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%. 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 investi- gated. 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 Maq. 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 re-duction sequence[17] employing either (R)-benzoxoxyvinylglycinol [(R)-5] or (S)-benzoxoxyvinylglycinol [(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%.

---

[a] Leiden Institute of Chemistry, Leiden University, P. O. Box 9502, 2300 RA Leiden, The Netherlands
Fax: +31-71-5274537
E-mail: h.s.overkleeft@chem.leidenuniv.nl
[b] Leiden Amsterdam Centre for Drug Research, Leiden University, P. O. Box 9502, 2300 RA Leiden, The Netherlands
[c] Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200377.
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-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 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 NaBH4 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-allo-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 2S,5S configuration is separable from the 2S,5R 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-allo-1-DNJ had been obtained. Hydrogenation under acidic conditions gave d-allo-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]
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) \[16\] in an overall yield of 75% over the three steps (Scheme 4).\[16\]

![Scheme 4. Preparation of 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, H2O; d) 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 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 imino sugars 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,[13] 2[12] and 3–13[18] have been reported previously.

**tert-Butyl (2R,3S,4R,5S)-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-toluene sulfonic 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 preparative silica gel column chromatography (PE/EtOAc, 96:4 → 90:10) to afford the target compound as a colourless oil (764 mg, 72%).

**[a]$$^\beta = \sim 30.2$$ (c = 1.0, CHCl3).** IR (film): $\tilde{\nu}$ = 2933, 2859, 1696, 1393, 1366, 1145, 1104, 1057, 990 cm$^{-1}$. 1H NMR (400 MHz, CDCl3): $\delta$ = 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, $J$ = 6.9 Hz, 2 H, Ph), 4.56 (s, 2 H, CH2Ph), 4.24–3.80 (m, 4 H, 2-H, 5-H, 6-H, CH2O), 3.77 (s, 1 H, 4-H), 3.71 (app. t, $J$ = 8.9 Hz, 1 H, CH2O), 3.21 (d, $J$ = 13.4 Hz, 1 H, 6-H), 1.39 (s, 9 H, OeBu), 1.33 (s, 3 H, CH3), 1.22 (s, 3 H, CH3), 1.07 (s, 9 H, SiBu$^+$) ppm. 13C NMR (101 MHz, CDCl3): $\delta$ = 156.56 (C=O), 138.54 (Cq, Ph), 135.73 (Ph), 133.54 (Cq, Ph), 133.19 (Cq, Ph), 129.77, 129.70, 128.18, 127.63, 127.58, 127.55, 127.47 (Ph), 107.67 (O-C=O), 79.90 (Cq, OeBu), 75.03 (Cq, Ph), 73.08 (CH2Ph), 70.97 (C-3), 69.55 (C-4), 50.75 (C-2), 28.27 (OeBu), 26.94 (SiBu$^+$), 26.63 (CH3), 24.18 (CH3), 19.13 (Cq, SiBu$^+$) ppm. HRMS: calcd. for [C37H49NO6Si + H]$^+$ 632.34019; found 632.34040.

**tert-Butyl (2R,3S,4R,5S)-2-(Benzyloxymethyl)-3,4-O-isopropylidene-5-hydroxy-piperidine-1-carboxylate (14):** A solution of TBAF in
(2R,3S,4S,5R)-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 H₂ 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. \([\delta_1]^{22}O = +3.6 (c = 1.0, \text{MeOH})\), \([\delta_1]^{22}O = +2.4 (c = 1.0, \text{H}_{2}O)\) [ref[220] [\delta_1]^{22}O = -21 (MeOH)]. 1H NMR (400 MHz, D_2O): \(\delta = 4.26\) (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. \(J = 6.3\) Hz, 1 H, 2-H), 3.35–3.25 (m, 1 H, 6-H) ppm. 13C NMR (101 MHz, D_2O): \(\delta = 67.66\) (C-3), 67.16 (C-4), 66.67 (C-5), 60.41 (C-2), 59.21 (CH_2O), 48.42 (C-6) ppm. HRMS: calculated for [C_6H_13NO_4 + H]^+ 164.09173; found 164.09144.

terr-Butyl (2S,5R)-(5-Benzyloxy)methyl-5,6-dihydro-5-hydroxy- 
ipiperidine-1(2H)-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) and washed with water (25 mL) and brine (25 mL), dried (MgSO_4), filtered and concentrated to afford the crude product, which was purified by gel column chromatography (EtOAc/CH_2Cl_2, 1:2) to afford the product as a white solid (0.221 g, 0.473 mmol). 1H NMR (400 MHz, CDCl_3): \(\delta = 7.54–7.18\) (m, 5 H, Ph), 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, CH_2O) ppm. 13C NMR (101 MHz, CDCl_3): \(\delta = 155.15\) (C-5), 137.91 (C-3), 130.20 (C-4), 129.47 (C-4), 128.20, 127.38, 127.27 (Ph), 79.89 (C_6H_5), 79.23 (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 (CH_2O) ppm. HRMS: calculated for [C_{27}H_{32}NO_5 + Na]^+ 420.18563; found 420.18588.

terr-Butyl (2S,5S)-(5-Benzoxyloxy)-2-(benzyloxy)methyl-5,6-dihydro-5- 
ipiperidine-1(2H)-carboxylate: A solution of the previous alcohol (1.9 g, 3.73 mmol), triphenylphosphine (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. After 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 gel column chromatography (EtOAc/CH_2Cl_2, 1:2) to afford the product as a white solid (0.410 g, 0.94% yield). \([\delta_1]^{22}O = +287 (c = 1.0, \text{CHCl}_3)\). IR (film): \(\tilde{\nu} = 3429, 2976, 2857, 1686, 1420, 1365, 1294, 1171, 1128\) cm⁻¹. 1H NMR (400 MHz, CDCl_3): \(\delta = 7.46–7.16\) (m, 5 H, Ph), 7.06 (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), 3.41–3.06 (m, 2 H, 5-H, 6-H), 3.21 (br. s, 2 H, CH_2O), 2.57 (s, 1 H, OH), 1.44 (s, 9 H, OCH_2) ppm. 13C NMR (101 MHz, CDCl_3): \(\delta = 155.15\) (C-5), 137.89 (C-3), 130.20 (C-4), 129.47 (C-4), 128.20, 127.38, 127.27 (Ph), 79.79 (C_6H_5), 79.23 (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 (CH_2O) ppm. HRMS: calculated for [C_{27}H_{32}NO_5 + Na]^+ 420.18563; found 420.18588.

FULL PAPER

H. S. Overkleeft et al.
and 40.58 (C-6), 28.20 (OrBu) ppm. 1H NMR (400 MHz, CDCl3, 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, CH3Ph), 4.53 (d, J = 12.2 Hz, 1 H, CH3Ph), 4.51 (br. s, 1 H, 6-H) 3.70–3.57 (m, 2 H, CH2O), 3.04 (app. t, J = 11.0 Hz, 1 H, 6-H), 1.47 (s, 9 H, OrBu) ppm. 13C NMR (101 MHz, CDCl3, 333 K); δ = 165.63 (C=O), 154.24 (NC=O), 138.19 (C6H5Ph), 133.19, 132.90 (Ph), 130.14 (C6H5Ph), 130.00, 129.58, 129.05, 128.23, 127.85, 127.45, 127.36 (C-3, C-4, Ph) 80.31 (C6H5OrBu), 73.18 (CH2Ph), 70.73 (CH2O), 66.25 (C-5), 51.67 (C-2), 28.31 (C6H5OrBu) ppm. HRMS: calcld. for [C8H14NO + Na]+ = 446.19397; found 446.19379.

tert-Butyl (2S,3S,4R,5R)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxypropyridine-1(2H)-carboxylate (17): The above benzoyl (155 mg, 0.366 mmol) was dissolved in a mixture of MeOH (4.0 mL) and H2O (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 (MgSO4), 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%). 1H NMR (400 MHz, CDCl3); 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, CH2Ph), 4.51 (d, J = 12.1 Hz, 1 H, CH2Ph), 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, CH2O), 2.76 (m, 2 H, 6-H, OH), 1.43 (s, 9 H, OrBu) ppm. IR (film): ν = 3426, 2928, 1695, 1456, 1418, 1366, 1257, 1155, 1071, 1020 cm⁻¹. 1H NMR (400 MHz, CDCl3); 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, CH2Ph), 4.48 (d, J = 12.0 Hz, 1 H, CH2Ph), 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, CH2O), 2.85 (t, J = 1.8 Hz, 1 H, 6-H), 2.49 (br. s, 1 H, OH), 2.25 (br. s, 1 H, OH), 1.34 (s, 9 H, OrBu), 1.08 (s, 9 H, SiBu) ppm. 13C NMR (101 MHz, CDCl3); δ = 154.47 (C=O), 137.90 (C6H5Ph), 133.14 (C6H5), 131.70, 129.96, 128.34, 127.60 (Ph), 127.48 (C-3), 80.16 (C6H5OrBu), 73.10 (CH2Ph), 70.48 (CH2O), 63.49 (C-5), 28.38 (OrBu) ppm. HRMS: calcld. for [C8H14NO2 + Na]+ = 342.1764; found 342.17662.

tert-Butyl (2R,3R,4S,5R)-2-(Benzyloxymethyl)-3,4,5-trihydroxypropyridine-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, K2OsO4·2H2O (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 NaH2SO4 (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 (MgSO4), 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%). 1H NMR (400 MHz, CDCl3, δ = 5.3 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, 2 H, CH2O), 3.38–3.27 (m, 2 H, 2-H, 6-H), 2.49 (br. s, 1 H, OH), 2.25 (br. s, 1 H, OH), 1.34 (s, 9 H, OrBu), 1.08 (s, 9 H, SiBu) ppm. 13C NMR (101 MHz, CDCl3); δ = 153.67 (C=O), 141.73 (C6H5Ph), 133.14, 131.70, 129.96, 128.34, 127.60 (Ph), 127.48 (C-3), 80.16 (C6H5OrBu), 73.10 (CH2Ph), 70.48 (CH2O), 63.49 (C-5), 28.38 (OrBu) ppm. HRMS: calcld. for [C8H14NO2 + Na]+ = 342.17668; found 342.17662.

1-Deoxyribojirimycin Isomers from a Single Chiral Cyanohydrin
chloride (L-)
EtOAc (100 mL) and washed with water (15 mL) and brine solution was concentrated to 25% of its volume, diluted with tert Bu, 73.14 (C-2), 72.88 (CH2Ph), 69.33 (C-3), 67.55 (CH2O), 66.80 (C-4), 28.27 (OrBu) ppm. HRMS: calced. for [C18H27NO6 + H]+ 354.19111; found 354.19122.

tert-Butyl (2R,5R)-2-(Benzyloxymethyl)-5,6-dihydro-5-hydroxy-pyridine-1(2H)-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 (MgSO4), 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%). [a]21 =+140 (c = 1.0, CHCl3). IR (film): ν = 3242, 2978, 2868, 1694, 1418, 1366, 1155, 1112, 1072 cm−1. 1H NMR (400 MHz, CDCl3): δ = 7.38–7.22 (m, 5 H, Ph), 5.93 (d, J = 10.4 Hz, 1 H, 4-H), 5.79 (d, J = 10.4, 2.7 Hz, 1 H, 3-Ch), 6.66–4.02 (m, 5 H, CH2-Ph, 2-H, 5- H, 6-H), 3.73–3.42 (m, 2 H, CH2O), 3.40–2.60 (m, 2 H, 6-H, OH), 1.43 (s, 9 H, OrBu) ppm. 13C NMR (101 MHz, CDCl3): δ = 154.33 (C=O), 137.80 (Cq) ppm. 1H NMR (333 K, CDCl3): δ = 7.35–7.18 (m, 5 H, Ph), 5.89 (d, J = 10.4, 1.5 Hz, 1 H, 4-H), 5.78 (d, J = 10.4, 3.7 Hz, 1 H, 3-Ch), 4.60–4.43 (m, 3 H, 2-H, CH2Ph), 4.28–4.11 (m, 2 H, 5- H, 6-H), 3.57 (d, J = 5.7 Hz, 2 H, CH2O), 2.77 (d, J = 11.9, 8.7 Hz, 1 H, 6-H), 2.23 (s, 1 H, OH), 1.44 (s, 9 H, OrBu) ppm. 13C NMR (101 MHz, CDCl3): δ = 154.54 (C=O), 137.31 (Cq), 131.89, 131.81, 129.57, 127.51, 127.35 (C-3, C-4, Ph), 80.06 (Cq OrBu), 73.35 (CH2Ph), 70.96 (CH2O), 63.69 (C-5), 51.91 (C-2), 45.48 (C-6), 28.43 (OrBu) ppm. HRMS: calced. for [C18H23NO5 + Na]+ 342.16758; found 342.16753.

tert-Butyl (2R,5S)-5-(Benzyloxy)-2-(benzyloxymethyl)-5,6-dihydro-pyridine-1(2H)-carboxylate: A mixture of the alcohol from above (1.05 g, 3.29 mmol), triphenylphosphine (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 NaHCO3 (20 mL) and brine (20 mL). After drying (MgSO4), filtration and concentration in vacuo, the crude product was obtained. At this stage RP-HPLC analysis indicated <1% of the 2S,5R 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%). [a]21 =+299 (c = 1.0, CHCl3). IR (film): ν = 2972, 2861, 1717, 1690, 1419, 1363, 1335, 1266, 1169, 1107, 1069, 1025 cm−1. 1H NMR (400 MHz, CDCl3): 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 (1 H, 2-H), 4.64–4.40 (m, 3 H, CH2Ph, 6-H), 3.61 (m, 2 H, CH2O), 3.31–3.21 (m, 1 H, 6-H), 1.38 (m, 9 H, OrBu) ppm. 13C NMR (101 MHz, CDCl3): δ = 169.82 and 165.95 (C=O), 154.62 (NC=O), 137.92 (Cq), 133.47 (C-3), 133.15, 132.90, 132.47, 129.67, 129.89 (Ph), 129.56 (Cq), 128.20, 128.10, 127.45, 127.31 (Ph), 129.31, 123.54 (C-4), 79.73 (Cq OrBu), 72.92 (CH2O), 70.29 (CH2Ph), 65.31 (C-5), 50.25 and 51.02 (C-2), 43.25 and 42.09 (C-6), 28.20 (OrBu) ppm. 1H NMR (400 MHz, CDCl3, 25°C): 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, CH2Ph, 6-H), 3.61 (d, J = 5.0 Hz, 2 H, CH2O), 3.31 (d, J = 13.8 Hz, 1 H, 6-H), 1.36 (s, 9 H, OrBu) ppm. 13C NMR (101 MHz, CDCl3, 25°C): δ = 165.99 (C=O), 154.70 (NC=O), 138.16 (Cq), 130.07 (C-3), 132.74, 134.00 (Ph), 129.97 (Cq), 129.67, 128.25, 128.11, 127.49, 127.37 (Ph), 127.78 (C-4), 79.83 (Cq OrBu), 73.19 (CH2O), 70.60 (CH2Ph), 65.53 (C-5), 51.67 (C-2), 43.15 (C-6), 28.20 (OrBu) ppm. HRMS: calced. for [C18H23NO7 + Na]+ 446.19379; found 446.19348; calced. for [C18H23NO7 + H]+ 424.21185; found 424.21196.
13.8 Hz, 1 H, 6-H), 2.01 (br. s, 1 H, OH), 1.45 (s, 9 H, O\textsubscript{Bu}) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}, 333 K): \(\delta = 155.29\) (C=O), 138.23 (C\textsubscript{q}, Ph), 130.12, 128.27, 127.63, 127.49, 127.39, 124.87, 124.68, 124.61, 121.38 (C=O), 120.12, 112.70, 112.68, 112.51, 112.44, 112.39, 112.36, 112.02, 106.85 ppm. HRMS: calcd. for \(\text{C}_{34}\text{H}_{43}\text{NO}_6\text{Si} + \text{H}\) \(m/e = 592.29089\); found 592.29089.

text-Butyl (2R,5S)-2-(Benzyloxy)methyl)-5,6-dihydro-5-(text-butylidenedi-phenylsilyloxy)-pyridinidine-1\(\text{H}\)-carboxylate (24): Alkyl (1.02 g, 3.19 mmol) was dissolved in DMF (20 mL) and subsequently imidazole (2.34 g, 34.5 mmol) and 
\(\text{K}_2\text{O}_2\text{O}_4\) (0.6 g, 0.77 mmol) was added. The mixture was stirred at ambient temperature overnight after which TLC indicated complete conversion of 24. Water (60 mL) was added and the mixture extracted with diethyl ether (3 \times 30 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried (MgSO\textsubscript{4}), and concentrated. The crude product was purified by silica gel column chromatography (PE/EtOAc, 95:5 to 90:5) to afford the product as a mixture of compound 24 and TBDPS-OH \([\text{clear colourless oil}, 2.49 \, g, 140\%\text{ of isolated yield}]\) by compound 24, determined from \(\text{HRMS}\) data. 
\[ \text{[a]}^{21}_\text{D} = +185 \text{ (c = 1.0, CHCl}_3) \]. From a second column chromatography a white solid of compound 24 was obtained. 
\[ \text{[a]}^{21}_\text{D} = +185 \text{ (c = 1.0, CHCl}_3) \]. IR (film): \(\nu = 2932, 2985, 1648, 1428, 1366, 1249, 1106, 1028, 822 \text{ cm}^{-1}\). \(\text{IH NMR (400 MHz, CDCl}_3)\): \(\delta = 7.11\) (d, \(J = 7.4\text{ Hz}, 2\text{ H}, \text{Ph})\), 7.66 (d, \(J = 7.4\text{ Hz}, 2\text{ H}, \text{Ph})\), 7.46–7.33 (m, 6 \text{H, Ph}), 7.32–7.22 (m, 5 \text{H, Ph}), 8.56–8.43 (dd, \(J = 10.1, 3.9\text{ Hz}, 1\text{ H}, 4\text{-H}), 5.67\) (br. s, 1 H, 3-H), 4.81–4.56 (m, 1 H, 2-H), 4.51 (d, \(J = 12.4\text{ Hz}, 1\text{ H}, \text{CH}_2\text{Ph})\), 4.47 (d, \(J = 12.4\text{ Hz}, 1\text{ H}, \text{CH}_2\text{Ph})\), 4.41–4.12 (m, 1 H, 5-H), 4.07 (br. s, 1 H, 6-H), 3.51 (m, 2 H, CH\text{O})\), 3.35–2.86 (m, 5 H, 6-H), 1.49 (s, 9 H, O\text{Bu}, 1.05 (s, 9 H, Si\text{Bu} ppm). \(\text{IH NMR (101 MHz, CDCl}_3)\): \(\delta = 154.85\) (C=O), 138.15 (C\textsubscript{q}, Ph), 135.70 (Ph), 135.45 (C\textsubscript{q}, Ph), 134.75 (Ph), 133.85 (C\textsubscript{q}, Ph), 129.67, 124.79, 124.34, 121.58, 127.53, 127.39, 127.28 (Ph), 79.49 (C\textsubscript{q}, O\text{Bu}), 79.47 (C\textsubscript{q}, CH\text{O}), 63.82 (C-S), 28.38 (O\text{Bu}), 26.83 (Si\text{Bu}), 19.13 (C\textsubscript{q} Si\text{Bu} ppm). \(\text{IH NMR (400 MHz, CDCl}_3, 333 K)\): \(\delta = 7.73–7.68\) (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, \(J = 10.2, 3.9\text{ Hz}, 1\text{ H}, 4\text{-H}), 5.70–5.61\) (m, 1 H, 3-H), 4.68 (br. s, 1 H, 2-H), 4.50 (d, \(J = 12.2\text{ Hz}, 1\text{ H}, \text{CH}_2\text{Ph})\), 4.46 (d, \(J = 12.2\text{ Hz}, 1\text{ H}, \text{CH}_2\text{Ph})\), 4.25 (d, \(J = 13.4\text{ Hz}, 1\text{ H}, 6\text{-H}), 4.12–4.06 (m, 1 H, 5-H), 3.51 (d, \(J = 5.4\text{ Hz}, 2\text{ H}, \text{CH}_2\text{O})\), 3.01 (d, \(J = 13.4\text{ Hz}, 1\text{ H}, 6-H), 1.48\) (s, 9 H, O\text{Bu}), 1.05 ppm. \(\text{IH NMR (101 MHz, CDCl}_3)\): \(\delta = 154.97\) (C=O), 138.46 (C\textsubscript{q}, Ph), 135.85, 135.84, 134.85 (Ph), 134.66 (C\textsubscript{q}, Ph), 134.27 (C\textsubscript{q}, Ph), 129.64, 129.57, 129.52, 128.29, 127.64, 127.56, 127.47, 127.41 (Ph), 79.55 (C\textsubscript{q}, O\text{Bu}), 73.20 (C\textsubscript{q}, CH\text{O}), 70.82 (O\text{Bu}), 64.16 (C-S), 51.52 (C-2), 46.30 (C-6), 28.52 (O\text{Bu}), 27.00 ppm. \[ \text{IR (film)}: \nu = 1548.30 (\text{CHCl}_3)\].

(2S,3R,4S,5R)-2-(Benzyloxy)methyl)-3,4,5-triroyhydropiperidine-1-carboxylate (27): The N-Boc-2-OBn-protected 1-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 H2 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. [α]D25 = –51.4 (c = 1.0, H2O). 1H NMR (400 MHz, D2O): δ = 4.15 (d, δ = 2.9, 1.3 Hz, 1 H, 1-H), 3.46 (d, J = 9.6, 1.8 Hz, 1 H, 4-H), 3.50 (d, J = 12.5, 5.3 Hz, 1 H, 6-H), 3.41 (d, δ = 8.6, 4.8 Hz, 1 H, 2-H), 2.87 (app. t, J = 12.0 Hz, 1 H, 6-H) ppm. 13C NMR (101 MHz, D2O): δ = 72.86 (C-4), 65.83 (C-3), 64.58 (C-5), 60.03 (C-2), 59.05 (CH2O), 46.04 (C-6) ppm. HRMS: calculated for [C6H11NO4 + H]+ 164.09173; found 164.09195.

tert-Butyl (2S,3R,4S,5R)-2-(Benzyloxy)methyl)-3,4,5-O-isopropylidene-5-(tert-butylidihydroxilosilyl)piperidine-1-carboxylate: Diol 26 (670 mg, 1.13 mmol) was dissolved in a mixture of acetone (20 mL) and 2,2-dimethoxypropane (5.0 mL). At 5 °C, BF3·Et2O (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 and washed with brine, dried (Na2SO4), filtered and concentrated to afford a crude product that was purified by silica gel column chromatography (PE/EtOAc, 90:10) to afford the target compound as a colourless oil (628 mg, 82%). [α]D25 = –37.5 (c = 1.0, CHCl3). IR (film): δ = 2933, 1697, 1454, 1428, 1393, 1366, 1252, 1145, 1057, 989, 878 cm–1. 1H NMR (400 MHz, CHCl3): δ = 7.67 (d, δ = 7.9, 1.5 Hz, 2 H, Ph), 7.62 (d, J = 7.9, 1.5 Hz, 2 H, Ph), 7.45–7.23 (m, 1 H, Ph), 4.68–6.41 (m, 1 H, 3-H), 4.56 (s, 2 H, CH2O), 4.24–3.80 (m, 4 H, 2-H, 5-H, 6-H, CH2O), 3.76 (d, J = 1.4 Hz, 1 H, 4-H), 3.70 (app. t, J = 8.9 Hz, 1 H, CH2O), 3.20 (d, J = 13.7 Hz, 1 H, 6-H), 1.39 (s, 9 H, OrBu), 1.33 (s, 3 H, CH3). 1H NMR (CDCl3): 1.07 (s, 9 H, SiBu2) ppm. 13C NMR (101 MHz, CHCl3): δ = 156.62 (C-10), 138.56 (C-8, Ph), 135.76 (C-10), 133.55 (C8, Ph), 133.20 (C7, Ph), 129.80, 129.72, 128.22, 127.65, 127.60, 127.43 (Ph), 107.70 (C-5), 79.96 (C5, OrBu), 75.01 (C-5), 73.11 (CH2O), 70.97 (C-3), 69.53 (C4, C5) ppm. 1H NMR (400 MHz, CDCl3): δ = 14.3 (1 H, 1-H, 6-H), 3.00 (s, 9 H, OrBu) ppm. HRMS: calculated for [C7H9NO3Si + Na]+ 592.30889; found 592.30913; calcd. for [C7H8H2NO3 + Na]+ 614.29018.

tert-Butyl (2S,3R,4S,5R)-2-(Benzyloxy)methyl)-3,4,5-triol Hydrochloride (1-allyl-1-DNJ Chloride, 28): 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 H2 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. [α]D25 = +31.2 (c = 1.0, CHCl3). IR (film): δ = 3396, 2976, 2881, 1686, 1420, 1366, 1170, 1136, 1088 cm–1. 1H NMR (400 MHz, MeOD): δ = 3.73–7.23 (m, 5 H, Ph), 4.62 (br. s, 1 H, 2-H), 4.53 (d, J = 11.9 Hz, 1 H, CH2O), 4.48 (d, J = 11.9 Hz, 1 H, CH2Ph), 4.20 (d, J = 14.1 Hz, 1 H, 6-H), 3.97 (br. s, 1 H, 3-H), 3.38 (br. s, 1 H, 5-H), 3.07 (app. t, J = 3.0 Hz, 1 H, 4-H), 3.56 (d, J = 6.5 Hz, 2 H, CH2O), 3.08 (d, J = 14.1 Hz, 1 H, 6-H), 1.44 (s, 9 H, OrBu) ppm. HRMS: calculated for [C6H13NO4 + H]+ 164.09173; found 164.09195.

[CH3H2NO3Si]+ + H+} 592.30889; found 592.30913; calcd. for [CH3H8H2NO3 + Na]+ 614.29018.

www.eurjoc.org © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
1.44 (s, 3 H, CH₃), 1.43 (s, 9 H, Br₆), 1.35 (s, 3 H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 138.43 (C₆), 128.22, 127.49, 127.47 (Ph), 108.28 (O-CO), 80.37 (C₆), Br₆, 76.20 (C₄), 72.92 (CH₃Ph), 71.05 (C-3), 68.71 (C-5), 68.42 (CH₂O), 51.03 (C-2), 28.27 (O-Br, CH₃), 24.71 (CH₃) ppm. HRMS: calcd. for [C₆H₁₄NO₆ + H]⁺ [M − BoC]⁺ 294.16998; found 294.16937.

tert-Butyl (2R,3S,4S)-2-(Benzyloxymethyl)-3,4-O-isopropylidene-5-oxopiperidine-1-carboxylate: Dесс—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%).

1H NMR (400 MHz, CDCl₃): 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, CH₂Ph), 4.27 (d, J = 18.0 Hz, 1 H, 1-H), 3.79 (d, J = 18.0 Hz, 1 H, 1-H), 3.62 (br. s, 1 H, CH₂O), 3.40 (d, J = 7.9 Hz, 1 H, CH₂), 1.47 (t, J = 6.0 Hz, 3 H, Bu), 1.40 (s, 3 H, CH₃) ppm. HRMS: calcd. for [C₂₁H₂₉NO₆ + H]⁺ 394.22186; found 394.22186.

3.02 mmol) was added to a solution of alcohol 28 (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 (213 mg, 78%).

1H NMR (400 MHz, D₂O): δ = 4.23 (s, 1 H, 5-H), 4.15 (s, 1 H, 3-H), 3.86 (m, 3 H, CH₂O, 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. ¹³C NMR (101 MHz, D₂O): δ = 67.55 (C-3), 67.05 (C-4), 66.58 (C-5), 60.35 (C-2), 59.16 (CH₂O), 48.34 (C-6) ppm. HRMS: calcd. for [C₂₁H₂₉NO₆ + H]⁺ 394.22186; found 394.22186.

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.

Acknowledgments

We thank the Netherlands Organization for Scientific Research (NWO) for financial support.


Received: March 26, 2012
Published Online: May 10, 2012