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Synthesis and α-amylase inhibitory activity of glucose–deoxynojirimycin conjugates

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ABSTRACT

Inhibitors of α-amylase have attracted attention for their putative effects against diabetes mellitus. Although numerous studies have explored natural small molecule inhibitors, acarbose is currently the only compound with sufficient inhibitory potency and drug-like characteristics to be considered as a potential therapeutic agent. We have synthesized conjugates of the potent glucosidase inhibitor, 1-deoxynojirimycin, and glucose, with the aim of enhancing inhibitory activity against α-amylase. This synthetic conjugate showed increased inhibition of α-amylase compared to 1-deoxynojirimycin alone, suggesting that similar modifications of existing glucosidase inhibitors may yield more potent α-amylase inhibitors.

1. Introduction

Glucosidases play roles in a variety of crucial processes in the human body, one of which is the digestion of energy-containing polysaccharides. Several different glucosidases participate in this process, including salivary/pancreatic α-amylase and intestinal α-glucosidases (e.g., maltase–glucoamylase complex and sucrase–isomaltase complex). These enzymes hydrolyze polysaccharides to monosaccharides, which are then absorbed from the intestine into the blood stream. In type 2 diabetes mellitus (T2DM), failure to remove monosaccharides from the blood into the tissues leads to hyperglycemia in patients, which raises the risk of cardiovascular disease, renal failure, blindness and neurological disorders.[1] Inhibition of polysaccharide digestion prevents rapid glucose uptake from the intestine and alleviates the hyperglycemic threat caused by food intake. Accordingly, much effort has been put into the development of glycosidase inhibitors for the treatment of T2DM.

For intestinal α-glucosidases, several potent inhibitors are known including deoxynojirimycin (DNJ),[2] salacinol,[3] miglitol, and voglibose.[4] The last two compounds are currently used therapeutically for T2DM. Moreover, many natural compounds are reported to have α-glucosidase inhibitory activity.[5] However, few small molecule inhibitors have been reported for α-amylase. Acarbose, a compound used for the treatment of T2DM, is the only widely utilized small molecule inhibitor.[6] Several peptide inhibitors have been identified,[7] but instability in the harsh gastric environment prohibits their use as medicines against T2DM. Development of a small molecule α-amylase inhibitor will increase clinicians' options for the treatment of T2DM. We here show our approach toward the design and synthesis of a small molecule α-amylase inhibitor.

α-Amylase is an enzyme that hydrolyzes polysaccharides, such as starch. Although a member of the glucosidase family, their substrate recognition is more specific toward polysaccharides. Its binding site consists of several partitions called 'sub-sites', which individually recognize a sugar unit.[8,9] Each sub-site has relatively low affinity toward the sugar unit, but by recognizing multiple sugar units with multiple sub-sites, α-amylase increases its affinity toward a polysaccharide, enabling specific binding and hydrolysis.[9] This multiple sub-site system precludes a low molecular weight compound from being an efficient inhibitor. Most glucosidase inhibitors work as an active site inhibitor by mimicking glucose or its activated state.[10] α-Amylase possesses a similar active site to other glucosidases,[9] but small molecule inhibitors like DNJ mimics only a single glucose unit and thus can have only low affinity toward α-amylase. The small molecule α-amylase inhibitor, acarbose, inhibits the active site of α-amylase by its core structure, acarviosine, but has increased affinity toward α-amylase due to additional sugar units within its molecular structure. We believe that the addition of a sugar unit to an active site inhibitor could be the key to developing small molecule α-amylase inhibitors. Accordingly, we have designed and synthesized a series of glucose–DNJ conjugates

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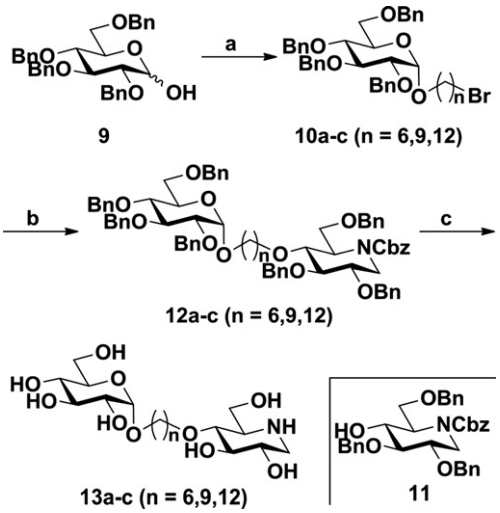
that have DNJ as an active site inhibitor connected through an alkyl linker to an additional glucose. These conjugates were tested for inhibitory activity against α-amylase.

2. Results and discussion

2.1. Synthesis of glucose–DNJ conjugates

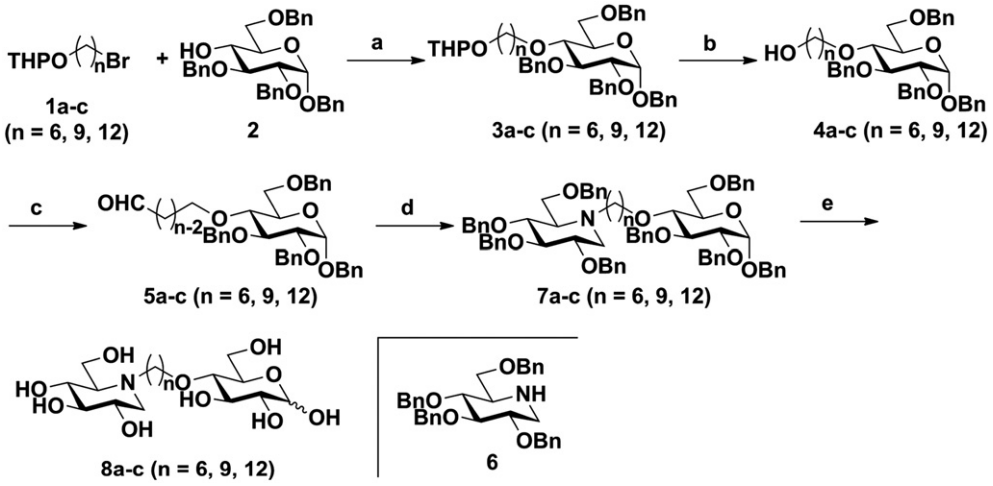
We chose two types of glucose–DNJ conjugates (**8a**–**c**, **13a**–**f**) to develop and test for α-amylase inhibitory activity. Compounds **8a**–**c** have a glucose attached through the nitrogen atom of DNJ, while in Compounds **13a**–**f** it is attached through the DNJ 4-OH group to place the glucose at an alternative sub-site. The length of the alkyl linker was varied to optimize its flexibility and to place the glucose accurately at a sub-site.

For the synthesis of **8a**–**c**, benzyl protected DNJ (**6**) was prepared and coupled with the glucose-linker conjugate (**5**).[11] 1,2,3,6-Tetra-*O*-benzyl-α-D-glucopyranose (**2**) was reacted with alkyl bromide (**1**) to give 4-*O*-bromoalkylated glucose (**3**). After removal of the THP group, the resulting alcohol (**4**) was oxidized by Dess–Martin periodinane to an aldehyde (**5**). Aldehyde (**5**) and **6** were then coupled by a reductive amination method, and removal of benzyl groups from the resulting conjugate (**7**) gave the products (**8a**–**c**), in which the DNJ and glucose are connected by alkyl linkers of 6, 9, and 12 atom lengths, respectively (Scheme 1).



Scheme 2. Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2 then TMU, TEAB, bromoalkyl alcohol; (b) **11**, NaH, DMF; (c) $Pd(OH)_2$, H_2, 1 M HCl aq, THF, EtOH.

elimination of a bromide. It is reported that bromobutyl glycosides can be utilized as a glycosyl donor by assisting the formation of an intramolecular furan ring, which is considered as an activated state.[13] As a pyrane ring can also be formed stably, bromopentyl



Scheme 1. Reagents and conditions: (a) NaH, DMF; (b) PPTS, EtOH, 55 °C; (c) Dess–Martin periodinane, CH_2Cl_2; (d) **6**, $NaBH_3CN$, AcOH, MeOH, CH_2Cl_2; (e) Pd/C, H_2, 1 M HCl aq, EtOH.

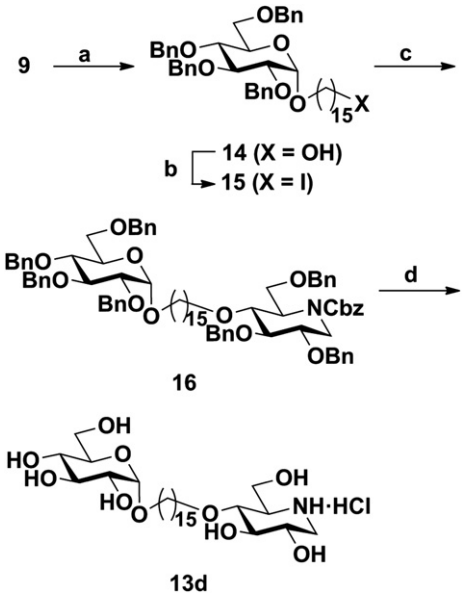
Conjugates **13a**–**c** were prepared in the following order. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**9**) was subjected to α-selective glycosylation with bromoalkyl alcohol to afford **10**.[12] This was then coupled with DNJ (**11**) under basic conditions using NaH (with DMF as a solvent), which gave **12** at a low yield. Removal of the protective groups from **12** afforded **13a**–**c** (Scheme 2).

Synthesis of **13d** required modification of a reaction condition, as the procedure using ω-bromopentadecyl glucoside and **11** with NaH as a base gave no product. To increase the reactivity, the leaving group was replaced from a bromide to an iodide, and as the solubility of **15** in DMF was relatively low compared to **10a**–**c**, THF was used as a solvent. Using this fixed substrate and solvent, reaction of **15** and **11** was facilitated and gave **16** as a product, which was then applied to a hydrogenation step to remove the protective groups to give **13d** (Scheme 3).

Synthesis of **13e** and **13f** also required modification of a reaction, as the reaction of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(4-bromobutyl)-α-D-glucopyranose and 2,3,4,6-tetra-*O*-benzyl-1-*O*-(5-bromopentyl)-α-D-glucopyranose, under basic conditions, resulted only in the glycoside may act in the same manner. Thus, attributing this intramolecular ring formation as the reason for bromide elimination, we chose to connect an alkyl linker with DNJ (**11**) before attaching glucose. Alkyl iodide (**17**) was first reacted with **11**, and subsequent removal of the PMB group gave **19**. This was then used as a glycosyl acceptor in the α-selective glycosylation reaction to give **20** as the product. Deprotection of **20** gave **13e**,**f** (Scheme 4). Also, to ensure the effect of glucose in α-amylase inhibition, compounds **23a**–**f** were synthesized either by deprotection of the intermediate product or by coupling alkyl halide with **11** (Scheme 5).

2.2. α-Amylase inhibitory activity of glucose–DNJ conjugates

Initially, **8a**–**c** and **13a**–**c** were tested for their α-amylase inhibitory activity to assess the effects of linking DNJ and glucose through different linker groups. Commercial porcine pancreatic α-amylase was used as an enzyme source and 2,4-dinitrophenyl maltotriose was used as a model substrate.[14] Fig. 1 shows the inhibitory activity of tested compounds at 3 mM. It can be seen that



Scheme 3. Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2 then TMU, TEAB, 15-hydroxypentadecanol; (b) NIS, PPh_3, imidazole, CH_2Cl_2; (c) **11**, NaH, THF; (d) $Pd(OH)_2$, H_2, 1 M HCl aq, THF, EtOH.

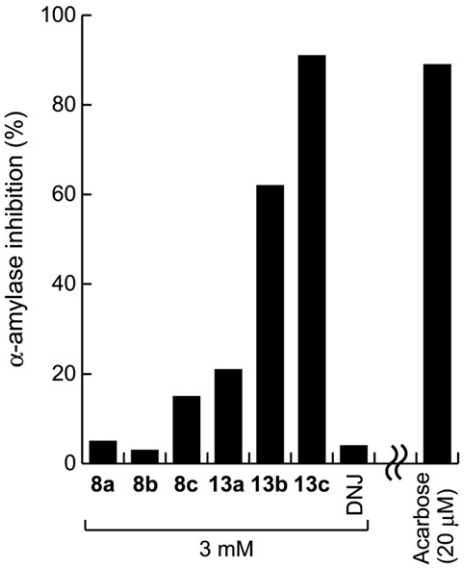
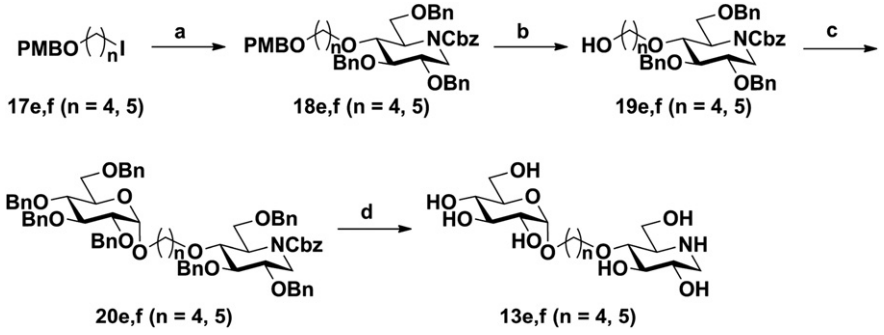
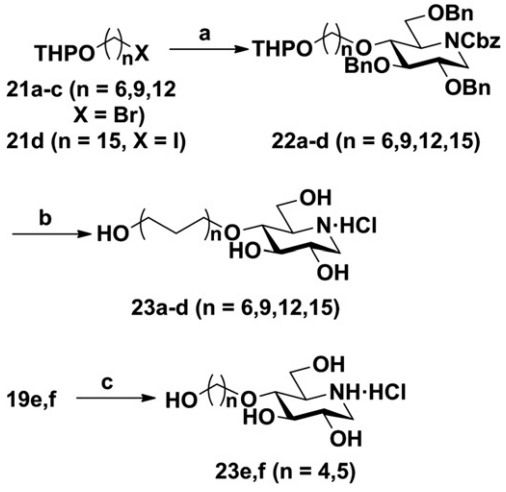


Fig. 1. α-Amylase inhibitory activity of **8a**–**c** and **13a**–**c** tested at 3 mM. Acarbose (20 μM) was used as a positive control.



Scheme 4. Reagents and conditions: (a) **11**, NaH, DMF; (b) TFA, CH_2Cl_2; (c) 2,3,4,6-tetra-*O*-benzyl-D-glycosyl bromide, TMU, TEAB, CH_2Cl_2; (d) $Pd(OH)_2$, H_2, 1 M HCl aq, THF, EtOH.



Scheme 5. Reagents and conditions: (a) **11**, NaH, THF/DMF, TBAI (for synthesis of **22a**–**c**); (b) PPTS, MeOH then 1 M HCl aq, $Pd(OH)_2$, H_2; (c) $Pd(OH)_2$, H_2, 1 M HCl aq, MeOH.

DNJ has negligible inhibitory activity toward α-amylase, as do Compounds **8a** and **8b**, with only a minor increase in inhibitory activity in Compound **8c**, suggesting that the glucose moiety in these compounds has little effect on DNJ activity. In contrast, the glucose moiety in conjugates **13a**–**c** seems to increase effectively the inhibitory activity of DNJ depending on the length of the alkyl linker, with the greatest activity being in Compound **13c** that has a 12-carbon linker.

The nitrogen atom of DNJ plays a key role in the inhibition of α-glucosidase by giving a positive charge at the position resembling the activated state of α-glucoside hydrolysis by α-glucosidase. The weak inhibitory activity of **8a**–**c** may be due to modification of this nitrogen atom by an interfering alkyl chain. However, as a similar nitrogen-modified compound, miglitol, retains α-glucosidase inhibitory activity,[4a] this is unlikely to account for its comparatively low inhibitory activity relative to **13a**–**c**. From the study of α-amylase, the sub-site of the enzyme located at the non-reducing end contributes more than that at the reducing end in the recognition of substrate.[15] The results shown in Fig. 1 appear to confirm this and indicate the benefits of attaching an additional moiety through the 4-OH group of DNJ.

To investigate the effect of linker length on α-amylase inhibition, and also to optimize the efficacy of the glucose moiety, we tested and compared **13a**–**f** together with **23a**–**f**. The results are summarized in Table 1. Compounds **13a**,**e**,**f** and **23a**,**e**,**f** had relatively low inhibitory activity and we were unable to define IC_{50} values for these compounds. Therefore, these compounds were compared at 5 mM. For Compounds **13b**,**c**,**d** and **23b**,**c**, IC_{50} values were calculated, but **23d** had low solubility under assay conditions and could

Table 1
α-Amylase inhibitory activity of synthetic glucose–DNJ conjugates

	Linker length (number of atoms)	Inhibition at 5 mM (%)		IC_{50} (mM)	
		13	**23**	**13**	**23**
e	4	22	12	>5.00	>5.00
f	5	23	19	>5.00	>5.00
a	6	32	25	>5.00	>5.00
b	9	70	64	2.29	3.15
c	12	97	—	0.77	1.20
d	15	—	—	1.12	—
DNJ	0	7		>5.00	

—: Unable to define inhibition due to low solubility.

not be tested. From our results, the length of the linker has a primary effect on α-amylase inhibition, and the inhibition gradually increased by adding length to the linker. The most potent was **13c**, and shorter or longer linkers negatively affected the inhibitory activity, although reduced solubility of **13d** (15 carbon linker) might be masking a further increase in activity in this compound. The effect of the glucose moiety can be seen from the inhibitory activity of **13** and **23**. Regardless of the linker length, addition of a glucose moiety increases the inhibitory activity. However, the increase induced by addition of the glucose moiety was smaller than expected, and the enhancement of inhibitory activity appears to depend heavily on the length of the alkyl linker. From the structure of α-amylase, the substrate-binding site of the enzyme is surrounded by a hydrophobic surface.[16] The effect of the alkyl linker is presumably a result of binding to this surface. Furthermore, although the glucose moiety is generally hydrophilic, the top and bottom of the pyranose ring are hydrophobic, and may thus contribute somewhat to its affinity. The fact that addition of an extra moiety to the small molecule glucosidase inhibitor, DNJ, increased its inhibition against α-amylase is an important breakthrough in the development of small molecule glucosidase inhibitors against α-amylase using rationally designed modification.

3. Conclusion

In conclusion, we have synthesized glucose–DNJ conjugates connected by alkyl linkers of various lengths. Addition of glucose through the nitrogen atom of DNJ had a negligible effect on α-amylase inhibition but addition through the 4-OH group dramatically increased α-amylase inhibitory activity. Among the synthesized compounds, the most effective was **13c**, which has dodecyl linker between the DNJ and glucose moieties. Our results show the importance of hydrophobic interactions in α-amylase inhibition. We aim to utilize this hydrophobic interaction to develop more potent DNJ-based α-amylase inhibitors.

4. Experimental section

4.1. General methods

Porcine pancreatic amylase was purchased from Sigma–Aldrich Co. and 2,4-dinitrophenyl α-maltotriose was synthesized according to the literature.[14] All other commercially available chemicals were purchased from Wako Pure Chem. Ind. Ltd. and used without further purification. Structures of synthetic compounds were determined by NMR and mass spectrometry. Bruker AMX500 or Jeol JNM-EX 270 was used to obtain NMR spectra and either tetramethylsilane (TMS), *tert*-butanol or residual solvent peaks were used as an internal standard (^{1}H NMR: TMS 0.00 ppm ($CDCl_3$), CD_3OD 3.30 ppm, *tert*-butanol 1.24 ppm (D_2O); ^{13}C NMR: $CDCl_3$ 77.0 ppm, CD_3OD 49.0 ppm, *tert*-butanol 30.3 ppm (D_2O)). Jeol JMS SX-102A FAB-MS or Jeol JMS-T100GCV (FD-MS) or Thermo Scientific Exactive (ESI-MS) was used to obtain mass spectra. Absorbance was measured using a Synergy™ MX (Bio-tech Instruments Inc.,) microplate reader.

4.2. Synthesis of glucose–DNJ conjugate

*4.2.1. General procedure for the synthesis of **3**.* 1,2,3,6-Tetra-*O*-benzyl-α-D-glucopyranose (**2**, 1 equiv) was dissolved in DMF and 60% NaH (2 equiv) in oil was added at 0 °C. After stirring the mixture for 30 min at room temperature (rt), **1** (1.2 equiv) dissolved in DMF was added and stirred for 24 h. The reaction was quenched by adding MeOH and water was added to the resulting solution. The solution was extracted by EtOAc, dried over sodium sulfate, and evaporated to dryness. The residue was purified by silica-gel column chromatography to give **3**.

*4.2.1.1. 1,2,3,6-Tetra-O-benzyl-4-O-[6-(tetrahydropyranyloxy) hexyl]-α-D-glucopyranose (**3a**).* Oil, yield 69%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.8 Hz), 4.80 (1H, d, *J*=3.5 Hz), 4.76 (1H, d, *J*=10.8 Hz), 4.59–4.69 (3H, m), 4.46–4.54 (4H, m), 3.90 (1H, dd, *J*=9.3, 9.3 Hz), 3.84 (1H, m), 3.63–3.76 (4H, m), 3.56 (1H, dd, *J*=1.9, 10.6 Hz), 3.45–3.49 (2H, m), 3.36–3.41 (2H, m), 3.32 (1H, dt, *J*=6.7, 9.6 Hz), 1.17–1.83 (14H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.8, 137.1, 128.3, 128.2, 127.74, 127.72, 127.68, 127.64, 127.53, 127.46, 127.3, 98.7, 95.4, 81.9, 79.6, 77.7, 75.5, 73.3, 73.0, 72.8, 70.4, 68.9, 68.3, 67.4, 62.1, 30.6, 30.2, 29.5, 26.0, 25.9, 25.3, 19.5 ppm; $[\alpha]_D^{25}$ +52.0 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 747.3854, $C_{45}H_{56}O_8Na^+$ requires *m*/*z* 747.3867.

*4.2.1.2. 1,2,3,6-Tetra-O-benzyl-4-O-[9-(tetrahydropyranyloxy) nonyl]-α-D-glucopyranose (**3b**).* Oil, yield 89%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.8 Hz), 4.80 (1H, d, *J*=3.6 Hz), 4.77 (1H, d, *J*=10.8 Hz), 4.47–4.69 (7H, m), 3.91 (1H, dd, *J*=9.3, 9.3 Hz), 3.86 (1H, m), 3.69–3.77 (3H, m), 3.65 (1H, dd, *J*=3.7, 10.6 Hz), 3.56 (1H, dd, *J*=1.9, 10.6 Hz), 3.46–3.50 (2H, m), 3.34–3.42 (3H, m), 1.14–1.85 (20H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.8, 137.1, 128.2, 128.1, 127.72, 127.70, 127.63, 127.49, 127.42, 127.31, 98.6, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 73.0, 72.8, 70.4, 68.8, 68.3, 67.5, 62.1, 30.6, 30.2, 29.6, 29.4, 29.31, 29.26, 26.1, 26.0, 25.3, 19.5 ppm; $[\alpha]_D^{25}$ +50.4 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 789.4326, $C_{48}H_{62}O_8Na^+$ requires *m*/*z* 789.4337.

*4.2.1.3. 1,2,3,6-Tetra-O-benzyl-4-O-[12-(tetrahydropyranyloxy) dodecyl]-α-D-glucopyranose (**3c**).* Oil, yield 80%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.8 Hz), 4.80 (1H, d, *J*=3.6 Hz), 4.77 (1H, d, *J*=10.8 Hz), 4.47–4.69 (7H, m), 3.91 (1H, dd, *J*=9.3, 9.3 Hz), 3.85 (1H, m), 3.69–3.77 (3H, m), 3.65 (1H, dd, *J*=3.7, 10.6 Hz), 3.56 (1H, dd, *J*=1.9, 10.6 Hz), 3.46–3.50 (2H, m), 3.34–3.42 (3H, m), 1.20–1.84 (26H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.9, 137.1, 128.3, 128.2, 128.1, 127.74, 127.66, 127.53, 127.45, 127.33, 127.31, 98.6, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 73.0, 72.8, 70.4, 68.8, 68.3, 67.5, 62.1, 30.6, 30.3, 29.6, 29.44, 29.40, 29.3, 26.1, 26.0, 25.4, 19.5 ppm; $[\alpha]_D^{25}$ +48.2 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 831.4790, $C_{51}H_{68}O_8Na^+$ requires *m*/*z* 831.4806.

*4.2.2. General procedure for the synthesis of **4**.* Compound **3** (1 equiv) was dissolved in EtOH and PPTS (10 mol %) was added. The solution was stirred for 6 h at 50 °C, poured in satd $NaHCO_3$ aq and extracted by EtOAc. Organic layer was dried over sodium sulfate, evaporated, and purified by silica-gel column chromatography to give **4**.

*4.2.2.1. 1,2,3,6-Tetra-O-benzyl-4-O-(6-hydroxyhexyl)-α-D-glucopyranose (**4a**).* Oil, yield 97%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.94 (1H, d, *J*=10.9 Hz), 4.80 (1H, d, *J*=3.6 Hz), 4.76 (1H, d,

J=10.9 Hz), 4.46–4.69 (6H, m), 3.91 (1H, dd, *J*=9.5 Hz), 3.70–3.76 (2H, m), 3.64 (1H, dd, *J*=3.6, 10.5 Hz), 3.56 (1H, m), 3.48 (1H, dd, *J*=3.6, 9.5 Hz), 3.38–3.42 (2H, m), 1.22–1.54 (8H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.8, 138.0, 137.8, 137.0, 128.3, 128.2, 127.74, 127.66, 127.54, 127.45, 127.32, 95.4, 81.8, 79.5, 77.6, 75.4, 73.2, 72.9, 72.8, 70.3, 68.8, 68.3, 62.5, 32.4, 30.1, 25.8, 25.5 ppm; $[\alpha]_D^{26}$ +67.1 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 663.3292, $C_{40}H_{48}O_7Na^+$ requires *m*/*z* 663.3292.

*4.2.2.2. 1,2,3,6-Tetra-O-benzyl-4-O-(9-hydroxynonyl)-α-D-glucopyranose (**4b**).* Oil, yield quant.; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.8 Hz), 4.80 (1H, d, *J*=3.6 Hz), 4.77 (1H, d, *J*=10.8 Hz), 4.47–4.69 (6H, m), 3.91 (1H, dd, *J*=9.2, 9.3 Hz), 3.70–3.76 (2H, m), 3.64 (1H, dd, *J*=3.8, 10.6 Hz), 3.61 (1H, m), 3.56 (1H, dd, *J*=2.0, 10.6 Hz), 3.48 (1H, dd, *J*=3.6, 9.6 Hz), 3.37–3.42 (2H, m), 1.17–1.56(14H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.7, 138.0, 137.8, 137.0, 128.2, 128.1, 127.69, 127.68, 127.60, 127.49, 127.40, 127.29, 95.3, 81.8, 79.5, 77.6, 75.4, 73.2, 73.0, 72.8, 70.3, 68.8, 68.3, 62.5, 32.5, 30.2, 29.32, 29.24, 29.17, 25.9, 25.5 ppm; $[\alpha]_D^{26}$ +62.8 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 705.3760, $C_{43}H_{54}O_7Na^+$ requires *m*/*z* 705.3762.

*4.2.2.3. 1,2,3,6-Tetra-O-benzyl-4-O-(12-hydroxydodecyl)-α-D-glucopyranose (**4c**).* Oil, yield 91%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.8 Hz), 4.80 (1H, d, *J*=3.6 Hz), 4.77 (1H, d, *J*=10.8 Hz), 4.47–4.69 (6H, m), 3.91 (1H, dd, *J*=9.3, 9.3 Hz), 3.70–3.77 (2H, m), 3.60–3.66 (3H, m), 3.56 (1H, dd, *J*=2.0, 10.6 Hz), 3.48 (1H, dd, *J*=3.6, 9.6 Hz), 3.37–3.42 (2H, m), 1.20–1.57 (20H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.9, 137.1, 128.3, 128.23, 128.19, 127.8, 127.7, 127.6, 127.5, 127.4, 95.5, 82.0, 79.6, 77.7, 75.5, 73.3, 73.2, 72.9, 70.4, 68.9, 68.4, 62.8, 32.7, 30.3, 29.5, 29.3, 26.1, 25.7 ppm; $[\alpha]_D^{26}$ +58.2 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 747.4236, $C_{46}H_{60}O_7Na^+$ requires *m*/*z* 747.4231.

*4.2.3. General procedure for the synthesis of **5**.* Compound **4** (1 equiv) was dissolved in CH_2Cl_2 and Dess–Martin Periodinane (1.2 equiv) was added at 0 °C. After stirring for 90 min at rt, MeOH was added to quench the reaction. To this solution, Et_2O was added and the precipitate was filtered off by passing through the Celite pad. Filtrate was evaporated and the residue was purified by silica-gel column chromatography to give **5**.

*4.2.3.1. 1,2,3,6-Tetra-O-benzyl-4-O-(6-oxohexyl)-α-D-glucopyranose (**5a**).* Oil, yield 82%; ^{1}H NMR (500 MHz, $CDCl_3$): 9.68 (1H, t, *J*=1.8 Hz), 7.23–7.40 (20H, m), 4.95 (1H, d, *J*=11.0 Hz), 4.81 (1H, d, *J*=3.6 Hz), 4.74 (1H, d, *J*=11.0 Hz), 4.46–4.70 (6H, m), 3.90 (1H, dd, *J*=9.3, 9.3 Hz), 3.72 (2H, m), 3.64 (1H, dd, *J*=3.7, 10.5 Hz), 3.55 (1H, dd, *J*=2.0, 10.5 Hz), 3.48 (1H, dd, *J*=3.6, 9.6 Hz), 3.35–3.41 (2H, m), 2.31 (2H, dt, *J*=1.8, 7.4 Hz), 1.52 (2H, m), 1.41 (2H, m), 1.14–1.28 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 202.4, 138.8, 138.0, 137.9, 137.1, 128.3, 128.22, 128.19, 127.80, 127.74, 127.70, 127.64, 127.59, 127.52, 127.37, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 72.8, 72.6, 70.3, 68.9, 68.3, 43.6, 30.0, 25.6, 21.8 ppm; $[\alpha]_D^{24}$ +58.1 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 661.3148, $C_{40}H_{46}O_7Na^+$ requires *m*/*z* 661.3136.

*4.2.3.2. 1,2,3,6-Tetra-O-benzyl-4-O-(9-oxononyl)-α-D-glucopyranose (**5b**).* Oil, yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$): 9.73 (1H, t, *J*=1.8 Hz), 7.23–7.39 (20H, m), 4.93 (1H, d, *J*=10.9 Hz), 4.81 (1H, d, *J*=3.7 Hz), 4.76 (1H, d, *J*=10.9 Hz), 4.47–4.69 (6H, m), 3.91 (1H, dd, *J*=9.3 Hz), 3.73 (2H, m), 3.64 (1H, dd, *J*=3.6, 10.6 Hz), 3.56 (1H, dd, *J*=2.0, 10.6 Hz), 3.48 (1H, dd, *J*=3.7, 9.6 Hz), 3.40 (2H, m), 2.38 (2H, dt, *J*=1.8, 7.3 Hz), 1.54–1.61 (2H, m), 1.42 (2H, m), 1.16–1.27 (8H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 202.5, 138.8, 138.0, 137.8, 137.0, 128.2, 128.14, 128.11, 127.71, 127.64, 127.60, 127.49, 127.41, 127.29, 95.4, 81.9, 79.5, 77.6, 75.4, 73.2, 73.0, 72.8, 70.3, 68.8, 68.3, 43.6, 30.1, 29.09, 29.07, 28.9, 25.9, 21.8 ppm; $[\alpha]_D^{25}$ +56.2 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 703.3621, $C_{43}H_{55}O_7Na^+$ requires *m*/*z* 703.3605.

*4.2.3.3. 1,2,3,6-Tetra-O-benzyl-4-O-(12-oxododecyl)-α-D-glucopyranose(**5c**).* Oil, yield 97%; ^{1}H NMR (500 MHz, $CDCl_3$): 9.74 (1H, t, *J*=1.8 Hz), 7.24–7.40 (20H, m), 4.93 (1H, d, *J*=10.9 Hz), 4.81 (1H, d, *J*=3.7 Hz), 4.76 (1H, d, *J*=10.9 Hz), 4.47–4.70 (6H, m), 3.91 (1H, dd, *J*=9.3 Hz), 3.73 (2H, m), 3.65 (1H, dd, *J*=3.6, 10.6 Hz), 3.57 (1H, dd, *J*=2.0, 10.6 Hz), 3.48 (1H, dd, *J*=3.7, 9.6 Hz), 3.40 (2H, m), 2.38 (2H, dt, *J*=1.8, 7.4 Hz), 1.20–1.64 (18H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 202.9, 138.9, 138.1, 137.9, 137.1, 128.36, 128.25, 128.23, 128.21, 127.84, 127.74, 127.72, 127.62, 127.53, 127.42, 95.5, 82.0, 79.6, 77.7, 75.6, 73.4, 73.2, 72.9, 70.4, 68.9, 68.4, 43.8, 30.3, 29.5, 29.4, 29.32, 29.26, 29.1, 26.1, 22.0 ppm; $[\alpha]_D^{25}$ +56.9 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ found *m*/*z* 745.4096, $C_{46}H_{58}O_7Na^+$ requires *m*/*z* 745.4075.

*4.2.4. General procedure for the synthesis of **7**.* Compound **5** (1 equiv) and **6** (1.2 equiv) were immersed in MeOH/AcOH (200/1) and CH_2Cl_2 was added until all the components dissolves. The solution was cooled to 0 °C, 90% $NaBH_3CN$ (2 equiv) was added and stirred for 12 h at rt. The reaction mixture was concentrated and purified by preparative TLC (PTLC) to give **7**.

*4.2.4.1. 1,2,3,6-Tetra-O-benzyl-4-O-[6-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-benzyloxymethylpiperidino]hexyl]-α-D-glucopyranose (**7a**).* Oil, yield 95%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.15–7.44 (40H, m), 4.99 (2H, dd, *J*=4.0, 10.9 Hz), 4.81–4.91 (5H, m), 4.65–4.74 (5H, m), 4.43–4.59 (6H, m), 3.97 (1H, dd, *J*=9.2, 9.3 Hz), 3.77–3.82 (2H, m), 3.60–3.71 (5H, m), 3.41–3.55 (5H, m), 3.10 (1H, dd, *J*=4.8, 11.3 Hz), 2.54–2.69 (2H, m), 2.32 (1H, br d, *J*=9.4 Hz), 2.25 (1H, dd, *J*=10.7, 10.8 Hz), 1.09–1.48 (8H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.93, 138.87, 138.48, 138.46, 138.1, 137.9, 137.7, 137.1, 128.3, 128.26, 128.22, 127.82, 127.76, 127.72, 127.62, 127.53, 127.44, 127.42, 127.33, 95.5, 87.3, 82.0, 79.7, 78.48, 78.44, 77.7, 75.5, 75.2, 75.1, 73.4, 73.3, 73.0, 72.9, 72.6, 70.4, 69.0, 68.4, 65.2, 63.5, 54.4, 52.3, 30.4, 27.4, 26.1, 23.4 ppm; $[\alpha]_D^{24}$ +37.5 (*c* 0.85, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ found *m*/*z* 1146.6078, $C_{74}H_{84}O_{10}N^+$ requires *m*/*z* 1146.6090.

*4.2.4.2. 1,2,3,6-Tetra-O-benzyl-4-O-[9-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-benzyloxymethylpiperidino]nonyl]-α-D-glucopyranose (**7b**).* Oil, yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.12–7.41 (40H, m), 4.95 (2H, d, *J*=10.9 Hz), 4.77–4.88 (5H, m), 4.61–4.70 (5H, m), 4.40–4.56 (6H, m), 3.93 (1H, dd, *J*=9.3, 9.3 Hz), 3.72–3.79 (2H, m), 3.57–3.68 (5H, m), 3.53 (1H, dd, *J*=2.2, 10.4 Hz), 3.50 (1H, dd, *J*=3.6, 9.6 Hz), 3.45 (1H, dd, *J*=9.0, 9.0 Hz), 3.39–3.44 (2H, m), 3.08 (1H, dd, *J*=4.8, 11.3 Hz), 2.52–2.68 (2H, m), 2.29 (1H, dd, *J*=2.2, 9.5 Hz), 2.22 (1H, dd, *J*=10.7, 10.8 Hz), 1.08–1.46 (14H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.92, 138.85, 138.47, 138.45, 138.1, 137.9, 137.7, 137.1, 128.3, 128.22, 128.18, 127.78, 127.72, 127.69, 127.58, 127.49, 127.38, 127.29, 95.5, 87.3, 82.0, 79.6, 78.48, 78.42, 77.7, 75.5, 75.2, 75.0, 73.3, 73.1, 73.0, 72.9, 72.6, 70.4, 68.9, 68.4, 65.2, 63.6, 54.4, 52.3, 30.3, 29.5, 29.4, 27.4, 26.1, 23.4 ppm; $[\alpha]_D^{24}$ +32.1 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ found *m*/*z* 1188.6549, $C_{77}H_{90}O_{10}N^+$ requires *m*/*z* 1188.6559.

*4.2.4.3. 1,2,3,6-Tetra-O-benzyl-4-O-[12-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-benzyloxymethylpiperidino]dodecyl]-α-D-glucopyranose (**7c**).* Oil, yield 61%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.15–7.43 (40H, m), 4.97 (2H, d, *J*=10.9 Hz), 4.80–4.91 (5H, m), 4.63–4.73 (5H, m), 4.43–4.58 (6H, m), 3.96 (1H, dd, *J*=9.3, 9.3 Hz), 3.75–3.82 (2H, m), 3.59–3.70 (5H, m), 3.56 (1H, dd, *J*=1.9, 10.4 Hz), 3.52 (1H, dd, *J*=3.6, 9.6 Hz), 3.42–3.50 (3H, m), 3.12 (1H, dd, *J*=4.8, 11.3 Hz),

2.56–2.72 (2H, m), 2.32 (1H, dd, *J*=2.2, 9.5 Hz), 2.25 (1H, dd, *J*=10.8, 10.8 Hz), 1.11–1.49 (20H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$): 138.98, 138.91, 138.53, 138.51, 138.2, 138.0, 137.7, 137.2, 128.36, 128.27, 128.24, 128.23, 127.85, 127.78, 127.75, 127.62, 127.54, 127.44, 127.34, 95.5, 87.3, 82.0, 79.7, 78.54, 78.49, 77.8, 75.6, 75.2, 75.1, 73.4, 73.2, 73.0, 72.7, 70.5, 69.0, 68.5, 65.2, 63.6, 54.4, 52.4, 30.4, 29.61, 29.56, 27.5, 26.1, 23.5 ppm; $[\alpha]_D^{24}$ +33.4 (*c* 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ found *m*/*z* 1230.7013, $C_{80}H_{96}O_{10}N^+$ requires *m*/*z* 1230.7029.

4.2.5. General procedure for the synthesis of ***8****.* Compound **7** was dissolved in EtOH and acidified by 1 M HCl aq to pH 2. To this solution, 10% Pd on carbon was added and stirred 24 h under hydrogen atmosphere. The reaction mixture was passed through Celite pad, dried under vacuo and purified by LiChrolut® RP-18 (Merck Co.) to afford **8** as a mixture of anomers.

*4.2.5.1. 4-O-[6-[(2R,3R,4R,5S)-3,4,5-Trihydroxy-2-hydroxymethylpiperidino]hexyl]-D-glucopyranose (**8a**).* Crystal, yield 54%; β anomer (major), ^{1}H NMR (500 MHz, D_2O): 4.48 (1H, d, *J*=8.0 Hz), 3.58–3.79 (5H, m), 3.54 (1H, m), 3.38–3.44 (2H, m), 3.32 (1H, ddd, *J*=1.9, 5.2, 9.8 Hz), 3.25 (1H, dd, *J*=9.5, 9.5 Hz), 3.09–3.17 (3H, m), 2.89 (1H, dd, *J*=4.9, 11.3 Hz), 2.46–2.64 (2H, m), 2.17 (1H, dd, *J*=11.3, 11.3 Hz), 2.12 (1H, br d, *J*=9.1 Hz), 1.17–1.47 (8H, m), ppm; ^{13}C NMR (125 MHz, D_2O): 98.7, 81.2, 80.7, 78.4, 77.9, 77.0, 76.0, 72.9, 71.7, 67.8, 63.3, 60.4, 58.0, 54.8, 31.9, 29.3, 27.9, 25.5 ppm; $[\alpha]_D^{27}$ +26.7 (*c* 1.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 426.2343, $C_{18}H_{36}NO_{10}^+$ requires *m*/*z* 426.2339.

*4.2.5.2. 4-O-[9-[(2R,3R,4R,5S)-3,4,5-Trihydroxy-2-hydroxymethylpiperidino]nonyl]-D-glucopyranose (**8b**).* Crystal, yield 37%; β anomer (major), ^{1}H NMR (500 MHz, D_2O): 4.51 (1H, d, *J*=7.9 Hz), 3.61–3.82 (5H, m), 3.55 (1H, m), 3.41–3.46 (2H, m), 3.34 (1H, ddd, *J*=2.1, 5.4, 9.8 Hz), 3.27 (1H, dd, *J*=9.5, 9.5 Hz), 3.11–3.20 (3H, m), 2.92 (1H, dd, *J*=4.9, 11.4 Hz), 2.48–2.66 (2H, m), 2.20 (1H, dd, *J*=11.0, 11.2 Hz), 2.15 (1H, dd, *J*=2.3, 9.7 Hz), 1.16–1.48 (14H, m) ppm; ^{13}C NMR (125 MHz, D_2O): 98.7, 81.2, 80.7, 78.4, 77.9, 77.0, 76.1, 73.0, 71.7, 67.8, 63.3, 60.5, 58.1, 54.9, 32.0, 31.3, 31.3, 31.2, 29.5, 27.9, 25.5 ppm; $[\alpha]_D^{27}$ +27.0 (*c* 2.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 468.2818, $C_{21}H_{42}NO_{10}^+$ requires *m*/*z* 468.2809.

*4.2.5.3. 4-O-[12-[(2R,3R,4R,5S)-3,4,5-Trihydroxy-2-hydroxymethylpiperidino]dodecyl]-D-glucopyranose (**8c**).* Crystal, yield 50%; β anomer (major), ^{1}H NMR (500 MHz, D_2O): 4.51 (1H, d, *J*=7.9 Hz), 3.49–3.79 (6H, m), 3.41–3.48 (2H, m), 3.34 (1H, m), 3.31 (1H, dd, *J*=9.4, 9.4 Hz), 3.12–3.16 (3H, m), 2.90 (1H, dd, *J*=4.3, 11.0 Hz), 2.52–2.67 (2H, m), 2.19 (1H, dd, *J*=11.0, 11.0 Hz), 2.11 (1H, br d, *J*=2.3, 9.8 Hz), 1.15–1.50 (20H, m) ppm; ^{13}C NMR (125 MHz, D_2O): 98.7, 81.3, 80.8, 78.7, 78.1, 77.2, 76.1, 72.8, 71.7, 67.9, 63.5, 60.3, 58.6, 55.1, 32.6, 32.3, 32.2, 32.2, 32.2, 32.1, 32.0, 29.5, 28.5, 25.8 ppm; $[\alpha]_D^{27}$ +24.6 (*c* 1.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 510.3271, $C_{24}H_{48}NO_{10}^+$ requires *m*/*z* 510.3278.

4.2.6. General procedure for the synthesis of ***10****.* Compound **9** (1 equiv) was dissolved in CH_2Cl_2 and Ph_3P (4.5 equiv), CBr_4 (4.5 equiv) was added. After stirring for 4 h, TMU (6.8 equiv), bromoalkyl alcohol (3 equiv) and TEAB (1.2 equiv) was added and further stirred for 12 h. The reaction mixture was diluted with $CHCl_3$, washed with satd $NaHCO_3$ aq and brine. The organic layer was dried over sodium sulfate, evaporated, and purified by silica-gel column chromatography to give **10**.

*4.2.6.1. 2,3,4,6-Tetra-O-benzyl-1-O-(6-bromohexyl)-α-D-glucopyranose (**10a**).* Oil, yield quant.; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.24 (18H, m), 7.16–7.12 (2H, m), 4.99 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.6 Hz), 4.82 (1H, d, *J*=10.8 Hz), 4.77 (1H, d, *J*=12.1 Hz), 4.75 (1H, d, *J*=3.6 Hz), 4.64 (1H, d, *J*=12.1 Hz), 4.59 (1H, d, *J*=12.1 Hz), 4.470 (1H, d, *J*=10.6 Hz), 4.468 (1H, d, *J*=12.1 Hz), 3.98 (1H, dd, *J*=9.0, 9.6 Hz), 3.77 (1H, ddd, *J*=1.9, 3.6, 10.0 Hz), 3.71 (1H, dd, *J*=3.6, 10.6 Hz), 3.65–3.60 (3H, m), 3.56 (1H, dd, *J*=3.6, 9.6 Hz), 3.41 (1H, dt, *J*=9.5, 6.5 Hz), 3.36 (2H, t, *J*=6.9 Hz), 1.83 (2H, tt, *J*=6.9, 7.3 Hz), 1.68–1.58 (2H, m), 1.44 (2H, tt, *J*=7.3, 7.3 Hz), 1.38 (2H, tt, *J*=7.2, 7.3 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 138.9, 138.3, 138.2, 137.9, 128.33, 128.29 (3C), 127.9, 127.86, 127.82, 127.80, 127.74, 127.60, 127.59, 127.45, 96.9, 82.0, 80.1, 77.7, 75.6, 75.0, 73.4, 73.1, 70.1, 68.5, 67.9, 33.7, 32.6, 29.1, 27.9, 25.3 ppm; $[\alpha]_D^{27}$ +39.0 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 701.2499, $C_{40}H_{46}BrO_6^+$ requires *m*/*z* 701.2478.

*4.2.6.2. 2,3,4,6-Tetra-O-benzyl-1-O-(9-bromononyl)-α-D-glucopyranose (**10b**).* Oil, yield quant.; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.24 (18H, m), 7.14–7.12 (2H, m), 4.99 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.6 Hz), 4.81 (1H, d, *J*=10.8 Hz), 4.77 (1H, d, *J*=12.2 Hz), 4.76 (1H, d, *J*=3.6 Hz), 4.64 (1H, d, *J*=12.2 Hz), 4.60 (1H, d, *J*=12.3 Hz), 4.470 (1H, d, *J*=10.6 Hz), 4.469 (1H, d, *J*=12.3 Hz), 3.99 (1H, dd, *J*=9.3, 9.5 Hz), 3.78 (1H, ddd, *J*=1.9, 3.7, 10.0 Hz), 3.72 (1H, dd, *J*=3.7, 10.5 Hz), 3.65–3.60 (3H, m), 3.56 (1H, dd, *J*=3.6, 9.5 Hz), 3.41 (1H, dt, *J*=9.8, 6.6 Hz), 3.37 (2H, t, *J*=6.9 Hz), 1.83 (2H, tt, *J*=6.9, 7.4 Hz), 1.65–1.59 (2H, m), 1.43–1.27 (10H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 138.9, 138.3, 138.2, 137.9, 128.32, 128.29 (2C), 128.27, 127.92, 127.87, 127.83, 127.80, 127.72, 127.60, 127.58, 127.45, 96.8, 82.1, 80.1, 77.7, 75.6, 75.0, 73.4, 73.0, 70.1, 68.5, 68.1, 33.9, 32.7, 29.32, 29.26, 29.23, 28.6, 28.1, 26.1 ppm; $[\alpha]_D^{27}$ +36.1 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 743.2980, $C_{43}H_{52}BrO_6^+$ requires *m*/*z* 743.2947.

*4.2.6.3. 2,3,4,6-Tetra-O-benzyl-1-O-(12-bromododecyl)-α-D-glucopyranose (**10c**).* Oil, yield 94%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.23 (18H, m), 7.17–7.12 (2H, m), 4.99 (1H, d, *J*=10.6 Hz), 4.83 (1H, d, *J*=10.7 Hz), 4.81 (1H, d, *J*=10.6 Hz), 4.77 (1H, d, *J*=12.0 Hz), 4.76 (1H, d, *J*=3.6 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.60 (1H, d, *J*=12.2 Hz), 4.47 (1H, d, *J*=10.7 Hz), 4.46 (1H, d, *J*=12.2 Hz), 3.99 (1H, dd, *J*=9.3, 9.6 Hz), 3.78 (1H, ddd, *J*=2.1, 3.6, 10.0 Hz), 3.72 (1H, dd, *J*=3.6, 10.6 Hz), 3.65–3.60 (3H, m), 3.56 (1H, dd, *J*=3.6, 9.6 Hz), 3.42 (1H, dt, *J*=9.7, 6.6 Hz), 3.37 (2H, t, *J*=6.9 Hz), 1.82 (2H, tt, *J*=6.9, 7.2 Hz), 1.65–1.59 (2H, m), 1.43–1.24 (16H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 138.9, 138.3, 138.2, 137.9, 128.28, 128.25 (2C), 128.24, 127.9, 127.81 (2C), 127.77, 127.68, 127.56, 127.54, 127.41, 96.8, 82.0, 80.1, 77.7, 75.6, 75.0, 73.4, 73.0, 70.0, 68.5, 68.1, 33.9, 32.7, 29.5, 29.44, 29.43, 29.33, 29.32 (2C), 28.7, 28.1, 26.1 ppm; $[\alpha]_D^{27}$ +28.1 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 785.3448, $C_{46}H_{58}BrO_6^+$ requires *m*/*z* 785.3417.

4.2.7. General procedure for the synthesis of ***12****.* Compounds **10** (1.2 equiv) and **11** (1 equiv) were dissolved in dry DMF. The solution was cooled to 0 °C and NaH (1.5 equiv) was added and stirred under nitrogen atmosphere. After 15 h, water was added and the solution was extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by PTLC to give **12**.

*4.2.7.1. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)hexyloxy] piperidine (**12a**).* Oil, yield 61%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.35–7.23 (38H, m), 7.14–7.12 (2H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.09 (1H, d, *J*=12.4 Hz), 4.98 (1H, d, *J*=10.9 Hz), 4.83 (1H, d, *J*=10.4 Hz), 4.81 (1H, d, *J*=10.9 Hz), 4.76 (1H, d, *J*=12.3 Hz), 4.75 (1H, d, *J*=3.7 Hz), 4.67 (1H, d, *J*=11.5 Hz), 4.65 (1H, d, *J*=11.9 Hz), 4.64 (1H, d, *J*=12.3 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.59 (1H, d, *J*=12.2 Hz), 4.51 (1H, d, *J*=11.9 Hz), 4.47 (1H, d, *J*=10.8 Hz), 4.45 (1H, d, *J*=12.2 Hz), 4.44 (1H, d, *J*=11.9 Hz), 4.42 (1H, d, *J*=11.9 Hz), 4.10–4.05 (2H, m), 3.98 (1H, dd, *J*=9.0, 9.6 Hz),

3.78–3.58 (11H, m), 3.55 (1H, dd, *J*=3.7, 9.6 Hz), 3.42–3.37 (2H, m), 3.34 (1H, dd, *J*=3.0, 14.2 Hz), 1.58 (2H, tt, *J*=7.0, 7.0 Hz), 1.49 (2H, tt, *J*=6.5, 6.5 Hz), 1.34–1.23 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 155.7, 138.9, 138.32, 138.30, 138.25, 138.1, 137.9, 136.6, 128.37, 128.36, 128.34, 128.28, 127.93, 127.90, 127.85, 127.82, 127.79, 127.74, 127.70, 127.64, 127.59, 127.56, 127.50, 127.46, 96.8, 82.2, 82.1, 80.1, 78.6, 77.7, 75.6, 75.04, 75.01, 73.4, 73.0 (2C), 72.9, 71.6, 70.6, 70.1, 68.5 (2C), 68.1, 67.1, 56.0, 41.5, 30.0, 29.3, 26.02, 25.95 ppm; $[\alpha]_D^{27}$ +25.7 (*c* 0.60, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 1188.5818, $C_{75}H_{82}NO_{12}^+$ requires *m*/*z* 1188.5837.

*4.2.7.2. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[9-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)nonyloxy] piperidine (**12b**).* Oil, yield 34%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.22 (38H, m), 7.17–7.11 (2H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.99 (1H, d, *J*=10.9 Hz), 4.83 (1H, d, *J*=10.9 Hz), 4.81 (1H, d, *J*=10.9 Hz), 4.77 (1H, d, *J*=12.0 Hz), 4.76 (1H, d, *J*=3.5 Hz), 4.68 (1H, d, *J*=11.5 Hz), 4.66 (1H, d, *J*=11.5 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.60 (1H, d, *J*=12.2 Hz), 4.51 (1H, d, *J*=12.0 Hz), 4.47 (1H, d, *J*=10.9 Hz), 4.46 (1H, d, *J*=12.2 Hz), 4.44 (1H, d, *J*=11.5 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.10–4.05 (2H, m), 3.99 (1H, dd, *J*=9.2, 9.4 Hz), 3.80–3.59 (11H, m), 3.56 (1H, dd, *J*=3.5, 9.4 Hz), 3.45–3.39 (2H, m), 3.34 (1H, dd, *J*=2.4, 14.6 Hz), 1.61 (2H, tt, *J*=7.2, 7.2 Hz), 1.51–1.47 (2H, m), 1.34–1.20 (10H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 155.7, 138.9, 138.31, 138.30, 138.2, 138.1, 137.9, 136.6, 128.34, 128.32, 128.28, 128.25, 127.9, 127.84, 127.80, 127.76, 127.72, 127.69, 127.58, 127.53, 127.48, 127.46, 96.8, 82.3, 82.1, 80.1, 78.6, 77.8, 75.6, 75.0, 73.4, 73.0, 72.9, 71.7, 70.6, 70.0, 68.5, 68.2, 67.1, 56.0, 41.5, 30.0, 29.48, 29.45, 29.40, 29.38, 26.12, 26.06 ppm; $[\alpha]_D^{27}$ +23.6 (*c* 0.52, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 1230.6293, $C_{78}H_{88}NO_{12}^+$ requires *m*/*z* 1230.6307.

*4.2.7.3. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[12-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)dodecyloxy] piperidine (**12c**).* Oil, yield 31%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.24 (38H, m), 7.14–7.12 (2H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.09 (1H, d, *J*=12.4 Hz), 4.99 (1H, d, *J*=10.9 Hz), 4.83 (1H, d, *J*=10.8 Hz), 4.81 (1H, d, *J*=10.9 Hz), 4.77 (1H, d, *J*=12.1 Hz), 4.76 (1H, d, *J*=3.5 Hz), 4.68 (1H, d, *J*=11.5 Hz), 4.65 (1H, d, *J*=12.0 Hz), 4.64 (1H, d, *J*=12.1 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.60 (1H, d, *J*=12.1 Hz), 4.51 (1H, d, *J*=12.0 Hz), 4.47 (1H, d, *J*=10.8 Hz), 4.46 (1H, d, *J*=12.1 Hz), 4.44 (1H, d, *J*=12.0 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.10–4.05 (2H, m), 3.99 (1H, dd, *J*=9.3, 9.6 Hz), 3.80–3.59 (11H, m), 3.55 (1H, dd, *J*=3.5, 9.6 Hz), 3.44–3.39 (2H, m), 3.34 (1H, dd, *J*=3.5, 14.2 Hz), 1.62 (2H, tt, *J*=7.2, 7.2 Hz), 1.51–1.46 (2H, m), 1.37–1.20 (16H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 155.7, 138.9, 138.34, 138.32, 138.26, 138.1, 137.9, 136.6, 128.36, 128.33, 128.29, 128.27, 127.9, 127.846, 127.81, 127.77, 127.72, 127.71, 127.61, 127.58, 127.54, 127.49, 127.47, 96.8, 82.3, 82.1, 80.1, 78.6, 77.8, 75.6, 75.0, 73.4, 73.0, 72.9, 71.7, 70.6, 70.1, 68.5, 68.2, 67.1, 56.0, 41.5, 30.0, 29.6, 29.58, 29.56, 29.49, 29.44, 29.38, 26.14, 26.08 ppm; $[\alpha]_D^{27}$ +23.4 (*c* 0.48, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 1272.6795, $C_{81}H_{94}NO_{12}^+$ requires *m*/*z* 1272.6776.

*4.2.8. General procedure for the synthesis of **13**.* Compound **12** was dissolved in EtOH/THF (2/1) and acidified by 1 M HCl aq to pH 2. To this solution $Pd(OH)_2$ was added and stirred under hydrogen atmosphere. After 15 h, the reaction mixture was passed through Celite pad, evaporated, and purified by LiCholut RP-18 (Merck Co.) to give **13**.

*4.2.8.1. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-[6-(α-D-glucopyranosyloxy)hexyloxy]piperidine hydrochloride (**13a**).* Crystal, yield 89%; ^{1}H NMR (500 MHz, CD_3OD, rt): 4.76 (1H, d, *J*=3.6 Hz), 3.95–3.90 (1H, m), 3.88 (1H, br d, *J*=11.4 Hz), 3.83 (1H, dd, *J*=3.7, 11.4 Hz), 3.79 (1H, dd, *J*=2.0, 11.8 Hz), 3.75–3.70 (1H, m), 3.69–3.59 (4H, m), 3.55 (1H, ddd, *J*=2.0, 5.5, 9.5 Hz), 3.48–3.42 (2H, m), 3.38 (1H, dd, *J*=3.6, 9.5 Hz), 3.35 (1H, dd, *J*=9.2, 9.2 Hz), 3.35–3.29 (1H, m), 3.28 (1H, dd, *J*=9.5, 9.5 Hz), 3.13–3.08 (1H, m), 2.86 (1H, dd, *J*=11.7, 11.7 Hz), 1.68–1.56 (4H, m), 1.46–1.36 (4H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, rt): 100.1, 81.4, 80.8, 75.1, 73.9, 73.7, 73.6, 73.1, 71.9, 69.0, 62.75, 62.67, 62.4, 51.0, 31.3, 30.6, 27.2, 27.0 ppm; $[\alpha]_D^{26}$ +59.6 (*c* 0.49, MeOH); HR-FAB-MS (negative): $[M-H]^-$ found *m*/*z* 424.2186, $C_{18}H_{34}NO_{10}^-$ requires *m*/*z* 424.2183.

*4.2.8.2. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-[9-(α-D-glucopyranosyloxy)nonyloxy]piperidine hydrochloride (**13b**).* Crystal, yield 77%; ^{1}H NMR (500 MHz, CD_3OD, rt): 4.76 (1H, d, *J*=3.6 Hz), 3.92 (1H, dt, *J*=8.9, 6.7 Hz), 3.86 (1H, dd, *J*=3.1, 11.7 Hz), 3.82 (1H, dd, *J*=4.7, 11.7 Hz), 3.78 (1H, dd, *J*=2.4, 11.9 Hz), 3.72 (1H, dt, *J*=9.6, 6.8 Hz), 3.69–3.64 (2H, m), 3.63 (1H, dd, *J*=9.1, 9.6 Hz), 3.60 (1H, dt, *J*=8.9, 6.7 Hz), 3.56 (1H, ddd, *J*=2.4, 5.5, 9.9 Hz), 3.46 (1H, dd, *J*=9.0, 9.0 Hz), 3.43 (1H, dt, *J*=9.6, 6.5 Hz), 3.38 (1H, dd, *J*=3.6, 9.6 Hz), 3.34 (1H, dd, *J*=9.0, 10.2 Hz), 3.31 (1H, dt, *J*=4.8, 11.9 Hz), 3.28 (1H, dd, *J*=9.1, 9.9 Hz), 3.09 (1H, ddd, *J*=3.1, 4.7, 10.2 Hz), 2.84 (1H, dd, *J*=11.9, 11.9 Hz), 1.68–1.54 (4H, m), 1.42–1.30 (10H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, rt): 100.1, 78.4, 77.3, 75.1, 74.5, 73.62, 73.57, 71.8, 69.1, 68.8, 62.7, 61.1, 58.7, 47.4, 31.2, 30.6, 30.5, 27.3, 27.1 ppm; $[\alpha]_D^{26}$ +61.4 (*c* 0.33, MeOH); HR-FAB-MS (negative): $[M-H]^-$ found *m*/*z* 466.2641, $C_{21}H_{40}NO_{10}^-$ requires *m*/*z* 466.2652.

*4.2.8.3. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-[12-(α-D-glucopyranosyloxy)dodecyloxy]piperidine hydrochloride (**13c**).* Crystal, yield 78%; ^{1}H NMR (500 MHz, CD_3OD, rt): 4.76 (1H, d, *J*=3.6 Hz), 3.92 (1H, dt, *J*=9.0, 6.4 Hz), 3.86 (1H, dd, *J*=2.4, 12.0 Hz), 3.82 (1H, dd, *J*=4.2, 12.0 Hz), 3.78 (1H, dd, *J*=2.3, 11.8 Hz), 3.71 (1H, dt, *J*=9.5, 6.9 Hz), 3.70–3.64 (2H, m), 3.63 (1H, dd, *J*=9.6, 9.7 Hz), 3.62–3.58 (1H, m), 3.56 (1H, ddd, *J*=2.4, 5.5, 9.6 Hz), 3.46 (1H, dd, *J*=9.2, 9.2 Hz), 3.43 (1H, dt, *J*=9.7, 6.4 Hz), 3.38 (1H, dd, *J*=3.6, 9.7 Hz), 3.34 (1H, dd, *J*=9.2, 10.0 Hz), 3.31 (1H, dt, *J*=4.8, 11.8 Hz), 3.28 (1H, dd, *J*=9.6, 9.6 Hz), 3.11–3.07 (1H, m), 2.84 (1H, dd, *J*=11.8, 11.8 Hz), 1.66–1.53 (4H, m), 1.42–1.26 (16H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, rt): 100.1, 78.4, 77.3, 75.1, 74.6, 73.60, 73.57, 71.8, 69.1, 68.8, 62.7, 61.1, 58.7, 47.4, 31.2, 30.7, 30.61, 30.56, 27.3, 27.1 ppm; $[\alpha]_D^{27}$ +67.1 (*c* 0.17, MeOH); HR-FAB-MS (negative): $[M-H]^-$ found *m*/*z* 508.3136, $C_{24}H_{46}NO_{10}^-$ requires *m*/*z* 508.3122.

*4.2.9. Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-(15-hydroxypentadecyl)-α-D-glucopyranose (**14**).* Compound **9** (204.9 mg, 0.379 mmol) was dissolved in CH_2Cl_2 (4 mL) and Ph_3P (294.9 mg, 1.12 mmol), CBr_4 (374.3 mg, 1.13 mmol) was added. After stirring for 4 h, THF (4 mL) solution of TMU (272 μL, 2.27 mmol), 15-hydroxypentadecanol (180.6 mg, 0.74 mmol), and TEAB (95.7 mg, 0.455 mmol) was added and further stirred for 12 h. The reaction mixture was diluted with 1 M HCl aq and extracted by EtOAc. The organic layer was washed with satd $NaHCO_3$ aq and brine, dried over sodium sulfate, evaporated and purified by silica-gel column chromatography (hexane/EtOAc=9/1 to 3/1) to give **14** (123.6 mg, 43%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.22 (18H, m), 7.15–7.12 (2H, m), 4.99 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.8 Hz), 4.81 (1H, d, *J*=10.8 Hz), 4.76 (1H, d, *J*=12.1 Hz), 4.76 (1H, d, *J*=3.7 Hz), 4.64 (1H, d, *J*=12.1 Hz), 4.59 (1H, d, *J*=12.1 Hz), 4.47 (1H, d, *J*=10.8 Hz), 4.45 (1H, d, *J*=12.1 Hz), 4.00 (1H, dd, *J*=9.2, 9.2 Hz), 3.79 (1H, ddd, *J*=1.9, 3.6, 9.9 Hz), 3.72 (1H, dd, *J*=3.6, 10.7 Hz), 3.66–3.60 (3H, m), 3.56 (1H, dd, *J*=3.7, 9.2 Hz), 3.55 (2H, t, *J*=6.7 Hz), 3.42 (1H, dt, *J*=9.8, 6.7 Hz), 1.63 (2H, tt, *J*=6.7, 7.0 Hz), 1.51 (2H, tt, *J*=6.7, 6.7 Hz), 1.38–1.24 (22H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, rt): 138.8, 138.2, 138.1, 137.8, 128.2, 128.1, 127.8, 127.72, 127.69, 127.6, 127.5, 127.3, 96.7, 81.9, 80.0, 77.7, 75.5, 74.9, 73.3, 72.9, 69.9, 68.4, 68.1, 62.6, 32.6, 29.48, 29.45, 29.43, 29.40, 29.27, 29.23, 26.0, 25.9 ppm;

$[\alpha]_D^{27}$ +31.1 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 765.4725, $C_{49}H_{65}O_7^+$ requires *m*/*z* 765.4730.

*4.2.10. Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-(15-iodopentadecyl)-α-D-glucopyranose (**15**).* Compound **14** (123.6 mg, 0.161 mmol) was dissolved in CH_2Cl_2 (3 mL) and Ph_3P (52.6 mg, 0.201 mmol), imidazole (16.6 mg, 0.244 mmol), *N*-iodosuccinimide (60.7 mg, 0.270 mmol) was added. After stirring for an hour, the reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (hexane/EtOAc=9/1 to 4/1) to give **15** (86.2 mg, 61%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.24 (18H, m), 7.16–7.12 (2H, m), 4.99 (1H, d, *J*=10.7 Hz), 4.83 (1H, d, *J*=10.7 Hz), 4.81 (1H, d, *J*=10.7 Hz), 4.77 (1H, d, *J*=12.0 Hz), 4.76 (1H, d, *J*=3.6 Hz), 4.65 (1H, d, *J*=12.0 Hz), 4.60 (1H, d, *J*=12.1 Hz), 4.47 (1H, d, *J*=10.7 Hz), 4.46 (1H, d, *J*=12.1 Hz), 3.99 (1H, dd, *J*=9.3, 9.5 Hz), 3.78 (1H, ddd, *J*=2.0, 3.6, 10.0 Hz), 3.72 (1H, dd, *J*=3.6, 10.5 Hz), 3.65–3.60 (3H, m), 3.55 (1H, dd, *J*=3.6, 9.5 Hz), 3.42 (1H, dt, *J*=9.7, 6.8 Hz), 3.16 (2H, t, *J*=7.1 Hz), 1.80 (2H, tt, *J*=7.1, 7.1 Hz), 1.62 (2H, tt, *J*=6.8, 6.8 Hz), 1.39–1.24 (22H, m) ppm ^{13}C NMR (125 MHz, $CDCl_3$, rt): 138.9, 138.3, 138.2, 137.9, 128.30, 128.26, 127.92, 127.83, 127.78, 127.69, 127.56, 127.55, 127.42, 96.8, 82.1, 80.1, 77.8, 75.6, 75.0, 73.4, 73.0, 70.0, 68.5, 68.2, 33.5, 30.4, 29.58, 29.56, 29.54, 29.49, 29.47, 29.37, 29.34, 28.5, 26.1, 7.2 ppm; $[\alpha]_D^{27}$ +25.3 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 875.3770, $C_{49}H_{64}IO_6^+$ requires *m*/*z* 875.3748.

*4.2.11. Synthesis of (2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[15-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pentadecyloxy] piperidine (**16**).* Compounds **15** (441.8 mg, 0.503 mmol) and **11** (224.1 mg, 0.395 mmol) were dissolved in dry THF. The solution was cooled to 0 °C and NaH (21.4 mg, 0.892 mmol) was added and stirred under argon atmosphere. After 17 h, water was added and the solution was extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by silica-gel column chromatography (hexane/EtOAc=4/1) to give **16** (62.8 mg, 12%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.24 (38H, m), 7.14–7.12 (2H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.09 (1H, d, *J*=12.4 Hz), 4.99 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.7 Hz), 4.81 (1H, d, *J*=10.8 Hz), 4.77 (1H, d, *J*=12.0 Hz), 4.76 (1H, d, *J*=3.6 Hz), 4.68 (1H, d, *J*=11.6 Hz), 4.65 (1H, d, *J*=11.7 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.63 (1H, d, *J*=11.6 Hz), 4.60 (1H, d, *J*=12.2 Hz), 4.51 (1H, d, *J*=12.0 Hz), 4.47 (1H, d, *J*=10.7 Hz), 4.46 (1H, d, *J*=12.2 Hz), 4.44 (1H, d, *J*=11.7 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.11–4.05 (2H, m), 3.99 (1H, dd, *J*=9.3, 9.6 Hz), 3.80–3.59 (11H, m), 3.56 (1H, dd, *J*=3.6, 9.6 Hz), 3.44–3.39 (2H, m), 3.34 (1H, dd, *J*=3.2, 14.3 Hz), 1.66–1.59 (2H, m), 1.53–1.46 (2H, m), 1.40–1.20 (22H, m) ppm ^{13}C NMR (125 MHz, $CDCl_3$, rt): 172.4, 155.7, 138.9, 138.31, 138.29, 138.23, 138.1, 137.9, 136.6, 128.35, 128.32, 128.29, 128.26, 128.0, 127.85, 127.81, 127.77, 127.73, 127.71, 127.65, 127.6, 127.53, 127.48, 127.46, 96.8, 82.3, 82.1, 80.1, 78.6, 77.7, 75.6, 75.00, 74.97, 73.4, 73.0, 72.9, 71.7, 70.6, 70.0, 68.5, 68.2, 67.1, 56.0, 41.4, 30.0, 29.65, 29.62, 29.58, 29.55, 29.47, 29.41, 29.35, 26.12, 26.06 ppm; $[\alpha]_D^{27}$ +21.3 (*c* 0.75, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ found *m*/*z* 1314.7247, $C_{84}H_{100}NO_{12}^+$ requires *m*/*z* 1314.7246.

*4.2.12. Synthesis of (2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[15-(α-D-glucopyranosyloxy)pentadecyloxy]piperidine hydrochloride (**13d**).* Protective groups of **16** (51.7 mg, 0.0393 mmol) was removed by the method written in Section 4.2.8 to give **13d** (19.4 mg, 74%) as a crystal.

^{1}H NMR (500 MHz, CD_3OD, rt): 4.76 (1H, d, *J*=3.6 Hz), 3.92 (1H, dt, *J*=8.9, 6.6 Hz), 3.85 (1H, dd, *J*=3.1, 11.8 Hz), 3.81 (1H, dd, *J*=4.6, 11.8 Hz), 3.78 (1H, dd, *J*=2.1, 12.0 Hz), 3.72 (1H, dt, *J*=9.6, 7.0 Hz), 3.68–3.59 (4H, m), 3.56 (1H, ddd, *J*=2.1, 5.5, 9.6 Hz), 3.45 (1H, dd, *J*=9.0, 9.0 Hz), 3.45–3.40 (1H, m), 3.38 (1H, dd, *J*=3.6, 9.6 Hz), 3.33 (1H, dd, *J*=9.0, 10.2 Hz), 3.33–3.28 (1H, m), 3.28 (1H, dd, *J*=9.6, 9.6 Hz), 3.08 (1H, ddd, *J*=3.1, 4.6, 10.2 Hz), 2.84 (1H, dd, *J*=12.0, 12.0 Hz), 1.67–1.53 (4H, m), 1.42–1.26 (22H, m) ppm ^{13}C NMR (125 MHz, CD_3OD, rt): 100.1, 78.4, 77.3, 75.1, 74.6, 73.6, 73.5, 71.8, 69.1, 68.8, 62.7, 61.0, 58.7, 47.3, 31.2, 30.71, 30.68, 30.61, 30.58, 27.3, 27.1 ppm; $[\alpha]_D^{26}$ +49.9 (*c* 0.63, MeOH); HR-FAB-MS (negative): $[M-H]^-$ found *m*/*z* 550.3555, $C_{27}H_{52}NO_{10}^-$ requires *m*/*z* 550.3591.

*4.2.13. General procedure for the synthesis of **18**.* Compound **17** (1.5 equiv) and **11** (1 equiv) were dissolved in DMF and NaH (4 equiv) was added. The mixture was stirred for 15 h under argon atmosphere and then satd NH_4Cl aq was added and extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by silica-gel column chromatography to give **18**.

*4.2.13.1. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[4-(p-methoxybenzyloxy)butyloxy]piperidine (**18e**).* Oil, yield 30%; ^{1}H NMR (270 MHz, $CDCl_3$, rt): 7.34–7.25 (22H, m), 6.86 (2H, d, *J*=8.6 Hz), 5.13 (1H, d, *J*=12.4 Hz), 5.07 (1H, d, *J*=12.4 Hz), 4.66 (1H, d, *J*=11.6 Hz), 4.64 (1H, d, *J*=11.6 Hz), 4.61 (1H, d, *J*=11.6 Hz), 4.50 (1H, d, *J*=12.0 Hz), 4.43 (1H, d, *J*=11.6 Hz), 4.41 (1H, d, *J*=12.0 Hz), 4.38 (2H, s), 4.10–4.04 (2H, m), 3.78 (3H, s), 3.76–3.62 (6H, m), 3.46–3.29 (4H, m), 1.63–1.54 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 159.0, 155.7, 138.3, 138.0, 136.6, 130.7, 129.2, 128.4, 128.3, 127.86, 127.82, 127.76, 127.64, 127.60, 127.54, 127.51, 113.7, 82.1, 78.6, 75.0, 73.0, 72.9, 72.5, 71.4, 70.6, 69.8, 68.5, 67.2, 56.0, 55.2, 41.4, 26.8, 26.4 ppm; $[\alpha]_D^{27}$ +13.6 (*c* 2.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 759.3785, $C_{47}H_{53}NO_8^+$ requires *m*/*z* 759.3771.

*4.2.13.2. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[5-(p-methoxybenzyloxy)pentyloxy] piperidine (**18f**).* Oil, yield 46%; ^{1}H NMR (270 MHz, $CDCl_3$, rt): 7.33–7.21 (22H, m), 6.85 (2H, d, *J*=8.6 Hz), 5.13 (1H, d, *J*=12.5 Hz), 5.08 (1H, d, *J*=12.5 Hz), 4.67 (1H, d, *J*=11.6 Hz), 4.64 (1H, d, *J*=11.7 Hz), 4.62 (1H, d, *J*=11.6 Hz), 4.50 (1H, d, *J*=12.1 Hz), 4.43 (1H, d, *J*=11.7 Hz), 4.42 (1H, d, *J*=12.1 Hz), 4.40 (2H, s), 4.12–4.05 (2H, m), 3.76 (3H, s), 3.76–3.63 (6H, m), 3.46–3.29 (4H, m), 1.61–1.45 (4H, m), 1.38–1.29 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 159.0, 155.7, 138.24, 138.21, 138.0, 136.6, 130.7, 129.1, 128.3, 128.2, 127.80, 127.76, 127.69, 127.62, 127.58, 127.53, 127.48, 127.47, 113.7, 82.1, 78.5, 74.9, 73.0, 72.9, 72.4, 71.5, 70.5, 69.9, 68.5, 67.1, 55.9, 55.2, 41.4, 29.8, 29.5, 22.7 ppm; $[\alpha]_D^{27}$ +11.9 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 773.3922, $C_{48}H_{55}NO_8^+$ requires *m*/*z* 773.3928.

*4.2.14. General procedure for the synthesis of **19**.* Compound **18** was dissolved in 10% TFA/CH_2Cl_2 and stirred for 2 h. The reaction mixture was evaporated and the residue was purified by PTLC to give **19**.

*4.2.14.1. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-(4-hydroxybutyloxy)piperidine (**19e**).* Oil, yield 66%; ^{1}H NMR (270 MHz, $CDCl_3$, rt): 7.34–7.23 (20H, m), 5.15 (1H, d, *J*=12.4 Hz), 5.09 (1H, d, *J*=12.4 Hz), 4.63 (1H, d, *J*=11.9 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.58 (1H, d, *J*=11.9 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.42 (1H, d, *J*=11.8 Hz), 4.42 (1H, d, *J*=12.0 Hz), 4.24 (1H, dd, *J*=4.7, 9.0 Hz), 4.14 (1H, br d, *J*=14.4 Hz), 3.74–3.59 (6H, m), 3.55–3.44 (3H, m), 3.28 (1H, dd, *J*=3.0, 14.4 Hz), 1.61–1.50 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 155.8, 138.1, 138.0, 137.9, 136.6, 128.33, 128.28, 128.25, 128.23, 127.80, 127.78, 127.73, 127.59, 127.52, 127.50, 80.5, 76.95, 74.7, 72.9, 72.7, 71.1, 70.4, 68.1, 67.1, 62.2, 55.1, 40.4, 29.7,

26.4 ppm; $[\alpha]_D^{27}$ +10.3 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 639.3193, $C_{39}H_{45}NO_7^+$ requires *m*/*z* 639.3196.

*4.2.14.2. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-(5-hydroxypentyloxy)piperidine (**19f**).* Oil, yield quant.; ^{1}H NMR (270 MHz, $CDCl_3$, rt): 7.40–7.23 (20H, m), 5.11 (2H, s), 4.66 (1H, d, *J*=11.8 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.62 (1H, d, *J*=11.8 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.44 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.17–4.04 (2H, m), 3.76–3.61 (6H, m), 3.55 (2H, t, *J*=6.5 Hz), 3.43 (1H, td, *J*=6.5, 9.0 Hz), 3.33 (1H, dd, *J*=2.8, 14.5 Hz), 1.62–1.45 (4H, m), 1.38–1.25 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 155.8, 138.2, 138.0, 136.6, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 81.6, 78.1, 74.9, 73.0, 72.8, 71.3, 70.6, 68.4, 67.2, 62.7, 55.7, 41.2, 32.4, 29.6, 22.3 ppm; $[\alpha]_D^{27}$ +7.2 (*c* 0.27, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 653.3339, $C_{40}H_{47}NO_7^+$ requires *m*/*z* 653.3353.

*4.2.15. General procedure for the synthesis of **20**.* Compound **9** (1 equiv) was dissolved in CH_2Cl_2 and Ph_3P (1.1 equiv), CBr_4 (1.2 equiv) was added. After stirring for 14 h at rt, CH_2Cl_2 solution of **19** (0.68 equiv), TMU (1.6 equiv) and TEAB (1 equiv) was added and further stirred for 20 h at 40 °C. The reaction mixture was diluted with water and extracted by $CHCl_3$. The organic layer was dried over sodium sulfate, evaporated, and purified by silica-gel column chromatography to give **20**.

*4.2.15.1. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)butyloxy] piperidine (**20e**).* Oil, yield 46%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.35–7.22 (38H, m), 7.14–7.12 (2H, m), 5.12 (1H, d, *J*=12.5 Hz), 5.08 (1H, d, *J*=12.5 Hz), 4.96 (1H, d, *J*=10.8 Hz), 4.82 (1H, d, *J*=10.8 Hz), 4.79 (1H, d, *J*=10.8 Hz), 4.74 (1H, d, *J*=12.1 Hz), 4.73 (1H, d, *J*=3.5 Hz), 4.65 (1H, d, *J*=11.6 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.62 (1H, d, *J*=12.1 Hz), 4.61 (1H, d, *J*=11.6 Hz), 4.59 (1H, d, *J*=12.2 Hz), 4.49 (1H, d, *J*=12.4 Hz), 4.46 (1H, d, *J*=10.8 Hz), 4.44 (1H, d, *J*=12.2 Hz), 4.43 (1H, d, *J*=11.5 Hz), 4.42 (1H, d, *J*=12.4 Hz), 4.10–4.05 (2H, m), 3.96 (1H, dd, *J*=9.0, 9.6 Hz), 3.75–3.57 (11H, m), 3.54 (1H, dd, *J*=3.5, 9.6 Hz), 3.45–3.39 (1H, m), 3.37–3.32 (1H, m), 3.33 (1H, dd, *J*=3.0, 14.4 Hz), 1.64–1.52 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 155.7, 138.8, 138.27, 138.22, 138.0, 137.9, 136.6, 128.36, 128.35, 128.30, 127.95, 127.87, 127.85, 127.80, 127.76, 127.73, 127.61, 127.52, 127.49, 127.47, 96.9, 82.10, 82.06, 80.0, 78.5, 77.6, 75.6, 75.0, 73.4, 73.0, 72.9, 71.3, 70.5, 70.1, 68.5, 68.4, 67.9, 67.1, 55.9, 41.3, 26.8, 26.2 ppm; $[\alpha]_D^{27}$ +16.5 (*c* 0.19, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 1161.5569, $C_{73}H_{79}NO_{12}^+$ requires *m*/*z* 1161.5602.

*4.2.15.2. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pentyloxy] piperidine (**20f**).* Oil, yield 59%; ^{1}H NMR (500 MHz, $CDCl_3$, rt): 7.36–7.22 (38H, m), 7.16–7.11 (2H, m), 5.12 (1H, d, *J*=12.3 Hz), 5.08 (1H, d, *J*=12.3 Hz), 4.97 (1H, d, *J*=10.9 Hz), 4.82 (1H, d, *J*=10.8 Hz), 4.79 (1H, d, *J*=10.9 Hz), 4.76 (1H, d, *J*=12.1 Hz), 4.73 (1H, d, *J*=3.6 Hz), 4.66 (1H, d, *J*=11.7 Hz), 4.64 (1H, d, *J*=11.7 Hz), 4.63 (1H, d, *J*=12.1 Hz), 4.62 (1H, d, *J*=11.7 Hz), 4.59 (1H, d, *J*=12.1 Hz), 4.50 (1H, d, *J*=12.1 Hz), 4.46 (1H, d, *J*=10.8 Hz), 4.45 (1H, d, *J*=12.1 Hz), 4.44 (1H, d, *J*=11.7 Hz), 4.42 (1H, d, *J*=12.1 Hz), 4.10–4.04 (2H, m), 3.97 (1H, dd, *J*=9.3, 9.3 Hz), 3.76–3.56 (11H, m), 3.54 (1H, dd, *J*=3.6, 9.6 Hz), 3.44–3.33 (2H, m), 3.33 (1H, dd, *J*=2.7, 14.5 Hz), 1.62–1.46 (4H, m), 1.37–1.24 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, rt): 155.7, 138.9, 138.8, 138.32, 138.29, 138.25, 138.1, 137.9, 136.6, 128.4, 128.3, 128.0, 127.93, 127.90, 127.84, 127.76, 127.6, 127.5, 96.9, 82.2, 82.1, 80.0, 78.6, 77.7, 75.7, 75.1, 75.0, 73.5, 73.10, 73.07, 72.96, 71.5, 70.6, 70.1, 68.51, 68.46, 68.1, 67.2, 56.0, 41.5, 29.9, 29.3, 22.6 ppm; $[\alpha]_D^{27}$ +24.6 (*c* 0.54, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 1175.5759, $C_{74}H_{81}NO_{12}^+$ requires *m*/*z* 1175.5759.

*4.2.16. Synthesis of **13e,f**.* Protective groups of **20** was removed by the method written in Section 4.2.8 to give **13e** or **13f**.

*4.2.16.1. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-[4-(α-D-glucopyranosyloxy)butyloxy]piperidine hydrochloride (**13e**).* Crystal, yield 81%; ^{1}H NMR (500 MHz, CD_3OD, rt): 4.77 (1H, d, *J*=3.6 Hz), 4.00–3.90 (1H, m), 3.86 (1H, br d, *J*=11.6 Hz), 3.83 (1H, br d, *J*=11.6 Hz), 3.79 (1H, dd, *J*=2.0, 11.8 Hz), 3.78–3.74 (1H, m), 3.69–3.63 (3H, m), 3.62 (1H, dd, *J*=9.3, 9.6 Hz), 3.56 (1H, ddd, *J*=2.0, 5.5, 9.5 Hz), 3.49–3.43 (2H, m), 3.38 (1H, dd, *J*=3.6, 9.6 Hz), 3.37–3.34 (1H, m), 3.33–3.28 (1H, m), 3.27 (1H, dd, *J*=9.3, 9.5 Hz), 3.12–3.07 (1H, m), 2.84 (1H, dd, *J*=11.8, 11.8 Hz), 1.74–1.68 (4H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, rt): 100.1, 78.4, 77.2, 75.1, 74.2, 73.7, 73.5, 71.9, 68.84, 68.78, 62.8, 61.0, 58.7, 47.4, 28.0, 27.2 ppm; $[\alpha]_D^{26}$ +59.4 (*c* 0.14, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 398.2005, $C_{16}H_{32}NO_{10}^+$ requires *m*/*z* 398.2026.

*4.2.16.2. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-[5-(α-D-glucopyranosyloxy)pentyloxy]piperidine hydrochloride (**13f**).* Crystal, yield 85%; ^{1}H NMR (500 MHz, CD_3OD, rt): 4.76 (1H, d, *J*=3.8 Hz), 3.94 (1H, td, *J*=6.3, 9.0 Hz), 3.85 (1H, dd, *J*=3.2, 11.7 Hz), 3.82 (1H, dd, *J*=4.6, 11.7 Hz), 3.79 (1H, dd, *J*=2.2, 11.8 Hz), 3.74 (1H, td, *J*=6.6, 9.5 Hz), 3.68–3.60 (4H, m), 3.57 (1H, ddd, *J*=2.2, 5.7, 9.8 Hz), 3.46 (1H, dd, *J*=9.0, 9.0 Hz), 3.45 (1H, td, *J*=6.2, 9.5 Hz), 3.38 (1H, dd, *J*=3.8, 9.8 Hz), 3.28 (1H, dd, *J*=9.0, 10.3 Hz), 3.32–3.28 (1H, m), 3.27 (1H, dd, *J*=8.9, 9.8 Hz), 3.09 (1H, ddd, *J*=3.2, 4.6, 10.3 Hz), 2.84 (1H, dd, *J*=11.9, 11.9 Hz), 1.72–1.58 (4H, m), 1.57–1.41 (2H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, rt): 100.0, 78.4, 77.3, 75.1, 74.4, 73.7, 73.6, 71.9, 68.89, 68.84, 62.8, 61.0, 58.8, 47.3, 30.9, 30.3, 23.9 ppm; $[\alpha]_D^{26}$ +65.4 (*c* 0.25, MeOH); HR-FAB-MS (negative): $[M-H]^-$ found *m*/*z* 410.2005, $C_{17}H_{32}NO_{10}^-$ requires *m*/*z* 410.2026.

*4.2.17. General procedure for the synthesis of **22a–c**.* Compounds **21** (2 equiv) and **11** (1 equiv) were dissolved in THF/DMF (1/1) and TBAI (1 equiv), NaH (4 equiv) was added. After stirring for 12 h, satd NH_4Cl aq was added and extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by silica-gel column chromatography to give **22a–c**.

*4.2.17.1. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[6-(tetrahydropyran-2-yloxy)hexyloxy] piperidine (**22a**).* Oil, yield 64%; ^{1}H NMR (270 MHz, CD_3OD, rt): 7.35–7.23 (20H, m), 5.13 (1H, d, *J*=12.5 Hz), 5.08 (1H, d, *J*=12.5 Hz), 4.68 (1H, d, *J*=11.5 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.62 (1H, d, *J*=11.5 Hz), 4.55 (1H, dd, *J*=2.8, 4.2 Hz), 4.52 (1H, d, *J*=11.9 Hz), 4.44 (1H, d, *J*=11.8 Hz), 4.42 (1H, d, *J*=11.9 Hz), 4.12–4.05 (2H, m), 3.85 (1H, ddd, *J*=3.9, 7.0, 11.0 Hz), 3.77–3.61 (7H, m), 3.52–3.30 (4H, m), 1.87–1.42 (10H, m), 1.42–1.21 (6H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 155.6, 138.22, 138.18, 138.0, 136.6, 128.3, 128.2, 127.76, 127.72, 127.65, 127.54, 127.49, 127.43, 126.50, 98.7, 82.1, 78.5, 74.9, 73.0, 72.9, 71.6, 70.5, 68.4, 67.4, 67.1, 62.2, 55.9, 41.4, 30.7, 29.9, 29.6, 26.0, 25.9, 25.4, 19.6 ppm; $[\alpha]_D^{27}$ +6.7 (*c* 0.51, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 751.4073, $C46H_{57}NO_8^+$ requires *m*/*z* 751.4084.

*4.2.17.2. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[9-(tetrahydropyran-2-yloxy)nonyloxy] piperidine (**22b**).* Oil, yield 29%; ^{1}H NMR (270 MHz, CD_3OD, rt): 7.35–7.23 (20H, m), 5.13 (1H, d, *J*=12.4 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.68 (1H, d, *J*=11.5 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.57 (1H, dd, *J*=2.8, 4.3 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.44 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.16–4.04 (2H, m), 3.87 (1H, ddd, *J*=3.7, 7.0, 10.9 Hz), 3.78–3.61 (7H, m), 3.54–3.30 (4H, m), 1.88–1.41 (10H, m), 1.41–1.20 (10H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 155.7, 138.3, 138.2, 138.0, 136.6, 128.4, 128.3, 127.82, 127.79, 127.7, 127.61, 127.55, 127.50, 127.47, 98.8, 82.3, 78.7, 74.9, 73.02, 72.96, 71.8, 70.6, 68.5, 67.6, 67.1, 62.3, 56.0, 41.5, 30.7, 30.0, 29.7, 29.5, 29.4, 26.2, 26.0,

25.4, 19.6 ppm; $[\alpha]_D^{27}$ +5.6 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 793.4580, $C_{49}H_{63}NO_8^+$ requires *m*/*z* 793.4554.

*4.2.17.3. (2R,3R,4R,5S)-4,5-Dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[12-(tetrahydropyran-2-yloxy)dodecyloxy] piperidine (**22c**).* Oil, yield 25%; ^{1}H NMR (270 MHz, CD_3OD, rt): 7.35–7.23 (20H, m), 5.13 (1H, d, *J*=12.4 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.69 (1H, d, *J*=11.6 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.63 (1H, d, *J*=11.6 Hz), 4.57 (1H, dd, *J*=2.8, 4.1 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.44 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.12–4.03 (2H, m), 3.87 (1H, ddd, *J*=3.9, 7.0, 11.0 Hz), 3.78–3.60 (7H, m), 3.54–3.30 (4H, m), 1.88–1.43 (10H, m), 1.43–1.18 (16H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 155.7, 138.33, 138.28, 138.1, 136.6, 128.4, 128.3, 127.86, 127.83, 127.76, 127.65, 127.58, 127.54, 127.50, 98.8, 82.4, 78.7, 75.0, 73.1, 73.0, 71.8, 70.6, 68.6, 67.7, 67.2, 62.3, 56.1, 41.6, 30.8, 30.1, 29.8, 29.6, 29.5, 26.2, 26.1, 25.5, 19.7 ppm; $[\alpha]_D^{27}$ +10.2 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 835.5048, $C_{52}H_{69}NO_8^+$ requires *m*/*z* 835.5023.

*4.2.18. Synthesis of (2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[15-(tetrahydropyran-2-yloxy)pentadecyloxy] piperidine (**22d**).* Compounds **21d** (249.3 mg, 0.569 mmol) and **11** (136.1 mg, 0.24 mmol) were dissolved in THF/DMF (3 mL, 1/1) and NaH (23.2 mg, 0.967 mmol) was added. After stirring for 6 h, satd NH_4Cl aq was added and extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (hexane/EtOAc=4/1) to give **22d** (80.9 mg, 38%) as an oil.

^{1}H NMR (270 MHz, CD_3OD, rt): 7.33–7.24 (20H, m), 5.13 (1H, d, *J*=12.4 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.69 (1H, d, *J*=11.5 Hz), 4.64 (1H, d, *J*=11.8 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.57 (1H, dd, *J*=3.0, 4.1 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.44 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.13–4.04 (2H, m), 3.87 (1H, ddd, *J*=3.8, 7.1, 11.0 Hz), 3.78–3.62 (7H, m), 3.53–3.30 (4H, m), 1.88–1.43 (10H, m), 1.43–1.21 (22H, m) ppm ^{13}C NMR (67.5 MHz, CD_3OD, rt): 155.7, 138.3, 138.2, 138.0, 136.6, 128.3, 128.2, 127.78, 127.75, 127.68, 127.58, 127.51, 127.46, 127.44, 98.7, 82.3, 78.6, 74.9, 73.0, 72.9, 71.7, 70.5, 68.5, 67.6, 67.1, 62.2, 56.0, 41.5, 30.7, 30.0, 29.7, 29.6, 29.5, 29.4, 26.2, 26.0, 25.4, 19.6 ppm; $[\alpha]_D^{27}$ +7.7 (*c* 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 877.5487, $C_{55}H_{75}NO_8^+$ requires *m*/*z* 877.5493.

*4.2.19. General procedure for the synthesis of **23a**-**d**.* Compound **22** (1 equiv) was dissolved in MeOH/THF (4/1), PPTS (0.5 equiv) was added and stirred for 15 h at 50 °C. The reaction mixture was acidified by 1 M HCl aq to pH 2, $Pd(OH)_2$ was added and stirred for 20 h under hydrogen atmosphere. The mixture was passed through Celite pad, evaporated and purified by LiChrolut® RP-18 (Merck Co.) to give **23**.

*4.2.19.1. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(6-hydroxyhexyloxy)piperidine hydrochloride (**23a**).* Crystal, yield 85%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.92 (1H, td, *J*=6.3, 9.0 Hz), 3.86 (1H, dd, *J*=3.3, 11.7 Hz), 3.80 (1H, dd, *J*=4.4, 11.7 Hz), 3.65 (1H, ddd, *J*=5.1, 9.0, 11.2 Hz), 3.61 (1H, td, *J*=6.9, 9.0 Hz), 3.54 (2H, t, *J*=6.5 Hz), 3.45 (1H, dd, *J*=9.0, 9.0 Hz), 3.33 (1H, dd, *J*=9.0, 10.0 Hz), 3.31 (1H, dd, *J*=5.1, 12.4 Hz), 3.08 (1H, ddd, *J*=3.3, 4.4, 10.0 Hz), 2.84 (1H, dd, *J*=11.2, 12.4 Hz), 1.65–1.48 (4H, m), 1.44–1.34 (4H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.4, 77.3, 74.4, 68.8, 62.9, 61.0, 58.7, 47.4, 33.5, 31.2, 27.0, 26.7 ppm; $[\alpha]_D^{27}$ +25.3 (*c* 1.20, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 264.1829, $C_{12}H_{26}NO_5^+$ requires *m*/*z* 264.1811.

*4.2.19.2. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(9-hydroxynonyloxy)piperidine hydrochloride (**23b**).* Crystal, yield 75%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.92 (1H, td, *J*=6.3, 8.9 Hz), 3.86 (1H, dd, *J*=3.3, 11.7 Hz), 3.81 (1H, dd, *J*=4.4, 11.7 Hz), 3.66 (1H, ddd, *J*=5.1, 8.9, 11.3 Hz), 3.60 (1H, td, *J*=6.6, 9.0 Hz), 3.53 (2H, t, *J*=6.5 Hz), 3.45 (1H, dd, *J*=8.9, 8.9 Hz), 3.33 (1H, dd, *J*=8.9, 10.0 Hz), 3.30 (1H, dd, *J*=5.1, 12.4 Hz), 3.08 (1H, ddd, *J*=3.3, 4.4, 10.0 Hz), 2.84 (1H, dd, *J*=11.3, 12.4 Hz), 1.64–1.46 (4H, m), 1.42–1.28 (10H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.4, 33.6, 31.3, 30.7, 30.5, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +19.7 (*c* 0.60, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 306.2252, $C_{15}H_{32}NO_5^+$ requires *m*/*z* 306.2280.

*4.2.19.3. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(12-hydroxydodecyloxy)piperidine hydrochloride (**23c**).* Crystal, yield 81%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.92 (1H, td, *J*=6.5, 8.9 Hz), 3.85 (1H, dd, *J*=3.3, 11.7 Hz), 3.80 (1H, dd, *J*=4.3, 11.7 Hz), 3.65 (1H, ddd, *J*=5.0, 8.9, 11.3 Hz), 3.60 (1H, td, *J*=6.6, 8.9 Hz), 3.53 (2H, t, *J*=6.5 Hz), 3.45 (1H, dd, *J*=8.9, 8.9 Hz), 3.33 (1H, dd, *J*=8.9, 10.2 Hz), 3.30 (1H, dd, *J*=5.0, 12.4 Hz), 3.08 (1H, ddd, *J*=3.3, 4.3, 10.2 Hz), 2.84 (1H, dd, *J*=11.3, 12.4 Hz), 1.62–1.46 (4H, m), 1.42–1.28 (16H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.3, 33.7, 31.3, 30.7, 30.6, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +20.4 (*c* 0.39, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 348.2726, $C_{18}H_{38}NO_5^+$ requires *m*/*z* 348.2750.

*4.2.19.4. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(15-hydroxypentadecyloxy)piperidine hydrochloride (**23d**).* Crystal, yield 48%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.92 (1H, td, *J*=6.4, 8.9 Hz), 3.85 (1H, dd, *J*=3.3, 11.7 Hz), 3.80 (1H, dd, *J*=4.2, 11.7 Hz), 3.63 (1H, ddd, *J*=5.1, 8.9, 11.3 Hz), 3.59 (1H, td, *J*=6.5, 9.0 Hz), 3.52 (2H, t, *J*=6.5 Hz), 3.44 (1H, dd, *J*=8.9, 8.9 Hz), 3.32 (1H, dd, *J*=8.9, 10.2 Hz), 3.30 (1H, dd, *J*=5.1, 12.2 Hz), 3.07 (1H, ddd, *J*=3.3, 4.4, 10.2 Hz), 2.83 (1H, dd, *J*=11.3, 12.2 Hz), 1.63–1.46 (4H, m), 1.40–1.27 (22H, m) ppm, ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.3, 33.6, 31.3, 30.8, 30.8, 30.7, 30.61, 30.59, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +22.6 (*c* 0.67, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 390.3199, $C_{21}H_{44}NO_5^+$ requires *m*/*z* 390.3219.

*4.2.20. Synthesis of **23e**,**f**.* Protective groups of **19e** and **19f** were removed by the method written in Section 4.2.8 to give **23e**,**f**.

*4.2.20.1. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(4-hydroxybutyloxy)piperidine hydrochloride (**23e**).* Crystal, yield 93%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.98–3.91 (1H, m), 3.83 (2H, d, *J*=3.9 Hz), 3.69–3.60 (2H, m), 3.57 (1H, t, *J*=6.1 Hz), 3.46 (1H, dd, *J*=8.9, 8.9 Hz), 3.34 (1H, dd, *J*=8.9, 10.2 Hz), 3.30 (1H, dd, *J*=4.9, 12.2 Hz), 3.08 (1H, dt, *J*=10.2, 3.9 Hz), 2.84 (1H, dd, *J*=11.4, 12.2 Hz) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.5, 77.3, 74.3, 68.8, 62.7, 61.0, 58.7, 47.3, 30.2, 27.7 ppm; $[\alpha]_D^{27}$ +28.1 (*c* 0.25, MeOH); HR-FAB-MS (positive): $[M+H]^+$ found *m*/*z* 236.1515, $C_{10}H_{22}NO_5^+$ requires *m*/*z* 236.1498.

*4.2.20.2. (2R,3R,4R,5S)-4,5-Dihydroxy-2-hydroxymethyl-3-(5-hydroxypentyloxy)piperidine hydrochloride (**23f**).* Crystal, yield 93%; ^{1}H NMR (270 MHz, CD_3OD, rt): 3.93 (1H, td, *J*=6.4, 9.0 Hz), 3.87 (1H, dd, *J*=3.0, 12.0 Hz), 3.82 (1H, dd, *J*=4.2, 12.0 Hz), 3.66 (1H, ddd, *J*=5.1, 8.9, 11.1 Hz), 3.65–3.58 (1H, m), 3.55 (2H, t, *J*=6.3 Hz), 3.46 (1H, dd, *J*=8.9, 8.9 Hz), 3.34 (1H, dd, *J*=8.9, 10.1 Hz), 3.30 (1H, dd, *J*=5.1, 12.4 Hz), 3.09 (1H, ddd, *J*=3.0, 4.2, 10.1 Hz), 2.84 (1H, dd, *J*=11.1, 12.4 Hz), 1.67–1.39 (6H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, rt): 78.4, 77.3, 74.4, 68.8, 62.8, 61.0, 58.7, 47.3, 33.4, 31.0, 23.5 ppm; $[\alpha]_D^{27}$ +26.0 (*c* 0.58, MeOH); HR-FD-MS (positive): $[M]^+$ found *m*/*z* 249.1594, $C_{11}H_{23}NO_5^+$ requires *m*/*z* 249.1576.

4.3. α-Amylase inhibition assay

Samples (dissolved in 20% DMSO (aq)) (10 μL), porcine pancreatic α-amylase (1 unit/mL, 10 μL), and buffer solution (100 mM sodium phosphate, 50 mM sodium chloride, pH 6.9, 30 μL) were mixed and pre-incubated at 37 °C for 5 min. To this mixture, 2,4-dinitrophenyl maltotriose (2 mM, 50 μL) dissolved in the buffer

solution was added to start the enzyme reaction. Absorbance at 405 nm was monitored temporally to determine the rate of enzyme reaction. Inhibition rate was determined by comparing the rate of hydrolysis between the control reaction (without sample) and sample reaction. Each experiment was repeated at least three times to determine IC_{50} values or % inhibition.

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