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Synthesis and Evaluation of Hybrid Structures Composed of Two Glucosylceramide Synthase Inhibitors

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Glucosylceramide metabolism and the enzymes involved have attracted significant interest in medicinal chemistry, because aberrations in the levels of glycolipids that are derived from glucosylceramide are causative in a range of human diseases including lysosomal storage disorders, type 2 diabetes, and neurodegenerative diseases. Selective modulation of one of the glycoprocessing enzymes involved in glucosylceramide metabolism—glucosylceramide synthase (GCS), acid glucosylceramidase (GBA1), or neutral glucosylceramidase (GBA2)—is therefore an attractive research objective. In this study we took two established GCS inhibitors, one based on deoxynojirimycin and the other a ceramide analogue, and merged characteristic features to obtain hybrid compounds. The resulting 39-compound library does not contain new GCS inhibitors; however, a potent (200 nM) GBA1 inhibitor was identified that has little activity toward GBA2 and might therefore serve as a lead for further biomedical development as a selective GBA1 modulator.

Introduction

Glucosylceramide synthase (GCS) has emerged in recent years as an attractive target for drug development both in relation to lysosomal storage disorders (in particular Gaucher disease) and type 2 diabetes.[1] GCS catalyzes the transfer of glucose from UDP-glucose to ceramide to form glucosylceramide (Figure 1, left panel).[2] In Gaucher disease, glucosylceramide accumulates due to an inherited deficiency in acid glucosylceramidase (GBA1).[3] Two decades ago Platt, Butters, and colleagues discovered that the modified iminosugar, *N*-butyldeoxynojirimycin (miglustat, Zavesca, **1**) is an inhibitor of GCS.[4] In 2002 Zavesca entered clinical practice in what has become known as substrate reduction therapy. Administration of Zavesca to mildly affected type 1 Gaucher patients that carry N370S GBA1 results in lowering glucosylceramide levels to such an extent that accumulation of this glycolipid due to partially impaired GBA1 action is prevented.[5] In 1998 we reported that enlarging the hydrophobic *N*-alkyl group that is appended to the deoxynojirimycin core, as in *N*-adamantanemethoxypentyl deoxynojirimycin (AMP-DNM, **2**) leads to a considerable increase in GCS inhibitory potency.[6] This finding has been confirmed in recent years in several studies, and a variety of iminosugar-based GCS inhibitors that differ in the nature of the N substituent but also in configuration of the piperidine iminosugar have been described.[7,8] Coinciding with these findings, studies were reported indicating that altered glycolipid levels, and in particular the ganglioside GM3 (αNeu5Ac(2-3)-β-D-Galp(1-4)-β-D-Glcp(1-1)Cer), which is the result of a high-fat diet, negatively influences insulin signaling by interfering with the insulin receptor.[9]

In 2007 we disclosed that AMP-DNM **2** decreases GM3 levels by partial inhibition of GCS in animal models of type 2 diabetes, and in this way restores insulin signaling.[10a] We recently extended this work by the generation of a focused library of *N*-alkyldeoxynojirimycin derivatives, and we found that biphenyl-substituted iminosugars are more potent GCS inhibitors than our aliphatic adamantyl derivatives.[10b] Next to deoxynojirimycin-type iminosugars, several other compound classes have been identified as GCS inhibitors. Ceramide analogues **3** have gained considerable attention in recent years. Eliglustat (**3**, $R = C_7H_{15}$) has been approved as an alternative to Zavesca in substrate reduction therapy for patients of Gaucher disease[11] and has also been shown to increase insulin signaling in animal models of type 2 diabetes.[12] Eliglustat is the result of extensive medicinal chemistry studies over the past decades based on a parent compound, 1-phenyl-2-decanoyl-3-morpholino-1-propanol (PDMP) described by Vunman and Radin in 1980 as a GCS inhibitor.[13] Finally, screening of large compound collections in a GCS inhibition assay followed by medicinal

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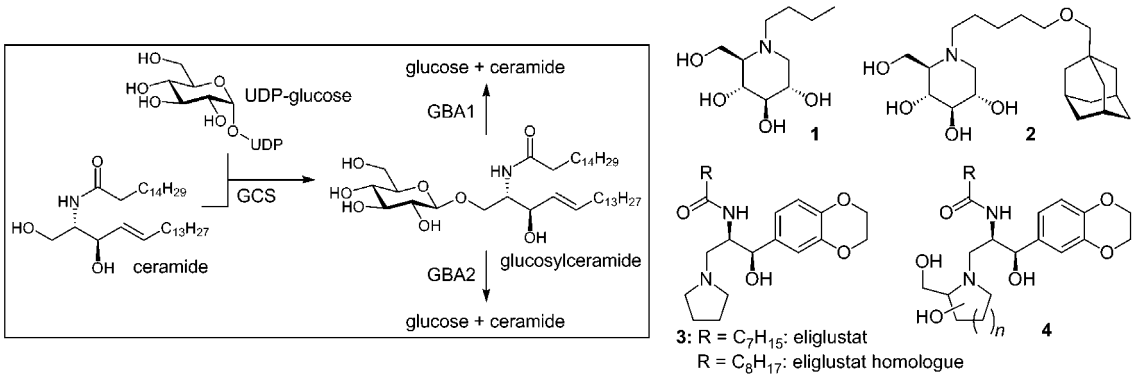


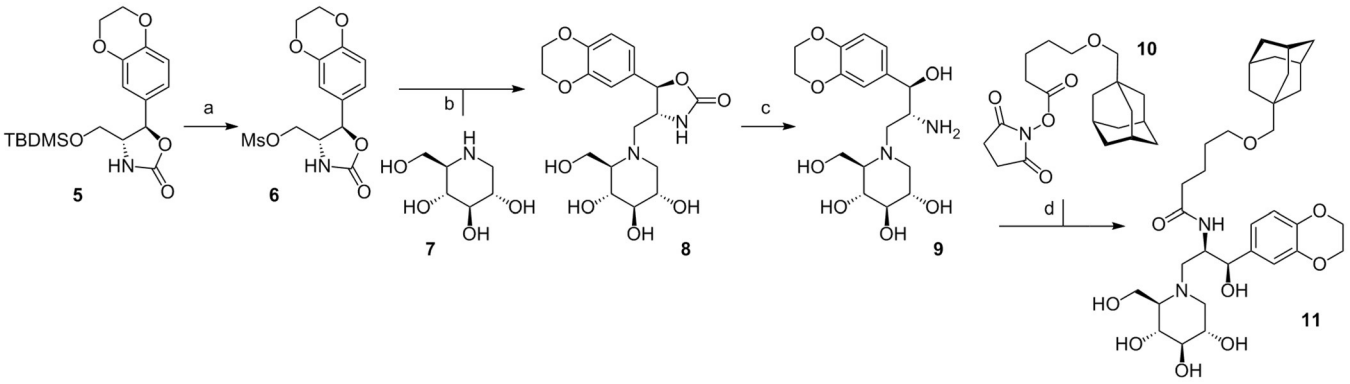
Figure 1. Glucosylceramide metabolism (left), established glucosylceramide synthase inhibitors **1**–**3** and hybrid structures **4** that are subject of the studies reported herein.

chemistry optimization has led to the identification of a number of functionalized amino acids (serine, tryptophan, phenylalanine cores) that are currently being pursued as leads for combating type 2 diabetes by GCS inhibition.[14]

In the search for new GCS inhibitors, selectivity with respect to other glycoprocessing enzymes is an important issue. In particular, glycosidases that hydrolyze glucosylceramide are potential off-targets. Next to GBA1, we and others have discovered a second non-lysosomal neutral glucosylceramidase termed GBA2 (Figure 1, left panel).[15] Ideally these enzymes are untouched, and we routinely screen potential GCS inhibitors also against GBA1 and GBA2. These glycosidases also have therapeutic potential in their own right. GBA1 inhibitors are extensively pursued in what has become known as chemical chaperone therapy: a conceptually new therapeutic strategy that has yet to be validated in the clinic and that aims at restoring active lysosomal GBA1 levels through stabilizing the fold of the nascent protein in the endoplasmic reticulum.[16] Mutations in GBA1 have also been implicated as risk factors for Parkinsonism,[17] whereas excessive degradation of glucosylceramide by GBA2 is thought to play a role in neuropathology.[18] When looking at the different compound classes currently pursued as GCS inhibitors, it is perhaps obvious that the ceramide analogues are GCS selective, at least with respect to GBA1 and GBA2 (next to **3**, these include the aforementioned amino acid derived leads; after all, ceramide itself is the result of a condensation between serine and palmitate, and it should thus come as no surprise that serine derivatives featuring hydrophobic substituents target GCS). The same cannot be said of the deoxynojirimycin derivatives **1** and **2**, both of which give considerable inhibition of GBA1, GBA2 and a range of other (including intestinal) glycosidases as well.[7b] In fact, deoxynojirimycin and its derivatives are renowned for their glycosidase inhibitory activity, and the finding by Platt and Butters that such compounds also target GCS came as a major surprise, considering that glycosyltransferases are generally not affected by iminosugars. One strategy to achieve GCS selectivity with respect to GBA1 and GBA2 is to alter the configuration of the iminosugar core. Indeed, GCS is effectively inhibited by both D-*galacto*- and L-*ido*-configured N-alkylated iminosugars, with the latter especially being much less potent at inhibition of a range of glycosyl hydrolases.[7b,8,19] A second strategy we recently investigated and that proved unrewarding is testing a model[20] proposed by Platt and Butters, who reasoned that *N*-butyldeoxynojirimycin acts on GCS not as a glucose mimic, but rather as a ceramide mimic. In this model, which has not yet been substantiated due to a lack of structural data on GCS (the membrane-associated enzyme has defied efforts to obtain crystallographic data), the hydroxy substituents at positions C2 and C3 and the hydroxymethyl group at C5 (glucopyranose numbering) of the piperidine core mimic the two hydroxy groups of ceramide, with the *N*-alkyl chain as one of the ceramide alkyl chains. According to this model the C2 OH group would be redundant, and we thought to capitalize on this by testing N-alkylated derivatives of the natural product fagomine (2-deoxydeoxynojirimycin) in its eight configurational isomers. This library contained no effective GCS inhibitors.[21] In the current work we report on a related strategy to design potentially new GCS inhibitors, which is based on potential structural similarities in iminosugars **1** and **2**, and ceramide analogue **3**. The pyrrolidine ring in **3** has been substituted for piperidine and morpholine in various studies, and all these varieties are accommodated by GCS.[22] We reasoned that **3** and its analogues might act as bisubstrate analogues, with the pyrrolidine moiety occupying the glucose binding side and the branched hydrophobic group that of ceramide.[22f] A similar model may apply to deoxynojirimycin derivatives **1** and **2**, with the iminosugar core binding at a putative glucose-binding site and the hydrophobic group in the corresponding ceramide-binding site.[23] We decided to investigate this model by designing a concise library of hybrid structures that are composed of the core amino alcohol structure in **3**, feature a polyhydroxylated pyrrolidine or piperidine iminosugar, and differ with respect to the *N*-acyl chain. Herein we report on the development and inhibitory activity against GCS, GBA1, and GBA2 of a 39-compound library designed according to these guidelines.

Results and Discussion

The synthetic strategy by which we assembled our 39-compound library of hybrid iminosugar–ceramide analogues is depicted in Scheme 1. In the first step, fully protected aminodiol



Scheme 1. *Reagents and conditions*: a) AcOH, THF/H_2O, then MsCl, pyridine, −20 °C; b) DMF, K_2CO_3, 80 °C, 72 h; c) LiOH, dioxane/H_2O, microwave, 30 min; d) DMF, RT.

5,[24] which featured as an advanced intermediate in the synthesis of **3**, was desilylated followed by introduction of the primary mesylate to give compound **6** in 98% overall yield. The mesylate in **6** was substituted for deoxynojirimycin **7** (**6**→**8**, 84%), after which the carbamate protecting group was removed under basic conditions (**8**→**9**, 91%). In the final step the secondary amine in **9** was acylated with the succinic ester of 5-adamantanemethyloxypentanoic acid **10** to give hybrid structure **11** in 77% yield.

By following this synthetic scheme, but with variation in the nature of the iminosugar (deoxynojirimycin **7** in Scheme 1)[25] that is reacted with the mesylate in **6**, the succinyl ester (adamantane spacer **10** in Scheme 1) that is condensed with the secondary amine in **9**, or both, we prepared a 39-compound library.

The library (Figure 2) was assembled from four polyhydroxylated piperidines, six polyhydroxylated pyrrolidines, as well as the bare pyrrolidine, piperidine, and morpholine substituents that have proven affinity for GCS (see the Experimental Section below for conditions, yields, and analytical data). Each of these 13 cyclic secondary amines was connected to the core aminodiol that is the common feature in all compounds, and further variation was provided by introducing three different *N*-acyl groups: next to the adamantane spacer (taken from lead **2**), the nonanoic acid moiety as present in lead **3**, and *O*-(*p*-methoxypenyl)hydroxyacetate as another hydrophobic moiety found in GCS inhibitors of the PDMP series.[12] In all, this led to the following 13 series of three compounds each: polyhydroxylated piperidines featuring the D-*gluco* configuration (**11**–**13**), the L-*ido* configuration (**14**–**16**), the D-*galacto* configuration (**17**–**19**) and the L-*altro* configuration (**20**–**22**); polyhydroxylated pyrrolidines featuring the D-*lyxo* configuration (**23**–**25**), the D-*arabino* configuration (**26**–**28**), the D-*xylo* configuration (**29**–**31**), the D-*ribo* configuration (**32**–**34**), the L-*arabino* configuration (**35**–**37**) and the L-*lyxo* configuration (**38**–**40**); along with the analogous compounds featuring an unsubstituted piperidine (**41**–**43**), morpholine (**44**–**46**), and pyrrolidine (**3**, **47**, **48**).

The library of compounds were next assessed for their inhibitory potential against GCS, GBA1, and GBA2 in comparison with lead structures **2** and **3**, which were at the basis of the design of the hybrid structures. For GCS we used a previously

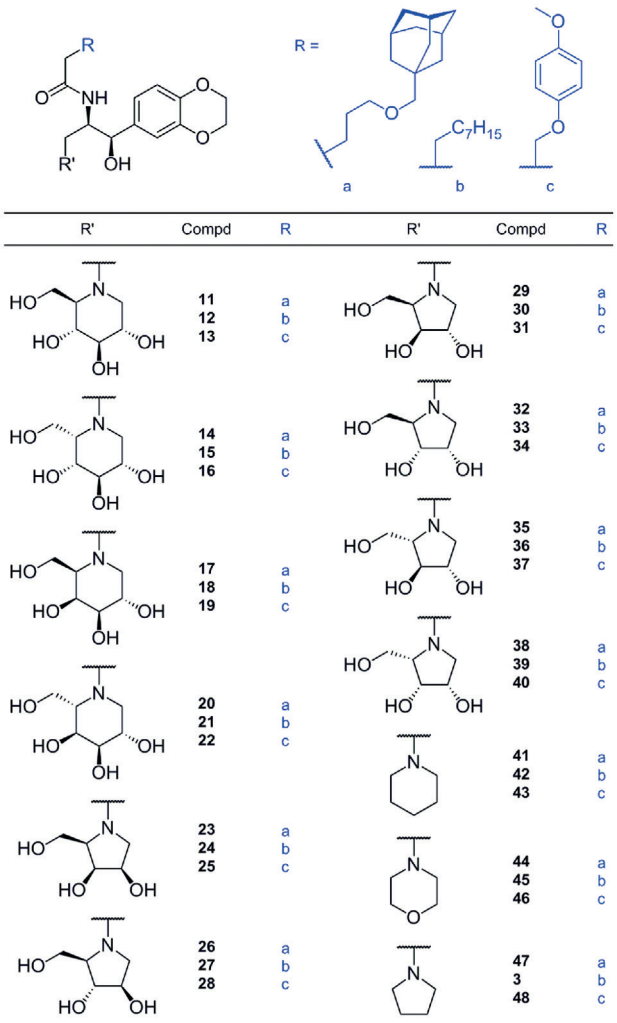


Figure 2. Structures of the 39-member compound library.

reported[6] in situ assay that relies on a fluorescent ceramide analogue as a readout. We selected 10 μM as a cutoff concentration, above which execution of this cell-based assay is cumbersome, and furthermore because GCS inhibitors with an IC_{50} value at or above 10 μM arguably have no therapeutic poten-

tial. GBA1 and GBA2 inhibition was measured in in vitro assays,[7b] and for this, we opted for 1 mM as cutoff. In this initial screen aimed to weed out inactive compounds, IC_{50} values were determined based on a single experiment. As can be immediately observed from Table 1, none of the polyhydroxylated pyrrolidines (compounds **23**–**40**) or piperidines (compounds **11**–**22**) inhibit GCS at concentrations up to 10 μM. We therefore conclude that our design to arrive at bisubstrate analogue type GCS inhibitors is at fault. Apparently (and one must be careful to draw conclusions on binding modes without structural data), the pyrrolidine (**3**, **47**, **48**), piperidine (**41**–**43**), and morpholine (**44**–**46**) series that inhibit GCS in the nanomolar to low micromolar range (as expected from published data) act through a mode that does not recruit a putative glucose binding site. Clearly, appending multiple hydroxy functions to the pyrrolidine/piperidine pharmacophore has a detrimental effect irrespective of the stereochemical information thus introduced (the wide range of configurational isomers we used at least allows this conclusion). These observations do not preclude the presence of a glucopyranose binding site in the GCS catalytic pocket, and that is the target of the deoxynojirimycin-type GCS inhibitors **2** and **3**. Perhaps introducing a spacer between the two pharmacophores would result in more effective GCS inhibitors. On the positive side, our compound library contains a number of rather potent GBA1 inhibitors in the pyrrolidine series. Of these, especially the D-*arabino*-configured derivatives are of interest, as they display good selectivity for GBA1 over GBA2. To further probe these results, we obtained IC_{50} values derived from triplicate measurements for D-*arabino* pyrrolidine derivatives **26**–**28** against GBA and GBA2, in a comparison with the L-*ido*-configured piperidine series **14**–**16** (about equally active toward GBA1 in our initial assessment, while at the same time less selective because of moderately good GBA2 activity) and AMP-DNM **2** as a positive control. These experiments (values listed in Table 2) confirm our initial findings.

Thus, D-*arabino*-pyrrolidine **26** inhibits GBA1 with an IC_{50} value of 1.8 μM, in the range of what we observed for AMP-DNM **2** (1.0 μM). In contrast, whereas **2** is a very potent (IC_{50}: 1 nM) GBA2 inhibitor, **26** is a relatively poor GBA2 inhibitor (IC_{50}: 67 μM). In comparison, pyrrolidines **26**–**28** are relatively poor GBA2 inhibitors, and this is in contrast to the L-*ido*-piperidine series **14**–**16** that we included in the triplicate measurements and that inhibit GBA1 in the same range, as evident from Table 2. Indeed we have experienced in the past that N-alkylated deoxynojirimycin derivatives and their configurational isomers that inhibit GBA1 without exception are more potent inhibitors of GBA2. Based on the results presented herein we believe it may be worthwhile to pursue polyhydroxylated N-alkylated pyrrolidines as potent and selective GBA1 inhibitors.

In conclusion, we have developed a straightforward synthetic route to obtain hybrid structures that encompass pharmacophores stemming from two distinct classes of glucosylceramide synthase (GCS) inhibitors. The fact that neither of these compounds are potent GCS inhibitors is of itself of interest, as it provides more, albeit circumstantial, information on how the separate compounds (**2** and **3**) may bind to the GCS active site. Our compound collection also adds to the growing list of functionalized iminosugar derivatives, and screening against a wider array of glycoprocessing enzymes may yield potentially

Table 2. GBA1 and GBA2 inhibition assay results for compounds **2**, **14**, **15**, **16**, **26**, **27**, and **28**.

Compd	IC_{50} [μM]	
	GBA1	GBA2
2	1.0 ± 0.1	0.000 ± 0.00019
14	2.4 ± 0.1	0.005 ± 0.0003
15	6.9 ± 1.2	0.1 ± 0.03
16	12.9 ± 0.5	1.6 ± 0.3
26	1.8 ± 0.2	67.2 ± 1.6
27	1.6 ± 0.1	41.5 ± 6.1
28	15.2 ± 0.5	118.8 ± 15.4

[a] Apparent IC_{50} values are the mean ± SD from triplicate measurements.

Table 1. GCS, GBA1, and GBA2 inhibition assay results.[a]

Compd	IC_{50} [μM]			Compd	IC_{50} [μM]			Compd	IC_{50} [μM]		
	GCS	GBA1	GBA2		GCS	GBA1	GBA2		GCS	GBA1	GBA2
2	0.2	0.2	0.001	**24**	>10	25	350	**39**	>10	150	500
3	0.1	70	>1000	**25**	>10	750	>1000	**40**	>10	175	>1000
11	>10	0.2	0.03	**26**	>10	2.0	90	**41**	1.5	120	>1000
12	>10	0.3	0.2	**27**	>10	0.2	60	**42**	1.0	100	750
13	>10	1.7	2.2	**28**	>10	12.5	200	**43**	0.8	>1000	>1000
14	>10	1.5	0.03	**29**	>10	5.0	>1000	**44**	0.75	30	>1000
15	>10	2.0	0.1	**30**	>10	30	200	**45**	0.8	30	150
16	>10	4.5	1.0	**31**	>10	100	>1000	**46**	0.8	500	>1000
17	>10	2.0	1.0	**32**	>10	40	50	**47**	0.1	45	500
18	>10	15	3.5	**33**	>10	50	150	**48**	0.05	>1000	>1000
19	>10	150	50	**34**	>10	200	>1000				
20	>10	37.5	6.0	**35**	>10	8.0	>1000				
21	>10	100	50	**36**	>10	10	>1000				
22	>10	>1000	>1000	**37**	>10	175	>1000				
23	>10	20	150	**38**	>10	30	500				

[a] Apparent IC_{50} values from single determinations.

new leads for development toward selective inhibitors, in analogy with the identified pyrrolidine **26**, which selectively inhibits GBA1.

Experimental Section

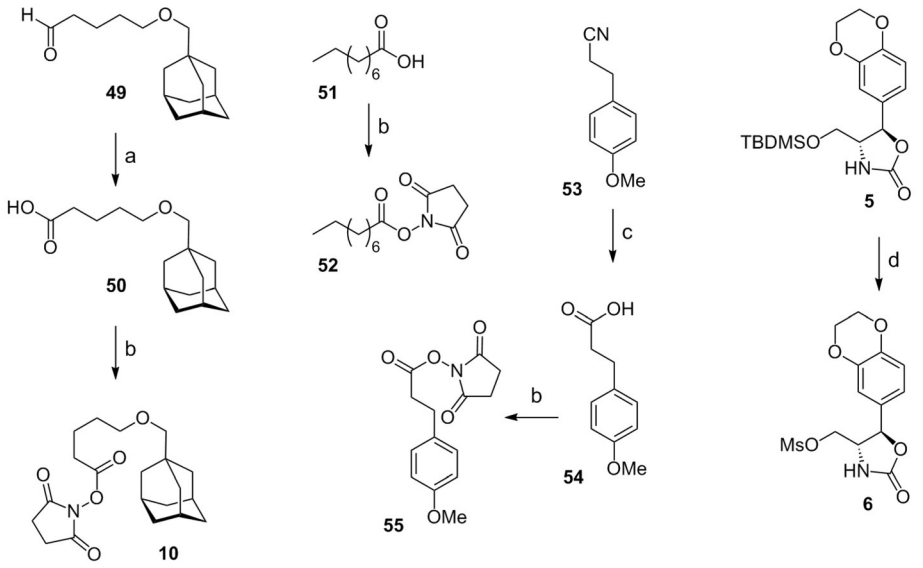
Enzyme inhibition assays. The inhibitory potencies (IC_{50} values) of the final compounds for GCS, GBA1, and GBA2 were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations. IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[26] Briefly, cells were incubated in 1 mL of medium with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2 h followed by lipid extraction and separation by thin-layer chromatography (TLC). Formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphorimaging device. IC_{50} values were determined from the titration curves. The experiment was repeated three times. IC_{50} values for lysosomal GBA1 were measured using 4-methylumbelliferyl-β-D-glucoside as substrate.[27] Briefly, recombinant GBA1 was incubated with increasing compound concentrations. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside (4-MU-β-glucoside) in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (*v*/*v*) and 0.2% (*w*/*v*) sodium taurocholate. Assays performed in triplicate were incubated at 37 °C and quenched by the addition of glycine/NaOH (pH 10.6). The amount of liberated 4-MU was determined with a PerkinElmer Life Sciences LS30 fluorimeter. IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with the same substrate as described earlier.[28,15b] Briefly, GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells and incubated with 3.7 mM 4-MU-β-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8, with or without pre-incubation for 30 min at 4 °C with 1 mM conduritol-B-epoxide (CBE, Sigma) to inhibit the lysosomal glucocerebrosidase, GBA1. Assays were incubated at 37 °C and quenched by the addition of glycine/NaOH (pH 10.6). The amount of liberated 4-MU was determined with a PerkinElmer Life Sciences LS30 fluorimeter. Assays were performed in triplicate.

Synthesis: **general information**. Reactions were monitored by TLC analysis using silica gel coated plates (0.2 mm) with detection by spraying with a solution of $KMnO_4$ (5 g L^{-1}) and K_2CO_3 (25 g L^{-1}) followed by charring. Column chromatography was performed on silica gel (40–63 μm). Microwave reactions were performed in a Biotage Initiator 2.5 microwave reactor. Wattage was automatically adjusted to maintain the desired temperature. Yields were not optimized. ^1H and ^{13}C NMR spectra were recorded on 500–125 MHz or 400–100 MHz spectrometers. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants (*J*) are given in Hz. All ^{13}C NMR spectra are proton decoupled. For LC–MS analysis, an HPLC system (detection simultaneously at λ 213, 254 nm and evaporative light detection) equipped with an analytical C_{18} column (4.6 mm (∅) × 250 mm (*l*), 5 μm particle size) in combination with buffers A: H_2O, B: MeCN, C: 1.0% aqueous trifluoroacetic acid (TFA), coupled with an electrospray interface (ESI) was used. For RP-HPLC purifications (detection simultaneously at λ 213, 254 nm), an automated HPLC system equipped with a semi-preparative C_{18} column (5 μm C_{18}, 10 Å, 150×21.2 mm) was used. The applied buffers were A: H_2O + TFA (1%) and B: MeCN. High-resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in H_2O/MeCN 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 mL min^{-1}, 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). Deoxynojirimycin **7**[25a] and its congeners L-*ido*-deoxynojirimycin,[7b] D-*galacto*-deoxynojirimycin,[28,15b] and L-altro-deoxynojirimycin[29] were prepared as reported previously by us. 2,3,5-Tri-*O*-benzyl-D-*lyxono*-1,4-lactone, 2,3,5-tri-*O*-benzyl-L-xylofuranose, 2,3,5-tri-*O*-benzyl-L-arabinofuranose, 2,3,5-tri-*O*-benzyl-D-ribofuranose, and 2,3,5-tri-*O*-benzyl-D-xylofuranose were synthesized as described.[30] 4-Methoxyphenyl-2-cyanoethyl ether was synthesized from 4-methoxyphenol as published by DeWald et al.[31]

General procedure for condensing *N*-hydroxysuccinimide with 50, 51 and 54. To a solution of the free acid in CH_2Cl_2 (1 mmol/5 mL) were added *N*-hydroxysuccinimide (1.1 mol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.2 mmol). The mixture was stirred for 6 h, after which TLC analysis showed complete consumption of the starting material. The organic layer was washed with aqueous saturated NH_4Cl (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography with EtOAc and petroleum ether (PE) as eluent (20:1→5:4, *v*/*v*) (Scheme 2).

5-(Adamantane-1-yl-methoxy)pentanoic acid (**50**): To a mixture of 5-(adamantan-1-yl-methoxy)-1-pentanal[24a] (**49**, 5.12 g, 20.5 mmol) in CH_2Cl_2/*t*BuOH/H_2O (100 mL, 6:3:1, *v*/*v*/*v*) was added TEMPO (0.624 g, 4.0 mmol) and BAIB (9.65 g, 30.0 mmol). After 24 h, a mixture of aqueous saturated $Na_2S_2O_3$ and aqueous saturated $NaHCO_3$ (30 mL, 2:1, *v*/*v*) was added, and the reaction mixture was stirred vigorously. Subsequently, the volatiles were removed and the aqueous layer extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with EtOAc and PE as solvent system (1:19→3:1, *v*/*v*) affording **50** as colorless oil (4.00 g, 15.0 mmol, 73%); $R_f=0.45$ (EtOAc/PE 1:4, *v*/*v*); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.52$ (br s, 6H, H_2 adamantane), 1.52–1.75 (m, 10H, H_2 adamantane, H_2-3 pentanoic acid, H_2-4 pentanoic acid), 1.95 (br s, 3H, CH adamantane), 2.39 (dd, $J=7.2$, 7.6 Hz, 2H, H_2-2 pentanoic acid), 2.95 (s, 2H, H_2 adamantane), 3.40 (t, $J=6.0$ Hz, H_2-2 pentanoic acid), 11.05 ppm, (br s, 1H, OH pentanoic acid); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.5$ (CH_2 pentanoic acid), 28.2 (CH adamantane), 28.8, 33.8 (CH_2 pentanoic acid), 34.0 (Cq adamantane), 37.2, 39.7 (CH_2 adamantane), 71.0 (CH_2 pentanoic acid), 81.9 (CH_2 methoxy), 179.9 ppm, (C=O pentanoic acid).

5-(Adamantane-1-yl-methoxy)pentanoic acid succinimide ester (**10**): Synthesized according to the general procedure for condensing *N*-hydroxysuccinimide starting from **50**. Yield 3.20 g (8.8 mmol, 88%); $R_f=0.30$ (EtOAc/PE 1:3, *v*/*v*); ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.52 (br s, 6H, H_2 adamantane), 1.63–1.72 (m, 8H, H_2 adamantane, H_2-4 pentanoic acid), 1.82 (dt, $J=7.2$, 7.6 Hz, 2H, H_2-3 pentanoic acid), 1.95 (br s, 3H, CH adamantane), 2.66 (dd, $J=7.2$, 7.6 Hz, 2H, H_2-2 pentanoic acid), 2.83 (br s, 4H, 2×H_2 succinimide), 2.95 (s, 2H, H_2 adamantane), 3.41 ppm, (t, $J=6.0$ Hz, H_2-2 pentanoic acid); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.6$ (CH_2 pentanoic acid), 25.5 (CH_2 succinimide), 28.2 (CH adamantane), 28.5, 30.6 (CH_2 pentanoic acid), 34.0 (Cq adamantane), 37.2, 40.0 (CH_2 adamantane), 70.6 (CH_2 pentanoic acid), 81.9 (CH_2 methoxy), 168.6 (C=O pentanoic acid), 169.1 ppm, (C=O succinimide); IR (thin film): $\tilde{\nu}=2895$, 1700, 1265, 1245, 1116, 1093 cm^{-1}.



Scheme 2. *Reagents and conditions*: a) TEMPO, BAIB, CH_2Cl_2/*t*BuOH/H_2O (6:3:1 *v/v/v*); b) EDC·HCl, *N*-hydroxysuccinimide; c) HCl, EtOH; d) AcOH, THF/H_2O, then MsCl, pyridine.

Nonanoic acid *N*-hydroxysuccinimide ester (**52**): Synthesized according to the general procedure for condensing *N*-hydroxysuccinimide starting from **51**. Yield 3.10 g (12.2 mmol, 96%); $R_f = 0.45$ (EtOAc/PE 1:3, *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H, CH_3), 1.28–1.44 (m, 10H, 5×H_2 nonanoic acid), 1.74 (dt, $J = 7.2$, 7.6 Hz, 2H, H_2-3 nonanoic acid), 2.60 (t, $J = 7.6$ Hz, 2H, H_2-2 nonanoic acid), 2.83 ppm, (br s, 4H, 2×H_2 succinimide); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 22.6, 24.5 (CH_2 nonanoic acid), 25.6 (CH_2 succinimide), 28.8, 29.0, 30.9, 31.7 (CH_2 nonanoic acid), 168.8 (C=O nonanoic acid), 169.1 ppm, (C=O succinimide); IR (thin film): $\tilde{\nu} = 2921$, 1815, 1784, 1720, 1208, 1069 cm^{-1}.

3-(4-Methoxyphenoxy)propanoic acid (**54**): 4-Methoxyphenyl-2-cyanoethyl ether (**53**, 15.0 g, 84.6 mmol) was dissolved in concentrated HCl (37%, 32 mL) and held at reflux for 8 h. The mixture was filtered and the filter cake rinsed with H_2O. The solids were dissolved in aqueous NaOH (1 M, 100 mL) and the mixture was filtered. The filtrate was acidified and the formed crystals were isolated by filtration, rinsed with H_2O and dried under reduced pressure. Yield 13.86 g (70.6 mmol, 83%); $R_f = 0.40$ (EtOAc/PE 1:1, *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.82$ (t, $J = 6.4$ Hz, 2H, H_2 propanoic acid), 3.76 (s, 3H, OMe), 4.20 (t, $J = 6.4$ Hz, 2H, H_2 propanoic acid), 6.81–6.87 ppm, (m, 4H, Harm phenoxy); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.5$ (CH_2 propanoic acid), 55.7 (OMe), 63.9 (CH_2 propanoic acid), 114.7, 118.8 (CHarm phenoxy), 152.5, 154.2 (Cq phenoxy), 177.1 ppm, (C=O propanoic acid); IR (thin film): $\tilde{\nu} = 2932$, 1687, 1506, 1222, 1047 cm^{-1}.

3-(4-Methoxyphenoxy)propanoic acid *N*-hydroxysuccinimide ester (**55**): Synthesized according to the general procedure for condensing *N*-hydroxysuccinimide starting from **54**. Yield 2.93 g (55.0 mmol, 98%); $R_f = 0.50$ (EtOAc/PE 1:1, *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.84$ (br s, 4H, 2×H_2 succinimide), 3.08 (t, $J = 6.4$ Hz, 2H, H_2 propanoic acid), 3.77 (s, 3H, OMe), 4.28 (t, $J = 6.4$ Hz, 2H, H_2 propanoic acid), 6.89–6.82 ppm, (m, 4H, Harm phenoxy); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.6$ (CH_2 succinimide), 31.7 (CH_2 propanoic acid), 55.7 (OMe), 63.4 (CH_2 propanoic acid), 114.7, 116.1 (CHarm phenoxy), 166.0 (C=O propanoic acid), 168.8 ppm, (C=O succinimide); IR (thin film): $\tilde{\nu} = 1816$, 1778, 1736, 1506, 1207, 1075 cm^{-1}.

Mesylate 6. Compound **5** (6.00 g, 12.3 mmol) was dissolved in a mixture of AcOH, THF and H_2O (100 mL, 3/1/1, *v/v/v*) and subsequently stirred for 48 h. The volatiles were evaporated and the residue purified by silica gel column chromatography with EtOAc and PE as eluent (1:1→1:0, *v/v*) yielding the free primary hydroxy compound as a white solid (2.87 g, 11.4 mmol 93%); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.59$ (d, 1H, $J = 10.2$ Hz, 1H, Ha hydroxymethyl), 3.75 (d, $J = 11.4$ Hz, 1H, Hb hydroxymethyl), 3.79 (m, 1H, H-4 oxazolidine), 4.20 (s, 4H, 2×H_2 ethylene), 4.50 (s, 1H, OH), 5.20 (d, $J = 6.0$ Hz, 1H, H-5 oxazolidine), 6.77–6.87 (m, 3H, Harm), 7.27 ppm, (s, 1H, NH); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 61.8$ (C-4 oxazolidine), 62.8 (CH_2 hydroxymethyl), 64.1, 64.2 (CH_2 ethylene), 79.6 (C-4 oxazolidine), 115.1, 117.6, 119.1 (CHarm), 131.4, 143.6, 144.0 (Cq Carm), 160.1 ppm, (C=O); IR (thin film): $\tilde{\nu} = 1733$, 1511, 1350, 1287, 1164, 1124, 1065 cm^{-1}; LC–MS: $t_R = 4.83$ min (linear gradient 10→90% B); ESI-MS: $m/z = 252.0$ $[M+H]^+$, 503.1 $[2M+H]^+$. To a cooled (−20 °C) solution of the desilylated compound (2.864 g, 11.4 mmol) in pyridine (110 mL) was added methanesulfonyl chloride (28.5 mmol, 3.26 g, 2.2 mL). After 2 h the reaction was quenched by the addition of EtOH (2 mL) and the volatiles evaporated. The residue was dissolved in EtOAc (100 mL), and the organic layer washed with aqueous HCl (1 M, 4×20 mL), aqueous saturated $NaHCO_3$ (2×20 mL), brine (20 mL) and subsequently dried (Na_2SO_4) and filtered. The volatiles were evaporated and the residue purified by silica gel column chromatography with EtOAc and PE as eluent (1:1→1:0, *v/v*) yielding the title compound as colorless oil (2.86 g, 11.4 mmol 76%); $R_f = 0.50$ (neat EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.11$ (s, 3H, H_3 Ms), 4.01 (dt, $J = 4.4$, 5.5 Hz, 1H, H-5 oxazolidine), 4.26 (dd, 1H, $J = 5.4$, 10.4 Hz, 1H, Ha methyl methanesulfonate), 4.27 (s, 4H, 2×H_2 ethylene), 4.34 (dd, $J = 4.4$, 10.7 Hz, 1H, Hb methyl methanesulfonate), 5.21 (d, $J = 5.7$ Hz, 1H, H-4 oxazolidine), 6.83–6.91 (m, 3H, Harm, NH), 7.33 ppm (s, 1H Harm); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 37.5$ (CH_3 Ms), 59.0 (C-5 oxazolidine), 64.2, 64.3 (CH_2 ethylene), 68.2 (CH_2 methyl methanesulfonate), 78.9 (C-4 oxazolidine), 114.8, 117.8, 118.8 (CHarm), 130.4, 143.8 ppm (Cq Carm); IR (thin film): $\tilde{\nu} = 1733$, 1511, 1350, 1287, 1164, 1124, 1065 cm^{-1}; LC–MS: $t_R = 4.63$ min (linear gradient 10→90% B); ESI-MS: $m/z = 330.1$ $[M+H]^+$, 346.9 $[M+NH_4]^+$, 659.1 $[2M+H]^+$, 676.1 $[2M+NH_4]^+$.

General procedure for reaction pyrrolidines, piperidines and morpholine with mesylate 6. Two stock solutions were prepared: stock solution **A** containing a pyrrolidine, a piperidine or morpholine in *N*,*N*-dimethylformamide (DMF, 0.4 mM), stock solution **B** with mesylate **6** in DMF (0.4 mM); 1 mL of stock solution **A** was added to 1 mL of stock solution **B** and successively 3 equivalents of K_2CO_3 were added. The mixture was stirred at 80 °C for 72 h. The mixture was filtered and the volatiles evaporated and the residue purified by silica gel column chromatography with MeOH, EtOAc and NH_4OH as solvent system (0:99:1→50:49:1, *v/v/v*) (Scheme 3).

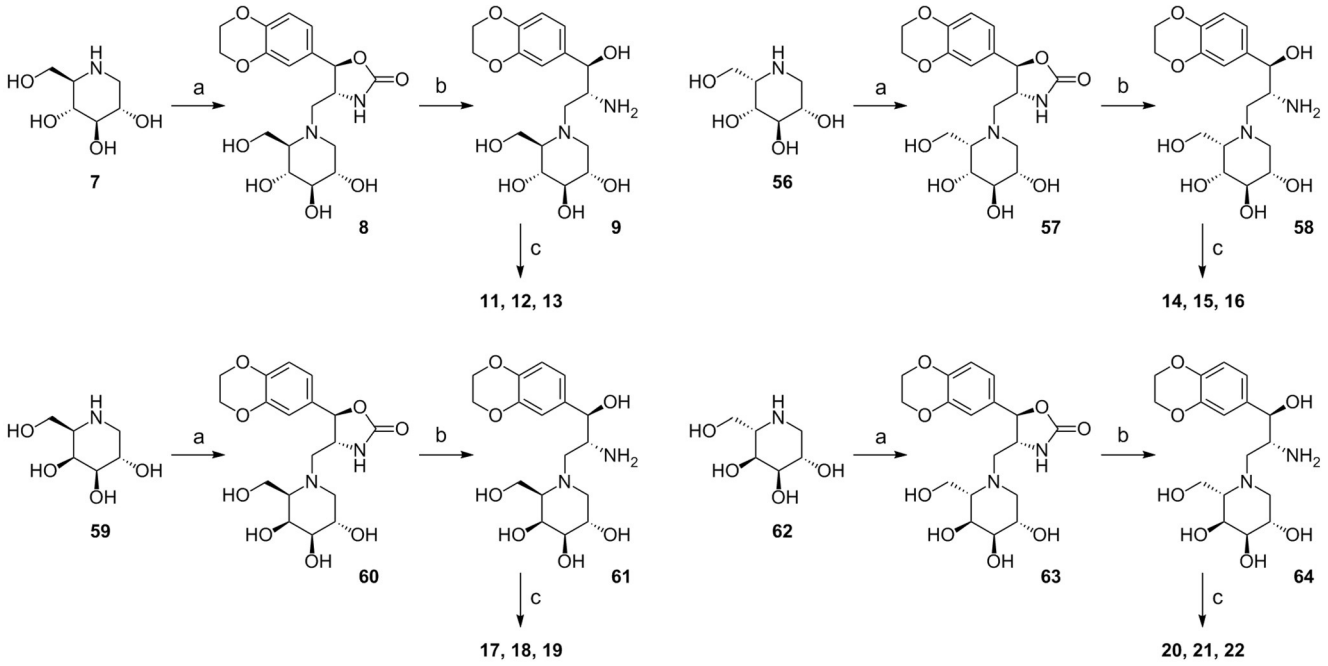
General procedure for oxazolidine saponification. The oxazolidine derivative (1 μmol/35 μL solvent system) was dissolved in a mixture of dioxane and H_2O (3:2, *v*/*v*) in a microwave tube. Subsequently, 13 equivalents of LiOH were added and the microwave tube sealed and heated for 30 min at 165 °C. The mixture was neutralized by the addition of aqueous HCl (1 M). The solvents were evaporated and the residue purified, for compounds **9**, **58**, **64**, **76**, **100**, **102** and **104** by silica gel column chromatography with MeOH, EtOAc and NH_4OH as solvent system (0:99:1→50:49:1, *v*/*v*/*v*). Compounds **61**, **70**, **82**, **88**, **94** and **98** were used as crudes in the next step, after HPLC analysis showed complete consumption of the starting oxazolidine derivative, without the column chromatography purification step.

General procedure for condensing hydroxysuccinimide esters 10, 42 and 55 with secondary amines. Three stock solutions were prepared: stock solution **A** containing amino alcohol in DMF (1 μmol/40 μL DMF), stock solution **B** with hydroxysuccinimide ester (1 μmol/70 μL DMF) and stock solution **C** consisting of DiPEA in DMF (1 μmol/2 μL DMF). To stock solution **A** were added 1.1 equivalents of stock solution **B** followed by addition of 1.75 equivalents of stock solution of **C**. The mixture was stirred for 18 h. The volatiles were evaporated and the residue purified by RP-HPLC.

Compound 8: Compound **7** was reacted with mesylate **6** according to the general procedure described above. Yield 0.081 g (0.204 mmol, 84%); R_f = 0.50 (MeOH/EtOAc/NH_4OH 40:60:5, *v*/*v*/*v*). $[\alpha]_D^{20}$ = 25.2 (*c* = 0.81 MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 2.07 (dd, *J* = 10.4, 11.4 Hz, 1H, H-1a), 2.12 (ddd, *J* = 2.5, 3.5, 9.6 Hz, 1H, H-5), 2.51 (dd, *J* = 5.3, 13.0 Hz, 1H, H-1′a), 2.85 (dd, *J* = 4.8, 11.3 Hz, 1H, H-1b), 3.13 (t, *J* = 8.9 Hz, 1H, H-3), 3.16 (dd, *J* = 8.8, 13.2 Hz, 1H, H-1′b), 3.22–3.28 (m, 1H, H-2), 3.33 (t, *J* = 8.8 Hz, 1H, H-4), 3.84–3.89 (m, 2H, H-2′, H-6a), 3.93 (dd, *J* = 2.6, 12.1 Hz, 1H, H-6b), 4.22 (s, 4H, 2×H_2 ethylene), 5.40 (d, *J* = 5.3 Hz, 1H, H-3′), 6.82–6.88 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 57.3 (C-1′), 58.6 (C-1), 59.8 (C-6), 59.9 (C-2′), 65.6 (2×CH_2O), 68.8 (C-5), 70.4 (C-2), 72.0 (C-4), 80.5 (C-3), 83.3 (C-3′), 116.0, 118.5, 120.0 (CHarm), 134.1, 145.2, 145.4 (Cq Carm), 161.6 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3332, 2920, 1734, 1647, 1593, 1508, 1437, 1288, 1067, 1010, 922 cm^{-1}; LC–MS: t_R = 5.44 min (linear gradient 0→50% B); ESI-MS: *m*/*z* = 397.0 $[M+H]^+$, 793.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{18}H_{25}N_2O_8$ 397.16054, found 397.16048.

Compound 9: The oxazolidine in compound **8** was hydrolyzed according to the saponification procedure described above. Yield 0.069 g (186 μmol, 91%); R_f = 0.40 (EtOH/Et_2O/NH_4OH 6:3:1, *v*/*v*/*v*). $[\alpha]_D^{20}$ = 15.1° (*c* = 0.33 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 2.34 (ddd, *J* = 3.0, 4.5, 9.8 Hz, 1H, H-5), 2.43 (dd, *J* = 10.8, 11.8 Hz, 1H, H-1a), 2.63 (dd, *J* = 10.3, 15.0 Hz, 1H, H-1′a), 2.74 (dd, *J* = 4.7, 14.9 Hz, 1H, H-1′b), 2.95 (dd, *J* = 4.9, 11.9 Hz, 1H, H-1b), 3.26 (t, *J* = 9.1 Hz, 1H, H-3), 3.35 (t, *J* = 9.4 Hz, 1H, H-4), 3.56 (ddd, *J* = 4.9, 9.2, 10.6 Hz, 1H, H-2), 3.60 (ddd, *J* = 4.7, 8.0, 10.4 Hz, 1H, H-2′), 3.69 (dd, *J* = 2.8, 12.5 Hz, H-6a), 3.81 (dd, *J* = 4.5, 12.6 Hz, H-6b), 4.34 (brs, 4H, 2×H_2 ethylene), 4.65 (d, *J* = 7.9 Hz, 1H, H-3′), 6.91–7.07 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 50.7 (C-1′), 56.0 (C-2′), 57.7 (C-1), 58.0 (C-6), 64.6 (2×CH_2O), 66.3 (C-5), 68.4 (C-2), 69.8 (C-4), 71.6 (C-3′), 78.2 (C-3), 115.5, 117.8, 120.0 (CHarm), 132.7, 143.4, 142.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3329, 2924, 1508, 1286, 1067, 1041 cm^{-1}; LC–MS: t_R = 4.08 min (linear gradient 0→50% B); ESI-MS: *m*/*z* = 370.9 $[M+H]^+$, 741.4 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{17}H_{27}N_2O_7$ 371.18128, found 371.18130.

Compound 11: Compound **9** was reacted with **10** according to the general condensation protocol described above. Yield 0.020 g (32 μmol, 77%). $[\alpha]_D^{20}$ = 11.0 (*c* = 0.40 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 1.16–1.35 (m, 4H, H_2-3″, H_2-4″), 1.54 (brs, 6H, H_2 adamantane), 1.66–1.75 (m, 6H, H_2 adamantane), 1.97 (brs, 3H CH adamantane), 2.15 (brs, 2H, H_2-2″), 2.79 (s, 2H, H_2 adamantane), 3.01 (dd, *J* = 10.4, 14.4 Hz, 1H, H-1a), 3.13 (brs, 1H, H-5), 3.31 (t, *J* = 6.0 Hz, H_2-2″), 3.40 (brs, 1H, H-1′a), 3.49 (t, *J* = 9.2 Hz, 1H, H-3), 3.58 (brd, *J* = 8.2 Hz, 1H, H-1b), 3.69 (t, *J* = 9.7 Hz, 1H, H-4), 3.77–3.84 (m, 2H, H-1′b, H-2), 4.06 (q, *J* = 12.4 Hz, H_2-6), 4.18 (brs, 4H, 2×H_2 ethylene), 4.51 (brs, 1H, H-2′), 4.96 (brs, 1H, H-3′), 6.80–6.92 ppm (m, 3H, Harm); ^{13}C NMR (150 MHz, D_2O): δ = 22.0 (C-3″), 28.3 (CH ada-



Scheme 3. *Reagents and conditions*: a) **6**, K_2CO_3, DMF, 80 °C; b) LiOH, dioxane/H_2O, microwave, 165 °C; c) **10**, **52** or **55**, DiPEA, DMF.

mantane), 28.4 (C-4″), 33.8 (Cq adamantane), 35.3 (C-2″), 37.1 (CH_2 adamantane), 39.4 (CH_2 adamantane), 50.7 (C-2′), 53.6 (C-1), 54.2 (C-1′), 54.8 (C-6), 64.4 (2×CH_2O), 66.0 (C-2), 66.5 (C-5), 67.2 (C-4), 71.3 (C-5″), 72.5 (C-3′), 76.1 (C-3), 81.7 (OCH_2 adamantane), 115.0, 117.0, 119.3 (CHarm), 131.8, 142.7, 142.8 (Cq Carm), 176.0 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3322, 2902, 2848, 1654, 1508, 1287, 1069 cm^{-1}; LC–MS: t_R = 7.10 min (linear gradient 10→90% B); ESI-MS: *m/z* = 619.3 $[M+H]^+$, 1237.4 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{33}H_{51}N_2O_9$ 619.35891, found 619.35883.

Compound 12: Compound **9** was reacted with **52** according to the general condensation protocol described above. Yield 0.017 g (33 μmol, 77%). $[\alpha]_D^{20}$ = 15.1 (*c* = 0.33 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 0.89 (t, *J* = 6.9 Hz, 3H, CH_3), 1.01–1.16 (m, 2H, 1×H_2 nonanoic amide), 1.21–1.33 (m, 8H, 4×H_2 nonanoic amide), 1.37–1.47 (m, 2H, 1×H_2 nonanoic amide), 2.22 (td, *J* = 3.3, 7.2 Hz, 2H, H_2-2″), 3.19 (t, *J* = 11.9 Hz, 1H, H-1a), 3.26 (brd, *J* = 9.4 Hz, 1H, H-5), 3.48–3.55 (m, 1H, H-1′a), 3.55 (t, *J* = 9.4 Hz, 1H, H-3), 3.62 (dd, *J* = 4.7, 12.3 Hz, 1H, H-1b), 3.74 (t, *J* = 9.9 Hz, 1H, H-4), 3.82–3.90 (m, 2H, H-1′b, H-2), 4.05 (dd, *J* = 2.6, 12.4 Hz, 1H, H-6a), 4.13 (d, *J* = 13.5 Hz, 1H, H-6b), 4.34 (brs, 4H, 2×H_2 ethylene), 4.58 (td, *J* = 2.9, 9.2 Hz, 1H, H-2′), 4.99 (d, *J* = 3.4 Hz, 1H, H-3′), 6.93–7.05 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 13.5 (CH_3), 22.1, 25.1 28.1, 28.2, 28.4, 31.2, 35.6 (CH_2 nonanoic amide), 50.7 (C-2′), 53.5 (C-1), 54.1 (C-1′), 54.4 (C-6), 64.6 (2×CH_2O), 65.7 (C-2), 66.6 (C-5), 67.0 (C-4), 72.7 (C-3′), 75.9 (C-3), 114.9, 117.3, 119.4 (CHarm), 133.6, 142.8, 142.9 (Cq Carm), 177.6 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3324, 2927, 2854, 1670, 1508, 1287, 1200, 1136, 1068 cm^{-1}; LC–MS: t_R = 9.00 min (linear gradient 10→50% B); ESI-MS: *m/z* = 511.3 $[M+H]^+$, 1021.1 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{26}H_{43}N_2O_8$ 511.30139, found 511.30099.

Compound 13: Compound **9** was reacted with **55** according to the general condensation protocol described above. Yield 0.020 g (30 μmol, 71%). $[\alpha]_D^{20}$ = 13.7 (*c* = 0.52 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 2.69 (t, *J* = 5.8 Hz, 2H, H_2 propanoic acid), 3.17 (t, *J* = 11.9 Hz, 1H, H-1a), 3.27 (brd, *J* = 10.4 Hz, 1H, H-5), 3.49 (dd, *J* = 8.8, 13.6 Hz, 1H, H-1′a), 3.53 (t, *J* = 9.4 Hz, 1H, H-3), 3.61 (dd, *J* = 4.9, 12.4 Hz, 1H, H-1b), 3.73 (t, *J* = 9.9 Hz, 1H, H-4), 3.80–3.87 (m, 5H, OMe, H-1′b, H-2), 4.03 (dd, *J* = 3.1, 13.5 Hz, 1H, H-6a), 4.09 (dd, *J* = 2.9, 13.5 Hz, 1H, H-6b), 4.12 (t, *J* = 5.8 Hz, 2H, H_2 propanoic acid), 4.20 (m, 4H, 2×H_2 ethylene), 4.62 (td, *J* = 3.2, 9.2 Hz, 1H, H-2′), 4.96 (d, *J* = 3.8 Hz, 1H, H-3′), 6.86–7.054 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 35.8 (CH_2 propanoic acid), 50.9 (C-2′), 53.6 (C-1), 54.1 (C-1′), 54.4 (C-6), 56.0 (OMe), 64.5 (2×CH_2O), 65.3 (CH_2 propanoic acid), 65.7 (C-2), 66.8 (C-5), 67.0 (C-4), 72.6 (C-3′), 75.8 (C-3), 114.9, 115.2, 116.5, 116.7, 117.3, 119.5 (CHarm), 133.3, 142.8, 142.9, 152.3, 153.7 (Cq Carm), 174.3 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3312, 1668, 1508, 1288, 1202, 1136, 1034 cm^{-1}; LC–MS: t_R = 6.46 min (linear gradient 10→50% B); ESI-MS: *m/z* = 549.2 $[M+H]^+$, 1097.0 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{27}H_{37}N_2O_{10}$ 549.24427, found 549.24407.

Compound 57: Compound **56** was reacted with mesylate **6** according to the general procedure described above. Yield 0.038 g (96 μmol, 39%); R_f = 0.40 (MeOH/EtOAc/NH_4OH 40:60:5, *v/v/v*). $[\alpha]_D^{20}$ = 28.8 (*c* = 0.764 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 2.82 (brs, 2H, H_2-1), 3.06–3.23 (brm, 3H, H_2-1′, H-5), 3.41–3.73 (brm, 3H, H-2, H-3, H-4), 3.83–3.97 (brm, 3H, H-2′, H_2-6), 4.24 (s, 4H, 2×H_2 ethylene), 5.19 (d, 1H, *J* = 5.4 Hz, 1H, H-3′), 6.86–6.70 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 52.9 (C-1), 58.2 (C-6), 59.7 (C-2′), 59.9 (C-1′), 65.6 (2×CH_2O), 66.4 (C-5), 70.8, 72.8, 74.8 (C-2, C-3, C-4), 83.0 (C-3′), 116.1, 118.6, 120.1 (CHarm), 133.31, 145.3 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3264, 2924, 1734, 1668, 1508, 1436, 1289, 1202, 1132, 1067 cm^{-1}; LC–MS: t_R = 5.57 min (linear gradient 10→50% B); ESI-MS: *m/z* = 397.0 $[M+H]^+$, 793.0 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{18}H_{25}N_2O_8$ 397.16054, found 397.16049.

Compound 58: The oxazolidine in compound **57** was hydrolyzed according to the saponification procedure described above. Yield 0.027 g (72 μmol, 74%); R_f = 0.35 (EtOH/Et_2O/NH_4OH 3:6:1, *v/v/v*). $[\alpha]_D^{20}$ = 12.8 (*c* = 0.53 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 2.64 (dd, *J* = 6.0, 14.0 Hz, 1H, H-1′a), 2.66 (dd, *J* = 6.0, 13.2 Hz, 1H, H-1a), 2.73 (dd, *J* = 5.4, 13.5 Hz, 1H, H-1b), 2.97 (m, 1H, H-5), 2.99 (dd, *J* = 4.4, 14.0 Hz, 1H, H-1′b), 3.32 (t, *J* = 9.6 Hz, 1H, H-3), 3.47 (dt, *J* = 5.6, 9.6 Hz, 1H, H-2), 3.59 (dd, *J* = 5.7, 9.8 Hz, 1H, H-4), 3.60–3.64 (m, 1H, H-2′), 3.77 (dd, *J* = 6.0, 12.0 Hz, 2H, H_2-6), 4.32 (s, 4H, 2×H_2 ethylene), 4.64 (d, *J* = 8.0 Hz, 1H, H-3′), 6.92–6.98 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 49.0 (C-1), 53.2 (C-1′), 55.4 (C-2′), 56.0 (C-6), 64.5 (C-5), 64.6 (2×CH_2O), 68.5 (C-2), 70.0 (C-4), 71.6 (C-3′), 74.4 (C-3), 115.5, 117.7, 120.0 (CHarm), 132.8, 145.3, 143.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3289, 2927, 1672, 1508, 1287, 1201, 1135, 1067, 1046 cm^{-1}; LC–MS: t_R = 3.84 min (linear gradient 0→50% B); ESI-MS: *m/z* = 371.0 $[M+H]^+$, 741.41 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{17}H_{27}N_2O_7$ 371.18128, found 371.18131.

Compound 14: Compound **58** was reacted with **10** according to the general condensation protocol described above. Yield 0.005 g (7 μmol, 29%). $[\alpha]_D^{20}$ = 9.7 (*c* = 0.21 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 1.30–1.34 (m, 2H, H_2-4″), 1.41–1.50 (m, 2H, H_2-3″), 1.53 (brs, 6H, H_2 adamantane), 1.66–1.77 (m, 6H, H_2 adamantane), 1.98 (brs, 3H CH adamantane), 2.25 (m, 2H, H_2-2″), 3.04 (s, 2H, H_2 adamantane), 3.41 (t. *J* = 6.2 Hz, H_2-5″), 3.53 (t, *J* = 4.9 Hz, 2H, H_2-1), 3.73 (brs, *2*H, H_2-1′), 3.83 (brd, *J* = 5.7 Hz, 1H, H-3), 3.93 (brs, 1H, H-5), 3.98–4.05 (m, *2*H, H-2, H-4), 4.09–4.17 (m, *2*H, H_2-6), 4.31 (s, 4H, 2×H_2 ethylene), 4.65 (brs, 1H, H-2′), 4.96 (d, *J* = 2.7 Hz, 1H, H-3′), 6.90–7.01 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 21.1 (C-3″), 27.7 (C-4″), 28.0 (CH adamantane), 35.4 (C-2″), 36.7 (CH_2 adamantane), 39.3 (CH_2 adamantane), 50.4 (C-2′), 52.9 (C-1), 56.3 (C-1′), 63.4 (C-5), 64.5 (2×CH_2O), 66.8, 69.3 (C-2, C-4), 71.0 (C-5″), 72.5 (C-3′), 81.5 (CH_2 adamantane), 114.8, 117.3, 119.2 ppm (CHarm); IR (thin film): $\tilde{\nu}$ = 3325, 1635, 1201, 1145, 1068 cm^{-1}; LC–MS: t_R = 7.08 min (linear gradient 10→90% B); ESI-MS: *m/z* = 619.4 $[M+H]^+$, 1237.1 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{33}H_{51}N_2O_9$ 619.35891, found 619.35889.

Compound 15: Compound **58** was reacted with **52** according to the general condensation protocol described above. Yield 0.004 g (6 μmol, 25%). $[\alpha]_D^{20}$ = 17.6 (*c* = 0.08 MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 0.89 (t, *J* = 6.9 Hz, 3H, CH_3), 0.97–1.33 (m, 10H, 5×H_2 nonanoic amide), 1.36–1.46 (m, 2H, 1×H_2 nonanoic amide), 2.16–2.29 (m, 2H, H_2-2″), 3.53 (d, *J* = 5.1 Hz, 2H, H_2-1), 3.72 (brs, *2*H, H_2-1′), 3.82 (brs, 1H, H-3), 3.91 (brs, 1H, H-5), 3.99–4.09 (m, *2*H, H-2, H-4), 4.11–4.17 (m, *2*H, H_2-6), 4.35 (s, 4H, 2×H_2 ethylene), 4.63–4.66 (m, 1H, H-2′), 4.97 (d, *J* = 3.0 Hz, 1H, H-3′), 6.92–7.01 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ = 13.3 (CH_3), 22.1, 25.2 28.1, 28.3, 28.5, 29.7, 31.2, 35.6 (CH_2 nonanoic amide), 50.5 (C-2′), 53.1 (C-1), 55.7 (C-6), 56.6 (C-1′), 63.6 (C-5), 64.7 (2×CH_2O), 66.6 (C-2), 68.8 (C-3), 69.2 (C-4), 72.3 (C-3′), 114.8, 117.4, 119.3 (CHarm), 133.9, 142.7, 142.9 (Cq Carm), 178.3 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3267, 2927, 2856, 1670, 1508, 1286, 1199, 1136, 1066 cm^{-1}; LC–MS: t_R = 6.29 min (linear gradient 10→90% B); ESI-MS: *m/z* = 511.3 $[M+H]^+$, 1021.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{26}H_{43}N_2O_8$ 511.30139, found 511.30114.

Compound 16: Compound **58** was reacted with **55** according to the general condensation protocol described above. Yield 0.007 g (10 μmol, 41%). $[\alpha]_D^{20}$ = 11.8 (*c* = 0.14 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ = 2.64–2.75 (m, 2H, H_2 propanoic acid), 3.50 (d, *J* = 5.0 Hz,

2H, H_2-1), 3.71 (brs, 2H, H_2-1′), 3.81 (brs, 1H, H-3), 3.84 (s, 3H, OMe), 3.89 (brs, 1H, H-5), 3.93 (q, J=5.4 Hz, 1H, H-2), 4.02 (brs, 1H, H-4), 4.05–4.13 (m, 4H, H_2 propanoic acid, H_2-6), 4.16–4.23 (m, 4H, 2×H_2 ethylene), 4.68 (m, 1H, H-2′), 4.94 (d, J=3.3 Hz, 1H, H-3′), 6.85–7.01 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, D_2O): δ= 35.9 (CH_2 propanoic acid), 50.7 (C-2′), 53.0 (C-1), 56.0 (OMe), 56.6 (C-1′), 57.3 (C-6), 63.5 (C-5), 64.5 (2×CH_2O), 65.4 (CH_2 propanoic acid), 66.7 (C-2), 69.3 (C-4), 72.3 (C-3′), 114.8, 115.2, 116.6, 117.3, 119.3 (CHarm), 133.7, 142.7, 142.9, 152.3, 153.7 (Cq Carm), 174.8 ppm (C=O); IR (thin film): $\tilde{\nu}$=3325, 1635, 1508, 1201, 1143, 1066 cm^{-1}; LC–MS: t_R=5.01 min (linear gradient 10→90% B); ESI-MS: m/z=549.2 $[M+H]^+$, 1096.9 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{27}H_{37}N_2O_{10}$ 549.24427, found 549.24410.

Compound 60: Compound **59** was reacted with mesylate **6** according to the general procedure described above. Yield 0.056 g (141 μmol, 65%); R_f=0.65 (EtOAc/*t*BuOH/AcOH/H_2O, 1:1:1:1, *v/v/v/v*). $[\alpha]_D^{20}$=37.5 (*c*=1.12 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ= 2.15 (dd, J=9.8, 11.3 Hz, 1H, H-1a), 2.46 (q, J=3.0 Hz, 1H, H-5), 2.63 (dd, J=7.1, 13.4 Hz, 1H, H-1′a), 2.94 (dd, J=4.6, 11.6 Hz, 1H, H-1b), 3.06 (dd, J=6.6, 13.5 Hz, 1H, H-1′b), 3.28 (dd, J=3.2, 8.8 Hz, 1H, H-3), 3.74 (td, J=4.6, 9.1 Hz, 1H, H-2), 3.78–3.86 (m, 3H, H-2′, H_2-6), 3.97 (dd, J=2.4, 2.8 Hz, 1H, H-4), 4.23 (s, 4H, 2×H_2 ethylene), 5.25 (d, J=5.7 Hz, 1H, H-3′), 6.84–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ=58.2 (C-1′, C-1), 60.6 (C-2′), 62.6 (C-6), 65.6 (2×CH_2O), 66.5 (C-5), 68.6 (C-2), 72.6 (C-4), 76.6 (C-3), 82.9 (C-3′), 116.0, 118.6, 120.1 (CHarm), 133.6, 145.2, 145.4 (Cq Carm), 161.4 ppm (C=O); IR (thin film): $\tilde{\nu}$=3371, 2931, 1735, 1643, 1589, 1512, 1434, 1288, 1211, 1172, 1049 cm^{-1}; LC–MS: t_R=7.78 min (linear gradient 0→50% B); ESI-MS: m/z=397.2 $[M+H]^+$, 793.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{18}H_{25}N_2O_8$ 397.16054, found 397.16014.

Compound 61: The oxazolidine in compound **60** was hydrolyzed according to the saponification procedure described above. The obtained imine **61** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: t_R=3.65 min (linear gradient 0→50% B); ESI-MS: m/z=371.1 $[M+H]^+$.

Compound 17: Compound **61** was reacted with **10** according to the general condensation protocol described above. Yield 0.017 g (28 μmol, 38%). $[\alpha]_D^{20}$=9.3 (*c*=0.11 in MeOH); ^{1}H NMR (400 MHz, CD_3CN): δ=1.24–1.38 (m, 4H, H_2-4″, H_2-3″), 1.52 (brs, 6H, H_2 adamantane), 1.68–1.75 (m, 6H, H_2 adamantane), 1.94 (brs, 3H CH adamantane), 2.28 (m, 2H, H_2-2″), 2.97 (s, 2H, H_2 adamantane), 3.01–3.67 (m, 8H, H_2-5″, H_2-1, H_2-1′, H-3, H-5), 3.87–4.16 (m, 8H, H-2, H-4, H_2-6, 2×H_2 ethylene), 4.48 (brs, 1H, H-2′), 4.85 (d, J=3.2 Hz, 1H, H-3′), 6.82–6.84 ppm (m, 3H, Harm); IR (thin film): $\tilde{\nu}$=3242, 2901, 2849, 1668, 1506, 1287, 1202, 1181, 1134, 1070, 1020 cm^{-1}; LC–MS: t_R=9.77 min (linear gradient 10→60% B); ESI-MS: m/z=619.4 $[M+H]^+$, 1259.3 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{33}H_{51}N_2O_9$ 619.35891, found 619.35878.

Compound 18: Compound **61** was reacted with **52** according to the general condensation protocol described above. Yield 0.010 g (20 μmol, 27%); ^{1}H NMR (400 MHz, CD_3CN): δ=0.88 (t, J=7.0 Hz, 3H, CH_3), 1.07–1.46 (m, 12H, 6×H_2 nonanoic amide), 2.18 (m, 2H, H_2-2″), 2.94–3.67 (m, 6H, H_2-1, H_2-1′, H-3, H-5), 3.82–4.04 (m, 3H, H-2, H_2-6)), 4.13 (brs, 1H H-4), 4.22 (s, 4H, 2×H_2 ethylene), 4.37 (brs, 1H, H-2′), 4.80 (brs, 1H, H-3′), 6.76–6.98 ppm (m, 3H, Harm); IR (thin film): $\tilde{\nu}$=3298, 2927, 2858, 1675, 1287, 1202, 1134, 1069, 1020 cm^{-1}; LC–MS: t_R=8.17 min (linear gradient 10→60% B); ESI-MS: m/z=511.3 $[M+H]^+$, 1043.1 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{43}N_2O_8$ 511.30139, found 511.30108.

Compound 19: Compound **61** was reacted with **55** according to the general condensation protocol described above. Yield 0.011 g (20 μmol, 27%); ^{1}H NMR (400 MHz, CD_3CN): δ=2.64 (m, 2H, H_2 propanoic acid), 2.96–3.67 (m, 6H, H_2-1, H_2-1′, H-3, H-5), 3.74 (s, 3H, OMe), 3.83–4.10 (m, 6H, H-2, H-4, H_2-6, H_2 propanoic acid), 4.21 (m, 4H, 2×H_2 ethylene), 4.47 (m, 1H, H-2′), 4.82 (m, 1H, H-3′), 6.76–6.88 ppm (m, 7H, Harm); IR (thin film): $\tilde{\nu}$=3297, 2927, 2856, 1675, 1287, 1203, 1179, 1128, 1012 cm^{-1}; LC–MS: t_R=5.85 min (linear gradient 10→60% B); ESI-MS: m/z=549.3 $[M+H]^+$, 1118.9 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{27}H_{37}N_2O_{10}$ 549.24427, found 549.24395.

Compound 63: Compound **62** was reacted with mesylate **6** according to the general procedure described above. Yield 0.055 g (138 μmol, 55%); R_f=0.30 (MeOH/EtOAc/NH_4OH 20:80:5, *v/v/v*). $[\alpha]_D^{20}$=66.5 (*c*=0.99 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ=2.61 (dd, J=7.2, 12.3 Hz, 1H, H-1a), 2.69 (dd, J=4.0, 12.3 Hz, 1H, H-1b), 2.99–3.06 (m, 2H, H-1′a, H-5), 3.03 (dd, J=8.5, 13.3 Hz, 1H, H-1′b), 3.56 (dd, J=3.3, 7.1 Hz, 1H, H-3), 3.71 (dd, J=4.9, 11.6 Hz, 1H, H-6a), 3.75 (m, 1H, H-2), 3.78 (dd, J=5.3, 11.6 Hz, 1H, H-6b), 3.84–3.90 (m, 2H, H-2′, H-4), 4.24 (s, 4H, 2×H_2 ethylene), 5.13 (d, J= 6.0 Hz, 1H, H-3′), 6.84–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ=53.3 (C-1), 59.2 (C-1′, C-6), 59.9 (C-2′), 65.6 (2×CH_2O), 66.3 (C-5), 68.9 (C-4), 69.8 (C-2), 73.1 (C-3), 82.7 (C-3′), 116.1, 118.6, 120.1 (CHarm), 133.5, 145.3, 145.6 (Cq Carm), 161.4 ppm (C=O); IR (thin film): $\tilde{\nu}$=3300, 2927, 2362, 1735, 1652, 1593, 1510, 1396, 1290, 1018 cm^{-1}; LC–MS: t_R=5.56 min (linear gradient 10→50% B); ESI-MS: m/z=396.9 $[M+H]^+$, 793.1 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{18}H_{25}N_2O_8$ 397.16054, found 397.16045.

Compound 64: The oxazolidine in compound **63** was hydrolyzed according to the saponification procedure described above; R_f= 0.35 (EtOH/Et_2O/NH_4OH 3:6:1, *v/v/v*). $[\alpha]_D^{20}$=15.1° (*c*=0.33 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ=2.64 (dd, J=5.7, 14.0 Hz, 1H, H-1′a), 2.66 (dd, J=5.9, 13.3 Hz, 1H, H-1a), 2.73 (dd, J=5.4, 13.5 Hz, 1H, H-1b), 2.97 (m, Hz, 1H, H-5), 2.98 (dd, J=4.8, 13.9 Hz, 1H, H-1′b), 3.32 (t, J=9.4 Hz, 1H, H-3), 3.47 (td, J=5.5, 9.9 Hz, 1H, H-2), 3.59 (dd, J=5.7, 9.8 Hz, 1H, H-4), 3.63 (m, 1H, H-2′), 3.77 (d, J= 6.4 Hz, 2H, H_2-6), 4.32 (brs, 4H, 2×H_2 ethylene), 4.64 (d, J=8.0 Hz, 1H, H-3′), 6.89–7.03 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ=49.0 (C-1), 53.2 (C-1′), 55.4 (C-2′), 56.0 (C-6), 64.5 (C-5), 64.6 (2× CH_2O), 68.5 (C-2), 70.0 (C-4), 71.6 (C-3′), 74.4 (C-3), 115.5, 117.7, 120.0 (CHarm), 132.8, 143.3, 143.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$=3324, 2927, 2854, 1670, 1508, 1287, 1200, 1136, 1068 cm^{-1}; LC–MS: t_R=3.72 min (linear gradient 0→50% B); ESI-MS: m/z=371.1 $[M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{27}N_2O_7$ 371.18128, found 371.18131.

Compound 20: Compound **64** was reacted with **10** according to the general condensation protocol described above. Yield 0.017 g (28 μmol, 60%); ^{1}H NMR (400 MHz, CD_3CN): δ=1.27–1.36 (m, 2H, H_2-4″), 1.42–1.48 (m, 2H, H_2-3″), 1.52 (brs, 6H, H_2 adamantane), 1.64–1.75 (m, 6H, H_2 adamantane), 1.97 (brs, 3H CH adamantane), 2.16 (t, J=7.6 Hz, 2H, H_2-2″), 2.93 (s, 2H, H_2 adamantane), 3.19–3.24 (m, 2H, H-1′a, H-5), 3.28 (t, J=6.1 Hz, H_2-5″), 3.32–3.35 (m 1H, H-1a), 3.63 (dd, J=2.3, 12.6 Hz, 1H, H-1b), 3.71 (dd, J=10.6, 13.3 Hz, 1H, H-1′b), 3.89 (t, J=3.5 Hz, 1H, H-4), 3.94–4.01 (m, 4H, H-2, H-3, H_2-6), 4.22 (s, 4H, 2×H_2 ethylene), 4.36 (brs, 1H, H-2′), 4.77 (d, J=3.3 Hz, 1H, H-3′), 6.80–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): δ=23.2 (C-3″), 29.3 (CH adamantane), 29.6 (C-4″), 34.8 (Cq adamantane), 36.0 (C-2″), 37.9 (CH_2 adamantane), 40.5 (CH_2 adamantane), 52.3 (C-2′), 53.4 (C-1), 55.0 (C-6), 57.7 (C-1′), 64.1 (C-4), 64.6 (C-5), 65.4 (2×CH_2O), 66.6 (C-2), 68.6 (C-3), 71.7 (C-5″), 72.5 (C-3′), 82.6 (CH_2 adamantane), 115.9, 118.0, 119.8 (CHarm), 134.9, 144.4, 144.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$=3222,

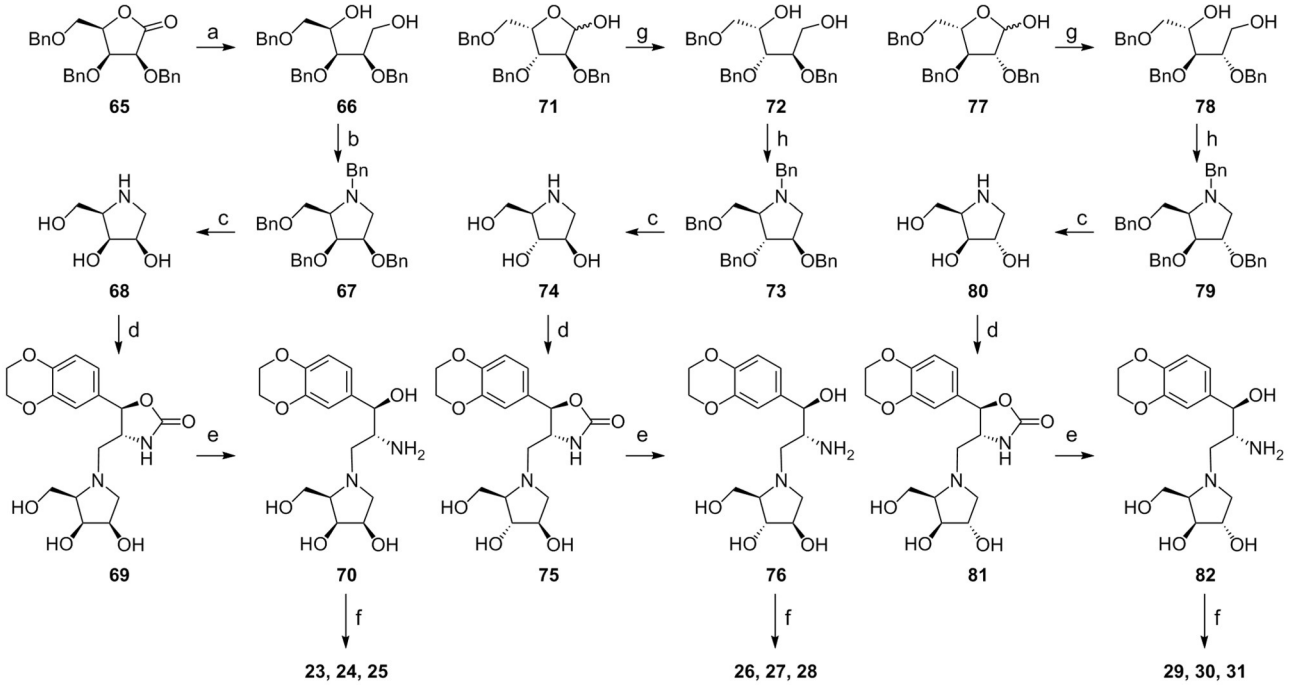
2904, 2850, 1662, 1436, 1287, 1200, 1179, 1066, 1017 cm^{-1}; LC–MS: t_R = 9.82 min (linear gradient 10→60% B); ESI-MS: m/z = 619.3 $[M+H]^+$, 1237.3 $[2M+H]^+$, 1259.3 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{33}H_{51}N_2O_9$ 619.35891, found 619.35877.

Compound 21: Compound **64** was reacted with **52** according to the general condensation protocol described above. Yield 0.013 g (25 μmol, 53%); ^{1}H NMR (400 MHz, CD_3CN): δ = 0.88 (t, J = 6.9 Hz, 3H, CH_3), 1.08–1.13 (m, 2H, H_2 nonanoic amide), 1.19–1.30 (m, 2H, 4×H_2 nonanoic amide), 1.35–1.42 (m, 2H, 1×H_2 nonanoic amide), 2.12 (t, J = 7.5 Hz, 2H, H_2-2″), 3.19–3.35 (m, 3H, H-1′a, H-5, H-1a), 3.63 (dd, J = 2.0, 12.8 Hz, 1H, H-1b), 3.71 (dd, J = 10.6, 13.2 Hz, 1H, H-1′b), 3.89 (dd, J = 3.2, 3.6 Hz, 1H, H-4), 3.95–4.01 (m, 4H, H-2, H-3, H_2-6), 4.22 (s, 4H, 2×H_2 ethylene), 4.36 (br s, 1H, H-2′), 4.77 (d, J = 3.2 Hz, 1H, H-3′), 6.81–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): δ = 14.4 (CH_3), 23.4, 26.3 29.7, 29.8, 30.0, 32.6, 36.3 (CH_2 nonanoic amide), 52.2 (C-2′), 53.4 (C-1), 55.0 (C-6), 57.9 (C-1′), 64.1 (C-4), 64.6 (C-5), 65.3 (2×CH_2O), 66.6 (C-2), 68.6 (C-3), 72.5 (C-3′), 115.9, 118.0, 119.8 (CHarm), 134.9, 144.3, 144.5 (Cq Carm), 173.7 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3293, 2928, 2854, 1675, 1506, 1287, 1202, 1184, 1130, 1068, 1020 cm^{-1}; LC–MS: t_R = 8.11 min (linear gradient 10→60% B); ESI-MS: m/z = 511.1 $[M+H]^+$, 1020.8 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{43}N_2O_8$ 511.30139, found 511.30106.

Compound 22: Compound **64** was reacted with **55** according to the general condensation protocol described above. Yield 0.009 g (16 μmol, 34%); ^{1}H NMR (400 MHz, CD_3CN): δ = 2.54–2.62 (m, 2H, H_2 propanoic acid), 3.21 (br s, 1H, H-1′a), 3.28–3.33 (m, 2H, H-5, H-1a), 3.63 (d, J = 12.3 Hz, 1H, H-1b), 3.73 (m, 4H, H-1′b, OMe), 3.89 (br s, 1H, H-3), 3.97–4.03 (m, 6H, H-2, H-4, H_2-6, H_2 propanoic acid), 4.20 (s, 4H, 2×H_2 ethylene), 4.39 (br s, 1H, H-2′), 4.79 (br s, 1H, H-3′), 6.78–6.89 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, CD_3CN): δ = 36.5 (CH_2 propanoic acid), 52.3 (C-2′), 53.6 (C-1), 55.1 (C-6), 56.2 (OMe), 58.0 (C-1′), 64.1 (C-4), 64.6 (C-5), 65.3 (2×CH_2O), 66.7 (C-2), 68.6 (C-3), 72.5 (C-3′), 115.6, 115.9, 116.6, 118.0, 119.8 (CHarm), 134.7, 144.4, 144.5, 153.3, 155.2 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3284, 2927, 2859, 1675, 1290, 1229, 1203, 1181, 1132, 1067, 1025 cm^{-1}; LC–MS: t_R = 5.86 min (linear gradient 10→60% B); ESI-MS: m/z = 549.1 $[M+H]^+$, 1096.7 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{27}H_{37}N_2O_{10}$ 549.24427, found 549.24394.

General procedure for Pd/C catalyzed hydrogenolysis. The perbenzylated iminosugar (7.5 mmol - 8 mmol) was dissolved in a mixture of 2 M HCl (aq.) in EtOH (0.05 M, 3/1, *v*/*v*) and transferred to a Parr high-pressure hydrogenation flask. The atmosphere was exchanged to argon after which a catalytic amount of palladium on carbon (~0.1 equiv, 10 wt% on carbon) was added. The flask was put under reduced pressure and ventilated with hydrogen gas. This procedure was repeated twice after which the pressure was adjusted to 4.5–5 bar hydrogen pressure. The reaction was allowed to react for 24 h while mechanically shaken and the pressure being kept at the value initially set. The mixture was filtered over a glass microfiber filter, followed by rinsing the filter with EtOH. The mixture was concentrated under reduced pressure followed by several co-evaporation steps with EtOH and MeOH to yield the deprotected iminosugar as hydrochloride salt (Scheme 4).

2,3,5-Tri-*O*-benzyl-D-lyxitol (**66**): 2,3,5-Tri-*O*-benzyl-D-lyxono-1,4-lactone (**65**, 11.9 g, 28.4 mmol) in THF (120 mL) was slowly added to a solution of $LiAlH_4$ (2.6 g, 68 mmol) in THF (120 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, after which the reaction was quenched with EtOAc. Sodium potassium tartrate (sat. aq.) was slowly added and the mixture was stirred for 30 min before EtOAc was added and the layers separated. The organic layer was washed with $NaHCO_3$ (sat. aq.) and brine before being dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (50% EtOAc/*n*-pentane) yielding the title compound (10.7 g, 25.4 mmol, 89% yield); R_f = 0.6 (EtOAc/*n*-pentane 1:1, *v*/*v*). $[\alpha]_D^{20}$ = −18.9° (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 2H, OH-1, OH-4), 3.46 (dd, J = 9.5, 6.1 Hz, 1H, H-5a), 3.53 (dd, J = 9.4,



Scheme 4. *Reagents and conditions*: a) $LiAlH_4$, THF, 0 °C; b) 1) PH_3P, I_2, imidazole, DMF, −35 °C, 2) $PhNH_2$, 55 °C; c) H_2, Pd/C, HCl, EtOH; d) **6**, K_2CO_3, DMF, 80 °C; e) LiOH, dioxane/H_2O, microwave, 165 °C; f) **10**, **52** or **55**, DiPEA, DMF; g) $NaBH_4$, EtOH; h) 1) MsCl, pyridine, 0 °C, 2) $PhNH_2$, 55 °C.

6.1 Hz, 1H, H-5b), 3.71–3.68 (m, 1H, H-2), 3.76–3.71 (m, 1H, H-1a), 3.79 (dd, $J=6.4$, 2.1 Hz, 1H, H-3), 3.90–3.82 (m, 1H, H-1b), 4.00 (td, $J=6.1$, 2.1 Hz, 1H, H-4), 4.46 (d, $J=11.9$ Hz, 1H, *H*H Bn), 4.51 (d, $J=12.0$ Hz, 1H, *H*H Bn), 4.52 (d, $J=11.1$ Hz, 1H, *H*H Bn), 4.61 (s, 2H, H_2 Bn), 4.73 (d, $J=11.1$ Hz, 1H, *H*H Bn), 7.24–7.39 ppm (m, 15H, Harm Bn); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=60.6$ (C-1), 69.8 (C-4), 71.3 (C-5), 72.5, 73.5, 74.4 ($3\times CH_2$ Bn), 77.1 (C-3), 79.6 (C-2), 127.9–128.6 (CHarm Bn), 137.9, 137.9, 138.0 ppm (Cq Bn); IR (thin film): $\tilde{\nu}=$ 3061, 3030, 2920, 2864, 1497, 1454, 1395, 1362, 1327, 1308, 1265, 1246, 1207, 1090, 1049, 1026 cm^{-1}; HRMS [QTOF, MH^+] *m/z* calculated for $C_{26}H_{30}O_5$ 423.21660, found 423.21629.

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-lyxitol (**67**): 2,3,5-Tri-*O*-benzyl-D-lyxitol (**66**, 5.30 g, 12.5 mmol), triphenylphosphine (7.5 g, 28.8 mmol) and imidazole (2.6 g, 37.5 mmol) were co-evaporated thrice with dry toluene before being dissolved in CH_2Cl_2 (125 mL) and cooled to −30 °C. Iodine (7.6 g, 30 mmol) was slowly added and the reaction mixture stirred for 3 days at −35 °C, then 1 day at −25 °C. The solution was concentrated under reduced pressure, dry toluene (125 mL) was added and the mixture held at reflux for 2 h. The reaction mixture was diluted with Et_2O, washed with $Na_2S_2O_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was co-evaporated with Et_2O to get rid of the residual toluene and then dissolved in Et_2O after which it was filtered to remove most of the Ph_3PO. The crude 1,4-dideoxy-1,4-diiodo-2,3,5-tri-*O*-benzyl-L-ribitol (~12.5 mmol) was dissolved in benzylamine (41 mL, 375 mmol) and stirred for 2 days at 55 °C. The mixture was diluted with EtOAc, washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12.5–15% Et_2O/*n*-pentane) yielding the title compound (3.40 g, 6.80 mmol, 55% over two steps); $R_f=0.55$ (Et_2O/*n*-pentane 2:3, *v/v*).$[\alpha]_D^{20}=-36.0^\circ$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 2.56 (dd, $J=10.7$, 6.1 Hz, 1H, H-1a), 3.07 (dd, $J=10.7$, 4.9 Hz, 1H, H-1b), 3.17 (q, $J=6.0$ Hz, 1H, H-4), 3.59 (d, $J=13.6$ Hz, 1H, *H*H *N*-Bn), 3.68 (dd, $J=9.4$, 6.0 Hz, 1H, H-5a), 3.91 (dd, $J=9.4$, 6.1 Hz, 1H, H-5b), 3.95 (dt, $J=6.1$, 5.0 Hz, 1H, H-2), 4.05 (d, $J=13.7$ Hz, 1H, *H*H *N*-Bn), 4.07 (t, $J=5.3$ Hz, 1H, H-3), 4.50 (s, 2H, *H*H Bn), 4.52 (d, $J=$ 12.3 Hz, 1H, *H*H Bn), 4.54 (d, $J=12.4$ Hz, 1H, *H*H Bn), 4.61 (d, $J=$ 12.1 Hz, 1H, *H*H Bn), 4.74 (d, $J=12.1$ Hz, 1H, *CH*H Bn), 7.14–7.44 ppm (m, 20H, CHarm Bn); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=54.9$ (C-1), 59.8 (CH_2 *N*-Bn), 64.4 (C-4), 70.7 (C-5), 71.7 (CH_2 Bn-2), 73.0 (CH_2 Bn-3), 73.5 (CH_2 Bn-5), 77.4 (C-2), 78.8 (C-3), 126.9–128.9 (CHarm Bn), 138.6, 138.7, 138.8, 139.4 ppm (Cq Bn); IR (thin film): $\tilde{\nu}=$ 3061, 3028, 2913, 2862, 2793, 1495, 1452, 1398, 1364, 1344, 1308, 1281, 1256, 1207, 1142, 1090, 1061, 1026 cm^{-1}; HRMS [QTOF, MH^+] *m/z* calculated for $C_{33}H_{35}NO3$ 494.26897, found 494.26804.

1,4-Dideoxy-1,4-imino-D-lyxitol hydrochloride (**68**): 1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-lyxitol (**67**, 3.95 g, 8 mmol) was subjected to the general hydrogenolysis procedure yielding the title compound (1.32 g, 7.8 mmol, 98%). $[\alpha]_D^{20}=23.4^\circ$ ($c=1.00$, MeOH); ^{1}H NMR (600 MHz, MeOD): $\delta=3.14$ (dd, $J=11.7$, 7.3 Hz, 1H, H-1a), 3.42 (dd, $J=11.7$, 7.3 Hz, 1H, H-1b), 3.64 (dt, $J=8.8$, 4.4 Hz, 1H, H-4), 3.89 (dd, $J=11.8$, 8.9 Hz, 1H, H-5a), 3.94 (dd, $J=$ 11.8, 4.6 Hz, 1H, H-5b), 4.21 (t, $J=4.0$ Hz, 1H, H-3), 4.40 ppm (td, $J=7.3$, 4.0 Hz, 1H, H-2); ^{13}C NMR (150 MHz, MeOD): $\delta=48.5$ (C-1), 59.3 (C-5), 64.5 (C-4), 71.3 (C-3), 71.8 ppm (C-2); IR (thin film): $\tilde{\nu}=$ 3404, 3221, 2976, 2930, 2891, 2783, 2733, 2716, 2666, 2583, 2480, 1601, 1460, 1412, 1350, 1287, 1269, 1202, 1115, 1040 cm^{-1}; HRMS [QTOF, MH^+] *m/z* calculated for $C_5H_{11}NO_3$ 134.08117, found: 134.08122.

Compound 69: Compound **68** was reacted with mesylate **6** according to the general procedure described above. Yield 0.084 g (230 μmol, 58%); $R_f=0.50$ (MeOH/EtOAc/NH_4OH 40:60:5, *v/v/v*). $[\alpha]_D^{20}=21.8$ ($c=0.96$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta=2.56$ (dd, $J=5.3$, 10.1 Hz, 1H, H-1a), 2.71 (dd, $J=5.8$, 12.4 Hz, 1H, H-1′a), 2.77 (dt, 1H, $J=4.3$, 7.3 Hz, H-4), 2.89 (dd, $J=3.2$, 10.4 Hz, 1H, H-1b), 2.91 (dd, $J=8.4$, 12.4 Hz, 1H, H-1′b), 3.67 (dd, $J=4.0$, 11.2 Hz, 1H, H-5a), 3.73 (ddd, $J=4.8$, 6.0, 8.4 Hz, 1H, H-2′), 3.74 (dd, $J=4.4$, 11.2 Hz, 1H, H-5b), 4.08 (dt, $J=3.3$, 5.1 Hz, 1H, H-2), 4.22 (dd, $J=$ 4.8, 6.4 Hz, 1H, H-3), 4.23 (s, 4H, $2\times H_2$ ethylene), 5.27 (d, $J=5.1$ Hz, 1H, H-3′), 6.83–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta=59.8$ (C-1), 60.8 (C-2′), 60.8 (C-1′), 61.4 (C-5), 65.6 ($2\times$ CH_2O), 68.3 (C-4), 71.9 (C-2), 73.5 (C-3), 82.9 (C-3′), 115.9, 118.6, 119.9 (CHarm), 133.9, 145.2, 145.3 (Cq Carm), 161.4 ppm (C=O); LC–MS: $t_R=9.00$ min (linear gradient 0→90% B); ESI-MS: $m/z=366.9$ $[M+H]^+$, 733.0 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15012.

Compound 70: The oxazolidine in compound **69** was hydrolyzed according to the saponification procedure described above. The obtained imine **70** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: $t_R=3.63$ min (linear gradient 0→50% B); ESI-MS: $m/z=341.0$ $[M+H]^+$, 681.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{16}H_{25}N_2O_6$ 341.17071, found 341.17078.

Compound 23: Compound **70** was reacted with **10** according to the general condensation protocol described above. Yield 0.003 g (5 μmol, 20%). $[\alpha]_D^{20}=4.3$ ($c=0.06$ in MeOH); ^{1}H NMR (400 MHz, D_2O): $\delta=1.39$ (brs, 2H, H_2-4″), 1.45 (brs, 2H, H_2-3″), 1.54 (brs, 6H, H_2 adamantane), 1.65–1.78 (m, 6H, H_2 adamantane), 1.98 (brs, 3H CH adamantane), 2.26 (brs, 2H, H_2-2″), 3.05 (brs, 2H, H_2 adamantane), 3.37–3.60 (brm, 4H, H-1′a,H-1, H_2-5″), 3.75–3.98 (brm, 3H, H-1b, H-2, H-1′b), 4.08 (brs, 2H, H_2-5), 4.35 (brs, 4H, $2\times H_2$ ethylene), 4.53 (brs, 3H, H-2′, H-3, H-4), 4.94 (s, 1H, H-3′), 6.91–7.01 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta=23.3$ (C-3″), 29.4 (CH adamantane), 29.7 (C-4″), 34.9 (Cq adamantane), 36.2 (C-2″), 38.0 (CH_2 adamantane), 40.5 (CH_2 adamantane), 53.0 (C-2′), 58.0 (C-5), 59.6 (C-1′), 60.0 (C-1), 65.4 ($2\times CH_2O$), 70.0 (C-2), 71.5 (C-3, C-4), 71.8 (C-5″), 73.3 (C-3′), 82.6 (OCH_2 adamantane), 116.1, 118.0, 120.0 (CHarm), 134.4, 144.5, 144.6 (Cq Carm), 177.0 ppm (C=O); IR (thin film): $\tilde{\nu}=3369$, 1670, 1286, 1201, 1136 cm^{-1}; LC–MS: $t_R=9.79$ min (linear gradient 10→60% B); ESI-MS: $m/z=589.3$ $[M+H]^+$, 1177.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34833.

Compound 24: Compound **70** was reacted with **52** according to the general condensation protocol described above. Yield 0.013 g (27 μmol, 36%); ^{1}H NMR (400 MHz, CD_3CN): $\delta=0.89$ (t, $J=6.4$ Hz, 3H, CH_3), 1.15–1.58 (m, 12H, $6\times H_2$ nonanoic amide), 2.28 (brs, 2H, H_2-2″), 3.27–3.33 (m, 2H, H-1′a, H-1a), 3.60–3.68 (m, 3H, H-1b, H-2, H-1′b), 4.00 (brs, 2H, H_2-5), 4.22 (s, 4H, $2\times H_2$ ethylene), 4.39–4.46 (m, 3H, H-2′, H-3, H-4), 4.81 (brs, 1H, H-3′), 6.66–7.01 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta=14.4$ (CH_3), 23.4, 26.3 29.7, 29.8, 30.0, 32.6, 36.5 (CH_2 nonanoic amide), 53.1 (C-2′), 56.4 (C-5), 60.1 (C-1′), 60.5 (C-1), 65.4 ($2\times CH_2O$), 69.7 (C-2), 72.2 (C-3, C-4), 73.2 (C-3′), 116.1, 118.3, 120.0 (CHarm), 134.4, 144.4, 144.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}=3369$, 2900, 2848, 1670, 1508, 1286, 1201, 1136 cm^{-1}; LC–MS: $t_R=8.16$ min (linear gradient 10→60% B); ESI-MS: $m/z=481.2$ $[M+H]^+$, 960.7 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29060.

Compound 25: Compound **70** was reacted with **55** according to the general condensation protocol described above. Yield 0.036 g (70 μmol, 91%); ^{1}H NMR (400 MHz, D_2O): $\delta=2.60$ (brs, 2H, H_2-2″),

3.26–3.36 (m, 2H, H-1′a, H-1a), 3.61–3.65 (m, 2H, H-1b, H-2), 3.70–3.74 (m, 4H, H-1′b, OMe), 3.84–4.01 (m, 2H, H_2-5), 4.04–4.10 (m, 2H, H_2 propanoic acid), 4.20 (s, 4H, 2×H_2 ethylene), 4.34 (m, 1H, H-3), 4.41 (m, 1H, H4), 4.53 (m, 1H, H-2′), 4.82 (d, J=3.6 Hz, 1H, H-3′), 6.67–6.88 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, CD_3CN): δ= 36.7 (CH_2 propanoic acid), 52.9 (C-2′), 56.4 (OMe), 57.9 (C-5), 59.2 (C-1′), 59.8 (C-1), 65.5 (2×CH_2O), 65.6 (OCH_2 propanoic acid), 70.0 (C-2), 71.5 (C-3), 72.1 (C-4), 73.4 (C-3′), 115.7, 116.3, 116.8, 118.1, 120.2 (CHarm), 134.3, 144.5, 144.6, 153.5, 155.3 (Cq Carm), 174.0 ppm (C=O); IR (thin film): $\tilde{\nu}$=3277, 2925, 2856, 1675, 1508, 1436, 1286, 1229, 1201, 1181, 1127, 1067, 1020 cm^{-1}; LC–MS: t_R= 5.84 min (linear gradient 10→60% B); HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23342.

2,3,5-Tri-*O*-benzyl-L-xylitol (**72**): 2,3,5-Tri-*O*-benzyl-l-xylofuranose (**71**, 11.9 g, 28.3 mmol) was dissolved in EtOH (283 mL), cooled to 0 °C and $NaBH_4$ (2.5 g, 65 mmol) was added. The reaction was stirred for 5 h at room temperature after which the reaction mixture was adjusted to pH 4–5 with AcOH and the mixture concentrated. The residue was taken up in EtOAc and washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (70% EtOAc/*n*-pentane) yielding the title compound (11.0 g, 25.9 mmol, 92% yield). $[\alpha]_D^{20}$=10.6° (c=100, $CHCl_3$). Analytical data was in full agreement with its D-enantiomer **90**.

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-arabinitol (**73**): 2,3,5-Tri-*O*-benzyl-L-xylitol (**72**, 10.5 g, 24.9 mmol) was dissolved in pyridine (52 mL), cooled to 0 °C and methanesulfonyl chloride (9.7 mL, 124 mmol) was added. The reaction mixture was stirred at this temperature after which the reaction was quenched with H_2O and diluted with EtOAc. The suspension was washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$ and concentrated. The crude 1,4-di-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-L-xylitol (14.4 g, 24.9 mmol) was dissolved in benzylamine (81 mL, 750 mmol) and stirred at 55 °C overnight after which the reaction mixture was allowed to cool to room temperature and subsequently diluted with EtOAc. The mixture was washed with 1 M HCl (aq., 3x), $NaHCO_3$ (sat. aq.) and brine before being dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10–15% Et_2O/*n*-pentane) yielding the title pyrrolidine (10.5 g, 21 mmol, 84% yield over two steps); R_f=0.9 (acetone/toluene 1:9, *v/v*). $[\alpha]_D^{20}$=−40.0° (c=1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.56 (dd, J=10.7, 5.1 Hz, 1H, H-1a), 2.86 (q, J=5.3 Hz, 1H, H-4), 3.04 (d, J=10.7 Hz, 1H, H-1b), 3.49 (d, J=13.8 Hz, 1H, C*H*H *N*-Bn), 3.60 (d, J=5.7 Hz, 2H, H-5), 3.86–3.93 (m, 2H, H-2, H-3), 4.14 (d, J=13.3 Hz, 1H, C*H*H *N*-Bn), 4.37 (d, J=12.2 Hz, 1H, C*H*H Bn-2), 4.45 (d, J=12.2 Hz, 1H, C*H*H Bn-2), 4.50 (s, 2H, CH_2 Bn-3), 4.52 (s, 2H, CH_2 Bn-5), 7.19–7.37 ppm (m, 20H, CH_{Ar} Bn); ^{13}C NMR (100 MHz, $CDCl_3$): δ=57.1 (C-1), 59.2 (CH_2 N-Bn), 68.5 (C-4), 71.0 (CH_2 Bn-2), 71.4 (C-5), 71.5 (CH_2 Bn-3), 73.3 (CH_2 Bn-5), 81.6 (C-2), 86.0 (C-3), 127.0–129.1 (CHarm Bn), 138.3, 138.3, 138.5, 138.9 ppm (Cq Bn); IR (thin film): $\tilde{\nu}$=3061, 3028, 2891, 2857, 2797, 1495, 1452, 1366, 1333, 1258, 1206, 1153, 1092, 1074, 1026 cm^{-1}; HRMS [QTOF, MH^+] m/z calculated for $C_{33}H_{35}NO_3$ 494.26897, found 494.26795.

1,4-Dideoxy-1,4-imino-D-arabinitol hydrochloride (**74**): Compound **73** (3.95 g, 8.0 mmol) was subjected to the general hydrogenolysis procedure yielding the title compound (1.36 g, 8.0 mmol, quant.). $[\alpha]_D^{20}$=36.4° (c=1.00, MeOH); ^{1}H NMR (600 MHz, MeOD): δ=3.29 (d, J=12.0 Hz, 1H, H-1a), 3.47 (dd, J=12.0, 4.0 Hz, 1H, H-1b), 3.52 (ddd, J=9.0, 4.5, 2.7 Hz, 1H, H-4), 3.80 (dd, J=11.6, 9.3 Hz, 1H, H-5a), 3.90 (dd, J=11.6, 4.7 Hz, 1H, H-5b), 3.98 (s, 1H, H-3), 4.18–4.22 ppm (m, 1H, H-2); ^{13}C NMR (150 MHz, MeOD): δ= 51.9 (C-1), 60.9 (C-5), 69.8 (C-4), 76.1 (C-3), 77.4 ppm (C-2); IR (thin film): $\tilde{\nu}$=3416, 3372, 3277, 3022, 2968, 2959, 2941, 2887, 2833, 2762, 2745, 2488, 1576, 1449, 1396, 1375, 1360, 1298, 1260, 1215, 1167, 1109, 1074, 1038, 1003 cm^{-1}; HRMS [QTOF, MH^+] m/z calculated for $C_5H_{11}NO_3$ 134.08117, found 134.08169.

Compound 75: Compound **74** was reacted with mesylate **6** according to the general procedure described above. Yield 0.029 g (79 μmol, 32%); R_f=0.80 (MeOH/EtOAc/NH_4OH 40:60:5, *v/v/v*). $[\alpha]_D^{20}$=24.8° (c=0.58 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ=2.52 (p, 1H, J=4.6 Hz, H-4), 2.69 (dd, J=5.6, 12.4 Hz, 1H, H-1′a), 2.72 (dd, J=5.2, 10.0 Hz, 1H, H-1a), 2.87 (d, J=9.9 Hz, 1H, H-1b), 3.01 (dd, J=8.4, 12.4 Hz, 1H, H-1′b), 3.65 (dd, J=4.7, 11.2 Hz, 1H, H-5a), 3.71 (dd, J=4.3, 11.3 Hz, 1H, H-5b), 3.75 (ddd, J=4.8, 5.6, 8.4 Hz, 1H, H-2′), 4.83 (dd, J=2.4, 3.6 Hz, 1H, H-3), 3.91 (dd, J=2.1, 4.6 Hz, 1H, H-2), 4.23 (s, 4H, 2×H_2 ethylene), 5.29 (d, J=5.0 Hz, 1H, H-3′), 6.83–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ=60.8 (C-1′), 60.9 (C-2′), 61.1 (C-1), 63.3 (C-5), 65.6 (2×CH_2O), 74.6 (C-4), 77.5 (C-2), 80.4 (C-3), 82.9 (C-3′), 115.9, 118.6, 119.9 (CHarm), 134.0, 145.2, 145.3 (Cq Carm), 161.5 ppm (C=O); IR (thin film): $\tilde{\nu}$=3318, 2930, 2877, 1734, 1508, 1288, 1065, 1011 cm^{-1}; LC–MS: t_R= 5.77 min (linear gradient 0→60% B); ESI-MS: m/z=366.9 $[M+H]^+$, 732.9 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15009.

Compound 76: The oxazolidine in compound **75** was hydrolyzed according to the saponification procedure described above. Yield 0.016 g (48 μmol, 60%); R_f=0.50(EtOH/Et_2O/NH_4OH 3:6:1, *v/v/v*). $[\alpha]_D^{20}$=3.0 (c=0.33 in MeOH); ^{1}H NMR (400 MHz, D_2O): δ=2.45 (dd, J=7.8, 13.2 Hz, 1H, H-1′a), 2.48 (q, 1H, J=4.8 Hz, H-4), 2.72 (dd, J= 5.9, 13.3 Hz, 1H, H-1′b), 2.83 (dd, J=5.6, 11.0 Hz, 1H, H-1a), 3.04 (dd, J=2.2, 11.0 Hz, 1H, H-1b), 3.22 (q, J=6.2 Hz, 1H, H-2′), 3.62 (dd, J=5.0, 7.2 Hz, 1H, H-5a), 3.65 (dd, J=5.0, 7.2 Hz, 1H, H-5b), 3.88 (dd, J=2.8, 4.7 Hz, 1H, H-3), 4.07 (dd, J=2.5, 5.3 Hz, 1H, H-2), 4.31 (s, 4H, 2×H_2 ethylene), 4.58 (d, J=6.4 Hz, 1H, H-3′), 6.89–6.84 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, D_2O): δ=55.2 (C-2′), 56.8 (C-1′), 60.1 (C-1), 61.2 (C-5), 64.6 (2×CH_2O), 72.4 (C-4), 74.0 (C-3′), 75.7 (C-2), 79.0 (C-3), 115.5, 117.3, 120.0 (CHarm), 134.4, 142.8, 143.0 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$=3286, 2928, 1590, 1507, 1458, 1284, 1258, 1065 cm^{-1}; LC–MS: t_R=3.77 min (linear gradient 0→50% B); ESI-MS: m/z=341.0 $[M+H]^+$, 681.3 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{16}H_{25}N_2O_6$ 341.17071, found 341.17070.

Compound 26: Compound **76** was reacted with **10** according to the general condensation protocol described above. Yield 0.003 g (4 μmol, 29%). $[\alpha]_D^{20}$=15.9 (c=0.05 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ=1.40–1.47 (m, 2H, H_2-4″), 1.41–1.57 (m, 8H, H_2-3″, H_2 adamantane), 1.67–1.78 (m, 6H, H_2 adamantane), 1.95 (br s, 3H CH adamantane), 2.18 (t, J=7.4 Hz, 2H, H_2-2″), 2.96 (s, 2H, H_2 adamantane), 3.26 (dd, J=8.4, 13.6 Hz, 1H, H-1′a), 3.35 (t, J=6.2 Hz, 2H, H_2-5″), 3.43–4.46 (m, 1H, H-4), 3.49 (dd, J=3.6, 11.7 Hz, 1H, H-1a), 3.60 (d, J=11.7 Hz, 1H, H-1b), 3.93–3.99 (m, 4H, H-3, H_2-5, H-1′b), 4.16 (br s, 1H, H-2), 4.21 (br s, 4H, 2×H_2 ethylene), 4.58 (dt, J=3.2, 8.4 Hz, 1H, H-2′), 4.81 (d, J=3.5 Hz, 1H, H-3′), 6.77–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ=23.4 (C-3″), 29.8 (CH adamantane), 30.2 (C-4″), 36.7 (C-2″), 38.3 (CH_2 adamantane), 40.8 (CH_2 adamantane), 52.9 (C-2′), 59.1 (C-1′), 60.7 (C-5), 61.0 (C-1), 65.6 (2×CH_2O), 72.1 (C-5″), 74.4 (C-3′), 75.9 (C-2), 77.5 (C-3), 79.8 (C-4), 83.1 (OCH_2 adamantane), 116.4, 118.0, 120.2 ppm (CHarm); IR (thin film): $\tilde{\nu}$=3317, 1635, 1510, 1286, 1201, 1143, 1064, 1018 cm^{-1}; LC–MS: t_R=7.34 min (linear gradient 10→90% B); ESI-MS: m/z=589.4 $[M+H]^+$, 1177.3 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34826.

Compound 27: Compound **76** was reacted with **52** according to the general condensation protocol described above. Yield 0.005 g (10 μmol, 64%). $[\alpha]_D^{20} = 8.6$ ($c = 0.09$ in MeOH); ^{1}H NMR (400 MHz, MeOD): 0.91 (t, $J = 6.9$ Hz, 3H, CH_3), 1.20–1.35 (m, 10H, 5×H_2 nonanoic amide), 1.44–1.50 (m, 2H, H_2 nonanoic amide), 2.14 (t, $J = 7.5$ Hz, 2H, H_2-2″), 3.26 (dd, $J = 8.4$, 13.4 Hz, 1H, H-1′a), 3.43–4.45 (m, 1H, H-4), 3.48 (dd, $J = 3.5$, 11.6 Hz, 1H, H-1a), 3.60 (d, $J = 11.7$ Hz, 1H, H-1b), 3.92–4.00 (m, 4H, H-3, H_2-5, H-1′b), 4.15 (brs, 1H, H-2), 4.21 (brs, 4H, 2×H_2 ethylene), 4.58 (dt, $J = 3.1$, 8.2 Hz, 1H, H-2′), 4.80 (d, $J = 3.1$ Hz, 1H, H-3′), 6.77–6.92 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 14.3$ (CH_3), 23.7, 26.7 30.3, 30.4, 30.5, 33.0, 37.0 (CH_2 nonanoic amide), 52.9 (C-2′), 60.7 (C-1′), 60.9 (C-5), 61.1 (C-1), 65.6 (2×CH_2O), 74.5 (C-3′), 75.9 (C-2), 77.5 (C-3), 79.9 (C-4), 116.4, 117.9, 120.2 (CHarm), 135.2, 144.8, 145.6 (Cq Carm), 176.5 ppm (C=O); IR (thin film): $\tilde{\nu} = 3282$, 2927, 2856, 1672, 1508, 1434, 1288, 1201, 1137, 1068 cm^{-1}; LC–MS: $t_R = 6.44$ min (linear gradient 10→90% B); ESI-MS: $m/z = 481.3$ $[M+H]^+$, 960.9 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29057.

Compound 28: Compound **76** was reacted with **55** according to the general condensation protocol described above. Yield 0.007 g (13 μmol, 86%). $[\alpha]_D^{20} = 13.0$ ($c = 0.14$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta = 2.47$–2.68 (m, 2H, H_2-2″), 3.25 (dd, $J = 8.7$, 13.4 Hz, 1H, H-1′a), 3.42–4.46 (m, 1H, H-4), 3.50 (dd, $J = 3.4$, 11.9 Hz, 1H, H-1a), 3.60 (d, $J = 11.8$ Hz, 1H, H-1b), 3.74 (m, 3H, OMe), 3.90–4.17 (m, 7H, H-3, H_2-5, H-1′b, H-2, H_2 propanoic acid), 4.19 (brs, 4H, 2×H_2 ethylene), 4.62 (dt, $J = 3.0$, 8.6 Hz, 1H, H-2′), 4.80 (d, $J = 3.6$ Hz, 1H, H-3′), 6.71–6.91 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 36.7$ (CH_2 propanoic acid), 53.1 (C-2′), 56.1 (OMe), 60.6 (C-1′), 61.0 (C-5), 61.1 (C-1), 65.6 (2×CH_2O), 65.9 (OCH_2 propanoic acid), 74.6 (C-3′), 76.0 (C-2), 77.4 (C-3), 80.2 (C-4), 115.7, 116.4, 116.6, 117.9, 120.4 (CHarm), 135.1, 144.7, 144.8, 154.0, 155.7 (Cq Carm), 173.8 ppm (C=O); IR (thin film): $\tilde{\nu} = 3257$, 1639, 1508, 1288, 1201, 1143, 1066, 1016 cm^{-1}; LC–MS: $t_R = 5.04$ min (linear gradient 10→90% B); ESI-MS: $m/z = 519.2$ $[M+H]^+$, 1036.9 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23303.

2,3,5-Tri-*O*-benzyl-L-arabinitol (**78**): To a cooled solution (0 °C) of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**77**, 20 g, 48 mmol) in EtOH (500 mL) was added $NaBH_4$ (4.2 g, 111 mmol). After stirring for 5 h at room temperature, TLC analysis showed complete conversion of the starting material into a lower running product. The reaction mixture was adjusted to pH 4–5 by the addition of AcOH and the resulting mixture was concentrated, taken up in EtOAc and washed consecutively with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.), and brine. The organic layer was dried (anhydrous $MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (30–60% EtOAc/PE) yielding the title compound (17.0 g, 41.0 mmol, 85% yield) as turbid syrup; $R_f = 0.6$ (EtOAc/PE 1/1, *v*/*v*). $[\alpha]_D^{20} = -2.7°$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.89$ (bs, 1H, OH), 3.07 (bs, 1H, OH), 3.57–3.65 (m, 2H, C-5), 3.66–3.79 (m, 4H, C-1, C-2, C-3), 3.99 (q, $J = 5.1$ Hz, 1H, C-4), 4.47 (d, $J = 11.8$ Hz, 1H, C*H*H Bn), 4.50 (d, $J = 11.0$ Hz, 1H, C*H*H Bn), 4.53 (d, $J = 11.1$ Hz, 1H, C*H*H Bn), 4.57 (d, $J = 12.2$ Hz, 2H, 2xC*H*H Bn), 4.61 (d, $J = 11.6$ Hz, 1H, C*H*H Bn), 7.18–7.35 ppm (m, 15H, CHarm); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 61.3$ (C-1), 70.5 (C-4), 71.1 (C-5), 72.8, 73.4, 73.7 (3×CH_2 Bn), 78.4 (C-3), 79.5 (C-2), 127.8–128.4 (CHarm Bn), 137.9, 138.0 ppm (C_q Bn); IR (thin film): $\tilde{\nu} = 3482$, 3447, 3372, 3310, 3030, 2868, 2338, 1715, 1454, 1396, 1352, 1321, 1209, 1092, 1072, 1028, 1003 cm^{-1}; HRMS: $[M+H^+]$ Calculated for $C_{26}H_{30}O_5$, 423.21660, found 423.21658 cm^{-1}.

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-xylitol (**79**): 2,3,5-Tri-*O*-benzyl-L-arabinitol (**78**, 10.0 g, 23.7 mmol) was dissolved in pyridine (50 mL), cooled to 0 °C and methanesulfonyl chloride (9.2 mL, 118 mmol) was added. The mixture was stirred at this temperature for 5 h. The reaction was quenched with H_2O and the mixture taken up in EtOAc/1 M HCl (aq.), washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude 1,4-di-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-L-arabinitol (13.7 g, 23.7 mmol) was dissolved in benzylamine (78 mL, 710 mmol) and stirred overnight at 55 °C. The reaction mixture was diluted with EtOAc and washed with 1 M HCl (aq.), Na_2CO_3 (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10–17.5% Et_2O/*n*-pentane) yielding the title pyrrolidine (10.7 g, 21.7 mmol, 92% yield over two steps); $R_f = 0.7$ (Et_2O/*n*-pentane 2:3, *v*/*v*). $[\alpha]_D^{20} = -35.5°$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (dd, $J = 10.2$, 5.5 Hz, 1H, H-1a), 3.18 (q, $J = 5.8$ Hz, 1H, H-4), 3.31 (dd, $J = 10.2$, 6.3 Hz, 1H, H-1b), 3.52 (d, $J = 13.3$ Hz, 1H, C*H*H *N*-Bn), 3.70 (dd, $J = 9.6$, 5.2 Hz, 1H, H-5a), 3.90 (dd, $J = 9.6$, 6.0 Hz, 1H, H-5b), 4.04 (td, $J = 5.9$, 3.0 Hz, 1H, H-2), 4.11 (dd, $J = 6.2$, 2.9 Hz, 1H, H-3), 4.16 (d, $J = 13.3$ Hz, 1H, C*H*H *N*-Bn), 4.46 (s, 2H, H_2 Bn-2), 4.55 (d, $J = 12.0$ Hz, 1H, C*H*H Bn-5), 4.59 (d, $J = 12.0$ Hz, 1H, C*H*H Bn-5), 4.61 (d, $J = 12.1$ Hz, 1H, C*H*H Bn-3), 4.66 (d, $J = 12.1$ Hz, 1H, C*H*H Bn-3), 7.24–7.41 ppm (m, 20H, CHarm Bn); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 57.3$ (C-1), 59.5 (CH_2 N-Bn), 65.4 (C-4), 69.6 (C-5), 71.5 (CH_2 Bn-2), 72.2 (CH_2 Bn-3), 73.6 (CH_2 Bn-5), 82.2 (C-2), 83.6 (C-3), 127.0–129.1 (CHarm Bn), 138.3, 138.5, 138.6, 139.1 ppm (Cq Bn); IR (thin film): $\tilde{\nu} = 3061$, 3028, 2911, 2859, 2799, 1495, 1452, 1364, 1344, 1308, 1246, 1206, 1088, 1072, 1026, 1003 cm^{-1}; HRMS [QTOF, MH^+] m/z calculated for $C_{33}H_{35}NO_3$ 494.26897, found 494.26807.

1,4-Dideoxy-1,4-imino-D-xylitol hydrochloride (**80**): 1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-xylitol (**79**, 3.95 g, 8.0 mmol) was subjected to the general hydrogenolysis procedure yielding the title compound (1.38 g, 8.0 mmol, quant.). $[\alpha]_D^{20} = 13.3°$ ($c = 1$, MeOH); ^{1}H NMR (600 MHz, MeOD): $\delta = 3.16$ (d, $J = 12.3$ Hz, 1H, H-1a), 3.56 (dd, $J = 12.3$, 4.1 Hz, 1H, H-1b), 3.80 (ddd, $J = 9.1$, 4.5, 3.2 Hz, 1H, H-4), 3.87 (dd, $J = 11.7$, 9.1 Hz, 1H, H-5a), 3.96 (dd, $J = 11.7$, 4.5 Hz, 1H, H-5b), 4.16 (dd, $J = 3.3$, 1.5 Hz, 1H, H-3), 4.25 ppm (dd, $J = 4.0$, 1.5 Hz, 1H, H-2); ^{13}C NMR (150 MHz, MeOD): $\delta = 52.0$ (C-1), 59.0 (C-5), 65.1 (C-4), 75.8 (C-3), 76.1 ppm (C-2); IR (thin film): $\tilde{\nu} = 3341$, 3026, 2955, 2805, 2714, 2650, 2540, 2469, 2399, 2351, 2295, 1578, 1454, 1402, 1385, 1366, 1294, 1281, 1246, 1204, 1098, 1082, 1055, 1034, 1016 cm^{-1}; HRMS [QTOF, MH^+] m/z calculated for $C_5H_{11}NO_3$ 134.08117, found 134.08186.

Compound 81: Compound **80** was reacted with mesylate **6** according to the general procedure described above. Yield 0.019 g (52 μmol, 19%); $R_f = 0.65$ (EtOAc/*t*BuOH/AcOH/H_2O, 1:1:1:1, *v*/*v*/*v*/*v*). $[\alpha]_D^{20} = 45.3$ ($c = 0.38$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta = 2.55$ (dd, $J = 4.8$, 10.1 Hz, 1H, H-1a), 2.72 (dd, $J = 5.6$, 12.3 Hz, 1H, H-1′a), 2.86 (q, 1H, $J = 5.3$ Hz, H-4), 3.01 (dd, $J = 8.8$, 12.4 Hz, 1H, H-1′b), 3.20 (dd, $J = 5.6$, 10.1 Hz, 1H, H-1b), 3.68 (dd, $J = 5.1$, 11.2 Hz, 1H, H-5a), 3.71–3.78 (m, 1H, H-2′), 3.82 (dd, $J = 5.4$, 11.2 Hz, 1H, H-5b), 3.97 (t, $J = 5.2$ Hz, 1H, H-3), 4.02 (dd, $J = 3.4$, 5.8 Hz, 1H, H-2), 4.24 (s, 4H, 2×H_2 ethylene), 5.28 (d, $J = 5.4$ Hz, 1H, H-3′), 6.79–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 60.5$ (C-1), 61.0 (C-2′), 61.2 (C-1′), 62.1 (C-5), 65.6 (2×CH_2O), 68.6 (C-4), 77.6 (C-3), 79.2 (C-2), 83.1 (C-3′), 115.9, 118.5, 119.9 (CHarm), 134.1, 145.2, 145.3 (Cq Carm), 161.4 ppm (C=O); IR (thin film): $\tilde{\nu} = 3355$, 1735, 1650, 1512, 1288, 1126, 1064 cm^{-1}; LC–MS: $t_R = 5.55$ min (linear gradient 0→50% B); ESI-MS: $m/z = 367.2$ $[M+H]^+$, 733.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15006.

Compound 82: The oxazolidine in compound **81** was hydrolyzed according to the saponification procedure described above. The obtained imine **82** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: $t_R = 3.55$ min (linear gradient 0→50% B); ESI-MS: $m/z = 341.2$ $[M+H]^+$.

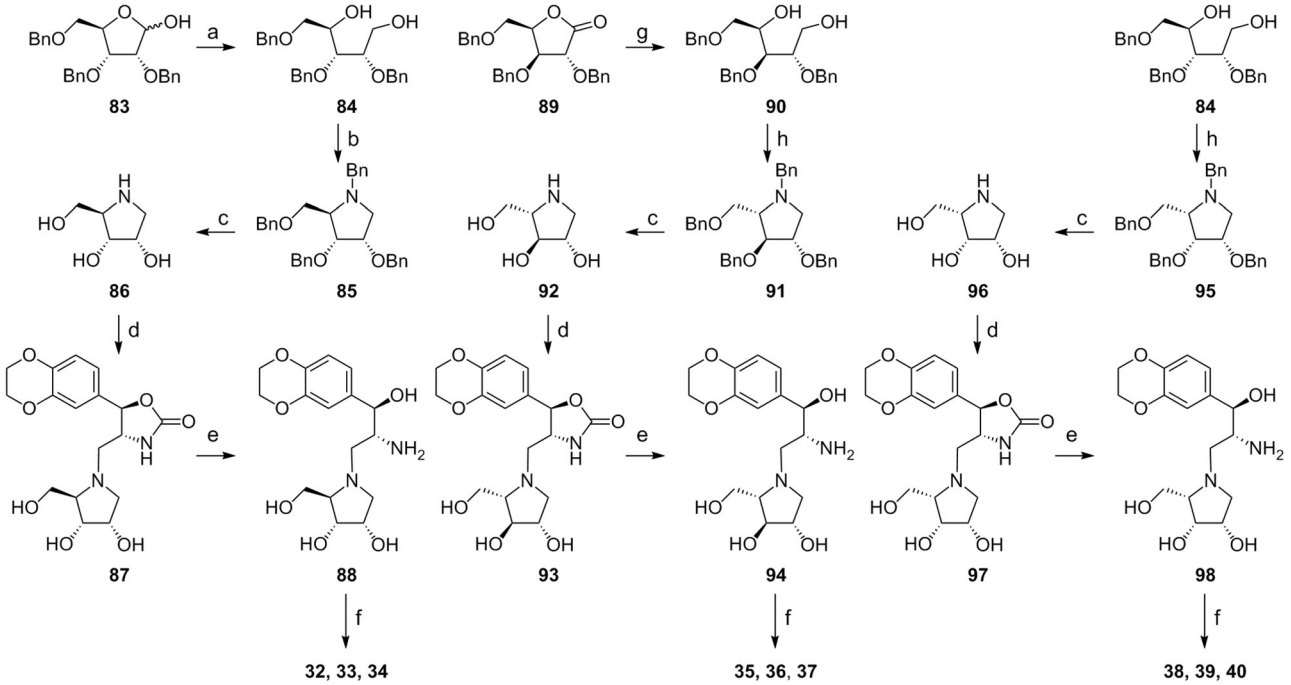
Compound 29: Compound **82** was reacted with **10** according to the general condensation protocol described above. Yield 0.003 g (5 μmol, 28%). (thin film): $\tilde{\nu} = 2931, 2856, 1700, 1684, 1653, 1509, 1423, 1205, 1183, 1136, 1017\ cm^{-1}$; LC–MS: $t_R = 9.95$ min (linear gradient 10→60% B); ESI-MS: $m/z = 589.3$ $[M+H]^+$, 1176.9 $[2M+H]^+$, 1201.5 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34810.

Compound 30: Compound **82** was reacted with **52** according to the general condensation protocol described above. Yield 0.002 g (4 μmol, 26%); IR (thin film): $\tilde{\nu} = 2929, 2856, 1684, 1653, 1509, 1206, 1131, 1022\ cm^{-1}$; LC–MS: $t_R = 8.40$ min (linear gradient 10→60% B); ESI-MS: $m/z = 481.2$ $[M+H]^+$, 961.0 $[2M+H]^+$, 983.1 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29053.

Compound 31: Compound **82** was reacted with **55** according to the general condensation protocol described above. Yield 0.002 g (3 μmol, 20%); IR (thin film): $\tilde{\nu} = 3360, 2625, 2857, 1684, 1506, 1205, 1180, 1134, 1131, 1027\ cm^{-1}$; LC–MS: $t_R = 6.01$ min (linear gradient 10→60% B); ESI-MS: $m/z = 519.1$ $[M+H]^+$, 1037.3 $[2M+H]^+$, 1058.9 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23339.

2,3,5-Tri-*O*-benzyl-D-ribitol (**84**): 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**83**, 25.4 g, 60.4 mmol) was dissolved in EtOH (600 mL) and cooled to 0 °C. $NaBH_4$ (5.25 g, 139 mmol) was added and the reaction stirred at room temperature for 3 h. The reaction mixture was adjusted to pH 4–5 with AcOH and the mixture concentrated. The residue was taken up in EtOAc and washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.), and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (30–60% EtOAc/*n*-pentane) yielding the title compound (24.6 g, 58.3 mmol, 97% yield); $R_f = 0.45$ (EtOAc/*n*-pentane 1:1, *v*/*v*). $[\alpha]_D^{20} = 18.1°$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.54$ (s, 1H, OH-1), 2.91 (s, 1H, OH-4), 3.56 (dd, $J = 9.7$, 5.9 Hz, 1H, H-5a), 3.60 (dd, $J = 9.8$, 3.7 Hz, 1H, H-5b), 3.72–3.89 (m, 4H, H-1, H-2, H-3), 3.95–4.05 (m, 1H, H-4), 4.47 (d, $J = 11.9$ Hz, 1H, C*H*H Bn), 4.51 (d, $J = 11.9$ Hz, 1H, C*H*H Bn), 4.58 (d, $J = 11.2$ Hz, 1H, C*H*H Bn), 4.58 (d, $J = 11.7$ Hz, 1H, C*H*H Bn), 4.63 (d, $J = 11.6$ Hz, 1H, C*H*H Bn), 4.72 (d, $J = 11.2$ Hz, 1H, C*H*H Bn), 7.13–7.47 ppm (m, 15H, CHarm Bn); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 61.1$ (C-1), 70.7 (C-4), 71.1 (C-5), 72.1, 73.5, 74.1 (3xCH_2 Bn), 79.4, 79.5 (C-2, C-3), 127.9–128.6 (CHarm Bn), 137.9, 138.1, 138.1 ppm (C_q Bn); IR (thin film): $\tilde{\nu} = 3348, 3063, 3030, 2866, 1719, 1497, 1452, 1395, 1360, 1329, 1314, 1273, 1207, 1088, 1067, 1026\ cm^{-1}$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{30}O_5$ 423.21660, found 423.21622 (Scheme 5).

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-ribitol (**85**): 2,3,5-Tri-*O*-benzyl-D-ribitol (**84**, 7.60 g, 18.0 mmol), triphenylphosphine (10.9 g, 41 mmol) and imidazole (3.7 g, 54 mmol) were co-evaporated thrice with dry toluene before being dissolved in CH_2Cl_2 (180 mL) and cooled to −30 °C. Iodine (11 g, 43 mmol) was slowly added and the reaction mixture stirred for 2 days at −30 °C, then 1 day at −20 °C. The solution was concentrated under reduced pressure, dry toluene (180 mL) added and the mixture held at reflux for 2 h. The reaction mixture was diluted with Et_2O, washed with $Na_2S_2O_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was co-evaporated with Et_2O to get rid of the residual toluene and then dissolved in Et_2O after which it was filtered to remove most of the Ph_3PO. The crude 1,4-dideoxy-1,4-diiodo-2,3,5-tri-*O*-benzyl-L-lyxitol (18 mmol) was dissolved in benzylamine (59 mL, 540 mmol) and stirred for 2 days at 55 °C. The mixture was diluted



Scheme 5. *Reagents and conditions*: a) $NaBH_4$, EtOH; b) 1) PH_3P, I_2, imidazole, DMF, −35 °C, 2) $PhNH_2$, 55 °C; c) H_2, Pd/C, HCl, EtOH; d) **6**, K_2CO_3, DMF, 80 °C; e) LiOH, dioxane/H_2O, microwave, 165 °C; f) **10**, **52** or **55**, DiPEA, DMF; g) $LiAlH_4$, THF, 0 °C; h) 1) MsCl, pyridine, 0 °C, 2) $PhNH_2$, 55 °C.

with EtOAc, washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15–22.5% Et_2O/*n*-pentane) yielding the title compound (6.10 g, 12.4 mmol, 69% yield over two steps); $R_f = 0.55$ (Et_2O/*n*-pentane 2:3, *v*/*v*). $[\alpha]_D^{20} = -32.9^\circ$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.68$ (dd, $J = 8.8$, 8.3 Hz, 1H, H-1a), 3.05 (dt, $J = 6.1$, 4.3 Hz, 1H, H-4), 3.11 (dd, $J = 9.0$, 5.7 Hz, 1H, H-1b), 3.32 (dd, $J = 9.9$, 6.2 Hz, 1H, H-5a), 3.39 (dd, $J = 9.9$, 4.6 Hz, 1H, H-5b), 3.58 (d, $J = 13.0$ Hz, 1H, *CH*H *N*-Bn), 3.85 (dd, $J = 5.1$, 3.6 Hz, 1H, H-3), 3.90 (dt, $J = 7.9$, 5.5 Hz, 1H, H-2), 3.99 (d, $J = 12.9$ Hz, 1H, *CH*H *N*-Bn), 4.42–4.52 (m, 4H, 2x*CH*H Bn-2, 2x*CH*H Bn-5), 4.59 (d, $J = 12.2$ Hz, 1H, *CH*H Bn-3), 4.64 (d, $J = 12.2$ Hz, 1H, *CH*H-Bn-3), 7.20–7.35 ppm (m, 20H, CHarm Bn); ^{13}C NMR (1001 MHz, $CDCl_3$): $\delta = 55.9$ (C-1), 60.2 (CH_2 N-Bn), 68.2 (C-4), 71.1 (C-5), 71.4 (CH_2 Bn-3), 71.6, 73.4 (CH_2 Bn-2, CH_2 Bn-5), 76.5 (C-2), 79.0 (C-3), 127.1–129.0 (CHarm Bn), 138.4, 138.4, 138.6, 139.2 ppm (Cq Bn); IR (thin film): $\tilde{\nu} = 3061$, 3028, 2857, 2799, 1495, 1452, 1364, 1321, 1310, 1258, 1207, 1092, 1072, 1051, 1026 cm^{-1}; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{33}H_{35}NO_3$ 494.26897, found: 494.26796.

1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride (**86**): 1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-D-ribitol (**85**, 3.95 g, 8.0 mmol) was subjected to the general hydrogenolysis procedure yielding the title compound (1.35 g, 7.9 mmol, 99%). $[\alpha]_D^{20} = 51.6^\circ$ ($c = 1.00$, MeOH); ^1H NMR (600 MHz, MeOD): $\delta = 3.26$ (dd, $J = 12.5$, 2.0 Hz, 1H, H-1a), 3.39 (dd, $J = 12.4$, 4.0 Hz, 1H, H-1b), 3.54 (ddd, $J = 8.8$, 5.9, 3.3 Hz, 1H, H-4), 3.78 (dd, $J = 12.0$, 5.9 Hz, 1H, H-5a), 3.91 (dd, $J = 12.0$, 3.3 Hz, 1H, H-5b), 4.13 (dd, $J = 8.3$, 4.0 Hz, 1H, H-3), 4.26 ppm (td, $J = 4.0$, 1.9 Hz, 1H, H-2); ^{13}C NMR (150 MHz, MeOD): $\delta = 51.1$ (C-1), 59.4 (C-5), 63.9 (C-4), 71.1 (C-2), 72.9 ppm (C-3); IR (thin film): $\tilde{\nu} = 3383$, 3345, 3289, 3256, 2938, 2895, 2849, 2747, 2716, 2695, 2596, 2538, 2475, 1449, 1418, 1385, 1323, 1233, 1192, 1132, 1098, 1051, 1034, 1003 cm^{-1}; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_5H_{11}NO_3$ 134.08117, found 134.08173.

Compound 87: Compound **86** was reacted with mesylate **6** according to the general procedure described above. Yield 0.084 g (230 μmol, 58%) $R_f = 0.65$ (EtOAc/*t*BuOH/AcOH/H_2O, 1:1:1:1, *v*/*v*/*v*/*v*). $[\alpha]_D^{20} = 30.7$ ($c = 1.05$ in MeOH); ^1H NMR (400 MHz, MeOD): $\delta =$ 2.42 (dd, $J = 6.6$, 9.3 Hz, 1H, H-1a), 2.66 (q, 1H, $J = 4.7$ Hz, H-4), 2.76 (dd, $J = 5.6$, 12.3 Hz, 1H, H-1′a), 2.99 (dd, $J = 6.0$, 9.6 Hz, 1H, H-1b), 3.00 (dd, $J = 8.4$, 12.4 Hz, 1H, H-1′b), 3.58 (dd, $J = 4.8$, 11.3 Hz, 1H, H-5a), 3.63 (dd, $J = 4.8$, 11.4 Hz, 1H, H-5b), 3.74 (dt, $J = 5.5$, 8.4 Hz, 1H, H-2′), 3.82 (t, $J = 4.8$ Hz, 1H, H-3), 3.97 (q, $J = 5.8$ Hz, 1H, H-2), 4.23 (s, 4H, 2x H_2 ethylene), 5.26 (d, $J = 5.5$ Hz, 1H, H-3′), 6.84–6.87 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 59.3$ (C-1), 60.7 (C-2′), 61.3 (C-1′), 63.6 (C-5), 65.6 (2×CH_2O), 71.5 (C-2), 72.4 (C-4), 74.1 (C-3), 83.2 (C-3′), 116.0, 118.5, 120.0 (CHarm), 133.9, 145.1, 145.3 (Cq Carm), 161.4 ppm (C=O); IR (thin film): $\tilde{\nu} = 3363$, 2939, 2885, 1728, 1643, 1512, 1427, 1288, 1064, 1018 cm^{-1}; LC–MS: $t_R =$ 4.91 min (linear gradient 0→50% B); ESI-MS: $m/z = 367.1$ $[M+H]^+$, 733.5 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15001.

Compound 88: The oxazolidine in compound **87** was hydrolyzed according to the saponification procedure described above. The obtained imine **88** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: $t_R = 3.70$ min (linear gradient 0→50% B); ESI-MS: $m/z = 341.2$ $[M+H]^+$, 681.6 $[2M+H]^+$.

Compound 32: Compound **88** was reacted with **10** according to the general condensation protocol described above. Yield 0.010 g (16 μmol, 21%); ^1H NMR (400 MHz, CD_3CN): $\delta = 1.31$–1.38 (m, 2H, H_2-4″), 1.45–1.53 (m, 8H, H_2-3″, H_2 adamantane), 1.64–1.76 (m, 6H, H_2 adamantane), 1.97 (s, 3H CH adamantane), 2.21 (t, $J = 7.3$ Hz, 2H, H_2-2″), 2.91 (s, 2H, H_2 adamantane), 3.29 (t, $J = 6.2$ Hz, 2H, H_2-5″), 3.31–3.40 (m, 3H, H-1a, H-1′a, H-4), 3.65 (dd, $J = 9.5$, 13.2 Hz, 1H, H-1′b), 3.80 (dd, $J = 7.9$, 12.7 Hz, H-5a), 3.88–3.97 (m, 3H, H-1b, H-3, H-5b), 4.19–4.27 (m, 6H, H-2, H-2′, 2×H_2 ethylene), 4.81 (d, $J =$ 3.9 Hz, 1H, H-3′), 6.84–6.97 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 23.3$ (C-3″), 29.4 (CH adamantane), 29.6 (C-4″), 37.8 (Cq adamantane), 36.1 (C-2″), 38.0 (CH_2 adamantane), 40.5 (CH_2 adamantane), 54.2 (C-2′), 59.8 (C-5), 61.3 (C-1), 62.3 (C-1′), 65.4 (2×CH_2O), 71.8 (C-5″), 72.7 (C-3′), 75.3 (C-2), 77.2 (C-3), 77.9 (C-4), 82.6 (OCH_2 adamantane), 116.1, 118.1, 119.9 (CHarm), 134.8, 144.5, 144.7 ppm (Cq Carm); IR (thin film): $\tilde{\nu} = 3311$, 2905, 2850, 1675, 1542, 1506, 1448, 1287, 1203, 1180, 1136, 1068, 1018 cm^{-1}; LC–MS: $t_R = 9.83$ min (linear gradient 10→60% B); ESI-MS: $m/z = 589.3$ $[M+H]^+$, 1177.1 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34818.

Compound 33: Compound **88** was reacted with **52** according to the general condensation protocol described above. Yield 0.014 g (28 μmol, 37%); ^1H NMR (400 MHz, CD_3CN): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3H, CH_3), 1.12–1.44 (m, 12H, 6×H_2 nonanoic amide), 2.16 (t, $J =$ 7.3 Hz, 2H, H_2-2″), 3.31–3.43 (m, 3H, H-1a, H-1′a, H-4), 3.68 (dd, $J =$ 9.5, 13.2 Hz, 1H, H-1′b), 3.80 (dd, $J = 7.7$, 12.1 Hz, 1H, H-5a), 3.85–3.93 (m, 3H, H-1b, H-3, H-5b), 4.19–4.15 (m, 6H, H-2, H-2′, 2×H_2 ethylene), 4.81 (d, $J = 3.9$ Hz, 1H, H-3′), 6.81–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 14.4$ (CH_3), 23.4, 26.4 29.7, 29.9, 30.0, 32.6, 36.5 (CH_2 nonanoic amide), 54.0 (C-2′), 59.7 (C-5), 61.3 (C-1), 62.1 (C-1′), 65.4 (2×CH_2O), 72.7 (C-3′), 75.3 (C-2), 77.3 (C-3), 77.9 (C-4), 116.0, 118.0, 119.9 (CHarm), 134.8, 144.5, 144.6 ppm (Cq Carm); IR (thin film): $\tilde{\nu} = 3313$, 2927, 2856, 1668, 1662, 1287, 1203, 1181, 1134, 1068, 1017 cm^{-1}; LC–MS: $t_R = 8.29$ min (linear gradient 10→60% B); ESI-MS: $m/z = 481.2$ $[M+H]^+$, 960.8 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29058.

Compound 34: Compound **88** was reacted with **55** according to the general condensation protocol described above. Yield 0.008 g (15 μmol, 19%); ^1H NMR (400 MHz, CD_3CN): $\delta = 2.64$ (brs, 2H, H_2-2″), 3.40 (brs, 3H, H-1a, H-1′a, H-4), 3.67–4.30 (brm, 16H, H-1′b, H-2′, H-1b, H-2, H-3, H_2-5, H_2 propanoic acid, 2×H_2 ethylene, OMe), 4.83 (brs, 1H, H-3′), 6.86 ppm (brs, 7H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 36.6$ (CH_2 propanoic acid), 54.1 (C-2′), 56.3 (OMe), 59.9 (C-5), 61.4 (C-1), 62.3 (C-1′), 65.4 (2×CH_2O), 65.5 (OCH_2 propanoic acid), 72.7 (C-3′), 75.3 (C-2), 77.1 (C-3), 80.0 (C-4), 115.6, 116.0, 119.0 (CHarm), 134.7, 144.4, 153.4 ppm (Cq Carm); IR (thin film): $\tilde{\nu} = 3307$, 2927, 2856, 1684, 1508, 1287, 1203, 1131, 1068, 1029 cm^{-1}; LC–MS: $t_R = 5.99$ min (linear gradient 10→60% B); ESI-MS: $m/z = 519.1$ $[M+H]^+$, 1036.6 $[2M+H]^+$; HRMS [QTOF, MH^+] *m*/*z* calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23337.

2,3,5-Tri-*O*-benzyl-D-xylitol (**90**): 2,3,5-Tri-*O*-benzyl-D-xylofuranose (**17**, 23 g, 54 mmol) was dissolved in EtOH (550 mL), put under an argon atmosphere and cooled to 0 °C. $NaBH_4$ (4.7 g, 123 mmol) was added and the reaction stirred at room temperature for 4 h. The reaction was adjusted to pH 4–5 by addition of AcOH and the resulting mixture was concentrated. The residue was taken up in EtOAc and washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (25–60% EtOAc/*n*-pentane) yielding the title compound (22 g, 52 mmol, 97% yield); $R_f = 0.65$ (50/50 EtOAc/*n*-pentane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.86$ (s, 1H, OH-1), 3.02 (s, 1H, OH-4), 3.41 (dd, $J = 9.4$, 6.2 Hz, 1H, C-5b), 3.50 (dd, $J = 9.4$, 6.4 Hz, 1H, C-5a), 3.73–3.63 (m, 2H, C-2, C-3), 3.81–3.73 (m, 2H, C-

1), 4.07–4.01 (m, 1H, C-4), 4.42 (d, $J=11.9$ Hz, 1H, CHH Bn-5), 4.51–4.46 (m, 2H, CHH Bn-3, CHH Bn-5), 4.57 (d, $J=11.8$ Hz, 1H, CHH Bn-2), 4.61 (d, $J=11.9$ Hz, 1H, CHH Bn-2), 4.65 (d, $J=11.4$ Hz, 1H, CHH Bn-3), 7.24–7.21 (m, 2H, CHAr Bn), 7.36–7.24 ppm (m, 13H, CHAr Bn), ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=138.1$, 138.0, 137.9 (Cq Bn), 128.5, 128.5, 128.5, 128.4, 128.0, 128.0, 127.9, 127.8 (CHAr Bn), 78.7 (C-2), 77.3 (C-3), 74.2 (CH2 Bn-3), 73.3 (CH2 Bn-5), 72.4 (CH2 Bn-2), 71.3 (C-5), 68.6 (C-4), 60.6 ppm (C-1). $[\alpha]_D^{20}=-9.7^\circ$ ($c=1$, $CHCl_3$); IR (thin film): $\tilde{\nu}=694$, 716, 733, 822, 881, 903, 918, 980, 1018, 1024, 1057, 1084, 1096, 1206, 1248, 1279, 1294, 1366, 1385, 1400, 1452, 1497, 1578, 1726, 2471, 2542, 2716, 2866, 3028, 3343 cm^{-1}; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{30}O$ 423.21660, found 423.21633.

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-L-arabinitol (**91**): 2,3,5-Tri-*O*-benzyl-D-xylitol (**90**, 10.0 g, 23.7 mmol) was dissolved in pyridine (50 mL), cooled to 0 °C and methanesulfonyl chloride (9.2 mL, 118 mmol) was added. The mixture was stirred at this temperature for 4 h. The reaction was quenched with H_2O and the mixture taken up in EtOAc/1 M HCl (aq.), washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude 1,4-di-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-D-xylitol (12.5 g, 21.6 mmol) was dissolved in benzylamine (71 mL, 650 mmol) and stirred overnight at 55 °C. The reaction mixture was diluted with EtOAc and washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10–15% Et_2O/*n*-pentane) yielding title compound (7.60 g, 15.4 mmol, 71% yield over two steps). Analytical data were in full accordance with its D-enantiomer **67**. $[\alpha]_D^{20}=38.0^\circ$ ($c=1.00$, $CHCl_3$).

1,4-Dideoxy-1,4-imino-L-arabinitol hydrochloride (**92**): 1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-L-arabinitol (3.70 g, 7.50 mmol) was subjected to general hydrogenolysis procedure yielding title compound (1.30 g, 7.50 mmol, quant.). Analytical data were in full accordance with its D-enantiomer **74**. $[\alpha]_D^{20}=-38.9^\circ$ ($c=1.00$, MeOH).

Compound 93: Compound **92** was reacted with mesylate **6** according to the general procedure described above. Yield 0.057 g (156 μmol, 39%); $R_f=0.65$ (EtOAc/*t*BuOH/AcOH/H_2O, 1:1:1:1, *v/v/v/v*). $[\alpha]_D^{20}=80.2$ ($c=0.38$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta=$ 2.47 (q, 1H, $J=4.2$ Hz, H-4), 2.57 (dd, $J=3.8$, 12.6 Hz, 1H, H-1′a), 2.58 (dd, $J=5.6$, 9.6 Hz, 1H, H-1a), 3.00 (dd, $J=9.6$, 12.4 Hz, 1H, H-1′b), 3.01 (dd, $J=8.8$, 9.2 Hz, 1H, H-1b), 3.64 (dd, $J=4.1$, 11.4 Hz, 1H, H-5a), 3.69 (dd, $J=4.6$, 11.4 Hz, 1H, H-5b), 3.82 (ddd, $J=3.1$, 6.7, 9.5 Hz, 1H, H-2′), 3.90–3.94 (m, *2*H, H-2, H-3), 4.24 (s, 4H, 2×H_2 ethylene), 5.12 (d, $J=6.6$ Hz, 1H, H-3′), 6.83–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta=59.5$ (C-1′), 60.4 (C-1), 61.0 (C-2′), 62.4 (C-5), 65.6 (2×CH_2O), 74.5 (C-4), 77.4 (C-2), 80.2 (C-3), 82.5 (C-3′), 116.2, 118.6, 120.1 (CHarm), 132.9, 145.3, 145.7 (Cq Carm), 161.2 ppm (C=O); IR (thin film): $\tilde{\nu}=3317$, 2939, 2831, 1743, 1651, 1512, 1450, 1288, 1110, 1018 cm^{-1}; LC–MS: $t_R=4.99$ min (linear gradient 0→50% B); ESI-MS: $m/z=366.9$ $[M+H]^+$, 733.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15004.

Compound 94: The oxazolidine in compound **93** was hydrolyzed according to the saponification procedure described above. The obtained imine **94** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: $t_R=3.29$ min (linear gradient 0→50% B); ESI-MS: $m/z=341.2$ $[M+H]^+$, 681.5 $[2M+H]^+$.

Compound 35: Compound **94** was reacted with **10** according to the general condensation protocol described above. Yield 0.014 g (23 μmol, 44%); ^{1}H NMR (400 MHz, CD_3CN): $\delta=1.33$–1.40 (m, 2H, H_2-4″), 1.45–1.53 (m, 8H, H_2-3″, H_2 adamantane), 1.64–1.76 (m, 6H, H_2 adamantane), 1.96 (s, 3H CH adamantane), 2.15 (t, $J=7.3$ Hz, 2H, H_2-2″), 2.93 (s, 2H, H_2 adamantane), 3.30 (t, $J=6.2$ Hz, 2H, H_2-5″), 3.31–3.38 (m, 2H, H-1a, H-1′a,), 3.49 (brs, 1H, H-4), 3.73–3.79 (m, 3H, H-1′b, H-1b, H-5a), 3.95 (dd, $J=3.3$, 12.7 Hz, 1H, H-5b), 4.13 (brs, 1H, H-3), 4.22 (s, 4H, 2×H_2 ethylene), 4.25 (brs, 1H, H-2), 4.35 (brs, 1H, H-2′), 4.78 (d, $J=3.7$ Hz, 1H, H-3′), 6.81–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta=23.1$ (C-3″), 29.3 (CH adamantane), 29.7 (C-4″), 34.9 (Cq adamantane), 36.3 (C-2″), 38.0 (CH_2 adamantane), 40.5 (CH_2 adamantane), 52.9 (C-2′), 58.1 (C-5), 61.1 (C-1), 62.6 (C-1′), 65.4 (2×CH_2O), 70.4 (C-2), 71.8 (C-5″), 72.6 (C-3), 72.8 (C-3′), 73.7 (C-4), 82.6 (OCH_2 adamantane), 116.1, 117.9, 120.0 (CHarm), 134.7, 144.4, 144.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}=3308$, 2904, 2849, 1675, 1506, 1287, 1257, 1202, 1180, 1128, 1068 cm^{-1}; LC–MS: $t_R=9.80$ min (linear gradient 10→60% B); ESI-MS: $m/z=$ 589.3 $[M+H]^+$, 1176.9 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34819.

Compound 36: Compound **94** was reacted with **52** according to the general condensation protocol described above. Yield 0.009 g (19 μmol, 37%); ^{1}H NMR (400 MHz, CD_3CN): $\delta=0.89$ (brs, 3H, CH_3), 1.25–1.58 (m, 12H, 6×H_2 nonanoic amide), 2.15 (brs, 2H, H_2-2″), 3.29–3.39 (m, 2H, H-1a, H-1′a), 3.50 (brs, 1H, H-4), 3.71–3.81 (m, 3H, H-1′b, H-1b, H-5a), 3.95 (brs, 1H, H-5b), 4.13 (brs, 1H, H-3), 4.22 (s, 4H, 2×H_2 ethylene), 4.25 (brs, 1H, H-2), 4.35 (brs, 1H, H-2′), 4.79 (brs, 1H, H-3′), 6.81–6.86 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta=14.4$ (CH_3), 23.4, 26.3 29.8, 29.9, 30.0, 32.6, 36.6 (CH_2 nonanoic amide), 53.0 (C-2′), 57.9 (C-5), 61.3 (C-1), 62.6 (C-1′), 65.4 (2×CH_2O), 70.4 (C-2), 72.6 (C-3), 72.9 (C-3′), 73.7 (C-4), 116.1, 118.0, 120.0 (CHarm), 134.4, 144.4, 144.5 ppm (Cq Carm); IR (thin film): $\tilde{\nu}=3305$, 2929, 2856, 1684, 1522, 1287, 1203, 1182, 1134, 1068 cm^{-1}; LC–MS: $t_R=8.42$ min (linear gradient 10→60% B); ESI-MS: $m/z=481.2$ $[M+H]^+$, 983.3 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29059.

Compound 37: Compound **94** was reacted with **55** according to the general condensation protocol described above. Yield 0.010 g (19 μmol, 38%); ^{1}H NMR (400 MHz, CD_3CN): $\delta=2.59$ (brs, 2H, H_2-2″), 3.33–3.39 (m, 2H, H-1a, H-1′a), 3.50 (brs, 1H, H-4), 3.70–3.84 (m, 6H, H-1′b, H-1b, H-5a, OMe), 3.91–4.12 (m, 4H, H-3, H-5b, H_2 propanoic acid), 4.20 (s, 4H, 2×H_2 ethylene), 4.25 (brs, 1H, H-2), 4.40 (brs, 1H, H-2′), 4.79 (brs, 1H, H-3′), 6.73–6.97 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta=36.8$ (CH_2 propanoic acid), 53.0 (C-2′), 56.3 (OMe), 59.9 (C-5), 61.4 (C-1), 62.4 (C-1′), 65.4 (2×CH_2O), 65.5 (OCH_2 propanoic acid), 70.4 (C-2), 72.5 (C-3), 72.9 (C-3′), 73.6 (C-4), 115.7, 116.2, 116.7, 118.0, 120.1 (CHarm), 134.3, 144.5, 144.6, 153.5, 155.3 ppm (Cq Carm); IR (thin film): $\tilde{\nu}=3305$, 2929, 2854, 1668, 1506, 1287, 1230, 1201, 1134, 1067, 1042 cm^{-1}; LC–MS: $t_R=5.90$ min (linear gradient 10→60% B); ESI-MS: $m/z=519.1$ $[M+H]^+$, 1036.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23346.

1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-L-lyxitol (**95**): 2,3,5-Tri-*O*-benzyl-D-ribitol (**84**, 6.30 g, 15.0 mmol) was dissolved in pyridine (32 mL), cooled to 0 °C and methanesulfonyl chloride (5.8 mL, 75 mmol) was added. The reaction mixture was stirred at this temperature for 2.5 h after which the reaction was quenched with H_2O and diluted with EtOAc. The suspension was washed with 1 M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$ and concentrated. The crude 1,4-di-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-D-ribitol (8.5 g, 14.7 mmol) was dissolved in benzylamine (49 mL, 450 mmol) and stirred at

55 °C for 2 days after which the reaction mixture was allowed to cool to room temperature and subsequently diluted with EtOAc. The mixture was washed with 1 M HCl (aq.), Na_2CO_3 (sat. aq.) and brine before being dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12.5–20% Et_2O/*n*-pentane) yielding the title pyrrolidine (5.20 g, 10.5 mmol, 70% yield over two steps). Analytical data was in full accordance with its D-enantiomer **67**. $[\alpha]_D^{20} = 34.9^\circ$ ($c = 1$, $CHCl_3$).

1,4-Dideoxy-1,4-imino-L-lyxitol hydrochloride (**96**): 1,4-Dideoxy-1,4-benzylimino-2,3,5-tri-*O*-benzyl-L-lyxitol (**69**, 3.95 g, 8 mmol) was subjected to the general hydrogenolysis procedure yielding title compound (1.37 g, 8.0 mmol, quant.). Analytical data was in full accordance with its D-enantiomer **68**. $[\alpha]_D^{20} = -28.5^\circ$ ($c = 0.90$, MeOH).

Compound 97: Compound **96** was reacted with mesylate **6** according to the general procedure described above. Yield 0.075 g (203 μmol, 51%); $R_f = 0.65$ (EtOAc/*t*BuOH/AcOH/H_2O, 1:1:1:1, *v*/*v*/*v*/*v*). $[\alpha]_D^{20} = 80.2$ ($c = 1.06$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta =$ 2.45 (dd, $J = 5.4$, 10.2 Hz, 1H, H-1a), 2.61 (dd, $J = 3.2$, 12.7 Hz, 1H, H-1′a), 2.74 (dt, 1H, $J = 4.6$, 7.0 Hz, H-4), 2.95 (dd, $J = 9.1$, 12.7 Hz, 1H, H-1′b), 3.03 (dd, $J = 3.1$, 10.3 Hz, 1H, H-1b), 3.65 (dd, $J = 3.8$, 11.3 Hz, 1H, H-5a), 3.74 (dd, $J = 5.0$, 11.3 Hz, 1H, H-5b), 3.80 (ddd, $J = 3.2$, 6.6, 9.4 Hz, 1H, H-2′), 4.10 (td, $J = 3.2$, 5.3 Hz, 1H, H-2), 4.21 (dd, $J = 5.0$, 6.8 Hz, 1H, H-3), 4.24 (s, 4H, 2×H_2 ethylene), 5.11 (d, $J = 6.6$ Hz, 1H, H-3′), 6.86–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 59.4$ (C-1), 59.9 (C-1′), 60.9 (C-2′), 62.9 (C-5), 65.6 (2×CH_2O), 68.4 (C-4), 71.8 (C-2), 73.4 (C-3), 82.4 (C-3′), 116.2, 118.6, 120.3 (CHarm), 132.9, 145.2, 145.6 (Cq Carm), 161.1 ppm (C=O); IR (thin film): $\tilde{\nu} = 3371$, 2927, 2939, 1735, 1651, 1512, 1404, 1288, 1126, 1064, 1018 cm^{-1}; LC–MS: $t_R = 5.58$ min (linear gradient 0→50% B); ESI-MS: $m/z = 367.0$ $[M+H]^+$, 733.0 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{23}N_2O_7$ 367.14998, found 367.15010.

Compound 98: The oxazolidine in compound **97** was hydrolyzed according to the saponification procedure described above. The obtained imine **98** was immediately condensed with the hydroxysuccinimide esters **10**, **42** and **55** as described in the general condensing procedure; LC–MS: $t_R = 3.61$ min (linear gradient 0→50% B); ESI-MS: $m/z = 341.1$ $[M+H]^+$, 681.6 $[2M+H]^+$.

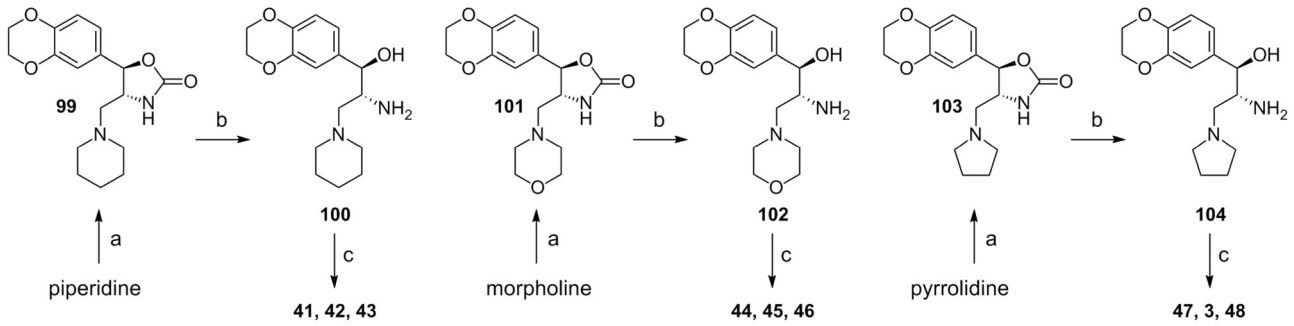
Compound 38: Compound **98** was reacted with **10** according to the general condensation protocol described above. Yield 0.011 g (19 μmol, 28%); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 1.28$ (m, 2H, H_2-4″), 1.44 (brs, 2H, H_2-3″), 1.50 (brs, 6H, H_2 adamantane), 1.62–1.73 (m, 6H, H_2 adamantane), 1.91 (brs, 3H CH adamantane), 2.16 (brs, 2H, H_2-2″), 2.93 (brs, 2H, H_2 adamantane), 3.27–3.34 (brm, 4H, H-1a,H-1′a, H_2-5″), 3.59–3.75 (m, 3H, H-1b, H-4, H-1′b), 3.85–3.96 (m, 2H, H_2-5), 4.21 (s, 4H, 2×H_2 ethylene), 4.23 (m, 3H, H-2′, H-2, H-3), 4.78 (s, 1H, H-3′), 6.79–6.87 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 23.1$ (C-3″), 29.3 (CH adamantane), 29.5 (C-4″), 34.8 (Cq adamantane), 36.2 (C-2″), 37.9 (CH_2 adamantane), 40.5 (CH_2 adamantane), 53.3 (C-2′), 57.8 (C-5), 58.8 (C-1), 60.1 (C-1′), 65.4 (2×CH_2O), 69.9 (C-2/C-3), 71.2 (C-4), 71.5 (C-2/C-3), 71.9 (C-5″), 72.8 (C-3′), 82.6 (OCH_2 adamantane), 116.0, 117.9, 120.0 (CHarm), 135.0, 144.3, 144.5 (Cq Carm), 174.3 ppm (C=O); IR (thin film): $\tilde{\nu} = 3287$, 2904, 2849, 1688, 1506, 1287, 1260, 1203, 1127, 1069, 1120 cm^{-1}; LC–MS: $t_R = 9.76$ min (linear gradient 10→60% B); ESI-MS: $m/z =$ 589.3 $[M+H]^+$, 1177.0 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{32}H_{49}N_2O_8$ 589.34834, found 589.34811.

Compound 39: Compound **98** was reacted with **52** according to the general condensation protocol described above. Yield 0.023 g (47 μmol, 70%); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 0.87$ (t, $J = 7.0$ Hz, 3H, CH_3), 1.09–1.57 (m, 12H, 6×H_2 nonanoic amide), 2.17 (m, 2H, H_2-2″), 3.22 (dd, $J = 5.1$, 12.1 Hz, 1H, H-1a), 3.33 (dd, $J = 2.2$, 13.7 Hz, 1H, H-1′a), 3.59 (m, 1H, H-2), 3.66 (dd, $J = 9.5$, 13.4 Hz, 1H, H-1′b), 3.78 (dd, $J = 3.4$, 12.1 Hz, 1H, H-1b), 3.88 (dd, $J = 4.2$, 12.9 Hz, 1H, H-5a), 3.95 (dd, $J = 5.4$, 12.7 Hz, 1H, H-5b), 4.21 (s, 4H, 2×H_2 ethylene), 4.27 (ddd, $J = 2.2$, 3.9, 8.8 Hz, 1H, H-2′), 4.37–4.42 (m, 2H, H-3, H-4), 4.81 (d, $J = 3.9$ Hz, 1H, H-3′), 6.90–6.92 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 14.5$ (CH_3), 23.4, 26.6 29.8, 30.0, 30.1, 32.7, 36.6 (CH_2 nonanoic amide), 53.6 (C-2′), 57.7 (C-5), 59.0 (C-1), 60.1 (C-1′), 65.5 (2×CH_2O), 70.0 (C-3), 71.2 (C-2), 71.6 (C-4), 72.9 (C-3′), 116.1, 118.2, 120.0 (CHarm), 134.8, 144.6, 144.7 (Cq Carm), 174.6 ppm (C=O); IR (thin film): $\tilde{\nu} = 3285$, 2927, 2857, 1675, 1436, 1287, 1202, 1131, 1066, 1017 cm^{-1}; LC–MS: $t_R = 8.24$ min (linear gradient 10→60% B); ESI-MS: $m/z = 481.2$ $[M+H]^+$, 960.7 $[2M+H]^+$, 982.9 $[2M+Na]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{25}H_{41}N_2O_7$ 481.29083, found 481.29061.

Compound 40: Compound **98** was reacted with **55** according to the general condensation protocol described above. Yield 0.012 g (23 μmol, 34%); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 2.59$ (m, 2H, H_2-2″), 3.24 (dd, $J = 5.1$, 11.9 Hz, 1H, H-1a), 3.35 (dd, $J = 4.1$, 13.2 Hz, 1H, H-1′a), 3.58 (brs, 1H, H-4), 3.65–3.76 (m, 5H, H-1′b, OMe, H-1b), 3.87 (dd, $J = 4.6$, 12.7 Hz, 1H, H-5a), 3.94 (dd, $J = 5.8$, 12.8 Hz, 1H H-5b), 3.98–4.06 (m, 2H, H_2 propanoic acid), 4.19 (s, 4H, 2×H_2 ethylene), 4.36 (brs, 1H, H-2′), 4.42 (brs, 2H, H-2, H-3), 4.79 (d, $J = 3.6$ Hz, 1H, H-3′), 6.78–6.88 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 36.7$ (CH_2 propanoic acid), 53.4 (C-2′), 56.4 (OMe), 57.9 (C-5), 58.9 (C-1), 60.2 (C-1′), 65.5 (2×CH_2O), 65.6 (OCH_2 propanoic acid), 70.0 (C-2/C-3), 71.3 (C-4), 71.5 (C-2/C-3), 72.9 (C-3′), 115.7, 116.1, 116.9, 118.1, 120.1 (CHarm), 134.3, 144.5, 144.6, 153.5, 155.3 (Cq Carm), 175.3 ppm (C=O); IR (thin film): $\tilde{\nu} = 3273$, 2927, 2856, 1668, 1506, 1287, 1229, 1200, 1180, 1037 cm^{-1}; LC–MS: $t_R = 5.89$ min (linear gradient 10→60% B); ESI-MS: $m/z = 519.1$ $[M+H]^+$, 1036.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{26}H_{35}N_2O_9$ 519.23371, found 519.23342.

Compound 99: Piperidine was reacted with mesylate **6** according to the general procedure described above. Yield 0.045 g (140 μmol, 56%); $R_f = 0.80$ (MeOH/EtOAc/NH_4OH 40:60:5, *v*/*v*/*v*). $[\alpha]_D^{20} = 58.2$ ($c = 0.45$ in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$–1.45 (m, *2*H, H_2 piperidine), 1.51–1.61 (m, 4H, H_2 piperidine), 2.30–2.47 (m, 4H, NCH_2 piperidine), 2.45 (dd, $J = 5.0$, 12.5 Hz, 1H, H-1′a), 2.57 (dd, $J = 8.6$, 12.5 Hz, 1H, H-1′b), 3.82 (dt, $J = 5.6$, 8.5 Hz, 1H, H-2′), 4.26 (s, 4H, 2×H_2 ethylene), 5.04 (d, $J = 5.9$ Hz, 1H, H-3′), 6.22 (s, 1H, NH), 6.83–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.0$ (CH_2), 25.7 (2×CH_2), 54.9 (2×CH_2N), 57.6 (C-2′), 63.0 (C-1′), 64.3 (2×CH_2O), 81.3 (C-3′), 114.9, 117.5, 118.9 (CHarm), 131.7, 143.7, 143.9 (Cq Carm), 158.7 ppm (C=O); IR (thin film): $\tilde{\nu} = 2935$, 1752, 1508, 1288, 1067 cm^{-1}; LC–MS: $t_R = 5.05$ min (linear gradient 0→90% B); ESI-MS: $m/z = 319.1$ $[M+H]^+$, 636.6 $[2M+H]^+$; HRMS [QTOF, MH^+] m/z calculated for $C_{17}H_{23}N_2O_4$ 319.16523, found 319.16532 (Scheme 6).

Compound 100: The oxazolidine in compound **99** was hydrolyzed according to the saponification procedure described above. Yield 0.036 g (122 μmol, 87%); $R_f = 0.50$ (MeOH/EtOAc/NH_4OH 16:4:1, *v*/*v*/*v*). $[\alpha]_D^{20} = 24.4$ ($c = 0.71$ in MeOH); ^{1}H NMR (400 MHz, MeOD): $\delta =$ 1.37–1.46 (m, *2*H, H_2 piperidine), 1.51–1.62 (m, 4H, H_2 piperidine), 2.06 (dd, $J = 4.7$, 12.6 Hz, 1H, H-1′a), 2.20 (dd, $J = 8.9$, 12.6 Hz, 1H, H-1′b), 2.28 (brs, 2H, NCH_2 piperidine), 2.43 (brs, 2H, NCH_2 piperidine), 3.11 (ddd, $J = 4.7$, 6.4, 8.8 Hz, 1H, H-2′), 4.22 (s, 4H, 2×H_2 ethylene), 4.34 (d, $J = 6.4$ Hz, 1H, H-3′), 6.75–6.82 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): $\delta = 25.3$ (CH_2), 27.0 (2×CH_2), 54.3 (C-2′), 56.1 (2×CH_2N), 62.9 (C-1′), 65.6 (2×CH_2O), 77.2 (C-3′), 116.6, 118.0, 120.7 (CHarm), 136.7, 144.5, 144.9 ppm (Cq Carm); IR (thin film):



Scheme 6. *Reagents and conditions*: a) **6**, K_2CO_3, DMF, 80 °C; b) LiOH, dioxane/H_2O, microwave, 165 °C; c) **10**, **52** or **55**, DiPEA, DMF.

$\tilde{\nu}$ = 3350, 2933, 1506, 1457, 1433, 1282, 1256, 1152, 1121, 1067 cm^{-1}; LC–MS: t_R = 4.56 min (linear gradient 0→50% B); ESI-MS: *m/z* = 293.2 $[M+H]^+$, 585.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{16}H_{25}N_2O_3$ 293.18597, found 293.18610.

Compound 41: Compound **100** was reacted with **10** according to the general condensation protocol described above. Yield 0.008 g (16 µmol, 39%). $[\alpha]_D^{20}$ = 14.2 (*c* = 0.17 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.35–1.42 (m, 2H, H_2-4″), 1.45–1.55 (m, 2H, H_2-3″), 1.56 (br s, 6H, H_2 adamantane), 1.66–1.86 (m, 10H, 3×H_2 adamantane, 2×H_2 piperidine), 1.94 (br s, 5H, 3×CH adamantane, 1×H_2 piperidine), 2.21 (m, 2H, H_2-2″), 2.91 (dt, *J* = 2.8, 12.4 Hz, 1H, H piperidine), 2.95 (s, 2H, H_2 adamantane), 3.03 (dt, *J* = 3.6, 12.4 Hz, 1H, H piperidine), 3.28–3.35 (m, 3H, H-1′a, H_2-5″), 3.40 (dd, *J* = 3.0, 13.6 Hz, 1H, H-1′b), 3.47 (br d, *J* = 12.5 Hz, 1H, H piperidine), 3.79 (br d, *J* = 12.5 Hz, 1H, H piperidine), 4.21 (s, 4H, 2×H_2 ethylene), 4.47 (dt, *J* = 3.2, 10.2 Hz, 1H, H-2′), 4.76 (d, *J* = 3.4 Hz, 1H, H-3′), 6.78–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 22.6 (CH_2 piperidine), 23.5 (C-3″), 24.1 (CH_2 piperidine), 29.8 (CH adamantane), 30.2 (C-4″), 35.2 (Cq adamantane), 36.7 (C-2″), 38.4 (CH_2 adamantane), 40.9 (CH_2 adamantane), 51.9 (C-2′), 54.1 (CH_2 piperidine), 56.2 (CH_2 piperidine), 60.9 (C-1′), 65.6 (2×CH_2O), 72.2 (C-5″), 73.5 (C-3′), 82.1 (OCH_2 adamantane), 116.2, 118.1, 120.0 (CHarm), 135.5, 144.7, 144.9 (Cq Carm), 177.3 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3369, 2902, 2846, 1670, 1508, 1286, 1207, 1068 cm^{-1}; LC–MS: t_R = 8.04 min (linear gradient 10→90% B); ESI-MS: *m/z* = 541.3 $[M+H]^+$, 1103.3 $[2M+Na]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{32}H_{49}N_2O_5$ 541.36360, found 541.36321.

Compound 42: Compound **100** was reacted with **52** according to the general condensation protocol described above. Yield 0.006 g (15 µmol, 37%). $[\alpha]_D^{20}$ = 17.1 (*c* = 0.13 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 0.91 (t, *J* = 6.9 Hz, 3H, CH_3), 1.14–1.99 (m, 18H, 6×H_2 nonanoic amide, 3×H_2 piperidine), 2.15 (m, 2H, H_2-2″), 2.91 (dt, *J* = 2.5, 12.3 Hz, 1H, H piperidine), 3.05 (dt, *J* = 3.0, 12.3 Hz, 1H, H piperidine), 3.32 (dd, *J* = 3.8, 13.6 Hz, 1H, H-1′a), 3.39 (dd, *J* = 3.0, 13.6 Hz, 1H, H-1′b), 3.47 (br d, *J* = 12.6 Hz, 1H, H piperidine), 3.80 (br d, *J* = 12.6 Hz, 1H, H piperidine), 4.21 (s, 4H, 2×H_2 ethylene), 4.47 (dt, *J* = 3.1, 10.0 Hz, 1H, H-2′), 4.76 (d, *J* = 3.4 Hz, 1H, H-3′), 6.77–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 14.4 (CH_3), 22.6, 23.7, 24.1, 26.7, 30.2, 30.3, 30.4, 33.0, 37.0 (2×CH_2 piperidine, 7×CH_2 nonanoic amide), 51.9 (C-2′), 54.1 (CH_2 piperidine), 56.2 (CH_2 piperidine), 61.0 (C-1′), 65.6 (2×CH_2O), 73.5 (C-3′), 116.2, 118.0, 120.0 (CHarm), 135.5, 144.7, 144.9 (Cq Carm), 177.5 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3342, 2927, 2856, 1670, 1508, 1458, 1286, 1199, 1134, 1068 cm^{-1}; LC–MS: t_R = 7.05 min (linear gradient 10→90% B); ESI-MS: *m/z* = 433.2 $[M+H]^+$, 864.6 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{25}H_{41}N_2O_4$ 433.30608, found 433.30569.

Compound 43: Compound **100** was reacted with **55** according to the general condensation protocol described above. Yield 0.012 g (25 µmol, 63%). $[\alpha]_D^{20}$ = 12.2 (*c* = 0.24 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.37–1.92 (m, 6H, 3×H_2 piperidine), 2.53–2.68 (m, 2H, H_2-2″), 2.92 (dt, *J* = 2.6, 12.2 Hz, 1H, H piperidine), 3.01 (dt, *J* = 2.9, 12.0 Hz, 1H, H piperidine), 3.31 (dd, *J* = 6.0, 13.6 Hz, 1H, H-1′a), 3.42 (dd, *J* = 2.8, 13.6 Hz, 1H, H-1′b), 3.47 (br d, *J* = 11.7 Hz, 1H, H piperidine), 3.74 (br s, 4H, H piperidine, OMe), 4.02 (dt, *J* = 5.9, 9.4 Hz, 1H, H_2 propanoic acid), 4.10 (dt, *J* = 6.2, 9.5 Hz, 1H, H_2 propanoic acid), 4.18 (s, 4H, 2×H_2 ethylene), 4.50 (dt, *J* = 3.1, 10.1 Hz, 1H, H-2′), 4.76 (d, *J* = 3.5 Hz, 1H, H-3′), 6.75–6.92 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 22.5 (CH_2 piperidine), 24.2 (CH_2 piperidine), 37.2 (C-2″), 52.1 (CH_2 propanoic acid), 54.4 (CH_2 piperidine), 56.0 (CH_2 piperidine), 56.2 (OMe), 60.7 (C-1′), 65.6 (2×CH_2O), 66.0 (OCH_2 propanoic acid), 73.5 (C-3′), 115.8, 116.3, 116.8, 118.0, 120.2 (CHarm), 134.3, 144.8, 144.9, 154.0, 155.8 (Cq Carm), 174.7 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3361, 1670, 1508, 1458, 1286, 1199, 1130, 1066 cm^{-1}; LC–MS: t_R = 5.61 min (linear gradient 10→90% B); ESI-MS: *m/z* = 471.3 $[M+H]^+$, 963.2 $[2M+Na]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{26}H_{35}N_2O_6$ 471.24896, found 471.24858.

Compound 101: Morpholine was reacted with mesylate **6** according to the general procedure described above. Yield 0.050 g (155 µmol, 62%); R_f = 0.80 (MeOH/EtOAc/NH_4OH 40:60:5, *v/v/v*). $[\alpha]_D^{20}$ = 47.2 (*c* = 0.50 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (m, *2*H, NH_2 morpholine), 2.47–2.53 (m, 4H, H_2 morpholine), 2.52 (dd, *J* = 6.0, 13.0 Hz, 1H, H-1′a), 2.58 (dd, *J* = 7.7, 12.5 Hz, 1H, H-1′b), 3.65–3.71 (m, 4H, 2×OCH_2 morpholine), 3.83 (q, *J* = 6.2 Hz, 1H, H-2′), 4.26 (s, 4H, 2×H_2 ethylene), 5.10 (d, *J* = 5.8 Hz, 1H, H-3′), 6.29 (s, 1H, NH), 6.83–6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8 (2×CH_2N morpholine), 57.4 (C-2′), 62.4 (C-1′), 64.2 (2×CH_2O), 66.7 (2×CH_2O morpholine), 81.3 (C-3′), 114.9, 117.6, 118.8 (CHarm), 131.6, 143.7, 143.9 (Cq Carm), 158.7 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3277, 2859, 2748, 1659, 1508, 1287, 1112, 1067, 1007 cm^{-1}; LC–MS: t_R = 4.77 min (linear gradient 0→90% B); ESI-MS: *m/z* = 321.1 $[M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{16}H_{21}N_2O_5$ 321.14450, found 321.14456.

Compound 102: The oxazolidine in compound **101** was hydrolyzed according to the saponification procedure described above. Yield 0.036 g (115 µmol, 74%); R_f = 0.40 (MeOH/EtOAc/NH_4OH 16:4:1, *v/v/v*). $[\alpha]_D^{20}$ = 31.1 (*c* = 0.68 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 2.07 (dd, *J* = 4.3, 12.5 Hz, 1H, H-1′a), 2.23 (dd, *J* = 9.5, 12.5 Hz, 1H, H-1′b), 2.26–2.32 (m, *2*H, NH_2 morpholine), 2.45–2.50 (m, *2*H, NH_2 morpholine), 3.11 (ddd, *J* = 4.3, 6.6, 10.2 Hz, 1H, H-2′), 2.60–2.70 (m, 4H, 2×OCH_2 morpholine), 4.23 (s, 4H, 2×H_2 ethylene), 4.32 (d, *J* = 6.6 Hz, 1H, H-3′), 6.76–6.83 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 54.4 (C-2′), 55.1 (2×CH_2N morpho-

line), 62.3 (C-1′), 65.6 (2×CH_2O), 68.0 (2×CH_2O morpholine), 76.8 (C-3′), 116.5, 118.0, 120.6 (CHarm), 136.8, 144.6, 144.9 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3370, 2871, 1590, 1506, 1457, 1283, 1258, 1112, 1067 cm^{-1}; LC–MS: t_R = 4.33 min (linear gradient 0→50% B); ESI-MS: *m/z* = 295.3 $[M+H]^+$, 589.1 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{15}H_{23}N_2O_4$ 295.16523, found 295.16537.

Compound 44: Compound **102** was reacted with **10** according to the general condensation protocol described above. Yield 0.018 g (31 μmol, 82%). $[\alpha]_D^{20}$ = 14.1 (*c* = 0.27 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.31–1.40 (m, 2H, H_2-4″), 1.44–1.53 (m, 2H, H_2-3″), 1.56 (br s, 6H, 3×H_2 adamantane), 1.67–1.78 (m, 6H, 3×H_2 adamantane), 1.95 (br s, 3H, 3×CH adamantane), 2.19 (m, 2H, H_2-2″), 2.95 (s, 2H, H_2 adamantane), 3.10–3.50 (m, 8H, 2×NCH_2 morpholino, H_2-1′, H_2-5″), 3.60–3.4.15 (m, 4H, 2×OCH_2 morpholino), 4.22 (s, 4H, 2×H_2 ethylene), 4.47 (dt, *J* = 3.2, 9.6 Hz, 1H, H-2′), 4.76 (d, *J* = 2.8 Hz, 1H, H-3′), 6.78–6.92 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 23.5 (C-3″), 29.8 (CH adamantane), 30.1 (C-4″), 35.2 (Cq adamantane), 36.7 (C-2″), 38.4 (CH_2 adamantane), 40.9 (CH_2 adamantane), 51.4 (C-2′), 54.3 (NCH_2 morpholino), 61.3 (C-1′), 64.8 (OCH_2 morpholino), 65.7 (2×CH_2O), 72.2 (C-5″), 73.4 (C-3′), 83.1 (OCH_2 adamantane), 116.2, 118.0, 120.0 (CHarm), 135.5, 144.7, 144.9 (Cq Carm), 177.3 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3369, 2902, 2848, 1670, 1508, 1286, 1199, 1136, 1066 cm^{-1}; LC–MS: t_R = 7.48 min (linear gradient 10→90% B); ESI-MS: *m/z* = 543.3 $[M+H]^+$, 1107.4 $[2M+Na]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{31}H_{47}N_2O_6$ 543.34286, found 543.34257.

Compound 45: Compound **102** was reacted with **52** according to the general condensation protocol described above. Yield 0.013 g (24 μmol, 62%). $[\alpha]_D^{20}$ = 16.1 (*c* = 0.26 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 0.91 (t, *J* = 7.0 Hz, 3H, CH_3), 1.12–1.47 (m, 12H, 6×H_2 nonanoic amide), 2.15 (m, 2H, H_2-2″), 3.10–4.05 (m, 10H, 2×NCH_2 morpholino, 2×OCH_2 morpholino H_2-1′), 4.21 (s, 4H, 2×H_2 ethylene), 4.50 (dt, *J* = 3.6, 9.4 Hz, 1H, H-2′), 4.77 (d, *J* = 3.2 Hz, 1H, H-3′), 6.77–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 14.4 (CH_3), 23.7, 26.6, 30.2, 30.3, 30.4, 33.0, 37.0 (CH_2 nonanoic amide), 51.4 (C-2′), 61.3 (C-1′), 64.8 (OCH_2 morpholino, NCH_2 morpholino), 65.6 (2×CH_2O), 73.5 (C-3′), 116.2, 118.0, 120.0 (CHarm), 135.5, 144.7, 144.9 (Cq Carm), 177.5 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3352, 2927, 2858, 1652, 1508, 1458, 1286, 1200, 1134, 1066 cm^{-1}; LC–MS: t_R = 6.70 min (linear gradient 10→90% B); ESI-MS: *m/z* = 435.3 $[M+H]^+$, 891.2 $[2M+Na]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{24}H_{39}N_2O_5$ 435.28535, found 435.28499.

Compound 46: Compound **102** was reacted with **55** according to the general condensation protocol described above. Yield 0.013 g (20 μmol, 54%). $[\alpha]_D^{20}$ = 9.8 (*c* = 0.37 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 2.60 (t, *J* = 6.1 Hz, 2H, H_2-2″ propanoic acid), 3.21 (br s, 2H, H_2 morpholino), 3.41 (dd, *J* = 10.2, 13.5 Hz, 1H, H-1′a), 3.50 (dd, *J* = 2.9, 13.5 Hz, 1H, H-1′b), 3.62–9.93 (br m, 9H, 3×H_2 morpholino, OMe), 4.00 (dd, *J* = 6.0, 9.4 Hz, 1H, H-3″a propanoic acid), 4.08 (dd, *J* = 6.2, 9.4 Hz, 1H, H-3″b propanoic acid), 4.17 (s, 4H, 2×H_2 ethylene), 4.53 (dt, *J* = 3.0, 10.1 Hz, 1H, H-2′), 4.78 (d, *J* = 3.3 Hz, 1H, H-3′), 6.74–6.92 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 37.2 (C-2″), 51.7 (C-2′), 56.1 (OMe), 61.1 (C-1′), 64.8 (OCH_2 morpholino, NCH_2 morpholino), 65.6 (2×CH_2O), 65.9 (OCH_2 propanoic acid), 73.5 (C-3′), 115.7, 116.2, 116.8, 118.0, 120.1 (CHarm), 135.3, 144.7, 144.9, 154.0, 155.8 (Cq Carm), 174.7 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3359, 1652, 1506, 1458, 1286, 1200, 1130, 1066 cm^{-1}; LC–MS: t_R = 5.31 min (linear gradient 10→90% B); ESI-MS: *m/z* = 473.2 $[M+H]^+$, 944.4 $[2M+H]^+$, 967.0 $[2M+Na]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{25}H_{33}N_2O_7$ 473.22823, found 473.22789.

Compound 103: Pyrrolidine was reacted with mesylate **6** according to the general procedure described above. Yield 0.042 g (137 μmol, 55%); R_f = 0.75 (MeOH/EtOAc/NH_4OH 40:60:5, *v/v/v*). $[\alpha]_D^{20}$ = 60.8 (*c* = 0.42 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71–1.79 (m, 4H, 2×H_2 pyrrolidine), 2.46–2.57 (m, 4H, 2×NH_2 pyrrolidine), 2.58 (dd, *J* = 4.9, 12.1 Hz, 1H, H-1′a), 2.80 (dd, *J* = 4.9, 12.1 Hz, 1H, H-1′b), 3.78 (dt, *J* = 5.5, 8.4 Hz, 1H, H-2′), 4.26 (s, 4H, 2×H_2 ethylene), 5.07 (d, *J* = 6.0 Hz, 1H, H-3′), 6.31 (s, 1H, NH), 6.83–6.89 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 (2×CH_2 pyrrolidine), 54.2 (2×CH_2N pyrrolidine), 59.3 (C-2′), 59.9 (C-1′), 64.3 (2×CH_2O), 81.3 (C-3′), 114.9, 117.5, 118.9 (CHarm), 131.8, 143.7, 143.9 (Cq Carm), 158.7 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3372, 2933, 2751, 1654, 1508, 1287, 1067, 1008 cm^{-1}; LC–MS: t_R = 4.90 min (linear gradient 0→90% B); ESI-MS: *m/z* = 305.1 $[M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{16}H_{21}N_2O_4$ 305.14958, found 305.14972.

Compound 104: The oxazolidine in compound **103** was hydrolyzed according to the saponification procedure described above. Yield 0.034 g (122 μmol, 89%); R_f = 0.30 (MeOH/EtOAc/NH_4OH 16:4:1, *v/v/v*). $[\alpha]_D^{20}$ = 21.5 (*c* = 0.68 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.75–1.82 (m, 4H, 2×H_2 pyrrolidine), 2.26 (dd, *J* = 4.1, 12.3 Hz, 1H, H-1′a), 2.42–2.51 (m, 2H, H_2 pyrrolidine), 2.56 (dd, *J* = 9.5, 12.4 Hz, 1H, H-1′b), 2.58–2.65 (m, 2H, H_2 pyrrolidine), 3.10 (ddd, *J* = 4.2, 6.4, 10.3 Hz, 1H, H-2′), 4.23 (s, 4H, 2×H_2 ethylene), 4.38 (d, *J* = 6.4 Hz, 1H, H-3′), 6.76–6.84 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 24.3 (2×CH_2 pyrrolidine), 55.3 (2×CH_2N pyrrolidine), 56.5 (C-2′), 59.6 (C-1′), 65.6 (2×CH_2O), 76.1 (C-3′), 116.5, 118.1, 120.6 (CHarm), 136.5, 144.6, 144.9 ppm (Cq Carm); IR (thin film): $\tilde{\nu}$ = 3350, 2877, 1590, 1507, 1458, 1284, 1067 cm^{-1}; LC–MS: t_R = 4.14 min (linear gradient 0→50% B); ESI-MS: *m/z* = 279.3 $[M+H]^+$, 557.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{15}H_{23}N_2O_3$ 279.17032, found 279.17032.

Compound 47: Compound **104** was reacted with **10** according to the general condensation protocol described above. Yield 0.010 g (15 μmol, 37%). $[\alpha]_D^{20}$ = 14.7 (*c* = 0.19 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.38 (dt, *J* = 7.0, 14.1 Hz, 2H, H_2-4″), 1.42 (dt, *J* = 7.1, 14.2 Hz, 2H, H_2-3″), 1.56 (br s, 6H, H_2 adamantane), 1.67–1.78 (m, 6H, 3×H_2 adamantane), 1.95 (br s, 3H, 3×CH adamantine) 2.02 (m, 2H, H_2 pyrrolidine), 2.15 (m, 2H, H_2 pyrrolidine), 2.20 (dt, *J* = 6.5, 14.2 Hz, 2H, H_2-2″), 2.95 (s, 2H, H_2 adamantane), 3.16 (m, 2H, H_2 pyrrolidine), 3.33 (t, *J* = 6.3 Hz, 2H, H_2-5″), 3.38–3.58 (m, 2H, H_2-1′), 3.63 (m, 1H, pyrrolidine), 3.79 (m, 1H, pyrrolidine), 4.21 (s, 4H, 2×H_2 ethylene), 4.44 (dt, *J* = 3.2, 10.2 Hz, 1H, H-2′), 4.77 (d, *J* = 3.1 Hz, 1H, H-3′), 6.78–6.91 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 23.5 (C-3″), 24.0 (CH_2 pyrrolidine), 29.8 (CH adamantane), 30.2 (C-4″), 36.7 (C-2″), 38.4 (CH_2 adamantane), 40.9 (CH_2 adamantane), 53.2 (C-2′), 55.4 (CH_2 pyrrolidine), 56.9 (CH_2 pyrrolidine), 58.6 (C-1′), 65.6 (2×CH_2O), 72.2 (C-5″), 73.4 (C-3′), 83.1 (OCH_2 adamantane), 116.2, 118.0, 120.0 (CHarm), 135.6, 144.6, 144.9 (Cq Carm), 177.1 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3394, 1750, 1203, 1132, 1064 cm^{-1}; LC–MS: t_R = 7.60 min (linear gradient 10→90% B); ESI-MS: *m/z* = 527.3 $[M+H]^+$, 1052.9 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{31}H_{47}N_2O_5$ 527.34795, found 527.34763.

Compound 3: Compound **104** was reacted with **52** according to the general condensation protocol described above. Yield 0.011 g (21 μmol, 53%). $[\alpha]_D^{20}$ = 18.6 (*c* = 0.23 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 0.91 (t, *J* = 7.0 Hz, 3H, CH_3), 1.14–1.50 (m, 12H, 6×H_2 nonanoic amide), 1.95–2.22 (m, 6H, H_2-2″, 2×H_2 pyrrolidine), 3.11–3.20 (m, 2H, H_2 pyrrolidine), 3.41 (dd, *J* = 3.6, 13.2 Hz, 1H, H-1′a), 3.47 (dd, *J* = 10.0, 13.2 Hz, 1H, H-1′b), 3.64 (br s, 1H, H pyrrolidine), 3.78 (br s, 1H, H pyrrolidine), 4.21 (s, 4H, 2×H_2 ethylene), 4.44 (dt, *J* = 3.5, 10.0 Hz, 1H, H-2′), 4.77 (d, *J* = 3.2 Hz, 1H, H-3′), 6.77–

6.90 ppm (m, 3H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 14.4 (CH_3), 23.7, 24.0, 26.7, 30.2, 30.3, 30.5, 31.1, 33.0, 37.1 (2×CH_2 pyrrolidine, 7×CH_2 nonanoic amide), 53.0 (C-2′), 55.4 (CH_2 pyrrolidine), 56.9 (CH_2 pyrrolidine), 58.6 (C-1′), 65.6 (2×CH_2O), 73.4 (C-3′), 116.2, 118.0, 120.0 (CHarm), 135.6, 144.6, 144.8 (Cq Carm), 177.3 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3352, 2931, 2856, 1670, 1508, 1286, 1200, 1134, 1068 cm^{-1}; LC–MS: t_R = 6.61 min (linear gradient 10→90% B); ESI-MS: *m/z* = 419.3 $[M+H]^+$, 836.7 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{24}H_{39}N_2O_4$ 419.29043, found 419.29007.

Compound 48: Compound **104** was reacted with **55** according to the general condensation protocol described above. Yield 0.012 g (21 μmol, 53%). $[\alpha]_D^{20}$ = 14.0 (*c* = 0.25 in MeOH); ^{1}H NMR (400 MHz, MeOD): δ = 1.98 (br s, 2H, H_2 pyrrolidine), 2.12 (br s, 2H, H_2 pyrrolidine), 2.62 (t, *J* = 6.2 Hz, 2H, H_2-2″), 3.11–3.19 (m, 2H, pyrrolidine), 3.41–3.19 (m, 2H, H_2-1′), 3.65 (br s, 1H, H pyrrolidine), 3.74 (br s, 3H, H piperidine, OMe), 3.77 (br s, 1H, H pyrrolidine), 4.02 (dt, *J* = 6.1, 9.4 Hz, 1H, propanoic acid), 4.08 (dt, *J* = 6.2, 9.5 Hz, 1H, propanoic acid), 4.17 (s, 4H, 2×H_2 ethylene), 4.47 (dt, *J* = 4.1, 7.8 Hz, 1H, H-2′), 4.77 (d, *J* = 3.2 Hz, 1H, H-3′), 6.74–6.91 ppm (m, 7H, Harm); ^{13}C NMR (100 MHz, MeOD): δ = 23.9 (CH_2 pyrrolidine), 24.0 (CH_2 pyrrolidine), 31.1 (C-2″), 53.4 (C-2′), 55.6 (CH_2 pyrrolidine), 56.1 (OMe), 56.8 (CH_2 pyrrolidine), 58.4 (C-1′), 65.6 (2×CH_2O), 65.9 (OCH_2 propanoic acid), 73.5 (C-3′), 115.7, 116.2, 116.8, 118.0, 120.1, 120.6 (CHarm), 135.4, 144.7, 144.9, 154.0, 155.8 (Cq Carm), 174.4 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3377, 1670, 1508, 1286, 1200, 1130, 1066 cm^{-1}; LC–MS: t_R = 5.24 min (linear gradient 10→90% B); ESI-MS: *m/z* = 457.2 $[M+H]^+$, 912.3 $[2M+H]^+$; HRMS [QTOF, MH^+] *m/z* calculated for $C_{25}H_{33}N_2O_6$ 457.23331, found 457.23299.

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