Organo-Catalytic Diastereoselective Aldol Reaction: Application for the Synthesis of Biologically Active Alkaloids

A THESIS

SUBMITTED TO

THE UNIVERSITY OF PUNE

FOR THE DEGREE OF

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IN

CHEMISTRY

BY

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UNDER THE GUIDANCE OF

Dr. C. V. RODE

Chemical Engineering & Process Development Division

National Chemical Laboratory

Pune - **411 008 (INDIA)**

September 2007

Dedicated to

My Beloved

Parents And Brothers……..

राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
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CERTIFICATE

This is to certify that the work incorporated in the thesis, **"Organo-Catalytic Diastereoselective Aldol Reaction: Application for the Synthesis of Biologically Active Alkaloids"** submitted by **Mr. Indresh Kumar,** for the Degree of **Doctor of Philosophy,** was carried out by him under my supervision at National Chemical Laboratory, Pune, India. Material that has been obtained from other sources is duly acknowledged in the thesis.

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DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled **"Organo-Catalytic Diastereoselective Aldol Reaction: Application for the Synthesis of Biologically Active Alkaloids."** submitted by me for the degree of Doctor of Philosophy to the University of Pune is the record of work carried out by me during the period from August 2004 to August 2007 under the guidance of Dr. C. V. Rode and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Date: September 2007 **Indresh Kumar**

Place: Pune **(Candidate)**

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I simply do not have words to thank my parents, my brothers Sharvan Kumar and Rajnish Kumar whose continuous support, encouragement and love, has helped me to reach this juncture.

September 2007 ***Indresh Kumar***

List of Contents

List of Abbreviations

Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
bp	Boiling point
Boc-	*tert*-Butoxycarbonyl
Cbz-	benzyloxycarbonyl
calcd.	Calculated
cat.	Catalytic/catalyst
$CDCl_3$	Deuterated chloroform
conc.	Concentrated
DCM	Dichloromethane
D_2O	Deuterium oxide
DIBAL-H	Diisobutyl aluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
de	Diastereomeric excess
ee	Diastereomeric excess
eq. or equiv	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate

Et_3N	Triethyl amine
g	Grams
h	Hours
Hz	Hertz
i-Pr	Isopropyl
LAH	Lithiumaluminum hydride
M	Molar
m-CPBA	*m*-Chloroperbenzoic acid
mL	Milliliter
mmol	Millimole
mg	Milligram
min	Minute
MOM-	Methoxymethyl
p-TsOH	*p*-Toluene sulfonic acid
rt	Room temperature
satd.	Saturated
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethyl silyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	*p*-Toluene sulfonyl

Research Student: Indresh Kumar **Research Guide: Dr. C. V. Rode**

Abstract of thesis

Title of the thesis: **Organo-catalytic Diastereoselective Aldol Reaction: Application for the Synthesis of Biologically Active Alkaloid**

This thesis is divided into five chapters.

Chapter 1: Introduction

This chapter gives an overview on the 'direct catalysis of aldol reaction' through biocatalysis, metal catalysis and organo-catalysis. In particular, organocatalysis is very fast growing area for enantioselective transformations through 'enamine and iminium ion' catalysis, especially the detailed mechanistic concept of enamine-catalysis for aldol reaction using proline as an organocatalysts have been described in detailed.

Chapter 2: Direct Diastereoselective Aldol Reaction: Towards the Synthesis of Amino-polyols

In chapter 2, studies on direct diastereoselective aldol reaction of various amino aldehydes with different ketones and further extension to the synthesis of core "backbone" of sphingolipids and phytosphingosines are compiled. The direct aldol reaction in diastereoselective fashion of using different amino aldehydes having cyclic core structure with acetone and other cyclic ketones provides aldol product with high level of diastereoselectivity (Figure1).

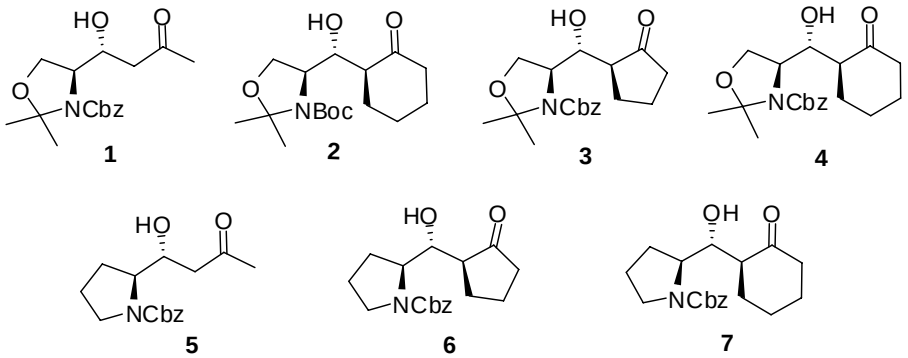
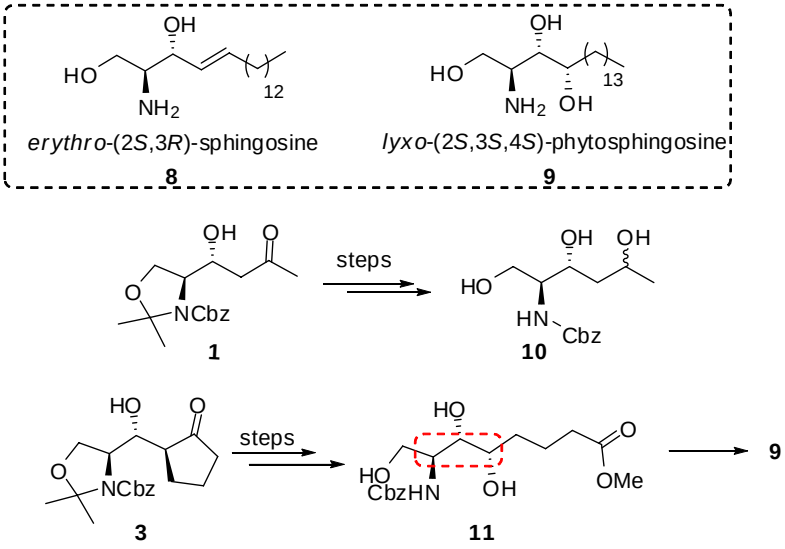


Figure 1: Direct diastereoselective aldol products of amino aldehydes with ketones

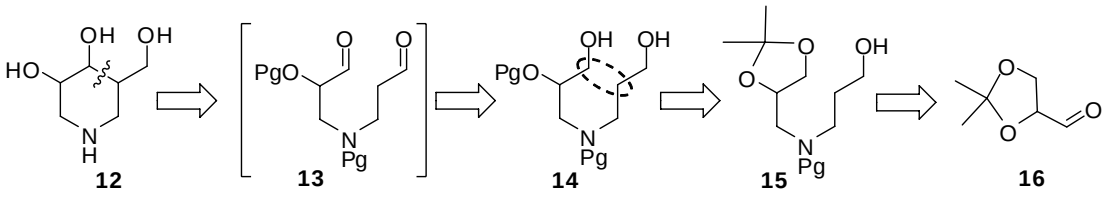
This diastereoselective approach was further utilized for the synthesis of amino polyol backbones structure of sphingosine and phytosphingosine, which are important core structure of biologically active compounds (Scheme 1).



Scheme 1: Synthesis for amino polyols

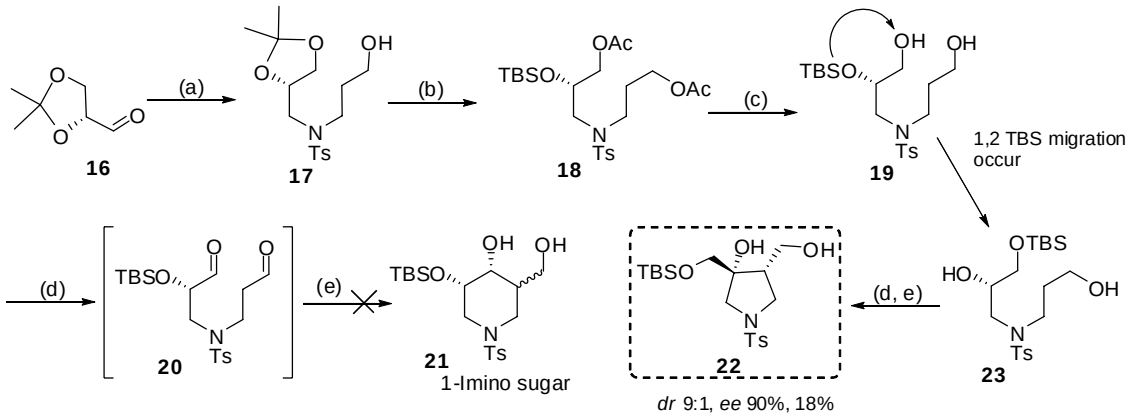
Chapter 3: Direct Organocatalytic *Enolexo* Aldolization: Synthetic Study towards 1-*N*-Imino Sugars

In this chapter, we have presented a new synthetic approach for 1-imino sugars via direct diastereoselective enolexo aldolization reaction, the main challenge of this approach was to discriminate between two aldehyde groups of dialdehyde **13** (Scheme 2). This chapter is divided in to two sections. The



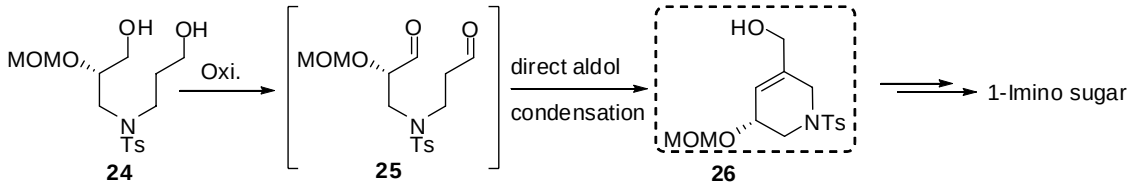
Scheme 2: New reterosynthetic analysis of 1-imino sugars

Sections A: In this study, we have presented very interesting result of 1,2-TBS migration under very mild basic conditions, which leads to the first 5-*enolexo* aldolization with reverse reactivity pattern of the aldehyde as donor and ketone as acceptor. The synthesis of a 3,4-substituted pyrrolidine have been achieved with high level of *syn*-selectivity through direct intramolecular aldolization catalyzed by L-proline (Scheme 3)



Scheme 3: (a) (i) amino propanol, Pd/C (10 mol%), MeOH, H_2 (1 atm.) rt, 12 h. (ii) TsCl (1.2 equiv.), Na_2CO_3 (2.2 equiv.), DCM: H_2O (1:1), 0^oC, 3 h, 83% in two steps. (b) (i) *p*-TSA, MeOH, rt, 8h. (ii) AcCl (2.2 equiv.), DCM: Pyridine (1:1), 0^oC, 3 h. (iii) TBSCl (1.1 equiv.), Imidazole, Dry DCM, 0^oC, 4 h, 73% yield in three steps. (c) K_2CO_3 (cat.), MeOH, rt, 30 min, 89% yield. (d) (i) IBX (5.0 equiv.), EtOAc, reflux, 4.5 h (ii) L-proline (15 mol%), $CHCl_3$:DMSO (3:1), 5^oC, 16 h (iii) $NaBH_4$, MeOH, 5^oC, 2 h, 65% yield after three steps.

Section B: In order to avoid the –TBS migration, we tried –MOM as a protecting group and the 6-enolexo aldol condensation occur very smoothly to provide the key product 17. This can be easily transformed in to various 1-imino sugars (Scheme 4).



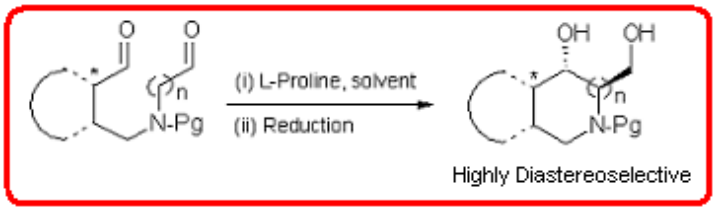
Scheme 4: Direct 6-enolexo aldolization for 1-imino sugars

Chapter 4: Direct Organocatalytic *Enolexo* Aldolization: Synthetic Study towards 1-*N*-Imino Sugars

In this chapter, we designed a new approach for the synthesis of the core structure of imino sugars which are nitrogen analogues of sugars through proline catalyzed direct *enolexo* aldol reaction of dialdehyde **18**, in which two new chiral centers can be formed in a single step as shown in Scheme 5.

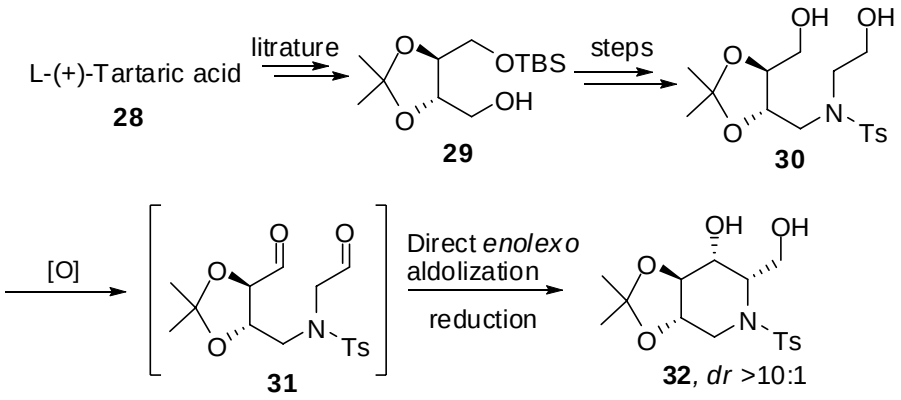
According to the designed plan, we first prepare a dialdehyde similar to **27** from L-(+)-tartaric acid and the direct diastereoselective intramolecular aldolization reaction proceed through high level of *syn*-selectivity with high diastereomeric ratio (*dr* >10:1). This syn-

selectivity was further confirmed through the X-ray analysis of cyclized derivative (Scheme 6)



Scheme 5: Direct diastereoselective *enolexo* aldolization for imino sugars

According to the designed plan, we first prepare a dialdehyde similar to **27** from L-(+)-tartaric acid and the direct diastereoselective intramolecular aldolization reaction proceed through high level of *syn*-selectivity with high diastereomeric ratio (*dr* >10:1) (Scheme 6).



Scheme 6: Study towards the 1-deoxynojirimycin analogues (*syn*-selectivity)

Chapter 4: Synthesis of Fused 1,2,3-Triazolo-*δ*-Lactams/Lactones using "Click-chemistry in Water"

In this chapter, we have presented the 1,3-dipolar cycloaddition reaction of various chiral azides with dimethylacetylene dicarboxylate as an activated alkyne has been performed in water and further utilization of this click reaction is investigated with its application for the synthesis of new class of hybrid 1,2,3-triazolo-*δ*-lactams **(A)**/lactones **(B)** as shown in Figure 2. The reterosynthetic analysis of this new class of 1,2,3-triazolo-*δ*-lactams/lactones is shown in Scheme 7.

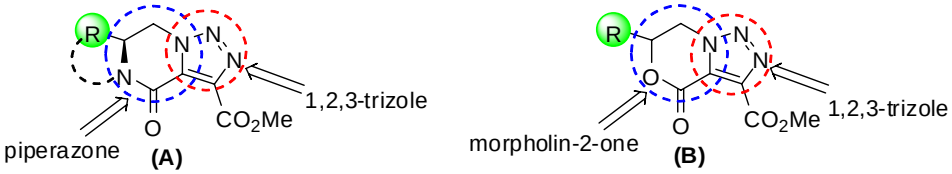
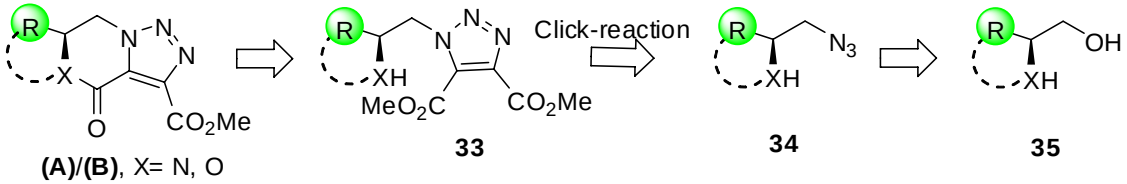


Figure 2: Hybrid 1,2,3-triazolo-*δ*-lactam/lactone



Scheme 7: Reterosynthetic analysis of hybrid 1,2,3-triazolo-*δ*-lactams/lactones

Through this approach, we have prepared various fused 1,2,3-triazolo-*δ*-lactams/lactones as shown in figure 3.

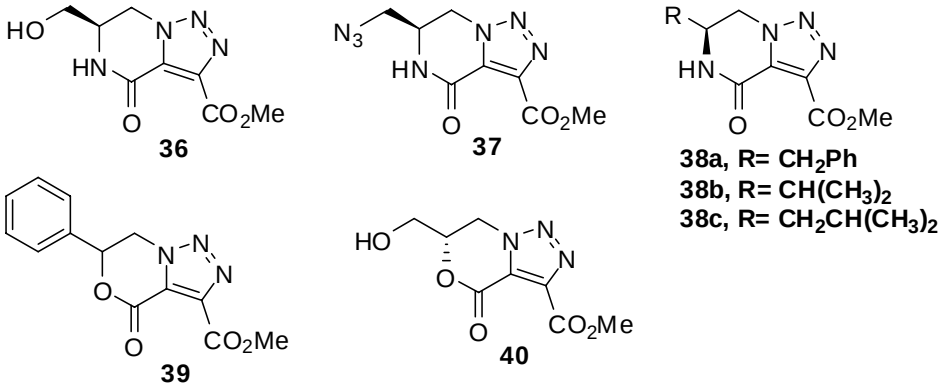


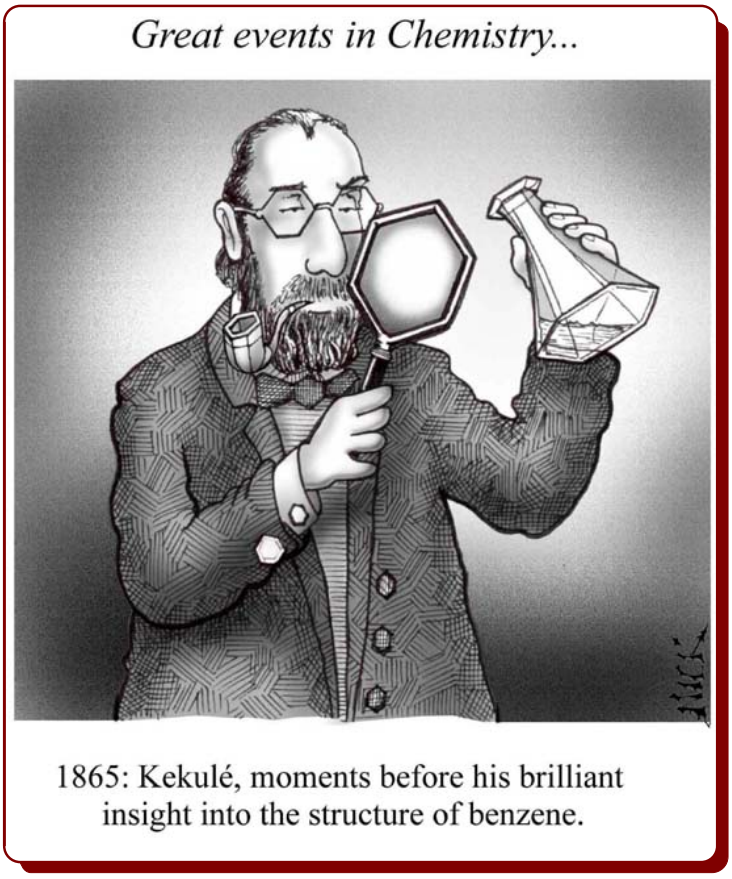
Figure 5: Fused 1,2,3-triazolo-*δ*-lactams/lactones

Indresh Kumar (Student)

Dr. C. V. Rode (Research Guide)

Chapter 1

Introduction

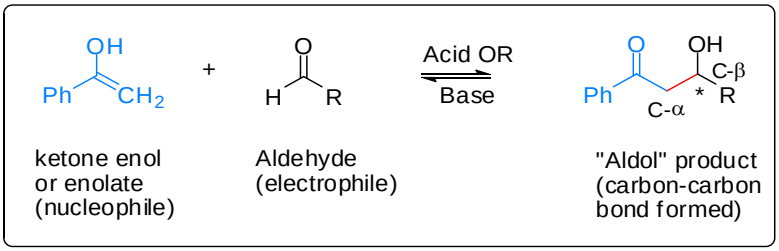


"Chemistry is all about getting lucky..... !
-"Robert Curl"

This thesis begins with a short review on aldol reaction, which is one of the important C-C bonds forming reaction in organic chemistry. The fundamental aspect of catalysis and direct catalytic asymmetric aldol reaction using biocatalysts, metal catalysts and organocatalysts will be discussed in details. A comprehensive mechanistic overview on direct organocatalytic asymmetric aldol reaction, which is of growing interest in the recent years, is presented. Finally the aim of this thesis and summary of its contents are outlined in this chapter.

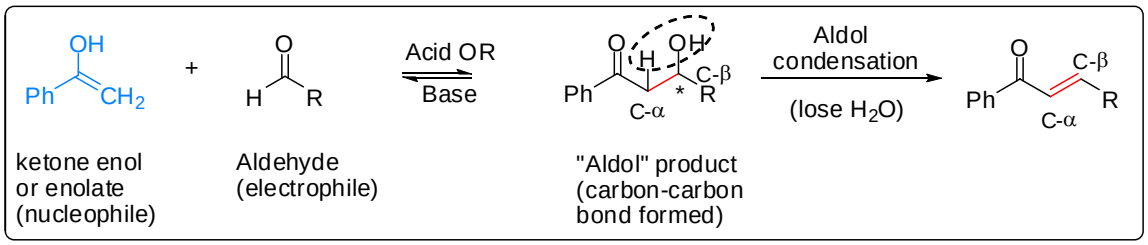
1.1 Aldol reaction

The formation of carbon-carbon bonds with complete control of stereochemical outcome of a reaction is one of the important aspects of modern organic synthesis. Among the several approaches, the aldol reaction is generally regarded as one of the most powerful and efficient method for carbon-carbon bond formation.[1] In general, this reaction involves the nucleophilic addition of *enol* or *enolate* from the enolizable carbonyl group to an aldehyde, which results into the formation of a new carbon-carbon bond between the *enol* α-carbon and aldehyde giving a β-hydroxy carbonyl or **aldol** (**ald**ehyde + alcoh**ol**). The name aldol is derived from "**ald**ehyde" and "alcoh**ol**". The carbonyl group should have at least one acidic proton at the α-position to transform into its corresponding *enol* or *enolate* form, which is catalyzed by a base or an acid. Since *enol* or *enolate* possess π- electron system, this act as a nucleophile, while the carbonyl carbon of aldehyde behaves as an electrophile (Scheme 1.1).



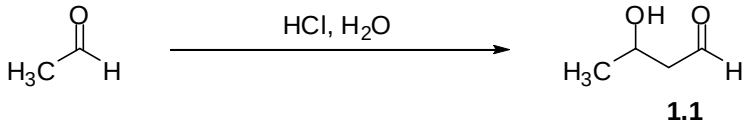
Scheme 1.1: A typical aldol reaction

The primary products of aldol reaction are always *β*-hydroxy carbonyl compounds but sometimes the aldol addition product loses a molecule of water during the reaction to form α, β-unsaturated carbonyl called as aldol condensation product (Scheme 1.2).



Scheme 1.2: Aldol condensation

The aldol reaction was discovered independently by *Charles-Adolphe Wurtz*[2] and by *Alexander Porfyrevich Borodin* in 1872 and observed simultaneous presence of aldehyde and alcohol moieties in 3-hydroxylbutanal "aldol" **1.1** resulting from the acid-induced reaction of acetaldehyde (Eq. 1.1).



1.1

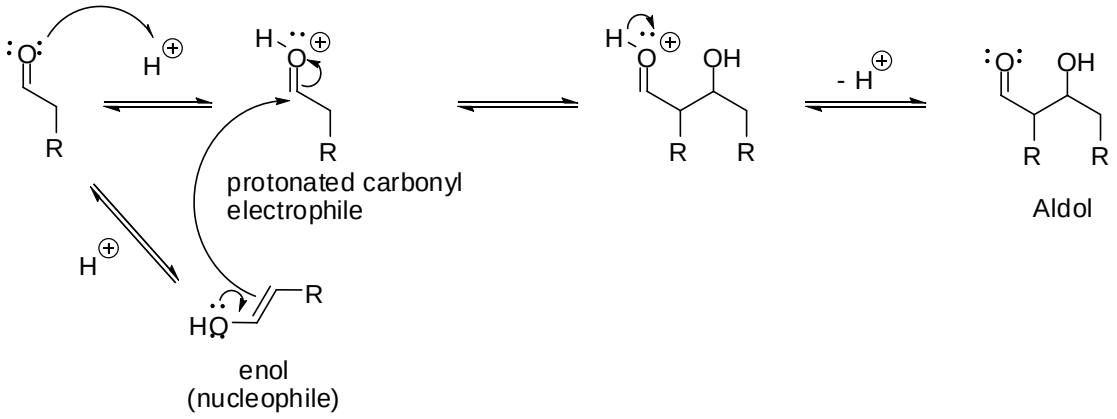
(1.1)

1.1.1 Catalysis of traditional aldol reaction

The 'traditional' aldol reaction is a reversible reaction, which is catalyzed by either acid or base in the protic solvents and proceed under thermodynamic control.[3] A variety of nucleophiles may be employed in the aldol reaction, including the enols, enolates, and enol ethers of enolizable carbonyl compounds such as aldehydes or ketones but the electrophilic reactant is usually an aldehyde. When the nucleophile and electrophile are different (usual case), the reaction is called as crossed aldol reaction. The aldol reactions proceeds via two fundamentally different mechanisms.[3]

1.1.2 Enol mechanism

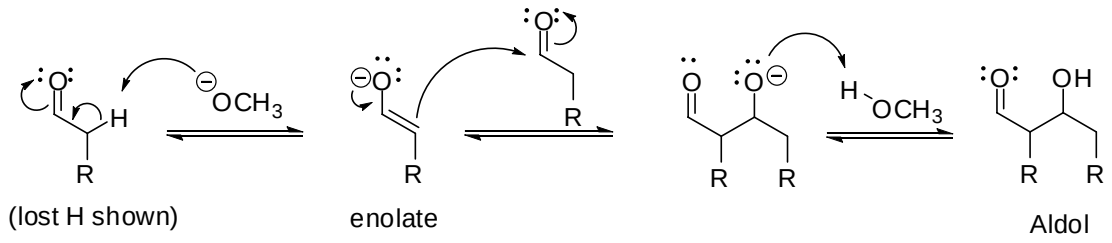
When an acid catalyst is used, the initial step in the reaction mechanism involves acid-catalyzed *tautomerization* of the carbonyl compound having an active methylene proton to give an enol. The acid also serves as an activator of carbonyl group of *another molecule* by protonation to make it more electrophilic which can be attacked by even a weak nucleophile. The enol, acts as a nucleophile (α-position) attacking at the activated carbonyl group to give aldol product after deprotonation as shown in Scheme 1.3.



Scheme 1.3: Acid catalyzed aldol mechanism

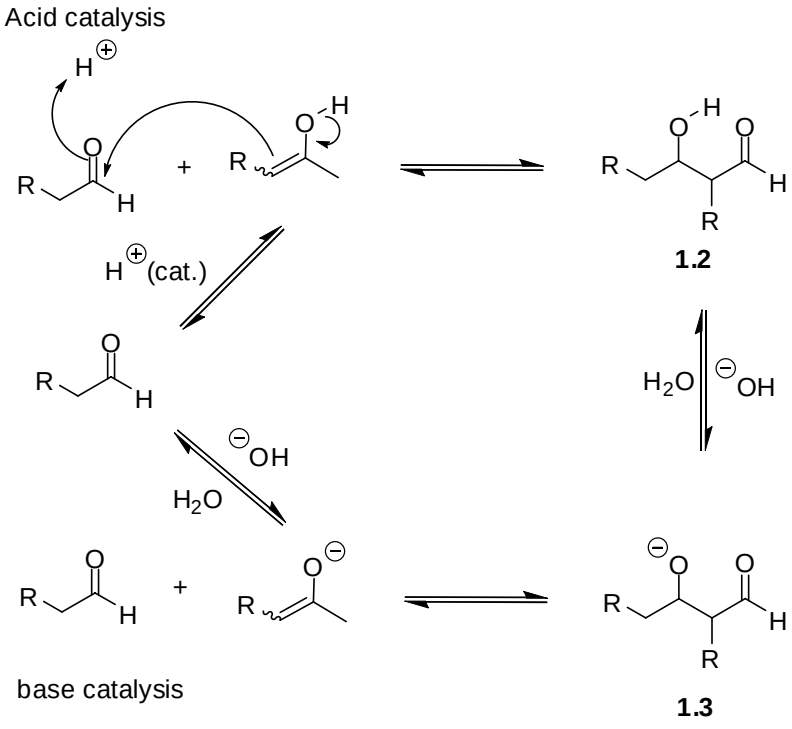
1.1.3 Enolate mechanism

When aldol reaction is catalyzed by a moderate base such as hydroxide ion or an alkoxide ion, the carbonyl compound (carbonic acid) gets deprotonated to form resonance-stabilized enolate that is more nucleophilic than enol or enol ethers. This enolate can attack on carbonyl group directly without any kind of the activation of carbonyl group, which is generally required in case of acid catalyzed reaction. Thus, this reaction proceeds through the nucleophilic attack of enolate ion on the carbonyl group of another molecule to give an aldol product after protonation (Scheme 1.4)



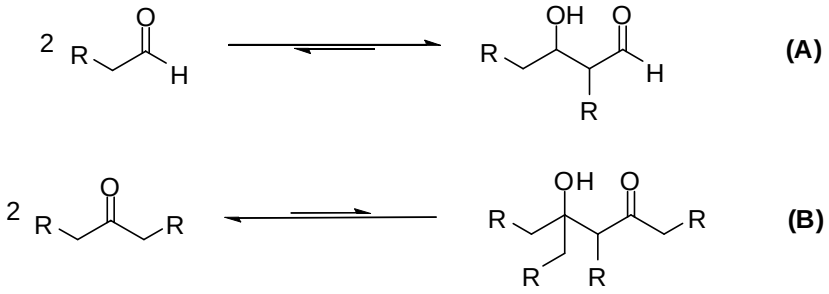
Scheme 1.4: Base catalyzed aldol reaction (showing $^{-}OCH_3$ as base)

Some of the typical features of 'traditional' aldol reactions are: reaction is carried out in protic solvents catalyzed by acid or base and the reaction is reversible under these conditions. Hence, this reaction is classified as *retrograde* aldol reaction. The reversibility of the aldol reaction can cause substantial problems from a synthetic point of view. Extensive studies carried out in order to determine the relative energies of an enolate and an aldehyde on one hand and the aldolate on the other hand showed that the outcome of the aldol reaction to be slightly exothermic.[4]



Scheme 1.5: General acid and base catalysis

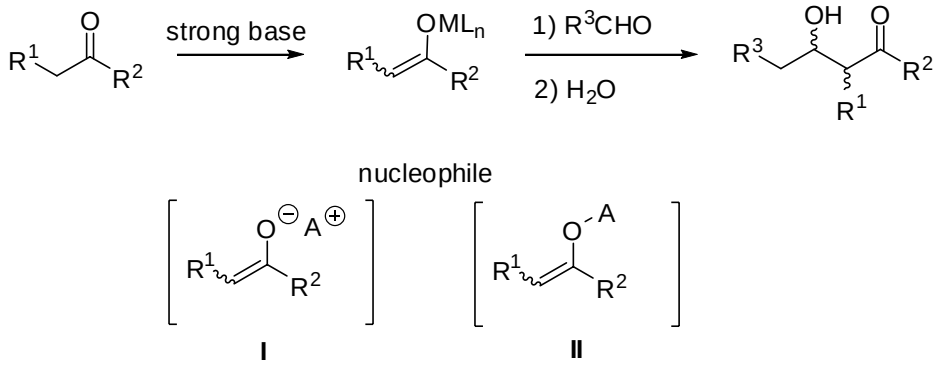
The aldol formed either by acid or base catalyzed reaction is significantly stabilized by a strong OH bond in aldol **1.2**, which arises either directly from acid-mediated addition or on protonation of the aldolate **1.3** in the base catalyzed variant as shown in Scheme 1.5. Alternatively, chelation of the counter-ion in aldolates resulting from preformed enolates in non-protic media serves as a driving force towards the product.[5] Since the 'traditional' aldol is a reversible reaction, so the yield of the reaction depends upon the position of the equilibrium. As a general rule, in the presence of protic solvents, the equilibrium of aldol addition is located on the product side when aldehydes react with each other (Eq. A), while it is on the side of starting material for the ketones (Eq. B) because the self condensation of the ketones is endothermic as shown in Scheme 1.6.



Scheme 1.6: Aldol reaction equilibrium with aldehydes and ketones

The self aldolization of the enolizable carbonyls proceeds much more efficiently in the combination with aldehydes rather than with ketones. This is due to the +I effect of the additional alkyl substituent and carbonyl carbon electrophilicity of ketones is lower than that of an aldehyde carbonyl carbon. Furthermore, a kinetic inhibition is possible due to the presence of the additional steric effect of an alkyl substituent. Mixed aldol reactions between different aldehydes or ketones usually result in the formation of a mixture of products, because each component can function as a C-H acidic and carbonyl-active compound. Thus, the traditional aldol reaction of non-identical carbonyl compounds is

only successful when applied within the framework of a limited substituent pattern. For example, a fruitful combination in case of mixed aldol reaction is that of an aldehyde with enolizable ketone. Although, the classical aldol reaction is highly atom-economic and having an undoubted versatility, this reaction suffers from problems of reversibility, dehydration reaction, selectivity issue due to chemo-, regio-, and stereoselectivity. A further challenge from both fundamental as well as applied point of view exists to perform this reaction asymmetrically.[6] In order to overcome these problems and for making this reaction more practical, new technique of "directed" stepwise aldol methodologies based on the use of preformed species **I** and **II** have been developed.[1, 7] The general principle involves a stepwise enolization-aldolization sequence under aprotic conditions as represented in Scheme 1.7.

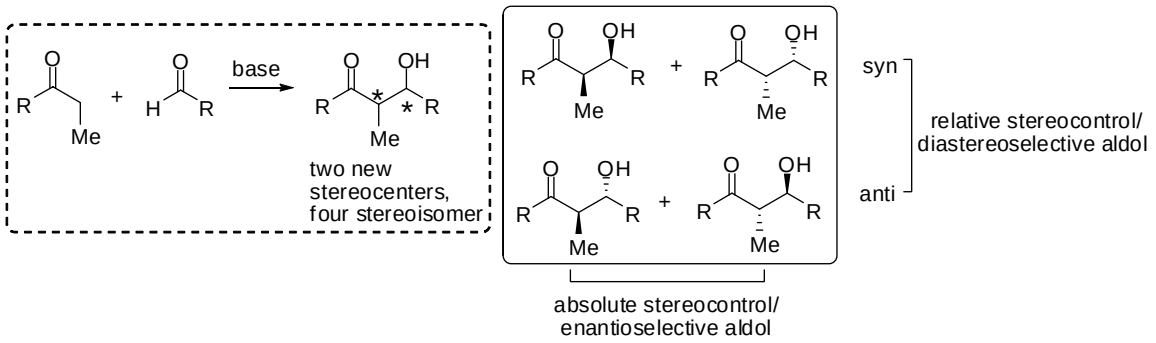


Scheme 1.7: Directed aldol reaction by stepwise enolization-aldolization sequence and the nucleophilic species involved

Such reactions are normally carried out by converting a carbonyl compound to an enolate by using stoichiometric amount of a strong base such as LDA (Lithium diisopropylamide) or LiHMDS (Lithium-*hexa*-methyldisilylamide), to act as a nucleophile. In this case, the enolate formation is irreversible and this enolate is then

allowed to react with a second carbonyl compound. The aldol product is not formed until the metal alkoxide of the aldol product is protonated in a separate work-up step.

Modern synthetic reactions in organic chemistry aim at the synthesis of compounds in enantiopure form. Since the aldol reaction creates two new stereocenters, up to four stereoisomers may result (Scheme 1.8). Because of the presence of this structural pattern in many molecules of practical interest, the aldol reaction has been one of the most widely used synthetic methods for designing complex natural and non-natural products.[8]



Scheme 1.8: Stereochemical outcome of the aldol reaction

The ability to control the absolute configuration of newly formed stereogenic center is of supreme importance for the synthesis of natural products. By utilizing the directed aldol reaction approach, control of stereochemistry has been accomplished by either using chiral aldehyde as starting material[9] or using chiral auxiliaries attached to the donor enolate.[1, 10] However, *the more elegant and economically most attractive way to introduce asymmetry is undoubtedly by using a catalytic amount of chiral controller.*[6]

1.2 Catalytic Asymmetric Aldol Reaction

The development of catalytic enantioselective reactions is one of the most challenging tasks of organic synthesis. The β-hydroxy carbonyl (aldol) and 1,3-diol units are

frequently found in complex natural products and have attracted a great deal of attention from synthetic organic chemists. The asymmetric aldol reaction is one of the useful and concise methods for the preparation of complex chiral polyol architectures.[11] One of the major areas being studied extensively in synthetic organic chemistry is the catalytic asymmetric aldol reaction, which can effectively and efficiently brings about the chiral transformation. A number of methods have been developed in recent years for the catalytic asymmetric aldol reaction with both high efficiency and selectivity.[6] In general, the catalytic asymmetric aldol reaction methodologies are classified in to two main types as shown in Figure 1.1.

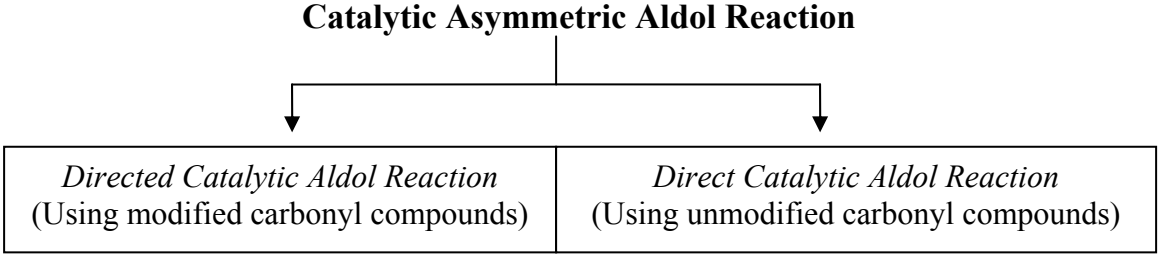
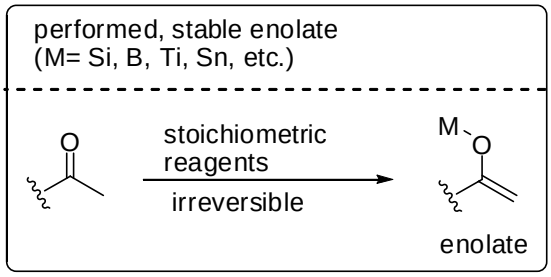


Figure 1.1: Types of catalytic asymmetric aldol reaction

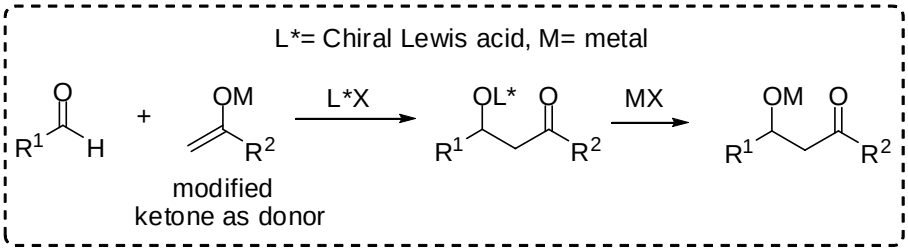
1.2.1 Directed Catalytic Asymmetric Aldol reaction

This type of aldol reactions require the preconversion of carbonyl compounds into a more active aldol donor, such as an enol ether or metal enolates by the use of chiral Lewis acid or Lewis base as a catalyst.[12] Thus, the utilization of irreversibly generated *"preformed and stereodefined stable"* metal enolates such as silyl, borane, titanium, and tin enolates in the presence of chiral Lewis acid or Lewis base catalyst is known as directed catalytic aldol reaction. In these cases, stoichiometric amount of base and/or adjunct reagents (such as silylating agents to form silyl enol ethers) are required, which is decreasing the atom efficiency of the process (Scheme 1.9).



Scheme 1.9: Preformed and stereodefined stable enolate for directed aldol reaction

The activation of the acceptor aldehyde by Lewis acid towards the addition of silyl enol ether to yield an aldol is commonly referred as the Mukaiyama aldol reaction.[13] This reaction has been rapidly improved from using stoichiometric amount of the (chiral) Lewis acid promoter to the catalytic versions.[7,14] Since stoichiometric generation of metal enolate/enol ether is involved in a separate step, Mukaiyama aldol reaction is only catalytic at Lewis acid (metal) promoter stage. (Scheme 1.10)

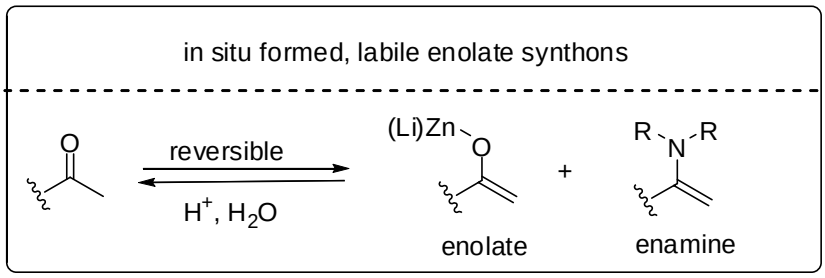


Scheme 1.10: The Mukaiyama aldol reaction

In this regards, a number of Lewis acids which consist of a metal, including early and late transition elements, and chiral ligands bearing nitrogen, oxygen, and phosphorous donors have been developed.[15] An exciting challenge in enhancing the efficiency of the aldol reaction is to develop a catalytic route for direct aldol addition without prior to the stoichiometric formation of a nucleophile from carbonyl compounds.

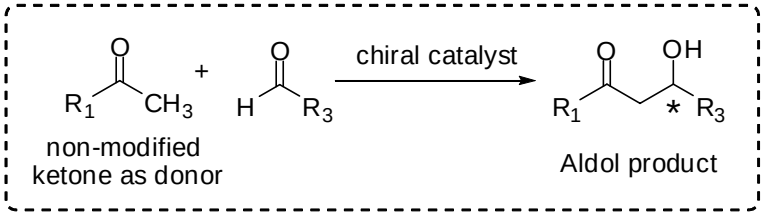
1.2.2 Direct Catalytic Asymmetric Aldol Reaction

Another type of aldol reaction, in which the preconversion of carbonyl compounds is not required and the nucleophile (enol or enolate, carbanion equivalent) can be generated *insitu* reversibly and catalytically is known as '*direct process'*.[16] In this process, carbanion equivalents (nucleophile) of unmodified carbonyl compounds are formed 'insitu' which are labile enolate synthons as a mixture of two reversible species, e.g., *keto-enolate* or *keto-enamine* (Scheme 1.11).



Scheme 1.11: Insitu formed reversible, labile enolate for direct catalytic aldol reaction

A major challenge of these direct *catalytic* strategies is that the carbanion generation takes place in the presence of an electrophile. The utilization of unmodified carbonyl compound as a nucleophile (aldol donor) for catalytic asymmetric aldol reaction is highly atom economic. The development of an efficient route that combines unmodified, hence commercially important carbonyl substrates as nucleophiles, and chiral catalytic system for direct asymmetric catalytic aldol reaction is a worthwhile attempt (Scheme 1.12).



Scheme 1.12: Direct catalytic asymmetric aldol reaction

In recent years, the exciting developments have been made in the field of asymmetric aldol reaction, utilizing unmodified carbonyl compound as a labile aldol donor in the presence of a catalytic chiral controller to induce chirality in the reaction. An important challenge of aldol reaction is the simultaneous control of the regio -, diastereo-, and enantioselectivity when unsymmetrical ketones are used. The three different approaches can be attempted for the direct asymmetric aldol reaction; (i) using biocatalysis such as aldolases and catalytic antibody, (ii) using metal catalysis and (iii) Organocatalysts (Figure 1.2).[1,6]

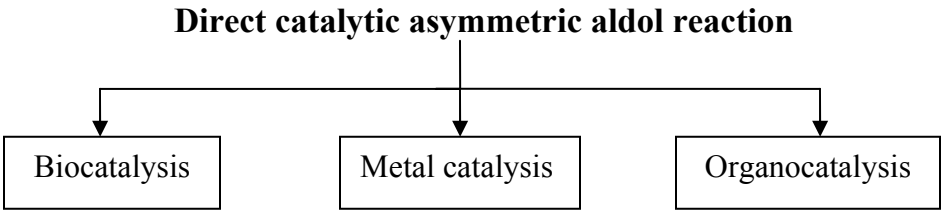


Figure 1.2: Direct catalysis of aldol reaction

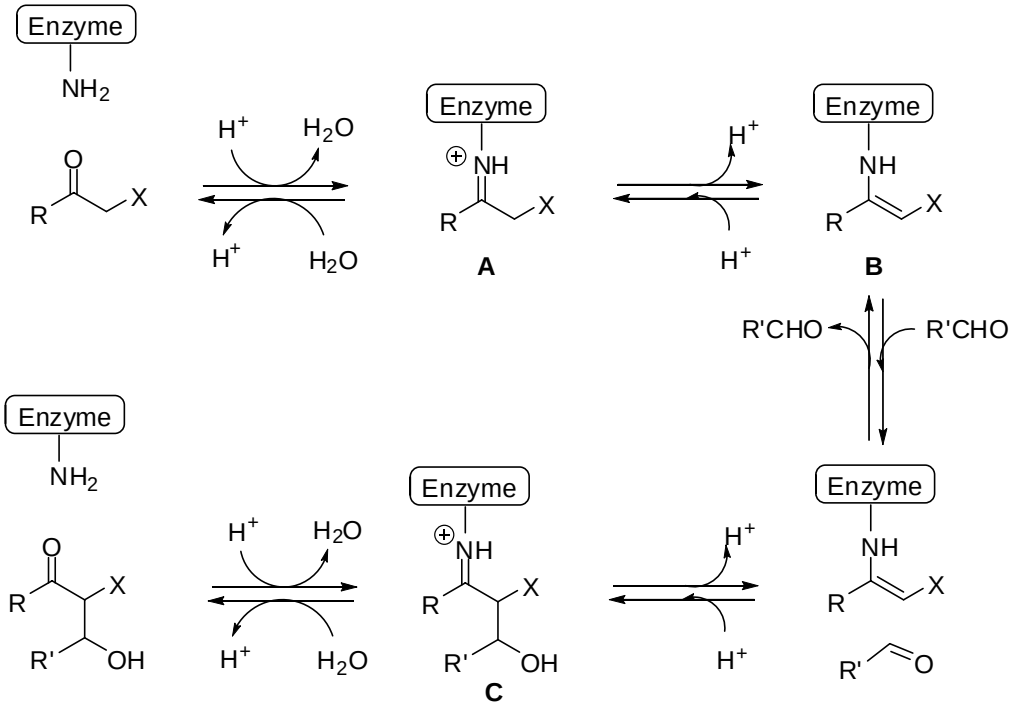
1.2.2.1. Biocatalysis

Enzymes are increasingly recognized as useful catalysts for organic synthesis.[17] Most enzymes used by Nature for C-C bond formation and cleavage ("lyases") catalyze a crossed aldol reaction in the form of a reversible, chemo-, regio-, diastereo-, and enantioselective addition of nucleophilic ketone donor to an aldehyde acceptor. As a result of high selectivity under mild conditions in aqueous solution at or near neutral pH values makes enzymes synthetically useful though in certain cases, the reaction is limited to a narrow range of substrates and the isolation of the products from water could be a problem. There are two types of enzymatic catalysis that effect the aldol reaction: the aldolases, a group of naturally occurring enzymes that catalyze in *vivo* aldol

condensation; and catalytic antibodies that have been developed in recent years to mimic the aldolases but with improved substrate specificity.[1d]

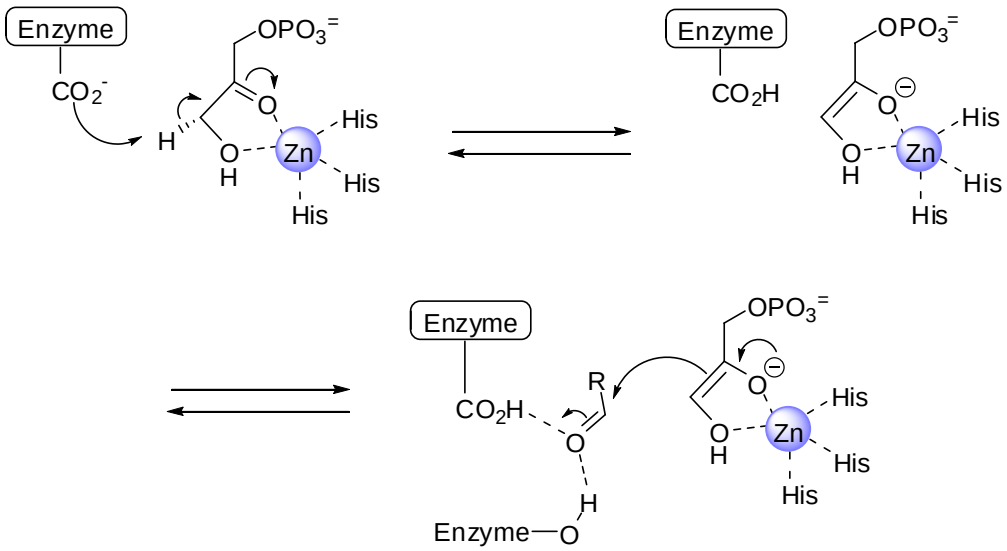
1.2.2.1.1 Aldolases

Two different types of aldolases have been identified and classified according to their mechanisms.[1d, 18] Class I aldolases bind the substrate covalently and activate the donor by forming an *imine-enamine* as an intermediate with the active site Lysine to initiate bond cleavage or formation. This activated donor then adds stereoselectively to the acceptor aldehyde (Scheme 1.13).



Scheme 1.13: Schematic mechanism for class I aldolases

Class II aldolases; on the other hand, utilize transition metal ion (Zn^{2+}) Lewis acid co-factor in the active site, which facilitates deprotonation by bidentate coordination of the donor to give the enediolate nucleophile[19] (Scheme 1.14).



Scheme 1.14: Schematic mechanism for DHAP-dependent class II aldolases

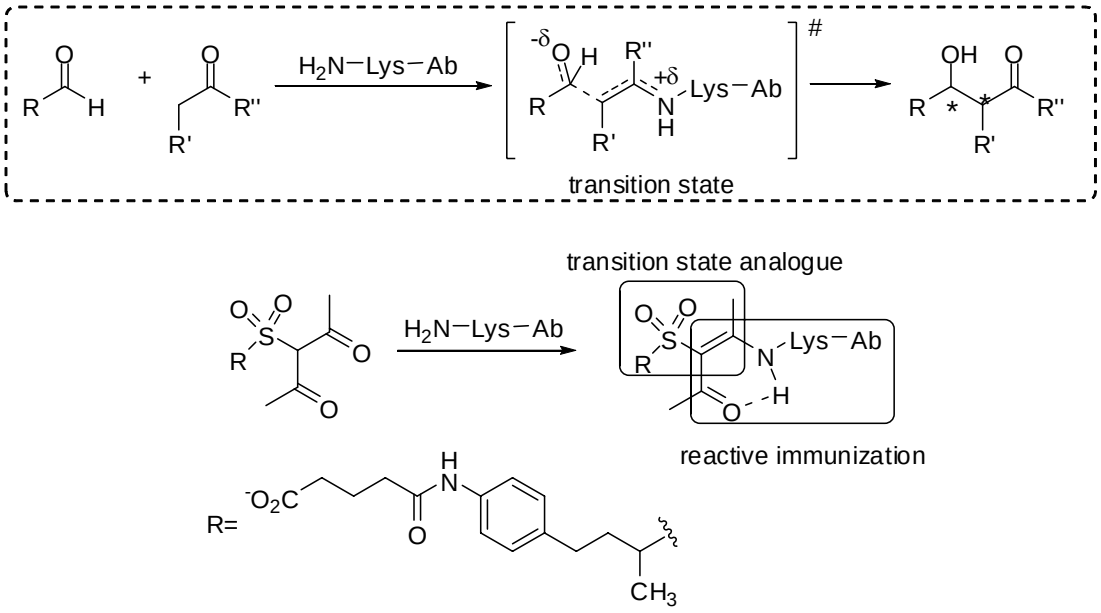
In both types of aldolases, formation of the enolate (that is, the deprotonation step) is rate determining. With only a few exceptions, the stereochemistry in both types of aldolases is controlled by an enzyme and does not depend on the structure or the stereochemistry of the substrate, which allows highly predictable product formation. These enzymes generally tolerate a broad range of acceptor substrates but have stringent requirement of donor substrates.

1.2.2.1.2 Antibodies

In recent years, catalytic antibody technology has been designed to process a wide range reactions, in particular aldol reaction.[20] Aldolases catalytic antibodies developed recently have the ability to match the efficiency of natural aldolases while accepting a more diverse range of substrate. Although many types of antibody catalysts have been generated, selection of antibody catalyst has typically been based on its binding to the

transition state analogues of the reactants or charged compounds designed using information from the reaction coordinate of a given chemical transformation.[21]

Further progress was made in this field with the development of catalytic function and residue-based selections by using 1,3-diketones for the concept of reactive immunization. Reactive immunization provides a means of selecting antibody catalyst in *vivo* on the basis of their capability to perform a chemical reaction.[22,23] In order to improve the concept of reactive immunization and to develop antibodies with complementary enantioselectivity, a β-diketone sulfone was used as hapten[24] (Scheme 1.15).



Scheme 1.15: Aldolases antibodies used for conceptual elements derived from reactive immunization and transition state analogue design

Unlike natural aldolases, the catalytic antibodies were found to accept a wide range of ketone donor substrates. Antibodies catalyze the direct aldol reaction similar to aldolases class I. It is clear that Nature's aldolases and antibodies use the combination of acids and bases in their active sites to accomplish direct asymmetric aldolization of unmodified carbonyl compounds. These aldolases are distinguished by their different strategy of

enolization mode for direct aldolization of two unmodified carbonyl compounds. Class I aldolases use the Lewis base catalysis of a primary amino group and proceeds through enamine based mechanism, while Class II aldolases use the Lewis acid catalysis of a Zn (II) cofactor and proceeds through zinc enolate mechanism as shown in Figure 1.3.

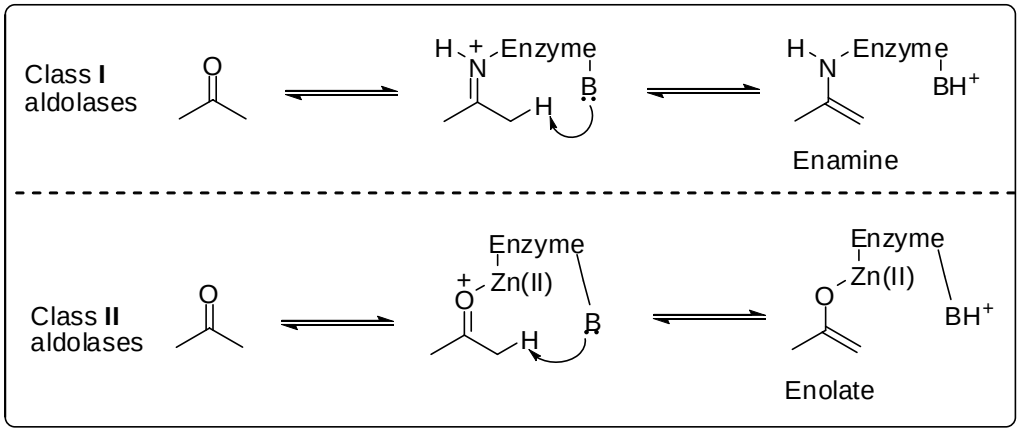
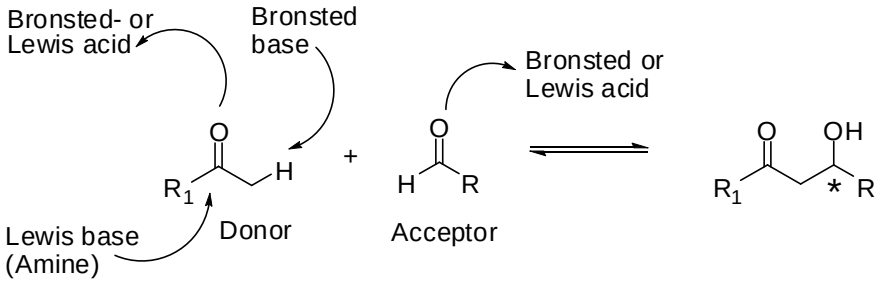


Figure 1.3: Two enzymatic strategies for enolization of carbonyl compounds

Although chemists also use acids and bases to catalyze aldolization reaction but the aldolases-like direct catalytic asymmetric aldol reaction remained a challenge for a long time. In the recent years, remarkable progress has been made in the direction of direct catalytic asymmetric aldol reaction using metal catalysis and organocatalysis.[16]

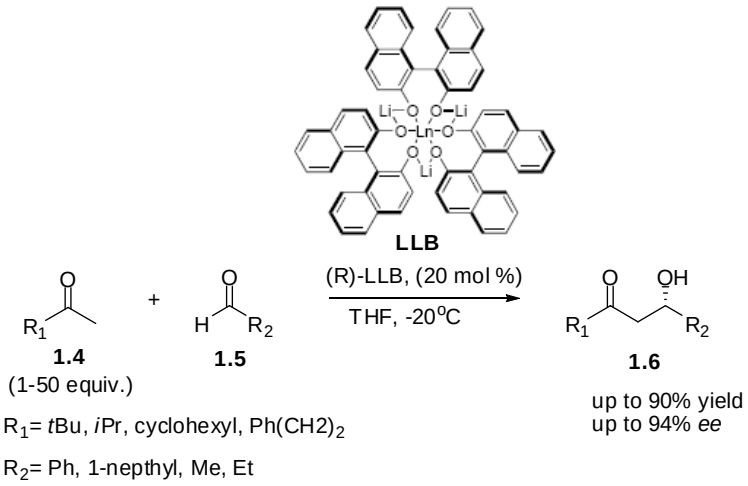
1.2.2.2 Metal catalysis

Enantioselective reactions catalyzed by metals have had the most significant impact on the development of synthetic organic chemistry.[25] The aldol reaction is catalyzed by both Lewis and Brønsted acids and bases.[1] This catalytic diversity is possible because the aldol reaction combines a nucleophilic addition, which is acid-catalyzed, with an enolization, which is catalyzed by both acids and bases as shown in Scheme 1.16.



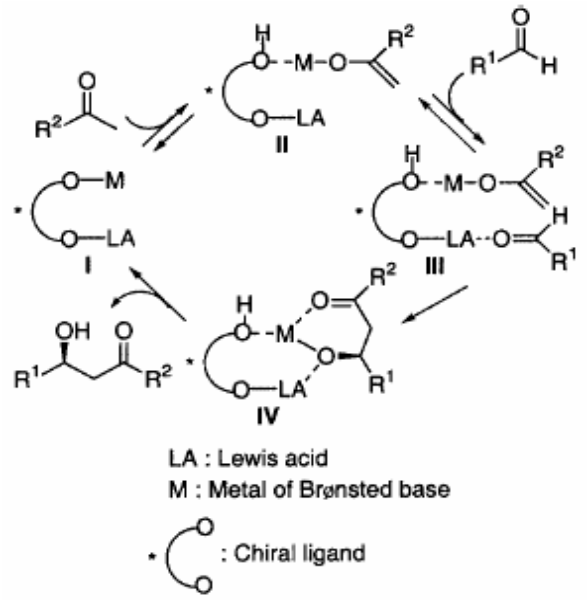
Scheme 1.16: Brønsted/Lewis acid and Brønsted/Lewis base catalysis of the aldol reaction

The catalytic activation of aldehyde acceptor by using chiral Lewis acid, using preformed enol/enolate as a nucleophile has achieved a great success and provides a viable strategy for catalytic asymmetric aldol reaction.[16, 26] An exciting challenge in enhancing the efficiency of the aldol reaction is to find a simple compound that will catalyze direct aldol addition without prior stoichiometric formation of a nucleophile and to do so asymmetrically similar to the enzymes. In the recent years, extensive study has been carried out to provide the synthetic alternatives of enzymatic strategy for direct asymmetric aldol reactions. The first direct catalytic asymmetric aldol reaction has been developed in 1997 by Prof. Shibasaki group, using bifunctional Lewis acid-Brønsted base metal complex which catalyze the direct aldol reaction similar to the class II aldolases.[27] This concept is based on the use of bifunctional catalysts such as the heterobimetallic catalyst $LaLi_3$tris(binaphthoxide) (LLB), which bears both a Lewis acid site and a Brønsted basic site, and is capable of simultaneously activating the nucleophilic ketone and the electrophilic aldehyde. This catalyst can be regarded as enzyme mimics of the metal containing type II aldolases. The reaction of methyl ketones **1.4** with aldehydes **1.5** under the presence of a 20 mol% of LLB in THF provides aldol adduct **1.6** in good yield and high enantioselectivity (Scheme 1.17).



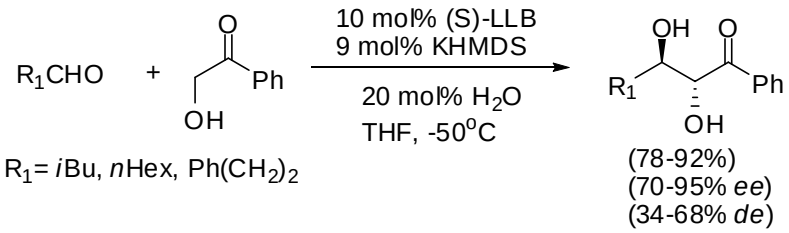
Scheme 1.17: Direct catalytic asymmetric aldol reaction between aldehyde and unmodified ketones catalyzed by (R)-LLB

Anhydrous LLB was more efficient than hydrated LLB, the higher yield and *ee* were obtained when excess of ketone was used. The catalyst incorporates a central lanthanum atom, which acts as a Lewis acid and a lithium binaphthoxide moiety, which acts as a Brønsted base. The synergistic effect of both functionalities allows the reaction to proceed without the need for any other activation of the starting materials. A proposed mechanism for this transformation is outlined in Scheme 1.18. The Brønsted acid unit **(OM)** of catalyst **I** could deprotonate an α-proton of a ketone to generate the metal enolate **II**, while at the same time a Lewis acid unit **(LA)** could activate an aldehyde to give **III**. These reaction partners might react in the chelation-controlled, asymmetric environment to afford a metal β-oxoalkoxide **IV.** Proton exchange between the metal alkoxide moiety and a hydroxy proton of the aryl unit or a *α*-proton of a ketone could then generate an optically active aldol product with regeneration of catalyst **I**. A major shortcoming of this catalyst is the need for excess ketone and long reaction time.



Scheme 1.18: Catalytic cycle for direct asymmetric aldol reaction with (R)-LLB

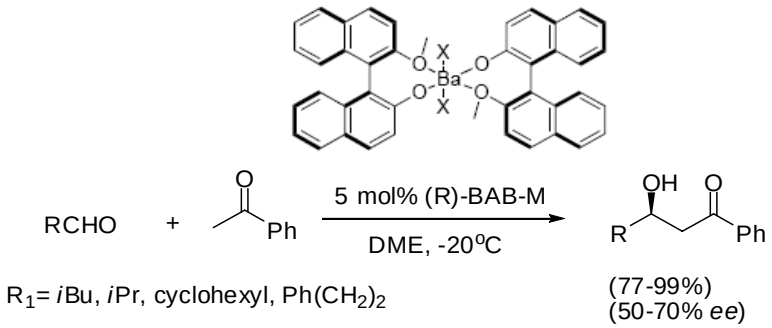
The catalytic activity of LLB can be enhanced by the incorporation of KOH (insitu generated from $KN(SiMe_3)_2$ and H_2O), into a heteropolymetallic complex that rapidly promotes the aldol reaction with lower catalyst loading (3-8 mo %).[28] The LLB·KOH complex was able to catalyze an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone, which provides the *anti*-*α*-*β*-dihydroxy ketones[29] (Scheme 1.19).



Scheme 1.19: LLB promoted direct catalytic asymmetric aldol reaction between 2-hydroxyacetophenone and aldehydes

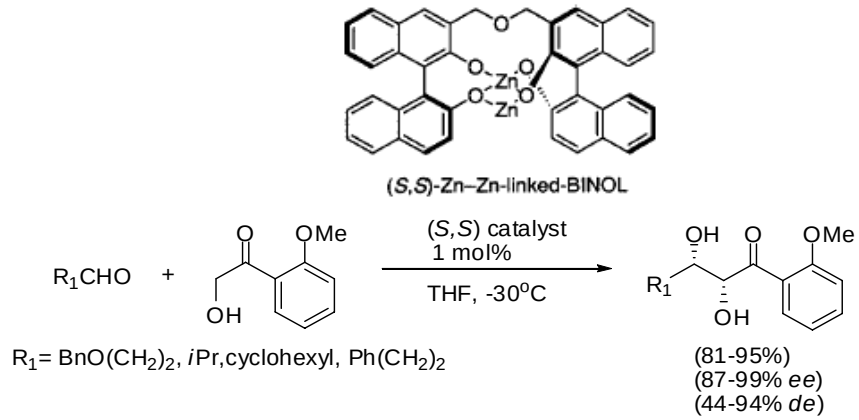
A similar catalyst BAB-M, derived from barium phenoxide was developed by Shibasaki group in order to eliminate the shortcomings of the LLB catalyst (long reaction time and

excess ketone).[30] The catalyst BAB-M prepared from Ba(O*i*Pr)$_2$ and BINOL-Me, effects the asymmetric aldol reaction between any aldehyde and 2 mol-equiv. of unmodified acetophenone in the presence of 5 mol% of BAB-M much more faster then 20 mol% of LLB at 5 mol-equiv. of ketone (Scheme 1.20).



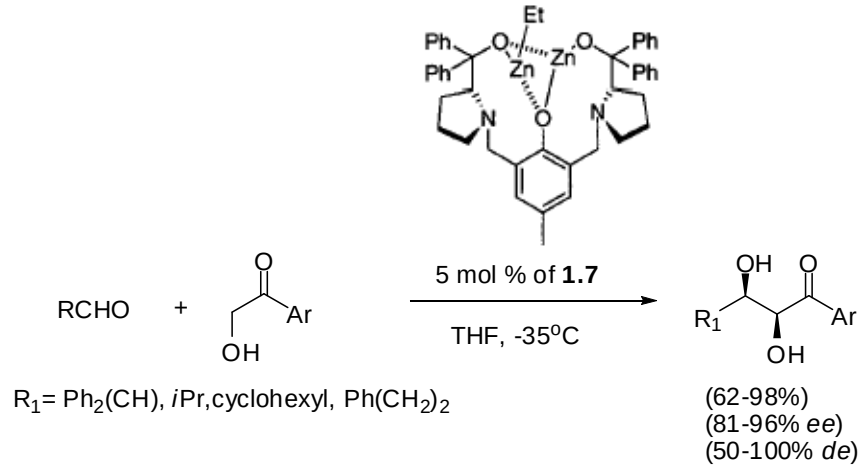
Scheme 1.20 Direct catalytic asymmetric aldol reaction between aldehyde and unmodified acetophenone, catalyzed by (R)-BaB-M

Recently, a highly enantio-, diastereoselective aldol reaction of different aldehydes and 2-hydroxy-2'methoxyacetophenone proceeded smoothly with as little as 1 mol% of a dinuclear zinc catalyst, Zn-Zn-linked BINOL, to afford *α*-*β*-dihydroxy ketone in high syn-selective manner and excellent yield. [31] This is found to be best in terms of catalytic loading (1 mol% for direct asymmetric aldol reactions (Scheme 1.21).



Scheme 1.21: Zn-Zn-linked BINOL catalyst for direct aldol asymmetric reaction

Prof. Trost and co-workers designed a novel catalyst (**1.7)** for direct asymmetric aldol reaction of α-hydroxy ketones as a donor[32]. The effectiveness of this catalyst permits the use of nearly molar equivalents amounts of both partners (Scheme 1.22).



Scheme 1.22: Direct catalytic aldol reaction of a-hydroxy ketones mediated by **1.7**

This catalytic system is very close to reaching the ideal atom-economic version of the asymmetric aldol addition. In this binuclear organometallic catalyst, the role of one of the two-zinc atoms is to form the requisite enolate and another zinc atom acts as a Lewis acid to coordinate the aldehyde. Thus, one important advantage of using chemically designed catalyst is that their structure can be modified to improve their efficiency.

1.2.2.3 Organocatalysis

Enzymes are highly efficient and enantioselective catalysts. While chemists use mostly metal-based catalysts, about half of the known enzymes do not contain metals in their active sites. Catalytic asymmetric reactions provide the new and powerful tools for the efficient synthesis of complex molecules.[33] For a long time, the field of asymmetric catalysis was dominated by the use of transition metal catalysis[25] and biocatalysis,[17]

which showed the substrate limitations. Synthetic chemists have hardly used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. In the recent years, between the extremes of both metal catalysis and enzymatic catalysis; a third approach for the production of enantiomerically pure compounds using metal-free catalysis has emerged, which is termed as *Organocatalysis*.[34] The term "organic catalysts" was introduced by Ostwald (1900), in order to differentiate the small organic molecules as catalytic principles from enzymes or inorganic catalysts.[35] Although the concept of organic catalysis was first introduced by the German chemist Langenbeck back in 1928,[36] and the expression "organische Katalyse" first appeared in the literature in 1931.[37] Generally, Organocatalysis is the catalysis of chemical transformations using a purely *"organic molecules"* which are composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus. These small organic molecules are providing synthetic alternative of enzymes to many established asymmetric transformations.[38] Recently, it was proposed to define an organic catalyst as: "an organic compound of relatively low molecular weight and simple structure capable of promoting a given transformation in substoichiometric quantity".[39] This definition is broad enough to cover the varying structural diversity of organic catalyst. Nature is the principle practitioner of asymmetric synthesis and uses enzymes to catalyze stereoselective reactions with high fidelity. Enzymes generally uses hydrogen bonding between the active sites and the substrates, together with nonbonding dipole-dipole, electrostatic, and steric interactions, to orient the substrates and stabilize the transition state, leading to high level of stereoselectivity.

Recently, the biocatalytic and metal catalytic processes are facing serious competition, mainly as a result of the blooming of organocatalysis in asymmetric catalysis and the 'organocatalysis' has become the catchword for this field of research.[34,40] Figure 1.4 illustrates the increase in publications containing the words "organocatalysis", or "organocatalytic" from 2000 to 2006.[34,39,40,41]

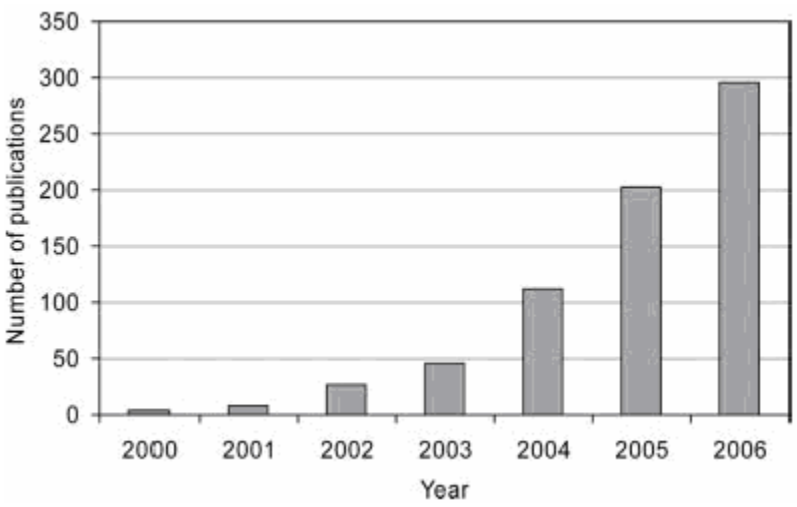
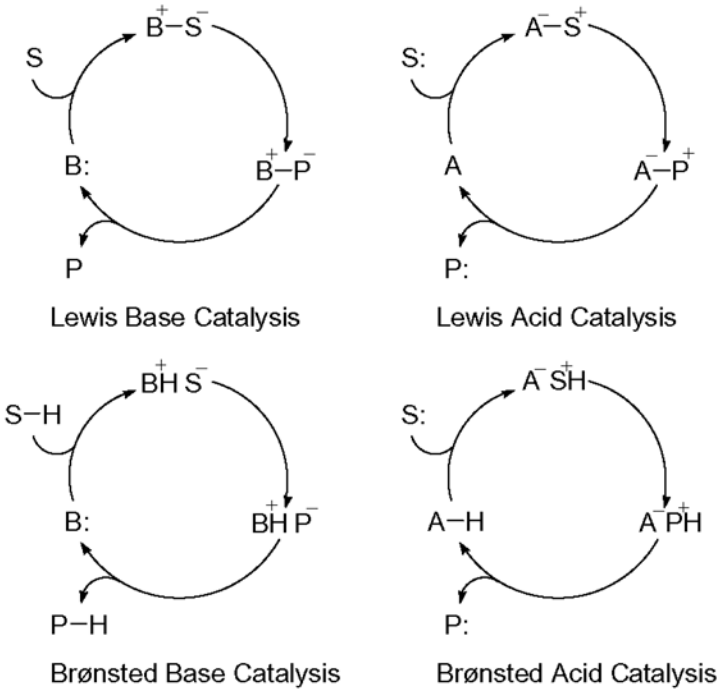


Figure 1.4: Publications on organocatalysis (SciFinder®)

The organocatalysts are low molecular weight, metal free, usually non-toxic, readily available, and easily separable from the reaction product without any kind of racemization. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination such as pharmaceutical products. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. A significant advantage of many organocatalysts is the capability of promoting several types of reactions through different activation mode proposed by Prof. List.[42] Most of the organocatalysts can be classified in the main category of Lewis acids, Lewis bases,

Brønsted acids, and Brønsted bases and their corresponding catalytic cycle is shown in Scheme 1.23.



Scheme 1.23: Catalytic cycle for organocatalysts

Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and regenerates the catalyst to further catalyse the reaction. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated *via* a (partial) deprotonation or protonation, respectively. Recently, significant efforts have been made to develop chiral Brønsted acids[43] and bifunctional chiral Brønsted acid/base[44] catalysts in this direction. In many cases, organocatalysts can be considered as "minimum version" of the metal free enzymes catalysis because of their similarity between mechanistic and catalytic actions. In both cases the rate acceleration observed depend on typical interaction between the

catalyst and organic molecules. A typical distinction can be made between the processes that involve the *formation of covalent adduct* between catalyst and substrate within the catalytic cycle and the other processes, which involves the non-covalent interactions such as hydrogen bonding or ion pair between the substrate and catalysts. The former interaction has termed as "covalent catalysis" and the later situation is denoted as "non-covalent catalysis". The catalysis of aldol reaction with the formation of *'enamine donor'* represents the category of covalent catalysis having a common mechanism for enzymatic and organo-catalytic processes.

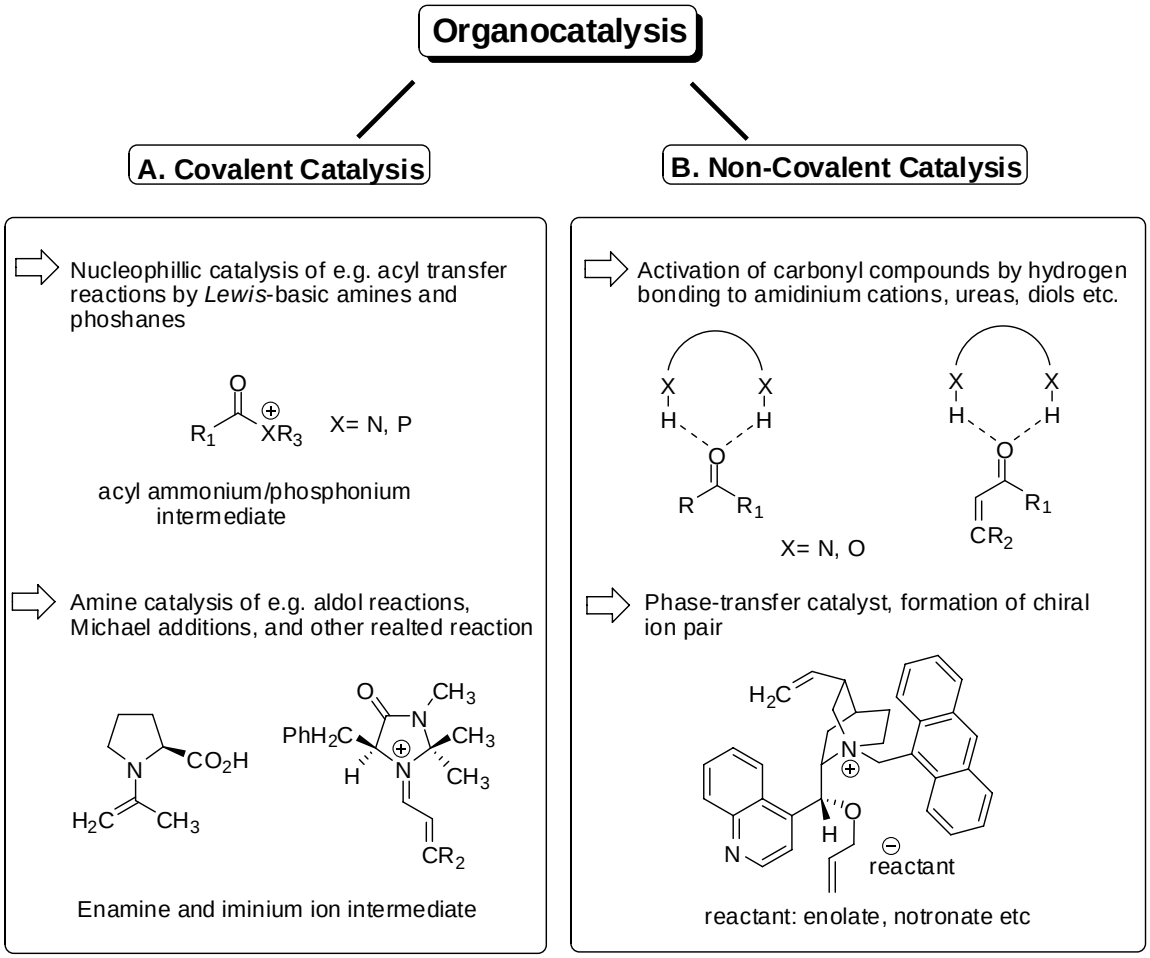


Figure 1.5: Covalent and non-covalent organo-catalysis

Whereas the non-covalent catalysis relies on the formation of hydrogen-bonded adducts between substrates and catalysts or on protonation/deprotonation processes. Phase-transfer catalysis (PTC) by organic phase-transfer catalyst falls into the category of "non-covalent catalysis"[34a] (Figure 1.5).

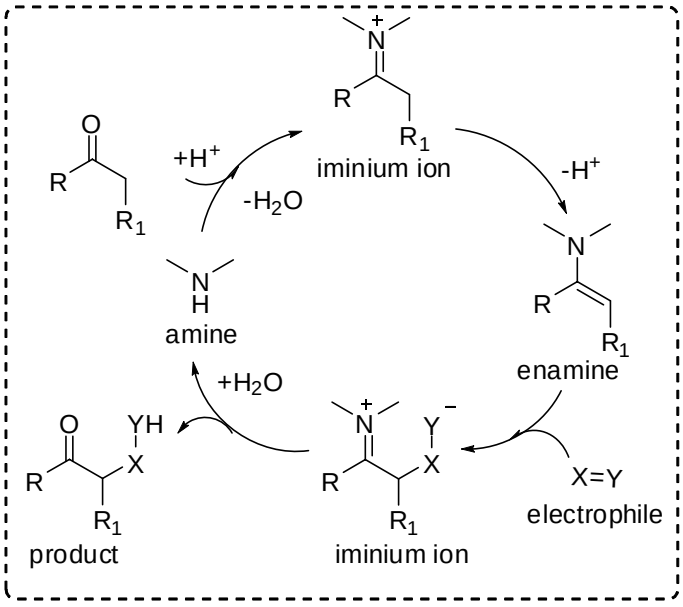
Organocatalysis is an emerging area in asymmetric synthesis, which is growing very rapidly and applied successfully to the several different enantioselective transformations in the recent years[39,40,41,45] Generally there are five different modes of catalysis to detail the scope of organocatalysis and how it can be applied successfully for the synthesis of pharmaceutically relevant compounds:[45,46]

(i) Secondary amine catalysis via enamines (ii) secondary amine catalysis via iminium ion (iii) phase transfer catalysis (iv) nucleophilic and Brønsted base catalysis; and (v) hydrogen bonding catalysis.

Since organocatalysis is a fast moving field and hundreds of papers have appeared in recent years from different distinguished research group worldwide. It is not possible here to cover all the development of different aspects of organocatalysis and its utility in asymmetric synthesis.[46]

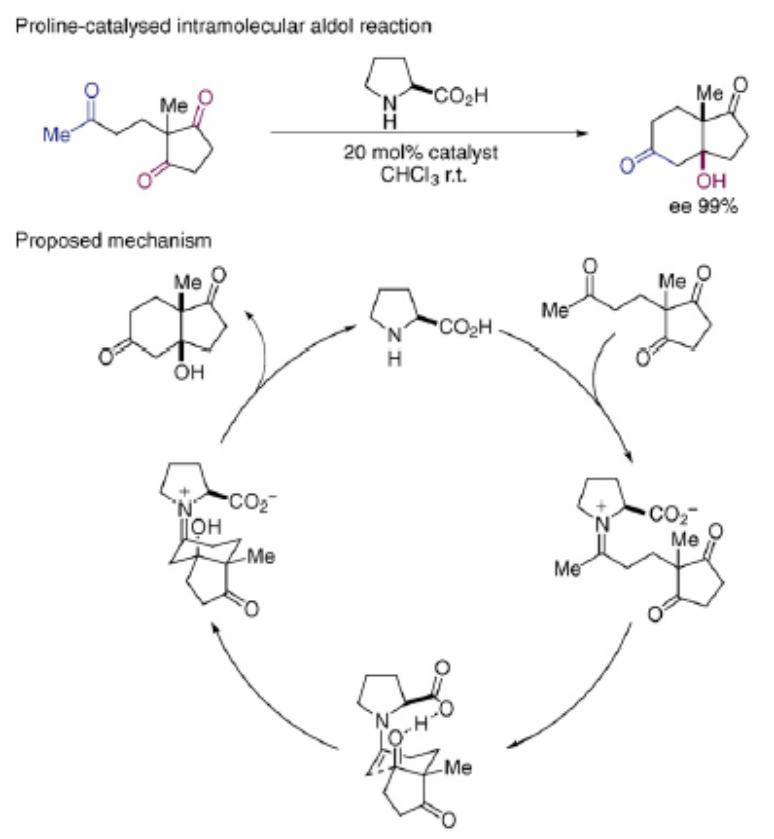
Here we are giving a brief report on the progress in the direction of amine catalysis via enamines intermediates for direct catalytic asymmetric aldol reaction in the recent years. Amino-catalysis is a biomimetic strategy for aldol reaction via enamine intermediates used by enzymes such as class I aldolases for the applications in preparative organic synthesis, particularly in intermolecular aldol addition reaction.[38a,38c] It is believed that the basis of *enamine catalysis* is reversible and catalytic generation of enamine takes place from amines and carbonyl compounds.

Enamine formation is facilitated by the dramatic increase in C-H acidity upon initial conversion of carbonyl compound in to an iminium ion. The catalytically generated enamine should be able to undergo addition reaction with various electrophiles (X = Y), similar to the well-studied chemistry of preformed enolates.[47,38c] The resulting new iminium ion furnishes, after hydrolysis by *insitu* generated water, the α-substituted carbonyl product (Scheme 1.24).



Scheme 1.24: Enamine catalysis

First organocatalysis was a proline catalyzed intramolecular aldol reaction that was reported during 1970s and termed as Hajos-Parrish-Eder-Sauer-Wiechert reaction.[48] The success of this aldol reaction is due to the proposed hydrogen bonding between the carboxylic acid group of proline and the carbonyl electrophile.[48,49] This reaction provides a simple method for the formation highly enantiopure progesterone intermediate that is useful in synthesis (Scheme 1.25).[50]



Scheme 1.25: First proline catalyzed intramolecular aldol reaction (1971)

L-Proline a "Universal Organocatalyst"

L-Proline (**1.8**) has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the *p*Ka value and better nucleophilicity as compared to other amino acids. It can be regarded as a bifunctional catalyst with the secondary amine acting as Lewis base and the acid group acts as Brønsted acid (Figure 1.6). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with hydrogen bonding frameworks.[47,38c]

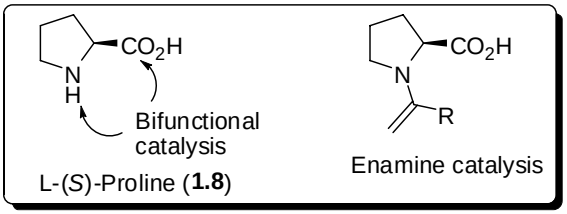
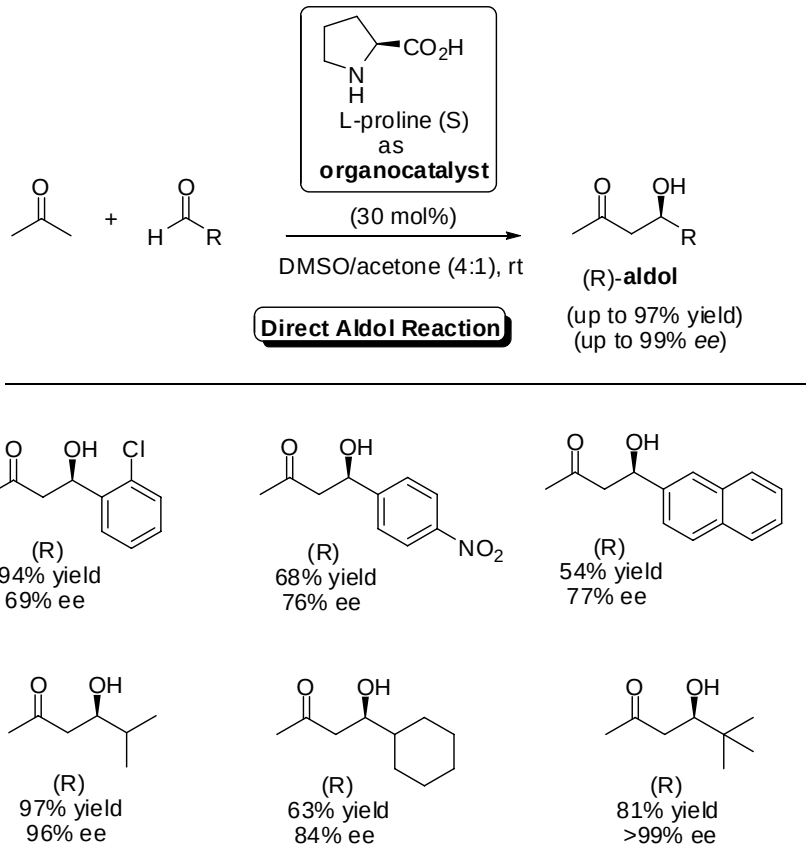


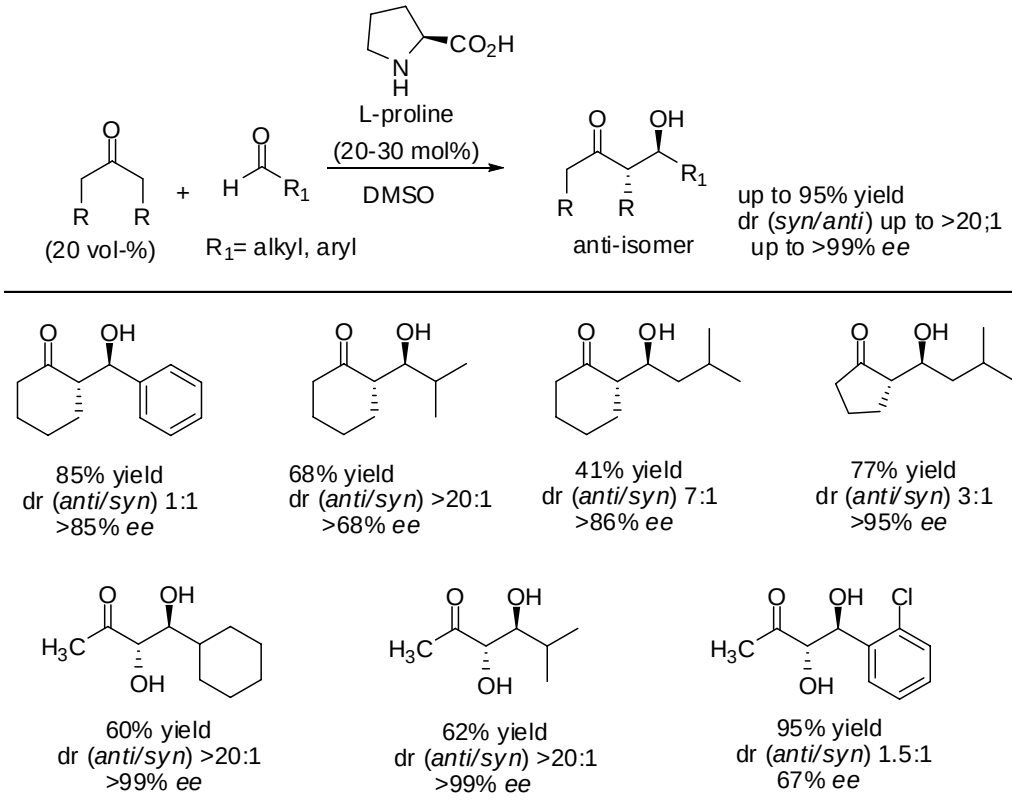
Figure 1.6: Proline as a universal catalyst



Scheme 1.26: The first proline catalyzed asymmetric aldol reaction (selected examples)

The historic roots of the use of amino acids as organocatalysts (amino-catalysis) for the aldol reactions was reported first time in 1931.[37,51] Although, the breakthroughs in asymmetric organocatalysis was achieved in 1970s by two industrial groups, [51] the proline catalyzed intramolecular aldol reaction remained little more than a laboratory curiosity and it took around thirty years for a revival of this chemistry, which was initiated by Prof. List, Barbas and Lerner with the discovery of the proline-catalyzed

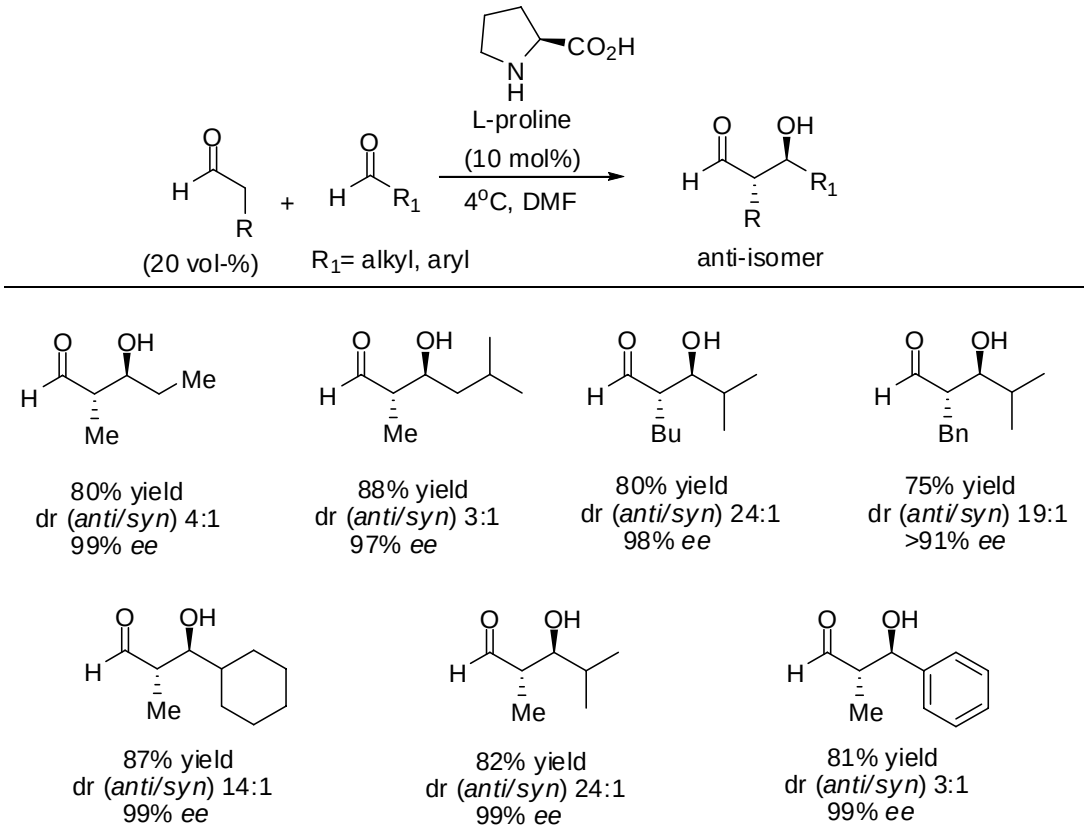
direct asymmetric aldol reaction in intermolecular fashion,[52] which proceeds through the similar manner as enzymatic conversion with class I aldolases. The reaction of acetone with different aldehydes proceeds nicely with good yield and high enantioselectivity (Scheme 1.26). This rediscovery has initiated an explosive growth of research activities in the area of organocatalysis both in industry and in academia. Organic molecules not only show a "green" advantage but also ease for functional manipulation to act as very efficient catalysts. Direct and indirect asymmetric aldol reaction with acetone (or equivalents) as donor are generally considered to be very challenging. This discovery not only provides a remarkable solution to one of the most intensively studied problems in catalysis, but also marked as a new beginning for the study of proline catalyzed enantioselective reactions.



Scheme 1.27: Direct aldol reaction with hydroxy acetone as a donor (selected examples)

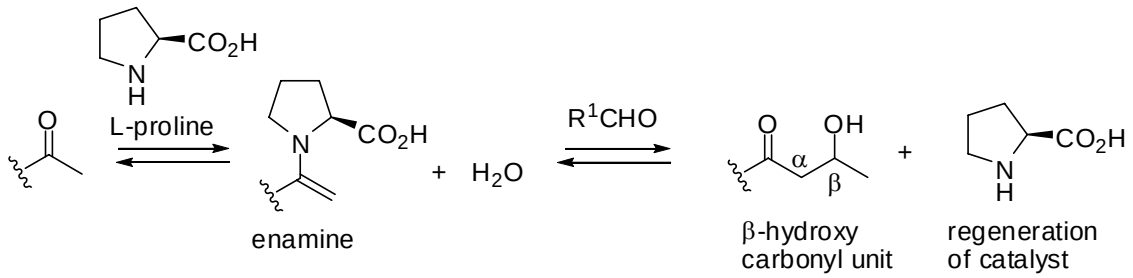
The potential of this proline catalyzed direct aldol reaction was also investigated with ketones other than acetone. With the use of inexpensive and smaller ketones such as butanone, cyclopentanone, cyclohexanone, and hydroxy acetone, higher enantio and diastereoselectivity (anti), can be achieved depends on the aldehyde used. (Scheme 1.27).[53]

In addition to ketones, aldehydes can be used as aldol donor in proline catalyzed aldol reactions.[54] Recently, Prof. McMillan's group found that proline also catalyzed cross aldolization of two different aldehydes under carefully developed conditions.[55] These reactions furnish *anti*-aldols in good yield with excellent enantio- and diastereoselectivity (Scheme 1.28).



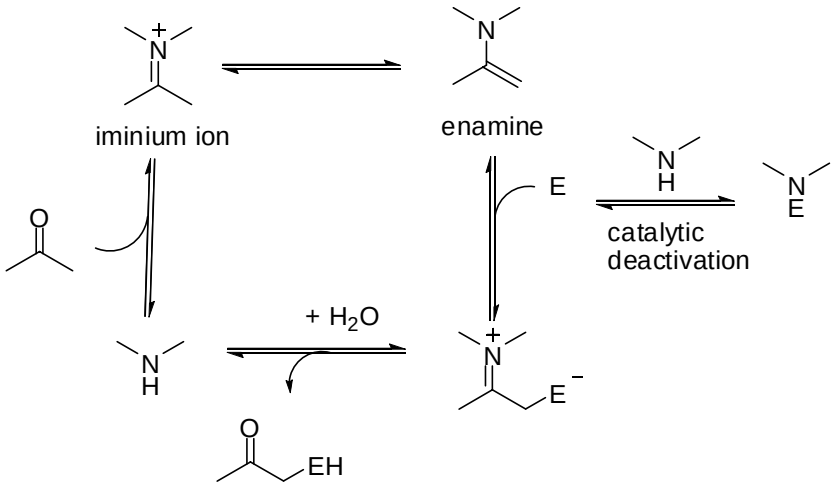
Scheme 1.28: Direct asymmetric aldolization of aldehydes (selected examples)

There have been numerous reports on small-molecule-catalyzed aldol reaction using the "*later enolate equivalents*" (enamine catalysis). In particular, '*the discovery of versatile catalytic nature of proline occurring via enamine intermediates*' has been the biggest breakthrough in this field of research.[38-47] (Scheme 1.29)



Scheme 1.29: Summary of proline catalyzed intermolecular aldol reaction

The generalized catalytic cycle for enamine as a carbanion equivalent that describes amine-catalyzed reaction of carbonyl compounds with electrophiles is shown in Scheme 1.30.

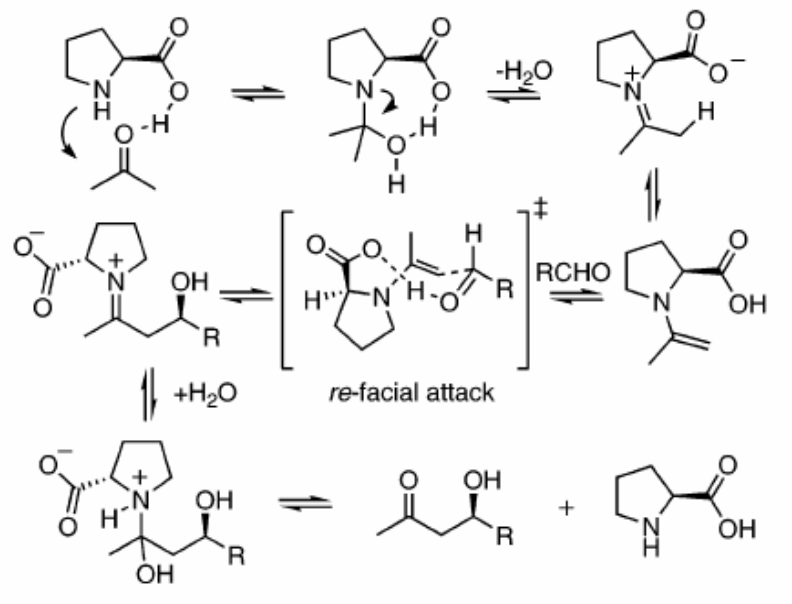


Scheme 1.30: The enamine catalytic cycle

According to this Scheme, a secondary (or primary) amine reacts with a ketone to furnish key intermediates as iminium ion and the enamine. Iminium ion formation lowers the LUMO energy of the system. As a result, both nucleophilic addition and α-deprotonation

become more facile. Deprotonation leads to the generation of enamine, which is the actual nucleophilic carbanion equivalent. This enamine reacts with an electrophile to give a modified iminium ion that upon hydrolysis furnishes the addition product with the regeneration of catalyst. A potential limitation of this cycle would be the irreversible deactivation of the nucleophilic amino-catalysis by the electrophile.

The mechanism of proline catalyzed intermolecular aldol reaction was proposed through enamine catalysis involving iminium ion, and enamine intermediates,[52,56] which is essentially identical to the accepted mechanism of class I aldolases(Scheme 1.31).

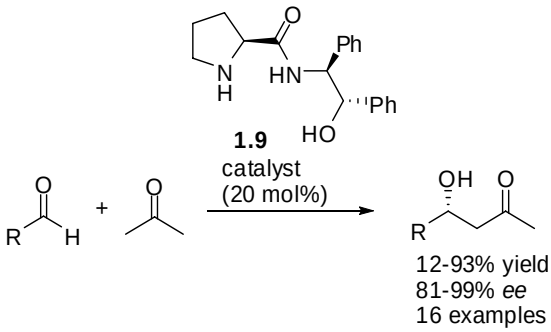


Scheme 1.31: L-Proline catalyzed enamine mechanism of the direct catalytic asymmetric aldol reaction

According to the fundamental nature of amino-acid catalysis, the acidic part of amine-acid catalyst seems to be largely responsible for rapidly promoting the step of enamine and carbon-carbon bond formation. The carboxylic acid was proposed to act as a general-purpose Brønsted cocatalyst, replacing the several acid/base functional groups involving in the aldolase mechanism. In this mechanism, proline functions as a "micro-aldolase"

that provides both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate. This cocatalyst may facilitate each individual step of the mechanism including (i) the nucleophilic attack of the amino group, (ii) dehydration of the carbinol amine intermediate, (iii) the deprotonation of the iminium ion (iv) the carbon-carbon bond formation and (v) the step of hydrolysis of the iminium-aldol intermediate.

Recently, the computational studies carried out by Prof. Houk and coworkers' confirmed[57] that this transition state is energetically the most favorable and predicts the stereochemistry correctly. This Houk-List model for proline catalyzed aldol reaction rationalizes the selectivity of both intramolecular[49] and intermolecular[52,55,56] variants. According to the Houk-List model, the role of carboxyl group is to activate the carbonyl acceptor by hydrogen bonding, which was further supported by the results of Gong, Wu, and co-workers using proline-derivative **1.9**, having two hydrogen bonding sites.



Scheme 1.32: Double hydrogen-bonding catalyst **1.9** for the direct enantioselective aldol reaction

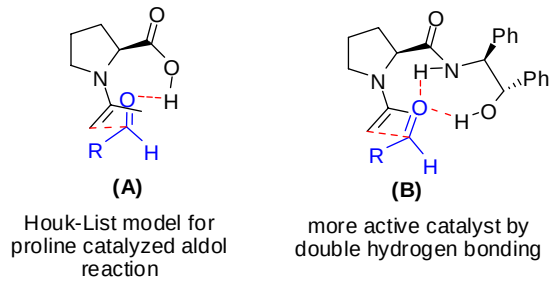
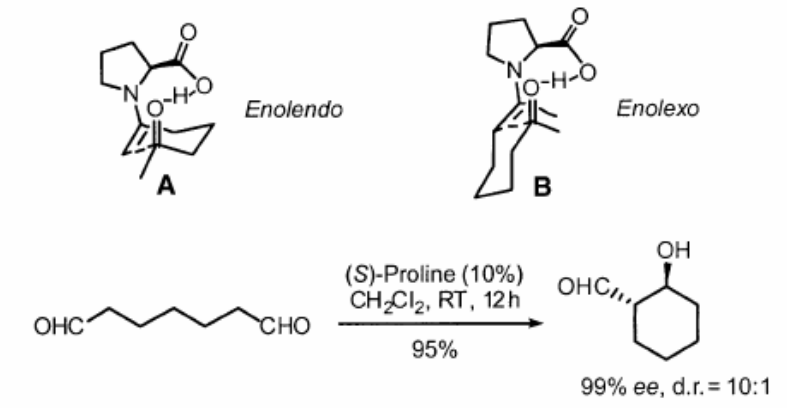


Figure 1.7: The Houk-List model for the proline catalyzed aldol reaction and the rational behind the success of the Gong-Wu aldol catalyst.

This catalyst is significantly more enantioselective than proline, even the reaction can be performed at lower temperature. For the reaction between acetone and benzaldehyde catalyzed by **1.9**, author could locate a double-hydrogen-bonded transition state by ab-

initio calculations. Both the amide and hydroxy group were hydrogen bonded to the aldehyde in transition state as shown in Scheme 1.32 and Figure 1.7.[58] Extensive studies in this direction to make modified proline catalysts have been carried out by different research groups, but the concept of the enamine catalysis remains the same for both inter- and intramolecular aldol reactions. Although, the catalytic asymmetric *enolendo* aldolization is known from 1970s,[48] the first catalytic asymmetric *enolexo* aldolization was developed recently by Prof. List and co-workers[59] and it was observed that a variety of achiral heptanedials on treatment with a catalytic amount of L-Proline furnished *anti*-aldols with excellent enantioselectivity.

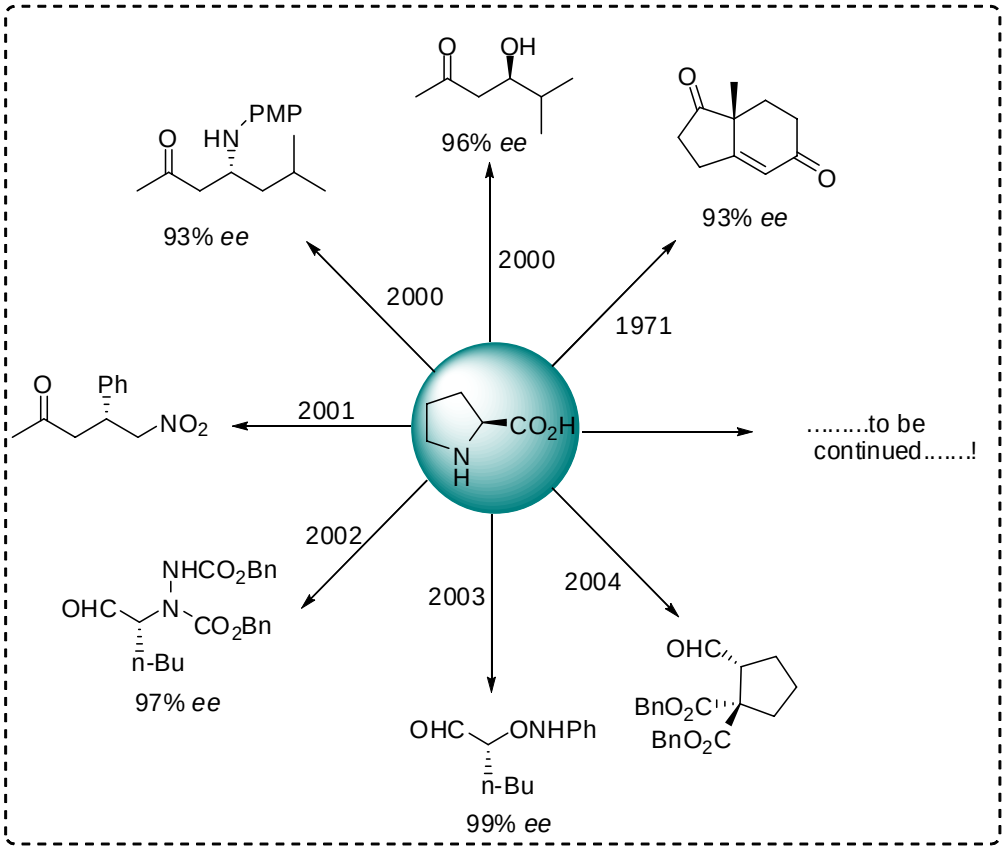


Scheme 1.33: Proline catalyzed first enantioselective 6-*enolexo* aldolization

A selected example of this 6-*enolexo* aldolization is given in Scheme 1.33; in which the desired *trans*-1, 2-disubstituted cyclohexane product is obtained with a diastereomeric ratio of *dr* = 10:1 and a highest enantioselectivity of 99% *ee*.

The catalytic generation of asymmetric enolate equivalents is an area for which there is no general solution and, perhaps, the most important factor for the growth of organocatalysis. Since 2000, research by a number of groups has demonstrated the tremendous generality of proline catalysis for the generation of carbon-carbon, carbon-

nitrogen, carbon-oxygen, and carbon halogen bonds in ketone or aldehyde substrates and this work is summarized very recently by Gaunt M. J and co-workers.[45b]



Scheme 1.34: Recent achievements of proline catalysis

Enamine catalysis using proline or related catalyst has now been applied to both intermolecular and intramolecular addition reactions with a variety of electrophiles such as, addition to carbonyl compounds (C=O) for direct aldol reactions, to imines (C=N) in Mannich reactions,[60] azodicarboxylates (N=N) for direct amination reactions,[61] nitrosobenzene (O=N) for direct oxygenation reactions,[62] and Michael acceptor (C=C) for 1,4-conjugate addition reactions,[63] along with the direct intramolecular alkylation reactions of aldehydes using enamine catalysis also have been established by Prof. List[64] recently. The recent achievements of enamine catalysis using proline as an

organocatalyst have been summarized in Scheme 1.34. Several other different synthetically important methods such as, fluorination,[65] chlorination,[66] bromination,[67] sulfenylation,[68] have been developed for the α-functionalization of aldehydes and ketones with high stereoselectivity. The catalysis for these reactions are carried out by the versatile enamine mechanism using chiral secondary amines derived from proline and imidazolidinones as an organocatalysts. Organocatalytic processes have been recently used for the synthesis of important drugs and bioactive compounds to further enhance its synthetic applications, which has been reviewed very recently.[47] We strongly believe that asymmetric aminocatalytic processes have great potential in academic and industrial synthesis.

We have presented a brief account on the "direct catalysis" of aldol reactions using biocatalysis, metal catalysis, and organocatalysis (small organic molecule catalysts or metal free catalysts). In particular, organocatalysis is very the fast growing area of the current research in organic chemistry and recently applied in several different enantioselective transformations. Particularly, the detailed mechanistic concept of enamine-catalysis e.g. amino-catalysis for aldol reaction using L-proline as an organocatalyst has been presented here. Tremendous progress has been made in the recent years and only selected L-proline catalyzed direct intermolecular and intramolecular aldol reactions have been summarized here. All the information collected and presented here has been well supported by providing about 100 latest references from various monograph and international journals.

1.3. Aim of the Thesis and survey of the contents

The first aim is to make a clear understanding of the original concept of the direct catalytic asymmetric aldol reactions using different catalytic processes like- biocatalysis, metal catalysis and organocatalysis. Critical literature search has been carried out and presented here on the direct aldol reaction particularly; the discovery of direct enantioselective aldol reaction using enamine catalysis can be viewed as a major breakthrough in the field of aldolization reaction. The specific objectives of this work were:

(i) To study organocatalysis using L-proline catalyzed aldol reaction of functionalized amino aldehydes with various ketones and for the synthesis of biological activities compounds like sphingosine and phytosphingosine base back bone.

(ii) The study the direct organocatalytic aldol reactions catalyzed by L-proline in intramolecular diastereoselective fashion and to provide the new organocatalytic route to the synthesis of some of the important biologically active compounds lime imino sugars.

(iii) The study on the Huisgen [3+2] dipolar cycloaddition "click-chemistry" reaction activated alkyne with various azides in water and further synthesis new class of of fused 1,2,3-triazolo-*δ*-lactams/lactones.

This thesis is divided into five chapters:

In chapter 1, the detailed understanding concept of direct catalysis of aldol reaction and the introduction of the subject of organocatalysis with special reference to the recent

published work in the area of direct catalytic asymmetric aldol reactions have been described.

In chapter 2, the results of the direct diastereoselective aldol reaction of different *α*-amino aldehydes and various ketones catalyzed by L-Proline and further synthesis of amino polyols have been discussed.

In chapter 3, detailed studies on direct diastereoselective intramolecular aldolization with *enolexo* fashion for the synthesis of 1-imino-sugar analogs has been described.

In chapter 4, the new general approach for the construction of structural framework for the aza-sugars (imino-sugars) using L-proline catalyzed direct diastereoselective 6-*enolexo* aldolization reaction has been discussed.

In chapter 5, the synthesis of a new class of hybrid triazolo-*δ*-lactams/lactones using Huisgen [3+2] dipolar cycloaddition between activated alkyne and various azides in water, followed by cyclization have been discussed in details.

1.4. References

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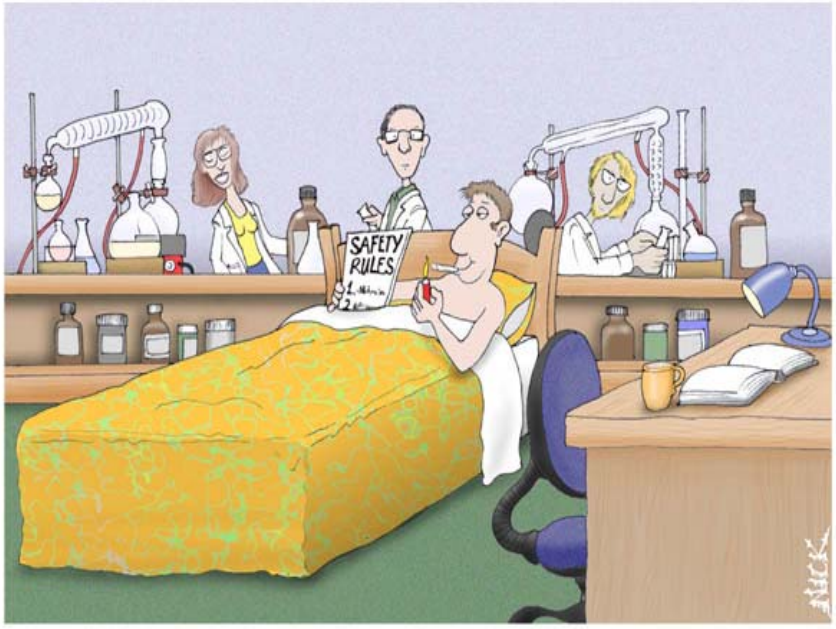
Chapter 2

Direct Diastereoselective Aldol Reaction: Towards the Synthesis of Amino-polyols



Recent Advances in Science, #32:

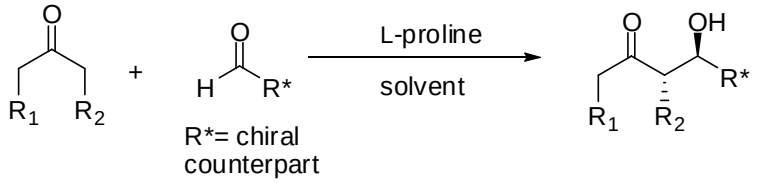
Dr Ed Henderson demonstrates that it IS possible for someone to become too familiar with the safety rules.

"The wave and the ocean are not different."
- Swami Vivekananda

2.1. Introduction

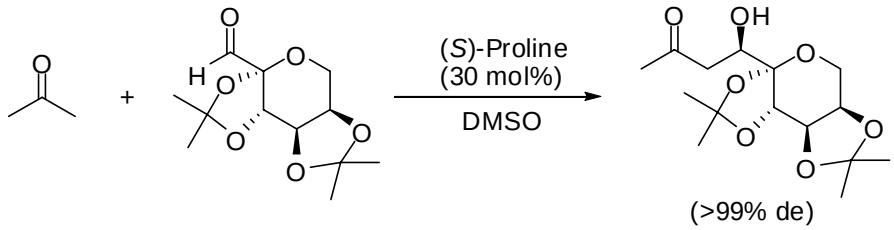
β-Hydroxy carbonyl and 1,3- diol units are frequently found in complex polyol architectures of natural products and have attracted a great deal of attention from synthetic organic chemists.[1] The asymmetric aldol reaction is a useful method for the preparation of these units in enantiomerically rich form. Recent years have witnessed the success of '*enamine-catalysis*' using proline and its derivatives for the direct enantioselective aldol reaction.[2] Although, proline catalysis for aldol reaction was known since 1970s in intramolecular fashion, its mechanism was poorly understood and its scope had not been much explored. Recently, the chemistry of organocatalysis was again initiated with the discovery of first direct intermolecular aldol reaction catalyzed by L-proline.[3] Since then organocatalysis in last few years has contributed to the development of several highly enantio-, and diastereoselective (*anti*) aldol reactions.[2,4] However, the scope of '*enamine-catalysis*' in the asymmetric synthesis needs to be explored extensively.

The direct aldol reaction of aldehyde/ketone with a branched aldehyde already having a chiral center can be regarded as a general diastereoselective aldol reaction and is highly useful for the synthesis of various complex frameworks of important compounds. (Scheme 2.1)



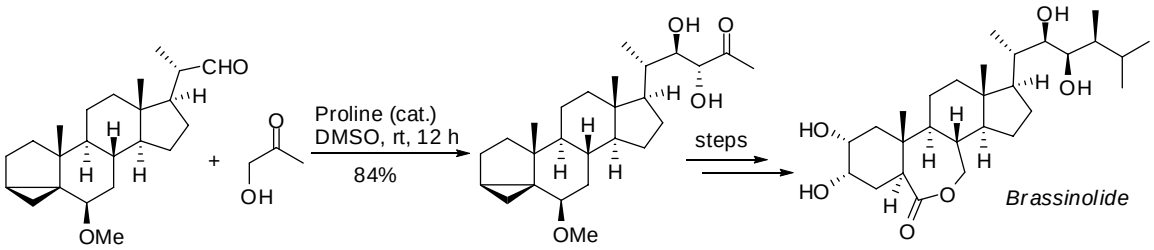
Scheme 2.1: General direct diastereoselective aldol reaction catalyzed by L-proline

Recently, highly stereoselective proline-catalyzed acetone aldol reaction has been used for the synthesis of sugar derivatives as shown in Scheme 2.2.[5]



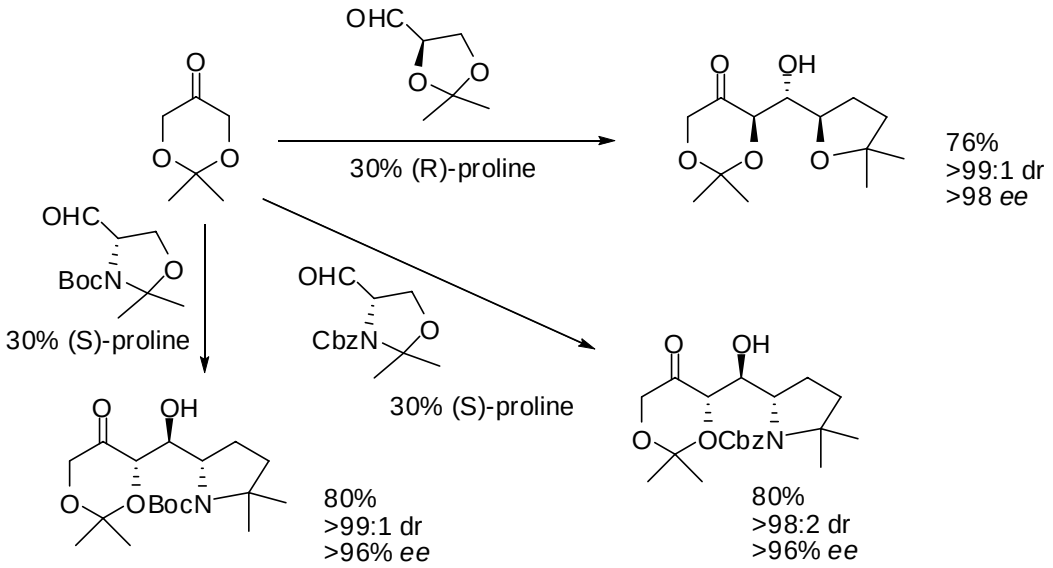
Scheme 2.2: Direct diastereoselective aldol reaction of acetone

The exceptionally high diastereoselectivity was achieved in proline-catalyzed aldol reaction involving hydroxy acetone and readily available chiral aldehyde for the total synthesis of *brassinolide,* a steroidal plant growth regulator (Scheme 2.3).[6]



Scheme 2.3: Direct diastereoselective aldol reaction for the synthesis of *brassinolide*

Highly direct diastereoselective aldol reaction of *N*,*N*-dibenzyl-*α*-amino aldehydes[7] and 4-oxoazetidine-2-carbaldehydes[8] with different ketones catalyzed by proline has been disclosed recently. Soon after, Enders and Grondal proposed the direct organocatalytic 'De Novo' synthesis of carbohydrates using direct diastereoselective aldol reaction of functionalized aldehydes with 2,2-dimethyl-1,3-dioxane-5-one (dioxanone) in high anti-diastereoselectivity (Scheme 2.4).[9a]



Scheme 2.4: Highly *anti*-diastereoselective aldol reaction of dioxanone with different aldehydes (selected examples)

Stereoselective synthesis of amino-polyols or poly hydroxy amino acids have been the focus of major interest because of their occurrence in the complex nucleoside antibiotics that exhibit a variety of biological activities.[10] For example, Sphingoids are long-chain amino-diol and triol bases that form the backbone and the characteristic unit of sphingolipids and are involved in several cellular events like regulation of cell growth, differentiation, adhesion, neuronal repair and signal transduction.[11] D-*erythro*-Sphingosine **2.1** is a structural unit common to almost all sphingolipids in eukaryotic cells,[11,12] defined as '*sphingoids base*' backbone. The anticancer activity of sphingosine **2.1** and other sphingolipids, particularly, against colon cancer lines has been established recently.[13] Phytosphingosines consist of an aliphatic chain with a 2-amino-1,3,4-triol head are important members of the sphingoids family. Phytosphingosine itself is a bioactive lipid and its glycolated derivatives display promising antitumer and antivirus activities[14] (Figure 2.1).

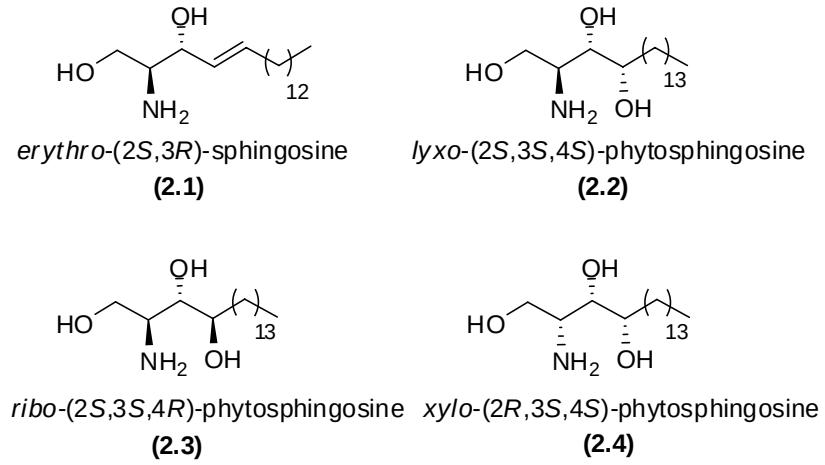
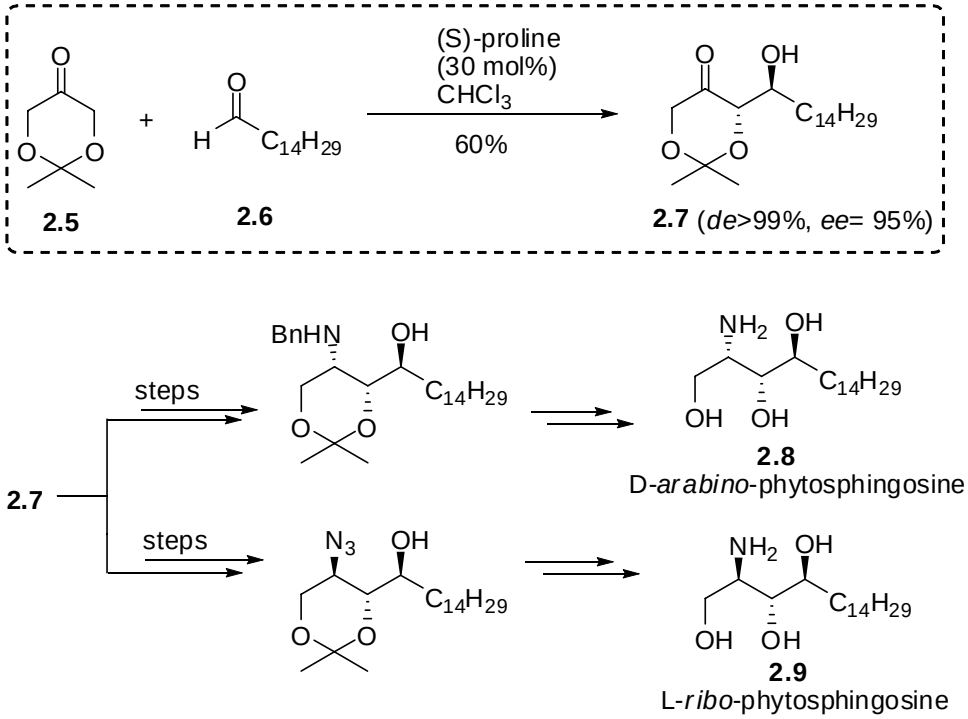


Figure 2.1: Some of the selected sphingoids

Due to the biological importance, many synthetic routes of these sphingoids have been described in the literature.[15-16] Most of these utilize starting materials from the chiral pool e.g. amino acids and carbohydrates,[15] while the asymmetric routes are rather rare.[16]



Scheme 2.5: (*S*)-proline catalyzed aldol reaction as key step to sphingoids

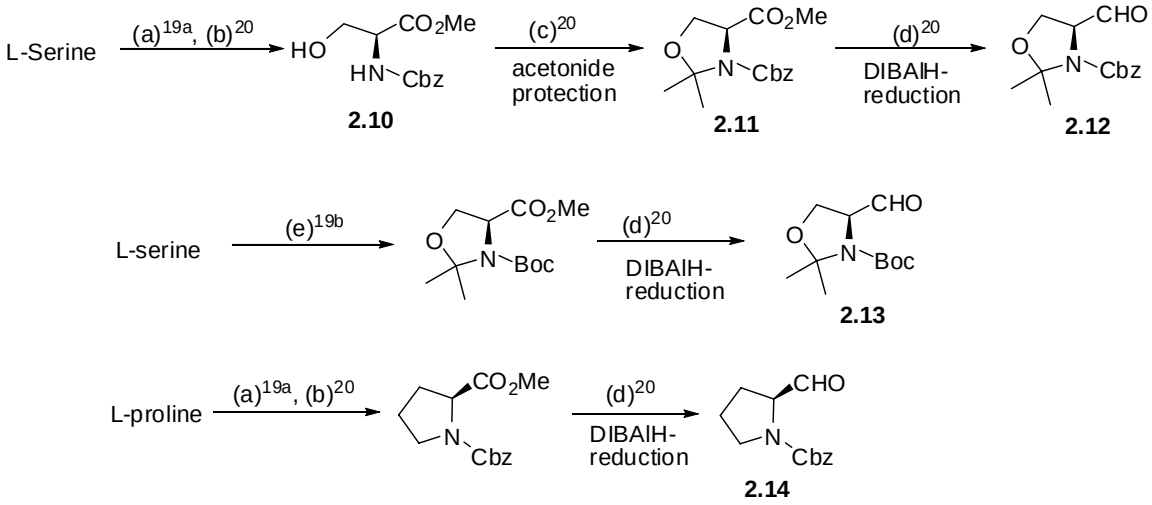
Recently, the direct organocatalytic route to the synthesis of sphingoids family with the asymmetric synthesis of D-*arabino*- and L-*ribo*-phytosphingosine has been described by Prof. D. Enders and his co-workers.[17] The direct aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one **2.5** with pentadecanal **2.6** provides high level of diastereo- (*de* > 99%) and enantioselectivity (*ee* > 95%) using 30 mol % of (*S*)-proline as an organocatalyst as a key step. The aldol adduct **2.7** was then transformed in to D-*arabino*- and L-*ribo*-phytosphingosine **2.8** and **2.9** respectively using standard synthetic transformations as shown in Scheme 2.5.

2.2. Results and Discussions

Our major focus was on the direct diastereoselective aldol reaction of α-amino aldehydes having cyclic structure with acetone and other cyclic ketones. Due to their easy availability, *α*-amino aldehydes have received considerable attention in organic synthesis as chiral starting materials.[18] However, the direct diastereoselective aldol reaction of *α*-amino aldehydes has not been explored extensively. Hence, we used α-amino aldehydes having cyclic core structure for the direct diastereoselective aldol reactions with different ketones. We further explored the direct diastereoselective aldol reactions of ketones with different aldehydes for the synthesis of stereoselective synthesis of 2-amino-1,3,5-hexane triols consisting of sphingosine base and (2*S*,3*S*,4*S*)-2-amino-1,3,4-triol base backbone unit of *lyxo*-phytosphingosine.

2.2.1 Direct diastereoselective aldol reaction of α-amino aldehydes with various ketones

We started our study with the preparation of different well-protected α-amino aldehydes from the corresponding amino acids and we chose the most utilized amino acids such as L-serine, which can be easily transformed in to its corresponding aldehyde with cyclic structures and L-proline, which is the only amino acid already having cyclic structure along with secondary amine. These amino acids were first converted in to their corresponding N-Cbz, or N-Boc protected esters following the reported procedures.[19] In order to do this, firstly L-serine was protected with CbzCl (1.2 mol equiv) in 4M-NaOH solution at 0°C for 1 h, giving –NCbz protected amino acid which was treated with followed $SOCl_2$ in MeOH for over night to give corresponding esters **2.10**.[19a]

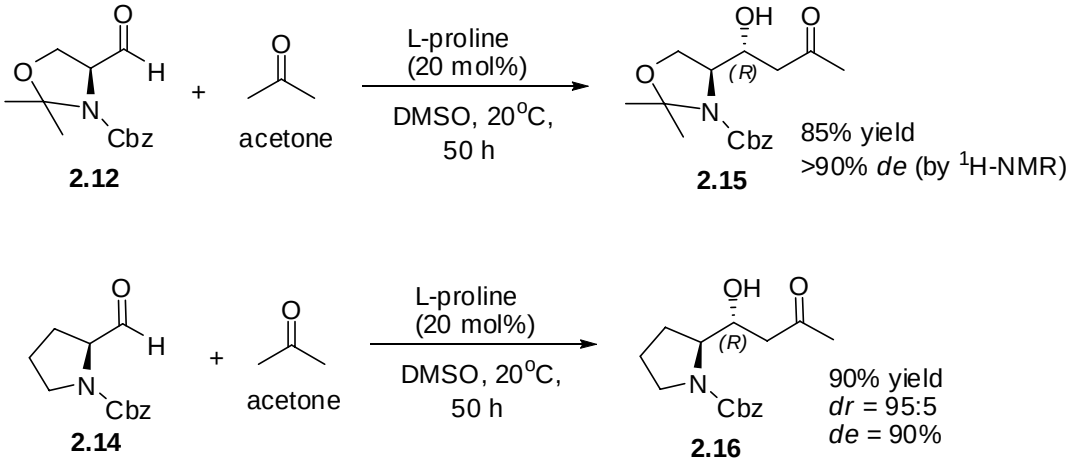


Scheme 2.6: General Scheme for the preparation of α-amino aldehyde (a) 4N-NaOH sol., CbzCl, 0°C, 1 h; (b) $SOCl_2$ (1.2 equiv), MeOH, rt, overnight; (c) 2,2-dimethoxy propane, acetone, $BF_3.OEt_2$, 24 h; (d) DIBAL-H (1.2M sol. in toluene), dry toluene, -78°C; (e) i)AcCl, MeOH; ii) $(Boc)_2O$, Et_3N, THF, 50°C, 3 h; iii) 2,2-dimethoxy propane, $BF_3.OEt_2$, 24 h.

The N-Cbz serine ester **2.10** was then transformed in to acetonide protected ester **2.11** by treating with 2,2-dimethoxy propane in acetone as a solvent.[20] This protected ester **2.11** was then transformed into corresponding aldehydes **2.12** in gram scale by using DIBAL-H (Diisobutylaluminium hydride, 1.2 M in toluene) reduction at -78°C in dry toluene.[20]

Similarly, the corresponding N-Boc serine aldehyde **2.13** (Garner-aldehyde) and N-Cbz proline aldehyde **2.14** were prepared by following the reported procedure.[19-20] The general methods for the preparation of α-amino aldehydes from their corresponding amino acid using literature procedures are shown in Scheme 2.6. These freshly prepared *α*-amino aldehydes can be used for the direct diastereoselective aldol reaction catalyzed by L-proline.

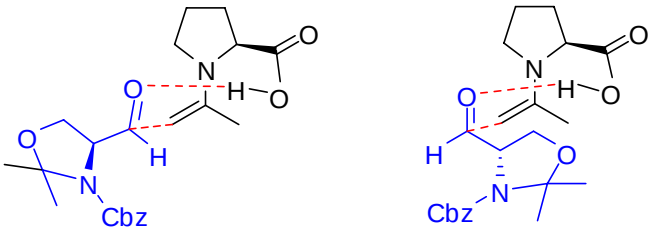
We first examined the direct diastereoselective aldol reactions of α-amino aldehydes **2.12** and **2.14** with acetone. These reactions were carried out with 1 mmol of aldehyde in 10 ml acetone and 2 ml DMSO at 20°C for 50 h in presence of 20 mol% of L-proline as a catalyst, to afford β-hydroxy ketones **2.15** and **2.16** in reasonably good yield and high diastereoselectivity as shown in Scheme 2.7.



Scheme 2.7: Direct diastereoselective aldol reaction with acetone as donor

In case of compound **2.15**, the *de* (diastereomeric excess) of unseparated diastereomer was determined by ^{1}H and ^{13}C NMR, whereas in case of **2.16**, the *de* (diastereomeric excess) was determined by weighing separately after separation by column chromatography. The high diastereoselectivity and formation of the (*R*)-stereochemical

outcome of the reaction product can be explained through the Houk-List model[21] of L-proline catalyzed aldol reaction as shown in Figure 2.2. According to this mechanism, the *Ri*-facial attack **(a)** on the acceptor amino-aldehyde by the *anti*-enamine donor of acetone with the activation of aldehyde carbonyl though hydrogen bonding is more favored over the *Si*-facial attack **(b)**, which is sterically more hindered with respect to the steric demand of acceptor aldehydes. This leads to the high level of diastereoselective out come of the direct aldol reaction catalyzed by L-proline.



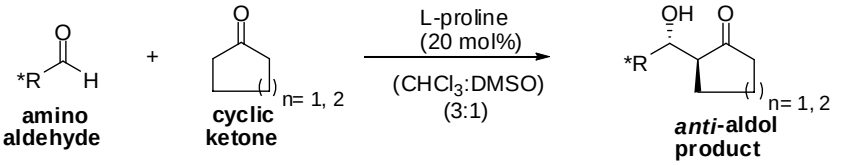
(a) faovred **(b) disfavored**

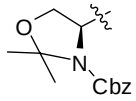
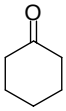
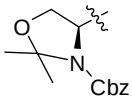
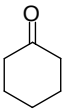
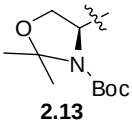
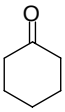
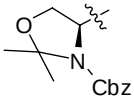
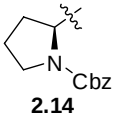
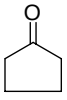
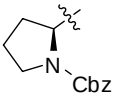
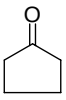
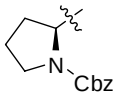
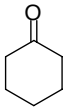
Figure 2.2: Houk-List model for the diastereoselective outcome using acetone donor

We continued our study on the L-proline catalyzed direct diastereoselective aldol reaction using cyclic ketones such as cyclopentanone, cyclohexanone as aldol donor with amino-aldehydes as acceptors. Our studies of these reactions at 20°C are presented as entries 1 and 5 in Table 2.1. It was found that the amino-aldehydes **2.12** and **2.14** reacted with cyclohexanone and cyclopentanone in $CHCl_3$: DMSO (3:1) at 20°C for 48 h in presence of L-proline (20 mol %) to give aldol adducts **2.17** and **2.21** in 78% and 84% yields, with *dr* (diastereomeric ratio) of 83:17 and 88:12 respectively. Enders et al. have reported the direct diastereoselective aldol reaction of similar type of branched aldehydes with dioxanone at lower temperature with high level of diastereoselectivity.[9a] These results prompted us to perform a set of direct diastereoselective aldol reactions at lower temperature of 5°C shown as the entries 2, 3, 4, 6, 7 of Table 2.1. We also observed the

further enhancement in the diastereomeric ratio *dr* (>95:5) by carrying out the reactions at 5^{o}C for 60 h (little longer time), with yields up to 80-85% in case of aldol products **2.18**, **2.22**. The enhancement in the diastereoselectivity at lower temperature can be explained through better facial selection due to higher rigidity in the transition state. These results are very similar to those reported by Enders et al., in which they also established the concept of matched/mismatched situation required for both proline catalysts and α-branched chiral aldehydes through the kinetic-resolution in the transition states which depends upon the steric requirement of chiral aldehydes.[9] This assumption was further supported by direct mannich reaction for the synthesis of amino sugars and derivatives.[9b] The use of L-proline as organocatalyst for the direct diastereoselective aldol reactions of amino aldehydes derived from (*S*)-amino acids falls in the category of matched situation, and further helps us to explain the high level of diastereoselectivity of these reactions at lower temperature. The results of our study for the diastereoselective aldol reaction of cyclic ketones with amino aldehydes are further summarized in Table 2.1. In all the cases *anti*-diastereomeric ratios obtained were in the range of 83-98% and all the direct aldol reactions were carried out by stirring a mixture of 1.0 mmol of α-amino aldehydes and 2.0 mmol of cyclic ketones with 20 mol% of L-proline as a catalyst in the solvent system of (3:1) mixture of $CHCl_3$: DMSO at the mentioned temperatures. The progresses of all the reactions were monitored by thin-layer chromatography (TLC) and after appropriate time, these reactions were quenched with aqueous $NaHCO_3$ solution. After work-up of the reactions, the crude products were isolated by flash column chromatography and the *dr* (syn:anti) ratio was determined by weighing separately after chromatographic purification.

Table 2.1: Direct diastereoselective aldol reaction of α-amino aldehydes with cyclic ketones



Entry	R*	ketone[a]	temperature (°C)	time (h)	product yield (%)[b]	*dr* (anti:syn)[c]
1	 **2.12**		20	48	**2.17** (78%)	83:17
2	 **2.12**		5	60	**2.18** (81%)	>96:4
3	 **2.13**		5	60	**2.19** (83%)	>98:not observed
4	 **2.12**		5	60	**2.20** (78%)	>98:not observed
5	 **2.14**		20	48	**2.21** (84%)	88:12
6	 **2.14**		5	60	**2.22** (81%)	>95:5
7	 **2.14**		5	60	**2.23** (86%)	>98:not observed

[a] General reaction conditions: 1.0 mmol of aldehyde, 2.0 mmol of cyclic ketone, 20 mol% L-proline, solvents $CHCl_3$: DMSO (3:1). [b] Isolated Yields of **7**. [c] Determined by weighing separately after flash chromatography on silica gel. [d] Abbreviations: Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl.

The high level of *anti*-diastereoselectivity was obtained when the reaction was carried out at 5°C and in case of entries 3, 4, 7 of table 2.1, we did not observe the *syn*-aldol adduct of these reactions and could isolate an almost pure *anti*-aldol adducts **2.19**, **2.20**, **2.23**. The observed high *anti*-diastereoselectivity can be explained by the Houk-List model for proline-catalyzed aldol reaction with cyclic ketones, where an enamine intermediate and an intermolecular hydrogen bond play the decisive role (Figure 2.3).[20]

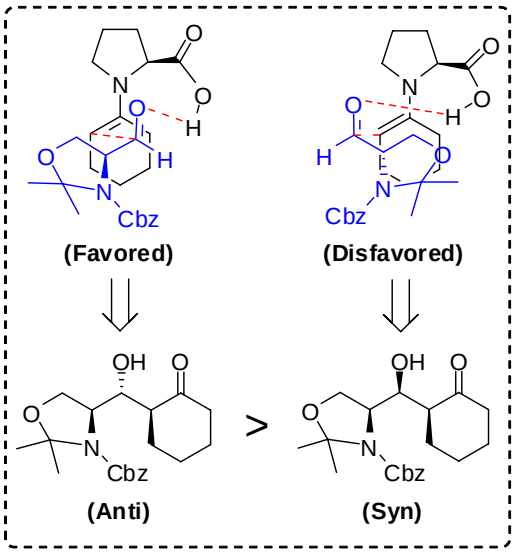


Figure 2.3: Houk-List model of L-proline catalyzed aldol reaction of cyclic ketones for anti-diastereoselectivity

The formation of *anti*-aldol products and the absolute configuration given are consistent with the related proline-catalyzed aldol reactions,[22] in which the attack of the *anti*-enamine on the aldehyde carbonyl proceeds through the activation through hydrogen bonding and facial selection. The amino aldehyde derived from (*S*)-amino acids consists of a chiral centre with fixed stereochemistry will further force the enamine attack from the *Ri*-face of the amino aldehydes with a better hydrogen bonding activation leads to the *anti*-aldol adducts. While, the *Si*-facial selection was disfavored due to the steric requirment for the attacks of the *anti*-enamine on the aldehyde carbonyl as well as poor

hydrogen bonding activation. Lowering the reaction temperature further provides more rigidity during the transition state and leads to the high level of *anti*-diastereoselectivity. Thus, we have developed the highly diastereoselective aldol reactions of α-amino aldehydes with acetone and other cyclic ketones. These encouraging results prompted us to utilize the scope of these diastereoselective aldol reactions for the quick route to the core structural synthesis of some of the important amino polyols, which are the structural units widely distributed in several biologically active products such as sphingoids family.

2.2.2 Synthesis of amino-polyols

We have recently reported the stereoselective synthesis of 2-amino-1,3,5 hexane triols (**2.25a** and **2.25b**)[23] and (2*S*,3*S*,4*S*)-amino-triol base (**2.26**), [24] which are the backbone units of sphingosine and *lyxo*-phytosphingosine as shown in Figure 2.4. The details of these syntheses are discussed below:

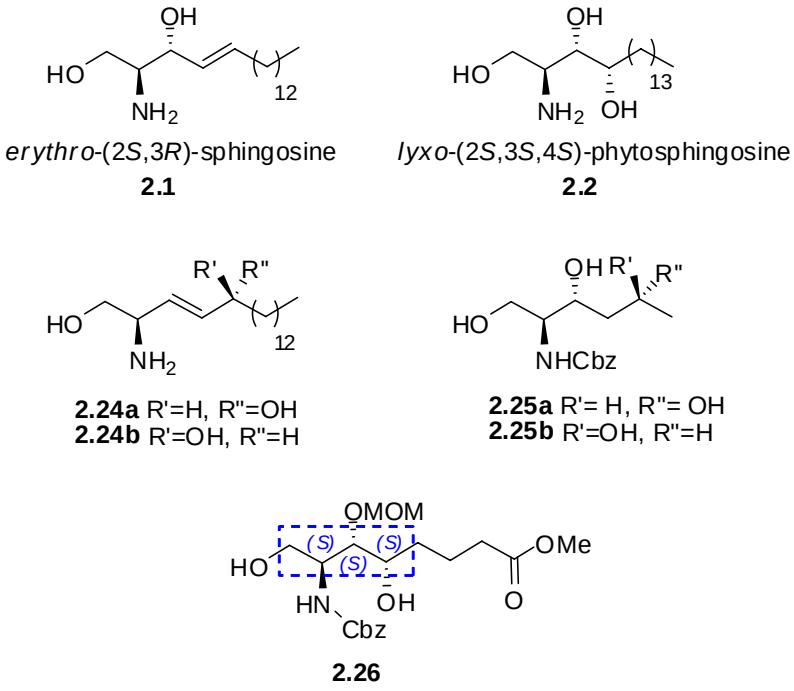
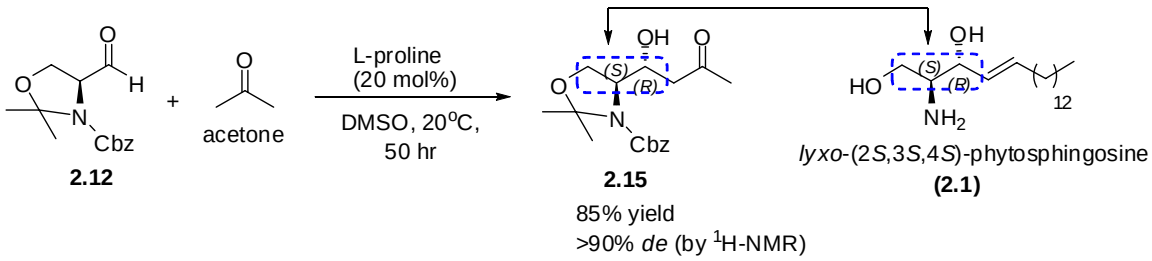


Figure 2.4: Amino polyols as the backbone of sphingoids

2.2.2.1 Stereoselective synthesis of 2-amino-1,3,5-hexane triols

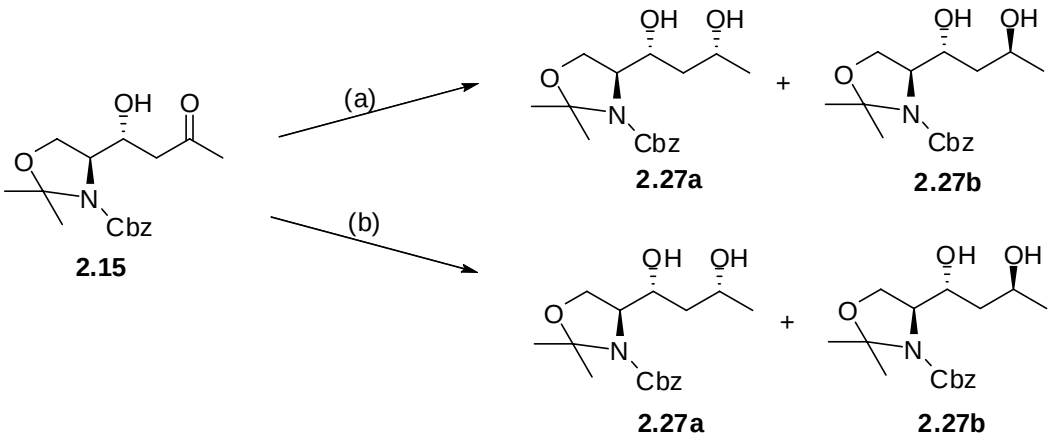
The efficiency of the L-proline catalyzed direct diastereoselective aldol reaction can be demonstrated by a reaction in which *β*- hydroxy carbonyl product **2.15** was prepared in one step from aldehyde **2.12** and acetone. This aldol product **2.15** has the (2*S*,3*R*)-2-amino-1,3-amino diol base, which is common to almost all sphingolipids **2.1** (Scheme 2.8).



Scheme 2.8: L-Proline catalyzed direct diastereoselective aldol reaction with acetone

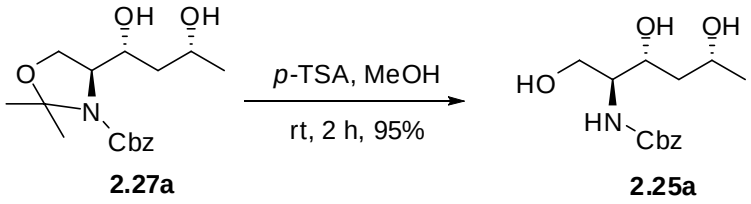
Our next aim was to propagate the existing stereocenters created in the diastereoselective aldol reaction through successive highly diastereoselective transformations involving the reduction of the β-hydroxy carbonyl moiety to give 1,3-diols using different reaction conditions. The relative stereochemistry of the reduction product can be controlled by choosing the appropriate reduction conditions, which will be directed by the stereochemistry of the existing hydroxyl group. In order to do that the β- hydroxy ketone **2.15** was diastereoselectively reduced to 3,5-*syn*-diol **2.27a** (*dr* = 95:5) using $Et_2B(OMe)/NaBH_4$ in dry THF/MeOH at -78°C with a combined yield of 89%.[25] Similarly 3,5-*anti*-diol **2.27b** (*dr* = 20:80) was obtained in 82% combined yield using $NaBH(OAc)_3$/acetic acid/CH_3CN at room temperature,[26] as shown in Scheme 2.9. These directed 1,3-reductions are very selective and the *syn*/*anti* diols appears with different R_f values on the TLC and can be easily separated by column chromatography. The

diastereomeric ratio of the stereoselective reduction was determined by weighing separately the products, after purification by column chromatography.



Scheme 2.9: Reagents and conditions: (a) $Et_2B(OMe)/NaBH_4$, dry THF/MeOH, -78°C, 5 h, 89% (*dr*, **2.15a**/**2.15b** 95:5); (b) $NaBH(OAc)_3$/acetic acid/CH_3CN, rt, 4 h, 82%, (*dr*, **2.15a**/**2.15b** 20:80).

The synthesis of 2-amino-1,3,5-triols pattern was achieved by deprotection of acetonide moiety (Scheme 2.10). For this purpose, **2.15a** was treated with *p*-TSA/MeOH at room temperature for 2 h to afford the **2.13a** amino triol unit as a white solid in 95% yield. In the same manner, **2.15b** was transformed to **2.13b**.



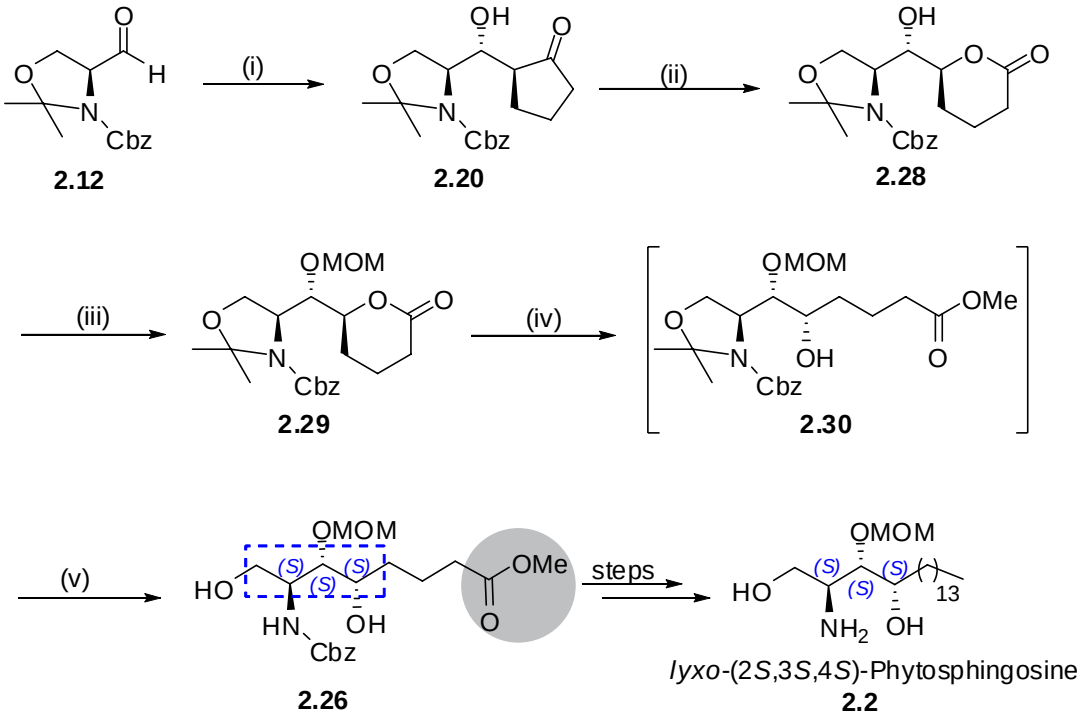
Scheme 2.10: Synthesis of 2-amino-1,3,5-hexane triols

Thus, highly diastereoselective aldol reaction of acetone with *α*-amino aldehyde **2.8** catalyzed by L-proline has been achieved and the potential of this reaction was further utilized for the quick synthesis of versatile 2-amino-1,3,5-hexane triol pattern, which is found in most of the sphingoids.

2.2.2.2 Synthesis of *lyxo*-Phytosphingosine backbone

We have already described the biological importance and synthetic approaches for the members of sphingoids family. Recently, only one organocatalytic route was described in the literature by Enders and his coworkers.[17] We attempted another organocatalytic route to the synthesis of this class of compounds utilizing our previous work on the direct diastereoselective aldol reaction of α-amino aldehydes with the cyclic ketones. Therefore first, the aldol product **2.20** was prepared by the reaction of amino aldehyde **2.12** with cyclopentanone in presence L-proline (20 mol %) as a catalyst at 5^{o}C for 60 h with almost complete purity to *anti*-diastereomeric form. This aldol product **2.20** was then subjected to the Baeyer-Villiger oxidation by treating with 3 equiv of *m*-CPBA (55% activity) and 3 equiv of $NaHCO_3$ in dry CH_2Cl_2 for 4 h and the reaction was continued further by adding another portion of the same amount of *m*-CPBA and $NaHCO_3$ with additional stirring for 8 h at the same temperature to give the desired hydroxy-lactone compound **2.28** in 85% isolated yield.

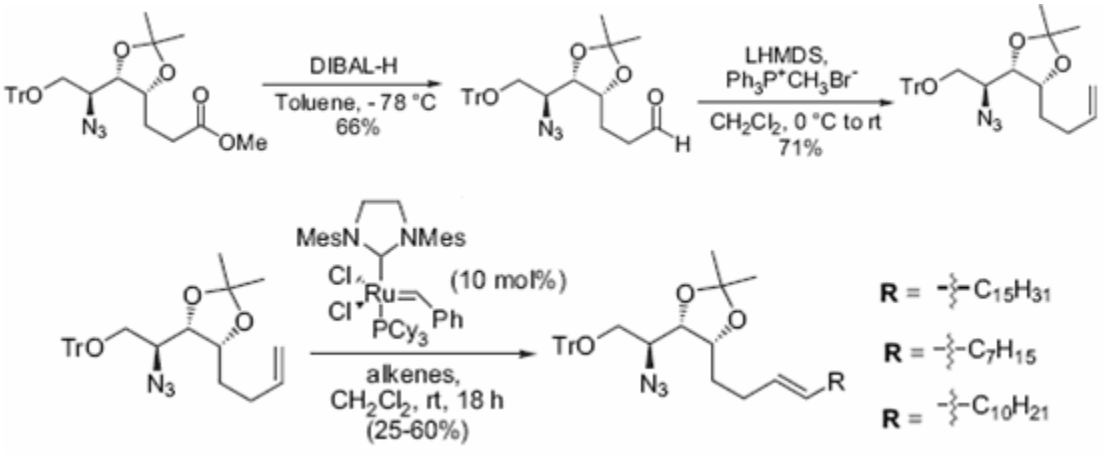
The hydroxy group of compound **2.28** was then protected with MOMCl using standard conditions to provide MOM-protected compound **2.29** with 91% yield.[27] Further, compound **2.29** was treated with K_2CO_3 (cat.)/MeOH at room temperature for 2 h for the delactonization of **2.29** and the progress of this reaction was monitored by TLC to give hydroxy ester **2.30**. This reaction was then acidified with 2N-HCl solution and stirred further for 3 h to deprotonate the acetonide moiety insitu to give the 2-amino-1,3,4 triol unit **2.26** backbone. The solvent was evaporated and crude material was passed through the small pad of column to give **2.26** as a white solid with 76% yield, which was having the (2*S*,3*S*,4*S*)-2-amino-1,3,4-triol unit of *lyxo*-phytosphingosine **2.2** (Scheme 2.11).



Scheme 2.11: Reagents and conditions: (i) Cyclopentanone (2 equiv.), L-proline (20 mol%), DMSO:$CHCl_3$(3:1), 5°C, 60 h, 78%, *dr* >98%; (ii) *m*-CPBA (6 equiv.), $NaHCO_3$ (6 equiv.), dry DCM, rt, 12 h, 85%; (iii) *i*-Pr_2EtN (1.5 equiv.), MOMCl (1.2 equiv.), dry CH_2Cl_2, rt, overnight, 91%; (iv) K_2CO_3(cat)/MeOH, rt, 2 h, quantitative yield; (v) *p*-TSA, MeOH, rt, 3 h, 81%.

This approach provides a quick access to phytosphingosine backbone, towards the synthesis of *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine **2.2**, because the resulting compound **2.26** can be easily transformed in to *lyxo*-phytosphingosine by converting the ester moiety to long chain carbon unit by using a similar way as reported by Lin and co-workers,[28] in which the ester moiety was first converted in to alkene and then underwent cross-metathesis with alkenes of different size (carbon numbers), this transformed the ester moiety to give long chain carbon units as shown in Scheme 2.12. Thus, we have successfully demonstrated the highly diastereoselective aldol reaction of Cbz-Garner aldehyde **2.7** with cyclopentanone using L-proline as an organocatalyst. This reaction was

further used for the synthesis of the amino-polyol core structure of *lyxo*-phytosphingosine.



Scheme 2.12: Transformation of ester moiety to long chain carbon units by Lin et al.[27]

2.3. Conclusions

In conclusion, we have developed the highly efficient direct diastereoselective aldol reaction of α-amino aldehydes derived from L-serine and L-proline having cyclic structure with acetone and other cyclic ketones using L-proline (20 mol%) as an organocatalyst. Studies at different temperatures were also carried out, which revealed that the high level of diastereoselectivity (*dr* >98) can be achieved at lower temperatures. We have further extended the scope of these direct aldol reactions to the synthesis of amino-polyols, which are existing as a structural fragment in several biologically active compounds. In particular, the synthesis of 2-amino-1,3,5-hexane-triols has been achieved using L-proline catalyzed aldol reaction with acetone as a donor and the highly diastereoselective 1,3-reduction of aldol products under different reduction conditions. We also designed the organocatalytic approach for the synthesis phytosphingosine and successfully achieved the synthesis of (2*S*,3*S*,4*S*)-2-amino-1,3,4-triol base backbone unit,

towards the synthesis of *lyxo*-phytosphingosine. This approach is very flexible and can be applied to other phytosphingosine because stereochemical outcome of this reaction can be altered by different isomer of starting amino-aldehyde and of course using proline as catalyst which is available in both D and L-form.

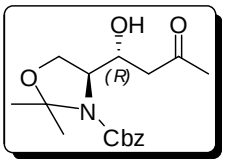
2.4 Experimental Section

General

All the reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under argon atmosphere using oven-dried glassware. Dichloromethane and dimethyl sulfoxide were distilled over CaH_2 under argon atmosphere and stored on molecular sieves. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin-Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^{1}H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^{1}H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC-MS was recorded using electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100-200 and 230-400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

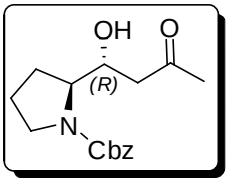
General procedure for the direct diastereoselective aldol reaction of amino-aldehydes with acetone:

To a stirred solution of amino aldehydes **2.7** (1 mmol) in 10 ml acetone and 2 ml DMSO at 20^{o}C, was added L-proline (23 mg, 20 mol %). The reaction mixture was stirred further for 50 h at same temperature, followed by TLC. The reaction mixture was reduced in vacuo. The resulting residue was taken in EtOAc (30 mL) and stirred with 10% $NaHCO_3$ solution (10 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reside was purified by column chromatography, eluting with (20% EtOAc/Pet ether) to give aldol adduct in good yield.



(*S*)-Benzyl 4-((*R*)-1-hydroxy-3-oxobutyl)-2,2-dimethyloxazolidine-3-carboxylate (2.8)

Yield = 85%, $[\alpha]_D^{25}$ +5.7 (*c* 1 $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ = 1.54 (s, 6H), 2.14 (s, 3H), 2.40-2.65 (m, 2H), 3.80-4.15 (m, 4H), 5.15 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75MHz, $CDCl_3$): δ = 24.2, 26.7, 30.7, 45.9, 61.0, 64.8, 67.4, 68.7, 94.3, 127.9, 128.1, 128.4, 135.8, 154.2, 209.3. LCMS (ESI-TOF): m/z for $C_{17}H_{23}NO_5$ found $[M+H]^+$ 321.48.



(*S*)-Benzyl 2-((*R*)-1-hydroxy-3-oxobutyl) pyrrolidine-1-carboxylate (2.9)

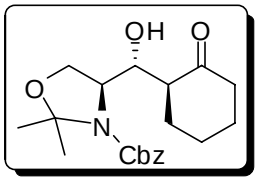
Yield = 89%, $[\alpha]_D^{25}$ -31.73 (*c* 1 $CHCl_3$); ^{1}H NMR (200 MHz $CDCl_3$): δ = 1.85 (m, 4H), 2.15 (s, 3H), 2.43-2.56 (m, 2H), 3.30 (m, 2H), 3.52 (m, 1H), 3.88 (bs, 1H, OH), 4.14 (m, 1H), 5.10 (s, 2H), 7.33 (s, 5H). ^{13}C NMR (75MHz, $CDCl_3$): δ = 23.73, 26.63, 30.59,

46.30, 47.18, 62.10, 66.86, 68.86, 127.65, 127.86, 128.31, 136.44, 156.04, 209.03. LCMS (ESI-TOF): m/z for $C_{17}H_{23}NO_5$ found $[M+H]^+$ 292.16 and $[M+Na]^+$ 314.14.

General procedure for the direct diastereoselective aldol reaction of amino-aldehydes with cyclic ketones:

To a stirred solution of *α*-amino aldehyde **2.7** (1 mmol) and cyclic ketone (2 mmol) in solvent $CHCl_3$: DMSO (3:1, 8 mL), was added 20 mol % (*S*)-Proline at 5^oC and the reaction was further stirred for 60 h at the same temperature, followed by TLC. The reaction mixture was reduced in vacuo. The resulting residue was taken EtOAc (30 mL) and stirred with 10% $NaHCO_3$ solution (10 mL). The organic layer was separated and washed with brine solution, dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by flash chromatography on silica-gel with hexane: ethyl acetate (8:2 to 7:3) to give aldol product in good yield and diastereoselectivity, which was determined by weighing separately after chromatographic purification.

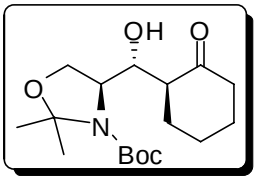
(*S*)-Benzyl 4-((*R*)-hydroxy-((*S*)-2-oxocyclohexyl) methyl)-2,2-dimethyloxazolidine-3-carboxylate (2.10b)



Combined yield 81%, **2.10b** (*anti*, major) $[\alpha]_D^{25}$ -78.70 (*c* 1, $CHCl_3$), **2.10b** (*syn*, minor) $[\alpha]_D^{25}$ +10.76 (*c* 0.8, $CHCl_3$). ^1H NMR (200MHz, $CDCl_3$) for **2.10b** (*anti*): δ = 1.42-1.62 (m, 8H), 1.72-2.05 (m, 5H), 2.27 (m, 1H), 2.43 (m, 1H), 3.32-3.48 (m, 1H), 3.89 (m, 1H), 4.10-4.25 (m, 2H), 4.90-5.20 (m, 2H), 7.34 (s, Ar, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.86, 24.19, 25.20, 28.47, 32.97, 42.60, 50.63, 60.09, 64.87, 67.03, 73.40, 93.92, 127.76, 128.01, 128.35, 136.35, 153.70, 215.91. LC-MS (ESI-TOF): m/z for $C_{20}H_{27}NO_5$ $[M+H]^+$

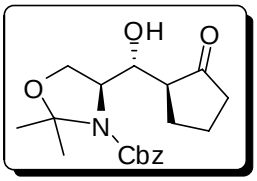
362.12, $[M+Na]^+$ 384.08. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.41; H, 7.58; N, 3.85.

(*S*)-tert-Butyl4-((*R*)-hydroxy-((*S*)-2-oxocyclohexyl) methyl)-2,2-dimethoxazolidine-3-carboxylate (2.10c)



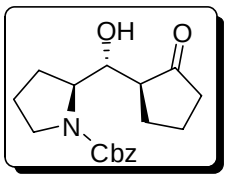
Yield 83%, **2.10c** (*anti*): $[\alpha]_D^{25}$ -119.67 (*c* 0.85, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.38-1.42 (m, 14H), 1.56-1.78 (m, 3H), 1.82-2.15 (m, 4H), 2.31-2.42 (m, 2H), 2.45-2.57 (m, 1H), 3.62-3.75 (m, 1H), 3.81-3.92 (m, 1H), 4.05-4.21 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.18, 25.68, 27.88, 28.31, 28.72, 33.24, 43.06, 50.87, 59.61, 64.89, 73.60, 80.29, 93.72, 153.23, 216.21. LC-MS (ESI- TOF): m/z for $C_{17}H_{29}NO_5$ $[M+H]^+$ 328.22, $[M+Na]^+$ 350.21. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.32; H, 8.89; N, 4.31.

(*S*)-Benzyl 4-((*R*)-hydroxy-((*S*)-2-oxocyclopentyl) methyl)-2,2-dimethyloxazolidine-3-carboxylate (2.10d)



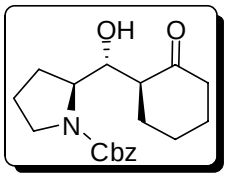
Yield 78%, **2.10d**, (*anti*): $[\alpha]_D^{25}$ -66.46 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.42-1.63 (m, 8H), 1.81-2.28 (m, 5H), 3.85-4.02, (m, 2H), 4.12-4.25 (m, 2H), 5.15 (s, 2H), 7.34 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.22, 23.16, 25.51, 26.67, 37.97, 50.63, 59.59, 63.18, 66.77, 70.78, 94.43, 127.94, 128.11, 128.35, 136.01, 152.04, 216.23. LC-MS (ESI-TOF): m/z for $C_{19}H_{25}NO_5$ $[M+H]^+$ 348.27, $[M+Na]^+$ 370.26. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.62; H, 7.31; N, 4.09.

(*S*)-Benzyl2-((*R*)-hydroxy-((*S*)-2-oxocyclopentyl) methyl) pyrrolidine-1-carboxylate (2.10f)



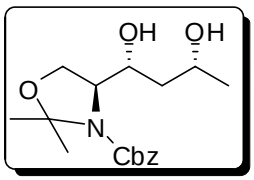
Yield 81%, **2.10f**, (*anti*, major): $[\alpha]_D^{25}$ -99.49 (*c* 1, $CHCl_3$), (*syn*, minor): $[\alpha]_D^{25}$ +18.52 (*c* 1, $CHCl_3$),^{1}H NMR (200MHz, $CDCl_3$): for **2.10f** (*anti*): δ = 1.62-1.85 (m, 4H), 1.94-2.25 (m, 6H), 2.28-2.31, (m, 1H), 3,38-3.61 (m, 2H), 3.75-4.02 (m, 1H), 4.11-4.28 (m, 1H), 5.12 (dd, *J* = 11.6 Hz, 2H), 7.34 (s, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.46, 23.71, 24.45, 26.24, 37.99, 46.86, 50.72, 59.96, 66.32, 71.67, 127.49, 127.62, 128.20, 136.74, 154.79, 216.09. LC-MS (ESI-TOF): m/z for $C_{18}H_{23}NO_4$ $[M+H]^+$ 318.01, $[M+Na]^+$ 339.98. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.19; H, 7.25; N, 4.49.

(*S*)-Benzyl 2-((*R*)-hydroxy-((*S*)-2-oxocyclohexyl) methyl) pyrrolidine-1-carboxylate (2.10g)



Yield 86%, **2.10g**, (*anti*): $[\alpha]_D^{25}$ -90.92 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.50-2.02 (m, 10H), 2.14 (m, 1H), 2.34, (m, 1H), 2.45 (m, 1H), 3.38 (m, 1H), 3.40-3.71 (m, 2H), 4.07 (m, 1H), 5.09 (s, 2H), 7.33 (s, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.80, 24.99, 25.65, 28.18, 31.87, 42.68, 46.94, 52.11, 59.70, 66.57, 72.91, 127.63, 127.77, 128.34, 136.98, 155.50, 215.68. LC-MS (ESI-TOF): m/z for $C_{19}H_{25}NO_4$ $[M+H]^+$ 332.10, $[M+Na]^+$ 354.07. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.71; H, 7.55; N, 4.29.

(*R*)-Benzyl 4-((1*R*, 3*R*)-1,3-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (2.15a):

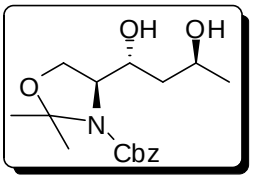


To a stirred solution of β-hydroxy ketone **2.8** (321 mg, 1 mmol) in dry THF (8 mL) and anhydrous Methanol (2 mL) at –78^{o}C under argon, was added dropwise Et_2B (OMe) (1.1 mmol). The solution was stirred for 20 min and then $NaBH_4$ (42 mg, 1.1 mmol) was

added. The resulting mixture was stirred further for 5 h at same temperature. The reaction was quenched with 1 mL of acetic acid. The reaction was warmed to rt and solvent was removed in vacuo. The crude mass was taken in EtOAc (25 mL) and stirred with saturated $NaHCO_3$ (8 mL) for 2 h. The organic layer was separated, washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with (15% EtOAc/5% Acetone/Pet ether) to gave pasty mass **2.15a**, (272 mg, R_f = 0.35, *syn*) TLC (15% EtOAc/5% Acetone/Pet ether) and **2.15b**, in combined 85% yield.

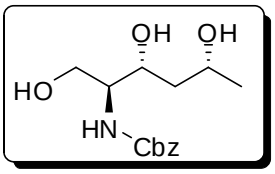
2.15a: $[\alpha]_D^{25}$ –13.19 (*c* 1 $CHCl_3$), FT-IR (cm^{-1}): 3423, 1698, 1413, 1362, 1089, 757. ^1H NMR (200MHz $CDCl_3$): δ = 1.15 (d, *J* = 7Hz, 3H), 1.3-1.6 (m, 8H), 2.4-2.8 (brs, 2H, OH), 3.75-4.20 (m, 5H), 5.13 (s, 2H), 7.33 (s, 5H). ^{13}C NMR (75MHz $CDCl_3$): δ = 23.4, 24.3, 26.3, 40.4, 61.1, 62.3, 64.6, 67.5, 69.1, 94.4, 128.0, 128.1, 128.4, 135.6, and 154.5. LCMS (ESI-TOF): m/z for $C_{17}H_{25}NO_5$ $[M+H]^+$ 323.18.

(*R*)-Benzyl 4-((1*R*, 3*S*)-1,3-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (2.15b):



To a stirred solution of $NaBH(OAc)_3$ (1.899g, 9 mmol) (freshly prepared) in dry CH_3CN (6mL) and glacial acetic acid (3 mL), was added β-hydroxy ketone **2.8** (321 mg, 1 mmol) in CH_3CN dropwise. The combined reaction mixture was stirred further for 4 h at rt. The solvent was removed in vacuo. Similar workup procedure and flash column chromatography gave pasty mass **2.15b** (212 mg, R_f = 0.28, anti) TLC (15% EtOAc/5% Acetone/Pet ether) and **2.15a** in combined 82% yield.

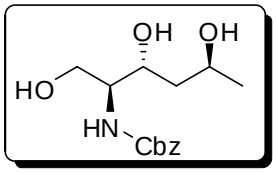
2.15b: $[\alpha]_D^{25}$ –9.67 (*c* 1 $CHCl_3$) (c 1 $CHCl_3$), FT-IR (cm^{-1}): 3423, 1698, 1413, 1362, 1089, 757. ^1H NMR (200MHz $CDCl_3$): δ = 1.14 (d, *J* =7 Hz, 3H), 1.3-1.7 (m, 8H), 2.6-3.0 (brs, 2H, OH), 3.75-4.20 (m, 5H), 5.14 (s, 2H), 7.34 (s, 5H). ^{13}C NMR (75MHz $CDCl_3$): δ = 23.4, 24.3, 26.3, 40.4, 61.1, 62.3, 64.6, 67.5, 69.1, 94.4, 128.0, 128.1, 128.4, 135.6, and 154.5. LCMS (ESI-TOF): m/z for $C_{17}H_{25}NO_5$ $[M+H]^+$ 323.20.



Benzyl (2*R*, 3*R*, 5*R*)-1,3,5-trihydroxyhexan-2-ylcarbamate (2.13a)

To a solution of **2.15a** (200 mg, 0.62 mmol) in MeOH (8 mL) at rt, was added *p*-TSA (catalytic amount) and mixture was further stirred for 2 h at rt. Small amount of solid K_2CO_3 was added and the solvent was removed in vacuo. The residue was dissolved in diethyl ether and precipitated material was filtered. Organic solvent was dried over Na_2SO_4 and concentrated to give white solid material **2.13a** (167 mg, 95 %yield):

2.13a $[\alpha]_D^{25}$ +2.25 (*c* 0.5 MeOH), FT-IR (cm^{-1}): 3452, 3317, 2958, 2884, 1686, 1470, 1238, 1049. ^1H NMR (200MHz $CDCl_3/D_2O$ exchange): δ = 1.13 (m, 3H), 1.58 (m, 2H), 3.45-3.70 (m. 3H), 3.8- 4.0 (m, 2H), 5.05 (s, 2H), 7.29 (s, 5H). ^{13}C NMR (75MHz $CDCl_3$): δ = 25.9, 40.5, 60.7, 61.8, 63.5, 66.2, 68.8, 128.2, 128.5, 128.8, 135.4 and 155.1. LCMS (ESI-TOF): m/z for $C_{14}H_{21}NO_5$ $[M+H]^+$ 284.12.

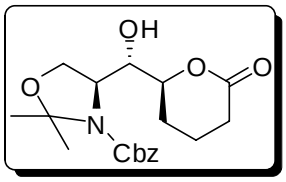


Benzyl (2*R*, 3*R*, 5*S*)-1,3,5-trihydroxyhexan-2-ylcarbamate (2.13b)

In the similar way, **2.15b** was converted in to **2.13b:**

2.13b $[\alpha]_D^{25}$ +6.56 (*c* 0.5 MeOH), FT-IR (cm^{-1}): 3452, 3317, 2958, 2884, 1686, 1470, 1238, 1049. ^{1}H NMR (200MHz $CDCl_3/D_2O$): δ = 1.13 (m, 3H), 1.58 (m, 2H), 3.45-3.70 (m. 3H), 3.8- 4.0 (m, 2H), 5.05 (s, 2H), 7.29 (s, 5H). ^{13}C NMR (75MHz $CDCl_3$): δ = 25.9, 40.5, 60.7, 61.8, 63.5, 66.2, 68.8, 128.2, 128.5, 128.8, 135.4 and 155.1. LCMS (ESI-TOF): m/z for $C_{14}H_{21}NO_5$ $[M+H]^+$ 284.17

(*S*)-Benzyl 4-((*S*)-hydroxy((*S*)-6-oxotetrahydro-2*H*-2-pyran-2-yl)methyl)-2,2-dimethyloxazolidin-3-carboxylate (2.16)

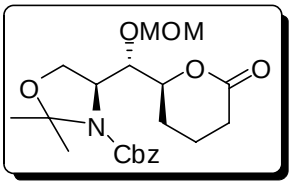


To a stirred solution of compound **2.10d** (700 mg, 2.02 mmol) in dry CH_2Cl_2 (30 mL) at 0^oC were added *m*-CPBA (55% activity; 1.0 g, 6 mmol), $NaHCO_3$ (508 mg, 6 mmol) and the solution was stirred at room temperature for 4 h and than added another portion of same amounts of *m*-CPBA and $NaHCO_3$ with stirring for additional 8 h. After completion of reaction the excess of *m*-CPBA was quenched with aq $Na_2S_2O_3$. The insoluble material was removed by filtration and washed with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were washed with saturated $NaHCO_3$, brine solutions and dried over Na_2SO_4 and concentrated under reduced pressure, the resulting pasty mass was purified by column chromatography (pet ether: EtOAc, 3:2) to give **2.16** (625 mg, 85% yield) as a colorless pasty liquid, which gets solidified on freezing.

2.16 $[\alpha]_D^{25}$ -14.20 (*c* 0.70, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.42-1.75 (m, 8H), 1.75-2.01 (m, 2H), 2.52 (m, 2H), 3.41-3.62 (m, 3H), 2.98-3.105 (m, 1H), 3.63-3.84 (m, 3H), 4.06 (m, 1H), 4.27 (m, 1H), 5.13 (dd, *J* = 12.5, 2H), 7.35 (s, 25H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.33, 22.83, 24.25, 26.33, 29.48, 60.13, 63.45, 67.10, 78.94, 81.29, 93.70, 128.13, 128.22, 128.51, 135.97, 152.59, 170.62. LC-MS (ESI-TOF): m/z

$C_{19}H_{25}NO_6$ $[M+H]^+$ 364.18, $[M+Na]^+$ 386.01. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.77; H, 6.89; N, 3.91.

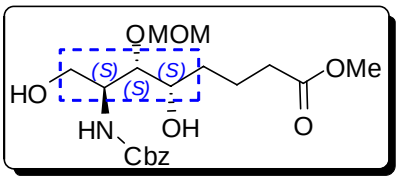
(*S*)-Benzyl-4- ((*S*)-(methoxymethoxy)((S)-6-oxotetrahydro-2*H*-2-pyran-2-yl)methyl)-2,2-dimethyloxazolidin-3-carboxylate (2.17)



To a stirred solution of compound **2.16** (0.6 g, 1.65 mmol) and diisopropylethyl amine (DIPEA) (0.27g, 2.14 mmol) in dry CH_2Cl_2 (8mL) was added MOMCl (0.16g, 1.98 mmol) at 0°C. The resulting reaction mixture was stirred further for overnight at rt. After completion of the reaction, the solvent was evaporated and residue was chromatograph over silica gel to give compound **2.17** (0.58g, 87% yield) as a colorless pasty liquid.

2.17 $[\alpha]_D^{25}$ -5.85 (*c* 0.6, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.41-1.65 (m, 10H), 2.28-2.62 (m, 2H), 3.37 (s, 3H), 3.85-4.15 (m, 3H), 4.20-4.48 (m, 2H), 4.69 (dd, *J* =6.5 Hz, 2H), 5.15 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.43, 22.93, 24.35, 25.96, 29.59, 56.42, 58.62, 63.56, 67.20, 79.05, 80.96, 93.80, 98.55, 128.23, 128.32, 128.61, 136.08, 152.54, 170.72. LC-MS (ESI-TOF): m/z $C_{21}H_{29}NO_7$ $[M+H]^+$ 408.05, $[M+Na]^+$ 430.03. Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.97; H, 7.14; N, 3.49.

(5*S*,6*S*,7*S*)-methyl 7-(benzyloxycarbonylamino)-5,8-dihydroxy-6-(methoxymethoxy)octanoate (2.14)



To a solution of compound **9** (0.5 g, 1.23 mmol) in MeOH 10 mL), was added K_2CO_3 in catalytic amount and stirred at rt. The reaction reached to completion in about 2 h, monitored by TLC. This reaction was quenched with the excess of dilute HCl and

additionally stirred for 2 h at the same temperature. The solvent was evaporated under reduced pressure and passed through a small pad of column to give white solid compound **1** (0.37 g, 76% yield) after two steps.

2.14 $[\alpha]_D^{25}$ -6.58 (*c* 0.7, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.45-1.78 (m, 4H), 2.15-2.30 (m, 2H), 3.36 (s, 3H,) 3.68 (s, 3H), 3.75-4.02 (m, 2H), 4.10-4.45 (m, 3H), 4.65-4.75 (m, 2H), 5.18 (s, 2H), 7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3/D_2O$): δ = 18.33, 30.93, 33.78, 50.35, 53.35, 56.31, 63.45, 67.10, 68.99, 86.90. 98.44, 128.05, 128.22, 128.51, 135.97, 153.56, 173.55. Anal. Calcd for $C_{19}H_{29}NO_8$: C, 57.13; H, 7.32; N, 3.51. Found: C, 57.18; H, 7.29; N, 3.59.

2.5 References

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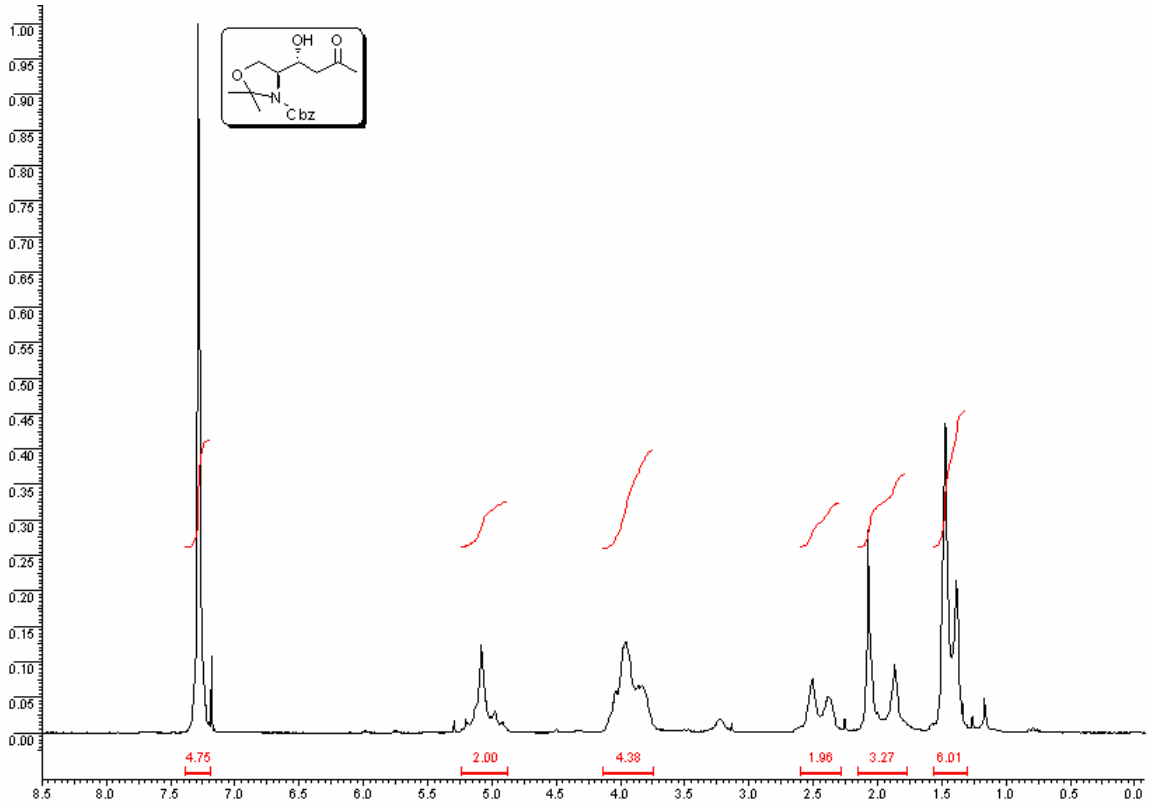
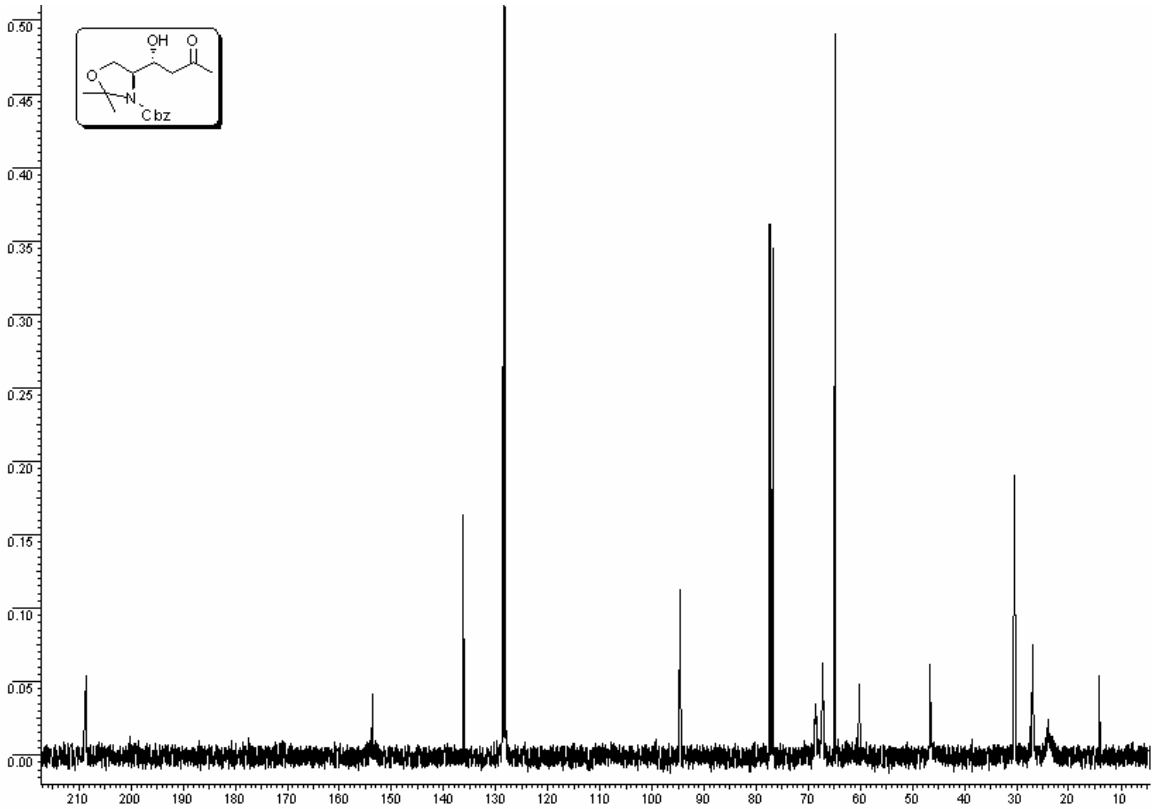
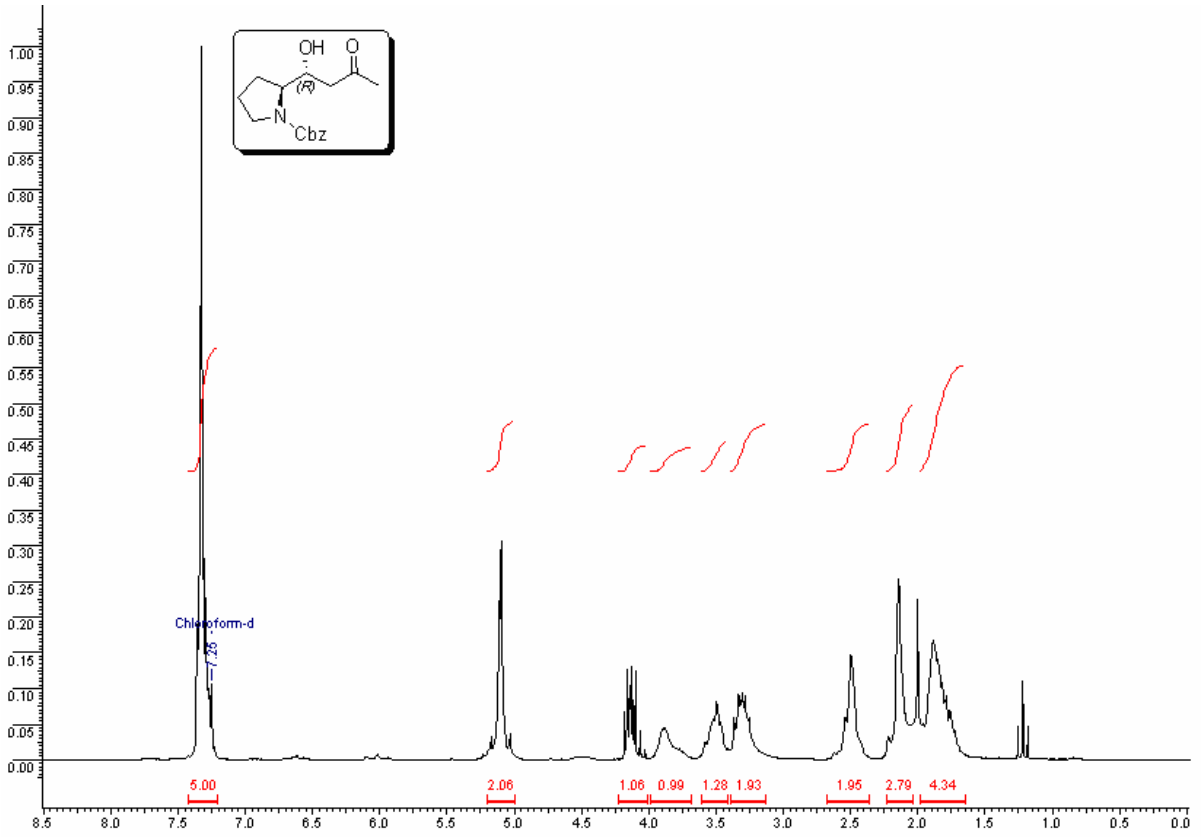
2.6 Spectral Data of Selected Compounds



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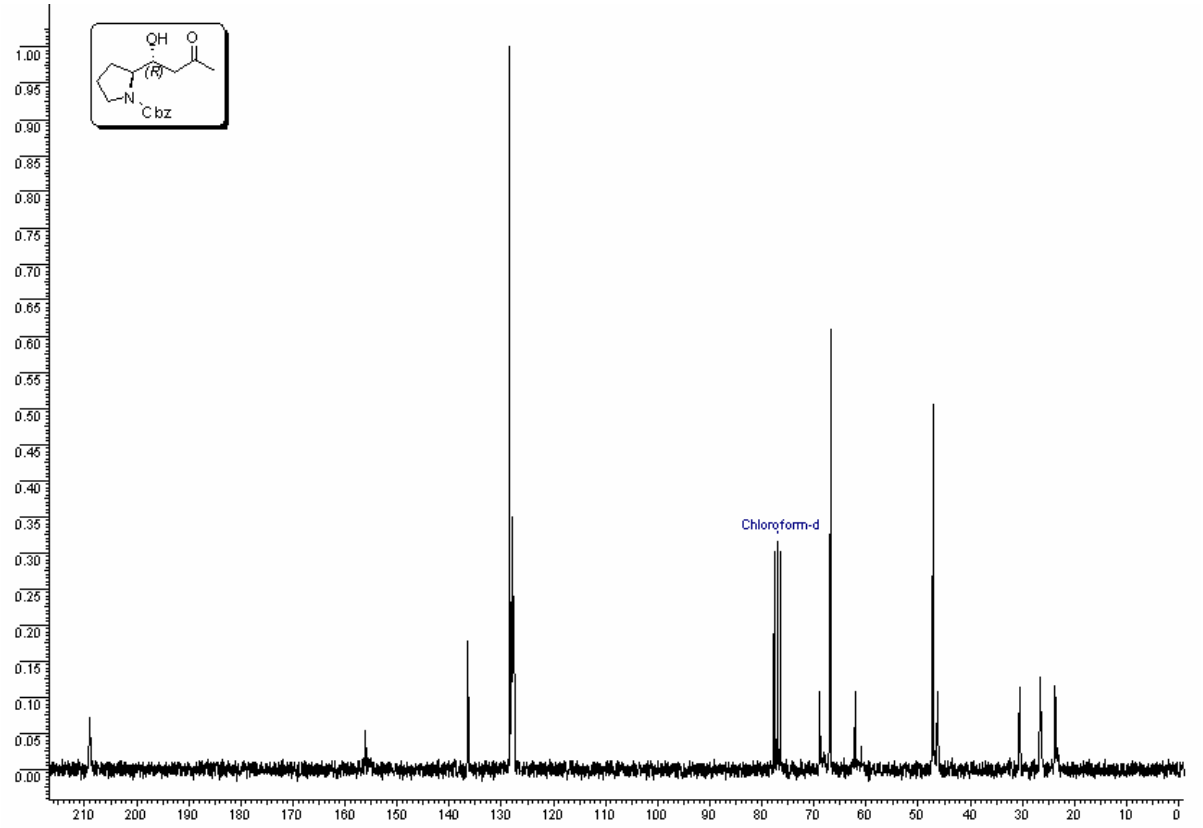
4.34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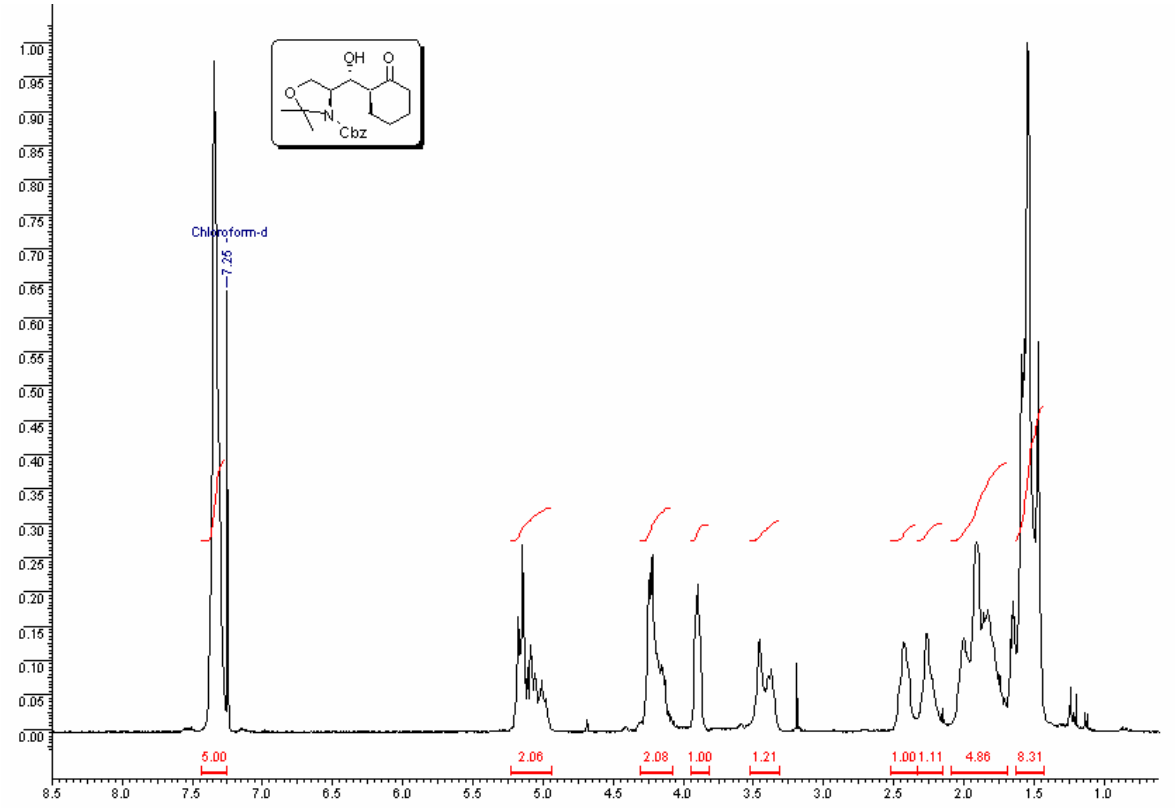
Chloroform-d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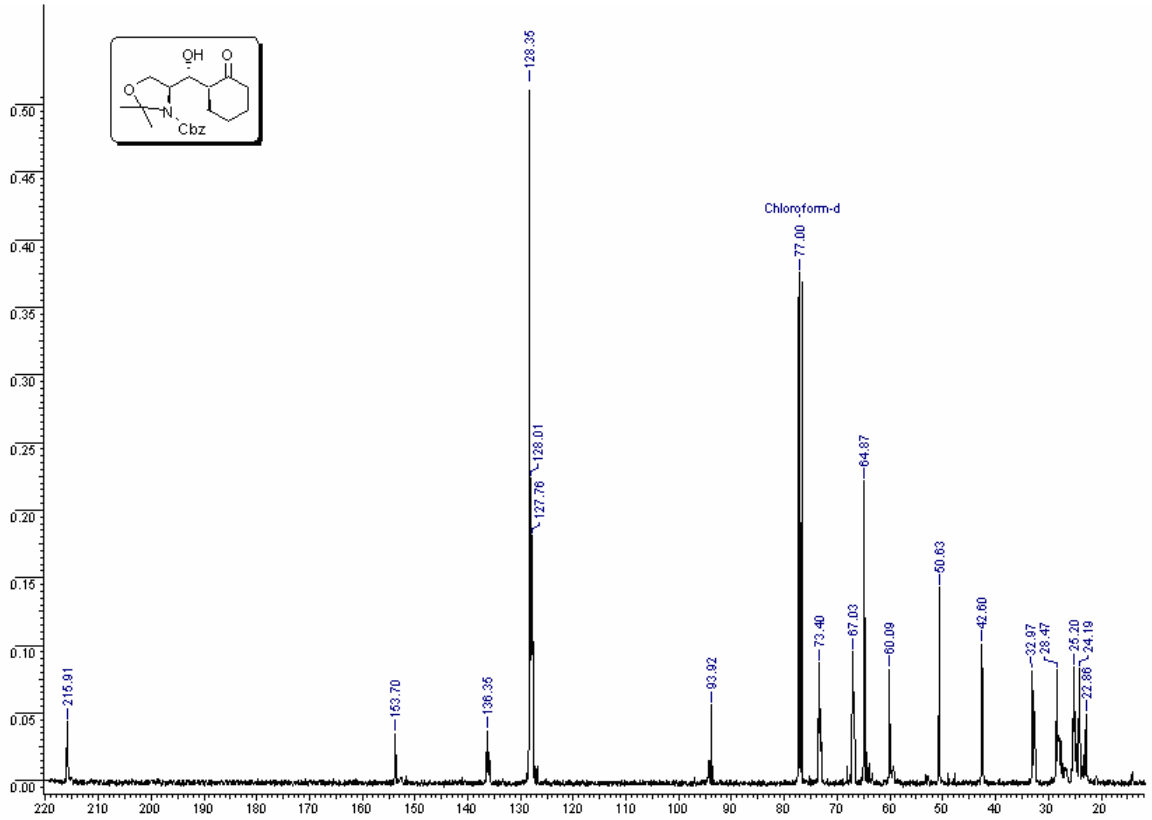
8.31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60.63
42.60
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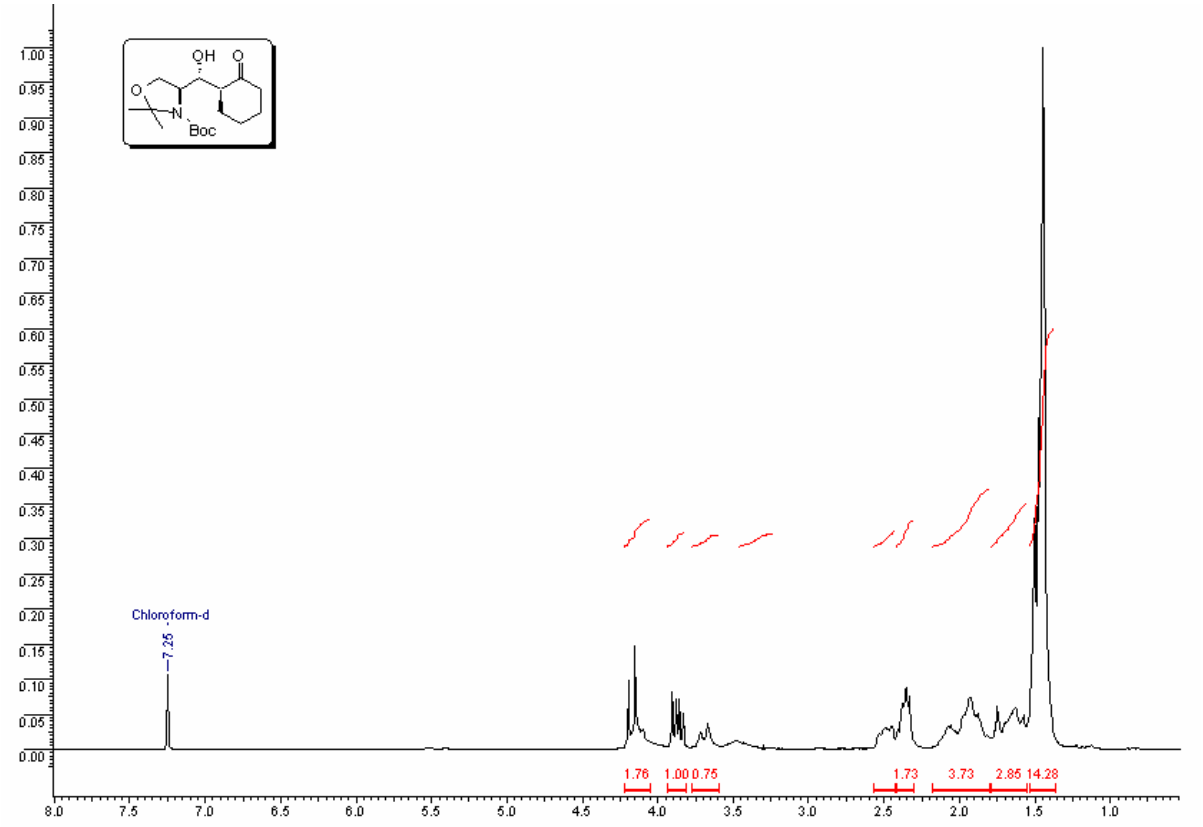
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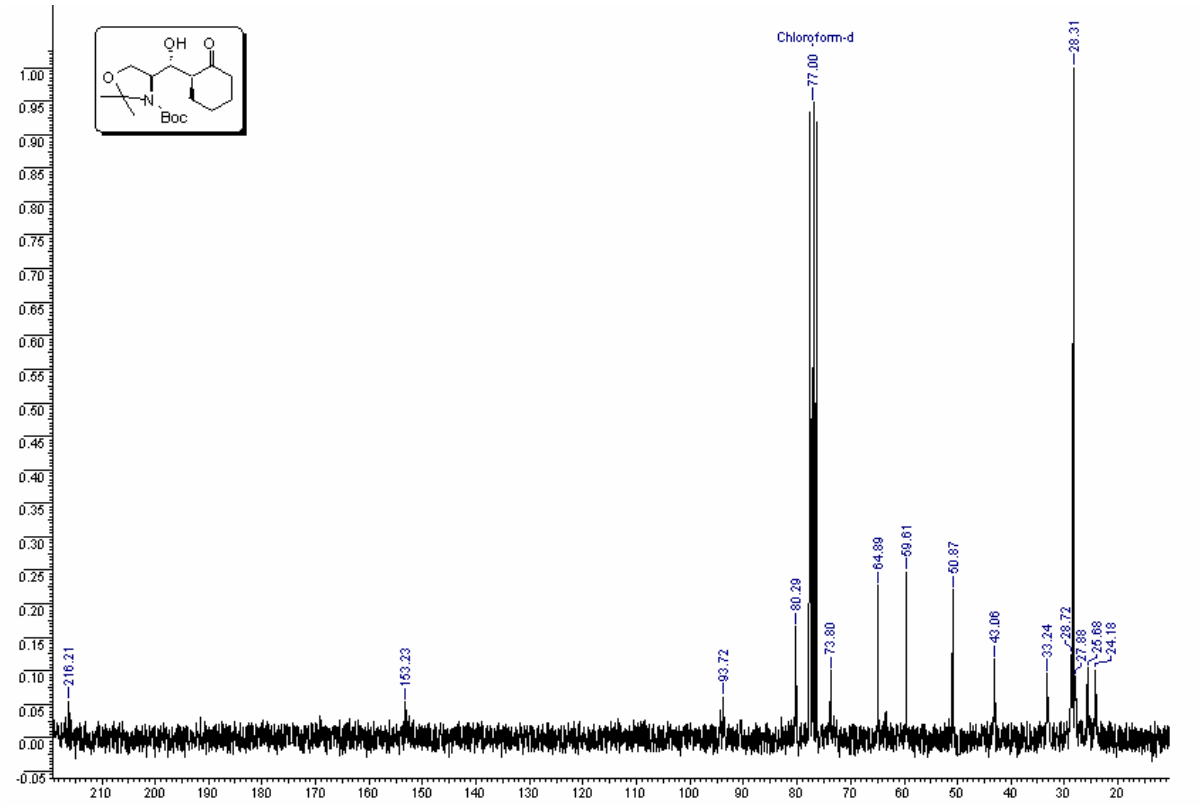
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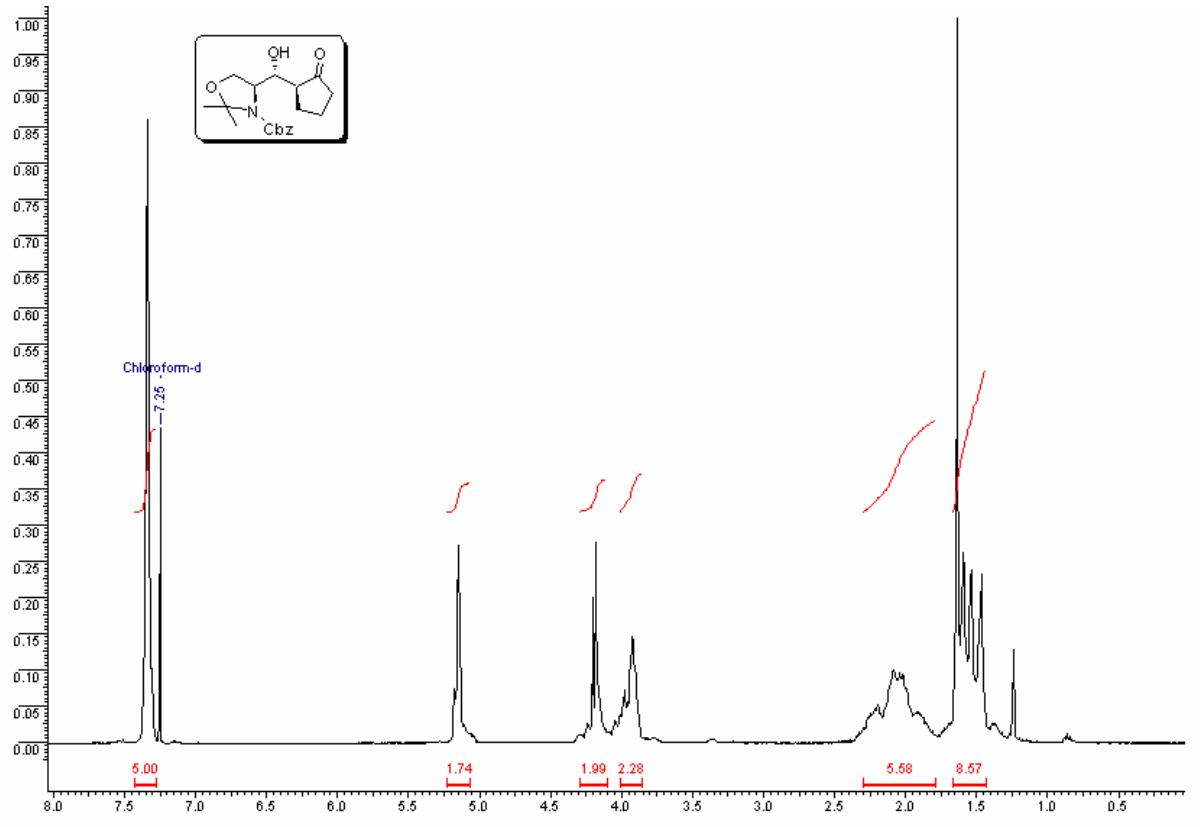
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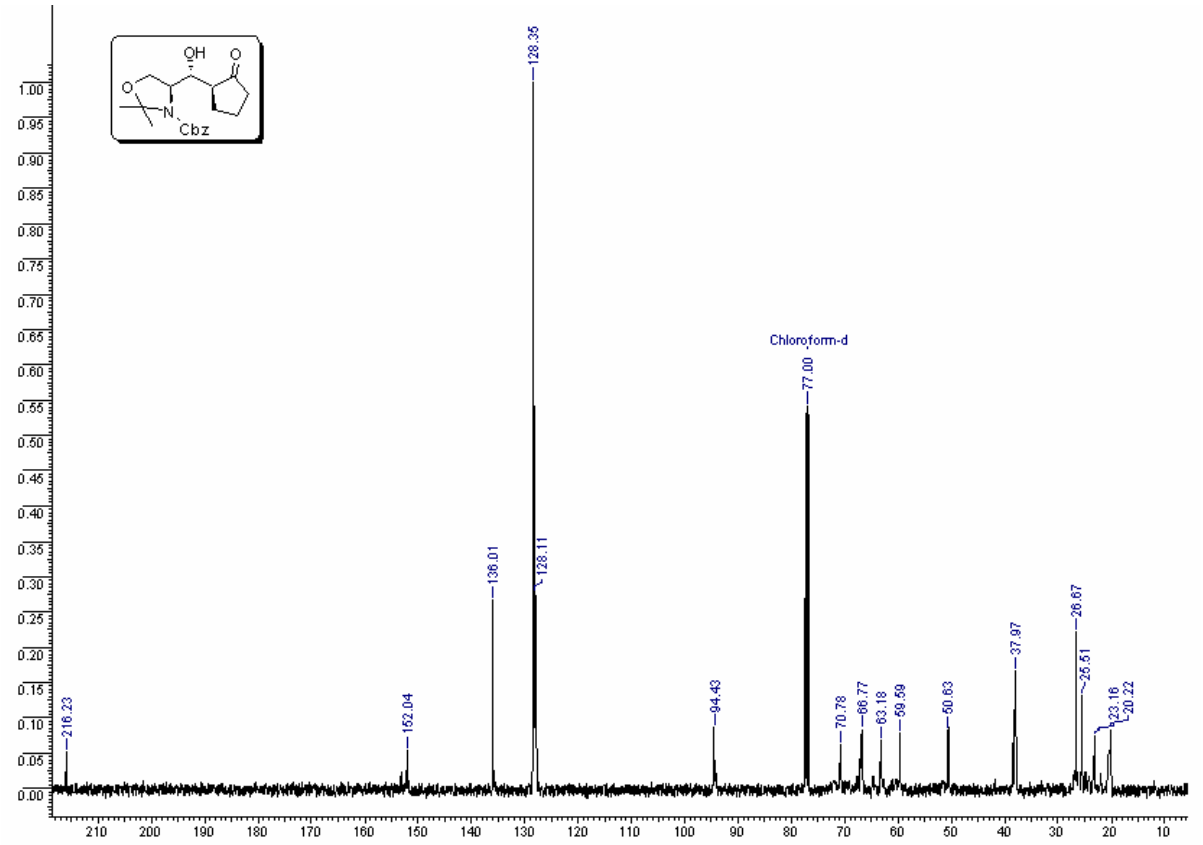
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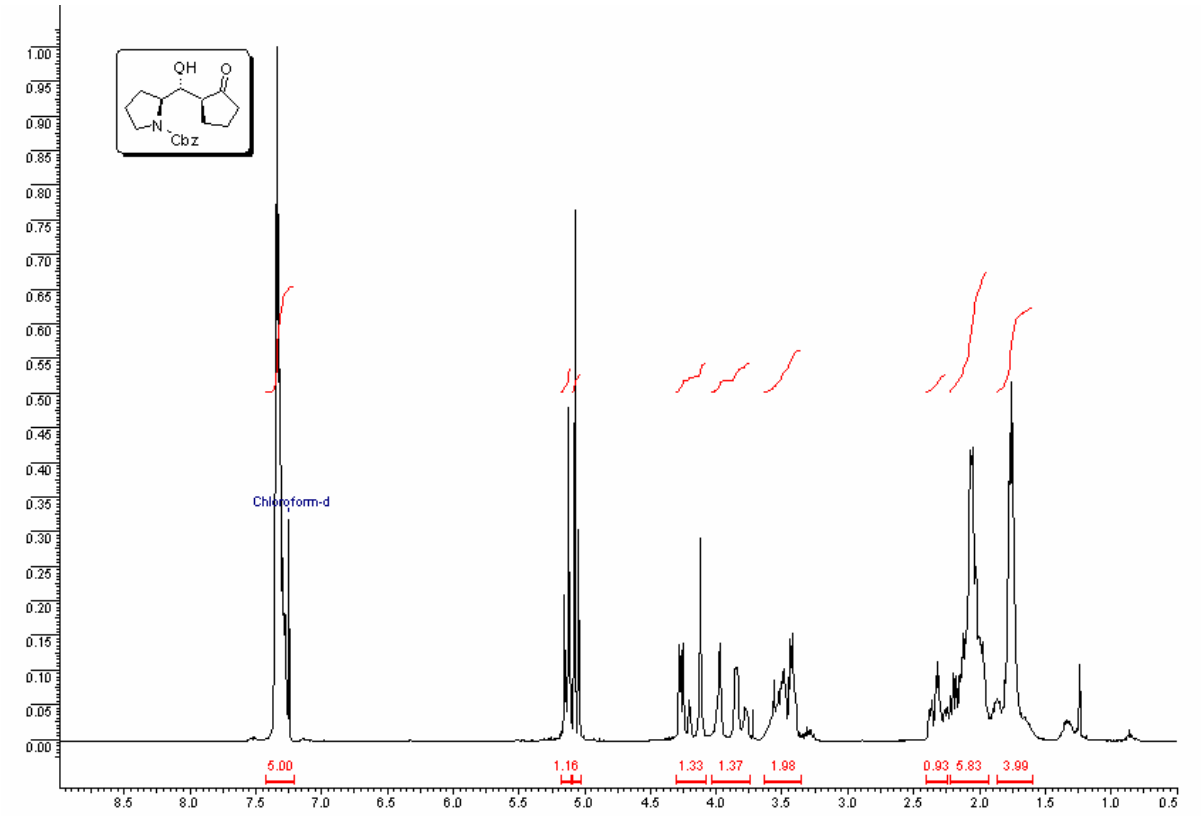
20.22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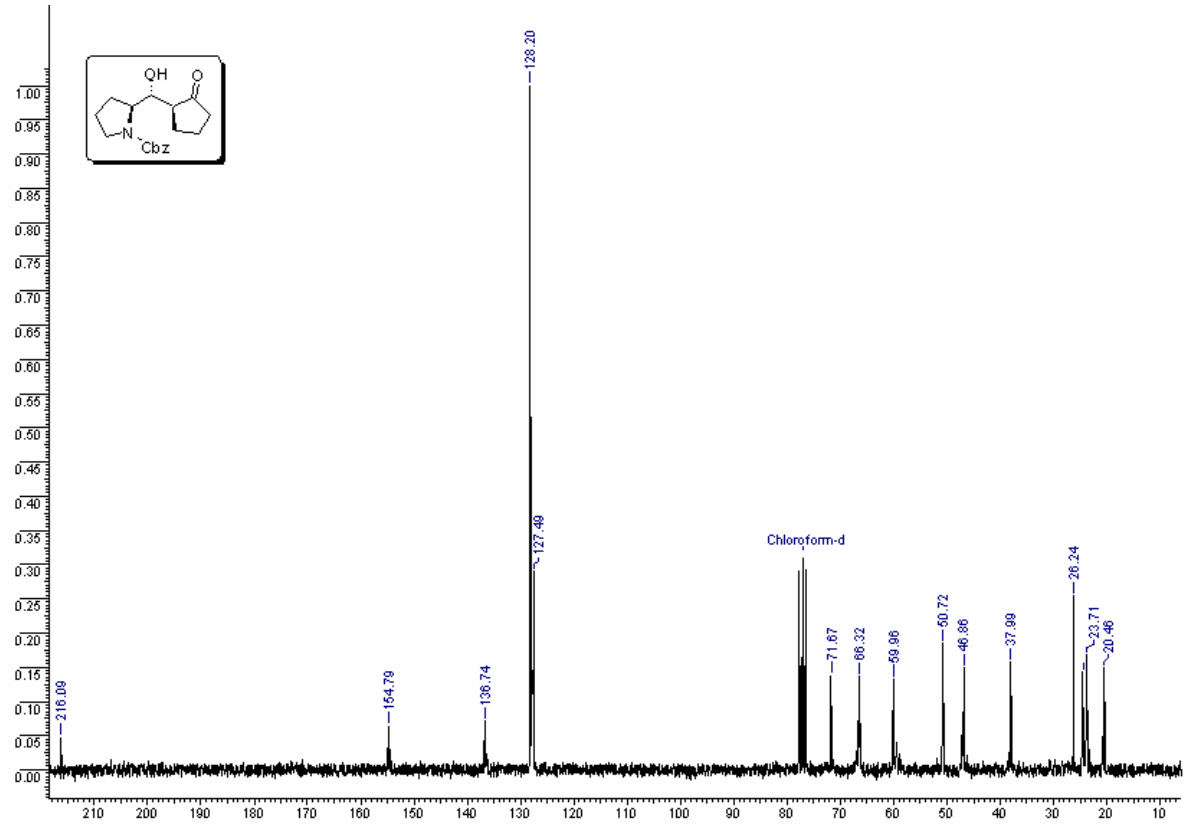
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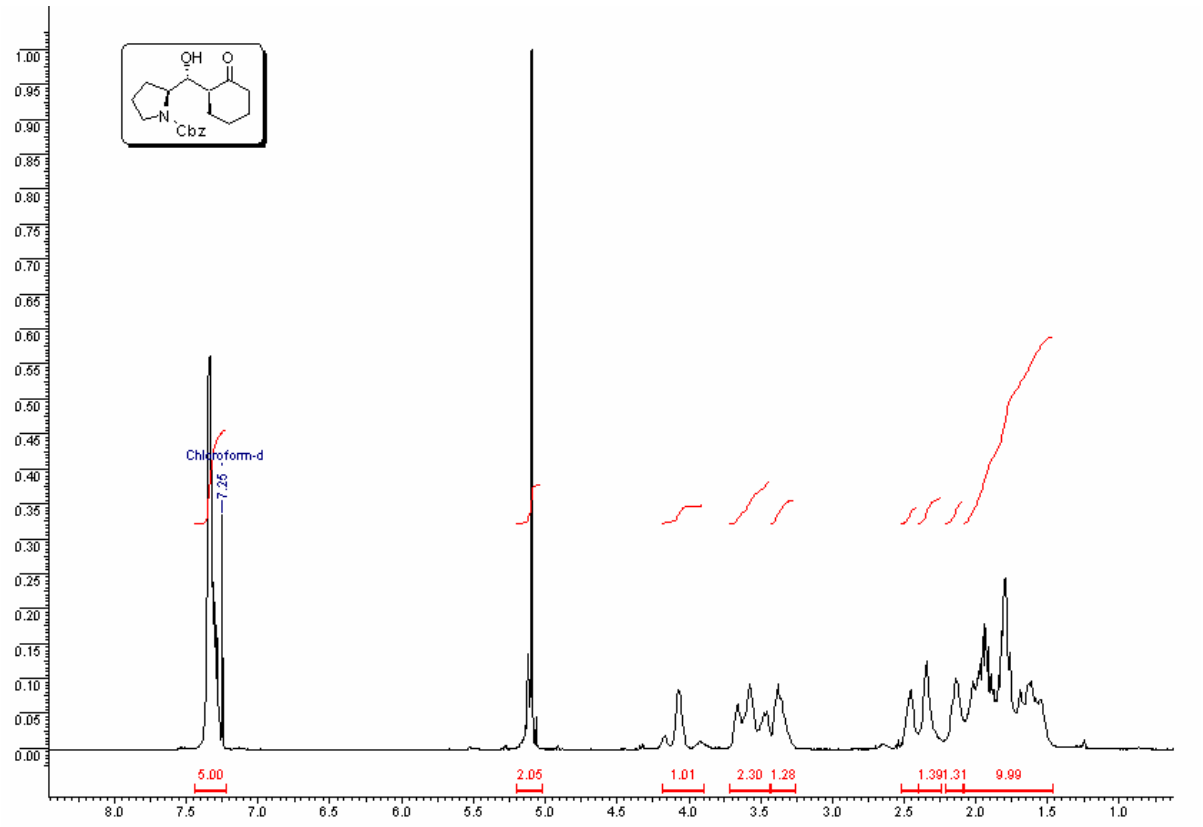
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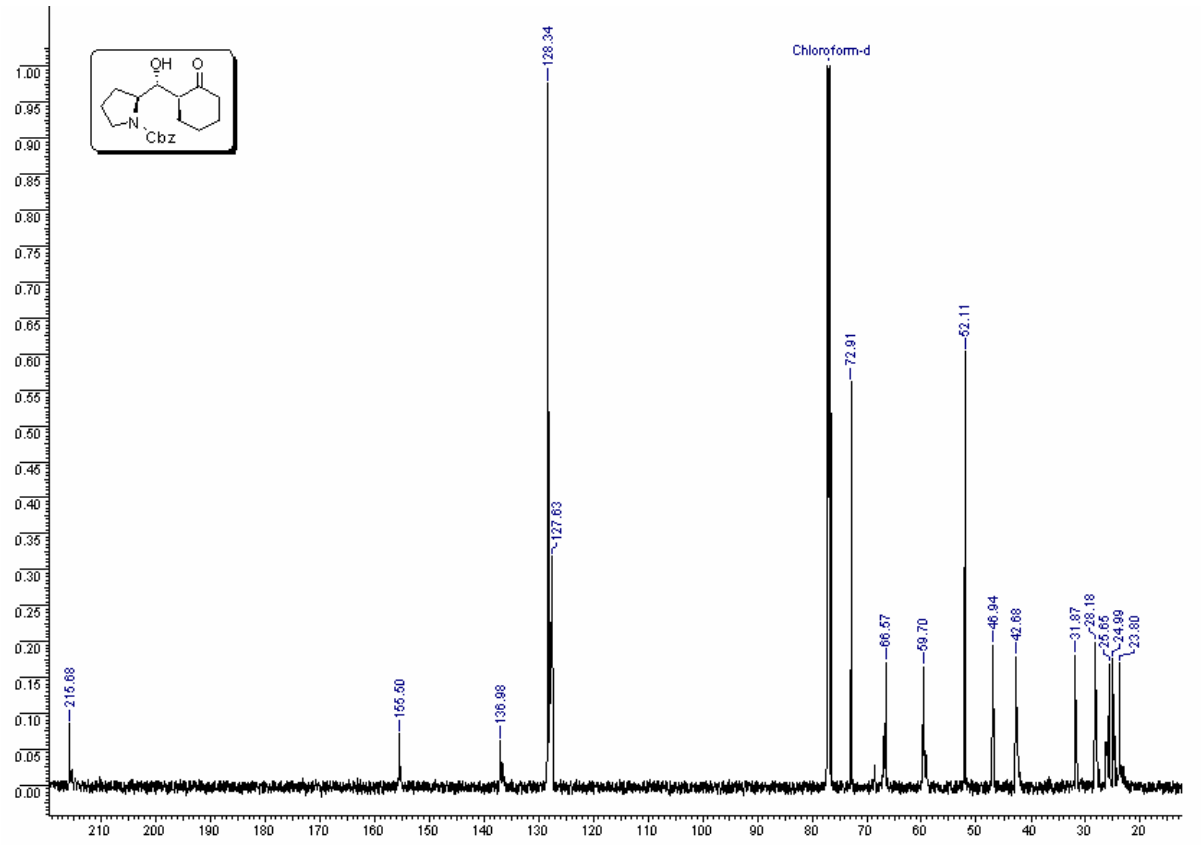
9.99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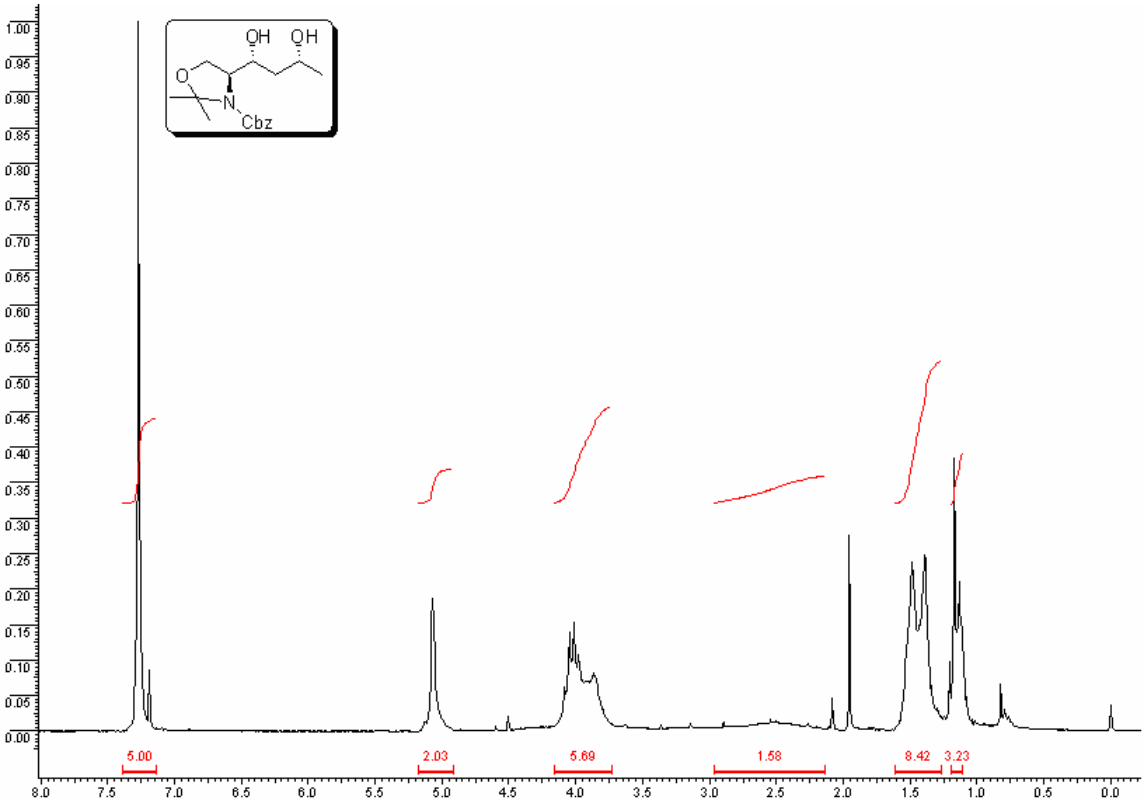
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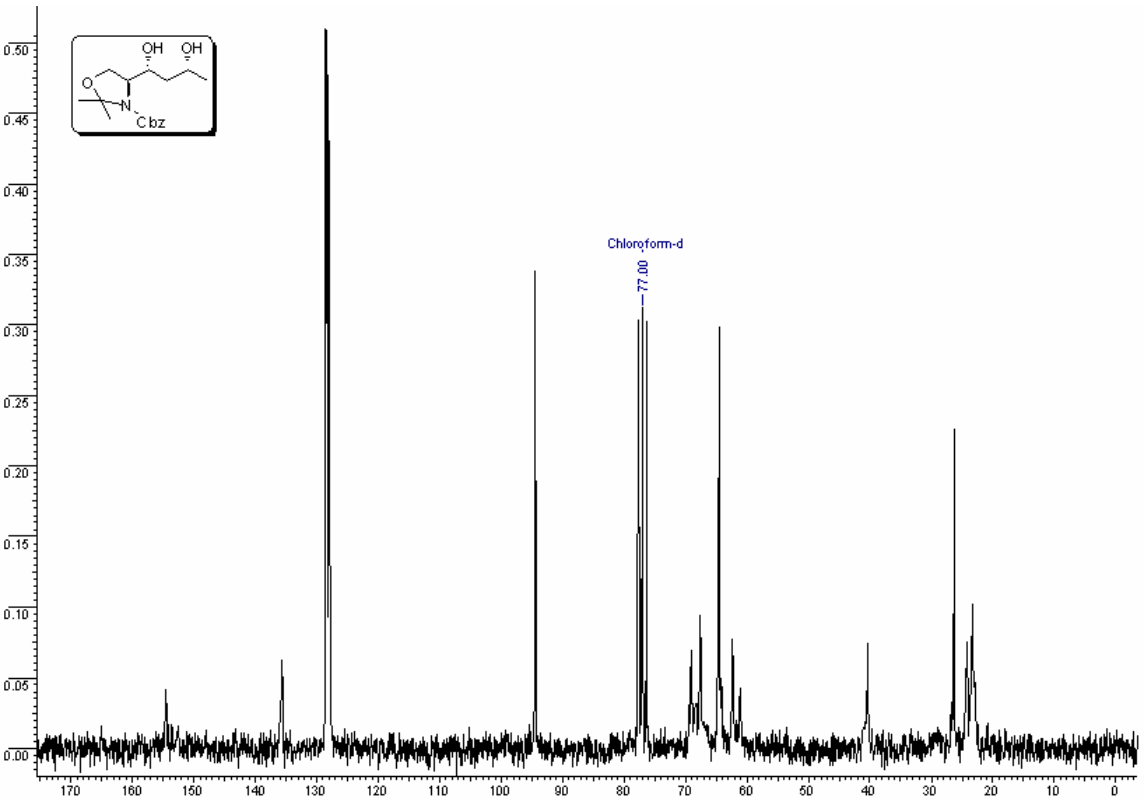
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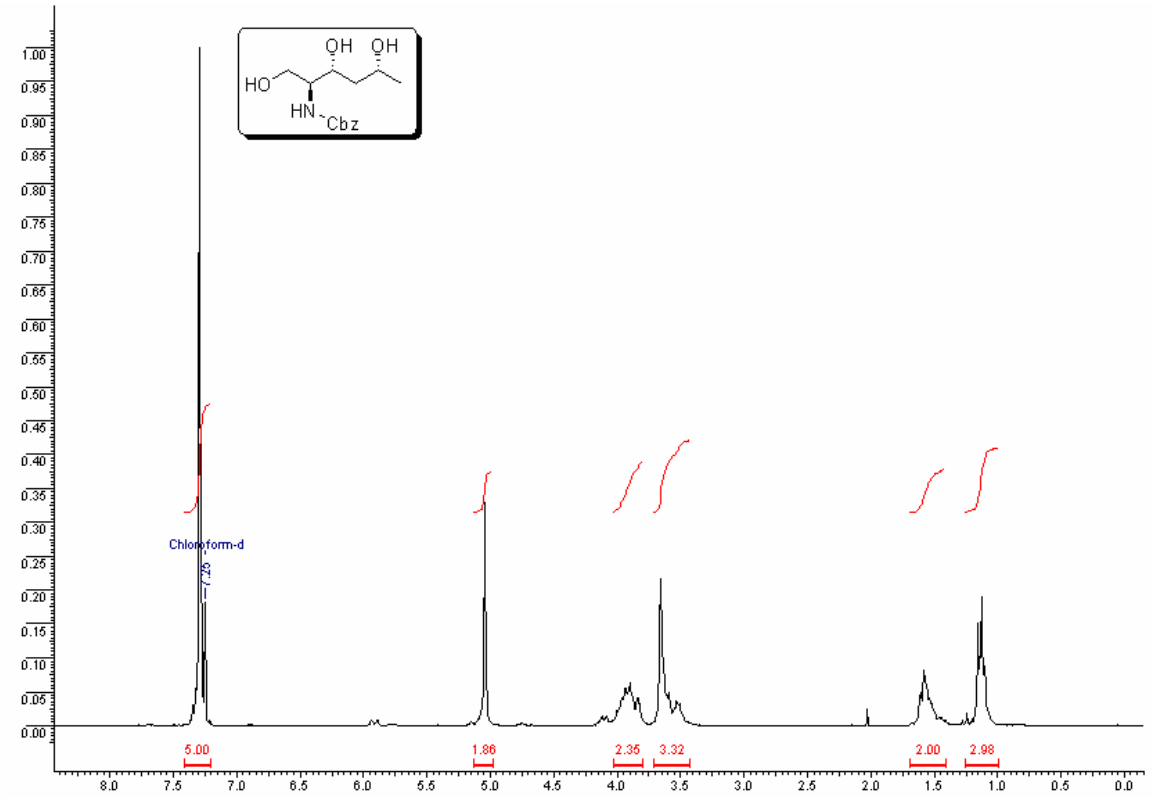
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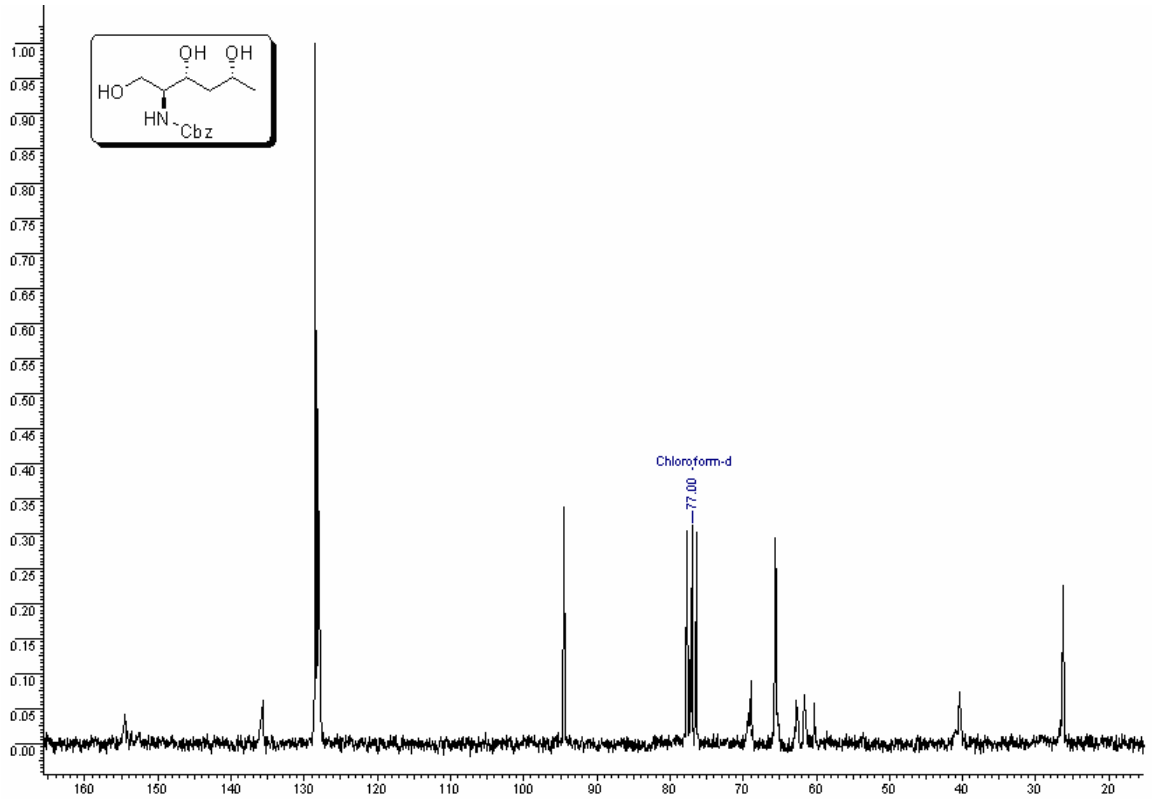
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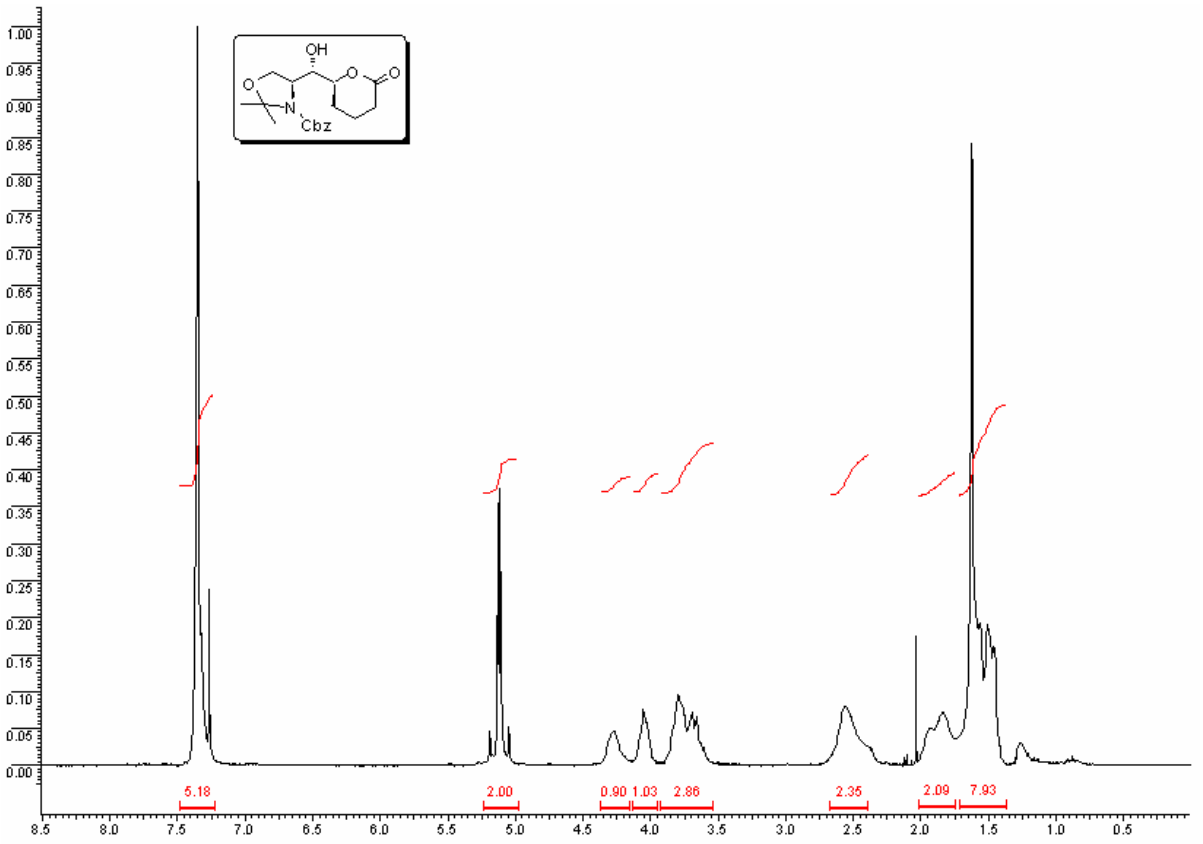
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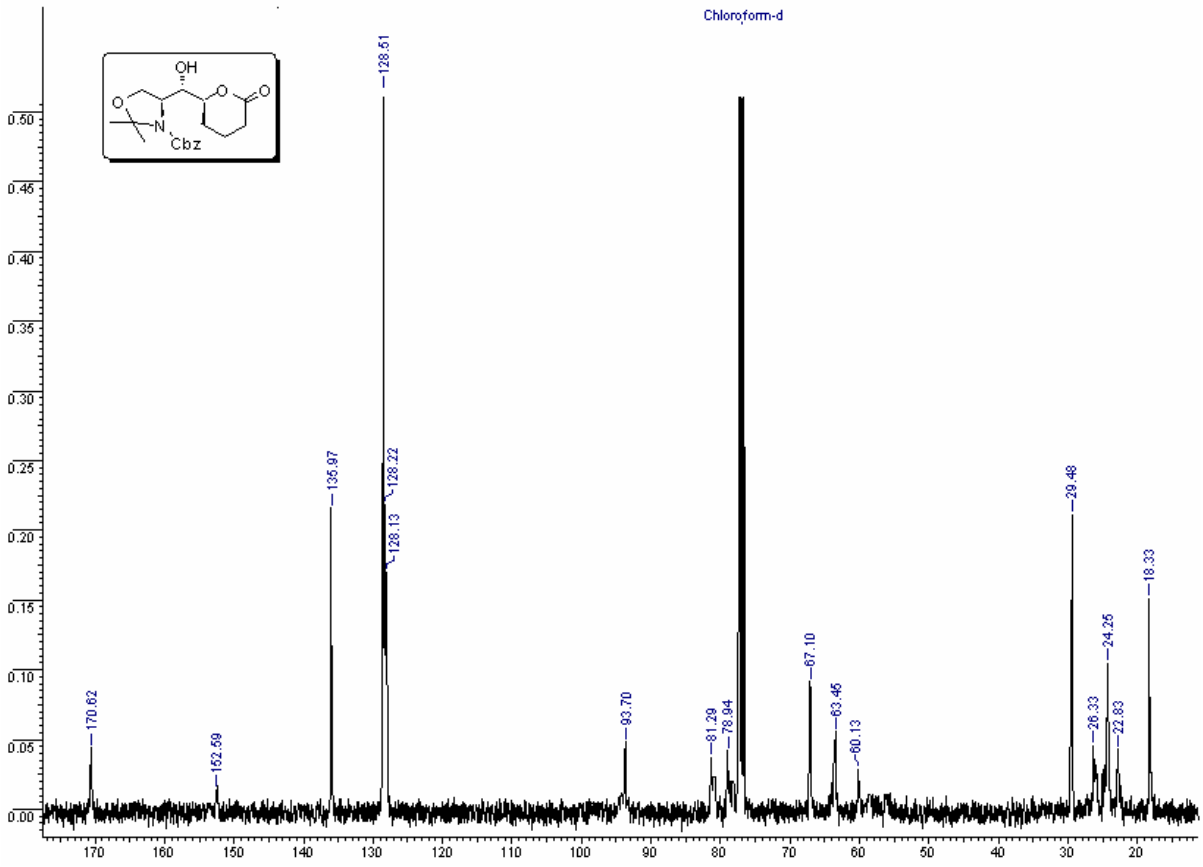
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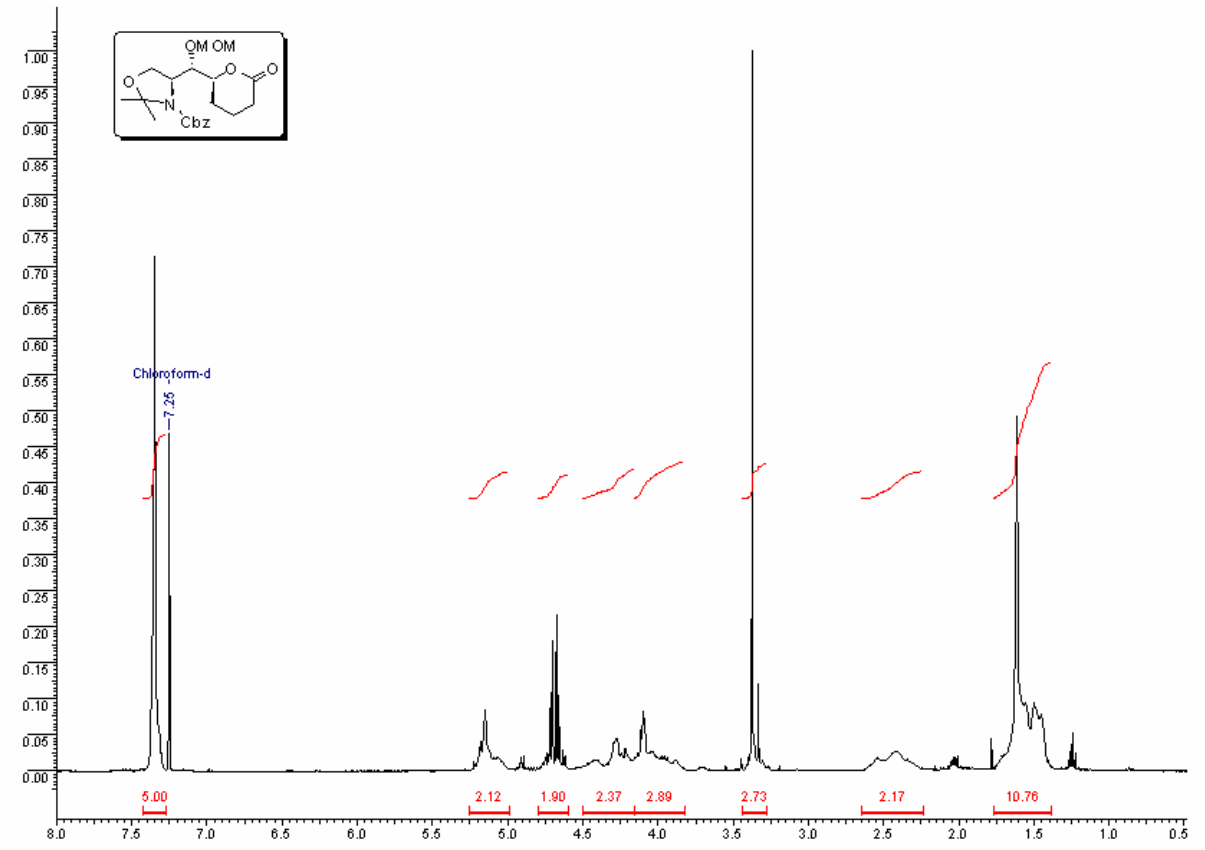
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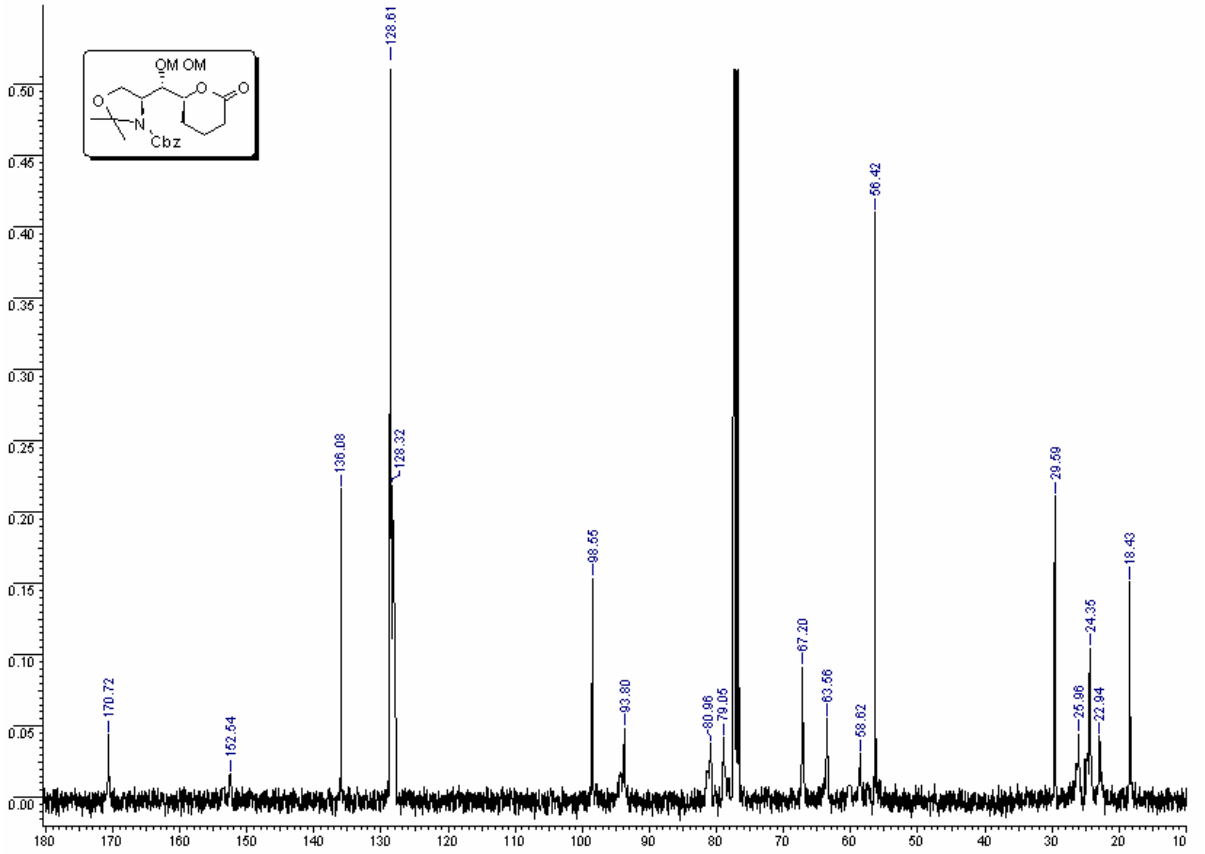
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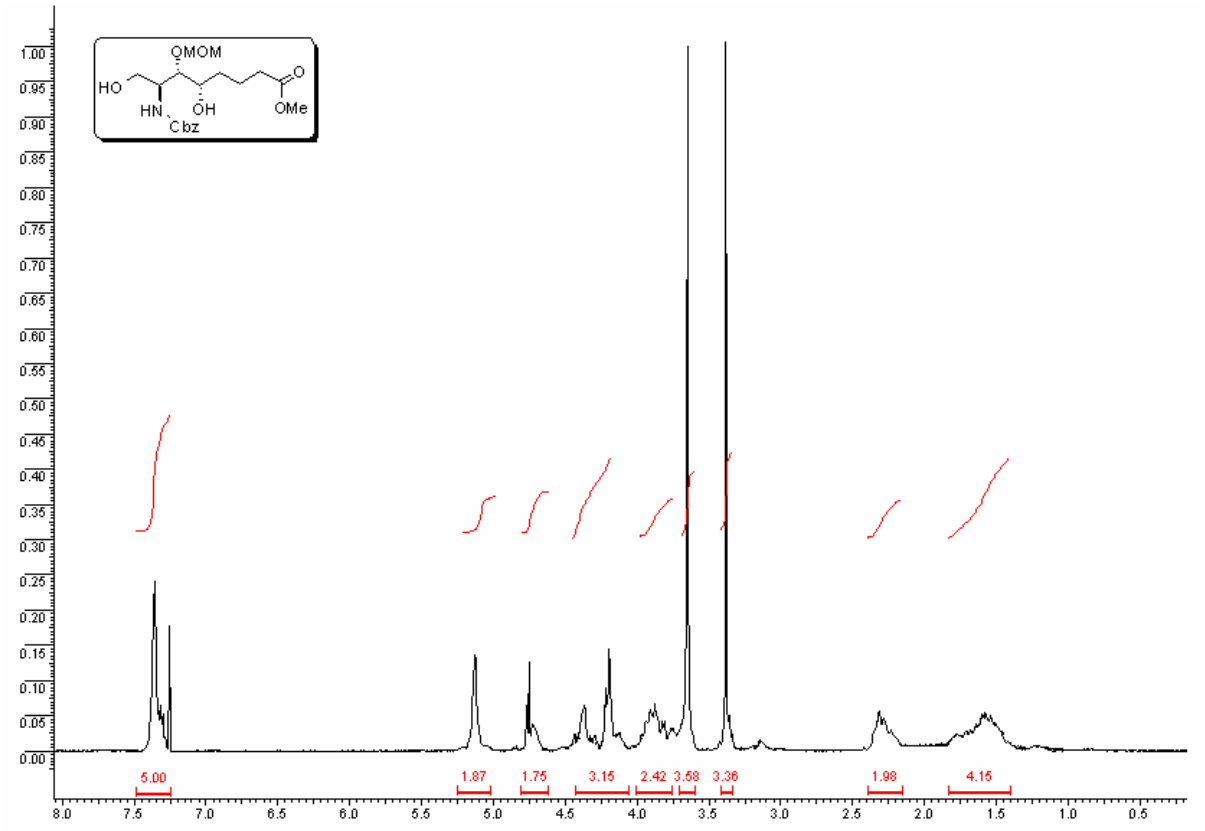
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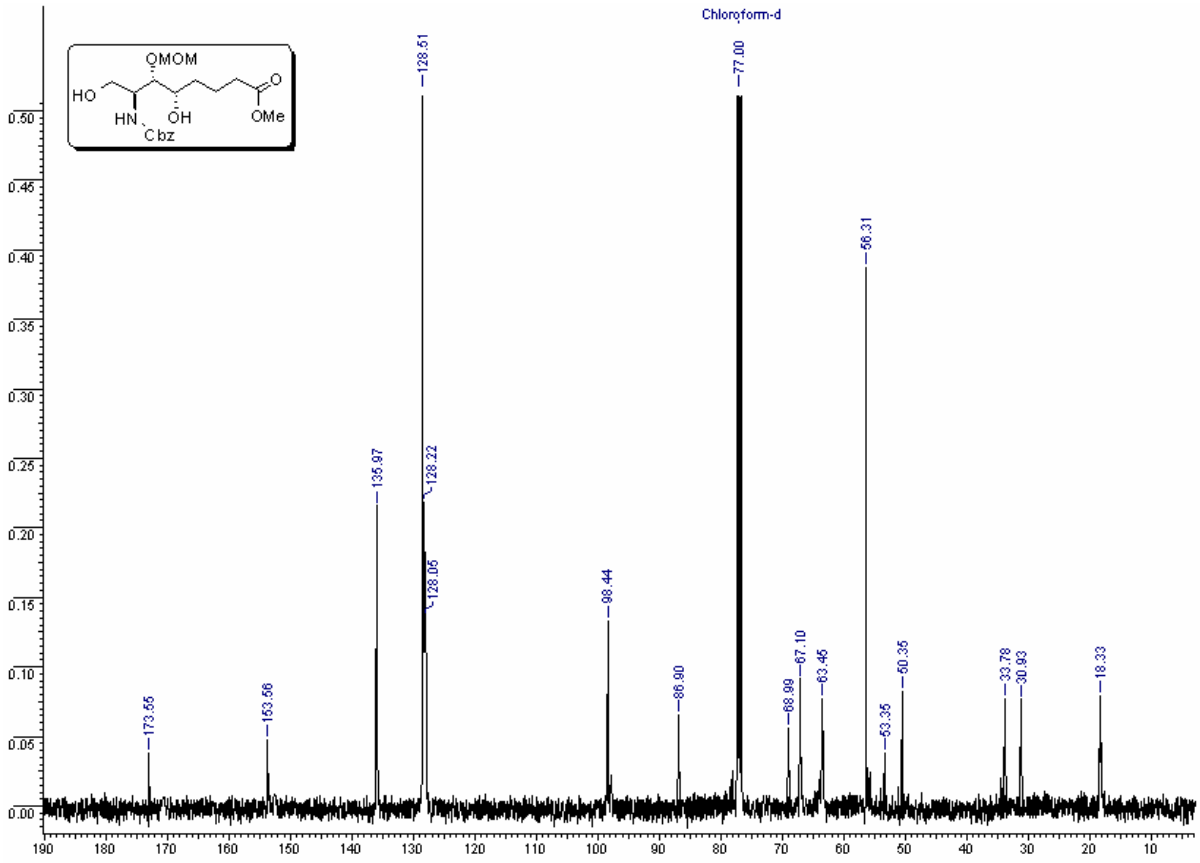
1.98
4.15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98.44
86.90
77.00
68.99
67.10
63.45
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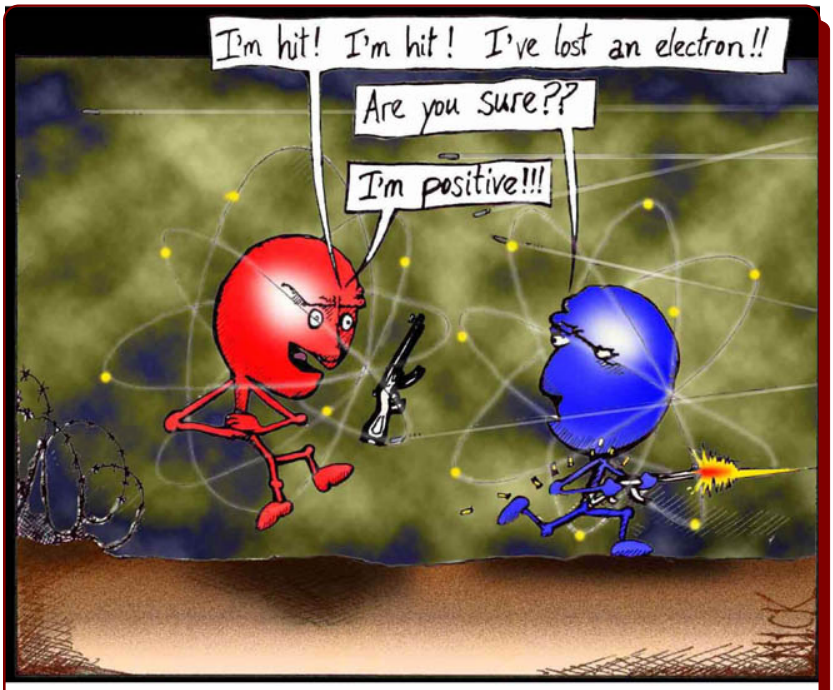
33.78
30.93
18.33

Chapter 3

Direct Organocatalytic *Enolexo* Aldolization: Synthetic study towards 1-*N*-Imino sugars



Another casualty in the War of the Atoms.

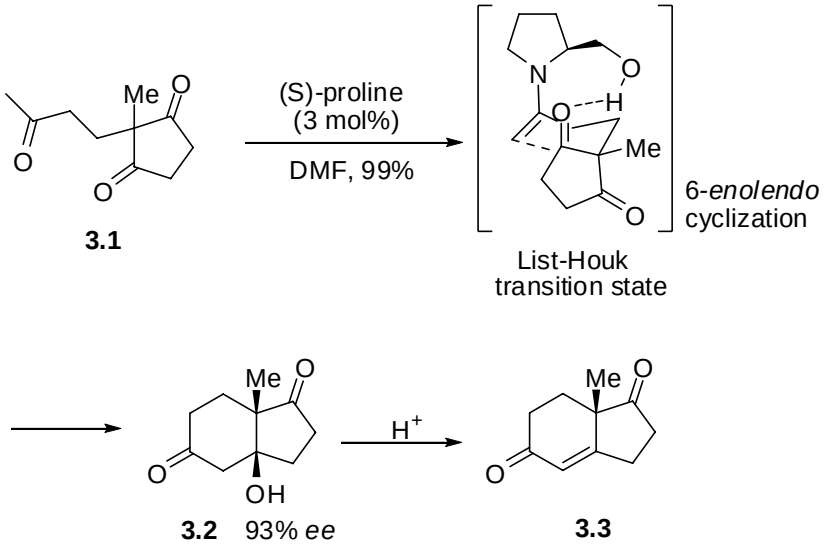
"The most beautiful and most profound emotion we can experience is the sensation of the mystical. It is this sower of all true science. He, to whom this emotion is a stranger, who can no longer wonder and stand rapt in awe, is as good as dead"

-"Albert Einstein"

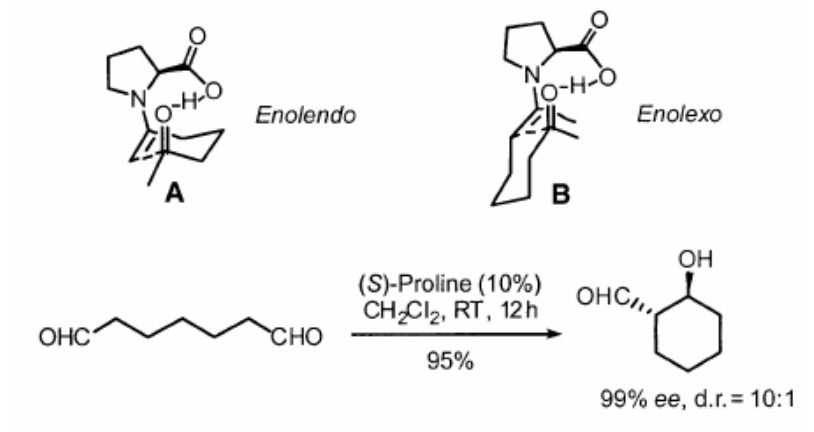
3.1 Introduction

In the year 2000, List and co-workers developed the first proline catalyzed direct asymmetric aldol reaction taking place in an intermolecular fashion.[1] After this discovery, this reaction has been studied most extensively in last few years with several different types of organocatalysts and has been applied for the synthesis of bioactive natural products.[2] While, the proline catalyzed intramolecular aldol reaction of triketones **3.1** was developed independently by two industrial groups, Hajos and Parrish at Hoffmann-La Roche[3] and Eder, Sauer and Wiechert at Schering[4] in early 1970s. This reaction is a powerful method for the synthesis of bicyclic compounds in good yield with an excellent enantioselectivity. These carbocyclic compounds, **3.2** and **3.3** are extremely important intermediates for the synthesis of many natural products particularly the steroids.[5] However, the scope of this intramolecular aldol reaction has not been explored so well as has been done for the intermolecular aldol reaction. The mechanism of intramolecular aldol was also poorly understood and still remains the subject of research.[6] However, the transition state as a result of work of List and Houk[7] has been accepted to explain the probable mechanism of intramolecular aldol reaction as shown in Scheme 3.1. From the suitability of the starting material, this intramolecular aldolization can formally be considered for a 6-*enolendo* cyclization, with the enamine C-C bond constituting part of the newly formed carbocycle. The first catalytic asymmetric 6-*enolexo* aldol reaction involving the intramolecular aldolization was developed in 2003 by List and coworkers and also reported a variety of dienal systems which furnished the synthesis of chiral cyclohexanecarbaldehydes catalyzed by proline in excellent enantioselectivity (Scheme 3.2).[8] In this *enolexo* process, the enamine C-C bond is not constituting the part of the

newly formed carbocycle, as it is shown by two different transition states **A** and **B**, in Scheme 3.2.



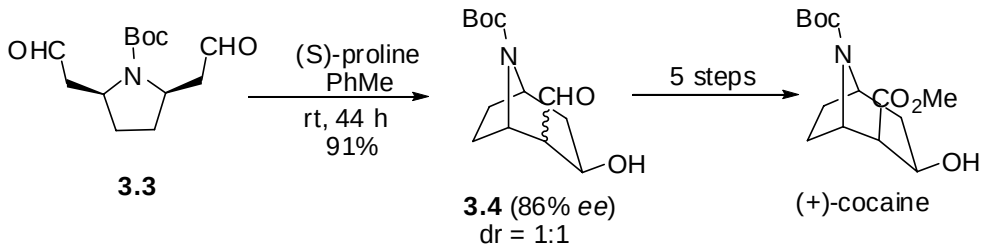
Scheme 3.1: Intramolecular *enolendo* aldolization reaction



Scheme 3.2: First 6-*enolexo* aldolization catalyzed by proline

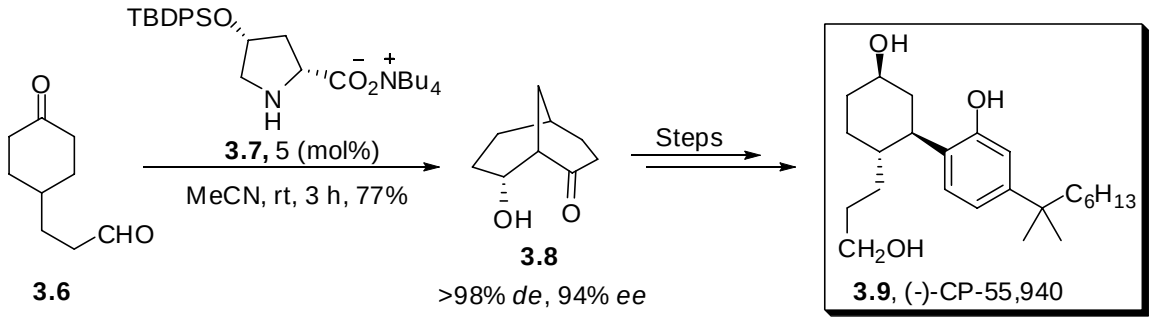
This process is particularly appropriate for the desymmetrization of *meso* compounds,[9] which was further explored by Pearson and Mans for the synthesis of (+)-cocaine.[10] The treatment of *meso*-dialdehyde **3.4** with 10 mol% of (*S*)-proline gave a mixture of epimers

in 91% yield as a tropane skeleton **3.5**, which was suitable for its further transformation in to (+)-cocaine as shown in Scheme 3.3.



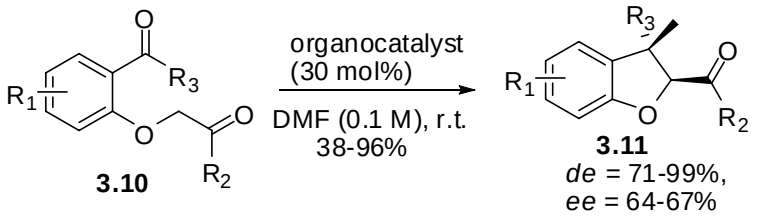
Scheme 3.3: Enolexo aldolization. Application for the synthesis of (+)-cocaine

Iwabuchi and coworkers have developed an intramolecular *enolexo* aldolization-based desymmetrization of σ-symmetric 4-substituted cyclohexanones (keto-aldehyde) **3.6** as shown in Scheme 3.4. With 5mol % of siloxyproline ammonium salt **3.7** as a catalyst, the desired bicyclic[3.3.1]alkanone **3.8** was obtained in 77% yield and with 94% *ee*. This material was used in the total synthesis of the cannabinoid receptor agonist (-)-CP55,940 **3.9** (Scheme 3.4).[11]



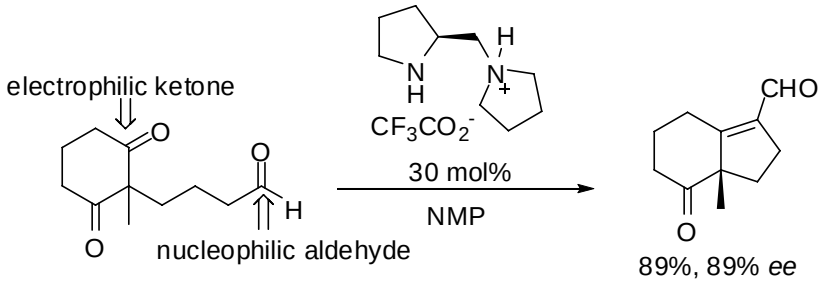
Scheme 3.4: Intramolecular aldolization for (-)-CP-55,940

Recently, Enders and coworkers developed the organocatalytic intramolecular 5-*enolexo* aldolization of keto-aldehyde **3.10** with *syn*-selectivity, for the synthesis of dihydrobenzofuranols **3.11** as a new entry to the coumarine natural products (Scheme 3.5).[12]



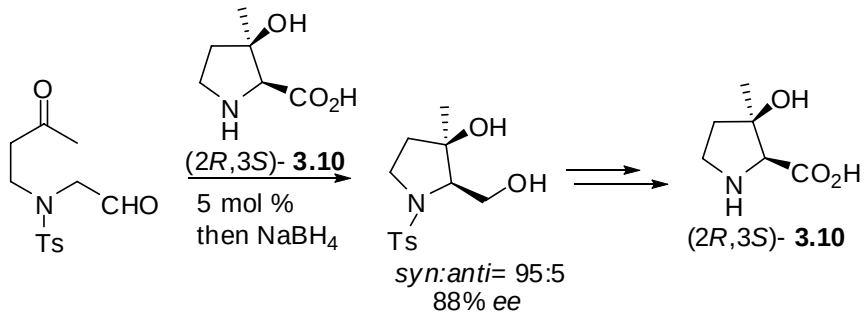
Scheme 3.5: Intramolecular 5-*enolexo* aldolization reaction for dihydrobenzofuranols

In general, aldehydes are more reactive than ketones as electrophiles. Thus, in most of the direct asymmetric aldol reactions catalyzed by organocatalysts, ketones are used as donors, while aldehydes are used as the acceptors. The reverse combination, in which an aldehyde is used as a donor and ketone is employed as an acceptor, is very rare. For example, very recently Hayashi and his coworkers disclosed a direct intramolecular enantioselective aldol reaction, in which aldehyde and ketone act as a donor and an acceptor, respectively (Scheme 3.6).[13]



Scheme 3.6: Intramolecular aldolization of keto-aldehyde with reverse reactivity

Similar results of intramolecular aldolization of keto-aldehyde were reported by the Hamada and coworkers, for the organocatalytic synthesis of (2*S*,3*R*)-3-Hydroxy-3-methyl-proline using proline derivative **3.10** as an organocatalyst.[14] In this process, intramolecular aldolization takes place in 5-*enolexo* fashion with high *syn*-selectivity as shown in Scheme 3.7.



Scheme 3.7: Organocatalytic Intramolecular 5-enolexo aldolization

Although, the organocatalytic asymmetric intramolecular aldol reactions through *enolendo* or *enolexo* fashion have received great attention only in the recent years, these reactions have a further scope in the synthesis of natural products. We had a strong interest in the synthesis of amino-polyols and nitrogen heterocycles, hence the first 6-*enolexo* aldolization developed by List et al.[8] led us to propose an entirely new approach with direct *enolexo* aldolization for the 1-imino sugar analogues.

Naturally occurring and synthetic polyhydroxylated alkaloids with glycosidases inhibitory properties[15] have been used for studying the biological functions of oligosaccharides with emerging therapeutic potential[16] for a variety of carbohydrate mediated diseases such as HIV,[17] diabetes,[18] hepatitis,[19] cancer,[18,20] and viral infection such as influenza.[21] Iminosugars are the polyhydroxy nitrogen heterocycles, in which the replacement of the oxygen by nitrogen in a sugar molecule gives a class of both synthetic and naturally occurring glycosidases inhibitors.[15,16] As glycoside cleavage is a biologically widespread process, glycosidases inhibitors, also called the "sugar-shaped alkaloids" are the carbohydrate analogues and have many potential medical applications. Polyhydroxy-piperidine derivatives comprise the main class of glycosidases inhibitors, along with pyrrolidine imino sugars, which are much weaker inhibitors of glycosidases

than piperidine class of aza-sugars. It has been demonstrated that polyhydroxylated piperidine alkaloids can mimic enzymatic substrates and can act as transition state analogues of various enzymes that bind and metabolize glycoproteins because it is widely accepted that *a compound which mimic the transition states of enzymatic glycoside cleavage is an inhibitor of glycosidases* e.g. (glycoside hydrolases).[15,16] There are many known compounds that fulfill theses criteria. One group of compounds that resemble the natural product is nojirimycin (Figure 3.1).[15,22]

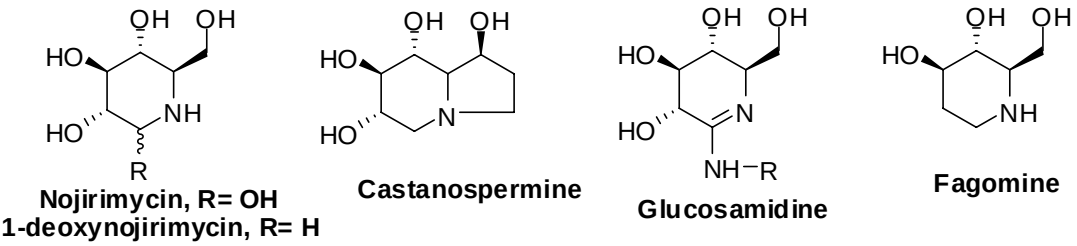


Figure 3.1: Imino sugars as glycosidase inhibitors

Although a plethora of natural as well as synthetic α-glycosidases inhibitors are known, the development of anomer-selective β-glycosidases inhibitors took place only in the past decade, pioneered by the studies from the groups of Bols[23] and Ichikawa.[24] In their studies, a new type of monosaccharide analogues with a nitrogen atom in place of an anomeric carbon atom, termed as 1-azasugars or 1-*N*-iminosugars, have been designed and studied (Figure 3.2).

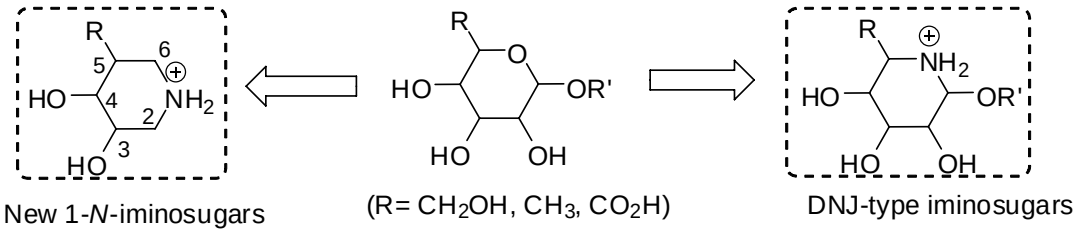


Figure 3.2: Designing of glycosidase inhibitors

The members of a new class of 1-*N*-iminosugars glycosidases inhibitors like isofagomine **3.11** (D-Glucose type 1-*N*-iminosugar),[25] **3.12** (D-Glucouronic acid type),[24] **3.13** (D-Galactose type),[24] **3.14** (L-Fucose type),[24,26] and **3.15** have been developed in the recent years.[25] Isofagomine **3.11** in particular, has been found to be the most potent inhibitor of β-glycosidases from sweet almond showing (K_i : inhibition constant = 0.11 μm) a value which is almost 440 times lower than that of 1-deoxynojirimycin.[25] The 5-hydroxy analogue of isofagomine was also found to be the inhibitor of glycolipid biosynthesis,[27] and a five membered analogue **3.16** also inhibit purine nucleoside phosphorylase with a K_i of 180 μm[23b] (Figure 3.3).

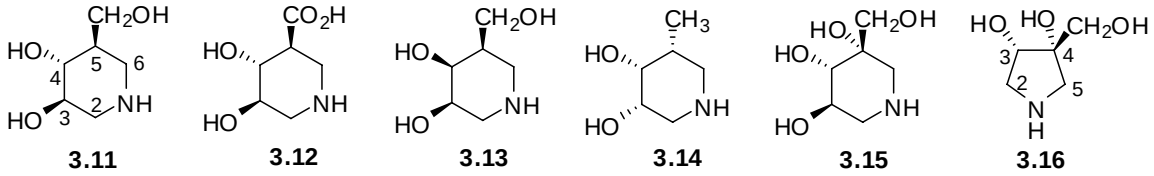
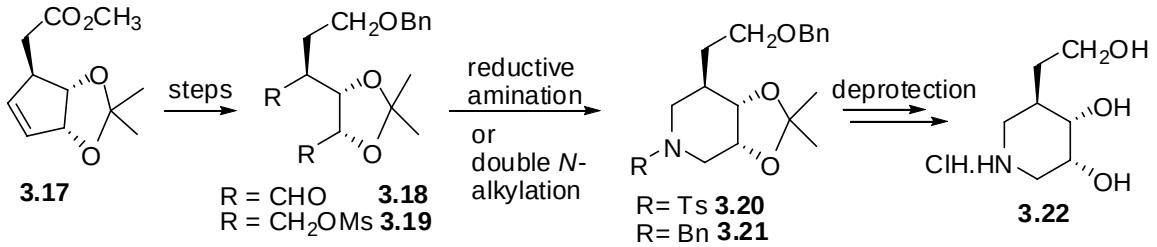


Figure 3.3: 1-N-imino sugars as glycosidases inhibitors

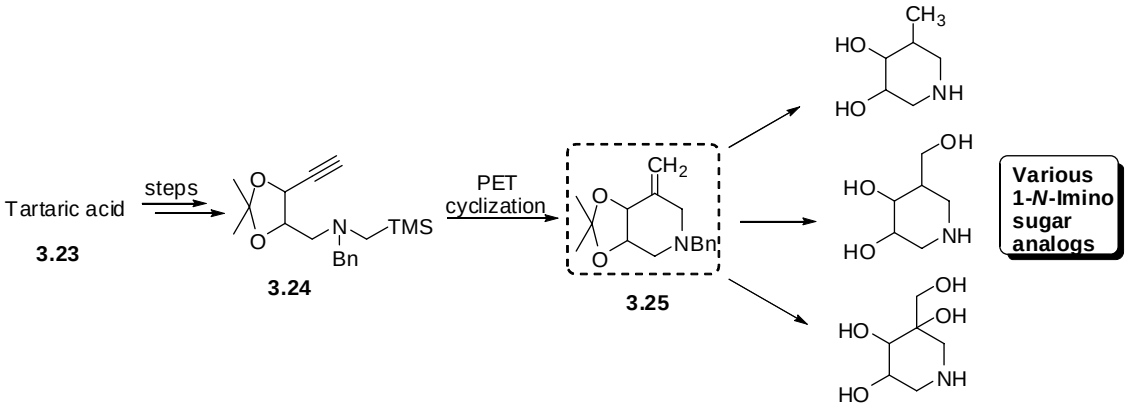
Although, these molecules look relatively simple but their syntheses have not been straightforward. The main challenge in the synthesis of these piperidines has been the introduction of the aminomethyl group next to the stereocenter. Initial studies for the synthesis of 1-*N*-iminosugars by Bols and Ichikawa was carried out by starting from carbohydrates,[24,25] after which several novel approaches for the synthesis of these compounds have been reported.[28-32.]

Mehta et al. developed a norbornyl route for the stereoselective synthesis of isofagomine analogues, through the double reductive amination or inter-, intramolecular *N*-alkylation of compounds derived from cyclopentene precursor **3.17** (Scheme 3.8),[28a] which is similar to the cyclization approach reported previously.[28b]



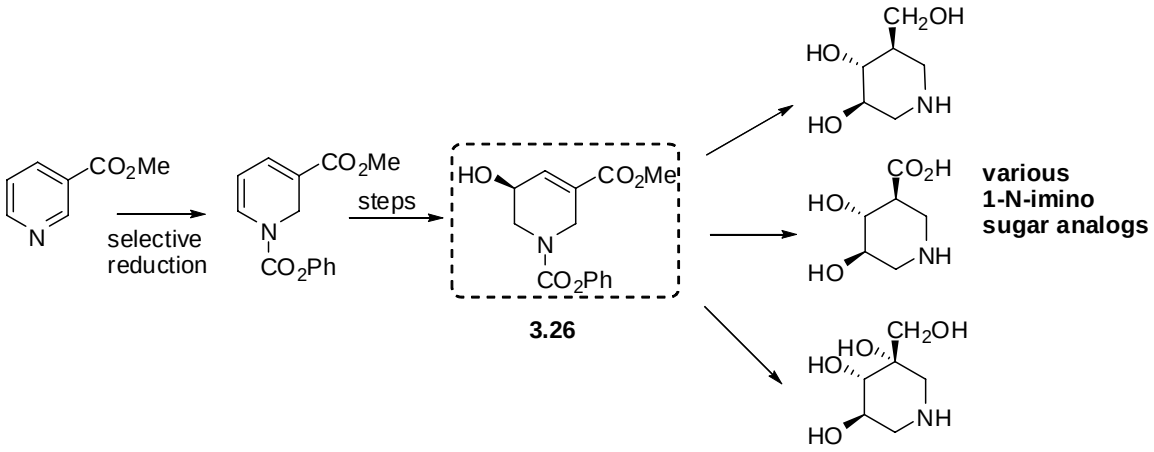
Scheme3.8: 1-imino sugar synthetic approach from Mehta group[28a]

Pandey et al. developed a general strategy using intramolecular PET (photo electron transfer) cyclization through α-trimethylsilylmethylamine radical cation with the appropriate acetylene moiety and synthesized a variety of 1-*N*-imino sugar analogues from a common intermediate, this strategy has been summarized in Scheme 3.9.[29] In this approach, the pyrrolidine ring was prepared through the PET assisted C-C bond formation between C5 and C6, while the stereochemistry at C3 and C4 were taken from D(+)- and L(-)-tartaric acid and the stereochemistry at C5 was prepared through other known synthetic transformations.



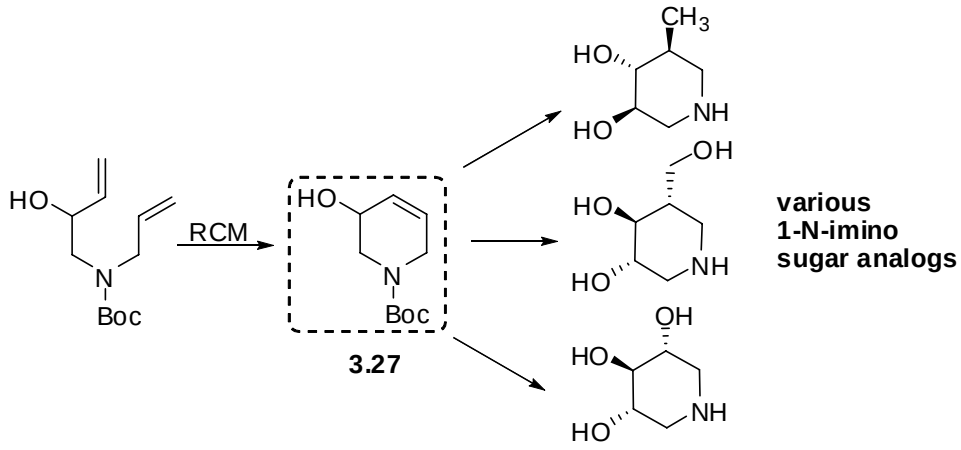
Scheme 3.9: General strategy for isofagomine analogue developed by Pandey et al.[29]

Gamen et al. developed a new strategy using selective 1,2-reduction of substituted pyridines followed by transformation steps to give 1-imino sugars as summarized in Scheme 3.10.[30]



Scheme 3.10: 1-imino sugar approach developed by Gamen et al.[30]

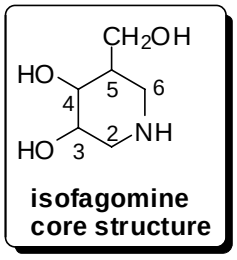
Takahata et al. developed another important approach for the synthesis of various 1-N-iminosugars through the resolution of hydroxy piperidine **3.27**, which was prepared using ring closing metathesis (RCM), followed by functionalization on ring double bond as summarized in Scheme 3.11.[31]



Scheme 3.11: RCM approach developed by Takahata et al.[31]

3.2 Results and Discussions

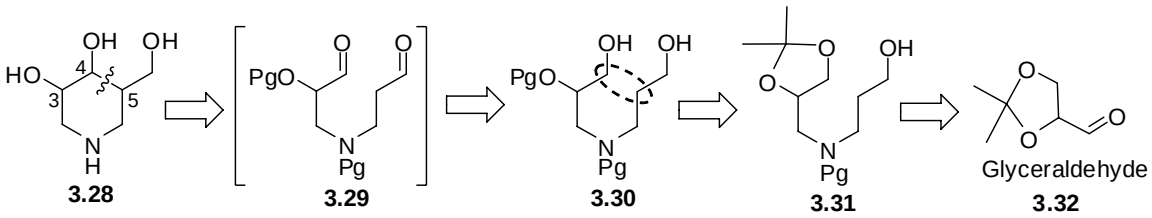
Most of the main recent strategies described above involved a large number of steps or resolution to complete the synthesis. Also in some of these approaches, the construction of piperidine ring occurs by the cyclization through the C-N bond on C2 or C6[24,25,28] while in other reported approaches, the construction of isofagomine core structure occurs through the C-C bond at different carbon centers,[29,31] and none of the reported approaches provides the study towards the construction of amino-methyl at C5 and adjacent chiral centre at C4 in one step with complete stereochemical control. Thus, the designing of a new cost effective approach which provides the access to all the stereoisomers of 1-N-imino sugars is always in demand.



Isofagomine **(3.28)**

In the continuation of our interest on the organocatalytic diastereoselective aldol reactions, we proposed an entirely new organocatalytic route for the construction of 1-*N*-imino sugar core structure with the C-C bond formation between C4 and C5, with the formation of two chiral centers in one step, which are (i) the hydroxy group at C4 and (ii) amino-methyl at C5, thus achieving the stereochemical control of two chiral centers.

Recently, List et al. have shown the first direct asymmetric 6-*enolexo* aldolization reaction with high level of enantioselectivity (99%) for the synthesis of *β*-hydroxy cyclohexane carbonyl derivatives (Scheme 3.2).[8] This led us to design a new reterosynthetic approach for isofagomine ring skeleton through the cleavage of C-C bond between C4 and C5, which can be formed through the direct diastereoselective 6-*enolexo* aldolization reaction, as shown in Scheme 3.12.



Scheme 3.12: New reterosynthetic approach for 1-*N*- imino sugars

According to this reterosynthetic analysis, the formation of C-C bond between C4 and C5 from a dialdehyde compound **3.29** through direct 6-enolexo aldolization is the key step. Dialdehyde compound **3.29** can be prepared by the oxidation of diol **3.30**, which was visualized as a key intermediate and can be easily prepared from the glyceraldehyde. Thus, the stereochemistry at C3 comes from the glyceraldehyde, which is available easily in both enantiomeric forms. The main challenge of this approach is to differentiate between two aldehyde groups by putting a well-defined stereocenter at the active methylene position of one of the aldehyde groups; so that the proline catalyzed 6-*enolexo* aldolization can occur via an enamine intermediate with different aldehyde functionality. The already existing stereocenters due to the stereochemistry of starting glyceraldehyde in synthon **3.30**, having a protected alcohol group, will have some impact on the diastereoselective outcome of its direct aldolization reaction.

3.2.1 Synthesis of 3,4-substituted pyrrolidine

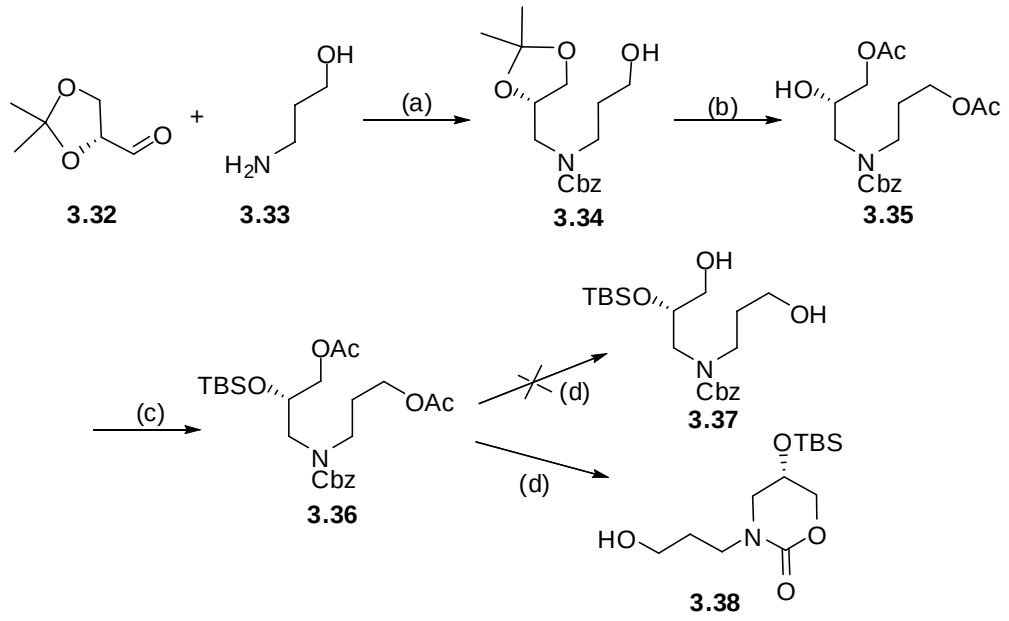
According to the reterosynthetic analysis, we started our synthetic route by taking first the preparation of the key intermediate **3.30** with a well protected secondary alcohol and two free primary alcohol groups. Thus, we started from (*R*)-glyceraldehyde **3.32**, which was easily prepared from commercially available D-mannitol through the steps of diacetonide protection followed by $NaIO_4$ cleavage, according to the reported

procedure.[33] The reductive amination of (*R*)-glyceraldehyde **3.32** was carried out with 3-aminopropanol **3.33** on Pd/C (10%) under hydrogen atmosphere for 12 h at rt, followed by insitu protection of the resulting secondary amine with CbzCl (1.2 equiv) in a biphasic medium of dichloromethane and aqueous Na_2CO_3 solution for 3 h at 0^oC to provide a Cbz-protected compound **3.34** with isolated 85% yield after two steps.[34]

The acetonide moiety of **3.34** was deprotected using *p*-TSA (*p*-toluene sulfonic acid) in a catalytic amount in MeOH at rt. After completion of the deprotection reaction, solvent was evaporated under reduced pressure and protected with acetyl group using 2.2 equiv of acetyl chloride in a solvent system of pyridine/CH_2Cl_2 (1:1) at 0^oC for 3 h to give diacetyl derivative **3.35** in 83% yield after two steps. The secondary alcohol of compound **3.35** was then protected with 1.1 equiv of TBSCl/imidazole in dry CH_2Cl_2 at 0^oC for 4 h to provide corresponding TBS-protected compound **3.36** with 92% yield.

In order to prepare the key synthon like **3.30**, we carried out the deprotection of acetyl groups of compound **3.36** by stirring it with catalytic amount of potassium carbonate (K_2CO_3) in MeOH for 30 min at rt to get a compound **3.37**.[35] But surprisingly, instead of compound **3.37**, we obtained compound **3.38** as a cyclic carbamate in almost quantitative yield.

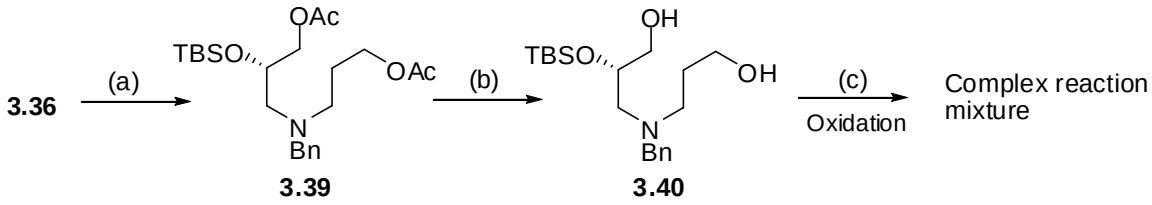
This was possible through the first deprotection of acetyl followed by intramolecular cyclization through the removal of –OBn group from -NCbz. Even though –OBn group is not a good leaving group, the formation of six membered cyclic carbamate might be the driving force for this reaction as shown in Scheme 3.13.



Scheme 3.13: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm.) rt, 12 h. (ii) CbzCl (1.2 equiv.), Na_2CO_3 (2.2 equiv.), CH_2Cl_2: H_2O (1:1), 0^oC, 3 h, 85 % in two steps. (b) (i) *p*-TSA, MeOH, rt, 8h. (ii) AcCl (2.2 equiv.), dry CH_2Cl_2: Pyridine (1:1), 0^oC, 3 h, 83 % yield after two steps. (c) TBSCl (1.1 equiv.), Imidazole, dry CH_2Cl_2, 0^oC, 4 h, 92 % yield. (d) K_2CO_3 (cat.), MeOH, rt, 30 min, 93 % yield.

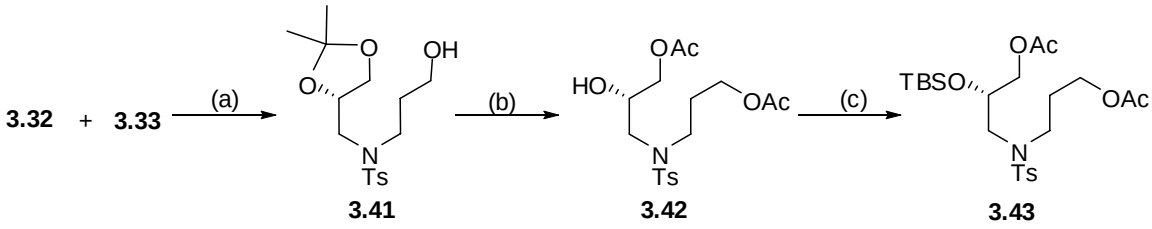
To overcome this problem of unexpected cyclization under deprotection conditions, we used benzyl as a protecting group on amino functionality. This was carried out in two steps from compound **3.36** by performing first, the cleavage of –Cbz protecting group from amino functionality using Pd/C (10%) under hydrogen atmosphere followed by the insitu protection with benzyl bromide (BnBr) under biphasic basic conditions to give compound **3.39** with 87% yield after two steps.[34] The deprotection of -OAc groups of **3.39** was carried out with K_2CO_3 (cat)/MeOH at rt to provide a diol **3.40** in 92% yield. In order to prepare the corresponding dialdehyde compound like **3.29**, the diol compound **3.40** was subjected to oxidation under different (IBX, DMP, or Swern) conditions. Unfortunately, all these attempts for the oxidation of compound **3.40** to the dialdehyde gave a complex reaction mixture and the oxidized compound could not be isolated. This

indicates that the β-amino-dialdehyde formed during the oxidation was unstable due to the amino-benzyl moiety. (Scheme 3.14)



Scheme 3.14: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm.), rt (ii) BnBr (1.2 equiv.), Na_2CO_3 (2.2 equiv.), CH_2Cl_2: H_2O (1:1), reflux, 3 h, 87 % in two steps. (b) K_2CO_3 (cat.), MeOH, rt, 30 min, 92 % yield. (c) IBX, DMP or Swern oxidation conditions.

These unsuccessful attempts for the preparation of dialdehyde compound prompted us to consider a new protecting group such as tosyl group, because N-Tosyl was known to be very stable under acidic and basic conditions. Similar to the Scheme 3.13, we did the reductive amination of (*R*)-glyceraldehyde **3.32** with 3-aminopropanol **3.33** and then insitu protection with tosyl chloride under biphasic basic conditions to give a compound **3.41** with 83% yield after two steps. Acetonide deprotection of compound **3.41** under acidic conditions followed by diacetyl protection gave a compound **3.42** with 77% yield after two steps. This compound **3.42** was then protected with TBSCl (1.1 equiv)/ imidazole to provide a compound **3.43** with 87% yield as shown in Scheme3.15.

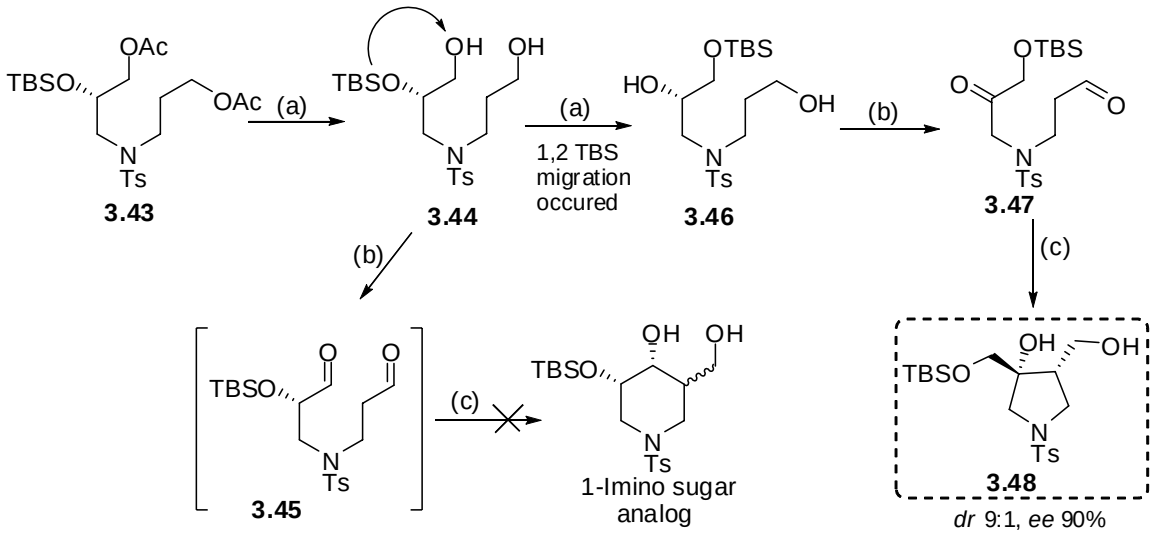


Scheme 3.15: (a) (i) Pd/C (10 mol %), MeOH, H_2 (1 atm.) rt, 12 h. (ii) TsCl (1.2 equiv.), Na_2CO_3 (2.2 equiv.), CH_2Cl_2:H_2O (1:1), 0^oC, 3 h, 83% in two steps. (b) (i) *p*-TSA, MeOH, rt, 8 h. (ii) AcCl (2.2 equiv.), CH_2Cl_2: Pyridine (1:1), 0^oC, 3 h, 77% yield after two steps. (iii) TBSCl (1.1 equiv.), Imidazole, dry CH_2Cl_2, 0^oC, 4 h, 87 %.

The acetyl deprotection of compound **3.43** was successfully carried out using standard conditions, K_2CO_3 (cat.)/MeOH at rt to give key synthon diol compound **3.44** with 89% yield. In order to prepare the dialdehyde compound **3.45** for the direct enolexo aldolization as a key step, the oxidation of compound **3.44** was carried out using o-iodoxy benzoic acid (IBX) (5.0 equiv) in EtOAc under reflux conditions for 4.5 h.[36] This reaction was monitored by TLC and after the complete consumption of diol **3.44**, reaction was cooled down to rt and IBX was filtered out. The resulting reaction mixture was washed with $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude oxidized compound **3.45** was then used for the direct aldolization without any purification. The direct enolexo aldolization reaction was carried out with L-proline (20 mol %) at 5^oC for 16 h in a solvent mixture of $CHCl_3$:DMSO (3:1), followed by insitu reduction with $NaBH_4$/MeOH at the same temperature to give stable diol with 65% yield after three steps, whose ^1H and ^{13}C NMR spectral data confirmed the cyclization. However, this cyclized product showed the four -CH_2 groups in the ^{13}C-DEPT NMR. While in case of 6-*enolexo* cyclization the cyclized product should show only three -CH_2 in the ^{13}C-DEPT NMR. A close interpretation of the spectral data showing four -CH_2 at δ = 48.88, 57.38, 59.40, 66.39 in ^{13}C NMR indicates the attachment of these methylene proton to the heteroatom which was possible for the product having a five membered ring. This was possible only when the aldolization reaction occurs through the 5-*enolexo* fashion instead of 6-*enolexo* cyclization (Scheme 3.16).

Thus, we looked back at our reactions and found that 1,2-TBS migration occurred during the –OAc deprotection using K_2CO_3/MeOH (mild basic) conditions and gave diol

compound **3.46** instead of compound **3.44**, which on oxidation gave keto-aldehyde **3.47** and went through an intramolecular aldolization with 5-*enolexo* fashion to give 3,4-substituted pyrrolidine compound **3.48**.

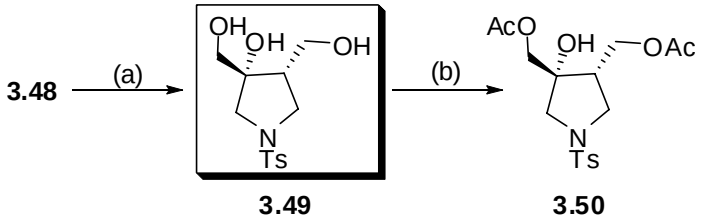


Scheme 3.16: (a) K_2CO_3 (cat.), MeOH, rt, 30 min, 89 % yield. (b) IBX (5.0 equiv.), EtOAc, reflux, 4.5 h, quantitative. (c) (i) L-Proline (20 mol%), $CHCl_3$:DMSO (3:1), 5^{o}C, 16 h. (ii) $NaBH_4$, MeOH, 5^{o}C, 2 h, 65 % yield after three steps.

Although the -OTBS migration is known under strong basic conditions and also that the parent -OTBS was held in sterically hindered place which would prefer to move to less hindered position through 1,2- or 1,3-migration, however, the 1,2-migration of –TBS occurred in our work inspite of very mild basic conditions and even the –OTBS in **3.44** was not sterically hindered. Interestingly, in this –TBS migration, the chirality of the compound **3.46** was lost during the oxidation, but the cyclization occurred through 5-*enolexo* fashion giving high level of diastereomeric ratio (*dr*) >9:1 and enantioselectivity (>90%) as determined by chiral HPLC (using OD-H column). In case of aldol reactions, aldehydes act as acceptors and ketones act as a donors, whereas in our case of intramolecular aldolization of keto-aldehyde **3.47** which gave the 3,4-substituted

pyrrolidine with high level of *syn*-selectivity occurs through the typical case of reverse reactivity, in which the aldehyde acts as a donor and ketone acts as an acceptor as shown in Scheme 3.16.

In order to confirm the structure and stereochemical outcome of the direct 5-*enolexo* aldol reaction product, further transformations were done starting with first, the TBS deprotection of **3.48** using PTA (Phosphotungstic acid) (cat.) in MeOH at rt to provide a triol compound **3.49** with quantitative yield.[37] Compound **3.49** was treated with 2.1 equiv of AcCl in dry CH_2Cl_2/pyridine (1:1) at 0^oC for 3 h and after usual work up of this reaction, the crude product was isolated by column chromatography to give corresponding diacetyl derivative **3.50** with 87% yield. The ^1H and ^{13}C NMR spectra of compound **3.50** showed that this was almost a pure diastereomer (Scheme 3.17).



3.49 **3.50**

Scheme 3.17: (a) PTA (cat.), MeOH, rt, 30 min. quantitative yield. (b) AcCl (2.1 equiv), dry CH_2Cl_2: pyridine (1:1), 0^oC, 3 h, 87% yield.

The exact stereochemical outcome of diacetyl derivative **3.50** was determined and explained by NOSEY experiments which revealed NOE correlation between the proton at C4 and the two protons of $–CH_2OAc$ at C3 (strong) and with the proton H^β at C5 (strong) as well as with H^β at C2 (weak) and also the correlation between H^β at C2 and the proton of $–CH_2OAc$ at C3 in **A**, which allowed us to confirm the *syn*-selectivity of the 5-enolexo aldolization reaction (Figure 3.4).

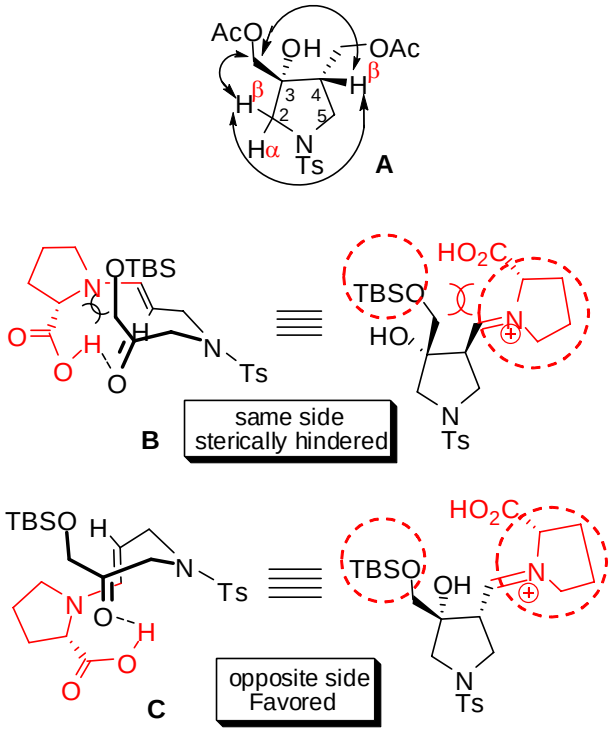


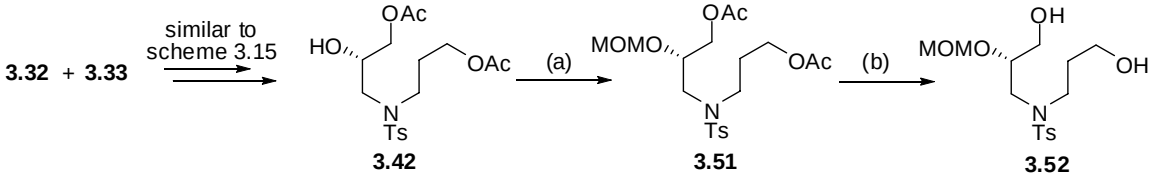
Figure 3.4: Structural elucidation by NOSY-correlation and preferred transition states.

The high level of *syn*-selectivity of this aldol reaction can be explained by the two different transition states during cyclization as shown in Figure 3.4. In the transition state **B**, the bulky –OTBS group and iminium-ion are on the same side, which proceed through the *syn*-enamine formation and this suffers from the problem of steric hindrance while in the transition state **C**, these groups are on the opposite side, which proceed through the more stable *anti*-enamine formation and does not suffer from the problem of steric hindrance. This makes the transition state **C** energetically more favored over transition state **B**, leading to the *syn*-selective out come of this reaction as shown in Figure 3.3. Hence, the bulky –OTBS group, due to its bulkiness play an important role in directing the stereochemistry at C4 to give *syn*- outcome of this reaction. Thus, the synthesis of a 3,4-substituted pyrrolidine ring has been achieved by the direct 5-*enolexo*-aldolization

reaction catalyzed by L-proline with *syn*-selectivity which proceeds through the reverse reactivity pattern of general reactivity of aldehyde and ketones.

3.2.2 Synthesis of 1-imino sugars analogues

As described above, the synthesis of a 3,4-substituted pyrrolidine ring with the first 5-*enolexo* aldolization reaction proceeded through the *syn*-selectivity via 1,2-TBS migration which occurred in the intermediate step. In order to avoid the migration of –TBS, we attempted another protecting group such as MOM (methoxymethyl) for the secondary alcohol as mentioned in the retrosynthetic analysis of 1-*N*-imino sugar in Scheme 3.12, which is necessary for the direct 6-*enolexo*-aldolization reaction. Thus, compound **3.42** was prepared by following the similar procedure as shown in Scheme 3.15 starting from (*R*)-glyceraldehyde **3.32** and 3-amino propanol **3.33**. This compound **3.42** was then protected under standard conditions[38] using MOMCl (1.2 equiv) and *i*-Pr_2EtN (1.2 equiv) in dry CH_2Cl_2 at rt for 5 h to provide corresponding MOM derivative **3.51** with 85% isolated yield. The acetyl deprotection was carried out using K_2CO_3 (cat.)/MeOH at rt for 30 min to provide corresponding diol compound **3.52** in almost quantitative yield as shown in Scheme 3.18.

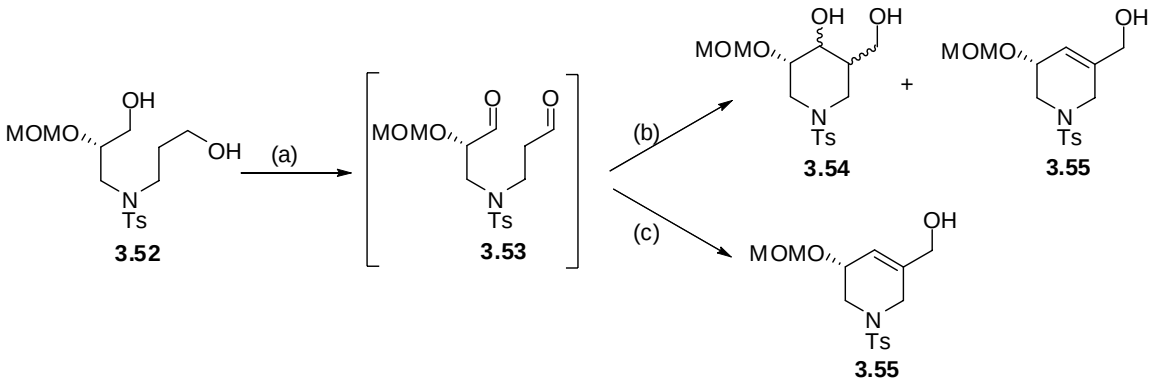


Scheme 3.18: (a) MOMCl (1.2 equiv), *i*-Pr_2EtN (1.2 equiv), dry CH_2Cl_2, rt, 5 h, 85% yield. (b) K_2CO_3 (cat.), MeOH, rt, 30 min, quantitative yield.

In order to perform the direct 6-enolexo aldolization reaction, compound **3.52** was oxidized into dialdehyde **3.53** using 5 equiv of IBX (o-iodoxybezoic acid) using EtOAc

as a solvent under reflux conditions.[36] This reaction was monitored by TLC and after complete consumption of the starting diol **3.52**, this reaction was cooled down to rt and filtered under suction. The filtrate was washed with $NaHCO_3$, brine solution and dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The resulting dialdehyde compound was further used for direct aldolization reaction without purification. The Direct 6-*enolexo* aldol reaction was carried out using 15 mol% of L-proline in $CHCl_3$:DMSO (3:1) for 20 h at rt followed by insitu reduction with $NaBH_4$/MeOH at rt for 3 h to get a stable diol compound **3.54**. After standard workup and chromatographic purification of the crude product, we found that the cyclized aldol product diol **3.54** as a mixture of diastereomers (<23%) and the insitu dehydrated aldol condensation product **3.55** was isolated as a major product (>65%).

The separation of the mixture of the diastereomers from cyclized diol **3.54** was another difficult task. However, the aldol condensation product **3.55** could be isolated as a pure stereoisomer because the stereochemistry generated during cyclization was destroyed due to dehydration and the stereochemistry at C3 remained similar to the starting glyceraldehyde. This reaction was then standardized to get aldol-condensation compound **3.55** as a sole product by carrying out the dehydration of the crude product of proline catalyzed direct *enolexo*-aldolization reaction for 20 h at rt, then stirring with *p*-TsOH for 1 h, with >85% yield of **3.55**, which is now direct 6-*enolexo* aldol condensation reaction as shown in Scheme 3.19. This dehydrated product **3.55** contained the ring double bond between C4 and C5 which is very similar to the key products of the strategies developed for the synthesis of 1-*N*-imino sugars by Gamen et al.[30] and Takahata et al.[31] separately shown in Figure 3.5.



Scheme 3.19: (a) IBX (5 equiv), EtOAc, reflux, 4.5 h, quantitative yield of crude material, (b) (i) L-proline (15 mol %), $CHCl_3$: DMSO (3:1), rt, 20 h, (ii) $NaBH_4$, MeOH, rt, 2 h, 88% combined yield of **3.54** and **3.55**. (c) (i) L-proline (15 mol %), $CHCl_3$: DMSO (3:1), rt, 20 h, (ii) *p*-TSA, MeOH, rt, 1h, (iii) $NaBH_4$, rt, 2 h, 85% of **3.55**.

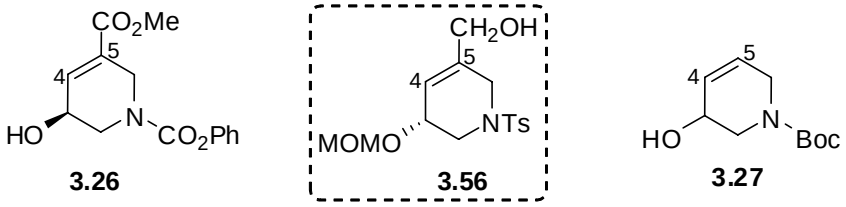


Figure 3.5: Key intermediates for 1-imino sugars

Although, the amine-catalyzed *enolexo* aldolization reaction was known and applied by Woodward in 1952 for the total synthesis of steroids (Eq. 1),[39] and other *enolexo* aldolization (Eq.2-4) were also known using piperidine with AcOH with poor yields and under hard conditions,[40] the first direct catalytic 6-*enolexo* aldolization reaction was established very recently.[8] The corresponding proline catalyzed direct aldol condensation reaction needs to be explored because the resulting product has α-β-unsaturated carbonyl group in which the double bond is the part of the ring system, which can be further functionalized. The corresponding direct *enolendo*-aldol condensation reaction is known since 1971 as the first direct aldolization catalyzed by proline (Eq 5) (Figure 3.6).

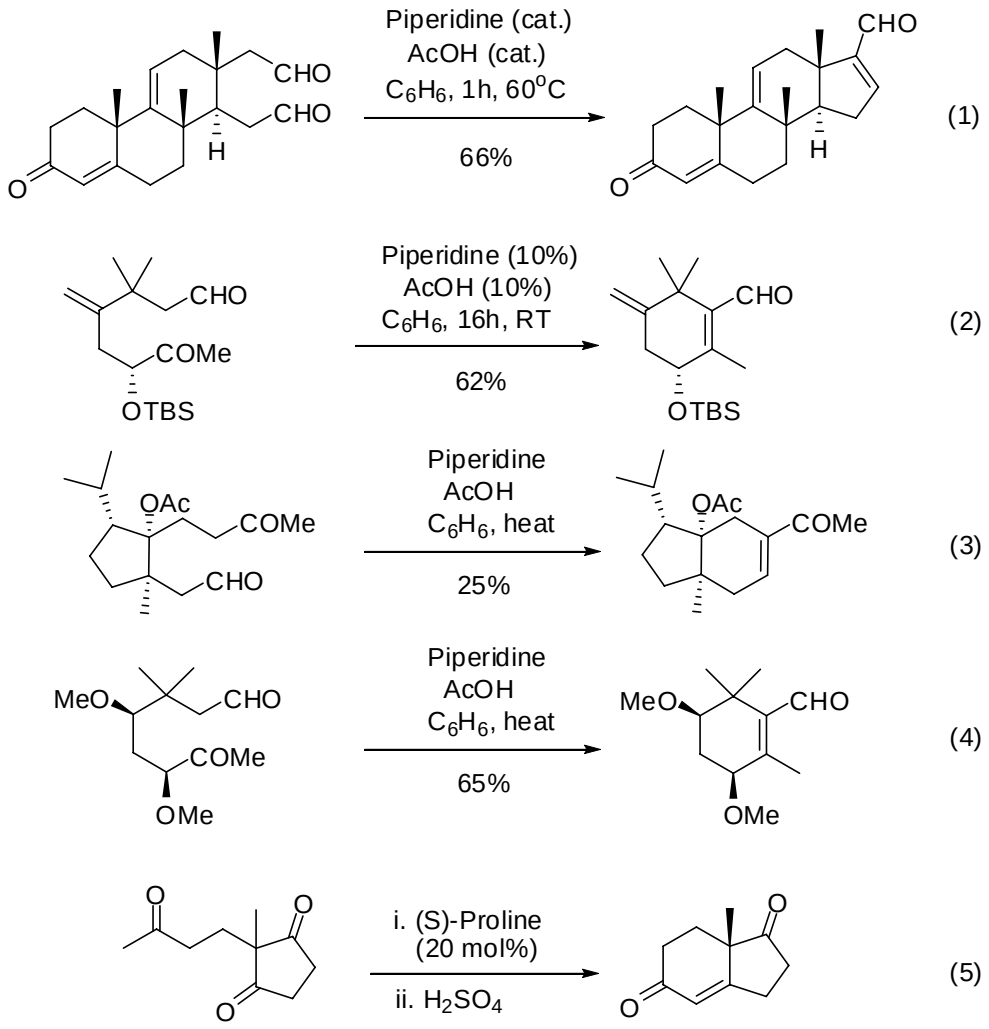
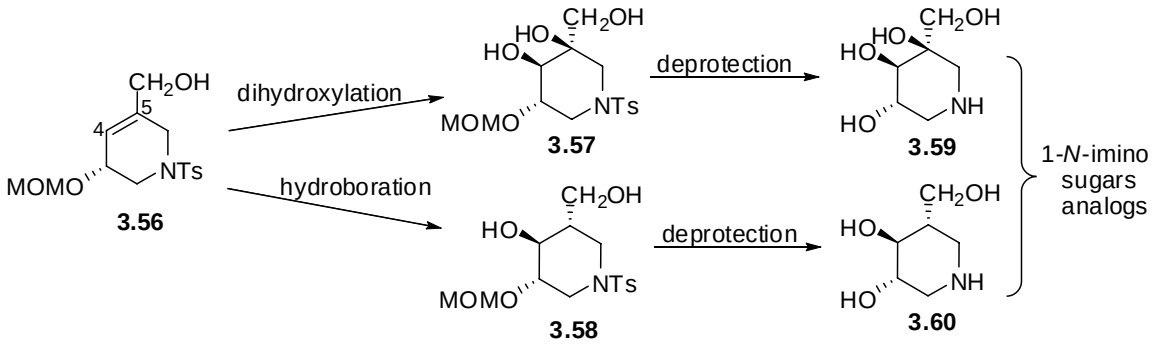


Figure 3.6: Amine catalyzed enolexo aldolization reactions

The compound **3.56**, which has the functionality similar to the previously reported key synthons **3.26** and **3.27** by Gamen et al.[30] and Takahata et al.[31] for the synthesis of 1-*N*-imino sugars and recognized as an important compound, this can be utilized for the synthesis of variety of 1-*N*-imino sugars with the derivatization of double bond. This work is the part of our further study, which is in progress in our laboratory (Scheme 3.20).



Scheme 3.20: Transformation of direct aldol condensation product in to 1-imino sugars

3.3 Conclusions

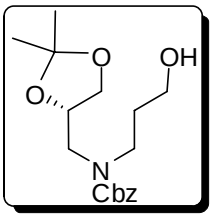
In conclusion, we have designed a new direct organocatalytic *enolexo* aldolization approach for the synthesis of 1-*N*-imino sugars, in which the differentiation between two aldehyde groups of a dialdehyde was achieved by creating a stereocenter at active methylene position. The synthesis of a 3,4-substituted pyrrolidine system has been achieved with the development of the first direct 5-*enolexo* aldolization reaction with *syn*-selectivity using L-proline as an organocatalyst, via 1,2-TBS migration under mild basic condition. The study towards 1-N-imino sugars (six membered rings) was continued by selecting a different protecting group and the synthesis of a key synthon, having allylic alcohol functionality in which the double bond is the part of the piperidine ring has been carried out using direct 6-*enolexo* aldol condensation reaction. This key synthon is an important intermediate for the synthesis of variety of 1-*N*-imino sugars and the study in this direction is under progress in our laboratory.

3.4 Experimental Section

General

All the reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under argon atmosphere using oven-dried glassware. Dichloromethane and dimethyl sulfoxide were distilled over CaH_2 under argon atmosphere and stored on molecular sieves. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin-Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^1H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC-MS was recorded using electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100-200 and 230-400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

Benzyl {[(4*S*)-2,2-dimethyl -1,3-dioxolan-4yl] methyl}(3-hydroxypropyl)carbamate (3.34)

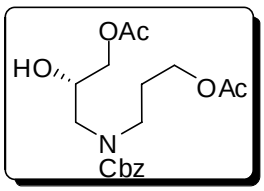


To a stirred solution of (*R*)-Glyceraldehyde **3.32** (1.5 g, 11.5 mmol) and 3-aminopropanol **3.33** (1.0 g, 13.84 mmol) in MeOH (25 mL), was added Pd/C (120 mg, 10 mol %) at rt. The resulting solution was stirred further for 12 h under hydrogen atmosphere followed

by TLC. The reaction mixture was filtered to remove Pd/C and concentrated under reduced pressure to give a slight yellowish liquid that were dissolve in CH_2Cl_2 (20 mL). To the resulting solution was added a solution of Na_2CO_3 (2.68 g, 25.36 mmol) in water (20 mL) and CbzCl (2.15 g, 12.694 mmol) at 0^oC and the mixture was stirred further for 2 h at the same temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography on silica-gel eluting with hexane: ethyl acetate (8:2 to 6:4) to give **3.34** (3.15 g, 85% yield in two steps) as a colorless liquid.

(3.34): $[\alpha]_D^{25}$ -7.56 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.35 (s, 3H), 1.72 (m, 2H), 3.15-3.25 (m, 1H), 3.51 (m, 6H), 3.88-4.05 (m, 1H), 4.19 (m, 1H), 5.10 (s, 2H), 7.30 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.09, 26.85, 30.06, 44.95, 49.85, 58.76, 67.14, 67.34 (overlapping signals), 74.92, 109.18, 127.83, 128.03, 128.46, 136.32, 156.89. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.09; H, 7.82; N, 4.39.

Benzyl (2*S*)-3-acetoxy-2-hydroxypropyl 3-acetoxypropylcarbamate (3.35)

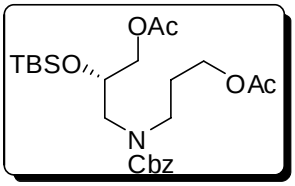


A solution of **3.34** (1.2 g, 3.71 mmol) in MeOH (25 mL) was stirred with the catalytic amount of *p*-TSA at rt for 8 h followed by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure to give a pasty residue. This was used further by dissolving in DCM: Pyridine (1:1) solvents (14 mL) at 0^oC followed by the addition of the solution of AcCl (0.62 g, 2.1 mmol) in 5 mL dry DCM at the same temperature for 25

minutes and stirred additionally for 3 h. The reaction mixture was poured into ice water and extracted with (3x20 mL) DCM. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was further purified by column chromatography to give **3.35** (1.13 g, 83 % in two steps) as a pasty liquid.

(3.35): $[\alpha]_D^{25}$ -4.96 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.80-2.10 (m, 8H), 3.30-3.45 (m, 4H), 3.95-4.10 (m, 5H), 5.09 (s, 2H), 7.31 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.54, 27.39, 45.80, 51.05, 61.74, 66.04, 67.37, 68.87, 127.65, 127.91, 128.32, 136.03, 157.17, 170.77. Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86; N, 3.81. Found: C, 58.91; H, 6.79; N, 3.91.

Benzyl (2*S*)-3-acetoxy-2-*tert*-butyldimethyl-silyloxypropyl 3-acetoxypropylcarbamate (3.36)

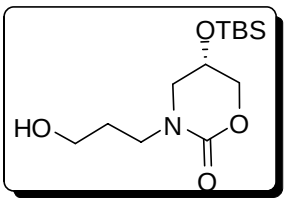


To a stirred solution of compound **3.35** (1.2 g, 3.26 mmol) and Imidazole (0.267 g, 3.91 mmol) with a catalytic amount of DMAP in dry CH_2Cl_2 (8 mL), was added a solution of TBSCl (0.591 g, 3.92 mmol) in dry DCM (5 mL) at 0^{o}C for 10 min. The resulting mixture was stirred further for 2 h at the same temperature followed by 1 h at rt. This reaction was quenched by 20% aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica-gel eluting with hexane: ethyl acetate (9:1) to give **3.36** (1.45 g, 92% yield) as a colorless liquid.

(3.36): $[\alpha]_D^{25}$ -9.19 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.01 (t, 6H), 0.85 (s, 9H), 1.75-2.05 (m, 8H), 3.09-3.19 (m, 1H), 3.23-3.70 (m, 4H), 3.89-4.18 (m, 4H), 5.10

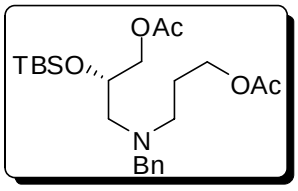
(s, 2H), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.19, 17.69, 20.60, 25.49, 27.40, 46.01, 51.13, 61.74, 66.09, 67.10, 68.53, 127.73, 128.09, 128.32, 136.30, 155.93, 170.66. LC-MS (ESI-TOF): m/z $[M+H]^+$ 482.23. Anal. Calcd for $C_{24}H_{39}NO_7Si$: C, 59.85; H, 8.16; N, 2.91. Found: C, 59.79; H, 8.11; N, 2.95.

(5*S*)-5-*tert*-Butyldimethylsilyloxy-3-(3-hydroxypropyl)-1,3-oxazinan-2-one (3.38)



To a stirred solution of compound **3.36** (1.0g, 2.01 mmol) in distilled MeOH (10 mL) was added K_2CO_3 (cat.) at ambient temperature, and the reaction was followed by TLC. The starting material was completely consumed within half-an-hour. The solvent was evaporated under reduced pressure and the residue was purified by just passing through the small pad of column giving compound **3.38** (0.56 g, 93% yield) as a colorless liquid. **(3.38):** $[\alpha]_D^{25}$ -5.28 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.12 (s, 6H), 0.89 (s, 9H), 1.77 (m, 2H), 3.25-3.75 (m, 8H), 4.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.20, 17.92, 25.32, 29.76, 45.52, 50.83, 60.13, 66.94, 72.31, 152.86. LC-MS (ESI-TOF): m/z $[M+H]^+$ 290.13. Anal. Calcd for $C_{13}H_{27}NO_4Si$: C, 53.94; H, 9.40; N, 4.84. Found: C, 53.87; H, 9.32; N, 4.90.

3-{[(2*S*)-3-Acetoxy-2-*tert*-butyldimethylsilyloxypropyl](benzyl)amino}propyl acetate (3.39)

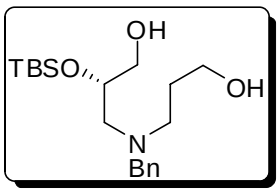


To a stirred solution of compound **3.36** (1.5 g, 3.11 mmol) in distilled MeOH (15 mL), was added Pd/C (32 mg, 10 mol %) at rt. The resulting mixture was hydrogenated under atmospheric pressure of hydrogen for 3 h, and the reaction was followed by TLC. The

resulting mixture was filtered and solvent was removed in vacuo to give oily product that was taken in dichloromethane (10 mL). To the resulting solution, was added a solution of Na_2CO_3 (0.726 g, 6.85 mmol) in water (10 mL) and benzyl bromide (0.64 g, 3.37 mmol) and the mixture was refluxed for 3 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica-gel to give compound **3.39** (1.18 g, 87 % in two steps) as a colorless liquid.

(3.39): $[\alpha]_D^{25}$ -12.20 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.01 (s, 6H), 0.82 (s, 9H), 1.73 (m, 2H), 1.92 (s, 3H), 1.96 (s, 3H), 2.47 (m, 4H), 3.52 (d, *J*= 13.5 Hz, 1H, -NCH_2Ar), 3.58 (d, *J*= 13.5 Hz, 1H, -NCH_2Ar), 3.80-3.95 (m, 2H), 4.01 (t, *J*= 6.4 Hz, 2H), 4.17 (dd, *J*= 10.5, 2.5 Hz, 1H), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.82, 17.93, 20.90, 25.60, 26.21, 51.23, 57.63, 59.78, 62.33, 67.21, 69.13, 126.91, 128.12, 128.76, 139.09, 170.68. Anal. Calcd for $C_{23}H_{39}NO_5Si$: C, 63.12; H, 8.98; N, 3.20. Found: C, 63.07; H, 8.91; N, 3.26.

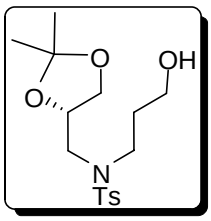
(2*S*)-2-*tert*-Butyldimethylsilyloxy-3-[benzyl(3-hydroxypropyl)amino]propanol (3.40)



Similar to the acetyl deprotection of compound **3.36**, deprotection of **3.39** followed by chromatographic purification over silica-gel gave compound **3.40** (1.12 g, 92 % yield from 1.5 g of **3.40**) as a pasty liquid.

(3.40): $[\alpha]_D^{25}$ -13.38 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.02 (s, 6H), 0.85 (s, 9H), 1.63-1.77 (m, 2H), 2.44-2.76 (m, 4H), 3.41-3.58 (m, 3H), 3.65-3.85 (m, 4H), 7.30

(s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.59, 18.06, 25.70, 28.60, 52.86, 56.48, 59.07, 62.18, 65.40, 69.02, 127.04, 128.21, 128.98, 138.18. Anal. Calcd for $C_{19}H_{35}NO_3Si$: C, 64.54; H, 9.98; N, 3.96. Found: C, 64.43; H, 9.93; N, 3.98.



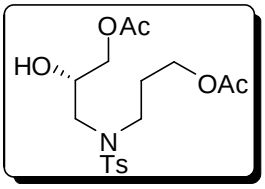
_N_-{[(4_S_)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-_N_-(3-hydoxypropyl)-4-methylbenzenesulfonamide (3.41)

To a stirred solution of (*R*)-Glyceraldehyde **3.32** (2.0 g, 15.36 mmol) and 3-aminopropanol **3.33** (1.38 g, 118.44 mmol) in MeOH (32 mL), was added Pd/C (150mg, 10 mol%) at rt. The resulting solution was stirred further for 12 h under hydrogen atmosphere followed by TLC. The reaction mixture was filtered to remove Pd/C and concentrated under reduced pressure to give slight yellowish liquid that was dissolved in CH_2Cl_2 (20 mL). To the resulting solution, was added a solution of Na_2CO_3 (3.58 g, 33.81 mmol) in water (20 mL) and tosyl chloride (3.50 g, 118.37 mmol) at 0^oC and the mixture was stirred further for 2 h at the same temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica-gel eluting with hexane: ethyl acetate (8:2 to 7:3) to give **3.41** (4.38 g, 83% yield in two steps) as a colorless liquid.

(3.41): $[\alpha]_D^{25}$ -11.03 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.35 (s, 3H), 1.79 (m, 2H), 2.39 (s, 3H), 2.97 (m, 1H), 3.14 (m, 1H), 3.32-3.48 (m, 2H), 3.60-3.72 (m, 3H), 4.05 (dd, *J*= 8.4, 6.3 Hz, 1H), 4.26 (m, 1H), 7.28 (d, *J*= 8.0 Hz, 2H, Ar), 7.66 (d,

J= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.22, 25.09, 26.52, 31.09, 46.50, 51.80, 58.67, 67.23, 74.88, 109.45, 126.95, 129.57, 135.60, 143.38. LC-MS (ESI-TOF): m/z $[M+H]^+$ 344.14, $[M+Na]^+$ 366.12. Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.96; H, 7.34; N, 4.08. Found: C, 55.89; H, 7.28; N, 4.15.

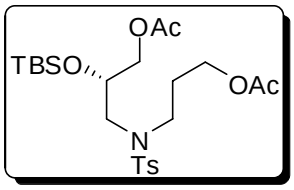
(*S*)-3-(*N*-(3-Acetoxy-2-hydroxypropyl)-4-methylphenylsulfonamido)propyl acetate (3.42)



Similar to the preparation of compound **3.35**, for corresponding N-Ts protected compound **3.42:**

(3.42): $[\alpha]_D^{25}$ -5.14 (*c* 1.6, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.90 (m, 2H), 2.01 (s, 3H), 2.06 (s, 3H), 2.40 (s, 3H), 3.05-3.26 (m, 4H), 3.97-4.16 (m, 5H), 7.28 (d, *J*= 8.0 Hz, 2H, Ar), 7.66 (d, *J*= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ =20.44, 20.50 (overlapping), 21.11, 27.47, 47.16, 51.67, 61.46, 65.75, 68.33, 126.94, 129.52, 135.21, 143.43, 170.67, 170.71 (overlapping). LC-MS (ESI-TOF): m/z $[M+H]^+$ 388.16, $[M+Na]^+$ 410.13. Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62. Found: C, 52.78; H, 6.43; N, 3.63.

(*S*)-3-(*N*-(3-Acetoxy-2-(*tert*-butyldimethylsilyloxy) propyl)-4-methylphenylsulfonamido)propyl acetate (3.43)

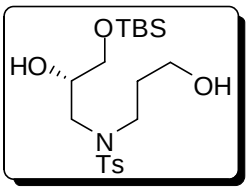


Following the previous preparation procedure for **3.36**.

(3.43): $[\alpha]_D^{25}$ +5.25 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.06 (s, 6H), 0.85 (s, 9H), 1.85 (m, 2H), 2.01 (s, 3H), 2.05 (s, 3H), 2.41 (s, 3H), 3.06-3.32 (m, 4H), 3.69 (d, *J*= 4.3 Hz, 0.5H), 3.95-4.04 (m, 3H), 4.07-4.16 (m, 2H), 4.20 (d, *J*= 4.1 Hz, 0.5H), 7.29 (d,

J= 8.0 Hz, 2H, Ar), 7.66 (d, *J*= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.89, 17.76, 20.66, 21.29, 25.52, 27.49, 47.56, 51.73, 61.61, 65.88, 69.57, 127.13, 129.62, 135.83, 143.46, 170.40, 170.63 (overlapping). LC-MS (ESI-TOF): m/z $[M+H]^+$ 502.14, $[M+Na]^+$ 524.13. Anal. Calcd for $C_{23}H_{39}NO_7SSi$: C, 55.06; H, 7.84; N, 2.79. Found: C, 55.01; H, 7.79; N, 2.83.

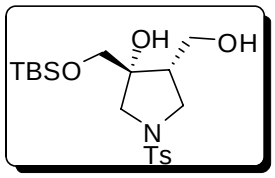
(*S*)-*N*-(3-(*tert*-butyldimethylsilyloxy)-2-hydroxypropyl)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide (3.46)



To a stirred solution of compound **3.43** (1.5g, 2.98 mmol) in distilled MeOH (12 mL), was added K_2CO_3 (cat.) at ambient temperature, followed by TLC. The starting material gets over with in half-an-hour. The solvent was evaporated under reduced pressure and the residue was purified by passing through a small pad of silica-gel giving compound **3.46** (1.10 g, 89% yield) as a colorless pasty liquid.

(3.46): $[\alpha]_D^{25}$ -7.54 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.86 (s, 9H), 1.80 (m, 2H), 2.40 (s, 3H), 2.68 (bs, 2H, exchangeable) 2.98-3.105 (m, 1H), 3.15-3.31 (m, 3H), 3.54-3.88 (m, 5H), 7.29 (d, *J*= 8.0 Hz, 2H, Ar) 7.62 (d, *J*= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.53, 18.11, 21.39, 25.73, 31.17, 47.35, 52.53, 58.98, 64.64, 70.89, 127.19, 129.69, 135.52, 143.51. LC-MS (ESI-TOF): m/z $[M+H]^+$ 418.11, $[M+Na]^+$ 440.09. Anal. Calcd for $C_{19}H_{35}NO_5SSi$: C, 54.64; H, 8.45; N, 3.35. Found: C, 54.57; H, 8.39; N, 3.41.

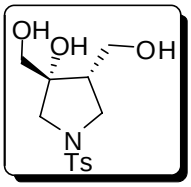
(3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)-*N*-[4-methylphenylsulfonyl]pyrrolidin-3-yl-methyl-*tert*-butyldimethylsilylether (3.48)



A mixture of **3.43** (0.80 g, 1.91 mmol) and IBX (2.67 g, 9.57 mmol) in EtOAc (38 mL) was heated under reflux for 4.5 h at 80^{o}C, followed by TLC. The reaction temperature was brought to rt and filtered. The filtrate was washed with 20% solution of $NaHCO_3$ (3x 20 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude oxidized product was used further for the cyclization without purification. This slight yellowish material was dissolved in $CHCl_3$: DMSO (3:1, 12 mL) at 5^{o}C, followed by the addition of L-proline (0.032 g, 15 mol%). The resulting solution was further stirred for 16 h at the same temperature followed by the addition of 5 mL of MeOH and insitu reduction with $NaBH_4$ (0.075 g, slight excess) for 2 h. The reaction mixture was evaporated in vacuo and poured into cold water (15 mL), followed by the extraction with EtOAc (4x20 mL). The combined reaction mixture was dried over Na_2SO_4 and concentrated under reduced pressure; the resulting pasty mass was purified by flash column chromatography to give **3.48** (0.51 g, 65 % yield after three steps) as a white semi-solid at low temperature.

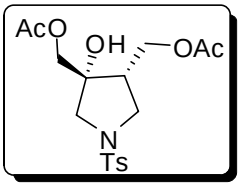
(3.48): $[\alpha]_D^{25}$ -5.09 (*c* 0.5, MeOH), ^{1}H NMR (400MHz, $CDCl_3$/D2O): δ = 0.06 (s, 6H), 0.87 (s, 9H), 1.63 (bs, 1H, exchangeable), 2.11 (m, 1H), 2.42 (s, 3H), 3.06 (d, *J*= 10.8 Hz, 1H), 3.12 (m, 1H), 3.40 (d, *J*= 10.5 Hz, 1H), 3.47-3.53 (m, 3H), 3.60-3.63 (m, 2H), 7.31 (d, *J*= 8.0 Hz, 2H, Ar), 7.69 (d, *J*= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.74, 17.98, 21.36, 25.60, 44.53, 48.89 (dept), 57.39 (dept), 59.40 (dept), 66.41 (dept), 80.38, 127.48, 129.54, 132.88, 143.50. LC-MS (ESI-TOF): m/z $[M+H]^+$ 416.09, $[M+Na]^+$ 438.08. Anal. Calcd for $C_{19}H_{33}NO_5SSi$: C, 54.91; H, 8.00; N, 3.37. Found: C, 54.83; H, 7.92; N, 3.44.

(3*R*,4*S*)-3,4-Bis(hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-ol (3.49)



To a solution of compound **3.48** (0.50 g, 1.2 mmol) in MeOH (8 mL), was added phosphotungstic acid-hydrate (PTA) in catalytic amount and stirred further for 30 min at rt. The solvent was removed in vacuo and residue was purified by passing through a small pad of silica-gel with $CHCl_3$/MeOH to give triol **3.49** in almost quantitative yield. **(3.49):** $[\alpha]_D^{25}$ -3.92 (*c* 1, MeOH), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 2.09 (m, 1H), 2.41 (s, 3H), 3.06 (m, 2H,) 3.15-3.68 (m, 6H), 7.30 (d, *J*= 8.0 Hz, 2H, Ar), 7.68 (d, *J*= 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3/D_2O$): δ = 21.39, 42.35, 48.75 (dept), 57.09 (dept), 59.85 (dept), 65.93 (dept), 79.82, 127.41, 129.49, 132.74, 143.55. Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65. Found: C, 51.78; H, 6.31; N, 4.68.

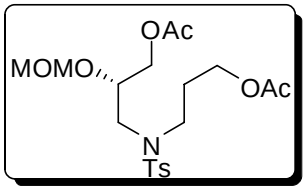
{(3*R*,4*S*)-3-Hydroxy-*N*-[-4-methylphenyl) sulfonyl]pyrrolidine-3,4-diyl}bis(methylene) diacetate (3.50)



To a stirred solution of **3.49** (0.35 g, 1.16 mmol) and in dry CH_2Cl_2/pyridine (1:1) (8 mL), was added a solution of acetyl chloride (0.19 g, 2.43 mmol) in dry CH_2Cl_2 (2.5 mL) at 0^{o}C for 30 minutes. The combined reaction mixture was further stirred for 2 h at the same temperature and then was poured into the cold water (10 mL), which was further extracted with CH_2Cl_2 (2x10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to give diacetyl derivative **3.50** with 87% yield as a single diastereomer confirmed by ^{1}H and ^{13}C-NMR.

(3.50): $[\alpha]_D^{25}$ +2.93 (*c* 0.5, $CHCl_3$), ^1H NMR (400MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.07 (s, 3H), 2.31 (m, 1H,) 2.42 (s, 3H), 3.09 (t, *J*= 9.8 Hz, 1H), 3.26 (d, *J*= 11.0 Hz, 1H), 3.42 (d, *J*= 11.0 Hz, 1H), 3.56 (t, *J*= 8 Hz, 1H), 3.98 (d, *J*= 12.2 Hz, 1H), 4.00 (dd, *J*= 7.0, 10.5Hz, 1H), 4.15 (d, *J*= 12.2 Hz, 1H), 4.20 (dd, *J*= 7.0, 11.3 Hz, 1H), 7.32 (d, *J*= 8.0 Hz, 2H, Ar), 7.69 (d, *J*= 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.66, 20.75 (overlapping), 21.51, 43.46, 49.56 (dept), 58.12 (dept), 61.24 (dept), 67.73 (dept), 127.55, 129.78, 133.24, 143.89, 170.78, 171.04. LC-MS (ESI-TOF): m/z $[M+H]^+$ 386.38, $[M+Na]^+$ 408.39. Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.97; H, 6.05; N, 3.69.

(*S*)-3-(*N*-(3-Acetoxy-2-(methoxymethoxy)propyl)-4-methylphenylsulfonamido)propyl acetate (3.51)

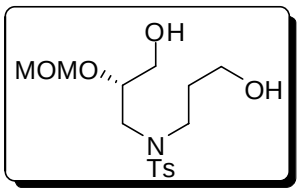


To a stirred solution of compound **3.42** (1.4 g, 3.6 mmol) and *i*-Pr_2EtN (0.560 g, 4.3 mmol) in dry CH_2Cl_2 (8 mL), was added a solution of MOMCl (0.349 g, 4.3 mmol) in at 0^oC. The resulting mixture was stirred further for 5 h at rt. This reaction was quenched by 20% aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica-gel eluting with hexane: ethyl acetate (8:2) to give **3.51** (1.32 g, 85% yield) as a colorless liquid.

3.51: $[\alpha]_D^{25}$ +7.42 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.90 (m, 2H), 2.03 (s, 3H), 2.07 (s, 3H), 2.42 (s, 3H), 3.10-3.18 (m, 2H), 3.27-3.36 (m, 5H), 4.00-4.07 (m, 3H), 4.08-4.14 (m, 1H), 4.26 (m, 1H), 4.60-4.69 (m, 2H), 7.31 (d, *J*= 8.0 Hz, 2H, Ar), 7.69 (d,

J= 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.51, 20.55 (overlapping), 21.20, 27.39, 47.09, 49.91, 55.39, 61.42, 63.87, 74.18, 96.18, 127.09, 129.54, 135.50, 143.42, 170.32, 170.57 (overlapping). LC-MS (ESI-TOF): for $C_{19}H_{29}NO_8S$: m/z $[M+H]^+$ 432.07, $[M+Na]^+$ 454.06.

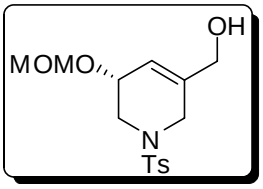
(*S*)-*N*-(3-hydroxy-2-(methoxymethoxy)propyl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (3.52)



Similar to the previous deprotection of –OAc using K_2CO_3/MeOH;

For **3.52:** $[\alpha]_D^{25}$ +2.08 (*c* 1, MeOH), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.78 (m, 2H), 2.42 (s, 3H), 3.08-3.26 (m, 4H), 3.34 (s, 3H), 3.53-3.86 (m, 5H), 4.60 (m, 2H), 7.29 (d, *J*= 8.0 Hz, 2H, Ar), 7.68 (d, *J*= 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.26, 31.03, 47.25, 49.83, 55.43, 58.86, 62.13, 78.10, 96.35, 127.05, 129.59, 135.28, 143.47. Anal. Calcd for $C_{15}H_{25}NO_6S$: C, 51.86; H, 7.25; N, 4.03. Found: C, 51.91; H, 7.19; N, 4.09.

(*R*)-(5-methyoxymethoxy)-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (3.55)



3.55: $[\alpha]_D^{25}$ -4.5 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): *δ* = 2.45 (s, 3H), 3.10 (m, 1H), 3.28-3.45 (m, 4H), 3.55-3.84 (m, 2H), 4.05-4.30 (m, 3H), 4.60-4.75 (m, 2H), 5.82 (m, 1H), 7.29 (d, *J*= 8.0 Hz, 2H, Ar), 7.68 (d, *J*= 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 21.29, 46.85, 54.13, 55.89, 66.61, 69.56, 96.41, 120.67, 127.05, 129.59, 135.28, 138.21, 143.47. LC-MS (ESI-TOF): for $C_{15}H_{21}NO_5S$: m/z $[M+H]^+$ 329.07, $[M+Na]^+$ 350.00.

3.5 References

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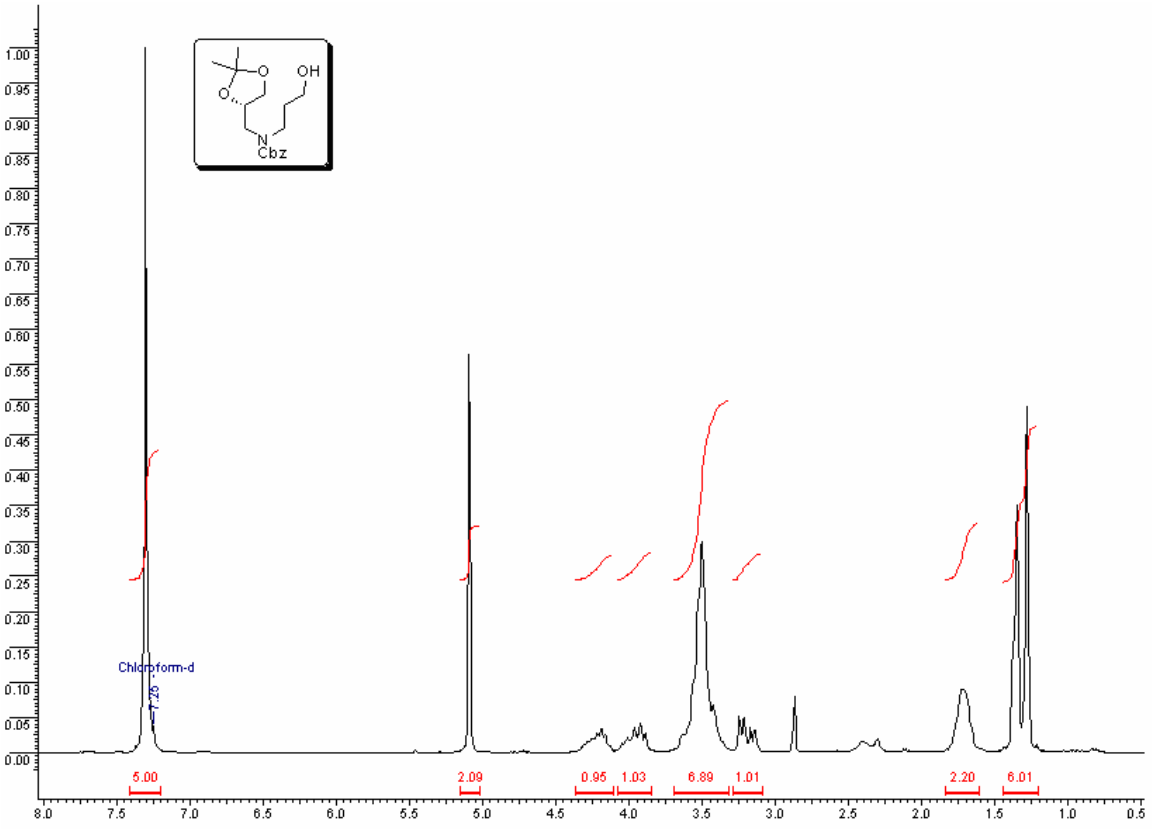
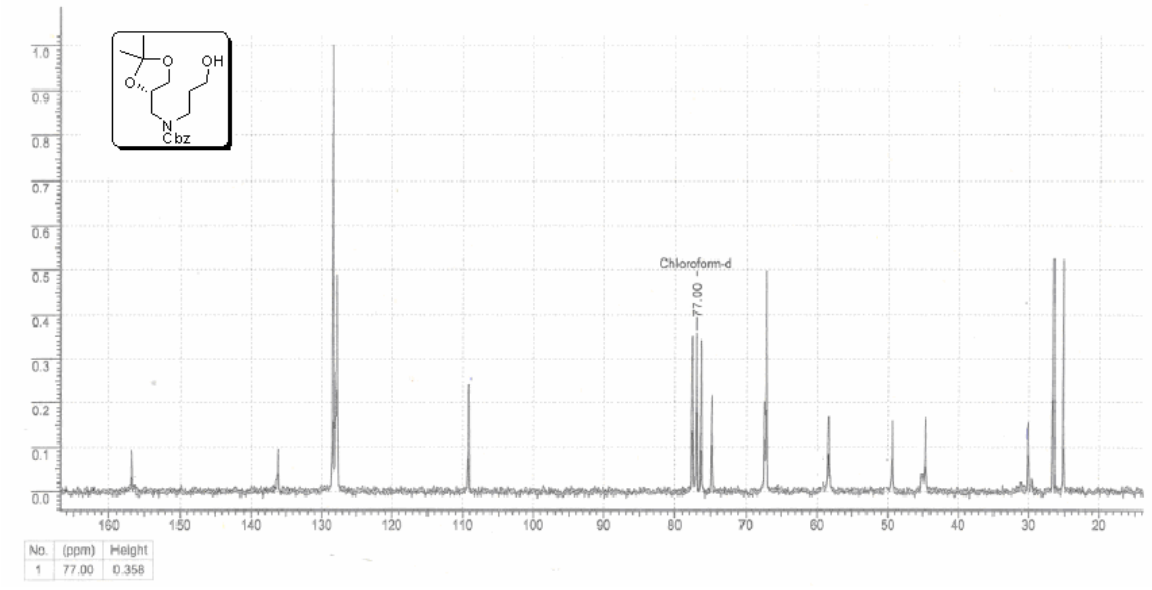
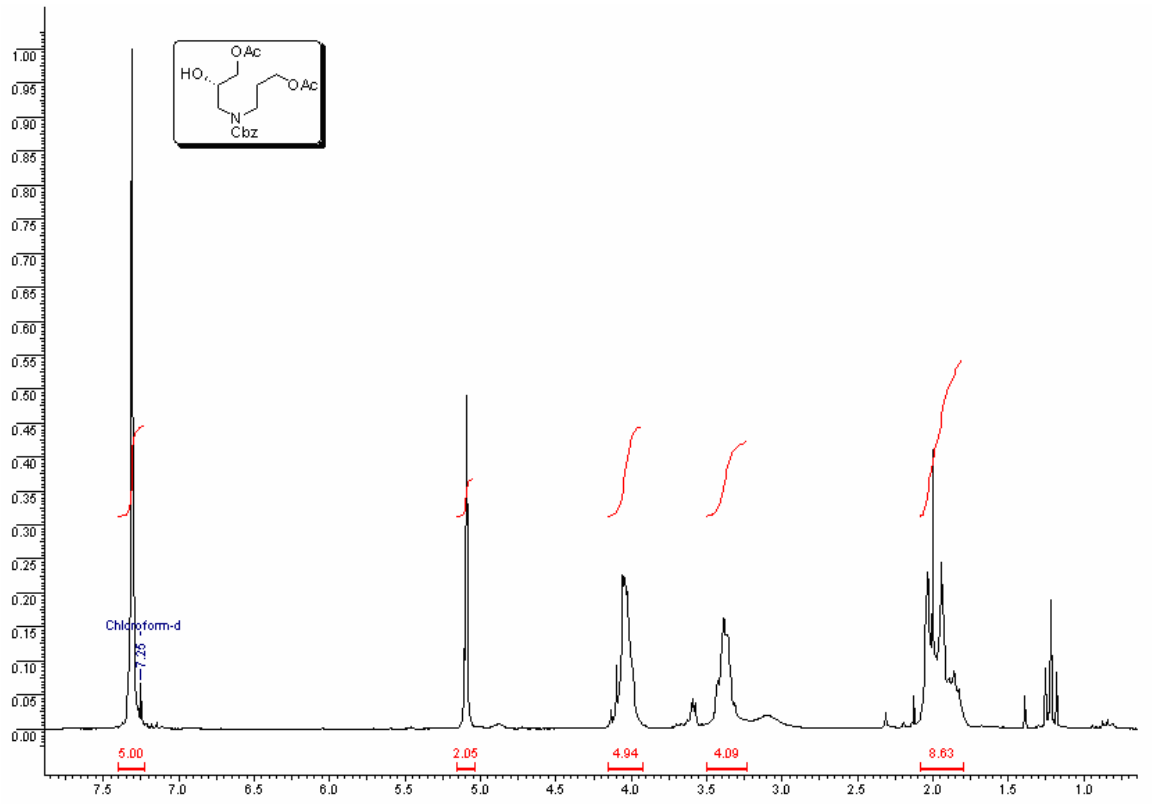
3.6 Spectra of Selected compounds



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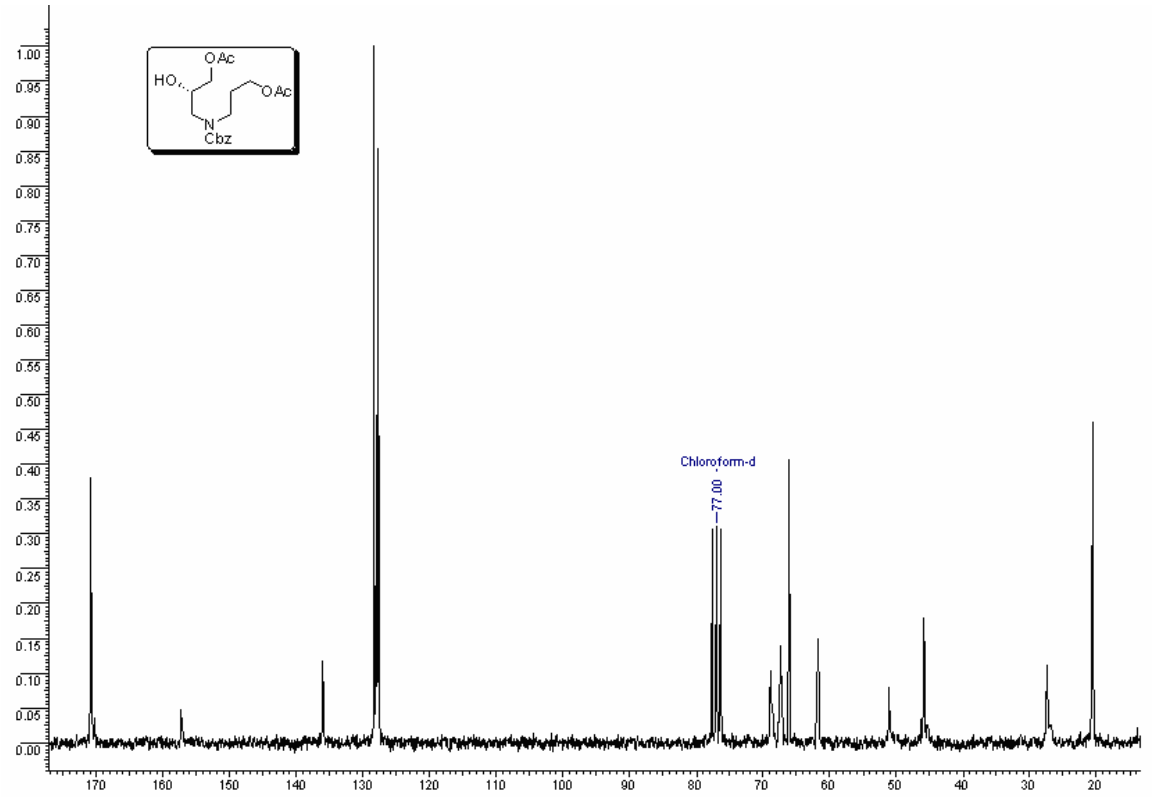
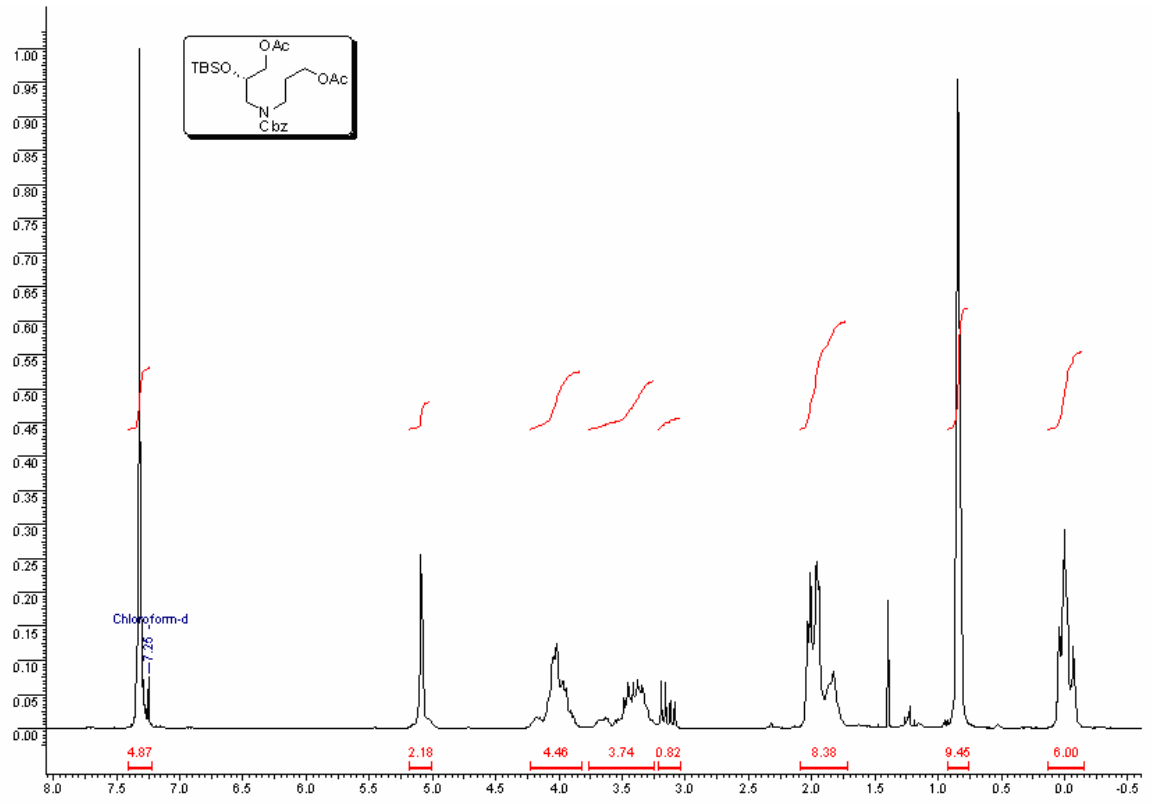
HO
OAc
N
Cbz
Chloroform-d
7.25
5.00
2.05
4.94
4.09
8.63


OAc
HO
OAc
N
Cbz
Chloroform-d
77.00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TBSO
OAc
N
Cbz
Chloroform-d
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2.18
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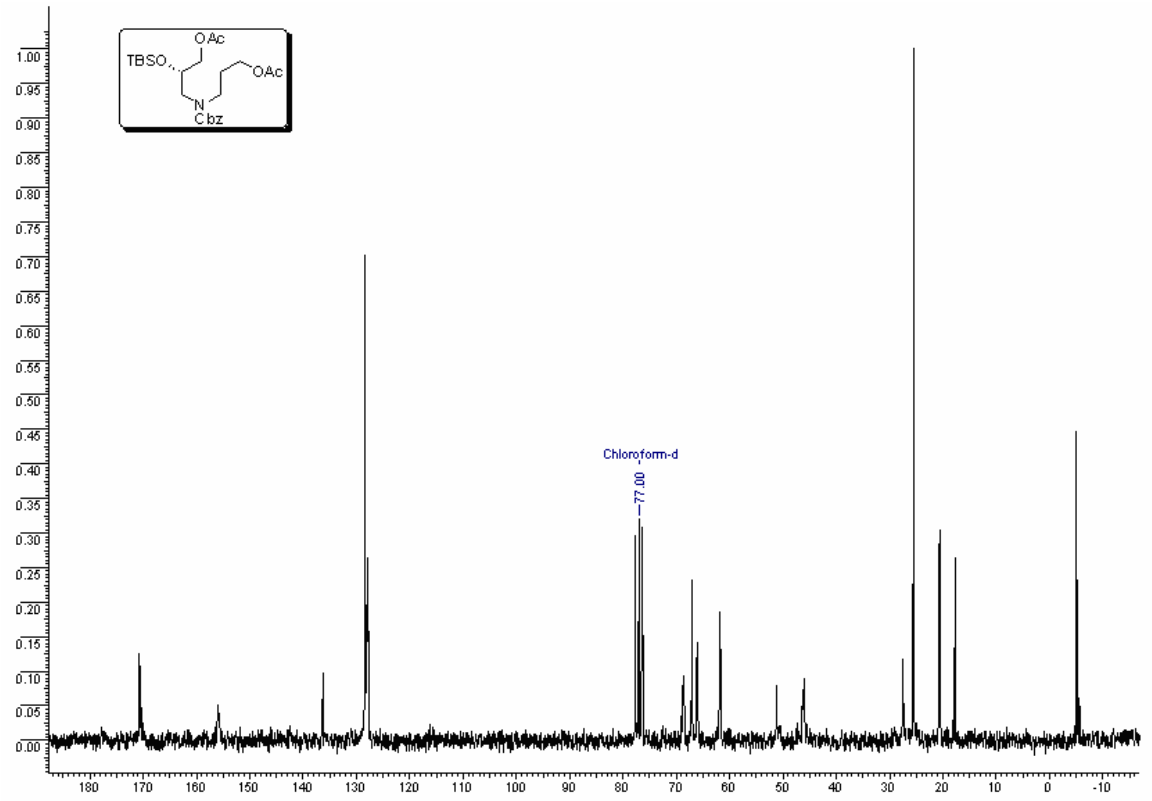
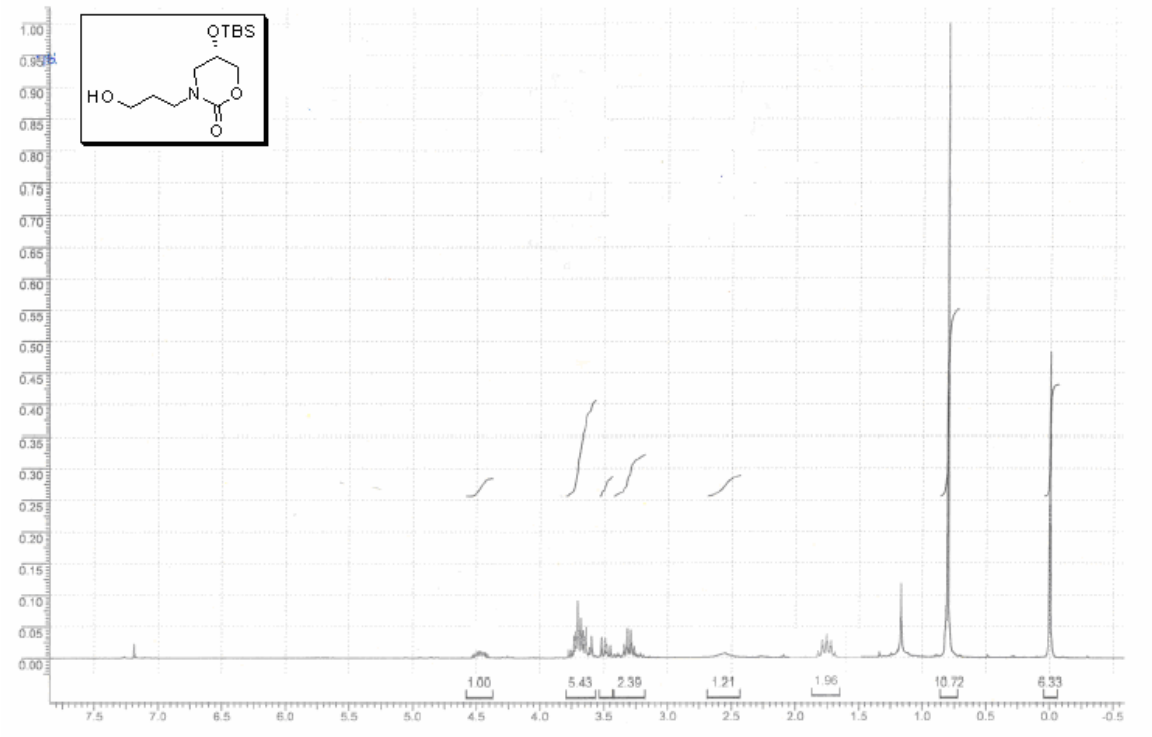
3.74
0.82
8.38
9.45
6.00


OAc
TBSO
OAc
N
Cbz
Chloroform-d
77.00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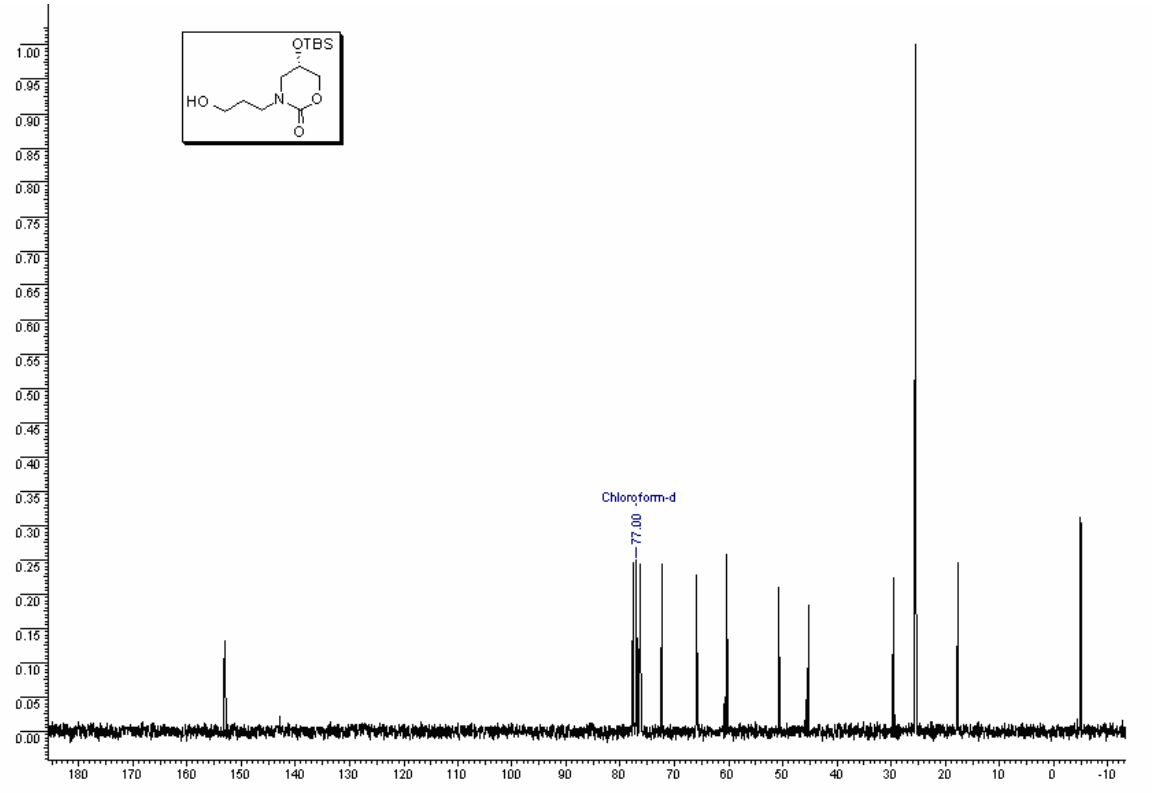
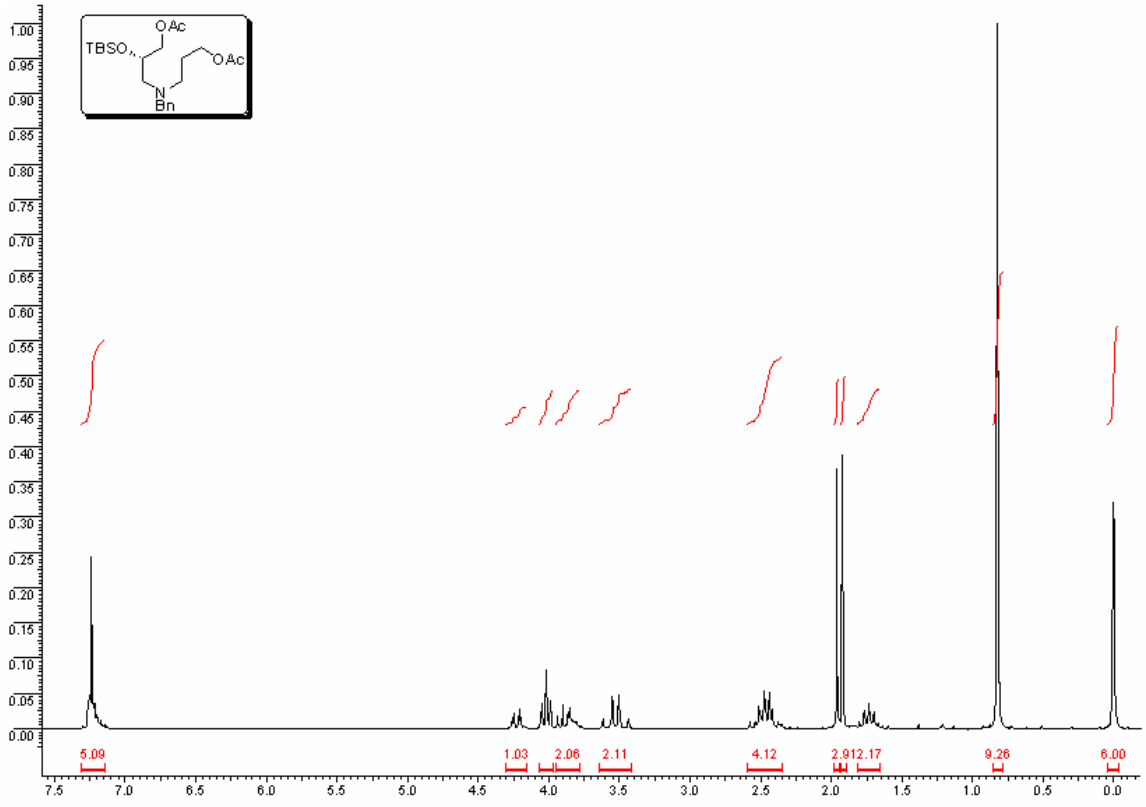
HO
N
O
O
1.00
5.43
2.39
1.21
1.96
10.72
6.33


OTBS
HO
N
O
O
Chloroform-d
77.00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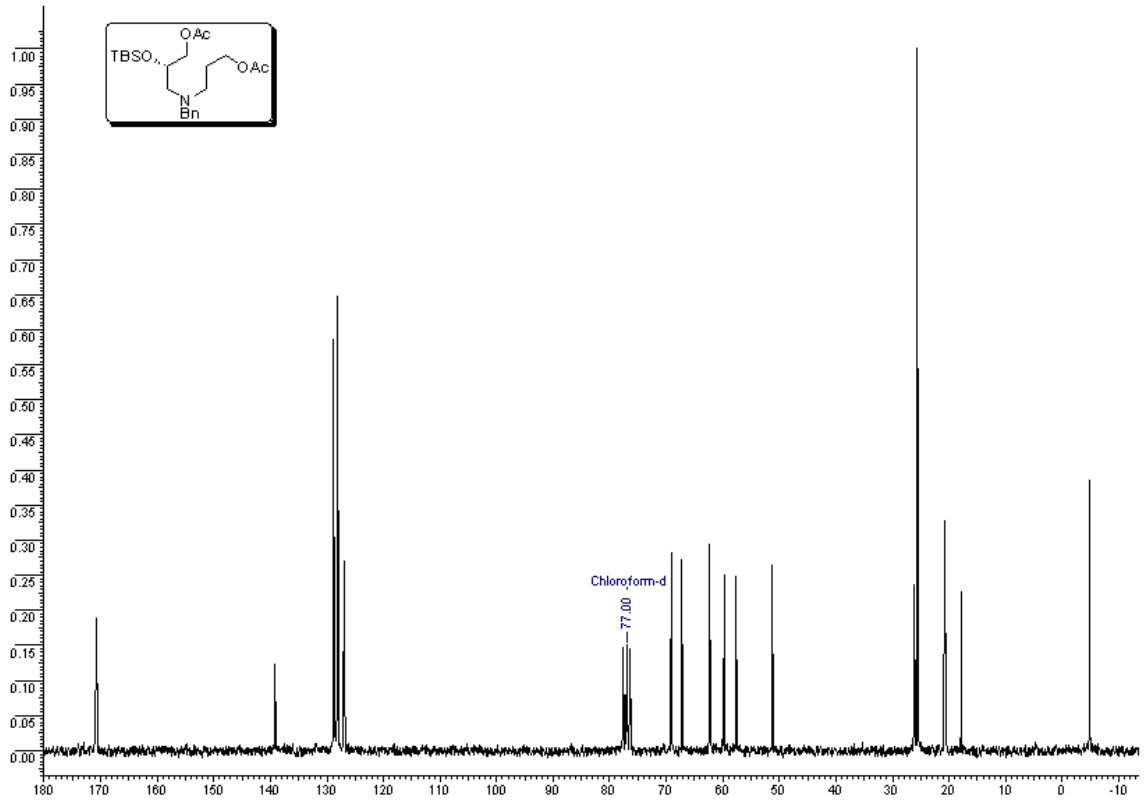
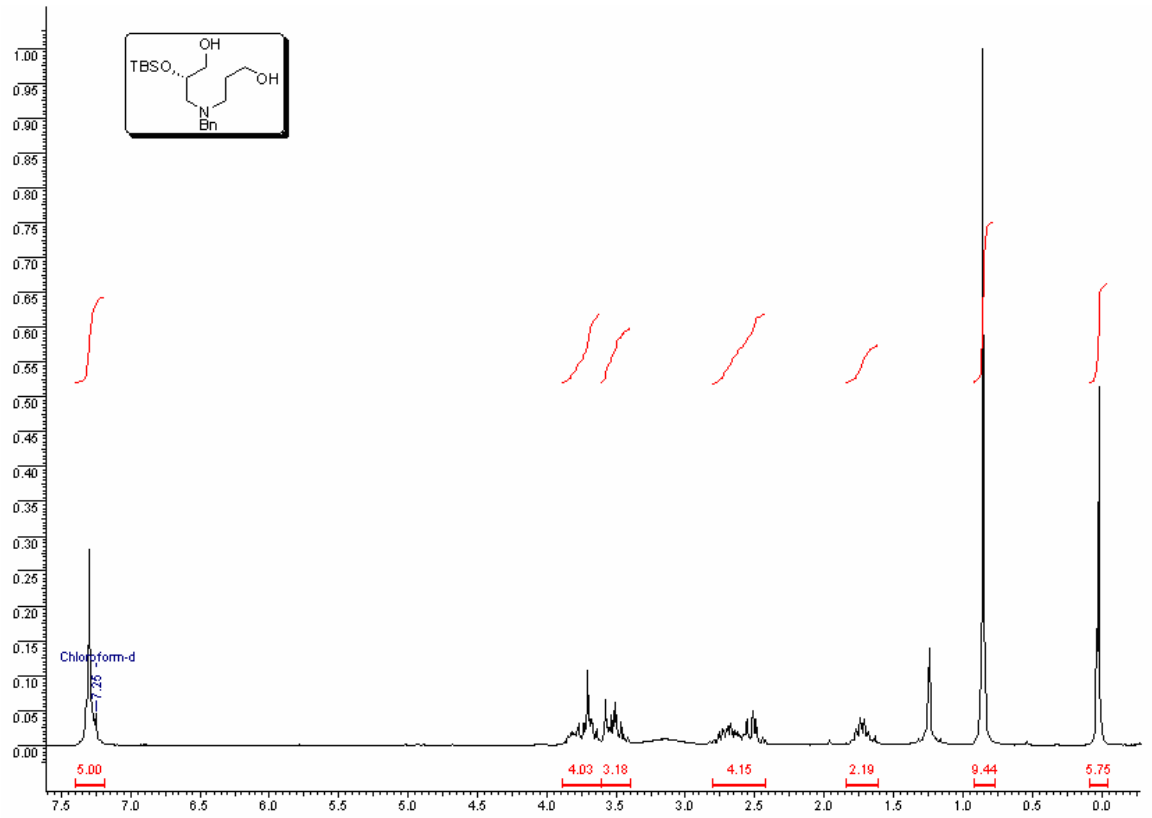
TBSO
OAc
N
Bn
5.09
1.03
2.06
2.11
4.12
2.91
2.17
9.26
6.00


OAc
TBSO
OAc
N
Bn
Chloroform-d
77.00


OH
TBSO
OH
N
Bn
Chloroform-d
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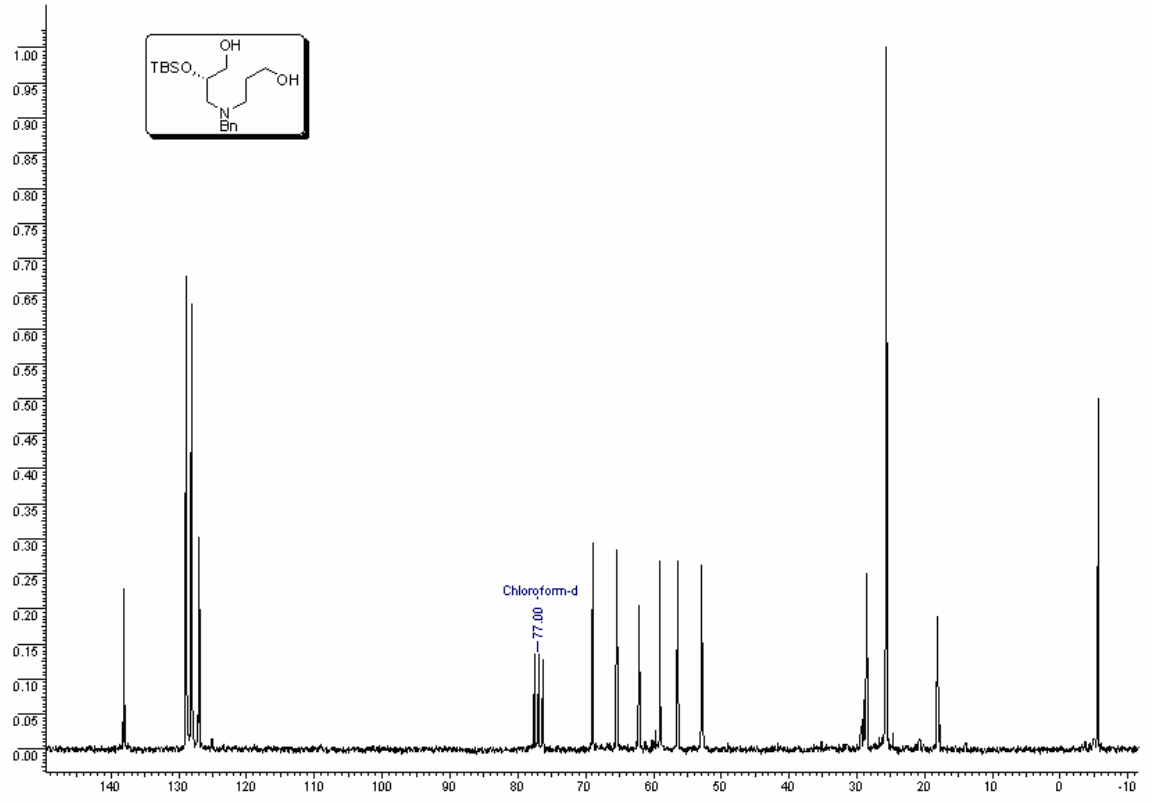
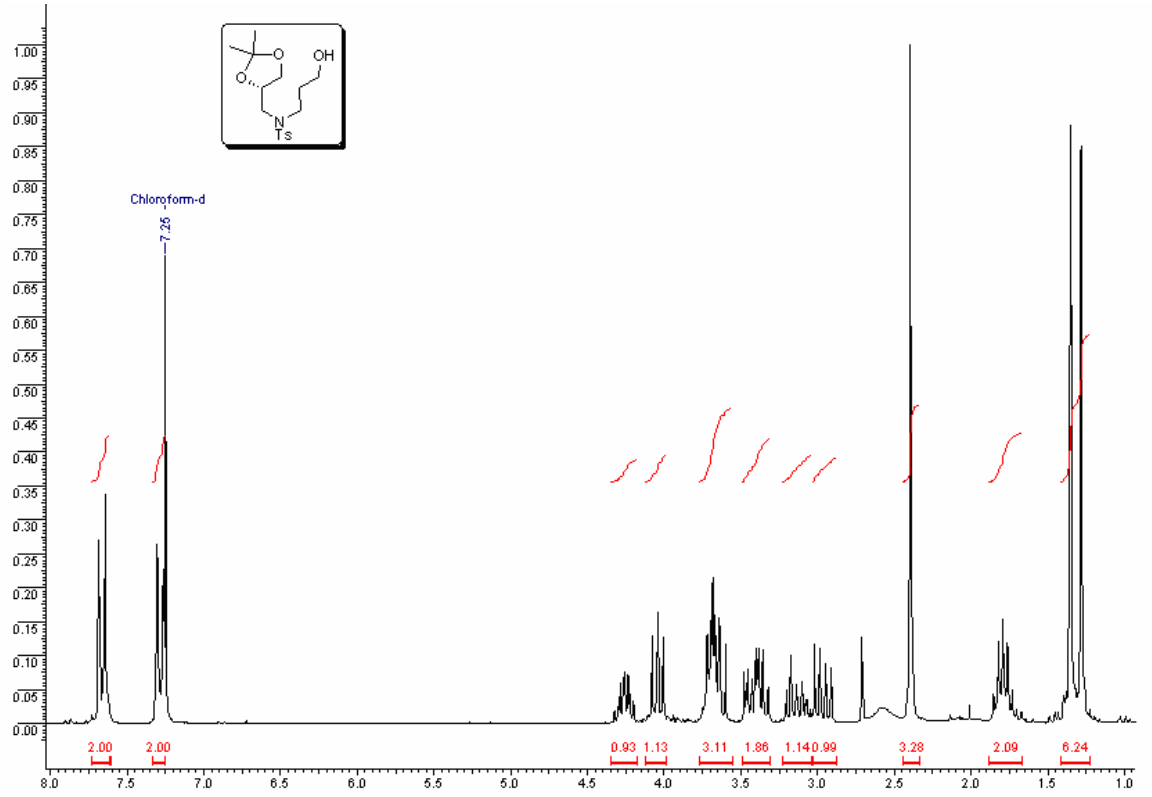
5.00
4.03
3.18
4.15
2.19
9.44
5.75


OH
TBSO
OH
N
Bn
Chloroform-d
77.00


OH
O
O
N
Ts
Chloroform-d
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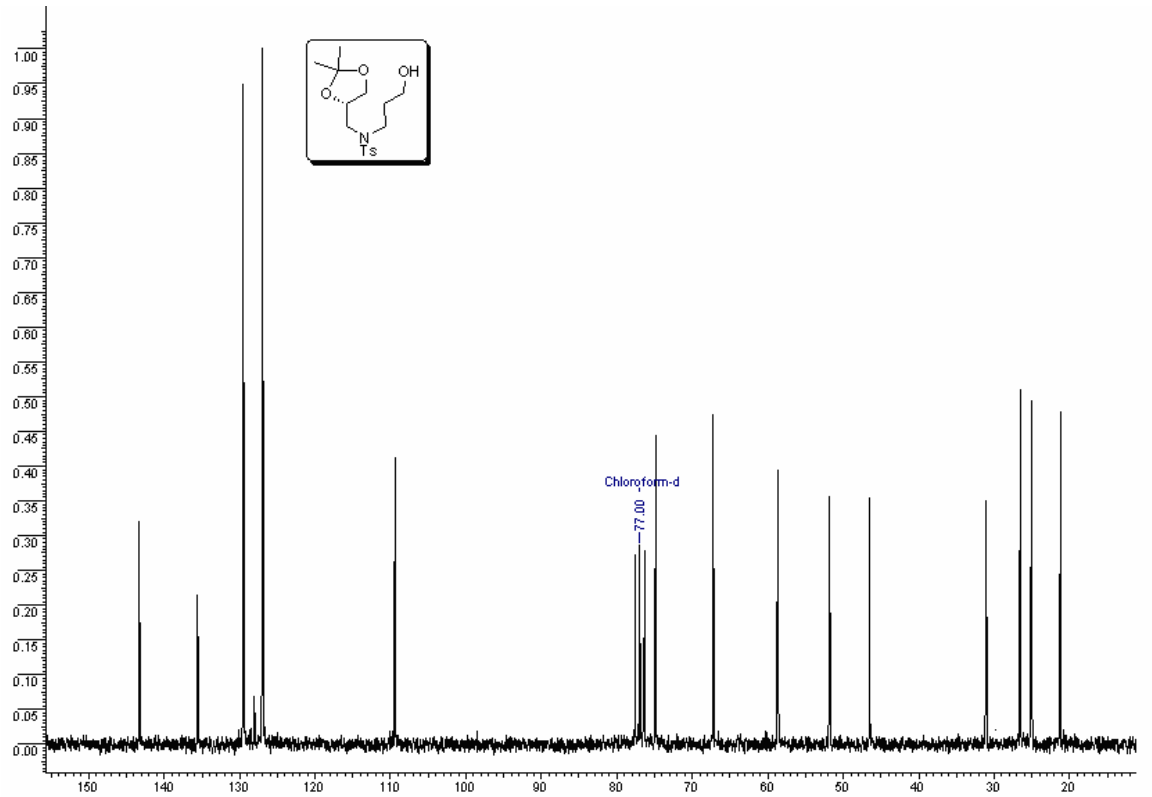
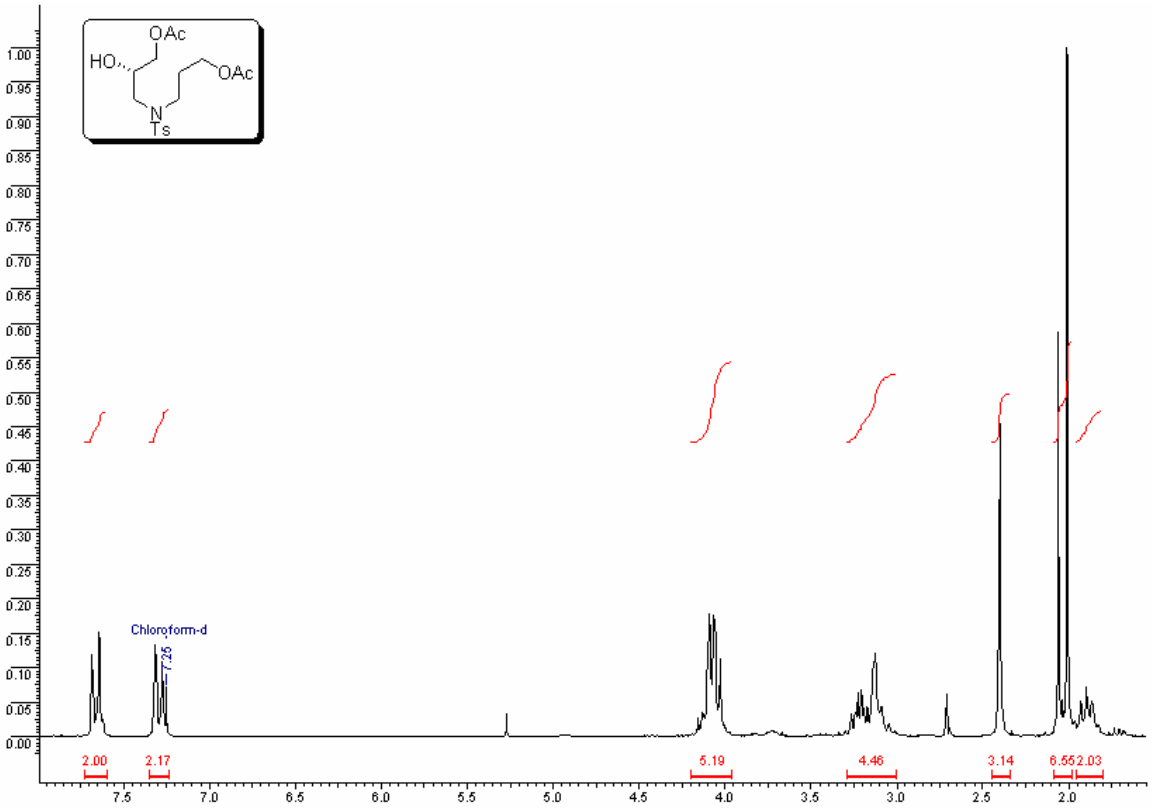
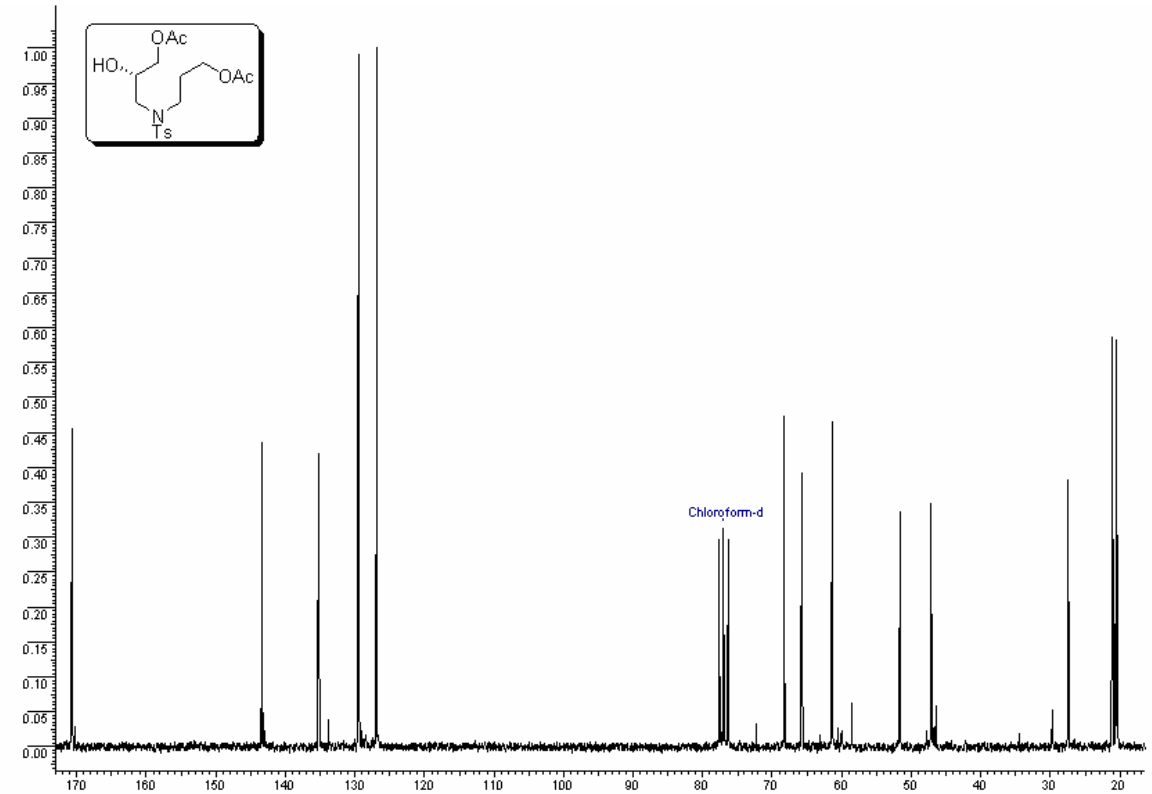
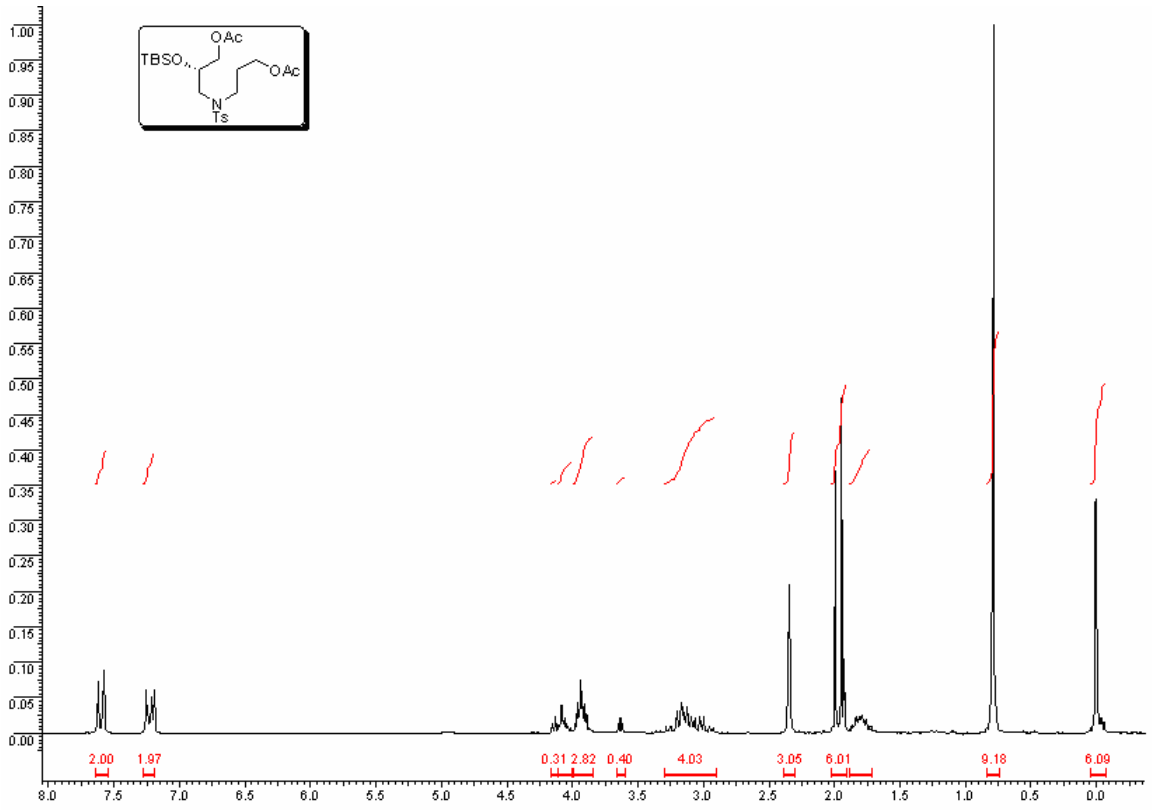
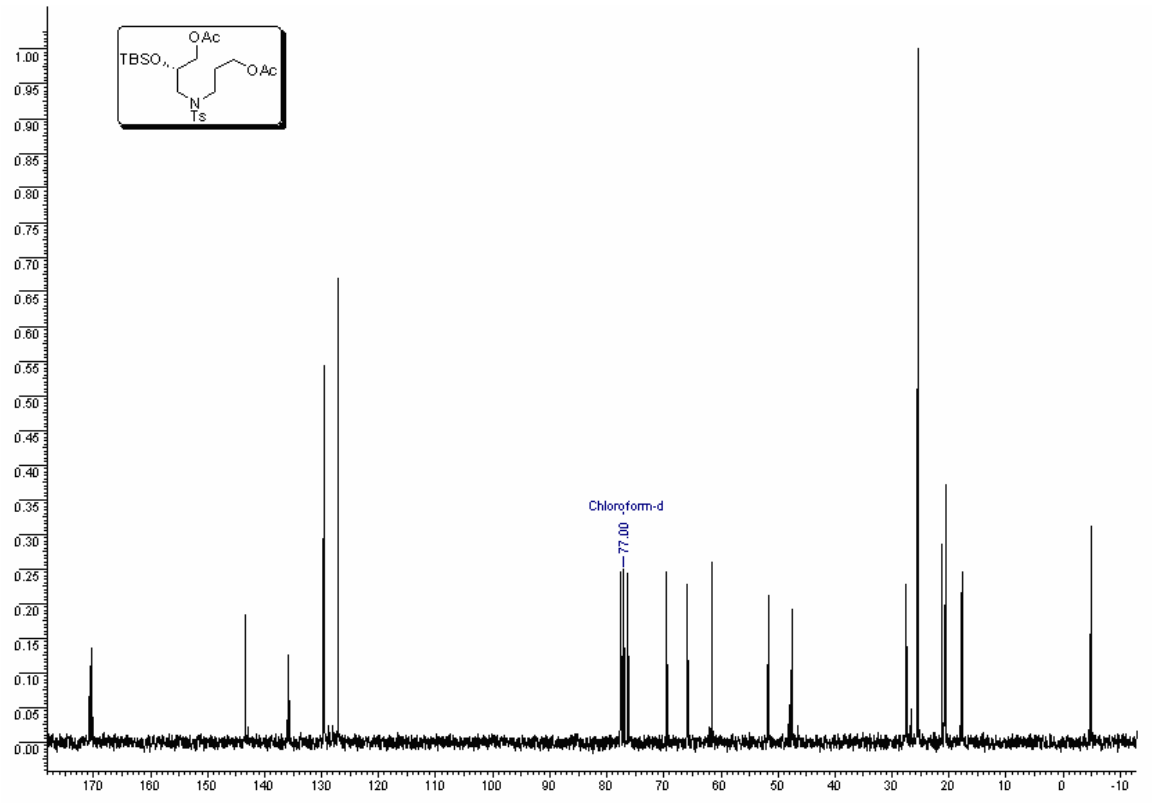
2.00
2.00
0.93
1.13
3.11
1.86
1.14
0.99
3.28
2.09
6.24

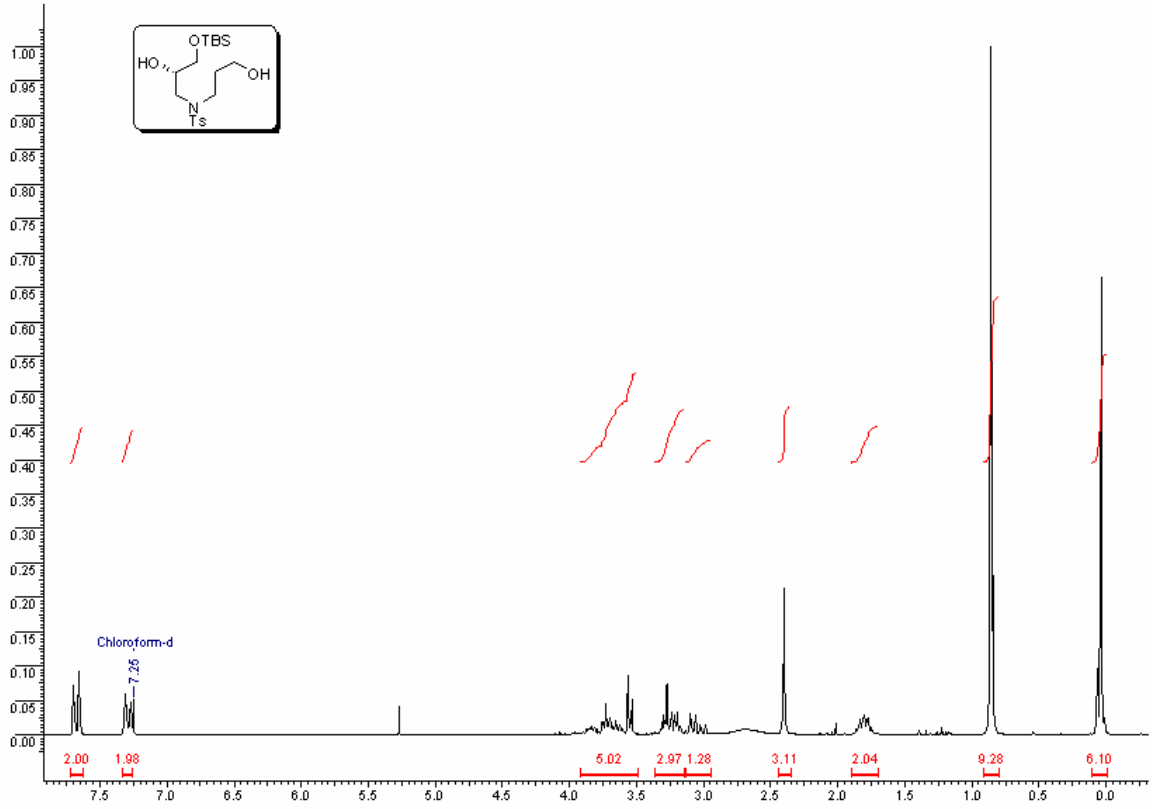

OH
O
O
N
Ts
Chloroform-d
77.00


OAc
HO
OAc
N
Ts
Chloroform-d
7.25
2.00
2.17
5.19
4.46
3.14
6.55
2.03


OAc
HO
OAc
N
Ts
Chloroform-d


OAc
TBSO
OAc
N
Ts
2.00
1.97
0.31
2.82
0.40
4.03
3.05
6.01
9.18
6.09


OAc
TBSO
OAc
N
Ts
Chloroform-d
77.00


OTBS
HO
OH
N
Ts
Chloroform-d
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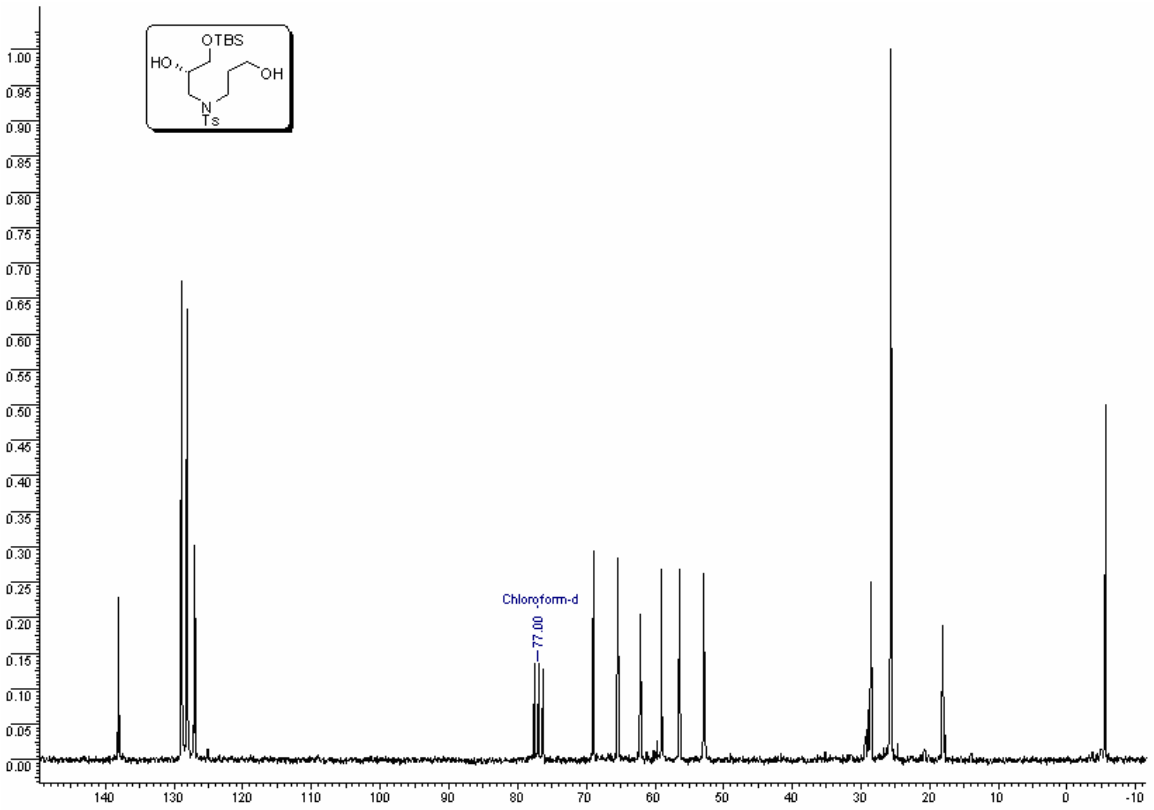
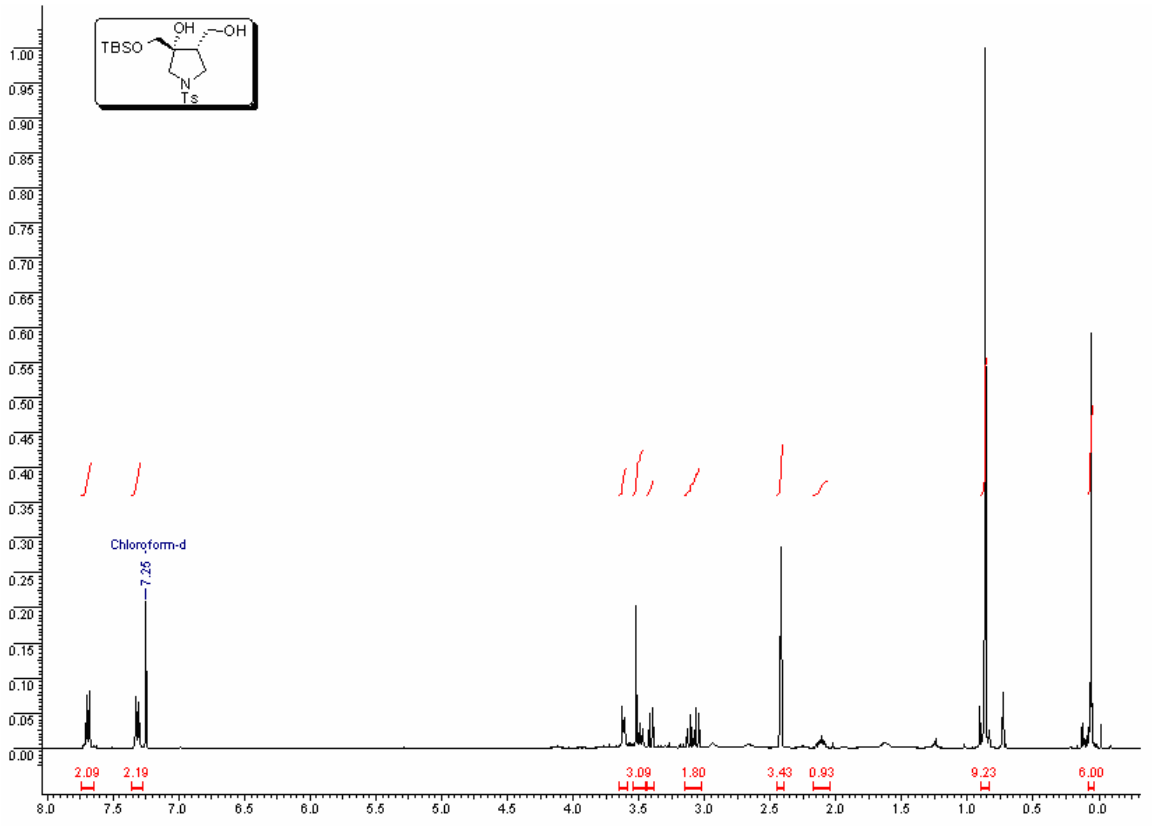
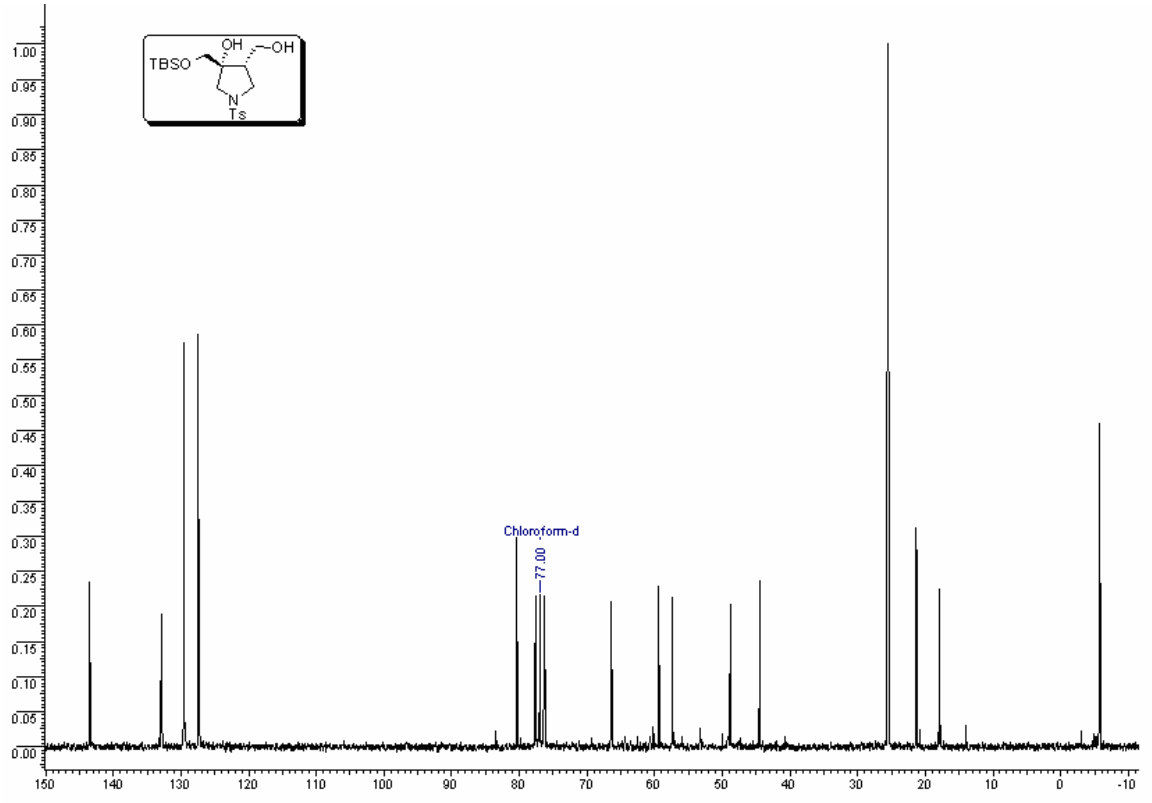
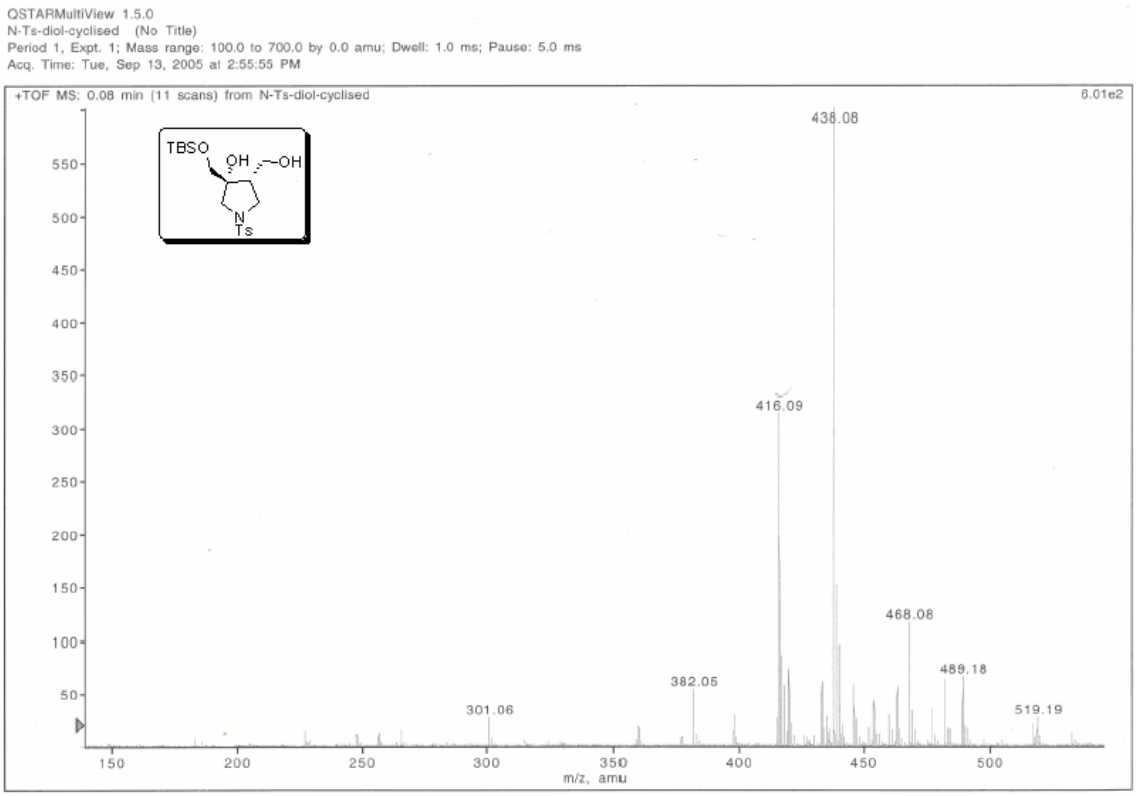
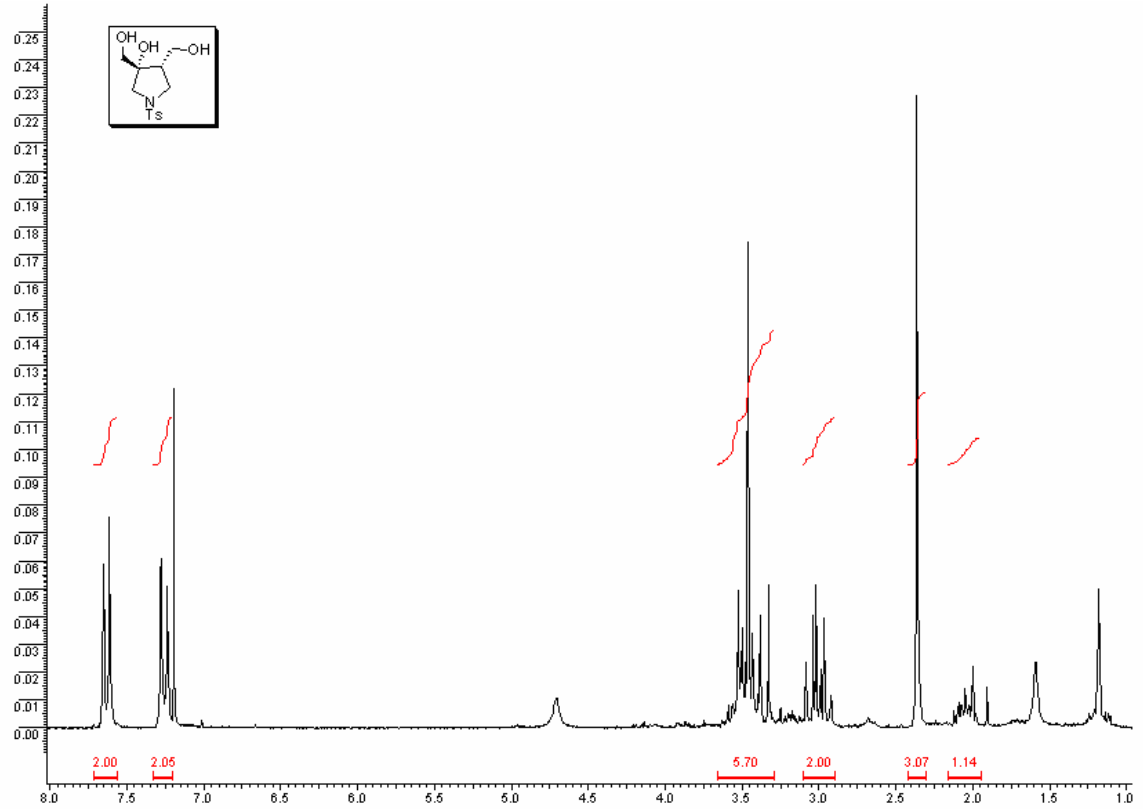
2.00
1.98
5.02
2.97
1.28
3.11
2.04
9.28
6.10

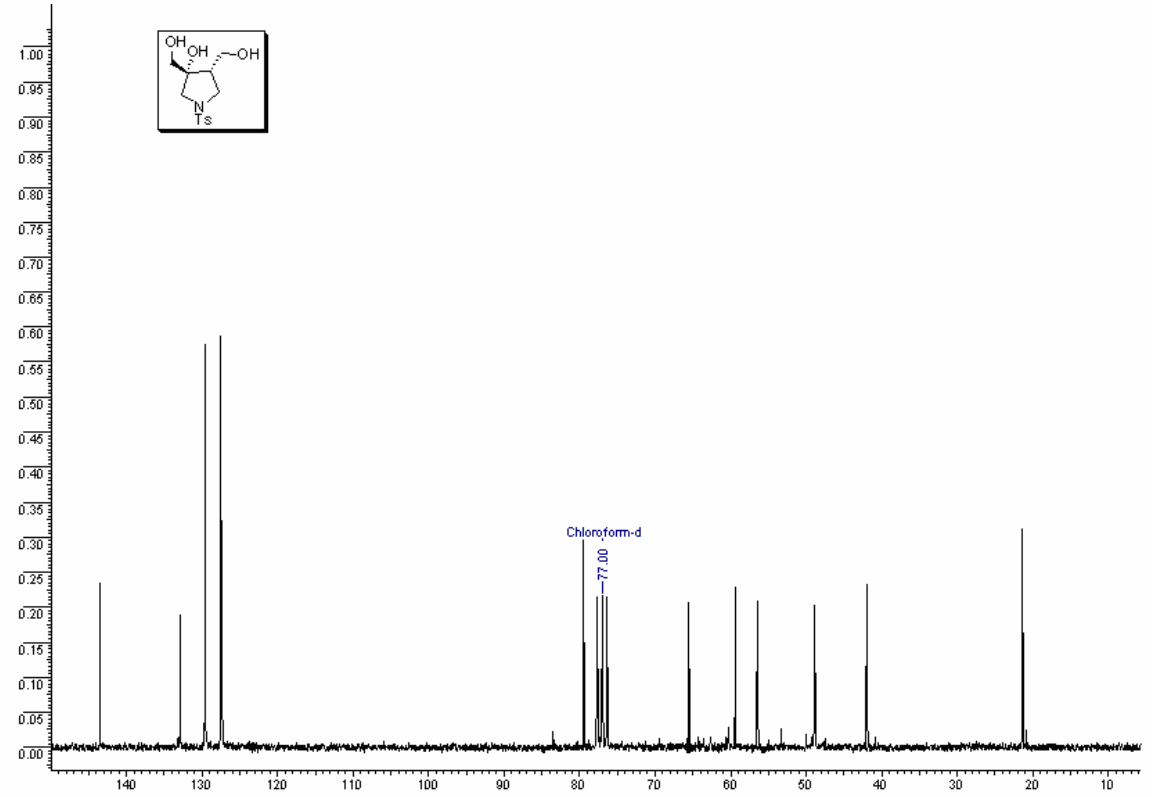

OTBS
HO
OH
N
Ts
Chloroform-d
77.00

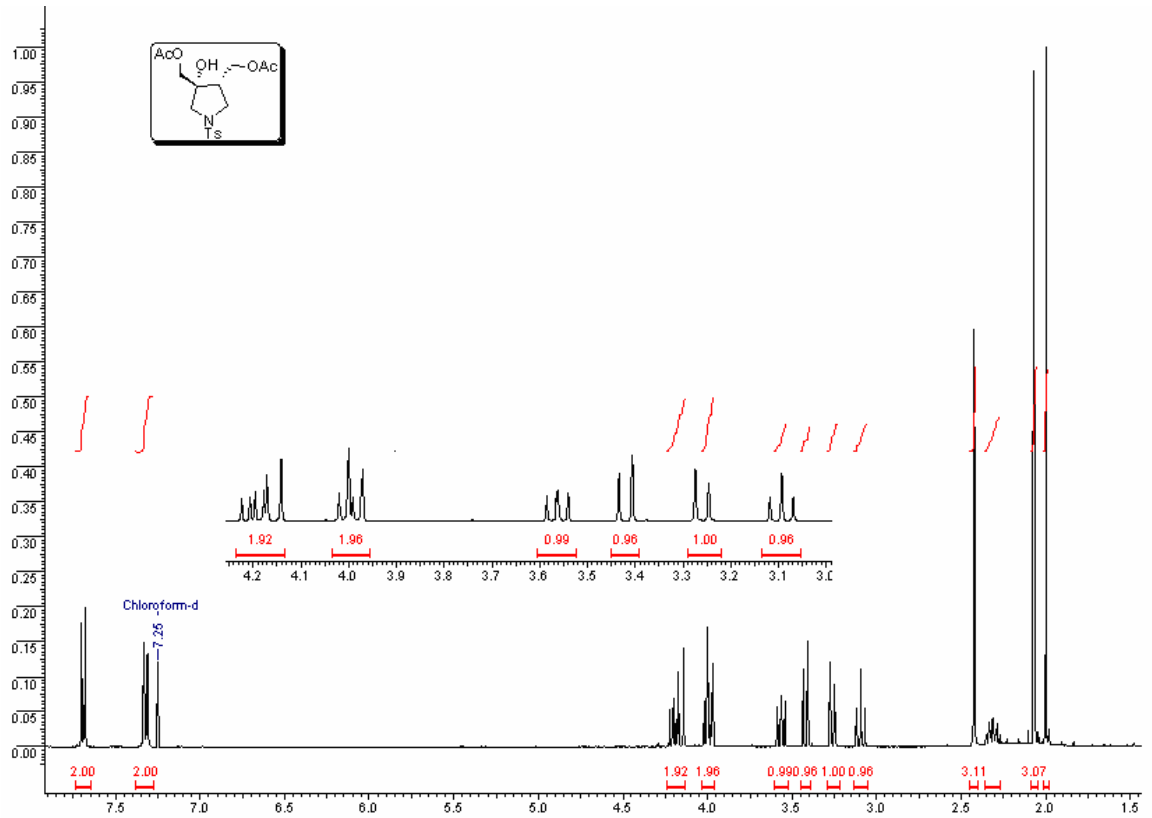

TBSO
OH
OH
N
Ts
Chloroform-d
7.25
2.09
2.19
3.09
1.80
3.43
0.93
9.23
6.00

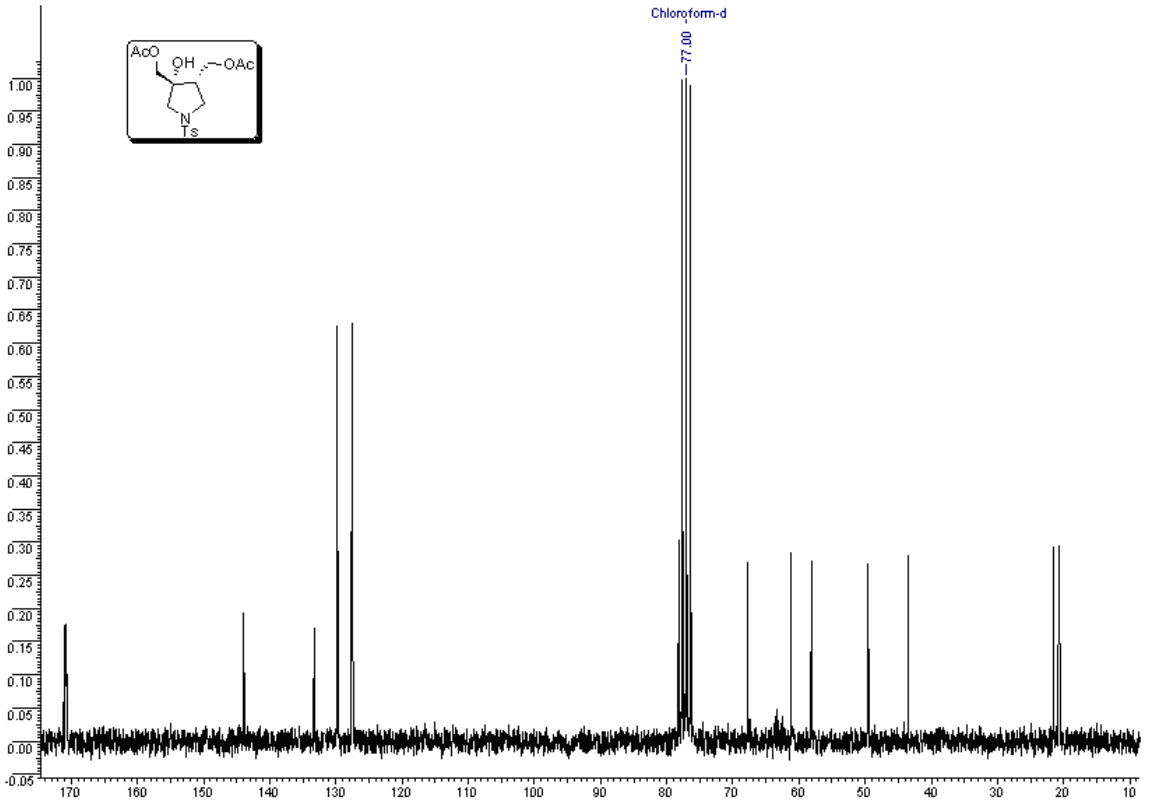

TBSO
OH
OH
N
Ts
Chloroform-d
77.00

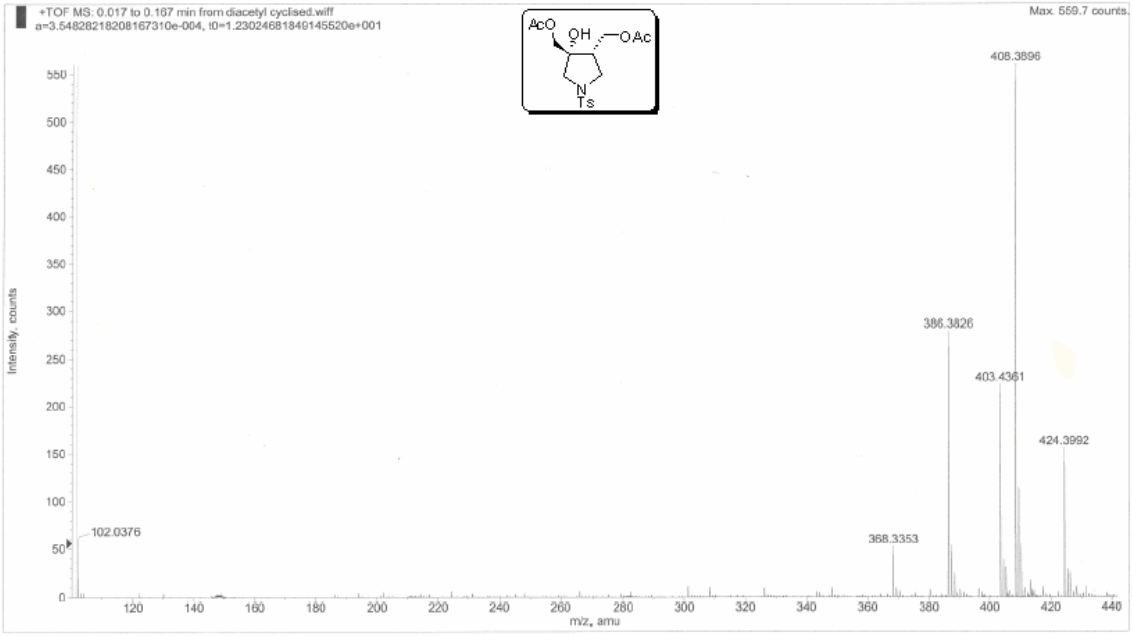

QSTARMultiView 1.5.0
N-Ts-diol-cyclised (No Title)
Period 1, Expt. 1; Mass range: 100.0 to 700.0 by 0.0 amu; Dwell: 1.0 ms; Pause: 5.0 ms
Acq. Time: Tue, Sep 13, 2005 at 2:55:55 PM
+TOF MS: 0.08 min (11 scans) from N-Ts-diol-cyclised
6.01e2
TBSO
OH
OH
N
Ts
438.08
416.09
468.08
489.18
382.05
301.06
519.19
m/z, amu

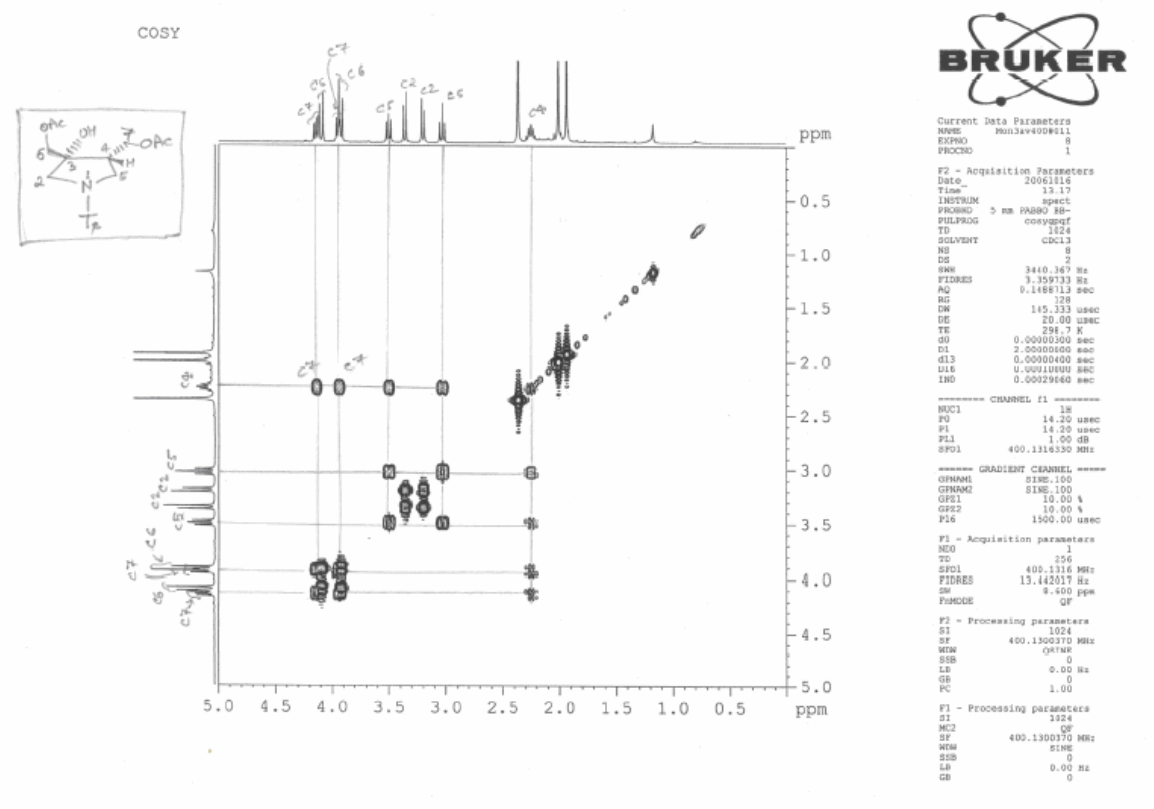

OH
OH
OH
N
Ts
2.00
2.05
5.70
2.00
3.07
1.14


OH
OH
OH
N
Ts
Chloroform-d
77.00


AcO
OH
OAc
N
Ts
1.92
1.96
0.99
0.96
1.00
0.96
Chloroform-d
7.26
2.00
2.00
1.92
1.96
0.99
0.96
1.00
0.96
3.11
3.07


Chloroform-d
77.00
AcO
OH
OAc
N
Ts


+TOF MS: 0.017 to 0.167 min from diacetyl cyclised.wiff
a=3.5482821820816731 0e-004, t0=1.2302468184914552 0e+001
Max. 559.7 counts.
AcO
OH
OAc
N
Ts
408.3896
386.3826
403.4361
424.3992
368.3353
102.0376
Intensity, counts
m/z, amu



BRUKER

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PROCNO                  1

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PULPROG          cosygpqf
TD                   1024
SOLVENT              CDCl3
NS                      8
DS                      2
SWH              3440.367 Hz
FIDRES           3.359733 Hz
AQ               0.1488713 sec
RG                    128
DW                145.333 usec
DE                 20.00 usec
TE                 298.7 K
d0              0.00000300 sec
D1              2.00000000 sec
d13             0.00000400 sec
D16             0.00011000 sec
IN0             0.00029040 sec

======== CHANNEL f1 ========
NUC1                   1H
P0                  14.20 usec
P1                  14.20 usec
PL1                  1.00 dB
SFO1         400.1316330 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPZ1                10.00 %
GPZ2                10.00 %
P16               1500.00 usec

F1 - Acquisition parameters
NDO                     1
TD                    256
SFO1         400.1316 MHz
FIDRES        13.442017 Hz
SW                8.600 ppm
FnMODE                QF

F2 - Processing parameters
SI                    1024
SF           400.1300370 MHz
WDW                  QSINE
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00

F1 - Processing parameters
SI                    1024
MC2                     QF
SF           400.1300370 MHz
WDW                  SINE
SSB                     0
LB                   0.00 Hz
GB                      0
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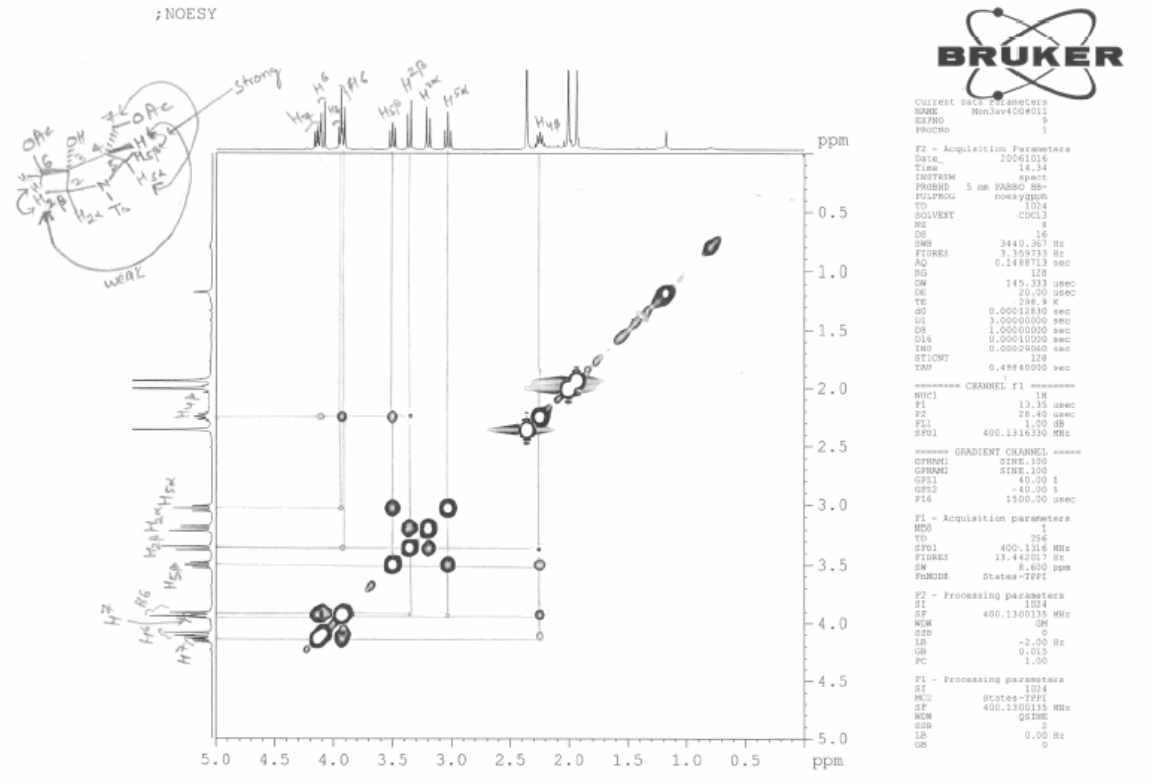

BRUKER

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Current Data Parameters
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EXPNO                   9
PROCNO                  1

F2 - Acquisition Parameters
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Time                 14.34
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG          noesygpph
TD                   1024
SOLVENT              CDCl3
NS                      8
DS                     16
SWH              3440.367 Hz
FIDRES           3.359733 Hz
AQ               0.1488713 sec
RG                    128
DW                145.333 usec
DE                 20.00 usec
TE                 298.9 K
d0              0.00012830 sec
D1              3.00000000 sec
D8              1.00000000 sec
D16             0.00010000 sec
IN0             0.00029060 sec
ST1CNT                128
TM0             0.49840000 sec

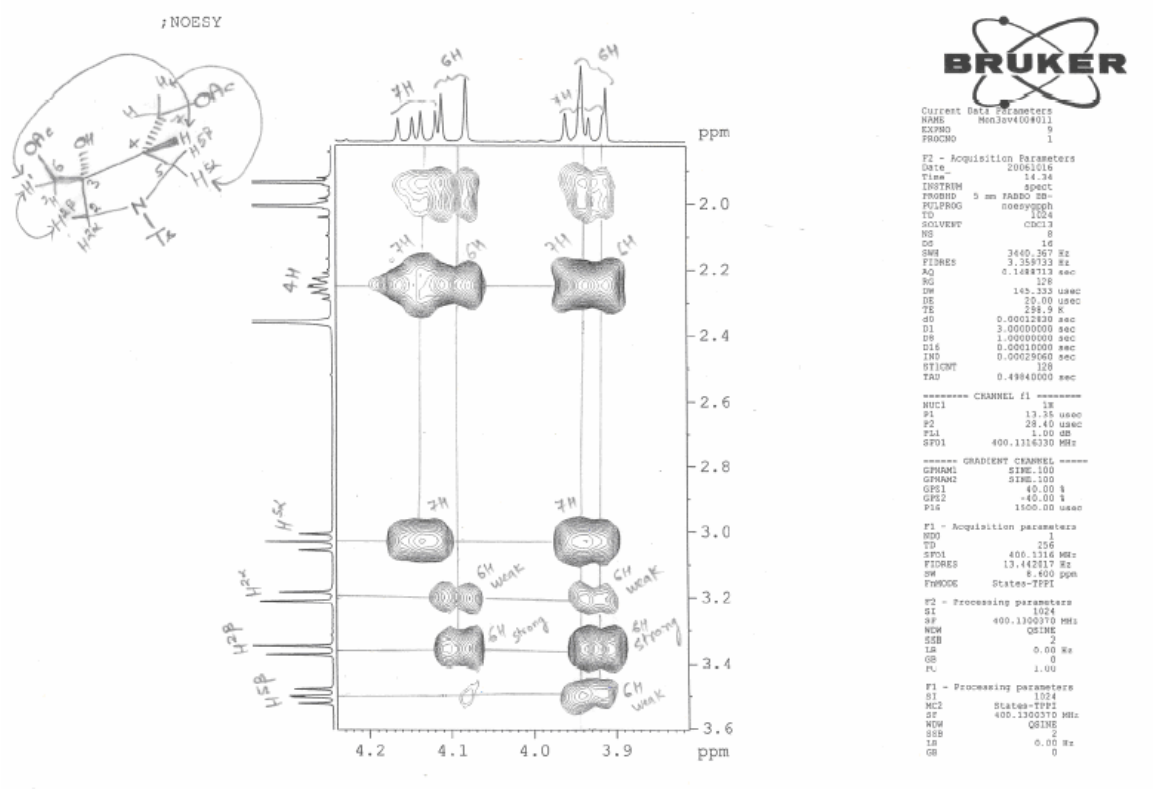
======== CHANNEL f1 ========
NUC1                   1H
P1                  13.35 usec
P2                  26.40 usec
PL1                  1.00 dB
SFO1         400.1316330 MHz

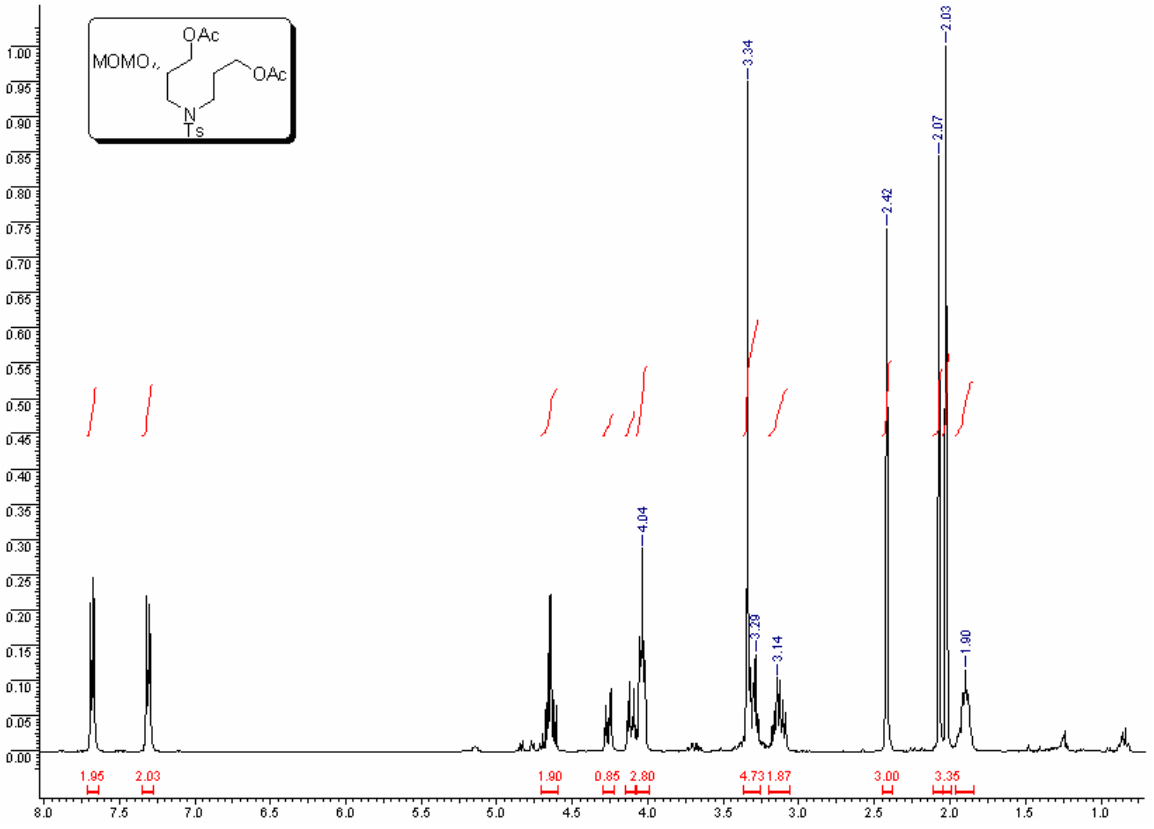
====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPZ1                40.00 %
GPZ2               -40.00 %
P16               1500.00 usec

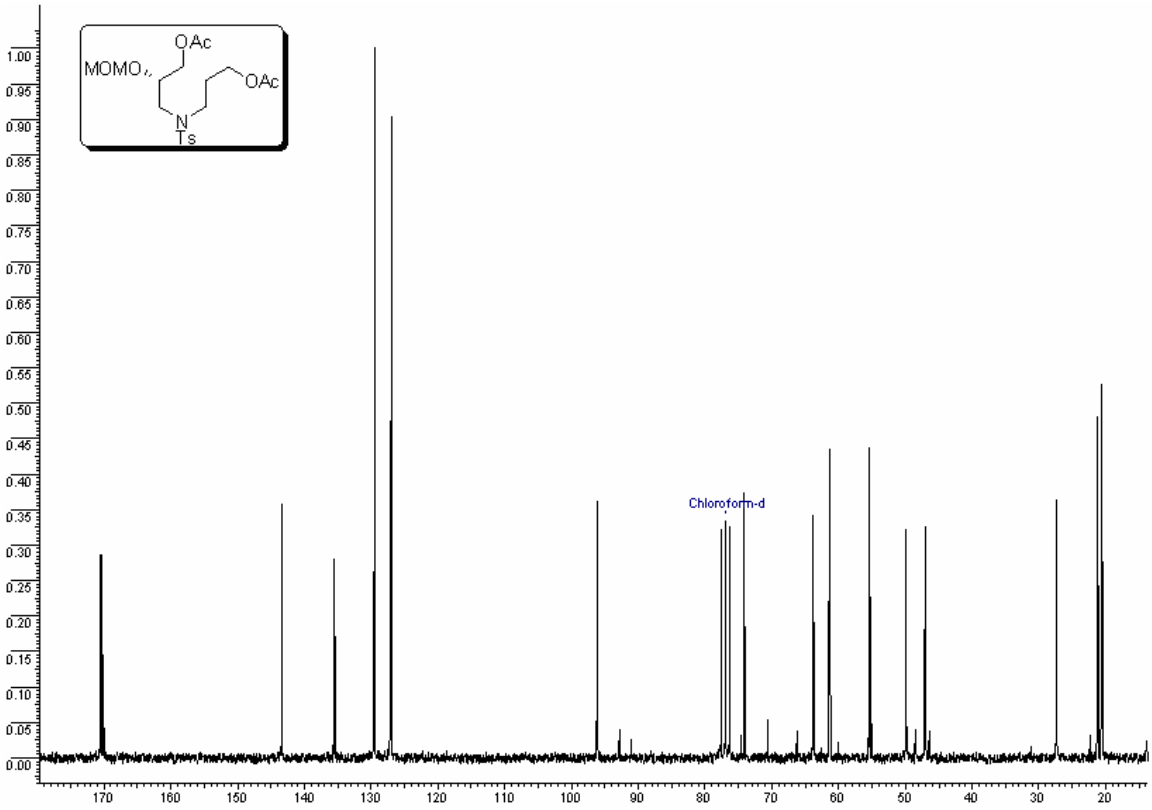
F1 - Acquisition parameters
NDO                     1
TD                    256
SFO1         400.1316 MHz
FIDRES        13.442017 Hz
SW                8.600 ppm
FnMODE        States-TPPI

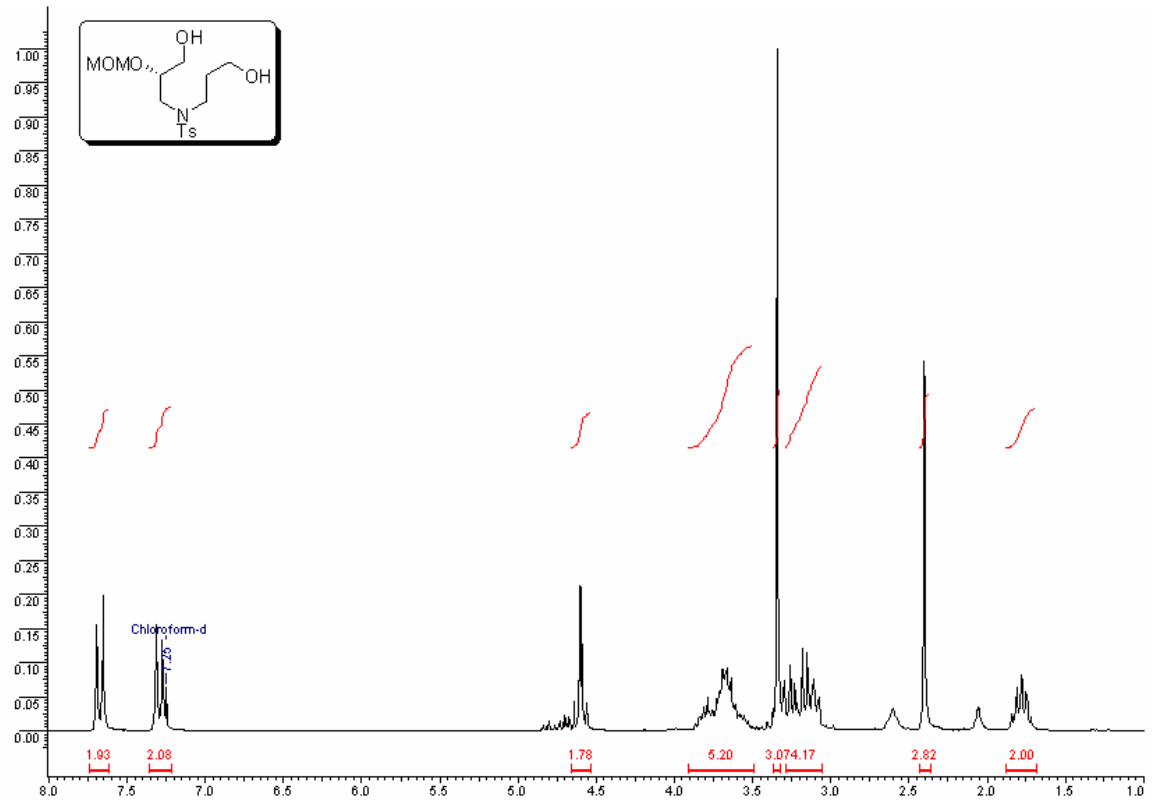
F2 - Processing parameters
SI                    1024
SF           400.1300135 MHz
WDW                    GM
SSB                     0
LB                   -2.00 Hz
GB                   0.015
PC                   1.00

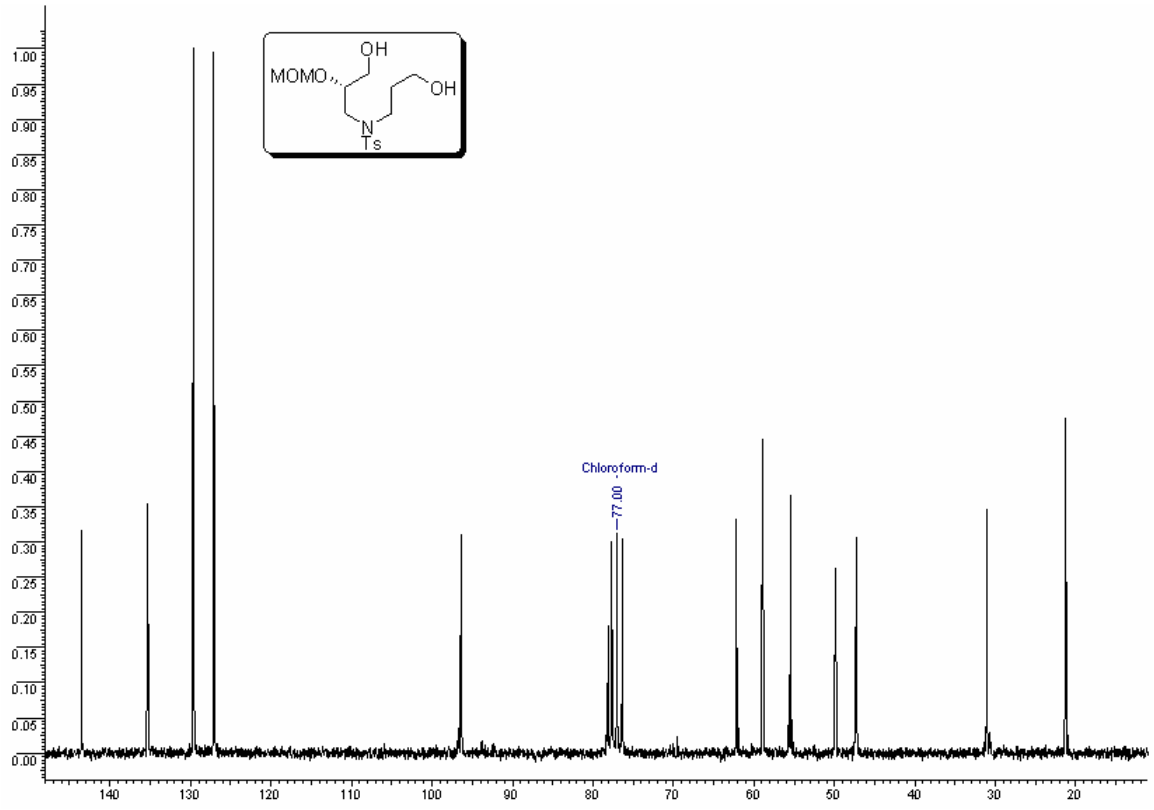
F1 - Processing parameters
SI                    1024
MC2           States-TPPI
SF           400.1300135 MHz
WDW                  QSINE
SSB                     2
LB                   0.00 Hz
GB                      0
```

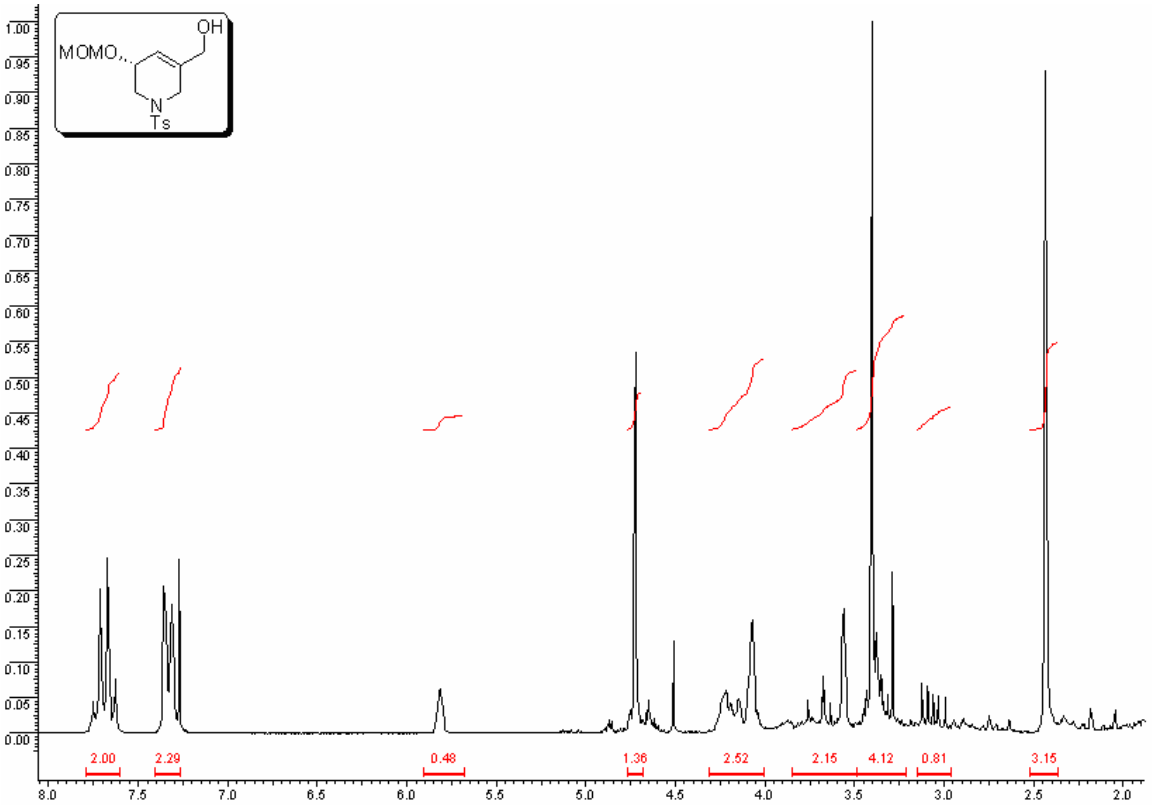

; NOESY
ppm
4.2
4.1
4.0
3.9
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
4H
7H
6H
6H weak
6H strong
BRUKER

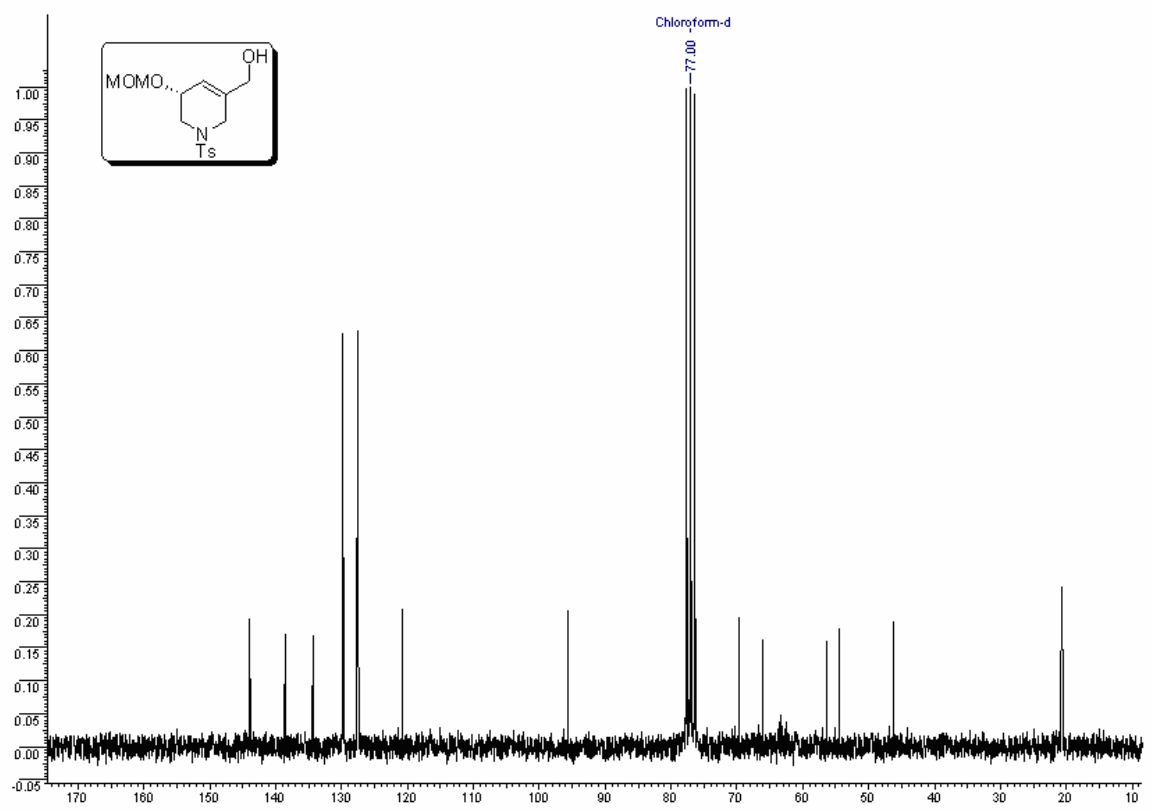

MOMO
OAc
OAc
N
Ts
3.34
2.03
2.07
2.42
4.04
3.29
3.14
1.90
1.95
2.03
1.90
0.85
2.80
4.73
1.87
3.00
3.35

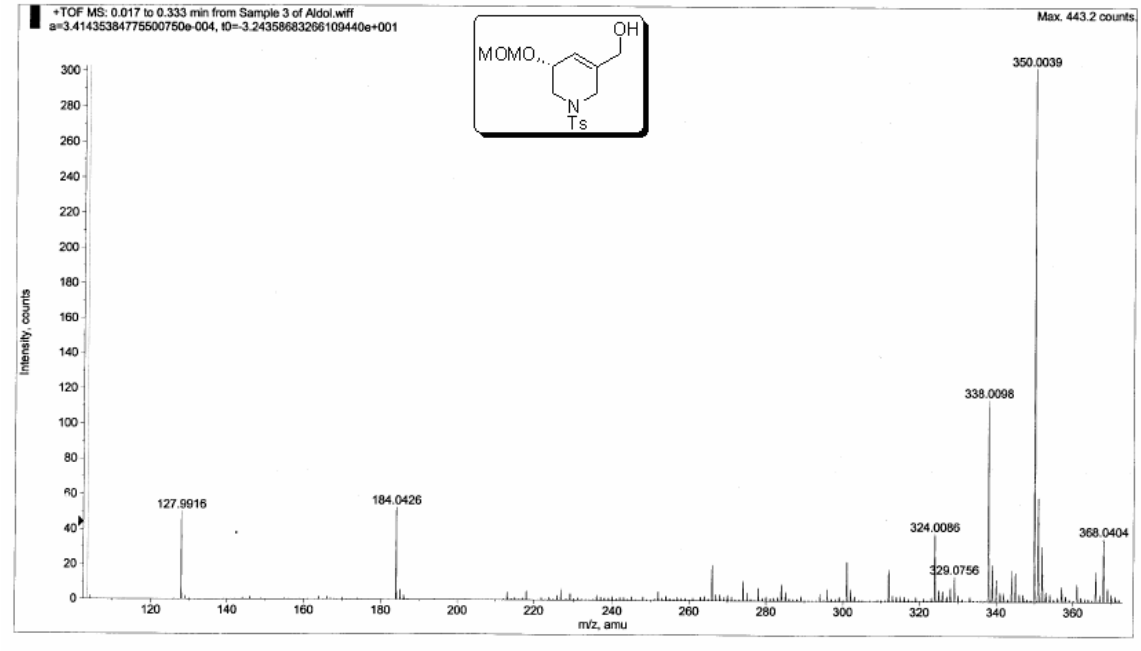

OAc
MOMO
OAc
N
Ts
Chloroform-d


OH
MOMO
OH
N
Ts
Chloroform-d
1.93
2.08
1.78
5.20
3.07
4.17
2.82
2.00


OH
MOMO
OH
N
Ts
Chloroform-d
77.00


OH
MOMO
N
Ts
2.00
2.29
0.48
1.36
2.52
2.15
4.12
0.81
3.15


Chloroform-d
77.00
MOMO
OH
N
Ts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Max. 443.2 counts.
MOMO
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Intensity, counts
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338.0098
127.9916
184.0426
324.0086
368.0404
329.0756

Chapter 4

Direct Diastereoselective Aldol Reaction: New Approach towards Imino Sugars

"I'm on the verge of a major breakthrough, but I'm also at that point where chemistry leaves off and physics begins, so I'll have to drop the whole thing."

"The man who cannot wonder, who does not habitually wonder is a pair of spectacles behind which there are no eyes"
-"Carlyle"

4.1 Introduction

Glycosidases are the enzymes that catalyze the cleavage of glycosidic bonds in glycoconjugates and also responsible for the biosynthesis of oligosaccharides, play an important role in biochemistry and metabolism (Figure 4.1).

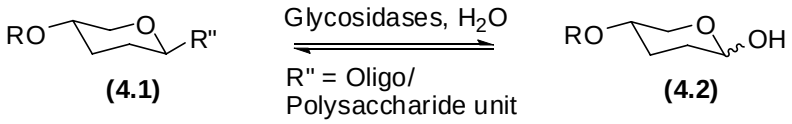
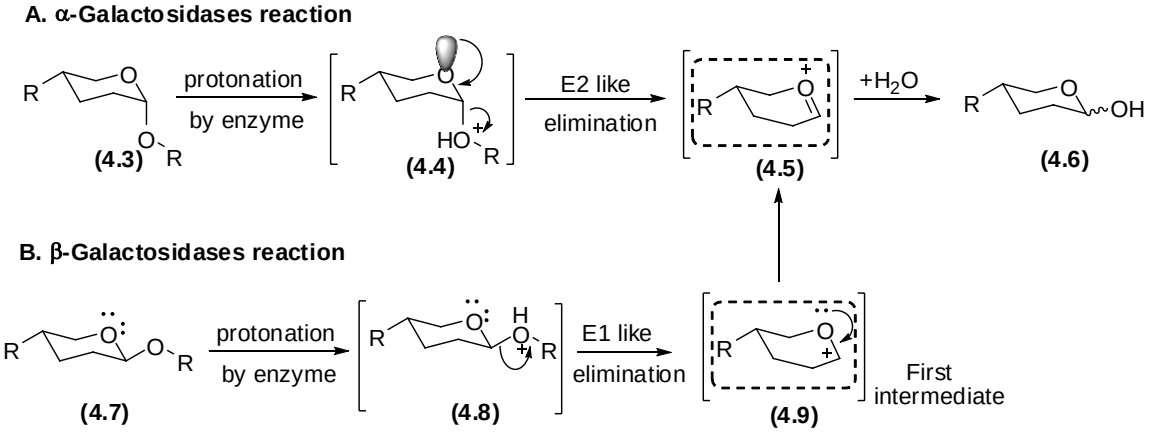


Figure 4.1: Glycosidic cleavage

A primary classification of glycosidases can be done based on the position of the glycosidic bond that is cleaved by the enzymes. Enzymes catalyzing the cleavage of α-glycosidic bond are termed as α-glycosidases while those cleaving β-glycosidic bond are termed as β-glycosidases. A typical glycosidase reaction mechanism is shown in Scheme 4.1.



Scheme 4.1: α- and β-Glycosidases reactions

α-Glycosidases are generally believed to act through an E2 type elimination mechanism during which a positively charged aglycon (the leaving group) and the lone pair of the ring oxygen are positioned antiperiplaner, cooperatively facilitating the glycosidic bond

cleavage.[1] In case of a β-glycosidases reaction, the positive charged aglycon leaves via E1 like mechanism, involving the glycosyl cation **4.9**, further stabilized by the ring oxygen to give intermediate **4.5** (transition state). Thus as seen in Scheme 4.1, although the final reaction intermediate of both the reaction mechanisms is the same flattened half chair oxocarbenium ion **4.5**.

As is the case with any other enzyme, any chemical entity that is capable of mimicking either the charge or shape (or both) of the substrate or that of any of the transition states, can act as a reversible inhibitors of that particular glycosidase. These entities are termed as ***glycosidase inhibitors***. Several comprehensive reviews and accounts on glycosidases and glycosidase inhibitors have been published, covering various aspects of this field.[2]

In particular, iminosugars are an attractive class of carbohydrate mimics, many of which exhibit glycohydrolase inhibition activity.[3] These imino sugars are the polyhydroxylated nitrogen heterocycles (azasugars) represent the sugar analogues in which the ring oxygen has been substituted by nitrogen atom. These "sugar-shaped alkaloids" are widespread in plants and microorganisms[4] and are believed to bind to the active site of the glycosidases by closely mimicking the charge and shape of the transition state of the glycosidic cleavage reaction.

Ever since the pioneering work by Paulsen on sugar analogues with basic nitrogen instead of oxygen in the ring (also called the azasugars or iminosugars)[5] and the discovery of such a natural product (nojirimycin),[6] over three dozen naturally occurring iminosugars have been identified and many additional analogues and homologues have been synthesized, opening up an active research area (Figure 4.2).

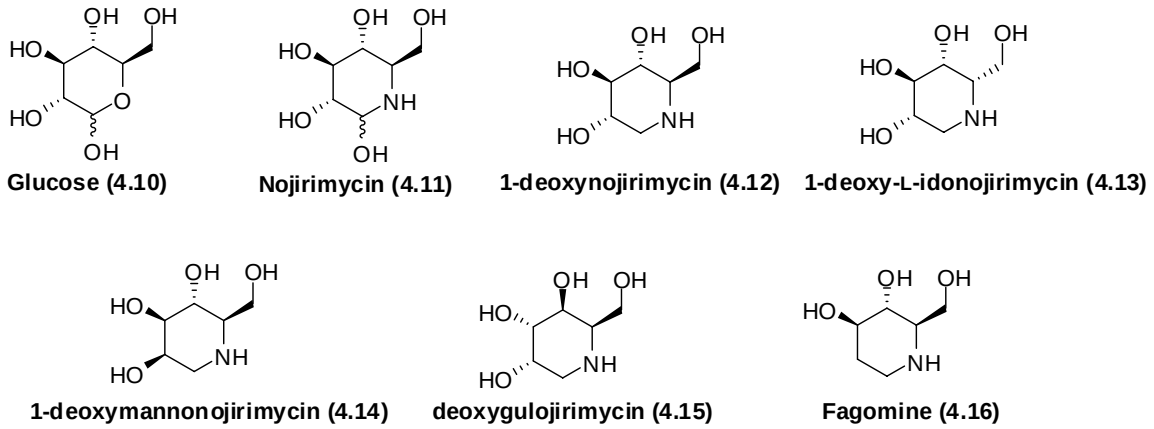
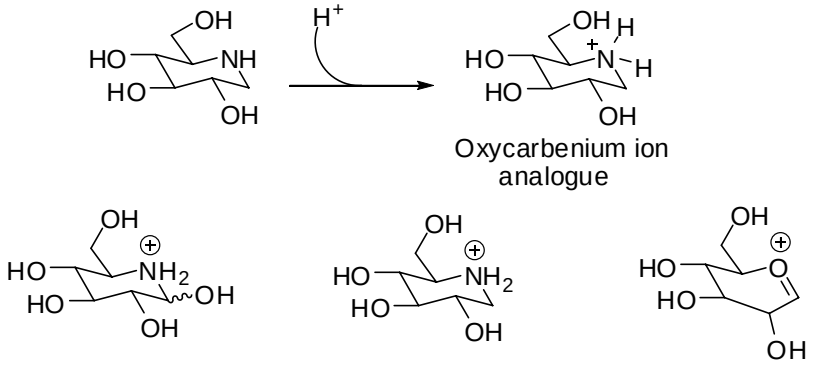


Figure 4.2: Imino sugars

These iminosugars or polyhydroxylated alkaloids are low molecular-weight compounds, able to inhibit glycosidases because they mimic the conformation and charge of the oxocarbenium ion intermediate **4.5** normally generated in the transition state with sp^2 character during the glycosidic bond cleavage (Scheme 4.2).



Scheme 4.2: Proposed mechanism and transition state analogue for α-glycosidase inhibition by iminosugars

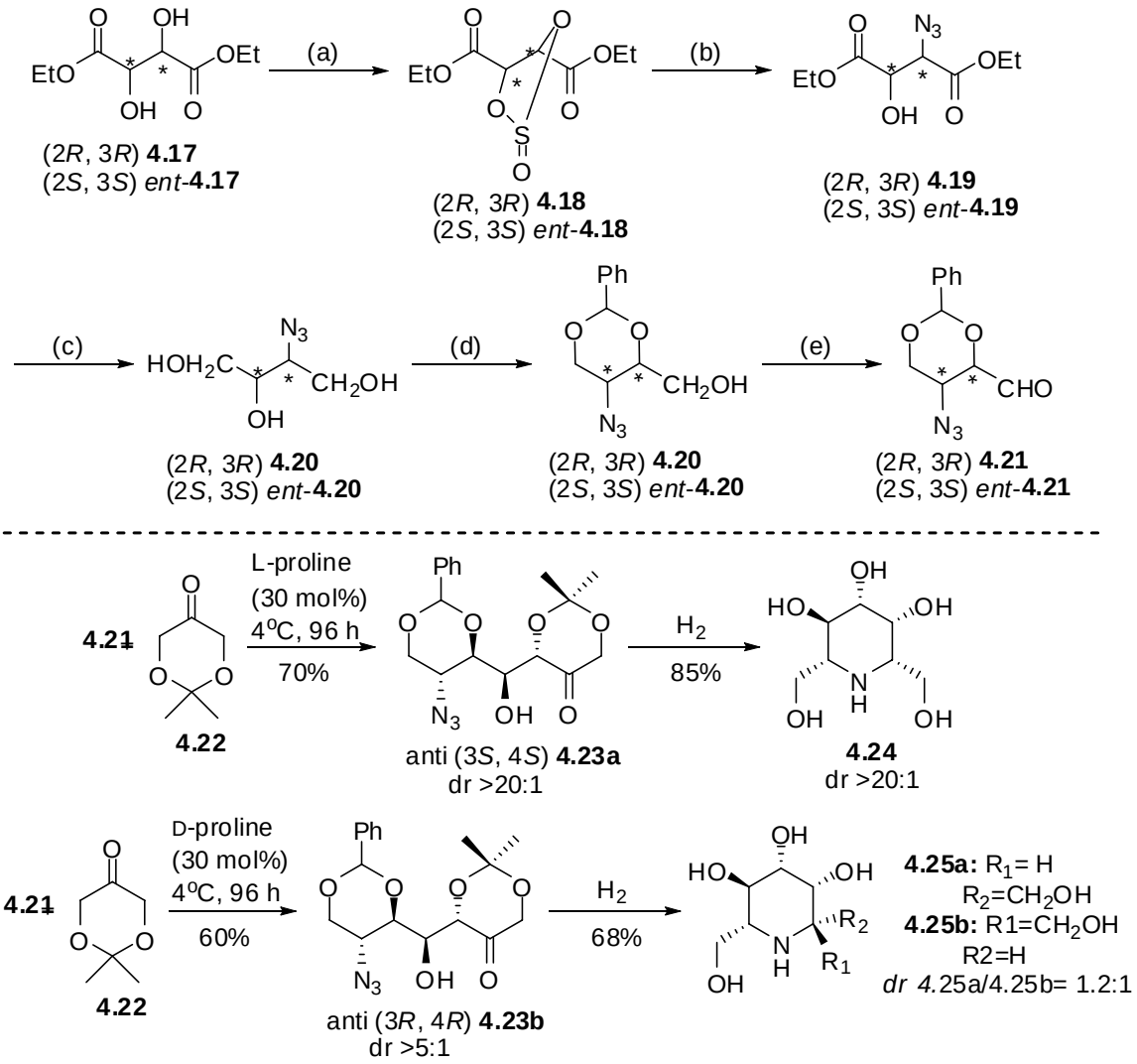
Recently, many azasugars (Figure 4.2) were found to be efficient inhibitors of the carbohydrate hydrogenase and transferase. In these azasugars, nojirimycin **4.11** was discovered in 1966 as the first glucose analogue, which is having endocyclic nitrogen in place of the oxygen pyranosidic atom. This polyhydroxy piperidine **4.11** was initially

isolated as an antibiotic from microorganisms (*Streptomyces*) by Ishida et al.[7] and shown to be a potent inhibitor of both α- and β-glycosidases of different origins. However, the presence of a hydroxyl group at C-1 adds instability that affects the biological assays. Subsequently, 1-deoxynojirimycin **4.12** was obtained by Inouye et al.[8] by the catalytic hydrogenation or reduction of **4.11** or by isolated from bacterial culture,[9] a more stable and potent glycosidase inhibitors. Several other structural analogues of 1-deoxynojirimycin **4.12** are also shown to be the potent inhibitors of glycosidases (Figure 4.2).

The investigation of these alkaloids for therapeutic potential has so far been concentrated on three major applications i.e., for treatment of cancer and inhibition of metastatis, as anti-diabetic drugs and for anti-viral activities.[4] Among the polyhydroxylated piperidines of recent interest are 1-deoxynojirimycin **4.11** and its derivatives. These compounds are strong inhibitors of α-galactosidase A and are currently in preclinical trials as a potent therapy for Farby's disease, a severe lysosomal storage disorder.[10] Their prospective therapeutic uses range from diabetes[11] through cancer[12] and viral diseases[13] to metabolic and neurological disorders.[14] Because of the biological importance of 1-doxynojirimycin and its analogues, a large number of synthetic approaches based on carbohydrates[15] and non-carbohydrates[16] precursors have been developed by different groups, which have been reviewed recently.[17] Out of several synthetic approaches reported in the literature, we summarize here the recent organocatalytic approach for the synthesis of azasugars using proline catalyzed reaction.[18]

The direct diastereoselective aldol reaction in intermolecular fashion of the aldehydes derived from commercially available L- and D-diethyl tartarate and catalysis by both L-

and D-proline was the key step of this approach. The resulting *anti*-aldol products with high level of diastereoselectivity were transformed in to various azasugars under the reductive amination process as shown in Scheme 4.3.

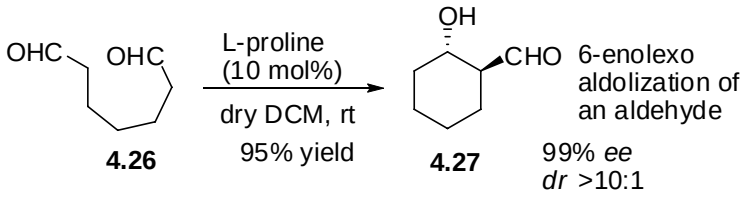


Scheme 4.3: (a) Et_3N, thionyl chloride, 3h, 100%; (b) NaN_3, DMF, 5 h, 70%; (c) $NaBH_4$, LiCl, EtOH, 4 h, 63%; (d) benzaldehyde dimethylacetal, *p*-TSA, MeCN, 3 h, 45%; (e) TEMPO, trichloroisocianuric acid, CH_2Cl_2, 30 min, 60%.

Thus, several azasugars have been prepared using L- and D-proline as organocatalysts for the direct aldol reaction of the aldehyde **4.20** with different ketone donor.

4.2 Results and Discussions

Organocatalysis via asymmetric enamine for the formation of new C-C bonds has emerged as an important tool in the synthesis of carbohydrates.[19] However, the utilization of the organocatalytic aldol reaction in the synthesis of biologically important compounds needs to be explored which is also a challenging area of research for the chemists. As a part of our research program on the direct organocatalytic aldol reaction in diastereoselective fashion for the synthesis of amino polyols, we thought to design an entirely new organocatalytic route for the synthesis of imino sugars, based on the recent discovery of List and his group[20] on the first direct *enolexo* aldolization catalyzed by proline (Scheme 4.4).



4.26 **4.27**

Scheme 4.4: First direct 6-enolexo aldolization reaction catalyzed by L-proline

The direct 6-*enolexo* aldolization proceeds with high level of enantio- and diastereoselectivity for the preparation of β-hydroxy cyclohexane carbonyl derivatives. This led us to think a new approach for imino sugars through the direct enolexo aldolization reaction by introducing nitrogen and well protected hydroxyl groups at the proper place on the substrate **4.26**. We designed a dialdehyde compound **4.28**, in which one of the aldehydic groups was substituted at the α-position so that proline catalyzed direct intramolecular aldolization reaction through the enamine of another aldehyde group can lead to the cyclic diol after insitu reduction of resulting cyclized aldehyde. This may proceed with the high level of *anti*-diastereoselectivity and provides the control of

the stereochemistry of the newly formed two chiral centers with one C-C bond as proposed by List et al. (Figure 4.3).

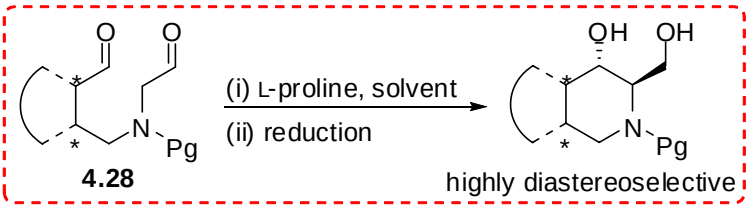
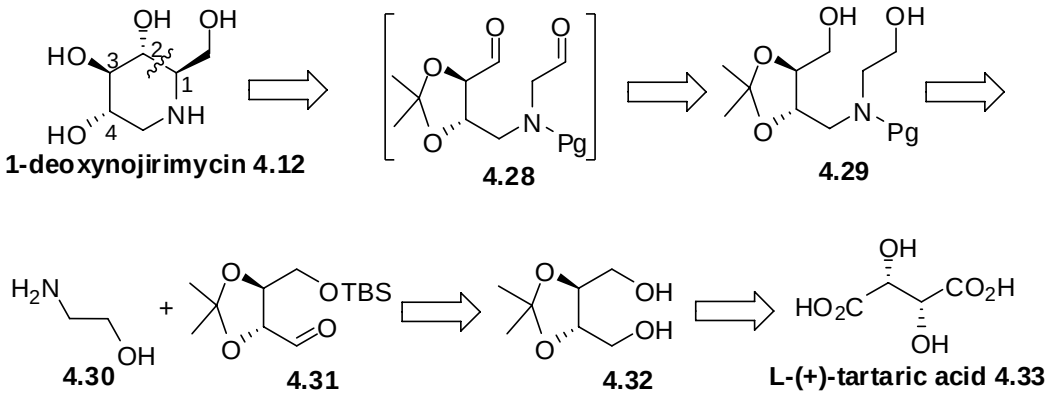


Figure 4.3: New organocatalytic approach for imino sugars

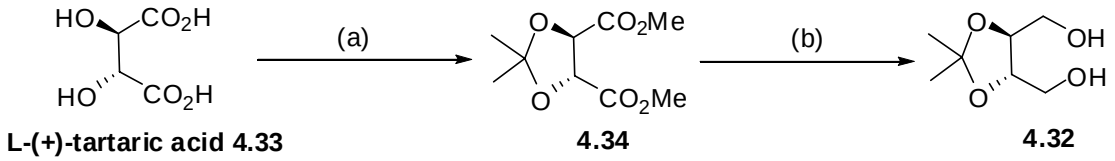
With this modification, the reterosynthetic analysis of the 1-deoxynojirimycin was done through the breaking of the bond between C1 and C2 of **4.12**, which can be prepared through the proline catalyzed direct diastereoselective intramolecular aldolization reaction of **4.28** which is the key step of this approach. The construction of the two chiral centers with complete stereocontrol through one C-C bond formation is one of the important challenges in synthetic organic chemistry. None of the approaches reported in the literature provides access to these imino sugars through the bond formation between C1 and C2 intramolecularly with the control on the stereochemical out come. Thus, this is a new reterosynthetic analysis of this class of compounds. The dialdehyde **4.28** can be prepared from the corresponding diol compound **4.29** which can be prepared from the reductive amination of aldehyde **4.31** with ethanolamine **4.30**. This aldehyde **4.31** can be prepared from diol compound **4.32** which is a known compound and can be easily prepared from commercially available L-(+)-tartaric acid **4.33** as shown in Scheme 4.5. The diol **4.29** was a key synthon. The main challenge of this route is to discriminate between the two aldehyde groups of **4.38** by putting a well defined stereocenter at the active methylene position of one of the aldehydic group, so that enamine will form with another aldehydic group which is unsubstituted at the active methylene position. So far

this enolexo aldolization reaction was particularly appropriate for the desymmetrization of *meso* compounds.[21]



Scheme 4.5: New reterosynthetic analysis of imino sugars (1-deoxynojirimycin)

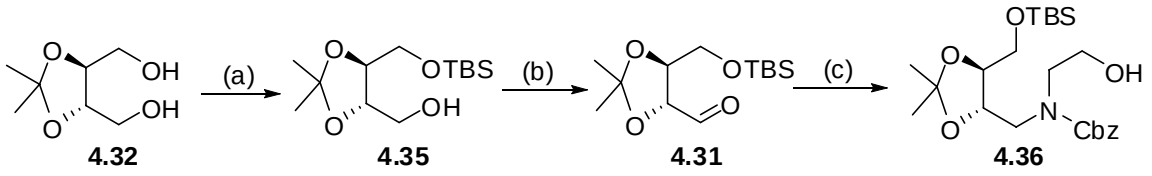
As per the reterosynthetic analysis, we started our synthetic scheme from L-(+)-tartaric acid **4.32** because of the similarity between the stereochemistry of **4.32** and the stereochemistry of **4.12** at C3 and C4. This diol compound **4.32** was obtained in high yield by following a two step procedure (Scheme 4.6). One pot acetonide protection and esterification[22] of L-(+)-tartaric acid **4.33** followed by LAH reduction afforded **4.32**. Spectral characteristics were in good agreement with those reported in the literature.[23]



Scheme 4.6: (a) 2,2-dimethoxypropane, MeOH, cyclohexane, *p*-TSA, heat, 95 %; (b) LAH, dry THF, reflux, 6 h, 95%.

The next step of this strategy was to carry out the monoprotection of **4.32**. For this purpose, a protecting group was required that would be stable and could later be removed easily under mild non-reductive conditions. The *tert*-Butyldimethyl silyl (TBS) protection

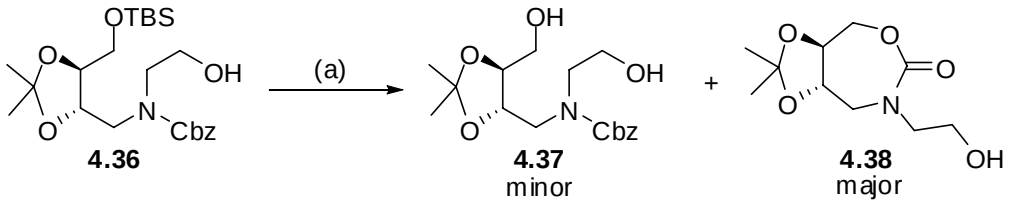
seemed acceptable under these conditions. This was carried out by treating **4.32** with 1.1 equiv of NaH in dry THF, followed by quenching with TBSCl (1.1 equiv) at 0^oC to give monoprotected **4.35** with 95% isolated yield.[24] The aldehydic compound **4.31** was prepared quantitatively through the IBX oxidation[25] of compound **4.35** under reflux condition for 4 h using EtOAc as solvent and the resulting oxidized product was used further for the reductive amination without any purification. The reductive amination of **4.31** with ethanolamine **4.30** was carried out with Pd/C (10%) under hydrogen atmosphere for 24 h, followed by insitu protection of resulting amine compound with CbzCl under biphasic basic condition[26] to give compound **4.36** with 85% isolated yield after three consecutive steps (Scheme 4.7).



4.32 **4.35** **4.31** **4.36**

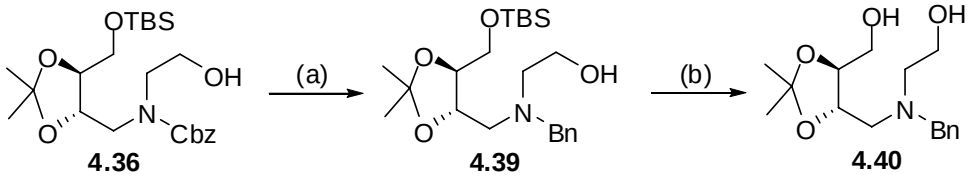
Scheme 4.7: (a) NaH (1.1 equiv), TBSCl (1.1 equiv), dry THF, 0^oC, 2 h, 95%; (b) IBX (3 equiv), EtOAc, 4 h, quantitative; (c) (i) ethanolamine **4.30** (1.1 equiv), Pd/C (10%), MeOH, H_2, 24 h, (ii) CbzCl (1.2 equiv), CH_2Cl_2:H_2O (1:1), Na_2CO_3 (2.2 equiv), 0^oC, 2 h, 85% after three steps.

The deprotection of –TBS of compound **4.36** was carried out under standard Corey's method[27] using TBAF reagent to prepare the diol **4.37** similar to the key synthon **4.29** type. Under these conditions, the desired diol compound **4.37** was isolated as a minor product (<30%) whereas the insitu cyclized compound **4.38** was found to be the major product (>60%) in this reaction (Scheme 4.8).



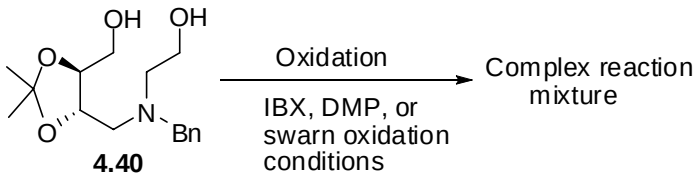
Scheme 4.8: (a) TBAF (1M solution in dry THF, 2 molar equiv), dry THF, 0°C to rt 3 h, 90% combined yield.

To overcome this problem of unexpected cyclization under deprotection conditions, we then used benzyl as a protecting group on amino functionality. This was carried out by deprotection of Cbz group of compound **4.36** under hydrogenation condition followed by insitu protection with Benzyl bromide (BnBr) under biphasic basic condition to give compound **4.39** with 87% yield after two steps.[26] The –TBS deprotection was successfully carried out by using TBAF to give key synthon diol **4.40** with 85% isolated yield (Scheme 4.9).



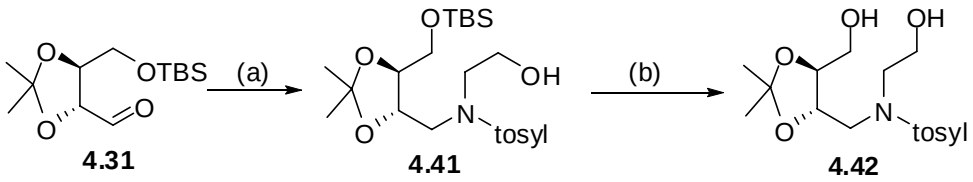
Scheme 4.9: (a) (i) Pd/C (10%), MeOH, rt, 24 h, (ii) BnBr (1.2 equiv), Na_2CO_3 (2.2 equiv), CH_2Cl_2:H_2O (1:1), heat, 3 h, 87%; (b) TBAF (1M, 1.5 equiv), dry THF, 0°C-rt 4 h, 85% yield.

Further, compound **4.40** was subjected to oxidation under different (IBX, DMP, or Swern) conditions to convert in to its corresponding dialdehyde compound. Unfortunately, all these attempts for the oxidation of compound **4.40** to the dialdehyde gave a complex reaction mixture and the oxidized compound could not be isolated from this reaction (Scheme 4.10).



Scheme 4.10: Unsuccessful attempts for the oxidation

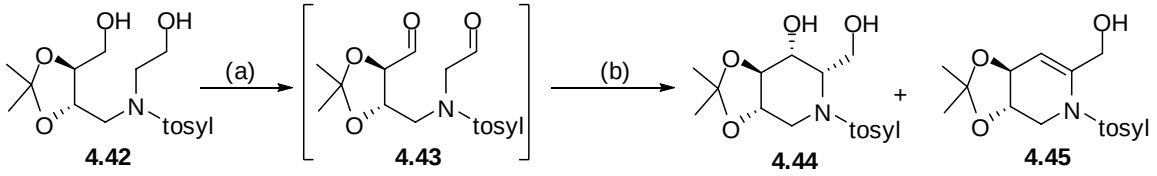
After these unsuccessful attempts, we used tosyl group as a protecting group and compound **4.41** was easily prepared from aldehyde **4.31** using the sequence of reductive amination followed by insitu protection with tosyl chloride under biphasic basic conditions with 86% isolated yield. The –TBS deprotection was than carried out with TBAF solution to give key synthon diol compound **4.42** with 90% yield (Scheme 4.11).



Scheme 4.11: (a) (i) ethanolamine **4.30** (1.1 equiv), Pd/C (10%), MeOH, H_2, 24 h, (ii) TsCl (1.2 equiv), CH_2Cl_2:H_2O (1:1), Na_2CO_3 (2.2 equiv), 0^oC, 2 h, 86%; (b) TBAF (1M, 1.5 equiv), dry THF, 0^oC-rt 4 h, 90% yield.

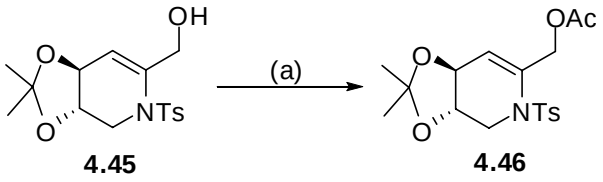
In order to prepare the dialdehyde compound **4.43** for the direct 6-*enolexo* aldolization as a key step for the synthesis of the core structure of imino sugars, the oxidation of compound **4.42** was carried out using o-iodoxy benzoic acid (IBX) (5.0 equiv) in EtOAc under reflux conditions for 5 h. This reaction was monitored by TLC and after the complete consumption of diol **4.42**; reaction was cooled down to rt and the IBX was filtered out. The resulting reaction mixture was washed with sat. $NaHCO_3$ and with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude oxidized dialdehyde compound **4.43** was used for the next step of direct aldolization without any purification. The key step of direct *enolexo* aldolization

reaction was carried out using L-proline (20 mol %) as an organocatalyst at rt for 20 h in a solvent mixture of $CHCl_3$:DMSO (3:1), followed by in situ reduction with $NaBH_4$/MeOH at the same temperature. The solvent was evaporated and the resulting residue was taken in EtOAc and stirred with $NaHCO_3$ solution for 10 min at rt and an organic layer was separated. The aqueous layer was further extracted with EtOAc and the combined organic mixture was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude aldol adduct. This was purified over flash column chromatography using EtOAc/Pet ether as eluting solvents to give diol compound **4.44** with 69% yield along with 20% of the corresponding dehydrated product **4.45** after three steps (Scheme 4.12).



Scheme 4.12: (a) IBX (5 equiv), EtOAc, reflux, 5 h; (b) (i) L-proline (20 mol %), $CHCl_3$: DMSO (3:1), rt, 20 h, (ii) $NaBH_4$, MeOH, rt, 2 h, 69% of **4.44** and 20% of **4.45**.

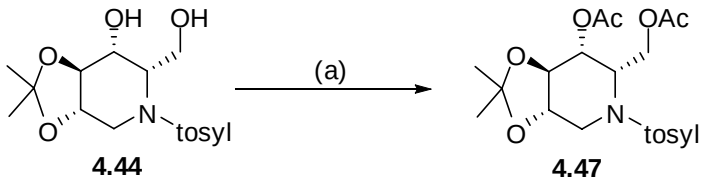
The ^1H and ^{13}C NMR spectral data showed the agreement with the cyclization with *dr* (>10:1), ^{13}C NMR showed the two signals at δ 44.35 and 59.57 in DEPT for CH_2 and four signal at δ 58.10, 70.35, 73.75, and 79.96 for CH of the corresponding cyclized compound **4.44**. For compound **4.45**, ^1H NMR showed an alkene proton at δ 5.72 and two CH_2 in ^{13}C-DEPT at δ 47.97 (dept), 63.92 (dept) and alkene carbon (CH) at δ 114.49 and other two –CH at δ 74.99, and 76.07. The structure of compound was further confirmed by making its acetyl derivative, by treating the compound **4.45** with 1 equiv of AcCl in dry CH_2Cl_2: pyridine (1:1) at 0^oC for 2 h which after purification gave its corresponding acetyl derivative **4.46** with 89% isolated yield (Scheme 4.13).



4.45 **4.46**

Scheme 4.13: (a) AcCl (1.1 equiv), dry CH_2Cl_2: pyridine (1:1), 0^oC, 2 h, 89%.

In order to confirm the stereochemical outcome of this *enolexo* aldol reaction, the aldol product **4.44** was transformed in to its corresponding diacetyl derivative **4.47** by treating with two equivalent of AcCl in dry CH_2Cl_2/pyridine at 0^oC for 2 h followed by chromatographic purification (Scheme 4.14). This diacetyl derivative **4.47** was isolated as almost pure diastereomer by ^1H and ^{13}C NMR with 84% isolated yield, which was used to prove the stereochemistry through NOSY experimentation.



4.44 **4.47**

Scheme 4.14: (a) AcCl (2.1 equiv), dry CH_2Cl_2: pyridine (1:1), 0^oC, 2 h, 84%.

The exact stereochemical outcome of diacetyl derivative **4.47** was determined and explained by NOSEY experiments and it was shown that the direct diastereoselective 6-*enolexo* aldolization is highly *syn*-selective. The observed strong NOE correlation of the proton at C1 and the proton at C2 and with the proton H^{β} at C5 (strong) which shows the correlation with H^{β} at C5 confirmed that these were on the same side, while the two protons of $–CH_2OAc$ at C1 shows the correlation with the H^{α} protons of C5 and C2 allowed *syn*-selectivity to be attributed (Figure 4.4).

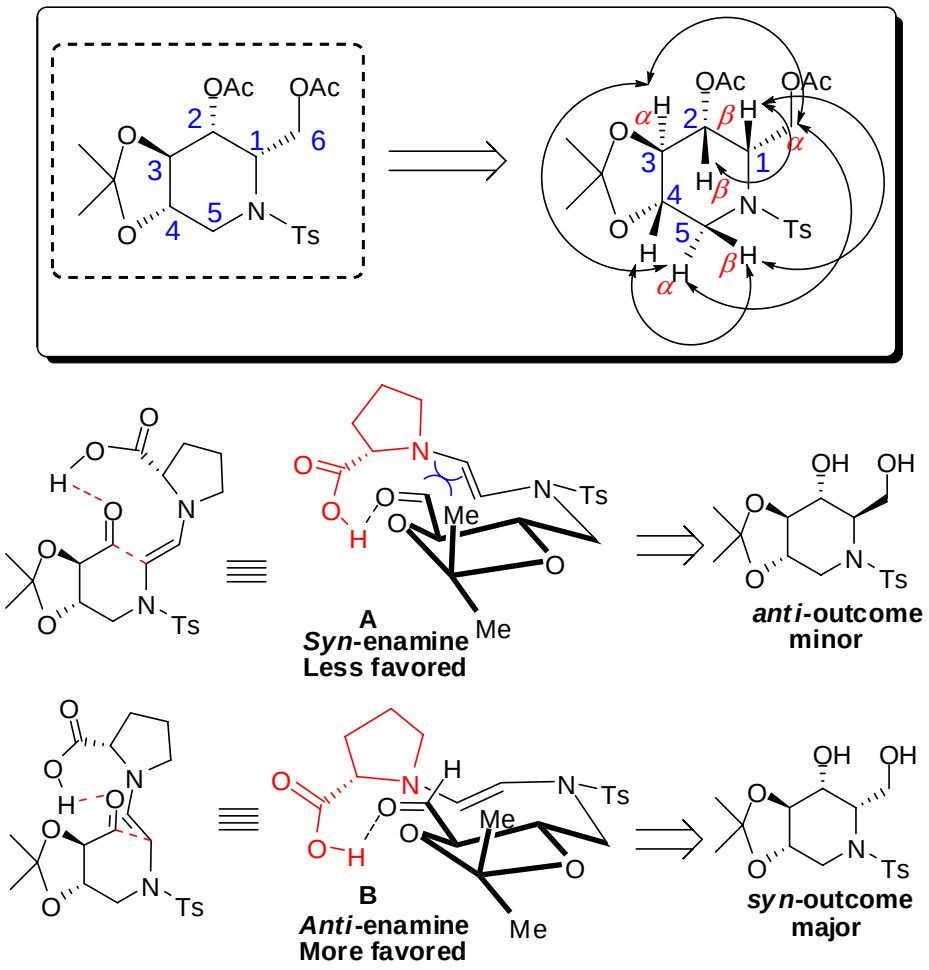
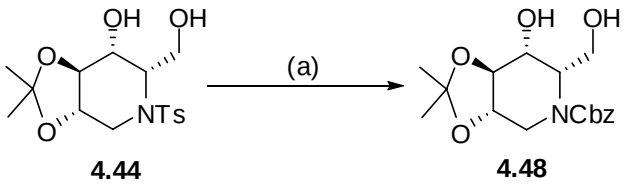


Figure 4.4: Structural elucidation by NOE correlation and transition states

This stereochemical outcome can be explained through the two different transition states **A** and **B** with respect to the fixed stereochemistry at C3 and C4, in which the *Ri*-facial attack on acceptor aldehyde by the enamine nucleophile proceeds through the less favored *syn*-enamine intermediate **A** leads to the minor *anti*-product formation, while the major *syn*-out come of this reaction can be explained through the more favored *anti*-enamine intermediate **B** (Figure 4.4).

In order to confirm our results on the *syn*-selectivity for the direct diastereo-selective 6-*enolexo* aldolization reaction, we tried to get the single crystal X-ray of the cyclized

product **4.44** which was a sticky solid and all the attempts of further crystallization could not lead to any result, while the diacetyl derivative **4.47** was a pasty liquid and could prove the stereochemistry of cyclized product through NOSY correlation. Then we thought to deprotect the N-Tosyl group of compound **4.44** and again protected it as N-Cbz to get a good crystal for single crystal X-ray analysis to provide the full proof of the stereochemical outcome of the aldolization reaction. This was carried out in a one pot two step procedure, in which the first deprotection of N-tosyl was done by treating compound **4.44** with Red Al (Sodium bis(2-methoxyethoxy)aluminum hydride, 70% solution in toluene)[28a] under reflux conditions for 8 h. This type of deprotection under these conditions on the same system has been already reported.[28b] After this deprotection the crude amine was protected with CbzCl under biphasic basic conditions[26] using CH_2Cl_2:H_2O (1:1) with Na_2CO_3 at 0^oC gave the corresponding –NCbz protected compound **4.48** with 60% yield after two steps. This material was a solid but not very crystalline and could not give a very good quality single crystal for X-ray analysis (Scheme 4.15).



4.44 **4.48**

Scheme 4.15: (a) i. Red Al (Sodium bis(2-methoxyethoxy)aluminum hydride, 70% in toluene) THF, reflux, 8 h; ii. CbzCl (1.2 equiv), CH_2Cl_2:H_2O (1:1), Na_2CO_3, 0^oC to rt, 2 h, 60% after two steps.

However, the high through-put experiment for the resulting crystal could produce the structure of the compound with crystallographic data which further showed the relative stereochemistry at C1 and C2 with *syn*-selectivity. We are putting the crystal structure

data with stick and ball model of the crystal structure of compound **4.48**. The crystal structure data further explained the structure of the compound **4.48** as given below.

Crystals of **4.48** obtained from cyclized compound **4.44** were thin in the third dimension. Intensity data measurements were carried out at room temperature (297K) on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo K_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.3° at four different settings of φ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data collection was monitored by SMART program (Bruker, 2003). Only low angle very weak reflections were observed during data collection. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2003). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.

Crystal data for 4.48 ($C_{17}H_{23}NO_6$): M = 337.36, Crystal dimensions 0.59 x 0.19 x 0.02 mm^3, monoclinic, space group $P2_1$, a = 5.9264(18), b = 17.946(6), c = 16.598(5) Å, β = 91.282(7)°, V = 1764.8(9) $Å^3$; Z = 4; T = 297(2) K, ρ_{calcd} = 1.270 gcm^{-3}, μ (Mo-K_α) = 0.096 mm^{-1}, *F(000)* = 720, $2\theta_{max}$ = 46.00°, 18905 reflections collected, 4907 unique, 3248 observed ($I > 2\sigma(I)$) reflections, 173 refined parameters, R value 0.2020, $wR2$ = 0.4396 (all data R = 0.2425, $wR2$ = 0.4600), S = 1.528, minimum and maximum transmission 0.9454 and 0.9981 respectively, maximum and minimum residual electron densities +0.858 and –1.053 e $Å^{-3}$.

During anisotropic refinement, the displacement ellipsoids were non-positive definite for some of the atom due to poor quality X-ray diffraction data. Therefore,

refinement of the structure treating all non-H atoms as isotropic was carried out. The isotropic refinement of the structure gave very high R-value (R1 = 0.21) compared to that of the anisotropic structure refinement of non-H atom with non-positive displacement ellipsoids for some of the atoms (R1 = 0.12). Hydrogen atoms were included in the refinement as per the riding model option in SHELXL.

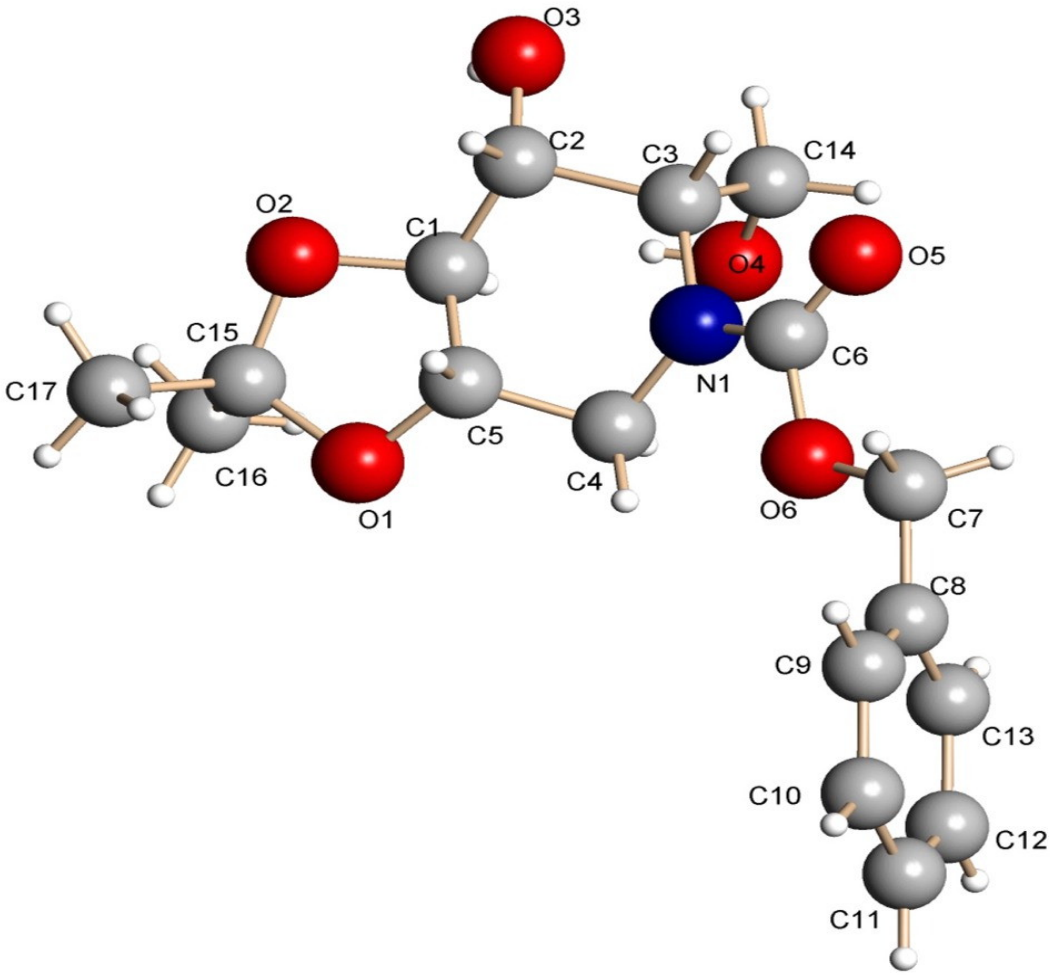
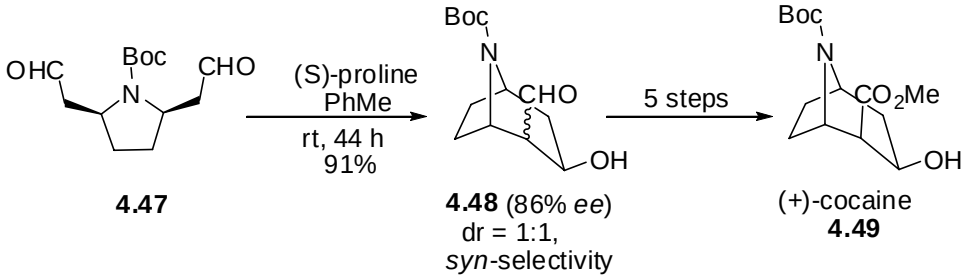


Figure 4.5: Crystal structure of compound **4.48** (stick & ball model)

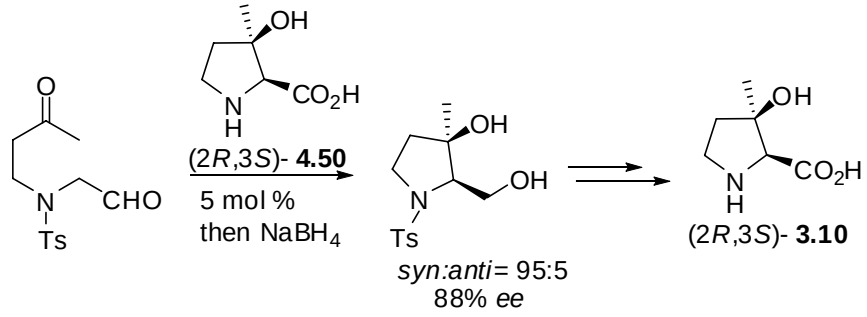
Thus, we have also confirmed the exact stereochemical out come of the intramolecular aldolization reaction by single crystal X-ray of compound **4.48**, which also showed the *syn*-selectivity of the relative stereochemistry at C1 and C2 supporting the structure of

diacetyl compound **4.47** determined by NOE experiments. We were expecting this cyclization to give the *anti*-selectivity as the first 6-*enolexo* aldol cyclization catalyzed by L-proline was achieved by List at al.[20] However, previously reported direct intramolecular 6-*enolexo* aldol cyclization for the synthesis of (+)-cocaine was also found to proceed through *syn*-selectivity (Scheme 4.16).[29]



Scheme 4.16: direct 6-*enolexo* aldolization with *syn*-selectivity

Similar result was reported recently,[30] with high *syn*-selectivity for the direct 5-*enolexo* aldol reaction catalyzed by proline derivative **4.51** as shown in Scheme 4.17, and further support by our these results.



Scheme 4.17: direct 5-*enolexo* aldolization with *syn*-selectivity

4.3 Conclusions

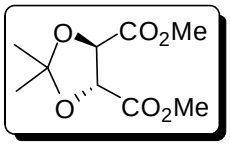
In conclusion, we have designed and developed an entirely new general approach for the imino sugars, in which the direct diastereoselective aldol reaction catalyzed by proline is the key step and the aldolization occurred through the 6-*enolexo* fashion with high level (*dr* >10:1) of diastereoselectivity. This intramolecular aldolization reaction proceeds with *syn*-selectivity which has been explained through two different transition states. The stereochemical out come of the reaction was confirmed by the NOSY experimental correlation of the diacetyl derivative of the cyclized product. Further the relative and absolute configuration of the aldol product was proved by the X-ray structure of the corresponding cyclized product. This is the first organocatalytic approach for imino sugars in which the one C-C bond formation between C1 and C2 controlled the stereochemistry of two new stereocenters with high level of *syn*-selectivity and completed the synthesis of derivative of 1-deoxy-L-idonojirimycin. This approach can be applied to the synthesis of other imino sugar analogues starting from compounds with different stereochemistry at C3 and C4 and the stereochemistry at C1 and C2 can be controlled with the aldol reaction catalyzed by proline which is available in both D- and L-forms. Thus, variety of iminosugars can be synthesized using this new approach. Further study towards this direction is under progress in our laboratory.

4.4 Experimental Section

General

All the reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under argon atmosphere using oven-dried glassware. Dichloromethane and dimethyl sulfoxide were distilled over CaH_2 under argon atmosphere and stored on molecular sieves. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin-Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^1H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC-MS was recorded using electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100-200 and 230-400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

(4*R*,5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (4.34)

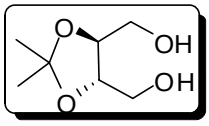


To a suspension of L-(+)-tartaric acid **4.33** (5.0 g, 33.3 mmol) in dry methanol (2.0 mL), was added 2,2-methoxypropane (9.4 mL, 76.8 mmol) and p-toluene sulfonic acid (0.010 g). The resulting mixture was warmed for about two hours, on a water bath at 50°C, till the dark orange color developed. Dry cyclohexane (22.5 mL) and a further quantity of

2,2-dimethoxy propane (3.9 mL) were added to the cooled reaction mixture. The reflux condenser was replaced with a long distillation head and the resulting two-layered reaction mixture was heated to afford a slow removal of azeotropes of cyclohexane-methanol and the cyclohexane-acetone over a period of 24 h. When the vapor temperature fall below 50^{o}C, 2,2-dimethoxypropane (1 mL) was added and the oil temperature was increased till the vapor temperature reached 78^{o}C. The reaction mixture was cooled; the solvent and excess 2,2-dimethoxy propane were removed at the rotary evaporator. The resulting thick liquid was then distilled under vacuum (bp -90^{o}C/0.5 mm, lit. bp = 82-90^{o}C/0.02 mm) to afford the title compound **4.34** (6.90 g, 95%) as a pale yellow liquid.

(4.34): ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.5 (s, 6H), 3.8 (s, 6H), 4.8 (s, 2H).

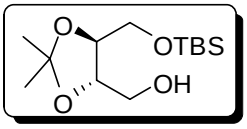
((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (4.32)



A solution of **4.34** (2.0 g, 9.20 mmol) in dry THF (18 mL) was added to a stirring suspension of lithium aluminium hydride (LAH) (0.37 g, 9.74 mmol) in dry THF (9 mL) at 0^{o}C, over a period of 15 min. After stirring for about an hour at rt, the reaction mixture was refluxed for about 6 h. Upon cooling at 0^{o}C, it was quenched by a slow addition of an aqueous solution of NaOH (20%). To the resulting white suspension was added anhydrous Na_2SO_4 and the slurry was filtered at the suction pump. The solid residue was washed with distilled THF (20 mL) and the combined filtrate was concentrated under vacuum. This crude mixture upon column chromatography (silica, pet ether-ethyl acetate, 2:3) afforded **4.32** (1.416 g, 95%) as a syrupy mass.

(4.32): ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.45 (s, 6H), 3.10 (bs, 2H, D_2O exchangeable) 3.75 (m, 4H), 4.0 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.41, 61.80, 78.13, 108.71.

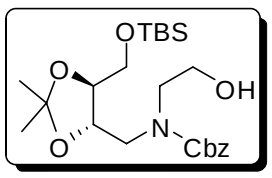
((4*S*,5*S*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (4.35)



To a cold solution of **4.32** (1.0 g, 6.2 mmol) in dry THF (10 mL) was added in portion sodium hydride (250 mg of a 60% mineral oil dispersion, 6.2 mmol) and the mixture was stirred for 5 min under argon atmosphere. To this was added dropwise a solution of *tert*-butyldimethyl silyl chloride (930 mg, 6.2 mmol) in dry THF (10 mL) during 10 min at 0oC, and the mixture was stirred for 2 h at room temperature under argon atmosphere. The reaction mixture was poured into water (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2x10 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was passed through a small pad of silica gel with ethyl acetate: pet ether (1:10 to 1:5) to give **4.35** (1.61 g, 95%) as colorless oil.

(4.35): ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.06 (s, 6H), 0.88 (s, 9H), 1.38 (s, 3H), 1.39 (s, 3H), 2.47 (m, 1H), 3.59-3.75 (m, 3H), 3.79-3.90 (m, 2H), 3.93-4.01 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.72, -5.69 (overlapped), 18.07, 25.65, 26.69, 26.84 (overlapped), 62.46, 63.40, 77.70, 79.73, 108.85.

Benzyl ((4*S*,5*S*)-5-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl(2-hydroxyethyl) carbamate (4.36)



A mixture of **4.35** (1.1 g, 3.98 mmol) and IBX (3.33 g, 11.94 mmol) in EtOAc (60 mL) was heated under reflux for 4 h at 80^{o}C, followed by TLC. The reaction temperature was

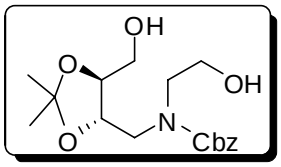
brought to rt and filtered. The filtrate was washed with 20% solution of $NaHCO_3$ (2x 20 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure gave aldehyde compound **4.31** which was used further for reductive amination without purification. For doing this, a solution of **4.31** (1.0 g, 3.64 mmol) and ethanol amine **4.30** (0.25 g, 4.0 mmol) in MeOH (20 mL), was added Pd/C (40 mg, 10 mol%) at rt and the resulting solution was stirred further for 12 h under hydrogen atmosphere followed by TLC. The reaction mixture was filtered to remove Pd/C and concentrated under reduced pressure to give a slight yellowish liquid that were dissolve in CH_2Cl_2 (20 mL). To the resulting solution was added a solution of Na_2CO_3 (0.85 g, 8.2 mmol) in water (20 mL) and CbzCl (0.682 g, 1.14 mL (50 % solution in toluene), 4.0 mmol) at 0^oC and the mixture was stirred further for 2 h at the same temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography on silica-gel eluting with hexane: ethyl acetate solution to give **4.36** (1.53 g, 85% yield after three steps) as a colorless liquid.

(4.36): $[\alpha]_D^{25}$ -16.24 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 0.07 (m, 6H), 0.85 (m, 9H), 1.38 (m, 6H), 3.07-3.48 (m, 3H), 3.53-3.89 (m, 7H), 3.99-4.31 (m, 1H), 5.13 (s, 2H), 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.73, -5.67 (overlapped), 18.10, 25.61, 26.65, 26.81 (overlapped), 48.35, 52.88, 59.61, 64.10, 68.45, 78.91, 80.15, 108.76, 127.98, 128.13, 128.43, 136.39, 156.87. Anal. Calcd for $C_{23}H_{39}NO_6Si$: C, 60.89; H, 8.67; N, 3.09. Found: C, 60.83; H, 8.61; N, 3.13.

TBS-deprotection of compound 4.36:

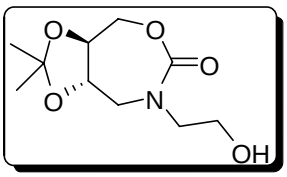
To a solution of compound **4.36** (0.5 g, 1.10 mmol) in dry THF (5 mL) was added tetra-n-butylammonium fluoride (2.22 mL, 2.22 mmol, 1M in THF), and the mixture was stirred at rt for additional 3 h at the same temperature. The solvent was evaporated and the residue was taken in EtOAc (10 mL) and stirred with water (3 mL), after that the organic layer was separated and dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was column chromatographed over silica gel gave diol **4.37** (0.10 g, <30% yield) and **4.38** (0.158 g, >60% yield).

Benzyl 2-hydroxyethyl(((4*S*,5*S*)-5-(hyrroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)carbamate (4.37)



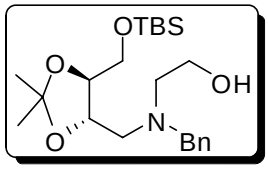
(4.37): $[\alpha]_D^{25}$ -26.19 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.41 (s, 6H), 3.03-3.95 (m, 11H), 3.98-4.30 (m, 1H), 3.99-4.31 (m, 1H), 5.14 (s, 2H), 7.37 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.67, 26.79 (overlapped), 48.49, 53.41, 60.19, 64.67, 67.59, 77.35, 80.15, 108.71, 127.81, 128.01, 128.22, 136.31, 156.61.

(3a*S*,8a*S*)-7-(2-hydroxyethyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3]oxazepin-6(7*H*)-one (4.38)



(4.38): ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.48 (s, 6H), 3.03-3.95 (m, 11H), 2.69 (bs, 1H, -OH), 3.25-3.95 (m, 8H), 4.05-4.19 (m, 1H), 4.32-4.41 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.81, 26.89 (overlapped), 47.19, 52.27, 69.87, 66.81, 79.92, 87.21, 108.66, 155.89.

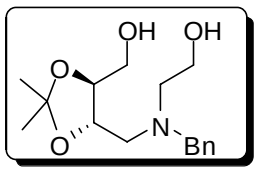
2-(Benzyl(((4*S*,5*S*)-5-((tert-butyldimethylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) amino)ethanol (4.39)



To a stirred solution of compound **4.36** (1.2 g, 2.64 mmol) in distilled MeOH (15 mL), was added Pd/C (27 mg, 10 mol %) at rt. The resulting mixture was hydrogenated under atmospheric pressure of hydrogen for 3 h, and the reaction was followed by TLC. The resulting mixture was filtered and solvent was removed in vacuo to give oily product that was taken in dichloromethane (10 mL). To the resulting solution, was added a solution of Na_2CO_3 (0.62 g, 5.81 mmol) in water (10 mL) and benzyl bromide (0.49 g, 2.91 mmol) and the mixture was refluxed for 3 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica-gel to give compound **4.39** (0.95 g, 87 % in two steps) as a colorless liquid.

(4.39): $[\alpha]_D^{25}$ -15.46 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.87 (s, 9H), 1.38 (s, 6H), 2.65-2.83 (m, 4H), 3.54-3.71 (m, 6H), 3.75 (s, 2H), 4.05-4.11 (m, 1H), 7.24-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.63, -5.53 (overlapped), 18.18, 25.76, 26.80, 55.98, 56.14, 59.14, 59.42, 63.61, 77.16, 79.13, 108.78, 126.97, 128.13, 128.82, 138.62. LC-MS (ESI-TOF): m/z $[M-H]^+$ 408.04.

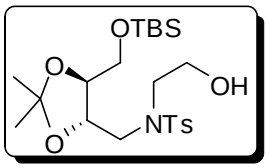
2-(Benzyl(((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) amino)ethanol (4.40)



Similar to the –TBS deprotection of compound **4.36**.

(4.40): $[\alpha]_D^{25}$ -31.97 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.34 (s, 6H), 2.60-2.69 (m, 1H), 2.71-2.83 (m, 3H), 3.51-3.73 (m, 8H), 3.77-3.90 (m, 2H), 7.30 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.57, 26.74 (overlapped), 55.94, 56.62, 59.16, 59.87, 61.97, 76.90, 80.49, 108.49, 127.22, 128.17, 129.16, 137.33. LC-MS (ESI-TOF): m/z $[M+H]^+$ 295.92.

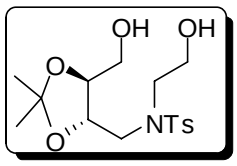
***N*-(((4*S*,5*S*)-5-((*tert*-butyldimethylsiloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (4.41)**



Similar to the preparation of compound **4.36** from aldehydic compound **4.31**.

(4.41): $[\alpha]_D^{25}$ -22.23 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 0.08 (s, 6H), 0.89 (s, 9H), 1.35 (s, 3H), 1.38 (s, 3H), 2.40 (s, 3H), 2.90-3.07 (m, 2H), 3.45-3.61 (m, 2H), 3.65-3.89 (m, 5H), 4.20-4.29 (m, 1H), 7.28 (d, *J*= 8.1Hz , 2H), 7.67 (d, *J*= 8.3Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.61, -5.46 (overlapped), 18.27, 21.37, 25.82, 26.69, 26.91 (overlapped), 52.49, 53.24, 61.42, 63.23, 78.41, 79.27, 109.32, 127.23, 129.65, 135.54, 143.51. LC-MS (ESI-TOF): m/z $[M+H]^+$ 474.17, $[M+Na]^+$ 496.14.

***N*-(2-hydroxyethyl)-*N*-(((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl-4-methylbenzenesulfonamide (4.42)**

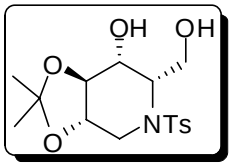


Similar to the –TBS deprotection of compound **4.36**.

(4.42): $[\alpha]_D^{25}$ -22.23 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3$): δ = 1.36 (s, 3H), 1.38 (s, 3H), 2.39 (s, 3H), 2.80-3.12 (m, 3H), 3.38-3.93 (m, 8H), 4.14-4.25 (m, 1H), 7.28 (d, *J*= 7.9Hz , 2H), 7.65 (d, *J*= 8.3Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.28, 26.69, 26.78 (overlapped), 52.18 (dept), 53.12 (dept), 61.17 (dept), 61.80 (dept), 76.80, 79.31, 109.21,

127.15, 129.68, 135.01, 143.67. LC-MS (ESI-TOF): m/z $[M+H]^+$ 360.03, $[M+Na]^+$ 382.03.

(3*aS*,6*S*,7R,7*aS*)-6-(hydroxymethyl)-2,2-dimethyl-5-tosylhexahydro-[1,3]dioxolo[4,5-*c*]pyridine-7-ol (4.44)

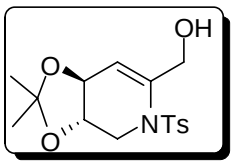


A mixture of 4**.42** (0.50 g, 1.39 mmol) and IBX (1.94 g, 6.95 mmol) in EtOAc (30 mL) was heated under reflux for 5 h at 80^{o}C, followed by TLC. The reaction temperature was brought to rt and filtered. The filtrate was washed with 20% solution of $NaHCO_3$ (2x 20 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude oxidized product was used further for the cyclization without purification. This slight yellowish material was dissolved in $CHCl_3$: DMSO (3:1, 8 mL) at rt followed by the addition of L-proline (0.030 g, 20 mol %). The resulting solution was further stirred for 20 h at the same temperature followed by the addition of 5 mL of MeOH and insitu reduction with $NaBH_4$ (0.065 g, 1.66 mmol, slight excess) for 2 h. The reaction mixture was evaporated in vacuo and poured into cold water (15 mL), followed by the extraction with EtOAc (4x20 mL). The combined reaction mixture was dried over Na_2SO_4 and concentrated under reduced pressure; the resulting pasty mass was purified by flash column chromatography to give **4.44** (0.343 g, 69%) and **4.45** (0.095 g, 20%) with combined 89% yield after three steps.

(4.44): $[\alpha]_D^{25}$ +9.25 (*c* 0.5, MeOH), ^{1}H NMR (400MHz, $CDCl_3/D_2O$): δ = 1.34 (s, 3H), 1.40 (s, 3H), 1.83 (bs, 2H, -OH, exchangeable), 2.41 (s, 3H), 3.04-3.16 (m, 2H), 3.55-3.60 (m, 1H), 3.69-3.76 (s, 1H), 3.86-3.90 (m, 1H), 4.00-4.04 (m, 1H), 4.16-4.23 (m, 1H), 4.36-4.41 (m, 1H), 7.30 (d, *J* = 8.0Hz, 2H), 7.74 (d, *J* = 8.1Hz, 2H). ^{13}C NMR (75

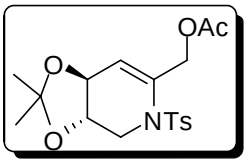
MHz, $CDCl_3$): δ = 21.52, 26.48, 26.68 (overlapped), 44.35 (dept), 58.10, 59.57 (dept), 70.35, 73.75, 79.96, 111.45, 126.99, 130.01, 137.17, 144.04. LC-MS (ESI-TOF): m/z $[M+H]^+$ 474.17, $[M+Na]^+$ 496.14.

((3*aS*,7*aS*)-2,2-dimethyl-5-tosyl-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-6-yl)methanol (4.45)



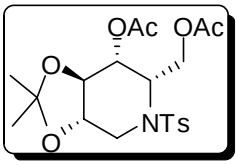
(4.45): $[\alpha]_D^{25}$ +291.40 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.37 (s, 3H), 2.43 (s, 3H), 3.24-3.40 (m, 2H), 3.45-3.58 (m, 1H), 4.01 (m, 1H), 4.35 (dd, *J*= 14.2Hz,1H), 5.72 (s, 1H), 7.33 (d, *J* = 8.0Hz, 2H), 7.69 (d, *J* = 8.3Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.49, 26.40, 26.60 (overlapped), 47.97 (dept), 63.92 (dept), 74.99, 76.07, 113.38, 114.49, 126.87, 129.89, 134.47, 137.75, 144.45. LC-MS (ESI-TOF): m/z $[M+H]^+$ 340.19, $[M+Na]^+$ 362.20.

((3*aS*,7*aS*)-2,2-dimethyl-5tosyl-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-6-yl)methyl acetate (4.46)



(4.46): $[\alpha]_D^{25}$ +187.68 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.36 (s, 3H), 2.06 (s, 3H), 2.42 (s, 3H), 3.10-3.22 (m, 1H), 3.30-3.51 (m, 2H), 3.87-3.94 (m, 1H), 4.78-5.06 (dd, *J* =14Hz, 1H), 5.77 (s, 1H), 7.32 (d, *J* = 8.0Hz, 2H), 7.69 (d, *J* = 8.3Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.89, 21.60, 26.48, 26.72 (overlapped), 47.54 (dept), 64.27 (dept), 75.06, 76.57, 113.53, 116.24, 127.15, 129.89, 133.41, 134.61, 144.42. LC-MS (ESI-TOF): m/z $[M+H]^+$ 382.24, $[M+Na]^+$ 404.22.

((3*aS*,6*S*,7*R*,7*aR*)-7-acetoxy-2,2-dimethyl-5-tosylhexahydro-[1,3]dioxolo[4,5-*c*]pyridine-6-yl)methyl acetate (4.47)



Similar to the preparation of compound (**4.46**)

(4.47): $[\alpha]_D^{25}$ +13.95 (*c* 1, $CHCl_3$), ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.33 (s, 3H), 1.42 (s, 3H), 2.02 (s, 3H), 2.15 (s, 3H), 2.45 (s, 3H), 3.01-3.07 (m, 1H), 3.20-3.26 (m, 1H), 3.59-3.64 (m,1H), 4.16-4.20 (m, 1H), 4.21-4.26 (m, 1H), 4.31-4.36 (m, 1H), 4.79-4.84 (m, 2H), 7.32(d, *J* = 8.0Hz, 2H), 7.75 (d, *J* = 8.3Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.72, 20.75 (overlapped), 21.48, 26.42, 26.48 (overlapped), 43.85 (dept), 53.62, 59.11 (dept), 70.36, 73.74, 76.72, 111.61, 126.97, 129.79, 137.26, 143.98, 169.59, 170.60. LC-MS (ESI-TOF): m/z $[M+H]^+$ 442.12, $[M+Na]^+$ 464.09.

4.5 References

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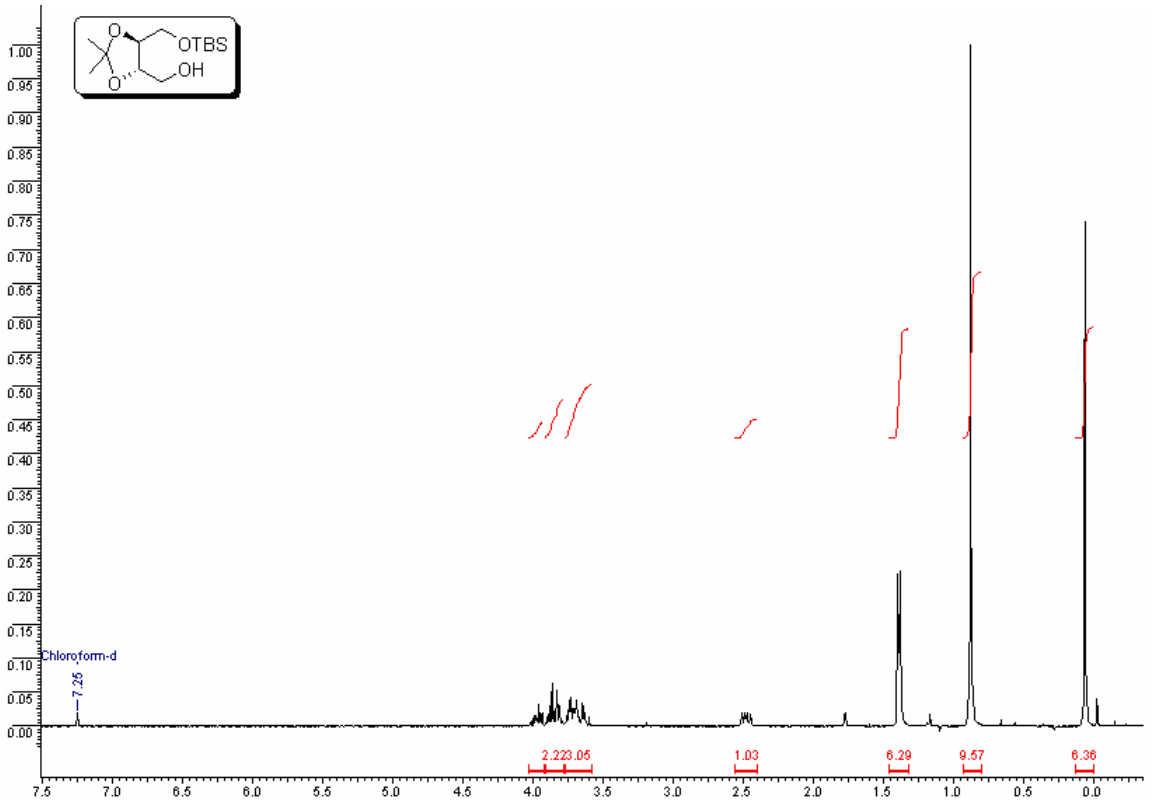
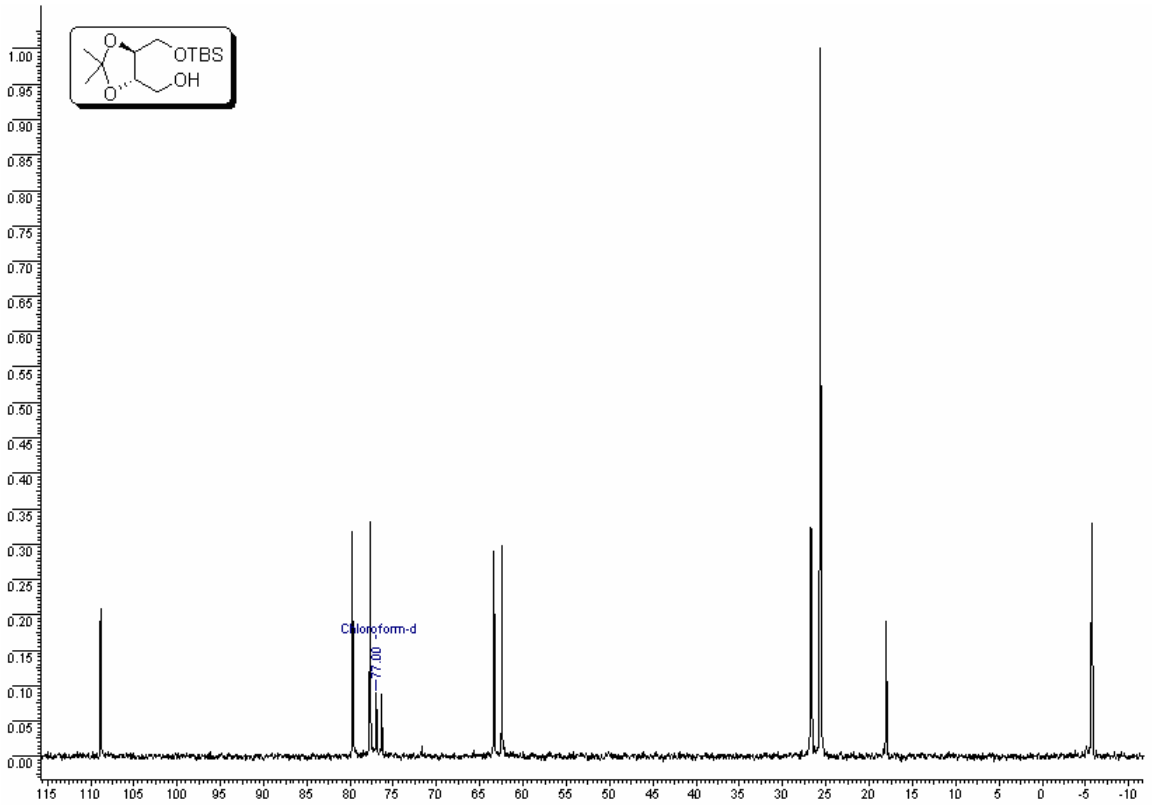
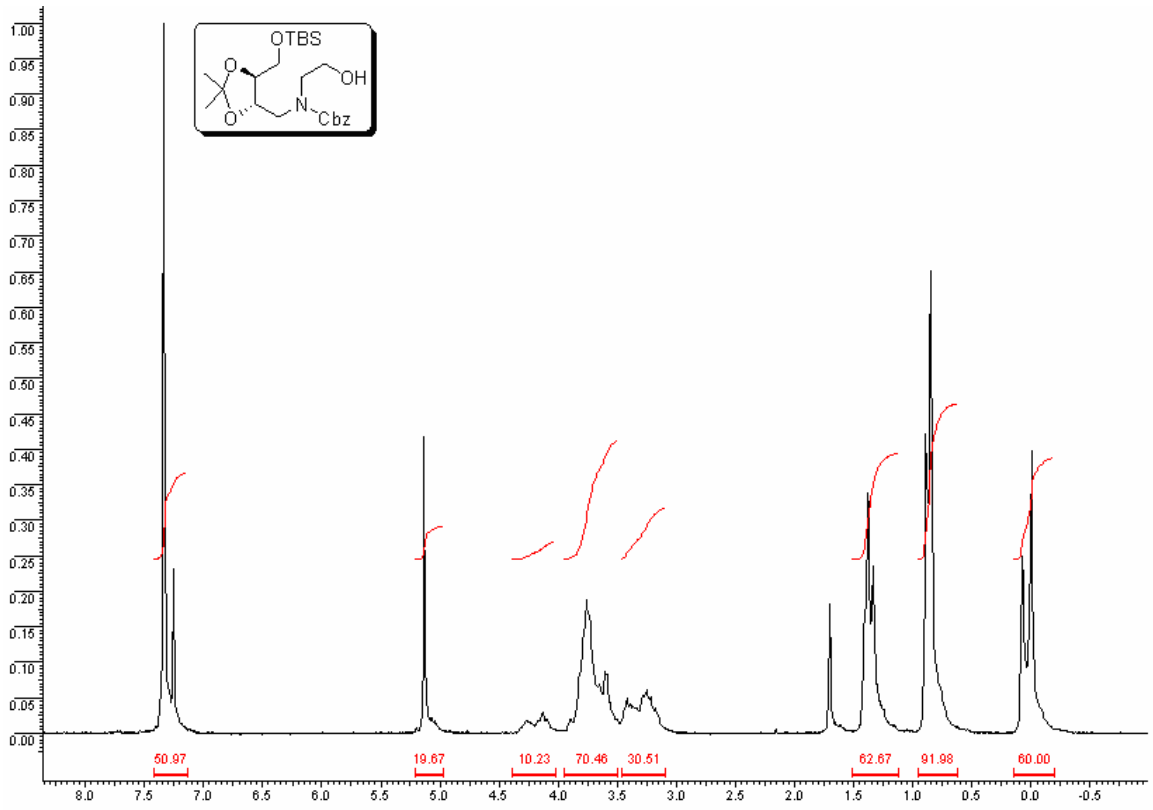
4.6 Spectra of selected compounds



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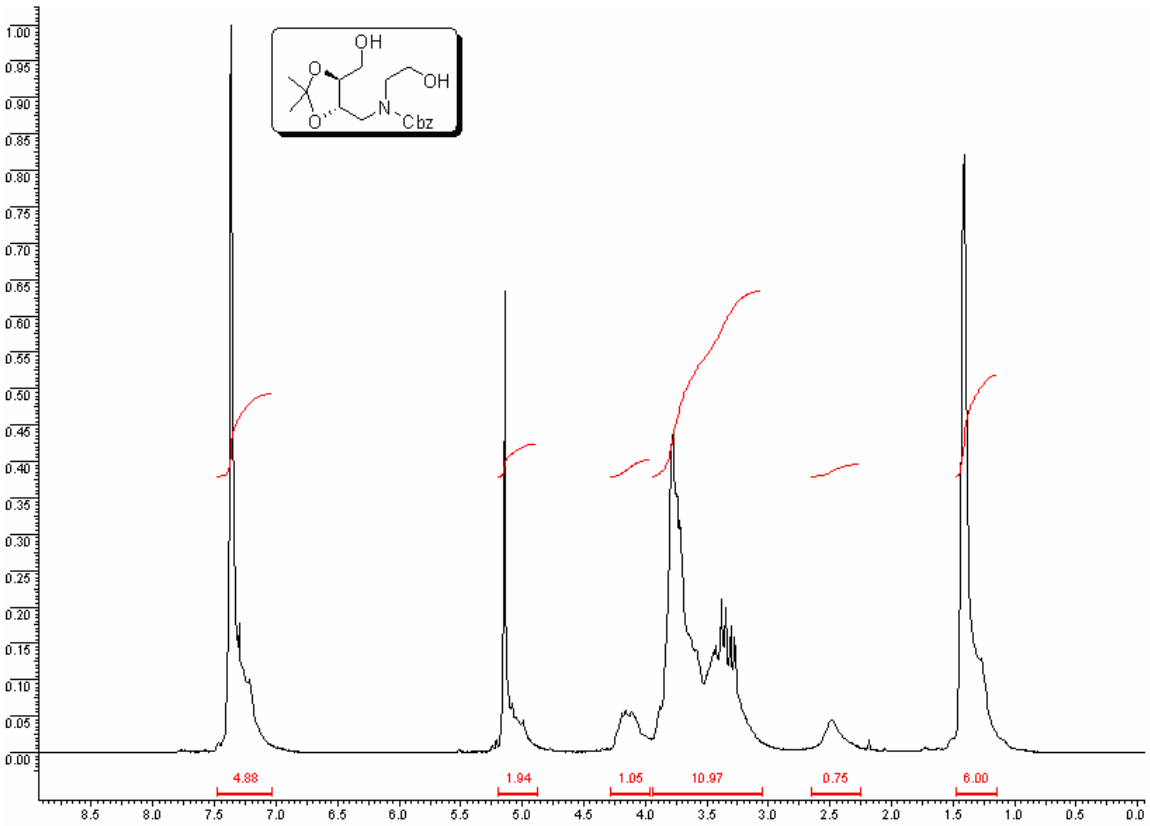
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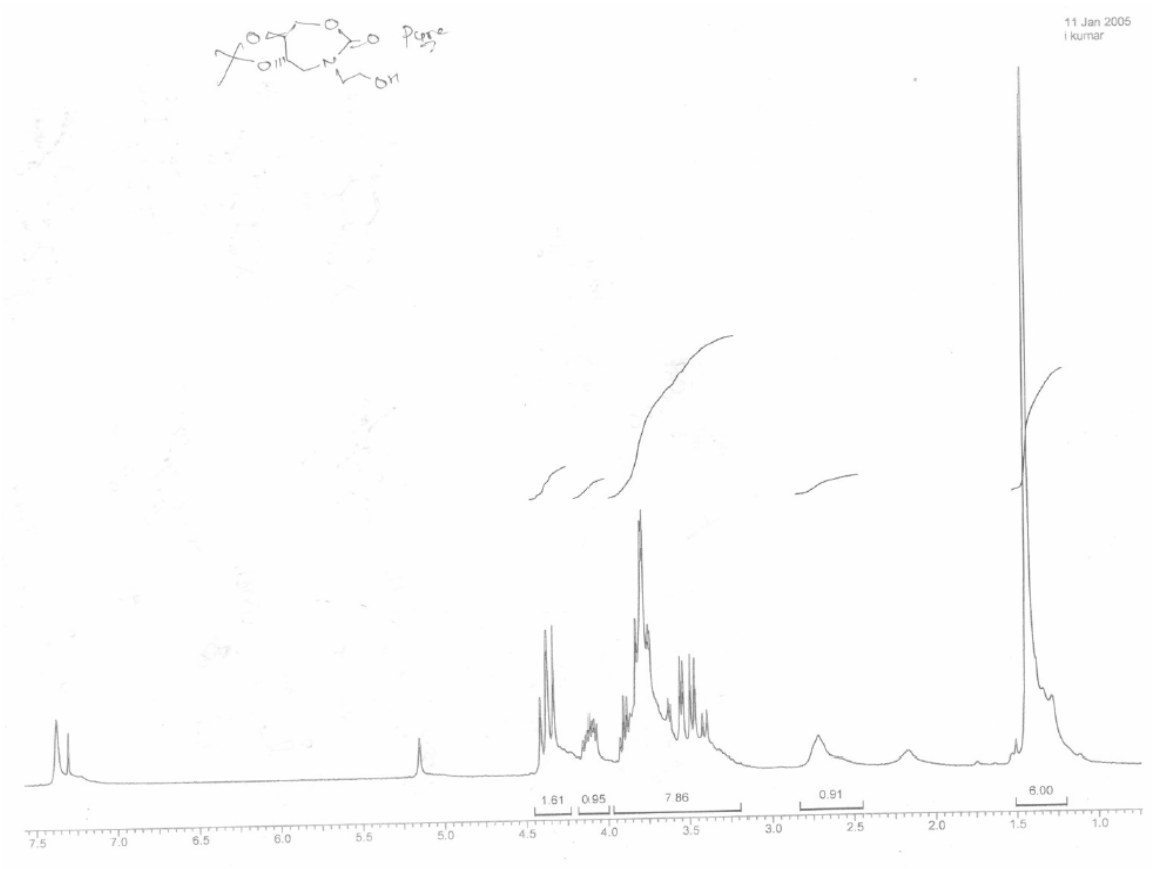
11 Jan 2005
i kumar
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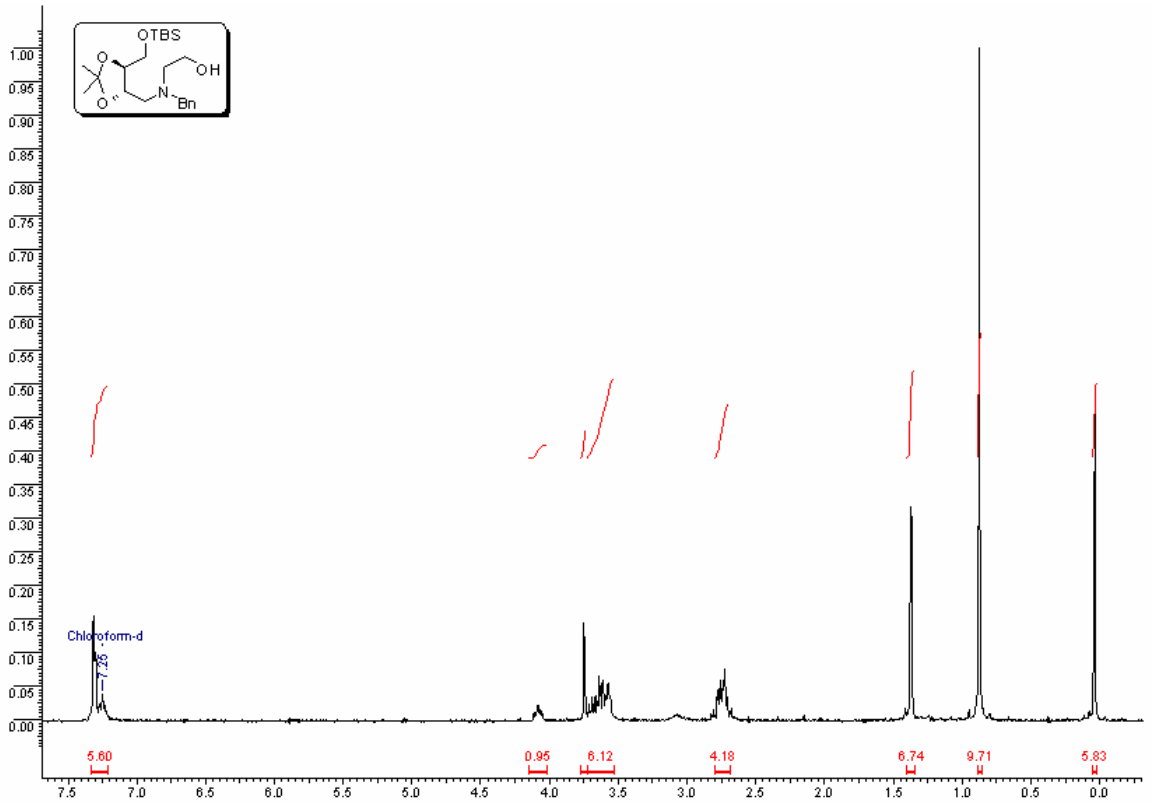
6.00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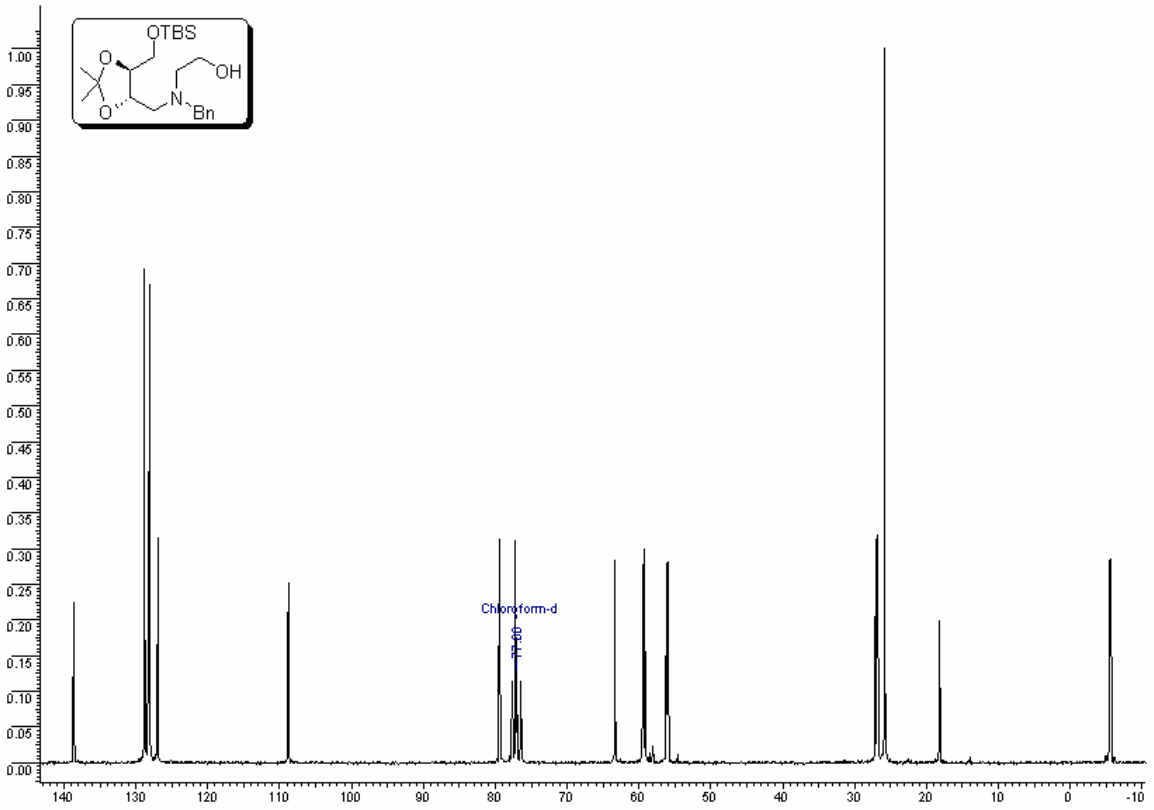
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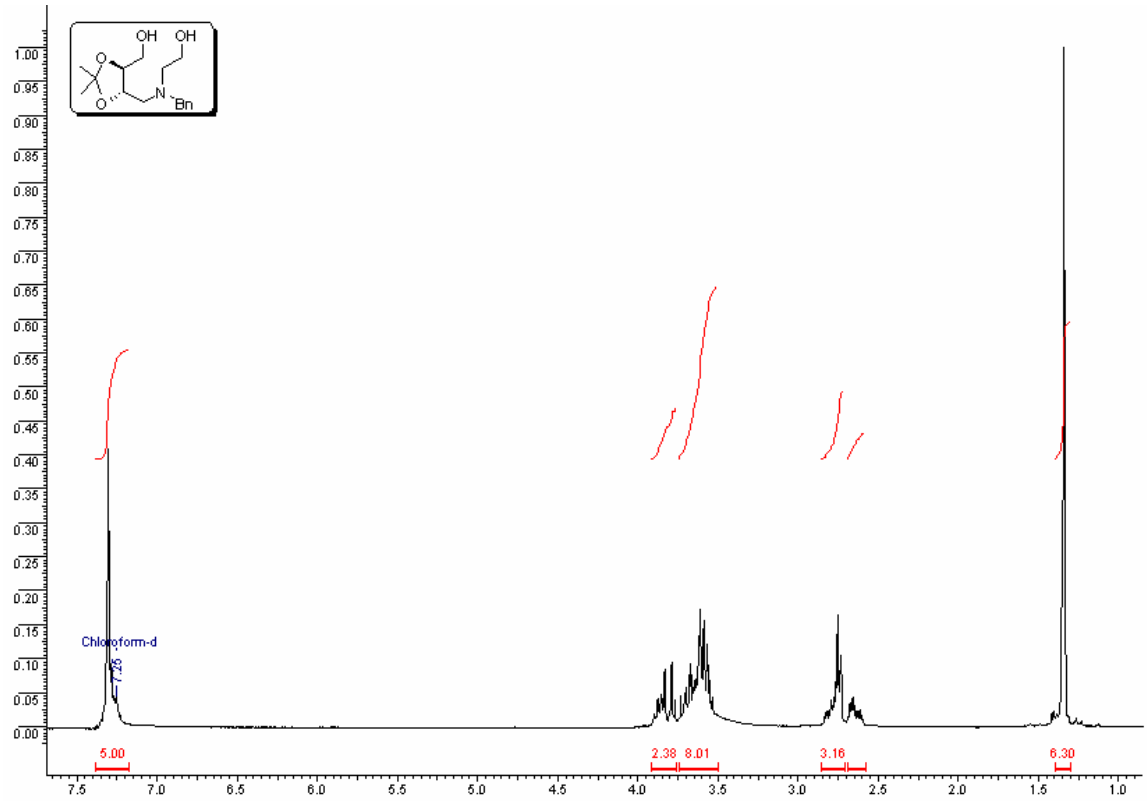
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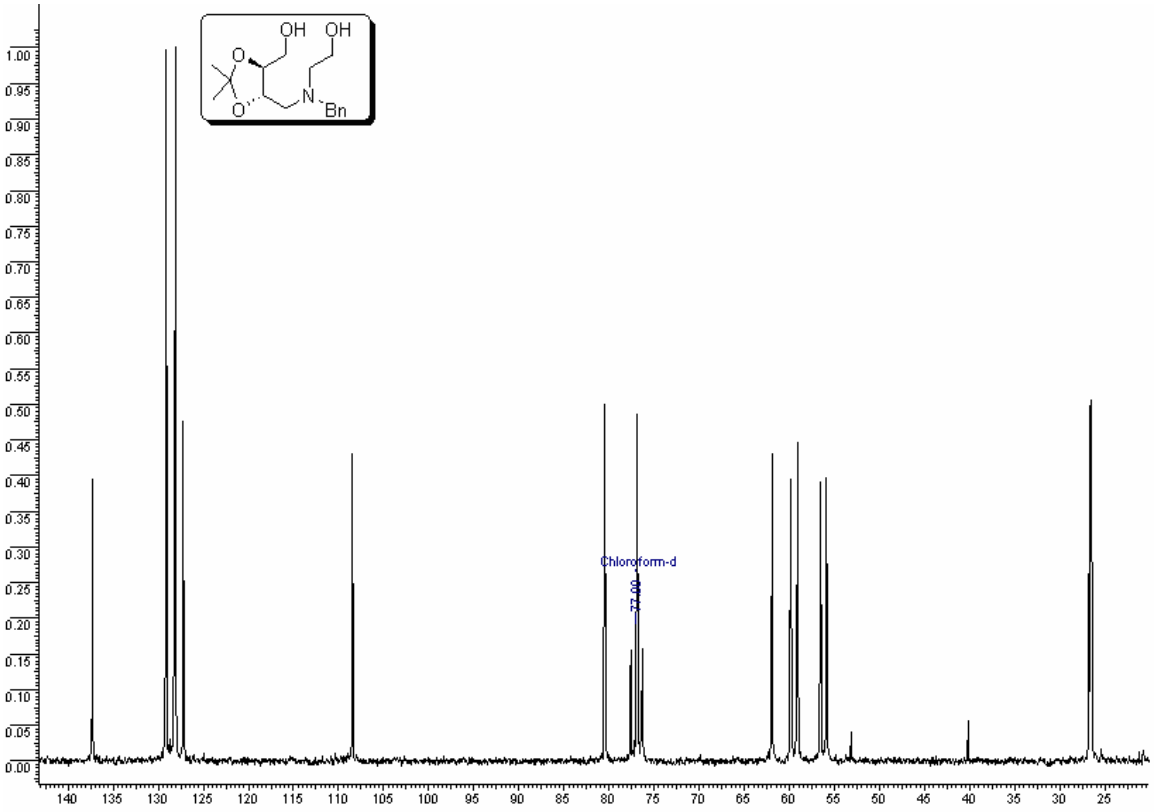
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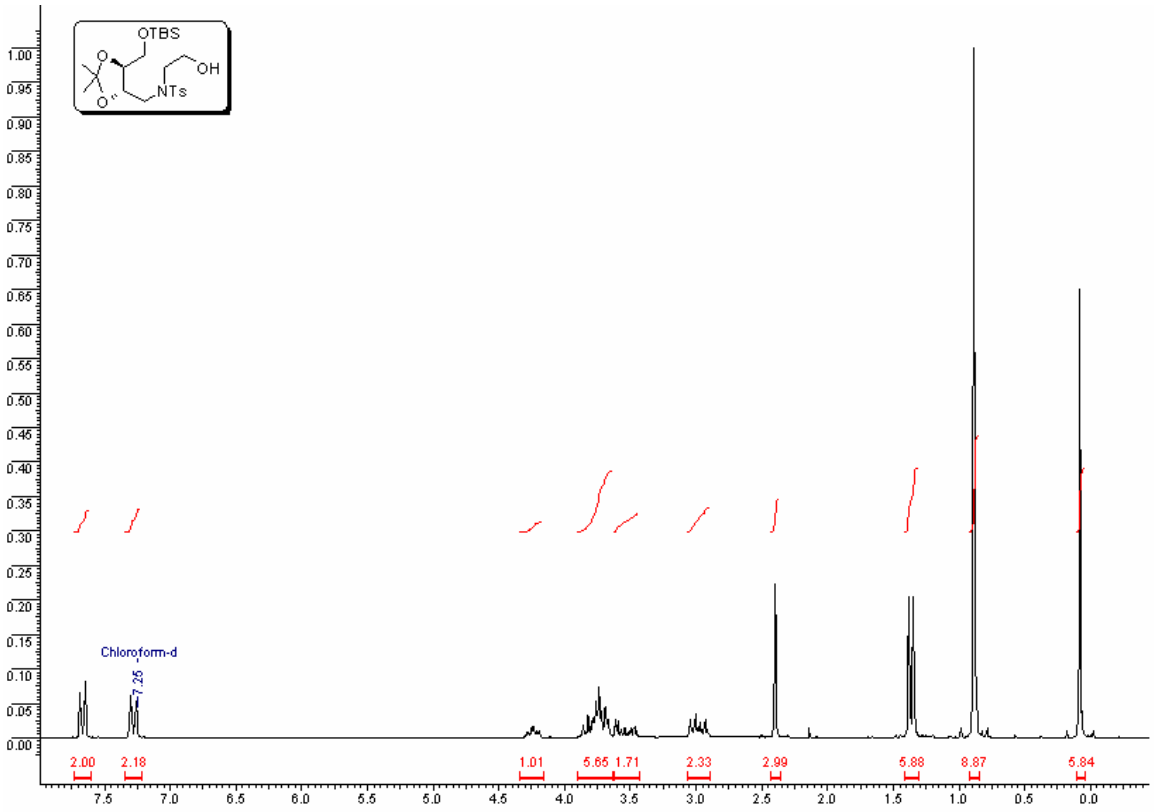
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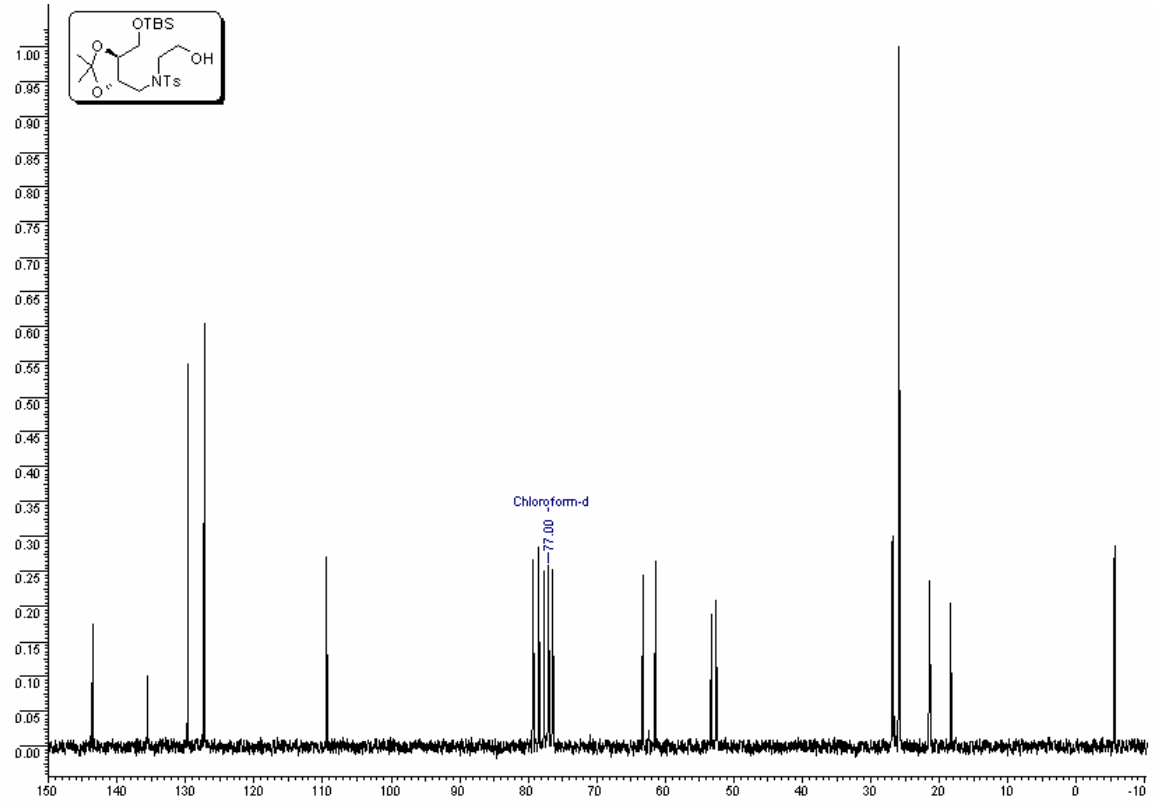
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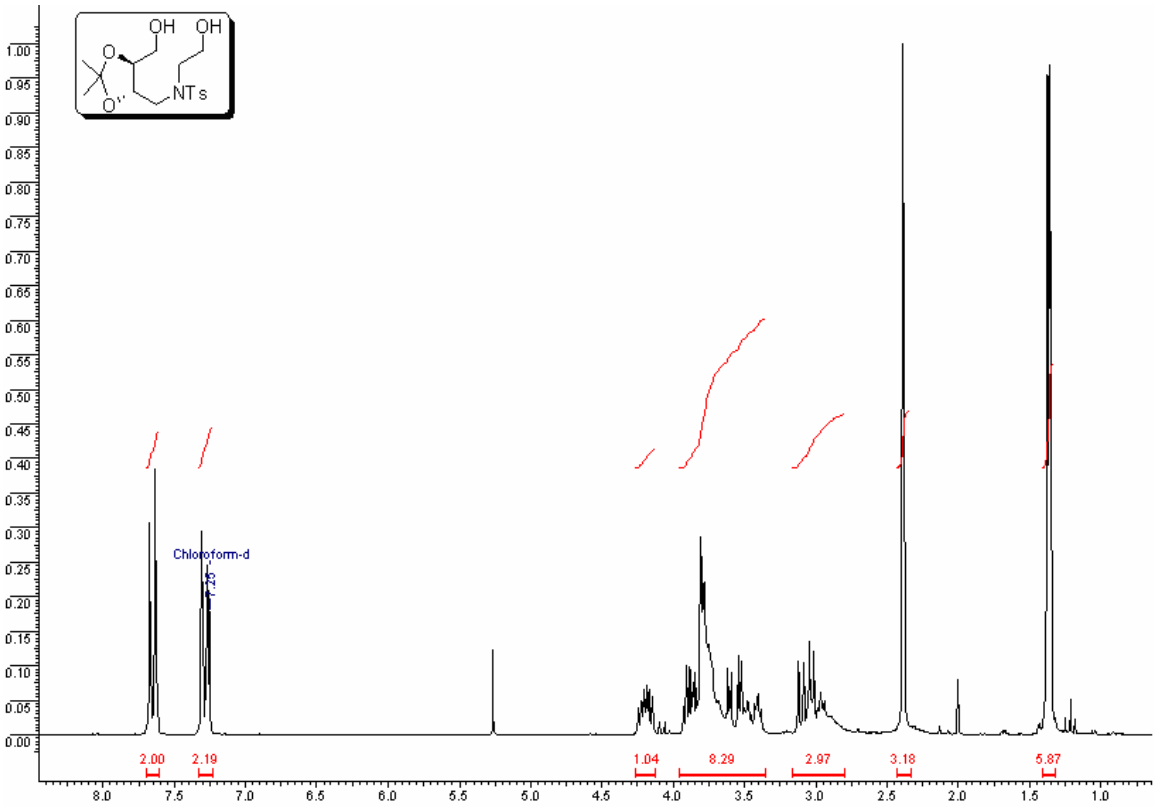
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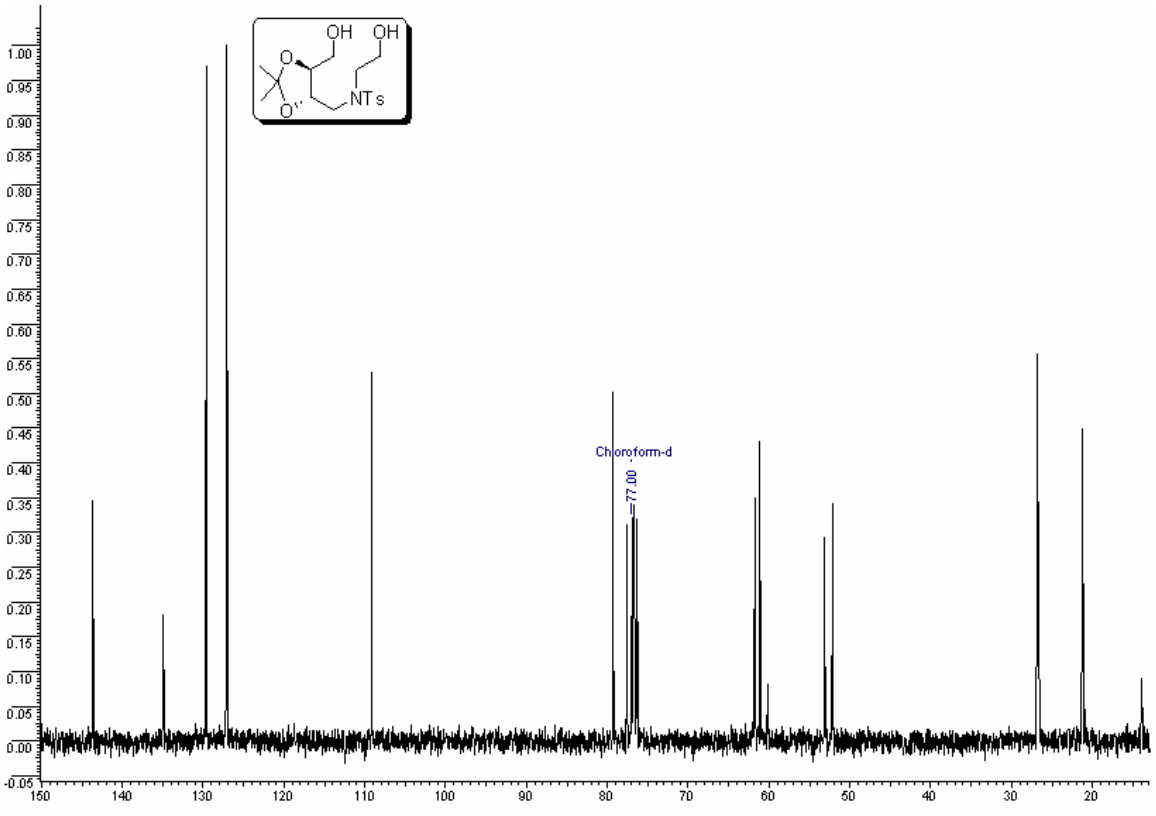
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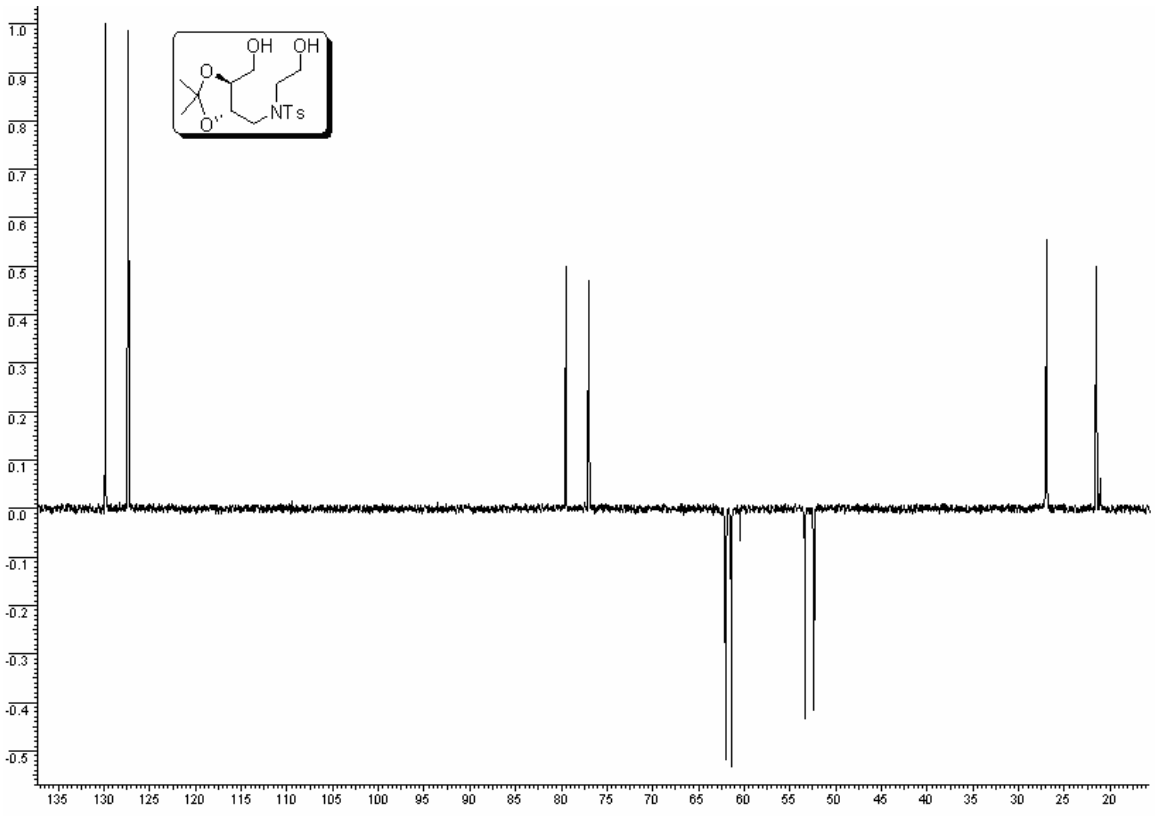
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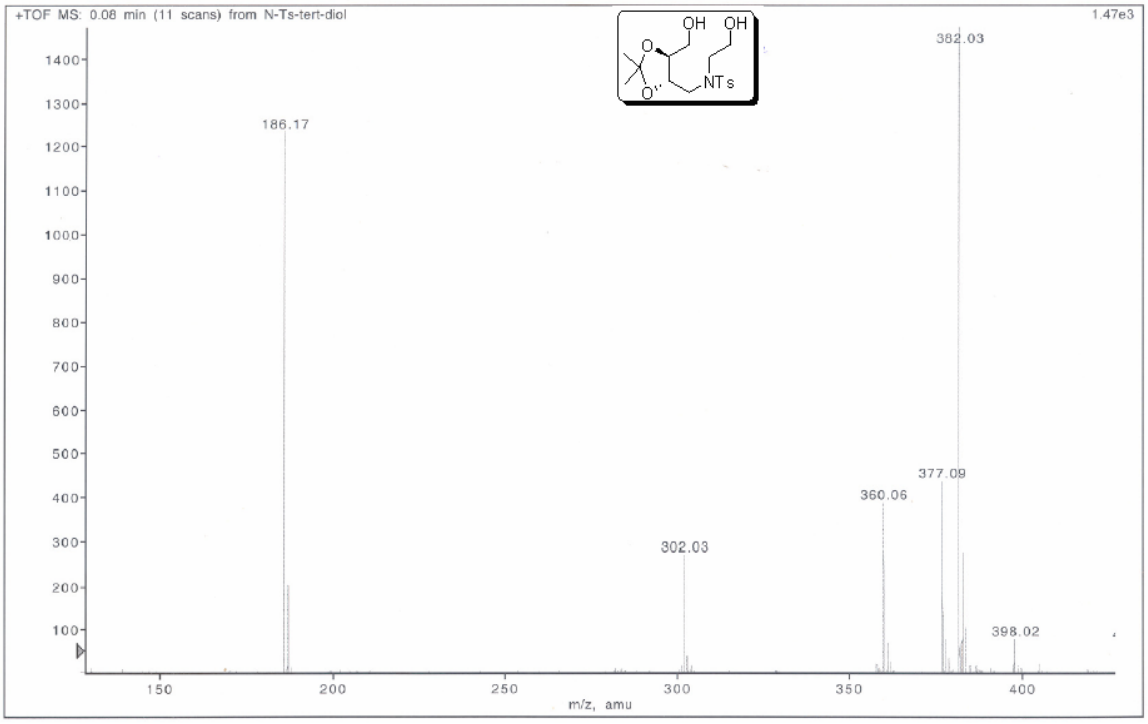
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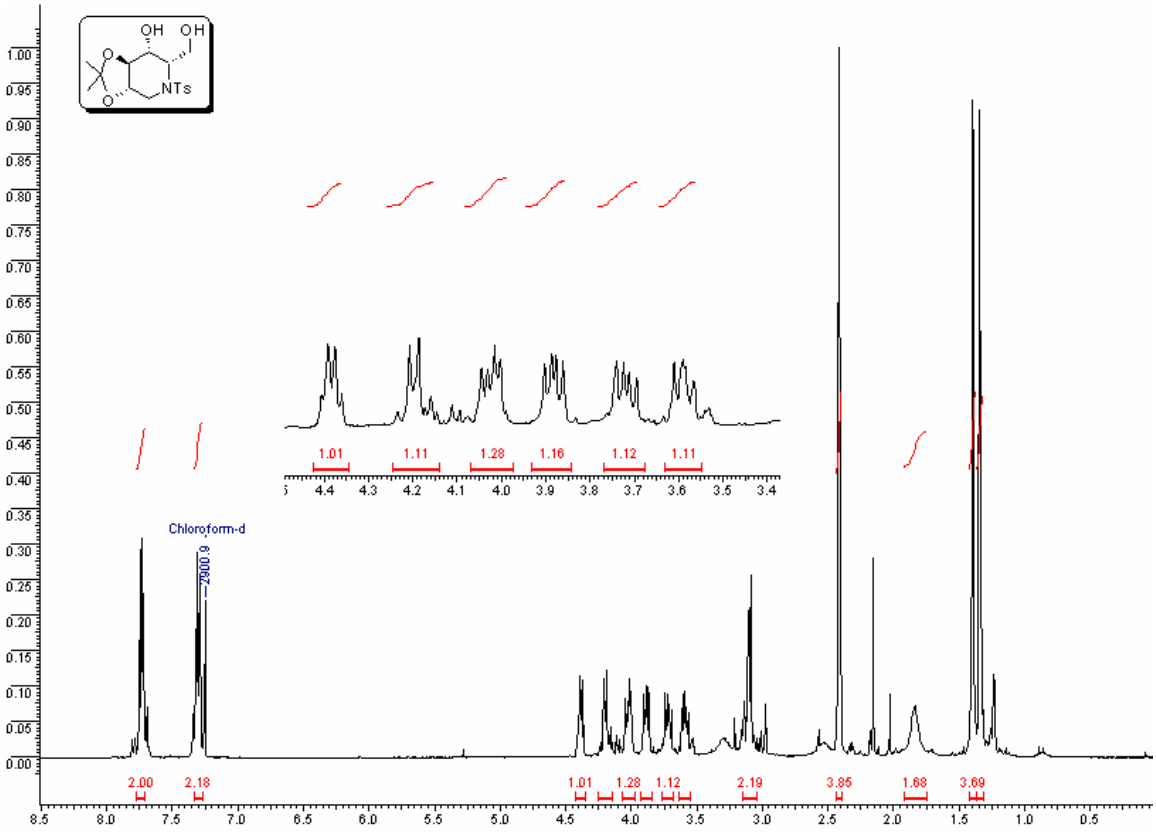
m/z, amu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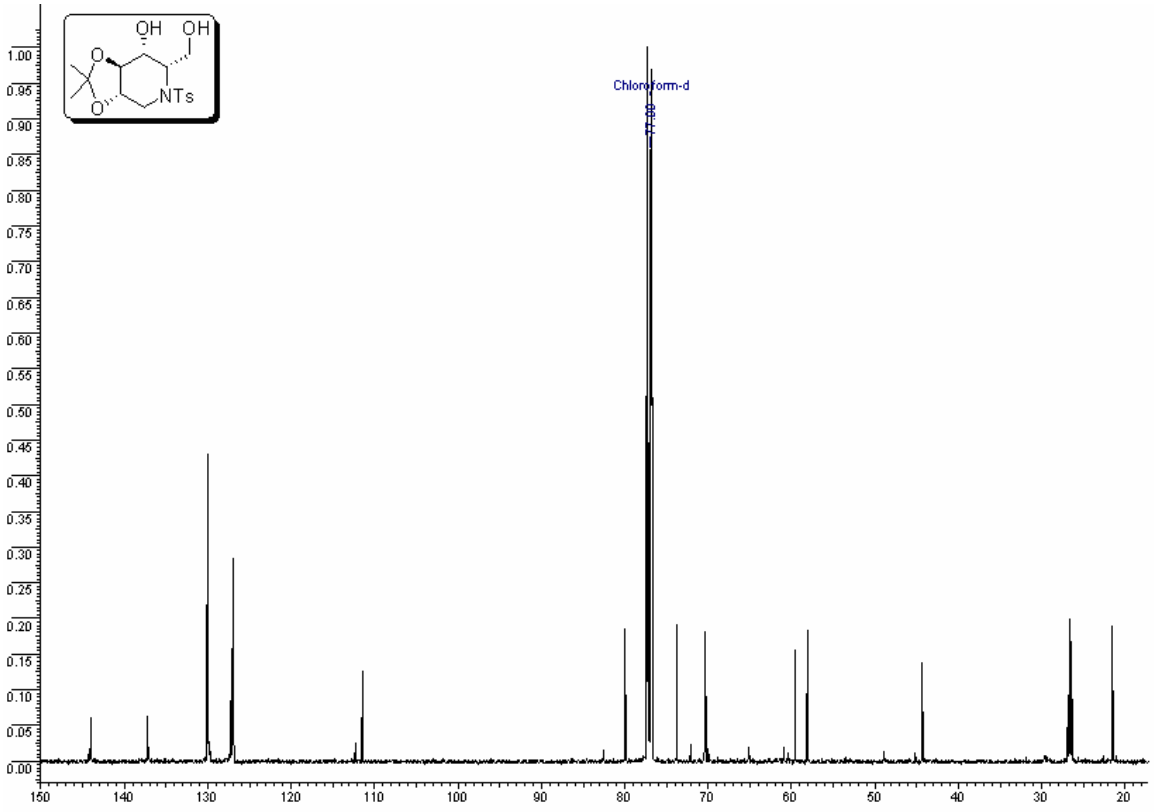
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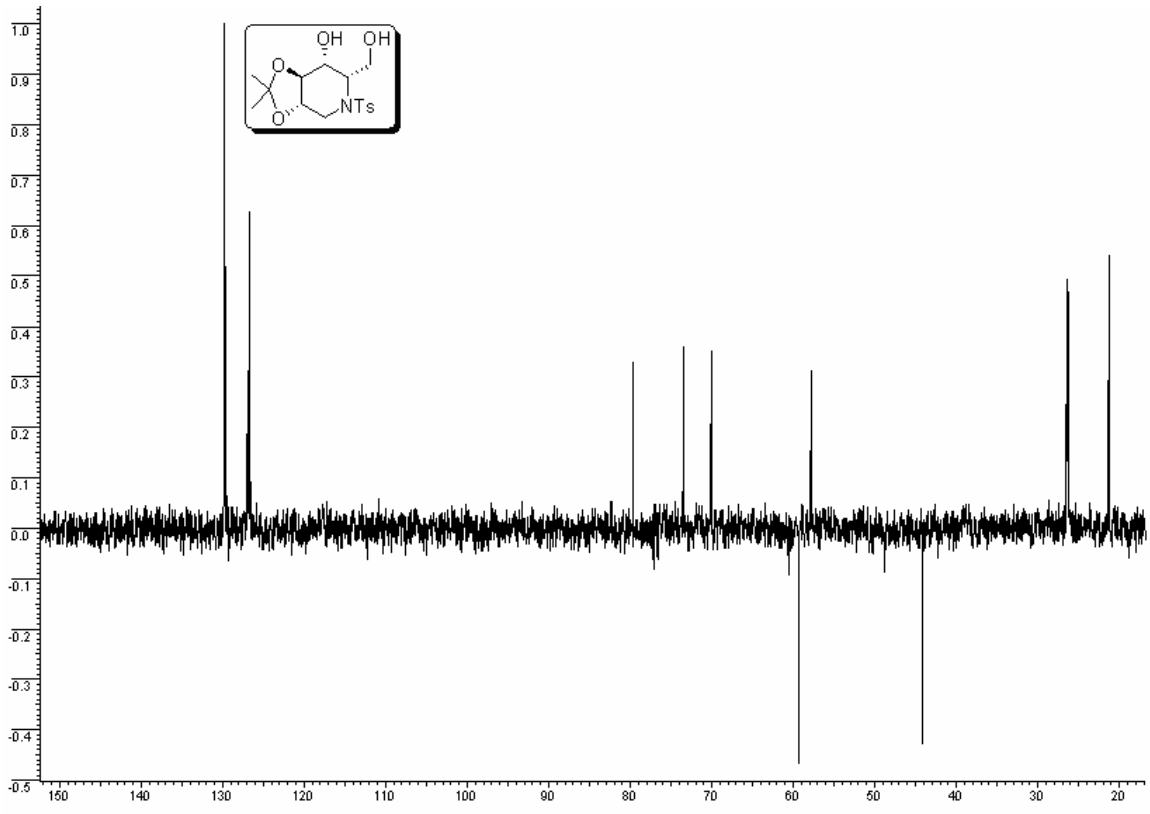
Chloroform-d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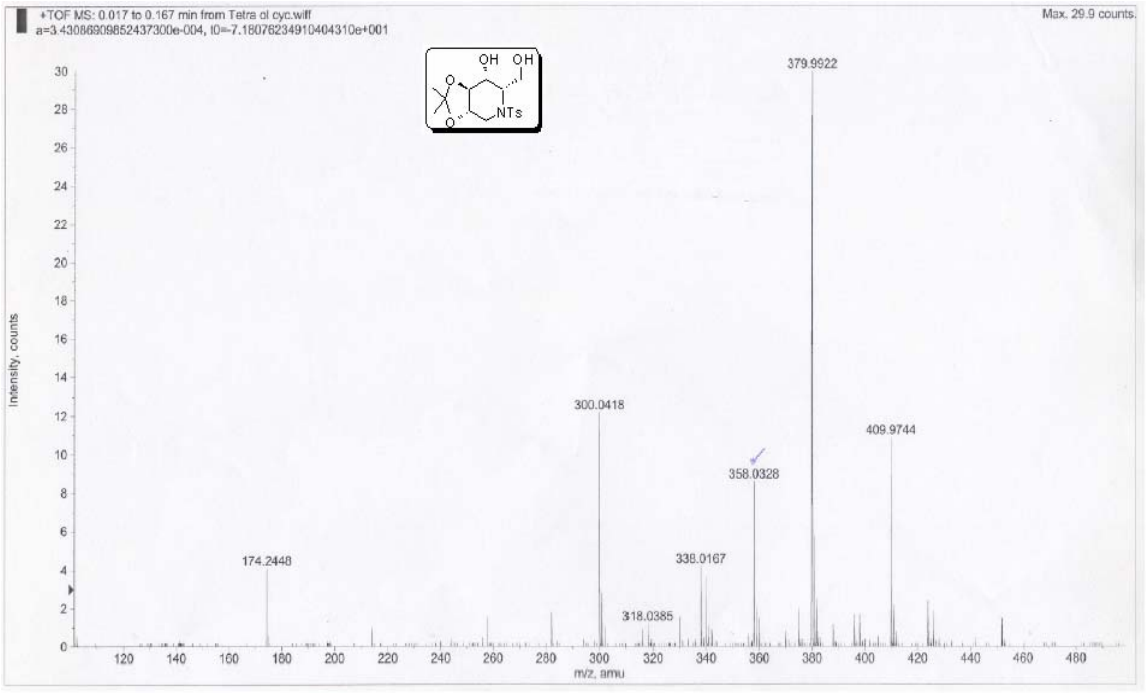
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Intensity, counts
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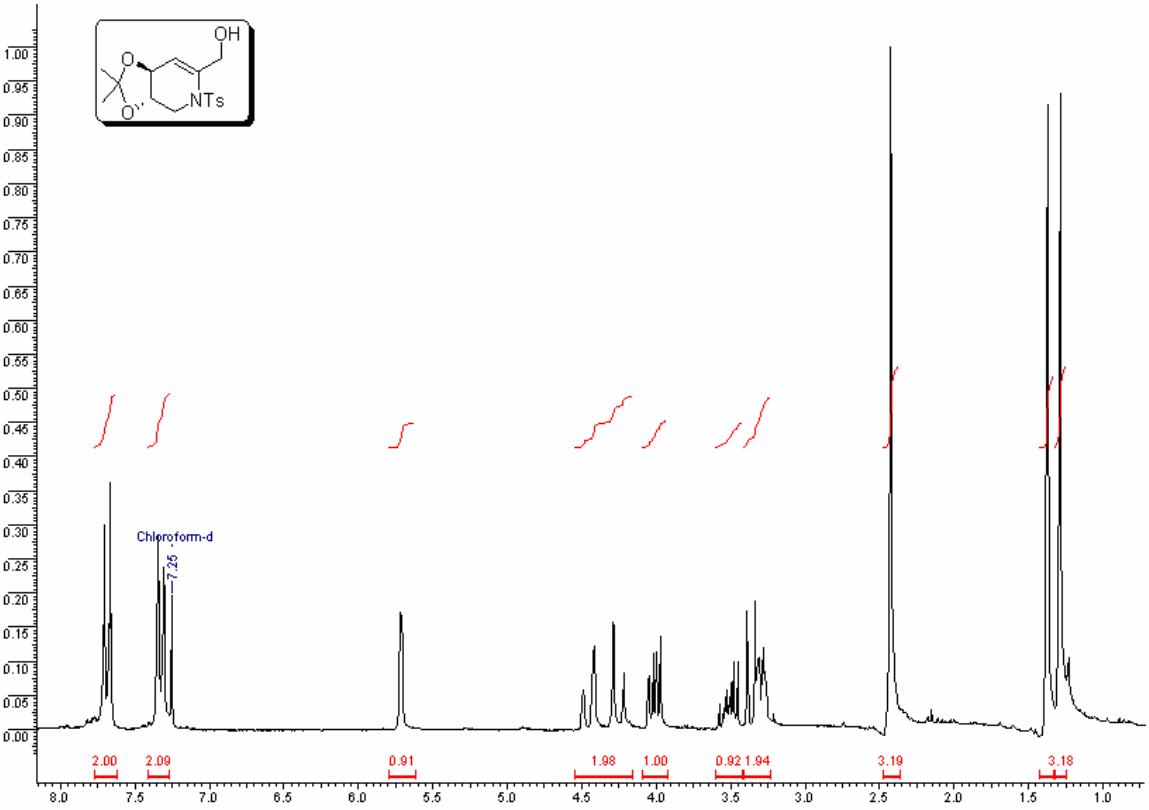
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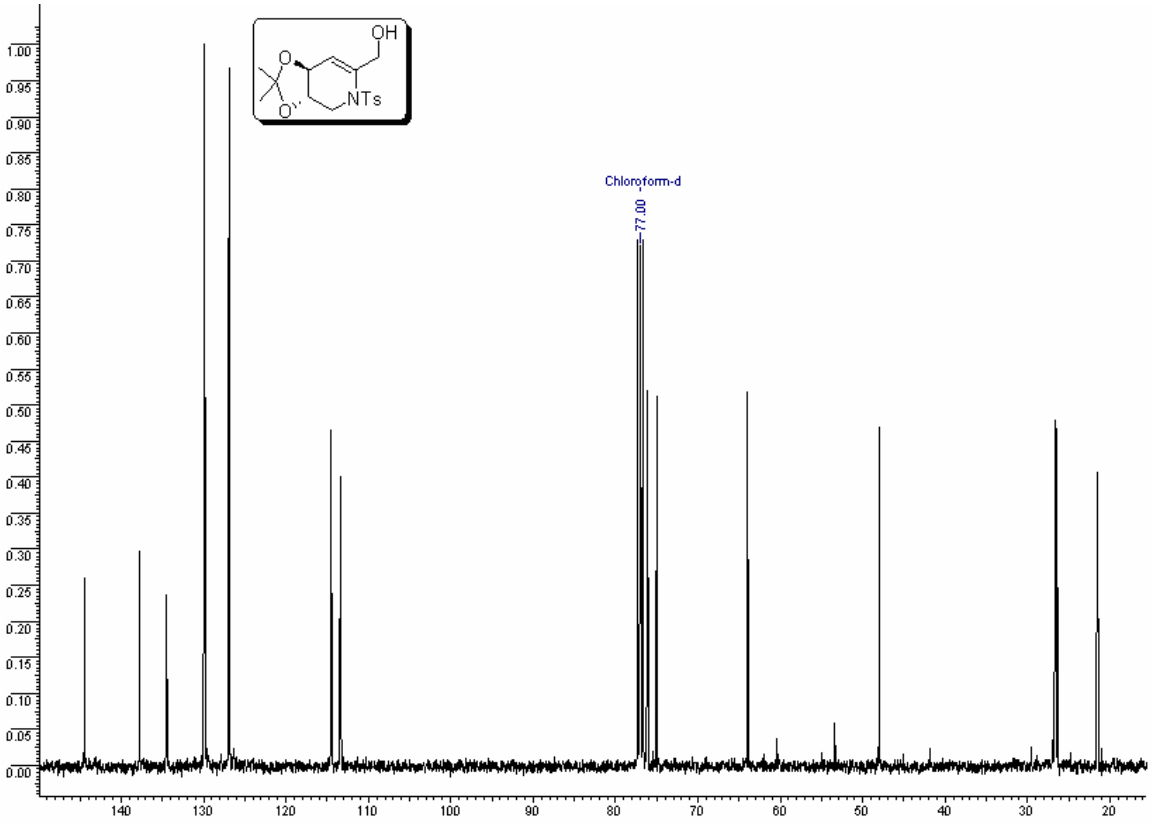
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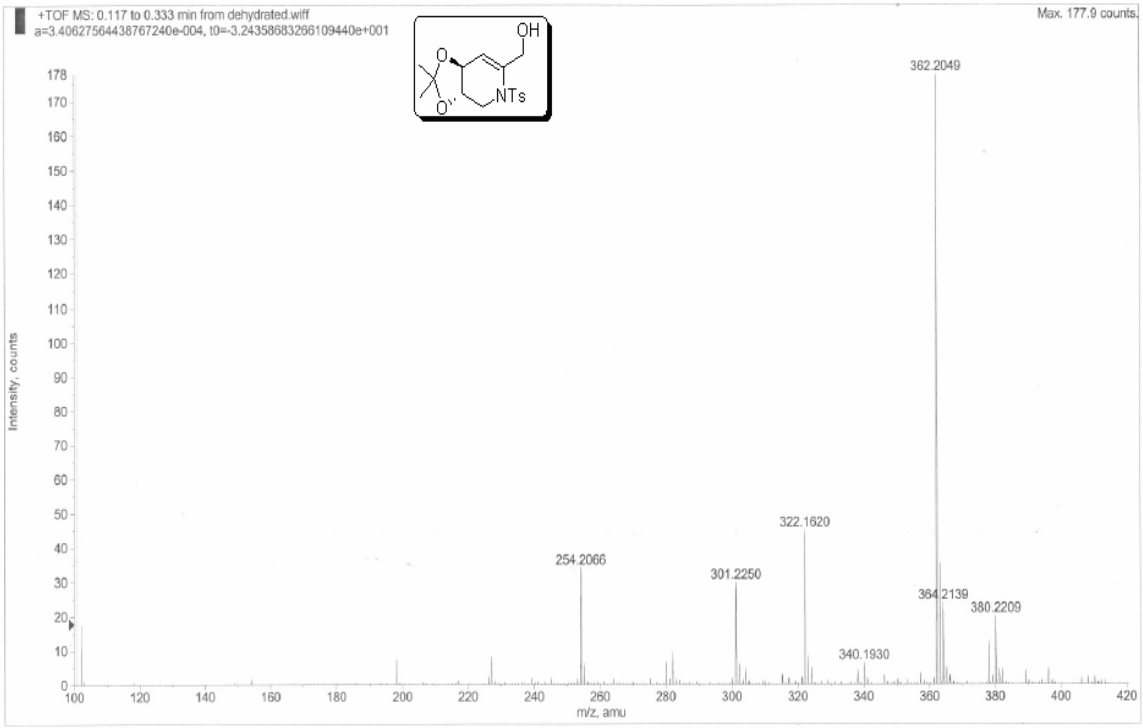
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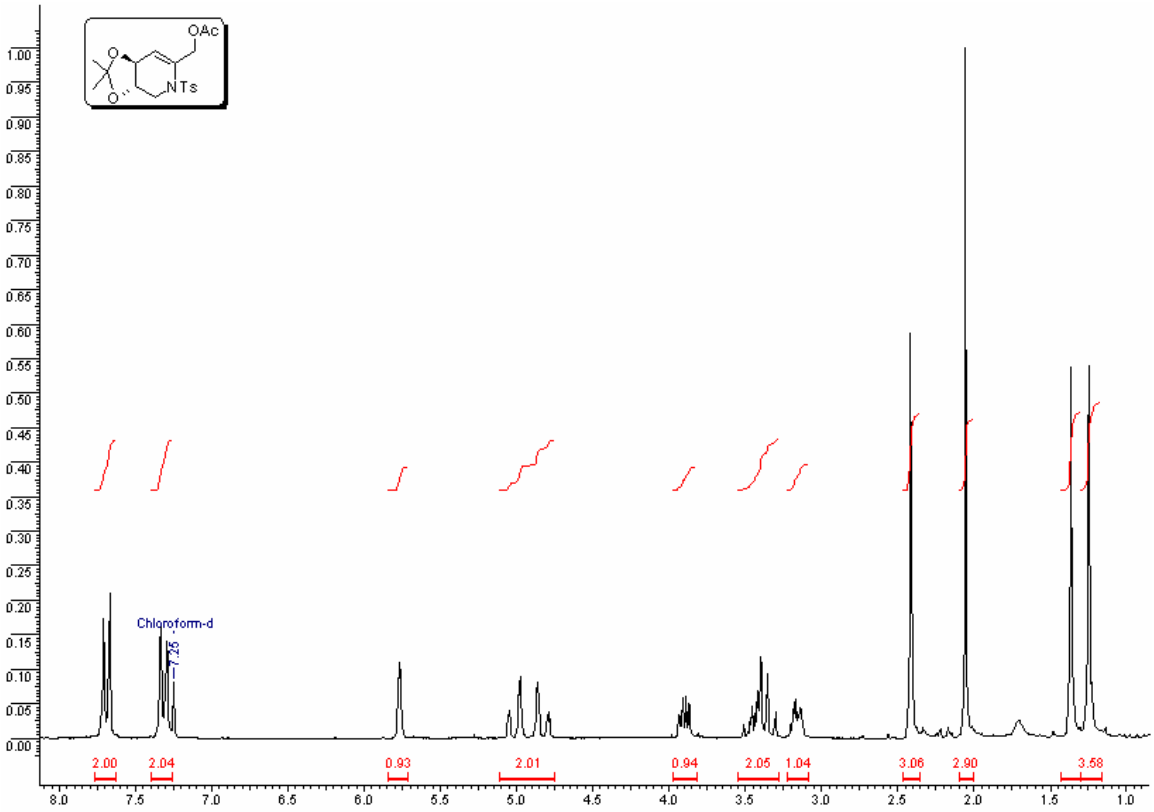
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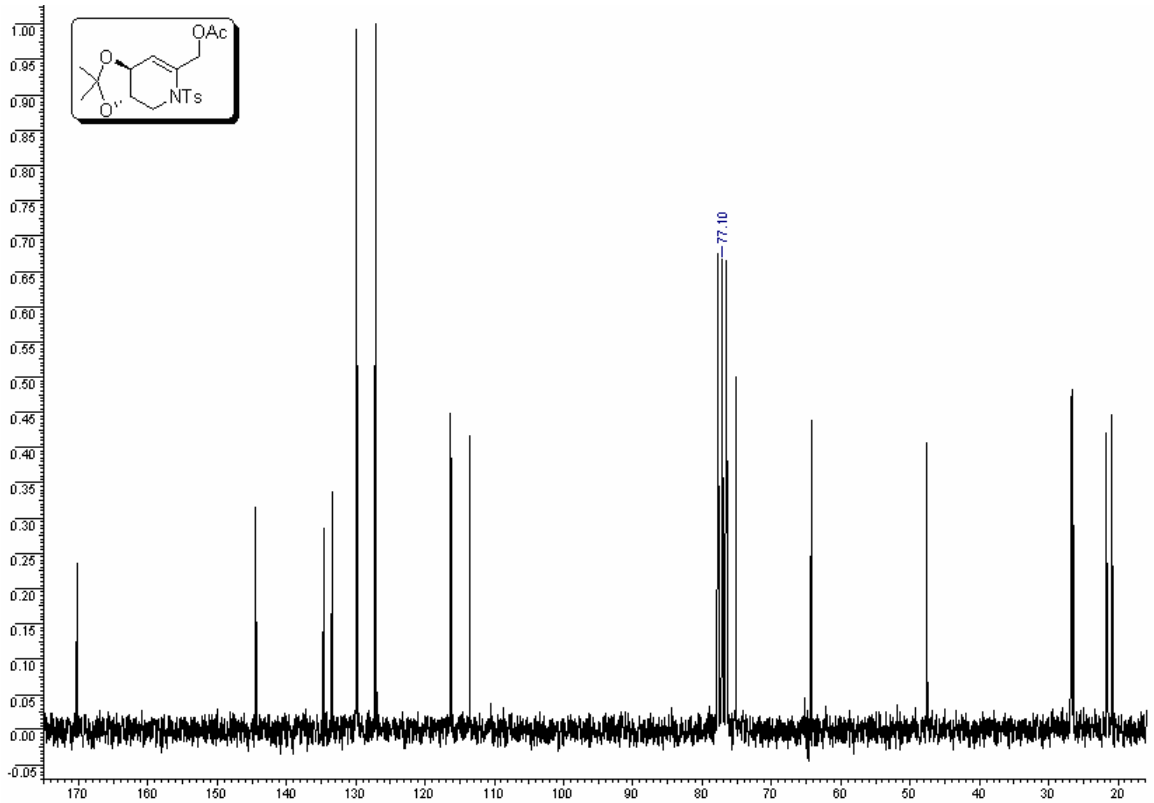
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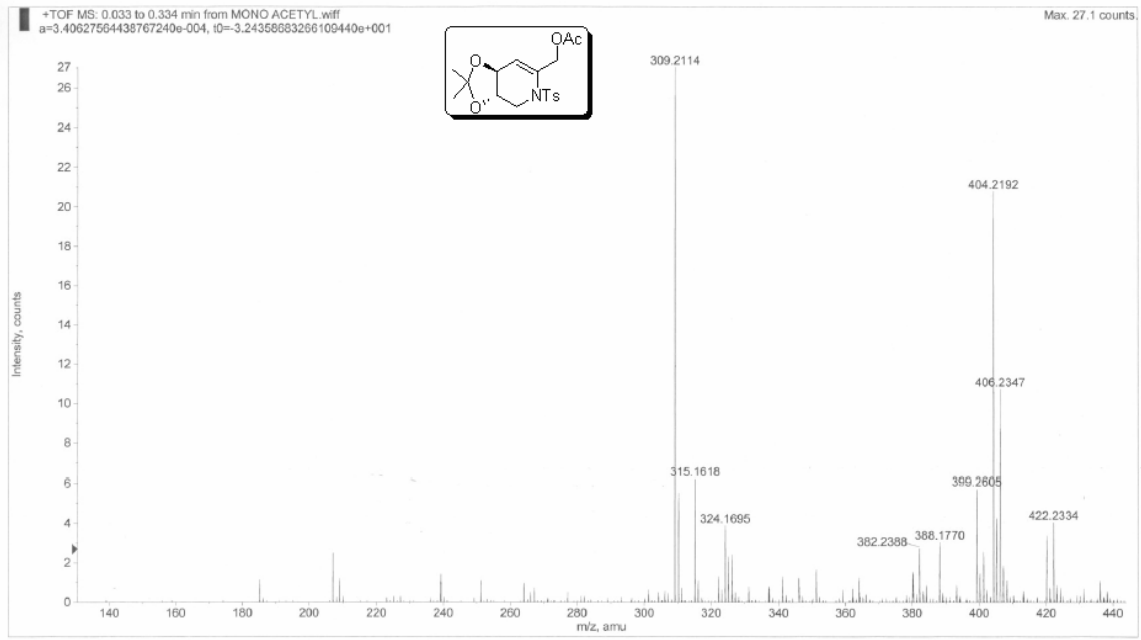
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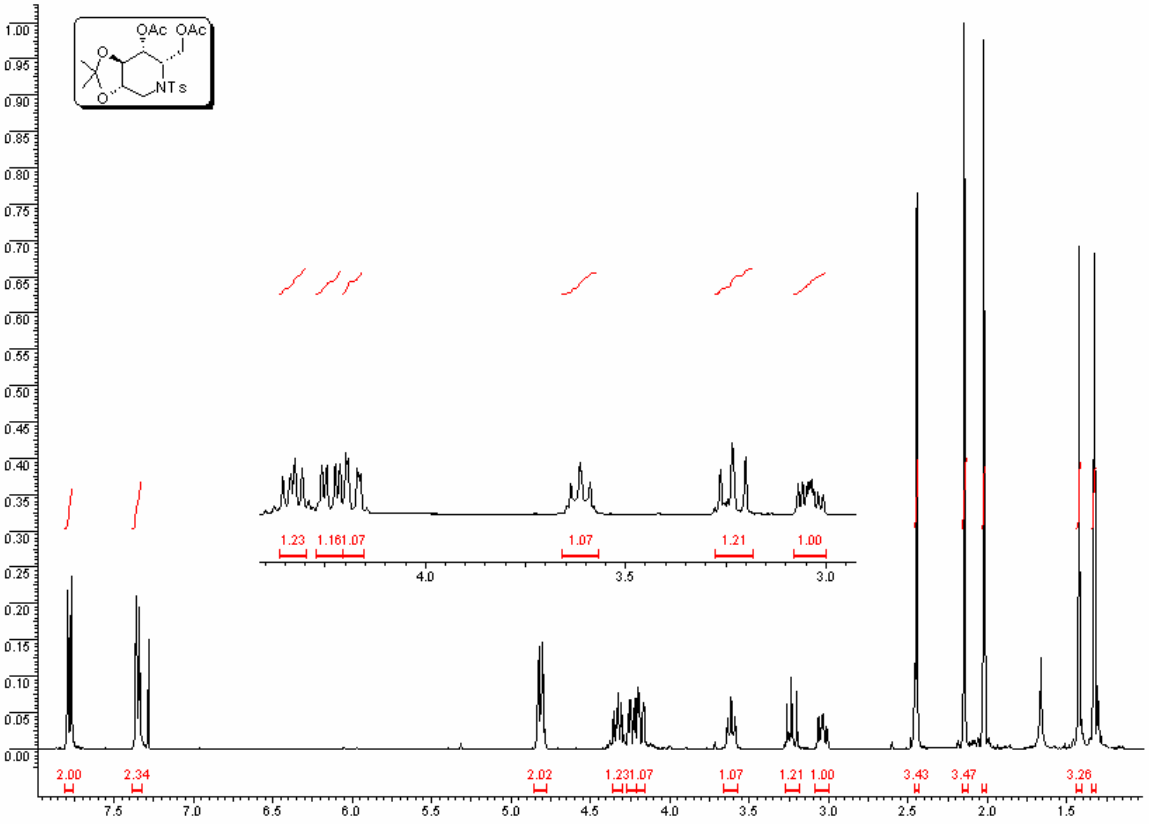
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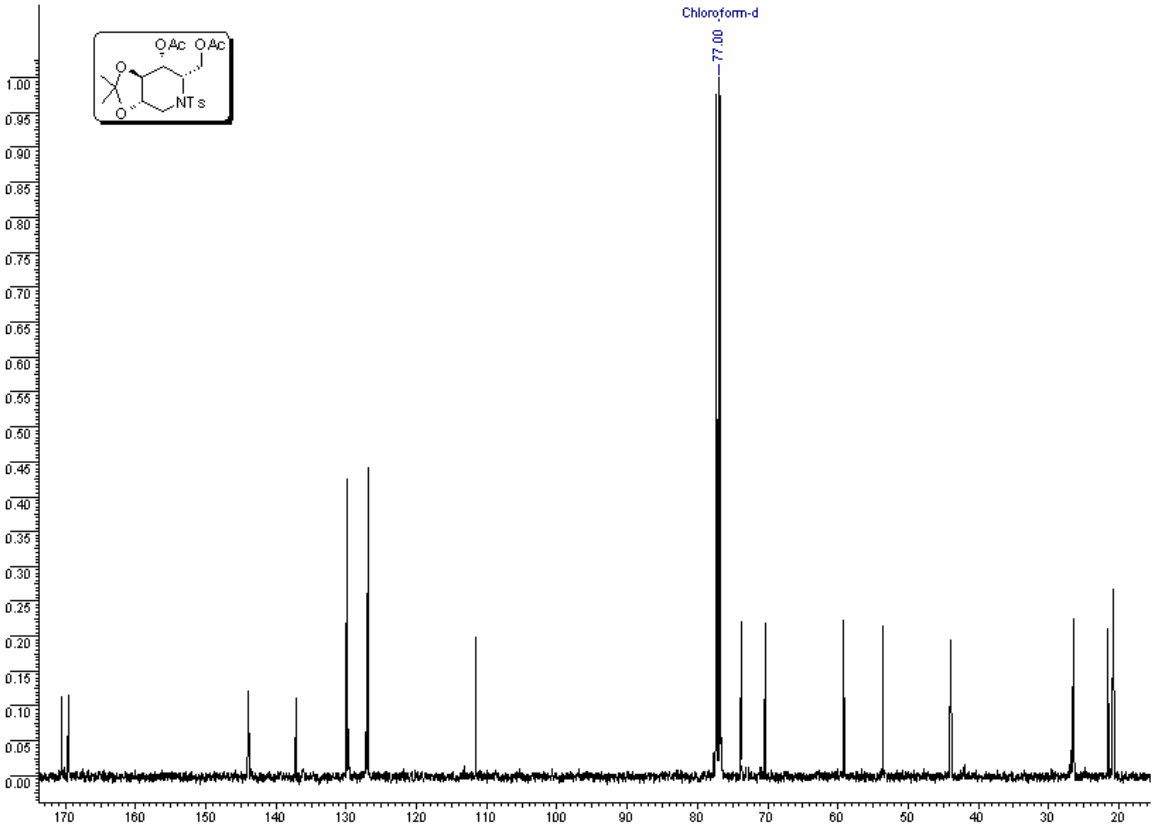
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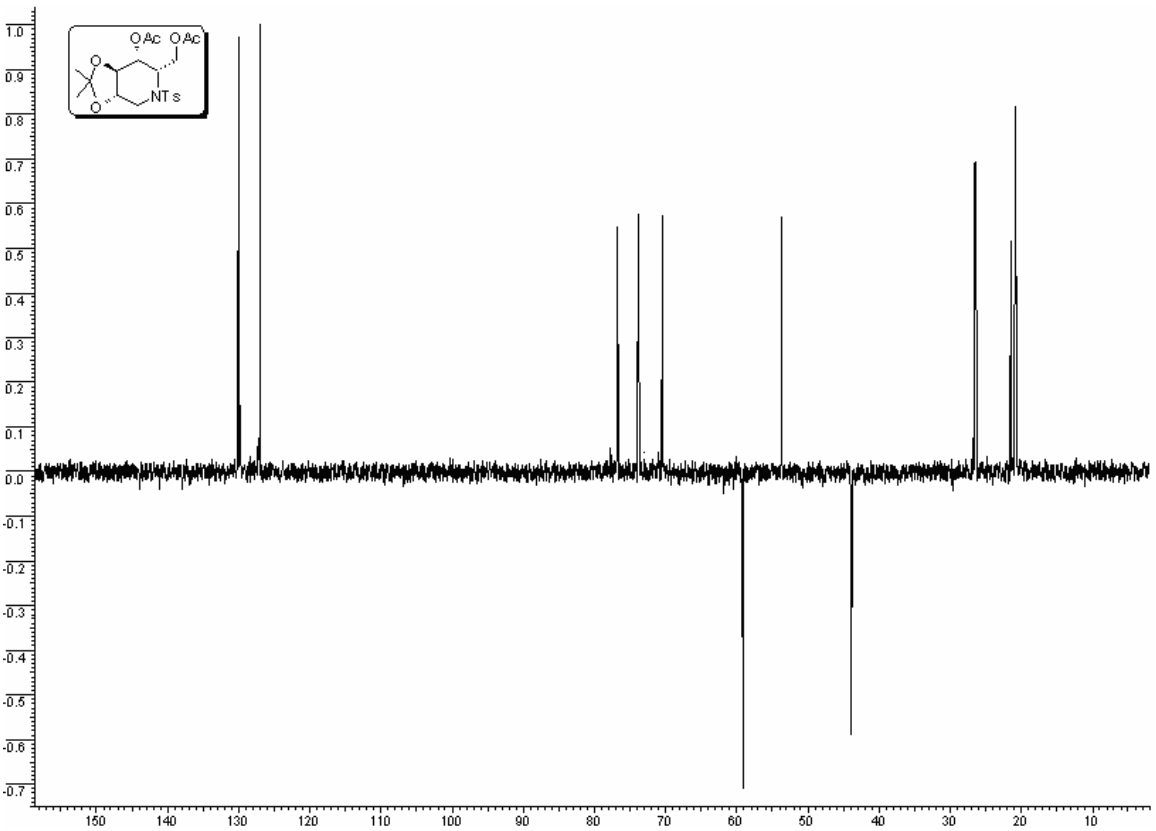
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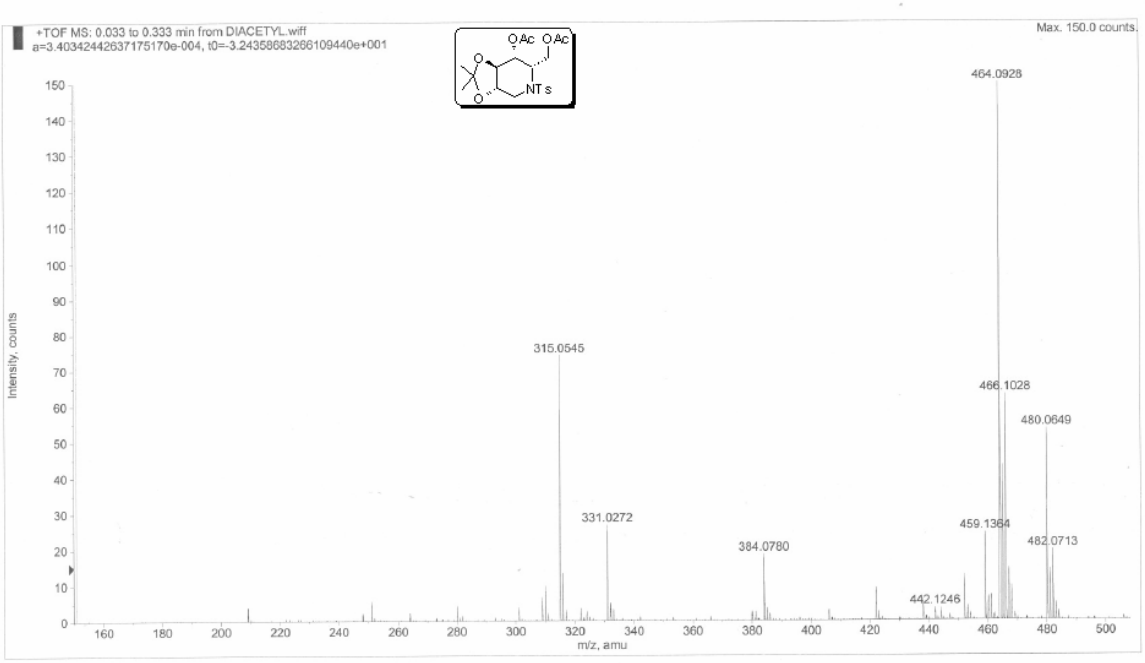

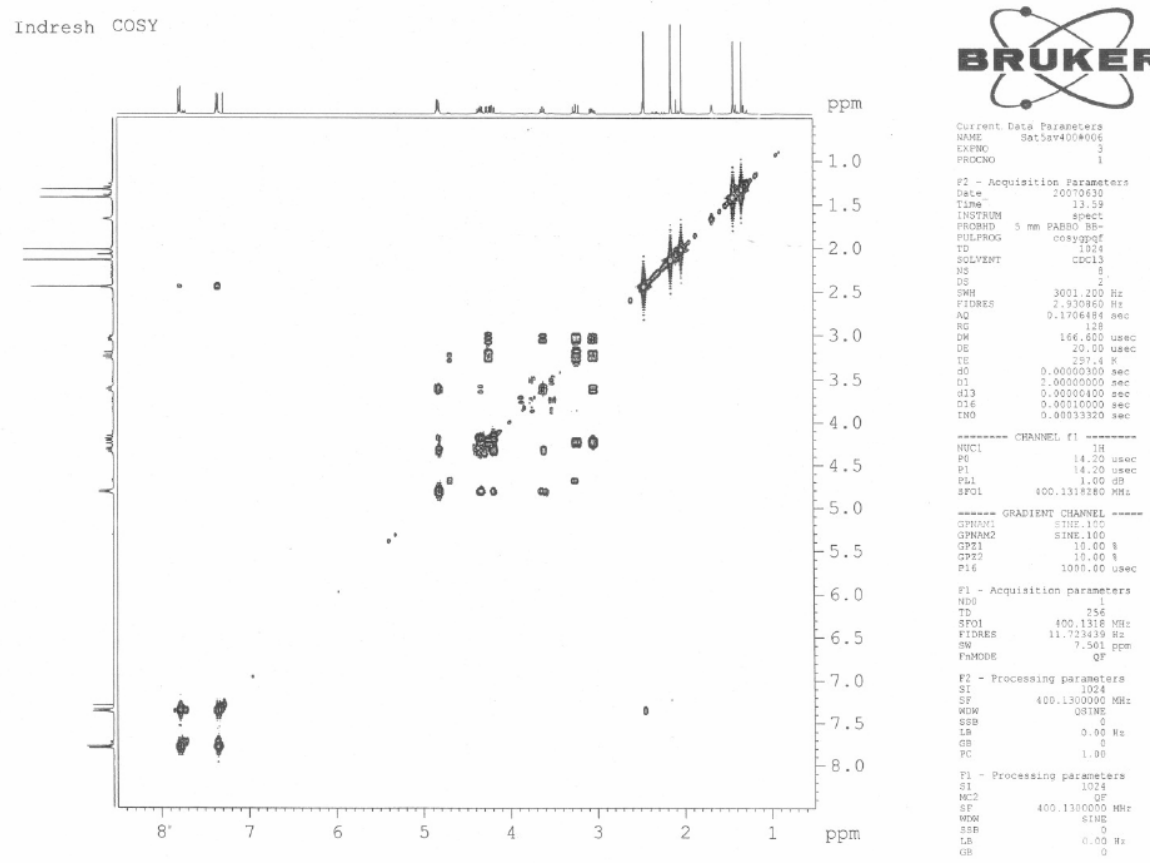

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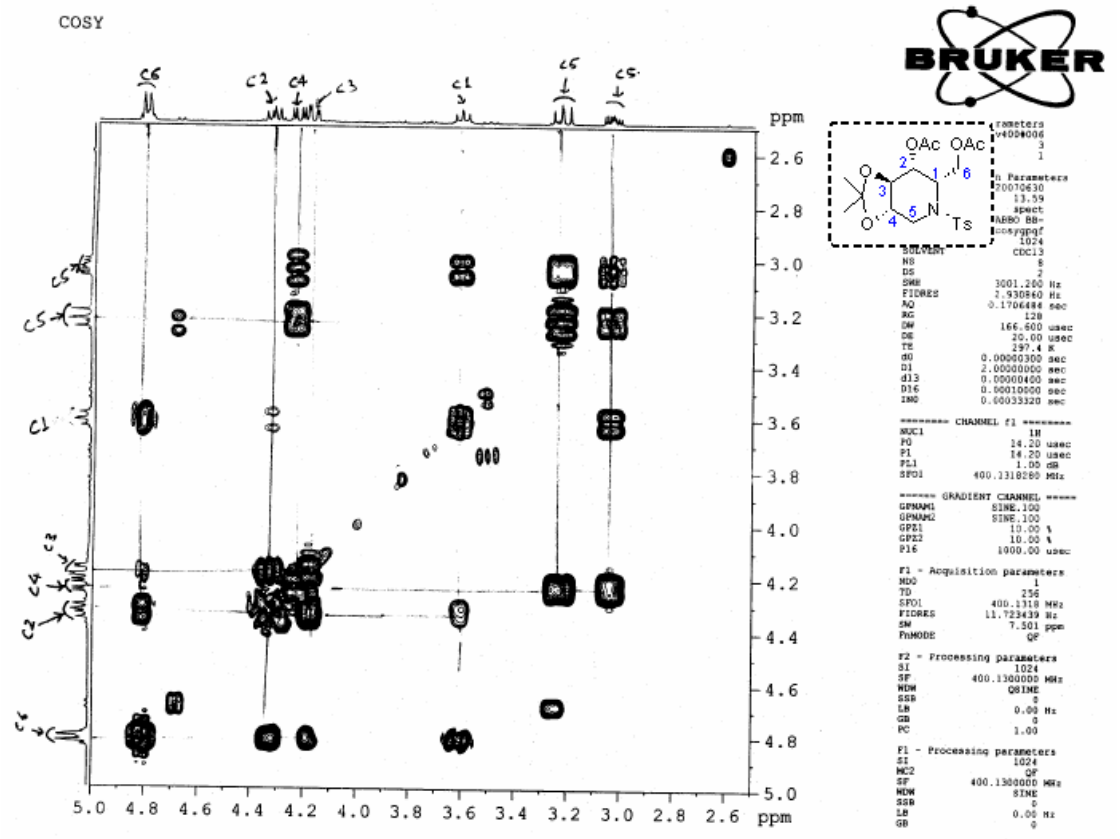
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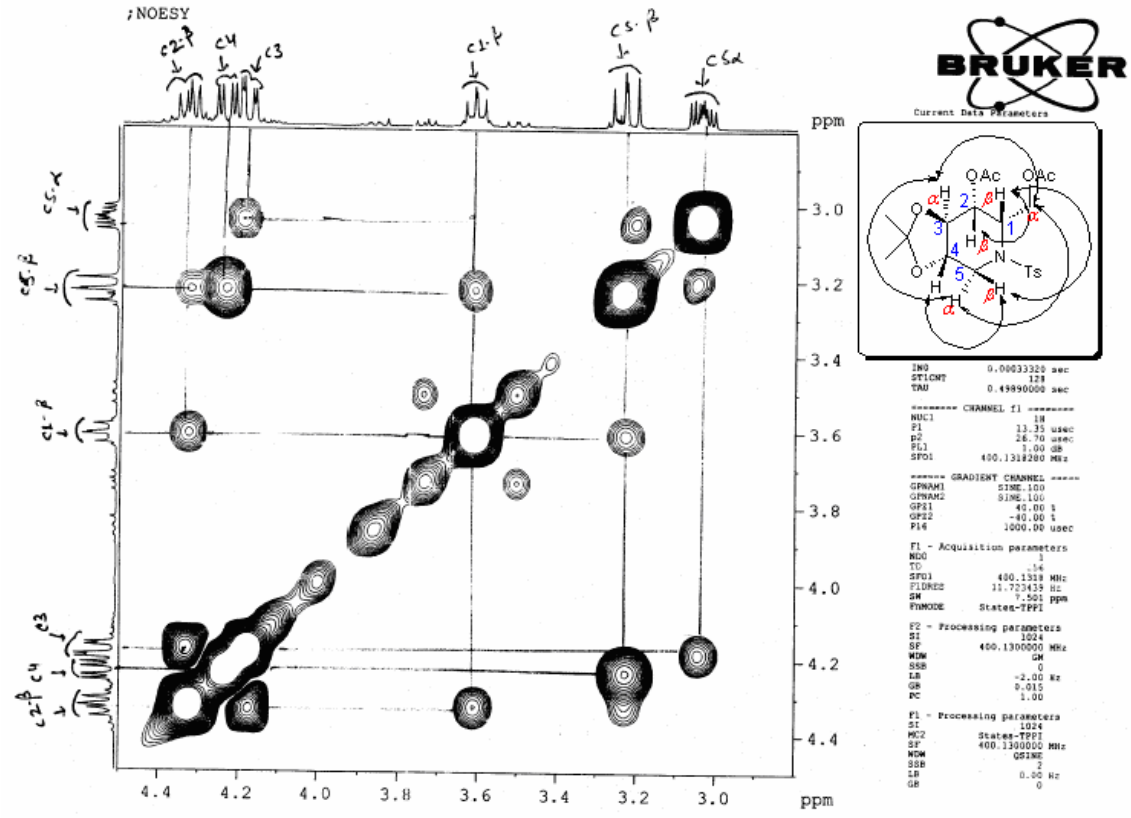
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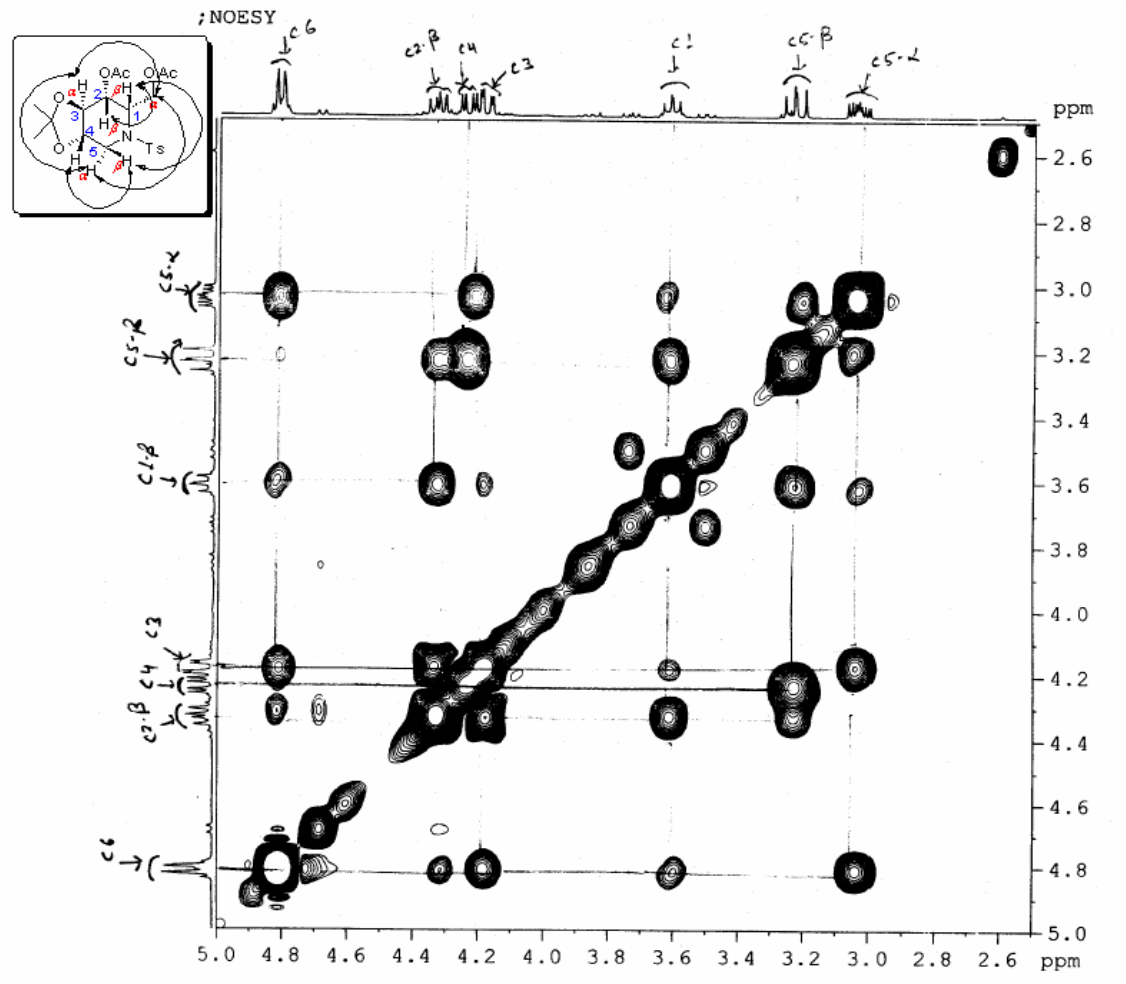
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3.0
2.8
2.6

Chapter 5

Synthesis of Fused 1,2,3-Triazolo-δ-Lactams/Lactones using "Click-chemistry in Water"

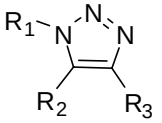
"Imagination is more important than knowledge."
-"Albert Einstein"

5.1 Introduction

Small nitrogen heterocycles containing amine and amine-derived functionalities are frequently found in a variety of natural and non-natural compounds showing biological importance. The role of nitrogen in biological system can be easily recognized because of its participation in ionic and hydrogen bonding interactions and hence, nitrogen heterocycles play an important role in drug discovery.[1] Due to the emergence of high-throughput screening technology in pharmaceutical industry, there is a need for the efficient methods for the rapid generation of libraries of small molecules particularly, the synthesis of nitrogen containing heterocyclic compounds. This can be achieved by developing an expanding set of powerful, selective, and modular methods that works reliably in both small- and large-scale applications.

Recently, a set of criteria defining reactions known as "click chemistry" was proposed by Sharpless and coworkers in order to accelerate the synthesis of drug molecules.[2] The click-reactions can be broadly defined as set of powerful reactions which prepare useful synthetic units together with heteroatom links (C-X-C), where X is an heteroatom and can be applied in both small- and large-scale applications. These reactions must be *modular*, *wide in scope*, *should* give *very high yields*, generate *no* or only *inoffensive byproducts* that can be removed by *nonchromatographic methods* and be *stereospecific* (but not necessarily enantioselective). Some of other major characteristics of these reactions include *simple reaction conditions* (insensitive to oxygen and water), *utilize readily available starting materials and reagents*, without solvent or in *benign solvent* (such as water), *simple product isolation*, and have a thermodynamic driving force of at least 20 kcal mol^{-1}. Such types of reactions proceed rapidly to completion and are very

selective for a single product and hence, following this approach an ideal chemical process can be developed for the synthesis of specially designed building blocks. Two types of click reactions that have great influence on drug discovery are the nucleophilic opening of strained ring systems[3] and 1,3-dipolar cycloadditions.[4] In particular, the Huisgen [3+2] dipolar cycloaddition reaction is of major interest which is a reaction between a alkyne and an azide to generate substituted 1,2,3-triazoles, **5.1** (Figure 5.1).[5]

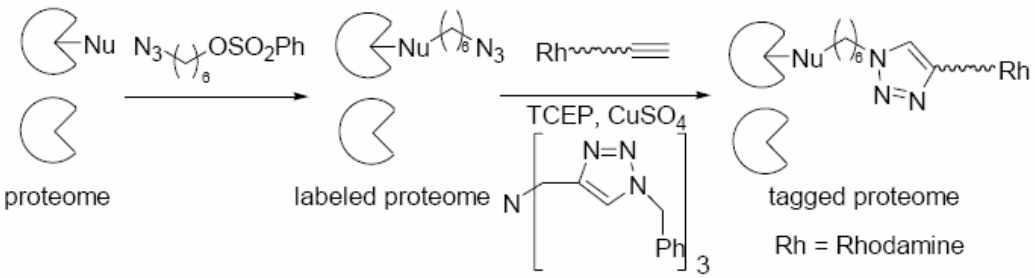


(5.1)

Figure 5.1

Substituted 1,2,3-Triazole

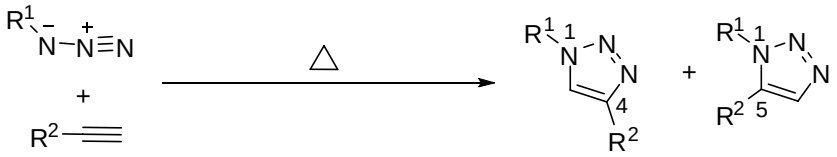
This reaction has been termed as the "cream of the crop" of the click reactions[2] and has found applications in various facets of drug discovery[6] such as target identification by activity-based protein profiling. Activity-based protein profiling (ABAP) utilizes active site-directed chemical probes with the broad target selectivity to label active proteins within various enzymes classes and allows for the discovery of new drug targets.[7] The use of an azide containing a phenyl sulfonate ester reactive group allowed the *in vivo* profiling of glutathione *S*-transferases, aldehyde dehydrogenases, and enoyl CoA hydratases (Scheme 5.1).[8]



Scheme 5.1: Activity-based protein profiling (ABAP) using click chemistry

The introduction of azide moiety within organic molecules by nucleophilic substitution of halides/leaving group or ring opening of heterocycles with sodium azide is a facile

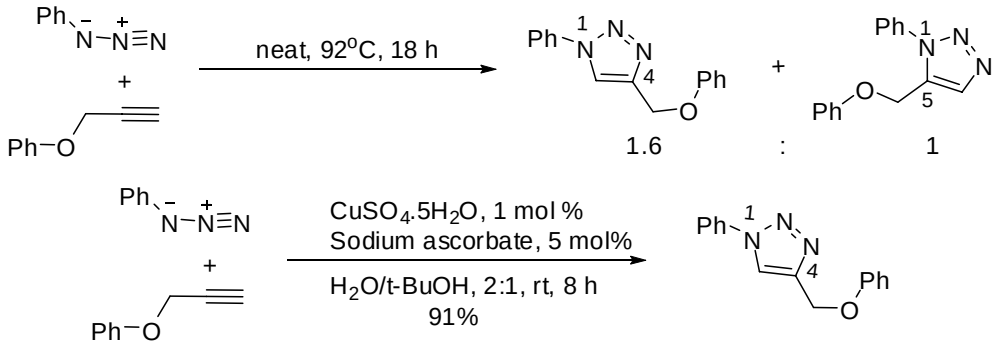
reaction.[9] However, probably because of concerns about the safe handling of azide moiety,[10] medicinal chemists have not given the attention to the transformations involving azides that they deserve. Azides are very important functional groups due to the ease introduction and their reduction to amino group. With few exceptions, the stable azides remain 'unreactive' unless a good electrophile is present. The 1,3-dipolar cycloaddition reaction between alkyne and azide developed by Huisgen et. al.[5,11] is the most popular reaction because the resulting five member substituted 1,2,3-triazole heterocyclic ring derivatives have been reported to exhibit antimicrobial activity,[12a] as inhibitors of human leukocyte elastases,[12b] as synthons for the preparation of antitumer dehydropyrrolizidine alkaloids,[12c] for the modification of nucleosides as antiviral agents,[12d] as well as have a wide range of industrial applications such as dyes, photo stabilizers, and agrochemicals.[12e-12h] However, there are major problems associated with this reaction, including the need for longer reaction times (12-24 h) and higher temperature (>100^{o}C), which usually generates a mixture of 1,4- and 1,5-disubstituted regioisomeric triazole products with unsymmetrical alkynes. (Scheme 5.2)



Scheme 5.2: 1,2,3-Triazole formation via Huisgen 1,3-dipolar cycloaddition

It was recently reported that some degree of regioselectivity can be introduced into this thermal cycloaddition by utilizing sterically or electronically modified alkynes.[12b,13] As a part the work by the Sharpless group on so-called "click" reactions,[2,14] whereby heteroatom links between two or more molecules can be generated under mild conditions, it was found that cycloaddition of terminal alkynes with alkyl azides catalyzed by Cu(I)

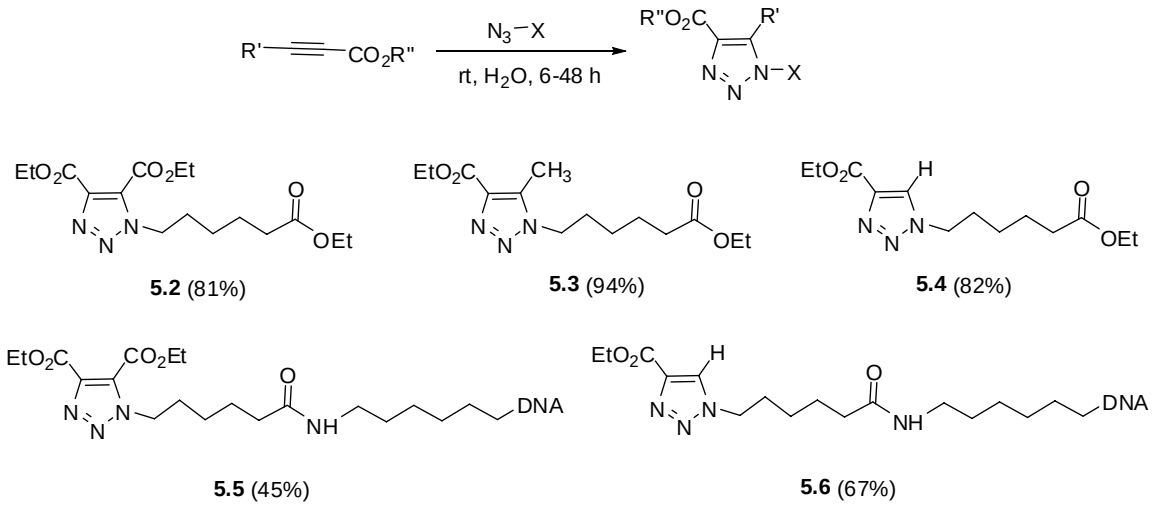
can be conducted at room temperature to give exclusively 1,4-regioselective triazole product with complete regioselectivity.[15] This methodology was also independently developed by Meldal et al. at about the same time.[16] The *in situ* reduction of copper (II) salt such as $CuSO_4.5H_2O$ with sodium ascorbate in aqueous alcoholic solvents allows the formation of 1,4-triazoles at room temperature in high yield with less then 2 mol% of catalyst loading. Mechanistic studies have demonstrated that these reactions involve terminal copper acetylides and proceed via a stepwise non-concerted process.[15,17]



Scheme 5.3: Thermal and Cu(I)-catalyzed 1,3-dipolar cycloaddition

The comparison of a thermal reaction (>90°C) between benzyl azide and phenyl propargyl ether and the reaction of the same substrates with the copper at room temperature demonstrates the role of copper catalyst in this reaction (Scheme 5.3). In case of a thermal reaction, mixture of 1,4- and 1,5-regioisomers was obtained in almost equal ratio whereas, the reaction catalyzed by copper leads to only 1,4-regioselective product with almost quantitative yield. Due to the reliability and applicability of this Cu(I)-catalyzed cycloaddition reaction to generate N-heterocycles pharmocophores, this reaction has been used in various biological applications including target guided synthesis[18] and activity based protein profiling.[8]

Replacement of volatile organic solvents with environmental benign solvents has received considerable attention in organic synthesis due to increased environmental regulations.[19] In the recent years, several transformations have been reported in water.[20] Water is an ideal heat sink, due to its high heat capacity and has a convenient boiling temperature; both these properties are useful for large-scale processes. Water is regarded as an ideal solvent in terms of its minimum environmental impact and low cost. The main benefit of using water as a solvent is that the most hydroxy (-OH) and amide (-NH) groups does not interfere with click reactions in water. As a consequence, the introduction and removal of a protecting group is avoided, which is probably the best single reason for adopting 'click chemistry in water' approach.

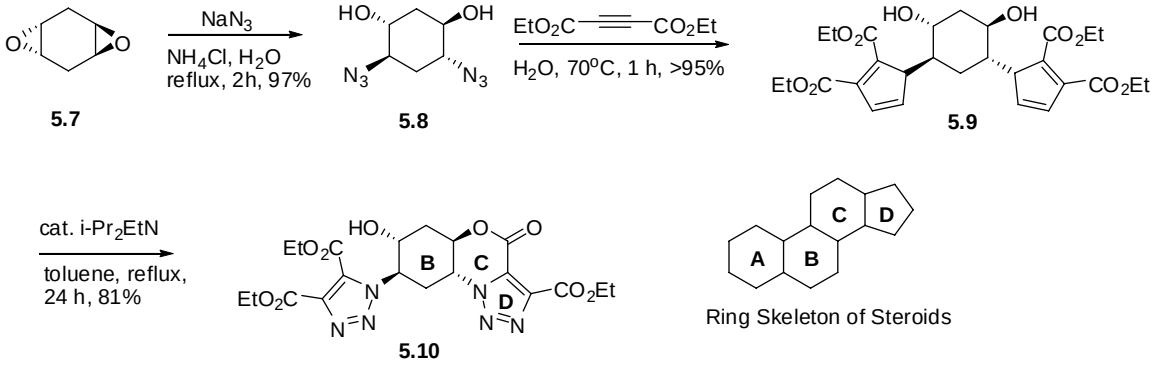


Scheme 5.4: 1,3-dipolar cycloaddition of azides with activated alkynes

It is known that the electron deficient alkynes usually are the most reactive, because an electron withdrawing functional group on alkyne favor irreversible Huisgen cycloaddition of azides and alkynes.[2,21] Recently, it has been reported that the 1,3-dipolar cycloaddition reaction of azides and alkynes having at least one electron-withdrawing group proceed successfully without any catalyst at room temperature in water. This was

further utilized for the coupling of azido-DNA molecules with electron-deficient alkynes for the formation of [1,2,3]-triazole heterocycle, providing a potential method for introducing functional group to DNA under biological conditions (Scheme 5.4).[22]

Complex structure can be rapidly assembled using short sequence of simple click chemistry transformations such as nucleophilic ring opening and 1,3-dipolar cycloaddition. The construction of steroid-like skeletons are possible from diepoxides developed by Sharpless and coworkers.[2] The nucleophilic opening of **5.7** with buffered azide is highly regioselective and yielded crystalline azido alcohol **5.8** in excellent yield. The bis-triazole product **5.9,** formed by the 1,3-dipolar cycloaddition "click-chemistry" reaction of **5.8** with diethylacetylene dicarboxylate, and the product can be isolated from the reaction mixture merely by filtration. The C2-symmetry of **5.9** is then broken during base-catalyzed lactonization to furnish lactone **5.10**, having three rings which resemble the B, C, and D rings found in steroid natural products.[2] This tricycilc compound **5.10** can be prepared in a one-pot synthesis involving three high yielding steps. Click chemistry methods demonstrate the promise of creating natural product derivatives quickly and efficiently (Scheme 5.5).



Scheme 5.5: Steroids-like skeletons assembled from cyclohexadiene diepoxide

Medium sized ring lactams/lactones are important building blocks for the synthesis of bioactive molecules, e.g. a number of *δ*-lactams (piperazone) **5.11** have been synthesized and evaluated as potent elastases inhibitors.[23] The synthesis of various 1,2,3-triazolo[1,5-a]quinoxaline compounds **5.12** and their binding to benzodiazepine and adenosine receptors have also been studied (Figure 5.2).[24]

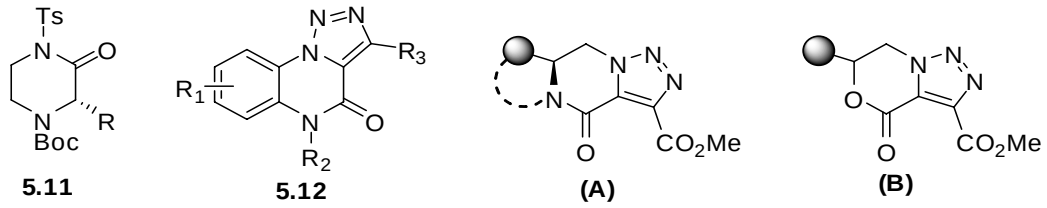


Figure 5.2: Fused triazolo-lactams/lactones

In the continuing search for the new compounds having triazole ring, the click reactions should provide an excellent starting point for further investigation in this direction.

5.2 Results and discussions

As a continuation of our work for the synthesis of biologically active core structures, starting from amino acids and hydroxy acids, we also planed to use the "click" 1,3-dipolar cycloaddition reaction of various chiral azides derived from amino and hydroxy acids with activated alkyne in water since, the click reaction on these azides have not been studied extensively. Therefore, the "click" 1,3-dipolar cycloaddition reaction of various chiral azides with dimethylacetylene dicarboxylate as an activated alkyne has been performed in water and further utilization of this click reaction is investigated with its application for the synthesis of new class of hybrid 1,2,3-triazolo-*δ*-lactams **(A)**/lactones **(B)** as shown in Figure 5.3. The reterosynthetic analysis of this new class of 1,2,3-triazolo-*δ*-lactams/lactones is shown in Scheme 5.6. The hybrid 1,2,3-triazolo-*δ*-

lactams **(A)**/lactones **(B)** can be easily synthesized from 1,2-amino alcohol/1,2-diol **5.15**, by performing the click reaction on their corresponding azide **5.14** using dimethyl acetylene dicarboxylate as an activated alkyne counterpart followed by cyclization.

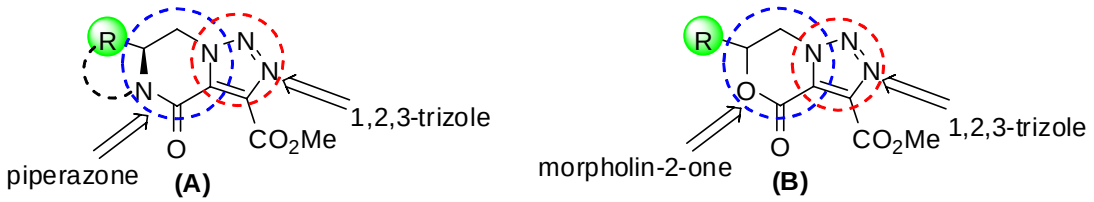
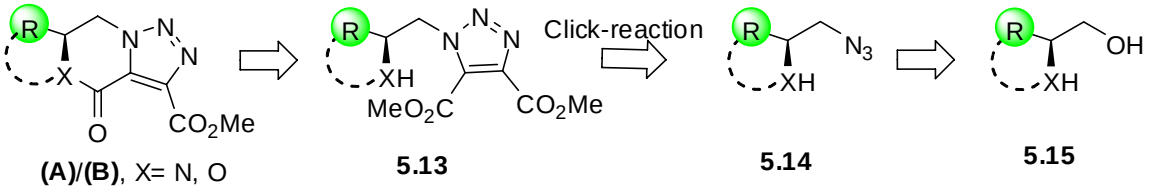


Figure 5.3: Hybrid 1,2,3-triazolo-*δ*-lactam/lactone



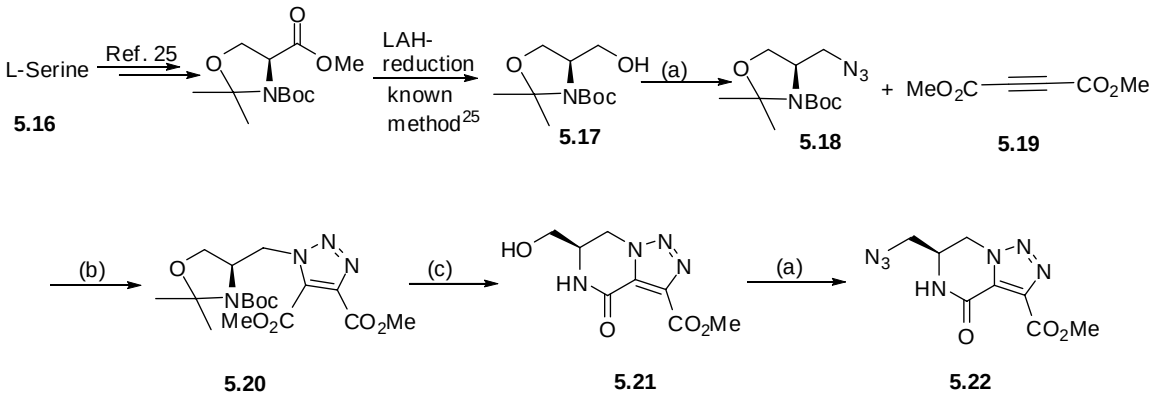
Scheme 5.6: Reterosynthetic analysis of hybrid 1,2,3-triazolo-*δ*-lactams/lactones

We prepared various azido compounds **5.14** starting from amino acids for the synthesis of 1,2,3-triazolo-*δ*-lactams **(A)**, and from hydroxy acids or 1,2-diols for the synthesis of 1,2,3-triazolo-*δ*-lactones **(B)** through click reaction in water.

5.2.1 Synthesis of 1,2,3-triazolo-*δ*-lactams

In order to synthesize the fused 1,2,3-triazolo-*δ*-lactams, we need to prepare the azido compound **5.14** with amino functionality and this was carried out by starting from commercially available α-amino acids. Initially, the acid functionality was converted in to alcohol moiety and then transformed to the corresponding azido derivative using two step-one pot procedures. As shown in Scheme 5.7, L-serine **5.16** was easily transformed to the corresponding alcohol **5.17** by following a reported procedure.[25] Accordingly, L-serine was first protected as N-Boc-acetonide ester, followed by LAH-reduction to give

the corresponding alcohol **5.17**. This amino alcohol **5.17** was then subjected to tosyl protection with tosyl chloride (1.1 equiv)/Et_3N (1.2 equiv) in dry CH_2Cl_2 at 0°C for 4 h, to make its corresponding –OTs as a good leaving group, followed by nucleophilic substitution with sodium azide (NaN_3) 2.2 equiv., in 1,4-dioxane/DMSO at 65°C for 6 h to provide azido derivative **5.18** with 85% yield in two steps. Our next aim was to carry out the Huisgen [3+2] dipolar cycloaddition 'click' reaction of azido compound **5.18** with an activated alkyne dimethylacetylene dicarboxylate **5.19** in water. For this purpose, a mixture of **5.17** and **5.18** was heated in water at 70°C for 1 h to provide cycloadduct **5.20** with 95% yield, as white a solid after passing through a small bed of silica gel column.

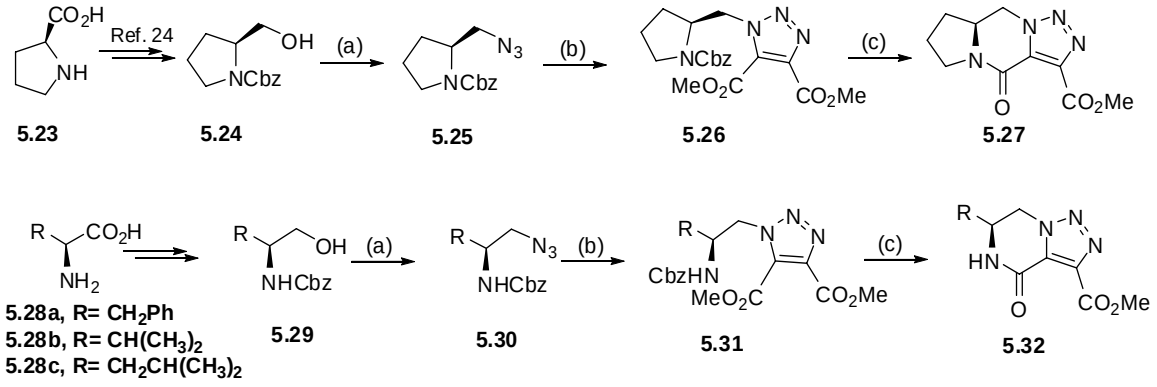


Scheme 5.7: (a) (i) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry DCM, 0°C, 4 h (ii) NaN_3 (2.2 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 85% in two steps. (b) Dimethylacetylene dicarboxylate **5.19** (1.1 equiv.), H_2O (8 mL), 70°C, 1 h, 95% yield (c) (i) TFA (2.5 equiv), dry DCM, 6 h, (ii) MeOH/DMSO (5:1), reflux, 3.5 h, 78% in two steps.

In order to achieve the synthesis of the corresponding fused 1,2,3-triazolo-*δ*-lactam **5.21**, the sequential deprotection of N-Boc and acetonide moiety followed by cyclization were successfully carried out in a single pot two step procedure using TFA (2.0 equiv) in CH_2Cl_2 at rt for 4 h, followed by refluxing in MeOH/DMSO for 3.5 h to provide bicyclic fused compound **5.21** with 78% isolated yield. Further, conversion of compound **5.21** in

to its corresponding azido derivative **5.22** was carried out with 88% isolated yield in two steps, similar to the previous conversion of alcohol to azide derivates.

In order to prepare the fused tricycilc compound with pyrrolidine ring **5.27**, amino acid L-proline **5.23** containing pyrrolidine ring was transformed into its corresponding N-Cbz protected alcohol **5.24** by following a standard procedure, similar to the preparation of other alcohols derived from corresponding amino acids.[25] The resulting alcohol **5.24** was then transformed into its corresponding azido compound **5.25** using the sequence of tosyl protection/azide substitution by single pot two steps procedure with 87% isolated yield. The 1,3-dipolar cycloaddition of 1 mmol of **5.25** with **5.19** (1.1 mol equiv) in water (8 mL) at 70°C for 1 h gave corresponding cycloadduct **5.26** in almost quantitative yield as shown in Scheme 5.8.



Scheme 5.8: (a) (i) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry DCM, 0°C, 4 h (ii) NaN_3 (2.2 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 87% in two steps. (b) Dimethylacetylene dicarboxylate **(5.19)** (1.1 equiv), H_2O (8 mL), 70°C, 1 h, quantitative yield (c) (i) Pd/C (10 mol %), H_2 (1 atm), MeOH, rt, 2 h (ii) reflux, 4 h, yield mentioned in the text.

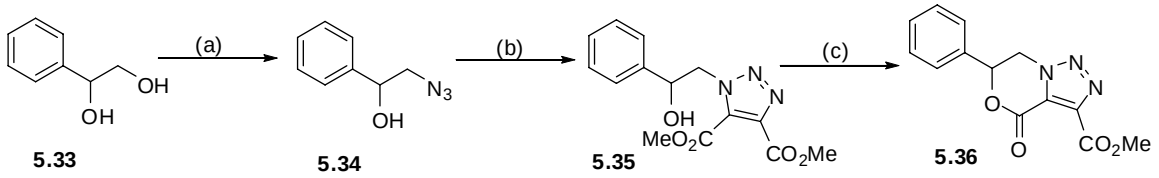
The sequential deprotection of N-Cbz and further cyclization was successfully carried out by one pot two step procedure using 10 mol % of Pd/C (10%) in methanol under hydrogen atmosphere at rt for 2 h. This involves first deprotection, followed by refluxing for additional 4 h for intramolecular peptide bond formation to give fused tricycilc

triazolo-*δ*-lactam **5.27** with 80% yield in two steps. Similarly, the other amino acids like L-phenyl alanine **5.28a**, L-valine **5.28b**, L-lucine **5.28c**, were transformed in to their corresponding azido derivatives **5.30**. The 1,3-dipolar 'click' reaction of these azides with **5.19** in water under similar conditions, followed by intramolecular cyclization leads to the synthesis of corresponding triazolo-*δ*-lactams **5.32** in excellent yields (Scheme 5.8). Thus, the synthesis of various fused 1,2,3-triazolo-*δ*-lacatms have been achieved efficiently by starting from different amino acids with a sequence of cycloaddition in water followed by cyclization.

5.2.2 Synthesis of fused 1,2,3-triazolo-*δ*-lactones

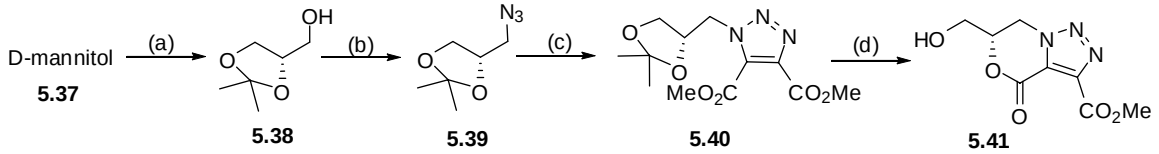
With the successful establishment of our methodology for the synthesis of fused 1,2,3-triazolo-*δ*-lactams, we further extended this work for the synthesis of fused 1,2,3-triazolo-*δ*-lactones. In order to do that, we initially took a very simple 1,2-diol,e.g. 1-phenylethane-1,2-diol **5.33** as starting material, the mono-protection of this compound was carried out with tosyl chloride (1.1 equiv) and Et_3N (1.3 equiv) in dry CH_2Cl_2 for 4 h at rt followed by standard work-up and the crude tosylated compound was treated with NaN_3 in 1,4-dioxane/DMSO at 65^oC for 6 h to give azido compound **5.34** with 79% isolated yield after two steps.

The 'click' 1,3-dipolar cycloaddition reaction of **5.34** (1 mmol) with **5.19** (1.1 mol equiv) in water (8 mL) at 70^oC for 1 h provided triazolo cycloadduct **5.35** as a slight yellowish solid with 86% isolated yield. Compound **5.35** was treated with 1.2 mol equiv of NaH (55% in paraffin oil) in dry THF under reflux condition for 12 h to provide hybrid 1,2,3-triazolo-*δ*-lactone **5.36** in 67% isolated yield (Scheme 5.9).



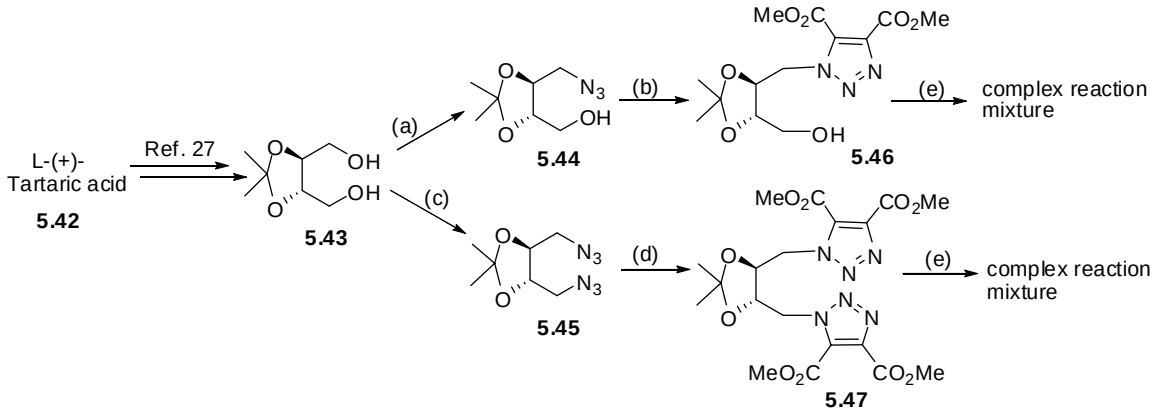
Scheme 5.9: (a) (i) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry DCM, 0°C, 4 h (ii) NaN_3 (2.2 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 79% in two steps. (b) Dimethylacetylene dicarboxylate **(5.19)** (1.1 equiv), H_2O (8 mL), 70°C, 1 h, 86% yield. (c) NaH (1.2 equiv, 55% in paraffin oil), dry THF, reflux, 12 h, 67% isolated yield.

In order to prepare some chiral 1,2,3-triazolo-*δ*-lactones, we started from suitably protected alcohol **5.38** prepared by $NaBH_4$ reduction of (*R*)-glyceraldehyde, which was easily prepared in larger amount from D-mannitol following a reported procedure. According to this procedure, D-mannitol was first transformed in to diacetonide derivative followed by $NaIO_4$ cleavage to give glyceraldehyde,[26] which was then transformed in to the corresponding alcohol **5.38** by $NaBH_4$ reduction. This alcohol **5.38** was transformed into corresponding azido compound **5.39** with a sequence of tosyl protection/substitution with NaN_3 in the excellent yield. Compound **5.39** (1 mmol) underwent smooth cycloaddition with **5.19** (1.1 mol equiv) in water to provide an adduct **5.40** in almost quantitative yield. Further, deprotection of acetonide moiety and lactonization was performed in one pot procedure by treating with 1N-HCl/MeOH followed by heating in benzene to provide fused 1,2,3-triazolo-*δ*-lactone **5.41** in 61% yield after two steps as shown in Scheme 5.10.



Scheme 5.10: (a) (i) Ref. 26 (ii) $NaBH_4$, MeOH, rt. (b) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry CH_2Cl_2, 0°C, 4 h (ii) NaN_3 (2.2 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 86% in two steps. (c) Dimethylacetylene dicarboxylate **(5.19)** (1.1 equiv.), H_2O (8 mL), 70°C, 1 h, quantitative. (d) 1N-HCl, MeOH, Benzene, heat, 4 h, 61%.

We further tried to explore this methodology for the synthesis of some more fused triazolo-lactones such as starting from other chiral sources. In order to do that L-(+)-tartaric acid **5.42** was transformed into its corresponding well protected diol **5.43** easily by following the reported procedure.[27] The azido-alcohol **5.44** was easily prepared by using NaH (1 mol equiv) and TsCl (1.1 mol equiv) followed by nucleophilic substitution with NaN_3 with 79% yield from **5.43.** Similarly, the diazido compound **5.45** was prepared using two equivalents of NaH and TsCl followed by nucleophilic substitution with NaN_3 with 83% yield from **5.43**.



Scheme 5.11: (a) NaH (1.1 equiv), dry THF, TsCl (1.2 equiv), 0°C, 2 h (ii) NaN_3 (2.2 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 81% in two steps. (b) Dimethylacetylene dicarboxylate **(5.19)** (1.1 equiv), H_2O (8 mL), 70°C, 1 h, 79%. (c) NaH (2.2 equiv), TsCl (2.2 equiv.), dry THF, 0°C, 2 h (ii) NaN_3 (3.5 equiv), 1,4-Dioxan/DMSO (10:1), 65°C, 6 h, 89%. (d) Dimethylacetylene dicarboxylate **(5.19)** (2.2 equiv), H_2O (8 mL), 70°C, 1 h, 95%. (e) 1N-HCl, MeOH, Benzene, heat, 4 h, complex reaction mixtures.

The 1,3-dipolar cycloaddition 'click' reaction of these azides proceeded smoothly with **5.19** (1.1 mol equiv) for **5.44** and (2.2 mol equiv) for **5.45** in water at 70°C for 1 h to provide cycloadducts **5.46** and **5.47** in excellent yields as shown in Scheme 5.11. Further cyclization of these cycloadducts **5.46** and **5.47** to the fused triazolo-lactones under different acidic conditions provided the complex reactions mixture, from which the desired lactones could not be isolated.

5.3 Conclusions

In conclusion, we have developed the Huisgen 1,3-dipolar cycloaddition 'click' reaction of various chiral azides derived from 1,2-amino alcohols/diols with dimethylacetylene dicarboxylate as an activated alkyne in water. The 1,2-amino alcohols/diols moieties are commonly found in the variety of existing organic compounds. This reaction was further explored for the synthesis of new class of hybrid 1,2,3-triazolo-*δ*-lactams/lactones using intramolecular cyclization reactions. The synthesis of these fused compounds having biologically important moieties can provide access to a variety of new compounds with different biological significance. The existence of free ester moiety on the triazole ring, which can further transformed in to a variety of other functional group, provides access to the other synthetic transformations.

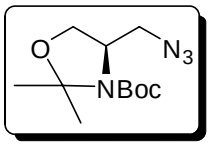
5.4 Experimental

General

All the reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under argon atmosphere using oven-dried glassware. Dichloromethane and dimethyl sulfoxide were distilled over CaH_2 under argon atmosphere and stored on molecular sieves. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin-Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^{1}H and 75 MHz for ^{13}C). The

chemical shifts are reported using the δ (delta) scale for ^{1}H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC-MS was recorded using electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100-200 and 230-400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

(*R*)-*tert*-Butyl 4-(azidomethyl)-2,2-dimethyloxazolidine-3-carboxylate (5.18)

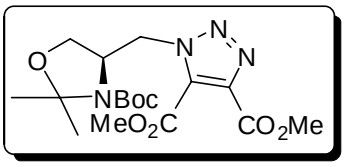


To a stirred solution of **5.17** (0.85 g, 3.67 mmol) and Et_3N (0.615 mL, 4.41 mmol) in dry CH_2Cl_2 (8.0 mL), was added drop wise a solution of tosyl Chloride (0.771 g, 4.01 mmol) in dry CH_2Cl_2 (4.0 mL) at 0^oC. The combined reaction mixture was stirred further for 4 hr at the same temperature, than reaction was warmed to rt and solvent was removed in vacuo. The crude mass was taken in EtOAc (25 mL) and stirred with 3% $NaHCO_3$ solution. The organic layer was separated, washed with brine and dried over Na_2SO_4 after that it was concentrated under reduced pressure. The resulting solid residue (approx. 1.45 g) was further heated with NaN_3 (0.525 g, 8.08 mmol) in 1, 4-Dioxane/DMSO (3:1) 8 mL at 65^oC for 6 h. The reaction was cooled to rt, using similar work-up procedure and concentrated under reduced pressure provide crude residue, which was purified by column chromatography to gave colorless liquid azide compound **5.18** (0.80 g) with 85% yield in two consecutive steps.

(5.18): $[\alpha]_D^{25}$ -30.32 (*c* 1.5, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 12H), 1.52 (s, 3H), 3.15-3.55 (m, 2H), 3.80-4.05 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.34, 27.10, 28.31, 51.09, 56.39, 65.23, 80.64, 93.82, 151.31. LC-MS (ESI-TOF): m/z $[M+H]^+$

256.16, $[M+Na]^+$ 279.15. Anal. Calcd for $C_{11}H_{20}N_4O_3$: C, 51.55; H, 7.87; N, 21.86. Found: C, 51.63; H, 7.91; N, 21.83.

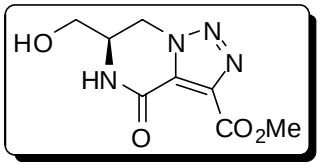
(*R*)-Dimethyl 1-((3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)1*H*-1,2,3-trazole-4,5-dicarboxylate (5.20)



A mixture of compound **5.18** (0.51 g, 1.99 mmol) and dimethylacetylenedicarboxylate **8** (0.31g, 2.19 mmol) in water (8.0 mL) was heated at 70°C with constant stirring for 1.0 hr. The resulting mixture was cooled to rt and stirred further with EtOAc (15 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to provide a pasty mass, which was passed through a small pad of silica-gel to gave slightly yellowish compound **5.20** (solidify slowly) in almost quantitative yield.

(5.20): $[\alpha]_D^{25}$ +22.18 (*c* 1.5, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ =1.32-1.55 (m, 15H), 3.85-4.02 (m, 8H), 4.39 (m, 1H), 4.71 (t, *J*= 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.92, 27.23, 28.08, 51.37, 52.45, 53.29, 56.22, 64.76, 80.70, 94.01, 130.68, 139.53, 152.12, 160.36. LC-MS (ESI-TOF): m/z $[M+H]^+$ 398.35. Anal. Calcd for $C_{17}H_{26}N_4O_7$: C, 51.25; H, 6.85; N, 14.06. Found: C, 51.32; H, 6.91; N, 14.01.

(*R*)-Methyl 6-(hydroxymethyl)-4-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (5.21)

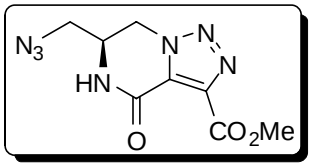


To a stirred solution of **5.20** (0.65 g, 1.63 mmol) in dry CH_2Cl_2 (8.0 mL), tri-fluoro acetic acid (TFA) (0.31 mL, 4.08 mmol) was added at 0°C drop wise and stirred further for 4 h

at rt. The solvent was removed at low pressure and further refluxed in MeOH/DMSO (5:1) 10 mL for 3.5 h. The reaction mixture was cooled to rt and concentrated in vacuo. The crude mass was taken in EtOAc (25 mL) and stirred with 10% $NaHCO_3$ solution. The organic layer was separated, washed with brine and concentrated under reduced pressure to give crude mixture. This was further purified through column chromatography to gave slightly yellowish semi-solid compound **5.21** (0.28 g) with 78% yield in two consecutive steps.

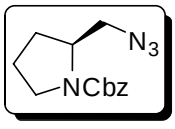
(5.21): $[\alpha]_D^{25}$ +16.78 (*c* 0.5 MeOH), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 3.75-3.96 (m, 5H), 4.52 (m, 1H), 4.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.48, 52.83, 54.62, 63.57, 132.18, 147.54, 154.83, 161.42. Anal. Calcd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.26; H, 4.76; N, 24.51.

(*R*)-Methyl 6-(azidomethyl-4-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (5.22)



Similar to the previous conversion of alcohol to azide 78% yield from corresponding **(5.21)**, For **(5.22)**: $[\alpha]_D^{25}$ +27.31 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 2.84 (m, 2H), 3.75 (s, 3H), 4.05 (m, 1H), 4.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.82, 52.68, 53.92, 55.65, 132.31, 147.67, 154.21, 160.94. Anal. Calcd for $C_8H_9N_7O_3$: C, 38.25; H, 3.61; N, 39.03. Found: C, 38.36; H, 3.68; N, 39.17.

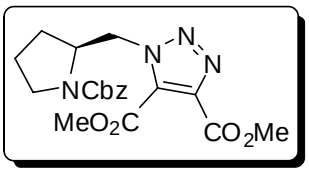
(*S*)-Benzyl 2-(azidomethyl)pyrrolidine-1-carboxylate (5.25)



Similar to the previous conversion of alcohol to azide 78% yield from corresponding **(5.24)**, For **(5.25)**: $[\alpha]_D^{25}$ -46.57 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.90 (m,

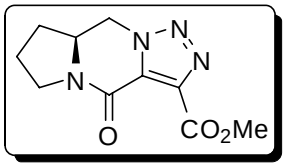
4H), 3.45 (m, 4H), 3.99 (m, 1H), 5.13 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.89, 26.35, 44.67, 49.85, 54.37, 66.93, 127.91, 128.04, 128.55, 136.53, 156.32. Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.93; H, 6.17, N, 21.54.

(*S*)-Dimethyl 1-((1-(benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazolo-4,5-dicarboxylate (5.26)



Similar to the previous cycloaddition with **(5.19)** in water at 1 mmol scale; quantitative yield for **(5.26)**: $[\alpha]_D^{25}$ +17.83 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.62-1.95 (m, 4H), 3.30 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.31 (m, 1H), 4.57-4.82 (m, 2H), 4.9 (d, 0.5H), 5.1 (d, 1.5H), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.52, 27.65, 46.58, 51.73, 52.48, 53.38, 57.05, 66.91. 54.37, 66.93, 127.79, 127.97, 128.37, 135.97, 136.29, 139.30, 155.16, 158.81, 160.19. Anal. Calcd for $C_{19}H_{22}N_4O_6$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.68; H, 5.37, N, 13.98.

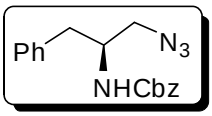
(*S*)-Methyl 4-oxo-4,6,7,8,8a,9-hexahydropyrrolo [1,2,3]triazolo[1,5-*d*]pyrazine-3-carboxylate (5.27)



To a solution of compound **5.26** (0.45 g, 1.11 mmol) in MeOH (10 mL) was added 10 mol% of Pd/C (10%) and the mixture was hydrogenated at room temperature under hydrogen atmosphere for 2 h and further heated under reflux for 4 h. The catalyst was filtered and solvent was removed under reduced pressure. The crude mass was purified by column chromatography to gave white solid compound **5.27** (0.21 g) with 80% yield. $[\alpha]_D^{25}$ +12.53 (*c* 0.5, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.46-1.73 (m, 4H), 3.56 (m, 2H), 3.93 (s, 3H), 4.35 (m, 1H), 4.62-4.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ =

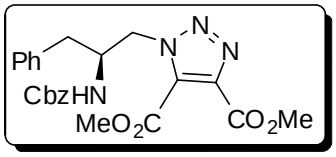
23.35, 28.43, 46.87, 51.92, 53.08, 56.57, 136.41, 141.29, 157.47, 160.93. Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.76; H, 5.06, N, 23.83.

(*S*)-Benzyl 1-azido-3phenylpropan-2-ylcarbamate (5.30a)



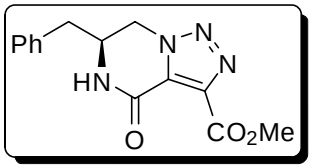
85% yield from corresponding alcohol **(5.29a)**, For **(5.30a)**: $[\alpha]_D^{25}$ -12.21 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 2.75-2.82 (m, 2H), 3.20-3.48 (m, 2H), 4.06 m, 1H), 5.08 (s, 2H), 7.18-7.41 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.97, 51.77, 53.01, 66.78, 126.79, 127.98, 128.48, 128.66, 129.17, 136.21, 136.79, 155.56. LC-MS (ESI-TOF): m/z $[M+Na]^+$ 333.12. Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.72; H, 5.79, N, 18.23.

(*S*)-Dimethyl 1-(2-(benzyloxycarbonylamino)-3-phenylpropyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.31a)



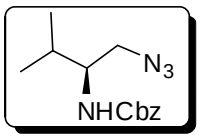
93% from corresponding azide **(5.30a)**, For **(5.31a):** $[\alpha]_D^{25}$ +14.12 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 2.94 (m, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 4.49 (m, 1H), 4.67-4.89 (m, 2H), 5.05 (s, 2H), 7.20-7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.05, 52.31, 52.49, 52.53, 53.25, 66.55, 126.85, 127.76, 127.88, 128.26, 128.57, 129.03, 130.50, 135.76, 136.04, 139.60, 155.50, 158.68, 160.18. LC-MS (ESI-TOF): m/z $[M+H]^+$ 453.69. Anal. Calcd for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.12; H, 5.39, N, 12.53.

(*S*)-Methyl 6-benzyl-4-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (5.32a)



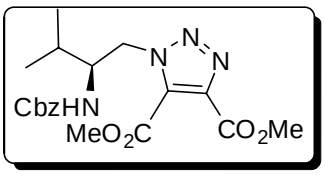
86% from compound **(5.31a)**, For **(5.32a)**: $[\alpha]_D^{25}$ +9.58 (*c* 0.5, MeOH), ^{1}H NMR (200MHz, $CDCl_3$): δ = 2.89 (m, 2H), 3.99 (s, 3H), 4.51 (m, 1H), 4.77 (m, 2H), 5.19 (bd, 1H, -NH), 7.23-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.29, 49.31, 52.72, 53.48, 127.05, 127.99, 128.49, 130.74, 136.27, 141.89, 157.73, 160.41. Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.65; H, 4.86; N, 19.63.

(*S*)-Benzyl 1-azido-3-methylbutan-2ylcarbamate (5.30b)



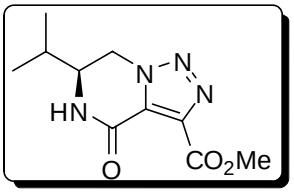
83% from corresponding alcohol **(5.29b)**; For **(5.30b)**: $[\alpha]_D^{25}$ -40.90 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.94 (m, 6H), 1.79 (m, 1H), 3.44 (m, 2H), 3.58 (m, 1H), 5.11 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.12, 19.16, 29.54, 52.68, 55.99, 66.54, 127.76, 127.87, 128.87, 136.25, 156.04. LC-MS (ESI-TOF): m/z $[M+Na]^+$ 285.15. Anal. Calcd for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 58.48; H, 6.86; N, 21.39.

(*S*)-Dimethyl 1-(2-(benzyloxycarbonylamino)-3-methylbutyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.31b)



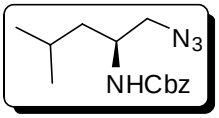
91% from corresponding azide **(5.30b)**; For **(5.31b)**: $[\alpha]_D^{25}$ +51.17 (*c* 2, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.03 (m, 6H), 1.86 (m, 1H), 3.91-4.06 (m, 7H), 4.62 (dd, *J*= 13.7, 9.6 Hz, 1H), 4.85 (dd, *J*= 13.6, 4.2 Hz, 1H), 4.97 (s, 2H), 5.05 (d, 1H, exchangeable), 7.32 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.79, 18.96, 30.16, 51.91, 52.44, 53.20, 56.32, 66.54, 127.72, 127.81, 128.21, 129.86, 136.01, 139.74, 155.85, 158.92, 160.25. LC-MS (ESI-TOF): m/z $[M+Na]^+$ 427.14. Anal. Calcd for $C_{19}H_{24}N_4O_6$: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.41; H, 5.89; N, 13.92.

(*S*)-Methyl 6-isopropyl-4-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (5.32b)



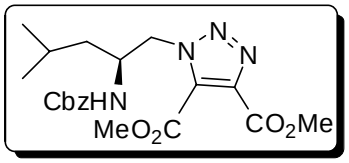
81% from (5.31b); For **(5.32b):** $[\alpha]_D^{25}$ +23.17 (*c* 1.2, MeOH), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.01 (m, 6H), 1.95 (m, 1H), 3.94 (s, 3H), 4.12 (m, 1H), 4.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.85, 18.74, 31.46, 52.04, 54.65, 61.89, 136.97, 141.09, 156.73, 162.23. Anal. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.36; H, 5.859; N, 23.59.

(*S*)-benzyl 1-azido-4-methylpentan-2-ylcarbamate (5.30c)



82% from corresponding alcohol; For **(5.30c)**: $[\alpha]_D^{25}$ -33.68 (*c* 2, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.92 (d, 6H), 1.21-1.41 (m, 2H), 1.64 (m, 1H), 3.29-3.51 (m, 2H), 3.86 (m, 1H), 5.10 (s, 2H), 7.34 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.76, 22.77, 24.43, 40.93, 48.92, 54.91, 66.51, 127.78, 127.88, 128.28, 136.23, 155.72. LC-MS (ESI-TOF): m/z $[M+Na]^+$ 299.14. Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.78; H, 7.25; N, 20.33.

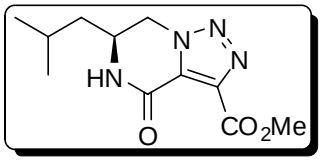
(*S*)-Dimethyl 1-(2-(benzyloxycarbonylamino)-4-methylpentyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.31c)



93% from corresponding azide **(5.31b)**; For **(5.31c)**: $[\alpha]_D^{25}$ +11.17 (*c* 0.5, MeOH), ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.91 (m, 6H), 1.33 (m, 2H), 1.68 (m, 1H), 3.91 (s, 3H), 3.93 (s, 3H), 4.18 (m, 1H), 4.58 (dd, *J*= 13.7, 7.8 Hz, 1H), 4.75 (dd, *J*= 13.6, 4.2 Hz, 1H), 4.97 (s, 2H), 7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.73, 22.55, 24.19, 40.51,

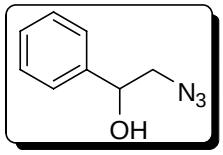
49.27, 52.16, 52.96, 53.64, 66.24, 127.54, 127.60, 128.01, 130.21, 135.94, 139.26, 155.56, 158.65, 160.06. LC-MS (ESI-TOF): m/z $[M+Na]^+$ 441.15. Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.41; H, 6.26; N, 13.39. Found: C, 57.36; H, 6.19; N, 13.44.

(*S*)-methyl 6-isobutyl-4-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (5.32c)



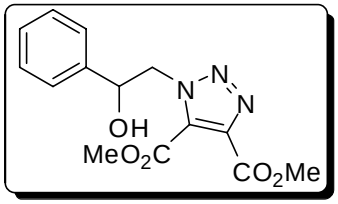
77% from **(5.31c)**; For **(5.32c)**: $[\alpha]_D^{25}$ +7.68 (*c* 0.75, MeOH), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.01 (d, 6H), 1.35 (m, 2H), 1.71 (m, 1H), 3.94 (s, 3H), 4.23 (m, 1H), 4.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.05, 22.91, 24.23, 40.89, 49.93, 52.34, 53.87, 136.78, 142.91, 156.39, 162.53. Anal. Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21. Found: C, 52.31; H, 6.34; N, 22.26.

2-Azido-1-phenylethanol (5.34)



76% from corresponding alcohol **(5.33)**; For **(5.34):** ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 2.95-3.08 (m, 2H), 4.65 (m, 1H), 7.17-7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.24, 75.78, 127.19, 127.31, 128.89, 139.42. LC-MS (ESI-TOF): m/z $[M+H]^+$ 163.19, $[M+Na]^+$ 186.78.

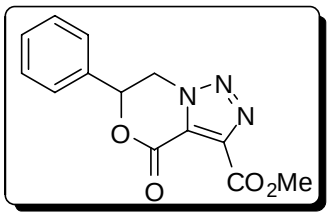
Dimethyl 1-(2-hydroxy-2-phenylethyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.35)



89% from **(5.34)**; For **(5.35):** ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 3.81 (s, 3H), 3.98-4.15 (m, 5H), 4.84 (m, 1H), 7.15-7.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.17,

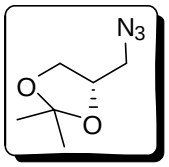
52.41, 62.54, 76.31, 126.89, 127.11, 128.81, 128.98, 129.23, 139.51, 161.15, 163.92. LC-MS (ESI-TOF): m/z $[M+H]^+$ 306.21, $[M+Na]^+$ 328.82.

Methyl 4-oxo-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine-3-carboxylate (5.36)



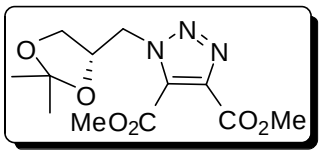
67% from **(5.35)**; For **(5.36):** ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 3.91 (s, 3H), 4.32-4.38 (m, 2H), 4.98-5.10 (m, 1H), 7.27-7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.43, 62.91, 79.13, 121.71, 124.83, 127.73, 128.19, 128.95, 139.94, 162.14, 168.12. Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.19; H, 4.11; N, 15.31.

(*S*)-4-(azidomethyl)-2,2-dimethyl-1,3-dioxolane (5.39)



77% from **(5.38)**; For **(5.39)**: ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.43 (s, 3H), 1.46 (s, 3H), 3.05-3.18 (m, 2H), 3.75-4.05 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.41, 26.72, 55.93, 69.96, 80.69, 109.85. LC-MS (ESI-TOF): m/z $[M+H]^+$ 158.26, $[M+Na]^+$ 180.86.

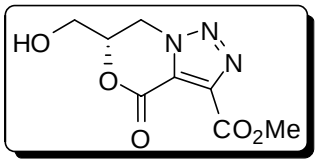
(*S*)-Dimethyl 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.40)



96% from **(5.39)**; For **(5.40)**: $[\alpha]_D^{25}$ +11.19 (*c* 1.0, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3$): δ =1.45 (s, 3H), 1.49 (s, 3H), 3.87 (s, 3H), 3.92-4.15 (m, 5H), 4.18-4.25 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.38, 25.97, 52.23, 54.69, 57.42, 69.59, 78.91, 109.13, 121.23,

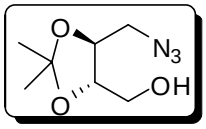
122.95, 154.76, 164.23. Anal. Calcd for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.10; H, 5.65; N, 14.12.

(*S*)-Methyl 6-(hydroxymethyl)-4-oxo-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine-3-carboxylate (5.41)



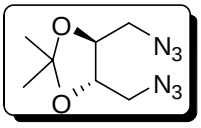
61% from **(5.40)**; For **(5.41):** $[\alpha]_D^{25}$ +5.74 (*c* 0.75, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 3.95 (s, 3H), 4.12-4.35 (m, 4H), 4.51-4.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.34, 59.81, 69.95, 80.05, 123.56, 126.93, 162.12, 167.23. LC-MS (ESI-TOF): m/z $[M+H]^+$ 228.26, $[M+Na]^+$ 150.85. Anal. Calcd for $C_8H_9N_3O_5$: C, 42.30; H, 3.99; N, 18.50. Found: C, 42.26; H, 4.89; N, 18.59.

((4*S*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.44)



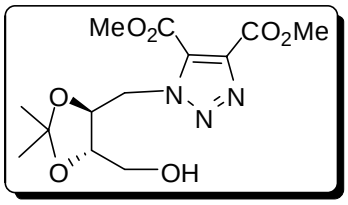
81% from **(5.43)**; For **(5.44):** $[\alpha]_D^{25}$ -60.30 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.40 (s, 3H), 1.43 (s, 3H), 2.33 (bs, 1H, -OH) 3.30 (dd, *J*= 4.6 Hz, 1H), 3.54 (dd, *J*= 3.8 Hz, 1H), 3.58-3.82 (m, 2H), 3.90-4.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.67, 26.87, 51.63, 61.62, 76.07, 78.31, 109.70. LC-MS (ESI-TOF): m/z $[M+H]^+$ 187.18, $[M+Na]^+$ 210.17.

(4*S*,5*S*)-4,5-bis(azidomethyl)-2,4-dimethyl-1,3-dioxalane (5.45)



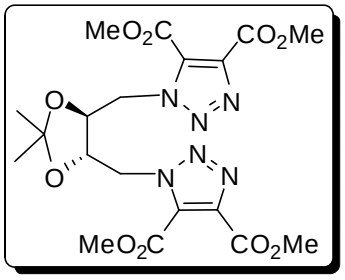
89% from **(5.43)**; For **(5.45):** $[\alpha]_D^{25}$ -114.95 (*c* 1, $CHCl_3$), ^{1}H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.44 (s, 6H), 3.31 (dd, *J*= 4.7 Hz, 2H), 3.53 (dd, *J*= 3.8 Hz, 2H), 4.00-4.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.81, 51.56, 76.88, 110.33. Anal. Calcd for $C_7H_{12}N_6O_2$: C, 39.62; H, 5.70; N, 39.60. Found: C, 39.59; H, 5.73; N, 39.69.

Dimethyl 1-(((4*S*,5*S*)-5-hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl(methyl-1*H*-1,2,3-triazole-4,5-dicarboxylate (5.46)



79% from **(5.44)**; For **(5.46):** $[\alpha]_D^{25}$ -34.55 (*c* 1, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.41 (s, 3H), 1.45 (s, 3H), 3.61-3.68 (m, 2H), 3.72-4.02 (m, 8H), 4.35-4.55 (dd, *J*= 3.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.65, 26.77, 51.83, 54.29, 56.32, 61.79, 76.16, 78.28, 110.05, 129.51, 132.45, 159.19, 163.32. LC-MS (ESI-TOF): m/z $[M+H]^+$ 329.38, $[M+Na]^+$ 352.46.

Tetramethyl 1,1'-((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(1*H*-1,2,3-triazole-4,5-dicarboxylate) (5.47)



95% from **(5.45)**; For **(5.47):** $[\alpha]_D^{25}$ -46.87 (*c* 0.5, $CHCl_3$), ^1H NMR (200MHz, $CDCl_3/D_2O$): δ = 1.03 (s, 6H), 3.89 (s, 6H), 3.91 (s, 6H), 3.96 (m, 2H), 4.78 (dd, *J*= 3.9 Hz, 2H), 4.96 (dd, *J*= 3.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.12, 49.31, 52.53, 53.24, 74.97, 110.66, 131.66, 139.46, 158.76, 160.02. Anal. Calcd for $C_{19}H_{24}N_6O_{10}$: C, 45.97; H, 4.87; N, 16.93. Found: C, 45.91; H, 4.84; N, 16.98.

5.5 References

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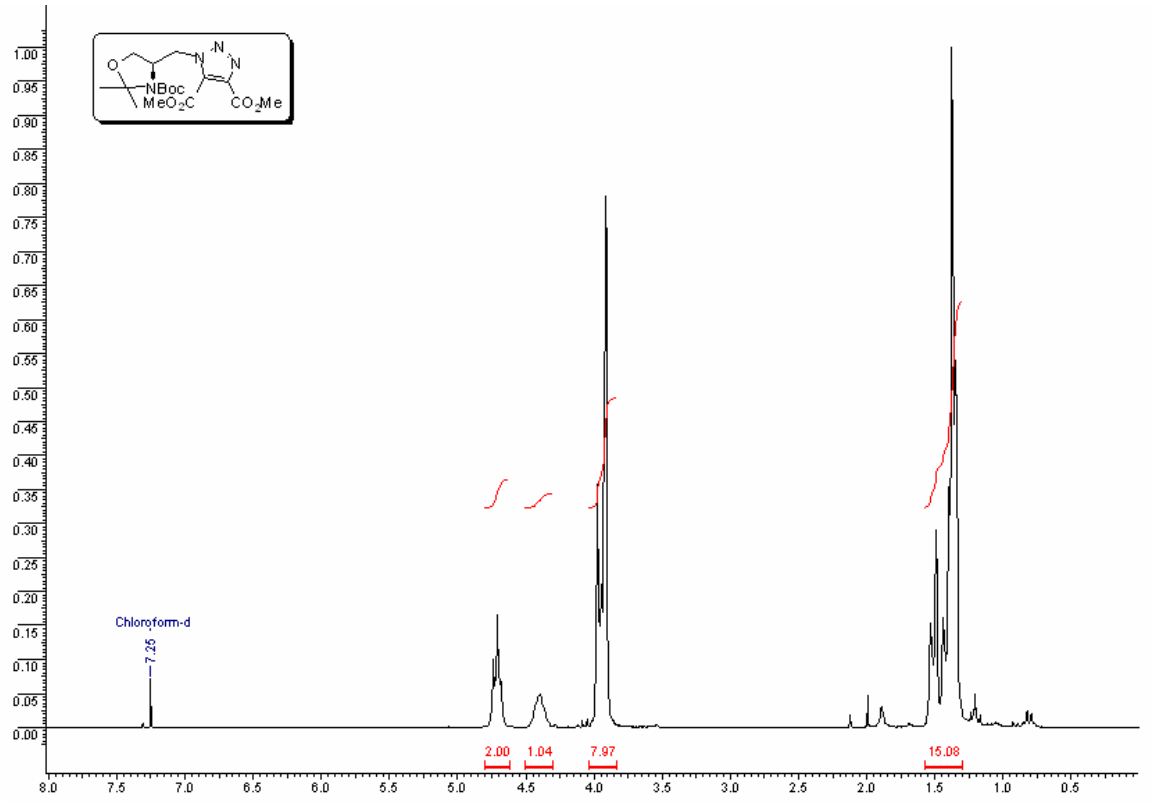
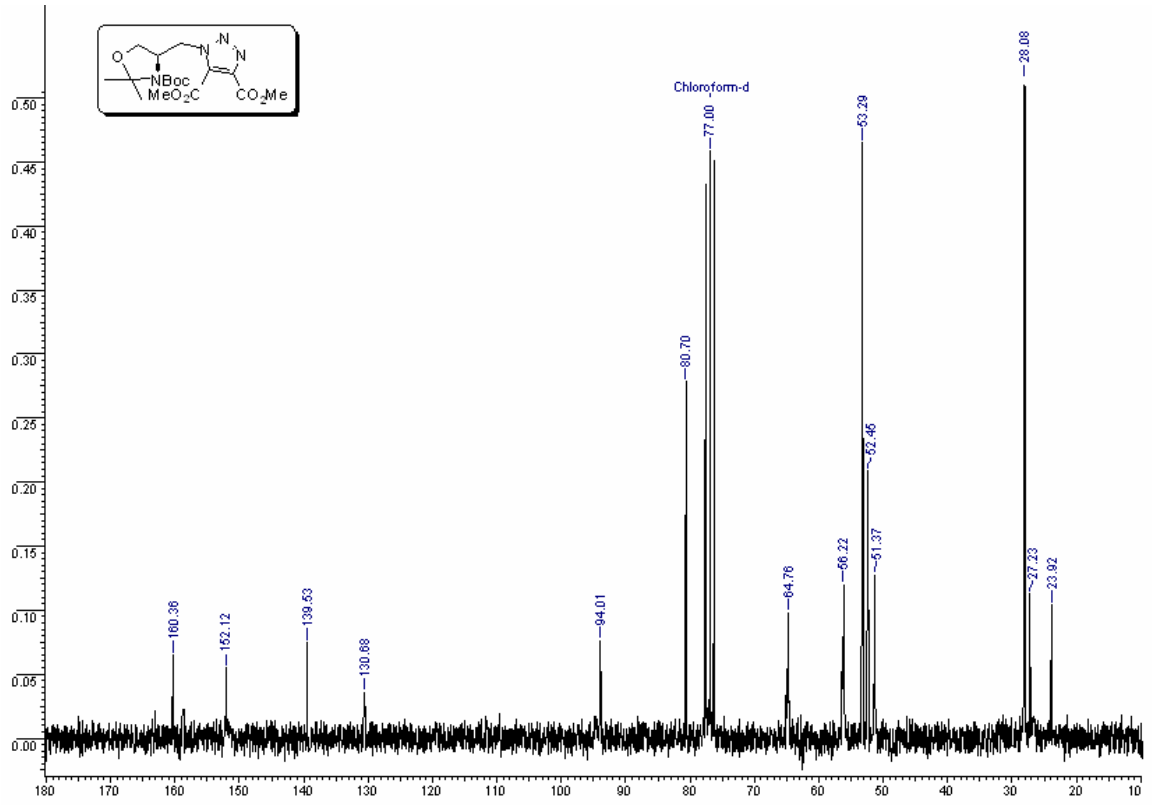
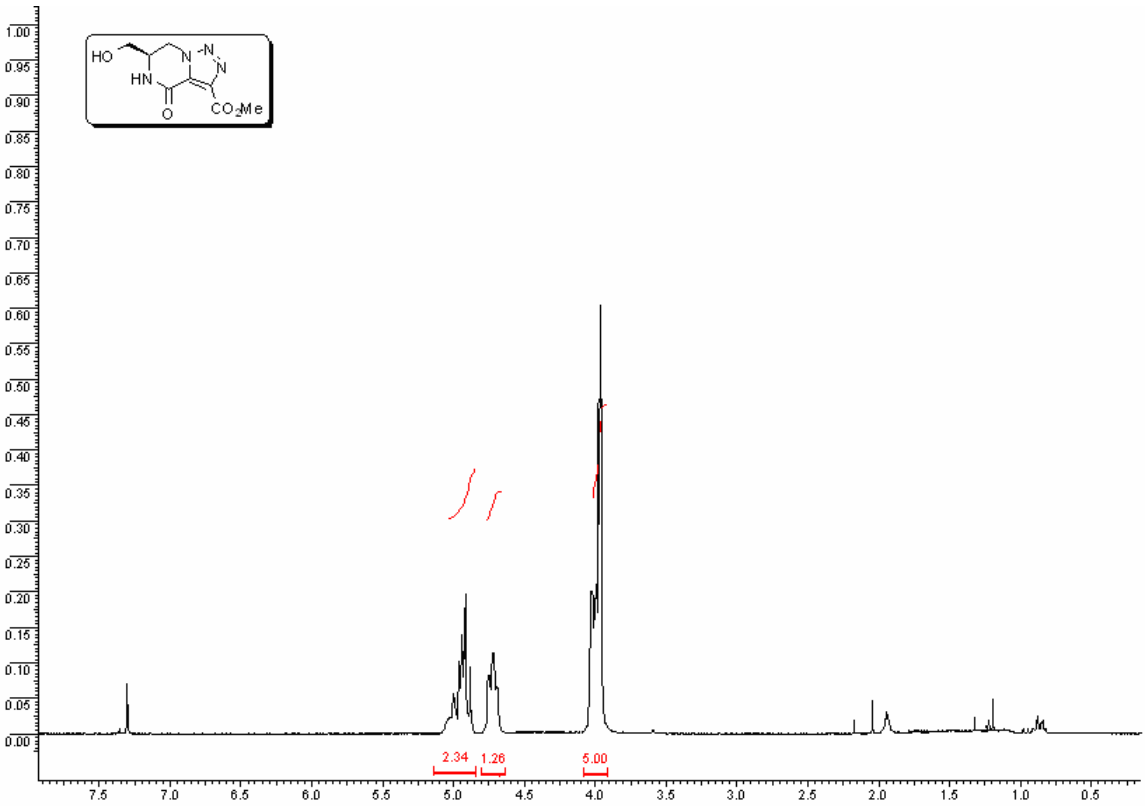
5.6 Spectra of selected compounds



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N
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N
CO2Me
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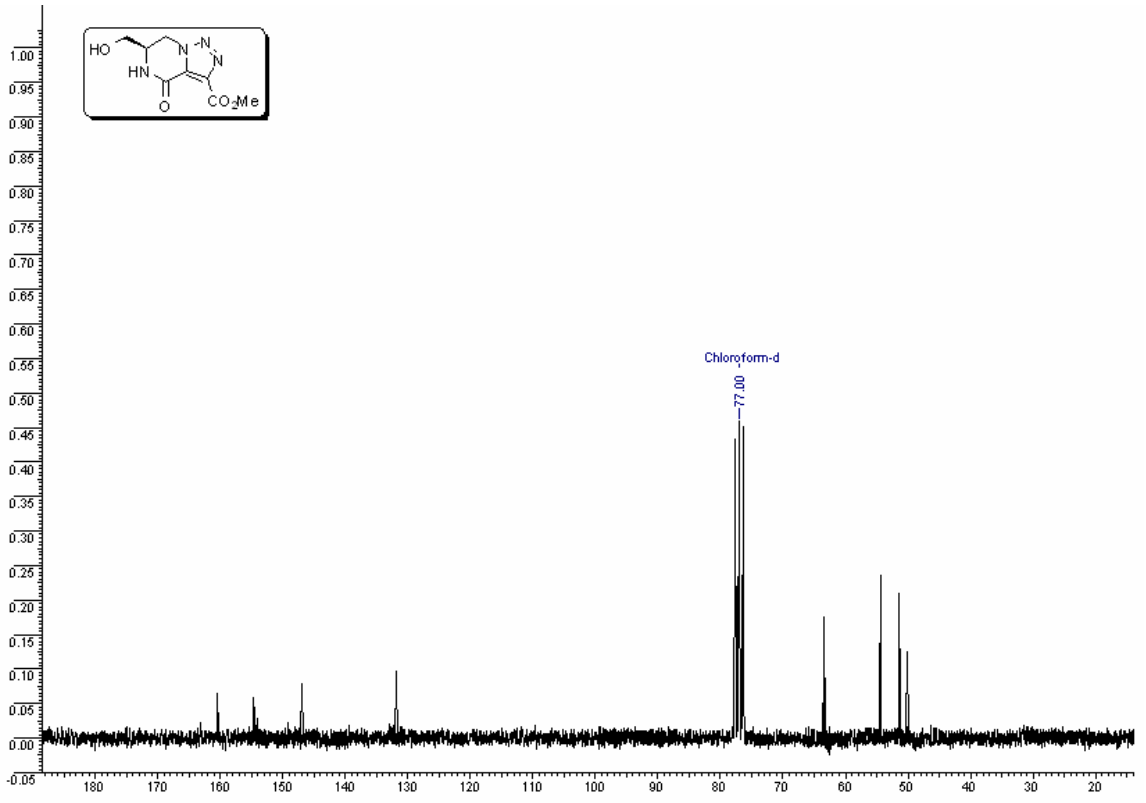
1.26
5.00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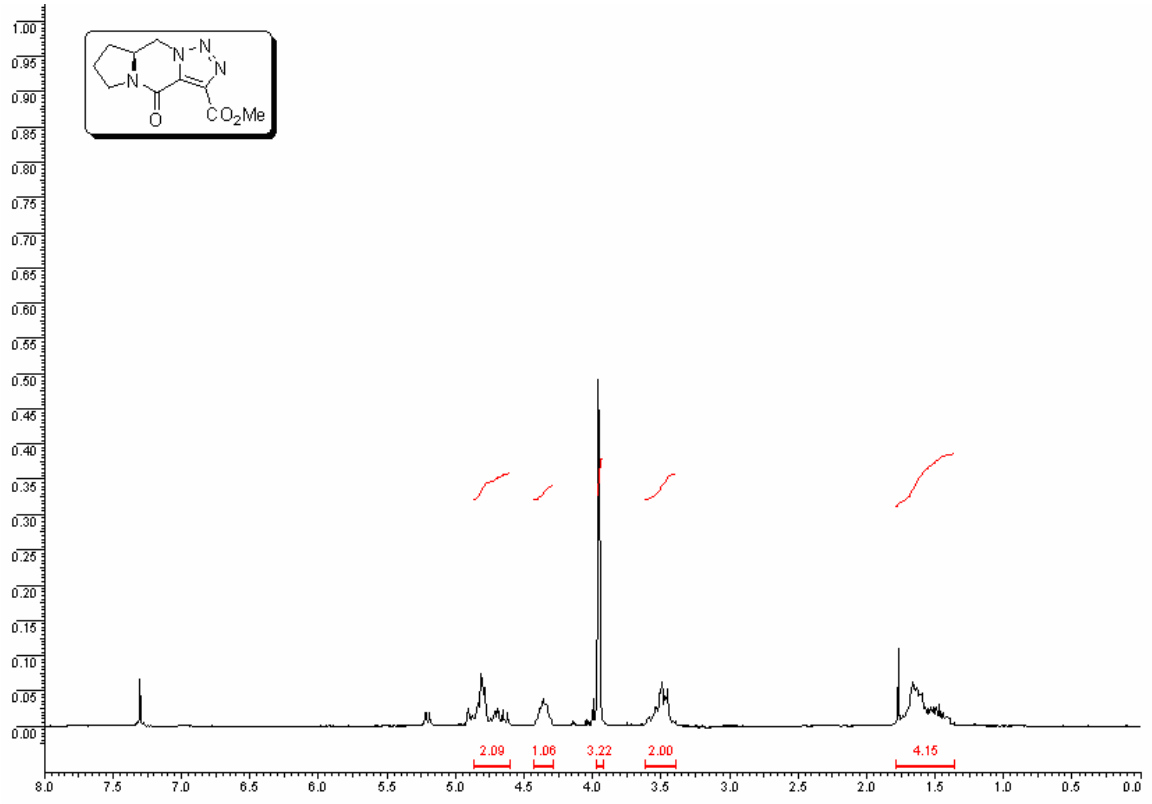
N
N
N
CO2Me
Chloroform-d
77.00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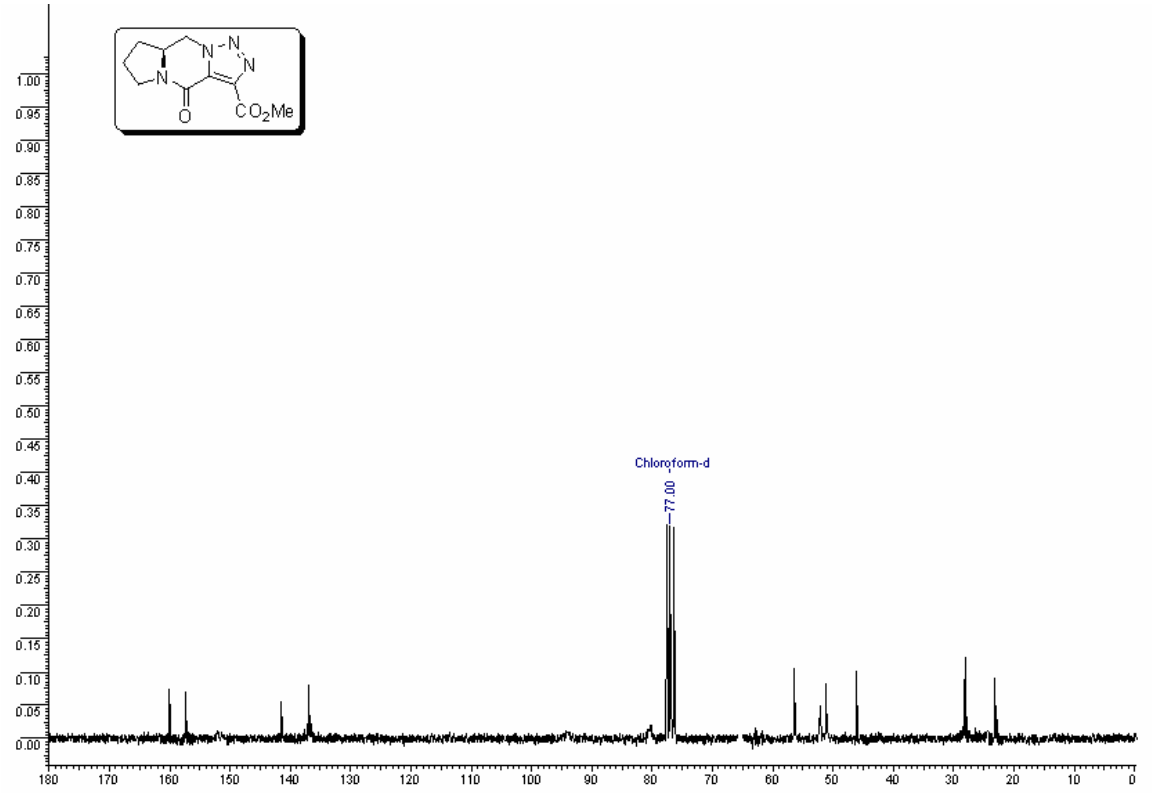
1.06
3.22
2.00
4.15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Chloroform-d
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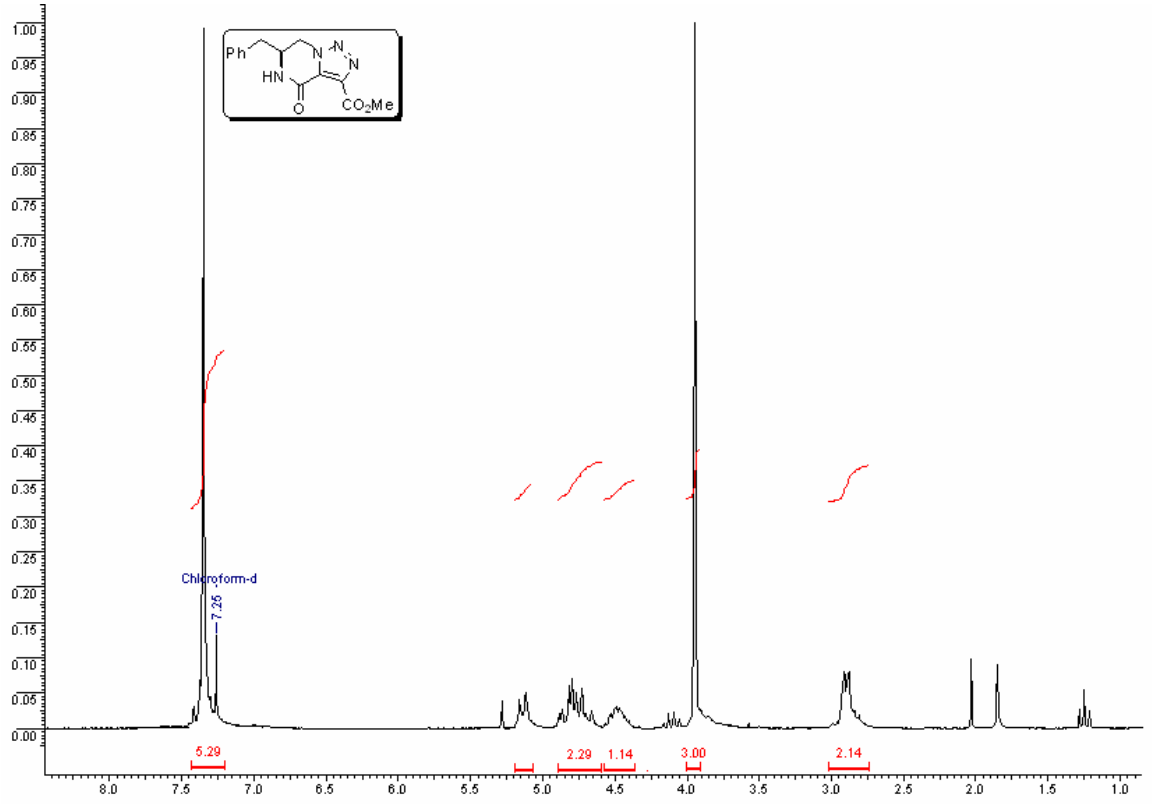
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N
N
N
CO2Me
Chloroform-d
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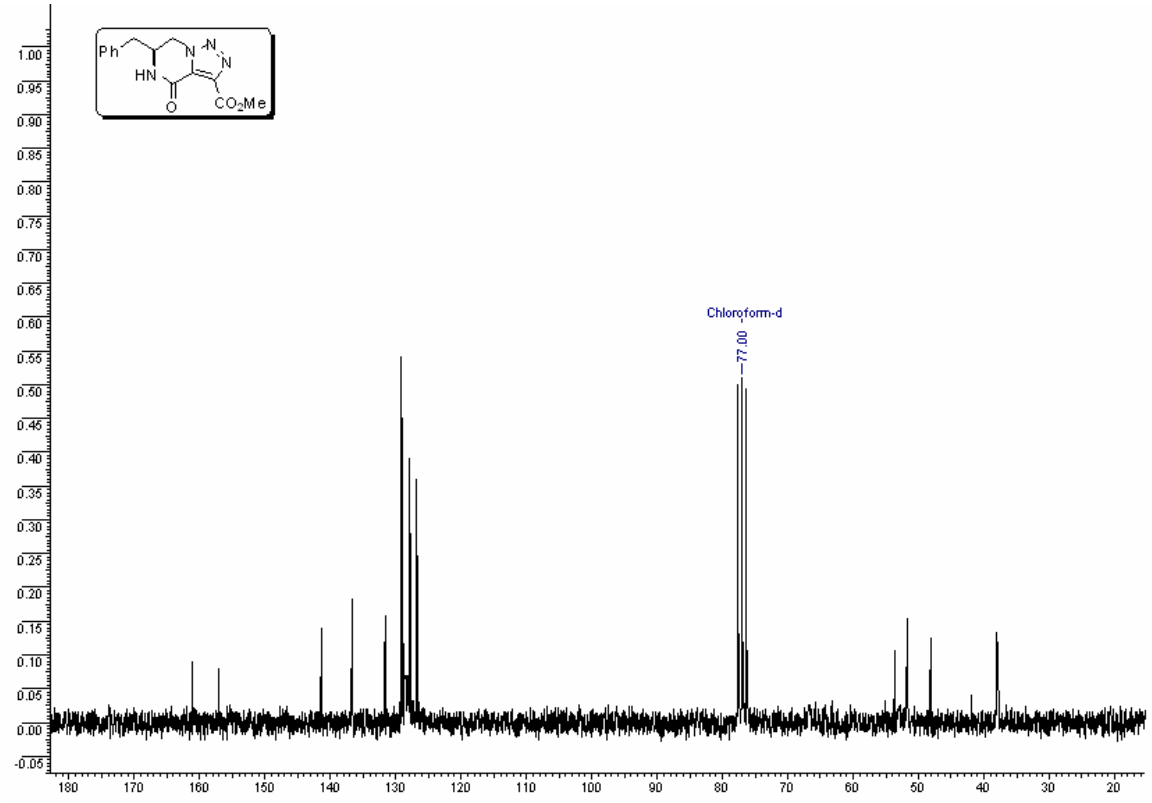
5.29
2.29
1.14
3.00
2.14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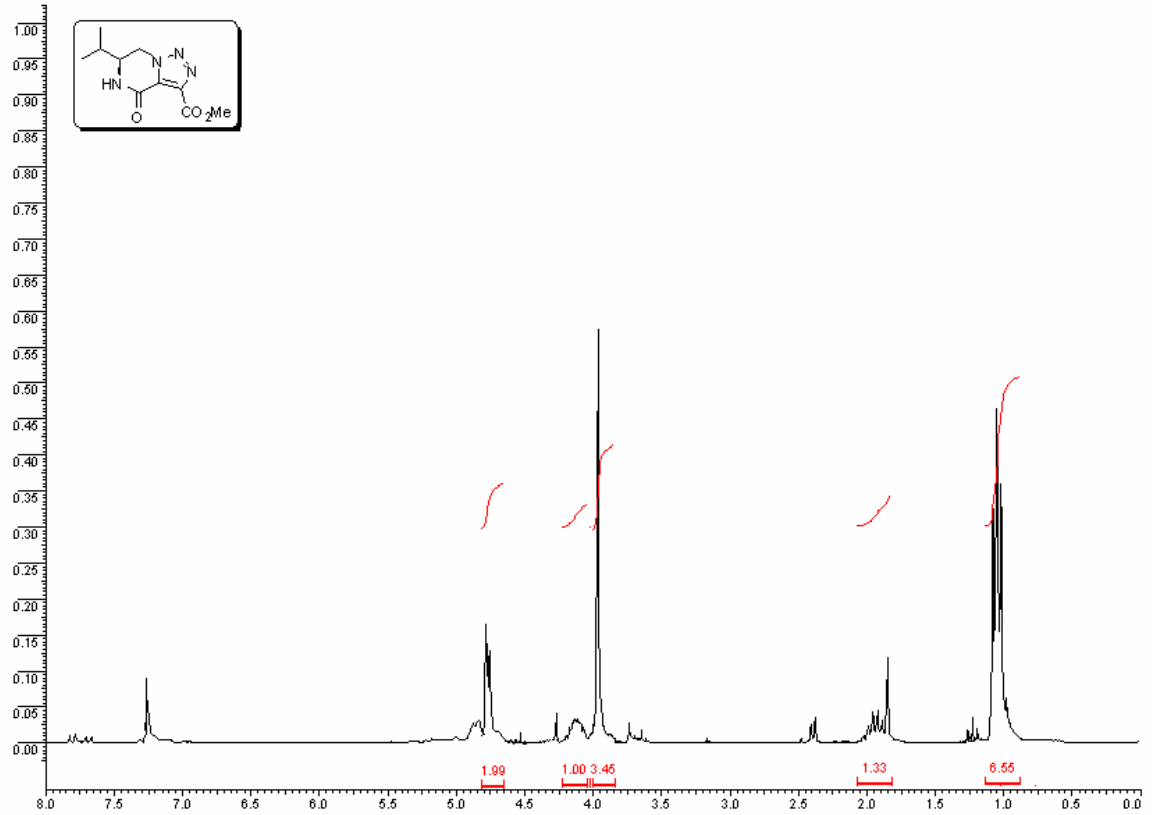
HN
O
N
N
N
CO2Me
Chloroform-d
77.00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N
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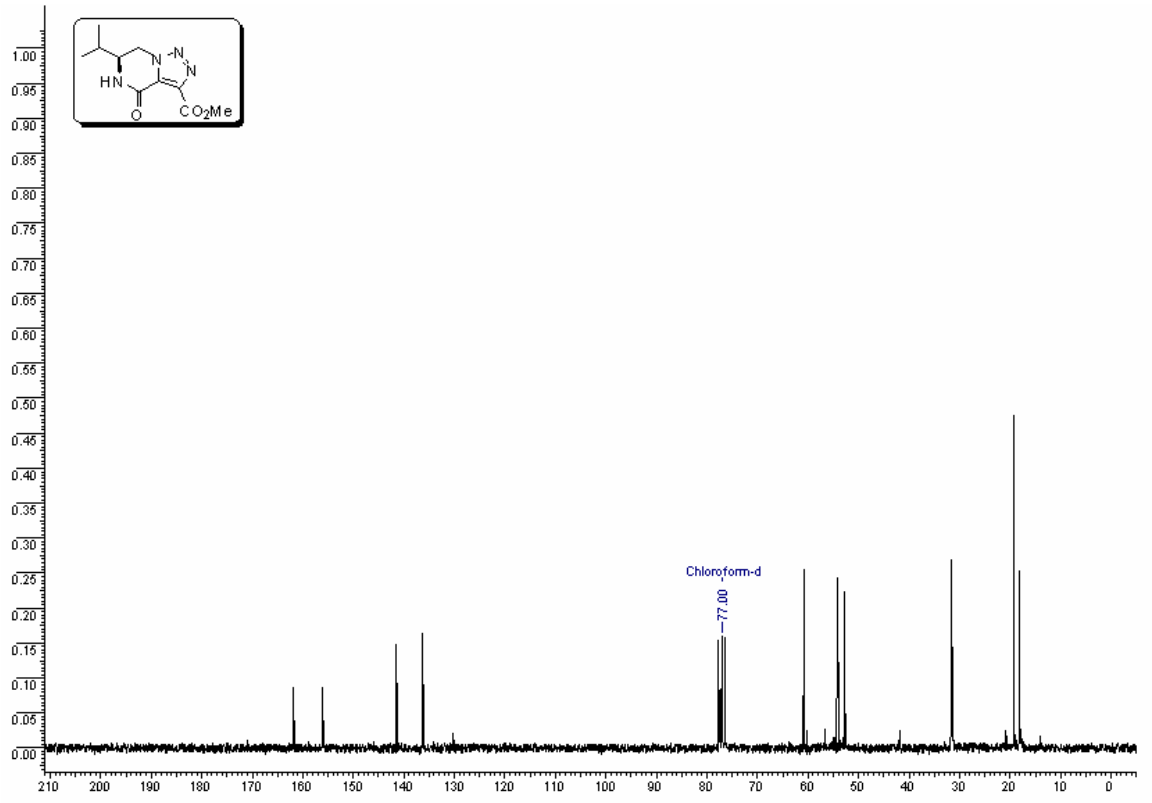
1.33
6.55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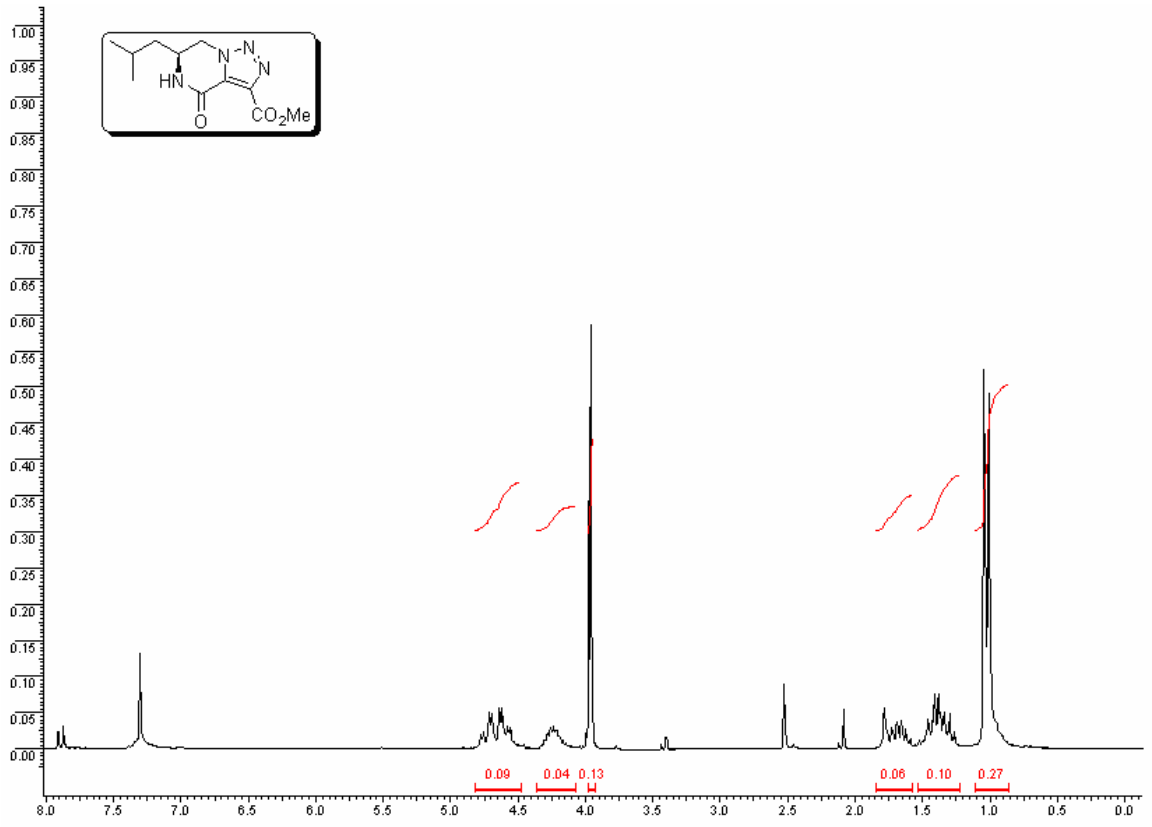
CO2Me
Chloroform-d
77.00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N
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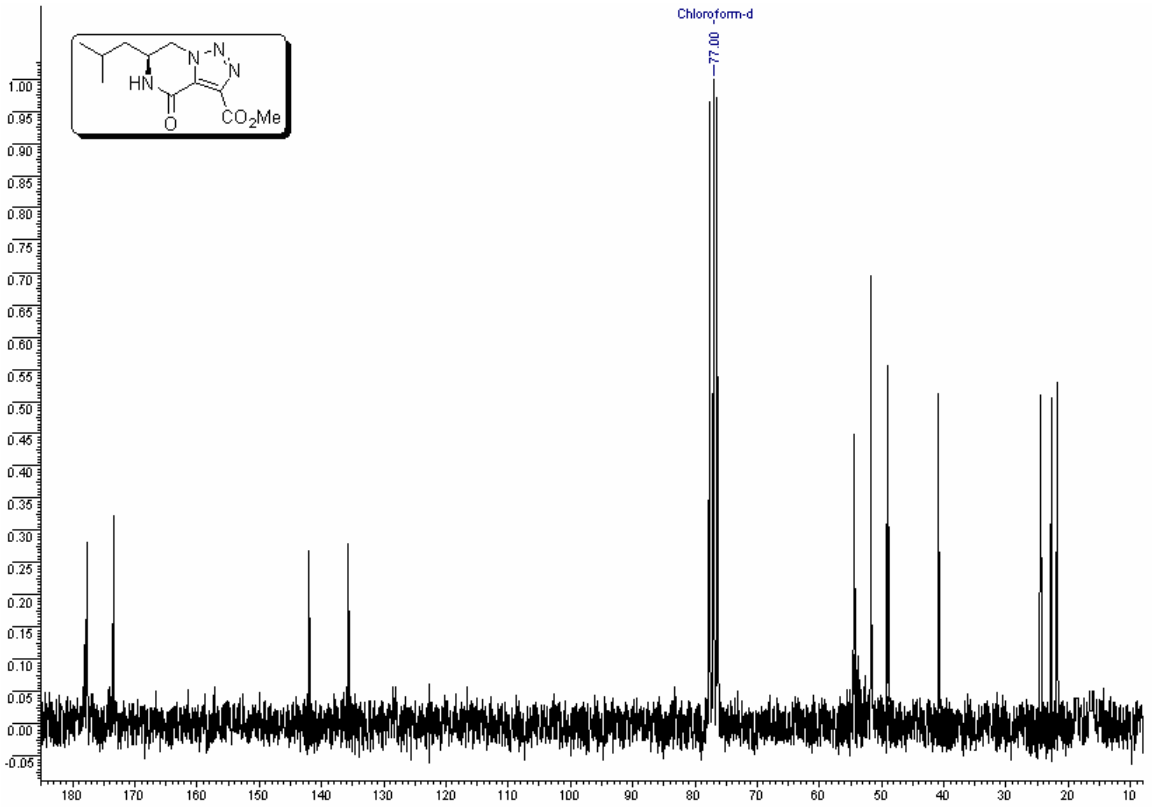
0.13
0.06
0.10
0.27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CO2Me
Chloroform-d
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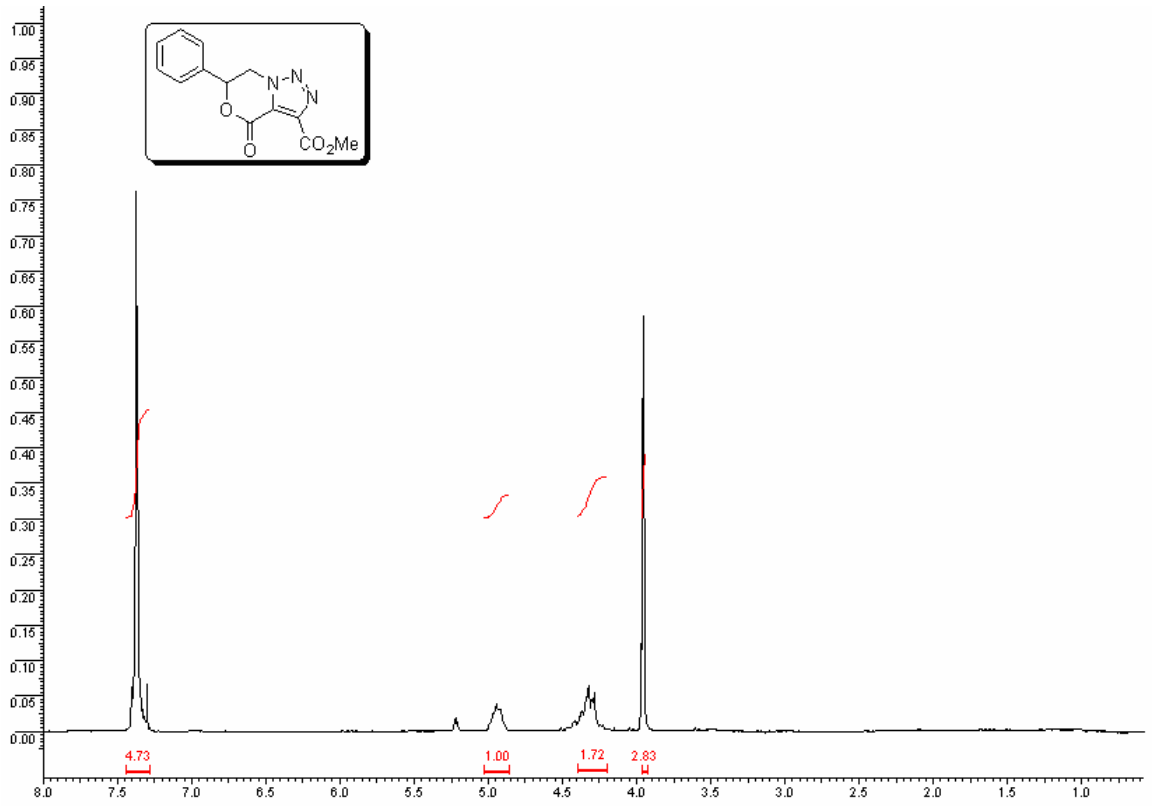
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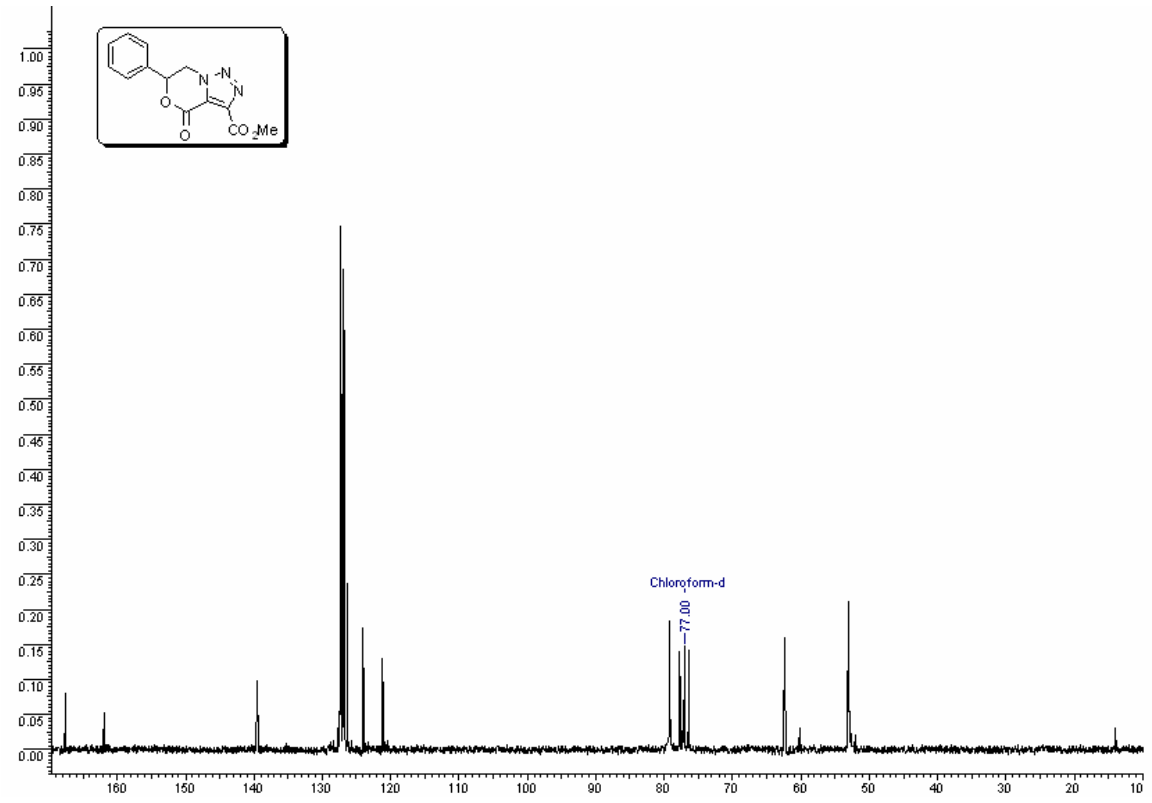
1.00
1.72
2.83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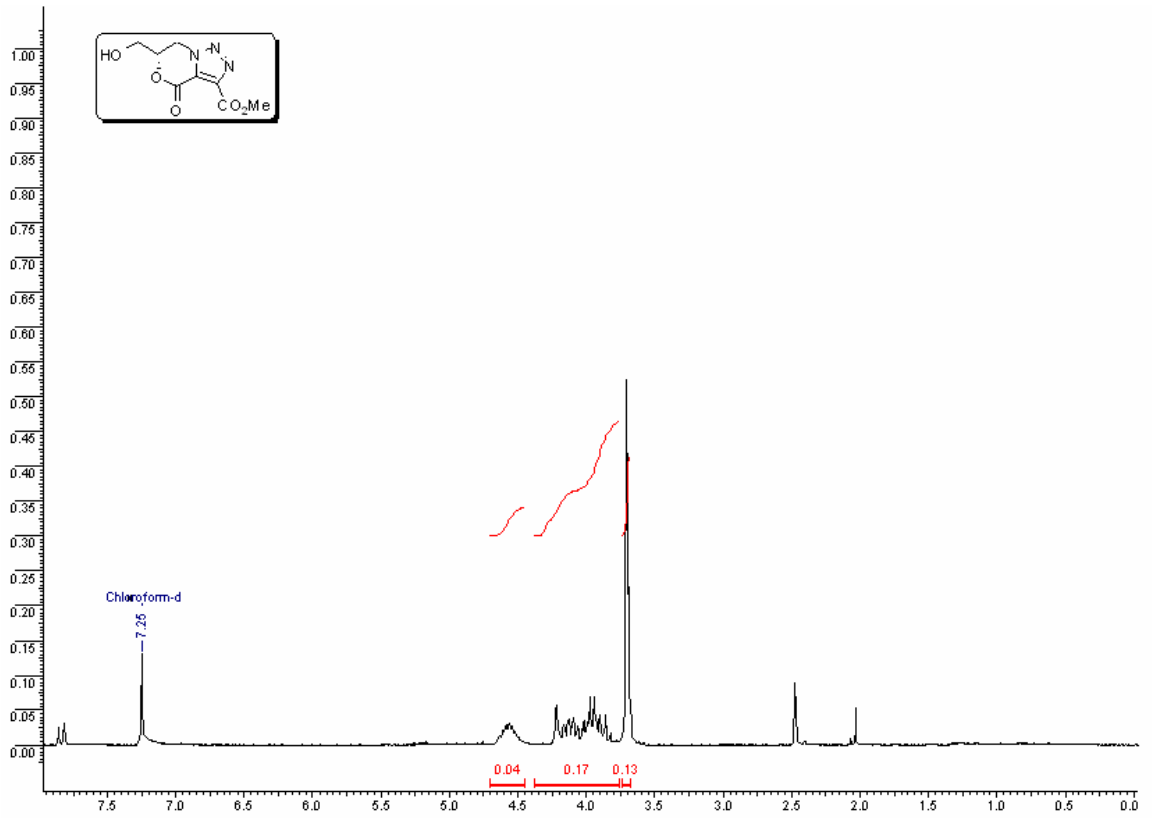
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O
N
N
N
O
O
CO2Me
Chloroform-d
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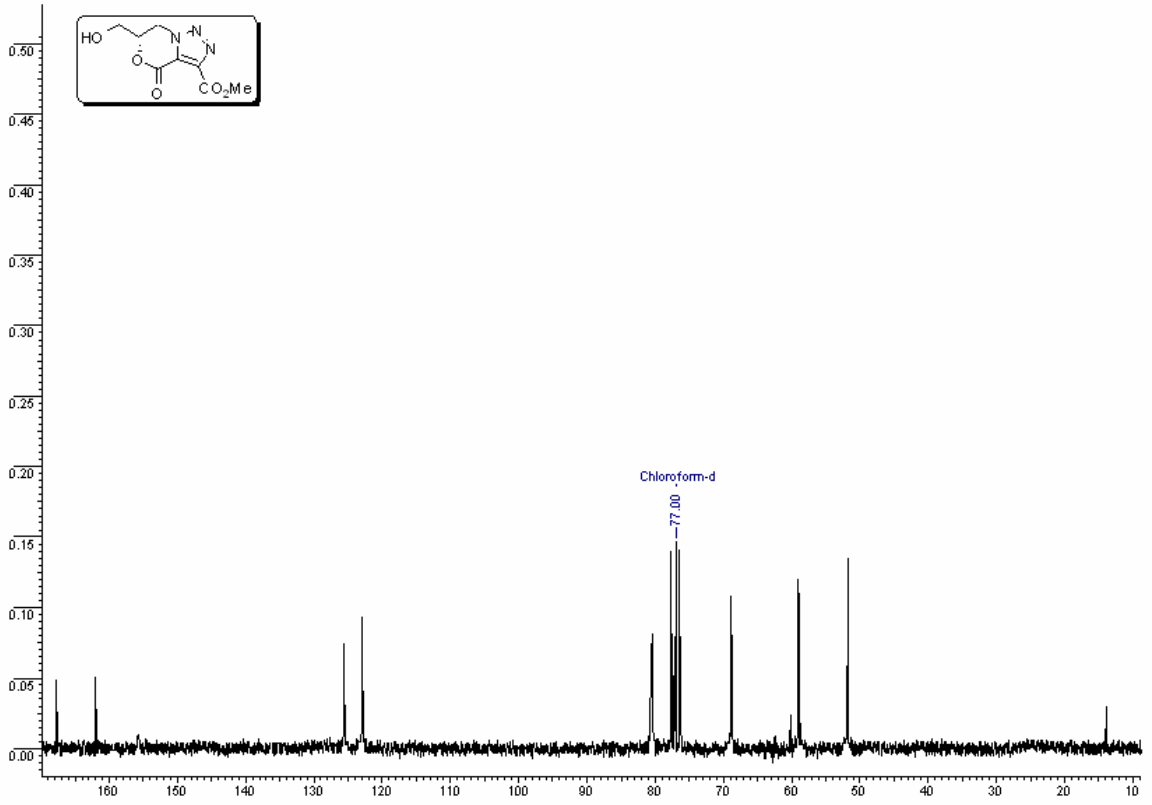
0.04
0.17
0.13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CO2Me
Chloroform-d
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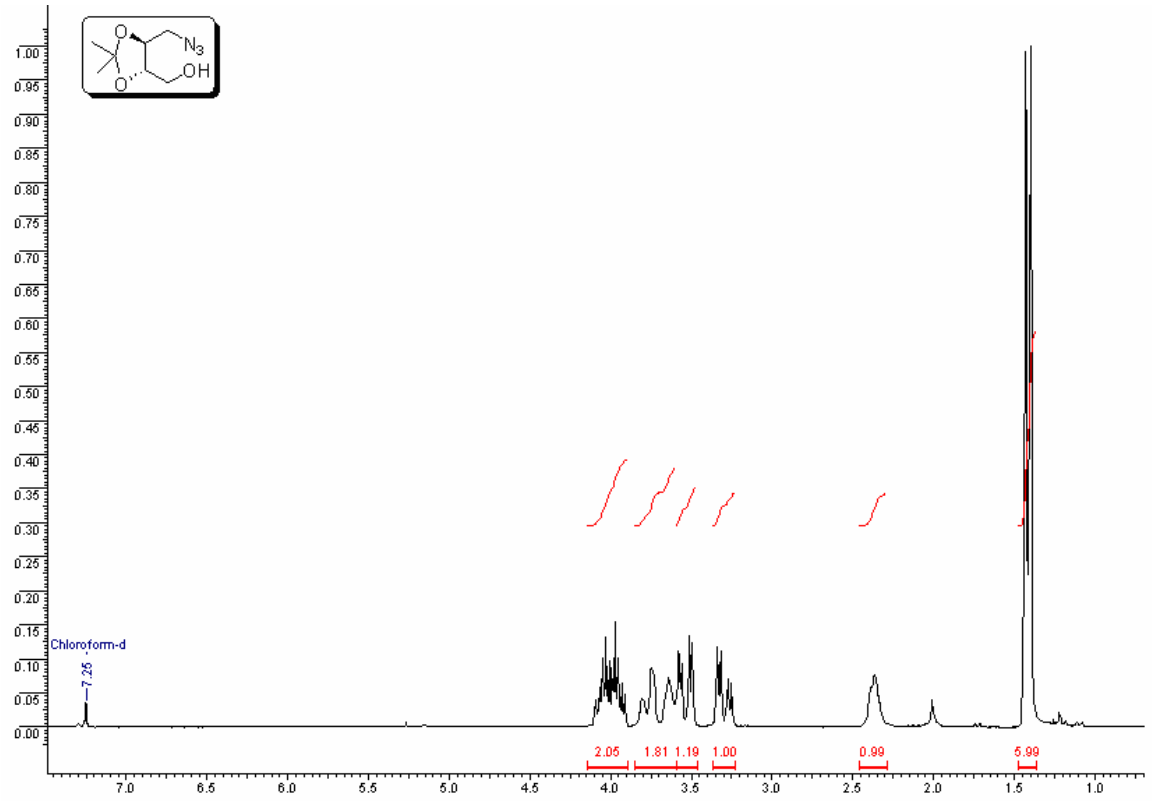
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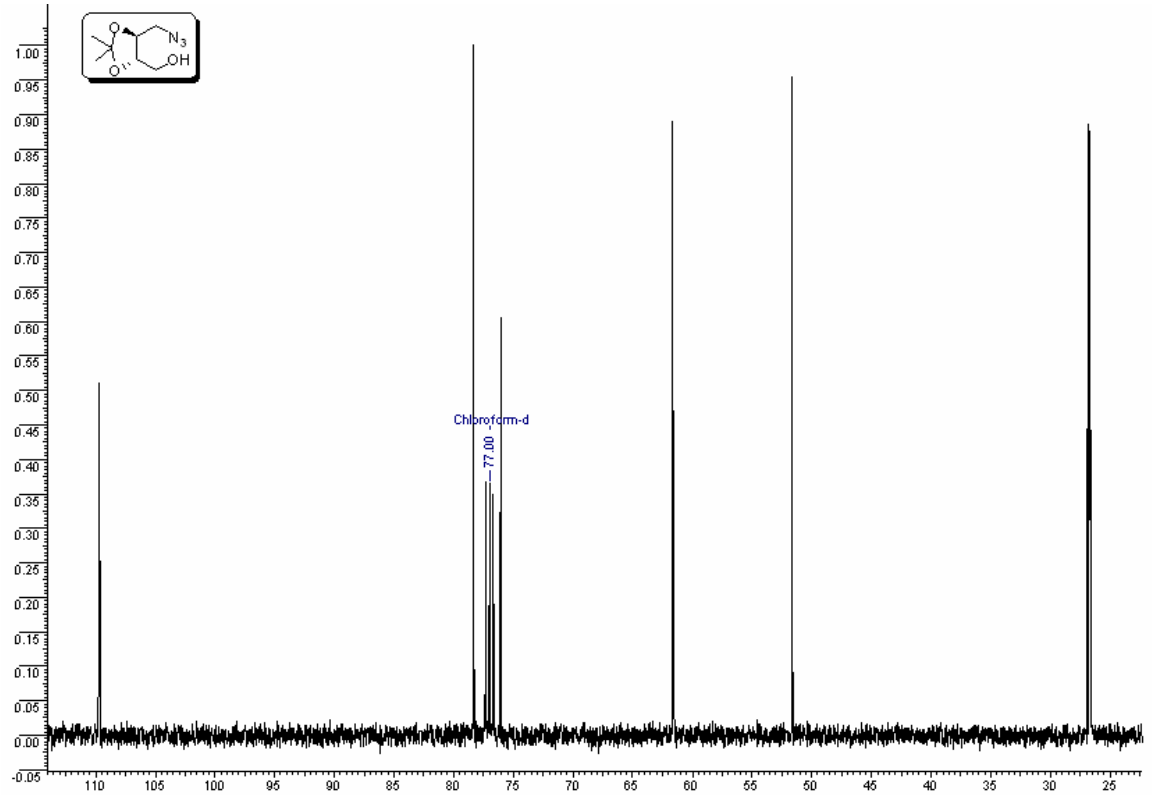
5.99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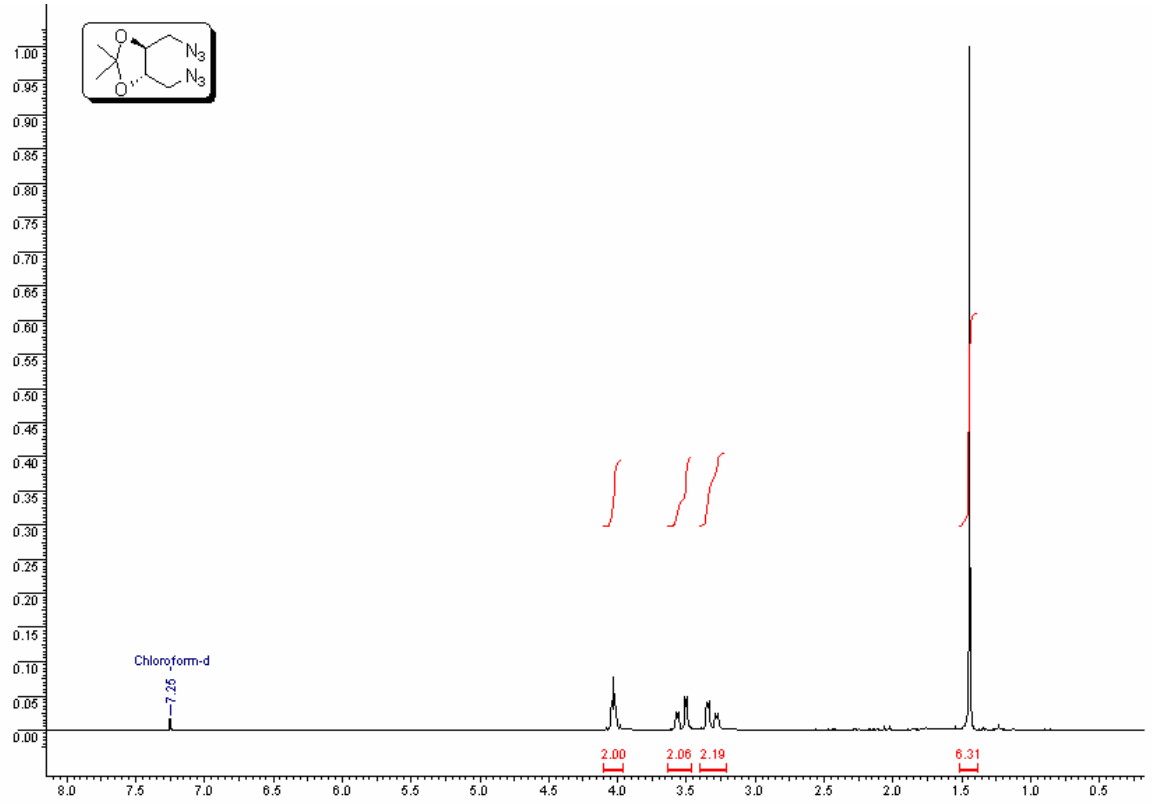
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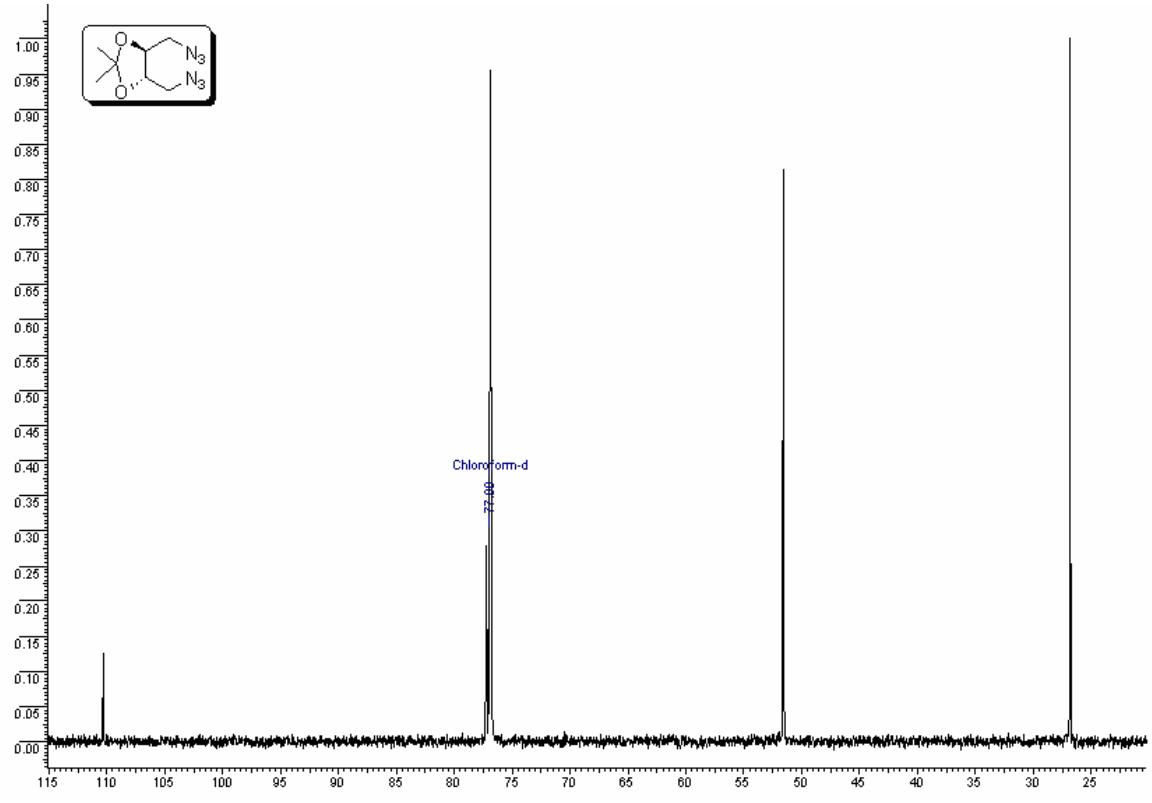
2.06
2.19
6.31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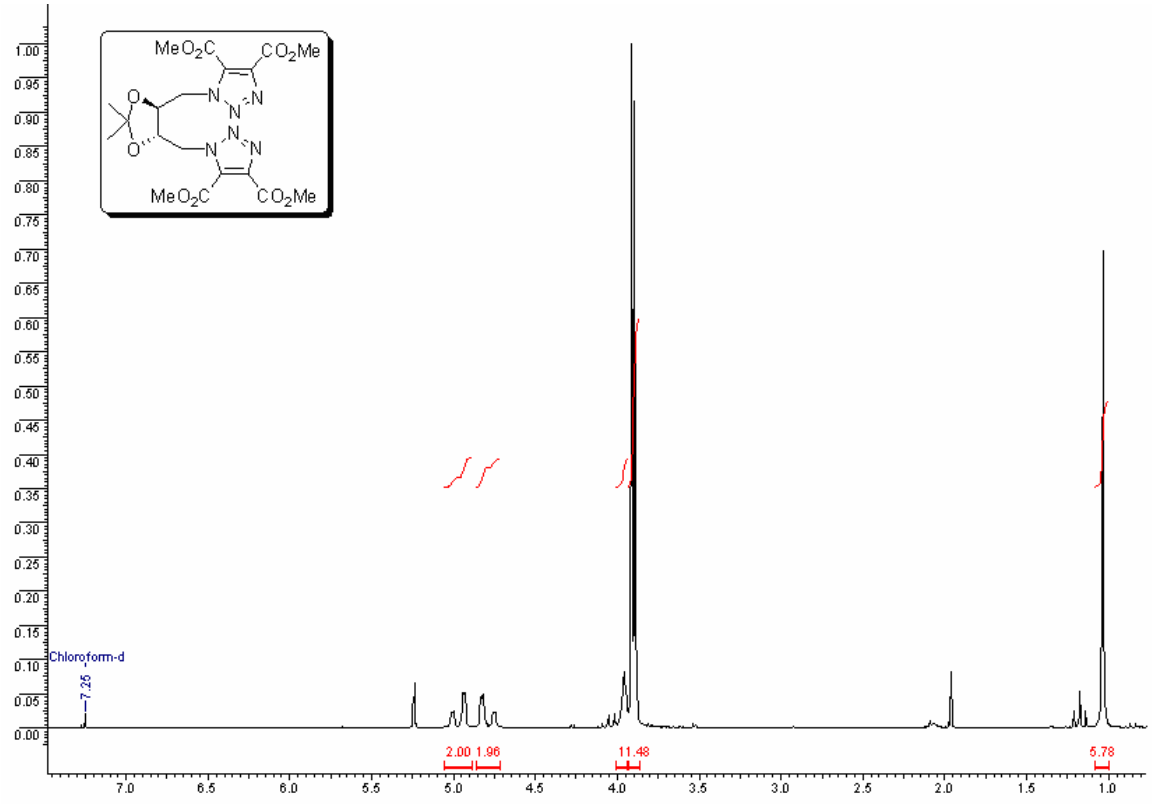
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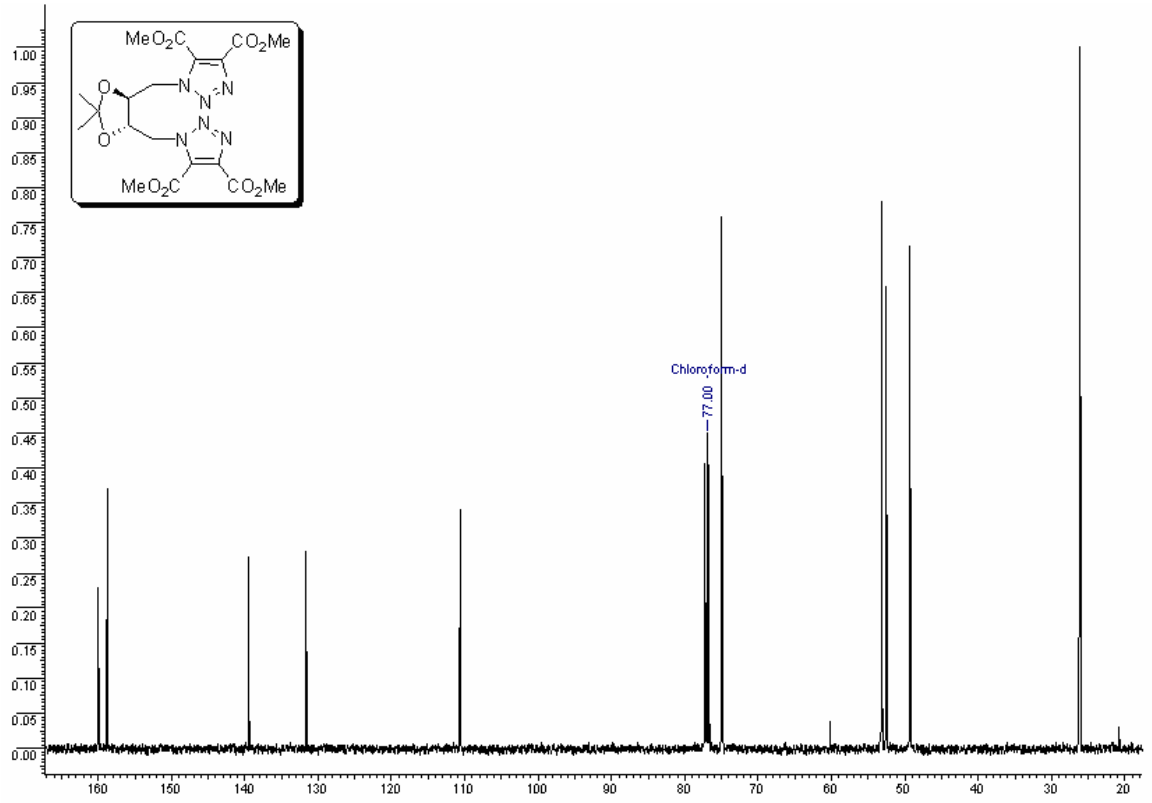
11.48
5.78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Chloroform-d
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Conclusions/ Summary of the thesis

In summary of this thesis, we have demonstrated the L-proline catalyzed direct diastereoselective aldol reaction of amino aldehydes with ketones in intermolecular fashion with high level of selectivity (>95%) and organocatalytic route for the synthesis of amino-polyols such as sphingosine and phytosphingosine base backbone. We have also presented a new organocatalytic route for the synthesis of 1-imino sugars and completed the synthesis of 3,4-substitued pyrrolidine ring system through the L-proline catalyzed first 5-*enolexo* aldolization reaction occurs through 1,2-TBS migration under mild basic conditions and also prepared a key intermediate through direct 6-*enolexo* aldolization reaction, for the synthesis of 1-imino sugars. We have established the direct diastereoselective intramolecular aldolization reaction for the synthesis of imino sugars particularly for the synthesis of 1-deoxynojirimycin analogues with high level of *syn*-selectivity (*dr*>10:1). Finally, we have established the Huisgen [3+2] dipolar cycloaddition reaction of activated alkyne with various azides in water and this reaction was further utilized for the synthesis of new class of fused 1,2,3-triazolo-*δ*-lactams/lactones. Thus, this thesis provides a novel study in the area of organocatalysis particularly, L-proline catalyzed direct diastereoselective aldol reaction in inter- and intramolecular fashion and click reaction in water for the synthesis of important compounds.

List of Publications:

1. 2-Iodoxy Benzoic Acid (IBX): A versatile reagent
   Indresh Kumar *Syn Lett*. **2005,** 1488.
2. Stereoselective synthesis of 2-amino-1, 3, 5 hexane triols using L-Proline catalyzed aldol reaction
   Indresh Kumar and C. V. Rode* Tetrahedron: *Asymmetry* 17, **2006**, 763-766.
3. Efficient synthesis of fused 1,2,3-triazolo-*δ*-lactams using Huisgen [3+2] dipolar cycloaddition "click-chemistry' in water
   Indresh Kumar and C. V. Rode* *Chemistry Letters* **2007**, 5, 592-5593.
4. Asymmetric synthesis of a 3,4-substituted pyrrolidine by L-proline catalyzed direct *enolexo* aldolization
   Indresh Kumar and C. V. Rode* Tetrahedron: *Asymmetry* **2007**, 18, 1210-1218.
5. L-Proline Catalyzed Direct Diastereoselective Aldol Reactions: Towards the Synthesis of *lyxo*-(2*S*,3*S*,4*S*)-Phytosphingosine
   Indresh Kumar and C. V. Rode* Tetrahedron: *Asymmetry* **2007**, (*In press*)
6. A facile and highly selective deprotection of *tert*-butyldimethyl silyl ethers using sulfated SnO_2 as a solid catalyst
   Mahesh H. Bhure, Indresh Kumar, Arun D. Natu, Chandrashekhar V. Rode*
   (Manuscript accepted in *Syn Commun* **2007**)
7. Functionalization of Single-Walled Carbon Nanotubes with Azides Derived from Amino Acids Using Click Chemistry
   Indresh Kumar, Sravendra Rana, Chandrashekhar V. Rode, and Jae Whan Cho*
   (Manuscript accepted in *Journal of Nanoscience and Nanotechnology*, **2007**)
8. Tuning Acidity of Silica supported Phosphotungstic acid: Simple and Highly Selective Deprotection of *tert*-Butyldimethylsilyl Ethers
   Mahesh H. Bhure, Indresh Kumar, Chandrashekhar V. Rode* (submitted)
9. Synthesis of hybrid 1,2,3-triazolo-*δ*-lactams/lactones using Huisgen [3+2] dipolar cycloaddition "click-chemistry" in water
   Indresh Kumar, C. V. Rode* (manuscript submitted, full paper)

10. L-Proline catalyzed direct diastereoselective *enolexo* aldolization: New approach for the synthesis of imino sugars (1-deoxynojirimyicn) and 1-imino sugars (isofagomine) Indresh Kumar and C. V. Rode (Unpublished results)

Awards:

* Award of "Young Indian Scientist travel Grant-2006" by BASF-India.
* Best poster award on the Science Day (28 Feb. 2006) at National Chemical Laboratory, Pune.

Symposium attented:

* Fourth National Symposium in Chemistry (1-3 Feb. 2002) at National Chemical Laboratory, Pune, India.
* Post NOST Mini Symposium in Organic Chemistry (3rd November 2003) at National Chemical Laboratory, Pune, India.
* Poster etitled *"Organocatalytic Diastereoselective Intramolecular Aldol Reaction: A New Approach towards Imino Sugars"* presented at 'International Symposium on Advances in Organic Chemistry (INSOC)' 9-12 January 2006 at M. G. University, Karela, India
* Poster entitled "*Organocatalytic Diastereoselective Intramolecular Aldol Reaction: A New Approach towards Imino Sugars*" presented on Science day (28 Feb. 2006) at National Chemical Laboratory, Pune, India.
* Three months *workshop* (2005-06) in organic chemistry for asymmetric synthesis, spectroscopic analysis and Oral presentation at National Chemical Laboratory,Pune. India
* 6th International Symposium on Catalysis in Multiphase Reactors (CAMURE-6) and 5th International Symposium on Multifunctional Reactors (ISMR-5) (14-17 January 07) at National Chemical Laboratory, Pune, India.
* "International Conference on Asymmetric Organocatalysis" 28-29 May 07 at Otsu, Japan and visitng Young Scientist at Tokyo University of Science for two weeks (May 2007).
