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Evaluation of nonnatural L-iminosugar C,C-glycosides, a new class of C-branched iminosugars, as glycosidase inhibitors

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Abstract: Capitalizing on a previously developed Staudinger/azaWittig/Grignard (SAWG)-ring contraction sequence that furnished protected six-membered L-iminosugar C,C-glycosides bearing an allyl group and various substituents at the pseudoanomeric position, the synthesis and glycosidase inhibition of a small library of six- and seven-membered L-iminosugar C,C-glycosides is reported. Their hydrogenolysis or cyclization by RCM followed by deprotection afforded eleven L-iminosugars including spirocyclic derivatives. All compounds adopt a ¹C₄ conformation in solution according to NMR data. Compared to previously reported branched L-iminosugars, the L-iminosugar C,C-glycosides reported herein were less potent glycosidase inhibitors. However, some of these compounds showed micromolar inhibition of human lysosome β-glucocerebrosidase suggesting that such iminosugars could be useful to access potent CGase inhibitors by adjusting the structure/length of the pseudoanomeric substituents.

Introduction

1-Deoxynojirimycin (DNJ), first synthesized by Paulsen in 1966¹ before it was isolated from the root bark of a *Morus* species in 1976,² is a potent inhibitor of various α-glucosidases. As a consequence, DNJ and its analogues have been investigated as anti-bacterial, anti-viral, anti-diabetic, anti-inflammatory and anti-tumor agents in the last four decades.³⁻⁵ More recently, DNJ,⁶ N-substituted derivatives⁷ including N-butyl-DNJ (Miglustat)⁸ and N-nonyl-DNJ (NN-DNJ)⁹ (Figure 1a) were also evaluated against SARS-CoV-2. To improve DNJ therapeutic potency, N-substitution was initially examined as illustrated by Miglitol and Miglustat (Figure 1a), two approved drugs for the treatment of type II diabetes and Gaucher's disease respectively.¹⁰ Since, many N-substituted DNJ derivatives with therapeutic potential have been released.^{11,12} In the last two decades, 1-C-branched DNJ derivatives,¹³ coined iminosugar C-glycosides, have also been extensively scrutinized as they proved to have potent glycosidase inhibitory activities and improved selectivity as illustrated by 1-C-nonyl-DNJ, an almost 1000-fold more potent inhibitor than DNJ against β-glucosidase (Figure 1a).¹⁴ Finally, in the last decade, other branched iminosugars such as 5-C-alkyl-DNJ derivatives, iminosugar C-glycosides in which the alkyl chain has been moved from C1 to C5 carbon atom,^{15,16} have emerged as potent α-glucosidase inhibitors.¹⁷

Counter-intuitively, L-iminosugars have also gained increased interest as this class of compounds holds higher therapeutic promises than initially anticipated when considering their mismatching stereochemistry.^{18,19} As an example, 1-C-hexyl-L-ido-DNJ is a potent β-glucocerebrosidase inhibitor²⁰ while 5-C-methyl-L-ido-DNJ showed a strong affinity comparable to DNJ for lysosomal acid α-glucosidase which deficiency is responsible for Pompe disease²¹ (Figure 1a). Accordingly, "branching" of the L-ido-DNJ motif is worth investigating further as it could provide molecules with interesting potential as glycoside processing enzyme inhibitors.

While introduction of one alkyl chain at the C1 carbon or nitrogen of DNJ has been extensively studied, introduction of multiple alkyl chains on the DNJ motif is scarce in the literature but worth investigating. Indeed, capitalizing on the potency developed by N-butyl DNJ as an inhibitor of glucosyl ceramide synthase, an enzyme targeted for the

treatment of Gaucher disease, introduction of an additional alkyl chain either at the pseudoanomeric carbon or on one of the hydroxyl groups of DNJ has been explored to mimic the ceramide moiety of the enzyme substrate.²³ More recently, similar compounds and closely related dialkylated iminoxylitol derivatives have been designed as START domain ligands of the ceramide transport protein (CERT), which dysregulation is associated with several diseases.²⁴ In addition, scarce examples in the literature showed that quaternarization of the carbon adjacent to the nitrogen in polyhydroxylated piperidines either abolished glycosidase inhibition²⁵ or led to potent glycosidase inhibitors.¹⁵ To the best of our knowledge, there are only two reports, respectively using a chemoenzymatic route²⁶ and an allylic azide rearrangement,²⁷ of DNJ derivatives bearing two pseudoanomeric substituents. Unfortunately, the glycosidase inhibition profile of these derivative has not been disclosed. In this context, we report herein the synthesis and the glycosidase inhibition of new six- and seven-membered L-iminosugars including C,C-dialkyl analogues of type **A** and **C** and spirocyclic structures of type **B** and **D** where the two alkyl chains are located at C1 carbon (Figure 1b).

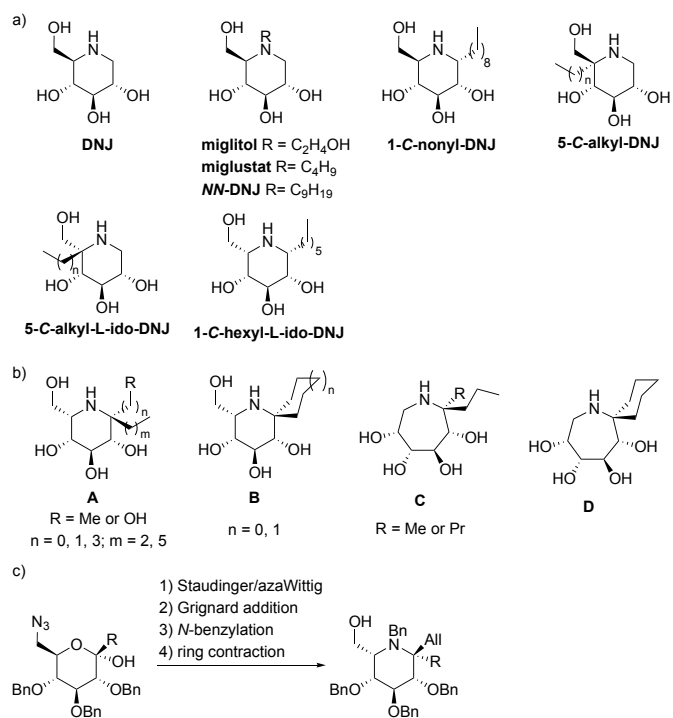
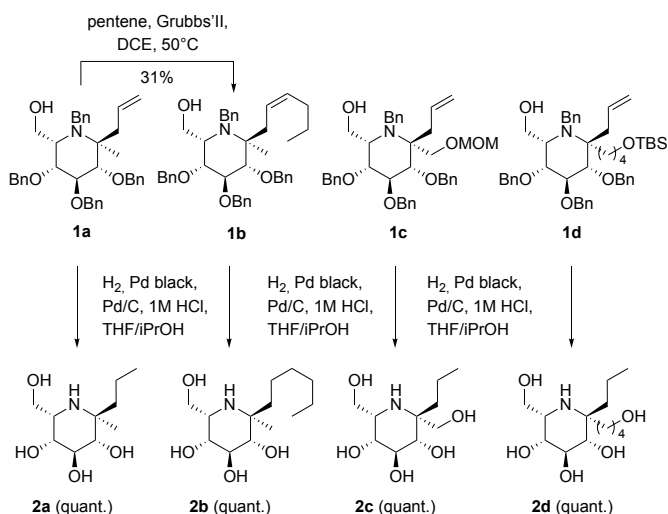


Figure 1: a) Structures of canonical DNJ derivatives and branched DNJ derivatives; b) L-iminosugars **A-D** synthesized in this work; c) strategy used to access the iminosugar precursors.

Results and discussion

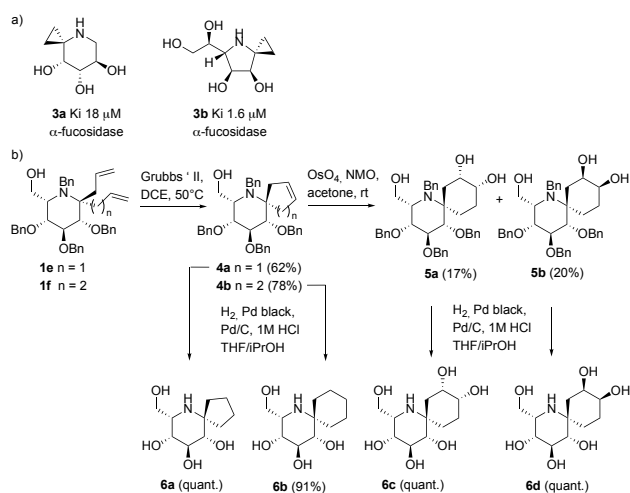
Synthesis

With the aim to develop a general access to iminosugars with a quaternarized pseudoanomeric position, we have recently reported the stereoselective access to a range of protected L-iminosugar C,C-glycosides from 6-azidoketopyranoses by a Staudinger/azaWittig/Grignard (SAWG)-ring contraction sequence (Figure 1c).²⁸ From this library, three piperidines **1a**, **1c** and **1d**, possessing all an α -configured pseudoanomeric allyl group and a distinct α -configured pseudoanomeric group were selected and further deprotected to study the impact of the structure of the pseudoanomeric substituent on the glycosidase inhibition profile. To introduce a six-carbon chain at C1 position found in the potent β -glucocerebrosidase inhibitor 1-C-hexyl-L-ido-DNJ, the 3 carbon atoms chain in **1a** was elongated via a cross-metathesis reaction using Grubbs' II catalyst and pentene to furnish the corresponding piperidine **1b** in modest 31% yield. Piperidines **1a-d** were hydrogenolysed under acidic conditions to furnish the L-ido-DNJ C,C-glycosides **2a-d** in quantitative yield (Scheme 1). Compound **2c** can be seen as a 1-C-alkyl-L-homoiminosugar, the first branched homoiminosugar²⁹ to the best of our knowledge, and compound **2d** is a **2c** analogue in which the CH₂OH group has been elongated to a four-carbon chain (Scheme 1).



Scheme 1: Synthesis of L-imosugar C,C-glycosides **2a-d**

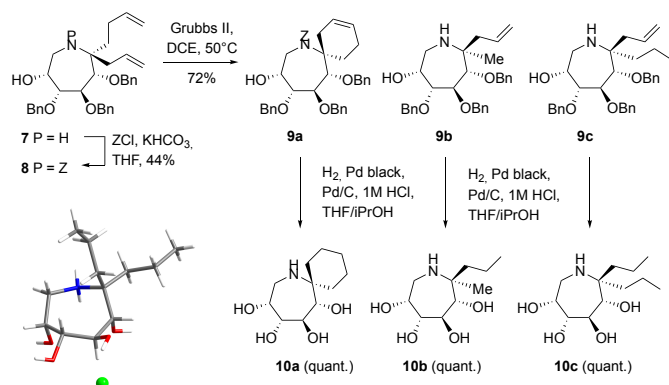
To exploit further the synthetic potential of these iminosugar C,C-glycosides, those bearing two terminal alkenes at the pseudoanomeric position were converted into the corresponding spirocyclic iminosugars that are scarce in the literature.^{30,31,32} Indeed, the α -L-fucosidase inhibitory potency in the low micromolar range exhibited by derivatives **3a** and **3b**^{33,34} (Scheme 2a) encouraged us to access structural analogues bearing a pseudoanomeric five- or six-membered ring imposed by the alkene chain length.



Scheme 2: a) Spirocyclic iminosugars **3a-b** reported in the literature demonstrating fucosidase inhibition; b) Synthesis of spirocyclic derivatives of L-ido-DNJ **6a-d**.

The RCM of C,C-diallyl iminosugar **1e** and previously reported C-allyl, C-homoallyl iminosugar **1f**²⁸ using Grubbs' II catalyst in dichloroethane at 50°C furnished the corresponding bicycles **4a** and **4b** in satisfactory 62% to 78% yields respectively. Compound **4b** was further dihydroxylated with OsO₄/NMO in acetone to provide in modest yield the triols **5a** (17%) and **5b** (20%). Their hydrogenolysis under mild acidic conditions furnished the spirocyclic iminosugars **6a-d** in nearly quantitative yield (Scheme 2b). NMR analysis of the six-membered L-imosugar C,C-glycosides **2a-d** and spiro derivatives **6a-d** indicated that the piperidine ring in CD₃OD adopts an inverted ¹C₄ conformation according to the small coupling constants observed for H-3 and H-2 (see SI).

We were also interested in accessing seven-membered derivatives^{35–37} also exhibit potency as glycosidase inhibitors.^{38,39} Therefore the same chemical transformations as above were applied to a selection of available seven-membered iminosugar *C,C*-glycosides. To access a tetrahydroxylated spirocyclic azepane, the *C*-allyl, *C*-homoallyl azepane **7** was protected as its benzyl carbamate **8** (44%) and submitted to RCM with Grubbs' II catalyst to afford compound **9a** in 72% yield. The hydrogenolysis of **9a** and available azepanes *C,C*-glycosides **9b**²⁸ and **9c**²⁸ furnished the corresponding polyhydroxylated iminosugars **10a-c** in quantitative yields (Scheme 3), the structure of **10c** being confirmed by X-ray crystallography (CCDC 2248973).














Scheme 3: Synthesis of seven-membered L-iminosugar *C,C*-glycosides and X-ray structure of compound **10c** (CCDC 2248973).

Glycosidase inhibition

The eleven iminosugar *C,C*-glycosides **2a-d**, **6a-d** and **10a-c** were assayed against a panel of twenty glycosidases (Table 1). In search for therapeutic candidates to treat Gaucher disease, the most prevalent lysosomal storage disorder, *N*- and *C*-alkyl iminosugars bearing long alkyl hydrophobic chains have been extensively studied as glucocerebrosidase inhibitors owing to their mimicry of the substrate ceramide moiety.⁴⁰ Accordingly, our library of compounds were assayed on a range of lysosomal glycosidases including human lysosomal β -glucocerebrosidase (GCCase), human lysosomal acid α -glucosidase (GAA) involved in Pompe disease⁴¹ and human α -galactosidase A (α -Gal A) which deficiency is responsible for Fabry disease.⁴² The six-membered L-iminosugar *C,C*-glycosides **2a-d** proved to be weak glycosidase inhibitors. Compound **2a** was a selective α -glucosidase inhibitor, being a moderate rice α -glucosidase inhibitor (K_i 11 μ M), a weak inhibitor of rat intestinal maltase (IC_{50} 132 μ M) and human lysosomal α -glucosidase (IC_{50} 255 μ M). Lengthening of the propyl chain in **2a** to a hexyl chain (**2b**) abolished α -glucosidase inhibition and changed inhibition profile of **2b** to a weak human lysosome β -glucosidase (IC_{50} 95 μ M), *E. Coli* β -glucuronidase (IC_{50} 136 μ M) and bovine liver β -galactosidase (IC_{50} 165 μ M) inhibitor. The inhibition profile of **2a** and **2b** is very distinct from the corresponding iminosugar *C*-glycosides reported as weak α -L-fucosidase inhibitors,⁴³ demonstrating the impact of C1 dialkylation on inhibition. Compound **2c** was a selective albeit weak human lysosome β -glucosidase (IC_{50} 280 μ M) while its analogue **2d** was less selective, being a poor yeast α -glucosidase (IC_{50} 522 μ M), *E. Coli* β -glucuronidase (IC_{50} 284 μ M) and human lysosomal β -glucosidase (IC_{50} 138 μ M) inhibitor. Introduction of the pseudoanomeric propyl chain in **2c** changed the inhibition profile of the parent homoiminosugar previously identified as a weak rice α -glucosidase inhibitor.⁴⁴

Unlike tetrahydroxylated azepanes and the corresponding *C*-glycosides that are potent glycosidase inhibitors,^{35,45,46} the azepanes *C,C* glycosides **10b** and **10c** remained inactive against all enzymes. On the contrary, spirocyclic derivatives proved to be more interesting compounds. Spirocyclopentanyl compound **6a** was a selective albeit weak human lysosome β -glucosidase (IC_{50} 224 μ M). Increasing the size of the pseudoanomeric ring from a five- (**6a**) to a six-membered ring (**6b**) increased human lysosome β -glucosidase inhibition 10-fold (IC_{50} 23 μ M) but was detrimental to selectivity as **6b** weakly inhibited β -glucuronidase (IC_{50} 95 μ M), yeast α -glucosidase (IC_{50} 380 μ M) and human lysosome α -galactosidase (IC_{50} 286 μ M). When the piperidine in **6b** was replaced by an azepane ring to lead **10a**, selectivity toward human lysosome β -glucosidase was restored and improved compared to **6a** (IC_{50} 90 μ M). Interestingly, spirocycle **6b** and iminosugar *C,C*-glycoside **2b** mainly differ by the spatial presentation of the pseudoanomeric hydrophobic moiety (spirohexyl versus *C*-methyl, *C*-hexyl motif) and share a similar glycosidase inhibition profile although spirocycle **6b** proved more potent toward β -glucuronidase and human lysosome β -glucosidase. Dihydroxylation of cyclohexane ring of **6b** to lead compounds **6c** and **6d** completely abolished glycosidase inhibition including CGase, an enzyme known to accommodate lipophilic aglycons.

Table 1. Concentration of iminosugars giving 50 % inhibition of various glycosidases

Enzyme / Compound	IC 50 (μM)										
											
α-Glucosidase											
Yeast	^a NI ^b (10 %)	NI (1.4 %)	NI (4.2 %)	522	NI(9.1 %)	380	^c NI ^d (0 %)	NI (0 %)	NI (16 %)	NI (0 %)	NI (3.0 %)
Rice	60 (Ki 11)	NI (25.7 %)	NI (0 %)	NI (5.7 %)	NI (13.5 %)	^c NI ^d (9.9 %)	NI (0 %)	NI (1.8 %)	NI (7.2 %)	NI (1.8 %)	NI (6.3 %)
Rat intestinal maltase	132	NI (6.3 %)	NI (0 %)	NI (0 %)	NI (0 %)	NI (4.7 %)	NI (0 %)	NI (6.3 %)	NI (7.1 %)	NI (1.9 %)	NI (1.4 %)
Human Lysosome (GAA)	255	NI (3.2 %)	NI (0 %)	NI (7.5 %)	NI (5.0 %)	NI (10.8 %)	NI (2.9 %)	NI (0.2 %)	NI (3.9 %)	NI (0 %)	NI (0.1 %)
β-Glucosidase											
Almond	NI (9.9 %)	NI (14.1 %)	NI (23 %)	NI (23.8 %)	NI (33.8 %)	210	NI (0 %)	NI (0 %)	NI (10.1 %)	NI (6.5 %)	NI (0 %)
Bovine liver	NI (15.2 %)	NI (26.2 %)	NI (12.8 %)	NI (14.7 %)	NI (13.4 %)	NI (30.1 %)	NI (11 %)	NI (15 %)	NI (17.2 %)	NI (9.6 %)	NI (8.1 %)
Human Lysosome (CGase)	689 (Ki 661)	95	280	138	224 (Ki 114)	23 (Ki 15)	NI (0 %)	NI (0 %)	90 (Ki 64)	NI (18.4 %)	NI (10.8 %)
α-Galactosidase											
Coffee beans	NI (15 %)	NI (0 %)	NI (6.4 %)	NI (11.4 %)	NI (2.7 %)	NI (44.9 %)	NI (0 %)	NI (0 %)	NI (6.7 %)	NI (1.9 %)	NI (2.7 %)
Human Lysosome (α-Gal A)	NI (31.3 %)	ND	NI (5.2 %)	NI (38.5 %)	NI (16.1 %)	286	ND	ND	NI (45.8 %)	NI (3.5 %)	NI (4.2 %)
β-Galactosidase											
Bovine liver	NI (35.3 %)	165	NI (24.9 %)	NI (17.3 %)	NI (33.2 %)	NI (49.1 %)	NI (30.1 %)	1000	NI (34.9 %)	NI (27.2 %)	NI (26.7 %)
α-Mannosidase											
Jack bean	NI (7 %)	NI (0 %)	NI (19.4 %)	NI (16 %)	NI (0 %)	NI (17.5 %)	NI (0 %)	NI (0 %)	NI (1.4 %)	NI (0 %)	NI (0 %)
β-Mannosidase											
Snail	NI (0.4 %)	NI (3.0 %)	NI (17.3 %)	NI (11.8 %)	NI (0 %)	NI (10.8 %)	NI (0 %)	NI (3.0 %)	NI (0 %)	NI (0 %)	NI (0 %)
α,α-Trehalase											
Porcine kidney	NI (0 %)	NI (3.9 %)	NI (0 %)	NI (0 %)	NI (7.6 %)	NI (4.1 %)	^c NI ^d (2.0 %)	NI (2.0 %)	NI (0 %)	NI (4.1 %)	NI (3.5 %)
Amyloglucosidase											
<i>Aspergillus niger</i>	NI (0 %)	NI (3.7 %)	NI (0 %)	NI (8.2 %)	NI (0.4 %)	NI (2.2 %)	NI (5.2 %)	NI (1.5 %)	NI (4.5 %)	NI (3.8 %)	NI (0.8 %)
α-L-Rhamnosidase											
<i>Penicillium decumbens</i>	NI (7.8 %)	NI (0.9 %)	NI (4.3 %)	NI (0 %)	NI (0 %)	NI (0.4 %)	NI (3.5 %)	NI (0.3 %)	NI (0 %)	NI (0.4 %)	NI (0 %)
β-Glucuronidase											
<i>E. coli</i>	NI (1.8 %)	136	NI (32.8 %)	284	NI (25.8 %)	95	NI (0 %)	NI (0 %)	NI (34.7 %)	NI (3.7 %)	NI (7.9 %)
Bovine liver	NI (4.5 %)	NI (27 %)	NI (21.9 %)	NI (30.5 %)	NI (0 %)	723	NI (0 %)	NI (0 %)	NI (0 %)	NI (0 %)	NI (0 %)
α-N-Acetylglucosaminidase											
Human recombinant	^e ND	NI (13.3 %)	NI (9.7 %)	ND	ND	ND	NI (16.7 %)	NI (10.0 %)	ND	ND	ND
β-N-Acetylglucosaminidase											
Bovine kidney	ND	NI (0 %)	NI (26.9 %)	ND	ND	ND	NI (2.8 %)	NI (0 %)	ND	ND	ND
HL60	ND	NI (2.7 %)	NI (10.0 %)	ND	ND	ND	NI (7.6 %)	NI (3.7 %)	ND	ND	ND
Jack bean	ND	NI (0 %)	NI (17.5 %)	ND	ND	ND	NI (1.6 %)	NI (0 %)	ND	ND	ND
β-N-Acetylhexosaminidase											
HL60	ND	NI (15.2 %)	NI (1.2 %)	ND	ND	ND	NI (5.1 %)	NI (6.8 %)	ND	ND	ND
α-N-Acetylgalactosaminidase											
Chicken liver	ND	NI (0 %)	NI (18.5 %)	ND	ND	ND	NI (5.2 %)	NI (2.2 %)	ND	ND	ND

^aNI: no inhibition (less than 50 % inhibition at 1000 μM); ^b(): inhibition % at 1000 μM; ^cNI: no inhibition (less than 50 % inhibition at 100 μM); ^d(): inhibition % at 100 μM; ^eND: not determined.

Conclusion

In conclusion, the synthesis and glycosidase inhibition profile of a range of L-ido-DNJ derivatives and analogues in which two alkyl substituents have been introduced in a stereoselective manner at the pseudoanomeric position including spirocyclic derivatives, is disclosed. These iminosugar C,C-glycosides, that adopt a 1C_4 chair conformation in solution, were assayed on a range of glycosidases including the lysosomal enzymes CGase, GAA and α -Gal A. Amongst all derivatives, the derivatives bearing hydrophobic moieties proved to be the most promising ones as selective or potent inhibition of CGase was recorded depending on the size of the spirocycle and the length of the alkyl chains at C1 position. Despite mitigated inhibition results, these data suggest that introduction of more lipophilic moieties through longer alkyl chains or modified spirocycles could lead to improved CGase inhibitors. Such molecules could be accessed from iminosugars **1e** and **1f**. Altogether, this work expands the structural diversity introduced at the pseudoanomeric position of DNJ, an important glycomimetic.

Experimental

General methods

All commercially available reagents were used as supplied without further purification. THF was distilled under anhydrous conditions. Petroleum ether (PE) refers to the 40–60 °C boiling fraction. Air and water sensitive reactions were performed in oven dried glassware under Ar atmosphere. TLC plates were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of phosphomolybdic acid in ethanol (3 g/100 mL) followed by heating with a heat gun. Flash chromatography columns were performed using silica gel 60 (15–40 μ m) or carried on a combiflash[®]Rf automated apparatus (Teledyne-Isco) using columns specified in each protocol. NMR experiments were recorded with a Bruker Avance 400 spectrometer at 400 MHz for 1H and 100 MHz for ${}^{13}C$ nuclei and a Bruker Avance Neo 500 spectrometer at 500 MHz for 1H and 125 MHz for ${}^{13}C$ nuclei. The chemical shifts are expressed in part per million (ppm) relative to TMS ($\delta = 0$ ppm) and the coupling constant J in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: b = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, etc... The numbering used for NMR assignment is given following carbohydrates numbering. HRMS were obtained with a Q-TOF spectrometer from the Mass Spectrometry Service (IC2MP, UMR CNRS 7285-Poitiers University, France). Optical rotations were measured using a Modular Circular Polarimeter MCP100 (Anton Paar). Compounds **1a**, **1c**, **1d**, **1f**, **6b**, **7**, **9b** were previously fully described by our group.²⁵

General procedure A for azepane ring contraction. A solution of azepane (1.0 eq.) in anhydrous toluene (0.1 M) and Et₃N (2.0 eq.) under Ar was stirred 20 min at room temperature, then cooled down to 0 °C, and TFAA (1.5 eq.) was added. The reaction mixture was stirred for 4h at 120 °C, then allowed to reach room temperature. A solution of NaOH (1M, 1.5 mL) was added, then the reaction mixture was stirred for 1h30 at room temperature and extracted with AcOEt. The organic layer was dried over MgSO₄, filtered and concentrated. The crude was purified over a flash chromatography column.

General procedure B for ring closing metathesis. To a solution of 1,1-bis-allyl or 1-allyl-1-homoallyl derivative (1.0 eq.) in dry dichloroethane (DCE, 0.05 M) under an Ar atmosphere was added 2nd generation Grubbs catalyst (0.1 eq.). The reaction mixture was stirred at 50 °C for 2 h by which time TLC monitoring showed the total consumption of the starting material. The mixture was concentrated under reduced pressure and purified by flash chromatography.

General procedure C for hydrogenolysis. The benzylated substrate was dissolved in a 1:1 mixture of *i*-PrOH/THF (0.05 M). The mixture was flushed 4 times with Ar then 1N HCl (3 eq.), palladium black (0.5 mass eq.) and 5% or 10% Pd/C (0.5 mass eq.) were added. The mixture was flushed 4 times with H₂ and stirred at room temperature under H₂ atmosphere. After 24 h, the mixture was filtered through a pad of celite (previously washed with 1N HCl, H₂O and then MeOH) and the filtrate was concentrated under reduced pressure to give the fully deprotected product as its hydrochloride salt.

Synthesis

α -C-((E)-hex-2-en-1-yl)- β -C-methyl-2,3,4-tri-O-benzyl-N-benzyl-1-deoxy-L-idonojirimycin (1b). To a solution of **1a** (30 mg, 0.052 mmol, 1.0 eq.) and pentene (45.4 μ L, 0.311 mmol, 6.0 eq.) in dry CH₂Cl₂ (0.5 mL, 0.05 M), under Ar atmosphere, was added 2nd generation Grubbs catalyst (26 mg, 0.041 mmol, 0.8 eq.). The reaction mixture was stirred at 50 °C for 48 h by which time TLC monitoring showed the total consumption of the starting material. The mixture was concentrated under reduced pressure and the crude was purified over a flash chromatography column (Interchim[®] 4 g, PE/EtOAc 95:5 to 85:15) to afford **1b** (10 mg, 31%) as a colorless oil. $R_f = 0.4$ (PE/EtOAc 95/5). $[\alpha]_D^{20} = -55.8$ (c 0.5, CHCl₃); 1H NMR (500 MHz, CDCl₃) δ 7.40 - 7.10 (m, 20H, H-Ar), 5.73 - 5.65 (m, 1H, H-8), 5.45 - 5.32 (m, 1H, H-9), 4.95 (d, 1H, $J = 11.3$ Hz, OCHH-Ph), 4.78 (d, 1H, $J = 10.6$ Hz, OCHH-Ph), 4.73 (d, 1H, $J = 10.6$ Hz, OCHH-Ph), 4.60 (m, 2H, OCHH-Ph), 4.52 (d, 1H, $J = 11.4$ Hz, OCHH-Ph), 3.92 - 3.82 (m, 4H, NCHH-Ph, H-6b, H-4, H-3), 3.72 - 3.62 (m, 3H, NCHH-Ph, H-6a, H-5), 3.42 (d, 1H, $J = 9.4$ Hz, H-2), 2.45 (dd, 1H, $J = 15.3, 8.9$ Hz, H-7b), 2.30 - 2.21 (m, 1H, H-7a), 2.00 - 1.81 (m, 2H, H-10), 1.30 - 1.12 (m, 5H, H-11, H-13), 0.80 (t, 3H, $J = 7.4$ Hz, H-12); ${}^{13}C$ NMR (125

MHz, CDCl₃) δ 142.2, 139.3, 138.6, 138.2 (C^{IV}-Ar), 133.7 (C9), 128.4 - 126.2 (CH-Ar), 126.2 (C8), 81.0 (C2), 80.3 (C4), 78.9 (C3), 75.5, 74.7, 73.5 (OCH₂-Ph), 67.0 (C6, NCH₂Ph), 62.3 (C^{IV}-1), 58.0 (C5), 43.0 (C7), 35.1 (C10), 22.7 (C11), 20.5 (C13), 13.9 (C12); HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₄₁H₄₉NO₄Na 642.3559; Found 642.3480.

α-C-methyl-β-C-propyl-1-deoxy-L-idonojirimycin (2a). Application of procedure C to compound **1a** (22 mg, 0.038 mmol) afforded compound **2a** (10 mg, quant., hydrochloride salt) as a colorless oil. [α]_D²⁰ = -25.6 (c 0.5, MeOH); ¹H NMR (500 MHz, CD₃OD) δ 3.97 (t, 1H, *J* = 3.1 Hz, H-3), 3.85 - 3.79 (m, 1H, H-4), 3.76 (d, 2H, *J* = 6.7 Hz, H-6), 3.65 (br.d, 1H, *J* = 2.2 Hz, H-2), 3.56 (t, 1H, *J* = 6.1 Hz, H-5), 2.23 (td, 1H, *J* = 12.4, 4.9 Hz, H-7b), 1.70 - 1.52 (m, 1H, H-7a), 1.35 (s, 3H, H-10), 1.34 - 1.26 (m, 2H, H-8), 0.86 (t, 3H, *J* = 7.2 Hz, H-9); ¹³C NMR (125 MHz, CD₃OD) δ 70.15 (C2), 69.6 (C3), 67.6 (C4), 62.3 (C^{IV}-1), 59.2 (C6), 52.8 (C5) 35.5 (C7), 20.9 (C10), 16.6 (C8), 13.4 (C9); HRMS (ESI) m/z [M+H]⁺ calcd for C₁₀H₂₂NO₄ 220.1543; Found 220.1542.

α-C-methyl-β-C-hexyl-1-deoxy-L-idonojirimycin (2b). Application of procedure C to compound **1b** (10 mg, 0.016 mmol) afforded compound **2b** (5 mg, quant., hydrochloride salt) as a colorless oil. [α]_D²⁰ = -21.2 (c 0.25, MeOH); ¹H NMR (500 MHz, CD₃OD) δ 3.95 (t, 1H, *J* = 3.1 Hz, H-3), 3.79 (m, 1H, H-4), 3.77 - 3.71 (m, 2H, H-6), 3.64 (br d, 1H, *J* = 2.2 Hz, H-2), 3.55 (m, 1H, H-5), 2.35 - 2.19 (m, 1H, H-7b), 1.71 - 1.51 (m, 1H, H-7a), 1.34 (s, 3H, H-13), 1.31 - 1.18 (m, 8H, H-8, H-9, H-10, H-11), 0.81 (m, 3H, H-12); ¹³C NMR (125 MHz, CD₃OD) δ 70.2 (C2), 69.7 (C3), 67.7 (C4), 62.3 (C^{IV}1), 59.3 (C6), 52.9 (C5), 33.3 (C7), 31.3, 29.3, 23.1, 22.2 (C8, C9, C10, C11), 20.8 (C13), 13.0 (C12); HRMS (ESI⁺) m/z [M+H]⁺: calcd for C₁₃H₂₈NO₄ 262.2013; Found 262.2023.

α-C-hydroxymethyl-β-C-propyl-1-deoxy-L-idonojirimycin (2c). Application of procedure C to compound **1c** (8.5 mg, 13.3 μmol), using an excess of 10N HCl (16 μL, 160 μmol, 12 eq), afforded compound **2c** (3.6 mg, quant., hydrochloride salt) as a colorless oil. [α]_D²⁰ = -8.4 (c 0.9, MeOH); ¹H NMR (500 MHz, CD₃OD) δ 3.96 (t, 1H, *J* = 3.1 Hz, H-3), 3.91 (m, 2H, H-10b, H-2), 3.84 - 3.79 (m, 3H, H-6, H-4), 3.70 (d, 1H, *J* = 11.8 Hz, H-10a), 3.56 (t, 1H, *J* = 6.2 Hz, H-5), 2.18 (m, 1H, H-7b), 1.88 - 1.79 (m, 1H, H-7a), 1.43 - 1.33 (m, 2H, H-8), 0.90 (t, 3H, *J* = 7.2 Hz, H-9); ¹³C NMR (125 MHz, CD₃OD) δ 69.6 (C3), 68.6 (C4), 67.6 (C2), 65.2 (C^{IV}-1), 61.3 (C10), 58.6 (C6), 52.2 (C5), 30.3 (C7), 16.2 (C8), 13.3 (C9); HRMS (ESI) m/z: [M+H]⁺ calcd for C₁₀H₂₂NO₅ 236.1492; Found 236.1486.

α-C-(4-hydroxybutyl)-β-C-propyl-1-deoxy-L-idonojirimycin (2d). Application of procedure C to compound **1d** (10.5 mg, 14 μmol), using an excess of 1N HCl (168 μL, 168 μmol, 12 eq), afforded compound **2d** (4.4 mg, quant., hydrochloride salt) as a colorless oil after freeze drying. [α]_D²⁰ = -17.6 (c 0.45, MeOH); ¹H NMR (500 MHz, CD₃OD) δ 4.06 (t, 1H, *J* = 3.0 Hz, H-3), 3.94 (m, 1H, H-4), 3.85 (m, 2H, H-6), 3.73 (dd, 1H, *J* = 0.8, 2.8 Hz, H-2), 3.59 (m, 3H, H-5, H-13), 2.31 (td, 1H, *J* = 4.1, 16.0 Hz, H-7a), 1.93 (td, 1H, *J* = 4.5, 12.8 Hz, H-10a), 1.85 - 1.72 (m, 2H, H-7b, H-10b), 1.58 (m, 2H, H-12), 1.49 - 1.32 (m, 4H, H-8, H-11), 0.98 (t, 3H, *J* = 7.2 Hz, CH₃); ¹³C NMR (125 MHz, CD₃OD) δ 71.4 (C3), 71.4 (C2), 69.2 (C4), 66.6 (C^{IV}-1), 62.4 (C13), 60.4 (C6), 54.5 (C5), 33.7 (C12), 33.4 (C10), 32.0 (C7), 19.8 (C11), 16.7 (C8), 14.7 (C9); HRMS (ESI) m/z: [M+H]⁺ Calcd for C₁₃H₂₈NO₅ 278.1962; Found 278.1961.

C,C-diallyl-2,3,4-tri-O-benzyl-N-benzyl-1-deoxy-L-idonojirimycin (1e). To a solution of (5*R*,4*R*,3*R*,2*S*)-1,1-diallyl-2,3,4-tris(benzyloxy) azepan-5-ol²⁵ (90 mg, 0.175 mmol, 1.0 eq.) in a mixture EtOAc/H₂O (2 mL/2 mL) were added at room temperature KHCO₃ (350 mg, 1.75 mmol, 10 eq.), KI (cat) and benzyl bromide (64 μL, 0.525 mmol, 3.0 eq.), then the mixture was stirred for 24h at 80 °C. The reaction mixture was extracted twice with EtOAc, the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude was purified over a flash chromatography column (Interchim[®] 4 g, EP/AcOEt 95/5 to 80/15) to afford the expected *N*-benzylated azepane (80 mg, 75 %) as a colorless oil. R_f = 0.23 (PE/EtOAc 90/10); [α]_D²⁰ = -7.0 (c 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.54 - 7.11 (m, 20H, H-Ar), 6.22 - 5.87 (m, 2H, H-8, H-11), 5.21 - 5.06 (m, 4H, H-9, H-12), 4.91 (d, 1H, *J* = 11.8 Hz, OCHH-Ph), 4.79 (d, 1H, *J* = 11.1 Hz, OCHH-Ph), 4.76 (d, 1H, *J* = 11.1 Hz, OCHH-Ph), 4.73 - 4.65 (m, 2H, 2xOCHH-Ph), 4.40 (d, 1H, *J* = 11.1 Hz, OCHH-Ph), 4.21 - 4.16 (m, 2H, H-3, NCHH-Ph), 3.83 (d, 1H, *J* = 13.9 Hz, NCHH-Ph), 3.76 - 3.71 (m, 1H, H-5), 3.66 (dd, 1H, *J* = 8.1, 2.8 Hz, H-4), 3.63 (d, *J* = 5.6 Hz, H-2), 3.06 (dd, 1H, *J* = 15.3, 1.7 Hz, H-6b), 2.93 (dd, 1H, *J* = 15.3, 6.1 Hz, H-6a), 2.71 - 2.58 (m, 3H, H-7b, H-10), 2.50 (dd, 1H, *J* = 15.2, 7.2 Hz, H-7a); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 138.7, 138.1 (C^{IV}-Ar), 135.5, 134.7 (C8, C10), 128.6 - 127.1 (CH-Ar), 118.3, 118.1 (C12, C9), 85.98 (C4), 83.1 (C2), 80.8 (C3), 74.75, 74.4, 72.8 (OCH₂-Ph), 68.6 (C5), 64.7 (C^{IV}-1), 54.8 (NCH₂-Ph), 49.8 (C6), 39.8, 38.4 (C10, C7); HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₄₀H₄₅NO₄Na 626.3240; Found 626.3236.

The obtained azepane (68 mg, 0.112 mmol, 1.0 eq.) was reacted with TFAA (23.6 μL, 0.225 mmol, 1.5 eq.) in the presence of Et₃N (23.6 μL, 0.169 mmol, 2.0 eq.) following general procedure A. The crude was purified over a flash chromatography column (Interchim[®] 4g, PE/EtOAc 95:5 to 90:10) to afford **1e** (23 mg, 34 %) as a colorless oil. R_f = 0.41 (PE/EtOAc 90/10); [α]_D²⁰ = +33.1 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.50 - 7.11 (m, 20H, H-Ar), 6.02 (ddt, 1H, *J* = 10.0, 8.0, 7.0 Hz, H-8), 5.83 (dddd, 1H, *J* = 17.0, 10.3, 8.3, 5.4 Hz, H-11), 5.08 (m, 2H, H-9), 5.05 - 4.95 (m, 3H, H-12, OCHH-Ph), 4.90 (d, 1H, *J* = 10.7 Hz, OCHH-Ph), 4.81 (d, 1H, *J* = 10.7 Hz, OCHH-Ph), 4.73 (d, 1H, *J* = 11.3 Hz, OCHH-Ph), 4.67 (d, 1H, *J* = 11.5 Hz, OCHH-Ph), 4.55 (d, 1H, *J* = 11.3 Hz, OCHH-Ph), 4.12 (d, 1H, *J* = 15.4 Hz, NCHH-Ph), 4.06 - 4.00 (m, 1H, H-6b), 3.97 (t, 1H, *J* = 9.6 Hz, H-3), 3.88 - 3.76 (m, 2H, H-6a, NCHH-Ph), 3.69 (dd, 1H, *J* = 9.7, 6.2 Hz, H-4), 3.55 (d, 1H, *J* = 9.5 Hz, H-2), 3.19 (t, 1H, *J* = 6.6 Hz, H-5), 2.82 - 2.58 (m, 2H, H-10b, OH), 2.52 (dd, 1H, *J* = 14.6, 6.8 Hz, H-7b), 2.41 (dd, 1H, *J* = 16.2, 8.3 Hz, H-10a), 2.17 (dd, 1H, *J* = 14.6, 8.1 Hz, H-7a); ¹³C NMR (125 MHz, CDCl₃) δ 140.9, 139.7, 139.0, 138.6, 137.6 (C^{IV}-Ar), 135.7 (C8), 134.3 (C11), 128.6 - 126.7 (CH-Ar), 118.55 (C9), 117.8 (C12), 82.6 (C2), 81.7 (C4), 81.3 (C3), 75.5, 75.2, 74.2 (OCH₂-Ph), 64.2 (C^{IV}-1), 59.7 (C6), 58.2 (C5), 49.6 (NCH₂Ph), 41.1 (C7), 38.0 (C10); HRMS (ESI⁺) m/z calcd for C₄₀H₄₆NO₄ [M+]⁺: 604.3427; Found: 604.3458.

Compound (4a). Compound **1e** (23 mg, 0.038 mmol, 1.0 eq.) was reacted according to procedure B. The crude was purified over a flash chromatography column (Interchim[®] 4 g, EP/AcOEt 95:5 to 85:15) to afford **4a** (13.5 mg, 62 %) as a colorless oil. R_f

= 0.14 (PE/EtOAc 95/5); $[\alpha]_{\text{D}}^{20} = +7.6$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.51 - 7.00 (m, 20H, H-Ar), 5.65 (br.d, 1H, $J = 5.9$ Hz, H-8), 5.52 (d, 1H, $J = 5.9$ Hz, H-9), 4.93 (d, 1H, $J = 11.5$ Hz, OCHH-Ph), 4.84 (d, 1H, $J = 10.9$ Hz, OCHH-Ph), 4.75 (d, 1H, $J = 10.9$ Hz, OCHH-Ph), 4.70 (d, 1H, $J = 11.1$ Hz, OCHH-Ph), 4.62 (d, 1H, $J = 11.5$ Hz, OCHH-Ph), 4.54 (d, 1H, $J = 11.1$ Hz, OCHH-Ph), 3.80 (m, 4H, H-6, H-4, H-3), 3.69 (d, 1H, $J = 15.9$ Hz, NCHH-Ph), 3.64 (d, 1H, $J = 15.9$ Hz, NCHH-Ph), 3.46 (d, 1H, $J = 8.5$ Hz, H-2), 3.10 (ddd, 1H, $J = 8.5, 5.6, 2.9$ Hz, H-5), 2.97 (d, 1H, $J = 9.6$ Hz, OH), 2.67 (d, 1H, $J = 17.5$ Hz, H-10b), 2.52 (d, $J = 18.0$ Hz, H-7b), 2.40 (d, 1H, $J = 18.0$ Hz, H-7a), 2.02 (d, 1H, $J = 17.5$ Hz, H-10a); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 140.7, 138.8, 138.6, 137.6 (C^{IV} -Ar), 130.5 (C9), 128.0 (C8), 128.6 - 126.7 (CH-Ar), 86.0 (C2), 82.0 (C3), 81.3 (C4), 75.3, 75.2, 74.3 (OCH₂-Ph), 69.0 (C^{IV} -1), 59.7 (C6), 59.5 (C5), 50.2 (NCH₂Ph), 45.7 (C10), 38.6 (C7); HRMS (ESI⁺) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{38}\text{H}_{41}\text{NNaO}_4$ 598.2927; Found 598.2956.

Compound (4b). Compound **1f** (83 mg, 0.134 mmol, 1.0 eq.) was reacted according to procedure B. The crude was purified over a flash chromatography column (Interchim[®] 4 g, EP/AcOEt 95:5 to 85:15) to afford **4b** (62 mg, 78 %) as a colorless oil. $R_f = 0.26$ (PE/EtOAc 90/10); $[\alpha]_{\text{D}}^{20} = +3.8$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.29 - 7.14 (m, 20H, H-Ar), 5.77 (br.d, $J = 8.8$ Hz, H-9), 5.62 (d, 1H, $J = 10.0$ Hz, H-8), 5.02 (d, 1H, $J = 11.4$ Hz, OCHH-Ph), 4.86 (d, 1H, $J = 10.7$ Hz, OCHH-Ph), 4.79 (d, 1H, $J = 10.7$ Hz, OCHH-Ph), 4.72 (d, 1H, $J = 11.2$ Hz, OCHH-Ph), 4.58 (d, 1H, $J = 11.5$ Hz, OCHH-Ph), 4.53 (d, 1H, $J = 11.2$ Hz, OCHH-Ph), 4.30 (d, 1H, $J = 16.1$ Hz, NCHH-Ph), 4.08 (dd, 1H, $J = 10.9, 8.7$ Hz, H-6b), 4.02 - 3.90 (m, 2H, H-3, NCHH-Ph), 3.77 (dd, 1H, $J = 9.4, 6.6$ Hz, H-4), 3.73 (d, 1H, $J = 10.9$ Hz, H-6a), 3.26 (d, 1H, $J = 8.9$ Hz, H-2), 3.14 (t, 1H, $J = 6.2$ Hz, H-5), 2.61 (br.d, 1H, $J = 18.3$ Hz, H-7b), 2.15 - 2.02 (m, 3H, H-10, H-11b), 1.84 (br.d, 1H, $J = 18.2$ Hz, H-7a), 1.53 (m, 1H, H-11a); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 142.3, 138.8, 138.6, 137.7 (C^{IV} -Ar), 128.6 - 127.0 (CH-Ar), 126.9 (C8), 126.6 (C9), 86.0 (C2), 81.5 (C4), 80.8 (C3), 75.9, 75.3, 74.2 (OCH₂-Ph), 61.5 (C6), 59.8 (C^{IV} -1), 59.7 (C5), 52.0 (NCH₂Ph), 34.3 (C7), 29.0 (C11), 23.3 (C10); HRMS (ESI⁺) m/z calcd for $\text{C}_{39}\text{H}_{44}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 590.3264; Found: 590.3285.

Compounds (5a) and (5b). To a solution spiro-iminosugar **4b** (61 mg, 0.103 mmol, 1.0 eq.) in a 1:1 mixture of acetone/H₂O (1 mL/1 mL) were added citric acid (24 mg, 0.113 mmol, 1.1 eq.), 4-methylmorpholine *N*-oxide (14.5 mg, 0.123 mmol, 1.2 eq) and OsO₄ (131.5 mL, 0.020 mmol, 0.2 eq.). The mixture was stirred at room temperature for 18 h when TLC showed total consumption of the starting material. Na₂S₂O₅ (24.5 mg, 0.113 mmol, 1.2 eq.) was added and the mixture was stirred at room temperature for 1 h. The mixture was extracted 3 times with EtOAc (15 mL), the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude was purified over a flash chromatography column (Interchim[®] 4 g, EP/AcOEt 85:15 to 70:30) to afford **5a** (11 mg, 17 %) and **5b** (13 mg, 20 %) as colorless oils. These two compounds were directly engaged in the next step of hydrogenolysis to give **6c** and **6d**.

Compound (6a). Application of procedure C to compound **4a** (13 mg, 0.022 mmol) afforded compound **6a** (5 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -18.8$ (c 0.25, MeOH); $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 3.96 (t, 1H, $J = 3.2$ Hz, H-3), 3.86 - 3.81 (m, 1H, H-4), 3.76 (dd, 1H, $J = 9.3, 4.2$ Hz, H-6b), 3.73 (dd, 1H, $J = 9.3, 5.0$ Hz, H-6a), 3.52 (dd, 1H, $J = 3.0, 1.0$ Hz, H-2), 3.46 (t, 1H, $J = 6.2$ Hz, H-5), 2.53 - 2.46 (m, 1H, H-10b), 2.29 - 2.20 (m, 1H, H-7b), 1.75 (m, 2H, H-7a, H-9b), 1.68 (m, 2H, H-8b, H-10a), 1.58 (m, 2H, H-8a, H-9a); $^{13}\text{C NMR}$ (125 MHz, CD_3OD) δ 71.4 (C2), 69.7 (C^{IV} -1), 69.2 (C3), 67.6 (C4), 59.0 (C6), 54.7 (C5), 34.8 (C10), 32.1 (C7), 24.2 (C9), 22.6 (C8); HRMS (ESI⁺) m/z calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 218.1386; Found: 218.1387.

Compound (6b). Application of procedure C to compound **4b** (17 mg, 0.028 mmol) afforded compound **6b** (6 mg, 91%, hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -20.4$ (c 0.25, MeOH); $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 4.03 (br.d, 1H, $J = 2.4$ Hz, H-5), 3.99 (t, 1H, $J = 3.1$ Hz, H-4), 3.84 - 3.80 (m, 1H, H-3), 3.76 (dd, 1H, $J = 10.6, 5.4$ Hz, H-2'b), 3.72 (dd, 1H, $J = 10.6, 6.6$ Hz, H-2'a), 3.56 (m, 1H, H-2), 2.76 (br.d, 1H, $J = 8.9$ Hz, H-7b), 2.31 (dd, 1H, $J = 13.5, 4.7$ Hz, H-11b), 1.71 - 1.57 (m, 3H, H-8b, H-9b, H-10b), 1.48 - 1.29 (m, 4H, H-7a, H-8a, H-10a, H-11a), 1.28 - 1.20 (m, 1H, H-9a); $^{13}\text{C NMR}$ (125 MHz, CD_3OD) δ 69.5 (C4), 67.8 (C3), 66.6 (C5), 61.8 (C IV -6), 59.1 (C2'), 52.1 (C2), 32.3 (C7), 29.5 (C11), 24.7 (C9), 21.8 (C8), 20.9 (C10); HRMS (ESI⁺) m/z Calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 232.1543; Found: 232.1546.

Compound (6c). Application of procedure C to compound **5a** (11 mg, 0.018 mmol) afforded compound **6c** (6 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -90.0$ (c 0.5, MeOH); $^1\text{H NMR}$ (500 MHz, D_2O) δ 4.28 (br.s, 1H, H-2), 4.03 (t, 1H, $J = 3.3$ Hz, H-3), 3.91 (dd, 2H, H-8, H-4), 3.77 (dd, 1H, $J = 11.9, 5.6$ Hz, H-6b), 3.74 - 3.66 (m, 2H, H-6a, H-9), 3.60 (t, 1H, $J = 6.0$ Hz, H-5), 2.63 (br.s, 1H, H-7b), 2.17 (br.d, 1H, $J = 12.3$ Hz, H-10b), 1.78 (dd, 1H, $J = 14.3, 2.8$ Hz, H-7a), 1.61 (m, 1H, H-10a), 1.51 (m, 2H, H-11); $^{13}\text{C NMR}$ (125 MHz, D_2O) δ 69.27 (C3), 69.2 (C9), 68.6 (C2), 67.0 (C8), 66.9 (C4), 61.3 (C^{IV} -1), 58.9 (C6), 52.6 (C5), 32.7 (C7), 28.4 (C10), 23.1 (C11); HRMS (ESI⁺) m/z calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 264.1442; Found: 264.1448.

Compound (6d). Application of procedure C to compound **5b** (13 mg, 0.022 mmol) afforded compound **6d** (6.5 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -64.0$ (c 0.5, MeOH); $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 3.96 (t, 1H, $J = 3.3$ Hz, H-3), 3.92 - 3.87 (m, 1H, H-8), 3.82 - 3.74 (m, 3H, H-4, H-6), 3.73 - 3.68 (m, 1H, H-5), 3.57 (m, 1H, H-9), 3.47 (d, 1H, $J = 2.1$ Hz, H-2), 2.75 (br.d, 1H, $J = 13.5$ Hz, H-7a), 2.28 (br.d, 1H, $J = 11.2$ Hz, H-10b), 1.80 - 1.53 (m, 4H, H-7a, H-10a, H-11); $^{13}\text{C NMR}$ (125 MHz, CD_3OD) δ 72.8 (C2), 69.3 (C9), 69.1 (C3), 69.0 (C8), 67.5 (C4), 60.6 (C^{IV} -1), 59.4 (C6), 52.7 (C5), 31.8 (C7), 30.1 (C10), 22.9 (C11); HRMS (ESI⁺) m/z calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 264.1442; Found: 264.1452.

Benzyl (1S,2S,3R,4R,5R)-1-allyl-2,3,4-tris(benzyloxy)-1-(but-3-en-yl)-5-hydroxyazepane-*N*-carboxylate (8). To a solution of compound **7²⁵** (174 mg, 0.329 mmol, 1.0 eq.) in EtOAc/H₂O (1:1, 0.1 M) were added at room temperature KHCO₃ (329 mg, 3.290 mmol, 10 eq.) and CbzCl (216 μL , 0.987 mmol, 3.0 eq.). The mixture was stirred for 16h at room temperature, then extracted twice with EtOAc. The organic layers were dried over MgSO₄, filtered and concentrated. The crude was purified over a flash chromatography column (Interchim[®] 4g, PE/EtOAc 95:5 to 85:15) to afford compound **8** (95 mg, 44 %) as a colorless oil. $R_f = 0.26$ (PE/EtOAc 90/10); $[\alpha]_{\text{D}}^{20} = -25.3$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.51 - 7.04 (m, 20H, H-Ar), 5.79 - 5.62 (m,

2H, H-8, H-12), 5.08 (d, 1H, $J = 12.4$ Hz, *OCHH*-Ph), 5.03 (m, 3H, H-9, *OCHH*-Ph), 4.84 (m, 2H, H-13), 4.73 (d, 1H, $J = 11.3$ Hz, *OCHH*-Ph), 4.70 - 4.66 (m, 2H, 2*OCHH*-Ph), 4.65 (d, 1H, $J = 11.1$ Hz, *OCHH*-Ph), 4.40 (d, 1H, $J = 11.1$ Hz, *OCHH*-Ph), 4.16 (dq, 1H, $J = 10.6, 3.5$ Hz, H-5), 4.03 (dd, 1H, $J = 9.2, 3.9$ Hz, H-3), 3.80 (m, 3H, H-6, H-2), 3.71 (dd, 1H, $J = 9.0, 3.5$ Hz, H-4), 3.27 (br.s, 1H, 6b), 2.72 (dd, 1H, $J = 14.0, 7.8$ Hz, H-7a), 2.59 (br.s, 1H, OH), 2.26 - 2.16 (m, 1H, H-11b), 2.07 - 1.94 (m, 2H, H-10b, H-11a), 1.81 (m, H-10a); ^{13}C NMR (125 MHz, CDCl_3) δ 155.9 (C=O), 139.0 (C8), 138.3, 138.1, 137.7, 136.6 (C^{IV} -Ar), 134.3 (C12), 128.6 - 127.0 (CH-Ar), 119.1 (C9), 114.1 (C13), 84.8 (C2), 82.0 (C3), 81.8 (C4), 74.5, 74.4, 73.7 (OCH_2 -Ph), 67.3 (C5), 67.1 (OCH_2 -Ph), 65.4 (C^{IV} -1), 46.6 (C6), 38.5 (C7), 34.6 (C10), 29.3 (C11); HRMS (ESI⁺) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{42}\text{H}_{47}\text{NNaO}_6$ 684.3295; Found 684.3303.

Compound (9a). To a solution of **8** (41 mg, 0.061 mmol, 1.0 eq.) in dry CH_2Cl_2 (2.7 mL, 0.05 M) under Ar atmosphere was added 2nd generation Grubbs catalyst (5.1 mg, 0.006 mmol, 0.1 eq.). The reaction mixture was stirred at 50 °C for 1 h by which time TLC monitoring showed the total consumption of the starting material. The mixture was then concentrated under reduced pressure and the crude was purified over a flash chromatography column (Interchim[®] 4 g, PE/EtOAc 98:2 to 90:10) to afford **9a** (28 mg, 72 %) as a colorless oil. $R_f = 0.28$ (PE/EtOAc 90/10); $[\alpha]_{\text{D}}^{20} = -6.8$ (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.34 - 7.17 (m, 20H, H-Ar) 5.64 (br.d, 1H, $J = 10.1$ Hz, H-10), 5.59 (br.d, 1H, $J = 10.1$ Hz, H-9), 4.98 (s, 2H, 2*OCHH*-Ph), 4.72 (d, $J = 11.2$ Hz, *OCHH*-Ph), 4.66 (s, 2H, 2*OCHH*-Ph), 4.60 (d, 1H, $J = 11.2$ Hz, *OCHH*-Ph), 4.50 (d, 1H, $J = 11.2$ Hz, *OCHH*-Ph), 4.24 (d, 1H, $J = 11.2$ Hz, *OCHH*-Ph), 4.23 - 4.17 (m, 1H, H-3), 4.06 (dd, 1H, $J = 15.0, 8.2$ Hz, H-2b), 4.01 (dd, 1H, $J = 9.4, 2.3$ Hz, H-5), 3.93 (d, 1H, $J = 2.3$ Hz, H-6), 3.77 (dd, 1H, $J = 9.4, 3.6$ Hz, H-4), 3.71 (dd, 1H, $J = 15.0, 9.3$ Hz, H-2a), 3.52 (d, 1H, $J = 16.7$ Hz, H-8b), 2.53 - 2.42 (m, 2H, H-8a, OH), 2.40 - 2.29 (m, 1H, H-11b), 2.09 - 1.88 (m, 3H, H-9a, H-12); ^{13}C NMR (125 MHz, CDCl_3) δ 155.1 (C=O), 138.4, 138.2, 138.0, 136.7 (C^{IV} -Ar), 128.5 - 127.2 (CH-Ar), 125.4, 125.4 (C10, C9), 82.7 (C6), 81.1 (C4), 80.6 (C5), 73.9, 73.9, 73.4 (OCH_2 -Ph), 67.6 (C3), 66.72 (OCH_2 -Ph), 63.4 (C^{IV} -7), 45.4 (C2), 29.4 (C8), 26.5 (C11), 23.5 (C12); HRMS (ESI⁺) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{40}\text{H}_{43}\text{NO}_6\text{Na}$ 656.2982; Found 656.2996.

(5R,4R,3R,2R,1S)-1-allyl-2,3,4-tris(benzyloxy)-1-propylazepan-5-ol (9c). To a solution of 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-D-glucono lactone²⁵ (410 mg, 0.86 mmol) in anhydrous THF (9 mL), at 0 °C under Ar, was added a solution of propylmagnesium chloride (2M in THF, 0.65 mL, 1.30 mmol, 1.5 eq.). The mixture was stirred for 2h at room temperature, then quenched by addition of aq. NH_4Cl (10 mL) and extracted three times with dichloromethane (3 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude was purified over a flash chromatography column (Interchim[®] 12 g, PE/EtOAc 90:10 to 85:15) to afford the expected 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl- β -propyl- α -D-gluco pyranose (190 mg, 43 %) as a colorless oil. $R_f = 0.23$ (PE/EtOAc 90/10); $[\alpha]_{\text{D}}^{20} = +107.8$ (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.38 - 7.26 (m, 15H, H-Ar), 4.97 - 4.90 (m, 4H, 4*OCHH*-Ph), 4.71 (d, 1H, $J = 11.1$ Hz, *OCHH*-Ph), 4.64 (d, 1H, $J = 11.0$ Hz, *OCHH*-Ph), 4.07 - 4.00 (m, 2H, H-3, H-5), 3.56 (t, 1H, $J = 9.6$ Hz, H-4), 3.51 (dd, 1H, $J = 13.2, 2.4$ Hz, H-6b), 3.46 (d, 1H, $J = 9.2$ Hz, H-2), 3.31 (dd, 1H, $J = 13.2, 4.6$ Hz, H-6a), 2.61 (s, 1H, OH), 1.68 - 1.61 (m, 2H, H-7a, H-7b), 1.50 - 1.39 (m, 1H, H-8b), 1.31 (m, 1H, H-8a), 0.87 (t, 3H, $J = 7.3, 7.9$ Hz, H-9); ^{13}C NMR (125 MHz, CDCl_3) δ 138.4, 137.9, 137.8 (C^{IV} -Ar), 128.6 - 127.8 (CH-Ar), 98.6 (C^{IV} -1), 83.6 (C3), 81.3 (C2), 78.8 (C4), 75.7, 75.6, 75.2 (OCH_2 -Ph), 71.3 (C5), 51.2 (C6), 40.8 (C7), 15.9 (C8), 14.3 (C9); HRMS (ESI⁺) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{NaO}_5$ 540.2474; Found 540.2476.

To a solution of 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl- β -propyl- α -D-gluco pyranose (139 mg, 0.269 mmol, 1.0 eq.) in anhydrous MeOH (3 mL) under Ar, was added at room temperature, triphenylphosphine polymer bound (3.0 mmol.g⁻¹, 269 mg, 0.806 mmol, 3.0 eq.). The reaction mixture was stirred at 45 °C for 36h, then filtered over a pad of Celite, eluted with DCM and concentrated to give the expected bicyclic hemiaminal which was directly used for the next step without further purification. This crude bicyclic hemiaminal was dissolved in anhydrous THF (3 mL) under Ar, then AlIMgBr (1 M, 0.806 mL, 0.806 mmol, 3.0 eq.) was added at 0 °C. The reaction mixture was stirred at room temperature for 1h30. The reaction mixture was quenched with a saturated solution of NH_4Cl , then extracted thrice with DCM. The combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude was purified over a flash chromatography column (EP/ACOEt 60/40 to 40/60) to afford **9c** (33 mg, 24 %, 2 steps) as a colorless oil. $R_f = 0.32$ (PE/EtOAc 70/30); $[\alpha]_{\text{D}}^{20} = -10.1$ (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.45 - 7.09 (m, 15H, H-Ar), 5.82 - 5.71 (m, 1H, H-8), 5.02 (m, 2H, H-9), 4.67 (d, 1H, $J = 11.6$ Hz, *OCHH*-Ph), 4.67 (d, 1H, $J = 11.6$ Hz, *OCHH*-Ph), 4.62 (d, 1H, $J = 11.6$ Hz, *OCHH*-Ph), 4.57 (d, 1H, $J = 11.6$ Hz, *OCHH*-Ph), 4.56 (d, 1H, $J = 11.1$ Hz, *OCHH*-Ph), 4.16 (d, 1H, $J = 11.0$ Hz, *OCHH*-Ph), 3.94 (dd, 1H, $J = 6.9, 2.7$ Hz, H-3), 3.84 (brd, 1H, $J = 4.3$ Hz, H-5), 3.77 (dd, 1H, $J = 6.9, 1.6$ Hz, H-4), 3.32 (d, 1H, $J = 2.7$ Hz, H-2), 2.89 (dd, 1H, $J = 15.2, 5.0$ Hz, H-6b), 2.78 (d, 1H, $J = 15.2$ Hz, H-6a), 2.31 (dd, 1H, $J = 15.1, 7.0$ Hz, H-7b), 2.14 (dd, 1H, $J = 15.1, 7.3$ Hz, H-7a), 1.27 - 1.15 (m, 3H, H-10b, H-11), 0.90 - 0.79 (m, 1H, H-10a), 0.69 (t, 3H, $J = 7.0$ Hz, H-12); ^{13}C NMR (125 MHz, CDCl_3) δ 138.3, 138.3, 136.6 (C^{IV} -Ar), 133.5 (C8), 128.7 - 127.7 (CH-Ar), 117.6 (C9), 88.0 (C4), 82.8 (C3), 81.3 (C2), 73.9, 73.1, 72.5 (OCH_2 -Ph), 71.2 (C5), 60.1 (C^{IV} -1), 46.4 (C6), 39.7 (C10), 34.5 (C7), 16.9 (C11), 14.6 (C12); HRMS (ESI⁺) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{33}\text{H}_{42}\text{NO}_4$ 516.3114; Found 516.3117.

Compound (10a). Application of procedure C to compound **9a** (22 mg, 0.035 mmol) afforded compound **10a** (9.5 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -26.0$ (c 0.5, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 4.14 (dt, 1H, $J = 5.8, 1.6$ Hz, H-5), 4.03 (m, 2H, H-2, H-3), 3.97 (dd, 1H, $J = 6.3, 1.7$ Hz, H-4), 3.41 (dd, 1H, $J = 14.3, 1.3$ Hz, H-6b), 3.24 (dd, 1H, $J = 14.3, 5.9$ Hz, H-6a), 2.25 - 2.15 (m, 2H, H-11b, H-7b), 1.77 - 1.54 (m, 7H, H-7a, H-8, H-19b, H-10, H-11a), 1.44 (m, 1H, H-9a); ^{13}C NMR (125 MHz, CD_3OD) δ 77.9 (C4), 77.8 (C3), 72.1 (C2), 69.8 (C5), 63.9 (C^{IV} -1), 44.4 (C6), 33.2 (C7), 28.8 (C11), 24.5 (C9), 21.1 (C8, C10); HRMS (ESI⁺) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_4$ 232.1543; Found 232.1546.

Compound (10b). Application of procedure C to compound **9b** (30 mg, 0.061 mmol) afforded compound **10b** (15.7 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -14.6$ (c 0.5, MeOH), ^1H NMR (500 MHz, CD_3OD) δ 4.15 (d, 1H, $J = 5.8$ Hz, H-5), 3.93

(dd, 1H, $J = 6.7, 4.7$ Hz, H-3), 3.89 (dd, 1H, $J = 6.7, 1.8$ Hz, H-4), 3.66 (d, 1H, $J = 4.7$ Hz, H-6), 3.36 (d, 1H, $J = 10.9$ Hz, H-6b), 3.25 (dd, 1H, $J = 14.3, 6.1$ Hz, H-6a), 1.86 (td, 1H, $J = 13.7, 4.2$ Hz, H-7b), 1.77 - 1.69 (m, 1H, H-7a), 1.55 (m, 1H, H-8b), 1.47 (m, 1H, H-8a), 1.43 (s, 3H, H-10), 1.01 (t, 3H, $J = 7.2$ Hz, H-9), ^{13}C NMR (125 MHz, CD_3OD) δ 77.2 (C4), 75.2 (C3), 74.7 (C2), 68.3 (C5), 63.9 (C^{IV} -1), 44.1 (C6), 36.5 (C7), 21.0 (C10), 16.3 (C8), 13.3 (C9), HRMS (ESI⁺) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{22}\text{NO}_4$ 220.1549; Found 220.1538.

Compound (10c). Application of procedure C to compound **9c** (17 mg, 0.033 mmol) afforded compound **10c** (9.5 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -21.2$ (c 0.25, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 4.03 (d, 1H, $J = 5.9$ Hz, H-5), 3.87 (dd, 1H, $J = 6.5, 3.6$ Hz, H-3), 3.84 (dd, 1H, $J = 6.5, 1.7$ Hz, H-4), 3.64 (d, 1H, $J = 3.6$ Hz, H-2), 3.23 (m, 1H, H-6b), 3.15 (dd, 1H, $J = 14.3, 5.9$ Hz, H-6a), 1.79 (td, 1H, $J = 13.4, 4.6$ Hz, H-7b), 1.65 (m, 2H, H-10), 1.59 - 1.51 (m, 1H, H-7a), 1.40 - 1.20 (m, 4H, H-8, H-11), 0.90 (m, 6H, H-9, H-12); ^{13}C NMR (125 MHz, CD_3OD) δ 77.6 (C4), 77.0 (C3), 73.5 (C2), 69.3 (C5), 66.8 (C^{IV} -1), 44.7 (C6), 35.5 (C7), 31.7 (C10), 15.9, 15.6 (C8, C11), 13.2, 13.2 (C9, C12); HRMS (ESI⁺) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{26}\text{NO}_4$ 248.1856; Found 248.1856.

Material and methods for enzymes inhibition assays

The affinity of human lysosomal acid α -glucosidase (GAA) was performed according to our usual method. Briefly, GAA activity was used in combination with Myozyme (Genzyme; Boston, MA) and 4-methylumbelliferyl- α -D-glucopyranoside (Sigma-Aldrich Co; St. Louis, Mo, USA). The reaction mixture consisted of 100 mM Mcllvaine buffer (pH 5.2), 0.25% sodium taurocholate, 0.1% Triton X-100 (Nacalai Tesque Inc.; Kyoto, Japan), and an appropriate amount of enzyme. The reaction mixture was pre-incubated at 0 °C for 45 min, and the reaction was started by using 4 mM substrate solution, followed by incubation at 37 °C for 30 min. The reaction was stopped by the addition of 1.6 mL of the solution of 400 mM glycine-NaOH solution (pH 10.6). The released 4-methylumbelliferone was measured (excitation 362 nm and emission 450 nm) with a F-4500 fluorescence spectrophotometer (Hitachi, Tokyo, Japan).

Kinetic parameters were determined by the double-reciprocal plot method of Lineweaver-Burk plots at increasing substrate concentrations.

The inhibitory activity toward β -glucocerebrosidase was measured with Cerezyme (Genzyme; Boston, MA) as the enzyme source and 4-methylumbelliferyl- β -D-glucopyranoside (Sigma-Aldrich Co; St. Louis, Mo, USA) as the substrate. Brush border membranes were prepared from the rat small intestine according to the method of Kessler and were assayed at pH 6.8 for rat intestinal maltase and sucrase using the appropriate disaccharides as substrates.

Other enzymes were purchased from Sigma-Aldrich Chemical Co. (St. Louis, Mo, USA).

For rat intestinal maltase activities, the reaction mixture contained 25 mM maltose or sucrose and the appropriate amount of enzyme, and the incubations were performed for 10-30 min at 37 °C. The reaction was stopped by heating at 100 °C for 3 min. After centrifugation (600 g; 10 min), 0.05 mL of the resulting reaction mixture was added to 3 mL of the Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was measured to determine the amount of the released D-glucose.

Other glycosidase activities were determined using an appropriate amount of *p*-nitrophenyl glycoside as a substrate in a buffer solution at the optimum pH value of each enzyme. The reaction was stopped by adding 400 mM Na_2CO_3 . The released *p*-nitrophenol was measured spectrometrically at 400 nm.

Conflicts of interest

"There are no conflicts to declare".

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