Iminosugars as glucosylceramide processing enzymes inhibitors: design, synthesis and evaluation

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2 Synthesis of Deoxynojirimycin and its Substituted Analogues: Highlights from the Literature

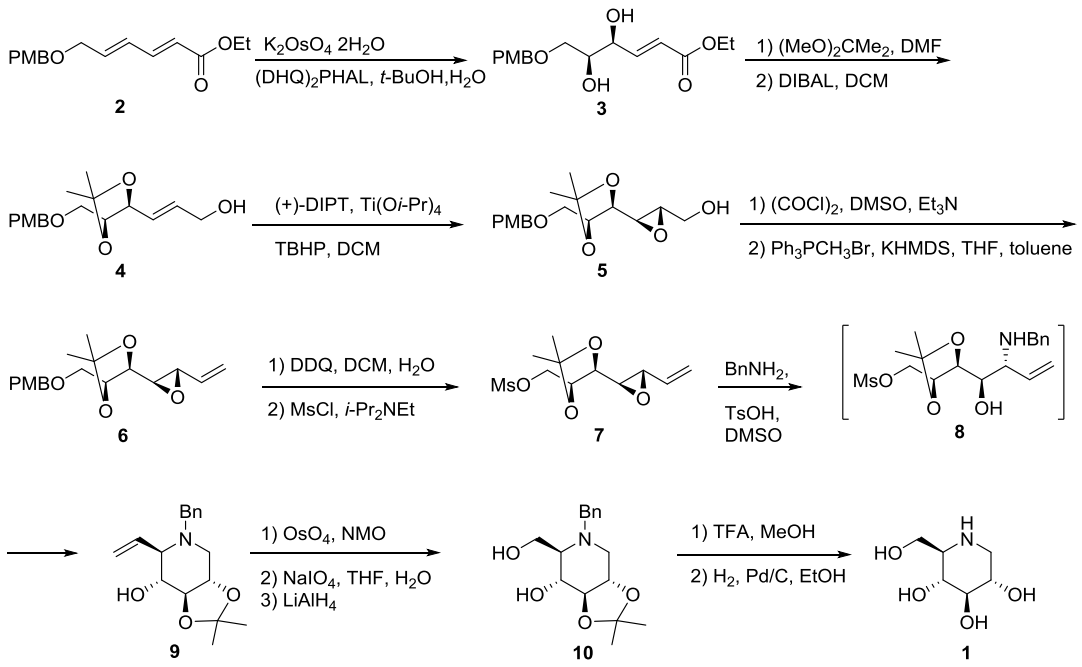
Introduction

Following the first synthesis of nojirimycin (NJ) and deoxynojirimycin (DNJ) reported by Paulsen and co-workers in 1967,[1] many studies on the synthesis of iminosugar derivatives have emerged.[2-7] In the course of these studies, many conceptually different strategies have been developed. Most of these synthesis strategies can be classified as being part of two overarching strategies, namely, those starting from simple, often achiral starting materials (*de novo* synthesis) and those starting from an abundant natural compound (chiral pool synthesis). Perhaps not surprisingly, carbohydrates often feature as the chiral pool starting material: many monosaccharides are abundant in nature, and a wealth of chemical transformations is known

by means of which the individual functional groups of a carbohydrate can be addressed individually. Last but not least, many of these functional groups present in the target iminosugar are also found in the parent sugar and therefore 'just' need to be retained in a synthesis campaign. In this chapter, a literature survey of some of the most versatile *de novo* synthesis and chiral pool-based synthesis strategies towards the archetypal iminosugar, 1-deoxynojirimycin (DNJ) will be given, with a focus on reductive amination chemistry as a key step in the synthesis.

Synthesis from achiral compounds

***Scheme 1**: Synthesis of DNJ featuring consecutive Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation steps*



The synthesis of DNJ, which has four consecutive chiral centers, from non-chiral starting materials can be time-consuming and requires both the introduction (through for instance the use of chiral auxiliaries or the application of asymmetric catalysis strategies) and the transfer of chirality.[5, 8-13] One of the earliest examples of an asymmetric synthesis of DNJ was reported by Somfai and co-workers in 1998 (Scheme 1).[14] In the first step of this synthesis *p*-methyloxybenzyl (PMB) protected diene **2** was subjected to a Sharpless asymmetric dihydroxylation reaction (treatment with AD-α-mix), giving diol **3** in high enantiomeric excess. Protection of the secondary alcohols in **3** was followed by reduction of the ethyl ester to

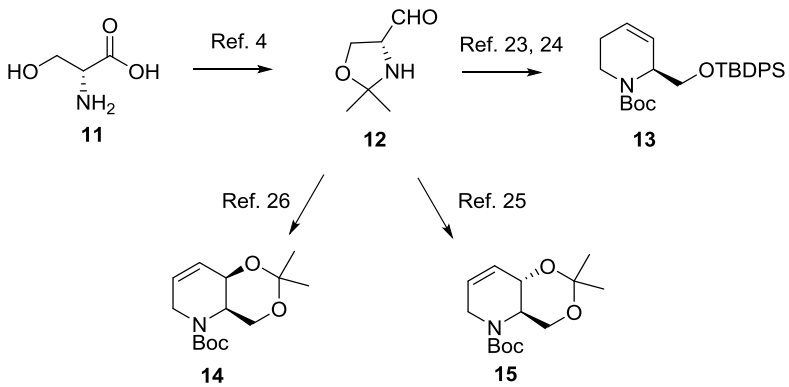
generate allylic alcohol **4**, which was converted to epoxide **5** by means of a Sharpless asymmetric epoxidation. Swern oxidation of the primary alcohol **5** to the aldehyde was followed by Wittig olefination, yielding vinyl epoxide **6** as a key intermediate bearing four consecutive chiral carbon centers.

Oxidative removal of the PMB group in **6** was followed by reaction of the thus liberated primary alcohol with methanesulfonyl chloride and diisopropylethyl amine to provide mesylate **7**. Treatment of **7** with benzylamine gave regioselective opening of the epoxide to *in situ* form compound **8**, after which intramolecular substitution of the mesylate in **8** provided piperidine **9**. Dihydroxylation of the vinyl moiety in **9** followed by oxidative cleavage and reduction of the resulting aldehyde gave partially protected DNJ **10** and ensuing global deprotection finally yielded DNJ **1**.

Synthesis from amino acids

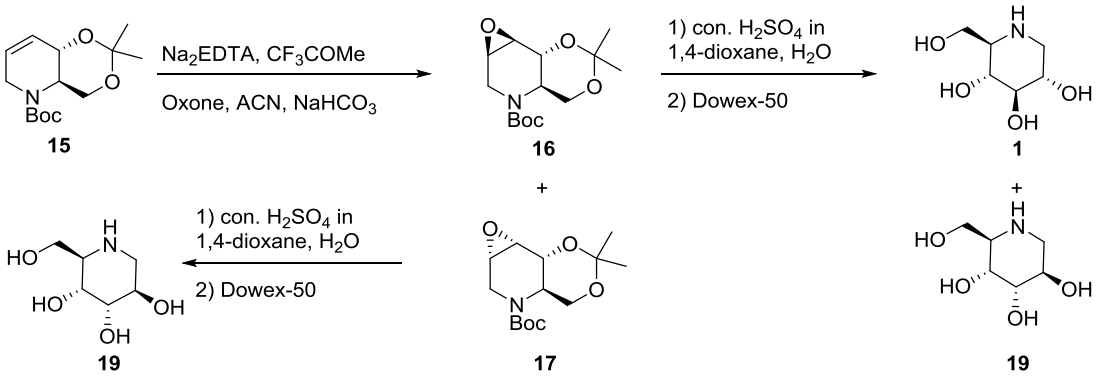
Compared with *de novo* synthesis strategies relying on the introduction of chirality during chemical transformations and that start with achiral starting materials, routes starting with chiral pool compounds are often more concise. Amino acids are sometimes used as starting points in the synthesis of iminosugars, and several routes of synthesis starting from (*S*)-isoserine,[15] serine[16-21] and alanine[22] have been reported. A relevant example of such a strategy is depicted in Scheme 2 and comprises the use of Garner's aldehyde **12**, itself easily prepared from D-serine, in the preparation of a variety of protected and functionalized piperideines.[4] These chiral piperideines (**13** - **15**) function as advanced intermediates in the preparation of DNJ (**1**) and some configurational analogues. D-Fagomine and its isomers were generated from methoxypiperideine **13**,[23, 24] DNJ and its D-*allo*, D-*altro* and D-*manno* congeners are synthesized via the dioxanyl piperideine intermediate **15**,[25] while D-*gal*, D-*gulo*, D-*ido* and D-*talo* isomers are generated from **14**.[26]

Scheme 2**: Chiral building blocks from Garner's aldehyde **12



As an example of how piperideines can serve as advanced intermediates towards iminosugars, the transformation of **15** to DNJ **1** is depicted in Scheme 3. Treatment of **15** with oxone gave a near equimolar amount of the two epoxides **16** and **17** (44% and 45% yield, respectively). Acid hydrolysis of **16** gave a mixture of DNJ (**1**) and its D-*altro* epimer (**19**), again in a 1:1 ratio. Under the same conditions **17** was transformed to the D-altro epimer as the sole product.

Scheme 3**: Synthesis of DNJ from piperideine **15



Takahata and co-workers revealed the use of the D-serine-derived piperideines in the synthesis of both configurational DNJ isomers and configurational fagomine isomers resembling naturally occurring D-configured monosaccharides. Moreover, by switching to the Garner's aldehyde derived from L-serine the corresponding enantiomeric isomers can be prepared following the same sequence of reactions. A recent route reported by Singh *et al*. describes such a synthesis of L-DNJ starting from L-serine-derived Garner's aldehyde.[21,27]

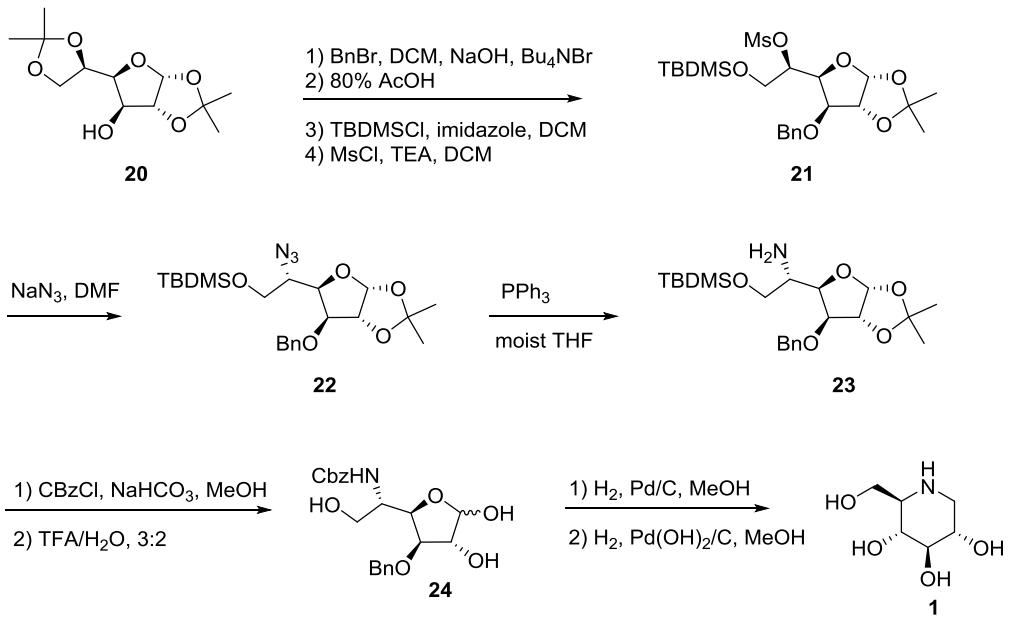
Synthesis from carbohydrates

Carbohydrates are often used as starting point for the chemical synthesis of iminosugar derivatives. Mannitol,[28, 29] D-ribose,[30] D-fructose[31] as well as a number of other monosaccharides all feature in iminosugar synthesis strategies, and a reductive amination event (single or double) often is applied to create the piperidine core structure.[32-48]

Owing to the structural similarity of DNJ and glucose, the use of glucose and its derivatives as chiral pool starting compounds is obvious, and many groups have devoted efforts to the synthesis of DNJ using glucose as starting material. One popular approach that starts from D-glucose is to prepare DNJ via a 5-azido intermediate.[32-40] A representative example is given in Scheme 4.[39] The synthesis scheme starts with diacetone glucose, and after a series of standard protective group and functional group transformations compound **21** featuring a mesylate at C-5 is obtained. S_N2 substitution of the mesylate by sodium azide yielded **22**, after which

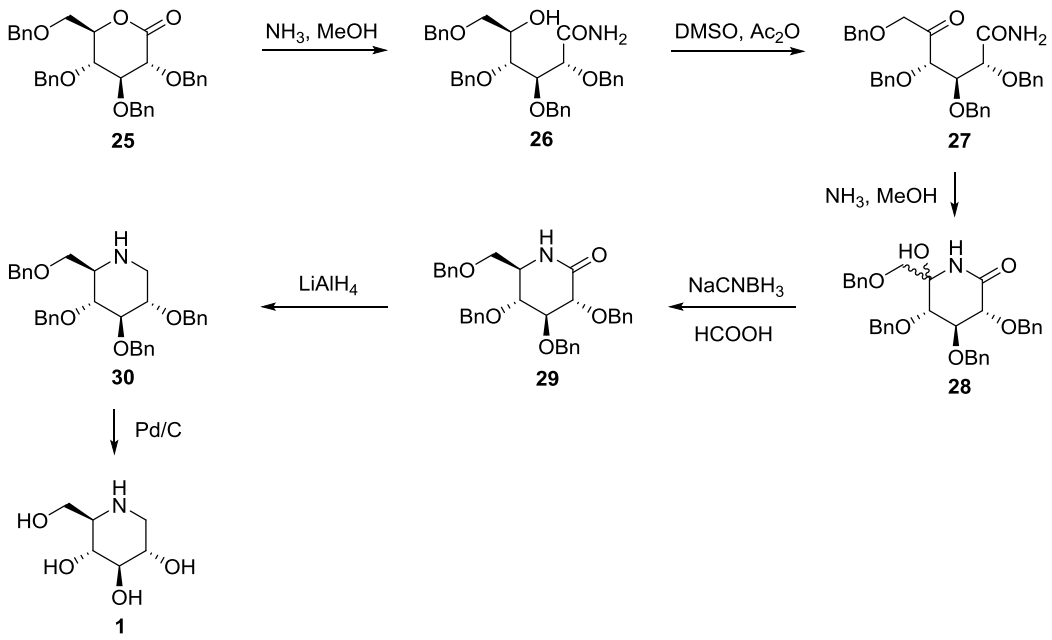
Staudinger reduction (**22** to **23**), Cbz protection of the amine in **23** followed by acidolysis provided lactol **24**. Compound **24** was subjected to catalytic hydrogenation, resulting in deprotection of the amino group, intramolecular nucleophilic attack of the amine on the aldehyde (masked in **24** as the hemi-acetal) and dehydration to *in situ* form the imine, which is reduced in one pot to form DNJ (**1**). The last steps – imine formation followed by reduction, in other words a reductive amination, is found in many DNJ synthesis schemes.

***Scheme 4**: Synthesis of DNJ via C-5 azido intermediate*



Two closely related DNJ syntheses that start from perbenzylated D-gluconolactone was reported independently by two groups about 25 years ago.[41-43] In a representative procedure (see in Scheme 5), 2,3,4,6-tetra-*O*-benzyl-α-glucopyranose was oxidized to lactone **25**. Treatment of **25** with methanolic ammonia gave 5-hydroxylamide **26**. The C-5 hydroxyl group was then oxidized to the ketone (**27**), after which ring closure provided hydroxylactam **28**. Reduction of the hydroxylactam under acidic conditions (*in situ* formation of an *N*-acyliminium ion, which is then reduced thanks to the presence in the reaction mixture of sodium cyanoborohydride) provided lactam **29**. Lithium aluminum hydride reduction of the lactam to the piperidine followed by catalytic hydrogenation to remove the benzyl protective groups yielded DNJ (**1**) in 29% yield over the 7 steps starting from 2,3,4,6-tetra-*O*-benzyl-α-glucopyranose.

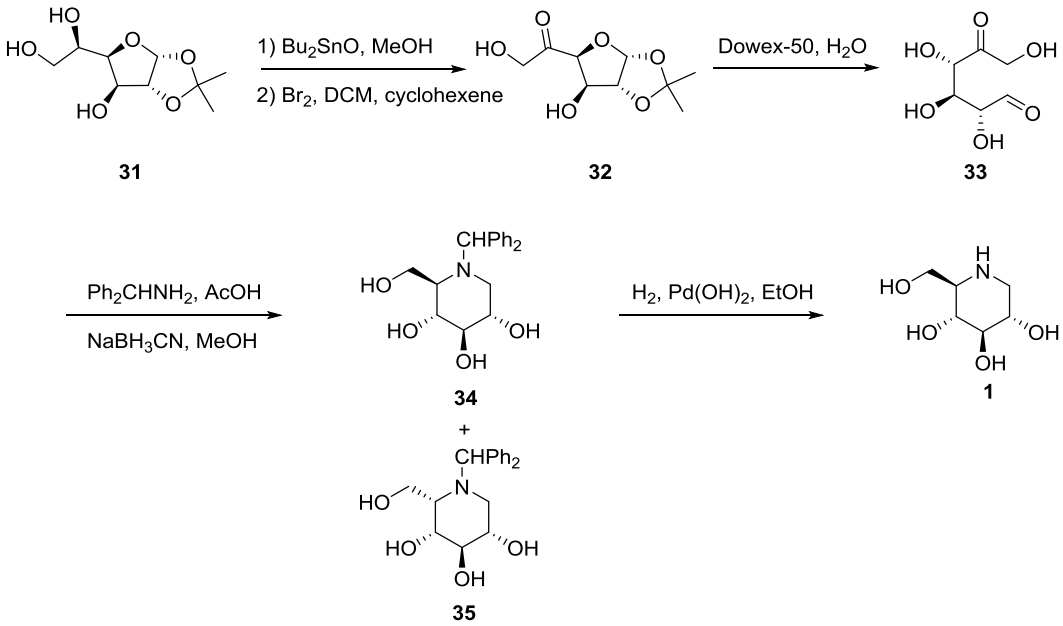
***Scheme 5**: Synthesis of DNJ from gluco-δ-lactone*



Synthesis via double reductive amination

Baxter and Reitz reported in 1990[44, 45] the first synthesis of DNJ featuring as key step a stereoselective intramolecular reductive amination of a 1,5-dicarbonyl derivative (**33**) (scheme 6). The synthesis of **33** started from acetone-D-glucose **31**. In the first step, the free secondary alcohol in **31** is oxidized with dibutyltin oxide and bromine, after which the isopropylidene group was removed with acid resin to give dicarbonyl compound **33**. This intermediate was subjected to a double reductive amination procedure using sodium cyanoborohydride and the appropriate primary amine to form *N*-substituted piperidines (**34** and **35**) with a high stereoselectivity (**34**:**35** = 96:4). The yield and stereoselectivity in the formation of the *N*-alkyl DNJ derivatives described in this report was found to depend on the primary amine used.[44] Application of the double reductive amination protocol to either peracetylated or perbenzylated **33** gave much lower yields.[45] Due to the high stereoselectivity and because hydroxyl protecting groups are not required, the double reductive amination procedure is very attractive and is widely applied in the preparation of different iminosugars and iminosugar derivatives.

***Scheme 6**: Double reductive amination procedure towards DNJ*

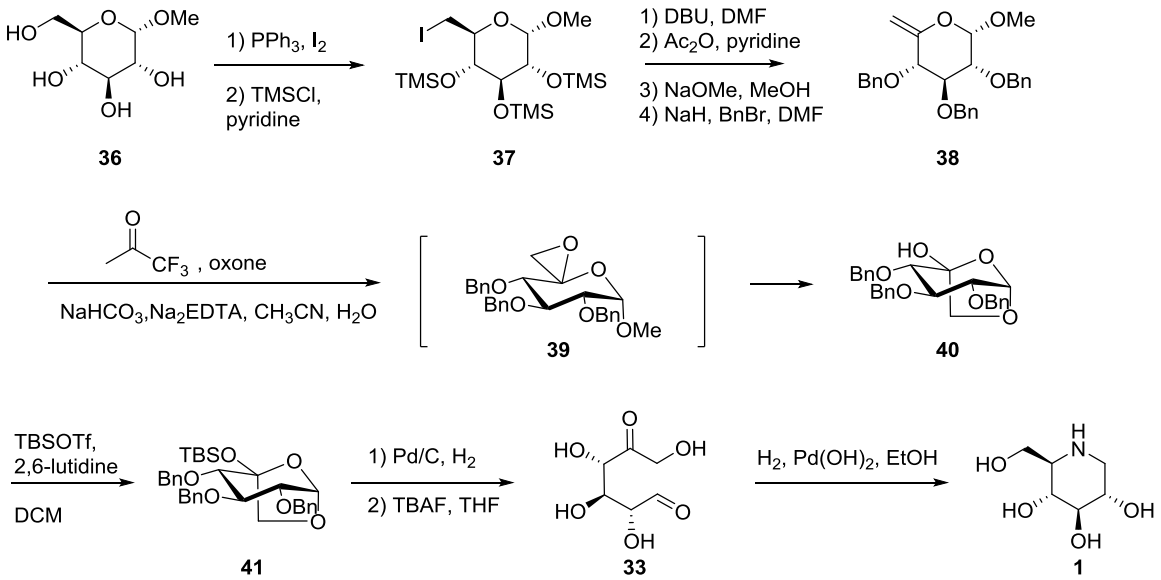


Different synthesis strategies have been developed to prepare hexos-5-uloses (**33**) for ensuing application in double reductive amination protocols.[46] For example, exo-glucal **38** can be transformed into 1,5-dicarbonyl **33** as depicted in scheme 7.[47] Compound **38** was generated from fully protected 6-deoxy-6-iodoglucopyranose **37**, which in turn was obtained in 2 steps from α-methyl glucose following treatment with DBU and ensuing protective group manipulations. Oxidation of **38** with 1,1,1-trifluoroacetone and oxone generated oxirane **39**, which was *in situ* hydrolyzed to give D-hexos-5-ulose **40**, after which subsequent silylation gave **41**. Removal of the protecting groups yielded 5-oxo-aldehyde **33**, which was converted into DNJ following conditions essentially as described by Baxter and Reitz.[45]

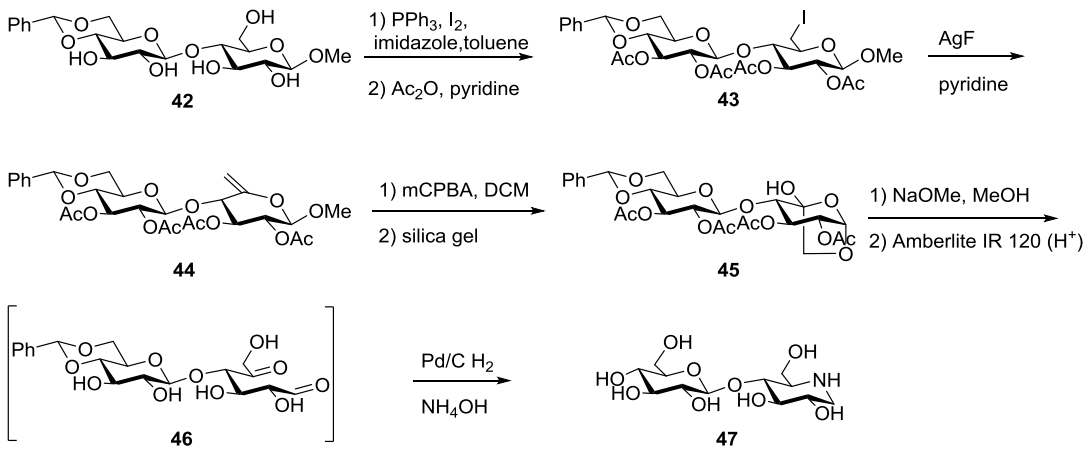
This strategy – generation of an exo-glucal and conversion to the keto-aldehyde – can be carried out on appropriately functionalized disaccharide derivatives as well. Steiner *et al*. developed a route to synthesize glucosyl-4-*β*-DNJ from cellobiose via a 5,6-glucal intermediate (Scheme 8).[48] In this synthesis, cellobiose was converted to its methyl cellobioside and the 4', 6' hydroxyl groups protected to give benzylidene acetal **42**. Following treatment with PPh_3 and iodine, the remaining free hydroxyl groups were acetylated to provide **43**. Silver fluoride mediated elimination of hydrogen iodide formed 5,6-enone **44**, the alkene moiety of which was epoxidized (treatment with mCPBA) after which *in situ* hydrolysis of the anomeric acetal formed **45**. Deacetylation (**45** to **46**) followed by double reductive amination yielded **47** (the

benzylidene protective group is removed under the applied conditions as well). This methodology can also be applied for the synthesis of glucosyl-4-α-DNJ from maltose.[48]

***Scheme 7**: Synthesis of DNJ via a 5,6-exo-glucal intermediate*



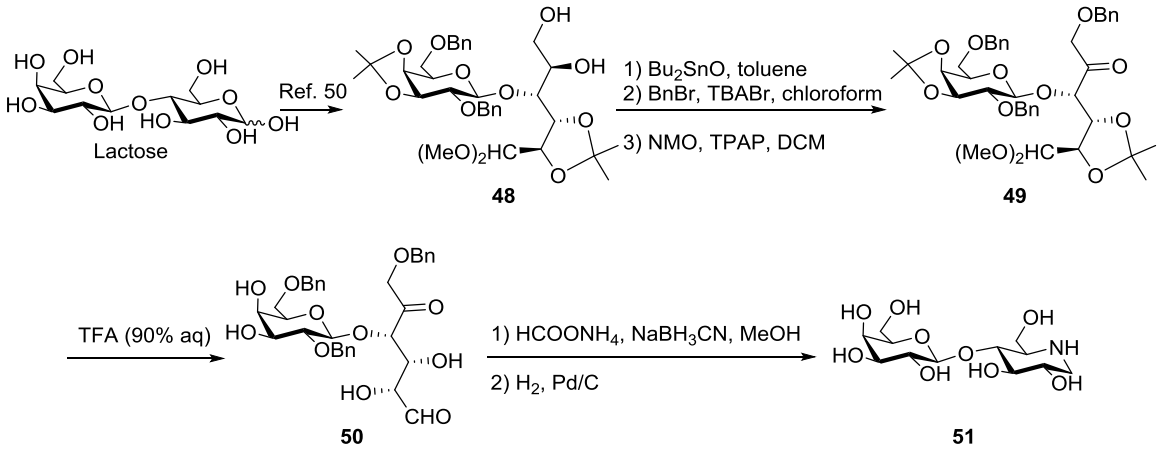
***Scheme 8**: Synthesis of gluco-4-β-DNJ via 5,6-intermediate intermediate*



A related 5-ulose compound proved also to be a versatile intermediate in the synthesis of galactyl-4-β-DNJ **51** as depicted in Scheme 9.[49] Lactose was transformed into partially protected disaccharide **48** in a series of standard transformations,[50] after which 6-*O*-benzyl protected ketone **49** was obtained through regioselective benzylation and oxidation of the remaining secondary alcohol. Treatment of **49** with 90% aqueous TFA gave 1,5-di-carbonyl

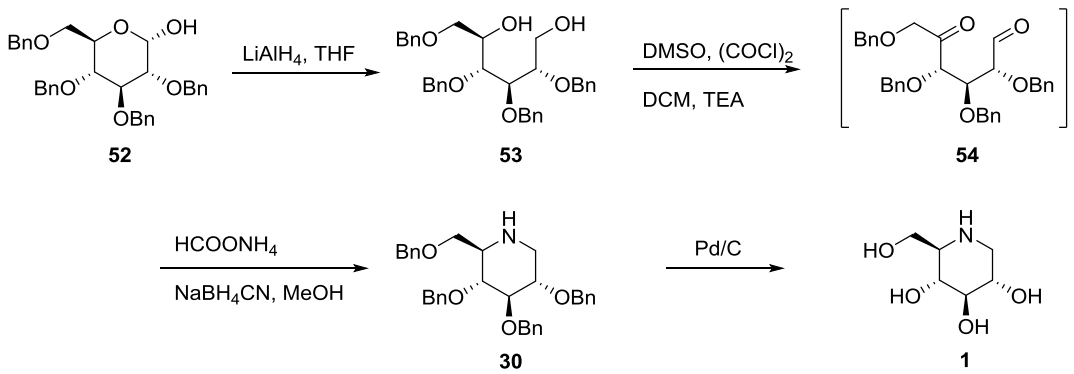
disaccharide **50**, which was subjected to double reductive amination. Finally, catalytic hydrogenation of the thus obtained partially protected aza-disaccharide gave target iminosugar **51**.

*Scheme **9**: Synthesis of galacto-4-β-D-DNJ from lactose*



As a last example, returning to the synthesis of DNJ **1**, a concise synthetic route with perbenzylated 5-keto-aldehyde intermediate **54** as key intermediate is depicted in Scheme 10. The synthesis starts from commercially available 2,3,4,6-*tert*-*O*-benzyl-glucose (**52**).[51] Lactol **52** was reduced by lithium aluminum hydride to give 1,5-diol **53**. Swern oxidation of both primary and secondary alcohol in **53** and subsequent double reductive amination of crude **53** yielded 2,3,4,6-tetra-*O*-benzyl-DNJ **30**. Palladium-catalyzed hydrogenolysis of the benzyl ethers in **30** yielded DNJ. The overall yield in this procedure is up to 65% starting from **52** and moreover the procedure can be executed on a multi-gram scale.[52]

Scheme 10**: Synthesis of DNJ from 2,3,4,6-tert-O-benzyl-glucose **52** via 1,5-diol intermediate **53



Summary

This chapter details some representative and versatile routes of synthesis to obtain DNJ **1** and some structural and configurational analogues. Amongst the routes presented, those starting from carbohydrates, and in particular those featuring double reductive amination steps, are arguably the most versatile for the construction of DNJ type iminosugars. Such routes proceed through the synthesis of a 5-keto-aldehyde intermediate, and thus the stereocenter at C-5 is lost during the synthesis. This stereocenter however is in almost all examples presented close to completely recovered during reduction of the intermediate imine. Thus the strategy is particularly suited for the construction of DNJ-configured iminosugars, although it should be noted that the synthesis of differently configured iminosugars by means of a double reductive amination step is likely to be less effective.

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