METHODOLOGY DEVELOPMENT FOR THE SYNTHESIS OF IMINOSUGARS

BY

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“true nobility is being superior to your former self.”

Ernest Hemingway

Abstract

This thesis investigated the development and application of methodology for the synthesis of iminosugars. The first portion of this thesis (Chapters 2 and 3) explored the scope of previously established protecting-group-free Vasella-reductive-amination and I_2-mediated carbamate annulation methodology initially developed within the Stocker-Timmer group for the synthesis of pyrrolidines and piperidines from aldose sugars. In this thesis, the Vasella-reductive-amination methodology was extended to include the use of ketose sugars as starting materials, thereby allowing for the synthesis of primary amines directly from *in situ* formed ketones under protecting-group-free conditions. The scope of the carbamate annulation was then explored, whereby it was determined that both steric and electronic effects appear to affect transition state energies during the annulation reaction. Here, formation of pyrrolidines with the 2,5-*trans* and 3,4-*cis* relationships are favoured, however, in circumstances were conflicting electronic- and steric-effects are present, steric-effects dominate thereby favouring the formation of the 2,5-*trans* product. Using a combination of this Vasella-reductive-amination and carbamate annulation methodology, 2,5-dideoxy-2,5-imino-L-iditol was thus synthesised in 6 steps and 18% overall yield from D-fructose. Next, the same methodology was applied to the synthesis of the promising molecular chaperone 2,5-dideoxy-2,5-imino-D-altritol. Thus, 2,5-dideoxy-2,5-imino-D-altritol was synthesised over 7 steps and in 22% yield from D-tagatose, which is the most efficient synthesis of this iminosugar to date.

The second part of this thesis (Chapters 4 and 5) focused on the optimisation and development of synthetic methodology that would allow for the highly efficient synthesis of a variety of iminosugars including piperidines and azepanes. To this end, modifications to existing synthetic methodology allowed for the rapid synthesis of a variety of iodoglycosides, which are important synthons. Next, reductive amination/cyclisation methodology that allowed for the direct transformation of methyl iodoglycosides or isopropylidene-protected iodoglycosides into iminosugars was developed. As such, the piperidines 1-Deoxynojirimycin, 1-Deoxymannojirimycin (DMJ), L-1-Deoxygalactojirimycin (L-DGJ), and (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol were prepared in 4 steps and good overall yields (44%, 62%, 67%, and 53%, respectively). In the case of DMJ and (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol, these are the most efficient syntheses of these materials to date. Factors influencing the stereochemical outcome of the reductive amination reaction were also explored, and evidence suggests that the reduction occurs from the least sterically hindered face of an intermediate cyclic imine, whereby the preferred conformation of the imine is the one which places the largest number of substituents in the *pseudo*-equatorial position. Using analogous methodology, the azepane (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol was also prepared in 4 steps and good yield (53%).

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Copyright notice

Some of this work described in this thesis has been reported in the following publications:

A. A. Hunt-Painter, G. J. Moggre, P. C. Tyler, B. L. Stocker and M. S. M. Timmer, *Chemistryselect*, 2017, **2**, 8028-8032.

A. A. Hunt-Painter, B. L. Stocker and M. S. M. Timmer, *Tetrahedron*, 2018, DOI:https://doi.org/10.1016/j.tet.2018.01.011.

Table of Contents

List of abbreviations

α-Gal	Alpha-galactsidase
Ac	Acytel
AD	Asymmetric dihydroxylation
Bn	Benzyl
CBz	Carboxylbenzyl
CMT	Chaperone mediated therapy
COSY	Correlation spectroscopy
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DAJ	1-Deoxyallonojirimycin
DGJ	1-Deoxygalactojirimycin
DIA	
DIP	Diisopinocampheyl
DMF	*N*,*N*-dimethyl formaldehyde
DMJ	1-Deoxymannojirimycin
DMDP	(*2S*,*3S*,*4R*,*5S*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine
DNJ	1-Deoxynojirimycin
ER	Endoplasmic reticulum
ERT	Enzyme replacement therapy
EtOH	Ethanol
FSA	D-fructose-6-phosphate aldolase
GBA1	Glucocerebrosidase-1
GCS	Glucosylceramidase synthase
GlcCer	Glucosylceramide
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
LG	Leaving group
m	Multiplet
MeOH	Methanol
Ms	Mesyl
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PG	Protecting group
PGF	Protecting group free
Ph	Phenyl
PPTS	pyridinium paratoluenesulfonate
Pyr	pyridine
s	Singlet
Sat	Saturated
Soln	Solution
SRT	substrate reduction therapy
TBAF	Tert-*n*-butylammonium fluoride
TBDPS	*O*-*tert*-butyldiphenylsilyl
ONH_2	hydroxylamine
td	Triplet of doublets
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Chapter 1

Iminosugars

1.1 Introduction

Iminosugars are naturally occurring structural analogues of native carbohydrates, where the ring oxygen is replaced with a nitrogen. By virtue of being carbohydrate analogues, iminosugars have interesting biological activity and consequently have multiple pharmacological uses. Accordingly, iminosugars are an important target for synthetic chemists, with methodology development for the efficient synthesis of known and novel iminosugars remaining a pressing goal.

Unlike most naturally occurring compounds, iminosugars were initially synthesised before being isolated as natural products. The almost simultaneous publications by Jones,[1, 2] Paulsen,[3] and Hanessian[4] on the synthesis towards various stereoisomers of iminosugar **1** (**Figure 1**) was swiftly followed by nojirimycin (**2**) being isolated from *Streptomyces reseochromogenes*, where it was found to have anti-microbial activity and inhibit glycoside hydrolase enzymes.[5] The more stable 1-deoxynojirimycin (DNJ, **3**), synthesised in 1967 by Paulsen,[6] was also found to be a potent α-glycosidase inhibitor.[7] Ten years after the isolation of nojirimycin, the first five-membered iminosugar (or pyrrolidine) was extracted from the leaves of *Derris ellepticain*, identified as (*2S,3S,4R,5S*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP, **4**),[8] and later found to be an effective glycosidase inhibitor.[9] The bicyclic pyrrolidine-containing iminosugars also exhibit interesting biological activity, with pyrrolizidine casuarine (**5**) being identified as a potential chemotherapeutic agent[10] and indolizidine (-)-swainsonine

(**6**, the first bicyclic alkaloid to be discovered) showing α-mannosidase II inhibitory and potential anti-cancer activity.[11] The most recently discovered class of pyrrolidine-containing iminosugars are the nortropanes and include members such as calstegine A3 (**7**), which was first isolated from the roots of *calstegia sepium* in 1988.[12]

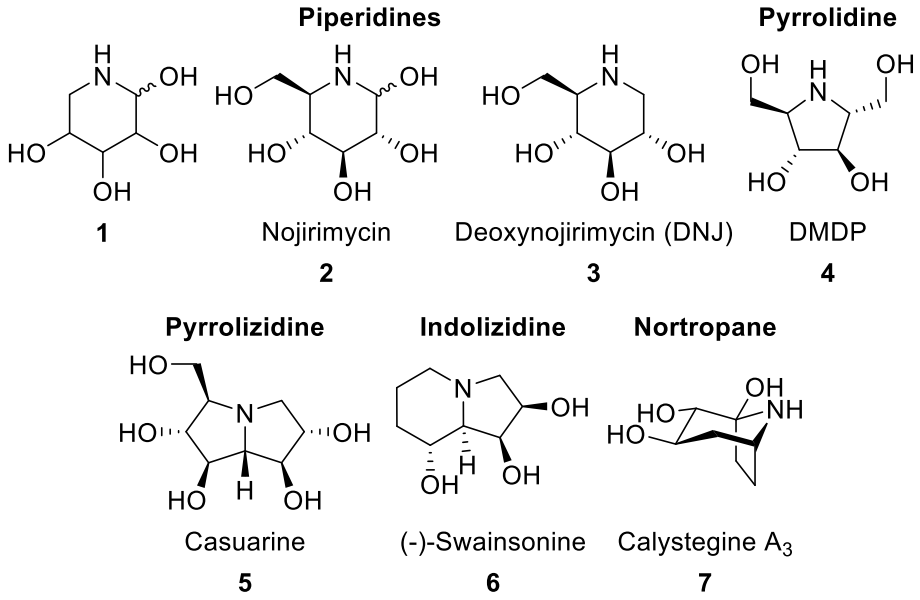
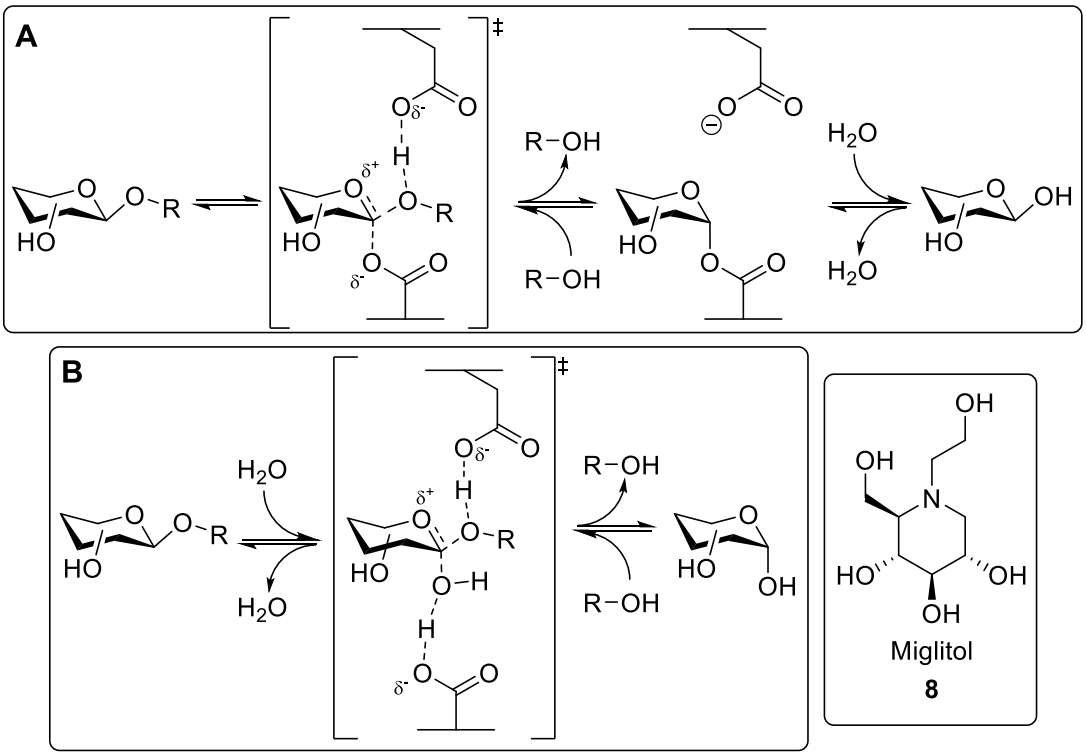


Figure 1: Examples of each class of iminosugar.

1.2 Biological activity and pharmacological application of iminosugars

The most renowned biological activity of iminosugars is the ability to reversibly bind to the active site of glycosidases, and to a lesser extent, glycosyltransferases.[13, 14] Glycosylation is a fundamental cellular process that is key to many biochemical pathways, including the synthesis of endoplasmic reticulum (ER) derived proteins.[15] These glycosidase enzymes follow a retaining or inverting reaction pathway, as shown in **Scheme 1** (A and B respectively).[16] Both pathways begin with the hydrolysis of the glycosidic bond, passing through an oxocarbenium transition state. Whilst the inversion pathway sees hydrolysis and monosaccharide release in one step, the retaining pathway passes through an intermediate where the monosaccharide is bound to the enzyme. The distance between the two catalytic acid residues in the active site determines if the enzyme will have a retaining or inverting mechanism.[17]

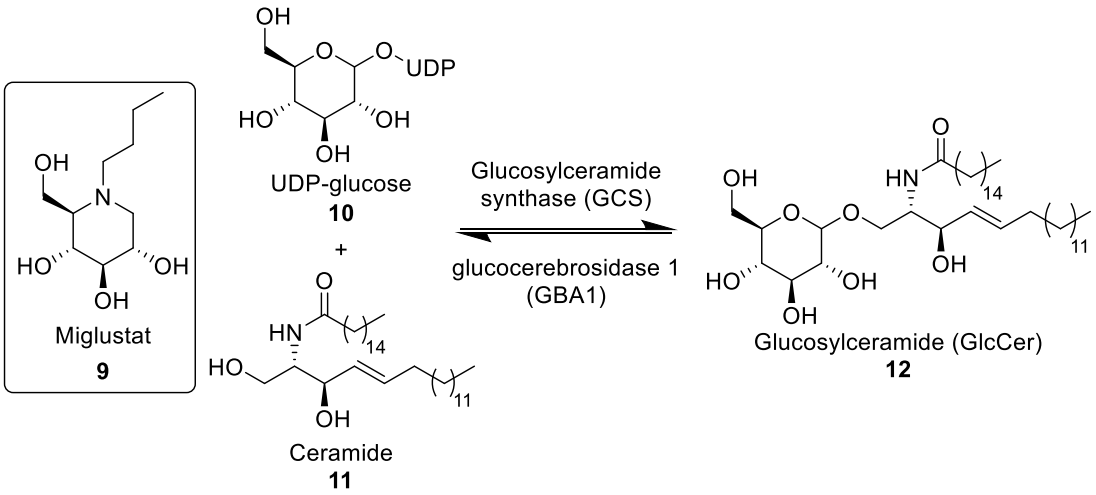


*Scheme 1: The retaining (A) and inverting (B) mechanisms of glycoside hydrolase enzymes; Boxed: the diabetic drug miglitol (**8**).*

At physiological pH, the ring nitrogen present in an iminosugar is protonated, making iminosugars able to mimic the oxocarbenium transition state and thus reversibly bind to the active site of carbohydrate handling enzymes. As a result, iminosugars have found pharmacological application in the treatment of various diseases, including type II diabetes. In particular, Miglitol (**8**, **Scheme 1**) is a commercial drug that inhibits the glycosidases responsible for breaking down complex polysaccharides in the body.[18] Miglitol (**8**) is able to selectively bind to alpha-glycosidases by closely mimicking the structure and stereochemistry of the oxocarbenium transition state of alpha-glycosidases.[19]

Another commercially available iminosugar is Miglustat (**9**, **Scheme 2**), which is used to treat Gaucher disease.[20] Gaucher disease is an inherited lysosomal storage disorder where glucosylceramide (GlcCer, **12**) accumulates within the lysosomes of cells and certain organs.[21, 22] Normally, GlcCer is generated by the glucosylceramidase synthase (GCS) catalysed condensation of UDP-glucose (**10**) with ceramide (**11**), where glucocerebrosidase 1 (GBA1) prevents accumulation of GlcCer and allows recycling of

ceramide and glucose.[23] The accumulation of GlcCer occurs when GBA1 is either in low abundance or shows abnormal catalytic abilities.[21, 22]



*Scheme 2: Simplified biosynthesis and bio-decomposition of glucosylceramide; Boxed: glucosylceramidase synthase inhibitor Miglustat (**9**).*

Miglustat can be used to treat Gaucher disease through substrate reduction therapy (SRT, **Figure 2A**) by reversibly binding to GCS, thus reducing the biosynthesis and resulting accumulation of GlcCer (**12**).[24, 25] While Miglustat was approved by the Food and Drug Administration and European Medicines Agency in 2003 for SRT of Gaucher disease,[26] Miglustat has also been investigated as a pharmacological chaperone for chaperone mediated therapy (CMT) of Gaucher disease.[27] Most simply, a pharmacological chaperone is a compound that reversibly binds to a specific enzyme, usually at the active site, stabilising the enzyme or re-shaping the active site. In this way, a pharmacological chaperone may assist in protein folding, reshaping a deformed protein, or help stabilise a protein to minimalise normal degradation processes during transport.[28] The restoration of GBA1 activity through CMT restores the equilibrium between biosynthesis and degradation of GlcCer, thus normalising GlcCer concentrations.

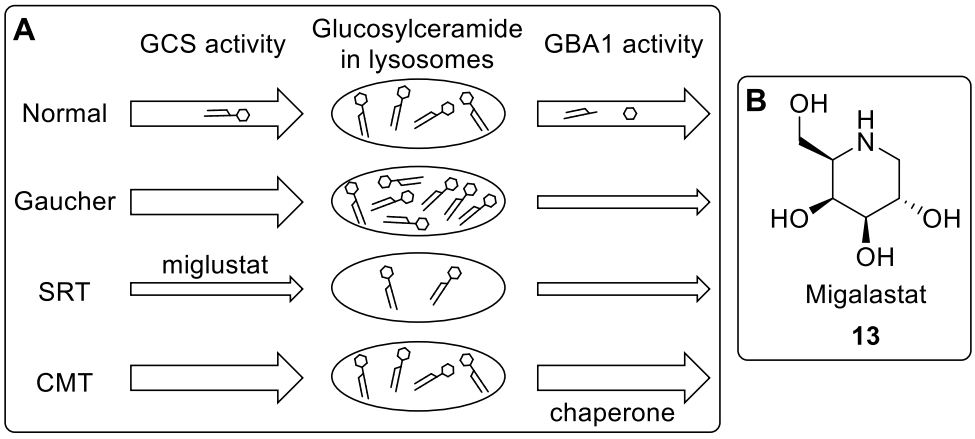


*Figure 2: A) Schematic representation comparing normal GlcCer biosynthesis with that observed in Gaucher disease patients and those undergoing substrate reduction therapy (SRT) and chaperone mediated therapy (CMT); B) Pharmacological chaperone migalastat (**13**) used to treat Fabry disease.*

Similarly, the galacto-configured Migalastat (or DGJ, **13, Figure 2B**) is used for CMT of Fabry disease.[29] Migalastat reversibly binds to α-galactosidase, the enzyme lacking in patients with Fabry disease that leads to the undesired accumulation of globotriaosylceramide.[30] Iminosugars are also under investigation for SRT and CMT of other lysosomal storage diseases such as Tay-Sachs, Sandhoff, Niemann-Pick, and pompe diseases.[31-33]

In addition to their ability to bind to carbohydrate-active enzymes associated with lysosomal storage diseases, iminosugars have also shown promise in the treatment of viral infections such as HIV,[34, 35] hepatitis C,[36] herpes,[37] dengue virus,[38] Japanese encephalitis virus,[39] and influenza viruses.[40] In this context, the ability of certain *gluco*- and *galacto*-configured iminosugars (e.g. Miglustat (**9**), Migalastat (**13**), and the DNJ derivatives **14-17, Figure 3**) to treat viral infections stems from their ability to competitively bind to endoplasmic reticulum (ER) α-glucosidases, which disrupts normal protein folding processes that may lead to retention or degradation of these enzymes.[41] During infection and replication, a virus manipulates host cell processes for protein synthesis. In this way, infected cells use natural protein synthesis pathways more than a healthy cell, meaning partial inhibition of ER-α-glucosidases disrupts assisted protein folding enough to selectively inhibit or kill infected cells. Unlike more common viral-directed treatments such as vaccines, iminosugar treatment is host directed and thus thought to be less susceptible to viral resistance.[42] Note that the key challenge in applying imunisuagrs toward the treatment of viral infection is the various side-effecs of iminosugars (e.g.

inhibition of gastrointestinal tract glycosidases), requiring the development of either more selecetive or potent (lower dose) inhibitors.[43]

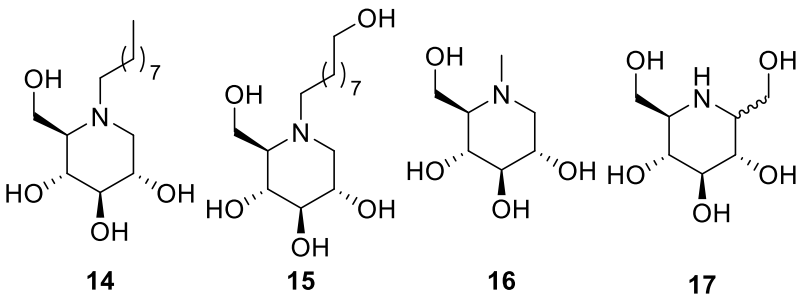


Figure 3: Iminosugars under investigation as potential anti-viral agents.

1.3 Syntheses of iminosugars

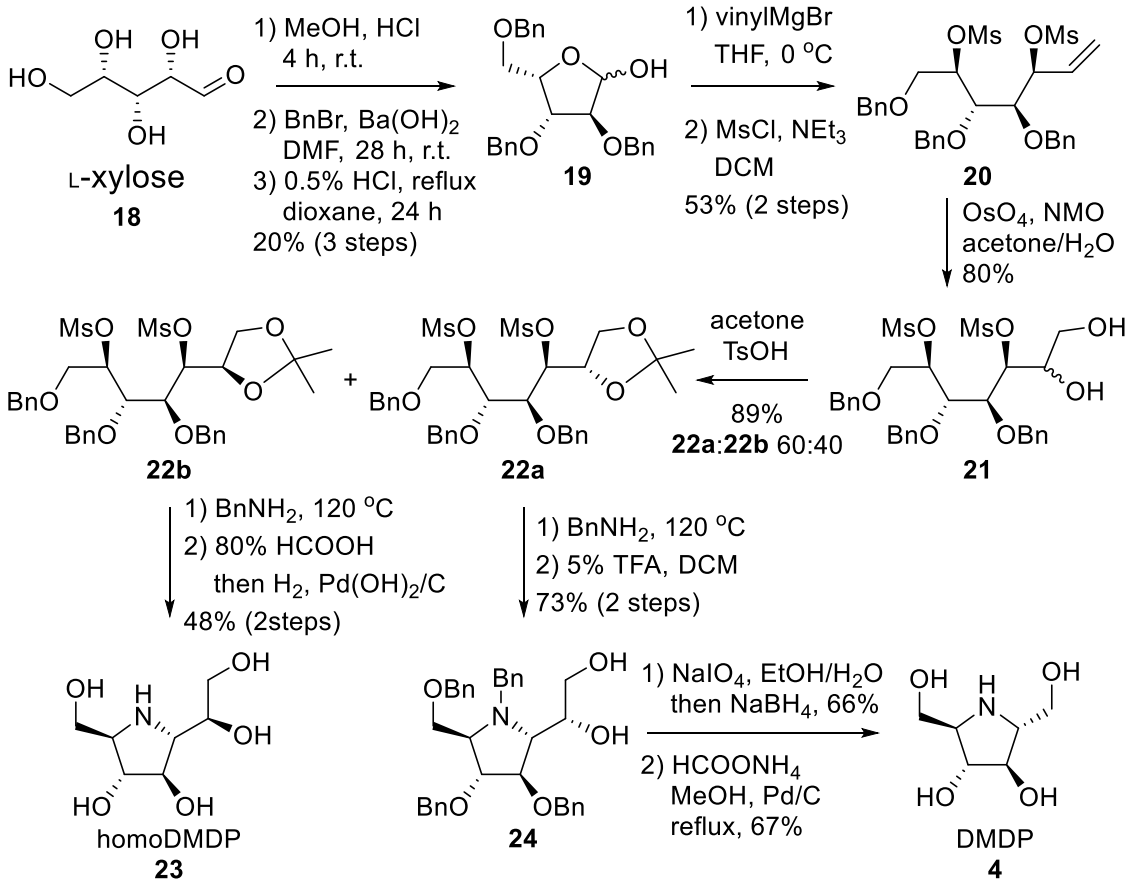
The low natural abundance and growing pharmacological applications of iminosugars has led to this class of compounds remaining a relevant and interesting target for synthetic chemists. As such, there is a large body of work retaining to the synthesis of iminosugars, of which the reader is directed to the relevant reviews.[44-47] To give context to the work described within this thesis, specific examples are explored below that show the possible strategies used to synthesise iminosugars from simple carbohydrates, specifically with and without the use of protecting groups.

1.3.1 Syntheses using Protecting groups

The use of protecting groups (PG) is ubiquitous in carbohydrate chemistry. The commonality of PG arises from the numerous hydroxyls present in native carbohydrates, making regio- and chemo-selectivity difficult to achieve. The use of PG has not only advanced carbohydrate chemistry, but also facilitated the initial syntheses of iminosugars. Despite that use of PG increases the number of steps for a synthesis (from instalment and subsequent removal), there are a number of synthetic routes that, through the use of PG, have allowed for the efficient syntheses of several classes of iminosugars.

The first example discussed here, reported by Behr and Guillerm in 2007, achieved *N*-cyclisation though a double substitution (**Scheme 1**).[48] The synthesis began with the Fischer glycosidation of L-xylose (**18**) with methanol, followed by benzylation and anomeric deprotection to give the protected glycoside **19**. Grignard addition and mesylation of the protected glycoside **19** then gave the di-mesylate **20**. Dihydroxylation,

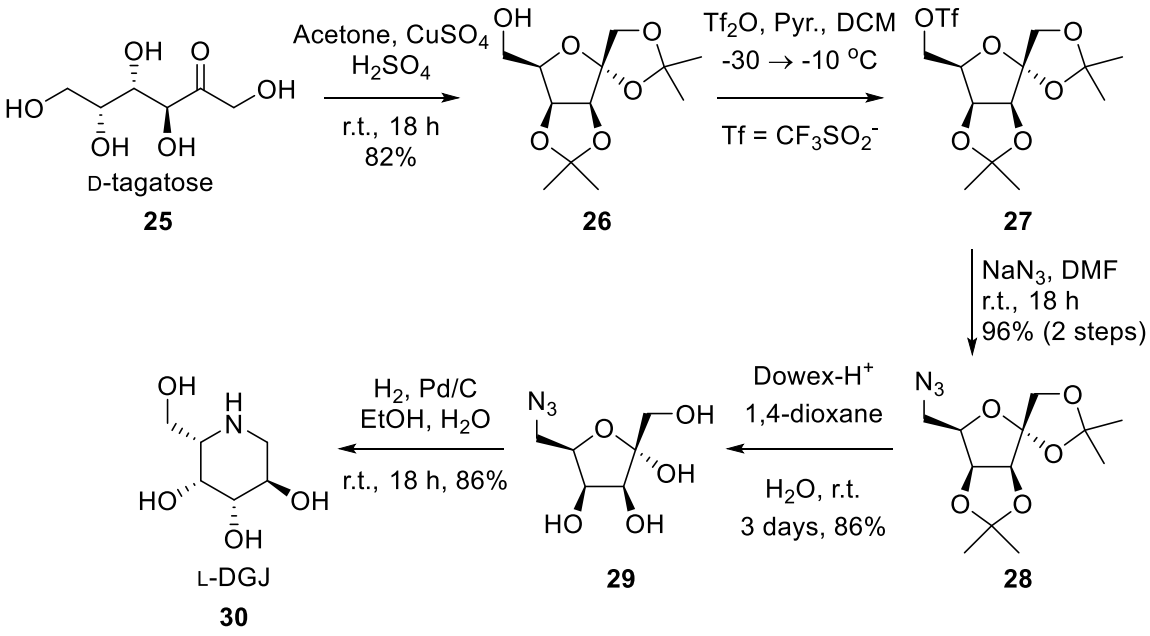
which resulted in the formation of the diastereomers **21**, followed by isopropylidene protection then gave the protected mesylates **22a** and **22b** in a 60:40 ratio, respectively, which were separated by silica gel flash column chromatography. The protected mesylate **22b** was treated with $BnNH_2$ and globally deprotected to give homoDMDP (**23**) in a 1.4% overall yield (9 steps). Similarly, the protected mesylate **22a** was treated to $BnNH_2$, which after isopropylidene deprotection gave the protected iminosugar **24**. Oxidative cleavage reduction, and global deprotection of the vinyl diol of the iminosugar **24** was then performed to give DMDP (**4**) in 1.4% overall yield (11 steps). It was noted that for both **22a** and **22b**, like other di-mesylates used in *N*-cyclisation, high temperatures and long reaction times were required to obtain high yields.



*Scheme 3: The Synthesis of DMDP (**4**) homoDMDP (**23**) by Behr and Guillerm utilising a double substitution for N- cyclisation.*

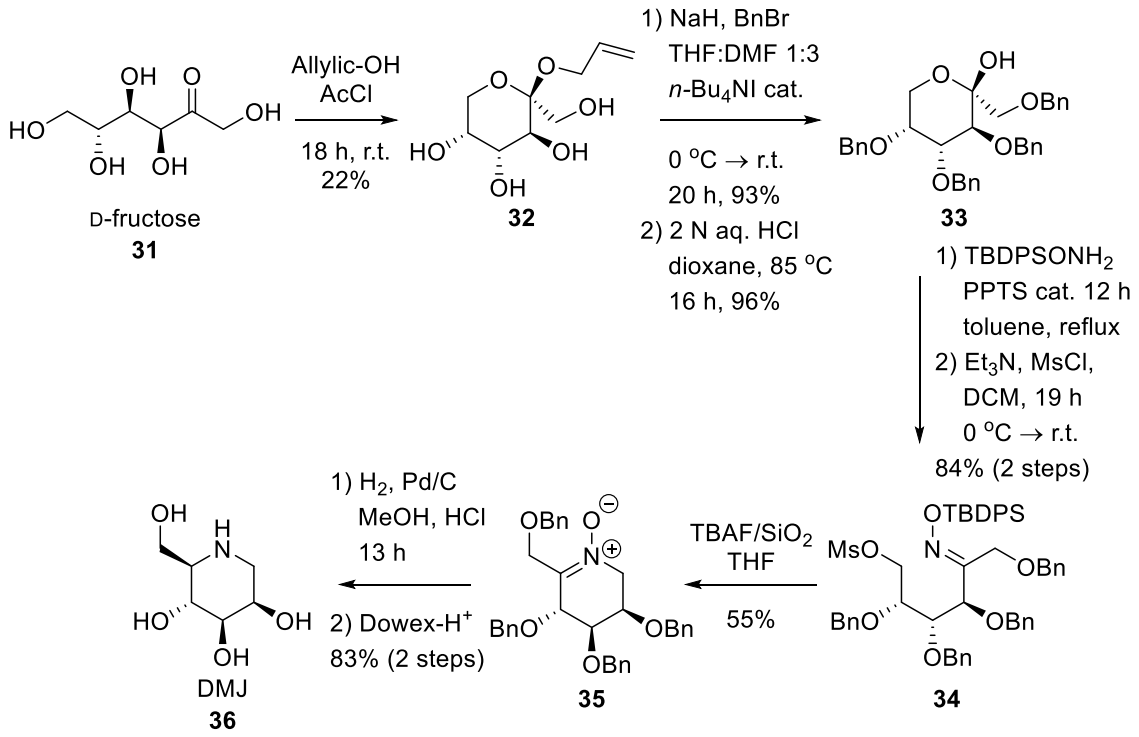
Fleet et al. has elegantly exemplified the strategy of instaling an amine functionality suitable to undergo *N*-cyclisation *via* reductive amination in his synthesis of L-DGJ (**Scheme 4**).[49] The synthesis began with the isopropylidine protection of D-tagatose (**25**) to form the protected glycoside **26**, followed by triflation (giving **27**) and azide

substitution to give the protected azide **28**. Following acid-mediated deprotection, the azide in **29** is then reduced using Pd/C, with the resultant amine undergoing immediate cyclisation *via* intramolecular reductive amination to give L-DGJ (**30**) over 5 steps and in 85% overall yield. Note that this synthetic strategy led to the original synthesis of iminosugars by Jones,[1, 2] Paulsen,[3] and Hanessian,[4] and was also used in the first synthesis of DMDP by Card and Hitz in 1985.[50]



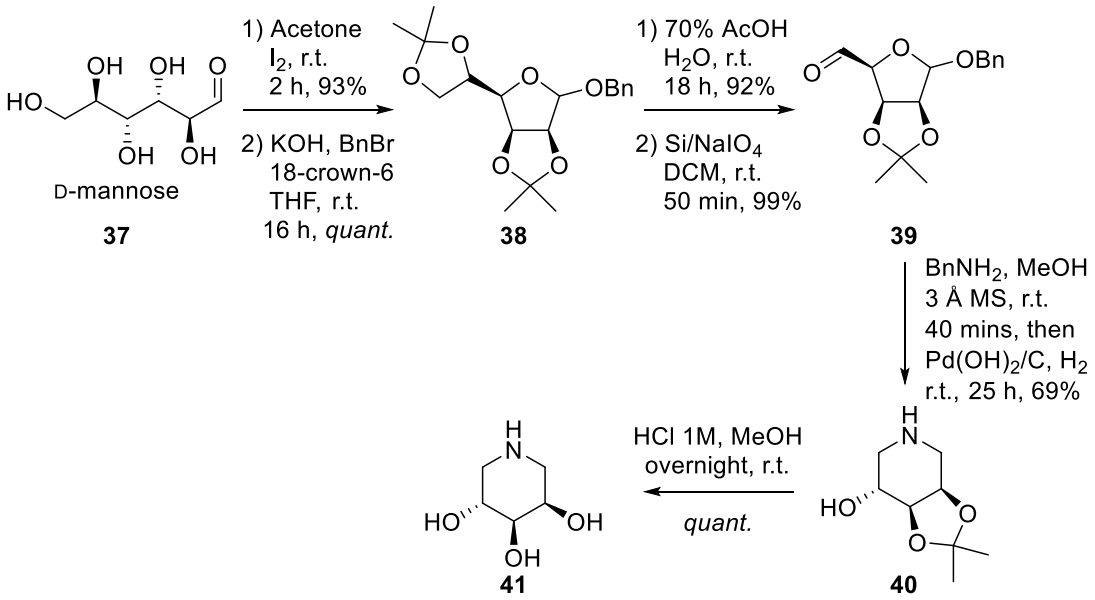
*Scheme 4: Fleet's synthesis of L-DGJ (**30**) utilising an intralocular reductive amination during N-cyclisation.*

Racine and co-workers used the ketone of D-fructose (**31**) to form an imine that, in the presence of a good leaving group, facilitates *N*-cyclisation (**Scheme 5**).[51] In the first step of this strategy, D-fructose (**31**) is cyclised under Fischer glycosidation conditions in the presence of allylic alcohol to give the pyranose **32**. Subsequent global benzylation and acid-mediated anomeric deprotection then gave the protected ketone **33**. Imine formation *via* the treatment of ketone **33** with *O*-*tert*-butyldiphenylsilylhydroxylamine ($TBDPSONH_2$) in the presence of pyridinium paratoluenesulfonate (PPTS) followed by mesylation resulted in the formation of the protected imine **34**. Tetra-*n*-butylammonium fluoride (TBAF)-mediated deprotection of the silyl group then facilitated *N*-cyclisation to give the oxy-imine **35**, which after deprotection under reducing conditions, gave DMJ (**36**) in 8.4% overall yield (8 steps).



*Scheme 5: DMJ (**36**) synthesis* via *imine facilitated N-cyclisation as reported by Racine.*

N-cyclisation *via* reductive amination can also be achieved through the reaction of di-carbonyl derivatives. A recent example by Matassini *et al.*[52] (**Scheme 6**) demonstrates this with D-mannose (**37**) first undergoing isopropylidene and *O*-benzyl protection to form the protected furan **38**. Selective deprotection and oxidative cleavage then gives the protected aldehyde **39**. Subsequent imine formation, followed by primary imine reduction, double benzyl deprotection, and intramolecular reductive amination in the presence of $Pd(OH)_2/C$ and H_2 gave the protected iminosugar **40**. Finally, acid-catalysed deprotection of **40** gave 3,4,5-trihydroxypiperidine **41** over 7 steps and in 53% overall yield. Matassini *et al.* then went on to demonstrate the scope of such a double reductive amination strategy, however, it is worth noting that the orthogonality of the protecting groups quickly became an issue during synthesis of derivitives, where several additional steps were required.



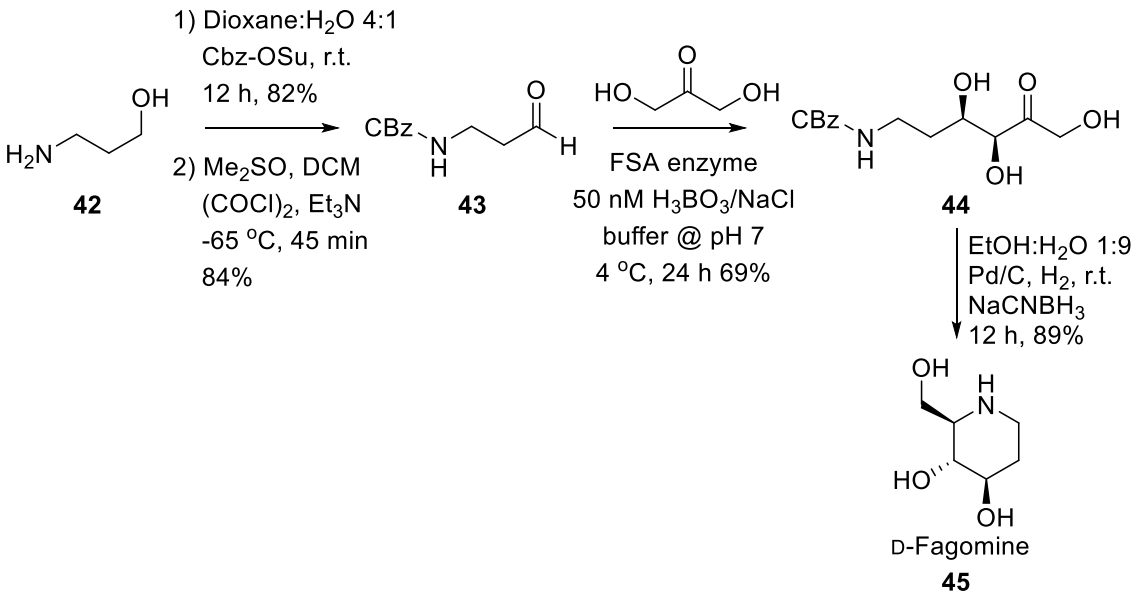
*Scheme 6: The synthesis of 3,4,5-trihydroxypiperidine **41** utilising a double reductive amination by Matassini* et al.

1.3.2 Protecting group free synthesis of iminosugars

Initially, the use of PG was essential in organic syntheses, however, PG manipulations remain a significant portion of many synthetic strategies. In developing the PGF synthesis of known and novel iminosugars, it is possible to simultaneously reduce synthetic steps and increase overall yields.[53, 54] This in turn makes a synthetic route more efficient, impacting factors such as atom economy and financial costs. Increased efficiency makes the synthesis of a compound more economical, something of vital importance to industry.[55] While developing protecting group free (PGF) syntheses is a significant challenge, there are some elegant examples described below that showcase the preparation of iminosugars using minimal or no protecting groups.

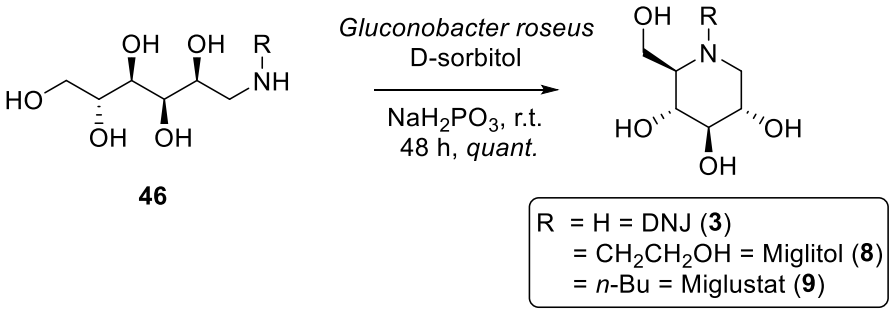
The use of enzymes in chemical synthesis is an area of research that has seen much growth over recent years because enzymatic reactions display excellent chemo- and stereo-selectivity on minimally or unprotected substrates. Through careful enzyme selection, the synthesis of iminosugars such as DNJ and its *N*-alkylated derivatives can be realised on large scales. For example, the patent by Clapes Saborit *et al.* describes the use of a known enzymatic aldol addition[56] in the large-scale synthesis of a variety of iminosugars and *N*-functionalised derivatives.[57] Clapes Saborit's method was exemplified by the total synthesis of fagomine (**45**) shown in **Scheme 7**. Beginning with 3-amino-pran-1-ol (**42**),

the amine of **42** is carboxybenzyl (CBz) protected and the remaining alcohol oxidised to give the aminoaldehyde **43**. Next, D-fructose-6-phosphate aldolase (FSA) catalysed the aldol addition of dihydroxyacetone to give the ketone **44**.[58] After Pd-catalysed deprotection and subsequent reductive amination, fagomine (**45**) was obtained in 42% overall yield (4 steps), with the stereochemistry of the secondary hydroxyls of **44** determined by the enzyme.



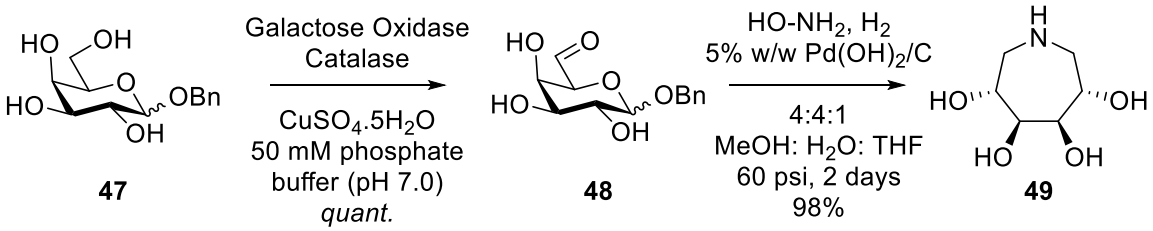
*Scheme 7: The synthesis of D-fagomine (**45**) utilising an enzymatically driven aldol addition.*

The efficiency of enzymatic syntheses is further demonstrated in the patent of Sethi *et al.* utilising the selective 5-hydroxy oxidation of various readily avaliable 1-amino-gluitols (**46**, **Scheme 8**).[59] Here, a 1-amino-gluitol, made in one step from D-glucose *via* a simple reductive amination, is selectively oxidised by *gluconobacter roseus* in an acidic NaH_2PO_3 buffer at room temperature for 48 hours to give the respective iminosugar in quantitative yields.



Scheme 8: Enzyme catalysed oxidation and subsequent cyclisation via *reductive amination of 1-amino-gluitols* ***46****.*

Similarly, the galacto-configured azepane **49** was efficiently synthesised using galactose oxidase catalase in studies by Andreana *et al.* (**Scheme 9**).[60] Readily available *O*-benzy-pyrano-D-galactose (**47**) was chemoselectively oxidised by galactose oxidase catalase at the 6-position to give aldehyde **48**. After deprotection and sequential reductive amination in the presence of HO-NH_2, H_2, and $Pd(OH)_2$, the azepane **49** was formed in 98% yield. While a powerful synthetic strategy, galactose oxidase catalase, however, is limited to carbohydrates and analogues that have galacto-stereochemistry.

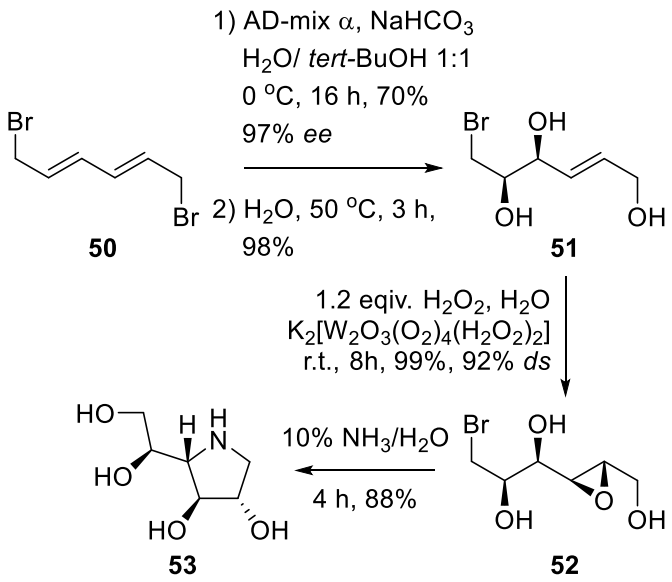


Scheme 9: Azepane synthesis via *chemoselective enzymatic oxidation and subsequent reductive amination by Andreana* et al.

Enzyme mediated synthesis is efficient, selective, and can often lead to a very short total synthesis. However, enzymes are often very specific and the use of starting materials that differ in functionality or chirality can impede the enzymatic reaction. Additionally, enzymes are not always cheap or readily accessible outside of industry. As a result, the need for alternative efficient syntheses of iminosugars remains.

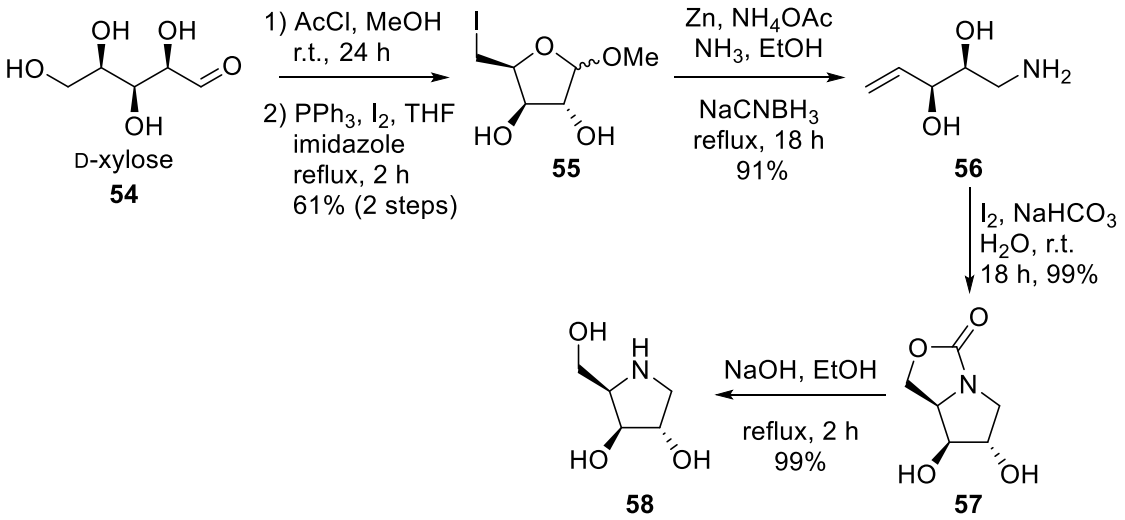
In 2005, Lindstrom *et al.* reported on a PGF synthesis of 2-(1,2-dihydroxyethyl)-3,4-pyrrolidinediol **53** by utilising two consecutive substitution reactions (**Scheme 10**).[61] In this work, the starting material, dibromo alkene **50**, was subjected to a Sharpless

asymmetric dihydroxylation followed by hydrolysis to give the triol **51** in high yields and with excellent (97%) enantiomeric excess (ee). Subsequent asymmetric epoxidation using a peroxotungstate catalyst gave the epoxide **52**, which underwent spontaneous ring closure in the presence of aqueous NH_3 to give the iminosugar **53** in 60% overall yield (4 steps). Note that Lindstrom used ammonia as the nucleophilic source of amine, allowing the final compound to be formed without requiring deprotection.



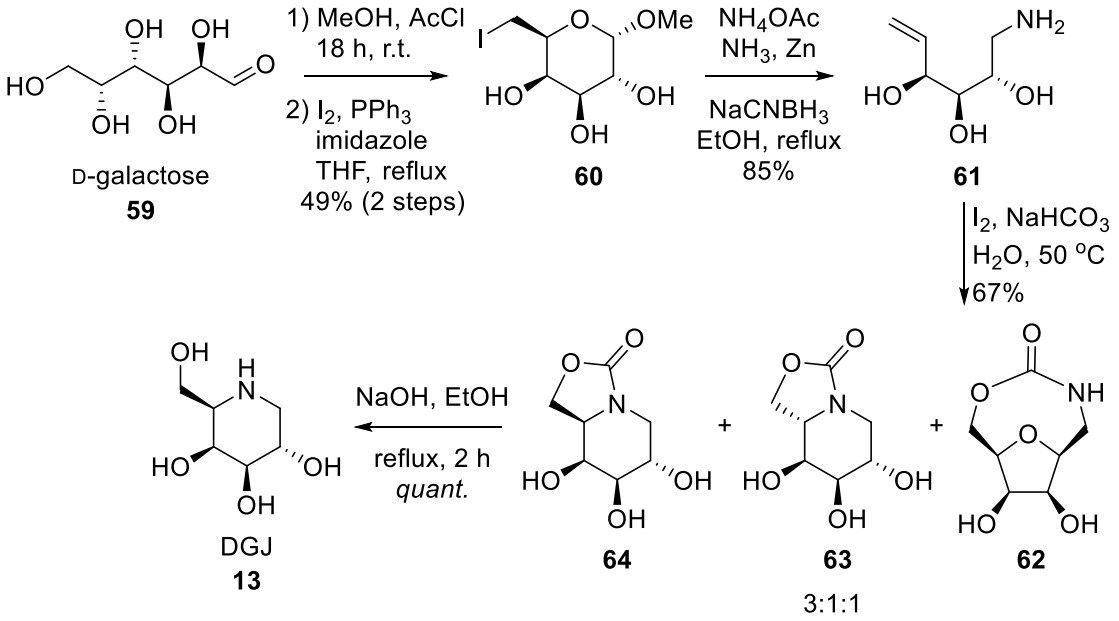
*Scheme 10: The efficient PGF synthesis of 2-(1,2-dihydroxyethyl)-3,4-pyrrolidinediol **53**, as reported by Lindstrom et al.*

In 2009, the Stocker-Timmer group reported the first of several PGF syntheses of iminosugars utilising the novel Vasella-reductive-amination and carbamate annulation methodologies (Scheme 11).[62] This synthesis began with the Fischer glycosidation and subsequent iodination of D-Xylose (**54**) to give the methyl iodoglycoside **55**. The methyl iodoglycoside **55** was then subjected to Vasella-reductive-amination conditions to give alkenylamine **56**, followed by I_2-mediated carbamate annulation to give the carbamate **57** stereoselectively and in 90% yield (two steps). Base hydrolysis then gave 1,4-dideoxy-1,4-imino-D-xylitol (**58**) in 57% yield over the 5 steps.



*Scheme 11: The protecting group free synthesis of 1,4-dideoxy-1,4-imino-D-xylitol (**58**) as reported by the Stocker-Timmer group.*

The synthetic strategy employing the Vasella-reductive-amination and carbamate annulation has been expanded to include the synthesis of piperidines. For example, synthesis of DGJ (**13**) began with the Fischer glycosidation of D-galactose (**59**), followed by selective iodination to give the methyl iodoglycoside **60** (**Scheme 12**).[63] Subsequent Vasella-reductive-amination gave the alkenylamine **61**, which after I_2-mediated carbamate annulation gave a mixture of furan **62** and carbamates **63** and **64** in 1:1:3 ratio, respectively. From this reaction mixture the carbamate **63** was isolated *via* silica gel column chromatography, with the remaining mixture of furan **62** and carbamate **64** being further reacted as a mixture. Following hydrolysis, the desired product DGJ (**13**) was purified by silica gel flash chromatography, resulting in a 16% overall yield of this compound.



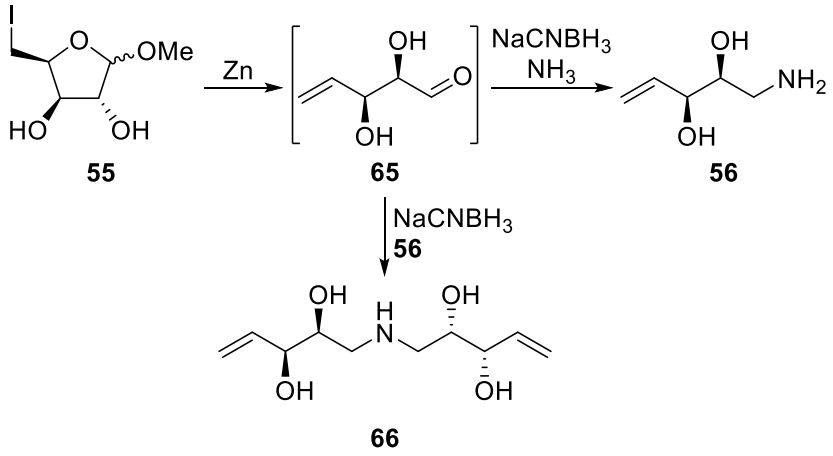
Scheme 12: Piperidine synthesis utilising the novel methodologies developed by the Stockter-Timmer group.

Unlike in the synthesis of pyrrolidines, the carbamate annulation of alkenylamine **61** was not stereoselective, with both possible stereoisomers **63** and **64** forming together with by-product **62**. Whilst the formation of the 4,5-*cis* carbamate **64** forms preferentially in a 3:1 ratio with carbamate **63** (respectively), minimalising O-cyclisation was desired. Selectivity for *N*-cyclisation over *O*-cyclisation was achieved by increasing the reaction temperature to 50 °C and iodine concentration, raising the ratio of **62**:**63**:**64** from 3:1:3 to 1:1:3 (respectively). This decrease in selectivity was later observed in a similar synthesis by Corkran, with multiple products forming during carbamate annulation.[64] However, formation of the desired carbamates was favoured only when higher equivalents of iodine was present, with increased temperature favouring by-product formation.

1.3.2.1 The Vasella-Reductive-Amination

When developing the PGF Vasella-reductive-amination protocol, a key challenge was preventing the undesired dimerisation of the product amine with the *in situ* formed aldehyde (**Scheme 13**). In a specific example, the Vasella-reductive-amination reaction pathway begins with zinc-mediated Vasella ring opening of the methyl iodoglycoside **55**, followed by the reductive amination of the resulting aldehyde (**65**) using aqueous NH_3 to

generate the desired alkenylamine **56**. However, undesired dimerisation occurs when the aldehyde **65** undergoes reductive amination with the newly formed alkenylamine **56** to give the dimer **66**. This dimerisation occurs because the primary amine of alkenylamine **56** is more nucleophilic than NH_3. Whilst it was initially observed that the use of excess $AcONH_4$ salt gave reasonable yields of desired alkenylamine **56** with dimer **66** (1:1 ratio), it was the use of both excess aq. NH_3 (60 equiv.) and $AcONH_4$ (sat.) that gave a 20:1 selective formation of alkenly amine **50** to dimer **61** (respectively) in 96% yield. During optimisation it was deduced that the combination of excess NH_3 and the correct balance between free and protonated NH_3 was essential to the optimisation of this reaction, with the use of excess aq. NH_3 (60 equiv.) giving the ratio of protonated to deprotonated NH_3 required.[62]

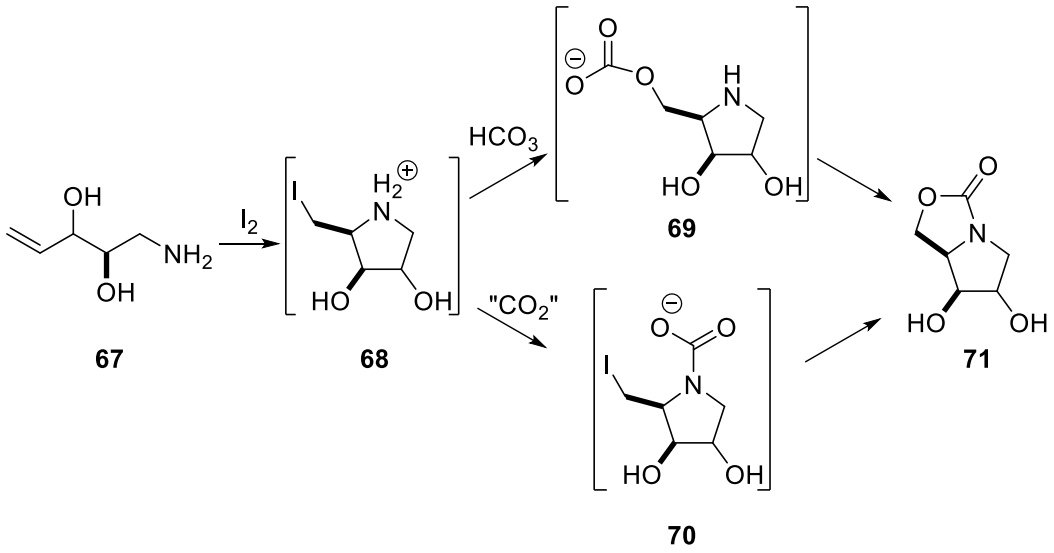


*Scheme 13: Vasella-reductive amination of **55** to give desired alkenylamine **56** and undesired dimer **66.***

1.3.2.2 The Carbamate Annulation

To date, all alkenylamines containing a primary amine undergo a carbamate annulation favouring the formation of pyrrolidines with the corresponding 3,4-*cis* stereochemistry.[65-70] Similarly, 4,5-*cis* stereochemistry is favoured in piperidine synthesis, however the annulation is not stereoselective.[63, 64] In the case of pyrrolidine formation beginning from the alkenylamine **67**, the carbamate annulation is postulated to proceed through an I_2–alkene complex, followed by intramolecular nucleophilic attack passing through a 5-membered ring transition state to form the iminoiodide intermediate **68** (**Scheme 14**).

Following this, intermediate **68** undergoes carbamate formation either by iodide displacement to form carbonate **69** or through amine attack of CO_2 to form carbamide **70**, where it remains unclear which path dominates to ultimately give carbamate **71**.[68]



*Scheme 14: The proposed reaction pathways of the carbamate annulation of alkenylamine **67**.*

The selective formation of the 3,4-*cis* configuration in carbamate **71** is rationalised through the possible orbital overlap between the alkene $\pi_{C=C}$ orbitals and the neighbouring electron-withdrawing σ^*_{C-O} orbital during formation of intermediate **68**, illustrated in **Figure 4**.[70] During cyclisation two possible conformations are possible, with the 3-hydroxyl being either in-plane (**A**) or perpendicular (**B**) to the neighbouring alkene undergoing nucleophilic attack. Conformation **A**, with the 3-hydroxyl in the plane of the alkene, minimalises the unfavourable overlap between the alkene $\pi_{C=C}$ and σ^*_{C-O} orbitals. Conversely, conformation **B** has the Hydrogen in-plane with the alkene, causing $\pi_{C=C}$ and σ^*_{C-O} orbital overlap. This $\pi_{C=C}$ and σ^*_{C-O} orbital overlap deactivates the alkene though weak delocalisation of the $\pi_{C=C}$ electrons to the σ^*_{C-O} orbital, thus increasing the activation energy for the formation of the I_2–alkene complex, favouring the O-in-plane pathway which leads to the observed stereoselectivity during carbamate annulation.[67, 68]

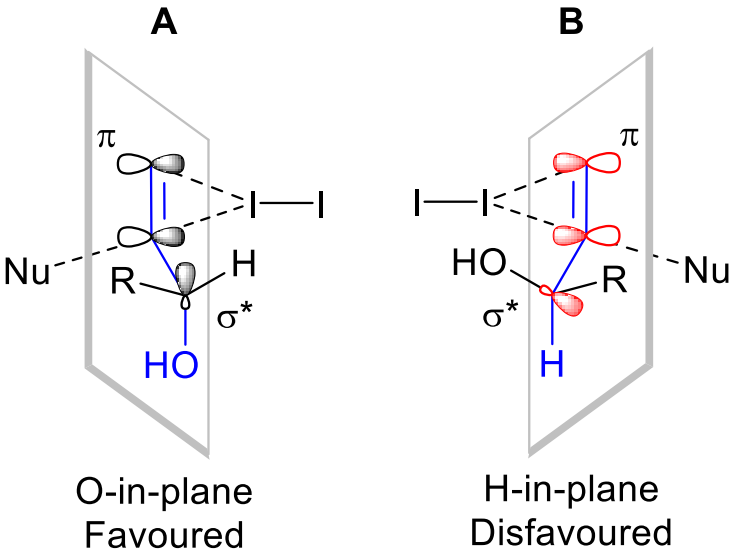


Figure 4: O-in-plane vs H-in-plane conformations during carbamate annulation.

The formation of carbamates leading to piperidine formation is proposed to occur through the same reaction pathway, with formation of the respective 6 membered ring intermediate similarly preferring a 4,5-*cis* relationship to minimalise $\pi_{C=C}$ and σ^*_{C-O} orbital overlap. However, unlike in a 5-membered ring, the 1,3-diaxial interactions of each hydroxyl significantly impacts the transition state energy, further complicating the conformational requirements during cyclisation. As a result, other reactions such as *O*-cyclisation can become energetically favourable, causing undesired side products to form.[64]

1.4 Thesis Outline

The research in this thesis explores the development of synthetic methodology in order to efficiently synthesise known and novel iminosugars through the minimal use of PG. **Chapter 2** builds on the PGF-synthesis of iminosugars reported by the Stocker-Timmer group that utilises the Vasella-reductive-amination and carbamate annulation, with the added challenge of applying these approaches to synthesis of iminosugars from the ketose sugar D-fructose (**31**). **Chapter 3** reports the application of the synthetic strategy developed in chapter 2 to D-tagatose, leading to the efficient synthesis of 2,5-dideoxy-2,5-imino-D-altritol (DIA). **Chapter 4** describes the discovery and subsequent development of a novel imine-ring-closing methodology, leading to the efficient

synthesis of DMJ (**36**) from D-fructose (**31**). The methodology developed in **Chapter 4** is explored in **Chapter 5**, where the scope and effect of carbohydrate starting materials is examined. Finally, **Chapter 6** covers future prospects and conclusions.

Chapter 2

Synthesis of 2,5-bis-hydroxymethyl pyrrolidines

2.1 Introduction

To date, a protecting-group-free (PGF) approach has been successfully applied to the syntheses of mono-substituted pyrrolidines (*e.g.* 1,4-dideoxy-1,4-imino-D-xylitol, **58**) with high over-all yield and stereoselectivity,[62] and also for the syntheses of piperidines (*e.g.* DGJ, **13**),[63] and deoxygenated derivatives.[64] Key in these synthetic strategies was the use of a PGF Vasella-reductive-amination reaction[71] and an I_2-mediated carbamate annulation.[68] However, for the synthesis of piperidines, avoiding protecting groups was challenging and on occasion, mixtures of products were formed.[63, 64]

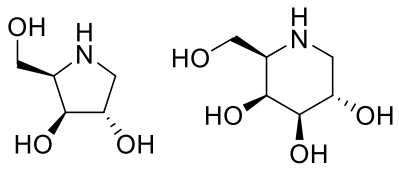
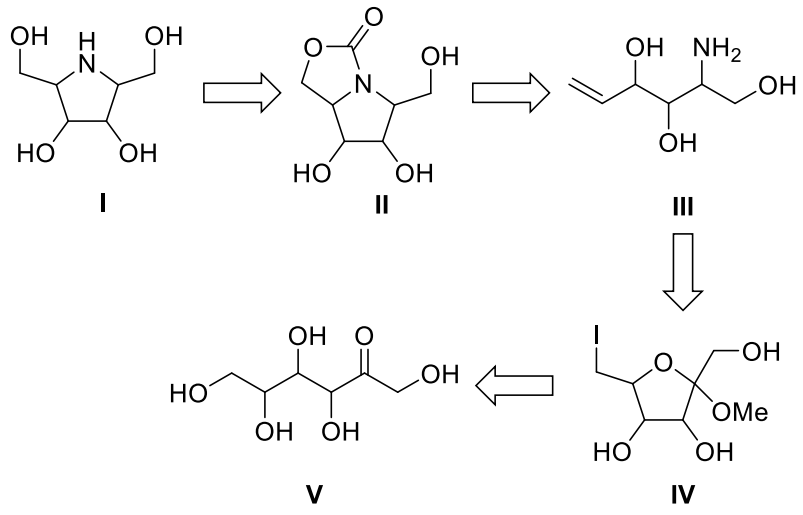


Figure 5: Representative piperidines and pyrrolidines.

To further explore the scope of the reductive amination and carbamate annulation methodologies, it was desired to apply the PGF-route to the synthesis of more complex pyrrolidines, such as the 2,5-*bis*-hydroxymethyl derivatives (**Scheme 15**). It was desired to understand how the use of a keto-sugar starting material would affect the

stereochemistry of the reductive amination and subsequent carbamate annulation. While it was envisioned that base-mediated hydrolysis would readily allow for the synthesis of pyrrolidine **I** from carbamate **II**, it was not known if the formation of carbamate **II,** which could in principle be achieved *via* an I_2-mediated carbamate annulation from alkenylamine **III**,[62] would be stereoselective. Previously, it was demonstrated that the carbamate annulation is highly 4,5-*cis* stereoselective for pyrrolidines without a substituent at the 2-position, however the syntheses of amino-imino-hexitols using protecting groups[66, 67] revealed that the stereochemistry of the 2-substituent can affect the stereochemical outcome of the annulation.[62, 68, 69] Others have also revealed that steric effects can influence the outcome of related electrophilic cyclisations.[68] To synthesise the alkenylamine **III**, it was envisioned that a PGF-free Vasella-reductive-amination using iodomethyl-furan **IV** could be undertaken,[71] thereby establishing the stereocentre at the 2-position in the target pyrrolidine. The Furan **IV**, in turn, was envisioned to be available from keto sugar **V** *via* Fischer glycosidation and regioselective iodination of the 6-position.

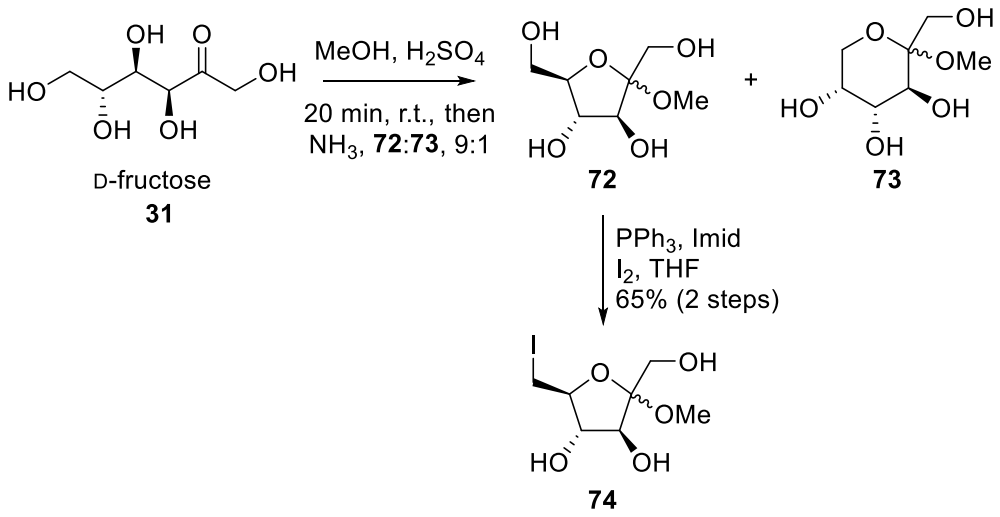


*Scheme 15: Retrosynthesis of 2,5-bis-hydroxymethyl pyrrolidines (**I**).*

2.2 The synthesis of 2,5-bis-hydroxymethyl pyrrolidines from D-fructose

To begin the synthesis, readily available D-fructose (**31**) was subjected to Fischer glycosidation with methanol under kinetic conditions,[72] which yielded a 9:1 ratio of methyl furanoside **72** to pyranoside **73** , respectively (**Scheme 16**). Separation of the

desired furanose product, while possible by silica gel flash column chromatography, was not necessary as purification was more convenient after the next step. Regioselective iodination at the most sterically accessible 6-position of furanoside **72** gave methyl iodoglycoside **74** in 65% yield over 2-steps, as evidenced by the diagnostic CH_2I ^{13}C-NMR signals of the α- and β-anomers of **74** at δ 5.2 and 6.9 ppm, respectively.[73] The successful synthesis of methyl iodoglycoside **74** was achieved by slowly adding a solution of I_2 in THF to the reaction vessel. A complex mixture of products was observed *via* TLC if I_2 was added too quickly.

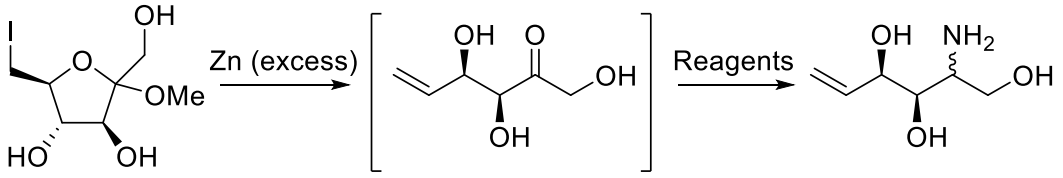


*Scheme 16: Synthesis of methyl iodofucoside **74**.*

Next, the Vasella-reductive-amination of methyl iodoglycoside **74** was attempted. Conditions previously optimised for the PGF Vasella-reductive-amination of pentoses, which utilised buffered conditions involving the use of excess NH_4OAc in NH_3 (pH = 12),[62] were applied to the methyl iodoglycoside **74** (Entry 1, **Table 1**). Following this, however, no identifiable product was observed by ^1H NMR of crude reaction mixtures. In order to assist in the optimisation of the reductive amination step, the isolation of intermediate ketone (**VI**) was attempted (entry 2). In the absence of ammonium and hydride reducing agent, the Vasella reaction rapidly went to completion, as determined by TLC (R_f = 0.4, petroleum ether/ethyl acetate, 1/1, v/v) and HRMS (*m/z* calcd. for $[C_6H_{10}O_4+H]^+$: 147.0652, obsd: 147.0655). However, analysis of the crude reaction product, after filtration and concentration, by ^1H NMR spectroscopy showed a complex mixture of products, which were attributed to the polymerisation of the trihydroxyketone. Thus, further attempts to isolate ketone **VI** were abandoned, with focus returning to a one

pot procedure. As the reductive amination of ketone **VI** appeared to be sluggish, weak-acid catalysis was employed to enhance the rate of the reductive amination. In a two-step one-pot protocol, methyl iodoglycoside **74** was first subjected to zinc in ethanol at room temperature, and after the disappearance of the starting material (1 h, as gauged by TLC), $NaBH_3CN$, AcOH and NH_4OAc were added (Entry 5). Gratifyingly, this procedure led to the isolation of the desired alkenylamine **75** in a 1:1 diasteromeric mixture, albeit in a very modest yield (13%). Following the same conditions except for heating the reaction mixture to reflux, the yield of alkenylamine **75** was slightly improved to 21% (entry 4). Greater yields could be obtained by adding all reagents to the reaction vessel at once, followed by refluxing the mixture for 3 days (entry 5), which improved the yield to 42% and simplified the protocol. Finally, methyl iodoglycoside **74** was treated with Zn, $NaBH_3CN$, AcOH and NH_4OAc in EtOH under reflux for 7 days, which led to a much improved (65%) yield of **75** in a 1:1 disastereomeric ratio (entry 6). However, treating **75** to the same reaction conditions for shorter or longer lengths of time did not improve the reaction yield.

Table 1: Optimisation of the PGF Vasella-Reductive-Amination.



74 **VI** **75**

Entry	Reagents[a]	Solvent (conc.)	Temp. (time)	pH	Yield[e,f,g] (**75**)
1[b]	$NH_{3\,(aq.)}$ (144 equiv.), NH_4OAc (130 equiv.)	EtOH (28 mL/mmol)	Reflux (2 days)	11	NA
2[b,c]	AcOH (17 equiv.)	EtOH (5 mL/mmol)	Reflux (1 h)	6	Ketone **VI**
3[d]	AcOH (17 equiv.), NH_4OAc (10 equiv.)	EtOH (5 mL/mmol)	r.t. (3 days)	6	13%
4[d]	AcOH (17 equiv.), NH_4OAc (10 equiv.)	EtOH (5 mL/mmol)	Reflux (3 days)	6	21%
5[b]	AcOH (17 equiv.), NH_4OAc (10 equiv.)	EtOH (5 mL/mmol)	Reflux (3 days)	6	42%
6[b]	AcOH (17 equiv.), NH_4OAc (10 equiv.)	EtOH (5 mL/mmol)	Reflux (7 days)	6	65%

[a] All reactions used 5 equiv. of Zn and 3 equiv. of $NaBH_3CN$.

[b] All reagents added in one step.

[c] Only attempted to isolate intermediate Ketone **VI**.

[d] Two step reaction in which $NaCNBH_3$, AcOH, and NH_4OAc were added after completion of the Vasella reaction.

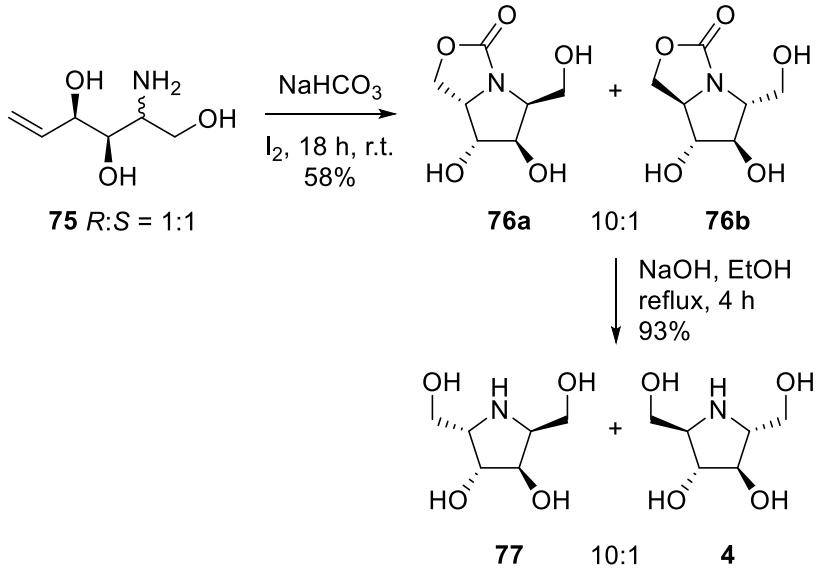
[e] NA = product not detected by ^1H NMR from the reaction mixture.

[f] All reported yields are calculated from isolated product.

[g] All reactions gave a 1:1 mixture of diasteromers.

Unfortunately, separating the two disasteromers of **75** *via* silica gel flash chromatography proved problematic, and attempts to increase the diastereoselectivity of the reductive amination using $Ti(O^iPr)_4$, (+)-DIP-Chloride, $NaBH(OAc)_3$, $B(OMe)_3$, $Mn(OAc)_2$, or $MnCl_2$ as chiral catalysts or chelating agents also did not alter the diastereoselectivity.[74-77] As a result, the diastereomic mixture of **75a** and **75b** was used for the subsequent carbamate annulation, with the hope that the carbamate diastereomers could be more readily separated by column chromatography.

To this end, a solution of I_2 (1.5 equiv.) in sat. aq. $NaHCO_3$ was added to alkenylamines **75** using the previously reported protocol[62] (**Scheme 17**). This resulted in the complete consumption of the starting material after 18 hours, as observed by TLC analysis. Following work-up and ^{1}H NMR analysis of the crude reaction mixture, it was evident that one major and one minor carbamate product had been formed in a ratio of 10:1. At this stage it was not possible to determine which isomers had been formed, however subsequent analysis (*vide infra*) revealed the major carbamate to be **76a**, with 2,5-*trans* and 4,5-*cis* relationships, while the minor carbamate was **76b** with 2,5-*trans* and 4,5-*trans* relationships. Attempts to separate the carbamate diastereomers using silica gel column chromatography proved unsuccessful.

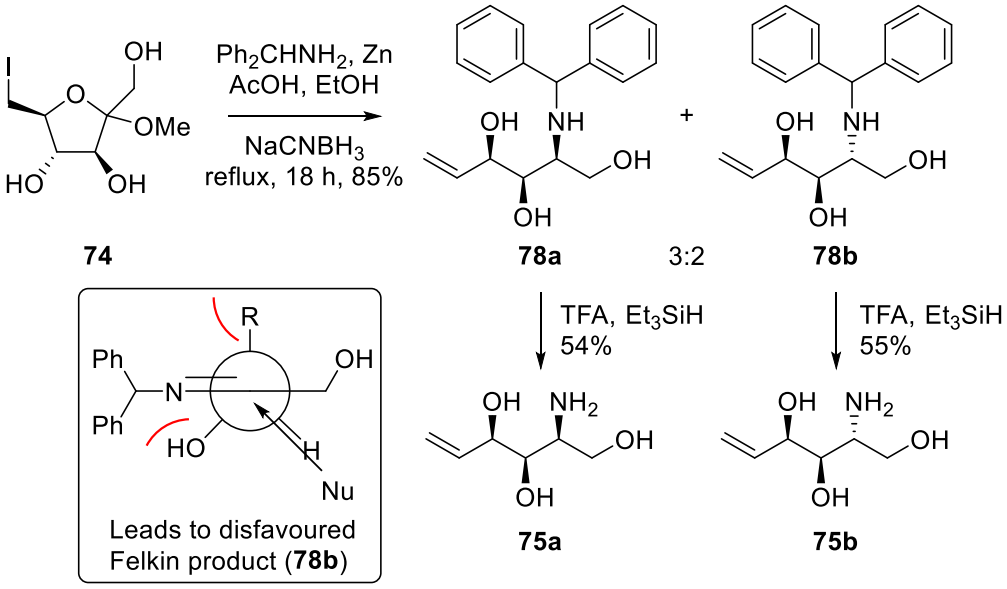


*Scheme 17: Synthesis of 2,5-dideoxy-2,5-imino-L-iditol (**77**) and 2,5-dihydroxymethyl-2,5-imino-D-mannitol (DMDP, **4**).*

The mixture of carbamates was then subjected to base mediated hydrolysis to give the target pyrrolidines **77** and **4** in 93% total yield, and again in a 10:1 ratio (**Scheme 17**). The stereochemistry of the resulting pyrrolidines could now be established by comparison of the ^{1}H- and ^{13}C-NMR data to those reported in literature, which confirmed that the major pyrrolidine to be the α- and β-glucoside inhibitor 5-dideoxy-2,5-imino-L-iditol (**77**).[62, 78, 79] Key in the structural elucidation of L-iditol **77** was the presence of only three resonances in the ^{13}C-NMR (D_2O) spectrum at δ 74.5, 62.8 and 57.4 ppm, immediately implying a symmetrical structure. The minor pyrrolidine was also symmetrical, with three carbon resonances in the ^{13}C-NMR (D_2O) at δ 74.1, 62.3 and 57.7 ppm, correlating to the

known 2,5-dihydroxymethyl-2,5-imino-D-mannitol (DMDP, **4**).[8, 80] Notwithstanding, our difficulties in separating these two products made the overall route unfeasible.

While we demonstrated that the Vasella reductive amination using NH_4OAc/AcOH was successful when using ketose sugars as starting materials, our inability to separate the alkenylamine diastereomers necessitated a modified protocol. To this end, we envisioned that the use of a bulky amine nucleophile might lead to better diastereoselectivity during the reductive amination and/or assist with the purification of the target amines. Thus, the methyl iodoglycoside **74** was subjected to the optimised Vasella-reductive-amination conditions, but with the use of diphenylmethylamine as the amine nucleophile (**Scheme 18**). This resulted in the formation of alkenylamines **78a** and **78b** in 85% total yield and in an, albeit modest, improved 3:2 ratio, in favour of the anti-Felkin Ahrn product.[81]



*Scheme 18: Synthesis of alkenylamines **75a** and **75b** using diphenylmethylamine. Insert: Newman projection showing the disfavoured steric interactions resulting in **78b** forming as the minor product.*

Formation of the desired product was evidenced by HRMS (*m/z* calcd. for $[C_{19}H_{24}NO_3]^+$: 314.1751, obsd.: 314.1752) and also by NMR analyses, where an HMBC between the benzylic proton and the C-2 carbon established the incorporation of the nitrogen atom onto the sugar framework. Fortunately, these diastereomers were readily separable by silica gel flash column chromatography. Each diastereomer was then subjected to TFA and Et_3SiH at reflux to remove the diphenylmethyl group, giving the deprotected amines **75a** and **75b** in 54% and 55% yield, respectively (**Scheme 18**).

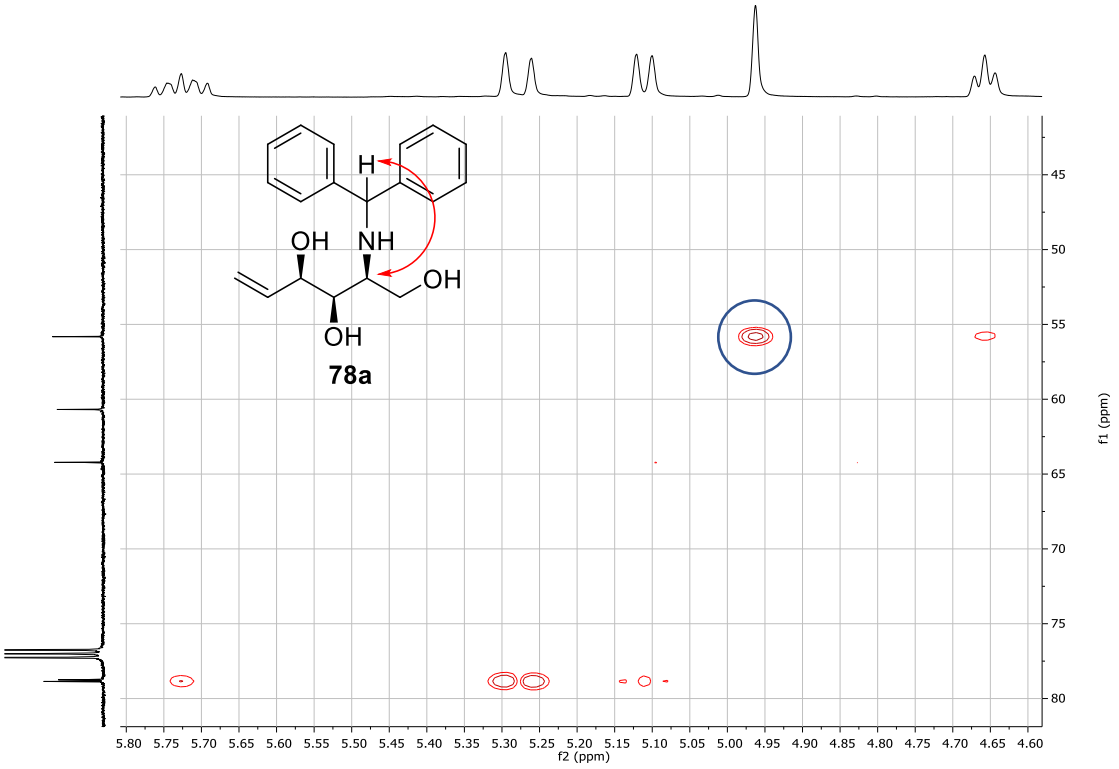
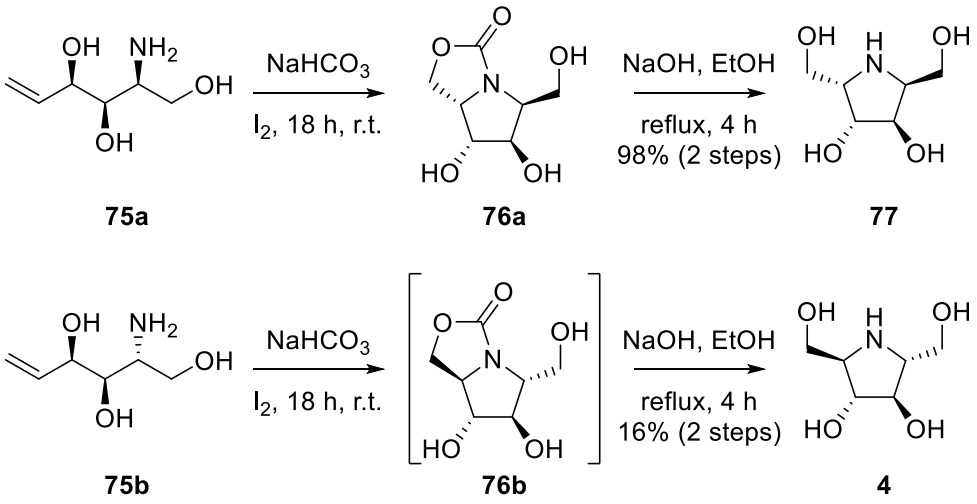


*Figure 6: HMBC spectrum of alkenylamine **78a** showing the correlation between the benzylic proton and the C-2 carbon (circled).*

With the alkenylamines **75a** and **75b** in hand, the respective carbamate annulations were performed, followed by subsequent base hydrolysis (**Scheme 19**). As anticipated, alkenylamine **75a** gave carbamate **76a** which, after hydrolysis, gave the α-fucosidase and α- and β-glucoside inhibitor 2,5-dideoxy-2,5-imino-L-iditol (**4**)[62, 78, 79] in an excellent 98% yield over the two steps. There have been several total syntheses of L-iditol **4** to date,[82-85] however two particularly notable examples include the 5-step and 6-step syntheses by Shing and co-workers[86, 87] and Wong and co-workers,[79] respectively, both of which commence from D-mannitol (45% in 5 steps and 60% in 4 steps, respectively). The synthesis of L-iditol **77** reported here was achieved in 6-steps and in 18% overall yield, and though lower yielding, it minimises the use of protecting groups, which is a new challenge in synthetic chemistry.[54]



*Scheme 19: Synthesis of 2,5-dideoxy-2,5-imino-l-iditol (**77**) and DMDP (**4**).*

Although the carbamate annulation of alkenylamine **75a** proceeded smoothly, the attempted annulation of **75b** gave a complex mixture of products, despite full-conversion of starting material, as observed by TLC analysis. Purification of these products proved difficult and it is proposed that a mixture of pyrrolidines, piperidines, and O-cyclised products formed, as previously observed during the development of other PGF-syntheses of piperidines from aldoses.[63, 64] Thus the annulation mixture of **75b** was subjected to base hydrolysis, which gave a mixture of iminosugars in which DMDP (**4**) could be identified as the major product, but in a much lower yield over the two steps (16%) as compared to the 4,5-*cis* product **77** (98%).

2.3 Factors impacting stereoselectivity during carbamate annulation

To explain the observed stereochemistry of the carbamate products and the respective yields for the annulation reactions of alkenylamines **75a** and **75b**, it is instructive to first describe the potential pyrrolidine products from the annulation reaction (**Figure 7**). Each diastereomer of **75** can form two products, for which the transition state needs to adopt a conformation in which either the allylic OH or allylic H is in the plane of the double bond. Computational studies by Gouverneur and co-workers[88] and empirical observations by Chamberlin *et al.*[89-91] and within the group[68] have identified that the OH-in-plane conformer has a lower transition state energy, due to minimal overlap of the electron

withdrawing σ* C-O and reacting π C=C orbitals, which in turn favours the formation of 3,4-*cis* products. The configuration at the 2-position, however, can significantly reduce the diastereoselectivity of the annulation.[66, 67] As illustrated for the 2*S* alkenylamine **75a** (**Figure 7**A), the OH-in-plane conformer (→ **76a**) has the electronically favourable 3,4-*cis* configuration and the sterically favourable 2,5-*trans* relationship between the hydroxylmethyl and iodomethyl groups. Conversely, the less electronically favoured H-in-plane transition state (→ **76c**) also has the sterically unfavourable 2,5-*cis* relationship and as a consequence, diastereomer **76a** is formed in the cyclisation of 2*S*-alkenylamine **75a**.

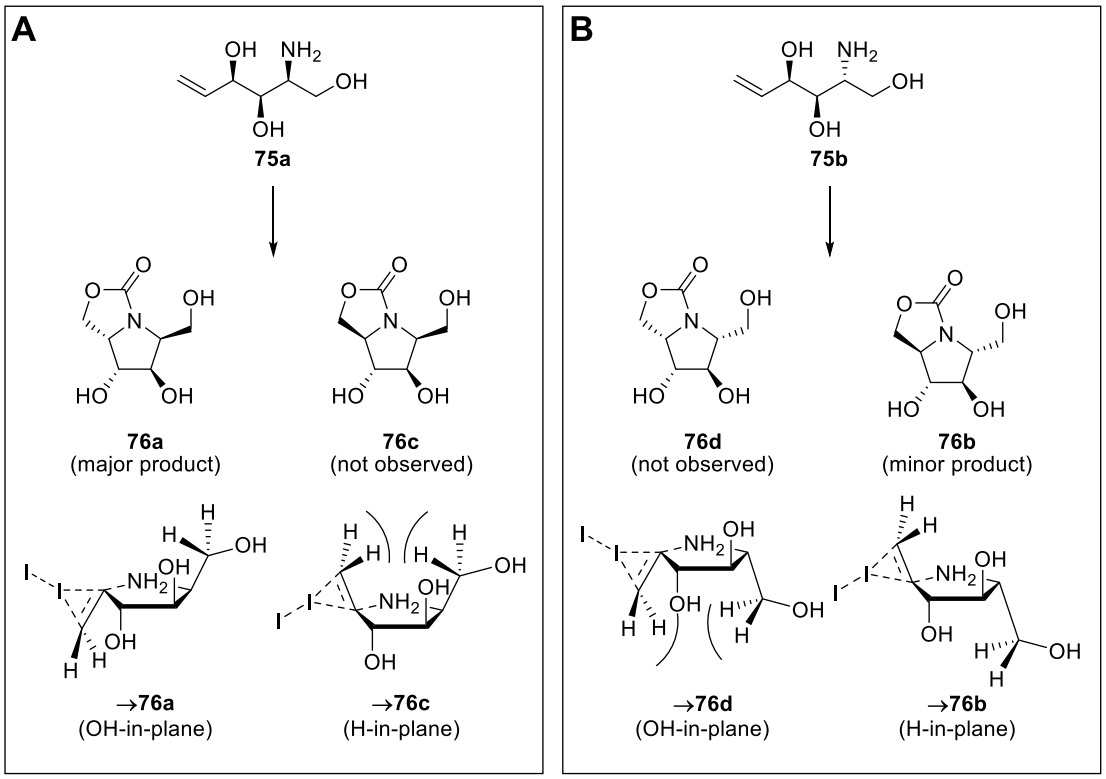


*Figure 7: Transition states for the formation of diastereomers **76a-d**.*

On the other hand, for 2*R* isomer **75b** (**Figure 7B**) the OH-in-plane conformation leads to an unfavourable 2,5-*trans* relationship, while the 2,5-*cis* conformer suffers from an unfavourable electronic interaction in the H-in-plane transition state. Consequently, there is no obvious lowest energy transition state for the cyclisation of **75b**, and only a small amount of isomer **76b** is isolated, meaning that the 2,5-interaction overrides the electronic effect of the allylic alcohol. Indeed, this finding is consistent with the work of Davies and Bouix, whereby halocyclisation of a protected alkenylamine resulted in the preferential formation of the cross-ring *trans* isomer.[92, 93]

2.4 Conclusion

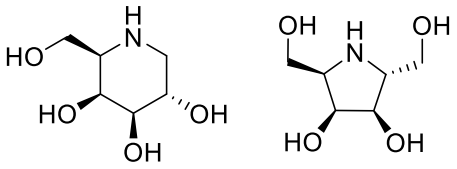
In summary, the synthesis of 2,5-dideoxy-2,5-imino-L-iditol (**77**) has been achieved in 6-steps and in 18% overall yield. This synthesis is comparable to other existing syntheses, and moreover, the route reported here minimises the use of protecting groups. In achieving the target compound, it was also demonstrated that the Vasella-reductive-amination methodology could be applied to the amination of ketones, although the diastereoselectivity of this reaction was poor. This may be attributed to the chirality of the starting iodo-sugar and is explored further in Chapter 3. Moreover, during this total synthesis it was demonstrated that the I_2-mediated carbamate annulation favours the formation of pyrrolidines with the 2,5-*trans*, 3,4-*cis* relationships. This finding can be translated to the synthesis of other 2,5-bis(hydroxymethyl)-pyrrolidines as the chirality of the intermediate alkenylamine will allow one to better predict the success and diastereoselectivity of the ensuing carbamate annulation.

Chapter 3

Synthesis of 2,5-dideoxy-2,5-imino-D-altritol

3.1 Introduction

In recent years, remarkable progress has been made towards the treatment of Fabry disease. Notably, in 2001, enzyme replacement therapy (ERT) was approved, thereby enhancing the quality and length of life for Fabry patients.[94] ERT, however, is restricted to the non-neuronopathic forms of the disease because the proteins cannot pass the blood-brain barrier.[95] Moreover, the therapy has no benefit for the prevention of premature stroke and fails to remove accumulated Gb3 from kidney podocytes and blood vessel walls.[96] Accordingly, the development of pharmacological chaperones to assist with the correct folding of the mutant α-Gal A is a promising treatment for Fabry disease that has gained much traction in recent years. In particular, the α-Gal A inhibitor 1-deoxygalactonojirimycin (DGJ, **13**, Figure 8)[97] can stabilise the native folding state of α-Gal A and allow for the trafficking of the enzyme to the lysosome.[98] Once in the lysosome, the residual activity of the mutant α-Gal A is sufficient to allow for the breakdown of Gb3.[97, 99] Pharmacological chaperones may also improve the efficacy of ERT[96] and this has sparked further interest in the development of small molecule inhibitors for α-Gal A and other enzymes associated with lysosomal storage disorders.[96, 98, 100-102]



DGJ **13** DIA **79**

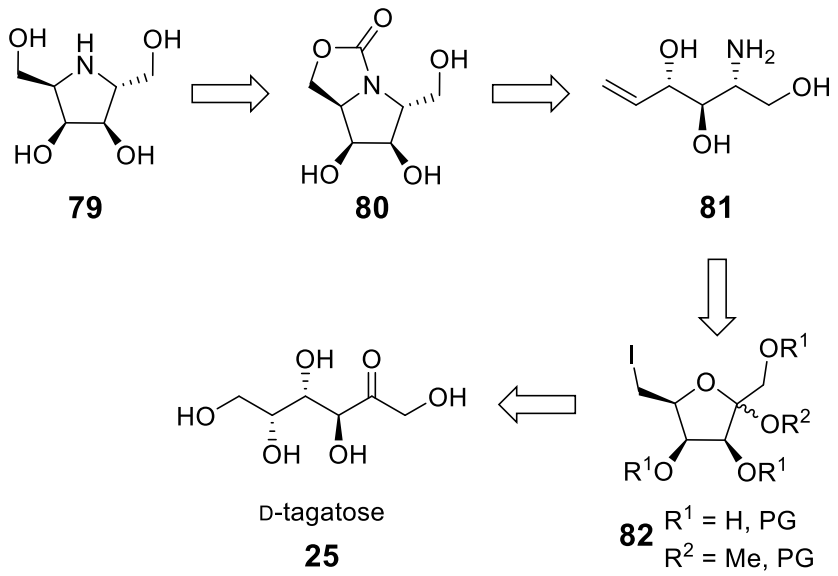
Figure 8: Molecular chaperones for Fabry disease.

There are several classes of small molecule molecular chaperones that have shown promise for the treatment of Fabry disease,[102] however, the potential of furanose sugar mimetics for this purpose was only realised in 2010 with the discovery that 2,5-dideoxy-2,5-imino-D-altritol (DIA, **79**) was a powerful competitive inhibitor of α-Gal A.[103] In this work DIA, which was isolated from the roots of *Adenophora triphylla*, inhibited α-Gal A with a K_i value of 0.5 μM, improved the thermostability of α-Gal A *in vitro*, and increased intracellular α-Gal A activity by almost 10-fold, thus demonstrating that DIA has very real potential as a pharmacological chaperone. Notwithstanding, there are few reported syntheses of DIA, with the most efficient being those by Fleet *et al.* from a protected glucuronolactone derivative (9 steps, 16% overall yield)[84] and Singh and Han from a previously synthesised olefin starting material (7 steps, 3.5% yield).[104]

3.2 Retrosynthesis

As better access to DIA would allow for more in depth investigations into the potential of this molecule as a treatment for Fabry disease, it was desired to establish a highly efficient route for its preparation by utilising the previously developed carbamate annulation methodology (see Chapter 2). It was envisioned that 2,5-dideoxy-2,5-imino-D-altritol (**79**) could be synthesised *via* base-mediated hydrolysis of the corresponding carbamate **80**, with **80** being formed *via* the I_2-mediated carbamate annulation of alkenylamine **81** (Scheme 20). The work in Chapter 2 demonstrated that the application of carbamate annulations *en route* to the synthesis of 2,5-dideoxy-2,5-imino-L-iditol (**77**) favours the 2,5-*trans*, 4,5-*cis* configuration, which makes **81** an ideal substrate from which to generate DIA. In turn, it was envisioned that alkenylamine **81** could be synthesised from the corresponding iodo-glycoside **82** *via* a Vasella reaction and diastereoselective reductive amination of the ensuing ketone functionality. Initially it was

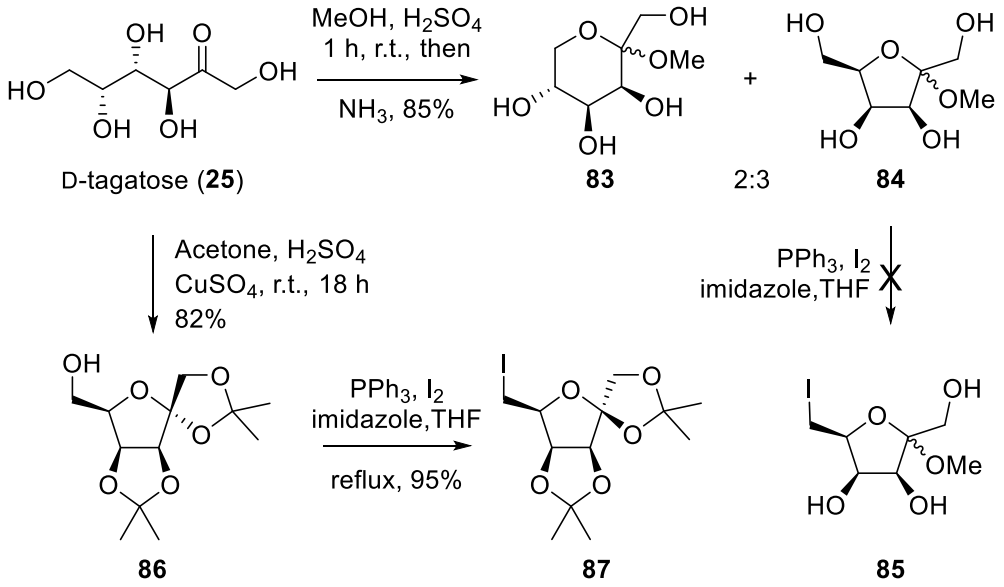
proposed that **82** could be prepared without the need for protecting groups (R^1 = H, R^2 = Me), as the annulation strategy is amenable to such an approach,[105] however, the synthesis of iminosugars in the absence of PGs is not without its challenges[63, 64] and thus, the use of PGs was also considered in the retrosynthetic plan (R^1 = R^2 = PG). Finally, methyl iodo-glycoside **82** could be prepared from commercially available D-tagatose (**25**).



*Scheme 20: Retrosynthesis for 2,5-dideoxy-2,5-imino-d-altritol (DIA, **79**).*

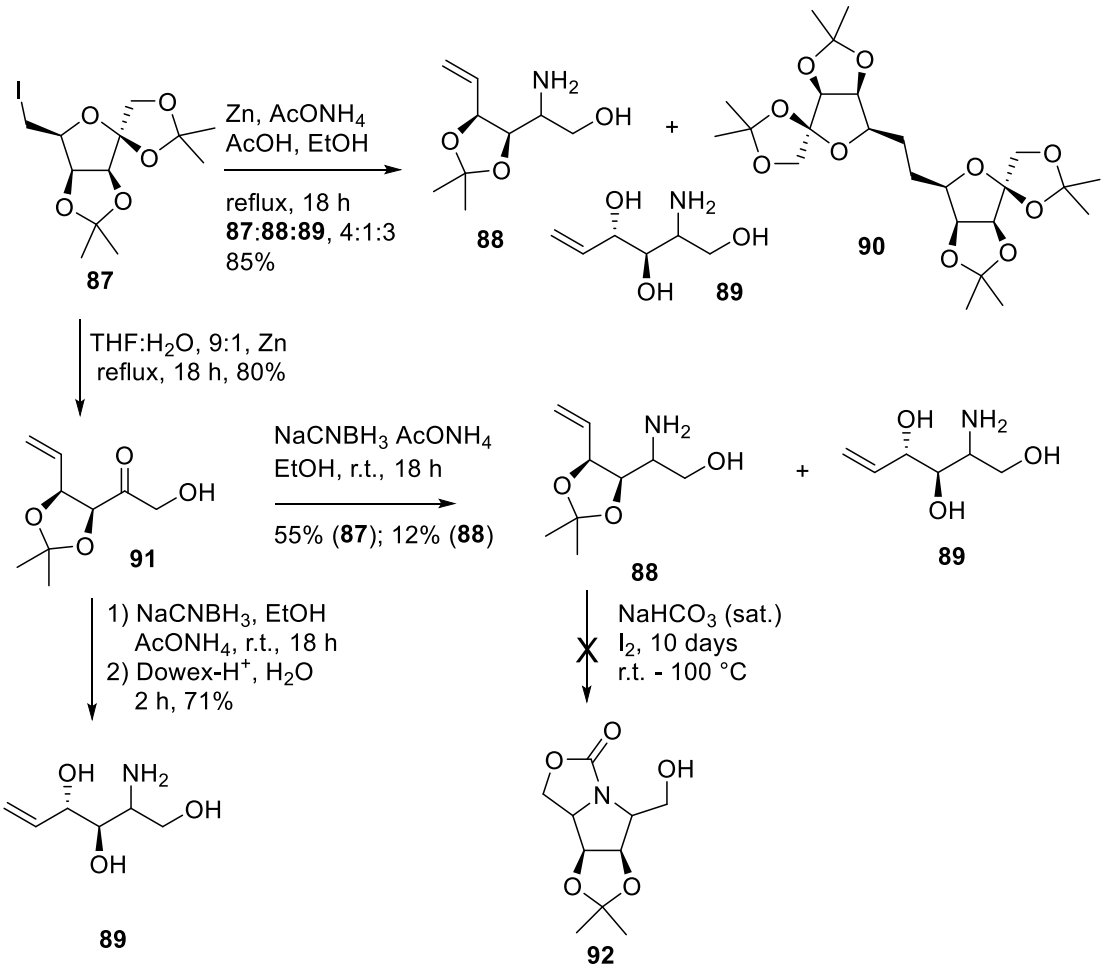
3.3 Synthesis of 2,5-dideoxy-2,5-imino-D-altritol and 2,5-dideoxy-2,5-imino-L-altritol

For this synthesis, it was initially proposed a PGF approach whereby D-tagatose (**25**) would be converted to the methyl furanoside, iodinated at the 6-position, and then subjected to a two-step one-pot Vasella-reductive-amination to yield alkenylamine **81** (see Chapter 2). Accordingly, D-tagatose (**25**) was subjected to a Fischer glycosidation with methanol[8, 106] to give an anomeric mixture of methyl glycosides **83** and **84** in a 2:3 ratio and in 85% overall yield (Scheme 21). Subsequent regioselective iodination at the 6-position of methyl glycosides **84** (→**85**), however, proved difficult, with TLC revealing the formation of a complex mixture of products resulting from the reaction. Therefore, the 1,2- and 3,4-positions in D-tagatose (**25**) were protected with isopropylidene groups (→**86**)[107] and the 6-position iodinated[62] to readily afford isopropylidene-protected iodotagatoside **87** in 80% yield over the two-steps.



*Scheme 21: Synthesis of isopropylidene-protected iodotagatoside **86** from D-tagatose (**25**).*

It was then anticipated that a one pot Vasella-reductive amination would give the desired alkenylamine. To this end, iodide **87** was subjected to Zn (10 equiv), AcOH (17 equiv.) and NH_4OAc (10 equiv.) in EtOH under reflux for 18 h (Scheme 22). Following purification using Dowex-H^+ ion exchange resin and silica gel flash column chromatography it was determined that diastereomeric mixtures of protected alkenylamines **88** and deprotected alkenylamines **89**, along with the dimer **90**, were obtained in a 4:1:3 ratio, respectively, and in 85% combined yield. While the *in situ* deprotection of the isopropylidene PG was unsurprising, given the acidic aqueous conditions of the reductive amination, the formation of dimer **90**, which is the result of a Wurtz-type coupling reaction, was unusual as hydrogenation is often difficult to prevent.[108]

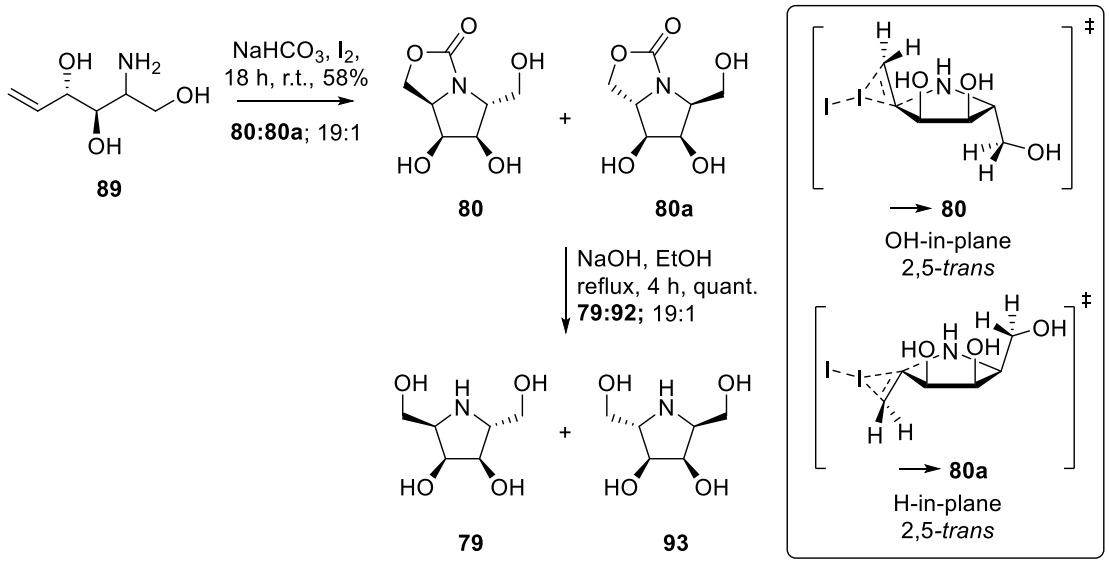


*Scheme 22: Vasella-reductive-amination of protected iodide **87**.*

To eliminate the possibility of dimer formation, the Vasella ring opening and reductive amination were then performed sequentially (Scheme 22). Accordingly, iodide **87** was refluxed with zinc in a solution of THF:H_2O (9:1) to give ketone **91** in 80% yield following purification. Ketone **91** was then subjected to reductive amination using $AcONH_4$ and $NaBH_3CN$ in ethanol, which resulted in a 1:1 diasteromeric mixture of isopropylidine protected alkenylamine **88** and the deprotected adduct **89**. While the protected alkenylamine **88** could be isolated in 55% yield following purification of the crude reaction mixture by silica gel flash column chromatography, this alkenylamine was not amenable to the previously optimised annulation conditions (→**92**, see Chapter 2), with only starting material being isolated despite prolonged reaction times and heating the solution to 100 °C. Given this result, there was no purpose in isolating **88** and following the reductive amination of ketone **91**, the crude reaction mixture was treated with water and Dowex-H^+ for 2 hours to give the deprotected alkenylamine **89** as the sole product in 71% yield and in 1:1 diastereomeric mixture. Unfortunately, the

diastereoisomers of **89** were inseparable *via* silica gel column flash chromatography, despite multiple attempts, and the material was further reacted as a mixture in the hope that the diasteromers could be separated at a later stage in the synthesis.

Next, alkenylamine **89** was subjected to I_2 and $NaHCO_3$ (*sat. soln*) for 18 hours at room temperature to induce the carbamate annulation (Scheme 23). The reaction mixture was lyophilised, extracted using methanol, and the residue columned over silica to give an inseparable mixture of carbamates **80**:**80a** (19:1) in 60 % overall yield. While the stereochemistry of **80** and **80a** could not be ascertained at this stage, it was reasoned that the major carbamate would be **80**, with the 2,5-*trans*, 4,5-*cis* configuration, which would result from the annulation of the 2*R* isomer of the alkenylamine. Here, the transition state adopted by the 2*R* isomer of alkenylamine **89** has both the electronically favourable OH in the plane of the double bond (→4,5-*cis* configuration),[88] and the sterically favourable 2,5-*trans* relationship (Chapter 2), which leads to the preferential formation of carbamate **80**. In contrast, cyclisation of the 2*S* isomer of **89** could give carbamates with either the 2,5-*trans*, 4,5-*trans* configuration (→**80a**) or the 2,5-*cis*, 4,5-*trans* configuration. As discussed in Chapter 2, it was determined that the 2,5-*cis* steric interaction showed greater influence on the transition state energy, and thus it was expected that carbamate **80a** would be preferentially formed.

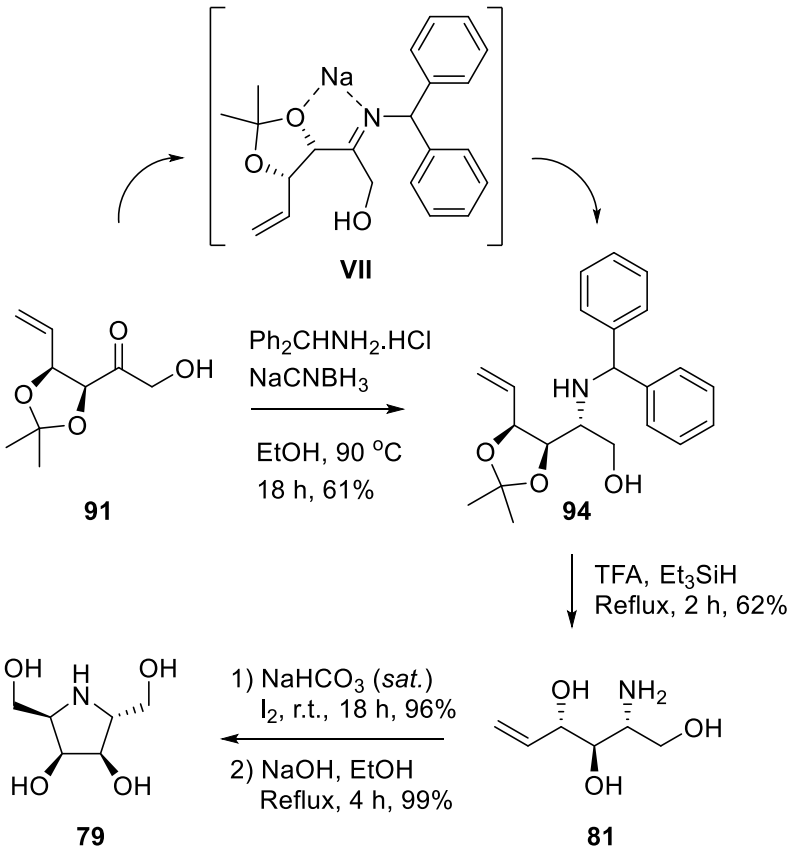


*Scheme 23: Carbamate annulation of alkenylamines **89** and base-mediated hydrolysis to yield DIA **79** and 2,5-dideoxy-2,5-imino-L-altritol (**93**).*

To confirm the stereochemistry of the carbamates, the mixture of **80** and **80a** was subjected to NaOH in ethanol at reflux for 4 hours. One product was observed by TLC (R_f = 0.15; DCM/EtOH/MeOH/28% aq. NH_3 5/2/2/1; v/v/v/v), which was obtained in quantitative yield following purification using Dowex-H^+ resin. Analysis by NMR revealed the product to have six discrete environments in both the ^1H and ^{13}C spectra, revealing an asymmetrical product. The spectral data matches those of DIA (**79**),[84, 103] however as 2,5-dideoxy-2,5-imino-L-altritol (**93**),[109] the enantiomer of DIA (**79**), would have an identical NMR spectra, the optical rotation of the mixture was measured to establish that DIA was present in 89% ee. Being enantiomers, DIA (**79**) and L-altritol (**93**) were inseparable by conventional chromatographic techniques, and this was problematic from a total synthesis point of view. Notwithstanding, the generation of these two hydroxy pyrrolidines, with only minor amounts of L-altritol (**92**), further supported our hypothesis that carbamate annulations with complementary electronic and steric effects give excellent yields of the 4,5-*cis* carbamate (2*R* isomer of alkenylamine **89** →**80**), while those annulation reactions with opposing steric and electronic factors give poorer yields of the corresponding carbamates (2*S* isomer of alkenylamine **89** →**80a**).

3.4 Asymmetric synthesis of 2,5-dideoxy-2,5-imino-D-altritol

Having demonstrated the potential of the carbamate annulation *en route* to the formation of DIA (**79**), attention was then directed towards a strategy for the improved synthesis and isolation of required 2*R* isomer of alkenylamine **89**. It was observed previously that *N*-diphenylmethyl diastereomers of alkenylamines were more readily separable by silica gel flash column chromatography (Chapter 2). Moreover, when using diphenylmethylamine as the nucleophile for the reductive amination of ketone **91**, it was possible that chelation control[81] and the larger size of the amine nucleophile would favour formation of the 2*R* isomer of alkenylamine **89** *via* intermediate **VII**. Gratifyingly, this proposition was correct, with the protected alkenylamine **94** being the only product observed following the treatment of ketone **91** with diphenylmethylamine and $NaCNBH_3$ (**Scheme 24**). Alkenylamine **94** was then treated with TFA and triethylsilane at reflux for 2 hours to give 2*R*-alkenylamine **81** in 62% yield following purification using Dowex-H^+ resin. The subsequent annulation of **81** and hydrolysis then gave DIA (**79**) in excellent yield. Taken together, this completed the synthesis of 2,5-dideoxy-2,5-imino-D-altritol (**79**) in seven steps and in a 22% overall yield.



***Scheme 24**: Synthesis of DIA (**79**) from isopropylidine-protected ketone **91**.*

3.5 Conclusion

In conclusion, the total synthesis of 2,5-dideoxy-2,5-imino-D-altritol (DIA, **79**) was successfully completed in 7 steps and 22% yield. This is not only the shortest synthesis of DIA from commercially available starting materials, but is also the highest yielding. It is envisioned that ready access to DIA will allow for more in-depth studies into the potential of this molecule as a pharmacological chaperone for the treatment of Fabry disease. Additionally, this work also further illustrates how electronic and steric influences can affect the diastereoselectivity of the I_2-mediated carbamate annulation and show how these factors can be used as a predictive tool in the planning of efficient total syntheses.

Chapter 4

Novel DMJ synthesis

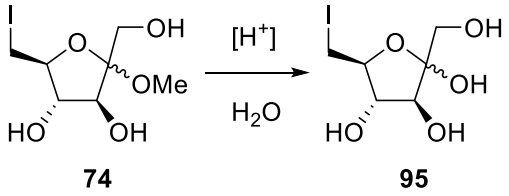
4.1 Introduction

Minimalizing or eliminating the use of protecting groups requires a concise synthetic strategy, sometimes helped by the development of novel methodology. It was the development of the Vasella-reductive-amination and the I_2-mediated carbamate annulation by Dangerfield *et al.*[110] that led to the efficient synthesis of numerous iminosugars[111-115], and alteration of this methodology leading to the efficient synthesis of DIA (**79**, Chapter 3). While new synthetic methodologies can be developed through the logical modification of existing chemistries, it is often an unexpected side-reaction that forms the starting point in the development of a new reaction. This chapter describes the exploration of a side reaction, which led to the discovery of a novel one-pot-two-step substitution/reduction reaction that, once optimised, was then used for the efficient synthesis of 1-deoxymannojirimycin (DMJ, **36**).

4.2 Acid mediated decomposition of 2-*O*-Methyl-6-deoxy-6-iodo-D-Fructofuranoside

During the early stages of optimising the protecting group free Vasella-reductive-amination used in the synthesis of 2,5-dideoxy-2,5-imino-L-iditol (**77**, see chapter 2), methyl iodofructoside **74** was observed to be acid labile. Concentrating methyl

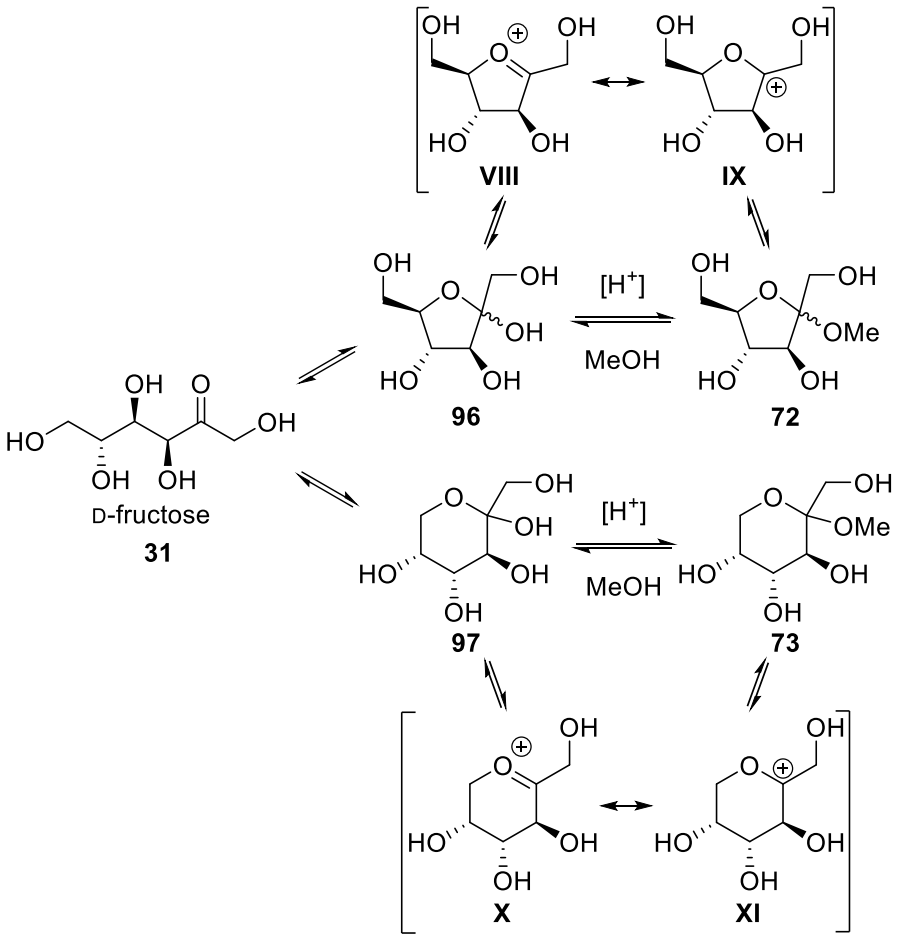
iodofructoside **74** under slightly acidic conditions or leaving the material in a flask with trace iodine and atmospheric H_2O would occasionally lead to the formation of a decomposition product. This product was isolated and examined using HRMS and NMR spectroscopy. Analysis by ^1H NMR showed all peaks present in methyl iodofructoside **74**, with exception of the *O*-methyl peak, with HRMS further indicating the absence of a methyl group (*m/z* obsd: 290.9728; matching calcd. mass for $[C_6H_{11}IO_5+H]^+$: 290.9724). Further examination using 2D NMR identified the decomposition product as 6-deoxy-6-iodo-D-fructose (**95**), with spectral data matching that previously reported in literature (**Scheme 25**).[116, 117]



74 **95**

*Scheme 25: Acid degradation of methyl iodofructoside **74.***

Normally, methyl glycosides are very stable, with an *O*-methyl group considered difficult to remove.[118] However, Fischer glycosidation is an equilibrium reaction that, in principle, is reversible. Thus, to understand why iodofructoside **95** formed, it is useful to examine the Fischer glycosidation of D-fructose in methanol (**31**, **Scheme 26**). Here, Fischer glycosidation begins with either furan **96** or pyran **97** undergoing acid catalysed dehydration to give the respective oxocarbenium intermediates **VIII** and **X** (respectively), with corresponding carbocation resonance structures **IX** and **XI** (respectively).[118] Nucleophilic attack by methanol of **VIII**/**IX** gives the desired furan methyl glycoside **72** and similarly, attack by methanol of **X**/**XI** gives pyran methyl glycoside **73**. Note that until the reaction is neutralised, D-fructose (**31**) and methyl glycosides **72** and **73** remain in equilibrium.



*Scheme 26: Fischer glycosidation of D-fructose (**31**) to form methyl glycosides **72** and **73**.*

Under kinetic conditions the furan methyl glycoside **72** is formed preferentially, with thermodynamic conditions favouring formation of pyran methyl glycoside **73**. Under kinetic conditions, the ratio of furan **72** and pyran **73** formed during glycosidation reflect the ratio of cyclic precursors **96** and **97** (respectively) that are present in solution at room temperature, where D-fructose is predominantly present as furan **96**. Furthermore, intermediates **VIII**/**IX** are more stable than intermediates **X**/**XI**, with the geometry of the furan ring in **VIII**/**IX** better able to stabilise the positively charged sp^2 carbon over a pyran ring. Conversely, thermodynamic conditions favour the formation of pyran methyl glycoside **73**, with a pyran ring providing a final product of lower energy.

The Fischer glycosidation of D-fructose (**31**) is more facile than that of its aldose analogues, the latter of which used in the original work by Dangerfield *et al. en route* to the synthesis of pyrrolidines.[62, 65-67] As such, glycosidation of D-fructose (**31**) requires a lower concentration of acid and shorter reaction times. This increased reactivity of D-fructose (**31**) is due to the greater stability of the oxocarbenium intermediate **VIII**, as

compared to the analogous oxocarbenium ion from the aldose sugars (**XII**, **Figure 9**). With D-fructose (**31**), as with any ketose sugar, the formation of the oxocarbenium intermediate is aided by the extra hydroxyl-methyl group at the anomeric carbon, which is better able to inductively stabilise the positive charge of the oxocarbenium intermediate than the hydrogen substituent present in aldoses. The steric and electronic factors that make formation of methyl glycoside **72** facile are also the same factors that make methyl iodofructoside **74** comparatively less stable. Thus, slightly acidic conditions in the presence of H_2O are sufficient to cause decomposition of methyl iodofructoside **74** in to iodofructoside **95**.

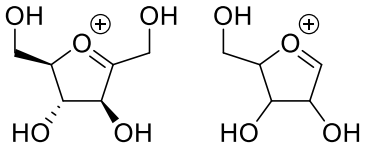
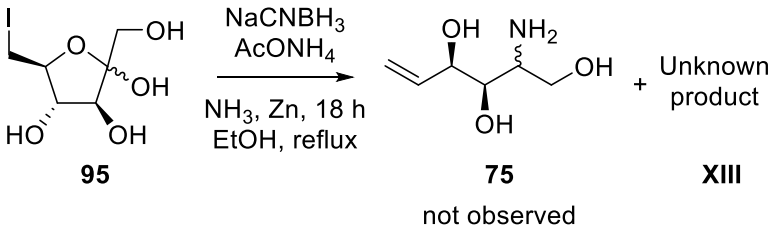


*Figure 9: The oxocarbenium intermediates **VIII** and **XII** resulting from D-fructose (**31**) and aldopentoses (respectively) during Fischer glycosidation.*

4.3 Attempted Vasella-reductive-amination of 6-deoxy-6-iodo-D-fructose (95)

Having isolated and identified iodofructoside **95**, the ability of this substrate to undergo Vasella-reductive-amination to yield alkenylamine **75** was explored. Thus, iodofructoside **95** was subjected to a Vasella-reductive-amination reaction (**Scheme 27**).[62] Monitoring product formation by TLC proved difficult due to the presence of excess $AcONH_4$, although starting material was observed to react completely within 30 minutes. After 18 hours at reflux, the reaction was concentrated *in vacuo* and purified using Dowex-H^+ exchange resin. The resulting mixture was examined by NMR spectroscopy, and, despite the ^1H spectra of the crude reaction mixture being poorly resolved and indicating a mixture of products, it was apparent that a single major product had formed that was not the desired alkenylamine **75**. This unknown product **XIII** (R_f = 0.1 (DCM/EtOH/MeOH/30% NH_3 (aq.), 5/2/2/1, v/v/v/v) was subsequently purified by silica gel flash column chromatography (DCM/EtOH/MeOH/NH_3(aq.) 20/2/2/1; v/v/v/v).



*Scheme 27: attempted Vasella-reductive-amination of iodofructoside **95** resulting in unknown product **XIII**.*

Following isolation, the structural elucidation of product **XIII** began with HRMS. Here, the mass of **XIII** was determined to be 164.0915, corresponding to the chemical formula $C_6H_{13}NO_4$ (calcd. $[C_6H_{13}NO_4+H]^+$: 164.0917). This mass formula suggested the loss of iodine and, with a double bond equivalence of 1, the presence of either an alkene, carbonyl, or ring within the structure. Furthermore, both the even mass ion peak and accuracy of the mass spectrometry peak suggest the presence of one nitrogen atom. Subsequent ^{1}H NMR spectroscopy revealed six distinct proton environments integrating for one proton, and a mulitplet (suspected as two overlapping proton environments) integrating for 2 protons, between 3.0 - 4.4 ppm (**Figure 10**). The ^{13}C NMR spectrum showed six signals between 45 – 75 ppm. Having all ^{1}H signals between 3.0-4.4 ppm eliminated the presence of an alkene, while the absence of ^{13}C signals below 10 ppm, or above 80 ppm, suggested that the molecule did not contain iodine or carbonyl groups, respectively. Taken together, the NMR data and HRMS suggested product **XIII** had an asymmetric poly-hydroxylated ring structure containing a nitrogen.

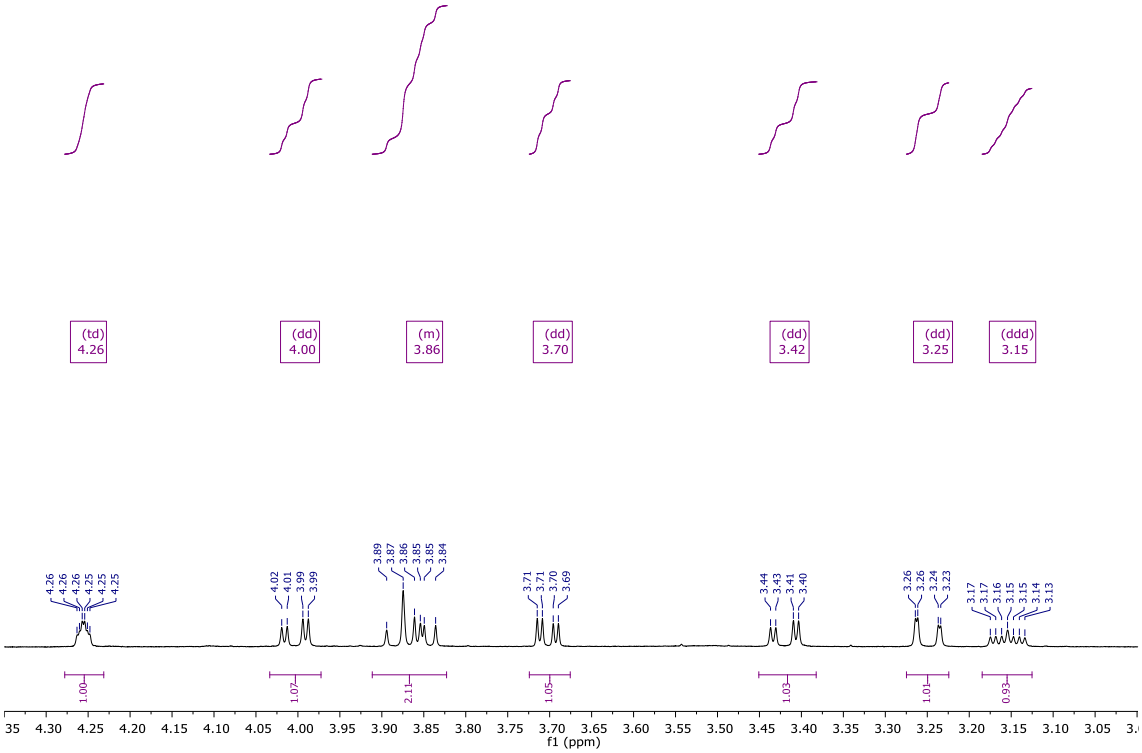
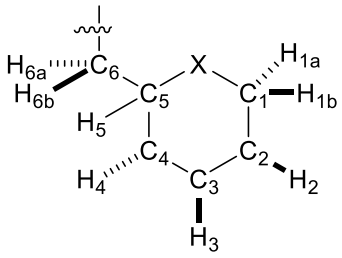


*Figure 10: ^{1}H NMR spectrum of unknown product **XIII**.*

Further structural elucidation was achieved by more closely examining the 1D and 2D NMR data (see **Figure 10**, and **Table 2**). Beginning with the apparent tenting doublet of doublets at 3.42 ppm and 3.25 ppm within the ^{1}H NMR spectrum, these environments both integrated for one and, as shown by HSQC, were bound to the same carbon at 47.4 ppm (assigned **C1**). As such, these two proton environments were assigned **H1a** and **H1b** (respectively). Analysis by COSY indicated that these two protons coupled with one another (J = 13.6 Hz) and to a third proton (J = 3.1 Hz and 1.5 Hz, for **H1a** and **H1b** respectively), establishing an easily recognisable ABX system. The third proton environment, a triplet of doublets at 4.26 ppm (assigned **H2**), integrated for one proton and was bound to the carbon at 65.7 ppm (**C2**). As well as the ABX couplings, **H2** also coupled to a doublet of doublets at 3.70 ppm (**H3**, **C3** = 72.2 ppm). The J = 3.1 Hz coupling constant between **H2** and **H3** suggested a *syn* stereochemical relationship. Moreover, COSY revealed that **H3** coupled to a multiplet at 3.86 ppm, with HSQC indicating that this multiplet consisted of two overlapping proton resonances— one a methyne (attached to a carbon with δ 65.6 ppm), and the other one proton of a methylene (attached to a carbon with δ 57.9 ppm). Due to the multiplicity (i.e. doublet of doublets)

of **H3**, it was clear **H3** was not coupling to both protons in the multiplet at 3.86 ppm or the other proton of the methylene. Thus, it was proposed that **C4** is likely the methyne carbon at 65.6 ppm, where the relative stereochemistry between **H3** and **H4** would be *trans* (J = 9.5 Hz). Further analysis by COSY then suggested that both protons at 3.86 ppm (**H4** and the methylene proton attached to the carbon at δ 57.9 ppm) and the proton at 4.00 ppm (also attached to the carbon at δ 57.9 ppm) coupled to a doublet of doublet of doublets (ddd) at 3.15 ppm, thereby indicating the presence of an ABNX system. As such, the ddd at 3.15 ppm was assigned **H5** (**C5** = 60.0 ppm), with **H5** coupling to both **H6a** (δ 4.00 ppm, $J_{5\text{-}6a}$ = 3.3 Hz) and **H6b** (δ 3.86, $J_{5\text{-}6b}$ = 6.8 Hz) forming the ABX system, with coupling between **H5** and **H4** ($J_{5\text{-}4}$ = 10.6 Hz) completing the observed ABNX system. The presence of a ring structure was confirmed *via* an HMBC of **H5** with **H1a** and **H1b**. Though **H5** was near **C1** (HMBC), **H1a** and **H1b** only showed ABX coupling, suggesting that there is either an oxygen or nitrogen atom between **C1** and **C5**.

*Table 2: NMR data used in the structural elucidation of unknown product **XIII**.*



XIII

Position	^{1}H shift (δ, ppm)	^{13}C shift (ppm)
1a	3.42 (dd, $J_{1a,1b}$ = 13.6 Hz, $J_{1a,2}$ =3.1 Hz, 1H)	47.4
1b	3.25 (dd, $J_{1b,1a}$ = 13.6 Hz, $J_{1b,2}$ =1.5 Hz, 1H)	
2	4.26 (td, $J_{2,1a}$ = $J_{2,3}$ =3.1 Hz, $J_{2,1b}$ = 1.5 Hz, 1H)	65.7
3	3.70 (dd, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 3.1 Hz, 1H)	72.2
4	3.86 (m, 2H) [dd, $J_{4,5}$ = 10.3 Hz, $J_{3,4}$ = 9.5 Hz, 1H]	65.6
5	3.15 (ddd, $J_{5,4}$ = 10.3 Hz, $J_{5,6a}$ = 6.7 Hz, $J_{5,6b}$ = 3.3 Hz, 1H)	60.0
6a	3.86 (m, 2H) [dd, $J_{6a,6b}$ = 12.6 Hz, $J_{6a,5}$ = 6.7 Hz, 1H]	57.9
6b	4.00 (dd, $J_{6b,6a}$ = 12.6 Hz, $J_{6b,5}$ = 3.3 Hz, 1H)	

Relevant HMBC coupling: C5-H1; C1-H5; C4-H5 (strong), H6 (weak).

The IR of this compound, however, did not show a clear doublet above 3200 cm^{-1}, implying there is only one N-H stretch, which requires X to be nitrogen. Based on the HRMS data, four oxygen atoms and four hydrogen atoms were unaccounted for, thus suggesting that **C2**, **C3**, **C4**, and **C6** were attached to a hydroxyl group. Whilst the stereochemistry about C5 remained unclear, it was quickly noted that the proposed structure of unknown product **XIII** (**Figure 11**) resembled the relative configuration of well-known iminosugars 1-deoxymannojirimycin (DMJ) and its 5-epimer. Examination of published spectral data[119] and subsequent optical rotation measurements ($[\alpha]_D^{20}$ -15.7 [c 1.6, H_2O]; lit.[120] $[\alpha]_D^{20}$ -15.0 [c 2, H_2O]) confirmed the structure of unknown product **XIII** as 1-deoxymannojirimycin (DMJ, **36**). DMJ was first isolated in 1979 by Fellows and Bell from *Lonchocarpus sericeus*[121], and found to be a moderate α-mannosidase and strong mammalian α-fucosidase inhibitor,[122] several notable syntheses of DMJ were subsequently achieved.[120, 123, 124]

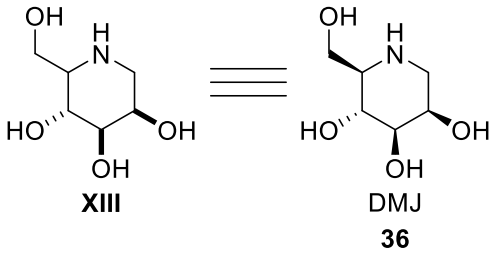
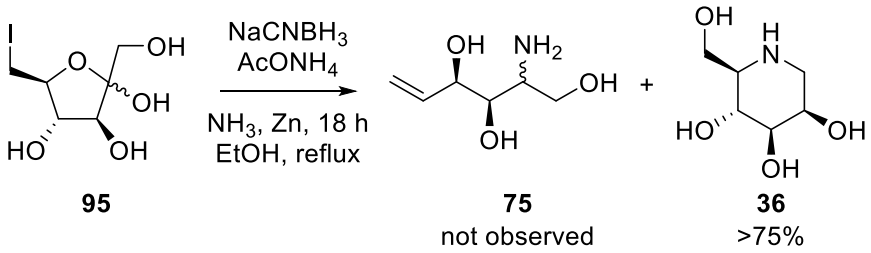


*Figure 11: Elucidation of unknown product **XIII** as DMJ (**36**)* via *comparing NMR spectra and optical rotation data to literature.*

Having determined that the structure of the unknown product was DMJ, it remained to be determined how this product could be formed from iodofructoside **95** under Vasella-reductive-amination reaction conditions (**Scheme 28**). The stereochemistry at C3, C4, and C5 in iodofructoside **95** matched that of C4, C3, and C2, respectively, in DMJ and suggested that a cascade of reactions was occurring, including a reductive amination, cyclisation, and iodide displacement, which would in turn dictate the stereochemistry at C5 in DMJ (**36**). However, before the details of the reaction mechanism were explored, efforts were made towards optimising the synthesis of DMJ, which required both an efficient synthesis of iodofructoside **95** and its subsequent conversion into DMJ.

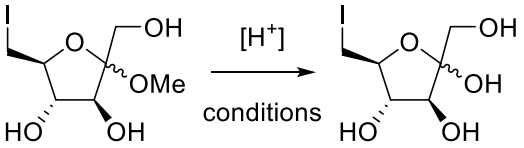


*Scheme 28: The attempted Vasella-reductive-amination of iodofructoside **95** resulting in DMJ (**36**) formation.*

4.3 Optimising the synthesis of 1-deoxymannojirimycin (DMJ)

The optimisation of converting methyl iodofructoside **74** to iodofructoside **95** began with subjecting methyl iodofructoside **74** to aqueous HCl at 0.09 M (entry 1, **Table 3**). Here, it was thought that exposing methyl iodofructoside **74** to the same acid concentration used for the Fischer glycosidation of D-fructose (**3**) would be sufficient to re-establish the equilibrium between methyl iodofructoside **74** and iodofructoside **95**, with the presence of excess of H_2O favouring the formation of iodofructoside **95**. Analysis of the reaction by TLC, however, revealed only partial demethylation occurred after stirring at r.t. for 3 hours (entry 1), with extending the reaction time to 18 hours (entry 2) also not improving product yields. Bringing the reaction mixture to reflux led to greater formation of iodofructoside **95**, however after half an hour, all material had degraded (entry 3). Thus, rather than heating at reflux, the reaction was warmed to 50 ^{o}C under reduced pressure (0.3 atm) in an effort to remove the MeOH that formed during the reaction (entry 4). This resulted in approximately 75% conversion to the desired iodofructoside **95** after 7 hours (entry 4). While this was encouraging, it was preferable to avoid the need for heat or reduced pressure and thus the acid concentration was increased to 0.15 M, thereby allowing for complete conversion of methyl iodofructoside **74** to iodofructoside **95** (*via* TLC) after 3 days (entry 5). This reaction time can be dramatically reduced *via* the use of reduced pressure and a 50 ^{o}C water bath (entry 6). All reactions were performed with the substrate at a dilute concentration of 10 mL/mmol to further favour demethylation, with larger scale reactions (> 0.5 g) requiring slightly longer reaction times.

Table 3: Optimisation of acid mediated demethylation



74 **95**

Entry	HCl conc (molar)[a]	Temp. (time)	Pressure (atm)[b]	Conversion[c]
1	0.09	r.t. (3 h)	1	50%
2	0.09	r.t. (18 h)	1	50%
3	0.09	reflux (0.5 h)	1	degraded
4	0.09	50 (7 h)	0.3	75%
5	0.15	r.t. (3 d)	1	completion
6	0.15	50 (2-3 h)	0.3	completion

[a)] All reactions done at a substrate concentration of 10 mL/mmol

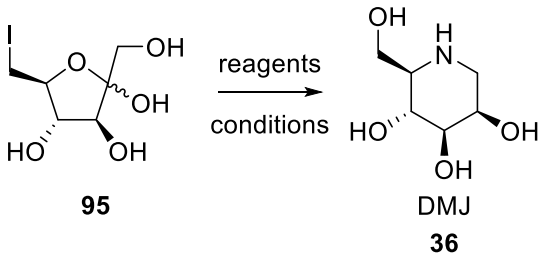
[b)] reduced pressure achieved using a rotatory evaporator

[c)] All conversions approximated by TLC

With the conditions for demethylation optimised, the next step was to determine the optimal conditions for the formation of DMJ (**36**). Initially, the synthesis of DMJ (**36**) was achieved using a batch of iodofructoside **95** that had unintentionally formed from the long-term storage methyl iodofructoside **74**. Thus, upon subjecting this batch of iodofructoside **95** to Vasella-reductive-amination conditions, DMJ (**36**) was formed in ≈80% yield (entry 1, **Table 4**). Whilst encouraging, it was important to develop a robust protocol that could be consistently repeated, therefore methyl iodofructoside **74** was demethylated using optimised conditions and subjected to further reaction conditions (entries 2-7). To assess the requirement of zinc in the reaction, freshly made iodofructoside **95** was subjected to NH_3 and NH_4OAc in the presence of $NaCNBH_3$ at 80 ^oC for 18 hours (entry 2). The reaction mixture was then concentrated and purified *via* Dowex-H^+ resin and by silica flash column chromatography to give DMJ (**36**) in 88% yield. In proving that zinc was not required for the reaction, the need for the use of

ammonium salts was explored. To this end, iodofructoside **95** was treated to the same reaction conditions but in the absence of NH_4OAc (entry 3). Again, this led to the desired product in approximately the same yield (89%). Next it was hoped that increasing the reaction concentration would allow the reaction to be performed at lower temperatures. As such, iodofructoside **95** was subjected to the same reagents at a reduced substrate concentration of 15 mL/mmol and at room temperature for 18 hours (entry 4). Gratifyingly, this gave an isolated yield of DMJ (**36**) of 96%. Next, the effect of reaction time on product yield was explored. Here, shorter reaction times (9 h, entry 6; 6 h entry 7) showed decreased yields of DMJ (**36**), while longer reaction times (3 days, entry 8) did not increase product yield.

*Table 4: Optimisation of DMJ (**36**) formation from iodofructoside **95**.*



95 DMJ **36**

Entry	Reagents[a,b]	Solvent (conc)	Temp. (time)	Yield[c,d]
1[e]	Zn (10 equiv.), $NH_{3\,(aq.)}$ (144 equiv.), NH_4OAc (130 equiv.)	EtOH (28 mL/mmol)	Reflux (18 h)	> 80 %
2[f]	$NH_{3\,(aq.)}$ (90 equiv.), NH_4OAc (130 equiv.)	H_2O (28 mL/mmol)	80 °C (18 h)	88 %
3[f]	$NH_{3\,(aq.)}$ (90 equiv.)	H_2O (28 mL/mmol)	80 °C (18 h)	89 %
4[f]	$NH_{3\,(aq.)}$ (90 equiv.)	H_2O (15 mL/mmol)	r.t. (18 h)	96 %
6[f]	$NH_{3\,(aq.)}$ (90 equiv.)	H_2O (15 mL/mmol)	r.t. (9 h)	92 %
7[f]	$NH_{3\,(aq.)}$ (90 equiv.)	H_2O (15 mL/mmol)	r.t. (6 h)	91 %
7[f]	$NH_{3\,(aq.)}$ (90 equiv.)	H_2O (15 mL/mmol)	r.t. (72 h)	96 %

[a] All reactions used 4 equiv. of $NaCNBH_3$

[b] All reagents added in one step

[c] All reported yields are calculated from isolated product

[d] All reactions gave DMJ (**36**) stereoselectively

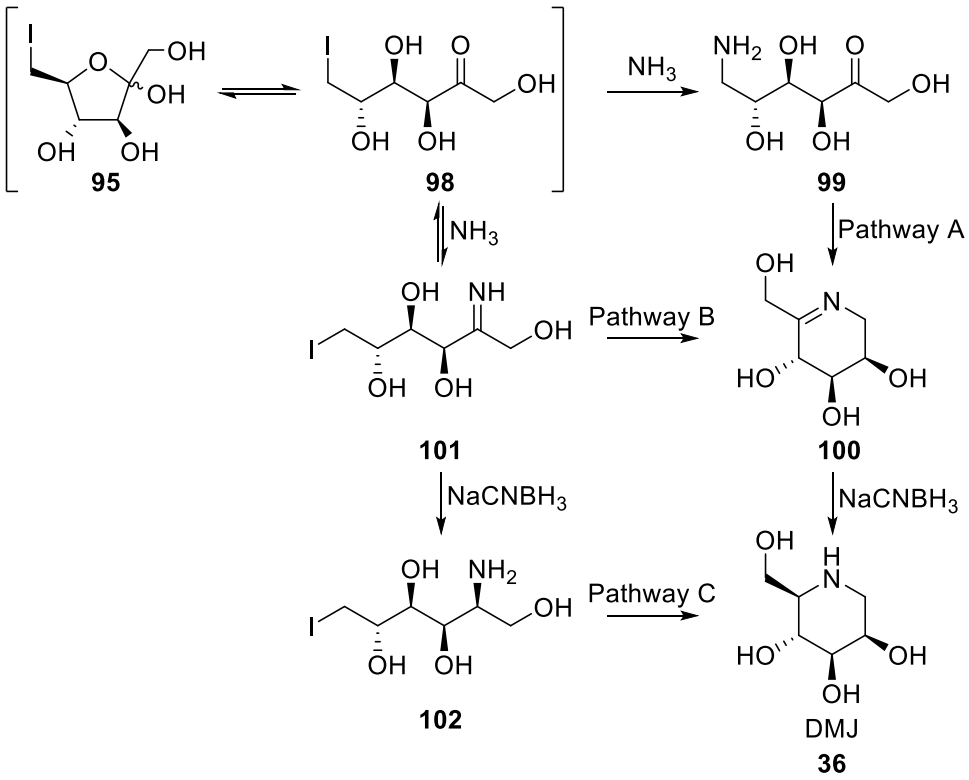
[e] iodofructoside **95** was formed unintentionally, neat, in the presence of I_2 and used without concentrating or purification

[f] iodofructoside **95** formed using optimised conditions, all reagents were added to the crude reaction mixture

In summary, the initially formed iodofructoside **95**, prepared *via* an *in situ* acid mediated deprotection of methyl iodofructoside **74**, can be converted to DMJ (**36**) over a two-step-one-pot reaction in 96% yield. As a result, the total synthesis of DMJ (**36**) is achieved over 3 steps in 62% overall yield from readily available D-fructose (**31**), representing the shortest and highest yielding total synthesis of DMJ (**36**) from readily available starting material. DMJ has been synthesised using various stratergies, the most comparable synthesis was published by Furneaux, Tyler, and Whitehouse, where their seminal synthesis gave DMJ (**36**) from D-fructose (**31**) in 5 steps and 25% overall yield.[120] Similarly, Maier, Anderson, and Lundt reported on DMJ synthesis over 7 steps and 35% overall yield from 1,5-anhydro-D-fructose.[123] Whilst difficult to discern if the work reported here bests all known enzymatic processes developed for the synthesis of other norijirymicins that could be employed for the synthesis of DMJ (**36**),[57, 59] the work reported here does improve on published DMJ (**36**) syntheses utilising enzymatic catalysis.[125, 126]

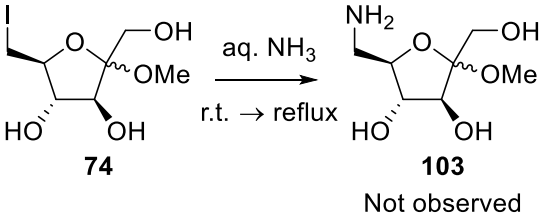
4.4 The mechanism of DMJ formation from 6-deoxy-6-iodo-D-fructose (94)

When examining how iodofructoside **95** can form DMJ (**36**) in the presence of only NH_3 and $NaCNBH_3$, it is important to note that there are three possible reaction pathways, each requiring a different sequence of imine formation, iodide substitution, and imine reduction (**Scheme 29**). Key in pathway A is the nucleophilic substitution of iodine in iodofructoside **95** (or linear ketone **98**) in the presence of NH_3 to form linear amine **99**, which then undergoes intramolecular imine formation to give cyclic imine **100** and subsequent stereoselective reduction to give DMJ (**36**). Pathway B begins with formation of linear imine **101** followed by intramolecular iodide substitution to again give cyclic imine **100**, which, following reduction, gives DMJ (**36**). Finally, pathway C also involves formation of linear amine **101**, with stereoselective reduction giving linear amine **102** and subsequent intramolecular iodide substitution giving DMJ (**36**).



*Scheme 29: The possible reaction pathways of DMJ (**36**) formation from 6-deoxy-6-iodo-D-fructose (**95**).*

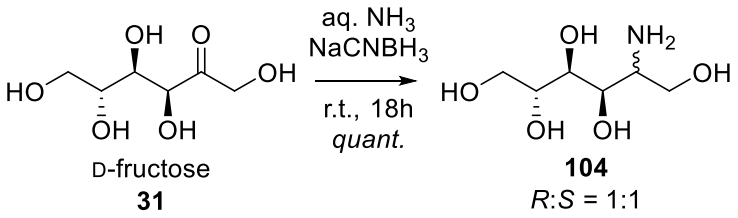
Examination of the mechanism for the synthesis of DMJ (**36**) from iodofructoside **95** began with exploring the likelihood of pathway A. To test the feasibility of NH_3 causing nucleophilic displacement of iodide, methyl iodofructoside **74** was subjected to concentrated aqueous NH_3 (**Scheme 30**). Despite extended reaction times and eventually bringing the reaction to reflux, no formation of amine **103** was observed. Thus, pathway A was considered unlikely.



*Scheme 30: The attempted synthesis of amine **103** via iodide displacement.*

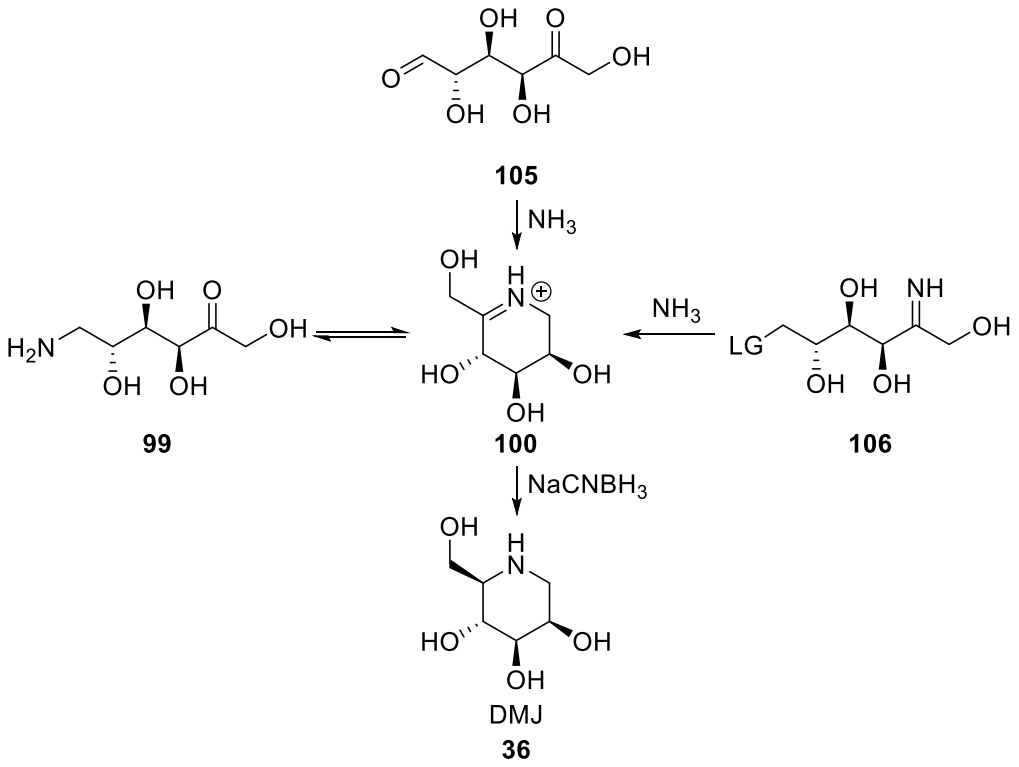
Next, the stereospecificity of pathway C was explored, whereby D-fructose (**31**) was exposed to the reductive amination conditions used to prepare DMJ (**36**) from iodofructoside **95** (**Scheme 31**). The resulting amine **104** was formed as a mixture of

diastereomers, with no apparent diastereoselectivity. This result is in agreement with the reductive amination studies described earlier in Chapters 2 and 3, however, the lack of stereoselectivity observed *en route* to the synthesis of DMJ (**36**) indicates that pathway C is unlikely.



*Scheme 31: Reductive amination of D-fructose (**31**).*

To provide evidence to support the likelihood of Pathway B being the mechanism that leads to the synthesis of DMJ (**36**), the relevant literature was examined. The key piece of evidence for the reaction following pathway B can be found by considering the stereoselective formation of DMJ (**36**). Previous syntheses of DMJ (**36**) resulting from the reduction of cyclic imine **100**, formed either *in situ* or through the use of protecting groups, demonstrated that reduction of cyclic imine **100** consistently favours the formation of DMJ (**36**, **Scheme 32**). Through amine instalation to generate ketone **99**,[120, 127] the *in situ* formation and subsequent reduction of cyclic imine **100** gave DMJ formation stereoselectively, with cyclic imine **100** being proposed as an intermediate during reduction. The use of a double reductive amination of di-carbonyl **105** to give DMJ is similarly postulated to pass through cyclic imine **100**.[128, 129] Here, the more reactive aldehyde at the 6-position is proposed to undergo reductive amination first (giving **99**), which after subsequent cyclisation, leads to the formation of cyclic imine **100**. Note however, that synthesis of DMJ (**36**) *via* double reductive amination is not stereoselective, with the DMJ 5-epimer having been isolated as a minor product from the reaction. The formation of the DMJ 5-epimer was considered a result of minor amounts of the ketone in di-carbonyl **105** undergoing a non-stereoselective reductive amination first. Lastly, cyclic imine **100** has been synthesised through the reaction of ketone **106** (*vide supra* Scheme 5, page 9)**.** Here, a protected imine equivalent of **106** was partially deprotected to undergo intramolecular displacement of a mesylate leaving group (LG) at the 6-position to generate the oxy-imine equivalent of cyclic imine **100**, which was actually isolated before being reduced.[130]



*Scheme 32: Strategies leading to the formation of cyclic imine **100** towards the synthesis of DMJ (**36**).*

All the publications that postulate or knowingly form, and subsequently reduce, cyclic imine **100** note that the preferential or selective formation of DMJ (**36**) is a result of conformation, where the lowest energy pathway of imine reduction occurs on a conformation with the maximum number substituents of cyclic imine **100** in a *pseudo*-equatorial orientation. Examining both possible conformers of cyclic imine **100** (**100a**, **100b**, **Figure 12**), conformer **100a** can undergo reduction from the *Re* or *Si* face, resulting in formation of **107a** and **36a** (respectively) and conformer **100b** can undergo *Re* or *Si* facial reduction to give **107b** and **36b** (respectively). Whilst **107a**,**b** and **36a**,**b** are just conformers of each other, it is the conformation during reduction that determines the relative transition state energies. Here, the conformer **100a** has the greatest number of substituents in *pseudo*-equatorial position, where reduction from the *Si* face of this conformer puts the bulky hydroxy methyl group (denoted R) into *pseudo*-equatorial orientation during the transition state, thus favouring formation of **36a**, and, in turn, DMJ (**36**).

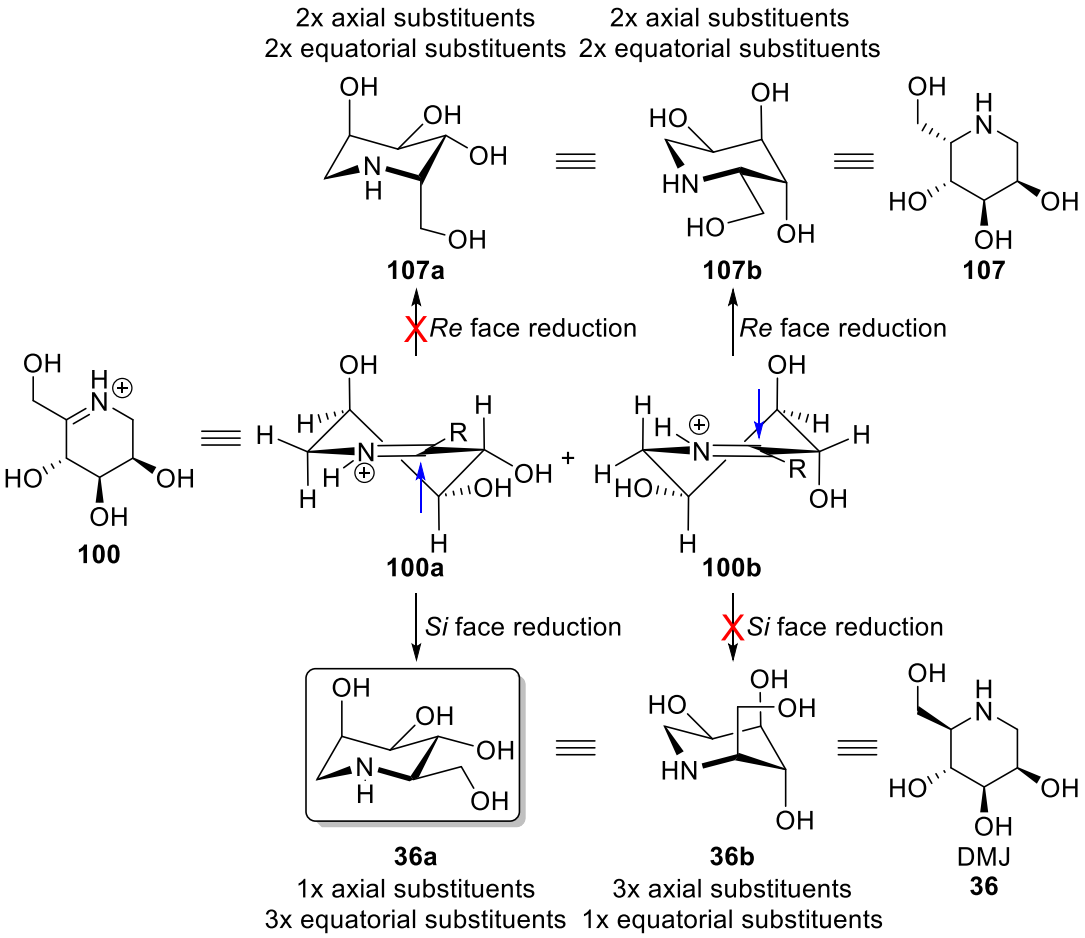
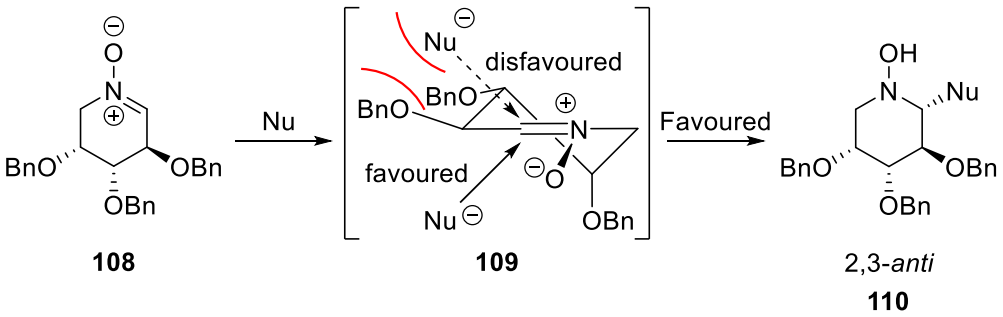


*Figure 12: possible conformers of cylic imine **100** and the possible reductions leading to DMJ (**36**) and the 4-epimer **107**.*

Whilst preferential formation of DMJ from the reduction of cyclic imine **100** has been explained by the impact of conformation on transition state energies, minimal attention has been given to the steric effects of the neighbouring 4-hydroxyl. Cheng *et al.* explored the steric factors impacting the nucleophilic attack of the related cyclic imine **108** (**Scheme 33**).[131] Here, the attack of a sterically bulky nucleophile (Nu, e.g. isopropylMgBr or BnMgBr) occurs preferentially from the opposite face of the neighbouring benzyl protected hydroxyl (**109**). As the Nu becomes smaller (e.g. vinylMgBr) facial selectivity is reduced, with the 2,3-*anti* adduct remaining the major product **110** (*anti*:*syn* 95:5, respectively). In the reduction of cyclic imine **100**, the major product DMJ (**36**) results from the attack of imine **100** from the more sterically hindered face, suggesting that conformation impacts the transition state energy greater than the minimal steric interactions between $NaCNBH_3$ and neighbouring 4-hydroxyl of imine **100**.



*Scheme 33: Synthesis of iminosugar derivatives (**110**) via the nucleophilic attack of cyclic imine **108**.*

Through the examination of each possible pathway, both observed results and literature suggest that iodofructoside **95** undergoes imine formation, intramolecular substitution, and finally stereoselective imine reduction to give DMJ. The stereoselective formation of DMJ is rationalised through cyclic imine **100** forming the conformation with the most substituents in *pseudo*-equatorial positions to reduce the transition state energy of imine reduction, with the unfavourable steric interactions between $NaCNBH_3$ and neighbouring 4-hydroxyl of imine **100** considered to have minimal effects**.** This theory implies that imine-mediated cyclisation of linear imine **101** to give cyclic imine **100** is faster than the reduction of **101** to give linear amine **102**, thus also suggesting that imine reduction is the rate determining step.

4.5 Conclusion

In conclusion, the acid-mediated degradation of methyl iodofructoside **74** lead to the discovery that iodofructoside **95** can be converted into DMJ (**36**) stereoselectively in one step when treated with NH_3 and $NaCNBH_3$. Iodofructoside **95** is proposed to form DMJ (**36**) through rapid imine formation, followed by intramolecular iodide substitution and subsequent stereoselective imine reduction. Here, reduction of cyclic imine **100** occurs on the conformer with the greatest number of substituents in *pseudo*-equatorial position, with reduction preferentially occurring from the face that puts the bulky hydroxy methyl group into *pseudo*-equatorial orientation, minimalising the resulting transition state energy. The disfavoured steric interactions between $NaCNBH_3$ and the neighbouring 4-hydroxyl of imine **100** are considered to have minimal impact on the transition state energy. After optimisation, the total synthesis of DMJ (**36**) from D-fructose (**31**) was

achieved over 3 steps in an impressive 62% overall yield. To date, this synthesis is the highest yielding and shortest synthesis of DMJ (**36**) from cheap, readily available starting materials. Moreover, the synthetic route is applicable to the synthesis of numerous other iminosugars and iminosugar derivatives.

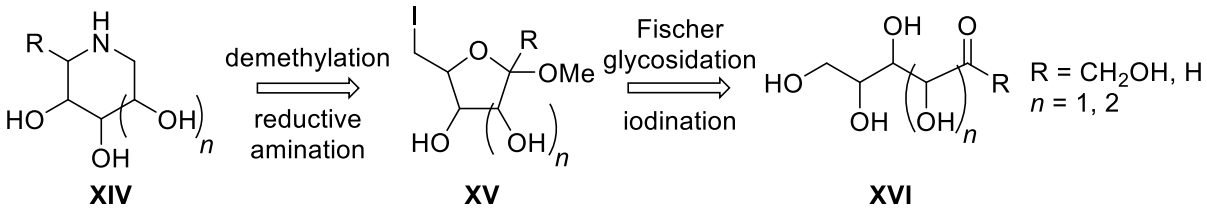
Chapter 5

Novel synthesis of piperidines and an azepane

5.1 Introduction and retro synthesis

During the synthesis of 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidines from D-fructose (Chapter 2), it was discovered that methyl 6-deoxy-6-iodo-D-fructofuranoside was acid labile. Furthermore, it was discovered that exposing the product resulting from acid-mediated degradation (6-deoxy-6-iodo-D-fructofuranoside) to reductive amination conditions gave DMJ selectively and in high yield (Chapter 4). As a result, a novel method of DMJ synthesis was developed, giving DMJ over 3 steps from D-fructose in 62% overall yield, and a mechanism was postulated that suggested the stereoselective formation of DMJ resulted from the selective reduction of a cyclic imine intermediate.

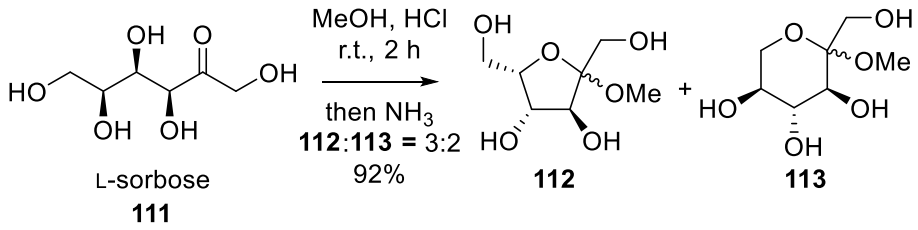
In this chapter, studies into the scope and limitations of this newly identified synthetic strategy will be presented. Thus, a general retrosynthetic strategy employing the aforementioned reductive amination methodology was proposed for the synthesis of a variety of iminosugars (Scheme 34). Here, the desired iminosugar **XIV** would be generated from the respective methyl iodoglycoside **XV** *via* demethylation and subsequent reductive amination, with methyl iodoglycoside **XV** being synthesised from a given naturally occurring carbohydrate **XVI** through Fischer glycosidation and subsequent iodination. Initially, it was desired to examine the effect of configuration on the efficiency and selectivity of imine reduction, thus syntheses beginning from various stereoisomers of D-fructose (n = 1, R = CH_2OH) would be performed. Following this, the scope of this synthetic strategy would be explored using various aldose sugar starting materials (n = 1 or 2, R = H).



Scheme 34: The retrosynthesis of iminosugars utilising the synthetic strategy developed in Chapter 4.

5.2 Synthesis of 6-deoxynojirimycin (DNJ)

First, the synthesis of 1-deoxynojirimycin from L-sorbose (**111**) was studied. Accordingly, L-sorbose (**111**) was subjected to previously reported[132] Fischer glycosidation conditions, which, after purification, gave α/β-furan methyl glycosides **112** in 55% yield (Scheme 35). Along with furans **112,** the pyran methyl sorbosides **113** were also formed (**112**:**113** = 3:2).

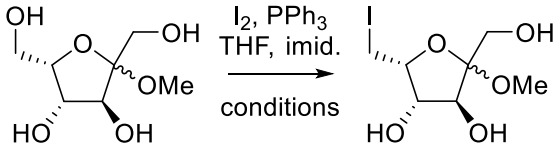


*Scheme 35: Fischer glycosidation of L-sorbose (**111**).*

Next, the iodination of methyl glycosides **112** was attempted. Initial attempts using previously optimised conditions on a mixture of impure methyl sorbosides **112** and **113** did not yield any desired methyl iodoglycoside **114**. As such, methyl sorbofuranosides **112** were isolated and iodination of this material attempted, first using PPh_3, I_2, and imidazole at 150 °C (entry 1, Table 5). Here, no desired product was observed, although TLC analysis revealed that methyl sorboside **112** was being consumed during the reaction. It was thought that either the starting materials or desired products were decomposing at the high reaction temperature (70 °C). Thus, iodination of methyl sorbosides **112** was attempted at the lower temperature of 55 °C (entry 2), with the desired product being isolated in a modest 35% yield. Using a higher number of equivalents of

iodine led to increased reaction yields to give methyl iodoglycoside **114** in an isolated yield of 78% (entry 3).

*Table 5: Iodination conditions for the formation of methyl iodosorbosides **114**.*

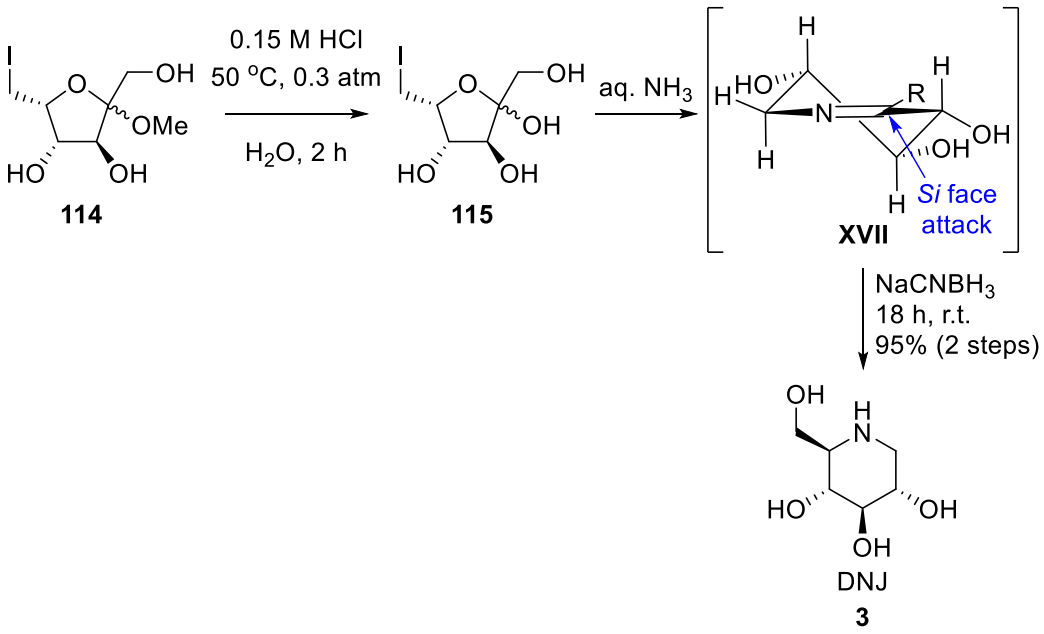


112 **114**

Entry	Reagents[a]	Temp (°C)	Yield
1	PPh_3 (2 equiv.) I_2 (1.5 equiv.)	70	NA
2	PPh_3 (2 equiv.) I_2 (1.5 equiv.)	55	35 %
3	PPh_3 (2.5 equiv.) I_2 (2 equiv.)	55	78%

a) All reactions used 3 equiv. of imidazole, in THF, with I_2 dissolve in THF and added dropwise to a heated solution of all other reagents.

With methyl iodosorboside **114** now in hand, the material was deprotected using previously optimised conditions to give full conversion to iodosorboside **115**, as observed by TLC (Scheme 36). Exposure of the crude iodosorboside **115** to reductive amination conditions, followed by purification using Dowex-H^+ ion exchange resin and silica gel flash column chromatography gave DNJ (**3**) in 95% yield from methyl iodosorboside **114**. As observed during DMJ synthesis (Chapter 4), the lowest energy pathway of imine reduction seems to occur *via* the conformation of cyclic imine **XVII.** Here, the maximum number of substituents of cyclic imine **XVII** are in a *pseudo*-equatorial orientation, with reduction occurring selectively at the *Si* face to put the bulky hydroxy methyl group (denoted R) also in a *pseudo*-equatorial orientation. As a result, the total synthesis of DNJ (**3**) was completed in 3 steps and 41% overall yield from cheap, readily available L-sorbose (**111**).



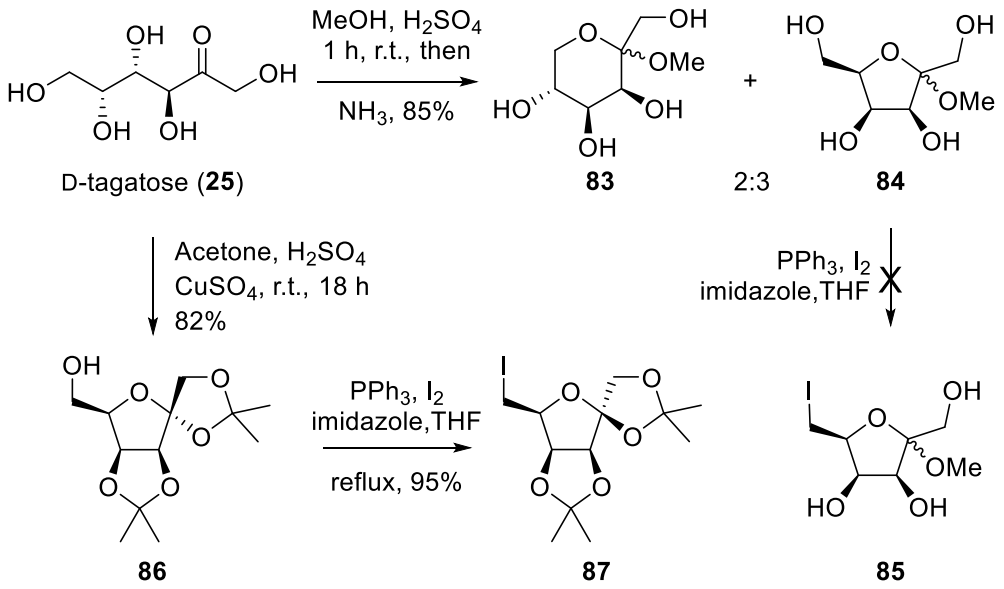
*Scheme 36: The synthesis of DNJ (**3**) from methyl iodosorboside **114**.*

Due to the valuable biological activity of DNJ (**3**) and its *N*-functionalised derivatives (see Chapter 1), much attention has been given to its synthesis. The shortest and highest yielding syntheses of DNJ and its respective *N*-functionalised derivatives currently belongs to strategies utilising enzyme catalysis (3 steps, 55-65% overall yields),[133-135] with Demailly reporting the most efficient synthesis of DNJ formation without the use of enzymes in 1989.[136] Here, Demailly synthesised DNJ in 4 steps and 54% overall yield from L-sorbose through azide functionalisation of the 6-position, followed by global deprotection and subsequent reduction. Thus, the formation of DNJ reported herein is comparable stepwise to the synthetic strategies utilising enzymes, and in yields comparable to those achieved by Demailly.

5.3 Synthesis of L-1-deoxygalactojirimycin (L-DGJ)

The synthesis of L-1-deoxygalactojirimycin (L-DGJ) began with D-tagatose (**25**). As previously described (Chapter 3), Fischer glycosidation of D-tagatose (**25**) showed modest selectivity for the formation of furan methyl glycosides **84** (Scheme 37), however, the subsequent iodination of methyl glycosides **84** proved difficult. Accordingly, D-tagatose (**25**) was protected using isopropylidene groups to give the protected tagatoside

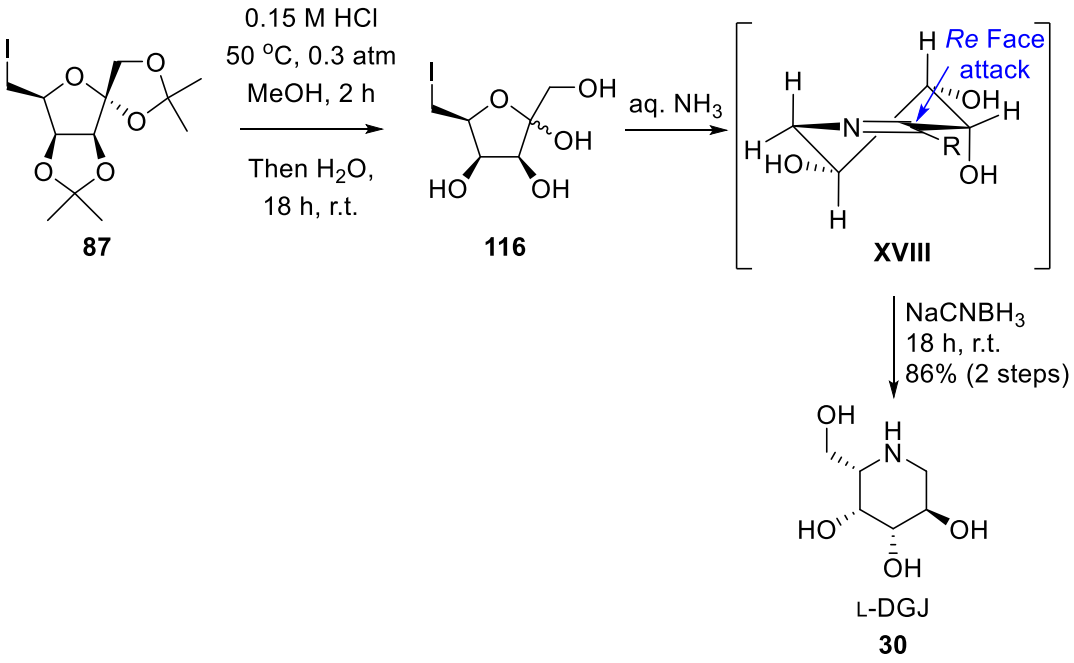
86, which was then iodinated at the 6-position to give protected iodotagatoside **87** in 78% yield over 2 steps.



*Scheme 37: Synthesis of methyl tagatosides **83** and **84** and isopropylidene-protected iodotagatoside **87** from D-tagatose (**25**).*

With protected iodotagatoside **87** in hand, subsequent acid-mediated deprotection was explored. Due to being water insoluble, protected iodotagatoside **87** was treated with 0.15 M HCl at 0.3 atm in a 50 ^{o}C water bath, with MeOH, rather than just H_2O, as the reaction solvent (**Scheme 38**). Monitoring the reaction by TLC indicated complete conversion of protected iodotagaside **87** to a mixture of partially deprotected iodoglycosides. Exposing this mixture to 0.15 M HCl in H_2O at room temperature for 18 hours was required to give complete conversion to iodotagatoside **116**, as observed by TLC. Following this, iodotagatoside **116** was subjected to the previously optimised reductive amination conditions involving treatment with NH_3 (aq.) and $NaCNBH_3$. Following purification of the resulting reaction mixture using Dowex-H^+ exchange resin and silica gel flash column chromatography, L-DGJ (**30**) was isolated in 86% yield (from protected iodotagatoside **87**) with trace amounts of an inseparable minor product. As with DMJ and DNJ, the formation of the major product L-DGJ appears to result from the reduction of cyclic imine **XVIII** from the face of the conformer that gives the greatest number substituents in *pseudo*-equatorial orientation. Unfortunately, at the time of submission, the minor product could not be separated from L-DGJ, where it is envisioned that further

optimisation may result in the total synthesis of L-DGJ (**30**) in 3 steps and approximately 67% overall yield from D-tagatose (**25**).

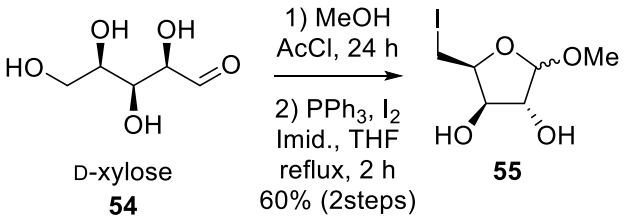


***Scheme 38**: The synthesis of L-DGJ (**30**) from protected iodoglycoside **87**.*

First synthesised in 1990,[137] L-DGJ (**30**) has since been identified as an inhibitor and molecular chaperone of galactosidases and galactotranserases.[138-141] Reports of L-DGJ (**30**) synthesis and biological testing are scarce,[142-146] with the most comparable and efficient synthesis being reported by Fleet in 2011,[147] with L-DGJ (**30**) being synthesised over 4 steps in 66% overall yield from D-tagatose (**25**). Thus, it is envisioned that further optimisation of the methods reported here may result in the total synthesis of L-DGJ (**30**) in 3 steps and an overall yield comparable to that reported in literature.

5.5 Synthesis of (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol

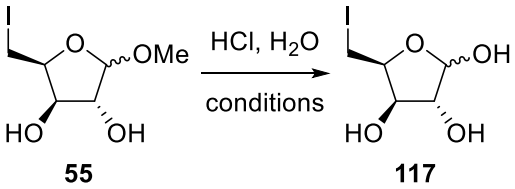
Following iminosugar synthesis from ketohexose sugars, the scope of this synthetic strategy using aldose carbohydrate starting materials was explored. To this end, it was proposed that (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol could be synthesised from D-xylose. As such, D-xylose (**54**) was subjected to AcCl in methanol to give methyl xylofuranoside which was subsequently iodinated using PPh_3 and I_2 in the presence of imidazole to give methyl iodoxyloside **55** in 60% yield (2 steps, Scheme 39).



*Scheme 39: Synthesis of methyl iodoglycoside **55** from D-xylose (**54**).*

Following the isolation of methyl iodoxyloside **55**, acid mediated demethylation was attempted. It was initially observed by TLC that exposing methyl iodoxyloside **55** to an aqueous 0.15 M HCl solution at a reduced pressure of 0.3 atm and 50 ^{o}C water bath gave minimal deprotection to iodoxyloside **117** (entry 1 **Table 6**). Next, methyl iodoxyloside **55** was exposed to the same reaction conditions but at double the HCl concentration (entry 2), which even after 7 hours showed minimal formation of iodoglycoside **117**. In an attempt to drive the reaction to completion, methyl iodoxyloside **55** was refluxed in a 0.3 M HCl solution (entry 4). Following the reaction by TLC showed complete conversion of methyl iodoxyloside **55** to iodoglycoside **117** after an hour.

***Table 6**: Optimisation of the demethylation of methyl iodoxyloside **55**.*



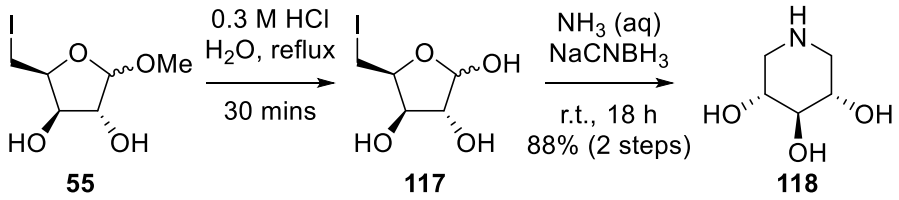
Entry	HCl conc.[a] (M)	Temp. (time)	Pressure[b] (atm)	Conversion[c]
1	0.15	50 ^{o}C (2 h)	0.3	<25%
2	0.3	50 ^{o}C (7 h)	0.3	50%
3	0.3	reflux (1 h)	1	100%

[a] All reactions done at a substrate dilution of 10 mL/mmol

[b] Reduced pressure achieved using a rotary evaporator

[c] As indicated by complete consumption of **25** by TLC

With the deprotection of methyl iodoxyloside **55** optimised, a solution of iodoxyloside **117** was exposed to NH_3 (aq.) and $NaCNBH_3$ at room temperature for 18 hours. Following purification *via* Dowex-H^+ and silica gel flash column chromatography, the (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (**118**) was isolated in 88% yield (53% overall yield).



***Scheme 40**: The synthesis of (3R,4r,5S)-piperidine-3,4,5-triol (**118**) from methyl iodoglycoside **55**.*

Here, triol **118** was identified as the major product using HRMS (*m/z* calcd. for $[C_5H_{11}NO_3+H]^+$: 134.0812, obsd.: 134.0808) and NMR spectroscopy. The ^1H NMR and ^{13}C NMR spectra of the highly symmetric (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (**118**) contained only four and three environments (respectively). More specifically, the ^1H NMR spectrum (Figure 13) indicated the presence of an ABNX system, with a ddd at 3.64 ppm coupling to the triplet at 3.40 ppm, which further couples to both of the remaining signals (dd) that were observed at 3.30 and 2.71 ppm. These proton environments all integrated for two protons except for the triplet at 3.40 ppm, which was assigned as the proton on the meso-chiral 4*r* center. (3*R*,4*r*,5*S*)-Piperidine-3,4,5-triol (**118**) belongs to the class of iminosugars, and was first synthesised in the 1960s.[1, 3, 4, 148] Historically, the shortest and highest yielding synthesis of (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (**118**) was reported by Ganem, whereby the iminosugar was prepared in 5 steps and 40% overall yield from methyl 6-deoxyl-6-bromo-α-D-glucopyranoside.[149] Thus, the preparation of (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol described here is the shortest and highest yielding synthesis reported to date.

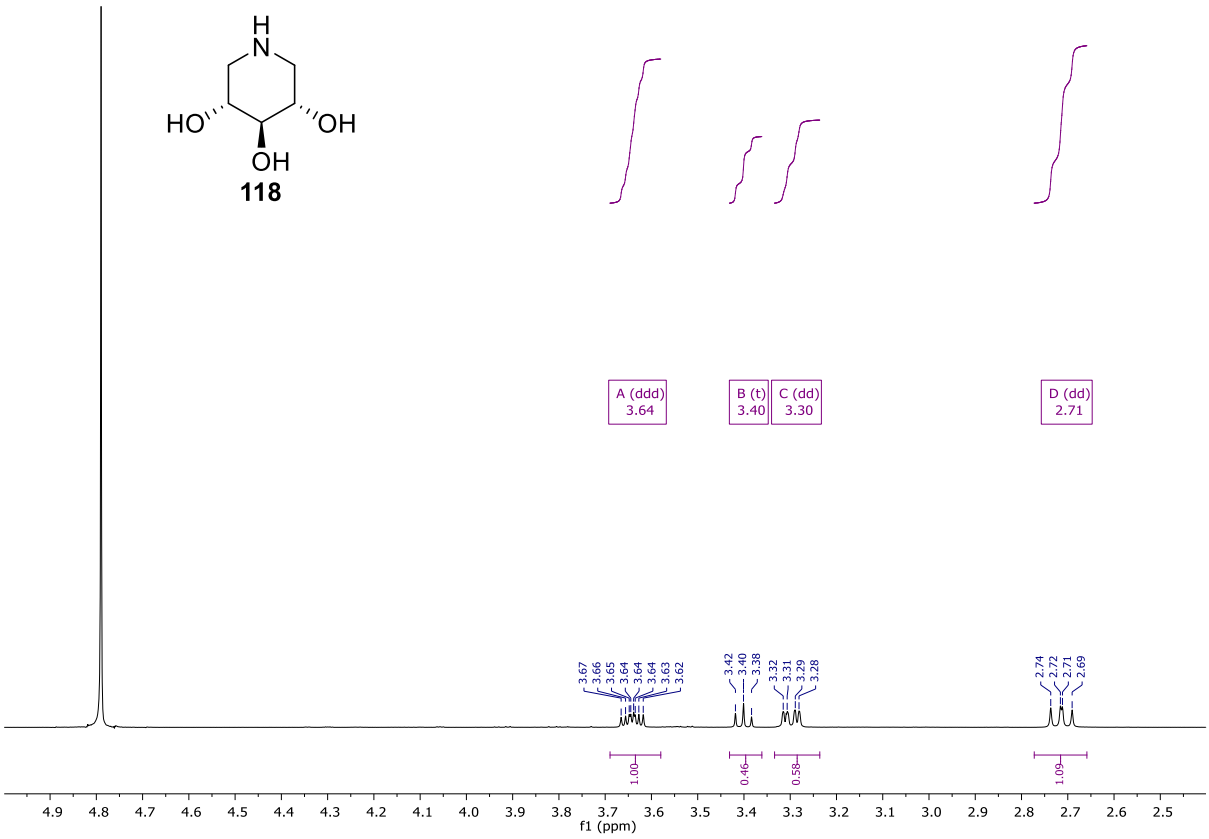
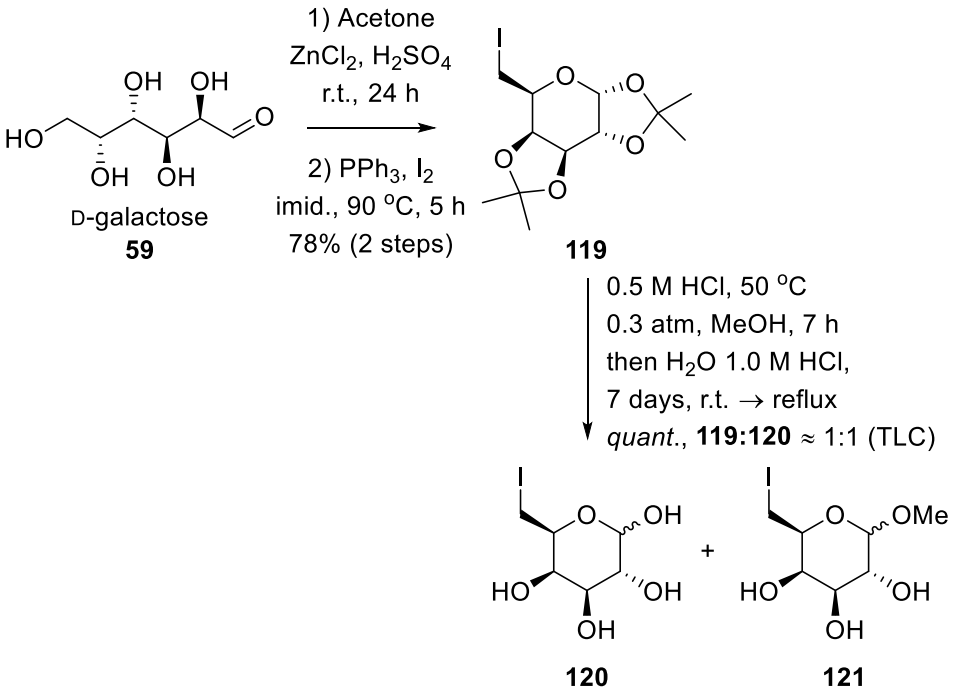


*Figure 13: ^{1}H NMR spectrum of (3R,4r,5S)-piperidine-3,4,5-triol (**118**)*

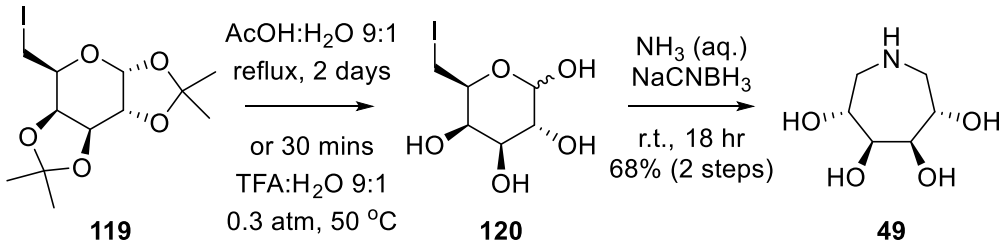
5.6 Synthesis of (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol

Following the successful synthesis of (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (**118**) from D-xylose (**54**), the synthesis of an azepane from an aldohexose carbohydrate was attempted. The difficulty associated with demethylation of aldohexoses has been well documented,[118] thus, azepane synthesis was initially attempted *via* the use of an aldohexose with the more acid labile isopropylidene protecting group at the 1- and 2-positions. Accordingly, D-galactose (**59**) was isopropylidene protected and iodinated at the 6 position to give protected iodogalactoside **119** in 78% yield (2 steps) using previously reported methods (**Scheme 41**).[63] Exposing iodogalactoside **119** to a methanolic 0.5 M HCl solution in the presence of water at 0.3 atm in a 50 °C water bath for 7 hours resulted in a 1:1 mixture of the desired iodogalactoside **120** and stable methyl iodogalactcoside **121**. Subsequent treatment of this mixture with 1.0 M HCl in H_2O did not alter the ratio of **120** and **121**, despite keeping the reaction at reflux for 7 days.



*Scheme 41: The synthesis and subsequent acid mediated deprotection of isopropylidene protected iodogalactoside **119** from D-galactose (**59**).*

As methyl iodogalactoside **121** was forming as a result from the use of methanol during deprotection of protected iodogalactoside **119**, an alternative method for the removal of the isopropylidene groups was sought. It was reported previously that isopropylidene deprotection was viable by dissolving isopropylidene-protected glycosides in a 9:1 mixture of AcOH:H_2O and bringing the mixture to reflux for 2 days. As such, subjecting protected iodogalactoside **119** to these conditions showed full conversion (*via* TLC) to iodogalactoside **120** after 2 days (**Scheme 42**). Whilst successful, it was thought that the deprotection of iodogalactoside **119** could be achieved more rapidly using a stronger acid. To this end, protected iodogalactoside **119** was dissolved in a 9:1 mixture of TFA:H_2O at 50 °C and 0.3 atm.[150] Analysis by TLC revealed complete conversion of protected iodogalactoside **119** to iodogalactoside **120** after 30 minutes, with **120** being isolated following a CH_2Cl_2:H_2O extraction and subsequent concentration *in vacuo*. This represents the first known isolation of iodogalactoside **120**. Next, iodogalactoside **120** was exposed to the reductive amination conditions using NH_3 (aq.) and $NaCNBH_3$ at r.t. for 18 hours. Following purification by Dowex-H^+, which required careful elution (0.1% NH_3), pure (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) was isolated in 68% yield (in 2 steps from protected iodogalactcoside **119**). As such, azepane **49** was synthesised over 4 steps and 55% overall yield from readily available D-galactose (**59**).



*Scheme 42: Formation of (3S,4R,5S,6R)-azepane-3,4,5,6-tetraol (**49**) from protected iodoglycoside **119**.*

Key in the identification of (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) as the major product was HRMS (*m/z* calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0921) coupled with NMR analysis, which suggested a highly symmetrical compound with four and three distinct environments observed in ^1H and ^{13}C NMR spectra, respectively. In the ^1H NMR spectrum (**Figure 14**), four environments that each integrated for one proton were observed, which was identified as an ABNX system. The synthesis of (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) reported here is comparable to the most efficient synthesis of **49** that was reported by Wong and co-workers that was achieved in 4 steps and 63% overall yield from D-galactose (**59**).[151] In the same communication, azepane **49** was shown to inhibit numerous glycosidases, including α- and β-galactosidase, β-glucosidase, and α-fucosidase.

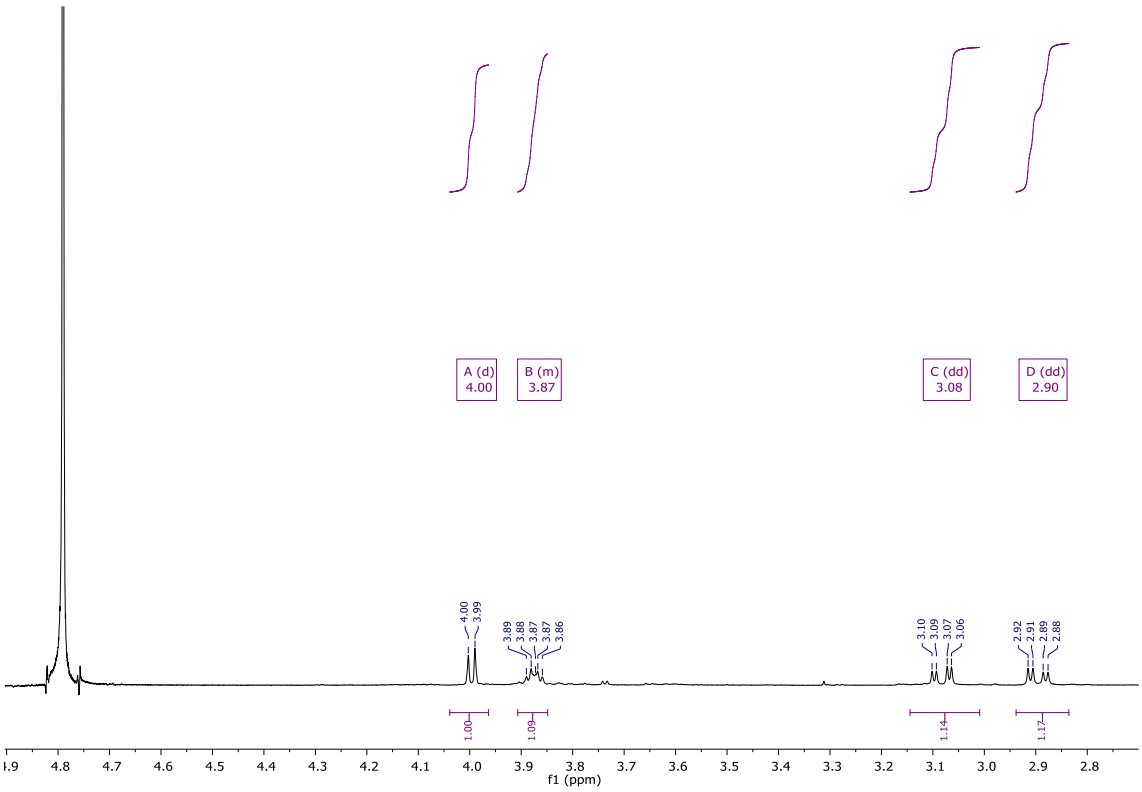
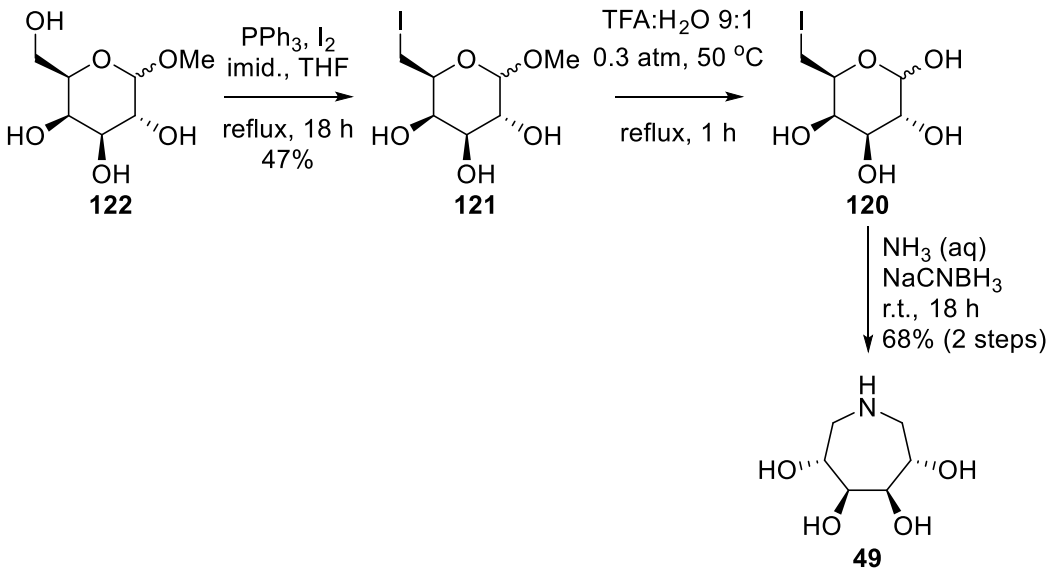


*Figure 14: ^{1}H NMR spectrum of (3S,4R,5S,6R)-azepane-3,4,5,6-tetraol (**49**).*

Following the successful synthesis of (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**), it was desired to achieve the synthesis of this compound *via* methyl iodogalactoside **120** in order to eliminate the need for isopropylidene protecting groups. First, methyl iodoglycoside **121** was synthesised from the respective methyl galactoside **122** *via* selective iodination of the 6-position using PPh_3 and I_2, which was achieved in 47% yield. Following isolation, methyl iodogalactoside **121** was exposed to a 9:1 mixture of TFA:H_2O at 0.3 atm in a 50 ^{o}C water bath (**Scheme 43**). Pleasingly, exposure of methyl iodogalactoside **121** to these conditions gave complete conversion to iodogalactoside **120** after an hour (observed *via* TLC). Subsequent CH_2Cl_2/H_2O extraction and treatment of iodoglycoside **120** to reductive amination conditions once again gave (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) in a 69% yield (2 steps), and 32% overall yield from methyl galactoside **122**.



***Scheme 43**: The synthesis of (3S,4R,5S,6R)-azepane-3,4,5,6-tetraol (**49**)* via *methyl iodogalactoside **121**.*

Gratifyingly, this result confirmed that azepane synthesis *via* aldohexose-derived methyl iodoglycosides was possible. However, comparing the two routes developed for the synthesis of (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) revealed that the use of isopropylidene protecting groups was more efficient. Here, it was the yield of iodinating methyl galactoside **122** that made the synthesis of iodogalactoside **121** lower than that of protected iodogalactcoside **119**, an observation that has been previously reported by the Stocker-Timmer group.[112] Thus, it is foreseeable that where iodination of the respective methyl glycoside is high yielding, efficient azepane synthesis would be achievable.

5.8 Conclusion

In summary, DNJ (**3**) and L-DGJ (**30**) were synthesised from cheap, readily available carbohydrates in a 4 step-3 pot fashion and 44% and 67% overall yield (respectively) using the synthetic strategy developed in Chapter 4. Examining the major product resulting from reductive amination of each synthesised iodoglycoside, in combination with the result observed during DMJ synthesis described in chapter 4, further suggested that reduction occurs with the most substituents in *pseudo*-equatorial position, where the steric effects of the neighbouring 4-hydroxyl appeared to be minimal. Following this, iminosugar synthesis beginning from aldose sugars was successfully achieved, with

(3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (**118**) and (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (**49**) having been synthesised in 3 steps and both in 53% overall yield and of which are the most step efficent and highest yielding. Additionally, the isolation of the potentially useful synthon 6-dexoy-6-iodo-galactose was achieved for the first time. However, it is most notable that all of the total syntheses reported here are in comparable or greater yields and step efficientcy than that of current literature, validating the power and scope of the explored synthetic strategy.

Chapter 6

Conclusions and future prospects

6.1 Conclusion

The overall objective of this thesis was to develop synthetic methodology that would allow for the rapid synthesis of iminosugars through minimalising the use of protecting groups. Initially, the PGF Vasella-reductive-amination and carbamate annulation methodologies developed in the Stocker-Timmer research group were exemplified and applied to the efficient synthesis of 2,5-dideoxy-2,5-imino-L-iditol and 2,5-dideoxy-2,5-imino-D-altritol. From this work came the discovery and development of a novel imine-ring-closing methodology, which was subsequently used for the efficient synthesis of 1-deoxymannojirimycin (DMJ), 1-deoxynojirimycin (DNJ), L-1-deoxygalactojirimycin (L-DGJ), (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol, and (3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol.

In **Chapter 2** a synthetic strategy was developed for the synthesis of 2,5-dideoxy-2,5-imino-L-iditol from D-fructose utilising PGF Vasella-reductive-amination and carbamate annulation methodologies. Key in the development of the Vasella-reductive-amination of ketones (as compared to aldehydes) was the use of acidic conditions (pH = 6). Moreover, diphenylmethylamine, rather than NH_3, was required to generate alkenylamine diastereoisomers that could be subsequently separated by silica gel flash column chromatography. Following this, the carbamate annulation of each alkenylamine was explored. It was demonstrated that the I_2-mediated carbamate annulation favours the formation of pyrrolidines with a 2,5-*trans*, 3,4-*cis* relationship, and when in competition,

the 2,5-steric interaction overrides the electronic 3,4-*cis* effect of the allylic alcohol. In summary, 2,5-dideoxy-2,5-imino-L-iditol was synthesised in 6-steps and in 18% overall yield from D-fructose, utilising minimal protecting groups.

The synthetic strategy developed for the synthesis of 2,5-dideoxy-2,5-imino-L-iditol was applied to the synthesis of 2,5-dideoxy-2,5-imino-D-altritol in **Chapter 3**. Beginning from D-tagatose, the application of the PGF Vasella-reductive-amination to 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-tagatose resulted in dimerisation *via* a Wurtz-type coupling reaction, thereby requiring the Vasella and reductive amination reactions to be performed sequentially. The reductive amination of the intermediate isopropylidene-protected alkenylketone, however, was stereoselective, which can be attributed to chelation control and the use of a bulky nucleophile such as diphenylmethylamine. The subsequent carbamate annulation again favoured the 2,5-*trans*, 3,4-*cis* relationship, allowing for the total synthesis of 2,5-dideoxy-2,5-imino-D-altritol in 7 steps and 22% yield, the shortest and highest yielding synthesis of this iminosugar to date.

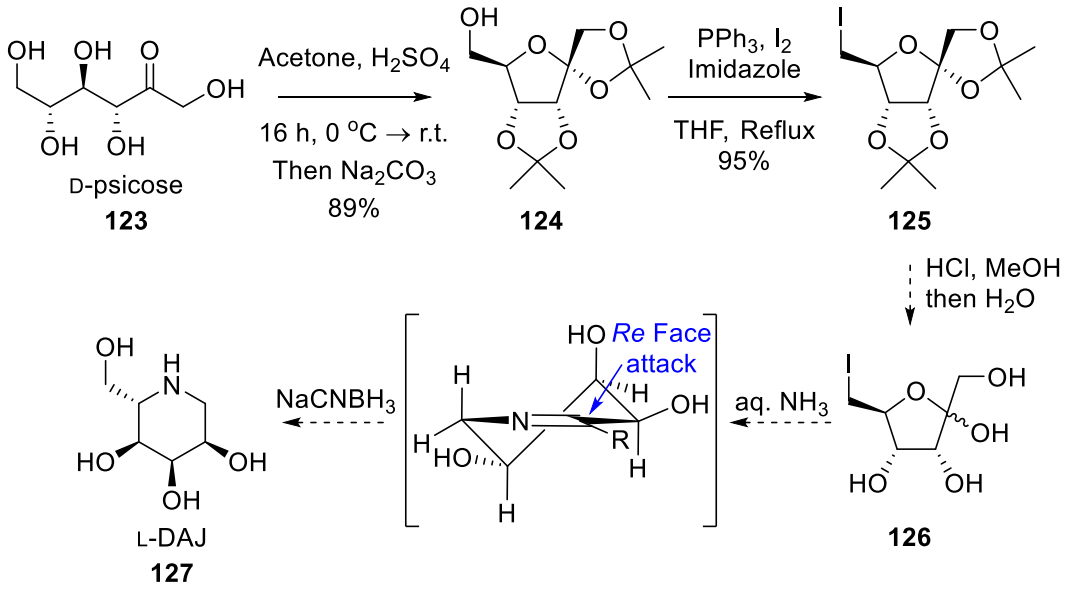
Chapter 4 describes the identification and attempted Vasella-reductive-amination of a decomposition product isolated from a synthetic intermediate used in the synthesis of 2,5-dideoxy-2,5-imino-L-iditol. The product resulting from the attempted Vasella-reductive-amination of 6-deoxy-6-iodo-D-fructose led to the discovery of novel imine-ring-closing methodology, which allowed for the shortest and highest yielding synthesis of DMJ to date (3 steps, 62% overall yield). Further investigation of this imine-ring-closing methodology suggested that the reaction occurs *via* imine formation, and intramolecular substitution, followed by stereoselective reduction. Here, stereoselective reduction occurs from the lowest energy transition state, which has the imine adopting a conformation with the greatest number of substituents in *pseudo*-equatorial position. Reduction with a small reducing agent, such as $NaCNBH_3$, then occurs from the face that will result in the bulky hydroxy methyl group being in the equatorial orientation.

Lastly, **Chapter 5** explores the scope and application of the imine-ring-closing methodology through the use of numerous carbohydrate starting materials. First, DNJ and L-DGJ were synthesised from inexpensive, readily available carbohydrates in 3 steps and in 44% and 67% overall yield, respectively. Once again, reduction of the respective cyclic imines preferentially occurred from the transition state which had the most substituents in *pseudo*-equatorial positions, and where the resulting hydroxymethyl substituent would be in the equatorial orientation. Following this, (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol and

(3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol were synthesised from D-xylose and D-galactose, respectively, both in 3 steps and in 53% overall yield. The total syntheses of these two iminosugars reported herein are the most step efficient and highest yielding reported to date. Additionally, isolation of the useful synthon 6-dexoy-6-iodo-D-galactose was achieved for the first time.

6.2 Future prospects

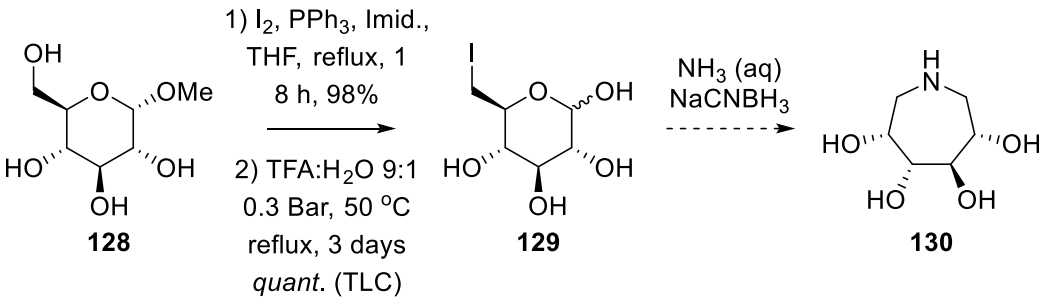
The scope of the imine-ring-closing methodology is not limited to the synthesis of the iminosugars described above. For example, a similar synthetic strategy commencing with D-psicose would be expected to yield L-1-deoxyallonojirimicin (L-DAJ, **Scheme 44**). Preliminary results indicated that D-psicose (**123**) can be isopropylidene protected (→**124**), followed by iodination to give protected iodopsicoside **125** in 85% yield (2 steps). While the acid mediated deprotection (→**126**) and subsequent reductive amination of protected iodopsicoside **125** has yet to be optimised, the major product from this reaction is expected to be L-DAJ (**127**), which would result from reduction from the *Re* face of the cyclic imine containing the most substituents in *pseudo*-equatorial position.



*Scheme 44: Proposed synthesis of L-1-deoxyallonojirimicin (L-DAJ, **127**) from D-psicose (**123**).*

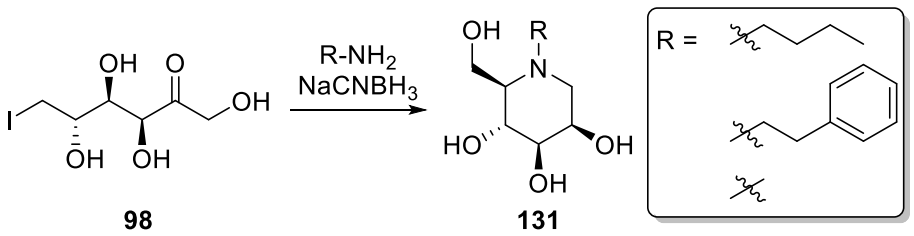
Similarly, it is it is conceivable that additional azepanes could be synthesised using analogous methodology. For example, the commercially available methyl α-D-

glucopyranoside (**128**, **Scheme 45**) can be iodinated selectively at the 6-position followed by TFA-mediated demethylation to give 6-deoxy-6-iodo-D-glucose (**129**) as a white crystalline solid in excellent overall yield. At the time of submission, the reductive amination of 6-deoxy-6-iodo-D-glucose **129** to give the expected product (3*S*,4*R*,5*R*,6*R*)-azepane-3,4,5,6-tetraol (**130**) remains unoptimised, however it is envisioned that this route could give azepane **130** in very high overall yields in only 3 steps. It is also viable that other iminosugars such as (3*R*,5*R*)-piperidine-3,4,5-triol, (3*R*,4*s*,5*S*)-piperidine-3,4,5-triol, or 1-deoxygalactojirimycin (DGJ) could be prepared from D-arabinose, D-ribose, and L-tagatose, respectively, by applying the aforementioned synthetic strategy utilising the imine-ring-closing methodology.



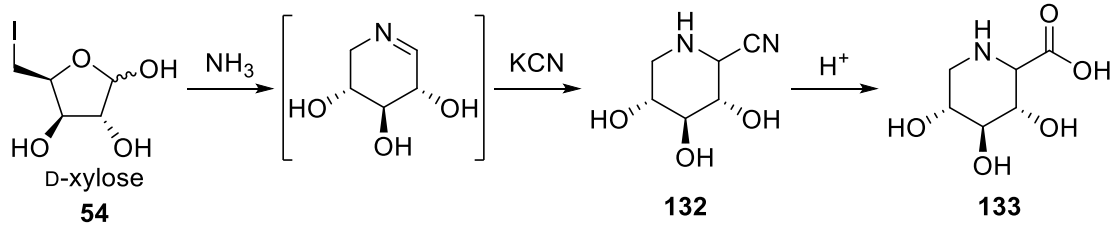
*Scheme 45: Proposed synthesis of (3S,4R,5R,6R)-azepane-3,4,5,6-tetraol (**130**) from commercially available methyl α-D-glucopyranoside **128**.*

In addition to applying the imine-ring-closing methodology to the synthesis of additional iminosugars, it is envisioned that the use of various of primary amines in place of NH_3 during the reductive amination could directly lead to a series of *N*-functionalised iminosugars, without the need for additional steps. For example, using *N*-phenylethylamine, *n*-butylamine, and methylamine during the reductive amination of 6-deoxy-6-iodo-D-fructose (**98**) should allow for the synthesis of *N*-phenylethyl, *N*-butyl, and *N*-methyl derivatives of DMJ (**131**, Scheme 46). Given the importance of DMJ and related analogues for the inhibition of mannosidase enzymes associated with viral and fungal infection[152], the efficient synthesis of such derivatives could find wide application.



*Scheme 46: Proposed synthesis of N-functionalised derivatives of DMJ (**131**) directly from 6-deoxy-6-iodo-D-fructose (**98**)*

Finally, building on the studies by Cheng et al.,[131] it is possible that a variety of iminosugar derivatives could be prepared by reacting different nucleophiles, in place of $NaCNBH_3$, with an in situ formed cyclic imine. For example, exposing 5-deoxy-5-iodo-D-xylose (**54**) to NH_3 and KCN in a stepwise fashion should result in the synthesis of (3S,4S,5R)-3,4,5-trihydroxypiperidine-2-carbonitrile (**132**), which after exposure to acid would give (3S,4S,5R)-3,4,5-trihydroxypiperidine-2-carboxylic acid (**133**, Scheme 47). While the biological applications of such compounds are relatively unexplored, with only two papers having been published on the biological testing of carboxylic acids **133** thus far,[153, 154] the efficient synthesis of such derivatives would greatly facilitate further biological investigations into these and other novel compounds.



*Scheme 47: Proposed synthesis of (3S,4S,5R)-3,4,5-trihydroxypiperidine-2-carboxylic acid (**133**) from 5-deoxy-5-iodo-D-xylose (**54**).*

Chapter 7

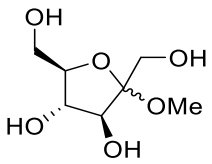
Experimental

7.1 Experimental details:

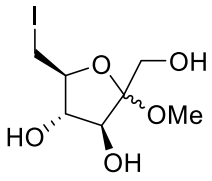
Unless otherwise stated all reactions were performed under atmospheric air. THF (Lab-Scan) was distilled from activated zinc prior to use. MeOH (Pure Science), EtOH (absolute, Pure Science), AcOH (Lab Scam), CH_2Cl_2 (LabServ), 30% aqueous NH_3 (Fisher Science), isopropanol (BDH), triethylsilane (Fluka), D-fructose (carbosynth), D-xylose (carbosynth), D-galactose (carbosynth), $NaCNBH_3$ (Aldrich), imidazole (Aldrich), I_2 (BDH), Triphenyl phosphine (Acros), $AcONH_4$ (Aldrich), aqueous 35% HCl (Univar), and 98% H_2SO_4 (Panreac) were used as received. D-tagatose (carbosynth), NaOH (Pure Science), $Ti(O^iPr)_4$ (Aldrich), anhydrous $Cu^{II}SO_4$ (Scientific & chemical supplies), TFA (Aldrich), aminodiphenylmethane (Aldrich), were used as received. Drum Pretrolium ether, and ethyl acetate were distilled before use. Distilled H_2O was generated using a Millipore RiOs 8 purifier. Zn dust was activated by the careful addition of conc. H_2SO_4 to Zn powder in the presence of ethanol, the solid decanted, washed with ethanol, diethyl ether, and then finally washed (and stored) in petroleum ether. All solvents were removed by evaporation under reduced pressure (*in vacuo)*. Reactions were monitored by TLC-analysis on Macherey-Nagel silica gel coated plastic sheets (0.20 mm, with fluorescent indicator UV254) with detection by UV-absorption (254 nm), by dipping in 10% H_2SO_4 in MeOH or 3% ninhydrin in EtOH followed by charring at ~150 °C. Column chromatography was performed on Pure Science silica gel (40-63 micron). DOWEX®

H^+ 50wx8-100 ion exchange resin was activated by 1-hour exposure to 1 M HCl. High-resolution mass spectra were recorded on a Waters Q-TOF PremierTM Tandem Mass Spectrometer using positive electro-spray ionisation. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter at the sodium D-line. Infrared spectra were recorded as thin films using a Bruker Tensor 27 FTIR spectrometer, equipped with an Attenuated Total Reflectance (ATR) sampling accessory, and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at 20 °C in $CDCl_3$ or D_2O using either a Varian Unity-INOVA operating at 300 MHz or a Varian Unity operating at 500 MHz. Chemical shifts are given in ppm (δ) and are relative to chloroform or water, all given ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY, HSQC, and HMBC experiments.

7.2 Chapter 2 experimental

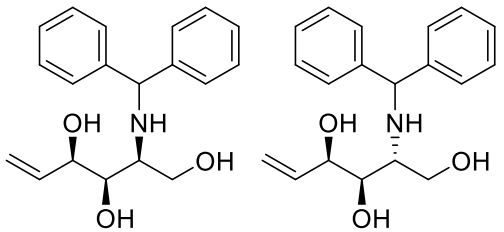


Methyl D-Fructofuranoside (**72**). D–Fructose (**31**) (3.6 g, 20 mmol) and H_2SO_4 (1.0 mL, 18 mmol) were added to 200 mL of MeOH. After the solution was stirred for 15 min, aq. NH_3 (4 mL, 30%) was added, the reaction concentrated to ~50 mL *in vacuo*, cooled over ice, filtered, and finally concentrated *in vacuo*. The remaining oil was purified over by silica gel flash column chromatography (EtOAc\MeOH 99\1 to 95\5 v\v) to afford **72** in an anomeric mixture (3.43 g, 87%). α-anomer, R_f = 0.57, β-anomer, R_f = 0.70 (EtOAc*i*PrOH\H_2O 6\4\1 v\v\v). IR and NMR spectral data matched those previously reported.[72] HRMS: *m/z* calcd for $[C_7H_{14}O_6+Na]^+$: 217.0682, obsd.: 217.0690.



Methyl 6-deoxy-6-iodo-D-Fructofuranoside (**74**). Methyl glycoside **72** (2.02 g, 10.5 mmol), PPh_3 (4.12 g, 15.7 mmol), and imidazole (1.54 g, 20.9 mmol) were dissolved in dry THF (84 mL) and brought to reflux. A solution of I_2 (3.99 g, 15.7 mmol) in THF (42 mL) was added drop wise (1 drop every 4 seconds) to the refluxing solution. The resulting solution was refluxed for a further 10 mins, cooled to room temperature, filtered over celite (washing with THF), and concentrated *in vacuo*. The remaining orange oil was purified *via* normal (Petroleum ether\EtOAc 4\1 to 1\2 v\v) and reverse (H_2O\MeOH 100\0 to 9\1 v\v) phase column chromatography, affording an anomeric mixture of iodo glycoside **74** (2.37 g, 75% yield), α-**74**, R_f = 0.34, β-**74**, R_f = 0.29 (DCM\MeOH 5\1 v\v). Spectral data matched those previously reported.[73] IR (film) 3350, 2895, 1462, 1039, 1031 cm^{-1}. α-**74** ^{1}H-NMR

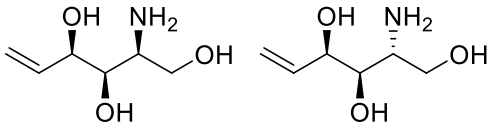
(500 MHz, D_2O) δ 4.16 (d, $J_{3,4}$ = 2 Hz, 1H, H-3), 3.93-3.89 (m, 2H, H-4, H-5), 3.79 (d, $J_{1a,1b}$ = 12.5 Hz, 1H, H-1a), 3.68 (d, $J_{1b,1a}$ = 12.5 Hz, 1H, H-1b), 3.49 (dd, $J_{6a,6b}$ = 4.5 Hz, $J_{6b,5}$ = 10.5 Hz, 1H, H-6a), 3.41-3.41 (m, 1H, H–6b), 3.32 (s, 3H, OMe). ^{13}C-NMR (125 MHz, D_2O) δ 108.1 (C-2), 81.7 (C-5), 80.7 (C-4), 80.4 (C-3), 57.7 (C-1), 48.2 (OMe), 5.2 (C-6). β-**74** ^{1}H-NMR (500 MHz, D_2O) δ 4.20 (d, $J_{3,4}$ = 8 Hz, 1H, H-3), 4.06 (t, $J_{4,3}$ = 8 Hz, 1H, H-4), 3.88-3.84 (m, 1H, H-5), 3.71 (d, $J_{1a,1b}$ = 12.5 Hz, H-1a), 3.66 (d, $J_{1b,1a}$ = 12.5 Hz, H-1b), 3.49 (dd, $J_{6a,6b}$ = 4.5 Hz, $J_{6b,5}$ = 10.5 Hz, 1H, H-6a), 3.41-3.41 (m, 1H, H-6b), 3.36 (s, 3H, OMe). ^{13}C-NMR (125 MHz, D_2O) δ 103.7 (C-2), 80.1 (C-5), 78.6 (C-4), 77.0 (C-3), 59.4 (C-1), 49.3 (OMe), 6.9 (C-6). HRMS: *m/z* calcd. for $[C_7H_{13}IO_5+Na]^+$: 326.9699, obsd.: 326.9704.



78a **78b**

(*2S,3R,4R*)-2-(Diphenylmethyl)amino-hex-5-ene-1,3,4-triol (78a) and (*2R,3R,4R*)-2-(Diphenylmethyl)amino-hex-5-ene-1,3,4-triol (78b). A solution of methyl iodofructosides **74** (0.514 g, 1.69 mmol), activated Zn (1.108 g, 16.9 mmol), Ph_2CHNH_2.HCl (1.862, 8.45 mmol), and $NaCNBH_3$ (0.425 g, 6.76 mmol) in EtOH (34 mL) was refluxed for 18 hours, cooled, filtered over celite, then concentrated *in vacuo*. The remaining mixture was dissolved in DCM (50 mL) and washed with a saturated solution of Na_2CO_3\Na_2SO_3\NaCl, 1\1\1, v\v\v (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting colourless oil was purified *via* silia gel flash column chromatography to give **78a** (0.269 g, 0.85 mmol) and **78b** (0.183 g, 5.86 mmol) in 51% and 35% yield, respectively. 78a R_f = 0.4 (DCM\EtOH\MeOH\30% aq. NH_3 45\2\2\1 v\v\v\v). $[\alpha]_D^{20}$ + 80.1 (c = 0.48, DCM). IR (film) 3552, 3113, 3052, 2891, 1636, 1547, 1088 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.54-7.13 (m, 10H, Ph-H), 5.81 (ddd, $J_{5,4}$ = 4.4 Hz, $J_{5,6b}$ = 10.6 Hz, $J_{5,6a}$ = 17.0 Hz, 1H, H-5), 5.45 (d, $J_{6a,5}$ = 17.2 Hz, 1H, H-6a), 5.27 (d, $J_{6b,5}$ = 10.6 Hz, 1H, H-6b), 5.05 (s, 1H, H7), 4.31 (t, $J_{4,5}$ = $J_{4,3}$ = 4.6 Hz, 1H, H-4), 3.97 (dd, $J_{1a,2}$ = 4.3 Hz, $J_{1a,1b}$ = 11.8 Hz, 1H, H-1a), 3.77 (dd, $J_{1b,2}$ = 1.7 Hz, $J_{1b,1a}$ = 11.8 Hz, 1H, H-1b), 3.71 (bs, 1H, H-3), 2.78-2.76 (m, 1H, H-2). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 143.3 (C-Ph), 141.8 (C-Ph), 136.8 (C-5), 128.9-126.9 (C-Ph), 116.6 (C-6), 75.1 (C-3), 74.3 (C-4), 64.0 (C-7), 61.7 (C-1), 57.8 (C-2). 78b R_f = 0.39 (DCM\EtOH\MeOH\30% aq. NH_3 45\2\2\1 v\v\v\v). $[\alpha]_D^{20}$ – 6.1 (c =

0.65, DCM). IR (film) 3537, 3098, 3052, 2898, 1636, 1544, 1075 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.50-7.22 (m, 10H, Ph-H), 5.74 (ddd, $J_{5,4}$ = 5.9 Hz, $J_{5,6b}$ = 10.5 Hz, $J_{5,6a}$ = 16.8 Hz, 1H, H-5), 5.29 (d, $J_{6a,5}$ = 17.0 Hz, 1H, H-6a), 5.16 (d, $J_{6b,5}$ = 10.5 Hz, 1H, H-6b), 5.00 (s, 1H, H-7), 4.24 (t, $J_{4,5}$ = $J_{4,3}$ = 5.4 Hz, 1H, H-4), 3.78-3.61 (m, 3H, H-3, H-1a, H-1b), 2.70-2.68 (m, 1H, H-2). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 143.4 (C-Ph), 143.0 (C-Ph), 137.0 (C-5), 128.6-127.2 (C-Ph), 117.3 (C-6), 73.4 (C-3), 73.4 (C-4), 64.1 (C-7), 60.2 (C-1), 56.7 (C-2). HRMS: *m/z* calcd for $[C_{19}H_{23}NO_3+H]^+$: 314.3982, obsd.: 314.3985.



75a **75b**

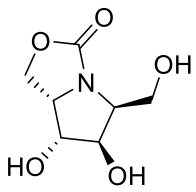
(*2S,3R,4R*)-2-amino-hex-5-ene-1,3,4-triol (75a) and (*2R,3R,4R*)-2-amino-hex-5-ene-1,3,4-triol (75b). *Method 1:* A solution of methyl iodofructosides **74** (0.264 g, 0.87 mmol), Zn (0.295 g, 4.5 mmol), $AcONH_4$ (0.678 g, 8.8 mmol), $NaCNBH_3$ (0.188 g, 3 mmol), in AcOH (0.87 mL) and ethanol (3.47 mL) was stirred at reflux for 7 days, after which time the reaction was purified over Dowex-H^+ resin followed by silica-gel column chromatography to give the title products **75a** and **75b** as a 1:1 diastereomeric mixture (0.085 g, 67% yield).

Method 2: A solution of **78a** (or **78b**) (0.58 g, 1.858 mmol) and Et_3SiH (0.6 mL, 3.23 mmol) in TFA (15 mL) was refluxed for 2 hours, concentrated *in vacuo*, and purified using Dowex-H^+, with the product being eluted using a 35% ammonia solution, to give the respective alkenylamine **75a** (or **75b,** 55%) (0.147 g, 54%). **75a** R_f = 0.30 (DCM\EtOH\MeOH\30% aq. NH_3 25\2\2\1 v\v\v\v). $[\alpha]_D^{20}$ + 23.5 (c = 0.89, MeOH). IR (film) 3475, 3150, 2905, 2847, 1672, 1609, 1472, 1046 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 5.91 (ddd, $J_{5,4}$ = 6.2 Hz, $J_{5,6b}$ = 10.6 Hz, $J_{5,6a}$ = 17.0 Hz, 1H, H-5), 5.37 (d, $J_{6a,5}$ = 17.4 Hz, 1H, H-6a), 5.29 (d, $J_{6b,5}$ = 10.6 Hz, 1H, H-6b), 4.24 (dd, $J_{4,3}$ = 5.4 Hz, $J_{4,5}$ = 6.6 Hz, 1H, H-4), 3.67, (dd, $J_{1a,1b}$ = 11.3 Hz, $J_{1a,2}$ = 5.6 Hz, 1H, H-1a), 3.63-3.54 (m, 2H, H-3, H-1b), 3.08-2.98 (m, 1H, H-2). ^{13}C-NMR (125 MHz, D_2O) δ 136.5 (C-5), 117.9 (C-6), 73.3 (C-4), 72.3 (C-3), 62.5 (C-1), 53.0 (C-2). **75b** R_f = 0.30 (DCM\EtOH\MeOH\30% aq. NH_3 25\2\2\1 v\v\v\v). $[\alpha]_D^{20}$ + 12.6 (c = 1.50, MeOH). IR (film) 3395, 3112, 2893, 1621, 1498, 1056 cm^{-1}^{1}H-NMR (500 MHz, D_2O) δ 5.95 (ddd, $J_{5,4}$ = 6.2 Hz, $J_{5,6b}$ = 10.6 Hz, $J_{5,6a}$ = 17.0 Hz, 1H, H5), 5.38 (d, $J_{6a,5}$ = 17.3 Hz, 1H, H6a), 5.30 (d, $J_{6b,5}$ = 10.8 Hz, 1H, H6b), 4.33-4.27 (m, 1H, H4), 3.80 (dd, $J_{1a,2}$ = 3.9 Hz, $J_{1a,1b}$ = 11.4 Hz, 1H, H1a), 3.58 (dd, $J_{1b,2}$

= 7.1 Hz, $J_{1b,1a}$ = 11.4 Hz, 1H, H1b), 2.79 (td, $J_{2,1a}$ = 3.8 Hz, $J_{2,1b}$ = $J_{2,3}$ = 7.0 Hz, 1H, H2). ^{13}C-NMR (125 MHz, D_2O) δ 136.8 (C-5), 117.1 (C-6), 74.3 (C-4), 72.5 (C-3), 62.5 (C-1), 52.8 (C-2). HRMS: *m/z* calcd. for $[C_6H_{13}NO_3+H]^+$: 148.0968, obsd.: 148.0967.

Carbamate annulation general procedure:

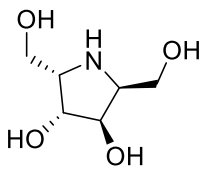
A solution of alkenylamine (1 mmol) and I_2 (1.5 mmol) were dissolved in a sat. aq. $NaHCO_3$ solution (10 mL) and stirred at room temperature for 18 hours. The resulting reaction mixture was lyophilised, dissolved in MeOH, decanted, and purified *via* silica gel flash column chromatography (Petroleum ether/EtOAc 1\1 v\v to EtOAc\MeOH 95\5 v\v), affording the desired product as a white amorphus solid which was reacted further without recording yield.



(*5S,6R,7R,7aS*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (**76a**). By subjecting alkenylamine **75a** (0.046 g, 0.32 mmol) to the general procedure gave carbamate **76a**. $[\alpha]_D^{20}$ + 42.8 (c = 0.86, H_2O). IR (film) 3365, 2941, 1702, 1678, 1422, 1247, 1130, 1034, 794, 705 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 4.64 (t, $J_{6a,6}$ = $J_{6a,5}$ = 9 Hz, 1H, H-6a), 4.51 (dd, $J_{6b,5}$ = 3.4 Hz, $J_{6b,6a}$ = 9.3 Hz, 1H, H-6b), 4.48 (d, $J_{3,2}$ = 5 Hz, 1H, H-3), 4.36-4.30 (m, 1H, H-5), 4.08 (s, 1H, H-4), 3.94-3.88 (m, 1H, H-2), 3.83 (dd, $J_{1a,2}$ = 5.8 Hz, $J_{1a,1b}$ = 11.5 Hz, 1H, H-1a), 3.76 (dd, $J_{1b,2}$ = 7.3 Hz, $J_{1b,1a}$ = 11.5 Hz, 1H, H-1b). ^{13}C-NMR (125 MHz, D_2O) δ 164.7 (C-7), 77.2 (C-3), 75.4 (C-4), 63.9 (C-6), 61.7 (C-2), 62.0 (C-5), 59.7 (C-1) HRMS: m/z calcd. for $[C_7H_{11}NO_5+Na]^+$: 212.0529, obsd.: 212.0530.

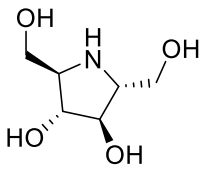
Base hydrolysis general procedure:

A solution of a carbamate (1 mmol) and NaOH (10 mmol) in 20 mL of EtOH was stirred at reflux for 4 hours. The reaction mixture was cooled to room temperature and neutralised with Dowex-H^+. The resulting product was eluted from the resin using 35% ammonia solution, and concentrated *in vacuo*, to afford the desired product.



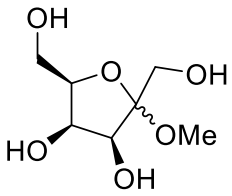
2,5-dideoxy-2,5-imino-l-iditol (**77**). Subjecting carbamate **76a** to the general procedure gave desired product imino-iditol **4** in 98% yield (from alkenylamine **75a**), R_f = 0.15 (DCM/EtOH/MeOH/30% aq. NH_3 5/2/2/1 v/v/v/v). $[\alpha]_D^{20}$ + 16.7 (c 1.4, H_2O). IR (film) 3347, 2899, 1329,

1070 cm^{-1}. **Free base** ^{1}H-NMR (500 MHz, D_2O) δ 4.14 (d, J3,2 = 3.9 Hz, 2H, H-3), 3.75 (dd, $J_{1a,2}$ = 6.6 Hz, $J_{1a,1b}$ = 11.1 Hz, 2H, H-1a), 3.65 (dd, $J_{1b,2}$ = 6.5 Hz, $J_{1b,1a}$ = 11.1 Hz, 2H, H-1b), 3.40 (td, $J_{2,3}$ = 4.0 Hz, $J_{2,1a}$ = $J_{2,1b}$ = 6.5 Hz, 2H, H-2). ^{13}C-NMR (125 MHz, D_2O) δ 77.0 (C-3), 60.3 (C-1), 59.9 (C-2). **HCl salt** ^{1}H-NMR (500 MHz, D_2O) δ 4.32 (d, $J_{3,2}$ = 2.8 Hz, 2H, H-3), 4.00-3.91 (m, 4H, H-1a & H-2), 3.87 (dd, $J_{1b,2}$ = 7.0 Hz, $J_{1a,1b}$ = 10.2, 2H, H-1b). ^{13}C-NMR: (125 MHz, D_2O) δ 74.4 (C-3), 62.7 (C-2), 57.3 (C-1). HRMS: m/z calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0921

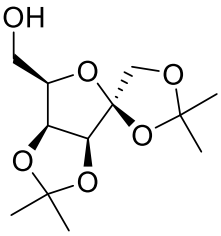


DMDP.HCl (4). Subjecting carbamate **76b** to the general procedure gave a mixture that was purified using silica gel column chromatography (DCM/EtOH/MeOH/30% aq. NH_3, 95\2\2\1 to 62.5/15/15/7.5, v/v/v/v) to give desired product DMDP (**4**) as it's HCl salt in 16% yield (from alkenylamine **75b**), R_f = 0.15 (DCM/EtOH/MeOH/aq. NH_3, 5/2/2/1, v/v/v/v). $[\alpha]_D^{20}$ + 52.9 (c = 0.74, H_2O). IR (film) 3293, 2947, 1290, 1104, 921 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 4.00-3.93 (m, 2H, H-3), 3.91-3.68 (m, 4H, H-1a,b), 3.51-3.40 (m, 2H, H-2). ^{13}C-NMR: (125 MHz, D_2O) δ 74.1 (C-3), 62.2 (C-2), 57.7 (C-1). HRMS: m/z calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0920

7.3 Chapter 3 experimental

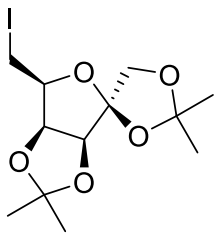


Methyl D-tagatofuranoside (84). A solution of D-tagatose (1.33 g, 7.38 mmol) and H_2SO_4 (11.8 µL, 98 %) in MeOH (67 mL) was stirred at room temperature for 1 h. The reaction was quenched with aq. 35% NH_3 (2 mL), concentrated to ¼ the volume and filtered over celite (MeOH wash). The mother liquor was concentrated and purified *via* silica gel flash column chromatography (Petroleum ether/EtOAc, 100/0 to 0/100, v/v) to give α-methyl D-tagatofuranoside **84** in 47% yield. Spectral data matched those previously reported.[8, 106]

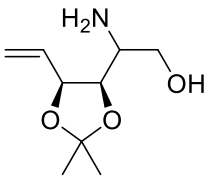


1,2:3,4-Di-*O*-isopropylidene-D-tagatose (86). Anhydrous Cu(II)SO_4 (4.17 g, 26 mmol) and D-tagatose (1.17 g, 6.5 mmol) were added to a flask under argon atmospheres. To this flask, H_2SO_4 (36 mM) in acetone (distilled and degassed, 22 mL) was added and the resulting mixture stirred at room temperature for 18 hours. The reaction was quenched with sodium carbonate, filtered over celite, concentrated, and

purified *via* silica gel flash column chromatography (Petroleum ether/EtOAc, 100/0 to 4/1, v/v) to give **85** as a colourless oil (1.47 g, 87% yield), R_f = 0.3 (petroleum ether/EtOAc, 1/1, v/v). Spectral data matched those previously reported.[49]

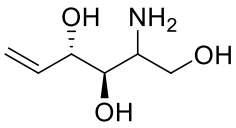


1,2:3,4-Di-*O*-isopropylidene-6-deoxy-6-iodo-D-tagatose (87). Diisopropylidene-protected sugar **86** (2.31 g, 8.9 mmol), PPh_3 (6.75 g, 25.8 mmol), and imidazole (1.81 g, 26.6 mmol) were added to freshly distilled THF (89 mL) and the solution brought to reflux. To this, I_2 (4.56 g, 18 mmol) in THF (44 mL) was added dropwise over 1.5 hours. The resulting mixture was refluxed for a further 12 hours then quenched with methanol and concentrated. The residue was subjected to silica gel flash column chromatography (Petroleum ether/EtOAc, 100/0 to 4/1, v/v) to give iodide **87** as a white crystalline solid (2.84 g, 87% yield), R_f = 0.8 (petroleum ether/EtOAc, 1/1, v/v). Spectral data matched those previously reported.[62] $[\alpha]_D^{20}$ = + 46.1 (c = 1.1, $CDCl_3$). IR (film) 2989, 2391, 1376, 1209, 1028, 851 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.82 (m, 1H, H-4), 4.63 (d, $J_{3,4}$ = 5.5 Hz, 1H, H-3), 4.23 (dd, $J_{1a,1b}$ = 9.5 Hz, $J_{1a,3}$ = 1 Hz, 1H, H-1a), 4.20 (dd, $J_{1a,1b}$ = 9.5 Hz, $J_{1b,3}$ = 1 Hz, 1H, H-1b), 4.20 (m, 1H, H-5), 3.28 (m, 2H, H-6a,b), 1.41 (s, 3H, H-8), 1.32 (s, 3H, H-9), 1.47 (s, 3H, H-11), 1.39 (s, 3H, H-12); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 112.9 (C-2), 111.8 (C-10), 111.8 (C-7), 85.4 (C-3), 79.8 (C-5), 79.7 (C-4), 69.3 (C-1), 26.4 (C-11), 26.4 (C-12), 26.0 (C-8), 25.0 (C-9), -0.9 (C-6). HRMS: *m/z* calcd. for $[C_{12}H_{20}IO_5+H]^+$: 371.0350, obsd.: 371.0347. Spectral data matched that previously reported.[155]

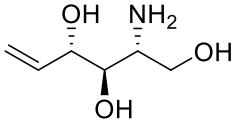


(*S*)-2-amino-2-((*4R,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol and (*R*)-2-amino-2-((*4R,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol (88). Ketone **90** (0.20 g, 1.10 mmol), $AcONH_4$ (0.86 g, 11.0 mmol), and $NaCNBH_3$ (0.27 g, 5.5 mmol) were added to distilled ethanol (11 mL) and the solution stirred at reflux for 18 hours. The resulting mixture was concentrated *in vacuo* then purified by silica gel flash column chromatography (DCM/EtOH/MeOH/30% aq. NH_3, 105/2/2/1 to 10/2/2/1, v/v/v/v), to give 12 as a 1:1 mixture of diastereomers (0.11 g, 55%). R*f* = 0.4 and 0.39, (DCM/EtOH/MeOH/ 30% aq. NH_3, 55/2/2/1, v/v/v/v) for the 2*S* and 2*R* diastereomers, respectively. IR (film) 3321, 3093, 2972, 1634, 1356, 1128 cm^{-1}. (*S*)-2-amino-2-((*4R,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.01 (ddd, $J_{2,3}$ = 7.5 Hz, $J_{2,1b}$ = 10.3 Hz, $J_{2,1a}$ = 17.5 Hz, 1H, H-2), 5.39 (d, $J_{1a,2}$ = 17.3 Hz, 1H, H-1a), 5.34 (d, $J_{1b,2}$ = 10.0 Hz, 1H, H-1b), 4.64 (t, $J_{3,2}$ = $J_{3,4}$ = 7.5 Hz, 1H, H-3), 4.20 (dd,

$J_{4,5}$ = 4.3 Hz, $J_{4,3}$ = 7.0 Hz, 1H, H-4), 3.83-3.62 (m, 3H, H-5, H-6a, H-6b), 1.47 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.5 (C-2), 118.6 (C-1), 108.9 (C-7), 78.9 (C-3), 77.7 (C-4), 69.7 (C-5), 64.2 (C-6), 27.7 (CH_3), 25.2 (CH_3). (*R*)-2-amino-2-((*4R,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.01 (ddd, $J_{2,3}$ = 7.5 Hz, $J_{2,1b}$ = 10.3 Hz, $J_{2,1a}$ = 17.5 Hz, 1H, H-2), 5.47 (d, $J_{1a,2}$ = 17.2 Hz, 1H, H-1a), 5.33 (d, $J_{1b,2}$ = 10.5 Hz, 1H, H-1b), 4.71 (t, $J_{3,2}$ = $J_{3,4}$ = 6.8 Hz, 1H, H-3), 4.11 (dd, $J_{4,3}$ = 6.5 Hz, $J_{4,5}$ = 8.5 Hz, 1H, H-4), 3.83-3.62 (m, 3H, H-5, H-6a, H-6b), 1.54 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.7 (C-2), 119.9 (C-1), 109.0 (C-7), 78.48 (C-3), 78.1 (C-4), 69.7 (C-5), 64.3 (C-6), 27.2 (CH_3), 24.9 (CH_3). HRMS *m/z* calcd. for $[C_9H_{16}NO_3+H]^+$: 186.1125, obsd.: 186.1130.

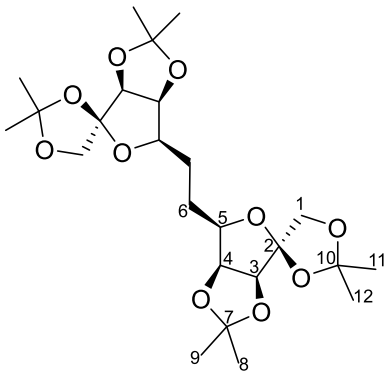


(*2R,3R,4S*)-2-aminohex-5-ene-1,3,4-triol and (*2S,3R,4S*)-2-aminohex-5-ene-1,3,4-triol (89). Ketone **91** (0.17 g, 0.96 mmol), $AcONH_4$ (0.71 g, 9.3 mmol), and $NaCNBH_3$ (0.32 g, 5.0 mmol) were added to distilled ethanol (9.4 mL) and the solution was stirred at room temperature for 18 hours. To the resulting mixture were added distilled H_2O and Dowex-H^+ and the reaction occasionally stirred over 2 hours, after which time the product was removed from Dowex-H^+ (25% aq. NH_3), concentrated *in vacuo*, and purified by silica gel flash column chromatography (DCM/EtOH/MeOH/30% aq. NH_3, 105/2/2/1 to 10/2/2/1, v/v/v/v) to give a 1:1 diastereomeric mixture of **89** as a colourless oil (0.095 g, 71%). R*f* = 0.25 (DCM/EtOH/MeOH/30% aq. NH_3 35/6/6/3 v/v/v/v). IR (film) 3389, 3092, 2982, 2912, 1669, 1615, 1452, 1052 cm^{-1} **(*2R,3R,4S*)-2-aminohex-5-ene-1,3,4-triol:** ^{1}H-NMR (500 MHz, D_2O) δ 5.93 (ddd, $J_{2,3}$ = 7.0 Hz, $J_{2,1b}$ = 10.5 Hz, $J_{2,1a}$ = 17.3 Hz, 1H, H-2), 5.37 (d, $J_{1a,2}$ = 17.3 Hz, 1H, H-1a), 5.31 (d, $J_{1b,2}$ = 10.5 Hz, 1H, H-1b), 4.20 (t, $J_{3,2}$ = $J_{3,4}$ = 7.0 Hz, 1H, H-3), 3.83 (dd, $J_{6a,6b}$ = 11.6 Hz, $J_{6a,5}$ = 3.7 Hz, 1H, H-6a), 3.66-3.57 (m, 2H, H4, H-6b). ^{13}C-NMR (125 MHz, D_2O) δ 135.7 (C2), 118.3 (C-1), 73.3 (C-4), 73.1 (C-3), 61.3 (C-6), 53.3 (C-5). **(*2S,3R,4S*)-2-aminohex-5-ene-1,3,4-triol:** ^{1}H-NMR (500 MHz, D_2O) δ 5.91 (m, 1H, H-2), 5.32 (m,2H, H-1a,b), 4.15 (t, $J_{2,3}$= 6.5 Hz, 1H, H-3), 3.56 (m, 1H, H-4, H6a,b), 2.90 (m, 1H, H-5); ^{13}C-NMR (125 MHz, D_2O) δ 136.3 (C-2), 118.1 (C-1), 72.8 (C-3), 72.4 (C-4), 62.7 (C-6), 52.1 (C-5). HRMS: *m/z* calcd. for $[C_6H_{13}NO_3+H]^+$: 148.0968, obsd.: 148.0972.

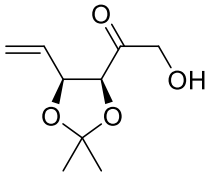


Method for the synthesis of pure (*2R,3R,4S*)-2-aminohex-5-ene-1,3,4-triol (81). A solution of diphenylmethyl amine protected alkenylamine **94** (135 mg, 0.38 mmol) and Et_3SiH (0.12 mL, 0.76 mmol) in TFA (1.9 mL) was refluxed for 2 hours. The solution was then concentrated *in*

vacuo and the residue purified using Dowex-H^+, with alkenylamine **13a** (34.8 mg, 62%) being eluted using a 35% ammonia solution. $[\alpha]_D^{20}$ + 40.1 (c 0.6, MeOH).

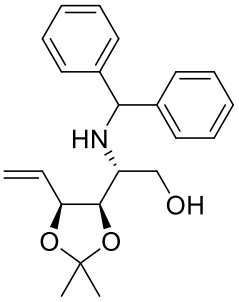


1,2-bis((*3aS,4S,6R,6aS*)-2,2,2',2'-tetramethyldihydro-6H-spiro[furo[3,4-d][1,3]dioxole-4,4'-[1,3]dioxolan]-6-yl)ethane (90). Isopropylidine-protected iodide **87** (0.11 g, 0.31 mmol), activated zinc (0.10 g, 1.55 mmol), and AcOH (0.31 mL) were added to ethanol (1.25 mL) and the resulting solution refluxed for 12 hours. The mixture was then cyclic loaded onto Dowex-H^+, from which dimer **90** (H_2O), and alkenylamines **12** and **13** (35% aq. NH_3) were eluted. The title compound was isolated as a white solid (35.3 mg, 0.072 mmol, 12%) without further purification, with **88** and **89** then being separated *via* silica gel column chromatography (DCM/EtOH/MeOH, 30% aq. NH_3, 105/2/2/1 to 10/2/2/1, v/v/v/v) to give **88 (**18.1 mg, 0.096 mmol) and **89** (3.5 mg, 0.023 mmol) as a 1:1 mixture of diastereoisomers. Dimer **90**, R_f = 0.8 (petroleum ether/EtOAc, 1/1, v/v). $[\alpha]_D^{20}$ + 60.2 (c 1.1, DCM). IR (film) 2982, 1479, 1355, 1224, 1041 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.69 (dd, $J_{4,5}$ = 3.6 Hz, $J_{3,4}$ = 5.8 Hz, 1H, H-4), 4.60 (d, $J_{3,4}$ = 5.8 Hz, 1H, H-3), 4.24 ($J_{1a,1b}$ = 9.7 Hz, 1H, H-1a), 4.02 ($J_{1b,1a}$ = 9.7 Hz, 1H, H-1b), 3.96 (m, 1H, H-5), 1.95-1.73 (m, 2H, H-6a,6b), 1.45 (s, 3H, H-11), 1.41 (s, 3H, H-8), 1.39 (s, 3H, H-12), 1.31 (s, 3H, H-9). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 112.4 (C-7), 111.7 (C-2), 111.6 (C-10), 85.4 (C-3), 80.5 (C-4), 79.0 (C-5), 69.3 (C-1), 25.0 (C-6), 26.5 (C-11), 26.4 (C-12), 26.0 (C-8), 24.9 (C-9). HRMS: *m/z* calcd. for $[C_{24}H_{38}O_{10}+H]^+$: 487.2538, obsd.: 487.2542.

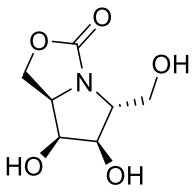


1-((*4S,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethan-1-one (91). Iodide **87** (1.03 g, 2.8 mmol), activated zinc (1.96 g, 29 mmol), and H_2O (7 mL) were added to 63 mL of distilled THF. The solution was brought to reflux and stirred at room temperature for 12 hours. The reaction mixture was then cooled to room temperature and decanted into a separating funnel, in which ether (80 mL) and water (15 mL) were added. The organic layer was collected and the aq. layer washed with ether (20 mL x 3). The organic fractions were combined, dried over $MgSO_4$, filtered over celite, concentrated *in vacuo*, and the residue purified by silica gel flash column chromatography (Petroleum ether/EtOAc, 100/0 to 1/1, v/v) to yield the title compound (0.41 g, 80% yield) as a colourless oil. R*f* = 0.5 (petroleum ether/EtOAc, 1/1, v/v). $[\alpha]_D^{20}$ + 9.4 (c 1.38, DCM). IR

(film) 3523, 3098, 2899, 1710, 1632, 1226, 1052 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.59 (m, 1H, H-1), 5.42 (d, $J_{1a,2}$ = 17 Hz, 1H, H-1a), 5.24 (d, $J_{1b,2}$ = 10.5 Hz, 1H, H-1b), 4.87 5.42 (t, $J_{3,4}$ = 8 Hz, 1H, H-3), 4.69 (d, $J_{3,4}$ = 8.5 Hz, 1H, H-4). 4.49 (d, $J_{6a,b}$ = 20.5 Hz, 1H, H-6a), 4.19 (d, $J_{6a,b}$ = 20.5 Hz, 1H, H-6b), 1.58 (s, 3H, H-8), 1.38 (s, 3H, H-9). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 209.2 (C-5), 131.2 (C-2), 119.0 (C-1), 110.8 (C-7), 81.7 (C-4), 78.4 (C-3), 67.8 (C6), 26.5 (C-8), 24.4 (C-9). HRMS *m/z* calcd. for $[C_9H_{14}O_4+Na]^+$: 209.0784, obsd.: 209.0780.

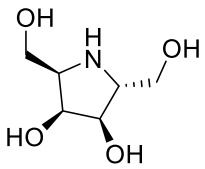


(*R*)-2-(benzhydrylamino)-2-((*4R,5S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol (94). Ketone **91** (0.20, 1.08 mmol), Ph_2CHNH_2.HCl (1.43 g, 1.48mmol), and NaCNBH3 (0.27 g, 1.24 mmol) were added to EtOH (21 mL) and the resulting solution refluxed for 18 hours. The mixture was then concentrated *in vacuo*, dissolved in EtOAc (20 mL), washed with brine (3 x 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The remaining oil was purified *via* silica gel flash column chromatography (Petroleum ether/EtOAc, 100/0 to 9/1, v/v) to give the protected alkenylamine **94** (0.23 g, 61%) as a colourless oil, R_f = 0.31 (petroleum ether/EtOAc, 1/1, v/v). $[\alpha]_D^{20}$ - 19.2 (c 0.9, DCM). IR (film) 3598, 3480, 3087, 2925, 1671, 1564, 1288, 1028 cm^{-1} ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.21 (m, 10H, phenyl-H) 5.73 (ddd, $J_{5,4}$ = 7.3 Hz, $J_{5,6b}$ = 10.5 Hz, $J_{5,6a}$ = 17.4 Hz, 1H, H-5), 5.28 (d, $J_{6a,5}$ = 17.1 Hz, 1H, H-6a), 5.11 (d, $J_{6b,5}$ = 10.3 Hz, 1H, H-6b), 4.96 (s, 1H, H-7), 4.66 (t, $J_{4,5}$ = $J_{4,3}$ = 7.0 Hz, 1H, H-4), 4.29 (t, $J_{3,4}$ = $J_{3,2}$ = 6.9 Hz, 1H, H-3), 3.78-3.50 (m, 2H, H-1a,1b), 2.73 (dt, $J_{2,1a}$ = $J_{2,1b}$ = 3.7 Hz, $J_{2,3}$ = 7.1 Hz, 1H, H-2), 1.46 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 144.1 (C-Ph), 143.3 (C-Ph), 133.8 (C-6), 128.5-127.1 (C-Ph), 118.6 (C-2), 108.4 (C-Hemiacetal), 78.8 (C-4), 78.7 (C-3), 64.22 (C-7), 60.6 (C-1), 55.8 (C-2), 27.5 (CH_3), 25.1 (CH_3). HRMS: *m/z* calcd. for $[C_{22}H_{27}NO_3+H]^+$: 354.2064, obsd.: 354.2059.



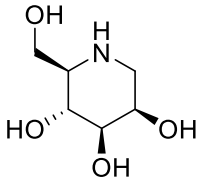
(*5R,6R,7S,7aR*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (**80**) By subjecting alkenylamine **81** (0.046 g, 0.32 mmol) to the general procedure gave carbamate **80**. $[\alpha]_D^{20}$ - 6.4 (c 0.8, MeOH). IR (film) 3601, 2989, 1715, 1648, 1193, 1031, 725 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) 4.62-4.53 (m, 2H, H-1a, H-1b), 4.34 (dd, $J_{3,4}$ = 3.6 Hz, $J_{2,3}$ = 7.7 Hz, 1H, H-3), 4.21-4.15 (m, 1H, H-5), 4.08 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-4), 3.89 (dd, $J_{6a,5}$ = 3.6 Hz, $J_{6a,6b}$ = 12.1 Hz, 1H, H-6a), 3.71 (dd, $J_{6b,5}$ = 5.5 Hz, $J_{6b,6a}$ = 12.1 Hz, 1H, H-6b). ^{13}C-NMR (125 MHz, D_2O) δ 74.6 (C-3), 71.5 (C-4), 64.1 (C-6), 63.0

(C-2), 61.4 (C-5), 61.02 (C-1). HRMS: m/z calcd. for $[C_7H_{11}NO_5+Na]^+$: 212.0529, obsd.: 212.0530.



2,5-dideoxy-2,5-imino-D-altritol (**79**) Subjecting carbamate **80** (0.035 g, 0.18 mmol) to the general procedure gave desired product imino-iditol **79** (0.30 g, 98% yield), R_f = 0.10 (DCM/EtOH/MeOH/30% aq. NH_3, 5/2/2/1, v/v/v/v). $[\alpha]_D^{20}$ + 35.4 (c 0.9, H_2O). IR (film) 3562, 2922, 1280 cm^{-1}. **Free Base** ^{1}H-NMR (500 MHz, D_2O) δ 4.19 (t, $J_{4,3} = J_{4,5}$ = 4.1 Hz, 1H, H-4), 4.01 (dd, $J_{3,4}$ = 4.3 Hz, $J_{3,2}$ = 8.5 Hz, 1H, H-3), 3.83-3.72 (m, 2H, H-1a, H-6a), 3.69-3.61 (m, 2H, H-1b, H-6b), 3.33 (dt, $J_{5,4}$ = 3.8 Hz, $J_{5,6a} = J_{5,6b}$ = 6.7 Hz, 1H, H-5), 3.15 (ddd, $J_{2,1a}$ = 3.9 Hz, $J_{2,1b}$ = 5.9 Hz, $J_{2,3}$ = 8.5 Hz, 1H, H-2). ^{13}C-NMR (125 MHz, D_2O) δ 73.4 (C-4), 71.8 (C-3), 61.7 (C-1), 61.2 (C-2), 60.3 (C-6), 59.7 (C-5). **HCl salt** ^{1}H-NMR (500 MHz, D_2O) δ 4.35 (t, $J_{4,3} = J_{4,5}$ = 3.5 Hz, 1H, H-4), 4.28 (dd, $J_{3,4}$ = 3.9 Hz, $J_{3,2}$ = 9.2 Hz, 1H, H-3), 4.04-3.83 (m, 4H, H-1a,b, H-6a,6b), 3.77 (ddd, $J_{5,4}$ = 3.2 Hz, $J_{5,6a}$ = 5.2 Hz, $J_{5,6b}$ = 8.3 Hz, 1H, H-5), 3.65 (ddd, $J_{2,1a}$ = 3.3 Hz, $J_{2,1b}$ = 5.9 Hz, $J_{2,3}$ = 9.3 Hz, 1H, H-2). ^{13}C-NMR (125 MHz, D_2O) δ 71.1 (C-3), 70.0 (C-4), 62.1 (C-5), 61.6 (C-2), 58.0 (C-6), 57.4 (C-1). HRMS: m/z calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0915

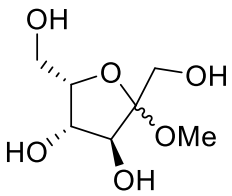
7.4 Chapter 4 experimental



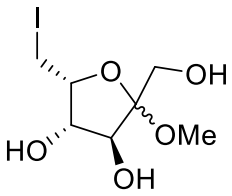
1-Deoxymannojirimycin (**36**): Methyl iodofructoside **74** (0.48 g, 1.56 mmol) was dissolved in 16 mL of a 0.15 M HCl solution and stirred at room temperature until TLC confirmed full conversion to iodofructoside **95** (ca. 3 days). [R_f = 0.25 (DCM/MeOH, 5/1, v/v), ^{1}H-NMR (500 MHz, D_2O) δ 4.20 (d, $J_{3,4}$ = 8.4 Hz, 1H, H-3), 4.13 (t, $J_{4,3} = J_{4,5}$ = 7.7 Hz, 1H, H-4), 3.85 (m, 1H, H-5), 3.65 (d, $J_{1a,1b}$ = 12.3 Hz, 1H, H-1a), 3.60 (d, $J_{1b,1a}$ = 12.3 Hz, 1H, H-1b), 3.56 (dd, $J_{6a,6b}$ = 10.8 Hz, $J_{6a,5}$ = 5.2 Hz, 1H, H-6a), 3.45 (dd, $J_{6b,6a}$ = 10.8 Hz, $J_{6b,5}$ = 6.3 Hz, 1H, H-6b). ^{13}C-NMR (125 MHz, D_2O) δ 101.5 (C-2), 79.5 (C-5), 78.4 (C-4), 75.5 (C-3), 62.7 (C-1), 7.3 (C-6). HRMS: *m/z* calcd. for $[C_6H_{11}IO_5+H]^+$: 290.9724, obsd.: 290.9728] Next, aq. NH_3 (8 mL, 144 mmol) and $NaCNBH_3$ (0.40 g, 6.4 mmol) were then added to the reaction flask and stirred for a further 18 hours. The resulting reaction mixture was concentrated *in vacuo* and purified using Dowex-H^+ (1% aq. NH_3) and silica gel flash column chromatography (DCM/EtOH/MeOH/aq. NH_3, 20/2/2/1, v/v/v/v) to give pure DMJ (**36**) as a white solid in 96% yield (0.24 g, 1.50 mmol). R_f = 0.10 (DCM/EtOH/MeOH/aq. NH_3, 5/2/2/1, v/v/v/v). $[\alpha]_D^{20}$ -15.7 [c 1.6, H_2O]; lit.[120] $[\alpha]_D^{20}$

-15.0 [c 2, H_2O]. IR (film) 3420, 3305, 2992, 2883 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 4.26 (td, $J_{2,1a} = J_{2,3}$ =3.1 Hz, $J_{2,1b}$ = 1.5 Hz, 1H, H-2), 4.00 (dd, $J_{6b,6a}$ = 12.6 Hz, $J_{6b,5}$ = 3.3 Hz, 1H, H-6b), 3.86 (m, 2H, H6a, H-4), 3.70 (dd, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 3.1 Hz, 1H), 3.42 (dd, $J_{1a,1b}$ = 13.6 Hz , $J_{1a,2}$ =3.1 Hz, 1H, H-1a), 3.25 (dd, $J_{1b,1a}$ = 13.6 Hz , $J_{1b,2}$ =1.5 Hz, 1H, H-1b), 3.15 (ddd, $J_{5,4}$ = 10.3 Hz, $J_{5,6a}$ = 6.7 Hz, $J_{5,6b}$ = 3.3 Hz, 1H, H-5). ^{13}C-NMR (125 MHz, D_2O) δ 72.2 (C-3), 65.7 (C-2), 65.6 (C-4), 60.0 (C-5), 57.9 (C-6), 47.4 (C-1). HRMS: *m/z* calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0915. Spectral data matched that previously reported.[119]

7.5 Chapter 5 experimental

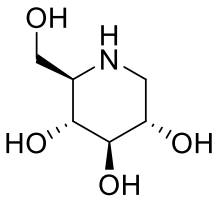


Methyl L-sorbofuranoside (112). To a flask containing H_2SO_4 in MeOH (0.03 M, 400 mL) was added L-sorbose (2.00 g, 11.1 mmol) and stirred at room temperature. After 2 h, aq. 35% NH_3 was added (3 mL), the reaction concentrated *in vacuo* to ¼ the volume and filtered over celite (cold MeOH wash). The mother liquor was collected, concentrated, and purified using silica gel flash column chromatography (EtOAc to EtOAc/MeOH 9/1) to give an α,β mixture of methyl-D-sorbofuranoside (1.19 g, 55%), which was subsequently used as a mixture. A: R_f = 0.32 (EtOAc/i-PrOH/H_2O, 6/4/1, v/v/v), β: R_f = 0.30 (EtOAc/i-PrOH/H_2O 6/4/1, v/v/v). Spectral data matched those previously reported.[132]

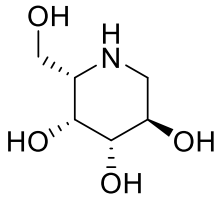


Methyl 6-deoxy-6-iodo-L-sorbofuranoside (114). To a α,β-mixture of methyl L-sorbofuranoside (0.55 g, 2.8 mmol) in THF (28 mL) was added PPh_3 (1.85 g, 70 mmol) and imidazole (0.57 g, 84 mmol). The reaction was brought to 70 °C and a solution of I_2 (1.43 g, 56 mmol) in THF (14 mL) was added portion wise over 5 mins. The reaction mixture was stirred at 70 °C until TLC showed complete conversion of starting material to desired product (≈ 7 h), after which MeOH was added and the reaction concentrated *in vacuo.* The resulting mixture was purified using silica gel flash column chromatography (Petroleum ether/EtOAc 4/1 to 1/1, v/v) and HP20 (H_2O to H_2O/MeOH, 9/1, v/v) to give an α,β-mixture (predominately β) of methyl 6-deoxy-6-iodo-L-sorbofuranoside (0.67 g 78 %), which was subsequently used as a mixture. α R_f = β R_f = 0.35 (DCM/MeOH, 5/1, v/v). IR (film) 3401, 2980, 2880, 1462, 1039, 1031 cm^{-1}. β-**113** ^{1}H-NMR (500 MHz, D_2O) δ 4.41 (m, 2H, H-4, H-5), 4.36 (m, 1H, H-3), 3.76 (d, $J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 3.66 (d, $J_{1b,1a}$ = 12.2 Hz, 1H, H-1b), 3.35 (dd, $J_{6a,6b}$ = 9.3 Hz, $J_{6a,5}$ = 5.4 Hz, 1H, H-6a), 3.29-3.23 (m,

1H, H-6b), 3.31 (s, 3H, OMe).[13]C-NMR (125 MHz, D_2O) δ 108.2 (C-2), 80.6 (C-4), 75.2 (C-3), 71.5 (C-5), 58.5 (C-1), 48.8 (OMe), -0.4 (C-6). HRMS: *m/z* calcd. for $[C_7H_{13}IO_5+Na]^+$: 326.9699, obsd.: 326.9694.

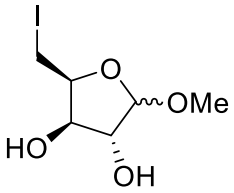


1-Deoxynojirimycin (3). To a solution of aq. HCl (0.15 M, 13 mL) was added methyl 6-deoxy-6-iodo-L-sorbofuranoside (0.42 g, 1.3 mmol) and the solution put under reduced pressure (0.3 atm) in a 50 ^oC water bath until TLC analysis showed full conversion to 6-deoxy-6-iodo-L-sorbose (≈2 h). Following this, aq. 35% NH_3 (6.5 mL, 120 mmol) and $NaCNBH_3$ (0.35 g, 5.2 mmol) were added sequentially to the reaction, which was stirred at room temperature for 18 h. The resulting mixture was concentrated *in vacuo* and purified using Dowex-H^+ (5% NH_3) and silica gel flash column chromatography (DCM/EtOH/MeOH/aq. NH_3, 20/2/2/1, v/v/v/v) to give 1-deoxynojirimycin (0.21 g, 95%). R_f = 0.10 (DCM/EtOH/MeOH/aq. NH_3, 5/2/2/1, v/v/v/v). $[\alpha]_D^{20}$ 46 [c 0.8, H_2O]; lit.[136] $[\alpha]_D^{20}$ 44 [c 0.2, H_2O]. IR (film) 3420, 3305 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 3.93 (dd, $J_{6a,6b}$ = 12.8 Hz, $J_{6a,5}$ = 3.1 Hz, 1H, H-6a), 3.86 (dd, $J_{6b,6a}$ = 12.7 Hz, $J_{6b,5}$ = 5.3 Hz, 1H, H-6b), 3.77 (ddd, $J_{2,1b}$ = 11.6 Hz, $J_{2,3}$ = 9.2 Hz, $J_{2,1a}$ = 5.1 Hz, 1H, H-2), 3.58 (dd, $J_{4,5}$ = 10.5 Hz, $J_{4,3}$ = 9.3 Hz, 1H, H-4), 3.52-3.44 (m, 2H, H-1a, H-3), 3.18 (ddd, $J_{5,4}$ = 10.6 Hz, $J_{5,6b}$ = 5.3 Hz, $J_{5,6a}$ = 3.1 Hz, 1H, H-5), 2.95 (dd, $J_{1b,1a}$ = 12.5 Hz, $J_{1b,2}$ = 11.6 Hz, 1H, H-1b). ^{13}C-NMR (125 MHz, D_2O) δ 76.0 (C-3), 67.6 (C-4), 66.8 (C-2), 59.8 (C-5), 57.5 (C-6), 45.7 (C-1). HRMS: *m/z* calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0918. Spectral data matched those previously reported.[156]

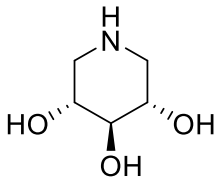


L-1-Deoxygalactonojirimycin (30). To a solution of HCl in MeOH (0.15 M, 12 mL) was added 1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-iodo-D-tagatose (**87**, 0.45 g, 1.21 mmol) and the solution put under reduced pressure (0.3 atm) and heated in a 50 ^oC water bath until the starting material had completely reacted (observed *via* TLC analysis, 2 hours), following which H_2O (12 mL) was added, the MeOH removed *in vacuo*, and the remaining solution stirred at room temperature for 18 hours to give complete conversion to 6-deoxy-6-iodo-D-tagatoside (observed *via* TLC analysis). Following this, 35% aq. NH_3 (6.0 mL, 111 mmol) and $NaCNBH_3$ (0.30 g, 4.84 mmol) were added sequentially to the reaction, which was stirred at room temperature for a further 18 hours. The resulting mixture was concentrated *in vacuo* and purified using Dowex-H^+ (5% aq. NH_3) and silica gel flash column chromatography (DCM/EtOH/MeOH/ aq. NH_3, 20/2/2/1, v/v/v/v) to give 1-deoxygalactojirimycin (0.17 g, 86%) with trace amounts of an unidentified minor

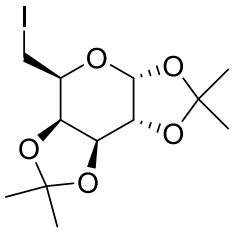
product. R_f = 0.10 (DCM/EtOH/MeOH/ aq. NH_3, 5/2/2/1, v/v/v/v). IR (film) 3380 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 4.19 (dd, $J_{4,3}$ = 3.0 Hz, $J_{4,5}$ = 1.4 Hz, 1H, H-4), 4.09 (ddd, $J_{2,1b}$ = 11.4 Hz, $J_{2,3}$ = 9.6 Hz, $J_{2,1a}$ = 5.3 Hz, 1H, H-2), 3.90 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{6a,5}$ = 4.9 Hz, 1H, H-6a), 3.82 (dd, $J_{6b,6a}$ = 12.2 Hz, $J_{6b,5}$ = 8.8 Hz, 1H, H-6b), 3.66 (dd, $J_{3,2}$ = 9.7 Hz, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 3.53 (dd, $J_{1a,1b}$ = 12.5 Hz, $J_{1a,2}$ = 5.4 Hz, 1H, H-1a), 3.44 (ddd, $J_{5,6b}$ = 8.9 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,4}$ = 1.4 Hz, 1H, H-5), 2.90 (dd, $J_{1b,1a}$ = 12.5 Hz, $J_{1b,2}$ = 11.5 Hz, 1H, H-1b). ^{13}C-NMR (125 MHz, D_2O) δ 72.8 (C-3), 66.8 (C-4), 64.6 (C-2), 60.0 (C-5), 59.0 (C-6), 46.0 (C-1). HRMS: *m/z* calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0912. Spectral data matched those previously reported.[147]



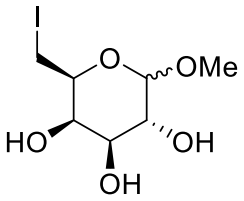
Methyl 5-deoxy-5-iodo-α/β-D-xyloside (55). To a solution of D-xylose (4.16 g, 27.7 mmol) in MeOH (138 mL), AcCl (0.42 mL) was added and the reaction was stirred at room temperature for 24 h. The reaction was neutralised by the addition of Dowex-OH^-, filtered and concentrated. The resulting oil was purified by flash chromatography (MeOH/EtOAc, 1/9, v/v) to give the pure methyl xylofuranosides. To a solution of the methyl xylofuranosides (27.7 mmol) in dry THF (152 mL) under an argon atmosphere, PPh_3 (10.9 g, 41.5 mmol) and imidazole (3.71 g, 55.4 mmol) were added. I_2 (10.4 g, 41.5 mmol) in dry THF (42 mL) was cannulated into the reaction vessel. The reaction was refluxed for 2 h, then cooled, filtered, and concentrated. The product was dissolved in Petroleum ether/EtOAc (3/1, v/v), filtered, then purified by reverse phase HP20 (MeOH/H_2O, 5/1, v/v) to give methyl 5-deoxy-5-iodo-α/β-D-xyloside (**55**) as a colourless oil (4.63 g, 61%). R_f = 0.65 (EtOAc/MeOH, 9/1, v/v); $[\alpha]_D^{20}$ = -19.7 (c = 1.5, $CHCl_3$); IR (film) 3446, 1216, 770 cm^{-1}. **α-55** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, $J_{1,2}$ = 4.4, 1H, H-1), 4.40 (m, 1H, H-4), 4.29 (dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 4.6 Hz, 1H, H-3), 4.17 (dd, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 3.3 Hz, 1H, H-2), 3.51 (s, 3H, OMe), 3.31 (dd, $J_{4,5a}$ = 7.6 Hz, $J_{5a,5b}$ = 9.8 Hz, 1H, H-5a), 3.25 (dd, $J_{4,5b}$ = 6.1 Hz, $J_{5a,5b}$ = 9.8 Hz, 1H, H-5b).^{13}C NMR (125 MHz, $CDCl_3$) 102.2 (C-1), 79.1 (C-4), 78.4 (C-2), 76.9 (C-3), 56.2 (OMe), 1.6 (C-5); **β-55** 4.93 (s, 1H, H-1), 4.60 (dt, $J_{3,4}$ = 3.9 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 7.7 Hz, 1H, H-4), 4.28 (s, 1H, H-2), 4.14 (d, $J_{3,4}$ = 3.9 Hz, 1H, H-3), 3.40 (s, 3H, OMe), 3.32 (d, $J_{4,5}$ = 7.7 Hz, 2H, H-5a,b); ^{13}C NMR (125 MHz, $CDCl_3$)109.0 (C-1), 83.7 (C-4), 79.7 (C-2), 76.0 (C-3), 55.5 (OMe), 1.9 (C-5); HRMS: *m/z* calcd. for $[C_6H_{11}O_4I+Na]^+$: 296.9594, obsd.: 296.9601.



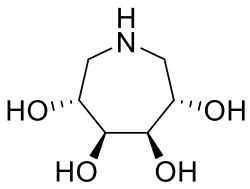
(3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (118). A solution of methyl 5-deoxy-5-iodo-α/β-D-xyloside (0.39 g, 1.42 mmol) in aqueous HCl (0.3 M, 14 mL) was refluxed until full conversion of starting material was observed *via* TLC (ca. 1 h). Following this, 35% aq. NH_3 (7 mL, 130 mmol) and $NaCNBH_3$ (0.36 g, 5.68 mmol) were added sequentially to the reaction, which was stirred at room temperature for a further 18 hours. The resulting mixture was concentrated *in vacuo* and purified using Dowex-H^+ (5% aq. NH_3) and silica gel flash column chromatography (DCM/EtOH/MeOH/aq. NH_3, 20/2/2/1, v/v/v/v) to give (3*R*,4*r*,5*S*)-piperidine-3,4,5-triol (0.16 g, 88 %). R_f = 0.10 (DCM/EtOH/MeOH/aq. NH_3 5/2/2/1 v/v/v/v). IR (film) 3420, 3350, 2902, 2887 cm^{-1}. ^{1}H-NMR (500 MHz, D_2O) δ 3.64 (ddd, $J_{2,1b}$ = 10.4 Hz, $J_{2,3}$ = 8.7 Hz, $J_{2,1a}$ = 4.8 Hz, 1H, H-2), 3.40 (t, $J_{3,2}$ = 8.7 Hz, 1H, H-3), 3.30 (dd, $J_{1a,1b}$ = 12.7 Hz, $J_{1a,2}$ = 4.8 Hz, 1H, H-1a), 2.71 (dd, $J_{1b,1a}$ = 12.7 Hz, $J_{1b,2}$ = 10.4 Hz, 1H, H-1b). ^{13}C-NMR (125 MHz, D_2O) δ 76.1 (C-3), 68.5 (C-2), 47.4 (C-1). HRMS: *m/z* calcd. for $[C_6H_{12}NO_3+H]^+$: 135.0812, obsd.: 135.0817. Spectral data matched those previously reported.[157]



6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (119). To a mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[63] (2.6 g, 10 mmol), PPh_3 (3.93 g, 15 mmol) and imidazole (1.36 g, 20 mmol) in dry THF (100 mL), was added I_2 (3.81 g, 15 mmol) in small portions. After refluxing for 1 h, the reaction mixture was cooled to room temperature, and quenched by the addition of 10% aq. $Na_2S_2O_4$. The product was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Distillation of the residue gave 6-deoxy-6-iodo-1,2:3,4-*O*-di-isopropyl-α-D-galactopyranose as a yellow oil (3.14 g, 85%). R_f = 0.55 (Petroleum ether/EtOAc, 4/1, v/v); $[\alpha]_D^{20}$ -52.1 [c 1, DCM]; lit.[158] $[\alpha]_D^{20}$ -57.3 [c 1, DCM]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.52 (d, $J_{1,2}$ = 5.0 Hz, 1H, H-1), 4.59 (dd, $J_{3,4}$ = 7.9 Hz, $J_{3,2}$ = 2.5 Hz, 1H, H-3), 4.38 (dd, $J_{4,3}$ = 7.9 Hz, $J_{4,5}$ = 1.9 Hz, 1H, H-4), 4.28 (dd, $J_{2,1}$ = 5.0 Hz, $J_{2,3}$ = 2.5 Hz, 1H, H-2), 3.92 (ddd, $J_{5,6b}$ = 7.2 Hz, $J_{5,6a}$ = 6.8 Hz, $J_{5,4}$ = 1.9 Hz, 1H, H-5), 3.29 (dd, $J_{6a,b}$ = 10 Hz, $J_{6a,5}$ = 6.8 Hz, 1H, H-6a), 3.19 (dd, $J_{6b,a}$ = 10 Hz, $J_{6b,5}$ = 7.2 Hz, 1H, H-6b), 1.52 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 109.7 (C-7), 109.0 (C-10), 96.8 (C-1), 71.5 (C-4), 71.1 (C-3), 70.5 (C-2), 68.9 (C-5), 26.2 (C-8), 26.1 (C-11), 25.0 (C-9), 24.6 (C-12), 2.5 (C-6). HRMS: *m/z* calcd. for $[C_{12}H_{20}IO_5+H]^+$: 371.0350, obsd.: 371.0355.



Methyl 6-deoxy-6-iodo-α/β-D-galactopyranoside (121). To a solution of methyl α/β-galactopyranoside (1.24 g, 6.38 mmol) in dry THF (35 mL) under an atmosphere of N_2, PPh_3 (2.51 g, 9.58 mmol) and imidazole (0.87 g, 12.7 mmol) were added. I_2 (2.42g, 9.58 mmol) in dry THF (9.5 mL) was cannulated into the reaction vessel. The reaction was refluxed for 2 h, then cooled, filtered and concentrated. The product was taken up in Petroleum ether/EtOAc, 3/1, v/v, and filtered through a silica plug to removed excess iodine, then purified by column chromatography on reverse phase HP20 beads (MeOH/water, 5/1, v/v) to give methyl 6-deoxy-6-iodo-α/β-D-galactopyranose. The mixture was concentrated *in vacuo* and the residue crystallised from MeOH, giving the title compound (1.78 g, 47%) as white crystals. Mp 175.0-175.6 °C; R_f = 0.43 (MeOH/EtOAc, 1/9, v/v); IR (film) 3354, 2953, 2906, 1454, 1360, 1297, 1132, 1102, 1078, 691 cm-1; ^{1}H NMR (500 MHz, D_2O) δ 4.69 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1), 3.97 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 3.90 (ddd, $J_{4,5}$ = 1.2 Hz, $J_{5,6a}$ = 5.3, $J_{5,6b}$ = 8.0 Hz 1H, H-5), 3.75 (dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 10.2 Hz, 1H, H-2), 3.69 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 3.46 (s, 3H, OMe), 3.37 (dd, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 10.2 Hz, 1H, H-6a), 3.33 (dd, $J_{5,6b}$ = 8.0, $J_{6a,6b}$ = 10.2 Hz, 1H, H-6b); ^{13}C NMR (125 MHz, D_2O) δ 100.2 (C1), 71.4 (C5), 70.4 (C4), 69.9 (C2), 68.4 (C3), 54.6 (OMe), 2.3 (C6). HRMS: *m/z* calcd. for $[C7H13IO5+Na]^+$: 326.9700, obsd.: 326.9709.



(3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol (49). A 9:1 mixture of TFA:H_2O (4.3 mL) and 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.32 g, 0.86 mmol) was put under reduced pressure (0.3 atm) and heated in a 50 ºC water bath for 30 minutes, when complete consumption of starting material was observed by TLC. The resulting mixture was concentrated *in vacuo* and redissolved in a mixture of DCM and H_2O, from which the product was extracted with H_2O and concentrated to give 6-deoxy-6-iodo-D-galactose (**120**) as a brown oil that was used without further purification. [R_f = 0.35 (DCM/MeOH, 5/1, v/v, **α:** ^{1}H NMR (500 MHz, D_2O) δ 5.19 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1), 4.20-4.14 (m, 1H, H-5), 4.10 (dd, $J_{4,3}$ = 3.3 Hz, $J_{4,5}$ = 1.1 Hz, 1H, H-4), 3.81 (m, 1H, H-3), 3.79 (dd, $J_{2,3}$ = 10.3 Hz, $J_{2,1}$ = 3.9 Hz, 1H, H-2), 3.35-3.16 (m, 2H, H6a,6b); ^{13}C NMR (125 MHz, D_2O) δ 92.2 (C-1), 70.7 (C-5), 69.9 (C-4), 69.0 (C-3), 67.8 (C-5), 2.3 (C-6). **β:** ^{1}H NMR (500 MHz, D_2O) δ 4.54 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 4.06 (dd, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.81 (m, 1H, H-5), 3.59 (dd, $J_{3,2}$ = 10 Hz, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 3.43 (dd, $J_{2,3}$ = 10 Hz, $J_{2,1}$ = 7.9 Hz, 1H, H-2), 3.35-3.16 (m, 2H, H-6a,6b); ^{13}C

NMR (125 MHz, D_2O) δ 92.2 (C-1), 70.7 (C-5), 69.9 (C-4), 69.0 (C-3), 67.8 (C-5), 2.3 (C-6) HRMS: *m/z* calcd. for $[C_6H_{11}IO_5+H]^+$: 290.9724, obsd.: 290.9730]. Next, 6-deoxy-6-iodo-D-galactopyranose (**120**) was dissolved in H_2O (8.6 mL), after which aq. NH_3 (4.3 mL, 80 mmol) and $NaCNBH_3$ (0.22 g, 3.45 mmol) were added and the reaction stirred at room temperature for 2 days. The resulting mixture was concentrated *in vacuo* and purified using Dowex-H^+ exchange resin (0.1% NH_3) to give the title compound as an off white solid (95.4 mg, 68% 2 steps). R_f = 0.10 (DCM/EtOH/MeOH/aq. NH_3, 5/2/2/1, v/v/v/v). IR (film) 3401, 2988, 2896 cm^{-1}; ^{1}H-NMR (500 MHz, D_2O) δ 4.00 (d, $J_{3,2}$ = 6.5 Hz, 1H, H-3), 3.87 (ddd, $J_{2,3}$ = 6.5 Hz, $J_{2,1b}$ = 4.8 Hz, $J_{2,1a}$ = 4.2 Hz, 1H, H-2), 3.08 (dd, $J_{1a,1b}$ = 14.7 Hz, $J_{1a,2}$ = 4.2 Hz, 1H, H-1a), 2.90 (dd, $J_{1b,1a}$ = 14.7 Hz, $J_{1b,2}$ = 4.8 Hz, 1H, H-1b). ^{13}C-NMR (125 MHz, D_2O) δ 73.9 (C-3), 70.0 (C-2), 51.0 (C-1). HRMS: *m/z* calcd. for $[C_6H_{13}NO_4+H]^+$: 164.0917, obsd.: 164.0923. Spectral data matched those previously reported.[151]

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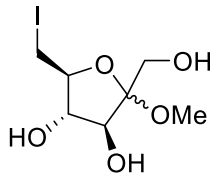
Appendix

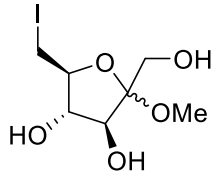
Chapter 2 spectra

^{1}H NMR, D_2O, 500 MHz

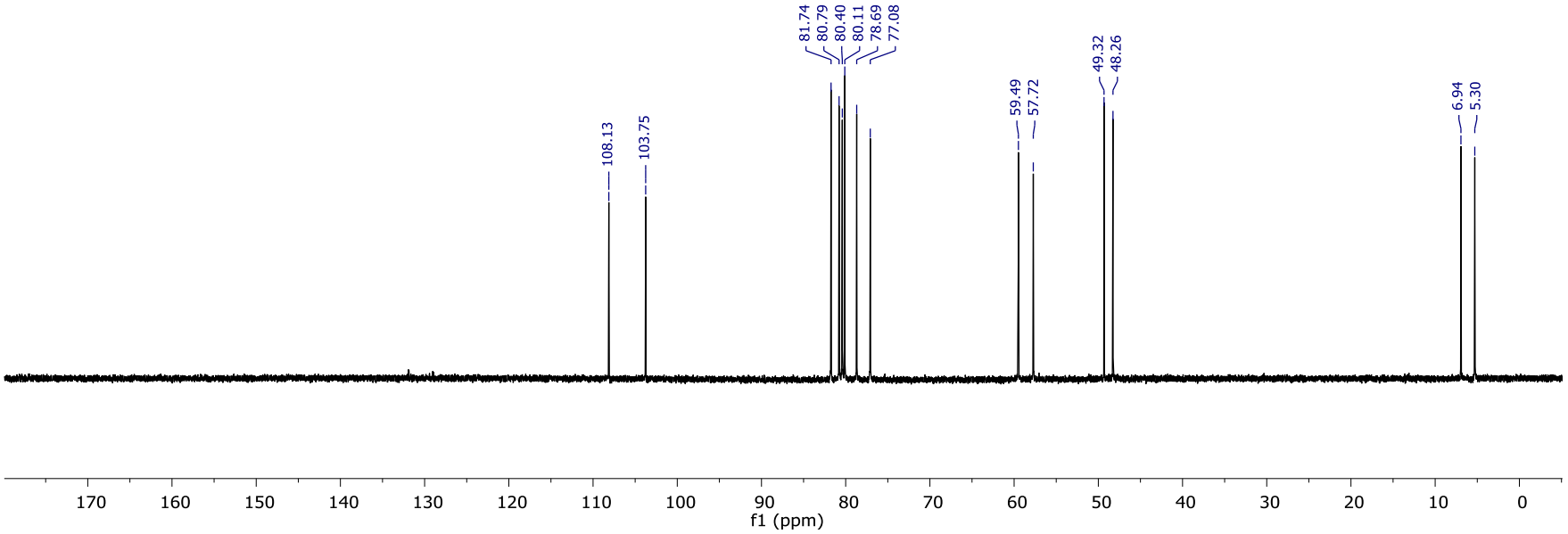


Methyl 6-deoxy-6-iodo-D-fructofuranoside
(74)

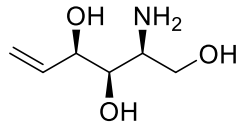
^{13}C NMR, D_2O, 125 MHz



Methyl 6-deoxy-6-iodo-D-fructofuranoside
(74)



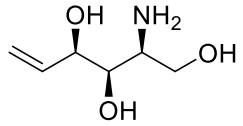
^{1}H NMR, D_2O, 500 MHz



(2*S*,3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

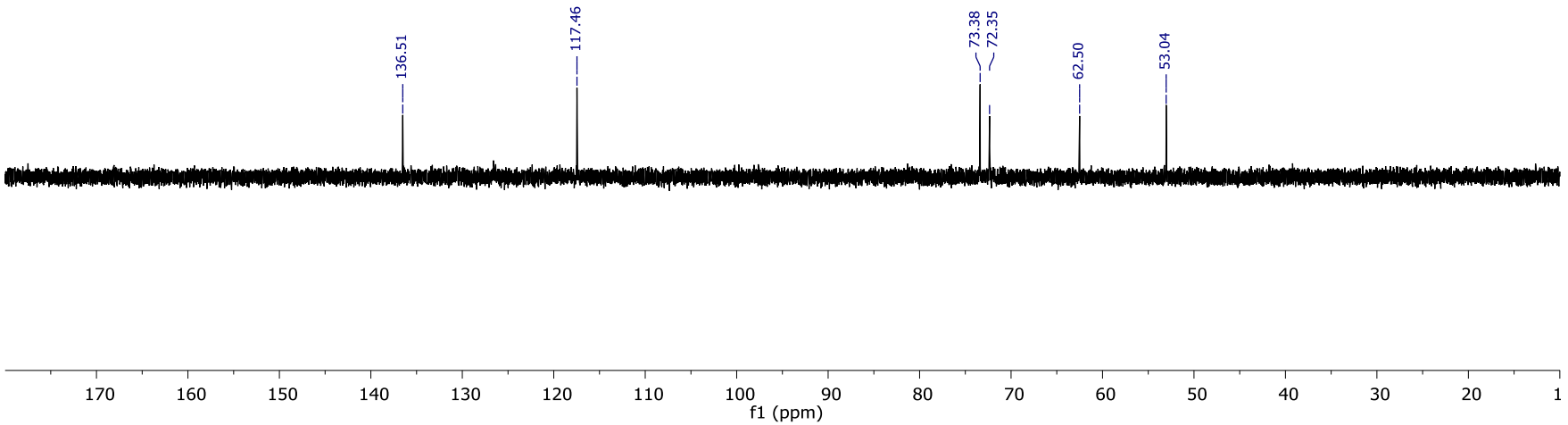
75a

^{13}C NMR, D_2O, 125 MHz

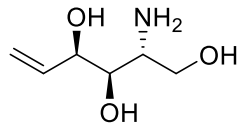


(2*S*,3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

75a



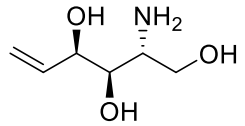
^{1}H NMR, D_2O, 500 MHz



(2*R*,3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

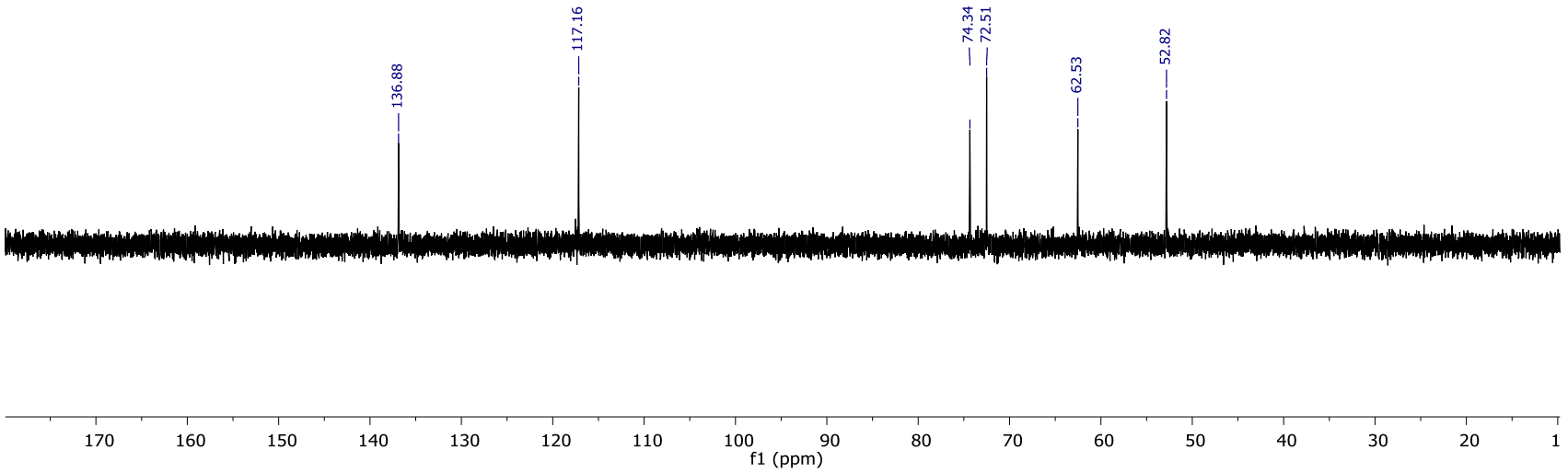
75b

^{1}H NMR, D_2O, 500 MHz

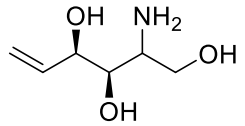


(2*R*,3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

75b



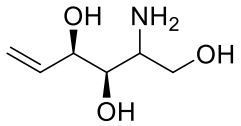
^{1}H NMR, D_2O, 500 MHz



(3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

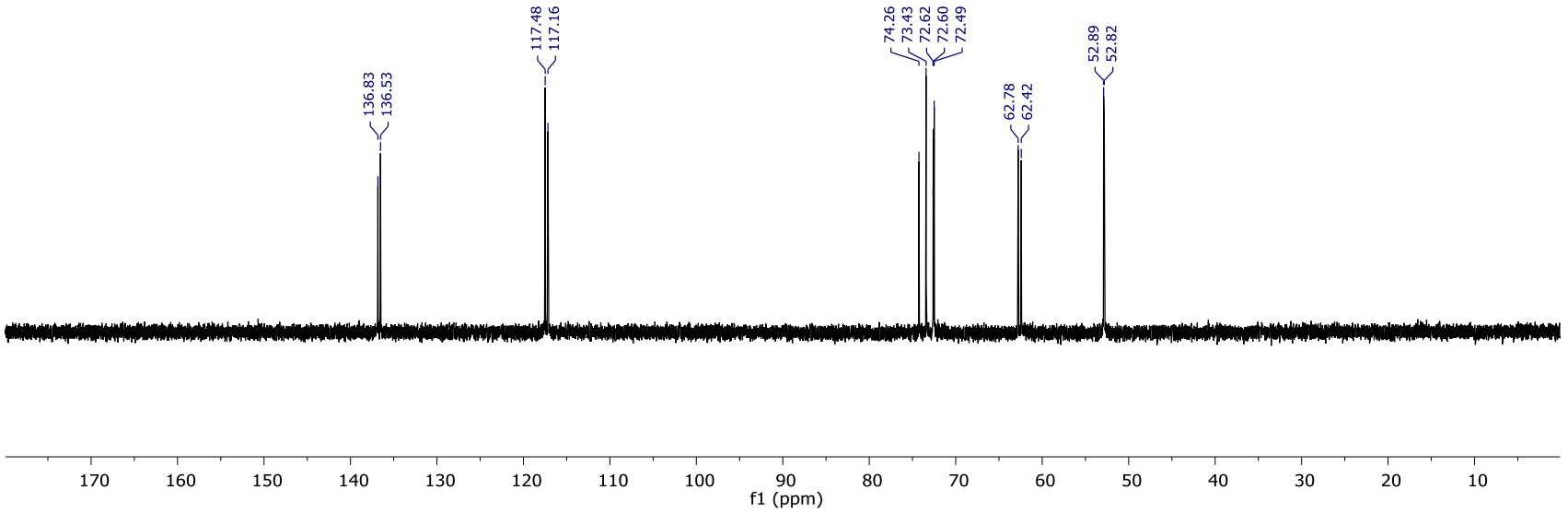
75

^{13}C NMR, D_2O, 125 MHz

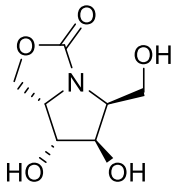


(3*R*,4*R*)-2-aminohex-5-ene-1,3,4-triol

75



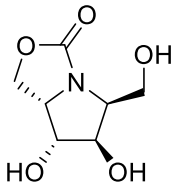
^{1}H NMR, D_2O, 500 MHz



(5*S*,6*R*,7*R*,7a*S*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

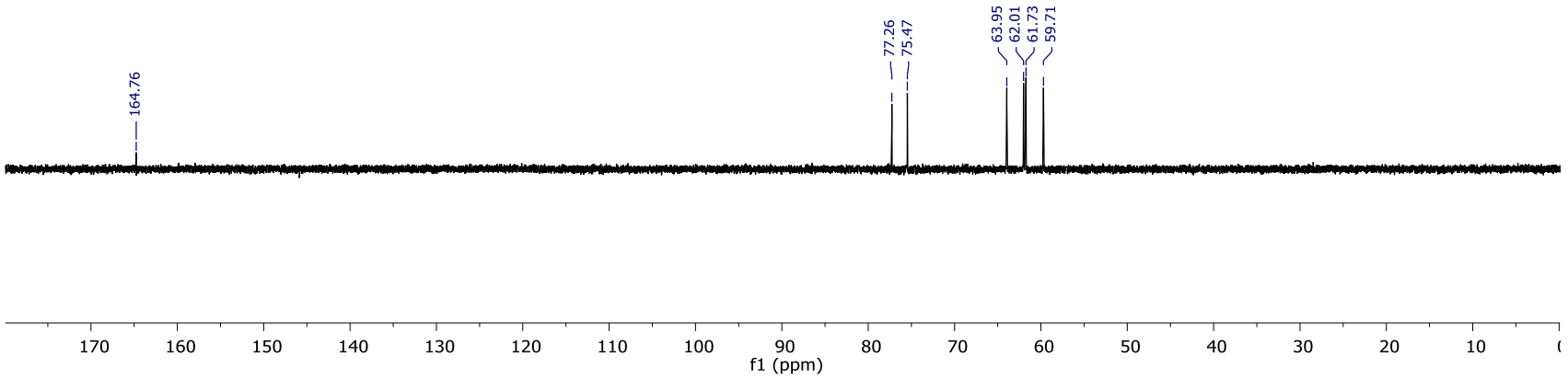
(76a)

^{13}C NMR, D_2O, 125 MHz

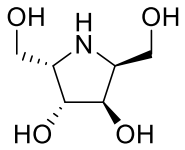


(5*S*,6*R*,7*R*,7a*S*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

76a



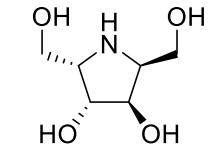
^{1}H NMR, D_2O, 500 MHz



2,5-dideoxy-2,5-imino-L-iditol

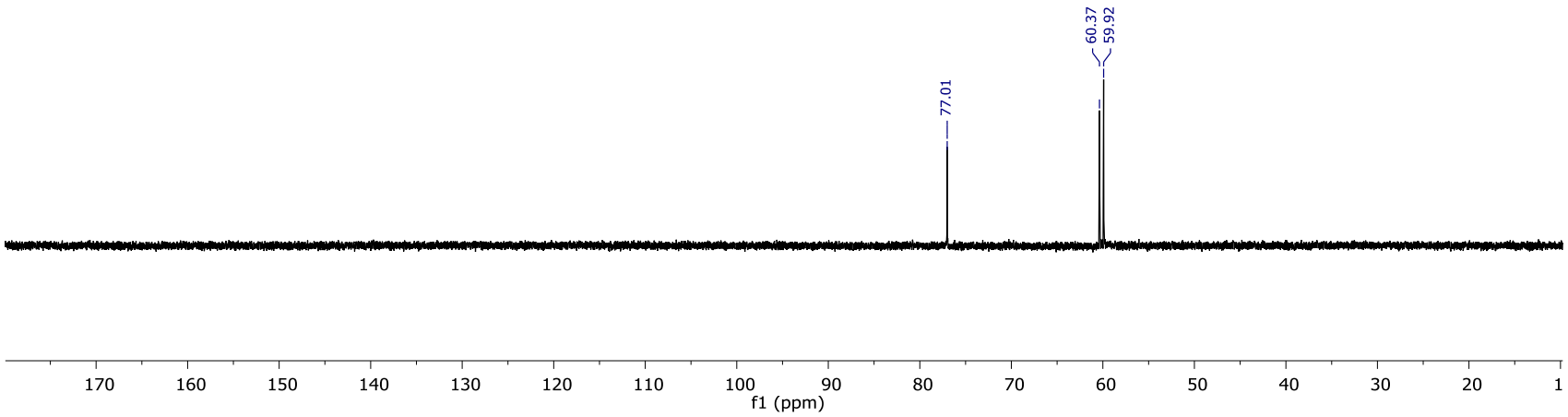
77

^{13}C NMR, D_2O, 125 MHz

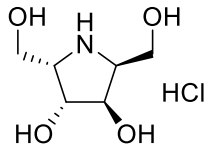


2,5-dideoxy-2,5-imino-L-iditol

77



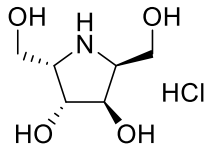
^{1}H NMR, D_2O, 500 MHz



2,5-dideoxy-2,5-imino-L-iditol.HCl

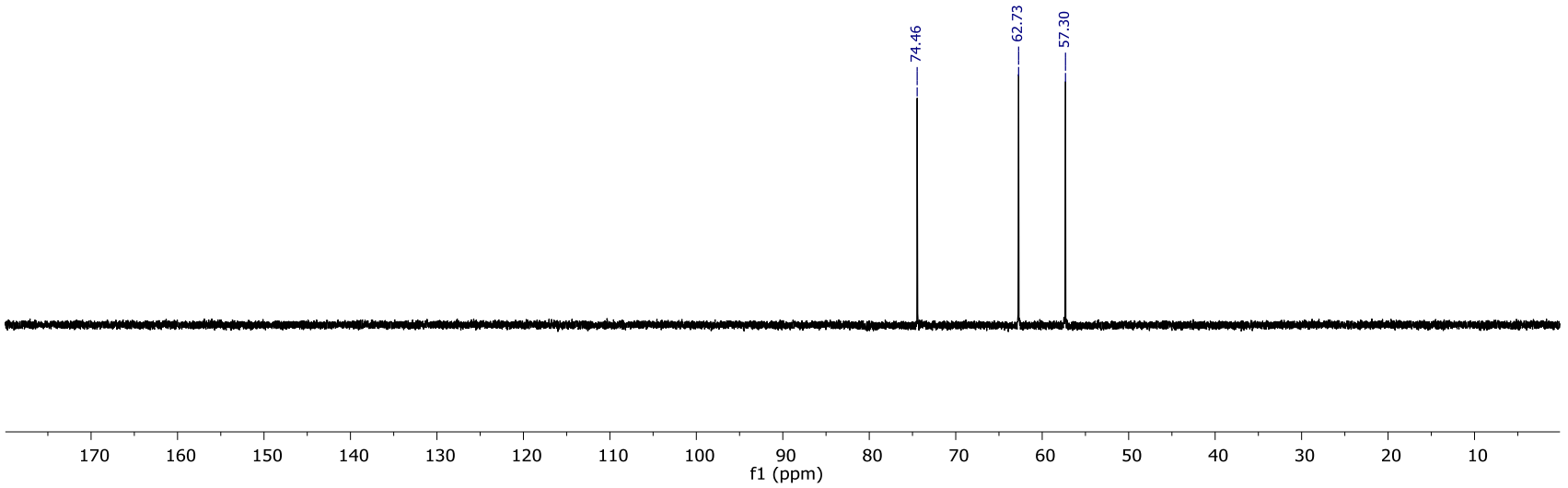
77

^{13}C NMR, D_2O, 125 MHz

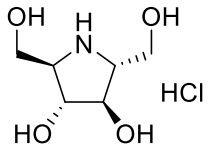


2,5-dideoxy-2,5-imino-L-iditol.HCl

77



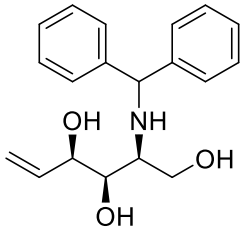
^{1}H NMR, D_2O, 500 MHz



DMDP

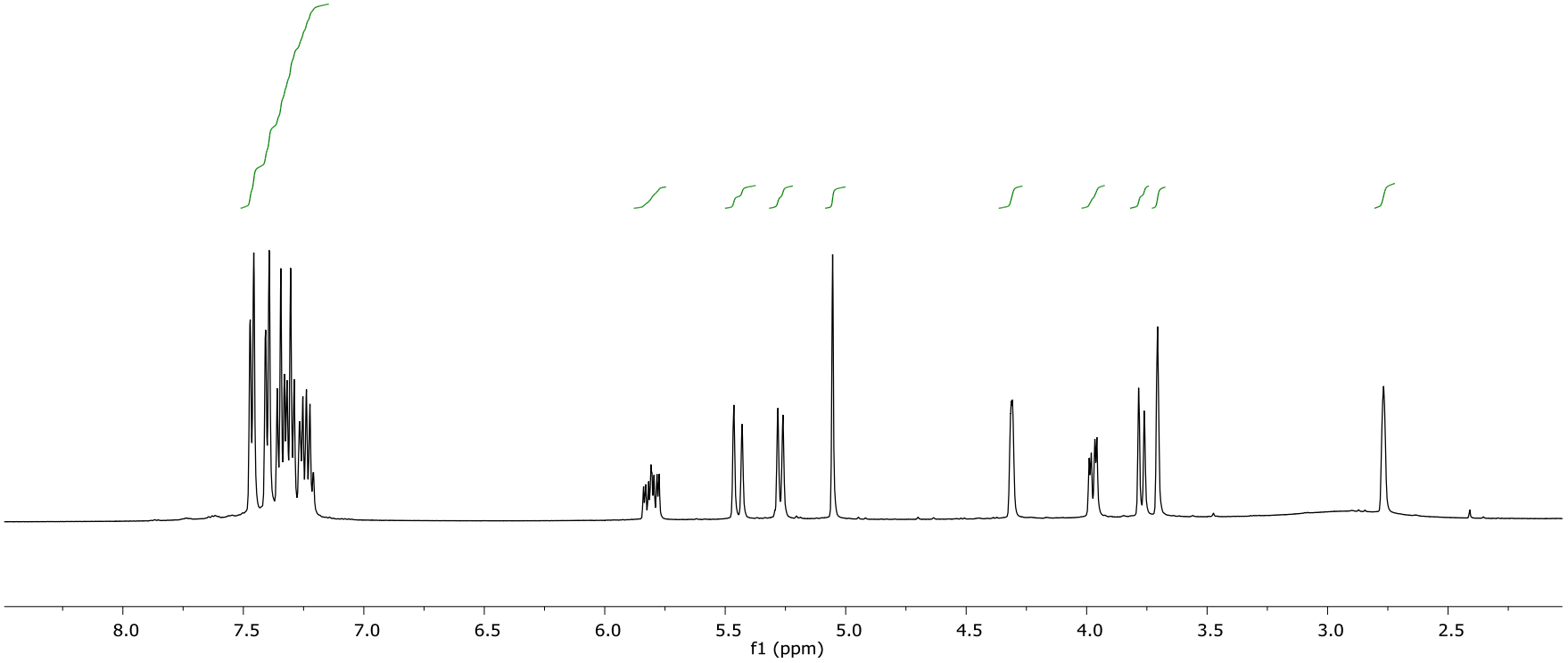
4

^{1}H NMR, $CDCl_3$, 500 MHz

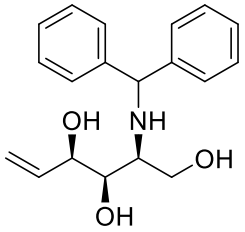


(2*S*,3*R*,4*R*)-2-(benzhydrylamino)hex-5-ene-1,3,4-triol

78a



^{13}C NMR, $CDCl_3$, 125 MHz



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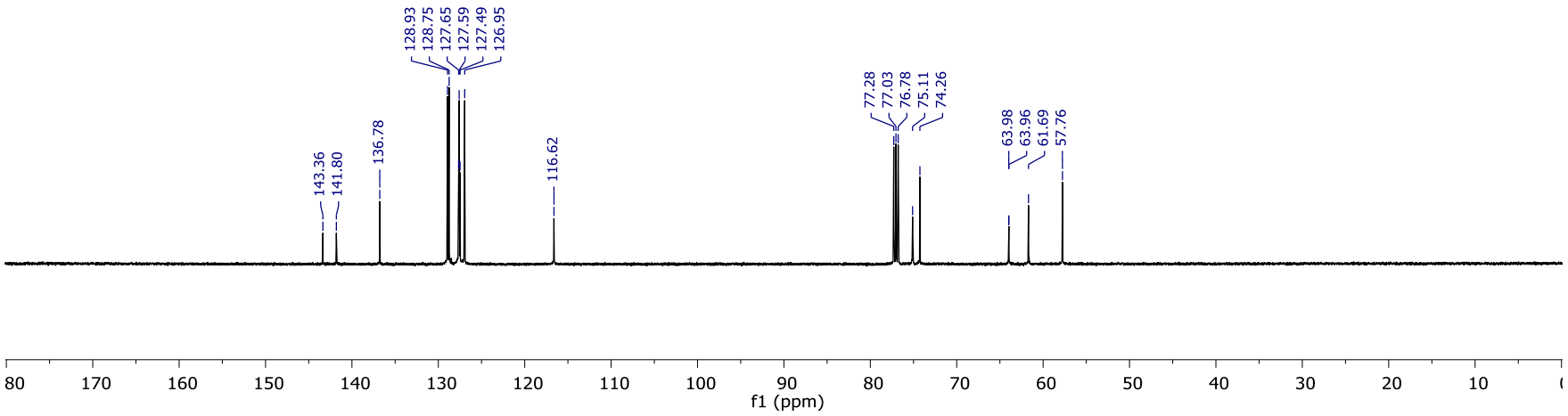
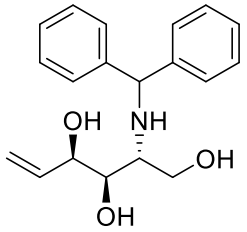
78a



^{1}H NMR, $CDCl_3$, 500 MHz



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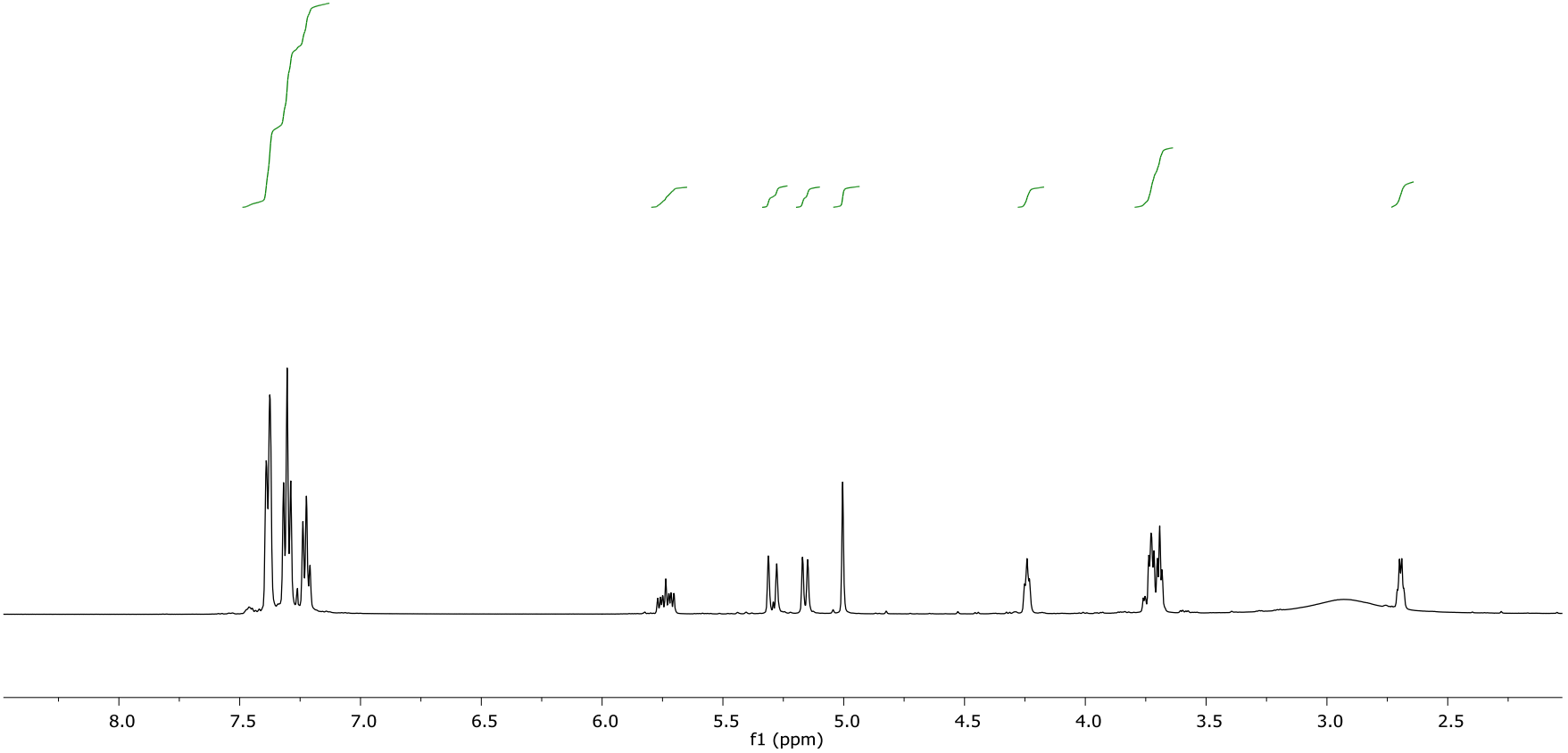
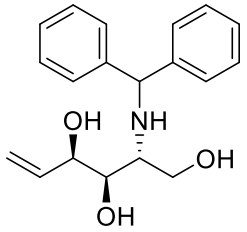
78b

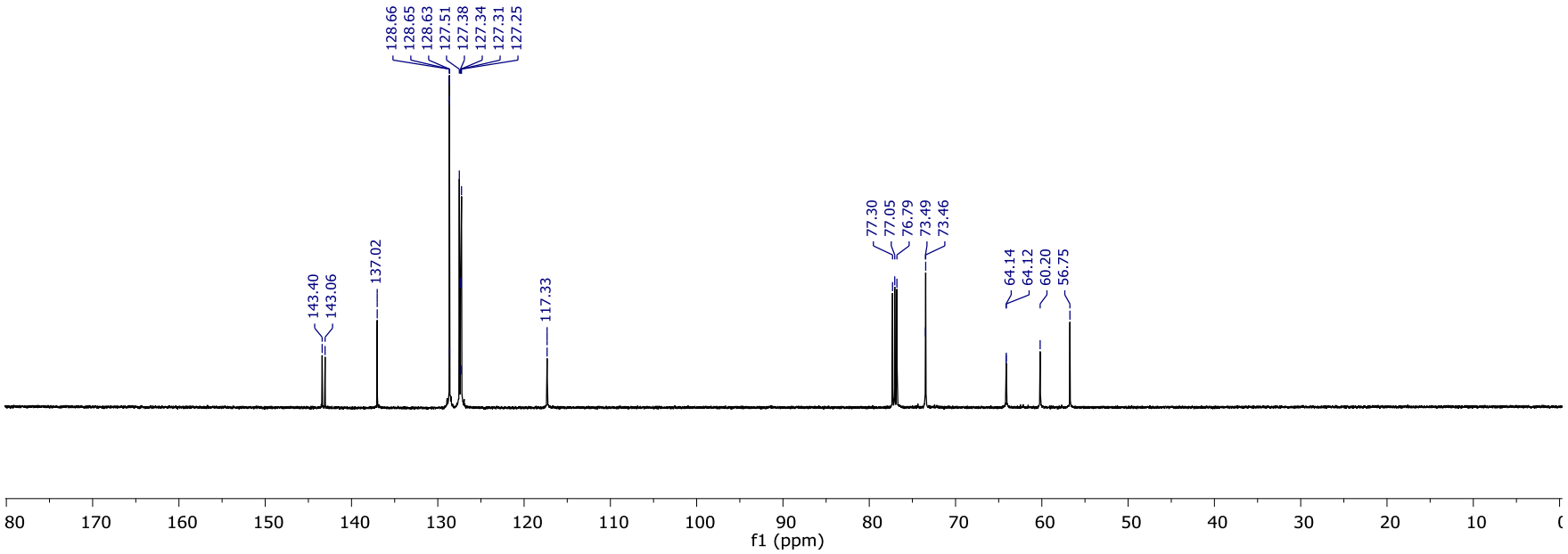


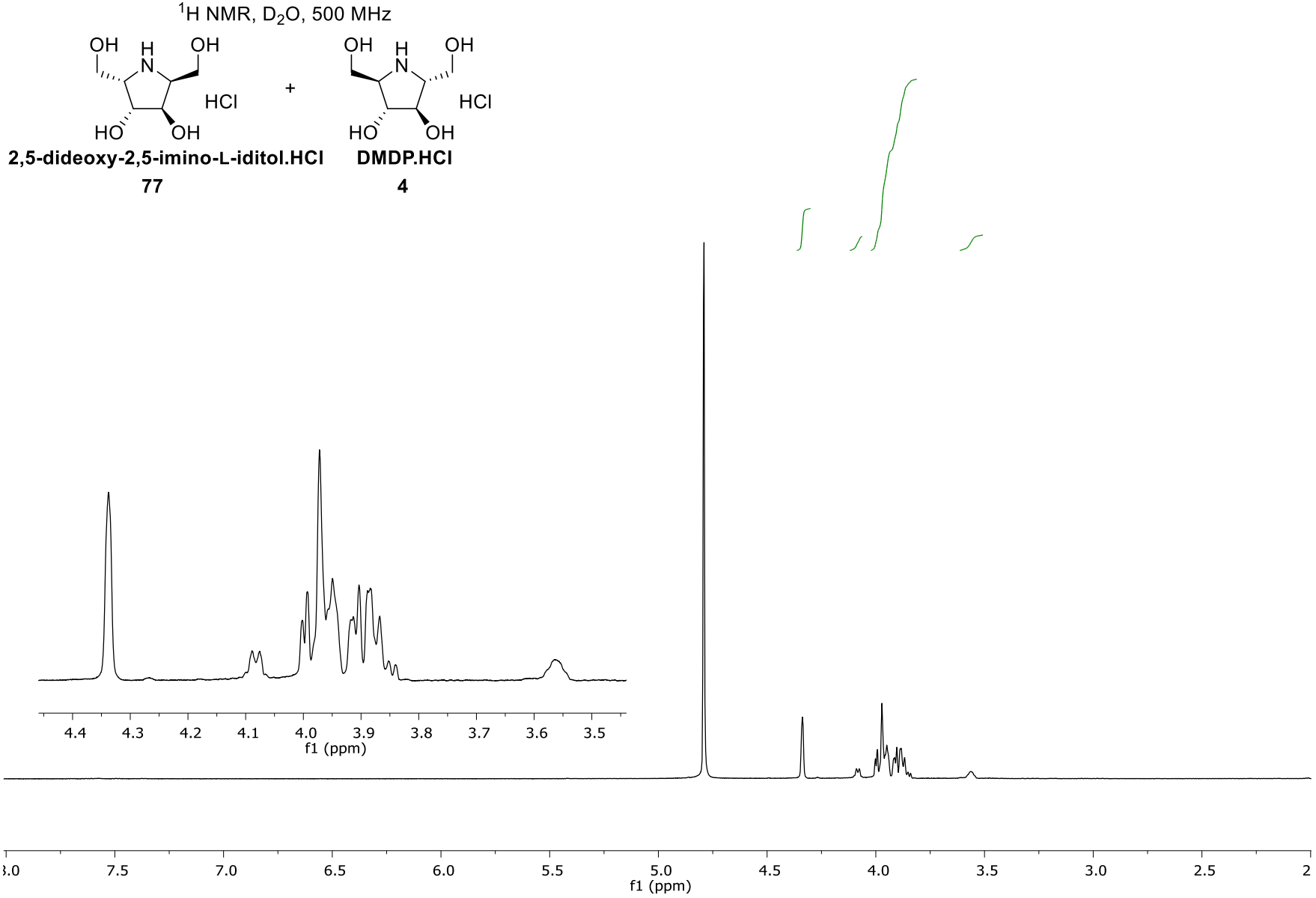
^{13}C NMR, $CDCl_3$, 125 MHz



(2*R*,3*R*,4*R*)-2-(benzhydrylamino)hex-5-ene-1,3,4-triol

78b




^{1}H NMR, D_2O, 500 MHz
OH
H
N
OH
HCl
HO
OH
+
OH
H
N
OH
HCl
HO
OH
2,5-dideoxy-2,5-imino-L-iditol.HCl
77
DMDP.HCl
4
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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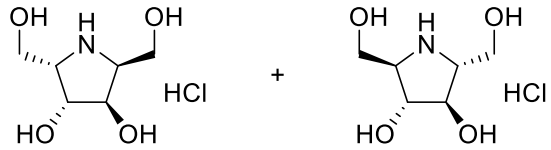
3.5
3.0
2.5
f1 (ppm)

^{13}C NMR, D_2O, 125 MHz



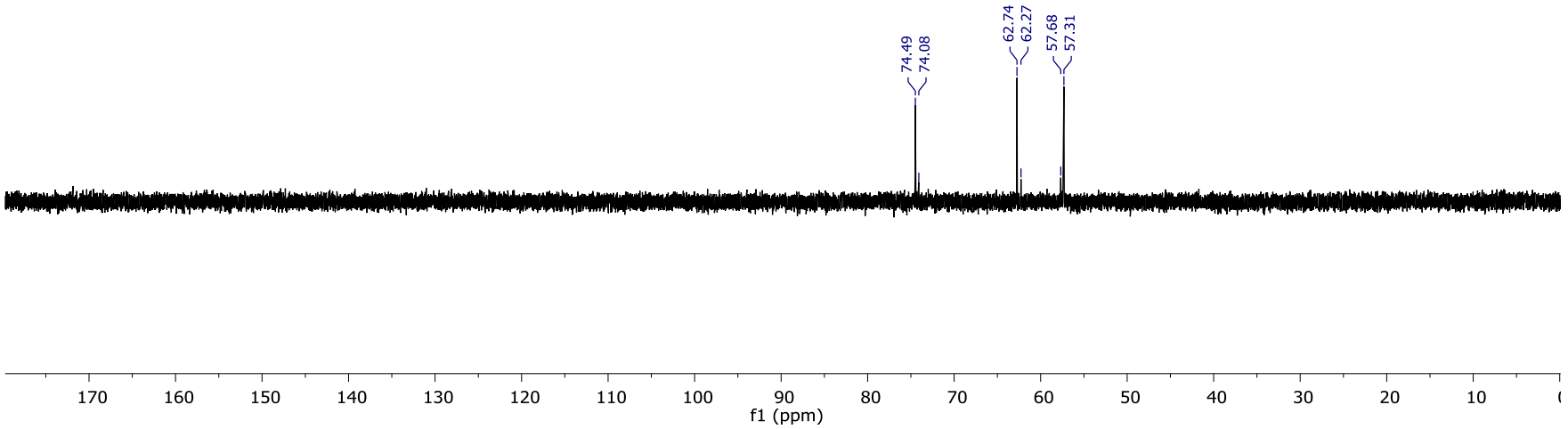
2,5-dideoxy-2,5-imino-L-iditol.HCl

77

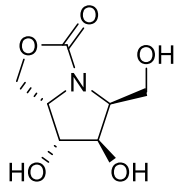
+

DMDP.HCl

4



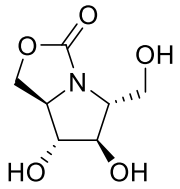
^{1}H NMR, D_2O, 500 MHz



(5*S*,6*R*,7*R*,7a*S*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

76a

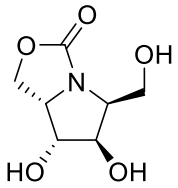
+



(5*R*,6*R*,7*R*,7a*R*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

76b

^{13}C NMR, D_2O, 500 MHz



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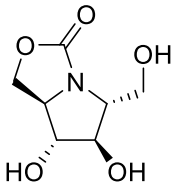
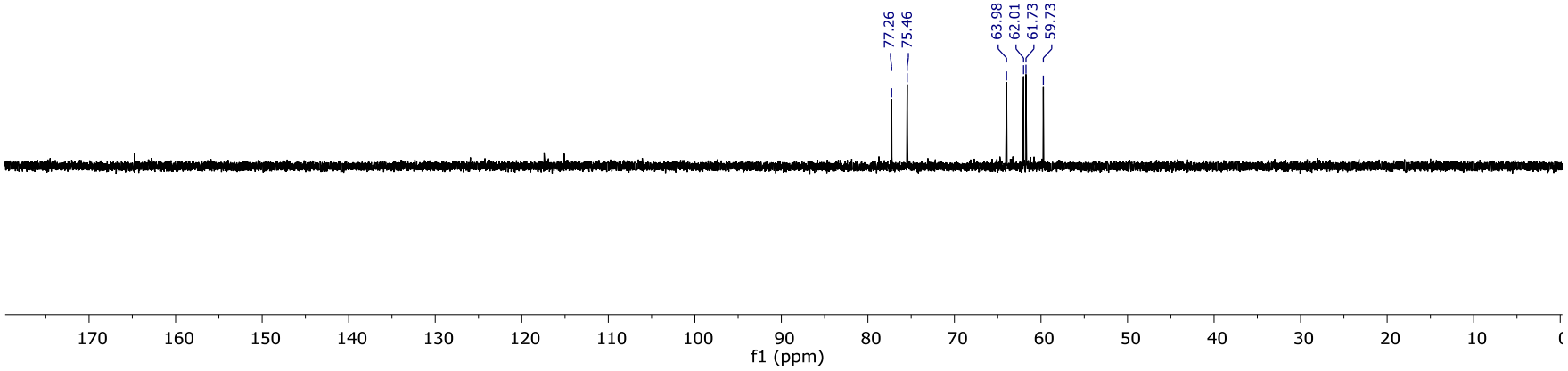


(5*S*,6*R*,7*R*,7a*S*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

76a

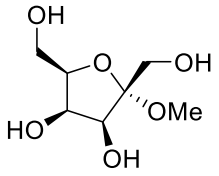
(5*R*,6*R*,7*R*,7a*R*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one

76b

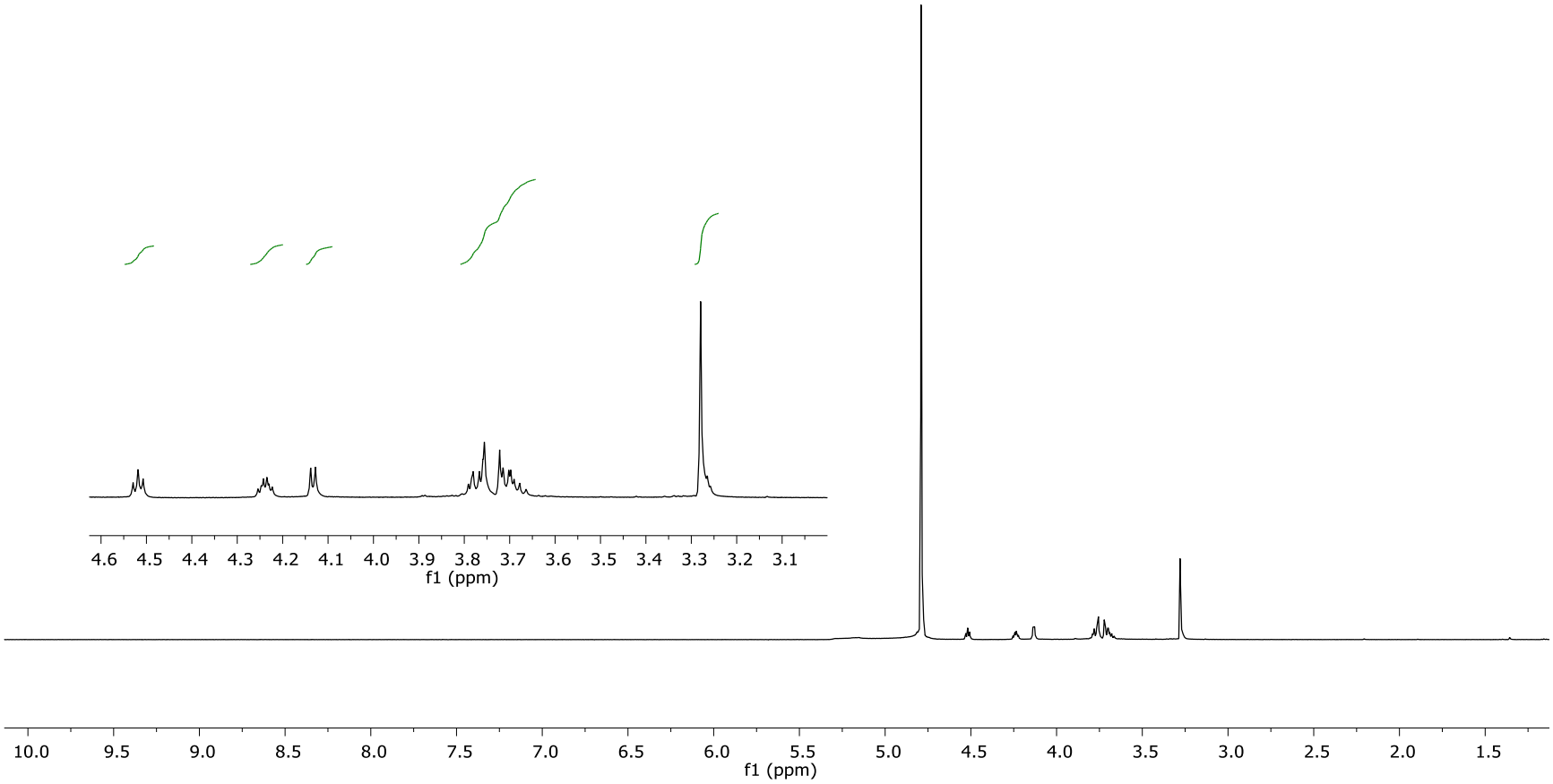


Chapter 3 spectra

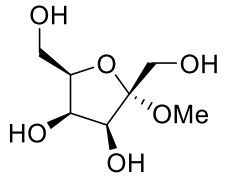
^{1}H NMR, D_2O, 500 MHz



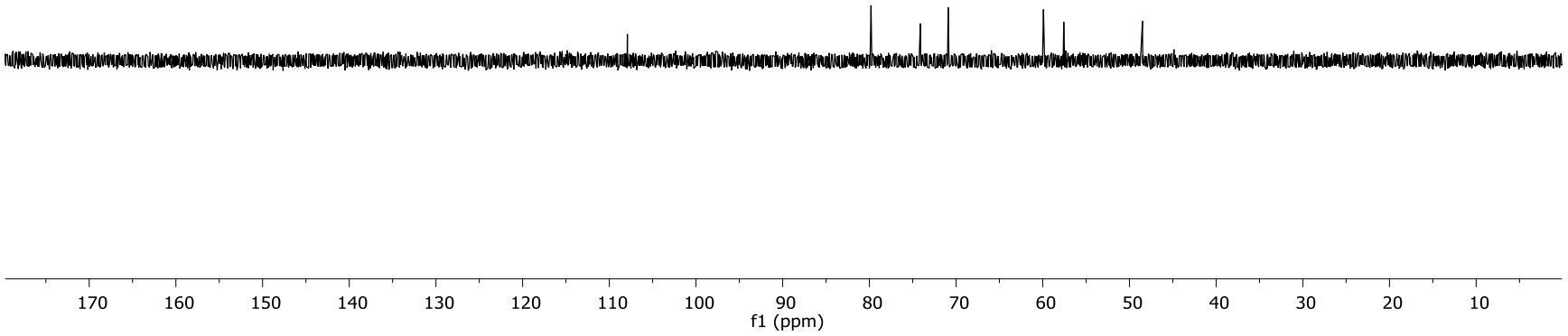
methyl α-D-tagatofuranoside
83



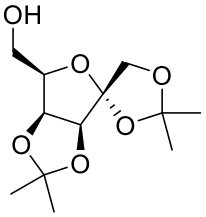
^{13}C NMR, D_2O, 125 MHz



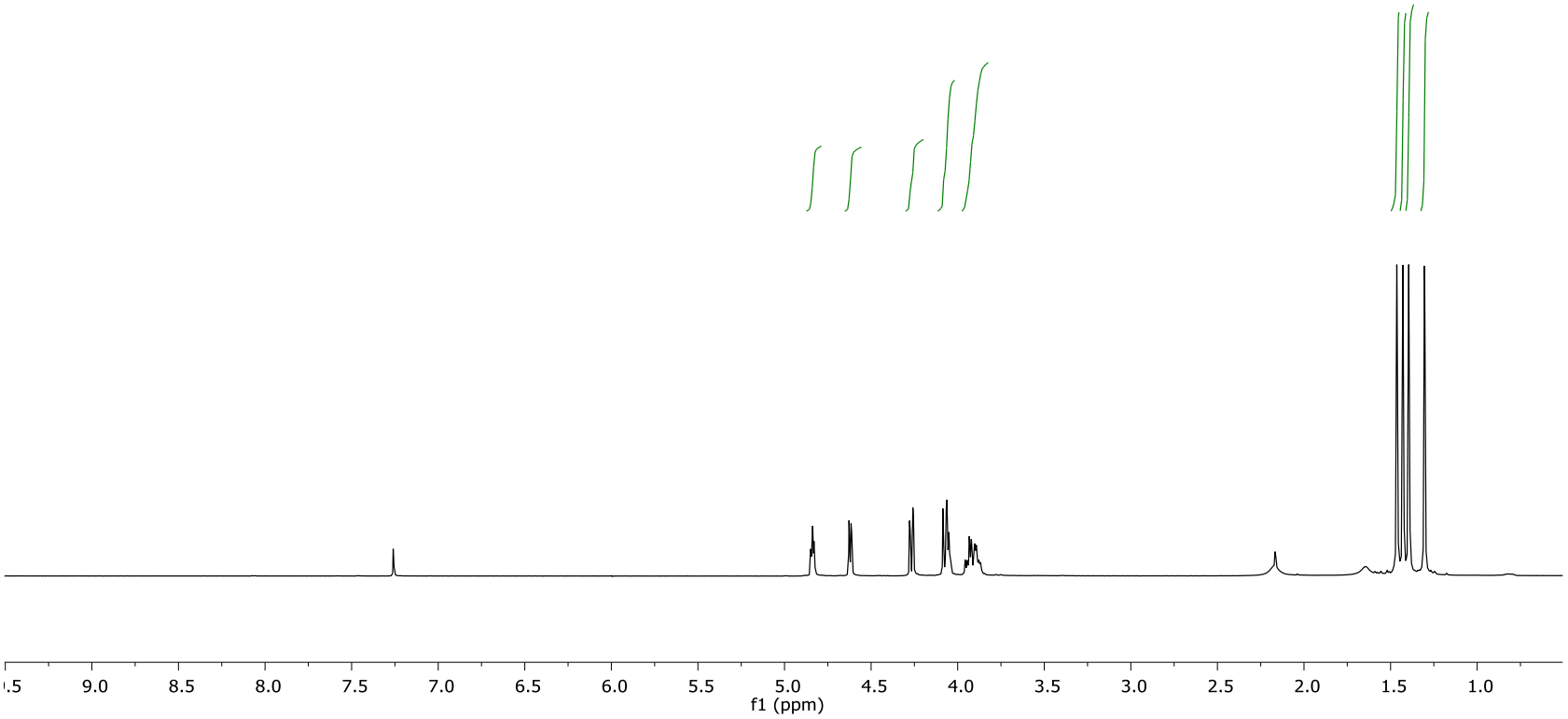
methyl α-D-tagatofuranoside
83



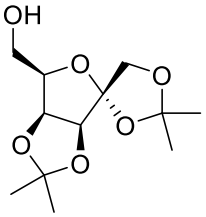
^{1}H NMR, $CDCl_3$, 500 MHz



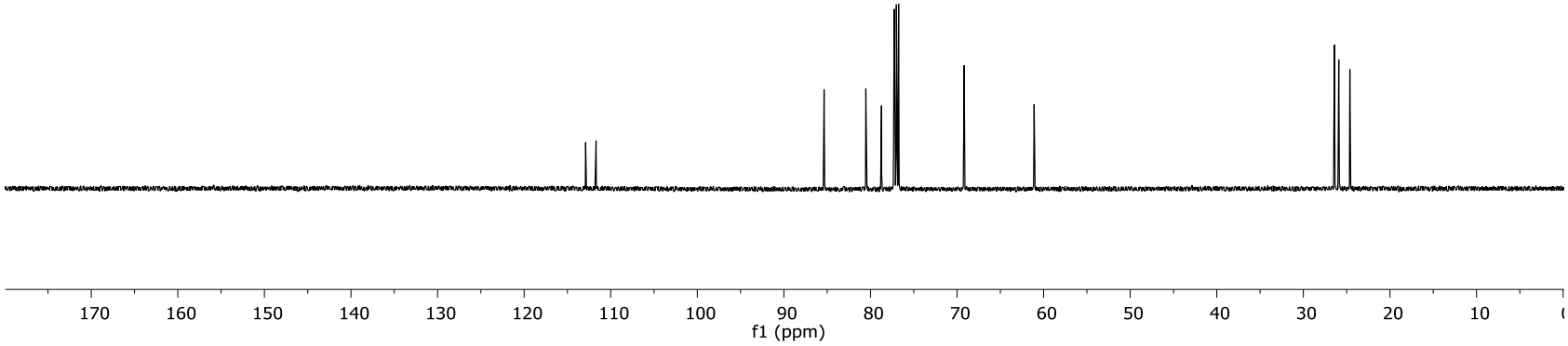
1,2:3,4-di-*O*-isopropylidene-α-D-tagatofuranoside
85



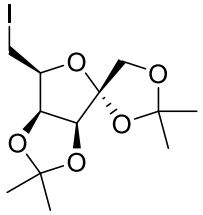
^{13}C NMR, $CDCl_3$, 125 MHz



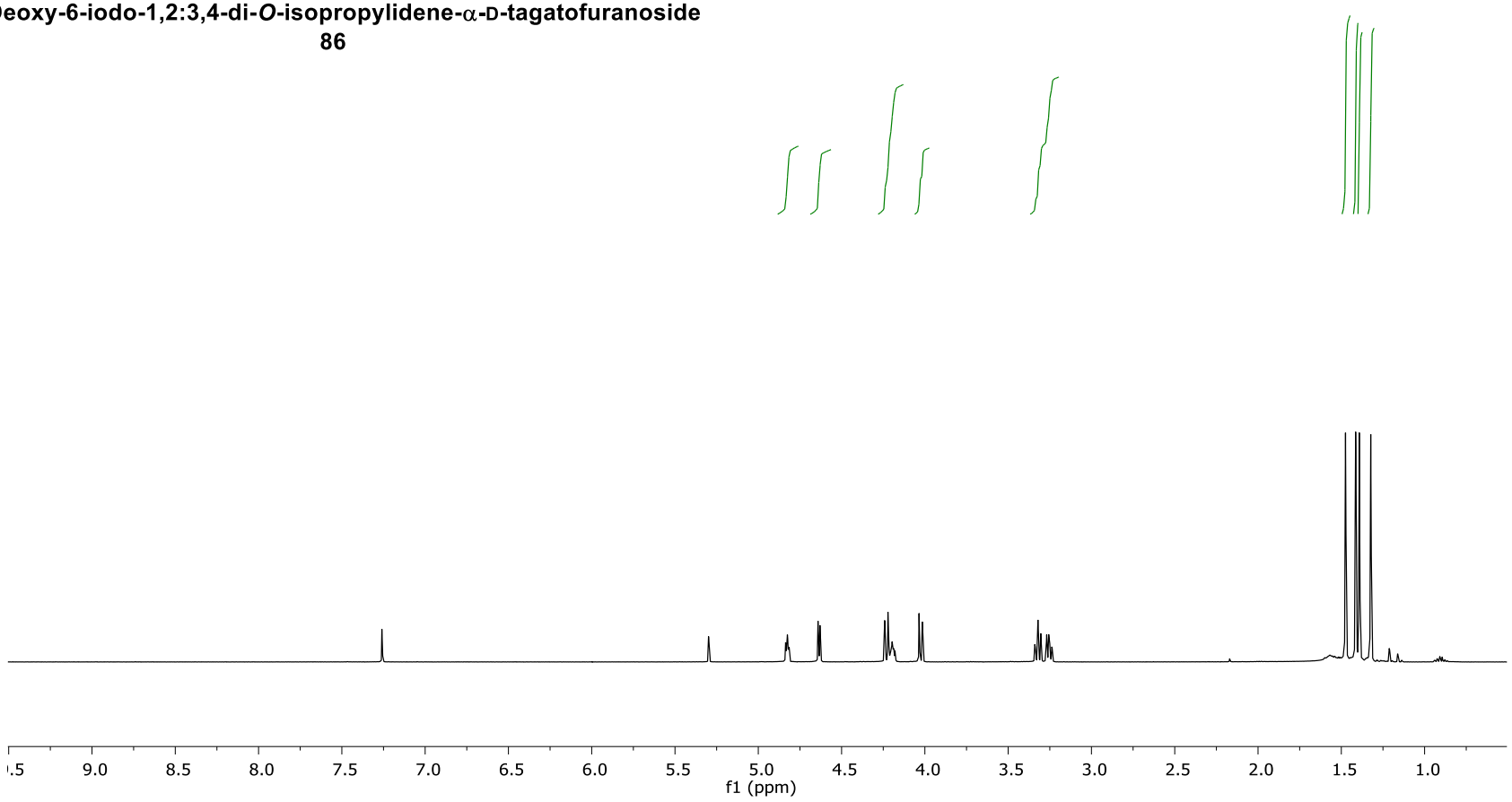
1,2:3,4-di-*O*-isopropylidene-α-D-tagatofuranoside
85



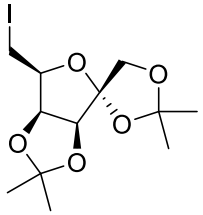
^{1}H NMR, $CDCl_3$, 500 MHz



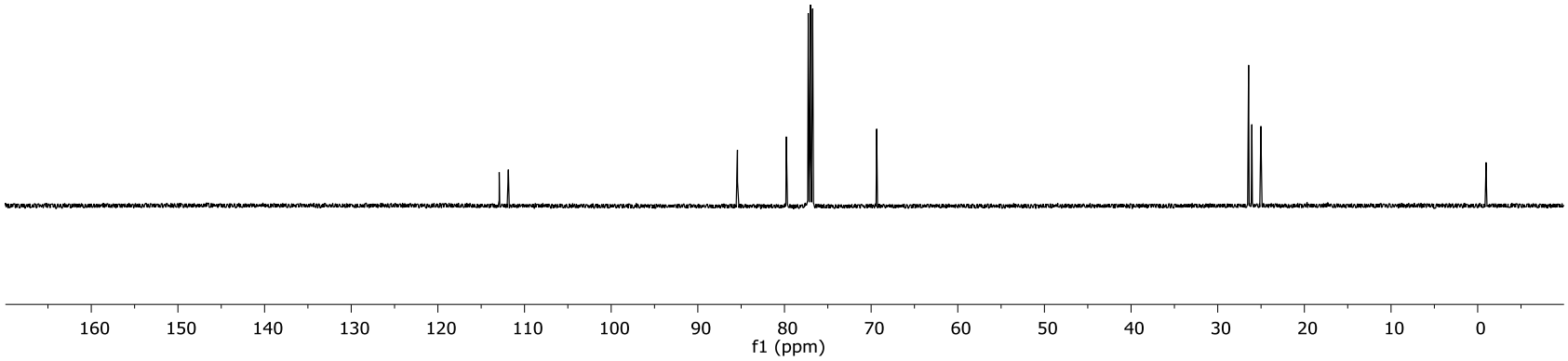
6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-tagatofuranoside
86



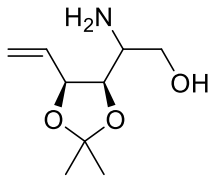
^{13}C NMR, $CDCl_3$, 125 MHz



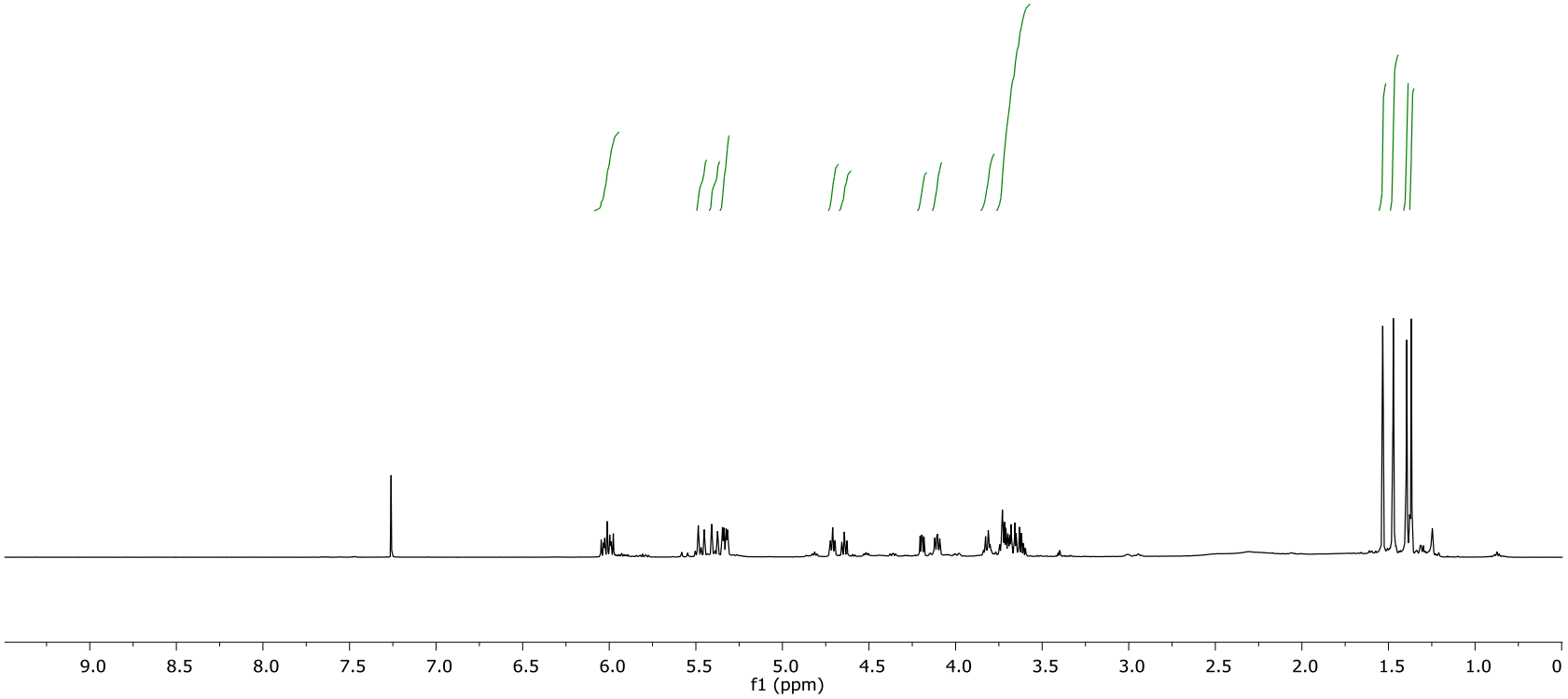
6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-tagatofuranoside
86



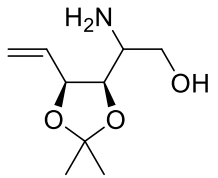
^{1}H NMR, $CDCl_3$, 500 MHz



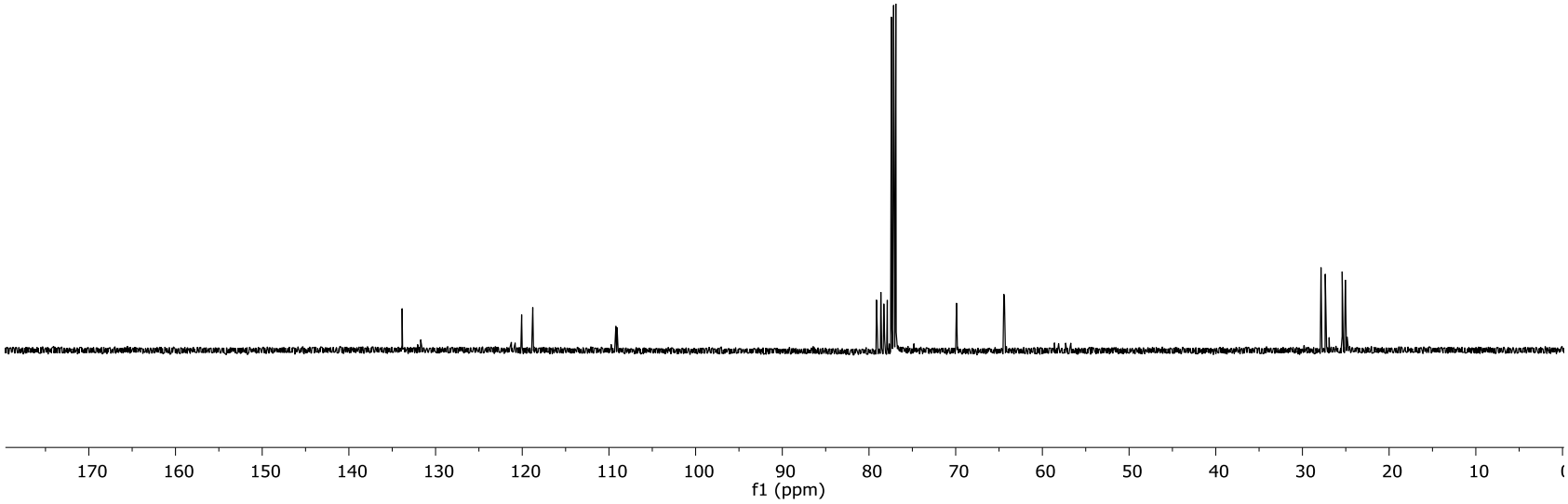
2-amino-2-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol
87



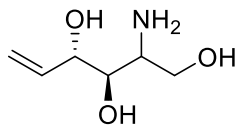
^{13}C NMR, $CDCl_3$, 125 MHz



2-amino-2-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol
87

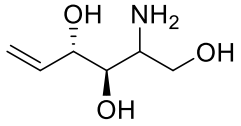


^{1}H NMR, D_2O, 500 MHz

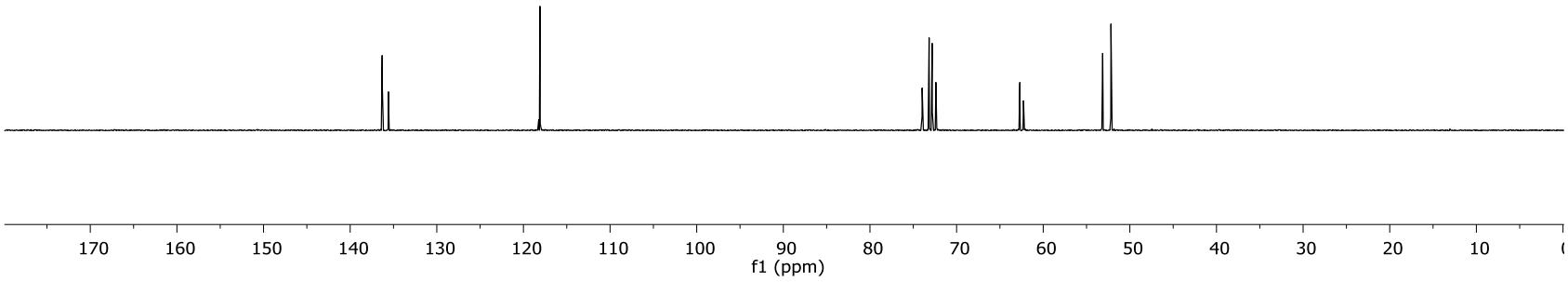


(3*R*,4*S*)-2-aminohex-5-ene-1,3,4-triol
88

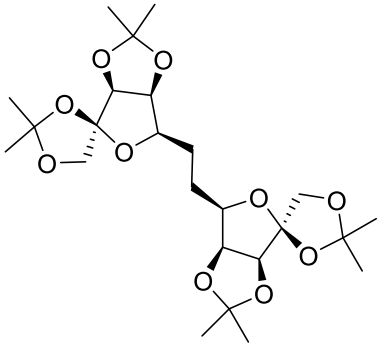
^{13}C NMR, D_2O, 125 MHz



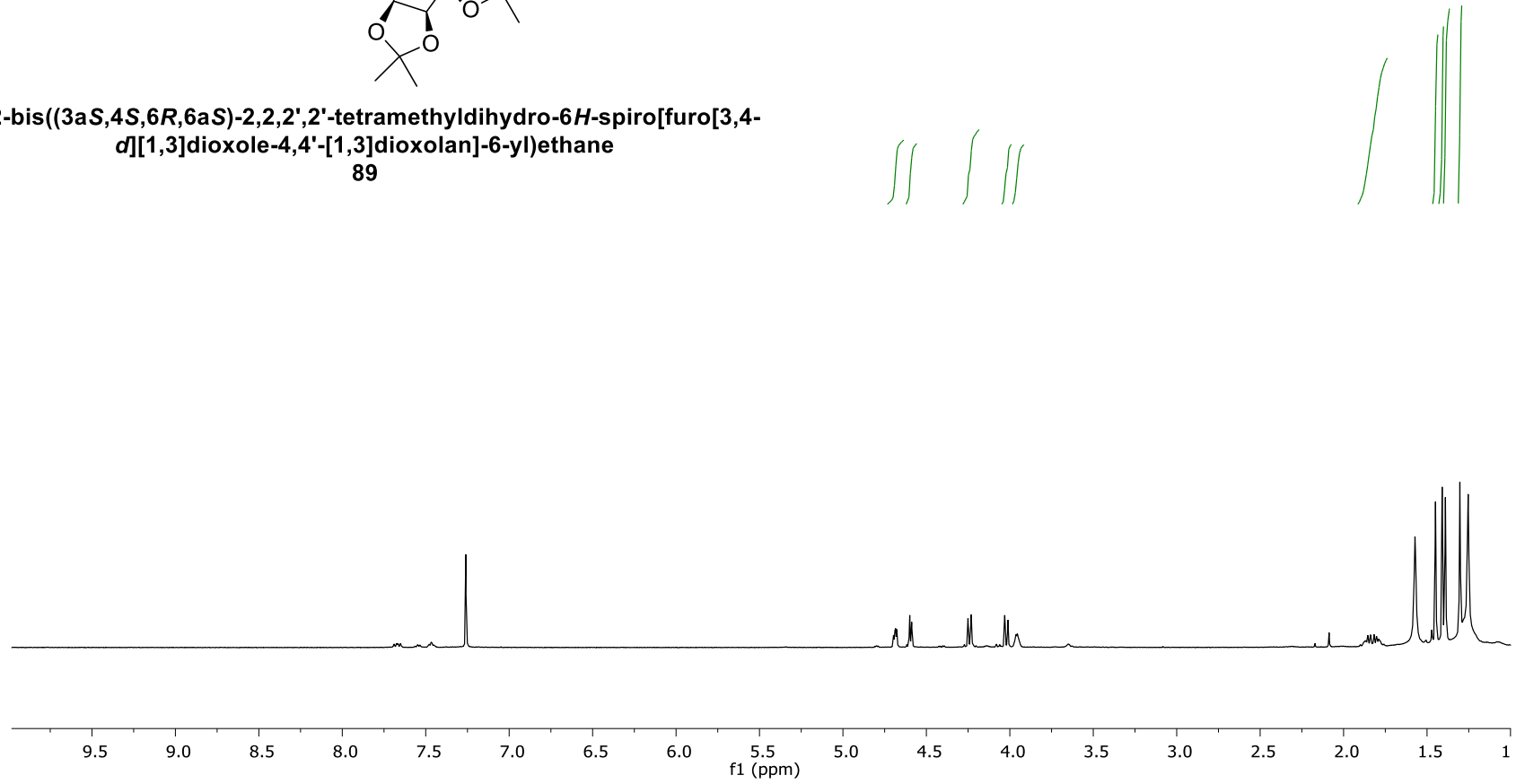
(3*R*,4*S*)-2-aminohex-5-ene-1,3,4-triol
88



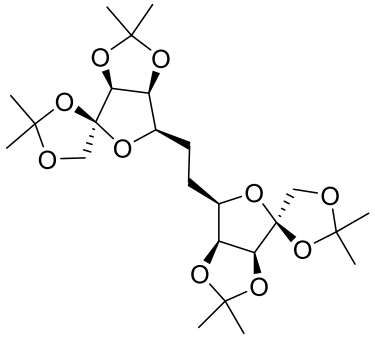
^{1}H NMR, $CDCl_3$, 500 MHz



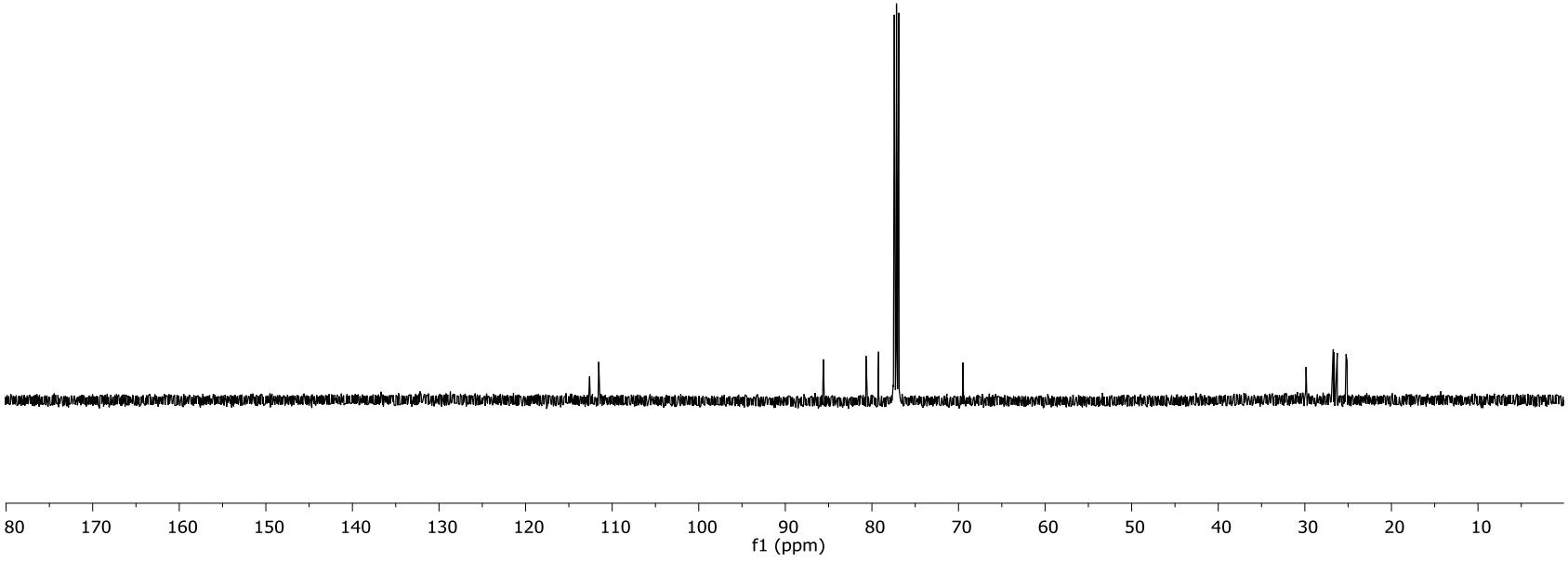
1,2-bis((3a*S*,4*S*,6*R*,6a*S*)-2,2,2',2'-tetramethyldihydro-6*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,4'-[1,3]dioxolan]-6-yl)ethane
89



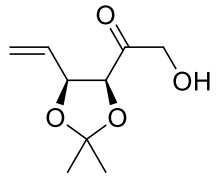
^{13}C NMR, $CDCl_3$, 125 MHz



1,2-bis((3a*S*,4*S*,6*R*,6a*S*)-2,2,2',2'-tetramethyldihydro-6*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,4'-[1,3]dioxolan]-6-yl)ethane
89

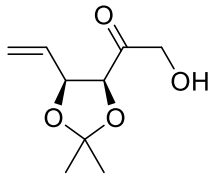


^{1}H NMR, $CDCl_3$, 500 MHz

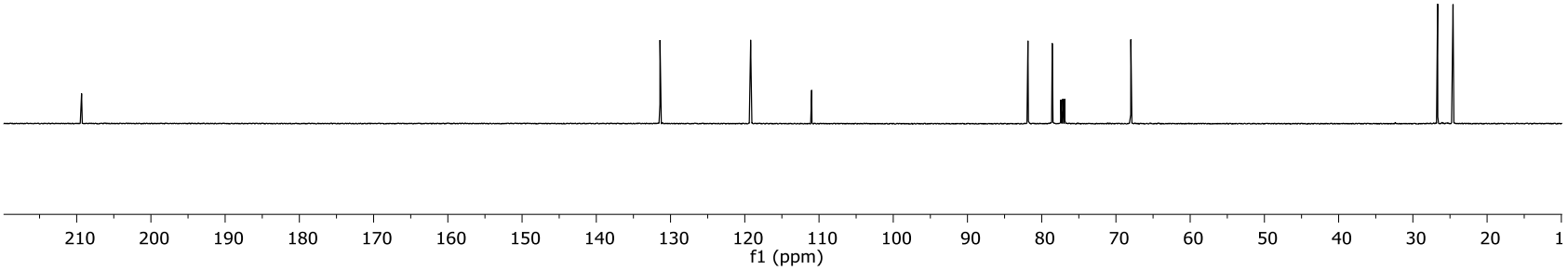


1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethan-1-one
90

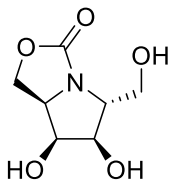
^{13}C NMR, $CDCl_3$, 125 MHz



1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethan-1-one
90

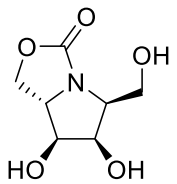


^{1}H NMR, D_2O, 500 MHz

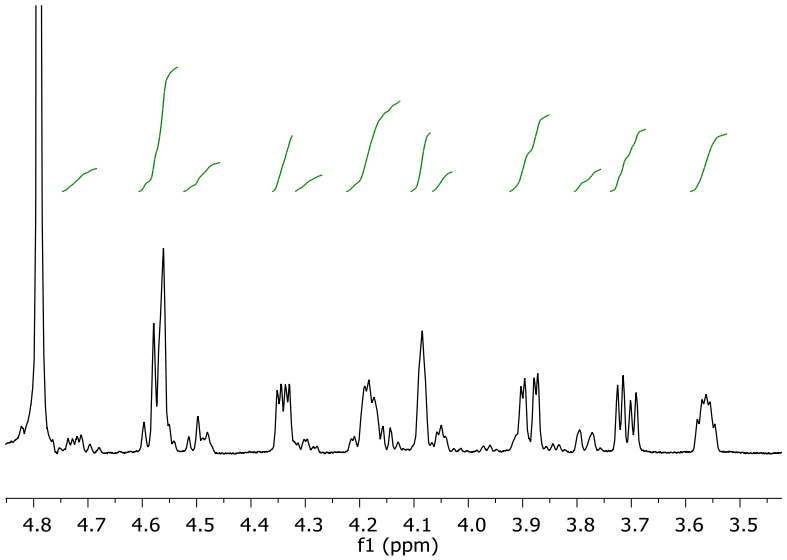


(5*R*,6*R*,7*S*,7a*R*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one
79

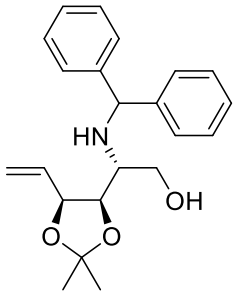
+



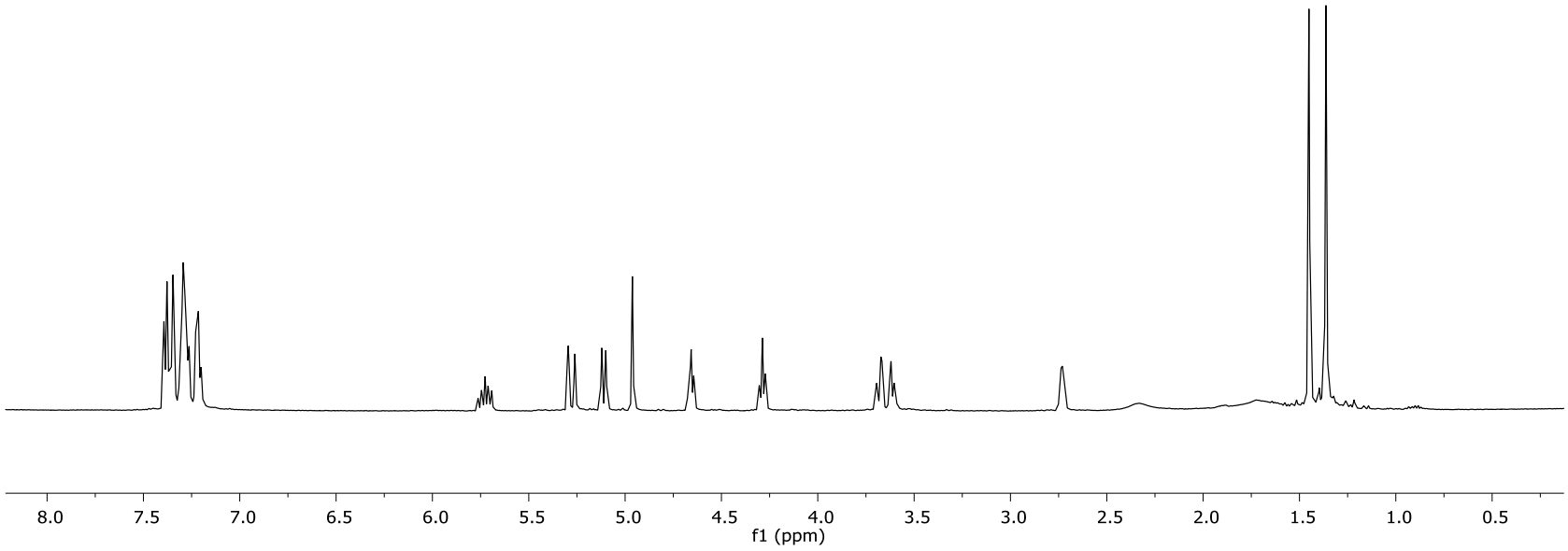
(5*S*,6*R*,7*S*,7a*S*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one
79a



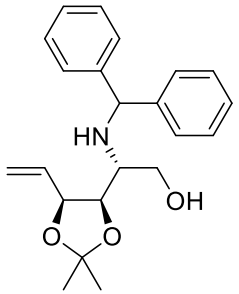
^{1}H NMR, $CDCl_3$, 500 MHz



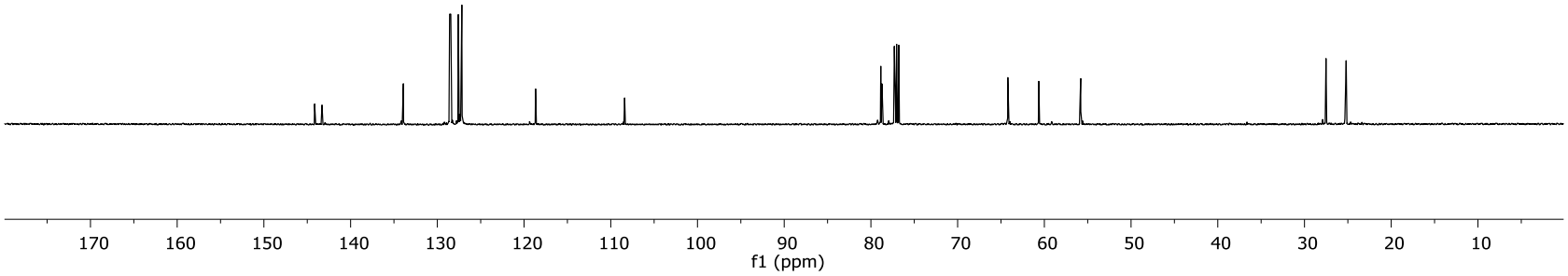
(*R*)-2-(benzhydrylamino)-2-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol
93



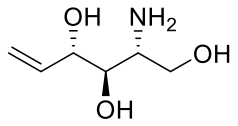
^{13}C NMR, $CDCl_3$, 125 MHz



(*R*)-2-(benzhydrylamino)-2-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethan-1-ol
93

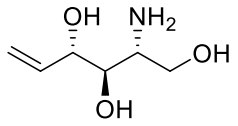


^{1}H NMR, D_2O, 500 MHz

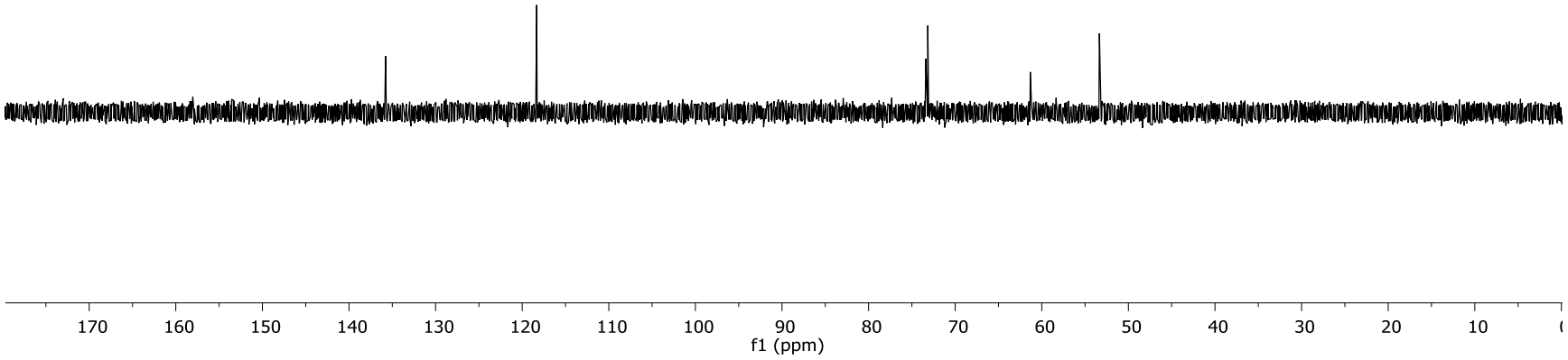


(2*R*,3*R*,4*S*)-2-aminohex-5-ene-1,3,4-triol
80

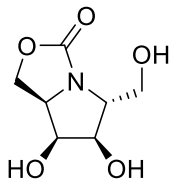
^{13}C NMR, D_2O, 125 MHz



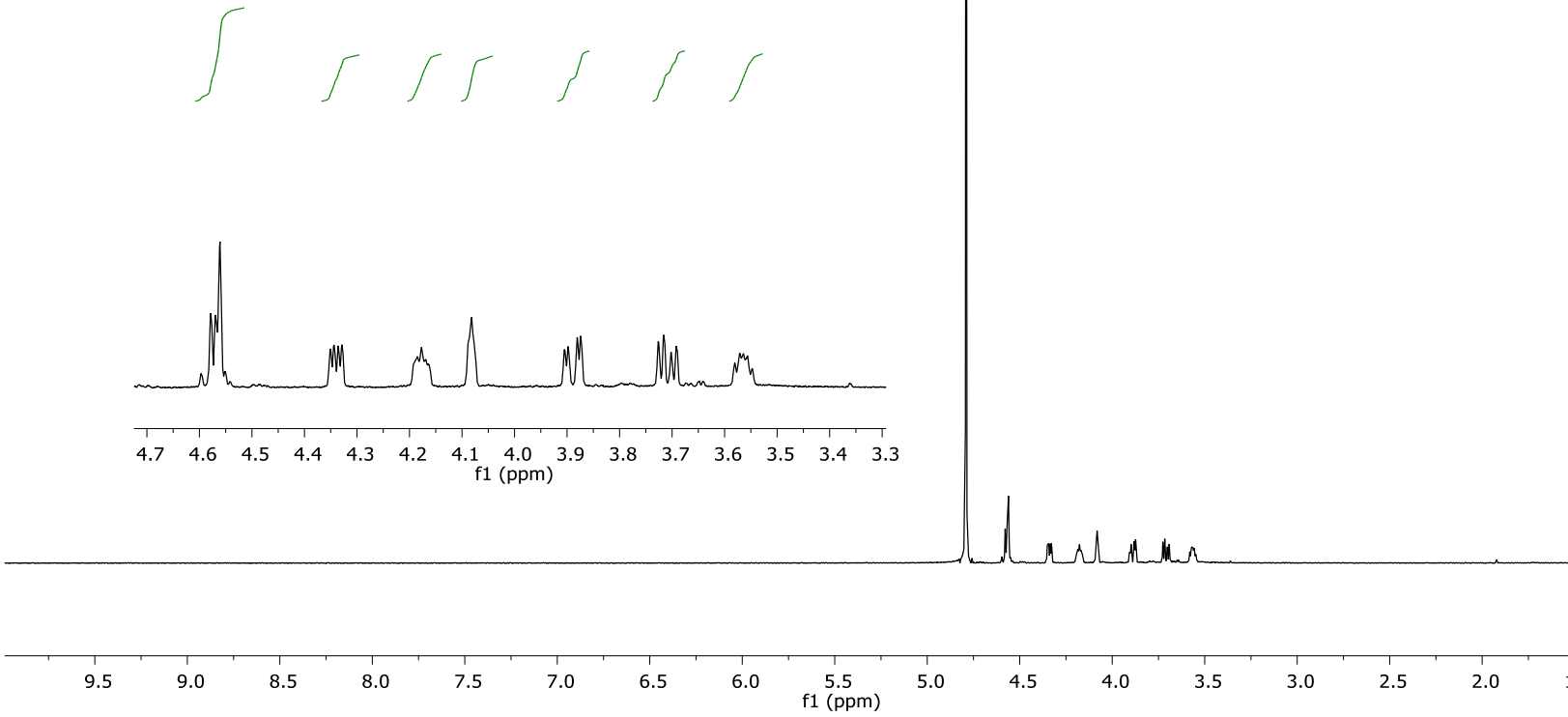
(2*R*,3*R*,4*S*)-2-aminohex-5-ene-1,3,4-triol
80



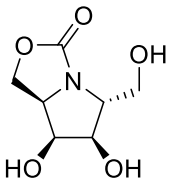
^{1}H NMR, D_2O, 500 MHz



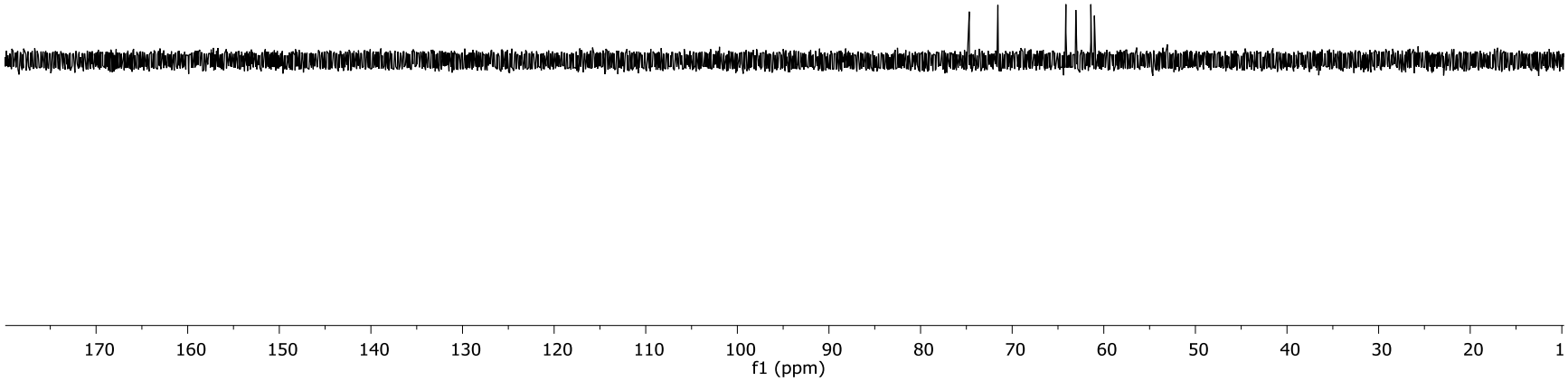
(5*R*,6*R*,7*S*,7a*R*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one
79



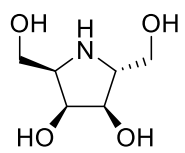
^{13}C NMR, D_2O, 125 MHz



(5*R*,6*R*,7*S*,7a*R*)-6,7-dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one
79

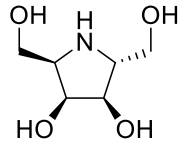


^{1}H NMR, D_2O, 500 MHz

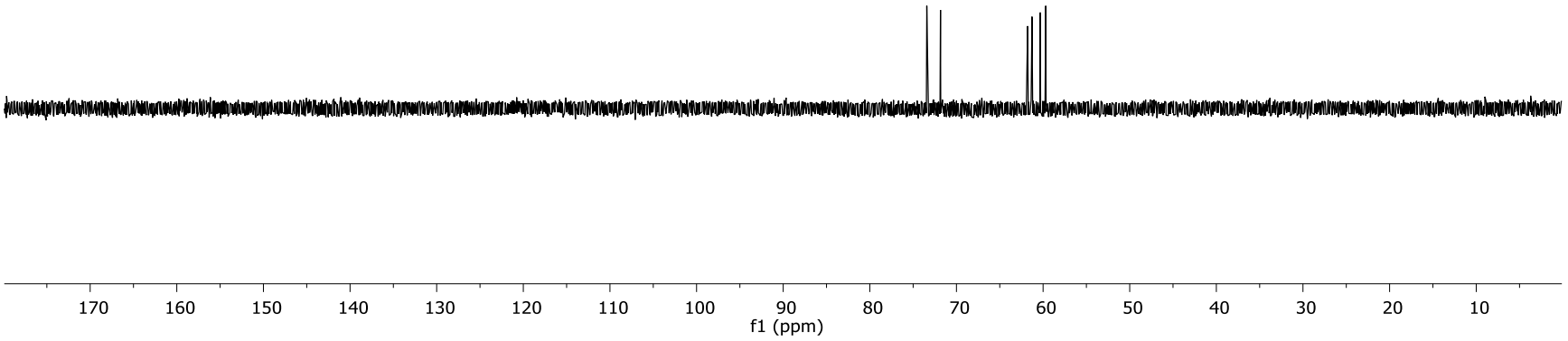


2,5-dideoxy-2,5-imino-D-altritol (DIA)
78

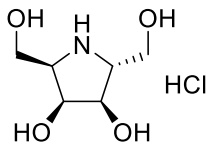
^{13}C NMR, D_2O, 125 MHz



2,5-dideoxy-2,5-imino-D-altritol (DIA)
78

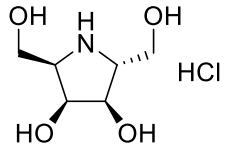


^{1}H NMR, D_2O, 500 MHz

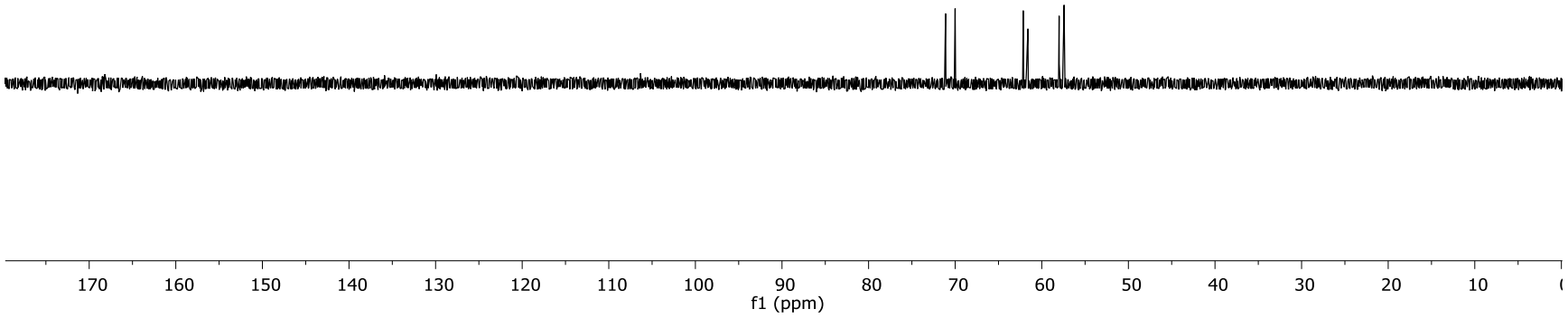


2,5-dideoxy-2,5-imino-D-altritol HCl (DIA)
78

^{13}C NMR, D_2O, 125 MHz

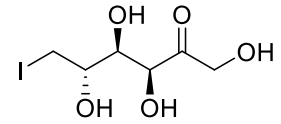


2,5-dideoxy-2,5-imino-D-altritol HCl (DIA)
78



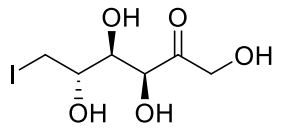
Chapter 4 Spectra

^{1}H NMR, D_2O, 500 MHz

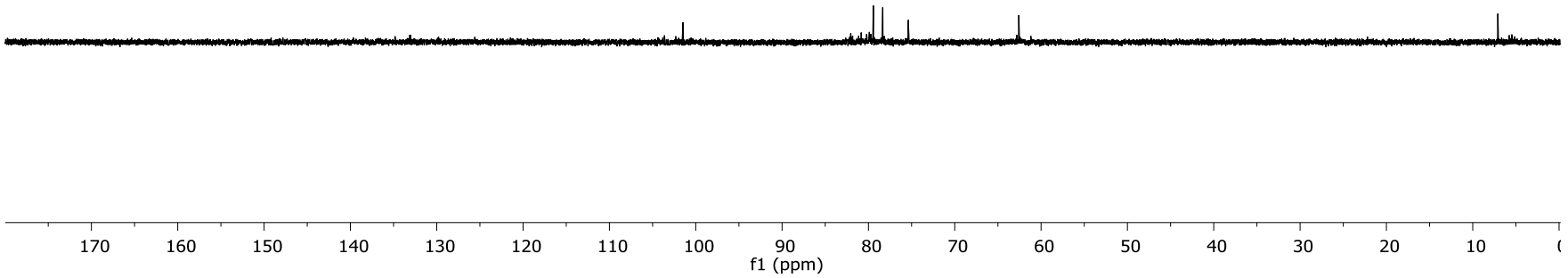


6-deoxy-6-iodo-D-Fructose
94

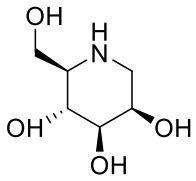
^{13}C NMR, D_2O, 125 MHz



6-deoxy-6-iodo-D-Fructose
94

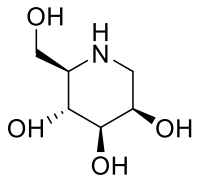


^{1}H NMR, D_2O, 500 MHz

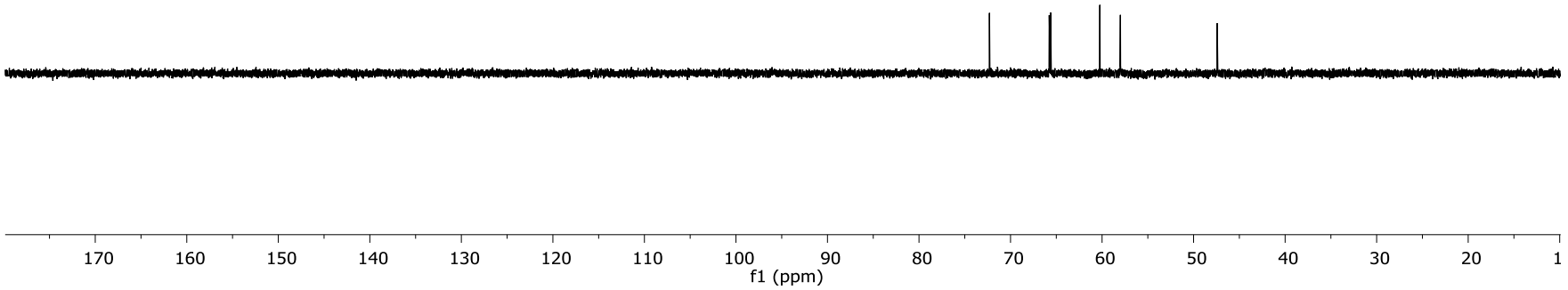


DMJ
36

^{13}C NMR, D_2O, 125 MHz

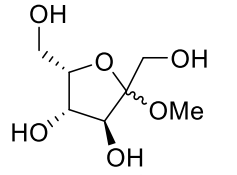


DMJ
36



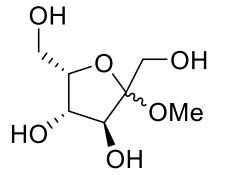
Chapter 5 spectra

^{1}H NMR, D_2O, 500 MHz

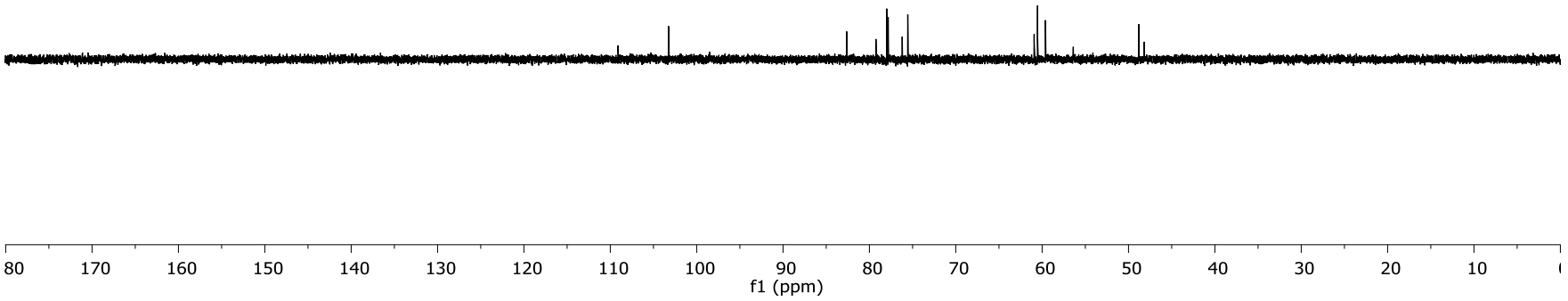


Methyl L-sorbofuranoside
(111)

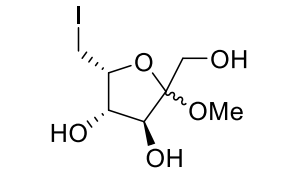
^{13}C NMR, D_2O, 125 MHz



Methyl L-sorbofuranoside
(111)

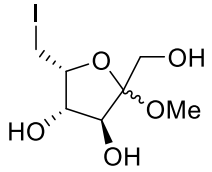


^{1}H NMR, D_2O, 500 MHz

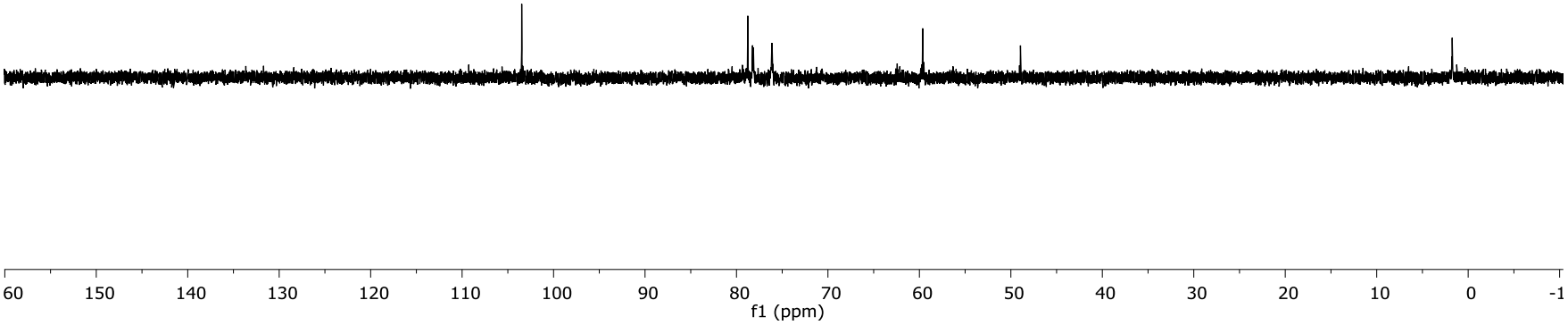


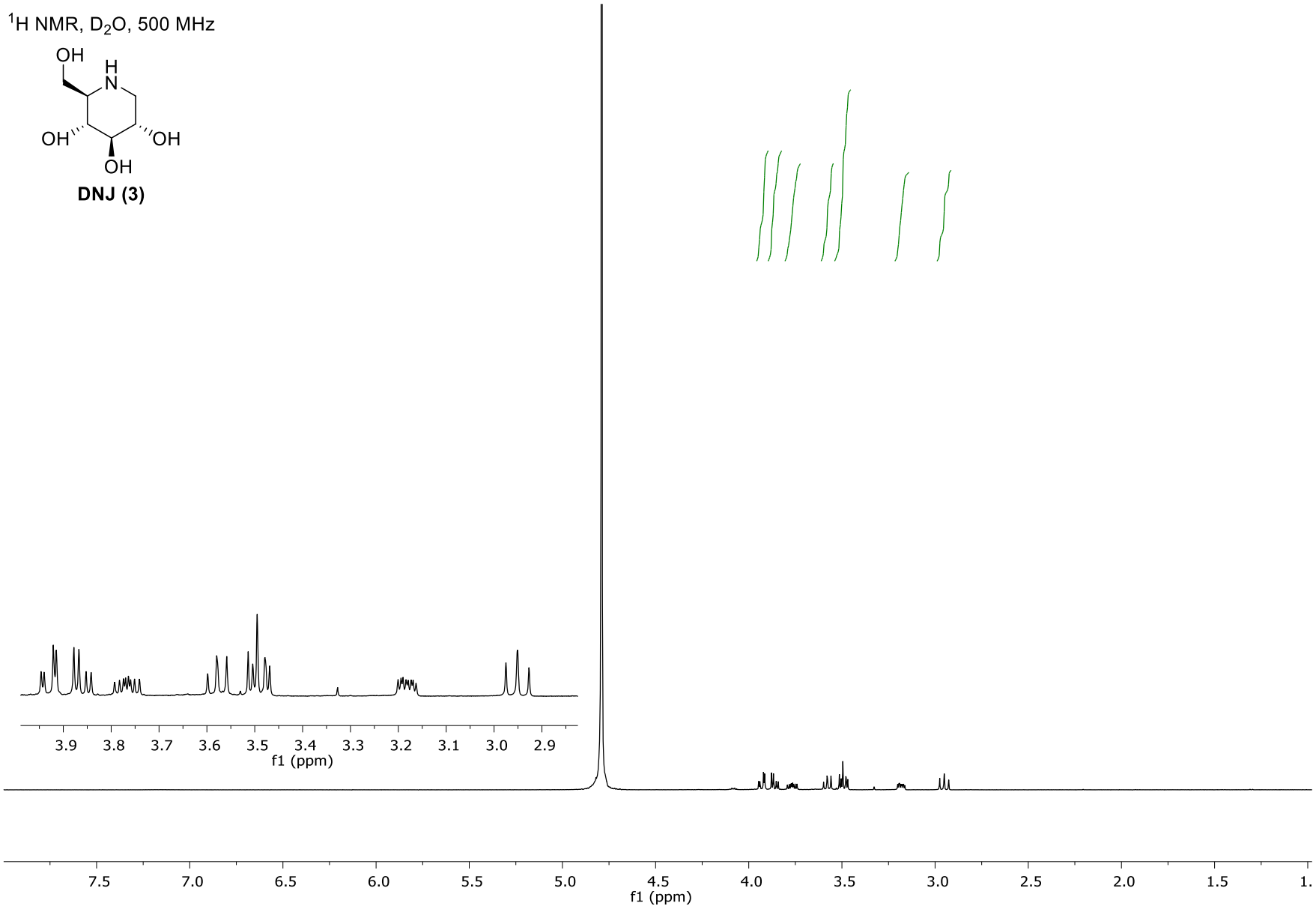
Methyl 6-deoxy-6-iodo-L-sorbofuranoside
(113)

^{13}C NMR, D_2O, 125 MHz

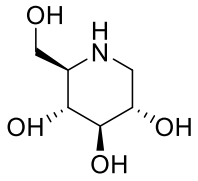


Methyl 6-deoxy-6-iodo-L-sorbofuranoside
(113)

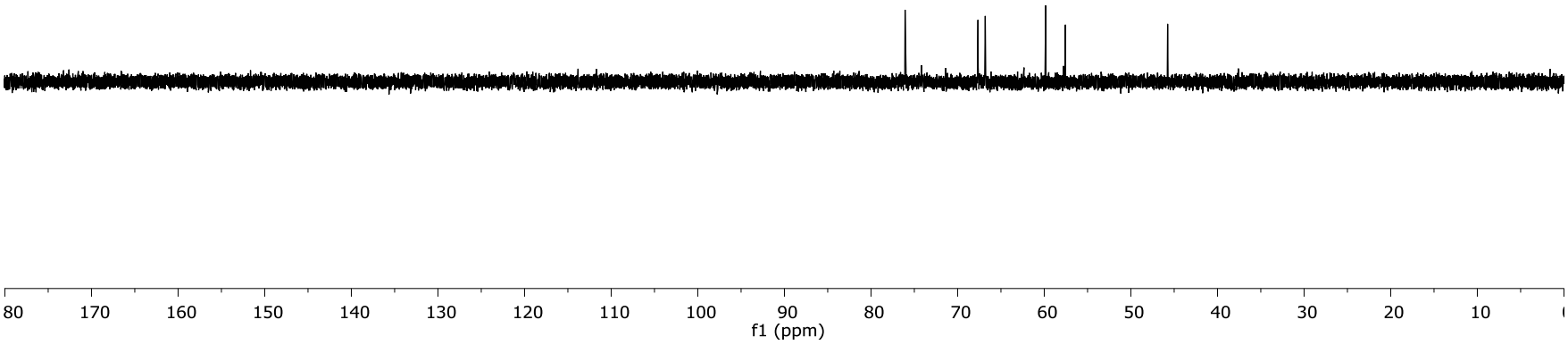


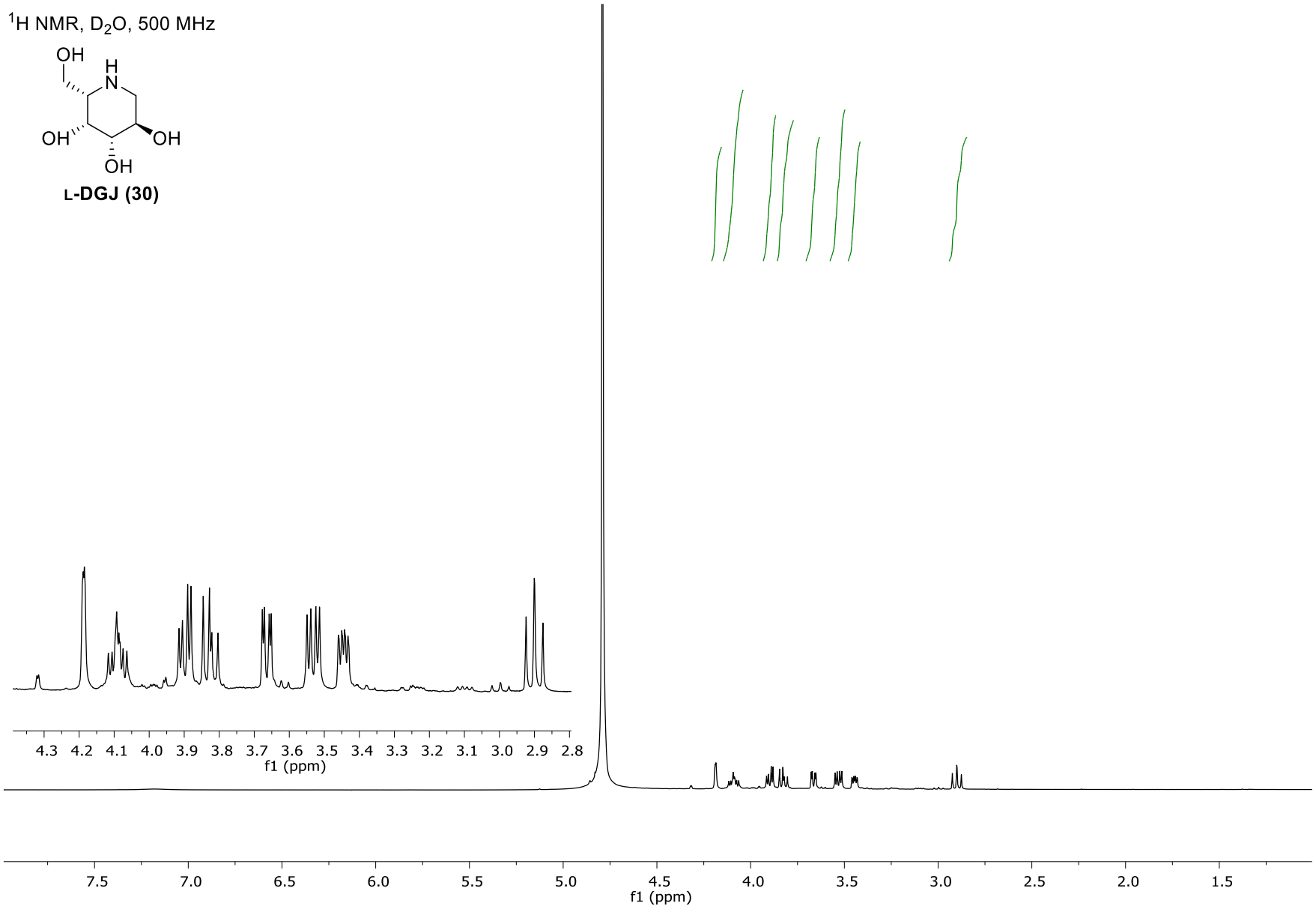

^{1}H NMR, D_2O, 500 MHz
OH
H
N
OH
OH
OH
DNJ (3)
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.
f1 (ppm)

^{13}C NMR, D_2O, 125 MHz

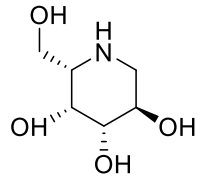


DNJ (3)

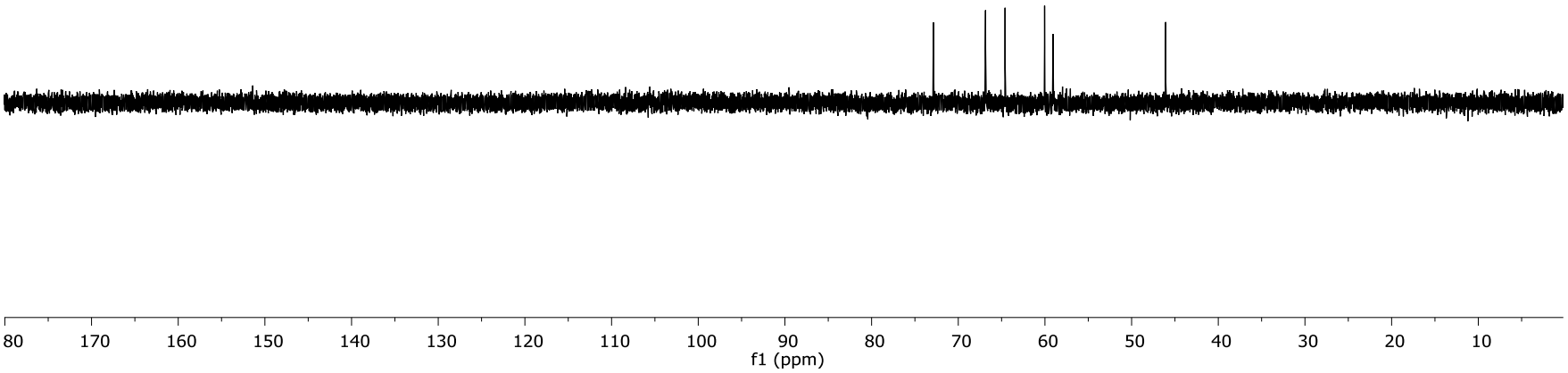



^{1}H NMR, D_2O, 500 MHz
OH
H
N
OH
OH
OH
L-DGJ (30)
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)

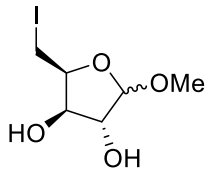
^{13}C NMR, D_2O, 125 MHz



L-DGJ (30)

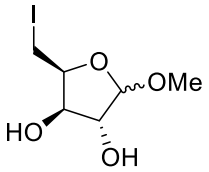


^{1}H NMR, D_2O, 500 MHz

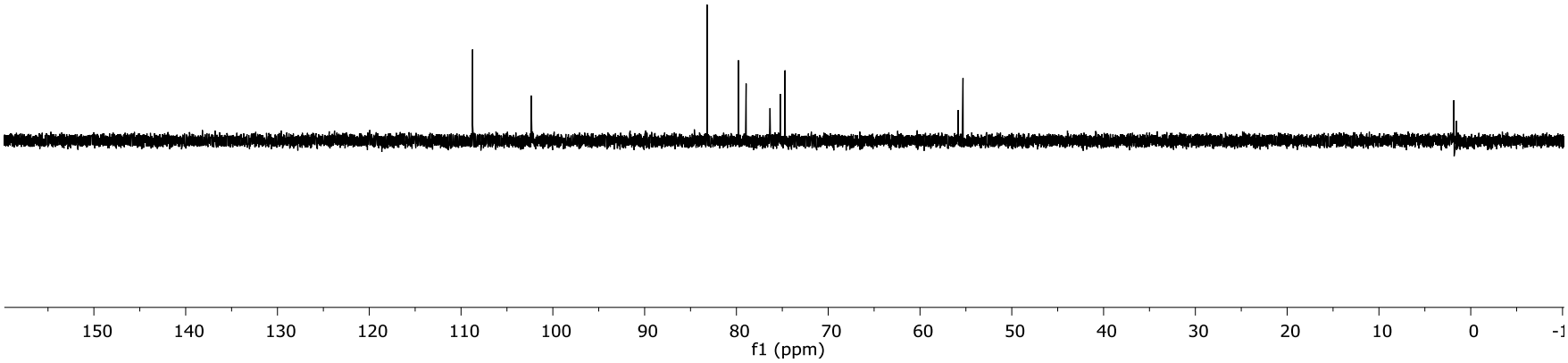


Methyl 6-deoxy-6-iodo-D-xylofuranoside
(55)

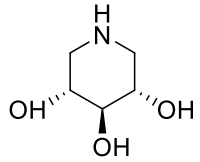
^{13}C NMR, D_2O, 125 MHz



Methyl 6-deoxy-6-iodo-D-xylofuranoside
(55)

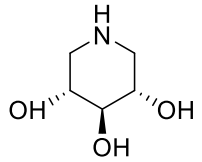


^{1}H NMR, D_2O, 500 MHz

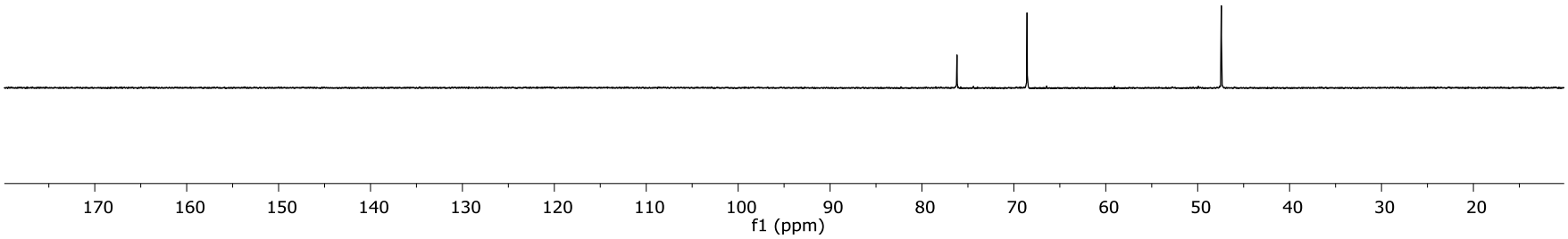


(3*R*,4*r*,5*S*)-piperidine-3,4,5-triol
(117)

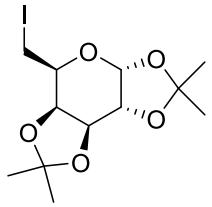
^{13}C NMR, D_2O, 125 MHz



(3*R*,4*r*,5*S*)-piperidine-3,4,5-triol
(117)

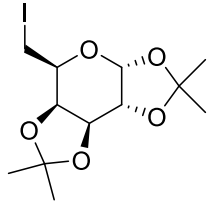


^{1}H NMR, $CDCl_3$, 500 MHz

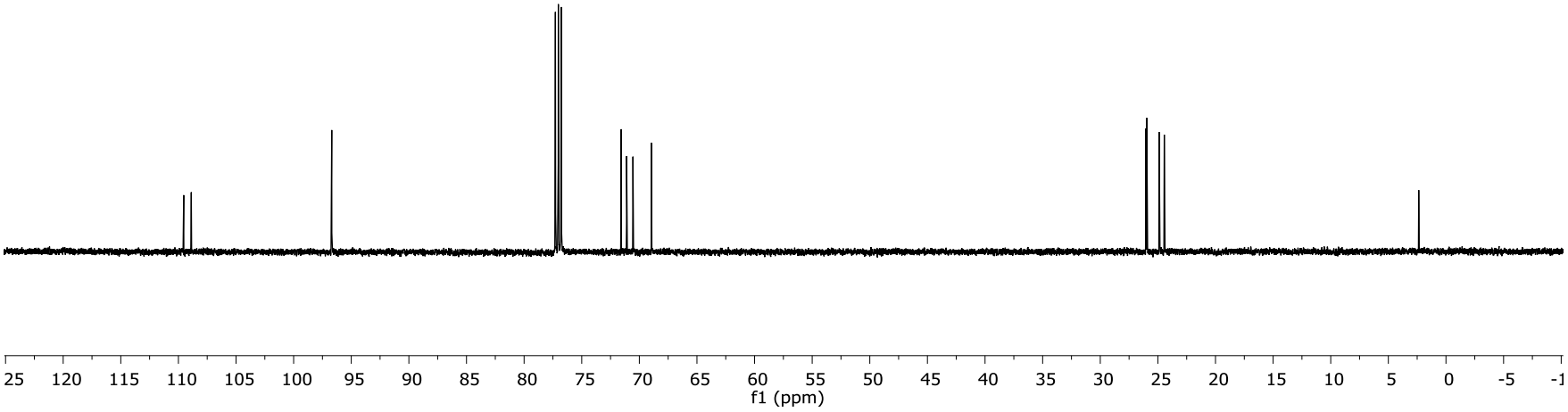


6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropyl-α-D-galactopyranose
(118)

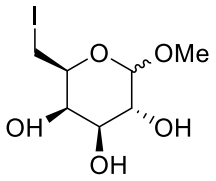
^{13}C NMR, $CDCl_3$, 125 MHz



6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropyl-α-D-galactopyranose (118)

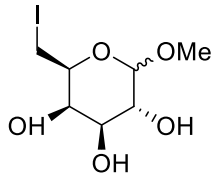


^{1}H NMR, D_2O, 500 MHz

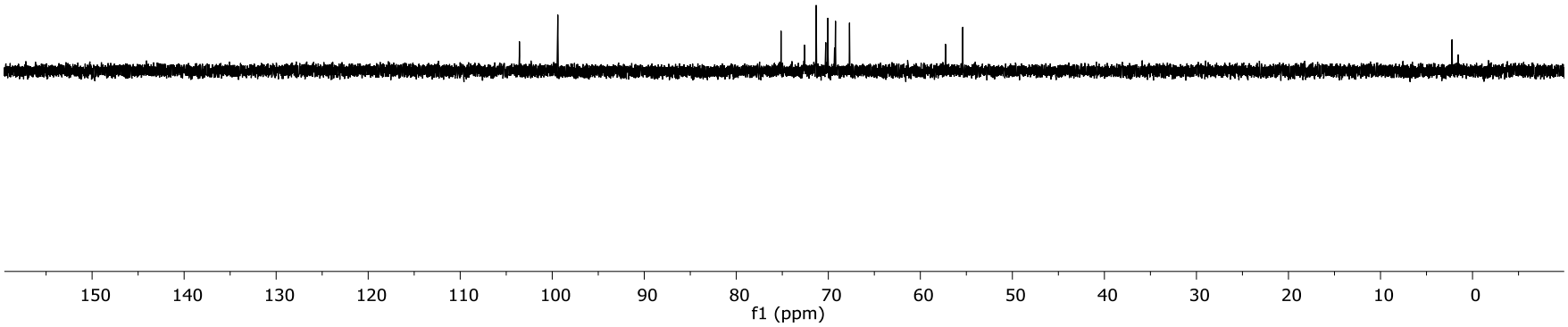


Methyl 6-deoxy-6-iodo-α/β-D-galactopyranose
(120)

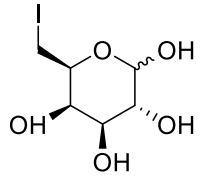
^{13}C NMR, D_2O, 125 MHz



Methyl 6-deoxy-6-iodo-α/β-D-galactopyranose (120)

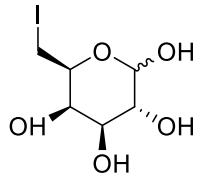


^{1}H NMR, D_2O, 500 MHz

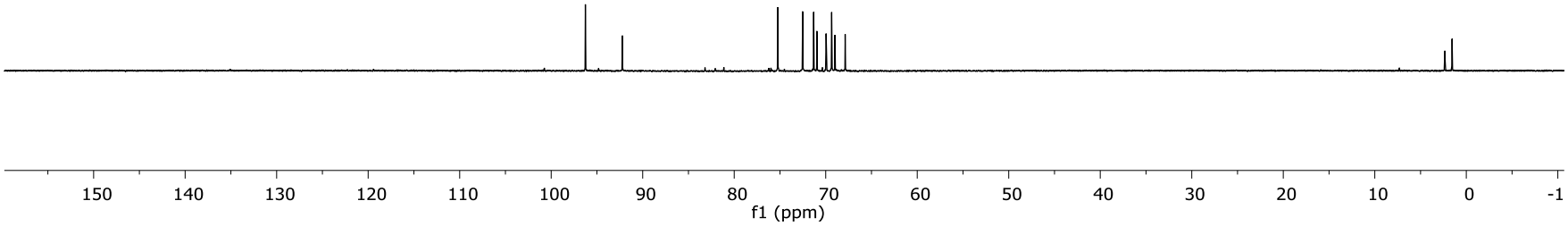


6-deoxy-6-iodo-D-galactose
(119)

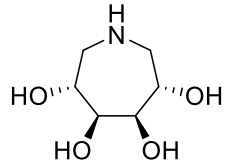
^{13}C NMR, D_2O, 125 MHz



6-deoxy-6-iodo-D-galactose
(119)

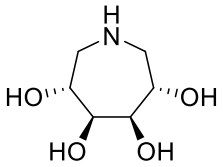


^{1}H NMR, D_2O, 500 MHz



(3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol
(49)

^{13}C NMR, D_2O, 125 MHz



(3*S*,4*R*,5*S*,6*R*)-azepane-3,4,5,6-tetraol
(49)