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Large-Scale Synthesis of the Glucosylceramide Synthase Inhibitor *N*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin

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Abstract:

A synthetic route for the preparation of glucosylceramide synthase inhibitor *N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin methanesulfonic acid salt (AMP-DNM) has been developed. Herein we report the development and optimization of this synthetic route from its initial version in an academic research laboratory at milligram-scale to the final optimized route that was implemented in a cGMP miniplant on kilogram-scale. The definitive route starts with the separate synthesis of building blocks 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin and 5-(adamantan-1-yl-methoxy)-pentanal. The aldehyde was synthesized from 1,5-pentanediol in five steps and 45% overall yield. Protected 1-deoxynojirimycin was prepared by a successive hemiacetal reduction/Swern oxidation/double reductive amination sequence of 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose in 52% overall yield. Reductive amination of the two building blocks produced the benzyl-protected penultimate that was isolated as its crystalline (+)DTTA salt in 68% yield. Hydrogenolysis of the penultimate and crystallization of the end product as its methanesulfonic acid salt produced AMP-DNM in 76% yield with a purity of >99.5%. The described route enables the production of multikilogram amounts of inhibitor AMP-DNM as a stable crystalline solid with high purity under cGMP control.

Introduction

Ever since the discovery of iminosugars during the 1960s and the unearthing of their ability to inhibit glycosidases[1,2] in the 1970s, they have been subject of extensive studies in both organic chemistry and biochemistry. 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**; Figure 1). Its chemical synthesis from L-sorbose, by Paulsen and co-workers in 1966,[3,4] preceded its discovery as a natural product in 1976, when it was isolated from the leaves of mulberry trees[5] and certain species of bacteria.[6] Since then numerous processes for the preparation of **1** have been reported that include synthetic approaches based on both carbohydrate and non-carbohydrate precursors[7–9] as well as chemoenzymatic syntheses.[10] Further research into the synthesis and biological activity of 1-deoxynojirimycin derivatives has already spawned two registered drugs. Miglitol (**2**)[11] is an oral drug for the treatment of non-insulin-dependent diabetes and Zavesca (**3**)[12,13] is an oral drug for the treatment of Gaucher's disease. In the latter case drug action takes place by inhibition of the enzyme glucosylceramide synthase (GCS). The product of GCS action is glucosylceramide (**4**), which is a member of the glycosphingolipid family and the crucial metabolic precursor in the biosynthesis of almost all complex glycosphingolipids. Glycosphingolipids are com-

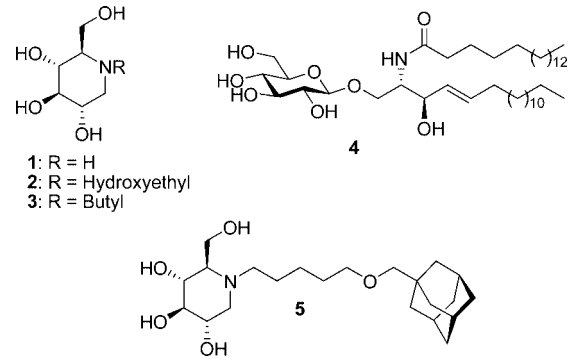

Figure 1. **Structures of 1-deoxynojirimycin (1), Miglitol (2), Zavesca (3), glucosylceramide (4), and *N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (5).**

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ponents of the outer plasma membrane and as such are involved in many (patho)physiological processes, including intercellular recognition, signaling processes, and interactions with pathogens.[14–28] The biosynthesis of **4** occurs at the outer membrane of the Golgi apparatus where GCS is membrane bound. Catabolism of **4** is effected in the lysosomes where the enzyme glucocerebrosidase (GBA1) assisted by activator protein saposin C, cleaves the glycosidic bond in **4**.[29] There is also a second enzymatic activity that is capable of cleaving this glycosidic bond about which we reported in 1993.[30,31] Although the exact function of this membrane-bound enzyme, located at the plasma membrane, is still unknown, it has recently been identified by us and Yildiz and co-workers as β-glucosidase 2 (GBA2).[32,33]

During our research focussing on the development of selective and potent inhibitors of the three enzymes involved in glucosylceramide metabolism (GCS, GBA1, and GBA2)[30,32,34] we found *N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (**5**) to be a remarkably potent inhibitor of glucosylceramide biosynthesis (100-fold more potent than **3** in inhibiting GCS; **3**: IC_{50} = 25–50 μM; **5**: IC_{50} = 200 nM in our assay). Besides a potential application of **5** in the treatment of Gaucher's disease and related sphingolipidoses,[35] the role of glycosphingolipids in many other (patho)biological processes points towards a wider range of applications. Recently, we showed that inhibition of GCS through oral dosage of compound **5** to *ob*/*ob* mice, which is a type II diabetes model, downregulates glycosphingolipid biosynthesis and restores insulin receptor sensitivity.[36] We have also found that administration of **5** to mice with hapten-induced ulcerative colitis resulted in beneficial antiinflammatory responses.[23] The crucial role of GCS at the root of glycosphingolipid biosynthesis and its role in these pathological processes make it an interesting drug target and thereby GCS inhibitor **5** a promising therapeutic lead.

For potential clinical development we needed access to a large supply of compound **5**. Consequently, a study was started to develop an efficient chemical synthesis of **5**, suitable for preparation of kilogram amounts in a miniplant. In this report we describe the development and optimization of the synthetic route for compound **5** 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 **5** was reported by us in 1998, where it was part of a library of lipophilic iminosugars generated to produce a specific inhibitor for GBA2.[30] The strategy for its synthesis then was to first prepare two building blocks, 1-deoxynojirimycin (**1**) and 5-(adamantan-1-yl-methoxy)-pentanal (**17**) and condense these via a reductive amination to provide **5**. In this synthesis, **1** was derived from commercially available 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose (**6**) by transformation of its lactone **7** to lactam intermediate **11**, which could be further reduced and deprotected to provide **1** in 29% yield over seven steps (Scheme 1).[30,37,38] Aldehyde **17** was obtained from commercially available glutaric dialdehyde[39] in five steps and 2% overall yield. Finally, reductive amination of **1** and **17** provided 60 mg of **5** in 50% yield. Although this route successfully produced **5**, we deemed it unsuitable for larger-scale synthesis of **5**. The main objections to this route were the low overall yield in the synthesis of **5** and the need for several column chromatography purifications. The larger quantities ($\sim$100 g) of **5** that were needed at that time for investigations into its biological applications[23,32,36,40] prompted us to search for alternate procedures for the production of **5**.

Development of an alternative route commenced with changing the starting material for the synthesis of **17** to 1,5-pentanediol (**18**; Scheme 2). Transformation of **18** into **17** now started according to a literature procedure[41] with successive monotosylation (**19**), Swern oxidation (**20**) and protection of the resulting aldehyde (**20**) as the 1,3-dioxolane acetal to

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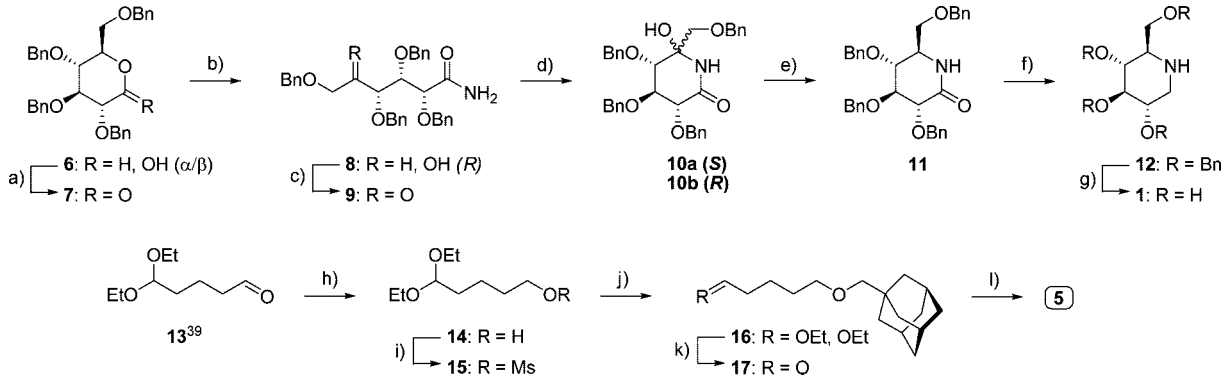
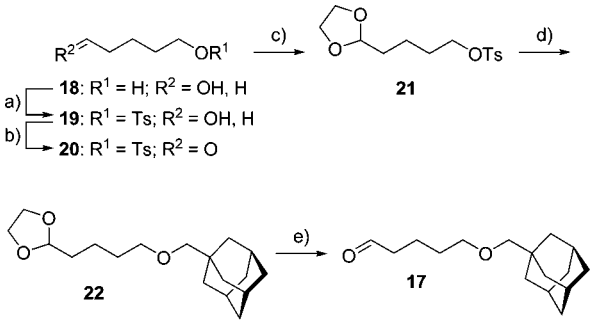
Scheme 1



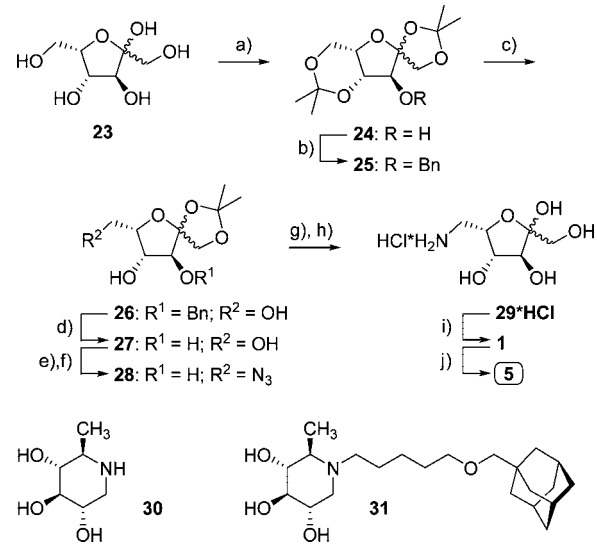
Reagents and conditions: (a) DMSO, Ac_2O, 12 h, used crude. (b) NH_3 in MeOH, 1.5 h, 86% 2 steps. (c) DMSO, Ac_2O, 12 h, used crude. (d) NH_3 in MeOH, 1.5 h, **10a**:**10b**; 1.8:1 92% 2 steps. (e) $NaBH_3CN$, HCOOH/CH_3CN, reflux, 2 h, 79%. (f) $LiAlH_4$, THF, 70 °C, 3 h, 63%. (g) $Pd(OH)_2$/C, 5 bar H_2, MeOH/EtOH, HCl, 48 h, 74%. (h) $NaBH_4$, EtOH, 3 h, 41%. (i) MsCl, Et_3N, CH_2Cl_2, 1 h, used crude. (j) 1: adamantanemethanol, NaH, DMF, 1 h; 2: addition **15**, 70 °C, 4 h, 34%. (k) 5% aq HCl, acetone, 1 h, quantitative. (l) **1*HCl**, $NaBH_3CN$, AcOH, MeOH, 20 h, 50%.

Scheme 2[a]



[a] Reagents and conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 16 h, 70%. (b) 1: DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2: addition **19**, 1.5 h; 3: Et_3N, −75 °C to rt, 2 h, 91%. (c) Ethylene glycol, pTsOH, benzene, reflux, 95%. (d) 1: adamantane−methanol, NaH, DMF, 1 h; 2: addition **21**, 70 °C, 4 h, 71%. (e) 6 M aq HCl, acetone, 74 °C, 15 min, quantitative.

Scheme 3[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, $SnCl_4$, reflux, 4 h, used crude. (b) 1: NaH, DMSO/THF, 1.5 h; 2: addition BnCl, 16 h, used crude. (c) 0.24% aq H_2SO_4, acetone, 48 h, 24% 3 steps. (d) Pd/C, 1 bar H_2, EtOAc, 16 h, quantitative. (e) TsCl, Et_3N, pyridine, 16 h, used crude. (f) NaN_3, DMF, 100 °C, 20 h, 50% 2 steps. (g) PPh_3, H_2O/THF, 16 h, used crude. (h) 12 M aq HCl, 0 C, 87% 2 steps. (i) PtO_2, 5 bar H_2, 16 h, 70%. (j) **17**, Pd/C, 5 bar H_2, NaOAc, AcOH, EtOH, 67%.

produce **21** in 61% yield over the three steps. Substitution of the tosylate (**21**) with adamantanemethanol proved more productive than that of mesylate **15** in the previous route and yielded **22** in 71% yield after purification by distillation. Subsequent acidic hydrolysis of the acetal in **22** provided building block **17** in a yield of 43% over five steps. Compound **17** was used without further purification and proved stable when stored at −20 °C.

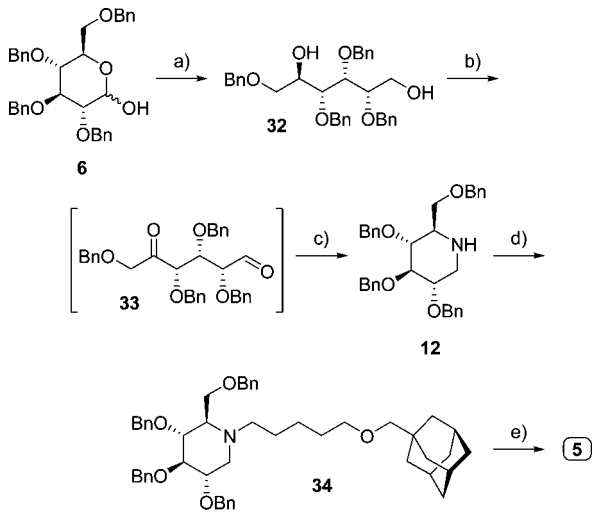
For larger-scale synthesis of the second building block (**1**) we selected a route reported by Behlings and co-workers[9] and also found in patent literature.[42] The route uses L-sorbose (**23**) as an economical starting material and is claimed to be suitable for kg-scale preparation of **1**. In the first step **23** is protected as 1,2;4,6 diacetonide **24**, followed by selective hydrolysis of the 4,6 acetonide. Installation of an amine functionality at the C6 position and cyclization via a reductive amination after first hydrolyzing the 4,6 acetonide produces **1** (Scheme 3). However, when the first two steps were attempted at a scale of 500 g, several problems arose that prevented the isolation of reasonable amounts of **27**. Diacetonide **24**, produced after the first step, turned out not to be the thermodynamically more stable isomer under most reaction conditions. Also, during workup of the second step, the acidic aqueous hydrolysis of **24**, the 1,2 acetonide in product **27**, isomerized considerably. An optimized procedure for the first step was found in treating 100-g batches of **23** with $SnCl_4$ in dimethoxypropane.[43] Unfortunately, the isomerization side reaction of the second step could only be circumvented by first protecting the 3-hydroxyl as a benzyl ether, adding two additional steps to the route. Hydrolysis of the 1,2 acetonide in benzylated **25** with dilute sulfuric acid produced **26** in 24% yield over the three steps. After quantitative debenzylation with Pd/C catalyzed hydrogenolysis and 6-*O*-tosylation,[44] azide **28** was obtained in 50% yield over two steps via substitution of the crude tosylate. Purification of **28** by column chromatography proved to be an unavoidable necessity. Staudinger reduction of **28** and hydrolysis of the 1,2-acetonide

(42) Stoltefuss, J. Preparation of 1-deoxynojirimycin and *N*-substituted derivatives. U.S. Patent 4,220,782, 1979.

(43) Chen, C. C.; Whistler, R. L. *Carbohydr. Res.* **1988**, *175*, 265–271.

(44) Instead of the tri-isopropylbenzenesulfonyl group used in the original procedure by Behling and co-workers, we found that the tosyl group can successfully be used instead.

Scheme 4[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 20 h, used crude. (b) 1. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2. Et_3N, −75 to 0 °C, 2 h, reaction mixture used neat. (c) $NaBH_3CN$, excess NH_4HCO_2, 3Å mol sieves, MeOH, 0 °C to rt, 20 h, 65% 3 steps. (d) 1.1 equiv of **17**, Pd/C, 5 bar H_2, AcOH, EtOH, 20 h, used crude. (e) Pd/C, 1 bar H_2, HCl, EtOH, 20 h, 89% 2 steps.

produced labile **29** in 87% yield over two steps, which when isolated as its HCl salt proved stable when stored at 4 °C. The final reductive amination was carried out on 20-g batches of **29** via a Pt-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 **17**. Initially, the best reproducible conditions were the use of sodium triacetoxyborohydride in ethanol, with additional sodium acetate to liberate the HCl salt of **1**. These conditions, however, produced **5** on a 1-g scale in an unimproved yield of 50%. Furthermore, workup of the reaction would be complicated on a larger scale. Instead we found that Pd/C-catalyzed hydrogenolysis at 5 bar of a suspension of **1** and NaOAc in an ethanol/acetic acid mixture with **17** was more efficient and produced 17 g of **5** in an average yield of 67%. However, column purification of **5** proved necessary to remove a side product, 6-deoxy derivative **31**. This side product originated from 6-deoxy **30** that was formed by a side reaction during the Pt-catalyzed hydrogenolysis of **29**. Overall, this route produced 64 g of **5** in 8% yield over nine steps, and the five-step synthesis of building block **17** was optimized from 2% to 43% yield.

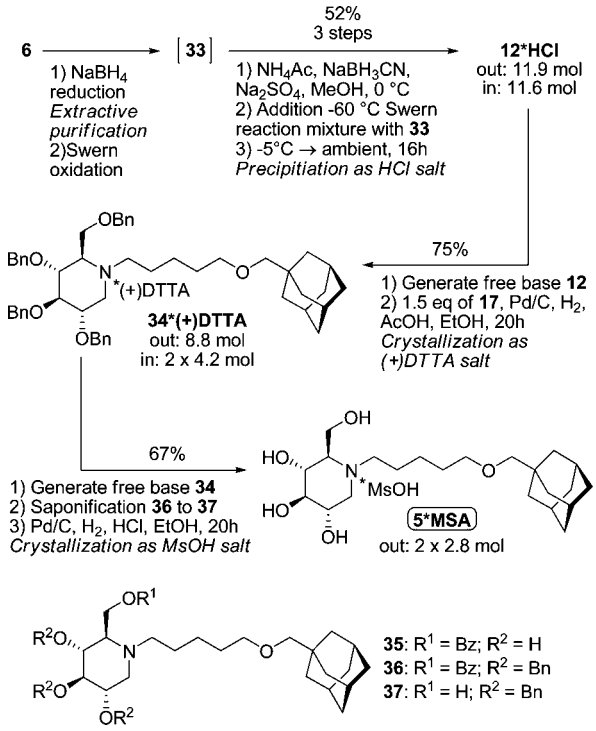
The route for building block **17** was now set for translation to kg-scale synthesis. On the other hand, we deemed the route explored for the second building block, 1-deoxynojirimycin (**1**) unsuitable for this next stage, mainly because of the low overall yield and the requirement for column chromatography purification of intermediate **28** and target compound **5**. In search of a shorter and more efficient route for the large-scale synthesis of **1** we evaluated a procedure reported by Matos and co-workers that transforms **6** into **1** in four steps.[45] The key reaction in this synthesis is the cyclization of hexosulose **33** via a double reductive amination with ammonium formate to produce **12** (Scheme 4). By switching to *N*-butylammonium formate in the reductive amination Matos and co-workers were also able, after hydrogenolysis, to produce **3**. Recently, we successfully employed a modified version of this procedure for the synthesis of derivatives of **5**.[34] Application of the original protocol, which uses a Pfitzner−Moffat oxidation and a double reductive amination at room temperature to produce **12**, led to irreproducible and low yields in our hands. We found that the procedure could be optimized by using a Swern oxidation to give **33** and most importantly to execute the double reductive amination of **33** at 0 °C in the presence of a larger excess of ammonium salt. First, **6** was reduced to glucitol **32** with $LiAlH_4$ in THF. Crude **32** was subjected to a Swern oxidation, which after completion was concentrated under reduced pressure with moderate heating to minimize degradation of the unstable intermediate **33**. The reductive amination was carried out on crude **33** 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 multigram amounts of **12** in yields of 60–65% over the three steps.

However, when the scale of this process 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 **33** and, as a result, significantly lower yields of **12**. Because degradation of **33** increases at elevated temperature, we reasoned that omitting the concentration step and adding the crude Swern reaction mixture to the mixture of reductive amination components might improve the overall yield. This adaptation indeed efficiently produced 10 g of **12** in 73% yield over the three steps. The next reaction would be deprotection of **12** to **1**, but because of the persistent moderate yields obtained in the previous large-cale reactions of **1** with aldehyde **17**, we chose to first explore the reductive amination of **12** with **17**. When **12** and **17** were exposed to Pd/C-catalyzed hydrogenolysis at 5 bar in an ethanol/acetic acid mixture, the sole product was **34**. After filtration and concentration, a second hydrogenolysis of crude **34**, now in the presence of hydrochloric acid, produced 2.8 g of target compound **5** in 89% over the two steps.

With this tandem reductive amination/deprotection method and the optimized synthesis of building blocks **12** and **17** in hand, the stage was set for translating the improved synthesis of **5** to a kg-scale miniplant process. Process development of the route for building block **17** focussed on optimizing the purity of all intermediates and **17** itself without using column purification. This was quite a challenge as all intermediates are oily liquids and only **22** is stable enough for distillation. Suitable in-process control by HPLC (up to **21**) and GC (**22** and **17**) was developed, which enabled the reactions to be monitored and controlled in an efficient way to ensure complete conversions and effective workup procedures. The synthesis of **17** started with monotosylation of 1,5-pentanediol (**18**). The formation of ditosylate could be minimized to <5% by using 0.5 equiv of tosylchloride to produce **19**. Swern oxidation of **19** 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 **20** with ethylene glycol and catalytic *p*-toluenesulfonic acid resulted in

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

Scheme 5. **Overview of cGMP miniplant process for the synthesis of building block 12 and target compound 5**



the 1,3-dioxolane acetal **21** 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 (**20**) and product (**21**). As fractional distillation is not feasible on kg-scale, 0.85 equiv of adamantanemethanol was used in the S_N2 substitution of **21** to minimize the amount of unreacted adamantanemethanol. Remaining traces of adamantanemethanol could be removed with an extractive purification in which a **21**-containing heptane phase was washed repeatedly with a methanol/water mixture. Finally, short-path distillation provided **22** (92.3 area % by GC) as a colourless oil in 92% yield related to adamantanemethanol or 68% related to **21**. During process development for the acidic hydrolysis of **22** we observed that an equilibrium is reached at 8% remaining starting material and that prolonged reaction times only lead to degradation of product **17**. A solution for this problem was found in performing the reaction two consecutive times with extractive workup in between. This diminishes the remaining starting material to <2% and yielded 5.1 kg of crude **17** in 45% yield over the five steps. The obtained purity of **17** (86.8 area % by GC) allowed implementing the crude product in the subsequent reductive amination of **17** with **12**.

Process development of the route for the second building block **12** concentrated on adapting the challenging tandem oxidation/double reductive amination sequence to the miniplant and finding a suitable purification procedure for **12**. In the final production run two 8.5-kg batches of **6** (Scheme 5) were reduced quantitatively with $NaBH_4$ in refluxing dichloromethane/methanol (Scheme 5). After extractive workup, a 12.5 kg portion of crude **32** was oxidized to hexosulose **33** using the Swern protocol. As isolation of the unstable **33** is not desirable, a telescoped procedure was developed for the consecutive double reductive amination of crude **33**. Thus, the reaction mixture resulting from the Swern oxidation was kept below −60 °C and directly transferred to a 0 °C suspension of $NaBH_3CN$, NH_4OAc, and Na_2SO_4 in methanol. Laboratory development had shown that the order of addition, the ammonium source, the temperature, and the methanol dilution (>0.1 M) are critical for this process. Molecular sieves could be replaced by Na_2SO_4 and instead of 20 equiv of NH_4HCO_2 10 equiv of NH_4OAc were used. The resulting reaction mixture, containing **12**, 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 **12** with an aqueous solution of sodium hypochlorite during workup accomplished this. During process development we observed that **12** 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 **12** was generated that could be precipitated from acetone at 0 °C and isolated via centrifugation to provide **12*HCl** as an off-white solid in 52% yield over the three reactions. Minor impurities were removed by means of an additional reslurrying step in acetone that produced **12*HCl** with 93% recovery in high purity as a white solid (6.7 kg; 98.7 area % by HPLC).

The synthesis of **34** was accomplished in the miniplant via the earlier described selective Pd/C-catalyzed hydrogenation of the intermediate imine of **12** and **17** in the presence of acetic acid (Scheme 5). Aldehyde **17** was now applied in a larger excess (1.5 equiv) to ensure complete consumption of **12**. Afterwards, excess **17** was removed by formation of the HCl salt of **34** in methanol/water and repeated washing with heptane. As a minor side reaction partial debenzylation was detected (∼10%), but this did not effect further processing to **5**. Penultimate **34** was chosen to be the cGMP starting material and was therefore required to be of defined composition and high in purity. As **34*HCl** is a noncrystalline hygroscopic solid, a salt screening was performed in order to identify a stable nonhygroscopic salt that allows efficient purification by crystallization. The (+)-di-*p*-toluoyl-L-tartaric acid ((+)DTTA) salt provided a stable crystalline solid that proved most convenient for purification and isolation. In the production run, 6.5 kg of **12** furnished 10.0 kg (75% yield) of **34*(+)DTTA** salt, which could be isolated in high purity (98.4 area % by HPLC including the debenzylated side products).

The miniplant procedure for debenzylation of the penultimate **34*(+)DTTA** was identical to the earlier described catalytic hydrogenation in the presence of hydrochloric acid. However, just before the scheduled start of the production run, HPLC analysis of a laboratory test batch of **5** indicated the presence of previously undetected 6-*O*-benzoylated **35** as a minor side product (∼1%). Byproduct **35** was most probably generated by oxidation of the 6-*O*-benzyl ether of **12** during workup of the double reductive amination reaction mixture with sodium hypochlorite. Laboratory experiments showed that removal of this side product was best accomplished before the catalytic hydrogenation of **34** by basic saponification of the benzoyl ester. Correspondingly, deprotection during miniplant production commenced with the generation of free base **34** in MTBE, after which the solvent was exchanged from MTBE to ethanol, and 6 M sodium hydroxide was added. When HPLC analysis

indicated complete saponification of **36** to **37**, 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. The good solubility of **5*HCl** in various solvents including water made it difficult to remove the inorganic salts from the reaction mixture. This problem was solved by treating crude **5*HCl** with ammonia in methanol and subsequently exchanging the solvent for dichloromethane from which all inorganic salts precipitated and in which **5** remained dissolved.

Previous biological studies were performed with **5*HCl**, but it was evident that an alternative for this highly hygroscopic and noncrystalline HCl salt had to be found. Free amine **5** also showed the same hygroscopic property and also proved to be unstable after prolonged storage at room temperature. Therefore, a salt screening was initiated to identify a suitable counterion that forms a stable, crystalline and nonhygroscopic salt of defined composition. From a number of possible pharmaceutically accepted counterions the sulfonic acid salts of methansulfonic acid (MSA), ethanesulfonic acid, and *p*-toluenesulfonic acid showed the desired properties. A brief toxicological study showed identical results for the **5*MSA** salt when compared to the previously evaluated **5*HCl** salt. On production scale the MSA salt of **5** was prepared by addition of a slight excess of methanesulfonic acid to a hot solution of **5** in isopropanol. Slow cooling to ambient temperature and seeding with crystals of **5*MSA** resulted in crystallization, which after filtration yielded **5*MSA** in 69.5% with a purity of >99.5 area % by HPLC.

Conclusion

In summary, we have developed and successfully implemented a synthetic route for the preparation of kilogram amounts of GCS inhibitor **5*MSA** in a cGMP miniplant. This large-scale synthetic preparation of *N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (**5**) complements the chemoenzymatic synthesis of *N*-butyl-1-deoxynojirimycin (**3**) reported in 2002 by Landis and co-workers, in which the key step is a selective oxidation of *N*-butylglucamine on C-5 by *Gluconobacter oxidans*.[46] The synthesis of **5** started with the preparation of the two building blocks **12** and **17**. Benzyl-protected 1-deoxynojirimycin (**12**) was synthesized from commercially available **6** in three steps in an overall yield of 52%. The second building block (**17**) was prepared from 1,5-pentandiol (**18**) in five steps and 45% overall yield. Aldehyde **17** was used crude in a selective reductive amination with the free base of **12** to provide **34**, which was purified by crystallization as its (+)DTTA salt in 75% yield. The production batch of penultimate **34*(+)DTTA** was split up and deprotected to provide a batch for toxicological studies and a second clinical batch under full cGMP control. Crystallization of **5** as its MSA salt resulted in two lots of 1.4 kg of **5*MSA** (average yield 68.4%) as an air-stable, nonhygroscopic, crystalline white solid in a purity of >99.5 area % by HPLC. With the well-defined batches of **5*MSA**, prepared via the here reported route, we are currently investigating the clinical development of **5*MSA** as an inhibitor for GCS.

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

Experimental Section

General. 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 (details in Supporting Information). ^{1}H NMR spectra were recorded on a Bruker DRX-400, except spectra for **5*MSA** were recorded on a Bruker AV-500. 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 DMSO-d_6. Coupling constants (J) are given in Hz. DSC measurements were conducted on a Mettler Toledo DSC822e (temperature program 50 to 300 °C at 10 °C/min). Optical rotation for **5*MSA** was measured on an automatic Propol polarimeter (Sodium D-line, $\lambda = 589$ nm).

5-(Toluene-4-sulfonyloxy)-1-pentanol (19). To a cooled (0 °C) solution of pentane-1,5-diol (**18**, 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 CH_2Cl_2 (9.76 L) over a 2 h period. The reaction mixture was kept at 0 °C for 2 h after which it was warmed to 20 °C within a 1 h period and stirred for an additional 18 h. Water (39.04 L) was added to the reaction mixture over a 30 min period, followed by 2 M aqueous HCl (19.52 L). After stirring the mixture for 30 min, the organic layer was isolated and washed with saturated aqueous NaCl (2 × 19.52 L). The organic layer was concentrated using moderate heating (T_{max} < 40 °C: **19** slowly decomposes when heated) to produce a yellow oil. A solution of crude **19** in 2-propanol (24.4 L) was stirred for 1 h at rt during which the ditosylate byproduct precipitated as a white solid. The mixture was cooled at −5 °C for 2 h 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 h to provide **19** (8.82 kg, 34.14 mol, 84.8 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. ^{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 (20). To a solution of **19** (7.93 kg, 30.69 mol) and TEMPO (52.4 g, 0.33 mol) in CH_2Cl_2 (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 aqueous $NaHCO_3$ (~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 **19**. 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 h at 5 °C to the mixture containing **19**, which caused an initial orange coloration of the reaction mixture that slowly disappeared. The reaction mixture was stirred for an additional 30 min 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 min periods with 30 min of additional stirring at 5 °C and intermittent HPLC analysis in between until less than 1% of **19** remained. The reaction mixture was warmed to 20 °C, and the aqueous layer was separated and extracted with CH_2Cl_2 (11.34 L). Aqueous 2.87 M HCl (34.92 L) containing KI (87 g) was slowly added to the combined organic layers. The aqueous layer was removed, and the organic layer was successively extracted with aqueous $Na_2S_2O_3$ (34.9 L; 10%), saturated aqueous $NaHCO_3$ (34.9 L), and water (34.9 L). The organic layer was isolated, concentrated using moderate heating (T_{max} < 40 °C: **20** slowly decomposes when heated), and degassed at 30 °C under full vacuum for 2 h to afford **20** (7.93 kg, 30.93 mol, 90.5 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. ^{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 (21). To an emulsion of ethylene glycol (2.8 kg, 5.9 mol) and TsOH (171 g; 0.1 mol) in MTBE (27.27 L) was added a solution of **20** in MTBE (27.27 L) over a period of 30 min. The water liberated up to now was removed, and the reaction mixture was refluxed (∼56 °C) for 3 h or until HPLC analysis indicated complete conversion. The reaction mixture was cooled to 20 °C, and saturated aqueous $NaHCO_3$ (35.06 L) was added over a 30 min period. The organic layer was washed with saturated aqueous NaCl (35.06 L), concentrated using moderate heating (T_{max} < 40 °C: **21** slowly decomposes when heated) and degassed at 30 °C under full vacuum for 2 h. Compound **21** (8.81 kg, 29.33 mol, 89.5 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. ^{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 (22). 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 h. After additional stirring for 30 min a 40 °C solution of **21** (7.79 kg, 28.96 mol) in DMF (17.4 L) was added over a 1 h period. The reaction mixture was stirred for 2 h after which it was cooled to 20 °C, and methanol (3.48 L) was carefully added over a 1 h 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 aqueous 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 **22** (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. ^{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).

5-(Adamantan-1-yl-methoxy)-1-pentanal (17). At 30 °C and under rapid stirring 6 M aqueous HCl (113.6 L) was added to a solution of **22** (5.68 kg, 19.29 mol) in acetone (56.9 L). The turbid reaction mixture was heated to 40 °C and stirred for 30 min. Stirring was stopped, and the organic layer was analyzed with GC. After stirring for an additional 30 min at 40 °C, the reaction mixture was quenched by transfer to a 0 °C mixture of 3 M aqueous NaOH (227.2 L) and MTBE (113.6 L) with the temperature being kept below 25 °C (additional 3 M NaOH was added if pH was not >7). The layers were separated, and the aqueous 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 6 M aqueous HCl (56.8 L) was added with the temperature being kept below 40 °C. The reaction mixture was stirred for 1 h to 40 °C with midway analysis by GC. The reaction mixture was quenched by rapid transfer to a 0 °C mixture of 3 M aqueous NaOH (113.6 L) and MTBE (56.8 L) with the temperature being kept below 25 °C (additional 3 M NaOH was added if pH was not >7). The layers were separated, and the aqueous layer was extracted with MTBE (28.4 L). The combined organic layers were successively washed with water (28.4 L) and saturated aqueous NaCl (28.4 L). The organic layer was isolated, concentrated at 40 °C (**17** slowly decomposes when heated above 40 °C for prolonged time), and degassed at 30 °C under full vacuum for 2 h to afford **17** (5.10 kg, ∼16 mol, 86.8 area % by GC) as a light-yellow oil in ∼91% yield, which still contained residual MTBE and was stable when stored under inert atmosphere, at −20 °C in the dark.^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, J = 1.6, 1H), 3.34 (t, J = 6.1, 2H), 2.90 (s, 2H), 2.42 (td, J = 1.6, 7.2, 2H), 1.90 (s, 3H), 1.72–1.50 (m, 10H), 1.47 (d, J = 2.3, 6H).

2,3,4,6-Tetra-*O*-benzyl-D-glucitol (32). A solution of **6** (8.50 kg, 15.72 mol) in CH_2Cl_2 (42.5 L + 1.7 L for rinsing) was added to a suspension of $NaBH_4$ (1.61 kg, 42.45 mol) in CH_2Cl_2 (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 h 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 2 M aqueous H_3PO_4 (21.3 L) under vigorous stirring over a 2 h period, cooling the reaction mixture to keep the temperature below 30

C°. After the addition, the mixture was vigorously stirred for 30 min, whilst evacuating the remaining hydrogen gas with a nitrogen flow. After the two-phase mixture had settled for 1 h, the organic phase was isolated, and the turbid aqueous phase was back-extracted once with CH_2Cl_2 (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 h to produce **32** (8.58 kg, 15.72 mol, 97.6 area % by HPLC) as a colorless oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.19 (m, 20H), 4.71 (d, J = 11.3, 1H), 4.68–4.47 (m, 7H), 4.07–3.99 (m, 1H), 3.89 (dd, J = 3.7, 6.4, 1H), 3.82–3.68 (m, 3H), 3.68–3.60 (m, 2H), 3.60–3.52 (m, 1H), 2.98 (d, J = 4.9, 1H), 2.17 (s, 1H).

2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin Hydrochloric Acid Salt (12*HCl). A solution (water content was verified to be KF < 0.05%) of DMSO (9.54 kg; 122.10 mol) in CH_2Cl_2 (8.68 L) was slowly added to a cooled (−75 °C) solution of oxalylchloride (12.56 kg; 9.91 mol) in CH_2Cl_2 (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 min at −75 °C, whereupon a solution of **32** (12.5 kg; 23.03 mol) in CH_2Cl_2 (14.47 L) was slowly added so the internal temperature of the reaction mixture did not exceed −65 °C (**32** was dried by azeotropic distillation with CH_2Cl_2 until water content was KF < 0.03%). After addition of **32**, the reaction mixture was stirred for 2 h 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 h at −75 °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 h 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 min period so the internal temperature of the mixture did not exceed 35 °C.* An aqueous NaOH (18.3 L, 50 wt %) solution was added to the mixture** followed by addition of water (414.6 L) over a 1 h period (T < 35 °C). The two-phase mixture was stirred for 1 h at 18–25 °C after which the organic phase was isolated. The aqueous phase was back-extracted once with CH_2Cl_2 (102.5 L). The combined organic phases were cooled to 5–10 °C, and under vigorous stirring an aqueous NaOCl solution (131.1 L, 12 wt %) was added over a 1 h period (T < 35 °C). The two-phase reaction mixture was vigorously stirred for 1 h at 18–25 °C and then the organic phase was isolated and cooled to 5–10 °C. Aqueous 2 M HCl (115.2 L) was added to the organic phase over a 1 h period (T < 35 °C) after which the mixture was vigorously stirred for another hour at 18–25 °C. Isolation of **12** through precipitation was achieved by solvent exchange from CH_2Cl_2 to acetone. The organic phase was isolated, and CH_2Cl_2 (∼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 min during which **12*HCl** precipitated as white floccules. Residual CH_2Cl_2 was removed by successively evaporating ∼50 L of solvent and adding acetone (23.1 L). The suspension was vigorously stirred for 1 h at ambient temperature and another hour whilst cooling 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 **12*HCl** (7.27 kg; 12.97 mol) as an off-white solid in 56% yield. Remaining impurities were removed through a reslurrying step in which a suspension of **12*HCl** (7.15 kg; 12.76) was vigorously stirred in acetone (46.3 L) for 3 h 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, **12*HCl** (6.66 kg; 11.89 mol; 98.7 area % by HPLC) as a white solid with 93% recovery.*** ^{1}H NMR (400 MHz, DMSO-d_6) 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). Mp (DSC) 174 °C. *: Precautions should be taken for possible liberation of hydrogen cyanide gas from the mixture. **: The pH of the aqueous layer was checked to be above 10 to ensure fixation of hydrogen cyanide. ***: Solubility of **12*HCl** in acetone at ambient temperature was determined to be ∼6 g L^{-1}.

2,3,4,6-Tetra-*O*-benzyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin DTTA Salt (34*(+)DTTA). Aqueous 1 M 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 min period. After stirring the two-phase mixture for 10 min, the organic phase was isolated and successively washed with aqueous 1 M NaOH (19.5 L) and a saturated aqueous 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 **12** as a light-yellow oil. Crude **17** (4.50 kg, 17.97 mol) and Pd/C catalyst (650 g, slurry in ethanol) were successively added to a solution of **12** 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 min. Hydrogen was bubbled through the vigorously stirred reaction mixture for 20 h (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 min, and reaction progress was determined with HPLC. If the amount of remaining **12** was still above 0.5%, the reaction mixture was placed under hydrogen for a further 20 h. 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 min period to methanol (32.5 L) at 5–10 °C and stirring for an additional 30 min. 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 min 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 aqueous 1 M NaOH (2 × 32.5 L) and a saturated

aqueous 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 **34** in the heptane solution) in ethanol (8.4 L) over a 15 min period. The stirred solution was seeded with **34*(+)DTTA** that resulted in precipitation of **34*(+)DTTA** as a white solid. Heptane (25.1 L) was added, and the mixture was stirred for 30 min at ambient temperature followed by 1 h 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 h under vacuum (T < 40 °C), **34*(+)DTTA** (10.01 kg, 8.74 mol; 98.4 area % by HPLC) was obtained as a white solid in 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6) 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). Mp (DSC) 106 °C. *: Absence of acetaldehyde in the 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 (5*MSA).** A solution of **34*(+)DTTA** (4.90 kg, 4.28 mol) in MTBE (49.0 L) was washed successively with aqueous 1 M NaOH (1 × 24.5 L; then 1 × 12.3 L) and saturated aqueous 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 **34** (3.24 kg; 4.28 mol) as a colorless oil. The byproduct **36** contaminating **34** was debenzoylated by adding aqueous 6 M NaOH (3.3 L) to a cooled (0–10 °C) solution of **34** (3.24 kg; 4.28 mol) in ethanol (63.7 L) over a 10 min period (T < 10 °C) and stirring the resulting turbid reaction mixture for 2 h at 20–25 °C. The reaction mixture was cooled (10 °C), aqueous 10.17 M HCl (1.9 L) was added over a 10 min period (altering the pH to 5–8), and subsequently aqueous 2 M 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 min with nitrogen. Hydrogen was bubbled through the vigorously stirred reaction mixture for 6–12 h (initially with cooling to keep T < 30 °C). The reaction mixture was purged of hydrogen by flushing with nitrogen for 15 min, and reaction progress was determined by HPLC analysis. If the amount of **34** and partially debenzylated intermediates was higher than 1 area % compared to generated toluene, the reaction mixture was placed under hydrogen for further 2–4 h 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 h 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 7 M 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 CH_2Cl_2 (5 × 122.5 L; or until ethanol level <2%). The remaining mixture was diluted to a total volume of 24.5 L with CH_2Cl_2, and the precipitated salts were removed by filtration. The precipitate was washed with CH_2Cl_2 (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 4 h at T < 45 °C to provide **5** as an off-white hygroscopic foam.) ^{1}H NMR (400 MHz, CD_3OD) δ 3.96 (d, J = 12.0, 1H), 3.88 (dd, J = 2.6, 12.2, 1H), 3.64−3.53 (m, 1H), 3.47 (dd, J = 9.5, 1H), 3.40 (t, J = 6.2, 2H), 3.28−3.14 (m, 2H), 3.04 (s, 1H), 2.97 (s, 2H), 2.87 (s, 1H), 2.54 (s, 2H), 1.95 (s, 3H), 1.76 (d, J = 12.1, 3H), 1.72−1.58 (m, 7H), 1.56 (d, J = 2.1, 6H), 1.46−1.35 (m, 2H). The solution of **5** in CH_2Cl_2 was coevaporated with isopropanol (3 × 24.5 L; or until CH_2Cl_2 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 **5**. The solution was heated to 70 °C and slowly cooled to ambient temperature over a 4–8 h period during which at ∼50 °C seed crystals of **5*MSA** (5 g) were added. The solution slowly turned turbid, and **5*MSA** precipitated as a coarse white solid. The mixture was stirred for 16 h at ambient temperature and filtered, and the collected solids were washed with isopropanol (3 × 2.4 L). Drying of the product under vacuum (T < 40 °C) provided **5*MSA** (1.38 kg, 2.80 mol; 99.9 area % by HPLC) as a stable white solid in 65% yield. ^{1}H NMR (500 MHz, D_2O, COSY) δ 4.06 (d, J = 13.1, 1H, H-6a), 3.92 (dd, J = 2.5, 13.2, 1H, H-6b), 3.78 (td, J = 4.9, 11.0, 1H, H-2), 3.63 (dd, J = 9.9, 1H, H-4), 3.52 (dd, J = 4.9, 12.2, 1H H-1a), 3.47 (dd, J = 4.8, 14.2, 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 (m, 1H, H-1b), 3.02 (s, 2H, OCH_2-adamantane), 2.75 (s, 3H, CH_3 MsOH), 1.92 (br s, 3H, 3 × CH adamantane), 1.81−1.56 (m, 10H, CH_2-4′ pentyl, 3 × CH_2 adamantane, CH_2-2′ pentyl), 1.50 (d, J = 1.5, 6H, 3 × CH_2 adamantane), 1.46−1.33 (m, 2H, CH_2-3′ pentyl).^{13}C NMR (126 MHz, D_2O, HSQC) δ 81.68 (OCH_2-adamantane), 75.90 (C-3), 71.42 (OCH_2-5′ pentyl), 67.05 (C-4), 65.96 (C-2), 65.33 (C-5), 53.94 (C-6), 53.00 (C-1), 52.69 (NCH_2-1′ pentyl), 39.31 (3 × CH_2 adamantane), 38.50 (CH_3 MsOH), 36.91 (3 × CH_2 adamantane), 33.72 (C_q adamantane), 28.23 (CH_2-4′ pentyl), 28.09 (3 × CH adamantane), 22.67(CH_2-3′ pentyl), 22.33(CH_2-2′ pentyl). Mp (DSC) 178 °C. $[\alpha]^{20}_D$ = –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.

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Supporting Information Available

HPLC and GC in-process control details and chromatograms for all reactions; ^{1}H NMR (for all compounds; ^{13}C-APT, COSY and HSQC for **5*MSA**) and DSC (for **12*HCl**, **34*(+)DTTA**, **5**, and **5*MSA**) spectra for all reported compounds and purity information for **5*MSA**. This material is available free of charge via the Internet at http://pubs.acs.org.

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