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

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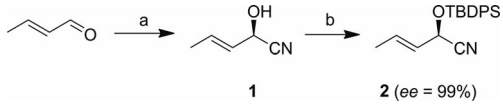
Eight configurational 1-deoxynojirimycin isomers have been synthesized starting from a chiral cyanohydrin as the common precursor. The cyanohydrin chiral pool building block is easily accessible in large quantities by using almond hydroxynitrile lyase as the chiral catalyst in condensing hydrogen cyanide 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 (*pa*HNL) 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 *pa*HNL 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 *pa*HNL. 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, (2*R*,3*E*)-2-hydroxypent-3-enenitrile (**1**), derived from crotonaldehyde and HCN can be prepared in 99% enantiomeric purity by using either purified *pa*HNL[6] or defatted almond meal containing the enzyme (Scheme 1).[7] (2*R*,3*E*)-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,[12] α-hydroxy-β-amino acids,[13] 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, *pa*HNL; 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/$NaBH_4$ reduction sequence[17] employing either (*R*)-benzyloxyvinylglycinol [(*R*)-**5**] or (*S*)-benzyloxyvinylglycinol [(*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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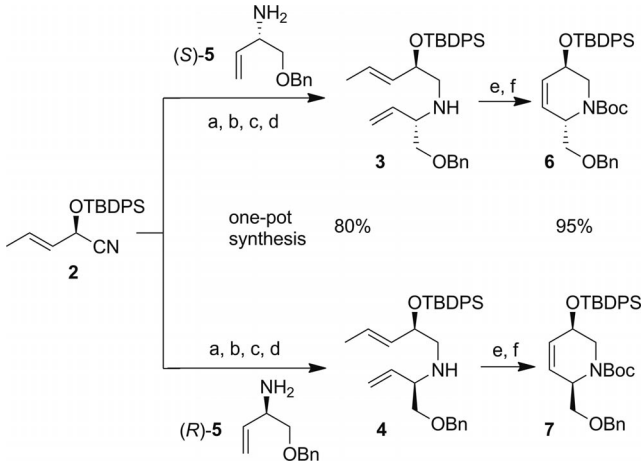
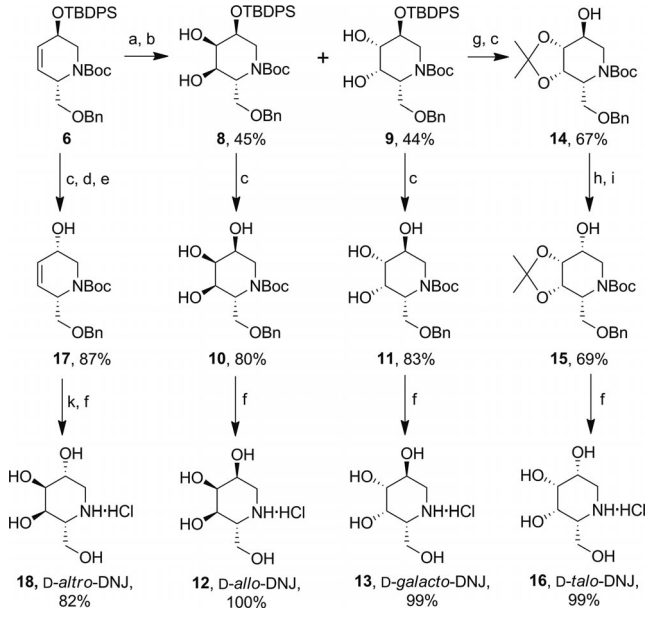


Scheme 2. Conversion of cyanohydrin **2** into the building blocks **6** and **7**. Reagents and conditions: a) diethyl ether, DIBAL-H, –80 °C→0 °C; b) MeOH, –90 °C; c) amine **5** (3 equiv.), room temp., 20 h; d) $NaBH_4$; e) Boc_2O, TEA, THF, 50 °C, 20 h; f) Grubbs G_1 cat., 4 mol-%, DCM, reflux, 48 h.



Scheme 3. Preparation of D-1-deoxynojirimycin isomers from precursor **6**. Reagents and conditions: a) $K_2OsO_4{\cdot}2H_2O$, NMO, THF/H_2O (85:15), 24–72 h; b) separation by silica gel column chromatography; c) TBAF, THF, 18 h; d) Ph_3P, DEAD, $PhCO_2H$, THF, –75 °C for 12 h, then room temp.; e) NaOH, MeOH, H_2O; f) MeOH, 6 M HCl, H_2, Pd/C (10%); g) acetone, 2,2-dimethoxypropane, *p*TsOH, 1 h; h) Dess–Martin, DCM; i) $NaBH_4$, EtOH, –75 °C→room temp.; k) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone/H_2O (1:1), 18 h.

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 D-*allo*- and D-*galacto*-1-DNJ (**12** and **13**) from **6** (Scheme 3) and the preparation of L-*altro*-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 D-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 D-*allo*- and D-*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 D-*talo*-1-DNJ (**16**), the protected *galacto*-1-DNJ (**9**) served as the starting compound. The 3,4-*cis*-diol was protected as the acetonide 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 $NaBH_4$ reduction at –75 °C afforded **15** as the sole product in 69% yield over the two steps. Catalytic hydrogenation of **15** under acidic conditions afforded D-*talo*-1-DNJ (**16**) in quantitative yield (Scheme 3).[22]

To prepare D-*altro*-1-DNJ (**18**) from compound **6**, we turned to an approach in which the silyl protection in **6** was removed and the resulting alcohol was subjected to a Mitsunobu reaction at 0 °C. In this way the benzoic ester of compound **17** was obtained as an inseparable mixture of two diastereoisomers in a ratio of 85:15. Decreasing the starting temperature of the Mitsunobu reaction to –70 °C and subsequent warming to room temperature improved the diastereoselectivity to 98:2. Retaining the temperature at –75 °C for 12 h, followed by slow warming to room temperature afforded the benzoate of **17** as a single diastereoisomer, as determined by RP-HPLC. Unfortunately, we could not separate the benzoate of **17** completely from the side-products of the Mitsunobu reaction. However, subsequent saponification afforded the pure alcohol **17** in 87% yield. Note that alcohol **17** with a 2*S*,5*S* configuration is separable from the 2*S*,5*R* diastereoisomer by column chromatography. Alcohol **17** was subjected to Upjohn dihydroxylation,[23] which afforded a single stereoisomeric compound in 82% yield.

Comparison of the NMR and optical rotation data of **17** with the earlier prepared L isomer revealed that indeed the *N*-Boc-2-OBn-protected D-*altro*-1-DNJ had been obtained. Hydrogenation under acidic conditions gave D-*altro*-1-DNJ (**18**) in 80% yield over two steps and in 70% overall yield based on starting compound **6**. The analytical and spectroscopic data are in complete agreement with literature data.[24]

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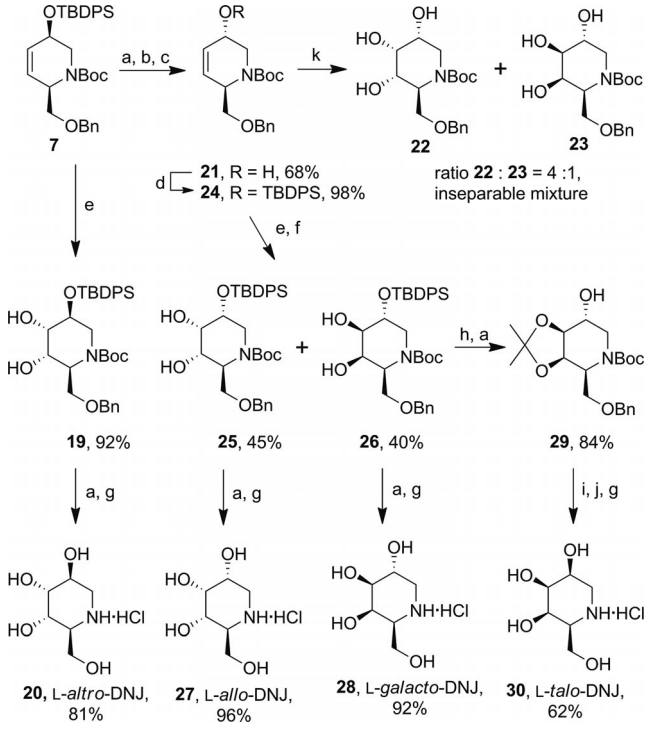
The enantiomers of the four 1-DNJ isomers presented above are accessible from building block **7** in a similar fashion. Direct dihydroxylation of compound **7** afforded diol **19** exclusively. Desilylation using TBAF and subsequent catalytic hydrogenation under acidic conditions gave L-*altro*-1-DNJ (**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) Ph_3P, DEAD, $PhCO_2H$, THF, –75 °C for 12 h, then room temp.; c) NaOH, MeOH, H_2O; d) DMF, TBDPS-Cl, imidazole; e) $K_2OsO_4{\cdot}2H_2O$, NMO, THF/H_2O (85:15), 24–72 h; f) separation by silica gel column chromatography; g) MeOH, 6 M HCl, H_2, Pd/C (10%); h) acetone, 2,2-dimethoxypropane, *p*TsOH, 1 h; i) Dess–Martin, DCM; j) $NaBH_4$, EtOH, –75 °C→room temp.; k) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone/H_2O (1:1), 48 h.

Compound **7** was transformed into *trans*-substituted building block **21** by a three-step procedure that involved removal of the TBDPS group, Mitsunobu substitution with benzoic acid and subsequent saponification. Dihydroxylation of **21** led to an inseparable mixture of the diols **22** and **23** in a ratio of 4:1. Therefore we deemed it necessary to re-install a TBDPS group on **21** to obtain compound **24** in almost quantitative yield. Unfortunately, we were unable to completely remove the impurities resulting from the silyl protection reaction. Nonetheless, compound **24** was subjected to Upjohn dihydroxylation and in this way protected L-*allo*-1-DNJ (**25**)[26] and L-*galacto*-1-DNJ (**26**)[27] were obtained in a ratio of around 1:1. After separation by column chromatography and two deprotection steps, L-*allo*-1-DNJ (**27**) and L-*galacto*-1-DNJ (**28**) were obtained in high yields. By protecting the diol in **26** as an acetonide and subsequent removal of the TBDPS group, we obtained alcohol **29**. This alcohol was converted into the corresponding ketone by Dess–Martin oxidation and after a completely selective $NaBH_4$ 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 1-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 1-DNJ derivatives and its analogues from chiral pool carbohydrates[29] and de novo synthetic strategies,[24a,30] often from chiral building blocks.[31] We are currently investigating the potential of using orthogonally protected iminosugars **8**, **9**, **15**, **19**, **25** and **26** as starting points in the synthesis of the other eight 1-DNJ isomers.

Experimental Section

Compounds 1–13: Detailed experimental procedures for the synthesis of compounds **1**,[12] **2**[12] and **3**–**13**[16] have been reported previously.

***tert*-Butyl (2*R*,3*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-(*tert*-butyldiphenylsilyloxy)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 $NaHCO_3$ and brine. Drying (Na_2SO_4), filtration and evaporation of the solvent gave a crude product that was purified by silica gel column chromatography (PE/EtOAc, 96:4→90:10) to afford the target compound as a colourless oil (764 mg, 72%). $[\alpha]_D^{23}$ = –30.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2933, 2859, 1696, 1393, 1366, 1145, 1104, 1057, 990 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 6.9 Hz, 2 H, Ph), 7.63 (d, *J* = 6.9 Hz, 2 H, Ph), 7,42–7.21 (m, 11 H, Ph), 4.64 (d, *J* = 4.2 Hz, 1 H, 3-H), 4.56 (s, 2 H, CH_2Ph), 4.24–3.80 (m, 4 H, 2-H, 5-H, 6-H, CH_2O), 3.77 (s, 1 H, 4-H), 3.71 (app. t, *J* = 8.9 Hz, 1 H, CH_2O), 3.21 (d, *J* = 13.4 Hz, 1 H, 6-H), 1.39 (s, 9 H, O*t*Bu), 1.33 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.07 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.56 (C=O), 138.54 (C_q, Ph), 135.73 (Ph), 133.54 (C_q, Ph), 133.19 (C_q, Ph), 129.77, 129.70, 128.18, 127.63, 127.58, 127.55, 127.40 (Ph), 107.67 (O-C-O), 79.90 (C_q, O*t*Bu), 75.03 (C-5), 73.08 (CH_2Ph), 70.97 (C-3), 69.55 (C-4), 50.75 (C-2), 28.27 (O*t*Bu), 26.94 (Si*t*Bu), 26.63 (CH_3), 24.18 (CH_3), 19.13 (C_q, Si*t*Bu) ppm. HRMS: calcd. for $[C_{37}H_{49}NO_6Si + H]^+$ 632.34019; found 632.34040.

***tert*-Butyl (2*R*,3*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-hydroxypiperidine-1-carboxylate (14):** A solution of TBAF in

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THF (1 M, 2.60 mL, 2.60 mmol) was added to a solution of the above TBDPS 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%). $[\alpha]_D^{21}$ = –26.6 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3434, 2978, 1676, 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_2Ph), 4.54 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 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_2O, 5-H, 6-H), 3.36 (d, *J* = 12.5 Hz, 1 H, 6-H), 3.00 (br. s, 1 H, OH), 1.44 (s, 3 H, CH_3), 1.43 [s, 9 H, $(CH_3)_3$], 1.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.85 (C=O), 138.39 (C_q, Ph), 128.14, 127.41, 127.36 (Ph), 108.18 (O-C-O), 80.24 (C_q, O*t*Bu), 76.23 (C-4), 72.84 (CH_2Ph), 71.05 (C-3), 68.47 (C-5), 68.42 (CH_2O), 51.01 (C-2), 42.90 (C-6), 28.21 (O*t*Bu), 26.70 (CH_3), 24.43 (CH_3) ppm. HRMS: calcd. for $[C_{21}H_{31}NO_6 + Na]^+$ 416.20436; found 416.20421.

***tert*-Butyl (2*S*,3*R*,4*R*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-oxopiperidine-1-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%). $[\alpha]_D^{21}$ = +27.8 (*c* = 0.80, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2981, 1744, 1698, 1369, 1163, 1099, 872 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H, Ph), 5.14–4.80 (m, 2 H, 2-H, 3-H), 4.41 (m, 4 H, 4-H, 6-H, CH_2Ph), 3.78 (d, *J* = 18.8 Hz, 1 H, 6-H), 3.62 (br. s, 1 H, CH_2O), 3.40 (br. s, 1 H, CH_2O), 1.47 (s, 3 H, CH_3), 1.46 (s, 9 H, O*t*Bu), 1.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.21 (C=O), 154.71 (NC=O), 137.56 (C_q, Ph), 128.19, 127.54, 127.40 (Ph), 111.01 (O-C-O), 81.09 (C_q, O*t*Bu), 77.37 (C-4), 73.23 (C-3), 72.89 (CH_2Ph), 65.75 (CH_2O), 28.11 (O*t*Bu), 26.06 (CH_3), 24.15 (CH_3) ppm. HRMS: calcd. for $[C_{21}H_{29}NO_6 + H]^+$ 392.20676; found 392.20668.

***tert*-Butyl (2*R*,3*S*,4*R*,5*R*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-hydroxypiperidine-1-carboxylate (15):** $NaBH_4$ (48.0 mg, 1.26 mmol) was added to a solution of the aforementioned ketone (185 mg, 0.473 mmol) in ethanol (20 mL) at –75 °C. The mixture was warmed slowly in a cooling bath to –20 °C over around 2 h. At that moment TLC analysis revealed complete conversion. The reaction mixture was diluted with EtOAc (100 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by silica gel column chromatography (PE/EtOAc, 90:10→75:25→50:50) afforded alcohol **15** as a clear colourless oil (155 mg, 83%). $[\alpha]_D^{21}$ = –19.8 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3475, 2980, 2934, 1694, 1455, 1367, 1252, 1161, 1088, 1030, 873 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H, Ph), 4.77–4.66 (m, 1 H, 3-H), 4.55 (s, 2 H, CH_2Ph), 4.35 (app. t, *J* = 5.9 Hz, 1 H, 4-H), 4.13 (d, *J* = 3.3 Hz, 1 H, 2-H), 3.87 (m, 2 H, 6-H, CH_2O), 3.70 (app. t, *J* = 8.8 Hz, 1 H, CH_2O), 3.63–3.52 (m, 1 H, 5-H), 3.02–2.92 (app. t, *J* = 12.0 Hz, 1 H, 6-H), 2.87 (br. s, 1 H, OH), 1.49 (s, 3 H, CH_3), 1.43 (s, 9 H, O*t*Bu), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.15 (C=O), 138.34 (C_q, Ph), 128.11, 127.41, 127.36 (Ph), 108.47 (O-C-O), 80.22 (C_q, O*t*Bu), 72.86 (CH_2Ph), 72.61 (C-3), 72.16 (C-4), 67.67 (CH_2O), 66.24 (C-5), 50.70 (C-2), 42.18 (C-6), 28.18 (O*t*Bu), 26.18 (CH_3), 24.51 (CH_3) ppm. HRMS: calcd. for $[C_{21}H_{31}NO_6 + H]^+$ 394.22241; found 394.22209.

(2*R*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (D-*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. $[\alpha]_D^{21}$ = +3.6 (*c* = 1.0, MeOH), $[\alpha]_D^{21}$ = +2.4 (*c* = 1.0, H_2O) {ref.[22f] $[\alpha]_D$ = –21 (MeOH)}. ^1H NMR (400 MHz, D_2O): δ = 4.26 (s, 1 H, 5-H), 4.18 (s, 1 H, 3-H), 3.89 (m, 3 H, CH_2O, 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. ^{13}C NMR (101 MHz, D_2O): δ = 67.66 (C-3), 67.16 (C-4), 66.67 (C-5), 60.41 (C-2), 59.21 (CH_2O), 48.42 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09144.

***tert*-Butyl (2*S*,5*R*)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyridine-1(2*H*)-carboxylate:** Silyl ether **6** (2.20 g, 3.95 mmol) was dissolved in THF (25 mL) and cooled to 0 °C after which a 1 M solution of TBAF (6.00 mL, 6.00 mmol) was added dropwise. The mixture was warmed to room temperature and stirred overnight. It was then diluted with EtOAc (200 mL), washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude product, which was purified by silica gel column chromatography (PE/EtOAc, 4:1→7:3→3:2) to afford the product as a clear colourless oil (1.19 g, 94%). $[\alpha]_D^{21}$ = –287 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3429, 2976, 2857, 1686, 1420, 1365, 1249, 1171, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.18 (m, 5 H, Ph), 6.06 (dd, *J* = 10.1, 5.6 Hz, 1 H, 4-H), 5.94 (dd, *J* = 10.1, 3.9 Hz, 1 H, 3-H), 4.78–4.45 (m, 3 H, 2-H, CH_2Ph), 4.32–3.98 (m, 2 H, 5-H, 6-H), 3.53 (br. s, 2 H, CH_2O), 3.16 (m, 1 H, 6-H), 2.57 (s, 1 H, OH), 1.44 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.15 (C=O), 137.91 (C_q, Ph), 130.20 (C-3), 129.47 (C-4), 128.20, 127.38, 127.27 (Ph), 79.89 (C_q, O*t*Bu), 72.93 (CH_2Ph), 70.11 (CH_2O), 62.36 (C-5), 51.91 and 50.83 (C-2), 46.49 and 45.02 (C-6), 28.23 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{25}NO_4 + H]^+$ 320.18563; found 320.18588.

***tert*-Butyl (2*S*,5*S*)-5-(Benzoyloxy)-2-(benzyloxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate:** A solution of the previous alcohol (1.19 g, 3.73 mmol), triphenylphosphane (1.17 g, 4.46 mmol) and benzoic acid (0.741 g, 6.07 mmol) in THF (20 mL) was cooled to –75 °C at which temperature a solution of diethyl azodicarboxylate (0.784 g, 4.51 mmol) in THF (7 mL) was dropwise over 1 h. Stirring was continued at –75 °C for 12 h after which the temperature was slowly raised to room temperature over 5 h. TLC analysis confirmed complete conversion of the starting alcohol and the reaction mixture was diluted with EtOAc (100 mL) and washed with 1 M HCl (10 mL), an aqueous saturated solution of $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the crude product, which was purified by silica gel column chromatography (PE/EtOAc, 95:5→90:10) to afford the product as a clear colourless oil (1.57 g, 100%). $[\alpha]_D^{21}$ = –27.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2979, 2863, 2359, 1721, 1694, 1417, 1364, 1316, 1260, 1156, 1108, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.5 Hz, 2 H, Ph), 7.54 (app. t, *J* = 7.4 Hz, 1 H, Ph), 7.43 (m, 2 H, Ph), 7.36–7.23 (m, 5 H, Ph), 5.99 (m, 2 H, 3-H, 4-H), 5.52 (br. s, 1 H, 5-H), 4.80–4.40 (m, 4 H, 2-H, 6-H, CH_2Ph), 3.62 (m, 2 H, CH_2O), 3.17–2.94 (m, 1 H, 6-H), 1.47 (ds, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.51 and 165.64 (C=O), 154.11 (NC=O), 138.02 (C_q, Ph), 133.28, 132.99 (C_q, Ph), 129.93, 129.74, 129.52, 129.13, 128.20, 127.94, 127.64, 127.43, 127.28 (C-3, C-4, Ph), 80.28 (C_q, O*t*Bu), 72.94 (CH_2Ph), 70.38 (CH_2O), 66.06 (C-5), 51.88 and 50.93 (C-2), 42.16

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and 40.58 (C-6), 28.20 (O*t*Bu) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 333 K): δ = 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, CH_2Ph), 4.53 (d, J = 12.2 Hz, 1 H, CH_2Ph), 4.51 (br. s, 1 H, 6-H) 3.70–3.57 (m, 2 H, CH_2O), 3.04 (app. t, J = 11.0 Hz, 1 H, 6-H), 1.47 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 333 K): δ = 165.63 (C=O), 154.24 (NC=O), 138.19 (C_q, Ph), 133.19, 132.90 (Ph), 130.14 (C_q, Ph), 130.00, 129.58, 129.05, 128.23, 127.85, 127.45, 127.36 (C-3, C-4, Ph) 80.31 (C_q, O*t*Bu), 73.18 (CH_2Ph), 70.73 (CH_2O), 66.25 (C-5), 51.67 (C-2), 28.31 (C_q, O*t*Bu) ppm. HRMS: calcd. for $[C_{25}H_{29}NO_5 + Na]^+$ 446.19357; found 446.19379.

***tert*-Butyl (2*S*,5*S*)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyridine-1(2*H*)-carboxylate (17):** The above benzoate (155 mg, 0.366 mmol) was dissolved in a mixture of MeOH (4.0 mL) and H_2O (1.0 mL). The mixture was cooled on ice and 4 M NaOH (0.40 mL) was added. The mixture was stirred at room temp. overnight. TLC showed complete conversion of the ester and the mixture was diluted with EtOAc (30 mL), washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated. After purification by silica gel column chromatography (PE/EtOAc, 90:10→80:20→70:30), the title alcohol was obtained as a colourless oil (109 mg, 93%). $[\alpha]^{21}_D$ = –146 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3426, 2928, 1695, 1456, 1418, 1366, 1257, 1155, 1071, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.19 (m, 5 H, Ph), 5.94 (d, J = 10.3 Hz, 1 H, 4-H), 5.80 (dd, J = 10.3, 3.0 Hz, 1 H, 3-H), 4.56 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.51 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.48 (s, 1 H, 2-H), 4.42–4.06 (m, 2 H, 5-H, 6-H), 3.59–3.48 (m, 2 H, CH_2O), 2.76 (m, 2 H, 6-H, OH), 1.43 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.47 (C=O), 137.90 (C_q, Ph), 133.14 (C-4), 131.70, 129.96, 128.34, 127.60 (Ph), 127.48 (C-3), 80.16 (C_q, O*t*Bu), 73.10 (CH_2Ph), 70.48 (CH_2O), 63.49 (C-5), 28.33 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{25}NO_4 + Na]^+$ 342.16758; found 342.16762.

***tert*-Butyl (2*R*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-3,4,5-trihydroxypiperidine-1-carboxylate:** Alcohol **17** (350 mg, 1.10 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (NMO) (205 mg, 1.52 mmol) were dissolved in a mixture of acetone (10 mL) and water (10 mL). Subsequently, $K_2OsO_4{\cdot}2H_2O$ (20 mg, 0.054 mmol) was added and the reaction stirred at ambient temperature overnight, after which TLC analysis showed complete conversion of alcohol **17**. The reaction mixture was quenched with a saturated aqueous solution of $NaHSO_3$ (30 mL) and stirred for 1 h. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude product. After purification by silica gel column chromatography (PE/EtOAc, 1:1→0:1), the title triol was obtained as a colourless oil (320 mg, 82%). $[\alpha]^{22}_D$ = –52.2 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3404, 2977, 2906, 1654, 1420, 1366, 1166, 1078 cm^{-1}. ^{1}H NMR (400 MHz, MeOD): δ = 7.33–7.25 (m, 5 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 4.47 (s, 1 H), 4.25–4.08 (m, 1 H), 4.01 (s, 1 H), 3.83–3.68 (m, 1 H), 3.56 (dd, J = 16.5, 4.8 Hz, 3 H), 2.68 (d, J = 11.3 Hz, 1 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (101 MHz, MeOD): δ = 139.40, 129.38, 128.68, 81.36, 74.02, 73.93, 70.62, 68.64, 67.75, 59.25, 45.56, 28.61 ppm. HRMS: calcd. for $[C_{18}H_{27}NO_6 + H]^+$ 354.19111; found 354.19120; calcd. for $[C_{18}H_{27}NO_6 + Na]^+$ 376.17306; found 376.17311.

(2*R*,3*R*,4*S*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (D-*altro*-1-DNJ Hydrochloride, 18): The triol from above (550 mg, 1.56 mmol) was dissolved in a mixture of MeOH (20 mL) and 6 M HCl (6 mL). The solution was purged with nitrogen after which Pd/C (10%, 60 mg) was added and the reaction mixture was stirred under a balloon of H_2 overnight. The mixture was filtered through a Whatman® glass-fibre filter and concentrated to afford the title compound as a white solid (310 mg, quant.). $[\alpha]^{21}_D$ = +39.2 (c = 0.5 MeOH) {ref.[24a] $[\alpha]^{25}_D$ = +31.1 (c = 0.5 MeOH), ref.[24d] $[\alpha]_D$ = +33.2 (c = 0.5 MeOH)}. ^{1}H NMR (400 MHz, D_2O): δ = 4.14–4.08 (m, 1 H, 5-H), 4.02–3.96 (m, 2 H, 3-H, 4-H), 3.93 (dd, J = 12.6, 3.3 Hz, 1 H, CH_2O), 3.79 (dd, J = 12.6, 6.8 Hz, 1 H, CH_2O), 3.38–3.27 (m, 2 H, 2-H, 6-H), 3.18 (dd, J = 13.5, 2.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 68.15 (C-3), 65.89 (C-5), 63.28 (C-4), 57.86 (CH_2O), 55.53 (C-2), 43.60 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09169.

***tert*-Butyl (2*S*,3*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxypiperidine-1-carboxylate (19):** Compound **7** (651 mg, 1.17 mmol) was dissolved in a mixture of THF (6.0 mL) and water (0.60 mL) and cooled to 0 °C. *N*-Methylmorpholine *N*-oxide monohydrate (665 mg, 4.93 mmol) and $K_2OsO_4{\cdot}2H_2O$ (20.0 mg, 0.054 mmol, 4.6 mol-%) were then added. After 24–48 h, TLC analysis showed complete conversion of the starting material. The reaction mixture was quenched with a saturated aqueous solution of $NaHSO_3$ (10 mL) and stirred for 30 min. Then the mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 0.6 M HCl, saturated $NaHCO_3$ and brine. Drying (Na_2SO_4), filtration and evaporation of the solvent afforded a crude product that was purified by silica gel column chromatography (PE/EtOAc, 7:3→1:1) to afford **19** (635 mg, 92%) as a colourless oil. $[\alpha]^{22}_D$ = +52.0 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3396, 2976, 2358, 1664, 1420, 1365, 1251, 1167, 1073, 750, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.64 (m, 4 H, Ph), 7.45–7.25 (m, 11 H, Ph), 4.53 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.48 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.45 (br. s, 1 H, 2-H), 4.03 (s, 1 H, 3-H), 3.98–3.88 (m, 1 H, 4-H), 3.79 (s, 1 H, 5-H), 3.56 (d, J = 5.3 Hz, 2 H, CH_2O), 2.85 (t, J = 11.8 Hz, 1 H, 6-H), 2.49 (br. s, 1 H, OH), 2.25 (br. s, 1 H, OH), 1.34 (s, 9 H, O*t*Bu), 1.08 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.13 (C=O), 137.82 (C_q, Ph), 135.70, 135.61 (Ph), 133.59 (C_q, Ph), 129.89, 128.34, 127.80, 127.74, 127.60, 127.36 (Ph), 80.01 (C_q, O*t*Bu), 73.88 (C-5), 73.04 (CH_2Ph), 69.77 (C-4), 69.51 (C-3), 68.62 (CH_2O), 28.20 (O*t*Bu), 26.94 (Si*t*Bu), 19.26 (C_q, Si*t*Bu) ppm. ^{1}H NMR (400 MHz, DMSO, 353 K): δ = 7.74 (d, J = 6.5 Hz, 2 H, Ph), 7.66 (d, J = 6.5 Hz, 2 H, Ph), 7.47–7.36 (m, 6 H, Ph), 7.36–7.25 (m, 5 H, Ph), 4.53 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.49 (d, J = 12.2 Hz, 1 H, CH_2Ph), 4.43 (d, J = 3.5 Hz, 1 H, OH), 4.25 (m, 1 H, 2-H), 4.09 (d, J = 6.5 Hz, 1 H, OH), 3.99–3.87 (m, 3 H, 3-H, 4-H, 6-H), 3.71–3.64 (m, 1 H, 5-H), 3.64–3.53 (m, 2 H, CH_2O), 2.74 (td, J = 12.0, 2.6 Hz, 1 H, 6-H), 1.29 (s, 9 H, O*t*Bu), 1.06 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, DMSO, 353 K): δ = 153.92 (C=O), 138.01 (C_q, Ph), 135.08, 134.90 (Ph), 133.91 (C_q, Ph), 133.47 (C_q, Ph), 129.12, 129.06, 127.68, 127.06, 127.01, 126.87, 126.79 (Ph), 78.24 (C_q, O*t*Bu), 72.43 (C-5), 71.86 (C_q, Ph), 69.48 (C-4), 68.63 (C-3), 67.65 (CH_2O), 56.23 (C-2), 45.09 (C-6), 27.60 (O*t*Bu), 26.51 (Si*t*Bu), 18.58 (C_q, Si*t*Bu) ppm. HRMS: calcd. for $[C_{34}H_{45}NO_6Si + Na]^+$ 614.29084; found 614.29086.

***tert*-Butyl (2*S*,3*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-3,4,5-trihydroxypiperidine-1-carboxylate:** TBDPS ether **19** (688 mg, 1.16 mmol) was dissolved in THF (20 mL). A 1 M solution of TBAF in THF (2.0 mL, 2.0 mmol) was added at room temperature and the reaction mixture was stirred at ambient temperature overnight. TLC indicated complete conversion and the mixture was concentrated. The crude compound was purified by silica gel column chromatography (PE/EtOAc, 3:1→1:1→0:1) to afford the title compound as a colourless oil (337 mg, 82%). $[\alpha]^{20}_D$ = +48.8 (c = 1.0, $CHCl_3$). IR

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(film): $\tilde{\nu}$ = 3396, 2976, 2358, 1664, 1420, 1365, 1251, 1167, 1073, 750 cm^{-1}. ^{1}H NMR (400 MHz, MeOD): δ = 7.40–7.22 (m, 5 H, Ph), 4.56 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.51 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.46 (br. s, 1 H, 2-H), 4.19–4.07 (m, 1 H, 6-H), 4.00 (br. s, 1 H, 3-H), 3.80–3.69 (m, 1 H, 5-H), 3.59 (d, J = 6.6 Hz, 2 H, CH_2O), 3.54 (dd, J = 9.4, 3.1 Hz, 1 H, 4-H), 2.68 (br. s, 1 H, 6-H), 1.44 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.84 (C=O), 137.69 (C_q, Ph), 128.34, 127.64, 127.48 (Ph), 80.51 (C_q, O*t*Bu), 73.14 (C-2), 72.88 (CH_2Ph), 69.33 (C-3), 67.55 (CH_2O), 66.80 (C-4), 28.27 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{27}NO_6 + H]^+$ 354.19111; found 354.19122.

(2*S*,3*S*,4*R*,5*S*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (L-*altro*-1-DNJ Hydrochloride, 20): The protected L-*altro*-1-deoxynojirimicin (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. $[\alpha]_D^{21}$ = –31.4 (c = 0.5, MeOH) {ref.[25] $[\alpha]_D^{20}$ = –31.4 (c = 1.0, MeOH)}. ^{1}H NMR (400 MHz, MeOD): δ = 4.11 (app. t, J = 1.2 Hz, 1 H, 5-H), 4.01–3.97 (m, 2 H, 3-H, 4-H), 3.93 (dd, J = 12.8, 3.2 Hz, 1 H, CH_2O), 3.79 (dd, J = 12.8, 6.8 Hz, 1 H, CH_2O), 3.36–3.28 (m, 2 H, 2-H, 6-H), 3.18 (dd, J = 13.6, 2.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 68.41 (C-3), 66.15 (C-5), 63.55 (C-4), 58.12 (CH_2O), 55.79 (C-2), 43.86 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09157.

***tert*-Butyl (2*R*,5*R*)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyridine-1(2*H*)-carboxylate:** TBDPS ether **7** (3.40 g, 6.10 mmol) was dissolved in THF (50 mL), cooled on an ice bath and a 1 M solution of TBAF in THF (12 mL, 12 mmol) was added. After stirring on the ice bath for 1 h 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→80:20→60:40) afforded the product as a clear colourless oil (1.75 g, 90%). $[\alpha]_D^{21}$ = +140 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3422, 2978, 2868, 1694, 1418, 1366, 1155, 1112, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H, Ph), 5.93 (d, J = 10.4 Hz, 1 H, 4-H), 5.79 (dd, J = 10.4, 2.7 Hz, 1 H, 3-H), 4.66–4.02 (m, 5 H, CH_2Ph, 2-H. 5-H, 6-H), 3.73–3.42 (m, 2 H, CH_2O), 3.40–2.60 (m, 2 H, 6-H, OH), 1.43 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.33 (C=O), 137.80 (C_q, Ph), 131.92, 128.17, 127.42, 127.32 (C-3, C-4, Ph), 80.01 (C_q, O*t*Bu), 72.89 (CH_2Ph), 70.32 (CH_2O), 64.32 (C-5), 63.20 (C-2), 51.69 (C-2), 44.07 (C-6), 28.19 (O*t*Bu) ppm. ^{1}H NMR (400 MHz, 333 K, $CDCl_3$): δ = 7.35–7.18 (m, 5 H, Ph), 5.89 (dd, J = 10.4, 1.5 Hz, 1 H, 4-H), 5.78 (ddd, J = 10.4, 3.7, 1.5 Hz, 1 H, 3-H), 4.60–4.44 (m, 3 H, 2-H, CH_2Ph), 4.28–4.11 (m, 2 H, 5-H, 6-H), 3.57 (d, J = 5.7 Hz, 2 H, CH_2O), 2.77 (dd, J = 11.9, 8.7 Hz, 1 H, 6-H), 2.23 (s, 1 H, OH), 1.44 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, 333 K, $CDCl_3$): δ = 154.54 (C=O), 138.31 (C_q, Ph), 131.89, 128.31, 127.53, 127.51, 127.35 (C-3, C-4, Ph), 80.06 (C_q, O*t*Bu), 73.35 (CH_2Ph), 70.96 (CH_2O), 63.69 (C-5), 51.91 (C-2), 45.48 (C-6), 28.43 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{25}NO_4 + Na]^+$ 342.16758; found 342.16753.

***tert*-Butyl (2*R*,5*S*)-5-(Benzoyloxy)-2-(benzyloxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate:** A mixture of the alcohol from above (1.05 g, 3.29 mmol), triphenylphosphane (1.11 g, 4.24 mmol) and benzoic acid (0.736 g, 6.03 mmol) was dissolved in THF (20 mL). At –75 °C a solution of DEAD (0.690 mL, 4.44 mmol) in THF (7 mL) was added dropwise over 10 min. After stirring at –75 °C for 12 h, the mixture was slowly warmed to room temperature. TLC analysis revealed complete conversion and the reaction mixture was diluted with EtOAc (100 mL) and then washed with aqueous 0.5 M HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). After drying ($MgSO_4$), filtration and concentration in vacuo, the crude product was obtained. At this stage RP-HPLC analysis indicated <1% of the 2*S*,5*R* isomer in the crude product. Purification by silica gel column chromatography (PE/EtOAc, 95:5→90:10) afforded the product as a clear colourless oil (1.32 g, 94%). $[\alpha]_D^{21}$ = +299 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2972, 2861, 1717, 1690, 1419, 1363, 1335, 1266, 1169, 1107, 1069, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (m, 2 H, Ph), 7.65–7.12 (m, 8 H, Ph), 6.16 (m, 2 H, 3-H, 4-H), 5.30 (m, 1 H, 5-H), 4.90–4.70 (m, 1 H, 2-H), 4.64–4.40 (m, 3 H, CH_2Ph, 6-H), 3.61 (m, 2 H, CH_2O), 3.31–3.21 (m, 1 H, 6-H), 1.38 (m, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.82 and 165.95 (C=O), 154.62 (NC=O), 137.92 (C_q, Ph), 133.47 (C-3), 133.15, 132.90, 132.47, 129.96, 129.89 (Ph), 129.56 (C_q, Ph), 128.20, 128.10, 127.45, 127.31 (Ph), 123.91, 123.54 (C-4), 79.73 (C_q, O*t*Bu), 72.92 (CH_2Ph), 70.29 (CH_2O), 65.31 (C-5), 52.05 and 51.02 (C-2), 43.25 and 42.09 (C-6), 28.02 (O*t*Bu) ppm. ^{1}H NMR (400 MHz, 333 K, $CDCl_3$): δ = 8.10–7.96 (d, J = 7.8 Hz, 2 H, Ph), 7.50 (dd, J = 15.2, 7.8 Hz, 1 H, Ph), 7.43–7.19 (m, 7 H, Ph), 6.13 (s, 2 H, 3-H, 4-H), 5.28 (s, 1 H, 5-H), 4.81 (br. s, 1 H, 2-H), 4.62–4.39 (m, 3 H, CH_2Ph, 6-H), 3.61 (d, J = 5.0 Hz, 2 H, CH_2O), 3.31 (d, J = 13.8 Hz, 1 H, 6-H), 1.36 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, 333 K, $CDCl_3$): δ = 165.99 (C=O), 154.70 (NC=O), 138.16 (C_q, Ph), 133.07 (C-3), 132.74, 130.40 (Ph), 129.97 (C_q, Ph), 129.67, 128.25, 128.11, 127.49, 127.37 (Ph), 123.78 (C-4), 79.83 (C_q, O*t*Bu), 73.19 (CH_2Ph), 70.60 (CH_2O), 65.53 (C-5), 51.67 (C-2), 43.15 (C-6), 28.20 (O*t*Bu) ppm. HRMS: calcd. for $[C_{25}H_{29}NO_5 + Na]^+$ 446.19379; found 446.19348; calcd. for $[C_{25}H_{29}NO_5 + H]^+$ 424.21185; found 424.21196.

***tert*-Butyl (2*R*,5*S*)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypyridine-1(2*H*)-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→80:20→60:40) to afford the product as a clear colourless oil (1.00 g, 80%). $[\alpha]_D^{20}$ = +270 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3422, 2976, 2830, 1686, 1420, 1364, 1248, 1170, 1126, 1069, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5 H, Ph), 6.07 (dd, J = 10.0, 5.5 Hz, 1 H, 3-H), 5.95 (dd, J = 10.1, 3.8 Hz, 1 H, 4-H), 4.72 (br. s, 1 H, 2-H), 4.54 (d, J = 12.1 Hz, 1 H. CH_2Ph), 4.50 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.34–3.99 (m, 2 H, 2-H, 6-H), 3.54 (br. s, 2 H, CH_2O), 3.17 (d, J = 34.6 Hz, 1 H, 6-H), 2.35 (br. s, 1 H, OH), 1.45 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.21 (C=O), 137.96 (C_q, Ph), 129.64, 128.25, 127.45, 127.33 (C-3, C-4, Ph), 79.98 (C_q, O*t*Bu), 73.00 (CH_2Ph), 70.16 (CH_2O), 62.56 (C-2), 28.29 (O*t*Bu) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 333 K): δ = 7.35–7.20 (m, 5 H, Ph), 6.04 (dd, J = 10.1, 5.5 Hz, 1 H, 4-H), 5.94 (dd, J = 10.1, 4.0 Hz, 1 H, 3-H), 4.64 (s, 1 H, 2-H), 4.53 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.49 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.21 (d, J = 13.8 Hz, 1 H, 6-H), 4.07–4.00 (m, 1 H, 2-H), 3.55 (d, J = 5.4 Hz, 2 H, CH_2O), 3.16 (d, J =

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13.8 Hz, 1 H, 6-H), 2.01 (br. s, 1 H, OH), 1.45 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 333 K): δ = 155.29 (C=O), 138.23 (C_q, Ph), 130.12, 128.27, 127.63, 127.49, 127.39 (C-3, C-4, Ph), 79.98 (C_q, O*t*Bu), 73.20 (CH_2Ph), 70.44 (CH_2Ph), 62.81 (C-5), 51.68 (C-2), 46.00 (C-6), 28.37 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{25}NO_4 + Na]^+$ 342.16758; found 342.16764; calcd. for $[C_{18}H_{25}NO_4 + H]^+$ 320.18563; found 320.18579.

***tert*-Butyl (2*R*,5*S*)-2-(Benzyloxymethyl)-5,6-dihydro-5-(*tert*-butyldiphenylsilyloxy)pyridine-1(2*H*)-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 after which 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 ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (PE/EtOAc, 97:3 → 95:5) to afford the product as a mixture of compound **24** and TBDPS-OH [clear colourless oil, 2.49 g, 140%; contained 1.74 g (98%) of compound **24**, determined from ^{1}H NMR data]. $[\alpha]^{21}_D$ = +167 (*c* = 1.0, $CHCl_3$). From a second column chromatography an analytical sample of **24** was obtained. $[\alpha]^{21}_D$ = +185 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2932, 2858, 1694, 1428, 1366, 1249, 1172, 1106, 1028, 822 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.4 Hz, 2 H, Ph), 7.66 (d, *J* = 7.4 Hz, 2 H, Ph), 7.46–7.33 (m, 6 H, Ph), 7.32–7.22 (m, 5 H, Ph), 5.86–5.78 (dd, *J* = 10.1, 3.9 Hz, 1 H, 4-H), 5.67 (br. s, 1 H, 3-H), 4.81–4.56 (m, 1 H, 2-H), 4.51 (d, *J* = 12.4 Hz, 1 H, CH_2Ph), 4.47 (d, *J* = 12.4 Hz, 1 H, CH_2Ph), 4.41–4.12 (m, 1 H, 5-H), 4.07 (br. s, 1 H, 6-H), 3.51 (m, 2 H, CH_2O), 3.35–2.86 (m, 1 H, 6-H), 1.49 (s, 9 H, O*t*Bu), 1.05 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.85 (C=O), 138.15 (C_q, Ph), 135.70 (Ph), 135.44 (C_q, Ph), 134.75 (Ph), 133.85 (C_q, Ph), 129.61, 129.47, 129.39, 128.21, 127.58, 127.53, 127.39, 127.28 (Ph), 79.49 (C_q, O*t*Bu), 72.91 (CH_2Ph), 70.47 (CH_2O), 63.82 (C-5), 28.38 (O*t*Bu), 26.83 (Si*t*Bu), 19.13 (C_q, Si*t*Bu) ppm. ^{1}H NMR (400 MHz, $CDCl_3$ 333 K): δ = 7.73–7.68 (m, 2 H, Ph), 7.68–7.63 (m, 2 H, Ph), 7.41–7.30 (m, 6 H, Ph), 7.29–7.18 (m, 5 H, Ph), 5.80 (dd, *J* = 10.2, 3.9 Hz, 1 H, 4-H), 5.70–5.61 (m, 1 H, 3-H), 4.68 (br. s, 1 H, 2-H), 4.50 (d, *J* = 12.2 Hz, 1 H, CH_2Ph), 4.46 (d, *J* = 12.2 Hz, 1 H, CH_2Ph), 4.25 (d, *J* = 13.4 Hz, 1 H, 6-H), 4.12–4.06 (m, 1 H, 5-H), 3.51 (d, *J* = 5.4 Hz, 2 H, CH_2O), 3.01 (d, *J* = 13.4 Hz, 1 H, 6-H), 1.48 (s, 9 H, O*t*Bu), 1.05 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$ 333 K): δ = 154.97 (C=O), 138.46 (C_q, Ph), 135.85, 135.84, 134.85 (Ph), 134.66 (C_q, Ph), 134.27 (C_q, Ph), 129.64, 129.57, 129.52, 128.29, 127.64, 127.56, 127.47, 127.41 (Ph), 79.55 (C_q, O*t*Bu), 73.20 (CH_2Ph), 70.82 (CH_2O), 64.16 (C-5), 51.52 (C-2), 46.30 (C-6), 28.52 (O*t*Bu), 27.00 (Si*t*Bu), 19.25 (C_q, Si*t*Bu) ppm. HRMS: calcd. for $[C_{34}H_{43}NO_4Si + H]^+$ 558.30341; found 558.30334.

***tert*-Butyl (2*S*,3*S*,4*R*,5*R*)-2-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxypiperidine-1-carboxylate (25) and *tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxypiperidine-1-carboxylate (26):** The silyl ether **24** [2.49 g, 70% purity, 3.12 mmol] from above was dissolved in a mixture of THF (10.0 mL) and water (1.50 mL) and cooled to –10 °C. *N*-Methylmorpholine *N*-oxide monohydrate (1.35 g, 10.0 mmol) and $K_2OsO_4 \cdot 2H_2O$ (53.0 mg, 0.144 mmol, 4.4 mol-%) were added subsequently. After 48 h, LC–MS analysis showed complete conversion of the starting material. The reaction mixture was quenched with a saturated aqueous solution of Na_2SO_3 (10 mL) and stirred for 30 min. Then the mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 0.6 M HCl, saturated $NaHCO_3$ and brine. Drying (Na_2SO_4), filtration and evaporation of the solvent 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 clear colourless oil.

***tert*-Butyl (2*S*,3*S*,4*R*,5*R*)-2-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxypiperidine-1-carboxylate (25):** $[\alpha]^{21}_D$ = –10.4 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3496, 2932, 2858, 1694, 1455, 1428, 1393, 1365, 1250, 1170, 1104, 935 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 4 H, Ph), 7.47–7.36 (m, 6 H, Ph), 7.32–7.20 (m, 5 H, Ph), 4.68 (s, 1 H, 2-H), 4.44 (s, 2 H, CH_2Ph), 4.04 (s, 2 H, 5-H, 6-H), 3.97–3.63 (m, 3 H, 3-H, 4-H, OH), 3.52 (d, *J* = 5.1 Hz, 2 H, CH_2O), 2.87 (d, *J* = 11.2 Hz, 1 H, 6-H), 2.77 (d, *J* = 10.6 Hz, 1 H, OH), 1.44 (s, 9 H, O*t*Bu), 1.11 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.75 (C=O), 137.63 (C_q, Ph), 136.10, 135.82, 135.61 (Ph), 132.65 (C_q, Ph), 132.07 (C_q, Ph), 130.15, 130.03, 128.37, 127.83, 127.80, 127.67, 127.41 (Ph), 80.14 (C_q, O*t*Bu), 73.16 (CH_2Ph), 72.04 (C-5), 71.31 (C-3), 69.12 (CH_2O), 67.62 (C-4), 28.26 (O*t*Bu), 27.02 (Si*t*Bu), 19.22 (C_q, Si*t*Bu) ppm. ^{1}H NMR (400 MHz, $CDCl_3$ 333 K): δ = 7.71 (m, 4 H, Ph), 7.45–7.34 (m, 6 H, Ph), 7.30–7.20 (m, 5 H, Ph), 4.66 (app. t, *J* = 5.3 Hz, 1 H, 2-H), 4.44 (s, 2 H, CH_2Ph), 4.07 (d, *J* = 13.3 Hz, 1 H, 6-H), 4.05 (s, 1 H, 5-H), 3.90 (d, *J* = 11.1 Hz, 1 H, 3-H), 3.66 (d, *J* = 11.1 Hz, 2 H, 4-H, OH), 3.57–3.48 (m, 2 H, CH_2O), 2.87 (d, *J* = 13.3 Hz, 1 H, 6-H), 2.69 (d, *J* = 10.2 Hz, 1 H, OH), 1.43 (s, 9 H, O*t*Bu), 1.11 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.84 (C=O), 137.87 (C_q, Ph), 136.18, 135.96, 135.72 (Ph), 132.96 (C_q, Ph), 132.48 (C_q, Ph), 130.13, 130.04, 128.41, 127.87, 127.82, 127.70, 127.50 (Ph), 80.15 (C_q, O*t*Bu), 73.36 (CH_2Ph), 72.20 (C-5), 71.38 (C-3), 69.26 (CH_2O), 67.87 (C-4), 58.41 (C-2), 45.98 (C-6), 28.38 (O*t*Bu), 27.16 (Si*t*Bu), 19.31 (C_q, Si*t*Bu) ppm. HRMS: calcd. for $[C_{34}H_{45}NO_6Si + H]^+$ 592.30889; found 592.30908.

***tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,4-dihydroxypiperidine-1-carboxylate (26):** Further elution until the faster running isomer had disappeared (TLC monitoring) afforded 82 mg of a mixture of two diastereoisomers. Elution with PE/EtOAc (7:3) then afforded the slower running isomer (737 mg, 40%) as a colourless oil. $[\alpha]^{20}_D$ = +9.4 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3405, 2933, 1664, 1428, 1365, 1157, 1106, 882 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 2 H, Ph), 7.63 (d, *J* = 8.3 Hz, 2 H, Ph), 7.41–7.23 (m, 11 H, Ph), 4.61 (br. s, 1 H, 2-H), 4.51 (d, *J* = 12.3 Hz, 1 H, CH_2Ph), 4.47 (d, *J* = 12.3 Hz, 1 H, CH_2Ph), 4.38 (m, 1 H, 3-H), 4.17–3.72 (m, 5 H, 6-H, 5-H, CH_2O, OH), 3.67 (s, 1 H, 4-H), 3.16 (d, *J* = 12.8 Hz, 1 H, 6-H), 2.83 (br. s, 1 H), 1.45 (s, 9 H, O*t*Bu), 1.06 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.45 (C_q, Ph), 135.75 (Ph), 135.56 (Ph), 133.48 (C_q, Ph), 133.11 (C_q, Ph), 129.77, 128.54, 128.12, 127.83, 127.65, 127.63 (Ph), 79.97 (C_q, O*t*Bu), 73.61 (CH_2Ph), 70.54 (C-5), 70.19 (C-4), 68.31 (CH_2O), 66.19 (C-3), 28.31 (O*t*Bu), 26.87 (Si*t*Bu), 19.12 (C_q, Si*t*Bu) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 333 K): δ = 7.72–7.59 (m, 4 H, Ph), 7.47–7.18 (m, 11 H, Ph), 4.61–4.54 (m, 1 H, 2-H), 4.50 (s, 2 H, CH_2Ph), 4.35 (d, *J* = 6.9 Hz, 1 H, 3-H), 3.92 (d, *J* = 13.3 Hz, 1 H, 6-H), 3.89 (s, 1 H, 5-H), 3.82 (d, *J* = 4.3 Hz, 2 H, CH_2O), 3.67 (s, 2 H, 4-H, OH), 3.16 (d, *J* = 13.3 Hz, 1 H, 6-H), 2.69 (s, 1 H, OH), 1.44 (s, 9 H, O*t*Bu), 1.07 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 333 K): δ = 155.27 (C=O), 136.85 (C_q, Ph), 135.88 (Ph), 135.71 (Ph), 133.85 (C_q, Ph), 133.51 (C_q, Ph), 129.84, 129.82, 128.62, 128.16, 127.90, 127.74, 127.71 (Ph), 80.00 (C_q, O*t*Bu), 73.83 (CH_2Ph), 71.00 (C-5), 70.78 (C-4), 68.70 (CH_2O), 66.64 (C-3), 52.79 (C-2), 42.42 (C-6), 28.45 (O*t*Bu), 27.06 (Si*t*Bu), 19.26 (C_q, Si*t*Bu) ppm. HRMS: calcd. for

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$[C_{34}H_{45}NO_6Si + H]^+$ 592.30889; found 592.30913; calcd. for $[C_{34}H_{45}NO_6Si + Na]^+$ 614.29084; found 614.29042.

***tert*-Butyl (2*S*,3*S*,4*R*,5*R*)-2-(Benzyloxymethyl)-3,4,5-trihydroxypiperidine-1-carboxylate (22):** Silyl ether **25** (715 mg, 1.21 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. 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%). $[\alpha]_D^{21}$ = +35.0 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3396, 2976, 2881, 1686, 1420, 1366, 1249, 1170, 1136, 1088 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.37–7.23 (m, 5 H, Ph), 4.62 (br. s, 1 H, 2-H), 4.53 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.48 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.20 (d, *J* = 14.1 Hz, 1 H, 6-H), 3.97 (br. s, 1 H, 3-H), 3.84 (br. s, 1 H, 5-H), 3.70 (app. t, *J* = 3.0 Hz, 1 H, 4-H), 3.56 (d, *J* = 6.5 Hz, 2 H, CH_2O), 3.08 (d, *J* = 14.1 Hz, 1 H, 6-H), 1.44 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, MeOD): δ = 158.01 (C=O), 139.42 (C_q, Ph), 130.72, 129.38, 128.70 (Ph), 81.35 (C_q, O*t*Bu), 73.97 (CH_2Ph), 71.78 (C-3), 70.81 (C-5), 68.93 (CH_2O), 67.89 (C-4), 28.61 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{27}NO_6 + H]^+$ 354.19111; found 354.19138.

(2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (L-*allo*-1-DNJ Hydrochloride, 27): The *N*-Boc-2-OBn-protected L-*allo*-1-DNJ from above (408 mg, 1.16 mmol) was dissolved in a mixture of MeOH (25 mL) and 6 M HCl (5 mL). The flask was purged with argon, Pd/C (10%, 89 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 filtering through a Whatman® glass-fibre filter and evaporation of the solvents, the crude product (233 mg) was obtained in quantitative yield. $[\alpha]_D^{23}$ = –27.8 (*c* = 1.0, H_2O) {ref.[26a] $[\alpha]_D^{25}$ = –37.5 (*c* = 1.0, MeOH)}. ^1H NMR (400 MHz, D_2O): δ = 4.17 (s, 1 H, 3-H), 4.01 (ddd, *J* = 11.9, 4.8, 2.5 Hz, 1 H, 5-H), 3.94 (dd, *J* = 12.7, 3.0 Hz, 1 H, CH_2O), 3.89–3.81 (m, 2 H, CH_2O, 4-H), 3.33 (ddd, *J* = 10.4, 4.8, 3.0 Hz, 1 H, 2-H), 3.27 (dd, *J* = 11.9, 4.8 Hz, 1 H, 6-H), 3.11 (dd, *J* = 11.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 69.85 (C-3), 65.27 (C-4), 64.46 (C-5), 57.61 (CH_2O), 54.65 (C-2), 41.52 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09173.

***tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-3,4,5-trihydroxypiperidine-1-carboxylate (23):** Silyl ether **26** (710 mg, 1.20 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. A 1.0 M solution of TBAF (3.00 mL, 3.00 mmol) was added dropwise. Stirring was continued on the ice bath and after 2 h TLC indicated no conversion of **26**. An extra portion of the 1 M solution of TBAF (4.00 mL, 4.00 mmol) was added and the reaction stirred overnight. TLC indicated complete conversion of **26** and 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 (390 mg, 92%). $[\alpha]_D^{21}$ = +39.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, MeOD): δ = 7.35–7.22 (m, 5 H, Ph), 4.63–4.54 (m, 2 H, 2-H, Ch_2Ph), 4.45 (d, *J* = 11.9 Hz, 1 H, Ch_2Ph), 4.07–3.98 (m, 2 H, CH_2O), 3.84 (d, *J* = 14.3 Hz, 1 H, 6-H), 3.81–3.71 (m, 3 H, 3-H, 4-H, 5-H), 3.20 (dd, *J* = 14.3, 1.1 Hz, 1 H, 6-H), 1.44 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (101 MHz, MeOD): δ = 157.81 (C=O), 139.80 (C_q, Ph), 130.71, 129.27, 128.72, 128.54 (Ph), 81.07 (C_q, O*t*Bu), 73.61 (CH_2Ph), 72.45 (C-4), 70.71 (C-3), 67.18 (CH_2O), 67.05 (C-5), 28.68 (O*t*Bu) ppm. HRMS: calcd. for $[C_{18}H_{27}NO_6 + H]^+$ 354.19111; found 354.19138.

(2*S*,3*R*,4*S*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (L-*galacto*-1-DNJ Hydrochloride, 28): The *N*-Boc-2-OBn-protected L-*galacto*-1-DNJ (305 mg, 0.864 mmol) from above was dissolved in a mixture of MeOH (20 mL) and 6 M HCl (5 mL) and transferred into a 250 mL Parr flask. The flask was purged with argon, Pd/C (10%, 60 mg) was added and the mixture was shaken vigorously under 4 bar H_2 pressure overnight at room temperature. After filtering through a Whatman® glass-fibre filter and evaporation of the solvents, the crude product (172 mg) was obtained in quantitative yield. $[\alpha]_D^{22}$ = –57.8 (*c* = 1.0, H_2O) {ref.[27a] $[\alpha]_D$ = –51.4 (*c* = 1.0, D_2O), ref.[27b] $[\alpha]_D$ = –51.4 (*c* = 1.0, H_2O)}. ^1H NMR (400 MHz, D_2O): δ = 4.15 (dd, *J* = 2.9, 1.3 Hz, 1 H, 3-H), 4.06 (ddd, *J* = 11.4, 9.6, 5.4 Hz, 1 H, 5-H), 3.87 (dd, *J* = 12.1, 8.9 Hz, 1 H, CH_2O), 3.79 (dd, *J* = 12.1, 8.9 Hz, 1 H, CH_2O), 3.63 (dd, *J* = 9.6, 2.8 Hz, 1 H, 4-H), 3.50 (dd, *J* = 12.5, 5.3 Hz, 1 H, 6-H), 3.41 (dd, *J* = 8.6, 4.8 Hz, 1 H, 2-H), 2.87 (app. t, *J* = 12.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 72.86 (C-4), 66.83 (C-3), 64.58 (C-5), 60.03 (C-2), 59.05 (CH_2O), 46.04 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09195.

***tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-3,4-*O*-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, $BF_3 \cdot Et_2O$ (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_2SO_4), filtered and concentrated to afford a crude product that was purified by silica gel column chromatography (PE/EtOAc, 98:2→96:4→90:10) to afford the target compound as a colourless oil (628 mg, 88%). $[\alpha]_D^{22}$ = +31.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2933, 1697, 1454, 1428, 1393, 1366, 1252, 1145, 1105, 1057, 989, 878 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 7.9, 1.5 Hz, 2 H, Ph), 7.62 (dd, *J* = 7.9, 1.5 Hz, 2 H, Ph), 7.45–7.23 (m, 11 H, Ph), 4.68–4.61 (m, 1 H, 3-H), 4.56 (s, 2 H, CH_2Ph), 4.24–3.80 (m, 4 H, 2-H, 5-H, 6-H, CH_2O), 3.76 (d, *J* = 1.4 Hz, 1 H, 4-H), 3.70 (app. t, *J* = 8.9 Hz, 1 H, CH_2O), 3.20 (d, *J* = 13.7 Hz, 1 H, 6-H), 1.39 (s, 9 H, O*t*Bu), 1.33 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.07 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.62 (C=O), 138.56 (C_q, Ph), 135.76 (Ph), 133.55 (C_q, Ph), 133.20 (C_q, Ph), 129.80, 129.72, 128.22, 127.65, 127.60, 127.43 (Ph), 107.70 (O-C-O), 79.96 (C_q, O*t*Bu), 75.01 (C-5), 73.11 (CH_2Ph), 70.97 (C-3), 69.53 (C-4), 50.73 (C-2), 28.29 (O*t*Bu), 26.95 (Si*t*Bu), 26.65 (CH_3), 24.20 (CH_3), 19.15 (C_q, Si*t*Bu) ppm. HRMS: calcd. for $[C_{37}H_{49}NO_6Si + H]^+$ 632.34019; found 632.34081.

***tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-hydroxypiperidine-1-carboxylate (29):** A solution of TBAF in THF (1 M, 1.50 mL, 1.50 mmol) was added to a solution of the above TBDPS ether (628 mg, 0.995 mmol) in THF (15 mL). After stirring overnight, 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 (370 mg, 95%). $[\alpha]_D^{21}$ = +25.4 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3414, 2983, 2936, 1695, 1455, 1368, 1254, 1212, 1166, 1146, 1056, 875 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, Ph), 4.62 (dd, *J* = 6.8, 5.3 Hz, 1 H, 3-H), 4.58 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.54 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.21 (br. s, 1 H, 4-H), 4.03 (dd, *J* = 6.8, 1.2 Hz, 1 H, 2-H), 3.82 (m, 2 H, 6-H, CH_2O), 3.73 (app. t, *J* = 8.8 Hz, 2 H, 5-H, CH_2O), 3.36 (d, *J* = 13.2 Hz, 1 H, 6-H), 2.46 (br. s, 1 H, OH),

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1.44 (s, 3 H, CH_3), 1.43 (s, 9 H, O*t*Bu), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.43 (C_q, Ph), 128.22, 127.49, 127.45 (Ph), 108.28 (O-C-O), 80.37 (C_q, O*t*Bu), 76.20 (C-4), 72.92 (CH_2Ph), 71.05 (C-3), 68.71 (C-5), 68.42 (CH_2O), 51.03 (C-2), 28.27 (O*t*Bu), 26.78 (CH_3), 24.51 (CH_3) ppm. HRMS: calcd. for $[C_{16}H_{24}NO_4 + H]^+$ $[M - Boc]^+$ 294.16998; found 294.16937.

***tert*-Butyl (2*R*,3*S*,4*S*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-oxopiperidine-1-carboxylate:** Dess–Martin reagent (1.28 g, 3.02 mmol) was added to a solution of alcohol **29** (360 mg, 0.916 mmol) in DCM (20 mL). After 3 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, 95:5→90:10→75:25) to afford the product as a clear colourless oil (338 mg, 79%). $[\alpha]_D^{23}$ = –27.4 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2981, 2915, 1743, 1696, 1455, 1368, 1344, 1238, 1212, 1162, 1096, 982, 872 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H, Ph), 5.06 (s, 1 H, 2-H), 4.97–4.82 (m, 1 H, 3-H), 4.58–4.36 (m, 4 H, 4-H, 6-H, CH_2Ph), 4.27 (d, *J* = 18.0 Hz, 1 H, 6-H), 3.79 (d, *J* = 18.0 Hz, 1 H, 6-H), 3.62 (br. s, 1 H, CH_2O), 3.40 (d, *J* = 7.9 Hz, 1 H, CH_2O), 1.47 (s, 3 H, CH_3), 1.46 (s, 9 H, O*t*Bu), 1.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.29 (C=O), 154.74 (NC=O), 137.57 (C_q, Ph), 128.22, 127.57, 127.43 (Ph), 111.04 (O-C-O), 81.13 (C_q, O*t*Bu), 77.39 (C-4), 73.21 (C-3), 72.91 (CH_2Ph), 65.80 (CH_2O), 50.71 (C-6), 49.76 (C-2), 28.13 (O*t*Bu), 26.09 (CH_3), 24.16 (CH_3) ppm. HRMS: calcd. for $[C_{21}H_{29}NO_6 + H]^+$ 392.20676; found 392.20654.

***tert*-Butyl (2*S*,3*R*,4*S*,5*S*)-2-(Benzyloxymethyl)-3,4-*O*-isopropylidene-5-hydroxypiperidine-1-carboxylate:** $NaBH_4$ (60.0 mg, 1.58 mmol) was added to a solution of the previous ketone (270 mg, 0.690 mmol) in ethanol (25 mL) at –75 °C. The mixture was warmed slowly on the cooling bath to –20 °C in around 3 h. After that time, TLC analysis revealed complete conversion. The reaction mixture was diluted with EtOAc (100 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by silica gel column chromatography (PE/EtOAc, 90:10→75:25) afforded the title alcohol as a clear colourless oil (213 mg, 78%). $[\alpha]_D^{21}$ = +19.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3462, 2982, 2934, 1690, 1455, 1393, 1367, 1251, 1212, 1161, 1089, 1030, 874 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H, Ph), 4.73 (app. t, *J* = 5.8 Hz, 1 H, 3-H), 4.56 (s, 2 H, CH_2Ph), 4.36 (app. t, *J* = 5.8 Hz, 1 H, 4-H), 4.14 (br. s, 1 H, 2-H), 3.88 (br. s, 2 H, 6-H, CH_2O), 3.70 (app. t, *J* = 8.8 Hz, 1 H, CH_2O), 3.62–3.55 (m, 1 H, 5-H), 3.23–2.67 (m, 2 H, 6-H, OH), 1.49 (s, 3 H, CH_3), 1.43 (s, 9 H, O*t*Bu), 1.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.16 (C=O), 138.32 (C_q, Ph), 128.13, 127.73, 127.43, 127.38 (Ph), 108.48 (O-C-O), 80.25 (C_q, O*t*Bu), 72.86 (CH_2Ph), 72.61 (C-3), 72.11 (C-4), 67.64 (CH_2O), 66.25 (C-5), 50.66 (C-2), 42.17 (C-6), 28.19 (O*t*Bu), 26.21 (CH_3), 24.53 (CH_3) ppm. HRMS: calcd. for $[C_{21}H_{31}NO_6 + H]^+$ 394.22241; found 394.22186.

(2*S*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (L-*talo*-1-DNJ Hydrochloride, 30): The previous alcohol (213 mg, 0.542 mmol) was dissolved in a mixture of MeOH (15 mL) and aqueous 6 M HCl (3 mL) and transferred into a 250 mL Parr flask. The flask was purged with argon, Pd/C (10%, 50 mg) was added and the mixture was shaken vigorously under 4 bar H_2 pressure overnight at room temperature. After filtering through a Whatman® glass-fibre filter and evaporation of the solvents, the title product (109 mg) was obtained in quantitative yield. $[\alpha]_D^{22}$ = –3.3 (*c* = 0.90, H_2O). {ref.[28a] $[\alpha]_D$ = +22 (*c* = 0.5, MeOH)}. ^{1}H NMR (400 MHz, D_2O): δ = 4.23 (s, 1 H, 5-H), 4.15 (s, 1 H, 3-H), 3.86 (m, 3 H, CH_2O, 4-H), 3.50 (d, *J* = 13.7 Hz, 1 H, 6-H), 3.40 (app. t, *J* = 6.4 Hz, 1 H, 2-H), 3.26 (d, *J* = 13.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 67.55 (C-3), 67.05 (C-4), 66.58 (C-5), 60.35 (C-2), 59.16 (CH_2O), 48.34 (C-6) ppm. HRMS: calcd. for $[C_6H_{13}NO_4 + H]^+$ 164.09173; found 164.09168.

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

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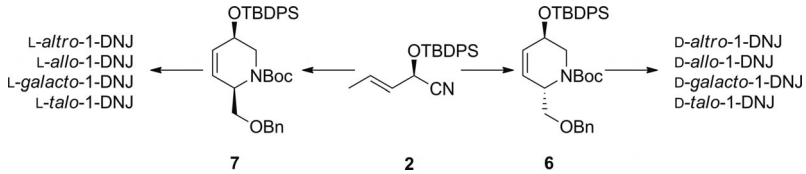

The orthogonally protected heterocyclic building blocks **6** and **7** have been prepared from cyanohydrin **2** in overall yields of 76%. Compounds **6** and **7** were converted into eight different stereoisomers of 1-deoxynojirimycin in overall yields of 14–75% in three to ten steps.

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

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

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