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Synthesis of Chiral Nonracemic Homo-1-Deoxyazasugars with D-Talo-and L-Allo-Configuration via Tandem Wittig [2+3] Cycloaddition Reaction

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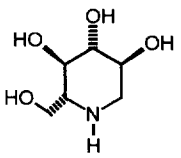
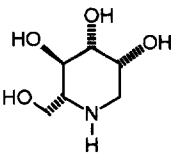
Abstract: Wittig reaction of **6a,b** proceeds with concomitant 1,3-dipolar cycloaddition of the azido function to the nonisolable triazoline **20** which isomerizes to diazoamine **7**. Elimination of nitrogen from **7** provides vinylogous urethane **8** which can be transformed to heterocyclic ß-amino acid **10** and D-homo-1-deoxyazatalose (**13**). Catalytic hydrogenation of **7** and manipulation of functional groups give L-homo-1-deoxyazaallose (**16**) and ß-amino acid **18**.

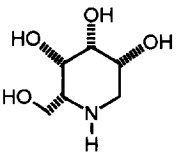
There is continuing interest in the synthesis and biological activity of chiral nonracemic piperidine derivatives[1] especially in the field of polyhydroxylated piperidines[2] and pyrrolidines. These compounds constitue a major class of glycosidase inhibitors. These azasugars are potentially useful antiviral, antimetastatic or immunostimulating agents.[3]



1-deoxynojirimycin (**1**)



1-deoxymannojirimycin (**2**)

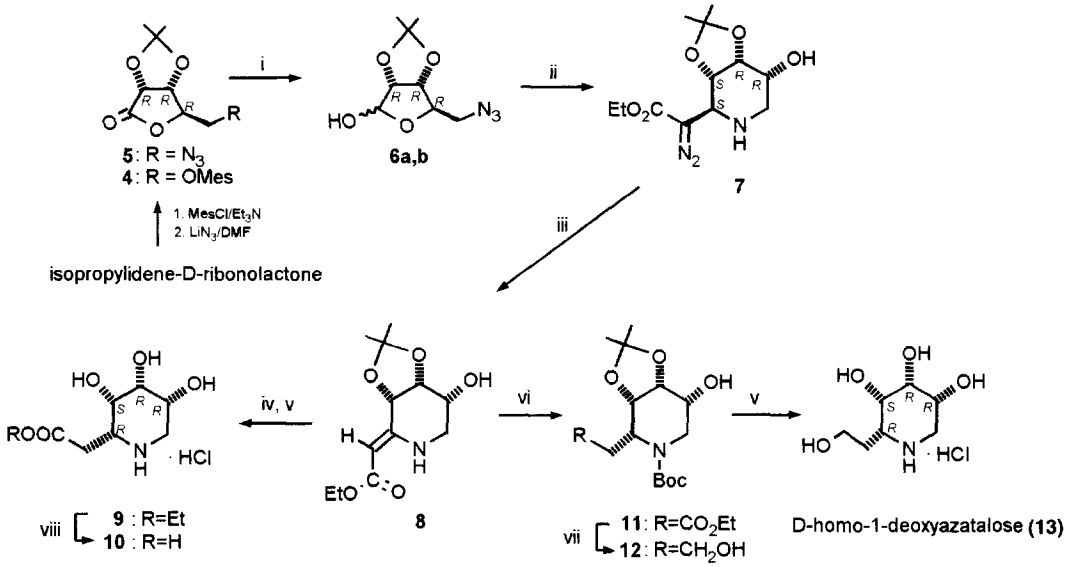


1-deoxytalojirimycin (**3**)

Deoxynojirimycin (**1**), isolated from morus species, was the first type of polyhydroxylated piperidine alkaloids inhibiting specific glycosidic enzymes.[4] A major challenge in the synthesis of **1** and its stereoisomers is the construction of the four contiguous stereogenic centres. While glucose-based synthesis[5] and cycloaddition methodology[6] have been described to produce gluco- and manno-configurated azasugars like **1** and **2**, straightforward approaches e. g. to all-cis configurated talo[7]-and allo[8]-azasugars are rare to find in the literature. Furthermore homoazasugars[9] with a CH_2-homologisation in the side chain may be interesting compounds for testing structure activity relationships.

In this report we describe a new method for the preparation of highly substituted piperidine derivatives based on a ring enlargement reaction via tandem Wittig 1,3-dipolar cycloaddition reaction. To this end we started from isopropylidene-D-ribonolactone which was transformed to the azidolactone **5**. We envisioned the construction of a piperidinotriazoline **20** by cycloaddition of the azido function[10] to the α,ß-unsaturated ester moiety of **19** (Scheme 2). When **5** was treated with diisobutyl aluminum hydride a diastereomeric mixture of acetals **6a,b** resulted. When **6a,b** was treated with triphenylcarbethoxymethylene phosphorane at room temperature a smooth Wittig reaction took place. To our surprise diazoamine **7** was isolated as the only stereoisomer in 61 % yield as yellow crystals (Scheme 1).

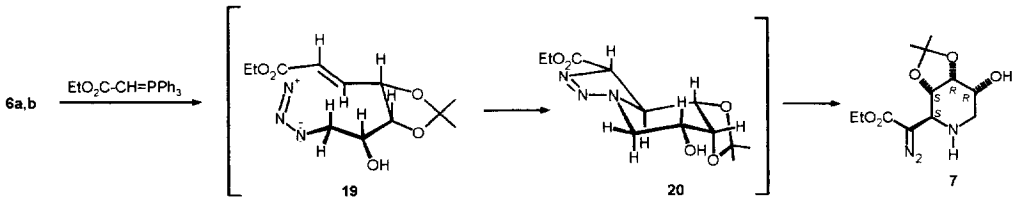
Scheme 1



i: DIBAl-H, -78°C; **ii**: $Ph_3P{=}CH\text{-}CO_2Et$, toluene; **iii**: 90-100°C, toluene; **iv**: Pd/C, H_2; **v**: EtOH/HCl; **vi**: Pd/C, H_2, Boc_2O; **vii**: $LiAlH_4$; **viii**: HCl/H_2O.

The Wittig reaction of **6a,b** to **19** is followed by an intramolecular 1,3-dipolar cycloaddition of the azido function to the double bond. This cycloaddition is well known,[10] but to the best of our knowledge, this tandem reaction[11] has not been used for the preparation of piperidinoses. The obvious intermediate, compound **19** and the triazoline **20**, could not be isolated.[12] **20** isomerises quantitatively to the diazoamine **7** which resulted as a single diastereomer (Scheme 2).

Scheme 2

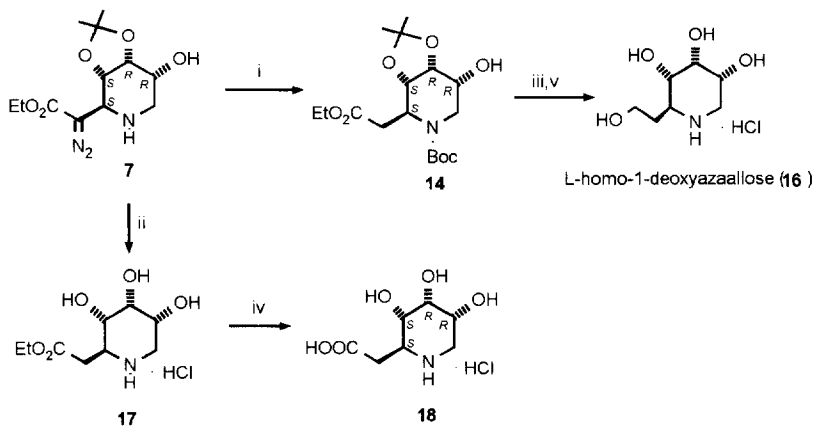


The configuration and conformation of **7** are determined by its spectroscopic data. The IR spectrum shows an NH and OH band at 3320 and 3300-3120 cm^{-1}, respectively. The $C=N_2$ absorption is observed at 2080 cm^{-1}. The diequatorial position of the diazoester function and the OH group in 5-position is based on the vicinal coupling constants $J_{2',3'}$ and $J_{5',6'}$.

Further evidence for the trans configuration of the substituents in 2,5-position of the diazoester **7** is obtained by the following reaction sequence **7→13** in comparison with **7→16**. When compound **7** was heated in toluene, elimination of nitrogen took place and concomitant 1,2-H shift[13] provided vinylogous urethane **8**, in which an internal hydrogen bond stabilises the Z-configuration[14]. Hydrogenation of the double bond of compound **8** which occurred exclusively from the less shielded ß-face and protection of the amino function with Boc_2O, give the all *cis* configurated compound **11**. Stereochemistry was readily assigned in comparison with the J values of the diastereomeric compound **14** (Scheme 3).

Reduction of the N-Boc protected amino ester **11** with lithium aluminum hydride provided compound **12**, from which both protecting groups were removed with ethanolic hydrochloric acid to give the all-*cis* configurated D-homo-1-deoxyazatalose **13**. On the other hand, the homopipecolic acid derivative **10** was prepared by catalytic hydrogenation of **8** and hydrolysis of the amino ester **9**.

Scheme 3



i: Pd/C, H_2, Boc_2O; **ii**: a: Pd/C, H_2, b: EtOH/HCl; **iii**: $LiAlH_4$; **iv**: HCl/H_2O; **v**: EtOH/HCl.

As an entry to the diastereomer of **11**, compound **7** was hydrogenated in ethanol to remove the diazo group[15] and the resulting ß-amino ester was treated with Boc_2O to give the N-Boc protected heteocyclic ß-amino ester **14** in 63% yield, which was reduced with $LiAlH_4$ to compound **15**. Further transformation to the L-homo-1-deoxyazaallose **16** and to the homopipecolic acid derivative **18** was accomplished as shown for **13** and **10**.

In summary an efficient synthesis of homo-1-dexyazasugars with talo- and allo-configuration via tandem Wittig-[2+3] cycloaddition chemistry was developed. This aproach with its excellent diastereocontrol is currently applied to the synthesis of natural products with substituted piperidine structure.[12]

EXPERIMENTAL

General: Solvents were dried according to common methods and distilled before use. TLC: Merck precoated silica gel 60 F-254 plates; detection with iodine vapour or UV light. Column chromatography :silica gel Merck 60 (0.063-0.2 mm). M.p. are uncorrected. Optical rotations: Perkin Elmer 241 spectrometer. IR spectra (KBr): Perkin Elmer 681. Mass spectra: Finnigan Mat 8200 spectrometer. ^1H, ^{13}C NMR, ^1H-^1H and ^1H-^{13}C COSY NMR (200 MHz) spectra: Bruker AC 200 spectrometer; chemical shifts in ppm relative to the solvent as internal standard, coupling constants in Hz.

(3*R*, 4*R*, 5*R*)-4,5-Dihydro-3,4- (O,O)-isopropylidene-5-mesyloxymethyl-2-(3H) furanone (4): To a solution (-30°C) of commercially available isopropylidene-D-ribonolactone (5.60 g, 29.78 mmol) and triethylamine (4.50 ml, 32.0 mmol) in dichloromethane (300 ml) mesyl chloride (2.51 ml, 32.0 mmol) was added with vigorous stirring. After 1 h at -30°C the mixture was allowed to reach room temperature. Stirring was continued for 2 h. The reaction was quenched by the addition of 0.5 M hydrochloric acid (40 ml). The organic layer was separated, washed with water (2 x 50 ml) and dried with sodium sulfate. The solvent was evaporated, and the pale yellow residue was recrystallised from ether / hexane. Yield: 7.45 g (94 %), colourless needles, m.p. 56°C. - ^1H NMR ($CDCl_3$): δ = 4.83 - 4.76 (m, 3 H, 3,4,5-H), 4.45 (d, J = 2.3 Hz, 2 H, 6-H), 3.04 (s, 3 H, CH_3-SO_2), 1.46 (s, 3 H, $(CH_3)_2C$), 1.37 (s, 3 H, $(CH_3)_2C$).- ^{13}C NMR ($CDCl_3$): δ = 173.3 (s, C=O), 113.7 (s, $(C(CH_3)_2)$, 79.3 (d, C-5), 77.2 (d, C-3), 74.8 (d, C-4), 68.1 (t, C-6), 37.4 (q, CH_3-SO_2), 26.5 ((q,$CH_3)_2C$), 25.2 (q, $(CH_3)_2C$).- IR (KBr): ν = 3020 cm^{-1}, 2990, 2950 (C-H), 1790 (C=O), 1460 (C-H), 1360, 1170 (S=O). - $[\alpha]_D^{20}$ = -51.8 (c = 1, $CHCl_3$). - $C_9H_{14}O_7S$, (266.08): calcd C 40.60, H 5.30, S 12.04, found C 40.58, H 5.37, S 11.89.

(3*R*, 4*R*, 5*R*)-5-Azidomethyl-4,5-dihydro-3,4-(O,O)-isopropylidene-2-(3H) furanone (5): To a solution of **4** (7.00 g, 26.30 mmol) in DMF (100 ml) lithium azide (1.54 g, 31.50 mmol) was added. The mixture was heated to 75°C for 18 h. After evaporation of the solvent the residue

was dissolved in water (120 ml) and extracted with ether (5 x 60 ml). The combined organic layers were dried with sodium sulfate and the solvent was evaporated. The pale yellow oil was purified by column chromatography on silica gel with ethyl acetate. Yield: 5.1 g (91 %), colourless crystals, R_f = 0.65 (EtOAc), m.p. 40°C. - ^{1}H NMR ($CDCl_3$): δ = 4.76 (d, $J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 4.61 - 4.57 (m, 2 H, 4,5-H), 3.72 (dd, $J_{6a,6b}$ = 13.3 Hz, $J_{6b,5}$ = 3.1Hz, 1 H, 6-H_b), 3.61 (dd, $J_{6a,6b}$ = 13.3 Hz, $J_{6a,5}$ = 2.7 Hz, 1 H, 6-H_a), 1.36 (s, 3 H, (CH_3)$_2$C), 1.28 (3 H, s, (CH_3)$_2$C).- ^{13}C NMR ($CDCl_3$): δ = 173.3 (s, C=O), 113.2 (s, C(CH$_3$)$_2$), 80.0 (d, C-5), 77.7 (d, C-3), 74.8 (d, C-4), 52.1 (t, C-6), 26.3 (q, (CH_3)$_2$C), 25.1 (q, (CH_3)$_2$C).- IR (neat): ν = 2980 cm^{-1}, 2930 (C-H), 2100 (N_3), 1780 (C=O), 1440, 1380. - $[\alpha]_D^{20}$ = +15.1 (c = 1, $CHCl_3$).- $C_8H_{11}O_4N_3$ (213.19): calcd C 45.09, H 5.16, N 19.71, found C 44.84, H 5.30, N 19.62.

(3*R*, 4*R*, 5*R*)-5-Azidomethyl-2,4-tetrahydro-2(R,S)-hydroxy-3,4-(O,O)-isopropylidene furan (6a,b): To a solution (-100°C) of **5** (5.01 g, 23.5 mmol) in THF (15 ml) diisobutylaluminum hydride (23.5 ml, 1 M solution in hexane) was added carefully. The mixture was stirred for 45 min. An additional portion of the DiBAl-H solution (12 ml) were added and the mixture was stirred for at least 6 h at -78°C. Then it was cooled to -100°C and quenched by the addition of water (20 ml) with vigorous stirring. The mixture was allowed to reach room temperature and 0.25 N hydrochloric acid (100 ml) and dichloromethane (600 ml) were added. The organic layer was separated, dried with sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 3.98 g (78%), colourless oil, R_f = 0.61 (EtOAc) for both epimers. - ^{1}H NMR ($CDCl_3$): δ = 5.42 / 5.38* (d, $J_{2,3}$ = 4.1 / 3.5 Hz, 1 H, 2-H), 4.64 - 4.56 (m, 2 H, 4-H, 5-H), 4.30 - 3.90 (m, 2 H, 3-H, OH), 3.53 (dd, $J_{6b,6a}$ = 12.6 Hz, $J_{6b,5}$ = 7.4 Hz, 1 H, 6-H_b), 3.33 (dd, $J_{6a,6b}$ = 12.6 Hz, $J_{6a,5}$ = 5.9 Hz, 1 H, 6-H_a), 1.44 / 1.53 (s, 3 H, (CH_3)$_2$C), 1.28 / 1.35 (s, 3 H, (CH_3)$_2$C). - ^{13}C NMR ($CDCl_3$): δ = 113.0 / 114.8* (s, (CH$_3$)$_2$$C$), 103.4 / 97.2 (d, C-2), 85.9 / 81.6 (d, C-3), 85.3 / 79.6 (d, C-5), 82.4 / 81.8 (d, C-4), 54.1 / 53.2 (t, C-6), 26.5 / 26.3 (q, (CH_3)$_2$C), 25.0 / 24.9 (q, (CH_3)$_2$C). - MS (70 eV), *m/z* (%) : 233.3 (38.0) [M+NH_4^+], 215.2 (72.2) [M^+], 172.2 (100) [M^+-C_3H_7]. - IR (neat): ν = 3420 cm^{-1}(O-H), 2980, 2930 (C-H), 2090 (N_3), 1450, 1435, 1375. - $C_8H_{13}O_4N_3$ (215.20): calcd. C 44.65, H 6.08, N 19.53, found C 44.96, H 6.14, N 18.12.

Ethyl (2'*S*, 3'*S*, 4'*R*, 5'*R*)-2-diazo-2'-(5'-hydroxy-3',4'-(O,O)-isopropylidene) piperidyl acetate (7): To a solution of **6a,b** (3.98 g, 18.49 mmol) in toluene (12 ml) triphenylcarbethoxymethylene phosphorane (6.44 g, 18.00 mmol) was added. The mixture was stirred for 48 h at room temperature and the solvent was evaporated at room temperature. The yellow residue was purified from Ph_3PO by column chromatography on silica gel with dichloromethane / methanol 9 : 1. Yield: 3.21 g (61 %), bright yellow crystals, R_f = 0.26 (CH_2Cl_2 / MeOH 9:1), m.p.: 96°C. - ^{1}H NMR ($CDCl_3$): δ = 4.40 (t, $J_{4',5'}$= $J_{4',3'}$= 4.3 Hz, 1 H, 4'-H), 4.17 (q, J_{vic}= 7.1 Hz, 2 H, CH_3-CH_2-), 3.90 (dd, $J_{3',2'}$ = 9.5 Hz, $J_{3',4'}$ = 4.3 Hz, 1 H, 3'-H), 3.82 (m, 1

* ratio of epimers 4:1

H, 5'-H), 3.46 (d, $J_{2',3'}$ = 9.5 Hz, 1 H, 2'-H), 2.99 (dd, $J_{6'eq,6'ax}$ = 11.5 Hz, $J_{6'eq,5}$ = 5.5 Hz, 1 H, 6'-H_{eq}), 2.75 (t, $J_{6'ax,6'eq} = J_{6'ax,5'}$ = 11.5 Hz, 1 H, 6'-H_{ax}), 2.55 - 2.30 (br, 1 H, OH), 1.48 (s, 3 H, $(CH_3)_2C$), 1.32 (s, 3 H, $(CH_3)_2C$), 1.21 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2). - ^{13}C NMR ($CDCl_3$): δ = 166.3 (s, C=O), 109.8 (s, $C(CH_3)_2$), 75.6 (d, C-4'), 74.8 (d, C-3'), 66.7 (d, C-5'), 60.8 (t, CH_3CH_2-), 58.0 (s, C-2'), 54.3 (d, C-2'), 48.0 (t, C-6'), 27.9 (q, $(CH_3)_2C$), 26.2 (q, $(CH_3)_2C$), 14.3 (q, CH_3CH_2-). - MS (70 eV), *m/z* (%): 285.3 (1.0) [M+H$^+$], 257.3 (83.2) [M+H$^+$-C_2H_5], 242.2 (32.0) [M$^+$-C_3H_7], 212.2 (35.6), 154.1 (79.9), 124.0 (59.5), 83.0 (84.6), 43.0 (100) [$C_3H_7^+$]. IR (KBr): ν = 3320 cm^{-1} (N-H), 3300-3120 (O-H), 2980, 2940, 2890, 2840 (C-H), 2080 (C=N_2), 1690 (C=O), 1445, 1375. - $[\alpha]_D^{20}$ = -73.6 (c = 1, $CHCl_3$). - $C_{12}H_{19}O_5N_3$ (285.29): calcd. C 50.52, H 6.71, N 14.73 , found C 50.55, H 6.64 , N 14.80.

Ethyl (3*S*, 4*R*, 5*R*)-2-(5-hydroxy-3,4-(O,O)-isopropylidene) piperidylidene carboxylate (8): A solution of **7** (1.08 g, 3.78 mmol) in toluene (20 ml) was heated for 18 h to 90-100°C. The solvent was evaporated and the residue purified by column chromatography on silica gel with ethyl acetate. For further purification the pale yellow solid was recrystallized from ether / hexane. Yield: 830 mg (85 %), colourless crystals, m.p.: 126°C, R_f = 0.53 (EtOAc). - ^1H NMR ($CDCl_3$): δ = 8.28 (br, 1 H, NH), 4.72 (s, 1 H, C*H*-CO_2Et), 4.55 - 4.43 (m, 2 H, 3,5-H), 4.06 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 3.80 - 3.71 (m, 1 H, 4-H), 3.28 (dd, $J_{6b,6a}$ = 9.2 Hz, $J_{6b,5}$ = 3.1 Hz, 1 H, 6-H_b), 3.23 - 3.12 (m, 1 H, 6-H_a), 1.50 (s, 3 H, $(CH_3)_2C$), 1.39 (s, 3 H, $(CH_3)_2C$), 1.21 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-). - ^{13}C NMR ($CDCl_3$): δ = 170.6 (s, C=O), 155.7 (s, C-2), 110.6 (s, $C(CH_3)_2$), 85.3 (d, CH-CO_2Et), 75.4 (d, C-5), 73.5 (d, C-4), 67.3 (d, C-3), 59.1 (t, CH_3CH_2-), 41.7 (t, C-6), 26.3 (q, $(CH_3)_2C$), 24.5 (q, $(CH_3)_2C$), 14.8 (q, CH_3CH_2-). - MS (70 eV), *m/z* (%): 258.0 (11.4) [M+H$^+$], 257.0 (77.0) [M+], 212.0 (33.0) [M$^+$-C_2H_5O], 199.0 (48.0), 170.0 (65.2), 154.1 (100), 136.0 (63.1), 124.0 (68.9), 43.0 (77.2) [$C_3H_7^+$]. - IR (neat): ν = 3280 cm^{-1} (N-H), 2960, 2920 (C-H), 1645 (C=O), 1605 (C=C). - $[\alpha]_D^{20}$ = +14.8 (c = 0.2, $CHCl_3$). - $C_{12}H_{19}O_5N$ (257.28): calcd. C 56.02, H 7.44, N 5.44; found C 55.96, H 7.60, N 5.32.

Ethyl-(2'*R*, 3'*S*, 4'*R*, 5'*R*)-2-(3', 4', 5'-trihydroxy) piperidyl acetate hydrochloride (9): A solution of **8** (445 mg, 1.73 mmol) in ethanol (15 ml) was hydrogenated with 100 mg Pd/C under 70 atm pressure for 36 h at 45°C. The catalyst was separated by filtration and the filtrate was evaporated. The oily residue was used without further purification and treated with ethanolic hydrochloric acid. (5 ml). The solution was stirred for 36 h at room temperature. After evaporation of the solvent the residue was recrystallized from ethanol / ether. Yield: 437 mg (98 %), colourless crystals, m.p. 178°C.- ^1H NMR (CD_3OD): δ = 4.14 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 4.08 (m 1 H, 3'-H), 3.98 (m, 1 H, 5'-H), 3.74 (t, $J_{4',3'} = J_{4',5'}$ = 3.1 Hz, 1 H, 4'-H), 3.67 (1 H, "t", $J_{2',2a}$ _ $J_{2',2b}$ = 6.5 Hz, 2'-H), 3.38 (dd, $J_{6'b,6'a}$ = 13.5 Hz, $J_{6'b,5'}$ = 2.7 Hz, 1 H, 6'-H_b), 3.28 - 3.23 (m, 1 H, 6'-H_a), 2.91 (dd, $J_{2b,2a}$ = 17.6 Hz, $J_{2b,2'}$ = 6.5 Hz, 1 H, 2-H_b), 2.81 (dd, $J_{2a,2b}$ = 17.6 Hz, $J_{2a,2'}$ = 6.9 Hz, 1 H, 2-H_a), 1.22 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-).- ^{13}C NMR (CD_3OD): δ = 171.6 (s, CO_2Et), 70.8 / 68.0 /

68.8 (d, C-3′,4′,5′), 62.4 (t, CH_3CH_2-), 57.1 (d, C-2′), 49.8 (t, C-6′), 34.3 (t, C-2), 14.4 (q, CH_3CH_2-).- MS (70 eV), *m/z* (%): 257.1 (1.1) [M+H$^+$], 220.2 (1.0) [M$^+$-Cl], 201.2 (43.5), 184.1 (18.3), 174.1 (18.2), 158.1 (20.8), 132.1 (60.4), 129.1 (54.7), 116.1 (52.3), 84.0 (26.0), 70.0 (57.5), 56.2 (88.4), 36.0 (100) [HCl$^+$].- IR (KBr): ν = 3500 - 3200 cm^{-1} (O-H), 3040 (>NH_2^+), 2970, 2920, 2840 (C-H), 1725 (C=O), 1510 (>NH_2^+). - $[\alpha]_D^{20}$ = -8.8 (c = 1.0, CH_3OH).- $C_9H_{18}NO_5Cl$ (255.69): calcd C 42.27, H 7.09, N 5.48, found C 41.52, H 6.44, N 5.38.

(2*R* 3*S*, 4*R*, 5*R*)-2′(3′, 4′, 5′-trihydroxy) piperidyl acetic acid hydrochloride (10):
9 (520 mg, 2.00 mmol) was dissolved in 5 N hydrochloric acid (4 ml) and stirred for 5 h at 80°C. The solvent was evaporated, the dark residue was washed with warm methanol, until the crystals got colourless. Yield: 435 mg (97 %), m.p. 205°C (decomposition). ^{1}H NMR (D_2O): δ = 4.95 (m, 1 H, 4′-H), 4.39 (m, 1 H, 3′-H), 4.15 - 4.09 (m, 2 H, 2′-H, 5′-H), 3.48 - 3.43 (m, 1 H, 6′-H_b), 3.31 - 3.24 (m, 2 H, 2-H_b, 6′-H_a), 2.94 - 2.81 (m, 1 H, 2-H_a).- ^{13}C NMR (D_2O): δ = 176.6 (s, C=O), 78.3 (d, C-3′), 64.7 / 66.7 (d, C-4′,5′), 54.0 (d, C-2′), 46.7 (t, C-6′), 35.3 (t, C-2).- MS (70 eV), *m/z* (%): 247.3 (0.2) [M+NH_4^+], 202.2 (3.6), 191.2 (100) [M$^+$-Cl], 174.2 (9.2), 157.1 (1.2).- IR (KBr): ν = 3500, 3420, 3290 cm^{-1} (O-H), 3020 (NH_2^+), 2840 (C-H), 1780 (C=O), 1155, 1105 (C-O), 955. - $[\alpha]_D^{20}$ = +56.4 (c = 1.0, H_2O), $C_7H_{14}NO_5Cl$ (227.63): calcd C 36.93, H 6.19, N 6.15, found C 36.95, H 6.19, N 5.95.

Ethyl (2*R*, 3*S*, 4*R*, 5*R*)-N-tert.-butoxycarbonyl-2(5′-hydroxy-3′,4′-(O,O)-isopropylidene) piperidyl acetate (11): A solution of **8** (1.10 g, 4.27 mmol) in ethanol (25 ml) was hydrogenated with 200 mg Pd/C under 70 atm pressure for 36 h at 45°C. The catalyst was removed by filtration, the solvent was evaporated and the residue was dissolved in THF (10 ml) and triethylamine (2 ml). Di-*tert.*-butyldicarbonate (930 mg, 4.27 mmol) was added and the mixture was stirred for 18 h at 45°C. After evaporation of the solvent ether (100 ml) was added and the solution was washed with 0.25 N hydrochloric acid (25 ml) and 2 N sodium hydrogencarbonate solution. The organic layer was separated, dried with sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel with ether. Yield: 1.25 g (81 %), colourless crystals, m.p. 59°C, R_f = 0.45 (ether). - ^{1}H NMR ($CDCl_3$): δ = 4.39 (t, $J_{4',3'} = J_{4',5'}$ = 6.1 Hz, 1 H, 4′-H), 4.31 - 4.16 (m, 2 H, 3′,5′-H), 3.90 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2), 3.65 - 3.47 (m, 2 H, 2′-H, 6′-H_b), 3.04 (br, 1 H, 6′-H_a), 2.81 (dd, $J_{2a,2b}$ = 12.5 Hz, $J_{2b,2'}$ = 10.2 Hz, 1 H, 2-H_b), 2.60 (br, 1 H, 2-H_b), 1.29 (s, 3 H, $(CH_3)_2C$), 1.23 (s, 9 H, $(CH_3)_3C$), 1.14 (s, 3 H, $(CH_3)_2C$), 1.02 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-). - ^{13}C NMR ($CDCl_3$): δ = 170.9 (s, CO_2Et), 154.2 (s, NCO_2t-Bu), 108.3 (s, $(CH_3)_2C$), 79.8 (s, $(CH_3)_3C$), 72.8 (d, C-4′), 72.5 (d, C-5′), 65.3 (C-3′), 59.7 (t, CH_3CH_2-), 48.3 (t, C-6′), 41.3 (d, C-2′), 35.0 (t, C-2), 27.8 (s, 3 C, $(CH_3)_3C$), 25.5 (s, $(CH_3)_2C$), 24.0 (s, $(CH_3)_2C$), 13.7 (q, CH_3CH_2-). - IR (neat): ν = 3550-3300 cm^{-1} (O-H), 2980, 2940 (C-H), 1730, 1690 (C=O), 1455, 1390. - $[\alpha]_D^{20}$ = -10.3 (c = 0.7, $CHCl_3$). - $C_{17}H_{29}O_7N$, (359.40): calcd. C 56.81, H 8.12, N 3.90, found C 56.72, H 8.21, N 3.90.

(2*R*, 3*S*, 4*R*, 5*R*)-N-tert.-butoxycarbonyl-2-(2′-hydroxyethyl)-5-hydroxy-3,4(O,O)-isopropylidene piperidine (12): A solution of **11** (825 mg, 2.29 mmol) in ether (20 ml) was added carefully to a suspension of lithium aluminum hydride (152 mg, 4.0 mmol) in ether (50 ml) by a dropping funnel at 0°C. Stirring was continued for another 3 h. The mixture was quenched by the addition of methanol (20 ml) and filtered. The solvent of the filtrate was evaporated and the residue was purified by a short column chromatography on silica gel with chloroform / methanol (2 : 1). For further purification the product was recrystallized from *tert.*-butyl-methyl ether. Yield: 1.16 g (66 %), colourless crystals, m.p.: 94-95°C. - ^{1}H NMR ($CDCl_3$): δ = 4.65 - 4.60 (m, 2 H, 3,4-H), 4.35 - 4.32 (m, 1 H, 5-H), 4.01 - 3.84 (m, 2 H, 2-H, 6-H_e), 3.70 (t, $J_{2',1'}$ = 7.2 Hz, 2 H, 2′-H), 3.17 (dd, 1 H, $J_{6a,6e}$ = 11.7 Hz, $J_{6a,5}$ = 10.5 Hz, 6-H_a), 2.24 - 2.13 (m, 2 H, 1′-$H_{a,b}$), 1.71 (s, 3 H, (CH_3)2C), 1.65 (s, 9 H, (CH_3)3C), 1.57 (s, 3 H, (CH_3)2C). - ^{13}C NMR ($CDCl_3$) δ = 156.8 (s, NCO_2*t*-Bu), 110.0 (s, $(CH_3)_2C$), 81.4 (s, $(CH_3)_3C$), 74.6 / 75.1 (2 d, C-3,4), 66.9 (d, C-5), 60.1 (t, C-2′), 50.6 (d, C-2), 41.8 (t, C-6), 33.7 (t, C-1′), 28.6 (s, 3 C, $(CH_3)_3C$), 26.3 (s, $(CH_3)_2C$), 25.2 ($(CH_3)_2C$). - MS (70 eV), *m/z* (%): 317.3 (3.1) [M^+], 246.2 (7.0), 216.2 (9.7) [M^+-Boc], 172.2 (18.7), 142.2 (25.9), 87.1 (34.3), 57.2 (100) [$C_4H_9^+$]. - IR (Film): ν = 3450 cm^{-1} (O-H, br), 2970, 2920 (C-H), 1660 (C=O), 1250, 1210, 1160 (C-O). - $[\alpha]_D^{20}$ = - 12.8 (c = 1.1, CH_3OH). - $C_{15}H_{27}O_6N$ (317.37): calcd. C 56.71, H 8.57, N 4.41, found C 56.13, H 9.76, N 4.34.

(2*R*, 3*S*, 4*R*, 5*R*)-2-(2′-hydroxyethyl)-3,4,5-trihydroxypiperidine (13), D-Homo-2-deoxyazatalose: A solution of **12** (240 mg, 0.76 mmol) in ethanol (10 ml) and 5 drops of aqueous hydrochloric acid was stirred for 36 h at room temperature. The solvent was evaporated and the residue was recrystallized from methanol / ether. Yield: 159 mg (98 %), colourless crystals, m.p. 151°C. - ^{1}H NMR (CD_3OD): δ = 4.35 (m, 1 H, 3-H), 4.20 (m, 1 H, 4-H), 3.98 - 3.89 (m, 3 H, 2′-$H_{a,b}$, 5-H), 3.63 - 3.39 (m, 3 H, 2-H, 6-$H_{a,b}$), 2.23 - 2.14 (m, 2 H, 1′-$H_{a,b}$). - ^{13}C NMR (DMSO-d_6): δ = 68.6 (d, C-5), 66.7 / 67.4 (d, C-3,4), 56.3 (t, C-2′), 55.7 (d, C-2), 48.2 (t, C-6), 31.3 (t, C-1′). - MS (70 eV), *m/z* (%): 243.3 (2.7), 215.3 (1.3) [$M+H^+$], 142.2 (30.2), 132.1 (64.7), 74.1 (95.2), 56.2 (62.1), 36.0 (100) / 38.0 (34.2) [HCl]. - IR (KBr): n = 3480 cm^{-1}, 3380, 3270 (O-H, N-H), 2950, 2820 (C-H), 1450, 1120 (C-O). - $[\alpha]_D^{20}$ = - 24.1 (c = 0.5, CH_3OH). - $C_7H_{16}O_4NCl$ (213.65): calcd. C 39.35, H 7.54, N 6.56, found C 39.51, H 7.83, N 6.35.

Ethyl (2′*S*, 3′*S*, 4′*R*, 5′*R*)-N-tert.-butoxycarbonyl-2-(5′-hydroxy-3′,4′-(O,O)-isopropylidene) piperidyl acetate (14): A solution of **7** (1.42 g, 4.98 mmol) in ethanol (25 ml) was hydrogenated over Pd/C (200 mg) under 70 atm pressure for 36 h at 20°C. The catalyst was removed by filtration, the solvent was evaporated and the residue was dissolved in THF (10 ml) and triethylamine (2 ml). Di-*tert.*-butyldicarbonate (1.09 g, 4.98 mmol) was added and the mixture was stirred for 18 h at 45°C. After evaporation of the solvent ether (150 ml) was added and the solution was washed with 0.25 M hydrochloric acid and 2 M sodium hydrogencarbonate solution. The organic layer was separated, dried with sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel with ethyl

acetate. Yield: 812 mg (63%), colourless oil, R_f = 0.45 (EtOAc).- ^{1}H NMR ($CDCl_3$): δ = 4.54 - 4.41 (m, 2 H, 4'-H, 3'-H), 4.12 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2), 3.85 - 3.77 (m, 1H, 2 H), 3.56 (dd, $J_{5',6a}$ = 12 Hz, $J_{5',6b}$ = 4.5 Hz, 1 H, 5'-H), 3.40 (dd, $J_{6a,6b}$ = 11.7 Hz, $J_{6b,5'}$ = 4.5 Hz, 1 H, 6'-H_b), 2.99 (t, $J_{6a,6b}$ = $J_{6a,5'}$ = 11.8 Hz, 1 H, 6'-H_a), 2.47 (dd, $J_{2a,2b}$ = 15.3 Hz, $J_{2a,2'}$ = 4.7 Hz, 1 H, 2-H_a), 2.17 (dd, $J_{2b,2a}$ = 15.3 Hz, $J_{2b,2'}$ = 9.6 Hz, 1 H, 2-H_b), 1.32 (s, 3 H, (CH_3)$_2$C), 1.30 (s, 9 H, (CH_3)$_3$C), 1.21 (s, 3H, (CH_3)$_2$C), 1.11 (t, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2).- ^{13}C NMR ($CDCl_3$): δ = 170.1 (s, CO_2Et), 154.4 (s, NCO_2*t*-Bu), 108.7 (s, (CH$_3$)$_2$C), 79.9 (s, (CH$_3$)$_3$*C*), 75.0 (d, C-4'), 71.6 (d, C-3'), 64.7 (d, C-5'), 60.5 (t, CH_3-*C*H_2), 48.3 (t, C-6'), 41.4 (d, C-2'), 37.0 (t, C-2), 28.0 (q, 3 C, (*C*H$_3$)$_3$C)), 25.8 (q, (*C*H$_3$)$_2$C), 24.0 (q, (*C*H$_3$)$_2$C).- IR (neat): ν = 3500 - 3250 cm^{-1} (O-H), 2980, 2930 (C-H), 1730, 1690 (C=O), 1455, 1375.- $[\alpha]_D^{20}$ = +4.2 (c = 0.6, $CHCl_3$).- $C_{17}H_{29}O_7N$ (359.40): calcd C 56.81, H 8.12, N 3.90, found C 56.55, H 8.22, N 3.90.

(2*S*,3*S*,4*R*,5*R*)-N-tert.-Butoxycarbonyl-2-(2'-hydroxyethyl)-5-hydroxyethyl)-5-hydroxy-3,4-(O,O)-isopropylidene piperidine (15): Analogous procedure as described for **12**: 320 mg (0.89 mmol) of **13** were used. Yield: 259 mg (92 %).- m.p. 146°C.- ^{1}H NMR ($CDCl_3$): δ = 4.37 - 4.25 (m, 2 H, 4-H, 3-H), 3.89 - 3.83 (m, 1 H, 5-H), 3.58 - 3.48 (m, 2 H, 2'-$H_{a,b}$), 3.41 (dd, $J_{6a,6b}$ = 11.6 Hz, $J_{6a,5}$ = 4.8 Hz, 1 H, 6-H_a), 3.10 (t, $J_{6a,6b}$ = $^3J_{6b,5}$ = 11.6 Hz, 1 H, 6-H_b), 2.66 (d, $J_{2,3}$ = 9.7 Hz, 1 H, 2-H), 1.74 - 1.69 (m, 1 H, 2'-H_a), 1.44 (s, 3 H, (C*H*$_3$)$_2$C), 1.43 (s, 9 H, (C*H*$_3$)$_3$C), 1.36 (m, 1 H, 2'-H_b) 1.33 (s, 3 H, (C*H*$_3$)$_2$C).- ^{13}C NMR ($CDCl_3$): δ = 157.0 (s, NCO_2*t*-Bu), 108.9 (s, (CH$_3$)$_2$*C*), 80.7 (s, (CH$_3$)$_3$*C*), 76.7 (d, C-4), 71.7 (d, C-3), 64.4 (d, C-5), 58.2 (t, C-2'), 48.8 (d, C-2), 43.0 (t, C-6), 36.2 (t, C-1'), 28.3 (q, 3 C, (*C*H$_3$)$_3$C)), 26.1 (q, (*C*H$_3$)$_2$C), 24.3 (q, (*C*H$_3$)$_2$C).- IR (neat): ν = 3550 - 3200 cm^{-1} (O-H), 2980, 2920 (C-H), 1660 (C=O), 1450, 1395.- $[\alpha]_D^{20}$ = + 30.5 (c = 0.1, $CHCl_3$).- $C_{15}H_{27}O_6N$ (317.37): calcd C 56.71, H 8.57, N 4.41, found C 55.89, H 8.68, N 4.40.

(2*S*,3*S*,4*R*,5*R*)-2-(2'-Hydroxyethyl)-3,4,5-trihydroxypiperidine (16), L-Homo-2-deoxyazaallose: Analogous procedure as described for **13**: 245mg (0.77 mmol) of **15** were used. Yield: 158 mg (96 %), pale yellow crystals, very hygroscopic.- ^{1}H NMR (CD_3OD): δ = 4.23 (t, $J_{4,3}$ = $J_{4,5}$ = 2.4 Hz, 1 H, 3-H), 4.16 - 3.89 (m, 3 H, 2'-$H_{a,b}$, 5-H), 3.80 (dd, $J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 2.4 Hz, 1 H, 6-H_a), 3.61 - 3.27 (m, 3 H, 2-H, 6-$H_{a,b}$), 2.45 - 2.30 (m, 1 H, 1'-H_a), 2.08 - 1.93 (m, 1 H, 1'-H_b).- ^{13}C NMR (CD_3OD): δ = 71.6 (d, C-4), 70.2 (d, C-3), 66.3 (d, C-5), 60.2 (t, C-2'), 55.4 (d, C-2), 43.9 (t, C-6), 31.9 (t, C-1'). - IR (neat): ν = 3550 - 3200 cm^{-1} (O-H), 2920, 2800 (C-H), 1660 (C=O), 1420, 1150. -$[\alpha]_D^{20}$ = -18 (c = 1.6, CH_3OH)

Ethyl (2'*S*, 3'*S*, 4'*R*, 5'*R*)-2-(3', 4', 5'-trihydroxy)piperidyl acetate hydrochloride (17) : A solution of **7** (500 mg, 1.75 mmol) in ethanol (10 ml) was hydrogenated with 100 mg Pd/C under 70 atm pressure for 36 h at room temperature. The catalyst was separated by filtration and 3 drops of concentrated hydrochloric acid (37 %) were added. The mixture was stirred for 18 h at 45°C . The solvent was evaporated, the residue was recrystallized from ethanol / ether. Yield: 412 mg (92 %), colourless crystals, m.p. 89 - 91 °C. - ^{1}H NMR (CD_3OD): δ = 4.35 (d,

$J_{3',2'}$ = 10.2 Hz, 1 H, 3'-H), 4.15 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 4.06 - 4.03 (m, 1 H, 5'-H), 3.95 (m, 1 H, 4'-H), 3.84 - 3.78 (m, 1 H, 2'-H), 3.70 (dd, $J_{6a,6b}$ = 10.4 Hz, $J_{6a,5'}$ = 2.3 Hz, 1 H, 6'-H_a), 3.57 - 3.45 (m, 1 H, 6'-H_b), 3.15 - 2.91 (m, 1 H, 2-H_b), 2.68 - 2.55 (m, 1 H, 2-H_a), 1.20 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-).- ^{13}C NMR (CD_3OD): δ = 172.2 (s, CO_2Et), 72.2 / 71.6 (d, C-3',4'), 66.3 (d, C-5'), 61.9 (t, CH_3CH_2-), 52.5 (d, C-2'), 44.1 (t, C-6'), 34.0 (t, C-2), 14.5 (q, CH_3CH_2-).- IR (KBr): ν = 3500 - 3200 cm^{-1} (O-H), 3040 (>NH_2^+), 2980, 2920, 2840 (C-H), 1725 (C=O), 1510 (>NH_2^+).- $[\alpha]_D^{20}$ = -31.4 (c = 1.0, CH_3OH).- $C_9H_{18}NO_5Cl$ (255.69): calcd C 42.27, H 7.09, N 5.48, found C 40.84, H 7.83, N 6.44.

(2'*S*, 3'*S*, 4'*R*, 5'*R*)-2'-(3', 4', 5'-Trihydroxy) piperidyl acetic acid hydrochloride (18): **17** (320 mg, 1.25 mmol) was dissolved in 5 N hydrochloric acid (4 ml) and stirred for 18 h at 80°C. The solvent was evaporated, the dark residue was dissolved in methanol (20 ml) charcoal (100 mg) was added and the mixture was refluxed for 20 min and filtered. The methanol was evaporated and the pale yellow residue got crystallized by the addition of acetone. Yield: 228 mg (80 %), colourless crystals, m.p. 68°C.- ^{1}H NMR (CD_3OD): δ = 4.25 (m, 1 H, 4'-H), 4.20 - 4.14 (m, 1 H, 5'-H), 3.98 - 3.92 (m, 1 H, 3'-H), 3.90 - 3.74 (m, 2 H, 2'-H, 6'-H_a), 3.37 - 3.31 (m, 1 H, 6'-H_b), 3.24 (dd, $J_{2a,2b}$ = 17.7 Hz, $J_{2a,2'}$ = 3.2 Hz, 1 H, 2-H_a), 2.92 (dd, $J_{2a,2b}$ = 17.7 Hz, $J_{2b,2'}$ = 7.7 Hz, 1 H, 2-H_b).- ^{13}C NMR (CD_3OD): δ = 172.6 (s, C=O), 71.6 / 69.6 / 66.2 (3 d, C-3',4',5'), 52.8 (d, C-2'), 44.1 (t, C-6'), 33.9 (t, C-2).- $[\alpha]_D^{20}$ = -28.7 (c = 2.1, CH_3OH).- $C_7H_{14}NO_5Cl$ (227.63): calcd C 36.94, H 6.19, N 6.15, found C 36.60, H 5.86, N 5.81.

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REFERENCES AND NOTES

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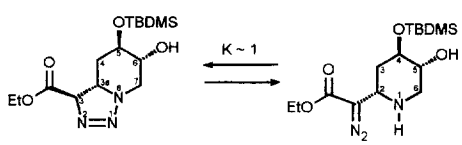

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