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Stereoselective syntheses of polyhydroxylated azepane derivatives from sugar-based epoxyamides. Part 1: synthesis from D-mannose

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ABSTRACT

An approach to the synthesis of polyhydroxyazepane derivatives from sugar-based epoxyamides or epoxyalcohols, in which the total regioselective epoxide opening by nitrogen nucleophiles is the key step, is described. Thus, novel polyhydroxyazepane carboxamides and aminomethyl polyhydroxyazepanes, with potential pharmacological interest, are synthesized from diacetone D-mannose. Configurational assignments of the obtained products were determined.

1. Introduction

Nitrogen-containing sugar analogues, known as iminoalditols or iminosugars, have attracted considerable attention from synthetic and medicinal chemists, biologists and clinical researchers due to their potential ability to inhibit glycosidases and glycosyl transferases.[1] The design and synthesis of glycosidase inhibitors have focused mainly on five- and six-membered iminoalditols, which are considered to mimic the substrate transition states with oxycarbenium ion character. Nevertheless, polyhydroxyazepanes or seven-membered iminoalditols,[2] although known since 1967,[3] received little attention before Wong et al. revealed that tetrahydroxyazepanes are promising inhibitors against a broad range of glycosidases.[4] It was suggested that the greater flexibility of the seven-membered ring, compared to a five- or six-membered ring, could improve binding to the active site of the enzyme.[5] However to date, 1,6-dideoxy-1,6-iminoalditols have shown only moderate inhibitory activities; the published results emphasize the difficulty for predicting the inhibition profile in this family of polyhydroxyazepanes.[6] All these facts have stimulated a growing interest in developing strategies for synthesizing new derivatives, including bicyclic compounds.[7]

Several syntheses of polyhydroxyazepanes start from carbohydrate derivatives, taking advantage of their stereocenters.[8] However, a number of these syntheses suffer from lengthy procedures and new strategies have to be considered. In connection with our interest in the synthesis of epoxyamides derived from carbohydrates, we have developed a methodology, which has led to iminocompounds with different ring sizes.[9] In these syntheses, the regioselective epoxide opening by nitrogen nucleophiles is the key step. There are few research groups working on efficient syntheses of optically active 2,3-epoxyamides,[10] and their regioselective ring-opening reactions have not been widely investigated. In our laboratory, we studied the optimal conditions in order to provide 2-[N]-substituted 3-hydroxyamides with total regioselectivity.[9a–d] With this type of intermediates in hand and the adequate hydroxylated chain, we could obtain the desired azepanes derivatives. Thus, previous experiences carried out with ribose derivatives permitted us to synthesize new polyhydroxyazepanes derivatives but in low yield.[9a]

With the aim of obtaining new and more potent inhibitors with an azepane ring, we prepared a similar route but starting from dialdehyde sugars (Scheme 1). This methodology would lead to polyhydroxyazepanes type I, II or III, as promising drug candidates. Some of them can mimic iminosugar C-glycosides, which have become an important class of iminosugars with promising biological and therapeutic properties.[11] To date, the potential inhibition of azepane carboxamides has not been described, but their six-membered analogues, pipecolic acid amides, hold great promise for the construction of pharmacologically active agents.[12] Analogously, the 6-aminomethylpolyhydroxy-azepanes are products which, to the best of our knowledge, have not been published, but their pyrrolidine[13] and piperidine[14] analogues have been well documented and show good profiles as inhibitors of glycosidases.

Herein, we report the synthesis and biological evaluation of new polyhydroxylated azepanes with the configuration depicted in Scheme 1.[15] For this purpose, we chose aldehyde **2**, obtained from D-manno compound **1**, as starting material, and prepared a variety of epoxyamides to obtain azido derivatives as precursors of the diverse target azepanes.

2. Results and discussion

The first step in the preparation of aldehyde **2** was benzylation of 2,3:5,6-di-*O*-isopropylidene-D-mannose **1**. A mixture of anomers **6α**:**6β** (5.5:1) was obtained, which was separated by column

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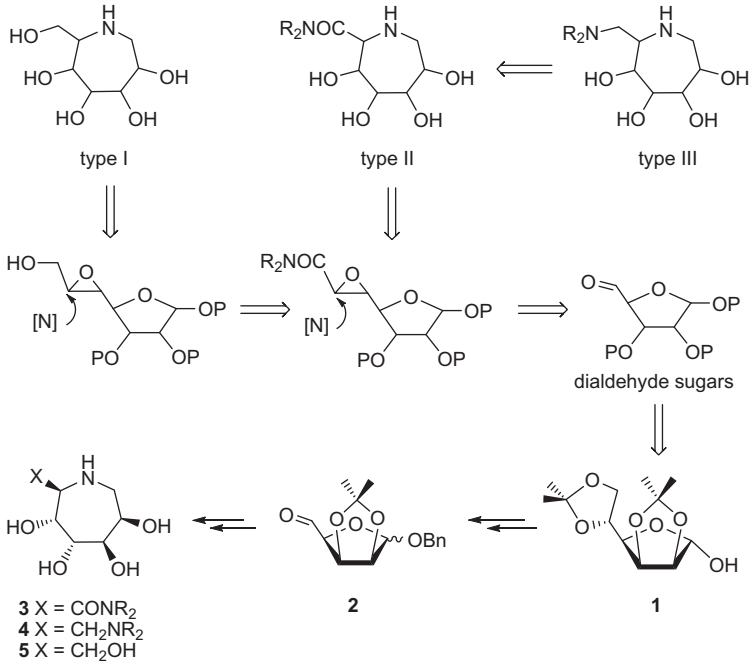
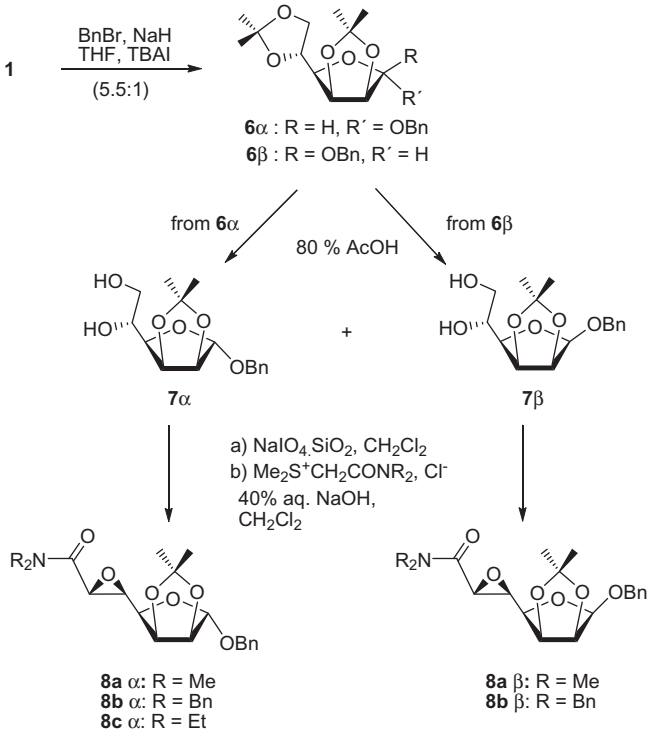


Scheme 1.

chromatography. In previous references,[16] only the α-isomer was isolated by crystallization, the β-anomer was not considered, and as a consequence its data have not been reported. We isolated both isomers and demonstrated their utility in this synthesis because they both lead to the same azepane derivative. Selective acid hydrolysis of **6α** or **6β** gave diols **7α** or **7β**, respectively (Scheme 2). Periodic oxidation of **7α** or **7β**, in the presence of SiO_2,[17] gave the corresponding aldehydes **2α** or **2β** which, without further purification, were reacted with the sulfur ylides. These ylides $Me_2SCHCONR_2$ (R: Me, Et, Bn) were obtained in situ from their sulfonium salts (two phases method) and their reactions let us to obtain the *trans* epoxyamides **8a**, **8b** or **8c** (α and β series) with complete stereoselectivity. The best result was obtained with the anomer α and for R = Me. (Table 1).

The configurational assignment for the epoxide ring in compounds **8** was assumed as *trans* ($J_{5,6}$ ~2) and with the absolute configuration 5*S*,6*R*, based on previous configurational studies done for other epoxyamides.[18] In order to assign this configuration, we carried out the catalytic transfer hydrogenation of **8cα**, to obtain the hemiacetal **9**, which was treated with aqueous periodic acid, following the method previously described.[18a] The obtained aldehyde solution gave a positive specific rotation, confirming the epoxide configuration as that of **10** (Scheme 3).

The regioselective epoxide opening of epoxyamides **8aα** or **8bα** gave 2-azido derivatives **11aα** or **11bα**, respectively (Scheme 4). Catalytic hydrogenation of **11aα** or **11bα** gave the corresponding azepane carboxamides **12a** or **12b**. The same sequence of reactions was followed with the β-series giving the same final products **12a** or **12b** from **8aβ** or **8bβ**. The β-anomers of epoxy compounds showed a significantly lower reactivity in the epoxide opening but azido **11aβ** or **11bβ** had similar behaviour with slightly lower yields. The NMR data for compounds β were clearly distinguishable from the α-series NMR data. Thus, in ^{13}C NMR, anomeric carbon signal is about 105.5 ppm in the α-series and about 102 ppm in the β-series. The signals corresponding to C-2 and C-4 are displaced to a higher field in the β compounds. Compounds α, δ ppm: C-2 (84.3–84.9), C-4 (78.9–79.8). Compounds β, δ ppm: C-2 (79.1–79.7), C-4 (75.9–77.2).



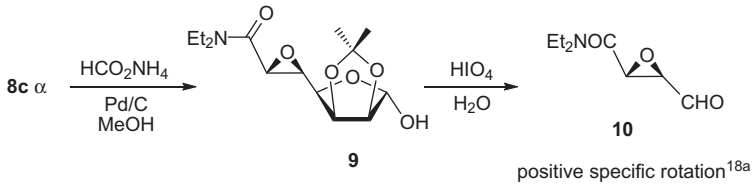
Scheme 2.

Deprotection of the isopropylidene group in **12a** or **12b** with aq. HCl/MeOH gave *N*,*N*-dimethyl or *N*,*N*-dibenzyl tetrahydroxy azepane carboxamides **3a** or **3b**. Reduction of the amide group with the complex BH_3–SMe_2, followed by acid hydrolysis, gave dimethyl or dibenzyl amino azepane derivatives **4a** or **4b**, as the principal products.

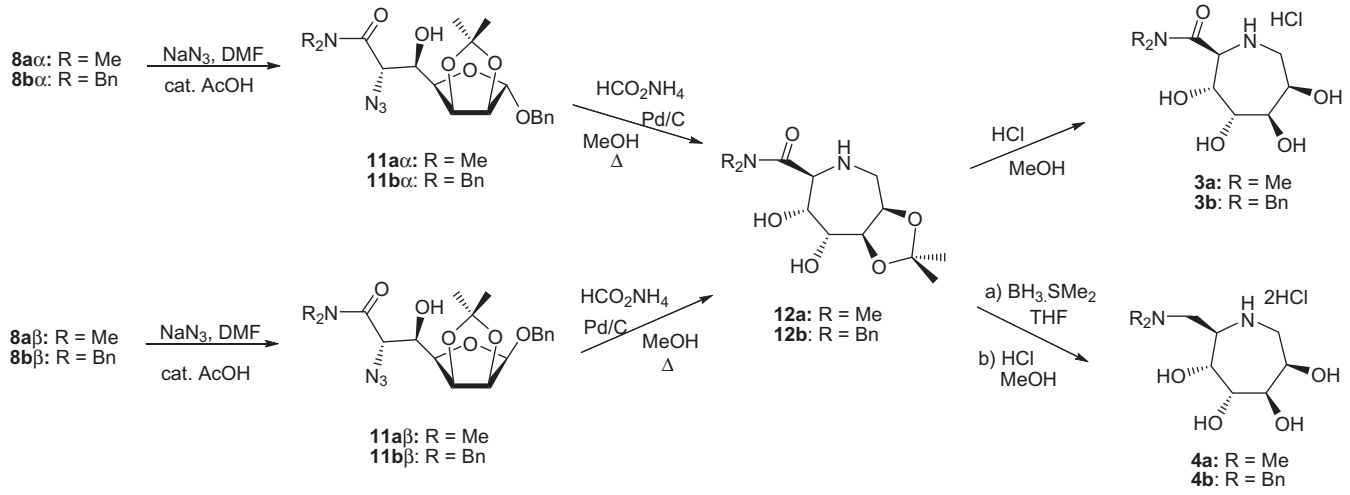
Table 1
Experimental conditions in the synthesis of epoxyamides

Entry	RCHO	Sulfonium salt (equiv) $Me_2S^+CH_2CONR_2$, Cl	*t* (min)	Product	Yield (%) (two steps)
1	**2α**	1.7, R = Me	40	**8aα**	82
2	**2α**	1.3, R = Bn	40	**8bα**	60
3	**2α**	1.2, R = Et	60	**8cα**	59
4	**2β**	2.0, R = Me	60	**8aβ**	59
5	**2β**	2.0, R = Bn	180	**8bβ**	65

Amounts for 1 mmol of starting diol **7α** or **7β**. The extraction solvent was CH_2Cl_2.



Scheme 3.



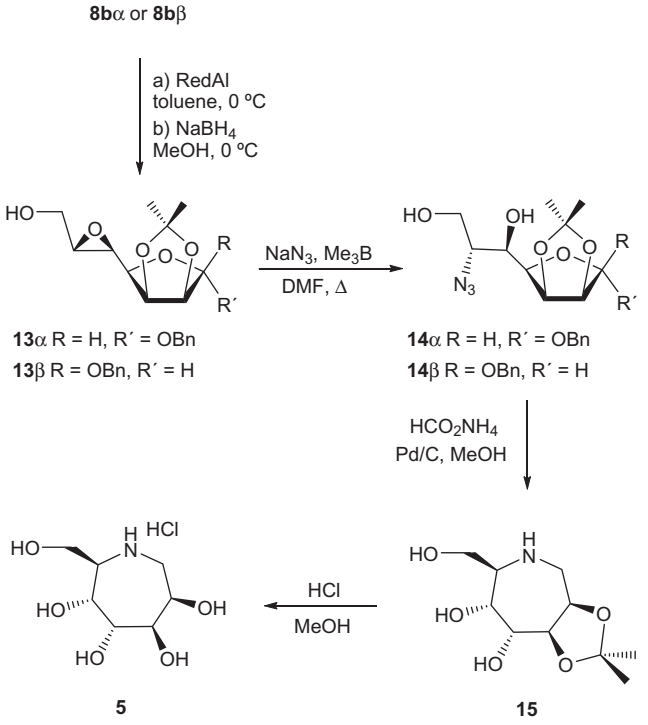
Scheme 4.

On the other hand, the reduction of epoxyamides **8bα** or **8bβ** with Red-Al® in THF at 0 °C, followed by treatment with $NaBH_4$ in MeOH, gave epoxy alcohols **13α** or **13β** (Scheme 5). Epoxide opening of **13α** or **13β** with NaN_3 gave, in a totally regioselective fashion, the azido derivatives **14α** or **14β**, respectively. Both compounds **14α** and **14β** gave the same azepane **15** by reduction with ammonium formate in the presence of 10% Pd/C. Hydrolysis of the isopropylidene group in compound **15**, with hydrochloric acid in methanol, gave the deprotected azepane **5** as its hydrochloride salt.

3. Inhibitory activities toward glycosidases

The novel 3,4,5,6-tetrahydroxyazepanes[19] **3a**, **3b**, **4a** and **5** have been assayed for their inhibitory activities towards α-D-galactosidase from coffee beans, β-D-galactosidase from *Escherichia coli* and from *Aspergillus orizae*, α-D-glucosidase from yeast and from rice, amyloglucosidase from *Aspergillus niger*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans, β-D-mannosidase from snail, β-D-xylosidase from *A. niger*, and towards β-D-*N*-acetylglucosaminidase from Jack beans and from bovine kidney. Except for **3a** which showed selective inhibition of the two latter enzymes (65% and 56%, respectively, at 1 mM concentration) none of these twelve glycosidases were inhibited by **3a**, **3b**, **4a** and **5** at 1 mM concentration and at optimal pH of the enzymes.

In the case of 2-(aminomethyl)pyrrolidine-3,4-diols,[20] 2-(aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diols[21] and conduramine derivatives[22] we had observed that *N*-alkyl or *N*-acyl substitution might generate more selective and more potent glycosidase inhibitors. This was also reported by Wong et al. for 1-(aminomethyl)-1-deoxy-L-fuconojirimycin.[23] In their pioneer work, Wong et al.[4] showed that 1,6-dideoxy-1,6-iminohexitol **16** with the D-*manno* configuration, as for our 3,4,5,6-tetrahydroxyazepane derivatives, is a weak inhibitor of α-D-glucosidase from yeast and of α-L-fucosidase from bovine kidney, but a good (K_i = 4.6 μM) inhibitor of β-D-*N*-acetylglucosaminidase from Jack bean. The inhibitory activity was reduced significantly, in this case, upon N-benzylation, but improved inhibitory activity towards α-L-fucosidase from bovine kidney (K_i = 23 μM) was found. It can be concluded (Table 2) that contrary to our initial hopes substitution of 1,6-dideoxy-1,6-iminohexitol **16** to generate derivatives **3a**, **3b**, **4a** and **5** does not enhance the glycosidase inhibitory activity, but improves the selectivity towards β-D-*N*-acetylglucosaminidase for the *N*,*N*-dimethyl carboxamido derivative **3a** only. In fact, upon substitution at C(6) of iminohexitol **16** by (6*S*)-**17** or (6*R*)-(hydroxymethyl) group **5**, by



Scheme 5.

(6*R*)-(dimethylaminomethyl) **4a**, or (6*R*)-(dibenzylaminomethyl) group **4b** compounds devoid of glycosidase inhibitory activity are obtained.

4. Conclusion

We have demonstrated the utility of D-mannose-derived epoxyamides in the synthesis of tetrahydroxylated azepane-2-carboxamides and 2-(aminomethyl)-3,4,5,6-tetrahydroxy-azepanes, using regioselective epoxide ring-opening protocol. The complete selectivity in the processes and the use of inexpensive and readily available reagents open up the possibility to scale up these procedures in order to obtain higher amounts of the intermediate products. The combination of two reducing agents: Red-Al® and $NaBH_4$, has been shown to be a good choice to obtain epoxyalcohols from carbohydrate-derived epoxyamides, leading to the preparation of the corresponding 1,6-dideoxy-1,6-iminoheptitols. With regards to epoxide ring opening by azides, the better method for epoxyamides was the combination of NaN_3 in DMF with a catalytic amount of AcOH, while terminal epoxyalcohols were more efficiently opened with NaN_3/Me_3B, leading to the exclusive formation of the corresponding 2-azidomethyl analogue. The novel *N*,*N*-dimethyl 3,4,5,6-tetrahydroxyazepane-2-carboxamide **3a** is a selective albeit modest inhibitor of β-*N*-acetylglucosaminidase from Jack bean and from bovine kidney.

5. Experimental

5.1. General

Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using UV light (254 nm) and/or heating with phosphomolybdic acid/cerium sulfate(IV)/H_2SO_4 aq solution. Flash chromatography was performed on E. Merck Silica Gel (60, particle size 0.040–0.063 mm). NMR spectra were recorded on a Bruker Avance-400 or WP200SY spectrometers at room temperature. Chemical shifts (ppm) are reported relative to the residual solvent peak. Multiplicities are designated as: singlet (s), doublet (d), triplet (t), multiplet (m) and br (broad). Coupling constants *J* are expressed in hertz units. NMR assignments were undertaken based on two-dimensional COSY and gHMQC experiments. IR spectra of the azido compounds showed the N_3 typical band at 2324–2352 cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded with a Micromass AutoSpecQ instrument of the University of Granada.

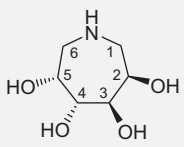
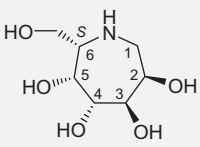
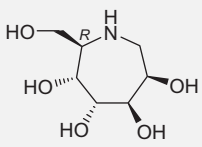
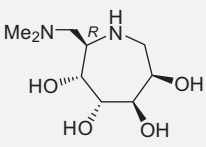
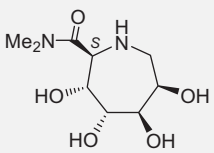
5.2. Benzyl 2,3:5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranose 6α and 6β

To a cooled solution (0 °C) of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (1.5 g, 5.76 mmol) and BnBr (2.4 mL, 20 mmol) in anhyd DMF (7.5 mL) was slowly added NaH (60% mineral oil, 1.2 g, 50 mmol). The reaction is monitored by TLC (1:1, Hex/AcOEt). After 2 h at 0 °C, the mixture is left at rt for 10 h. Then, MeOH (15 mL) and toluene (50 mL) were added. The mixture is filtered through Celite and the filtrates washed with aq $NaHCO_3$ and satd NH_4Cl. Organic solvents are evaporated and the residue is purified by column chromatography to afford **6α** (1.02 g) and **6β** (0.25 g). Total yield: 63%. NMR data of compound **6β** are not described in the literature: ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.31–7.19 (m, 5H, Ph), 4.84 (m, 1H), 4.68–4.58 (m, 3H), 4.51 (m, 1H), 4.39 (m, 1H), 4.02 (dd, 2H), 3.50 (m, 1H), 1.49 and 1.37 (2s, 2 × 3H, C*Me*$_2$) 1.31 and 1.29 (2s, 2 × 3H, C*Me*$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 136.9–127.5 (Ph), 113.3 and 108.8 (2CMe_2), 100.9 (C-1), 79.4, 78.8 and 76.8 (C-2, C-3 and C-4), 73.0, 71.1 66.5 (C-5, C-6 and CH_2Ph), 26.7, 25.4, 25.0 and 24.8 (2C*Me*$_2$).

5.3. Benzyl 2,3-*O*-isopropylidene-β-D-mannofuranose 7β

Compound **6β** (442 mg, 1.26 mmol) was dissolved in 80% acetic acid (50 ml), heated for 3 h (35 °C) and evaporated to dryness. The residue was purified by column chromatography (AcOEt 100%), to

Table 2
Percentage of inhibition of β-D-*N*-acetylglucosaminidase from Jack bean at 1 mM concentration of various D-*manno*-1,6-dideoxy-1,6-iminohexitols derivatives (NI = no inhibition, NR: not reported)

				
16	**17**	**5**	**4a**	**3a**
89%	NR[a]	NI	NI	65%

[a] This compound is a very weak, but selective inhibitor of α-L-fucosidase (IC_{50} = 1.7 mM).[15b]

obtain compound **7β** (265 mg, 80%). R_f: 0.5 (AcOEt 100%) ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 7.40–7.25 (m, 5H, Ph), 4.77–4.91 (m, 4H), 4.16–4.04 (m, 2H), 3.86 (dd, 1H), 3.78–3.67 (m, 2H), 2.48 (s, 2H), 1.56 and 1.37 (2s, 3H, C*Me*$_2$). ^{13}C NMR ($CDCl_3$, 50 MHz, δ ppm): 136.8–127.4 (Ph), 113.5 (C*Me*$_2$), 100.8 (C-1), 79.4, 79.1 and 75.9 (C-2, C-3 and C-4), 70.9 and 69.6 (C-5 and CH_2Ph), 63.7 (C-6), 25.3 and 25.0 (C*Me*$_2$).

5.4. Typical procedure for epoxyamides

The crude aldehyde obtained from diol **7α** (4.45 g, 14.33 mmol) by periodic oxidation[17] was dissolved in dichloromethane (100 mL) and the sulfonium salt $Me_2S^+CH_2CONMe_2{\cdot}Cl$ (4.55 g, 24.8 mmol) and 40% aq NaOH (50 mL) were added. The reaction mixture was stirred at room temperature and monitored by TLC. After 40 min, water (10 mL) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 × 15 mL) and the organic layers were washed with water, dried with sodium sulfate and evaporated in vacuo to obtain epoxide as a syrup which was purified by column chromatography to afford pure **8aα** (4.27 g, 82%, two steps). R_f 0.2 (1:1, Hex/AcOEt). $[\alpha]_D^{17} = +31$ (*c* 0.52, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.36–7.24 (m, 5H, Ph), 5.08 (s, 1H, H-1), 4.82 (dd, 1H, *J* = 3.7, 5.9, H-3), 4.66 (d, 1H, *J* = 5.9, H-2), 4.62 and 49.3 (2d, 2 × 1H, *J* = 11.8, CH_2Ph), 3.90 (dd, 1H, *J* = 4.8, 3.76, H-4), 3.62 (d, 1H, *J* = 2.1, H-6), 3.48 (dd, 1H, *J* = 2.1, H-5), 3.12 and 2.97 (2s, 2 × 3H, NMe_2) 1.42 and 1.30 (s, 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 50 MHz, δ ppm): 166.1 (CO), 136.9–127.3 (Ph), 112.3 (CMe_2), 105.3 (C-1), 84.6 (C-2), 79.2 (C-3), 78.4 (C-4), 68.8 (CH_2Ph), 54.0 (C-5), 51.4 (C-6), 35.8 and 35.0 (NMe_2), 25.5 and 24.0 (CMe_2). (FAB): *m*/*z* 386.1591 $[M+Na]^+$ ($C_{19}H_{25}NO_6Na$ requires 386.1579). The same procedure was carried out with **2α** and **2β** to obtain **8bα** and **8bβ** (Table 1). Epoxyamide **8bα** had R_f 0.3 (3:1, Hex/AcOEt). $[\alpha]_D^{17} = +42$ (*c* 0.82, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.45–7.12 (m, 15H, 3Ph), 4.99 (s, 1H, H-1), 4.77 (dd, 1H, *J* = 3.8, 5.4, H-3), 4.76, 4.39, 4.47, 4.43, 4.35 and 4.32 (6d, 6 × 1H, *J* = 14.5, 16.6, 11.8, 3CH_2Ph), 4.59 (d, 1H, *J* = 5.4, H-2), 3.77 (dd, 1H, *J* = 3.8, 5.4, H-4), 3.64 (d, 1H, *J* = 2.1, H-6), 3.60 (dd, 1H, *J* = 2.1, 5.4, H-5), 1.33 and 1.24 [2s, 2 × 3H, 2CMe_2]. ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 167.3 (CO), 137.1, 136.5, 135.9 and 129–126 (3Ph), 112.9 [CMe_2], 105.6 (C-1), 85.1 (C-2), 79.7 (C-3), 79.1 (C-4), 69.2 (CH_2Ph), 54.9 (C-5), 52.2 (C-6) 49.0 and 48.2 (2NCH_2), 25.7 and 24.2 [CMe_2]. HRMS (FAB): *m*/*z* 516.2385 $[M+H]^+$ ($C_{31}H_{34}NO_6$ requires 516.2386). Compound **8bβ** had R_f 0.4 (1:1, Hex/AcOEt). $[\alpha]_D^{17} = -2$ (*c* 1.68, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm). 7.33–7.14 (m, 15H, 3Ph), 5.01 (s, 1H), 4.78–4.74 (m, 2H), 4.66 (d, 1H), 4.59 (d, 1H), 4.45 (t, 2H), 4.34 (dd, 2H), 3.78 (dd, 1H), 3.65 (d, 1H), 3.60 (dd, 1H), 1.33 and 1.24 (2s, 2 × 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 167.2 (CO), 136.8–126.7 (3Ph), 114.1 (CMe_2), 100.9 (C-1), 79.7, 79.1 and 75.9 (C-2, C-3 and C-4), 71.0 (CH_2Ph), 55.4, 51.9, 48.8 and 47.9 (2NCH_2, C-5 and C-6), 25.5 and 25.0 (CMe_2). HRMS (FAB): *m*/*z* 516.2384 $[M+H]^+$ ($C_{31}H_{34}NO_6$ requires 516.2386).

5.5. Debenzylation of epoxyamide 8cα and periodic oxidation of 9c: (2*R*,3*R*)-*N*,*N*-diethyl-3-formyl-2-oxirane carboxamide 10

To a solution of **8cα** (620 mg, 1.58 mmol) in MeOH (15 mL) were added 10% Pd/C (130 mg) and ammonium formate (0.80 g), and the mixture was refluxed for 3 h. The reaction mixture was filtered through Celite and the filtrate was evaporated and the residue was purified by column chromatography to give crude **9**. Purification by flash column chromatography (AcOEt 100%) gave pure **9**. A portion of hemiacetal **9** (80 mg) was placed in an NMR tube with D_2O and HIO_4 (484 mg, 8 equiv). The reaction was monitored by ^{1}H NMR and ^{13}C NMR and after a day, it was judged to be complete. The NMR data and positive specific rotation were concordant with those of **10**.[18a]

5.6. Epoxide opening with NaN_3 in epoxyamides: *N*,*N*-dimethyl-6-azido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-D-glycero-α-D-manno-heptofuranuronamide 11aα

To a solution of epoxyamide **8aα** (3.06 g, 8.42 mmol) in DMF (29.3 mL) were added NaN_3 (1.08 g, 16.61 mmol) and AcOH (0.48 mL). The reaction mixture was heated (95 °C) with stirring under argon for 2 d and monitored by TLC, after which the reaction was judged complete. The mixture was eluted with AcOEt and washed with aq. NH_4Cl and then with water. The organic layer was dried ($MgSO_4$) and solvents evaporated under vacuo. Purification by column chromatography gave **11aα** (2.45 g, 72% yield) as a colourless solid. Compound **11aα** had R_f: 0.3 (2:1, Hex/AcOEt), mp: 129–130 °C. $[\alpha]_D^{17} = +101$ (*c* 0.98, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.30–7.18 (m, 5H, Ph), 5.00 (s, 1H, H-1), 4.85 (dd, 1H, *J* = 3.8, 5.9, H-3), 4.57 (d, 1H, *J* = 5.9, H-2), 4.47 and 4.33 (2d, 2 × 1H, CH_2Ph), 4.41 (dd, 1H, *J* = 3.8, 9.1, H-4), 3.99 (d, 1H, *J* = 3.7, H-2), 3.93 (dd, 1H, *J* = 3.7, 9.1, H-5), 3.07 and 2.93 (2s, 2 × 3H, NMe_2), 1.41 and 1.27 (2s, 2 × 3H, CMe_2), ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.3 (CO), 136.6–127.5 (Ph), 112.4 [$C(CH_3)_2$], 105.2 (C-1), 84.3 (C-2), 80.1 (C-3), 79.3 (C-4), 71.4 (CH_2Ph), 68.4 (C-6), 55.5 (C-5), 37.1 and 35.1 (NMe_2), 25.7 and 24.3 (CMe_2). HRMS (FAB): *m*/*z* 407.1866 $[M+H]^+$ ($C_{19}H_{27}N_4O_6$ requires 407.1852).

5.7. *N*,*N*-Dibenzyl 6-azido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-D-glycero-α-D-manno-heptofuranuronamide 11bα

To a solution of the epoxyamide **8bα** (0.74 g, 1.43 mmol) in DMF (5 mL) were added NaN_3 (0.19 g, 2.92 mmol) and AcOH (0.08 mL, 1.43 mmol). The reaction mixture was heated (95 °C) with stirring under argon for 2 d and monitored by TLC, after which the reaction was judged complete. The mixture was eluted with AcOEt and washed with aq NH_4Cl and then with water. The organic layer was dried ($MgSO_4$) and solvents evaporated under vacuo. Purification by column chromatography gave **11bα** (0.65 g, 81% yield). Compound **11bα** had R_f 0.6 (3:1, Hex/AcOEt). $[\alpha]_D^{17} = -31$ (*c* 0.86, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.32–7.16 (m, 15H, 3Ph), 5.02 (s, 1H), 4.88 (dd, 1H), 4.63–4.49 (m, 6H), 4.44 (d, 1H), 4.27 (d, 1H), 4.15 (dd, 1H), 4.07 (d, 1H), 1.38 (s, 3H, $C(CH_3)_2$) and 1.27 (s, 3H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.9 (CO), 136.8–127.0 (Ph), 112.7 [$C(CH_3)_2$], 105.5 (C-1), 84.5, 80.3 and 79.8 (C-2, C-3 and C-4), 71.9 and 68.9 (C-5 and CH_2Ph), 57.1 (C-6), 49.9 and 47.9 (2NCH_2), 25.9 and 24.4 [CMe_2]. HRMS (FAB): *m*/*z* 559.2555 $[M+H]^+$ ($C_{31}H_{35}N_4O_6$ requires 559.2556). The same procedure was carried out with **8bβ** to obtain **11bβ**. Compound **11bβ** had R_f 0.5 (3:1, Hex/AcOEt). $[\alpha]_D^{17} = +35$ (*c* 2.2, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 7.33–7.13 (m, 15H, 3Ph), 4.82–4.78 (m, 2H), 4.70 (d, 1H), 4.64 (d, 1H), 4.60 (s, 1H), 4.56 (dd, 1H), 4.52–4.43 (m, 5H), 3.97 (d, 1H), 3.70 (dd, 1H), 1.50 and 1.31 (2s, 2 × 3H, C*Me*$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 170.0 (CO), 137.0–126.7 (3Ph), 113.8 (C*Me*$_2$), 102.0 (C-1), 79.3, 79.0 and 77.2 (C-2, C-3 and C-4), 72.0 and 71.7 (C-5 and CH_2Ph), 56.3 (C-6), 49.8 and 47.7 (2NCH_2), 25.6 and 25.0 (C*Me*$_2$). HRMS (FAB): *m*/*z* 559.2553 $[M+H]^+$ ($C_{31}H_{35}N_4O_6$ requires 559.2556).

5.8. *N*,*N*-Dimethyl-1,6-dideoxy-1,6-imino-2,3-*O*-isopropylidene-D-glycero-D-manno-heptonamide 12a

To a solution of azide **11aα** (282 mg, 0.69 mmol) in MeOH (51 mL), were added 10% Pd/C (170 mg) and ammonium formate (0.76 g, 12.05 mmol), and the mixture was refluxed for 3 d. The

reaction mixture was filtered through Celite, the filtrate evaporated and the residue purified by column chromatography to give **12a** as a white solid (147 mg, 77%). R_f: 0.6 (AcOEt), mp: 170 °C (dec). $[\alpha]_D^{17} = +10$ (*c* 1.05, MeOH). ^{1}H NMR (D_2O, 400 MHz, δ ppm): 4.30 (m, 2H, H-2,3), 4.08 (br s, 1H, H-5), 3.93 (d, 1H, *J* = 9.7), 3.78 (d, 1H, *J* = 9.7,), 2.95 (m, 2H), 2.98 and 2.79 (2s, 2 × 3H, N*Me*$_2$), 1.38 and 1.23 (2s, 2 × 3H, C*Me*$_2$). ^{13}C NMR (D_2O, 100 MHz, δ ppm): 173.6 (CO), 108.1 (*C*Me$_2$), 76.1, 74.8, 74.6 and 71.9 (C-2, C-3, C-4 and C-5), 56.3 (C-6), 44.8 (C-1), 37.5 and 35.5 (N*Me*$_2$), 24.9 and 22.5 (C*Me*$_2$). HRMS (FAB): *m*/*z* 275.1528 $[M+1]^+$ ($C_{12}H_{23}N_2O_5$ requires 275.1524).

5.9. *N*,*N*-Dibenzyl-1,6-dideoxy-1,6-imino-2,3-*O*-isopropylidene-D-glycero-D-manno-heptonamide 12b

To a solution of azide **11bα** (100 mg, 0.179 mmol) in MeOH (15 mL) were added 10% Pd/C (50 mg) and ammonium formate (0.220 g, 3.49 mmol), and the mixture was refluxed for 2 d. The reaction mixture was filtered through Celite and the filtrate was evaporated and the residue purified by column chromatography to give **12b** as a white solid (59 mg, 69%). R_f: 0.64 (AcOEt 100%); mp: 118 °C. $[\alpha]_D^{17} = -25$ (*c* 0.93, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.35–7.10, (m, 10H, Ph), 4.71 (m, 2H, NC*H*$_2$Ph), 4.58 (d, 1H, NC*H*$_2$Ph), 4.31 and 4.20 (2 m, 2 × 3H), 3.8 (m, 1H), 3.20 and 2.98 (dd and br d, 2 × 1H, *J* = 3.2 and 15.6, C*H*$_2$NH), 1.48 and 1.30 (2s, 2 × 3H, C*Me*$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 173.6 (CO), 136.6–127.1 (Ph), 107.3 [*C*(CH$_3$)$_2$], 76.8, 75.5, 75.0, 72.5, 58.8 (NCHCO), 49.8 and 47.4 (2NCH$_2$Ph), 46.7 (*C*H$_2$NH), 26.1 and 23.5 (C*Me*$_2$). HRMS (FAB): *m*/*z* 449.2053 $[M+Na]^+$ ($C_{24}H_{30}N_2O_5Na$ requires 449.2052).

5.10. *N*,*N*-Dimethyl-1,6-dideoxy-1,6-imino-D-glycero-D-manno-heptonamide chlorhydrate 3a

A solution of azepane **12a** (60 mg, 0.22 mmol) in MeOH (4 mL) with 10% HCl (2 mL) was left for 3 d at rt. The mixture was concentrated under vacuo to give **3a** as yellowish syrup (59.3 mg, 100%). R_f: 0.3 (3:2 AcOEt/MeOH). $[\alpha]_D^{30} = +9$ (*c* 1.2, MeOH). ^{1}H NMR (D_2O, 400 MHz, δ ppm): 4.38 (d, 1H), 4.03 (d, 2H), 3.72 (d, 1H), 3.66 (d, 1H), 3.19 (d, 2H), 2.85 (s, 3H, NCH$_3$), and 2.71 (s, 3H, NCH$_3$). ^{13}C NMR (D_2O, 100 MHz, δ ppm): 166.4 (CO), 71.5, 71.1, 68.9 and 64.8 (C-2, C-3, C-4 and C-5), 55.7 (C-6), 43.8 (C-1), 36.7 and 35.4 (2NCH$_3$). HRMS (FAB): (as free amine): *m*/*z* 235.1290 $[M+1]^+$ ($C_9H_{19}N_2O_5$ requires 235.1294).

5.11. *N*,*N*-Dibenzyl 1,6-dideoxy-1,6-imino-D-glycero-D-manno-heptonamide chlorhydrate 3b

A solution of azepane **7b** (80 mg, 0.187 mmol) in MeOH (4 mL) with 10% HCl (2 mL) was left for 3 d at rt. The mixture was concentrated under vacuo to give **3b** as a white solid (79 mg, 100%). R_f: 0.5 (4:1 AcOEt/MeOH); mp: 60 °C. $[\alpha]_D^{28} = -27$ (*c* 1.1, MeOH). ^{1}H NMR (D_2O, 200 MHz, δ ppm): 7.24–7.03 (m, 10H, 2Ph), 4.89–4.66 (m, 2H), 4.26 (d, 2H), 4.20–4.02 (m, 2H), 3.92 (d, 1H), 3.76 (dd, 2H), 3.21 (dd, 1H), 2.90 (dd, 1H). ^{13}C NMR (D_2O, 50 MHz, δ ppm): 169.6 (CO), 136.8–127.9 (Ph), 73.7, 73.6, 70.2 and 66.2 (C-2, C-3, C-4 and C-5), 56.9 (C-6), 51.7 and 51.2 (2NCH$_2$) and 45.3 (C-1). HRMS (FAB): (as free amine): *m*/*z* 387.1922 $[M+H]^+$ ($C_{21}H_{27}N_2O_5$ requires 387.192).

5.12. 7-*N*-Dimethylamino-1,6,7-trideoxy-1,6-imino-D-glycero-D-manno-heptitol dichlorhydrate 4a

To a solution of azepane **12a** (80 mg, 0.29 mmol) in THF (5 mL) was added $BH_3{\cdot}SMe_2$ (0.0.28 mL, 2.95 mmol). The reaction mixture was heated (60 °C) for 1 d, quenched with EtOH and evaporated to dryness. Then, MeOH (4 mL) and 10% HCl (2 mL) were added with stirring and left for 3 d, after which the mixture is concentrated and purified by column chromatography to give amino azepane **4a** as a pale yellow solid (81 mg, 94%). XPS (X-ray photoelectron spectroscopy): $C_9H_{22}Cl_2N_2O_4$ (for 2HCl). R_f: 0.3 (4:1 AcOEt/MeOH); R_f: 0.2 (2:1 AcOEt/MeOH), mp: dec; $[\alpha]_D^{17} = +19$ (*c* 1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz, δ ppm): 4.18 (d, 1H), 3.98 (dd, *J* = 10.75, 3.22, 1H), 3.91 (dd, *J* = 5.37, 1H), 3.87 (dd, *J* = 5.37, 1H), 3.50 (m, 3H), 3.38 (m, 1H), 3.24 (br s, 3H), 2.78 and 2.77 (2s, NMe$_2$), 2.85 and 2.80 (2 m, 2H), 2.50 (d, *J* = 13.9). ^{13}C NMR (D_2O, 100 MHz, δ ppm): 74.3, 70.7, 67.1 and 66.7 (C-2, C-3, C-4 and C-5), 63.8 (C-7), 54.2 (C-6), 49.4 (C-1), 48.4 and 47.7 (2NCH$_3$). Compound **4a** (2HCl) was treated with ammonia to give the free amine **4a** with HRMS (FAB): *m*/*z* 221.1499 $[M+H]^+$ ($C_9H_{21}N_2O_4$ requires 221.1501).

5.13. 7-*N*-Dibenzylamino-1,6,7-trideoxy-1,6-imino-D-glycero-D-manno-heptitol dichlorhydrate 4b

To a solution of azepane **12b** (48 mg, 0.11 mmol) in THF (5 mL) was added $BH_3{\cdot}SMe_2$ (0.10 mL, 1.05 mmol). The reaction mixture was heated (60 °C) for 1 d, quenched with EtOH and evaporated to dryness. Then, MeOH (4 mL) and 10% HCl (2 mL) were added with stirring and left for 3 d, after which the mixture was concentrated and purified by column chromatography to give **4b** as a yellowish syrup (34 mg, 68%). R_f: 0.3 (4:1 AcOEt/MeOH). $[\alpha]_D^{20} = -3$ (*c* 0.85, MeOH). ^{1}H NMR (CD_3OD, 400 MHz, δ ppm): 7.41–7.16 (m, 10H, 2Ph), 4.00–3.72 (m, 3H), 3.46, 3.59 (m, 2H), 3.26 (d, 2H), 2.99–2.50 (m, 2H). ^{13}C NMR (CD_3OD, 100 MHz, δ ppm): 138.5–128.8 (Ph), 74.9, 72.4, 69.3 and 67.4 (C-2, C-3, C-4 and C-5), 59.2 (2NCH$_2$), 56.3 and 53.4 (C-6 and C-7), 44.3 (C-1). HRMS (as free amine): *m*/*z* 373.2125 $[M+H]^+$ ($C_{21}H_{29}N_2O_4$ requires 373.2127).

5.14. 5,6-Anhydro-1-*O*-benzyl-2,3-*O*-isopropylidene-D-glycero-α-D-manno-heptofuranose 13α

A 70% Red-Al® solution in toluene (0.21 mL, 0.73 mmol) was added dropwise to a solution of **8bα** (339 mg, 0.66 mmol) in THF (7.4 mL) at 0 °C. After stirring for 35 min, ethyl acetate was added followed by a solution of aqueous sodium potassium tartrate and the mixture was stirred for a further 15 min. The reaction mixture was extracted with AcOEt, dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and then carried to the next step without purification. R_f: 0.3 (3:1, Hex/AcOEt). The obtained aldehyde (yellowish syrup) was dissolved in dry MeOH (5 mL), cooled at 0 °C and treated with $NaBH_4$ (13 mg, 0.34 mmol). After stirring for 20 min, the reaction was quenched with several drops of water and concentrated under reduced pressure. The residue was purified by column chromatography to give **13α** (168 mg, 80%, two steps) as a colourless oil. R_f: 0.2 (2:1, Hex/AcOEt). $[\alpha]_D^{21} = +41$ (*c* 1.26, CH_2Cl_2).^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 7.44–7.26 (m, 5H, Ph), 5.12 (s, 1H), 4.84 (dd, 1H), 4.69–4.45 (m, 4H), 3.97 (dd, 1H), 3.86 (dd, 1H), 3.70 (dd, 1H), 3.33 (dd, 1H), 3.21 (m, 1H), 1.47 (s, 3H, CMe$_2$) and 1.32 (s, 3H, CMe$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 137.1–127.7 (Ph), 112.6 [CMe$_2$], 105.5 (C-1), 84.8, 79.8 and 79.0 (C-2, C-3 and C-4), 69.0 (CH$_2$Ph), 61.3 (C-7), 57.2 and 52.3 (C-5 and C-6), 25.8 and 24.4 [CMe$_2$]. The same procedure was carried out with **8bβ** to obtain **13β** (97%, two steps). Compound **13β** had R_f 0.3 (1:2, Hex/AcOEt). $[\alpha]_D^{21} = -37$ (*c* 0.22, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 7.40–7.21 (m, 5H, Ph), 4.95–4.59 (m, 5H), 3.95 (dd, 1H), 3.82 (s, 1H), 3.70–3.51 (m, 2H), 3.39 (dd, 1H), 3.26 (ddd, 1H), 1.57 and 1.37 (2s, 2 × 3H, CMe$_2$). ^{13}C NMR ($CDCl_3$, 50 MHz, δ ppm): 139.4–126.7 (Ph), 113.8 (CMe$_2$), 100.9 (C-1), 79.5, 79.2 and 76.5 (C-2, C-3 and C-4), 70.9 (CH$_2$Ph), 61.2 (C-7), 57.4 and 52.5 (C-5 and C-6), 25.5 and 25.0 (CMe$_2$). HRMS (FAB): *m*/*z* 323.1490 $[M+H]^+$ ($C_{17}H_{23}O_6$ requires 323.1494).

5.15. 6-Azido-1-*O*-benzyl-2,3-*O*-isopropylidene-D-glycero-α-D-manno-heptofuranose 14α

To a stirred solution of **13α** (536 mg, 1.66 mmol) in DMF (16 mL) were added NaN_3 (0.20 mg, 3.08 mmol) and Me_3B (0.37 mL, 3.32 mmol). The reaction mixture was heated at 70 °C and monitored by TLC. After 2 d, aqueous $NaHCO_3$ was added portionwise at 0 °C and the mixture was stirred for 30 min and then extracted with AcOEt. The combined organic extracts were dried (anhyd $MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:1, Hex/AcOEt), to give **14α** (495 mg, 82%) as a colourless oil. R_f: 0.5 (3:2, Hex/AcOEt). $[\alpha]_D^{19} = +59$ (*c* 1.08, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.31–7.20 (m, 5H, Ph), 5.07 (s, 1H), 4.83 (dd, 1H), 4.60 (m, 2H), 4.43 (d, 1H), 4.12–4.03 (m, 3H), 3.82 (m, 2H), 3.68 (q, 1H), 3.22 (d, 1H), 1.42 and 1.27 (2s, 2 × 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 136.8–127.6 (Ph), 112.4 (CMe_2), 105.2 (C-1), 84.3, 79.9 and 78.3 (C-2, C-3 and C-4), 70.1, 68.9, 64.7 and 61.7 (CH_2Ph, C-5, C-6 and C-7), 25.6 and 24.2 (CMe_2). The same procedure was carried out with **13β** to obtain **14β** (%). R_f: 0.4. $[\alpha]_D^{17} = -59$ (*c* 1.28, CH_2Cl_2) (1:2, Hex/AcOEt) ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 7.51–7.24 (m, 5H, Ph), 4.91–4.51 (m, 5H), 4.24 (dd, 1H), 3.89–3.73 (m, 4H), 4.43 (d, 1H), 1.56 and 1.37 (2s, 2 × 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 50 MHz, δ ppm): 136.8–127.3 (Ph), 114.0 (CMe_2), 101.1 (C-1), 79.5, 79.4 and 75.8 (C-2, C-3 and C-4), 71.4, 71.0, 64.5 and 61.8 (CH_2Ph, C-5, C-6 and C-7), 25.5 and 25.1 (CMe_2). HRMS (FAB): *m*/*z* 366.1665 $[M+H]^+$ ($C_{17}H_{24}N_3O_6$ requires 366.1665).

5.16. 1,6-Dideoxy-1,6-imino-2,3-*O*-isopropylidene-D-glycero-D-manno-heptitol 15

To a stirred solution of **14α** (495 mg, 1.36 mmol) in MeOH (100 mL) were added ammonium formate (1.5 g, 23. 8 mmol) and 10% Pd/C (0.34 g). The reaction mixture was refluxed for 3 d and then filtered with Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography (4:1, Hex/AcOEt), to give **15** (315 mg, 99%) as a colourless oil. R_f: 0.3 (4:1, AcOEt/MeOH). $[\alpha]_D^{19} = +4$ (*c* 1.28, MeOH). ^1H NMR (D_2O, 400 MHz, δ ppm): 4.31 (t, 1H), 4.00 (d, 1H), 3.80 (d, 1H), 3.74 (dd, 1H), 3.66 (dd, 1H), 3.35–3.21 (m, 3H), 3.15 (s, 3H), 1.35 [s, 3H, $C(CH_3)_2$] and 1.22 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (D_2O, 100 MHz, δ ppm): 109.0 [$C(CH_3)_2$], 75.1, 73.5, 72.1 and 67.7 (C-2, C-3, C-4 and C-5), 59.4 and 58.9 (C-6 and C-7), 43.8 (C-1), 25.2 and 22.9 [$C(CH_3)_2$]. HRMS (FAB): *m*/*z* 234.1342 $[M + H]^+$ ($C_{10}H_{20}NO_5$ requires 234.1341).

5.17. 1,6-Dideoxy-1,6-imino-D-glycero-D-manno-heptitol chlorhydrate 5

To a stirred solution of **15** (150 mg, 0.64 mmol) in MeOH (4 mL) was added a 10% aqueous solution of HCl (2 mL). After 2 d, the reaction mixture was concentrated under reduced pressure to give chlorhydrate **5** (147 mg, 100%). R_f: 0.1 (4:1 AcOEt/MeOH). $[\alpha]_D^{22} = +2$ (*c* 1.65, MeOH/H_2O 1:1). ^1H NMR (D_2O, 400 MHz, δ ppm**):** 4.04 (m, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 3.73–3.56 (m, 2H) and 3.29–3.01 (m, 4H). ^{13}C NMR (D_2O, 100 MHz, δ ppm): 69.4, 69.2, 66.9 and 65.4 (C-2, C-3, C-4 and C-5), 58.9 and 58.8 (C-6 and C-7) and 44.6 (C-1). HRMS (as free amine): *m*/*z* 194.1028 $[M+H]^+$ ($C_7H_{16}NO_5$ requires 194.1028).

5.18. Glycosidase inhibition assays

The experiments were performed essentially as previously described.[24] Briefly, 0.01–0.5 units/mL of enzyme (1 unit = 1 μmol of glycoside hydrolyzed/min), pre-incubated for 5 min at 20 °C with the inhibitor, and increasing concentration of aqueous solution of the appropriate *p*-nitrophenyl glycoside substrates buffered to the optimal pH of the enzyme were incubated for 20 min at 37 °C (45 °C for the amyloglucosidases). The reaction was stopped by the addition of a 2.5 volume of 0.2 M sodium borate buffer pH 9.8. The *p*-nitrophenolate formed was quantified at 410 nm.

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