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

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Synthesis and Biological Evaluation of *N*-substituted α -Geminal Bis-hydroxymethyl Piperidine Iminosugars

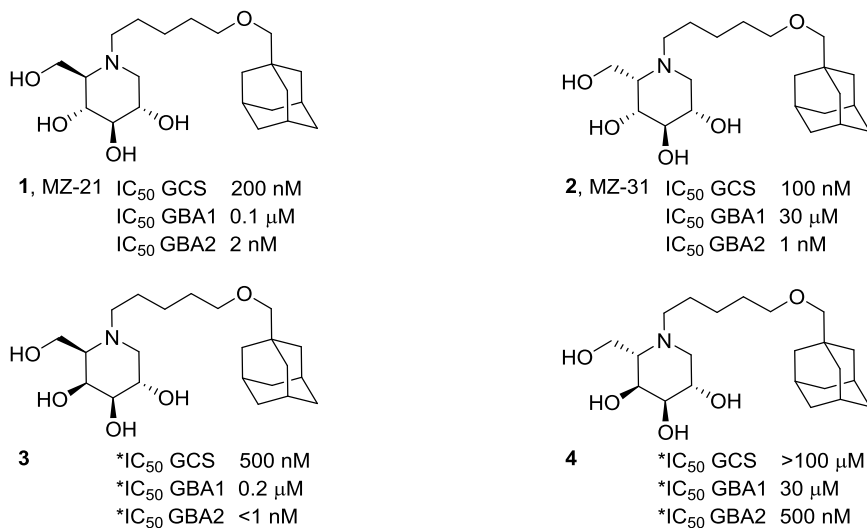
Introduction

Deoxynojirimycin (DNJ) and its congeners are inhibitors of a wide variety of glycosidases as well as some glycosyltransferases. *N*-alkyl DNJ derivatives have been identified as compounds with considerable therapeutic potential for the treatment of various diseases including diabetes and several lysosomal storage disorders (LSDs). Two characteristic iminosugars often included in studies aimed for the design of glycoprocessing enzymes are the natural product, DNJ, and its C-5 epimer, *L-ido*-DNJ.¹ *N*-butyl-DNJ is a moderately potent

glucosylceramide synthase (GCS) inhibitor and based on this virtue used in the clinic for the treatment of Gaucher disease in what is termed substrate reduction therapy. Enlarging the substituent on the DNJ nitrogen improves GCS inhibitory potency, but at the same time results in more potent off-target inhibition. Similarly substituted, *L-ido*-configured iminosugars appear to be much cleaner: they inhibit GCS with equal or (slightly) superior potency compared to their DNJ counterparts and are, with the exception of neutral glucosylceramidase (GBA2), remarkably more selective. These observations invite the question, which underlies the work described in this Chapter, whether hybrid piperidines bearing two α -geminal hydroxymethyl moieties (thus featuring both DNJ and *L-ido*-DNJ hydroxymethyls) would be valid GCS inhibitors, and if so, would be (even) more selective than existing *N*-alkyl-iminosugars.

Figure 1 depicts the lead-iminosugars that led to the studies described here. *N*-AMP-DNJ (**1**, MZ-21) is a potent GCS/GBA1/GBA2 inhibitor, and its *L-ido* congener (**2**, MZ-31), has (slightly) improved GCS/GBA2 inhibitory potency offset by considerable loss in GBA1 inhibitory activity. *N*-AMP D-*galacto* DNJ (**3**) and *N*-AMP L-*altro* DNJ (**4**) are the C-4 epimers of *N*-AMP DNJ and *N*-AMP L-*ido*-DNJ, respectively. Compound **3** is a moderately potent GCS inhibitor and a potent GBA2 inhibitor, and intestinal glycosidases are also inhibited by this compound. Epimer **4** in contrast is only a moderate GBA2 inhibitor with low or no inhibition of intestinal glycosidases, GCS and GBA1.

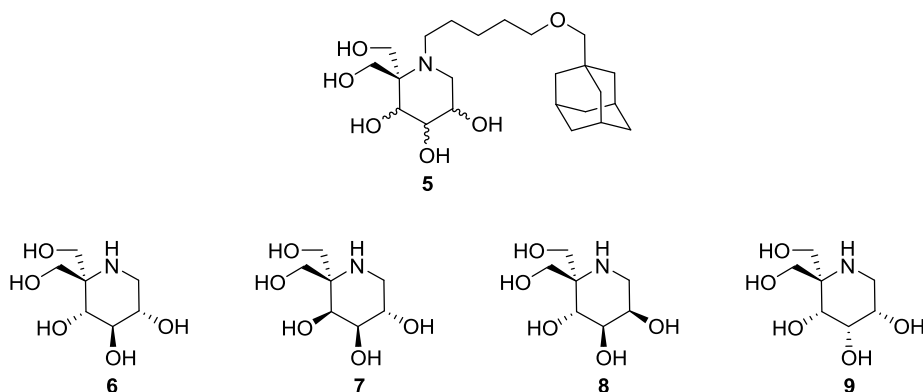
Figure 1: IC_{50} values of *N*-AMP DNJ isosteres for GlcCer metabolizing enzymes



* IC_{50} data from Wennekkes *et al.*¹

These findings led to the design of a number of hybrid iminosugars bearing two geminal hydroxymethyl substituents, as depicted in Figure 2. The list of target compounds encompasses the configurational *D*-gluco-*L*-ido (**6**) and *D*-galacto-*L*-altro (**7**) pairs, but also a choice number of compounds emulating in configuration other pyranosides and that may be of interest in their own right (**8**, **9** and their *N*-alkyl derivatives).

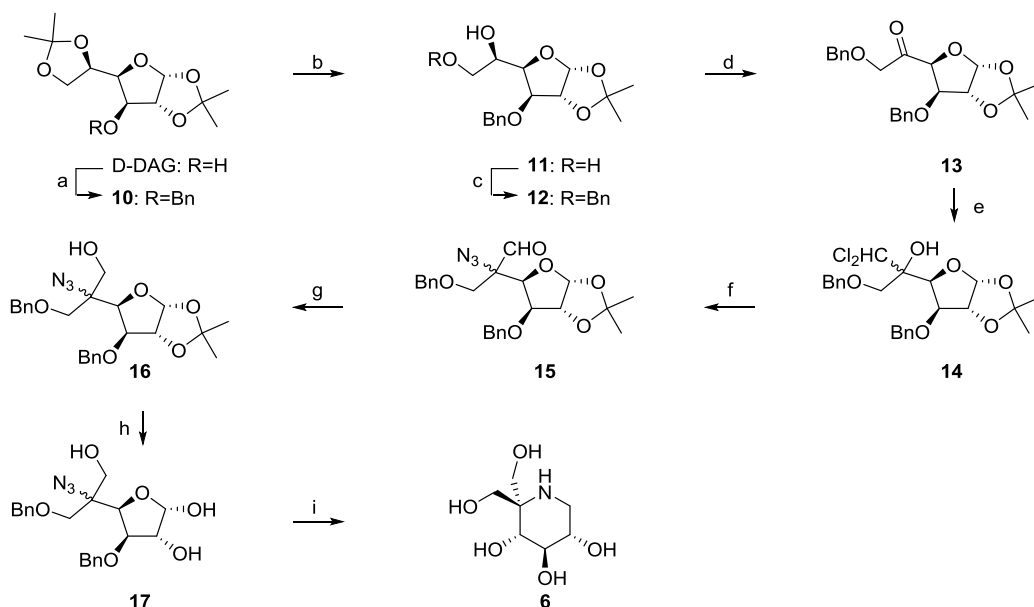
Figure 2: Structures of *N*-AMP α -geminal bishydroxymethyl iminosugars



Results and discussion

Synthesis of 5-C-hydroxymethyl-DNJ (**6**)

Pawar *et al.* documented the synthesis of α -geminal bishydroxymethyl piperidines, which was adopted in the synthesis of *D*-gluco-*L*-ido configured compounds **6** and its C-2 and C-3 epimers.² In the first instance, the synthesis of *D*-gluco-*L*-ido DNJ (**6**) was undertaken following the literature procedure (Scheme 1).² Correspondingly, *D*-diacetone glucose (*D*-DAG) was treated with sodium hydride and benzyl bromide to give **10**. Protonolysis of **10** afforded diol **11**. Regioselective benzylation under the agency of dibutyltin oxide, sodium hydride and benzyl bromide afforded **12** in high yield. The secondary alcohol in **12** was oxidized using PCC to yield ketone **13**. *In situ* formation of dichloromethane carbanion, from dichloromethane and lithium di-isopropyl amide, and subsequent addition to ketone **13** afforded methylene dichloride **14**. An α -azido group was introduced at C-5 in **14** via a Joci Reeve reaction to give **15**. Azido-aldehyde **15** was reduced using sodium borohydride to afford azido alcohol **16**. Demasking of the isopropylidene protecting group, followed by hydrogenation and subsequent reductive amination yielded the target α -geminal bishydroxymethyl DNJ **6** in an overall yield of 6%.

Scheme 1: Synthesis of 5-C-hydroxymethyl-1-deoxynojirimycin (**6**)

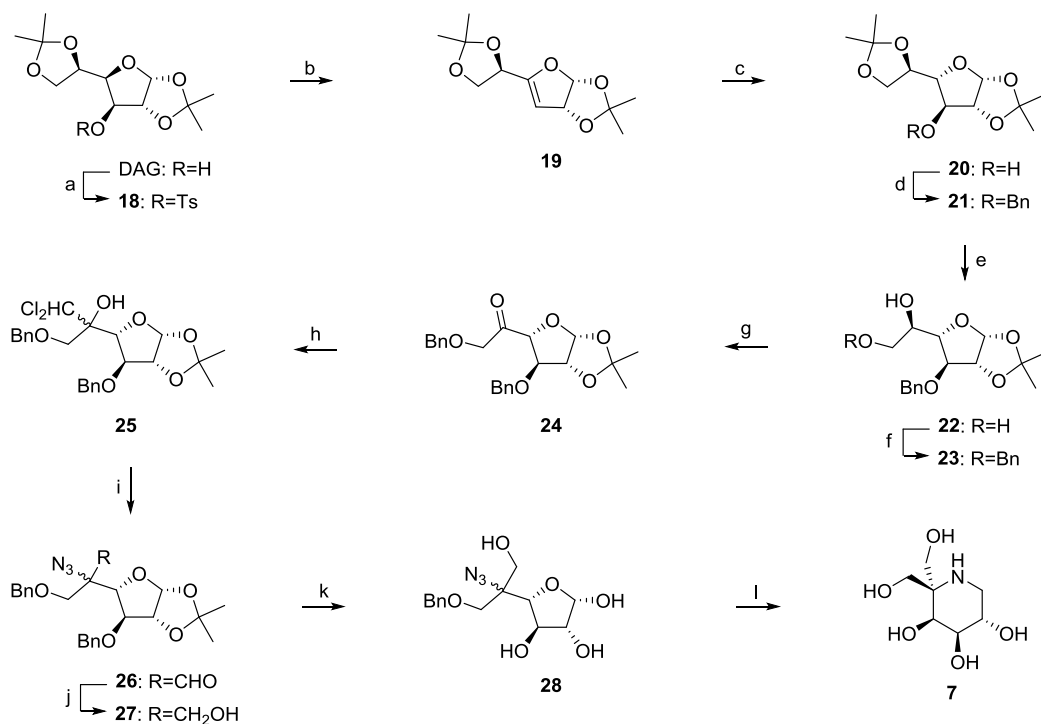
Reagents and conditions: [a] NaH, BnBr, DMF, 97%; [b] AcOH, H₂O, 80%; [c] 1) Bu₂SnO, toluene, 2) NaH, BnBr, 90%; [d] PCC, DCM, 53%; [e] LDA, DCM, THF, 55%; [f] NaN₃, DMF, TBAI, 115 °C, 69%; [g] NaBH₄, 89%; [h] TFA, H₂O, 68%; [i] H₂, Pd/C, 5 bar, 74%.

Synthesis of 5-C-hydroxymethyl-1-deoxy-D-galactonojirimycin (**7**)

It was anticipated that the chemical transformation depicted in Scheme 1 could also be applied on the C-4 epimer of diacetone glucose: diacetone galactose, which would give access to D-galacto-L-altro-iminosugar **7**. Tosylation of DAG³ and subsequent β -elimination of tosylate **18** gave glycal **19**⁴ in high yield (Scheme 2). Hydroboration and subsequent diastereoselective oxidation afforded the desired diacetone galactose **20** in good yield.⁵ Compound **20** was subjected to the transformations as outlined above for the synthesis of **6**. The hydroxyl functionality in **20** was protected using benzyl bromide to give **21**. Isopropylidene demasking of **21** with aqueous acidic acid afforded diol **22**. Regioselective benzylation with the aid of dibutyltin oxide afforded **23**. Alcohol **23** was oxidized with PCC to give ketone **24**. The key step in this synthesis is the introduction of dichloromethylene onto the 5-ketone **24** to form **25**, a reaction that proceeded in an even better yield than that on glucose isomer **14**. Compound **25** was next reacted with sodium azide in DMF at 115 °C to uneventfully give **26** in a yield of 93%. Aldehyde **26** was reduced to give alcohol **27**, which underwent a TFA-water hydrolysis to remove the isopropyl protecting group after which the resulting intermediate **28** was exposed

to 5 bar H₂ atmosphere and a catalytic amount of palladium on carbon to remove the benzyls, reduce the azide to the amine and effect an ensuing intramolecular reductive amination to yield target iminosugar **7** (12% over 12 steps).

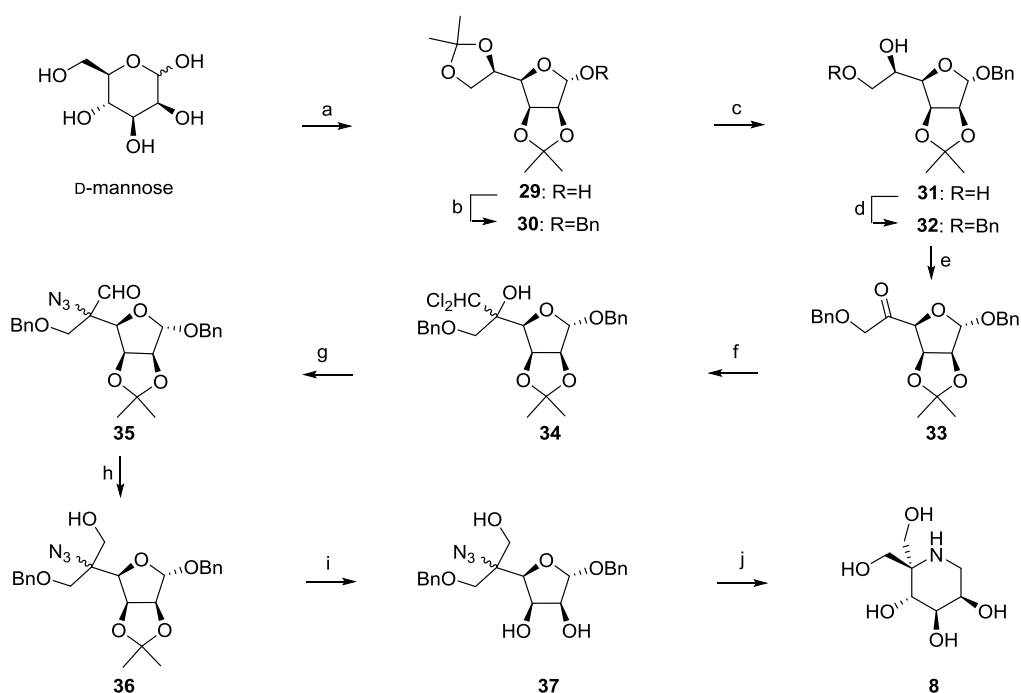
Scheme 2: Synthesis of 5-*C*-hydroxymethyl-1-deoxy-*D*-galactonojirimycin (**7**)



Reagents and conditions: [a] *p*-TsCl, pyridine, DCM, 60 °C, 98%; [b] *t*BuOK, THF, 0 °C, 91%; [c] 1) BH₃·THF, THF; 2) NaOH, H₂O₂, 75%; [d] NaH, BnBr, DMF; [e] AcOH, H₂O, 86%, 2 steps; [f] 1) Bu₂SnO, tol, 2) TBABr, BnBr, 82%; [g] PCC, DCM, 92%; [h] LDA, DCM, -78 °C, 74%; [i] NaN₃, TBAI, DMF, 115 °C, 93%; [j] NaBH₄, MeOH, 0 °C, 82%; [k] TFA, H₂O, 0 °C, 63%; [l] Pd/C, H₂, EtOH, 5 bar, 91%.

Synthesis of 5-*C*-hydroxymethyl-1-deoxy-*D*-mannonojirimycin (**8**) and 5-*C*-hydroxymethyl-1-deoxy-*D*-allonojirimycin (**9**)

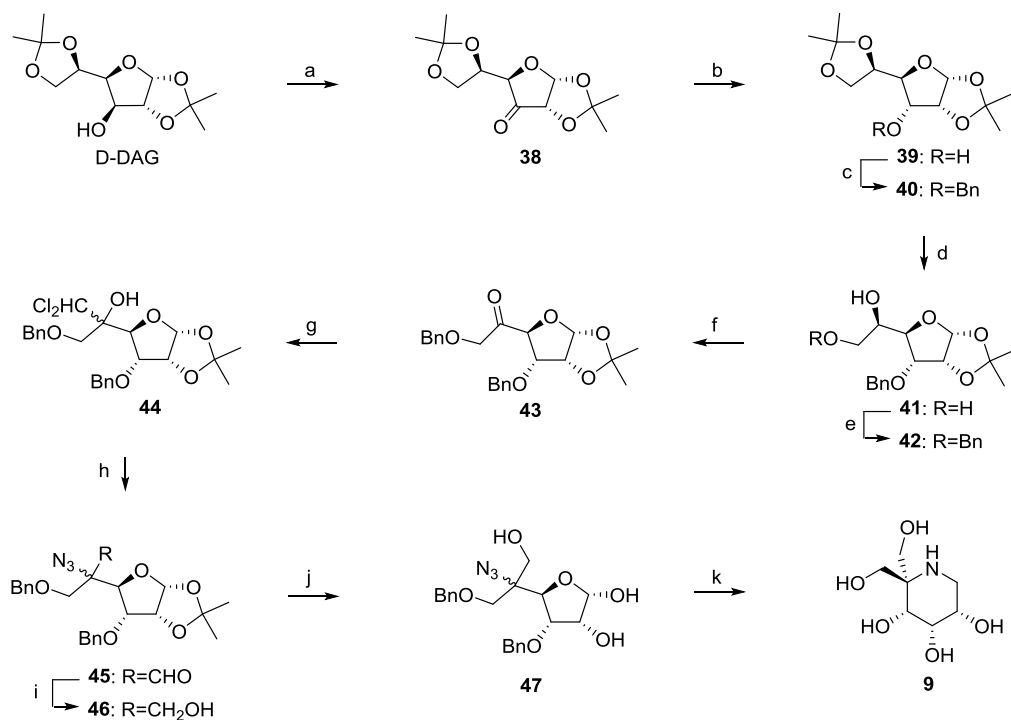
The *D*-manno-*L*-*gulo* iminosugar **8** and *D*-allo-*L*-*talo* iminosugar **9** were synthesized as described by Pawar *et al.*² The synthesis of **8** starts with TBATB catalyzed isopropylidenation of *D*-mannose to give **29**.⁶ Benzylation of **29** gained **30** and subsequent acidic hydrolysis of the acetal protecting group afforded **31**. Alcohol **31** underwent the 7-step transformation as described above for the preparation of **6** and **7**, which generated **8** in an overall yield of 9% (10 steps).

Scheme 3: Synthesis of 5-C-hydroxymethyl-1-deoxy-D-mannonojirimycin (**8**)

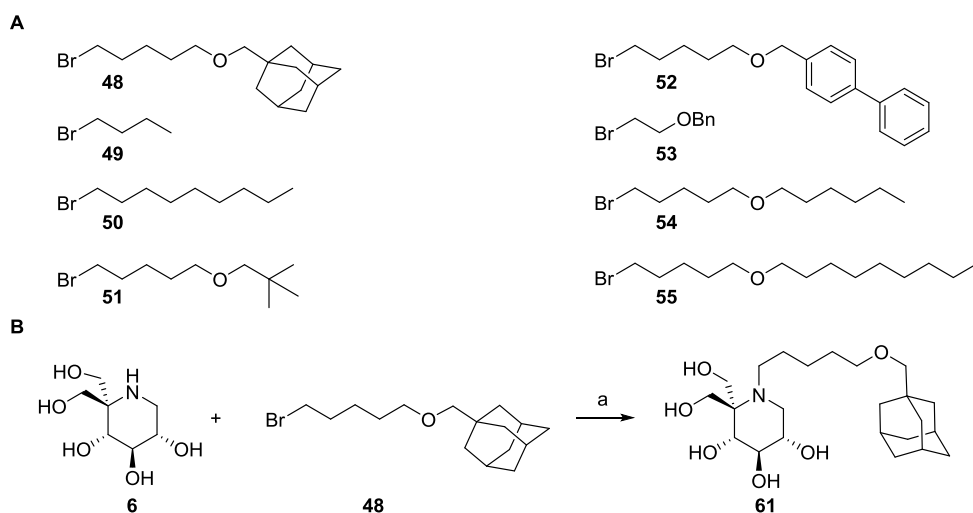
Reagents and conditions: [a] TBATB, acetone, 64%; [b] 18-crown-6, BnBr, KOH, THF, 75%; [c] AcOH, H₂O, r.t., 81%; [d] 1) Bu₂SnO, tol; 2) BnBr, TBABr, 76%; [e] PCC, DCM, 30 °C, 88%; [f] LDA, THF, -78 °C, 66%; [g] NaN₃, TBAl, DMF, 115 °C, 87%; [h] NaBH₄, MeOH, 0 °C, 80%; [i] TFA, H₂O, 0 °C, 45%; [j] Pd/C, H₂, EtOH, 5 bar, 82%.

In a similar vein, diacetone allose **39**, obtained via oxidation and stereoselective reduction from D-DAG, was transformed to produce compound **9** (Scheme 4). The C-3 alcohol of D-DAG was oxidized to form aldehyde **38**, which was reduced by sodium borohydride to give diacetone D-allose **39** in 74% yield over the 2 steps. Compound **9** was prepared from **39** as described previously for the synthesis of **6** with an overall yield of 9% in 9 steps.

With the four α -geminal bis-(hydroxymethyl) piperidines (**6**, **7**, **8** and **9**) in hand, the target hydrophobic iminosugars were prepared by treating **6** - **9** with bromides **48** - **55** (Scheme 5A; see for the final structures Figures 4, 5, 6 and 7). As an example, the synthesis of *N*-AMP D-*gluco*-L-*ido* DNJ (**61**) is depicted in Scheme 5B. Treatment of D-*gluco*-L-*ido* DNJ (**6**) with bromide **48** and potassium carbonate in DMF gave **61** in 11% yield (Scheme 5B). Yields of the *N*-alkyl derivatives vary from 2% to 46% after HPLC purification (see the experimental section for details).

Scheme 4: 5-*C*-Hydroxymethyl-1-deoxy-*D*-allonojirimycin (**9**)

Reagents and conditions: [a] PCC, DCM, 81%; [b] NaBH₄, EtOAc, H₂O, 92%; [c] NaH, BnBr, DMF, 90%; [d] AcOH, H₂O, 46%; [e] 1) Bu₂SnO, tol; 2) BnBr, TBABr, 76%; [f] PCC, DCM, 64%; [g] DCM, LDA, THF, -78 °C, 99%; [h] NaN₃, DMF, 115 °C, 71%; [i] NaBH₄, MeOH, 0 °C, 81%; [j] TFA, H₂O, 0 °C, 70%; [k] Pd/C, H₂, EtOH, 5 bar, 81%.

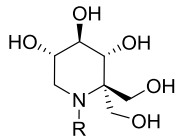
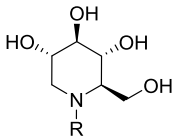
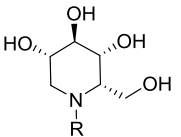
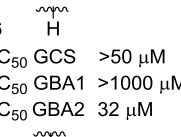
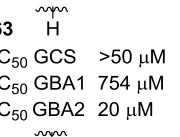
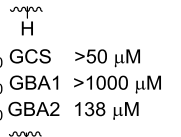
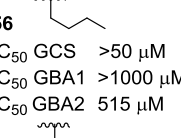
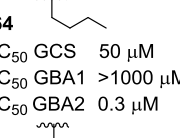
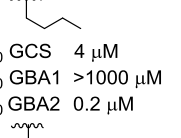
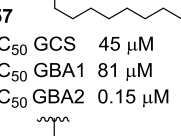
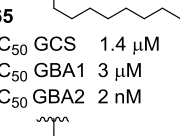
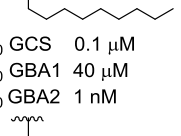
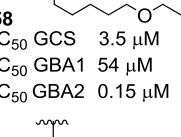
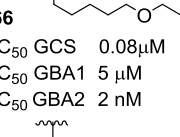
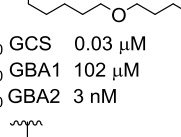
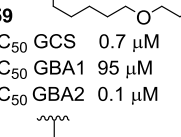
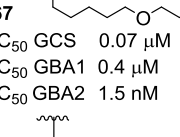
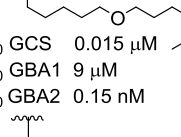
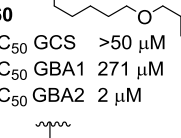
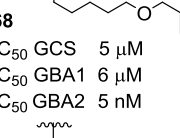
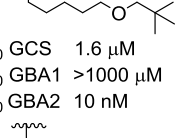
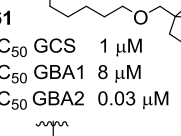
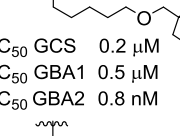
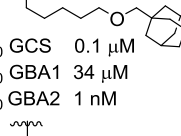
Scheme 5: *N*-alkylation of α -geminal hydroxymethyl iminosugars

Reagents and conditions: [a] K₂CO₃, DMF, 80 °C, 11%.

Biological evaluation

D-Gluco-L-ido hybrid iminosugars

Figure 3: Enzyme inhibition assay results: IC_{50} values, for D-gluco-L-ido DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparison with the corresponding D-gluco-DNJ and L-ido-DNJ analogues

 6 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 32 μM	 63 IC_{50} GCS >50 μM IC_{50} GBA1 754 μM IC_{50} GBA2 20 μM	 70 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 138 μM
 56 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 515 μM	 64 IC_{50} GCS 50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.3 μM	 71 IC_{50} GCS 4 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.2 μM
 57 IC_{50} GCS 45 μM IC_{50} GBA1 81 μM IC_{50} GBA2 0.15 μM	 65 IC_{50} GCS 1.4 μM IC_{50} GBA1 3 μM IC_{50} GBA2 2 nM	 72 IC_{50} GCS 0.1 μM IC_{50} GBA1 40 μM IC_{50} GBA2 1 nM
 58 IC_{50} GCS 3.5 μM IC_{50} GBA1 54 μM IC_{50} GBA2 0.15 μM	 66 IC_{50} GCS 0.08 μM IC_{50} GBA1 5 μM IC_{50} GBA2 2 nM	 73 IC_{50} GCS 0.03 μM IC_{50} GBA1 102 μM IC_{50} GBA2 3 nM
 59 IC_{50} GCS 0.7 μM IC_{50} GBA1 95 μM IC_{50} GBA2 0.1 μM	 67 IC_{50} GCS 0.07 μM IC_{50} GBA1 0.4 μM IC_{50} GBA2 1.5 nM	 74 IC_{50} GCS 0.015 μM IC_{50} GBA1 9 μM IC_{50} GBA2 0.15 nM
 60 IC_{50} GCS >50 μM IC_{50} GBA1 271 μM IC_{50} GBA2 2 μM	 68 IC_{50} GCS 5 μM IC_{50} GBA1 6 μM IC_{50} GBA2 5 nM	 75 IC_{50} GCS 1.6 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 10 nM
 61 IC_{50} GCS 1 μM IC_{50} GBA1 8 μM IC_{50} GBA2 0.03 μM	 1 IC_{50} GCS 0.2 μM IC_{50} GBA1 0.5 μM IC_{50} GBA2 0.8 nM	 2 IC_{50} GCS 0.1 μM IC_{50} GBA1 34 μM IC_{50} GBA2 1 nM
 62 IC_{50} GCS 0.6 μM IC_{50} GBA1 26 μM IC_{50} GBA2 6 nM	 69 IC_{50} GCS 8 nM IC_{50} GBA1 0.4 μM IC_{50} GBA2 0.7 nM	 76 IC_{50} GCS 6 nM IC_{50} GBA1 15 μM IC_{50} GBA2 1 nM

The *D*-*gluco*-*L*-*ido* iminosugars (**6**, **56** - **62**) were tested on their inhibitory potency against the glucosylceramide metabolizing enzymes, GCS, GBA1 and GBA2. The corresponding *D*-*gluco* (**1**, **63** - **69**) and *L*-*ido* (**2**, **70** - **76**) iminosugar derivatives were included as reference compounds to determine the effect of the additional hydroxymethyl group on the C-5 position. The results are tabulated in Figure 3. From the results it can be seen that the DNJ and *L*-*ido*-DNJ derivatives are without exception the more potent GCS inhibitors when compared with their *D*-*gluco*-*L*-*ido* configured α -geminal bishydroxymethyl piperidine counterparts, irrespective of the nature of the *N*-alkyl substituent. In line with what was reported previously the *L*-*ido* iminosugars proved to be the more potent GCS inhibitor when compared with the *D*-*gluco*-configured equivalent. Based on this result, it can be concluded that installment of an extra C-5 hydroxymethyl group at the carbon already bearing such a substituent is detrimental for GCS inhibition.

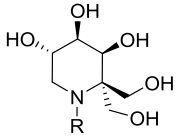
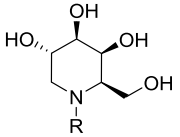
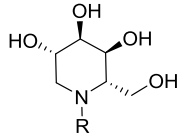
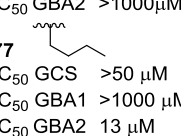
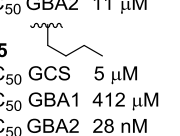
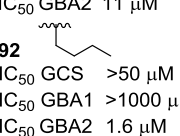
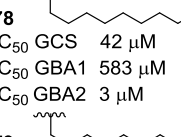
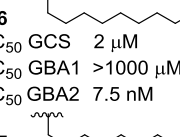
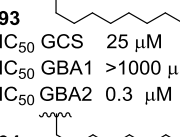
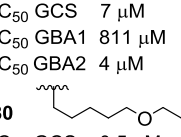
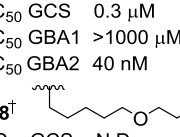
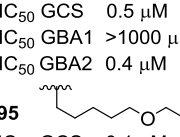
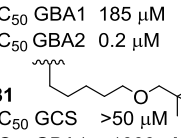
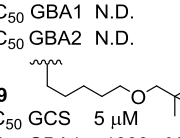
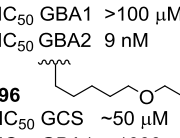
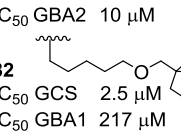
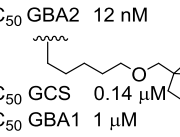
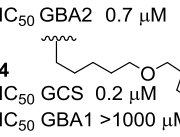
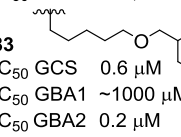
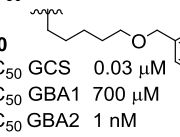
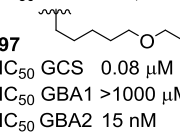
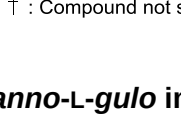
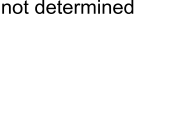
When looking at GBA1 inhibition values, it is remarkable that, whereas the hybrid iminosugars are all weaker inhibitors compared to the *D*-*gluco* configured molecules, they sometimes outperform their *L*-*ido* counterparts. This may indicate that the *D*-*gluco* configuration is preferred by GBA1, that an additional hydroxymethyl group may increase the steric hindrance and thus affect the inhibitory activity, but that this may be less detrimental than altering the configuration at C-5.

The effect of adding an extra hydroxymethyl at C-5 on GBA2 inhibition is as was noted for GCS inhibitory activity: the *D*-*gluco*-*L*-*ido* hybrid iminosugars are still relatively potent GBA2 inhibitors, but much less so than the corresponding *D*-*gluco* and *L*-*ido* compounds.

***D*-Galacto-*L*-altro hybrid iminosugars**

In Figure 4, the inhibitory potencies towards GCS, GBA and GBA2 of the *D*-*galacto*-*L*-*altro* hybrid iminosugars (**7**, **77** - **83**) as well as that of their and the parent compounds (*D*-*galacto* isomers, **3**, **84** - **90**; *L*-*altro* isomers, **4**, **91** - **97**) are depicted. The *D*-*galacto*-*L*-*altro* hybrids do inhibit GCS to some extent, however not at the concentrations at which the *D*-*galacto* and *L*-*altro* iminosugars inhibit GCS. None of the compounds, with the exception of *D*-*galacto* AMP (**3**, IC₅₀ GBA1 = 1 μ M) inhibit GBA. In contrast, several of the *D*-*galacto* configured iminosugars inhibit GBA2 in the nanomolar range and are even more potent than the corresponding DNJ (i.e. **64**, **1** and **69**) and *L*-*ido*-DNJ derivatives (i.e. **71**, **2** and **76**). The *D*-*galacto*-*L*-*altro* hybrid compounds, though, are only weak GBA2 inhibitors, if at all, and also here it appears that the extra appendage at C-5 is detrimental for inhibition potency.

Figure 4: Enzyme inhibition assay results: IC_{50} values, for *D*-galacto-*L*-altro-DNJ and its *N*-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparison with the corresponding *D*-galacto-DNJ and *L*-altro-DNJ analogues

 7 H IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM	 84 H IC_{50} GCS >50 μM IC_{50} GBA1 237 μM IC_{50} GBA2 11 μM	 91 H IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 11 μM
 77 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 13 μM	 85 IC_{50} GCS 5 μM IC_{50} GBA1 412 μM IC_{50} GBA2 28 nM	 92 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 1.6 μM
 78 IC_{50} GCS 42 μM IC_{50} GBA1 583 μM IC_{50} GBA2 3 μM	 86 IC_{50} GCS 2 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 7.5 nM	 93 IC_{50} GCS 25 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.3 μM
 79 IC_{50} GCS 7 μM IC_{50} GBA1 811 μM IC_{50} GBA2 4 μM	 87 IC_{50} GCS 0.3 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 40 nM	 94 IC_{50} GCS 0.5 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.4 μM
 80 IC_{50} GCS 0.5 μM IC_{50} GBA1 185 μM IC_{50} GBA2 0.2 μM	 88[†] IC_{50} GCS N.D. IC_{50} GBA1 N.D. IC_{50} GBA2 N.D.	 95 IC_{50} GCS 0.1 μM IC_{50} GBA1 >100 μM IC_{50} GBA2 9 nM
 81 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 10 μM	 89 IC_{50} GCS 5 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 12 nM	 96 IC_{50} GCS ~50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.7 μM
 82 IC_{50} GCS 2.5 μM IC_{50} GBA1 217 μM IC_{50} GBA2 0.6 μM	 3 IC_{50} GCS 0.14 μM IC_{50} GBA1 1 μM IC_{50} GBA2 1 nM	 4 IC_{50} GCS 0.2 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 0.1 μM
 83 IC_{50} GCS 0.6 μM IC_{50} GBA1 ~1000 μM IC_{50} GBA2 0.2 μM	 90 IC_{50} GCS 0.03 μM IC_{50} GBA1 700 μM IC_{50} GBA2 1 nM	 97 IC_{50} GCS 0.08 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 15 nM

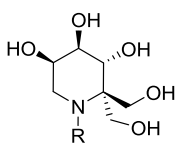
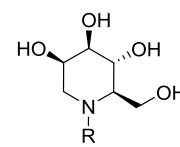
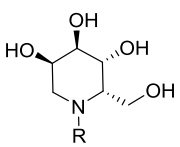
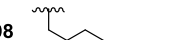
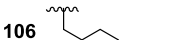
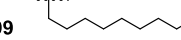
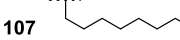
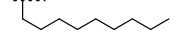
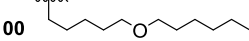
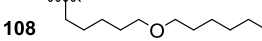
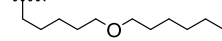
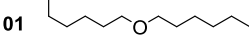
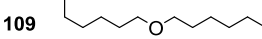
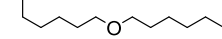
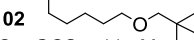
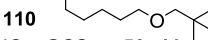
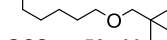
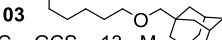
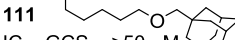
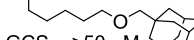
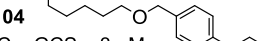
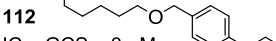
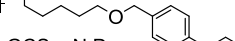
† : Compound not synthesized; N.D.: Activity not determined

D-Manno-L-gulo iminosugars

As shown in Figure 5, none of the *D*-manno-*L*-gulo hybrid iminosugars potently inhibit GCS. The most active GCS inhibitor in this series is the biphenyl derivative **104**. Remarkably, however, the hybrid molecules do sometimes outperform their *D*-manno and *L*-gulo configured

counterparts, in terms of GCS inhibitory potency (compare, for instance the GCS inhibitory potency of **102** with **110** and **118**, and **103** with **111** and **109**). The potency of this series as GBA1 and GBA2 inhibitors is modest at most.

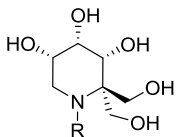
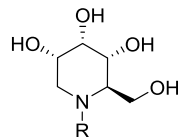
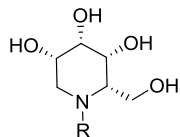
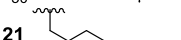
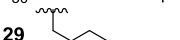
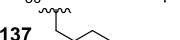
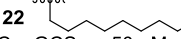
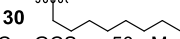
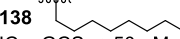
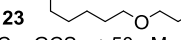
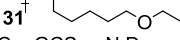
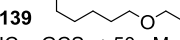
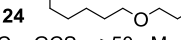
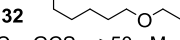
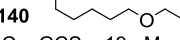
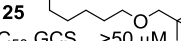
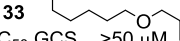
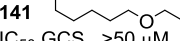
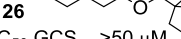
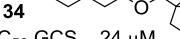
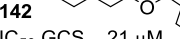
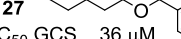
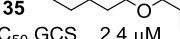
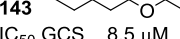
Figure 5: Enzyme inhibition assay results: IC_{50} values, for *D*-manno-*L*-gulo-DNJ and its *N*-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparison with the corresponding *D*-manno-DNJ and *L*-gulo-DNJ analogues

 8 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM	 105 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >100 μM	 113 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM
 98 IC_{50} GCS 40 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 18 μM	 106 IC_{50} GCS ~10 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM	 114 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM
 99 IC_{50} GCS >50 μM IC_{50} GBA1 594 μM IC_{50} GBA2 4 μM	 107 IC_{50} GCS >50 μM IC_{50} GBA1 >100 μM IC_{50} GBA2 >1000 μM	 115 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 7.5 μM
 100 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 3 μM	 108 IC_{50} GCS 8 μM IC_{50} GBA1 929 μM IC_{50} GBA2 3 μM	 116 IC_{50} GCS 21 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 10 μM
 101 IC_{50} GCS >50 μM IC_{50} GBA1 >200 μM IC_{50} GBA2 25 μM	 109 IC_{50} GCS >50 μM IC_{50} GBA1 110 μM IC_{50} GBA2 31 μM	 117 IC_{50} GCS 4 μM IC_{50} GBA1 972 μM IC_{50} GBA2 2 μM
 102 IC_{50} GCS 11 μM IC_{50} GBA1 394 μM IC_{50} GBA2 10 μM	 110 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >1000 μM	 118 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 42 μM
 103 IC_{50} GCS 13 μM IC_{50} GBA1 389 μM IC_{50} GBA2 3 μM	 111 IC_{50} GCS >50 μM IC_{50} GBA1 62 μM IC_{50} GBA2 61 μM	 119 IC_{50} GCS >50 μM IC_{50} GBA1 988 μM IC_{50} GBA2 3 μM
 104 IC_{50} GCS 3 μM IC_{50} GBA1 898 μM IC_{50} GBA2 1 μM	 112 IC_{50} GCS 3 μM IC_{50} GBA1 133 μM IC_{50} GBA2 N.D.	 120[†] IC_{50} GCS N.D. IC_{50} GBA1 N.D. IC_{50} GBA2 N.D.

[†] : Compound not synthesized; N.D.: Activity not determined

D-Allo-L-talo hybrid iminosugars

Figure 6: Enzyme inhibition assay results: IC_{50} values, for D-allo-L-talo-DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparison with the corresponding D-allo-DNJ and L-talo-DNJ analogues

 9 IC_{50} GCS >50 μM IC_{50} GBA1 898 μM IC_{50} GBA2 567 μM	 128 IC_{50} GCS >50 μM IC_{50} GBA1 >100 μM IC_{50} GBA2 >1000 μM	 136 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >100 μM
 121 IC_{50} GCS >50 μM IC_{50} GBA1 594 μM IC_{50} GBA2 31 μM	 129 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 351 μM	 137 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 18 μM
 122 IC_{50} GCS >50 μM IC_{50} GBA1 >200 μM IC_{50} GBA2 9.2 μM	 130 IC_{50} GCS >50 μM IC_{50} GBA1 306 μM IC_{50} GBA2 0.3 μM	 138 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 18 μM
 123 IC_{50} GCS >50 μM IC_{50} GBA1 898 μM IC_{50} GBA2 10 μM	 131[†] IC_{50} GCS N.D. IC_{50} GBA1 N.D. IC_{50} GBA2 N.D.	 139 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >100 μM
 124 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 15 μM	 132 IC_{50} GCS >50 μM IC_{50} GBA1 48 μM IC_{50} GBA2 23 μM	 140 IC_{50} GCS 19 μM IC_{50} GBA1 >100 μM IC_{50} GBA2 0.4 μM
 125 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 1 μM	 133 IC_{50} GCS >50 μM IC_{50} GBA1 815 μM IC_{50} GBA2 17 μM	 141 IC_{50} GCS >50 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 >100 μM
 126 IC_{50} GCS >50 μM IC_{50} GBA1 394 μM IC_{50} GBA2 3 μM	 134 IC_{50} GCS 24 μM IC_{50} GBA1 65 μM IC_{50} GBA2 0.5 μM	 142 IC_{50} GCS 21 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 2 μM
 127 IC_{50} GCS 36 μM IC_{50} GBA1 389 μM IC_{50} GBA2 5 μM	 135 IC_{50} GCS 2.4 μM IC_{50} GBA1 49 μM IC_{50} GBA2 0.4 μM	 143 IC_{50} GCS 8.5 μM IC_{50} GBA1 >1000 μM IC_{50} GBA2 30 μM

[†] : Compound not synthesized; N.D.: Activity not determined

The results of the biological assays of the D-allo-L-talo hybrid iminosugar series (**9**, **121** - **127**), D-allo series (**128** - **135**) and L-talo series (**136** - **143**) are given in Figure 6. As can be

seen, the series contains no GCS/GBA/GBA2 inhibitors with remarkable potency. Obviously, the rather drastic deviation of the glucose configuration is detrimental for inhibition of the three glucose-processing enzymes, and addition of an extra hydroxymethyl does not help.

Conclusion

In this Chapter, iminosugars that encompass both the D-glucose and L-idose structural properties in one molecule as well as its C-2, C-3 and C-4 epimers were synthesized. These four sets of hybrid compounds (**6**, **7**, **8** and **9**) were *N*-alkylated with various hydrophobic substitutes which produced a library of 28 *N*-alkylated derivatives. This set and their corresponding DNJ congeners have been tested as inhibitors for the GlcCer metabolic enzymes (GCS, GBA1 and GBA2).

Figure 7: Enzyme inhibition assay results: IC_{50} values of the *N*-AMP iminosugar derivatives

D-glucose L-idose		D-galactose L-altrose		D-mannose L-gulose		D-allose L-talose	
	61		82		103		126
IC_{50} GCS 1 μ M IC_{50} GBA1 8 μ M IC_{50} GBA2 30 nM		IC_{50} GCS 2.5 μ M IC_{50} GBA1 218 μ M IC_{50} GBA2 0.5 μ M		IC_{50} GCS 13 μ M IC_{50} GBA1 389 μ M IC_{50} GBA2 3 μ M		IC_{50} GCS >50 μ M IC_{50} GBA1 394 μ M IC_{50} GBA2 3 μ M	
	1		3		111		134
IC_{50} GCS 0.2 μ M IC_{50} GBA1 0.5 μ M IC_{50} GBA2 0.8 nM		IC_{50} GCS 0.14 μ M IC_{50} GBA1 1 μ M IC_{50} GBA2 1 nM		IC_{50} GCS >50 μ M IC_{50} GBA1 62 μ M IC_{50} GBA2 61 μ M		IC_{50} GCS 24 μ M IC_{50} GBA1 65 μ M IC_{50} GBA2 0.5 μ M	
	2		4		119		142
IC_{50} GCS 0.1 μ M IC_{50} GBA1 34 μ M IC_{50} GBA2 1 nM		IC_{50} GCS 0.2 μ M IC_{50} GBA1 >1000 μ M IC_{50} GBA2 0.1 μ M		IC_{50} GCS >50 μ M IC_{50} GBA1 988 μ M IC_{50} GBA2 3 μ M		IC_{50} GCS 21 μ M IC_{50} GBA1 >1000 μ M IC_{50} GBA2 2 μ M	

Generally, the hybrid compounds are weaker GCS inhibitors compared to both D-configured and L-configured iminosugars (Figure 7), with the D-manno-L-gulose compound **103** being an exception. Concerning GBA1 inhibitory activity, the bis-hydroxymethyl compounds are

generally more potent than their corresponding L-compounds while less potent than the D-compounds. This may indicate that the D-configuration at C-5 is more beneficial for the iminosugar to bind to GBA1, and that an additional hydroxymethyl has a negative effect in binding to the active site of the enzyme. There is no specific rule observed for how the extra hydroxymethyl group affects GBA or GBA2 activity, and general trends appear the same as for GCS activity. It should be noted that many of the compounds described here are of a configuration that is rather far removed from that of glucopyranose. It may therefore well be that the compound collections may contain inhibitors for glycoprocessing enzymes other than those assayed here. It would therefore be of interest to screen the compound collections against other glycosidases, including galactosidases and mannosidases that are of interest in their own right in biological and biomedical research.

Experimental Section

Enzyme inhibition assays: The potencies (IC_{50} values) of the *N*-alkyl-DNJ derivatives as GCS, GBA1 and GBA2 inhibitors were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.⁷ Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbelliferyl- β -D-glucoside as substrate.⁸ Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl- β -D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and sodium taurocholate (0.2%, w/v). Assays performed in triplicate were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbelliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm.

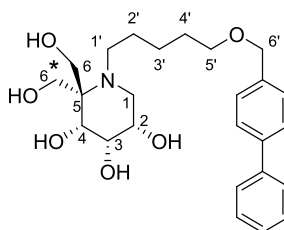
GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with 4-methylumbelliferyl- β -D-glucoside as substrate.⁸ GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbelliferyl- β -D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbelliferyl was determined

with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General compound synthesis, purification and analysis methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of KMnO_4 (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at $\approx 200^\circ\text{C}$. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C -APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz) or Bruker 600 (600/150 MHz) spectrometer in CDCl_3 , MeOD or D_2O . Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in CDCl_3) or the signal of the deuterated solvent.⁹ Coupling constants (J) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution $R = 60000$ at m/z 400 (mass range $m/z = 150$ -2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1} . Optical rotation were measured on an automatic polarimeter of sodium D-line, at $\lambda = 589$ nm. Size-exclusion purifications were performed on an ÄKTA-explorer, column size $d = 26$ mm, $l = 60$ mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O , flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 μm , 19 x 150 mm column).

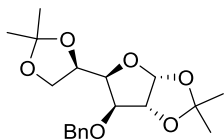
General Procedure: Alkylation of iminosugars. To a mixture of the bromide chain (0.3 mmol, see Scheme 5A) and K_2CO_3 (0.4 mmol) was added a solution of the 5-hydroxymethyl nojirimycin derivative (0.2 mmol) in DMF (1 mL). The reaction suspension was stirred at 80°C overnight. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified with HPLC.

Figure 8: Proton and carbon NMR numbering of *N*-alkylated iminosugars



Synthesis of 5-C-hydroxymethyl-1-deoxynojirimycin (6)

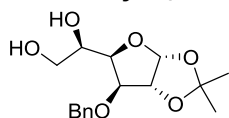
3-O-Benzyl-1,2:5,6-di-O-isopropylidene- α -D-glucopyranoside (10):



BnBr (7.10 mL, 59.8 mmol) was added to a cooled (0°C) and stirred mixture of diacetone-D-glucose (13.0 g, 49.9 mmol) and NaH (60% on mineral oil, 6.00 g, 150 mmol) in DMF (150 mL). After 18 h, TLC analysis showed complete conversion of starting material. Methanol was added to quench the excess NaH . The reaction mixture was diluted with water

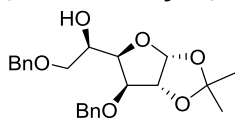
(250 mL) and extracted with Et₂O (3 x). The organic layers were combined and washed successively with sat. aq. NaHCO₃ and water, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica gel column chromatography (4:1, PE:EtOAc) to give pure **10** (16.9 g, 48.2 mmol) in yield of 97% as light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.25 (m, 5H, H_{Ar} Bn), 5.90 (d, *J* = 3.7 Hz, 1H, H-1), 4.72 – 4.55 (m, 3H, 2 x CHH Bn, H-2), 4.37 (dt, *J* = 7.8, 6.0 Hz, 1H, H-5), 4.16 – 4.10 (m, 2H, H-6a, H-4), 4.05 – 3.97 (m, 2H, H-6b, H-3), 1.50 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.31 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.7 (C_q Bn), 128.5, 128.0, 127.8 (CH_{Ar} Bn), 111.7, 108.9 (2 x C_q isopropyl), 105.2 (C-1), 82.6 (C-2), 81.6 (C-3), 81.3 (C-4), 72.5 (C-5), 72.3 (CH₂ Bn), 67.4 (C-6), 27.0, 26.9, 26.4, 25.6 (4 x CH₃).

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucopyranoside (**11**):



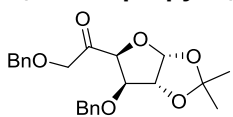
11 (14.0 g, 40.0 mmol) was dissolved in a mixture of acetic acid (45 mL) and water (20 mL), and the reaction mixture was stirred for 72 h at r.t. After TLC analysis showed complete consumption of starting material, ethyl acetate (100 mL) was added. The organic layer was washed successively with sat. aq. NaHCO₃, water and brine. The organic layer was dried (Na₂SO₄), filtrated and concentrated. The crude product was purified by silica gel column chromatography to gain **20** (9.92 g, 32.0 mmol) in 80% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.27 (m, 5H, H_{Ar} Bn), 5.91 (dd, *J* = 3.9, 1.5 Hz, 1H, H-1), 4.70 (dd, *J* = 11.8, 1.9 Hz, 1H, CHH Bn), 4.60 (dd, *J* = 3.9, 1.5 Hz, 1H, H-2), 4.56 (d, *J* = 11.8 Hz, 1H, CHH Bn), 4.13 – 4.06 (m, 2H, H-3, H-4), 4.02 (dd, *J* = 8.9, 4.8 Hz, 1H, H-5), 3.79 (d, *J* = 11.0 Hz, 1H, H-6a), 3.67 (dd, *J* = 11.6, 5.5 Hz, 1H, H-6b), 1.47 (s, 3H, CH₃), 1.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.3 (C_q Bn), 128.7, 128.2, 127.9 (CH_{Ar} Bn), 111.9 (C_q isopropyl), 105.2 (C-1), 82.2 (C-2), 82.0 (C-3), 80.0 (C-4), 72.2 (C-5), 69.2 (CH₂ Bn), 64.7 (C-6), 26.8, 26.3 (2 x CH₃).

3,6-Di-O-benzyl-1,2-O-isopropylidene-α-D-glucopyranoside (**12**):



To a solution of **11** (8.29 g, 26.7 mmol) in toluene (250 mL) was added dibutyl tin oxide (10.0 g, 40.0 mmol). The reaction mixture was heated to reflux and stirred for 8 hours under Dean-Stark conditions. TBABr (1.03 g, 4.04 mmol) and benzyl bromide (6.36 mL, 53.6 mmol) were added to the solution. The reaction mixture was refluxed for another 18 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography (5:1 → 3:1, PE:EtOAc) to give **12** (9.61 g, 24.0 mmol, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.27 (m, 10H, H_{Ar} Bn), 5.94 (d, *J* = 3.7 Hz, 1H, H-1), 4.68 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.59 – 4.47 (m, 3H, 3 x CHH Bn), 4.61 (d, *J* = 3.6 Hz, 1H, H-2), 4.21 – 4.15 (m, 2H, H-3, H-5), 4.11 (d, *J* = 1.9 Hz, 1H, H-4), 3.75 (d, *J* = 9.2 Hz, 1H, H-6a), 3.61 (d, *J* = 9.9 Hz, 1H, H-6b), 1.49 (s, 3H, CH₃), 1.32 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 138.0, 137.3 (C_q Bn), 128.6, 128.5, 128.1, 127.8 (CH_{Ar} Bn), 111.8 (C_q isopropyl), 105.1 (C-1), 82.3 (C-2), 82.1 (C-4), 79.8 (C-3), 73.5 (CH₂ Bn), 72.4 (CH₂ Bn), 72.1 (C-6), 68.1 (C-5), 26.8, 26.3 (2 x CH₃).

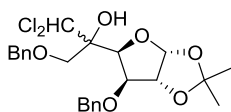
1,2-O-Isopropyl-3,6-di-O-benzyl-α-D-xyllo-hexofuranoside-5-ulose (**13**):



12 (8.62 g, 21.5 mmol) dissolved in dry DCM (100 mL) was added to a suspension of pyridinium chlorochromate (PCC, 15.34 g, 71.1 mmol) and activated 4 Å molecular sieves in dry DCM (300 mL). The reaction mixture was stirred under argon atmosphere at 30 °C overnight. 2-Propanol was then added to quench the reaction. Diethyl ether (200 mL) was added to dilute the dark brown suspension and the mixture was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel column chromatography and to give pure **13** (4.54 g, 11.40 mmol, yield 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.22 (m, 10H, H_{Ar} Bn), 6.05 (d, *J* = 3.6 Hz, 1H, H-1), 4.82 (d, *J* = 3.7 Hz, 1H, H-4), 4.62 (d, *J* = 3.6 Hz, 1H, H-2), 4.60 (d, *J* = 12.0, 1H, CHH Bn), 4.59 (d, *J* = 12.0 Hz, CHH Bn), 4.50 (d, *J* = 11.8 Hz, 1H, CHH Bn), 4.49 (d, *J* = 11.8 Hz, 1H, CHH Bn), 4.46 (d, *J* = 18.8 Hz, 1H, H-6a), 4.39 (d, *J* = 18.8 Hz, 1H, H-6b),

4.38 (d, $J = 3.7$ Hz, 1H, H-3), 1.49 (s, 3H, CH₃), 1.34 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 204.6 (C=O), 137.4, 136.7 (C_q Bn), 128.6, 128.5, 128.2, 127.9 (CH_{Ar} Bn), 112.5 (C_q isopropyl), 105.9 (C-1), 84.9 (C-4), 83.6 (C-3), 82.1 (C-2), 74.4 (C-6), 73.2, 72.6 (CH₂ Bn), 26.9, 26.3 (2 x CH₃).

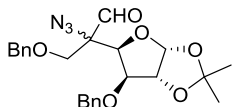
1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-5-*C*-dichloromethyl- α -D-glucopyranoside (**14**):



To a cooled (-78 °C) solution of LDA (36 mmol, 18 mL, 2 M in THF) in dry THF (45 mL) was added DCM (18 mL). After 30 minutes, **13** (4.48 g, 11.3 mmol) dissolved in DCM (18 mL) was added. After another 30 minutes temperature was allowed to rise to r.t. When TLC analysis indicated

complete conversion of starting material, sat. aq. NH₄Cl was added. The mixture was extracted with EtOAc (100 mL) and the organic layer was washed successively with water and brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by silica gel column chromatography (20:1 → 10:1, pentane:EtOAc) to gain **14** (3.00 g, 6.21 mmol, yield 55%), as a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.00 (m, 10H, H_{Ar} Bn), 6.11 (s, 1H, CHCl₂), 5.89 (d, $J = 3.9$ Hz, 1H, H-1), 4.58 (d, $J = 3.9$ Hz, 1H, H-2), 4.56 – 4.43 (m, 5H, H-4, 2 x CH₂ Bn), 4.36 (d, $J = 3.0$ Hz, 1H, H-4), 3.94 (d, $J = 10.0$ Hz, 1H, H-6a), 3.85 (d, $J = 10.0$ Hz, 1H, H-6b), 1.41 (s, 3H, CH₃), 1.25 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.9, 135.9 (C_q Bn), 128.8 – 127.7 (CH_{Ar} Bn), 112.0 (C_q isopropyl), 103.7 (C-1), 84.9 (C-3), 81.5 (C-2), 79.7 (C-5), 75.8 (C-4), 73.8, 72.2 (CH₂ Bn), 72.2 (C-6), 26.7, 26.3 (2 x CH₃).

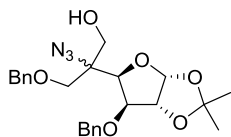
5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl- α -D-glucopyranoside (**15**):



A mixture of **14** (2.69 g, 5.58 mmol), TBAI (1.07 g, 2.89 mmol) and NaN₃ (1.96 g, 30.0 mmol) in DMF (60 mL) was stirred at 115 °C for 18 h. After TLCMS analysis showed complete consumption of **14**, the reaction was quenched by the addition of water (100 mL) and extracted with EtOAc

(75 mL x 3). The combined organic layers were washed with water (2 x) and brine (2 x), dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (10:1, pentane:EtOAc) to give **15** (1.74 g, 3.85 mmol, yield 69%). It is a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ 9.69 (s, 1H, CHO), 7.47 – 7.30 (m, 10H, H_{Ar} Bn), 5.93 (d, $J = 3.6$ Hz, 1H, H-1), 4.67 – 4.41 (m, 5H, H-4, 2 x CH₂ Bn), 4.28 (d, $J = 3.0$ Hz, 1H, H-4), 4.08 (d, $J = 10.2$ Hz, 1H, H-6a), 4.05 (d, $J = 3.0$ Hz, 1H, H-3), 3.86 (d, $J = 10.2$ Hz, 1H, H-6b), 1.48 (s, 3H, CH₃), 1.32 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 195.3 (C=O), 137.2, 136.3 (C_q Bn), 128.6, 128.6, 128.3, 127.9, 127.6 (CH_{Ar} Bn), 112.3 (C-5), 105.2 (C-1), 81.9 (C-2), 81.4 (C-4), 81.1 (C-3), 73.7, 72.8 (2 x CH₂ Bn), 70.3 (C-6), 26.8, 26.2 (2 x CH₃).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl- α -D-glucopyranoside (**16**):

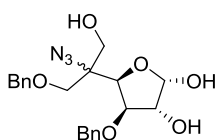


NaBH₄ (0.33 g, 1.85 mmol) was added to a solution of **15** (1.68 g, 3.85 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, and quenched by the addition of sat. aq. NH₄Cl. The volatiles were evaporated. The residue was extracted with EtOAc (3 x). The organic layer was washed with water and brine, dried (Na₂SO₄), filtered and concentrated.

The crude product was purified by silica gel column chromatography (20:1 → 10:1, pentane:EtOAc) to give **16** (1.56 g, 3.43 mmol, yield 89%), as a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.24 (m, 10H, H_{Ar} Bn), 5.91 (d, $J = 3.8$ Hz, 1H, H-1), 4.63 (d, $J = 11.5$ Hz, 1H, CHH Bn), 4.56 (d, $J = 3.5$ Hz, 1H, H-2), 4.52 (d, $J = 12.0$ Hz, 1H, CHH Bn), 4.47 (d, $J = 12.4$ Hz, 1H, CHH Bn), 4.30 (d, $J = 3.2$ Hz, 1H, CHH Bn), 4.02 (d, $J = 3.2$ Hz, 1H, H-3), 3.90 (d, $J = 11.9$ Hz, 1H, H-6a),

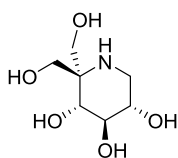
3.87 (d, $J = 11.5$ Hz, 1H, H-6b), 3.75 (d, $J = 10.0$ Hz, 1H, CHHOH), 3.67 (d, $J = 10.1$ Hz, 1H, CHHOH), 1.46 (s, 3H, CH₃), 1.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.6, 136.5 (C_q Bn), 128.6, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 112.0 (C_q isopropyl), 104.4 (C-1), 82.2 (C-4), 81.7 (C-2), 80.0 (C-3), 73.6, 72.1 (CH₂ Bn), 71.2 (CH₂OH), 66.0 (C-5), 63.6 (C-6), 26.8, 26.3 (2 x CH₃).

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-D-glucopyranoside (17):



16 (1.50 g, 3.29 mmol) was dissolved in a mixture of H₂O (15 mL) and TFA (15 mL) at 0 °C, the temperature was allowed to rise to r.t. and the mixture was stirred for 18 h. After TLC analysis indicated complete conversion of the starting material, TFA was removed by repetitive coevaporation with toluene. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (90 mL) and washed with brine (2 x). The organic layer was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica gel column chromatography to give **17** (0.93 g, 2.24 mmol, yield 68%). It is a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.24 (m, 10H, H_{Ar} Bn), 5.47 (d, $J = 4.6$ Hz, 1H, H-1), 4.49 – 4.30 (m, 4H, 2 x CH₂ Bn), 4.21 (d, $J = 2.8$ Hz, 1H, H-3), 4.16 (dd, $J = 4.0, 1.7$ Hz, 1H, H-2), 3.99 (dd, $J = 4.0, 1.6$ Hz, 1H, H-4), 3.89 (d, $J = 11.9$ Hz, 1H, H-6a), 3.83 (d, $J = 11.8$ Hz, 1H, H-6b), 3.70 (d, $J = 10.0$ Hz, 1H, CHHOH), 3.67 (d, $J = 10.2$ Hz, 1H, CHHOH). ¹³C NMR (100 MHz, CDCl₃) δ 137.6, 137.0 (C_q Bn), 128.7, 128.5, 128.2, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 103.2 (C-1), 84.2 (C-4), 77.2 (C-3), 74.1 (C-2), 72.5, 71.9 (2 x CH₂ Bn), 70.4 (CH₂OH), 66.4 (C-5), 63.6 (C-6).

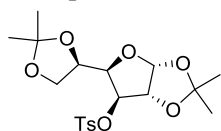
5-C-Hydroxymethyl-1-deoxynojirimycin (6):



Pd/C (10%, 0.28 g) was added to a solution of **17** (1.17 g, 2.82 mmol) in ethanol (50 mL) and pH of the solution was adjusted to 1 with 1M HCl. The reaction mixture was exposed to 5 bar of hydrogen and kept shaking for 24 hours. The reaction mixture was filtered over a pad of Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% → 20% methanol in DCM + 1% NH₄OH) to gain **6** as light yellow oil (0.40 g, 2.09 mmol, yield 74%). ¹H NMR (400 MHz, MeOD) δ 3.86 (d, $J = 12.1$ Hz, 1H, H-6*a), 3.81 (d, $J = 11.1$ Hz, 1H, H-6a), 3.68 (d, $J = 12.0$ Hz, 1H, H-6*b), 3.67 (d, $J = 11.1$ Hz, 1H, H-6b), 3.64 (d, $J = 9.6$ Hz, 1H, H-4), 3.56 (dd, $J = 9.2, 8.8$ Hz, 1H, H-3), 3.58 – 3.51 (m, 1H, H-2), 3.07 (dd, $J = 12.6, 4.6$ Hz, 1H, H-1a), 2.86 – 2.78 (m, 1H, H-1b). ¹³C NMR (100 MHz, MeOD) δ 74.7 (C-3), 71.3 (C-4), 70.1 (C-2), 62.0 (C-5), 61.8 (C-6), 57.3 (C-6*), 43.7 (C-1). $[\alpha]^{20}_D = -0.3$ (c = 0.54, MeOH). IR/cm⁻¹: 3277, 2926, 1612, 1450, 1406, 1259, 1076, 1039, 933. HRMS: found 194.10222 [C₇H₁₅NO₅+H]⁺, calculated for [C₇H₁₅NO₅+H]⁺ 194.10230.

Synthesis of 5-C-Hydroxymethyl-1-deoxy-D-galactonojirimycin (7)

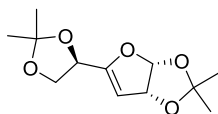
3-O-(*p*-Toluenesulfonyl)-1,2:5,6-di-O-isopropylidene- α -D-glucopyranoside (18):



p-Toluenesulfonyl chloride (3.60 g, 1.88 mmol) was added to a solution of diacetone-D-glucose (2.50 g, 8.61 mmol) in pyridine (24 mL) and DCM (24 mL). The reaction mixture was stirred overnight at a temperature of 60 °C. The volatiles were removed, and the residue was dissolved in DCM (30 mL), and the organic layer was washed with sat. aq. NaHCO₃, dried (Na₂SO₄), filtered, concentrated and purified by silica gel column chromatography to give **18** (3.50 g, 8.44 mmol, yield 98%). *R*_F = 0.41 (5:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, $J = 8.3$ Hz, 2H, H_{Ar} Ts), 7.34 (d, $J = 8.1$ Hz, 2H, H_{Ar} Ts), 5.92 (d, $J = 3.6$ Hz, 1H, H-1), 4.83 (d, $J = 3.7$ Hz, 1H, H-2), 4.80 (d, $J = 2.3$ Hz, 1H, H-3), 4.07 – 3.96 (m, 3H, H-4, H-5, H-6a), 3.91 (dd, $J = 8.2, 3.9$ Hz, 1H, H-6b), 2.46 (s, 3H, CH₃ Ts), 1.48 (s, 3H, CH₃), 1.31 (s, 3H, CH₃), 1.20 (s, 3H, CH₃), 1.15 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 132.7, 130.2, 129.7, 128.4, 128.0 (C_{Ar} Ts), 112.5

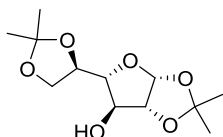
(C_q isopropyl), 109.1 (C_q isopropyl), 105.1 (C-1), 83.3 (C-2), 82.1 (C-3), 79.9 (C-4), 71.8 (C-5), 67.1 (C-6), 26.6, 26.2, 24.9, 21.7 (4 x CH₃), 14.2 (CH₃ Ts).

1,2:5,6-Di-*O*-isopropylidene-3- α -D-glucal (**19**):



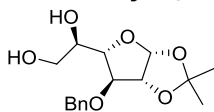
Potassium tert-butoxide (6.30 g, 10.1 mmol) was added to a solution of **18** (2.73 g, 6.59 mmol) in dried THF (40 mL) at 0 °C, and the mixture was stirred at 0 °C under argon atmosphere for 5 hours. Water (100 mL) was added and the reaction mixture was extracted with DCM (2 x 50 mL). The combined organic layers were washed successively with water and brine, dried (Na₂SO₄), filtered, concentrated and the residue was purified by silica gel column chromatography (5:1, PE:EtOAc) to give **19** (1.45 g, 5.99 mmol, yield 91%). *R*_F = 0.78 (5:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 6.09 (d, *J* = 5.2 Hz, 1H, H-1), 5.31 (ddd, *J* = 5.3, 2.3, 1.5 Hz, 1H, H-2), 5.26 (dd, *J* = 2.4, 1.2 Hz, 1H, H-3), 4.60 (dd, *J* = 7.0, 5.6 Hz, 1H, H-5), 4.17 (d, *J* = 8.4 Hz, 1H, H-6a), 3.99 (d, *J* = 8.5 Hz, 1H, H-6b), 1.48 (s, 6H, 2 x CH₃), 1.45 (s, 3H, CH₃), 1.40 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 160.0 (C-4), 112.3 (C_q isopropyl), 110.3 (C_q isopropyl), 106.6 (C-1), 99.0 (C-3), 83.4 (C-2), 71.3 (C-5), 67.0 (C-6), 28.2, 27.9, 26.2, 25.5 (4 x CH₃).

1,2:5,6-Di-*O*-isopropylidene- α -D-galacto-furanoside (**20**):

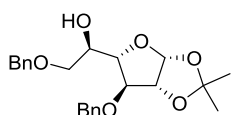


To a solution of **19** (0.49 g, 2.02 mmol) in THF (3 mL) was added BH₃·THF complex (1M, 2.5 mL, 2.5 mmol) at 0 °C under argon atmosphere. After 4 hours a mixture of aq. NaOH (2M, 0.9 mL) and 30% H₂O₂ (0.4 mL) was added to the reaction mixture. The reaction was stirred at r.t. for 1 hour, and the volatiles were evaporated. The residue was diluted with water (5 mL), and the water layer extracted with EtOAc (4 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and evaporated. The crude product was crystallized from EtOAc and pentane to give **20** as a crystalline product (0.40 g, 1.53 mmol, 75%). *R*_F = 0.24 (5:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 5.88 (d, *J* = 3.9 Hz, 1H, H-1), 4.55 (dd, *J* = 3.9, 1.4 Hz, 1H, H-2), 4.37 (q, *J* = 6.8 Hz, 1H, H-5), 4.13 (dd, *J* = 4.5, 1.3 Hz, 1H, H-3), 4.08 (dd, *J* = 8.4, 6.6 Hz, 1H, H-6a), 3.88 (d, *J* = 6.8 Hz, 1H, H-4), 3.86 (dd, *J* = 8.0, 7.0 Hz, 1H, H-6b), 1.55 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.36 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 113.8, 110.0 (2 x C_q isopropyl), 105.1 (C-1), 87.7 (C-2), 86.0 (C-4), 76.3 (C-3), 75.5 (C-4), 65.8 (C-6), 27.6, 26.9, 26.7, 25.4 (4 x CH₃).

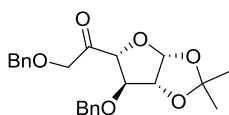
3-*O*-Benzyl-1,2-*O*-isopropylidene- α -D-galacto-furanoside (**22**):



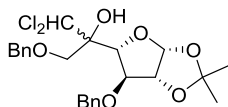
To a solution of **20** (4.00 g, 15.4 mmol) in DMF (150 mL) at 0 °C under argon atmosphere, was added NaH (60% mineral oil, 1.85 g, 46.3 mmol). After 30 minutes, BnBr (40 mL, 33.7 mmol) was added. The reaction mixture was stirred at r.t. overnight. The excess NaH was quenched by the addition of methanol, and the volatiles were evaporated. The residue was dissolved in DCM, washed with water and brine, dried (Na₂SO₄), filtered and concentrated. The crude product **21** (*R*_F = 0.18, 5:3, PE:EtOAc) was dissolved in water (10 mL) and AcOH (60 mL). The reaction mixture was stirred at r.t. overnight. The volatiles were evaporated, and the residue was purified by silica gel column chromatography (3:2 → 1:1, PE:EtOAc) to give **22** (4.12 g, 13.2 mmol, 86% yield over the 2 steps). *R*_F = 0.82 (5:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.30 (m, 5H, H_{Ar} Bn), 5.92 (d, *J* = 4.1 Hz, 1H, H-1), 4.69 (dd, *J* = 4.1, 1.1 Hz, 1H, H-2), 4.65 (d, *J* = 11.8 Hz, 1H, CHH Bn), 4.57 (d, *J* = 11.8 Hz, 1H, CHH Bn), 4.14 (dd, *J* = 6.7, 3.5 Hz, 1H, H-4), 4.01 (dd, *J* = 3.5, 1.1 Hz, 1H, H-3), 3.80 (ddd, *J* = 6.7, 4.8, 3.8 Hz, 1H, H-5), 3.70 (dd, *J* = 11.8, 3.8 Hz, 1H, H-6a), 3.59 (dd, *J* = 11.7, 4.8 Hz, 1H, H-6b), 1.53 (s, 3H, CH₃), 1.35 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.1 (C_q Bn), 128.7, 128.3, 128.0 (CH_{Ar} Bn), 113.3 (C_q isopropyl), 105.7 (C-1), 85.4 (C-2), 85.4 (C-4), 83.1 (C-3), 72.0 (CH₂ Bn), 70.9 (C-5), 63.9 (C-6), 27.2, 26.5 (2 x CH₃).

3,6-Di-O-Benzyl-1,2-O-isopropylidene- α -D-galacto-furanoside (23):

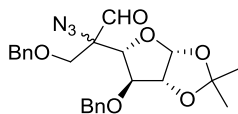
23 was synthesized from **22** (3.30 g, 10.6 mmol) in a yield of 82% (3.49 g, 8.72 mmol), as a thick yellow oil, as described for the synthesis of **12**. R_F = 0.80 (9:1, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.30 (m, 10H, H_{Ar} Bn), 5.95 (d, J = 4.2 Hz, 1H, H-1), 4.71 (d, J = 3.9 Hz, 1H, H-2), 4.61 (d, J = 11.4 Hz, 1H, CHH Bn), 4.57 (s, 2H, CH_2 Bn), 4.54 (d, J = 11.7 Hz, 1H, CHH Bn), 4.19 (dd, J = 6.5, 3.4 Hz, 1H, H-4), 4.12 (dd, J = 3.4, 1.1 Hz, 1H, H-3), 3.98 (q, J = 5.8 Hz, 1H, H-5), 3.59 (dd, J = 9.9, 5.7 Hz, 1H, H-6a), 3.55 (dd, J = 9.9, 5.3 Hz, 1H, H-6b), 1.57 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 137.9, 137.2 (C_q Bn), 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.8, 127.8 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 105.5 (C-1), 85.6 (C-2), 85.2 (C-4), 83.1 (C-3), 73.6 (CH_2 Bn), 71.9 (CH_2 Bn), 71.4 (C-6), 69.7 (C-5), 27.1, 26.4 (2 x CH_3).

3,6-Di-O-Benzyl-1,2-O-isopropylidene- α -D-arabino-hexofuranoside-5-ulose (24):

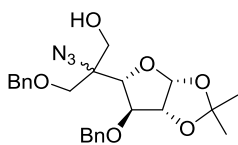
24 was synthesized from **23** (3.50 g, 8.74 mmol) in a yield of 92% (3.20 g, 8.04 mmol), as a thick yellow oil, as described for the synthesis of **13**. R_F = 0.67 (10:3, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.27 (m, 10H, H_{Ar} Bn), 5.98 (d, J = 3.8 Hz, 1H, H-1), 4.70 (d, J = 18.4 Hz, 1H, CHH Bn), 4.65 – 4.61 (m, 3H, H-2, H-3, CHH Bn), 4.60 – 4.56 (m, 3H, H-2-6, CHH Bn), 4.52 (d, J = 1.0 Hz, 1H, H-4), 4.37 (d, J = 18.4 Hz, 1H, CHH Bn), 1.31 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 205.0 (C-5), 137.2 – 127.8 (C_{Ar} Bn), 112.3 (C_q isopropyl), 106.5 (C-1), 88.6 (C-2), 83.6 (C-4), 83.5 (C-3), 73.4 (CH_2 Bn), 73.1 (CH_2 Bn), 72.0 (C-6), 25.7, 25.6 (2 x CH_3).

1,2-O-Isopropyl-3,6-di-O-benzyl-5-C-dichloroemethyl- α -D-galacto/ β -L-altro-furanoside (25):

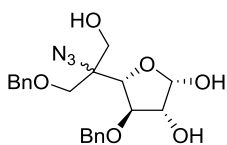
25 was synthesized from **24** (3.20 g, 8.03 mmol) in a yield of 74% (2.87 g, 5.94 mmol) as a thick yellow oil as described for the synthesis of **14**. R_F = 0.52 (9:1, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.24 (m, 10H, H_{Ar} Bn), 5.95 – 5.93 (m, 1H, CHCl_2), 5.80 (dd, J = 3.9, 1.6 Hz, 1H, H-1), 4.66 (d, J = 11.6, 1H, CHH Bn), 4.63 (dd, J = 3.8, 1.4 Hz, 1H, H-2), 4.60 (d, J = 11.6, 1H, CHH Bn), 4.56 (d, J = 1.7 Hz, 2H, CH_2 Bn), 4.50 – 4.46 (m, 1H, H-3), 4.44 – 4.38 (m, 1H, H-4), 3.81 (m, 2H, H-2-6), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 137.5 – 127.8 (C_{Ar} Bn), 114.1 (C_q isopropyl), 104.8 (C-1), 85.2 (C-2), 84.8 (C-4), 81.7 (C-3), 76.6 (C-5), 75.7 (CHCl_2), 73.8 (CH_2 Bn), 72.3 (CH_2 Bn), 70.1 (C-6), 27.2, 26.7 (2 x CH_3). HRMS: found 505.11521 [$\text{C}_{24}\text{H}_{28}\text{Cl}_2\text{O}_6 + \text{Na}$] $^+$, calculated for [$\text{C}_{24}\text{H}_{28}\text{Cl}_2\text{O}_6 + \text{Na}$] $^+$ 505.11552.

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-1,2-O-isopropyl- α -D-galacto/ β -L-altro-furano-1,6-dialdose (26):

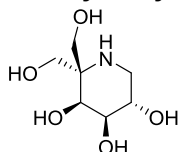
26 was synthesized from **25** (2.90 g, 6.00 mmol) in a yield of 93% as a thick yellow oil as described for the synthesis of **15**. R_F = 0.52 (9:1, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 9.70 (s, 1H, CHO), 7.54 – 7.19 (m, 10H, H_{Ar} Bn), 5.75 (d, J = 4.0 Hz, 1H, H-1), 4.69 (d, J = 11.3 Hz, 1H, CHH Bn), 4.64 (dd, J = 4.0, 1.5 Hz, 1H, H-2), 4.54 (d, J = 11.3 Hz, 1H, CHH Bn), 4.52 (d, J = 4.1 Hz, 2H, CH_2 Bn), 4.14 (dd, J = 6.3, 1.5 Hz, 1H, H-3), 4.11 (d, J = 6.3 Hz, 1H, H-4), 3.96 (d, J = 10.0 Hz, 1H, H-6a), 3.60 (d, J = 10.0 Hz, 1H, H-6b), 1.61 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 196.8 (CHO), 136.9, 136.7 (C_q Bn), 128.5, 128.2, 128.1, 128.0, 127.7 (CH_{Ar} Bn), 115.1 (C_q isopropyl), 104.6 (C-1), 85.4 (C-2), 82.0 (C-3), 81.9 (C-4), 73.8 (CH_2 Bn), 72.4 (CH_2 Bn), 70.8 (C-5), 70.5 (C-6), 27.5, 27.1 (2 x CH_3). HRMS: found 476.17913 [$\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_6 + \text{Na}$] $^+$, calculated for [$\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_6 + \text{Na}$] $^+$ 476.19721.

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-1,2-O-isopropyl- α -D-galacto/ β -L-altro-furanoside (27):

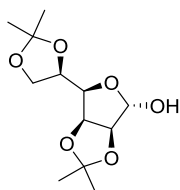
27 was synthesized from **26** (2.50 g, 5.51 mmol) in a yield of 82% (2.06 g, 4.52 mmol), as thick yellow oil, as described for the synthesis of **16**. R_F = 0.22 (9:1, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.18 (m, 10H, H_{Ar} Bn), 5.76 (d, J = 4.0 Hz, 1H, H-1), 4.67 (d, J = 11.3 Hz, 1H, CHH Bn), 4.62 (dd, J = 4.1, 1.5 Hz, 1H, H-2), 4.50 (d, J = 12.0, 1H, CHH Bn), 4.49 (s, 2H, CH_2OH), 4.22 (dd, J = 6.4, 1.5 Hz, 1H, H-3), 3.99 (d, J = 12.0 Hz, 1H, H-6a), 3.95 (d, J = 6.4 Hz, 1H, H-4), 3.93 (d, J = 11.9 Hz, 1H, H-6b), 4.04 – 3.86 (m, 3H, H-4, H-2-6), 3.61 (d, J = 9.9 Hz, 1H, CHH Bn), 3.52 (d, J = 10.0 Hz, 1H, CHH Bn), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 137.7 – 127.9 (C_{Ar} Bn), 115.2 (C_q isopropyl), 104.7 (C-1), 86.1 (C-2), 83.4 (C-4), 82.4 (C-3), 74.0 (CH_2OH), 72.7 (CH_2Bn), 71.4 (CH_2Bn), 66.1 (C-5), 63.9 (C-6), 27.8, 27.4 (2 x CH_3). HRMS: found 478.19451 [$\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6 + \text{Na}$] $^+$, calculated for [$\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6 + \text{Na}$] $^+$ 478.19486.

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl- α -D-galacto/ β -L-altro-furanoside (28):

28 was synthesized from **27** (2.08 g, 4.57 mmol) in a yield of 63% (1.31 g, 2.88 mmol), as a thick yellow oil, as described for the synthesis of **17**. **28** was obtained as an inseparable mixture of diastereo isomers (ratio 1:0.9). NMR data of the major diastereoisomer: ^1H NMR (400 MHz, CDCl_3) δ 5.20 (d, J = 3.9 Hz, 1H, H-1), 4.61 (d, J = 11.8 Hz, 1H, CHH Bn), 4.45 (d, J = 11.8 Hz, 1H, CHH Bn), 4.43 (s, 2H, CH_2OH), 4.07 (d, J = 3.8 Hz, 1H, H-3), 4.03 (t, J = 4.0 Hz, 1H, H-2), 3.93 (dd, J = 11.8, 4.7 Hz, 1H, H-6a), 3.89 (d, J = 5.3 Hz, 1H, H-4), 3.85 (d, J = 11.8 Hz, 1H, H-6b), 3.59 (d, J = 10.1 Hz, 1H, CHH Bn), 3.42 (d, J = 10.0 Hz, 1H, CHH Bn). ^{13}C NMR (100 MHz, CDCl_3) δ 137.6, 137.4 (C_q Bn), 128.7, 128.7, 128.4, 128.4, 128.2, 128.2, 127.8, 127.8 (CH_{Ar} Bn), 97.1 (C-1), 84.0 (C-3), 81.3 (C-4), 76.0 (C-2), 73.9 (CH_2OH), 72.1 (CH_2Bn), 71.1 (CH_2Bn), 66.5 (C-5), 62.4 (C-6). HRMS: found 438.16347 [$\text{M} + \text{Na}$] $^+$, calculated for [$\text{M} + \text{Na}$] $^+$ 438.19486.

5-C-Hydroxymethyl-1-deoxy-D-galactonojirimycin (7):

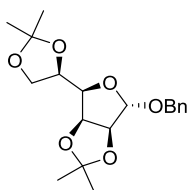
7 was synthesized from **28** (1.00 g, 2.42 mmol) in a yield of 91% (0.42 g, 2.20 mmol), as thick yellow oil, as described for the synthesis of **6**. R_F = 0.26 (1% NH_4OH in MeOH). ^1H NMR (400 MHz, MeOD) δ 3.99 (d, J = 3.3 Hz, 1H, H-4), 3.87 (d, J = 11.3 Hz, 1H, H-6a), 3.83 (td, J = 7.8, 4.3 Hz, 1H, H-2), 3.75 (d, J = 11.4 Hz, 1H, H-6*a), 3.71 (dd, J = 7.6, 3.3 Hz, 1H, H-3), 3.68 (d, J = 11.2 Hz, 1H, H-6b), 3.63 (d, J = 11.3 Hz, 1H, H-6*b), 3.13 (dd, J = 13.2, 4.3 Hz, 1H, H-1a), 2.71 (dd, J = 13.2, 7.9 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 72.0 (C-3), 68.4 (C-4), 68.3 (C-2), 61.9 (C-6), 60.9 (C-5), 59.7 (C-6*), 43.6 (C-1). $[\alpha]^{20}_D$ = +0.8 (c = 0.57, MeOH). IR/ cm^{-1} : 3275, 2922, 2497, 1608, 1049, 1338, 1247, 1114, 1056, 1024. HRMS: found [$\text{C}_7\text{H}_{15}\text{NO}_5 + \text{H}$] $^+$ 194.10221, calculated for [$\text{C}_7\text{H}_{15}\text{NO}_5 + \text{H}$] $^+$ 194.10230.

Synthesis of 5-C-hydroxymethyl-1-deoxy-D-mannonojirimycin (8)**2,3:5,6-Di-O-isopropyl- α -D-manno-furanoside (29):**

To a solution of D-mannose (36.0 g, 180 mmol) in dry acetone (1000 mL) at r.t. was added tetrabutylammonium tribromide (TBATB, 1.97 g, 4.08 mmol).⁶ The reaction was monitored by TLC analysis. After complete conversion of the starting material, acetone was removed on a rotary evaporator. Title compound **29** was isolated by crystallization (3:1, pentane:EtOAc, 30.2 g, 116 mmol, yield 64%). R_F = 0.40 (10:3, PE:EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 5.36 (d, J = 2.7 Hz, 1H, H-1), 4.80 (dd, J = 5.9, 3.7 Hz, 1H, H-3), 4.60 (d, J = 5.9 Hz, 1H, H-2), 4.40 (q, J = 4.0 Hz, 1H, H-5), 4.16 (dd, J = 7.2, 3.6 Hz, 1H, H-4), 4.07 (d, J = 5.9 Hz, 2H, H-6a, H-6b), 1.46 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR

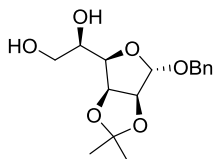
(100 MHz, CDCl₃) δ 112.3, 108.9 (2 x C_q isopropyl), 100.8 (C-1), 85.3 (C-2), 79.7 (C-4), 79.4 (C-3), 73.1 (C-5), 66.2 (C-6), 26.5, 25.6, 24.9, 24.2 (4 x CH₃).

Benzyl-2,3,5,6-di-O-isopropyl- α -D-manno-furanoside (**30**):



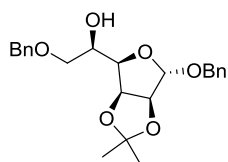
To a solution of **29** (1.28 g, 4.92 mmol) in THF (10 mL) was successively added freshly powdered potassium hydroxide (0.48 g, 8.56 mmol), 18-crown-6 (0.055 g, 0.21 mmol) and benzyl bromide (0.67 mL, 0.96 g, 5.64 mmol). The mixture was stirred at r.t. and the reaction was monitored by TLC analysis. After complete conversion of the starting material, the mixture was diluted with DCM and washed with water (3 x). The organic layer was dried (Na₂SO₄), filtered and concentrated, and the residue was purified by silica gel column chromatography (9:1, PE:EtOAc) to gain **30** (1.29 g, 3.68 mmol, yield 75%), R_F = 0.70 (6:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.27 (m, 5H, H_{Ar} Bn), 5.08 (s, 1H, H-1), 4.80 (dd, J = 5.9, 3.6 Hz, 1H, H-3), 4.67 (d, J = 5.9 Hz, 1H, H-2), 4.64 (d, J = 11.6 Hz, 1H, CHH Bn), 4.49 (d, J = 11.8 Hz, 1H, CHH Bn), 4.11 (ddd, J = 7.9, 6.3, 4.3 Hz, 1H, H-5), 4.14 (dd, J = 8.7, 6.3 Hz, 1H, H-6a), 4.02 (dd, J = 8.8, 4.4 Hz, 1H, H-6b), 4.00 (dd, J = 8.0, 3.6 Hz, 1H, H-4), 1.46 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.32 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.4 (C_q Bn), 128.6 – 127.9 (CH_{Ar} Bn), 112.7, 109.4 (2 x C_q isopropyl), 105.7 (C-1), 85.2 (C-2), 80.5 (C-4), 79.7 (C-3), 73.2 (C-5), 69.3 (CH₂ Bn), 67.1 (C-6), 27.1, 26.0, 25.3, 24.6 (4 x CH₃).

Benzyl-2,3-O-isopropyl- α -D-manno-furanoside (**31**):



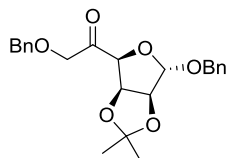
31 was synthesized from **30** (15.00 g, 42.84 mmol) in a yield of 81% (10.8 g, 34.8 mmol) as described for the synthesis of **11**. R_F = 0.19 (5:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, H_{Ar} Bn), 5.10 (s, 1H, H-1), 4.85 (dd, J = 5.9, 3.6 Hz, 1H, H-3), 4.65 (d, J = 6.0 Hz, 1H, H-2), 4.62 (d, J = 11.9 Hz, 1H, CHH Bn), 4.48 (d, J = 11.8 Hz, 1H, CHH Bn), 4.05 – 3.98 (m, 1H, H-5), 3.95 (dd, J = 8.3, 3.6 Hz, 1H, H-4), 3.82 (dd, J = 11.5, 3.2 Hz, 1H, H-6a), 3.65 (dd, J = 11.5, 5.9 Hz, 1H, H-6b), 3.28 (s, 1H, OH), 2.96 (s, 1H, OH), 1.46 (s, 3H, CH₃), 1.32 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.2 (C_q Bn), 128.4, 128.0, 127.8 (CH_{Ar} Bn), 112.6 (C_q isopropyl), 105.3 (C-1), 84.7 (C-2), 80.0 (C-3), 79.2 (C-4), 70.1 (C-5), 69.1 (CH₂ Bn), 64.3 (C-6), 28.8, 24.5 (2 x CH₃).

Benzyl-2,3-O-isopropyl-6-O-benzyl- α -D-manno-furanoside (**32**):



32 was synthesized from **31** (10.7 g, 34.4 mmol) in a yield of 76% (10.5 g, 26.2 mmol) as thick yellow oil, as described for the synthesis of **12**. R_F = 0.64 (5:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.27 (m, 10H, 2 x H_{Ar} Bn), 5.09 (s, 1H, H-1), 4.87 (dd, J = 5.9, 3.7 Hz, 1H, H-3), 4.65 (d, J = 5.9 Hz, 1H, H-2), 4.64 (d, J = 11.9 Hz, 1H, CHH Bn), 4.62 (d, J = 11.7 Hz, 1H, CHH Bn), 4.58 (d, J = 11.9 Hz, 1H, CHH Bn), 4.44 (d, J = 11.7 Hz, 1H, CHH Bn), 4.15 (ddd, J = 8.4, 5.8, 3.3 Hz, 1H, H-5), 4.03 (dd, J = 8.3, 3.6 Hz, 1H, H-4), 3.73 (dd, J = 9.8, 3.3 Hz, 1H, H-6a), 3.63 (dd, J = 9.8, 5.7 Hz, 1H, H-6b), 1.47 (s, 3H, CH₃), 1.33 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 138.1, 137.4 (2 x C_q Bn), 128.6 – 127.8 (CH_{Ar} Bn), 112.7 (C_q isopropyl), 105.4 (C-1), 85.0 (C-2), 80.2 (C-3), 79.1 (C-4), 73.6 (CH₂ Bn), 71.9 (C-6), 69.1 (CH₂ Bn), 69.0 (C-5), 26.1, 24.7 (2 x CH₃).

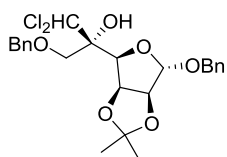
Benzyl-2,3-O-isopropyl-6-O-benzyl- α -D-lyxo-hexofuranoside-5-ulose (**33**):



33 (4.21 g, 10.5 mmol) was synthesized from **32** in a yield of 88% (3.66 g, 9.18 mmol), as described for the synthesis of **13**. R_F = 0.63 (3:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.17 (m, 10H, H_{Ar} Bn), 5.23 (s, 1H, H-1), 5.11 (dd, J = 5.8, 4.2 Hz, 1H, H-3), 4.73 (d, J = 4.2 Hz, 1H, H-4), 4.67 (d, J = 11.6 Hz, CHH Bn), 4.65 (d, J = 11.6 Hz, CHH Bn), 4.64 (d, J = 5.8 Hz, 1H, H-2), 4.61 (d, J = 11.6 Hz, CHH Bn), 4.49 (d, J = 11.6 Hz, CHH Bn),

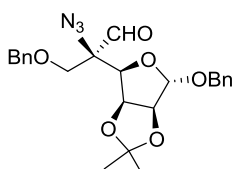
4.35 (s, 2H, H₂-6), 1.35 (s, 3H, CH₃), 1.26 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 203.0 (C=O), 137.2, 136.8 (2 x C_q Bn), 128.6 – 128.0 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 105.4 (C-1), 84.3 (C-2), 84.2 (C-4), 80.7 (C-3), 74.1, 73.4 (2 x CH₂ Bn), 69.3 (C-6), 25.7, 24.5 (2 x CH₃).

Benzyl-2,3-O-isopropyl-6-O-benzyl-5-C-dichloromethyl-β-L-gulo-furanoside (34):



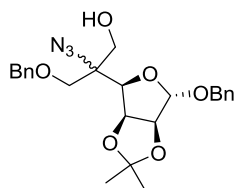
34 was synthesized from **33** in a yield of 66% (3.90 g, 8.34 mmol) as described for the synthesis of **14**. *R*_F = 0.53 (9:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.15 (m, 10H, H_{Ar} Bn), 6.19 (s, 1H, CHCl₂), 5.17 (s, 1H, H-1), 5.05 (dd, *J* = 5.9, 3.4 Hz, 1H, H-3), 4.87 (s, 1H, -OH), 4.71 – 4.57 (m, 4H, H-4, 3 x CHH Bn), 4.39 (d, *J* = 11.4 Hz, 1H, CHH Bn), 4.28 (d, *J* = 3.4 Hz, 1H, H-2), 3.76 (d, *J* = 9.8 Hz, 1H, H-6a), 3.61 (d, *J* = 9.8 Hz, 1H, H-6b), 1.51 (s, 3H, CH₃), 1.34 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 138.0 – 127.8 (C_{Ar} Bn), 113.3 (C_q isopropyl), 105.0 (C-1), 85.0 (C-4), 81.7 (C-3), 77.9 (C-2), 73.9 (CH₂ Bn), 73.3 (CHCl₂), 70.8 (C-5), 69.1 (C-6), 25.8, 24.2 (2 x CH₃).

Benzyl-5-deoxy-5-azido-5-C-benzylloxymethyl-2,3-O-isopropylidene-α-D-manno-furano-1,6-dialdose (35):



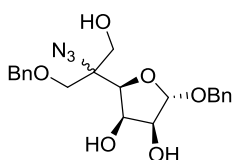
35 was synthesized from **34** (2.82 g, 5.84 mmol) in a yield of 87% (2.30 g, 5.07 mmol), as described for the synthesis of **15**. *R*_F = 0.52 (9:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H, CHO), 7.39 – 7.28 (m, 10H, H_{Ar} Bn), 5.18 (s, 1H, H-1), 4.84 (dd, *J* = 5.9, 3.4 Hz, 1H, H-3), 4.70 – 4.60 (m, 4H, H-4, 3 x CHH Bn), 4.51 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.29 (d, *J* = 3.4 Hz, 1H, H-2), 3.90 (d, *J* = 10.2 Hz, 1H, H-6a), 3.82 (d, *J* = 10.2 Hz, 1H, H-6b), 1.45 (s, 3H, CH₃), 1.32 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 195.8 (CHO), 137.2 (C_q Bn), 128.6 – 127.7 (CH_{Ar} Bn), 113.3 (C_q isopropyl), 105.6 (C-1), 84.6 (C-4), 80.4 (C-2), 79.2 (C-3), 73.9 (CH₂ Bn), 70.5 (C_q CN₃), 69.9 (C-6), 69.5 (CH₂ Bn), 25.3, 24.2 (2 x CH₃).

Benzyl-5-deoxy-5-azido-5-C-benzylloxymethyl-2,3-O-isopropyl-α-D-manno/β-L-gulo-furanoside (36):



36 was synthesized from **35** (0.37 g, 0.82 mmol) in a yield of 80% (0.30 g, 0.65 mmol) as two inseparable diastereomers as described for the synthesis of **16**. *R*_F = 0.22 (9:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.27 (m, 10H, CH_{Ar} Bn), 5.09 (s, 1H, H-1), 4.77 (dd, *J* = 5.8, 3.3 Hz, 1H, H-3), 4.64 (d, *J* = 11.9 Hz, 1H, CHH Bn), 4.63 (d, *J* = 5.8 Hz, H-4), 4.62 (d, *J* = 11.6 Hz, 1H, CHH Bn), 4.55 (d, *J* = 11.9 Hz, 1H, CHH Bn), 4.45 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.23 (d, *J* = 3.2 Hz, 1H, H-2), 3.91 (d, *J* = 2.1 Hz, 2H, CH₂OH), 3.87 (d, *J* = 10.1 Hz, 1H, H-6a), 3.78 (d, *J* = 10.1 Hz, 1H, H-6b), 1.45 (s, 3H, CH₃), 1.29 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.5, 137.4 (C_q Bn), 128.5 – 127.7 (CH_{Ar} Bn), 112.9 (C_q isopropyl), 104.8 (C-1), 85.1 (C-4), 79.8 (C-2), 79.5 (C-3), 73.8 (CH₂ Bn), 70.9 (C-6), 69.3 (CH₂ Bn), 66.6 (C_q N₃), 63.7 (CH₂OH), 25.7, 24.3 (2 x CH₃).

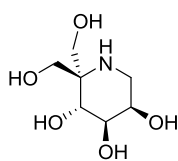
Benzyl-5-deoxy-5-azido-5-C-benzylloxymethyl-α-D-manno/β-L-gulo-furanoside (37):



36 (0.19 g, 0.43 mmol) was dissolved in a mixture of H₂O (0.6 mL) and TFA (1.8 mL) at 0 °C, the temperature was allowed to rise to r.t. and the mixture was stirred for 18 h. After TLC analysis indicated complete conversion of the starting material, the reaction mixture was diluted with water (5 mL), extracted with EtOAc (20 mL) and washed with brine (2 x). The organic layer was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica gel column chromatography to give **37** (0.08 g, 0.19 mmol, yield 45%). *R*_F = 0.16 (5:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.27 (m, 10H, CH_{Ar} Bn), 5.09 (d, *J* = 2.2 Hz, 1H, H-1), 4.66 (d, *J* = 11.6 Hz, 1H, CHH Bn), 4.60 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.57 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.55 (d, *J* = 11.9 Hz, 1H, CHH Bn), 4.33 (ddd, *J* = 5.1,

4.1, 1.0 Hz, 1H, H-3), 4.14 (dd, $J = 2.3, 5.3$ Hz, 1H, H-2), 4.13 (dd, $J = 4.0, 0.8$ Hz, 1H, H-4), 3.94 (d, $J = 11.6$ Hz, 1H, H-6a), 3.84 (dd, $J = 11.7, 0.8$ Hz, 1H, H-6b), 3.75 (s, 2H, CH₂OH). ¹³C NMR (100 MHz, CDCl₃) δ 137.6, 136.8 (C_q Bn), 128.7 – 127.8 (CH_{Ar} Bn), 107.2 (C-1), 79.7 (C-4), 77.1 (C-2), 74.0 (CH₂ Bn), 71.6 (C-3), 70.4 (CH₂ Bn), 70.2 (CH₂OH), 66.8 (C-5), 63.8 (C-6).

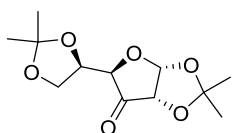
5-C-Hydroxymethyl-1-deoxy-D-mannonojirimycin (8):



8 was synthesized from **37** (0.83 g, 2.0 mmol) in a yield of 82% (0.32 g, 1.64 mmol) as described for the synthesis of **6**. ¹H NMR (400 MHz, MeOD) δ 4.17 (ddd, $J = 1.5, 3.0, 3.7$ Hz, 1H, H-2), 4.10 (d, $J = 9.2$ Hz, 1H, H-4), 3.95 (d, $J = 11.6$ Hz, 1H, H-6a), 3.94 (d, $J = 12.6$ Hz, 1H, H-6a'), 3.86 (dd, $J = 9.2, 3.0$ Hz, 1H, H-3), 3.77 (d, $J = 11.6$ Hz, 1H, H-6b), 3.71 (d, $J = 12.5$ Hz, 1H, H-6b'), 3.40 (dd, $J = 1.5, 13.2$ Hz, 1H, H-1a), 3.28 (dd, $J = 3.7, 13.1$ Hz, 1H, H-1b). ¹³C NMR (100 MHz, MeOD) δ 71.9 (C-3), 68.5 (C-4), 67.8 (C-2), 67.0 (C-5), 61.6 (C-6), 58.5 (C-6'), 45.7 (C-1). IR/cm⁻¹: 3307, 1636, 1451, 1229, 1073. HRMS: found 194.10223 [C₇H₁₅NO₅+H]⁺, calculated for [C₇H₁₅NO₅+H]⁺ 194.10230.

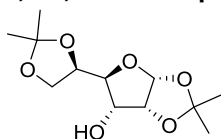
Synthesis of 5-C-hydroxymethyl-1-deoxy-D-allonojirimycin (9)

1,2:5,6-Di-O-isopropylidene- α -D-allo-furanoside-3-ulose (38):



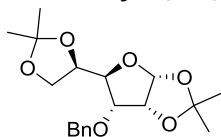
To a mixture of diacetone-D-glucose (15.0 g, 57.7 mmol) in anhydrous DCM (350 mL) and activated 4Å molecular sieves at 0 °C, was added pyridinium chlorochromate (PCC, 24.3 g, 112 mmol). The reaction mixture was stirred at r.t. overnight under argon atmosphere. The dark brown mixture was then filtered through a pad of silica gel, and the silica gel pad was rinsed with EtOAc (2 x 200 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (5:1 → 2:1, PE:EtOAc) to gain **38** (12.1 g, 47.0 mmol, yield 81%), $R_F = 0.2$ (19:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 6.16 (d, $J = 4.5$ Hz, 1H, H-1), 4.41 (d, $J = 4.6$ Hz, 1H, H-2), 4.38 (d, $J = 0.7$ Hz, 1H, H-4), 4.37 (td, $J = 2.5, 0.6$ Hz, 1H, H-5), 4.06 (d, $J = 0.7$ Hz, 1H, H-6a), 4.05 – 4.03 (m, 1H, H-6b), 1.48 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 1.36 (s, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 208.9 (C=O), 114.3 (C_q isopropyl), 110.4 (C_q isopropyl), 103.1 (C-1), 78.9 (C-4), 77.2 (C-2), 76.4 (C-5), 64.3 (C-6), 27.6, 27.2, 26.0, 25.3 (4 x CH₃).

1,2:5,6-Di-O-isopropylidene- α -D-allo-furanoside (39):



38 (12.1 g, 47.0 mmol) was dissolved in a mixture of water and ethanol (72 mL, 4:5). In small portions NaBH₄ (8.70 g, 230 mmol) was added. After stirred for 7 hours, the reaction mixture was extracted with DCM (3 x). The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered, concentrated and the residue was purified by silica gel column chromatography (5:1 → 3:2, PE:EtOAc), to give **39** (11.2 g, 43.1 mmol, yield 92%). $R_F = 0.4$ (1:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 5.82 (d, $J = 3.8$ Hz, 1H, H-1), 4.62 (dd, $J = 5.2, 3.8$ Hz, 1H, H-2), 4.31 (td, $J = 6.6, 4.7$ Hz, 1H, H-5), 4.09 (dd, $J = 8.5, 6.6$ Hz, 1H, H-6a), 4.02 (dd, $J = 8.5, 6.6$ Hz, 1H, H-6b), 3.82 (dd, $J = 8.5, 4.7$ Hz, 1H, H-4), 2.55 (br s, 1H, -OH), 1.58 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.38 (d, $J = 5.2$ Hz, 6H, 2 x CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 113.0 (C_q isopropyl), 110.0 (C_q isopropyl), 104.1 (C-1), 79.9 (C-4), 79.1 (C-2), 75.7 (C-5), 72.7 (C-3), 66.0 (C-6), 26.7, 26.7, 26.5, 25.4 (4 x CH₃).

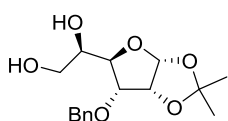
3-O-Benzyl-1,2:5,6-di-O-isopropylidene- α -D-allo-furanoside (40):



NaH (60% on mineral oil, 0.042 g, 1.05 mmol) was added to a solution of **39** (0.14 g, 0.54 mmol) in DMF (2 mL) at 0 °C under argon atmosphere. The mixture was stirred for 1 hour, subsequently, BnBr (0.1 mL, 0.84 mmol) was added. The suspension was stirred overnight at r.t. The

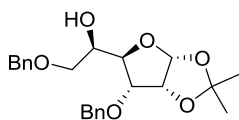
reaction was quenched by the addition of methanol (3 mL), and volatiles were evaporated. The residue was dissolved with EtOAc (10 mL), washed with brine (3 x), dried (Na₂SO₄), filtered, concentrated and purified by silica gel column chromatography to give **40** (0.17 g, 0.48 mmol, yield 90%). *R*_F = 0.8 (1:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 5.76 (d, *J* = 3.7 Hz, 1H, H-1), 4.78 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.60 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.59 (t, *J* = 4.2 Hz, 1H, H-2), 4.37 (td, *J* = 7.0, 3.2 Hz, 1H, H-5), 4.15 (dd, *J* = 8.7, 3.2 Hz, 1H, H-4), 4.02 (dd, *J* = 8.3, 6.9 Hz, 1H, H-6a), 3.97 (dd, *J* = 8.3, 7.1 Hz, 1H, H-6b), 3.90 (d, *J* = 4.5 Hz, 1H, H-3), 1.60 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.37 (s, 4H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.5 (C_q Bn), 128.4, 128.2, 128.0 (CH_{Ar} Bn), 112.9 (C_q isopropyl), 109.6 (C_q isopropyl), 103.9 (H-1), 78.0 (C-4), 77.8 (C-2), 77.5 (C-3), 74.8 (C-5), 72.2 (CH₂ Bn), 65.0 (C-6), 26.8, 26.6, 26.2, 25.1 (4 x CH₃).

3-O-Benzyl-1,2-di-O-isopropylidene- α -D-*allo*-furanoside (**41**):



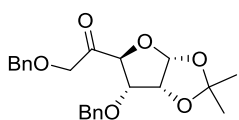
41 was synthesized from **40** (9.0 g, 25.68 mmol) in a yield of 46% (3.67 g, 11.8 mmol), as described for the synthesis of **11**. *R*_F = 0.15 (1:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.31 (m, 5H, H_{Ar} Bn), 5.79 (d, *J* = 3.7 Hz, 1H, H-1), 4.81 (d, *J* = 11.3 Hz, 1H, CHH Bn), 4.63 (t, *J* = 4.1 Hz, 1H, H-2), 4.58 (d, *J* = 11.3 Hz, 1H, CHH Bn), 4.13 (dd, *J* = 8.9, 3.4 Hz, 1H, H-4), 4.07 – 4.00 (m, 1H, H-5), 3.96 (dd, *J* = 8.9, 4.4 Hz, 1H, H-3), 3.77 – 3.64 (m, 2H, H-6), 1.62 (s, 3H, CH₃), 1.39 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 136.7 (C_q Bn), 128.6, 128.4, 128.3 (CH_{Ar} Bn), 113.2 (C_q isopropyl), 104.2 (C-1), 79.1 (C-4), 77.4 (C-2), 76.8 (C-3), 72.2 (CH₂ Bn), 70.1 (C-5), 63.1 (C-6), 26.8, 26.6 (2 x CH₃).

3,6-Di-O-Benzyl-1,2-di-O-isopropylidene- α -D-*allo*-furanose (**42**):



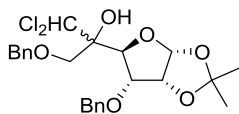
42 was synthesized from **41** (0.45 g, 1.45 mmol) in a yield of 76% (0.44 g, 1.10 mmol), as thick yellow oil, as described for the synthesis of **12**. *R*_F = 0.27 (10:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.30 (m, 10H, H_{Ar} Bn), 5.75 (d, *J* = 3.7 Hz, 1H, H-1), 4.74 (d, *J* = 11.6 Hz, 1H, CHH Bn), 4.57 – 4.54 (m, 3H, 2 x CHH Bn, H-2), 4.56 (d, *J* = 11.7 Hz, 1H, CHH Bn), 4.15 (m, 1H, H-5), 4.14 – 4.09 (m, 1H, H-4), 3.98 (dd, *J* = 8.7, 4.4 Hz, 1H, H-3), 3.60 – 3.55 (m, 2H, H₂-6), 1.61 (s, 3H, CH₃), 1.37 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 138.0, 137.5 (C_q Bn), 128.5 – 127.6 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 104.2 (C-1), 78.5 (C-4), 77.7 (C-2), 77.1 (C-3), 73.4, 72.1 (CH₂ Bn), 70.7 (C-6), 70.1 (C-5), 26.9, 26.7 (2 x CH₃).

1,2-O-Isopropyl-3,6-di-O-benzyl- α -D-*ribo*-hexofurano-5-ulose (**43**):



43 was synthesized from **42** (14.0 g, 35.0 mmol) in a yield of 64% (8.91 g, 22.4 mmol), as described for the synthesis of **13**. *R*_F = 0.4 (10:3, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.21 (m, 10H, H_{Ar} Bn), 5.77 (d, *J* = 3.5 Hz, 1H, H-1), 4.72 (d, *J* = 12.0 Hz, 1H, CHH Bn), 4.63 – 4.55 (m, 4H, 2 x CHH Bn, H-6, H-4), 4.54 – 4.52 (m, 1H, H-2), 4.31 (d, *J* = 5.0 Hz, 2H, CH₂ Bn), 3.82 (dd, *J* = 9.0, 4.3 Hz, 1H, H-3), 1.58 (s, 3H, CH₃), 1.35 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 203.8 (C=O), 137.1, 136.9 (C_q Bn), 128.6 – 128.0 (CH_{Ar} Bn), 113.7 (C_q), 104.6 (C-1), 80.4 (C-4), 79.3 (C-3), 77.7 (C-2), 73.3 (CH₂ Bn), 72.8 (C-6), 72.4 (CH₂ Bn), 26.9, 26.6 (2 x CH₃).

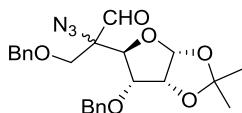
1,2-O-Isopropyl-3,6-di-O-benzyl-5-C-dichloromethyl- α -D-*allo*/ β -L-*talo*-furanoside (**44**):



44 was synthesized from **43** (10.0 g, 25.1 mmol) in a yield of 99% (12.0 g, 24.8 mmol) as two inseparable isomers (ratio 1:1) as described for the synthesis of **14**. *R*_F = 0.63 (5:1, PE:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.31 (m, 10H, H_{Ar} Bn), 6.12 (s, 1H, CHCl₂), 5.78 (d, *J* = 3.6 Hz, 1H, H-1), 4.70 (d, *J* = 11.5 Hz, 1H, CHH Bn), 4.58 – 4.52 (m, 3H, H₂-6, H-2), 4.49 (d, *J* = 11.6 Hz, 1H, CHH Bn), 4.41 (d, *J* = 8.3 Hz, 1H, H-4), 4.12 (dd, *J* = 8.3, 4.4 Hz, 1H, H-3), 3.90 (d, *J* = 10.2 Hz, 1H, CHH Bn), 3.74 (d, *J* = 10.2 Hz, 1H, CHH Bn), 1.60 (s, 3H, CH₃), 1.38 (s, 3H,

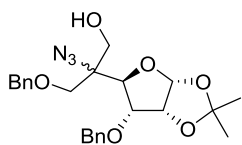
CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.3, 137.3 (C_q Bn), 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 113.5 (C_q isopropyl), 104.1 (C-1), 78.9 (C-4), 77.9 (C-2), 77.8 (C-3), 76.1 (C-5), 75.8 (CHCl₂), 73.8 (C-6), 72.1 (CH₂ Bn), 67.1 (CH₂ Bn), 27.1, 26.9 (2 x CH₃).

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-1,2-O-isopropyl-α-D-allo/β-L-talo-furano-1,6-dialdose (45):



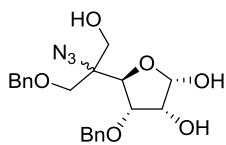
45 was synthesized from **44** (12.0 g, 24.8 mmol) in a yield of 71% (7.99 g, 17.6 mmol), as described for the synthesis of **15**. *R_F* = 0.25 (10:1, PE:EtOAc). **45** is an inseparable mixture of diastereomers (ratio = 5:3). NMR data of the major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H, CHO), 7.50 – 7.20 (m, 10H, H_{Ar} Bn), 5.73 (d, *J* = 3.5 Hz, 1H, H-1), 4.64 – 4.42 (m, 5H, 2 x CHH Bn, H₂-6, H-2), 4.35 (d, *J* = 8.7 Hz, 1H, H-4), 4.12 (d, *J* = 10.0 Hz, 1H, CHH Bn), 3.99 (d, *J* = 10.0 Hz, 1H, CHH Bn), 3.97 (dd, *J* = 8.7, 4.3 Hz, 1H, H-3), 1.59 (s, 3H, CH₃), 1.35 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 195.7 (CHO), 137.0, 136.7 (C_q Bn), 128.6 – 127.7 (CH_{Ar} Bn), 113.6 (C_q isopropyl), 104.6 (C-1), 77.8 (C-4), 77.2 (C-3), 76.9 (C-2), 73.8 (C-6), 72.4, 71.0 (2 x CH₂ Bn), 69.5 (C-5), 26.9, 26.4 (2 x CH₃).

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-1,2-O-isopropyl-α-D-allo/β-L-talo-furanoside (46):



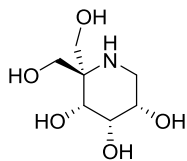
46 was synthesized from **45** (7.46 g, 16.5 mmol) in a yield of 81% (6.06 g, 13.3 mmol) as two inseparable diastereomers as described for the synthesis of **16**. *R_F* = 0.23 (9:1, PE:EtOAc). NMR-data of the major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.30 (m, 10H, H_{Ar} Bn), 5.82 (d, *J* = 3.7 Hz, 1H, H-1), 4.81 (d, *J* = 11.0 Hz, 1H, CHH Bn), 4.67 – 4.60 (m, 3H, H₂-6, H-2), 4.58 (d, *J* = 11.0 Hz, 1H, CHH Bn), 4.22 (d, *J* = 8.6 Hz, 1H, H-4), 4.11 – 4.08 (m, 1H, H-3), 3.93 (d, *J* = 9.9 Hz, 1H, CHH Bn), 3.86 (d, *J* = 9.9 Hz, 1H, CHH Bn), 3.86 (d, *J* = 9.9 Hz, 1H, CHHOH), 3.67 (dd, *J* = 9.9, 3.7 Hz, 1H, CHHOH), 1.60 (s, 3H, CH₃), 1.41 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 137.7, 136.4 (C_q Bn), 128.7 – 127.7 (CH_{Ar} Bn), 113.4 (C_q isopropyl), 104.3 (C-1), 79.5 (C-4), 77.8 (C-3), 77.2 (C-2), 73.7 (C-6), 72.3, 69.9 (CH₂ Bn), 66.6 (C-5), 62.3 (CH₂OH), 26.9, 26.7 (2 x CH₃).

5-Deoxy-5-azido-5-C-benzyloxymethyl-3-O-benzyl-α-D-allo/β-L-talo-furanoside (47):

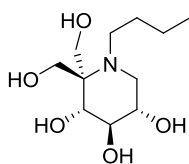


47 was synthesized from **46** (1.40 g, 3.07 mmol) in a yield of 70% (0.89 g, 2.15 mmol), as two inseparable diastereoisomer (ratio = 5:3) as described for the synthesis of **17**. *R_F* = 0.15 (5:3, PE:EtOAc). NMR data of the major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.31 (m, 10H, H_{Ar} Bn), 5.29 (s, 1H, H-1), 4.71 – 4.38 (m, 5H, CH₂ Bn, H₂-6, H-2), 4.30 – 4.23 (m, 1H, H-4), 4.08 – 4.03 (m, 1H, H-3), 3.81 – 3.73 (m, 2H, CH₂ Bn), 3.69 – 3.51 (m, 2H, CH₂OH). ¹³C NMR (100 MHz, CDCl₃) δ 137.6 – 127.7 (CH_{Ar} Bn), 96.9 (C-1), 81.5 (C-4), 77.9 (C-2), 77.0 (C-3), 73.8 (C-6), 72.9 (CH₂ Bn), 69.5 (CH₂ Bn), 66.6 (C-5), 62.9 (CH₂OH).

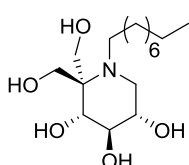
5-C-Hydroxymethyl-1-deoxy-D-allonojirimycin (9):



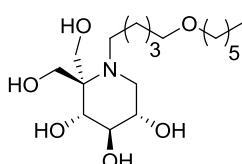
9 was synthesized from **47** (0.79 g, 1.90 mmol) in a yield of 81% (0.30 g, 1.54 mmol) as described for the synthesis of **6**. ¹H NMR (400 MHz, MeOD) δ 4.02 (d, *J* = 11.5 Hz, 1H, H-6a), 3.98 (t, *J* = 3.2 Hz, 1H, H-3), 3.81 (d, *J* = 3.2 Hz, 1H, H-4), 3.75 – 3.71 (m, 1H, H-2), 3.73 (d, *J* = 10.8 Hz, 1H, H-6*a), 3.67 (d, *J* = 11.6 Hz, 1H, H-6b), 3.59 (d, *J* = 11.1 Hz, 1H, H-6*b), 3.03 (dd, *J* = 13.1, 8.2 Hz, 1H, H-1a), 2.87 (dd, *J* = 13.1, 4.0 Hz, 1H, H-1b). ¹³C NMR (100 MHz, MeOD) δ 70.0 (C-3), 69.5 (C-4), 68.3 (C-2), 61.3 (C-6), 60.8 (C-6*), 60.3 (C-5), 42.3 (C-1). [α]_D²⁰ = +0.23 (c = 1.31, MeOH). IR/cm⁻¹: 3263, 2900, 1607, 1450, 1413, 1257, 1033. HRMS: found 194.10218 [M+H]⁺, calculated for [C₇H₁₅NO₅+H]⁺ 194.10230.

N*-Alkylated final compounds:*5-*C*-Hydroxymethyl-*N*-butyl-1-deoxynojirimycin (56):**

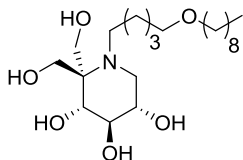
6 (0.10 mmol) and butyl bromide (0.16 mmol) was subjected to general alkylation procedure to provide **56** (0.5 mg, 0.002 mmol, yield 2%). ^1H NMR (600 MHz, MeOD) δ 4.04 (d, J = 13.3 Hz, 1H, H-6a), 3.90 (d, J = 12.0 Hz, 1H, H-6*a), 3.87 (d, J = 12.9 Hz, 1H, H-6b), 3.86 (t, J = 9.6 Hz, 1H, H-3), 3.78 (d, J = 12.0 Hz, 1H, H-6*b), 3.76 – 3.72 (m, 1H, H-2), 3.68 (d, J = 10.0 Hz, 1H, H-4), 3.59 – 3.51 (m, 2H, H-1a, H-1'a), 3.47 – 3.43 (m, 1H, H-1b), 3.14 (td, J = 12.3, 5.0 Hz, 1H, H-1'b), 1.93 – 1.83 (m, 1H, H-2'a), 1.78 – 1.68 (m, 1H, H-2'b), 1.53 – 1.41 (m, 2H, H₂-3'), 1.04 (t, J = 7.4 Hz, 3H, H₃-4'). ^{13}C NMR (150 MHz, MeOD) δ 74.1 (C-3), 72.9 (C-5), 70.0 (C-4), 67.9 (C-2), 56.8 (C-6*), 56.5 (C-6), 52.6 (C-1), 52.5 (C-1'), 27.9 (C-2'), 20.7 (C-3'), 13.5 (C-4'). IR/cm⁻¹: 3471, 2970, 1738, 1442, 1365, 1216, 1139. $[\alpha]^{20}_{\text{D}}$ = -2.00 (c = 0.01, MeOH). HRMS: found 250.16502 [$\text{C}_{11}\text{H}_{23}\text{NO}_5 + \text{H}$]⁺, calculated for [$\text{C}_{11}\text{H}_{23}\text{NO}_5 + \text{H}$]⁺ 250.16490.

5-*C*-Hydroxymethyl-*N*-nonyl-1-deoxynojirimycin (57):

6 (0.20 mmol) and nonyl bromide (0.31 mmol) was subjected to general alkylation procedure to provide **57** (5.0 mg, 0.016 mmol, yield 8%). ^1H NMR (600 MHz, MeOD) δ 4.04 (d, J = 13.3 Hz, 1H, H-6a), 3.90 (d, J = 12.0 Hz, 1H, H-6*a), 3.86 (d, J = 13.6 Hz, 1H, H-6b), 3.86 (t, J = 10.0 Hz, 1H, H-3), 3.77 (d, J = 11.9 Hz, 1H, H-6*b), 3.78 – 3.71 (m, 1H, H-2), 3.68 (d, J = 10.0 Hz, 1H, H-4), 3.58 – 3.50 (m, 2H, H-1a, H-1'a), 3.44 (t, J = 11.7 Hz, 1H, H-1b), 3.12 (td, J = 12.3, 5.0 Hz, 1H, H-1'b), 1.96 – 1.83 (m, 1H, H-2'a), 1.80 – 1.70 (m, 1H, H-2'b), 1.47 – 1.25 (m, 12H, H₂-3', H₂-4', H₂-5', H₂-6', H₂-7', H₂-8'), 0.93 (t, J = 7.1 Hz, 3H, H₃-9'). ^{13}C NMR (150 MHz, MeOD) δ 74.0 (C-3), 72.9 (C-5), 70.0 (C-4), 67.9 (C-2), 56.8 (C-6*), 56.5 (C-6), 52.6 (C-1'), 52.6 (C-1), 32.6, 30.1, 29.9, 29.9, 27.4, 25.9, 23.3, 14.0 (C-2' – C-9'). IR/cm⁻¹: 3675, 2988, 2901, 1677, 1394, 1226, 1056. $[\alpha]^{20}_{\text{D}}$ = -0.1 (c = 0.10, MeOH). HRMS: found 320.24321 [$\text{C}_{16}\text{H}_{33}\text{NO}_5 + \text{H}$]⁺, calculated for [$\text{C}_{16}\text{H}_{33}\text{NO}_5 + \text{H}$]⁺ 320.24315.

5-*C*-Hydroxymethyl-*N*-[5-(hexyloxy)pentyl]-1-deoxynojirimycin (58):

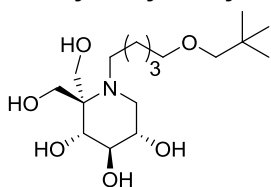
6 (0.20 mmol) and pentyloxyhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **58** (3.0 mg, 0.008 mmol, yield 4%). ^1H NMR (600 MHz, MeOD) δ 4.02 (d, J = 13.3 Hz, 1H, H-6a), 3.88 (d, J = 12.0 Hz, 1H, H-6*a), 3.84 (t, J = 9.6 Hz, 1H, H-3), 3.84 (d, J = 13.2 Hz, 1H, H-6b), 3.75 (d, J = 11.9 Hz, 1H, H-6*b), 3.75 – 3.69 (m, 1H, H-2), 3.66 (d, J = 10.0 Hz, 1H, H-4), 3.56 – 3.50 (m, 2H, H-1a, H-1'a), 3.44 – 3.40 (m, 1H, H-1b), 3.46 (t, J = 6.3 Hz, 2H, H₂-5'), 3.43 (t, J = 6.7 Hz, 2H, H₂-6'), 3.12 (td, J = 12.2, 5.0 Hz, 1H, H-1'b), 1.94 – 1.86 (m, 1H, H-2'a), 1.81 – 1.69 (m, 1H, H-2'b), 1.68 – 1.60 (m, 2H, H₂-4'), 1.60 – 1.53 (m, 2H, H₂-7'), 1.52 – 1.43 (m, 2H, H₂-3'), 1.40 – 1.26 (m, 6H, H₂-8', H₂-9', H₂-10'), 0.91 (t, J = 6.9 Hz, 3H, H₃-11'). ^{13}C NMR (150 MHz, MeOD) δ 74.4 (C-3), 73.3 (C-5), 72.1 (C-6'), 71.4 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 52.9 (C-1'), 32.9 (C-9'), 30.7 (C-7'), 30.2 (C-4'), 27.0 (C-8'), 26.1 (C-2'), 24.6 (C-3'), 23.7 (C-10'), 14.4 (C-11'). IR/cm⁻¹: 3316, 2933, 1673, 1439, 1366, 1205, 1135. $[\alpha]^{20}_{\text{D}}$ = -1.00 (c = 0.06, MeOH). HRMS: found 364.26940 [$\text{C}_{18}\text{H}_{37}\text{NO}_6 + \text{H}$]⁺, calculated for [$\text{C}_{18}\text{H}_{37}\text{NO}_6 + \text{H}$]⁺ 364.26936.

5-*C*-Hydroxymethyl-*N*-[5-(nonyloxy)pentyl]-1-deoxynojirimycin (59):

6 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **59** (2.4 mg, 0.006 mmol, yield 3%). ^1H NMR (600 MHz, MeOD) δ 4.02 (d, J = 13.3 Hz, 1H, H-6a), 3.88 (d, J = 12.0 Hz, 1H, H-6*a), 3.84 (t, J = 9.6 Hz, 1H, H-3), 3.84 (d, J = 13.8 Hz, 1H, H-6b), 3.74 (d, J = 12.0 Hz, 1H, H-6*b), 3.73 – 3.69

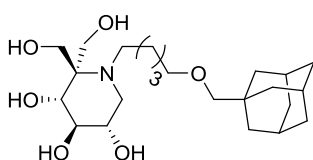
(m, 1H, H-2), 3.66 (d, $J = 10.0$ Hz, 1H, H-4), 3.57 – 3.49 (m, 2H, H-1a, H-1'a), 3.46 (t, $J = 6.3$ Hz, 2H, H₂-5'), 3.43 (t, $J = 6.6$ Hz, 2H, H₂-6'), 3.44 – 3.40 (m, 1H, H-1b), 3.12 (td, $J = 12.2, 5.0$ Hz, 1H, H-1'b), 1.90 (ddt, $J = 20.9, 12.1, 5.8$ Hz, 1H, H-2'a), 1.75 (dt, $J = 22.4, 12.0, 5.1$ Hz, 1H, H-2'b), 1.68 – 1.61 (m, 2H, H₂-4'), 1.59 – 1.53 (m, 2H, H₂-7'), 1.53 – 1.42 (m, 2H, H₂-3'), 1.40 – 1.23 (m, 12H, H₂-8', H₂-9', H₂-10', H₂-11', H₂-12', H₂-13'), 0.90 (t, $J = 7.0$ Hz, 3H, H₃-14'). ¹³C NMR (150 MHz, MeOD) δ 74.4 (C-3), 73.3 (C-5), 72.1 (C-6'), 71.4 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 52.9 (C-1'), 33.1 (C-9'), 30.8 (C-7'), 30.7, 30.6, 30.4 (C-10', C-11', C-12'), 30.2 (C-4'), 27.3 (C-8'), 26.1 (C-2'), 24.6 (C-3'), 23.7 (C-13'), 14.4 (C-14'). $[\alpha]^{20}_D = -0.63$ ($c = 0.05$, MeOH). IR/cm⁻¹: 3357, 2928, 1738, 1676, 1438, 1365, 1216, 1137, 801, 724, 527. HRMS: found 406.31624 [C₂₁H₄₃NO₆+H]⁺, calculated for [C₂₁H₄₃NO₆+H]⁺ 406.31631.

5-C-Hydroxymethyl-N-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxynojirimycin (60):



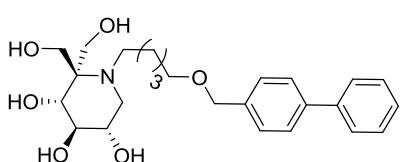
6 (0.10 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy) pentane (0.15 mmol) was subjected to general alkylation procedure to provide **60** (1.1 mg, 0.0032 mmol, yield 3%). ¹H NMR (600 MHz, MeOD) δ 4.02 (d, $J = 13.3$ Hz, 1H, H-6a), 3.88 (d, $J = 12.0$ Hz, 1H, H-6*a), 3.84 (d, $J = 13.3$ Hz, 1H, H-6b), 3.75 (d, $J = 12.0$ Hz, 1H, H-6*b), 3.86 – 3.81 (m, 1H, H-3), 3.75 – 3.69 (m, 1H, H-2), 3.65 (d, $J = 10.0$ Hz, 1H, H-4), 3.56 – 3.50 (m, 2H, H-1a, H-1'a), 3.45 (t, $J = 6.3$ Hz, 2H, H₂-5'), 3.44 – 3.38 (m, 1H, H-1b), 3.12 (td, $J = 12.2, 5.0$ Hz, 1H, H-1'b), 3.08 (s, 2H, H₂-6'), 1.94 – 1.89 (m, 1H, H-2'a), 1.77 – 1.73 (m, 1H, H-2'b), 1.69 – 1.65 (m, 2H, H₂-3'), 1.61 – 1.42 (m, 2H, H₂-4'), 0.91 (s, 9H, 3 x CH₃). ¹³C NMR (150 MHz, MeOD) δ 82.6 (C-6'), 74.4 (C-3), 73.3 (C-5), 72.0 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 53.0 (C-1'), 32.9 (C_q), 30.3 (C-4'), 27.1 (C-2'), 26.2 (C-3'), 24.6 (3 x CH₃). $[\alpha]^{20}_D = -1.36$ ($c = 0.02$, MeOH). IR/cm⁻¹: 3460, 3016, 2970, 1738, 1442, 1365, 1216, 1132. HRMS: found 350.25376 [C₁₇H₃₅NO₆+H]⁺, calculated for [C₁₇H₃₅NO₆+H]⁺ 350.25371.

5-C-Hydroxymethyl-N-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (61):



6 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.29 mmol) was subjected to general alkylation procedure to provide **61** (9.1 mg, 0.022 mmol, yield 11%). ¹H NMR (600 MHz, MeOD) δ 4.02 (d, $J = 13.4$ Hz, 1H, H-6a), 3.88 (d, $J = 12.2$ Hz, 1H, H-6b), 3.85 (d, $J = 13.8$ Hz, H-6*a), 3.86 – 3.82 (m, 1H, H-3), 3.76 (d, $J = 12.2$ Hz, 1H, H-6*b), 3.76 – 3.72 (m, 1H, H-2), 3.66 (d, $J = 10.0$ Hz, 1H, H-4), 3.55 – 3.50 (m, 2H, H-1a, H-1'a), 3.42 (t, $J = 6.3$ Hz, 2H, H₂-5'), 3.43 – 3.39 (m, 1H, H-1b), 3.16 – 3.08 (m, 1H, H-1'b), 2.99 (s, 2H, H₂-6'), 1.94 (p, $J = 3.0$ Hz, 3H, 3 x CH ada), 1.94 – 1.90 (m, 1H, H-2'a), 1.77 – 1.66 (m, 7H, 3 x CH₂ ada, H-2'b), 1.63 (m, 2H, H₂-4'), 1.56 (d, $J = 2.9$ Hz, 6H, 3 x CH₂ ada), 1.53 – 1.41 (m, 2H, H₂-3'). ¹³C NMR (150 MHz, MeOD) δ 83.1 (C-6'), 74.4 (C-3), 73.2 (C-5), 72.1 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 52.9 (C-1'), 40.8 (CH₂ ada), 38.3 (CH₂ ada), 35.1 (C_q ada), 30.1 (C-4'), 29.7 (CH ada), 26.1 (C-2'), 24.6 (C-3'). $[\alpha]^{20}_D = -0.77$ ($c = 0.18$, MeOH). IR/cm⁻¹: 3346, 2902, 2848, 1738, 1673, 1448, 1365, 1205, 1136. HRMS: found 428.30048 [C₂₃H₄₁NO₆+H]⁺, calculated for [C₂₃H₄₁NO₆+H]⁺ 428.30066.

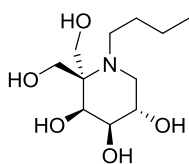
5-C-Hydroxymethyl-N-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxynojirimycin (62):



6 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **62** (40.8 mg, 0.092 mmol, yield 46%). ¹H NMR (600 MHz, MeOD) δ 7.63 (dd, $J = 8.3, 1.7$ Hz, 4H, H_{Ar} BiPh), 7.48 – 7.41 (m, 4H, H_{Ar} BiPh), 7.39 – 7.32 (m, 1H, H_{Ar} BiPh), 4.58 (s, 2H, H₂-6'), 4.03 (d, $J = 13.3$ Hz, 1H, H-6a), 3.90 (d, $J = 12.1$ Hz, 1H, H-6*a), 3.86 (d, $J = 10.1$ Hz, 1H, H-3), 3.86 (d, $J = 13.2$ Hz, 1H, H-6b), 3.77 (d, $J = 12$ Hz, 1H, H-6*b), 3.77 – 3.63 (m, 1H, H-2), 3.68 (d, $J = 10.0$ Hz, 1H, H-4), 3.59

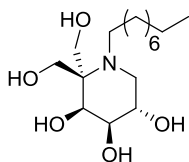
(*t*, *J* = 6.2 Hz, 2H, H₂-5'), 3.57 – 3.51 (m, 2H, H-1a, H-1'a), 3.44 (*t*, *J* = 11.8 Hz, 1H, H-1b), 3.15 (*td*, *J* = 12.2, 5.0 Hz, 1H, H-1'b), 2.01 – 1.86 (m, 1H, H-2'a), 1.84 – 1.76 (m, 1H, H-2'b), 1.76 – 1.69 (m, 2H, H₂-4'), 1.64 – 1.45 (m, 2H, H₂-3'a). ¹³C NMR (150 MHz, MeOD) δ 141.7, 141.5 (C_q BiPh), 138.5 – 127.5 (C_{Ar} BiPh), 74.1 (C-3), 73.3 (C-6'), 72.9 (C-5), 70.6 (C-5'), 70.1 (C-4), 67.9 (C-2), 56.8 (C-6), 56.5 (C-6*), 52.6 (C-1), 52.6 (C-2), 29.8 (C-4'), 25.7 (C-2'), 24.3 (C-3'). [α]²⁰_D = -0.1 (c = 0.82, MeOH). IR/cm⁻¹: 3361, 3016, 2970, 1738, 1675, 1440, 1365, 1205, 1134. HRMS: found 446.25357 [C₂₅H₃₅NO₆+H]⁺, calculated for [C₂₅H₃₅NO₆+H]⁺ 446.25371.

5-C-Hydroxymethyl-*N*-butyl-1-deoxy-D-galactonojirimycin (77):



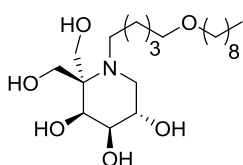
7 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **77** (11.2 mg, 0.044 mmol, yield 22%). ¹H NMR (600 MHz, MeOD) δ 4.27 (*d*, *J* = 3.4 Hz, 1H, H-4), 4.24 (*d*, *J* = 14.0 Hz, 1H, H-6a), 4.00 (*td*, *J* = 4.8, 1.8 Hz, 1H, H-2), 3.98 (*d*, *J* = 11.4 Hz, 1H, H-6'a), 3.94 (*t*, *J* = 4.1 Hz, 1H, H-3), 3.89 (*d*, *J* = 12 Hz, 1H, H-6*b), 3.89 (*d*, *J* = 14.4 Hz, 1H, H-6b), 3.76 (*dd*, *J* = 13.1, 1.6 Hz, 1H, H-1a), 3.62 (*ddd*, *J* = 13.1, 10.1, 6.6 Hz, 1H, 1'a), 3.42 (*dd*, *J* = 13.8, 3.6 Hz, 1H, H-1b), 3.24 – 3.17 (m, 1H, H-1'b), 1.89 – 1.79 (m, 1H, H-2'a), 1.74 – 1.64 (m, 1H, H-2'b), 1.52 – 1.36 (m, 2H, H₂-3'), 1.01 (*t*, *J* = 7.4 Hz, 3H, H₃-4'). ¹³C NMR (150 MHz, MeOD) δ 73.6 (C-5), 70.2 (C-3), 66.8 (C-2), 65.1 (C-4), 56.9 (C-6*), 56.5 (C-6), 51.8 (C-1'), 49.5 (C-1), 28.5 (C-2'), 20.0 (C-3'), 13.5 (C-4'). [α]²⁰_D = +0.04 (c = 0.22, MeOH). IR/cm⁻¹: 3271, 2968, 2879, 1674, 1435, 1201, 1134, 1082. HRMS: found 250.16488 [C₁₁H₂₃NO₅+H]⁺, calculated for [C₁₁H₂₃NO₅+H]⁺ 250.16490.

5-C-Hydroxymethyl-*N*-nonyl-1-deoxy-D-galactonojirimycin (78):



7 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **78** (11.8 mg, 0.036 mmol, yield 18%). ¹H NMR (400 MHz, MeOD) δ 4.30 (*d*, *J* = 3.3 Hz, 1H, H-4), 4.27 (*d*, *J* = 14.0 Hz, 1H, H-6a), 4.04 – 4.00 (m, 1H, H-2), 4.00 (*d*, *J* = 11.9 Hz, 1H, H-6'a), 3.98 – 3.95 (m, 1H, H-3), 3.91 (*d*, *J* = 11.5 Hz, 1H, H-6*b), 3.91 (*d*, *J* = 14.2 Hz, 1H, H-6b), 3.78 (*dd*, *J* = 13.0, 1.6 Hz, 1H, H-1a), 3.63 (*ddd*, *J* = 13.0, 10.0, 6.7 Hz, 1H, H-1'a), 3.43 (*dd*, *J* = 13.1, 3.4 Hz, 1H, H-1b), 3.23 (*ddd*, *J* = 13.6, 9.6, 4.9 Hz, 1H, H-1'b), 1.96 – 1.82 (m, 1H, H-2'a), 1.80 – 1.66 (m, 1H, H-2'b), 1.51 – 1.28 (m, 12H, H₂-3', H₂-4', H₂-5', H₂-6', H₂-7', H₂-8'), 0.93 (*t*, *J* = 7.1 Hz, 3H, H₃-9'). ¹³C NMR (100 MHz, MeOD) δ 72.6 (C-5), 69.2 (C-3), 65.8 (C-2), 64.1 (C-4), 55.8 (C-6*), 55.4 (C-6), 51.0 (C-1'), 48.4 (C-1), 31.6, 29.1, 28.9, 28.8, 25.7, 25.4, 22.3 (C-2' – C-8'), 13.0 (C-9'). [α]²⁰_D = +0.0 (c = 0.24, MeOH). IR/cm⁻¹: 3336, 2928, 1738, 1673, 1438, 1365, 1204, 1136, 1080. HRMS: found 320.24316 [C₁₆H₃₃NO₅+H]⁺, calculated for [C₁₆H₃₃NO₅+H]⁺ 320.24315.

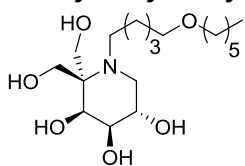
5-C-Hydroxymethyl-*N*-[5-(hexyloxy)pentyl]-1-deoxy-D-galactonojirimycin (79):



7 (0.20 mmol) and pentyloxyhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **79** (15.3 mg, 0.042 mmol, yield 21%). ¹H NMR (400 MHz, MeOD) δ 4.30 (*d*, *J* = 3.3 Hz, 1H, H-4), 4.26 (*d*, *J* = 14.0 Hz, 1H, H-6a), 4.05 – 4.02 (m, 1H, H-2), 4.00 (*d*, *J* = 12.0 Hz, 1H, H-6'a), 3.98 – 3.95 (m, 1H, H-3), 3.92 (*d*, *J* = 11.7 Hz, 1H, H-6*b), 3.91 (*d*, *J* = 14.1 Hz, 1H, H-6b), 3.79 (*dd*, *J* = 13.1, 1.3 Hz, 1H, H-1a), 3.64 (*ddd*, *J* = 13.2, 10.1, 6.6 Hz, 1H, H-1'a), 3.48 (*t*, *J* = 6.3 Hz, 2H, H₂-5'), 3.45 (*t*, *J* = 6.6 Hz, 2H, H₂-6'), 3.43 (*dd*, *J* = 13.2, 3.5 Hz, 1H, H-1b), 3.24 (*ddd*, *J* = 13.0, 9.7, 4.4 Hz, 1H, H-1'b), 1.99 – 1.85 (m, 1H, H-2'a), 1.85 – 1.71 (m, 1H, H-2'b), 1.71 – 1.62 (m, 2H, H₂-4'), 1.57 (*dt*, *J* = 7.9, 6.6 Hz, 2H, H₂-7'), 1.54 – 1.43 (m, 2H, H₂-3'), 1.42 – 1.28 (m, 6H, H₂-8', H₂-9', H₂-10'), 0.93 (*t*, *J* = 7.1 Hz, 3H, H₃-11'). ¹³C NMR (150 MHz, MeOD) δ 71.8 (C-6'), 71.1 (C-5'), 70.5 (C-3), 66.8 (C-2), 65.3 (C-4), 58.4 (C-6*), 57.1 (C-6), 52.2 (C-1'), 49.8 (C-1), 32.6 (C-10'), 30.5 (C-7'), 29.9 (C-4'), 26.7 (C-8'), 26.3 (C-2'), 23.9 (C-3'), 23.5 (C-9'), 14.2 (C-10'). [α]²⁰_D = +0.1 (c = 0.31, MeOH). IR/cm⁻¹: 3346, 2931,

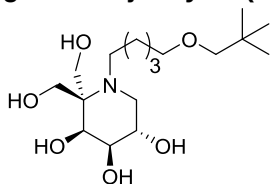
2860, 1670, 1458, 1431, 1201, 1132, 1082. HRMS: found 364.26934 $[\text{C}_{18}\text{H}_{37}\text{NO}_6 + \text{H}]^+$, calculated for $[\text{C}_{18}\text{H}_{37}\text{NO}_6 + \text{H}]^+$ 364.26936.

5-C-Hydroxymethyl-N-[5-(nonyloxy)pentyl]-1-deoxy-D-galactonojirimycin (80):



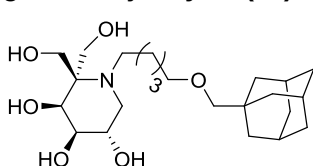
7 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **80** (11.5 mg, 0.028 mmol, yield 14%). ^1H NMR (400 MHz, MeOD) δ 4.29 (d, J = 3.3 Hz, 1H, H-4), 4.26 (d, J = 14.0 Hz, 1H, H-6a), 4.03 – 4.01 (m, 1H, H-2), 4.00 (d, J = 11.8 Hz, 1H, H-6*a), 3.97 – 3.94 (m, 1H, H-3), 3.91 (d, J = 11.2 Hz, 1H, H-6*b), 3.91 (d, J = 14.2 Hz, 1H, H-6b), 3.79 (dd, J = 13.1, 1.6 Hz, 1H, H-1a), 3.69 – 3.56 (m, 1H, H-1'a), 3.47 (t, J = 6.2 Hz, 2H, H-5'), 3.44 (t, J = 6.6 Hz, 2H, H-6'), 3.45 – 3.42 (m, 1H, H-1b), 3.23 (ddd, J = 14.1, 9.8, 4.4 Hz, 1H, H-1'b), 1.99 – 1.85 (m, 1H, H-2'a), 1.80 – 1.72 (m, 1H, H-2'b), 1.65 (dt, J = 8.1, 6.1 Hz, 2H, H-4'), 1.60 – 1.53 (m, 2H, H-2-7'), 1.53 – 1.41 (m, 2H, H-2-3'), 1.39 – 1.26 (m, 12H, H-2-8', H-2-9', H-2-10', H-2-11', H-2-12', H-2-13'), 0.93 (t, J = 6.8 Hz, 3H, H-3-14'). ^{13}C NMR (100 MHz, MeOD) δ 72.6 (C-5), 70.7 (C-6'), 69.9 (C-5'), 69.2 (C-3), 65.8 (C-2), 64.2 (C-4), 55.9 (C-6*), 55.5 (C-6), 50.9 (C-1'), 48.6 (C-1), 31.6 (C-9'), 29.4 (C-7'), 29.3, 29.2, 29.0 (C-10', C-11', C-12'), 28.7 (C-4'), 25.9 (C-8'), 25.2 (C-2'), 22.6 (C-3'), 22.3 (C-13'), 13.0 (C-14'). IR/cm $^{-1}$: 3675, 3353, 2971, 2924, 1674, 1394, 1203, 1067. $[\alpha]^{20}_{\text{D}}$ = +0.1 (c = 0.23, MeOH). HRMS: found 406.31615 $[\text{C}_{21}\text{H}_{43}\text{NO}_6 + \text{H}]^+$, calculated for $[\text{C}_{21}\text{H}_{43}\text{NO}_6 + \text{H}]^+$ 406.31631.

5-C-Hydroxymethyl-N-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-galactonojirimycin (81):



7 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy) pentane (0.30 mmol) was subjected to general alkylation procedure to provide **81** (14.3 mg, 0.04 mmol, yield 20%). ^1H NMR (400 MHz, MeOD) δ 4.30 (d, J = 3.3 Hz, 1H, H-4), 4.27 (d, J = 14.1 Hz, 1H, H-6a), 4.02 (td, J = 3.6, 1.6 Hz, 1H, H-2), 4.00 (d, J = 11.6 Hz, 1H, H-6*a), 3.97 (t, J = 3.6 Hz, 1H, H-3), 3.92 (d, J = 11.2 Hz, 1H, H-6*b), 3.91 (d, J = 14.0 Hz, 1H, H-6b), 3.79 (dd, J = 13.1, 1.7 Hz, 1H, H-1a), 3.64 (ddd, J = 13.1, 10.1, 6.7 Hz, 1H, H-1'a), 3.47 (t, J = 6.1 Hz, 2H, H-2-5'), 3.44 (dd, J = 13.2, 3.2 Hz, 1H, H-1b), 3.28 – 3.20 (m, 1H, H-1'b), 3.10 (s, 2H, H-2-6'), 2.03 – 1.88 (m, 1H, H-2'a), 1.85 – 1.74 (m, 1H, H-2'b), 1.71 – 1.63 (m, 2H, H-2-4'), 1.61 – 1.42 (m, 2H, H-2-3'), 0.93 (s, 9H, 3 x CH $_3$). ^{13}C NMR (100 MHz, MeOD) δ 81.1 (C-6'), 72.6 (C-5), 70.6 (C-5'), 69.2 (C-3), 65.8 (C-2), 64.1 (C-4), 55.9 (C-6*), 55.5 (C-6), 50.9 (C-1'), 48.5 (C-1), 31.5 (C-7'), 28.8 (C-4'), 25.7 (CH $_3$), 25.3 (C-2'), 22.7 (C-3'). $[\alpha]^{20}_{\text{D}}$ = -0.1 (c = 0.29, MeOH). IR/cm $^{-1}$: 3675, 3327, 2971, 1673, 1393, 1202, 1066. HRMS: found 350.25364 $[\text{C}_{17}\text{H}_{35}\text{NO}_6 + \text{H}]^+$, calculated for $[\text{C}_{17}\text{H}_{35}\text{NO}_6 + \text{H}]^+$ 350.25371.

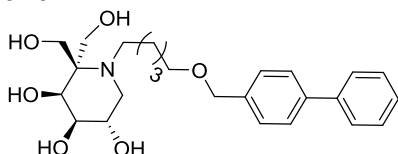
5-C-Hydroxymethyl-N-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-galactonojirimycin (82):



7 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **82** (36.5 mg, 0.09 mmol, yield 43%). ^1H NMR (400 MHz, MeOD) δ 4.28 (d, J = 3.0 Hz, 1H, H-4), 4.25 (d, J = 13.5 Hz, 1H, H-6a), 4.02 – 3.98 (m, 1H, H-2), 3.99 (d, J = 12.5 Hz, 1H, H-6*a), 3.95 (t, J = 3.9 Hz, 1H, H-3), 3.90 (d, J = 11.8 Hz, 1H, H-6*b), 3.90 (d, J = 13.7 Hz, 1H, H-6b), 3.77 (d, J = 12.9 Hz, 1H, H-1a), 3.62 (dt, J = 17.4, 8.1 Hz, 1H, H-1'a), 3.53 – 3.44 (m, 1H, H-1b), 3.42 (t, J = 6.1 Hz, 1H, H-5'), 3.28 – 3.16 (m, 1H, H-1'b), 2.98 (s, 2H, H-2-6'), 1.95 (t, J = 3.0 Hz, 3H, 3 x CH ada), 1.90 – 1.80 (m, 1H, H-2'a), 1.82 – 1.65 (m, 6H, 3 x CH $_2$ ada), 1.72 – 1.61 (m, 1H, H-2'b), 1.68 – 1.61 (m, 2H, H-2-4'), 1.57 (d, J = 2.8 Hz, 6H, 3 x CH $_2$ ada), 1.55 – 1.39 (m, 2H, H-2-3'). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (C-6'), 72.6 (C-5), 70.7 (C-5'), 69.2 (C-3), 65.4 (C-2), 64.1 (C-4), 55.8 (C-6*), 55.4 (C-6), 50.9 (C-1'), 47.7 (C-1), 39.4 (CH $_2$ ada), 36.9 (CH $_2$ ada), 33.7 (C $_q$ ada), 28.7 (C-4'), 28.3 (CH ada), 25.3 (C-2'), 22.7 (C-3'). $[\alpha]^{20}_{\text{D}}$ = +0.2 (c = 0.73,

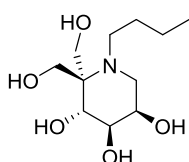
MeOH). IR/cm⁻¹: 3248, 2902, 2848, 1674, 1447, 1361, 1319, 1199, 1139, 1084, 1011. HRMS: found 428.30025 [C₂₃H₄₁NO₆+H]⁺, calculated for [C₂₃H₄₁NO₆+H]⁺ 428.30066.

5-C-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-galactonojirimycin (83):



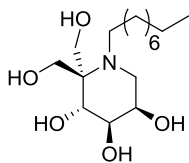
7 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **83** (18.6 mg, 0.04 mmol, yield 20%). ¹H NMR (400 MHz, MeOD) δ 7.68 – 7.60 (m, 4H, H_{Ar} BiPh), 7.52 – 7.41 (m, 4H, H_{Ar} BiPh), 7.39 – 7.32 (m, 1H, H_{Ar} BiPh), 4.57 (s, 2H, H₂-6'), 4.31 (d, *J* = 3.3 Hz, 1H, H-4), 4.26 (d, *J* = 14.0 Hz, 1H, H-6a), 4.02 – 3.99 (m, 1H, H-2), 4.00 (d, *J* = 11.7 Hz, 1H, H-6*a), 3.98 – 3.95 (m, 1H, H-3), 3.92 (d, *J* = 11.9 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.1 Hz, 1H, H-6b), 3.76 (d, *J* = 13.0 Hz, 1H, H-1a), 3.69 – 3.61 (m, 1H, H-1'a), 3.58 (t, *J* = 6.1 Hz, 2H, H₂-5'), 3.41 (dd, *J* = 13.0, 3.4 Hz, 1H, H-1b), 3.28 – 3.20 (m, 1H, H-1'b), 1.99 – 1.84 (m, 1H, H-2'a), 1.83 – 1.75 (m, 1H, H-2'b), 1.73 (dt, *J* = 7.9, 6.1 Hz, 2H, H₂-4'), 1.65 – 1.43 (m, 2H, H₂-3'). ¹³C NMR (100 MHz, MeOD) δ 132.0 – 128.6 (C_{Ar} BiPh), 74.9 (C-5), 74.5 (C-6'), 71.7 (C-5'), 71.4 (C-3), 68.0 (C-2), 66.4 (C-4), 58.1 (C-6*), 57.7 (C-6), 53.1 (C-1'), 50.8 (C-1), 30.9 (C-4'), 27.4 (C-2'), 24.9 (C-3'). [α]_D²⁰ = +0.8 (*c* = 0.37, MeOH). IR/cm⁻¹: 3675, 3313, 2971, 1671, 1407, 1278, 1200, 1077, 1132. HRMS: found 446.25342 [C₂₅H₃₅NO₆+H]⁺, calculated for [C₂₅H₃₅NO₆+H]⁺ 446.25371.

5-C-Hydroxymethyl-*N*-butyl-1-deoxy-D-mannonojirimycin (98):



8 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **98** (12.6 mg, 0.05 mmol, yield 25%). ¹H NMR (400 MHz, MeOD) δ 4.16 (td, *J* = 3.6, 1.2 Hz, 1H, H-2), 4.15 (d, *J* = 10 Hz, 1H, H-4), 4.06 (d, *J* = 13.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.6, 3.0 Hz, 1H, H-3), 3.92 (dd, *J* = 12.8, 0.8 Hz, 1H, H-1a), 3.90 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 12 Hz, 1H, H-6*a), 3.73 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.61 (dd, *J* = 12.8, 3.6 Hz, 1H, H-1b), 3.60 – 3.53 (m, 1H, H-1'a), 3.23 (ddd, *J* = 13.3, 9.7, 4.6 Hz, 1H, H-1'b), 1.96 – 1.82 (m, 1H, H-2'a), 1.74 (m, 1H, H-2'b), 1.52 – 1.44 (m, 2H, H₂-3'), 1.05 (t, *J* = 7.3 Hz, 3H, H₃-4'). ¹³C NMR (100 MHz, MeOD) δ 74.7 (C-5), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4 (C-6*), 58.1 (C-6), 55.1 (C-1), 52.6 (C-1'), 29.6 (C-2'), 21.3 (C-3'), 14.8 (C-4'). [α]_D²⁰ = -19.8 (*c* = 0.25, MeOH). IR/cm⁻¹: 3675, 3325, 2970, 1393, 1250, 1057. HRMS: found 250.16490 [C₁₁H₂₃NO₅+H]⁺, calculated for [C₁₁H₂₃NO₅+H]⁺ 250.16490

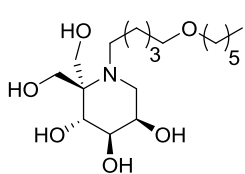
5-C-Hydroxymethyl-*N*-nonyl-1-deoxy-D-mannonojirimycin (99):



8 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **99** (16.3 mg, 0.052 mmol, yield 26%). ¹H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 9.6 Hz, 1H, H-4), 4.13 (d, *J* = 3.6 Hz, 1H, H-2), 4.05 (d, *J* = 13.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 3.90 (d, *J* = 13.2 Hz, 1H, H-1a), 3.88 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 12 Hz, 1H, H-6*a), 3.72 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.59 (dd, *J* = 13.2, 3.6 Hz, 1H, H-1b), 3.58 – 3.52 (m, 1H, H-1'a), 3.27 – 3.16 (m, 1H, 1'b), 1.95 – 1.84 (m, 1H, H-2'a), 1.80 – 1.70 (m, 1H, H-2'b), 1.53 – 1.23 (m, 12H, H₂-3' – H₂-8'), 0.90 (t, *J* = 7.0 Hz, 3H, H₃-9'). ¹³C NMR (100 MHz, MeOD) δ 72.4 (C-5), 69.7 (C-3), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6), 55.8 (C-6*), 52.8 (C-1), 50.5 (C-1'), 31.6, 29.1, 28.9, 28.8, 25.7, 25.3, 22.3 (C-2' – C-8'), 13.0 (C-9'). [α]_D²⁰ = -15.9 (*c* = 0.33, MeOH). IR/cm⁻¹: 3352, 2928, 2859, 1670, 1435, 1200, 1134, 1038. HRMS: found 320.24306 [C₁₆H₃₃NO₅+H]⁺, calculated for [C₁₆H₃₃NO₅+H]⁺ 320.24315.

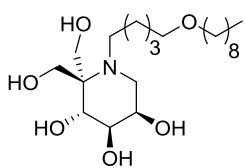
5-C-Hydroxymethyl-*N*-hexylpentyl-1-deoxy-D-mannonojirimycin (100):

8 (0.20 mmol) and pentyloxyhexyl bromide (0.31 mmol) was subjected to general alkylation procedure to provide **100** (14.0 mg, 0.038 mmol, yield 19%). ¹H NMR (400 MHz, MeOD) δ 4.14



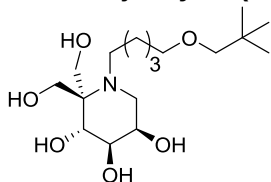
(d, $J = 9.6$ Hz, 1H, H-4), 4.14 (d, $J = 4.0$ Hz, 1H, H-2), 4.05 (d, $J = 13.2$ Hz, 1H, H-6a), 4.04 (dd, $J = 9.6, 3.0$ Hz, 1H, H-3), 3.91 (d, $J = 12$ Hz, 1H, H-1a), 3.89 (d, $J = 13.2$ Hz, 1H, H-6b), 3.87 (d, $J = 12$ Hz, 1H, H-6*a), 3.72 (d, $J = 11.7$ Hz, 1H, H-6*b), 3.60 (dd, $J = 12.8, 3.2$ Hz, 1H, H-1b), 3.60 – 3.51 (m, 1H, H-1'a), 3.48 (t, $J = 6.2$ Hz, 2H, H₂-5'), 3.45 (t, $J = 6.6$ Hz, 2H, H₂-6'), 3.26 – 3.19 (m, 1H, H-1'b), 2.01 – 1.72 (m, 2H, H₂-2'), 1.72 – 1.63 (m, 2H, H₂-4'), 1.63 – 1.53 (m, 2H, H₂-7'), 1.56 – 1.44 (m, 2H, H₂-3'), 1.43 – 1.29 (m, 6H, H₂-8', H₂-9', H₂-10'), 0.93 (t, $J = 6.7$ Hz, 3H, H₃-11'). ¹³C NMR (100 MHz, MeOD) δ 72.4 (C-5), 70.7 (C-6'), 69.9 (C-5'), 69.7 (C-3), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6*), 55.8 (C-6), 52.9 (C-1), 50.4 (C-1'), 31.5 (C-9'), 29.4 (C-7'), 28.7 (C-4'), 25.6 (C-8'), 25.1 (C-2'), 22.6 (C-3'), 22.3 (C-10'), 13.0 (C-11'). $[\alpha]^{20}_D = -15.0$ (c = 0.28, MeOH). IR/cm⁻¹: 3327, 2930, 2860, 1672, 1464, 1431, 1377, 1202, 1134, 1040. HRMS: found 364.27001 [C₁₈H₃₇NO₆+H]⁺, calculated for [C₁₈H₃₇NO₆+H]⁺ 364.26936.

5-C-Hydroxymethyl-N-nonylpentyl-1-deoxy-D-mannonojirimycin (101):



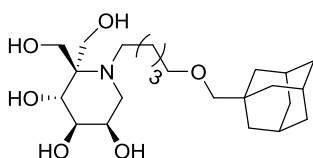
8 (0.20 mmol) pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **101** (14.2 mg, 0.034 mmol, yield 17%). ¹H NMR (400 MHz, MeOD) δ 3.98 (d, $J = 9.9$ Hz, 1H, H-4), 3.97 (d, $J = 4.0$ Hz, 1H, H-2), 3.93 – 3.87 (m, 1H, H-3), 3.91 (d, $J = 12.5$ Hz, 1H, H-6a), 3.86 (d, $J = 12.4$ Hz, 1H, H-6b), 3.84 (d, $J = 11.4$ Hz, 1H, H-6*a), 3.72 (d, $J = 11.3$ Hz, 1H, H-6*b), 3.47 (t, $J = 6.6$ Hz, 2H, H₂-5'), 3.45 (t, $J = 6.7$ Hz, 2H, H₂-6'), 3.53 – 3.42 (m, 1H, H-1a), 3.28 – 3.12 (m, 2H, H-1b, H-1'a), 2.82 – 2.58 (m, 1H, H-1'b), 1.78 – 1.53 (m, 6H, H₂-2', H₂-4', H₂-7'), 1.51 – 1.20 (m, 14H, H₂-3', H₂-8', H₂-9', H₂-10', H₂-11', H₂-12', H₂-13'), 0.91 (t, $J = 6.9$ Hz, 3H, H₃-14'). ¹³C NMR (100 MHz, MeOD) δ 72.9 (C-6'), 72.8 (C-5), 72.5 (C-5'), 70.8 (C-3), 68.9 (C-2), 67.5 (C-4), 53.7 (C-1), 51.6 (C-1'), 33.9 (C-9'), 31.7, 31.6, 31.6, 31.5, 31.4, 31.3, 28.1, 25.5, 24.6 (C-2', C-3', C-4', C-7', C-8', C-10', C-11', C-12', C-13'), 15.3 (C-14'). $[\alpha]^{20}_D = -15.5$ (c = 0.28, MeOH). IR/cm⁻¹: 3357, 2928, 1738, 1676, 1438, 1365, 1216, 1137. HRMS: found 406.31603 [C₂₁H₄₃NO₆+H]⁺, calculated for [C₂₁H₄₃NO₆+H]⁺ 406.31631.

5-C-Hydroxymethyl-N-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-mannonojirimycin (102):



8 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy)pentane (0.30 mmol) was subjected to general alkylation procedure to provide **102** (11.7 mg, 0.034 mmol, yield 17%). ¹H NMR (400 MHz, MeOD) δ 4.14 (d, $J = 9.6$ Hz, 1H, H-4), 4.14 (dd, $J = 3.1, 1.1$ Hz, 1H, H-2), 4.05 (d, $J = 13.6$ Hz, 1H, H-6a), 4.04 (dd, $J = 9.9, 3.1$ Hz, 1H, H-3), 3.92 (d, $J = 12.8$ Hz, 1H, H-1b), 3.89 (d, $J = 13.2$ Hz, 1H, H-6b), 3.87 (d, $J = 11.2$ Hz, 1H, H-6*a), 3.72 (d, $J = 11.7$ Hz, 1H, H-6*b), 3.61 (dd, $J = 12.6, 3.5$ Hz, 1H, H-1a), 3.58 – 3.53 (m, 2H, H₂-1'a), 3.48 (t, $J = 6.1$ Hz, 2H, H₂-5'), 3.29 – 3.19 (m, 1H, H-1'b), 3.11 (s, 2H, H₂-6'), 1.94 (m, 1H, H-2'a), 1.87 – 1.73 (m, 1H, H-2'b), 1.73 – 1.64 (m, 2H, H₂-3'), 1.54 (m, 2H, H₂-4'), 0.94 (s, 9H, 3 x CH₃). ¹³C NMR (100 MHz, MeOD) δ 83.4 (C-6'), 73.5 (C-5), 72.9 (C-5'), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4, 58.1 (C-6, C-6*), 55.1 (C-1), 52.7 (C-1'), 33.8 (C-7') 31.1 (C-3'), 28.0 (3 x CH₃), 27.4 (C-2'), 25.0 (C-4'). $[\alpha]^{20}_D = -15.4$ (c = 0.23, MeOH). IR/cm⁻¹: 3675, 2988, 2901, 1674, 1393, 1250, 1066. HRMS: found 350.25352 [C₁₇H₃₅NO₆+H]⁺, calculated for [C₁₇H₃₅NO₆+H]⁺ 350.25371.

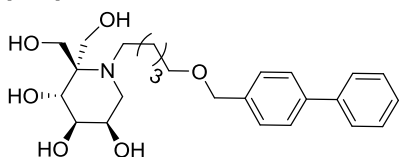
5-C-Hydroxymethyl-N-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-mannonojirimycin (103):



8 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **103** (10.5 mg, 0.024 mmol, yield 12%). ¹H NMR (400 MHz, MeOD) δ 4.14 (d, $J = 9.6$ Hz, 1H, H-4), 4.15 – 4.14 (m, 1H, H-2), 4.06 (d, $J = 13.2$ Hz, 1H, H-6a), 4.04 (dd, $J = 9.6, 2.8$ Hz, 1H, H-3), 3.92

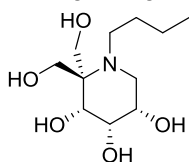
(dd, $J = 13.2, 1.2$, 1H, H-1b), 3.89 (d, $J = 13.6$, 1H, H-6b), 3.88 (d, $J = 11.6$, 1H, H-6*a), 3.73 (d, $J = 11.7$, 1H, H-6*b), 3.61 (dd, $J = 12.9, 3.4$ Hz, 1H, H-1a), 3.62 – 3.52 (m, 1H, H-1'a), 3.45 (t, $J = 6.1$ Hz, 2H, H₂-5'), 3.23 (ddd, $J = 13.4, 9.9, 4.6$ Hz, 1H, H-1'b), 1.98 (br s, 3H, CH ada), 1.96 – 1.89 (m, 1H, H-2'a), 1.85 – 1.75 (m, 1H, H-2'b), 1.83 – 1.68 (m, 6H, 3 x CH₂ ada), 1.70 – 1.63 (m, 2H, H₂-4'), 1.59 (d, $J = 2.8$ Hz, 6H, 3 x CH₂ ada), 1.57 – 1.48 (m, 2H, H₂-3'). ¹³C NMR (100 MHz, MeOD) δ 84.0 (C-6'), 74.7 (C-5), 73.0 (C-5'), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4 (C-6*), 58.1 (C-6), 53.8 (C-1), 52.7 (C-1'), 41.7 (CH₂ ada), 39.2 (CH₂ ada), 36.0 (C_q ada), 31.0 (C-4'), 30.6 (CH ada), 27.5 (C-2'), 25.0 (C-3'). $[\alpha]^{20}_D = -13.3$ ($c = 0.21$, MeOH). IR/cm⁻¹: 3675, 3330, 2901, 1673, 1450, 1203, 1134, 1077. HRMS: found 428.2999 [C₂₃H₄₁NO₆+H]⁺, calculated for [C₂₃H₄₁NO₆+H]⁺ 428.30066.

5-C-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-mannonojirimycin (104):



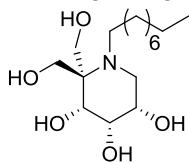
8 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.32 mmol) was subjected to general alkylation procedure to provide **104** (17.1 mg, 0.038 mmol, yield 19%). ¹H NMR (400 MHz, MeOD) δ 7.64 (m, 4H, H_{Ar} BiPh), 7.50 – 7.40 (m, 4H, H_{Ar} BiPh), 7.40 – 7.29 (m, 1H, H_{Ar} BiPh), 4.58 (s, 2H, H₂-6'), 4.14 (d, $J = 9.8$ Hz, 1H, H-4), 4.15 – 4.11 (t, $J = 3.2$ Hz, 1H, H-2), 4.04 (d, $J = 13.2$, 1H, H-6a), 4.03 (dd, $J = 10.0, 2.8$, 1H, H-3), 3.89 (d, $J = 13.2$, 1H, H-6b), 3.87 (d, $J = 12.0$, 1H, H-6*a), 3.87 (m, 1H, H-1a), 3.71 (d, $J = 11.6$, 1H, H-6*b), 3.65 – 3.54 (m, 1H, H-1'a), 3.59 (t, $J = 5.8$ Hz, 2H, H₂-5'), 3.64 – 3.55 (m, 1H, H-1b), 3.28 – 3.17 (m, 1H, H-1'b), 2.01 – 1.86 (m, 1H, H-2'a), 1.86 – 1.77 (m, 1H, H-2'b), 1.78 – 1.70 (m, 2H, H-4'), 1.68 – 1.46 (m, 2H, H-3'). ¹³C NMR (100 MHz, MeOD) δ 140.5, 137.5 (C_q BiPh), 129.7, 128.7, 128.5, 128.1, 127.0, 126.6, 126.5 (C_{Ar} BiPh), 72.4 (C-5), 72.2 (C-6'), 69.7 (C-3), 69.5 (C-5'), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6*), 55.8 (C-6), 52.8 (C-1), 50.4 (C-1'), 28.7 (C-2'), 25.0 (C-3'), 22.7 (C-4'). $[\alpha]^{20}_D = -14.6$ ($c = 0.34$, MeOH). IR/cm⁻¹: 3675, 3323, 2971, 1674, 1407, 1202, 1133, 1076. HRMS: found 446.25345 [C₂₅H₃₅NO₆+H]⁺, calculated for [C₂₅H₃₅NO₆+H]⁺ 446.25371.

5-C-Hydroxymethyl-*N*-butyl-1-deoxy-D-allonojirimycin (121):



9 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **121** (6.2 mg, 0.025 mmol, yield 12%). ¹H NMR (600 MHz, MeOD) δ 4.18 (d, $J = 14.2$ Hz, 1H, H-6a), 4.08 (t, $J = 2.9$ Hz, 1H, H-3), 3.97 (d, $J = 12.1$ Hz, 1H, H-6*a), 3.94 – 3.90 (m, 1H, H-2), 3.89 (d, $J = 12.6$ Hz, 1H, H-6*b), 3.89 (d, $J = 2.7$ Hz, 1H, H-4), 3.87 (d, $J = 14.2$ Hz, 1H, H-6b), 3.61 (ddd, $J = 13.0, 11.9, 5.0$ Hz, 1H, H-1'), 3.36 – 3.34 (m, 2H, H₂-1), 1.92 – 1.80 (m, 1H, H-2'a), 1.76 – 1.59 (m, 1H, H-2'b), 1.54 – 1.33 (m, 2H, H₂-3'), 1.01 (t, $J = 7.4$ Hz, 3H, H₃-4'). ¹³C NMR (150 MHz, MeOD) δ 72.6 (C-5), 71.8 (C-3), 67.5 (C-4), 65.1 (C-2), 57.0 (C-6), 57.0 (C-6*), 53.0 (C-1'), 49.0 (C-1), 28.4 (C-2'), 21.1 (C-3'), 13.9 (C-4'). $[\alpha]^{20}_D = -0.2$ ($c = 0.12$, MeOH). IR/cm⁻¹: 3352, 2970, 2879, 1674, 1430, 1201, 1136, 1056. HRMS: found 250.16502 [C₁₁H₂₃NO₅+H]⁺, calculated for [C₁₁H₂₃NO₅+H]⁺ 250.16490.

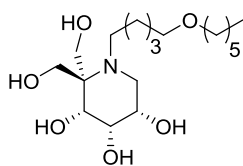
5-C-Hydroxymethyl-*N*-nonyl-1-deoxy-D-allonojirimycin (122):



9 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure with to provide **122** (8.3 mg, 0.026 mmol, yield 13%). ¹H NMR (400 MHz, MeOD) δ 4.21 (d, $J = 14.3$ Hz, 1H, H-6a), 4.10 (t, $J = 2.9$ Hz, 1H, H-3), 3.99 (d, $J = 12.1$ Hz, 1H, H-6*a), 3.95 (dd, $J = 6.5, 3.1$ Hz, 1H, H-2), 3.92 (d, $J = 12.4$ Hz, 1H, H-6*b), 3.91 (d, $J = 2.4$ Hz, 1H, H-4), 3.89 (d, $J = 14$ Hz, 1H, H-6b), 3.63 (td, $J = 12.4, 5.0$ Hz, 1H, H-1'a), 3.42 – 3.35 (m, 2H, H₂-1), 3.14 (dt, $J = 12.5, 6.3$ Hz, 1H, H-1'b), 1.98 – 1.66 (m, 2H, H₂-2'), 1.46 – 1.33 (m, 12H, H₂-3' - H₂-8'), 0.94 (t, $J = 7.1$ Hz, 3H, H₃-9'). ¹³C NMR (100 MHz, MeOD) δ 71.2 (C-5), 70.3 (C-3), 66.1 (C-4), 63.7 (C-2), 55.6 (C-6), 55.6 (C-6*), 51.8 (C-1'), 47.5 (C-1), 31.6, 29.1, 28.9, 28.8, 26.4, 25.0, 22.3 (C-2' - C-8'), 13.0 (C-9'). $[\alpha]^{20}_D = -0.2$ ($c = 0.17$, MeOH). IR/cm⁻¹: 3352, 2926, 2858, 1670, 1456, 1435, 1379,

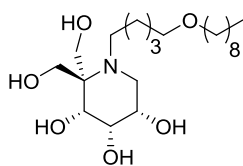
1201, 1134, 1056. HRMS: found 320.24328 $[\text{C}_{16}\text{H}_{33}\text{NO}_5+\text{H}]^+$, calculated for $[\text{C}_{16}\text{H}_{33}\text{NO}_5+\text{H}]^+$ 320.24315.

5-C-Hydroxymethyl-N-hexyloxypentyl-1-deoxy-D-allonojirimycin (**123**):



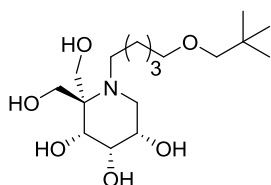
9 (0.20 mmol) and pentyloxylhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **123** (5.0 mg, 0.014 mmol, yield 7%). ^1H NMR (600 MHz, MeOD) δ 4.21 (d, J = 14.2 Hz, 1H, H-6a), 4.10 (t, J = 2.8 Hz, 1H, H-3), 3.99 (d, J = 12.1 Hz, 1H, H-6*a), 3.96 – 3.93 (m, 2H, H₂-2), 3.91 (d, J = 12.4 Hz, 1H, H-6*b), 3.91 (d, J = 2.7 Hz, 1H, H-4), 3.89 (d, J = 14.3 Hz, 1H, H-6b), 3.68 – 3.59 (m, 1H, H-1'a), 3.48 (t, J = 6.3 Hz, 2H, H₂-5'), 3.46 (t, J = 6.6 Hz, 2H, H₂-6'), 3.40 – 3.36 (m, 2H, H₂-1), 3.15 (td, J = 12.4, 5.0 Hz, 1H, H-1'b), 1.96 – 1.90 (m, 1H, H-2'a), 1.80 – 1.71 (m, 1H, H-2'b), 1.68 – 1.66 (m, 2H, H₂-4'), 1.60 – 1.56 (m, 2H, H₂-7'), 1.55 – 1.44 (m, 2H, H₂-3'), 1.42 – 1.30 (m, 6H, H₂-8', H₂-9', H₂-10'), 0.93 (t, J = 6.9 Hz, 3H, H₃-11'). ^{13}C NMR (150 MHz, MeOD) δ 72.3 (C-5), 71.7 (C-6'), 71.4 (C-3), 71.0 (C-5'), 67.1 (C-4), 64.7 (C-2), 56.6 (C-6), 56.6 (C-6*), 52.7 (C-1'), 48.5 (C-1), 31.9 (C-9'), 30.3 (C-7'), 29.8 (C-4'), 26.6 (C-8'), 25.8 (C-2'), 24.2 (C-3'), 23.3 (C-10'), 14.0 (C-11'). $[\alpha]^{20}_{\text{D}}$ = +0.0 (c = 0.10, MeOH). IR/cm⁻¹: 3352, 2929, 2860, 1751, 1676, 1431, 1371, 1205, 1132, 1080. HRMS: found 264.26942 $[\text{C}_{18}\text{H}_{37}\text{NO}_6+\text{H}]^+$, calculated for $[\text{C}_{18}\text{H}_{37}\text{NO}_6+\text{H}]^+$ 264.26936.

5-C-Hydroxymethyl-N-nonyloxypentyl-1-deoxy-D-allonojirimycin (**124**):

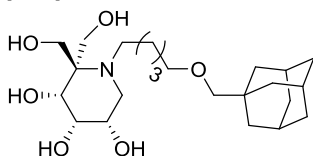


9 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **124** (3.3 mg, 0.008 mmol, yield 4%). ^1H NMR (600 MHz, MeOD) δ 4.21 (d, J = 14.3 Hz, 1H, H-6a), 4.10 (t, J = 2.9 Hz, 1H, H-3), 3.99 (d, J = 12.1 Hz, 1H, H-6*a), 3.96 – 3.93 (m, 1H, H-2), 3.91 (d, J = 12 Hz, 1H, H-6*b), 3.91 (d, J = 2.4 Hz, 1H, H-4), 3.89 (d, J = 14.4 Hz, 1H, H-6b), 3.67 – 3.60 (m, 1H, H-1'a), 3.48 (t, J = 6.3 Hz, 2H, H₂-5'), 3.46 (t, J = 6.6 Hz, 2H, H₂-6'), 3.39 – 3.33 (m, 2H, H₂-1), 3.15 (td, J = 12.5, 5.0 Hz, 1H, H-1'b), 1.99 – 1.88 (m, 1H, H-2'a), 1.84 – 1.72 (m, 1H, H-2'b), 1.68 – 1.66 (m, 2H, H₂-4'), 1.58 (dt, J = 8.0, 6.4 Hz, 2H, H₂-7'), 1.55 – 1.45 (m, 2H, H₂-3'), 1.41 – 1.27 (m, 12H, H₂-8' – H₂-13'), 0.93 (t, J = 7.1 Hz, 3H, H₃-14'). ^{13}C NMR (150 MHz, MeOD) δ 72.3 (C-5), 71.7 (C-6'), 71.4 (C-3), 71.0 (C-5'), 67.1 (C-4), 64.7 (C-2), 56.6 (C-6), 56.6 (C-6*), 52.7 (C-1'), 49.5 (C-1), 32.7 (C-9'), 30.4 (C-7'), 30.3, 30.2, 30.0 (C-10', C-11', C-12'), 29.8 (C-4'), 26.9 (C-8'), 25.8 (C-2'), 24.2 (C-3'), 23.3 (C-13'), 14.1 (C-14'). $[\alpha]^{20}_{\text{D}}$ = -0.2 (c = 0.07, MeOH). IR/cm⁻¹: 3292, 2924, 2856, 1676, 1425, 1205, 1134, 1055. HRMS: found 406.31623 $[\text{C}_{21}\text{H}_{43}\text{NO}_6+\text{H}]^+$, calculated for $[\text{C}_{21}\text{H}_{43}\text{NO}_6+\text{H}]^+$ 406.31631.

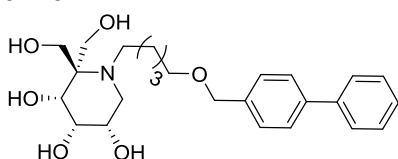
5-C-Hydroxymethyl-N-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-allonojirimycin (**125**):



9 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy)pentane (0.31 mmol) was subjected to general alkylation procedure with to provide **125** (13.8 mg, 0.04 mmol, yield 20%). ^1H NMR (400 MHz, MeOD) δ 4.21 (d, J = 14.3 Hz, 1H, H-6a), 4.11 (t, J = 2.9 Hz, 1H, H-3), 4.00 (d, J = 12.1 Hz, 1H, H-6*a), 3.98 – 3.94 (m, 1H, H-2), 3.92 (d, J = 12.4 Hz, 1H, H-6*b), 3.92 (d, J = 3.2 Hz, 1H, H-4), 3.90 (d, J = 14.8 Hz, 1H, H-6b), 3.65 (td, J = 12.4, 5.0 Hz, 1H, H-1'a), 3.47 (t, J = 6.2 Hz, 2H, H₂-5'), 3.42 – 3.38 (m, 2H, H₂-1), 3.22 – 3.13 (m, 1H, H-1'b), 3.10 (s, 2H, H₂-6'), 2.01 – 1.89 (m, 1H, H-2'a), 1.88 – 1.73 (m, 1H, H-2'b), 1.67 (dt, J = 7.9, 6.4 Hz, 2H, H₂-4'), 1.58 – 1.48 (m, 2H, H₂-3'), 0.93 (s, 9H, 3 x CH₃). ^{13}C NMR (100 MHz, MeOD) δ 81.1 (C-6'), 71.3 (C-5), 70.6 (C-5'), 70.3 (C-3), 66.2 (C-4), 63.7 (C-2), 55.7, 55.7 (C-6, C-6*), 51.7 (C-1'), 47.2 (C-1), 31.5 (C-7'), 28.9 (C-4'), 25.8 (CH₃), 24.8 (C-2'), 23.3 (C-3'). $[\alpha]^{20}_{\text{D}}$ = -0.3 (c = 0.28, MeOH). IR/cm⁻¹: 3675, 2971, 1672, 1393, 1202, 1066. HRMS: found 350.25347 $[\text{C}_{17}\text{H}_{35}\text{NO}_6+\text{H}]^+$, calculated for $[\text{C}_{17}\text{H}_{35}\text{NO}_6+\text{H}]^+$ 350.25371.

5-C-Hydroxymethyl-N-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-allonojirimycin (126):

9 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.29 mmol) was subjected to general alkylation procedure to provide **126** (9.5 mg, 0.022 mmol, yield 11%). ^1H NMR (400 MHz, MeOD) δ 4.21 (d, J = 14.2 Hz, 1H, H-6a), 4.10 (t, J = 2.9 Hz, 1H, H-3), 3.98 (d, J = 12.4 Hz, 1H, H-6*a), 3.96 – 3.92 (m, 1H, H₂-2), 3.91 (d, J = 12.4 Hz, 1H, H-6*b), 3.91 (d, J = 2.8 Hz, 1H, H-4), 3.90 (d, J = 14 Hz, 1H, H-6b), 3.64 (td, J = 12.3, 4.9 Hz, 1H, H-1'a), 3.44 (t, J = 6.2 Hz, 2H, H₂-5'), 3.41 – 3.35 (m, 2H, H₂-1), 3.22 – 3.10 (m, 1H, H-1'b), 1.97 (t, J = 3.2 Hz, 3H, 3 x CH₂ ada), 1.97 – 1.90 (m, 1H, H₂-2'a), 1.80 – 1.68 (m, 6H, 3 x CH₂ ada), 1.74 – 1.69 (m, 1H, H-2'b), 1.70 – 1.62 (m, 2H, H₂-4'), 1.59 (d, J = 2.9 Hz, 6H, 3 x CH₂ ada), 1.56 – 1.44 (m, 2H, H-3'). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (C-6'), 71.3 (C-5), 70.7 (C-5'), 70.3 (C-3), 66.1 (C-4), 63.7 (C-2), 55.6 (C-6), 55.6 (C-6*) 51.7 (C-1'), 48.3 (C-1), 39.4 (CH₂ ada), 36.9 (CH₂ ada), 33.8 (C_q ada), 28.8 (C-4'), 28.3 (CH ada), 24.8 (C-2'), 23.3 (C-3'). $[\alpha]^{20}_{\text{D}}$ = -0.1 (c = 0.19, MeOH). IR/cm⁻¹: 3675, 2988, 1673, 1394, 1205, 1131, 1066. HRMS: found 428.30043 [C₂₃H₄₁NO₆+H]⁺, calculated for [C₂₃H₄₁NO₆+H]⁺ 428.30066.

5-C-Hydroxymethyl-N-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-allonojirimycin (127):

9 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **127** (2.8 mg, 0.0062 mmol, yield 3%). ^1H NMR (600 MHz, MeOD) δ 7.65 – 7.57 (m, 4H, H_{Ar} BiPh), 7.43 (d, J = 8.0 Hz, 4H, H_{Ar} BiPh), 7.34 (d, J = 7.4 Hz, 1H, H_{Ar} BiPh), 4.56 (s, 2H, H-6'), 4.17 (d, J = 14.3 Hz, 1H, H-6a), 4.07 (t, J = 2.9 Hz, 1H, H-3), 3.96 (d, J = 12.2 Hz, 1H, H-6b), 3.92 – 3.89 (m, 1H, H-2), 3.90 (d, J = 14.4 Hz, 1H, H-6*a), 3.88 (d, J = 3 Hz, 1H, H-4), 3.86 (d, J = 13.8 Hz, 1H, H-6*b), 3.64 – 3.59 (m, 1H, H-1'a), 3.56 (t, J = 3.56, 2H, H₂-5'), 3.37 – 3.32 (m, 2H, H₂-1), 3.17 – 3.10 (m, 1H, H-1'b), 1.97 – 1.88 (m, 1H, H-2'a), 1.80 – 1.73 (m, 1H, H-2'b), 1.74 – 1.68 (m, 2H, H₂-4'), 1.59 – 1.46 (m, 2H, H₂-3'). ^{13}C NMR (150 MHz, MeOD) δ 142.1, 141.9 (C_q Bn), 138.8, 129.9, 129.4, 128.4, 128.0, 127.9 (C_{Ar} BiPh), 73.7 (C-6'), 71.8 (C-3), 71.0 (C-5'), 67.5 (C-4), 65.1 (C-2), 62.6 (C-5), 57.0 (C-6), 56.9 (C-6*), 53.1 (C-1'), 49.9 (C-1), 30.2 (C-4'), 26.2 (C-2'), 24.7 (C-3'). $[\alpha]^{20}_{\text{D}}$ = +0.54 (c = 0.06, MeOH). IR/cm⁻¹: 3337, 2928, 2863, 1738, 1673, 1442, 1365, 1205, 1130. HRMS: found [C₂₅H₃₅NO₆+H]⁺ 446.25357, calculated for [C₂₅H₃₅NO₆+H]⁺ 446.25371.

References:

1. Wennekes, T.; Meijer, A. J.; Groen, A. K.; Boot, R. G.; Groener, J. E.; van Eijk, M.; Ottenhoff, R.; Bijl, N.; Ghauharali, K.; Song, H.; O'Shea, T. J.; Liu, H. L.; Yew, N.; Copeland, D.; van den Berg, R. J.; van der Marel, G. A.; Overkleeft, H. S.; Aerts, J. M. Dual-action lipophilic iminosugar improves glycemic control in obese rodents by reduction of visceral glycosphingolipids and buffering of carbohydrate assimilation. *J. Med. Chem.* **2010**, *53*, 689-698.
2. Pawar, N. J.; Parihar, V. S.; Chavan, S. T.; Joshi, R.; Joshi, P. V.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. α -Geminal dihydroxymethyl piperidine and pyrrolidine iminosugars: synthesis, conformational analysis, glycosidase inhibitory activity, and molecular docking studies. *J. Org. Chem.* **2012**, *77*, 7873-82.
3. Muhizi, T.; Grelier, S.; Coma, V. Synthesis and antibacterial activity of aminodeoxyglucose derivatives against listeria innocua and salmonella typhimurium. *J. Agric. Food Chem.* **2009**, *57*, 8770-8775.

4. Kilaas, L.; Anthonsen, T. Synthesis of Some C-5 branched hexopyranoses. *Acta Chem. Scand.* **1992**, *46*, 994-999.
5. Hung, S. C.; Wang, C. C.; Thopate, S. R. Efficient synthesis of L-altrose and L-mannose. *Tetrahedron Lett.* **2000**, *41*, 3119-3122.
6. Khan, A. T.; Khan, M. M.; Adhikary, A. Tetrabutylammonium tribromide (TBATB): a mild and efficient catalyst for *O*-isopropylidenation of carbohydrates. *Carbohydr. Res.* **2011**, *346*, 673-677.
7. van Weely, S.; van Leeuwen, M. B.; Jansen, I. D. C.; Debruijn, M. A. C.; Brouwerkelder, E. M.; Schram, A. W.; Clarasamiranda, M.; Barranger, J. A.; Petersen, E. M.; Goldblatt, J.; Stotz, H.; Schwarzmamm, G.; Sandhoff, K.; Svennerholm, L.; Erikson, A.; Tager, J. M.; Aerts, J. M. F. G. Clinical phenotype of gaucher disease in relation to properties of mutant glucocerebrosidase in cultured fibroblasts. *Biochim. Biophys. Acta* **1991**, *1096*, 301-311.
8. Overkleeft, H. S.; Renkema, G. H.; Neele, J.; Vianello, P.; Hung, I. O.; Strijland, A.; van der Burg, A. M.; Koomen, G. J.; Pandit, U. K.; Aerts, J. M. F. G. Generation of specific deoxynojirimycin-type inhibitors of the non-lysosomal glucosylceramidase. *J. Biol. Chem.* **1998**, *273*, 26522-26527.
9. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR chemical shifts of trace impurities: common laboratory solvents, organics, and gases in deuterated solvents relevant to the organometallic chemist. *Organometallics* **2010**, *29*, 2176-2179.