Stereodivergent syntheses of *altro* and *manno* stereoisomers of 2-acetamido-1,2-dideoxynojirimycin

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Abstract: A stereoselective synthesis of 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer (**9**) is described. The synthetic approach is based on the key bicyclic carbamate **7**, which is easily accessible in high enantiomeric purity and multigram scale by Sharpless Asymmetric Epoxidation of 1,4-pentadien-3-ol or 2,4-pentadien-1-ol. This procedure completes an efficient stereodivergent approach to five isomers of 2-acetamido-1,2-dideoxyiminosugars with high overall yields starting from the same key intermediate **7**. The present approach is based on the stereoselective control of the sulphite ring-opening with retention of configuration due to the anchimeric effect of the endocyclic amine.

Introduction

Carbohydrates are involved in a variety of metabolic processes. The inhibitors of the enzymes related to carbohydrate metabolism, such as glycosidases or glycosyl transferases, have potential activity in the treatment of several diseases, including diabetes, viral and bacterial infections and cancer. Iminosugars—saccharides in which the oxygen ring atom has been substituted by a nitrogen—are potent glycosidase inhibitors, acting as mimics of the corresponding glycosidic substrates.[1–2] Derivatization of iminosugars by modification of the nitrogen and the pseudo-anomeric carbon has been widely reported.[3] However, the introduction of other substituents, such as halogens or amines, to replace some of the hydroxyl groups of the skeleton is relatively uncommon and synthetically challenging.[4] Iminosugars in which an acetamido moiety replaces a hydroxyl group have received considerable attention in recent years due to their high selectivity for hexosaminidases, thus making them potentially useful for the treatment of lysosomal storage disorders,[5] Alzheimer,[6] some cancers[7] and other *O*-GlNAcase-related diseases[8]. The acetamido moiety is crucial for the high affinity of these compounds.[9] Natural products of this family, such as siastatin B (**1**)[10], nagstatin (**2**)[11] and pochonicine (**3**),[12] have been reported to show inhibitory activity that ranges from low micromolar to nanomolar. Among synthetic compounds,[13] *N*-acetylglucosamine analogues such as 2-acetamido-1,2-dideoxynojirimycin (**4**),[14] and their *galacto* (**5**)[15] or *allo* (**6**)[16] isomers have received special attention (Figure 1). Most of the synthetic procedures for the synthesis of iminosugars described to date are based on the *chiral pool* starting from sugars or amino acids.[17] Conversely, our approach to iminosugar synthesis is based on the key precursor **7**, which is easily accessible in high enantiomeric purity and multigram scale by Sharpless Asymmetric Epoxidation of 2,4-pentadien-1-ol[18] or 1,4-pentadien-3-ol.[19a] Carbamate **7** is a versatile intermediate that has been widely used for the synthesis of several carbohydrate-related compounds.[19] Following this approach we have reported efficient stereoselective procedures to obtain (2*S*)-2-acetamido iminosugars **4**, **5** and **6**.[14f,16] In our previous work, the (*S*) configuration of the acetamide in position 2 was secured by substitution reactions that took place with complete inversion of configuration.

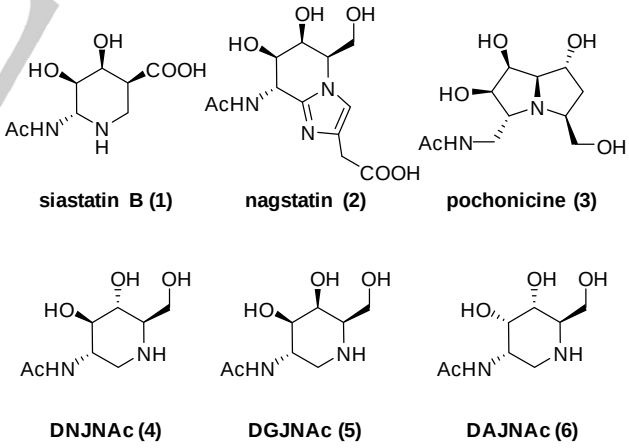

Figure 1. Natural and synthetic examples of acetamido iminosugars.

Herein we describe a new approach to obtain the previously unknown 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer (**9**), both with the (*R*) configuration in position 2 (Figure 2). To this end, we have taken advantage of the anchimeric effect of the nitrogen ring atom to perform substitution reactions with retention of configuration. These methodologies, which are short and give a high overall yield, have given access to a basic scaffold that can be easily modified to afford inhibitors with better drug-like properties.

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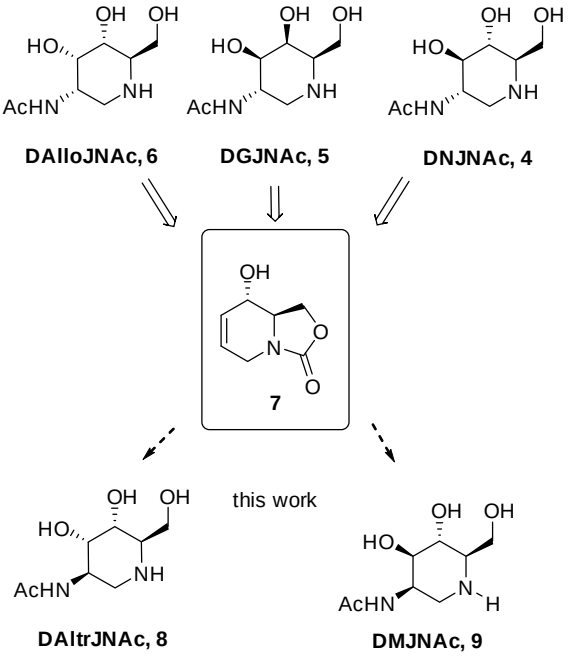
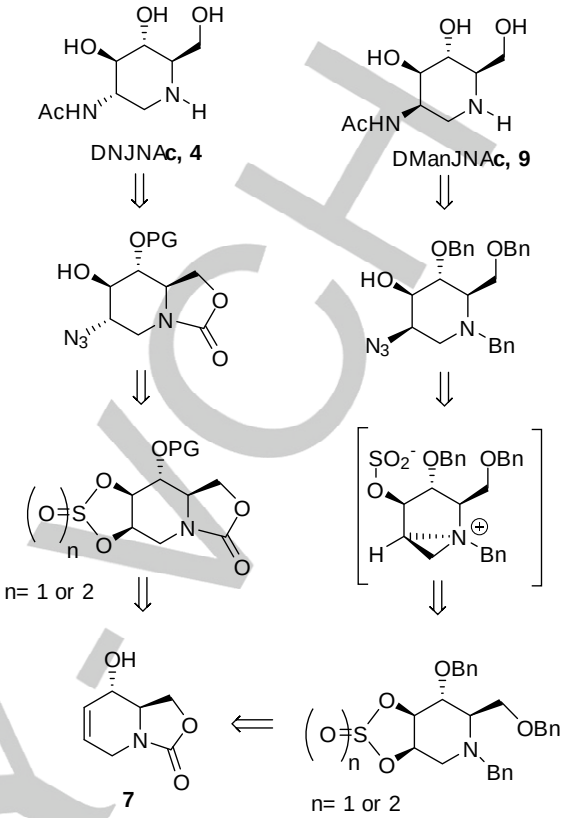


Figure 2. Stereodivergent approach to 2-acetamido-1,2-dideoxyiminosugars.

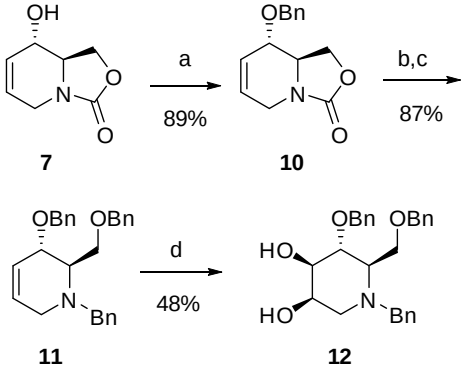
Results and Discussion

In our search to develop new methodologies through which to obtain (2*R*)-acetamido iminosugars, we envisaged exploiting the basic character of the nitrogen ring to generate a cyclic aziridinium cation susceptible to being opened by nitrogen nucleophiles, thereby leading to an overall retention of configuration process. Therefore, instead of having a carbamate protecting group during the ring-opening of the sulphate with azide (Scheme 1, left), we considered that, that by using an alkyl protecting group, the nucleophilic attack would take place with retention of configuration via the aziridinium ion (Scheme 1, right). The anchimeric assistance of heterogeneous atoms in cyclic systems has previously been studied.[20] Although this approach has been applied to ring expansion reactions in iminosugar synthesis by Cossy *et al*.[21], to the best of our knowledge, it has not been used to open an epoxide, a sulphite or a sulphate with retention of configuration.



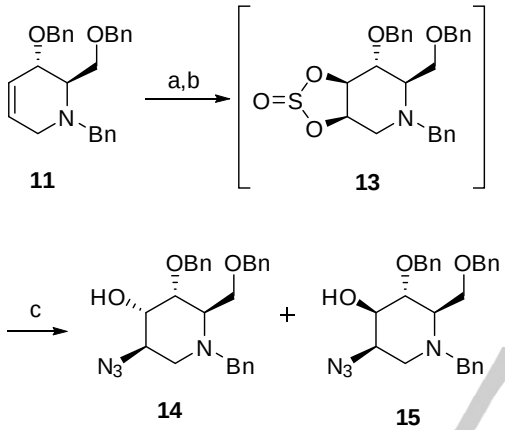
Scheme 1. Retrosynthetic analysis for 2*S* and *2R*-acetamido iminosugars.

We started our syntheses by preparing multigram amounts of carbamate **7** using the procedure described. Optically pure **7**, was first protected as the benzyl derivative **10** by treatment with BnBr/NaH. Hydrolysis of the 2-oxazolidinone ring and protection of the corresponding amino alcohol with BnBr/NaH gave the fully benzyl protected derivative **11** in 87% yield. Dihydroxylation of this olefin using Sharpless conditions[14f] rendered the diol **12** in 48% yield. The low yield was due to partial decomposition during chromatography (Scheme 2).



Scheme 2. a)BnBr, NaH, DMF, rt. b) NaOH 6M reflux, c) BnBr, NaH, DMF, rt; d) $(DHQD)_2Phal$, $K_2OsO_4{\cdot}2H_2O$, $K_3[Fe(CN)_6]$, K_2CO_3, $CH_3SO_2NH_2$, ACN:H_2O 1:1, rt.

Sulphite **13** was obtained as a mixture of diastereoisomers in moderate yield by treatment of **12** with $SOCl_2$/TEA. Its isolation was complex due to its tendency to decompose, so it was used directly in the next steps as a crude. Attempts to obtain the corresponding sulphate by oxidation of the sulphite or treatment of diol **12** with SO_2Cl_2/TEA[22] were unsuccessful. Therefore, the ring-opening reactions of **13** with NaN_3 were widely explored (Scheme 3, Table 1). Due to the difficulty in handling the intermediates, the three reactions were done consecutively. The ratio of azido alcohols was the same as when the reaction was performed on pure **13**, thereby demonstrating that the impurities of the first reactions have no effect on the opening reaction. After optimization of the reaction conditions, a 78:22 mixture of isomers was obtained in 47% yield in three steps. Separation of the two products by chromatography was achieved in a straightforward manner.



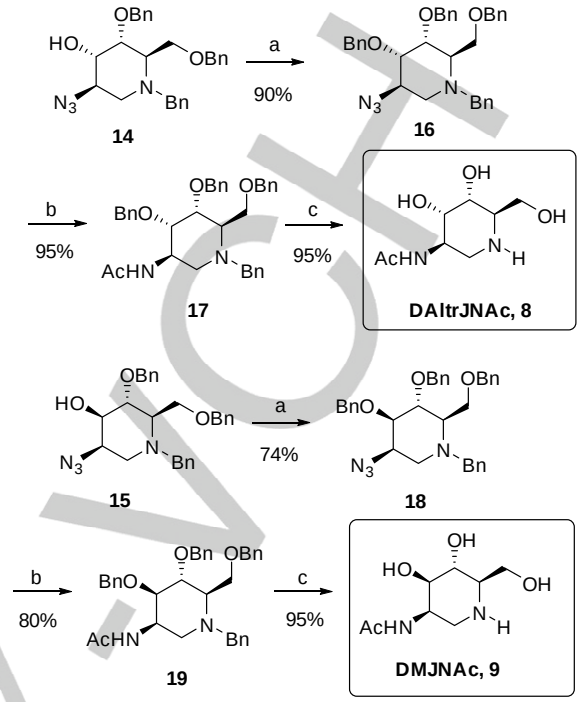
Scheme 3. a) $(DHQD)_2Phal$, $K_2OsO_4{\cdot}2H_2O$, $K_3[Fe(CN)_6]$, K_2CO_3, $CH_3SO_2NH_2$, ACN, H_2O, rt; b) $SOCl_2$/TEA; c) NaN_3, acetone, H_2O.

The stereochemistry of **14**/**15** could not be determined by either NMR or by X-Ray diffraction studies. Therefore, the same chemical transformations were applied to both isomers in order to achieve the final 2*R*-acetamido iminosugars. The following reaction sequence was used: protection of the free hydroxyl by BnBr/NaH; hydrogenation of the azide catalyzed by Pd/C; *in situ* formation of the acetamide with Ac_2O/pyridine; and cleavage of the benzyl groups by hydrogenolysis. In both cases, the final iminosugars were achieved in excellent yields (Scheme 4).

Table 1. Conditions, overall yields and d.r of the conversion of **11** into **14/15** (three steps).

Entry	NaN_3/equiv	T/ºC	Yield / %]	**14/15**
1[a]	3	50	71	54/47
2	3	50	19	60/40
3	2	rt	34	80/20
4	1.2	35	47	78/22

[a] Starting from pure **13**



Scheme 4. a) BnBr, NaH, DMF, rt; b) i) H_2 (3 bar), Pd/C, EtOAc, ii) Ac_2O, pyr; c) H_2 (5 bar), Pd/C, HCl 1.25M, MeOH, rt.

NMR analysis of the minor product allowed us to identify it as the already described 2-acetamido-1,2-dideoxymannojirimycin (DMJNAc, **9**), which was consistent with the previously reported data.[14c, 23] The stereochemistry of **8** in C2-C3 (according to iminosugar nomenclature) was determined using NMR techniques. Coupling constant analysis of H^3 showed an *eq-eq* (*J*= 2.0 Hz) and *ax-eq* (*J*= 4.5 Hz) correlation consistent with an *altro* configuration. Further NOESY analysis of this compound corroborated this configuration by the absence of NoE between H^3-H^5 and allowed us to identify the 2-acetamido-1,2-dideoxyaltronojirimycin as the major isomer (Figure 3).[14e]

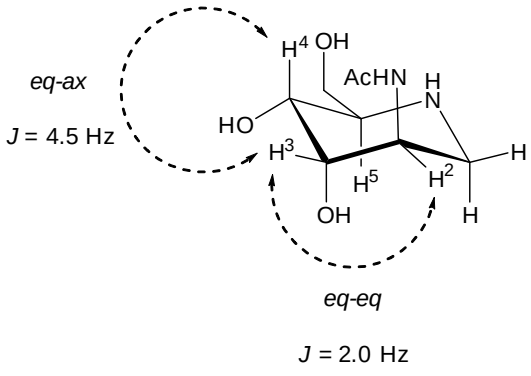
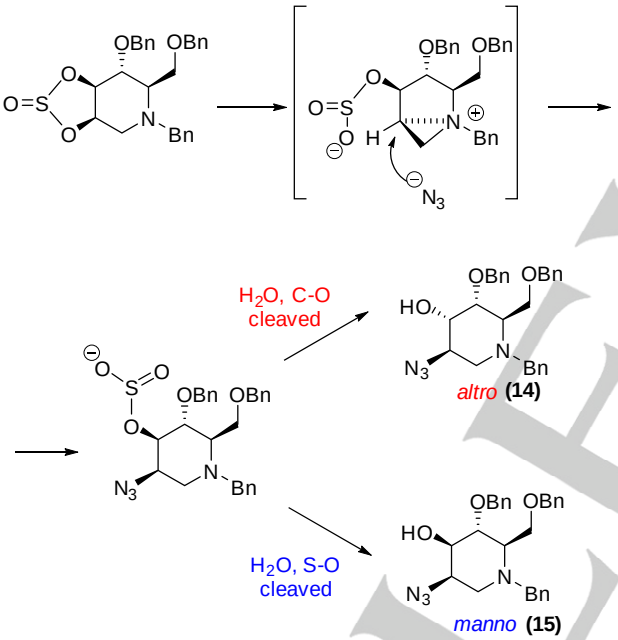


Figure 3. Stereochemistry determination of **8.**

In summary, here we synthetized both the *manno* and *altro* isomers of 2-acetamido-1,2-dideoxynojirimycin. Our procedure is based on the ring-opening of a sulphite with an azide that takes place with retention of configuration. We found that when the piperidine nitrogen is protected with an alkyl group such as benzyl, the nucleophilic ring-opening takes place with overall retention. Therefore, these results show the ability of the endocyclic amine to generate a putative aziridinium cation that can be attacked by the nucleophile. As the subsequent hydrolysis of the sulphite was not stereospecific, a substantial inversion of the secondary hydroxyl to obtain **14** was observed. It is known that the sulphite residual group can be hydrolysed both at the S-O or the C-O bond to afford two diastereomeric azido alcohols.[24] Although, in general, only the first product was observed, in this particular case the resulting C-O cleaved bond product resulted to be the major isomer affording an inverted alcohol (Scheme 5).



Scheme 5. Stereochemical pathway leading to isomers **14** and **15**.

Conclusions

A stereoselective synthesis of 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer (**9**) has been described using Sharpless epoxidation as a source of chirality. This procedure completes an efficient stereodivergent approach to five isomers of 2-acetamido-1,2-dideoxyiminosugars with high overall yields starting from the same key intermediate **7**. The present approach is based on the stereoselective control of the sulphite ring-opening with retention of configuration due to the anchimeric effect of the endocyclic amine.

Experimental Section

General considerations

All reactions were performed in flame-dried glassware under nitrogen. Anhydrous solvents used were taken from a Solvent Purification System (Pure solve-MD-3; Innovative Technology, Inc.). All reagents were used as received. Optical rotations were measured at room temperature (23 ºC), and concentrations are reported in g/100 mL. ^{1}H NMR spectra were obtained at 400 MHz with tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained at 100.6 MHz, and referenced to the solvent signal. Chemical shifts are recorded in ppm. Chromatographic separations were performed with SiO_2 (70-230 mesh).

(8*S*,8a*R*)-8-(Benzyloxy)-8,8a-dihydro-1H-oxazolo[3,4-a]pyridin-3-one (10)

To a stirred suspension of NaH (0.26 g, 10.83 mmol) in 10 mL of DMF at 0ºC was added via cannula a solution of compound **7** (0.75 g, 4.82 mmol) in DMF (7 mL). After 10 min, benzyl bromide (0.61 mL, 5.06 mmol) was added via syringe and the temperature was left to warm to room temperature. After 4 h of vigorous stirring the crude was treated with water (10 mL), extracted with EtOAc (3x20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel using hexane/ethyl acetate and increasing polarity ratio to give **10** as a slight grey solid (1.21 g, 89%).

[α]$^{20}_{D}$ = +64.8 (c=1.8, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.41 – 7.29 (m, 5H), 5.97 (dd, *J*= 10.5, 1.5 Hz, 1H), 5.82 (dd, *J*= 10.5, 2.5 Hz, 1H), 4.73 (d, *J*= 11.5 Hz, 1H), 4.52 (d, *J*= 11.5 Hz, 1H), 4.46 (dd, *J*= 9.0, 8.0 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.94 (m, 1H), 3.70 – 3.58 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 157.1 (CO), 137.3 (C), 128.6 (CH), 128.2 (CH), 127.9 (CH), 126.4 (CH), 124.8 (CH), 74.0 (CH), 71.1 (CH_2), 67.4 (CH_2), 54.5 (CH), 40.9 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 3033, 2911, 1761, 1478, 1454, 1420, 1389, 1204, 1082, 1030. **EM** (CI-NH_3, m/z): 246 (M+1, 64%), 263 (M+18, 100%). **El. Anal.** Calcd. for $C_{14}H_{15}NO_3$: C, 68.56%; H, 6.16%; N, 5.71%; found C, 68.85%; H, 6.01%; N, 5.64%

(2*R*,3*S*)-*N*-Benzyl-3-benzyloxy-2-benzyloxymethyl-1,2,3,6-tetrahydropyridine (11)

To a solution of **10** (0.17 g, 0.67 mmol) in MeOH : H_2O 9:1 (7 mL) was added NaOH 6M (1.1 mL, 6.73 mmol) and the reaction was stirred at reflux during 16 h. The reaction was quenched with HCl 1M until pH 8, extracted with EtOAc (3x 10 mL), washed with brine (1x 10 mL) and dried over $MgSO_4$. Solvent was removed under low pressure obtaining a white solid, which was dissolved in DMF (4 mL) and added via cannula to a suspension of NaH (68 mg, 2.69 mmol) in DMF (2 mL) cooled at 0ºC. After 10 min, benzyl bromide (0.21 mL, 6.73 mmol) was added and the reaction was allowed to stir at r.t. for 16h. H_2O (10 mL) was added and the crude was extracted with EtOAc (3x 5 mL), dried over $MgSO_4$ and purified on silica·Et_3N (2,5% v/v) using hexane/EtOAc to give **11** (0.23 mg, 87%) as a yellow oil.

$[\alpha]^{20}_D$ = +12.7 (c=0.2, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.42 – 7.20 (m, 15H), 5.86 (m, 2H), 4.53 (s, 2H), 4.46 (s, 2H), 3.97 (m, 2H), 3.77 (d, *J* = 14.5 Hz), 3.75 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.50 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.17 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.08 (s, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 139.2 (C), 138.8 (C), 138.3 (C), 129.4 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 124.1 (CH), 73.2 (CH_2), 72.3 (CH), 70.5 (CH_2), 66.5 (CH_2), 59.3 (CH), 58.2 (CH_2), 48.8 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 3028, 2857, 1494, 1452, 1098, 1069, 735, 696 **HRMS** (ES): Calcd. for $C_{27}H_{30}NO_2$: 400.22711, found 400.22695

4,6-Di-*O*-benzyl-5-*N*-Benzyl-1-deoxymannojirimycin (12)

$(DHQD)_2Phal$ (21 mg, 0.03 mmol), K_2OsO_4 (6 mg, 0.01 mmol), K_2CO_3 (135 mg, 0.97 mmol), and $K_3[Fe(CN)_6]$ (322 mg, 0.97 mmol) were dissolved in ACN:H_2O 1:1 (4 mL). The reaction was cooled to 0 ºC and $CH_3SO_2NH_2$ (32 mg, 0.32 mmol) was then added. After 10 min, a solution of **13** (0.13 g, 0.32 mmol) in ACN:H_2O 1:1 (2 mL) was added and the mixture was left to warm to r.t. and stirred until no starting material was observed by TLC. The reaction was treated with Na_2SO_3 (200 mg) and stirred for 1h. It was then extracted with EtOAc (3x 10mL) and the organic phase was washed with brine (1x 10mL), dried over $MgSO_4$, and purified on silica·Et_3N (2,5% v/v) using hexane/EtOAc to give **12** (72 mg, 48%) as one diastereomer as a yellow oil.

$[\alpha]^{20}_D$ = -7.2 (c=0.15, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.34 – 7.24 (m, 15H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.46 (s, 2H), 4.17 (d, *J* = 13.0 Hz, 1H), 3.83 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.0 Hz, 2H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.57 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.27 (d, *J* = 12.5 Hz, 1H), 2.91 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.38 (dt, *J* = 8.5, 2.5 Hz, 1H), 2.22 (dd, *J* = 12.5, 1.5 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 138.6 (C), 138.5 (C), 137.8 (C), 128.9 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 78.4 (CH), 75.9 (CH), 74.7 (CH_2), 73.3 (CH_2), 68.1 (CH), 66.8 (CH_2), 64.8 (CH), 56.6 (CH_2), 54.7 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 3406, 2911, 2859, 1452, 1097, 1066, 734, 697. **HRMS** (ES): Calcd. for $C_{27}H_{32}NO_4$: 434.23259, found 434.23314

2-Azido-4,6-di-*O*-benzyl-5-*N*-benzyl-1,2-dideoxyaltronojirimycin (14) and 2-Azido-4,6-di-*O*-benzyl-5-*N*-benzyl-1,2-dideoxymannojirimycin (15)

$(DHQD)_2Phal$ (0.12 g, 0.15 mmol), K_2OsO_4 (27 mg, 0.07 mmol), K_2CO_3 (882 mg, 6.38 mmol) and $K_3[Fe(CN)_6]$ (2.1 g, 6.38 mmol) were dissolved in ACN:H_2O 1:1 (15 mL). The reaction was cooled to 0 ºC and $CH_3SO_2NH_2$ (208 mg, 2.11 mmol) was then added. After 10 min, a solution of **13** (0.84 g, 2.11 mmol) in ACN:H_2O 1:1 (6 mL) was added and the mixture was left to warm to r.t. and stirred until no starting material was observed by TLC. The reaction was treated with Na_2SO_3 (3 g) and stirred for 1h. The crude was extracted with EtOAc (3x 30 mL) and the organic phase was washed with brine (1x 10 mL) and dried over $MgSO_4$. The resulting oil was redissolved in CH_2Cl_2 (35 mL) and cooled at 0ºC. TEA (1.23 mL, 8.84 mmol) was added followed by dropwise addition of $SOCl_2$ (490 µL, 7.58 mmol). The reaction was stirred at 0ºC for 1h. H_2O (30 mL) was added and the crude was extracted with CH_2Cl_2 (3x 20 mL). The resulting orange oil was redissolved in acetone:water 2:1 (66 mL) and NaN_3 (164 mg, 2.52 mmol) was added. The mixture was stirred at 35ºC overnight. Solvents were removed under low pressure and the resulting aqueous phase was extracted with EtOAc (3x 30 mL), dried over $MgSO_4$ and purified on silica·Et_3N (2,5% v/v) using hexane/EtOAc to give give **16** (0.34 g, 35%) as a colorless oil and **17** (110 mg, 11%) as a colorless oil.

$[\alpha]^{20}_D$ = +35.0 (c=0.80, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.37 – 7.21 (m, 15H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.10 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.97 (d, *J* = 14.0 Hz, 1H), 3.89 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 1H), 3.71 (d, *J* = 14.0 Hz, 1H), 3.60 (dd, *J* = 11.5, 8.5 Hz, 1H), 3.32 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.27 – 3.16 (m, 2H), 3.08 – 3.01 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 139.6 (C), 137.9 (C), 137.2 (C), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 86.0 (CH), 73.7 (CH_2), 73.6 (CH), 71.32 (CH_2), 71.0 (CH), 70.8 (CH_2), 67.1 (CH), 58.6 (CH_2), 50.2 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 3410, 2930, 2859, 2099, 1453, 1090, 1021. **HRMS** (ES): Calcd. for $C_{27}H_{31}N_4O_3$: 459.23907, found 459.23863

$[\alpha]^{20}_D$ = -19.3 (c=0.75, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.37 – 7.22 (m, 15H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.50 (s, 2H), 4.10 (d, *J* = 13.5 Hz, 1H), 3.80 (m, 3H), 3.71 (m, 2H), 3.86 – 3.66 (m, 5H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.03 (dd, *J* = 12.5, 5.5 Hz, 1H), 2.78 (br, 1H), 2.61 (m, 1H), 2.37 (dd, *J* = 12.5, 2.5 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 138.6 (C), 138.1 (C), 137.7 (C), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 78.3 (CH), 73.9 (CH_2), 73.3 (CH_2), 73.2 (CH), 67.7 (CH_2), 62.8 (CH), 59.0 (CH), 57.6 (CH_2), 50.6 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 3423, 2917, 2099, 1452, 1270, 1097, 1027. **HRMS** (ES): Calcd. for $C_{27}H_{31}N_4O_3$: 459.23907, found 459.23833

2-Azido-3,4,6-tri-*O*-benzyl-5-*N*-benzyl-1,2-dideoxyaltronojirimycin (16)

To a suspension of NaH (27 mg, 1.05 mmol) in DMF (1 mL) cooled at 0ºC was added via cannula a solution of **16** (161 mg, 0.35 mmol) in DMF (4 mL). After 10 min, benzyl bromide (64 µL, 0.52 mmol) was added dropwise and the reaction was allowed to stir at r.t. until no starting material was observed by TLC. Then, H_2O (5 mL) was added and the reaction was extracted with CH_2Cl_2 (3x 5 mL), dried over $MgSO_4$ and purified by chromatography on silica gel using hexane/EtOAc to give **16** (172 mg, 89%) as a colorless oil.

$[\alpha]^{20}_D$ = +10.5 (c=1.55, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.35 – 7.15 (m, 20H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 12.0 Hz, 1H), 4.00 –

3.96 (m, 2H), 3.89 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.44 (dd, *J* = 11.5, 8.5 Hz, 1H), 3.37 (m, 1H), 3.25 (m, 1H), 3.20 – 3.12 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 139.3 (C), 138.4 (C), 138.2 (C), 137.8 (C), 129.00 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 82.5 (CH), 82.0 (CH), 72.9 (CH_2), 71.9 (CH_2), 71.8 (CH_2), 71.1 (CH_2), 68.9 (CH), 65.9 (CH), 59.9 (CH_2), 50.4 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 2923, 2861, 2099, 1453, 1093, 1059. **HRMS** (ES): Calcd. for $C_{34}H_{37}N_4O_3$: 549.28602, found 549.28552

2-Acetamido-3,4,6-tri-*O*-benzyl-5-*N*-benzyl-1,2-dideoxyaltronojirimycin (17)

To a solution of **16** (133 mg, 0.24 mmol) in EtOAc (5 mL) was added Pd/C (13 mg, 0.01 mmol) and was charged with H_2 (5 barg) and stirred at r.t. for 20h. Palladium was filtered over Celite washing with MeOH and solvents were removed under low presure. The obtained colorless oil was redisolved in pyridine (2 mL) and Ac_2O (48 µL, 0.39 mmol) was added. The reaction was stirred at 40ºC for 16h. Then, H_2O (5 mL) was added and the reaction was extracted with EtOAc (3x 5 mL), dried over $MgSO_4$ and purified by chromatography on silica gel using hexane/EtOAc to give **17** (110 mg, 80%) as a slightly yellow oil.

$[\alpha]^{20}_D$ = +24.8 (c=1.21, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.38 – 7.20 (m, 20H), 5.81 (t, *J* = 5.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 2H), 3.98 (t, *J* = 3.5Hz, 1H), 3.89 (m, 2H), 3.72 (d, *J* = 13.5 Hz, 1H), 3.42 (ddd, *J* = 13.5, 5.5, 3.5 Hz, 1H), 3.35 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.28 (m, 1H), 3.19 (m, 2H), 3.09 (m, 1H), 1.62 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 169.7 (CO), 138.9 (C), 138.3 (C), 138.2 (C), 137.8 (C), 129.2 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 127.2 (CH), 83.1 (CH), 81.7 (CH), 73.0 (CH_2), 71.7 (CH_2), 71.3 (CH_2), 70.7 (CH_2), 67.9 (CH), 63.4 (CH), 58.5 (CH_2), 38.0 (CH_2), 23.0 (CH_3). **IR** (film, ν_{max} / cm^{-1}): 3295, 2861, 1652, 1453, 1098, 1066, 735, 697. **HRMS** (ES): Calcd. for $C_{36}H_{41}N_2O_4$: 565.30608, found 565.30538

2-Acetamido-1,2-dideoxyaltronojirimycin (8)

To a solution of **19** (74 mg, 0.13 mmol) in HCl 1,25 M MeOH (3 mL) was added Pd/C (12 mg, 0.01 mmol) and the reaction was charged with H_2 (5 barg) and stirred at r.t. for 20h. Palladium was filtered over Celite washing with MeOH and solvents were removed under low presure. The crude was purified by chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:8:2 to give **8** (23 mg, 85%) as a colorless oil.

$[\alpha]^{20}_D$ = +11.7 (c=0.55, H_2O). **^{1}H-NMR** (400 MHz, D_2O, δ/ppm): 4.04 (dd, *J* = 4.5, 2.5 Hz, 1H), 3.89 (dd, *J* = 5.0, 2.5 Hz, 1H), 3.73 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.66 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.45 (m, 1H), 3.32 – 3.24 (m, 2H), 3.01 (m, 1H), 2.02 (s, 3H). **^{13}C-NMR** (100 MHz, D_2O, δ/ppm, TFA internal reference): 174.4 (CO), 79.1 (CH), 77.3 (CH), 65.2 (CH), 642.0 (CH_2), 59.3 (CH), 38.6 (CH_2), 21.8 (CH_3). **IR** (film, ν_{max} / cm^{-1}): 3212, 3051, 2894, 1661, 1437, 1200, 1130. **HRMS** (ES): Calcd. for $C_8H_{17}N_2O_4$: 205.11828, found 205.11812

2-Azido-3,4,6-tri-*O*-benzyl-5-*N*-benzyl-1,2-dideoxymannojirimycin (18)

To a suspension of NaH (17 mg, 0.67 mmol) in DMF (1 mL) cooled at 0ºC was added via cannula a solution of **17** (102 mg, 0.22 mmol) in DMF (4 mL). After 10 min, benzyl bromide (41 µL, 0.34 mmol) was added dropwise and the reaction was allowed to stir at r.t. until no starting material was observed by TLC. Then, H_2O (5 mL) was added and the reaction was extracted with CH_2Cl_2 (3x 5 mL), dried over $MgSO_4$ and purified by chromatography on silica·Et_3N (2,5% v/v) using hexane/EtOAc to give **18** (90 mg, 74%) as a slightly yellow oil.

$[\alpha]^{20}_D$ = -30.1 (c=0.59, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.38 – 7.17 (m, 20H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.43 (s, 2H), 4.12 (d, *J* = 13.5 Hz, 1H), 3.86 (t, *J* = 7.5 Hz, 1H), 3.77 (m, 2H), 3.74 (dt, *J* = 5.5, 3.0 Hz, 1H), 3.64 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 2.96 (dd, *J* = 12.5, 5.5 Hz, 1H), 2.65 (m, 1H), 2.27 (dd, *J* = 12.5, 3.0 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 138.7 (C), 138.3 (C), 138.2 (C), 137.8 (C), 128.7 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 81.6 (CH), 75.4 (CH), 74.2 (CH_2), 73.0 (CH_2), 72.3 (CH_2), 67.6 (CH_2), 63.4 (CH), 57.7 (CH_2), 56.7 (CH), 50.6 (CH_2). **IR** (film, ν_{max} / cm^{-1}): 2853, 2096, 1452, 1102, 1066. **HRMS** (ES): Calcd. for $C_{34}H_{37}N_4O_3$: 549.2860, found 549.2855

2-Acetamido-3,4,6-tri-*O*-benzyl-5-*N*-benzyl-1,2-dideoxymannojirimycin (19)

To a a solution of **18** (90 mg, 0.16 mmol) in EtOAc (4 mL) was added Pd/C (17 mg, 0.01 mmol) and the reaction was charged with H_2 (5 barg) and stirred at r.t. for 20h. Palladium was filtered over Celite washing with MeOH and solvents were removed under low presure. The obtained colorless oil was redisolved in pyridine (2 mL) and Ac_2O (24 µL, 0.23 mmol) was added. The reaction was stirred at r.t. for 16h. Then, H_2O (5 mL) was added and the reaction was extracted with EtOAc (3x 5 mL), dried over $MgSO_4$ and purified on silica·Et_3N (2,5% v/v) using hexane/EtOAc to give **19** (74 mg, 80%) as a slightly yellow oil.

$[\alpha]^{20}_D$ = -8.1 (c=0.79, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ/ppm): 7.37 – 7.20 (m, 20H), 6.19 (d, *J* = 9.5 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.53 (m, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 13.5 Hz, 1H), 3.81 (m, 2H), 3.71 (t, *J* = 8.5 Hz, 1H), 3.55 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 2.72 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.47 (dt, *J* = 8.5, 3.0 Hz, 1H), 2.22 (dd, *J* = 12.0, 2.0 Hz, 1H), 1.93 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$, δ/ppm): 169.8 (CO), 138.7 (C) , 138.5 (C), 138.1 (C), 137.9 (C), 128.9 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 81.7 (CH), 77.0 (CH), 74.8 (CH_2), 73.3

(CH_2), 71.1 (CH_2), 66.5 (CH_2), 64.5 (CH), 56.7 (CH_2), 52.8 (CH_2), 44.3 (CH), 23.5 (CH_3). **IR** (film, ν_{max} / cm^{-1}): 2860, 1674, 1496, 1452, 1011. **HRMS** (ES): Calcd. for $C_{36}H_{40}N_2O_4$: 565.3061, found 565.3050

2-Acetamido-1,2-dideoxymannojirimycin (9)

A solution of **19** (20 mg, 0.04 mmol) in HCl 1,25 M MeOH (3 mL) was added Pd/C (espatula tip) and was charged with H_2 (5 barg) and stirred at r.t. for 20h. Palladium was filtered over Celite washing with MeOH and solvents were removed under low presure. The crude was purified by chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:8:2 to give **9** (7 mg, 95%) as a white solid. Spectroscopic data were consistent with previously reported data.[23]

^{1}H-NMR (400 MHz, CD_3OD, δ/ppm): 4.50 (s, 1H), 3.82 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.72 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.60 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.45 (t, *J* = 9.5 Hz, 1H), 3.00 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.79 (dd, *J* = 13.0, 2.5 Hz, 1H), 2.47 (ddd, *J* = 9.5, 5.5, 3.0 Hz, 1H), 2.04 (s, 3H). **HRMS** (ES): Calcd. for $C_8H_{17}N_2O_4$: 205.11828, found 205.11830.

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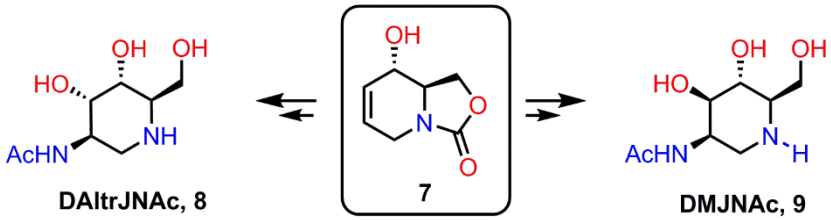

Iminosugars*

*Alex de la Fuente, Xavier Verdaguer, Antoni Riera**

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Stereodivergent syntheses of *altro* and *manno* stereoisomers of 2-acetamido-1,2-dideoxynojirimycin

The *altro* and *manno* isomers (**8** and **9**) of 2-acetamido-1,2-dideoxynojirimycin have been synthetized from the key intermediate **7**. The key step was the stereoselective sulphite ring-opening with retention of configuration due to the anchimeric effect of the endocyclic amine.