THE DOUBLE REDUCTIVE AMINATION APPROACH TO THE SYNTHESIS OF POLYHYDROXYPIPERIDINES

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Camilla Matassini*, Francesca Clemente, Francesca Cardona
Department of Chemistry "Ugo Schiff", University of Firenze,
Via della Lastruccia 3-13, 50019 Sesto Fiorentino (FI), Italy
(e-mail: camilla.matassini@unifi.it)

Abstract. *As a consequence of their inhibitory activity towards a number of carbohydrate-processing enzymes, polyhydroxypiperidines constitute lead compounds for the development of new therapeutic agents in a wide range of diseases. The double reductive amination (DRA) reaction on dicarbonyl compounds represents a straightforward tool to efficiently access the piperidine skeleton. The use, in most cases, of sugar-derived dicarbonyl substrates ensure the absolute configurations desired of the hydroxyl groups, while the variety of amines available as the nitrogen atom source guarantee the versatility of this method. This review collects the representative examples of DRA applied to the synthesis of polyhydroxipiperidines reported to date, together with a concise remark on their biological activity.*

Contents

1. Introduction

This account focuses on the synthesis, through the double reductive amination approach, of polyhydroxypiperidines as glycosidase inhibitors. According to IUPAC nomenclature, carbohydrates in which the endocyclic oxygen is replaced by a nitrogen atom are called *iminosugars*, while those where a carbon atom is replaced by a nitrogen atom are called *azasugars*.[1] However, if we escape from this comparison with carbohydrate structure, both iminosugars and azasugars can be considered as belonging to the family of polyhydroxypiperidines (Figure 1).

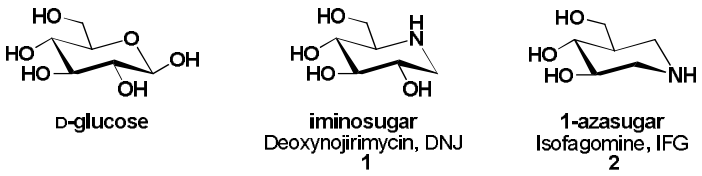


Figure 1. Nitrogen containing glycomimetics: the *iminosugar* deoxynojirimycin **1** and the *1-azasugar* isofagomine **2**.

The biological interest in these compounds, often isolated from natural sources, derives from the fact that they are transition state analogues in the enzyme-catalyzed hydrolysis of glycosydic bonds in carbohydrates and glycoconjugates. Indeed, at physiological pH the nitrogen atom is protonated, allowing favourable interactions with basic residues at the enzyme active site and perfectly mimicking the charge and the orientation of the hydroxyl groups on the glycosyl cation (Figure 2).[2]

Therefore, polyhydroxypiperidines are well known to inhibit or moderate the activity of a wide range of this kind of enzymes, especially glycosidases, which can act on carbohydrates and can affect the function

of other carbohydrate-recognizing proteins. These effects can be exploited to develop new therapies against cancer, viruses, diabetes, and hereditary metabolic disorders.[3]

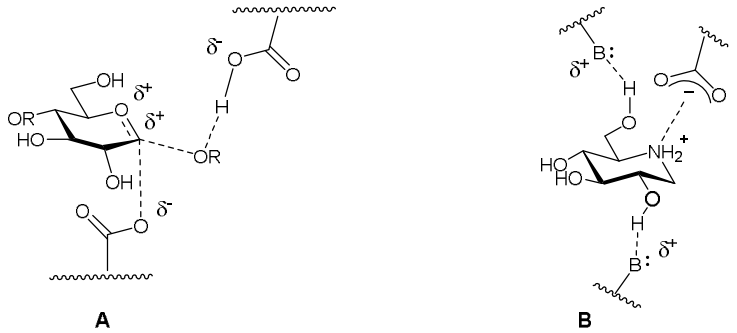


Figure 2. A Schematic representation of a typical transition state involved in the enzyme-catalyzed hydrolysis of a polysaccharide. **B** Interactions of iminosugar DNJ **1** with the active site of a generic carbohydrate-processing enzyme.

The intense research carried out over the last 20 years in the synthesis and biological evaluation of these natural compounds and their analogues resulted in the formulation of three drugs, which are currently on the market. In particular, *N*-hydroxyethyl-DNJ **3**, commonly known as Miglitol (trade name Glyset®), is a potent human α-glucosidase inhibitor and is used to treat type II diabetes (Figure 3).

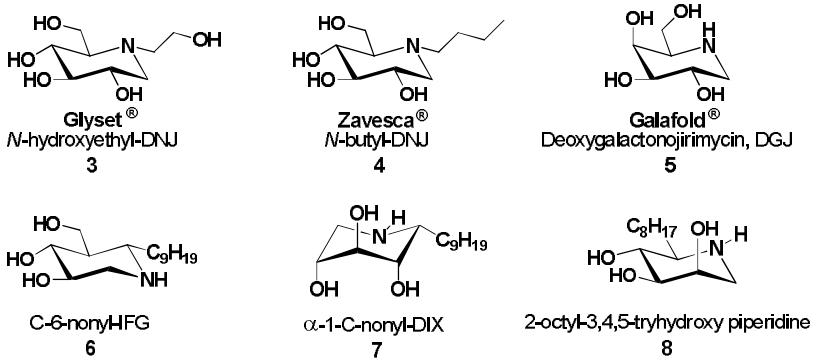


Figure 3. Polyhydroxypiperidines **3**, **4** and **5**, approved for the treatment of different diseases and other potentially active alkylated polyhydroxypiperidines **6-8**.

The *N*-butyl derivative of DNJ **4** (Figure 3), commonly known as Miglustat (trade name: Zavesca®), is approved for the substrate reduction therapy (SRT) in the treatment of Gaucher disease and Niemann-Pick disease, two inherited metabolic disorders belonging to the family of lysosomal storage disorders (LSDs).[4] Searching for novel therapeutic approaches to LSDs, the D-galacto configured analogue of DNJ, deoxygalactonojirimycin **5** (also known as DGJ) (Figure 3), was recently launched on the European market as the first pharmacological chaperone for the treatment of Fabry disease (another LSD), with the trade name of Galafold®. In addition, isofagomine **2** (Figure 1) reached Phase II clinical trials as pharmacological chaperone for Gaucher disease and some of its alkylated analogues, such as C-6 nonyl IFG **6**,[5,6] α-1-C-nonyl-DIX **7**[7] or 2-octyl-3,4,5-trihydroxy piperidine **8**[8] have been recently developed for the same purpose (Figure 3). Since isolation of these compounds from natural sources is an expensive and tiring task, the development of efficient and stereocontrolled syntheses of natural polyhydroxypiperidines and their bioactive analogues represents a major challenge both for academics and pharmaceutical industries.

A plethora of synthetic procedures to access bioactive polyhydroxypiperidines have been reported both exploiting "chiral pool" strategies, which used different carbohydrates as starting materials, and employing enantioselective approaches (also involving enzyme-catalyzed reactions) that allow diversity oriented synthesis.[3] Especially regarding the family of 3,4,5-trihydroxypiperidines, this topic has been recently reviewed in exhaustive manner by Simone and co-workers, addressing both the synthetic pathways developed to obtain these compounds as well as their biological activities.[9,10,11]

The present review will focus on the privileged key step employed for the piperidine skeleton formation: the double reductive amination procedure. Double reductive amination (DRA) of a dicarbonyl compound and an amine allows to form C5-N and C1-N bonds in a single synthetic step generating the piperidine ring (Figure 4). Sugars are often the starting materials chosen to readily access dicarbonyl substrates because they already possess a masked aldehyde (the anomeric carbon) and a second carbonyl moiety can be easily obtained through the selective oxidation of one of the several hydroxyl groups. On the other hand, intermolecular introduction of amine functionality guarantees versatility to this method, giving access to a diversity of *N*-substituted polyhydroxypiperidines.[12]

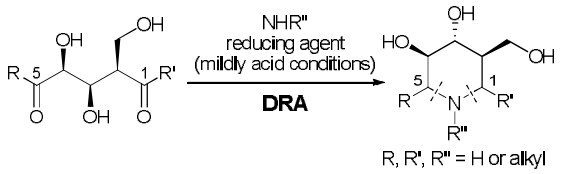


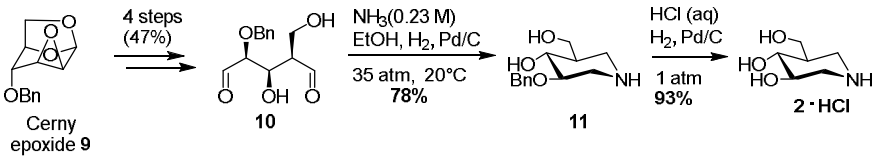
Figure 4. General strategy for the synthesis of a polyhydroxypiperidines applying the DRA procedure to a sugar-derived dicarbonyl compound.

Only few examples of synthetic strategies employing not-sugar derived starting materials to access polyhydroxypiperidines through DRA were reported and these will be described in section 3. Conversely, section 2 will collect strategies that start from carbohydrates from the chiral pool, classifying the procedures according to the nature of the dicarbonyl compound subjected to the DRA procedure, namely a dialdehyde, a diketone or a ketoaldehyde.

2. Sugar-derived substrates

2.1. Dialdehydes

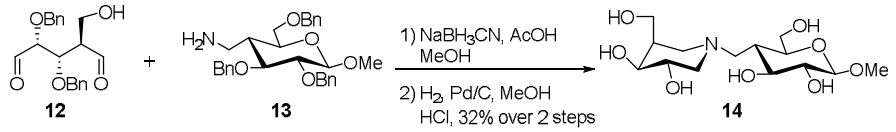
In 1994 Bols and co-workers reported the first synthesis of isofagomine **2**,[13] using ammonia as the nitrogen source in the cyclization of pentadialdose **10** derived from Cerny epoxide **9**, in turn obtained from levoglucosan. The double reductive amination reaction was performed employing hydrogen as the reducing agent at 35 atm and afforded mono-protected isofagomine **11** in 78% yield (Scheme 1).



Scheme 1. First synthesis of isofagomine by Bols group.

An isofagomine isomer (analogous to β-L-idopyranose) was also included in the structure of a pseudo-disaccharide designed on the basis of molecular modelling and conformational analyses, with the aim of developing a new class of cellulases inhibitors.[14] Cellulases are glycosidases responsible for the catalysis of β-1,4-glycosidic linkages in cellulose, the most abundant biopolymer on earth, and thus finding new cellulose inhibitors may have industrial applications in the field of detergents, textiles and paper industries. Driguez and co-workers reported the synthesis of *C*-linked imino-disaccharide **14**, exploiting a DRA reaction between the sugar derived dialdehyde **12** and the amino sugar **13**, which was employed as the nitrogen source for the generation of the isofagomine analogue skeleton (Scheme 2). The double reductive

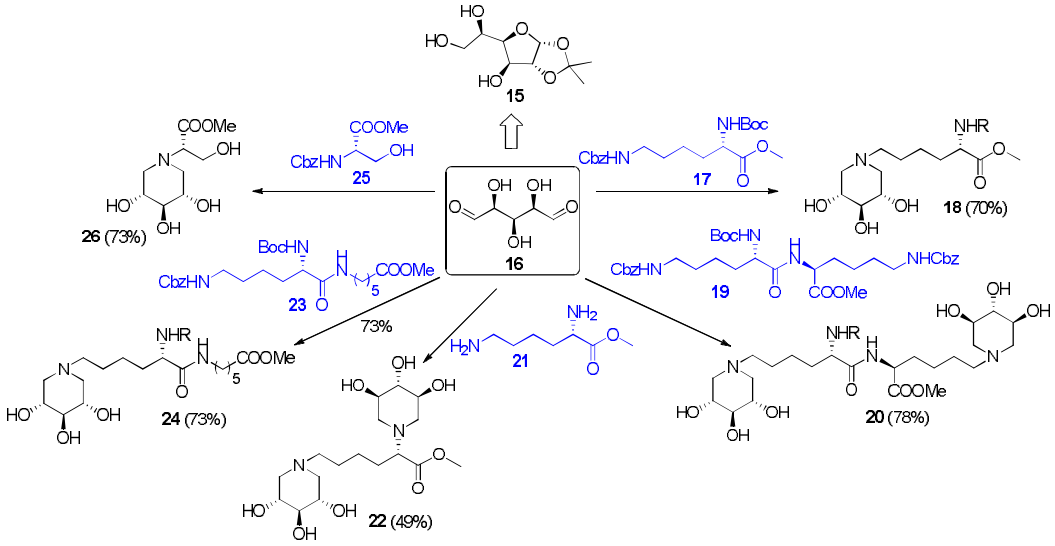
amination, performed in tandem with the de-*O*-benzylation (acidic MeOH, H_2, Pd/C), was carried out in MeOH and acetic acid, using $NaBH_3CN$ as reducing agent and afforded final compound **14** in 32% yield over 2 steps. Pseudo-disaccharide **14** behaved as competitive inhibitor of *endo*-cellulase Cel7B from *Humicola insolensellulase* with K_i=200 μM.



Scheme 2. Synthesis of *C*-linked imino-disaccharide **14**, *via* DRA on sugar-derived dialdehyde **12** with amino sugar **13**.

Another example of DRA that employed a biomolecule as nitrogen source was reported in 2009 by Wrodnigg and co-workers for the synthesis of 1,5-dideoxy-1,5-iminoxylitol (DIX)-amino acid hybrids as potential xylosidase inhibitors.[15] In this case, the target compounds were obtained by cyclization of a *xylo*-pentodialdose *via* DRA with the amino group of an amino acid, namely a lysine or a serine derivative.

Similarly to cellulases, xylosidases are glycosidases responsible for the cleavage of internal glycosidic bonds of polysaccharides, selectively devoted to release xylo-oligosaccharides. They find application in the pulp and paper industry as well as in food and feed industry. In order to obtain a small collection of iminosugar-amino acid hybrids as xylosidases inhibitors, the *xylo*-pentodialdose **16** (in turn obtained from commercially available 1,2-*O*-isopropylidene-α-D-glucofuranose **15** in 97% yield over two steps) was subjected to DRA with *N*-Cbz protected lysine and serine derivatives **17**, **19**, **21**, **23** and **25** (Scheme 3).

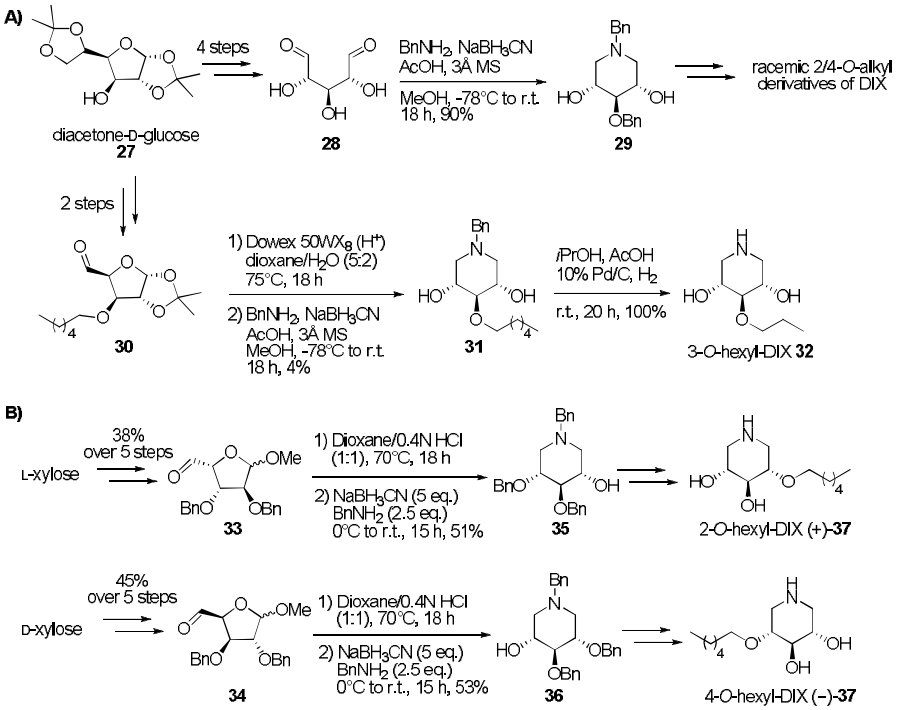


Scheme 3. Synthesis of iminosugar-amino acid hybrids **18**, **24**, **26** and di-iminosugar-amino acid hybrids **20** and **22**, through DRA. Reaction conditions: MeOH, H_2, $Pd(OH)_2/C$.

In this case, by performing the DRA reaction in conditions of hydrogenolysis in the presence of $Pd(OH)_2/C$ catalyst, the benzyloxycarbonyl deprotection and the formation of the polyhydroxypiperidine skeleton occurred in "one pot" manner, affording derivatives **18**, **20**, **24** and **26** in very good yields (70-78%) and di-iminosugar hybrid **22** in 49% yield. In lysine-containing derivatives the α-amine was subsequently deprotected and a dansyl moiety introduced to obtain fluorescent iminosugar conjugates.

The whole set of new DIX-hybrids was screened towards β-xylosidase from *Thermoanairobacterium saccharolyticum*, showing that the insertion of a dansyl moiety at the α-position of the lysine-containing derivatives allowed access to fluorescent iminosugars conjugates that showed higher inhibitory potencies with respect to their *N*-Boc protected analogues. Conversely, the derivatives bearing two iminosugar residues showed inhibitory activities similar to those of their monomeric analogues, suggesting that the additional iminosugar motif has no beneficial influence on the activity.

With the aim of identifying novel potential pharmacological chaperones (PCs) by means of a synthesis shorter than the one used for α-1-C-nonyl-DIX **7** (Figure 3),[7] Martin, Compain and co-workers exploited the efficacy of a DRA reaction between a readily available sugar-derived dialdehyde and commercial $BnNH_2$ for the preparation of a series of *O*-alkyl iminoxylitol derivatives.[16] In particular, a straightforward racemic synthesis of 2/4-*O*-alkyl derivatives of DIX was performed starting from cheap diacetone-D-glucose, in six overall steps. DRA reaction on the meso-dialdehyde **28** with $BnNH_2$ using sodium cyanoborohydride led to the key intermediate **29**, further subjected to not selective alkylation (Scheme 4A). The same diacetone-D-glucose was alternatively converted into 3-*O*-hexyl-DIX **31**, with a straightforward strategy involving minimal group manipulations, which employed aldehyde **30** as the substrate of a "one-pot" synthesis of the bis-aldehyde by acidic treatment and subsequent reductive amination (Scheme 4A).

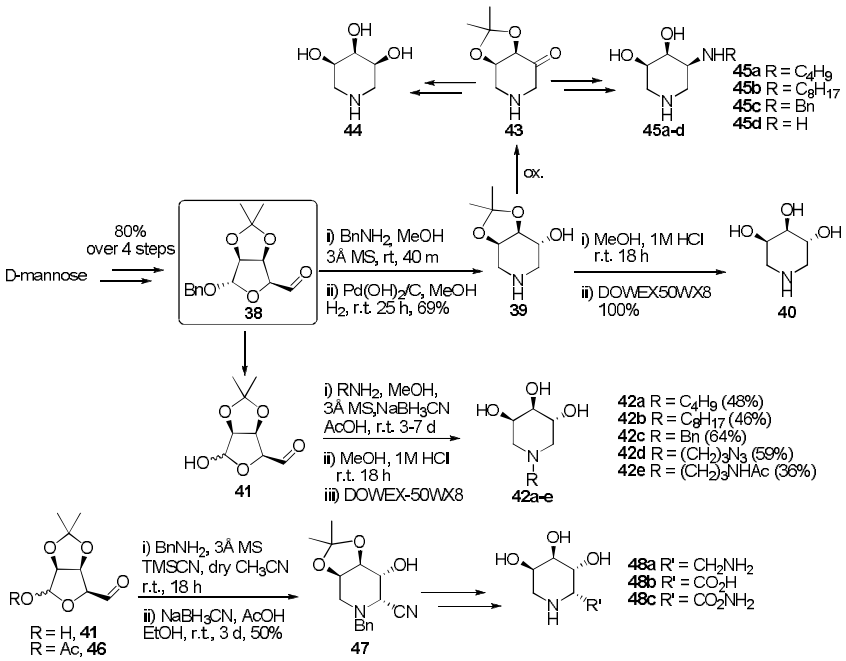


Scheme 4. A) Synthesis of racemic 2/4-*O*-alkyl derivatives of DIX and 3-*O*-hexyl DIX **32** *via* DRA, starting from diacetone-D-glucose **27**. **B)** Enantiopure synthesis of 2-*O*-hexyl DIX (+)-**37** and 4-*O*-hexyl DIX (−)-**37** starting from L- and D-xylose, respectively.

The "one-pot" obtainment of a bis-aldehyde by acidic treatment and subsequent reductive amination was the key step also in the straightforward synthesis of enantiopure 2-*O*-hexyl-DIX (+)-**37** and 4-*O*-hexyl-DIX (−)-**37** starting from L-xylose and D-xylose, respectively (Scheme 4B). It should be noticed that in the enantiopure strategy higher amounts of $NaBH_3CN$ (5 eq. *vs* 3 eq.) and $BnNH_2$ (2.5 eq. *vs* 0.9 eq.) were employed for the DRA reaction, while AcOH was replaced by 0.4 N HCl, already present in the reaction mixture for the previous deprotection step.

A structure-activity study was carried out demonstrating a dramatic influence of the position of the alkyl chain (α-C1, O2, O3, or O4) on human GCase inhibition. In particular, the L-xylose derived enantiomer (+)-**37** was the best GCase inhibitor (IC_{50}=9 nM) and showed a remarkable chaperoning activity in N370S fibroblasts cultured for four days (1.6-fold maximal increase at 10 nM concentration).

In this context, we envisaged that the "masked" dialdehyde **38**, with the configuration of D-lyxose, might be a versatile building block for the synthesis of natural 3,4,5-trihydroxypiperidines and related analogs through the DRA strategy.[17] In our hands, aldehyde **38** can be easily synthesized in four steps and 80% overall yield from D-mannose, without the need for any chromatographic purification. Different aromatic and aliphatic amines were employed as nitrogen source, since we were particularly interested in the introduction of lipophilic chains, for cell permeability and chaperoning activity purposes, and different reaction conditions were screened to optimize the DRA step. For example, the hydrogenation catalyzed by $Pd(OH)_2/C$ allowed removal of the benzyl protecting group at the anomeric position of **38** in the same step, resulting in the liberation of the second aldehyde moiety necessary to perform the required cyclization and providing trihydroxypiperidine **40** (enantiomer of natural compound) in excellent yield (69% over 4 steps, Scheme 5). However, this "one pot" procedure suffered from scarce reproducibility with alkyl amines and better results were obtained using $NaBH_3CN$ as the reducing agent (in MeOH and in the presence of 3Å molecular sieves and AcOH). The latter strategy required preliminary deprotection of aldehyde **38** by catalytic hydrogenation, but guaranteed higher versatility through the functionalization of the endocyclic nitrogen, as shown for compounds **42a-e** (Scheme 5).



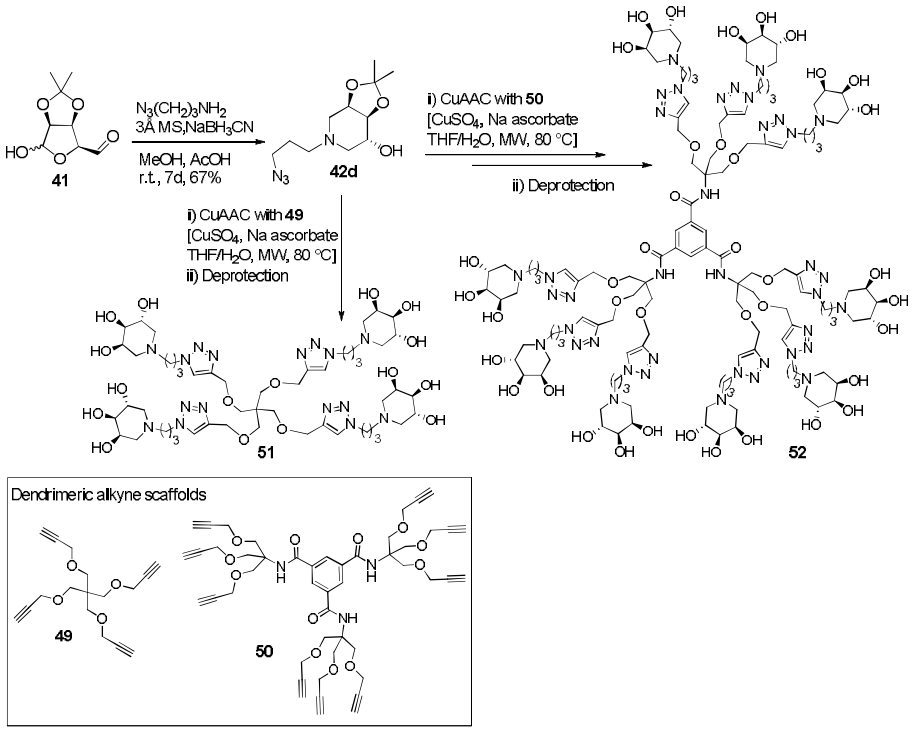
Scheme 5. Synthesis of diversely functionalized 3,4,5-trihydroxypiperidines through DRA on aldehydes **38**, **41** or **46**.

We were also able to invert the configuration at C5-OH in compound **39** to access natural trihydroxypiperidine **44** (Scheme 5) through an oxidation-reduction sequence; moreover, exploiting ketone **43** as the substrate of another reductive amination, we prepared the trihydroxypiperidines **45a-c** substituted at the exocyclic nitrogen. Surprisingly, for this reductive amination, hydrogen performed as a better reducing agent than $NaBH_3CN$. Finally, the functionalization of the α-position was achieved taking advantage of a

highly stereoselective Strecker reaction on aldehyde **41** (or on its *O*-acetylated analogue **46**) and further conversion of the cyano group (of intermediate **47**) into biological relevant moieties (namely, amine **48a**, carboxylic acid **48b** or amide **48c**).[18]

Albeit preliminary evaluation of all these 3,4,5-trihydroxypiperidines on a panel of commercial glycosidases did not identify any potent inhibitor, compounds **42b** and **45b**, bearing an octyl chain on the endocyclic or exocyclic nitrogen atom, later emerged as potent human GCase inhibitors and good chaperones, enabling a rescue of GCase activity in Gaucher patients cell up to 1.5-fold.[19]

In recent years the impact of multivalency on glycosidase inhibition was largely investigated, showing unprecedent effects on enhancement and modulation of binding with some target enzymes.[20,21] In this context, compound **42d**, in which an azido-ended substituent was introduced onto the endocyclic nitrogen atom through a DRA reaction with 3-azidopropyl-1-amine, was successfully employed for the synthesis of multivalent polyhydroxypiperidine iminosugars **51** and **52** (Scheme 6).[22] A tetra- and a nonavalent derivative were prepared by exploiting the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[23] between **42d** and two different dendrimeric alkyne scaffolds **49** and **50** (Scheme 6). Biological evaluation against a panel of eleven commercially available glycosidases demonstrated that the multimerization of the polyhydroxypiperidine moiety affects the selectivity of the final architecture.



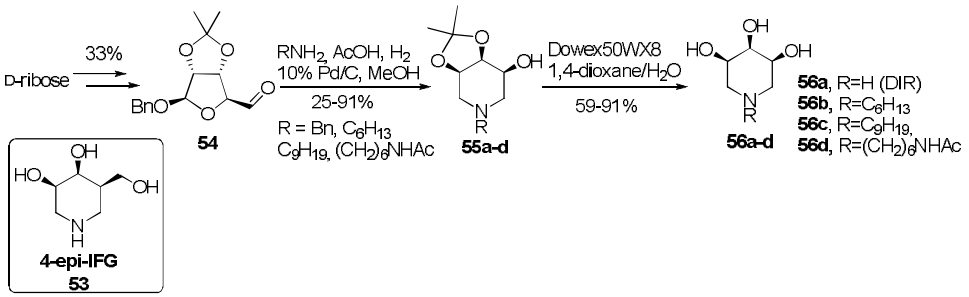
Scheme 6. Synthesis of tetra- and nonavalent polyhydroxypiperidines **51** and **52**, prepared *via* CuAAC reaction between a poly-alkyne scaffold and azido derivative **42d** obtained *via* DRA.

Starting from D-ribose, the analogue of the D-mannose derived dialdehyde **38** was prepared by Martin and co-workers and employed as the substrate for a DRA reaction with different amines, aiming at the synthesis of novel *N*-alkyl 1,5-dideoxy-1,5-imino-(L)-ribitol (DIR) derivatives expected to behave as selective β-galactosidases inhibitors.[24] Indeed, 4-epi-IFG **53** (Scheme 7) is known to be a very potent galactosidase inhibitor and these trihydroxypiperidines are in principle simplified mimics of **53**, that have the same configuration as a galactoside at the C3, C4, and C5 positions, but contain an OH group at C5 instead

of CH_2OH (Scheme 7), with potential application as pharmacological chaperones in β-galactosidase-linked lysosomal storage diseases, such as GM1-gangliosidosis, Morquio B, and Krabbe disease.

Reaction of aldehyde **54** in the presence of an amine under mildly acidic hydrogenation conditions afforded DIR **56a** (using $BnNH_2$) and *N*-alkylated derivatives **56b-d** in good yields, after isopropylidene group deprotection.

Compounds **56a-d** were assayed toward bovine β-galactosidase and other β-galactosidases including the human lysosomal enzyme to investigate their potential application as pharmacological chaperones in β-galactosidase-linked lysosomal storage diseases, such as GM1-gangliosidosis, Morquio B, and Krabbe disease. Unfortunately, both DIR **56a** and its *N*-alkyl derivatives **56b-d** were much less potent inhibitors with respect to 4-epi-IFG **53**.



Scheme 7. Synthesis of 1,5-dideoxy-1,5-imino-(L)-ribitol (DIR) **56a** and its *N*-alkyl derivatives **56b-d**, *via* DRA reaction on masked dialdehyde **54**.

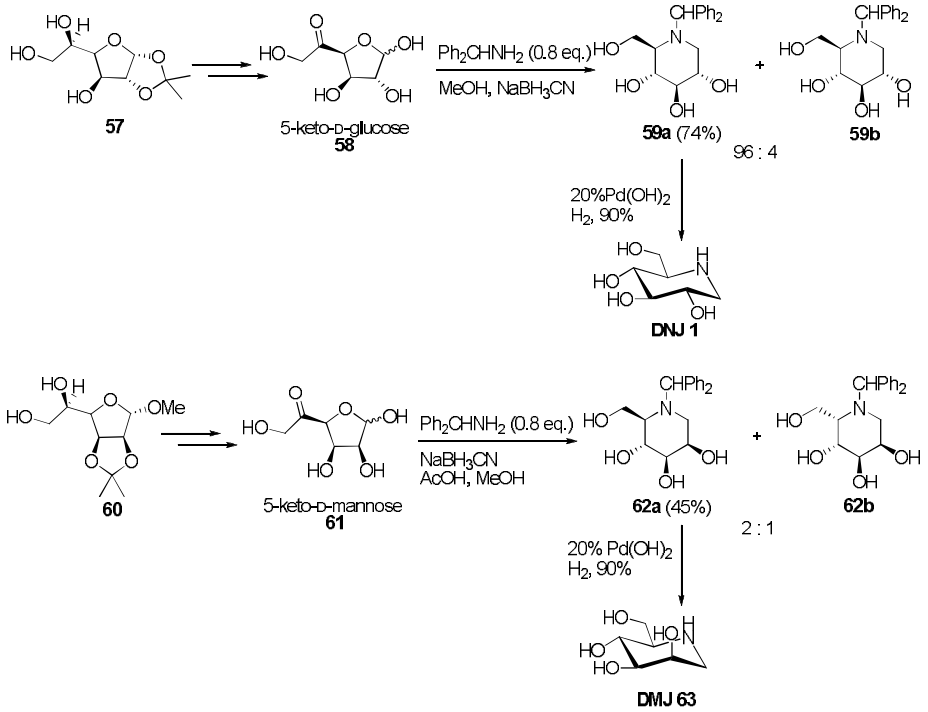
2.2. Ketoaldehyde substrates

In the early '90s Reitz and Baxter reported the total synthesis of 1-deoxynojirimycin **1** (DNJ) (Figure 1)[25] and 1-deoxymannojirimyicn (DMJ) **63** (Scheme 8)[26] through DRA of appropriate dicarbonyl sugars, poorly studied at that time, and without employing tedious protecting-group manipulations. It should be noticed that unlike isofagomine and 3,4,5-hydroxypiperidines, the synthesis of DNJ (and of its analogues) involves the formation of a new stereocenter during the cyclization step, therefore the 4 steps-one pot process (first amination, imine reduction, second amination, second imine reduction) present an additional stereoselectivity issue. By treating 5-keto-D-glucose **58** with benzhydrylamine in MeOH and using $NaBH_3CN$ as the reducing agent, at 0 °C, deoxynojirimycin derivative **59a** was obtained as the major diastereoisomer in a 96:4 ratio with respect to **59b**. The authors suggested that the excellent diastereoselectivity of the reaction is due to the higher reactivity of the aldehyde over the ketone in the first reductive amination and, more importantly, to the strong stereocontrol played by the hydride addition in the second stereodeterming reduction of the cyclic imine. This example corroborates the peculiar stereocontrol observed in the reduction of imines with borohydride sources, compared with hydrogenations catalyzed by noble metal. In addition, the special role of the free hydroxyl groups in **58** in promoting an efficient and stereoselective reductive amination was established. After deprotection of **59a** (with H_2, $Pd(OH)_2/C$), elution through Dowex50W-X8 resin and recrystallization, DNJ **1** identical to the natural product was obtained in 67% yield from 5-keto-D-glucose.

Attempt to extend this methodology to the synthesis of the D-manno-configured analogue **63**, resulted in a lower steroselectivity and efficacy of the DRA reaction. Indeed, treatment of 5-keto-D-mannose **61**, readily obtained from 2,5-anhydroimino-D-glucitol **60**, with benzhydrylamine and $NaBH_3CN$ in MeOH and acetic acid, afforded a 2:1 mixture of diastereoisomers **62a** and **62b** in 45% yield; subsequent deprotection by hydrogenolysis of **62a** furnished desired product DMJ **63** in 17% overall yield (4 steps). In the latter example, the lower selectivity observed for the DRA reaction appears difficult to be rationalized: the authors suggested that the seemingly remote hydroxyl group at C-2 could probably interact with the hydride reducing agent or stabilize a different cyclic iminium ion intermediate with respect to the case of DNJ.

In a slightly later work,[27] the same authors expanded the scope of the DRA on 5-keto-D-glucose **58**, with several aliphatic and aromatic amines to obtain different *N*-alkyl derivatives of DNJ, confirming the

high stereoselectivity of the DRA reaction starting from the D-glucose configured ketoaldehyde and demonstrating the versatility of this method. Additional hints to probe the role of the C-2 hydroxyl group in directing the stereochemical outcome of the reduction at C-5 in reactions of **58** and **61** were also provided.

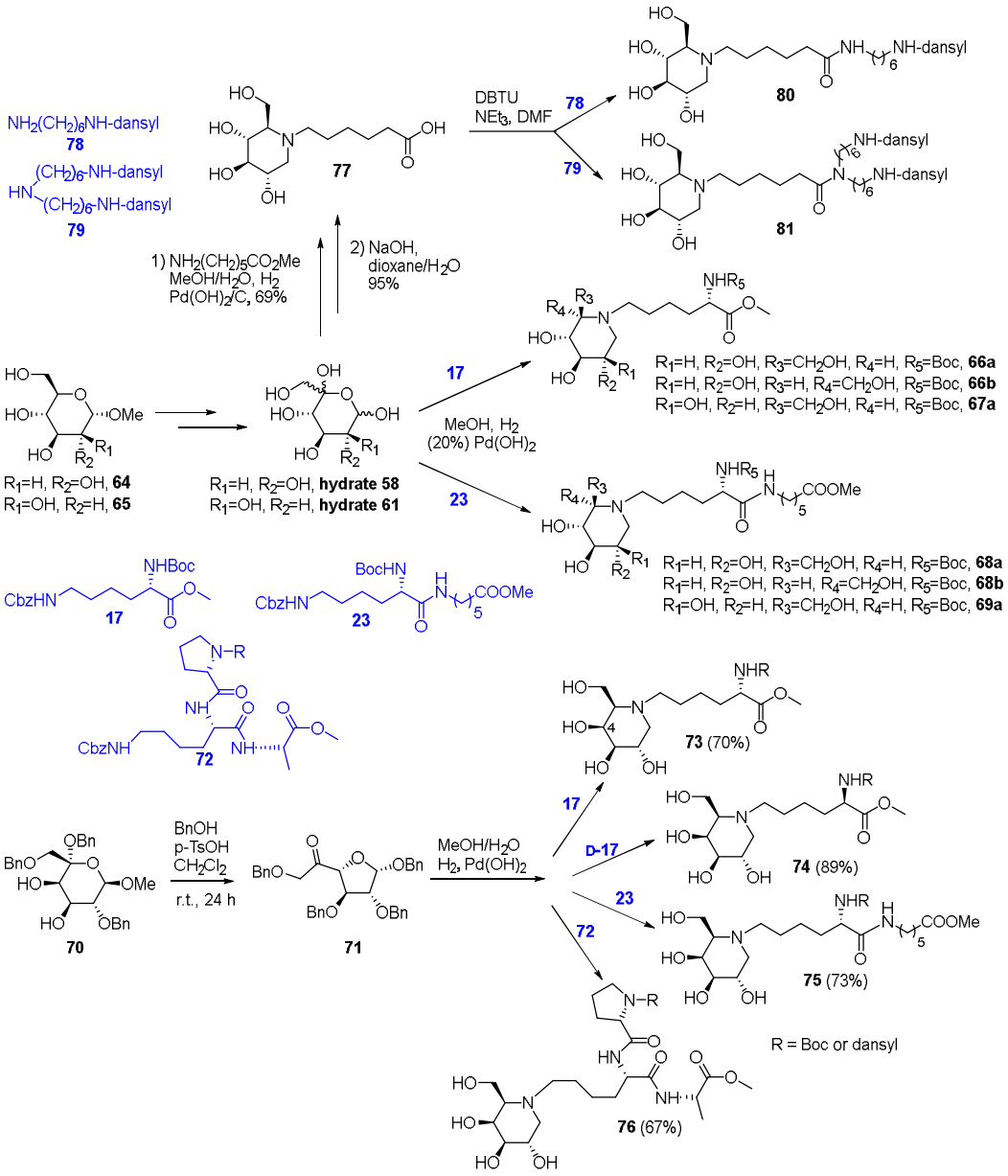


Scheme 8. Synthesis of 1-deoxynojirimycin (DNJ) **1** and 1-deoxymannonojirimycin (DMJ) **63** *via* DRA reaction on 5-keto-D-glucose **58** and 5-keto-D-mannose **61**, respectively.

As a part of the work by Wrodnigg group on the synthesis of iminosugar-amino acid hybrids through a DRA (see Scheme 3, section 2.1.), this reaction was investigated on different 5-ketosugars, such as 5-keto-D-glucose **58** or 5-keto-D-mannose **61**, to conjugate the DNJ (or DMJ) skeleton with the terminal group of properly protected amino acids (Scheme 9).[28] The final introduction of a dansyl moiety on the amino acid pendant allowed access to fluorescent compounds, showing in most cases glycosidase inhibitory activities enhanced with respect to the parent compounds. Starting from methyl-α-D-glucopyranoside **64** and methyl-α-D-mannopyranoside **65**, the hydrate 5-keto-D-glucose and 5-keto-D-mannose were obtained, respectively.

Hydrate **58** was reacted with *N*-Cbz protected lysine derivative **17** at ambient pressure under H_2 atmosphere in the presence of $Pd(OH)_2$ on carbon. In these hydrogenolytic conditions, deprotection of the terminal amine followed by DRA occurred, providing a 4:1 mixture of diastereoisomeric *N*-alkylated derivatives **66a** (D-glucose configured) and **66b** (L-idose configured). A mixture of chain-extended derivatives **68a** and **68b** (*dr*>7:2), when the same reaction was performed using L-lysine derivative **23** as the nitrogen source. In the D-*manno* series the DRA with L-lysine derivatives **17** and **23** was more stereoselective, furnishing exclusively the D-mannose configured products **67a** and **69a** (Scheme 9). The final introduction of a dansyl moiety on the amino acid pendant allowed access to fluorescent compounds, showing in most cases glycosidase inhibitory activities enhanced with respect to the parent compounds.

A small series of 1-deoxygalactonojirimycin (DGJ) **5** (Figure 3) lysine hybrids were subsequently obtained starting from 5-ulofuranoside **71**, through acidic treatment of pyranoid ulososide **70** in benzyl alcohol (Scheme 9).[29]



Scheme 9. Synthesis of DNJ- **66, 68**, DMJ- **67, 69**, DGJ- **73-76** amino acid hybrids and *N*-dansyl derivatives **80** and **81** through DRA on different 5-ketosugars.

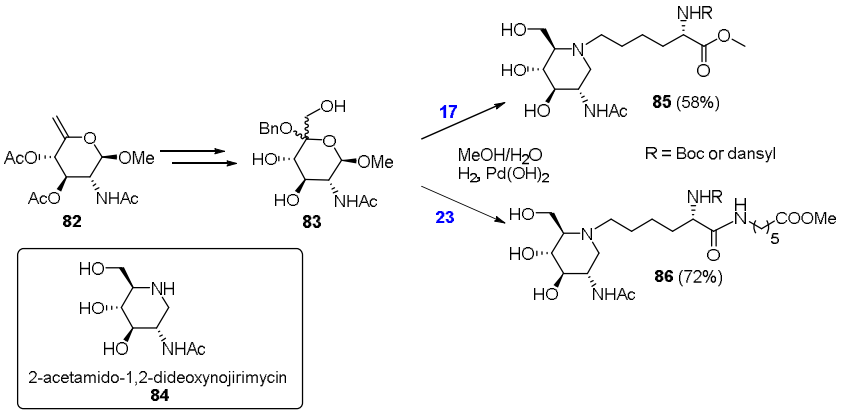
Several *N*-Cbz protected L- and D-lysine derivatives L-**17**, D-**17**, **23** and **72** were employed as nitrogen source in the cyclization reaction. It is noteworthy that the formation of the polyhydroxypiperidine skeleton was more challenging in this case, because deprotection of both sugar unit and terminal lysine amino group, followed by reductive amination at C-1 and subsequent intramolecular cyclization, occurred with the formation of a new stereocenter at C-5. Despite of the complexity of this DRA, hydrogenation with

$Pd(OH)_2/C$ in $MeOH/H_2O$ afforded final products **73-76** in very good yields (67%-89%) and with excellent selectivity for the desired D-galactose configuration, probably due to the favourable influence of the C-4 substituent (Scheme 9). After the replacement of Boc with dansyl group, the corresponding fluorescent compounds were tested as commercial β-galactosidase inhibitors, obtaining for compounds **73**, **74** and **75** lower K_i than the parent DGJ **5**. In addition, fluorescent derivative of **75** rescued human lysosomal β-galactosidase activity in mutated cell lines.

A slight modification of the described protocol allowed the same authors to access a branched-di-*N*-dansyl derivative which showed not only stronger β-glucosidase inhibitory activity, but also remarkable chaperoning activity in Gaucher patients cells.[30] DRA was performed on hydrate **58** with methyl 6-aminoheanoate in the same conditions reported above and, after basic ester hydrolysis of the methyl ester, afforded intermediate **77** in 66% yield over two steps (Scheme 9). Amidic coupling with the amino-dansyl derivatives **78** and **79** led to final compounds **80** and **81**, both showing remarkable inhibitory activities towards commercial and recombinant lysosomal β-glucosidases, with K_i values in the low μM range. In addition, compound **81** was found able to increase the residual GCase activity of 60% at 30 μM, in fibroblasts from Gaucher patients bearing N370S mutation, showing remarkable chaperoning activity.

Application of the same procedure of hydrogenation/reductive amination to the sugar substrate **83** allowed access to different *N*-alkyl derivatives of 2-acetamido-1,2-dideoxynojirimycin **84** (Scheme 10), known to be a strong inhibitor of hexosaminidase, whose deficiency is responsible for the lysosomal storage disorders Tay-Sachs' and Sandhoff's diseases.[31]

Cyclization of intermediate **83**, obtained in several steps from commercially available **82**, with *N*-Cbz protected **17** and **23** (Scheme 9) provided 2-acetamido-1,2-dideoxynojirimycin derivatives **85** and **86**, without any observable epimer formation at C-5. Once again, compounds **85** and **86**, bearing a lipophilic residue linked to the endocyclic nitrogen showed better inibitory activities than the unsubstituted parent compound **84** towards β-*N*-acetylhexosaminidase from *Streptomyces plicatus*. In contrast with previous results, the presence of the dansyl moiety did not result in an improved inhibitory activity if compared with the *N*-Boc precursor. However, dansyl derivative **86** gave remarkable results as pharmacological chaperone for Tay-Sachs' disorders, being able to double the activity of lysosomal β-*N*-acetylhexosaminidase A/S in fibroblasts derived from Tay-Sachs'disease.

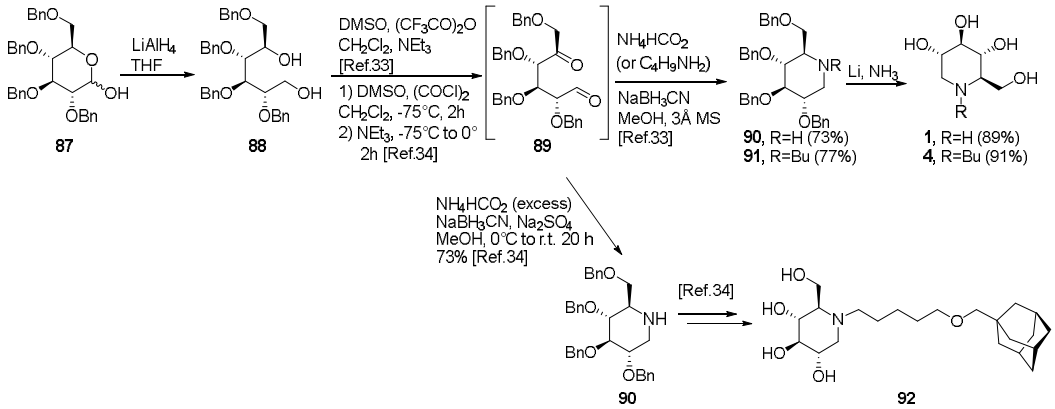


Scheme 10. Synthesis of 2-acetamido-1,2-dideoxynojirimycin **84** *N*-alkyl derivatives **85** and **86**, obtained through DRA of **83** with *N*-Cbz protected amino acids **17** and **23** (see Scheme 9).

In 2010, Stubbs and co-workers succesfully applied the methodology presented by Stütz group to the preparation of biological relevant compounds, namely DNJ **1**, its *N*-alkyl derivatives Glyset **3** and Zavesca **4**, and its D-galacto and D-manno configured analogues DGJ **5** and DMJ **63**.[32] They envisaged that the efficacy of the cyclization/reductive amination, coupled with a strategy that easily provided stable precursors could allow access to significant amounts of these compounds, as absolutely required for potential or effective

drugs. Performing DRA with ammonium acetate in the presence of $Pd(OH)_2/C$ and hydrogen on the proper benzylated precursor, they were able to access DNJ **1** in 42% over five steps from methyl β-glucopyranoside. By using 2-aminoethanol or butylamine under the established conditions, *N*-(2-hydroxyethyl)-DNJ (Glyset) **3** (Figure 3) and *N*-butyl-DNJ (Zavesca) **4** (Figure 3) were obtained, respectively, in high yields. Analogous routes from methyl β-galactopyranoside and methyl α-mannopyranoside allowed access to DGJ (Galafold) **5** (Figure 3) in 33% overall yield, and DMJ **63** (Scheme 8) in 32% overall yield through the debenzylation/reductive amination with ammonium acetate, proving this method to be highly versatile and efficient.

The synthesis of DNJ **1** and *N*-butyl-DNJ **4** through DRA had been previously reported also by Lopes and co-workers starting from a protected sugar, with excellent yields (64% and 70% respecively) over four steps.[33] In particular, the 1,5-dicarbonyl sugar derivative **89** was obtained in two steps starting from 2,3,4,6-tetra-*O*-benzyl-α-glucopyranose **87**, which was converted into the corresponding 1,5-diol by reduction of the hemiketal group with $LiALH_4$ in THF and then subjected to a double Pftizner-Moffat oxidation, affording **89**. The crude 1,5-dicarbonyl sugar derivative **89** was cyclized by treatment using ammonium formate (or butyl amine) as the source of nitrogen, and $NaBH_3CN$ as the hydride source in a stereocontrolled intramolecular reductive amination. Compounds **90** and **91** were obtained in 73 and 77% yields, respectively, and provided, after deprotection, DNJ **1** and *N*-butyl-DNJ **4** (Scheme 11).



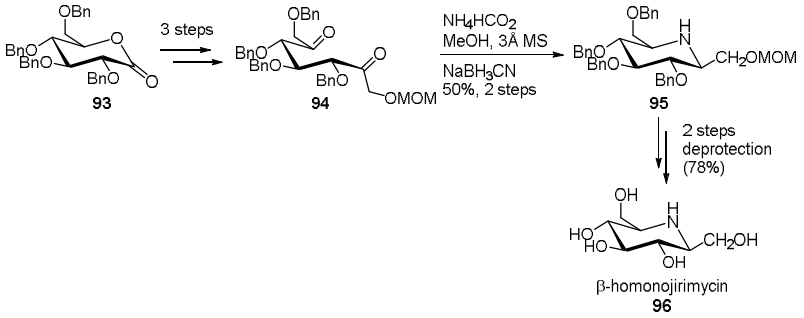
Scheme 11. Synthesis of DNJ **1** and of its analogue, *N*-butyl-DNJ **4**, *via* DRA on 1,5-dicarbonyl sugar derivative **89** and ammonium formate or butyl amine as the nitrogen source. A slight modification of the same procedure was employed by Overkleeft and co-workers to access the *N*-adamantyl-DNJ derivative **92**.

A slight modification in the construction of intermediate **89** was reported by Overkleeft and co-workers in their impressive study on the synthesis of a collection of adamantan-1-yl-methoxyfunctionalized DNJ derivatives as selective inhibitors of glucosylceramide metabolism.[34] A Swern oxidation on glucitol **88** allowed to isolate the keto-aldehyde **89**, which was subsequently treated with $NaBH_3CN$ and ammonium formate (excess), in MeOH in the presence of Na_2SO_4. Addition of reagents was performed at 0° C, and after warming to room temperature, derivative **90** was obtained in 73% over three steps. Further functionalization of protected DNJ **90** *via* reductive amination with an adamantan-ending aldehyde afforded, after deprotection, the lead compound **92**, which was found to be a more potent inhibitor of glucosylceramide synthase than the therapeutic agent *N*-butyl-DNJ **4** (IC_{50}=0.2 μM *vs* IC_{50}=50 μM).

2.3. Diketone substrates

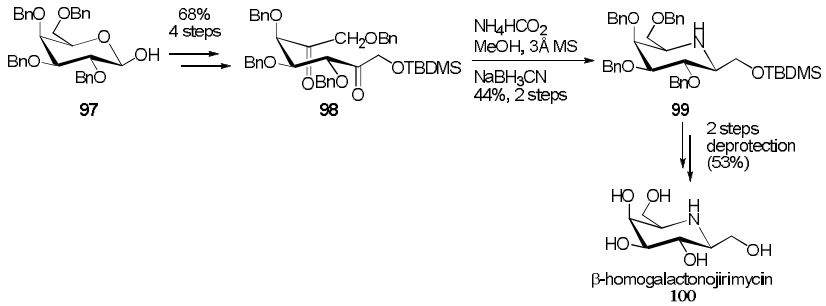
Martin and Saavedra described the first chemical synthesis of β-homonojirimycin **96** in six steps from tetra-*O*-benzyl-D-glucono-l,5-1actone **93** with an overall yield of 27% based on the DRA between a diketone and ammonium formate as the nitrogen source.[35] The required diketone 2,6-heptodiulose **94** was synthesized

in three steps from tetra-*O*-benzyl-D-glucono-l,5-1actone. Because of its tendency to undergo internal aldol addition, compound **94** was directly submitted (without purification) to reductive amination using ammonium formate and $NaBH_3CN$ as reducing agent in MeOH. DRA allowed to obtain the desired β-homonojirimycin derivative **95** as a single isomer, in 50 % yield on two steps, after purification by flash chromatography. Final deprotection of the MOM protecting groups under mildly acidic conditions and the benzyl groups under dissolving-metal reduction conditions, afforded the final compound **96** with good yield (Scheme 12).



Scheme 12. Synthesis of β-homonojirimycin **96**, *via* DRA on diketone **94** and ammonium formate as the nitrogen source.

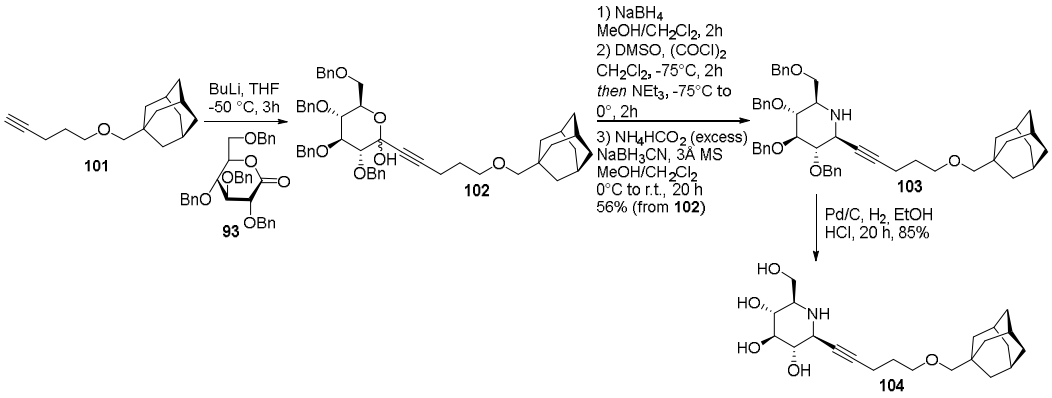
Another example of DRA that employed the diketone **98** and ammonium formate as the nitrogen source was described by Asano and co-workers for the synthesis of β-homogalactonojirimycin as potential α and β galactosidases inhibitor.[36] The 2,6-heptodiulose **98** was obtained in 4 steps from tetra-*O*-benzyl-D-galactopyranose and was submitted to reductive amination conditions (ammonium formate and $NaBH_3CN$), which provided control of the pseudoanomeric configuration giving a single piperidine derivative **99** in 44% yield over two steps. Cleavage of the *t*-butyldimethylsilyl ether and final debenzylation afforded β-homogalactonojirimycin **100** thus completing a seven steps synthesis from **97** with an overall yield of 20%. Compound **100** is a weak α-galactosidase inhibitor (α-Gal, *coffee beans* IC_{50}=2.4 μM K_i=0.107 μM and α-Gal, *E. Coli* 17% inhibition at 1 mM) and is completely devoid of activity towards β-galactosidases (Scheme 13).



Scheme 13. Synthesis of β-homogalactonojirimycin **100**, *via* DRA on diketone **98** and ammonium formate as the nitrogen source.

The DRA reaction on a diketone in a more complex "one-pot" version was employed also by Overfkleeft and co-workers for the synthesis of the DNJ β-aza-*C*-glycoside analogue **104**, in order to investigate the relocating of the lipophilic moiety from the nitrogen atom of the lead compound **92** (Scheme 11) to other positions of the DNJ ring system.[34] In particular, the functionalization at the C-1 position was obtained through a 3 steps "one pot" reaction on the hemiketal intermediate **102**, in turn obtained *via*

nucleophilic addition of the acetylenic anion of **101** to *O*-benzyl-D-glucono-l,5-1actone **93** (Scheme 14). Indeed, reduction of hemiketal **102** was followed by Swern oxidation to obtain the diketone, which was directly subjected to DRA with an excess of ammonium formate (in $MeOH/CH_2Cl_2$ with 3Å molecular sieves), allowing the formation of piperidine **103** in 56% overall yield. After deprotection, the final compound **104** was screened towards a panel of enzymes involved in glucosylceramide metabolism and other lysosomal glycosidase. Compound **104** showed the highest glucosylceramide inhibitory activity of the modified derivatives series, thought being a 50 times less potent inhibitor than lead compound **92**.



Scheme 14. Synthesis of DNJ β-aza-*C*-glycoside analogue **104** *via* "one-pot" reduction/oxidation and diketone DRA of **102**.

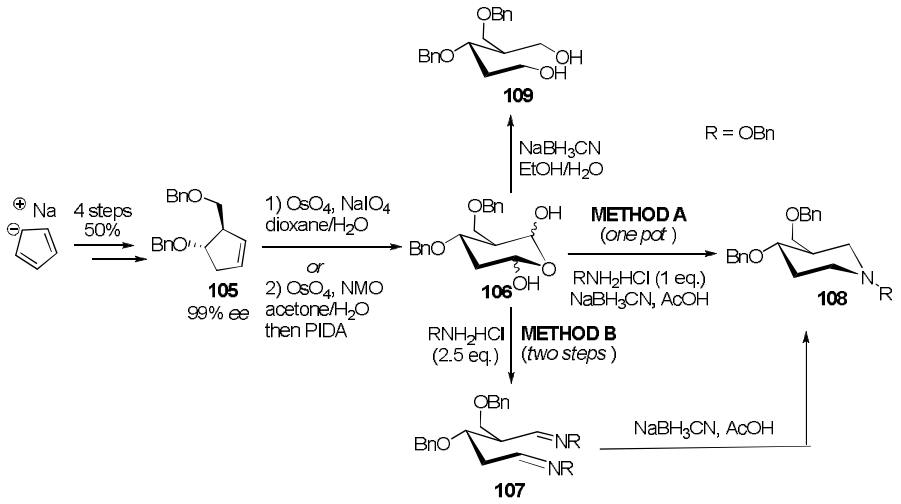
3. Not sugar-derived substrates

Crich and co-workers described for the first time an asymmetric strategy to access novel polyhydroxylated *N*-alkoxypiperidines, based on the ring-closing DRA of protected 1,5-dialdehydes with *O*-substituted hydroxylamines.[37,38] Interestingly, the dialdehyde substrates were not derived from sugars of the chiral pools, but were obtained by oxidative cleavage of cyclopentene derivatives. In particular, the dialdehydes derived from an approach that relies on the desymmetrization of cyclopentadiene (through highly enantioselective hydroboration with (−)-diisopinocampheylborane ((−)-Ipc_2BH), to give an optically enriched functionalized cyclopentene derivative **105**, followed by oxidative cleavage to yield the required dialdehyde. The experimental conditions of the DRA step were optimized starting from the disubstituted dialdehyde **106**. Compound **106** was obtained from cyclopentene derivative **105** (50% yield, over 4 steps from cyclopentadienyl anion) by oxidative cleavage (Scheme 15). The oxidative step was investigated both with sodium periodate and osmium tetroxide in a mixture of dioxane and water and with Nicolaou's modified procedure, that employs osmium tetroxide/*N*-methylmorpholine *N*-oxide followed by treatment with phenyliodine diacetate (PIDA). In order to probe the efficiency of the oxidative cleavage, the dialdehyde was reduced to the corresponding diol **109** with sodium borohydride, due to the existence of the cyclic hydrate dialdehyde as a mixture of various diastereomeric forms.

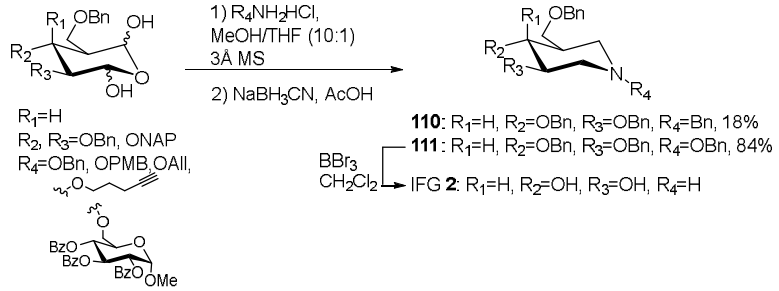
The DRA reaction was initially investigated by treating freshly prepared dialdehyde **106** with *O*-benzylhydroxylamine, in a single step (Scheme 15, Method A), and gradually increasing the number of equivalents of the dialdehyde. The addition of 2.0 equivalents of dialdehyde allowed to obtain the product in 57% yield. Then, the DRA reaction was performed in two steps (Scheme 15, Method B): in this higher yielding protocol, 2.5 equivalents of hydroxylamine was first added to generate the intermediate dioxime **107**. The formation of the dioxime was monitored by LC-MS analysis, and the sodium cyanoborohydride was added once the formation of the dioxime was complete (approximately 2.5 h) achieving alkoxyamine **108** in 81% yield (Scheme 15). Unlike Method A, the presence of molecular sieves was necessary in Method B for the efficient generation of the dioxime.

After optimization of the DRA reaction conditions, Crich and co-workers expanded the scope of the reaction by varying the nature of both the hydroxylamine and using di- or trisubstituted dialdehydes. The

employ of a variety of *N*-substituted hydroxylamines demonstrated that this protocol nicely accommodates the presence of protected sugar, ester, alkyne, allyl and benzyl functionalities in the hydroxylamine component, providing a wide series of novel trihydroxypiperidine derivatives analogous to isofagomine (Scheme 16).[38] Interestingly, the DRA with benzylamine in the presence of sodium cyanoborohydride afforded the protected isofagomine derivative **110** in a low 18% yield, while the ring closing DRA performed with *O*-benzylhydroxylamine (under the previously optimized conditions) afforded the *N*-benzyloxypiperidine **111** in an excellent 84% yield. Deprotection of the benzyl and naphthylmethyl groups using BCl_3 afforded the target *N*-alkoxypiperidines, all analogues of isofagomine characterized by the presence of a *N-O* bond linked to various functional groups. Conversely, deprotection of **111** with BBr_3 rather than BCl_3 allowed to remove the ether functionality and additionally o cleave the hydroxylamine N-O bond, affording isofagomine **2** in 72% yield (Scheme 16).



Scheme 15. Ring-closing DRA of **106** with *O*-benzylhydroxylamine. Reaction conditions of DRA
Method A: $R_2NH_2{\cdot}HCl$ (1 eq.), $NaBH_3CN$ (5 eq.), AcOH (20 eq.), 3Å MS, MeOH (0.04 M).
Method B: $R_2NH_2{\cdot}HCl$ (2.5 eq.), $NaBH_3CN$ (5 eq.), AcOH (10 eq.), 3Å MS, MeOH/THF (0.25 M, 10:1).



Scheme 16. Synthetic strategy to access novel trihydroxypiperidine analogous to isofagomine (IFG), *via* ring-closing DRA of diversely substituted dialdehydes and hydroxylamines.

Later on, Crich and co-workers adapted their asymmetric synthesis route to an iterative double ring-closing reductive amination reaction in order to obtain di- and trimeric hydroxylamine-based mimetics of β-(1→3)-glucans (Figure 5), as potential immunomodulating agents.[39]

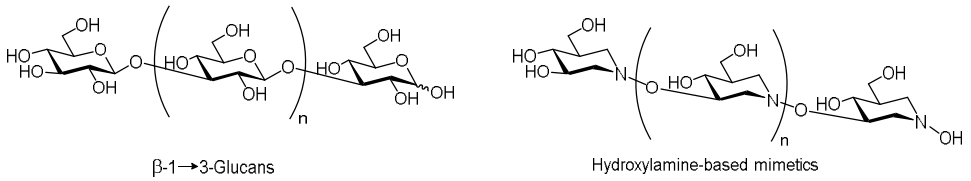
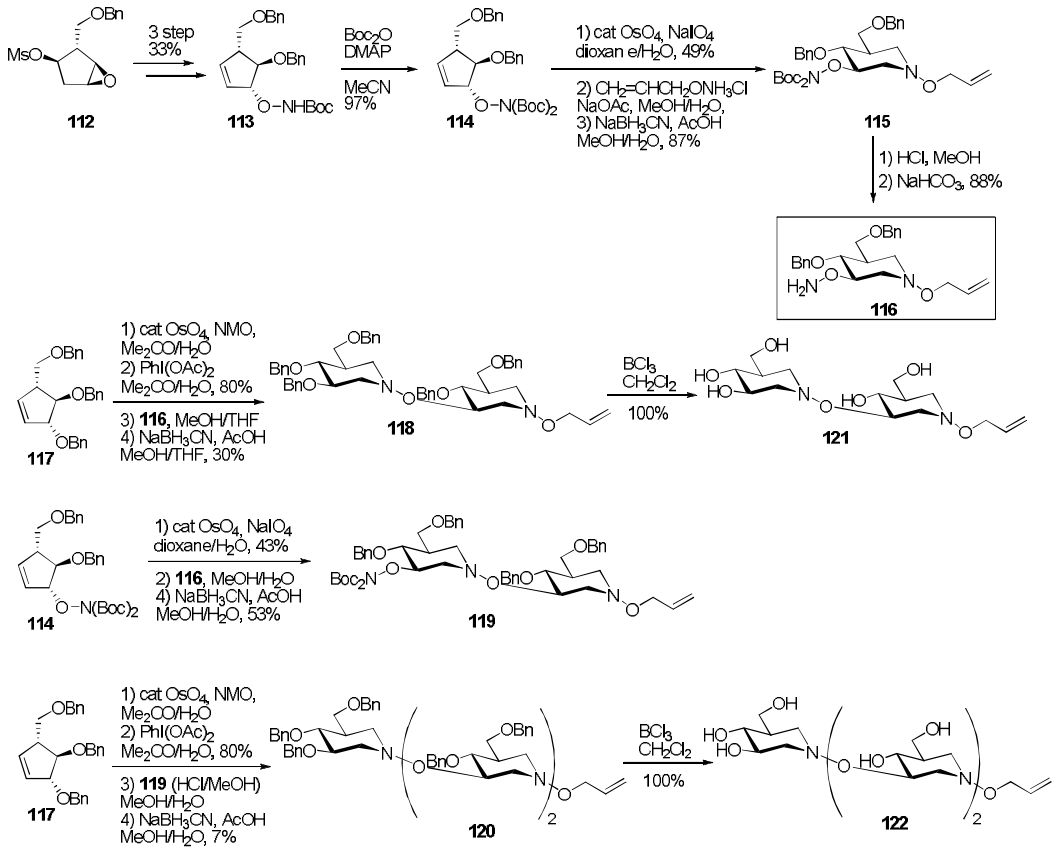


Figure 5. β-(1→3)-glucans structure and structure of their hydroxylamine-based mimetics prepared by Crich and co-workers.

Cyclopentadiene-derived mesyloxy epoxide **112** was initially converted into carbamate **113**, in three steps and 33% overall yield. Attempt of subjecting carbamate **113** to the oxidative cleavage and subsequent double ring closing reductive amination failed, while the same procedure applied to the corresponding imide **114** afforded the *N*,*N*-di-Boc protected product **115** in 43% yield over 3 steps (Scheme 17).



Scheme 17. Synthesis of di- and trimeric hydroxylamine-based glucan mimetics **121** and **122**, by oxidative cleavage and subsequent double ring-closing reductive amination.

A carefully optimization of the procedure revealed that best results were obtained by performing the cleavage of **114** with catalytic OsO_4 and $NaIO_4$ thus accessing the crude dialdehyde, which was subsequently subjected DRA with *O*-allylhydroxylamine, $NaBH_3CN$ and AcOH in MeOH. Treatment of **115** with HCl in MeOH and subsequent washing with $NaHCO_3$ allowed isolation of dihydroxylamine **116** as the

free base, ready for being employed in the formation of dimer and trimer. In particular, protected dimer disaccharide mimetic **118** was accessed by subjecting **117** to Upjohn protocol (OsO_4 and *N*-methyl morpholine *N*-oxide) and obtaining a diol that was directly transformed in the corresponding dialdehyde, in turn subjected to the ring closing DRA reaction with 2 equivalents of hydroxylamine **116**. Reductive amination of the same hydroxylamine **116** with 2 equivalents of the dialdehyde obtained by oxidative cleavage of **114**, afforded a second dimer **119** that, after Boc removal, furnished the corresponding free hydroxylamine, which was coupled to the dialdehyde derived from **117** in order to access the protected trimer **120** (Scheme 17).

Deprotection of **118** and **120** with BCl_3 in CH_2Cl_2 provided the final compounds **121** and **122**, respectively, in quantitative yield. The biological evaluation showed that these di- and trimeric hydroxylamine-based mimetics of β-(1→3)-glucans are able to inhibit the staining of human neutrophils and of mouse macrophages by fluorescent anti-CR3 and anti-dectin-1 antibodies and to stimulate phagocytosis in a length- and linkage-dependent manner.

4. Conclusions

Many naturally occurring polyhydroxypiperidines and their synthetically functionalized analogues are well known as glycosidase inhibitors, and their potential as new therapeutic agents for the treatment of diabetes, viral infections, cancer and rare genetic diseases, for which they have recently received renewed attention, has been widely investigated. *N*-alkyl deoxynojirimycin (DNJ) **1** derivatives, deoxygalactonojirimycin (DGJ) **5** and isofagomine (IFG) **2**, are some of the most famous structures that have been, or are currently, involved in clinical trials for the treatment of Gaucher and Fabry diseases.

Among the plethora of synthetic strategies proposed for the synthesis of biologically relevant polyhydroxypiperidines, the double reductive amination (DRA) reaction is undoubtedly the method of choice for the construction of the piperidine skeleton. Therefore, the present account collects synthetic strategies that exploit a DRA reaction between a dicarbonyl compound and an amine (or hydroxylamine) for the preparation of polyhydroxypiperidines.

DRA is a “one-pot” efficient reaction, that usually involves at least four cascade steps (first imine formation, reduction, cyclic imine formation, reduction) but that can be further coupled with previous deprotection or oxidation reactions, resulting in even more complex versions that attest the robustness of such method.

Readily available sugars are the most common starting materials for the preparation of the dicarbonyl derivatives employed as the substrate of the DRA reaction. For this reason, in section 2 the syntheses that used sugar-derived substrates were described, and classified based on the carbonyl groups nature (dialdehydes, ketohaldehydes or diketones). In particular, isofagomine **2** and its derivatives are obtained essentially starting from dialdehydes (section 2.1.), while for the syntheses of deoxynojirimycin **1** derivatives, which involve the formation of a newly formed stereocenter and therefor an additional stereoselectivity issue, the use of ketoaldehydes or diketones (sections 2.2. and 2.3.) is employed. In sharp contrast, DRA reactions on not-sugar derived dicarbonyl compounds to access polyhydroxypiperidines are very rare and were reviewed in section 3. A wide variety of amines, from the simplest ammonia to complex amino sugars or amino acids derivatives were used as the nitrogen atom source, attesting the versatility of the DRA approach. Hydroxylamines were also shown to be efficient in fulfilling this task. Regarding the reducing agent, only $NaBH_3CN$ and H_2 (this latter in the presence of catalytic amounts of Pd/C or $Pd(OH)_2/C$) were reported, while reactions conditions (solvent, temperature, presence or absence of drying agents) greatly vary from one case to another. In addition, when possible, an overview of the biological properties of the obtained polyhydroxypiperidines was provided.

Acknowledgements

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