Pseudo-sugars. 4. A Facile Synthesis of DL-Validamine and Its Derivative[1]

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Penta-*N,O*-acetyl-DL-validamine was prepared from readily available *endo*-2, *exo*-3-diacetoxy-*endo*-6-acetoxymethyl-7-oxabicyclo[2.2.1]heptane in three steps in an overall yield of 36%.

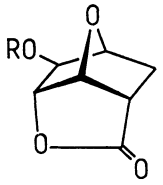
As a part of a synthetic study of antibiotic validamycins,[2] we wish to report a facile synthesis of DL-validamine, starting from tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**7**), which was readily obtained by the bromination of *endo*-2, *exo*-3-diacetoxy-*endo*-6-acetoxymethyl-7-oxabicyclo[2.2.1]-heptane (**4**).[3]

The *exo*-3-acetoxy (**4**), *exo*-3-methoxy (**5**), and *exo*-3-tosyloxy derivatives (**6**) of *endo*-2-acetoxy-*endo*-6-acetoxymethyl-7-oxabicyclo[2.2.1]heptane were prepared in high yields by lithium aluminium hydride (LAH) reduction followed by acetylation of the corresponding lactones (**1**,[3,4] **2**, and **3**). Treatment of **4** with 15% hydrogen bromide in acetic acid in a sealed tube at 75 °C for 24 h led to a cleavage of the anhydro ring to give single crystalline **7** in 70% yield. Under the similar reaction conditions, **5** also gave **7** in 59% yield. The structure of **7** was established on the basis of elemental and ^{1}H NMR analyses, and analogy of the bromination of the corresponding *exo*-3-bromo derivative.[5] Thus, the ^{1}H NMR spectrum contained three singlets (δ 1.99, 2.04, and 2.07) due to the acetoxyl methyl protons and the relatively narrow three-proton multiplet (δ 5.00) due to the protons on the carbon atoms bearing the acetoxyl groups. The one-proton symmetric broad multiplet (δ 3.90) could be attributable to H-4, indicating that the ring bromine atom was in an equatorial position in the favored conformation. The previous results[5] suggested that the anhydro ring of this system would be cleaved by a bromide ion at the carbon atom (C-4) adjacent to the ring methylene group.

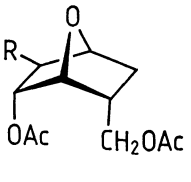
The similar bromination of **6** yielded in 62% yield the sole crystalline dibromo diacetate (**8**) which contained a tosyloxyl function. Reaction of **8** with methanolic sodium methoxide followed by acetylation gave the dibromo epoxy acetate (**12**), which was also derived by the same treatment of 1,2-di-*O*-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol.[5] These results allowed to assign **8** as 1,2-di-*O*-acetyl-3-*O*-tosyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol.

Preferential substitution of the primary bromo substituent of **7** by an acetate or an azide ion was effected by treatment with a slight excess of its sodium salt in aqueous 2-methoxyethanol giving the corresponding 7-acetoxy (**9**, 72%) or 7-azido compounds (**11**, 91%). On the other hand, reaction of **7** and **9** with an excess of sodium azide in *N,N*-dimethylformamide resulted in displacement of the C-4 bromine atom by an azido group *via* S_N2 fashion to give selectively the diazido (**13**, 76%) as crystals and the azido compounds (**14**, 96%) as a syrup, respectively. Catalytic hydrogenation of **14** in the presence of Raney nickel[6] in methanol containing acetic anhydride gave the known penta-*N,O*-acetyl-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (DL-validamine) (**16**)[3,5] in 53% yield. Its 7-amino-7-deoxy derivative (**17**) was obtained by the similar hydrogenation of **13** in 51% yield. These data also confirmed the structure of **13** and **14**.

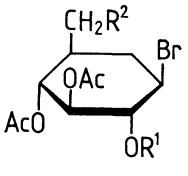
Compound **8** was converted similarly to the corresponding 7-acetoxy derivative (**10**) in 63% yield. On treatment with a slight excess of sodium azide in *N,N*-dimethylformamide **10** gave a syrupy azide tosylate (**15**), which, without further purification, was hydrogenated as described above to the crystalline amide tosylate (**18**) in an over all yield of 35%. In this case, replacement of the C-4 bromine atom by an azide ion seemed to occur faster than that of C-3 tosyloxyl group *via* an anchimeric reaction.[7] Treatment of **18** with methanolic sodium methoxide gave the epoxide, which was directly acetylated by a mixture of acetic anhydride and pyridine followed by the usual work-up giving **16** in 74% yield.



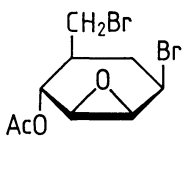
1 R=H
2 R=Me
3 R=Ts



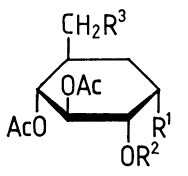
4 R=OAc
5 R=OMe
6 R=OTs



	R^1	R^2
7	Ac	Br
8	Ts	Br
9	Ac	OAc
10	Ts	OAc
11	Ac	N_3



12



	R^1	R^2	R^3
13	N_3	Ac	N_3
14	N_3	Ac	OAc
15	N_3	Ts	OAc
16	NHAc	Ac	OAc
17	NHAc	Ac	NHAc
18	NHAc	Ts	OAc

Experimental

Melting points were measured in a capillary in a liquid bath and are uncorrected. Solutions were evaporated under diminished pressure at 40—50 °C. ^{1}H NMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in $CDCl_3$ with reference to tetramethylsilane as an internal standard and the peak positions are given in δ-values. Values given for coupling constants are of first-order. TLC was performed on silica gel (Wakogel B-10, Wako Pure Chemical Industries, Ltd.). Elemental analyses were performed by Mr. Saburo Nakada, to whom our thanks are due.

exo-9-Methoxy-2,7-dioxatricyclo[4.2.1.0^{4,8}]nonan-3-one (2). A mixture of *exo*-9-hydroxy-2,7-dioxatricyclo[4.2.1.0^{4,8}]nonan-3-one (**1**)[3,4] (5 g), methyl iodide (10 ml), and silver oxide (10 g) in *N,N*-dimethylformamide (20 ml) was vigorously stirred at a room temperature under dark for 20 h. Acetone was added to the reaction mixture, an insoluble material was removed by filtration, and the filtrate was evaporated to give a solid product. Crystallization from ethanol gave **2** (4.2 g, 77%) as needles: mp 85—86 °C; ^{1}H NMR δ 1.86 (1H, dd, $J_{4,5\,endo}$=3 Hz, $J_{5\,gem}$=12.5 Hz, H-5endo), 2.21 (1H, ddd, $J_{4,5exo}$=10 Hz, $J_{5exo,6}$=5 Hz, H-5exo), 2.69 (1H, ddd, $J_{4,8}$=5 Hz, H-4), 3.37 (3H, s, OMe), 3.43 (1H, s, H-9), 4.59 (2H, t, $J_{1,8}$=5 Hz, H-1 and H-6), 5.29 (1H, t, H-8).

Found: C, 56.42; H, 5.92%. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92%.

exo-9-Tosyloxy-2,7-dioxatricyclo[4.2.1.0^{4,8}]nonan-3-one (3). Compound **1** (1 g) was treated with tosyl chloride (2.5 g, 2 mol equiv) in pyridine (5 ml) at a room temperature overnight. The reaction mixture was poured into ice-water, and the precipitates were collected and recrystallized from ethyl acetate to give **3** (1.4 g, 71%) as needles: mp 174—175 °C. ^{1}H NMR δ 2.48 (3H, s, tosyl Me), 4.51 (1H, s, H-9), 4.60 (1H, d, $J_{1,8}$=5 Hz, H-1), 4.77 (1H, d, $J_{5exo,6}$=5 Hz, H-6), 5.33 (1H, t, $J_{4,8}$=5 Hz, H-8).

Found: C, 53.95; H, 4.56; S, 10.06%. Calcd for $C_{14}H_{14}O_6S$: C, 54.18; H, 4.55; S, 10.33%.

endo-2, exo-*3-Diacetoxy*-endo-*6-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (4).* To a stirred mixture of LAH (3 g, 2.5 mol equiv) in dry tetrahydrofuran (THF) (100 ml) was added in several portions pulverized **1** (5 g) under external ice-cooling. The reaction mixture was stirred at this temperature for 15 min and then at a room temperature for 2 h. An excess hydride was destroyed by addition of water (10 ml), and the precipitates were filtered and washed thoroughly with a mixture of acetone and water. The filtrate and washings were combined and evaporated to dryness. The residue was treated with a mixture of acetic anhydride (20 ml) and pyridine (20 ml) at a room temperature overnight. An insoluble material was removed by filtration, and the filtrate was evaporated and co-distilled with toluene to give a syrup, which was dissolved in chloroform and passed through a short alumina column. Evaporation of the solvent gave **4** (8.4 g, 93%) as a practically homogeneous syrup, whose IR and ^{1}H NMR spectra were identical to those of an authentic sample.[3]

endo-*2-Acetoxy*-endo-*6-acetoxymethyl*-exo-*3-methoxy-7-oxabicyclo[2.2.1]heptane (5).* Compound **2** (5 g) was reduced with LAH (1.2 g) in THF (100 ml) similarly as described above and the product was successively acetylated in the usual manner. Crystallization of the crude product from ethyl acetate–hexane gave **5** (5.9 g, 78%) as needles: mp 58—59 °C; ^{1}H NMR δ 1.16 (1H, dd, $J_{5endo,6}$=5 Hz, J_{5gem}=11 Hz, H-5endo), 2.01 (3H, s) and 2.03 (3H, s) (OAc), 3.31 (3H, s, OMe), 3.42 (1H, d, $J_{2,3}$=2 Hz, H-3), 4.22 (2H, dd, C$\underline{H_2}$OAc), 4.48 (1H, d, $J_{4,5exo}$=6 Hz, H-4), 4.60 (1H, t, $J_{1,2}$=$J_{1,6}$=4 Hz, H-1), 4.90 (1H, broad d, H-2).

Found: C, 55.89; H, 6.93%. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03%.

endo-*2-Acetoxy*-endo-*6-acetoxymethyl*-exo-*3-tosyloxy-7-oxabicyclo[2.2.1]heptane (6).* Compound **3** (5 g) was reduced with LAH (0.67 g) in THF (130 ml) similarly as described in the preparation of **4** and the product was acetylated as usual. Crystallization of the crude product from ethyl acetate gave **6** (4.3 g, 67%) as needles: mp 117—118 °C; ^{1}H NMR δ 1.23 (1H, dd, $J_{5endo,6}$=5 Hz, J_{5gem}=12 Hz, H-5endo), 1.94 (3H, s) and 1.99 (3H, s) (OAc), 2.44 (3H, s, tosyl Me), 4.18 (2H, dd, C$\underline{H_2}$OAc).

Found: C, 54.37; H, 5.39; S, 7.88%. Calcd for $C_{18}H_{22}O_8S$: C, 54.26; H, 5.57; S, 8.05%.

Tri-O-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (7). a) A mixture of **4** (2.5 g) and 15% hydrogen bromide in acetic acid (20 ml) was heated in a sealed tube at 75 °C for 24 h. The brown reaction mixture was poured into ice–water (1 l), and the resulting crystals were collected and washed thoroughly with water. The crude crystals were recrystallized from ethanol to give **7** (2.6 g, 70%) as needles or prisms: mp 162—163 °C; ^{1}H NMR δ 1.99 (3H, s), 2.04 (3H, s), and 2.07 (3H, s) (OAc), 3.30 (2H, m, C$\underline{H_2}$Br), 3.90 (1H, m, H-4), 5.00 (3H, m, H-1, H-2, and H-3).

Found: C, 36.37; H, 4.18; Br, 36.95%. Calcd for $C_{13}H_{18}O_6Br_2$: C, 36.30; H, 4.22; Br, 37.16%.

b) Compound **5** (4.5 g) was treated similarly with 15% hydrogen bromide in acetic acid (35 ml) at 80 °C for 50 h, and the reaction mixture was processed as described above. The crude product was crystallized from isopropyl alcohol to give **7** (4.4 g, 59%) as needles: mp 159—161 °C

1,2-Di-O-acetyl-3-O-tosyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (8). Compound **6** (1 g) was treated with 15% hydrogen bromide in acetic acid (6 ml) as described in the preparation of **7**. The product was crystallized from ethanol to give **8** (0.85 g, 62%) as needles: mp 161—163 °C; ^{1}H NMR δ 2.03 (6H, s, OAc), 2.42 (3H, s, tosyl Me), 3.85 (1H, m, H-4).

Found: C, 40.05; H, 4.06%. Calcd for $C_{18}H_{22}O_7Br_2S$: C, 39.87: H, 4.09%.

1-O-Acetyl-2,3-anhydro-(1/2,3,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (12). a) Compound **8** (0.7 g) was dissolved in a mixture of chloroform (3 ml) and methanol (5 ml) and the solution was treated with 1.3 M methanolic sodium methoxide (10 ml) at a room temperature for 3 h. The reaction mixture was evaporated to dryness and the residual product was acetylated in the usual manner. The crude acetyl derivative was crystallized from ethanol to give **12** (0.12 g, 50%) as needles: mp 83—84.5 °C; ^{1}H NMR δ 2.15 (3H, s, OAc), 3.3—3.6 (4H, m, C$\underline{H_2}$Br, H-2, and H-3), 4.43 (1H, m, H-4), 4.93 (1H, m, H-1).

Found: C, 32.85; H, 3.64; Br, 48.84%. Calcd for $C_5H_{12}O_3Br_2$: C, 32.96; H, 3.69; Br, 48.72%.

b) Treatment of di-*O*-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol[5] (1.35 g) with methanolic sodium methoxide as described above gave **12** (0.76 g, 78%), identical with the compound obtained above.

Tetra-O-acetyl-(1,3/2,4,6)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (9). A mixture of **7** (2 g), anhydrous sodium acetate (1.5 g, 3.5 mol equiv), and 90% aqueous 2-methoxyethanol (50 ml) was heated at 80 °C with stirring for 24 h, and evaporated to dryness. The residue was acetylated as usual and the solid product was extracted with chloroform. TLC (1: 15 acetone–benzene, v/v) showed the product to be consist of one major (R_f 0.42) and two minor components (R_f 0.58 and 0.30). The extracts were filtered through a short alumina column and evaporated to give a syrup, which

crystallized from isopropyl alcohol affording **9** (1.4 g, 72%) as needles: mp 119—120 °C; ^{1}H NMR δ 1.97 (3H, s), 2.00 (3H, s), and 2.06 (6H, s) (OAc), 3.8—4.2 (3H, m, C$\underline{H}_2$OAc and H-4), 5.01 (1H, t, $J_{1,2}=J_{1,6}=11$ Hz, H-1), 5.10 (1H, t, $J_{2,3}=J_{3,4}=11$ Hz, H-3), 5.20 (1H, t, H-2).

Found: C, 43.72; H, 5.06; Br, 19.82%. Calcd for $C_{15}H_{21}O_8Br$: C, 44.02; H, 5.17; Br, 19.53%.

1,2,7-Tri-O-*acetyl-3*-O-*tosyl-(1,3/2,4,6)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (**10**).* Compound **8** (1 g) was treated with anhydrous sodium acetate (1.2 g) in 90% aqueous 2-methoxyethanol (50 ml) at 90 °C for 2 days. The reaction mixture was processed similarly and the product was acetylated. Crystallization of the acetate from ethanol gave **10** (0.61 g, 63%) as prisms: mp 179—180 °C; ^{1}H NMR δ 2.04 (6H, s) and 2.08 (3H, s) (OAc), 2.45 (3H, s, tosyl Me), 4.00 (2H, broad s, C$\underline{H}_2$OAc).

Found: C, 45.85; H, 4.76%. Calcd for $C_{20}H_{25}O_9BrS$: C, 46.07; H, 4.83%.

Tri-O-*acetyl-(1,3/2,4,6)-6-azidomethyl-4-bromo-1,2,3-cyclohexanetriol (**11**).* A mixture of **7** (1 g), sodium azide (0.45 g), and 90% aqueous 2-methoxyethanol (15 ml) was heated at 95 °C for 2 h, and evaporated to dryness. The residual solid was acetylated as usual and the crude product was purified by passage through a short alumina column with chloroform. Crystallization from ligroin gave **11** (1.7 g, 91%) as needles: mp 136—138 °C; ^{1}H NMR δ 1.95 (3H, s), 2.01 (3H, s), and 2.03 (3H, s) (OAc), *ca.* 3.3 (2H, m, C$\underline{H}_2N_3$), 3.95 (1H, m, H-4).

Found: C, 39.78; H, 4.67; N, 10.85; Br, 20.66%. Calcd for $C_{13}H_{18}N_3O_6Br$: C, 39.81; H, 4.64; N, 10.71; Br, 20.37%.

Penta-N,O-*acetyl-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (**16**).* A mixture of **9** (3 g), sodium azide (1.9 g), and *N,N*-dimethylformamide (100 ml) was heated at 90 °C for 24 h, and evaporated to dryness. The solid residue was extracted with chloroform and the extracts were filtered through a short alumina column. The filtrate was evaporated to give **14** (2.6 g, 96%) as a homogeneous syrup: IR (neat) 2100 (N_3), 1745 cm^{-1} (ester); ^{1}H NMR δ 2.00 (6H, s) and 2.02 (6H, s) (OAc), 5.01 (1H, dd, $J_{1,2}=9.5$ Hz, $J_{1,6}=5.5$ Hz, H-1), 5.39 (1H, t, $J_{2,3}=9.5$ Hz, H-2).

A solution of the crude **14** (2.8 g) in methanol (50 ml) containing acetic anhydride (2 ml) was hydrogenated in a Parr shaker apparatus in the presence of Raney nickel T-4[6] at hydrogen pressure of 3 kg·cm^{-2} at a room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to give a crystalline residue. Recrystallization from ethanol gave **16** (1.5 g, 53%) as plates: mp 197—198 °C. This compound was identical with an authentic sample[3] in all respects.

Tri-O-*acetyl-(1,3,4/2,6)-4-azido-6-azidomethyl-1,2,3-cyclohexanetriol (**13**).* Compound **7** (1 g) was treated with sodium azide (0.9 g, 6 mol equiv) in *N,N*-dimethylformamide (40 ml) at 85 °C for 20 h. The reaction mixture was processed similarly as described above and the product was acetylated. Crystallization of the crude acetate from ligroin gave **13** (0.62 g, 76%) as prisms: mp 120—121 °C; ^{1}H NMR δ 2.00 (3H, s), 2.05 (3H, s), and 2.07 (3H, s) (OAc), 3.30 (2H, d, $J=4$ Hz, C$\underline{H}_2N_3$), 4.11 (1H, q, $J=3$ Hz, H-4), 4.82 (1H, t, $J_{1,2}=J_{1,6}=9.5$ Hz, H-1), 4.93 (1H, dd, $J_{2,3}=9.5$ Hz, H-3), 5.37 (1H, t, H-2).

Found: C, 44.23; H, 5.18; N, 23.48%. Calcd for $C_{13}H_{18}N_6O_6$: C, 44.06; H, 5.13; N, 23.72%.

Penta-N,O-*acetyl-(1,3,4/2,6)-4-amino-6-aminomethyl-1,2,3-cyclohexanetriol (**17**).* Compound **13** (0.5 g) was hydrogenated similarly as described in the preparation of **16**. The crude product was crystallized from ethyl acetate to give **17** (0.28 g, 51%) as needles: mp 258—259 °C (lit,[4] 246—248 °C). This compound was identified with an authentic sample[3] by comparison with IR and ^{1}H NMR spectra.

1,2,7-Tri-O-*acetyl-3*-O-*tosyl-(1,3,4/2,6)-4-acetamido-6-hydroxymethyl-1,2,3-cyclohexanetriol (**18**).* Compound **10** (1 g) was treated with sodium azide (0.6 g) in *N,N*-dimethylformamide (20 ml) at 85 °C for 24 h. The product was acetylated and purified by chromatography on alumina with chloroform to give the azide (**15**, 0.9 g, 97%) as a practically pure syrup: ^{1}H NMR δ 1.93 (3H, s), 2.00 (3H, s), and 2.06 (3H, s) (OAc), 2.45 (3H, s, tosyl Me).

The crude **15** (0.78 g) was hydrogenated as described in the preparation of **16**. The product was crystallized from ethanol to give **18** (0.28 g, 34% based on **10** used) as needles: mp 157—158 °C; ^{1}H NMR δ 1.90 (3H, s, NAc), 1.96 (3H, s), 2.00 (3H, s), and 2.06 (3H, s) (OAc), 2.54 (3H, s, tosyl Me), 3.96 (2H, narrow m, C$\underline{H}_2$OAc), 6.38 (1H, d, $J=7$ Hz, N$\underline{H}$).

Found: C, 53.05; H, 5.89; N, 2.62; S, 6.57%. Calcd for $C_{22}H_{29}NO_{10}S$: C, 52.90; H, 5.85; N, 2.80; S, 6.42%.

Compound **18** (0.13 g) was treated with methanolic sodium methoxide as described in the preparation of **12**. The product was treated with acetic anhydride (7 ml) and pyridine (7 ml) at 50 °C for 2 h, and the mixture was worked up in the usual manner. The product was crystallized from ethanol to give **16** (0.073 g, 74%) as prisms: mp 194—196 °C, identical with the compound obtained before in all respects.

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References

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7) In the case of tri-*O*-acetyl-(1,3/2,4,6)-3,4-dibromo-6-hydroxymethyl-1,2-cyclohexanediol,[5] the displacement of the C-3 bromine atom by an azide ion *via* neighboring group participation of the C-2 acetoxyl group occurred almost simultaneously to give rise to a diazido compound.