SUPPLEMENTARY MATERIAL

Stereoselective synthesis of (+)-1-deoxyaltronojirimycin

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A stereocontrolled, facile and high-yield approach for producing (+)-*altro*DNJ, has been developed starting from the inexpensive commercial *cis* 2-butene-1,4-diol. The Sharpless epoxidation and a subsequent dihydroxylation were used for the introduction of all stereocenters; finally the ring closure in basic conditions afforded the piperidine heterocycle.

Keywords: iminosugar; stereoselective synthesis; heterocycles; dihydroxylation; 1-deoxyaltronojirimycin

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General: Organic solvents and reagents were purchased and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light (254 nm) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (5 g), ethanol (100 mL)] or ninhydrin dip [ninhydrin (5g), sulfuric acid (5 mL), n-butanol (100mL)] and heating. Low temperature reactions were performed in a Haake EK 101cryostat using an acetone bath. Unless otherwise stated, reactions were carried out under standard atmosphere. ¹H and ¹³C NMR spectra were recorded using a Varian Mercury 300 instrument (¹H, 300 MHz; ¹³C, 75 MHz). Residual solvent peaks were used as internal references: chloroform (¹H, d 7.26 ppm; ¹³C, d 77.00 ppm), acetone (¹H, d 2.05ppm; ¹³C, d 30.83 ppm) and methanol (¹H, d 3.31 ppm; ¹³C, 49.05 ppm). Chemical shifts (d) are reported in parts per million (ppm) relative to the internal standard and coupling constant (J) in Hz. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet;

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q, quartet; m, multiplet. Unless otherwise stated, all spectra are registered in deuterated chloroform. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell pathway length of 10 cm; solution concentrations are reported in grams per 100 ml. All chromatographic purifications were performed using forced flow on flash silica gel (Kiesegel 200–400 mesh from E. Merck, Germany). All procedures are referred to 1 mmol and the yields to isolated and spectroscopically homogeneous compounds.

The synthesis started from 4 g (45.5 mmol) of *cis* 2-butene-1,4-diol, achieving 561 mg (2.8 mmol) of (+)-1-deoxyaltronojirimycin hydrochloride.

Synthesis of epoxy aldehyde **3** starting from *cis*-2-butene-1,4-diol is already known (Roush et al. 1991).

(*E*)-methyl 3-((2*S*,3*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)acrylate **4**

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In a round bottom flask 1 mmol of aldehyde was dissolved in 10 ml of THF and LiOH (1,1 mmol, 0.027 g) and trimethylphosphonoacetate (1,1 mmol, 0.200 g, 0,16 ml) were added. The mixture was stirred at 30°C for 15 hours (TLC monitoring). A saturated solution of NH₄Cl was then added and the reaction mixture concentrated in vacuo to evaporate the THF. The aqueous residue was then extracted with ethyl acetate and the organic layer washed with NH₄Cl saturated solution and brine until pH=7. The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo to leave the crude product that was then purified by flash chromatography on silica gel using a solvent mixture hexane / ethyl acetate 9:1 to give the desired product. Yellow oil. 77% yield from **2**. ¹H NMR (300 MHz, CDCl₃) δ: 7.76-7.63 (4H, m, Ar), 7.47-7.36 (6H, m, Ar), 6.69 (1H, dd, *J* 15.7, 7.1 Hz, CHCHCOOCH₃), 6.13 (1H, d, *J* 15.7 Hz, CHCHCOOCH₃), 3.87-3.83 (2H, m, CH₂), 3.76 (3H, s, CH₃), 3.38 (1H, dd, *J* 7.1, 1.4 Hz, OCHCH=CH), 3.12-3.06 (1H, m, CHOHCH=CH), 1.07 (9H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ: 166.0, 144.3, 135.5, 134.8, 133.0, 132.9, 129.8, 127.6, 127.6, 123.6, 62.9, 60.8, 53.7, 51.7, 26.7, 26.5, 19.2. Anal. Calcd for C₂₃H₂₈O₄Si: C 69.66; H 7.12. Found C 69.75; H 7.2.

(2*S*,3*S*)-methyl 3-((2*S*,3*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)-2,3-dihydroxypropanoate (5A**) and (2*R*,3*R*)-methyl 3-((2*S*,3*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)-2,3-dihydroxypropanoate (**5B**)**

To a solution of 1 mmol of **4** in 9 ml of acetone/water (8:1) were added 2 mmol (0.270 g) of NMO and 0.63 ml of a 2.5% solution of OsO₄ in *tert*-butanol (0.05 mmol of OsO₄) and the mixture left stirring overnight at room temperature. The reaction was then quenched with a saturated solution of Na₂S₂O₃, the mixture left stirring for 1h and then transferred in a separative funnel. The aqueous layer was extracted with ethyl acetate, the combined organic layers dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude was used without purification. Brown oil. 60:40 d.r.¹H NMR (300 MHz CDCl₃) δ: 7.37-7.61 (4H, m, Ar), 7.47-7.30 (6H, m, Ar), 4.36-4.32 (0,6H, m, CHOHCOOMe product A), 4.32-4.27 (0,4H, m, CHOHCOOMe product B), 3.97-3.67 (6H, m, CH₂OTBDPS, CHOH-CHOH-COOCH₃), 3.26-3.21 (1H, m, CH-O-CH-CH₂OTBDPS), 3.10 (1H, m, CH-O-CH-CH₂OTBDPS), 2.36 (2H, s, OH), 0.94 (9H, s, C(CH₃)₃). ¹³C NMR (300 MHz, CDCl₃) δ: 172.8; 135.6; 135.5; 134.8; 133.2; 129.8; 127.7; 127.7; 72.4; 70.3; 63.2; 55.7; 55.1; 52.9; 26.8; 19.2

(4*S*,5*R*)-methyl 5-((2*R*,3*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 6A and (4*R*,5*S*)-methyl 5-((2*R*,3*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 6B

1 mmol of diol was dissolved in 2 ml of dichloromethane and 2 ml of 2,2-dimethoxypropane and 0.047 g of 4-toluenesulphonic acid were added and the mixture stirred at r.t. until completion (24 h, TLC monitoring). The solvent was evaporated in vacuo and the mixture was dissolved in ethyl acetate, washed with brine and NaHCO₃ saturated solution until pH 7. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent evaporated in vacuo. The crude was used without purification. Pale yellow oil. ¹H NMR (300 MHz CDCl₃) δ: 7.77-7.56 (4H, m, Ar), 7.52-7.29 (6H, m, Ar), 4.45 (0.4H, d, *J* 7.9 Hz, CHOCOOME product B), 4.40-4.25 (1.6H, m, CHOCHOCOOME, CHOCOOME product A), 4.19-3.66 (5H, m, CH₃, CH₂), 3.42-3.29 (0.4H, m,

CHO-acetonide product B), 3.29-3.12 (1.6H, m, CHO-acetonide product A, $\underline{\text{CHO}}\text{-CH}_2$), 1.49 (3H, s, CH_3 acetonide), 1.47 (3H, s, CH_3 acetonide), 1.06 (9H, s, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ : 171.2, 135, 130.2, 128.1, 112.3, 78.4, 78.1, 76.4, 76.0, 63.2, 56.3, 55.0, 52.9, 27.1, 26.0, 19.5.

(4*S*,5*R*)-methyl 5-((1*R*,2*R*)-2-azido-3-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **7A**

1 mmol of epoxide was dissolved in 10 ml of MeOH and NaN_3 (5 mmol, 0.325 g) and NH_4Cl (2 mmol, 0.107 g) were added and the mixture left stirring at 70°C until complete consumption of the substrate (12 h, TLC monitoring). The mixture was filtered, concentrated in vacuo and the residue diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and the solvent evaporated in vacuo to leave the crude. The crude was purified by flash chromatography on silica gel using a solvent mixture hexane / ethyl acetate 8:2. Yellow oil. 58% yield (**7A**+**7B** from **4**; 31% of isolated **7A**). $[\alpha]_{\text{D}}^{25} = -7.95^\circ$ (c 3.4, CHCl_3). ^1H NMR (300 MHz CDCl_3) δ : 7.75-7.67 (4H, m, Ar), 7.45-7.36 (6H, m, Ar), 4.57 (1H, d, J 6.5 Hz, OCHCOOMe), 4.48-4.42 (1H, m, CHOCHCOOMe), 4.15-3.87 (6H, m, $\text{CH}_2\text{CHN}_3\text{CHOHCHOCHOCOOCH}_3$), 3.72-3.64 (1H, m, CHN_3), 2.85 (1H, s, CHOH) 1.46 (3H, s, CH_3CCH_3), 1.42 (3H, s, CH_3CCH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$). ^{13}C NMR (75 MHz, CDCl_3) δ : 171.6, 135.5, 135.4, 132.5, 129.7, 127.7, 127.6, 111.2, 79.0, 74.9, 70.2, 64.4, 63.4, 52.4, 26.6, 26.5, 25.2, 18.9. Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_6\text{Si}$: C 60.79; H 6.87. Found C 60.70; H 6.92.

(4*S*,5*R*)-methyl 5-((1*R*,2*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **8**

1 mmol of **7A** was dissolved in 2 ml of ethyl acetate and 1.1 mmol (0.240 g) of $(\text{Boc})_2\text{O}$ were added and the mixture left stirring under H_2 atmosphere (1 atm) at r.t. until completion (6 h, TLC monitoring). The reaction mixture was filtered through a pad of celite and the solvent was

evaporated in vacuo. The product was used without chromatographic purification. Yellow oil. ^1H NMR (300 MHz, CDCl_3) δ : 7.76-7.68 (4H, m, Ar), 7.50-7.37 (6H, m, Ar), 5.27 (1H, d, J 7.2 Hz, NH), 4.54 (1H, d, J 5.6 Hz, CHO-COOCH_3), 4.37 (1H, dd, $J_1=J_2$ 5.6 Hz, CHOCHOCOOME), 4.15-3.49 (7H, m, CHOH , CHN_3 , CH_2 , COOCH_3), 1.51 (15H, m, CH_3 acetonide x2, $\text{NHCOC}(\text{CH}_3)_3$), 1.05 (9H, s, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ : 171.3, 146.4, 136.2, 129.8, 127.7, 111.7, 84.8, 79.2, 73.8, 64.0, 52.3, 52.2, 27.2, 26.7, 26.6, 18.9.

(4S,5R)-methyl 5-((1R,2R)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyldiphenylsilyl)oxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 9

In a two neck flask under argon atmosphere 1 mmol of **8** was dissolved in 6 ml of anhydrous dichloromethane and 2 mmol of 2,6-lutidine and 3 mmol of TBSOTf were added and the mixture stirred at r.t. until completion (12 h, TLC monitoring). The reaction was quenched with water, then the two phases were separated and the aqueous layer was extracted twice with dichloromethane, the combined organic layers were washed with brine and NaHCO_3 saturated solution until pH 7. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel using a solvent mixture hexane / ethyl acetate 95:5. Yellow oil. 80% yield (2 steps). ^1H NMR (300 MHz, CDCl_3) δ : 7.72-7.47 (4H, m, Ar), 7.43-7.27 (6H, m, Ar), 5.31 (1H, d, J 6.7 Hz, NH), 4.56 (1H, d, J 5.4 Hz, CHO-COOCH_3), 4.39 (1H, dd, $J_1=J_2$ 5.4 Hz, CHOCHOCOOME), 4.13-3.54 (7H, m, CHOH , CHN , CH_2 , COOCH_3), 1.57 (CH_3 acetonide) 1.46-1.25 (1H, m, CH_3 acetonide, $\text{NHCOC}(\text{CH}_3)_3$), 1.03 (9H, s, CH_3) 0.82 (3H, s, CH_3OSi , -0.01 (3H, s, CH_3OSi). ^{13}C NMR (75 MHz, CDCl_3) δ : 171.3, 146.2, 135.1, 129.6, 127.5, 116.7, 85.4, 79.2, 76.3, 63.7, 60.04, 52.2, 52.1, 27.5, 26.5, 26.3, 25.3, 20.7, 18.8, -3.2. Anal. Calcd for $\text{C}_{37}\text{H}_{59}\text{NO}_8\text{Si}_2$: C 63.30; H 8.47. Found C 63.23; H 8.60.

tert-butyl ((5R,6R)-5-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,10-hexamethyl-9,9-diphenyl-4,8-dioxo-3,9-disilaundecan-6-yl)carbamate 10

1 mmol of **9** was dissolved in a solution THF / H₂O 10 ml / 1 ml and 3 mmol (0.113 g) of NaBH₄ were added and the mixture left stirring for four hours (TLC monitoring). 15 ml of water were added to the reaction mixture and it was subsequently transferred in a separative funnel, the layers separated, and the aqueous one extracted trice with ethyl acetate. The combined organic layers were washed with brine and NaHCO₃ until pH 7, then dried over Na₂SO₄. The solvent was evaporated in vacuo to leave the crude, that was purified by flash chromatography on silica gel using a solvent mixture hexane / ethyl acetate 95:5. Yellow oil. 94% yield. ¹H NMR (300 MHz CDCl₃) δ: 7.69-7.60 (4H, m, Ar), 7.45-7.31(6H, m, Ar), 4.70 (1H, d, *J* 8.12 Hz, CHNHBoc), 4.15-3.54 (8H, m CH₂CHNHBocCHOTBSCHOCHOCH₂OH), 3.15 (1H, br s, CH₂OH), 1.47 (3H, s, CH₃CCH₃), 1.44-1.41 (12H, m, CH₃CCH₃, NHCOC(CH₃)₃), 1.06 (9H, s, Ph₂SiC(CH₃)₃), 0.79 (9H s (CH₃)₂SiC(CH₃)₃), 0.066 (3H, s, CH₃CH₃SiC(CH₃)₃), 0.009 (3H, s, CH₃CH₃SiC(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ: 156.0, 135.6, 135.5, 133.3, 133.3, 129.7, 127.8, 127.7, 108.5, 79.6, 78.7, 72.9, 66.8, 63.0, 62.6, 54.8, 28.3, 27.8, 26.9, 26.8, 25.9, 21.0, 19.2, 18.0, -4.0, -4.5. Anal. Calcd for C₃₆H₅₉NO₇Si₂: C 64.15; H 8.82. Found C 64.02; H 8.89.

((4*R*,5*S*)-5-(((5*R*,6*R*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl methanesulfonate
11

11

In a two neck round bottom flask, under argon atmosphere, 1 mmol of **10** was dissolved in 30 ml of anhydrous CH₂Cl₂, were subsequently added 1.2 mmol (0.09 ml) of MsCl, 2 mmol (0.27 ml) of Et₃N and 0.01 mmol (0.001 g) of DMAP and the mixture left stirring at room temperature until completion (6 h, TLC monitoring). The mixture was transferred in a separative funnel, water and ice were added, the layers separated and the organic one washed with HCl 2N and brine until pH 7, then dried over Na₂SO₄. The solvent was evaporated in vacuo to leave the crude that was used without purification. Pale yellow oil. ¹H NMR (300 MHz CDCl₃) δ: 7.68-7.59 (4H, m, Ar), 7.45-7.31(6H, m, Ar), 4.54 (1H, d, *J* 8.22 Hz, CHNHBoc), 4.24-3.53 (8H, m CH₂CHNHBocCHOTBSCHOCHOCH₂OMs), 3.02 (3H, s, CH₂OSO₂CH₃), 1.46 (3H, s, CH₃CCH₃), 1.43-1.40 (12H, m, CH₃CCH₃, NHCOC(CH₃)₃), 1.04 (9H, s, Ph₂SiC(CH₃)₃), 0.80 (9H s (CH₃)₂SiC(CH₃)₃), 0.053 (3H, s, CH₃CH₃SiC(CH₃)₃), 0.037 (3H, s, CH₃CH₃SiC(CH₃)₃). ¹³C NMR

(75 MHz, CDCl₃) δ : 155.4, 135.5, 133.1, 129.7, 127.7, 127.6, 127.6, 110.1, 79.5, 77.2, 73.0, 70.3, 62.6, 55.2, 45.9, 37.5, 28.3, 27.0, 26.8, 26.7, 25.8, 20.9, 19.1, 17.9, -4.2, -4.4.

(3a*R*,6*R*,7*R*,7a*S*)-tert-butyl 7-((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate **12**

In a two neck round bottom flask, under argon atmosphere, 1 mmol of **11** was dissolved in 20 ml of anhydrous THF and 2 mmol (0.224 g) of *t*BuOK were added at 0°C and the mixture left stirring at room temperature until completion (8 h, TLC monitoring). 5 ml of saturated solution of NH₄Cl were added in the reaction flask and the mixture left stirring for 5 minutes, then it was transferred in a separative funnel, the layers separated, the aqueous one extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and the solvent was evaporated in vacuo. The crude was purified by chromatography on silica gel using a solvent mixture hexane / ethyl acetate 95:5. Yellow oil. 62% yield (2 steps). ¹H NMR (300 MHz CDCl₃) δ : 7.68-7.59 (4H, m, Ar), 7.48-7.35 (6H, m, Ar), 4.62 (1H, dd, *J* 4.7 12.1 Hz, H-3), 4.58-4.50 (1H, m, H-4), 4.49-4.35 (1H, m, Ha-6), 3.96- 3.82 (1H, m, H-4), 3.70-3.55 (2H, m, Hb-6 + Ha-1), 3.45 (1H, ddd *J* 9.3 9.3 2.1 Hz, H-5), 2.80-2.66 (1H, m, Hb-1), 1.44 (3H, s, CH₃CCH₃), 1.43-1.40 (12H, m, CH₃CCH₃, NHCOC(CH₃)₃), 1.07 (9H, s, Ph₂SiC(CH₃)₃), 0.92 (9H s (CH₃)₂SiC(CH₃)₃), 0.13 (3H, s, CH₃CH₃SiC(CH₃)₃), 0.11 (3H, s, CH₃CH₃SiC(CH₃)₃). ¹³C NMR (75 MHz CDCl₃) δ : 155.3, 150.0, 135.6, 135.6, 135.4, 134.8, 132.8, 130.0, 129.9, 129.8, 127.9, 127.8, 127.8, 127.7, 110.1, 80.2, 80.2, 79.9, 79.8, 79.4, 79.2, 69.9, 69.4, 66.9, 66.8, 62.4, 61.4, 44.1, 43.9, 28.3, 27.0, 26.8, 25.8, 25.6, 19.1, 18.2, 18.0, -4.6, -5.1. Anal. Calcd for C₃₆H₅₇NO₆Si₂: C 65.91; H 8.76. Found C 65.82; H 8.89.

(2*R*,3*R*,4*S*,5*R*)-2-(hydroxymethyl)piperidine-3,4,5-triol (D-(+)-1-deoxyaltronojirimycin hydrochloride).

1 mmol of **12** was dissolved in 2 mL of methanol, 2 mL of HCl 37% were added and the mixture left stirring for four hours at 70°C. After completion of the reaction, the mixture was diluted with ethanol and acetonitrile and concentrated at reduced pressure and then extracted with water. The residual oil was purified by flash chromatography (CHCl₃–MeOH 1:1) to give the altroDNJ·HCl salt as white solid. 92% yield; Mp 98-104 (Ikota et al 1997). $[\alpha]_{\text{D}}^{25} = +26.8^\circ$ (*c* 1.7, MeOH); lit. $[\alpha]_{\text{D}}^{25} +33.2$ (*c* 0.5, MeOH) (Singh et al 2003); ¹H NMR (400 MHz D₂O) δ : 4.14-4.10 (1H, m, C4-H), 4.03-3.97 (2H, m, C2-H, C3-H), 3.94 (1H, dd, *J* 3.4, 12.7 Hz, C6-Ha), 3.80 (1H, dd, *J* 6.8, 12.7 Hz, C6-Hb), 3.39- 3.30 (2H, m, C5-H, C1-Ha), 3.19 (1H, dd, *J* 2.6 13.4 Hz, C1-Hb); ¹³C NMR (100 MHz, D₂O) δ : 69.0, 66.8, 64.2, 58.7, 56.4, 44.5. Anal. Calcd for C₆H₁₄ClNO₄: C 36.10; H 7.07; N 7.02. Found C 35.82; H 7.29; N 6.78.

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