Synthesis of Eight 1-Deoxynojirimycin Isomers from a Single Chiral Cyanohydrin


Keywords: Enzymes / Enzyme catalysis / Inhibitors / Enantioselectivity / Synthesis design

Eight configurational 1-deoxynojirimycin isomers have been synthesized starting from a chiral cyanohydrin as the common precursor. The cyanohydrin chiral pool building block is easily accessible in large quantities by using almond hydroxynitrile lyase as the chiral catalyst in condensing hydrogen cyanide and crotonaldehyde. Our work complements the large body of literature on the synthesis of 1-deoxynojirimycin derivatives with the distinguishing feature that eight stereoisomers of this important class of glycosidase inhibitors can be derived from a common precursor in an efficient manner.

Introduction

Hydroxynitrile lyases (HNLs), also known as oxynitrilases, have attracted great interest from the synthetic organic chemistry community for more than a century. The first use of a HNL derived from almonds (puHNL) was reported by Rosenthaler in 1908.[1] In 1965 a range of optically active cyanohydrins, starting from both aromatic and aliphatic aldehydes, were synthesized by Becker and Pfeil, who used a buffered aqueous ethanol mixture as the solvent.[2,3] These early results demonstrated for the first time the potential of puHNL in the construction of chiral compounds, although the highest ee reported was 87%.[2] Further significant progress was made in 1987 when Effenberger et al. reported the synthesis of (R)-mandelonitrile, catalysed by puHNL. By performing the reaction in a two-phase system, they obtained (R)-mandelonitrile in 99.3% ee and 95% yield.[4] Since then, the role of HNLs in organic synthesis has gradually grown and today they are an important synthetic tool in the production of a wide range of both (R)- and (S)-cyanohydrins with high enantioselectivity and high yields.[5]

The versatility of cyanohydrins as optically active building blocks in synthetic chemistry has been widely investigated. We have reported on a number of conversions involving cyanohydrins that lead to valuable chiral building blocks.[5] For example, (2R,3E)-2-hydroxypent-3-enenitrile (1), derived from crotonaldehyde and HCN can be prepared in 99% enantiomeric purity by using either purified puHNL[6] or defatted almond meal containing the enzyme (Scheme 1).[7] (2R,3E)-2-Hydroxypent-3-enenitrile bears three individual functionalities that can be addressed independently. In the unprotected form it has been used in the synthesis of α-hydroxy esters,[8] α-hydroxy acids[9] and vicinal diols.[10] The protected forms can be used to produce chiral nitrones,[11] cyclic 1,2-ethanolamines,[12] chiral piperidinols,[13] α-hydroxy-β-amino acids,[14] tetronic acids[14] and 1,2-ethanolamines.[15]

Scheme 1. Preparation of cyanohydrins 1 and 2. Reagents and conditions: a) HCN, EtOAc, 0.1 M aq. citrate buffer, pH 5.4, puHNL; b) TBDPS-Cl, imidazole, DMF, 0 °C → room temp.

Recently we reported on the synthesis of two new orthogonally protected building blocks for the stereoselective synthesis of 1-deoxynojirimycin (1-DNJ) isomers.[16] Starting from cyanohydrin 2, building blocks 6 and 7 were obtained after a three-step synthesis, as depicted in Scheme 2. Cyanohydrin 2 was converted into secondary amines 3 and 4 in a one-pot DIBAL-H reduction/transimination/NaBH₄ reduction sequence[17] employing either (R)-benzoxypyruvylglycinol [(R)-5] or (S)-benzoxypyruvylglycinol [(S)-5] in the transimination step.[16] Subsequent N-Boc protection and ring-closing metathesis readily afforded 6 and 7 in overall yields of 72%.

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We anticipated that compounds 6 and 7 would be good starting materials in the synthesis of a number of the 16 possible 1-DNJ isomers by oxidation of the double bond present in 6 and 7. We demonstrated the validity of this reasoning through the synthesis of \( \delta \)-allo- and \( \delta \)-galacto-1-DNJ (12 and 13) from 6 (Scheme 3) and the preparation of \( \lambda \)-allo-1-DNJ (20) from 7 (Scheme 4).[16] As part of an ongoing program to synthesize new potential inhibitors of enzymes involved in the glycosylceramide metabolism,[18] we report herein the synthesis of eight configurational isomers of 1-deoxynojirimycin, more specifically, all the isomers featuring a 3,4-cis-diol moiety.[19]

**Results and Discussion**

To synthesize the \( \delta \)-1-DNJ isomers, as depicted in Scheme 3, the trans-substituted cyclic compound 6 served as the starting material. By means of an Upjohn dihydroxylation reaction, diols 8 and 9 were obtained in a 1:1 ratio, as determined by LC–MS. The mixture was separated by careful silica gel column chromatography to afford 8 and 9 in equal amounts. Subsequent removal of the TBDPS group followed by catalytic hydrogenation under acidic conditions afforded \( \delta \)-allo- and \( \delta \)-galacto-1-DNJ (12 and 13) in high yields.[16] All the spectral and analytical data are in agreement with those reported in the literature.[20,21]

To prepare \( \delta \)-talo-1-DNJ (16), the protected galacto-1-DNJ (9) served as the starting compound. The 3,4-cis-diol was protected as the acetone and subsequently the TBDPS group was removed to give alcohol 14. An attempted Mitsunobu reaction on 14 failed and the starting material was recovered. Hence, the free hydroxy in 14 was oxidized to the corresponding ketone after which NaBH₄ reduction at \(-75^\circ\text{C}\) afforded 15 as the sole product in 69% yield over the two steps. Catalytic hydrogenation of 15 under acidic conditions afforded \( \delta \)-talo-1-DNJ (16) in quantitative yield (Scheme 3).[22]
The enantiomers of the four 1-DNJ isomers presented above are accessible from building block 7 in a similar fashion. Direct dihydroxylation of compound 7 afforded diol 19 exclusively. Desilylation using TBAF and subsequent catalytic hydrogenation under acidic conditions gave L-allo-1-DNJ (20)\([25]\) in an overall yield of 75% over the three steps (Scheme 4).\([16]\)

Scheme 4. Preparation of L-1-deoxynojirimycin isomers from precursor 7. Reagents and conditions: a) TBAF, THF, 18 h; b) Ph3P, DEAD, PhCO2H, THF, −75 °C for 12 h, then room temp.; c) NaOH, MeOH, 6 k; d) Dess–Martin, DCM; e) NaBH4, EtOH, −75 °C; f) DMF, 3437–3446 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim www.eurjoc.org 3439

Dess–Martin oxidation and after a completely selective NaBH4 reduction and complete deprotection by catalytic hydrogenation under acidic conditions we obtained L-talo-1-DNJ (30)\([28]\) in 62% yield after three steps.

Conclusions

We have successfully synthesized a pallet of eight L-deoxynojirimycin isomers out of the 16 possible isomers, all starting from the common precursor cyanohydrin 2. The process involved transformation of 2 into the cyclic building blocks 6 and 7 in overall yields of 76%. Compound 6 was converted into D-1-DNJ isomers 12 and 13 (36% overall, three steps), 16 (20%, six steps) and 18 (71%, five steps). Building block 7 provided the L-1-DNJ isomers 20 (75%, three steps), 27 and 28 (29 and 25%, respectively, seven steps) and 30 (14%, ten steps). The chemistry described above renders compounds 6 and 7 valuable extensions to the already known strategies for the synthesis of L-DNJ derivatives and its analogues from chiral pool carbohydrates\([29]\) and de novo synthetic strategies\([30]a,30\) often from chiral building blocks\([31]\) We are currently investigating the potential of using orthogonally protected imino-sugars 8, 9, 15, 19, 25 and 26 as starting points in the synthesis of the other eight L-DNJ isomers.

Experimental Section

Compounds 1–13: Detailed experimental procedures for the synthesis of compounds 1,\([12]\) 2,\([33]\) and 3–13,\([10]\) have been reported previously.

**tert-Butyl (2R,3S,4R,5S)-2-(Benzyloxymethyl)-3,4-O-isopropylidene-5-(tert-butylidene)phosphoryl)piperidine-1-carboxylate: Diol 9 (800 mg, 1.69 mmol) was dissolved in a mixture of THF (20 mL) and 2,2-dimethoxypropane (2.00 mL). A few crystals of p-toluenesulfonic acid were added and the mixture was stirred at room temperature overnight. TLC analysis showed complete conversion and the mixture was diluted with EtOAc and washed with an aqueous solution of NaHCO3 and brine. Drying (Na2SO4), filtration and evaporation of the solvent gave a crude product that was purified by gel column chromatography (PE/EtOAc, 96:4 (1:1); 48 h).

**tert-Butyl (2R,3S,4R,5S)-2-(Benzyloxymethyl)-3,4-O-isopropylidene-5-(tert-butylidene)piperidine-1-carboxylate:**

\[ \text{Diol 9} \]

\[ \text{(800 mg, 1.69 mmol) was dissolved in a mixture of THF (20 mL) and 2,2-dimethoxypropane (2.00 mL). A few crystals of } p\text{-toluenesulfonic acid were added and the mixture was stirred at room temperature overnight. TLC analysis showed complete conversion and the mixture was diluted with } \text{EtOAc and washed with an aqueous solution of } \text{NaHCO}_3 \text{ and brine. Drying (Na}_2\text{SO}_4) \text{, filtration and evaporation of the solvent gave a crude product that was purified by gel column chromatography (PE/EtOAc, 96:4 (1:1); 48 h).} \]
THF (1 mL, 2.60 mL, 2.60 mmol) was added to a solution of the above TBDDS ether (764 mg, 1.21 mmol) in THF (15 mL). After 2 h, TLC analysis revealed complete conversion. The mixture was concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc, 95:5→90:10→75:25) to afford the product as a clear colourless oil (445 mg, 93%). ν\text{ir} (film) 3434, 2978, 1645, 1454, 1367, 1253, 1212, 1165, 1145, 1054, 993, 875 cm\(^{-1}\). 1H NMR (400 MHz, CDCl\(_3\)): δ = 7.35–7.23 (m, 5 H, Ph), 4.61 (dd, J = 6.7, 5.3 Hz, 1 H, 3-H), 4.57 (d, J = 12.1 Hz, 1 H, CH\(_2\)Ph), 4.54 (d, J = 12.1 Hz, 1 H, CH\(_2\)Ph), 4.20 (br. s, 1 H, 2-H), 4.03 (dd, J = 6.7, 1.6 Hz, 1 H, 4-H), 3.85–3.65 (m, 4 H, CH\(_2\)O, 5-H, 6-H), 3.63 (d, J = 12.5 Hz, 1 H, 6-H), 3.40 (br. s, 1 H, OH), 1.44 (s, 3 H, CH\(_3\)), 1.34 (s, 3 H, CH\(_3\)) ppm. 13C NMR (101 MHz, CDCl\(_3\)): δ = 156.85 (C=O), 138.39 (C\(_6\)H, Ph), 128.14, 127.41, 127.36 (Ph), 108.18 (O-C=O), 80.24 (CH\(_2\)Ph), 76.23 (C-4), 72.84 (CH\(_2\)Ph), 71.05 (C-3), 68.47 (C-5), 68.42 (CH\(_2\)O), 51.01 (C-2), 42.90 (C-6), 28.21 (CH\(_3\)), 24.43 (CH\(_3\)) ppm. HRMS: calcd. for [C\(_{21}\)H\(_{31}\)NO\(_6\) +Na\(^+\)] 416.20436; found 416.20421.

terr-Butyl (2\(S\),3\(S\),4\(R\),5\(R\))-2-(Benzyloxy)-3,4,5,6-tetrahydropyridine-1(2H)-carboxylate: 20% Triton X-100 (1445 mg, 1.13 mmol) in DCN (30 mL). After 5 h, TLC analysis revealed complete conversion. The mixture was filtered through a pad of Celite, concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc, 90:10→75:25) to afford the product as a clear colourless oil (368 mg, 83%). ν\text{ir} (film) 3434, 2978, 1645, 1454, 1367, 1253, 1212, 1165, 1145, 1054, 993, 875 cm\(^{-1}\). 1H NMR (400 MHz, CDCl\(_3\)): δ = 7.35–7.21 (m, 5 H, Ph), 3.14–4.80 (m, 2 H, 2-H, 3-H), 4.41 (m, 4 H, 4-H, 6-H), 3.78 (d, J = 18.8 Hz, 1 H, 6-H), 3.62 (br. s, 1 H, CH\(_2\)O), 3.40 (br. s, 1 H, CH\(_2\)O), 1.47 (s, 3 H, CH\(_3\)), 1.46 (s, 9 H, O\(_2\)Bu), 1.37 (s, 3 H, CH\(_3\)) ppm. 13C NMR (101 MHz, CDCl\(_3\)): δ = 203.21 (C=O), 154.71 (NC=O), 137.56 (C\(_6\)H, Ph), 128.19, 127.54, 127.40 (Ph), 111.01 (O-C=O), 81.09 (C\(_6\)H, Ph), 77.37 (C-4), 73.23 (C-3), 72.89 (CH\(_2\)Ph), 65.75 (CH\(_2\)O), 28.11 (O\(_2\)Bu), 26.06 (CH\(_3\)), 24.15 (CH\(_3\)) ppm. HRMS: calcd. for [C\(_{21}\)H\(_{31}\)NO\(_6\) +Na\(^+\)] 416.20436; found 416.20421.

(2\(R\),3\(S\),4\(R\),5\(R\))-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (\(t\)-talo-1-DNJ Hydrochloride, 16): Alcohol 15 (184 mg, 0.468 mmol) was dissolved in a mixture of MeOH (15 mL) and aqueous 6 M HCl (3 mL). The flask was purged with argon, Pd/C (10%, 25 mg) was added and a balloon filled with H\(_2\) was placed on top of the reaction mixture, which was stirred vigorously overnight at room temperature. After filtration and evaporation of the solvents, the crude product (93 mg) was obtained in quantitative yield. [\(\text{[\text{enolate}] + \text{HCl}}\)] = +3.6 (c = 1.0, MeOH), [\(\text{[\text{enamine}] + \text{HCl}}\)] = +2.4 (c = 1.0, H\(_2\)O) \cite{ref22}. 1H NMR (400 MHz, D\(_2\)O): δ = 4.26 (s, 1 H, 5-H), 4.18 (s, 1 H, 3-H), 3.89 (m, 3 H, CH\(_2\)O, 4-H), 3.54 (d, J = 13.7 Hz, 1 H, 6-H), 3.43 (app. t, J = 6.3 Hz, 1 H, 2-H), 3.35–3.25 (m, 1 H, 6-H) ppm. 13C NMR (101 MHz, D\(_2\)O): δ = 67.66 (C-3), 67.16 (C-4), 66.67 (C-5), 60.41 (C-2), 59.21 (CH\(_2\)O), 48.42 (C-6) ppm. HRMS: calcd. for [C\(_{10}\)H\(_{13}\)NO\(_4\) +H\(^+\)] 164.09173; found 164.09144.

terr-Butyl (2\(S\),5\(S\),4\(R\),5\(R\))-5-bromo-5-(1,3,4-oxopiperidine-alkyl)carboxylate: Dess–Martin reagent (0.903 g, 2.13 mmol) was added to a solution of alcohol 14 (445 mg, 1.13 mmol) in DCM (30 mL). After 5 h, TLC analysis revealed complete conversion. The mixture was filtered through a pad of Celite, concentrated in vacuo and purified by silica gel column chromatography (PE/EtOAc, 90:10→75:25) to afford the product as a clear colourless oil (368 mg, 83%). ν\text{ir} (film) 3434, 2978, 1645, 1454, 1367, 1253, 1212, 1165, 1145, 1054, 993, 875 cm\(^{-1}\). 1H NMR (400 MHz, CDCl\(_3\)): δ = 7.35–7.21 (m, 5 H, Ph), 3.14–4.80 (m, 2 H, 2-H, 3-H), 4.41 (m, 4 H, 4-H, 6-H), 3.78 (d, J = 18.8 Hz, 1 H, 6-H), 3.62 (br. s, 1 H, CH\(_2\)O), 3.40 (br. s, 1 H, CH\(_2\)O), 1.47 (s, 3 H, CH\(_3\)), 1.46 (s, 9 H, O\(_2\)Bu), 1.37 (s, 3 H, CH\(_3\)) ppm. 13C NMR (101 MHz, CDCl\(_3\)): δ = 203.21 (C=O), 154.71 (NC=O), 137.56 (C\(_6\)H, Ph), 128.19, 127.54, 127.40 (Ph), 111.01 (O-C=O), 81.09 (C\(_6\)H, Ph), 77.37 (C-4), 73.23 (C-3), 72.89 (CH\(_2\)Ph), 65.75 (CH\(_2\)O), 28.11 (O\(_2\)Bu), 26.06 (CH\(_3\)), 24.15 (CH\(_3\)) ppm. HRMS: calcd. for [C\(_{21}\)H\(_{31}\)NO\(_6\) +Na\(^+\)] 416.20436; found 416.20421.
and 40.58 (C-6), 28.20 (OrBu) ppm. \(^1\)H NMR (400 MHz, CDCl₃, 333 K): \(\delta = 8.02\) (d, \(J = 7.9\) Hz, 2 H, Ph), 7.51 (dd, \(J = 10.9, 4.0\) Hz, 1 H, Ph), 7.43–7.36 (m, 2 H, Ph), 7.34–7.21 (m, 5 H, Ph), 6.01–5.91 (m, 2 H, 3-H, 4-H), 5.51 (dd, \(J = 9.1, 6.5\) Hz, 1 H, 5-H), 4.64 (br, s, 1 H, 2-H), 4.57 (d, \(J = 12.2\) Hz, 1 H, CH₂Ph), 4.53 (d, \(J = 12.2\) Hz, 1 H, Ph), 4.51 (br, s, 1 H, 6-H), 3.70–3.57 (m, 2 H, CHO), 3.04 (app. t, \(J = 11.0\) Hz, 1 H, 6-H), 1.47 (s, 9 H, OrBu) ppm. \(^13\)C NMR (101 MHz, CDCl₃, 333 K): \(\delta = 165.63\) (C=O), 154.24 (NC(O)=), 138.19 (Cq, Ph), 133.19, 132.90 (Ph), 130.14 (Cq, Ph), 130.00, 129.58, 120.05, 128.73, 127.85, 127.95 (C-3, C-4, Ph) 80.31 (Cq, OrBu), 73.18 (CH₂Ph), 70.73 (CHO), 66.25 (C-5), 51.67 (C-2), 28.31 (Cq, OrBu) ppm. HRMS: calcd. for [C₃₅H₄₅NO₆Si + Na\(^+\)] 614.29373; found 614.29376.

tert-Butyl (2S,5S)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyrrolidine-1(2H)-carboxylate (17): The above benzoin (155 mg, 0.366 mmol) was dissolved in a mixture of MeOH (4.0 mL) and H₂O (1.0 mL) was added. The mixture was stirred at room temp. overnight. TLC showed complete conversion of the ester and the mixture was dissolved in EtOAc (30 mL), washed with water (5 mL) and brine (5 mL), dried (MgSO₄), filtered, and concentrated. Purification by continuous silica gel column chromatography (PE/MeOH 90:10 to 80:20 to 70:30), the title alcohol was obtained as a colourless oil (337 mg, 82%).

-Butyl (2S)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyrrolidine-1(2H)-carboxylate (18): The crude compound was purified by silica gel column chromatography (PE/EtOAc, 3:1 to 2:1) to afford a colourless oil (109 mg, 93%).

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(2S,3S,4R,5S)-2-(Benzyloxy)methyl)piperidine-3,4,5-triol Hydrochloride (t-altro-1-1DNJ Hydrochloride, 20): The protected t-altro-1-deoxynojirimycin (335 mg, 0.949 mmol) from above was dissolved in a mixture of MeOH (20 mL) and aqueous 6 M HCl (4 mL). The flask was purged with argon, Pd/C (10 %, 30 mg) was added and a balloon filled with hydrogen gas was placed on top of the reaction. The mixture was stirred overnight at room temperature. Pd/C was removed by filtration and the filtrate evaporated to yield the crude product (187 mg, 99%) as a white foam that needed no further purification. \[ \delta = -31.4 \ (c = 0.5, \text{MeOH}) \text{ref}^{[23]} \delta = -31.4 \ (c = 1.0, \text{MeOH}). \]

1H NMR (400 MHz, MeOH-\(d_4\)): \(\delta = 4.11 \text{ (app. t, } J = 1.2 \text{ Hz, 1 H, 5-H}, \) 4.0–3.97 (m, 2 H, 3-H, 4-H), 3.93 (dd, \(J = 12.8, 3.2 \text{ Hz, 1 H, CH}_2\text{O}), 3.79 \text{(dd, } J = 12.8, 6.8 \text{ Hz, 1 H, CH}_3\text{O}), 3.36–3.28 \text{(m, 2 H, 2-H, 6-H), 3.18 (dd, } J = 13.6, 2.6 \text{ Hz, 1 H, 6-H ppm)}. \)

13C NMR (101 MHz, MeOH-\(d_4\)): \(\delta = 68.41 \text{ (C-4), 66.15 (C-5), 63.55 (C-4), 58.12 \text{(CH}_2\text{O), 55.79 (C-2), 43.86 (C-6) ppm}}. \text{HRMS: calcd. for } [\text{C}_{16}\text{H}_{27}\text{NO}_4 + Na}^+] 246.19379; found 246.19384.

**tert-Butyl (2R,5R)-2-(Benzyloxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate: TBDBPS ether 7 (3.40 g, 6.10 mmol) was dissolved in a mixture of MeOH (100 mL) and aqueous 4 M NaOH (10 mL). Subsequently aqueous 4 M NaOH (10 mL) was added at 0 °C. The reaction mixture was warmed up to room temperature and a solution of the starting material. The reaction mixture was stirred overnight at room temperature. Pd/C was added at 0 °C. The reaction mixture was warmed up to room temperature and then for 4 h at room temperature. TLC analysis revealed complete conversion of the starting material. The solution was concentrated to 25% of its volume, diluted with EtOAc (100 mL) and washed with water (15 mL) and brine (15 mL). Drying (MgSO\(_4\), filtration, evaporation of the solvents and purification by silica gel column chromatography (PE/EtOAc, 90:10 to 80:20) afforded the product as a clear colourless oil (1.67 g, 80%). \[ \delta = +299 \ (c = 1.0, \text{CHCl}_3). \text{HRMS: calcd. for } [\text{C}_{25}\text{H}_{29}\text{NO}_5 + Na}^+] 446.19379; found 446.19384; calcd. for } [\text{C}_{18}\text{H}_{25}\text{NO}_4 + H]^+ 342.11858; found 342.21196.

**tert-Butyl (2R,5S)-2-(Benzyloxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate (21): The benzoate from above (1.67 g, 3.94 mmol) was dissolved in a mixture of MeOH (100 mL) and water (20 mL). Subsequently aqueous 4 M NaOH (10 mL) was added at 0 °C. The reaction mixture was warmed up to room temperature and after 3 h TLC analysis revealed complete conversion of the starting material. The reaction mixture was concentrated to a quarter of its volume and diluted with EtOAc (200 mL), washed with brine (2 × 50 mL), dried (MgSO\(_4\)), filtered and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc, 90:10 to 80:20) to afford the product as a clear colourless oil (1.67 g, 80%). \[ \delta = +270 \ (c = 1.0, \text{CHCl}_3). \text{HRMS: calcd. for } [\text{C}_{18}\text{H}_{25}\text{NO}_4 + Na}^+] 446.19379; found 446.19384; calcd. for } [\text{C}_{18}\text{H}_{25}\text{NO}_4 + H]^+ 342.21196;
13.8 Hz, 1 H, 5-H), 2.01 (br. s, 1 H, OH), 1.45 (s, 9 H, OMe) ppm. 13C NMR (101 MHz, CDCl3, 333 K): δ = 155.29 (C=O), 138.23 (Cq, Ph), 130.12, 128.27, 127.63, 127.49, 127.39, Cq, Ph, 79.98 (Cq, OMe), 73.20 (CH2Ph), 70.44 (CH2Ph), 62.81 (Cq, Ph), 51.68 (Cq, Ph), 46.00 (Cq, Ph), 28.37 (OMe) ppm. HRMS: calcd. for [C34H43NO4Si + Na+] 342.16758; found 342.16764; calcd. for [C34H43NO4Si + H+] 320.18536; found 320.18579.

tert-Butyl (2R,5S)-2-(Benzoxymethyl)-5,6-dihydroxy-5-(tert-butyldiphenylsilyloxy)pyridine-1(2H)-carboxylate (24): Alcohol 21 (1.02 g, 3.19 mmol) was dissolved in DMF (20 mL) and subsequently imidazole (340 mg, 5.00 mmol) and TBDPS-Cl (1.30 g, 4.72 mmol) were added. The reaction mixture was stirred at ambient temperature overnight which after TLC indicated complete conversion of 21. Water (60 mL) was added and the mixture extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried (MgSO4), filtered and concentrated. The crude product was purified by silica gel column chromatography (PE/EtOAc, 97:3→95:5) to afford a crude mixture of two diastereomers which, after column chromatography (PE/EtOAc, 97:3) then afforded the slower running isomer as a white solid. Drying (Na2SO4) and filtration of the dried product afforded a crude 1:1 mixture of two diastereoisomers (determined by LC–MS and TLC). Silica gel column chromatography (PE/EtOAc, 4:1) afforded the faster running isomer (830 mg, 45%) as a colourless oil.

1-Deoxynojirimycin Isomers from a Single Chiral Cyanohydrin
\[ \text{[C}_3\text{H}_4\text{NO}_2\text{Si} + \text{H}]^* \] 592.30889; found 592.30913; calcd. for \[ \text{[C}_3\text{H}_4\text{NO}_2\text{Si} + \text{Na}]^* \] 614.29084; found 614.29042.

**tert-Butyl (2S,3S,4S,5R)-2-(Benzyloxy)methyl)-3,4,5-tri hydroxy piper idine-1-carboxylate (22):** Silyl ether 25 (715 mg, 1.21 mmol) was added and the reaction stirred overnight. A 1 M solution of TBAF in THF (3.00 mL, 3.00 mmol) was added dropwise. Stirring was continued on the ice bath and after 2 h TLC indicated complete conversion of 25. The mixture was diluted with EtOAc (150 mL) and washed with water (10 mL) and brine (10 mL). After drying (MgSO\(_4\)), filtration and evaporation of the solvents, the crude product was purified by silica gel column chromatography (PE/EtOAc, 3:1→1:1→0:1). The title triol was obtained as a colourless oil (408 mg, 96%).

\[ \alpha \text{δ}_2 = 11.4, 9.5, 6.5 \text{ Hz}, 1 \text{ H}, 5-\text{H} \], 3.87 (dd, \( J = 12.1, 8.9 \text{ Hz}, 1 \text{ H}, 1\text{-CH}\)), 3.79 (dd, \( J = 12.1, 8.9 \text{ Hz}, 1 \text{ H}, 1\text{-CH}\)), 3.63 (dd, \( J = 9.6, 2.8 \text{ Hz}, 1 \text{ H}, 4-\text{H} \)), 3.50 (dd, \( J = 12.5, 5.3 \text{ Hz}, 1 \text{ H}, 4-\text{H} \)), 3.41 (dd, \( J = 8.6, 4.8 \text{ Hz}, 1 \text{ H}, 2-\text{H} \)), 2.87 (app. \( J = 12.0 \text{ Hz}, 1 \text{ H}, 6-\text{H} \)).

**tert-Butyl (2S,3S,4S,5R)-2-(Benzyloxy)methyl)-3,4,5-tri isopropylidene-5-(tert-butyldiphenylsilyloxy)piperidine-1-carboxylate: Diol 26** (670 mg, 1.13 mmol) was dissolved in a mixture of acetone (20 mL) and 2,2-dimethoxypropane (5.00 mL). At 5 °C, BF\(_3\)·Et\(_2\)O (50 μL) was added and the mixture was stirred for 30 min on an ice bath and then for 30 min at room temperature. After that time, TLC analysis showed complete conversion and TEA (2 mL) was added. The mixture was diluted with EtOAc, washed with brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated to afford a crude product that was purified by silica gel column chromatography (PE/EtOAc, 82:8→94:6→90:10) to afford the target compound as a colourless oil (628 mg, 88%).

\[ \alpha \text{δ}_2 = +35.0 (c = 1.0, \text{CHCl}_3) \] IR (film): \( \nu = 3396, 2976, 2881, 1686, 1420, 1366, 1249, 1170, 1136, 1088 \text{ cm}^{-1} \). 1H NMR (400 MHz, MeOD): \( \delta = 7.37-7.23 \text{ (m, 5 H, Ph), 4.62 (br. s, 1 H, 2-\text{H})} \), 4.53 (d, \( J = 11.9 \text{ Hz}, 1 \text{ H}, 1\text{-CH}\)), 4.48 (d, \( d = 11.9 \text{ Hz}, 1 \text{ H}, \text{CH}_2\text{Ph}\)), 4.20 (d, \( d = 14.1 \text{ Hz}, 1 \text{ H}, 6-\text{H} \)), 3.97 (br. s, 1 H, 3-\text{H}), 3.84 (br. s, 1 H, 5-\text{H}), 3.70 (app. t, \( J = 3.0 \text{ Hz}, 1 \text{ H}, 4-\text{H} \)), 3.56 (d, \( J = 6.5 \text{ Hz}, 2 \text{ H}, \text{CH}_2\text{O}\)), 3.08 (d, \( J = 14.1 \text{ Hz}, 1 \text{ H}, 6-\text{H} \)), 1.44 (s, 9 H, \text{OrBu} ppm).

13C NMR (101 MHz, MeOD): \( \delta = 158.01 \text{(C=O)}, 139.42 \text{ (Cq, Ph)}, 130.72, 129.38, 127.80 \text{ (Ph)}, 81.35 \text{ (Cq, OrBu)}, 73.97 \text{ (CH}_2\text{Ph)}, 71.78 \text{ (C-3)}, 70.81 \text{(C-5)}, 68.93 \text{(CH}_3\text{O)}, 67.89 \text{(C-4)}, 28.61 \text{(OrBu) ppm. HRMS: calcd. for [C}_3\text{H}_4\text{NO}_2\text{Si} + \text{H}]^* 354.19173; found 354.19138.**
1.44 (s, 3 H, CH₃), 1.43 (s, 9 H, OrBu), 1.35 (s, 3 H, CH₃) ppm.

**13C NMR (101 MHz, CDCl₃): δ = 138.43 (C₆), 128.22, 127.49, 127.45 (Ph), 108.28 (O-C-O), 80.37 (C₆, OrBu), 76.20 (C-4), 72.92 (CH₂Ph), 71.05 (C-3), 68.71 (C-5), 68.42 (CH₂O, C₇), 51.03 (C-2), 28.27 (OrBu) ppm. HRMS: calcd. for [C₅H₁₂NO₄ + H⁺]⁺ [M – Boč] = 294.16998; found 294.16937.

**Supporting Information** (see footnote on the first page of this article): General remarks and the ¹H and ¹³C NMR spectra of all intermediates and final products.

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