New Synthesis of Penta-*N,O*-acetyl-DL-validamine and Pseudo-2-amino-2-deoxy-α-DL-mannopyranose, and Their Uronate Analogs[1)]

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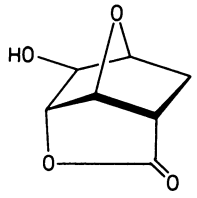
Synopsis. Treatment of the hydroxy lactone derived from (±)-*endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid with hydrogen bromide–acetic acid, followed by esterification, gave 48% of ethyl DL-(1,3,5/2,4)-5-bromo-2,3,4-trihydroxy-1-cyclohexanecarboxylate, from which DL-validamine and pseudo-2-amino-2-deoxy-α-DL-mannopyranose, and their uronate analogs have been synthesized as the totally acetylated derivatives.

Naturally occurring branched-chain aminocyclitols, viz. pseudo-amino sugars such as validamine,[2)] valienamine,[3)] and valiolamine[4)] were isolated from a fermentation broth of *Streptomyces hygroscopicus* sp. *limoneus*. These compounds and their derivatives[5)] show a remarkable inhibitory activity against α-glucosidase, stimulating much interest in their application for a clinical use.



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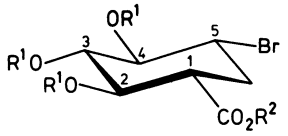
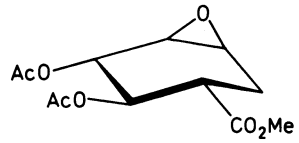


	R^1	R^2
2	H	Et
3	H	Me
4	Ac	Me



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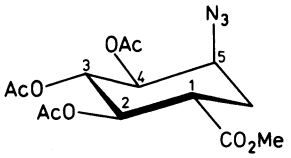

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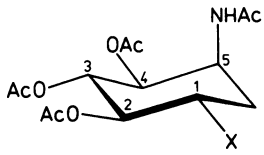
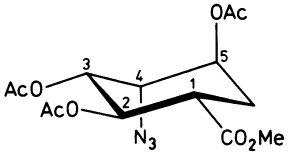


7 X = CO_2Me
8 X = CH_2OAc



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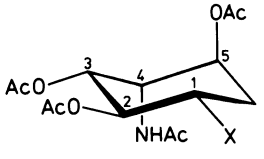

10 X = CO_2Me
11 X = CH_2OAc

We describe now a preparation of DL-validamine and a pseudo-sugar analog of 2-amino-2-deoxy-α-D-mannopyranose, by a novel sequence from the hydroxy lactone[6,7)] **1** obtained from (±)-*endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid.[6,7)]

Treatment of the lactone **1** with 20% hydrogen bromide–acetic acid at 95 °C gave after esterification with ethanol 48% of crystalline bromide **2**, which was converted into the methyl ester **3** and its triacetate **4** in the usual way. The ^1H NMR spectrum of **4** revealed three coupled triplets (J=10 Hz) at δ 5.35, 5.23, and 5.03, attributable to the axial protons at C-2, C-3, and C-4, being consistent with the structure assigned. The structure of **2** was further confirmed by conversion of **3** into the known epoxide[8)] **5** by treatment with methanolic sodium methoxide followed by acetylation.

Azidolysis of **4** with excess sodium azide in *N,N*-dimethylformamide (DMF) gave a single crystalline azide **6**, the ^1H NMR spectrum of which showed a narrow quartet (J=3.5 Hz) at δ 4.18, indicating that the azido group was introduced at C-5 in an axial position. Hydrogenation of **6** in ethanol containing acetic anhydride with Raney nickel gave the *N*-acetyl derivative **7** in 61% yield. On the other hand, **6** was converted, in 56% yield, into DL-penta-*N,O*-acetylvalidamine[7)] (**8**) by reduction with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) followed by acetylation.

When similar azidolysis of **3** was carried out in aqueous 2-methoxyethanol, a single known azido triacetate[8)] **9** was obtained in 65% yield after acetylation. This compound was considered to be obtained through the neighboring group participation of the 4-hydroxyl group, involving a formation of the intermediate 4,5-epoxide, which was successively cleaved by an azide ion via diaxial ring-opening. Catalytic hydrogenation of **9** followed by acetylation gave the *N*-acetyl derivative **10** (84%). Reduction of **9** with LAH and successive acetylation afforded penta-*N,O*-acetyl-pseudo-2-amino-2-deoxy-α-DL-mannopyranose (**11**, 61%). These pseudo-amino sugars are of interest because their corresponding normal sugars occur in biological system.

Experimental

General Methods. Melting points were determined with a MEL-TEMP capillary melting-point apparatus and are

uncorrected. The ^{1}H NMR spectra were measured with a Varian EM-390 (90 MHz) spectrometer for solution of chloroform-*d* (TMS) or dimethyl-d_6 sulfoxide (DSS). Spectrum at 270 MHz was recorded with a Jeol GX-1 instrument. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka).

Ethyl (±)-(1,3,5/2,4)-5-Bromo-2,3,4-trihydroxy-1-cyclohexanecarboxylate (2). A mixture of (±)-2-*exo*-hydroxy-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonan-5-one[7] (**1**) (3.0 g, 10.6 mmol) and 20% hydrogen bromide–acetic acid (15 ml) was heated in a sealed tube at 95 °C for 24 h, and poured into ice–water (20 ml). The mixture was refluxed for 9 h and then concentrated. The residue was treated with ethanol (20 ml) at reflux for 5.5 h, and the mixture was concentrated and the residue was crystallized from ethanol to give the bromide **2** (2.6 g, 48%) as prisms: mp 155.5—156 °C.

Found: C, 38.25; H, 5.23%. Calcd for $C_9H_{15}BrO_5$: C, 38.18; H, 5.34%.

Methyl (±)-(1,3,5/2,4)-5-Bromo-2,3,4-trihydroxy-1-cyclohexanecarboxylate (3). To a solution of **2** (5.0 g, 18 mmol) in methanol (100 ml) was added acetyl chloride (1.5 ml, 21 mmol) and it was refluxed for 21 h. The mixture was neutralized with sodium hydrogencarbonate and then concentrated. The residue was crystallized from ethanol to give **3** (3.8 g, 80%) as prisms: mp 137—138 °C.

Found: C, 35.91; H, 4.76%. Calcd for $C_8H_{13}BrO_5$: C, 35.71; H, 4.87%.

Compound **3** (2.3 g, 8.5 mmol) was treated with acetic anhydride (12 ml) and pyridine (12 ml) at room temperature overnight. The mixture was concentrated and the residue was extracted with ethyl acetate. The extract was washed with water, dried, and concentrated. The residue was recrystallized from ethanol to give the triacetate **4** (3.2 g, 96%) as prisms: mp 153—154 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ=2.00 (6H, s) and 2.08 (3H, s) (OAc), 2.21 (1H, q, $J_{1,6ax}=J_{5,6ax}=J_{6gem}$=13 Hz, H-6ax), 2.62 (1H, dt, $J_{1,6eq}=J_{5,6eq}$= 4 Hz, H-6eq), 2.69 (1H, ddd, $J_{1,2}$=11 Hz, H-1), 3.72 (3H, s, CO_2Me), 3.92 (1H, m, $J_{4,5}$=10.5 Hz, H-5), 5.03 (1H, t, $J_{2,3}=J_{3,4}$=10 Hz, H-3), 5.23 (1H, dd, H-2).

Found: C, 42.74; H, 4.80%. Calcd for $C_{14}H_{19}BrO_8$: C, 42.55; H, 4.85%.

Methyl (±)-(1,3/2,4,5)-2,3,4-Triacetoxy-5-azido-1-cyclohexanecarboxylate (6). A mixture of **4** (1.7 g, 4.3 mmol), sodium azide (1.3 g, 20 mmol), and aqueous 95% DMF (30 ml) was stirred at 90 °C for 20 h, and then concentrated. The residue was extracted with ethyl acetate, and the extract was washed with water, dried, and concentrated. The residue was recrystallized from ethanol to give **6** (0.72 g, 47%) as needles: mp 110—112 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.98 (6H, s) and 2.08 (3H, s) (OAc), 2.91 (1H, td, $J_{1,2}=J_{1,6ax}$=9.5 Hz, $J_{1,6eq}$=3.5 Hz, H-1), 3.67 (3H, s, CO_2Me), 4.18 (1H, q, $J_{4,5}=J_{5,6ax}=J_{5,6eq}$=3.5 Hz, H-5), 5.04 (1H, dd, $J_{3,4}$= 9.5 Hz, H-4), 5.20 (1H, t, $J_{2,3}$=9.5 Hz, H-2), 5.37 (1H, t, H-3).

Found: C, 47.11; H, 5.43; N, 11.57%. Calcd for $C_{14}H_{19}N_3O_8$: C, 47.06; H, 5.36; N, 11.76%.

Methyl (±)-(1,3/2,4,5)-5-Acetamido-2,3,4-triacetoxy-1-cyclohexanecarboxylate (7). A solution of **6** (0.30 g, 0.85 mmol) in ethanol (10 ml) was hydrogenated in the presence of Raney nickel T-4 (1 ml) and acetic anhydride (0.5 ml) in an initial hydrogen pressure of 50 psi at room temperature for 17 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was crystallized from ethanol to give **7** (0.19 g, 61%) as prisms: mp 231.5—233.5 °C. ^{1}H NMR (DMSO-d_6, 90 MHz) δ=1.90 (6H, s), 1.94 (3H, s), and 1.95 (3H, s) (NAc and OAc), 3.62 (3H, s, CO_2Me), 4.30—4.67 (1H, m, H-5), 4.87 (1H, dd, $J_{3,4}$=9.8 Hz, $J_{4,5}$=4.5 Hz, H-4), 5.17 (1H, t, $J_{2,3}$=9.8 Hz, H-2), 5.33 (1H, H-2), 8.07 (1H, d, $J_{5,NH}$=5 Hz, NH).

Found: C, 51.41; H, 6.06; N, 3.61%. Calcd for $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75%.

(±)-[(1,3/2,4,5)-5-Acetamido-2,3,4-triacetoxycyclohexyl]-methyl Acetate (8) [(±)-Penta-*N,O*-acetylvalidamine]. Compound **7** (0.30 g, 0.84 mmol) was treated with LAH (0.25 g, 6.6 mmol) in tetrahydrofuran (10 ml) at room temperature for 30 h. To the mixture was added water (1.5 ml), aqueous 15% sodium hydroxide, water (1.5 ml), and aqueous acetone (1:1, 2 ml) in turn, and then it was filtered through a bed of Celite. The filtrate was neutralized with 1 mol dm^{-3} hydrochloric acid and concentrated. The residue was acetylated in the usual way, and the product was crystallized from ethanol to give **8** (0.18 g, 56%) as prisms: mp 197—199 °C (lit,[7] mp 197—198 °C). This compound was identical to an authentic sample[7] in all respects.

Methyl (±)-(1,3,4/2,5)-2,3,5-Triacetoxy-4-azido-1-cyclohexanecarboxylate (9). A mixture of **3** (0.49 g, 1.8 mmol), sodium azide (0.49 g, 7.5 mmol), and 90% aqueous 2-methoxyethanol (20 ml) was refluxed for 3 h, and then concentrated. The residue was refluxed with methanol (50 ml) and acetyl chloride (1 ml), and then the mixture was neutralized with sodium hydrogencarbonate. The mixture was concentrated and the residue was extracted with ethyl acetate. The extract was concentrated and the residue was acetylated in the usual way and the product was crystallized from ethanol to give **9** (0.51 g, 80%) as plates: mp 95.5—96 °C. (lit,[8] mp 92.5—94 °C). This compound was identical with an authentic sample[8] in all respects.

Methyl (±)-(1,3,4/2,5)-4-Acetamido-2,3,5-triacetoxy-1-cyclohexanecarboxylate (10). Into a solution of **9** (0.14 g, 0.38 mmol) in a mixture of pyridine (5 ml) and water (5 ml) was bubbled hydrogen sulfide at room temperature for 4 h. Excess hydrogen sulfide was removed by a stream of nitrogen and the mixture was concentrated. The residue was acetylated in the usual way and the product was crystallized from ethanol to give **10** (0.11 g, 84%) as needles: mp 178.5—180.5 °C. ^{1}H NMR ($CDCl_3$, 90 MHz): δ=1.90 (3H, s), 2.07 (3H, s), 2.26 (3H, s), and 2.30 (3H, s) (NAc and OAc), 2.87 (1H, bq, J=7 Hz, H-1), 3.71 (3H, s, CO_2Me), 4.50 (1H, dt, $J_{3,4}=J_{4,5}$=4 Hz, $J_{4,NH}$=9 Hz, H-4), 5.13 (1H, dd, $J_{2,3}$=7 Hz, H-3), 5.20 (1H, m, H-5), 5.46 (1H, t, $J_{1,2}$=7 Hz, H-2), 6.75 (1H, d, $J_{4,NH}$=9 Hz, NH).

Found: C, 51.40; H, 6.13; N, 3.62%. Calcd for $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75%.

(±)-[(1,3,4/2,5)-5-Acetamido-2,3,4-triacetoxycyclohexyl]-methyl Acetate (11). Compound **10** (0.30 g, 0.86 mmol) was reduced with LAH in THF as in the preparation of **8**. The product was acetylated in the usual way and the acetate was purified by a silica-gel column with ethanol–toluene (1:10) to give **11** (0.20 g, 61%) as a syrup. ^{1}H NMR (DMSO-d_6, 90 MHz): δ=1.90 (3H, s), 1.91 (3H, s), 2.01 (6H, s), and 2.08 (3H, s) (NAc and OAC), 3.73—4.18 (2 H, m, CH_2OAc), 4.41 (1H, dt, $J_{3,4}=J_{4,5}$=4 Hz, $J_{4,NH}$=9 Hz, H-4), 4.65—4.87 (1H, m, H-5), 4.97 (1H, dd, $J_{2,3}$=9.7 Hz, H-3), 5.22 (1H, t, $J_{1,2}$=9.7 Hz, H-2), 7.92 (1H, d, NH). Mass spectrum, *m/z*; Found: 388.1658 (M$^+$). Calcd for $C_{17}H_{26}NO_9$: 388.1666 (M$^+$).

Found: C, 52.06; H, 6.20; N, 3.62%. Calcd for $C_{17}H_{25}NO_9 \cdot 0.25H_2O$: C, 52.10; H, 6.43; N, 3.75%.

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