Lipophilic iminosugars : synthesis and evaluation as inhibitors of glucosylceramide metabolism

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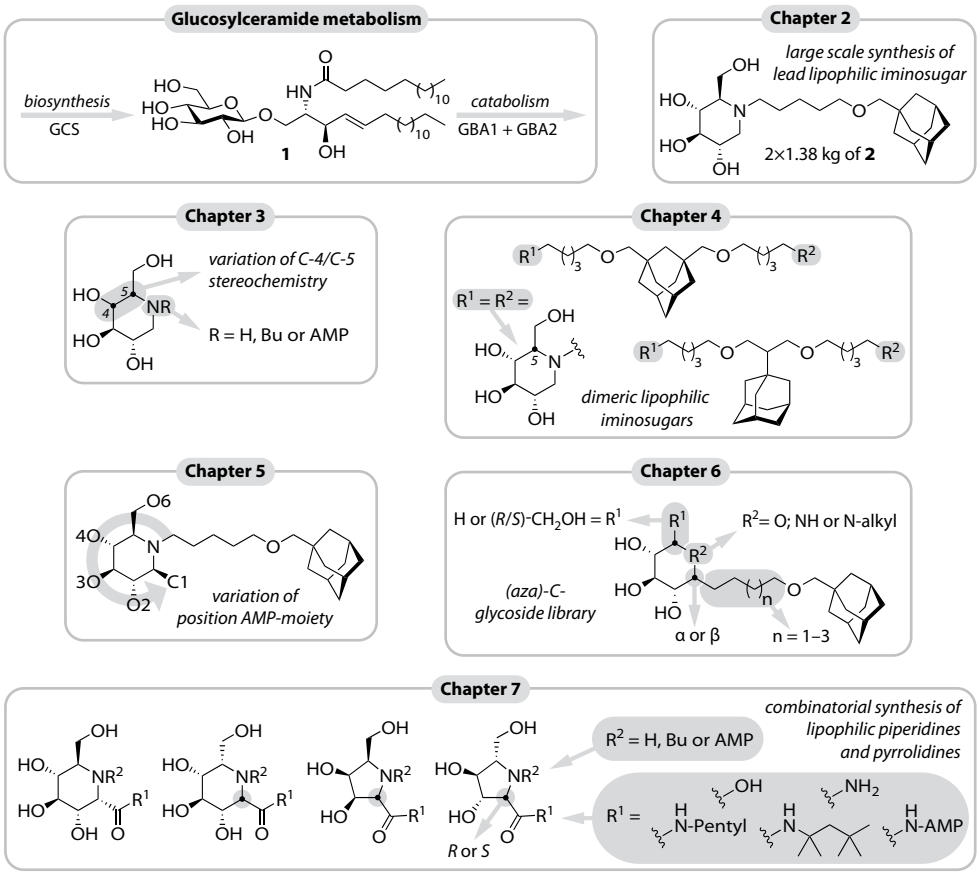
8 Summary, Work in Progress and Prospects

Summary

The primary goal of the research described in this thesis was to develop selective inhibitors for each of the three enzymes associated with glucosylceramide metabolism (Figure 1). Glucosylceramide (**1**) and its more complexly glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho)physiological processes in humans. The exact functions and influence of GSLs in these processes however is often still not fully understood. Manipulation of the cellular levels of GSL is one of the ways to investigate their functions. Control of GSL levels can be achieved by targeted inhibition of the enzymes that carry out their biosynthesis and degradation that is their metabolism. The enzymes involved in the metabolism of **1** are an ideal target to accomplish this, because **1** represents the most basic GSL from which almost all more complex GSLs are made in their biosynthesis. Consequently, **1** also represents the substrate in the final step of the degradation of most GSLs. Biosynthesis of **1** is carried out by the glycosyltransferase, glucosylceramide synthase (GCS). The primary catabolism of **1** is achieved by the glycosidase, glucocerebrosidase (GBA1). A second glycosidase, β-glucosidase 2 (GBA2), is also capable of cleaving the glycosidic bond in **1**, but has an unknown function as of yet. Lipophilic iminosugar **2** is a known potent inhibitor of all three these enzymes, but also inhibits several other glycosidases not involved in the metabolism of **1** (Figure 1 and Table 1). More selective inhibitors for each of the three enzymes are needed in order to achieve more accurate

control of the metabolism of **1**. Additionally, the effects on biological processes resulting from selective inhibition of one of the enzymes will be better interpretable due to a decrease in side effects. In this study, **2** was chosen as the lead compound for developing more selective inhibitors through the design, synthesis and evaluation of analogs.

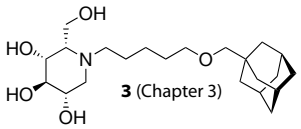
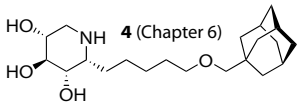
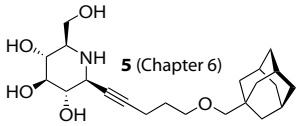
Figure 1. Overview of glucosylceramide metabolism and the research chapters presented in this thesis.



The general introduction of this thesis (**Chapter 1**) discusses the biological background of the study from a historical point of view. First, the metabolism of GSLs is discussed with a focus on GCS, GBA1 and GBA2. Next, the known functions of GSLs in health and disease are discussed together with the therapeutic uses of inhibitors of the metabolism of **1** in treating various GSL related diseases. Finally, an overview of all currently known inhibitors of GCS, GBA1 and GBA2 is provided. The here presented study started with the development and optimization of a route for the large-scale synthesis of **2** in order to obtain a sufficient supply of **2** needed for the principal biological studies (**Chapter 2**; Figure 1). One of these studies investigated the effect of **2** on improvement of glycemic control in type 2 diabetes animal models under the influence of **2**. The research described in **Chapter 3** investigated the mechanism by which **2** achieves this. Evaluation of

derivatives of **2** with altered C-4/C-5 stereochemistry and *N*-alkylation showed that the C-5 epimerized L-*ido*-analogue **3** is a more selective inhibitor of GCS (Table 1). Head to head comparison of this **3** and **2** in rodent models of type 2 diabetes revealed that the improvement of insulin resistance by **2** is due to its dual action as both an inhibitor of GCS and intestinal glycosidases. The synthesis of dimeric derivatives of **2** and **3** is described in **Chapter 4**. Four distinct dimeric compounds were evaluated for bivalent-type inhibition of GCS, GBA1 and GBA2. This was found not to be the case, but all compounds did still showed appreciable inhibition of these enzymes. **Chapter 5** describes the synthesis of derivatives of **2** in which the 5-(adamantan-1yl-methoxy)-pentyl (AMP) moiety is moved to five alternate positions on the 1-deoxynojirmycin ring. Their evaluation showed that moving the AMP moiety to alternate positions causes the loss of inhibition of GCS except in the case of the β-aza-*C*-1-glycoside derivatives. In **Chapter 6**, the structure–activity relationship (SAR) of these aza-*C*-glycoside derivatives was further investigated through the synthesis of a small library. This showed that the β-AMP derivative from chapter 5 already represented the optimal GCS inhibitor for this class and that α-D-*xylo*-derivatives are very potent and selective GBA1 inhibitors (*e.g.* **4** in Table 1). β-Aza-*C*-1-glycoside **5** proved to be a selective inhibitor of GBA2.

Table 1. Enzyme inhibition profiles of **2** and optimized derivatives: IC_{50} values in μM.

Compound	GCS	GBA1	GBA2	Non-related glycosidases
Lead lipophilic iminosugar **2**	0.2	0.2	0.001	0.4–35
 **3** (Chapter 3)	0.1	2	0.001	> 100
 **4** (Chapter 6)	> 10	0.001	10	≥ 100
 **5** (Chapter 6)	> 10	20	0.075	≥ 100

The research described in the chapters leading up to chapter 7 mainly relied on long linear synthetic routes to prepare the various target compounds. In a different approach, the tandem Staudinger/aza-Wittig/Ugi three-component reaction was used to prepare four diverse libraries of pyrrolidine and piperidine iminosugars in a combinatorial fashion (**Chapter 7**). Evaluation of these libraries yielded several inhibitors of GBA1 and GBA2 and a GCS inhibitor. The second part of this **Chapter (8)** presents work in

progress on new classes of lipophilic iminosugar inhibitors of GCS, GBA1 and GBA2. It also discusses some prospects for the development of inhibitors and their applications for future research.

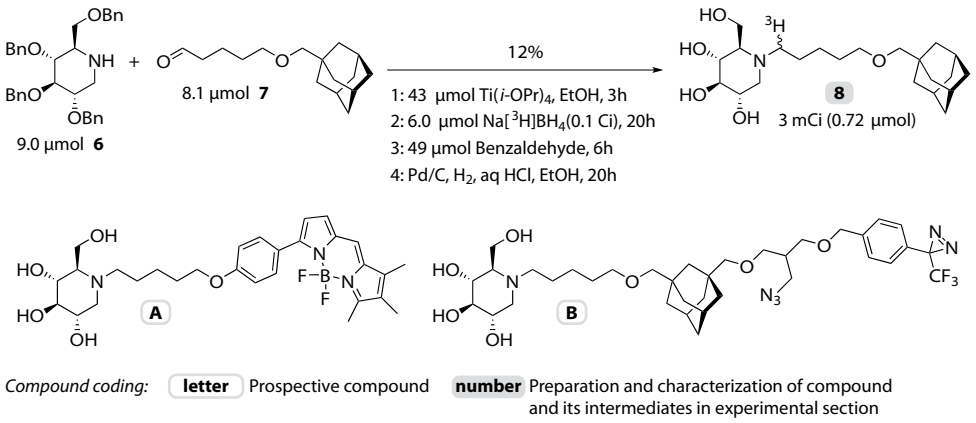
The research described in this thesis has resulted in many novel inhibitors of GCS, GBA1 and GBA2, among which several that improve upon the inhibition profile of lead compound **2** (Table 1). A remaining challenge here lies in the development of a lipophilic iminosugar that solely inhibits GCS without also inhibiting GBA2. The successful use of lipophilic iminosugars in type 2 diabetes models and the partial elucidation of their mechanism of action therein provide prospects for their development towards therapeutics for diabetes type 2. Finally, the evaluation of all the here presented iminosugars for inhibition of GCS, GBA1, GAB2 and several other relevant glycosidases has resulted in extensive additional knowledge on the selectivity of lipophilic iminosugar based inhibitors in general.

Work in Progress and Prospects

The research described in this thesis has led to the development of several potent and selective inhibitors of GCS, GBA1 or GBA2. As discussed in Chapter 1 such compounds hold potential for the treatment of various diseases and as small-molecule tools in the study of GSL functioning. The next stage in the research of these lipophilic iminosugars and a way to facilitate both their potential clinical development and their functionality in fundamental research is to adapt them to molecular probes. These probes can be used to more closely study the behavior of the inhibitor itself in the body and its targets. A pilot study in this direction has already led to the development of probe **8** (Scheme 1). This tritium ($t_{½}$ = 12.3 years) labeled version of lead compound **2** can be used in animal studies to determine with high accuracy and sensitivity the lifetime and distribution of **8** in the body after administration. The use of $Na[^3H]BH_4$ to reduce the imine of **6** and **7** in its synthesis also represents an economic alternative to the use of $Na[^3H]CNBH_3$ by Butters *et al.* in the preparation of similar tritiated labels.[1]

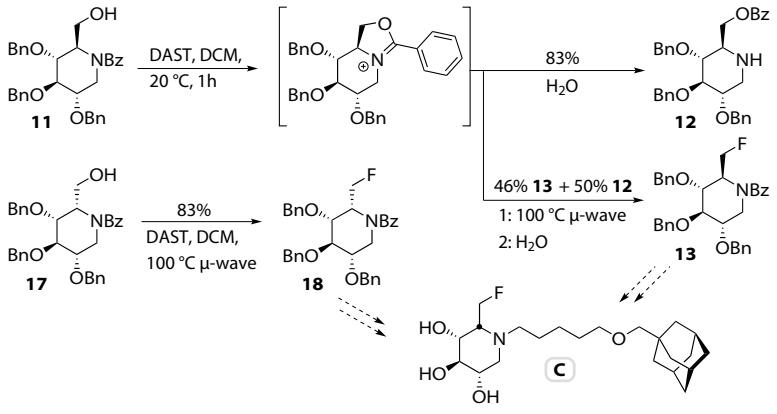
Swapping the adamantane group in **2** for a hydrophobic and fluorescent BODIPY would – if still an inhibitor of the targeted enzymes – produce visual probe **A** (Scheme 1) that could be used to study the localization of lipophilic iminosugars in various cells and tissues.[2] Finally, it would be helpful to investigate more precisely which proteins have an affinity for lipophilic iminosugar based on **2**. The dimeric compounds of Chapter 4 have shown that attachment of a substantial second group to the adamantane does not abolish inhibition of the target enzymes. This fact might be used in the development of probe **B** (Scheme 1) that is equipped with a diazirine photophore.[3] In a living cell or cell lysate this group can be activated to create a nitrene that creates a covalent bond with the protein to which **B** is bound. The azide in **B** can then be used as a post labeling tag to visualize or isolate these proteins as has been successfully demonstrated in various proteomics studies.[4-6]

Scheme 1. Synthesis of tritiated probe **8** and structure of potential probes **A** and **B**.



Although several promising compounds with improved selectivity for one of the three enzymes have been developed during the research described in the previous chapters there are many possibilities left to explore. In Chapter 3 it was revealed that epimerization of the C-5 position in **2** produced a more potent and selective GCS inhibitor. However, this derivative also still inhibited GBA1 and GBA2. A study is ongoing to further explore the SAR of the C-5 and C-6 position of **2** with respect to GCS, GBA1 and GBA2 inhibition. One target herein is to evaluate C-6 fluorinated derivatives (**C**) of **2** and its L-*ido* epimer (**3**) (Scheme 2). Introduction of a fluorine atom has found widespread application in drug development in enhancing binding and selectivity in potential pharmaceuticals.

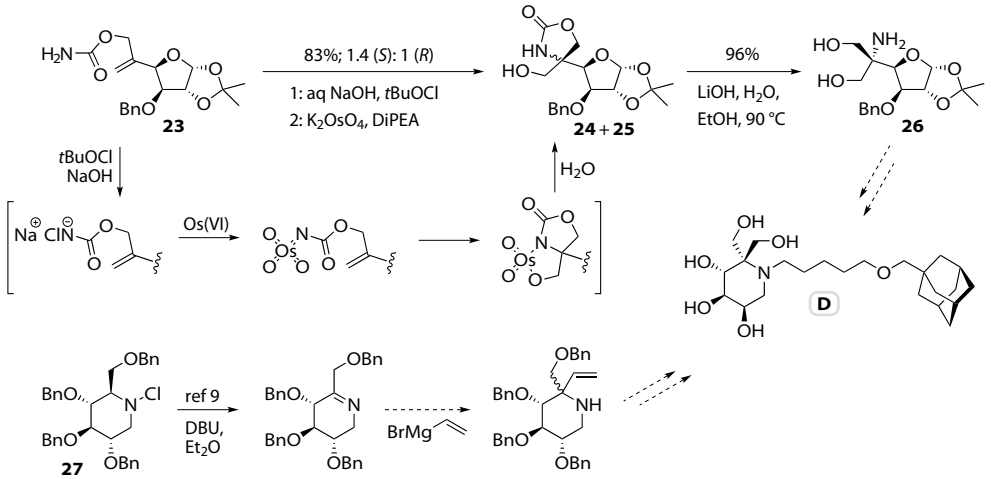
Scheme 2. Synthesis of C-6 fluorinated building blocks **13** and **18** and general structure of target (**C**).



Treatment of building block **11** with DAST at rt resulted in efficient but unwanted benzoyl migration to give **12** that presumably proceeds via an oxazolinium intermediate (Scheme 2).[7] Treatment of **17** with DAST at room temperature only led to retrieval of the starting material. However, heating **11** or **17** to a 100 °C in the presence of DAST did produce fluorinated **13** and **18** that with additional steps can lead to the target derivatives (**C**).

Another C-5 derivative of **2** in development is **D** that contains two hydromethylene groups (Scheme 3). A tethered aminohydroxylation was chosen to simultaneously introduce the required C-5 amino and additional C-5 hydroxymethylene onto a D-glucose starting material.[8] To this end the allylic primary carbamate **23** was prepared in 37% yield over 8 steps from diacetonglucose. In a one-pot procedure the amide of **23** is first chlorinated and deprotonated to yield an intermediate that reacts with and oxidizes the subsequently added potassium osmate (VI) to produce a tethered osmium(VIII)tetraoxide intermediate. This intermediate underwent intramolecular aminohydroxylation and hydrolysis to produce a diastereoisomeric mixture of **24** and **25** in 83% yield. Hydrolysis of the cyclic carbamate produced **26** that with a few additional steps might be advanced to target **D**. Alternatively, C-5 selective elimination of chloro-amine **27**[9] as reported by Davis *et al.* and a subsequent Grignard on the cyclic imine with vinyl magnesiumbromide might represent a quicker route to **D**.

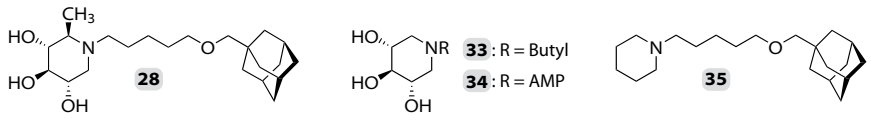
Scheme 3. Synthesis of a C-5 bis(hydroxymethylene)derivative (**D**) of **2**.



6-Deoxy derivative **28** was isolated as a byproduct in the research described in Chapter 2 and has since been analyzed in an enzyme assay for inhibition of GCS, GBA1 and GBA2 (Figure 2 and Table 2 on page 288). These results show that removal of the C-6 hydroxyl has relatively little impact on the inhibition of the three enzymes. D-*Xylo*-derivatives **33** and **34** that completely lack the C-5 hydroxymethylene were synthesized and they no longer inhibited GCS but still inhibited GBA1 and GBA2 (Figure 2 and Table 2).

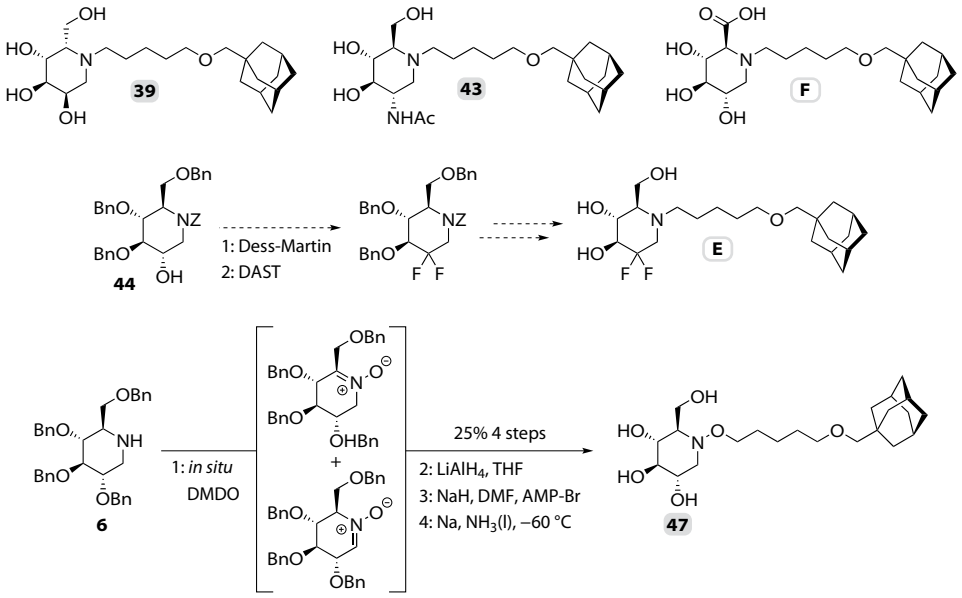
These results indicate that further exploration of deoxygenated derivatives of **2** on other positions of the 1-deoxynojirimycin ring might represent a handle to modify the selectivity of inhibition of GCS, GBA1 and GBA2. The fact that piperidine derivative **35** is still capable of inhibiting GBA1 shows that this enzyme tolerates a lot of structural modifications in this respect (Figure 2 and Table 2).

Figure 2. Structures of C-6-deoxy (**28**), D-*xylo* (**33** and **34**); and piperidine (**35**) derivatives of **2**.



The substitution pattern can of course also be explored beyond the C-4/C-5 position of Chapter 3. For a more comprehensive SAR of the stereochemistry of the iminosugar core in **2**, all remaining twelve stereochemical possibilities should also be synthesized. A start in this direction was made by the synthesis and evaluation of derivative **39** with L-*gulo*-stereochemistry that showed diminished inhibition of GCS, GBA1 and GBA2 (Scheme 4 and Table 2).

Scheme 4. Derivatives of **2** with an altered substitution pattern of the iminosugar core and synthesis of **47**.



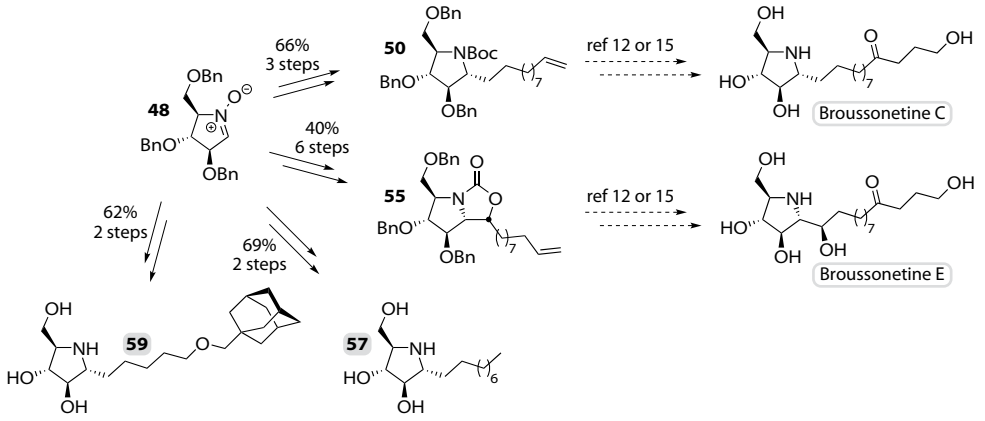
Alternatively, leaving the stereochemistry of **2** unchanged and introducing an acetamide at C-2 (**43**) abolished all inhibition of these enzymes. Finally, another variation of the substitution pattern that should be easily accessible is a difluorinated derivative (*e.g.* **E** in Scheme 4). These can be made straightforward by oxidation and DAST treatment of the C-2 (**44** in Scheme 4), C-3, C-4 and C-6 hydroxyl building blocks from Chapter 5.

The presence of a basic nitrogen function is a prerequisite for inhibition of GCS, GBA1 or GBA2. Therefore modifications at this site could also have an effect on inhibition. For a pilot study in this area aminoxy-derivative **47** was designed, which should posses a less basic nitrogen function. Its synthesis commenced with the generation of the mixed C1-N/C-5-N cyclic nitrones by oxidation of **6** as reported by van den Broek (Scheme 4).[10]

Subsequent reduction of this mixture yielded a hydroxylamine intermediate that could be alkylated and debenzylated by a Birch reduction to provide target **47**. Evaluation of **47** in an enzyme assay showed substantial loss in inhibitory potency for all three enzymes and no improvement in selectivity. Another potential target with a modified nitrogen could be C-6 oxidized **F** that would protonate the nitrogen function and form an intramolecular salt (Scheme 4). A similar compound from Chapter 7, an α-aza-C1-carboxylate of **2**, proved to still inhibit GCS, GBA1 and GBA2.

The results from Chapter 7 have shown that lipophilic pyrrolidine iminosugars can also be inhibitors of GCS, GBA1 and probably also GBA2. A specific class of plant alkaloids and known glycosidase inhibitors represents a naturally occurring source of lipophilic pyrrolidines. They are called Broussonetines and have been isolated from the Asian indigenous *Broussonetia kazinoki* tree that is related to the mulberry tree.[11] Up till now total syntheses for only two of the over thirty known broussonetines have been reported in literature.[12-15] In order to evaluate this class of compounds as inhibitors of GCS, GBA1 and GBA2 it was decided to synthesize two representative members, Broussonetine C and E. Known cyclic nitrone **48** was chosen as a novel and convenient building block for the start of the total synthesis of both.[16-18]

Scheme 5. Synthesis of Broussonetine C and E intermediates **50** and **55**; and Broussonetine analogs **57** and **59**.

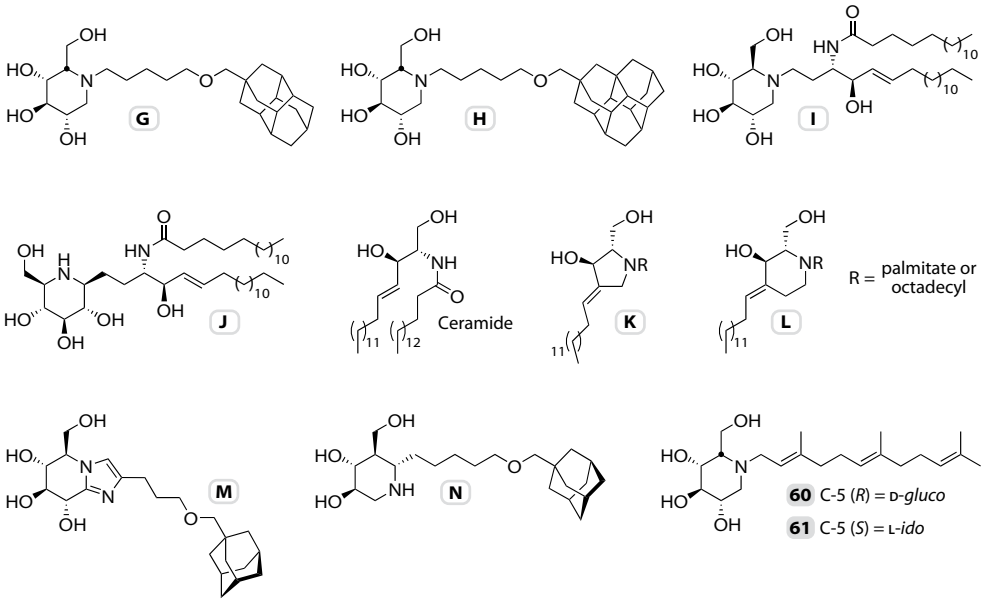


Reaction of **48** with undecenyl magnesiumbromide stereoselectively produced an intermediate hydroxylamine that could be reduced and protected as Boc-carbamate **50** (Scheme 5). This intermediate will be further transformed into Broussonetine C via either of two previously reported syntheses of Broussonetine C that share this intermediate. A similar sequence of reactions with **48** produced a vinyl intermediate that was successively cleaved by ozonolysis, subjected to a second Grignard and transformed into cyclic carbamate **55**. This intermediate will be transformed into Boussontine E via the same steps as planned for Broussonetine C from **50**. Reaction of **48** with either nonyl magnesiumbromide or the acetylene anion from 5-(adamantan-1yl-methoxy-pentyn and

subsequent hydrogenolysis produced Broussonetine derivatives **57** and **59** (Scheme 5). These were evaluated as inhibitors of the three enzymes and both proved to be inhibitors of GBA1 with **59** also moderately inhibiting GCS (Table 2).

With the exception of Chapter 7, the research described in this thesis has mostly left the AMP hydrophobic tail of lead compound **2** untouched. Several alternatives to the pentyl spacer and adamantane moiety have already been investigated in previous studies, but provided less potent or non-active inhibitors. As discussed in Chapter 4, one of the functions of the adamantane group in **2** might be to target, concentrate and stabilize the inhibitor in the cellular membrane by binding hydrophobic pockets created by unsaturated lipids. Synthesis and evaluation of the more bulky diamantine and triamantane derivatives **G** and **H** might function to further elucidate this (Figure 3).

Figure 3. Structures of derivatives of **2** with an alternate hydrophobic tail or iminosugar core.



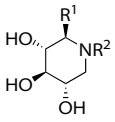
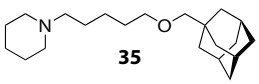
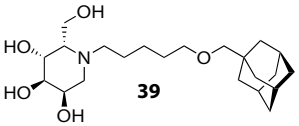
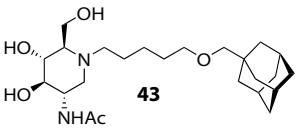
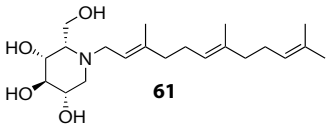
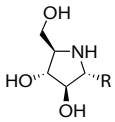
The AMP moiety should however not be viewed as the optimal or only suitable option for a hydrophobic tail. *N*-Alkylation of 1-deoxynojirmycin and L-*ido*-1-deoxynojirmycin with a *trans*,*trans*-farnesylbromide produced **60** and **61** that upon evaluation proved to inhibit GCS, GBA1 and GBA2 to an almost similar extent as **2** and **3** (Table 2).

Another direction for the development of other hydrophobic tails for **2** and new inhibitors in general lies in more closely mimicking the natural substrates and products of the three targeted enzymes. If the 1-deoxynojirmycin core in **2** is viewed as a mimic of glucose and the AMP-moiety as a mimic of ceramide than the development of derivatives of **2** with a ceramide tail such as **I** or **J** might provide new inhibitors (Figure 3). On the other hand if the *N*-alkylated iminosugar as a whole is viewed as a ceramide mimic – as advocated by Butters – then ceramide mimicking structures such as pyrrolidine **K** or

piperidine **L** might represent targets for the further development of inhibitors.

Extensive kinetic analysis studies of the inhibition of glycosidases by 1-deoxynojirmycin-based iminosugars have shown that they are not true transition-state mimics.[19] To achieve this and the associated tighter binding of the active site an iminosugar requires sp^2-hybridization at its pseudo anomeric center (C-1). Modification of **2** to incorporate this as in **M**, its design based on work by Vasella,[20] could result in more potent and selective inhibitors of GBA1 and GBA2 (Figure 3). Finally, lipophilic isofagomines have so far resulted in the most potent inhibitors of GBA1 reported to date.[21] Based on their design, isofagomine **N** might represent an interesting target for a GBA1 inhibitor (Figure 3).

Table 2. Enzyme inhibition assay results for : apparent IC_{50} values in μM.[a,b]

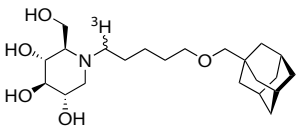
Compound	GCS *in vivo*	GBA1	GBA2	Lysosomal α-glucosidase
 **2**: $R^1 = CH_2OH$; R^2 = AMP	0.2	0.2	0.001	0.4
28: $R^1 = CH_3$; R^2 = AMP	0.8	0.33	0.03	150
33: R^1 = H (D-*xylo*); R^2 = Butyl	-	500	6.0	-
34: R^1 = H (D-*xylo*); R^2 = AMP	> 30	2.2	0.8	-
47: $R^1 = CH_2OH$; R^2 = -O-AMP	20; 35%	75	0.5	500
60: $R^1 = CH_2OH$; R^2 = *trans*,*trans*-Farnesyl	0.35	0.28	0.013	3.7
 **35**	> 100	11	-	3.7
 **39**	15	100	2	> 1000
 **43**	> 100	160	100	> 1000
 **61**	0.15	5	0.011	450
 **57**: R = Nonyl	> 100	6.5	50	> 1000
59: R = AMP	60	3.0	-	> 1000

[a]AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b]Except for GCS all other enzyme assays are *in vitro*.

Experimental section

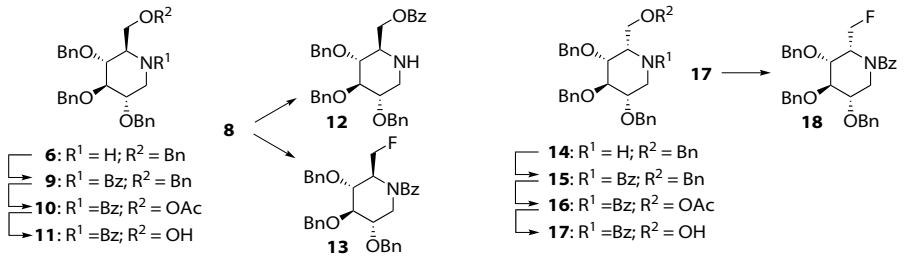
General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. R_F values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt% in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 µm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Low resolution mass spectra were recorded on a Perkin Elmer Sciex API 165 equipped with an electron spray interface (ESI). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

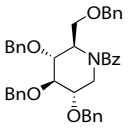
General procedure A – Hydrogenolysis at atmospheric H_2 pressure: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (~50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 minutes and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. In the case of incomplete reduction hydrogenolysis was repeated after workup and coevaporation (3×) with 'acetaldehyde free' EtOH), at atmospheric pressure in the presence of Pd/C (~50 mg) and Pd black (~5 mg) or at higher H_2 pressure in a Parr-apparatus. *Hydrogenolysis in Parr-apparatus*: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (50 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h.



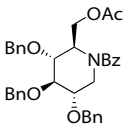
(1'-*R*/*S*)-*N*-[5-(Adamantan-1-yl-methoxy)-1-tritium-pentyl]-1-deoxynojirimycin (8). Stock solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 104.8 mg in 2 mL EtOH; synthesis described in Chapter 2) and 5-(adamantan-1yl-methoxy)-pentanal (**7**: 38.1 mg in 1.7 mL EtOH, synthesis described in Chapter 2) were prepared and stored under argon (ethanol absolute AR Biosolve; distilled from zinc/KOH and stored on 3Å molecular sieves before use). 90 µL of the stock solutions of **6** (9.0 µmol) and **7** (8.1 µmol) were combined in a vial (Supelco vial, screw top, clear glass, 1.5 mL) with a stirring magnet. Under stirring titanium(IV)isopropoxide (13 µL; 43.2 µmol; 99.999% from Aldrich) was added to the mixture and the vial was flushed with argon and closed with a screw cap. The mixture was stirred for 3 h during which it turned turbid. An ampoule with sodium boro[^{3}H]hydride (purple solid, 100±20 mCi, 6.0±1.2 µmol; 16.7 Ci/mmol ±15% specific activity; MW 39 g/mol; from Amersham Biosciences) was opened and EtOH (60 µ L) was added. The content was transferred to the reaction vial. The ampoule was rinsed with EtOH (1: 60 µL; 2: 30 µL) and both portions were transferred to the reaction vial. The reaction vial was flushed with argon, closed with a screw cap and stirred for 20 h. TLC analysis indicated the formation of the radiolabeled penultimate (R_F penultimate = 0.60; **6** = 0.05; **7** = 0.70; alcohol of **7** = 0.30; TLC eluent: 25% EtOAc in PE; TLC staining: molecular iodine vapour). Benzaldehyde (5 µ L, 49 µmol, ≥99.5% from Fluka) was added to the reaction vial and the reaction mixture was stirred for 6h whilst enclosed. Aqueous 1M HCl (75 µL) and EtOH (200 µL) were added to the vial. The reaction vial was enclosed with a suitable rubber septa and argon gas (from a filled balloon) was bubbled trough the reaction mixture via 0.8 mm needle (0.3 mm needle as outlet) for 10 min (gas from outlet was passed through container with 20 ml water). Palladium on activated charcoal (15 mg, 10% Pd basis from Fluka) was added to the vial and it was enclosed with a new septa. Hydrogen gas was bubbled through the reaction mixture for 10 min via the same method as used for argon. The hydrogen balloon was replaced with a newly filled one, the gas-outlet was removed and the reaction vial was sealed with parafilm. The reaction set-up was left stirring for 20 h after which the balloon and septa were removed. The reaction mixture was filtered over a 2 mL filter syringe fitted with 2 layers of glass fibre material (GF/T from Whatman). The reaction vial was rinsed with MeOH (4×1 mL) and the resulting Pd/C pellet was also rinsed with MeOH (4×1 mL). The combined filtrate was collected in 100 mL round-bottom flask. The flask was placed in a water bath (40 °C) and the content was concentrated by a gentle air-flow. The residue was suspended in 0.2 mL of 10% MeOH in $CHCl_3$ and transferred to a filter syringe (2 mL) that contained packed silica gel (0.8 cm^3 in 10% MeOH in $CHCl_3$ + 5% NH_4OH). The flask was rinsed a further 4 times with the same mixture. The silica gel column was eluted with 30 mL of eluent (10% MeOH in $CHCl_3$ + 5% NH_4OH) and 0.5 mL fractions were collected. The product eluted in fractions 5–16 (as determined by triple spotting and elution on TLC) and was collected in a 100 mL round-bottom flask (R_F **8** = 0.30; TLC eluent: 20% MeOH in $CHCl_3$ + 2% NH_4OH; TLC staining: molecular iodine vapour). The collected fractions were concentrated via the same method as mentioned previously to yield compound **8** as a colourless oil. In cold runs of the above procedure a stock solution of $NaBH_4$ (30 µL, 6.2 µmol in EtOH) was added instead of the radiolabel. This produced cold **2** in yields of 30-40% with a purity of 90–95% as judged by ^{1}H-NMR. A 3 mL DMSO stock solution of **8** was analyzed for radioactivity by performing a scintillation counting of various dilutions in water of the stock solution. From these measurements the activity of the 3 mL DMSO solution of **8** was determined to be 3 mCi ±15%. If it is assumed that a maximum of 25% of the specific activity of the sodium boro[^{3}H]hydride was transferred to **8** then 3 mCi equates to 0.72 µmol of **8** and 12% yield over the two steps. The lower yield might be caused by the extra amount of EtOH (120 µL) needed to transfer the sodium boro[^{3}H]hydride from the ampoule to the reaction vial. The specific activity of **8** is not yet known and can only be determined if the chemical concentration of **8** in the DMSO stock solution is determined by either ^{1}H-NMR or HPLC.

Synthesis of C-6 fluorinated iminosugars 13 and 18:

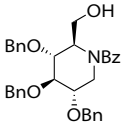




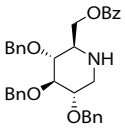
***N*-Benzoyl-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (9).** Benzoylchloride (2.25 mL, 19.38 mmol) was added to a dry solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 6.76 g, 12.92 mmol; synthesis described in Chapter 2) in pyridine (80 mL). The reaction mixture was stirred at rt over a period of 45 min. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 33% EtOAc in PE) to provide **9** (6.52 g, 10.46 mmol) in 80% yield as a colourless oil. R_F = 0.86 (40% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.45 – 7.12 (m, 25H, H_{Ar} Bn/Bz), 4.85 – 3.26 (m, 16H, 4×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6). ^{13}C NMR (150 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.0 (C=O Bz), 138.4, 138.2, 138.1, 138.1 (4×C_q Bn), 136.4 (C_q Bz), 129.3, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn/Bz), 74.1(CH), 73.2, 70.8 (CH_2 Bn), 68.1 (C-6). MS (ESI): found 628.2 $[M+H]^+$, calculated for $[C_{41}H_{41}NO_5+H]^+$ 628.3.



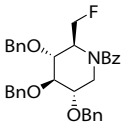
6-*O*-Acetyl-*N*-benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (10). Zinc chloride (13.96 g, 102.4 mmol) was added to a dry solution of **9** (6.42 g, 10.24 mmol) in a mixture of Ac_2O/AcOH (102.4 mL, 2/1, v/v). The reaction mixture was stirred at rt over a period of 20 hr. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. After coevaporation with toluene the residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to afford **10** (5.29 g, 9.12 mmol) in 89% yield as a colourless oil. R_F = 0.17 (25% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.43 – 7.20 (m, 20H, H_{Ar} Bn/Bz), 4.51 (dd, *J* = 7.8, 11.5, 1H, H-6a), 4.73 – 3.26 (m, 13H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, H-6b), 2.01 (s, 3H, CH_3 Ac). ^{13}C NMR (150 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.3 (C=O Bz), 170.6 (C=O Ac), 137.9, 137.8, 137.6 (C_q Bn), 136.1 C_q Bz), 129.3, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4 (CH_{Ar} Bn/Bz), 73.7 (CH), 72.9, 70.7 (CH_2 Bn), 61.6 (C-6), 20.9 (CH_3 Ac).



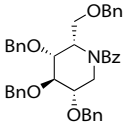
***N*-Benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (11).** A sodium methoxide solution (169 µL, 0.9 mmol; 30 wt%) was added to a dry solution of **10** (5.24 g, 9.04 mmol) in MeOH (90 mL). The reaction mixture was stirred at rt for 20 h. The reaction was quenched by addition of amberlite H^+ resin (IR-50). The reaction mixture was filtered and the resin was rinsed with MeOH (3×5 mL). The combined filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (33% » 67% EtOAc in PE) to produce **11** (2.56 g, 4.77 mmol) in 53% yield as a white crystalline solid. R_F = 0.31 (50% EtOAc in PE). ^{1}H NMR (300 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.46 – 7.06 (m, 20H, H_{Ar} Bn, H_{Ar} Bz), 4.70 – 3.23 (m, 14H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6), 1.67 (s, 1H, OH-6). ^{13}C NMR (75 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.9 (C=O Bz), 138.0, 137.7 (C_q Bn), 135.8 (C_q Bz), 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn/Bz), 74.7 (CH), 73.3, 71.0 (CH_2 Bn), 61.3 (C-6), 58.6 (C-5).



6-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (12). A dry and cooled (0 °C) solution of **11** (107 mg, 0.2 mmol) in DCM (2 mL) was charged with DAST (37 µL 0.3 mmol). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was quenched by addition of MeOH and diluted with EtOAc (20 mL). The organic phase was washed successively with sat aq $NaHCO_3$ (10 mL) and sat aq NaCl (10 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (isocratic 25% EtOAc in PE) to yield **12** (89 mg, 0.17 mmol) in 83% yield as a colourless oil and 7% of starting material **11** (8 mg, 0.02 mmol). R_F = 0.44 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2, 2H, H_{Ar} Bz), 7.51 – 7.10 (m, 18H, H_{Ar} Bn/Bz), 5.01 (d, *J* = 10.8, 1H, C*H*H Bn), 4.93 (d, *J* = 10.9, 1H, C*H*H Bn), 4.86 (d, *J* = 10.8, 1H, CH*H* Bn), 4.68 (d, *J* = 11.3, 1H, C*H*H Bn), 4.65 (d, *J* = 11.3, 1H, CH*H* Bn), 4.62 (d, *J* = 10.9, 1H, CH*H* Bn), 4.57 (dd, *J* = 2.3, 11.2, 1H, H-6a), 4.39 (dd, *J* = 5.3, 11.3, 1H, H-6b), 3.62 (dd, *J* = 8.9, 1H, H-3), 3.53 (ddd, *J* = 5.0, 9.4, 10.4, 1H, H-2), 3.44 (dd, *J* = 8.9, 9.7, 1H, H-4), 3.26 (dd, *J* = 5.1, 12.3, 1H, H-1a), 2.88 (ddd, *J* = 2.4, 5.2, 9.8, 1H, H-5), 2.53 (dd, *J* = 10.3, 12.3, 1H, H-1b), 2.49 – 2.33 (m, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2 (C=O Bz), 138.7, 138.4, 138.0 (C_q Bn), 129.8 (C_q Bz), 129.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4 (CH_{Ar} Bn/Bz), 87.2 (C-3), 80.5 (C-2), 79.5 (C-4), 75.7, 75.2, 72.6 (CH_2 Bn), 64.8 (C-6), 59.1 (C-5), 48.1 (C-1).

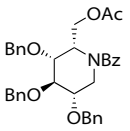


***N*-Benzoyl-2,3,4-tri-*O*-benzyl-6-fluoro-1,6-dideoxynojirimycin (13).** DAST (24 µL, 200 µmol) was added to a dry solution of **11** (54 mg, 100 µmol) in DCM (1 mL) and stirred at rt over a period of 30 min. The reaction mixture was heated in a sealed tube in the microwave at 70 °C for 30 min, after which TLC analysis indicated ~50% conversion into a higher running product. The reaction mixture was heated for an additional 30 min at 100 °C. The reaction mixture was quenched with MeOH, diluted with EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc in PE) to produce **13** (25 mg, 46 µmol) in 46% yield as a colorless oil and **12** (27 mg, 50 µmol) in 50% yield. R_F = 0.90 (1:1; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.53 – 7.16 (m, 20H, H_{Ar} Bn/Bz), 4.98 – 3.22 (m, 14H, 3×CH_2 Bn, CH_2-1, H-2, H-3, H-4, H-5, CH_2-6). ^{13}C NMR (126 MHz, $CDCl_3$) collapsed iminosugar signals δ 172.3, 138.1, 138.0, 137.9, 136.0, 128.7, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 73.7, 73.5, 70.9. MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{34}FNO_4+H]^+$ 540.3.

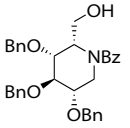


***N*-Benzoyl-2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (15).** Benzoylchloride (2.07 mL, 17.85 mmol) was added to a dry solution of 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin **14** (6.24 g, 11.90 mmol; synthesis described in Chapter 3) in pyridine (70 mL). The reaction mixture was stirred at rt for 20 h. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (2×50 mL), dried ($MgSO_4$) and concentrated. The residue was purified with silica gel column chromatography (25% » 50% EtOAc in PE) to provide **15** (6.43 g, 10.25 mmol) in 86% yield as a light yellow oil. R_F = 0.90 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/0.6) rotamers δ 7.47 – 7.16 (m, 50H, H_{Ar} Bn/Bz a/b), 5.42 – 5.37 (m, 1H, H-5 B), 4.92 – 4.40 (m, 17H, CH_2 Bn/Bz A/B, H-1a A), 4.25 – 4.20 (m, 1H, H-5 A), 3.95 (dd, *J* = 8.1, 10.5, 1H, H-6a B), 3.91 (dd, *J* = 9.2, 1H, H-3 B), 3.85 (dd, *J* = 3.4, 10.5, 1H, H-6b B), 3.76 (dd, *J* = 10.1, 1H, H-6a A), 3.74 – 3.63 (m, 4H, H-3 A, H-4 A, H-1a B, H-4 B), 3.64 (dd, *J* = 3.3, 10.1, 1H, H-6b A), 3.62 – 3.56 (m, 1H, H-2 A), 3.52 (dd, *J* = 6.2, 9.5, 1H, H-4 A), 3.41 – 3.36 (m, 1H, H-2 B), 3.22 (dd, *J* = 11.6, 12.8, 1H, H-1b B), 2.81 (dd, *J* = 11.5, 12.9, 1H, H-1b A). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/0.6) rotamers δ 172.4, 171.5 (C=O Bz A/B), 138.9, 138.8, 138.3, 138.2, 138.0, 137.6 (C_q Bn A/B), 135.9, 135.8 (C_q Bz A/B), 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.7, 127.6, 127.2 (H_{Ar} Bn/Bz A/B), 82.9 (C-3 B), 82.8 (C-3 A), 79.1 (C-4 B), 78.6 (C-4 A), 78.3 (C-2 A), 78.2 (C-2 B), 75.9, 75.8, 73.4, 73.3, 73.2, 73.1, 73.1 (CH_2 Bn A/B), 66.4 (C-6 B), 64.8 (C-6 A), 56.9 (C-5 A), 49.9 (C-5 B), 46.3 (C-1 B), 39.4 (C-1 A). IR ν_{max}(thin film)/ cm^{-1}: 2853,

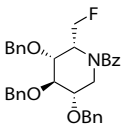
1636, 1541, 1454, 1364, 1256, 1088, 1072, 1026, 733, 694, 652, 611. $[\alpha]^{20}_{D}$: 8.9 (*c* 0.4, $CHCl_3$). MS (ESI): found 628.2 $[M+H]^+$, calculated for $[C_{41}H_{41}NO_5+H]^+$ 628.3.



6-*O*-Acetyl-*N*-benzoyl-2,3,4-tri-*O*-benzyl-L-*ido*-1-deoxynojirimycin (16). Zinc chloride (13.97 g, 102.5 mmol) was added in to a dry solution of **15** (6.41 g, 10.25 mmol) in a mixture of Ac_2O/AcOH (102.5 mL, 2/1, v/v). The mixture was stirred at rt over a period of 24 h. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. After coevaporation with toluene the residue was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide **16** (2.63 g, 4.53 mmol) in 80% yield as a colourless oil. R_F = 0.25 (25% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.49 – 7.11 (m, 40H, H_{Ar} Bn/Bz A/B), 5.51 – 5.45 (m, 1H, H-5 B), 4.96 – 4.68 (m, 10H, CH_2 Bn A/B, H-1a A), 4.63 (dd, *J* = 11.1, 1H, H-6a B), 4.60 – 4.51 (m, 2H, C*H*H Bn A/B, C*H*H Bn A/B), 4.48 (dd, *J* = 2.9, 12.1, 1H, H-6b B), 4.44 (d, 1H, *J* = 11.7, 1H, CH*H* Bn A/B) 4.39 (dd, *J* = 11.2, 1H, H-6a A), 4.32 (dd, *J* = 2.6, 11.9, 1H, H-6b A), 4.30 – 4.24 (m, 1H, H-5 A), 3.73 – 3.67 (m, 3H, H-1a B, H-3 B, H-4 B), 3.62 – 3.55 (m, 2H, H-2 A, H-4 A), 3.40 – 3.33 (m, 1H, H-2 B), 3.18 (dd, *J* = 11.8, 13.1, 1H, H-1b B), 2.83 (dd, *J* = 11.8, 12.8, 1H, H-1b A), 2.06 (s, 3H, CH_3 Ac A/B), 2.03 (s, 3H, CH_3 Ac A/B). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 172.0, 171.7, 171.3, 170.5 (C=O Bz/Ac A/B), 138.7, 138.1, 137.9, 137.8, 137.5 (C_q Bn A/B), 135.5 (C_q Bz A/B), 130.2, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 126.8 (H_{Ar} Bn/Bz A/B), 82.6, 78.5 (C-3 A, C-3 B, C-4 B), 78.1, 78.0 (C-2 A, C-4 A), 77.9 (C-2 B), 76.0, 75.9, 73.3, 73.2 (CH_2 Bn A/B), 59.2 (C-6 B), 59.1 (C-6 A), 56.0 (C-5 A), 50.0 (C-5 B), 45.6 (C-1 B), 39.3 (C-1 A), 21.1, 21.1 (CH_3 Ac A/B). MS (ESI): found 580.1 $[M+H]^+$, calculated for $[C_{36}H_{37}NO_6+H]^+$ 580.3.



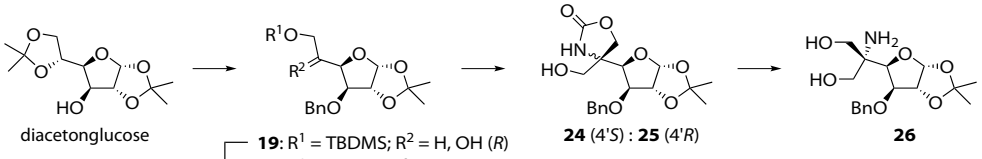
***N*-Benzoyl-2,3,4-tri-*O*-benzyl-L-*ido*-1-deoxynojirimycin (17).** A sodium methoxide solution (82 µL, 0.44 mmol; 30 wt%) was added to a dry solution of **16** (2.53 g, 4.36 mmol) in MeOH (43.6 mL). The reaction mixture was stirred at rt over a period of 20 h. The reaction was quenched by addition of Amberlite H^+ resin (IR-50). The reaction mixture was filtered and the resin was rinsed with MeOH (3×5 mL). The combined filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (33% » 67% EtOAc in PE) to afford **17** (2.16 g, 4.01 mmol) in 92% yield as a white crystalline solid. R_F = 0.40 (50% EtOAc in PE). ^{1}H NMR (600 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.55 – 7.10 (m, 40H, H_{Ar} Bn/Bz A/B), 5.27 – 5.19 (m, 1H, H-5 B), 4.91 – 4.41 (m, 13H, H-1a A, CH_2 Bn A/B), 4.16 – 4.05 (m, 3H, H-6a A, H-4 B, H-6b B), 3.92 (dd, *J* = 9.9, 1H, H-6a B), 3.86 – 3.76 (m, 3H, H-4 A/B, H-5 A, H-6b A), 3.76 – 3.65 (m, 3H, H-1b B, H-3 A, H-3 B), 3.62 – 3.54 (m, 1H, H-2 A), 3.54 – 3.49 (m, 1H, H-4 A/B), 3.48 – 3.39 (m, 1H, H-2 B), 3.13 (dd, *J* = 12.1, 1H, H-1a B), 3.02 (s, 1H, OH-6), 2.77 (dd, *J* = 11.9, 1H, H-1b A). ^{13}C NMR (150 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 172.7, 172.4 (C=O Bz A/B), 138.7, 138.1, 137.8, 137.7, 137.4 (C_q Bn A/B), 135.5, 135.3 (C_q Bz A/B), 128.6, 128.4, 128.1, 128.0, 127.9, 127.7 (CH_{Ar} Bn/Bz A/B), 82.6 (C-3 A/B), 82.4 (C-4 A/B), 79.1 (C-3 A/B), 78.8 (C-4 A/B), 78.1 (C-2 A), 77.8 (C-2 B), 75.8, 75.7, 73.3, 73.3, 73.1, 72.9 (CH_2 Bn A/B), 59.3 (C-6 B), 58.2 (C-5 A), 58.1 (C-6 A), 52.4 (C-5 B), 45.7 (C-1 B), 39.3 (C-1 A).

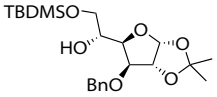


***N*-Benzoyl-2,3,4-tri-*O*-benzyl-6-fluoro-L-*ido*-1,6-dideoxynojirimycin (18).** DAST (24 µL, 200 µmol) was added to a dry solution of **17** (54 mg, 100 µmol) in DCM (1 mL) and stirred at rt over a period of 30 min. The reaction mixture was heated in a sealed tube in the microwave at 70 °C for 30 min, after which TLC analysis indicated ~50% conversion into a higher running product. The reaction mixture was heated for an additional 30 min at 100 °C. The mixture was quenched with MeOH, diluted with EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (25%

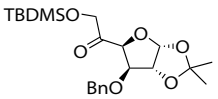
EtOAc in PE) to produce **18** (44 mg, 83 µmol) in 83% yield. R_F = 0.85 (1:1; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of (A/B; 0.8/1) rotamers δ 7.48 – 7.08 (m, 40H), 5.21 (d, *J* = 32.6, 1H, H-5 B), 5.08 – 4.41 (m, 18H, H-1a A, CH_2-6 A (J_{H-F} = 113.2), CH_2-6 B (J_{H-F} = 90.1), CH_2 Bn A/B), 4.15 (d, *J* = 20.8, 1H, H-5 A), 3.89 (dd, *J* = 8.7, 1H, H-3 B), 3.82 – 3.65 (m, 3H, H-1a B, H-3 A, H-4 B), 3.61 – 3.55 (m, 1H, H-2 A), 3.55 – 3.49 (m, 1H, H-4 A), 3.47 – 3.36 (m, 1H, H-2 B), 3.24 (dd, *J* = 12.3, 1H, H-1b B), 2.89 (dd, *J* = 12.1, 1H, H-1b A). ^{13}C NMR (125 MHz, $CDCl_3$) mixture of (A/B; 0.8/1) rotamers δ 172.0, 171.6 (C=O Bz A/B), 138.9, 138.7, 138.4, 138.1, 137.9 (C_q Bn A/B), 135.4, 135.3 (C_q Bz A/B), 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0, 126.8, 126.7, 83.4 (C-3 B), 83.0 (C-3 A), 82.4 (d, J_{C-F} = 174.1, C-6 B), 79.7 (d, J_{C-F} = 171.8, C-6 A), 78.4 (C-4 B), 78.1 (C-2 A, C-4 A), 77.9 (C-2 B), 75.9, 73.8, 73.2, 73.2, 72.5, 72.0 (CH_2 Bn A/B), 57.1 (d, J_{C-F} = 17.9, C-5 A), 50.8 (d, J_{C-F} = 18.2, C-5 B), 47.1 (d, J_{C-F} = 2.2, C-1 B), 39.8 (C-1 A). MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{34}FNO_4+H]^+$ 540.3.

Synthesis of a precursor towards C-5 bis(hydroxymethylene)-1-deoxynojirimycin:

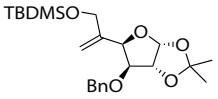




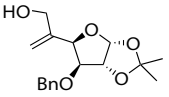
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose (19). Sodium hydride (1.73 g, 43.2 mmol, 60% in mineral oil) was added in portions over 2 min to a dry and cooled (0 °C) solution of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (10.33 g, 39.7 mmol) and benzylbromide (5.2 mL, 43.2 mmol) in DMF (118 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The reaction mixture was cooled to 0 °C and poured into water (500 mL). The aqueous mixture was extracted with Et_2O (3×150 mL) and the combined organic phases were evaporated. The crude benzylated product (R_F = 0.8 (25% EtOAc in PE) was dissolved in a mixture of acetic acid/water (200 mL, 3/1, v/v). The resulting mixture was stirred for 20 h at rt. The reaction mixture was washed with PE (3×100 mL) to remove excess benzylbromide. The washed mixture was concentrated and coevaporated with toluene (3×). The residue was dissolved in DCM (100 mL) and washed with a mixture of sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated to provide the 3-*O*-benzylated-5,6-diol (~40 mmol) that was used crude in the next reaction (R_F = 0.35 (50% EtOAc in DCM). *Tert*-butyldimethylsilylchloride (6.63g, 44 mmol) was added to a dry solution of the crude diol (~40 mmol) and DMAP (10 mg) in pyridine (227 mL). The reaction mixture was stirred for 20 h at rt after which the mixture was concentrated and coevaporated with toluene (3×). The residue was dissolved in EtOAc (100 mL) and washed successively with 1M aq HCl (2×100 mL), sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to produce **19** (14.8 g, 34.9 mmol) in 88% yield over three steps as a colorless oil. R_F = 0.37 (16% EtOAc in toluene). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 – 7.24 (m, 5H, H_{Ar} Bn), 5.89 (d, *J* = 3.7, 1H, H-1), 4.70 (d, *J* = 11.8, 1H, C*H*H Bn), 4.63 (d, *J* = 11.8, 1H, CH*H* Bn), 4.57 (d, *J* = 3.8, 1H, H-2), 4.17 – 4.06 (m, 2H, H-3, H-4), 4.06 – 3.89 (m, 1H, H-5), 3.80 (dd, *J* = 3.7, 10.2, 1H, H-6a), 3.72 (dd, *J* = 4.9, 10.2, 1H, H-6b), 2.66 (d, *J* = 6.4, 1H, 5-OH), 1.45 (s, 3H, CH_3 isoprop), 1.29 (s, 3H, CH_3 isoprop), 0.88 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.06 (s, 6H, 2×CH_3 TBDMS). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.0 (CH_{Ar}-4 Bn), 127.9 (CH_{Ar}-2,6 Bn), 111.7 (C_q isoprop), 105.3 (C-1), 82.6, 82.0, 79.6 (C-2, C-3, C-4), 72.6 (CH_2 Bn), 68.6 (C-6), 64.6 (C-5), 26.8, 26.4 (2×CH_3 isoprop), 26.0 (CH_3 *t*-Bu TBDMS), 18.4 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



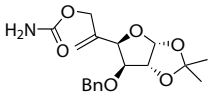
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-ulose (20). Dess-Martin periodinane (4.98 g, 12 mmol, synthesis described in Chapter 6) was added to a dry and cooled (0 °C) solution of **19** (4.14 g, 9.77 mmol) in DCM (50 mL). The reaction mixture was stirred for 3 h and allowed to warm to rt. A mixture of sat aq $NaHCO_3$ (20 mL) and 1M aq $Na_2S_2O_3$ (20 mL) was added to the reaction and stirred vigorously for 15 min. The organic phase was separated and washed with sat aq NaCl (2×50 mL). The organic phase was dried and concentrated. The resulting ketone **20** was used crude in the next reaction. A small sample was purified by silica gel column chromatography (5% » 25% EtOAc in PE) for characterization to yield **20** as a colourless oil. R_F = 0.69 (16% EtOAc in toluene). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H, H_{Ar} Bn), 6.05 (d, *J* = 3.6, 1H, H-1), 4.89 (d, *J* = 3.6, 1H, H-2), 4.75 – 4.30 (m, 6H, H-3, H-4, CH_2-6, CH_2 Bn), 1.47 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop), 0.90 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.04 (s, 6H, 2×CH_3 TBDMS).^{13}C NMR (50 MHz, $CDCl_3$) δ 205.2 (C(O)-5), 136.9 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.1 (CH_{Ar}-4 Bn), 127.8 (CH_{Ar}-2,6 Bn), 112.4 (C_q isoprop), 105.8 (C-1), 84.7, 83.5, 81.8 (C-2, C-3, C-4), 72.5 (CH_2 Bn), 68.9 (C-6), 27.0, 26.4 (2×CH_3 isoprop), 25.9 (CH_3 *t*-Bu TBDMS), 18.4 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



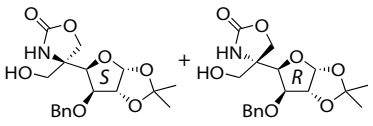
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (21).[22] A solution of butyllithium (6.49 mL, 10.38 mmol, 1.6M in hexane) was added to a dry and cooled (−50 °C) suspension of methyltriphenylphosphonium bromide (4.05 g, 11.33 mmol; dried *in vacuo* for 20 h at 140 °C) in THF (28 mL). The bright yellow suspension was allowed to warm to 0 °C. The suspension was cooled to −50 °C and a dry solution of crude **20** (9.44 mmol) in THF (20 mL) was added over a period of 1 min. The resulting thick suspension was allowed to warm to rt and stirred for 20 h. The mixture poured into sat aq NH_4Cl (200 mL) and EtOAc (100 mL). The organic phase was washed successively with water (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (0% » 15% EtOAc in toluene) to produce **21** (2.03 g, 4.82 mmol) in 49% yield over two steps as a colorless oil. The silylether in **21** hydrolyzes to **22** over time (3 months) when stored on the bench. R_F = 0.52 (16% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H, H_{Ar} Bn), 5.98 (d, *J* = 3.8, 1H, H-1), 5.29 (s, 2H, =CH_2), 4.84 – 4.74 (m, 1H, H-4), 4.63 (d, *J* = 3.8, 1H, H-2), 4.63 (d, *J* = 11.9, 1H, C*H*H Bn), 4.52 (d, *J* = 11.9, 1H, CH*H* Bn), 4.16 (s, 2H, CH_2-6), 3.97 (d, *J* = 3.1, 1H, H-3), 1.50 (s, 3H, CH_3 isoprop), 1.33 (s, 3H, CH_3 isoprop), 0.90 (s, 9H, 3×CH_3 *t*-Bu TBDMS), 0.04 (s, 3H, CH_3 TBDMS), 0.02 (s, 3H, CH_3 TBDMS). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.8 (=C_q-5), 137.7 (C_q Bn), 128.6 (CH_{Ar}-3,5 Bn), 128.1 (CH_{Ar}-4 Bn), 128.0 (CH_{Ar}-2,6 Bn), 111.6, 111.6 (=CH_2, C_q isoprop), 104.5 (C-1), 82.8, 82.7, 80.5 (C-2, C-3, C-4), 72.2 (CH_2 Bn), 64.5 (C-6), 26.9, 26.5 (2×CH_3 isoprop), 26.1 (CH_3 *t*-Bu TBDMS), 18.5 (C_q *t*-Bu), -5.3 (CH_3 TBDMS).



3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (22). A solution of tetrabutylammoniumfluoride (0.5 mL, 0.5 mmol, 1M in THF) was added to a dry solution of **21** (136 mg, 0.32 mmol) in THF (1.6 mL). The reaction mixture was stirred for 3h after which it was poured into EtOAc (50 mL) and washed with sat aq NaCl (3×20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 66% EtOAc in PE) to produce **22** (90 mg, 0.29 mmol) in 91% yield as a colorless oil that crystallized over time. R_F = 0.32 (33% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H, H_{Ar} Bn), 5.98 (d, *J* = 3.9, 1H, H-1), 5.30 – 5.25 (m, 2H, =CH_2), 4.81 (d, *J* = 3.4, 1H, H-4), 4.65 (d, *J* = 12.0, 1H, C*H*H Bn), 4.64 (d, *J* = 3.9, 1H, H-2), 4.49 (d, *J* = 12.0, 1H, CH*H* Bn), 4.12 (d, *J* = 13.0, 1H, H-6a), 4.07 (d, *J* = 13.0, 1H, H-6b), 3.98 (d, *J* = 3.4, 1H, H-3), 2.23 (s, 1H, OH-6), 1.50 (s, 3H, CH_3 isoprop), 1.33 (s, 3H, CH_3 isoprop). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (=C_q-5), 137.2 (C_q Bn), 128.7 (CH_{Ar}-3,5 Bn), 128.2 (CH_{Ar}-4 Bn), 128.0 (CH_{Ar}-2,6 Bn), 114.5 (=CH_2), 111.8 (C_q isoprop), 104.7 (C-1), 83.4 (C-3), 82.4 (C-2), 81.5 (C-4), 72.1 (CH_2 Bn), 64.3 (C-6), 26.9, 26.4 (2×CH_3 isoprop).

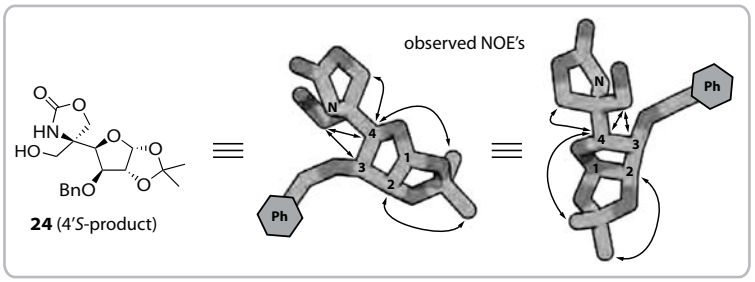


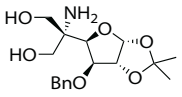
3-*O*-Benzyl-6-*O*-carbamoyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (23). Trichloroacetyl isocyanate (479 µL, 4.04 mmol) was added over a 1 min period to a dry and cooled (0 °C) solution of **22** (1.03 g, 3.37 mmol) in DCM (5 mL). The reaction mixture was stirred for 1h after which it was concentrated to provide the crude intermediate (R_F = 0.70 in 33% EtOAc in PE). The intermediate was immediately dissolved in MeOH (7 mL) and cooled to 0 °C. An aqueous 2M potassium carbonate solution (1.4 g, 10.1 mmol in 5 mL) was added to the methanolic solution and the reaction mixture was stirred for 4 h (warming to rt). The reaction mixture was concentrated until most methanol had evaporated and the suspension was diluted with water (20 mL) and extracted with DCM (3×25 mL). The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (5% » 40% EtOAc in PE) to produce **23** (1.12 g, 3.21 mmol) in 95% yield as a colourless oil. R_F = 0.25 (33% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H, H_{Ar} Bn), 5.96 (d, *J* = 3.8, 1H, H-1), 5.36 (d, *J* = 34.2, 2H, =CH_2), 5.02 (s, 2H, NH_2), 4.72 (d, *J* = 3.0, 1H, H-4), 4.62 (d, *J* = 3.8, 1H, H-2), 4.62 (d, *J* = 12.0, 1H, C*H*H Bn), 4.57 (s, 2H, CH_2-6), 4.50 (d, *J* = 12.0, 1H, CH*H* Bn), 3.96 (d, *J* = 3.3, 1H, H-3), 1.48 (s, 3H, CH_3 isoprop), 1.31 (s, 3H, CH_3 isoprop).^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (C=O), 138.6 (=C_q-5), 137.4 (C_q Bn), 128.5 (CH_{Ar}-3,5 Bn), 128.0 (CH_{Ar}-4 Bn), 127.8 (CH_{Ar}-2,6 Bn), 115.2 (=CH_2), 111.7 (C_q isoprop), 104.6 (C-1), 82.6 (C-3), 82.5 (C-2), 80.5 (C-4), 72.0 (CH_2 Bn), 65.5 (C-6), 26.8, 26.3 (2×CH_3 isoprop).



(4*R*, 4'*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-*C*-[4-(hydroxymethyl)-2-oxooxazolidin-4-yl]-α-D-erythofuranose (24) and (4*R*, 4'*R*)-3-*O*-benzyl-1,2-*O*-isopropylidene-4-*C*-[4-(hydroxymethyl)-2-oxooxazolidin-4-yl]-α-D-erythofuranose (25). A freshly prepared aqueous solution of NaOH (109 mg, 2.72 mmol in 34 mL; 0.5 mL was held back) was added to a solution of **23** (1.0 g, 2.86 mmol) in *n*-propanol (34 mL). The mixture was stirred for 5 min after which the reaction vessel was darkened by wrapping it in aluminium foil. *Tert*-butyl hypochlorite (341 µL, 2.86 mmol; prepared according to a reported[23] procedure) was added and the mixture was allowed to stir for 5 min after which diisopropylethylamine (30 µL, 0.14 mmol) was added. The reaction mixture was allowed to stir for 5 min after which a suspension of potassium osmate(VI) dihydrate (53 mg, 0.14 mmol) in aq NaOH (0.5 mL) was added. The reaction mixture colored green, which disappeared quickly and left pale yellow solution. The still darkened reaction mixture was stirred for 20 h during which it slowly colored black. Aqueous 1M Na_2SO_3 (50 mL) was added and the mixture was stirred vigorously for 30 min. The mixture was further diluted with aq 1M Na_2SO_3 (50 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (33% » 75% EtOAc in PE) to produce **24** (508 mg, 1.39 mmol) and **25** (364 mg, 1.0 mmol) in a combined yield of 83% as off-white foams. R_F **24** = 0.45; **25** = 0.32 (8% MeOH in DCM + 2% NH_4OH). **24 (4'*S*-product)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H, H_{Ar} Bn), 5.96 (d, *J* = 3.8, 1H, H-1), 5.87 (s, 1H, NH-3'), 4.66 (d, *J* = 11.4, 1H, C*H*H Bn), 4.63 (d, *J* = 3.8, 1H, H-2), 4.45 (d, *J* = 11.4, 1H, CH*H* Bn), 4.44 (d, *J* = 8.4, 1H, C*H*H-5'), 4.33 (d, *J* = 8.4, 1H, CH*H*-5'), 4.13 (d, *J* = 3.5, 1H, H-4), 4.05 (d, *J* = 3.5, 1H, H-3), 3.54 (d, *J* = 11.3, 1H, HO-C*H*H), 3.43 (d, *J* = 11.3, 1H, HO-CH*H*), 3.20 – 2.80 (m, 1H, OH), 1.47 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (C(O)-2'), 136.2 (C_q Bn), 129.1 (CH_{Ar}-3,5 Bn), 128.9 (CH_{Ar}-4 Bn), 128.7 (CH_{Ar}-2,6 Bn), 112.1 (C_q isoprop), 104.7 (C-1), 82.4 (C-3), 81.9 (C-2), 79.5 (C-4), 72.4 (CH_2 Bn), 70.6 (C-5'), 64.8 (CH_2-OH), 62.3 (C_q-4'), 26.9, 26.3 (2×CH_3 isoprop). MS (ESI): found 366.1 $[M+H]^+$, calculated for $[C_{18}H_{23}O_7N+H]^+$ 366.2. **25 (4'*R*-product)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H, H_{Ar} Bn), 6.55 (s, 1H, NH-3'), 5.97 (d, *J* = 3.8, 1H, H-1), 4.63 (d, *J* = 3.9, 1H, H-2), 4.62 (d, *J* = 11.2, 1H, C*H*H Bn), 4.55 (d, *J* = 9.3, 1H, C*H*H-5'), 4.42 (d, *J* = 11.2, 1H, CH*H* Bn), 4.41 (d, *J* = 3.4, 1H, H-4), 4.02 (d, *J* = 9.3, 1H, CH*H*-5'), 3.98 (d, *J* = 3.4, 1H, H-3), 3.97 – 3.89 (m, 1H, OH), 3.53 (s, 2H, HO-CH_2), 1.50 (s, 3H, CH_3 isoprop), 1.32 (s, 3H, CH_3 isoprop). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (C(O)-2'), 136.6 (C_q Bn), 128.9 (CH_{Ar}-3,5 Bn), 128.5 (CH_{Ar}-4 Bn), 128.1 (CH_{Ar}-2,6 Bn), 112.4 (C_q isoprop), 104.9 (C-1), 81.9 (C-2, C-3),

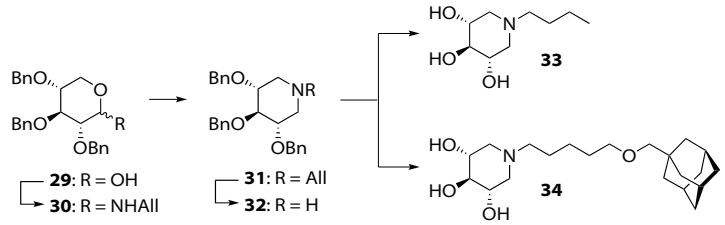
80.2 (C-4), 72.1 (CH_2 Bn), 69.0 (C-5′), 65.3 (CH_2-OH), 63.6 (C_q-4′), 26.9, 26.5 (2×CH_3 isoprop). MS (ESI): found 366.1 $[M+H]^+$, calculated for $[C_{18}H_{23}O_7N+H]^+$ 366.2.

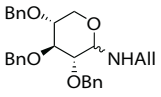




(4*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-*C*-(2-amino-1,3-dihydroxy-propane-2-yl)-α-D-erythofuranose (26). Lithium hydroxide (232 mg, 9.65 mmol) was added to a mixture of **24** and **25** (70 mg, 0.19 mmol) in EtOH/water (5 mL, 7/3, v/v). The suspension was refluxed (95 °C) for 4 h after which TLC analysis indicated complete consumption of the starting material. The mixture was passed over glass fibre filter and the filtrate was concentrated. The residue was purified by silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) to afford **26** (63 mg, 0.19 mmol) in 96% yield as a colourless oil. R_F = 0.20 (8% MeOH in DCM + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H, H_{Ar} Bn), 5.86 (d, *J* = 3.8, 1H, H-1), 4.62 (d, *J* = 11.2, 1H, C*H*H Bn), 4.55 (d, *J* = 11.2, 1H, CH*H* Bn), 4.53 (d, *J* = 3.8, 1H, H-2), 4.21 (s, 4H, OH-1′, OH-2′, NH_2-2′), 4.13 (d, *J* = 3.1, 1H, H-3), 4.06 (d, *J* = 3.1, 1H, H-4), 3.75 – 3.57 (m, 4H, CH_2-1′, CH_2-3′), 1.45 (s, 3H, CH_3 isoprop), 1.29 (s, 3H, CH_3 isoprop).^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (C_q Bn), 129.0 (CH_{Ar}-3,5 Bn), 128.6 (CH_{Ar}-4 Bn), 128.6 (CH_{Ar}-2,6 Bn), 112.1 (C_q isoprop), 104.5 (C-1), 83.3 (C-3), 81.7 (C-4), 79.4 (C-4), 72.3 (CH_2 Bn), 64.2, 63.0 (CH_2-1′, CH_2-3′), 59.5 (C_q-2′), 26.9, 26.4 (2×CH_3 isoprop).

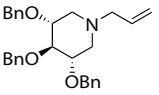
Synthesis of D-*xylo*-derivatives 33 and 34:



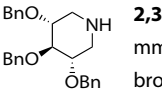


α/β-Mixture of *N*-allyl-2,3,4-tri-*O*-benzyl-D-xylopyranosylamine (30). A suspension of **29** (2.1 g, 5 mmol), allylamine (3.76 mL, 50 mmol), (±)-camphor-10-sulfonic acid (1.16 g, 5 mmol) and Na_2SO_4 (3.40 g, 24 mmol) in toluene (50 mL) was refluxed for 3 h, after which TLC analysis indicated complete consumption of **29**. The reaction mixture was cooled to rt, diluted with EtOAc (200 mL) and successively washed with sat aq $NaHCO_3$ (2×100 mL) and sat aq NaCl (100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 20% EtOAc in PE) to provide **30** (2.07 g, 4.51 mmol) in 90% yield as a white solid. R_F = 0.61 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) 0.75:1 α/β-mixture δ 7.39 – 7.22 (m, 15H, H_{Ar} Bn α/β), 5.96 – 5.80 (m, 1H, =CH allyl α/β), 5.24 – 5.01 (m, 2H, =CH_2 allyl α/β), 4.96 – 4.56 (m, 6H, 3×CH_2 Bn), 4.46 (d, *J* = 4.0, 1H, H-1α), 3.93 (d, *J* = 8.5, 1H, H-1β), 3.91 – 3.12 (m, 7H, H-2, H-3, H-4, CH_2-5 α/β), 1.96 (s, 1H, NH).^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.6, 138.6, 138.4, 138.3 (C_q Bn α/β), 136.9, 136.8 (=CH allyl α/β), 128.6 – 127.7 (CH_{Ar} Bn α/β), 115.9, 115.8 (=CH_2 allyl α/β), 90.8 (C-1 β), 85.2

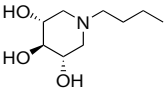
(CH β), 84.4 (C-1 α), 81.9 (CH β), 79.4 (CH α), 79.0 (CH α), 78.6 (CH β), 77.3 (CH α), 75.8, 75.2, 74.8 (3×CH_2 Bn α), 73.4, 73.3, 72.8 (3×CH_2 Bn β), 65.1 (C-5 β), 60.4 (C-5 α), 48.6 (NCH_2 allyl β), 48.2 (NCH_2 allyl α). MS (ESI): found 460.4 $[M+H]^+$, calculated for $[C_{29}H_{33}NO_4+H]^+$ 460.2.



***N*-Allyl-2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-xylitol (31).** Lithium aluminum hydride (291 mg, 7.65 mmol) was added to a dry and cooled (0 °C) solution of **30** (1.17 g, 2.55 mmol) in THF (26 mL). The reaction mixture was stirred for 20 h and allowed to warm to rt. The mixture was cooled to 0 °C and quenched by slow addition of EtOAc. The mixture was stirred for 1 h and subsequently poured into a mixture of sat aq NH_4Cl and sat aq NaCl (200 mL, 1/1, v/v). The mixture was extracted with EtOAc (3×150 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was used crude in subsequent reactions (R_F = 0.24 in 100% EtOAc + 2% NH_4OH). Diethyl azodicarboxylate (0.28 mL, 0.61 mmol; 2.2M in toluene) was added over a 1 min period to a dry solution of crude aminoalcohol (~0.55 mmol) and PPh_3 (161 mg, 0.61mmol) in DCM (5.5 mL). The reaction mixture was stirred for 20 h and subsequently quenched by addition of water. The mixture was concentrated and purified by silica gel column chromatography (0% » 20% EtOAc in toluene) to produce **31** (178 mg, 0.40 mmol) in 73% yield as a colorless oil. R_F = 0.73 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 15H, H_{Ar} Bn), 5.79 (ddt, *J* = 6.5, 10.2, 16.8, 1H, =CH allyl), 5.19 – 5.08 (m, 2H, =CH_2 allyl), 4.88 (s, 2H, CH_2 Bn), 4.70 (d, *J* = 11.6, 2H, 2×C*H*H Bn), 4.64 (d, *J* = 11.6, 2H, 2×CH*H* Bn), 3.64 – 3.54 (m, 2H, H-2, H-4), 3.41 (dd, *J* = 8.7, 1H, H-3), 3.07 (dd, *J* = 3.7, 10.8, 2H, H-1a, H-5a), 3.01 (d, *J* = 6.5, 2H, NCH_2 allyl), 1.94 (t, *J* = 10.8, 2H, H-1b, H-5b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (C_q Bn), 138.7 (2×C_q Bn), 134.5 (=CH allyl), 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 118.4 (=CH_2 allyl), 86.4 (C-3), 78.8 (C-2, C-4), 75.5 (CH_2 Bn), 73.1 (2×CH_2 Bn), 60.9 (NCH_2 allyl), 56.1 (C-1, C-5). MS (ESI): found 444.3 $[M+H]^+$, calculated for $[C_{29}H_{33}NO_3+H]^+$ 444.3.

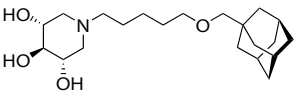


2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-xylitol (32). Potassium *tert*-butoxide (32 mg, 0.29 mmol) was added to a solution of **31** (170 mg, 0.38 mmol) in DMSO (2 mL) and the resulting brown reaction mixture was heated at 100 °C for 30 minutes. The reaction mixture was charged with 1M aq HCl (2 mL) and stirred vigorously for 15 minutes. The mixture was poured into sat aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3×50 mL). The organic phase was isolated, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (33% » 100% EtOAc in PE+2% NH_4OH) to produce **32** (106 mg, 0.26 mmol) in 69% yield as a yellow oil. R_F = 0.37 (EtOAc+2% NH_4OH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.28 (15H, m, H_{Ar} Bn), 4.91 – 4.58 (6H, m, 3×CH_2 Bn), 3.61 3.54 (m, 2H, H-2, H-4), 3.39 (dd, *J* = 7.1, 1H, H-3), 3.04 (2H, dd, *J* = 10.8, 4.2, 1H, H-1a, H-5a), 2.41 (2H, dd, *J* = 10.8, 8.4, 1H, H-1b, H-5b), 1.93 (s, 1H, NH). MS (ESI): found 404.5 $[M+H]^+$, calculated for $[C_{26}H_{29}NO_3+H]^+$ 404.2.

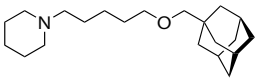


***N*-Butyl-1,5-dideoxy-1,5-imino-D-xylitol (33).** A mixture of **32** (50 mg, 124 µmol), butyraldehyde (56 µL, 0.62 mmol) and Na_2SO_4 (50 mg, 0.35 mmol) in CH_3CN/MeOH/AcOH (2 mL, 20/20/1, v/v) was charged with $NaCNBH_3$ (39 mg, 0.62 mmol). The reaction mixture was stirred for 20 h after which it was poured into a mixture of sat aq $NaHCO_3$ (25 mL) and sat aq NaCl (25 mL). The mixture was extracted with EtOAc (3×50 mL), dried ($MgSO_4$) and concentrated (R_F *N*-alkylated intermediate = 0.55 in 3:1; PE:EtOAc). The crude residue was subjected to Pd-catalyzed hydrogenation as described in general procedure A to provide **33** (17 mg, 88 µmol) in 71% yield as a crystalline white solid after silica gel column purification (1% » 20% MeOH in $CHCl_3$ + 2% NH_4OH). R_F = 0.33 (25% MeOH in $CHCl_3$ + 2% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.54 – 3.45 (m, 2H, H-2, H-4), 3.09 (d, *J* = 8.9, 1H, H-3), 3.01 – 2.94 (m, 2H, H-1b, H-5b), 2.41 (dd, *J* = 6.7, 8.8, 2H, NCH_2-1 butyl), 1.92 (dd, *J* = 10.8, 2H, H-1b, H-5b), 1.55 – 1.43 (m, 2H, CH_2-2 butyl), 1.42 – 1.27 (m, 2H, CH_2-3 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl).^{13}C NMR (100 MHz, MeOD) δ 80.6 (C-3), 71.5 (C-2, C-4), 59.6 (C-1,

C-5), 58.9 (NCH_2-1 butyl), 30.1, 21.8 (2×CH_2 butyl), 14.5 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3288, 2932, 2876, 1636, 1456, 1067, 1036, 976, 878. MS (ESI): found 190.0 $[M+H]^+$, calculated for $[C_9H_{19}NO_3+H]^+$ 190.1.

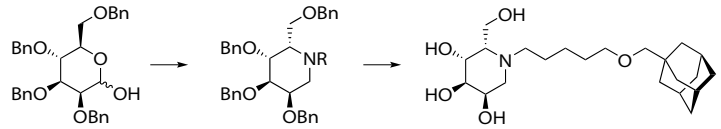


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1,5-dideoxy-1,5-imino-D-xylitol (34).** Compound **34** (8 mg, 22 µmol) was obtained in 31% yield as a colourless oil from **32** (70 µmol) after silica gel column purification (1% » 15% MeOH in $CHCl_3$ + 2% NH_4OH) via the same 2 step procedure as described for **33**, but now with 5-(adamantane-1-yl-methoxy)-1-pentanal (**7**). R_F **34** = 0.72 (25% MeOH in $CHCl_3$ + 2% NH_4OH); R_F *N*-alkylated intermediate = 0.44 in 3:1; PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD; 1/1; 40 °C) δ 3.72 (dd, *J* = 3.9, 10.9, 1H), 3.52 (dd, *J* = 7.8, 10.9, 1H), 3.52 – 3.41 (m, 1H), 3.37 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.20 (dd, *J* = 7.7, 1H, H-3), 3.06 – 2.99 (m, 1H), 2.98 – 2.91 (m, 3H, OCH_2-Ada, CH), 2.66 – 2.52 (m, 2H), 2.36 – 2.27 (m, 1H), 1.93 (s, 3H, 3×CH Ada), 1.76 – 1.37 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). MS (ESI): found 368.2 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_4+H]^+$ 368.3.

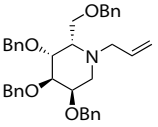


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-piperidine (35).** Formic acid (30 µL, 0.8 mmol) was added to a solution of piperidine (79 µL, 0.8 mmol) in DCM (5 mL). The solution was concentrated and coevaporated with dichloroethane. The residue was dissolved in EtOH (1 mL) and a solution 5-(adamantan-1yl-methoxy)-pentanal (70 mg, 0.28 mmol, synthesis described in Chapter 2) in EtOH (0.4 mL) and 3Å molecular sieves were added. The mixture was stirred for 15 min after which $NaCNBH_3$ (38 mg, 0.6 mmol) was added and the reaction mixture was stirred for 20h at rt. The mixture was filtered and the filtrate was concentrated and redissolved in EtOAc (50 mL). The solution was washed successively with sat aq $NaHCO_3$ (50 mL) and sat aq NaCl (50 mL). The organic phase was dried and concentrated. The residue was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ + 1% NH_4OH) to afford **32** (58 mg, 0.18 mmol) in 64% yield as a colourless oil. R_F = 0.44 (100% EtOAc + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 2.71 – 2.59 (m, 4H, NCH_2-2/6 piperidine), 2.54 (d, *J* = 16.7, 1H, NC*H*H-1 pentyl), 2.54 (t, *J* = 2.9, 1H, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.78 – 1.51 (m, 16H, 3×CH_2 Ada, 3×CH_2 piperidine, 2×CH_2 pentyl), 1.52 (d, *J* = 2.6, 6H, 3×CH_2 Ada), 1.44 – 1.32 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.1 (OCH_2-Ada), 71.5 (CH_2-5 pentyl), 59.0 (NCH_2-1 pentyl), 54.3 (NCH_2-2/6 piperidine), 40.0 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 29.5 (CH_2-4 pentyl), 28.5 (CH Ada), 25.6 (CH_2-2 pentyl), 24.8 (CH_2-3/5 piperidine), 24.3 (CH_2-3 pentyl), 23.6 (CH_2-4 piperidine). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1651, 1450, 1119. HRMS: found 320.2948 $[M+H]^+$, calculated for $[C_{21}H_{37}NO+H]^+$ 320.2956.

Synthesis of L-*gulo*-derivative 39:

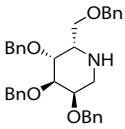


36 **37**: R = Allyl **38**: R = H **39**

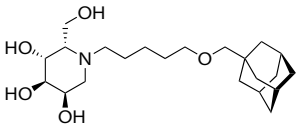


***N*-Allyl-2,3,4,6-tetra-*O*-benzyl-L-*gulo*-1-deoxynojirimycin (37).** A solution of $LiAlH_4$ (4.4 mL, 10.6 mmol, 2.4M in THF) was added in portions to a cooled (0 °C) and dry solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**36**, 1.64 g, 3.0 mmol; prepared according to a known procedure[24]) in THF (15 mL). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched successively with EtOAc (5 mL, 1 h of stirring) and water at 0 °C. The mixture was diluted with EtOAc (100 mL) and washed with sat aq NH_4Cl (2×100 mL) and sat aq NaCl (100 mL). The

organic phase was dried ($MgSO_4$) and concentrated to yield the mannitol derivative, which was used crude in the next reaction (R_F mannitol der. = 0.25; **36** = 0.46 in 33% EtOAc in PE). Methanesulfonyl chloride (0.59 mL, 7.58 mmol) was added dropwise to a cooled (0 °C) solution of the crude mannitol deribative (~3 mmol) in pyridine (6 mL). After TLC analysis indicated complete consumption of starting material (2 hours), water (2 mL) was added and the reaction mixture was concentrated. The residue was dissolved in EtOAc (50 mL) and washed successively with 1M aq HCl (2×50 mL), sat aq $NaHCO_3$ (50 mL) and sat aq NaCl (50 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated to yield the mesylate as a yellow oil, which was used crude in the next step. (R_F mesylate = 0.74 in 1:1; PE:EtOAc). The crude mesylate (~3 mmol) was coevaporated with toluene, dissolved in allylamine (15 mL) and refluxed for 20 hours. The reaction mixture was concentrated, dissolved in EtOAc (50 mL) and washed successively with sat aq $NaHCO_3$ (2×50 mL) and sat aq NaCl (50 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (isocratic 15% EtOAc in PE) to produce **37** (943 mg, 1.67 mmol) in 56% yield over three steps as an orange oil. R_F = 0.45 (16% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 – 7.13 (m, 20H, H_{Ar} Bn), 6.05 – 5.84 (m, 1H, =CH allyl), 5.16 – 5.08 (m, 2H, $=CH_2$ allyl), 4.68 – 4.42 (m, 8H, 4×CH_2 Bn), 3.90 – 3.78 (m, 1H, H-2), 3.77 – 3.67 (m, 2H, H-4, H-6a), 3.63 (dd, *J* = 3.2, 4.2, 1H, H-3), 3.49 (dd, *J* = 5.8, 9.5, 1H, H-6b), 3.33 (dd, *J* = 6.3, 14.2, 1H, NC*H*H allyl), 3.13 (dd, *J* = 7.2, 14.2, 1H, NCH*H* allyl), 3.00 (td, *J* = 1.8, 5.8, 1H, H-5), 2.80 (dd, *J* = 4.5, 10.9, 1H, H-1a), 2.68 (dd, *J* = 9.8, 10.9, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 138.8, 138.4, 138.3 (4×C_q Bn), 134.4 (=CH allyl), 128.4, 128.3, 128.0, 127.8, 127.6, 127.5 (CH_{Ar} Bn), 118.2 ($=CH_2$ allyl), 76.6 (C-4), 74.2 (C-2), 73.8 (C-3), 73.2, 72.5, 72.6, 71.2 (4×CH_2 Bn), 69.3 (C-6), 58.4 (C-5), 57.4 (NCH_2 allyl), 50.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3026, 2860, 1497, 1454, 1364, 1205, 1072, 1026, 995, 914, 733, 694. $[\alpha]^{20}_D$: −0.8 (*c* 0.98, $CHCl_3$). MS (ESI): found 564.3 $[M+H]^+$, calculated for $[C_{37}H_{41}NO_4+H]^+$ 564.3.



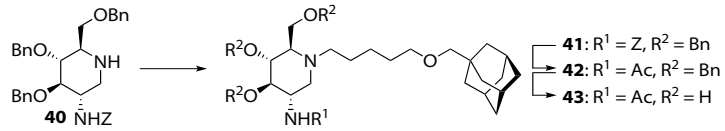
2,3,4,6-Tetra-*O*-benzyl-L-*gulo*-1-deoxynojirimycin (38). Potassium *tert*-butoxide (181 mg, 1.61 mmol) was added to a solution of **37** (1.20 g, 2.12 mmol) in DMSO (10 mL) and the resulting brown reaction mixture was heated at 100 °C for 60 minutes. The reaction mixture was charged with 1M aq HCl (6 mL) and stirred vigorously for 15 minutes. The mixture was poured into sat aq $NaHCO_3$ (100 mL) and extracted with Et_2O (3×100 mL). The organic phase was isolated, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (1: 33% » 100% EtOAc in PE+1% NH_4OH; 2: isocratic 10% MeOH in EtOAc) to furnish **38** (1.00 g, 1.91 mmol) in 90% yield as a yellow oil. R_F = 0.14 (50% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 20H, H_{Ar} Bn), 4.79 – 4.26 (m, 8H, 4×CH_2 Bn), 3.80 (dd, *J* = 2.7, 4.0, 1H, H-3), 3.78 – 3.67 (m, 1H, H-2), 3.54 (dd, *J* = 1.7, 4.0, 1H, H-4), 3.47 (dd, *J* = 7.4, 8.6, 1H, H-6a), 3.41 – 3.22 (m, 2H, H-5, H-6b), 3.01 (d, *J* = 8.1, 2H, CH_2-1), 2.15 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 138.9, 138.3, 138.2 (4×C_q Bn), 128.4, 128.3, 128.1, 127.9, 127.6, 127.3, 127.1 (CH_{Ar} Bn), 75.6 (C-4), 75.2 (C-2), 73.4 (C-3), 73.3, 72.9, 72.7, 71.0 (4×CH_2 Bn), 70.6 (C-6), 53.7 (C-5), 44.4 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3034, 2862, 1495, 1452, 1366, 1205, 1092, 1059, 1026, 733, 694. $[\alpha]^{20}_D$: 0.2 (*c* 1.14, $CHCl_3$). MS (ESI): found 524.6 $[M+H]^+$, calculated for $[C_{34}H_{37}NO_4+H]^+$ 524.3.

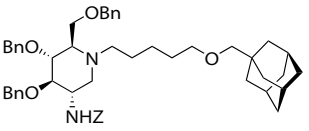


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-L-*gulo*-1-deoxynojirimycin (39).** A solution of **38** (100 mg, 0.19 mmol) and 5-(adamantane-1-yl-methoxy)-1-pentanal **7** (53 mg, 0.21 mmol) in EtOH/AcOH (50 mL, 9/1, v/v) was purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 50 mg) was added to the solution and the reaction mixture was exposed to 4 bar of hydrogen for 20 hours. Removal of Pd/C by filtration over a glass micro fibre filter and concentration of the filtrate provided the crude *N*-alkylated intermediate (R_F = ~0.5 in 4:1; PE:EtOAc) as a light yellow oil. A solution of crude intermediate in EtOH (50 mL) was acidified with 2M aq HCl (5 mL) and purged of oxygen by bubbling argon through the solution. Pd/C (10 wt%, 50 mg) was added to the solution and the reaction mixture was exposed to 4 bar of

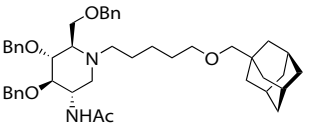
hydrogen for 20 hours. After removal of Pd/C and concentration, the residue was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ + 1% NH_4OH) to afford **39** (48 mg, 0.12 mmol) in 61% yield over two steps as white foam. R_F = 0.2 (4:1; $CHCl_3$:MeOH + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.98 (ddd, *J* = 3.3, 4.4, 9.7, 1H, H-2), 3.92 (dd, *J* = 2.6, 4.7, 1H, H-4), 3.84 (dd, *J* = 5.3, 11.5, 1H, H-6a), 3.79 (dd, *J* = 4.7, 11.5, 1H, H-6b), 3.76 (dd, *J* = 3.3, 4.7, 1H, H-3), 3.39 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.97 (s, 2H, OCH_2-Ada), 2.79 – 2.76 (m, 1H, H-5), 2.75 – 2.69 (m, 2H, H-1a, NC*H*H-1 pentyl), 2.66 – 2.57 (m, 2H, H-1b, NCH*H*-1 pentyl), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.7, 30.9, 6H, 3×CH_2 Ada), 1.63 – 1.50 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.39 – 1.27 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 73.1 (C-4), 72.7 (CH2-5 pentyl), 72.3 (C-3), 67.6 (C-2), 61.7 (C-6), 60.9 (C-5), 55.0, 53.2 (C-1, NCH_2-1 pentyl), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7 (CH_2-4 pentyl), 29.9 (CH Ada), 25.5 (CH_2-2 pentyl), 25.4 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3359, 2902, 2848, 1453, 1065, 1057. $[\alpha]^{20}_D$: 24.5 (*c* 0.4, MeOH). HRMS: found 398.2899 $[M+H]^+$, calculated for $[C_{22}H_{39}O_5N_1+H]^+$ 398.2901.

Synthesis of C-2 acetamido derivative 43:



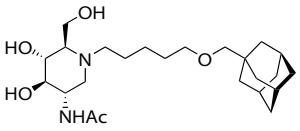


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-2-(benzyloxycarbonyl) amino-3,4,6-tri-*O*-benzyl-1,2-deoxynojirimycin (41).** A dry mixture of 2-(benzyloxycarbonyl)amino-3,4,6-tri-*O*-benzyl-1,2-dideoxynojirimycin (**40**: 180 mg, 0.32 mmol; prepared according to a known procedure[25]), 5-(adamantane-1-yl-methoxy)-1-pentanal (160 mg, 0.64 mmol) and Na_2SO_4 (91 mg, 0.64 mmol) in MeOH/AcOH (3 mL, 20/1, v/v) was charged with $NaCNBH_3$ (41 mg, 0.64 mmol). The reaction mixture was stirred for 20 h after which it was poured into a mixture of sat aq $NaHCO_3$ (25 mL) and sat aq NaCl (25 mL). The mixture was extracted with EtOAc (3×50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to produce **41** (233 mg, 0.29 mmol) in 91% yield as a colorless oil. R_F = 0.22 (25% EtOAc in PE). ^{1}H NMR (300 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.37 – 7.16 (m, 20H, H_{Ar} Bn/Z), 5.25 (s, 1H, NH), 5.13 – 5.00 (m, 2H, CH_2 Z), 4.73 – 4.38 (m, 6H, 3×CH_2 Bn), 3.90 – 3.78 (m, 1H, H-2), 3.76 – 3.68 (m, 2H, CH_2-6), 3.68 – 3.59 (m, 1H, H-3/4), 3.45 – 3.27 (m, 3H, H-3/4, CH_2-5 pentyl), 3.05 (dd, *J* = 3.4, 11.7, 1H, H-1a), 2.97 – 2.90 (m, 2H, OCH_2-Ada), 2.81 – 2.72 (m, 1H, H-5), 2.65 – 2.50 (m, 2H, NCH_2-1 pentyl), 2.37 – 2.24 (m, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.75 – 1.21 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) collapsed iminosugar signals δ 156.1 (C=O Z), 138.5, 138.4, 138.4, 136.9 (C_q Bn/Z), 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5 (CH_{Ar} Bn/Z), 82.1 (OCH_2 Ada), 79.7, 77.3 (C-3, C-4), 73.4, 71.7, 66.6, 65.5 (CH_2 Z, CH_2 Bn, C-6, CH_2-5 pentyl), 62.3 (C-5), 53.4, 51.1 (C-1, NCH_2-1 pentyl), 50.0 (C-2), 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.5 (CH Ada), 29.6, 25.9, 24.0 (3×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2897, 2847, 1699, 1539, 1497, 1454, 1362, 1094, 1070, 1028, 733, 696. $[\alpha]^{20}_D$: 12.9 (*c* 2.8, $CHCl_3$). MS (ESI): found 801.4 $[M+H]^+$, calculated for $[C_{51}H_{64}O_6N_2+H]^+$ 801.5.



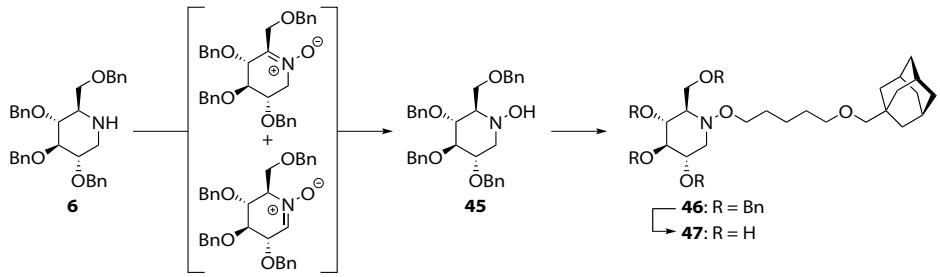
2-Acetamide-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-3,4,6-tri-*O*-benzyl-1,2-deoxynojirimycin (42). A solution of compound **41** (233 mg, 0.29 mmol) in EtOAc (5 mL) was acidified with AcOH (0.1 mL). Argon was passed through the solution for 5 minutes, after which a catalytic amount of Pd/C Degussa-type (50 mg) was added. A gentle flow of hydrogen gas was passed through the reaction mixture for 2 h after which TLC analysis indicated complete consumption of **41**. Pd/C was removed by

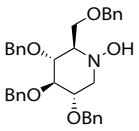
filtration over a glass micro fibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. The residue was dissolved in pyridine (5 mL) and Ac_2O (0.2 mL) was added. The reaction mixture was stirred for 20 h. The mixture was concentrated and purified by silica gel column chromatography (0% » 5% MeOH in DCM) to provide **42** (144 mg, 0.20 mmol) in 70% yield as a colourless oil. R_F = 0.85 (5% MeOH in DCM). ^{1}H NMR (200 MHz, $CDCl_3$/MeOD, 2/1) δ 7.41 – 7.20 (m, 15H, H_{Ar} Bn), 4.72 – 4.47 (m, 6H, 3×CH_2 Bn), 4.09 – 3.98 (m, 1H, H-2), 3.85 – 3.39 (m, 2H, H-3, H-4, CH_2-6), 3.35 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 2.99 (dd, *J* = 3.7, 11.7, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.89 – 2.70 (m, 1H, H-5), 2.62 – 2.53 (m, 1H, NCH_2-1 pentyl), 2.23 (dd, *J* = 7.3, 11.7, 1H, H-1b), 1.96 (s, 3H, 3×CH Ada), 1.79 (s, 3H, CH_3 Ac), 1.76 – 1.26 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). MS (ESI): found 709.3 $[M+H]^+$, calculated for $[C_{45}H_{60}O_5N_2+H]^+$ 709.5.



2-Acetamide-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1,2-deoxynojirimycin (43). Compound **42** (78 mg, 0.18 mmol) was obtained after silica gel column chromatography (5% » 20% MeOH in DCM + 2% NH_4OH) in 90% yield by subjecting **43** (0.20 mmol) to Pd-catalyzed hydrogenation according to general procedure A. R_F = 0.47 (20% MeOH in DCM+2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD, 1/1) δ 3.90 – 3.84 (m, 2H, CH_2-6), 3.98 (dd, *J* = 4.4, 10.4, 1H, H-2), 3.46 (dd, *J* = 9.1, 1H, H-3/4), 3.40 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 3.21 (dd, *J* = 8.9, 10.2, 1H, H-3/4), 3.08 (dd, *J* = 4.3, 11.3, 1H, H-1a), 2.98 (s, 2H, OCH_2-Ada), 2.81 – 2.73 (m, 1H, NC*H*H-1 pentyl), 2.59 – 2.52 (m, 1H, NCH*H*-1 pentyl), 2.19 – 2.11 (m, 2H, H-1b, H-5), 1.98 (s, 3H, CH_3 Ac), 1.96 (s, 3H, 3×CH Ada), 1.71 (dd, *J* = 11.7, 30.9, 6H, 3×CH_2 Ada), 1.61 – 1.48 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.35 – 1.27 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$/MeOD, 1/1) δ 173.1 (C=O Ac), 82.8 (OCH_2 Ada), 77.2, 72.5 (C-3, C-4), 72.4 (CH_2-5 pentyl), 66.2 (C-5), 59.4 (C-6), 55.2, 53.1 (C-1, NCH_2-1 pentyl), 51.5 (C-2), 40.5 (CH_2 Ada), 37.9 (CH_2 Ada), 34.8 (C_q Ada), 29.1 (CH Ada), 30.1, 25.1, 24.8 (3×CH_2 pentyl), 22.9 (CH_3 Ac). MS (ESI): found 439.4 $[M+H]^+$, calculated for $[C_{24}H_{42}O_5N_2+H]^+$ 439.3.

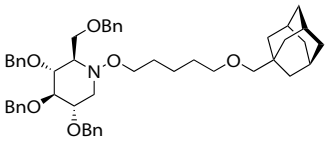
Synthesis of aminoxy-derivative 47:



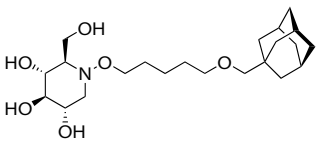


***N*-Hydroxy-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (45).** An aqueous solution of $NaHCO_3$ (378 mg, 4.5 mmol, 5 mL H_2O) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**6**: 522 mg, 1.0 mmol; synthesis described in Chapter 2) in DCM/acetone (10 mL, 1/1, v/v) and the resulting two-phase mixture was cooled to 0 °C. A solution of Oxone (potassium peroxymonosulfate, 1.54 g, 2.5 mmol) in water (5 mL) was added dropwise to the vigorously stirred mixture. The reaction mixture was stirred for 90 min at 0 °C after which TLC analysis indicated complete consumption of **6**. The mixture was diluted with DCM (50 mL) and successively washed with 5% aq $KHSO_4$ (50 mL) and sat aq $NaHCO_3$ (50 mL). The organic phase was dried (Na_2SO_4) and concentrated at ~30 °C to yield the crude intermediate cyclic nitrone (R_F = 0.29 in 25% PE in EtOAc+ 2% Et_3N). A dry and cooled (0 °C) solution of the cyclic nitrone in THF (20 mL) was charged in a dropwise fashion with $LiAlH_4$ (2 mL, 2.8 mmol, 2.4M in THF). After stirring for 1h at 0 °C the reaction mixture was quenched by slow addition of EtOAc (5 mL). After stirring for 1h

at 0 °C the mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The residue was purified by silica gel column chromatography (25% » 75% EtOAc in PE + 1% Et_3N) to produce **45** (416 mg, 0.77 mmol) in 77% yield over two steps as an off-white solid. R_F = 0.85 (25% PE in EtOAc+ 2% Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.35 – 7.10 (m, 20H, H_{Ar} Bn), 6.63 (s, 1H, N–OH), 4.95 (d, *J* = 11.0, 1H, C*H*H Bn), 4.87 – 4.78 (m, 2H, CH*H* Bn, C*H*H Bn), 4.71 – 4.38 (m, 5H), 3.99 – 3.77 (m, 1H), 3.81 – 3.51 (m, 5H), 2.63 (t, *J* = 11.0, 1H), 2.65 – 2.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) collapsed iminosugar signals δ 138.9, 138.4, 138.3, 137.9 (4×C_q Bn), 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 76.5, 75.6, 75.5, 73.4, 73.1. MS (ESI): found 540.2 $[M+H]^+$, calculated for $[C_{34}H_{37}NO_5+H]^+$ 540.3.



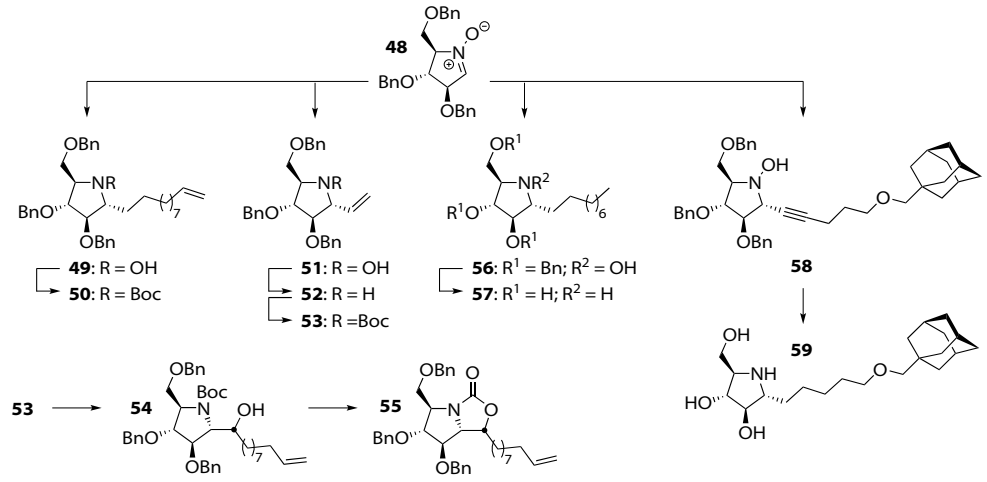
***N*-[5-(Adamantan-1-yl-methoxy)-pentyloxy]-2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (46).** Sodium hydride (17 mg, 0.42 mmol, 60% in mineral oil) was added to a dry and cooled (0 °C) solution of **45** (225 mg, 0.417 mmol) in DMF (2 mL). The mixture was stirred for 10 min at 0 °C after which a solution of 5-(adamantan-1yl-methoxy)-1-bromo-pentane (132 mg, 0.42 mmol, synthesis described in Chapter 5) in DMF (0.5 mL) was added. The reaction mixture was stirred for 2h at rt after which TLC indicated ~50% conversion. The mixture was cooled to 0 °C and an additional equivalent of NaH and bromide were successively added. After stirring for 1h at rt the reaction mixture was quenched by addition of water. The mixture was diluted with water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to produce **46** (190 mg, 0.25 mmol) in 60% yield as a colourless oil. R_F = 0.53 (25% EtOAc in PE). ^{1}H NMR (200 MHz, $CDCl_3$) collapsed iminosugar signals δ 7.49 – 7.07 (m, 20H, H_{Ar} Bn), 4.95 (d, *J* = 11.1, 1H, CHH Bn), 4.89 – 4.77 (m, 2H, CH*H* Bn, C*H*H Bn), 4.71 (d, *J* = 11.6, 1H, C*H*H Bn), 4.64 (d, *J* = 11.6, 1H, CH*H* Bn), 4.57 – 4.40 (m, 3H, CH*H* Bn, CH_2 Bn), 3.95 – 3.43 (m, 9H, H-1a, H-2, H-3, H-4, H-5, CH_2-6, $NOCH_2$-1 pentyl), 3.37 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.96 (s, 2H, OCH_2-Ada), 2.48 (dd, *J* = 10.8, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.82 – 1.11 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl).^{13}C NMR (50 MHz, $CDCl_3$) collapsed iminosugar signals δ 139.0, 138.5, 138.5, 138.0 (4×C_q Bn), 128.5, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6 (CH_{Ar} Bn), 82.1 (OCH_2-Ada), 76.4 (CH), 75.5, 73.6, 73.2, 73.1, 71.6, 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 28.4 (CH Ada), 29.6, 28.6, 23.1 (3×CH_2 pentyl). MS (ESI): found 774.7 $[M+H]^+$, calculated for $[C_{50}H_{63}NO_6+H]^+$ 774.5.

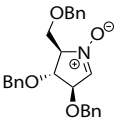


***N*-[5-(Adamantan-1-yl-methoxy)-pentyloxy]-1-deoxynojirimycin (47).** A dry (100 mL) three-neck roundbottom flask was cooled to –60 °C and ammonia gas (via a CaO filled drying column) was passed through it until 20-30 mL ammonia has condensed. The ammonia gasflow was stopped and sodium (50–100 mg, rinsed beforehand with heptane) was added to the liquid ammonia. After stirring the dark blue mixture at –60 °C for 1 min, a solution of the **46** (95 mg, 120 µmol) in *t*BuOH/ THF (0.2 mL/1 mL) was added. The reaction mixture was stirred for 1-2 h at –60 °C and additional sodium was added if the blue color of the mixture disappears. The reaction was quenched by slow addition of sat aq NH_4HCOOH (1 mL). The ammonia was evaporated and the resulting residue was coevaporated with dioxane. The solid residue was redissolved in MeOH and concentrated in the presence of celite. The celite-compound mixture was purified by silica gel column chromatography (10% » 20% MeOH in $CHCl_3$+5% NH_4OH) to afford **47** (26 mg, 63 µmol) in 53% yield as a colourless oil. R_F = 0.39 (3:1; EtOAc:MeOH +1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) collapsed iminosugar signals δ 3.93 (dd, *J* = 3.1, 11.2, 1H, H-6a), 3.87 – 3.78 (m, 1H, H-6b), 3.75 (t, *J* = 6.3, 2H, $NOCH_2$-1 pentyl), 3.50 – 3.44 (m, 1H)3.47 (dd, *J* = 4.5, 11.4, 1H, H-1a), 3.39 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.19 (dd, *J* = 8.9, 1H), 2.97 (s, 2H, OCH_2-Ada), 2.50 – 2.36 (m, 1H, H-1b), 1.95 (s, 3H, 3×CH Ada), 1.72 (dd, *J* = 11.6, 30.4, 6H, 3×CH_2 Ada), 1.63 – 1.52 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.47 – 1.38 (m, 2H, CH_2-3 pentyl). ^{13}C

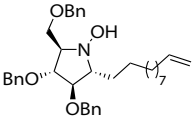
NMR (100 MHz, MeOD) collapsed iminosugar signals δ 83.2 (OCH_2-Ada), 80.4 (CH), 74.0 ($NOCH_2$-1 pentyl), 72.7 (CH_2-5 pentyl), 70.6 (CH), 69.2 (CH), 61.4 (C-1), 60.2 (C-6), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 30.7, 29.8 (2×CH_2 pentyl), 29.9 (CH Ada), 24.3 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3359, 2902, 2849, 1453, 1105, 1043. $[\alpha]^{20}_D$: 1.0 (*c* 0.4, MeOH). HRMS: found 414.2848 $[M+H]^+$, calculated for $[C_{22}H_{39}O_6N_1+H]^+$ 414.2850.

Synthesis of Broussonetine C and E intermediates 50 and 55; and Broussonetine analogs 57 and 59:



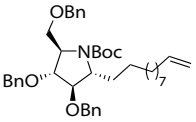


1,4-Anhydro-2,3,5-tri-*O*-benzyl-1-deoxy-1-imino-D-arabinitol *N*-oxide (48). Cyclic nitrone **48** was prepared according to a procedure reported[16] by Vogel *et al.* from D-arabinose and obtained as a white solid that was stable for several weeks when stored at −20 °C. R_F = 0.50 (5% MeOH in Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 15H, H_{Ar} Bn), 6.88 (t, *J* = 1.9, 1H, H-1), 4.66 (td, *J* = 0.8, 2.2, 1H, H-2), 4.61 (d, *J* = 12.0, 1H, C*H*H Bn), 4.55 (s, 2H, CH_2 Bn), 4.54 (s, 2H, CH_2 Bn), 4.51 (d, *J* = 12.0, 1H, CH*H* Bn), 4.37 (dd, *J* = 2.1, 3.7, 1H, H-3), 4.04 (dd, *J* = 5.1, 10.0, 1H, C*H*H-5), 4.01 (ddd, *J* = 1.1, 2.3, 5.1, 1H, H-4), 3.77 (dd, *J* = 2.8, 10.0, 1H, CH*H*-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9, 137.4, 137.3 (C_q Bn), 133.1 (C-1), 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9 (CH_{Ar} Bn), 83.0, 80.6, 77.7 (C-2), 73.7 (C-3), 72.1 (C-4), 71.9 (CH_2 Bn), 66.3 (C-5). MS (ESI): found 418.2 $[M+H]^+$, calculated for $[C_{26}H_{28}NO_4+H]^+$ 418.2.

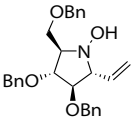


(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-(undec-1-en-11-yl)-D-arabinitol (49). A solution of undec-1-en-11-ylmagnesium bromide was prepared by combining 'dry strirred'[26] magnesium (350 mg, 14.4 mmol), 11-bromoundec-1-ene (2.61 mL, 12 mmol) and two drops of ethylenedibromide in THF (12 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. The solution of the undec-1-en-11-ylmagnesium bromide was added over a period of 1 min to a dry and cooled (−50 °C) solution of **48** (1.42 g, 3.41 mmol) in THF (34 mL). The reaction mixture was stirred for 1h at −50 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (200 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 20% EtOAc in PE) to afford **49** (1.61 g, 2.82 mmol) in 82% as an off-white solid. R_F = 0.36 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 15H, H_{Ar} Bn), 6.67 (s, 1H, N-OH), 5.80 (ddt, *J* = 6.7, 10.2, 16.9, 1H,=CH undecenyl), 5.06 – 4.86 (m, 2H, =CH_2 undecenyl), 4.60 – 4.38 (m, 6H, 3×CH_2 Bn), 3.94 (dd, *J* = 2.8, 3.8, 1H, H-3), 3.82 – 3.76 (m, 2H, H-2, H-5a), 3.58 (dd, *J* = 6.9, 9.3, 1H, H-5b), 3.55 – 3.48 (m, 1H, H-4), 3.16 (dt, *J* = 8.1, 5.4, 1H, H-1a), 2.07 – 1.98 (m, 2H, CH_2-9 undecenyl), 1.93 – 1.78 (m, 1H, C*H*H-1 undecenyl), 1.57

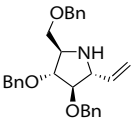
– 1.42 (m, 1H, CH*H*-1 undecenyl), 1.42 – 1.19 (m, 14H, 7×CH_2 undecenyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (=CH undecenyl), 138.4, 138.3 (C_q Bn), 128.8, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8 (H_{Ar} Bn), 114.3 (=CH_2 undecenyl), 87.0 (C-2), 84.9 (C-3), 73.5, 71.9, 71.8 (CH_2 Bn), 70.3 (C-1), 70.3 (C-4), 68.6 (C-5), 34.0 (CH_2-9 undecenyl), 30.0, 29.8, 29.7, 29.6, 29.3, 29.2, 26.8, 25.9 (8×CH_2 undecenyl). MS (ESI): found 572.4 $[M+H]^+$, calculated for $[C_{37}H_{49}NO_4+H]^+$ 572.4.



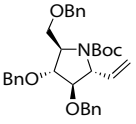
(1*R*)-2,3,5-Tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1,4-dideoxy-1,4-imino-1-*C*-(undec-1-en-11-yl)-D-arabinitol (50). Zinc powder (553 mg, 8.46 mmol) was added to a mixture of **49** (1.61 g, 2.82 mmol) in EtOH (40 mL) and sat aq NH_4Cl (20 mL). The suspension was refluxed at 88 °C for 1h. The mixture was cooled to rt and filtered over celite. The filter cake was washed with EtOH (3×) and the combined filtrate was concentrated. The residue was divided between EtOAc (100 mL) and sat aq $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissolved in dioxane (20 mL) and aq 5% $NaHCO_3$ (10 mL) was added. Boc-anhydride (872 mg, 4 mmol) was added to the mixture and the resulting milk white mixture was stirred for 20h. The mixture was diluted with water (100 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to provide **50** (1.48 g, 2.26 mmol) in 80% yield over two steps as a colourless oil. R_F **50** = 0.71 (20% EtOAc in PE); R_F intermediate amine = 0.20 (20% EtOAc in PE + 5% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 7.35 – 7.10 (m, 30H, H_{Ar} Bn A/B), 5.79 (ddt, *J* = 6.7, 10.2, 16.9, 2H, =CH undecenyl A/B), 5.03 – 4.88 (m, 4H, =CH_2 undecenyl A/B), 4.66 – 4.28 (m, 12H, CH_2 Bn A/B), 4.23 (dd, *J* = 4.0, 10.4, 1H, H-4 B), 4.17 (s, 1H, H-3 B), 4.14 (s, 1H, H-3 A), 4.06 (dd, *J* = 3.9, 10.3, 1H, H-4 A), 4.04 (dd, *J* = 4.2, 8.7, 1H, H-5a B), 3.82 (dd, *J* = 2.8, 10.8, 1H, H-1 A/B), 3.80 (s, 1H, H-2 A/B), 3.80 – 3.75 (m, 2H, H-2 A/B, H-5a A), 3.68 (dd, *J* = 2.7, 11.0, 1H, H-1 A/B), 3.53 – 3.41 (m, 2H, H-5b A, H-5b B), 2.07 – 1.97 (m, 2H, CH_2-9 undecenyl A/B), 1.85 – 1.49 (m, 2H, CH_2-1 undecenyl A/B), 1.49 – 1.10 (m, 46H, 3×CH_3 Boc A/B, CH_2 undecenyl A/B). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of (A/B; 1/1) rotamers δ 154.1, 153.7 (C=O Boc A/B), 139.1, 139.0 (=CH undecenyl A/B), 138.6, 138.3, 138.0, 137.8, 137.7 (C_q Bn A/B), 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn A/B), 114.2, 114.2 (=CH_2 undecenyl A/B), 84.6, 83.3, 83.2, 81.8, 79.5, 79.4 (C_q Boc A/B), 72.9, 72.9 (C-2 A/B), 71.1 (C-3 B), 70.9 (C-3 A), 70.8 (CH_2 Bn A/B), 68.7 (C-5 A), 68.0 (C-5 B), 64.7, 64.5 (C-1 A/B), 62.6 (C-4 A), 62.5 (C-4 B), 33.8 (CH_2-9 undecenyl A/B), 31.4, 30.2, 29.6, 29.5, 29.5, 29.3, 29.1, 28.9 (CH_2 undecenyl A/B), 28.5, 28.4 (CH_3 Boc A/B), 26.6 (CH_2 undecenyl A/B). MS (ESI): found 656.3 $[M+H]^+$, calculated for $[C_{42}H_{57}NO_5+H]^+$ 656.4.



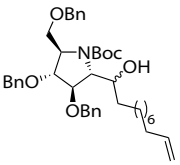
(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-vinyl-D-arabinitol (51). Vinyl magnesiumbromide from a new bottle (3.2 mL, 3.2 mmol; 1M in THF) was added over a 1 min period to a dry and cooled (−50 °C) solution of **48** (334 mg, 0.8 mmol) in THF (8 mL). The reaction mixture was stirred at −50 °C until TLC analysis indicated complete consumption of **48**. The reaction mixture was poured into sat aq NH_4Cl (100 mL) and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 30% EtOAc in PE) to afford **51** (295 mg, 0.66 mmol) in 83% yield as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 15H, H_{Ar} Bn), 6.09 – 5.98 (m, 1H, =CH vinyl), 5.33 – 5.24 (m, 1H, =CH_2 vinyl), 4.60 – 4.40 (m, 6H, CH_2 Bn), 4.05 – 3.95 (m, 1H, H-3), 3.95 – 3.86 (m, 1H, H-2), 3.82 – 368 (m, 2H, H-1, H-5a), 3.68 – 3.56 (m, 1H, H-5b), 3.55 – 3.46 (ddd, 1H, H-4). ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.1, 138.0, 137.9 (C_q Bn), 135.5 (=CH vinyl), 128.3 – 127.4 (CH_{Ar} Bn), 119.1 (=CH_2 vinyl), 86.0 (C-2), 83.7 (C-3), 73.2, 71.8, 71.5 (CH_2 Bn), 72.7 (C-1), 69.5 (C-4), 67.7 (C-5). MS (ESI): found 446.2 $[M+H]^+$, calculated for $[C_{28}H_{31}NO_4+H]^+$ 446.2.



(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-1-*C*-vinyl-D-arabinitol (52). Zinc powder (559 mg, 8.55 mmol) was added to a mixture of **51** (1.270 g, 2.85 mmol) in EtOH (20 mL) and sat aq NH_4Cl (10 mL). The suspension was refluxed at 88 °C for 1h. The mixture was cooled to rt and filtered over celite. The filter cake was washed with EtOH (3×) and the combined filtrate was concentrated. The residue was divided between EtOAc (50 mL) and sat aq $NaHCO_3$ (100 mL). The aqueous phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was used crude in the next reaction. A small sample was purified by silica gel chromatography (15% » 20% EtOAc in PE) for characterization. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 15H, H_{Ar} Bn), 5.95 – 5.75 (m, 1H, =CH vinyl), 5.33 – 5.15 (m, 2H, $=CH_2$ vinyl), 4.60 – 4.40 (m, 6H, CH_2 Bn), 3.97-3.75 (m, 2H, H-2, H-3), 3.68 – 3.24 (m, 4H, H-1, H-4, CH_2-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0 (=CH vinyl), 128.1 – 127.0 (CH_{Ar} Bn), 117.7 ($=CH_2$ vinyl), 87.9, 85.5 (C-2, C-3), 73.0, 71.3, 71.1 (CH_2 Bn), 70.0 (C-1), 68.5 (C-5), 64.7 (C-4). MS (ESI): found 429.5 $[M+H]^+$, calculated for $[C_{28}H_{31}NO_3+H]^+$ 430.2.

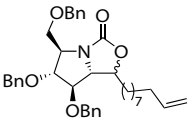


(1*R*)-2,3,5-Tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1,4-dideoxy-1,4-imino-1-*C*-vinyl-D-arabinitol (53). Crude **52** (~2.85 mmol) was dissolved in dioxane (20 mL) and aq 5% $NaHCO_3$ (10 mL) was added. Boc-anhydride (1.27 g, 5.81 mmol) was added to the mixture and the resulting milk white mixture was stirred for 20h. The mixture was diluted with water (100 mL) and extracted with Et_2O (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to provide **53** (1.393 g, 2.63 mmol) in 92% yield over two steps as a colourless oil. R_F = 0.79 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of (A/B; 2/1) rotamers δ 7.39 – 7.10 (m, 30H, H_{Ar} Bn A/B), 5.92 – 5.78 (m, 2H, =CH vinyl A/B), 5.28 – 5.00 (m, 4H, $=CH_2$ vinyl A/B), 4.69 – 4.38 (m, 13H, CH_2 Bn A/B, H-1 B), 4.30 – 4.23 (m, 2H, H-1 A, H-4 A), 4.17 (s, 1H, H-3 B), 4.16 (s, 1H, H-3 A), 4.10 (dd, *J* = 3.7, 10.2, 1H, H-4 B), 3.98 (dd, *J* = 4.2, 8.9, 1H, H-5a A), 3.84 (s, 1H, H-2 B), 3.83 (s, 1H, H-2 A), 3.78 (dd, *J* = 4.0, 8.7, 1H, H-5a B), 3.57 – 3.47 (m, 2H, H-5b A/B), 1.40 (s, 18H, 3×CH_3 Boc A/B). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of (A/B; 2/1) rotamers δ 154.6 (C=O Boc A/B), 138.1, 137.7 (C_q Bn A/B), 137.4, 137.0 (=CH vinyl A/B), 128.7, 128.6, 128.5, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn A/B), 116.3, 116.0 ($=CH_2$ vinyl A/B), 87.1, 86.0 (C-2 A/B), 83.1, 81.6 (C-3 A/B), 80.1, 79.9 (C_q Boc A/B), 73.1, 71.5, 71.2, 71.0 (CH_2 Bn A/B), 68.9, 68.3 (C-5 A/B), 67.5, 66.6 (C-1 A/B), 63.1, 62.7 (C-4 A/B), 28.6, 28.5 (CH_3 Boc A/B). MS (ESI): found 530.3 $[M+H]^+$, calculated for $[C_{33}H_{40}NO_5+H]^+$ 530.3.

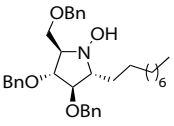


Mixture of 3,4,6-tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-mannitol and 3,4,6-tri-*O*-benzyl-*N*-*t*-butyloxycarbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-glucitol (54). A solution of **53** (530 mg, 1 mmol) in DCM (5 mL; EtOH stabilized) was cooled to –80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for detection of ozone generation). After the reaction mixture had turned blue, ozone flow was continued for a further 15 min. Ozone generation was stopped and oxygen was bubbled through the reaction mixture for ~15 min or until blue coloration had completely disappeared. Dimethylsulfide (0.2 mL, 2.7 mmol) was added and the mixture was stirred and allowed to warm to rt (~1h). The mixture was diluted with Et_2O (100 mL). and washed with water (100 mL). The organic phase was dried ($MgSO_4$), concentrated at ~30°C and the resulting crude aldehyde (colourless oil) was used crude in the next reaction. Next, a solution of dec-1-en-10-ylmagnesium bromide was prepared by combining 'dry strirred'[26] magnesium (146 mg, 6 mmol), 10-bromodec-1-ene (1.81 mL, 5 mmol) and two drops of ethylenedibromide in THF (5 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. The solution of the undec-1-en-11-ylmagnesium bromide was added over a period of 1 min to a dry and cooled (–70 °C) solution of the crude aldehyde (~1 mmol) in THF

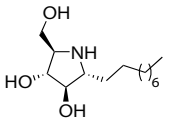
(10 mL). The reaction mixture was stirred for 30 min at −70 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (10% » 15% EtOAc in PE) to produce **54** (521 mg, 0.78 mmol) in 78% over two steps as a colourless oil. R_F = 0.52 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereoisomers and rotamers δ 7.29 – 7.17 (m, 15H, H_{Ar} Bn), 5.83 – 5.75 (m, 1H, =CH decenyl), 5.10 – 4.85 (m, 2H, =CH_2 decenyl), 4.60 – 3.40 (m, 13H, 3×CH_2 Bn, H-1, H-2, H-3, H-4, H-5, CH_2-6), 2.03 – 1.94 (m, 2H, CH_2-8 decenyl), 1.43 (s, 9H, 3×CH_3 Boc), 1.70 – 1.10 (m, 14H, 7×CH_2 decenyl). ^{13}C NMR (400 MHz, $CDCl_3$) mixture diastereoisomers and rotamers δ 155.5, 154.7 (C=O Boc), 139.8 (=CH decenyl), 139.3 – 137.8 (C_q Bn), 128.2 – 127.9 CH_{Ar} Bn), 115.1 (=CH_2 decenyl), 85.6, 84.2 (C-3), 82.3, 80.8 (C-4), 74.0 (C_q Boc), 72.6 – 71.8 (CH_2 Bn), 71.5, 71.4 (C-1, C-2), 69.3, 68.7 (C-6, rotamers), 64.1, 63.9 (C-5), 34.7 – 29.8 (CH_2 decenyl), 29.0, 28.8 (CH_3 Boc), 27.1, 26.5 (CH_2 decenyl). MS (ESI): found 671.7 $[M+H]^+$, calculated for $[C_{42}H_{57}NO_6+H]^+$ 672.4.



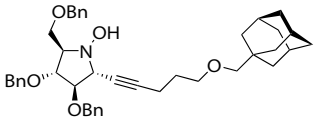
Mixture of 3,4,6-tri-*O*-benzyl-*N*,1-*O*-carbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-mannitol and 3,4,6-tri-*O*-benzyl-*N*,1-*O*-carbonyl-1-*C*-(dec-1-en-10-yl)-2,5-dideoxy-2,5-imino-D-glucitol (55). Sodium hydride (10 mg, 0.26 mmol; 10% in mineral oil) was added to a dry and cooled (0 °C) solution of **54** (92 mg, 130 µmol) in DMF (10 mL). The reaction mixture was stirred at 0 °C for 2h. The reaction was quenched with H_2O, concentrated and the resulting residue was diluted with Et_2O (50 mL) and washed with H_2O (50 mL). The organic phase was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel chromatography (10% » 13% EtOAc in PE) to yield **55** (52 mg, 87 µmol) as a 1:6 mixture of diastereoisomers in 67%. R_F = 0.71 (1:4; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) major isomer δ 7.41 – 7.18 (m, 15H, H_{Ar} Bn), 5.81 (ddt, *J* = 6.6, 10.1, 16.9, 1H, =CH decenyl), 5.09 – 4.93 (m, 2H, =CH_2 decenyl), 4.93 – 4.89 (m, 1H, H-1), 4.68 – 4.35 (m, 6H, 3×CH_2 Bn), 4.29 – 3.48 (m, 6H, H-2, H-3, H-4, H-5, CH_2-6), 2.11 – 1.95 (m, 2H, CH_2-8 decenyl), 1.84 – 1.48 (m, 2H, CH_2-1 decenyl), 1.48 – 1.14 (m, 20H, 6×CH_2 decenyl). ^{13}C NMR (50 MHz, $CDCl_3$) major isomer δ 154.1 (C=O), 139.3 (=CH decenyl), 137.0, 136.5 (C_q Bn), 128.6, 128.4, 128.3, 128.1, 127.9, 127.8 (CH_{Ar} Bn), 114.4 (=CH_2 decenyl), 88.2, 85.9 (C-3, C-4), 80.4 (C-1), 73.5, 72.7, 72.2 (CH_2 Bn), 69.9 (C-6), 67.6 (C-2), 62.5 (C-5), 34.1 (CH_2-8 decenyl), 29.8 – 24.8 (CH_2 decenyl). MS (ESI): found 598.3 $[M+H]^+$, calculated for $[C_{38}H_{47}NO_5+H]^+$ 598.3.



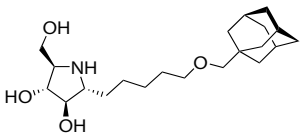
(1*R*)-2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-1-*C*-nonyl-D-arabinitol (56). A solution of nonyl magnesiumbromide was prepared by combining 'dry stirrred'[26] magnesium (58 mg, 2.4 mmol), 1-bromononane (0.38 mL, 2.0 mmol) and a drop of ethylenedibromide in THF (2 mL). The reaction was stirred for 1h with optional heating if the reaction stalled and cooled to rt when finished. A portion of the nonyl magnesiumbromide solution (0.5 mL, ~0.5 mmol) was added drop wise to a dry and cooled (−50 °C) solution of **48** (70 mg, 0.17 mmol) in THF (2 mL). The reaction mixture was stirred for 1h at −50 °C after which sat aq NH_4Cl was added carefully. The mixture was poured into sat aq NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to afford **56** (75 mg, 0.14 mmol) in 82% as an off-white solid. R_F = 0.30 (20% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 15H, H_{Ar} Bn), 6.59 (s, 1H, N-OH), 4.62 – 4.41 (m, 6H, 3×CH_2 Bn), 3.94 (dd, *J* = 2.7, 4.0, 1H, H-3), 3.82 – 3.76 (m, 2H, H-2, H-5a), 3.58 (dd, *J* = 6.9, 9.3, 1H, H-5b), 3.54 – 3.49 (m, 1H, H-4), 3.16 (dt, *J* = 5.4, 8.1, 1H, H-1), 1.95 – 1.80 (m, 1H, C*H*H-1 nonyl), 1.56 – 1.40 (m, 1H, CH*H*-1 nonyl), 1.40 – 1.17 (m, 14H, 7×CH_2 nonyl), 0.88 (t, *J* = 6.9, 3H, CH_3 nonyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 138.3 (C_q Bn), 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8 (CH_{Ar} Bn), 86.9, 84.8 (C-2, C-3), 73.5, 71.9, 71.8 (CH_2 Bn), 70.3 (C-1, C-4), 68.5 (C-5), 32.1, 30.0, 29.8, 29.6, 28.9, 26.8, 22.9 (CH_2 nonyl), 14.3 (CH_3 nonyl). MS (ESI): found 546.3 $[M+H]^+$, calculated for $[C_{35}H_{47}NO_4+H]^+$ 546.4.



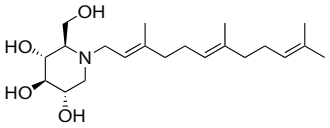
(1*R*)-1,4-dideoxy-1,4-imino-1-*C*-nonyl-D-arabinitol (57). Compound **56** (69 µmol) was subjected to general procedure A to provide **57** (15 mg, 58 µmol) after silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ +5% NH_4OH) in 84% yield as a colourless oil. R_F = 0.25 (20% MeOH in $CHCl_3$ +5% NH_4OH). ^{1}H NMR (300 MHz, MeOD) δ 3.85 (dd, *J* = 5.9, 6.5, 1H, H-3), 3.76 (dd, *J* = 4.2, 11.5, 1H, H-5a), 3.71 (dd, *J* = 5.9, 7.0, 1H, H-2), 3.68 (dd, *J* = 6.2, 11.5, 1H, H-5b), 3.22 – 3.16 (m, 1H, H-4), 3.07 (ddd, *J* = 5.7, 7.0, 8.2, 1H, H-1), 1.86 – 1.68 (m, 1H, C*H*H-1 nonyl), 1.65 – 1.48 (m, 1H, CH*H*-1 nonyl), 1.48 – 1.23 (m, 14H, 7×CH_2 nonyl), 0.90 (t, *J* = 6.9, 3H, CH_3 nonyl). ^{13}C NMR (100 MHz, MeOD) δ 80.8 (C-2), 77.1 (C-3), 65.8 (C-4), 64.6 (C-1), 59.9 (C-5), 32.4 (CH_2-1 nonyl), 33.2, 30.8, 30.6, 30.6, 30.6, 27.4, 23.9 (7×CH_2 nonyl), 14.6 (CH_3 nonyl). MS (ESI): found 260.1 $[M+H]^+$, calculated for $[C_{14}H_{29}NO_3+H]^+$ 260.1.



(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-hydroxylimino-D-arabinitol (58). A dry solution of 5-(adamantane-1-yl-methoxy)-pent-1-yne (46 mg, 0.2 mmol; see Chapter 5 for synthesis) in THF (2 mL) was cooled to –50 °C and BuLi (0.13 mL, 0.2 mmol, 1.6M in toluene) was added slowly to the solution. After stirring for 1 h at –50 °C, a dry solution of **48** (83 mg, 0.2 mmol) in THF (1 mL) was slowly added and the reaction was stirred at –50 °C for 1 h. The reaction mixture was quenched (sat aq NH_4Cl), warmed to rt and poured into sat aq NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to provide **58** (92 mg, 0.14 mmol) in70% yield as a colourless oil. R_F = 0.49 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 15H, H_{Ar} Bn), 5.68 (s, 1H, N-OH), 4.63 (d, *J* = 11.9, 1H, C*H*H Bn), 4.58 (d, *J* = 12.1, 1H, C*H*H Bn), 4.51 – 4.42 (m, 4H, 2×CH*H* Bn, CH_2 Bn), 4.22 (d, *J* = 2.1, 1H, H-1), 4.04 (dd, *J* = 2.4, 1H, H-2), 3.92 (dd, *J* = 2.5, 6.6, 1H, H-3), 3.71 (dd, *J* = 3.6, 9.4, 1H, H-5a), 3.68 (dd, *J* = 3.4, 9.4, 1H, H-5b), 3.43 (t, *J* = 6.1, 2H, CH_2-5 pentyn), 3.35 (dt, *J* = 4.3, 6.5, 1H, H-4), 2.92 (s, 2H, OCH_2-Ada), 2.33 (td, *J* = 2.0, 7.2, 2H, CH_2-3 pentyn), 1.93 (s, 3H, 3×CH Ada), 1.80 – 1.72 (m, 2H, CH_2-4 pentyn), 1.66 (dd, *J* = 12.1, 28.5, 6H, 3×CH_2 Ada), 1.50 (d, *J* = 2.6, 6H, 3×CH_2 Ada). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.2, 137.7 (C_q Bn), 128.5, 128.4, 128.1, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 88.4 (C_q pentyn), 86.6, 82.8 (C2. C-3), 82.1 (OCH_2-Ada), 75.0 (C_q pentyn), 73.5, 72.0, 71.9, 70.0 (3×CH_2 Bn, CH_2-5 pentyn), 69.3 (C-1), 68.1 (C-5), 62.2 (C-4), 39.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.0 (CH_2-4 pentyn), 28.4 (CH Ada), 15.9 (CH_2-3 pentyn). MS (ESI): found 650.3 $[M+H]^+$, calculated for $[C_{42}H_{52}NO_5+H]^+$ 650.4.

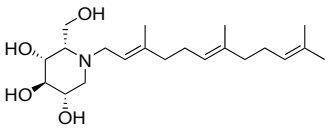


(1*R*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-1,4-dideoxy-1,4-imino-D-arabinitol (59). Compound **58** (80 µmol) was subjected to general procedure A to provide **59** (26 mg, 71 µmol) after silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ +5% NH_4OH) in 89% yield as a colourless oil. R_F = 0.25 (20% MeOH in $CHCl_3$ +5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.98 (dd, *J* = 5.6, 6.3, 1H, H-3), 3.88 (dd, *J* = 4.1, 12.1, 1H, H-5a), 3.86 (dd, *J* = 5.6, 6.6, 1H, H-2), 3.82 (dd, *J* = 6.4, 12.1, 1H, H-5b), 3.49 (td, *J* = 3.8, 6.3, 1H, H-4), 3.40 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.36 – 3.33 (m, 1H, H-1), 2.97 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.92 – 1.83 (m, 1H, C*H*H-1 pentyl), 1.82 – 1.41 (m, 19H, 6×CH_2 Ada, CH*H*-1 pentyl, 3×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.2 (OCH_2-Ada), 80.5 (C-2), 76.8 (C-3), 72.6 (CH_2-5 pentyl), 65.8 (C-4), 64.6 (C-1), 59.7 (C-5), 41.0 (CH_2 Ada), 38.5 (CH_2 Ada), 35.3 (C_q Ada), 32.2 (CH_2-2 pentyl), 30.5 (CH_2-4 pentyl), 29.9 (CH Ada), 27.2, 27.1 (2×CH_2 pentyl). MS (ESI): found 368.3 $[M+H]^+$, calculated for $[C_{21}H_{37}NO_4+H]^+$ 368.3.



***N*-[1-(*trans*,*trans*-3,7,11-trimethyl-2,6,10-dodecatriene)]-1-deoxynojirimycin (60).** Potassium carbonate (34 mg, 0.25 mmol) was added to a dry solution of 1-deoxynojirmycin (24 mg, 0.15 mmol; synthesis described in Chapter 3) and *trans*,*trans*-farnesyl bromide (43 µL,

0.16 mmol) in DMF (0.5 mL). The reaction mixture was heated at 105 °C for 5h after which the mixture was filtered over a glass fibre filter and concentrated. The residue was purified by silica gel column chromatography (10% » 20% MeOH in DCM + 1% NH_4OH) to afford **60** (45 mg, 0.12 mmol) in 80% yield as a colourless oil. R_F = 0.17 (20% MeOH in DCM + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 5.48 – 5.29 (m, 1H, =CH-2 farnesyl), 5.27 – 5.02 (m, 2H, =CH-6, =CH-10 farnesyl), 4.23 – 4.05 (m, 1H, H-6a), 4.04 – 3.85 (m, 2H, H-6b, NC*H*H-1 farnesyl), 3.83 – 3.73 (m, 1H, NCH*H*-1 farnesyl), 3.73 – 3.62 (m, 1H, H-2), 3.62 – 3.51 (m, 1H, H-4), 3.46 – 3.33 (m, 2H, H-3, H-1a), 3.05 – 2.88 (m, 1H, H-5), 2.86 – 2.66 (m, 1H, H-1b), 2.40 – 1.91 (m, 8H, CH_2-4,5,8,9 farnesyl), 1.91 – 1.46 (m, 12H, 4×CH_3 farnesyl). ^{13}C NMR (50 MHz, MeOD) δ 149.1, 137.0, 132.3 (=C_q-3,7,11 farnesyl), 125.5, 124.8, 114.0 (=CH-2,6,10 farnesyl), 78.6, 69.3, 68.2, 67.3 (C-2, C-3, C-4, C-5), 55.7, 54.6, 51.7 (C-1, C-6, NCH_2-1 farnesyl), 41.0, 40.9, 27.9, 27.3 (4×CH_2 farnesyl), 26.0, 17.9, 17.2, 16.3 (4×CH_3 farnesyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2962, 2924, 1643, 1443, 1381, 1080, 1026. $[\alpha]^{20}_D$: −1.3 (*c* 0.9, MeOH). HRMS: found 368.2820 $[M+H]^+$, calculated for $[C_{21}H_{37}O_4N+H]^+$ 368.2795.



***N*-[1-(*trans*,*trans*-3,7,11-trimethyl-2,6,10-dodecatriene)]-L-*ido*-1-deoxynojirimycin (61).** Potassium carbonate (648 mg, 4.69 mmol) was added to a dry solution of L-*ido*-1-deoxynojirmycin (521 mg, 3.19 mmol; synthesis described in Chapter 3) and *trans*,*trans*-farnesyl bromide (924 µL, 3.44 mmol) in DMF (16 mL). The reaction mixture was heated at 90 °C for 4h after which the mixture was filtered over a glass fibre filter and concentrated. The residue was purified by silica gel column chromatography (10% » 20% MeOH in DCM + 1% NH_4OH) to afford **61** (905 mg, 2.36 mmol) in 77% yield as an off-white hygroscopic foam. R_F = 0.19 (20% MeOH in DCM + 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 5.32 (t, *J* = 6.9, 1H, =CH-2 farnesyl), 5.17 – 5.01 (m, 2H, =CH-6, =CH-10 farnesyl), 3.91 (d, *J* = 5.2, 2H, CH_2-6), 3.87 – 3.78 (m, 1H, H-4), 3.73 – 3.63 (m, 1H, H-2), 3.63 – 3.46 (m, 3H, H-3, NCH_2-1 farnesyl), 3.26 – 3.12 (m, 1H, H-5), 3.07 – 2.93 (m, 1H, H-1a), 2.92 – 2.71 (m, 1H, H-1b), 2.22 – 1.95 (m, 8H, CH_2-4,5,8,9 farnesyl), 1.73, 1.67, 1.61, 1.60 (4×s, 4×3H, 4×CH_3 farnesyl). ^{13}C NMR (100 MHz, MeOD) δ 136.7, 132.3 (=C_q-3,7,11 farnesyl), 125.6, 125.1 (=CH-2,6,10 farnesyl), 72.7, 70.6, 64.1 (C-2, C-3, C-4, C-5), 59.1, 53.1, 53.0 (C-1, C-6, NCH_2-1 farnesyl), 41.1, 41.0, 27.9, 27.5 (4×CH_2 farnesyl), 26.0, 17.9, 16.9, 16.3 (4×CH_3 farnesyl). IR ν_{max}(thin film)/ cm^{-1}: 3317, 2962, 2916, 2862, 1666, 1443, 1381, 1242, 1072, 1042, 980, 833. MS (ESI): found 368.5 $[M+H]^+$, calculated for $[C_{21}H_{37}O_4N+H]^+$ 368.3.

References

(1) Mellor, H. R.; Nolan, J.; Pickering, L.; Wormald, M. R.; Platt, F. M.; Dwek, R. A.; Fleet, G. W. J.; Butters, T. D. *Biochem. J.* **2002**, *366*, 225-233.

(2) Verdoes, M.; Florea, B. I.; Menendez-Benito, V.; Maynard, C. J.; Witte, M. D.; Van der Linden, W. A.; Van den Nieuwendijk, A.; Hofmann, T.; Berkers, C. R.; van Leeuwen, F. W. B.; Groothuis, T. A.; Leeuwenburgh, M. A.; Ovaa, H.; Neefjes, J. J.; Filippov, D. V.; Van der Marel, G. A.; Dantuma, N. P.; Overkleeft, H. S. *Chem. Biol.* **2006**, *13*, 1217-1226.

(3) Hashimoto, M.; Hatanaka, Y. *Eur. J. Org. Chem.* **2008**, 2513-2523.

(4) Ovaa, H.; van Swieten, P. F.; Kessler, B. M.; Leeuwenburgh, M. A.; Fiebiger, E.; van den Nieuwendijk, A.; Galardy, P. J.; van der Marel, G. A.; Ploegh, H. L.; Overkleeft, H. S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3626-3629.

(5) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007-2010.

(6) Romaniouk, A. V.; Silva, A.; Feng, J.; Vijay, I. K. *Glycobiology* **2004**, *14*, 301-310.

(7) Nomoto, T.; Fukuhara, T.; Hara, S. *Synlett* **2006**, 1744-1746.

(8) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934-12935.

(9) Maughan, M. A. T.; Davies, I. G.; Claridge, T. D. W.; Courtney, S.; Hay, P.; Davis, B. G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3788-3792.

(10) van den Broek, L. A. G. M. *Tetrahedron* **1996**, *52*, 4467-4478.
(11) Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539-1553.
(12) Perlmutter, P.; Vounatsos, F. *J. Carbohydr. Chem.* **2003**, *22*, 719-732.
(13) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5987-5990.
(14) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.-Eur. J.* **2006**, *12*, 6607-6620.
(15) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335-1336.
(16) Carmona, A. T.; Whigtman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066-3073.
(17) Desvergnes, S.; Py, S.; Vallee, Y. *J. Org. Chem.* **2005**, *70*, 1459-1462.
(18) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485-504.
(19) Stütz, A. E.; (Ed) *Chapter 9 in Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond* Wiley-VCH, **1999**.
(20) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 750-770.
(21) Zhu, X. X.; Sheth, K. A.; Li, S. H.; Chang, H. H.; Fan, J. Q. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 7450-7453.
(22) Liang, D.; DeCamp Schuda, A.; Fraser-Reid, B. *Carbohydr. Res.* **1987**, *164*, 229-240.
(23) Mintz, M. J.; Walling, C. *Org. Syntheses* **1973**, *Coll. Vol. 5*, 184.
(24) Rathore, H.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 1945-1952.
(25) van den Berg, R. J. B. H. N.; Noort, D.; Milder-Enacache, E. S.; van der Marel, G. A.; van Boom, J. H.; Benschop, H. P. *Eur. J. Org. Chem.* **1999**, 2593-2600.
(26) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698-703.