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Synthesis of intermediates in the formation of hydroxy piperidines and 2-azido lactones from D-erythrose

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Abstract—A new stereodivergent synthesis towards piperidine iminosugar and azido lactones is described. The reaction of ethylidene-D-erythrose with amide sulfur ylides gave two isomeric *trans*-epoxyamides which were converted to 2-azido derivatives. Hydrolysis of the *allo* isomer gave 2-azido-1,4-lactone while the *manno* isomer gave the open chain epoxyamide. The latter gave a DMJ derivative in two steps. Direct hydrolysis of ethylidene epoxyamides gave the 3,6-anhydro glyconamides.

1. Introduction

Hydroxylated piperidines have attracted increasing interest as synthetic targets because of their important activity as medicinally active compounds.[1] These carbohydrate mimics are among the most known iminosugars. Deoxymannojirimycin (DMJ) **1**, isolated from natural sources,[2] has been shown to inhibit α-L-fucosidase, α-D-mannosidase and α-D-glucosidase activities,[3] and therefore various methods have been developed to improve its synthesis.[4] Later, it has been reported that l-*allo*-DNJ (l-deoxyallonojirimycin) **2** is a better inhibitor than DMJ of both plant and lysosomal α-mannosidases.[5] Although several efficient syntheses towards these piperidines have been described, most of them involve long processes.[6]

On the other hand, 2-azido lactones can have several applications. They have been shown to be key compounds in the synthesis of pyrrolidine iminosugars.[7] Some of these hydroxylated pyrrolidines showed selective inhibition of glycosidases.[8] In addition, 2-azido lactones are masked amino acids and can be useful for novel amino acid preparation.[9a] Finally, they may be related to 2-azido monosaccharides, which allow greater selectivity for glycosylation reactions.[9b]

In previous papers,[10] we have described a methodology to synthesize iminosugar derivatives with different ring sizes starting from a ribose derivative, which gave an unique 2,3-epoxyamide. Now, our objective is to extend the strategy to different monosaccharides, in order to develop short and efficient routes to prepare different iminosugars. The use of a tetrose as a starting material would lead to piperidine iminosugars.

2. Results and discussion

Herein we report the synthesis of potential precursors of DMJ and l-*allo*-DNJ derivatives. We envisioned a retrosynthetic strategy whereby the starting monosaccharide might have the proper configuration in order to obtain both the D-*manno* and l-*allo* piperidine frameworks. Ethylidene-D-erythrose **3** was the monosaccharide derivative chosen (Scheme 1). The reaction of its epimer, ethylidene D-threose, with ylide **4** (R = Me) was described to be moderately stereoselective, yielding the two *trans*-isomers in a 3:2 rate, and (2*R*,3*S*) being the configuration of the predominant isomer.[11a,c] In a similar way, ethylidene-D-erythrose should lead to a mixture of stereoisomers with a predictable configuration of the predominant (2*S*,3*R*)-isomer. Previous configurational studies have been carried out for other epoxyamides.[11a,b,d,e] In other cases,[11f,g] configuration was assigned by comparison with NMR data of related compounds obtained by Sharpless asymmetric epoxidation.

Ethylidene D-erythrose **3**, obtained by periodate oxidation of ethylidene D-glucose **5**,[12] was converted by the

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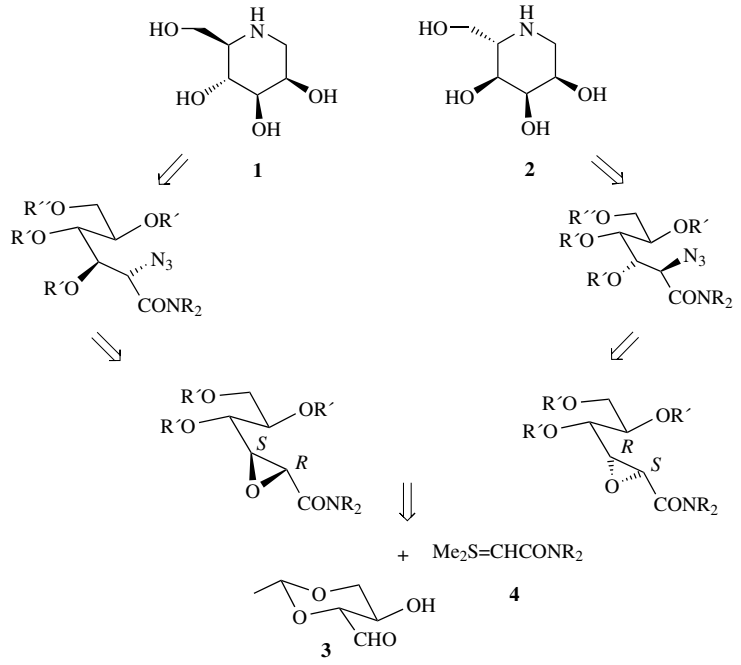
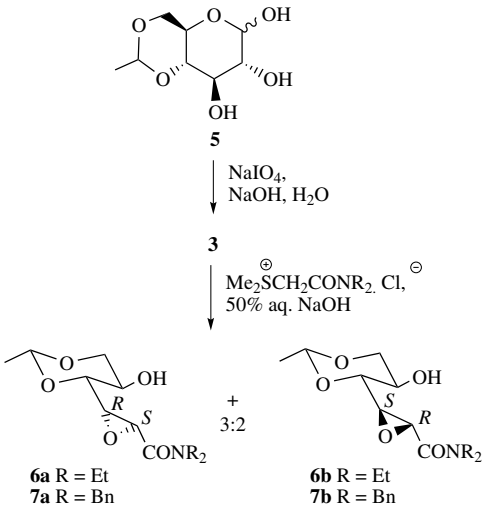


Scheme 1. Retrosynthetic scheme for preparing piperidine iminosugars.

corresponding sulfur ylides (R = Et, Bn), generated in situ, in the *trans* epoxides **6a**,**b** and **7a**,**b**, respectively, in a 3:2 rate (a:b, approximately by ^{1}H NMR), (Scheme 2). Whereas in the case of R = Et, the isomers could not be separated, for R = Bn column chromatography allowed us to isolate both isomers **7a** and **7b.** A similar isomer ratio was obtained for R = Me. In order to have a separate configurational assignment, we hydrolyzed the mixture of stereoisomers **6a**,**b** with periodic oxidation in water. The resulting mixture gave a negative rotatory power,[11d] revealing the configuration of the predominant epoxyamide as (2*S*,3*R*)-**6a**. Configurational determination of these structures is described in the text by chemical transformations.



Scheme 2. Synthesis of ethylidene-D-erythrose **3** and *trans*-epoxyamides.

The best results in the epoxide opening of **6a**,**b** were obtained with sodium azide in DMF, with catalytic AcOH, to regioselectively give the 2-azido derivatives **8a** and **8b**. Other attempts were made with $NaN_3/MgSO_4$/MeOH, but reaction times were longer and mixtures with the 3-azido isomers were obtained.

With the appropriate stereoisomers **8** in hand, the next step was to find adequate protection. Diols **8a** and **8b** were benzylated to give **9a** and **9b.** However hydrolysis of the ethylidene group of **9a** and **9b**, with AcOH or TFA, did not give the desired acyclic products in appreciable yield. Under mild conditions, the starting material was recovered. A better result was observed with Amberlyst® 15 in methanol (40–60 °C), although the open chain product **11** could only be isolated from isomer **9b**. Hydrolysis of **9a** under analogous conditions gave lactone **10**. At rt, hydrolysis was incomplete and product **9a** was recovered.

The different behaviour of isomers **9a** and **9b** in the hydrolysis can be explained by the high steric hindrance that the *manno* isomer presents in the transition state towards the lactone. The cyclization is avoided by nearby groups with a *cis* relationship.

The acyclic compound **11** was treated with tosyl chloride to give tosylated **12**. Hydrogenation of the azido group in **12**, with subsequent cyclization, allowed us to obtain a piperidine amide derivative **13**. The NMR data of **13** showed values in accordance with a DMJ derivative. The large value of $J_{4,3} = J_{4,5} = 9.1$ Hz, clearly requires the *trans*-diaxial relationship of these protons,[13] thus indicating the $^4C_1$ conformation and confirming the D-*manno* configuration. These results are in agreement with the conformational analysis carried out by computational molecular modelling

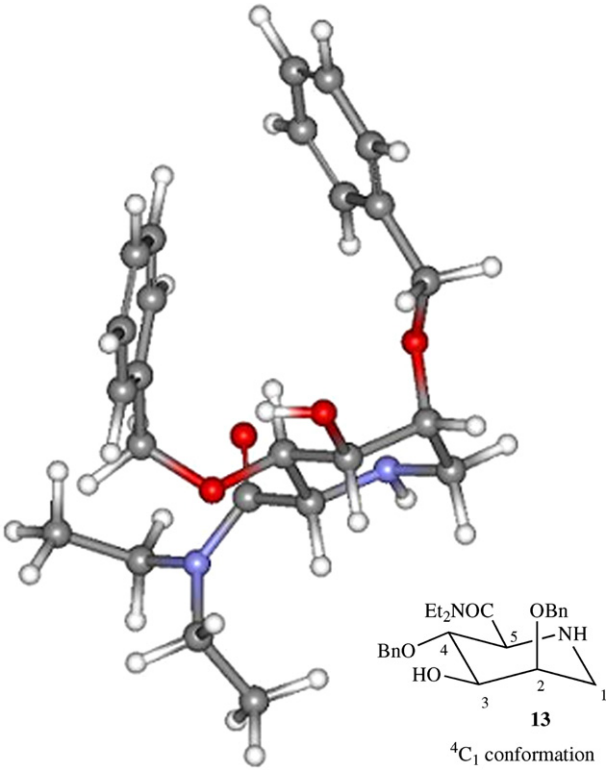


Figure 1. Preferred conformation of compound **13**.

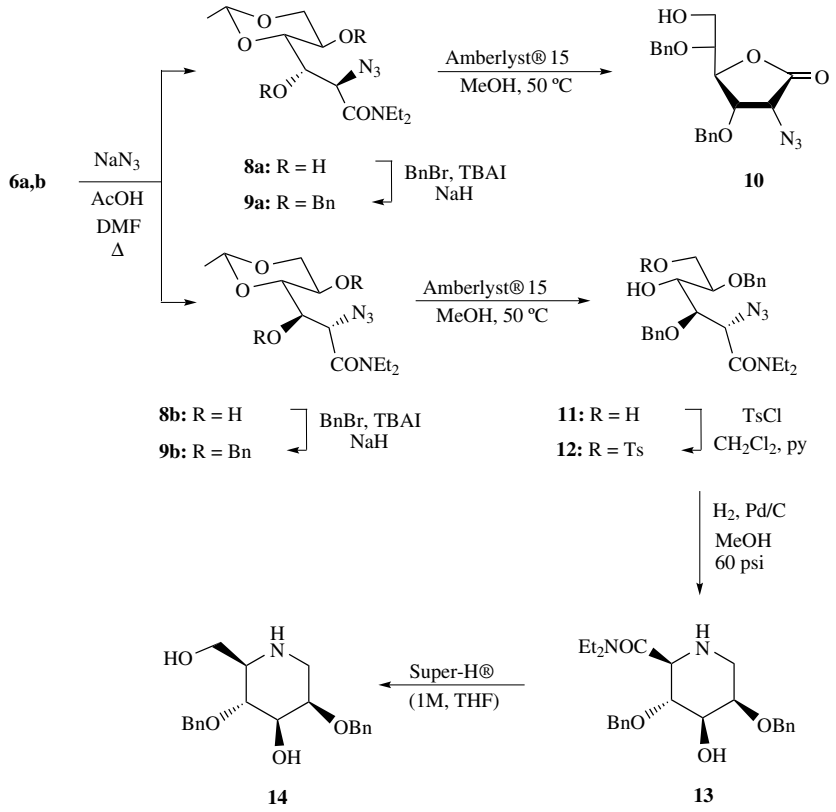
as can be seen in Figure 1.[14] The theoretical coupling constants, obtained by molecular modelling calculations, are similar to the experimental values. Consequently, there is no doubt about the configurational assignment.

Reduction of the amide group with Super-Hydride® gave 2,4-di-*O*-benzyl-1-deoxymannojirimycin **14** (Scheme 3).

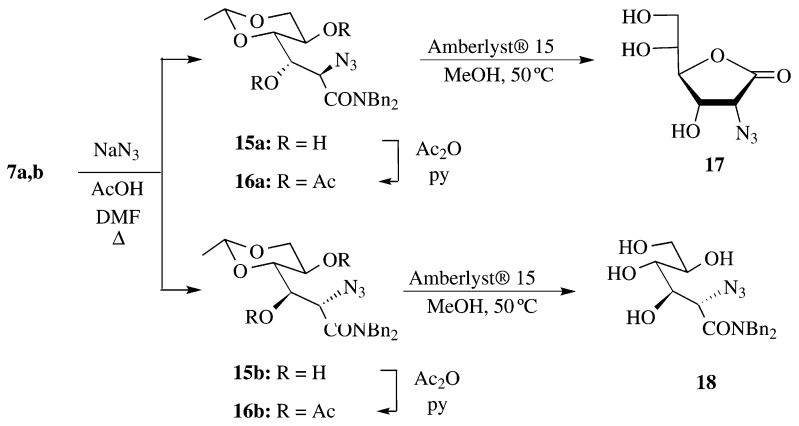
In order to study the influence of the neighbouring groups in the hydrolysis of the acetal, we prepared the acetyl derivatives **16a** and **16b** (Scheme 4). The results were analogous to those of the benzylated products **9a** and **9b.** The acetylated compound **16a**, after treatment with Amberlyst 15 in MeOH at 50–60 °C, gave lactone **17**. Under the same conditions, compound **16b** gave tetrol **18** (Scheme 4).

The formation of the deprotected lactone **17** allowed us to test the absolute configuration of the isomers obtained. The mixture of isomers **7a**,**b** could lead to lactones with D-allo or D-manno configuration. The known 2-azido-2-deoxy-D-mannono-1,4-lactone[8b] showed a positive specific rotation and different NMR data[15] ($J_{3,4} = 2.8$ and $J_{4,5} = 9.4$ Hz, *manno*), to those obtained by us [$J_{3,4} = 0$ (*anti*) and $J_{4,5} = 4.8$ Hz] besides negative specific rotation. Thus, lactone **17** formed from **16a** should have the *allo* configuration.

At first, experiments were performed with mixtures of isomers (**a**,**b**) in higher amounts, but the polarities of the isomeric products were sometimes inverted in relation to the starting isomers, thus complicating the isolation and characterization of these compounds. In order to correlate each isomer with its product, reactions had to be repeated with each isomer separately.



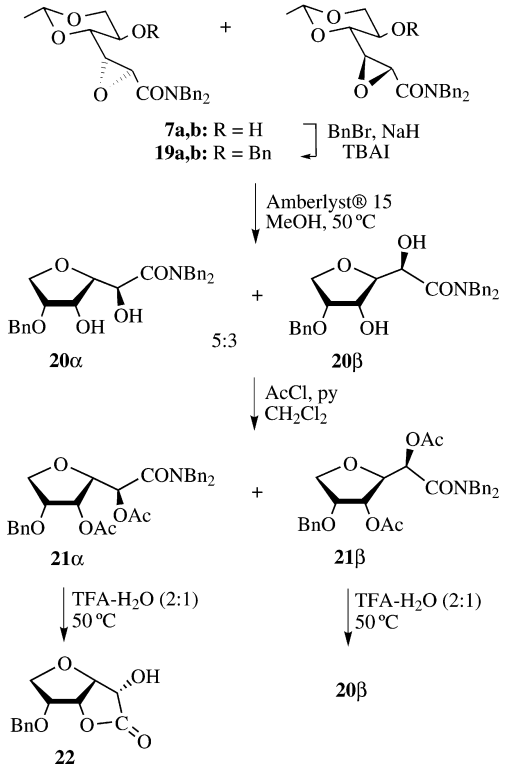
Scheme 3. Synthesis of azido lactone **10** and 2,4-di-*O*-benzyl-1-deoxymannojirimicyn **14**.



Scheme 4. Synthesis of azido lactone **17** and azido tetrol **18**.

An alternative route involved the deprotection of the acetal before epoxide opening. Epoxides **7a**,**b** were benzylated and the new products **19a**,**b** treated with acid resin. However, acetal hydrolysis of **19a**,**b** gave subsequent cyclization through intramolecular epoxide opening. Thus, 3,6-anhydro derivatives **20α**,**β** were obtained, after purification, in approximately 5:3 ratio (^{1}H NMR), (Scheme 5). Acetylation of **20α**,**β** gave two isomers **21α** and **21β** which could be separated by column chromatography and identified, the more polar isomer being the predominant product. If we assume the predominant absolute configuration in the starting epoxyamides mixture **7a**,**b**, as 2*S*,3*R*, and consider the regioselective and stereospecific cyclization processes, we must assign the α configuration to the more polar product. In fact, **19α** showed $J_{3,4} = 3.76$ and $J_{4,5} = 4.30$, compatible values for an α-configuration, compared with other analogous products.[11c,16]

The definitive confirmation of the structures **21α** and **21β** was given by their hydrolysis using TFA–H_2O (2:1). The α-compound was the one that could lactonize to give bicyclic **22**, while the β-isomer, under the same conditions gave the deacetylated **20β**. ^{13}C NMR data of **22** were compared with that of the known debenzylated compound,[17] confirming the α-configuration.



Scheme 5. Hydrolysis of ethylidene epoxyamides **19a**,**b** and structural confirmation of the predominant isomer.

3. Conclusion

In conclusion, we have developed a new synthesis of 2,4-di-*O*-benzyl-1-deoxymannojirimycin **14** from an inexpensive starting material. In addition, we have obtained new α-azido lactones **10** and **17**, which can be converted into other glycosidase inhibitors or novel amino acids. Structural assignments have been verified by NMR data with bidimensional experiments, and by chemical transformations to give products with verifiable stereochemistry. We are currently developing other routes, with different protecting groups, in order to increase the yields and obtain the D-*allo* piperidine derivatives.

4. Experimental

4.1. 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 7% ethanolic phosphomolybdic acid 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. Multiplic-

ities are designated as singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants *J* are expressed in Hertz units. Equatorial and axial protons are named as H_e an H_a. NMR assignments were undertaken based on two-dimensional COSY and gHMQC experiments. 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.

4.2. 2,3-Anhydro-*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*altro*-hexonamide 6a and 2,3-anhydro-*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*gluco*-hexonamide 6b

To a solution of **3** (960 mg, 6.56 mmol) in dichloromethane (16 mL) were added the sulfonium salt **4** (R = Et) (1.64 g, 7.74 mmol) and 50% aqueous NaOH (8 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After 30 min, water (24 mL) was added and the organic phase separated. The aqueous phase was extracted with *tert*-butylmethyl ether (3 × 25 mL) and the organic layers were washed with water, dried over $MgSO_4$ and evaporated in vacuo to obtain an irresoluble mixture **6a**,**b** as a white solid (1.44–1.53 g, 85–90%), in a 3:2 isomer ratio (^{1}H NMR). R_f: 0.3 (ethyl acetate) ^{1}H NMR (400 MHz, $CDCl_3$) two isomers (**a**,**b**): δ 4.66 (m, $J = 4.8$, 2H, 2 OC*H*CH_3), 4.10 (m, $J_{5,6e} = 5.4$, $J_{6e,6a} = 10.7$, 2 × 1H, H_e-6a,6b), 3.77 (d, $J_{2,3} = 1.8$, 1H, H-2b), 3.74 (d, $J_{2,3} = 2.1$, 1H, H-2a), 3.75 and 3.72 (2m, $J_{5,6a} = 10.2$, 2 × 1H, H-5a, b), 3.58–3.30 (m, 2 × 8H, 4, 3, H-6_a, OH and 2 × 2C$H_2$$CH_3$), 1.25 (at, 2 × 3H, CHC$H_3$), 1.18 (m, 2 × 3H, 2$CH_2CH_3$) and 1.07 (m, 2 × 3H, 2$CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (*C*O), 98.7 and 98.6 (*C*HCH$_3$), 79.3 and 78.3, (C-4b, C-4a), 63.5 and 61.9, (C-5a, C-5b), 2 × 70.4 (C-6a, C-6b), 57.4 and 56.8 (C-3a, C-3b), 50.9 and 50.7 (C-2b, C-2a), 41.6, 41.5, 40.7 and 40.7 (*C*$H_2$$CH_3$) 20.3 (CH*C*H$_3$), 14.5, 14.5, 12.8 and 12.7 (CH_2*C*H$_3$). HRMS (FAB): $[M+H]^+$ calcd for $C_{12}H_{22}NO_5$, 260.1499; found, 260.1505.

4.3. 2,3-Anhydro-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*altro*-hexonamide 7a and 2,3-anhydro-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*gluco*-hexonamide 7b

The same procedure performed to obtain compound **6a**,**b** was followed with **3** (796 mg, 5.45 mmol) and **4** (R = Bn) (2.20 g, 6.55 mmol), obtaining **7a**,**b** as a white solid (1.77 g, 85%), in a 3:2 isomer relation (^{1}H NMR). A small portion was purified by column chromatography at atmospheric pressure to give the two pure isomers. Compound **7a**: R_f: 0.22 (3:2, hexane/ethyl acetate) mp: 138 °C, $[\alpha]_D^{22} = -0.3$ (*c* 2.25, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (m, 5H, 2CH_2–Ph, C*H*–CH_3), 4.10 (dd, $J_{5,6e} = 5.4$, $J_{6e,6a} = 10.9$, 1H, H-6_e), 3.89 (d, $J_{2,3} = 2.4$, 1H, H-2), 3.78 (ddd, $J_{3,4} = 3.7$, $J_{4,5} = 10.3$, 1H, H-5), 3.52 (dd, 1H, H-3), 3.32 (t, 1H, H-6_a), 3.29 (dd, 1H, H-4), 1.25 (d, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9 (*C*O), 126–136 (Ph), 98.6 (*C*HCH$_3$), 78.4 (C-4), 70.5 (C-6), 61.8 (C-5), 57.3 (C-3), 50.8, (C-2), 49.4 and 48.8 (*C*H_2Ph), 20.3 (CH*C*H$_3$). EM: 292 $[M-91]^+$, 91 (100%). Compound **7b**: R_f: 0.16 (3:2, hexane/ethyl acetate). $[\alpha]_D^{22} = -0.1$ (*c* 2, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (m, 5H, 2CH_2–Ph, C*H*CH_3), 4.07 (dd, $J_{5,6e} = 5.4$, $J_{6a,6e} = 10.4$, 1H, H-6_e), 3.87 (d, 1H, $J_{2,3} = 2.4$, H-2), 3.59 (ddd, $J_{3,4} = 3.7$, $J_{5,6a} = J_{4,5} = 10.3$, 1H, H-5), 3.50 (dd, 1H, H-3), 3.46 (dd, 1H, H-4), 3.37 (t, 1H, H-6_a), 1.29 (d, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 168.2 (*C*O), 126–137 (Ph), 98.6 (*C*HCH$_3$), 78.0 (C-4), 70.3 (C-6), 63.3 (C-5), 57.8 (C-3), 50.9 (C-2), 49.3 and 48.5 (*C*H_2Ph),20.3 (CH*C*H$_3$). EM: 292 $[M-91]^+$, 91 (100%). HRMS (FAB): $[M+H]^+$ calcd for $C_{22}H_{26}NO_5$, 384.1811; found, 384.1825.

4.4. 2-Azido-*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*allo*-hexonamide 8a and 2-azido–*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*manno*-hexonamide 8b

To a solution of the epoxyamide mixture obtained above **6a**,**b** (1.02 g, 3.9 mmol) in DMF (22 mL) were added NaN_3 (0.39 g, 6 mmol) and AcOH (0.26 mL). The reaction mixture was heated (95 °C) with stirring under argon and monitored by TLC. After 5 h, the reaction mixture was eluted with AcOEt and washed with aq NH_4Cl and then with water. The organic layer was dried over $MgSO_4$ and the solvents were evaporated in vacuo. Purification by column chromatography gave 425 mg of **8a**, 375 mg of **8b** and 57 mg of mixtures (72% yield). Compound **8a** had R_f 0.7 (AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.60 (q, 1H, C*H*–CH_3), 4.22 and 4.13 (2 dd, 2H, H-3, H-6_e), 3.98 (d, 1H, H-2), 3.78 (m, H-5), 3.40 (m, 6H, H-2, H-4, H-6_a and CH_2CH_3), 1.28 (d, 3H, H–CH_3), 1.20 and 1.15 (2t, 2 × 3H, 2CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.1 (*C*O), 98.0 (*C*HCH$_3$), 79.8 (C-4), 75.3 (C-3), 69.4 (C-6), 64.2 (C-5), 54.6 (C-2), 41.8 and 40.4 (N*C*H_2), 20.0 (CH*C*H$_3$), 13.7 and 12.3 (2CH_2*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{12}H_{22}N_4O_5Na$, 325.1487; found, 325.1489. Compound **8b** had R_f 0.5 (AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.62 (q, 1H, C*H*–CH_3), 4.32 (d, 1H, H-3), 4.10 (d + m, 2H, H-2 and H-6_e), 3.82 (m, 1H, H-5), 3.35 (m, 6H, H-4, H-6_a and 2C$H_2$$CH_3$), 1.22 (d, 3H, CH–C$H_3$), 1.12 and 1.03 (2t, 2 × 3H, 2CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.7 (*C*O), 98.7 (*C*HCH$_3$), 79.7 (C-4), 70.2 (C-6), 68.0 (C-3), 59.7 (C-5), 56.7 (C-2), 42.3 and 41.1 (N*C*H_2), 20.0 (CH*C*H$_3$), 14.1 and 12.5 (2CH_2*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{12}H_{22}N_4O_5Na$, 325.1487; found, 325.1490.

4.5. 2-Azido-3,5-di-*O*-benzyl-*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*allo*-hexonamide 9a and 2-azido-3,5-di-*O*-benzyl-*N*,*N*-diethyl-4,6-*O*-ethylidene-D-*manno*-hexonamide 9b

To a solution of **8a** (250 mg, 0.82 mmol) in THF (8 mL), with stirring at 0 °C, were added 66 mg of 60% NaH (mineral oil), 0.2 mL of BnBr and 30 mg of tetrabutyl ammonium iodide. The reaction was monitored by TLC (1:1, hexane/ethyl acetate) and left for 34 h at rt. Then, solvents were evaporated and the residue was extracted with dichloromethane. The solution was washed with aq 5% NaOH and water, dried over $MgSO_4$ and concentrated giving a residue which was purified by column chromatography to give **9a** (298 mg, 75%). R_f: 0.7 (2:1, hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.40 (m, 10H, 2Ph), 4.75 (d, 1H, CH_2Ph), 4.67 (q, 1H, C*H*CH_3), 4.45–4.60 (m, 3H, CH_2Ph), 4.20 (m, 3H), 3.90 (m, 2H), 3.44 (m,

2H, CH_2CH_3, H-6_a), 3.20 (m, 2H, CH_2CH_3), 2.92 (m, 1H, CH_2CH_3), 1.32 (d, 3H, $CHCH_3$), 1.04 (t, 3H, CH_2CH_3), 0.81 (t, 3H, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2 (*C*O), 127–138 (Ph), 99.7 (*C*HCH$_3$), 80.2 and 79.9 (C-4, C-3), 74.8 and 71.8 (2*C*H$_2$Ph), 69.7 and 69.3 (C-5, C-6), 57.7 (C-2), 42.5 and 41.9 (2*C*H$_2$CH$_3$), 20.6 (CH*C*H$_3$), 13.1 and 14.5 (2CH$_2$*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{26}H_{34}N_4O_5Na$, 505.2427; found, 505.2432. The same procedure as described above was used with **8b** (400 mg, 1.31 mmol) in THF (13 mL), with the addition of 105 mg of 60% NaH, 0.32 mL of BnBr and 50 mg of tetrabutyl ammonium iodide. After 72 h, the reaction mixture was worked up as above and the product purified by column chromatography to give **9b** (411 mg, 65%). R_f: 0.65 (2:1, hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.40 (m, 10H, 2Ph), 4.64 (q, 1H, C*H*CH$_3$), 4.53 (d, 1H, CH_2Ph), 4.36 (t, 2H, CH_2Ph), 4.1–4.3 (m, 4H, CH_2Ph) 3.70 (m, 2 H), 3.6–3.0 (m, 5H, CH_2CH$_3$), 1.28 (d, 3H, CHCH_3), 1.10 and 1.02 (2t, 2 × 3H, CH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2 (*C*O), 127–138 (Ph), 99.7 (CH*C*H$_3$), 78.6 and 76.9 (C-4, C-3), 74.8 and 71.8 (2*C*H$_2$Ph), 69.6 and 68.5 (C-5, C-6), 56.7 (C-2), 42.5 and 41.9 (*C*H$_2$CH$_3$), 20.6 (CH*C*H$_3$), 14.7 and 13.0 (2CH$_2$*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{26}H_{34}N_4O_5Na$, 505.2427; found, 505.2433.

4.6. Hydrolysis of 9a and 9b. 2-Azido-2-deoxy-3,5-di-*O*-benzyl-D-allono-1,4-lactone 10 and 2-azido-3,5-di-*O*-benzyl-*N*,*N*-diethyl-D-*manno*-hexonamide 11

The benzylated **9a** (330 mg, 0.68 mmol) or **9b** (124 mg, 0.25 mmol) was dissolved in MeOH, separately, and stirred with Amberlyst® 15 at 50–60 °C. After 1 d, reaction mixtures were filtered, the resin washed with MeOH and the solvent evaporated, giving residues, which were purified by column chromatography. Compound **9a** gave lactone **10** (186 mg, 71%) and compound **9b** gave diol **11** (70 mg, 60%). Lactone **10** had R_f: 0.6 (1:1, hexane/ethyl acetate). $[\alpha]_D^{27} = +11$ (*c* 1.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.10 (m, 10H, Ph), 4.67, 4.62, 4.53 and 4.43 (m + d, $J = 9.8$, 4H, 2CH_2Ph), 4.62 (d, $J_{4,5} = 3.2$, 1H, H-4), 4.37 (d, $J_{3,2} = 5.9$, 1H, H-3), 4.11 (d, 1H, H-2), 3.67 (m, 1H, H-5), 3.58 (m, 2H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (CO), 136.6 (2C) and 128.7–127.8 (Ph), 84.3 (C-4), 78.0 (C-5), 75.2 (C-3), 73.4 and 72.3 (2*C*H$_2$Ph), 60.3 (C-6), 59.5 (C-2). HRMS (FAB): $[M+Na]^+$ calcd for $C_{20}H_{21}N_3O_5Na$, 406.1378; found, 406.1374. Compound **11** had R_f: 0.3 (3:2 hexane/ethyl acetate). mp: 115 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$): 7.40–7.10 (m, 10H, Ph), 4.64 (d, $J = 11.8$, 1H, CH_2Ph), 4.52 (d, $J = 11.3$, 1H CH_2Ph), 4.35 (d, 1H, CH_2Ph, $J = 11.8$), 4.27 (d, 1H, $J_{2,3} = 9.7$, H-3), 4.18 (d, $J = 11.3$, 1H, CH_2Ph), 4.06 (d, 1H, H-2), 3.97 (d, $J_{4,5} = 8.6$, 1H, H-4), 3.95 (m, $J_{6a,5} = 3.8$, H-6_a), 3.89 (dd, $J_{6a,6b} = 11.8$, $J_{6b,5} = 2.7$, H-6_b), 3.40–3.50 and 3.24 (2m, 4H + 1H, H-5 and 2NCH_2), 1.06 (2t, 6H, CH$_2$CH_3). ^{13}C NMR δ (100 MHz, $CDCl_3$): 168.4 (*C*O), 138.0–127.0 (Ph), 78.1 and 76.8 (C-3, C-5), 74.7 and 71.3 (2 *C*H$_2$Ph), 70.3 (C-4), 60.9 (C-6), 56.5 (C-2), 41.5 and 42.5 (2*C*H$_2$CH$_3$), 13.1 and 14.9 (2CH$_2$*C*H$_3$). HRMS (FAB): $[M+H]^+$ calcd for $C_{24}H_{33}N_4O_5$, 457.2451; found, 457.2459.

4.7. Tosylation of compound 11

A solution of diol **11** (310 mg, 0.68 mmol) in CH_2Cl_2 (4 mL) with pyridine (0.1 mL) and tosyl chloride (388 mg, 3 mmol) was kept at rt for 1 d, to give compound **12** (333 mg, 80%) after work-up and purification by column chromatography. R_f: 0.5 (3:2 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.00 (m, 14H, Ph), 4.55 (d, $J = 11.8$, 1H, CH_2Ph), 4.45 (t, $J = 11.8$, 2H, CH_2Ph), 4.15 (m, $J = 11.8$, $J = 9.7$, 3H, CH_2, H-3), 4.05 (d, $J = 11.3$, 1H), 3.96 (d, $J = 9.6$, 1H, H-2), 3.70 (d, $J = 9.1$, 1H, H-4), 3.50 (m, 1H, H-5), 3.40–3.10 (m, 4H, 2CH_2CH$_3$), 2.35 (s, 3H, CH_3 of Ts), 1.06 (m, 6H, CH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 (*C*O), 145.0–127.5 (Ph), 76.4 and 76.3 (C-3, C-5), 74.5 and 71.6 (2CH_2Ph), 69.4 (C-6), 69.1 (C-4), 56.2 (C-2), 42.3 and 41.3 (2*C*H$_2$CH$_3$), 21.6 (*C*H$_3$ of Ts), 14.7 and 12.9 (2CH$_2$*C*H$_3$).

4.8. 1,5-Dideoxy-1,5-imino-2,4-di-*O*-benzyl-*N*,*N*-diethyl-D-mannopyranosiduronamide 13

To a vessel with tosylated compound **12** (290 mg, 0.47 mmol) under an argon atmosphere were added methanol (10 mL) and a catalytic amount of Pd/C. The mixture is purged and maintained under hydrogen atmosphere at rt (by a H_2 filled balloon). After 2 h the reaction is complete. The mixture was filtered over Celite™ and purified by column chromatography to give piperidine **13** as a white solid (180 mg, 90%), mp: 143–144 °C. R_f: 0.6 (9:1, ethyl acetate/methanol). $[\alpha]_D^{27} = -83$ (*c* 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 10H, Ph), 4.77 (d, $J = 10.7$, 1H, CH_2Ph), 4.57 (d, $J = 11.8$, 1H, CH_2Ph), 4.54 (2d, 2H, CH_2Ph), 3.82 (t, $J_{3,4} = J_{4,5} = 9.1$, 1H, H-4), 3.71 (br s, 1H, H-2), 3.61 (ddd, $J_{3,2} = 3.2$, $J_{3,4} = 9.1$, $J_{3,OH} = 9.1$, 1H, H-3), 3.58–3.13 (4m, 4H, 2CH_2CH$_3$), 3.36 (d, $J_{4,5} = 9.1$, 1H, H-5), 3.16 and 2.53 (2d, $J_{1e,1a} = 15.0$, 2H, 1-H_e and 1-H_a), 1.11 and 1.10 (at, 2 × 3H, 2CH$_2$CH_3). ^{13}C NMR δ (100 MHz, $CDCl_3$): 171.1 (*C*O), 139.1, 138.4 and 128.9–127.9 (Ph), 81.5 (C-4), 78.1 (C-2), 75.9 (C-3), 59.4 (C-5), 75.6 and 71.9 (*C*H$_2$Ph), 46.5 (C-1), 42.6 and 41.3 (*C*H$_2$CH$_3$), 15.0 and 13.4 (CH$_2$*C*H$_3$). HRMS (FAB): $[M+H]^+$ calcd for $C_{24}H_{33}N_2O_4$, 413.2443; found, 413.2440.

4.9. 2,4-Di-*O*-Benzyl-1-deoxymannojirimicin 14

To a stirred solution of piperidine **13** (35 mg, 0.08 mmol) in THF (1.5 mL), with an ice bath and under an argon atmosphere, was added Super-Hydride®, 1 M in tetrahydrofuran (0.6 mL, 0.6 mmol). The reaction was left at rt for a day and then, more hydride was added (0.2 mL, 0.2 mmol). After 2 d, TLC indicated the conversion of the starting material to a more polar product. Then, the mixture was diluted with MeOH, treated with acid resin, filtered and concentrated. The residue was purified by column chromatography to obtain pure **14** (20 mg, 69%). R_f: 0.2 (9:1, ethyl acetate/methanol). $[\alpha]_D^{27} = -5.5$ (*c* 0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 10H, Ph), 4.90, 4.70, 4.63 and 4.51 (4d, $J = 10.9$ and 11.6, 4H, 2CH_2Ph), 3.85 (dd, $J = 3.7$ and 10.9, 1H, H-6), 3.75 (br s, 1H, H-2), 3.67 (m, 2H, H-3 and H-6), 3.50 (t, $J_{3,4} = J_{4,5} = 9.8$, 1H, H-4), 3.27 (dd, $J_{1e,2} = 3.0$, $J_{1e,1a} = 14.6$, 1H, 1-H_e), 2.62 (d, 1H,

H-1$_a$), 2.60 (m, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138, 137 and 129–127, 78, 77 and 75 (C-2, C-3 and C-4), 74 and 71 (CH_2Ph), 62 and 60 (C-5 and C-6), 45 (C-1). HRMS (FAB): $[M+Na]^+$ calcd for $C_{20}H_{25}NO_4Na$, 366.1681; found, 366.1683.

4.10. 2-Azido-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*allo*-hexonamide 15a and 2-azido-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*manno*-hexonamide 15b

To a stirred solution of the epoxy amide mixture **7a**,**b** (530 mg, 1.38 mmol) in DMF (7.8 mL) were added NaN_3 (138 mg, 2.12 mmol) and AcOH (0.09 mL). The mixture was heated (95 °C) under an argon atmosphere and monitored by TLC. After 2.5 h, the reaction mixture was eluted with AcOEt and washed with aq NH_4Cl and then with water. The organic layer was dried ($MgSO_4$) and the solvents were evaporated in vacuo. Purification by column chromatography gave 235 mg of **15a** and 218 mg of **15b** (77% yield). Isomers **15a** and **15b** could be separated by column chromatography. **15a** had R_f: 0.4 (3:2 hexane/ethyl acetate), $[\alpha]_D^{25} = -171$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H, 2Ph), 4.74 and 4.52 (2d, $J = 15.0$ and 16.6, 2H, CH_2Ph), 4.40 (m, 3H, *C*HCH$_3$ and CH_2Ph), 4.21 (dd, $J_{2,3} = 2.7$, $J_{3,4} = 8.8$, 1H, H-3), 4.12 (d, 1H, H-2), 4.07 (dd, $J_{5,6a} = 5.4$, $J_{6a,6e} = 10.2$, 1H, H-6$_e$), 3.73 (ddd, 1H, H-5), 3.38 (t, 1H, H-4), 3.32 (t, $J_{5,6e} = J_{6a,6e} = 10.2$, 1H, H-6$_a$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.1 (*C*O), 136–126 (Ph), 98.6 (*C*HCH$_3$), 79.1 (C-4), 78.4 (C-3), 69.8 (C-6), 66.4 (C-5), 54.2 (C-2), 49.8 and 48.0 (2*C*H$_2$Ph), 20.3 (CH*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{22}H_{26}N_4O_5Na$, 449.1801; found, 449.1798. Compound **15b** had R_f: 0.3 (3:2 hexane/ethyl acetate). $[\alpha]_D^{25} = +40$ (*c* 0.8, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H, 2Ph), 4.80 (d, $J = 15.0$, 1H, CH_2Ph), 4.63 (m, 2H, OC*H*CH$_3$ and CH_2Ph), 4.47 (m, 3H, H-3 and CH_2Ph), 4.27 (d, $J_{2,3} = 9.1$, 1H, H-2), 4.10 (dd, $J_{5,6e} = 5.4$, $J_{6a,6e} = 10.7$, 1H, H-6$_e$), 3.85 (ddd, 1H, H-5), 3.57 (dd, $J_{3,4} = 1,1$, $J_{4,5} = 9.7$, 1H, H-4), 3.42 (t, $J_{5,6a} = J_{6a,6e} = 10.7$, 1H, H-6$_a$), 2.52 (br s, OH), 1.22 (d, 3H, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (*C*O), 136–126 (Ph), 98.9 (*C*HCH$_3$), 79.5 (C-4), 70.4 (C-6), 68.8 (C-3), 60.2 (C-5), 57.8 (C-2), 50.5 and 49.5 (2*C*H$_2$Ph), 20.3 (CH*C*H$_3$). HRMS (FAB): $[M+Na]^+$calcd for $C_{22}H_{26}N_4O_5Na$, 449.1801; found, 449.1806.

4.11. 3,5-Di-*O*-Acetyl-2-azido-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*altro*-hexonamide 16a and 3,5-di-*O*-acetyl-2-azido-*N*,*N*-dibenzyl-4,6-*O*-ethylidene-D-*gluco*-hexonamide 16b

Diols **15a** or **15b** (40 mg, 0.09 mmol) were stirred in pyridine (1 mL) with acetic anhydride (0.3 mL) in an ice bath for 5 h. The reactions were left at rt overnight. Ice was added and a white precipitate was formed in both cases. The precipitates were filtered and washed, and according to their NMR data, pure diacetylated products **16a** (57 mg, 95%) or **16b** (53 mg, 88%) were, respectively, obtained. Compound **16b** had R_f: 0.7 (3:2, hexane/ethyl acetate). $[\alpha]_D^{25} = -21$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H, 2Ph), 5.56 (dd, $J_{3,4} = 1.6$, $J_{2,3} = 10.2$, 1H, H-3), 5.11 (d, $J = 14.5$, 1H, CH_2Ph), 4.60 (m, 2H, CH_2Ph, C*H*Me), 4.50 (dt, 1H, $J_{5,6a} = 5.4$, $J_{5,4} = J_{5,6e} = 10.2$, H-5), 4.39 (d, 1H, H-2), 4.32 (d, $J = 17.2$, 2H, CH_2Ph), 4.17 (dd, 1H, $J_{6,6'} = 10.2$, H-6$_e$), 3.97 (d, $J = 14.5$, 1H, CH_2Ph), 3.89 (dd, 1H, H-4), 3.33 (t, 1H, H-6$_a$), 1.99 and 1.67 (2s, 2 × 3H, 2CH_3CO), 1.20 (d, $J = 4.8$, 3H, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.5 and 168.1 (3CO), 136.6, 135.7 and 129.0–126.3 (2Ph), 99.5 (*C*HMe), 75.9 (C-4), 68.7 (C-3), 67.3 (C-6), 61.6 (C-5), 55.4 (C-2), 49.5 and 49.2 (2N*C*H$_2$), 20.6, 20.2 and 20.1 (2*C*H$_3$CO, CH*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{26}H_{30}N_4O_7Na$, 533.2013; found, 533.2016. Compound **16a** had R_f: 0.65 (3:2 hexane/ethyl acetate). $[\alpha]_D^{25} = -37$ (*c* 1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.00 (m, 10H, 2Ph), 5.44 (dd, $J_{3,4} = 2.2$, $J_{2,3} = 8.8$, 1H, H-3), 5.02 (d, $J = 14.6$, 1H, CH_2Ph), 4.96 (ddd, $J_{5,6e} = 5.1$, $J_{5,4} = J_{5,6a} = 10.2$, 1H, H-5), 4.59 (m, 2H, CH_2Ph and OC*H*CH$_3$), 4.36 (2d, $J = 8.8$, 16.8, 2H, CH_2Ph and H-2), 4.20 (dd, $J_{6a,6e} = 10.2$, 1H, H-6$_e$), 4.08 (d, $J = 14.6$, 1H, CH_2Ph), 3.94 (dd, 1H, H-4), 3.27 (t, 1H, H-6$_a$), 1.91 and 1.78 (2s, 2 × 3H, 2CH_3CO), 1.20 (d, $J = 5.1$, 3H, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 168.8 and 168.0 (3CO), 136.7, 135.5 and 129.1–126.3 (2Ph), 99.2 (O*C*HMe), 77.7 (C-4), 70.8 (C-3), 67.5 (C-6), 63.6 (C-5), 56.1 (C-2), 49.4 and 48.9 (2N*C*H$_2$), 20.54, 20.48 and 20.2 (2*C*H$_3$CO, CH*C*H$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{26}H_{30}N_4O_7Na$, 533.2012; found, 533.2016.

4.12. 2-Azido-2-deoxy-D-allono-1,4-lactone 17 and 2-azido-*N*,*N*-dibenzyl-D-*manno*-hexonamide 18

The acetylated **16a** (97 mg, 0, 19 mmol) was dissolved in MeOH and stirred with Amberlyst® 15 at 60 °C. After 1 d, the reaction mixture was filtrated, the resin washed with MeOH and the solvent evaporated, giving a residue which was washed with hexane (2 mL) and further purified by column chromatography to give lactone **17** (30 mg, 77%). R_f: 0.45 (ethyl acetate). $[\alpha]_D^{20} = -3.5$ (*c* 1.3, MeOH). ^{1}H NMR (400 MHz, D_2O): δ 4.58 (d, $J_{2,3} = 5.91$, 1H, H-3), 4.54 (d, 1H, H-2), 4.38 (d, $J_{4,5} = 4.8$ Hz, 1H, H-4), 3.74 (1H, ddd, H-5), 3.54 (dd, $J_{5,6} = 4.3$ Hz, $J_{6,6'} = 11.8$ Hz, 1H, H-6), 3.48 (dd, $J_{5,6'} = 5.9$ Hz, 1H, H-6′), ^{13}C NMR (100 MHz, D_2O): δ 174.7 (CO), 86.8 (C-4), 69.8 (C-5), 68.4 (C-6), 61.5 (C-3), 60.5 (C-2). HRMS (FAB): $[M+Na]^+$, calcd for $C_6H_9N_3O_5Na$, 226.0440; found, 226.0441. The same procedure was followed with isomer **16b** (67 mg, 0.13 mmol) to give tetrol **18** (36 mg, 69%). R_f: 0.45 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3 + CD_3OD$): δ 4.83 and 4.62 (2d, $J = 15.0$, 17.2, 2 × 1H, CH_2Ph), 4.27 and 4.15 (2m, 4 H), 3.61 (m), 3.0 (m). ^{13}C NMR δ (100 MHz, $CDCl_3 + CD_3OD$): 170.9 (CO), 136.0, 135.6 and 130–126 (Ph), 71.1, 69.95 and 69.88 (3C, C-5, C-4, C-3), 63.6 (C-6), 57.8 (C-2), 48.8 and 45.8 (N*C*H$_2$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{20}H_{24}N_4O_5Na$, 423.1645; found, 423.1644.

4.13. 2,3-Anhydro-*N*,*N*-dibenzyl-5-*O*-benzyl-4,6-*O*-ethylidene-D-*altro*-hexonamide 19a and 2,3-anhydro-*N*,*N*-dibenzyl-5-*O*-benzyl-4,6-*O*-ethylidene-D-*gluco*-hexonamide 19b

Benzylation of epoxyamides **7a**,**b** (160 mg, 0.42 mmol) in THF (2 mL), HNa (16 mg, 0.67 mmol), TBAI (1/10 equiv) and BnBr (0.05 mL) gave compounds **19a**,**b** (159 mg, 80%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.00 (m, 2 × 15H, 2 × 3Ph), 4.75–4.25 (m, 2 × 7H, 2 × 3CH_2Ph, 2CHCH$_3$), 4.10 (2dd, 2 × 1H, $J_{6e,6a} = 10.7$, $J_{6e,5} = 4.8$, H-6$_e$), 3.81 (d, 1H, $J_{2,3} = 2.15$, H-2 isomer **a**), 3.78 (d, 1H, $J_{2,3} = 2.15$, H-2 isomer **b**), 3.54 (m, 2 × 2H, H-3 and H-5), 3.30 (m, 2 × 2H, H-4 and H-6$_a$), 1.21 and 1.18 (2d, 2 × 3H, 2CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (2CO), 137.3–135.9 and 129.0–126.6 (Ph), 98.7 and 98.6 (CHCH$_3$), 77.5, 76.5, 72.5, 72.1, 70.0, 69.6, 68.7 and 68.5 (2 × 4 C, C-4, C-5, C-6 and CH$_2$Ph), 57.6 and 57.1 (C-3a, C-3b), 50.9 and 50.5 (C-2a, C-2b), 49.1, 48.6 and 48.4 (4C, one double, 2 × 2NCH$_2$Ph), 20.2 (2CHCH$_3$). HRMS (FAB): $[M+Na]^+$ calcd for $C_{29}H_{31}NO_5Na$, 496.2099; found, 496.2098.

4.14. 3,6-Anhydro-5-*O*-benzyl-*N*,*N*-dibenzyl-D-mannonamide 20α and 3,6-anhydro-5-*O*-benzyl-*N*,*N*-dibenzyl-D-allonamide 20β

To a solution of epoxyamides **19a**,**b** (300 mg, 0.634 mmol) in methanol was added Amberlyst® 15. The mixture was stirred and heated (45–50 °C). After 24 h, resin was filtered and the solution concentrated in vacuo to give a syrup, which was purified by column chromatography. NMR data showed this to be an irresoluble mixture of compounds **20α**,**β** (180 mg, 63%) R_f: 0.3 (2:1), 0.5 (1:1) (hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$), mixture of isomers, δ 7.45–7.15 (m, 15H, *Ph*), 5.17 (d, 1H, CH_2Ph, $J = 15.28$), 5.06 (m, 2H, CH_2Ph), 4.97 (d, 1H, CH_2Ph, $J = 17.1$), 4.73–4.57 (m, 5H, CH_2Ph), 4.49 (t, 1H, $J = 4.1$, isomer α), 4.38 (t, 1H, $J = 5.3$, isomer β), 4.32–4.4 and 4.00–3.80 (2m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 and 172.3, (2C=O), 137–126 (2 × 3Ph), 84.6 and 83.7 (C-3α, 3β), 78.7 and 78.3 (C-5α, 5), 72.7 and 72.4 (C-4α, 4β), 70.8, 70.3, 70.2, 69.7 and 69.3 (2 × 2CH$_2$O, C-2β), 65.9 (C-2α), 49.4, 49.0, 48.2 and 48.1 (2 × 2 CH$_2$N).

4.15. 2,4-Di-*O*-Acetyl-3,6-anhydro-5-*O*-benzyl-*N*,*N*-dibenzyl-D-mannonamide 21α and 2,4-di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-*N*,*N*-dibenzyl-D-allonamide 21β

To a solution of the mixture of isomers **20α**,**β** (145 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) and pyridine (5 mL) was added 1.5 equiv of acetyl chloride. After a day, work-up as usual gave, after evaporation of the solvent, a residue that was purified to give pure **21β**, less polar, (47 mg) and pure **21α**, more polar, (62 mg). (65% yield). Compound **21β** had R_f: 0.5 (2:1, hexane/ethyl acetate). ^{1}H NMR δ (400 MHz, $CDCl_3$): δ 7.35–7.05 (m, 15H, *Ph*), 5.45 (m, 2H, H-2 and H-4), 4.79 (d, $J = 15.0$, 1H, CH_2Ph), 4.56–4.34 (3d, 3H, CH_2Ph), 4.32 (t, $J_{2,3} = J_{3,4} = 4.3$, 1H, H-3), 4.24 (d, $J = 15.0$, 1H, CH_2Ph), 4.11 (m, 1H, H-5), 3.88 (dd, $J_{5,6} = 5.9$, $J_{6,6'} = 9.1$, 1H, H-6), 3.71 (dd, $J_{5,6'} = 6.5$, 1H, H-6′), 2.03, 2.01, (2s, 2 × 3H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 169.9 and 167.1 (3C=O), 137.5, 136.4, 135.5 and 129–127 (Ph), 80.5 (C-3), 76.7 (C-5), 72.7 (CH$_2$Ph), 72.0 and 70.7 (C-2, C-4), 70.3 (C-6), 49.5 and 48.0 (NCH$_2$), 20.8 and 20.5 (2CH$_3$CO). HRMS (FAB): $[M+Na]^+$ calcd for $C_{31}H_{33}NO_7Na$, 554.2154; found, 554.2153. Compound **21α** had R_f: 0.4 (2:1, hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.05 (m, 15H, *Ph*), 5.68 (d, $J_{2,3} = 9.7$, 1H, H-2), 5.60 (dd, $J_{3,4} = 3.8$, $J_{4,5} = 4.3$, 1H, H-4), 4.77 (2d, $J = 15.4$, 16.7, 2H, CH_2Ph), 4.55 (d, $J = 11.3$, 1H, CH_2Ph), 4.51 (dd, 1H, H-3), 4.42–4.27 (3d, 3H, CH_2Ph), 4.24 (m, 1H, H-5), 3.95 (dd, $J_{5,6} = 7.5$, $J_{6,6'} = 8.1$, 1H, H-6), 3.67 (dd, $J_{5,6'} = 7.5$, 1H, 6′-H), 1.98 and 2.06 (2s, 2 × 3H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.6 and 168.5 (3 CO), 137.0, 136.4 and 136.0 (3 quat. Ph), 128–127 (Ph), 78.9 (C-3), 77.6 (C-5), 72.7 (CH$_2$Ph), 70.4 (C-4), 69.2 (C-6), 66.7 (C-2), 49.8 and 47.9 [N(CH$_2$Ph)$_2$], 20.6 and 20.4 (2CH$_3$CO). HRMS (FAB): $[M+Na]^+$ calcd for $C_{31}H_{33}NO_7Na$, 554.2154; found, 554.2154.

4.16. Hydrolysis of compounds 21α and 21β. 3,6-Anhydro-5-*O*-benzyl-D-mannono-1,4-lactone 22

To a small amount of **21α** was added TFA/H_2O (2:1) and the mixture was stirred at 50 °C for a day. Then, solvents were evaporated and the residue was characterized by NMR spectroscopy, giving lactone **22**. The same procedure was followed with **21α** giving the deacetylated **20**. Lactone **22** was purified by column chromatography. R_f: 0.2 (1:1, hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 5H, Ph), 4.91 (t, 1H, $J_{3,4} = J_{4,5} = 3.8$, H-4), 4.71 and 4.58 (2d, $J = 11.3$, 2H, CH_2Ph), 4.62 (dd, 1H, H-3), 4.38 (d, $J_{2,3} = 5.4$, 1H, H-2), 4.25 (ddd, 1H, H-5), 4.08 (dd, $J_{5,6} = 7.5$, $J_{6,6'} = 8.6$, 1H, H-6) and 3.74 (t, $J_{5,6'} = 8.6$, 1H, 6′-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.4 (CO), 136.7 and 129.0–128.0 (Ph), 78.2 (C-4), 76.7 (2C, C-5 and C-3), 72.8 (CH_2Ph), 69.6 (C-6) and 69.2 (C-2). HRMS (FAB): $[M+Na]^+$ calcd for $C_{13}H_{14}O_5Na$, 273.0739; found, 273.0740.

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