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Iminosugars

# 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 key bicyclic carbamate **7**, which is easily accessible with high enantiomeric purity on a 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 in high overall yields starting from the same key intermediate **7**. The approach described in this paper is based on control of the stereoselectivity of the sulfite ring-opening reaction to give retention of configuration through anchimeric assistance from the endocyclic amine.

## Introduction

Carbohydrates are involved in a variety of metabolic processes. Inhibitors of enzymes related to carbohydrate metabolism, such as glycosidases or glycosyltransferases, have potential applications in the treatment of several diseases, including diabetes, viral and bacterial infections, and cancer. Iminosugars — saccharides in which the ring oxygen 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. This makes them potentially useful for the treatment of lysosomal storage disorders,[5] Alzheimer's disease,[6] some cancers,[7] and other *O*-GlcNAcase-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 activities that range from low micromolar to nanomolar. Among the synthetic compounds that have been reported,[13] *N*-acetylglucosamine analogues such as 2-acetamido-1,2-dideoxynojirimycin (**4**),[14] and their *galacto* (**5**)[15] and *allo* (**6**)[16] isomers, have received special attention (Figure 1). Most procedures for the synthesis of iminosugars that have been 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 on a 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 substituent at the 2-position was secured by substitution reactions that took place with complete inversion of configuration.

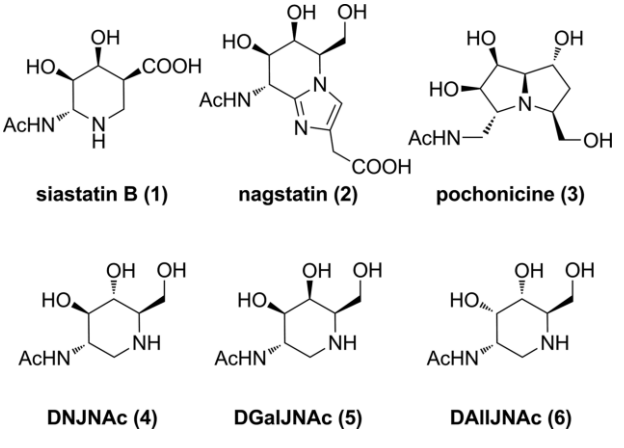


Figure 1. Natural and synthetic examples of acetamido iminosugars.

In this paper, we describe a new approach to the previously unknown 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer **9**, both with the (*R*) configuration at the 2-position (Figure 2). To achieve this, we took advantage of the anchi-

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meric effect of the ring nitrogen to carry out substitution reactions with retention of configuration. These syntheses, which are short, and gave high overall yields, give access to scaffolds that can be easily modified to give inhibitors with more drug-like properties.

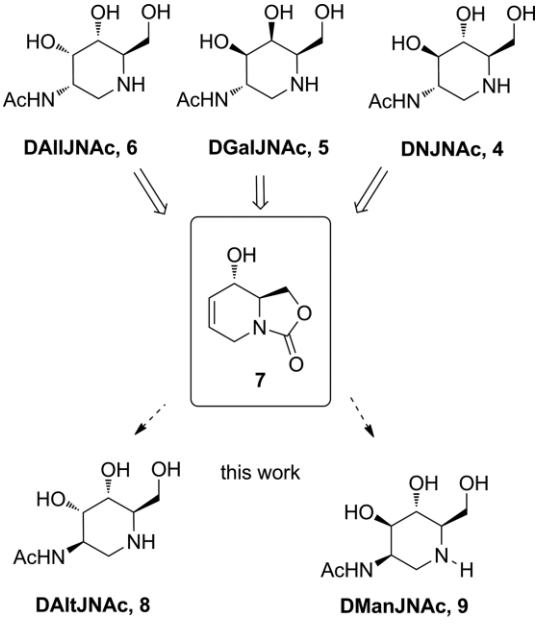


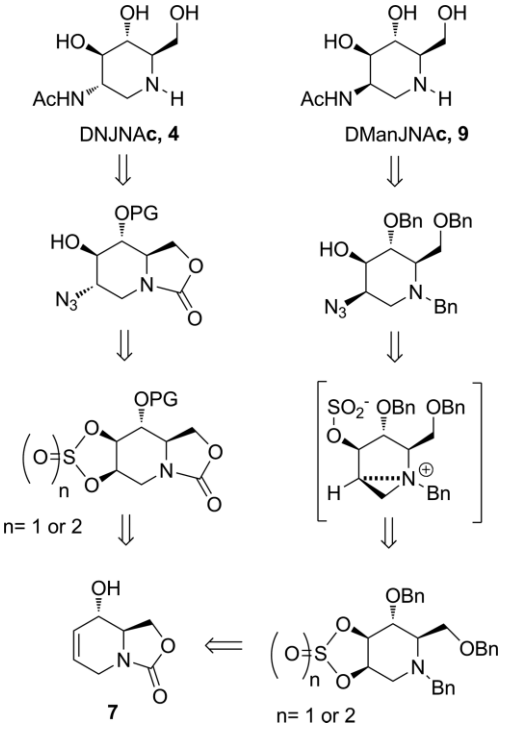

Figure 2. Stereodivergent approach to 2-acetamido-1,2-dideoxyiminosugars.

## Results and Discussion

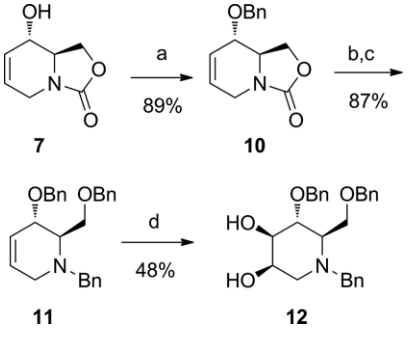
In our search to develop new methods to obtain (2*R*)-acetamido iminosugars, we envisaged exploiting the basic character of the ring nitrogen to generate a cyclic aziridinium cation; this could be opened by nitrogen nucleophiles, resulting in a process with overall retention of configuration. Thus, instead of having a carbamate protecting group during the ring-opening of the sulfate with azide (Scheme 1, left), we considered that with an alkyl protecting group, the nucleophilic attack would take place via the aziridinium ion with overall retention of configuration (Scheme 1, right). Anchimeric assistance by heteroatoms in cyclic systems has been studied previously.[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 sulfite, or a sulfate with retention of configuration.

We started our syntheses by preparing multigram amounts of carbamate **7** using the reported procedure. Optically pure **7** was first protected as 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 fully benzyl-protected derivative **11** in 87 % yield. Dihydroxylation of this olefin under Sharpless conditions[14f] gave diol **12** in 48 % yield. The low yield was due to partial decomposition during chromatography (Scheme 2).

Sulfite **13** was obtained as a mixture of diastereoisomers in moderate yield by treatment of **12** with $SOCl_2/Et_3N$. Its isolation was complex due to its tendency to decompose, so the crude



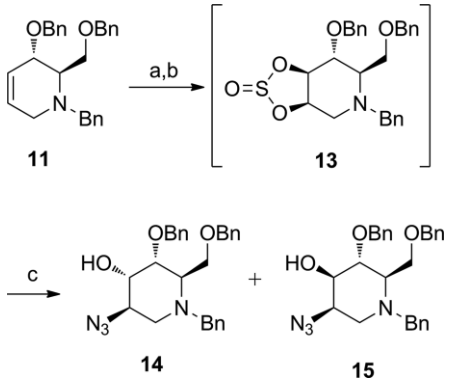

Scheme 1. Retrosynthetic analysis for (2*S*) and (2*R*)-acetamido iminosugars. PG = protecting group.




Scheme 2. a) BnBr, NaH, DMF, room temp.; b) NaOH (6 M aq.), reflux; c) BnBr, NaH, DMF, room temp.; d) $(DHQD)_2Phal$ (hydroquinidine 1,4-phthalazinediyl diether), $K_2OsO_4{\cdot}2H_2O$, $K_3[Fe(CN)_6]$, $K_2CO_3$, $CH_3SO_2NH_2$, MeCN/$H_2O$ (1:1), room temp.

product was used directly in the next step. Attempts to obtain the corresponding sulfate by oxidation of the sulfite or treatment of diol **12** with $SO_2Cl_2/Et_3N$[22] were unsuccessful. Therefore, ring-opening reactions of **13** with $NaN_3$ were widely explored (Scheme 3, Table 1). Due to difficulties in handling the intermediates, the three reactions were carried out consecutively. The ratio of azido alcohols obtained was the same as when the reaction was carried out on pure **13**; this shows that the impurities formed in the first reactions have no effect on the ring-opening reaction. After optimization of the reaction conditions, a 78:22 mixture of isomers was obtained in 47 % yield over three steps. Separation of the two products by chromatography was achieved in a straightforward manner.

The stereochemistry of **14** and **15** could not be determined by either NMR spectroscopy or by X-ray diffraction studies.



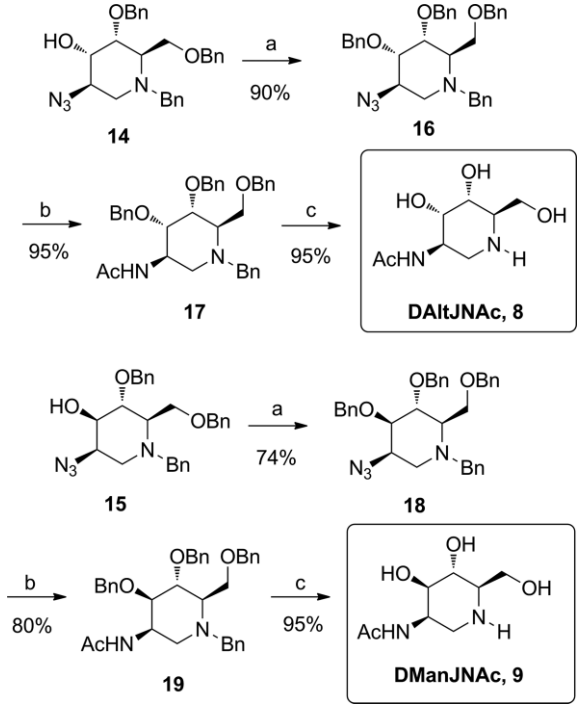

Scheme 3. a) $(DHQD)_2Phal$, $K_2OsO_4{\cdot}2H_2O$, $K_3[Fe(CN)_6]$, $K_2CO_3$, $CH_3SO_2NH_2$, MeCN, $H_2O$, room temp.; b) $SOCl_2/Et_3N$; c) $NaN_3$, acetone, $H_2O$.

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

| Entry | $NaN_3$ [equiv.] | *T* [°C] | Yield [%] | **14/15** ratio |
|---|---|---|---|---|
| 1[a] | 3 | 50 | 71 | 54:47 |
| 2 | 3 | 50 | 19 | 60:40 |
| 3 | 2 | r.t. | 34 | 80:20 |
| 4 | 1.2 | 35 | 47 | 78:22 |

[a] Starting from pure **13**.

Therefore, the same chemical transformations were applied to both isomers to form the final (2*R*)-acetamido iminosugars. The following reaction sequence was used: protection of the free hydroxy group using BnBr/NaH; hydrogenation of the azide catalysed 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 formed in excellent yields (Scheme 4).




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

NMR spectroscopic analysis of the minor product allowed us to identify it as the known 2-acetamido-1,2-dideoxymannojirimycin (DMJNAc; **9**), as its spectroscopic data were consistent with the previously reported data.[14c,23] The stereochemistry of **8** at C-2 and C-3 (iminosugar numbering) was determined using NMR spectroscopic techniques. Coupling constant analysis of 3-H showed an *eq*,*eq* coupling ($J$ = 2.0 Hz) and an *ax*,*eq* coupling ($J$ = 4.5 Hz), consistent with an *altro* configuration. Further NOESY analysis of this compound corroborated this configuration through the absence of an nOe between 3-H and 5-H. This allowed us to identify 2-acetamido-1,2-dideoxyaltronojirimycin as the major isomer (Figure 3).[14e]

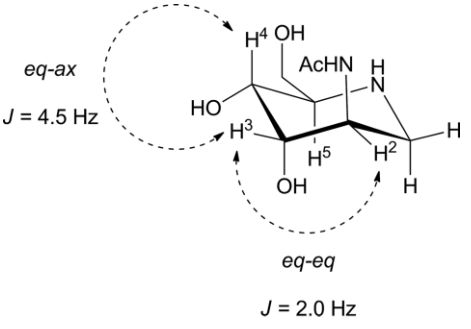
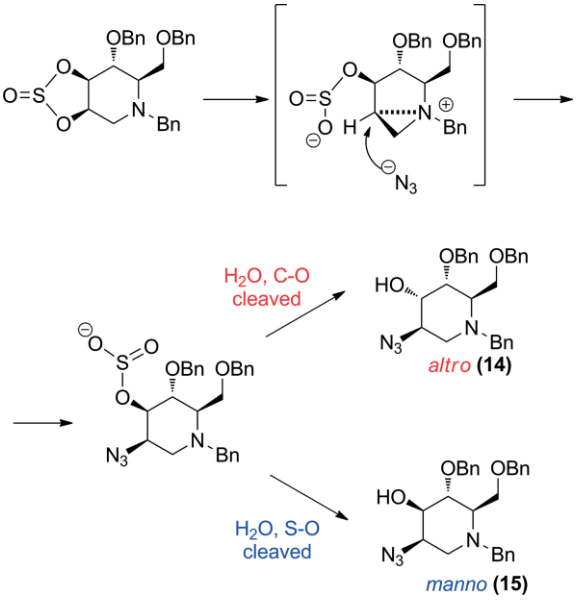



Figure 3. Determination of the stereochemistry of **8**.

In summary, we have synthesized both the *manno* and *altro* isomers of 2-acetamido-1,2-dideoxynojirimycin. Our procedure is based on the ring-opening of a sulfite 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 reaction 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. The subsequent hydrolysis of the sulfite was not stereospecific, and inversion of configuration of the secondary hydroxy group took




Scheme 5. Mechanism of formation of stereoisomers **14** and **15**.

place to a significant extent to give **14**. It is known that a sulfite residue can be hydrolysed at either the S–O or the C–O bond to give two diastereomeric azido alcohols.[24] Although in general, only the first product is observed, in this particular case, the product formed through C–O cleavage, with an inverted alcohol, turned out to be the major isomer (Scheme 5).

## Conclusions

Stereoselective syntheses of 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer **9** have been described, using Sharpless epoxidation as the 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 approach described in this paper is based on control of the stereoselectivity of the sulfite ring-opening reaction to obtain retention of configuration through anchimeric assistance from the endocyclic amine.

## Experimental Section

**General Remarks:** All reactions were carried out in flame-dried glassware under nitrogen. Anhydrous solvents were obtained using a solvent purification system (PureSolv MD-3; Innovative Technology, Inc.). All reagents were used as received. Optical rotations were measured at room temperature (23 °C), and concentrations are reported in g/100 mL. $^1$H NMR spectra were obtained at 400 MHz with tetramethylsilane as an internal standard. $^{13}$C NMR spectra were obtained at 100.6 MHz, and were referenced to the solvent signal. Chemical shifts are given in ppm. Chromatographic separations were carried out with $SiO_2$ (70–230 mesh).

**(8*S*,8a*R*)-8-(Benzyloxy)-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyridin-3-one (10):** A solution of compound **7** (0.75 g, 4.82 mmol) in DMF (7 mL) was added by cannula to a stirred suspension of NaH (0.26 g, 10.83 mmol) in DMF (10 mL) at 0 °C. After 10 min, benzyl bromide (0.61 mL, 5.06 mmol) was added by syringe, and the mixture was allowed to warm to room temperature. The mixture was stirred vigorously for 4 h, then water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, increasing the polarity ratio) to give **10** (1.21 g, 89 %) as a slightly grey solid. $[\alpha]_D^{20}$ = +64.8 (*c* = 1.8, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41–7.29 (m, 5 H), 5.97 (dd, *J* = 10.5, 1.5 Hz, 1 H), 5.82 (dd, *J* = 10.5, 2.5 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.46 (dd, *J* = 9.0, 8.0 Hz, 1 H), 4.15–4.06 (m, 2 H), 3.94 (m, 1 H), 3.70–3.58 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 3033, 2911, 1761, 1478, 1454, 1420, 1389, 1204, 1082, 1030 cm$^{-1}$. MS (CI-$NH_3$): *m/z* (%) = 246 [M + 1] (64), 263 [M + 18] (100). $C_{14}H_{15}NO_3$ (245.28): calcd. 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):** NaOH (6 M aq.; 1.1 mL, 6.73 mmol) was added to a solution of **10** (0.17 g, 0.67 mmol) in MeOH/$H_2O$ (9:1; 7 mL), and the reaction mixture was stirred at reflux for 16 h. The reaction then was quenched with HCl (1 M aq.) until pH 8, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), and dried with $MgSO_4$. The solvent was removed under low pressure to give a white solid.

This material was dissolved in DMF (4 mL), and the resulting solution was added by cannula to a suspension of NaH (68 mg, 2.69 mmol) in DMF (2 mL) at 0 °C. After 10 min, benzyl bromide (0.21 mL, 6.73 mmol) was added, and the reaction mixture was stirred at room temp. for 16 h. $H_2O$ (10 mL) was then added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, and the mixture was purified on silica•$Et_3N$ (2.5 % v/v) using hexane/EtOAc to give **11** (0.23 mg, 87 %) as a yellow oil. $[\alpha]_D^{20}$ = +12.7 (*c* = 0.2, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.20 (m, 15 H), 5.86 (m, 2 H), 4.53 (s, 2 H), 4.46 (s, 2 H), 3.97 (m, 2 H), 3.77 (d, *J* = 14.5 Hz), 3.75 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.50 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.17 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.08 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 3028, 2857, 1494, 1452, 1098, 1069, 735, 696 cm$^{-1}$. HRMS (ESI): 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 MeCN/$H_2O$ (1:1; 4 mL). The reaction mixture was cooled to 0 °C, and $CH_3SO_2NH_2$ (32 mg, 0.32 mmol) was added. After 10 min, a solution of **11** (0.13 g, 0.32 mmol) in MeCN/$H_2O$ (1:1; 2 mL) was added, and the mixture was allowed to warm to room temp. The mixture was stirred until no starting material was observed by TLC. $Na_2SO_3$ (200 mg) was then added, and the mixture was stirred for 1 h. It was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), and dried with $MgSO_4$. The mixture was purified on silica•$Et_3N$ (2.5 % v/v) using hexane/EtOAc to give **12** (72 mg, 48 %) as a yellow oil, as a single diastereomer. $[\alpha]_D^{20}$ = –7.2 (*c* = 0.15, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.24 (m, 15 H), 4.90 (d, *J* = 11.0 Hz, 1 H), 4.56 (d, *J* = 11.0 Hz, 1 H), 4.46 (s, 2 H), 4.17 (d, *J* = 13.0 Hz, 1 H), 3.83 (dd, *J* = 10.5, 2.5 Hz, 1 H), 3.76 (dd, *J* = 10.5, 3.0 Hz, 2 H), 3.64 (t, *J* = 8.5 Hz, 1 H), 3.57 (dd, *J* = 8.5, 3.0 Hz, 1 H), 3.27 (d, *J* = 12.5 Hz, 1 H), 2.91 (dd, *J* = 12.5, 4.5 Hz, 1 H), 2.38 (dt, *J* = 8.5, 2.5 Hz, 1 H), 2.22 (dd, *J* = 12.5, 1.5 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 3406, 2911, 2859, 1452, 1097, 1066, 734, 697 cm$^{-1}$. HRMS (ESI): 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 MeCN/$H_2O$ (1:1; 15 mL). The reaction mixture was cooled to 0 °C, and $CH_3SO_2NH_2$ (208 mg, 2.11 mmol) was added. After 10 min, a solution of **11** (0.84 g, 2.11 mmol) in MeCN/$H_2O$ (1:1; 6 mL) was added, and the mixture was allowed to warm to room temp. The mixture was stirred until no starting material was observed by TLC. $Na_2SO_3$ (3 g) was then added, and the mixture was stirred for 1 h. The mixture was extracted with EtOAc (3 × 30 mL). The organic phase was washed

with brine (1 × 10 mL), and dried with $MgSO_4$, and concentrated in vacuo.

The resulting oil was dissolved in $CH_2Cl_2$ (35 mL), and the solution was cooled to 0 °C. Triethylamine (1.23 mL, 8.84 mmol) was added, followed by the dropwise addition of $SOCl_2$ (490 μL, 7.58 mmol). The reaction mixture was stirred at 0 °C for 1 h. $H_2O$ (30 mL) was then added, and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), and concentrated in vacuo.

The resulting orange oil was dissolved in acetone/water (2:1; 66 mL), and $NaN_3$ (164 mg, 2.52 mmol) was added. The mixture was stirred at 35 °C overnight. After this time, the acetone was removed under low pressure, and the resulting aqueous phase was extracted with EtOAc (3 × 30 mL). The organic phase was dried with $MgSO_4$, and the crude material was purified on silica•$Et_3N$ (2.5 % v/v) using hexane/EtOAc to give **14** (0.34 g, 35 %) as a colourless oil, and **15** (110 mg, 11 %) as a colourless oil.

Data for **14**: $[\alpha]_D^{20}$ = +35.0 (*c* = 0.80, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.21 (m, 15 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.39 (d, *J* = 12.0 Hz, 1 H), 4.10 (dd, *J* = 11.0, 4.0 Hz, 1 H), 3.97 (d, *J* = 14.0 Hz, 1 H), 3.89 (d, *J* = 11.5 Hz, 1 H), 3.81 (s, 1 H), 3.71 (d, *J* = 14.0 Hz, 1 H), 3.60 (dd, *J* = 11.5, 8.5 Hz, 1 H), 3.32 (dd, *J* = 10.5, 3.0 Hz, 1 H), 3.27–3.16 (m, 2 H), 3.08–3.01 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 3410, 2930, 2859, 2099, 1453, 1090, 1021 $cm^{-1}$. HRMS (ESI): calcd. for $C_{27}H_{31}N_4O_3$ 459.23907; found 459.23863.

Data for **15**: $[\alpha]_D^{20}$ = –19.3 (*c* = 0.75, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.22 (m, 15 H), 4.68 (d, *J* = 11.5 Hz, 1 H), 4.57 (d, *J* = 11.5 Hz, 1 H), 4.50 (s, 2 H), 4.10 (d, *J* = 13.5 Hz, 1 H), 3.80 (m, 3 H), 3.71 (m, 2 H), 3.86–3.66 (m, 5 H), 3.46 (d, *J* = 13.5 Hz, 1 H), 3.03 (dd, *J* = 12.5, 5.5 Hz, 1 H), 2.78 (br., 1 H), 2.61 (m, 1 H), 2.37 (dd, *J* = 12.5, 2.5 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 3423, 2917, 2099, 1452, 1270, 1097, 1027 $cm^{-1}$. HRMS (ESI): 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):** A solution of **14** (161 mg, 0.35 mmol) in DMF (4 mL) was added by cannula to a suspension of NaH (27 mg, 1.05 mmol) in DMF (1 mL) at 0 °C. After 10 min, benzyl bromide (64 μL, 0.52 mmol) was added dropwise, and the reaction mixture was stirred at room temp. until no starting material was observed by TLC. Then, $H_2O$ (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic phase was dried with $MgSO_4$. The crude material was purified by chromatography on silica gel using hexane/EtOAc to give **16** (172 mg, 89 %) as a colourless oil. $[\alpha]_D^{20}$ = +10.5 (*c* = 1.55, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.15 (m, 20 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 11.5 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.28 (d, *J* = 12.0 Hz, 1 H), 4.00–3.96 (m, 2 H), 3.89 (d, *J* = 13.5 Hz, 1 H), 3.83 (d, *J* = 13.5 Hz, 1 H), 3.44 (dd, *J* = 11.5, 8.5 Hz, 1 H), 3.37 (m, 1 H), 3.25 (m, 1 H), 3.20–3.12 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 2923, 2861, 2099, 1453, 1093, 1059 $cm^{-1}$. HRMS (ESI): 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):** Pd/C (13 mg, 0.01 mmol) was added to a solution of **16** (133 mg, 0.24 mmol) in EtOAc (5 mL), and the mixture was put under $H_2$ (5 bar). The mixture was stirred at room temp. for 20 h. After this time, the palladium was removed by filtration through Celite, which was then washed with MeOH. The solvents were removed under low pressure.

The resulting colourless oil was dissolved in pyridine (2 mL), and $Ac_2O$ (48 μL, 0.39 mmol) was added. The reaction mixture was stirred at 40 °C for 16 h. Then, $H_2O$ (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the crude material was purified by chromatography on silica gel using hexane/EtOAc to give **17** (110 mg, 80 %) as a slightly yellow oil. $[\alpha]_D^{20}$ = +24.8 (*c* = 1.21, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38–7.20 (m, 20 H), 5.81 (t, *J* = 5.0 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.32 (d, *J* = 12.0 Hz, 1 H), 4.29 (d, *J* = 12.0 Hz, 2 H), 3.98 (t, *J* = 3.5 Hz, 1 H), 3.89 (m, 2 H), 3.72 (d, *J* = 13.5 Hz, 1 H), 3.42 (ddd, *J* = 13.5, 5.5, 3.5 Hz, 1 H), 3.35 (dd, *J* = 9.5, 7.5 Hz, 1 H), 3.28 (m, 1 H), 3.19 (m, 2 H), 3.09 (m, 1 H), 1.62 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_3$) ppm. IR (film): $\tilde{\nu}$ = 3295, 2861, 1652, 1453, 1098, 1066, 735, 697 $cm^{-1}$. HRMS (ESI): calcd. for $C_{36}H_{41}N_2O_4$ 565.30608; found 565.30538.

**2-Acetamido-1,2-dideoxyaltronojirimycin (8):** To a solution of **17** (74 mg, 0.13 mmol) in HCl (1.25 M in MeOH; 3 mL) was added Pd/C (12 mg, 0.01 mmol) and the reaction mixture was charged with $H_2$ (5 barg) and stirred at room temp. for 20 h. Palladium was filtered through Celite washing with MeOH and solvents were removed under low pressure. 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 colourless oil. $[\alpha]_D^{20}$ = +11.7 (*c* = 0.55, $H_2O$). $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 4.04 (dd, *J* = 4.5, 2.5 Hz, 1 H), 3.89 (dd, *J* = 5.0, 2.5 Hz, 1 H), 3.73 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.66 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.45 (m, 1 H), 3.32–3.24 (m, 2 H), 3.01 (m, 1 H), 2.02 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $D_2O$, $CF_3COOH$ internal reference): $\delta$ = 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 ($CH_3$) ppm. IR (film): $\tilde{\nu}$ = 3212, 3051, 2894, 1661, 1437, 1200, 1130 $cm^{-1}$. HRMS (ESI): 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):** A solution of **15** (102 mg, 0.22 mmol) in DMF (4 mL) was added by cannula to a suspension of NaH (17 mg, 0.67 mmol) in DMF (1 mL) at 0 °C. After 10 min, benzyl bromide (41 μL, 0.34 mmol) was added dropwise, and the reaction mixture was stirred at room temp. until no starting material was observed by TLC. Then, $H_2O$ (5 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the crude material was 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. $[\alpha]_D^{20}$ = –30.1 (*c* = 0.59, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38–7.17 (m, 20 H), 4.77 (d, *J* = 11.0 Hz, 1 H), 4.67 (d, *J* = 11.5 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.43 (s, 2 H), 4.12 (d, *J* = 13.5 Hz, 1 H), 3.86 (t, *J* = 7.5 Hz, 1 H), 3.77 (m, 2 H), 3.74 (dt, *J* = 5.5, 3.0 Hz, 1 H), 3.64 (dd,

*J* = 7.5, 3.5 Hz, 1 H), 3.49 (d, *J* = 13.5 Hz, 1 H), 2.96 (dd, *J* = 12.5, 5.5 Hz, 1 H), 2.65 (m, 1 H), 2.27 (dd, *J* = 12.5, 3.0 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 2853, 2096, 1452, 1102, 1066 $cm^{-1}$. HRMS (ESI): 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):** Pd/C (17 mg, 0.01 mmol) was added to a a solution of **18** (90 mg, 0.16 mmol) in EtOAc (4 mL), and the reaction mixture was put under $H_2$ (5 bar). The mixture was stirred at room temp. for 20 h. After this time, the palladium was removed by filtration through Celite, which was then washed with MeOH. The solvents were removed under low pressure.

The resulting colourless oil was dissolved in pyridine (2 mL), and $Ac_2O$ (24 µL, 0.23 mmol) was added. The reaction mixture was stirred at room temp. for 16 h. Then, $H_2O$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the crude material was purified on silica•$Et_3N$ (2.5 % v/v) using hexane/EtOAc to give **19** (74 mg, 80 %) as a slightly yellow oil. $[\alpha]_D^{20}$ = –8.1 (*c* = 0.79, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.20 (m, 20 H), 6.19 (d, *J* = 9.5 Hz, 1 H), 4.90 (d, *J* = 11.0 Hz, 1 H), 4.78 (d, *J* = 11.0 Hz, 1 H), 4.53 (m, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.42 (d, *J* = 12.0 Hz, 1 H), 4.14 (d, *J* = 13.5 Hz, 1 H), 3.81 (m, 2 H), 3.71 (t, *J* = 8.5 Hz, 1 H), 3.55 (dd, *J* = 8.5, 4.5 Hz, 1 H), 3.29 (d, *J* = 13.5 Hz, 1 H), 2.72 (dd, *J* = 12.0, 4.5 Hz, 1 H), 2.47 (dt, *J* = 8.5, 3.0 Hz, 1 H), 2.22 (dd, *J* = 12.0, 2.0 Hz, 1 H), 1.93 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ($CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2860, 1674, 1496, 1452, 1011 $cm^{-1}$. HRMS (ESI): calcd. for $C_{36}H_{40}N_2O_4$ 565.3061; found 565.3050.

**2-Acetamido-1,2-dideoxymannojirimycin (9):** Pd/C (spatula tip) was added to a solution of **19** (20 mg, 0.04 mmol) in HCl (1.25 M in MeOH; 3 mL), and the mixture was put under $H_2$ (5 bar). The mixture was stirred at room temp. for 20 h. After this time, the palladium was removed by filtration through Celite, which was then washed with MeOH. The solvents were removed under low pressure. The residue was purified by chromatography on silica gel ($CH_2Cl_2$/MeOH/$NH_3$, 90:8:2) to give **9** (7 mg, 95 %) as a white solid. The spectroscopic data were consistent with previously reported data.[23] $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 4.50 (s, 1 H), 3.82 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.72 (dd, *J* = 11.0, 5.5 Hz, 1 H), 3.60 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.45 (t, *J* = 9.5 Hz, 1 H), 3.00 (dd, *J* = 13.0, 3.0 Hz, 1 H), 2.79 (dd, *J* = 13.0, 2.5 Hz, 1 H), 2.47 (ddd, *J* = 9.5, 5.5, 3.0 Hz, 1 H), 2.04 (s, 3 H) ppm. HRMS (ESI): calcd. for $C_8H_{17}N_2O_4$ 205.11828; found 205.11830.

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