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Development of Adamantan-1-yl-methoxy-Functionalized 1-Deoxynojirimycin Derivatives as Selective Inhibitors of Glucosylceramide Metabolism in Man

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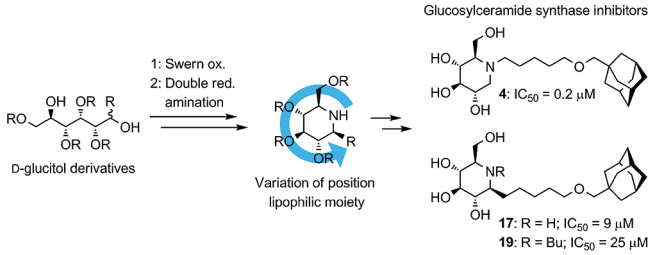
Received June 21, 2006



In this article, we present a straightforward synthesis of adamantan-1-yl-methoxy-functionalized 1-deoxynojirimycin derivatives. The used synthetic routes are flexible and can be used to create a wide variety of lipophilic mono- and difunctionalized 1-deoxynojirimycin derivatives. The compounds reported here are lipophilic iminosugar based on lead compound **4**, a potent inhibitor of the three enzymes involved in the metabolism of the glycosphingolipid glucosylceramide. Iminosugar-based inhibitors of glucosylceramide synthase, one of these three enzymes, have attracted increasing interest over the past decade due to the crucial role of this enzyme in glycosphingolipid biosynthesis. Combined with the fact that an increasing number of pathological processes are being linked to excessive glycosphingolipid levels, glucosylceramide synthase becomes a very attractive therapeutic and research target. Our results presented here demonstrate that relocating the lipophilic moiety from the nitrogen atom to other positions on the 1-deoxynojirimycin ring system does not lead to a more potent or selective inhibitor of glucosylceramide synthase. The β-aza-*C*-glycoside analogue (**17**) retained the best inhibitory potency for glucosylceramide synthase and is a more potent inhibitor than the therapeutic agent *N*-butyl-1-deoxynojirimycin (**3**), marketed as treatment for Gaucher disease under the commercial name Zavesca.

Introduction

Glucosylceramide (**1**), also referred to as glucocerebroside, is the precursor of complex glycosphingolipids (GSLs), such as the gangliosides (Figure 1). Glucosylceramide and more complex GSLs are involved in many (patho)physiological processes in humans, including intercellular recognition, signaling processes, and interactions with pathogens.[1−15]

The biosynthesis of glucosylceramide takes place at the cytosolic side of the Golgi apparatus where the membrane-bound

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10.1021/jo061280p CCC: $37.00
Published on Web 01/23/2007

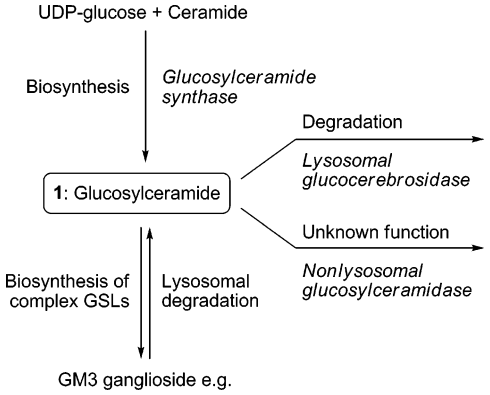
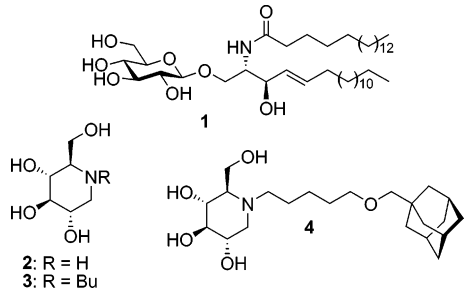


FIGURE 1. Overview of glucosylceramide metabolism.

glycosyl transferase, glucosylceramide synthase (GCS; EC 2.4.1.80), condenses UDP-glucose and ceramide to produce glucosylceramide (**1**). After translocation to the lumenal side of the Golgi apparatus, the more complex GSLs are assembled through the action of a number of glycosyltransferases. Catabolism of GSLs occurs in the lysosomes where specific glycosidases degrade the oligosaccharides of the GSLs in a stepwise fashion. As the penultimate catabolic step, glucosylceramide is hydrolyzed by glucocerebrosidase (EC 3.2.1.45) to produce glucose and ceramide. Ceramide is finally degraded inside the lysosome by acid ceramidase to give fatty acid and sphingosine.[16]

A recessively inherited disorder called Gaucher disease, the most common member of the sphingolipidoses, is caused by defective activity of glucocerebrosidase and is characterized by lysosomal accumulation of glucosylceramide in tissue macrophages.[17] Two distinct therapies have been developed for the treatment of Gaucher disease. Already widely applied is the so-called enzyme replacement therapy (ERT), a treatment based on chronic intravenous administration of a recombinant glucocerebrosidase (Cerezyme).[18] In most cases, ERT rapidly results in marked clinical improvements such as reduction in size of liver and spleen, corrections in blood abnormalities, and stabilization or improvement in skeletal deterioration.



More recently, an alternative treatment for Gaucher disease has been developed, the so-called substrate reduction therapy (SRT). Reduced biosynthesis of glycosphingolipids by partial inhibition of GCS is employed in SRT to balance the reduced catabolic capacity in Gaucher patients.[19] Platt, Butters, and co-workers were the first to demonstrate that oral administration of *N*-butyl-1-deoxynojirimycin (**3**) inhibits glycosphingolipid biosynthesis without overt side effects.[17,20] A multicenter clinical study with compound **3** in mild to moderately affected type 1 Gaucher patients revealed that oral administration of **3** (100 mg; TID) resulted in significant improvements in the size of abnormally enlarged organs, blood abnormalities, and spinal bone marrow abnormalities. These positive findings have led to the orphan drug registration of **3** (Zavesca) for treatment of moderate type 1 disease in adult Gaucher patients that are unsuitable for treatment by ERT. Presently, the application of **3** for treatment of other inherited disorders in which glycosphingolipids accumulate (sphingolipidoses: Tay-Sachs disease, Sandhoff disease, and Niemann-Pick disease type C) is being actively investigated in clinical trials.[21]

In 1993, we reported the existence of a nonlysosomal glycosidase activity that has the capacity to hydrolyze glucosylceramide.[22] To study the role of the nonlysosomal glucosylceramidase in the pathology of Gaucher disease, we developed a set of lipophilic 1-deoxynojirimycin-based inhibitors.[23] The most potent of these, *N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (**4**), proved to be a nanomolar inhibitor of the nonlysosomal glucosylceramidase. Inspired by the work of Platt, Butters, and co-workers, we analyzed compound **4** as an inhibitor of glucosylceramide synthase. Compound **4** proved to be at least 100-fold more potent than **3** in inhibiting glucosylceramide synthase (**4**: $IC_{50} = 0.2\ \mu M$; **3**: $IC_{50} = 50\ \mu M$ in our assay).[19] In addition to a potential application of **4** in the treatment of inherited sphingolipidoses, an increasing amount of research is revealing a role of GSLs in many other (patho)-biological processes,[1−15] pointing toward a wider range of applications. In a recent example, we showed that oral administration of **4** to mice with hapten-induced ulcerative colitis resulted in beneficial anti-inflammatory responses.[13]

The crucial role of glucosylceramide synthase (GCS) in glycosphingolipid biosynthesis makes it a highly promising drug target. Compound **4**, with a superior inhibition profile compared

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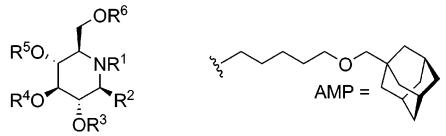
to that of the registered **3**, is a suitable lead compound for the development of more potent and selective glucosylceramide synthase inhibitors. It should be noted that **3**, next to inhibiting GCS, also targets a number of glucosidase activities such as intestinal sucrase and maltase. To a lesser extent, the same holds true for compound **4**. The search for potent and selective GCS inhibitors is hampered by the fact that no structural information of the enzyme, its binding site, and the binding of substrates is available.[24] Therefore, identification of new inhibitors has to proceed through structure−activity relationship studies by screening a diverse set of compounds. Several research groups have reported the development of potential inhibitors of GCS, and these compounds can be roughly characterized by being either a glucose analogue (next to 1-deoxynojirimycin derived[25−27] also pyrrolidine[28,29] and cyclohexitol-based[30] compounds) or a ceramide analogue (PDMP and its derivatives[31,32]). An intriguing, although as yet unsubstantiated, theory for the mode of action of **3** is that it acts as a mimic of the ceramide substrate in the GCS active site, rather than as a glucose- or transition-state mimetic.[24,27]

Our strategy for developing new GCS inhibitors is based on **4** as a lead compound. Structural analogues of **4** are screened for inhibitory potency against human GCS by an *in vivo* assay. At the same time, the compounds are assessed for their inhibitory activity toward the relevant human glucosidases: glucocerebrosidase, nonlysosomal glucosylceramidase, lysosomal α-glucosidase, debranching enzyme, and mammalian sucrase, lactase, and maltase. Modifications of the structure of **4** can be achieved as follows: (1) variation of the length and nature of the spacer, (2) altering the hydrophobic adamantan-1-yl-methoxy group, (3) modification of the stereochemistry and substitution patterns of the iminosugar moiety, and (4) alteration of the attachment site of the adamantan-1-yl-methoxy-spacer moiety on the iminosugar core.

We report here our results with respect to the last approach in the synthesis and biological evaluation of a set of 1-deoxynojirimycin derivatives having the adamantan-1-yl-methoxy-spacer moiety appended to either the C1 (as the *β*-aza-*C*-glycoside), O2, O3, O4, or O6 position (Table 1). To assess the influence of the substitution pattern of the endocyclic nitrogen atom, both *N*-methylated and *N*-butylated analogues of each modification were also prepared and compared with their non-*N*-alkylated iminosugar counterparts by analyzing their inhibitory effect on glucosylceramide synthase and the set of glucosidases.

TABLE 1. Design of Compounds 4−19



1-Deoxynojirimycin-core: Adamantan-1-yl-methoxy-spacer moiety:

compound	R^1	R^2	R^3	R^4	R^5	R^6
4	AMP	H	H	H	H	H
5−7	H, Me, or Bu	H	H	H	H	AMP
8−10	H, Me, or Bu	H	AMP	H	H	H
11−13	H, Me, or Bu	H	H	H	AMP	H
14−16	H, Me, or Bu	H	H	AMP	H	H
17−19	H, Me, or Bu	AMP	H	H	H	H

Results and Discussion

The synthesis of lead compound **4** is depicted in Scheme 1. Nucleophilic substitution of known tosylate **20**[33] with commercially available adamantanemethanol, followed by benzyl deprotection of the intermediate **21** through hydrogenolysis, afforded **22** in 89% yield over two steps. Swern oxidation of **22** provided aldehyde **23**, which enabled attachment to the 2,3,4,5-tetra-*O*-benzyl-1-deoxynojirimycin (**28**) core through reductive amination. Aldehyde **23** was condensed with **28** by reducing the intermediate imine to the corresponding amine under the agency of H_2, Pd/C in the presence of acetic acid. Crude product **24** was reexposed to hydrogenolysis conditions in the presence of aqueous hydrochloric acid to effect full deprotection and yielded lead compound **4** in 89% yield over two steps. Meanwhile, an efficient construction of **28** was attempted via $LiAlH_4$-mediated reduction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **25** to produce glucitol **26**. Application of the oxidation/double reductive amination protocol as advocated by Matos and co-workers (Pfitzer−Moffat oxidation followed by reductive amination under the agency of sodium cyanoborohydride and ammonium formate at room temperature)[34] proved to be cumbersome in our hands and gave irreproducible results. However, Swern oxidation of diol **26** followed by treatment of the resulting crude hexosulose **27** with sodium cyanoborohydride and ammonium formate at 0 °C led, after warming to room temperature, to efficient formation of **28** in 73% over the three steps.

The synthesis of the O6-functionalized iminosugars **5−7** started with pent-4-enoyl protection of the free amine in **28** to give **29** (Scheme 1).[35] Next, the primary benzyl ether in **29** was selectively cleaved and in situ acetylated by treatment with zinc chloride in acetic acid/acetic anhydride. Zemplén deacetylation of **30** thereafter provided **31** in 71% yield over the three steps.[36] The free hydroxyl function of **31** was deprotonated with sodium hydride in the presence of bromide **32** (prepared by subjecting alcohol **22** to Appel bromination conditions) in DMF at 0 °C to yield protected O6 analogue **33** in 92% yield. Removal of the pent-4-enoyl group with iodine in THF/water provided free

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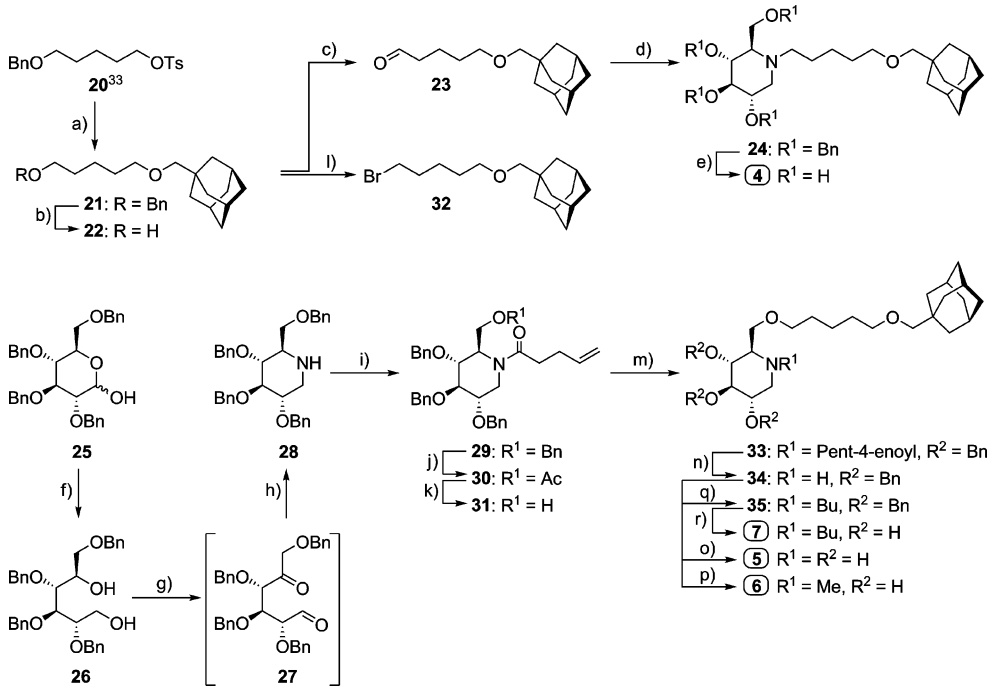
SCHEME 1. Synthesis of Lead Compound 4 and O6-Functionalized Iminosugars 5−7[a]



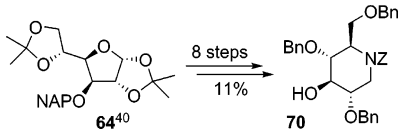
[a] Reagents and conditions: (a) 1. Adamantanemethanol, NaH, DMF, 90 min; 2. 1 equiv of **20**, 75 °C, 1 h, 92%. (b) Pd/C, 5 bar H_2, EtOH, 20 h, 97%. (c) 1. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2. Et_3N, −75 °C to rt, 2 h, 92%. (d) **28** and 1.5 equiv of **23**, Pd/C, atm H_2, AcOH, EtOH, 40 h. (e) Pd/C, 1 bar H_2, HCl, EtOH, 20 h, 89%, two steps. (f) $LiAlH_4$, THF, 20 h. (g) 1. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2. Et_3N, −75 to 0 °C, 2 h. (h) $NaBH_3CN$, excess NH_4HCO_2, Na_2SO_4, MeOH, 0 °C to rt, 20 h, 73%, three steps. (i) 1.5 equiv of pent-4-enoic anhydride, pyridine, 3 h, quantitative. (j) $ZnCl_2$, AcOH/Ac_2O (1:2), 20 h, 83%. (k) Cat. NaOMe, MeOH, 90 min, 86%. (l) PPh_3, CBr_4, acetonitrile, reflux, 2 h, 94%. (m) **32**, NaH, DMF, 0 °C to rt, 6 h, 92%. (n) I_2, THF/H_2O (3:2), 30 min, 81%. (o) Pd/C, H_2 atm, EtOH, HCl, 20 h, **5**: 75%. (p) 1. Formaldehyde, $NaBH_3CN$, AcOH, ACN, 20 h; 2. Pd/C, H_2 atm, EtOH, HCl, 20 h, **6**: 83%, two steps. (q) 1. Butyraldehyde, $NaBH_3CN$, EtOH/AcOH, 20 h, **35**: 82%. (r) Pd/C, H_2 atm, EtOH, HCl, 20 h, **7**: 93%.

amine **34** (81%).[35] Deprotection of **34** by Pd-catalyzed hydrogenolysis furnished O6 analogue **5** in 75% yield. Subjecting **34** to formaldehyde and sodium cyanoborohydride treatment followed by hydrogenolysis of the crude intermediate gave *N*-methylated O6 analogue **6** in 83%. Reductive amination of **34** with butyraldehyde in the presence of sodium cyanoborohydride and catalytic hydrogenation of product **35** provided the *N*-butylated O6 analogue (**7**) in 76% yield.

Construction of the O2- and O4-functionalized iminosugars was accomplished following a similar synthetic strategy for both, which started with *p*-methoxybenzylation of the free hydroxyl function of known allyl glucopyranosides **36**[37] and **43**[38] (Scheme 2). Deallylation of the resulting products was achieved by isomerization (Wilkinson's catalyst mediated isomerization in the case of O2-PMB **37** and KO*t*Bu/DMSO for O4-PMB **44**) followed by vinyl ether hydrolysis using iodine in THF/H_2O. The resulting hemiacetal products were not isolated but immediately subjected to $LiAlH_4$-mediated reduction to provide the O2-PMB (**38**) and O4-PMB (**45**) glucitol derivatives in 79 and 82% yield, respectively, over the two steps. Sequential Swern oxidation and double reductive amination, as described for **28**, produced orthogonally PMB-protected 1-deoxynojirimycins **39** (68%) and **46** (48%). Protection of the amine with a Z-group and subsequent deprotection of the PMB ethers with 2% TFA provided free 2′-OH iminosugar **41** and 4′-OH iminosugar **48** in 89 and 98% yield, respectively, over the two steps. The liberated hydroxyl functions were alkylated with bromide **32** to afford the protected O2 analogue **42** (91%) and O4 analogue **49** (91%). Cleavage of the benzyl ethers provided **8** (72%) and **11** (83%). *N*-Methylated **9** and *N*-butylated O2 analogue **10** were obtained by Pd-catalyzed hydrogenolysis of **8** in the presence of aqueous HCl and either formaldehyde or butyraldehyde. The *N*-methylated (**12**) and *N*-butylated (**13**) O4-functionalized iminosugars were prepared by a one-pot Z-deprotection and *N*-alkylation with formaldehyde or butyraldehyde, followed by benzyl ether hydrogenolysis to yield **12** in 94% and **13** in 83% yield.

The synthetic route for the O3-functionalized iminosugars **14**−**16** started with diacetoneglucose **50** (Scheme 3). Initial attempts to produce an O3-orthogonally protected glucitol derivative from **50** were hampered by partial cleavage of most of the suitable protecting groups during the initial isopropylidene hydrolysis/Fisher glycosidation steps (the O3 PMB-, TBDPS-, MOM ethers and pivaloyl ester all proved to be to labile under the acidic conditions, but the O3 2′-naphthylmethyl ether[39,40]

(39) 2′-Naphthylmethyl (NAP) ether protected diacetonglucose (**64**) could be successfully transformed in the orthogonally deprotectable 1-deoxynojirimycin derivative (**70**). For details, see the Supporting Information.



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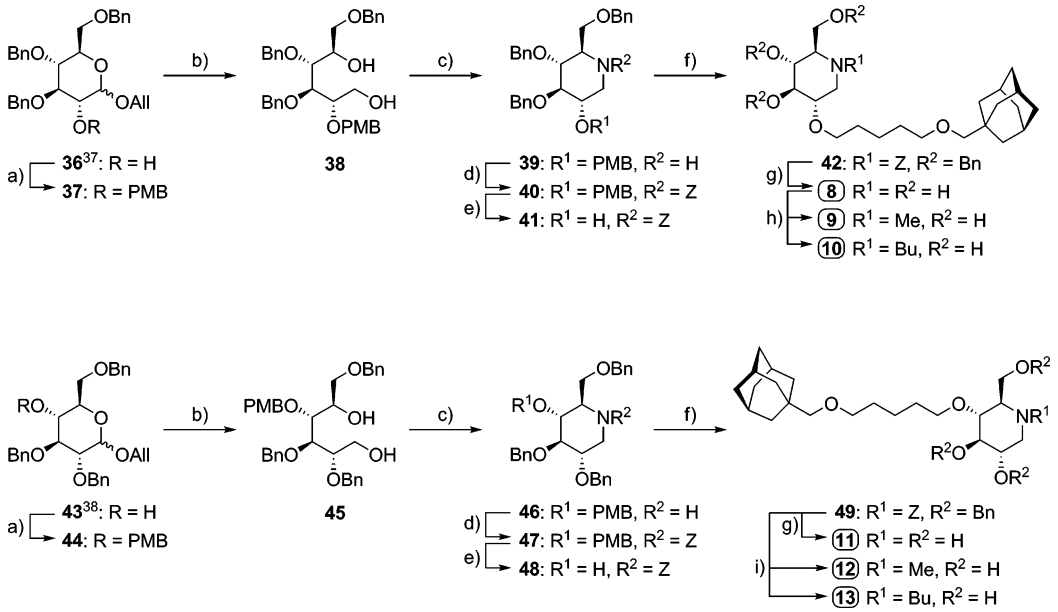
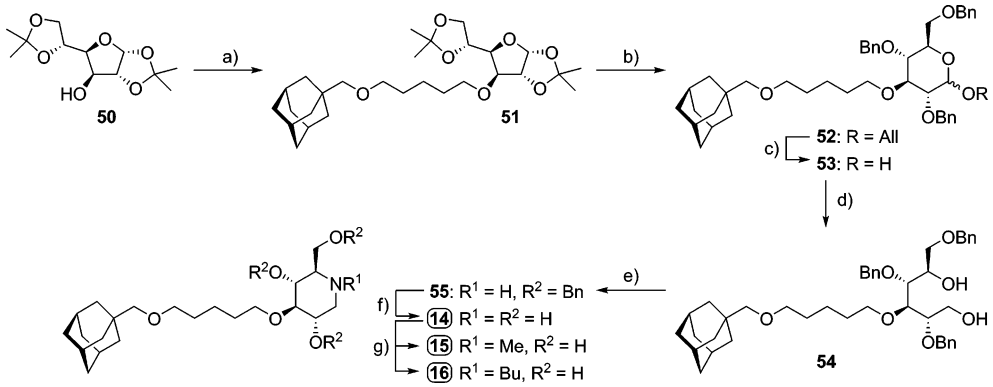
SCHEME 2. Synthesis of O2-Functionalized 8−10 and O4-Functionalized Iminosugars 11−13[a]



[a] Reagents and conditions: (a) PMBCl, NaH, DMF, 4 h, **37**: 83%; **44**: 90%. (b) From **37**: 1. $RhCl(PPh_3)_3$, DABCO, $EtOH/H_2O$, refluxing, 2 days; 2. I_2, THF/H_2O, 6 h; 3. $LiAlH_4$, THF, 20 h, **38**: 79%, two steps; from **44**: 1. 0.5 equiv of KOtBu, DMSO, 100 °C, 30 min; 2. I_2, THF/H_2O, 6 h; 3. $LiAlH_4$, THF, 20 h, **45**: 82%, two steps. (c) 1. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2. Et_3N, −75 °C to rt, 1 h; 3. $NaBH_3CN$, excess NH_4HCO_2, 3 Å mol sieves, MeOH, 0 °C to rt, 20 h, **39**: 68%; **46**: 48%. (d) BnOC(O)Cl, dioxane, aqueous $NaHCO_3$, 20 h, **40**: 99%; **47**: quantitative. (e) 2% TFA, CH_2Cl_2, 60 min, **41**: 90%; **48**: 98%. (f) **32**, NaH, DMF, 0 °C to rt, 4 h, **42**: 91%; **49**: 91%. (g) Pd/C, H_2 atm, EtOH, HCl, 20 h, **8**: 72%; **11**: 83%. (h) Pd/C, H_2 atm, formaldehyde or butyraldehyde, EtOH, HCl, 20 h, **9**: quantitative; **10**: 90%. (i) 1. Pd/C (Degussa-type), H_2 atm, EtOH, 90 min; 2. Formaldehyde or butyraldehyde, 90 min; 3. Pd/C, H_2 atm, EtOH, HCl, 20 h, **12**: 94%; **13**: 83%.

SCHEME 3. Synthesis of O3-Functionalized Iminosugars 14−16[a]

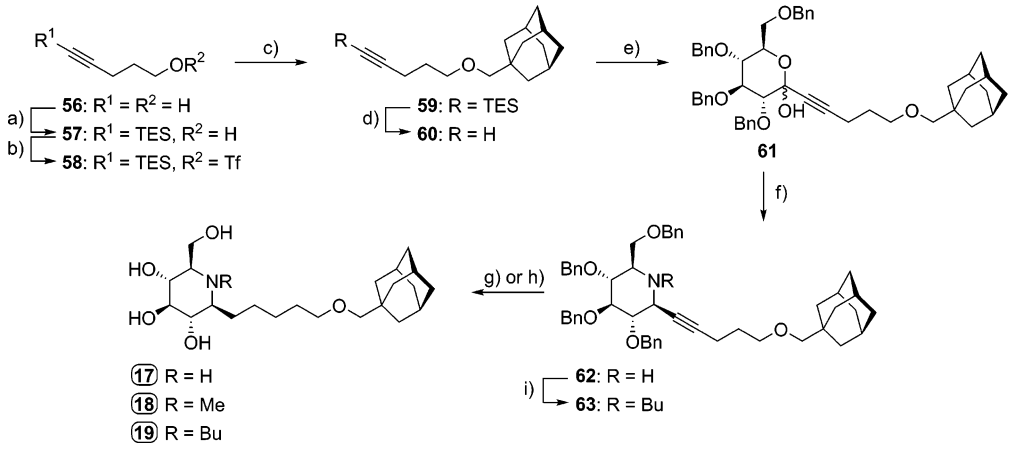


[a] Reagents and conditions: (a) **32**, NaH, DMF, 0 °C to rt, 4 h, 98%. (b) 1. $AcOH/H_2O$, 100 °C, 5 h; 2. AllOH, 5 mol % AcCl, reflux, 24 h; 3. BnBr, NaH, DMF, 0 °C to rt, 20 h, 56%, three steps. (c) 1. 0.5 equiv of KOtBu, DMSO, 100 °C, 35 min; 2. I_2, THF/H_2O, 6 h, 75%. (d) $LiAlH_4$, THF, 20 h, quantitative. (e) 1. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 2. Et_3N, −75 to −10 °C, 3 h; 3. $NaBH_3CN$, excess NH_4HCO_2, Na_2SO_4, MeOH, 0 °C to rt, 20 h, 67%, two steps. (f) Pd/C, H_2 atm, EtOH, HCl, 20 h, 86%. (g) 1. Pd/C (Degussa-type), H_2 atm, 10 equiv of formaldehyde or butyraldehyde, EtOH, 1 h; 2. Pd/C, H_2 atm, EtOH, HCl, 20h, **15**: 83%; **16**: 99%.

withstood these conditions). Alternatively, installation of the adamantane-spacer moiety at the beginning of the route by alkylation of **50** with bromide **32** provided **51** in excellent yield. The installed ether linkage in **51** withstood consecutive isopropylidene hydrolysis/Fisher glycosidation with allyl alcohol and benzylation to produce **52** in good yield. Isomerization and cleavage of the allyl group in **52** was followed by $LiAlH_4$-mediated reduction of the crude hemiacetal to produce **54** in 75% yield over the two steps. Swern oxidation of **54** produced the hexosulose, which was subjected to reductive amination conditions at 0 °C to produce the iminosugar (**55**) in 67% yield. Hydrogenolysis of **55** with Pd/C and H_2 produced O3 analogue **14**. One-pot Z-deprotection and reductive amination of **55** with either formaldehyde or butyraldehyde, followed by benzyl ether hydrogenolysis, produced *N*-methylated **15** and *N*-butylated O3 analogue **16**.

The synthesis of β-aza-C1-functionalized iminosugars **17**−**19**, depicted in Scheme 4, commenced with the preparation of acetylene **60**. Formation of the dianion of pent-4-yn-1-ol **56** with butyllithium followed by successive treatment with triethylsilylchloride and 2 M HCl produced **57** in 83% yield. Alkynol **57** was treated with triflic anhydride and triethylamine in DCM to provide triflate **58**. Reaction of the triflate with adamantanemethanol under the agency of potassium carbonate in DCM afforded compound **59** in 88% yield. Removal of the silyl protective group was accomplished by treatment of **59** with excess sodium methanolate in MeOH at 90 °C, giving **60** in 99% yield. Conversion of **60** into the acetylenic anion with

SCHEME 4. Synthesis of C1-Functionalized Iminosugars 17−18[a]



[a] Reagents and conditions: (a) 1. BuLi, THF, −68 °C, 1 h; 2. TESCl, −68 °C to rt, 20 h; 3. 2 M HCl, 48 h, 83%. (b) Tf_2O, Et_3N, CH_2Cl_2, −40 °C, 1 h. (c) Adamantanemethanol, K_2CO_3, CH_2Cl_2, reflux, 3 days, 88%. (d) 4 equiv of NaOMe, THF/MeOH (1:1), 90 °C, 20 h, 99%. (e) 1. BuLi, THF, −50 °C, 1 h; 2. 2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone,[41] −50 °C, 2 h, 77%. (f) 1. $NaBH_4$, MeOH/CH_2Cl_2 (5:1), 2 h; 2. DMSO, $(COCl)_2$, CH_2Cl_2, −75 °C, 2 h; 3. Et_3N, −75 °C to rt, 0.5; 4. $NaBH_3CN$, excess NH_4HCO_2, 3 Å mol sieves, MeOH/CH_2Cl_2 (5:1), 0 °C to rt, 20 h, 56%, three steps. (g) Pd/C, H_2 atm, EtOH, HCl, 20 h, 85% from **62** to **17**; 91% from **63** to **19**. (h) 1. Pd/C (Degussa-type), H_2 atm, formaldehyde, *n*-propanol, 1 h; 2. Pd/C, H_2 atm, EtOH, HCl, 20 h, 94% two steps from **62** to **18**. (i) Butyraldehyde, $NaBH_3CN$, EtOH/AcOH (3:1), 20 h, 80%.

butyllithium in THF at −60 °C was followed by addition of excess 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[41] to produce hemiketal **61** as an α/β mixture in 77% yield. Reduction of **61** with sodium borohydride in MeOH/DCM was followed by Swern oxidation to give the diketone. The crude diketone was subjected to excess ammonium formate and sodium cyanoborohydride in MeOH/DCM at 0 °C to produce β-aza-C1-analogue **62** as a single stereoisomer[42,43] in 58% yield over the three steps. Deprotection of the benzyl ethers with concomitant reduction of the triple bond under Pd/C-catalyzed hydrogenolysis conditions provided C1 analogue **17** in 85% yield. Concomitant benzyl deprotection and alkylation of the amine in **17** by Pd/C-catalyzed reductive amination with either formaldehyde or butyraldehyde proved to be troublesome. However, reductive amination of formaldehyde with the endocyclic amine in **62** with Pd/C (Degussa-type) and subsequent hydrogenolysis after addition of HCl to the reaction mixture yielded *N*-methylated **18** in 94% over the two steps. Sodium cyanoborohydride-mediated reductive amination of **62** with butyraldehyde yielded **63**, which was deprotected by catalytic hydrogenation to produce *N*-butylated **19** in 73% over the two steps.

The inhibitory potency and selectivity of the synthesized iminosugars **5**−**19** were assessed by testing the compounds in assays for the three enzymes involved in glucosylceramide metabolism, namely, GCS, glucocerebrosidase, and nonlysosomal glucosylceramidase (Table 2). To further establish the inhibitory profile of iminosugars **5**−**19**, they were also tested in assays for the lysosomal α-glucosidase, debranching enzyme, sucrase, lactase, and maltase. The lysosomal α-glucosidase was tested as it is known to be strongly inhibited by **3** as well as the lead compound **4**. Debranching enzyme is involved in cytosolic glycogen degradation, and it possesses both an α-1,4-transferase and α-1,6-glucosidase catalytic site for its substrate. The intestinal glucosidases are located in the outer membrane of epithelial cells lining the small intestine. The enzymes sucrase, lactase, and maltase are responsible for degrading the glucose containing disaccharides (sucrose, lactose, and maltose) derived from food and as a side effect are also inhibited in Gaucher patients receiving substrate deprivation therapy with Zavesca (**3**).[19,44]

The apparent IC_{50} values of the newly synthesized iminosugars **5**−**19** for the various enzymes were compared to the values obtained for **3**, **4**, and 1-deoxynojirimycin (**2**). As expected, analysis of the inhibitory activity of 1-deoxynojirimycin (**2**) revealed that it is a potent inhibitor of lysosomal α-glucosidase, but also clearly demonstrated the known necessity of a lipophilic moiety for inhibition of GCS (Table 2). Comparison of IC_{50} values of **3** and **4** reveals that the inhibitory activity toward the three glucosylceramide-metabolizing enzymes is dramatically improved by the added adamantan-1-ylmethoxy moiety. However, both **3** and **4** lack selectivity at higher concentrations. When compared to **4**, O6 analogue **5** shows decreased inhibition of GCS and the nonlysosomal glucosylceramidase, but remains a potent inhibitor of glucocerebrosidase. The five other human glucose-processing enzymes are also inhibited less strongly by this analogue. Its *N*-methylated derivative **6** is even more selective toward glucocerebrosidase (IC_{50}: 0.3 μM) as opposed to its butylated counterpart **7**. O2 analogue **8** has an inhibition profile similar to that of O6 analogue **5**. Again, both *N*-methylated (**9**) and *N*-butylated (**10**) O2-functionalized iminosugars show a general reduction in inhibitory capacity for all measured enzymes. The inhibitory potency for GCS of both O4-functionalized iminosugars (**11**−**13**) and O3-functionalized iminosugars (**14**−**16**) is very low, and a general decrease in inhibition for all the measured enzymes for these compounds is observed. Of all the synthesized iminosugars, compound **17** shows the most potent inhibition of GCS, with an *in vivo* IC_{50} value of 9 μM. However, it lacks improvement in selectivity for this enzyme when compared to **4**. *N*-Methylated analogue **18** showed strongly decreased inhibition of GCS and all other enzymes. Although

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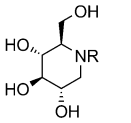
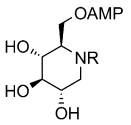
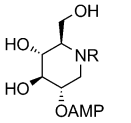
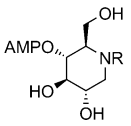
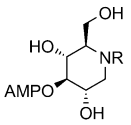
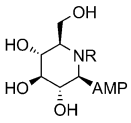
(42) Leeuwenburgh, M. A.; Picasso, S.; Overkleeft, H. S.; van der Marel, G. A.; Vogel, P.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, 1185−1189.

(43) Saavedra, O. M.; Martin, O. R. *J. Org. Chem.* **1996**, *61*, 6987−6993.

(44) Andersson, U.; Butters, T. D.; Dwek, R. A.; Platt, F. M. *Biochem. Pharmacol.* **2000**, *59*, 821−829.

TABLE 2. Enzyme Inhibition Assay: Apparent IC_{50} Values (in μM) for Compounds 2−19[a]

Compound	Glucosyl-ceramide synthase	Lysosomal glucocere-brosidase	Non-lysosomal glucosyl-ceramidase	Lysosomal α-gluco-sidase	Sucrase	Lactase	Maltase	De-branching enzyme
	in vivo	*in vitro*	*in vitro*	*in vitro*	*in vitro*	*in vitro*	*in vitro*	*in vitro*
 **2**: R = H	>100	250	21	1.5	2	62	2	10
3: R = Bu	50	400	0.230	0.1	0.5	>100	9	10
4: R = AMP	0.2	0.2	0.001	0.4	4.5	>100	19	10
 **5**: R = H	>100	0.5	10	120	25	>100	>100	>100
6: R = Me	>100	0.3	250	>2000	>100	>100	>100	>100
7: R = Bu	>100	2	40	630	39	>100	>100	>100
 **8**: R = H	>100	0.3	60	~50	57	>100	>100	>100
9: R = Me	>100	6	>100	27	63	>100	>100	>100
10: R = Bu	>100	6	5	156	>100	>100	>100	>100
 **11**: R = H	>100	25	55	190	50	>100	>100	>100
12: R = Me	>100	18	20	1000	50	>100	>100	>100
13: R = Bu	>100	250	100	1500	25	>100	>100	>100
 **14**: R = H	>100	11	60	18	17	>100	50	>100
15: R = Me	>100	50	50	120	30	>100	>100	>100
16: R = Bu	>100	100	40	150	35	>100	>100	>100
 **17**: R = H	9	3	0.04	6.25	>100	>100	>100	>100
18: R = Me	>100	25	1.4	48	>100	>100	>100	>100
19: R = Bu	25	40	10	255	>100	>100	>100	>100

[a] AMP = 5-(adamantan-1-yl-methoxy)-pentyl.

N-butyl analogue **19** also showed decreased inhibition of all tested enzymes, it did show a marked improvement of inhibition of GCS when compared to **18**. C1 analogue **17** is a 50 times less potent inhibitor of GCS than lead compound **4** but is still a more potent and selective inhibitor than **3**. In a recent article by Boucheron et al., derivatives of **3** were synthesized bearing one or two additional alkyl chains on the C1, O2, or O4 positions.[25] The outcome of this study corroborates our results in that lipophilic entities are best attached to the endocyclic nitrogen atom.

Conclusion

We have developed a collection of adamantan-1-yl-methoxy-functionalized 1-deoxynojirimycin derivatives based on the structure of the potent GCS inhibitor **4**. Determination of their IC_{50} values for the three glucosylceramide metabolism-related enzymes and comparison with **4** demonstrated that relocating the lipophilic moiety from the endocyclic nitrogen atom to other positions on the 1-deoxynojirimycin ring system does not lead to a more potent or selective inhibitor of GCS. However, the most potent iminosugar derivative from the series presented here, the β-aza-*C*-glucoside **17**, still inhibits GCS in the low micromolar range and shows decreased inhibition of intestinal glucosidases. When combined with the marked improvement of inhibitory potency for GCS when lengthening the *N*-alkyl moiety from methyl (**18**) to butyl (**19**), this class of analogues could hold potential for further development toward more potent and selective GCS inhibitors. Iminosugars **5**, **6**, and **8**, although being poor inhibitors of GCS, did show a potent and selective inhibition of glucocerebrosidase. As such, these compounds may find application as potential chemical chaperones of Gaucher disease associated glucocerebrosidases.[45] Studies in these directions as well as the synthesis and evaluation of compounds in which the configuration of the iminosugar core of **4** is altered are currently being carried out, and the outcome of these will be published in the near future.

Experimental Section

Enzyme Assays. IC_{50} values of compounds for the various enzyme activities were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations.

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All iminosugars were tested as their HCl salt from DMSO stock solutions. IC_{50} values for glucosylceramide synthase were measured using living cells with NBD ceramide as substrate.[23] Glucocerebrosidase activity was measured using recombinant enzyme and 4-methylumbelliferyl-β-glucose as substrate.[23] Nonlysosomal glucosylceramidase was measured using enzyme-containing membrane preparations from Gaucher spleen and 4-methylumbelliferyl-β-glucose as substrate.[23] Lysosomal α-glucosidase was measured using purified enzyme from human urine and 4-methylumbelliferyl-α-glucoside as substrate.[23] Lactase, maltase, and sucrase activities were determined with homogenates of freshly isolated rat intestine by measuring liberated glucose from the corresponding disaccharides.[44] The activity of debranching enzyme (α-1,6-glucosidase activity) was measured by determining liberated glucose from dextrin with an erythrocyte preparation as enzyme source.[46]

***N*-[5-(Adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (4):** ^{1}H NMR (400 MHz, CD_3OD, COSY): 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} = 4.8 Hz, 1H, H-2), 3.38 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2-5′ pentyl), 3.35 (dd, J_{H-H} = 9.4 Hz, 1H, H-4), 3.12 (dd, J_{H-H} = 9.1 Hz, 1H, H-3), 2.97 (dd, J_{H1a-H2} = 4.8 Hz, $J_{H1a-H1b}$ = 10.2 Hz, 1H, H-1a), 2.96 (s, 2H, OCH_2-adamantane), 2.79 (m, 1H, NC*H*H-1′ pentyl), 2.58 (m, 1H, NCH*H*-1′ pentyl), 2.17 (dd, J_{H-H} = 7.7 Hz, 1H, H-1b), 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 adamantane), 1.77−1.66 (m, 6H, 3×CH_2 adamantane), 1.58 (m, 2H, CH_2-4′ pentyl), 1.55 (d, J_{H-H} = 2.8 Hz, 6H, 3×CH_2 adamantane), 1.51 (m, 2H, CH_2-2′ pentyl), 1.33 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.6 (OCH_2-adamantane), 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 adamantane), 36.9 (3×CH_2 adamantane), 33.7 (C_q adamantane), 29.1 (CH_2-4′ pentyl), 28.3 (3×CH adamantane), 23.9 (CH_2-3′ pentyl), 23.6 (CH_2-2′ pentyl). ATR-IR (thin film): 3317.3, 2900.7, 2846.7, 1448.4, 1359.7, 1344.3, 1259.4, 1217.0, 1188.1, 1155.3, 1087.8, 1035.7, 1010.6, 914.2, 812.0, 754.1, 665.4 cm^{-1}. $[\alpha]^{20}_D$ −10.6° (*c* 2.30, MeOH). HRMS: found 398.2927 [M + H]$^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

6-*O*-[1-(Adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (5): ^{1}H NMR (400 MHz, CD_3OD, COSY): δ 3.76−3.70 (m, 2H, CH_2-6), 3.56−3.43 (m, 3H, H-2, OCH_2 pentyl), 3.39−3.34 (m, 3H, H-4 or H-3, OCH_2 pentyl), 3.17 (m, 1H, H-3), 3.02 (m, 1H, H-1a), 2.96 (s, 2H, OCH_2-adamantane), 2.49 (br s, 2H, 2×OH), 2.32 (m, 1H, H-5), 2.21 (m, 1H, H-1b), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.55 (m, 16H, 6×CH_2 adamantane, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2 pentyl). ^{13}C NMR (50 MHz, CD_3OD): δ 83.1, 80.6, 73.3, 72.5, 71.7, 61.3, 51.0, 40.8, 38.4, 35.2, 30.5, 29.8, 24.0. ATR-IR (thin film): 3332.8, 2900.7, 2846.7, 1674.1, 1450.4, 1365.5, 1319.2, 1257.5, 1103.2, 1041.5, 671.2, 609.5 cm^{-1}. $[\alpha]^{20}_D$ +16.4° (*c* 0.24, MeOH). HRMS: found 398.2910 [M + H]$^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

***N*-Methyl-6-*O*-[1-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (6):** ^{1}H NMR (400 MHz, CD_3OD, COSY): δ 3.73 (dd, J_{H6a-H5} = 2.1 Hz, $J_{H6a-H6b}$ = 10.5 Hz, 1H, CH-6a), 3.63 (dd, J_{H6b-H5} = 3.4 Hz, $J_{H6b-H6a}$ = 10.5 Hz, 1H, CH-6b), 3.53−3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2 pentyl), 3.32−3.28 (m, 1H, H-4), 3.12 (dd, J_{H-H} = 9.0 Hz, 1H, H-3), 2.96 (s, 2H, OCH_2-adamantane), 2.89 (dd, J_{H-H} = 4.8 Hz, J_{H-H} = 11.1 Hz, 1H, H-1a), 2.35 (s, 3H, NCH_3), 2.09 (dd, J_{H-H} = 10.9 Hz, H-1b), 1.98−1.88 (m, 4H, H-5, 3×CH adamantane), 1.77−1.66 (m, 6H, 3×CH_2 adamantane), 1.60−1.55 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.1 (OCH_2-adamantane), 80.5 (C-3), 72.6, 72.4 (2×OCH_2 pentyl), 71.8 (C-4), 70.4 (C-2), 69.2 (C-5), 68.7 (C-6), 62.1 (C-1), 42.7 (NCH_3), 40.9 (3×CH_2 adamantane), 38.4 (3×CH_2 adamantane), 35.2 (C_q adamantane), 30.5, 30.4 (2×CH_2 pentyl), 29.8 (3×CH adamantane), 24.1 (CH_2-3′ pentyl). ATR-IR (thin film): 3325.0, 2900.7, 2846.7, 2800.4, 2090.7, 1612.4, 1450.4, 1365.5, 1249.8, 1103.2, 1033.8, 833.2, 748.3 cm^{-1}. $[\alpha]^{20}_D$ −37.1° (*c* 0.62, MeOH). HRMS: found 412.3063 [M + H]$^+$, calcd for $[C_{23}H_{42}NO_5 + H]^+$ 412.3058.

***N*-Butyl-6-*O*-[1-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (7):** ^{1}H NMR (400 MHz, CD_3OD, COSY): δ 3.74 (d, $J_{H6a-H6b}$ = 10.5 Hz, 1H, CH-6a), 3.62 (dd, J_{H6b-H5} = 3.7 Hz, $J_{H6b-H6a}$ = 10.5 Hz, 1H, CH-6b), 3.45−3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2 pentyl), 3.24 (dd, J_{H-H} = 9.3 Hz, 1H, H-4), 3.11 (dd, J_{H-H} = 9.0 Hz, 1H, H-3), 2.98−2.93 (m, 3H, H-1a, OCH_2-adamantane), 2.78 (m, 1H, NC*H*H butyl), 2.55 (m, 1H, NCH*H* butyl), 2.24−2.22 (m, 1H, H-5), 2.16 (dd, J_{H-H} = 11.0 Hz, 1H, H-1b), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.66 (m, 6H, 3×CH_2 adamantane), 1.65−1.55 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.48−1.43 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.31 (m, 2H, CH_2 butyl), 0.94 (t, J_{H-H} = 7.3 Hz, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.1 (OCH_2-adamantane), 80.6 (C-3), 72.6, 72.3 (2×OCH_2 pentyl), 72.2 (C-4), 70.6 (C-2), 69.4 (C-6), 66.4 (C-5), 57.7 (C-1), 53.9 (NCH_2 butyl), 40.9 (3×CH_2 adamantane), 38.4 (3×CH_2 adamantane), 35.2 (C_q adamantane), 30.5 (2×CH_2 pentyl), 29.8 (3×CH adamantane), 27.5 (CH_2 butyl), 24.1 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). ATR-IR (thin film): 3363.6, 2900.7, 2846.7, 2106.1, 1828.4, 1650.9, 1458.1, 1365.5, 1257.5, 1103.2, 1018.3, 810.0 cm^{-1}. $[\alpha]^{20}_D$ −21.8° (*c* 0.66, MeOH). HRMS: found 454.3531 [M + H]$^+$, calcd for $[C_{26}H_{47}NO_5 + H]^+$ 454.3527.

2-*O*-[5-(Adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (8): ^{1}H NMR (400 MHz, CD_3OD): δ 3.82 (dd, J_{H6a-H5} = 2.8 Hz, $J_{H6a-H6b}$ = 10.9 Hz, 1H, H-6a), 3.65−3.56 (m, 3H, H-6b, OCH_2 pentyl), 3.37 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2 pentyl), 3.28−3.22 (m, 2H, H-3, H-1a), 3.18−3.12 (m, 2H, H-2, H-4), 2.96 (s, 2H, OCH_2-adamantane), 2.44 (m, 1H, H-5), 2.35 (dd, J_{H-H} = 10.6 Hz, 1H, H-1b), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.66 (m, 6H, 3×CH_2 adamantane), 1.63−1.55 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.0 (OCH_2-adamantane), 80.8 79.6 (C-2, C-3), 73.4 (C-4), 72.6, 71.7 (2×OCH_2 pentyl), 63.0 (C-6), 62.7 (C-5), 48.6 (C-1), 40.8 (3×CH_2 adamantane), 38.3 (3×CH_2 adamantane), 35.1 (C_q adamantane), 31.0, 30.5 (2×CH_2 pentyl), 29.7 (3×CH adamantane), 23.8 (CH_2-3′ pentyl). ATR-IR (thin film): 3332.8, 2900.7, 2846.7, 2476.4, 1450.4, 1365.5, 1257.5, 1095.5, 1049.2, 879.5, 840.9, 709.8 cm^{-1}. $[\alpha]^{20}_D$ +28.2° (*c* 1.44, $CHCl_3$). HRMS: found 398.2921 [M + H]$^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

***N*-Methyl-2-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (9):** ^{1}H NMR (400 MHz, CD_3OD, COSY): δ 3.84−3.83 (m, 2H, CH_2-6), 3.40−3.36 (m, 3H, H-4, OCH_2 pentyl), 3.25−3.17 (m, 2H, H-2, H-3), 3.04 (dd, J_{H1a-H2} = 4.4 Hz, $J_{H1a-H1b}$ = 11.3 Hz, 1H, H-1a), 2.96 (s, 2H, OCH_2-adamantane), 2.35 (s, 3H, NCH_3), 2.00 (dd, J_{H-H} = 10.5 Hz, H-1b), 1.95−1.93 (m, 4H, H-5, 3×CH adamantane), 1.79−1.66 (m, 6H, 3×CH_2 adamantane), 1.61−1.53 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD): δ 83.0, 79.5, 78.8, 72.6, 71.9, 71.6, 70.3, 59.6, 59.2, 42.5, 40.8, 38.3, 35.2, 31.0, 30.5, 29.7, 23.8. ATR-IR (thin film): 3301.9, 2900.7, 2846.7, 2353.0, 2106.1, 1658.7, 1612.4, 1450.4, 1365.5, 1234.4, 1234.4, 1095.5, 1049.2, 910.3, 825.5 cm^{-1}. $[\alpha]^{20}_D$ +6.3° (*c* 0.80, $CHCl_3$). HRMS: found 412.3076 [M + H]$^+$, calcd for $[C_{23}H_{41}NO_5 + H]^+$ 412.3058.

***N*-Butyl-2-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (10):** ^{1}H NMR (400 MHz, CD_3OD): δ 3.84−3.83 (m, 2H, CH_2-6), 3.65−3.56 (m, 2H, OCH_2 pentyl), 3.40−3.33 (m, 3H, H-4, OCH_2 pentyl), 3.24−3.15 (m, 2H, H-2, H-3), 3.08 (dd, $J_{H1eq-H2}$ = 4.2 Hz, $J_{H1eq-H1ax}$ = 11.2 Hz, 1H, H-1a), 2.96 (s, 2H, OCH_2-adamantane), 2.78 (m, 1H, NC*H*H butyl), 2.59 (m, 1H, NCH*H* butyl), 2.12−2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.66 (m, 6H, 3× CH_2 adamantane), 1.63−1.53 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.50−1.40 (m, 4H,

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CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, J_{H-H} = 7.4 Hz, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.0 (OCH_2-adamantane), 79.6, 79.2 (C-2, C-3), 72.6 (OCH_2 pentyl), 72.1 (C-4), 71.7 (OCH_2 pentyl), 67.1 (C-5), 59.4 (C-6), 55.2 (C-1), 53.6 (NCH_2 butyl), 40.9 (3×CH_2 adamantane), 38.4 (3×CH_2 adamantane), 35.1 (C_q adamantane), 31.0, 30.7 (2×CH_2 pentyl), 29.8 (3×CH adamantane), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). ATR-IR (thin film): 3371.3, 2900.7, 2846.7, 2090.7, 1689.5, 1458.1, 1365.5, 1149.5, 1103.2, 902.6, 825.5, 663.5 cm^{-1}. $[\alpha]^{20}_D$ +28.1° (*c* 0.32, $CHCl_3$/MeOH, 2:1). HRMS: found 454.3551 $[M + H]^+$, calcd for $[C_{26}H_{47}NO_5 + H]^+$ 454.3527.

4-*O*-[5-(Adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (11): ^1H NMR (400 MHz, CD_3OD, COSY): δ 3.89−3.85 (m, 1H, OC*H*H pentyl), 3.79 (dd, J_{H-H} = 2.5 Hz, J_{H-H} = 10.8 Hz, 1H, H-6a), 3.62−3.52 (m, 2H, H-6b, OCH*H* pentyl), 3.42−3.36 (m, 3H, H-2, OCH_2 pentyl), 3.28 (dd, J_{H-H} = 9.2 Hz, 1H, H-3), 3.07 (dd, J_{H1a-H2} = 5.1 Hz, $J_{H1a-H1b}$ = 12.2 Hz, 1H, H-1a), 3.00 (dd, J_{H-H} = 9.6 Hz, 1H, H-4), 2.96 (s, 2H, OCH_2-adamantane), 2.47 (ddd, J_{H-H} = 2.5 Hz, J_{H-H} = 5.6 Hz, J_{H-H} = 9.6 Hz, 1H, H-5), 2.40 (dd, J_{H1b-H2} = 10.8 Hz, $J_{H1b-H1a}$ = 12.2 Hz, 1H, H-1b), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.66 (m, 6H, 3×CH_2 adamantane), 1.64−1.55 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.0 (OCH_2-adamantane), 81.2 (C-4), 80.6 (C-3), 72.8 (C-2), 73.9, 72.6 (2×OCH_2 pentyl), 62.4 (C-6), 62.3 (C-5), 50.8 (C-1), 40.4 (3×CH_2 adamantane), 38.3 (3×CH_2 adamantane), 35.1 (C_q adamantane), 31.2, 30.5 (2×CH_2 pentyl), 29.7 (3×CH adamantane), 23.9 (CH_2-3′ pentyl). ATR-IR (thin film): 3371.3, 2900.7, 2846.7, 2476.4, 2067.5, 1674.1, 1450.4, 1365.5, 1257.5, 1195.8, 1095.5, 1049.2, 979.8, 879.5, 840.9, 717.5 cm^{-1}. $[\alpha]^{20}_D$ +16.9° (*c* 1.08, MeOH). HRMS: found 398.2905 $[M + H]^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

***N*-Methyl-4-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (12):** ^1H NMR (400 MHz, CD_3OD, COSY): δ 3.94−3.89 (m, 1H, OC*H*H pentyl), 3.82 (dd, J_{H6a-H5} = 2.3 Hz, $J_{H6a-H6b}$ = 11.9 Hz, 1H, CH-6a), 3.74 (dd, J_{H6b-H5} = 2.1 Hz, $J_{H6b-H6a}$ = 11.9 Hz, 1H, CH-6b), 3.65−3.60 (m, 1H, OCH*H* pentyl), 3.47 (m, 1H, H-2), 3.38 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2 pentyl), 3.23−3.21 (m, 2H, H-3, H-4), 2.96 (s, 2H, OCH_2-adamantane), 2.89 (dd, J_{H-H} = 4.8 Hz, J_{H-H} = 11.1 Hz, 1H, H-1a), 2.33 (s, 3H, NCH_3), 2.03 (dd, J_{H-H} = 10.8 Hz, 1H, H-1b), 1.93 (br s, 3H, 3×CH adamantane), 1.76−1.65 (m, 7H, H-5, 3×CH_2 adamantane), 1.63−1.55 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, CD_3OD): δ 83.1, 80.7, 79.5, 74.1, 72.6, 70.7, 69.8, 62.1, 58.5, 42.3, 40.8, 38.3, 35.2, 31.2, 30.6, 29.6, 23.9. ATR-IR (thin film): 3386.8, 2900.7, 2846.7, 2792.7, 2106.1, 1666.4, 1458.1, 1357.8, 1249.8, 1095.5, 1041.5, 987.5, 918.1, 825.5 cm^{-1}. $[\alpha]^{20}_D$ +11.5° (*c* 0.35, $CHCl_3$/MeOH, 2:1). HRMS: found 412.3074 $[M + H]^+$, calcd for $[C_{23}H_{42}NO_5 + H]^+$ 412.3058.

***N*-Butyl-4-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (13):** ^1H NMR (400 MHz, CD_3OD): δ 3.94−3.89 (m, 1H, OC*H*H pentyl), 3.83 (dd, J_{H6a-H5} = 2.1 Hz, $J_{H6a-H6b}$ = 11.8 Hz, 1H, CH-6a), 3.75 (dd, J_{H6b-H5} = 2.2 Hz, $J_{H6b-H6a}$ = 11.8 Hz, 1H, CH-6b), 3.65−3.59 (m, 1H, OCH*H* pentyl), 3.44 (ddd, J_{H-H} = 4.7 Hz, J_{H-H} = 10.0 Hz, J_{H-H} = 14.6 Hz, 1H, H-2), 3.38 (t, J_{H-H} = 6.3 Hz, 2H, OCH_2 pentyl), 3.24−3.19 (m, 2H, H-3, H-4), 2.97−2.93 (m, 3H, H-1a, OCH_2-adamantane), 2.76 (m, 1H, NC*H*H butyl), 2.58 (m, 1H, NCH*H* butyl), 2.15−2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.55 (m, 16H, 6×CH_2 adamantane, 2×CH_2 pentyl), 1.48−1.41 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, J_{H-H} = 7.2 Hz, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.0 (OCH_2-adamantane), 80.7, 79.9 (C-3, C-4), 74.0, 72.6 (2×OCH_2 pentyl), 71.0 (C-2), 66.6 (C-5), 58.5 (C-6), 57.5 (C-1), 53.3 (NCH_2 butyl), 40.8 (3×CH_2 adamantane), 38.3 (3×CH_2 adamantane), 35.2 (C_q adamantane), 31.2, 30.6 (2×CH_2 pentyl), 29.8 (3×CH adamantane), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). ATR-IR (thin film): 3363.6, 2900.7, 2846.7, 1666.4, 1458.1, 1365.5, 1249.8, 1103.2, 1041.5, 902.6, 817.8 cm^{-1}. $[\alpha]^{20}_D$ −2.5° (*c* 0.40, $CHCl_3$/MeOH, 1:1). HRMS: found 454.3539 $[M + H]^+$, calcd for $[C_{26}H_{47}NO_5 + H]^+$ 454.3527.

3-*O*-[5-(Adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (14): ^1H NMR (400 MHz, $CDCl_3/CD_3OD$, 2:1, COSY): δ 3.93−3.80 (m, 4H, CH_2-6, OCH_2 pentyl), 3.76 (m, 1H, H-2), 3.57 (dd, J_{H-H} = 9.1 Hz, 1H, H-4), 3.42 (t, J_{H-H} = 6.5 Hz, 2H, OCH_2 pentyl), 3.31 (dd, J_{H1a-H2} = 4.4 Hz, $J_{H1a-H1b}$ = 12.4 Hz, 1H, H-1a), 3.19 (m, 1H, H-3), 2.99 (s, 2H, OCH_2-adamantane), 2.98 (m, 1H, H-5), 2.78 (dd, J_{H-H} = 11.9 Hz, 1H, H-1b), 1.96 (br s, 3H, 3×CH adamantane), 1.75−1.57 (m, 10H, 3×CH_2 adamantane, 2×CH_2 pentyl), 1.54 (br d, J_{H-H} = 2.3 Hz, 6H, 3×CH_2 adamantane), 1.42 (m, 2H, CH_2-3′ pentyl). ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 2:1): δ 84.2, 81.5, 72.8, 71.2, 67.7, 67.0, 60.3, 57.7, 46.0, 39.1, 36.6, 33.6, 29.4, 28.7, 27.8, 21.9. ATR-IR (thin film): 3357.8, 2900.7, 2846.7, 1674.1, 1596.9, 1448.4, 1344.3, 1186.1, 1103.2, 1026.1, 732.9, 623.0 cm^{-1}. $[\alpha]^{20}_D$ +17.4° (*c* 0.46, MeOH). HRMS: found 398.2892 $[M + H]^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

***N*-Methyl-3-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (15):** ^1H NMR (600 MHz, CD_3OD): δ 4.04 (d, $J_{H6a-H6b}$ = 12.2 Hz, 1H), 3.88 (dd, $J_{H6b-H6a}$ = 12.2 Hz, J_{H6b-H5} = 2.7 Hz, 1H), 3.85 (m, 2H), 3.70 (m, 1H), 3.60 (dd, J_{H-H} = 9.7 Hz, 1H), 3.38 (t, J_{H-H} = 6.4 Hz, 2H), 3.32 (dd, J_{H1a-H2} = 4.7 Hz, $J_{H1a-H1b}$ = 12.1 Hz, 1H), 3.15 (dd, J_{H-H} = 9.2 Hz, 1H), 2.96 (s, 2H), 2.95−2.83 (m, 5H), 1.93 (br s, 3H), 1.76−1.63 (m, 8H), 1.60−1.55 (m, 8H), 1.44 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 86.6, 83.1, 74.5, 72.7, 69.3, 68.7, 68.0, 58.9, 41.3, 40.8, 38.3, 35.2, 31.1, 30.5, 29.7, 23.7. ATR-IR (thin film): 3350.7, 2902.7, 2846.7, 1656.7, 1454.2, 1357.8, 1101.3, 1039.6, 1020.3, 958.6, 611.4 cm^{-1}. $[\alpha]^{20}_D$ +6.9° (*c* 0.58, MeOH). HRMS: found 412.3047 $[M + H]^+$, calcd for $[C_{23}H_{42}NO_5 + H]^+$ 412.3058.

***N*-Butyl-3-*O*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (16):** ^1H NMR (600 MHz, CD_3OD/acetone-d_6, 3:1): δ 4.09 (m, 1H), 3.90 (m, 1H), 3.83 (m, 2H), 3.77 (m, 1H), 3.66 (m, 1H), 3.43 (m, 1H), 3.38 (m, 3H), 3.24−3.20 (m, 2H, H-3), 3.09 (m, 1H), 3.01 (m, 1H), 2.96 (s, 2H), 1.94 (br s, 3H), 1.76−1.64 (m, 10H), 1.58−1.55 (m, 8H), 1.43 (m, 4H), 1.00 (t, J_{H-H} = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3/CD_3OD$, 2:1): δ 81.6, 71.3, 66.8, 65.8, 39.2, 36.7, 33.7, 29.5, 28.8, 27.9, 22.0, 19.4, 12.8. ATR-IR (thin film): 3340.5, 2902.7, 2846.7, 1672.2, 1456.2, 1363.6, 1103.2, 1029.9, 1029.9, 607.5 cm^{-1}. $[\alpha]^{20}_D$ +2.8° (*c* 0.50, MeOH). HRMS: found 454.3510 $[M + H]^+$, calcd for $[C_{26}H_{47}NO_5 + H]^+$ 454.3527.

(1*S*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (17). ^1H NMR (300 MHz, CD_3OD, COSY): δ 3.91 (dd, J_{H6a-H5} = 3.0 Hz, $J_{H6a-H6b}$ = 10.9 Hz, 1H, H-6a), 3.49 (dd, J_{H6b-H5} = 7.8 Hz, $J_{H6b-H6a}$ = 10.9 Hz, 1H, H-6b), 3.38 (t, J_{H-H} = 6.4 Hz, 2H, OCH_2-5′ pentyl), 3.19 (dd, J_{H-H} = 8.9 Hz, 1H, H-3), 3.10 (dd, J_{H-H} = 9.1 Hz, 1H, H-4), 3.00−2.96 (m, 3H, H-2, OCH_2-adamantane), 2.53 (m, 1H, H-5), 2.41 (m, 1H, H-1), 1.95−1.85 (m, 5H, 3×CH adamantane, CH_2 pentyl), 1.76−1.66 (m, 6H, 3×CH_2 adamantane), 1.58−1.50 (m, 8H, 3×CH_2 adamantane, CH_2 pentyl), 1.45−1.25 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (75 MHz, CD_3OD, HMQC): δ 83.1 (OCH_2-adamantane), 79.1 (C-3), 74.2 (C-2), 72.5 (OCH_2-5′ pentyl), 70.4 (C-4), 62.2 (C-5), 60.7 (C-1), 60.1 (C-6), 40.8 (3×CH_2 adamantane), 38.3 (3×CH_2 adamantane), 35.2 (C_q adamantane), 31.7, 30.5 (2×CH_2 pentyl), 27.8 (3×CH adamantane), 27.4, 26.7 (2×CH_2 pentyl). ATR-IR (thin film): 3309.6, 2900.7, 2846.7, 1450.4, 1365.5, 1311.5, 1257.5, 1149.5, 1095.5, 1018.3, 910.3, 825.5, 732.9, 671.2 cm^{-1}. $[\alpha]^{20}_D$ −12.5° (*c* 0.40, $CHCl_3$). HRMS: found 398.2905 $[M + H]^+$, calcd for $[C_{22}H_{39}NO_5 + H]^+$ 398.2901.

(1*S*)-*N*-Methyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (18): ^1H NMR (400 MHz, CD_3OD, COSY): δ 3.90 (dd, $J_{H6a-H6b}$ = 11.8 Hz, J_{H6a-H5} = 3.0 Hz, 1H, H-6a), 3.82 (dd, $J_{H6b-H6a}$ = 11.8 Hz, J_{H6b-H5} = 3.9 Hz, 1H, H-6b), 3.40−3.35 (m, 3H, H-3, OCH_2-5′ pentyl), 3.22 (dd, J_{H-H} = 9.3 Hz, 1H, H-2),

3.15 (dd, J_{H-H} = 9.0 Hz, 1H, H-4), 2.96 (s, 2H, OCH_2-adamantane), 2.29 (s, 3H, NCH_3), 2.08−2.03 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.66 (m, 8H, 3×CH_2 adamantane, CH_2 pentyl), 1.61−1.55 (m, 8H, 3×CH_2 adamantane, CH_2 pentyl), 1.43−1.35 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (100 MHz, CD_3OD, HMQC): δ 83.1 (OCH_2-adamantane), 80.5 (C-3), 72.8 (C-2), 72.7 (OCH_2-5′ pentyl), 70.9 (C-4), 69.8 (C-5), 67.9 (C-1), 60.4 (C-6), 40.8 (3×CH_2 adamantane), 38.3 (3×CH_2 adamantane), 36.1 (NCH_3), 35.2 (C_q adamantane), 30.7, 29.8 (2×CH_2 pentyl), 29.8 (3×CH adamantane), 27.8, 25.4 (2×CH_2 pentyl). ATR-IR (thin film): 3348.2, 2900.7, 2846.7, 2792.7, 2677.0, 2499.6, 166.4, 1450.4, 1365.5, 1234.4, 1103.2, 1010.6, 864.1, 810.0, 686.6, 617.2 cm^{-1}. $[\alpha]^{20}_D$ +2.3° (*c* 0.52, $CHCl_3$). HRMS: found 412.3064 [M + H]$^+$, calcd for $[C_{23}H_{42}NO_5 + H]^+$ 412.3058.

(1*S*)-*N*-Butyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (19): ^{1}H NMR (400 MHz, CD_3OD, COSY): δ 3.90−3.80 (m, 2H, CH_2-6), 3.40−3.25 (m, 3H, H-4, OCH_2-5′ pentyl), 3.20−3.09 (m, 2H, H-2, H-3), 2.96 (s, 2H, OCH_2-adamantane), 2.82 (m, 1H, NC*H*H buty), 2.68 (m, 1H, NCH*H* butyl), 2.39−2.32 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH adamantane), 1.77−1.55 (m, 16H, 6×CH_2 adamantane, 2×CH_2 pentyl), 1.50−1.30 (m, 4H, CH_2 butyl, CH_2 pentyl), 1.25 (m, 2H, CH_2 butyl), 0.93 (t, J_{H-H} = 7.1 Hz, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, CD_3OD): δ 81.0, 80.5, 72.9, 71.6, 72.5, 65.8, 63.7, 60.2, 47.3, 40.9, 38.4, 35.0, 30.7, 29.1, 27.9, 25.8, 24.5, 21.6, 29.8, 14.4. ATR-IR (thin film): 3363.6, 2900.7, 2846.7, 2098.4, 1728.1, 1450.4, 1365.5, 1257.5, 1110.9, 1010.6, 925.8 cm^{-1}. $[\alpha]^{20}_D$ +1.2° (*c* 0.34, $CHCl_3$). HRMS: found 454.3543 [M + H]$^+$, calcd for $[C_{26}H_{47}NO_5 + H]^+$ 454.3527.

Acknowledgment. Jos M. M. Out, Saskia Scheij, and Karen Ghauharali-van der Vlugt are acknowledged for their technical assistance in performing the enzyme assays and determining the IC_{50} values. Macrozyme B. V. is acknowledged for financial support.

Supporting Information Available: Experimental procedures, characterization, and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **4**−**19**, **21**−**24**, **26**−**35**, **37**−**42**, **44**−**49**, **51**−**55**, and **57**−**70**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061280P