Lipophilic iminosugars : synthesis and evaluation as inhibitors of glucosylceramide metabolism

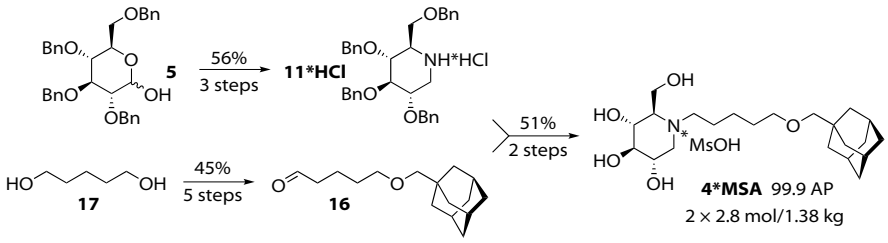
Wennekes, T.

2 The Lead Lipophilic Iminosugar

Development and Optimization of its Large-scale Synthesis

Abstract

The lipophilic iminosugar **4** is the lead compound in the study of inhibitors of glucosylceramide metabolism and their potential applications. This chapter describes the development process of a synthetic route for the large-scale preparation of **4** from its initial version in an academic research laboratory at milligram-scale to the final optimized route at kilogram-scale. The definitive route starts with the separate synthesis of the building blocks **11** and **16** from commercially available **5** and **17**. Reductive amination of the two building blocks and subsequent hydrogenolysis of the penultimate gave **4**. Crystallization of **4** as its methanesulfonic acid salt produced multi-kilogram amounts of **4*MSA** in high purity (99.9%) under cGMP control.

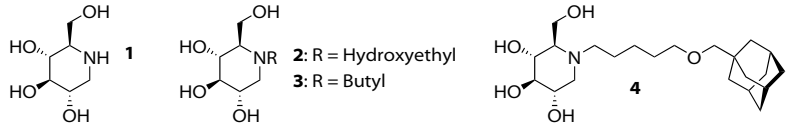


Partly published in: T. Wennekes, B. Lang, M. Leeman, G.A. van der Marel, E. Smits, M. Weber, J. van Wiltenburg, M. Wolberg, J.M.F.G. Aerts, H.S. Overkleeft, *Organic Process Research & Development* **2008**, *12*, 414–423.

Introduction

Ever since the discovery of iminosugars during the sixties and the unearthing of their ability to inhibit glycosidases in the seventies, they have been subject of extensive studies in both organic chemistry and biochemistry.[1,2] Iminosugars (also known as azasugars) are polyhydroxylated alkaloids that can be regarded as monosaccharide analogues with nitrogen replacing the ring oxygen. From this extensive family of compounds, the best known member is 1-deoxynojirimycin (**1**) – a D-glucose configured iminosugar analogue (Figure 1). The first reports of its chemical synthesis were by Paulsen and co-workers in 1966, from 2,3-*O*-isopropylidene-α-L-sorbofuranose, and by Inouye in 1968, from 1,2-*O*-isopropylidene-α-D-glucofuranose (Figure 2).[3-5] In 1976 **1** was also discovered to occur in nature, when it was isolated from the leaves of mulberry trees[6] and certain species of bacteria.[7]

Figure 1. Structures of 1-deoxynojirimycin (**1**), Miglitol (**2**), Miglustat (**3**) and lead compound **4**.

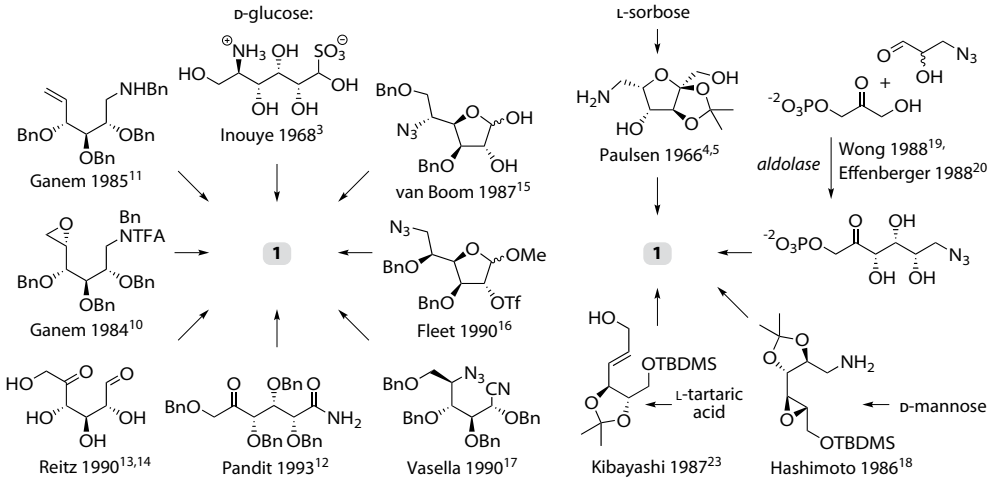


Since then numerous processes for the preparation of **1** have been reported.[8,9] Perhaps not surprisingly, most of these methods use D-glucose as a chiral starting material with an intramolecular cyclization as one of the last steps (Figure 2). Many methods first introduce a nitrogen containing function at C-1 and then create an electrophilic C-5 position for cyclization (L-*ido*-C-5/C-6 epoxide opening by Ganem[10]; aminomercuration of a C-5/C-6 alkene by Ganem[11]; reduction of a cyclic *N*-acyliminium ion from a C-5 keto-amide by Pandit[12]). Alternatively, Baxter and Reitz showed that C-1 nitrogen introduction and cyclization on C-5 can also be achieved in one step by double reductive amination of a hexosulose.[13,14] Alternatively, the nitrogen function can be introduced on C-5 (van Boom[15]) or C-6 (Fleet[16]). Vasella has synthesized **1** by a cycloaddition reaction of a D-glucose derived azido-nitrile.[17] D-Mannose has also been used as a starting material by Hasimoto.[18] Wong and Effenberger developed a chemoenzymatic syntheses for a C-5-keto-azide intermediate that could be cyclized to **1** under reductive conditions.[19-22] Finally, several syntheses starting from non-carbohydrate precursors have been reported, such as from L-tartaric acid by Kibayashi.[23] Many more syntheses of **1** have been published during recent years, but in most cases these are based on the above mentioned syntheses.

Further research into the biological activity of 1-deoxynojirimycin derivatives has already spawned two registered drugs. Miglitol (**2**)[24] is an oral drug for the treatment of type 2 diabetes and Miglustat (**3**)[25,26] is an oral drug for the treatment of Gaucher disease. In the latter case drug action takes place by inhibition of the enzyme glucosylceramide synthase (GCS). GCS is responsible for the biosynthesis of glucosylceramide, which is a member of the glycosphingolipid family and the crucial metabolic precursor in

the biosynthesis of almost all complex glycosphingolipids. Glycosphingolipids are components of the outer plasma membrane and as such are involved in many (patho) physiological processes.[27-30] Catabolism of glucosylceramide is effected by the glycosidase, glucocerebrosidase (GBA1). A second glycosidase – with unknown function – that is capable of cleaving the glycosidic bond of glucosylceramide has recently been identified independently by Aerts and Yildiz as β-glucosidase 2 (GBA2).[31,32]

Figure 2. Overview of synthetic strategies and intermediates in the synthesis of 1-deoxynojirimycin (**1**).



In the study of glucosylceramide metabolism and its inhibitors that is the subject of this thesis, the lipophilic iminosugar **4** was chosen as a lead compound for development of analogues and biological evaluation. Compound **4** inhibits all three enzymes involved in glucosylceramide metabolism and is a hundredfold more potent than Miglustat (**3**) in inhibiting GCS.[33] Besides a potential application of **4** in the treatment of Gaucher disease and related sphingolipidoses,[25,34] the role of glycosphingolipids in many other (patho)physiological processes points towards a wider range of applications. Recently, it became apparent that inhibition of GCS through oral dosage of compound **4** to *ob/ob* mice, which is a type 2 diabetes model, downregulates glycosphingolipid biosynthesis and restores insulin receptor sensitivity (see Chapter 3 for more details).[33] It has also been reported that administration of **4** to mice with chemically induced ulcerative colitis (inflammatory bowel disease) resulted in beneficial anti-inflammatory responses.[35] The crucial role of GCS at the root of glycosphingolipid biosynthesis and its role in these pathological processes makes it an interesting drug target and thereby GCS inhibitor **4** a promising therapeutic lead.

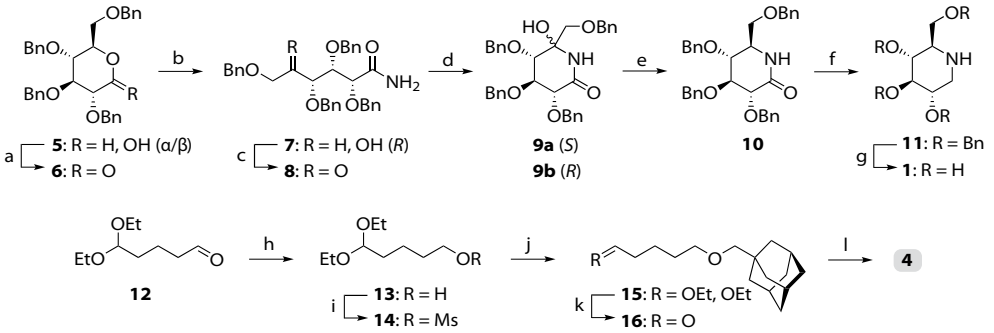
For potential clinical development of compound **4** access to a large supply was needed. Consequently, a study was started to develop an efficient chemical synthesis of **4**, suitable for preparation of kilogram amounts in a miniplant. This chapter describes the development and optimization of the synthetic route for compound **4** from its initial

synthesis in an academic research laboratory to the successfully implemented final synthetic route in a cGMP miniplant.

Results and Discussion

The first synthesis of compound **4** was reported by Pandit and Aerts in 1998, where it was part of a library of lipophilic iminosugars generated to produce a specific inhibitor for GBA2.[36,37] The strategy for its synthesis then was to first prepare two building blocks, 1-deoxynojirimycin (**1**) and 5-(adamantan-1-yl-methoxy)-pentanal (**16**) and condense these via a reductive amination to provide **4**. In this synthesis, **1** was derived from commercially available 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose (**5**) by transformation of its lactone **6** to lactam intermediate **10**, which could be further reduced and deprotected to provide **1** in 29% yield over seven steps (Scheme 1).[12,36-38] Aldehyde **16** was obtained from commercially available glutaric dialdehyde[39] in five steps and 2% overall yield. Finally, reductive amination of **1** and **16** provided 60 mg of **4** in 50% yield. Although this route successfully produced **4**, it was unsuitable for larger scale synthesis of **4**. The main objections to this route were the low overall yield in the synthesis of **4** and the need for several column chromatography purifications. The larger quantities (~100 g) of **4** that were needed at that time for initial investigations into its biological applications,[31,33,35,40] required a search for alternate procedures for the production of **4**.

Scheme 1. First reported synthesis of lead compound **4**.

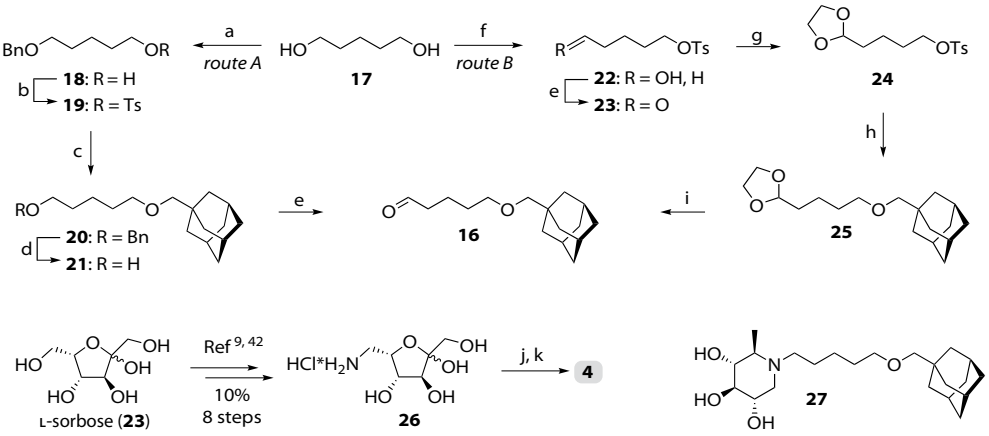


Reagents and conditions: [**a**] DMSO, Ac_2O, 12h, used crude. [**b**] NH_3 in MeOH, 1.5h, 86% 2 steps. [**c**] DMSO, Ac_2O, 12h, used crude. [**d**] NH_3 in MeOH, 1.5h, **9a**:**9b**; 1.8:1 92% 2 steps. [**e**] $NaBH_3CN$, HCOOH/CH_3CN, reflux, 2h, 79%. [**f**] $LiAlH_4$, THF, 70 °C, 3h, 63%. [**g**] $Pd(OH)_2$/C, 5 bar H_2, MeOH/EtOH, HCl, 48h, 74%. [**h**] $NaBH_4$, EtOH, 3h, 41%. [**i**] MsCl, Et_3N, DCM, 1h, used crude. [**j**] i: adamantanemethanol, NaH, DMF, 1h; ii: addition **14**, 70 °C, 4h, 34%. [**k**] 5% aq HCl, acetone, 1h, quantitative.

Development of an alternative route for **4** commenced with changing the starting material for the preparation of **16** to 1,5-pentanediol (**17**) and evaluation of two new synthetic routes for **16**. The first route (*A*; Scheme 2) started with the successive monobenzylation (**18**) and tosylation of **17**. Substitution of the tosylate (**19**) with adamantanemethanol proved more productive than that of mesylate **14** and provided **20** in 92% yield.

Hydrogenolysis of the benzyl ether and Swern oxidation of the resulting alcohol (**21**) provided **16** in 70% yield over 5 steps. The second route (*B*; Scheme 2) started according to a literature procedure[41] with successive monotosylation (**22**), Swern oxidation and protection of the resulting aldehyde (**23**) as the 1,3-dioxolane acetal to produce **24** in 61% yield over the three steps. Substitution of the tosylate (**24**) with adamantanemethanol yielded **25** in 71% yield after purification by distillation. Subsequent acidic hydrolysis of the acetal in **25** provided building block **16** in a yield of 43% over five steps. Despite the lower overall yield, route *B* was chosen for large scale process development, because crude **16** – contrary to **16** from route *A* – did not require column purification after the final step and was obtained more reproducible at a larger scale.

Scheme 2. First optimizations of synthesis 1-deoxynojirmycin (**1**), aldehyde **16** and lead compound **4**.



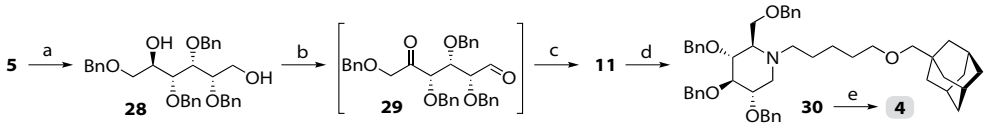
Reagents and conditions: [**a**] NaH (0.25 eq), BnBr (0.25 eq), THF, 80 °C, 20h, 94%. [**b**] TsCl, Et_3N, DMAP (cat), DCM, 0 °C » rt, 20h, 92%. [**c**] i: adamantanemethanol, NaH, DMF, 90 min; ii: 1 eq of **19**, 75 °C, 1h, 92%. [**d**] Pd/C, 5 bar H_2, EtOH, 20h, 97%. [**e**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: addition **21** or **22**, 1.5h; iii: Et_3N, –75 °C » rt, 2h, **16**: 92%; **23**: 91%. [**f**] TsCl, DMAP, Et_3N, DCM, 16h, 70%. [**g**] Ethylene glycol, *p*-TsOH, benzene, reflux, 95%. [**h**] 1: adamantanemethanol, NaH, DMF, 1h; 2: addition **21**, 70 °C, 4h, 71%. [**i**] 6M aq HCl, acetone, 74 °C, 15 min, quantitative. [**j**] PtO_2, 5 bar H_2, 16h, 70%. [**k**] **1*HCl**, **16**, Pd/C, 5 bar H_2, NaOAc, AcOH, EtOH, 65%.

Initially, for larger scale synthesis of the second building block (**1**) a route reported by Behlings and co-workers[42] and also found in patent literature[43] was selected. The route uses L-sorbose (**23**) as an economic starting material and is claimed to be suitable for kg-scale preparation of **1**. However, during process development this route proved low yielding at a large scale and several column purifications were unavoidable. Over eight steps this route yielded 10% of labile penultimate **26** (Scheme 2).[44] The final cyclization into **1** by reductive amination was carried out on 20 g batches of **26** via a platinum-catalyzed hydrogenolysis at 5 bar to produce the HCl salt of **1** in an average yield of 70%. The next stage was the optimization of the reductive amination between building blocks **1** and **16**. Initially, the best reproducible conditions were the use of sodium triacetoxyborohydride and sodium acetate in ethanol that provided **4** on a 1 g scale in an

unimproved yield of 50%. Alternatively, it was found that Pd/C catalyzed hydrogenolysis at 5 bar of **1** and **16** was more efficient and produced 17 g of **4** in a reproducible yield of ~65%. However, column purification of **4** proved necessary to remove an unexpected side product – 6-deoxy derivative **27** (its inhibitory profile is provided in Chapter 8). This side product originated from 1,6-dideoxynojirimcyin that was formed during the platinum-catalyzed hydrogenolysis of **26**. Overall, this route produced 64 g of **4** in 5% yield over ten steps.

The route for building block **16** was now set for translation to kg-scale synthesis (*B*; Scheme 2). On the other hand, the route explored for the second building block, 1-deoxynojirimycin (**1**) was unsuitable for this next stage, mainly because of the low overall yield and the requirement for column chromatography purification of several intermediates and lead compound **4**. In search of a shorter and more efficient route for the large scale synthesis of **1**, a procedure reported by Lopes *et al.* that transforms **5** into **1** in four steps was evaluated.[45] The key reaction in this synthesis is the cyclization of hexosulose **29** via a double reductive amination with ammonium formate to produce **11** (Scheme 3).

Scheme 3. Further optimization of synthesis lead compound **4**.



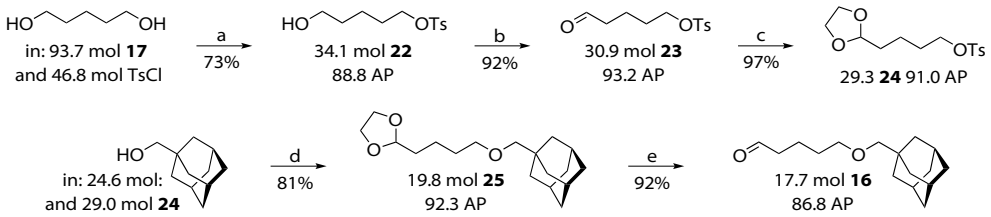
Reagents and conditions: [**a**] $LiAlH_4$, THF, 20h, used crude. [**b**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: addition **28**, 1.5h; iii: Et_3N, –75 °C » rt, 2h, **29** used crude. [**c**] $NaBH_3CN$, excess $HCOONH_4$, 3Å mol. sieves, MeOH, 0 °C to rt, 20h, 65% 3 steps. [**d**] 1.1 eq of **16**, Pd/C, 5 bar H_2, AcOH, EtOH, 20h, **30** used crude. [**e**] Pd/C, 1 bar H_2, HCl, EtOH, 20h, 89% 2 steps.

However, upon application of the original protocol, which uses a Pfitzner-Moffat oxidation and a double reductive amination at room temperature to produce **11**, irreproducible and low yields were obtained. After varying several parameters in the original protocol it was found that the procedure could be optimized by using a Swern oxidation to give **29** and most importantly to execute the double reductive amination of **29** at 0 °C in the presence of a larger excess of ammonium salt. First, **5** was reduced to glucitol **28** with $LiAlH_4$ in THF (Scheme 3). Crude **28** was subjected to a Swern oxidation, which after completion was concentrated under reduced pressure with moderate heating to minimize degradation of the unstable hexosulose intermediate (**29**). The reductive amination was carried out on crude **29** with an excess of ammonium formate in methanol at 0 °C under the agency of $NaBH_3CN$ and in the presence of 3Å molecular sieves. These conditions could reproducibly generate multi-gram amounts of **11** in yields of 60–65% over the three steps. The next reaction would be deprotection of **11** to **1**, but because of the persistent moderate yields obtained in the previous large scale reactions of **1** with aldehyde **16**, it was first investigated whether the reductive amination of **11** with **16** could improve

upon this. When **11** and **16** were exposed to Pd/C catalyzed hydrogenolysis at 5 bar in an ethanol/acetic acid mixture the sole product was **30**. After filtration and concentration, a second hydrogenolysis of crude **30**, now in the presence of hydrochloric acid, produced 2.8 g of target compound **4** in 89% over the two steps.

With this tandem reductive amination/deprotection method and the optimized synthesis of building blocks **11** and **16** in hand, the stage was set for translating the improved synthesis of **4** to a kg-scale miniplant process. Process development of the route for building block **16** focused on optimizing the purity of all intermediates and **16** itself without using column purification. This was quite a challenge as all intermediates are oily liquids and only **25** is stable enough for distillation. Suitable in-process control by HPLC (up to **24**) and GC (**25** and **16**) was developed, which enabled the reactions to be monitored and controlled in an efficient way to ensure complete conversions and effective work-up procedures. The synthesis of **16** started with monotosylation of **17** (Scheme 4). The formation of ditosylate could be minimized to <5% by using 0.5 equivalents of tosylchloride to produce **22**.

Scheme 4. cGMP miniplant synthesis of **4** with GC/HPLC purities of intermediates and **4** in area percent (AP).



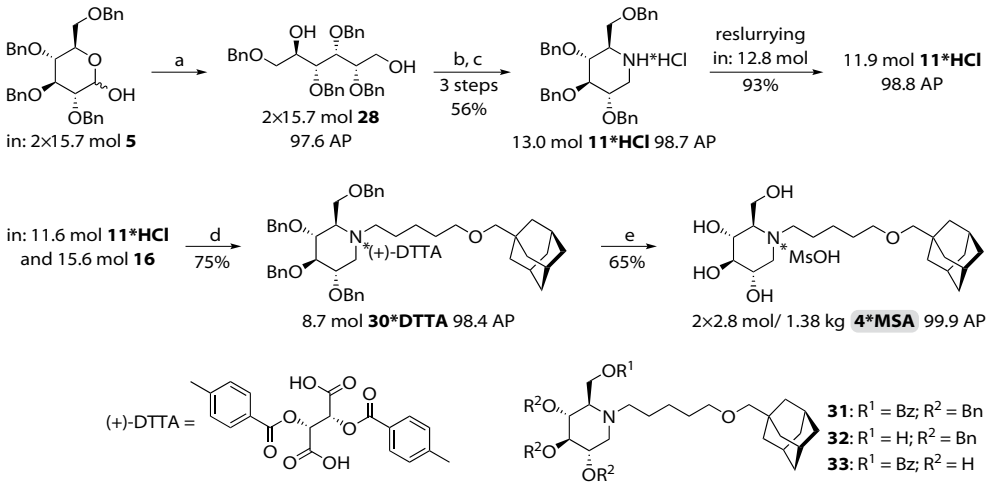
Reagents and conditions: [**a**] in: 93.7 mol **17**, 46.8 mol TsCl (0.5 eq), DMAP, Et_3N, DCM, 20h; Extractive purification. [**b**] in: 33.8 mol **22**, NaOCl, cat. TEMPO, cat. KBr, DCM, 3h; Extractive purification. [**c**] in: 30.4 mol **23**, ethyleneglycol, *p*-TsOH, MTBE, reflux, 3h; Extractive purification. [**d**] i: 24.6 mol adamantanemethanol (0.85 eq), NaH, DMF, 40 °C, 1.5h; ii: Addition 29.0 mol **24**, 40 °C, 3h; Extractive purification and short path distillation. [**e**] in: 19.3 mol **25**; 6M aq HCl, acetone, 40 °C, 1h; Extractive purification.

Swern oxidation of **22** was replaced by a TEMPO/bleach oxidation in order to prevent formation of dimethylsulfide and the difficult handling of all reaction phases thereof. Protection of aldehyde **23** resulted in the 1,3-dioxolane acetal **24** in 96 % yield. Instead of benzene, MTBE was used as reaction solvent because the lower reflux temperature prevented the onset of decomposition of both the starting material (**23**) and product (**24**). As fractional distillation is not feasible on kg-scale, 0.85 equivalent of adamantanemethanol was used in the S_N2 substitution of **24** to minimize the amount of unreacted adamantanemethanol. Remaining traces of adamantanemethanol could be removed with an extractive purification in which a **25** containing heptane phase was washed repeatedly with a methanol/water mixture. Finally, short path distillation provided **25** as a colorless oil in 92% yield related to adamantanemethanol or 68% related to **24**. During process development for the acidic hydrolysis of **25** it was observed that an equilibrium is reached at 8% remaining starting material and that prolonged reaction

times only lead to degradation of product **16**. A solution for this problem was found in performing the reaction two consecutive times with extractive workup in between. This diminished the remaining starting material to < 2% and yielded 5.1 kg of crude **16** in 45% yield over the five steps. The obtained purity of **16** allowed implementing the crude product in the subsequent reductive amination of **16** with **11**.

Process development of the route for the second building block **11** concentrated on adapting the challenging tandem oxidation/double reductive amination sequence to the miniplant and finding a suitable purification procedure for **11**. When the scale of this two-step sequence was increased the Swern reaction mixture took an increasing amount of time to concentrate. This extended exposure to heat resulted in marked degradation of intermediate **29** and as a result significantly lower yields of **11** (~20%). Omitting the concentration step and adding the crude Swern reaction mixture remedied this problem and test reactions now provided **11** in ~70% yield over the three steps.

Scheme 5. cGMP miniplant synthesis of **4** with GC/HPLC purities of intermediates and **4** in area percent (AP).



Reagents and conditions: [**a**] in: 2×15.7 mol **5**, $NaBH_4$, DCM/MeOH, 40 °C, 6h; Extractive purification. [**b**] i: $COCl_2$, DMSO, DCM, –75 °C, 0.5h; ii: Addition 23.0 mol **28**, –75 °C, 2h; iii: Addition Et_3N, –75 °C, 4h, No intermediate purification. [**c**] i: NH_4Ac, $NaCNBH_3$, Na_2SO_4, MeOH, 0 °C; ii: Addition neat Swern reaction mixture (**29**); iii: –5 °C » ambient, 16h; Precipitation as HCl salt. [**d**] i: in: 11.6 mol **11**; generation free base of **11**; ii: Addition 15.6 mol **16**; iii: 10 wt% Pd/C, atm H_2, AcOH/ EtOH (1/21, v/v), 20h; Crystallization as (+)-DTTA salt. [**e**] i: in: 2×4.3 mol **30**; generation freebase **30**; ii: aq NaOH saponification of **31** to **32**; iii: NaOH quench with HCl; iv: 10 wt% Pd/C, atm H_2, HCl/ EtOH, 20h; v: Precipitation as MsOH salt.

In the final production run two 8.5 kg batches of **5** were reduced quantitatively with $NaBH_4$ in refluxing DCM/methanol (Scheme 5). After extractive workup, a 12.5 kg portion of crude **28** was oxidized to hexosulose **29** and the reaction mixture resulting from the Swern oxidation was kept below –60°C and directly transferred (telescoped) to a 0 °C suspension of $NaBH_3CN$, NH_4OAc and Na_2SO_4 in methanol. Lab development had shown that the order of addition, the ammonium source, the temperature and the

methanol dilution (> 0.1M) are critical for this process. Molecular sieves could be replaced by Na_2SO_4 and instead of 20 eq. NH_4HCO_2 10 eq. NH_4OAc were used. The resulting reaction mixture, containing **11**, is contaminated with dimethylsulfide, which has to be completely removed to prevent poisoning of the palladium catalyst used in the final two steps. Treatment of crude **11** with an aq solution of sodium hypochlorite during workup accomplished this. During process development it was observed that **11** is an oil upon isolation, which in purified form only slowly solidifies over time. In order to facilitate purification and isolation, the hydrochloric acid salt of **11** was generated that could be precipitated from acetone at 0 °C and isolated via centrifugation to provide **11*HCl** as an off-white solid in 56% yield over the three reactions. Minor coloured impurities were removed by means of an additional reslurrying step in acetone that produced **11*HCl** with 93% recovery.

The synthesis of **30** was accomplished in the miniplant via the earlier described selective Pd/C catalyzed hydrogenation of the intermediate imine of **11** and **16** in the presence of acetic acid (Scheme 4). Aldehyde **16** was now applied in a larger excess (1.5 eq.) to ensure complete consumption of **11**. Excess **16** and its reduced form (**21**) were removed afterwards by formation of the HCl salt of **30** in methanol/water and washing repeatedly with heptane. As a minor side reaction partial de-benzylation was detected (ca. 10%), but this did not effect further processing to **4**. Penultimate **30** was chosen to be the cGMP starting material and was therefore required to be of defined composition and high in purity, but **30*HCl** is a difficult to handle non-crystalline hygroscopic solid Precipitation of **30** as the (+)-di-*p*-toluoyl-L-tartaric acid ((+)DTTA) salt provided 10.0 kg **30*(+)DTTA** as a stable crystalline solid (98.4 area% by HPLC incl. the de-benzylated side products).

The miniplant procedure for debenzylation of the penultimate **30*(+)DTTA** was identical to the earlier described catalytic hydrogenation in the presence of hydrochloric acid. However, HPLC analysis of a small test-batch of **4** indicated the presence of previously undetected 6-*O*-benzoylated **33** as a minor side product (~1%). Byproduct **33** probably originated from oxidation of the 6-*O*-benzyl ether in a minor amount of **11** during workup of the double reductive amination reaction mixture with sodium hypochlorite. The presence of side product **33** in end product **4** could be prevented by prior saponification of the benzoyl ester before starting the deprotection procedure during miniplant production. The free base of **30** was generated in MTBE, after which the solvent was exchanged from MTBE to ethanol and 6M sodium hydroxide was added. When HPLC analysis indicated complete saponification of **31** to **32**, the reaction mixture was acidified with hydrochloric acid and subjected to Pd/C hydrogenolysis at atmospheric hydrogen pressure. After removal of the catalyst by filtration, residual Pd was reduced to a level of < 20 ppm by a treatment with Ecosorb C-941. Inorganic salts were removed from the reaction mixture by treating crude **4*HCl** with ammonia in methanol and subsequently exchanging the solvent for dichloromethane from which all inorganic salts precipitated and in which **4** remained dissolved.

Previous biological studies were performed with **4*HCl** but it was evident that an alternative for this highly hygroscopic and non crystalline HCl salt had to be found. Free amine **4** also showed the same hygroscopic property and also proved to be unstable after prolonged storage at room temperature. A salt screening showed that the sulfonic acid salts of methansulfonic acid (MSA), ethanesulfonic acid and *p*-toluenesulfonic acid all provided stable, crystalline and non-hygroscopic salts. A brief toxicological study showed identical results for the **4*MSA** salt when compared to the previously evaluated **4*HCl** salt. Deprotection of two separate batches of **30*(+)DTTA** and crystallization of **4** with methanosulfonic acid in isopropanol provided two 1.38 kg batches of **4*MSA** in 65 % yield with a purity of 99.9 area% as judged by HPLC.

Conclusion

This chapter describes the development and implementation of a synthetic route for the reproducible preparation in a cGMP miniplant of kilogram amounts of GCS inhibitor **4*MSA** in high purity and with defined composition. This large scale synthetic preparation of **4** complements the large-scale chemoenzymatic synthesis of the related Miglustat (**3**) reported in 2002 by Landis and co-workers.[46] In this method − based on the work of Kinast and Schedel[47] − the key step is a regioselective oxidation of the C-5 hydroxyl function in *N*-butylglucamine by *Gluconobacter oxydans*.

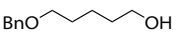
Experimental section

For research laboratory preparations: solvents and reagents were obtained commercially and used as received 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 dimethylsulfoxide 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 $(NH_4)_6Mo_7O_{24}\times 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times 2H_2O$ (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).

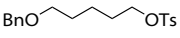
For cGMP glass plant preparations: all solvents and reagents were obtained commercially and used as received unless stated otherwise. Adamantanemethanol was obtained from Inter-Chemical Ltd. (Shenzhen, China) and 2,3,4,6-tetra-*O*-benzyl-D-glucose from Farmak (Olomouc, Czech Republic). Reactions were executed at ambient temperatures and under inert atmosphere unless stated otherwise. Reaction progress was monitored by HPLC and GC analysis. *HPLC in-process control*: Column: Waters Atlantis C_{18}; D: 4.6 mm × L: 150 mm; d_P: 3 µm; Eluent A: H_2O:MeOH = 80:20 + 0,05% TFA; Eluent B: MeOH:CH_3CN = 20:80 + 0.05%TFA; *Method A*: Gradient (t in min; A/B (v/v); flow in mL/ min): 0; 100/0; 0.8 » 1; 100/0;0.8 » 16; 17/83; 0.8 » 17; 100/0; 0.8. Injection volume: 10 µL; Temperature: 25 °C; Detection: λ = 225 nm; Runtime: 22 min; *Method B*: Gradient (t in min; A/B (v/v); flow in mL/ min): 0; 100/0; 0.80 » 1; 100/0; 0.80 » 16; 0/100; 0.80 » 18; 0/100; 0.80 » 19; 100/0; 0.80. Injection volume:

10 µL; Temperature: 25 °C; Detection: λ = 215 nm; Runtime: 24 min. *GC in-process control*: Column: HP1; L: 25 m × D: 320 µm, d_f: 1.05 µm; Flow: 2 mL/min; Oven temperature: 150 °C; 15 °C/min » 300 °C; 300 °C for 5 min; Split: 50; Injection / Detection temperature: 250 °C / 280 °C; Split/Flow: 100; Injection volume: 2 µL; Detection: FID; Runtime: 16 min. DSC measurements were conducted on a Mettler Toledo DSC822e (temperature program 50 °C to 300 °C at 10 °C/min). HPLC and GC in-process control chromatograms and DSC curves for miniplant preparations can be found in reference [44].

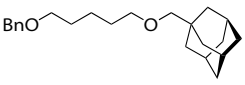
The ^{1}H- and ^{13}C-NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC experiments were recorded on a 200/50 MHz, 300/75 MHz, 400/100 MHz, 500/125 MHz or 600/150 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to the signal of the internal standard tetramethylsilane for $CDCl_3$ or the deuterated solvent signal for CD_3OD and *d6*-DMSO. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. 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). Optical rotations were measured on an automatic Propol 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}.



5-Benzyloxypentan-1-ol (18). Sodium hydride (60% in mineral oil, 1.75 g, 43.7 mmol) was added in portions to a dry and cooled (0 °C) solution of 1,5-pentanediol (**17**, 18.25 g, 175 mmol) in THF (350 mL). The mixture was stirred for 10 min at rt and a sticky solid was formed. NaH (12.0 g, 43.8 mmol) was added in portions. Benzyl bromide (4.2 mL, 35 mmol) was added dropwise over a 2 min period and the resulting reaction mixture was refluxed at 80 °C for 20 h. The reaction mixture was cooled to rt and quenched by addition of little water. The mixture was poured into sat aq NaCl (400 mL) and extracted with Et_2O (2×300 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 50% EtOAc in PE) to provide **18** (6.36 g, 32.8 mmol) in 94% yield as a colorless oil. R_F = 0.60 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 6H, H_{Ar} Bn, 2×H_{Ar} Ts), 4.49 (s, 2H, CH_2 Bn), 3.63 (t, *J* = 6.0, 2H, CH_2-1 pentyl), 3.47 (t, *J* = 6.5, 2H, CH_2-5 pentyl), 1.70 – 1.61 (m, 2H, CH_2 pentyl), 1.62 – 1.53 (m, 2H, CH_2 pentyl), 1.47 – 1.37 (m, 2H, CH_2 pentyl). MS (ESI): *m/z* 195.2 $[M+H]^+$.

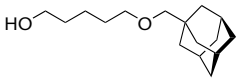


5-Benzyloxy-1-toluene-4'-sulfonyl-pentan (19). *Para*-toluenesulfonic chloride (8.86 g, 46.5 mmol) was added to a dry and cooled (0 °C) solution of **18** (6.02 g, 31.0 mmol), Et_3N (6.45 mL, 46.5 mmol) and DMAP (189 mg, 1.6 mmol) in DCM (93 mL). The reaction mixture was stirred for 20 h, warming to rt. The mixture was washed successively with 1M aq HCl (100 mL), sat aq $NaHCO_3$ (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% » 25% EtOAc in PE) to furnish **19** (9.98 g, 28.6 mmol) in 92% yield as a colorless oil. R_F = 0.70 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3, 2H, 2×H_{Ar} Ts), 7.36 – 7.23 (m, 6H, H_{Ar} Bn, 2×H_{Ar} Ts), 4.46 (s, 2H, CH_2 Bn), 4.01 (t, *J* = 6.5, 2H, CH_2-1 pentyl), 3.41 (t, *J* = 6.4, 2H, CH_2-5 pentyl), 2.42 (s, 3H, CH_3 Ts), 1.70 – 1.60 (m, 2H, CH_2 pentyl), 1.60 – 1.50 (m, 2H, CH_2 pentyl), 1.44 – 1.35 (m, 2H, CH_2 pentyl). MS (ESI): *m/z* 349.3 $[M+H]^+$.

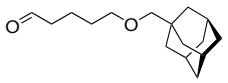


5-(Adamantan-1-yl-methoxy)-1-benzyloxy-pentane (20). A dry solution of adamantanemethanol (5.13 g, 30.9 mmol) in DMF (80 mL) was charged with NaH (1.895 g, 60% wt in mineral oil, 47.40 mmol) and subsequently stirred for 90 min. Next, a dry solution of **19** (9.77 g, 28.1 mmol) in DMF (5 mL) was added to the reaction and the mixture was

heated to 75 °C for 1 h, after which TLC analysis indicated complete consumption of **19** and the reaction mixture was allowed to cool to rt. The reaction was quenched (water, 5 mL) and concentrated. The residue was divided between Et_2O/sat aq $NaHCO_3$ (300 mL; 1/1) and extracted with Et_2O (3×150 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to furnish **20** (8.82 g, 25.8 mmol) in 92% yield as a colorless oil. R_F = 0.81 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.32 (m, 4H, 4×H_{Ar} Bn), 7.26 (m, 1H, H_{Ar} Bn), 4.49 (s, 2H, CH_2 Bn), 3.47 (t, *J* = 5.8 Hz, 2H, CH_2-1), 3.37 (t, *J* = 6.6 Hz, 2H, CH_2-5), 2.94 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 8H, 3×CH_2 Ada, CH_2-2/4), 1.60-1.55 (m, 2H, CH_2-2/4), 1.52 (br d, *J* = 2.4 Hz, 6H, 3×CH_2 Ada), 1.43 (m, 2H, CH_2-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6 (C_q Bn), 128.1 (2×CH_{Ar} Bn), 127.3 (2×CH_{Ar} Bn), 127.2 (CH_{Ar} Bn), 81.7 (OCH_2-Ada), 71.3 (CH_2-5), 70.2 (CH_2-1), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 29.5, 29.3 (CH_2-2, CH_2-4), 28.2 (3×CH Ada), 22.7 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1450, 1358, 1103, 1026, 910, 733, 694. MS (ESI): *m/z* 343.2 $[M+H]^+$.



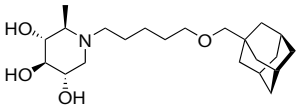
5-(Adamantan-1-yl-methoxy)-1-pentanol (21). Argon was passed through a solution of product **20** (8.82 g, 25.8 mmol) in EtOH (125 mL) for 30 min, after which a catalytic amount of Pd/C (300 mg, 10 wt % on act. carbon) was added. The reaction was shaken in a Parr-apparatus for 20 h under 5 bar of hydrogen pressure. Pd/C was removed by filtration over a glass microfiber filter and the filtrate was concentrated. The residue was purified by silica gel column chromatography (10% » 25% EtOAc in PE) to give **21** (6.24 g, 24.9 mmol) as a colorless oil in 97% yield. R_F = 0.31 (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.65 (t, *J* = 5.8 Hz, 2H, CH_2-1), 3.39 (t, *J* = 6.6 Hz, 2H, CH_2-5), 2.96 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.70-1.41 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 81.8 (OCH_2-Ada), 71.4 (CH_2-5), 62.3 (CH_2-1), 39.5 (3×CH_2 Ada), 37.0 (3×CH_2 Ada), 33.9 (C_q Ada), 32.2, 29.1 (CH_2-2, CH_2-4), 28.0 (3×CH Ada), 22.2 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 1728, 1450, 1366, 1258, 1103, 903, 733, 694. MS (ESI): *m/z* 253.2 $[M+H]^+$.



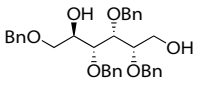
5-(Adamantan-1-yl-methoxy)-1-pentanal (16). A solution of oxalylchloride (789 µL, 9.0 mmol) in DCM (25 mL) was cooled to –78 °C. After dropwise addition of a solution of DMSO (1.28 mL, 18.0 mmol) in DCM (8.2 mL), the reaction mixture was stirred for 30 min while being kept below –70 °C. A dry solution of **21** (2.07 g, 8.2 mmol) in DCM (8.2 mL) was added dropwise to the reaction mixture at –78 °C. After stirring the reaction mixture for 2 h, while being kept below –65 °C, Et_3N (5.7 mL, 41 mmol) was added dropwise. The reaction mixture was allowed to warm to rt over 2 h. The reaction mixture was successively washed with 0.5M aq citric acid (2×30 mL) and water (2×30 mL). The organic phase was dried (Na_2SO_4), concentrated and the resulting residue was purified by flash silica gel column chromatography (5% » 15% EtOAc in PE) to give product **16** (8.82 g, 25.8 mmol) in 92% yield as a pale yellow oil.

Miniplant preparation procedure: At 30 °C and under rapid stirring 6M aq HCl (113.6 L) was added to a solution of **25** (5.68 kg, 19.29 mol) in acetone (56.9 L). The turbid reaction mixture was heated to 40 °C and stirred for 30 minutes. Stirring was stopped and the organic layer was analyzed with GC. After stirring for an additional 30 minutes at 40 °C, the reaction mixture was quenched by transfer to a 0 °C mixture of 3M aq NaOH (227.2 L) and MTBE (113.6 L) with the temperature being kept below 25 °C (additional 3M NaOH was added if pH was not >7). The layers were separated and the aq layer was extracted with MTBE (56.8 L). The combined organic layers were isolated, washed with water (56.8 L) and concentrated at 40 °C to a volume of ~5 L. The light yellow residue was dissolved in acetone (56.8 L) and under rapid stirring 6M aq HCl (56.8 L) was added with the temperature being kept below 40 °C. The reaction mixture was stirred for 1 hour to 40 °C with midway analysis by GC. The reaction mixture was quenched by rapid transfer to a 0 °C mixture of 3M aq NaOH (113.6 L) and MTBE (56.8 L)

with the temperature being kept below 25 °C (additional 3M NaOH was added if pH was not >7). The layers were separated and the aq layer was extracted with MTBE (28.4 L). The combined organic layers were successively washed with water (28.4 L) and saturated aq NaCl (28.4 L). The organic layer was isolated, concentrated at 40 °C (**16** slowly decomposes when heated above 40 °C for prolonged time) and degassed at 30 °C under full vacuum for 2 hours to afford **16** (5.10 kg, ~17.7 mol, 86.8 % area by GC) as a light yellow oil in ~92% yield, which still contained residual MTBE and was stable when stored under inert atmosphere, at -20 °C in the dark. GC in-process control: Method: see general methods; Sample preparation: 1 mL reaction mixture is extracted with 2 mL aq 3M NaOH and 1.5 mL MTBE. From the organic layer 1 mL is isolated as GC sample; t_R: **16** = 8.4 min; **25** = 10.2 min. R_F = 0.70 (1:3; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.78 (s, 1H, C(O)H-1), 3.39 (t, *J* = 5.9 Hz, 2H, CH_2-5), 2.95 (s, 2H, OCH_2-Ada), 2.47 (dt, *J* = 1.4 Hz, *J* = 7.3 Hz, 2H, CH_2-2), 1.95 (br s, 3H, 3×CH Ada), 1.76 – 1.52 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4 (C(O)H-1), 81.8 (OCH_2-Ada), 70.8 (CH_2-5), 43.5 (CH_2-2), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 28.8 (CH_2-4), 28.1 (3×CH Ada), 18.8 (CH_2-3). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2716, 1728, 1450, 1404, 1358, 1258, 1227, 1157, 1103, 1057, 1011, 941, 887, 810, 656. MS (ESI): *m/z* 251.3 $[M+H]^+$.



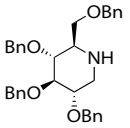
***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1,6-dideoxynojirimycin (27).** R_F = 0.44 (1:3; MeOH:$CHCl_3$ + 2% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$/ MeOD, 1/ 1) δ 3.69 – 3.62 (m, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, CH_2-5 pentyl), 3.25 (dd, *J* = 8.8, 1H, H-3), 3.19 – 3.11 (m, 2H, H-1a, H-4), 2.95 (s, 2H, OCH_2-Ada), 2.94 – 2.84 (m, 1H, C*H*H-1 pentyl), 2.80 – 2.67 (m, 1H, CH*H*-1 pentyl), 2.55 – 2.47 (m, 1H, H-5), 2.44 (dd, *J* = 11.2, 1H, H-1b), 1.93 (s, 3H, 3×CH Ada), 1.75 – 1.54 (m, 10H, 3×CH_2 Ada, CH_2-2, CH_2-4 pentyl), 1.52 (d, *J* = 2.2, 6H, 3×CH_2 Ada), 1.42 – 1.33 (m, 2H, CH_2-3 pentyl), 1.30 (d, *J* = 6.2, 3H, CH_3-6). ^{13}C NMR (100 MHz, $CDCl_3$/ MeOD, 1/ 1) δ 81.5 (OCH_2-Ada), 77.5, 73.8, 67.9 (C-2, C-3, C-4), 70.8 (CH_2-5 pentyl), 60.3 (C-5), 54.8 (C-1), 52.3 (CH_2-1 pentyl), 39.2 (CH_2 Ada), 36.7 (CH_2 Ada), 33.5 (C_q Ada), 28.7 (CH_2 pentyl), 27.8 (CH Ada), 23.4 (CH_2 pentyl), 22.7 (CH_2 pentyl), 13.7 (CH_3-6). HRMS: found 382.2961 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_4+H]^+$ 381.2957.



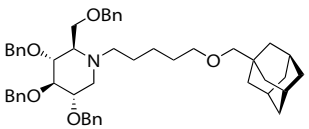
2,3,4,6-Tetra-*O*-benzyl-D-glucitol (28). $LiAlH_4$ (9.8 g, 259 mmol) was added in portions to a cooled (0 °C) and dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**, 40.0 g, 74 mmol) in THF (370 mL). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched successively with EtOAc (50 mL, 1 h of stirring) and water at 0 °C. The mixture was diluted with EtOAc (400 mL) and washed with sat aq NH_4Cl (2×500 mL) and sat aq NaCl (250 mL). The organic phase was dried ($MgSO_4$) and concentrated to yield **28**, which was used crude in the next reaction. A small sample was purified by silica gel column chromatography (20% » 50% EtOAc in PE) for characterization purposes to provide **28** as a colorless oil.

Miniplant preparation procedure: A solution of **5** (8.50 kg, 15.72 mol) in DCM (42.5 L + 1.7 L for rinsing) was added to a suspension of $NaBH_4$ (1.61 kg, 42.45 mol) in DCM (11.1 L). The resulting suspension was vigorously stirred and heated to reflux (36–40 °C), during which methanol (11.1 L) was carefully added over a 6 hour period. Following the addition of methanol, the reaction mixture was heated for an additional hour, after which it was cooled to 20 °C and remaining hydrogen gas was evacuated with a nitrogen flow. The reaction mixture was quenched by careful addition of 2M aq H_3PO_4 (21.3 L) under vigorous stirring over a 2 hour period, cooling the reaction mixture to keep the temperature below 30 °C. After addition, the mixture was vigorously stirred for 30 minutes, whilst evacuating remaining hydrogen gas with a nitrogen flow. After the two-phasic mixture had settled for 1 hour, the organic phase was isolated and the turbid aq phase was back-extracted once with DCM (11.1 L). The combined organic layers were washed with water (2×11.1 L), concentrated and degassed at 30 °C under full vacuum for 2 hours to produce **28** (8.58 kg, 15.72 mol, 98.6% area by HPLC) as a colorless oil in quantitative yield.

HPLC in-process control: Method B; Sample preparation: 200 µL reaction mixture is added to a freshly prepared solution of 0.1 mL 2M aq H_2SO_4 in 15 mL CH_3CN and filled to 25 mL with methanol; t_R: **28** = 17.1 min; **5** = 18.1 min. R_F = 0.45 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.08 (m, 20H, H_{Ar} Bn), 4.70 (d, *J* = 11.3 Hz, 1H, C*H*H Bn), 4.64 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.63 (d, *J* = 11.7 Hz, 1H, CH Bn), 4.61 – 4.56 (m, 2H, 2×CH Bn), 4.53 (d, *J* = 11.4 Hz, 1H, CH Bn), 4.52 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.47 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.03 (m, 1H, H-5), 3.89 (dd, *J* = 3.6 Hz, *J* = 6.3 Hz, 1H, H-3), 3.80 – 3.75 (m, 2H, H-2, H-4), 3.71 (dd, $J_{H1a\text{-}H2}$ = 4.3 Hz, $J_{H1a\text{-}H1b}$ = 11.9 Hz, 1H, H-1a), 3.65 – 3.59 (m, 2H, CH_2-6), 3.55 (dd, $J_{H1b\text{-}H2}$ = 4.7 Hz, $J_{H1b\text{-}H1a}$ = 11.9 Hz, 1H, H-1b), 3.04 (br s, 1H, OH), 2.35 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 137.8, 137.8 (4×C_q Bn), 128.25, 128.23, 127.9, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 79.4 (C-2), 78.9 (C-3), 77.3 (C-4), 74.4, 73.3, 73.1, 72.9 (4×CH_2 Bn), 71.0 (C-6), 70.6 (C-5), 61.6 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3420, 3030, 2866, 1497, 1454, 1398, 1358, 1308, 1209, 1065, 1026, 910, 851, 820, 731, 694, 631. $[\alpha]^{20}_D$: +8.9° (c = 3.94, $CHCl_3$). MS (ESI): *m/z* 543.2 $[M+H]^+$; 565.1 $[M+Na]^+$.

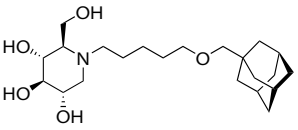


2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin (11). A solution of oxalylchloride (14.0 mL, 162.3 mmol) in DCM (296 mL) was cooled to –78 °C. After dropwise addition of a solution of DMSO (23.2 mL, 325.6 mmol) in DCM (99 mL) over 10 min, the reaction mixture was stirred for 40 min while being kept below –70 °C. Next, a dry solution of crude **28** (~74 mmol) in DCM (99 mL) was added dropwise to the reaction mixture over a 15 min period, while keeping the reaction mixture below –70 °C. After stirring the reaction mixture for 2 h below –65 °C, Et_3N (100 mL, 740 mmol) was added dropwise over a 10 min period, while keeping the reaction mixture below –65 °C. After addition, the reaction mixture was allowed to warm to –5 °C over 1 h (R_F hexosulose = 0.7 (1:1; EtOAc:PE). The reaction mixture was concentrated at a moderate temperature (~30 °C) with simultaneous coevaporation of dichloroethane (3×). The residue was dissolved in MeOH (1400 mL) and ammonium formate (80 g, 1258 mmol) was added. The mixture was cooled to 0 °C and stirred until all ammonium formate had dissolved. Activated 3Å molecular sieves (150 g) were added and reaction mixture was stirred for 10 min, after which sodium cyanoborohydride (18.6 g, 296 mmol) was added. The reaction mixture was kept at 0 °C for 1 h after which the cooling source was removed and the reaction was stirred for an additional 20 h. After removal of the molecular sieves over a glass microfibre filter, the filtrate was concentrated, dissolved in EtOAc (500 mL) and washed successively with sat aq $NaHCO_3$ (400 mL) and sat aq NaCl (300 mL). The combined aq phases were back-extracted with EtOAc (250 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel column chromatography (20% » 75% EtOAc in PE) to provide **11** (25.2 g, 48.1 mmol) in 65% yield over three steps as a light yellow crystalline solid. R_F = 0.25 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.14 (m, 20H, H_{Ar} Bn), 4.97 (d, *J* = 12.9 Hz, 1H, CH Bn), 4.87 – 4.82 (m, 2H, 2×CH Bn), 4.68 (d, *J* = 11.7 Hz, 1H, C*H*H Bn), 4.64 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 11.0 Hz, 1H, CH Bn), 4.45 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.40 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 3.65 (dd, $J_{H6a\text{-}H5}$ = 2.6 Hz, $J_{H6a\text{-}H6b}$ = 9.0 Hz, 1H, H-6a), 3.57 – 3.45 (m, 3H, H-2, H-3, H-6b), 3.34 (dd, *J* = 8.8 Hz, 1H, H-4), 3.22 (dd, $J_{H1a\text{-}H2}$ = 4.9 Hz, $J_{H1a\text{-}H1b}$ = 12.2 Hz, 1H, H-1a), 2.71 (ddd, $J_{H5\text{-}H6a}$ = 2.6 Hz, *J* = 5.9 Hz, *J* = 9.8 Hz, 1H, H-5), 2.48 (dd, $J_{H1b\text{-}H2}$ = 10.3 Hz, $J_{H1b\text{-}H1a}$ = 12.2 Hz, 1H, H-1b), 1.89 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.4, 138.3, 137.8 (4×C_q Bn), 128.24, 128.21, 127.84, 127.78, 127.70, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 87.2 (C-3), 80.5 (C-2), 80.0 (C-4), 75.5, 75.0, 73.2, 72.6 (4×CH_2 Bn), 70.1 (C-6), 59.6 (C-5), 48.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3030, 2843, 1497, 1358, 1310, 1209, 1092, 1061, 1028, 945, 908, 866, 733, 694. Melting point range: 44.5–46.8 °C. $[\alpha]^{20}_D$: +27.7° (c = 3.16, $CHCl_3$). MS (ESI): *m/z* 524.5 $[M+H]^+$.

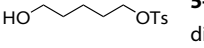


2,3,4,6-Tetra-*O*-benzyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (30). Argon was passed through a solution of compound **11** (4.19 g, 8.0 mmol) and **16** (3.00 g, 12.0 mmol) in EtOH/AcOH (50 mL; 10/1) for 15 min, after which a catalytic amount of Pd/C (419 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 30 min and the reaction was

stirred for 40 h under atmospheric hydrogen pressure, or until TLC analysis indicated complete consumption of **11**. Pd/C was removed by filtration over a glass microfiber filter, followed by thorough rinsing with EtOH. The filtrate was concentrated and coevaporated with toluene. The crude concentrated reaction mixture was used in the next step. A small sample was purified by silica gel column chromatography (0% » 10% Et_2O in toluene + 1% Et_3N) for characterization purposes to afford product **30** as a colorless oil. R_F = 0.52 (1:4; Et_2O:toluene + 1% Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 – 7.12 (m, 20H, H_{Ar} Bn), 4.95 (d, *J* = 11.1 Hz, 1H, C*H*H Bn), 4.87 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.81 (d, *J* = 11.1 Hz, 1H, CH*H* Bn), 4.68 (d, *J* = 11.6 Hz, 1H, C*H*H Bn), 4.65 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.46 (d, *J* = 12.2 Hz, 1H, C*H*H Bn), 4.41 (d, *J* = 12.2 Hz, 1H, CH*H* Bn), 3.67 – 3.64 (m, 2H, H-2, H-6a), 3.60 (dd, *J* = 9.0 Hz, 1H, H-4), 3.54 (d, $J_{H6b-H6a}$ = 10.2 Hz, 1H, H-6b), 3.45 (dd, *J* = 9.0 Hz, 1H, H-3), 3.34 (t, *J* = 6.5 Hz, 2H, OCH_2-5′ pentyl), 3.09 (dd, J_{H1a-H2} = 4.8 Hz, $J_{H1a-H1b}$ = 10.8 Hz, 1H, H-1a), 2.95 (s, 2H, OCH_2-Ada), 2.68 (m, 1H, NC*H*H-1′ pentyl), 2.58 (m, 1H, NCH*H*-1′ pentyl), 2.31 (d, *J* = 9.0 Hz, 1H, H-5), 2.23 (dd, $J_{H1b-H1a}$ = 10.8 Hz, 1H, H-1b), 1.96 (br s, 3H, 3×CH Ada), 1.72-1.64 (m, 6H, 3×CH_2 Ada), 1.54 (br d, *J* = 2.4 Hz, 6H, 3×CH_2 Ada), 1.51 (m, 2H, CH_2-4′ pentyl), 1.44 (m, 1H, C*H*H-2′ pentyl), 1.36 (m, 1H, CH*H*-2′ pentyl), 1.22 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.0, 138.5, 137.7 (4×C_q Bn), 128.8, 128.4, 128.3, 128.27, 128.26, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{Ar} Bn), 87.3 (C-3), 81.9 (OCH_2-Ada), 78.53, 78.51 (C-2, C-4), 75.3, 75.1, 73.4, 72.7 (4×CH_2 Bn), 71.4 (OCH_2-5′ pentyl), 65.1 (C-6), 63.6 (C-5), 54.4 (C-1), 52.3 (NCH_2-1′ pentyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.1 (C_q Ada), 29.4 (CH_2-4′ pentyl), 28.3 (3×CH Ada), 24.1 (CH_2-3′ pentyl), 23.3 (CH_2-2′ pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2799, 2183, 1497, 1454, 1367, 1315, 1258, 1207, 1173, 1155, 1092, 1070, 1028, 989, 910, 814, 731, 694, 648. $[\alpha]^{20}_D$: –3.3° (c = 0.86, $CHCl_3$). MS (ESI): *m/z* 758.0 $[M+H]^+$; 780.4 $[M+Na]^+$.

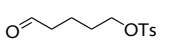


***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (4).** A solution of crude **30** (~8 mmol) in EtOH (40 mL) was acidified with 2M aq HCl (7.7 mL), after which argon was passed through the solution for 15 min. Next, a catalytic amount of Pd/C (600 mg, 10 wt % on act. carbon) was added and the reaction mixture was shaken in a Parr-apparatus under 1 bar hydrogen pressure for 20 h. Pd/C was removed by filtration over a glass microfiber filter, followed by thorough rinsing with EtOH. The filtrate was concentrated and coevaporated with toluene. The residue was purified by silica gel column chromatography (5% » 15% MeOH in EtOAc with 0.5% NH_4OH) to give **4** (2.83 g, 7.1 mmol) as a colorless oil in 89% yield. R_F = 0.20 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD): δ = 3.86 (dd, J_{H6a-H5} = 2.7 Hz, $J_{H6a-H6b}$ = 12.1 Hz, 1H, H-6a), 3.82 (dd, J_{H6b-H5} = 2.7 Hz, $J_{H6b-H6a}$ = 12.1 Hz, 1H, H-6b), 3.46 (ddd, J_{H2-H1a} = 4.9, 9.1, 10.6 Hz, 1H, H-2), 3.38 (t, *J* = 6.3 Hz, 2H, OCH_2-5′ pentyl), 3.35 (dd, *J* = 9.4 Hz, 1H, H-4), 3.12 (dd, *J* = 9.1 Hz, 1H, H-3), 2.97 (dd, J_{H1a-H2} = 4.8 Hz, $J_{H1a-H1b}$ = 10.2 Hz, 1H, H-1eq), 2.96 (s, 2H, OCH_2-Ada), 2.79 (m, 1H, NC*H*H-1′ pentyl), 2.58 (m, 1H, NCH*H*-1′ pentyl), 2.17 (dd, *J* = 10.2, 10.6 Hz, 1H, H-1ax), 2.09 (dt, J_{H5-H4} = 9.4 Hz, $J_{H5-H6a/b}$ = 2.7 Hz, 1H, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77-1.66 (m, 6H, 3×CH_2 Ada), 1.58 (m, 2H, CH_2-4′ pentyl), 1.55 (d, *J* = 2.8 Hz, 6H, 3×CH_2 Ada), 1.51 (m, 2H, CH_2-2′ pentyl), 1.33 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, MeOD): δ = 83.6 (OCH_2-Ada), 79.1 (C-3), 71.1 (OCH_2-5′ pentyl), 70.6 (C-4), 69.3 (C-2), 65.8 (C-5), 58.0 (C-6), 56.3 (C-1), 52.3 (NCH_2-1′ pentyl), 39.4 (3×CH_2 Ada), 36.9 (3×CH_2 Ada), 33.7 (C_q Ada), 29.1 (CH_2-4′ pentyl), 28.3 (3×CH Ada), 23.9 (CH_2-3′ pentyl), 23.6 (CH_2-2′ pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3317, 2901, 2847, 1448, 1360, 1344, 1259, 1217, 1188, 1155, 1088, 1036, 1011, 914, 812, 754, 665. $[\alpha]^{20}_D$: –10.6° (c = 2.30, MeOH). HRMS: found 398.29266 $[M+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.29010.

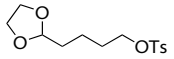


5-(Toluene-4-sulfonyloxy)-1-pentanol (22). To a cooled (0 °C) solution of pentane-1,5-diol (**17**, 9.76 kg, 93.71 mol), DMAP (390 g, 2.92 mol) and triethyl amine (4.88 kg, 51.72 mol) in MTBE (68.30 L) was added a cooled (0 °C) solution of TsCl (8.78 kg, 46.84 mol) in DCM (9.76 L) over a 2 hour period. The reaction mixture was kept at 0 °C for two hours after which it was warmed to 20 °C within a one hour period and stirred for an additional 18 hours. Water (39.04 L) was added to the reaction mixture over a 30 minute period, followed by 2M aq HCl (19.52 L). After stirring the mixture for 30 minutes, the organic layer was

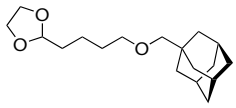
isolated and washed with saturated aq NaCl (2×19.52 L). The organic layer was concentrated using moderate heating (T_{max}< 40 °C: **22** slowly decomposes when heated) to produce a yellow oil. A solution of crude **22** in 2-propanol (24.4 L) was stirred for 1 hour at rt during which the ditosylate byproduct precipitated as a white solid. The mixture was cooled at –5 °C for 2 hours after which the precipitate was removed by centrifugation and washed with precooled 2-propanol (2×0.97 L; T = 0 °C). The mother liquor and washings were concentrated using moderate heating (T_{max}< 40 °C) and degassed at 30 °C under full vacuum for 2 hours to provide **22** (8.82 kg, 34.14 mol, 88.8 % area by HPLC) as a light yellow oil in 72.9% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **22** = 13.7 min; ditosylate byproduct = 18.4 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3, 2H), 7.29 (d, *J* = 8.1, 2H), 3.96 (t, *J* = 6.4, 2H), 3.80 (s, 1H), 3.52 (t, *J* = 6.5, 2H), 2.38 (s, 3H), 1.65 – 1.56 (m, 2H), 1.49 – 1.40 (m, 2H), 1.37 – 1.27 (m, 2H).



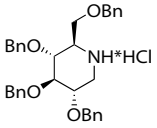
5-(Toluene-4-sulfonyloxy)-1-pentanal (23). To a solution of **22** (8.73 kg, 33.79 mol) and TEMPO (52.4 g, 0.33 mol) in DCM (43.65 L) was added a solution of KBr (0.43 kg) in water (1.74 L) and the mixture was cooled to 5 °C. Separately, sodium hypochlorite (~20.07 L; 12-15% in water; 30.69 mol) was diluted with enough aq $NaHCO_3$ (~20.07 L; 9%) to reach a pH between 8.5 and 9.5 and then cooled to 5 °C. Controlled addition of an equimolar amount of NaOCl was essential to prevent overoxidation of **22**. Therefore the exact concentration of the commercial NaOCl solution has to be determined. A portion (30.55 L) of the NaOCl/$NaHCO_3$ solution was added over a period of 2 hours at 5 °C to the mixture containing **22**, which caused initial orange coloration of the reaction mixture that slowly disappeared. The reaction mixture was stirred for an additional 30 minutes at 5 °C, after which the reaction progress was checked with HPLC by sampling the organic layer. Additional portions (1–2 L) of the NaOCl/$NaHCO_3$ solution were added over 15 minute periods with 30 minutes of additional stirring at 5 °C and intermittent HPLC analysis in between until less then 1% of **22** remained. The reaction mixture was warmed to 20 °C and the aq layer was separated and extracted with DCM (11.34 L). Aq 2.87M HCl (34.92 L) containing KI (87g) was slowly added to the combined organic layers. The aq layer was removed and the organic layer was successively extracted with aq $Na_2S_2O_3$ (34.9 L; 10%), saturated aq $NaHCO_3$ (34.9 L) and water (34.9 L). The organic layer was isolated, concentrated using moderate heating (T_{max}< 40 °C: **23** slowly decomposes when heated) and degassed at 30 °C under full vacuum for 2 hours to afford **23** (7.93 kg, 30.93 mol, 93.2 % area by HPLC) as a yellow oil in 91.5% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **22** = 13.6 min; **23** = 13.8 min; ditosylate byproduct = 18.1 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (t, *J* = 1.3, 1H), 7.74 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 8.0, 2H), 3.99 (t, *J* = 5.8, 2H), 2.44 – 2.37 (m, 5H), 1.68 – 1.58 (m, 4H).



2-(4-[Toluene-4-sulfonyloxy]-butyl)-1,3-dioxolane (24). To an emulsion of ethylene glycol (2.8 kg, 46.0 mol) and TsOH (171 g; 0.9 mol) in MTBE (27.27 L) was added a solution of **23** (7.79 kg, 30.39 mol) in MTBE (27.27 L) over a period of 30 minutes. The water liberated up to now was removed and the reaction mixture was refluxed (~56 °C) for 3 hours or until HPLC analysis indicated complete conversion. The reaction mixture was cooled to 20 °C and saturated aq $NaHCO_3$ (35.06 L) was added over a 30 minute period. The organic layer was washed with saturated aq NaCl (35.06 L), concentrated using moderate heating (T_{max}< 40 °C: **24** slowly decomposes when heated) and degassed at 30 °C under full vacuum for 2 hours. Compound **24** (8.81 kg, 29.33 mol, 91.0 % area by HPLC) was obtained as a light yellow oil in 96.5% yield, which was stable when stored under inert atmosphere, below 5 °C in the dark. HPLC in-process control: Method A; Sample preparation: 50 µL reaction mixture in 25 mL CH_3CN; t_R: **23** = 13.9 min; **24** = 15.6 min; ditosylate byproduct = 18.4 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 8.0, 2H), 4.76 (t, *J* = 4.6, 1H), 3.99 (t, *J* = 6.5, 2H), 3.95 – 3.84 (m, 2H), 3.84 – 3.75 (m, 2H), 2.41 (s, 3H), 1.71 – 1.61 (m, 2H), 1.61 – 1.54 (m, 2H), 1.46 – 1.36 (m, 2H).

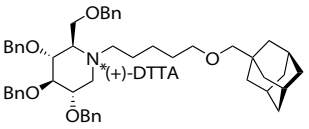


2-(4-[Adamantan-1-yl-methoxy]-butyl)-1,3-dioxolane (25). Water content of commercial adamantanemethanol (4.09 kg, 24.62 mol) was removed by azeotropic distillation with toluene (17.4 L) and the residue was dissolved in DMF (26.1 L) at 40 °C. Sodium hydride (1.97 kg, 60% in mineral oil, 49.23 mol) was suspended in DMF (26.1 L) and heated to 40 °C after which the adamantanemethanol solution was carefully added over a period of 1 hour. After additional stirring for 30 minutes a 40 °C solution of **24** (7.79 kg, 28.96 mol) in DMF (17.4 L) was added over a 1 hour period. The reaction mixture was stirred for 2 hours after which it was cooled to 20 °C and methanol (3.48 L) was carefully added over a 1 hour period keeping the temperature under 30 °C. Water (87 L) was added to the reaction mixture and after cooling to 20 °C the mixture was extracted with MTBE (2×87 L). The combined organic layers were washed with saturated aq NaCl (2×43.5 L) and concentrated using moderate heating (T_{max}<40 °C). The residue was dissolved in heptane (76.5 L) and extracted with a methanol/water mixture (4×84.2 L, 8/3 methanol/water, v/v). The heptane layer was isolated and concentrated (T_{max}<40 °C) to afford a light yellow oil. This residue was further purified by short path distillation at a temperature of 120 °C and a pressure below 0.1 mbar to afford **25** (5.84 kg, 19.83 mol; 92.3 % area by GC) in 80.5% yield as a colorless oil, which was stable when stored under inert atmosphere, below 5 °C in the dark. GC in-process control: Method: see general methods; Sample preparation: 100 µL reaction mixture is quenched with methanol and diluted with 1.4 mL DCM. t_R: adamantanemethanol = 4.78 min; 22 = 10.24 min, 21 = 10.80 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (t, *J* = 4.8, 1H), 3.98 – 3.88 (m, 2H), 3.87 – 3.77 (m, 2H), 3.35 (t, *J* = 6.5, 2H), 2.92 (s, 2H), 1.92 (s, 3H), 1.71 – 1.53 (m, 11H), 1.52 – 1.40 (m, 9H).



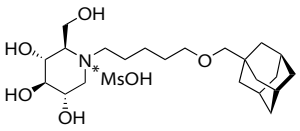
2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin hydrochloric acid salt (11*HCl). A solution (water content was verified to be KF < 0.05%) of DMSO (9.54 kg; 122.10 mol) in DCM (8.68 L) was slowly added to a cooled (–75 °C) solution of oxalylchloride (12.56 kg; 9.91 mol) in DCM (45.5 L; water content was verified to be KF < 0.03%) so the internal temperature of the reaction mixture did not exceed –65°C. The resulting mixture was stirred for 30 minutes at –75 °C, whereupon a solution of **28** (12.5 kg; 23.03 mol) in DCM (14.47 L) was slowly added so the internal temperature of the reaction mixture did not exceed –65 °C (**28** was dried by azeotropic distillation with DCM until water content was KF < 0.03%). After addition of **28**, the reaction mixture was stirred for 2 hours at –75 °C after which Et_3N (25.17 kg; 248.7 mol) was slowly added so the internal temperature of the reaction mixture did not exceed –65 °C. The resulting suspension was stirred for 4 hours, warming from –75 °C to –60 °C, and then transferred to a cooled (0–5 °C) mixture* of NH_4OAc (17.76 kg, 230.40 mol), Na_2SO_4 (9.81 kg, 69.06 mol) and $NaBH_3CN$ (5.79 kg, 92.10 mol) in methanol (207.3 L + 23.0 L for rinsing). The reaction mixture was stirred for 18 hours and allowed to warm to 20–25 °C. The reaction mixture was cooled to 5-10 °C and water (46.06 L) was slowly added over a 30 minute period so the internal temperature of the mixture did not exceed 35 °C.* An aq NaOH (18.3 L, 50 w%) solution was added to the mixture** followed by addition of water (414.6 L) over a one hour period (T < 35 °C). The two-phasic mixture was stirred for one hour at 18-25 °C after which the organic phase was isolated. The aq phase was back-extracted once with DCM (102.5 L). The combined organic phases were cooled to 5-10 °C and under vigorous stirring an aq NaOCl solution (131.1 L, 12 w%) was added over a one hour period (T < 35 °C). The two-phasic reaction mixture was vigorously stirred for one hour at 18-25 °C and then the organic phase was isolated and cooled to 5–10 °C. Aqueous 2M HCl (115.2 L) was added to the organic phase over a one hour period (T < 35 °C) after which the mixture was vigorously stirred for another hour at 18–25 °C. Isolation of **11** through precipitation was achieved by solvent exchange from DCM to acetone. The organic phase was isolated and DCM (~150 L) was evaporated until the residue reached 54–55 °C. Acetone (151.5 L) was added to the residue and the mixture was vigorously stirred (T < 35 °C) for 30 minutes during which **11*HCl** precipitated as white floccules. Residual DCM was removed by successively evaporating ~50 L of solvent and adding acetone (23.1 L). The suspension was vigorously stirred for one hour at ambient temperature and another hour whilst cooled at

0–5 °C. The product was isolated by centrifugation, washed twice with precooled acetone (T = 0–5 °C; portion 1 = 12.7 L; portion 2 = 6.5 L) and dried under vacuum at 35-40 °C to afford **11*HCl** (7.27 kg; 12.97 mol; 98.7% area by HPLC) as an off-white solid in 56% yield. Remaining impurities were removed through a reslurrying step in which a suspension of **11*HCl** (7.15 kg; 12.76) was vigorously stirred in acetone (46.3 L) for three hours at 20-25 °C and another hour at 0–5 °C. The solvent was removed by centrifugation and the product was washed with precooled acetone (T = 0–5 °C; 17.9 L) to afford, after drying under vacuum at 35–40 °C, **11*HCl** (6.66 kg; 11.89 mol; 98.8% area by HPLC) as a white solid with 93% recovery.*** HPLC in-process control: Method B; Sample preparation: 250 µL reaction mixture is added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: **11** = 15.6 min; **28** = 17.1 min; **29** = 17.5 min. ^{1}H NMR (400 MHz, *d6*-DMSO) δ 10.18 (s, 1H), 9.51 (s, 1H), 7.42 – 7.25 (m, 18H), 7.17 – 7.10 (m, 2H), 4.86 (d, *J* = 11.2, 1H), 4.77 – 4.67 (m, 3H), 4.62 (d, *J* = 11.7, 1H), 4.58 (d, *J* = 12.2, 1H), 4.50 (d, *J* = 12.2, 1H), 4.45 (d, *J* = 10.8, 1H), 3.91 (ddd, *J* = 5.0, 8.9, 11.0, 1H), 3.82 (dd, *J* = 2.3, 10.5, 1H), 3.79 – 3.62 (m, 3H), 3.41 (dd, *J* = 5.0, 12.1, 2H), 2.89 (dd, *J* = 11.6, 1H). DSC (50 °C » 300 °C; 10 °C/ min): 174.5 °C; 18.75 J/ g. *: Precautions should be taken for possible liberation of hydrogen cyanide gas from the mixture. **: The pH of the aq layer was checked to be above 10 to ensure fixation of hydrogen cyanide. ***: Solubility of **11*HCl** in acetone at ambient temperature was determined to be ~6 grams per liter.



2,3,4,6-Tetra-*O*-benzyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (+)DTTA salt (30*(+)DTTA). Aqueous 1M NaOH (65.0 L) was added to a suspension of **12*HCl** (6.50 kg, 11.60 mol) in EtOAc (65.0 L) over a 15 minute period. After stirring the two-phasic mixture for ten minutes, the organic phase was isolated and successively washed with aq 1M NaOH (19.5 L) and a saturated aq NaCl solution (19.5 L). The organic phase was concentrated (T < 40 °C) and coevaporated twice with ethanol (2×13.0 L) to produce free-base **11** as a light yellow oil. Crude **16** (4.50 kg, ~15.6 mol, 86.8 % area by GC) and Pd/C catalyst (650 g, slurry in ethanol) were successively added to a solution of **11** in ethanol (65.0 L)* and acetic acid (6.7 L). The reaction mixture was purged of oxygen by flushing it with nitrogen for 15 minutes. Hydrogen was bubbled through the vigorously stirred reaction mixture for 20 hours (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 minutes and reaction progress was determined with GC and HPLC. If the amount of remaining **11** was still above 0.5% the reaction mixture was placed under hydrogen for a further 20 hours. *GC analysis* (consumption of **16**): Method: see general methods; Sample preparation: 100 µL reaction mixture was dissolved in 1.4 mL DCM; t_R: **16** = 8.4 min. *HPLC analysis* (consumption of **11**): Method B; Sample preparation: 250 µL reaction mixture is added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: Toluene = 14.0 min; **11** = 15.7 min; Partially debenzylated **30** = 17.7 and 17.8 min; **30** = 18.4 min. Celite (1.3 kg) was added to the nitrogen flushed reaction mixture when HPLC analysis indicated reaction completion. The reaction mixture was filtered, the filter cake was washed with ethanol (3×12.5 L) and the combined filtrate was concentrated (T < 40 °C). A methanolic hydrochloric acid solution was prepared separately by adding acetylchloride (3.7 L, 52.16 mol) over a 30 minute period to methanol (32.5 L) at 5–10 °C and stirring for an additional 30 minutes. The residue resulting from the concentrated filtrate was dissolved in methanol (32.5 L) and added to the methanolic hydrochloric acid solution over a 15 minute period at 20-25 °C. The combined methanolic solutions were washed with heptane (3 × 32.5 L) and subsequently concentrated (T < 40 °C). The residue was dissolved in MTBE (65.0 L) and washed successively with aq 1M NaOH (2×32.5 L) and a saturated aq NaCl solution (32.5 L). The organic phase was isolated and concentrated (T < 40 °C). The residue was dissolved in heptane (16.7 L) and added to a solution of (+)-di-*p*-toluoyl-L-tartaric acid (4.29 kg; 11.10 mol; exact amount should be equimolar to HPLC determined amount of **30** in the heptane solution) in ethanol (8.4 L) over a 15 minute period. The stirred solution was seeded with **30*(+)DTTA** that resulted in precipitation of **30*(+)DTTA** as a white solid. Heptane (25.1 L) was added and the mixture was stirred for 30 minutes at ambient temperature followed by one hour at 0–5 °C. The precipitate was isolated

by centrifugation and washed with a heptane/ethanol mixture (2×8.4 L; 5/1 v/v). After drying for 20 hours under vacuum (T < 40 °C), **30*(+)DTTA** (10.01 kg, 8.74 mol; 98.4% area by HPLC) was obtained as a white solid in 75% yield. HPLC Purity (area percent) = **30** = 85.3%; Partially debenzylated-1 **30** = 6.84; Partially debenzylated-2 **30** = 5.76%; Total = 98.43%; Palladium content (determined by ICP-MS) = < 5 ppm. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 (d, *J* = 8.2, 4H), 7.37 (d, *J* = 8.2, 4H), 7.35 – 7.22 (m, 18H), 7.19 – 7.14 (m, 2H), 5.79 (s, 2H), 4.85 (d, *J* = 11.3, 1H), 4.76 (d, *J* = 10.9, 1H), 4.72 (d, *J* = 11.3, 1H), 4.65 (d, *J* = 11.9, 1H), 4.58 (d, *J* = 11.8, 1H), 4.47 – 4.36 (m, 3H), 3.67 – 3.57 (m, 2H), 3.57 – 3.50 (m, 1H), 3.40 (dd, *J* = 8.2, 16.3, 2H), 3.27 (t, *J* = 6.2, 2H), 3.18 (dd, *J* = 4.5, 11.2, 1H), 2.89 (s, 2H), 2.79 – 2.69 (m, 1H), 2.56 – 2.48 (m, 2H), 2.38 (s, 6H), 2.25 (dd, *J* = 9.9, 1H), 1.90 (s, 3H), 1.62 (dd, *J* = 11.8, 30.6, 6H), 1.48 (d, *J* = 1.9, 6H), 1.46 – 1.33 (m, 4H), 1.23 – 1.10 (m, 2H). DSC (50 °C » 300 °C; 10 °C/ min): 105.7 °C, 36.8 J/ g; 160.7 °C, –13.6 J/g. *: Absence of acetaldehyde in used batch of ethanol should be verified beforehand otherwise significant formation of a 2,3,4,6-tetra-*O*-benzyl-*N*-ethyl-1-deoxynojirimycin byproduct is possible.



***N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin methanesulfonic acid salt (4*MSA).** A solution of **30*(+)DTTA** (4.90 kg, 4.28 mol) in MTBE (49.0 L) was washed successively with aq 1M NaOH (1 × 24.5 L; then 1 × 12.3 L) and saturated aq NaCl (12.3 L). The organic phase was isolated, concentrated (T < 40 °C) to 5-10 L and coevaporated with ethanol (3 × 25 L; or until MTBE level < 2%) to quantitatively produce **30** (3.24 kg; 4.28 mol) as a colorless oil. The byproduct **31** contaminating **30** was debenzoylated by adding aq 6M NaOH (3.3 L) to a cooled (0–10 °C) solution of **30** (3.24 kg; 4.28 mol) in ethanol (63.7 L) over a 10 minute period (T < 10 °C) and stirring the resulting turbid reaction mixture for two hours at 20-25 °C. The reaction mixture was cooled (10 °C), aq 10.17M HCl (1.9 L) was added over a 10 minute period (altering the pH to 5-8) and subsequently aq 2M HCl (12.3 L) was added at 10-30 °C to produce a clear solution with acidic pH. Palladium on carbon (321 g; slurry in ethanol) was added to the solution and oxygen was purged by flushing the mixture for 15 minutes with nitrogen. Hydrogen was bubbled through the vigorously stirred reaction mixture for 6-12 hours (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 minutes and reaction progress was determined by HPLC analysis (method B; sample preparation: 250 µL reaction mixture was added to a solution of 2 mL 2M aq H_3PO_4 in 15 mL CH_3CN and filled to 25 mL with CH_3CN; t_R: **4** = 14.1 min; **30** = 18.3 min). If the amount of **30** and partially debenzylated intermediates was higher then 1 area% compared to generated toluene the reaction mixture was placed under hydrogen for further 2-4 hour periods until complete. When HPLC analysis indicated reaction completion the mixture was filtered and the Pd/C filter cake was washed with ethanol (3×7.3 L). Ecosorb (172 g) was added to the combined filtrate whereupon the mixture was stirred for 1 hour at ambient temperature. The mixture was filtered and the Ecosorb filter cake was washed with ethanol (3×7.3 L). The combined filtrate was concentrated (T < 50 °C) to a volume of 5-10 L and coevaporated with ethanol (3×32 L). The remaining mixture was diluted to a volume of 34.3 L with ethanol (water content was verified to be KF < 2%) and 7M methanolic NH_3 (3.9–6.9 L) was added to the solution until the pH was adjusted to 8-9.5. The mixture was concentrated (T < 45 °C) to 5–10 L and coevaporated with DCM (5×122.5 L; or until ethanol level < 2%). The remaining mixture is diluted to a total volume of 24.5 L with DCM and the precipitated salts were removed by filtration. The precipitate was washed with DCM (3×2.5 L) and the combined filtrate concentrated (T < 45 °C) to 5–10 L. The residue could at this stage be further concentrated and degassed under vacuum for four hours at T < 45 °C to provide **4** as an off-white hygroscopic foam. (DSC (50 °C » 300 °C; 10 °C/ min) free base **5**: 126.1 °C, 12.0 J/ g; 171.1 °C, 1.8 J/g)). However for this preparation the solution of **5** in DCM was coevaporated with isopropanol (3×24.5 L; or until DCM level < 1%). Any remaining particulate was removed by a polish filtration step followed by additional rinsing with isopropanol (3×2.4 L) of the reaction vessel and filter. At ambient temperature a solution of methanesulfonic acid (473 g, 4.92 mol) in isopropanol (3.9 L + 2.45 rinse) was added to the isopropanol solution of **4**. The solution was heated to 70 °C and slowly cooled to ambient temperature over a 4-8 hour period during which at ~50 °C

seed crystals of **4*MSA** (5 g) were added. The solution slowly turned turbid and **4*MSA** precipitated as a course white solid. The mixture was stirred for 16 hours at ambient temperature, filtered and the collected solids were washed with isopropanol (3×2.4 L). Drying of the product under vacuum (T < 40 °C) provided **4*MSA** (1.38 kg, 2.80 mol) as a stable white solid in 65% yield. HPLC Purity (area percent): **4** = 99.9%; Benzoic acid = < 0.1%. Residual Solvents: Ethanol = < 0.01%; Toluene = < 0.005%; Isopropanol = < 0.05%; Methanol = < 0.02%; DCM = < 0.04%.; Palladium content (determined by ICP-MS) = <0.01 ppm; Water content (KF) = 0.12%; Loss on drying = 0.62%; Sulphated Ash = 0.03%. ^{1}H NMR (500 MHz, D_2O) δ 4.06 (dd, *J* = 1.4, 13.1, 1H, H-6a), 3.92 (dd, *J* = 2.5, 13.2, 1H, H-6b), 3.78 (ddd, *J* = 5.0, 9.5, 11.3, 1H, H-2), 3.63 (dd, *J* = 9.3, 10.5, 1H, H-4), 3.52 (dd, *J* = 5.0, 12.2, 1H H-1eq), 3.47 (dd, *J* = 9.3, 9.3, 1H, H-3), 3.44 (t, *J* = 6.5, 2H, OCH_2-5′ pentyl), 3.37 – 3.28 (m, 1H, NC*H*H-1′ pentyl), 3.24 – 3.16 (m, 1H, NCH*H*-1′ pentyl), 3.14 (m, 1H, H-5), 3.04 (dd, *J* = 11.3, 12.2, 1H, H-1ax), 3.02 (s, 2H, OCH_2-Ada), 2.75 (s, 3H, CH_3 MsOH), 1.92 (br s, 3H, 3×CH Ada), 1.81 – 1.56 (m, 10H, CH_2-4′ pentyl, 3×CH_2 Ada, CH_2-2′ pentyl), 1.50 (d, *J* = 1.5, 6H, 3×CH_2 Ada), 1.46 – 1.33 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (125 MHz, D_2O) δ 81.7 (OCH_2-Ada), 75.9 (C-3), 71.4 (OCH_2-5′ pentyl), 67.1 (C-4), 66.0 (C-2), 65.3 (C-5), 53.9 (C-6), 53.0 (C-1), 52.7 (NCH_2-1′ pentyl), 39.3 (3×CH_2 Ada), 38.5 (CH_3 MsOH), 36.9 (3×CH_2 Ada), 33.7 (Cq Ada), 28.2 (CH_2-4′ pentyl), 28.1 (3×CH Ada), 22.7 (CH_2-3′ pentyl), 22.3 (CH_2-2′ pentyl). DSC (50 °C » 300 °C; 10 °C/ min): 178.0 °C, 65.2 J/ g. $[\alpha]^{20}_D$ = -3.2 (*c* 1.02, H_2O). Found C: 55.9; H: 8.9; N: 2.8, calculated for $C_{23}H_{43}NO_8S$ = C: 56.0%; H: 8.8%; N: 2.8%. DSC (50 °C » 300 °C; 10 °C/ min): 178.0 °C, 65.2 J/ g.

Method for quantitative determination of residual solvents in **4*MSA** with GC analysis: *Column*: Rtx-624; L: 30 m × D: 320 µm; d_f: 1.8 µm; *Flow*: Helium at 3 mL/min*; Oven temperature*: 40 °C, 2 min; 10 °C/ min » 150 °C; 150 °C, 1 min; *Split*: 50; inlet: 180 °C; *Detection temperature*: 250 °C; *Split/flow*: 150; *Injection volume*: 2 µL*; Detection*: FID; *Runtime*: 14 min; *Sample preparation*: dissolve 80 mg in 1 mL of dimethylacetamide (DMA). t_R (min): methanol = 1.55; ethanol = 2.09; isopropanol = 2.56; CH_2Cl_2 = 2.81; EtOAc = 4.08 min; THF = 4.27; heptane = 5.05; acetic acid = 6.88; toluene = 6.99; DMA = > 9.

Method for qualitative control of **4*MSA** with HPLC: *Column*: C_{18}; D: 2.1 × L: 150 mm; d_P: 3 µm (Waters Atlantis) *Eluent A*: 0.01M aq phosphate buffer/MeOH/CH_3CN = 90:6:4; *Eluent B*: 0.01M aq phosphate buffer/MeOH/CH_3CN = 10:54:36; *Gradient*: (t in min; A/B (v/v); flow in mL/min) 0; 50/50; 0.30 » 4; 50/50; 0.30 » 12; 5/95; 0.30 » 24; 5/95; 0.30 » 25 ; 50/50; 0.30; *Injection volume*: 5 µL; *Temperature*: 30 °C; *Detection*: λ = 203 nm, *Runtime*: 33 min; *Sample preparation*: 4 mg of **4** is dissolved in 1 mL eluent B and filled to 25 mL with CH_3CN. t_R: Benzoic acid = 1.5 min; **4** = 13.7 min; **33** = 18.2 min (detector response of benzoic acid compared to **5** at 203 nm is approximately 100/1).

References

(1) Martin, O. R.; Compain, P. *Iminosugars: From synthesis to therapeutic applications* Wiley-VCH, **2007**.

(2) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond* Wiley-VCH, **1999**.

(3) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125-2144.

(4) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 495-510

(5) Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802-815.

(6) Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *J. Agric. Chem Soc. Japan.* **1976**, *50*, 571-572.

(7) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219-221.

(8) La Ferla, B.; Nicotra, F. In *Iminosugars as Glycosidase Inhibitors*; Stutz, A. E., Ed.; Wiley-VCH, **1999**.

(9) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135-162.

(10) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165-168.

(11) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123-1126.

(12) Overkleeft, H. S.; Vanwiltenburg, J.; Pandit, U. K. *Tetrahedron Lett.* **1993**, *34*, 2527-2528.

(13) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777-6780.

(14) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175-3185.

(15) Broxterman, H. J. G.; van der Marel, G. A.; Neefjes, J. J.; Ploegh, H. L.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 571-576.

(16) Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409-412.

(17) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043-2053.

(18) Setoi, H.; Takeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 2642-2645.

(19) Pederson, R. L.; Kim, M. J.; Wong, C. H. *Tetrahedron Lett.* **1988**, *29*, 4645-4648.

(20) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 716-717.

(21) Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926-3932.

(22) Kajimoto, T.; Liu, K. K. C.; Pederson, R. L.; Zhong, Z. Y.; Ichikawa, Y.; Porco, J. A.; Wong, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6187-6196.

(23) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337-3342.

(24) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605-611.

(25) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683-4696.

(26) Platt, F. M.; Neises, G. R.; Dwek, R. A.; Butters, T. D. *J. Biol. Chem.* **1994**, *269*, 8362-8365.

(27) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1532-1568.

(28) Sillence, D. J. *International Review of Cytology - a Survey of Cell Biology, Vol 262* **2007**, *262*, 151-189.

(29) van Meer, G.; Wolthoorn, J.; Degroote, S. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **2003**, *358*, 869-873.

(30) Futerman, A. H.; Riezman, H. *Trends Cell Biol.* **2005**, *15*, 312-318.

(31) Boot, R. G.; Verhoek, M.; Donker-Koopman, W.; Strijland, A.; van Marle, J.; Overkleeft, H. S.; Wennekes, T.; Aerts, J. M. F. G. *J. Biol. Chem.* **2007**, *282*, 1305-1312.

(32) Yildiz, Y.; Matern, H.; Thompson, B.; Allegood, J. C.; Warren, R. L.; Ramirez, D. M. O.; Hammer, R. E.; Hamra, F. K.; Matern, S.; Russell, D. W. *J. Clin. Invest.* **2006**, *116*, 2985-2994.

(33) Aerts, J. M.; Ottenhoff, R.; Powlson, A. S.; Grefhorst, A.; van Eijk, M.; Dubbelhuis, P. F.; Aten, J.; Kuipers, F.; Serlie, M. J.; Wennekes, T.; Sethi, J. K.; O'Rahilly, S.; Overkleeft, H. S. *Diabetes* **2007**, *56*, 1341-1349.

(34) Platt, F. M.; Neises, G. R.; Reinkensmeier, G.; Townsend, M. J.; Perry, V. H.; Proia, R. L.; Winchester, B.; Dwek, R. A.; Butters, T. D. *Science* **1997**, *276*, 428-431.

(35) Shen, C.; Bullens, D.; Kasran, A.; Maerten, P.; Boon, L.; Aerts, J.; van Assche, G.; Geboes, K.; Rutgeerts, P.; Ceuppens, J. L. *Int. Immunopharmacol.* **2004**, *4*, 939-951.

(36) Overkleeft, H. S. PhD Thesis, University of Amsterdam, 1997.

(37) Overkleeft, H. S.; Renkema, G. H.; Neele, J.; Vianello, P.; Hung, I. O.; Strijland, A.; van der Burg, A. M.; Koomen, G. J.; Pandit, U. K.; Aerts, J. M. F. G. *J. Biol. Chem.* **1998**, *273*, 26522-26527.

(38) Overkleeft, H. S.; Vanwiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215-4224.

(39) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1995**, *60*, 5634-5637.

(40) Bussink, A. P.; van Swieten, P. F.; Ghauharali, K.; Scheij, S.; van Eijk, M.; Wennekes, T.; van der Marel, G. A.; Boot, R. G.; Aerts, J. M.; Overkleeft, H. S. *J. Lipid Res.* **2007**, *48*, 1417-1421.

(41) Borjesson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325-6334.

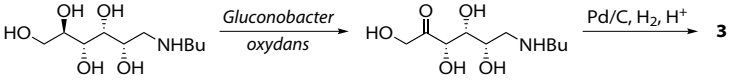
(42) Behling, J.; Farid, P.; Medich, J. R.; Scaros, M. G.; Prunier, M.; Weier, R. M.; Khanna, I. *Synth. Commun.* **1991**, *21*, 1383-1386.

(43) Stoltefuss, J. *US 4,220,782* **1979**.

(44) Wennekes, T.; Lang, B.; Leeman, M.; Marel, G. A. v. d.; Smits, E.; Weber, M.; Wiltenburg, J. v.; Wolberg, M.; Aerts, J. M. F. G.; Overkleeft, H. S. *Org. Process Res. Dev.* **2008**, *12*, 414-423.

(45) Matos, C. R. R.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **1999**, 571-573.

(46) Landis, B. H.; McLaughlin, J. K.; Heeren, R.; Grabner, R. W.; Wang, P. T. *Org. Process Res. Dev.* **2002**, *6*, 547-552.



(47) Kinast, G.; Schedel, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 805-806.