SYNTHETIC APPROACHES TOWARDS POLYHYDROXY CYCLIC AMINES: POTENT GLYCOSIDASE INHIBITORS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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To

My Parents

And

Sister Kriti

DECLARATION

I hereby declare that the work presented in the thesis entitled "**Synthetic Approaches Towards Polyhydroxy Cyclic Amines: Potent Glycosidase Inhibitors**" submitted for Ph. D. Degree to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthetic Approaches Towards Polyhydroxy Cyclic Amines: Potent Glycosidase Inhibitors**" submitted by Mr. Manmohan Kapur, was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

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Manmohan Kapur

CONTENTS

List of Abbreviations

aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
bp	boiling point
CAN	ceric ammonium nitrate
Cbz-	benzyloxycarbonyl-
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DCN	1,4-dicyanonaphthalene
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
g	gram
h	hour
HMDS	hexamethyldisilazane
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
M	molar
m-CPBA/ MCPBA	3-chloroperoxybenzoic acid
mL	milliliter
mmol	millimole

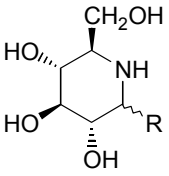
MOM-	methoxymethyl-
mp	melting point
NMO	4-methylmorpholine *N*-oxide
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Abstract of the Thesis.

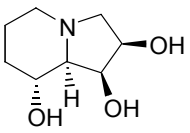
<u>Chapter I:</u> An introduction to 1-*N*-iminosugar type glycosidase inhibitors.

This chapter introduces the concept involved in the development of 1-*N*-iminosugar type glycosidase inhibitors and summarizes some of the important approaches towards these bioactive molecules.

Enzymes involved in the biosynthesis of carbohydrates are termed as glycosidases and glycosyl-transferases. Analogues of carbohydrates in which one or more of the oxygen atoms have been substituted by nitrogen are probably the best-known inhibitors of glycosidases. Subsequent to the isolation of potent glycosidase inhibitors like nojirimycin (**1**), 1-deoxynojirimycin (**2**), swainsonine (**3**), casuarine (**4**) and a mild glycosidase inhibitor like fagomine (**5**), from natural sources, there has been a growing interest in the chemistry, biochemistry and pharmacology of these compounds.



(1): R = OH
(2): R = H



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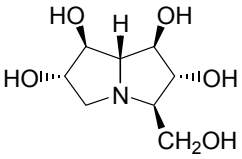

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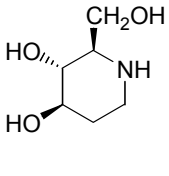

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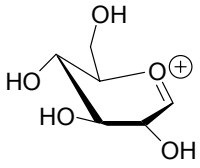

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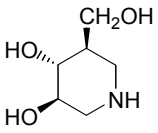
Not only have these unique molecules proved to be a tool for studying the biological functions of oligosaccharides, they have also been shown to possess a tremendous therapeutic potential in the treatment of a variety of diseases like diabetes, cancer, AIDS, Gaucher's disease and viral infections like influenza. The unraveling of the mechanism of the glycosidases and identification of the positively

charged flattened half chair oxocarbenium ion **6** as a transition state for the glycosidic bond cleavage reaction has led to pioneering studies on the relationship between structure and inhibitory activity in glycosidase inhibitors. Based on these studies, the last decade has seen a spurt in the activity of creative chemical design of a new class of sugar mimic inhibitors having a nitrogen atom at the anomeric position.

The studies of Bols and Ichikawa have resulted in the design of potent inhibitors like Isofagomine **7** (D-glucose type 1-*N*-iminosugar), **8** (D-glucouronic acid type), **9** (D-galactose type), **10** (L-fucose type), noeuromycin **11** and **12**. Isofagomine (**7**) and noeuromycin (**11**) in particular have been found to be extremely potent inhibitors of β-glucosidases.



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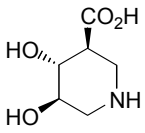

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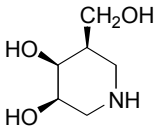

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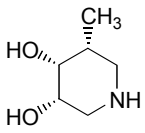

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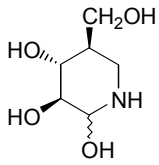

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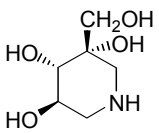

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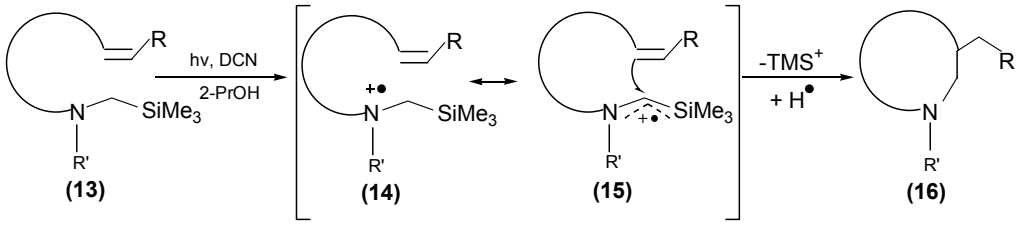
<u>Chapter II:</u> Design and development of a new synthetic strategy for 1-*N*-iminosugars.

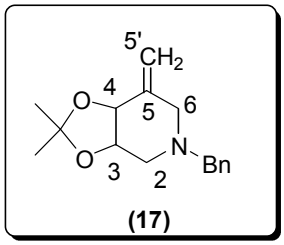
Although considerable effort has been directed to develop a synthetic approach for the 1-*N*-iminosugar type glycosidase inhibitors, the synthesis of these functionalized piperidines has not been easy. The main challenge involved in the development of a synthetic approach for these molecules has been the difficulty involved in the generation of the aminomethyl group next to a stereocenter. In this context we were encouraged to consider the evaluation of a methodology developed in our group for the construction of amines of the type **16** by the cyclization of the photoinduced electron transfer (PET) generated α-

trimethylsilylmethylamine radical cation **15** to a tethered π-functionality as shown in **Scheme-I.**

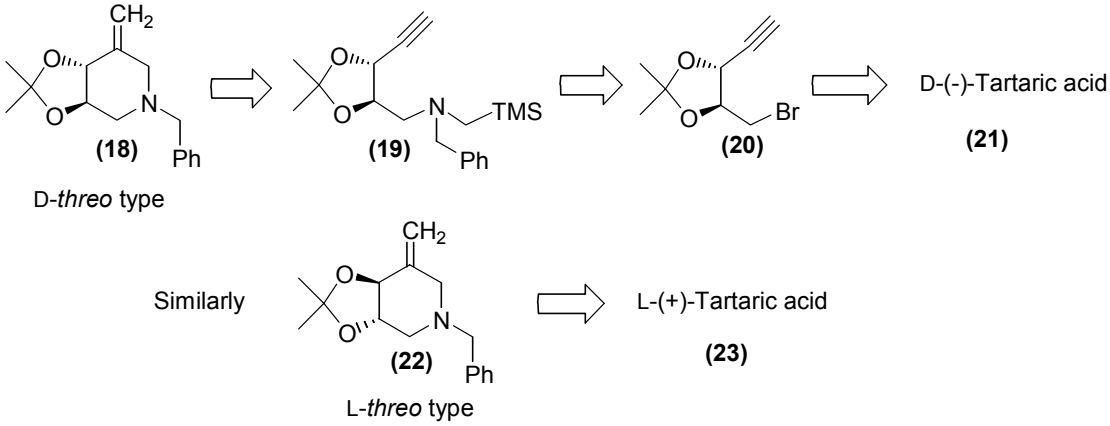


Scheme-I

Drawing consequences from this conceptual design, we envisaged a precursor of the type **17** for the synthesis of most of the 1-*N*-iminosugar type glycosidase inhibitors. It was assumed that by having the correct stereochemistry at C-3 and C-4 and by carrying out simple organic transformations at C-5—C-5' center, one can have a general route to access this class of inhibitors.

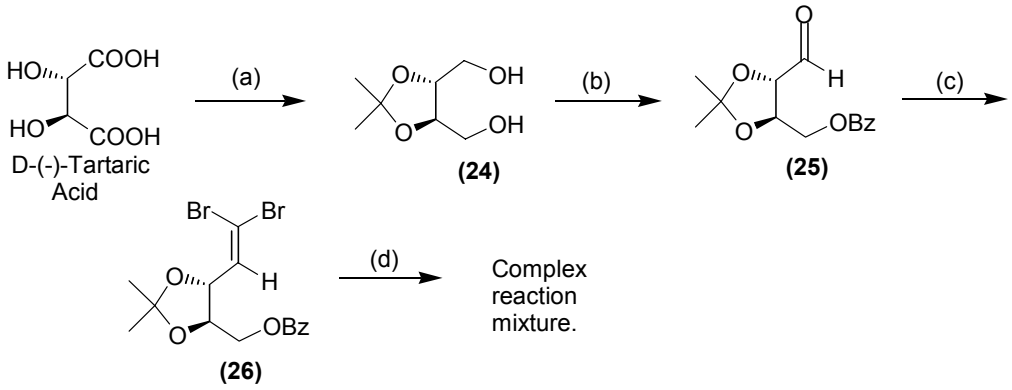


With these premises, we evaluated a retro-synthetic route for the synthesis of precursors of D- as well as L-*threo* class, as outlined in **Scheme-II.**



Scheme-II

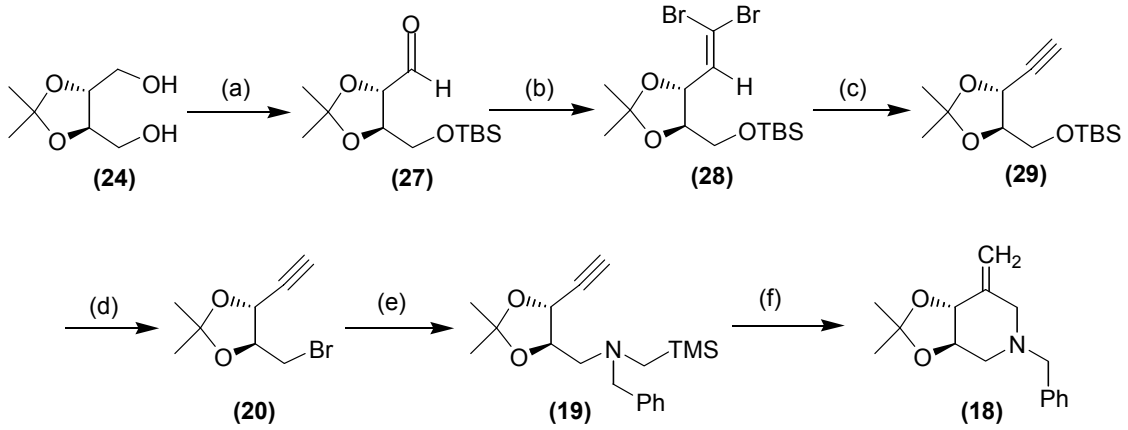
The synthesis of **18** started with D-(-)-Tartaric acid as shown below in **Scheme-III.**



Scheme-III

Reagents and Conditions: *(a) (i) 2,2-dimethoxypropane, MeOH, cyclohexane, pTSA, warm, 95%; (ii) LAH, THF, reflux, 6h, 95%; (b) (i) BzCl, pyridine, DCM, rt, 12h, 60%; (ii) Swern oxidation, -78°C, 96%; (c) CBr_4, PPh_3, DCM, 0°C, 3h, 85%; (d) n-BuLi, THF, -78°C, 1h.*

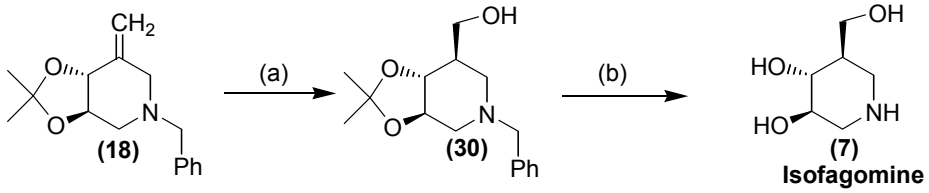
However, Corey's protocol to prepare the acetylene did not yield the required product and hence the benzoyl protecting group had to be replaced by the TBS group. The butyl lithium reaction on **28** proceeded smoothly to afford the acetylene **29** in good yield as depicted in **Scheme IV**. This was further transformed to the amine **19**, which was reacted under the PET cyclization condition (Pyrex filter, >280nm, 450W Medium pressure Hanovia lamp) to afford the D-*threo* precursor **18** in good yield. In the same fashion the L-*threo* precursor **22** was also synthesized starting from L-(+)-tartaric acid.



Scheme-IV

Reagents and conditions: *(a) (i) TBSCl, TEA, DCM, rt, 36h, 85%; (ii) Swern oxidation, -78 °C, 96%; (b) CBr_4, Ph_3P, DCM, 0 °C, 2 h, 65% (c) n-BuLi, THF, -78 °C, 1 h, 90% (d) (i) TBAF, THF, 0 °C to rt, 4 h, 85%; (ii) CBr_4, Ph_3P, DCM, 0 °C to rt, 1 h, 80% (e) $PhCH_2NHCH_2TMS$, K_2CO_3, TBAI, CH_3CN, reflux, 96 h, 65% (f) hν, DCN, 2-PrOH, 90 min, 60%.*

After the successful synthesis of the precursors for the 1-*N*-iminosugars, we proceeded to functionalize the exocyclic double bond. We decided to first synthesize the D-Glucose type 1-*N*-iminosugar, Isofagomine (**7**). Hydroboration using 9-BBN afforded the alcohol **30** as a single diastereomer. Removal of the protecting groups afforded (+)-Isofagomine as shown in **Scheme-V.** The stereochemistry of **7** was proved by ^{1}H COSY.

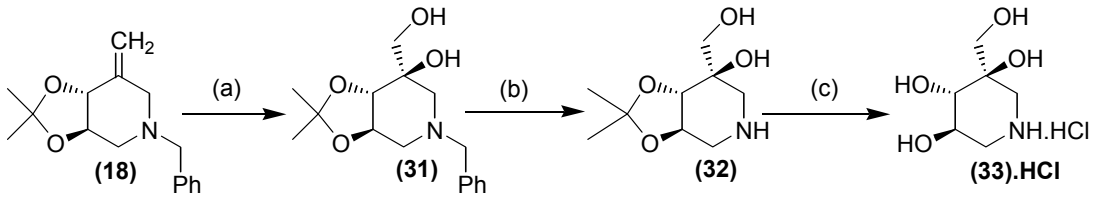


Scheme-V

Reagents and Conditions: *(a) 9-BBN, THF, 0° C to rt, 20 h, then NaOH, H_2O_2, 0° C to rt., 4 h, 45%; (b) (i) HCl, MeOH, rt., 1 h, then NH_4OH, ~100% (ii) $Pd(OH)_2$ on C, H_2, 75 psi, EtOH, 10 h, 95%.*

.

The successful synthesis of **7** was followed by the synthesis of a new entity of the 1-*N*-iminosugar class, the 5-hydroxy analogue of 5-epiisofagomine **33**, as depicted in **Scheme VI**. Osmium tetroxide dihydroxylation of **18** afforded the diol **31** in 95% yield as a single diastereomer. The stereochemistry of **31** was proved by COSY, NOESY, and HETCOR. Debenzylation followed by acetonide deprotection afforded **33** a new structural moiety.

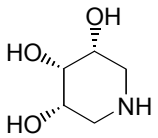


Scheme-VI

Reagents and conditions: *(a) OsO_4, NMO, pyridine, Acetone-water (9:1), rt, 24h, 95%; (b) $Pd(OH)_2$, H_2, EtOH, 65 psi, 6h, 90%; (c) HCl, MeOH, rt, 4h, quant.*

.

Some of the most important 3, 4, 5-piperidine triols were also synthesized utilizing the precursors **18** and **22**. These trihydroxypiperidines are regarded as derivatives of deoxynojirimycin and have been shown to possess glycosidase inhibitory activity almost equal to that of the parent molecule. These structural moieties can also be regarded as 1-*N*-iminosugar type glycosidase inhibitors although they do not resemble any of the existing pyranose sugars.



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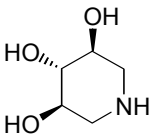

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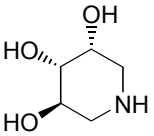

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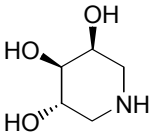

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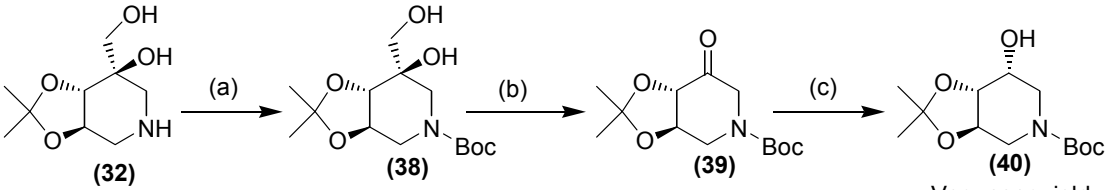
The piperidine triols **34**, **35**, **37** have been isolated from *Eupatorium fortunei* TURZ in 1995 by Kusano and coworkers. The triols **35**, **36**, **37** had been previously shown to possess high glycosidase inhibitory activity by Ganem and co-workers.

We realized that our precursors **18** and **22** were ideal for the synthesis of these molecules. The synthesis of **36** (des(hydroxymethyl)deoxymannojirimycin) started with the diol **31**, previously synthesized from **18**. In anticipation that the amine would be affected by the periodate oxidation, we replaced the benzyl group in **31** with *tert*-butoxycarbonyl (Boc) moiety as shown in **Scheme –VII** below. However, the sodium borohydride reduction of the ketone **39** failed to give good yield and so this route had to be discarded.



(32) **(38)** **(39)** **(40)**

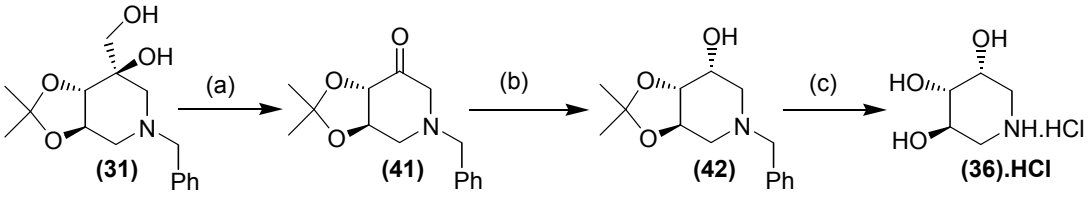
Very poor yield.

Scheme-VII

***Reagents and conditions**: (a) $(Boc)_2O$, TEA, DCM, 0 °C to rt, overnight, 80%; (b) $NaIO_4$, EtOH-H_2O (4:1), rt, 30 min, 70%; (c) $NaBH_4$, MeOH, rt, 36h then satd. NaCl, rt, 24h, 25%.*

The above failure forced us to revert back to the diol **31** and attempt the periodate oxidation as shown in **Scheme-VIII**. The ketone **41** was obtained in fairly good yield. This somewhat labile ketone was then reduced with sodium borohydride

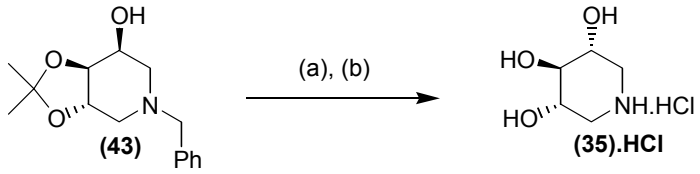
to afford the alcohol in a 9:1 diastereomeric ratio. One pot *N*-debenzylation and acetonide removal afforded the piperidine triol **36**, which could be purified completely by column chromatography (silica, chloroform-isopropanol-aq. ammonia, 8:1.5:0.5). The stereochemistry of **36** was proved by ^{1}H COSY.



Scheme-VIII

Reagents and conditions: *(a) $NaIO_4$, EtOH-H_2O (4:1), rt, 1h, 80%; (c) $NaBH_4$, MeOH, rt, 40h then satd. NaCl, rt, 24h, 85%; (c) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 36h, quant.*

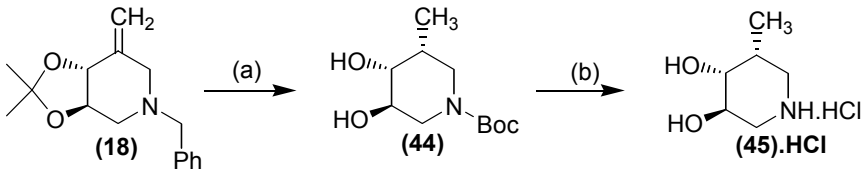
The piperidine triol **35** (des(hydroxymethyl)deoxynojirimycin) was then synthesized from **43** (*ent*-**42**) using Mitsunobo conditions. Removal of the benzyl and acetonide protecting groups followed by chromatographic purification gave **35** as depicted in **Scheme IX**.



Scheme-IX

Reagents and Conditions: *(a) (i) Diisopropyl azodicarboxylate, PPh_3, p-nitrobenzoic acid, THF, rt; (ii) LiOH, MeOH, 60% over two steps; (b) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 20h, quant.*

This was further followed by the synthesis of 5'-deoxyepiisofagomine **45**. As depicted in **Scheme-X** below, one pot olefin reduction as well as *N*-debenzylation and deprotection of acetonide using acidic medium yielded the compound in a 4:1 mixture of diastereomers, which were not separable. Therefore, these amines were converted to their –Boc derivatives and at this stage we were able to separate the diastereomers by careful column chromatography. Removal of the -Boc moiety from **44** yielded **45**. The stereochemistry of **44** was proved by ^{1}H COSY.

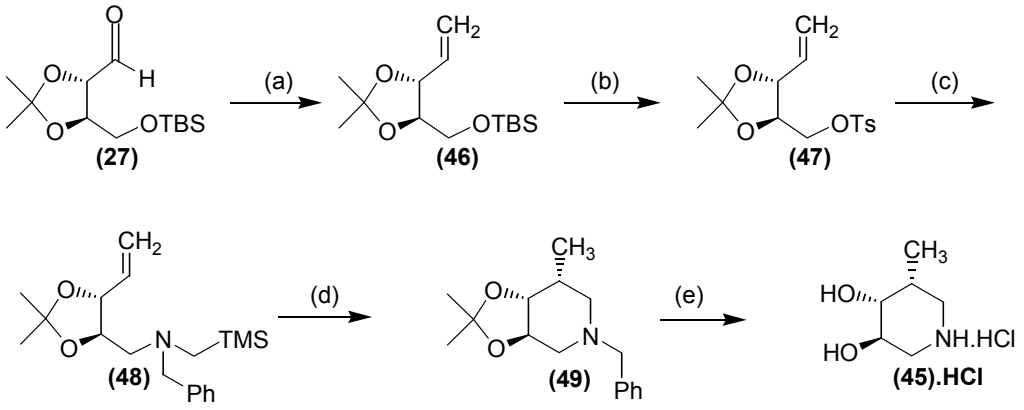


Scheme-X

Reagents and conditions: *(a) (i) Pd/ C, MeOH, HCl, H_2, 1atm, rt, 12h, 89%; (ii) $(Boc)_2O$, TEA, DCM, rt, 48h, 75%; (b) HCl, MeOH, 0 °C to rt, 4h, quant.*

Although a fairly acceptable diastereomeric ratio was obtained in the above case, we thought of a slightly different route towards the synthesis of **45,** employing the same cyclization method, depicted previously in **Scheme I**.

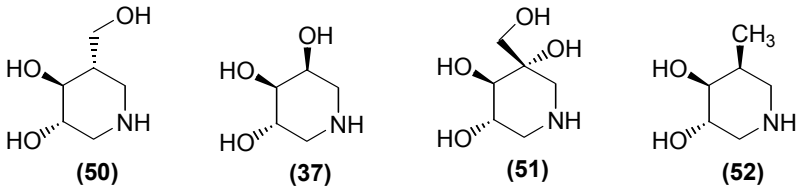
The synthesis, as depicted in **Scheme-XI**, started with the aldehyde **27**. Wittig olefination followed by removal of the –TBS group and conversion of the resultant alcohol to its tosylate gave **47** which was further reacted with $PhCH_2NHCH_2TMS$ to afford **48**. The amine **48** was reacted under PET cyclization conditions to afford **49** as a single detectable diastereomer, which was freed from the benzyl and acetonide groups to afford **45**.



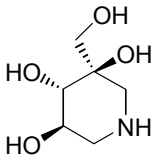
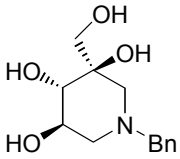
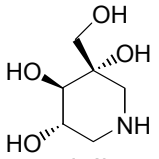
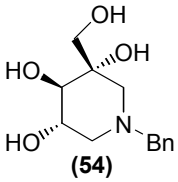
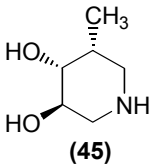
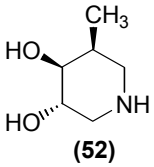
Scheme-XI

Reagents and conditions: *(a) PPh_3CH_3I, n-BuLi, THF, -15 °C to rt, 16h, 60%; (b) (i) TBAF, THF, rt, 4h, 90%; (ii) TsCl, Pyridine, DCM, rt, 24h, 95%; (c) $PhCH_2NHCH_2TMS$, Cs_2CO_3, TBAI, CH_3CN, reflux, 72h, 58%; (d) hν, DCN, 2-Propanol, 2h, 55%; (e) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1atm, 28h, quant.*

In a similar manner, (-)-Isofagomine **50**, des(hydroxymethyl)galactonojirimycin **37**, **51** (*ent*-**33)**, and **52** (*ent*-**45)** were synthesized from the L-*threo* precursor **22**.



The new molecules synthesized were tested for enzyme inhibition against β-glucosidase and β-mannosidase and the results are summarized below in tabular form.

Compound	K_i (M)	
	β-Glucosidase (Sweet almonds, pH 6.0)	**β-Mannosidase** (Snail acetone, pH 4.0)
 **(33)**	9.6×10^{-5}	nd
 **(53)**	5.9×10^{-4}	nd
 **(51)**	5.8×10^{-4}	2.9×10^{-4}
 **(54)**	3.7×10^{-4}	1.5×10^{-3}
 **(45)**	3.0×10^{-5}	NI
 **(52)**	3.0×10^{-4}	NI

nd = not determined

NI = No inhibition.

The compounds tested displayed moderate to weak inhibition for the corresponding enzymes. The *N*-benzyl derivatives were found to be weaker inhibitors as compared to the free amines.

Chapter-III: Experimental.

This chapter gives detailed experimental procedures and spectral characterization of all new compounds.

1. Introduction to Glycosidases and their mechanisms:

Enzymes, one of the four major classes of nature's biopolymers, play fundamental roles in life's processes. In particular, glycosidases and glycosyl transferases are ubiquitous macromolecules which catalyze glycosyl group transfer reactions that assemble, trim and shape bioactive glycoprotein and glycolipid conjugates. Overall, these processes involve cleavage of the glycosidic bond linking a sugar's anomeric carbon with an oligo- or polysaccharide or a nucleoside diphosphate group. The liberated glycosyl group is further transferred to water (by glycosidases) or to some other nucleophilic acceptor (by transferases).

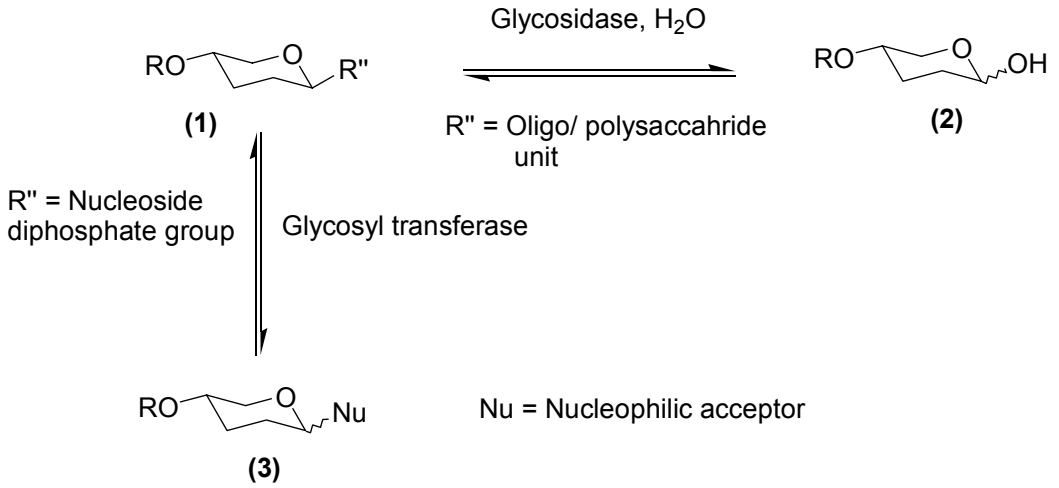


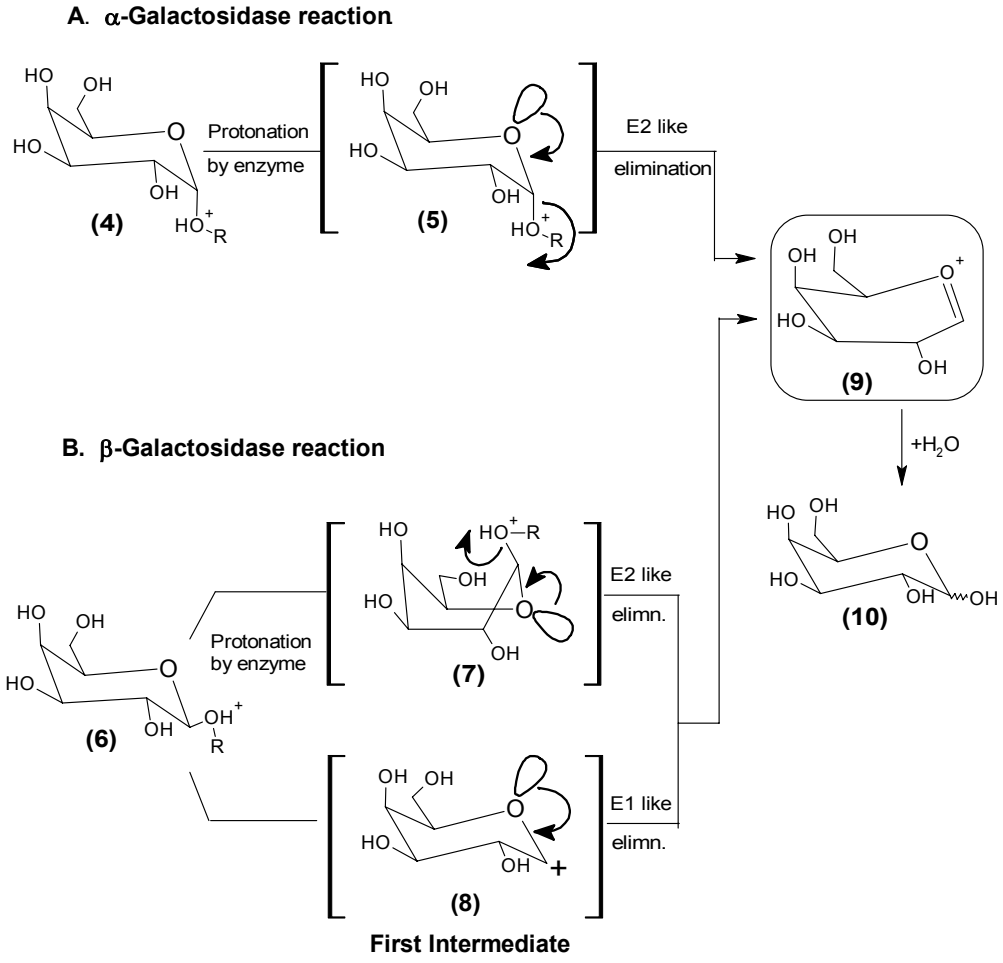
Figure 1.

Glycosidases, the enzymes responsible for the biosynthesis of oligosaccharides, play a fundamental role in biochemistry and metabolism. A primary classification of glycosidases can be done based on the position of the glycosidic bond that is cleaved by the enzyme. Exoglycosidases remove sugars one at a time, from the non-reducing end of an oligo or polysaccharide and are involved in the breakdown of starch and glycogen, the processing of eucaryotic glycoproteins, the biosynthesis and modification of glycosphingolipids and the catabolism of peptidoglycans and other glycoconjugates. Endoglycosidases cleave

interior glycosidic bonds within polysaccharides and are involved in the catabolism and clearance of the aged glycoproteins. These enzymes also catalyze the alteration of bacterial and plant cell walls as well as the hydrolysis of highly insoluble structural polysaccharides like chitin and cellulose.

Glycosidases are more rigorously classified based on the stereochemistry of the anomeric glycosidic bond that they cleave. Enzymes catalyzing the cleavage of a α-glycosidic bond are termed as α-glycosidases while those cleaving a β-glycosidic bond are termed as β-glycosidases.

Depicted below (Scheme 1) is a typical glycosidase reaction mechanism.



Scheme 1

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 antiperiplanar, cooperatively facilitating the glycosidic bond cleavage reaction.[1]

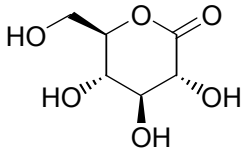
In the case of the β-glycosidase reaction, if the enzyme proceeds via an E2 type mechanism, similar to that of the α-glycosidases, the protonated substrate **6** has to go through a highly strained intermediate **7** that may not favor further reaction. Therefore, in the case of a β-glycosidase reaction, the positively charged aglycon leaves via an E1 like mechanism, involving the glycosyl cation **8**, further stabilized by the ring oxygen to give **9**. Thus, as seen in Scheme 1, although the final reaction intermediate in both the reaction mechanisms is the same flattened, half chair oxocarbenium ion **9**, the first intermediate in the case of β-glycosidase reaction differs with respect to the position of charge development.

Glycosidases are also classified on the basis of the stereochemical outcome of the newly formed anomeric bond. The enzymatic cleavage of the glycosidic bond liberates a sugar hemiacetal with either the same configuration as the substrate (retention) or less commonly, the opposite configuration (inversion). Based on this criterion glycosidases are classified as retaining or inverting glycosidases.

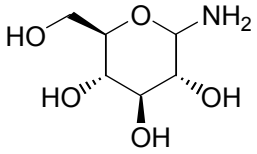
As is the case with any other enzyme, any chemical entity that is capable of mimicking either the charge or shape (or both) of the substrate or that of any of the transition states, can act as a reversible inhibitor of that particular glycosidase. These entities are termed as ***glycosidase inhibitors*****.**

2. Inhibitors of Glycosidases:

Historically, the first glycosidase inhibitors were the families of the monosaccharide-derived δ-aldonolactones (such as D-gluconolactone **11**),[2] and glycosyl amines (1-amino-1-deoxy pyranoses such as D-glucosyl amine **12**).[3]



(11)



(12)

Figure 2

Although, lacking long-term stability in aqueous solution, these families of compounds typically display competitive inhibition against glycosidases whose substrates they most closely resemble. 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)[4] and the discovery of such a natural product (nojirimycin **17**)[5], over three dozen naturally occurring iminosugars have been identified and many additional analogues and homologs have been synthesized, opening a dynamic research area.

A wide variety of structural motifs characterize glycosidase inhibitors. Prominent amongst them are:

(a) The nitrogen heterocycles incorporating four to seven membered rings as well as bicyclics like pyrrolizidines, indolizidines and nortropanes.

(b) The aminocyclitols like trehazolin, acarbose, mannostatins and allosamidins.

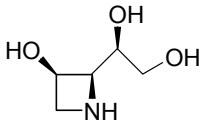
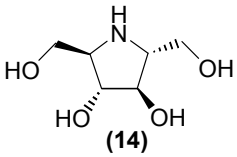
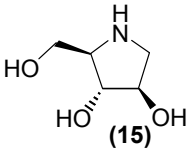
(c) Entities incorporating a nitrogen in more than one position, including the one in the ring, e.g.; Nagstatins, Siastatins, etc.

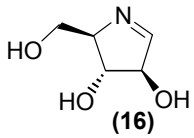
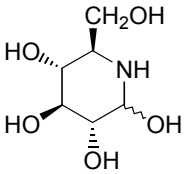
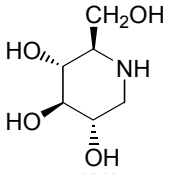
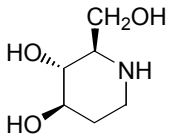
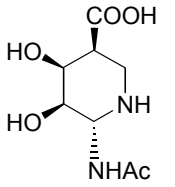
Several comprehensive reviews and accounts on glycosidases and glycosidase inhibitors have been published, covering various subsections of the field.[6] These “sugar-shaped alkaloids” are widespread in plants and microorganisms[7] and are

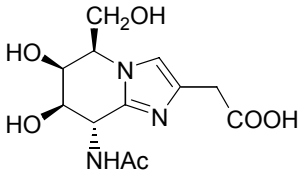
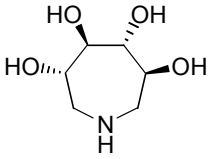
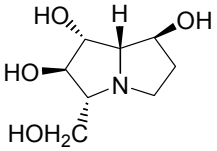
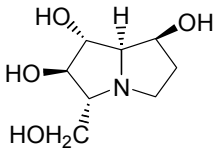
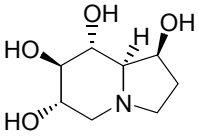
believed to bind to the active site of the glycosidases by closely mimicking the charge and shape of the transition state of the glycosidic cleavage reaction.

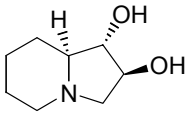
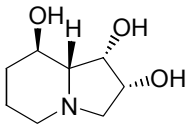
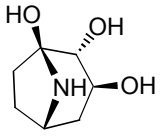
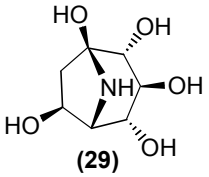
Some of the natural and synthetic glycosidase inhibitors are being depicted below in the tabular form. In order to keep this thesis in proper perspective, emphasis has been given to those compounds possessing a nitrogen atom in the ring.

Figure 3

Inhibitor	**Source**	**Activity**
		(Only the most inhibited enzymes are being listed)
(1) Four Membered Rings:		
 **(13)** 1,3-dideoxy-1,3-imino-L-xylitol	Synthetic Compound.[8]	Inhibits amyloglucosidase from Rhizopus mold. (K_i = 7.6μM, IC_{50} = 4.0 μM).[8]
(2) Five Membered Rings:		
 **(14)** **DMDP**: (2*R*,3*R*,4*R*,5*R*)-bis(hydroxymethyl)-dihydroxy pyrrolidine	Isolated from leaves of *Derris elliptica.*[9]	Inhibits α-glucosidase from *Bacillus stearothermophilus*. (K_i = 0.03 μM at pH 6.8).[10a] Inhibits trehalase from *corynebacterium sp.* (IC_{50} = 0.35 μM).[10b]
 **(15)** **DAB 1** 1,4-dideoxy-1,4-imino-D-arabinitol	Isolated from fruits of *Angylocalyx boutiqueanus.*[11]	Inhibits α-glucosidase from yeast. (IC_{50} = 0.18 μM at pH 6.8).[12]

Inhibitor	Source	Activity
 **(16)** **Necticine**	Isolated from culture broth of fungus *Nectria ludica.*[13]	Inhibits α-glucosidase from yeast. (IC_{50} = 0.08 μM).[14]
(3) Six Membered Rings:		
 **(17)** **Nojirimycin**	Isolated from *Streptomyes roseochromogenes.*[5]	Inhibits β-glucosidase from *Aspergillus wentii.* (K_i = 0.07 μM at pH 5.0) Inhibits β-glucosidase from sweet almond. (K_i = 0.9 μM at pH 5.0).[15]
 **(18)** **1-deoxynojirimycin (Moranoline)**	First synthesized.[4] Later was isolated from roots of Mulberry trees.[16]	Inhibits α-glucosidase from rice. (K_i = 0.01 μM at pH 6.0)[17] Inhibits α-glucosidase from *Bacillus stearothermophilus* (K_i = 0.44 at pH 6.8).[10]
 **(19)** **Fagomine**	Isolated from seeds of *Fagopyrum esculentum.*[18]	Inhibits α-galactosidase from rat intestine. (IC_{50} = 15 μM at pH 5.8).[19]
 **(20)** **Siastatin B**	Isolated from *Streptomyces verticillus var. quantum.*[20]	Inhibits β-glucuronidase from bovine liver (IC_{50} = 16 μM).[21a] Inhibits N-acetyl neuraminidase from *streptococcus*. (IC_{50} = 29 μM).[21b]

Inhibitor	Source	Activity
 **(21)** **Nagstatin**	Isolated from *Streptomyces amakusaesis.*[22]	Inhibits N-Ac-β-glucosamindine from bovine kidney (IC_{50} = 0.01 μM at pH 5.0).[23a, b] Also inhibits N-Ac-β-glucosamidine from hog kidney (K_i = 0.017 μM at pH 4.5).[23c]
(4) Seven Membered Rings:		
 **(22)** (3*S*,4*R*,5*R*,6*S*)-3, 4, 5, 6-tetrahydroxyazepane	Synthetic molecule.[24]	Inhibits α-glucosidase from *Bacillus stearothermophilus* (K_i = 4.8 μM at pH 6.8).[10a]
(5) Pyrrolizidines:		
 **(23)** **Alexine**	Isolated from *Alexa leiopetala* (plate 8).[25a]	Inhibits amyloglucosidase from *aspergillus niger*. (IC_{50} = 6 μM at pH 5.0).[25b]
 **(24)** **Australine**	Isolated from the seeds of *Castanospermum Australae.*[26]	Inhibits amyloglucosidase from *aspergillus niger*. (K_i = 7 μM).[26]
(6) Indolizidines:		
 **(25)** **Castanospermine**	Isolated from the seeds of *Castanospermum Australae.*[27]	Inhibits α-glucosidase from rice (K_i = 0.015 μM).[28a] Inhibits sucrase from caco-green coffee beans cell line. (K_i = 0.0026 μM at pH 8.0).[28b]

Inhibitor	Source	Activity
 **(26) Lentiginosine**	Isolated from *Astralagus lentiginous*.[29]	Inhibits amyloglucosidase from *aspergillus niger.* (K_i = 2.0 at pH 5.0).[30]
 **(27) Swainsonine**	Isolated from legumes of *Swainsona Canescens.*[31]	Inhibits α-mannosidase from human liver lysosomal (K_i = 0.07 at pH 4.0).[32a] Inhibits α-mannosidase from human liver, golgi II (IC_{50} = 0.04 μM at pH 5.7).[32b]
(7) Nortropanes:		
 **(28) Calystegine A_3**	Isolated from root cultures of *Calystegia sepium.*[33]	Inhibits β-glucosidase from *caldocellum saccharolyticum.* (K_i = 12 μM, IC_{50} = 37 μM).[34]
 **(29) Calystegine C_1**	Isolated from *M. bombysis, M. alba.*[35]	Inhibits β-glucosidase from sweet almonds. (K_i = 0.45 μM, IC_{50} = 0.82 μM).[34]

3. Biological significance of glycosidase inhibitors:

The tremendous potential of glycosidase inhibitors in studying the biological functions of oligosaccharides has resulted in opening up new avenues in glycobiology.[36] The capability of polyhydroxy alkaloids to disrupt the general cellular function of glycoprotein processing promises therapeutic potential for the treatment of various carbohydrate related disorders. Investigation of these alkaloids for

therapeutic potential has so far concentrated on three major disease states i.e., for treatment of cancer and inhibition of metastatis, as anti-diabetic drugs and for anti-viral activities.

Swainsonine (**27**) has received particular attention as an anti-metastatic agent. Clinical trials in humans with very advanced malignancies showed that lysosomal α-mannosidase and Golgi mannosidase II were inhibited and some improvement in clinical status occurred.[37] Castanospermine (**25**) has also been reported to suppress the metastasis in the mice but experiments with this alkaloid have not been as extensive as those with swainsonine.[38]

Castanospermine and 1-deoxynojirimycin (**18**) have been shown to be capable of suppressing the infectivity of a number of retroviruses, including the HIV responsible for AIDS.[39a] This effect is a consequence of disruption of glycoprotein processing enzyme resulting in the changes of the structure of the glycoprotein coat of the virus. Cellular recognition of the host is, thus, prevented and syncytum formation is suppressed. To reduce water-solubility (causative of rapid excretion), 6-*O*-butyryl castanospermine and *N*-butyl-deoxynojirimycin have been synthesized and both these compounds have undergone clinical trials against AIDS in humans, either alone or in combination with AZT.[39b]

Another structural modification of deoxynojirimycin, the *N*-hydroxyethyl derivative, miglitol, an inhibitor of α-glucosidase, has been clinically evaluated and released as an antidiabetic drug in insulin and non-insulin dependent diabetes. The alkaloid was shown to potently inhibit glucose induced insulin release and also suppressed the islet α-glucoside hydrolase activity, thus, controlling post-glycemia.[40] Another glycosidase inhibitor, voglibose, a synthetic derivative of

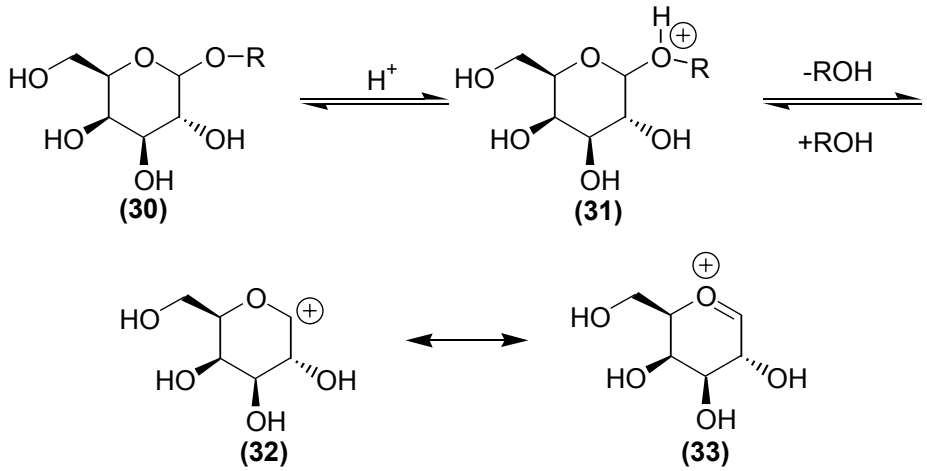
valiolamine is also being marketed as an anti-diabetic.[7] Acarbose, a naturally occurring glycosidase inhibitor, has also been used as an anti-diabetic agent.[7]

The ability of polyhydroxy alkaloid glycosidase inhibitors to prevent cellular recognition has resulted in their evaluation for clinical situations where suppression of an immune response is desirable. Thus, *in vivo* experiments have shown that castanospermine can be used as an immunosuppressive drug, promoting heart and renal allograft survival in rats.[41]

Glycosidase inhibitors are also showing tremendous promise as new therapeutics for lysosomal storage diseases like Gaucher's disease and Fabry disease.[7]

4. Development of 1-*N*-iminosugars as glycosidase inhibitors:

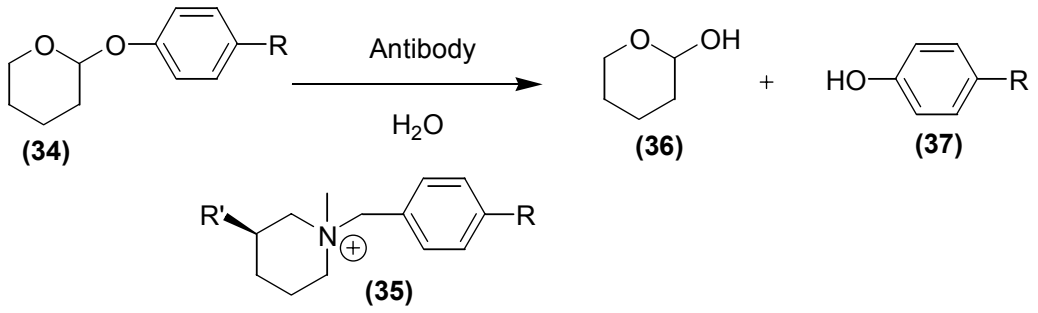
As depicted below, there are three important reaction intermediates **31**, **32**, and **33** depending upon the position of the charge buildup during the glycoside hydrolysis. It was observed that a compound that could resemble any of the intermediates **31 - 33** should be an inhibitor of the respective glycosidases.



Scheme 2

There are a number of compounds that fulfill this criterion. One group of compounds belongs to the nojirimycin class. These compounds resemble monosaccharides but the ring oxygen has been replaced with a nitrogen atom. Thus, if protonated at the basic nitrogen atom, these compounds become the analogues of **33**. Glucosamidines[6a] are a group of glycosidase inhibitors, designed by Ganem and co-workers that resemble **33**. Another group of glycosidase inhibitors belongs to the glycosyl amine class, which upon protonation, resemble **31**. Acarbose and similar compounds when protonated at nitrogen, also resemble intermediate **31**.

Until the last decade, no glycosidase inhibitor that was an analogue of **32** was known. It was long interpreted that **32** was insignificant in the glycoside cleavage process and in many theoretical discussions of glycosidic cleavage, **32** was indeed, ignored at the expense of **33**. In 1991, Reymond and co-workers reported isolating a catalytic antibody, (using transition state analogue **35** as a hapten) that could catalyse the hydrolysis of a tetrahydropyranyl ether, a simple model of a glycosidic bond.[42]



Scheme 3

Compound **35** was considered an analogue of a carbocation at the anomeric center and in principle, an analogue of ion **32**, except for the lack of hydroxyl groups. This report suggested that analogues of **32** could be good

transition state analogues of glycoside cleavage and since **32** was a significant transition state in the case of a β-glycosidase reaction; analogues of this would be good inhibitors of β-glycosidases. This finding led to a spurt of activity of creative chemical design of anomer selective β-glycosidase inhibitors led by the groups of Bols,[43] Ichikawa[52] and Nishimura.[6g] This new class of designed molecules was termed as 1-azasugar or 1-*N*-iminosugar class of glycosidase inhibitors.

The first 1-*N*-iminosugar synthesized was the D-glucose type 1-*N*-iminosugar, isofagomine (**38**). Designed by Bols and co-workers,[43] this molecule was nearly a perfect mimic of D-glucose and as expected, turned out to be an extremely potent inhibitor of β-glucosidase (sweet almonds, K_i = 0.11 μM).

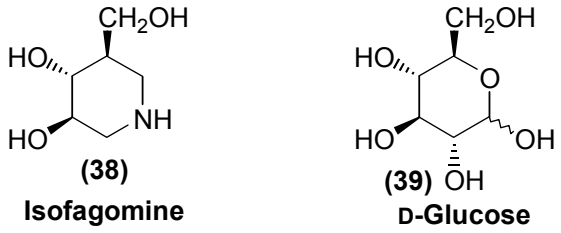
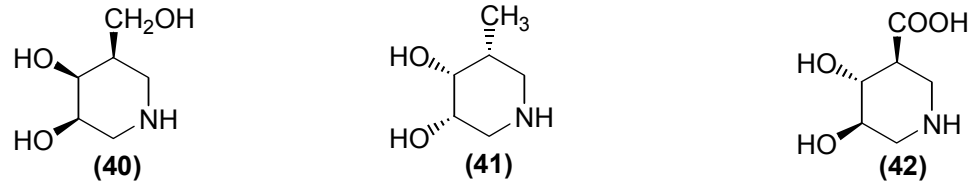


Figure 4

Subsequently, extremely potent and selective β-glycosidase inhibitors were designed and synthesized. The most prominent amongst them are depicted below (Figure 5).



Isogalactofagomine Isofucofagomine Isoglucuronofagomine

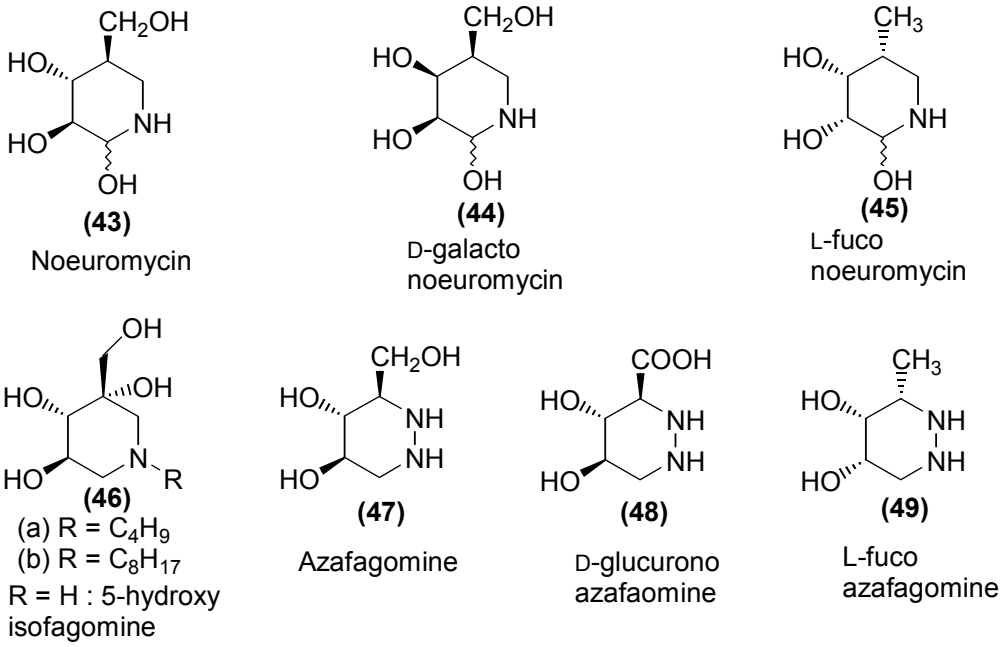


Figure 5

Isogalactofagomine (**40**) was designed and synthesized by Ichikawa and co-workers and was found to inhibit β-galactosidase in the nanomolar range (*Aspergillus oryzae*, K_i = 4.1 nM at pH 6.8).[44] Isofucofagomine (**41**) was simultaneously synthesized by the groups of Bols and Ichikawa and was an extremely potent inhibitor of α-fucosidases (bovine liver, IC_{50} = 26μM),[45] (human placenta, K_i = 6.4 μM).[46] Isoglucuronofagomine (**42**) was also designed and synthesized by the group of Ichikawa and exhibited nanomolar inhibition of β-glucuronidase (bovine liver, K_i = 79 nM at pH 5.0).[47] Noeuromycin (**43**), the 2-hydroxy analogue of isofagomine was designed and synthesized by Bols and co-workers and was found to be a better mimic of D-glucose as compared to isofagomine and inhibited glucosidases in the nanomolar range; (β-glucosidase from sweet almonds, K_i = 69 nM), (α-glucosidase from yeast, K_i = 22 nM).[48] The high inhibitory activity towards α-glucosidase was attributed to the 2-hydroxy group.

In a similar manner, D-galactonoeuromycin (**44**) and L-fuconoeuromycin (**45**) were synthesized and both exhibited nanomolar inhibition of the respective glycosidases.[48] Also notable is the compound **46** (5-hydroxy isofagomine), the N-alkyl derivatives of which (butyl and octyl) were found to be inhibitors of glycolipid biosynthesis.[49] *N*-Butyl-5-hydroxy isofagomine (**46a**) inhibited 50% of phorbol ester (TPA)-induced differentiation of HL-60 cells at 0.5 mM. It also inhibits 40 % of UDP-glucose:N-acylsphingosine glucosyltransferase (from rat brain) activity at 5 mM. *N*-Octyl-5-hydroxy isofagomine (**46b**) inhibits 50 % of the same enzyme activity at 1mM. Bols and co-workers also designed azafagomine (**47**) which mimicked the transition states of both α- as well as β- glycosidase reaction.[50a] This compound along with the D-glucurono (**48**) and L-fuco (**49**) analogs when compared with the isofagomines and noeuromycins, exhibited slightly poorer inhibitory properties for the respective glycosidases.[50b]

Driven by the promising biological activities and contiguous functionalities, these designed piperidines have been in the limelight for synthetic organic chemists. The foregoing section would focus on some of the notable synthetic approaches towards these molecules.

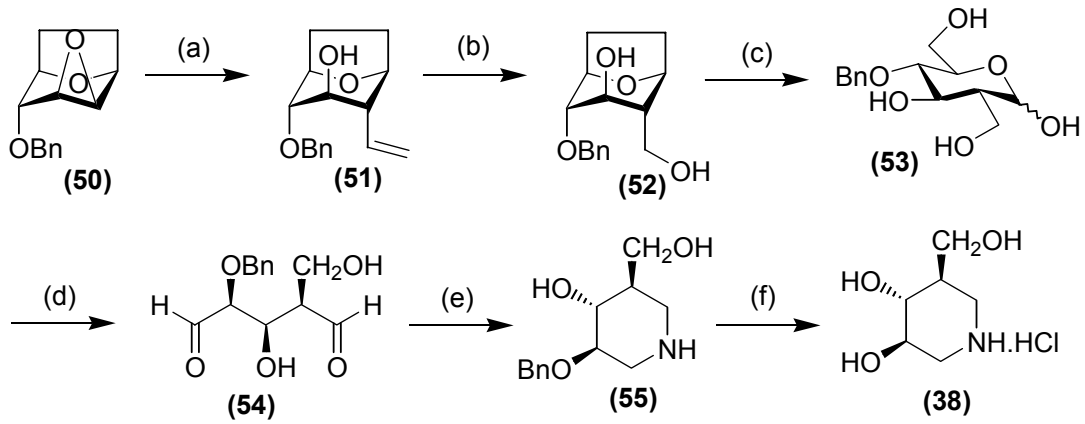
5. Synthetic approaches towards 1-*N*-iminosugars:

5.1 Approaches towards Isofagomine:

5.1.1 Bols and co-workers:

Approach I: (*Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1778-1779)[43]

Bols and co-workers first synthesized Isofagomine in ten steps with an overall yield of 6%. The synthesis started from the Cerny epoxide **50**, obtained in four steps from levoglucosan.

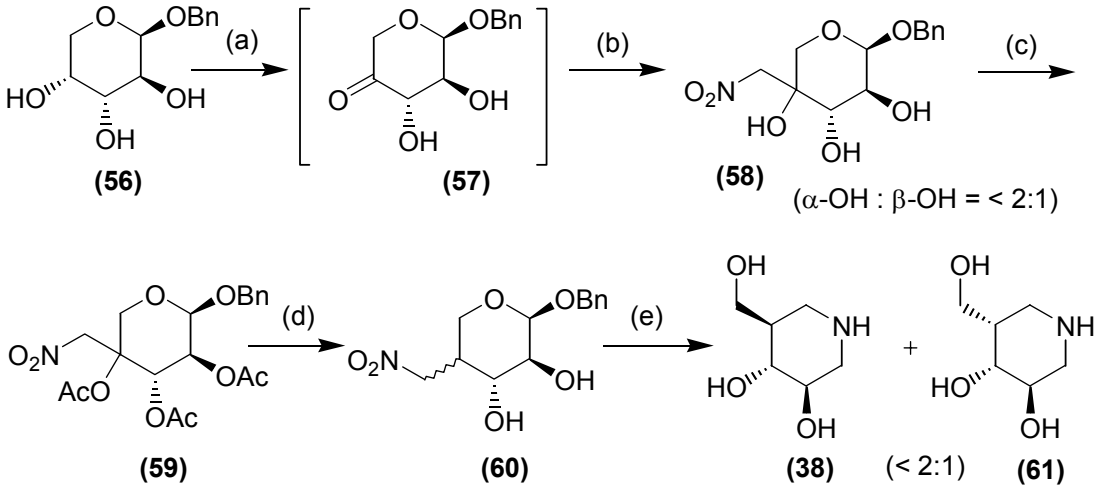


Scheme 4

***Reagents and conditions**: (a) CH_2=CHMgBr, THF, 87 %; (b) (i) O_3, EtOH, 0 ° C; (ii) $NaBH_4$, EtOH/ H_2O, 63 %; (c) 1M H_2SO_4, reflux, 98 %; (d) $NaIO_4$, H_2O/ MeOH, 45 ° C, 87 %; (e) NH_3, EtOH, H_2, Pd/C, 35 atm, 20 ° C, 78 %; (f) HCl (aq), H_2, Pd/C, 1 atm, 93 %.*

Approach II: (*Chem. Eur. J.* **2001**, *7*, 3744-3747)[51]

Recently, isofagomine has been synthesized from **56** via a much shorter route (five steps from **56**, in about 30% yield); albeit with extremely poor diastereoselectivity (dr = < 2:1).



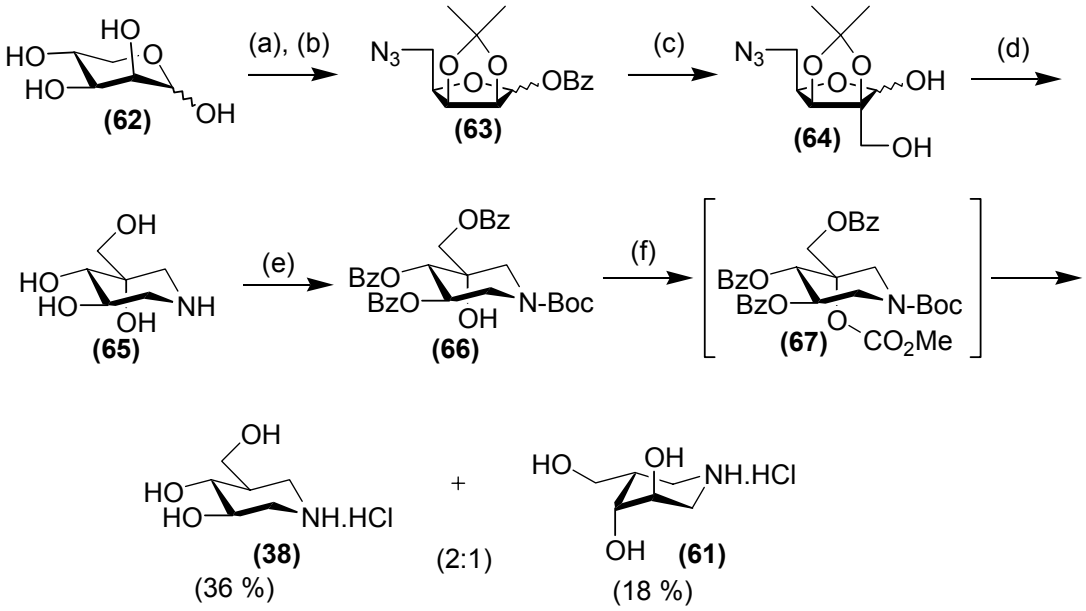
Scheme 5

Reagents and conditions: *(a) $(Bu_3Sn)_2O$, Br_2, $CHCl_3$, 80-95 %; (b) CH_3NO_2, TEA, 55-65 %; (c) Ac_2O, pTSA, 82 %; (d) $NaBH_4$, EtOH then NaOMe, 96 %; (e) H_2, Pd/C, MeOH, then chromatographic separation, 85-90 %.*

5.1.2 Ichikawa and co-workers:

Approach I: (*J. Am. Chem. Soc*. **1997**, *120*, 3007-3018)[52]

Isofagomine was synthesized in fourteen steps and in about 2% overall yield starting from D-Lyxose **62**. The diastereoselection in the final step was rather low (dr = 2:1).



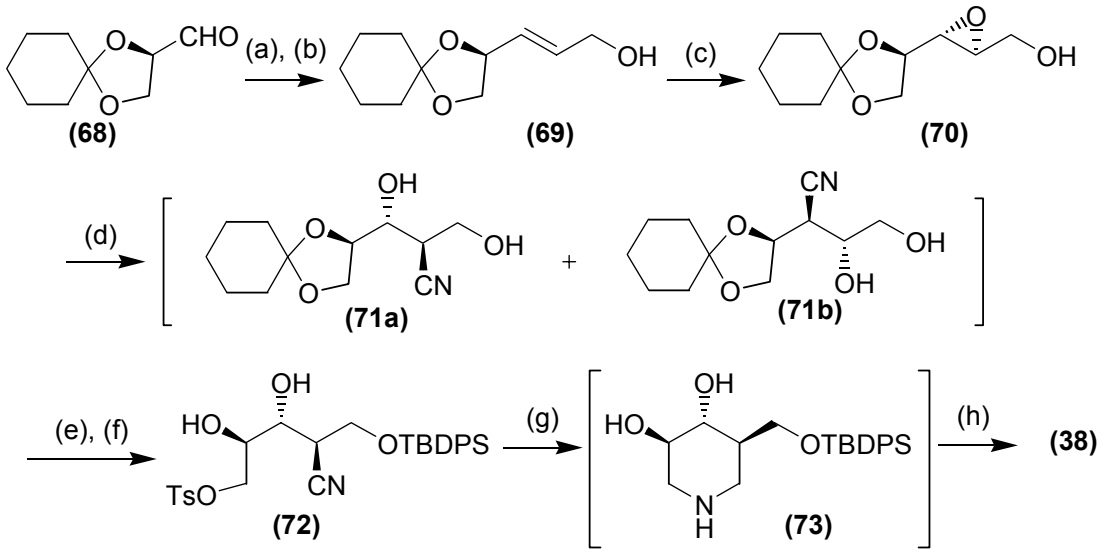
Scheme 6

Reagents and conditions: *(a) (i) Acetone-conc. H_2SO_4, rt, overnight; (ii) TsCl, py, 0 ° C to rt, overnight; (iii) BzCl, py, 0 ° C to rt, overnight, 41 % over three steps; (b) NaN_3, DMSO, 100 ° C, overnight, 74 %; (c) (i) NaOMe, MeOH, rt; (ii) K_2CO_3, 30 % HCHO-MeOH, 85 ° C, overnight, 80-90 %; (d) (i) H_2, $Pd(OH)_2$, MeOH, rt, overnight; (ii) 1N HCl; (e) (i) $(Boc)_2O$, TEA, MeOH, rt, overnight, 49%; (ii) BzCl, py, 0 ° C to rt, overnight, 41 % overall; (f) (i) MeOCOCOCl, DMAP, CH_3CN; (ii) Bu_3SnH, 1,1'-azobis (cyclohexane carbonitrile), toluene,*

100 ° C; (iii) NaOMe, MeOH, 2h, rt; (iv) 1N HCl, overnight; (v) Silica chromatography with iPrOH/ H_2O/ NH_4OH (7:2:1).

Approach II: (*J. Org. Chem.* **2000**, *65*, 2599-2602).[53]

An improved synthesis of isofagomine was later achieved in nine steps and in 25 % overall yield starting from readily available (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde **68**.

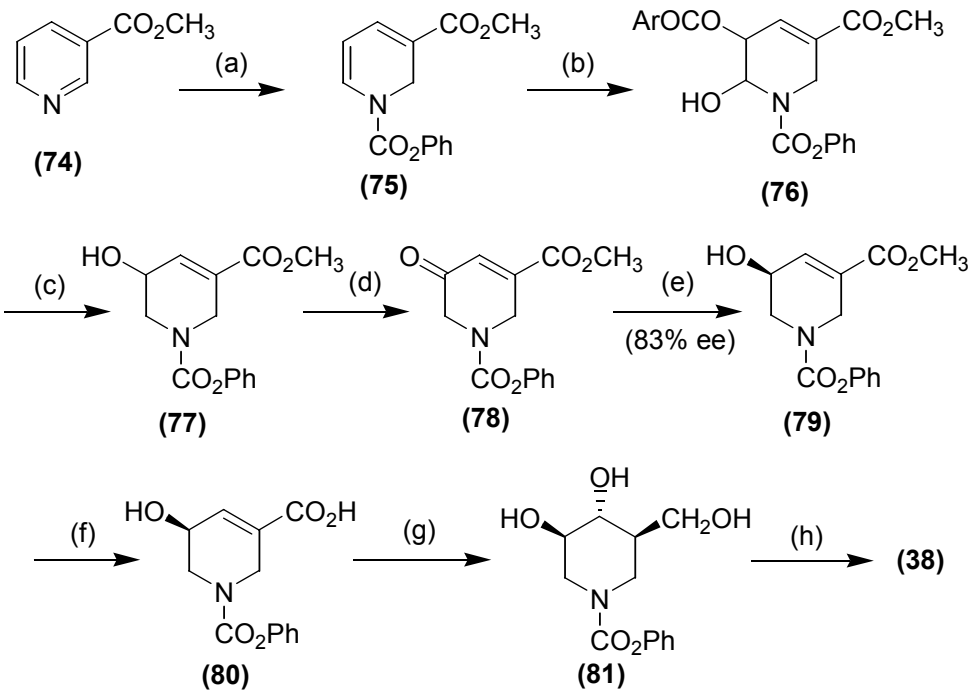


Scheme 7

Reagents and conditions: *(a) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene-THF (E:Z = 10:1), 83 %; (b) DIBAL, DCM, 92 %; (c) $Ti(O\text{-}iPr)_4$, (+)-diethyl tartrate, tBuOOH, DCM, 90 %; (d) KCN, Bu_4NI, $Ti(O\text{-}iPr)_4$, DMSO; (e) TBDPSCl, Imidazole, DMF, 88 % over two steps; (f) (i) 80 % AcOH; (ii) TsCl, py, 70 % over two steps; (g) H_2, Raney Ni, EtOH; (h) 2N HCl, 58 % over two steps.*

5.1.3 Ganem's approach: (*Org. Lett*. **2001**, *3*, 201-203).[54]

Ganem and co-workers synthesized isofagomine in an overall yield of 49%, starting from methyl nicotinate **74**, using Fowler reductions as their key step. The route employing eight steps from **74** had a moderate enantiomeric excess (83%).



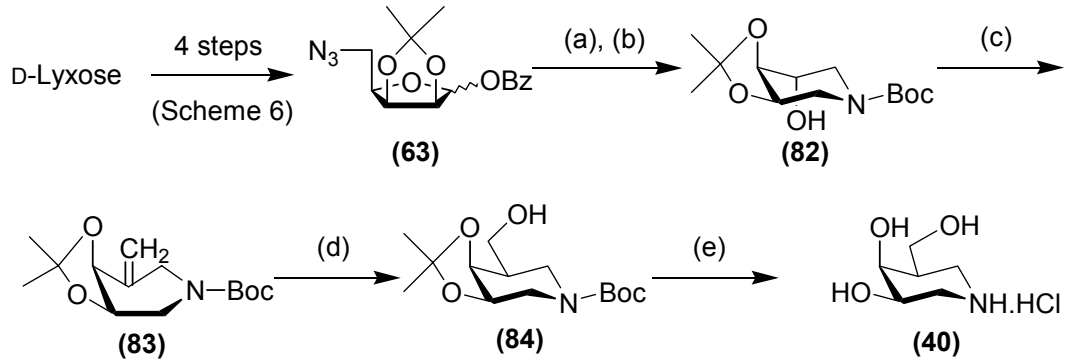
Scheme 8

Reagents and conditions: *(a) $NaBH_4$, PhOCOCl, MeOH, -78 °C, 97 %; (b) MCPBA, DCM, -70 °C to 0 °C, 92 %; (c) TMSOTf, BH_3-THF, -70 °C to 0 °C; (d) CrO_3, acetone; (e) LAH, (-)-N-Me-Ephedrine, 85 %; (f) 1N HCl, reflux, 99 %; (g) BH_3-THF, H_2O_2, NaOAc, 70 %; (h) LiOH, 95 %.*

5.2 Approaches towards Isogalactofagomine:

5.2.1 Ichikawa's approach: (*J. Am. Chem. Soc*. **1997**, *120*, 3007-3018)[44, 52]

Ichikawa and co-workers first designed and synthesized isogalactofagomine from D-Lyxose in eleven steps with an overall yield of 6 %.

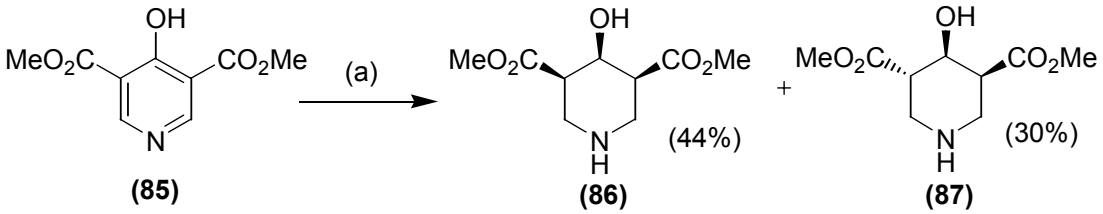


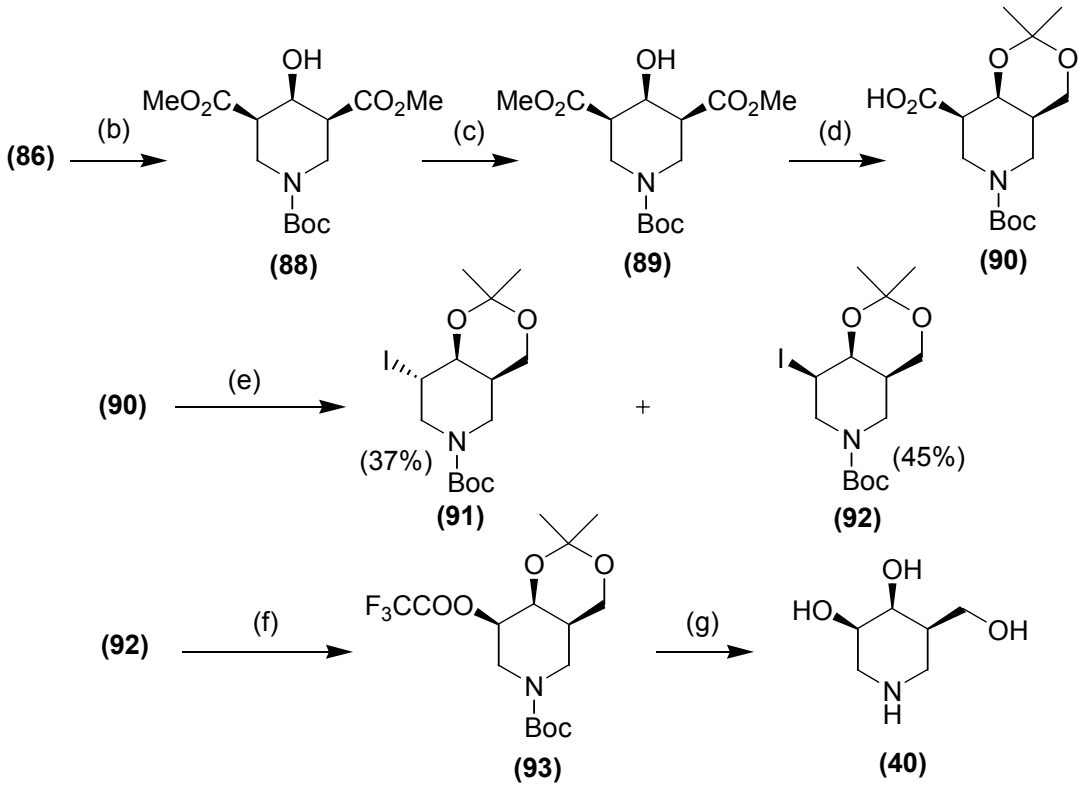
Scheme 9

Reagents and conditions: *(a) (i) NaOMe, MeOH, 30 min; (ii) H_2, $Pd(OH)_2$, MeOH, rt, overnight; (b) $(Boc)_2O$, TEA, MeOH; (c) (i) Swern oxidation, -78 ° C, 48 % over four steps; (ii) n-BuLi, Ph_3PCH_3Br, DME, 0 ° C to rt, overnight, 77 %; (d) 9-BBN, THF, 0 ° C to rt, 3 h, then NaOH, 30 % H_2O_2, rt, overnight, 56 %; (e) 1N HCl, rt, overnight, 94 %.*

5.2.2 Bols' approach: (*J. Org. Chem.* **2000**, *65*, 7432-7437).[55]

Bols and co-workers used a chemoenzymatic approach for the synthesis of Isogalactofagomine. The synthesis, starting from **85** utilized nine steps and had an overall yield of 14%.





Scheme 10

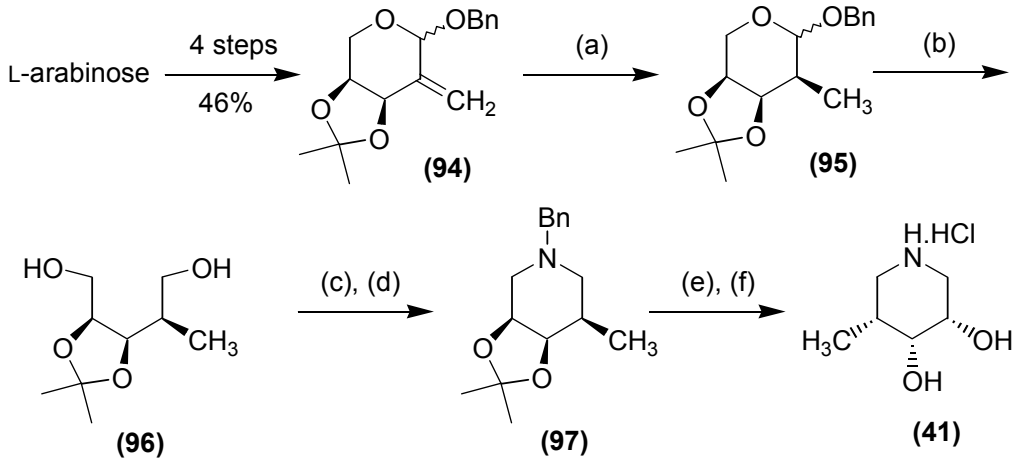
Reagents and Conditions: *(a) PtO_2, MeOH, H_2, 40 atm, 60 °C, 5 h; (b) $(Boc)_2O$, TEA, 91 %; (c) Lipase M, H_2O, 95 %, 99 % ee; (d) (i) BH_3.THF, 0 °C, 99 %; (ii) $Me_2C(OMe)_2$, TsOH, 93 %; (iii) LiOH-H_2O, 87 %; (e) $PhI(OAc)_2$, I_2, CCl_4, hν ; (f) CF_3CO_2Ag, EtOAc, 95 %; (g) TFA, H_2O, 100 %.*

5.3 Approaches towards Isofucofagomine:

Isofucofagomine was simultaneously conceived and synthesized by the groups of Ichikawa and Bols.

5.3.1 Bols' approach:(*Chem. Commun*. **1996**, 2649-2650)[46]

Bols and co-workers derived isofucofagomine from L-arabinose in six steps with an overall yield of 12%.

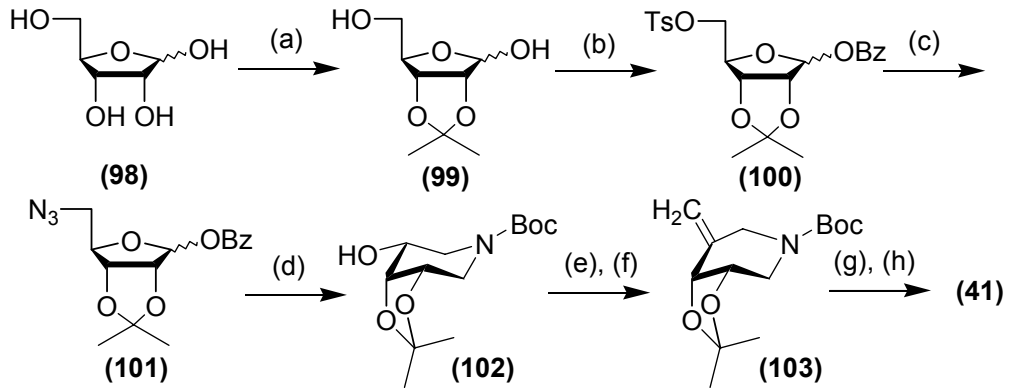


Scheme 11

Reagents and conditions: *(a) Pd/C, NH_3, H_2, 1 atm, 20 ° C, 18 h, 95-97%; (b) Na (8 equiv), NH_3, DME, -78 ° C, 3 h, 81 %; (c) TsCl, py, 5 ° C, 21 h, 62 %; (d) $BnNH_2$, 40 ° C, 2 days, 76 %; (e) TFA-H_2O, 1.5 h, rt; (f) 1M HCl, H_2, Pd/C, 1 atm, 3 days, 69 %.*

5.3.2 Ichikawa's approach: (*Bioorg. Med. Chem. Lett.* **1996**, *6*, 553-558)[45]

The group of Ichikawa synthesized isofucofagomine in eleven steps starting from D-Ribose **98**, with an overall yield of 11%,.



Scheme 12

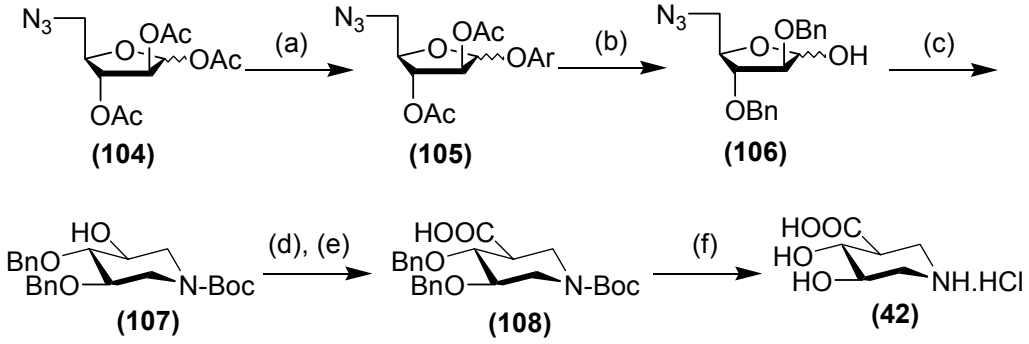
Reagents and conditions: *(a) 2,2-dimethoxypropane, TsOH, acetone, rt, 12 h; (b) (i) TsCl, py, 0-5 °C, 10 h; (ii) BzCl, py, 0-5 °C, 1 h, 48% over three steps; (c) NaN_3, DMF, 60-65 °C, 4h, 91 %; (d) (i) NaOMe, MeOH, MeOH, rt, 10 min; (ii) H_2, $Pd(OH)_2$, MeOH, H_2O, rt, 12 h, 75 % over 2 steps; (e) (i) BocON, TEA, H_2O-dioxane, rt, 8 h, 73 %; (ii) Swern oxidation, -70 °C, 30 min, 80 %; (f) Ph_3PCH_3Br, n-BuLi, DME, 0 °C to rt, 8 h, 77 %; (g) H_2, Pd/C, MeOH, rt, 5 h, 82 %; (h) 1N HCl, rt, 12 h, 90-95 %.*

5.4 Approaches towards Isoglucuronofagomine:

5.4.1 Ichikawa and co-workers:

Approach I: (*J. Am. Chem. Soc.* **1997**, *120*, 3007-3018)[47, 52]

The first design and synthesis of isoglucuronofagomine was achieved in thirteen steps and 5% yield from **104**, derived from D-arabinose.



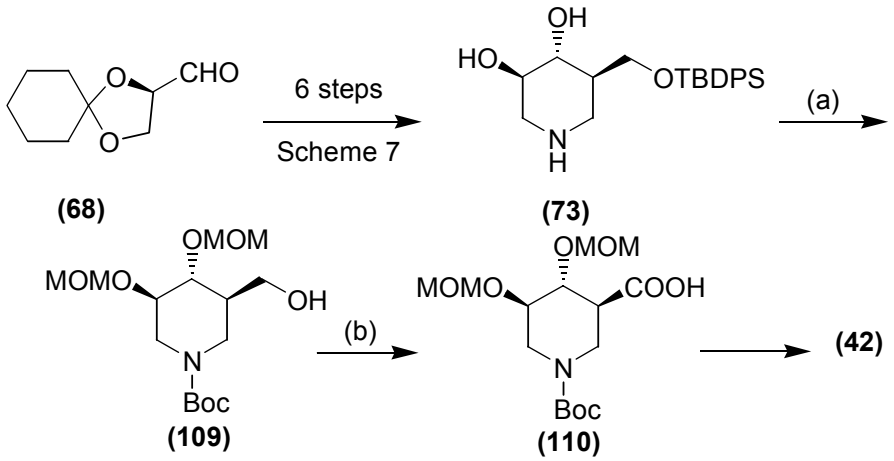
Scheme 13

Reagents and conditions: *(a) p-$MeOC_6H_4OH$, TMSOTf, DCM, rt, 6 h, 84 %; (b) (i) NaOMe, MeOH, rt, 10 min; (ii) BnBr, NaH, DMF, 0 °C to rt, 12 h, 99 %; (iii) CAN, CH_3CN-H_2O (5:1), 0 °C to 5 °C, 5 min, 89 %; (c) (i) H_2, Lindlar catalyst, MeOH, rt, 18 h, 67 %; (ii) $(Boc)_2O$, TEA, MeOH, 0 °C to rt, 8 h, 75 %; (d) (i) Swern oxidation, -70 °C, 78 %; (ii) Ph_3PCH_3Br, LiHMDS, DME, 0 °C to rt, 18 h, 81 %; (e)(i) 9-BBN, THF, 0 °C to rt, 12 h, then 10 % NaOH, H_2O_2, 0 °C to rt, 12 h, dr = 5:1, quant; (ii) Swern oxidation, -70 °C; (iii) $NaClO_2$, H_2O_2,*

NaH_2PO_4, CH_3CN-H_2O (1:1), 0 °C to rt, 1 h, 69 % in two steps; (f) (i) H_2, $Pd(OH)_2$, EtOH-EtOAc, rt, 18 h; (ii) 1N HCl ;(iii) Silica column chromatography and gel filtration , 32 %.

Approach II: (*J. Org. Chem.* **2000**, *65*, 2599-2602)[53]

Subsequently, an improved synthesis of isoglucuronofagomine was developed (twelve steps, 22 % yield) starting from the readily available (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde **63**.

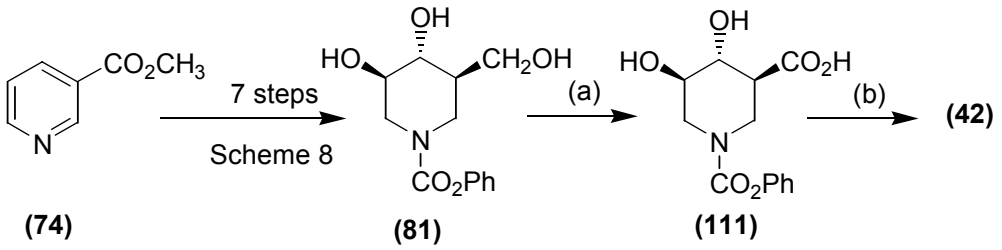


Scheme 14

Reagents and Conditions: *(a) (i) $(Boc)_2O$, TEA, MeOH, 12 h; (ii) MOMCl, iPr_2NEt, 0 °C to rt, DCM, 30 h; (iii) TBAF, THF, 4 h, 74 %; (b) (i) Swern oxidation, -78 °C; (ii) H_2O_2, $NaClO_2$, $NaHPO_4$, CH_3CN-H_2O, 82 % over two steps; (iii) 3 N HCl, 89 %.*

5.4.2 Ganem's approach (*Org. Lett*. **2001**, *3*, 201-203)[54]

Ganem and co-workers utilized Fowler reductions for their nine-step synthesis of isoglucuronofagomine. The overall yield of the synthesis was 40% but the enantiomeric excess was a moderate 83%.



Scheme 15

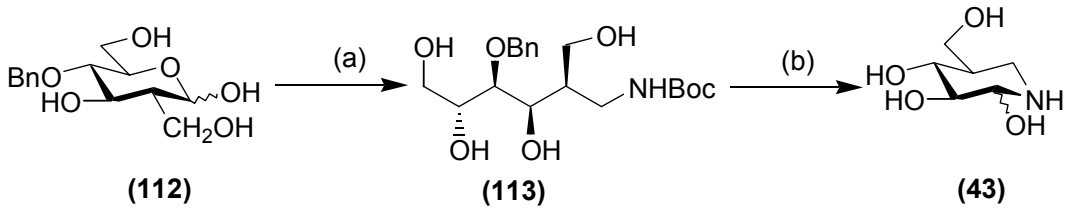
Reagents and conditions: *(a) Pt, O_2, 80 %; (b) LiOH, 95 %.*

5.5 Approaches towards Noeuromycin and analogs:

5.5.1 Bols and co-workers:

Approach I: (*J. Am. Chem. Soc*. **2001**, *123*, 5116-5117)[48]

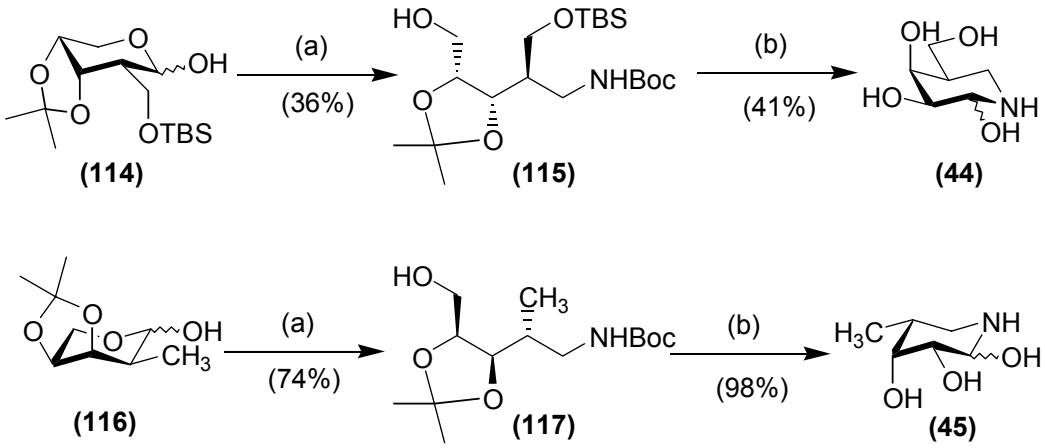
Noeuromycin and analogs were first designed and synthesized by the group of Bols.[48] The synthesis of noeuromycin (**43**) starting from the known 2-hydroxymethylglucose derivative **112**, utilized six steps with an overall yield of 40% from **112**.



Scheme 16

Reagents and conditions: *(a) (i) Allyl amine, $NaBH_3CN$, AcOH, 25 °C, 83 %; (ii) Wilkinson catalyst, CH_3CN/ H_2O reflux, then TFA/ H_2O, 25 °C; (iii) $(Boc)_2O$, $NaHCO_3$, Acetone-water, 25 °C, 87 % over two steps; (b) (i) $NaIO_4$; (ii) H_2, 1 atm, Pd/C, AcOH, 25 °C; (iii) TFA/ H_2O, 25 °C, 55 % over three steps.*

D-Galactonoeuromycin (**44**) and L-fuconoeuromycin (**45**) were synthesized from known derivatives **114** and **116**, respectively.

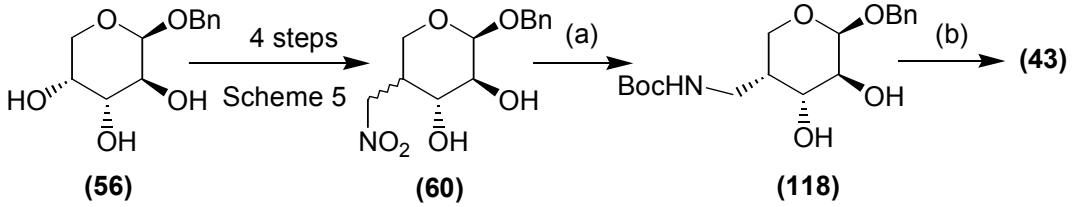


Scheme 17

Reagents and conditions: *(a) (i) Allyl amine, $NaBH_3CN$, AcOH, 25 ° C; (ii) Wilkinson catalyst, CH_3CN/ H_2O reflux; (iii) $(Boc)_2O$, $NaHCO_3$, Acetone-water, 25 ° C; (b) (i) TEMPO, MCPBA, DCM; (ii) HCl, H_2O.*

Approach II: (*Chem. Eur. J.* **2001**, *7*, 3744-3747)[51]

Subsequently, a short synthesis of noeuromycin (six steps from **56**, 19% yield) was also published, however, the diasteroselection was low (dr = < 2:1).



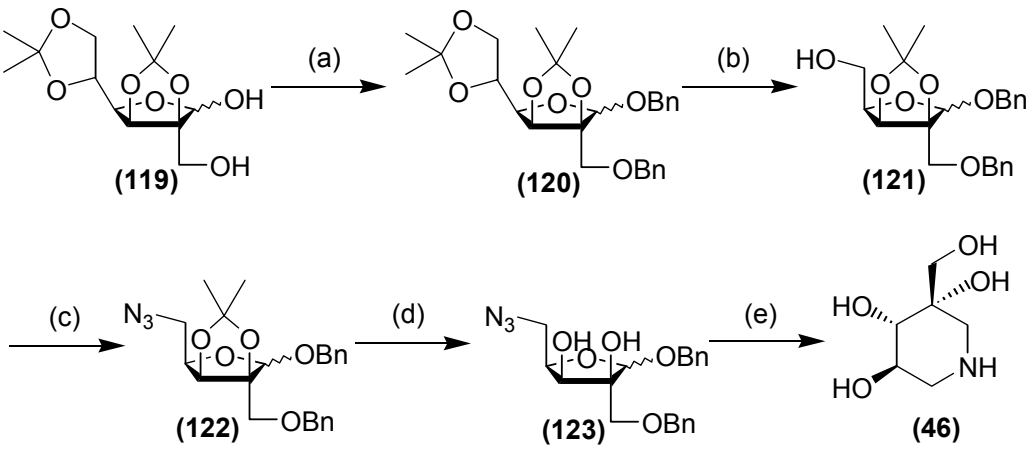
Scheme 18

Reagents and conditions: *(a) H_2, Pd/C, TEA, MeOH then $(Boc)_2O$, TEA, (dr = <2:1), chromatographic separation, 44 %; (b) H_2, Pd/C, EtOH, then HCl, H_2O, 98 %.*

5.6 Approaches towards 5-hydroxy isofagomine:

5.6.1 Ichikawa's approach: (*Tetrahedron Lett*. **1995**, *36*, 1767-1770)[49]

Ichikawa and co-workers first designed and synthesized 5-hydroxy isofagomine (**46**) in eight steps starting from **119** that was derived from D-mannose.

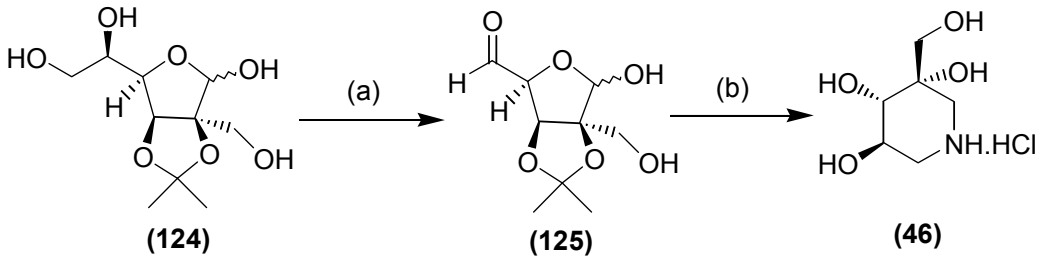


Scheme 19

***Reagents and conditions**: (a) Ag_2O, BnBr, KI, DMF, rt, 10 h, 85 %; (b) (i) 70 % AcOH, rt, overnight, 80 %; (ii) $NaIO_4$, MeOH-H_2O, 0 °C, 30 min; (iii) $NaBH_4$, rt, overnight, 84 %; (c) (i) $(CF_3SO_2)_2O$, DCM, py, -40 °C to 0 °C, 30 min; (ii) NaN_3, DMF, 80 °C, overnight, 94 % over two steps; (d) 60 % TFA, rt, overnight, 83 %; (e) (i) 20 % $Pd(OH)_2$, H_2, aq. HCl, pH = 3; (ii) Dowex 50W-X8 [H^+] eluted with 5 % NH_4OH, 95 %.*

5.6.2 Bols' approach: (*Tetrahedron Lett*. **1996**, *37*, 2097-3000).[56]

Bols and co-workers published a short three-step synthesis of 5-hydroxy isofagomine starting from **124** that in turn was derived from D-mannose in three steps.



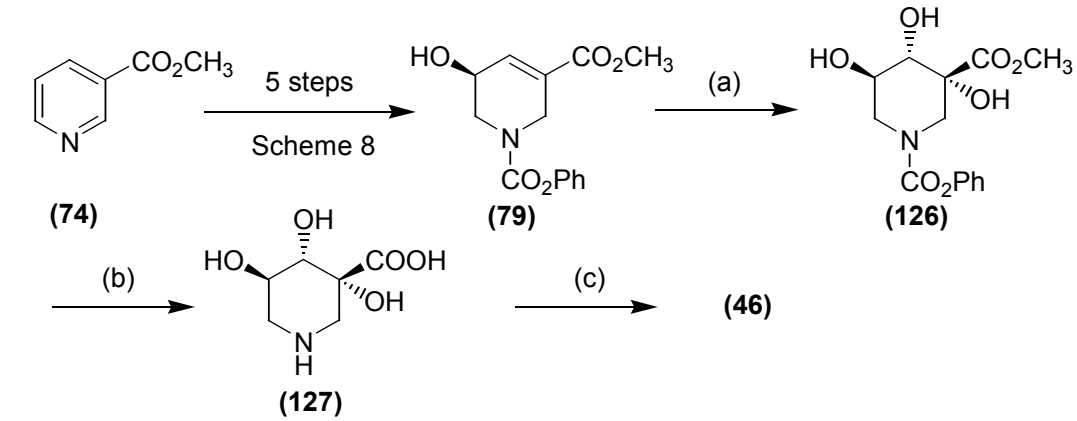
(124) **(125)** **(46)**

Scheme 20

Reagents and conditions: *(a) $NaIO_4$, MeOH-H_2O (1:1), 2 h, 0 °C, 93 %; (b) (i) NH_3, H_2, 37 atm, 5 % Pd/C, MeOH, 67 %; (ii) HCl, H_2O, MeOH, 50-55 °C, 2 h, ~100 %.*

5.6.3 Ganem's approach: (*Org. Lett*. **2001**, *3*, 201-203).[54]

The approach of Ganem and co-workers was based upon the use of selective Fowler reductions as the key step. The synthesis utilized nine steps and had an overall yield of 49 %. The enantioselectivity was a moderate 83 %.



(74) **(79)** **(126)** **(127)** **(46)**

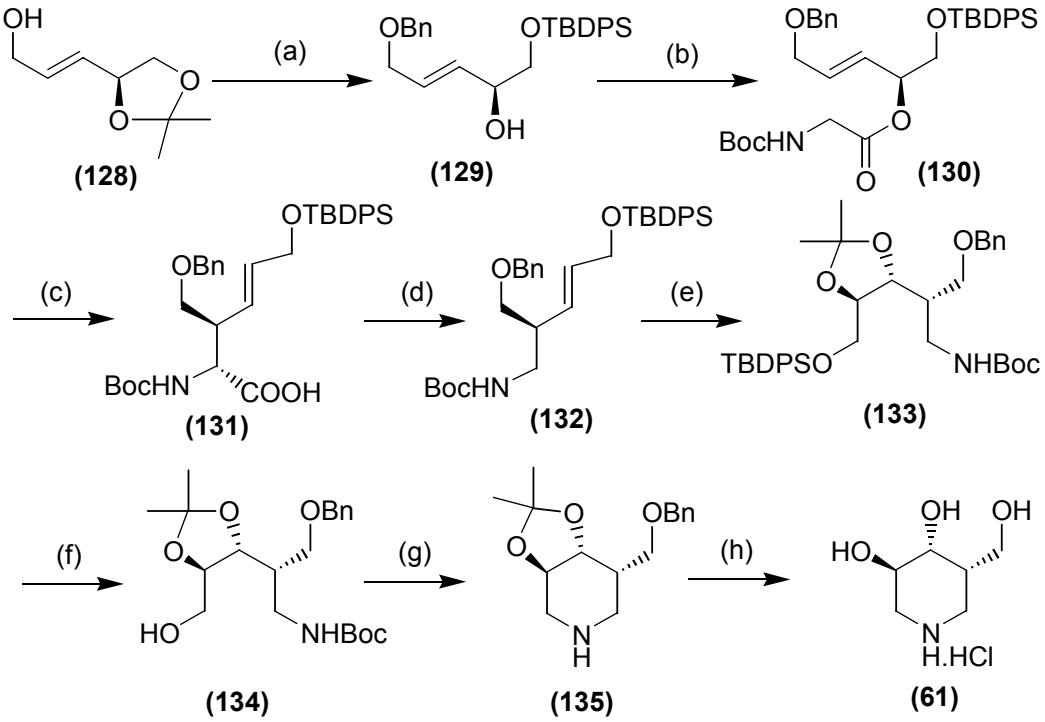
Scheme 21

Reagents and conditions: *(a) OsO_4, NMO, 81 %; (b) LiOH, 95 %; (c) (i) HMDS-py, 110 °C; (ii) LAH, THF, 83 %.*

5.7. Miscellaneous:

5.7.1 An approach towards the synthesis of 5-*epi*-isofagomine: (*Tetrahedron Lett*. **1998**, *39*, 817-818)[57]

Kazmaier and co-workers synthesized 5-*epi*-isofagomine (**61**) in seventeen steps with an overall yield of 9% from **128** utilizing an asymmetric chelate-controlled enolate Claisen rearrangement as the key step.



Scheme 22

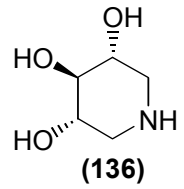
Reagents and conditions: *(a) (i) NaH, BnBr, DMF, 90 %; (ii) TFA, H_2O/ MeOH, 89 %; (iii) TBDPSCl, py, DCM, 10 % DMAP, 86 %; (b) DCC, 10 % DMAP, Boc-Gly-OH, 99 %; (c) LDA, $ZnCl_2$, THF, -78 ° C, 89 %; (d) (i) NMM, ClCOOR, THF; (ii) 2-mercaptopyridine-N-oxide sodium salt; (iii) tBuSH, hν, 70 %; (e) (i) AD-Mix-β, tBuOH, H_2O, 88 %; (ii) DMP, TsOH, Acetone, 94 %; (f) TBAF, THF, 97 %; (h) (i) $(CF_3SO_2)_2O$, py, DCM; (ii) HCl, dioxane; (iii) $NaHCO_3$, 50 ° C, dioxane-water, 49 %; (g) (i) TMSI, DCM; (ii) HCl, MeOH; (iii) Dowex 50W-X8, 57 %.*

In addition to these approaches towards 1-*N*-iminosugars, Mehta and co-workers have published an approach for Isofagomine analogs utilizing a Diels-Alder

cycloaddition approach.[58a] Various groups, including those of Bols[58b] and Horenstein,[58c] have synthesized many other structural analogs of these molecules, but these have not been covered here.

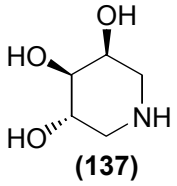
6. Piperidine triols as glycosidase inhibitors:

Dale and co-workers systematically studied the inhibition of sweet almond β-glucosidase by a wide variety of normal and deoxy sugars. While the stereochemical configurations of individual ring hydroxyls were important, removing the C-6 hydroxymethyl substituent altogether had remarkably little effect on enzyme substrate interactions.[59] This surprising finding led Ganem and co-workers to postulate that stereochemically simpler or nor-analogues of deoxynojirimycin **18** may also be good inhibitors of glycosidases.



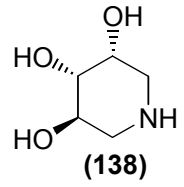
(136)

des(hydroxymethyl)
deoxynojirimycin



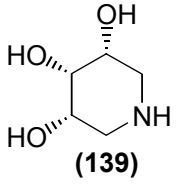
(137)

des(hydroxymethyl)
deoxygalactonojirimycin



(138)

des(hydroxymethyl)
deoxymannojirimycin



(139)

des(hydroxymethyl)
deoxyallonojirimycin

Figure 6

Along with the gluco- analog **136**, Ganem and co-workers prepared and studied the galactose- **137** and mannose- analogs **138** of des(hydroxymethyl) deoxynojirimycin and found that these molecules were almost as potent glycosidase inhibitors as their parent deoxynojirimycins[60] (Figure 6).

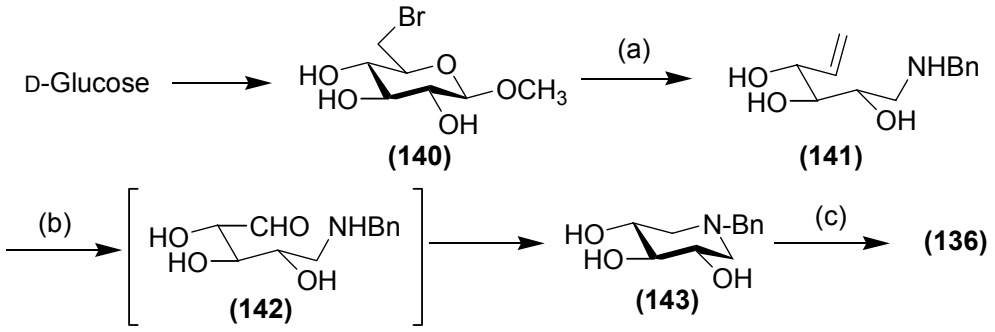
Five years later, Kusano and co-workers isolated triols **136, 137** and **139** from *Eupatorium fortunei* TURZ and showed that these triols were active components of the extracts of this plant, used in traditional Chinese and Japanese folk medicine as a diuretic, antipyretic, emmenagogue and anti-diabetic agent.[61]

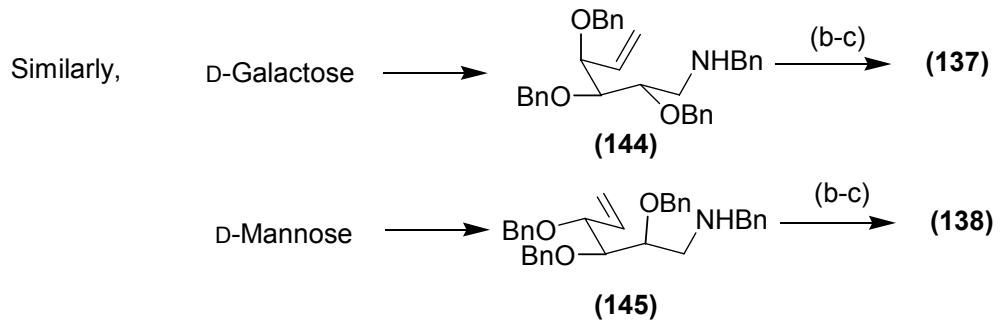
These structural analogues of the parent deoxynojirimycin can also be considered as 1-*N*-iminosugar type glycosidase inhibitors although they do not resemble any of the existing pyranose sugars. Not many syntheses of these molecules are known. We shall concentrate specifically only on the reported syntheses of these molecules and therefore, their structural analogs or the N-substituted compounds have been omitted.

7. Synthetic approaches towards 3,4,5-piperidine triols:

7.1 Ganem's approach: (*Tetrahedron Lett*. **1990**, *31*, 3393-3396)[60]

Ganem and co-workers synthesized **136**, **137** and **138**, utilizing their strategy of reductive opening of bromopyranose sugars.



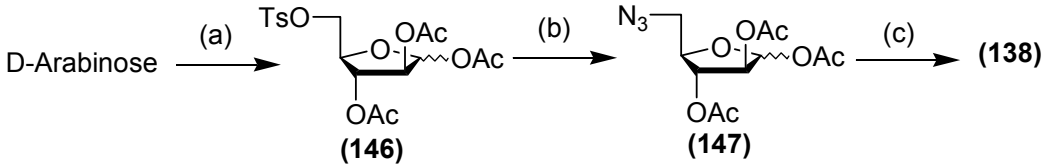


Scheme 23

Reagents and conditions: *(a) Zn, PrOH/H_2O (19:1), $NaBH_3CN$, $BnNH_2$, reflux, 2h; (b) (i) TFA, DCM; (ii) O_3, DCM, -78 °C; (ii) Me_2S, $NaBH_3CN$, MeOH, rt, 3 h; (c) H_2, Pd/C, MeOH.*

7.2 Legler's approach (*Carbohydr. Res*. **1995**, *272*, 17-30)[62]

Legler's group synthesized des(hydroxymethyl)mannojirimycin **138** from D-arabinose, in seven steps, with an overall yield of 41%.

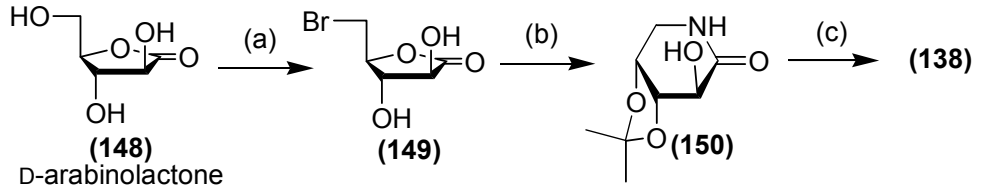


Scheme 24

Reagents and conditions: *(a) (i) Trityl chloride, py, 24 h; (ii) Ac_2O; (iii) $BF_3.Et_2O$, MeOH, 60 % over three steps; (iv) TsCl, py, 85 %; (b) NaN_3, DMF, 90 °C, 94 %; (c) (i) NaOMe, MeOH, quant.; (ii) Pd/C, H_2, 1 atm, 16 h, 85 %.*

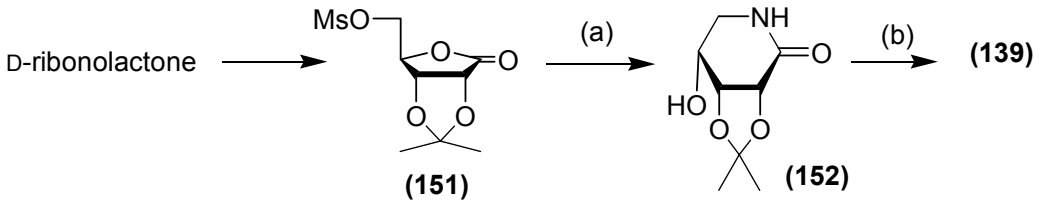
7.3 Lundt's approach (*Bioorg. Med. Chem*. **1996**, *4*, 1857-1865).[63]

Lundt and co-workers derived 3,4,5-piperidine triols from aldonolactones.



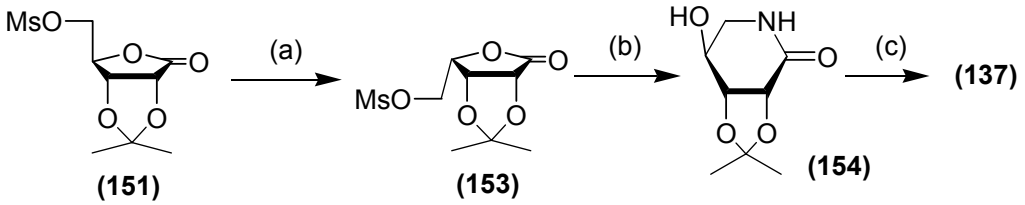
Scheme 25

Reagents and conditions: *(a) HBr-AcOH; (b) (i) 25 % aq. NH_3, 2 h, rt; (ii) 2,2-dimethoxypropane, TsOH, 50 % over three steps; (c) $NaBH_4$, TFA, dioxane, 100 °C, 3 h; IR 120 (H^+); aq. HCl, 66 %.*



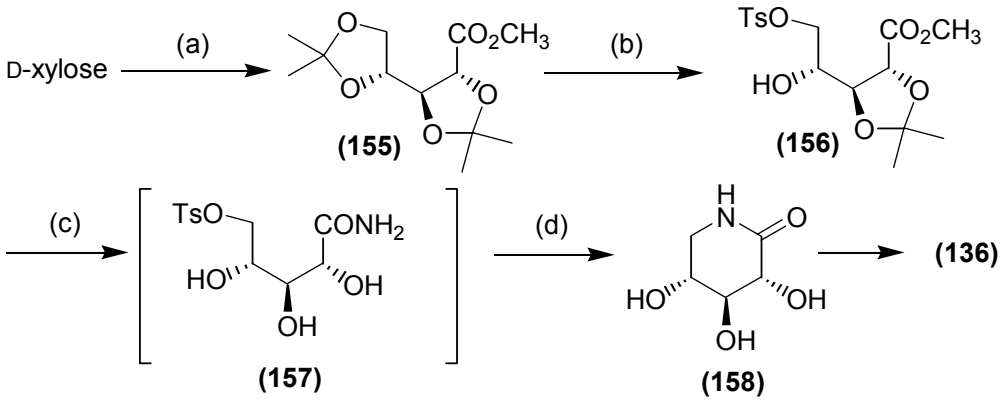
Scheme 26

Reagents and conditions: *(a) aq. NH_3, 84 %; (b) $NaBH_4$, AcOH, dioxane, 100 °C, 5 h; IR 120 (H^+); aq. HCl, 50 %.*



Scheme 27

Reagents and conditions: *(a) (i) KOH/ H_2O, 3 h; then aq. HCl to pH = 3, 84 %; (ii) MsCl, py, 1 h, 0 °C, 91 %; (b) 25 % aq. NH_3, 4h, rt, 70 %; (c) $NaBH_4$, AcOH, dioxane, 100 °C, 5 h; IR 120 (H^+); aq. HCl, 57 %.*

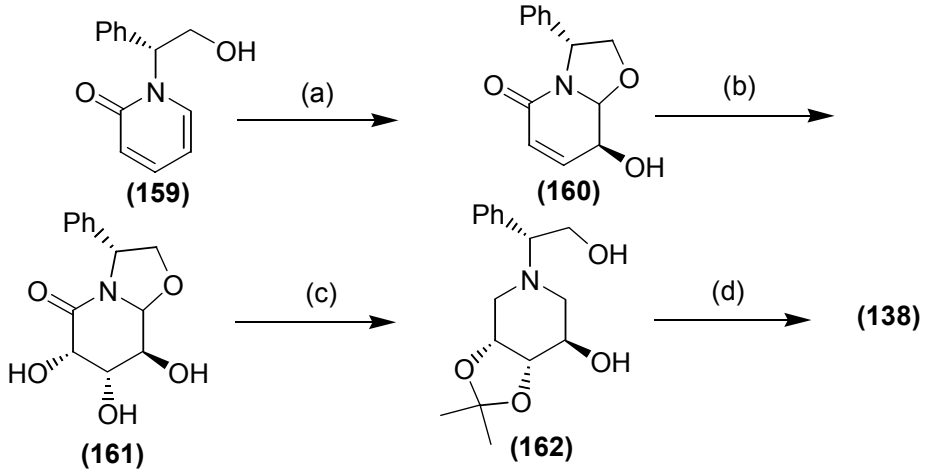


Scheme 28

Reagents and conditions: *(a) (i) Br_2, $NaHCO_3$, H_2O; then HCl / MeOH; (ii) Acetone, 2,2-dimethoxypropane, MeOH, 5 h, reflux, 89 %; (b) (i) TsCl, py, 0 °C, 0.5 – 1.5 h, 38 %; (c) aq. NH_3, rt, 16 h; then 1 % HCl-MeOH, 60 °C, 4 h, IR 400 (HCO_3^-), 38 %; (d) (i) HMDS, TMSCl, CH_3CN, 1 h, 82 °C; then $BH_3.SMe_2$, dioxane, 100 °C, 5 h; then 1M HCl, 100 °C, 1 h, 95 %.*

7.4 Amat's approach: (*Org. Lett.* **2001**, *3*, 3257-3260)[64]

Amat and co-workers based their approach on the stereoselective m-CPBA oxidation of phenylglycinol-derived 2-pyridone. The synthesis of **138** utilized six steps with an overall yield of 14%. The yield of the key step was rather low (~40%).

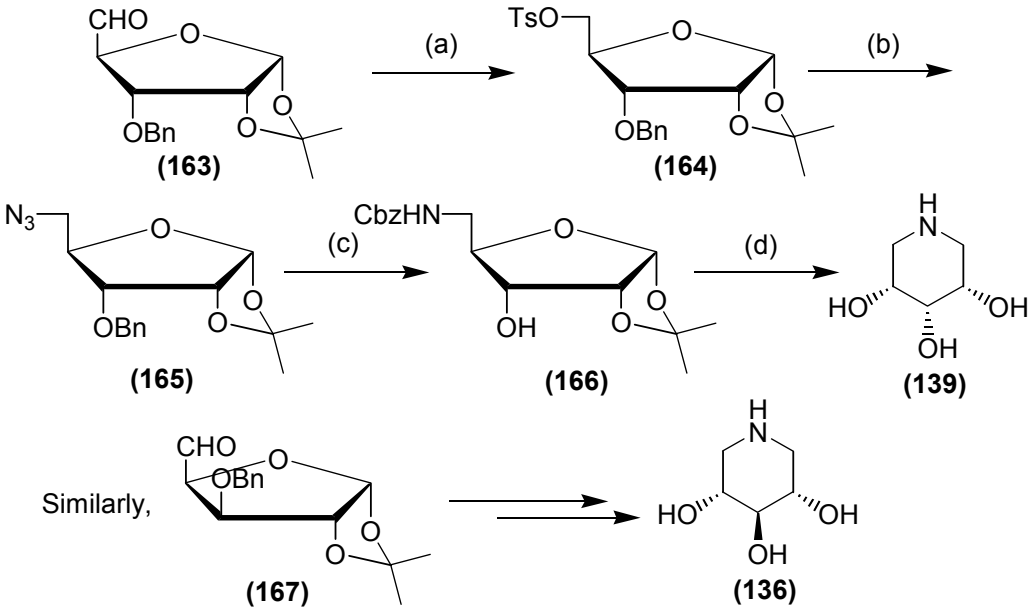


Scheme 29

Reagents and conditions: *(a) MCPBA, DCM, 25 ° C, 4 days, single diastereomer, 35-40 %; (b) OsO_4, NMO, aq. CH_3CN, 25 ° C, 24 h, 78 %; (c) (i) 2,2-Dimethoxypropane, p-TsOH, DCM, 25 ° C, 24 h, 85 %; (ii) BH_3.THF, -78 ° C (30 min) to 25 ° C (3 h), 87 %; (d) (i) H_2, Pd/C, MeOH, 65 %; (ii) MeOH, HCl, 95 %.*

7.5 Dhavale's approach: (*Bioorg. Med. Chem.* **2002**, *10*, 2155-2160)[65]

Dhavale's group utilized chiral pool derived aldehydes in their approach towards the two meso triols **136** and **139**.



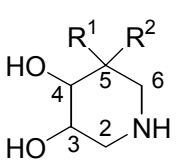
Scheme 30

Reagents and conditions: *(a) (i) $NaBH_4$, MeOH, rt, 15 min; (ii) TsCl, py, rt, 12 h, 85 %; (b) NaN_3, DMSO, 100 ° C, 6 h, 86 %; (c) (i) 10 % Pd/C, H_2, 80 psi, MeOH, 12 h; (ii) CbzCl, $NaHCO_3$, EtOH-H_2O (8:2), rt, 2 h, 93 % over two steps; (d) (i) TFA-H_2O (3:2), rt, 2 h; (ii) 10 % Pd/C, H_2, 8 psi, MeOH, 12 h, 94 %.*

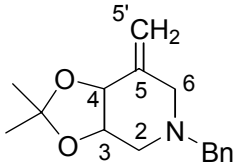
Along with these successful syntheses, a couple of syntheses of N-substituted piperidine triols have also been reported.[66]

8. Definition of the problem:

Upon careful consideration of the routes reported in the literature for the 1-*N*-iminosugar type glycosidase inhibitors, one can easily make out that although many of the approaches for these molecules are excellent, this class of compounds lacks a general route for their syntheses. Approaches utilizing the chiral pool have had to change the starting material for each of these compounds. A close look at these unique molecules reveals that they possess a general substitution pattern, as in **168**, varying only in the stereochemistry of the hydroxy groups at C-3 and C-4 and the nature of the R^1 and R^2 groups (Figure 7)



(168)



(169)

Figure 7

Therefore, we wondered whether a precursor of the type **169** could be used for the design of a general route for the synthesis of these molecules. By having the correct stereochemistry at C-3 and C-4 and by carrying out simple organic transformations at the C-5 -- C-5' center, one can have an access to a variety of these azasugars. In the chapters to follow we shall discuss the design and development of one such idea for the synthesis of a variety of 1-*N*-iminosugars.

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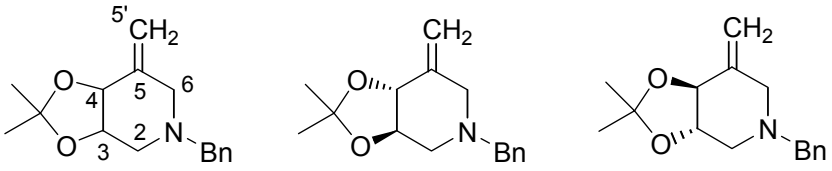
1. Introduction:

Analogues of carbohydrates in which one or more of the oxygen atoms have been substituted by a nitrogen are probably the best known inhibitors of glycosidases. Not only have these unique molecules proved to be a tool for studying the biological functions of oligosaccharides, they have also been shown to possess a tremendous chemotherapeutic potential in the treatment of a variety of carbohydrate related diseases like AIDS, diabetes, cancer and viral infections like influenza.[1]

It is obvious from the discussion in the previous chapter, that although these molecules are deceptively simple looking, their syntheses have not been straightforward. The unavailability of suitably substituted carbohydrates makes the matters more complicated. The greatest hurdle in the design of a synthetic approach for these functionalized piperidines has been the construction of the aminomethyl group next to a stereocenter. As discussed in the previous chapter, we envisaged an entity of the type **169** in order to have a veritable route for these 1-azasugars. In the same context, we designed precursors **170** and **171** (*ent*-**170**), both in which the C-3 and C-4 hydroxy are *anti* to each other.



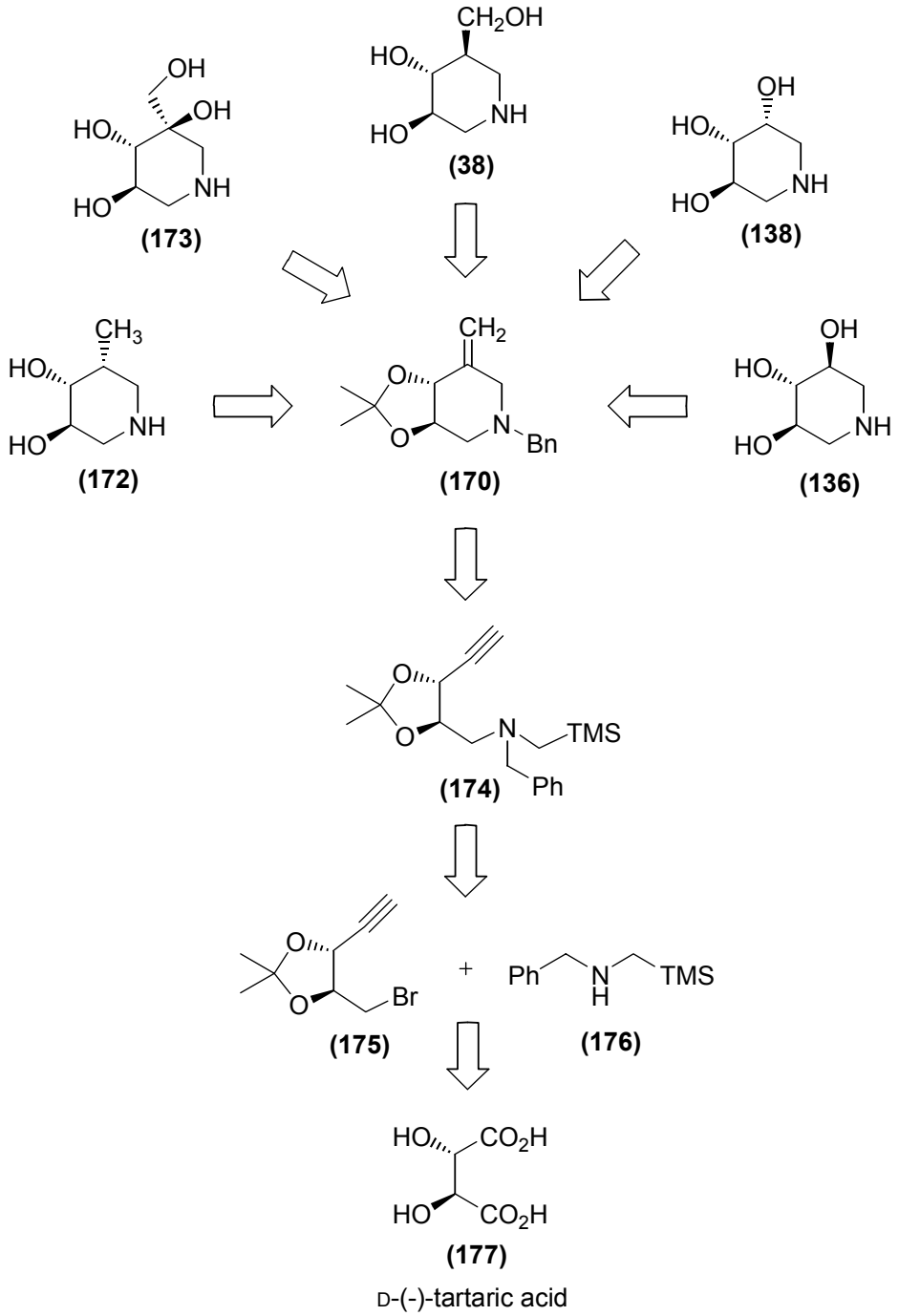
(169) **(170)** **(171)**

Figure 8

These precursors of the *threo* class were expected to act like “chemical multi-talents” in the design and development of a general synthetic route for 1-*N*-iminosugar class of glycosidase inhibitors.

2. Retrosynthetic plan:

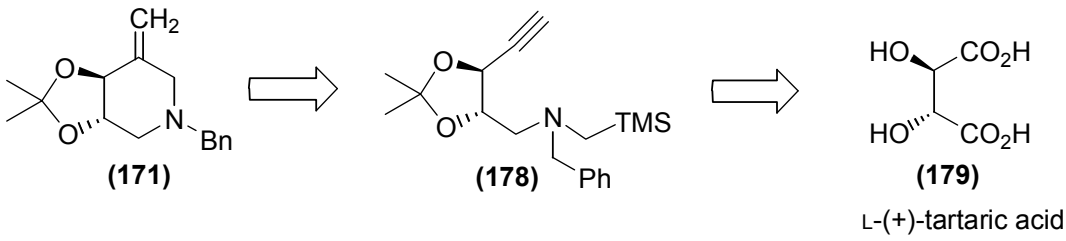
Towards this endeavor, we envisaged a retrosynthetic design for a variety of 1-*N*-iminosugars as depicted in Scheme 31.



Scheme 31

For an elegant design of a synthetic route to **170**, we were encouraged to consider the evaluation of a methodology developed in our group for the construction of nitrogen heterocycles by the cyclization of the photoinduced electron transfer (PET) generated α-trimethylsilylmethylamine radical cations to a tethered π-functionality.[2] This key step seemed to be an ideal transformation for the construction of **170** from **174**. It was decided to derive the substituted acetylene **174** from the bromide **175** which could be synthesized by simple organic transformations on D-(-)-tartaric acid.

In a similar manner, the L-*threo* precursor **171** was proposed to be obtained from **178** which in turn could be synthesized from L-(+)-tartaric acid.

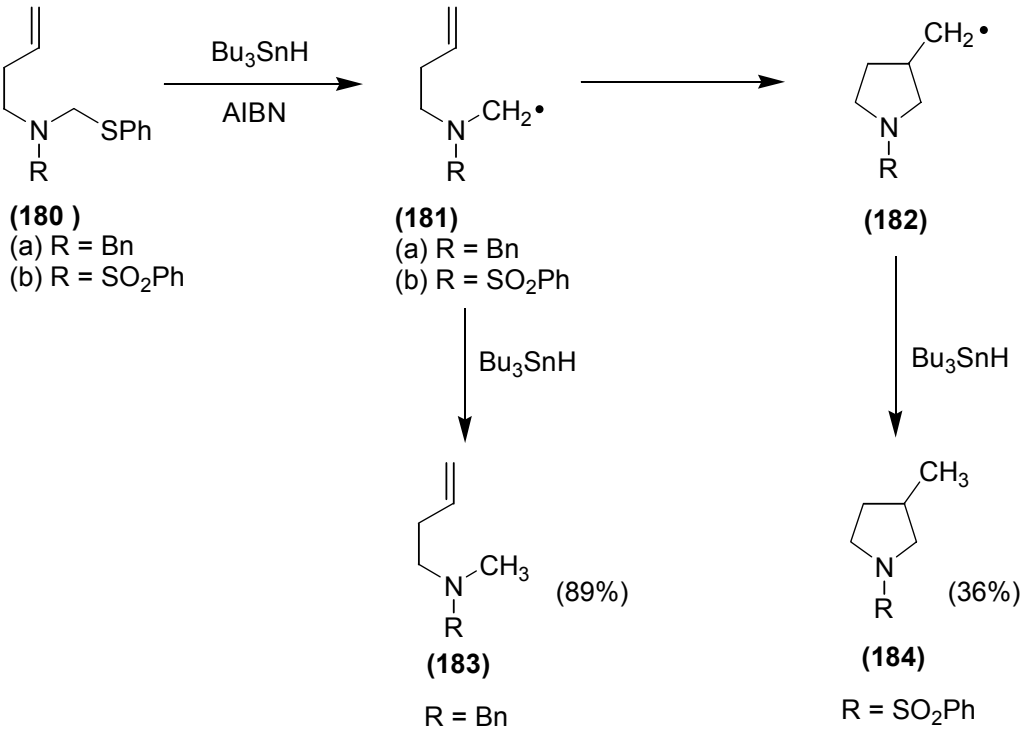


Scheme 32

3. The concept: A brief discussion on the methodology utilized:

Radical ions generated by single electron transfer from neutral organic compounds are known as important intermediates in a variety of interesting chemical processes and reactions.[3] The use of α-amino radicals in the synthesis of nitrogen heterocycles is limited. Attempts by Padwa and co-workers to cyclize free α-amino radicals, generated by the conventional reductive cleavage of –C-S- bond of *N*-alkenyl-*N*-(phenylthio)methylamine by Bu_3SnH, failed, owing to the reduced radicaloid character.[4] This was a direct consequence of the electronic assistance provided by the amine lone pair to the radical center. This argument

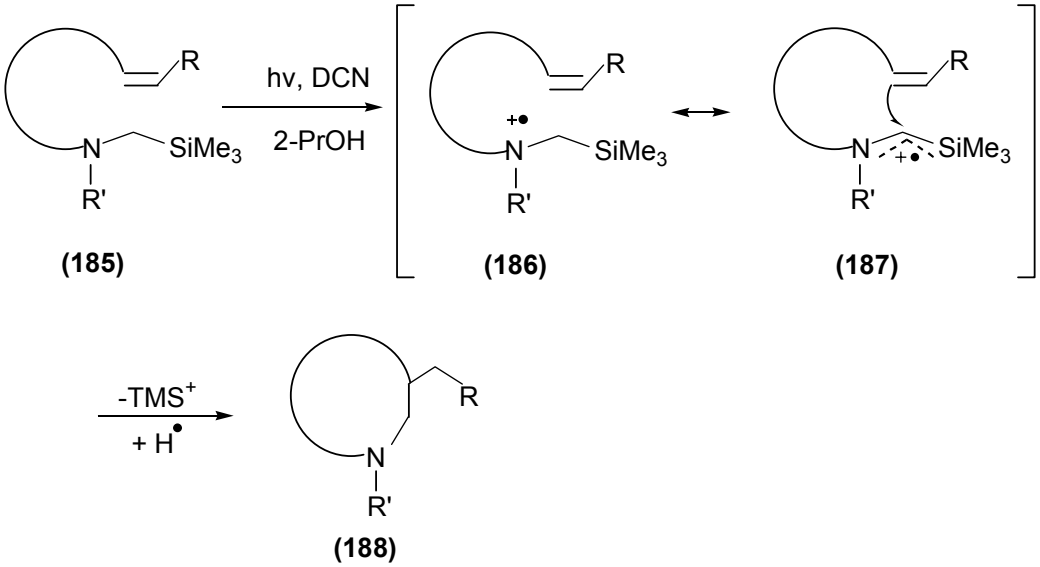
was substantiated by demonstrating the enhancement in the cyclization of radical **181b**, by placing an electron-withdrawing sulfonyl group on the nitrogen atom of the amine.



Scheme 33

Convinced by the fact that for cyclizable α-amino radicals, the electronic assistance of the amine group to the radical center must be reduced, Pandey and co-workers[2] developed a new concept for the synthesis of nitrogen heterocycles of the type **188** utilizing PET generated α-trimethylsilylmethylamine radical cations **187** as the reactive intermediate, as shown in Scheme 34. The concept in such cyclizations involved a three centered amine radical cationic species **187**, where the radical cation is delocalized between nitrogen and silicon atom due to the vertical overlap of the filled C-Si orbital and the half vacant nitrogen orbital.[5] The

photosystem to generate the reactive intermediate **187** utilized 1,4-dicyanonaphthalene (DCN) as the light harvesting electron acceptor (Figure 9).



Scheme 34

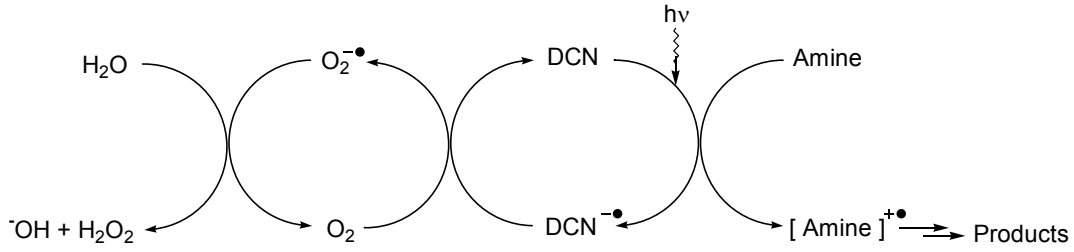
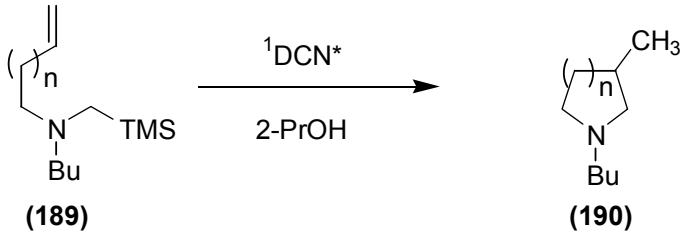


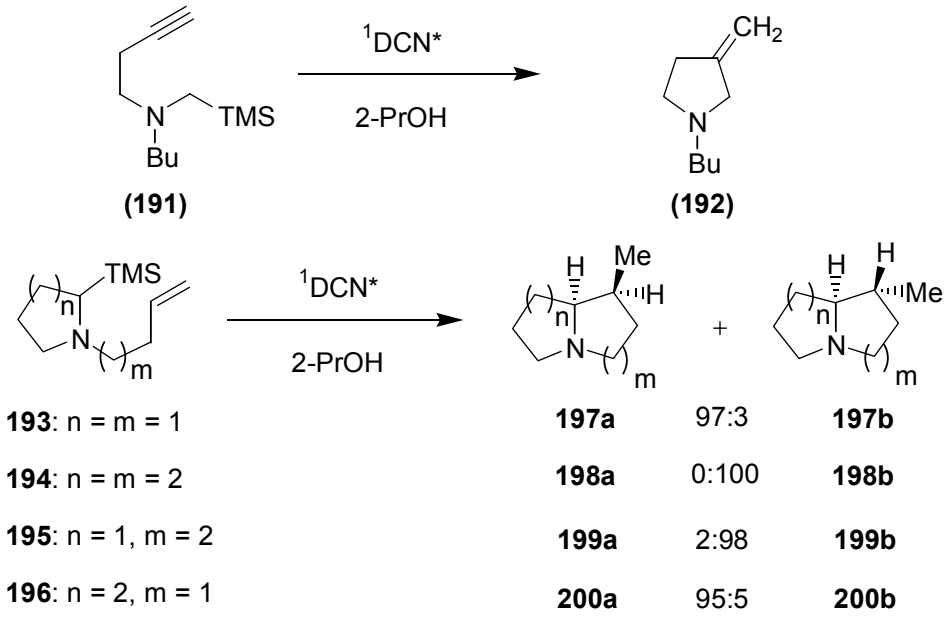
Figure 9: The Photosystem

A variety of substituted pyrrolidines, piperidines, pyrrolizidines as well as indolizidines have been synthesized[2] using this methodology.



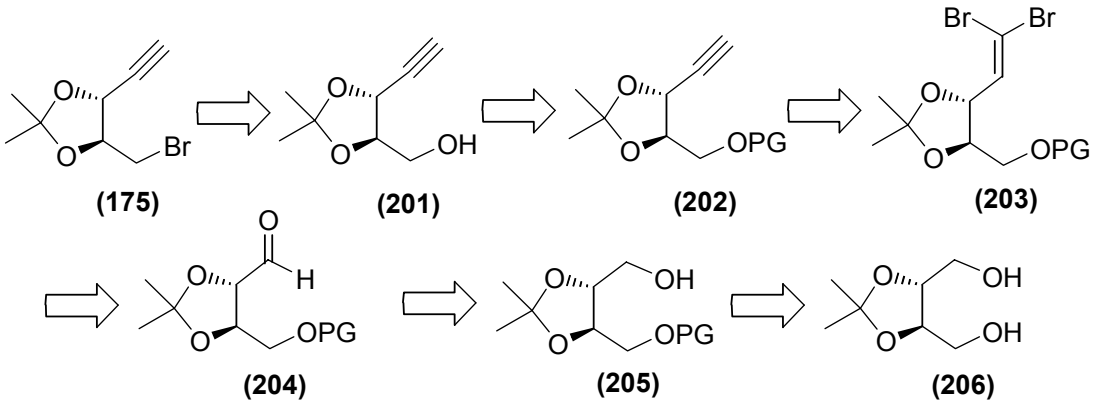
Scheme 35

Scheme 35 (contd.)



4. Development of a general synthetic route for 1-*N*-iminosugars:

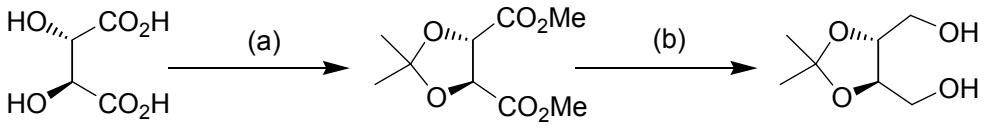
In order to access **170** via the PET cyclization of **174**, it was necessary to synthesize the bromide **175**. Corey-Fuchs' protocol[6] seemed ideal for generating **202** and therefore, it was proposed to evaluate the retrosynthetic route as shown in Scheme 36.



Scheme 36

4.1 Preparation of 1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-ynitol (201):

The synthesis of **170**, as perceived through the retrosynthetic strategy described in Scheme 31, was initiated with the preparation of **206**. This diol was obtained in high yield by following a two-step procedure (Scheme 37). One pot acetonide protection and esterification[7] of D-(-)-tartaric acid (**177**) followed by LAH reduction afforded **206**. Spectral characteristics are in good agreement to that reported in the literature.[8]

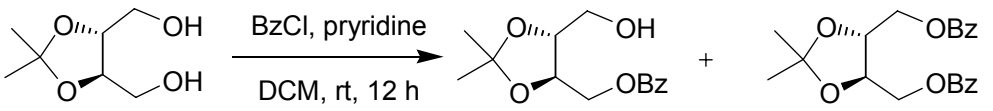


(177) **(207)** **(206)**

Scheme 37

Reagents and Conditions: *(a) 2,2-dimethoxypropane, MeOH, cyclohexane, pTSA, warm, 95 %; (b) LAH, THF, reflux, 6 h, 95 %.*

The next synthetic step in this planned strategy was to carry out the monoprotection of **206**. For this purpose, a protecting group was required that would be stable and could later be removed easily under mild non-reductive conditions. The benzoate protection seemed acceptable under these conditions.



(206) **(208)** (60%) **(209)** (30%)

Scheme 38

The monoprotection of **206** was carried out in DCM using benzoyl chloride and pyridine. Workup followed by column chromatography afforded **208** as a colorless oil.

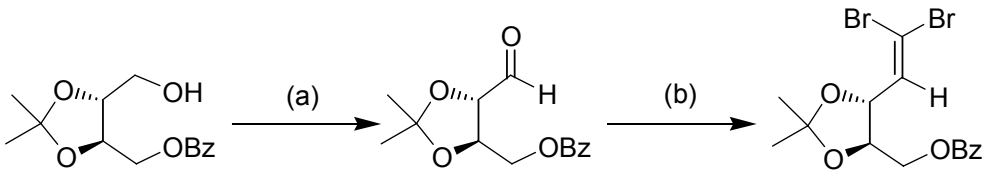
The IR spectrum of **208** displayed an absorption band at 1714 cm^{-1} indicating the presence of the benzoate functionality. A broad peak at 3471 cm^{-1} was the characteristic of a free hydroxy group.

The ^{1}H NMR spectrum displayed a set of three multiplets in the aromatic region (δ 8.10, 7.60, 7.50), integrating for a total of five protons, suggesting the presence of a monosubstituted phenyl ring. Two doublet of doublets at δ 4.52 (*J* = 11.7, 4.4 Hz) and 4.42 (*J* = 11.7, 4.9 Hz), integrating for two hydrogens, were attributed to the methylene protons next to the benzoate functionality. Two multiplets at δ 4.25 and 4.05, each integrating for one proton, were assigned to the H_4 and H_5 protons. The methylene protons of the 5-hydroxymethyl group appeared as two doublet of doublets at δ 3.90 (*J* = 12.2, 3.4 Hz) and 3.75 (*J* = 12.2, 4.4 Hz). The *gem*-dimethyl group appeared as a singlet at δ 1.49.

The ^{13}C spectra displayed a total of ten signals. The peak at δ 166.2 was attributed to the acyl carbon. The aromatic carbons appeared at δ 132.9, 129.4 and 128.2. The signal at δ 109.6 was assigned to the quaternary carbon of the isopropylidene moiety. The DEPT experiment revealed the presence of two methine carbons (C_4 and C_5) at δ 78.3 and 75.2, respectively. It also indicated the presence of two methylene carbons at δ 64.2 and 61.8. The signal appearing at δ 26.7 was assigned to the *gem*-dimethyl group.

The mass spectrum displayed a peak at *m/z* 251 (M^{+}-15) along with other peaks at *m/z* 235, 177 and 77. The base peak appeared at *m/z* 105 (COPh).

In order to introduce the acetylene functionality, it was proposed to utilize Corey-Fuch's protocol.[6] Although, an alternative method reported by Hijfte and co-workers[9] employing magnesium metal was also available, the previous methodology was perceived to be simpler and more straightforward. Towards this end, the monobenzoate **208** was converted to the corresponding dibromo-olefin **211** as shown in the scheme below.

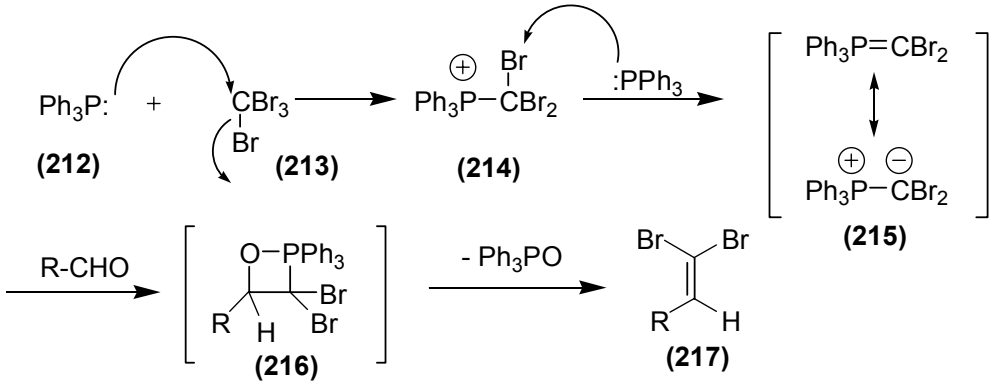


(208) **(210)** **(211)**

Scheme 39

Reagents and conditions: *(a) Oxalyl chloride, DMSO, DCM, -78 ° C, 2 h, then TEA, 96 %; (b) CBr_4, Ph_3P, DCM, 0 ° C, 3 h, 85 %.*

The primary alcohol functionality of **208** was converted to the corresponding aldehyde moiety at –78 °C by a clean and facile Swern oxidation.[10] Attempts to obtain this aldehyde via PCC oxidation of **208** were not very fruitful as the yield was rather low (*ca* 55%). Compound **210** was rather labile and was quickly converted to **211** utilizing CBr_4 and PPh_3 in DCM at 0 °C. A plausible mechanism for this reaction is depicted below.



(212) **(213)** **(214)** **(215)** **(216)** **(217)**

Scheme 40

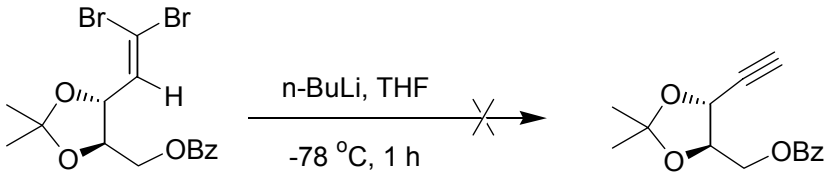
After getting rid of the triphenylphosphine oxide, the crude dibromo-olefin **211** was obtained in good yield (85%), upon purification by column chromatography. The structure of **211** was proved by conventional spectroscopic means.

The IR spectrum displayed an absorbance at 1720 cm^{-1} showing that the benzoate moiety was intact in the molecule. This was also confirmed by the ^{1}H NMR spectrum of the compound. The multiplets at δ 8.10, 7.60 and 7.50 together integrating for five protons were characterized as aromatic protons. A downfield doublet at δ 6.55 (J = 8.3 Hz) indicated the presence of an alkene and was attributed to the vinylic proton. A triplet at δ 4.68 (J = 8.3 Hz), integrating for one proton was assigned to H_5. Two doublet of doublets appearing at δ 4.60 (J = 12.2, 4.4 Hz) and 4.43 (J = 12.2, 4.9 Hz), each integrating for one proton were attributed to the methylene hydrogens. The H_4 proton appeared as a multiplet at δ 4.15. The *gem*-dimethyl group was observed as a singlet at δ 1.49.

The ^{13}C NMR spectrum displayed a total of eleven signals. The downfield peak at δ 165.2 was assigned to the benzoyl carbon. The methine vinyl carbon appeared at δ 134.4 (as proved by DEPT experiment). The aromatic carbons were observed at δ 132.4, 128.9 and 127.6, respectively. The carbons of the isopropylidene group were observed at δ 109.7 and 26.1, respectively. The carbon attached to the two bromine atoms was found at δ 93.9. The methine signals at δ 77.4 and 76.9 were assigned to C_5 and C_4 carbons, respectively. A methylene signal was observed at δ 62.5.

The mass spectral analysis of **211** showed a molecular ion peak at *m/z* 420, along with the base peak at *m/z* 105. Other prominent fragments were observed at *m/z* 405, 344, 256 and 177.

With the dibromo-olefin in hand, we proceeded to perform the Corey-Fuchs reaction.[6] Treatment of **211** with n-BuLi at –78 °C in THF was expected to lead to the acetylene **218** (Scheme 41). However, to our dismay, the reaction failed to yield the required product. Instead, an extremely complicated reaction mixture was obtained.

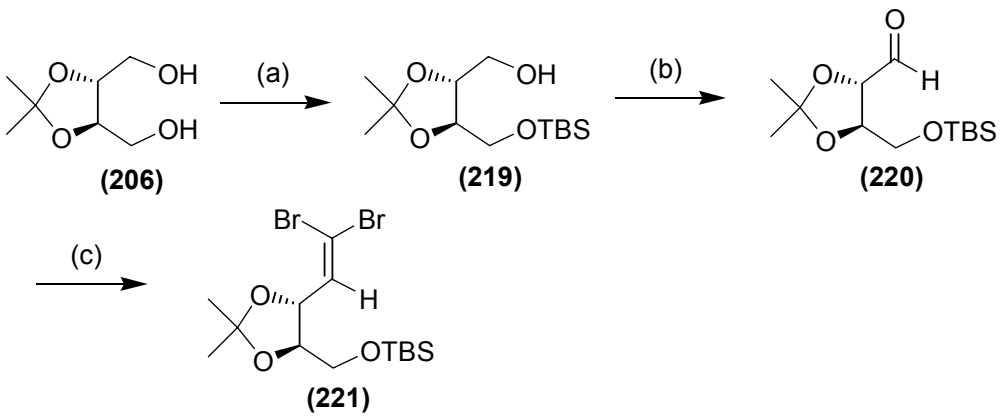


(211) **(218)**

Scheme 41

Attempts to obtain the product by a variety of permutations and combinations of the reagent and solvent did not yield any success. Therefore, at this stage, it was concluded that the benzoyl group may not be suitable for this reaction and hence it was decided to change the protecting group. At this juncture, the TBS group seemed to be the most suitable candidate and the efforts to obtain the acetylene were reinitiated as depicted in Scheme 42.

The mono-TBS ether was prepared by employing a slightly different procedure than that reported.[11] Stirring a dilute solution of **206** in dry DCM in the presence of TBSCl and triethyl amine, yielded **219** in 85% yield. A slight amount (*ca* 7%) of the corresponding di-protected compound was also obtained. The spectral data for **219** were found to be in good agreement with that reported[11] and are detailed in the experimental section.



Scheme 42

Reagents and conditions: *(a) TBSCl, TEA, DCM, rt, 36 h, 85 %; (b) Swern oxidation, -78 °C, 96 %; (c) CBr_4, Ph_3P, DCM, 0 °C, 2 h, 65 %.*

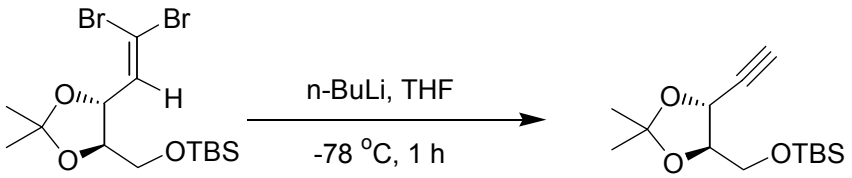
The Swern oxidation of **219** proceeded smoothly and afforded **220** in good yield (96 %). The unstable **220** was quickly transformed to **221** by treating with the CBr_4-PPh_3 combination in DCM at 0 °C. After passing the reaction mixture through a short pad of silica gel, the crude mixture was column chromatographed to afford pure **221** in 65 % yield.

The IR spectrum of **221** displayed prominent absorption peaks at 1626 and 1461 cm^{-1} indicating the presence of olefin functionality.

The ^1H NMR analysis of **221** indicated the presence of a vinylic proton, which appeared as a doublet at δ 6.50 (J = 8.8 Hz). The H_3 proton appeared as a doublet of doublet at δ 4.65 (J = 8.8, 7.3 Hz). A multiplet at δ 3.80 was assigned to the H_4 proton along with the two H_5 protons. The acetonide functionality was observed at δ 1.40 whereas the *t*-butyl and methyl protons of the TBS group were found appearing at δ 0.90 and 0.10, respectively.

The ^{13}C NMR spectrum displayed a total of ten signals. DEPT experiment indicated the presence of three methine carbons at δ 136.1, 80.6 and 77.9, respectively. These signals were assigned to the vinylic methine and the C_3 and C_4 carbons, respectively. The quaternary olefinic carbon signal was observed at δ 93.5. The C_5 methylene was found at δ 62.3 with the isopropylidene carbons appearing at δ 26.8. The peak at δ 25.7 was associated with the *t*-butyl group of the TBS group, the quaternary carbon of which was found at δ 18.1. The methyl carbons on the silicon atom were observed at δ -5.4. The mass spectrum of **221** displayed fragmentation peaks at *m/z* 415 (M^+-15, 1), 315 (39), 200 (11), 73 (86) along with the base peak at *m/z* 57.

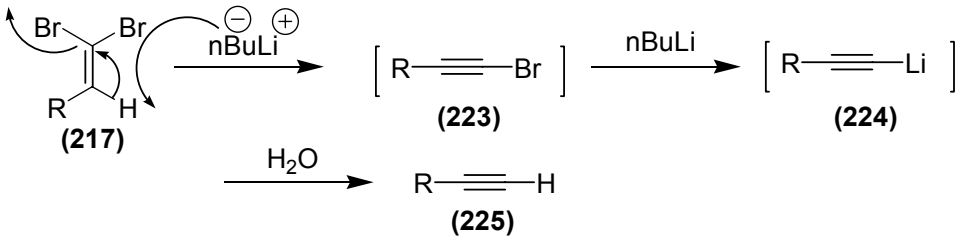
With **221** in hand, it was exposed to n-BuLi in THF at –78 °C, which afforded a smooth and clean conversion to the acetylene **222**. Workup followed by column chromatography of the crude mixture gave a high yield of **222** (90 %).



(221) **(222)**

Scheme 43

The mechanism of the reaction is depicted as follows:



(217) **(223)** **(224)** **(225)**

Scheme 44

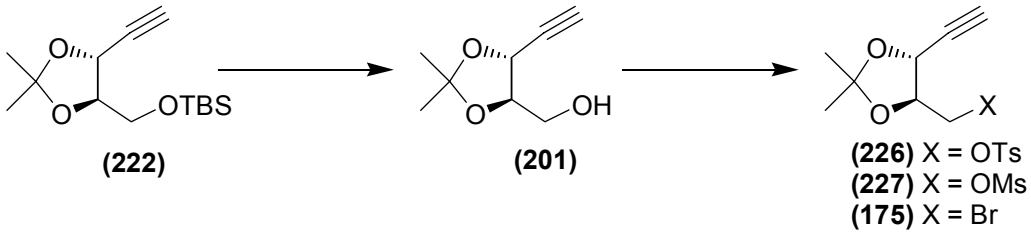
The compound **222** was characterized by spectroscopic methods. The IR spectrum displayed a sharp absorbance peak at 3300 cm^{-1}, characteristic of a monosubstituted acetylene.

The ^{1}H NMR spectrum displayed a doublet of doublet at δ 4.60 (J = 7.4, 1.9 Hz), assignable to the H_3 proton. The H_4 proton was observed as a multiplet at δ 4.15. The H_5 methylene protons were observed as a doublet at δ 3.80 (J = 4.4 Hz). Surprisingly, no geminal coupling was observed in this case. The doublet at δ 2.55 (J = 1.9 Hz) was characterized to the acetylenic proton. The acetonide moiety was assigned the singlets at δ 1.50 and 1.45 respectively, whereas the TBS group was responsible for the peaks at δ 0.90 and 0.10, respectively.

The ^{13}C spectrum displayed a total of eleven signals. The quaternary isopropylidene carbon was found appearing at its usual place at δ 110.4. The DEPT experiment suggested the presence of three methine carbons at δ 82.0, 66.8 and 61.8, belonging to the C_3, C_4 and the acetylene C_1 carbon, respectively. The quaternary acetylene carbon appeared at δ 74.1. The methyls of the isopropylidene group were found at δ 26.7 and 26.0, respectively. The signals at δ 25.6 and –5.6 were attributed to the *t*-butyl group and the dimethylsilyl carbons. The quaternary carbon of the TBS group appeared at δ 18.1

The mass spectral analysis of **222** displayed fragmentation peaks at *m/z* 255 (M^{+}-15, 8), 213 (2), 197 (3), 125 (67) and 73 (44), along with base peak at *m/z* 155.

With **222** in hand, our next job was to convert the protected hydroxy functionality to a good leaving group, capable of being displaced by a secondary amine.



(222) **(201)**

(226) X = OTs
(227) X = OMs
(175) X = Br

Scheme 45

Towards this endeavor, it was necessary to free the compound **222** of the TBS group. In this regard, TBAF mediated desilylation seemed to be the reagent of choice. Stirring a solution of **222** in THF in the presence of TBAF resulted in its smooth conversion to **201**. Protic workup followed by extraction in ethyl acetate and column chromatography of the crude product yielded **201** in good yield (85 %).

The IR spectrum of **201** displayed a broad peak at 3446 cm^{-1}, suggesting the presence of a free hydroxy functionality. A sharp peak at 3290 cm^{-1} was attributed to that arising out of the acetylene functionality.

The ^{1}H NMR experiment displayed the H_3 proton as a doublet of doublet at δ 4.60 (J = 7.9, 1.9 Hz). A multiplet appearing at δ 4.20 was attributed to the H_4 proton. The two methylene protons appeared as two doublet of doublets at δ 3.94 (J = 12.3, 3.0 Hz) and δ 3.68 (J = 12.3, 3.2 Hz). A doublet appearing at δ 2.55 (J = 1.9 Hz), integrating for one proton, was suggested to belong to the acetylenic proton. The two methyl groups appeared as singlets at δ 1.50 and 1.45, respectively.

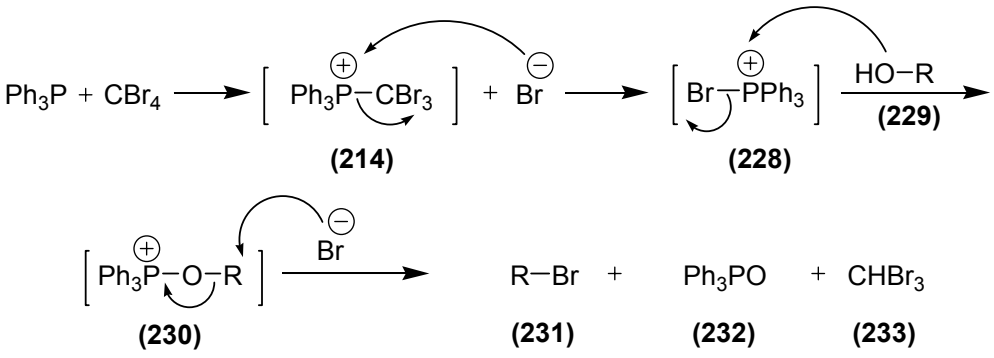
The ^{13}C spectrum displayed a total of eight signals. DEPT experiment revealed the presence of two quaternary carbons at δ 110.6 and 74.6, belonging to the isopropylidene and acetylene moieties, respectively. The C_3 and C_4 methine

carbons appeared at δ 82.0 and 66.2, respectively. Another methine carbon appearing at δ 80.7 was assigned to the unsubstituted acetylene carbon. The C_5 methylene was observed at δ 60.7. The signals for the *gem*-dimethyl group were found at δ 26.6 and 25.8, respectively.

The mass spectrum of **201** displayed prominent fragmentation peaks at *m/z* 141 (M^+-15, 64), 124 (11), 96 (47) along with the base peak at *m/z* 52.

4.2 Preparation of 1-[benzyl(trimethylsilylmethyl)amino]-1,4,5-trideoxy-2,3-*O*-(1-methylidene)-D-*threo*-pent-4-ynitol (174):

In order to transform **201** to the amine **174**, it was necessary to first transform the –OH functionality of **201** to a good leaving group. In this context, we decided to convert it to the corresponding bromide **175**. PBr_3 could be employed for this transformation but fears that the acetonide moiety may get affected, led us to choose Kocienski's method of CBr_4-PPh_3 combination for the conversion of alcohols to the corresponding bromides (Scheme 46).[12]



Scheme 46

To a stirring, ice-cold solution of CBr_4 and the alcohol **201**, Ph_3P was added and the resulting reaction mixture was stirred for about an hour at rt. After

passing through a short pad of silica, the reaction mixture was concentrated and used as such for the next step. A small portion was, however, purified for spectral characterization, using flash column chromatography.

The IR spectrum indicated the presence of the acetylene functionality based on the absorption peak at 3310 cm^{-1}.

The ^{1}H NMR spectrum displayed a doublet of doublet appearing at δ 4.58 (J = 6.4, 2.4 Hz), integrating for one proton, which can be attributed to H_5. A multiplet at δ 4.33 was assigned to H_4. The methylene protons appeared as a multiplet at δ 3.50. The doublet at δ 2.59 (J = 2.4 Hz) was assigned to the acetylene proton. The isopropylidene protons were found at their usual position at δ 1.50 and 1.45, respectively.

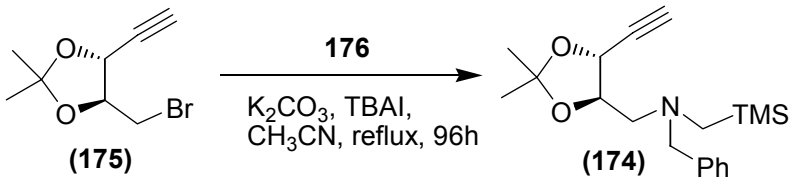
The ^{13}C NMR spectrum of **175** showed a total of eight peaks. The DEPT experiment suggested the presence of two quaternary carbons, at δ 111.6 and 75.0, respectively. The former was assigned to the acetonide group whereas the latter was found to belong to the acetylene moiety. The C_5 and C_4 methine carbons were responsible for the signals at 80.7 and 69.2, respectively. The acetylene methine carbon was found at δ 77.3 whereas the methylene carbon was associated with the peak at δ 31.1. The methyl carbons of the isopropylidine functionality appeared at δ 27.0 and 26.3, respectively.

The GC-MS analysis of **175** showed fragmentation peaks at *m/z* 205, 203 (both M^{+}-15), 145, 143 and 96.

In order to access **174**, it was necessary to couple the bromide **175** with the secondary amine $PhCH_2NHCH_2TMS$ (**176**). This secondary amine was easily prepared in 75 % yield by refluxing a 1:1 mixture of benzyl amine with $TMSCH_2Cl$ in dry CH_3CN using anhydrous K_2CO_3 as the base. The spectral characteristics of

176 were in good agreement with those reported in literature[13] and are detailed in the experimental section of chapter 3.

Initially the coupling of the tosylate **226** or mesylate **227** with this amine was attempted. However, the reaction was extremely sluggish and did not proceed to completion. Moreover, the recovery of the mesylate was difficult due to its high polarity. The amine **174** could finally be prepared in fairly good yield (65 %) by refluxing a mixture of the bromide **175** and the amine **176** in dry CH_3CN in the presence of anhydrous K_2CO_3 and a catalytic amount of TBAI (Scheme 47).



Scheme 47

In the absence of TBAI, the reaction took an extraordinarily long time to complete and longer refluxing hours led to the formation of many unidentifiable side products. Changing the base to cesium carbonate did accelerate the reaction to some extent, however the yields did not improve beyond 60 %.

The IR spectrum of **174** displayed an absorbance peak at 3310 cm^{-1}, characteristic of the monosubstituted acetylene. The peaks at 760 and 720 cm^{-1} were attributed to those belonging to a monosubstituted phenyl ring.

The ^1H NMR analysis revealed the presence of five aromatic protons appearing as a multiplet at δ 7.30 (Figure 15a). A doublet of doublet appearing as a multiplet at δ 4.39 (J = 7.1, 2.0 Hz), integrating for one proton, was attributed to H_3 proton. The H_2 proton was observed as a multiplet at δ 4.25. The benzylic protons appeared as a set of two doublets (J = 13.7 Hz) at δ 3.72 and 3.49,

respectively. A set of two doublet of doublets (J = 13.1, 5.3 Hz) appearing at δ 2.67 and 2.57, respectively, was attributed to the two methylene protons at C_1. The acetylenic proton was found appearing as a doublet at δ 2.50. The two methylene protons next to the TMS functionality (-N-C$\underline{H}_2$-TMS) appeared as two doublets (J = 14.7 Hz) at δ 2.16 and 2.02. The *gem*-dimethyl protons were as usual observed as two singlets at δ 1.47 and 1.37. The singlet at δ 0.05, integrating for nine protons, arose from the TMS functionality.

The ^{13}C NMR experiment displayed a total of fifteen signals (Figure 15c). The aromatic carbons were observed at δ 139.6, 128.8, 128.0 and 126.7. The signal at δ 110.2, which was absent in the DEPT experiment, was assigned to the quaternary isopropylidene carbon. Another quaternary carbon appearing at δ 81.6 was assigned to the acetylenic carbon. The C_3 and C_2 carbons were observed at δ 80.7 and 68.8, respectively, whereas another methine signal at δ 74.1 was thought to arise from the acetylene functionality. Three methylene peaks observed at δ 62.8, 58.4, 47.2, belonged to the benzylic (N-$\underline{C}H_2$-Ph), the C_1 carbon and the trimethylsilylmethylene (N-$\underline{C}H_2$-TMS) carbons, respectively. The methyl signals at δ 26.9, 25.9 and –1.3 were associated with the acetonide and the TMS functionalities.

The mass spectrum of **174** displayed a molecular ion peak at *m/z* 331 (8) along with the base peak at *m/z* 206 (Figure 15b). Other prominent peaks were observed at *m/z* 258 (10), 91 (80) and 73 (19).

The above-discussed spectral characterization proved the structure of **174** and the stage was now set for the crucial PET cyclization reaction.

4.3 PET cyclization of 174:

PET activation of **174** was carried out by irradiating a solution containing **174** (0.960 g, 2.9 mmol) and a catalytic amount of DCN (0.160 g, 0.9 mmol) (prepared by following the reported procedure[14]) in 2-propanol (500 mL) in an open vessel, using a 450 W Hanovia medium pressure mercury vapor lamp as the light source. The lamp was immersed in a Pyrex water-jacketed immersion well so as to allow wavelengths greater than 280 nm to pass through. The reaction was monitored by GC and when the consumption of the starting material was found to be almost complete, the irradiation was discontinued. Upon removal of the solvent, the crude photolysate was column chromatographed to afford the D-*threo* precursor **170** in 60 % yield.

The IR spectral analysis of **170** displayed a weak absorption peak at 1674 cm^{-1}, characteristic of the olefin functionality.

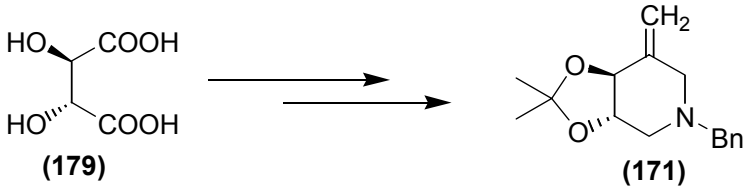
In the ^{1}H NMR spectrum of **170**, a multiplet at δ 7.30, assignable to five protons, was attributed to the aromatic ring (Figure 16a). Two doublets at δ 5.05 and 4.90 (J = 1.0 Hz), for one proton each, were associated with the exocyclic olefin moiety. The multiplet at δ 3.80, integrating for one proton was assigned to H_{7a}. The benzylic hydrogens (N-C$\underline{H}_2$-Ph) appeared as a set of two doublets (J = 13.2 Hz) at δ 3.73 and 3.65, respectively. The H_{3a} proton was observed as a multiplet at δ 3.57. The H_{4eq} and H_{6eq} were together responsible for the multiplet at δ 3.33. A broad doublet at δ 2.80 (J = 12.7 Hz) was attributed to the H_{6ax} proton. The H_{4ax} appeared as a triplet at δ 2.37 (J = 10.3 Hz). The singlet at δ 1.45, integrating for six protons, was assignable to the *gem*-dimethyl group.

In the ^{13}C NMR experiment, a total of fourteen signals were observed (Figure 16c). The signals for quaternary carbons, appearing at δ 140.4 and 110.9,

were attributed to the C_7 olefin carbon and the isopropylidene carbon. The peaks at 137.7, 128.8, 128.2 and 127.1 were together assigned to the phenyl ring. DEPT experiment suggested the presence of the olefinic methylene carbon at δ 105.1. The methine signals for C_{3a} and C_{7a} were observed at δ 81.7 and 77.5, respectively. The benzylic methylene carbon appeared at δ 61.5 whereas the other two methylene carbons (C_4 and C_6) were associated with the signals at δ 57.1 and 54.5, respectively. The methyl groups of the acetonide were found appearing at their usual chemical shift at δ 26.8 and 26.7.

The mass spectral analysis of **170** displayed a molecular ion peak at *m/z* 259 along with the tropylium ion peak at *m/z* 91, which appeared as the base peak (Figure 16b). Other fragmentation peaks were observed at *m/z* 201, 184 and 120.

The above spectral analysis confirmed the structure of the cyclized product. In a similar manner, we synthesized the L-*threo* precursor **171**, starting from L-tartaric acid **179**.



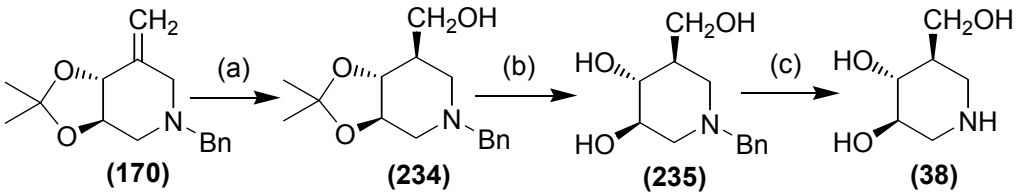
(179) **(171)**

Scheme 48

With the successful synthesis of the D- and L-*threo* precursors, we embarked upon the synthesis of various 1-*N*-iminosugars by functionalizing the exocyclic double bond.

5. Synthesis of Isofagomine:

In the context of the discussion in the previous section, we chose Isofagomine (**38**), the D-glucose type 1-*N*-iminosugar as our first target. Depicted below in Scheme 49 is the route adopted for the synthesis of isofagomine.



Scheme 49

Reagents and conditions: *(a) 9-BBN, THF, 0° C to rt, 20 h, then NaOH, H_2O_2, 0° C to rt., 4 h, 45 %; (b) (i) HCl, MeOH, rt., 1 h, then NH_4OH, ~100 % (ii) $Pd(OH)_2$ /C, H_2, 75 psi, EtOH, 10 h, 95 %.*

Hydroboration using 9-BBN followed by the removal of the acetonide and *N*-benzyl protecting groups was expected to lead to (+)-isofagomine. It was envisioned that the hydroboration would take place selectively from the α-face[15] based on the fact that steric hindrance would be exerted by H_{7a} and H_{6ax} to the bulky 9-BBN and possibly due to the preferential low energy equatorial orientation of the bulky bicyclic boron in the four membered transition state, as shown in the figure below.

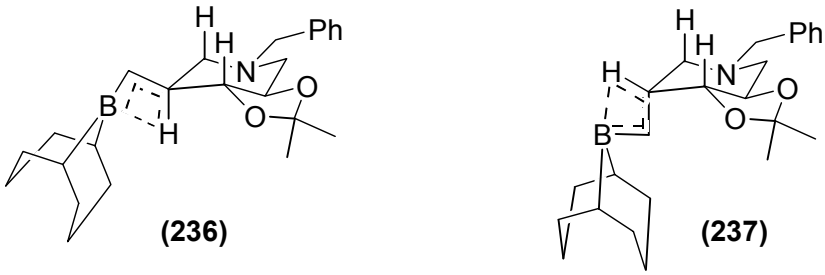


Figure 10

The hydroboration of **170** using 9-BBN, yielded **234** as a single diastereomer. At this stage, the stereochemical outcome was not very clear, since the peaks vital for the information of the stereochemistry of the hydroxymethyl group were occluded as multiplets. This could, however, be ascertained after the next step, when the acetonide moiety was removed and hence, the peak assignments for **234**, presented below, were unambiguous only after the ^{1}H spectral analysis of **235**.

The ^{1}H NMR spectrum of **234** displayed a multiplet for five aromatic protons at δ 7.30 (Figure 17a). The doublet of doublet at δ 3.70 (J = 10.3, 3.9 Hz) was attributed to one of the hydrogens of the hydroxymethyl group. A multiplet at δ 3.65, integrating for four protons, was assigned together to H_{7a} along with the benzylic methylene protons and the second hydroxymethyl proton. Two doublet of doublets at δ 3.24 (J = 9.3, 3.9 Hz) and 2.95 (J = 11.3, 3.9 Hz) arose from the H_{4eq} and H_{6eq} protons. The H_7 proton along with the H_{4ax} and H_{6ax} appeared as multiplets at δ 2.18 and 1.95, respectively. A clear indication of the stereochemistry at C_7 was provided by the peak for H_{7a}, which appeared as a doublet of doublet at δ 3.15 (J = 10.7, 8.9 Hz). The large coupling constants clearly pointed towards the *trans*-diaxial relation of H_{7a} with H_{3a} and H_7, thereby proving that H_7 was axial.

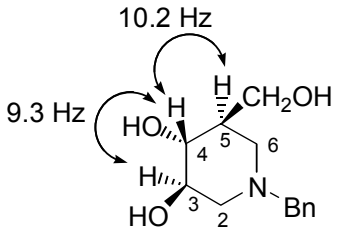
The ^{13}C spectral analysis displayed a total of twelve signals (Figure 17c). The aromatic carbons were observed at δ 129.0, 128.2 and 127.3. The quaternary aromatic carbon was not observed. The DEPT experiment suggested the presence of a quaternary carbon at δ 110.9, which was associated with the acetonide moiety. The methine carbon signals at δ 82.1 and 77.3 were attributed to C_{3a} and C_{7a} carbons. The four methylene signals appearing at δ 63.5, 61.9, 54.3

and 53.4 were thought to arise from the hydroxymethyl carbon (-$\underline{C}H_2OH$), the benzylic carbon (-N-$\underline{C}H_2$-Ph) and C_4 and C_6, respectively. The C_7 was observed at δ 41.5. The methyl signal at δ 26.7 was assigned to the isopropylidene moiety.

The GC-MS of **234** showed a molecular ion peak at *m/z* 277 with a base peak at *m/z* 91 (Figure 17b). Other fragmentation peaks were observed at *m/z* 262, 216, 201, 158, 132 and 120.

The acetonide moiety was cleaved quantitatively by stirring a methanolic solution of **234** in the presence of HCl. The amine salt was basified and the free amine was column chromatographed to afford *N*-benzyl isofagomine, **235**.

The peak assignments were done on the basis of ^{1}H-^{1}H COSY experiment (Figure 18b). The ^{1}H NMR spectrum showed the presence of five aromatic protons appearing together as a multiplet at δ 7.30 (Figure 18a). A doublet of doublet appearing at δ 3.73 (*J* = 11.3, 3.4 Hz), integrating for one proton, was assigned to one of the hydrogens of the hydroxymethyl group. The other hydrogen was found occluded in the multiplet at δ 3.55. This bunch also contained the benzylic hydrogens along with the H_3 proton. The H_4 proton appeared as a clear doublet of doublet at δ 3.15 (*J* = 10.2, 9.3 Hz). In the COSY experiment (Figure 22b), it was clear that this peak belonged to H_4 since only two couplings were observed for this peak, one with H_3 and the other with H_5. The H_{2eq} and H_{6eq} appeared together as multiplets at δ 2.95 whereas the multiplet at δ 1.95 was attributed to H_{2ax} and H_{6ax}. The H_5 proton was observed as a multiplet at δ 1.70.



(235)

Figure 11

The ^{13}C experiment displayed a total of ten signals (Figure 18c). The aromatic carbons were observed at δ 128.9, 127.1 and 126.5. The quaternary aromatic carbon was again not observed. DEPT experiment suggested the presence of three methine carbons at δ 72.4, 69.8 and 41.3, which were associated with C_4, C_3 and C_5 carbons, respectively. The four methylene carbons were observed at δ 60.0, 59.4, 55.5 and 52.4.

The *N*-benzyl group in **235** was removed by hydrogenation at 75 psi for 10 h in the presence of catalytic amount of $Pd(OH)_2$ on charcoal. Filtration of the catalyst followed by the removal of the solvent, afforded (+)-isofagomine in 95 % yield. The optical rotation of its hydrochloride salt ($[\alpha]_D^{20}$ = +20.7 (*c* 0.4, EtOH)) was found to be in good agreement with that reported in literature[15] ($[\alpha]_D^{20}$ = +19.6 (*c* 0.85, EtOH)). The spectral data of the free base was also in good agreement with that reported for the hydrochloride salt.[15]

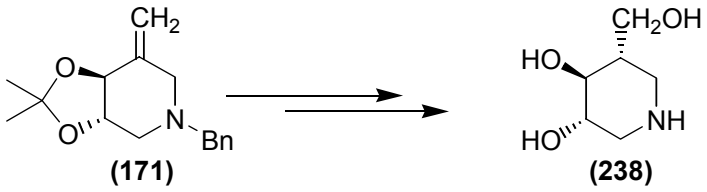
The ^1H NMR (Figure 19a) displayed two doublet of doublets at δ 3.76 (*J* = 11.4, 3.3 Hz) and δ 3.59 (*J* = 11.5, 6.7 Hz), both integrating for one proton each and were assigned to the protons of the hydroxymethyl group. The H_3 proton appeared as a multiplet at δ 3.48 whereas H_4 was observed as a doublet of doublet at δ 3.27 (*J* = 10.6, 8.8 Hz). The H_{2eq} and H_{6eq} protons appeared as a

multiplet at δ 3.12 whereas the corresponding axial protons were found as a multiplet at δ 2.43. The H_5 proton was assigned to the multiplet at δ 1.70.

The ^{13}C NMR experiment showed a total of six peaks (Figure 19c). DEPT experiment suggested the presence of three methine carbons at δ 70.2, 68.4 and 41.0, which were attributed to the C_4, C_3 and C_5 carbons, respectively. The methylene signal at δ 57.1 was thought to arise from the hydroxymethyl carbon whereas the C_2 and C_6 methylene carbons were found at δ 45.9 and 42.9, respectively.

The mass spectral analysis showed a molecular ion peak at *m/z* 147 (44), with the base peak at *m/z* 98 (Figure 19b). Other prominent fragmentation peaks were observed at *m/z* 129 (42) and 112 (62).

The effort, as outlined above, completed the successful synthesis of the D-glucose type 1-*N*-iminosugar (+)-isofagomine from the D-*threo* precursor. In a similar manner, we also synthesized (-)-isofagomine (**238**) from the L-*threo* precursor.

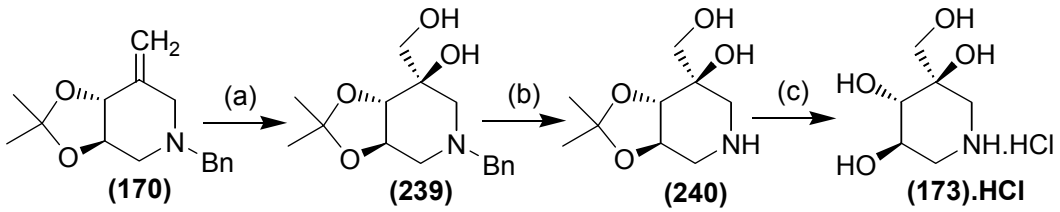


(171) **(238)**

Scheme 50

6. Synthesis of 5-hydroxy-5-*epi*-isofagomine:

The above success prompted us to go in for the further development of our strategy. Towards this endeavor, we attempted the dihydroxylation of **170** and obtained **239** as a single diastereomer. Removal of the benzyl and acetonide protecting groups yielded 5-hydroxy-5-*epi*-isofagomine (**173**).



(170) **(239)** **(240)** **(173).HCl**

Scheme 51

Reagents and conditions: *(a) OsO_4, NMO, pyridine, acetone-water (9:1), rt, 24 h, 95 %; (b) $Pd(OH)_2$, H_2, EtOH, 65 psi, 6 h, 90 %; (c) HCl, MeOH, rt, 4 h, quant.*

Osmium tetroxide mediated dihydroxylation in acetone-water medium, using NMO as the oxidant, yielded **239**, as a white crystalline solid (mp 150 –152 °C). NMR analysis showed that **239** was a single diastereomer. Stereochemical assignment was established based on extensive NMR experiments (COSY, HETCOR and NOESY (Figures 20d, 20e and 20f respectively)). The peak assignments in the ^{1}H NMR spectrum were carried out with the help of COSY and HETCOR experiments.

In the ^{1}H NMR spectrum of **239**, the multiplet at δ 7.40 for five protons was assigned to the aromatic hydrogens (Figure 20a). One of the hydroxymethyl protons was found as a doublet at δ 4.25 (J = 11.5 Hz) whereas the other was located at δ 3.78 (J = 11.5 Hz). The H_{3a} appeared as a doublet of doublet of doublet (ddd) at δ 3.85 (J = 9.9, 9.7 and 4.3 Hz). The two benzylic doublets were found very close to each other at δ 3.76 and 3.71 (J = 13.8 Hz). A doublet at δ 3.61 (J = 9.7 Hz), having a coupling only with the peak at δ 3.85 (H_{3a}) (as seen in the COSY plot) was assigned to the H_{7a} proton. The H_{4eq} appeared as a doublet of doublet at δ 3.30 (J = 9.7, 4.3 Hz) whereas the H_{6eq} was found appearing as a

doublet of doublet at δ 2.92 (*J* = 11.7 Hz). A doublet of doublet which looks like a triplet at δ 2.31 (*J* = 10.1, 9.9 Hz), integrating for one proton, was assigned to H_{4ax}. The H_{6ax}, in turn, appeared as a doublet at δ 2.21 (*J* = 12.0 Hz). The acetonide protons appeared at δ 1.50 as a singlet.

The ^{13}C NMR spectrum showed a total of thirteen signals (Figure 20c). The carbons at δ 137.7, 128.6, 128.3 and 127.3 were those of the aromatic ring. The carbons of the acetonide moiety were found appearing at δ 110.7 and 26.5, respectively. The C_{7a} was observed at δ 86.2 whereas C_{3a} was found at δ 73.6. The quaternary C_7 carbon was associated with the signal at δ 71.5. The hydroxymethyl carbon ($\underline{C}H_2OH$) was observed at δ 65.0 whereas the benzylic carbon (-N-$\underline{C}H_2$-Ph) was assigned to the signal at δ 61.5. The C_6 and C_4 methylenes were responsible for the peaks at δ 59.3 and 54.5, respectively.

The mass spectrum showed a molecular ion peak at *m/z* 293 (5) (Figure 20b). The tropylium ion peak at *m/z* 91 was the base peak whereas other fragmentation peaks were found at *m/z* 235 (25), 218 (16), 202 (4), 134 (45) and 120 (41).

The benzyl as well as the acetonide groups could be easily removed in a one-pot reaction by hydrogenation in acidic medium. However, although we did try this method, pure **173** could not be obtained since some unidentifiable rearrangement product (*ca* 10 %) was formed in the reaction and we were unable to get rid of it by chromatographic means. Hence, the deprotections had to be carried out in two steps. It was thought to first carry out the *N*-debenzylation since the debenzylated product **240** would come into use in the later part of our synthesis of other 1-*N*-iminosugars. This debenzylated product could be readily accessed by hydrogenation of an ethanolic solution of **239** at 60 psi for 6 h in the

presence of $Pd(OH)_2$ on charcoal (20 %) as the catalyst. Usual workup followed by column chromatography afforded **240** in 90 % yield.

The ^1H NMR of **240** indicated the absence of aromatic and benzylic protons. The two protons belonging to the hydroxymethyl group were now found close to each other, appearing as two doublets (J = 12.1 Hz) at δ 3.81 and 3.79, respectively. A ddd at δ 3.69 (J = 10.0, 9.9, 4.4 Hz) was associated with the H_{3a} proton, whereas the H_{7a} was observed as a doublet at 3.62 (J = 9.5 Hz). A doublet of doublet appearing at 3.35 (J = 11.9, 4.0 Hz), integrating for one proton, was assigned to H_{4eq}. The H_{6eq} proton was found at δ 3.24 as a doublet (J = 13.9 Hz). The axial counterparts H_{4ax} and H_{6ax} appeared as a dd like triplet at δ 2.70 (J = 11.1, 10.3 Hz) and a doublet at δ 2.37 (J = 13.9 Hz), respectively. The two singlets at δ 1.43 and 1.42 were as usual assigned to the acetonide moiety.

The ^{13}C NMR analysis revealed a total of eight signals. The DEPT experiment showed that the peaks appearing at δ 110.2 and 73.7 belonged to quaternary carbons and were assigned to the acetonide moiety and C_7 carbon, respectively. The C_{7a} and C_{3a} carbons were observed at δ 84.1 and 72.9, respectively. The methylene signal at δ 60.0 was attributed to the hydroxymethyl group. The C_6 and C_4 methylenes were observed at δ 49.6 and 46.0, respectively. The signal at δ 25.4 was assigned to the *gem*-dimethyl group.

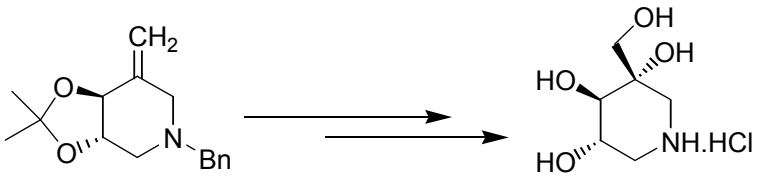
Upon debenzylation, the acetonide moiety was easily removed by stirring a methanolic solution of **240** in the presence of HCl. Removal of the solvent afforded **173** as its hydrochloride salt and was characterized by spectroscopic means.

The ^1H NMR of **173.HCl** displayed a multiplet at δ 4.11, for one hydrogen, which was attributed to H_3 proton (Figure 21a). The H_4 proton was observed as a

doublet at δ 3.85 (*J* = 4.4 Hz). The two hydroxymethyl protons appeared as two closely placed doublets (*J* = 12.0 Hz) at δ 3.71 and 3.64, respectively. The H_{6eq} proton was observed as a doublet at δ 3.43 (*J* = 13.6 Hz). A multiplet at δ 3.30 corresponding to two protons was associated with the hydrogens at C_2. The H_{6ax} was found appearing as a doublet at δ 3.16 (*J* = 13.6 Hz).

The ^{13}C NMR spectrum displayed a total of six signals (Figure 21b). DEPT experiment revealed that the signal at δ 71.5 belonged to a quaternary carbon and was associated with C_5. The C_3 and C_4 signals were found at δ 68.1 and 66.6 respectively. The signal for the hydroxymethyl group appeared at 63.6. The C_2 and C_6 methylenes were found at δ 46.1 and 45.2

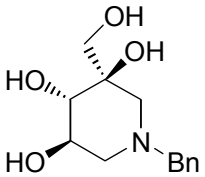
In this manner, a new 1-*N*-iminosugar, 5-hydroxy-5-*epi*-isofagomine was synthesized. Employing the same strategy, we also synthesized its enantiomer **241** (*ent*-**173**) from the L-*threo* precursor **171**.



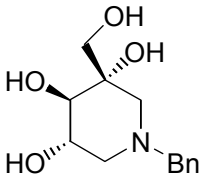
(171) **(241).HCl**

Scheme 52

We also prepared the corresponding *N*-benzyl derivatives (Figure 12) in order to compare their level of inhibition of glycosidases with the free amine. This was prepared simply by stirring a methanolic solution of **239** in the presence of HCl for about four hours. Neutralization of the salt, followed by column chromatography yielded **242**. Its enantiomer **243** was prepared in a similar manner.



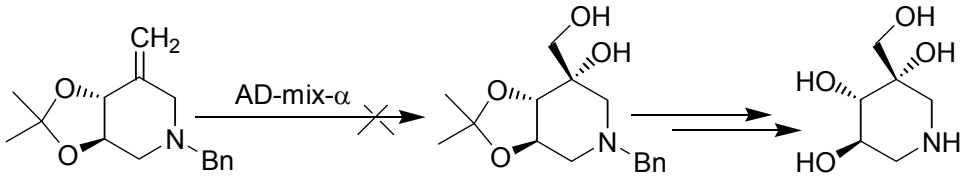
(242)



(243)

Figure 12

An attempt was also made to synthesize 5-hydroxy isofagomine (**46**) via Sharpless asymmetric dihydroxylation method.[17] However, **170** failed to react with AD-mix-α in t-BuOH-water system. Addition of methane sulfonamide did not help and hence the plan to synthesize **46** had to be abandoned.



(170) **(244)** **(46)**

Scheme 53

7. Synthesis of piperidine triols:

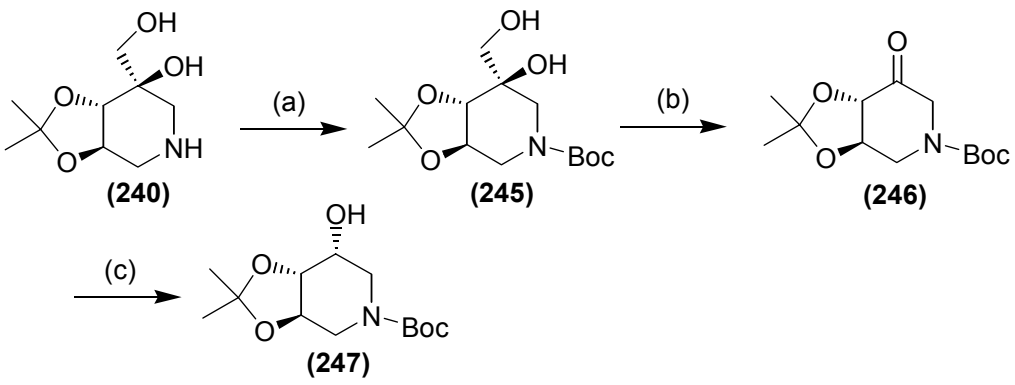
3,4,5-trihydroxy piperidines have been shown to be good selective inhibitors of glycosidases and are important structural analogs of the corresponding 1-deoxynojirimycin.[18] We realized that our precursors **170** and **171** were ideal for the synthesis of these molecules and we embarked upon devising a new synthetic route for these glycosidase inhibitors.

7.1 Synthesis of des(hydroxymethyl)deoxymannojirimycin:

In designing a route for piperidine triols, by utilizing the entities **170** and **171**, it was imperative to convert the olefin moiety to a hydroxy functionality via the reduction of the corresponding ketone. For this, two options were available: One

was ozonolysis and the other was by employing the periodate oxidation of the corresponding dihydroxy compound. The latter option seemed to be more feasible, since the dihydroxy functionality at C_5 was already available with us.

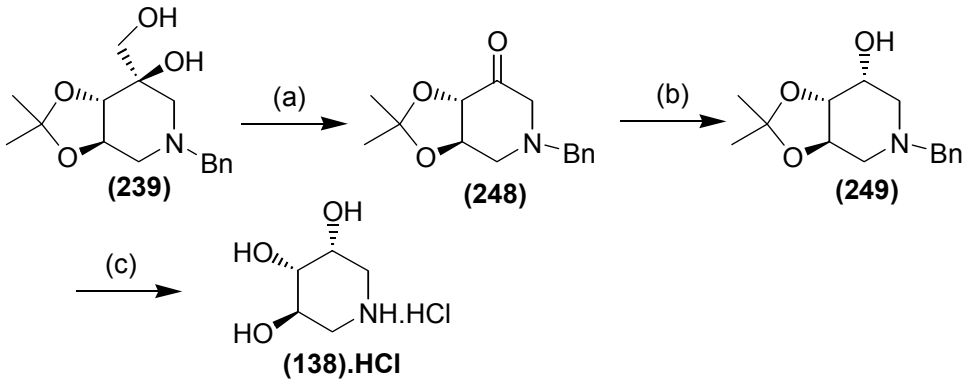
In this regard, it was envisioned that the amine functionality in **239** might get affected by the periodate oxidation and hence it was decided to replace the *N*-benzyl group by an electron withdrawing t-butoxycarbonyl (-Boc) group. For this purpose, the debenzylated product **240** was utilized. Depicted below (Scheme 54) is our initial effort toward the title molecule. Unfortunately, to our dismay and for reasons unknown, the sodium borohydride reduction of the ketone **246** failed to give good yield of **247** and therefore this route was concluded to be unsuitable.



Scheme 54

***Reagents and conditions**: (a) $(Boc)_2O$, TEA, DCM, 0 ° C to rt, overnight, 80 %; (b) $NaIO_4$, EtOH-H_2O (4:1), rt, 30 min, 70 %; (c) $NaBH_4$, MeOH, rt, 36 h then satd. NaCl, rt, 24 h, 25 %.*

The above failure led us to revert back to **239** and we attempted the same sequence of reactions as shown in Scheme 55. The periodate oxidation of **239** in ethanol-water system afforded **248** in 80% yield. It was necessary to work up the reaction within an hour since longer reaction times led to rapid decline in the yield. The ketone **248** was rather labile and had to be utilized immediately for the next step.



Scheme 55

Reagents and conditions: *(a) $NaIO_4$, EtOH-H_2O (4:1), rt, 1 h, 80 %; (c) $NaBH_4$, MeOH, rt, 40 h then satd. NaCl, rt, 24 h, 85 %; (c) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 36 h, quant.*

^{1}H NMR analysis of crude **248** revealed the presence of the aromatic protons appearing as a multiplet at δ 7.30. The H_{7a} proton appeared as a doublet of doublet at δ 4.26 (J = 10.2, 1.5 Hz), whereas the H_{3a} was observed as a ddd at 3.90 (J = 10.0, 9.8, 4.4 Hz). The benzylic protons appeared as a multiplet at δ 3.75. The doublet of doublet at δ 3.40 (J = 10.3, 4.4 Hz) integrating for one proton was assigned to H_{4eq}. The H_6 protons were observed as two doublets (J = 14.2 Hz) at δ 3.25 and 3.05, respectively. The H_{4ax} was associated with a dd like triplet at δ 2.72 (J = 10.2, 9.8 Hz). The singlets at δ 1.50 and 1.49 were attributed to the *gem*-dimethyl group.

The ketone **248** was subjected to sodium borohydride reduction in methanol to give the alcohol **249** in 85 % yield and 90:10 diastereomeric ratio (as confirmed by the GC analysis). The diastereomers were not separable at this stage.

In the ^{1}H NMR spectrum of **249**, the multiplet at δ 7.35 for five protons was attributed, as usual, to the aromatic hydrogens (Figure 22a). A multiplet appearing at δ 4.30, for one proton, was assigned to H_7. The H_{3a} proton was found appearing as a ddd (*J* = 10.3, 9.7, 4.4 Hz) at δ 4.10. The benzylic protons appeared as two extremely close doublets at δ 3.87 and 3.79 (*J* = 13.7 Hz), respectively. A multiplet between δ 3.45 - 3.30, integrating for two protons, was assigned to H_{7a} and H_{4eq}. The H_{6eq} proton was observed as a multiplet at δ 3.20. The hydroxy proton appeared as a broad singlet at δ 2.80. The H_{4ax} and H_{6ax} were found together as a multiplet at δ 2.40. The *gem*-dimethyl protons were assigned to the singlets at δ1.50 and 1.49 respectively.

The ^{13}C NMR spectrum displayed a total of thirteen signals (Figure 22c). The aromatic carbons were found appearing at δ 137.2, 128.7, 128.1 and 127.1, respectively. The signal at δ 110.1, which was absent in the DEPT experiment, was assigned to the quaternary isopropylidene carbon. The C_7 carbon appeared at δ 81.4 whereas C_{7a} and C_{3a} methine carbons were associated with the peaks at δ 70.6 and 65.7, respectively. The benzylic carbon was found at δ 61.5, whereas C_4 and C_6 carbons were assigned to the signals at δ 56.5 and 54.7, respectively. The signals at δ 26.5 and 26.3 were attributed to the *gem*-dimethyl group.

The GC-MS spectrum showed a molecular ion peak at *m/z* 263 (< 1 %), along with the tropylium ion peak at *m/z* 91 as the base peak (Figure 22b). Other prominent fragmentation peaks were observed at *m/z* 207, 172, 149 and 120.

Although, a rough indication of the stereochemistry of the newly formed hydroxy group was obtained at this stage, the outcome could be confirmed only after the removal of the two protecting groups.

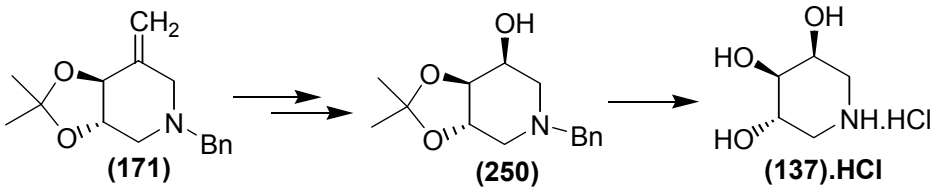
The molecule **249** was freed of its protecting groups in one-pot hydrogenation, at atmospheric pressure, in acidic medium using $Pd(OH)_2$ on charcoal as the catalyst. Removal of the solvent afforded des(hydroxymethyl)deoxymannojirimycin (**138**) as its hydrochloride salt. The salt was neutralized to obtain the free base and at this stage it was possible to separate the diastereomers by column chromatography (silica, chloroform-2-propanol-aq. NH_3, 8.5:1.5:0.5). The free amine was converted back to its hydrochloride salt for spectral characterization. The optical rotation ($[\alpha]_D^{25}$ = -12° (*c* 0.15, MeOH)) was found in close agreement with that reported[18] ($[\alpha]_D^{25}$ = -16° (*c* 0.9, MeOH)). The spectral data also matched well with literature values.[18]

The peak assignments in the ^1H NMR analysis (Figure 23a) were done on the basis of ^1H-^1H COSY experiment (Figure 23b). In the ^1H NMR spectrum, the multiplet appearing at δ 4.20, integrating for one proton, was assigned to H_5. The H_3 proton was observed as a ddd (*J* = 8.3, 7.8, 3.9 Hz) at δ 4.06. The H_4 proton was found appearing as a doublet of doublet at δ 3.75 (*J* = 7.6, 3.2 Hz). The coupling constants observed for H_4 showed that the relationship of H_4 and H_5 was *syn* and this, along with the optical rotation observed, proved the stereochemistry of the molecule. A doublet of doublet at δ 3.37 (*J* = 13.2, 3.9 Hz), was assigned to H_{2eq}. Another doublet of doublet at δ 3.26 (*J* = 12.9, 5.9 Hz), corresponding to one proton, was associated with H_{6eq}. The H_{6ax} was found appearing as a multiplet at δ 3.18, whereas H_{2ax} was observed as a doublet of doublet at δ 2.92 (*J* = 12.7, 8.4 Hz).

The ^{13}C NMR spectrum displayed a total of five peaks (Figure 23c). DEPT experiment confirmed that the molecule contained two methylene and three methine carbons. The methine peak at δ 70.7 was attributed to C_5, whereas the C_4

and C_3 carbons were found at δ 65.0 and 64.6, respectively. The C_2 and C_4 were observed at δ 45.9 and 45.4, respectively.

In a similar manner, adopting the same strategy, we successfully synthesized the naturally occurring[19] des(hydroxymethyl)deoxygalactonojirimycin **137**, starting from the L-*threo* precursor **170**. The optical rotation for **137**.HCl ($[\alpha]_D^{25}$ = +18° (*c* 0.14, MeOH)) was found to be in good agreement with that reported in literature[18] ($[\alpha]_D^{25}$ = +16° (*c* 0.5, MeOH)). The spectral data were also found to match exactly with that obtained for **138**.HCl.

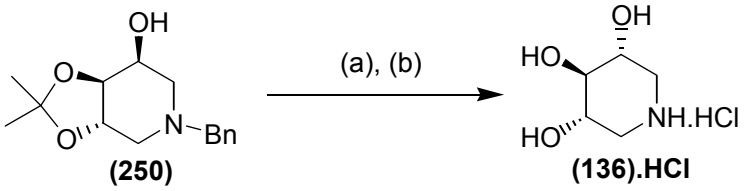


Scheme 56

7.2 Synthesis of des(hydroxymethyl)deoxynojirimycin:

The successful synthesis of the two enantiomeric piperidine triols was followed by the synthesis of another natural product, des(hydroxymethyl)deoxynojirimycin (**136**).[18, 19] This is a *meso* molecule and could be accessed easily by inverting the stereochemistry of the free hydroxy in either **249** or **250**. In our synthesis, we chose to start with **250** (Scheme 57) and invert the stereochemistry at C_7 by employing Mitsunobu protocol.[20] Cleavage of the p-nitrobenzoate, followed by the one pot removal of the protecting groups yielded **136**.HCl which was purified completely by column chromatography as the free base (silica, chloroform-2-propanol-aq. NH_3, 8.5:1.5:0.5), but was characterized as its hydrochloride salt. Since the molecule is *meso*, no rotation was observed

($[\alpha]_D^{25}$ = 0.0°, (*c* 0.2, MeOH), confirming the inversion of the hydroxy stereochemistry. The spectral data for **136**.HCl were in excellent agreement with those reported in literature.[18]



(250) **(136).HCl**

Scheme 57

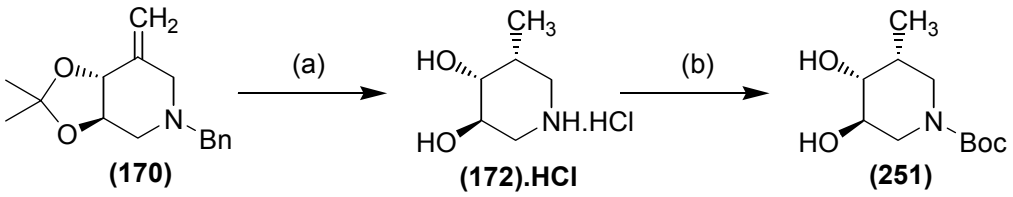
Reagents and Conditions: *(a) (i) Diisopropyl azodicarboxylate, PPh_3, p-nitrobenzoic acid, THF, rt; (ii) LiOH, MeOH, 60 % over two steps; (b) $Pd(OH)_2$ /C, HCl, MeOH, H_2, 1 atm, rt, 20 h, quant.*

In the ^{1}H NMR spectrum a doublet of doublet of doublet (ddd) at δ 3.72 (*J* = 10.2, 8.4, 4.4 Hz), integrating for two protons, was assigned to H_3 and H_5 protons (Figure 24a). The H_4 proton was observed as a triplet (*J* = 8.4 Hz) at δ 3.46. The H_{2eq} and H_{6eq} together appeared as a doublet of doublet at δ 3.40 (*J* = 12.7, 4.3 Hz) whereas their corresponding axial counterparts were observed as a doublet of doublet of doublet (ddd) at δ 2.86 (*J* = 12.7, 10.3 Hz).

The ^{13}C NMR spectrum displayed only three signals (Figure 24b). The C_4 methine carbon (as derived from the DEPT experiment) was observed at δ 74.3. The signal at δ 66.5 was assigned to C_3 and C_5. The methylene signal at δ 45.9 was assigned to C_2 and C_4.

8. Synthesis of 5′-deoxy-5-*epi*-isofagomine:

The success encountered in the synthesis of important glycosidase inhibitors (the piperidine triols), prompted us to go in for further development of our strategy. In this regard, we took up the synthesis of 5′-deoxy-5-*epi*-isofagomine (**172**) and its evaluation as a glycosidase inhibitor. As depicted in the scheme below (Scheme 58), one-pot reduction of the olefin followed by acetonide as well as *N*-benzyl deprotection afforded the title compound **172** in a diastereomeric ratio of 80:20. These diastereomers, however, were not separable and therefore, were converted to their corresponding *N*-Boc derivative **251**. At this stage, the diastereomers were separated by careful flash column chromatography to afford pure **251**. The stereochemistry of the methyl group was ascertained by COSY experiment.



(170) **(172).HCl** **(251)**

Scheme 58

Reagents and conditions: *(a) Pd/ C, MeOH, HCl, H_2, 1atm, rt, 12 h, 89 %; (b) $(Boc)_2O$, TEA, DCM, rt, 48 h, 75 %.*

The ^{1}H NMR spectrum of **251** displayed a doublet of doublet at δ 3.82, which could be attributed to the H_{2eq} proton (Figure 25a). This unusually deshielded position for this hydrogen was confirmed by COSY (Figure 25d). The H_3 proton appeared as a ddd at δ 3.72 (J = 10.8, 6.8 and 4.0 Hz), whereas H_4 was

found appearing as a doublet of doublet at δ 3.63 (*J* = 6.8, 4.0 Hz). The low coupling constant (*J* = 4.0 Hz) between H_4 and H_5 confirmed that H_5 was *cis* to H_4 and this confirmed the stereochemistry of the C_5 methyl group. A doublet of doublet appearing at δ 3.43 (*J* = 13.3, 6.7 Hz), integrating for one proton, was assigned to H_{6eq}. The H_{6ax} was observed as a doublet of doublet at δ 3.29 (*J* = 13.1, 2.8 Hz) whereas H_{2ax} was found at δ 3.18 as a doublet of doublet (*J* = 13.5, 6.7 Hz). The H_5 proton was found occluded at δ 2.15 as a multiplet, along with the two hydroxy protons. These hydroxy signals disappeared upon D_2O exchange. The *t*-butyl group of the –Boc moiety appeared as a singlet at δ 1.50. The C_5 methyl group was observed as a doublet (*J* = 7.1 Hz) at δ 0.98.

The ^{13}C NMR spectrum displayed a total of eight signals (Figure 25c). The signal at δ 155.7 was attributed to the carbonyl carbon of the –Boc group. The DEPT experiment revealed that the signal at δ 80.0 belonged to a quaternary carbon and was associated to the *t*-butyl group. The methyl carbons of the *t*-butyl group were found at δ 28.4. The C_4 and C_3 carbons appeared at δ 74.0 and 68.4, respectively. Both the C_2 and C_6 methylenes appeared together at δ 46.7. The signal at δ 32.5 was assigned to C_5, whereas the methyl group was observed at δ 12.1.

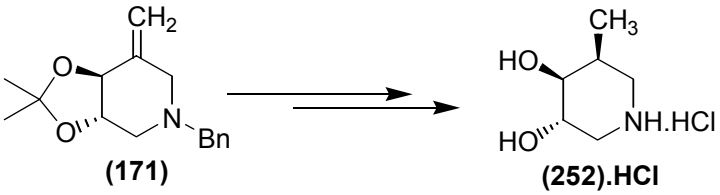
The GC-MS analysis of **251** showed a molecular ion peak at *m/z* 231 along with the base peak at *m/z* 57 (Figure 25b). Other fragmentation peaks were observed at *m/z* 186, 175, 158 and 145.

The molecule was easily freed of the *t*-Boc group by stirring its methanolic solution in the presence of conc. HCl for 4 h, affording quantitatively, **172** as its hydrochloride salt.

The ^{1}H NMR analysis of **172**.HCl (Figure 26a) showed the presence of two multiplets at δ 4.01 and 3.76, each integrating for one proton each and were attributed to the H_3 and H_4 protons, respectively. The H_{2eq} and H_{2ax} appeared as two close doublets of doublets at δ 3.25 (J = 13.2, 1.7 Hz) and 3.17 (14.7, 1.2 Hz), respectively. The H_{6eq} proton was observed as a doublet of doublet at δ 3.07 (J = 12.7, 4.3 Hz) whereas H_{6ax} appeared at δ 2.87 as a dd looking like a triplet (J = 12.7, 12.4 Hz). The H_5 proton was associated with the multiplet at δ 2.30 and the methyl group was responsible for the doublet at δ 0.9 (J = 7.1 Hz).

The ^{13}C NMR spectrum displayed a total of six signals (Figure 26b). The peaks at δ 68.2 and 65.4 were assigned to C_4 and C_3, respectively. As suggested by the DEPT experiment, the C_2 and C_6 methylenes appeared as two very close signals at δ 43.9 and 43.8, respectively. The C_5 carbon was attributed to the signal at δ 27.3, whereas the methyl group was found at δ 12.9.

Following exactly the same protocol, its enantiomer **252** was obtained from the L-*threo* precursor **171**.

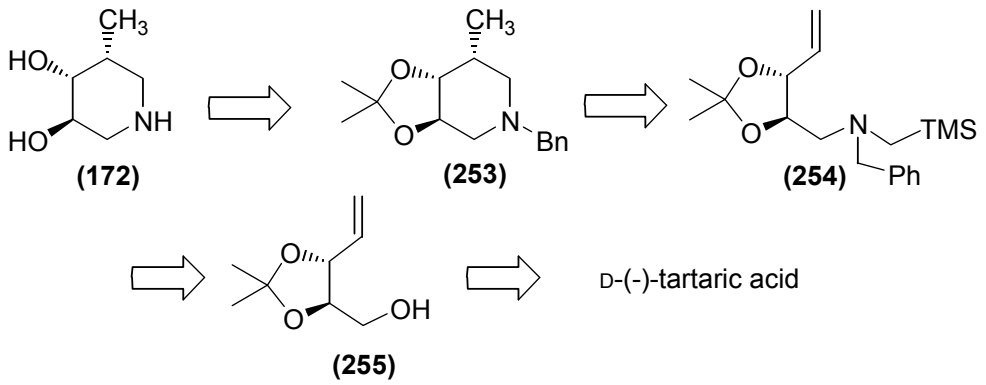


(171) **(252).HCl**

Scheme 59

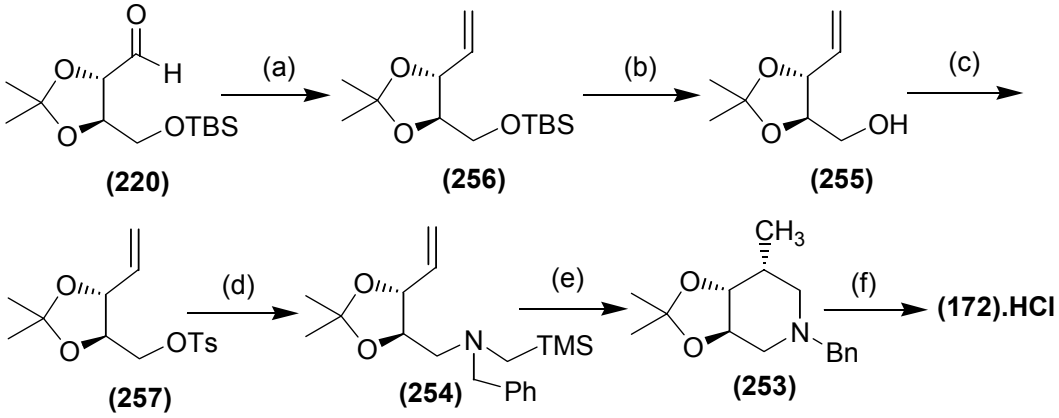
Although a fair diastereoselection was obtained in the reduction, we were not entirely satisfied by the outcome. Therefore, in order to obtain better diastereoselection, we decided to try a modified approach for the synthesis of **172**. In this regard, we wondered whether the same cyclization strategy, depicted

previously in Scheme 34, could be employed for the construction of **172**. Depicted in Scheme 60 is a new retrosynthetic approach for **172**.



Scheme 60

Therefore, in order to access **172** via **253**, we needed to carry out the PET mediated cyclization of **254**, which in turn, could be synthesized from **255**. The alcohol **255** could be derived from D-tartaric acid via a known route.[21] Depicted below, in Scheme 61, is our modified approach for **172**.



Scheme 61

Reagents and conditions: *(a) PPh_3CH_3I, n-BuLi, THF, -15 ° C to rt, 16 h, 60 %; (b) TBAF, THF, rt, 4 h, 90 %; (c) TsCl, Pyridine, DCM, rt, 24 h, 95 %; (d) $PhCH_2NHCH_2TMS$, Cs_2CO_3, TBAI, CH_3CN, reflux, 72 h, 58 %; (e) hν, DCN, 2-Propanol, 2h, 55 %; (f) $Pd(OH)_2$ /C, HCl, MeOH, H_2, 1atm, 28 h, quant.*

The synthesis started from the aldehyde **220**, previously synthesized from D-(-)-tartaric acid. Wittig olefination followed by the removal of the TBS group afforded **255** {($[\alpha]_D^{25}$ = +2.98 (*c* 1.4, $CHCl_3$)); lit.[21] for its enantiomer ($[\alpha]_D^{25}$ = -3.1 (*c* 1.01, $CHCl_3$))}. The compounds **255** and **256** were characterized by usual spectroscopic methods and the values were found to be in good accordance with those reported[21] and are detailed in the experimental section. The alcohol was converted to its corresponding tosylate **257** employing tosyl chloride and pyridine in dry DCM.

The ^{1}H NMR analysis of **257** displayed a set of two doublets (*J* = 8.3 Hz) at δ 7.75 and 7.35, respectively, indicating the presence of a 1,4-disubstituted phenyl ring. Two downfield multiplets at δ 5.75 and 5.25 integrating for one and two protons, respectively, pointed towards the presence of a monosubstituted olefin moiety. A bunch of peaks appearing as a multiplet between the region δ 4.25 to 4.0, integrating for three protons, was assigned to the H_4, H_5 and one of the hydrogens next to the -OTs moiety. The other hydrogen was found appearing as a multiplet at δ 3.85. The methyl protons of the tosyl group were found as a singlet at δ 2.45. The acetonide moiety appeared as two singlets at δ 1.40 and 1.35, respectively.

In the ^{13}C NMR analysis, a total of thirteen signals were found. DEPT experiment suggested that the signals at δ 144.8 and 132.3 belonged to quaternary carbons and were assigned to the substituted carbons of the phenyl ring. Other aromatic signals were found at δ 129.7 and 127.7. Another quaternary carbon present at δ 109.7 was attributed to the isopropylidene moiety. The methine signal at δ 134.0 and the methylene signal at δ 119.5 were assigned to the double bond. The signals at δ 78.5 and 77.7 belonged to C_4 and C_5,

respectively. The second methylene carbon, bearing the –OTs group, was found at δ 67.7. The *gem*-dimethyl group was observed at δ 26.7 and 26.4, respectively. The methyl carbon of the tosyl group was found appearing at 21.4.

The GC-MS spectrum of **257** displayed a peak at *m/z* 297 (M^+-15, 8%), with a base peak at *m/z* 43. The spectrum displayed other prominent fragmentation peaks at *m/z* 155 (34), 98 (29) and 83 (53).

With the tosylate now in hand, we now proceeded to prepare the amine **254**. This was done by the usual method of nucleophilic displacement of the –OTs group using $PhCH_2NHCH_2TMS$ as the nucleophile in refluxing acetonitrile and employing cesium carbonate as the base.

The IR spectrum of **254** displayed absorption peaks at 1454 and 1425 cm^{-1} respectively, characteristic of the olefin moiety. The peaks at 740 and 698 cm^{-1}, respectively, indicated the presence of a monosubstituted phenyl ring.

The ^1H NMR spectrum revealed the presence of five aromatic protons as a multiplet at δ 7.30 (Figure 27a). The olefinic protons appeared as two multiplets at δ 5.75 and 5.25, integrating for one and two protons, respectively. The H_4 and H_5 protons were observed as multiplets at δ 4.0 and 3.88, respectively. The benzylic protons were assigned to the set of two doublets at δ 3.75 (*J* = 13.7 Hz) and 3.45, respectively. The methylene protons (-C$\underline{H}_2$-N-), previously in the neighborhood of the -OTs group were now found shifted upfield, appearing as two doublet of doublets at δ 2.60 (*J* = 13.2, 4.1 Hz) and δ 2.53 (*J* = 13.2, 5.9 Hz). The methylene protons between the nitrogen and the TMS moiety (-N-C$\underline{H}_2$-TMS) were found appearing as two doublets (*J* = 14.6 Hz) at δ 2.13 and 2.01, respectively. The acetonide protons appeared as two singlets at δ 1.42 and 1.38. The singlet at δ 0.05 was associated with the TMS moiety.

The ^{13}C NMR spectral analysis showed a total of fifteen signals (Figure 27c). The peaks at δ 139.6 and 108.7 belonged to quaternary carbons and were assigned to the aromatic ring and the acetonide moieties, respectively. The rest of the aromatic carbons appeared at δ 128.8, 127.9, and 126.6, respectively. DEPT experiment suggested the presence of a methine signal at δ 135.4 and a methylene signal at δ 117.9, which belonged to the olefin functionality. The C_4 and C_5 methine carbons were found appearing at δ 80.9 and 79.8, respectively. The benzylic carbon (-N-$\underline{C}H_2$-Ph) was assigned to the signal at δ 62.6. The methylene carbon attached to C_5 was observed at δ 58.1. Another methylene signal at δ 46.9 arose from the carbon attached to the TMS functionality (-N-$\underline{C}H_2$-TMS). The *gem*-dimethyl signals were found at their usual place at δ 27.0 and 26.7, respectively. The carbons attached to the silicon atom appeared at δ -1.35.

The GC-MS spectrum displayed a molecular ion peak at *m/z* 333 (< 1%) with the base peak at *m/z* 91, along with other prominent fragmentation peaks at *m/z* 206 (57), 134 (12) and 73 (10) (Figure 27b).

For the PET activation, we proceeded to irradiate a solution of **254** in 2-propanol in the presence of DCN, using a Hanovia 450W medium pressure mercury vapor lamp as the light source. The progress of the reaction was monitored by GC and was found to be complete within two hours. Usual workup followed by column chromatography, yielded **253** in 55 % yield. To our pleasant surprise, the diastereoselection was found to be very high (>97 %, determined by GC).

In the ^1H NMR analysis of **253**, the aromatic protons were found appearing as a multiplet at δ 7.30 (Figure 28a). A multiplet at δ 3.65 was assigned to the benzylic protons. The H_{3a} proton was observed as a ddd at δ 3.59 (J = 10.3, 8.7

and 4.0 Hz). Another ddd at δ 3.24 (*J* = 9.9, 4.0 and 1.2 Hz) was assigned to the H_{7a} proton. The coupling constant of 1.2 Hz was attributed to the long-range coupling with one of H_6 protons. The low coupling constant (*J* = 4.0 Hz) for H_{7a} proved the *cis* relationship between H_{7a} and H_7 and thereby, the stereochemistry of the newly formed methyl group. The H_{4eq} appeared as a doublet of doublet at δ 2.97 (*J* = 10.6, 8.9 Hz), whereas H_{6eq} appeared as a doublet of doublet at δ 2.87 (*J* = 11.7 and 3.8 Hz). The H_{4ax} proton appeared as a triplet at δ 2.18 (*J* = 9.9 Hz). The H_{6ax} was also observed as a triplet at δ 1.82 (*J* = 11.1 Hz). The multiplet at δ 2.0 was assigned to H_7. The singlets at δ 1.46 and 1.44 were attributed to the isopropylidene methyls, whereas the doublet at δ 1.0 (*J* = 6.8 Hz) was associated with the C_7 methyl.

The ^{13}C NMR displayed a total of fourteen signals (Figure 28c). The peaks at δ 137.8, 128.7, 128.0 and 126.9 were assigned to the aromatic carbons. The isopropylidene quaternary carbon was found at δ 109.7. The DEPT experiment suggested the presence of three methine carbons at δ 85.3, 76.3 and 33.7, which were attributed to the C_{3a}, C_{7a} and the C_7 carbons, respectively. The three methylene signals at δ 61.7, 58.8 and 54.5 were associated with the benzylic, C_4 and C_6 carbons, respectively. The acetonide methyls were found at δ 26.7 and 26.5, respectively, whereas the C_7 methyl was found appearing at δ 15.2.

The GC-MS spectrum of **253** displayed a molecular ion peak at *m/z* 261 along with the base peak at *m/z* 91 (Figure 28b). Prominent peaks were also observed at *m/z* 246, 203, 134 and 120.

The protecting groups were easily removed by hydrogenation at atmospheric pressure under acidic conditions, using $Pd(OH)_2$ on charcoal as the catalyst, affording **172** as its hydrochloride salt.

9. Enzyme inhibition:

9.1 Enzyme inhibition and its types:

A number of substances may cause a reduction in the rate of an enzyme-catalyzed reaction. Some of these (eg. urea) are non-specific protein denaturants. Others, which generally act in a fairly specific manner, are known as inhibitors. Loss of activity may be either reversible, where activity may be restored by the removal of the inhibitor, or irreversible, where the loss of activity is time dependant and cannot be recovered during the time scale of interest. In the case of irreversible inhibition, the inhibitor (**I**) forms stable covalent bonds with the enzyme (**E**) (e.g. alkylation or acylation of an active site side chain). More important for most enzyme-catalyzed processes is the effect of reversible inhibitors. In the case of reversible inhibition, the inhibitor binds to an enzyme and prevents the formation of the enzyme-substrate (**ES**) complex or its breakdown to **E** + **P**.

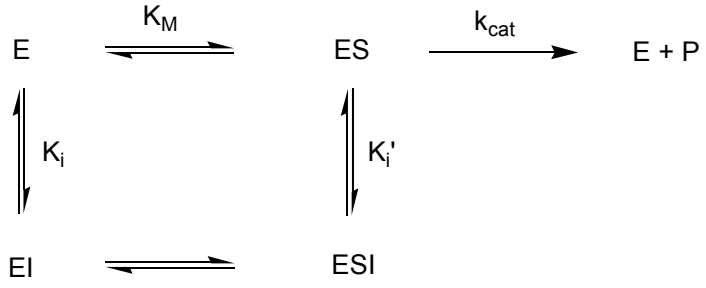
There are three basic mechanisms of reversible enzyme inhibition:

(a) Competitive

(b) Non-competitive

(c) Uncompetitive.

The difference between the three is in the nature of the binding of the enzyme and inhibitor and its effect on the enzyme substrate complex.



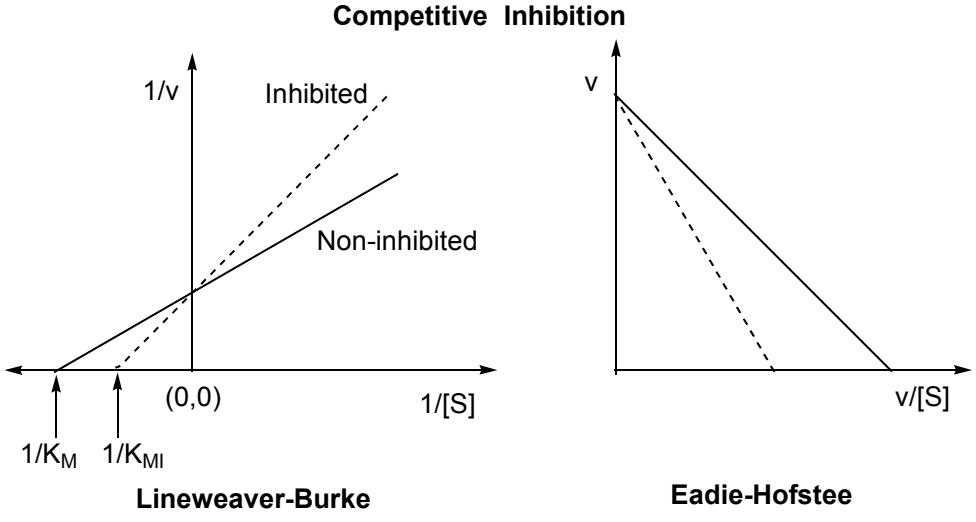
Scheme 62

In competitive inhibition, the inhibitor **I**, binds with the enzyme at the enzyme at the active site, thus making some of the enzyme unavailable to the substrate. This is the most common form of inhibition in single substrate enzyme systems.

In non-competitive inhibition, the inhibitor **I**, and the substrate **S**, bind simultaneously with the enzyme rather than competing for the same site. The resulting complex **ESI** is unable to form the product.

In the case of uncompetitive inhibition, the substrate binds with the active site to form the **ES** complex as normal, but the inhibitor **I**, then binds to the **ES** complex to form an **ESI** complex, which as with non-competitive inhibition, is unable to form the product. This particular form of inhibition is rare with single substrate enzyme systems.

The determination of the inhibition constant K_i is done based on the double-reciprocal Lineweaver-Burke or the Eadie-Hofstee plots. The effect of the three forms of inhibition on the Lineweaver-Burke and Eadie-Hofstee plots is illustrated below:



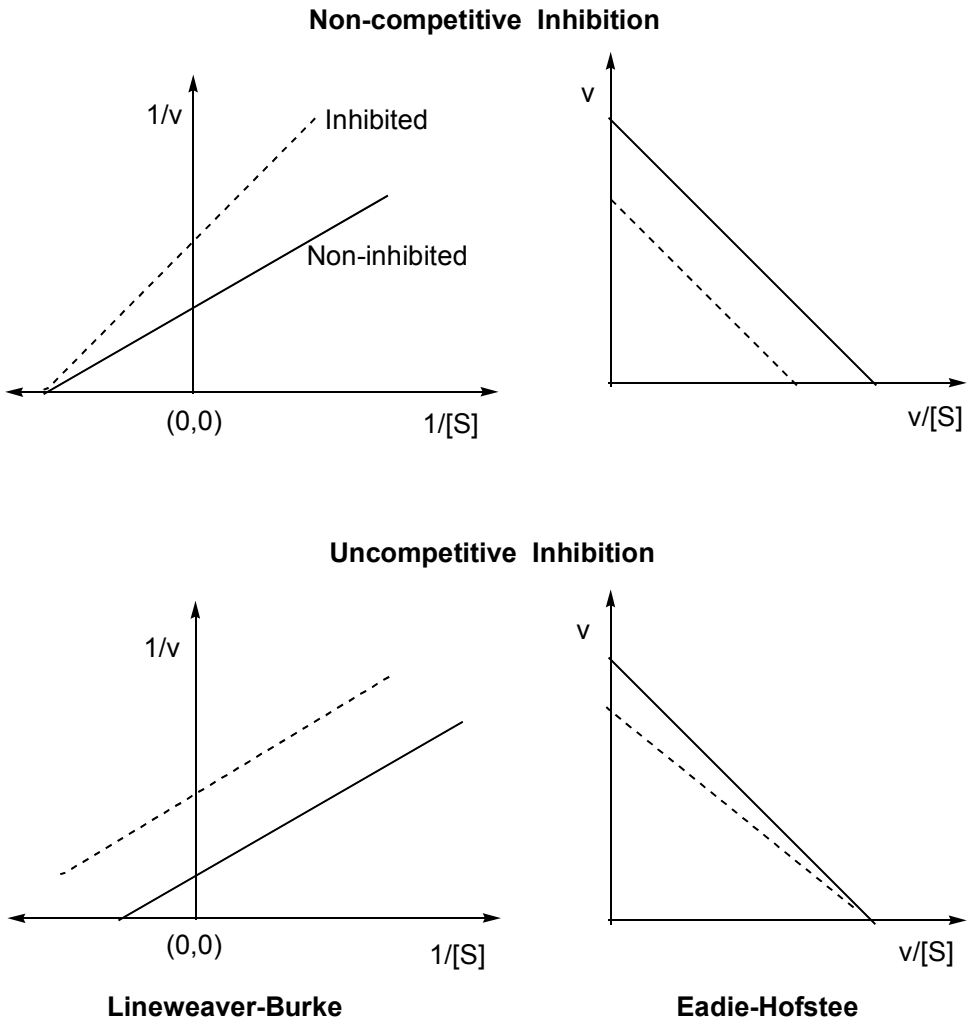
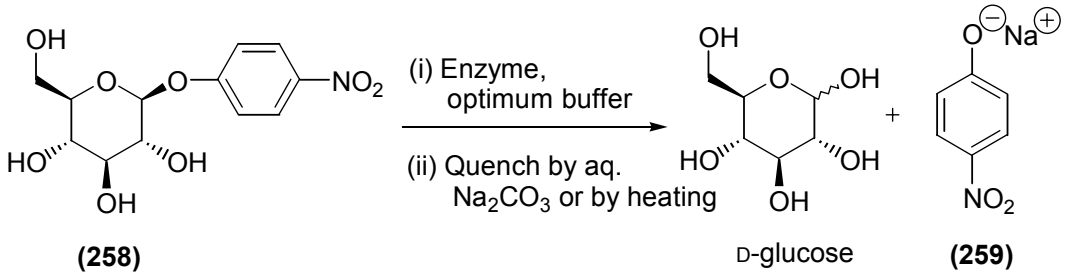


Figure 13

In the case of some glycosidases, an estimate of the rate of the reaction can be done by using the corresponding *o*- or *p*-nitrophenyl glycosides as substrates for the reaction. The amount of *o*- or *p*-nitrophenol released in the reaction can be estimated spectrometrically and the rate of the reaction (*v*) can be calculated, based on the optical density obtained.

Shown below, in Scheme 63, is an example for a β-glucosidase reaction using *p*-nitrophenyl β-D-glucoside as the substrate. The same principle is applied

for the inhibition assay and the type of inhibition obtained is easily determined from the Lineweaver-Burke plots.



(258) D-glucose **(259)**

Scheme 63

In the case of competitive inhibition, the lines have a common Y-intercept, whereas in the case of non-competitive inhibition, the lines meet on the X-axis. In the case of uncompetitive inhibition, the lines do not meet at all and are parallel.

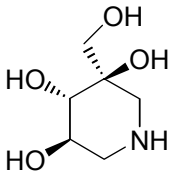
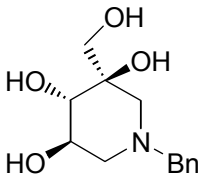
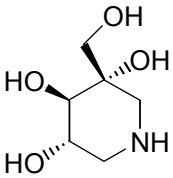
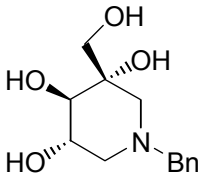
In a typical inhibition assay, the reaction is initiated by addition of appropriately diluted enzyme to a solution of the requisite quantities of substrate and inhibitor in a buffer optimum of the enzyme. The reaction is allowed to incubate at the temperature typical for that particular enzyme and at the end of a fixed reaction time, the reaction is quenched (the enzyme is inactivated) by chemical (aq. base) or thermal means (heating at high temperature). The optical density of this mixture is read at the spectrometer and the reaction rate determined.

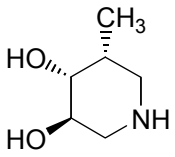
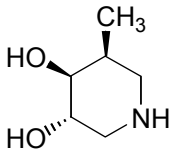
9.2 Enzyme inhibition studies:

The new compounds were tested for inhibition for β-glucosidase and β-mannosidase. Summarized below in tabular form are the results of the study. The

detailed procedures for the enzyme assay and inhibition study are given in the experimental section.

Figure 14

Compound	K_i (M)	
	β-Glucosidase (Sweet almonds, pH 6.0)	**β-Mannosidase** (Snail acetone, pH 4.0)
 **(173)**	9.6×10^{-5}	nd
 **(242)**	5.9×10^{-4}	nd
 **(241)**	5.8×10^{-4}	2.9×10^{-4}
 **(243)**	3.7×10^{-4}	1.5×10^{-3}

Compound	β-Glucosidase	β-Mannosidase
 **(172)**	3.0×10^{-5}	NI
 **(252)**	3.0×10^{-4}	NI

nd = Not determined.

NI = No inhibition.

The compounds tested displayed moderate to weak inhibition for the glycosidases under study (Figures 29 – 36). The dihydroxy compound **173** and the 5'-deoxy compound **172** displayed moderate inhibition for β-glucosidase. Compound **172**, however, did not inhibit β-mannosidase. The corresponding enantiomers were found to be weak inhibitors of β-glucosidase. The dihydroxy compound **241** displayed weak inhibition of β-mannosidase. The corresponding *N*-benzyl compounds were found to be weaker inhibitors of glycosidases as compared to the free bases.

10. Conclusions:

In short, we have designed and developed a new synthetic strategy for a general route towards 1-*N*-iminosugar type glycosidase inhibitors, utilizing PET

mediated cyclizations of α-trimethylsilylmethylamine radical cation to a proximate tethered π-functionality. The generality of the method developed, has been demonstrated by the synthesis of both the enantiomers of the potent glucosidase inhibitor, Isofagomine, along with selective inhibitors of the 3,4,5-trihydroxy piperidine class, of which two are naturally occurring. Good to moderate diastereoselection was observed in the generation of the new stereocenter. The acetonide protecting group was crucial in governing the diastereomeric ratio. Any other acyclic protecting group, probably, would not have resulted in good selectivity in the generation of the new stereocenter. The other molecular entities synthesized were tested for their inhibitory activity and some of them were found to be moderate inhibitors of the enzymes tested.

In this dissertation, we have synthesized precursors of the D- as well as L-*threo* class (in which the C_3 and C_4 hydroxy are *anti*) for the synthesis of a variety of 1-*N*-iminosugars. It is but obvious that the precursors of D- and L-*erythro* class (in which the C_3 and C_4 hydroxy are *syn*) would lead to other 1-*N*-iminosugars of the required stereochemistry.

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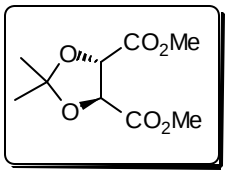
Experimental Section:

General:

All reagents were used as supplied. All reactions involving hygroscopic reagents were carried out under an argon atmosphere using oven-dried glassware. Dichloromethane, dimethyl sulfoxide and acetonitrile were distilled from CaH_2 under argon and stored over molecular sieves. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed either by TLC or by gas chromatography. Optical rotations were obtained using JASCO 181 digital polarimeter using Na light. ^{1}H and ^{13}C NMR were run on Bruker AC-200, MSL-300, DRX-500 instruments. IR spectra were recorded on a Perkin Elmer FT-IR model 1620. Mass spectra (EI, 70eV) were obtained on a Finnigan-Mat 1020 instrument. GC/MS was performed on a Shimadzu QP 5000 GC/MS coupled to Shimadzu 17A GC using a DB1 column. GC analysis was performed on Perkin Elmer 8700 and Varian CP 3800 GCs using a SGE BP1, BP20 and Varian Chrompack CP-Sil-5CB columns. Melting points were determined on a Thermonik Campbell melting point apparatus and are uncorrected. Column chromatography was performed using 100-200 mesh silica gel obtained from SRL India Ltd. The glycosidases and their corresponding *p*-nitrophenyl β-D-glycosides were obtained from Sigma-Aldrich Ltd. Optical density measurements were carried out on Varian CARY-50 BIO UV-Vis spectrophotometer.

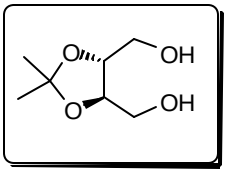
(1) Preparation of dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (207):



To a suspension of D-(-)-tartaric acid (5.0 g, 33.3 mmol) in dry methanol (2.0 mL), was added 2,2-dimethoxypropane (9.4 mL, 76.8 mmol) and *p*-toluene sulfonic acid (0.010 g). The resulting mixture was warmed for about two hours, on an oil bath at 50 ºC, till a dark orange color developed. Dry cyclohexane (22.5 mL) and a further quantity of 2,2-dimethoxy propane (3.9 mL, 38.2 mmol) 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 (bp 53.0 ºC) and cyclohexane-acetone (bp 54.5 ºC) over a period of 24 h. When the vapor temperature fell below 50 ºC, 2,2-dimethoxypropane (1 mL) was added and the oil bath temperature was increased till the vapor temperature reached 78 ºC. 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 ºC/ 0.5 mm, lit.[1] bp = 82-90 ºC/ 0.02 mm) to afford the title compound (6.90 g, 95 %) as a pale yellow liquid.

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

(2) Preparation of [(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (206):



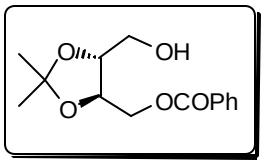
A solution of **207** (1.0 g, 4.60 mmol) in dry THF (9 mL) was added to a stirring suspension of lithium aluminium hydride (0.185 g, 4.87 mmol) in dry THF (4.5 mL) at 0 ºC, over a period of 15 min. After stirring for about an hour at rt, the reaction mixture was refluxed for about 6 h. Upon cooling to 0 ºC, 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 (10 mL) and the combined filtrate was concentrated under vacuum. This crude mixture upon column chromatography (silica, pet ether-ethyl acetate, 2:3) afforded **206** (0.707 g, 95 %) as a syrupy mass.

IR (neat) : 3450 cm^{-1} (broad)

^{1}H NMR (200 MHz, $CDCl_3$): : δ 4.0 (m, 2H), 3.75 (m, 4H), 2.75 (bs, 2H, D_2O exchangeable), 1.45 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): : δ 108.7, 78.1, 61.8, 26.4.

(3) Preparation of [(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl benzoate (208):

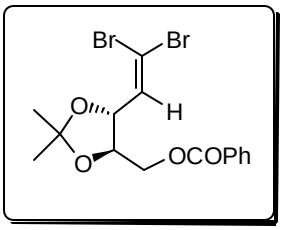


To a stirring solution of **206** (1.0 g, 6.17 mmol) in dry DCM (15 mL) was added pyridine (0.75 mL, 9.3 mmol) at 0 °C. This was followed by the addition of a solution of benzoyl chloride (0.72 mL, 6.17 mmol) in dry DCM (3 mL) over a period of 15 min. The resulting reaction mixture was maintained at 0 °C for another 30 min and then stirred at rt for about 15 h. Water (10 mL) was added and the layers were separated. The organic layer was washed successively with water (3 x 10 mL) and brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was column chromatographed (silica, pet ether-ethyl acetate, 7:3) to afford pure **208** (0.985 g, 60%) as a colorless oil.

$[\alpha]_D^{25}$	**:**	+7.9° (*c* 0.9, MeOH)
For the (4*S*,5*S*) isomer, $[\alpha]_D^{25}$	**:**	-7.4° (*c* 3.5, MeOH)
IR ($CHCl_3$)	**:**	3471 (broad), 1714, 756, 711 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 8.1 (m, 2H), 7.6 (m, 1H), 7.5 (m, 2H), 4.52 (dd, *J* = 11.7, 4.4 Hz, 1H), 4.42 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.25 (m, 1H), 4.05 (m, 1H), 3.90 (dd, *J* = 12.2, 3.4 Hz, 1H), 3.75 (dd, *J* = 12.2, 4.4 Hz, 1H), 2.25 (bs, 1H), 1.49 (s, 6H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 166.2, 132.9, 129.4, 128.2, 109.6, 78.3, 75.2, 64.2, 61.8, 26.7.

Mass: m/z (%) **:** 251 (M^+-15)(73), 177 (31), 105 (100), 77 (43)

(4) Preparation of [(4*R*,5*R*)-5-(2,2-bromovinyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl benzoate (211):



DMSO (0.53 mL, 7.52 mmol) in dry DCM (2 mL) was added to a stirring solution of oxalyl chloride (0.25 mL, 2.82 mmol) in dry DCM (5 mL) at –78 °C. After about 5 min, the solution of **208** (0.500 g, 1.88 mmol) in dry DCM (4 mL) was added drop wise over a period of 5 min. The resulting reaction mixture was stirred at –78 °C for another 2 h, following which a solution of triethyl amine (1.31 mL, 9.40 mmol) in dry DCM (3 mL) was added. The reaction mixture was allowed to warm to rt , extracted using DCM, washed with water and brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the aldehyde **210** (0.476 g, 96 %) which was quickly utilized for the next step.

To a stirring solution of carbon tetrabromide (1.068 g, 3.22 mmol) in dry DCM (9 mL) was added in small portions, triphenyl phosphine (1.689 g, 6.44 mmol), at 0 °C. After 5 min, a solution of the aldehyde **210** (0.425 g, 1.61 mmol) in dry DCM (2 mL) was added and the resulting mixture was stirred at 0 °C for over 4 h. A large excess of pet ether (25 mL) was added and the slurry was quickly passed through a short pad of silica. The precipitated solid was again dissolved in DCM and re-precipitated using pet ether. The supernatant liquid was also passed through the pad of silica. This procedure was repeated twice and the combined column fractions were concentrated under reduced pressure. The oily mass obtained was

further purified by flash column chromatography (silica, pet ether-ethyl acetate, 17:3) to afford **211** (0.322 g, 85 %) as colorless oil.

$[\alpha]_D^{25}$: +14.1° (*c* 2.08, $CHCl_3$)

For the (4*S*,5*S*) isomer, $[\alpha]_D^{25}$: -14.6° (*c* 2.26, $CHCl_3$)

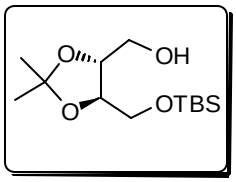
IR ($CHCl_3$) : 1720, 759, 713, 669 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.10 (m, 2H), 7.60 (m, 1H), 7.50 (m, 2H), 6.55 (d, *J* = 8.3 Hz, 1H), 4.68 (t, *J* = 8.3 Hz, 1H), 4.60 (dd, *J* = 12.2, 4.4 Hz, 1H), 4.43 (dd, *J* = 12.2, 4.9 Hz, 1H), 4.15 (m, 1H), 1. 49 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.2, 134.4, 132.4, 128.9, 127.6, 109.7, 93.9, 77.4, 76.9, 62.5, 26.1.

Mass: *m/z* (%) : 420 (M^+)(< 1), 405 (41), 362 (4), 344 (10), 256 (83), 177 (80), 105 (100).

(5) Preparation of [(4*R*,5*R*)-2,2-dimethyl-5-(*tert*-butyldimethylsilyloxymethyl)-1,3-dioxolan-4-yl]methanol (219):



Triethyl amine (0.95 mL, 6.79 mmol) was added to a dilute solution of **206** (1.0 g, 6.17 mmol) in dry DCM (24 mL) at 0 ºC. To this was added a solution of TBSCl (1.024 g, 6.79 mmol) in dry DCM (14 mL), over a period of 15 min. The reaction mixture was allowed to stir at rt for about 36 h. Usual work up and extraction of the reaction mixture in DCM (25 mL) followed by washing with water (3 x 10 mL), brine (10 mL) and drying over anhydrous Na_2SO_4 and removal of the

solvent gave a crude residue. This residue upon column chromatographic purification (silica, pet ether-ethyl acetate, 5:1) afforded pure **219** (1.450 g, 85 %) as a colorless liquid.

$[a]_D^{25}$ **:** +5.9° (*c* 9.4, MeOH)

For the (4*S*,5*S*)-isomer, $[a]_D^{25}$ **:** -4.8° (*c* 1.2, MeOH), lit.[2] $[a]_D^{25}$ = -5.4 (*c* 1.5, MeOH)

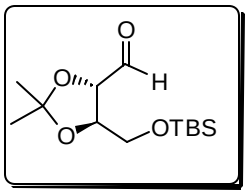
IR (neat): **:** 3463, 1253, 1379 cm^{-1}.

^{1}H NMR: (200 MHz, $CDCl_3$) **:** δ 4.0 (m, 1H), 3.85 (m, 2H), 3.65 (m, 3H), 2.65 (bs, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 0.85 (s, 9H), 0.05 (s, 6H).

^{13}C NMR: (50 MHz, $CDCl_3$) **:** δ 109.2, 80.2, 78.2, 63.9, 62.9, 27.2, 27.1, 26.0, 18.4, -5.3.

Mass *m/z* (%) **:** 261 (M^+-15)(6), 219 (8), 161 (23), 131 (67), 117 (36), 75 (100).

(6) Preparation of (4*S*,5*R*)-2,2-dimethyl-5-(*tert*-butyldimethylsilyloxymethyl)-1,3-dioxolane-4-carbaldehyde (220):



To a solution of oxalyl chloride (0.47 mL, 5.43 mmol) in dry DCM (5 mL) was added a solution of DMSO (1.03 mL, 14.4 mmol) in dry DCM (5 mL) at –78 ºC. After about 5 min, the alcohol **206** (1.0 g, 3.62 mmol) in dry DCM (5 mL) was added drop wise over a period of 5 min. After the resulting white suspension was stirred for 2 h at –78 ºC, a solution of triethyl amine (2.52 mL, 18.1 mmol) in dry DCM (2 mL) was added. The reaction mixture was allowed to warm to rt and was quenched by the

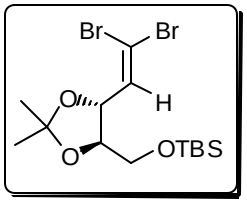
addition of water (10 mL). This mixture was extracted in DCM (20 mL) and the DCM layer was washed with water (4 x 10 mL) and brine (10 mL). The organic extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica, pet ether-ethyl acetate, 5:1) to afford **220** (0.955 g, 96 %).

IR (Nujol): **:** 1735, 1255, 1373 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 9.75 (d, *J* = 1.5 Hz, 1H), 4.35 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.10 (m, 1H), 3.75 (d, *J* = 4.4 Hz, 2H), 1.40 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H).

Mass *m/z* (%) **:** 259 (M^+-15) (4), 259 (6), 217 (18), 159 (57), 129 (81), 117 (100).

(7) Preparation of 5-[(*tert*-butyldimethylsilyl)oxy]-1,1-dibromo-1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-ene (221):



To a stirring solution of carbon tetrabromide (1.210 g, 3.65 mmol) and triphenyl phosphine (1.910 g, 7.3 mmol) in dry DCM (15 mL) at 0 °C, was added the solution of **220** (0.500 g, 1.82 mmol) in DCM (3 mL),. The reaction mixture was stirred at 0 °C for two hours and to it was added a large excess of hexane to precipitate the triphenyl phosphine oxide. The resulting mixture was quickly passed through a short pad of silica. The solvent was removed under reduced pressure and the residue was column chromatographed (silica, pet ether-ethyl acetate, 24:1) to afford pure **221** (0.508 g, 65 %) as a colorless liquid.

$[\alpha]_D^{20}$: +7.2° (*c* 0.44, $CHCl_3$).

L-isomer: $[\alpha]_D^{20}$: -8.0° (*c* 0.9, $CHCl_3$)

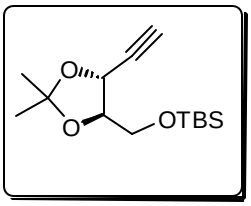
IR (neat) : 1625, 1461, 1371, 1217 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.50 (d, *J* = 8.8 Hz, 1H), 4.65 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.80 (m, 3H), 1.40 (s, 6H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 136.1, 109.7, 93.5, 80.6, 77.9, 62.3, 26.8, 25.7, 18.1, -5.4.

Mass *m/z* (%) : 415 (M^+-15) (1), 343 (1), 315 (39), 285 (6), 256 (5), 200 (11), 137 (45), 73 (86), 57 (100).

(8) Preparation of 5-[(*tert*-butyldimethylsilyl)oxy]-1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-yne (222):



To a solution of **221** (0.600 g, 1.39 mmol) in dry THF (4 mL) was added a 2M hexane solution of n-BuLi (3.5 mL, 7 mmol) at –78 °C, over a period of 5 min. The reaction mixture was stirred at –78 °C for an hour and was quickly brought up to 0 °C. It was quenched by rapid addition of a large excess of water (15 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed by rotary-evaporation and the residue was purified by column chromatography (silica, pet ether-ethyl acetate, 19:1) to afford **222** (0.340 g, 90 %) as a colorless oil.

$[\alpha]_D^{20}$: +11.1° (*c* 0.97, $CHCl_3$).

L-isomer: [α]$_D^{20}$: -10.7° (*c* 1.18, $CHCl_3$).

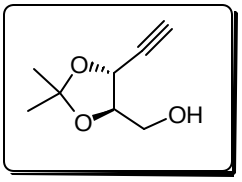
IR (neat) : 3300, 1460, 1380, 1260, 1220 cm^{-1}.

^{1}H NMR (200 MHz), $CDCl_3$) : δ 4.60 (dd, *J* = 7.4, 1.9 Hz, 1H), 4.15 (m, 1H), 3.80 (d, *J* = 4.4 Hz, 2H), 2.55 (d, *J* = 1.9 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 110.4, 82.0, 81.1, 74.1, 66.8, 61.8, 26.7, 26.0, 25.6, 18.1, -5.6.

Mass *m/z* (%) : 255 (M^+-15) (8), 213 (2), 197 (3), 155 (100), 125 (67), 73 (44).

(9) Preparation of 1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-ynitol (201):



To a solution of **222** (0.700 g, 2.59 mmol) in dry THF (3 mL), was added a 1M solution of TBAF in THF (3.10 mL, 3.10 mmol) at 0 °C. The reaction mixture was stirred at rt for about 4 h and to this was added water (3 mL) followed by ethyl acetate (7 mL) and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture upon column chromatography (silica, chloroform-ethyl acetate, 9:1) afforded pure **201** (0.345 g, 85 %) as a colorless liquid.

[α]$_D^{20}$: +6.9° (*c* 2.13, MeOH).

L-isomer: [α]$_D^{20}$: -7.3° (*c* 2.0, MeOH).

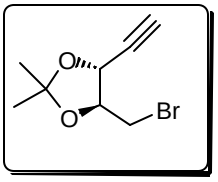
IR ($CHCl_3$) : 3446, 3290, 1460, 1379, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.60 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.20 (m, 1H), 3.94 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.68 (dd, *J* = 12.3, 3.2 Hz, 1H), 2.55 (d, *J* = 1.9 Hz, 1H), 1.80 (bs, 1H), 1.50 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 110.6, 82.0, 80.7, 74.6, 66.2, 60.7, 26.6, 25.8.

Mass *m/z* (%) : 141 (M^+-15) (64), 124 (11), 96 (47), 80 (31), 52 (100).

(10) Preparation of (4*S*,5*R*)-4-(bromomethyl)-5-ethynyl-2,2-dimethyl-1,3-dioxolane (175):



Triphenyl phosphine (1.488 g, 5.67 mmol) was added in small portions to a stirring solution of carbon tetrabromide (1.500 g, 4.54 mmol) and **175** (0.590 g, 3.78 mmol) in dry DCM (12 mL) at 0 °C. The resultant dark red solution was stirred at rt for an hour. Large excess of hexane was added to the reaction mixture and the contents were quickly filtered through a pad of silica. Removal of the solvent under reduced pressure followed by column chromatography (silica, pet ether-ethyl acetate, 94:6) afforded **175** (0.660 g, 80 %) as a colorless oil.

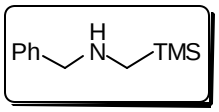
IR (neat) : 3310, 1400, 695 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.58 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.33 (m, 1H), 3.50 (m, 2H), 2.59 (d, *J* = 2.4 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 111.6, 80.7, 77.3, 75.0, 69.2, 31.1, 27.0, 26.3.

GC/MS: m/z : 205, 203 (both M^+-15), 145, 143, 96.

(11) Preparation of *N*-benzyl trimethylsilylmethylamine (176):



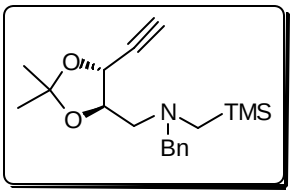
A mixture of benzyl amine (1.02 mL, 9.33 mmol), chloromethyltrimethylsilane (1.56 mL, 11.19 mmol) and anhydrous K_2CO_3 (2.579 g, 18.66 mmol) in dry CH_3CN (26 mL) was refluxed for about 8 h. The reaction mixture was filtered and the filtrate concentrated. The crude mixture upon column chromatography (silica, pet ether-ethyl acetate, 3:2) afforded **176** (1.35 g, 75 %) as a colorless oil.

IR (neat) : 1494, 1247, 860, 734, 698

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.3 (m, 5H), 3.82 (s, 2H), 2.05 (s, 2H), 1.30 (bs, 1H), 0.05 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) : 140.4, 128.2, 128.1, 126.7, 126.7, 58.0, 39.4, -2.6

(12) Preparation of 1-[benzyl(trimethylsilylmethyl)amino]-1,4,5-trideoxy-2,3-*O*-(1-methylethylidene)-D-*threo*-pent-4-ynitol (174):



A mixture of **175** (0.550 g, 2.51 mmol), $PhCH_2NHCH_2TMS$ (0.970 g, 5 mmol), anhydrous K_2CO_3 (1.73 g, 12.55 mmol) and TBAI (0.050 g, 0.13 mmol) in dry CH_3CN (12 mL) was refluxed under an argon atmosphere for about 96 h. The reaction mixture was filtered and the filtrate upon concentration afforded a dark orange residue, which was column chromatographed (silica, pet ethyl-ethyl acetate, 19:1) to afford pure **174** (0.540 g, 65 %) as a colorless liquid.

[a]$_D^{20}$: +1.2° (*c* 21.2, $CHCl_3$).

L-isomer, [a]$_D^{20}$: -0.7° (*c* 11.0, $CHCl_3$).

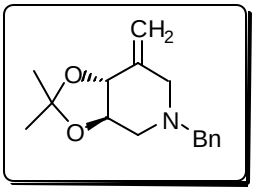
IR (neat) : 3310, 760, 720 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.30 (m, 5H), 4.39 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.25 (m, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 2.67 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.57 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.50 (d, *J* = 2.0 Hz, 1H), 2.16 (d, *J* = 14.7 Hz, 1H), 2.02 (d, *J* = 14.7 Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 0.05 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 139.6, 128.8, 128.0, 126.7, 110.2, 81.6, 80.7, 74.1, 68.8, 62.8, 58.4, 47.2, 26.9, 25.9, -1.3.

Mass *m/z* (%) : 331 (M^+) (8), 258 (10), 206 (100), 91 (80), 73 (19).

(13) Preparation of (3a*R*,7a*R*)-5-benzyl-2,2-dimethyl-7-methylenehexahydro[1,3]dioxolo[4,5-*c*]pyridine (170):



A solution containing **174** (0.960 g, 2.9 mmol) and 1,4-dicyanonaphthalene (0.160 g, 0.9 mmol) in 2-propanol (500 mL) was irradiated in an open vessel using a 450 W Hanovia medium pressure mercury vapor lamp as the light source. The lamp was immersed in a Pyrex water-jacketed immersion well so as to allow only wavelengths greater than 280 nm to pass through. After about 90 min of irradiation, the consumption of the starting material was found to be almost complete and the irradiation was discontinued. The solvent was removed under reduced pressure

and the residue was column chromatographed (silica, pet ether-acetone, 20:1) to afford the cyclized product **170** (0.450 g, 60 %) as a white crystalline solid.

m.p. : 94 – 96 °C.

$[\alpha]_D^{20}$: -50.9° (*c* 1.9, $CHCl_3$).

For (3a*S*,7a*S*) isomer $[\alpha]_D^{20}$: +49.2° (*c* 0.7, $CHCl_3$).

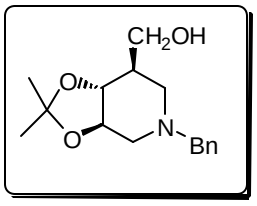
IR ($CHCl_3$) : 1674, 769, 669 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.30 (m, 5H), 5.05 (d, *J* = 1.0 Hz, 1H), 4.90 (d, *J* = 1.0 Hz, 1H), 3.80 (m, 1H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.57 (m, 1H), 3.33 (m, 2H), 2.80 (d, *J* = 12.7 Hz, 1H), 2.37 (t, *J* = 10.3 Hz, 1H), 1.45 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 140.4, 137.7, 128.8, 128.2, 127.1, 110.9, 105.1, 81.7, 77.5, 61.5, 57.1, 54.5, 26.8, 26.7.

Mass *m/z* (%) : 259 (M^+) (5), 201 (67), 91 (100).

(14) Preparation of [(3a*R*,7*R*,7a*R*)-5-benzyl-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-yl]methanol (234):



To a stirred solution of **170** (0.130 g, 0.5 mmol) in THF (4 mL), was added drop wise a 0.5M THF solution of 9-BBN (10 mL, 5 mmol). The resulting mixture was stirred at rt for about 20 h. To this was added successively water (2 mL), 1N NaOH solution (1.5 mL) and 30 % solution of H_2O_2 (1.5 mL) at 0 °C. The mixture was stirred at rt for 4 h and extracted thrice in ethyl acetate (5 mL). The organic

extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue upon chromatographic purification (silica, pet ether-ethyl acetate, 3:2) yielded **234** (0.063 g, 45 %) as a gummy mass.

$[\alpha]_D^{20}$: +14.8° (*c* 0.5, MeOH).

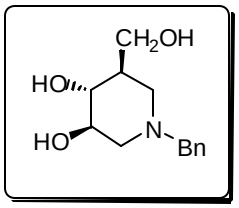
For (3a*S*,7*S*,7a*S*) isomer, $[\alpha]_D^{20}$: -14.0° (*c* 1.7, MeOH).

^{1}H NMR (200 MHz, $CDCL_3$) : δ 7.30 (m, 5H), 3.70 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.65 (m, 4H), 3.24 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.15 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.95 (dd, *J* = 11.3, 3.9 Hz, 1H), 2.18 (m, 2H), 1.95 (m, 1H), 1.45 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 129.0, 128.2, 127.3, 110.9, 82.1, 77.3, 63.5, 61.9, 54.3, 53.4, 41.5, 26.7.

GC/MS *m/z* : 277 (M^+), 262, 216, 201, 186, 158, 132, 120, 91.

(15) Preparation of (3*R*,4*R*,5*R*)-1-benzyl-5-(hydroxymethyl)-piperidine-3,4-diol (*N*-benzyl isofagomine) (235):



Conc. HCl (0.1 mL) was added to a stirring solution of the alcohol **234** (0.020 g, 0.07 mmol) in distilled methanol (1 mL) at 0 °C. The reaction mixture was allowed to stir at rt for over an hour and was basified by the addition of a slight excess of NH_4OH solution. The solvent was removed under reduced pressure and the residue was allowed to stand overnight in dry chloroform (2 mL). This residue was washed again with chloroform (1 mL) and the combined organic portion was

concentrated. Flash column chromatography (silica, chloroform-methanol, 20:1) afforded pure *N*-benzyl isofagomine (0.017 g, ~100 %) as a thick gum.

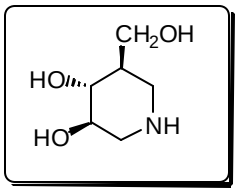
$[\alpha]_D^{20}$ **:** +12.6° (*c* 0.39, EtOH).

For (3*S*,4*S*,5*S*) isomer, $[\alpha]_D^{20}$ **:** -13.2° (*c* 1.1, EtOH).

^{1}H NMR (200 MHz, D_2O) **:** δ 7.30 (m, 5H), 3.73 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.55 (m, 4H), 3.15 (dd, *J* = 10.2, 9.3 Hz, 1H), 2.95 (m, 2H), 1.95 (m, 2H), 1.70 (m, 1H).

^{13}C NMR (75 MHz, D_2O) **:** δ 128.9, 127.1, 126.5, 72.4, 69.8, 60.0, 59.4, 55.5, 52.4, 41.3.

(16) Preparation of (3*R*,4*R*,5*R*)-5-(hydroxymethyl)piperidine-3,4-diol (Isofagomine) (38):



A solution of *N*-benzyl isofagomine (0.016 g, 0.06 mmol) in ethanol was hydrogenated (75 psi, rt) in the presence of $Pd(OH)_2$ on charcoal (20 %) (0.002 g) for about 10 h. The reaction mixture was passed through a pad of Celite and the solvent was evaporated off to yield **38** (0.0094 g, 95 %) as a semi-solid.

$[\alpha]_D^{20}$ **:** +16.2° (*c* 0.32, EtOH).

For 38.HCl, $[\alpha]_D^{20}$ **:** +20.7° (*c* 0.4, EtOH),

lit[3] $[\alpha]_D^{20}$ = +19.6° (*c* 0.85, EtOH).

For (-)-isofagomine

(238), [α]$_D^{20}$: -15.7° (*c* 0.19, EtOH)

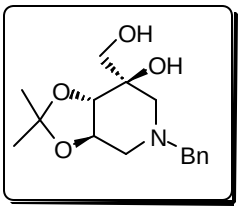
For 238.HCl, [α]$_D^{20}$: -20.2° (*c* 0.31, EtOH).

^{1}H NMR (300 MHz, D_2O) : δ 3.76 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.59 (dd, *J* = 11.5, 6.7 Hz, 1H), 3.48 (m, 1H), 3.27 (dd, *J* = 10.6, 8.8 Hz, 1H), 3.12 (m, 2H), 2.43 (m, 2H), 1.70 (m, 1H).

^{13}C NMR (75 MHz, D_2O) : δ 70.2, 68.4, 57.1, 45.9, 42.9, 41.0.

Mass *m/z* (%) : 147 (M^+) (44), 129 (42), 112 (62), 98 (100).

(17) Preparation of (3a*R*,7*R*,7a*S*)-5-benzyl-7-(hydroxymethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (239):



To a solution of **170** (0.119 g, 0.46 mmol) in acetone-water (3 mL, 9:1) was added pyridine (40 μL, 0.46 mmol), followed by *N*-methylmorpholine-*N*-oxide (0.108 g, 0.92 mmol). The reaction mixture was cooled to 0 °C and to it was added a catalytic amount of osmium tetroxide (0.002 g). The reaction mixture was allowed to come to rt and stirred for 24 h. It was passed through a short pad of Celite and the solvent evaporated off. The crude reaction mixture upon column chromatography (silica, pet ether-ethyl acetate, 3:2) afforded the diol **239** as a colorless solid (0.128 g, 95 %).

Mp : 150 – 152 °C

[α]$_D^{25}$: -21.6° (*c* 1.4, MeOH)

For (3a*S*,7*S*,7a*R*)

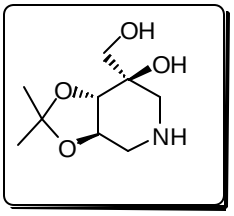
isomer, [α]$_D^{25}$ **:** +23.1° (*c* 0.46, MeOH)

^{1}H NMR (500 MHz, $CDCl_3$) **:** δ 7.40 (m, 5H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.85 (ddd, *J* = 9.9, 9.7, 4.3 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 13.8 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.61 (d, *J* = 9.7 Hz, 1H), 3.30 (dd, *J* = 9.7, 4.3 Hz, 1H), 2.92 (d, *J* = 11.7 Hz, 1H), 2.31 (dd like t, *J* = 10.1, 9.9 Hz, 1H), 2.21 (d, *J* = 12.0 Hz, 1H), 1.50 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 137.7, 128.6, 128.3, 127.3, 110.7, 86.2, 73.6, 71.5, 65.0, 61.5, 59.3, 54.5, 26.5

Mass: *m/z* (%) **:** 293 (M^+)(5), 235 (25), 134 (45), 120 (41), 91 (100).

(18) Preparation of (3a*R*,7*R*,7a*S*)-7-(hydroxymethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (240):



An ethanolic solution (2 mL) of the diol **239** (0.100 g, 0.34 mmol) was hydrogenated in the presence of $Pd(OH)_2$ on charcoal (20 %) (0.005 g) at 60 psi for 6 h. The catalyst was filtered off and the solvent removed in vacuo. The crude reaction mixture was column chromatographed (silica, chloroform-methanol, 9:1) to afford pure **240** (0.063 g, 90 %) as a colorless gum.

[α]$_D^{25}$ **:** -24.7° (*c* 0.9, MeOH)

For (3a*S*,7*S*,7a*R*)

isomer, [α]$_D^{25}$ **:** + 25.0° (*c* 0.2, MeOH)

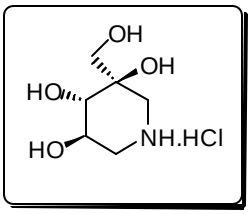
^{1}H NMR **:** δ 3.81 (d, *J* = 12.1 Hz, 1H), 3.79 (d, *J* = 12.1 Hz, 1H), 3.69 (ddd, *J* = 10.0, 9.9, 4.4 Hz, 1H), 3.62 (d, *J* = 9.5 Hz, 1H), 3.35 (dd, *J* = 11.9, 4.0 Hz, 1H), 3.24 (d, *J* = 13.9 Hz, 1H), 2.70 (dd like t, *J* = 11.1, 10.3 Hz, 1H), 2.37 (d, *J* = 13.9 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H).

(500 MHz, D_2O)

^{13}C NMR **:** 110.2, 84.1, 73.7, 72.9, 60.0, 49.6, 46.0, 25.4

(125 MHz, D_2O)

(19) Preparation of (3*R*,4*S*,5*R*)-3-(hydroxymethyl)piperidine-3,4,5-triol, hydrochloride salt (173.HCl):



To a solution of the substrate **240** (0.025 g, 0.12 mmol) in distilled methanol (0.5 mL) was added conc. HCl (2 drops) and the reaction mixture was stirred at rt for approximately 4 h. The solvent was evaporated to dryness to afford **173**.HCl (0.024 g, ~ 100 %) as a white foam.

[α]$_D^{25}$ **:** +11.0° (*c* 0.2, EtOH)

For the (3*S*,4*R*,5*S*)

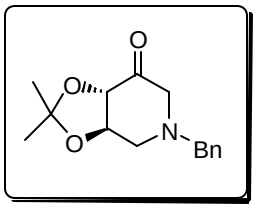
isomer, [α]$_D^{25}$ **:** -12.1° (*c* 0.15, EtOH)

^{1}H NMR **:** δ 4.11 (m, 1H), 3.85 (d, *J* = 4.4 Hz, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 3.64 (d, *J* = 12.0 Hz, 1H), 3.43 (d, 13.6 Hz, 1H), 3.30 (m, 2H), 3.16 (d, *J* = 13.6 Hz, 1H)

(500 MHz, D_2O)

^{13}C NMR (125 MHz, D_2O) : 71.5, 68.1, 66.6, 63.6, 46.1, 45.2

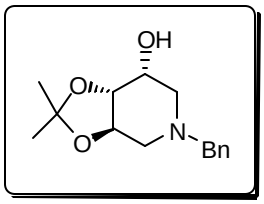
(20) Preparation of (3a*R*,7a*S*)-5-benzyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyridin-7(4*H*)-one (248):



To a solution of **239** (0.100 g, 0.34 mmol) in ethanol-water (2 mL, 8:2), was added sodium periodate (0.090 g, 0.4 mmol) in three portions over a period of 15 min. The white suspension was stirred for an additional hour and filtered. The solvent was evaporated off and the white pasty mass was extracted in ethyl acetate (3 x 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. Column chromatography (silica, pet ether-ethyl acetate, 4:1) of the crude mixture afforded pure **248** (0.071 g, 80 %) as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.30 (m, 5H), 4.26 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.90 (ddd, *J* = 10.0, 9.8, 4.4 Hz, 1H), 3.75 (m, 2H), 3.40 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.25 (d, *J* = 14.2 Hz, 1H), 3.05 (d, *J* = 14.2 Hz, 1H), 2.72 (dd like t, *J* = 10.2, 9.8 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H).

(21) Preparation of (3a*R*,7*R*,7a*R*)-5-benzyl-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (249):



Sodium borohydride (0.009 g, 0.23 mmol) was added to a solution of **248** (0.050 g, 0.019 mmol) in dry methanol (0.5 mL). The resulting mixture was stirred for 48 h and then quenched by the addition of excess of a saturated solution of NaCl. This white suspension was stirred overnight and then extracted in ethyl acetate (4 x 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated off. The residue was column chromatographed (silica, pet ether-ethyl acetate, 3:2) to afford **249** (0.043 g, 85 %) as a colorless oil.

$[\alpha]_D^{25}$: -36.2° (*c* 0.13, $CHCl_3$)

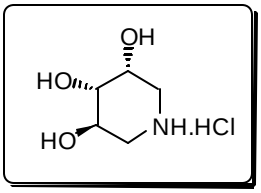
For (3a*S*,7*S*,7a*S*) isomer (250), $[\alpha]_D^{25}$: +35° (*c* 0.2, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.35 (m, 5H), 4.30 (m, 1H), 4.10 (ddd, *J* = 10.3, 9.7, 4.4 Hz, 1H), 3.87 (d, *J* = 13.7 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.45 – 3.30 (m, 2H), 3.20 (m, 1H), 2.80 (bs, 1H), 2.40 (m, 2H), 1.50 (s, 3H), 1.49 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 137.2, 128.7, 128.1, 127.1, 110.1, 81.4, 70.6, 65.7, 61.5, 56.5, 54.7, 26.5, 26.3.

GC/MS: *m/z* (%) : 263 (M^+)(<1%), 207 (3), 172 (7), 149 (20), 91 (100).

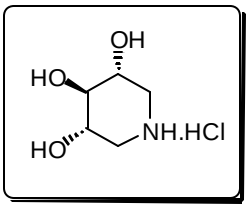
(22) Preparation of (3*R*,5*R*)-piperidine-3,4,5-triol, hydrochloride salt (138.HCl):



To a solution of **249** (0.030 g, 0.11 mmol) in distilled methanol (0.5 mL) was added conc. HCl (2 drops), followed by $Pd(OH)_2$ on C (20 %) (0.003 g) and the reaction mixture was hydrogenated at atmospheric pressure for approximately 16 h. After passing through a short pad of Celite, the solvent evaporated off to dryness to afford **138**.HCl (19 mg, ~100 %) as a white solid. Pure **138** could be obtained by column chromatography of the corresponding free base (silica, chloroform-2-propanol-aq NH_3, 8.5:1.5:0.5). **138** was converted back to its hydrochloride salt for spectral characterization.

$[\alpha]_D^{25}$	**:**	-12° (*c* 0.15, MeOH); lit[4] $[\alpha]_D^{25}$ = -16° (*c* 0.9 , MeOH)
For 137.HCl , $[\alpha]_D^{25}$	**:**	+18° (*c* 0.14, MeOH); lit[4] $[\alpha]_D^{25}$ = +16° (*c* 0.5, MeOH)
^{1}H NMR (500 MHz, D_2O)	**:**	δ 4.20 (m, 1H), 4.06 (ddd, *J* = 8.3, 7.8, 3.9 Hz, 1H), 3.75 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.37 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.26 (dd, *J* = 12.9, 5.9 Hz,1H), 3.18 (m, 1H), 2.92 (dd, *J* = 12.7, 8.4 Hz, 1H).
^{13}C NMR (125 MHz, D_2O)	**:**	70.7, 65.0, 64.6, 45.9, 45.4

(23) Preparation of (3*R*,5*S*)-piperidine-3,4,5-triol, hydrochloride salt (136.HCl):



To a solution of **250** (0.090 g, 0.34 mmol) in dry THF (2 mL) was added triphenyl phosphine (0.099 g, 0.38 mmol) and *p*-nitrobenzoic acid (0.063 g, 0.38 mmol). The resulting reaction mixture was cooled to 0 °C and to it was added diisopropyl azodicarboxylate (81 μL, 0.41 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. This was followed by extraction in DCM (5 mL) and sodium bicarbonate washes (2M, 3 x 3 mL). The organic layer, after drying over anhydrous Na_2SO_4, was concentrated under reduced pressure. This residue was dissolved in a minimum quantity of DCM and to it was added pet ether to precipitate out the phosphine oxide. The resulting slurry was loaded onto a column of silica gel and eluted. The combined fractions were concentrated in vacuo to afford the benzoate.

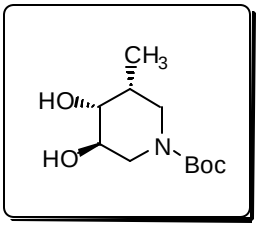
This benzoate was dissolved in distilled methanol (2 mL) and to it was added lithium hydroxide (0.016 g, 0.68 mmol) and the reaction mixture was stirred at rt for about 6 h. Water (5 mL) was added, followed by ethyl acetate (6 mL) and the layers were separated. The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to afford the alcohol (0.054 g, 60 %).

This alcohol was dissolved in distilled methanol (1.5 mL) and conc. HCl (2 drops) was added and the resulting reaction mixture was hydrogenated at atmospheric pressure in the presence of $Pd(OH)_2$ on carbon (20 %) (0.002 g) for about 7 h. The catalyst was filtered off and the filtrate pumped to dryness to afford **136** as a hydrochloride salt (0.035 g, ~ 100 %), which was further purified by

column chromatography as a free base (silica, chloroform-2-propanol-aq NH_3, 8.5:1.5:0.5). This was reconverted back to its hydrochloride salt for spectral characterization.

$[\alpha]_D^{25}$	**:**	0.0 ° (*c* 0.2, MeOH)
^{1}H NMR (500 MHz, D_2O)	**:**	δ 3.72 (ddd, *J* = 10.2, 8.4, 4.4 Hz, 2H), 3.46 (t, *J* = 8.4 Hz, 1H), 3.40 (dd, *J* = 12.7, 4.3 Hz, 2H), 2.86 (dd, *J* = 12.7, 10.3 Hz, 2H).
^{13}C NMR (125 MHz, D_2O)	**:**	δ 74.3, 66.5, 45.9.

(24) Preparation of *tert*-butyl (3*R*,4*R*,5*R*)-3,4-dihydroxy-5-methylpiperidine-1-carboxylate (251):



To an ethanolic solution (1 mL) of **170** (0.040 g, 0.15 mmol), was added conc. HCl (50 μL) followed by Pd/C (10 %) (0.005 g) and the mixture was hydrogenated at atmospheric pressure for over 12 h. The suspension was passed through a short pad of Celite and the mixture evaporated to dryness to afford the hydrochloride salt (0.023 g, 89 %). NMR analysis of the crude mixture showed the presence of diastereomers in a ratio of 80:20, which were inseparable. This salt was basified using conc. NH_4OH and the excess ammonia was evaporated off. This was dissolved in DCM (1 mL) and triethyl amine (0.1 mL, 0.7 mmol) was added and the resulting mixture was cooled to 0 °C. $(Boc)_2O$ (35 μL, 0.15 mmol) was added

and the reaction mixture was stirred at rt for 48 h. The excess triethyl amine was removed at the pump and the crude mixture upon column chromatography (silica, pet ether-ethyl acetate, 3:2) afforded pure **251** (0.032 g, 75 %) as a gummy mass.

$[\alpha]_D^{25}$: +50° (*c* 0.1, MeOH)

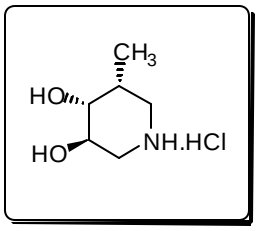
For the (3*S*,4*S*,5*S*) isomer, $[\alpha]_D^{25}$: -43° (*c* 0.25, MeOH)

^{1}H NMR (500 MHz, $CDCl_3$) : δ 3.82 (dd, *J* = 2.4, 1.0 Hz, 1H), 3.72 (ddd, *J* = 10.8, 6.8, 4.0 Hz, 1H), 3.63 (dd, *J* = 6.8, 4.0 Hz, 1H), 3.43 (dd, *J* = 13.3, 6.7 Hz, 1H), 3.29 (dd, *J* = 13.1, 2.8 Hz, 1H), 3.18 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.15 (m, 3H, 2H D_2O exchangeable), 1.50 (s, 9H), 0.98 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 155.7, 80.0, 74.0, 68.4, 46.7 (for two CH_2), 32.5, 28.4, 12.1

Mass: m/z (%) : 231(M^+), 207, 186, 175, 158, 145, 57

(25) Preparation of (3*R*,4*R*,5*R*)-5-methylpiperidine-3,4-diol (172.HCl):



To a solution of **251** (0.032 g, 0.13 mmol) in distilled methanol (0.5 ml) was added conc. HCl (100 μL) at 0 °C. The reaction mixture was stirred at rt for about 4 h and the solvent evaporated off to dryness to afford **172**.HCl (0.0217 g, ~100 %) as a colorless semi-solid mass.

$[\alpha]_D^{25}$: + 7.7° (*c* 0.2, MeOH)

For the (3*S*,4*S*,5*S*)

isomer $[\alpha]_D^{25}$: -7.0° (*c* 0.31, MeOH)

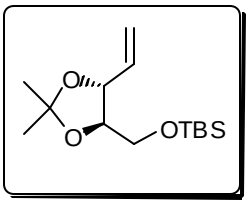
^{1}H NMR : δ 4.01 (m, 1H), 3.76 (m, 1H), 3.25 (dd, *J* = 13.3, 1.7 Hz,

(500 MHz, D_2O) 1H), 3.17 (dd, *J* = 14.7, 1.2 Hz, 1H), 3.07 (dd, *J* = 12.7, 4.3 Hz, 1H), 2.87 (dd like t, *J* = 12.7, 12.4 Hz, 1H), 2.30 (m, 1H), 0.9 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR : 68.2, 65.4, 43.9, 43.8, 27.3, 12.9

(125 MHz, D_2O)

(26) Preparation of (4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane (256):



HMPA (4 mL) was added to a suspension of the Wittig salt (1.770 g, 4.38 mmol) in dry THF (10 mL) and the reaction mixture was cooled to 0 °C. To this was added n-BuLi (1.62M in hexane, 3.24 mL, 5.26 mmol) and the resulting mixture was stirred for about 30 minutes. This was followed by the addition of **220** (1.0 g, 3.65 mmol) dissolved in THF (6 mL). The reaction mixture was allowed to stir at 0 °C for another hour and then brought up to rt. After about 12 h, the reaction was found to be complete and was worked up by careful addition of water (15 mL) with external cooling. Extraction in DCM (2 x 10 mL) followed by drying of the combined organic extracts over anhydrous Na_2SO_4 and the removal of the solvent under reduced pressure afforded a semi-solid mass which was dissolved in a minimum amount of DCM. Pet-ether was added to precipitate out the

phosphine oxide and the supernatant liquid was passed through a short pad of silica. The precipitated solid was dissolved in DCM and the procedure was repeated. The combined fractions were concentrated under reduced pressure and the resulting residue was column chromatographed (silica, pet ether-ethyl acetate, 98:2) to afford **256** (0.596 g, 60 %) as a colorless oil.

$[\alpha]_D^{25}$ **:** -4.0° (*c* 1.63, $CHCl_3$)

For the (4*S*,5*S*) isomer, $[\alpha]_D^{25}$ **:** + 4.17° (*c* 1.92, $CHCl_3$)

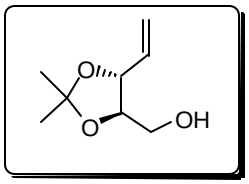
IR ($CHCl_3$) **:** 1471, 1461 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 5.90 (m, 1H), 5.30 (m, 2H), 4.35 (m, 1H), 3.75 (m, 3H), 1.40 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 135.6, 117.8, 108.9, 81.1, 79.1, 62.3, 26.8, 26.7, 25.7, 18.2, -5.5, -5.6.

GC/MS: *m/z* (%) **:** 257 (M^+-15) (3), 157 (67), 127 (71), 98 (31), 75 (100).

(27) Preparation of [(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methanol (255):

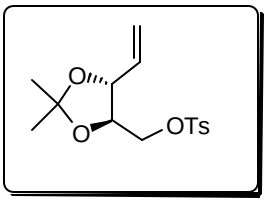


To a solution of **256** (0.500 g, 1.84 mmol) in dry THF (3 mL) was added TBAF (1M in THF, 2.1 mL, 2.1 mmol), at 0 °C. The reaction mixture was stirred at rt for about 4 h and then worked up by the addition of water (4 mL) followed by extraction in ethyl acetate (3 x 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

Column chromatography (silica, chloroform-ethyl acetate, 19:1) of the crude residue afforded **255** (0.261 g, 90 %) as a clear oil.

$[\alpha]_D^{25}$	**:**	+2.98° (*c* 1.40, $CHCl_3$).
For the (4*S*,5S) isomer, $[\alpha]_D^{25}$	**:**	-2.94° (*c* 1.36, $CHCl_3$). Lit[5] $[\alpha]_D^{25}$ = - 3.1 (*c* 1.01, $CHCl_3$).
IR ($CHCl_3$)	**:**	3446 (broad), 1647, 1380 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 5.85 (m, 1H), 5.35 (m, 2H), 4.30 (t, *J* = 8.3 Hz, 1H), 3.85 (m, 2H), 3.60 (m, 1H), 2.05 (dd, *J* = 8.0, 4.6 Hz, 1H), 1.40 (s, 6H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 134.8, 118.8, 109.0, 80.9, 78.2, 60.6, 26.7
GC/MS: *m/z* (%)	**:**	143 (M^+-15) (15), 127 (3), 98 (15), 83 (24), 59 (53), 43 (100).

(28) Preparation of [(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (257):



Pyridine (0.23 mL, 2.85 mmol) was added to a solution of **255** (0.300 g, 1.89 mmol) in dry DCM (3 mL) at 0 °C. To this was added *p*-toluene sulfonyl chloride (0.434 g, 2.28 mmol) in portions, over a period of 30 min. The reaction mixture was stirred overnight at rt and worked up by extraction in DCM. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The

residue upon column chromatography (silica, pet ether-ethyl acetate, 19:1) afforded the pure tosylate **257** (0.562 g, 95 %) as a colorless oil.

$[\alpha]_D^{25}$: + 8.39° (*c* 1.0, $CHCl_3$)

For the (4*S*,5*S*) isomer, $[\alpha]_D^{25}$: -8.63° (*c* 1.17, $CHCl_3$)

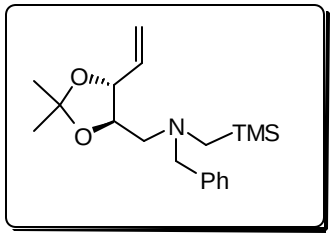
IR ($CHCl_3$) : 3020, 1367, 759, 669 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 5.75 (m, 1H), 5.25 (m, 2H), 4.25 – 4.0 (m, 3H), 3.85 (m, 1H), 2.45 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 144.8, 134.0, 132.3, 129.7, 127.7, 119.5, 109.7, 78.5, 77.7, 67.7, 26.7, 26.4, 21.4

GC/MS: *m/z* (%) : 297 (M^+-15) (8), 155 (34), 98 (29), 83 (53), 43 (100).

(29) Preparation of *N*-benzyl-*N*-[(trimethylsilyl)methyl]-*N*-{[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4yl]methyl}amine (254):



A mixture of **257** (0.325 g, 1.041 mmol), **176** (0.402 g, 2.083 mmol), anhydrous cesium carbonate (1.696 g, 5.2 mmol), and tetra-n-butyl ammonium iodide (0.020 g) in dry CH_3CN (4 mL) was refluxed under inert atmosphere for about 72 h. The reaction mixture was filtered and the solvent evaporated off. The crude residue upon column chromatography (silica, pet ether-ethyl acetate, 98:1) afforded **254** (0.201 g, 58 %) as a colorless oil.

$[\alpha]_D^{25}$: +28.3° (*c* 1.5, $CHCl_3$)

For the (4*S*,5S) isomer, $[\alpha]_D^{25}$: -28.6° (*c* 1.3, $CHCl_3$)

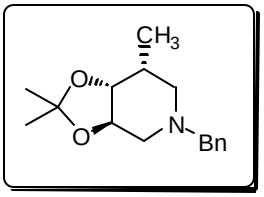
IR ($CHCl_3$) : 1454, 1425, 759, 740, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.30 (m, 5H), 5.75 (m, 1H), 5.25 (m, 2H), 4.0 (m, 1H), 3.88 (m, 1H), 3.75 (d, *J* = 13.7 Hz, 1H), 3.45 (d, *J* = 13.7 Hz, 1H), 2.60 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.53 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.13 (d, *J* = 14.6 Hz, 1H), 2.01 (d, *J* = 14.6 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 0.05 (s, 9H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 139.6, 135.4, 128.8, 127.9, 126.6, 117.9, 108.7, 80.9, 79.8, 62.6, 58.1, 46.9, 27.0, 26.7, -1.35.

GC/MS: *m/z* (%) : 333 (M+) (< 1%), 260 (< 1%), 206 (57), 134 (12), 91 (100), 73 (10).

(30) Preparation of (3a*R*,7*R*,7a*R*)-5-benzyl-2,2,7-trimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridine (253):



A solution containing **254** (0.200 g, 0.6 mmol) and 1,4-dicyanonaphthalene (0.015 mg, 0.08 mmol) in 2-propanol (100 mL) was irradiated using a 450W medium pressure Hanovia lamp as the light source. After about 2h, when most of the starting material (>90 %) had reacted, the irradiation was discontinued and the solvent was removed under reduced pressure. The crude photolysate was column chromatographed (silica, pet ether-acetone, 99:1) to afford **253** (0.086 g, 55 %) as a colorless oil.

$[\alpha]_D^{25}$: -8.0° (*c* 0.2, $CHCl_3$)

For (3a*S*,7*S*,7a*S*)

isomer, $[\alpha]_D^{25}$: +8.6° (*c* 0.25, $CHCl_3$)

IR ($CHCl_3$) : 769, 699 cm^{-1}

^{1}H NMR : δ 7.30 (m, 5H), 3.65 (m, 2H), 3.59 (ddd, *J* = 10.3, 8.7,

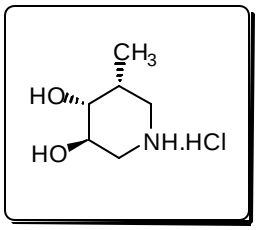
(500 MHz, $CDCl_3$) 4.0 Hz, 1H), 3.24 (ddd, *J* = 9.9, 4.0, 1.2 Hz, 1H), 2.97 (dd, *J* = 10.6, 8.9 Hz, 1H), 2.87 (dd, *J* = 11.7, 3.8 Hz, 1H), 2.18 (t, *J* = 9.9 Hz, 1H), 2.0 (m, 1H), 1.82 (t, *J* = 11.1 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.0 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR : δ 137.8, 128.7, 128.0, 126.9, 109.7, 85.3, 76.3, 61.7,

(125 MHz, $CDCl_3$) 58.8, 54.5, 33.7, 26.7, 26.5, 15.2.

GC/MS *m/z* : 261 (M^+), 246, 203, 134, 120, 91.

(31) Preparation of 172.HCl from 253



To a solution of **253** (0.021 g, 0.077 mmol) in distilled MeOH (0.5 mL) was added conc. HCl (2 drops) and the reaction mixture was hydrogenated for 7 h at atmospheric pressure in the presence of $Pd(OH)_2$ on charcoal (20%) (0.001 g). The reaction mixture was passed through a short pad of Celite and the solvent was removed under reduced pressure to afford **172**.HCl (0.013 g, ~100 %) as a amorphous solid.

(32) General procedure for and inhibition assay:

The inhibition assay for the inhibitory potencies of the 1-*N*-iminosugars were determined by measuring the residual hydrolytic activities of the glycosidases of the corresponding *p*-nitrophenyl glycosides in the presence of iminosugars spectrophotometrically on a Varian Model CARY-50 BIO UV-VIS spectrophotometer.

In the case of β-glucosidase, each assay was performed in citrate buffer (100 mM, pH 6.0) with *p*-nitrophenyl β-D-glucosidase as the substrate. Varying concentrations of the substrate and iminosugar were employed. The reaction was initiated by the addition of 100 μL of appropriately diluted enzyme and the reaction mixture, which had a final volume of 1 mL, was incubated for 10 min at 37 °C, and then quenched, by the addition of 2 mL of 1M Na_2CO_3 solution. The absorbance of the resulting solution was read at 405 nm.

In the case of β-mannosidase, the assay was performed in acetate buffer (100 mM, pH 4.0). The reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution. The K_i values were determined from the Lineweaver-Burke double-reciprocal plots of 1/*v* Vs 1/[S]. The K_i for competitive inhibition was determined using the formula:

$$K_i = \frac{[I]}{\left(\frac{K_{MI}}{K_M}\right) - 1}$$

References:

1) Carmack, M.; Kelley, C. J. *J. Org. Chem.* **1968**, *33*, 2171.

2) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

3) Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1778.

4) Bernotas, R. C.; Papendreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 3393.

5) Kang, S. H.; Lee, S. B. *Chem. Commun.* **1998**, 761.

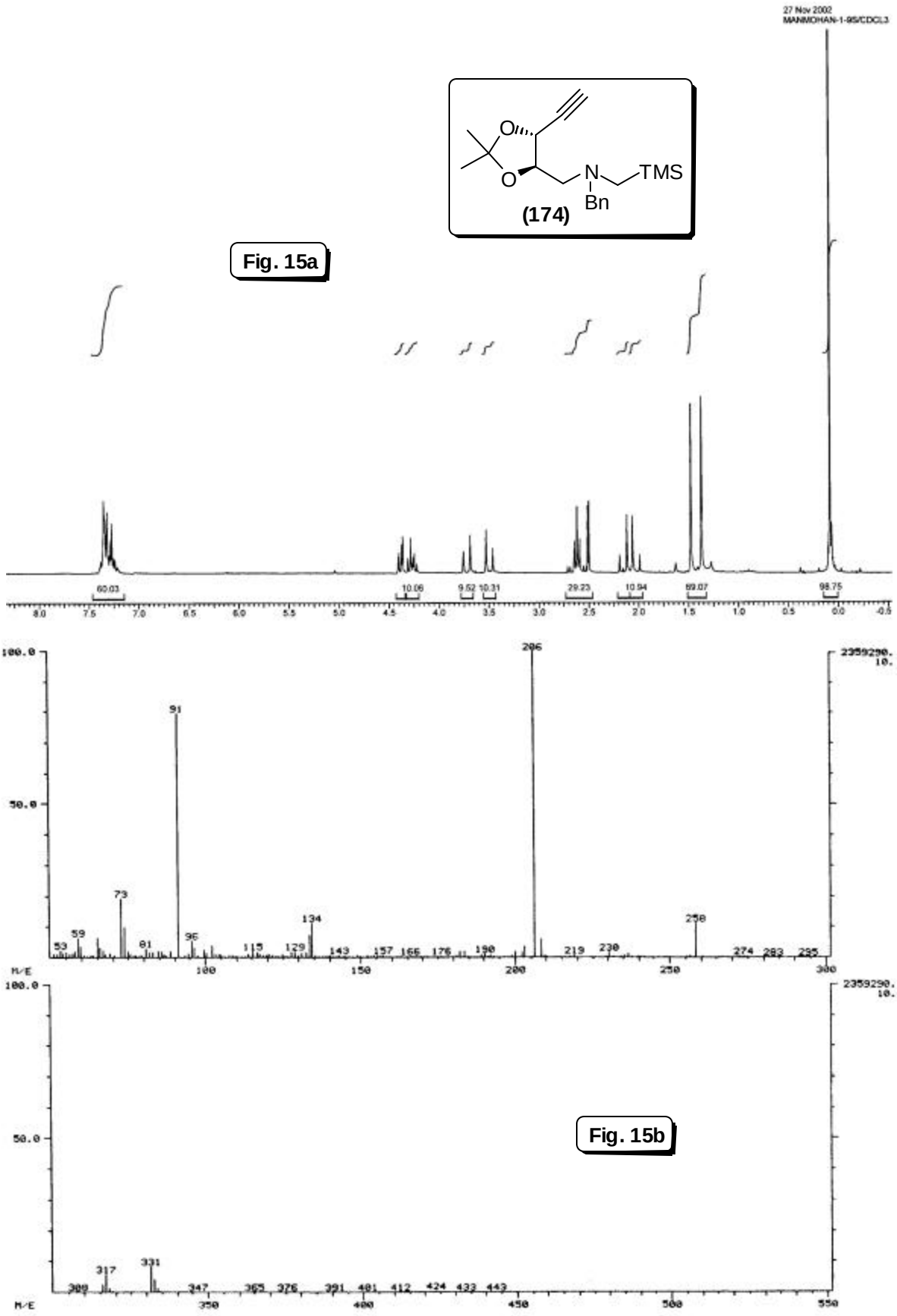


Fig. 15a

Fig. 15b

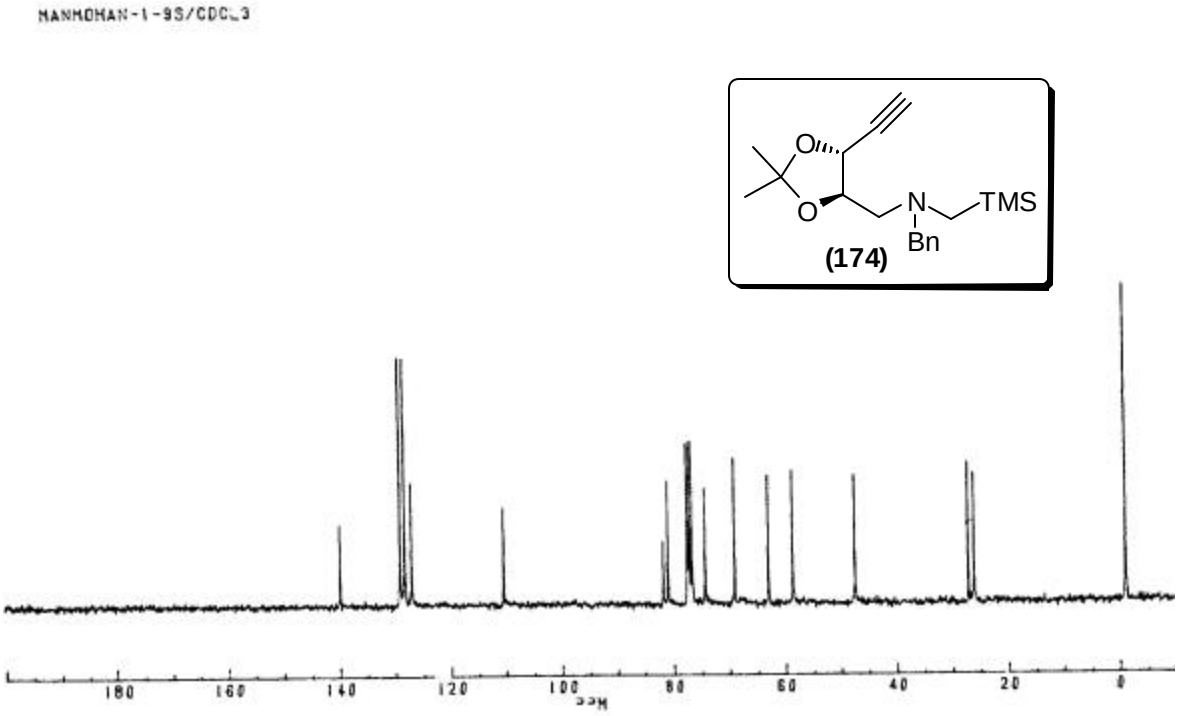
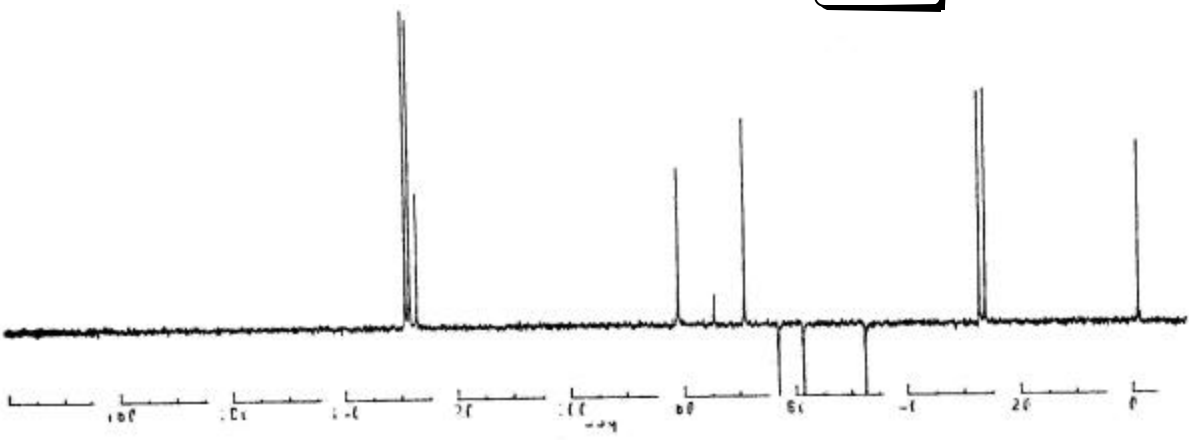

MANMOHAN-1-9S/CDCL3
O
O
N
TMS
Bn
(174)
180
160
140
120
100
80
60
40
20
0

Fig. 15c



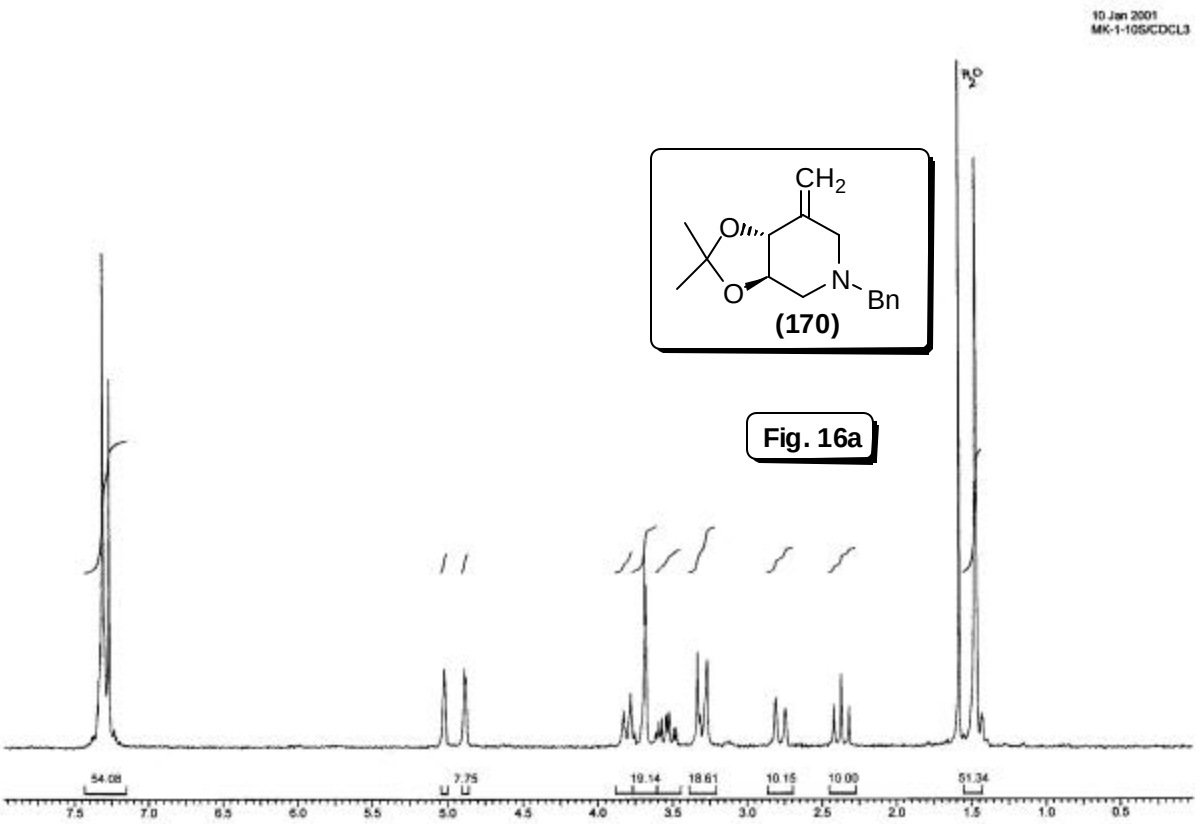


Fig. 16a

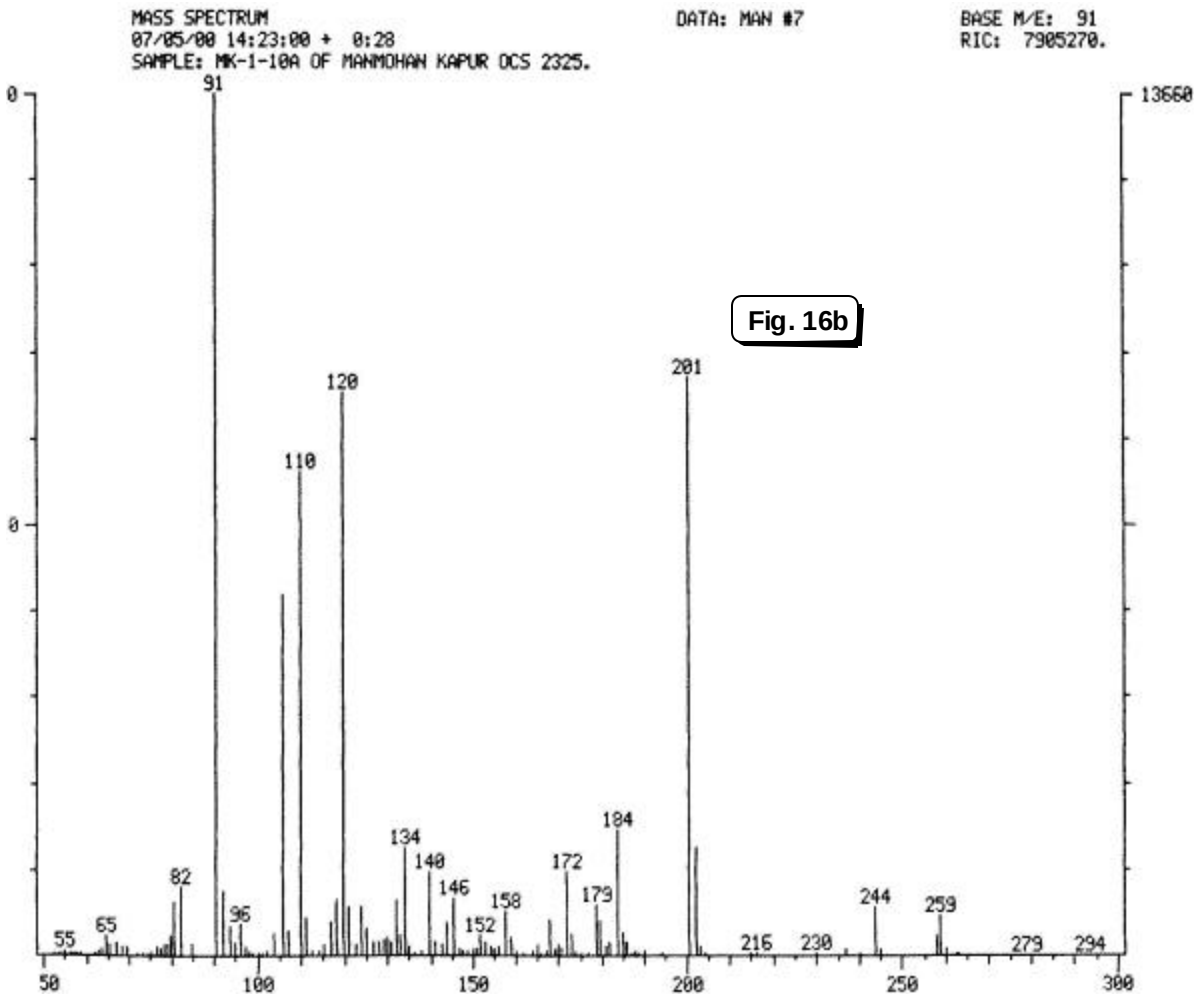
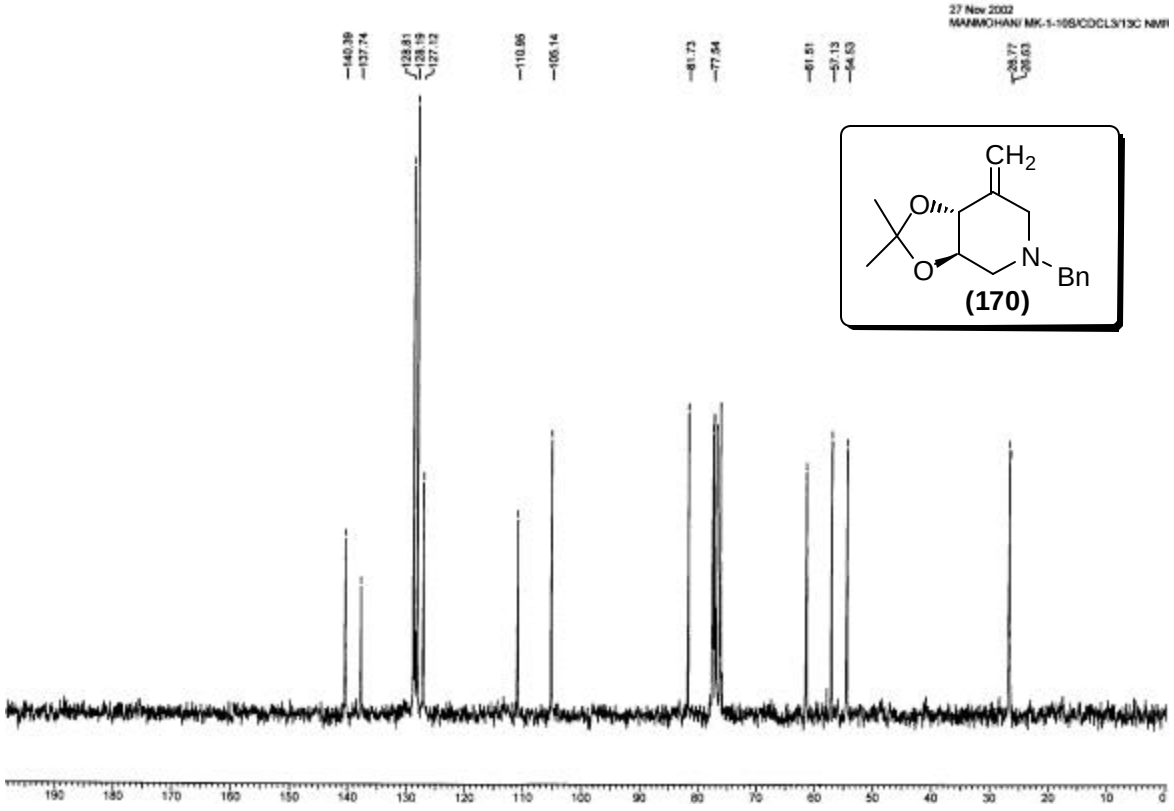


Fig. 16b


27 Nov 2002
MANMOHAN/ MK-1-10S/CDCL3/13C NMR
140.39
137.74
128.81
128.19
127.12
110.86
105.14
81.73
77.54
61.51
57.13
54.63
28.77
26.63
CH2
O
O
N
Bn
(170)

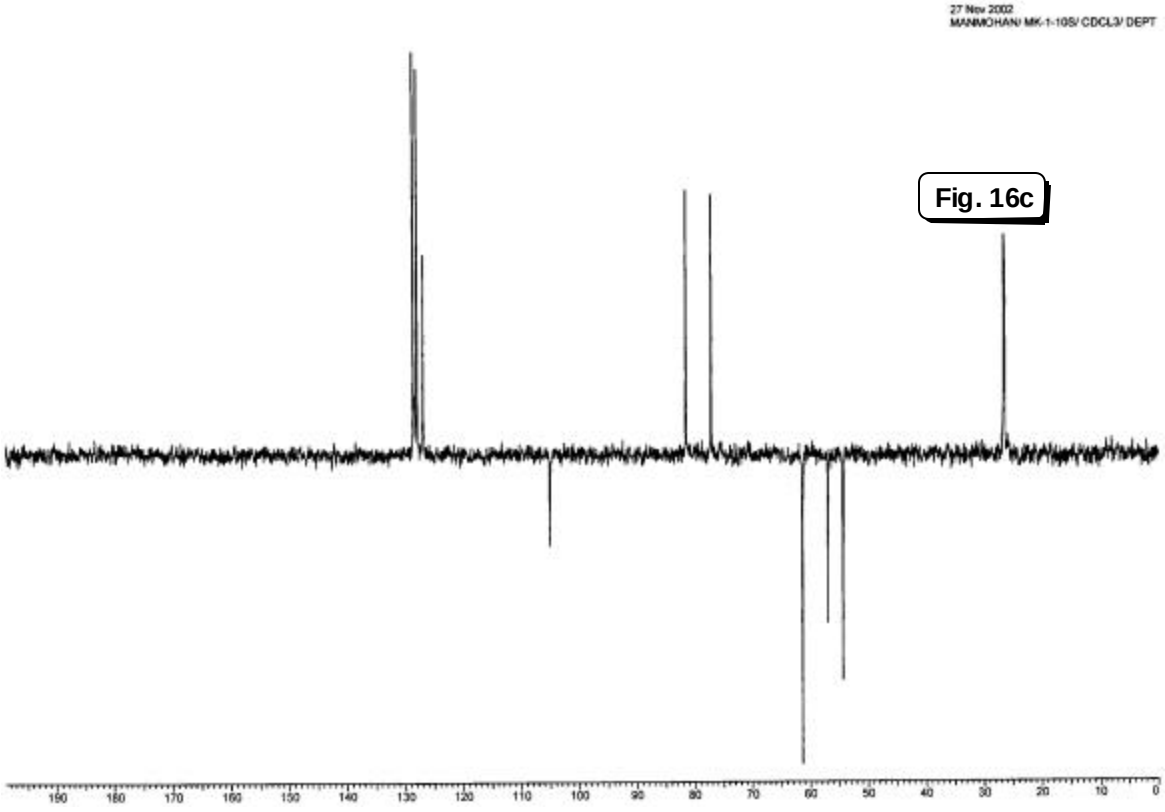

27 Nov 2002
MANMOHAN/ MK-1-10S/ CDCL3/ DEPT

Fig. 16c

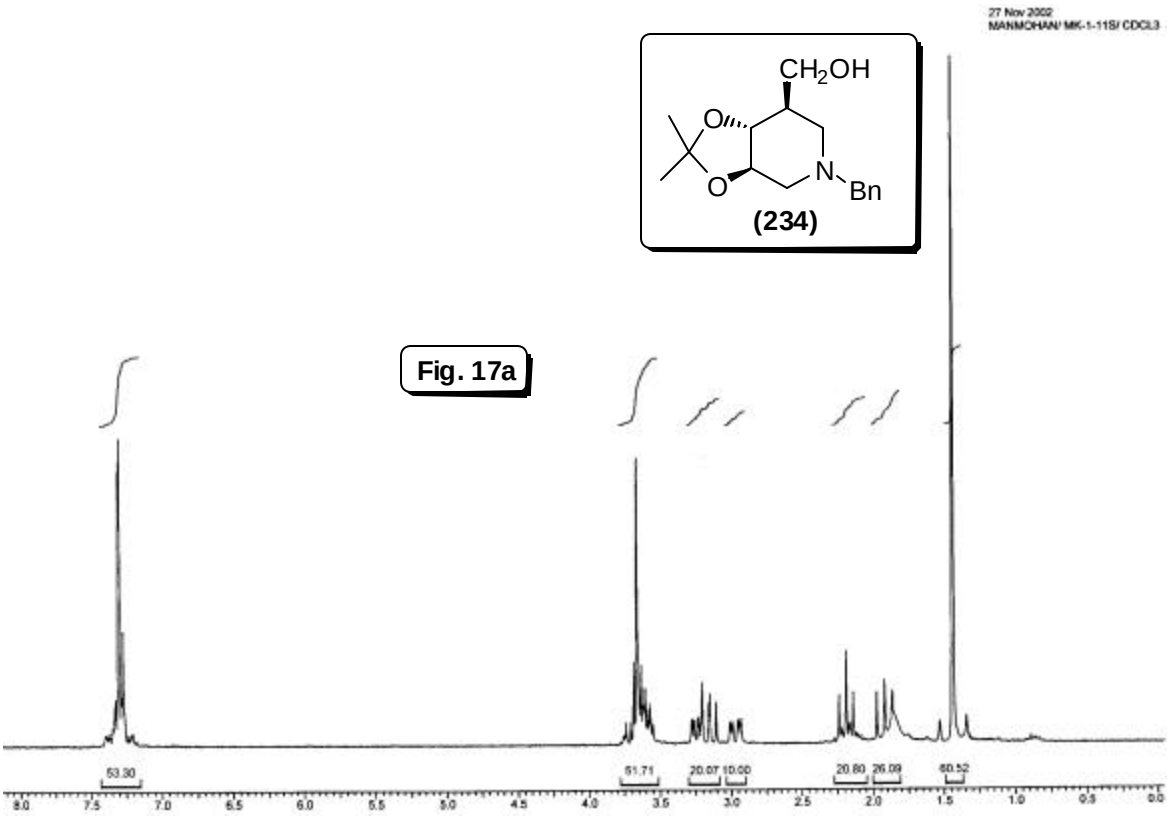


Fig. 17a

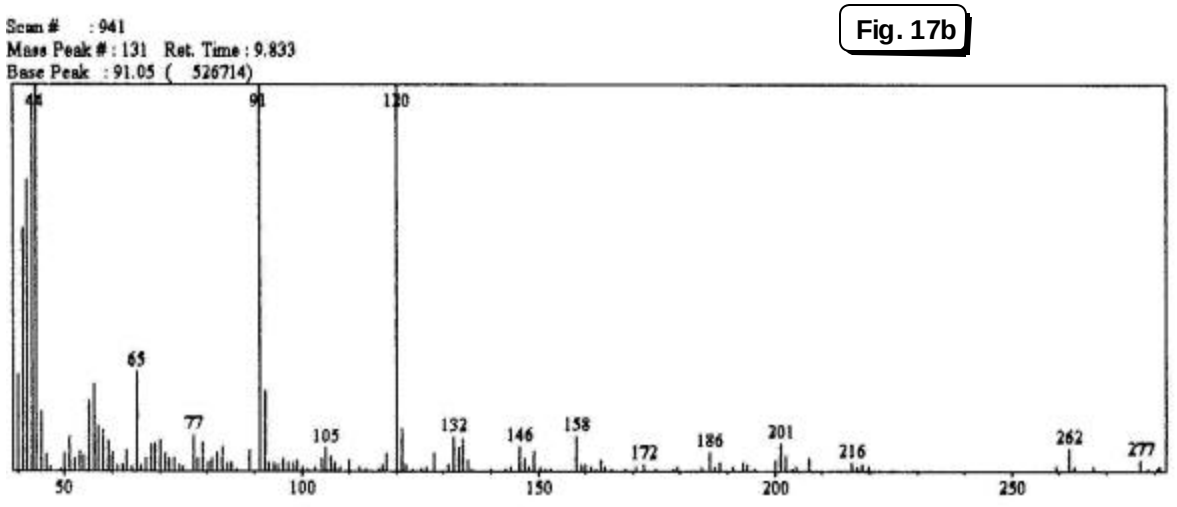
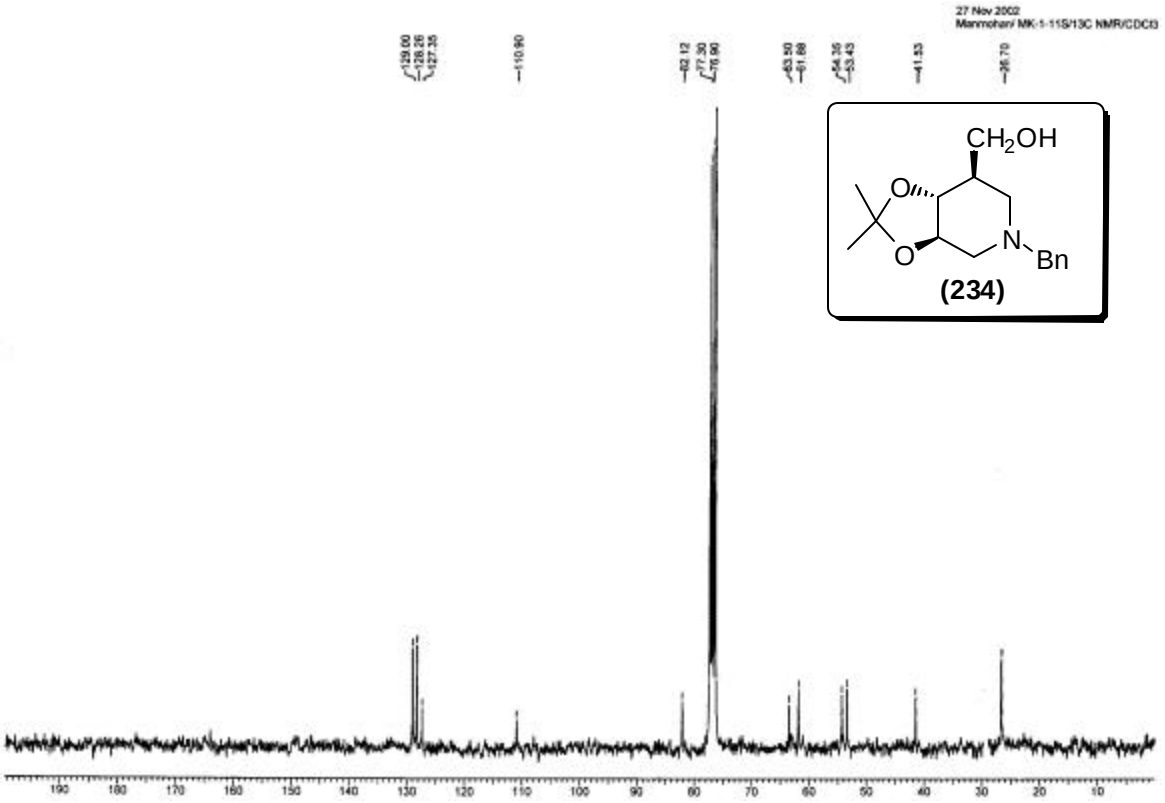


Fig. 17b


27 Nov 2002
Manmohan/ MK-1-11S/13C NMR/CDCD
129.00
126.26
127.35
110.90
82.12
77.30
76.90
63.50
61.88
54.35
53.43
41.53
26.70
CH2OH
O
O
N
Bn
(234)

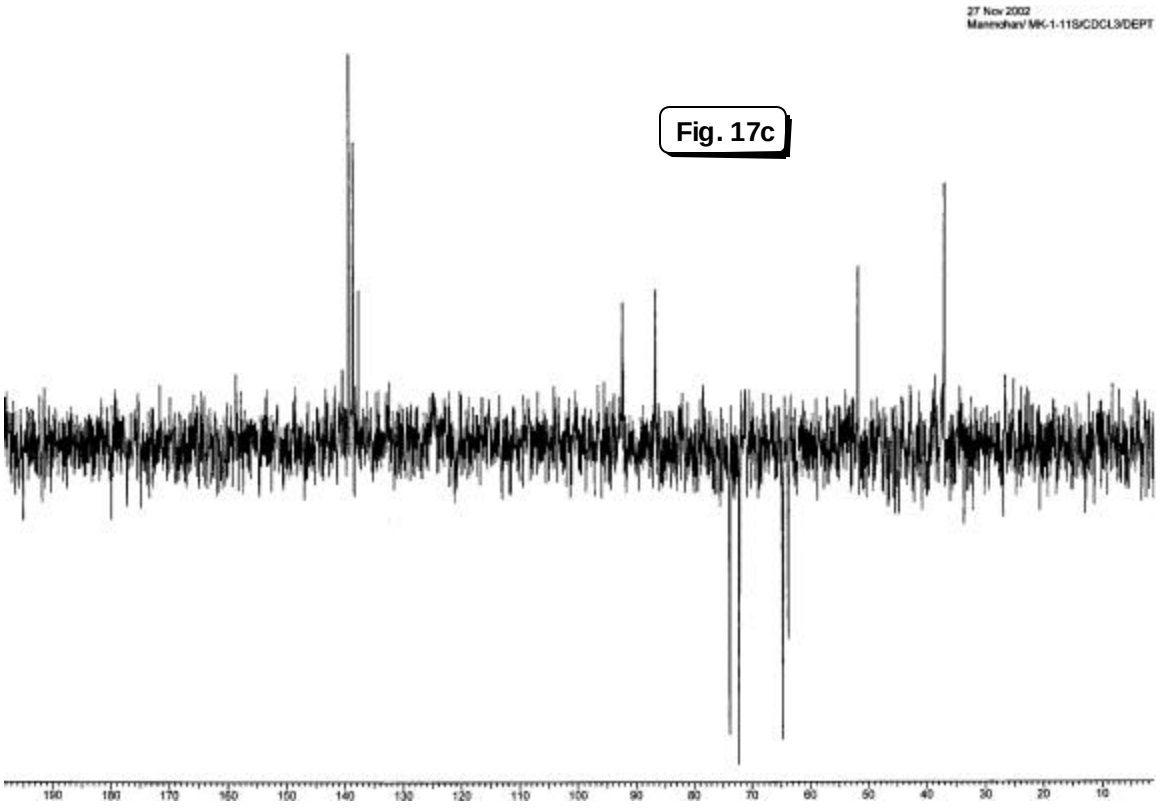

27 Nov 2002
Manmohan/ MK-1-11S/CDCL3/DEPT

Fig. 17c

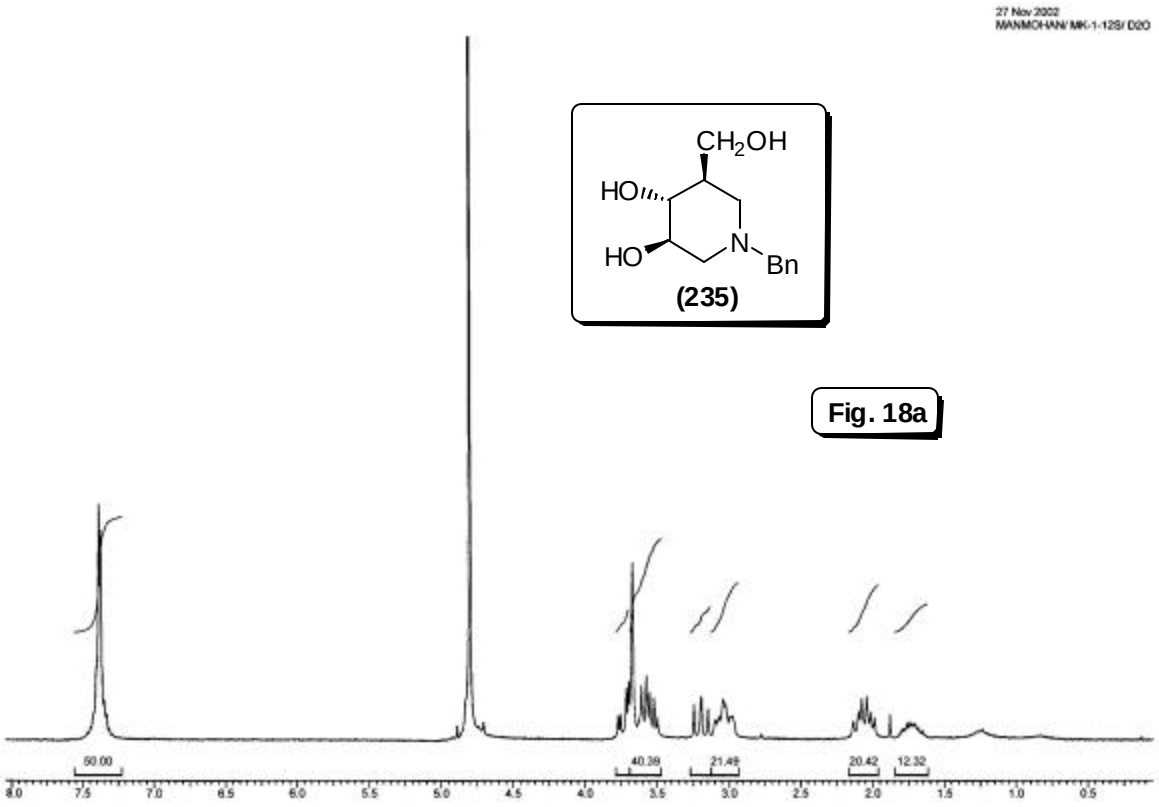


Fig. 18a

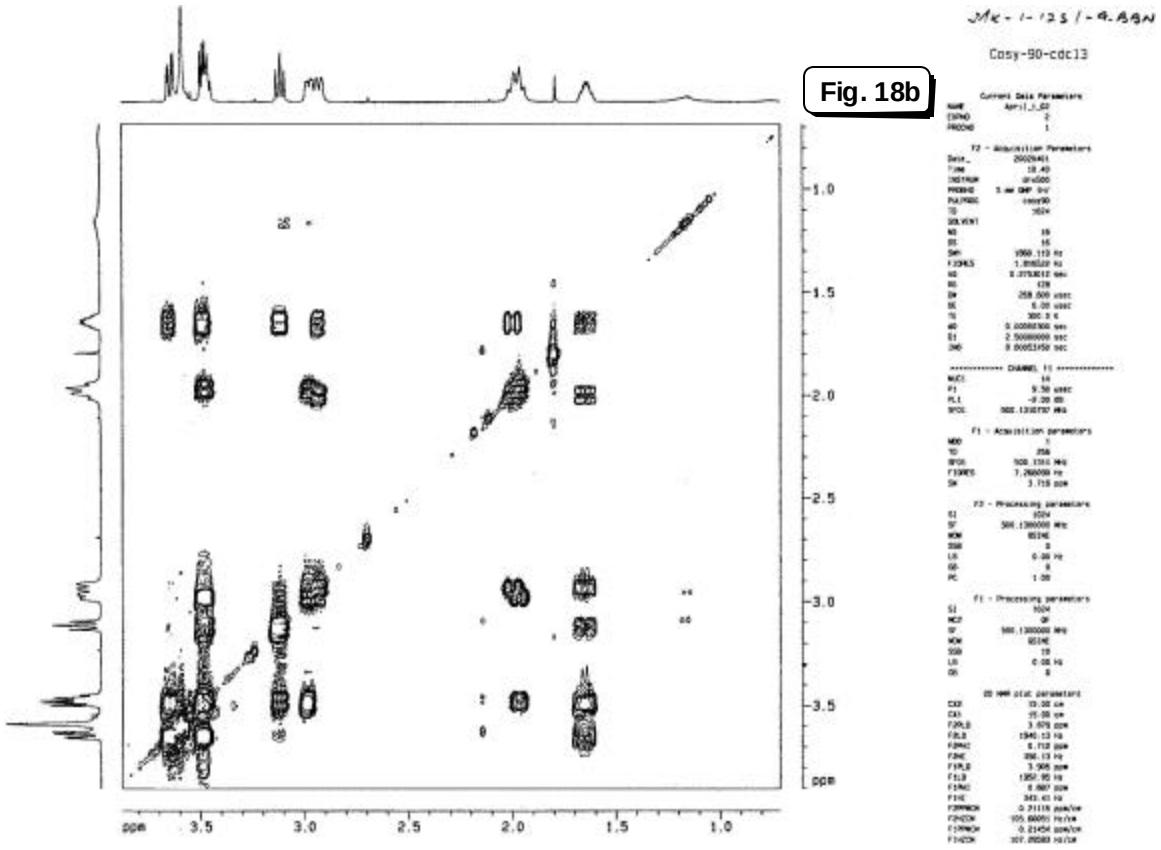


Fig. 18b

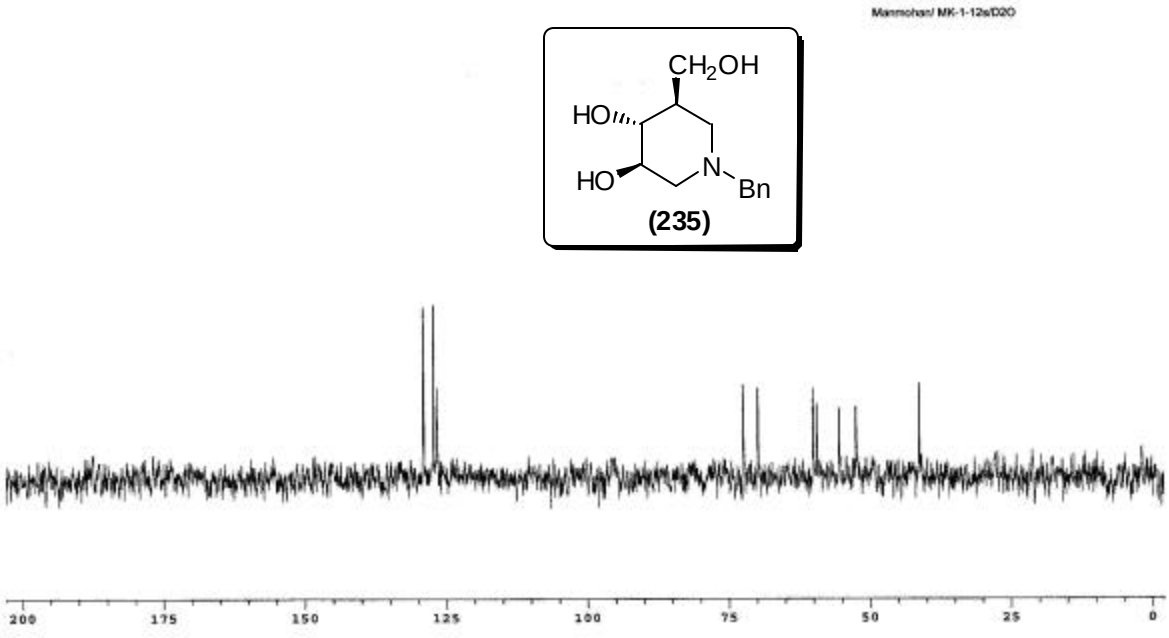
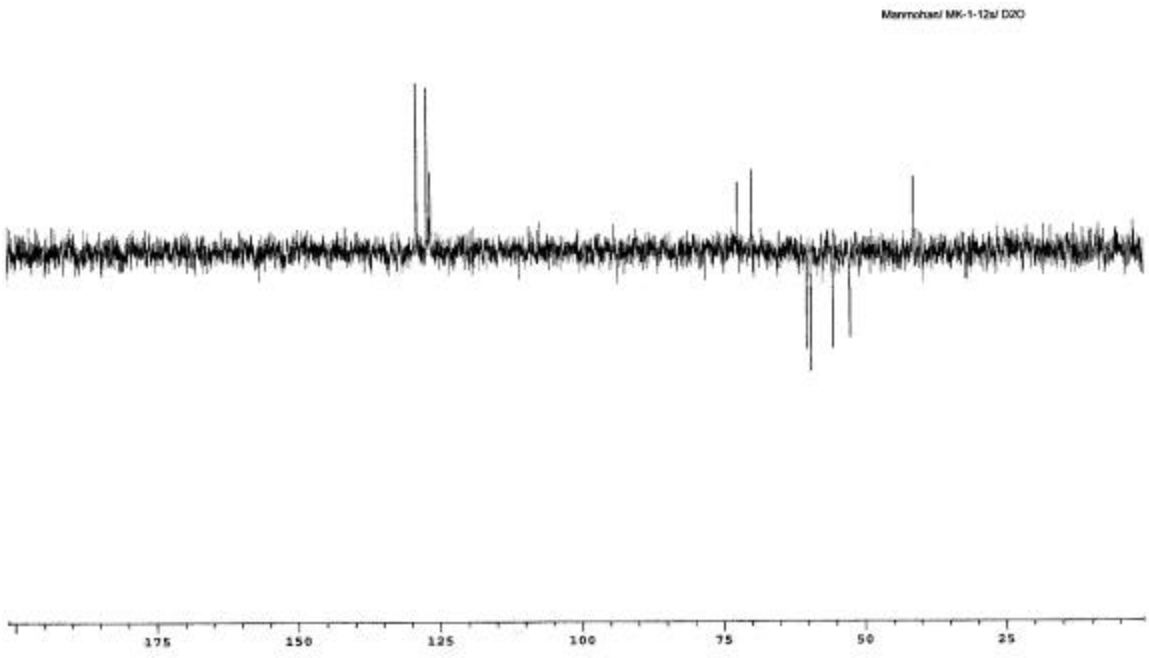
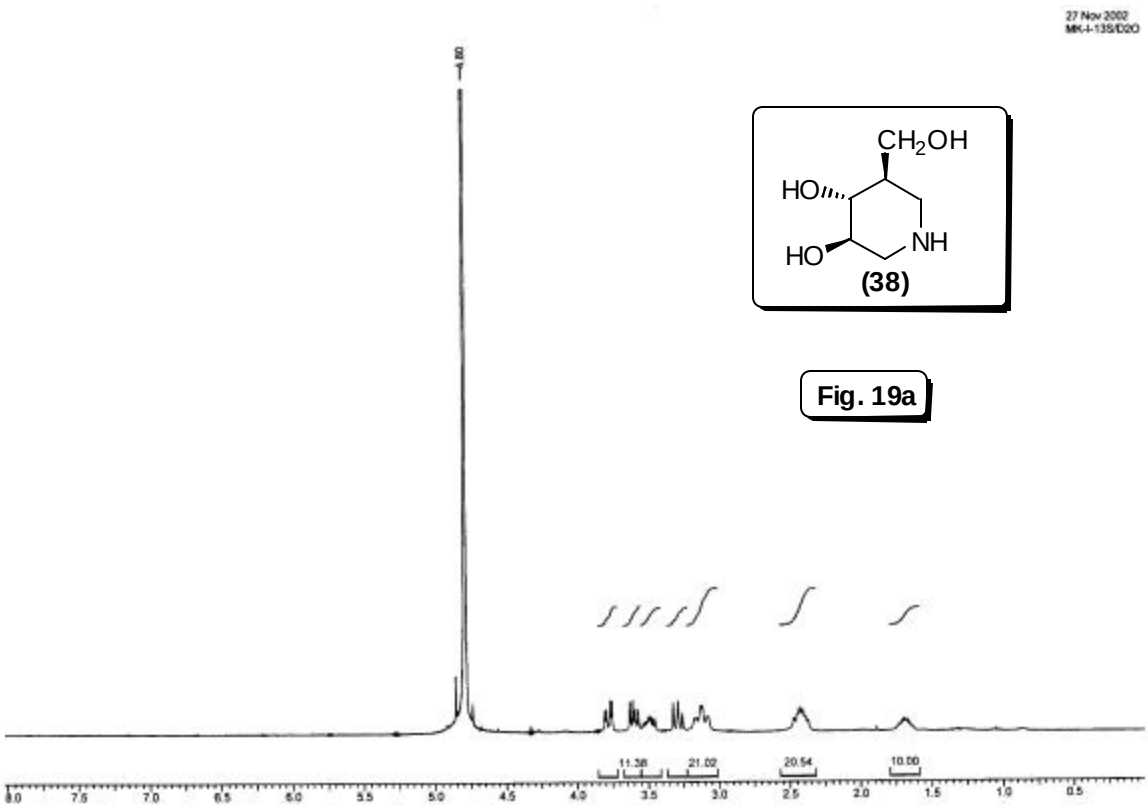

Manmohan/ MK-1-12a/D2O
CH2OH
HO
HO
N
Bn
(235)
200
175
150
125
100
75
50
25
0

Fig. 18c


Manmohan/ MK-1-12a/ D2O
175
150
125
100
75
50
25



(38)

Fig. 19a

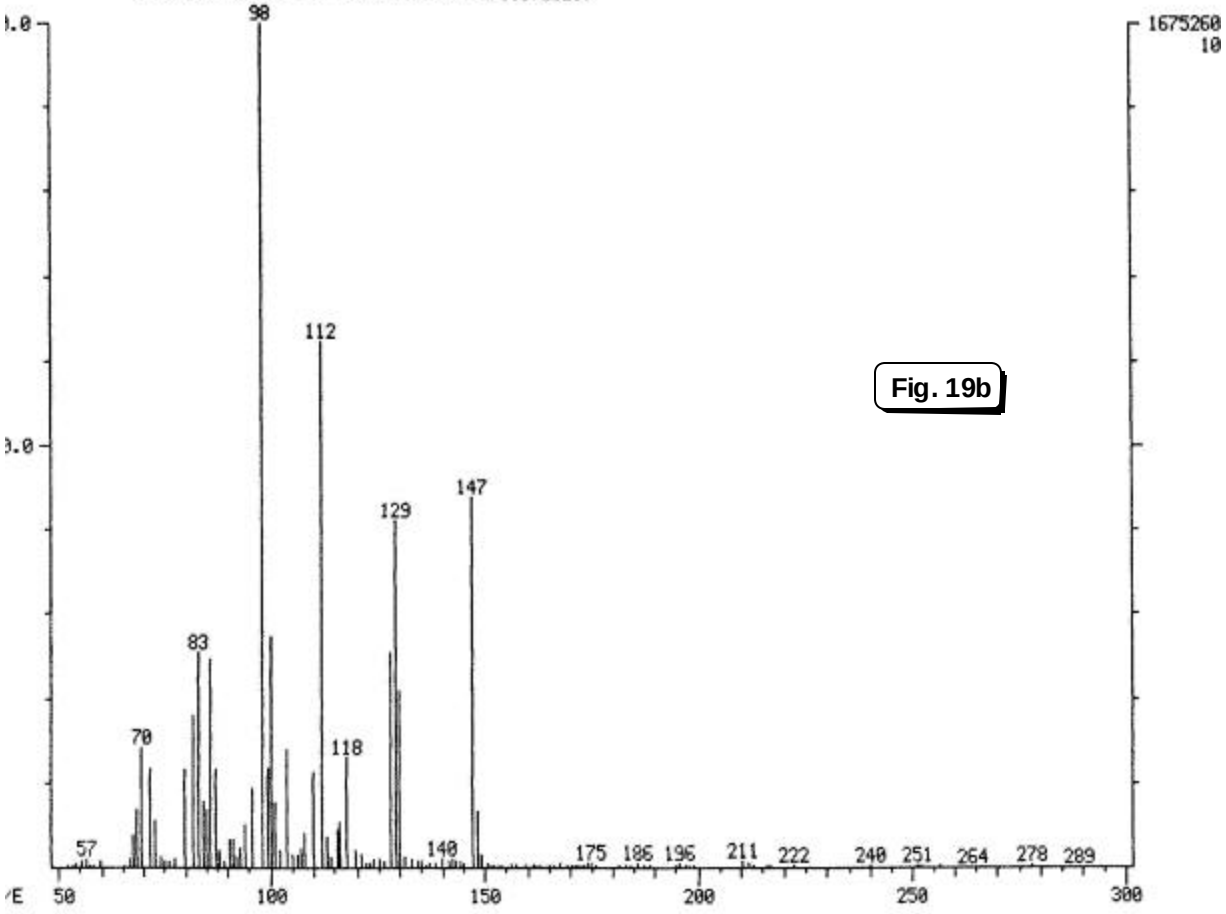
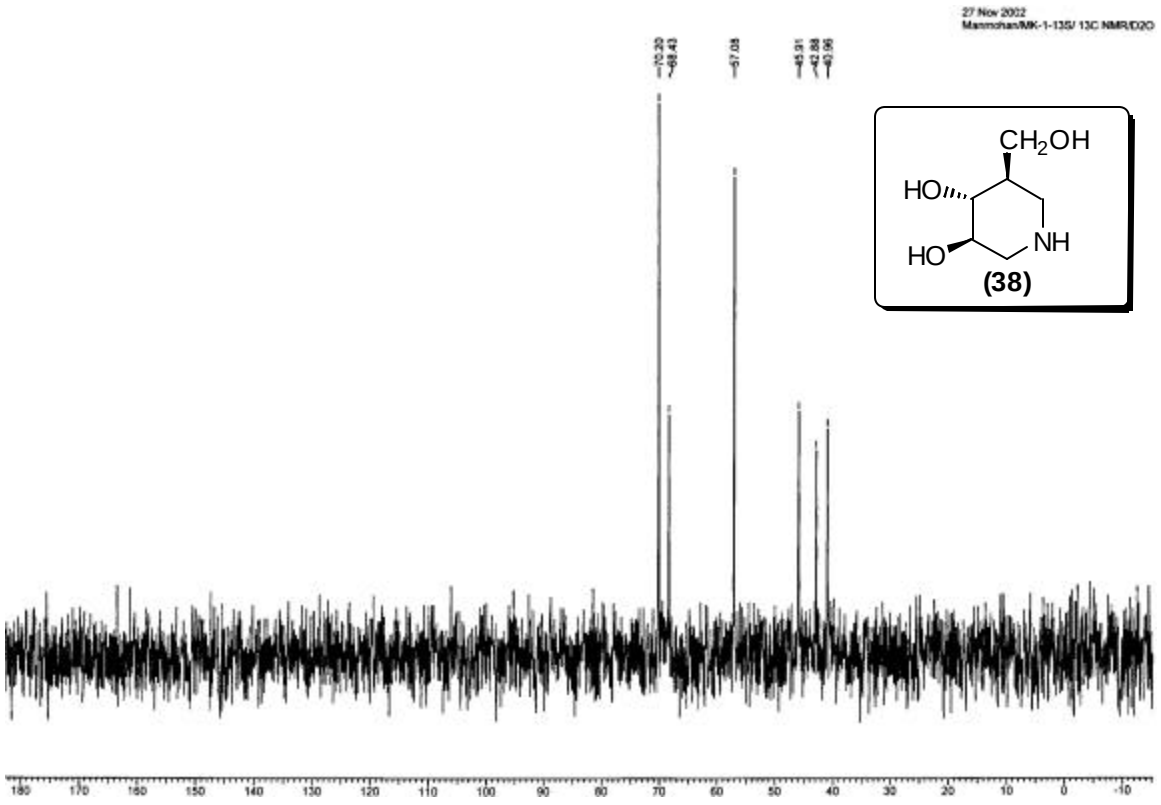


Fig. 19b


27 Nov 2002
Manmohan/MK-1-13S/ 13C NMR/D2O
70.20
68.43
57.08
45.91
42.84
40.96
CH2OH
HO
HO
NH
(38)

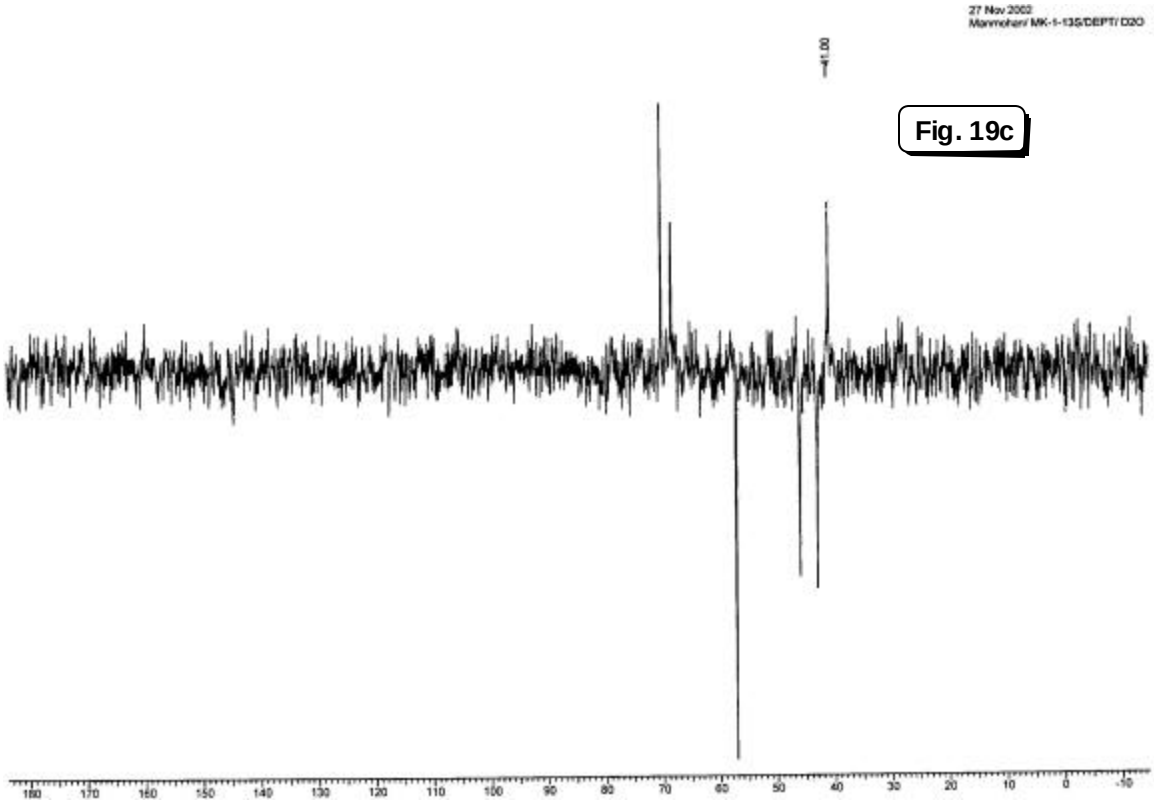

27 Nov 2002
Manmohan/ MK-1-13S/DEPT/ D2O
41.00

Fig. 19c

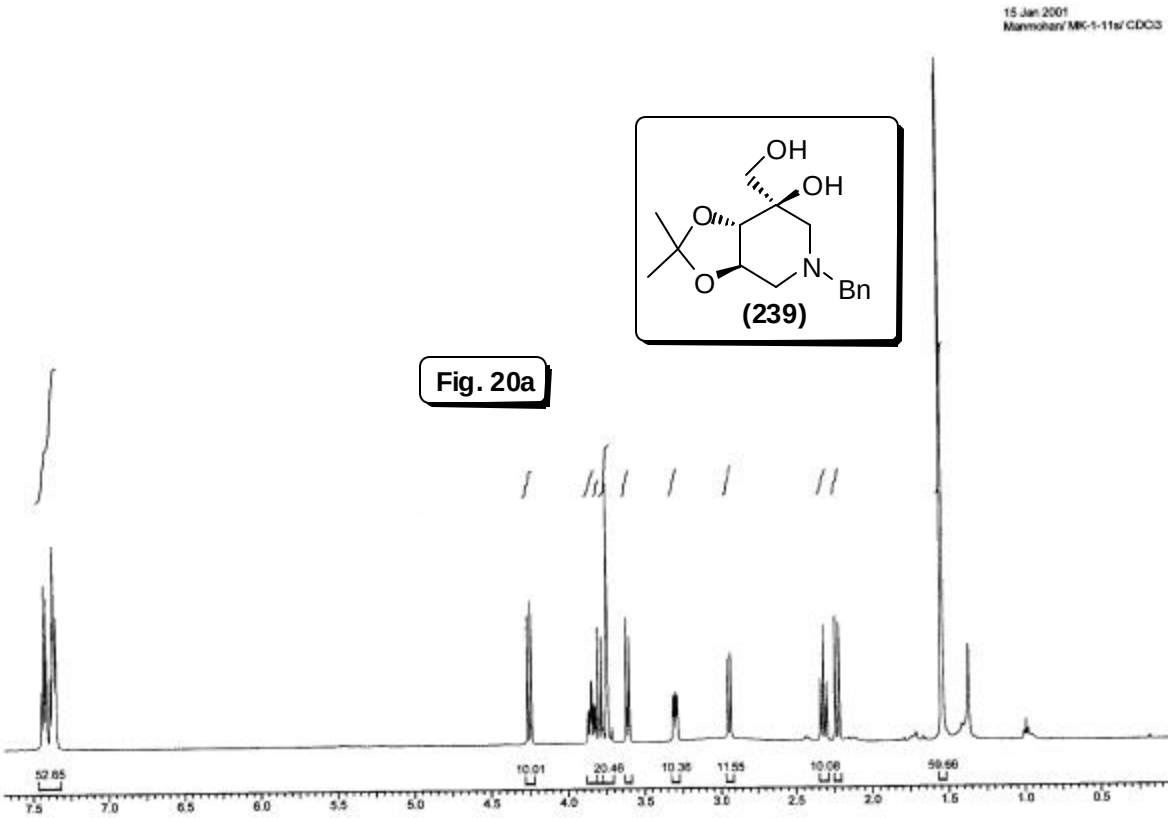


Fig. 20a

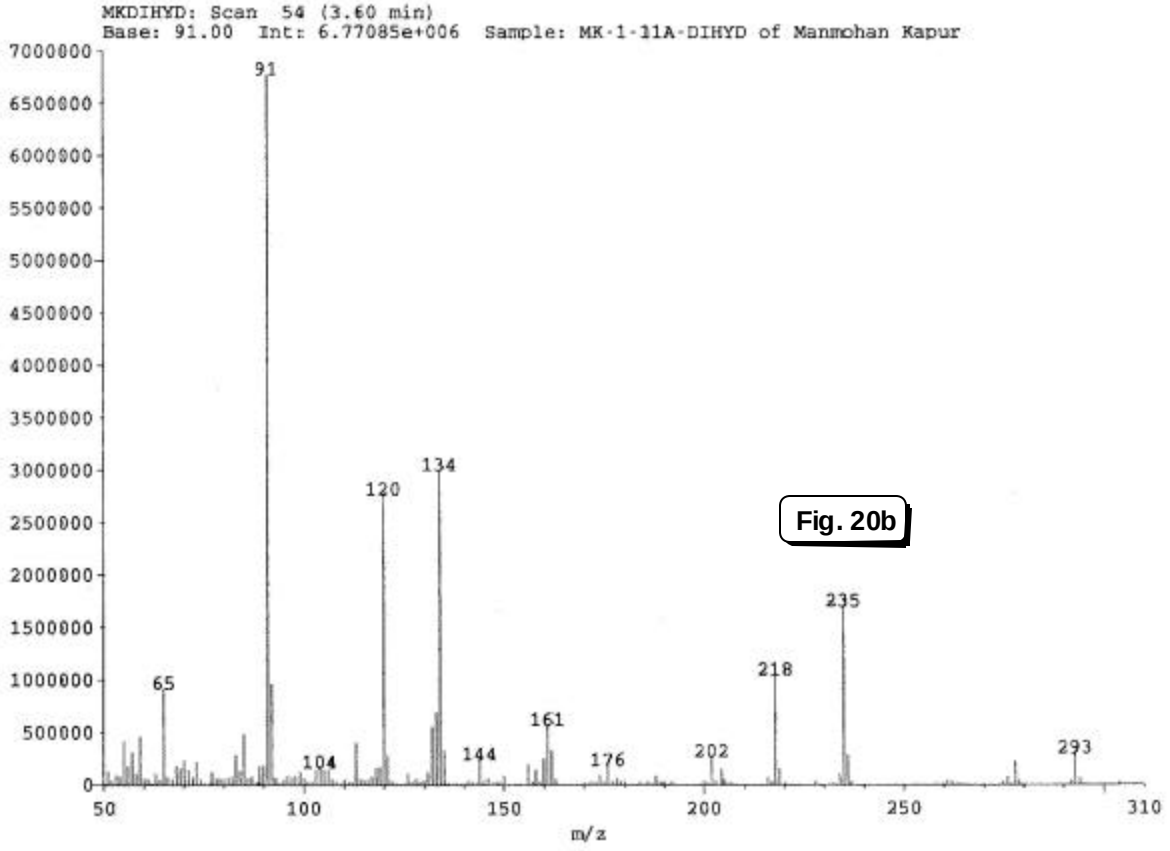
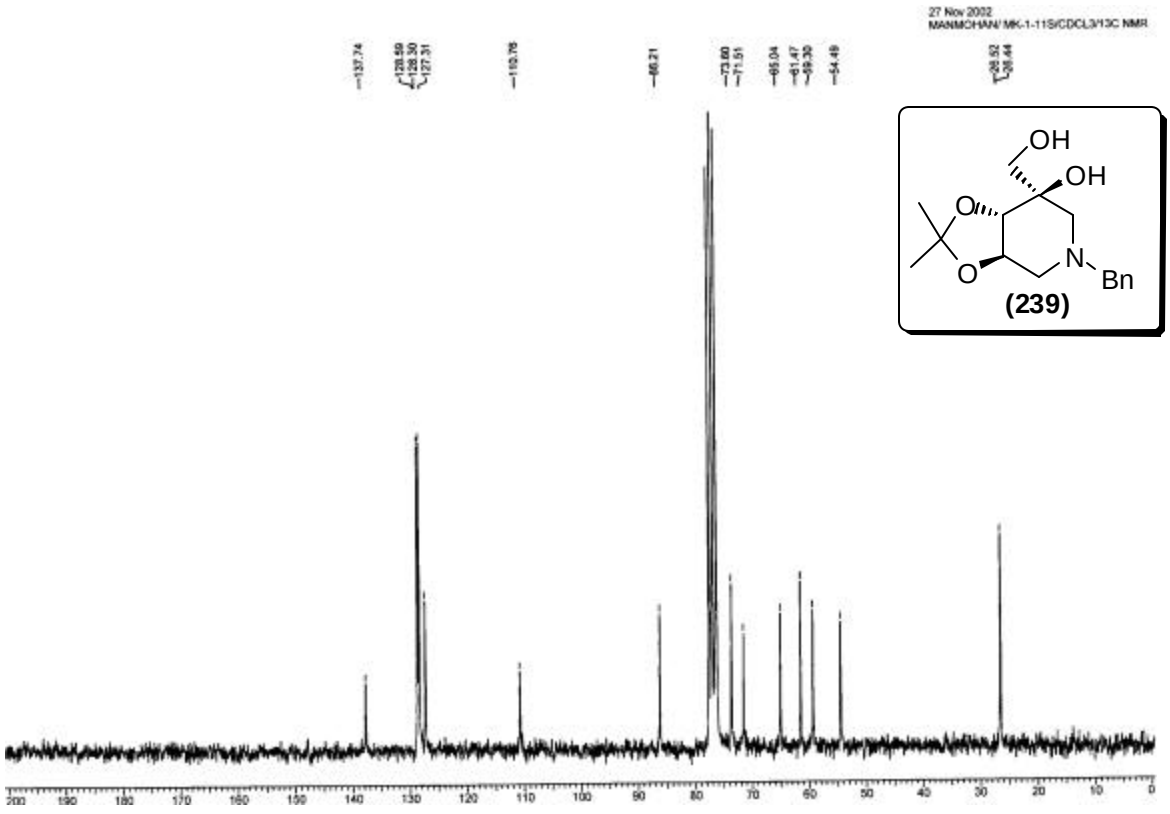


Fig. 20b


27 Nov 2002
MANMOHAN/ MK-1-11S/CDCL3/13C NMR
137.74
128.59
128.30
127.31
110.76
86.21
73.60
71.51
65.04
61.47
59.30
54.49
28.52
26.44
OH
OH
O
O
N
Bn
(239)

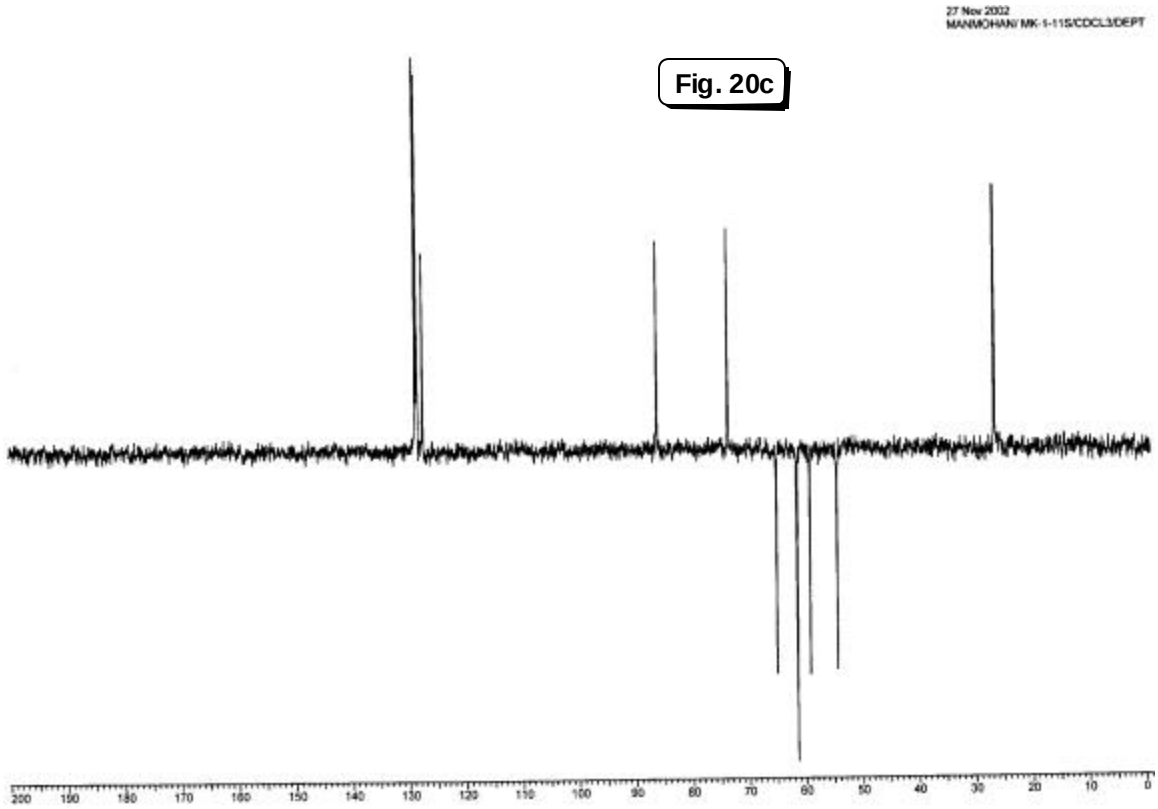

27 Nov 2002
MANMOHAN/ MK-1-11S/CDCL3/DEPT

Fig. 20c

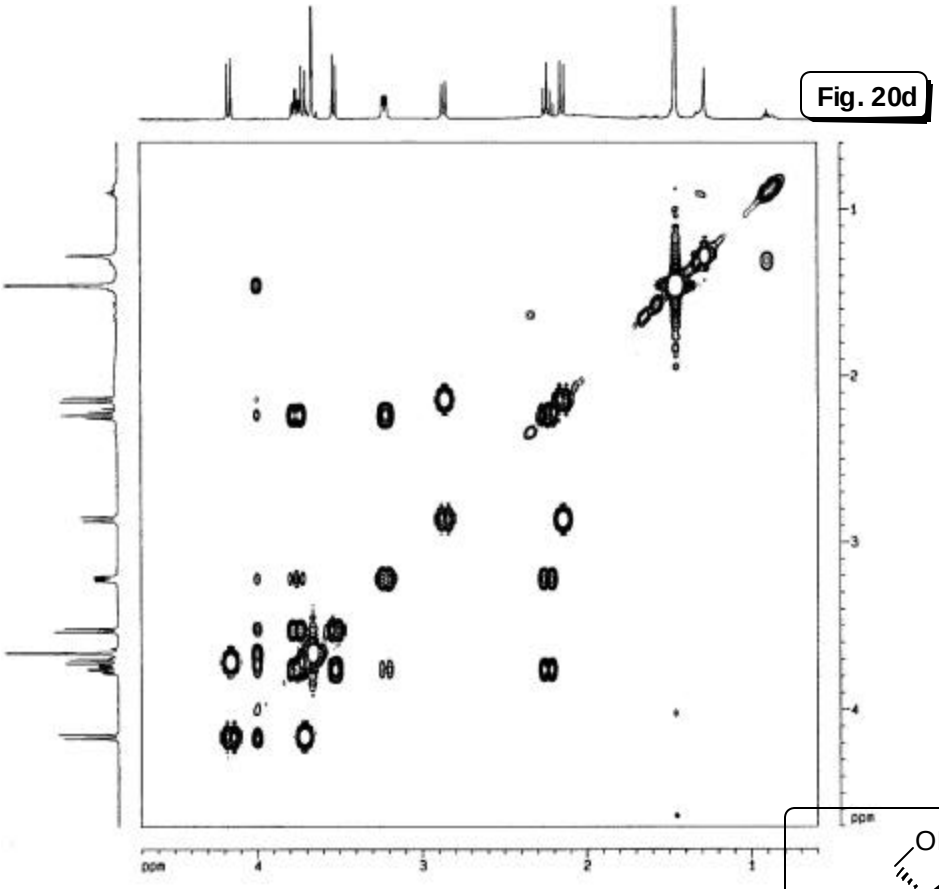
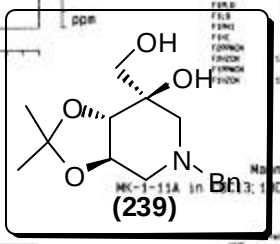


Fig. 20d



(239)

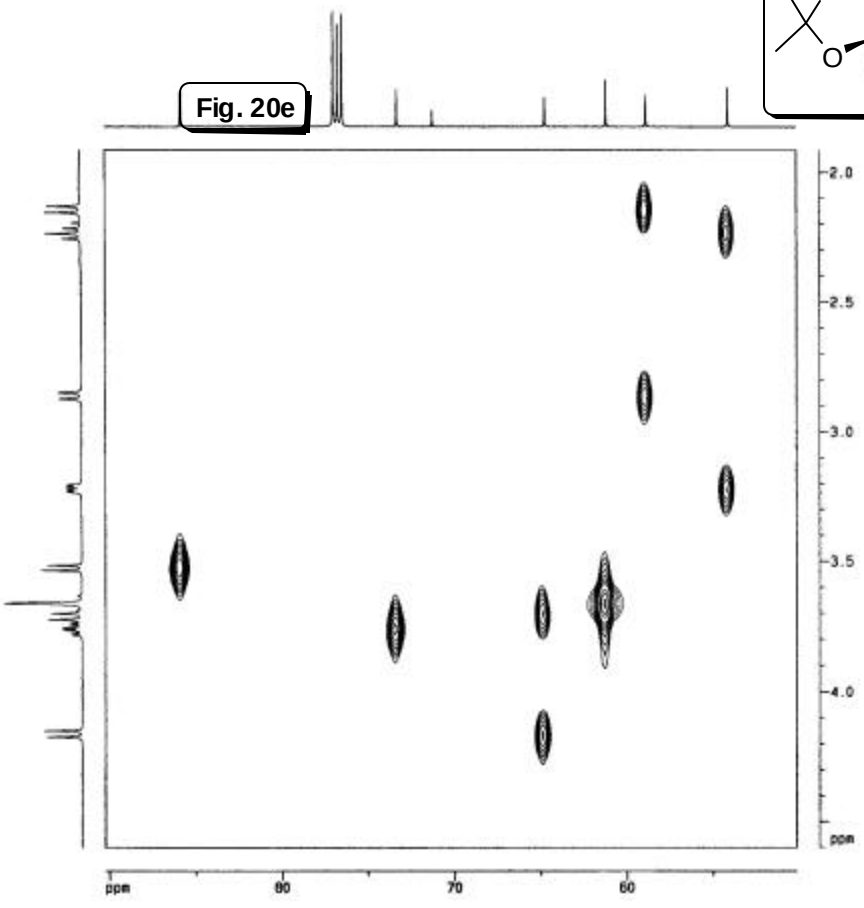
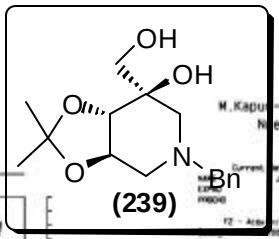


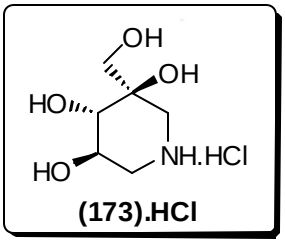
Fig. 20e

Fig. 20f



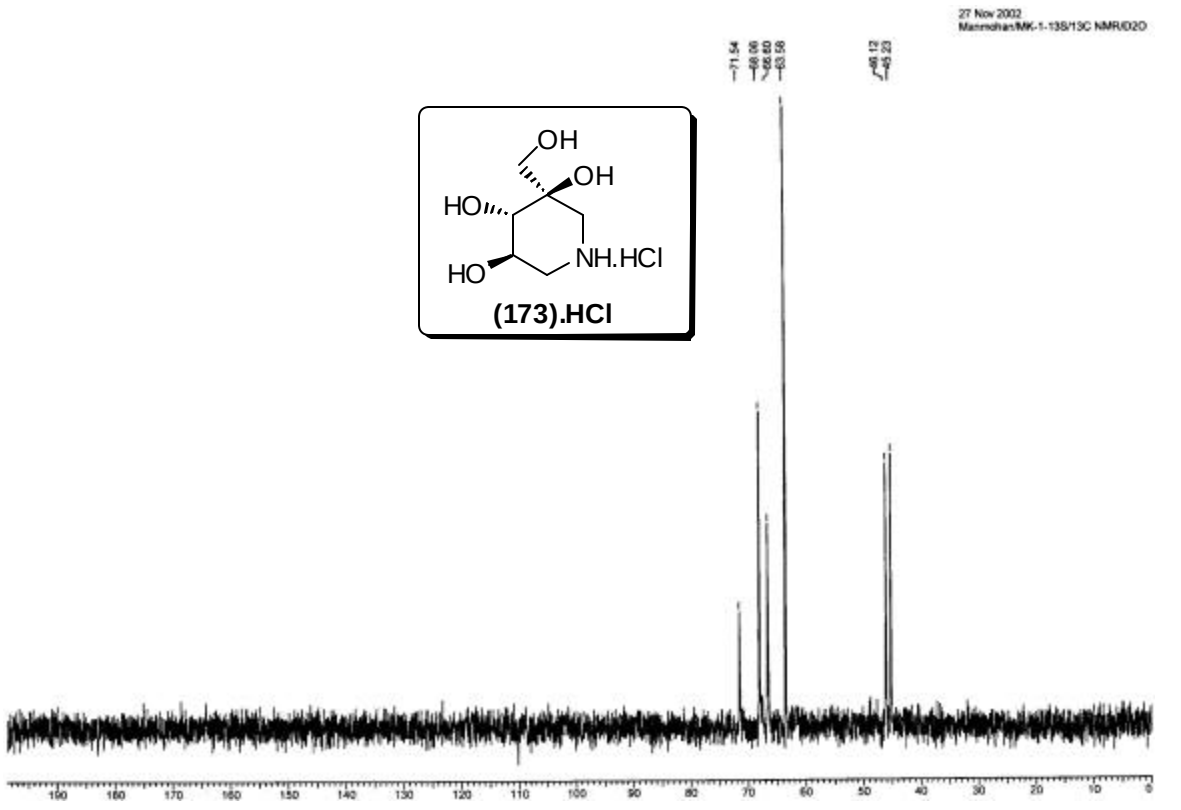
(239)

18 Mar 2002
Manmohan/MK-1-13s-dihydroxy/1H/D2O



(173).HCl

Fig. 21a


27 Nov 2002
Manmohan/MK-1-13S/13C NMR/D2O
OH
OH
HO
NH.HCl
HO
(173).HCl

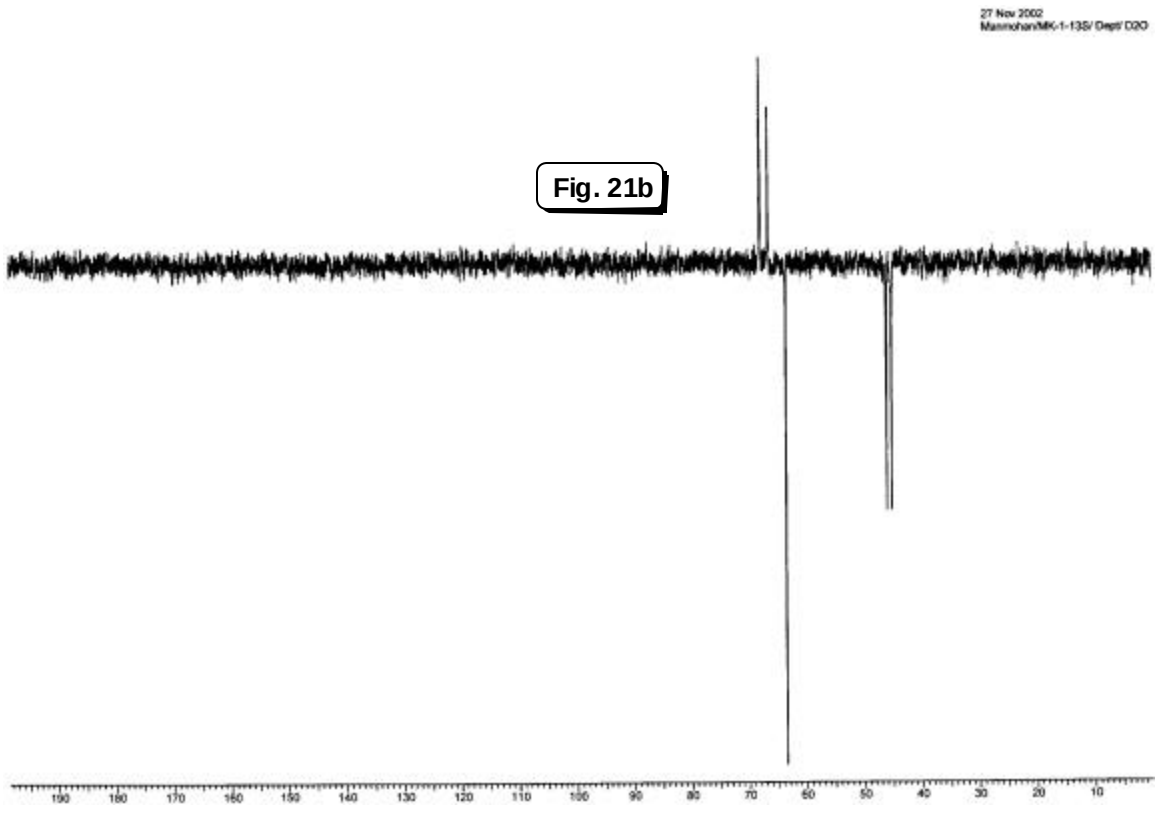

27 Nov 2002
Manmohan/MK-1-13S/ Dept/ D2O

Fig. 21b

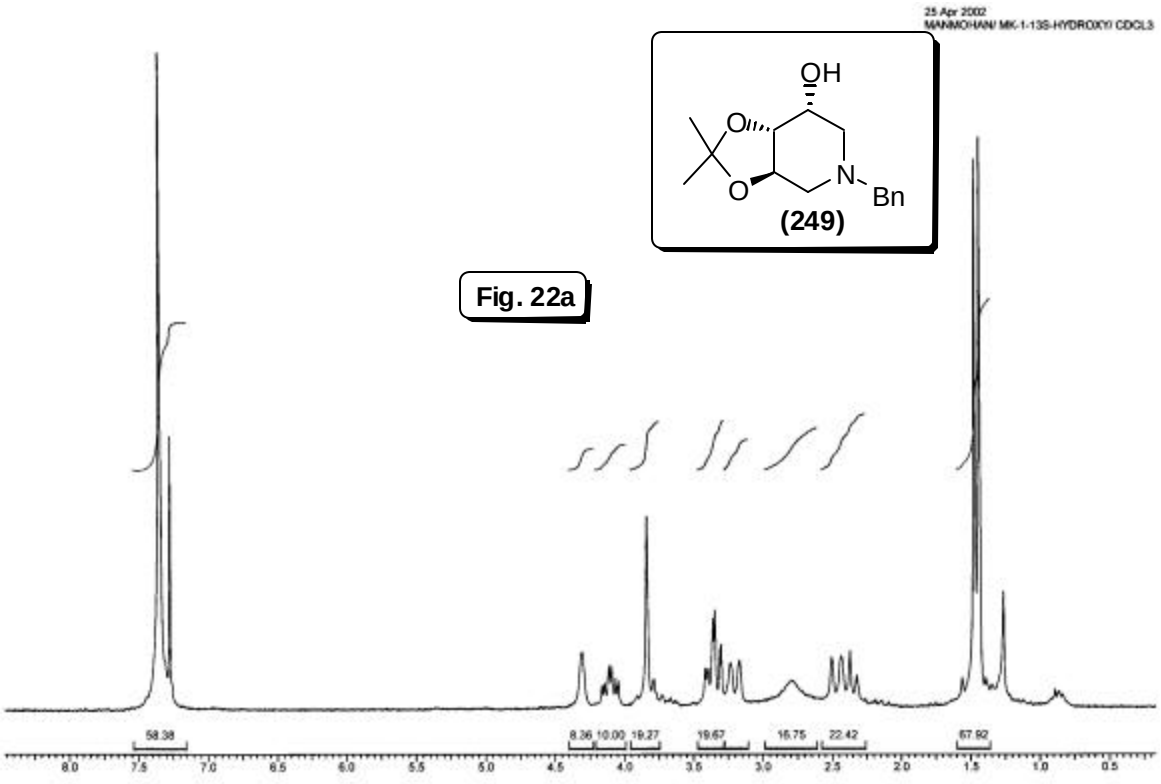
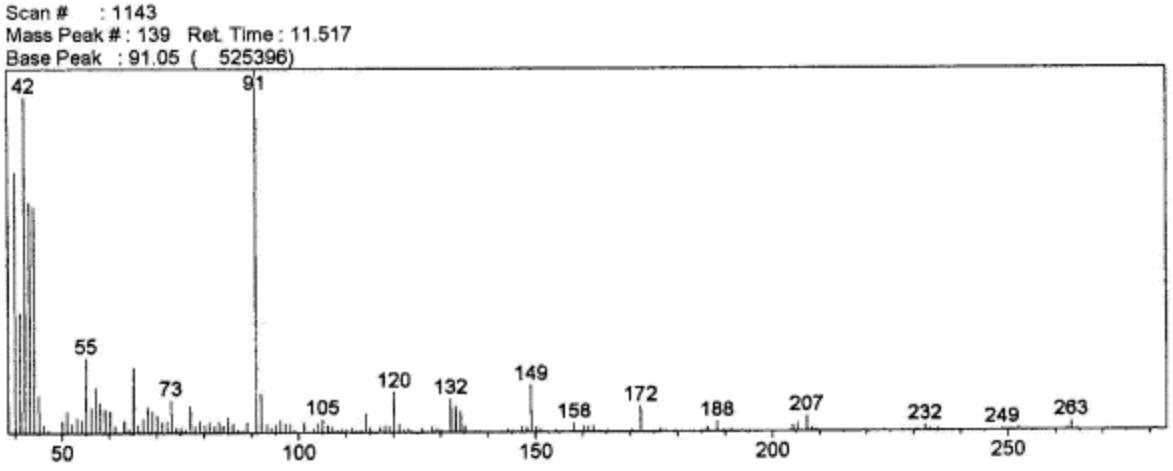
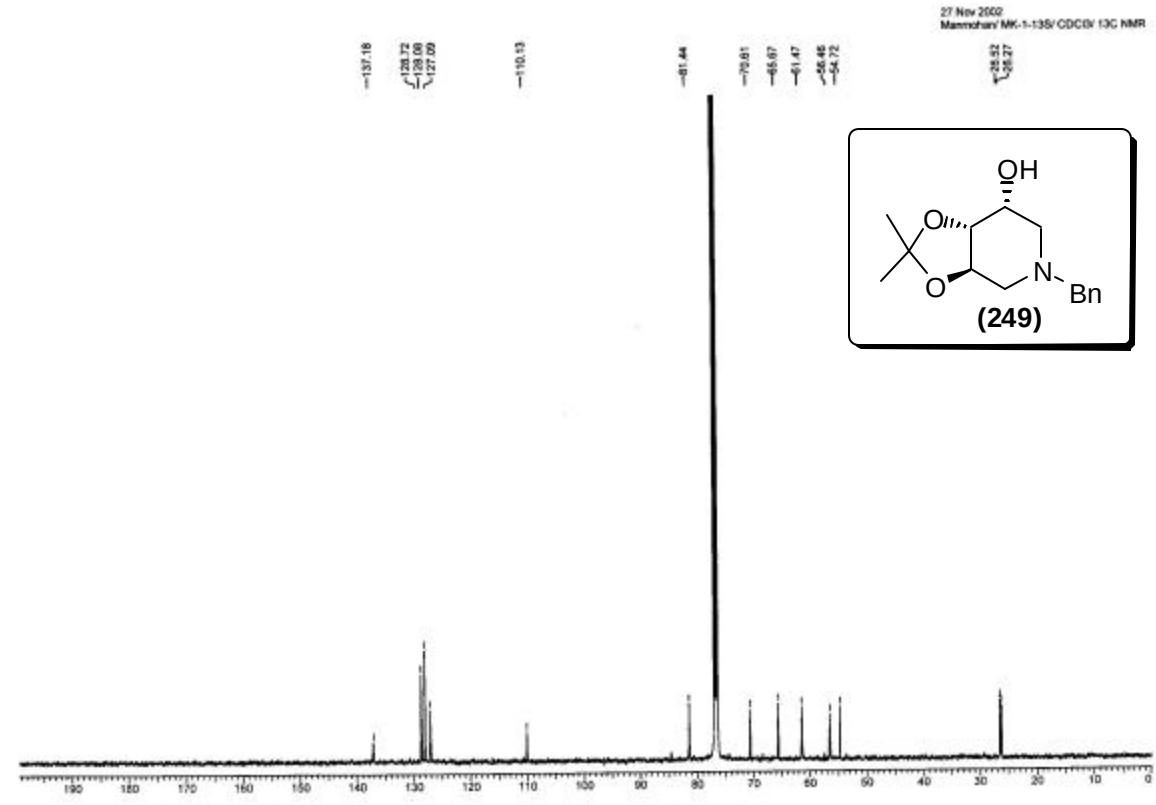


Fig. 22a

Fig. 22b




27 Nov 2002
Manmohan/ MK-1-13S/ CDCl3/ 13C NMR
OH
O
O
N
Bn
(249)

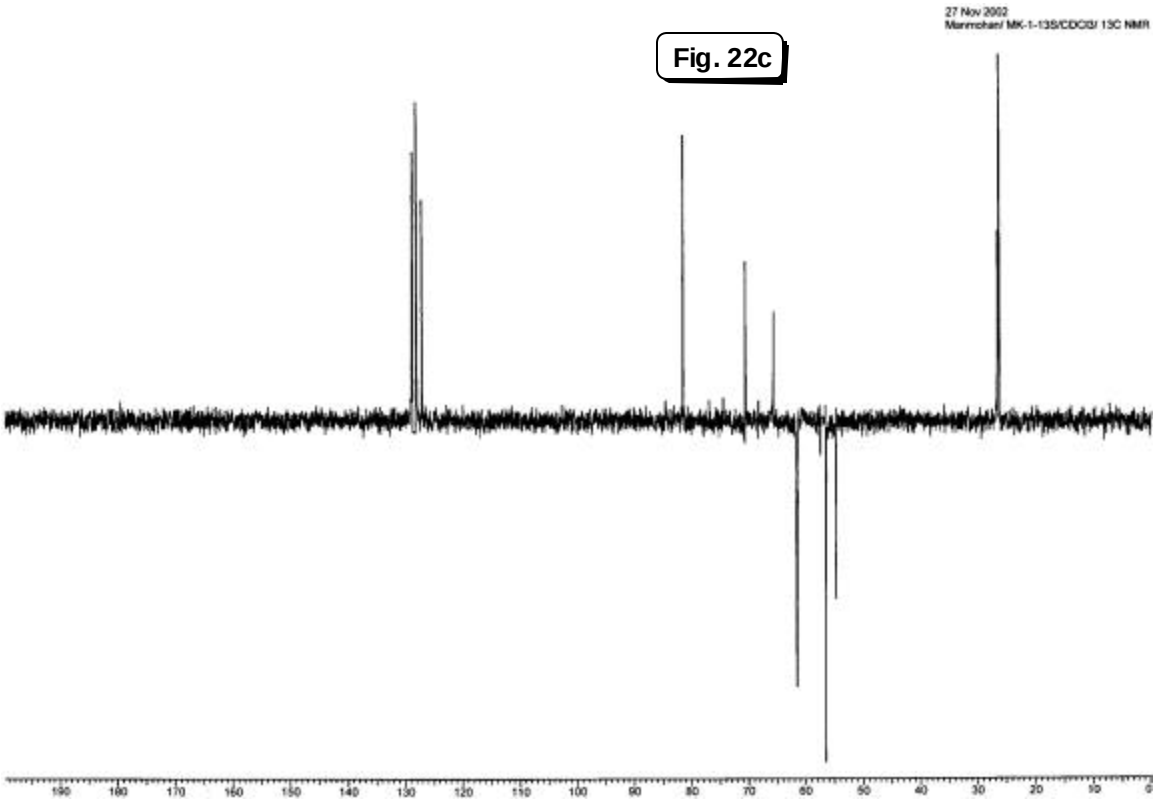
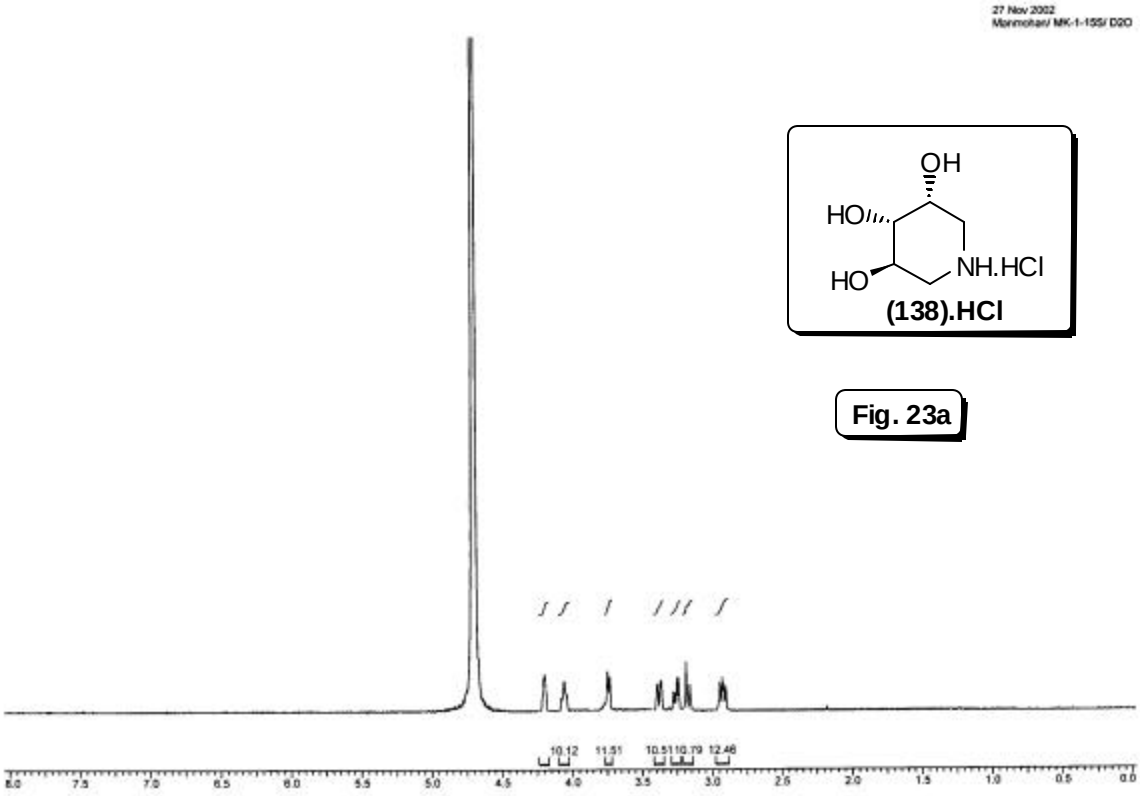

27 Nov 2002
Manmohan/ MK-1-13S/CDCl3/ 13C NMR

Fig. 22c



(138).HCl

Fig. 23a

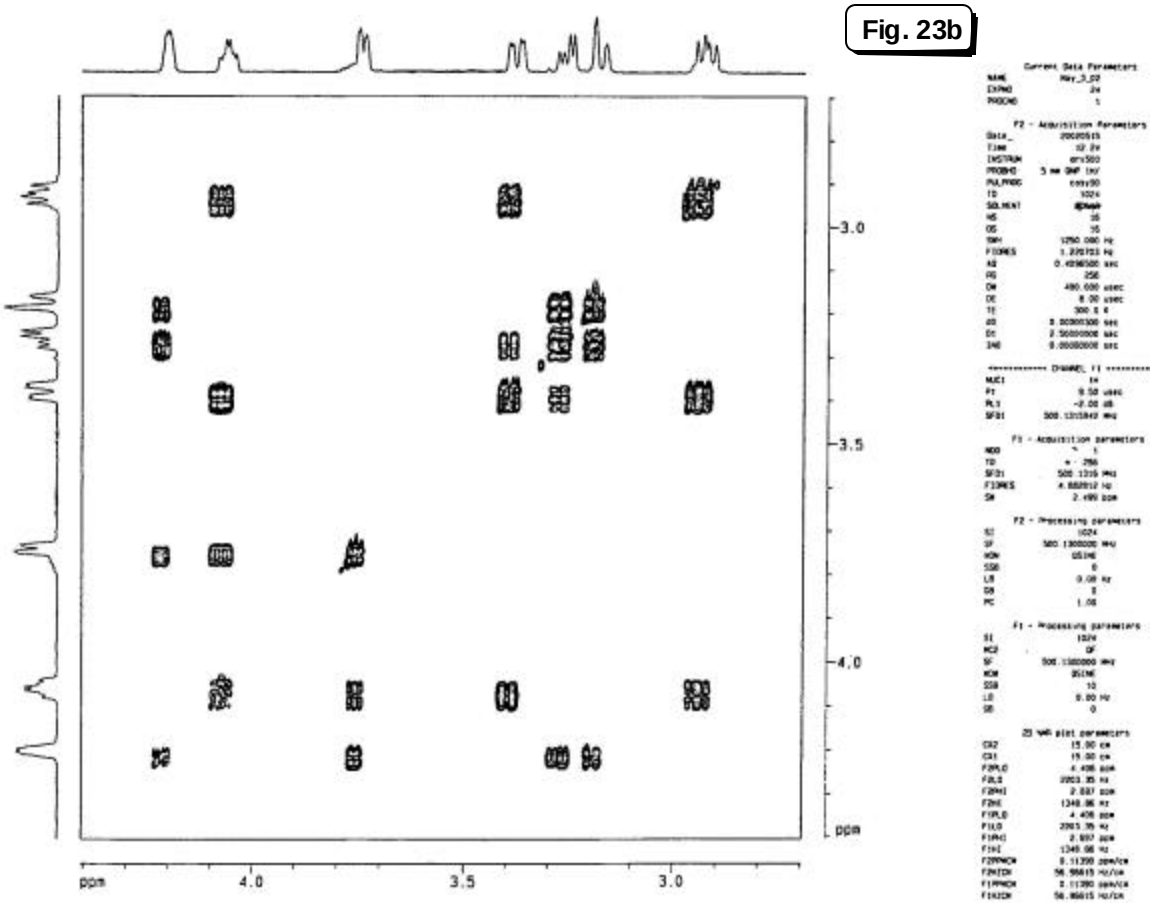


Fig. 23b

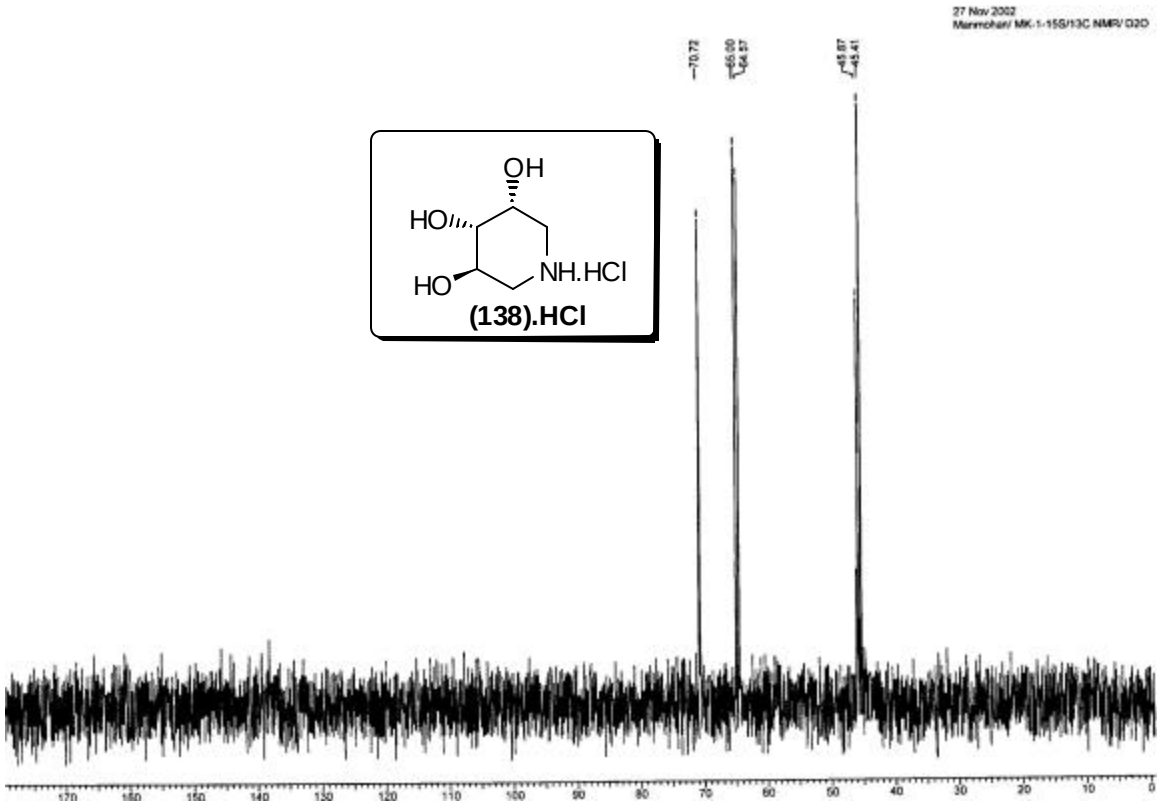
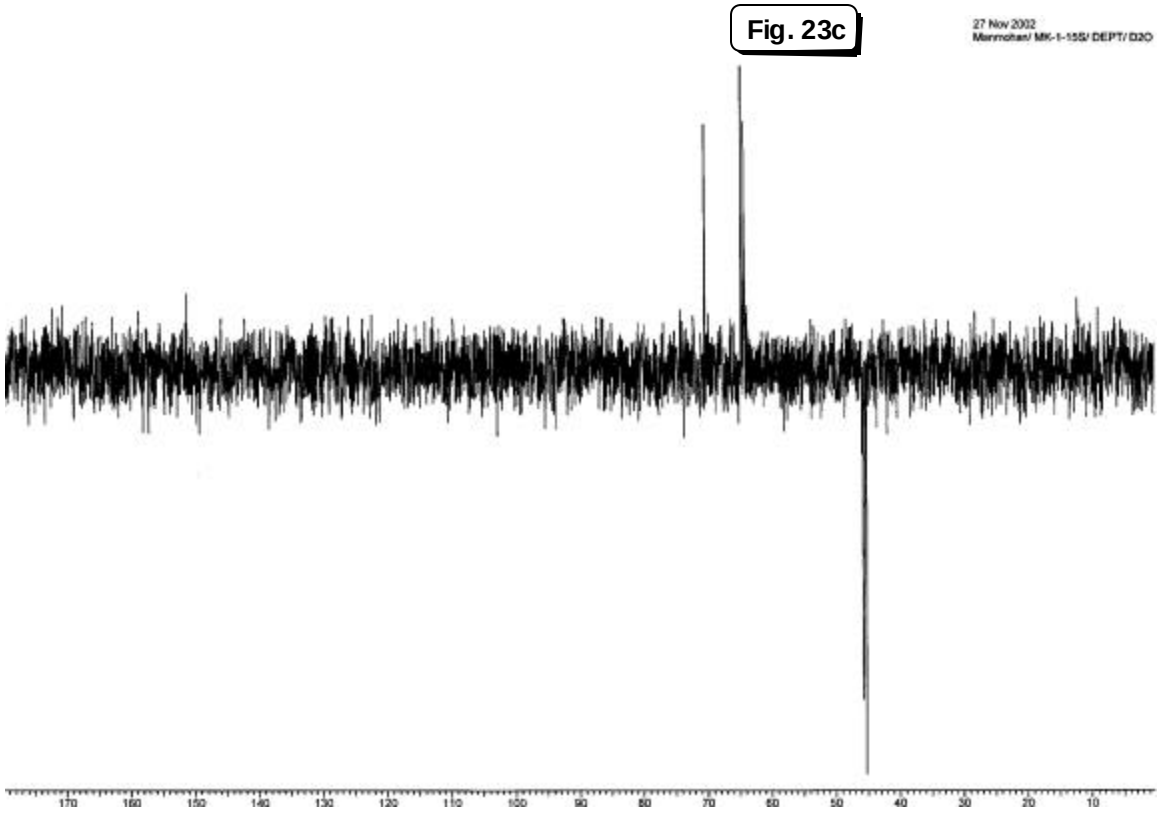

27 Nov 2002
Manmohan/ MK-I-15S/13C NMR/ D2O
70.72
65.00
64.57
45.87
45.41
OH
HO
HO
NH.HCl
(138).HCl

Fig. 23c


27 Nov 2002
Manmohan/ MK-I-15S/ DEPT/ D2O

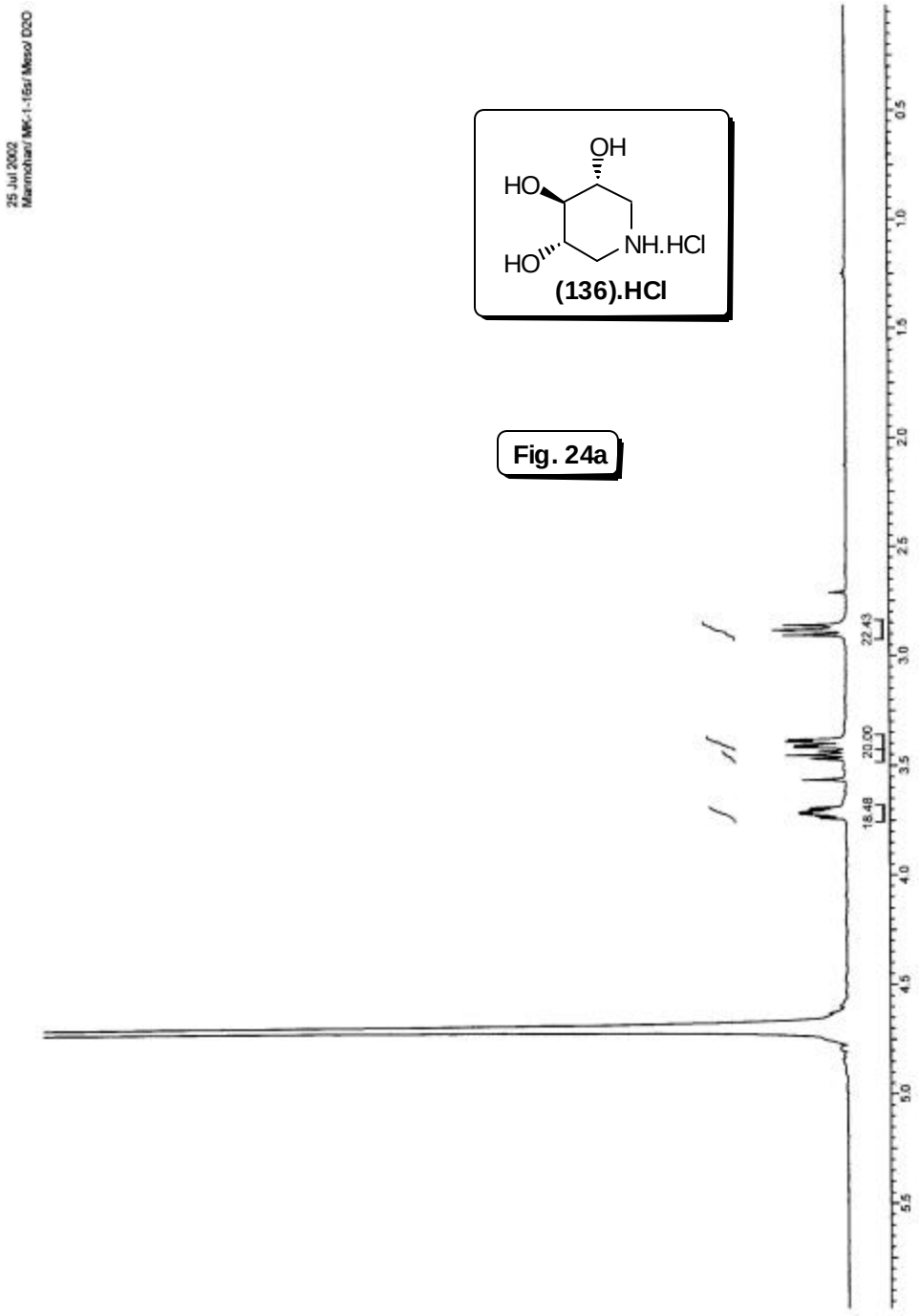

25 Jul 2002
Manmohan/ MK-1-16s/ Mesol/ D2O
OH
HO
NH.HCl
HO
(136).HCl
22.43
20.00
18.48
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

Fig. 24a

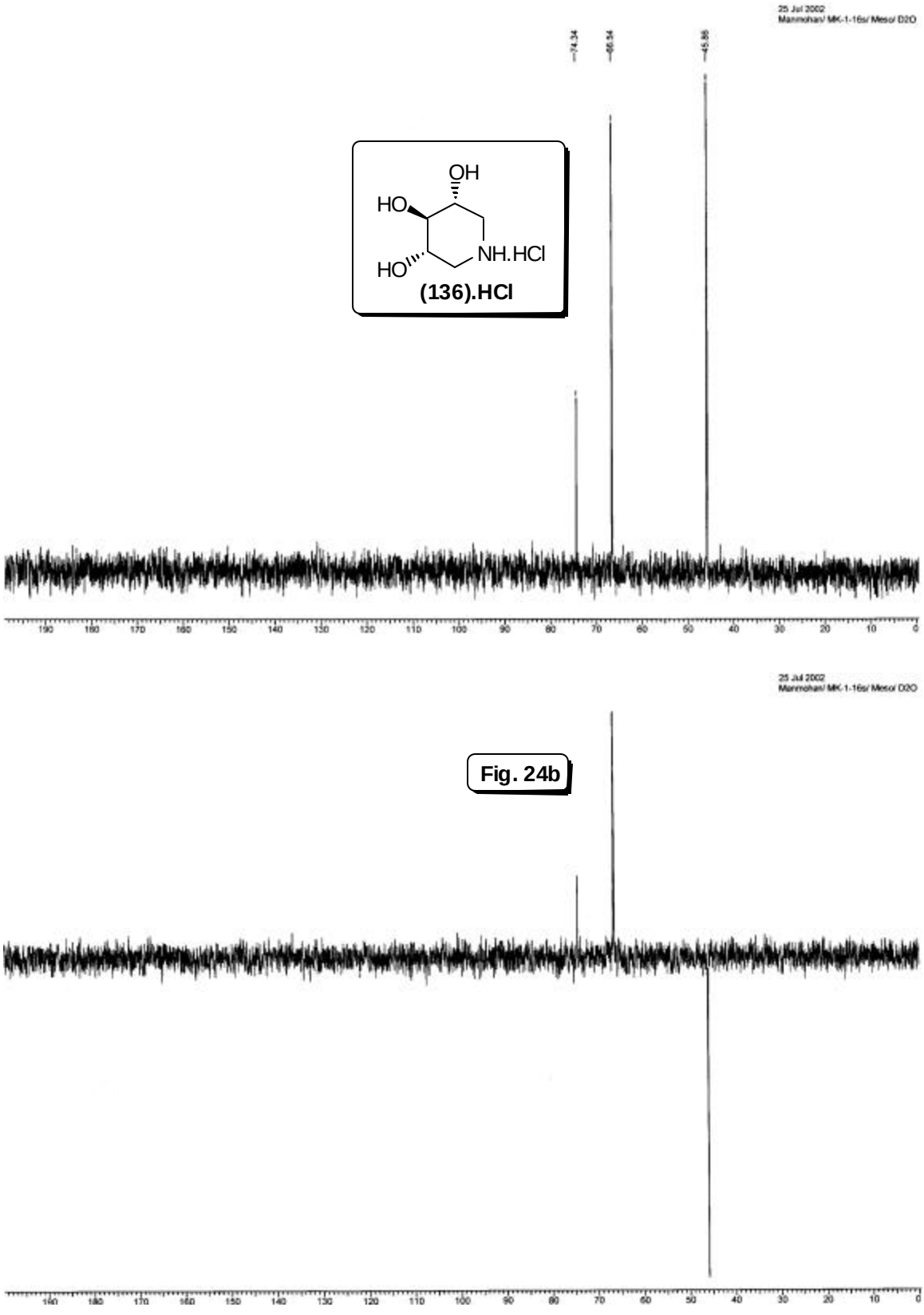

25 Jul 2002
Manmohan/ MK-1-16s/ Meso/ D2O
74.34
66.54
45.88
OH
HO
HO
NH.HCl
(136).HCl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
25 Jul 2002
Manmohan/ MK-1-16s/ Meso/ D2O
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Fig. 24b

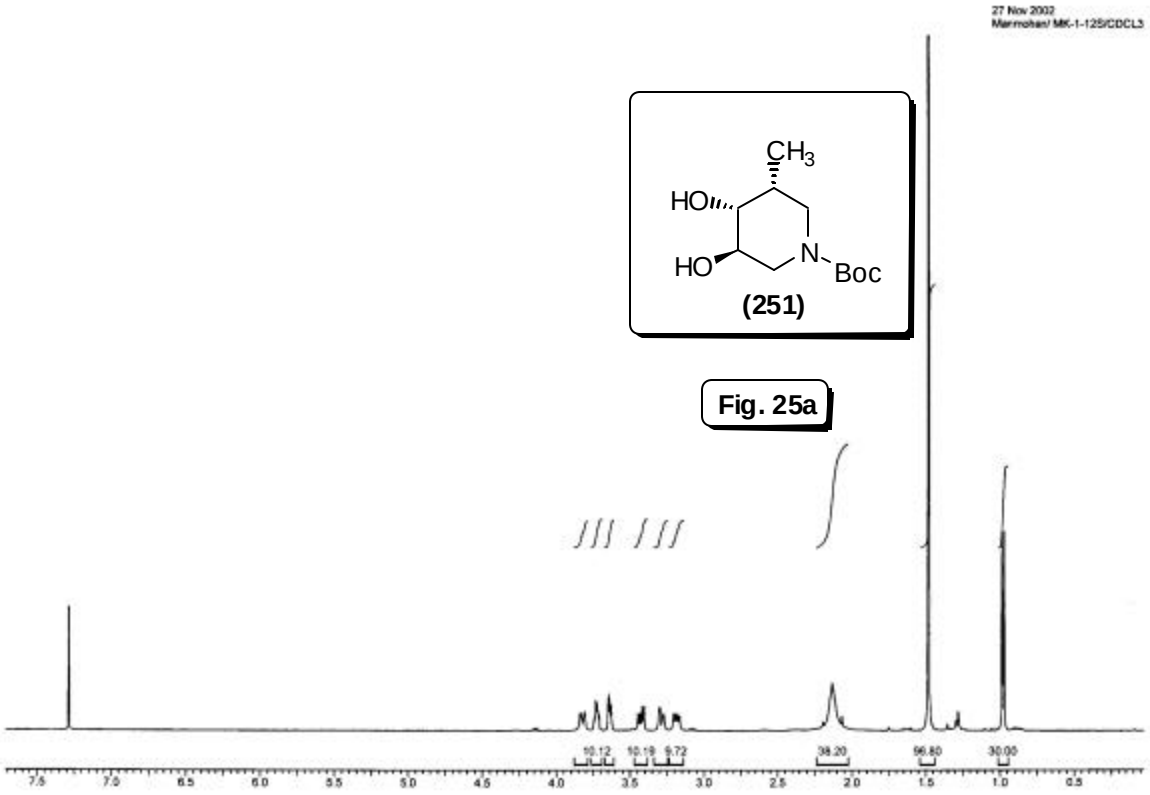
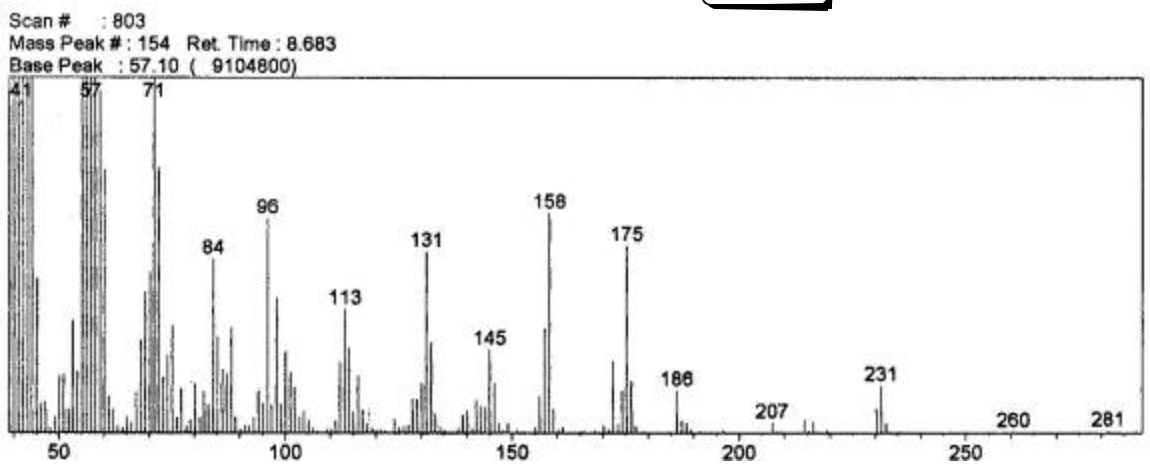


Fig. 25a

Fig. 25b



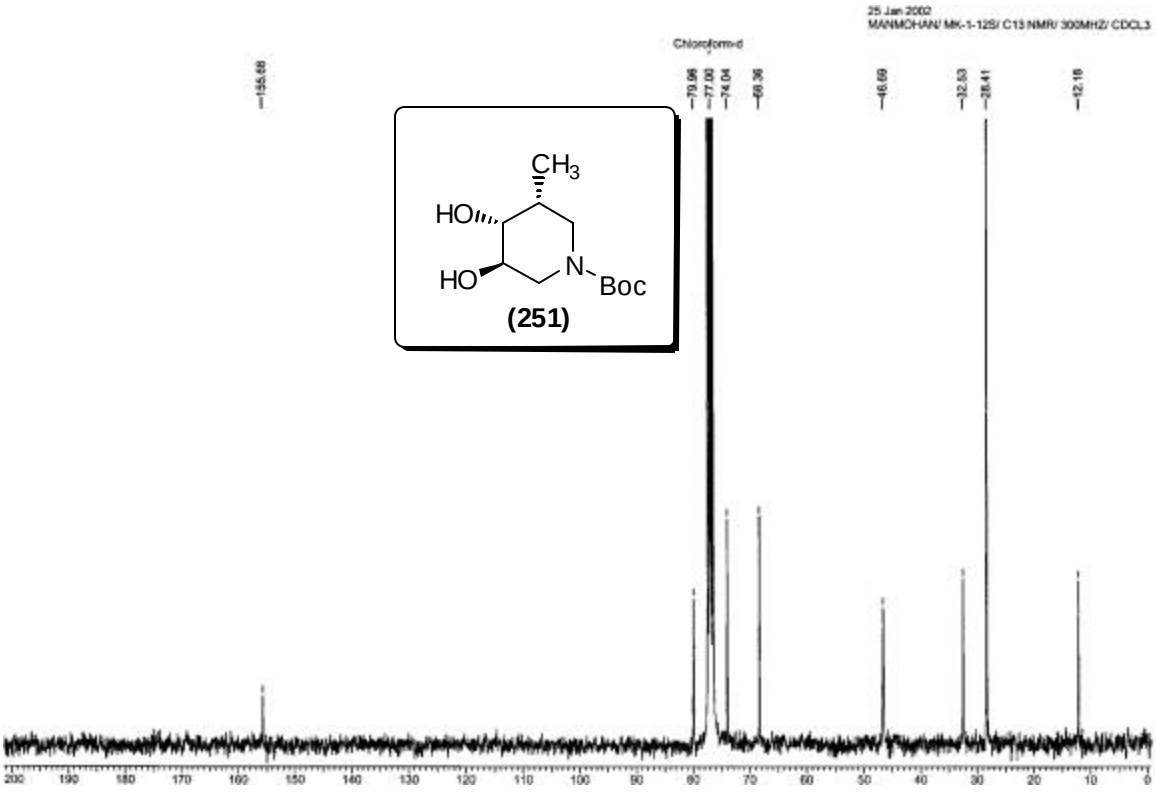
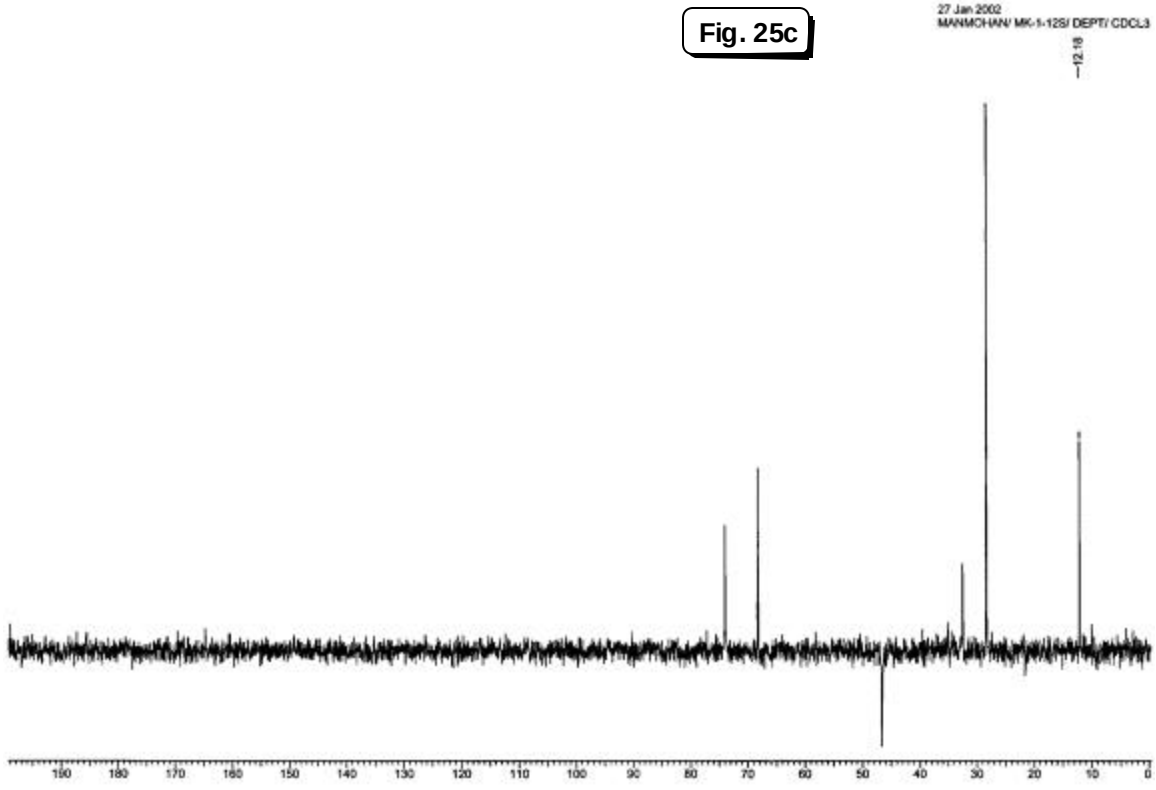

25 Jan 2002
MANMOHAN/ MK-1-12S/ C13 NMR/ 300MHZ/ CDCL3
Chloroform-d
155.88
79.98
77.00
74.04
69.36
46.69
32.53
28.41
12.18
CH3
HO
HO
N
Boc
(251)

Fig. 25c


27 Jan 2002
MANMOHAN/ MK-1-12S/ DEPT/ CDCL3
12.18

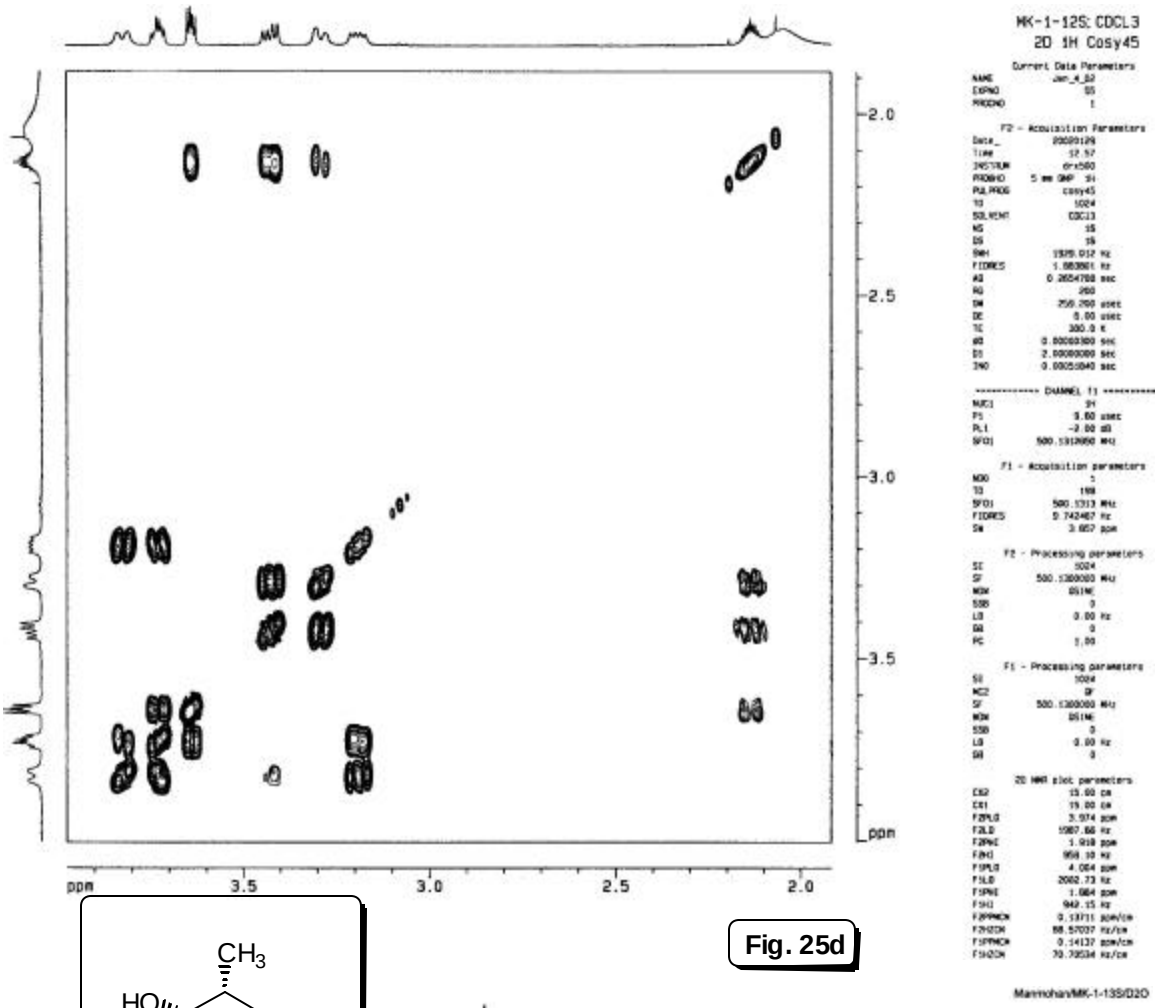
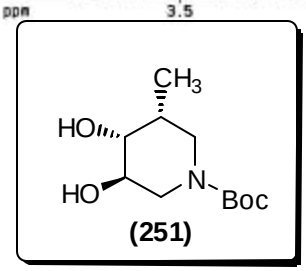
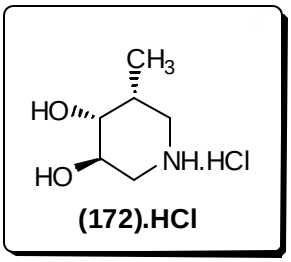


Fig. 25d

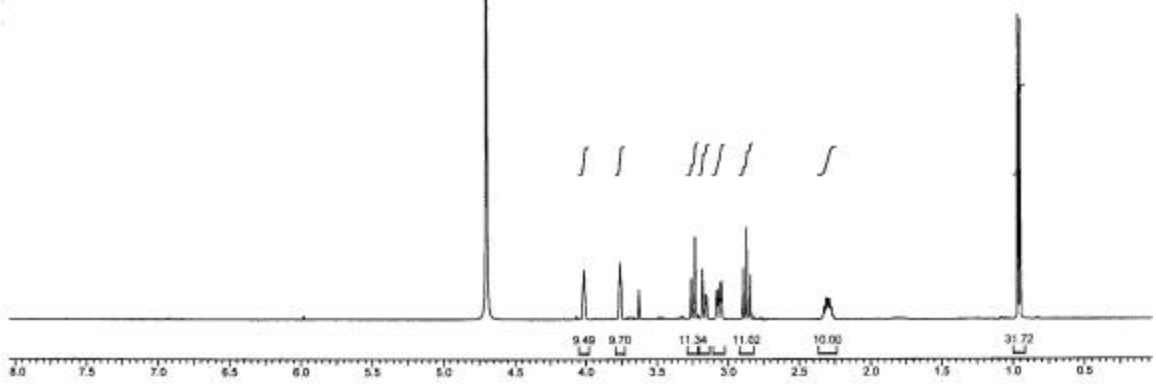


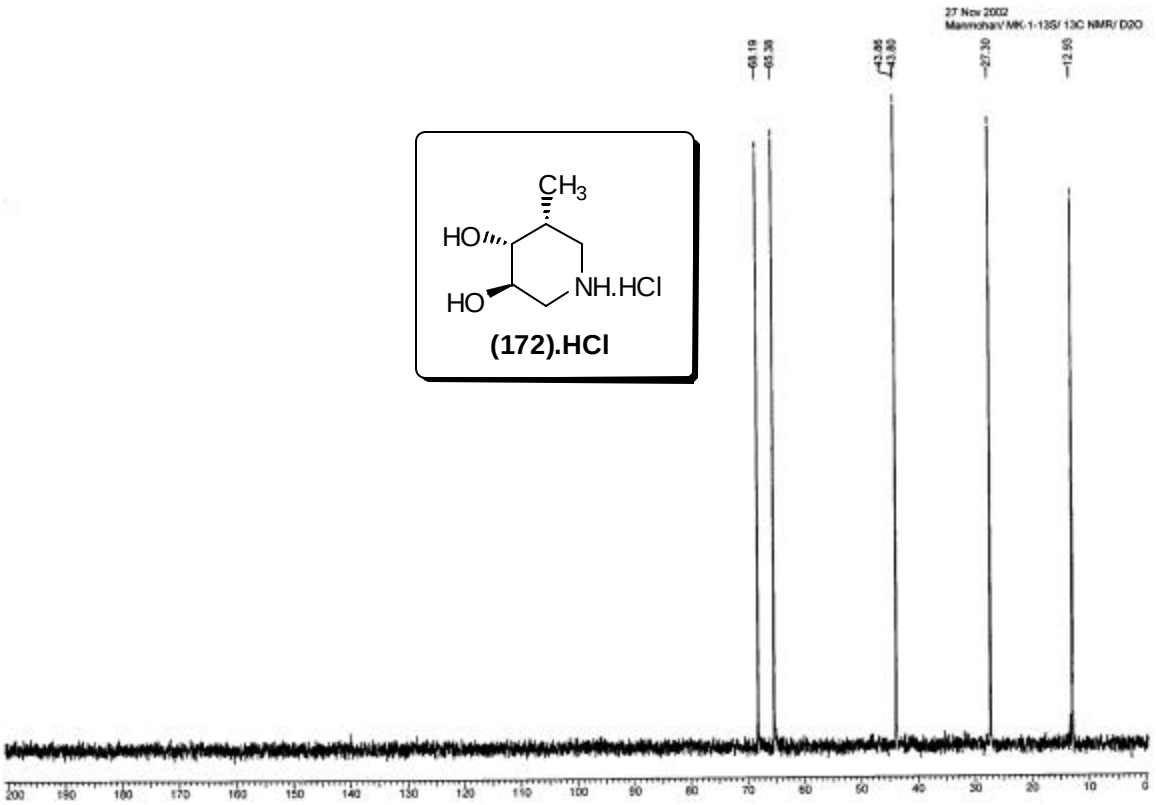
(251)



(172).HCl

Fig. 26a




27 Nov 2002
Manmohan/ MK-1-13S/ 13C NMR/ D2O
69.19
65.38
43.86
43.80
27.30
12.93
CH3
HO
HO
NH.HCl
(172).HCl

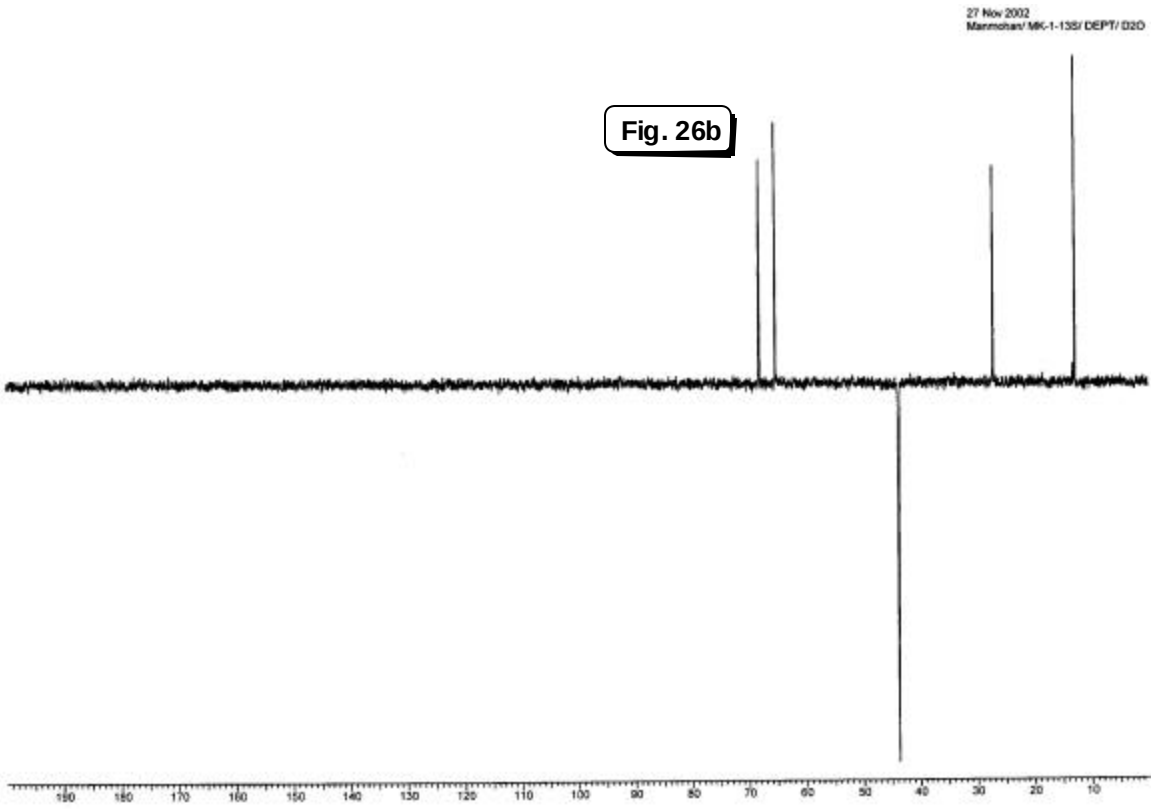

27 Nov 2002
Manmohan/ MK-1-13S/ DEPT/ D2O

Fig. 26b

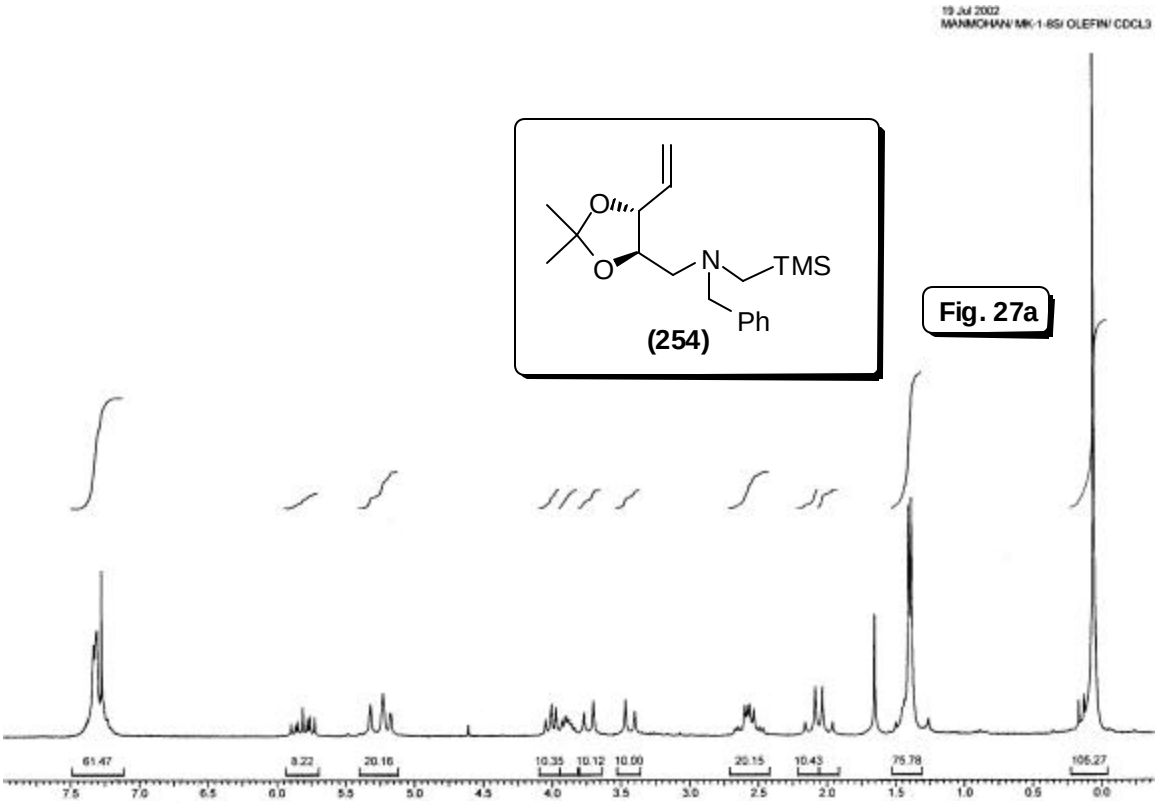


Fig. 27a

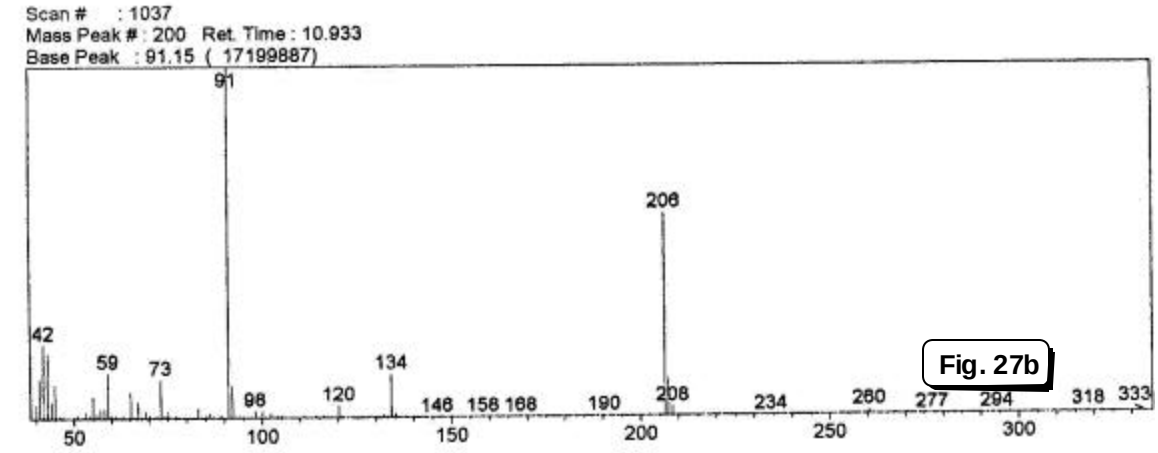
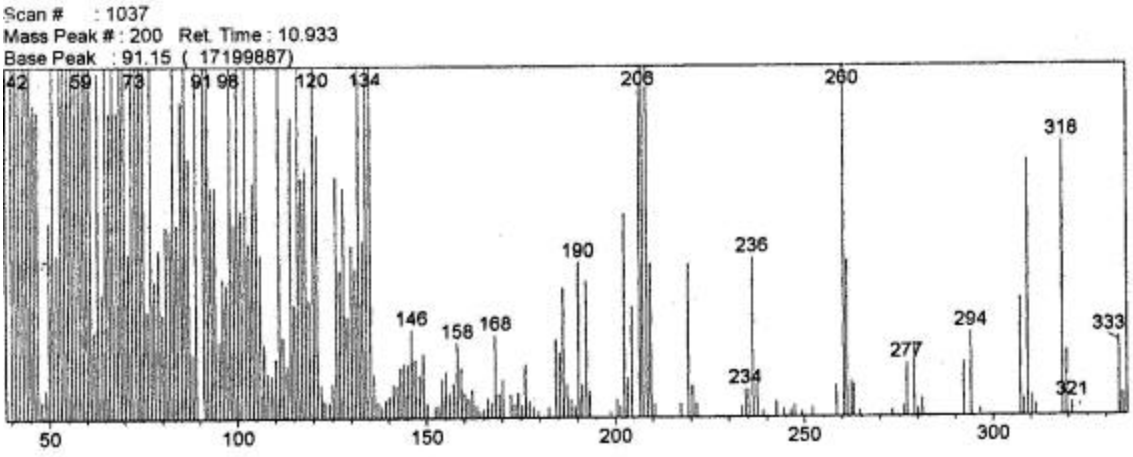
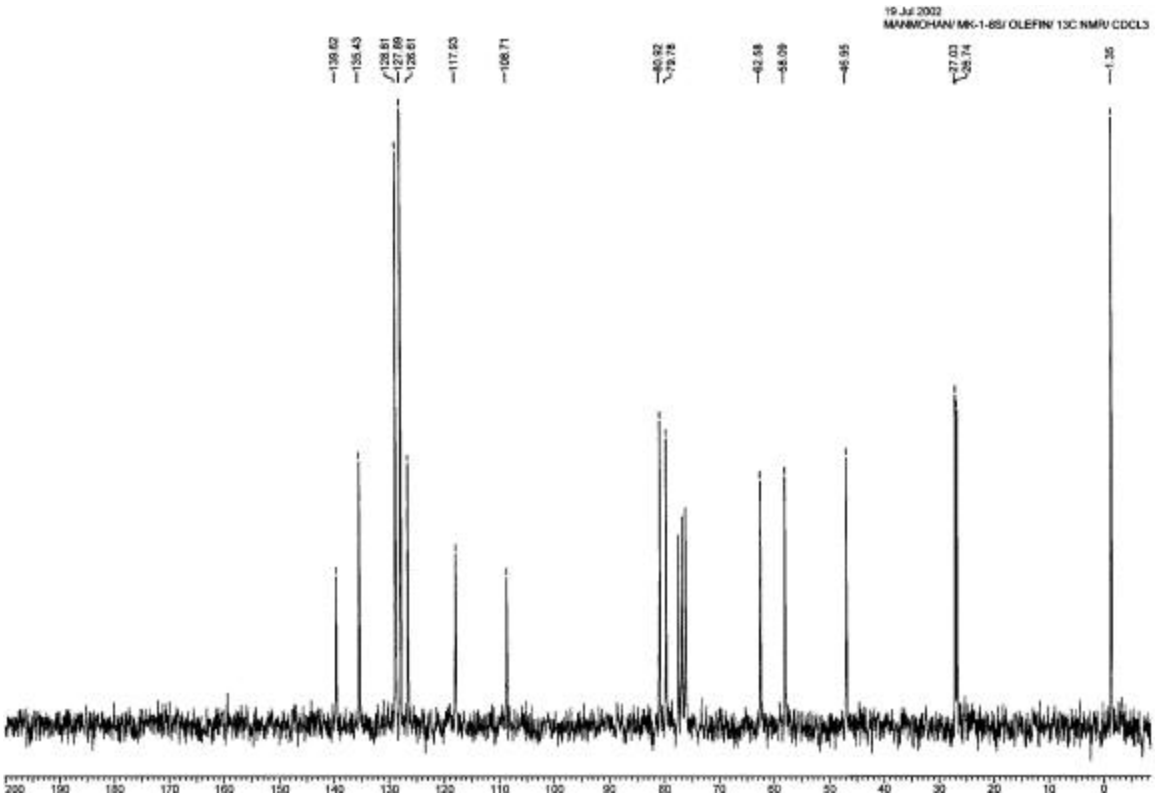
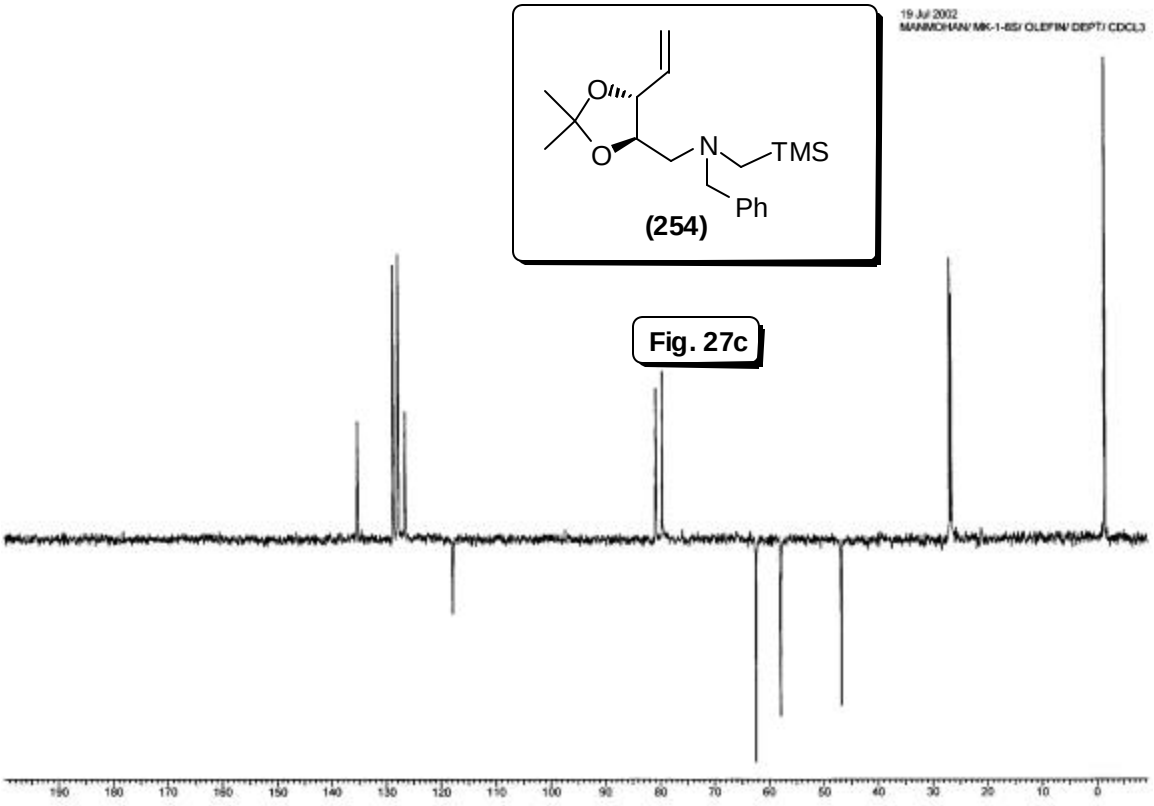


Fig. 27b




19 Jul 2002
MANMOHAN/ MK-1-65/ OLEFIN/ 13C NMR/ CDCL3
139.62
135.43
128.61
127.89
126.61
117.03
106.71
80.92
79.78
62.58
58.09
46.95
27.03
26.74
1.35


19 Jul 2002
MANMOHAN/ MK-1-65/ OLEFIN/ DEPT/ CDCL3

O
O
N
TMS
Ph

(254)

Fig. 27c

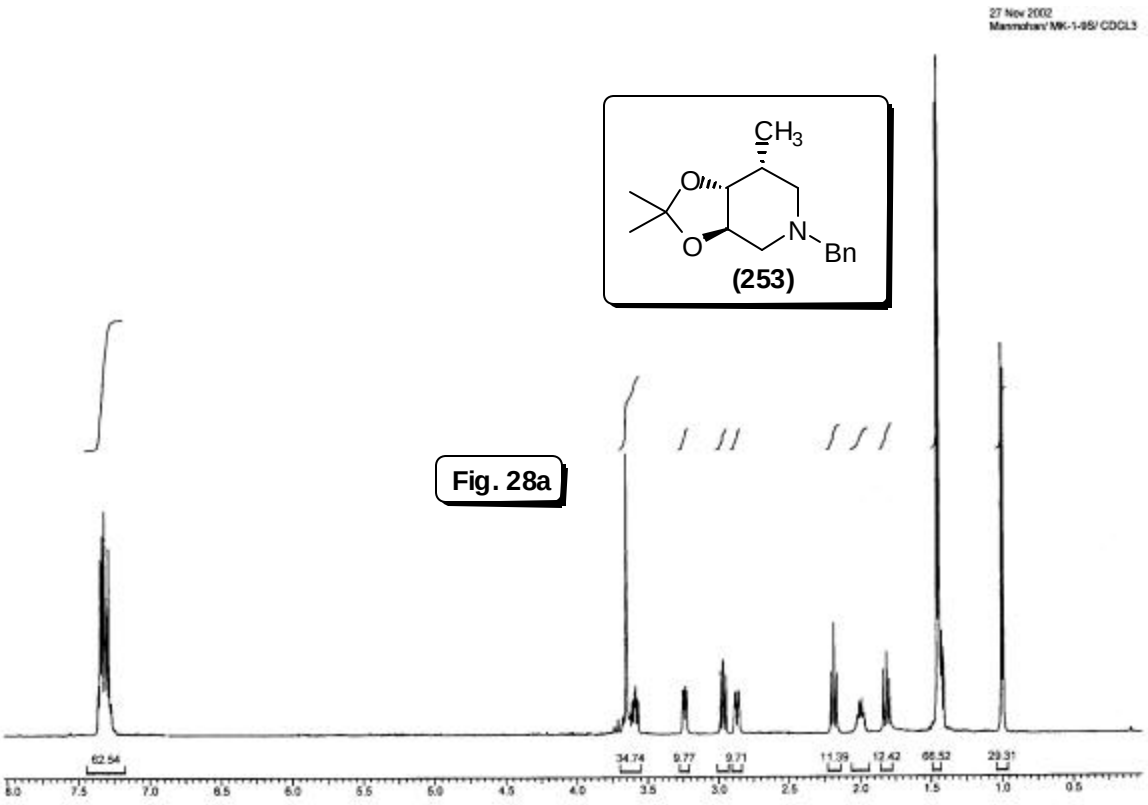
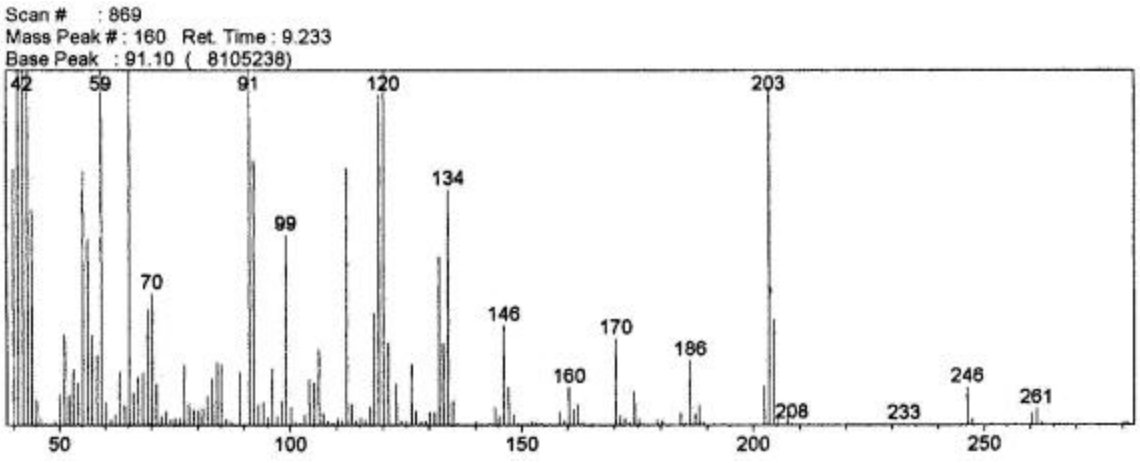
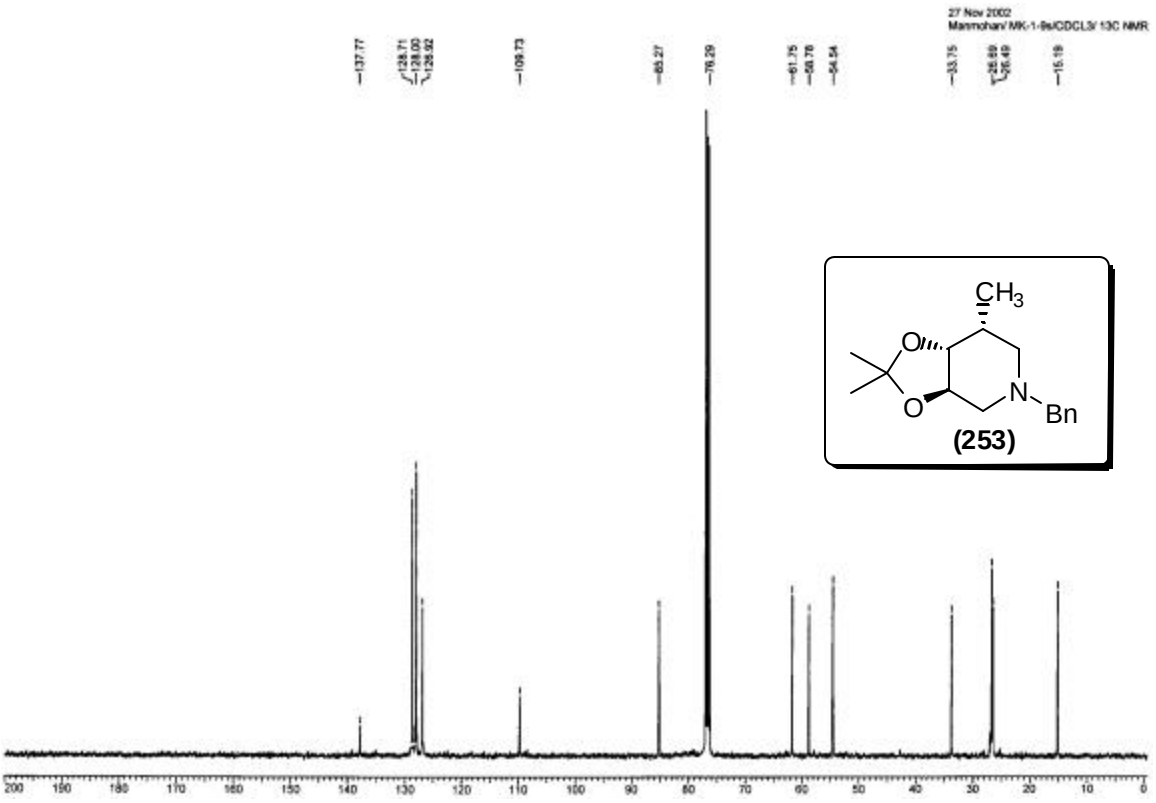


Fig. 28a

Fig. 28b




27 Nov 2002
Manmohan/ MK-1-8s/CDCL3/ 13C NMR
137.77
128.71
128.00
126.92
109.73
85.27
76.29
61.75
59.70
54.54
33.75
26.89
26.49
15.19
CH3
O
O
N
Bn
(253)

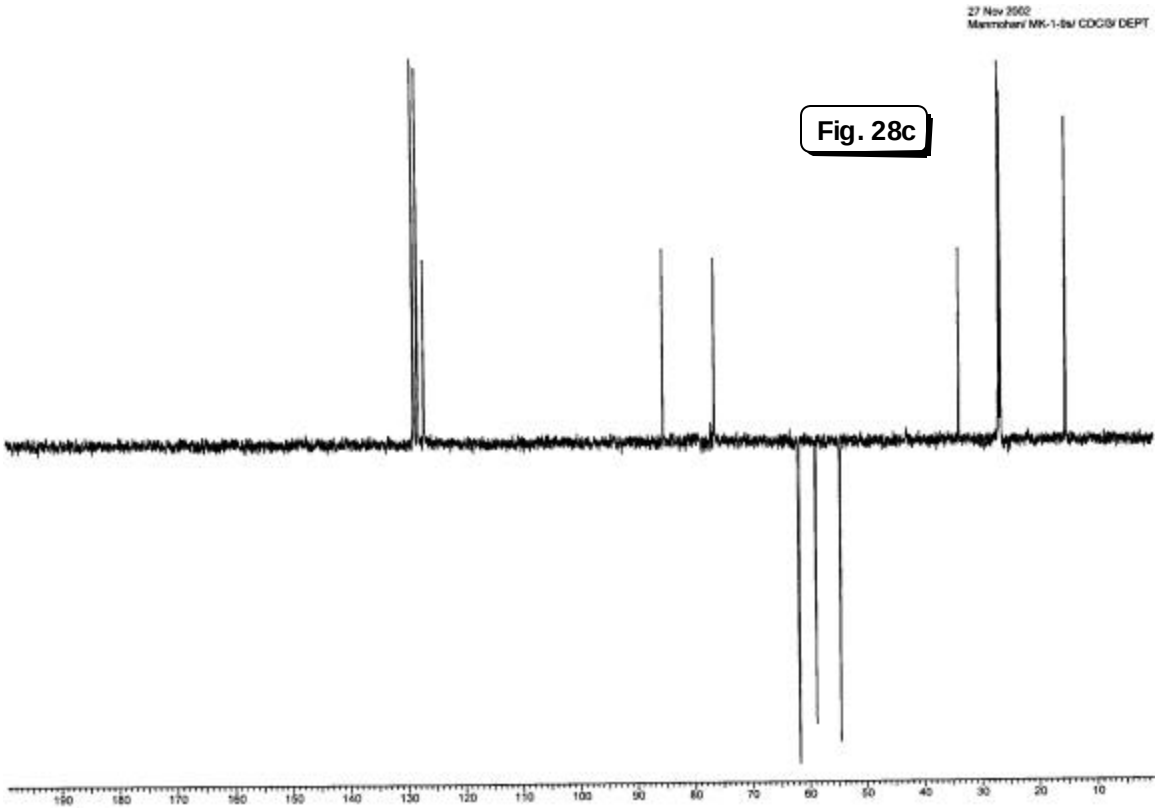
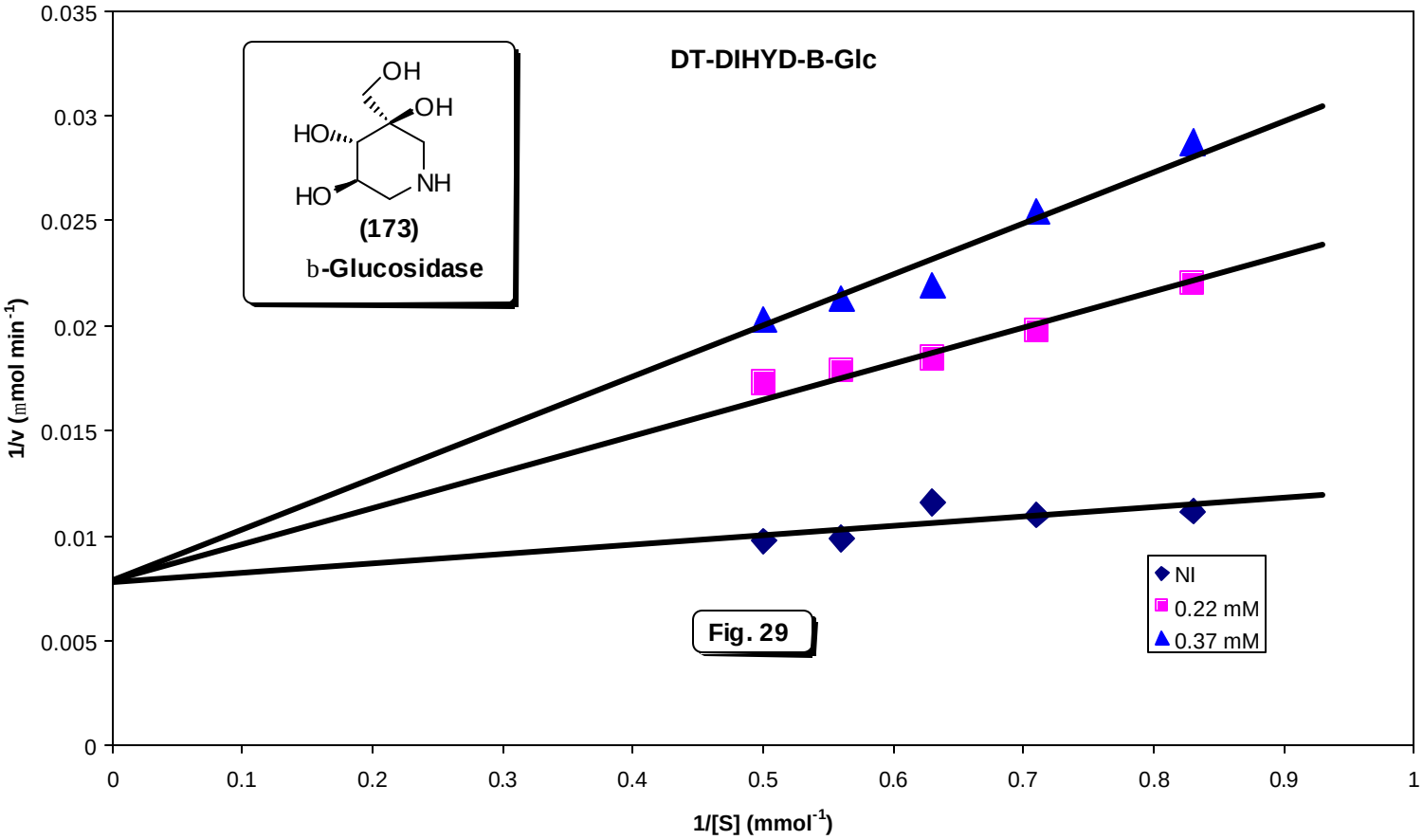
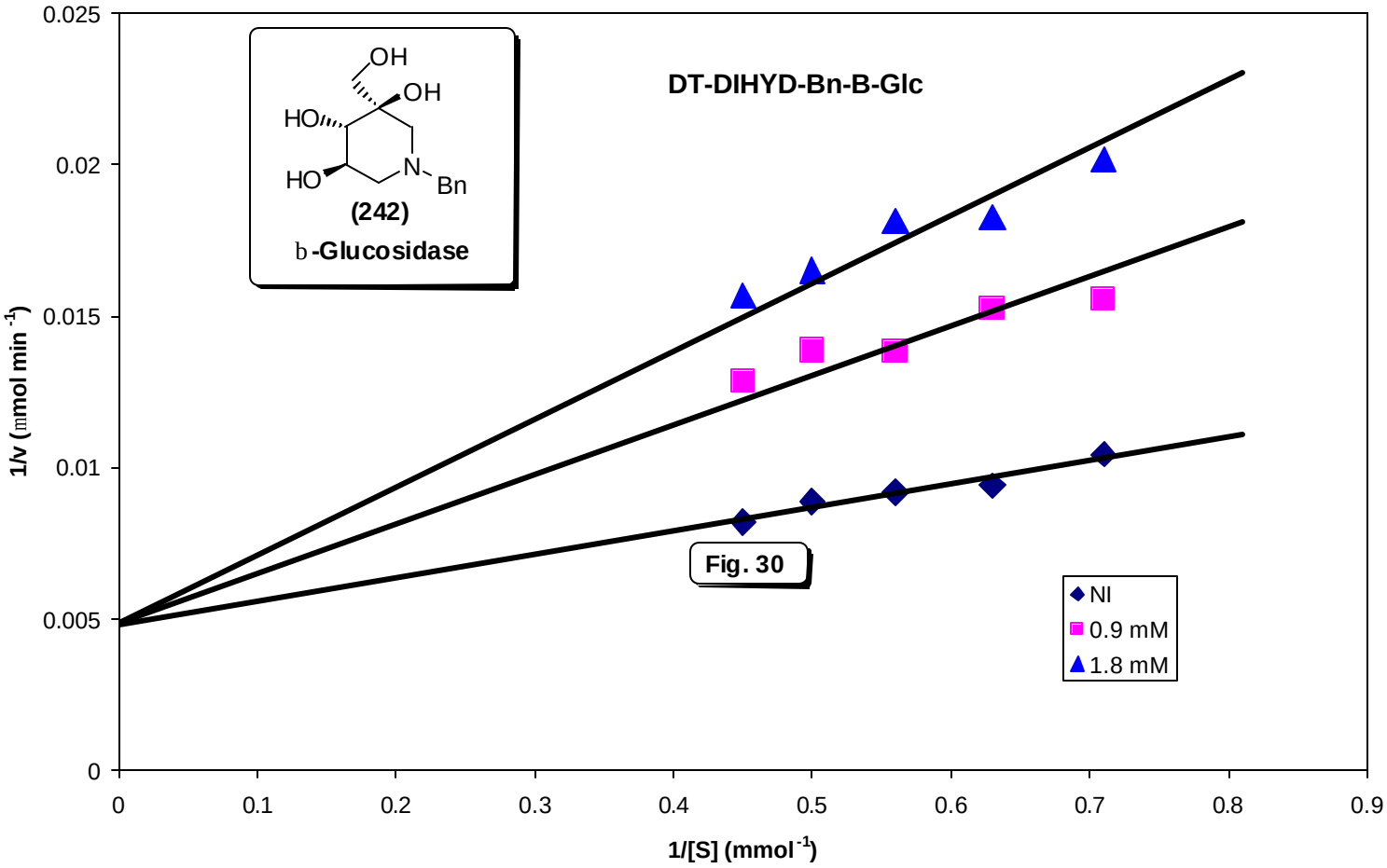
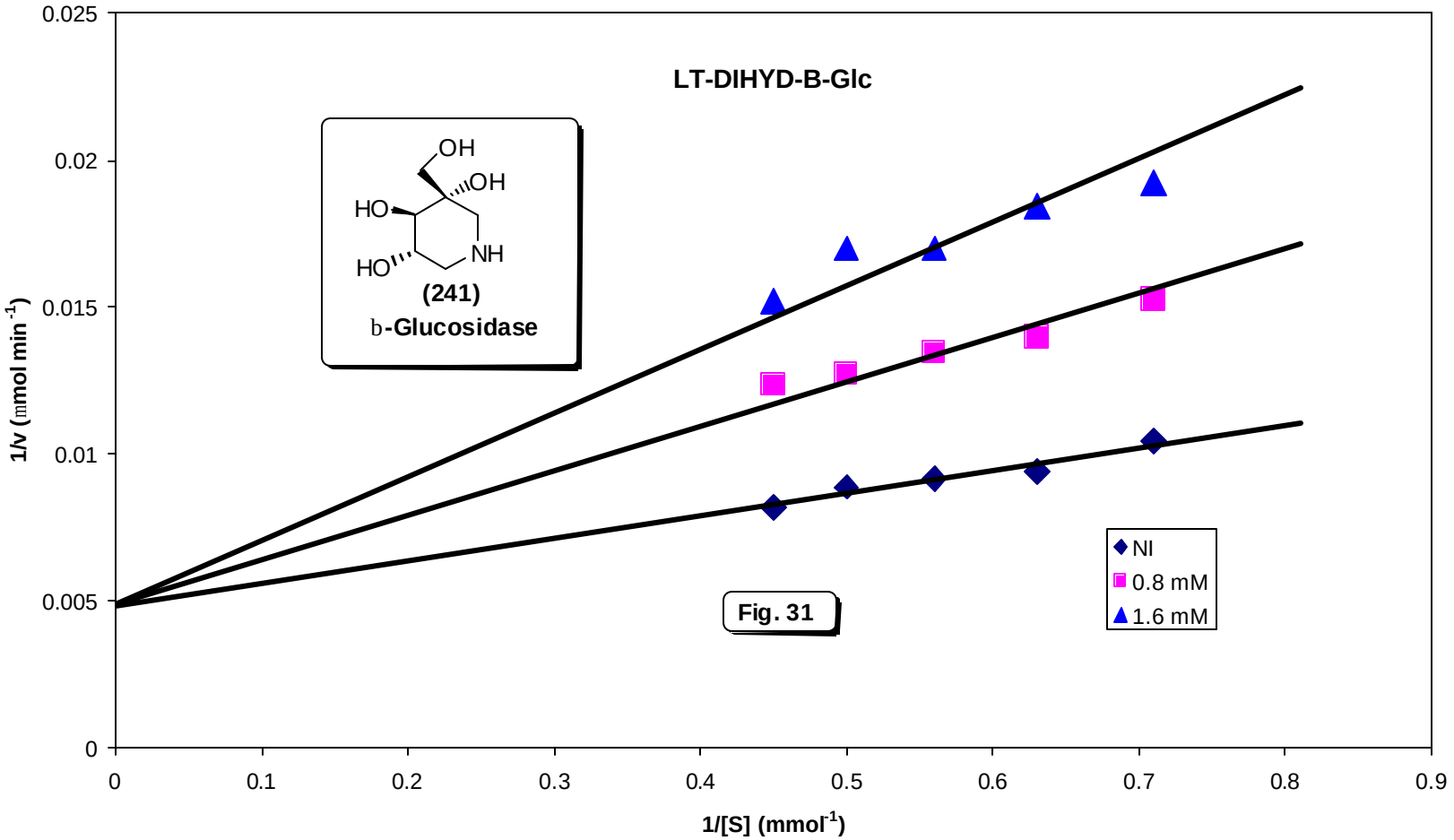
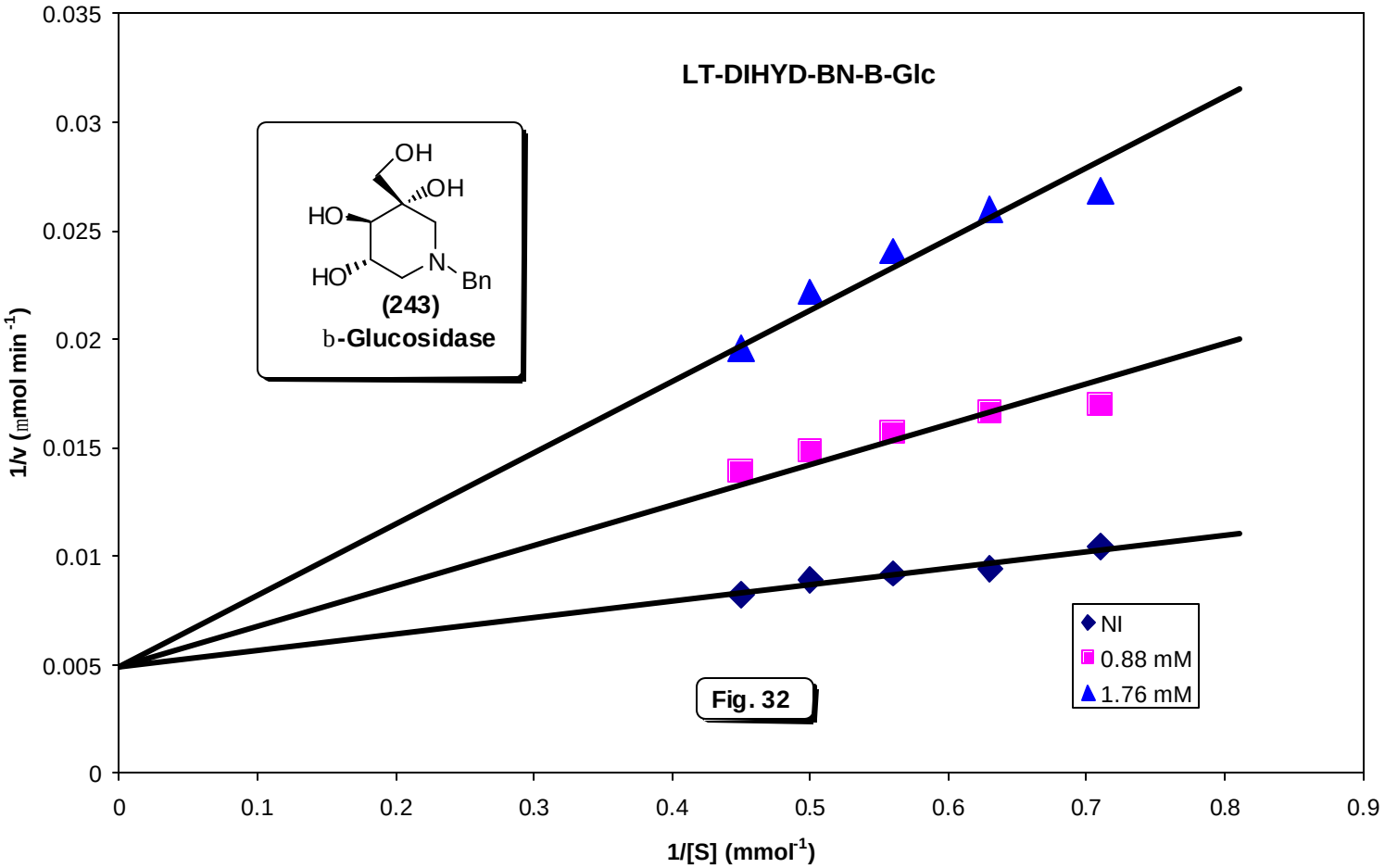

27 Nov 2002
Manmohan/ MK-1-8s/ CDCl3/ DEPT

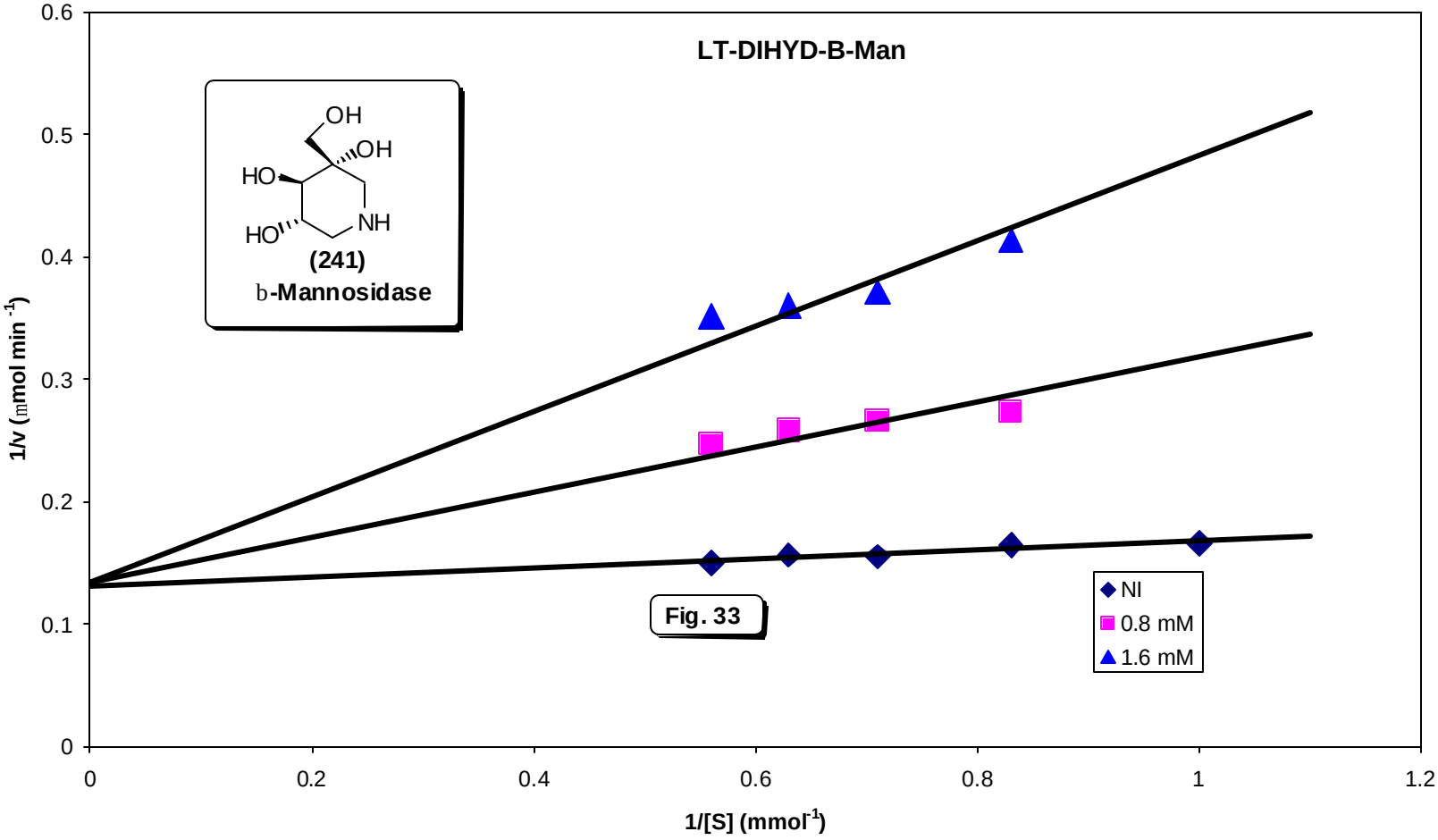
Fig. 28c


DT-DIHYD-B-Glc
OH
OH
HO
HO
NH
(173)
b-Glucosidase
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1/v (mmol min-1)
1/[S] (mmol-1)
NI
0.22 mM
0.37 mM
Fig. 29


DT-DIHYD-Bn-B-Glc
(242)
b-Glucosidase
Fig. 30
NI
0.9 mM
1.8 mM
1/v (mmol min-1)
1/[S] (mmol-1)
0
0.005
0.01
0.015
0.02
0.025
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9


LT-DIHYD-B-Glc
OH
OH
HO
HO
NH
(241)
b-Glucosidase
NI
0.8 mM
1.6 mM
Fig. 31
1/v (mmol min-1)
1/[S] (mmol-1)
0.025
0.02
0.015
0.01
0.005
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9


LT-DIHYD-BN-B-Glc
OH
OH
HO
HO
N
Bn
(243)
b-Glucosidase
1/v (mmol min-1)
1/[S] (mmol-1)
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
NI
0.88 mM
1.76 mM
Fig. 32


LT-DIHYD-B-Man
OH
OH
HO
HO
NH
(241)
b-Mannosidase
1/v (mmol min-1)
1/[S] (mmol-1)
0
0.1
0.2
0.3
0.4
0.5
0.6
0
0.2
0.4
0.6
0.8
1
1.2
NI
0.8 mM
1.6 mM
Fig. 33

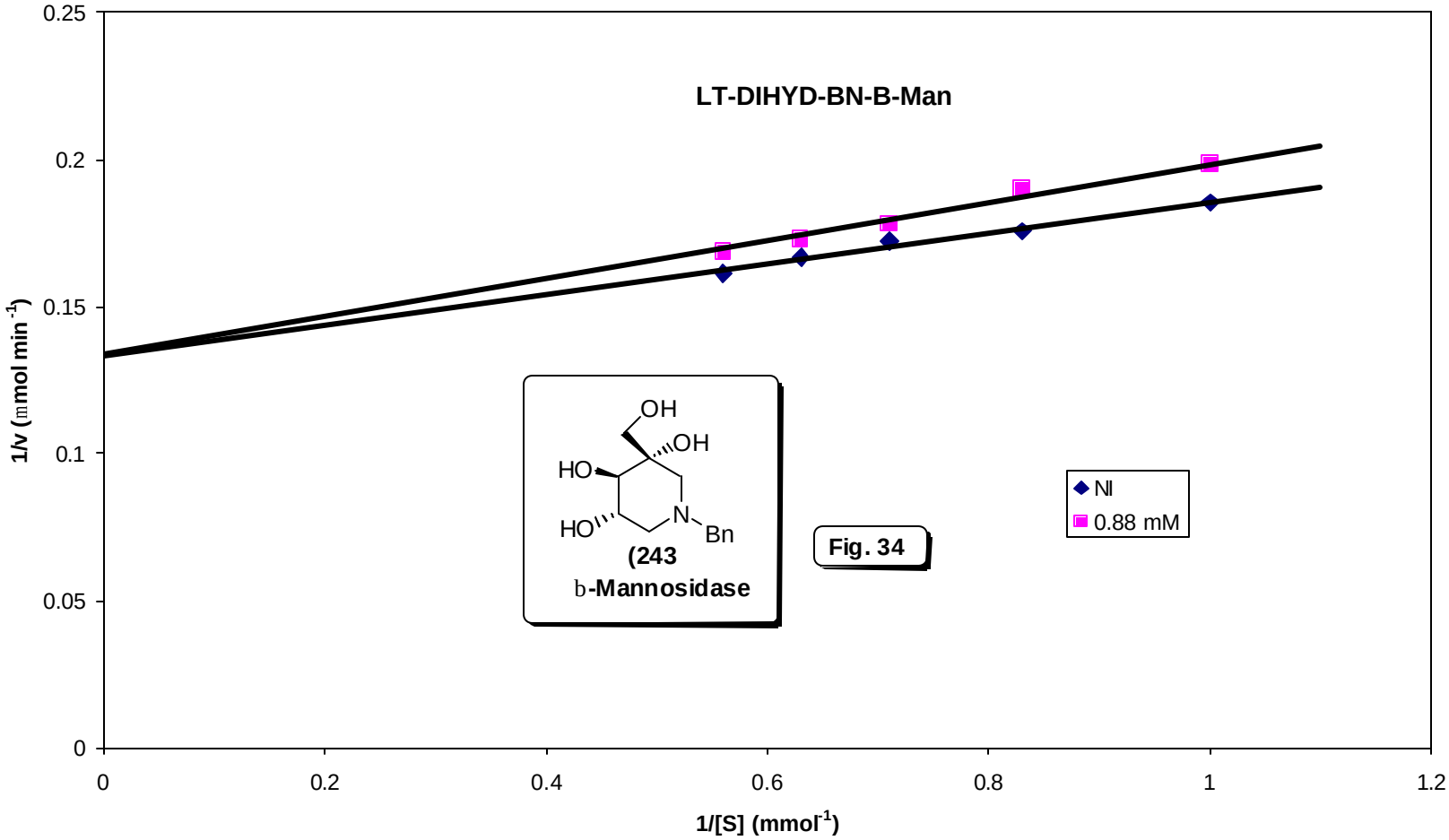
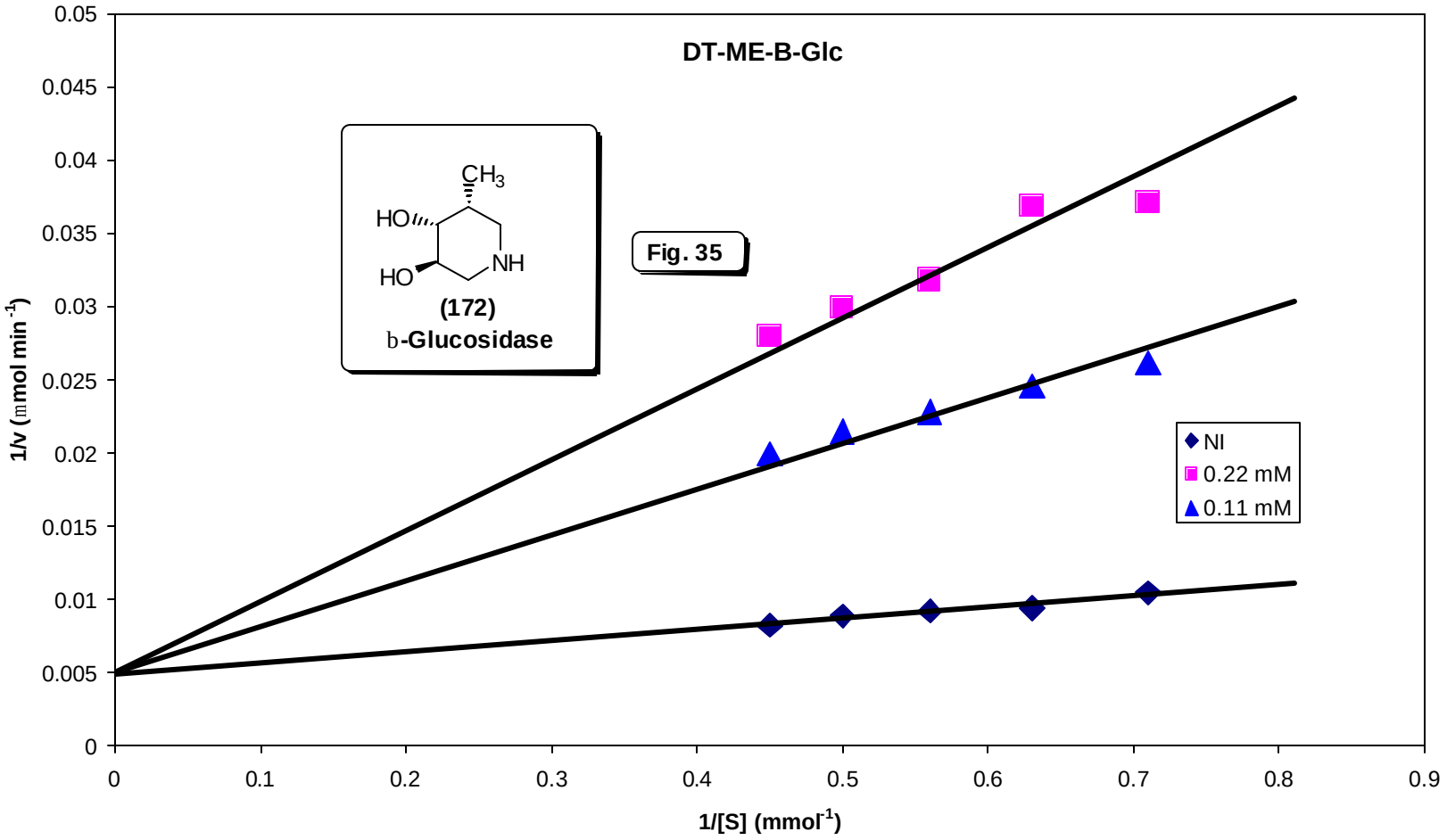
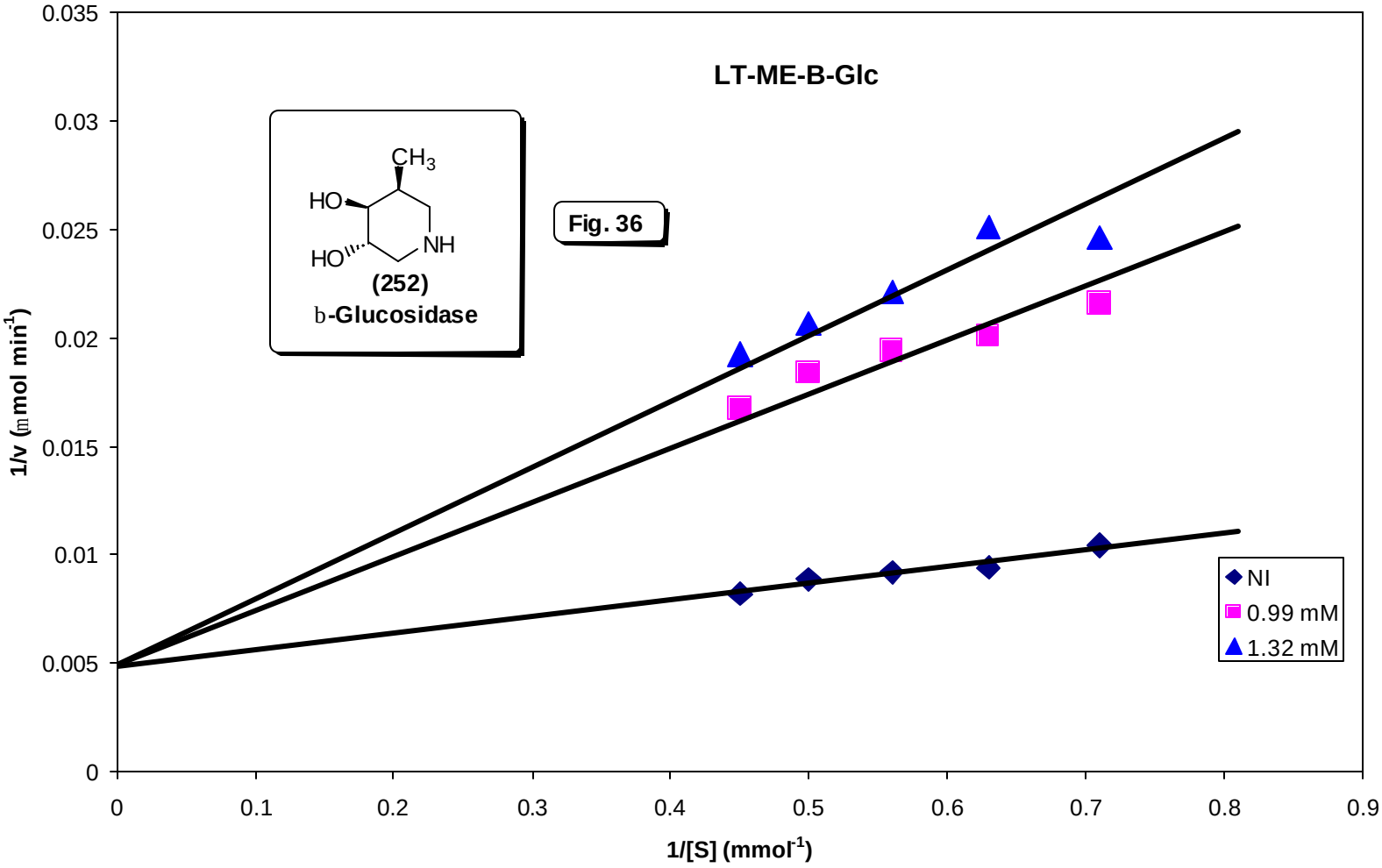

LT-DIHYD-BN-B-Man
1/v (mmol min-1)
1/[S] (mmol-1)
0.25
0.2
0.15
0.1
0.05
0
0
0.2
0.4
0.6
0.8
1
1.2
NI
0.88 mM
OH
OH
HO
HO
N
Bn
(243
b-Mannosidase

Fig. 34


DT-ME-B-Glc
Fig. 35
(172)
b-Glucosidase
NI
0.22 mM
0.11 mM
1/v (mmol min-1)
1/[S] (mmol-1)
0.05
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9


LT-ME-B-Glc
Fig. 36
(252)
b-Glucosidase
CH3
HO
HO
NH
1/v (mmol min-1)
1/[S] (mmol-1)
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
NI
0.99 mM
1.32 mM

List of publications:

- A general strategy towards the synthesis of 1-*N*-iminosugar type glycosidase inhibitors: demonstration by the synthesis of D- as well as L-glucose type iminosugars (isofagomines).

  Pandey, G.; Kapur, M. *Tetrahedron Lett.* **2000**, *41*, 8821-8824.

- A Novel Approach to Both the Enantiomers of Potent Glycosidase Inhibitor Isofagomine via PET-Promoted Cyclization of 1-[Benzyl(trimethylsilylmethyl)amino]-1,4,5-trideoxy-2,3-*O*-(1-methylethylidene)-*threo*-pent-4-ynitol.

  Pandey, G.; Kapur, M. *Synthesis* **2001**, 1263-1267.

- Design and Development of a Common Synthetic Strategy for a Variety of 1-*N*-iminosugars.

  Pandey, G.; Kapur, M. *Org. Lett.* **2002**, *4*, 3883-3886.