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Petasis-mediated exo-iminoglycals synthesis from glyconolactams allows access to unprecedented 1-spirocyclopropyl deoxynojirimycin

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A B S T R A C T

We report herein the olefination of a set of six *N*-Boc glyconolactams using Petasis reagent to yield unprecedented exoiminoglycals. In addition, a modified Simmons-Smith cyclopropanation was successfully applied to the D-*gluco*-configured olefin to furnish the unprecedented 1-spirocyclic deoxynojirimycin which proved to be a poor inhibitor of glycosidases in its unprotected form.

1. Introduction

Six-membered 1-deoxyiminosugars including emblematic 1-deoxynojirimycin (DNJ) [1] constitute one of the most promising classes of glycomimetics as therapeutic candidates [2,3]. Their mimicry of the oxocarbenium character of the glycosidases transition state (TS), through protonation of the endocyclic nitrogen atom [4], has been valuable to decipher the mechanism of a wide range of glycosidases. Their potential has been translated into several approved medicines to treat diabetes [5] and rare diseases [6,7]. However, the absence of aglycon moiety in these derivatives has an impact on their selectivity and is responsible for serious side effects [8]. Therefore, improving the selectivity of these iminoalditols is intensively investigated. One strategy consists in the introduction of a chemically stable pseudoanomeric substituent, to mimic the substrate's aglycon moiety, and a wide range of so-called iminosugar *C*-glycosides have been reported [9]. More recently, iminosugar *C,C*-glycosides, possessing a quaternary carbon adjacent to nitrogen [10], have been reached by various strategies, allowing access to densely functionalized piperidine motifs (Fig. 1a) [11–14]. Unlike fused bicyclic iminosugars based on pyrrolizidine or indolizidine scaffolds such as castanospermine, swainsonine, or australine [15], the field of spirocyclic iminosugars has emerged only recently [16]. Importantly, the azaspirocyclic structural motif is present in several natural products and biologically active compounds [17,18]. The introduction of such spiranic center is expected not only to provide conformational rigidity and give access to a diversity of conformations [19] but also to be a mean to explore unpopulated regions of chemical space. A few spirocyclic iminoalditols have been reported to possibly affect the biological properties of their monocyclic templates. Amongst these, spirocyclopropyl derivatives are of high interest as they combine an aglycon moiety with a small ring size that would fit in the glycoenzyme pocket accommodating the aglycon moiety and an orthogonal orientation of the extra spirocycle relative to the iminosugar ring. While spirocyclopropyl carbohydrates have been extensively studied [20], spirocyclopropyl iminosugars are scarce in the literature. We have previously reported the synthesis of a series of five-membered spirocyclopropyl iminoalditols (Fig. 1b) [21], capitalizing on a Kulinkovich-Szymoniak-Bertus cyclopropanation [22] applied to 4-methanesulfonyl-glyconitriles (Fig. 1c). Using the same strategy, two six-membered spirocyclopropyl iminoalditols in the L-*fuco* and L-*rhamno* series were produced in which the methyl group of the parent sugar was replaced by a cyclopropyl moiety (Fig. 1b) [23]. Surprisingly, the spirocyclopropyl derivative of DNJ, the canonical iminosugar, has not been reported to the best of our knowledge and is the aim of this work (Fig. 1d).

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2. Results and discussion

2.1. Synthesis

Exo-glycals or *C*-glycosylidene compounds, having an exocyclic double bond at the anomeric centre, are both valuable synthetic tools and biologically relevant structures [24]. Functionalization or addition reactions on the exocyclic enol ether moiety allows access to more complex exo-glycals, spiroheterocycles, *C*-glycosyl as well as *C, C*-glycosyl compounds [25]. Their nitrogen counterpart, exo-iminoglycals, albeit rare in the literature [26], also hold great potential through their enamide moiety [27]. We have recently investigated endo-iminoglycals through palladium-mediated coupling reactions [28]. Herein we report the first synthesis of exo-iminoglycals from six-membered sugar lactams and their use to access 1-deoxy-1-spirocyclopropyl-nojirimycin.

Easily available D-gluconolactam **1a** [29] was quantitatively *N*-protected with a Boc group to afford fully protected derivative **2a**. Its olefination was first scrutinized using Horner-Wadworth-Emmons [30] and Julia [31] conditions that failed to afford the expected olefin **3a**. However, use of Petasis reagent in refluxing toluene, that has been applied to related natural products [32], was more successful and afforded D-*gluco*-configured olefin **3a** in 53 % yield. To determine the scope of this reaction, these two steps were applied to a set of easily available glyconolactams **1b-f** [28,33], providing the D-*galacto* **3b**, D-*xylo* **3c**, L-*gulo* **3d**, D-*manno* **3e**, and 2-deoxy-D-*gluco* **3f** olefins in 30–58 % yields (see Scheme 1). Noteworthy, some of these compounds proved to have limited chemical stability over time even when stored at 0 °C as previously observed with similar enamides [34].

With the exoiminoglycals **3a-f** in hand, we then explored their cyclopropanation (Scheme 2) through a Simmons-Smith reaction [35] that has previously been reported with endo-iminoglycals [36] using a modified protocol reported by Furukawa [37]. The reaction was studied with **3a** used as a model compound. Treatment of **3a** with $ZnEt_2$ (5 eq.) and CH_2I_2 (10 eq.) in toluene from 0 °C to rt furnished the expected spirocyclopropyl iminosugar **4a** in 50 % yield (Entry 1). Its structure was evidenced by mass spectrometry ($[M+H]^+$ 650) and ^1H NMR with the absence of the olefinic protons and the appearance of four protons between 0.4 and 1.4 ppm. Increasing the amount of both reagents gave a lower yield of **4a** (Entry 2) while performing the reaction at room

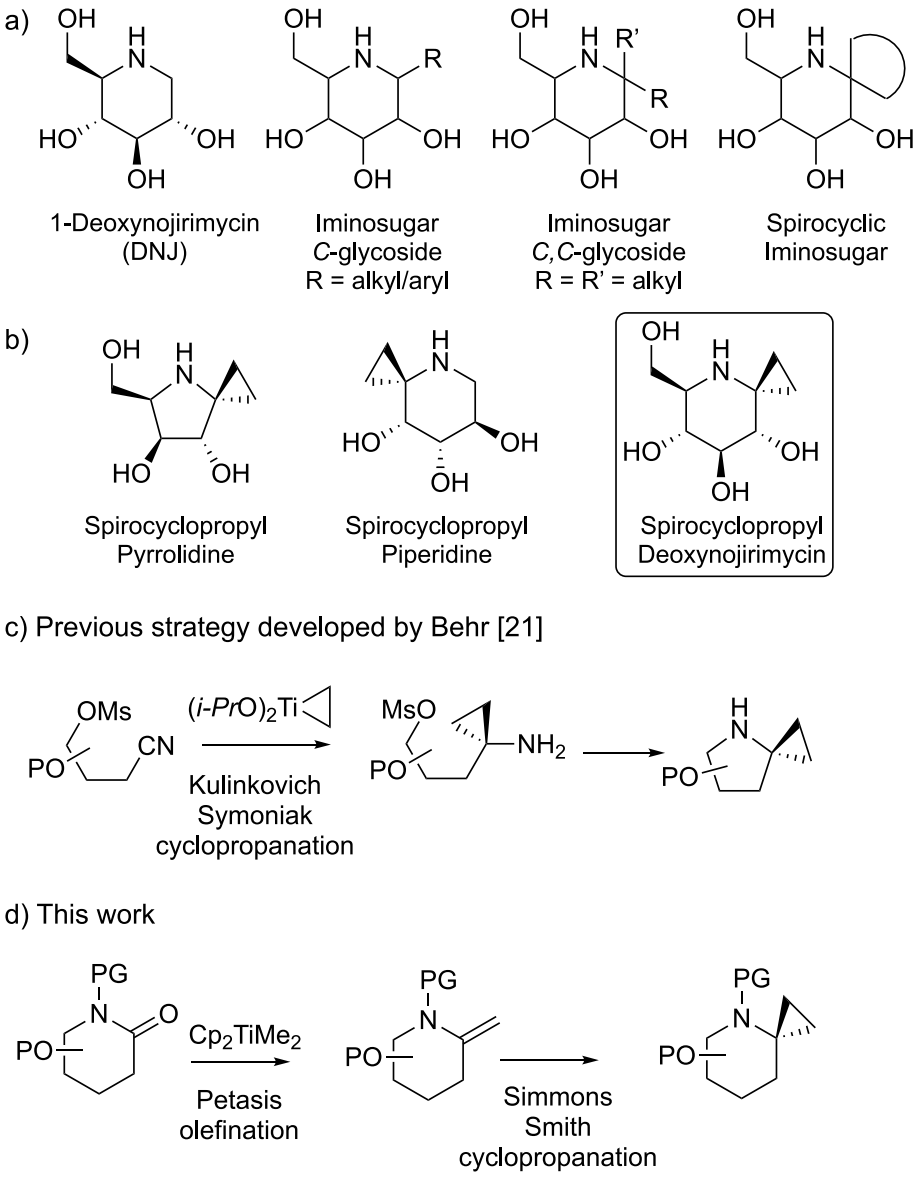
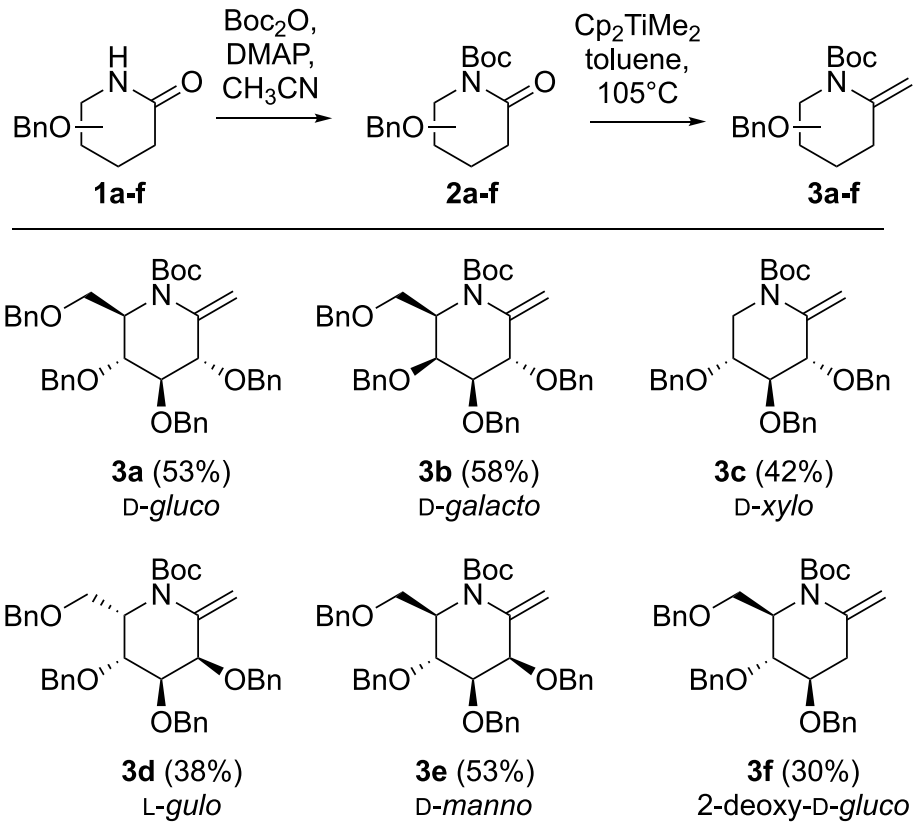


Fig. 1. a) structure of deoxynojirimycin, iminosugar *C*-glycoside, iminosugar *C,C*-glycoside and spirocyclic iminosugar; b) structure of known and targeted spirocyclopropyl iminosugars; c) strategy previously used to access spirocyclopropyl iminosugars; d) strategy used in this work.



Scheme 1. Synthesis of exoiminoglycals **3a-f**; (yields over two steps).

temperature furnished *N*-deprotected piperidine **4a**′ in 19 % yield, (Entry 3). Use of alternative conditions described by Vincent [38] (CH_2Cl_2, 4 Å MS) was unsuccessful (Entry 4). In addition, conditions reported by Denmark [39] (ICH_2Cl in CH_2Cl_2, -50 °C to rt, Entry 5), modified by Song [40] (Entry 6) and conditions developed by Shi [41] (reaction CH_2Cl_2 + TFA, Entry 7) failed to improve the yield of this reaction. Finally, compound **4a**′ was deprotected to afford DNJ analog **5a**. Its ^{1}H NMR analysis including coupling constants ($J_{2,3}$ 9.5 Hz; $J_{3,4}$ 9.4 Hz; $J_{4,5}$ 10.6 Hz) suggests that **5a** adopts a $^4C_1$ conformation in water. The successful cyclopropanation conditions were then applied to olefins **3b** and **3f** to check the scope of this reaction. However, TLC monitoring indicated a very minor conversion of these two substrates and the corresponding spirocyclopropyl derivatives **4b** and **4f** could not be isolated after flash chromatography. As a control experiment, the same reaction was performed on commercial tri-*O*-benzyl D-glucal **6** that furnished the known cyclopropylated D-glucal **7** [42] in 89 % yield. Altogether, these results emphasize the tricky reactivity of these exo-iminoglycals that still needs to be tamed.

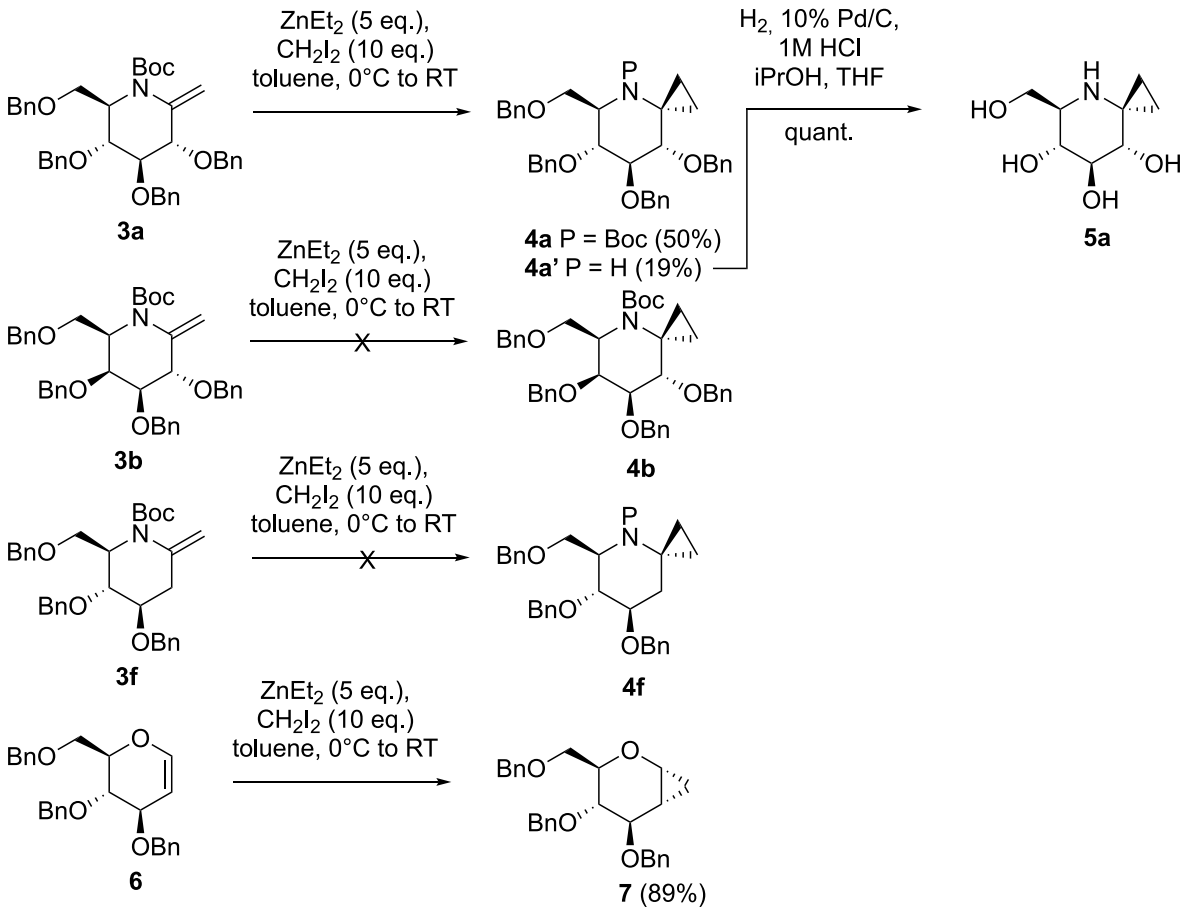
2.2. Enzymatic evaluation

Iminosugar **5a** was assayed on a panel of ten commercially available glycosidases, *ie* α-glucosidases (from rice and yeast), β-glucosidases (from almond and *A. niger*), β-galactosidase (from *A. oryzae*) and α-galactosidase (from green coffee beans), α-mannosidase (from Jack bean), α-rhamnosidase (from *A. niger*), β-*N*-acetylglucosaminidase (from Jack bean) and α-fucosidase (from bovine kidney). Enzymatic activity was evaluated at 1 mM concentration of inhibitor (Table 1) and DNJ was tested under the same conditions for comparison.

Complete loss (>95 %) of enzyme activity at 1 mM concentration is a prerequisite for high inhibition potencies, usually in the low micromolar range. On the opposite, %inhibition below this threshold is typical of modest inhibitors with half maximal inhibitory concentrations usually far above the 10-μM limit. Former results from our laboratories have always followed this empirical rule. With DNJ for instance, 100 % and 98 % inhibition of α-glucosidase (rice) and β-glucosidase (*A. niger*) respectively is characteristic of very favourable IC_{50} (0.035 μM and 0.380 μM). Conversely, 93 % inhibition of alpha-rhamnosidase at 1 mM induces a poor residual 17 % inhibition at 10 μM, which reveals an IC_{50} above this concentration. Concerning compound **5a**, unfortunately none of the tested enzymes were strongly affected at 1 mM, with inhibition ranging from 17 % (α-mannosidase) to 92 % (α-rhamnosidase). For this reason, IC_{50}'s were not further determined. The spirocyclopropyl moiety at the pseudo-anomeric carbon certainly induces steric clash in the catalytic site, which reduces affinity of **5a**, when compared to DNJ, towards glucose-processing enzymes. In return, this alkyl substituent provides polarity compatible with C-5 methyl group of 6-deoxy sugars, which might explain the unexpected inhibition of L-fucosidase.

3. Conclusion

In conclusion, the Petasis reagent-mediated olefination of *N*-Boc glyconolactams has been successfully achieved to furnish unprecedented exo-iminoglycals. Their synthetic potential has been examined through a Simmons-Smith cyclopropanation that delivered the corresponding 1-spirocyclic derivative only in the D-*gluco* series. However, this reaction failed with two other exo-iminoglycals. In its unprotected form, the 1-spirocyclic deoxynojirimycin proved to be a modest inhibitor of glycosidases compared to DNJ, suggesting the detrimental role played by the pseudoanomeric cyclopropyl moiety. Work is now in progress to explore the reactivity of these exo-iminoglycals in other coupling reactions.



Scheme 2. Synthesis of spirocyclopropyl derivative of DNJ **5a**.

Table 1
Inhibition profile of compound **5a** and **DNJ**[a,b].

Glycosidases	5a (%)	DNJ (%)
α-glucosidase (rice)	46	100
α-glucosidase (*S. cerevisiae*)	75	69
β-glucosidase (almond)	62	93
β-glucosidase (*A. niger*)	41	98
β-galactosidase (*A. orizae*)	45	16
α-mannosidase (Jack bean)	17	87
α-rhamnosidase (*A. niger*)	92	93
α-galactosidase (green coffee beans)	66	74
β-*N*-acetylglucosaminidase (Jack bean)	43	NI
α-fucosidase (bovine kidney)	90	NI

[a] Expressed as % inhibition at 1 mM concentration of drug.
[b] NI means no inhibition.

4. Experimental section

4.1. General information

All commercially available reagents were used as supplied without further purification. Petroleum ether (PE) refers to the 40–60 °C boiling fraction. Air and water sensitive reactions were performed in "flame" dried glassware under Ar atmosphere. For reactions that require heating, Radleys® Heat-On block systems were used. TLC plates (MachereyNagel – Alugram® SIL G/UV254) 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 μm) or carried on a Combiflash® Rf automated apparatus (Teledyne-Isco) using columns specified in each protocol. When no column is mentioned, the product was purified on standard silica (Macherey-Nagel 60, 14–40 μm). NMR experiments were recorded with a Bruker 400 Avance III Plus spectrometer at 400 MHz and 101 MHz for ^{1}H and ^{13}C respectively and with a Bruker Ultrashield 500 Avance NEO spectrometer at 500 MHz and 125 MHz for ^{1}H and ^{13}C nuclei respectively. Spectra were calibrated using the residual deuterated solvent peak and chemical shifts are expressed in part per million (ppm). NMR multiplicities are reported using the following abbreviations: b = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. 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). Numbering used for compound names are given according to corresponding carbohydrates.

4.2. Synthesis of glyconolactams, exo-iminoglycals, spirocyclopropyl DNJ derivatives

4.2.1. General procedure A for N-Boc protection of glyconolactams *1a-f*; synthesis of glyconolactams *2a-f*

To a stirred solution of glyconolactam **1a-f** in dry MeCN (50 mL per mmol of lactam), stirred at RT, were added DMAP (0.3 equiv.) and Boc_2O (2.1 equiv.), then the reaction was stirred at RT overnight under argon atmosphere. After consumption of the starting lactam (TLC monitoring), the reaction mixture was diluted with Et_2O (50 mL/mmol of lactam) and washed with water (50 mL/mmol of lactam). The aqueous layer was extracted three times with Et_2O (50 mL/mmol of lactam) and the combined organic layers were washed with brine (60

mL/mmol of lactam), dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel column chromatography using indicated system.

*4.2.1.1. N-(tert-Butoxycarbonyl)-2-3,4,6-tetra-O-benzyl-D-glucono-δ-lactam **2a**.* Synthesized following procedure A from **1a** (602 mg, 1.12 mmol, 1 equiv.), Boc_2O (539 mg, 2.35 mmol, 2.1 equiv.) and DMAP (48 mg, 0.34 mmol, 0.3 equiv.), stirred in dry MeCN (10 mL) under an Ar atmosphere. **2a** was isolated as a yellow oil (714 mg, quant.) after a flash chromatography column (EtOAc/PE 10:90 to 20:80). Rf = 0.69 (PE/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.49–7.27 (m, 20H, H_{Ar}), 5.13 (d, J = 11.7 Hz, 1H, OCHPh), 4.78 (d, J = 11.4 Hz, 1H, OCHPh), 4.70 (brs, 1H, H_5), 4.65 (d, J = 11.4 Hz, 1H, OCHPh), 4.62 (s, 2H, OCH_2Ph), 4.61 (d, J = 11.7 Hz, 1H, OCHPh), 4.51, 4.45 (d, J = 11.9 Hz, 2H, OCH_2Ph), 4.27 (d, J = 8.5 Hz, 1H, H_2), 3.97 (dd, J = 4.3, 2.7 Hz, 1H, H_4), 3.91 (dd, J = 8.5, 4.3 Hz, 1H, H_3), 3.67 (dd, J = 9.7, 6.2 Hz, 1H, H_{6a}), 3.54 (dd, J = 9.7, 4.7 Hz, 1H, H_{6b}), 1 0.57 (s, 9H, CH_3); Analytical data are in agreement with those reported in the literature [43].

*4.2.1.2. N-(tert-Butoxycarbonyl)-2-3,4,6-tetra-O-benzyl-D-galactono-δ-lactam **2b**.* Synthesized following procedure A from **1b** (300 mg, 0.53 mmol, 1 equiv.), Boc_2O (163 mg, 0.75 mmol, 2.1 equiv.) and DMAP (13 mg, 0.11 mmol, 0.3 equiv.), stirred in dry MeCN (10 mL) under an Ar atmosphere. **2b** was isolated as an orange oil (340 mg, quant.) after a flash chromatography column (PE/AcOEt 95:5 to 90:10). Rf = 0.76 (PE/AcOEt 70:30)); $[\alpha]_D^{20}$ = + 49.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.34 (m, 20H, H_{Ar}), 5.18 (d, J = 11.0 Hz, 1H, OCHPh), 4.90 (d, J = 11.3 Hz, 1H, OCHPh), 4.78 (d, J = 8.2 Hz, 2H, OCH_2Ph) 4.76 (d, J = 11.0 Hz, 1H,OCHPh), 4.71 (d, J = 11.3 Hz, 1H, OCHPh), 4.61 (d, J = 11.9 Hz, 1H, OCHPh), 4.55 (d, J = 11.9 Hz, 1H, OCHPh), 4.51 (dd, J = 10.8, 6.5 Hz, 1H, H_2), 4.43 (d, J = 6.8 Hz, 1H, H_5), 4.27 (dd, J = 4.1, 3.0 Hz, 1H, H_3), 4.01–3.95 (m, 2H, H_6 and H_4), 3.85 (dd, J = 9.4, 6.4 Hz, 1H, H_6), 1.59 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 169.7 (C_1), 152.4 (C═O Boc), 138.1, 137.0, 137.8 (Cq-Ar), 128.5, 127.0, 127.9, 127.8, 127.7 (CH-Ar), 83.9 (Cq-Boc), 79.1 (C_3), 79.0 (C_4), 74.4, 73.6, 73.3, 73.2 (OCH_2Ph), 73.1 (C_2), 68.6 (C_6), 56.7 (C_5), 27.9 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{39}H_{43}NNaO_7$: 660.2932, found: 660.2922.

*4.2.1.3. N-(tert-Butoxycarbonyl)-2,3,4-tri-O-benzyl-D-xylono-δ-lactam **2c**.* Synthesized following procedure A from **1c** (322 mg, 0.77 mmol, 1 equiv.), Boc_2O (374 mg, 1.62 mmol, 2.1 equiv.) and DMAP (30 mg, 0.25 mmol, 0.3 equiv.), stirred in dry MeCN under an Ar atmosphere. **2c** was isolated as a yellow oil (364 mg, 91 %) after a flash chromatography column (EtOAc/PE 10:90 to 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 6.5 Hz, 2H), 7.27–7.18 (m, 13H), 4.98 (d, J = 11.6 Hz, 1H), 4.54 (m, 4H), 4.40 (d, J = 11.9 Hz, 1H), 4.27 (dd, J = 13.7, 4.2 Hz, 1H), 3.98 (d, J = 7.0 Hz, 1H), 3.73 (d, J = 7.0 Hz, 1H), 3.68 (dt, J = 4.7, 2.4 Hz, 1H), 3.46 (dd, J = 14.3, 2.3 Hz, 1H), 1.47 (s, 9H). Analytical data are in agreement with those reported in the literature [33].

*4.2.1.4. N-(tert-Butoxycarbonyl)-2-3-4,6-tetra-O-benzyl-L-gulono- δ-lactam **2d**.* Synthesized following procedure A from **1d** (330 mg, 0.62 mmol, 1 equiv.), Boc_2O (281 mg, 1.39 mmol, 2.1 equiv.) and DMAP (22 mg, 0.18 mmol, 0.3 equiv.), stirred in dry MeCN under an Ar atmosphere. **2d** was isolated as a yellow oil (200 mg, 52 %) after a flash chromatography column (EtOAc/PE 5:95 to 10:90). Rf = 0.42 (PE/AcOEt 90:10); $[\alpha]_D^{20}$ = - 17.7 (*c* 0.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.15 (m, 20H, H_{Ar}), 4.85 (d, J = 12.1 Hz, 1H, OCHPh), 4.73 (d, J = 11.5 Hz, 1H, OCHPh), 4.60 (d, J = 11.5 Hz, 1H, OCHPh), 4.59 (s, 2H, OCH_2Ph), 4.53 (d, J = 12.1 Hz, 1H, OCHPh), 4.43 (d, J = 12.3 Hz, 1H, OCHPh), 4.39 (d, J = 12.3 Hz, 1H, OCHPh), 4.32–4.29 (m, 1H, H_5), 4.27 (dd, J = 8.7, 3.8 Hz, 1H, H_3), 4.19 (dd, J = 8.7, 6.2 Hz, 1H, H_4), 4.11 (d, J = 3.8 Hz, 1H, H_2), 3.85 (dd, J = 9.6, 1.9 Hz, 1H, H_6), 3.60 (dd, J = 9.6, 4.5 Hz, 1H, $H_{6'}$), 1.49 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C_1), 153.1 (C═O Boc), 138.5, 138.3, 137.9, 137.7 (Cq-Ar), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6 (CH-Ar), 83.3 (Cq-Boc), 77.4 (C_2), 76.8 (C_3), 75.3 (C_4), 73.7, 73.4, 72.7, 72.5 (OCH_2Ph), 66.6 (C_6), 55.1 (C_5), 28.1 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{39}H_{43}NNaO_7$: 660.2932, found: 660.2922.

*4.2.1.5. N-(tert-Butoxycarbonyl)-2-3-4,6-tetra-O-benzyl-D-mannono-δ-lactam **2e**.* Synthesized following procedure A from a mixture of **1a** and **1e** (253 mg, 0.47 mmol, 1 equiv.), Boc_2O (255 mg, 1.18 mmol, 2.1 equiv.) and DMAP (27 mg, 0.22 mmol, 0.3 equiv.), stirred in dry MeCN under an Ar atmosphere. **2a** (158 mg, 53 %) and **2e** (134 mg, 45 %) were isolated after a flash chromatography column (EtOAc/PE 5:95 to 10:90). **2e**: Rf = 0.74 (PE/AcOEt 80:20); $[\alpha]_D^{20}$ = + 16.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.08 (m, 20H, H_{Ar}), 4.87 (d, J = 12.1 Hz, 1H, OCHPh), 4.57–4.43 (m, 6H, OCHPh), 4.39 (m, 1H, H_5), 4.36 (d, J = 2.2 Hz, 1H, OCHPh), 4.22 (d, J = 3.1 Hz, 1H, H_2), 4.08 (dd, J = 5.4, 1.4 Hz, 1H, H_4), 3.87 (dd, J = 5.1, 3.1 Hz, 1H, H_3), 3.71 (t, J = 9.4 Hz, 1H, H_6), 3.58 (dd, J = 8.8, 5.3 Hz, 1H, $H_{6'}$), 1.41 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C_1), 152.0 (C═O Boc), 138.1, 137.8, 137.7 (Cq-Ar), 128.5, 128.4, 128.1, 127.9, 127.8, 127.6 (CH-Ar), 83.3 (Cq-Boc), 78.5 (C_3), 77.0 (C_2), 73.5 (C_4), 73.0, 72.7, 72.0 (OCH_2Ph), 70.1 (C_6), 59.8 (C_5), 28.0 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{39}H_{43}NNaO_7$: 660.2932, found: 660.2913.

*4.2.1.6. N-(tert-Butoxycarbonyl)-2-deoxy-3,4,6-tri-O-benzyl-D-glucono-δ-lactam **2f**.* Synthesized following procedure A from **1f** (235 mg. 0.54 mmol, 1 equiv.), Boc_2O (247 mg, 1.14 mmol, 2.1 equiv.) and DMAP (20 mg, 0.16 mmol, 0.3 equiv.), stirred in dry MeCN (12 mL) under an Ar atmosphere. **2f** was isolated as a colorless oil (272 mg, 94 %) after a flash chromatography column (EtOAc/PE 10:90 to 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 15H), 4.69–4.60 (m, 2H), 4.60–4.47 (m, 3H), 4.45 (s, 2H), 4.03 (dd, J = 5.9, 2.4 Hz, 1H), 3.85 (dt, J = 15.1, 4.9 Hz, 1H), 3.66 (dd, J = 9.4, 6.7 Hz, 1H), 3.52 (dd, J = 9.4, 4.2 Hz, 1H), 2.86 (dd, J = 16.7, 5.0 Hz, 1H), 2.64 (dd, J = 16.7, 8.9 Hz, 1H), 1.48 (s, 9H). Analytical data are in agreement with those reported in the literature [44].

*4.2.2. Synthesis of exo-iminoglycals **3a-f***

*4.2.2.1. N-(tert-Butoxycarbonyl)-2-3,4,6-tetra-O-benzyl-exo-imino-D-glucal **3a**.* A solution of methyllithium (1.6 M in Et_2O, 1.9 mL, 3.00 mmol, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (355 mg in 6 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (281 mg, 1.43 mmol) were diluted in dry toluene (3 mL) and directly engaged in the next step. To a solution of **2a** (344 mg. 0.54 mmol) in dry toluene (10 mL) was added the freshly prepared solution of Cp_2TiMe_2 (3 mL, 1.43 mmol, 2.6 eq) under argon. The resulting mixture was refluxed in the dark for 3h30, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE 5:95 to 10:90) to afford compound **3a** (184 mg, 53 %). Rf = 0.4 (EtOAc/PE 10:90); $[\alpha]_D^{20}$ = −11.3 (*c* 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.22–7.09 (m, 20H, H_{Ar}), 5.24 (s, 1H, H_7), 5.16 (s, 1H, H_7), 4.70 (d, J = 11.9 Hz, 1H, OCHPh), 4.63 (d, J = 11.6 Hz, 1H, OCHPh), 4.52 (d, J = 11.6 Hz, 1H, OCHPh), 4.48 (s, 2H, OCH_2Ph), 4.41 (d, J = 12.5 Hz, 1H, OCHPh), 4.34 (d, J = 12.5 Hz, 1H, OCHPh), 4.32 (d, J = 11.9 Hz, 1H, OCHPh), 4.26 (brs, 1H, H_2), 3.86 (d, J = 3.2 Hz, 1H, H_5), 3.76–3.70 (m, 2H, H_3, H_4), 3.67 (dd, J = 9.8, 5.6 Hz, 1H, H_6), 3.59 (dd, J = 9.8, 4.6 Hz, 1H, H_6), 1.32 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 154.0 (C═O Boc), 138.6–137.5 (C_q-Ar, C_1), 128.7–127.1 (CH-Ar), 116.2 (C_7), 82.0 (C_q-Boc), 80.4, 80.3 (C_4 and C_2), 73.4 (C_3), 72.8 (2 x OCH_2Ph), 72.4 (OCH_2Ph), 69.5 (OCH_2Ph), 68.4 (C_6), 56.3 (C_5), 28.3 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{40}H_{45}NNaO_6$: 658.3139, found:

658.3134.

*4.2.2.2. N-(tert-Butoxycarbonyl)-2-3-4,6-tetra-O-benzyl-exo-imino-D-galactal **3b**.* A solution of methyllithium (1.6 M in Et_2O, 3.2 mL, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (600 mg in 10 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (503 mg, 2.42 mmol) were diluted in dry toluene (8 mL) and directly engaged in the next step. To a solution of **2b** (573 mg. 0.89 mmol) in toluene (4 mL) was added the solution of Cp_2TiMe_2 freshly prepared (8 mL, 2.42 mmol, 2.7 eq) under argon. The resulting mixture was refluxed in the dark for 1h40, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE. 5:95 to 15:85) to afford compound **3b** (330 mg, 58 %).$R_f = 0.42$ (PE/EtOAc 8:2); $[\alpha]_D^{20} = -11.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.28–7.10 (m, 20H, H_{Ar}), 5.07 (brs, 2H, H_7), 4.63–4.55 (m, 3H, OCH_2Ph, H_5), 4.48 (d, *J* = 11.6 Hz, 1H, OCHPh), 4.45 (d, *J* = 12.3 Hz, 1H, OCHPh), 4.34 (d, *J* = 12.0 Hz, 1H, OCHPh), 4.21 (d, *J* = 11.7 Hz, 1H, OCHPh), 4.02 (m, 1H), 3.90 (dd, *J* = 11.0, 9.9 Hz, 1H, H_6), 3.79 (m, 3H, H6, 2H), 1.37 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 154.3 (C═O Boc), 139.1–138.0 (C_q-Ar), 136.4 (C_1), 128.3–127.3 (CH-Ar), 118.6 (C_7), 80.2 (Cq-Boc), 78.5, 77.7, 74.4 (C_2, C_3, C_4), 73.0, 72.3, 71.4, 69.5 (OCH_2Ph), 67.4 (C_6), 53.5 (C_5), 28.3 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{40}H_{45}NNaO_6$: 658.3139, found: 658.3127.

*4.2.2.3. N-(tert-Butoxycarbonyl)-3-4,6-tri-O-benzyl-exo-imino-D-xylal **3c**.* A solution of methyllithium (1.6 M in Et_2O, 2.1 mL, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (397 mg in 6 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (333 mg, 1.60 mmol) were diluted in dry toluene (7 mL) and directly engaged in the next step. To a solution of **2c** (330 mg, 0.64 mmol) in dry toluene (10 mL) was added the freshly prepared solution of Cp_2TiMe_2 (7 mL, 1.60 mmol, 2.5 eq.) under argon. The resulting mixture was refluxed in the dark for 2h30, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE. 5:95 to 15:85) to afford compound **3c** (236 mg, 46 %). $R_f = 0.44$ (PE/EtOAc 9:1); $[\alpha]_D^{20} = -54.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.29–7.18 (m, 15H, H_{Ar}), 5.19 (brs, 1H, H_7), 5.15 (d, *J* = 1.1 Hz, 1H, H_7), 4.70 (d, *J* = 11.3 Hz, 1H, OCHPh), 4.67–4.63 (m, 2H, OCH_2Ph), 4.60 (s, 2H, OCH_2Ph), 4.48 (d, *J* = 11.6 Hz, 1H, OCHPh), 4.05 (brs, 1H, H_5), 3.76 (d, *J* = 5.4 Hz, 1H, H_2), 3.52 (m, 2H, H_3, H_4) 2.99–2.92 (m, 1H, H_5), 1.37 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 153.8 (C═O Boc), 140.0 (C_1), 138.4–138.0 (C_q-Ar), 128.4–127.7 (CH-Ar), 108.7 (C_7), 85.0 (C_4), 80.7 (C_2, Cq-Boc), 77.7 (C_3), 74.0, 72.5, 71.9 (OCH_2Ph), 45.2 (C_5), 28.3 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{32}H_{37}NNaO_5$: 538.2564, found: 538.2559.

*4.2.2.4. N-(tert-Butoxycarbonyl)-2-3-4,6-tetra-O-benzyl-exo-imino-L-gulal **3d**.* A solution of methyllithium (1.6 M in Et_2O, 1.2 mL, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (221 mg in 5 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (184 mg, 0.89 mmol) were diluted in dry toluene (4 mL) and directly engaged in the next step. To a solution of **2d** (209 mg, 0.33 mmol) in dry toluene (2 mL) was added the freshly prepared solution of Cp_2TiMe_2 (4 mL, 0.89 mmol, 2.7 eq) under argon. The resulting mixture was refluxed in the dark for 2h. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE. 10:90 to 15:85) to afford compound **3d** (154 mg, 74 %). $R_f = 0.21$ (PE/EtOAc 9:1); $[\alpha]_D^{20} = +4.8$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)δ ppm: 7.32–7.17 (m, 20H, H_{Ar}), 5.02 (brs, 3H, H_5, H_7), 4.72 (d, *J* = 11.2 Hz, 1H, OCHPh) 4.68 (d, *J* = 12.6 Hz, 1H, OCHPh), 4.64 (d, *J* = 11.2 Hz, 1H, OCHPh), 4.53 (d, *J* = 12.0 Hz, 2H, OCH_2Ph), 4.47 (d, *J* = 12.0 Hz, 1H, OCHPh), 4.37 (d, *J* = 12.6 Hz, 1H, OCHPh), 4.32 (d, *J* = 12.1 Hz, 1H, OCHPh), 4.16 (dd, *J* = 10.0, 6.6 Hz, 1H, H_2 or H_4), 3.89 (d, *J* = 3.4 Hz, 1H,H_2 or H_4), 3.71 (dd, *J* = 10.4, 2.8 Hz, 1H, H_6), 3.53 (dd, *J* = 10.2, 3.5 Hz, 1H, H_3), 3.47 (t, *J* = 9.9 Hz, 1H, H_6), 1.40 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 154.3 (C═O Boc), 138.6–137.8 (C_q-Ar, C_1), 128.4–127.4 (CH-Ar), 116.4 (C_7), 80.5 (C_q Boc), 78.8 (C_3), 76.1 (C_2 or C_4), 75.8 (C_2 or C_4), 73.7 (OCH_2Ph), 72.6 (OCH_2Ph), 72.1 (OCH_2Ph), 69.2 (OCH_2Ph) 66.5 (C_6), 52.6 (C_5), 28.4 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{40}H_{45}NNaO_6$: 658.3139, found: 658.3110.

*4.2.2.5. N-(tert-Butoxycarbonyl)-2-3-4,6-tetra-O-benzyl-exo-imino-D-mannal **3e**.* A solution of methyllithium (1.6 M in Et_2O, 1.6 mL, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (191 mg in 5 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (156 mg, 0.75 mmol) were diluted in dry toluene (3 mL) and directly used in the next step. To a solution of **2e** (177 mg, 0.28 mmol) in dry toluene (4 mL) was added the freshly prepared solution of Cp_2TiMe_2 (3 mL, 0.75 mmol, 2.7 eq) under argon. The resulting mixture was refluxed in the dark for 1h30, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE. 5:95 to 15:85) to afford compound **3e** (94 mg, 53 %). $R_f = 0.62$ (PE/EtOAc 9:1); $[\alpha]_D^{20} = -56.1$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.29–7.13 (m, 20H, H_{Ar}), 5.40 (s, 1H, H_7), 5.09 (s, 1H, H_7), 4.69 (brs, 1H, H_5), 4.66 (d, *J* = 12.2 Hz, 1H, OCHPh), 4.63 (d, *J* = 12.5 Hz, 1H, OCHPh), 4.54 (d, *J* = 11.8 Hz, 1H, OCHPh),4.47 (d, *J* = 12.4 Hz, 1H, OCHPh), 4.44 (d, *J* = 12.0 Hz, 1H, OCHPh), 4.40 (d, *J* = 12.0 Hz, 1H, OCHPh), 4.35 (d, *J* = 12.0 Hz, 1H, OCHPh), 4.30 (d, *J* = 11.8 Hz, 1H, OCHPh), 4.13–4.09 (m, 1H, H_2), 3.78 (dt, *J* = 3.1, 2.4 Hz, 2H, H_3, H_4), 3.62 (qd, *J* = 9.6, 7.7 Hz, 2H, H_6), 1.36 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 154.5 (C═O Boc), 139.1 (C_1), 138.6–138.1 (C_q-Ar), 128.4–127.3 (CH-Ar), 110.6 (C_7), 80.3 (C_q Boc), 77.7 (C_3), 76.3 (C_2), 74.1 (C_4), 72.8, 72.8, 71.8, 71.2 (OCH_2Ph), 68.7 (C_6), 54.7 (C_5), 28.3 (CH_3); HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{40}H_{45}NNaO_6$: 658.3139, found: 658.3121.

*4.2.2.6. N-(tert-Butoxycarbonyl)-2-deoxy-3,4,6-tri-O-benzyl-exo-imino-D-glucal **3f**.* A solution of methyllithium (1.6 M in Et_2O, 0.4 mL, 2.1 eq.) was added dropwise to a solution of Cp_2TiCl_2 in dry Et_2O (66 mg in 1 mL) at 0 °C. After 1h, the solution was quenched with iced water and the organic phase was separated, dried over $MgSO_4$ then filtered and concentrated. The obtained orange crystals of Cp_2TiMe_2 (53 mg, 0.26 mmol) were diluted in dry toluene (1 mL) and directly used in the next step. To a solution of **2f** (45 mg, 0.09 mmol) in dry toluene (1.2 mL) was added the freshly prepared solution of Cp_2TiMe_2 (1 mL, 0.26 mmol, 2.7 eq) under argon. The resulting mixture was refluxed in the dark for 2h30, then concentrated under reduced pressure. The crude residue was purified by a flash chromatography column (EtOAc/PE. 5:95 to 15:85) to afford **3f** (14.4 mg, 32 %). $R_f = 0.50$ (PE/EtOAc 9:1); $[\alpha]_D^{20} = -11.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)δ ppm: 7.27–7.15 (m, 15H, H_{Ar}), 4.92 (s, 1H, H_7), 4.89 (s, 1H, H_7), 4.78 (s, 1H, H_5), 4.65 (d, *J* = 8.0 Hz, 1H, OCHPh), 4.62 (d, *J* = 1.8 Hz, 1H, OCHPh), 4.43–4.37 (m, 4H, OCH_2Ph), 3.73 (s, 1H, H_4), 3.67–3.58 (m, 3H, H_6, H_3), 2.61–2.55 (m, 1H, H_2), 2.29 (dd, *J* = 14.1, 2.9 Hz, 1H, H_2), 1.39 (d, *J* = 5.5 Hz, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, presence of rotamers) δ ppm: 153.2 (C═O Boc), 137.5–137.0 (C_q-Ar, C_1), 127.3–126.3 (CH-Ar), 109.9 (C_7), 79.1 (C_q Boc), 74.5 (C_4), 71.7 (OCH_2Ph), 71.0 (C_3), 70.0, 69.7 (OCH_2Ph), 67.8 (C_6), 54.3 (C_5),32.3 (C_2), 27.3 (CH_3); HRMS (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{33}H_{40}NO_5$: 530.2905, found: 530.2901.

4.2.3. Synthesis of spirocyclopropyl DNJ derivatives **4a, 4a′, 5a** and cyclopropylated-D-glucal **7**

*4.2.3.1. N-(tert-Butoxycarbonyl)-2-3,4,6-tetra-O-benzyl-1-spirocyclopropyl-1-deoxynojirymicin **4a**.* To a stirred solution of diethylzinc (400 μL, 0.40 mmol, 1 M/hexane) and diiodomethane (32 μL, 0.39 mmol) in dry toluene (600 μL) was added, at 0 °C under argon and in the dark, a solution of **3a** (50 mg, 0.08 mmol) in dry toluene (600 μL). The solution was stirred at 0 °C for 1h and 2h30 at RT. Then diiodomethane (32 μL, 0.39 mmol) was added and the solution was stirred overnight at RT. The reaction mixture was quenched with a solution of ammonium chloride, then diluted with DCM. The aqueous layer was extracted three times with DCM and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel chromatography column (EtOAc/PE. 5:95 to 15:85) to afford compound **4a** (26 mg, 50 %). Rf = 0.48 (PE/EtOAc 9:1); $[\alpha]_D^{20} = +5.4$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500z MHz, Acetone-d6) δ ppm: 7.31–7.06 (m, 20H, H_{Ar}), 4.97 (d, J = 11.6 Hz, 1H, OCHPh), 4.75 (d, J = 11.1 Hz, 1H, OCHPh), 4.57 (d, J = 11.8 Hz, 1H, OCHPh), 4.49 (t, J = 11.5 Hz, 2H, OCH_2Ph), 4.43 (d, J = 11.6 Hz, 1H, OCHPh), 4.40 (d, J = 12.1 Hz, 1H, OCHPh), 4.36 (d, J = 12.1 Hz, 1H, OCHPh), 4.09 (t, J = 8.7 Hz, 1H, H_4), 3.80 (d, J = 8.0 Hz, 1H, H_5), 3.68 (dd, J = 9.7, 3.3 Hz, 1H, H_6), 3.64–3.58 (m, 2H, H_6, H_3), 3.10 (d, J = 2.2 Hz, 1H, H_2), 1.43 (m, J = 8.3 Hz, 1H, $H_{7\ or\ 7'}$), 1.24 (s, 9H, CH_3), 1.16 (m, 1H, $H_{7\ or\ 7'}$), 1.02–0.97 (m, 1H, $H_{7\ or\ 7'}$), 0.52 (ddd, J = 10.1, 7.2, 4.7 Hz, 1H, $H_{7\ or\ 7'}$); ^{13}C NMR (125 MHz, Acetone-d6) δ ppm: 156.0 (C═O Boc), 139.4–138.7 (C_q-Ar), 128.2–127.1 (CH-Ar), 86.1 (C_3), 85.5 (C_2), 79.1 (C_q Boc), 75.5 (C_4), 74.0, 72.6, 71.5, 70.7 (OCH_2Ph), 68.2 (C_6), 58.2 (C_5), 34.6 (C_1), 27.6 (CH_3), 12.7 (C_7 or $C_{7'}$), 11.4 (C_7 or $C_{7'}$); HRMS (ESI$^+$) m/z: $[M+H]^+$ calcd. for $C_{41}H_{48}NO_6$: 650.3476, found: 650.3475.

*4.2.3.2. 2-3,4,6-Tetra-O-benzyl-1-spirocyclopropyl-1-deoxynojirimycin **4a′**.* To a stirred solution of diethylzinc (450 μL, 0.45 mmol, 1 M/hexane) and diiodomethane (35 μL, 0.42 mmol) in dry toluene (600 μL) was added dropwise at RT under argon and in the dark, a solution of **3a** (53 mg, 0.08 mmol) in dry toluene (600 μL). The solution was stirred at r.t. for 6h30 (TLC monitoring) then diiodomethane (35 μL, 0.42 mmol) was added and the solution was stirred overnight at r.t. Diethylzinc (450 μL, 0.45 mmol, 1 M/hexane) and diiodomethane (35 μL, 0.42 mmol) were added again at RT. The solution was stirred at r.t. for 5h, then quenched with a solution of ammonium chloride and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by a flash chromatography column (EtOAc/PE 5:95 to 15:85) to afford compound **4a′** (10.4 mg, 19 %). Rf = 0.52 (PE/EtOAc 8:2); $[\alpha]_D^{20} = 26.2$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.31–7.10 (m, 20H, H_{Ar}), 4.82 (d, J = 10.9 Hz, 1H, OCHPh), 4.79 (d, J = 3.3 Hz, 2H, OCH_2Ph), 4.75 (d, J = 11.1 Hz, 1H, OCHPh), 4.51 (d, J = 11.3 Hz, 1H, OCHPh), 4.45 (d, J = 10.8 Hz, 1H, OCHPh), 4.41 (d, J = 11.7 Hz, 1H, OCHPh), 4.30 (dd, J = 13.1, 6.4 Hz, 1H, OCHPh), 3.67 (dd, J = 9.1, 3.2 Hz, 1H, H_6), 3.56 (m, 3H, H_2, H_3, H_4), 3.46 (dd, J = 9.1, 2.5 Hz, 1H, H_6), 2.72–2.68 (m, 1H, H_5), 0.75 (ddd, J = 9.9, 6.1, 3.8 Hz, 1H, H_7 or $H_{7'}$), 0.70–0.63 (m, 1H, H_7 or $H_{7'}$), 0.49 (ddd, J = 10.4, 6.1, 4.4 Hz, 1H, H_7 or $H_{7'}$), 0.31 (ddd, J = 10.0, 6.0, 3.9 Hz, 1H, H_7 or $H_{7'}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 138.9–138.2 (C_q-Ar), 128.5–127.6 (CH-Ar), 87.7, 81.1, 81.0 (C_2, C_3, C_4), 75.8, 75.3, 75.2, 73.4 (OCH_2Ph), 69.2 (C_6), 58.0 (C_5), 38.2 (C_1), 9.2 (C_7 or $C_{7'}$), 8.1 (C_7 or $C_{7'}$); HRMS (ESI$^+$) m/z: $[M+H]^+$ calcd. for $C_{36}H_{40}NO_4$: 550.2952, found: 550.2939.

*4.2.3.3. 1-Spirocyclopropyl-1-deoxynojirimycin **5a**.* To a stirred solution of **4a** (10 mg, 0.084 mmol) in a mixture of THF/iPrOH (1/1, 0.6 mL) and HCl (1 M, 55 μL), was added Pd/C (10 % loading, 10 mg). The mixture was stirred for 18 h under H_2 atmosphere at RT, then filtered through a pad of Celite (previously washed with 1 M HCl, H_2O and CH_3OH). The filtrate was concentrated *in vacuo*, then diluted in water (0.5 mL) and freeze dried to give **5a** (4.2 mg, quant.) as a yellow foam. $[\alpha]_D^{20} = +7.8$ (*c* 0.50, CH_3OH); ^{1}H NMR (500 MHz, D_2O) δ: 3.93 (1H, dd, J = 12.9, 3.7 Hz, H_6), 3.87 (1H, d, J = 9.5 Hz, H_2), 3.80 (1H, dd, J = 12.9, 2.8 Hz, H_6), 3.68 (1H, dd, J = 10.6, 9.4 Hz, H_4), 3.50 (1H, t, J = 9.4 Hz, H_3), 3.26 (1H, dt, J = 10.7, 3.3 Hz, H_5), 1.08–1.03 (2H, m, H_7 or $H_{7'}$), 1.02–0.98 (1H, m, H_7 or $H_{7'}$), 0.91–0.87 (1H, m, H_7 or $H_{7'}$); ^{13}C NMR (125 MHz, D_2O) δ: 75.4 (C_3), 67.6 (C_4), 67.0 (C_2), 59.4 (C_5), 56.7 (C_6), 39.8 (C_1), 5.3 (C_7), 4.1 ($C_{7'}$); HRMS (ESI$^+$) m/z: $[M+H]^+$ calcd. for $C_8H_{16}NO_4$: 190.1074, found: 190.1072.

*4.2.3.4. 3,4,6-Tri-O-benzyl-1,2-cyclopropylated-D-glucal **7**.* To a stirred solution of diethylzinc (0.70 mL, 0.63 mmol, 0.9 M/hexane) and diiodomethane (50.5 μL, 0.63 mmol) was added dropwise at r.t. under argon and in the dark, a solution of 3,4,6-tri-O-benzyl-D-glucal (52.4 mg, 0.13 mmol) in dry diethyl ether/hexane (1.2 mL, 50/50). The solution was stirred at r.t. for 5h (TLC monitoring) then diiodomethane (50.5 μL, 0.629 mmol) was added and the solution was stirred overnight at r.t. The solution was quenched with a solution of ammonium chloride and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **7** which was obtain without further purification (48.7, 89 %). Rf = 0.49 (PE/EA 9:1). Analytical data are in agreement with those reported in the literature [42].

4.3. Glycosidase assays

Glycosidases and *p*-nitrophenyl glycosides used for the bioassays were purchased from Sigma Chemical Co. In a typical experiment, the glycosidase (0.013 U/mL) was pre-incubated at 33 °C for 5 min in the presence of 1 mM of the inhibitor in 50 mM acetate buffer (pH 5.1 for rice α-glucosidase, pH 6.1 for yeast α-glucosidase and pH 5.6 for all other enzymes). The reaction was started by addition of the appropriate *p*-nitrophenyl glycoside substrate (1 mM) to a final volume of 250 μl. The reaction was stopped after 10–15 min by addition of 300 μL of 0.4 M Na_2CO_3. The released p-nitrophenolate was quantified spectrometrically at 415 nm and the net absorbance of the sample (A_{sample}) was obtained after subtracting the blank. The blank was measured in an additional experiment, conducted in the absence of enzyme. The control experiment contained no inhibitor.

Percentage of inhibition was calculated as follows:

$$\%I = \left(1 - \frac{A_{sample}}{A_{control}}\right) * 100$$

CRediT authorship contribution statement

Lilou Chopin: Methodology, Investigation. **Aurélien Beato:** Investigation. **Dylan Yorga:** Investigation. **Nicolas Auberger:** Investigation, Formal analysis. **Jean-Bernard Behr:** Methodology, Investigation. **Jérôme Désiré:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Yves Blériot:** Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2025.109765.

Data availability

No data was used for the research described in the article.

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