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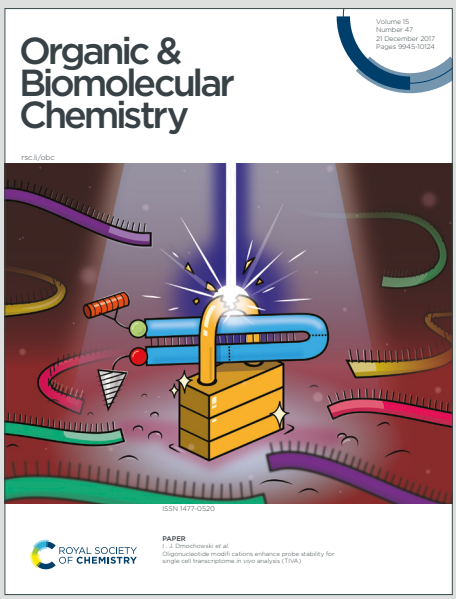

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ARTICLE

Synthesis and glycosidase inhibition of conformationally locked DNJ and DMJ derivatives exploiting a 2-oxo-C-allyl iminosugar

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A series of analogs of the iminosugars deoxynojirimycin (DNJ) and deoxymannojirimycin (DMJ), in which an extra five or six-membered ring has been fused to the C1-C2 bond have been prepared. The synthetic strategy exploits a key 2-keto-C-allyl iminosugar, easily accessible from gluconolactam, which upon Grignard addition and RCM furnishes a bicyclic scaffold that can be further hydroxylated at the C=C bond. This strategy furnished DNJ mimics with the piperidine ring locked in a $^1C_4$ conformation with all substituents in axial orientation when fused to a six-memebered ring. Addition of an extra ring to DNJ and DMJ motif proved to strongly modify the glycosidase inhibition profile of the parent iminosugars leading to modest inhibitors. The 2-keto-C-allyl iminosugar scaffold was further used to access N-acetylglycosamine analogs via oxime formation.

Introduction

The biology and synthesis of the polyhydroxylated indolizidine alkaloid castanospermine[1] has been the subject of intensive research. This naturally occuring bicyclic iminosugar, in which the endocyclic oxygen atom of the parent sugar is replaced by a nitrogen atom, has indeed demonstrated significant therapeutic potential[2] for the treatment of a number of pathologies.[3] Therefore, many synthetic analogues have been designed to improve the pharmacological properties and selectivity of the parent molecule.[3,4] Along with chemical modifications of the hydroxyl groups of this molecule,[5,6] branched derivatives,[7] as well as other analogs with a modified five-membered ring,[8] have been explored. As the five-membered ring present in castanospermine plays a crucial role to lock the deoxynojirimycin (DNJ) iminosugar moiety in a precise conformation, orientating the OH group at C-6 in a pseudoaxial orientation[9] that has been shown important for binding,[10] an array of bicyclic derivatives, in which the ring size of one of the two rings has been modified, leading respectively to polyhydroxylated quinolizidines,[11] perhydroazaazulenes[12] as well as conidines,[13] has been reported (Figure 1). In continuation of our efforts dedicated to the design and biological evaluation of conformationally biased iminosugars including flexible structures[14,15,16] and locked derivatives,[17] we have investigated herein the relevance as glycosidase inhibitors of bicyclic compounds in which the ring fused to the iminosugar ring found in castanospermine has been moved from the C5-N bond to the iminosugar C1-C2 bond as in **A** (Figure 1). Actually, such 1,2-annulated carbohydrate motif has attracted special attention within the structurally rich class of carbon-branched carbohydrates[18,19] but this scaffold is scarce in the iminosugar field.[20,21] We expected that introduction of a five- or six-membered ring 1,2-annulated to the polyhydroxylated piperidine ring would lock the iminosugar ring into a unique conformation[22,23] while maintaining the hydroxyl pattern of the polyhydroxylated piperidine affording unprecedented bicyclic analogs of the canonical deoxynojirimycin (Figure 1). We reasoned that structures of type **A** could be accessed from gluconolactam **1a** via a regioselective deprotection at C-2 followed by conversion into a *C*-allyl iminosugar with subsequent introduction of an alkene at C-2 to allow final RCM and deprotection.

Results and discussion

Synthesis

Furman has reported the synthesis of *C*-alkyl and *C*-aryl iminosugars exploiting sugar lactams[24] via formation of the corresponding imine, using the Schwartz's reagent,[25] followed by its trapping with nucleophiles. We envisioned that this sequence could be applied to a 2-hydroxy derivative that could be further modified at C-2 position en route to **A**. To this end,

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Electronic Supplementary Information (ESI) available: Copies of ^1H, ^{13}C NMR spectra of all new compounds and X-ray crystallography data for compound **10b**. See DOI: 10.1039/x0xx00000x

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the regioselective debenzylation of **1a** was achieved with BCl_3[26] to yield the 2-hydroxy lactam **2a** in 83% yield.

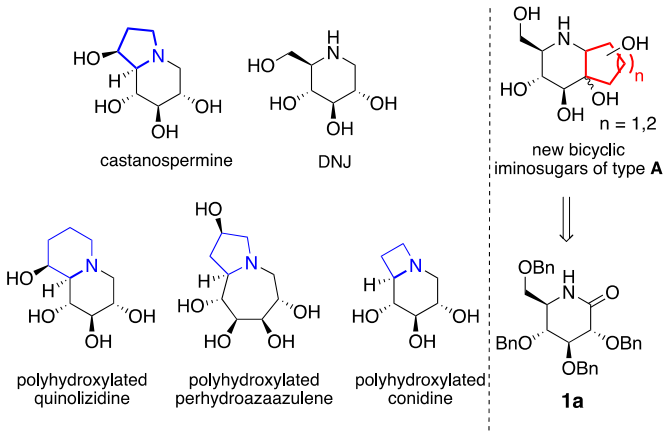
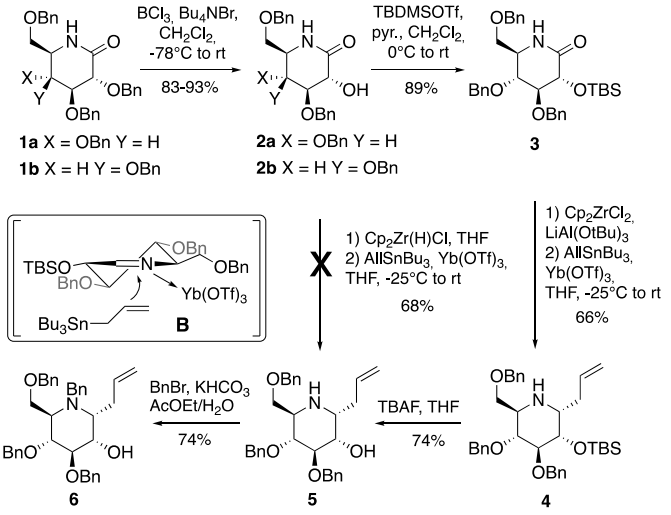


Figure 1: Structures of known natural and synthetic bicyclic iminosugars and proposed new synthetic derivatives To further exemplify the generality of this deprotection that also works with the D-manno configured lactam,[27] it was succesfully applied to the D-galactonolactam **1b** to produce the corresponding alcohol **2b** in good yield (93%). Alcohol **2a** was then treated with the Schwartz's reagent followed by $AllSnBu_3$ and $Yb(OTf)_3$. Unfortunately, no *C*-allyl iminosugar **5** was detected and only the starting lactam was recovered, demonstrating the detrimental role of the OH at C-2 in this transformation. The 2-OH was therefore orthogonally protected as its silyl ether with TBDMSOTf to afford lactam **3**[28] (89%) that, upon Furman's procedure, provided the α-*C*-allyl piperidine **4** (68%) as a single diastereomer, resulting from addition of $AllSnBu_3$ *syn* to the TBSO group of the imine **B** adopting a $^4H_3$ conformation, in agreement with Woerpel's model.[29] As manipulation of Schwartz's reagent proved tricky, we investigated a one-pot procedure,[30] in which the reagent was generated *in situ* from Cp_2ZrCl_2, that furnished compound **4** in a similar 66% yield. Removal of the TBDMS group with TBAF provided the 2-hydroxypiperidine **5** (74%) that was further *N*-benzylated to obtain the key intermediate **6** (74%) (Scheme 1).



Scheme 1 : Synthesis of C-allyl iminosugar **6** from D-gluconolactam **1a**

Overall, the *C*-allyl iminosugar **6** was obtained in 27% yield from D-gluconolactam **1** over five steps. This sequence is complementary to the one recently reported to access 2-hydroxy -*C*-allyl iminosugars.[31] Oxidation of **6** with PDCP and DMSO furnished the ketone **7** in 91% yield. Its allylation with allyl magnesium bromide at -78°C afforded a 1:1 separable mixture of the D-manno **8a** (39%) and D-gluco **8b** (39%) configured 1,2-di-*C*-allyl piperidines. Each compound was then submitted to ring closing metathesis using Hoveyda-Grubbs catalyst in CH_2Cl_2 at 40°C and provided the corresponding bicycles **9a** (89%) and **9b** (87%), which upon hydrogenolysis, uneventfully and quantitatively provided the expected tetrahydroxylated *cis*- and *trans*-decahydroquinolines **10a** and **10b** respectively (Scheme 2). The conformation in solution of the D- gluco-like isomer **10b** was studied by NMR, allowing the assignment of a $^1C_4$ conformation for the polyhydroxylated piperidine ring ($J_{3\text{-}4}$ = 2.4 Hz), a conformation also observed in the solid state by X-ray crystallography (Scheme 2). Interestingly, compound **10b** can be seen as a DNJ analogue with all hydroxyl groups adopting a pseudo-axial orientation. Such conformation has been invoked to explain the strong glucocerebrosidase inhibition developed by imino-D-xylitols (DIX) derivatives.[32] We next examined the dihydroxylation of alkenes **9a** and **9b**. Using a standard protocol (OsO_4, NMO in wet acetone), **9a** furnished the separable endo diol **11a** (22%) and exo diol **11a'** (39%) in reasonable yield (see SI). The same reaction applied to alkene **9b** furnished the endo diol **11b** (19%) along with the exo diol **11b'** (35%). Separate hydrogenolysis of these four triols provided the hexahydroxylated decahydroquinolines **12a, 12a', 12b** and **12b'** respectively (Scheme 2). To investigate the eventual impact of the size of the additional ring on the glycosidase inhibition profile of these derivatives, the synthesis of polyhydroxylated octahydro-1*H*-Cyclopenta[*b*] pyridine analogues bearing a six-five fused rings system was examined starting from ketone **7** (Scheme 3). Vinylation of **7** with CH_2=CHMgBr produced the separable D-manno (60%) and D-gluco- configured (15%) dienes **13a** and **13b** respectively. Their ring closing metathesis yielded the bicyclic alkene **14a** (87%) and **14b** (84%) that, upon hydrogenolysis, furnished the five-six fused analogs **15a** and **15b** respectively. Unlike the previous alkenes **9a** and **9b**, dihydroxylation of alkenes **14a** and **14b** failed in our hands while such reaction has been reported for related systems (Scheme 3).[33]

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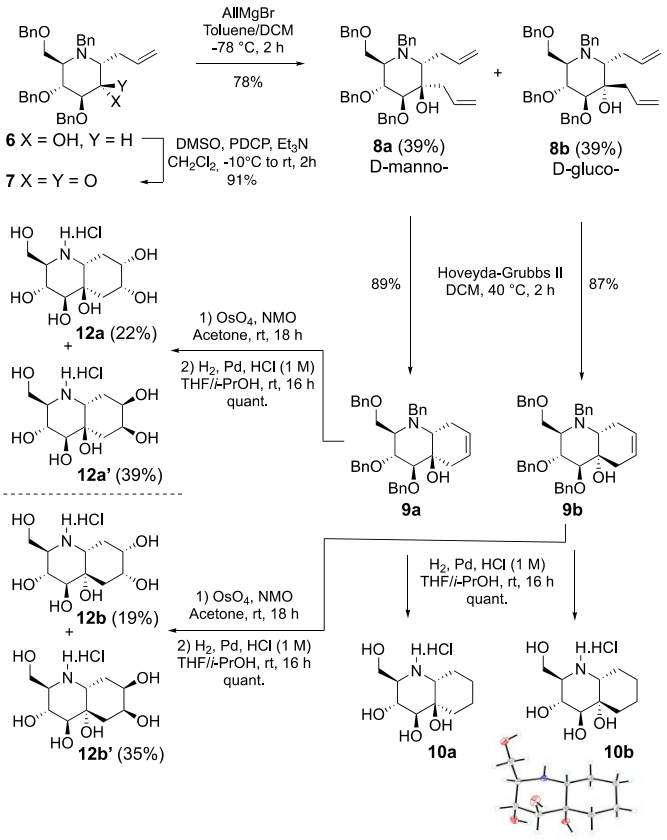
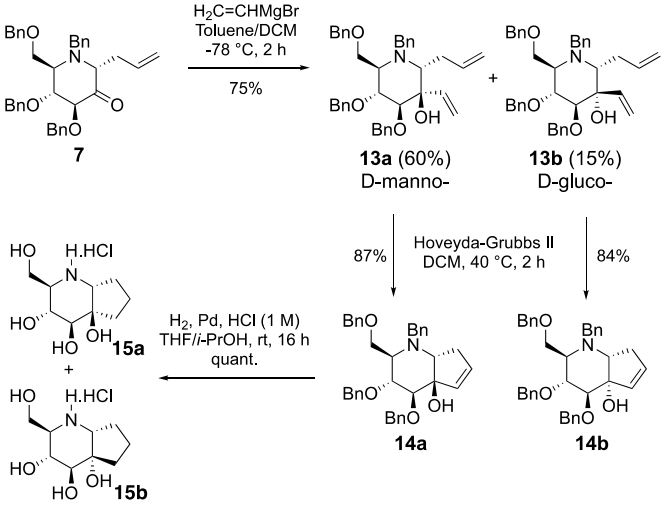
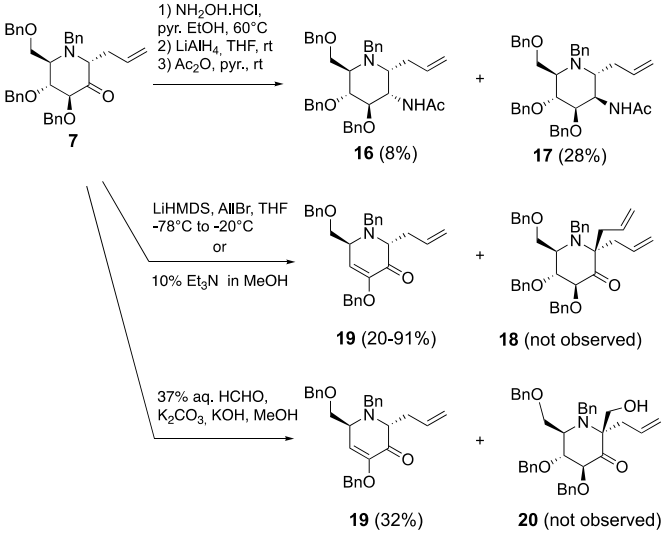


Scheme 2 : Synthesis of bicyclic iminosugars **10a, 10b, 12a, 12a', 12b, 12b'** and X-ray structure of **10b**

The 2-oxo-*C*-allyl iminosugar **7** holds an important synthetic potential and could be useful to access other types of iminosugars. Because of our interest for hexosaminidase inhibitors,[15,16] compound **7** was converted to its crude oxime (NH_2OH, pyr.) that was directly reduced with $LiAlH_4$ and further acetylated with Ac_2O to provide the D-gluco **16** (8%) and the D-manno- **17** (28%) configured 2-acetamido *C*-allyl iminosugars. This sequence, that does not involve nucleophilic displacement of the hydroxyl at C-2 position to introduce an acetamide, is appealing as it avoids competitive ring contraction,[31] providing only the piperidine derivatives albeit in modest yield. In parallel, we also examined the introduction of an additional allyl group at the pseudoanomeric position in order to access a 1,1-diallyl piperidine scaffold[12] en route to bisubstrate analogs and spiro-iminosugars.[34] We expected the ketone at C-2 to guide the allylation at C-1. Unfortunately, when derivative **7** was treated with LiHMDS and allyl bromide at -78°C in THF, no trace of the diallyl derivative **18** was detected and only an unsaturated product **19** resulting from the elimination of the benzyloxy group at C-4 was isolated in 20%. A similar product has been reported in the *C*-allyl glucoside series when treated with 10% Et_3N in MeOH.[35] Applying these reaction conditions to **7** raised the yield of this transformation to 91%. A similar result was observed when aldol conditions[36] were applied to **7** in order to introduce a pseudoanomeric CH_2OH group, yielding only **19** in 32% yield with no trace of the target compound **20** (Scheme 4). Nevertheless, compound **19** is a useful synthon to introduce structural diversity at the C-4 position of the C-allyl iminosugar scaffold.



Scheme 3 : Synthesis of bicyclic iminosugars **15a** and **15b**



Scheme 4 : Chemical exploration of 2-oxo-*C*-allyl iminosugar **7**

Glycosidase inhibition

Finally, all the polyhydroxylated bicyclic piperidines were assayed on a panel of fifteen targeted glycosidases and proved to be modest glycosidase inhibitors. As shown in Table 1, the basic structure, 1-deoxymannojirimycin (DMJ) is a known weak inhibitor of Jack bean α-mannosidase and bovine kidney α-L-fucosidase, with IC_{50} values of 803 and 354 µM, respectively. In

contrast, the corresponding bicyclic iminosugar **10a** was completely inactive on all glycosidases tested even at concentrations as high as 1000 µM demonstrating the detrimental role of the additional six-membered ring on inhibition. Cis-dihydroxylation of this ring as in **12a**' and **12a** led to molecules that weakly inhibited rice α-glucosidase, with IC_{50} values of 564 and 967 µM, respectively. These results clearly suggest that the presence of two hydroxyl groups in the tetrahydroquinoline ring is one of the essential features for recognition by the active site of α-glycosidase. It is noteworthy that **15a,** displaying a smaller five-membered fused ring, showed a broader inhibition spectrum including activity towards rice α-glycosidase, bovine liver β-glucosidase, coffee beans α-galactosidase and bovine liver β-galactosidase, with IC_{50} values of 654, 298, 560, and 359 µM, respectively.

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

	IC_{50} (µM)				
					
enzyme	**DMJ**	**10a**	**12a'**	**12a**	**15a**
α-glucosidase					
rice	[a] NI	NI	564	967	654
rat intestinal maltase	NI	NI	NI	NI	NI
yeast	NI	NI	NI	NI	NI
β-glucosidase					
Almond	NI	NI	NI	NI	NI
bovine liver	NI	NI	NI	NI	298
α-galactosidase					
coffee beans	NI	NI	NI	NI	560
β-galactosidase					
bovine liver	NI	NI	NI	NI	359
α-Mannosidase					
Jack bean	803	NI	NI	NI	NI
β-Mannnosidase					
snail	NI	NI	NI	NI	NI
α-L-fucosidase					
bovine kidney	354	NI	NI	NI	NI
Trehalase					
porcine kidney	NI	NI	NI	NI	NI
Amyloglucosidase					
A.niger	NI	NI	NI	NI	NI
α-L-rhamnosidase					
Penicillium decumbens	NI	NI	NI	NI	NI
β-glucronidase					
E.coli	NI	NI	477	NI	NI
bovine liver	NI	NI	NI	NI	NI

[a] NI : No inhibition (less than 50% inhibition at 1000 µM).

1-Deoxynojirimycin (DNJ) is well known as potent inhibitor toward rice and intestinal maltases (Table 2). This compound also showed porcine kidney trehalase and *A. niger* amyloglucosidase inhibition, with IC_{50} values of 64 and 781 µM, respectively. As for **10a**, introduction of an additional six-membered ring in **10b** almost completely abolished the inhibition profile of the parent DNJ and led only to a weak inhibitor of bovine liver β-galactosidase. Dihydroxylation of the extra ring present in **10b** produced **12b**' and **12b** that proved much weaker inhibitors against α-glucosidases compared to DNJ. However, it should be noted that **12b'** and **12b** showed some inhibition toward coffee beans α-galactosidase and *P. decumbens* α-L-rhamnosidase. As in the mannose series with **15a**, the gluco-configured bicycle **15b** showed a broader inhibition spectrum compared to its congeners and competitively inhibited bovine liver β-glucosidase, β-galactosidase, and *E.coli* β-glucuronidase. Altogether, these data clearly suggested that the size and hydroxylation pattern of the additional ring have a significant influence on the glycosidase inhibition spectrum of this family of iminosugars leading to molecules with profile distinct from the one found for the parent monocyclic compound.

Table 2. Concentration of iminosugars giving 50 % inhibition of various glycosidases

	IC_{50} (µM)				
					
enzyme	**DNJ**	**10b**	**12b'**	**12b**	**15b**
α-glucosidase					
rice	5,8	NI	331	651	NI
rat intestinal maltase	0,16	NI	NI	838	NI
yeast	[a] NI	NI	NI	NI	NI
β-glucosidase					
Almond	NI	NI	NI	NI	NI
bovine liver	NI	NI	NI	NI	313
α-galactosidase					
coffee beans	NI	NI	572	381	NI
β-galactosidase					
bovine liver	NI	975	NI	NI	271
α-Mannosidase					
Jack bean	NI	NI	NI	NI	NI
β-Mannnosidase					
snail	NI	NI	NI	NI	NI
α-L-fucosidase					
bovine kidney	NI	NI	703	NI	NI
Trehalase					
porcine kidney	64	NI	NI	NI	NI
Amyloglucosidase					
A.niger	781	NI	NI	NI	NI
α-L-rhamnosidase					
Penicillium decumbens	NI	NI	196	114	NI
β-glucronidase					
E.coli	NI	NI	217	NI	542
bovine liver	NI	NI	NI	NI	NI

[a] NI : No inhibition (less than 50% inhibition at 1000 µM).

Experimental

General Methods. All starting materials and reagents were purchased from commercial sources, and used as received without further purification. Air and H_2O sensitive reactions were performed in oven dried glassware under Ar atmosphere. Moisture sensitive reagents were introduced via a dry syringe. Anhydrous solvents were supplied over molecular sieves, and used as received. Petroleum ether (PE) refers to the 40-60 °C boiling fraction. Powdered molecular sieves were activated before use by heating for ~5 min under high vacuum. Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 F_{254} 0.25 mm pre-coated aluminum foil plates, visualized by using UV_{254} and/or phosphomolybdic acid stain [3 g $12MoO_3.H_3PO_4.xH_2O$ in 100 mL EtOH] followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15–40 µm). NMR experiments were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^1H nuclei and at 100 MHz for ^{13}C nuclei. The chemical shifts are expressed in part per million (ppm) relative to TMS (δ = 0 ppm) and the coupling constant *J* in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were recorded on a Bruker micrOTOF spectrometer. The melting points were recorded with a SMP50 Stuart Scientific melting point apparatus. Optical rotations were measured using an Anton Paar MCP100 Polarimeter.

General procedure A for RCM. To a solution of 1,2-bis-allyl or 1-allyl-2-vinyl derivative in dry CH_2Cl_2 (0.05 M) under Ar atmosphere was added Hoveyda-Grubbs catalyst 2nd generation (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. Lead(IV) acetate (1.5 eq. per eq. of catalyst) was added and the reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure and purified by flash chromatography.

General procedure B for total debenzylation. The benzylated substrate was dissolved in a 1:1 mixture of *i*-PrOH/THF (0.05 M - v/v). The mixture was flushed 4 times with Ar then a 1M solution of HCl (3 eq.), palladium black (0.5 mass eq.) and palladium on carbon (0.5 mass eq.) were added. The mixture was flushed 4 times with H_2 and stirred at room temperature under H_2 atmosphere. After 24 h, the mixture was filtered on a celite pad and the filtrate was concentrated under reduced pressure to give the fully deprotected product as its hydrochloride salt.

General procedure C for dihydroxylation. To a solution of olefin substrate in a 1:1 mixture of acetone/H_2O (0.06 M – v/v) were added citric acid (1.1 eq.), 4-methylmorpholine *N*-oxide (1.2 eq) and OsO_4 (0.2 eq.). The mixture was stirred at room temperature for 18 h when TLC showed total consumption of the starting material. $Na_2S_2O_5$ (1.2 eq.) was added and the mixture was stirred at room temperature for 1 h. The mixture was extracted 3 times with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

3,4,6-tri-*O*-benzyl-galactono-δ-lactam (2b). To a solution of lactam **1b** (119 mg, 0.22 mmol) in dry CH_2Cl_2 (0.03 M) under Ar atmosphere was added Bu_4NBr (106 mg, 0.33 mmol, 1.5 eq.). The solution was cooled to -78 °C and a 1M solution of BCl_3 in CH_2Cl_2 (420 µL, 0.44 mmol, 2 eq.) was added dropwise over a 30 min period. The mixture was stirred from -78 °C to 0 °C overnight when TLC analysis showed no trace of the starting material. The mixture was quenched with a saturated solution of Na_2CO_3 and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (RediSep® 4 g, petroleum ether/EtOAc 35:65) to give compound **2b** (91 mg, 0.21 mmol, 93%) as a white waxy solid. R*f* = 0.29 (PE/EtOAc 35:65); $[\alpha]_D^{20}$ = +25.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.25 (m, 15H, *CH*-Ar), 6.18 (br. s, 1H, NH), 4.99 (d, *J* = 11.5 Hz, 1H, O*CH*H-Ph), 4.93 (d, *J* = 12,1 Hz, 1H, O*CH*H-Ph), 4.76 (d, *J* = 12.1 Hz, 1H, O*CH*H-Ph), 4.61-4.57 (m, 2H, O*CH*H-Ph, H-2), 4.47 (ABq, *J* = 11.7 Hz, 2H, O*CH*$_2$-Ph), 3.99 (br. s, 1H, H-4), 3.75 (dd, *J* = 9.9 Hz, *J* = 1.8 Hz, 1H, H-3), 3.59-3.53 (m, 2H, H-6a, H-5), 3.43-3.40 (m, 1H, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (C-1), 138.3, 138.0, 137.4 (C^{IV}-Ar), 128.7-127.8 (*CH*-Ar), 81.0 (C-3), 74.5, 73.7 (O*CH*$_2$-Ph), 73.4 (C-4), 73.1 (O*CH*$_2$-Ph), 70.4 (C-2), 70.4 (C-6), 54.2 (C-5); HRMS (ESI+) calcld for $C_{27}H_{29}NaNO_5$ [M+Na]$^+$: 470.1938, found: 470.1947.

3,4,6-tri-*O*-benzyl-2-*O*-[(*tert*-butyl)dimethylsilyl]-D-glucono-δ-lactam (3). To a solution of compound **2a** (1.97 g, 4.44 mmol) in dry CH_2Cl_2 (44 mL) under Ar atmosphere was added pyridine (1.6 mL, 19.99 mmol, 4.5 eq.) The mixture was cooled to 0 °C and TBDMSOTf (1.5 mL, 6.66 mmol, 1.5 eq.) was added. The mixture was stirred for 1 h at room temperature and quenched with H_2O (80 mL). The mixture was extracted with CH_2Cl_2 (3x40 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (RediSep® 24 g, petroleum ether/EtOAc 100:0 to 70:30), affording compound **3** (2.30 g, 4.09 mmol, 92%) as a colorless oil. Analytical data were in agreement with literature.[28]

α-*C*-allyl-3,4,6-tri-*O*-benzyl-2-*O*-[(*tert*-butyl)dimethylsilyl]-1-deoxynojirimycin (4). Compound **3** (2.30 g, 4.09 mmol) and Cp_2ZrCl_2 (3.59 g, 12.28 mmol, 3 eq.) were dissolved in freshly distilled THF (82 mL) under Ar atmosphere at room temperature. A 1 M solution of LiAlH(OBu-*t*)$_3$ in THF (12.28 mL, 12.28 mmol, 3 eq.) was rapidly added and the mixture was stirred at room temperature. After 30 min, the solution became clear, indicating the end of the reduction. The mixture was cooled to -25 °C and $Yb(OTf)_3$ (2.54 g, 4.09 mmol, 1 eq.) and $AllSnBu_3$ (3.8 mL, 12.28 mmol, 3 eq.) were added. The mixture was stirred for 18 h at room temperature then concentrated under reduced pressure. The crude residue was purified by flash chromatography on a silica gel containing 10% of K_2CO_3 (petroleum ether/EtOAc 90:10), affording compound **4** (1.59 g, 2.70 mmol, 66%) as a yellow oil. R*f* = 0.35 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = +22.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.10 (m, 20H, *CH*-Ar), 5.82-5.72 (m, 1H, H-2'), 5.13-5.09 (m, 2H, H-3'), 4.91 (d, *J* = 11.4 Hz, 1H, O*CH*H-Ph), 4.80-4.77 (m, 2H, O*CH*H-Ph), 4.51 (d, *J* = 11.9 Hz, 1H, O*CH*H-Ph), 4.43 (d, *J* = 11.2 Hz, 2H, O*CH*H-Ph), 3.88 (dd, *J* = 9.2 Hz, *J* = 5.6 Hz, 1H, H-2), 3.64 (dd, *J* = 9.2 Hz, *J* = 2.6 Hz, 1H, H-6a), 3.56 (t, *J* = 9.1 Hz, 1H, H-3), 3.51 (dd, *J* = 9.1 Hz, *J* = 6.4 Hz, 1H, H-6b), 3.36 (t, *J* = 9.4 Hz, 1H, H-4), 3.06-3.01 (m, 2H, H-5, H-1), 2.56-2.49 (m, 1H, H-1'a), 2.34-2.26 (m, 1H, H-1'b), 0.91 (s, 9H, C(*CH*$_3$)$_3$), 0.08 (s, 3H, Si*CH*$_3$), 0.06 (s, 3H, Si*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.4, 138.3 (C^{IV}-Ar), 136.1 (C-2'), 128.5-127.4 (*CH*-Ar), 117.6 (C-3'), 84.1 (C-3), 80.6 (C-4), 75.5, 75.3 (O*CH*$_2$-Ph), 74.8 (C-2), 73.3 (O*CH*$_2$-Ph), 70.6 (C-6), 57.0 (C-1), 52.8 (C-5), 29.4 (C-1'), 26.1 (C(*CH*$_3$)$_3$), 18.1 (*C*(CH$_3$)$_3$), -4.4 (Si*CH*$_3$), -4.5 (Si*CH*$_3$); HRMS (ESI+) calcld for $C_{36}H_{49}NO_4Si$ [M+H]$^+$: 588.8733, found: 588.8731.

α-*C*-allyl-3,4,6-tri-*O*-benzyl-1-deoxynojirimycin (5). To a solution of compound **4** (1.59 g, 2.71 mmol) in dry THF (45 mL) under Ar atmosphere was added a TBAF solution (1 M/THF, 4.1 mL, 4.06 mmol, 1.5 eq.) at room temperature. The mixture was stirred overnight at room temperature and quenched with H_2O (90 mL). The mixture was extracted with EtOAc (3x45 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (RediSep® 24 g, petroleum ether/EtOAc 90:10 to 60:40) afforded compound **5** (948 mg, 2.00 mmol, 74%) as a white solid. Analytical data were in agreement with literature.[31]

α-*C*-allyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-1-deoxynojirimycin (6). To a solution a compound **5** (948 mg, 2.00 mmol) in a 1:1 mixture of EtOAc/H_2O (40 mL) were added benzyl bromide (476 µL, 4.00 mmol, 2 eq.) and $KHCO_3$ (2.00 g, 20.02 mmol, 10 eq.). The mixture was stirred at 80 °C for 24 h and quenched with H_2O (80 mL). The mixture was extracted with Et_2O (3x40 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 95:05 to 90:10) afforded compound **6** as a yellow oil (835 mg, 1.48 mmol, 74%). Analytical data were in agreement with literature.[31]

α-*C*-allyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-2-keto-1-deoxynojirimycin (7). To a solution of DMSO (1.14 mL, 16.02 mmol, 5 eq), Et_3N (2.25 mL, 16.02 mmol, 5 eq.) and phenyl dichlorophosphate (1.44 mL, 9.61 mmol, 3 eq) in dry CH_2Cl_2 (32 mL) at -10 °C under Ar atmosphere was added a solution of compound **5** (1.80 g, 3.20 mmol) in dry CH_2Cl_2 (32 mL) at -10 °C. The mixture was allowed to warm up to room temperature and after 2 h stirring, the mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (RediSep® 24 g, petroleum ether/EtOAc 90:10) afforded compound **7** (1.63 g, 91%) as a yellow oil. R*f* =

0.44 (PE/EtOAc 90 :10); $[\alpha]_D^{20}$ = -6.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.19 (m, 20H, *CH*-Ar), 5.78-5.68 (m, 1H, H-2'), 5.04-5.00 (m, 2H, H-3'), 4.88 (d, *J* = 11.5 Hz, 1H, O*CH*H-Ph), 4.65 (d, *J* = 11.3 Hz, 1H, O*CH*H-Ph), 4.54-5.47 (m, 3H, O*CH*H-Ph, H-3), 4.43 (s, 2H, O*CH*H-Ph), 3.96 (d, *J* = 14.3 Hz, 1H, N*CH*H-Ph), 3.88 (dd, *J* = 7.3 Hz, *J* = 5.1 Hz, 1 H, H-4), 3.83 (d, *J* = 14.3 Hz, N*CH*H-Ph), 3.68 (dd, *J* = 10.0 Hz, *J* = 5.3 Hz, 1H, H-6a), 3.57 (dd, *J* = 10.0 Hz, *J* = 4.7 Hz, 1H, H-6b), 3.41-3.37 (m, 2H, H-5, H-1), 2.60-2.44 (m, 2H, H-1'a, H-1'b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1 (C-2), 138.9, 138.3, 137.9, 137.8 (C^{IV}-Ar), 132.9 (C-2'), 128.5-127.1 (*CH*-Ar), 118.1 (C-3'), 86.0 (C-3), 81.7 (C-4), 73.4, 73.3, 72.9 (OCH_2-Ph), 67.5 (C-6), 67.0 (C-1), 58.4 (C-5), 52.7 (NCH_2-Ph), 34.4 (C-1'); HRMS (ESI+) calcld for $C_{37}H_{40}NaNO_4$ [M+Na]$^+$: 584.2771, found: 584.2779.

α-*C*-allyl-2-*C*-allyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-1-deoxymannojirimycin (8a) and α-*C*-allyl-2-*C*-allyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-1-deoxynojirimycin (8b). Compound **7** (1.00 g, 1.78 mmol) was dissolved in a 2:1 mixture of dry toluene/CH_2Cl_2 (24 mL) under Ar atmosphere. The mixture was cooled to -78 °C and a solution of AllMgBr (1M/THF, 4.6 mL, 4.63 mmol, 2.6 eq.) was added dropwise. The mixture was stirred for 2 h at -78 °C and quenched with a saturated aqueous solution of NH_4Cl (30 mL). The organic layer was extracted with Et_2O (3x15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 95:05) afforded compound **8a** (yellow oil, 419 mg, 39%) and **8b** (yellow oil, 419 mg, 39%). Analytical data for **8a**: R*f* = 0.31 (PE/EtOAc 95:05); $[\alpha]_D^{20}$ = -32.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.14 (m, 20H, *CH*-Ar), 5.81-5.64 (m, 2H, H-2', H-2''), 5.08-4.95 (m, 2H, H-3'), 4.93-4.88 (m, 3H, O*CH*H-Ph, H-3''), 4.80 (d, *J* = 10.9 Hz, 1H, O*CH*H-Ph), 4.63 (d, *J* = 11.1 Hz, 1H, O*CH*H-Ph), 4.48 (d, *J* = 10.9 Hz, 1H, O*CH*H-Ph), 4.22 (ABq, *J* = 16.1 Hz, 2H, O*CH*H-Ph), 4.08 (d, *J* = 13.9 Hz, 1H, N*CH*H-Ph), 3.98 (t, *J* = 9.1 Hz, 1H, H-4), 3.78-3.64 (m, 3H, N*CH*H-Ph, H-6a, H-6b), 3.47 (d, *J* = 8.7 Hz, 1H, H-3), 3.39 (broad s, 1H, OH), 2.96-2.94 (m, 1H, H-5), 2.81 (dd, *J* = 7.6 Hz, *J* = 4.6 Hz, 1H, H-1), 2.71-2.66 (m, 1H, H-1''a), 2.52-2.44 (m, 1H, H-1'a), 2.22-2.10 (m, 1H, H-1'b), 1.89-1.83 (m, 1H, H-1''b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 138.6, 138.4, 138.2 (C^{IV}-Ar), 137.8 (C-2'), 133.7 (C-2''), 128.8-127.0 (*CH*-Ar), 117.5 (C-3''), 116.1 (C-3'), 84.0 (C-3), 78.4 (C-4), 75.6 (C-2), 75.5, 75.3, 73.0 (O*CH2*-Ph), 67.0 (C-6), 62.4 (C-1), 59.5 (C-5), 53.6 (N*CH2*-Ph), 38.2 (C-1''), 29.3 (C-1'); HRMS (ESI+) calcld for $C_{40}H_{46}NO_4$ [M+H]$^+$: 604.3421, found: 604.3438. Analytical data for **8b**: R*f* = 0.38 (PE/EtOAc 95:05); $[\alpha]_D^{20}$ = -26.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d6): δ 7.42-7.22 (m, 20H, *CH*-Ar), 6.04-5.93 (m, 1H, H-2'), 5.59-5.49 (m, 1H, H-2''), 5.14-4.94 (m, 2H, H-3'), 4.90-4.80 (m, 5H, O*CH*H-Ph, H-3''), 4.55 (d, *J* = 11.1 Hz, 1H, O*CH*H-Ph), 4.35 (s, 2H, O*CH*H-Ph), 4.17 (d, *J* = 13.9 Hz, 1H, N*CH*H-Ph), 3.84-3.76 (m, 3H, H-6a, H-6b, H-4), 3.74-3.69 (m, 2H, N*CH*H-Ph, H-3), 3.23 (br. s, 1H, OH), 2.99-2.97 (m, 1H, H-5), 2.91-2.89 (m, 1H, H-1), 2.68-2.61 (m, 3H, H-1'a, H-1''), 2.53-2.49 (m, 1H, H1'b); ^{13}C NMR (100 MHz, acetone-d6): δ 141.6 (C^{IV} -Ar), 140.8 (C-2'), 140.3, 139.7, 139.5 (CIV-Ar), 135.1 (C-2''), 130.0-127.3 (*CH*-Ar), 118.4 (C-3''), 115.1 (C-3'), 85.6 (C-3), 78.6 (C-4), 76-6 (C-2), 75.4, 75.0, 73.3 (O*CH2*-Ph), 68.5 (C-6), 62.0 (C-1), 60.4 (C-5), 53.6 (N*CH2*-Ph), 38.3 (C-1''), 28.8 (C-1'); HRMS (ESI+) calcld for $C_{40}H_{46}NaNO_4$ [M+Na]$^+$: 626.3241, found: 626.3258.

(2*R*,3*R*,4*S*,4a*R*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1,3,4,5,8,8a-hexahydroquinolin-4a(2*H*)-ol (9a). Compound **9a** was synthesized according to procedure A from **8a** (400 mg, 0.66 mmol). Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 85:15) afforded compound **9a** (339 mg, 89%) as a brown oil. R*f* = 0.14 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = -0.95 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.20 (m, 20H, C*H*-Ar), 5.54-5.51 (m, 1H, H-7), 5.31-5.27 (m, 1H, H-6), 4.89 (dd, *J* = 11.1, 8.0 Hz, 2H, O*CH*H-Ph), 4.59 (d, *J* = 11.4 Hz, 1H, O*CH*H-Ph), 4.50 (d, *J* = 10.9 Hz, 1H, O*CH*H-Ph), 4.36 (m, 2H, O*CH*H-Ph), 4.16 (d, *J* = 13.4 Hz, 1H, N*CH*H-Ph), 3.99 (t, *J* = 9.5 Hz, 1H, H-3), 3.76 (m, 2H, CH_2-OBn), 3.61 (d, *J* = 9.3 Hz, 1H, H-4), 3.54 (s, 1H, OH), 3.42 (d, *J* = 13.3 Hz, 1H, N*CH*H-Ph), 2.96-2.80 (m, 2H, H-8a, H-2), 2.59 (dd, *J* = 17.7, 5.4 Hz, 1H, H-5), 2.29-2.12 (m, 2H, H-7), 1.87-1.82 (m, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.5, 138.2 (C^{IV}-Ar), 128.7-127.3 (*CH*-Ar), 124.8 (C-6), 124.2 (C-7), 80.37 (C-4), 78.6 (C-3), 75.6, 75.6, 73.1 (OCH_2-Ph), 71.0 (C-4a), 67.3 (CH_2-OBn), 60.1 (C-2), 58.9 (C-8a), 52.7 (NCH_2-Ph), 33.2 (C-5), 20.1 (C-8); HRMS (ESI+) calcld for $C_{38}H_{42}NO_4$ [M+H]$^+$: 576.3130, found: 576.3108.

(2*R*,3*R*,4*S*,4a*S*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1,3,4,5,8,8a-hexahydroquinolin-4a(2*H*)-ol (9b). Compound **9b** was synthesized according to procedure A from **8b** (400 mg, 0.66 mmol). Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 90:10) afforded compound **9b** (339 mg, 89%) as a brown oil. R*f* = 0.40 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = -75.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.18 (m, 20H, C*H*-Ar), 5.62-5.56 (m, 2H, H-6+H-7), 4.52 (d, *J* = 11.4 Hz, 1H, O*CH*H-Ph), 4.42 (d, *J* = 11.4 Hz, 1H, O*CH*H-Ph), 4.38-4.28 (m, 4H, O*CH*H-Ph), 4.20 (d, *J* = 2.4 Hz, 1H, O*H*), 4.04 (d, *J* = 14.1 Hz, N*CH*H-Ph), 3.92 (dd, *J* = 9.5 Hz, *J* = 5.5 Hz, 1H, *CH*-OBn), 3.85 (t, *J* = 2.3 Hz, 1H, H-3), 3.80 (dd, *J* = 9.4 Hz, *J* = 7.5 Hz, 1H, *CH*-OBn), 3.69 (d, *J* = 14.1 Hz, N*CH*H-Ph), 3.46 (broad s, 1H, H-4), 3.37-3.33 (m, 1H, H-2), 3.23 (dd, *J* = 10.4 Hz, *J* = 5.9 Hz, 1H, H-8a), 2.73-2.68 (m, 1H, H-5), 2.28-2.11 (m, 2H, H-8), 1.96-1.92 (m, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 138.6, 138.0, 137.8 (C^{IV}-Ar), 128.5-126.8 (*C*H-Ar), 123.9, 123.7 (C-6, C-7), 78.7 (C-4), 73.5 (C-3), 73.1, 73.0, 70.9 (OCH_2-Ph), 70.5 (C-4a), 65.5 (CH_2-OBn), 56.7 (C-2), 52.8 (C-8a), 51.7 (OCH_2-Ph), 32.9 (C-5), 27.8 (C-8); HRMS (ESI+) calcld for $C_{38}H_{42}NO_4$ [M+H]$^+$: 576.3108, found: 576.3131.

(2*R*,3*R*,4*S*,4a*R*,8a*R*)-2-(hydroxymethyl)octahydroquinoline-3,4,4a(2*H*)-triol hydrochloride (10a). Application of procedure B to compound **9a** (60 mg, 0.10 mmol) afforded compound **10a** (26 mg, 99%, hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = 14.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 3.93 (dd, *J* = 11.7 Hz, 1H, *CH*H-OH), 3.84-3.76 (m, 3H, *CH*H-OH, H-4, H-3), 3.28-3.27 (m, 1H, H-8a), 3.25-3.21 (m, 1H, H-2), 2.31-2.28, 1.92-1.80, 1.64-1.62, 1.44-1.35, 1.29-1.23 (m, 8H, H-5, H-6, H-7, H-8); ^{13}C NMR (100 MHz, methanol-d4): δ 72.8 (C-4a), 70.9 (C-4), 68-7 (C-3), 62.2 (C-8a), 59.5 (CH_2-OH), 57.4 (C-2), 34.7, 25.7, 25.4, 23.1 (C-5, C-6, C-7, C-8); HRMS (ESI+) calcld for $C_{10}H_{19}NO_4$: [M+H]$^+$: 218.1387, found: 218.1399.

(2*R*,3*R*,4*S*,4a*S*,8a*R*)-2-(hydroxymethyl)octahydroquinoline-3,4,4a(2*H*)-triol hydrochloride (10b). Application of procedure B to compound **9b** (60 mg, 0.10 mmol) afforded compound **10b** (26 mg, 99%, hydrochloride salt) as a white waxy solid. $[\alpha]_D^{20}$ = 45.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.17 (dd, *J* = 11.9, 10.5 Hz, 1H, *CH*H-OH), 3.88 (d, *J* = 1.3 Hz, 1H, H-3), 3.78 (dd, *J* = 12.3, 4.7 Hz, 1H, *CH*H-OH), 3.55 (dd, *J* = 10.0, 4.4 Hz, 1H, H-2), 3.50 (d, *J* = 2.4 Hz, 1H, H-4), 3.42-3.38 (m, 1H, H-8a), 1.85-1.35 (m, 8H, H-7, H-8, H-9, H-10); ^{13}C NMR (100 MHz, methanol-d4): δ 72.1 (C-4a), 71.7 (C-4), 70.2 (C-3), 63.1 (C-2), 58.4 (CH_2-OH), 51.9 (C-4a), 34.1, 25.7, 25.3, 20.5 (C-7, C-8, C-9, C-10); HRMS (ESI+) calcld for $C_{10}H_{19}NO_4$: [M+H]$^+$: 218.1387, found: 218.1396.

(2*R*,3*R*,4*S*,4a*R*,6*R*,7*S*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)octahydro quinolone-4a,6,7(2*H*)-triol (11a) and (2*R*,3*R*,4*S*,4a*R*,6*S*,7*R*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)octahydroquinoline-4a,6,7(2*H*)-triol (11a'). Compounds **11a** and **11a'** were synthesized according to procedure C from compound **9a** (200 mg, 0.35 mmol). Flash chromatography (RediSep® 4 g, petroleum ether/EtOAc 50:50 to 40:60) afforded compound **11a** (46 mg, 22%, yellow oil) and **11a'** (93 mg, 39%, yellow oil). Analytical data for **11a**: R*f* = 0.36 (PE/EtOAc

50:50); $[\alpha]_D^{20}$ = -4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d6): δ 7.45-7.21 (m, 20H, *CH*-Ar), 5.12 (d, *J* = 11.4 Hz, 1H, O*CH*H-Ph), 4.91-4.85 (m, 2H, O*CH*H-Ph), 4.60 (d, *J* = 11.1 Hz, 1H, O*CH*H-Ph), 4.39 (s, 2H, O*CH*H-Ph), 4.30-4.24 (m, 2H, N*CH*H-Ph, H-4), 3.92 (t, *J* = 9.7 Hz, 1H, H-3), 3.85-3.81 (m, 3H, CH_2-OBn, H-6), 3.70 (d, *J* = 13.8 Hz, 1H, N*CH*H-Ph), 3.49 (dt, *J* = 11.3 Hz, *J* = 4.1 Hz, 1H, H-7), 3.28 (br. s, 1H, OH), 3.00 (dt, *J* = 9.9 Hz, *J* = 2.3 Hz, 1H, H-2), 2.61 (dd, *J* = 12.9 Hz, *J* = 3.7 Hz, 1H, H-8a), 2.50 (dd, *J* = 14.6 Hz, *J* = 3.0 Hz, 1H, H-5), 2.03-1.94 (m, 1H, H-8), 1.83-1.78 (m, 1H, H-8), 1.18 (dd, *J* = 14.6 Hz, *J* = 3.3 Hz, 1H, H5); ^{13}C NMR (100 MHz, acetone-d6): δ 141.6, 140.8, 140.0, 139.4 (C^{IV}-Ar), 129.3-127.4 (*CH*-Ar), 84.3 (C-4), 79.3 (C-3), 75.4, 74.9, 73.4 (OCH_2-Ph), 73.0 (C-4a), 71.5 (C-7), 70.0 (C-6), 68.4 (CH_2-OBn), 62.1 (C-8a), 61.0 (C-2), 53.0 (NCH_2-Ph), 37.8 (C-5), 24.1 (C-8); HRMS (ESI+) calcld for $C_{38}H_{44}NO_6$: $[M+H]^+$: 610.3163, found: 610.3174. Analytical data for **11a'**: R*f* = 0.18 (PE/EtOAc 50:50); $[\alpha]_D^{20}$ = -1.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d6): δ 7.45-7.18 (m, 20H, *CH*-Ar), 4.93-4.79 (m, 2H, O*CH*H-Ph), 4.74 (d, *J* = 11.2 Hz, 1H, O*CH*H-Ph), 4.58-4.55 (m, 1H, O*CH*H-Ph), 4.36 (s, 2H, O*CH*H-Ph), 4.22 (d, *J* = 14.1 Hz, 1H, N*CH*H-Ph), 4.02 (br. s, 1H, H-7), 3.96 (t, *J* = 8.6 Hz, 1H, H-3), 3.87-3.80 (m, 3H, CH_2-OBn, H-6), 3.73-3.66 (m, 2H, N*CH*H-Ph, H-4), 3.13 (dd, *J* = 11.7 Hz, *J* = 3.9 Hz, 1H, H-8a), 2.99 (br. s, 1H, H-2), 2.29 (br. s, 1H, H-5), 2.02-1.97 (m, 1H, H-8), 1.85-1.79 (m, 1H, H-8), 1.66-1.60 (m, 1H, H-5); ^{13}C NMR (100 MHz, acetone-d6): δ 141.7, 139.8, 139.4, 139.4 (C^{IV}-Ar), 129.2-127.3 (*CH*-Ar), 82.3 (C-4), 78.9 (C-3), 75.7, 75.1 (OCH_2-Ph), 73.8 (C-4a), 73.3 (OCH_2-Ph), 69.8 (C-7), 69.3 (C-6), 68.2 (CH_2-OBn), 60.5 (C-2), 68.2 (C-8a), 52.9 (NCH_2-Ph), 36.7 (C-5), 25.1 (C-8); HRMS (ESI+) calcld for $C_{38}H_{44}NO_6$: $[M+H]^+$: 610.3163, found: 610.3180.

(2R,3R,4S,4aR,6R,7S,8aR)-2-(hydroxymethyl)octahydroquinoline-3,4,4a,6,7(2H)-pentaol hydrochloride (12a). Application of procedure B to compound **11a** (30 mg, 0.05 mmol) afforded compound **12a** (13 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +7.7 (*c* 2.2, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.19 (br. d, *J* = 7.9 Hz, 1H, H-4), 4.00-3.97 (m, 2H, CH*H*-OH, H-6), 3.83-3.79 (m, 2H, CH*H*-OH, H-7), 3.74 (t, *J* = 9.7 Hz, 1H, H-3), 3.42 (dd, *J* = 13.2 Hz, *J* = 3.9 Hz, 1H, H-8a), 3.26-3.23 (m, 1H, H-2), 2.57 (dd, *J* = 14.6 Hz, *J* = 3.4 Hz, 1H, H-5), 2.20 (dd, *J* = 24.2 Hz, *J* = 12.0 Hz, 1H, H-8), 1.96-1.90 (m, 1H, H-5), 1.44 (dd, *J* = 14.6 Hz, *J* = 2.9 Hz, 1H, H-8); ^{13}C NMR (100 MHz, methanol-d4): δ 74.0 (C-4), 72.0 (C-4a), 70.8 (C-7), 69.6 (C-6), 68.5 (C-3), 59.7 (C-8a), 59.6 (CH_2-OH), 58.1 (C-2), 37.9 (C-5), 28.2 (C-8); HRMS (ESI+) calcld for $C_{10}H_{20}NO_6$: $[M+H]^+$: 250.1285, found: 250.1285.

(2R,3R,4S,4aR,6S,7R,8aR)-2-(hydroxymethyl)octahydroquinoline-3,4,4a,6,7(2H)-pentaol hydrochloride (12a'). Application of procedure B to compound **11a'** (30 mg, 0.05 mmol) afforded compound **12a'** (13 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +3.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.06 (br. s, 1H, H-6), 3.96 (dd, *J* = 11.6 Hz, *J* = 3.0 Hz, 1H, CH*H*-OH), 3.82-3.77 (m, 2H, CH*H*-OH, H-3), 3.74-3.66 (m, 2H, H-8a, H-7), 3.63 (d, *J* = 9.1 Hz, 1H, H-4), 3.20-3.16 (m, 1H, H-2), 2.34 (dd, *J* = 12.5 Hz, *J* = 4.4 Hz, 1H, H-5), 2.08-2.01 (m, 2H, H-5), 1.76 (t, *J* = 12.4 Hz, 1H, H-8); ^{13}C NMR (100 MHz, methanol-d4): δ 72.7 (C-4a), 71.7 (C-4), 69.3 (C-6), 68.9 (C-7), 68.6 (C-3), 59.6 (CH_2-OH), 57.6 (C-2), 57.1 (C-8a), 36.1 (C-5), 29.9 (C-8); HRMS (ESI+) calcld for $C_{10}H_{20}NO_6$: $[M+H]^+$: 250.1285, found: 250.1285.

(2*R*,3*R*,4*S*,4a*S*,6*R*,7*S*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)octahydro quinolone-4a,6,7(2*H*)-triol (11b) and (2*R*,3*R*,4*S*,4a*S*,6*S*,7*R*,8a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)octahydroquinoline-4a,6,7(2*H*)-triol (11b'). Compounds **11b** and **11b'** were synthesized according to procedure C from compound **9b** (200 mg, 0.35 mmol). Flash chromatography (RediSep® 4 g, petroleum ether/EtOAc 60:40 to 50:50) afforded compounds **11b** (40 mg, 19%, yellow oil) and **11b'** (74 mg, 35%, yellow oil). Analytical data for **11b**: R*f* = 0.14 (PE/EtOAc 60:40); $[\alpha]_D^{20}$ = -46.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.17 (m, 20H, *CH*-Ar), 4.48-4.45 (m, 2H, O*H*-4a, O*CH*H-Ph), 4.40 (d, *J* = 12.1 Hz, 1H, O*CH*H-Ph), 4.36-4.30 (m, 3H, O*CH*H-Ph), 4.24 (d, *J* = 11.8 Hz, O*CH*H-Ph), 4.16 (d, *J* = 10.0 Hz, O*H*-6), 4.09 (d, *J* = 13.8 Hz, 1H, N*CH*H-Ph), 3.89-3.84 (m, 2H, CH*H*-OBn, H-6), 3.80 (t, *J* = 2.1 Hz, 1H, H-3), 3.77-3.70 (m, 2H, N*CH*H-Ph, CH*H*-OBn), 3.54-3.52 (m, 1H, H-7), 3.41 (br. s, 1H, H-4), 3.32 (t, *J* = 6.7 Hz, 1H, H-2), 3.04 (dd, *J* = 12.2 Hz, *J* = 4.1 Hz, 1H, H-8a), 2.56 (br. s, 1H, O*H*-7), 2.03 (dt, *J* = 11.8 Hz, *J* = 4.2 Hz, 1H, H-8), 1.91-1.90 (m, 2H, H-5), 1.64 (dd, *J* = 24.0 Hz, *J* = 12.0 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.4, 137.7, 137.4 (C^{IV}-Ar), 128.6-127.0 (*CH*-Ar), 78.4 (C-4), 73.2 (C-3), 73.1 (C-4a), 73.0, 72.8, 71.1 (OCH_2-Ph), 70.8 (C-7), 70.2 (C-6), 65.1 (CH_2-OBn), 56.8 (C-2), 54.0 (C-8a), 52.1 (NCH_2-Ph), 34.6 (C-5), 29.9 (C-8); HRMS (ESI+) calcld for $C_{38}H_{44}NO_6$: $[M+H]^+$: 610.3163, found: 610.3169. Analytical data for **11b'**: R*f* = 0.08 (PE/EtOAc 60:40); $[\alpha]_D^{20}$ = -24.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.18 (m, 20H, *CH*-Ar), 4.49 (d, *J* = 11.6 Hz, 1H, O*CH*H-Ph), 4.41 (d, *J* = 11.6 Hz, 1H, O*CH*H-Ph), 4.34-4.32 (m, 3H, O*CH*H-Ph), 4.29 (d, *J* = 11.8 Hz, 1H, O*CH*H-Ph), 4.15 (br. s, 1H, O*H*), 4.07-3.99 (m, 3H, N*CH*H-Ph, H-7, H-6), 3.85 (d, *J* = 6.7 Hz, 2H, CH_2-OBn), 3.81 (t, *J* = 2.1 Hz, 1H, H-3), 3.71 (d, *J* = 14.1 Hz, 1H, N*CH*H-Ph), 3.39-3.35 (m, 2H, H-8a, H-4), 3.31 (t, *J* = 6.6 Hz, 1H, H-2), 2.18 (t, *J* = 12.3 Hz, 1H, H-5), 2.06-2.03 (m, 1H, H-8), 1.70-1.64 (m, 1H, H-8), 1.57 (dd, *J* = 12.8 Hz, *J* = 4.3 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 138.6, 138.0, 137.8 (C^{IV}-Ar), 128.6-126.8 (*C*H-Ar), 79.3 (C-4), 73.5 (C-3), 73.1, 72.8 (OCH_2-Ph), 72.4 (C-4a), 71.0 (OCH_2-Ph), 69.6 (C-7), 67.7 (C-6), 65.5 (CH_2-OBn), 58.1 (C-2), 52.8 (NCH_2-Ph), 50.1 (C-8a), 34.5 (C-5), 30.8 (C-8); HRMS (ESI+) calcld for $C_{38}H_{44}NO_6$: $[M+H]^+$: 610.3163, found: 610.3189.

(2R,3R,4S,4aS,6R,7S,8aR)-2-(hydroxymethyl)octahydroquinoline-3,4,4a,6,7(2H)-pentaol hydrochloride (12b). Application of procedure B to compound **11b** (30 mg, 0.05 mmol) afforded compound **12b** (13 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +10.4 (*c* 2.3, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.16-4.11 (m, 2H, CH*H*-OH, H-6), 3.79-3.73 (m, 3H, CH*H*-OH, H-7, H-3), 3.61 (m, 1H, H-4), 3.57-3.52 (m, 2H, H-8a, H-2), 2.16-2.05 (m, 2H, H-8), 1.97-1.88 (m, 2H, H-5); ^{13}C NMR (100 MHz, methanol-d4): δ 73.8 (C-4a), 71.5 (C-6), 70.9 (C-4), 70.5 (C-3), 70.1 (C-7), 63.2 (C-2), 58.4 (CH_2-OH), 49.7 (C-8a), 35.9 (C-5), 28.3 (C-8); HRMS (ESI+) calcld for $C_{10}H_{20}NO_6$: $[M+H]^+$: 250.1285, found: 250.1284.

(2R,3R,4S,4aS,6S,7R,8aR)-2-(hydroxymethyl)octahydroquinoline-3,4,4a,6,7(2H)-pentaol hydrochloride (12b'). Application of procedure B to compound **11b'** (30 mg, 0.05 mmol) afforded compound **12b'** (13 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +21.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.14-4.07 (m, 2H, CH*H*-OH, H-6), 3.76-3.67 (m, 3H, CH*H*-OH, H-7, H-3), 3.59 (m, 1H, H-4), 3.55-3.50 (m, 2H, H-8a, H-2), 2.13-2.02 (m, 2H, H-8), 1.91 (qd, *J* = 15.1 Hz, *J* = 2.9 Hz, 2H, H-5); ^{13}C NMR (100 MHz, methanol-d4): δ 73.8 (C-4a), 71.5 (C-6), 71.0 (C-4), 70.5 (C-3), 70.1 (C-7), 63.3 (C-2), 58.4 (CH_2-OH), 49.7 (C-8a), 35.9 (C-5), 28.3 (C-8); HRMS (ESI+) calcld for $C_{10}H_{20}NO_6$: $[M+H]^+$: 250.1285, found: 250.1295.

α-*C*-allyl-2-*C*-vinyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-1-deoxymannojirimycin (13a) and α-*C*-allyl-2-*C*-vinyl-3,4,6-tri-*O*-benzyl-*N*-benzyl-1-deoxynojirimycin (13b). Compound **7** (1.00 g, 1.78 mmol) was dissolved in a 2:1 mixture of dry toluene/CH_2Cl_2 (24 mL) under Ar atmosphere. The mixture was cooled to -78 °C and a solution of vinylMgBr (1M/THF, 4.6 mL, 4.63 mmol, 2.6 eq.) was added dropwise. The mixture was stirred for 2 h at -78 °C and quenched with a saturated aqueous solution of NH_4Cl (30 mL). The organic layer was extracted with Et_2O (3x15 mL) and the combined organic layers were dried over $MgSO_4$,

filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc 95:05 to 90:10) afforded compounds **13a** (630 mg, 60%, yellow oil) and **13b** (157 mg, 15%, yellow oil). Analytical data for **13a**: R*f* = 0.43 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = -40.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.22 (m, 20H, *CH*-Ar), 5.90 (dd, *J* = 16.9 Hz, *J* = 10.7 Hz, 1H, H-1''), 5.80-5.70 (m, 1H, H-2'), 5.56 (dd, *J* = 17.0 Hz, *J* = 2.1 Hz, 1H, H-2"a), 5.19 (dd, *J* = 10.7 Hz, *J* = 2.1 Hz, 1H, H-2"b), 5.09-5.01 (m, 2H, H-3'), 4.86 (d, *J* = 11.0 Hz, 1H, O*CH*H-Ph), 4.80 (d, *J* = 10.8 Hz, 1H, O*CH*H-Ph), 4.71 (d, *J* = 10.8 Hz, 1H, O*CH*H-Ph), 4.58 (d, *J* = 10.9 Hz, 1H, O*CH*H-Ph), 4.36-4.30 (m, 2H, O*CH*H-Ph), 4.21 (d, *J* = 13.8 Hz, 1H, N*CH*H-Ph), 4.06 (t, *J* = 8.8 Hz, 1H, H-4), 3.86-3.80 (m, 2H, N*CH*H-Ph, H-6a), 3.76-3.73 (m, 2H, H-6b, H-3), 3.43 (br. s, 1H, OH), 3.04 (dt, *J* = 9.1 Hz, *J* = 3.3 Hz, 1H, H-5), 2.79 (t, *J* = 6.4 Hz, 1H, H-1), 2.55-2.47 (m, 1H, H-1'a), 2.36-2.29 (m, 1H, H-1'b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3 (C^{IV}-Ar), 139.1 (C-1''), 138.6, 138.3, 137.6 (C^{IV}-Ar), 137.6 (C-2'), 128.8-126.8 (*CH*-Ar), 115.8 (C-3'), 115.7 (C-2''), 83.6 (C-3), 77.1 (C-4), 77.0 (C-2), 75.1, 75.0, 72.9 (OCH_2-Ph), 67.4 (C-6), 64.9 (C-1), 58.9 (C-5), 53.2 (NCH_2-Ph), 30.2 (C-1'); HRMS (ESI+) calcld for $C_{39}H_{44}NO_4$: $[M+H]^+$: 590.6265, found: 590.6264. Analytical data for **13b**: R*f* = 0.49 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = +4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.14 (m, 20H, *CH*-Ar), 6.15 (dd, *J* = 17.1 Hz, *J* = 11.0 Hz, 1H, H-1''), 5.91-5.81 (m, 1H, H-2'), 5.46 (dd, *J* = 17.3 Hz, *J* = 1.6 Hz, 1H, H-2"a), 5.19 (dd, *J* = 10.9 Hz, *J* = 2.0 Hz, 1H, H-2"b), 5.01-4.94 (m, 2H, H-3'), 4.55-4.47 (m, 2H, O*CH*H-Ph), 4.43-4.35 (m, 2H, O*CH*H-Ph), 4.31-4.25 (m, 2H, O*CH*H-Ph), 4.15 (d, *J* = 14.2 Hz, 1H, N*CH*H-Ph), 3.90 (d, *J* = 14.2 Hz, 1H, N*CH*H-Ph), 3.83-3.78 (m, 2H, H-6a, H-4), 3.69 (dd, *J* = 9.6 Hz, *J* = 5.1 Hz, 1H, H-6b), 3.52 (d, *J* = 4.0 Hz, 1H, H-3), 3.22-3.18 (m, 2H, H-5, H-1), 2.47-2.32 (m, 2H, H-1'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1 (C^{IV}-Ar), 140.8 (C-1''), 138.6 (C^{IV}-Ar), 138.4 (C-2'), 138.2, 137.8 (C^{IV}-Ar), 128.7-126.8 (*CH*-Ar), 115.5 (C-3'), 114.5 (C-2''), 82.6 (C-3), 75.9 (C-2), 75.1 (C-4), 73.9, 72.9, 72.2 (OCH_2-Ph), 67.8 (C-6), 58.7 (C-1), 57.0 (C-5), 53.1 (NCH_2-Ph), 30.9 (C-1'); HRMS (ESI+) calcld for $C_{39}H_{44}NO_4$: $[M+H]^+$: 590.6265, found: 590.6295.

(2*R*,3*R*,4*S*,4a*R*,7a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1,2,3,4,7,7a-hexahydro-4a*H*-cyclopenta[b]pyridin-4a-ol (14a). Compound **14a** was synthesized according to procedure A from **13a** (400 mg, 0.66 mmol). Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 95:05 to 90:10) afforded compound **14a** (331 mg, 87%) as a brown oil. R*f* = 0.68 (PE/EtOAc 85:10); $[\alpha]_D^{20}$ = -13.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.15 (m, 20H, *CH*-Ar), 5.81-5.76 (m, 2H, H-6, H-5), 4.88 (d, *J* = 11.2 Hz, 1H, O*CH*H-Ph), 4.65 (d, *J* = 11.2 Hz, 1H, O*CH*H-Ph), 4.52-4.46 (m, 4H, O*CH*H-Ph), 3.94-3.90 (m, 2H, CH*H*-OBn, N*CH*H-Ph), 3.83-3.80 (m, 3H, CH*H*-OBn, H-4, H-3), 3.70 (d, *J* = 14.2 Hz, 1H, N*CH*H-Ph), 3.42 (t, *J* = 7.3 Hz, 1H, H-7a), 3.19-3.17 (m, 1H, H-2), 3.05 (broad s, 1H, OH), 2.67 (ddd, *J* = 16.2 Hz, *J* = 7.7 Hz, *J* = 1.9 Hz, 1H, H-7), 2.35 (ddd, *J* = 16.2 Hz, *J* = 9.0 Hz, *J* = 4.4 Hz, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.8, 138.7, 138.4 (C^{IV}-Ar), 135.7 (C-5), 130.4 (C-6), 128.5-126.5 (*CH*-Ar), 85.2 (C-4), 85.0 (C-4a), 80.5 (C-3), 75.1, 73.3, 71.7 (OCH_2-Ph), 67.0 (C-7a), 66.5 (*CH*$_2$-OBn), 60.2 (C-2), 54.6 (NCH_2-Ph), 38.1 (C-7); HRMS (ESI+) calcld for $C_{37}H_{40}NO_4$: $[M+H]^+$: 562.2952, found: 562.2960.

(2*R*,3*R*,4*S*,4a*S*,7a*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1,2,3,4,7,7a-hexahydro-4a*H*-cyclopenta[b]pyridin-4a-ol (14b). Compound **14b** was synthesized according to procedure A from **13b** (150 mg, 0.25 mmol). Flash chromatography (RediSep® 4 g, petroleum ether/EtOAc 95:05 to 90:10) afforded compound **14b** (120 mg, 84%) as a brown oil. R*f* = 0.75 (PE/EtOAc 85:15); $[\alpha]_D^{20}$ = -46.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.19 (m, 20H, *CH*-Ar), 6.05-6.03 (m, 1H, H-6), 6.00 (dd, *J* = 6.0 Hz, *J* = 1.8 Hz, 1H, H-5), 4.49-4.36 (m, 6H, O*CH*H-Ph), 4.26 (broad s, 1H, OH), 3.94-3.89 (m, 5H, N*CH*H-Ph, CH*H*-OBn, H-4, H-3), 3.81 (t, *J* = 8.8 Hz, 1H, CH*H*-OBn), 3.34 (dd, *J* = 8.3 Hz, *J* = 4.6 Hz, 1H, H-2), 3.28 (dd, *J* = 9.4 Hz, 6.5 Hz, 1H, H-7a), 2.41-2.35 (m, 1H, H-7), 2.22 (ddd, *J* = 14.3 Hz, *J* = 6.4 Hz, *J* = 2.9 Hz, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 138.5, 138.1, 137.9 (C^{IV}-Ar), 135.2 (C-6), 134.2 (C-5), 128.5-127.0 (*CH*-Ar), 80.2 (C-4a), 76.6 (C-4), 75.0 (C-3), 73.2, 72.1, 71.2 (OCH_2-Ph), 64.8 (*CH*$_2$-OBn), 60.2 (C-7a), 58.9 (C-2), 54.4 (NCH_2-Ph), 32.4 (C-7); HRMS (ESI+) calcld for $C_{37}H_{40}NO_4$: $[M+H]^+$: 562.2952, found: 562.2951.

(2*R*,3*R*,4*S*,4a*R*,7a*R*)-2-(hydroxymethyl)octahydro-4a*H*-cyclopenta[b]pyridine-3,4,4a-triol hydrochloride (15a). Application of procedure B to compound **14a** (60 mg, 0.10 mmol) afforded compound **15a** (26 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +29.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 3.95 (dd, *J* = 11.8, *J* = 3.4, 1H, CH*H*-OH), 3.87 (dd, *J* = 11.8, *J* = 6.4 Hz, 1H, CH*H*-OH), 3.78 (t, *J* = 16.4 Hz, 6.8 Hz, 1H, H-3), 3.67-3.62 (m, 1H, H-7a), 3.49 (d, *J* = 9.3 Hz, 1H, H-4), 3.29-3.25 (m, 1H, H-2), 2.24-1.60 (m, 6H, H-7, H-6, H-5); ^{13}C NMR (100 MHz, methanol-d4): δ 79.8 (C-4), 73.1 (C-4), 67.85 (C-3), 62.3 (C-7a), 59.4 (*CH*$_2$-OH), 57.7 (C-2), 34.2, 23.7, 19.0 (C-7, C-6, C-5); HRMS (ESI+) calcld for $C_{10}H_{18}NO_4$: $[M+H]^+$: 204.1230, found: 204.1232.

(2*R*,3*R*,4*S*,4a*S*,7a*R*)-2-(hydroxymethyl)octahydro-4a*H*-cyclopenta[b]pyridine-3,4,4a-triol hydrochloride (15b). Application of procedure B to compound **14b** (60 mg, 0.10 mmol) afforded compound **15b** (26 mg, quant., hydrochloride salt) as a colorless oil. $[\alpha]_D^{20}$ = +57.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, methanol-d4): δ 4.07 (dd, *J* = 12.0 Hz, *J* = 10.6 Hz, 1H, CH*H*-OH), 3.85-3.82 (m, 2H, H-4, H-3), 3.74 (dd, *J* = 12.1 Hz, 4.8 Hz, 1H, CH*H*-OH), 3.61 (dd, *J* = 10.4 Hz, *J* = 4.5 Hz, 1H, H-2), 3.40 (dd, *J* = 10.6 Hz, *J* = 7.7 Hz, 1H, H-7a), 2.09-1.58 (m, 6H, H-7, H-6, H-5); ^{13}C NMR (100 MHz, methanol-d4): δ 80.1 (C-4a), 70.8, 70.5 (C-4, C-3), 63.9 (C-2), 58.3 (*CH*$_2$-OH), 52.7 (C-7a), 31.1, 25.4, 19.1 (C-7, C-6, C-5); HRMS (ESI+) calcld for $C_{10}H_{18}NO_4$: $[M+H]^+$: 204.1230, found: 204.1226.

α-*C*-allyl-2-acetamido-3,4,6-tri-*O*-benzyl-*N*-benzyl-1,2-dideoxy-D-nojirimycin (16) and α-*C*-allyl-2-acetamido-3,4,6-tri-*O*-benzyl-*N*-benzyl-1,2-dideoxy-D-mannojirimycin (17). To a solution of compound **7** (339 mg, 0.60 mmol) in absolute ethanol (2 mL) under Ar atmosphere were added hydroxylamine hydrochloride (126 mg, 1.81 mmol, 3 eq.) and pyridine (195 µL, 2.41 mmol, 4 eq.) at room temperature. The mixture was stirred for 30 min at 60 °C and the reaction was quenched with H_2O (10 mL). The aqueous layer was extracted EtOAc (3x10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was directly used in the next step. The crude residue was dissolved in dry THF (2 mL) under Ar atmosphere and a 1 M solution of $LiAlH_4$ in THF was added (1.8 mL, 1.81 mmol, 3 eq.). The reaction mixture was stirred at 40 °C for 3 h by which time TLC monitoring revealed no trace of the starting material. The reaction was sequentially quenched with EtOAc (20 mL) and a 1 M solution of HCl (2.5 mL). The aqueous layer was neutralized with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in a 2:1 mixture of dry pyridine/Ac_2O (2 mL) under Ar atmosphere at room temperature. After 5 h stirring at room temperature, the mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (RediSep® 12 g, petroleum ether/EtOAc 90:10 to 60:40) afforded compounds **16** (29 mg, 8%, brown solid) and **17** (103 mg, 28%, brown oil). Analytical data for compound **16** were in agreement with literature.[31] Analytical data for compound **17**: R*f* = 0.28 (PE/EtOAc 60:40); $[\alpha]_D^{20}$ = +55.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.38-7.23 (m, 20H, *CH*-Ar), 6.10 (d, *J* = 9.5 Hz, 1H, NH), 5.67-5.57 (m, 1H, H-2'), 5.06-4.99 (m, 2H, H-3'), 4.92 (d, *J* = 10.8 Hz, 1H, O*CH*H-Ph), 4.78 (d, *J* = 11.1 Hz, 1H, O*CH*H-Ph), 4.49-4.37 (m, 5H, O*CH*H-Ph, H-2), 4.14 (d, *J* = 13.1 Hz, 1H, N*CH*H-Ph), 3.81-3.78 (m, 3H, H-6a, H-6b, H-3), 3.71 (t, *J* = 8.8 Hz, 1H, H-4), 3.46 (d, *J* = 13.1 Hz, 1H, N*CH*H-Ph), 2.88-2.85 (m, 1H, H-5), 2.73-2.68 (m, 1H, H-1), 2.45-2.39 (m, 1H, H-1'a), 2.23-2.15 (m, 1H, H-1'b), 1.88 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (CO), 140.0, 138.7, 138.2, 138.2 (C^{IV}-Ar), 134.9 (C-2'), 128.9-127.4 (*CH*-Ar), 117.7 (C-3'), 78.5 (C-3), 76.4 (C-4), 75.3, 73.3, 71.2 (OCH_2-Ph), 67.2 (C-6), 59.2 (C-5), 57.8 (C-1), 51.6 (NCH_2-Ph), 45.4 (C-2), 27.9 (C-7), 23.8 (CH_3); HRMS (ESI+) calcld for $C_{39}H_{45}N_2O_4$: $[M+H]^+$: 605.3374, found: 605.3381.

(2*R*,6*S*)-2-allyl-1-benzyl-4-(benzyloxy)-6-(benzyloxymethyl)-1,6-dihydropyridin-3(2*H*)-one (19). Compound **7** (50 mg, 0.09 mmol) was dissolved in a 9:1 mixture of MeOH/Et_3N (8 mL) at room temperature under Ar atmosphere. The mixture was stirred 18 h at room temperature and concentrated under reduced pressure. Flash chromatography (RediSep® 4 g, petroleum ether/EtOAc 90/10) afforded compound **19** (37 mg, 0.08 mmol, 91%) as a yellow oil. R*f* = 0.39 (PE/EtOAc 90:10); $[\alpha]_D^{20}$ = +16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.14 (m, 15H, *CH*-Ar), 5.77-5.67 (m, 2H, H-2', H-5), 5.03-4.95 (m, 2H, H-3'), 4.80 (s, 2H, O*CH*H-Ph), 4.35 (s, 2H, O*CH*H-Ph), 3.74-3.67 (m, 2H, N*CH*H-Ph, H-6),3.63-3.56 (m, 3H, N*CH*H-Ph, *CH*-OBn, H-2), 3.45 (dd, *J* = 9.4 Hz, *J* = 7.0 Hz, 1H, *CH*-OBn), 2.52-2.40 (m, 2H, H-1'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (C-3), 148.5 (C-4), 138.8, 136.0, 136.3 (C^{IV}-Ar), 134.8 (C-2'), 128.7-127.5 (C-3'), 115.5 (C-5), 73.4 (OCH_2-Ph), 71.3 (CH_2-OBn), 69.9 (OCH_2-Ph), 64.5 (C-2), 55.5 (C-6), 51.9 (NCH_2-Ph), 30.9 (C-1'); HRMS (ESI+) calcld for $C_{30}H_{32}NO_3$: $[M+H]^+$: 454.2387, found: 454.2384.

Biological Assays. Glycosidase inhibition profiling was performed using appropriate *p*-nitrophenyl glycosides as substrates at the optimum pH of each enzyme. The reaction was stopped by adding 400 mM of Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

Conclusions

In conclusion, a new route to 2-hydroxy-*C*-allyl iminosugars has been developed from sugar lactams exploiting the C-2 regioselective BCl_3-based deprotection and the Schwartz's reagent. The resulting D-gluco configured iminosugar has been oxidized to the corresponding ketone that was further exploited to access new bicyclic iminosugars as well as a 2-acetamido derivative. The glycosidase inhibition profile of these glycomimetics has been assessed on a panel of 15 glycosidases. These conformationally locked DNJ and DMJ derivatives showed clearly different glycosidase inhibition profiles from DNJ and DMJ demonstrating the significant role played by the additional ring (size, hydroxylation). Work is now in progress to access similar bicyclic iminosugars with improved efficacy as glycosidase inhibitors.

Conflicts of interest

"There are no conflicts to declare".

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Notes and references

‡ The registration number for the crystallographic data of compound **10b** is CCDC 1921458.

1 Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.
2 R. J. Nash, A. Kato, C.-Y. Yu and G. W. Fleet, *Future Medicinal Chemistry*, 2011, **3**, 1513–1521.
3 P. C. Tyler and B. G. Winchester, in *Iminosugars as Glycosidase Inhibitors*, ed. A. E. Stütz, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, 1998, pp. 125–156.
4 S. G. Pyne, *Curr. Org. Synth.* 2005, **2**, 39-57.
5 R. H. Furneaux, G. J. Gainsford, J. M. Manson and P. C. Tyler, *Tetrahedron*, 1994, **50**, 2131–2160.
6 P. S. Liu, M. S. Kang, P. S. Sunkara, *Tetrahedron Lett.* 1991, **32**, 719-720.
7 J. Boisson, A. Thomasset, E. Racine, P. Cividino, T. Banchelin Sainte-Luce, J.-F. Poisson, J.-B. Behr and S. Py, *Organic Letters*, 2015, **17**, 3662–3665.
8 K. Søndergaard, X. Liang and M. Bols, *Chemistry*, 2001, **7**, 2324–2331; M. I. García-Moreno, J. M. Benito, C. Ortiz Mellet and J. M. García Fernández, *J. Org. Chem.*, 2001, **66**, 7604; P. Díaz Pérez, M. I. García-Moreno, C. Ortiz Mellet and J. M. García Fernández, *Synlett*, 2003, **3**, 341; M. I. García-Moreno, D. Rodríguez- Lucena, C. Ortiz Mellet and J. M. García Fernández, *J. Org. Chem.*, 2004, **69**, 3578. S. Jarosz, K. Tiara and M. A. Potopnyk, *Pure App. Chem.* 2019, doi.org/10.1515/pac-2019-0116
9 N. Asano, H. Kizu, K. Oseki, E. Tomioka, K. Matsui, M. Okamoto and M. Babat, *J. Med. Chem.* 1995, **38**, 2349-2356.
10 D. Hendry, L. Hough and A. C. Richardson, *Tetrahedron*, 1988, **44**, 6143-6152.
11 M. Malik, G. Witkowski, M. Ceborska and S. Jarosz, *Organic Letters*, 2013, **15**, 6214–6217.
12 M. I. Torres-Sánchez, P. Borrachero, F. Cabrera-Escribano, M. Gómez-Guillén, M. Angulo-Álvarez, M. J. Diánez, M. D. Estrada, A. López-Castro and S. Pérez-Garrido, *Tetrahedron: Asymmetry*, 2005, **16**, 3897–3907.
13 S. P. Sanap, S. Ghosh, A. M. Jabgunde, R. V. Pinjari, S. P. Gejji, S. Singh, B. A. Chopade and D. D. Dhavale, *Organic & Biomolecular Chemistry*, 2010, **8**, 3307.
14 F. Marcelo, Y. He, S. A. Yuzwa, L. Nieto, J. Jiménez-Barbero, M. Sollogoub, D. J. Vocadlo, G. D. Davies and Y. Blériot, *Journal of the American Chemical Society*, 2009, **131**, 5390–5392.
15 M. Mondon, S. Hur, G. Vadlamani, P. Rodrigues, P. Tsybina, A. Oliver, B. L. Mark, D. J. Vocadlo and Y. Blériot, *Chemical Communications*, 2013, **49**, 10983.
16 H. Li, Y. Zhang, P. Vogel, P. Sinaÿ and Y. Blériot, *Chem. Commun.*, 2007, 183–185.
17 B. Luo, F. Marcelo, J. Désiré, Y. Zhang, M. Sollogoub, A. Kato, I. Adachi, F. J. Cañada, J. Jiménez-Barbero and Y. Blériot, *Journal of Carbohydrate Chemistry*, 2011, **30**, 641–654.
18 J. Yin and T. Linker, *Organic & Biomolecular Chemistry*, 2012, **10**, 2351.
19 Y. D. Vankar and T. Linker, *European Journal of Organic Chemistry*, 2015, **2015**, 7633–7642; F. Cardona, G. D'Orazio, A. M. S. Silva, F. Nicotra, B. La Ferla, *Eur. J. Org. Chem.* 2014, **2014**, 2549-2556; V. R. Doddi, P. K. Kancharla, Y. S. Reddy, A. Kumar, Y. D. Vankar, *Carbohydr. Res.* 2009, **344**, 606-612.
20 L. Sernissi, M. Petrović, D. Scarpi, A. Guarna, A. Trabocchi, F. Bianchini and E. G. Occhiato, *Chemistry - A European Journal*, 2014, **20**, 11187–11203; A. Boto, D. Hernandez and R. Hernandez, *J. Org. Chem.* 2008, **73**, 5287-5297.
21 J. Désiré and M. Shipman, *Synlett*, 2001, **2001**, 1332–1334.
22 R. Hensienne, D. Hazelard and P. Compain, *Arkivoc*, 2019, **2019**, 4–43.
23 C. Maaliki, C. Gauthier, O. Massinon, R. Sagar, S. P. Vincent and Y. Blériot in *Carbohydrate Chemistry: Chemical and Biological Approaches*, Royal Society of Chemistry, Cambridge, 2017, vol. 43. p 418-444.
24 P. Szcześniak, S. Stecko, O. Staszewska-Krajewska and B. Furman, *Tetrahedron*, 2014, **70**, 1880–1888.
25 M. M. Więcław and S. Stecko, *European Journal of Organic Chemistry*, 2018, **2018**, 6601–6623.
26 F. Stauffert, M. Lepage, M. Pichon, D. Hazelard, A. Bodlenner and P. Compain, *Synthesis*, 2016, **48**, 1177–1180.
27 T. Granier and A. Vasella, *Helvetica Chimica Acta*, 1998, **81**, 865–880.
28 M. Terinek and A. Vasella, *Tetrahedron: Asymmetry*, 2005, **16**, 449–469.
29 L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, *Journal of the American Chemical Society*, 2003, **125**, 15521–15528.
30 Y. Zhao and V. Snieckus, *Organic Letters*, 2014, **16**, 390–393.

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DOI: 10.1039/C9OB01402K

31 Q. Foucart, J. Marrot, J. Désiré and Y. Blériot, *Organic Letters*, 2019, 21, 4821-4825.
32 P. Compain, O. R. Martin, C. Boucheron, G. Godin, L. Yu, K. Ikeda and N. Asano, *ChemBioChem*, 2006, **7**, 1356–1359.
33 C. Hedberg, M. Estrup, E. Z. Eikeland and H. H. Jensen, *The Journal of Organic Chemistry*, 2018, **83**, 2154–2165.
34 D. Hazelard, R. Hensienne, J.-B. Behr and P. Compain, Springer Berlin Heidelberg, Berlin, Heidelberg, 2019.
35 W. Zou, Z. Wang, E. Lacroix, S.-H. Wu and H. J. Jennings, *Carbohydrate Research*, 2001, 9.
36 D.-X. Tan, J. You, M.-R. Xu and Y. Wu, *The Journal of Organic Chemistry*, 2016, **81**, 6792–6794.