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Synthesis and evaluation of dimeric lipophilic iminosugars as inhibitors of glucosylceramide metabolism

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ABSTRACT

Four dimeric and four monomeric lipophilic iminosugars were synthesized and subsequently evaluated on their inhibitory potential towards mammalian glucosylceramide synthase, glucocerebrosidase, β-glucosidase 2, sucrase and lysosomal α-glucosidase. Compared to their monomeric counterparts the dimeric inhibitors showed decreased inhibition of glucosylceramide synthase and generally a comparable inhibitory potency for the glycosidases.

1. Introduction

Glucosylceramide **1** (Fig. 1) and its more complex glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho) physiological processes in man, such as intercellular recognition, signalling processes (e.g., insulin signalling) and interactions with pathogens.[1,2] Glucosylceramide **1** functions as the crucial precursor for the biosynthesis of most complex GSLs. The biosynthesis of **1** takes place at the cytosolic side of the Golgi apparatus and is catalyzed by the membrane-bound enzyme, glucosylceramide synthase (GCS). This glycosyltransferase catalyzes the glycosylation of α-UDP-D-glucopyranose with ceramide to produce **1**. The main catabolic pathway of **1** occurs in the lysosome where glucocerebrosidase (GBA1) with assistance of activator protein saposin C catalyzes the hydrolysis of the β-glycosidic bond that connects the ceramide and glucose residues in **1**. The membrane-bound β-glucosidase 2 (GBA2), located on the outside of the plasma membrane can also hydrolyze **1**.[3,4]

In an ongoing study we aim to develop selective inhibitors for each of the three enzymes, GCS, GBA1 and GBA2.[5–8] Selective inhibitors can be used as tools to further investigate the diverse functions of GSLs, but also have potential as therapeutics for diseases associated with abnormal GSL metabolism such as lysosomal sphingolipidoses[9,10] and type 2 diabetes.[5] We have already shown that inhibition of GCS through oral dosage of lipophilic iminosugar **2** (Fig. 2) to *ob/ob* mice, which is a type II diabetes model, downregulates glycosphingolipid biosynthesis and restores insulin receptor sensitivity.[5] We selected compound **2**, a known potent inhibitor of all three enzymes, as a lead compound in our research efforts.[6,8]

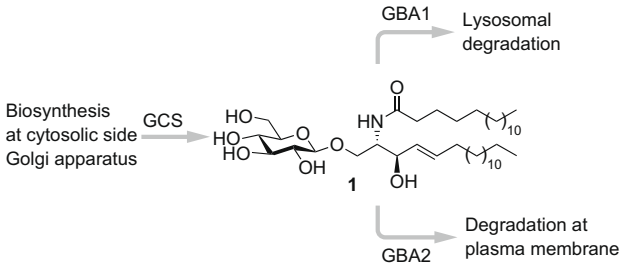

Figure 1. Structure of glucosylceramide **1** and an overview of its metabolism.

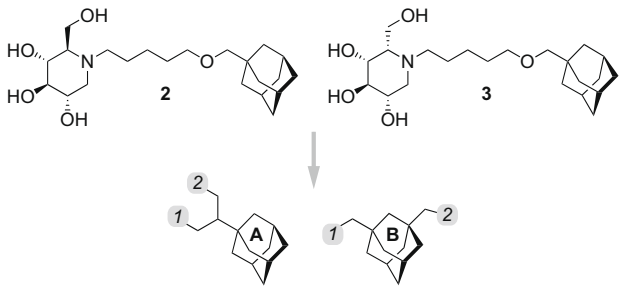

Figure 2. Structure of lead compound **2**, its L-*ido* derivative **3** and the general design of the two bis-functionalized adamantanes (**A** and **B**).

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The structure of **2** can be divided into three parts, the iminosugar core, a pentyl spacer and the adamantan-1-yl-methoxy hydrophobic moiety. There is literature precedence that C-5-epimerized L-*ido*-1-deoxynojirimycin derivatives are viable GCS inhibitors.[11,12] Indeed we observed that L-*ido* derivative **3** (Fig. 2) is a selective GCS inhibitor with a potency comparable to that of **2**.[13]

Results from our previous studies have also shown the importance of the adamantane moiety in achieving potent inhibition, especially for GBA2 and GCS. Both these enzymes are membrane-bound and the role of the hydrophobic adamantane might be to concentrate the iminosugar inhibitor at the location of these enzymes. If this hypothesis holds true, then appending a second iminosugar to the adamantane may increase the local concentration of the iminosugar near the enzyme's active site even further, with an altered inhibitory potency as a result.

In nature, related bivalent or even multivalent interactions are often encountered as a way of improving the interactions between receptor and ligand.[14] Multivalency is also adopted as a strategy in pharmaceutical research to improve interactions of natural receptors with designed ligands.[14,15] The most basic form of multivalency is bivalency and in general a bivalent ligand can bind to its target receptor in four ways that all cause increased specificity and/or strength of binding (Fig. 3).[15]

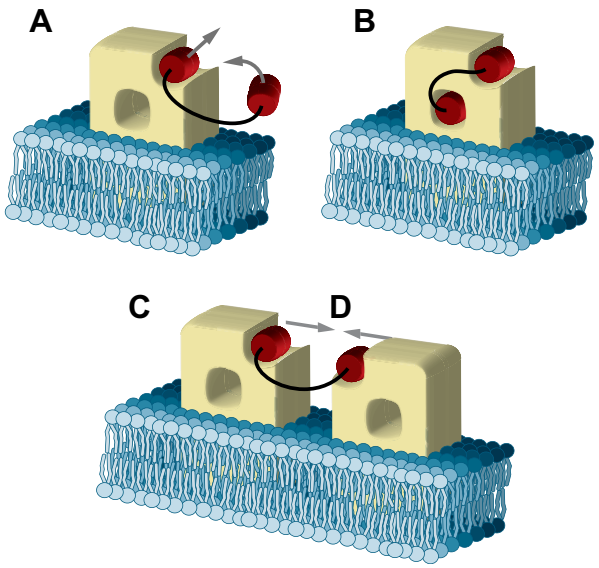


Figure 3. Overview of mechanisms of bivalent ligand binding. (A) Rapid rebinding of inhibitor by the high local concentration of 'free' ligand; (B) increased binding specificity and strength by additional binding at an allosteric site; (C) simultaneous inhibition of two neighbouring copies of the receptor; (D) dimerization/clustering of the two copies of the receptor.

There is currently no evidence that mammalian glycosyltransferases or glycosidases homodimerize or possess allosteric binding sites. Therefore a potential bivalent inhibitor of these enzymes would operate via mechanism A in Figure 3. Although the multivalency approach has been extensively used in optimization of receptor–ligand interactions it is relatively unexplored in the development of glycosidase/glycosyltransferase inhibitors. A literature search revealed only a few examples of previous studies with iminosugar-based multivalent glycosidase inhibitors.[16–18] These examples differ from the research presented here in that the multimeric inhibitors developed in those studies all target soluble enzymes, whereas GCS and GBA2 targeted in our research are membrane-bound.

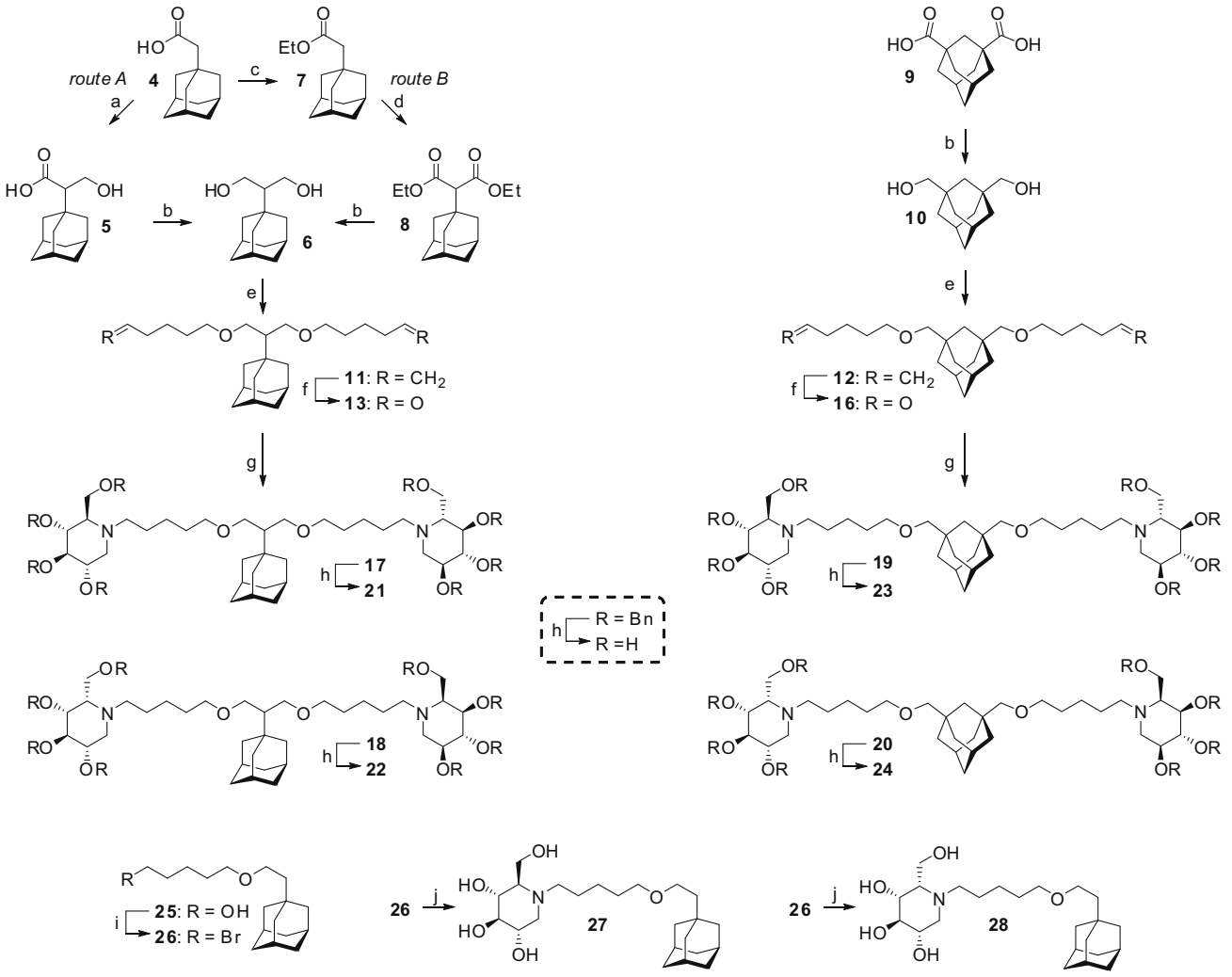
A critical aspect in the design of the bivalent inhibitors is the type and distance of separation between the two iminosugars. For inhibitor **2** it has already been ascertained that lengthening or shortening the pentyl spacer decreases inhibitory potency, as is the case with removal of the ether function. Also, hydrophobic N-alkylated iminosugars having a ether functionality in the *N*-alkyl portion are thought to be less cytotoxic than isosteric compounds without this functional group.[19] The orientation of the two binding elements in a bivalent inhibitor can also be critical. In this respect the adamantane moiety, besides targeting the inhibitors to the membrane, also functions as a rigid scaffold.[20] If the adamantane moiety indeed binds in hydrophobic lipid bilayer pockets then the two pentyl-spaced iminosugars should be oriented in the same direction in order to potentiate bivalent action as depicted in Figure 3. To this end we designed bifunctional adamantane **A** (Fig. 2). Scaffold **A,** however, does introduce an additional methylene in between the adamantane and the iminosugar. Therefore, a second difunctionalized adamantane **B** was designed. Scaffold **B** minimizes the change to the general design of the original inhibitor (**2** and **3**), but at the cost of the orientation of the two iminosugar moieties.

The research presented here describes the synthesis of the two types of dimeric scaffolds functionalized with two 1-deoxynojirimycin or L-*ido*-1-deoxynojirimycin iminosugars. To investigate the effect of the added methylene in scaffold **A** the monomeric analogues of this scaffold were also prepared. The resulting six compounds were evaluated together with known **2** and **3** in an enzyme assay for inhibition of the three glucosylceramide metabolism-related enzymes (GBA1, GBA2 and GCS) and two non-related glycosidases (sucrase and lysosomal α-glucosidase).

2. Results and discussion

Reductive amination was chosen as the means for condensation of the iminosugar cores to the difunctionalized adamantane scaffolds. This entailed the synthesis of dipentanal derivatized adamantanes that in turn are accessible by ozonolysis of dihex-1-ene precursors. The synthesis of the target compounds starts with the preparation of the two adamantane cores. Generation of the enolate of commercially available 1-adamantan-acetic acid **4** and condensation with formaldehyde produced **5** in 27% yield with 68% recovery of **4** (Scheme 1).[21] Reduction of **5** with $LiAlH_4$ provided **6**.

Upon increasing the scale of the aldol condensation with **4** the yield of **5** decreased due to the difficulties in handling gaseous formaldehyde. Therefore, a different route was developed. The ethyl ester **7** of **4** was prepared and deprotonated with LDA. Reaction of this enolate with ethyl chloroformate produced malonate derivative **8** (82% yield) that upon reduction with $LiAlH_4$ also gave **6**. Reduction of 1,3-adamantan-diacetic acid **9** gave diol **10**. Williamson etherification of **6** and **10** with excess 6-bromo-1-hexene produced almost no dialkylated product, but instead yielded predominantly the mono-alkylated products. Successively performing the deprotonation and bromide addition twice in one-pot did produce dienes **11** and **12**. Ozonolysis of **11** and workup with dimethylsulfide produced a mixture of products. Isolation and characterization of the major product (~30%) showed that it was not dialdehyde **13** but rather an intermediate ozonide (**14** or **15**, see note[22]). Ozonolysis of **11** and **12** and treatment of the intermediate ozonides with trimethylphosphine did provide dialdehydes **13** and **16**. Reductive amination of the dialdehydes with either 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin[7] or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin[13] provided the four penultimate compounds **17**, **18**, **19** and **20**. Palladium-catalyzed hydrogenation at 4 bar produced the dimeric compounds **21**, **22**, **23** and **24**. The two monomeric reference analogues **27** and **28** were prepared by selective nitrogen alkylation of 1-deoxynojirimycin and L-*ido*-1-deoxynojirimycin with bromide **26**.



Scheme 1. Synthesis of dimeric lipophilic iminosugars **21**–**24** and reference monomeric analogues **27** and **28**. Reagents and conditions: (a) (i) LDA (2 equiv) THF, −30 °C, 1 h; (ii) HMPA (1 equiv), −30 °C; (iii) formaldehyde gas, −30 °C, 20 min 3 mmol scale: **4**: 68% **5**: 27%; 39 mmol scale: **4**: 88% **5**: 11%; (b) $LiAlH_4$, THF, 0 °C→rt, 20 h, **6** from **5**: 86%; **6** from **8**: 96%; **10**: used crude; (c) EtOH, 18 M H_2SO_4, reflux, 5 h, 93%. (d) (i) LDA (1 equiv) THF, −30 °C, 1 h; (ii) HMPA (1 equiv), −30 °C; (iii) ethyl chloroformate, −30 °C, 1 h, 82%; (e) (i) 6-bromo-1-hexene, NaH, TBAI, DMF, 0 °C to rt, 2 h; (ii) 6-bromo-1-hexene, NaH, 20 h, **11**: 72%; **12**: 65%; (f) (i) O_3, DCM, −30 °C, 30 min; (ii) PMe_3, rt, 4 h, **13**: 80%; **16**: 72%; (g) 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (3 equiv), $NaCNBH_3$ (6 equiv), Na_2SO_4 (5 equiv), EtOH/AcOH (20/1), 20 h, 0 °C→rt, **17**: 60%; **18**: 55%; **19**: 62%; **20**: 64%; (h) Pd/C, H_2 4 bar, *n*-propanol/EtOAc, HCl, 20 h, **21**: 79%; **22**: 73%; **23**: 60%, **24**: 55%; (i) CBr_4, PPh_3, CH_3CN, reflux, 3 h, 87%; (j) 1-deoxynojirimycin or L-*ido*-1-deoxynojirimycin (0.66 equiv), K_2CO_3 (2 equiv), DMF, 90 °C, 48 h, **27**: 58%; **28**: 43%.

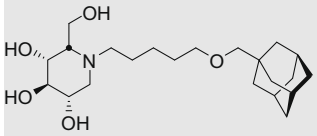
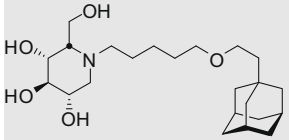
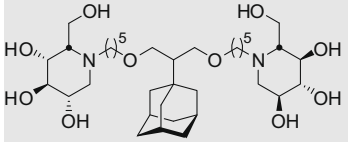
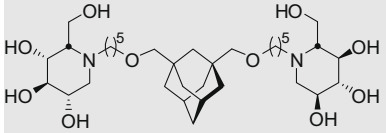
2.1. Biological evaluation

The six compounds were evaluated and compared to **2** and **3** in an enzyme assay for inhibition of the three glucosylceramide metabolism-related enzymes, GCS, GBA1 and GBA2 (Table 1). Introduction of an additional methylene between the ether and adamantane as in **27** and **28** hardly affects the inhibition profile when compared to **2** and **3**. The dimeric derivatives **21** and **22** also inhibit GBA1 and GBA2 comparable to the monomeric **27** and **28**, but are markedly less potent for GCS. The second type of dimeric iminosugars **23** and **24** again showed little change in inhibitory potency for GBA1 and GBA2. However, also for this type of dimeric iminosugars the inhibition of GCS decreases considerably upon introduction of a second pentyl-spaced iminosugar moiety.

Besides the steric implications of attaching a second iminosugar-pentyl moiety to the adamantane there is also a marked effect upon the overall polarity of the molecule: the number of hydroxyls are doubled. This phenomenon was already observed during purification of the bivalent end products. Lead compound **2** has an R_f of 0.3 upon elution (25% MeOH and 5% NH_4OH in $CHCl_3$) from a silica gel column as opposed to almost complete retention for **21** (R_f = 0–0.05). The increased polarity of the dimeric compounds might negatively affect their cell permeability as well as their concentration in the Golgi membranes where GCS resides. The cell permeability of compounds **21**–**24** was investigated by testing them in an in vitro assay for GCS inhibition. All four compounds showed comparable IC_{50} values to the in vivo assay indicating that cell permeability is probably not the cause for the decreased GCS inhibition.

Although GCS inhibition decreases for all compounds tested when compared with **2** and **3**, they are still more or equally potent as the commercial GCS inhibitor and Gaucher therapeutic,[23] *N*-butyl-1-deoxynojirimycin (Miglustat, Zavesca). This compound, which was first synthesized in 1988,[23] is currently used as a therapeutic for Gaucher disease.[24] A trend observed in the GCS inhibitory data is that the L-*ido* analogues are more potent and selective inhibitors of GCS than their D-*gluco* equivalents. This corresponds with our recent identification of **3** as a more potent and selective inhibitor of GCS than **2**.[13]

Table 1
Enzyme inhibition assay results (GCS: % inhibition at μM; the four glycosidases: apparent IC_{50} values in μM)

Compound		GCS in vivo		GCS in vitro		GBA1 in vitro	GBA2 in vitro	Lysosomal α-glucosidase in vitro	Sucrase in vitro
		(%)[a]	(μM)	(%)[b]	(μM)				
	**2**: C-5 = (*R*) D-*gluco*	50	0.2	36	0.5	0.2	0.001	0.4	0.5
	3: C-5 = (*S*) L-*ido*	75	0.1	—	—	2	0.03	>100	>100
	**27**: C-5 = (*R*) D-*gluco*	55	1	40	5	0.19	0.005	0.8	0.35
	28: C-5 = (*S*) L-*ido*	43	1	68	5	2	0.006	>100	200
	**21**: C-5 = (*R*) D-*gluco*	30	20	64	40	0.38	0.008	0.35	0.4
	22: C-5 = (*S*) L-*ido*	69	20	52	10	5	0.150	700	200
	**23**: C-5 = (*R*) D-*gluco*	35	20	47	40	0.34	0.010	0.5	0.5
	24: C-5 = (*S*) L-*ido*	46	5	59	10	6	0.013	>100	>100

[a] Average of three measurements.
[b] One measurement.

GBA2 and GCS are both membrane-bound enzymes that together with GBA1 process membrane-localized lipophilic substrates. To further test the bivalent properties of **21**–**24** they were also evaluated as inhibitors of the non-membrane-bound lysosomal α-glucosidase and the intestinal membrane-bound sucrase that both process non-lipophilic substrates. Both are potently inhibited by lead compound **2**, but not by L-*ido*-analogue **3**. The results of the enzyme assay confirm the fact that iminosugar-type inhibitors of lysosomal α-glucosidase and sucrase require D-glucose stereochemistry. Both bivalent iminosugars **21** and **23** show similar inhibition of the enzymes and are comparable to lead compound **2**. Bivalent **21** is twice as potent as its monomeric derivative **27** for lysosomal α-glucosidase but this trend is not observed for inhibition of sucrase.

3. Conclusion

The synthesis and evaluation of four monomeric and four dimeric lipophilic iminosugars **21**–**24** are reported. Evaluation of two novel monomeric analogues **27** and **28** and two known lipophilic iminosugars **2** and **3** showed that the structure–activity relationship (SAR) of GBA1, GBA2 and GCS inhibition tolerates the introduction of an additional methylene between the ether function and the adamantane. The four dimeric iminosugars **21**–**24** inhibit GBA1 and GBA2 with a potency comparable to that of their monomeric counterparts **2**, **3**, **27** and **28**. However, inhibition of GCS decreased markedly for all dimeric compounds. This was observed in both in vivo and in vitro GCS assays and thus reduced cell permeability of the more polar dimeric iminosugars was ruled out as a cause for the decrease.

Our results seem to indicate that dimeric lipophilic iminosugars do not inhibit GBA1, GBA2, GCS or lysosomal α-glucosidase and sucrase in a bivalent fashion (as in mode A in Fig. 3). However, the retained inhibitory potency for GBA1, GBA2 and GCS does show that the SAR tolerates the attachment of a second pentyl-spaced iminosugar, with no clear difference between the two adamantane scaffolds. It is possible that the length of the pentyl spacer is impeding bivalent binding modes, and therefore variation of its length is worth investigating in future analogues. The much-increased polarity of the presented bivalent inhibitors might make them less lipophilic and thereby less available for the membrane-bound enzymes. Targeting to the membrane-bound enzymes and stabilization inside the membrane could therefore perhaps be improved in future dimeric analogues of **2** and **3** by basing the scaffold on the more hydrophobic diamondoids, diamantane and triamantane.[25–28]

4. Experimental

4.1. General methods

All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Residual water was removed from starting compounds by repeated coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. Reaction grade acetonitrile, *n*-propanol and methanol were stored on 3 Å molecular sieves. Other reaction grade solvents were stored on 4 Å molecular sieves. THF was distilled prior to use from $LiAlH_4$. Ethanol was purged of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. Diisopropylamine was distilled from KOH and stored over KOH. Paraformaldehyde was dried prior to use in a P_2O_5 containing desiccator for 7 days. R_f values were determined from TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24} \times 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4 \times 2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt % in ethanol) followed by charring at ~150 °C. Visualization of all deprotected iminosugar compounds during TLC analysis was accomplished by exposure to iodine vapour. Column chromatography was performed on silica gel (40–63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz) or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$ or MeOD. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent. Coupling constants (J) are given in hertz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C-APT spectra are proton decoupled. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60,000 at m/z 400 (mass range m/z = 150–2000) and dioctylphthalate (m/z = 391.28428) as a 'lock mass'. The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal ATR-element and are reported in cm^{-1}.

Enzyme assays: Lipids were extracted according to Folch et al.[29] Neutral GSLs were analyzed as described previously.[30] Ganglioside composition was determined as described previously.[31] IC_{50} values of the iminosugars for the various enzyme activities were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations (DMSO stock solutions diluted with RPMI medium). In vivo glucosylceramide synthase assay: the mouse macrophage cell line RAW-267 was grown to 90–100% confluence in growth medium at 37 °C in a 5% CO_2 incubator. The growth medium consisted of RPMI-1640 + 10% FCS + penicillin (150 μg/mL) and streptomycin (250 μg/mL) + 50 mM Hepes buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid). The incubation flask was washed with RPMI medium without serum (3 × 5 mL) to remove serum. Cells were taken up in 3 mL RPMI + 50 mM Hepes + 300 μM conduritol B epoxide (10 mM stock in RPMI) + the inhibitor (0.1, 1, 10 μM (20 mM stock in DMSO diluted in RPMI) and 5 nmol C_6-NBD-ceramide/BSA complex (*N*-[7-(4-nitrobenzo-2-oxa-1,3-diazole)]-6-aminocaproyl-D-*erythro*-sphingosine) were added successively to the cell culture. The cells were incubated for 1 h at 37 °C in a 5% CO_2 incubator. At the end of incubation, the flask was inspected for potential cytotoxicity of the inhibitor and washed with medium without serum (5 × 5 mL). A 50 mM potassium phosphate buffer (KPi buffer, pH 5.8, 0.75 mL) was added and the flask was placed in ice. Cells were removed from the flask by scraping and the harvested cells were collected in a capped plastic vial and immediately immersed in liquid nitrogen. The frozen cell lysate (~0.75 mL) was suspended in methanol (3 mL) and extracted with chloroform (3 mL). After extraction a 0.73% NaCl solution (2.0 mL) was added to the biphasic. The aqueous phase was extracted once more with chloroform (1 mL). The combined chloroform layers were isolated and concentrated at 30–40 °C under a nitrogen flow. Lipids were separated by thin-layer chromatography (HP-TLC plates 20 × 10 Silica Gel 60 van Merck) using chloroform/methanol/15 mM aq $CaCl_2$ (60:35:8, v/v/v) as the developing solvent. The C_6-NBD-labelled (glyco)sphingolipids were identified using standards, visualized with a Typhoon Trio Variable Mode Imager (λ_{ex} 488 nM, λ_{em} 520 nM) and

quantified with IMAGEQUANT TL software. Glucocerebrosidase activity was measured using recombinant enzyme and 4-methylumbelliferyl-β-glucose as substrate.[32] GBA2 was measured using enzyme-containing membrane preparations from Gaucher spleen and 4-methylumbelliferyl-β-glucoside as substrate.[8] Lysosomal α-glucosidase was measured using purified enzyme from human urine and 4-methylumbelliferyl-α-glucoside as substrate.[8] Sucrase activity was determined with homogenates of freshly isolated rat intestine by measuring liberated glucose from the corresponding disaccharides.[33] In vitro assay of GCS activity was conducted with in spleen microsomes. Compounds **21**–**24** were tested as their dihydrochloric acid salt and **27** and **28** were assayed as their TFA-salt.

*General procedure A—Reductive amination of dialdehydes **13** and **16***: A dry and cooled (0 °C) mixture of the dialdehyde (1 equiv), Na_2SO_4 (5 equiv) and 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (3 equiv; synthesis as reported previously[6,7]) or 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin (3 equiv; synthesis as reported previously[13]) in EtOH/AcOH (20/1, v/v, 0.1 M) was charged with $NaCNBH_3$ (6 equiv). The reaction mixture was stirred for 20 h and allowed to warm to rt. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat aq $NaHCO_3$ (2 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column purification (1:5 EtOAc/PE→1:1 EtOAc/PE) to afford the product. TLC-analysis: R_f **13** = 0.55; **16** = 0.60 (2:3; EtOAc/PE).

General procedure B—Pd/C-catalyzed hydrogenolysis: A solution of compound (~300–400 μmol) in *n*-propanol/EtOAc (50 mL, 8/1, v/v) was acidified to pH ~2 with 1 M aq HCl (1 mL). Argon was passed through the solution for 5 min, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) and Pd black (5 mg) was added. The reaction vessel was placed under vacuum and subsequently ventilated with hydrogen gas. This cycle was repeated one more time after which the vessel was placed under 4 bar of hydrogen gas and mechanically shaken for 20 h. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene. The residue was purified by silica gel column purification (3:1 EtOAc/MeOH+5%NH_4OH→19:1 MeOH/NH_4OH) to give the product. Silica gel residue in the purified product was removed by dissolving the product in MeOH/$CHCl_3$ (1/9, v/v), passing the solution over a filter (0.5 μm) and concentrating the filtrate.

4.1.1. (*R*/*S*)-2-(Adamantan-1-yl)-3-hydroxypropanoic acid 5

Butyllithium (4.25 mL, 6.8 mmol; 1.6 M in hexane) was added to a dry and cooled (−30 °C) solution of diisopropylamine (0.95 mL, 6.8 mmol) in THF (20 mL). After 10 min, a dry solution of 1-adamantan-acetic acid (**4**: 602 mg, 3.1 mmol) in THF (15 mL) was added over a 1 min period at −30 °C, a yellow/orange turbid reaction mixture was formed. After 20 min, HMPA (0.56 mL, 3.1 mmol) was added that resulted in a clear orange reaction mixture. Paraformaldehyde (3–4 g) was decomposed at 200 °C and the resulting formaldehyde vapours were passed by a N_2 flow over the surface of the cooled (−30 °C) reaction mixture. After complete depolymerization of the paraformaldehyde the reaction mixture was stirred for an additional 30 min. The reaction mixture was quenched by addition of water (1 mL). Ethylacetate (50 mL) was added and the mixture was extracted with aq 0.1 M HCl (4 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (2:1 EtOAc/PE→19:1 EtOAc/AcOH) to produce **5** (185 mg, 0.82 mmol) as white solid in 27% yield with 68% recovery of 1-adamantaneacetic acid. R_f = 0.65 (19:1; EtOAc/AcOH); R_f 1-adamantaneacetic acid = 0.85 (19:1; EtOAc/AcOH). ^{1}H NMR (200 MHz, MeOD) δ 3.92–3.71 (m, 2H, CH_2-3), 2.23 (dd, *J* = 4.5, 9.9, 1H, CH-2), 1.95 (s, 3H, 3 × CH Ada), 1.88–1.45 (m, 12H, 6 × CH_2 Ada). ^{13}C NMR (50 MHz, MeOD) δ 177.6 (C(O)-1), 61.5 (CH-2), 60.6 (CH_2-3), 41.7 (CH_2 Ada), 38.1 (CH_2 Ada), 35.0 (C_q Ada), 30.2 (CH Ada). IR ν_{max}(thin film)/cm^{-1}: 3332, 2902, 2851, 1698, 1445, 1257, 1223, 1008, 808, 652, 618. HRMS: found 225.1485 [M+H]$^+$, calculated for $[C_{13}H_{20}O_3 + H]^+$ 225.1485.

4.1.2. 2-(Adamantan-1-yl)propane-1,3-diol 6

*Reduction of **5***: A dry and cooled (0 °C) solution of **5** (424 mg, 2.0 mmol) in THF (20 mL) was charged with $LiAlH_4$ (5 mL, 5.0 mmol; 1 M in THF), stirred for 20 h and warmed to rt. The reaction was quenched (1st EtOAc 30 min, 2nd water) and aq 1 M HCl (30 mL) was added. The mixture was extracted with EtOAc (2 × 50 mL) and the resulting combined organic phase was washed with sat aq $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (2:1 EtOAc/PE→4:1 EtOAc/MeOH) to furnish **6** (339 mg, 1.73 mmol) as white solid in 86% yield. *Reduction of **8***: Compound **8** (1.07 g, 3.64 mmol) was subjected to same procedure as described above, but with 4.1 equiv of $LiALH_4$ to produce **6** (685 mg, 3.49 mmol) in 96% yield after purification. R_f = 0.52 (19:1; EtOAc/AcOH). ^{1}H NMR (200 MHz, MeOD) δ 3.84 (dd, *J* = 4.0, 10.7, 2H, C*H*H-1,3), 3.66 (dd, *J* = 7.3, 10.8, 2H, CH*H*-1,3), 1.94 (s, 3H, 3 × CH Ada), 1.84–1.59 (m, 12H, 6 × CH_2 Ada), 1.26–1.12 (m, 1H, CH-2). ^{13}C NMR (50 MHz, MeOD) δ 61.5 (CH_2-1,3), 54.2 (CH-2), 41.7 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.3 (CH Ada). IR ν_{max}(thin film)/cm^{-1}: 3235, 2900, 2846, 1447, 1344, 1034, 1009, 973. HRMS: found 211.1694 [M+H]$^+$, calculated for $[C_{13}H_{22}O_2 + H]^+$ 211.1693.

4.1.3. Ethyl (adamantan-1-yl)acetate 7

Sulfuric acid (1 mL, 98%/18 M) was added to a solution of 1-adamantan-acetic acid **4** (10 g, 51.5 mmol) in ethanol (200 mL). The reaction mixture was refluxed for 5 h after which it was neutralized by addition of 4 M aq NaOH (~4.5 mL). The reaction mixture was concentrated to a quarter of its volume and EtOAc (100 mL) was added. The mixture was washed with sat aq $NaHCO_3$ (4 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE→1:9 EtOAc/PE) to furnish **7** (2.07 g, 9.3 mmol) as a colourless oil in 93% yield. R_f = 0.65 (1:12.5; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1, 2H, CH_2 ethyl), 2.05 (s, 2H, CH_2-COOEt), 1.97 (s, 3H, 3 × CH Ada), 1.72–1.62 (m, 12H, 6 × CH_2 Ada), 1.26 (t, *J* = 7.1, 3H, CH_3 ethyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C=O), 59.9 (CH_2 Et), 49.1 (*C*H_2-COOEt), 42.5 (CH_2 Ada), 36.9 (CH_2 Ada), 35.9 (C_q Ada), 28.7 (CH Ada), 14.5 (CH_3 Et). IR ν_{max}(thin film)/cm^{-1}: 2901, 2848, 1731, 1451, 1323, 1255, 1196, 1135, 1033, 700. HRMS: found 222.1694 [M+H]$^+$, calculated for $[C_{14}H_{22}O_2 + H]^+$ 222.1693.

4.1.4. Diethyl 2-(adamantan-1-yl)malonate 8

Butyllithium (3.75 mL, 6.0 mmol; 1.6 M in hexane) was added to a dry and cooled (−30 °C) solution of diisopropylamine (0.84 mL, 6.0 mmol) in THF (10 mL). After 10 min, a dry solution of **7** (1.20 g, 5.4 mmol) in THF (10 mL) was added over a 1 min period at −50 °C, a yellow turbid reaction mixture was formed. After 20 min, HMPA (0.95 mL, 5.4 mmol) was added that resulted in a clear yellow reaction mixture. Ethyl chloroformate (0.62 mL, 6.4 mmol) was added and the reaction mixture was stirred at (−30 °C for 1 h. The reaction mixture was quenched with water and EtOAc (100 mL) was added. The mixture was extracted with aq 0.1M HCl (4 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (1:19 EtOAc/PE→1:9 EtOAc/PE) to produce **8** (1.30 g, 4.41 mmol) as a colourless oil in 82% yield. R_f = 0.45 (1:12.5; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1,

4H, 2 × CH_2 Et), 3.08 (s, 1H, CH-2), 1.99 (s, 3H, 3 × CH Ada), 1.79 (d, J = 2.7, 6H, 3 × CH_2 Ada), 1.72–1.62 (m, 6H, 3 × CH_2 Ada), 1.27 (t, J = 7.1, 6H, 2 × CH_3 Et). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (C(O)-1,3), 62.7 (CH-2), 60.9 (CH_2 Et), 40.0 (CH_2 Ada), 36.9 (CH_2 Ada), 36.1 (C_q Ada), 28.7 (CH Ada), 14.4 (CH_3 Et). IR ν_{max}(thin film)/cm^{-1}: 2904, 2850, 1753, 1726, 1449, 1368, 1319, 1250, 1221, 1201, 1142, 1032. MS (ESI): found 295.3 $[M+H]^+$, calculated for $[C_{17}H_{26}O_4 + H]^+$ 295.2.

4.1.5. 1,1′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)dihex-5-ene 11

A dry cooled (0 °C) solution of **6** (210 mg, mmol) and TBAI (50 mg, 0.14 mmol) in DMF (5 mL) was charged with NaH (120 mg, 3 mmol; 60% in mineral oil). The reaction mixture was stirred for 1 h at after which 6-bromo-1-hexene (0.4 mL, 3 mmol) was added. The reaction mixture was stirred for 2 h and warmed to rt. The reaction mixture was cooled and additional NaH (120 mg) was added. After stirring for 15 min, additional 6-bromo-1-hexene (0.4 mL) was added and the reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched with water. The mixture was diluted with Et_2O (100 mL) and washed with water (3 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE→1:9 EtOAc/PE) to produce **11** (270 mg, 0.72 mmol) as a colourless oil in 72% yield. R_f product = 0.85; mono-alkylated side product = 0.38 (1:5; EtOAc/PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 6.7, 10.2, 17.0, 2H, 2 × =CH-5 hexenyl), 5.04–4.98 (m, 2H, 2 × =C*H*H-6 hexenyl), 4.97–4.91 (m, 2H, 2 × =CH*H*-6 hexenyl), 3.52 (dd, J = 4.2, 9.4, 2H, 2 × C*H*H-1,3 propyl), 3.45–3.33 (m, 6H, 2 × CH*H*-1,3 propyl, 2 × CH_2-1 hexenyl), 2.07 (dd, J = 7.2, 14.5, 4H, 2 × CH_2-4 hexenyl), 1.93 (s, 3H, 3 × CH Ada), 1.71–1.60 (m, 12H, 6×CH_2 Ada), 1.60–1.54 (m, 4H, 2 × CH_2-2 hexenyl), 1.49–1.42 (m, 4H, 2 × CH_2-3 hexenyl), 1.32–1.26 (m, 1H, CH-2 propyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1 (=CH-5 hexenyl), 114.6 (=CH_2-6 hexenyl), 70.9 (CH_2-1 hexenyl), 68.3 (CH_2-1,3 propyl), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.1 (C_q Ada), 33.7 (CH_2-4 hexenyl), 29.4 (CH_2-2 hexenyl), 29.0 (CH Ada), 25.8 (CH_2-3 hexenyl). IR ν_{max}(thin film)/cm^{-1}: 2902, 2849, 1640, 1450, 1366, 1110, 992, 908. HRMS: found 375.3259 $[M+H]^+$, calculated for $[C_{25}H_{42}O_2 + H]^+$ 375.3258.

4.1.6. 1,1′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)dihex-5-ene 12

*Synthesis of 1,3-adamantane-dimethanol **10***: A dry and cooled (0 °C) solution of 1,3-adamantane-diacetic acid (**9**: 1 g, 4.46 mmol) in THF (45 mL) was charged with $LiAlH_4$ (678 mg, 17.8 mmol), stirred for 20 h and warmed to rt. The reaction was quenched (first with EtOAc and then with water) and aq 1 M HCl (100 mL) was added. The mixture was extracted with EtOAc (3 × 100 mL) and the resulting combined organic phase was washed with sat aq $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and concentrated to produce 1,3-adamantane-dimethanol (**10**: 863 mg, ~4.4 mmol) as an off-white solid, which was used crude in the next reaction. R_f 1,3-adamantane-dimethanol = 0.52; R_f 1,3-adamantane-diacetic acid = 0.80 (19:1; EtOAc/AcOH). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD) δ 2.96 (s, 4H, 2 × OCH_2-Ada), 1.87 (s, 2H, CH-5,7 Ada), 1.43 (s, 2H, CH_2-6 Ada), 1.35–1.15 (m, 8H, CH_2-4,8,9,10 Ada), 1.04 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$/MeOD) δ 72.6 ($HOCH_2$-Ada), 40.2 (CH_2-2 Ada), 38.5 (CH_2-4,8,9,10 Ada), 36.5 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 28.1 (CH-5,7 Ada). *Synthesis of **12***: A dry cooled (0 °C) solution of **10** (196 mg, 1 mmol) and TBAI (50 mg, 0.14 mmol) in DMF (5 mL) was charged with NaH (120 mg, 3 mmol; 60% in mineral oil). The reaction mixture was stirred for 1 h at after which 6-bromo1-hexene (0.4 mL, 3 mmol) was added. The reaction mixture was stirred for 2 h, before warming to rt. The reaction mixture was cooled and additional NaH (120 mg) was added. After stirring for 15 min, additional 6-bromo-1-hexene (0.4 mL) was added and the reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched with water. The mixture was diluted with Et_2O (100 mL) and washed with water (3 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column purification (100% PE→1:9 EtOAc/PE) to produce **12** (233 mg, 0.65 mmol) as a colourless oil in 65% yield. R_f = 0.90 (1:4; EtOAc/PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 6.7, 10.2, 17.1, 2H, 2 × =CH-5 hexenyl), 5.00 (d, J = 17.2, 2H, 2 × =C*H*H-6 hexenyl), 4.94 (d, J = 10.3, 2H, 2 × =CH*H*-6 hexenyl), 3.39–3.35 (m, 4H, 2 × CH_2-1 hexenyl), 2.99 (s, 4H, 2 × OCH_2-Ada), 2.11–2.05 (m, 4H, 2 × CH_2-4 hexenyl), 2.03 (s, 2H, CH-5,7 Ada), 1.65–1.60 (m, 2H, CH_2-6 Ada), 1.60–1.53 (m, 4H, 2 × CH_2-3 hexenyl), 1.46 (ddd, J = 9.4, 17.9, 23.5, 12H, CH_2-4,8,9,10 Ada, 2 × CH_2-2 hexenyl), 1.31 (s, 2H, CH_2-2 Ada). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1 (=CH-5 hexenyl), 114.6 (=CH_2-6 hexenyl), 81.8 (OCH_2-Ada), 71.6 (CH_2-1 hexenyl), 42.0 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 37.0 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 33.8 (CH_2-4 hexenyl), 29.2 (CH_2-2 hexenyl), 28.5 (CH-5,7 Ada), 25.7 (CH_2-3 hexenyl). IR ν_{max}(thin film)/cm^{-1}: 2899, 2848, 1640, 1455, 1366, 1108, 993, 908. HRMS: found 361.3102 $[M+H]^+$, calculated for $[C_{24}H_{40}O_2 + H]^+$ 361.3101.

4.1.7. 5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)-dipentanal 13

A solution of **11** (400 mg, 1.1 mmol) in DCM (70 mL; EtOH stabilized) was cooled to −80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for detection of ozone generation). After the reaction mixture had turned blue, ozone flow was continued for a further 15 min. Ozone generation was stopped and oxygen was bubbled through the reaction mixture for ~15 min or until blue colouration had completely disappeared. Trimethylphosphine (5 mL, 1 M in toluene) was added and the mixture was stirred for 3 h at rt. The mixture was concentrated and the resulting residue was purified by silica gel column purification (1:5 EtOAc/PE→1:3 EtOAc/PE) to produce **13** (323 mg, 0.85 mmol) as a colourless oil in 80% yield. R_f = 0.25 (1:3; EtOAc/PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, J = 1.7, 2H, 2 × CH(O)-1 pentanal), 3.51 (dd, J = 4.2, 9.4, 2H, 2 × OC*H*H-1,3 propyl), 3.45–3.34 (m, 6H, 2 × OCH*H*-1,3 propyl, 2 × CH_2-5 pentanal), 2.46 (dt, J = 1.7, 7.3, 4H, 2 × CH_2-2 pentanal), 1.93 (s, 3H, 3 × CH Ada), 1.76–1.55 (m, 20H, 6 × CH_2 Ada, 4 × CH_2 pentanal), 1.31–1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4 (CH(O)-1 pentanal), 70.3 (CH_2-5 pentanal), 68.1 (OCH_2-1,3 propyl), 49.3 (CH-2 propyl), 43.6 (CH_2-2 pentanal), 40.6 (CH_2 Ada), 37.2 (CH_2 Ada), 33.9 (C_q Ada), 29.1 (CH_2-3 pentanal), 28.7 (CH Ada), 19.1 (CH_2-3 pentanal). IR ν_{max}(thin film)/cm^{-1}: 2901, 2848, 1723, 1451, 1367, 1109. HRMS: found 379.2843 $[M+H]^+$, calculated for $[C_{23}H_{38}O_4 + H]^+$ 379.2843.

4.1.8. 3,3′-{4,4′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)-bis(butane-4,1-diyl)}bis(1,2,4-trioxolane) 14 or 3,8-bis{4,4′-[2-(Adamantane-1-yl)propane-1,3-diyl]bis(oxy)bis(butane-4,1-diyl)}-1,2,4,6,7,9-hexaoxecane 15

See note 22: Treatment of the ozonolysis reaction mixture with DMS (0.5 mL, 6.8 mmol) for 1 h at rt resulted in a complex mixture of products from which **14** or **15** could be isolated in ~30% yield after concentration and silica gel column purification (1:5 EtOAc/PE→1:3 EtOAc/PE). Pure **14**/**15** in DCM proved stable to DMS treatment (0.5 mL; 15 min). Combination of **14**/**15** and other minor products and treatment with PMe_3 provided **13** in good yields (70–80%). R_f = 0.55 (1:5; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 2H, CH_2-5/5′ trioxolane), 5.13 (t, J = 4.9, 2H, 2 × CH-3 trioxolane), 5.03 (s, 2H, CH_2-5/5′ trioxolane), 3.51 (dd, J = 4.2, 9.4, 2H, 2 × C*H*H-1,3 propyl), 3.44–3.33 (m, 6H, 2 × CH*H*-1,3 propyl,

2 × CH_2-4 butane), 1.93 (s, 3H, 3 × CH Ada), 1.79–1.72 (m, 4H, 2 × CH_2-1 butane), 1.72–1.63 (m, 6H, 3 × CH_2 Ada), 1.63–1.46 (m, 16H, 3 × CH_2 Ada, 2 × CH_2-3 butane), 1.55–1.49 (m, 4H, 2 × CH_2-2 butane), 1.31–1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.9 (CH-3 trioxolane), 94.1 (CH_2-5/5′ trioxolane), 70.5 (CH_2-4 butane), 68.3 (CH_2-1,3 propyl), 49.5 (CH-2 propyl), 40.7 (CH_2 Ada), 37.4 (CH_2 Ada), 34.1 (C_q Ada), 31.0 (CH_2-1 butane), 29.6 (CH_2-3 butane), 28.9 (CH Ada), 20.9 (CH_2-2 butane).

4.1.9. 5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)-dipentanal 16

A solution of **12** (658 mg, 1.8 mmol) in DCM (75 mL; EtOH stabilized) was cooled to −80 °C. Ozone gas was generated and bubbled through the reaction mixture (reaction gas outlet was passed over silica gel blue for the detection of ozone generation). After the reaction mixture had turned blue, the ozone flow was continued for a further 15 min. Ozone generation was then stopped and oxygen was bubbled through the reaction mixture for ~15 min or until the blue colouration had completely disappeared. Trimethylphosphine (7.5 mL, 1 M in toluene) was added and the mixture was stirred for 20 h at 5 °C. The mixture was concentrated and the resulting residue was purified by silica gel column purification (1:5 EtOAc/PE→1:3 EtOAc/PE) to produce **16** (479 mg, 1.30 mmol) as a colourless oil in 72% yield. R_f = 0.30 (1:3; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, J = 1.7, 2H, 2 × CH(O)-1 pentanal), 3.38 (t, J = 6.2, 4H, 2 × CH_2-5 pentanal), 2.98 (s, 4H, 2 × OCH_2-Ada), 2.47 (dt, J = 1.7, 7.2, 4H, 2 × CH_2-2 pentanal), 2.07–1.99 (m, 2H, CH-5,7 Ada), 1.74 –1.67 (m, 4H, 2 × CH_2-3 pentanal), 1.63–1.55 (m, 6H, CH_2-6 Ada, 2 × CH_2-4 pentanal), 1.53–1.38 (m, 8H, CH_2-4,8,9,10 Ada), 1.30 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7 (CH(O)-1 pentanal), 81.6 (OCH_2-Ada), 70.9 (CH_2-5 pentanal), 43.6 (CH_2-2 pentanal), 41.8 (CH_2-2 Ada), 39.4 (CH_2-4,8,9,10 Ada), 36.8 (CH_2-6 Ada), 34.5 (C_q-1,3 Ada), 29.0 (CH_2-4 pentanal), 28.3 (CH-5,7 Ada), 19.0 (CH_2-3 pentanal). IR ν_{max}(thin film)/cm^{-1}: 2898, 2847, 1722, 1454, 1366, 1126, 1103. HRMS: found 365.2693 $[M+H]^+$, calculated for $[C_{22}H_{36}O_4 + H]^+$ 365.2686.

4.1.10. *N,N′*-{5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis-(oxy)bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin) 17

Dialdehyde **13** (159 mg, 0.42 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin to provide **17** (343 mg, 0.25 mmol) in 60% yield as a colourless oil after silica gel column purification. R_f = 0.58 (2:3; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 36H, CH_{Ar} Bn), 7.15–7.09 (m, 4H, CH_{Ar} Bn), 4.95 (d, J = 11.1, 2H, 2 × *CH*H Bn), 4.87 (d, J = 10.9, 2H, 2 × C*H*H Bn), 4.81 (d, J = 11.1, 2H, 2 × CH*H* Bn), 4.68 (d, J = 11.6, 2H, 2 × C*H*H Bn), 4.64 (d, J = 11.6, 2H, 2 × CH*H* Bn), 4.46 (s, 4H, 2 × CH_2 Bn), 4.40 (d, J = 10.9, 2H, 2 × CH*H* Bn), 3.70–3.62 (m, 4H, 2 × H-2, 2 × H-6a), 3.59 (dd, J = 9.3, 9.5, 2H, 2 × H-4), 3.56–3.38 (m, 8H, 2 × H-3, 2 × H-6b, 2 × CH_2-1,3 propyl), 3.38–3.27 (m, 4H, 2 × CH_2-5 pentyl), 3.08 (dd, J = 4.8, 11.1, 2H, 2 × H-1a), 2.72–2.63 (m, 2H, 2 × NC*H*H-1 pentyl), 2.63–2.54 (m, 2H, 2 × NCH*H*-1 pentyl), 2.30 (dt, J = 2.1, 9.5, 2H, 2 × H-5), 2.23 (dd, J = 10.5, 11.1, 2H, 2 × H-1b), 1.94 (s, 3H, 3 × CH Ada), 1.73–1.59 (m, 12H, 6 × CH_2 Ada), 1.56–1.46 (m, 4H, 2 × CH_2-4 pentyl), 1.45–1.17 (m, 9H, CH-2 propyl, 2 × CH_2-2 pentyl, 2 × CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.8, 138.8, 138.0 (4 × C_q Bn), 128.6, 128.6, 128.5, 128.0, 128.0, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 87.6 (C-3), 78.8, 78.7 (C2, C-4), 75.5, 75.3, 73.6, 72.9 (4×CH_2 Bn), 71.1, 71.0 (CH_2-5,5′ pentyl), 68.5 (CH_2-1,3 propyl), 65.5 (C-6), 63.9 (C-5), 54.7 (C-1), 52.6 (NCH_2-1,1′ pentyl), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.5 (CH_2 Ada), 34.2 (C_q Ada), 29.9 (CH_2-4,4′ pentyl), 29.0 (CH Ada), 24.5, 24.4 (CH_2-3,3′ pentyl), 23.6, 23.5 (CH_2-2,2′ pentyl). IR ν_{max}(thin film)/cm^{-1}: 3031, 2903, 2853, 1495, 1454, 1361, 1274, 1208, 1093, 1027, 734, 697. $[\alpha]_D^{20} = -2.4$ (*c* 3.7, $CHCl_3$). HRMS: found 1393.8394 $[M+H]^+$; 697.4230 $[M+2H]^{2+}$, calculated for $[C_{91}H_{112}N_2O_{10} + H]^+$ 1393.8390; $[C_{91}H_{112}N_2O_{10} + 2H]^{2+}$ 697.4231.

4.1.11. *N,N′*-{5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis(oxy)bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-L-ido-1-deoxynojirimycin) 18

Dialdehyde **13** (159 mg, 0.42 mmol) was subjected to General procedure A with 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin to provide **18** (322 mg, 0.23 mmol) in 55% yield as a colourless oil after silica gel column purification. R_f = 0.70 (2:3; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 40H, CH_{Ar} Bn), 4.85 (d, J = 11.0, 2H, 2 × *CH*H Bn), 4.79 (d, J = 11.0, 2H, 2 × CH*H* Bn), 4.70 (d, J = 11.4, 2H, 2 × *CH*H Bn), 4.67–4.59 (m, 6H, 2 × CH*H* Bn, CH_2 Bn), 4.51 (d, J = 12.2, 2H, 2 × *CH*H Bn), 4.47 (d, J = 12.2, 2H, 2 × CH*H* Bn), 3.80 (dd, J = 6.4, 10.1, 2H, 2 × H-6a), 3.72–3.63 (m, 4H, 2 × H-4, 2 × H-6b), 3.57–3.38 (m, 8H, 2 × H-2, 2 × H-3, 2 × CH_2-1,3 propyl), 3.38–3.30 (m, 6H, 2 × H-5, 2 × CH_2-5 pentyl), 2.86 (dd, J = 5.2, 11.8, 2H, 2 × H-1a), 2.75–2.64 (m, 2H, 2 × NC*H*H-1 pentyl), 2.58–2.46 (m, 4H, 2 × H-1b, 2 × NCH*H*-1 pentyl), 1.93 (s, 3H, 3 × CH Ada), 1.71–1.58 (m, 12H, 6×CH_2 Ada), 1.58–1.49 (m, 4H, 2 × CH_2-4 pentyl), 1.49–1.35 (m, 4H, 2 × CH_2-2 pentyl), 1.35–1.26 (m, 5H, CH-2 propyl, 2 × CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.9, 138.8, 138.7 (4×C_q Bn), 128.5, 128.5, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 83.3 (C-3), 80.5 (C-4), 79.1 (C-2), 75.5, 73.4, 73.2, 72.8 (4×CH_2 Bn), 71.1 (CH_2-5,5′ pentyl), 68.4 (CH_2-1,3 propyl), 64.6 (C-6), 59.9 (C-5), 54.9 (NCH_2-1 pentyl), 50.0 (C-1), 49.5 (CH-2 propyl), 40.8 (CH_2 Ada), 37.4 (CH_2 Ada), 34.2 (C_q Ada), 29.9 (CH_2-4 pentyl), 29.0 (CH Ada), 28.0 (CH_2-2 pentyl), 24.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3031, 2902, 2851, 1496, 1454, 1364, 1093, 1027, 734, 697. $[\alpha]_D^{20} = -21.8$ (*c* 1.8, $CHCl_3$). HRMS: found 1393.8392 $[M+H]^+$; 697.4230 $[M+2H]^{2+}$, calculated for $[C_{91}H_{112}N_2O_{10} + H]^+$ 1393.8390; $[C_{91}H_{112}N_2O_{10} + 2H]^{2+}$ 697.4231.

4.1.12. *N,N′*-{5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)-bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin) 19

Dialdehyde **16** (119 mg, 0.33 mmol) was subjected to general procedure A with 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin to provide **19** (282 mg, 0.20 mmol) in 62% yield as a colourless oil after silica gel column purification. R_f = 0.57 (2:3; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 36H, CH_{Ar} Bn), 7.15–7.10 (m, 4H, CH_{Ar} Bn), 4.95 (d, J = 11.1, 2H, 2 × *CH*H Bn), 4.87 (d, J = 10.8, 2H, 2 × *CH*H Bn), 4.81 (d, J = 11.1, 2H, 2 × CH*H* Bn), 4.69 (d, J = 11.6, 2H, 2 × *CH*H Bn), 4.64 (d, J = 11.6, 2H, 2 × CH*H* Bn), 4.49 (d, J = 12.3, 2H, 2 × *CH*H Bn), 4.45 (d, J = 12.3, 2H, 2 × CH*H* Bn), 4.41 (d, J = 10.8, 2H, 2 × CH*H* Bn), 3.70–3.63 (m, 4H, 2 × H-2, 2 × H-6a), 3.60 (dd, J = 9.3, 2H, 2 × H-4), 3.53 (dd, J = 2.1, 10.3, 2H, 2 × H-6b), 3.45 (dd, J = 9.1, 2H, 2 × H-3), 3.33 (t, J = 6.5, 4H, 2 × CH_2-5 pentyl), 3.09 (dd, J = 4.8, 11.1, 2H, 2 × H-1a), 2.99 (s, 4H, 2 × OCH_2-Ada), 2.72–2.63 (m, 2H, 2 × NC*H*H-1 pentyl), 2.62–2.52 (m, 2H, 2 × NCH*H*-1 pentyl), 2.29 (dt, J = 2.1, 9.6, 2H, 2 × H-5), 2.23 (t, J = 10.8, 2H, 2 × H-1b), 2.05 (s, 2H, CH-5,7 Ada), 1.62 (s, 2H, CH_2-6 Ada), 1.56–1.43 (m, 12H, CH_2-4,8,9,10 Ada, 2 × CH_2-4 pentyl), 1.43–1.33 (m, 4H, 2 × CH_2-2 pentyl), 1.31 (s, 2H, CH_2-2 Ada), 1.28–1.12 (m, 4H, 2 × CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.7, 138.7, 137.9 (4×C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 87.5 (C-3), 81.8 (OCH_2-Ada), 78.8, 78.7 (C-2, C-4), 75.4, 75.3, 73.6, 72.9 (4 × CH_2 Bn), 71.7 (CH_2-5 pentyl), 65.4 (C-6), 63.8 (C-5), 54.6 (C-1), 52.5 (NCH_2-1 pentyl), 42.0 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 36.9 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 29.6 (CH_2-4 pentyl), 28.5 (CH-5,7 Ada), 24.2 (CH_2-3 pentyl), 23.5 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3030, 2900, 2849, 1495, 1454, 1360, 1208, 1094, 1027, 734, 696. $[\alpha]_D^{20} = -3.0$ (*c* 2.4, $CHCl_3$). HRMS: found 1379.8234

$[M+H]^+$; 690.4150 $[M+2H]^{2+}$, calculated for $[C_{90}H_{110}N_2O_{10}+H]^+$ 1379.8233; $[C_{90}H_{110}N_2O_{10}+2H]^{2+}$ 690.4153.

4.1.13. *N,N′*-{5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)-bis(pentane-5,1-diyl)}-bis(2,3,4,6-tetra-*O*-benzyl-L-ido-1-deoxynojirimycin) 20

Dialdehyde **16** (119 mg, 0.33 mmol) was subjected to general procedure A with 2,3,4,6-tetra-*O*-benzyl-L-*ido*-1-deoxynojirimycin to provide **20** (293 mg, 0.21 mmol) in 64% yield as a colourless oil after silica gel column purification. R_f = 0.69 (2:3; EtOAc/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 40H, CH_{Ar} Bn), 4.85 (d, J = 11.0, 2H, 2 × C*H*H Bn), 4.79 (d, J = 11.0, 2H, 2 × CH*H* Bn), 4.70 (d, J = 11.5, 2H, 2 × C*H*H Bn), 4.67–4.60 (m, 6H, 2 × CH*H* Bn, CH_2 Bn), 4.52 (d, J = 12.2, 2H, 2 × C*H*H Bn), 4.48 (d, J = 12.2, 2H, 2 × CH*H* Bn), 3.80 (dd, J = 6.4, 10.1, 2H, 2 × H-6a), 3.70 (dd, J = 2.4, 10.1, 2H, 2 × H-6b), 3.66 (dd, J = 5.9, 9.4, 2H, 2 × H-4), 3.58–3.52 (m, 2H, 2 × H-2), 3.52–3.46 (m, 2H, 2 × H-3), 3.38–3.31 (m, 5H,, 2 × H-5, 2 × CH_2-5 pentyl), 2.98 (s, 4H, 2 × OCH_2-Ada), 2.86 (dd, J = 5.3, 11.9, 2H, 2 × H-1a), 2.70 (ddd, J = 6.5, 8.7, 12.5, 2H, 2 × NC*H*H-1 pentyl), 2.56–2.48 (m, 4H, 2 × H-1a, 2 × NCH*H*-1 pentyl), 2.03 (s, 2H, CH-5,7 Ada), 1.68–1.35 (m, 18H, CH_2-4,6,8,9,10 Ada, 2 × CH_2-2 pentyl, 2 × CH_2-4 pentyl), 1.35–1.22 (m, 6H, CH-2 Ada, 2 × CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.8, 138.8, 138.7 (4×C_q Bn), 128.5, 128.5, 128.4, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5 (CH_{Ar} Bn), 83.3 (C-3), 81.8 (OCH_2-Ada), 80.5 (C-4), 79.1 (C-2), 75.5, 73.4, 73.2, 72.8 (4×CH_2 Bn), 71.8 (CH_2-5 pentyl), 64.5 (C-6), 59.9 (C-5), 54.8 (NCH_2-1 pentyl), 50.0 (C-1), 42.1 (CH_2-2 Ada), 39.6 (CH_2-4,8,9,10 Ada), 36.9 (CH_2-6 Ada), 34.7 (C_q-1,3 Ada), 29.6 (CH_2-4 pentyl), 28.5 (CH-5,7 Ada), 28.0 (CH_2-2 pentyl), 24.0 (CH_2-3 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3030, 2900, 2849, 1496, 1454, 1363, 1207, 1094, 1027, 734, 697. $[\alpha]_D^{20} = -25.9$ (c 2.1, $CHCl_3$). HRMS: found 1379.8236 $[M+H]^+$; 690.4151 $[M+2H]^{2+}$, calculated for $[C_{90}H_{110}N_2O_{10}+H]^+$ 1379.8233; $[C_{90}H_{110}N_2O_{10}+2H]^{2+}$ 690.4153.

4.1.14. *N,N′*-{5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis-(oxy)bis(pentane-5,1-diyl)}-bis(1-deoxynojirimycin) 21

Compound **17** (377 mg, 0.27 mmol) was subjected to general procedure B to provide **21** (144 mg, 0.21 mmol) in 79% yield as a colourless oil after silica gel column purification. R_f = 0.40 (19:1; EtOAc/NH_4OH); R_f = 0.05 (1:1; EtOAc/MeOH+5%NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.93 (dd, J = 2.4, 12.1, 2H, 2 × H-6a), 3.88 (dd, J = 2.7, 12.1, 2H, 2 × H-6b), 3.59–3.53 (m, 4H, 2 × H-2, 2 × C*H*H-1,3 propyl), 3.49–3.37 (m, 8H, 2 × H-4, 2 × CH*H*-1,3 propyl, 2 × CH_2-5 pentyl), 3.22 (dd, J = 9.1, 9.1, 2H, 2 × H-3), 3.14 (dd, J = 4.8, 11.5, 2H, 2 × H-1a), 3.03–2.93 (m, 2H, 2 × NC*H*H-1 pentyl), 2.84–2.74 (m, 2H, 2 × NCH*H*-1 pentyl), 2.49–2.40 (m, 4H, 2 × H-1b, 2 × H-5), 1.94 (s, 3H, 3 × CH Ada), 1.78–1.64 (m, 12H, 6×CH_2 Ada), 1.64–1.56 (m, 8H, 2 × CH_2-2 pentyl, 2 × CH_2-3 pentyl), 1.45–1.35 (m, 4H, 2 × CH_2-3 pentyl), 1.31–1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, MeOD) δ 79.9 (C-3), 71.9 (CH_2-5 pentyl), 71.1 (C-4), 69.9 (C-2), 69.4 (CH_2-1,3 propyl), 67.5 (C-5), 58.2 (C-6), 56.9 (C-1), 54.0 (NCH_2-1 pentyl), 50.8 (CH-2 propyl), 41.9 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.7 (CH_2-4 pentyl), 30.3 (CH Ada), 25.3 (CH_2-3 pentyl), 24.8 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3344, 2902, 2849, 1448, 1370, 1108, 1032. $[\alpha]_D^{20} = -8.8$ (c 1.9, MeOH). HRMS: found 673.4633 $[M+H]^+$, calculated for $[C_{35}H_{64}N_2O_{10}+H]^+$ 673.4634.

4.1.15. *N,N′*-{5,5′-[2-(Adamantan-1-yl)propane-1,3-diyl]bis-(oxy)bis(pentane-5,1-diyl)}-bis(L-*ido*-1-deoxynojirimycin) 22

Compound **18** (435 mg, 0.31 mmol) was subjected to general procedure B to provide **22** (153 mg, 0.23 mmol) in 73% yield as a colourless oil after silica gel column purification. R_f = 0.45 (19:1; EtOAc/NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.05–3.95 (m, 6H, 2 × CH_2-6, 2 × H-4), 3.95–3.90 (m, 2H, 2 × H-2), 3.84–3.79 (m, 2H, 2 × H-3), 3.55 (dd, J = 4.2, 9.5, 2H, 2 × C*H*H-1,3 propyl), 3.50 (s, 2H, 2 × H-5), 3.48–3.36 (m, 8H, 2 × CH*H*-1,3 propyl, 2 × CH_2-5 pentyl), 3.34–3.24 (m, 4H, 2 × CH_2-1, 2 × CH_2-1 pentyl), 1.94 (s, 3H, 3 × CH Ada), 1.90–1.76 (m, 4H, 2 × CH_2-2 pentyl), 1.76–1.59 (m, 16H, 6 × CH_2 Ada, 2 × CH_2-4 pentyl), 1.51–1.41 (m, 4H, 2 × CH_2-3 pentyl), 1.31–1.25 (m, 1H, CH-2 propyl). ^{13}C NMR (100 MHz, MeOD) δ 72.0 (C-4), 71.7 (CH_2-5 pentyl), 69.4 (CH_2-1,3 propyl), 69.2 (C-2, C-3), 63.7 (C-5), 60.2 (C-6 collapsed), 55.2 (CH_2-1 pentyl), 53.9 (C-1), 50.8 (CH-2 propyl), 41.8 (CH_2 Ada), 38.4 (CH_2 Ada), 35.2 (C_q Ada), 30.4 (CH_2-4 pentyl), 30.3 (CH Ada), 24.8 (CH_2-3 pentyl), 24.3 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3314, 2902, 2849, 1447, 1065. $[\alpha]_D^{20} = +11.4$ (c 2.6, MeOH). HRMS: found 673.4633 $[M+H]^+$, calculated for $[C_{35}H_{64}N_2O_{10}+H]^+$ 673.4634.

4.1.16. *N,N′*-{5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)-bis(pentane-5,1-diyl)}-bis(1-deoxynojirimycin) 23

Compound **19** (624 mg, 0.45 mmol) was subjected to general procedure B to provide **23** (177 mg, 0.27 mmol) in 60% yield as a colourless oil after silica gel column purification. R_f = 0.40 (19:1; EtOAc/NH_4OH).^{1}H NMR (400 MHz, MeOD) δ 4.04 (dd, J = 1.7, 12.5, 2H, 2 × H-6a), 3.92 (dd, J = 2.7, 12.5, 2H, 2 × H-6a), 3.72 (ddd, J = 4.9, 9.3, 10.9, 2H, 2 × H-2), 3.57 (dd, J = 9.1, 9.6, 2H, 2 × H-4), 3.47–3.33 (m, 8H, 2 × CH_2-5 pentyl, 2 × H-1a, 2 × H-3), 3.27–3.15 (m, 2H, 2 × NC*H*H-1 pentyl), 3.14–3.03 (m, 2H, 2 × NCH*H*-1 pentyl), 3.02 (s, 4H, 2 × OCH_2-Ada), 2.86 (d, J = 9.8, 2H, 2 × H-5), 2.81 (dd, J = 10.5, 11.5, 2H, 2 × H-1b), 2.02 (s, 2H, 2 × CH-5,7 Ada), 1.72 (s, 4H, 2 × CH_2-2 pentyl), 1.67–1.58 (m, 6H, CH_2-6 Ada, 2 × CH_2-4 pentyl), 1.56–1.37 (m, 12H, CH_2-4,8,9,10 Ada, 2 × CH_2-3 pentyl), 1.32 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, MeOD) δ 82.8 (OCH_2-Ada), 78.6 (C-3), 72.3 (CH_2-5 pentyl), 69.8 (C-4), 68.7 (C-2), 67.4 (C-5), 56.6 (C-6), 55.6 (C-1), 54.1 (NCH_2-1 pentyl), 43.0 (CH_2-2 Ada), 40.6 (CH_2-4,8,9,10 Ada), 38.0 (CH_2-6 Ada), 35.7 (C_q-1,3 Ada), 30.3 (CH_2-4 pentyl), 29.8 (CH-5,7 Ada), 24.8 (CH_2-3 pentyl), 24.3 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3296, 2899, 2848, 1453, 1369, 1102, 1029. $[\alpha]_D^{20} = -3.6$ (c 3.6, MeOH). HRMS: found 659.4475 $[M+H]^+$, calculated for $[C_{34}H_{62}N_2O_{10}+H]^+$ 659.4477.

4.1.17. *N,N′*-{5,5′-[Adamantan-1,3-diylbis(methylene)]bis(oxy)-bis(pentane-5,1-diyl)}-bis(L-*ido*-1-deoxynojirimycin) 24

Compound **20** (611 mg, 0.44 mmol) was subjected to general procedure B to provide **24** (159 mg, 0.24 mmol) in 55% yield as a colourless oil after silica gel column purification. R_f = 0.45 (19:1; EtOAc:NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 4.08–3.99 (m, 6H, 2 × CH_2-6, 2 × H-4), 3.99–3.93 (m, 2H, 2 × H-2), 3.91–3.81 (m, 2H, 2 × H-3), 3.59–3.50 (m, 2H, 2 × H-5), 3.49–3.32 (m, 12H, 2 × NCH_2-1 pentyl, 2 × CH_2-5 pentyl, 2 × CH_2-1), 3.01 (s, 4H, 2 × OCH_2-Ada), 2.02 (s, 2H, 2 × CH-5,7 Ada), 1.92–1.71 (m, 4H, 2 × CH_2-2 pentyl), 1.69–1.58 (m, 6H, CH_2-6 Ada, 2 × CH_2-4 pentyl), 1.57–1.41 (m, 12H, CH_2-4,8,9,10 Ada, 2 × CH_2-3 pentyl), 1.32 (s, 2H, CH_2-2 Ada). ^{13}C NMR (100 MHz, MeOD) δ 82.9 (OCH_2-Ada), 72.3 (CH_2-5 pentyl), 71.7 (C-4), 68.9 (C-2, C-3), 63.7 (C-5), 60.5 (C-6 collapsed), 55.2 (CH_2-1 pentyl), 54.0 (C-1), 43.0 (CH_2-2 Ada), 40.6 (CH_2-4,8,9,10 Ada), 38.0 (CH_2-6 Ada), 35.7 (C_q-1,3 Ada), 30.2 (CH_2-4 pentyl), 29.8 (CH-5,7 Ada), 24.7 (CH_2-3 pentyl), 24.1 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3312, 2899, 2848, 1450, 1101, 1027. $[\alpha]_D^{20} = +13.2$ (c 3.1, MeOH). HRMS: found 659.4476 $[M+H]^+$, calculated for $[C_{34}H_{62}N_2O_{10}+H]^+$ 659.4477.

4.1.18. 5-(Adamantan-1-yl-ethoxy)-1-bromo-pentane 26

A solution of PPh_3 (5.53 g, 21.1 mol) in CH_3CN (50 mL) was added to a solution of 5-(adamantan-1-yl-ethoxy)-1-pentanol (**25**: 1.87 g, 7.0 mmol) and carbontetrabromide (4.66 g, 14.1 mmol) in CH_3CN (150 mL). The reaction mixture was refluxed for 3 h and subsequently concentrated. The residue was purified by silica gel

column purification (100% PE→1:19 EtOAc/PE) to provide **26** (2.01 g, 6.13 mmol) in 87% yield as a colourless oil. 5-(Adamantan-1-yl-ethoxy)-1-pentanol was obtained via the same route as previously described for 5-(adamantan-1-yl-methoxy)-1-pentanol,[6] but now with commercially available 2-adamantaneethanol. R_f = 0.15 (1:9; toluene/PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (dt, J = 6.9, 13.2, 6H, CH_2-1 pentyl, CH_2-5 pentyl, OCH_2 ethoxy), 1.93 (s, 3H, 3 × CH Ada), 1.92–1.84 (m, 2H, CH_2-2 pentyl), 1.73–1.61 (m, 6H, 3 × CH_2 Ada), 1.61–1.54 (m, 2H, CH_2-4 pentyl), 1.54–1.45 (m, 8H, 3 × CH_2 Ada, CH_2-3 pentyl), 1.37 (t, J = 7.5, 2H, CH_2-Ada ethoxy). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.6 (CH_2-5 pentyl), 66.9 (OCH_2 ethoxy), 43.8 (CH_2-Ada ethoxy), 42.9 (CH_2 Ada), 37.3 (CH_2 Ada), 33.9 (CH_2-1 pentyl), 32.8 (CH_2-2 pentyl), 31.8 (C_q Ada), 29.1 (CH_2-4 pentyl), 28.8 (CH Ada), 25.2 (CH_2-3 pentyl). IR ν_{max}(thin film)/cm^{-1}: 2897, 2845, 1728, 1450, 1362, 1344, 1271, 1109, 968.

4.1.19. *N*-[5-(Adamantan-1-yl-ethoxy)-pentyl]-1-deoxynojirimycin 27

Bromide **26** (148 mg, 0.45 mmol) was added to a mixture of 1-deoxynojirimycin (49 mg, 0.3 mmol; synthesis as reported previously[13]) and K_2CO_3 (124 mg, 0.9 mmol) in DMF (1.5 mL). The mixture was heated at 90 °C for 48 h. The mixture was filtered over a glass microfibre filter and the filtrate was concentrated. Silica gel column purification (100% EtOAc→3:1 EtOAc:MeOH+5%NH_4OH) of the residue provided **27** (70 mg, 0.17 mmol) in 58% yield as a colourless oil. R_f = 0.45 (1:2; MeOH/EtOAc + NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 3.88–3.83 (m, 2H, CH_2-6), 3.51–3.45 (m, 3H, H-2, OCH_2 ethoxy), 3.42 (t, J = 6.5, 2H, CH_2-5 pentyl), 3.36 (dd, J = 9.3, 1H, H-4), 3.14 (dd, J = 9.1, 1H, H-3), 3.01 (dd, J = 4.8, 11.2, 1H, H-1a), 2.86–2.79 (m, 1H, C*H*H-1 pentyl), 2.65–2.58 (m, 1H, CH*H*-1 pentyl), 2.21 (dd, J = 10.8, 1H, H-1b), 2.15 (d, J = 7.6, 1H, H-5), 1.93 (s, 3H, 3 × CH Ada), 1.71 (dd, J = 11.6, 41.9, 6H, 3 × CH_2 Ada), 1.62–1.56 (m, 2H, CH_2-4 pentyl), 1.56 (d, J = 2.6, 6H, 3 × CH_2 Ada), 1.55–1.49 (m, 2H, CH_2-2 pentyl), 1.39–1.31 (m, 4H, CH_2-3 pentyl, CH_2-Ada ethoxy). ^{13}C NMR (150 MHz, MeOD) δ 80.6 (C-3), 72.0 (C-4), 71.9 (CH_2-5 pentyl), 70.7 (C-2), 67.9 (OCH_2 ethoxy), 67.5 (C-5), 59.3 (C-6), 57.7 (C-1), 53.9 (CH_2-1 pentyl), 44.9 (CH_2-Ada ethoxy), 44.0 (CH_2 Ada), 38.3(CH_2 Ada), 32.9 (C_q Ada), 30.8 (CH_2-4 pentyl), 30.3 (CH Ada), 25.4 (CH_2-3 pentyl), 25.1 (CH_2-2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3360, 2899, 2844, 1673, 1456, 1097, 1013, 980. $[\alpha]_D^{20} = -16.6$ (c 0.8, MeOH). HRMS: found 412.3058 [M+H]$^+$, calculated for [$C_{23}H_{41}NO_5$ + H]$^+$ 412.3057.

4.1.20. TFA salt of *N*-[5-(Adamantan-1-yl-ethoxy)-pentyl]-L-*ido*-1-deoxynojirimycin 28·TFA

Bromide **26** (148 mg, 0.45 mmol) was added to a mixture of L-*ido*-1-deoxynojirimycin (49 mg, 0.3 mmol; synthesis as reported previously[13]) and K_2CO_3 (124 mg, 0.9 mmol) in DMF (1.5 mL). The mixture was heated at 90 °C for 48 h. The mixture was filtered over a glass microfibre filter and the filtrate was concentrated. Silica gel column purification (100% EtOAc→3:1 EtOAc/MeOH + 5%NH_4OH) of the residue provided **28** (53 mg, 0.13 mmol) in 43% yield as a colourless oil. R_f = 0.35 (2:3; MeOH/EtOAc + NH_4OH). ^{1}H NMR (400 MHz, D_2O) δ 4.06–3.46 (m, 4H, CH_2-6, H-2, H-3, H-4), 3.46–3.36 (m, 1H, H-5), 3.36–3.16 (m, 6H, CH_2-5 pentyl, CH_2-1 pentyl, OCH_2 ethoxy), 3.16–3.03 (m, 2H, CH_2-1), 1.74 (s, 3H, 3 × CH Ada), 1.69–1.27 (m, 8H, 6×CH_2 Ada, 2 × CH_2 pentyl), 1.27–1.04 (m, 3H, CH_2 pentyl, CH_2-Ada ethoxy). ^{13}C NMR (100 MHz, D_2O) δ 162.5, 162.1, 161.8, 161.4 (C=O TFA), 120.2, 117.3, 114.4, 111.5 (CF_3 TFA), 70.2 (CH_2-5 pentyl), 69.4, 67.2, 66.5 (C-2, C-3, C-4), 66.4 (OCH_2 ethoxy), 61.3 (C-5), 58.5 (C-6), 53.5 (C-1), 52.2 (CH_2-1 pentyl), 42.9 (CH_2-Ada ethoxy), 42.3 (CH_2 Ada), 36.9 (CH_2 Ada), 31.2 (C_q Ada), 28.6 (CH_2 Ada, CH_2 pentyl), 22.7, 22.1 (2 × CH_2 pentyl). IR ν_{max}(thin film)/cm^{-1}: 3362, 2902, 2848, 1670, 1450, 1182, 1139, 1067, 1024, 837. $[\alpha]_D^{20} = +11.9$ (c 0.8, MeOH). HRMS: found 412.3055 [M+H]$^+$, calculated for [$C_{23}H_{41}NO_5$ + H]$^+$ 412.3057.

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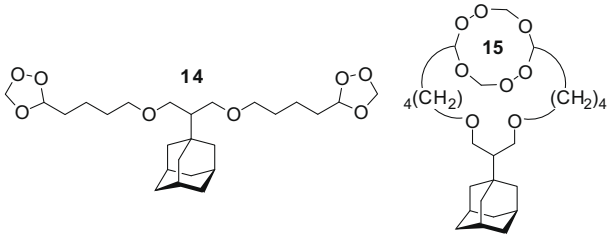

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