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Synthesis of (2S,3R)-3-Hydroxy Leucine: A Constituent of Lysobactin

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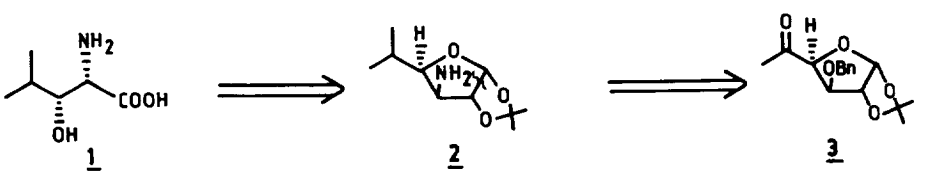
Abstract: *The known 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-xylohexofuranos-5-ulose was converted stereoselectively to the titled compound 1.*

(2S,3S)-3-Hydroxyleucine is an important aminoacid present in several peptide antibiotics viz., azinthricin,[1] telomycin[2] and A 83586c,[3] while lactacystin[4] incorporated its 2R,3S-diastereomer. Recently, yet another isomer of 3-hydroxyleucine i.e., the 2S,3R isomer was found to be a constituent of a macrocyclic peptide lactone antibiotic lysobactin[5] isolated from fermentations of Lysobacter Sp. ATCC 53042. The efficacy of this new antibiotic in vivo was found to compare favourably with that of clinically useful antibiotic vancomycin.[6] All isomers of 3-hydroxyleucine have attracted synthetic chemist owing to biological importance and several syntheses have been reported.[7]

As part of an ongoing programme on the synthesis of β-hydroxy-α-aminoacids from cheaply available D-glucose as chiral precursor,[8] herein, we report the synthesis of (2S,3R)-3-hydroxyleucine (Scheme 1).

Scheme 1



D-Glucose was converted into 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α -D-xylohexofuranos-5-ulose **3** by a known procedure.[9] Methylenation of ketone using methylene triphenyl phosphorane yielded olefin **4**. Catalytic hydrogenation using Pd-C in ethanol and hydrogen at 45 psi resulted in reduction of olefin along with simultaneous debenzylation and gave crystalline **5** (m.p. 88°C). The next aim of introducing amino group at C-3 of xylofuranose derivative **5** with retention of configuration followed a double inversion technique i.e., inversion of -OH group by

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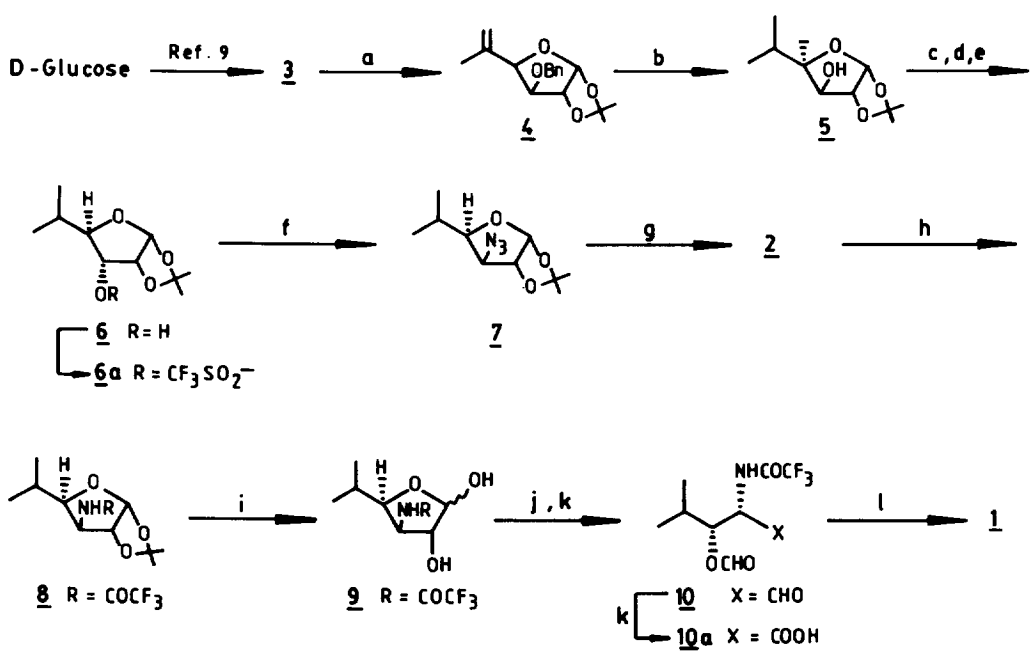
oxidation followed by reduction to get the ribose derivative **6** (m.p. 72°C). The azide group was introduced via trifluoromethansulfonate **6a** followed by treatment with NaN_3 in DMF to yield **7**. Reduction of azido group with Pd-C in ethanol gave amine **2** which was protected as trifluoroacetamide derivative **8** for operational convenience. Hydrolysis of isopropylidene group in **8** with trifluoroacetic acid furnished **9**, which on cleavage with lead tetracetate followed by Jones' oxidation of resultant **10** gave **10a**. Final amino acid **1** was isolated from **10a** by deprotection of O-CHO and NH-$COCF_3$ on exposure to 2N KOH and ion exchange chromatography, whose spectral data was identical with the literature values.[7e,10]

Scheme 2



a. $Ph_3P{=}CH_2$, THF; b. Pd-C, H_2, EtOH; c. PDC, Ac_2O, CH_2Cl_2; d. $NaBH_4$, MeOH, e. Tf_2O, Pyr, DMAD; f. NaN_3, DMF; g. Pd-C, H_2, EtOH; h. $(CF_3CO)_2O$, Na_2CO_3, Ether; i. TFA:H_2O (8:2); j. $Pb(OAc)_4$, CH_2Cl_2; k. Jones reagent, acetone; l. 2N KOH, Dowex H^+.

Experimental :

General: PMR spectra were recorded either on Jeol 90 or Varian FT 80 A spectrometer in $CDCl_3$ or D_2O solutions containing TMS as an internal standard with chemical shifts expressed in ppm downfield from TMS. Infrared spectra were recorded in KBr or $CHCl_3$ or neat on a Perkin-Elmer IR-683 spectrophotometer with NaCl optics. Mass spectra were recorded on a CEC-21-110 B double focussing mass spectrometer at 70 eV using direct inlet system. $[\alpha]_D$ were measured with Jasco Dip 181 digital polarimeter. Melting points were recorded on Mettler melting point apparatus FP-5+FP 51 and are uncorrected. All dry solvents were dried and purified

by standard techniques.

3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-5-C-methyl- α -D-xylo-hex-5-enofuranose (4)

A solution of methyltriphenyl phosphonium bromide (14.2 g, 40 mmol) in dry THF (100 mL) under N_2 atmosphere at 0°C was treated with n-BuLi (16 mL, 2.5N in hexane) and allowed to stir for 20 min at 0° and 30 min at room temperature. It was cooled to -55°C and THF (25 mL) solution of ketone **3** (5.8 g, 20 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 8 h. Aqueous NH_4Cl solution was added and extracted with ether. Ether layer was washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue by column chromatography (silica gel; 9:1, pet.ether, ethyl acetate) gave **4** (4.4 g) in 78% yield. $[\alpha]_D$ -46.5° (c 0.9, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 1.32 (s,3H,CH_3), 1.52 (s,3H,CH_3), 1.70 (s,3H,5-C-CH_3), 3.95 (d,1H, H-3), 4.58 (m,4H,$PhCH_2$,H-2,4), 5.09 (brd,2H,H-6,6'), 7.30 (s,5H,aromatic).

IR (neat): 2980 cm^{-1}, 2930 cm^{-1}, 1450 cm^{-1}, 1380 cm^{-1}.

Mass: 290 (M^+), 275 (M^+-15).

Analysis calcd. for $C_{17}H_{22}O_4$: C, 70.31; H, 7.64. Found: C, 70.33; H, 7.80%.

5,6-Dideoxy-1,2-O-isopropylidene-5-C-methyl-α-D-xylohexofuranose (5)

A suspension of 10% Pd-C (0.60 g) and compound **4** (3 g, 10.3 mmol) in ethanol (30 mL) was subjected to hydrogenation at 50 psi and room temperature for 6 h. Reaction mixture was filtered, washed with EtOH and filtrate was evaporated to furnish **5** (2 g) in 96% yield as white solid m.p. 88°C. $[\alpha]_D$ -19.90° (c 1.55, $CHCl_3$)

^1H NMR ($CDCl_3$): δ 0.85 (d,3H,CH_3), 1.04 (d,3H,CH_3), 1.33 (s,3H,CH_3), 1.52 (s,3H, CH_3), 1.8 (m,1H,3°H), 3.59 (dd,1H,H-4), 4.01 (brd,1H,H-3), 4.4 (d,1H,H-2), 5.86 (d, 1H,H-1)

IR ($CHCl_3$): 3300 cm^{-1} (-OH)

Mass: 202 (M^+), 187 (M^+-15)

Analysis calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.96. Found: C, 59.08; H, 8.86%.

5,6-Dideoxy-1,2-O-isopropylidene-5-C-methyl-α-D-ribohexofuranose (6)

A mixture of **5** (1.58 g, 7.4 mmol), Ac_2O (2.2 g, 22.5 mmol) and PDC (2 g, 5.25 mmol) in CH_2Cl_2 (20 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, diluted with 250 mL ether and filtered through a small pad of silica gel. Evaporation of volatiles followed treatment with $NaBH_4$ (0.43 g, 12 mmol) in methanol (10 mL) at 0°C. After 1 h, methanol was evaporated, residue dissolved in 2% HCl solution and extracted with $CHCl_3$. Organic layer was washed with water, dried (Na_2SO_4) and evaporated to afford **6** (1 g) in 83% yield as white solid (m.p. 72°C). $[\alpha]_D$ +51.79° (c 1.45, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 0.95 (d,3H,CH_3), 1.0 (d,3H,CH_3), 1.34 (s,3H,CH_3), 1.56 (s,3H, CH_3), 1.82 (m,1H,3°H), 3.30-3.70 (m,2H,H-3,4), 4.52 (t,1H,H-2), 5.8 (d,1H,H-1)

IR ($CHCl_3$): 3300 cm^{-1} (-OH)

Mass: 202 (M^+)

Analysis calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.96. Found: C, 59.60; H, 8.80%.

5,6-Dideoxy-1,2-O-isopropylidene-5-C-methyl-3-O-trifluoromethanesulfonyl- α -D-ribo-hexofuranose (6a)

A mixture of compound **6** (1 g, 4.9 mmol), pyridine (1.8 g, 15 mmol) and catalytic amount of DMAP was treated with trifluoromethane sulfonic anhydride (2.07 g, 7.35 mmol) at O°C and allowed to stir at the same temperature for 15 min. Ice cold water was added to the reaction mixture and extracted with CH_2Cl_2. Organic layer was washed sequentially with 5% aq. HCl, 5% aq. $NaHCO_3$, water and brine. Evaporation of the solvent after drying over Na_2SO_4 afforded **6a** (1.56 g) in 98% yield. The product **6a** was subjected to next reaction without further purification.

3-Azido-1,2-O-isopropylidene-5-C-methyl-3,5,6-trideoxy-α-D-xylohexofuranose (7)

A mixture of **6a** (1.50 g, 4.5 mmol) and NaN_3 (0.91 g, 14 mmol) in DMF (10 mL) was heated at 90°C for 12 h. Reaction mixture was cooled to room temperature, diluted with 30 mL water and extracted with ether. Ether layer was washed with water, dried (Na_2SO_4) and evaporated to furnish the azide **7** (0.828 g) in 82% yield as yellow liquid. $[\alpha]_D$ -56.61° (c 1.35, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 0.9 (d,3H,CH_3), 1.05 (d,3H,CH_3), 1.3 (s,3H,CH_3), 1.5 (s,3H,CH_3), 1.9 (m,1H,3H), 3.61-3.82 (m,2H,H-3,4), 4.65 (d,1H,H-2), 5.88 (d,1H,H-1)

IR (neat): 2090 cm^{-1} (N≡N)

Mass: 227 (M^+)

Analysis calcd. for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.53. Found: C, 52.65; H, 7.55%.

3-Amino-1,2-O-isopropylidene-5-C-methyl-3,5,6-trideoxy-α-D-xylohexofuranose (2)

Hydrogenation of compound **7** (0.80 g, 3.5 mmol) in ethanol (10 mL) in presence of 10% Pd-C (0.10 g) at 1 atm for 6 h and filtration of catalyst afforded amine **2** (0.637 g) in 90% yield as yellow liquid.

^1H NMR ($CDCl_3$): δ 0.85 (d,3H,CH_3), 1.04 (d,3H,CH_3), 1.2 (s,3H,CH_3), 1.46 (s,3H, CH_3), 1.8 (m,1H,3°H), 3.25 (d,1H,H-3), 3.62 (dd,1H,H-4), 4.31 (d,1H,H-2), 5.8 (d,1H,H-1)

IR (neat): 3150 cm^{-1} (-NH)

Mass: 201 (M^+), 186 (M^+-15)

Analysis calcd. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.50. Found: C, 59.82; H, 9.60%.

1,2-O-Isopropylidene-5-C-methyl-3,5,6-trideoxy-3-trifluoroacetamido- α -D-xylohexofuranose (8)

A cooled (O°C) mixture of **2** (0.45 g, 2.2 mmol) and anhydrous sodium carbonate (2.5 g) in dry ether (15 mL) was treated with trifluoroacetic anhydride (2.5 mL) in one lot and allowed to stir at room temperature for 1 h. Reaction mixture was diluted with $CHCl_3$ and poured into crushed ice. $CHCl_3$ layer was dried (Na_2SO_4) and

evaporated to furnish **8** (0.557 g) in 84% yield as colourless syrup. $[\alpha]_D$ -17.30° (c 2.97, $CHCl_3$)

^1H NMR ($CDCl_3$): δ 0.84 (d,3H,CH_3), 1.08 (d,3H,CH_3), 1.31 (s,3H,CH_3), 1.53 (s,3H, CH_3), 1.75 (m,1H,3H), 3.78 (dd,1H,H-4), 4.34 (d,1H,H-3), 4.38 (d,1H,H-2), 5.82 (d, 1H,H-1)

IR ($CHCl_3$): 1690 cm^{-1} (C=O)

Mass: 297 (M^+)

Analysis calcd. for $C_{12}H_{18}O_4NF_3$: C, 48.48; H, 6.09. Found: C, 48.40; H, 6.10%.

5-C-Methyl-3,5,6-trideoxy-3-trifluoroacetamido-α-D-xylohexofuranose (9)

Compound **8** (0.4 g, 1.3 mmol) in aqueous 80% trifluoroacetic acid (3 mL) was allowed to stir at room temperature for 1 h. TFA was removed under reduced pressure, residue diluted with ether and filtered through a small pad of $NaHCO_3$. Evaporation of the solvent furnished diol **9** (0.28 g) in 81% yield.

^1H NMR ($CDCl_3$): δ 0.8 (d,3H,CH_3), 1.04 (d,3H,CH_3), 1.8 (m,1H,3°H), 4.18 (m,3H,H-2, 3,4), 5.43 (d,1H,H-1)

IR ($CHCl_3$): 3400 cm^{-1} (-OH), 1700 cm^{-1} (C=O)

Mass: 257 (M^+)

Analysis calcd. for $C_9H_{14}NO_4F_3$: C, 42.03; H, 5.48. Found: C, 42.11; H, 5.50%.

(2S,3R)-3-Formyloxy-4-methyl-2-trifluoroacetamido pentan-1-oic acid (10a)

Lead tetracetate (0.66 g, 1.5 mmol) was added to a solution of **9** (0.257 g, 1 mmol) in dry CH_2Cl_2 (5 mL) under N_2 atmosphere at O°C and allowed to stir for 15 min. Excess LTA was destroyed by adding ethyleneglycol (3 drops); reaction mixture washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent afforded rather unstable aldehyde **10** (0.22 g) which was used as such for further reaction.

A solution of aldehyde **10** (0.22 g, 0.86 mmol) in acetone (3 mL) at -15°C was treated with Jones' reagent (0.3 mL) and stirred for 10 min at the same temperature. It was diluted with 10 mL water and extracted with ethyl acetate. Organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give acid **10a** (0.16 g) in 60% yield from diol. $[\alpha]_D$ +47.39° (c 0.73, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 0.9 (d,3H,CH_3), 1.04 (d,3H,CH_3), 1.92 (m,1H,3°H), 5.12 (m,2H,H-2,3), 8.1 (s,1H,O-CHO)

IR(neat): 3300 cm^{-1}, 1740 cm^{-1} (br)

Mass: 271 (M^+)

Analysis calcd. for $C_9H_{12}NO_5F_3$: C, 39.86; H, 4.45. Found: C, 39.70; H, 4.35%.

(2S,3R)-3-Hydroxyleucine (1)

Compound **9a** (0.062 g, 0.22 mmol) and 2N aq. KOH (1 mL) was heated at 100°C for 5 h, cooled to room temperature, acidified with Dowex H^+ (pH 4) and heated for 5 min at 80°C. The mixture was passed through a pad of Dowex H^+ with aqueous NH_3 (10%; 100 mL). The evaporation of the eluent by lyophilisation gave amino acid **1** (0.023 g) in 66% yield [m.p. 210° (decomp)], lit. 213-217° (decomp). $[\alpha]_D$-3.5°

(c 1.2, H_2O). Lit. -3.5° (c 2.2, H_2O).

^1H NMR (D_2O): δ 0.84 (d,3H,CH_3), 0.88 (d,3H,CH_3), 1.8 (m,1H), 3.20 (d,1H,H-2), 3.80 (dd,1H,H-3).

Analysis calcd. for $C_6H_{13}NO_3$: C, 48.97; H, 8.89. Found: C, 49.00; H, 8.90%.

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