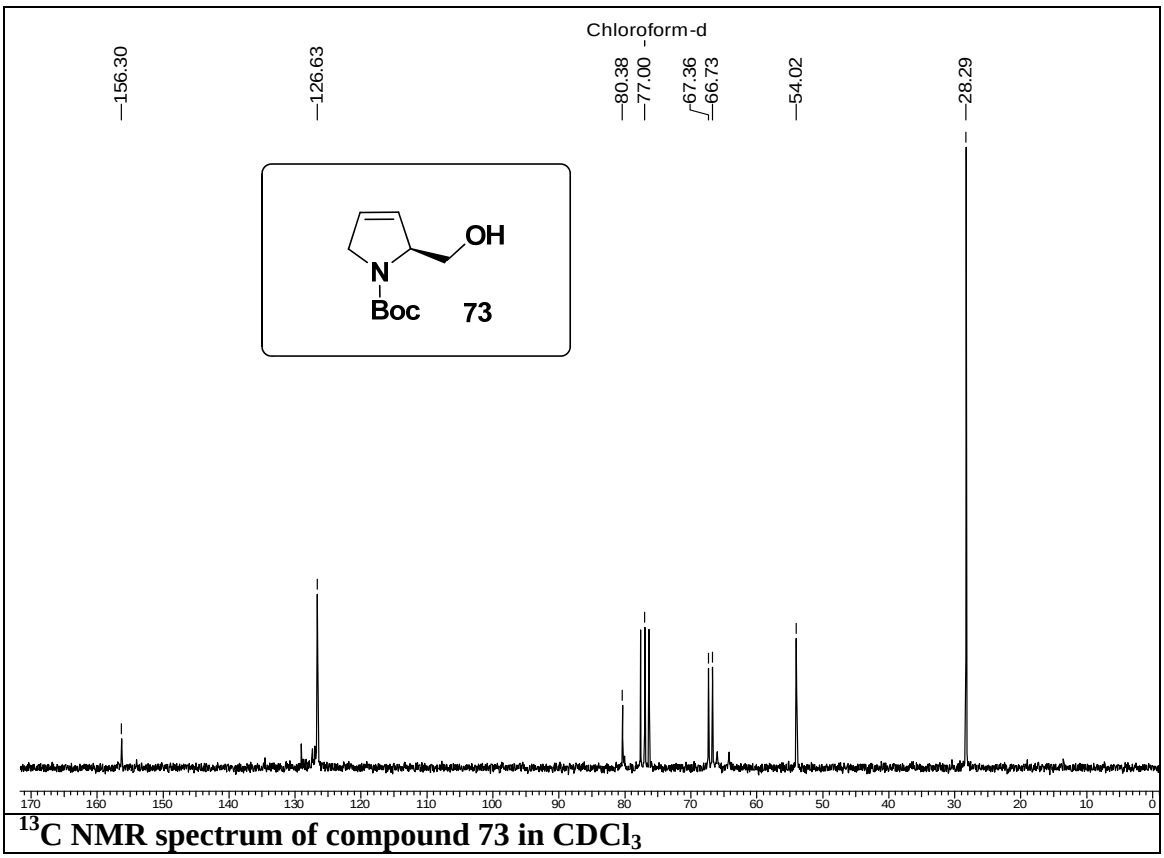
^{1}H NMR spectrum of compound 77 in $CDCl_3$



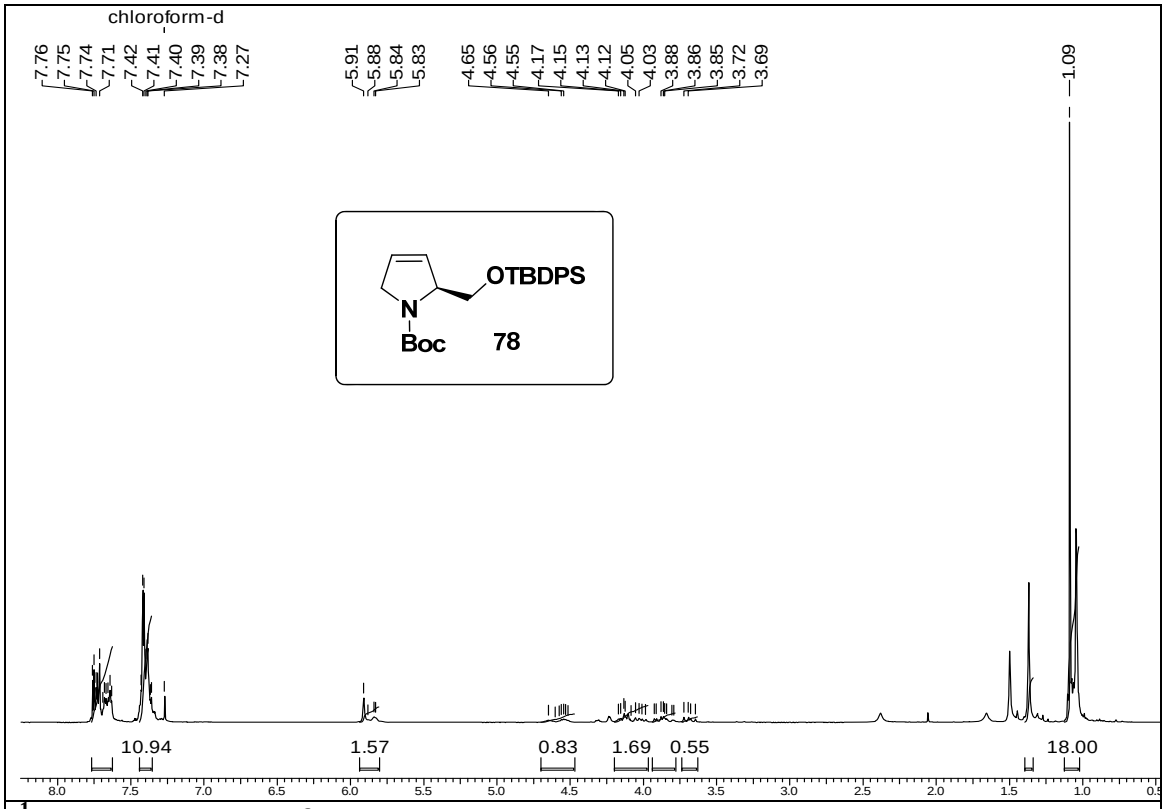
^{13}C NMR spectrum of compound 77 in $CDCl_3$



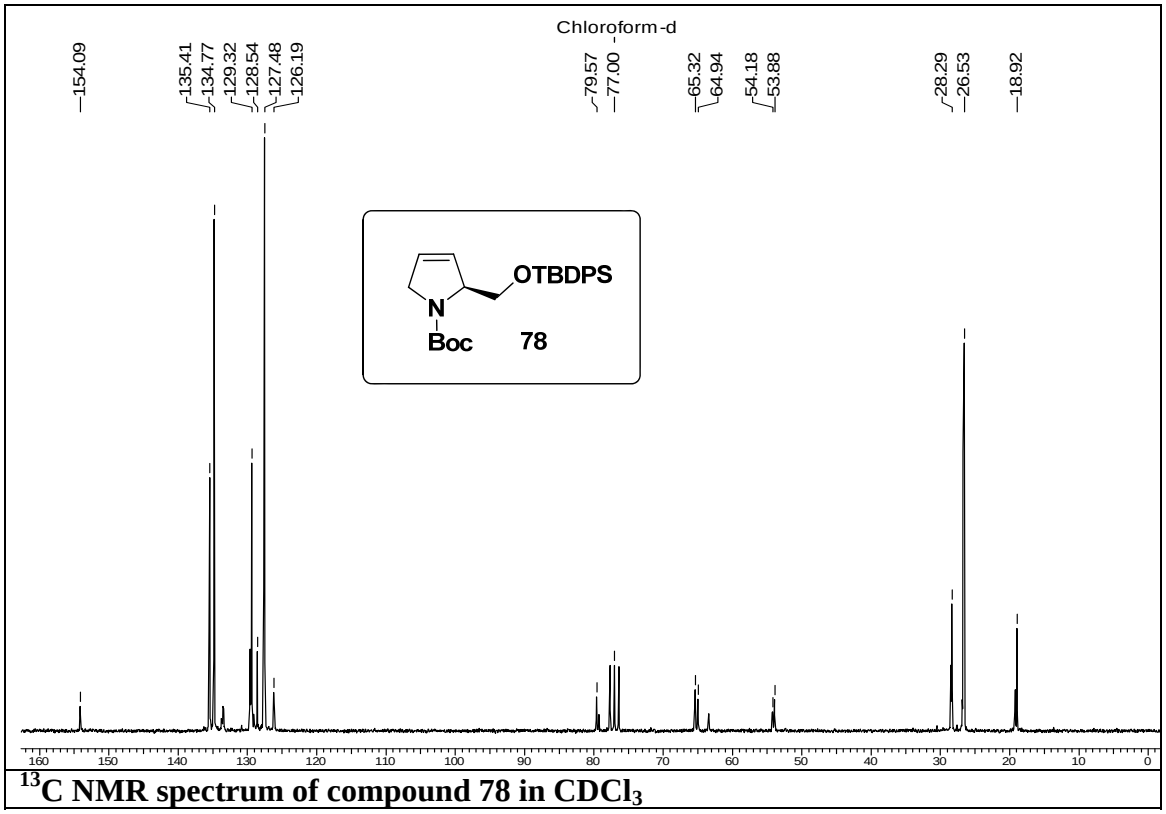
^{1}H NMR spectrum of compound 73 in $CDCl_3$



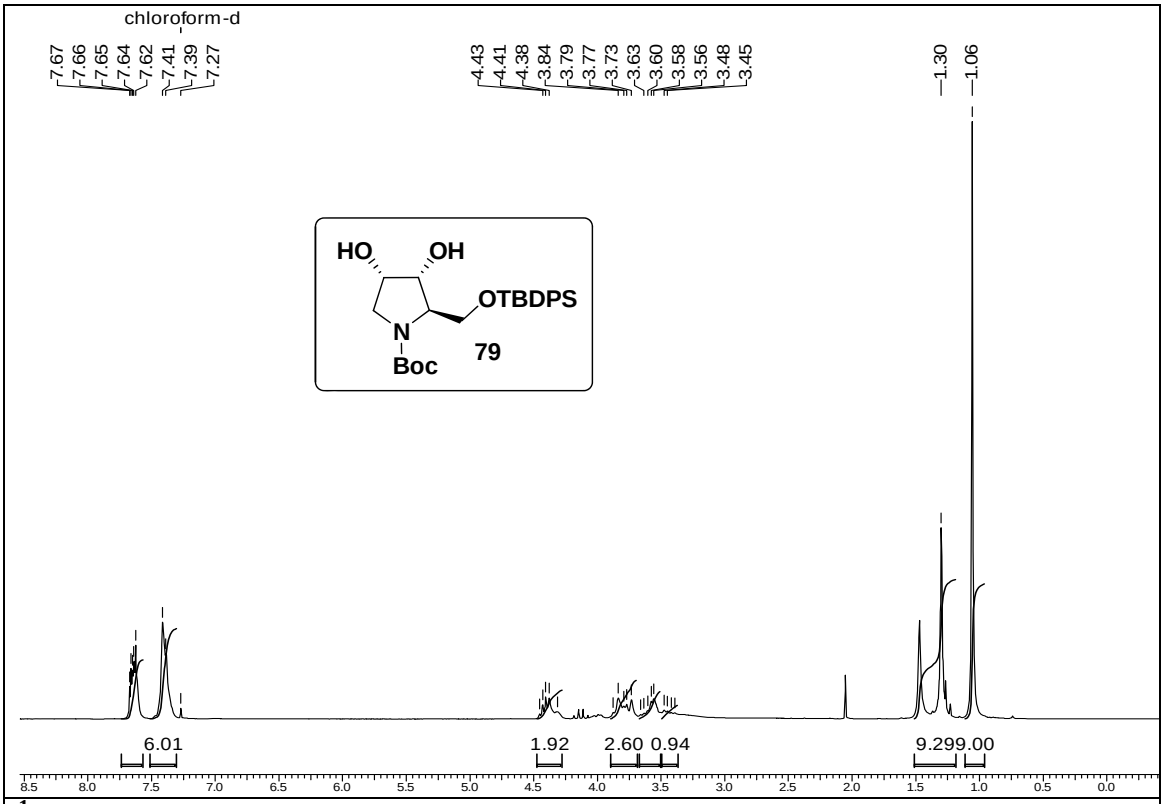
^{13}C NMR spectrum of compound 73 in $CDCl_3$



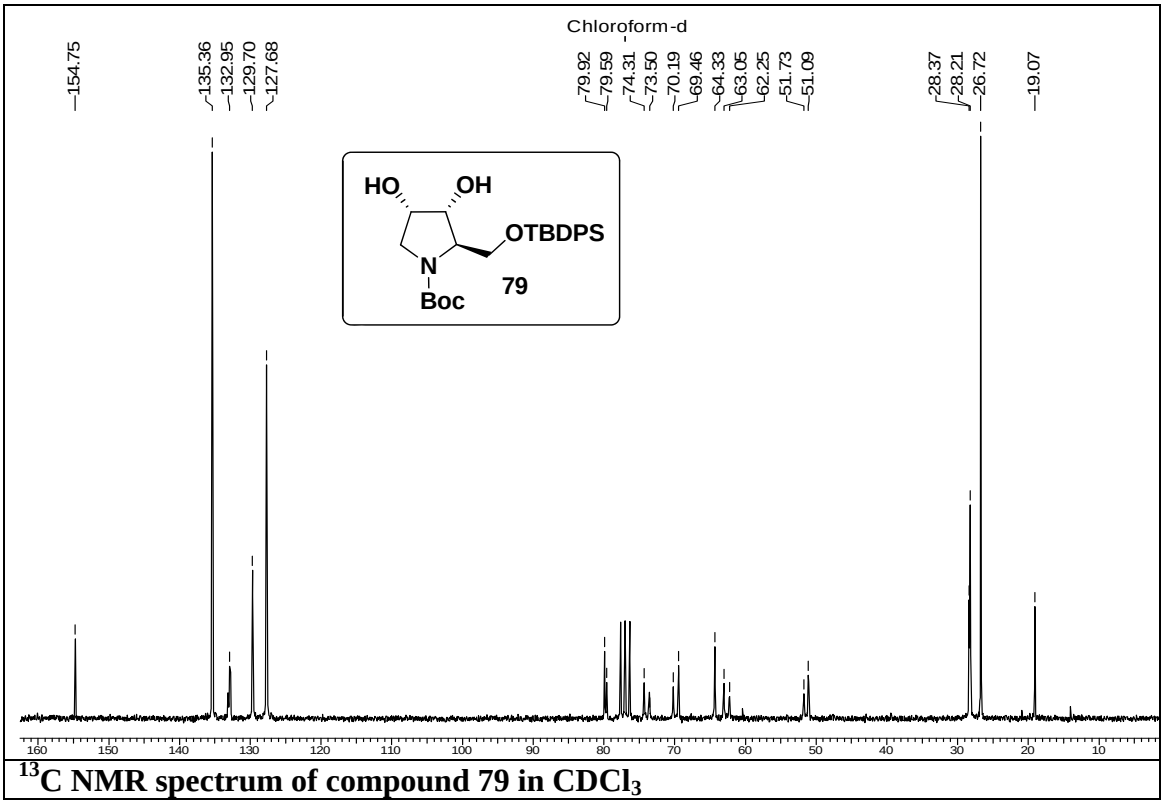
^{1}H NMR spectrum of compound 78 in $CDCl_3$



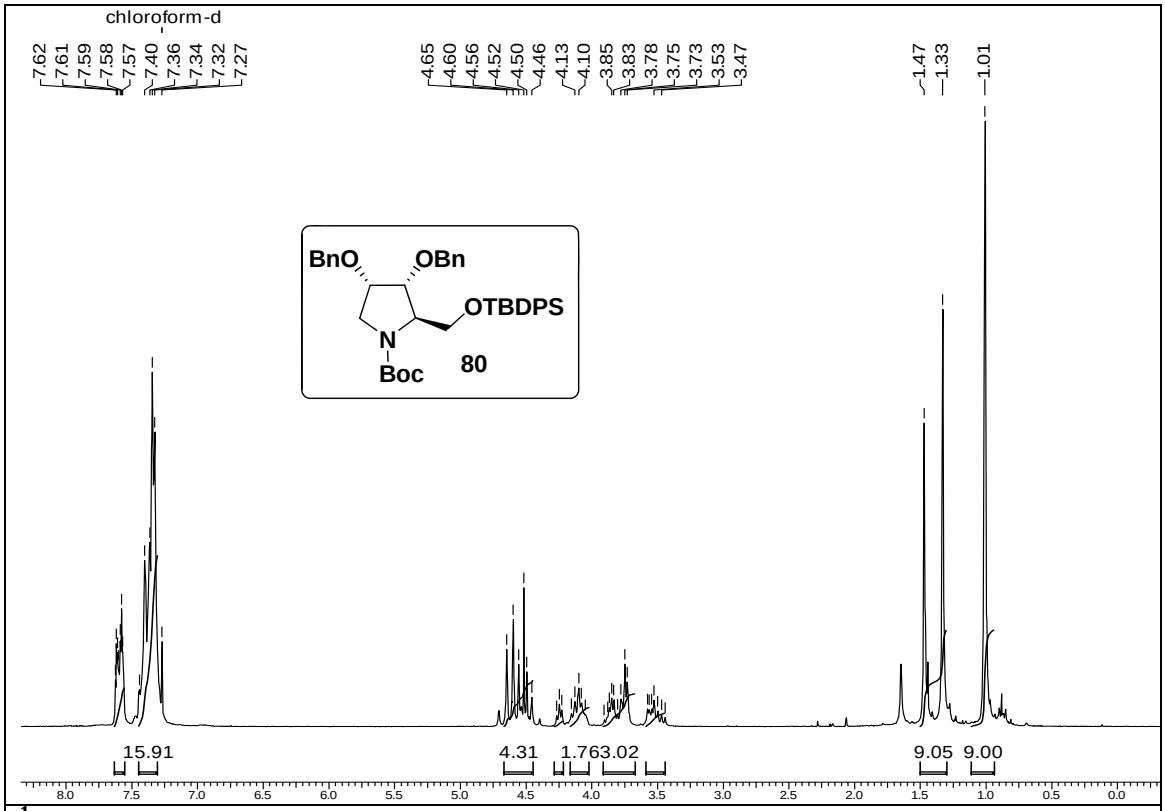
^{13}C NMR spectrum of compound 78 in $CDCl_3$



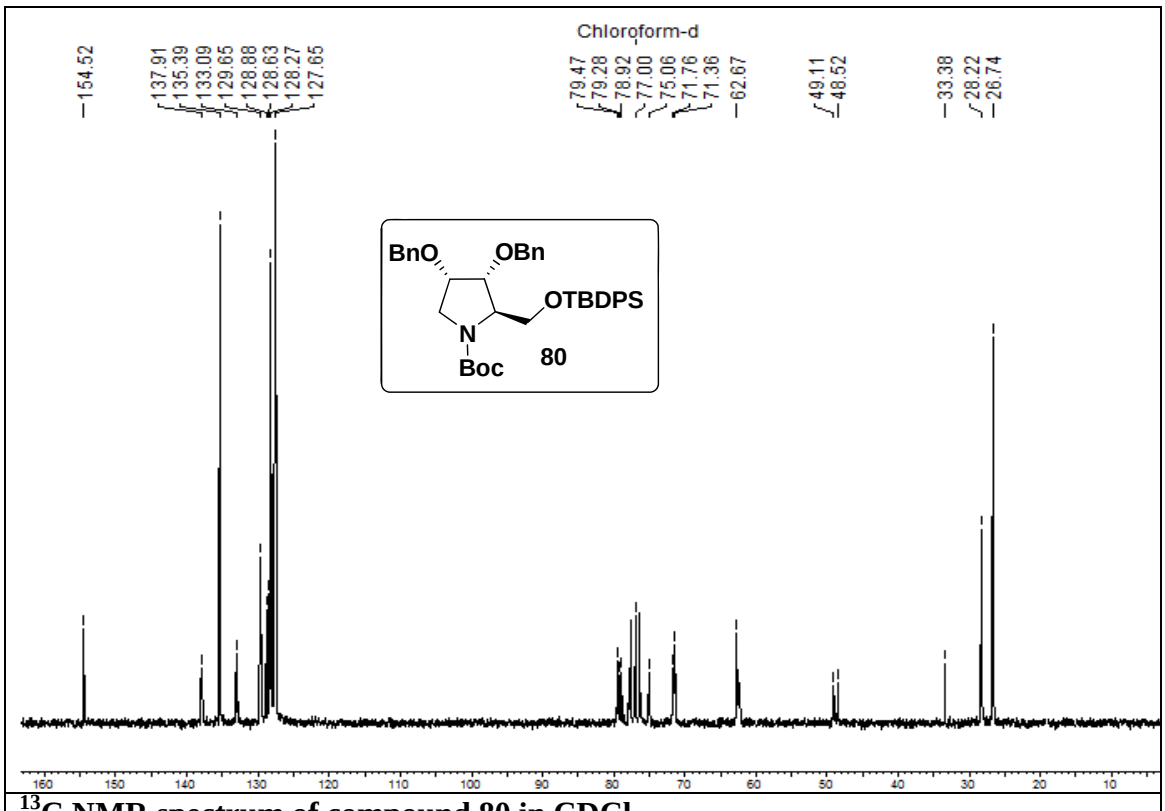
^{1}H NMR spectrum of compound 79 in $CDCl_3$



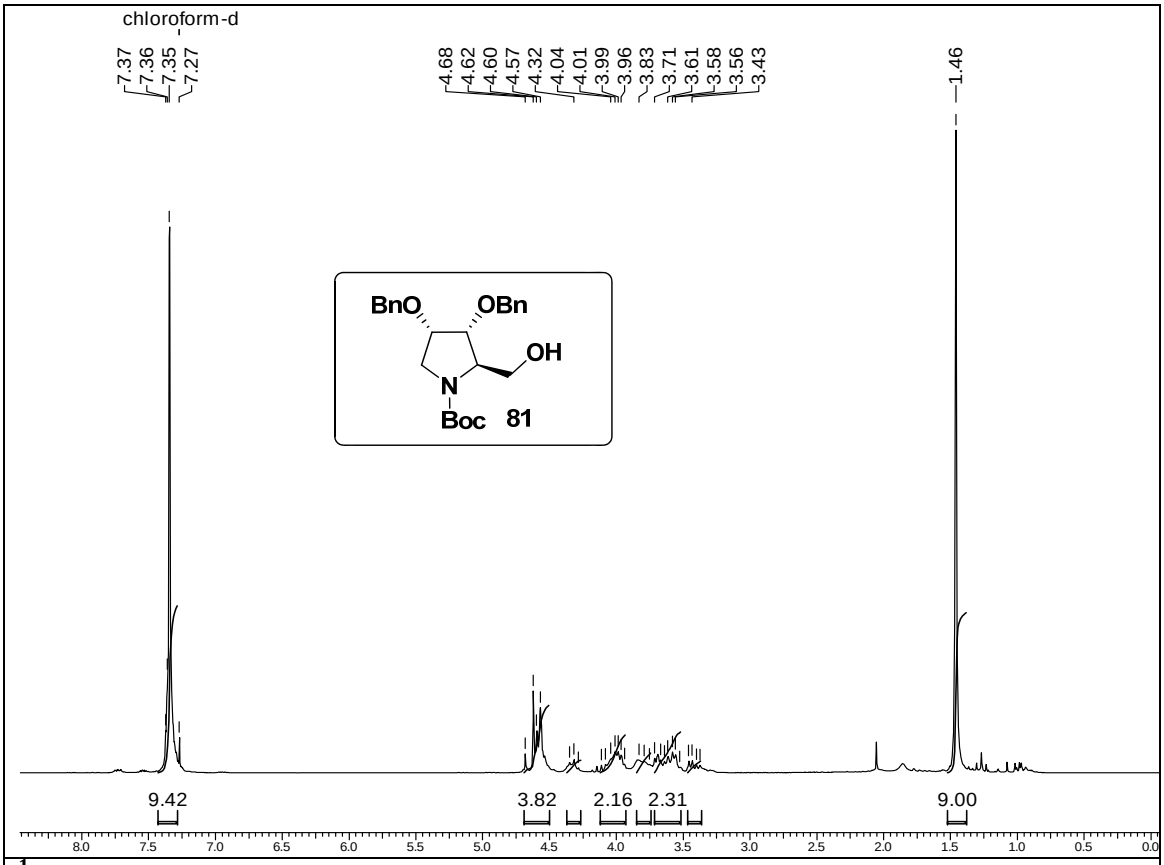
^{13}C NMR spectrum of compound 79 in $CDCl_3$



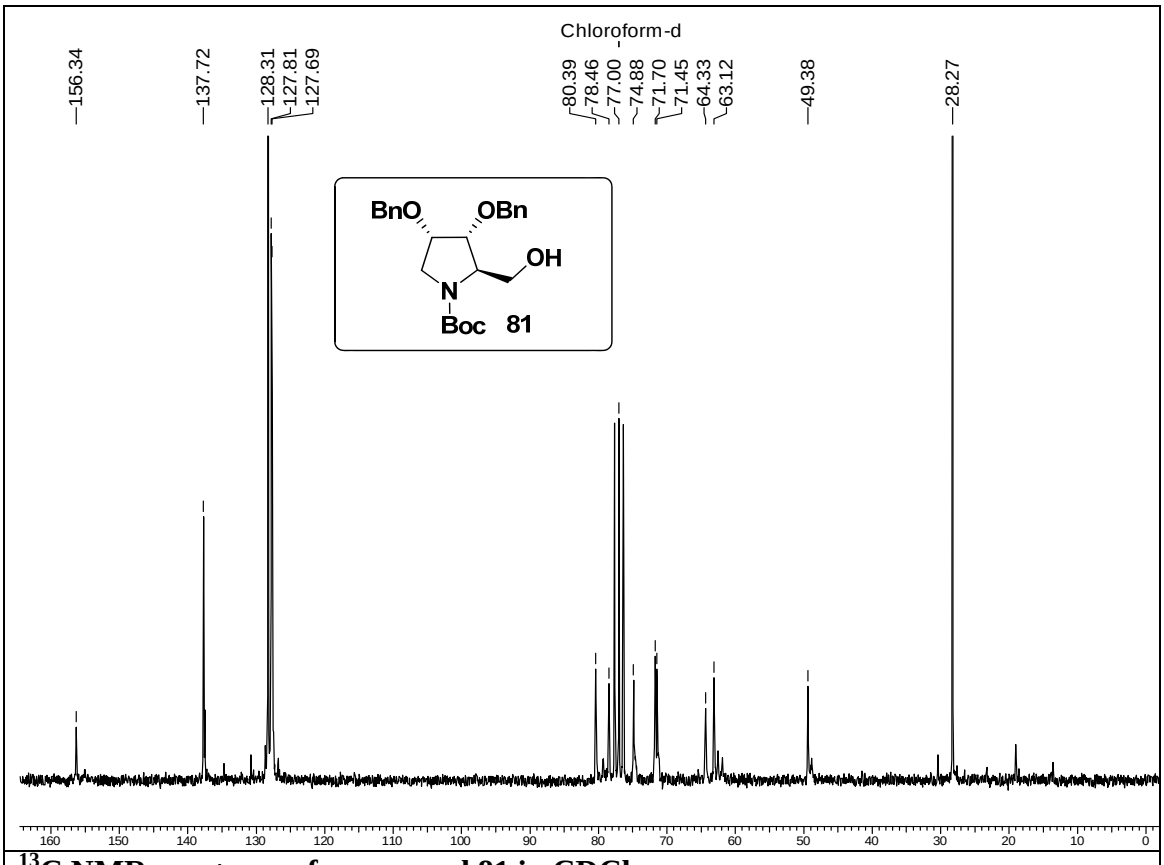
^{1}H NMR spectrum of compound 80 in $CDCl_3$



^{13}C NMR spectrum of compound 80 in $CDCl_3$



^{1}H NMR spectrum of compound 81 in $CDCl_3$



^{13}C NMR spectrum of compound 81 in $CDCl_3$

4.2.8. References

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CHAPTER 5

An easy access to enantiomerically pure (*S*)-3-hydroxy-γ–butyrolactone: a building block for pyrrolidine alkaloids

CHAPTER 5

AN EASY ACCESS TO ENANTIOMERICALLY PURE (*S*)-3-HYDROXY-γ-BUTYROLACTONE: A BUILDING BLOCK FOR PYRROLIDINE ALKALOIDS

5.1. Introduction

(*S*)-3-Hydroxy-γ-butyrolactone is an important synthetic intermediate for a variety of chiral compounds. It serves as key intermediate for the preparation of neuromediator (*R*)-GABOB, L-carnitine,[1] and HMG-CoA reductase inhibitor, CI-981.[2] (*S*)-3-Tetrahydrofuran derived from 3-hydroxy-γ-butyrolactone is an intermediate for an AIDS drug.[3] (*S*)-3-Hydroxy-γ-butyrolactone has been reported as a satiety agent as well as a potentiating agent to neuroleptic drugs.[4] Its utility as a synthetic intermediate for a variety of natural products is well documented.[5] (*S*)-3-hydroxy-γ-butyrolactone is an important building block for the synthesis of various hydroxylated pyrrolidinone derivative and butyric acid derivative (Fig. 1).

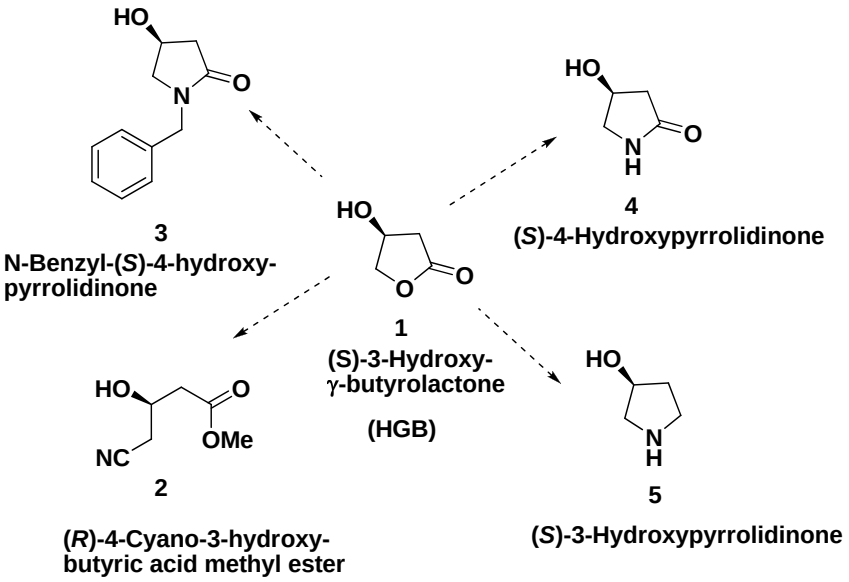
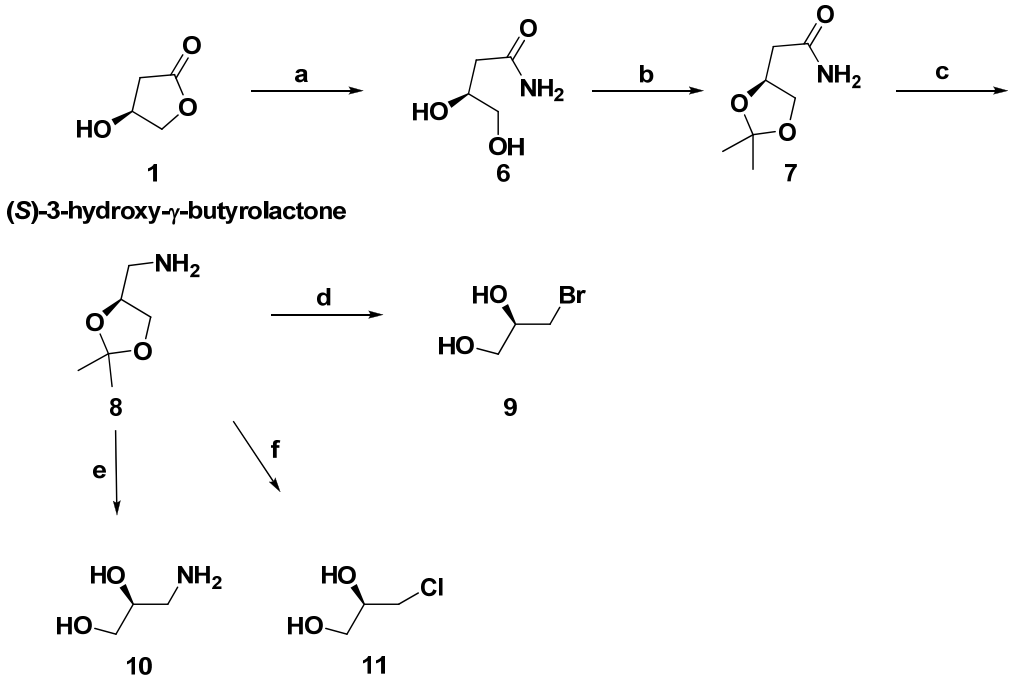


Fig. 1. Structure of various hydroxylated pyrrolidinone and butyric acid derivative

5.2. Review of Literature

The synthesis of (*S*)-3-hydroxy-γ-butyrolactone has been accomplished by employing various synthetic strategies. A commonly used strategy for its synthesis and for its intermediate (*S*)-3-hydroxybutyric acid derivatives is from the enzymatic or catalytic β-keto ester reduction.[6] It has also been prepared from the selective reduction of L-malic acid ester.[7] There have been reports of its synthesis from carbohydrate sources as well, either using just a base or a combination of a base and an oxidant. The treatment of a carbohydrate containing glucose substituent in the 4-position, such as cellobiose, amylase and cellulose with alkali, has been shown to produce a low yield of the desired material along with D, L-2,4-dihydroxybutyric acid, glycolic acid, isosaccharinic acid, ketones, diketones, glycolic acid, and a plethora of other degradation and condensation products.[8] Similarly, the alkaline oxidation of a carbohydrate containing a glucose substituent at the 4-position is known to give a dicarbonyl compound, which is then oxidized to furnish (*S*)-3,4-dihydroxybutyric acid.[9] The yield reported for the desired compound is very low due to the formation of a large number of by-products.

Hollingsworth *et al.* (1999)[10]

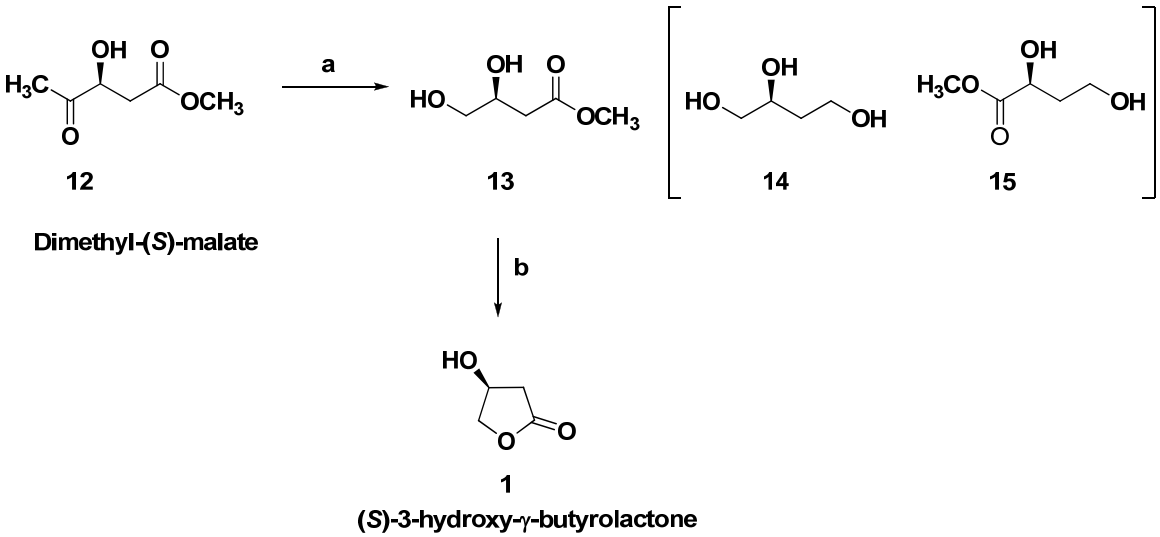


Scheme 1. *Reagents and conditions*: (a) NH_3; (b) $(CH_3)_2CO$/dimethoxypropane/H^+; (c) NaOCl/NaOH; (d) $NaNO_2/H^+/Br^-$; (e) HCl; (f) $NaNO_2/H^+/Cl^-$.

Hollingsworth *et al.*[10] reported the direct conversion of (*S*)-3-hydroxy-γ-butyrolactone **1** to chiral three carbon building blocks (Scheme 1). Thus, (*S*)-3-hydroxy-γ-butyrolactone **1** was converted into three other useful chiral building blocks such as (*S*)-3-amino-1,2-dihydroxypropane **10**, (*R*)-1-bromo-2,3-dihydroxypropane **9** and the corresponding chloro compound **11**. The latter two compounds are glycidol equivalents.

Moriwake *et al.* (1984)[7b]

Moriwake *et al.*[7b] reported the synthesis of (*S*)-3-hydroxy-γ-butyrolactone from reduction of dimethyl (*S*)-malate using $BH_3.SMe_2/NaBH_4$ as the reducing agent. None of the side product such as triol **14** and diol **15** was observed (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) $BH_3.SMe_2/NaBH_4$, THF, 1 h, 88%; (b) CF_3COOH/CH_2Cl_2, rt, 20 h.

5.3. Present Work

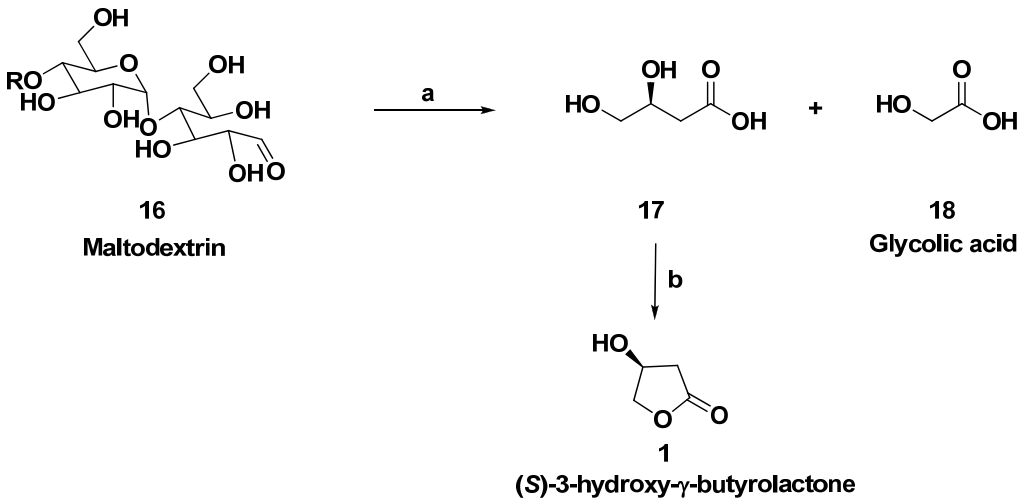
Objective

Defunctionalization of a carbohydrate has been attracting much attention as a useful synthetic tool for the enantioselective synthesis of a variety of compounds. The synthesis of a chiral compound with a desired number of stereogenic centers could be achieved by eliminating the unneeded stereogenic centers quickly from the carbohydrate precursors.

Though a large number of small scale complex syntheses of (*S*)-3-hydroxy-γ-butyrolactone have been developed, the majority of these methods suffer from drawbacks such as multi-step synthesis, long reaction times, high temperature, enzymatic methods, and use of expensive metal catalysts for the reduction of the prochiral center, side reactions, low enantiomeric purity, and overall low yield of product. Therefore, there is genuine need for a simple and inexpensive method for the large-scale preparation of (*S*)-3-hydroxy-γ-butyrolactone and its derivatives,[11] the synthesis of which was successfully accomplished by employing the oxidation of a 1,4-linked D-hexose sugar under basic conditions.

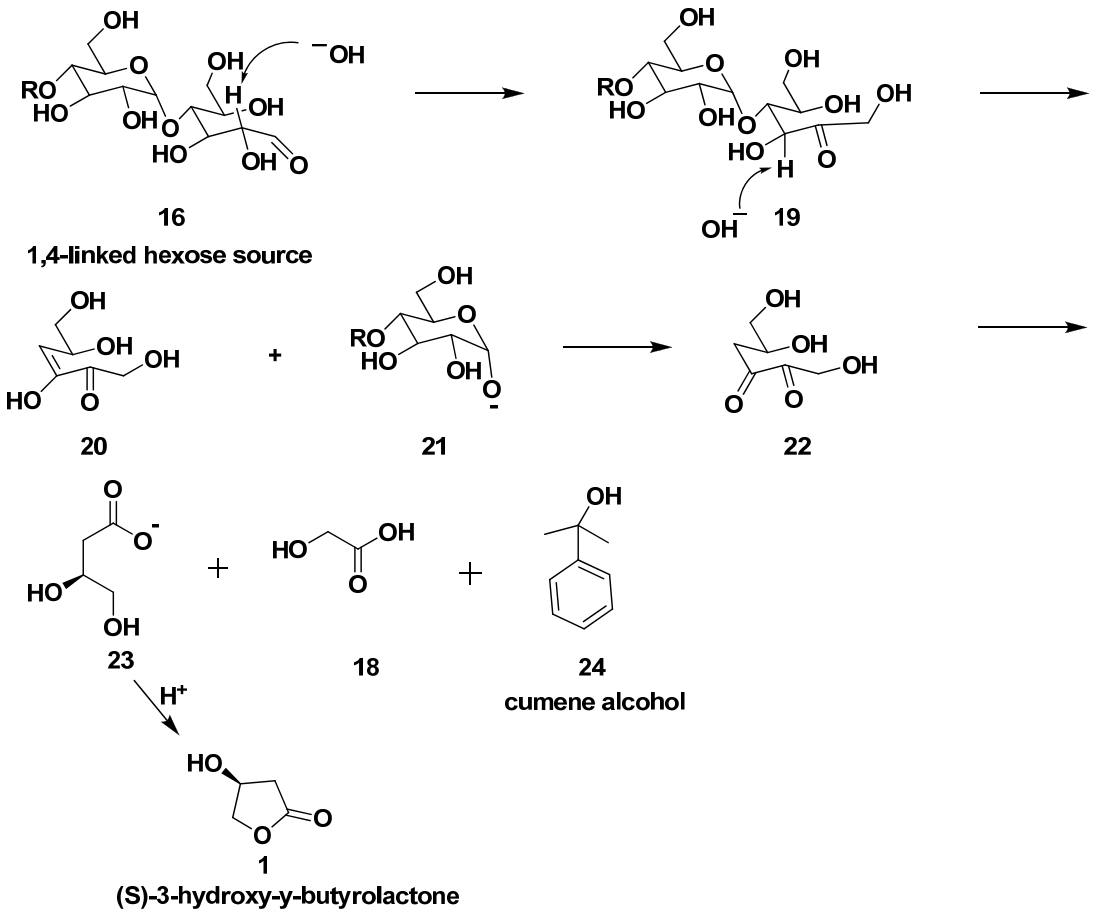
5.4. Results and Discussion

The synthesis of (*S*)-3-hydroxy-γ-butyrolactone started from the readily available carbohydrate source as depicted in Scheme 3.



Scheme 3. *Reagents and conditions:* (a) NaOH, 40 °C, 2 h, then 80% cumene hydroperoxide, 70 °C, 10 h, 56%.

Thus, a 1,4-linked D-hexose sugar **16**, such as maltose/maltodextrin/lactose, was treated with 80% cumene hydroperoxide under basic conditions at 70 °C to give 3,4-dihydroxybutyric acid **17** which was cyclized in the presence of an acid to afford the desired butyrolactone **1** in reasonably good yield (Scheme 3). The spectroscopic data of **1** was in full agreement with those reported in literature.[12, 13] The advantages of the present method was that it is simple, practical, and economical.



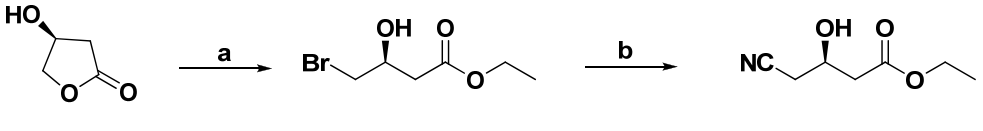
Scheme 4. The proposed mechanism for the formation of (*S*)-3-hydroxy-γ-butyrolactone from 1,4-linked hexose source with 80% cumene hydroperoxide in presence of base.

Initially, various D-hexose sugars were screened in order to obtain the best possible yield of the desired product. While the reaction of maltodextrin with 80% cumene hydroperoxide in the presence of sodium hydroxide gave 56% yield of the butyrolactone **1**, maltose under similar reaction conditions afforded a slightly lower yield (54%). However, other carbohydrate sources such as lactose gave only moderate yields of the desired product. Similarly, amongst the various oxidizing agents screened, cumene hydroperoxide proved to be an ideal reagent. The use of other oxidizing agents, such as hydrogen peroxide, *tert*-butyl hydroperoxide and oxone gave poor yields of product. The reaction mechanism for the formation of (*S*)-3-hydroxy-γ-butyrolactone **1** from a 1,4-linked hexose source **16**, such as maltodextrin, maltose, etc. is illustrated in Scheme 4.

Thus, treatment of 1,4-linked hexose source **16** with base leads to an isomerization to the 4-linked ketose **19** which readily undergoes β-elimination to form enone **20**.

Subsequent tautomerization leads to the formation of diketone **22** which is readily cleaved with cumene hydroperoxide to give the salt of (*S*)-3,4-dihydroxybutyric acid **23** and glycolic acid **18**. Cumene alcohol **24** is also formed as by-product. Acidification and concentration gave the desired lactone **1**.

Our next aim was to convert lactone **1** into useful chiral intermediate such as cyanoester **26** in two step (Scheme 5).



1 (*S*)-3-hydroxy-γ-butyrolactone **25** **26** cyanoester

Scheme 5. *Reagents and conditions:* (a) 30-33% HBr in AcOH/EtOH, reflux, 8 h, 85%; (b) NaCN, DMF, rt, 24 h, 50%.

When hydroxy lactone **1** was first treated with 30–33% HBr in AcOH/EtOH to afford the corresponding bromo ester **25** in 85% yield. The subsequent treatment with sodium cyanide furnished the cyano compound **26** (by direct displacement of bromo with cyano) in about 50% yield. The spectroscopic data of compound **25** and **26** were in accordance with the literature precedence.[15] Cyano ester **26** is a chiral intermediate for the preparation of statin based drugs (cholesterol lowering drugs), such as mevacor, atorvastatin, lipitor, etc.

5.5. Conclusion

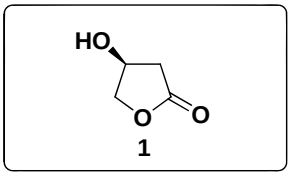
In conclusion, a method for preparing enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone by the oxidation of a (1,4)-linked disaccharide or oligosaccharide with cumene hydroperoxide has been developed.

5.6. Experimental Section

The solvents were purified and dried by the standard procedures prior to use; petroleum ether of boiling range 60-80 ^{o}C was used. Optical rotation was measured using sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-200

spectrometer. The mass spectra were recorded either by GC-MS or with a Finnigan LC-MS mass spectrometer. Enantiomeric excess was measured using either chiral HPLC or by comparison of specific rotations.

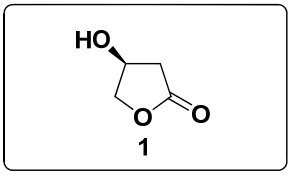
Synthesis of (*S*)-3-hydroxy-γ-butyrolactone (1).



1

In a two-necked 100 mL round bottom flask with a thermo well and reflux condenser was added maltodextrin **16** (1.0 g, 2.77 mmol) dissolved in 0.16 M NaOH solution (0.32 g in 50 mL water, 7.93 mmol, 2.86 equiv). The reaction mixture was heated at 40 ^{o}C for 2 h. The color of the reaction mixture became yellowish to dark red. To this solution was added slowly 80% cumene hydroperoxide (0.7 mL, 3.66 mmol, 1.32 equiv). The reaction temperature was increased slowly to 70 ^{o}C and heated for another 10 h. The reaction mixture was cooled to 25 ^{o}C, and then to 0 ^{o}C. The cooled reaction mixture was acidified with conc. H_2SO_4 to pH 1. The acidified solution was concentrated to dryness at 55 ^{o}C, in order to remove glycolic acid and water. To the yellow colored syrup formed, was added 10 g of ice and then the mixture neutralized with solid sodium bicarbonate, extracted with ethyl acetate, and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue obtained was purified by silica gel column chromatography using EtOAc/pet ether (4:6) as eluent to give **1** (0.16 g) as a colorless oil in 56% yield, $[\alpha]^{25}_{D}$ = -84.6 (*c* 3.1, EtOH), [lit.$[\alpha]^{25}_{D}$ = -86.1 (*c* 3.1. EtOH)].[13] The spectroscopic data (IR, ^{1}H NMR) are in full agreement with those described in literature.[13]

Modified work-up procedure for the removal of cumene alcohol (24).
Synthesis of (*S*)-3-hydroxy-γ-butyrolactone (1).

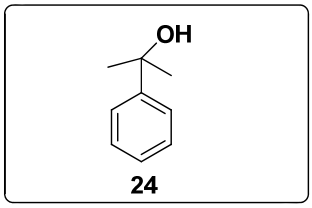


1

In a 500 mL two-necked round-bottom flask, was placed maltodextrin **16** (5.0 g) dissolved in 0.16 M NaOH solution (1.6 g in 250 mL water). The reaction mixture was

heated at 40 ^{o}C for 2 h. To the reaction mixture was added 80% cumene hydroperoxide (3.5 mL, 1.32 equiv). After addition, the reaction temperature was increased to 70 ^{o}C and heated for 10 h. After the reaction was over, it was cooled to room temperature and the reaction mixture extracted with ether (2 x 50 mL). The organic layer was separated and the aqueous layer cooled to 0 ^{o}C. The pH of the solution was 8.16 and the aqueous layer acidified with conc. H_2SO_4 (2.8 mL) to pH 1. The solution was concentrated to dryness at 60 ^{o}C and to the residue crushed ice was added and neutralized with sodium bicarbonate and then extracted with ethyl acetate (3 x 200 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The evaporation of the solvent and purification by silica gel column chromatography using pet ether/ethyl acetate (4:6) gave **1** (0.8 g) as a colorless oil in 56% yield.

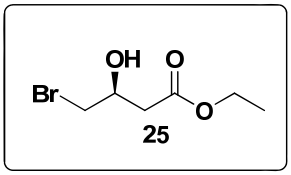
Cumene alcohol (24).



24

As mentioned in the modified work-up procedure, the reaction mixture was first extracted with diethyl ether (2 x 50 mL). The organic layer was separated and concentrated. The residue obtained was purified by column chromatography. The yield (3.22 g) of the organic layer extract comprises of unreacted cumene hydroperoxide and cumune alcohol which were fully characterized by NMR and GC-MS.

Synthesis of (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester (25).



25

To a cooled solution of (*S*)-3-hydroxy butyrolactone **1** (1.02 g, 10 mmol) was added with stirring 30-33% HBr (3 mL, 15 mmol) in glacial acetic acid. The reaction mixture was warmed to room temp and then heated to 60 ^{o}C under nitrogen for 5 h. Absolute ethanol was added to the reaction mixture and then the stirring was continue at the

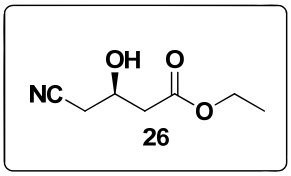
same temp for another 5 h. The solvent was evaporated and the residue taken in ethyl acetate, washed with 10% $NaHCO_3$ and then with water until the aq layer becomes neutral. The organic layer was dried over sodium sulfate and the solvent distilled. The residue was purified by silica gel column chromatography using ethyl acetate and pet ether (2:8) as eluent to give **25** as a colorless oil.

Yield: 1.91 g (85%).

$[\alpha]^{25}_D$ = -10 (*c* 1.2, EtOH); [lit. $[\alpha]^{20}_D$: -11 (*c* 1.0, EtOH)].[14]

The physical and spectroscopic data (IR, ^{1}H NMR) are in accordance with those described in literature.[15]

Synthesis of (*R*)-4-cyano-3-hydroxybutyric acid ethyl ester (26).



26

To a cooled solution of (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester **25** (1.13 g, 5 mmol) dissolved in 5 mL of dry DMF was added with stirring NaCN (0.98 g, 20 mmol). The reaction mixture was stirred at room temperature overnight. DMF was evaporated under reduced pressure, the residue left was extracted with diethyl ether. The solvent was evaporated to afforded **26** as a light yellow liquid.

Yield: 0.43 g (50%).

$[\alpha]^{25}_D$ = -32.5 (*c* 1.0, $CHCl_3$); [lit. $[\alpha]^{20}_D$: -33.1 (*c* 1.2, $CHCl_3$)].[2]

The physical and spectroscopic data (IR, ^{1}H NMR) are in accord with those described in literature.[15]

5.7. References

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Bio-Data

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Erratum