Synthesis of Pseudo-β-DL-galactopyranose and Pseudo-α-DL-altropyranose

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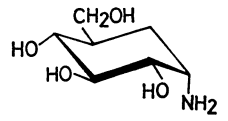
Pseudo-β-DL-galactopyranose and pseudo-α-DL-altropyranose pentaacetates (**10** and **11**) were obtained in a seven step reaction starting from DL-1,2-*O*-cyclohexylidene-5-deoxy-*chiro*-inositol (**2**).

The term "pseudo-sugar" was first given by McCasland and his coworkers[1] to a monosaccharide analog in which a ring oxygen is replaced by a methylene group. In connection with studies on aminocyclitols[2] and inositol derivatives,[3] we have attempted to synthesize validamine (**1**) which is a component of antibiotic validamycin.[4] Validamine has the structure (1*S*)-(1,2,4/3,5)-1-amino-5-hydroxymethyl-2,3,4-cyclohexanetriol[4] which is designated as pseudo-α-D-glucopyranosylamine.[5] It seems that a pseudo-hexopyranose with a proper configuration is the most promising intermediate for a synthesis of **1**.



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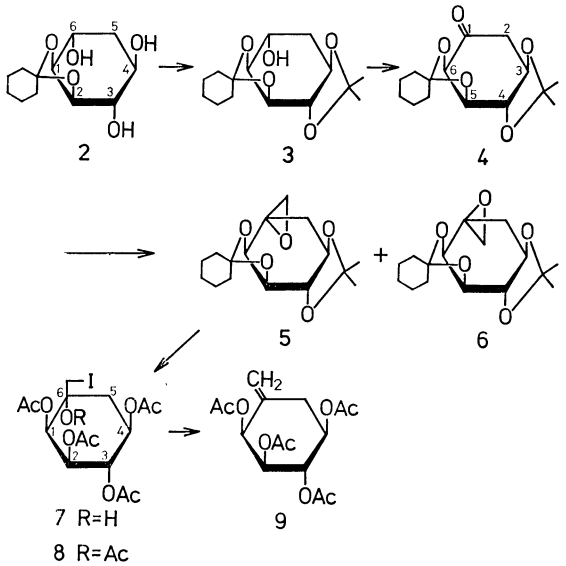
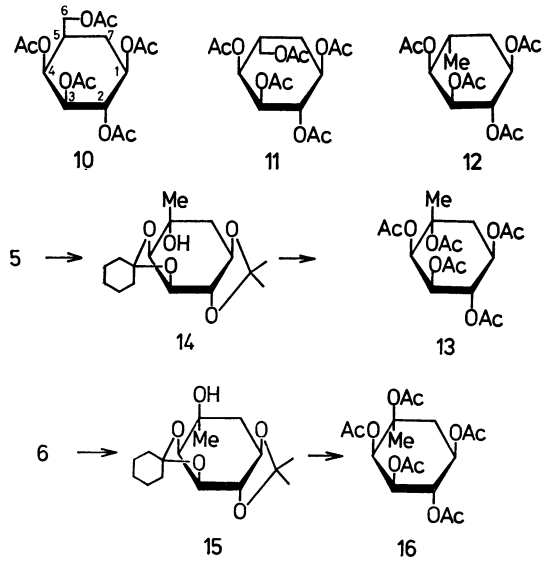
In the present study, DL-1,2-*O*-cyclohexylidene-5-deoxy-*chiro*-inositol (**2**) prepared from *myo*-inositol in four steps[6] was used as the starting material. Compound **2** was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid to give DL-1,2-*O*-cyclohexylidene-5-deoxy-3,4-*O*-isopropylidene-*chiro*-inositol (**3**). Oxidation of **3** in dimethyl sulfoxide–acetic anhydride afforded DL-5,6-*O*-cyclohexylidene-2-deoxy-3,4-*O*-isopropylidene-*chiro*-inosose-1 (**4**) in 74% yield. Compound **4** was treated with diazomethane to give DL-1,1′-anhydro-5,6-*O*-cyclohexylidene-2-deoxy-1-*C*-hydroxymethyl-3,4-*O*-isopropylidene-*chiro*-inositol (**5**) and DL-1,1′-anhydro-2,3-*O*-cyclohexylidene-6-deoxy-1-*C*-hydroxymethyl-4,5-*O*-isopropylidene-*myo*-inositol (**6**) in 82 and 9% yields, respectively.



Compound **5** reacted with hydriodic acid under reaction conditions analogous to those employed by Angyal and his coworkers[7] for the preparation of methylenecyclohexanepentols, to give DL-1,2,3,4,6-penta-*O*-acetyl-5-deoxy-6-*C*-iodomethyl-*chiro*-inositol (**8**). Compound **8** was converted into DL-1,2,3,4-tetra-*O*-acetyl-5,6-dideoxy-6-methylene-*chiro*-inositol (**9**) by refluxing in glacial acetic acid in the presence of zinc powder.

Hydroboration[8] of **9**, followed by oxidation with alkaline hydrogen peroxide and subsequent acetylation afforded pseudo-β-DL-galactopyranose pentaacetate (**10**), pseudo-α-DL-altropyranose pentaacetate (**11**) and DL-1,2,3,4-tetra-*O*-acetyl-(1,3,4/2,5)-5-methyl-1,2,3,4-cyclohexanetetrol (**12**) in 13, 17 and 13% yields, respectively. Besides these compounds, DL-1,2,3,4,5-penta-*O*-acetyl-(1,3,4/2,5)-5-*C*-methyl-1,2,3,4,5-cyclohexanepentol (**13**) was obtained in 6.5% yield, which was identified with an authentic sample prepared by another route (**5**→**14**→**13**). This compound was an epimer of **16** prepared from **6** by an analogous reaction route (**6**→**15**→**16**).

In the above reaction from **9** to **10** and **11**, only two types of pseudo-hexopyranose pentaacetates, *viz.* β-DL-galacto and α-DL-altro type compound, can be obtained. Their PMR spectra were measured to distinguish the two compounds.



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The PMR spectrum of **10** revealed a singlet at δ 2.14 for an axial acetoxy group and three singlets at δ 2.05 (6H), 2.03 (3H) and 1.99 (3H) for three equatorial acetoxy groups[9] and one side chain acetoxy group.

The side chain methylene protons revealed an eight line signal pattern, each proton showing a pair of doublets at δ 4.03 and 3.86 with a geminal coupling of 11 Hz and vicinal couplings of 6 and 8.5 Hz. The ring methylene protons showed multiplets between δ 1.54—2.27 overlapped with a multiplet of the methine proton (H-5).

The ring proton (H-4) revealed its signal at δ 5.50 as a triplet with $J_{3,4}=J_{4,5}=3$ Hz. This was demonstrated on irradiating the H-5 proton (δ 2.3), the triplet collapsing to a doublet ($J_{3,4}=3$ Hz). The small coupling constant indicated the nonexistence of an axial-axial arrangement between H-4 and H-5. The proton H-3 revealed a pair of doublets at δ 4.90 with $J_{3,4}=3$ Hz and $J_{2,3}=10$ Hz, indicating the existence of two vicinal axial protons: H-2 and H-3. The proton H-2 showed a triplet at δ 5.40 with $J_{1,2}=J_{2,3}=10$ Hz. The proton H-1 showed an eight signal pattern centered at δ 4.94 with $J_{1,2}=10$ Hz, $J_{1,7a}=11.5$ Hz and $J_{1,7e}=5$ Hz. The PMR spectral assignment was consistent with the β-DL-galactopyranose pentaacetate, a side-chain equatorial favoring conformation. These spectral assignments are consistent with those of pseudo-α-DL-galactopyranose pentaacetate[1] except for the axial acetoxy group on C-1 in the case of the α-epimer.

The PMR spectrum of **11** revealed five sharp signals for the five acetoxy groups at δ 2.05, 2.06, 2.08, 2.10 and 2.12. These signals could not be attributed to an axial or an equatorial acetoxy methyl proton, owing to a deviation from their typical values.[9] This indicates that there is a rapid ring inversion between two chair conformations. This has also been deduced from the fact that methyl α-altropyranoside exists in two chair conformations: Cl and 1C.[10]

The PMR spectrum of **12** showed a similar signal pattern for the acetoxy methyl protons, suggesting an analogous ring inversion as was observed in the case of **11**. Thus the above described structure was proposed for **12**.

Experimental*

Melting points were determined in a capillary tube in a liquid bath and are uncorrected. PMR spectra were obtained on Varian A-60D (60 MHz) and Varian XL-100 (100 MHz) spectrometers in deuteriochloroform with reference to tetramethylsilane as an internal standard, peak positions being given in δ-values. Values given for coupling constants are of first order. Solutions were evaporated under diminished pressure at 40—50 °C. TLC was performed on silica gel plates (Wakogel B-10, Wako Pure Chemical Industries Ltd.).

DL-*1,2-O-Cyclohexylidene-5-deoxy-3,4-O-isopropylidene*-chiro-*inositol (3).* DL-1,2-*O*-Cyclohexylidene-5-deoxy-*chiro*-inositol[6] (**2**, 3.70 g) was treated with 2,2-dimethoxypropane (37 ml) in *N,N*-dimethylformamide (80 ml) at 85—95 °C for 40 min in the presence of *p*-toluenesulfonic acid (0.1 g). Sodium hydrogencarbonate (0.21 g) was added to the solution and the mixture was evaporated. The residue was extracted with warm ethyl acetate and the solution was evaporated. The residue was recrystallized from hexane to give 3.25 g (76%) of **3**, mp 82—83 °C; PMR: δ 1.42 (s, 6, $2CH_3$), 1.48—1.75 (m, 10, C_6H_{10}), 1.87—2.18 (m, 2, CH_2), 2.60 (s, 1, OH). Found: C, 63.18; H, 8.49%. Calcd for $C_{13}H_{24}O_5$: C, 63.36; H, 8.51%.

DL-*5,6-O-Cyclohexylidene-2-deoxy-3,4-O-isopropylidene*-chiro-*inososе-1 (4).* To a solution of **3** (5.0 g) in dimethyl sulfoxide (100 ml) was added acetic anhydride (15 ml). The reaction mixture was stirred in a refrigerator for 24 h and poured into ice cold sodium hydrogencarbonate solution. The crystalline precipitates were collected and recrystallized from ethanol to give 3.67 g (74%) of **4**, mp 138—139.5 °C; PMR; δ 1.48 (s, 6, $2CH_3$), 1.54—1.80 (m, 10, C_6H_{10}), 2.45 (q, 1, $J_{2a,3}=10.5$ Hz, $J_{gem}=18.0$ Hz, H-2a), 2.99 (q, 1, $J_{2e,3}=7.0$ Hz, H-2e), 3.55 (q, 1, $J_{3,4}=10.5$ Hz, $J_{4,5}=6.5$ Hz, H-4), 4.13 (m, 1, H-3), 4.50 (d, 1, $J_{5,6}=8.0$ Hz, H-6), 4.65 (q, 1, H-5). Found: C, 63.78; H, 7.69%. Calcd for $C_{15}H_{22}O_5$: 63.81; H, 7.85%.

DL-*1,1'-Anhydro-5,6-O-cyclohexylidene-2-deoxy-1-C-hydroxymethyl-3,4-O-isopropylidene*-chiro-*inositol (5) and* DL-*1,1'-anhydro-2,3-O-cyclohexylidene-6-deoxy-1-C-hydroxymethyl-4,5-O-isopropylidene*-myo-*inositol (6).* To an ethereal solution of diazomethane prepared from 50.0 g of nitrosomethylurea was added a solution of **4** (5.0 g) in chloroform (50 ml) under ice-cooling. The reaction solution was settled in a refrigerator for 17 h and evaporated. The crystals were filtered and washed with ethanol to give 484 mg (9%) of **6**, mp 196—197 °C; PMR: δ 1.46 (s, 6, $2CH_3$), 1.52—1.75 (m, 10, C_6H_{10}), 1.70—2.14 (m, 2, H-6a and 6e), 2.40 and 3.12 (dd,2, $J_{gem}=6.5$ Hz, CH_2), 3.66 (m, 1, H-5), 4.08 (q, 1, $J_{3,4}=8.0$ Hz. $J_{4,5}=9.5$ Hz, H-4), 4.30 (d, 1, $J_{2,3}=6.5$ Hz, H-2), 4.41 (q, 1, H-3).

Found: C, 65.10; H, 8.38%. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%.

The filtrate and the ethanol washing were combined and evaporated to give 4.29 g (82%) of crude **5** as a syrup. PMR: δ 1.45 (s, 6, $2CH_3$), 1.51—1.82 (m, 10, C_6H_{10}), 2.08—2.41 (m, 2, H-2a and 2e), 2.81 and 2.95 (dd, 2, $J_{gem}=4.5$ Hz, CH_2), 3.56 (q, 1, $J_{3,4}=9.5$ Hz, $J_{4,5}=8.0$ Hz, H-4), 3.63 (d, 1, $J_{5,6}=6.0$ Hz, H-6), 3.74 (m, 1, H-3), 4.35 (1, 1, H-5).

DL-*1,2,3,4,6-Tetra-O-acetyl-5-deoxy-6-C-iodomethyl*-chiro-*inositol (7).* A 3.5-g portion of crude **5** was added to a saturated solution (25 ml) of sodium iodide containing 2.5 ml of concentrated hydriodic acid, and the mixture was agitated for 48 h. An insoluble matter was removed by filtration, and the filtrate was evaporated to dryness. The residue was acetylated in acetic anhydride (50 ml) with one drop of concentrated sulfric acid for 5 h. The solution was poured into ice-cold water (500 ml) to give 2.62 g (47%) of **7**, mp 209—211 °C; PMR: δ 1.98 (s, 3, OAc), 2.03 (s, 6, 2OAc), 2.15 (s, 3, OAc). Found: C, 38.46; H, 4.32; I, 26.84%. Calcd for $C_{15}H_{21}O_9I$: C, 38.15; H, 4.48; I, 26.87%.

The mother liquor was extracted repeatedly with chloroform and the chloroform solution was evaporated to give a mixture of **7** and **8** (1.96 g).

DL-*1,2,3,4,6-Penta-O-acetyl-5-deoxy-6-C-iodomethyl*-chiro-*inositol (8).* Compound **7** (2.62 g) was acetylated in acetic anhydride with a drop of concentrated sulfuric acid at 40 °C for 1 h, and the mixture was poured into ice cold water (400 ml) to give 2.37 g (83%) of **8**, mp 94—95 °C; PMR: δ 1.98 (s, 3, OAc), 2.03 (s, 6, 2OAc), 2.17 (s, 3, OAc), 2.21 (s, 3, OAc), 2.24—3.12 (m, 2, H-5a and 5e), 3.61 and 3.92 (dd, 2, $J_{gem}=11.5$ Hz, CH_2). Found: C, 39.91; H, 4.69; I, 24.52%. Calcd for $C_{17}H_{23}O_{10}I$: C, 39.90; H, 4.51; I, 24.68%.

Compound **8** (1.30 g) was obtained from a mixture of **7** and **8** (1.96 g) by the same procedure.

* Elemental analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

DL-*1, 2, 3, 4-Tetra-*O*-acetyl-5, 6-dideoxy-6-methylene*-chiro-*inositol* (**9**). A 3.0-g portion of **8** was heated in glacial acetic acid (40 ml) with zinc powder (25 g) under reflux for 1 h. The mixture was filtered and the filtrate was evaporated to give 1.2 g of crude **9**. The insoluble matter obtained by filtration was extracted twice with warm ethyl acetate and the ethyl acetate solution was evaporated to give another crop of **9**. Recrystallization from ethanol–hexane gave 1.44 g (75%) of **9**, mp 93—94 °C; PMR: δ 1.99 (s, 3, OAc), 2.01 (s, 3, OAc), 2.02 (s, 3, OAc), 2.10 (s, 3, OAc), 2.43—2.70 (m, 2, H-5a and 5e), 4.82 (m, 1, $J_{3,4}$=10 Hz, $J_{4,5a}$=10.5 Hz, $J_{4,5e}$=7.0 Hz, H-4), 4.86 (q, 1, $J_{1,2}$=3.5 Hz, $J_{2,3}$=10 Hz, H-2), 5.19 and 5.29 (dd, 2, J_{gem}=1.0 Hz, CH_2), 5.35 (t, 1, H-3), 5.65 (d, 1, H-1). Found: C, 54.91; H, 6.14%. Calcd for $C_{15}H_{20}O_8$: C, 54.88; H, 6.14%.

*Pseudo-β-*DL*-galactopyranose Pentaacetate* (**10**) *and Pseudo-α-*DL*-altropyranose Pentaacetate* (**11**). Sodium tetrahydroborate (0.24 g) was added to a solution of **9** (0.60 g) in tetrahydrofuran (15 ml). A solution of freshly distilled boron trifluoride etherate (2.4 ml) in tetrahydrofuran (4.8 ml) was slowly added to the mixture. After the mixture was agitated for 4 h at 25 °C, 50% aqueous tetrahydrofuran (5.0 ml) was added. Then 3M sodium hydroxide (6 ml) and 30% hydrogenperoxide (3.0 ml) were added to the mixture. The mixture was agitated for 1 h at 35 °C and evaporated to dryness. The residue was acetylated in acetic anhydride (20 ml) with a drop of concentrated sulfuric acid overnight and the reaction solution was poured into ice cold water. The aqueous solution was extracted repeatedly with chloroform and the combined chloroform solution was evaporated. The residue was fractionated on a silica gel (Wakogel C-300, 40 g) column in 2-butanone–toluene (1:7, v/v). Fractions which showed a single spot at R_f 0.50 on TLC in 2-butanone–toluene (1:4, v/v) were combined and evaporated to give 93 mg (13%) of **10**, mp 123—124 °C; PMR: δ 1.99 (s, 3, OAc), 2.03 (s, 3, OAc), 2.05 (s, 6, 2OAc), 2.14 (s, 3, OAc), 3.86 (q, 1, $J_{5,6}$=6.0 Hz, J_{gem}=11.0 Hz, H-6), 4.03 (q, 1, $J_{5,6'}$=8.5 Hz, J_{gem}=11.0 Hz, H-6'), 4.90 (q, 1, $J_{2,3}$=10.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 4.94 (qd, 1, $J_{1,7a}$=11.5 Hz, $J_{1,7e}$=5.0 Hz, $J_{1,2}$=10.0 Hz, H-1), 5.40 (t, 1, H-2), 5.50 (t, 1, $J_{4,5}$=3.0 Hz, H-4). Found: C, 52.52; H, 6.24%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.

Fractions showing a single spot at R_f 0.47 on TLC in the same solvent were combined and evaporated to give 119 mg (17%) of **11**, mp 115—116 °C; PMR: δ 2.05 (s, 3, OAc), 2.06 (s, 3, OAc), 2.08 (s, 3, OAc), 2.10 (s, 3, OAc), 2.12 (s, 3, OAc), 2.38 (m, 1, H-5), 4.16 (d, 2, $J_{5,6}$=6.0 Hz, H-6 and 6'). Found: C, 52.87; H, 6.29%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.

DL-2,3,4,5-Tetra-*O*-acetyl-(2,3,5/1,4)-1-methyl-2,3,4,5-cyclohexanetetrol (**12**, 77 mg, 13%), mp 111—112 °C, was obtained from fractions showing a single spot at R_f 0.60 on TLC. PMR: δ 0.96 (d, 3, J=6.0 Hz, CH_3), 1.45 (m, 2, CH_2), 1.97 (s, 3, OAc), 1.99 (s, 3, OAc), 2.00 (s, 3, OAc), 2.02 (s, 3, OAc). Found: C, 54.37; H, 6.73%. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71%.

From fractions showing a single spot at R_f 0.55 on TLC, DL-1,2,3,4,5-penta-*O*-acetyl-2-deoxy-1-*C*-methyl-*chiro*-inositol (**13**) was obtained as a syrup (46 mg, 6.5%), which was identified with an authentic sample prepared by the following reactions.

DL-*5, 6-*O*-Cyclohexylidene-2-deoxy-3, 4-*O*-isopropylidene-1-*C*-methyl*-chiro-*inositol* (**14**). To a solution of compound **5** (516 mg) in tetrahydrofuran (14 ml) was added lithium aluminum hydride (0.3 g). The mixture was heated under reflux for 1.5 h and then cold water (3 ml) was added to the iced reaction mixture. The mixture was filtered and the filtrate was evaporated. The residue was recrystallized from hexane to give 228 mg (44%) of **14**, mp 113—114 °C. PMR: δ 1.40 (s, 6, $2CH_3$), 1.44 (s, 3, CH_3 at C-1), 1.50—1.75 (m, 10, C_6H_{10}), 2.00 (s, 1, OH), 3.43 (q, 1, $J_{3,4}$=10.5 Hz, $J_{4,5}$=9.0 Hz, H-4), 3.81 (td, 1, $J_{2a,3}$=$J_{3,4}$=10.5 Hz, $J_{4,5}$=9.0 Hz, H-3), 3.90 (d, 1, $J_{5,6}$=5.0 Hz, H-6), 4.31 (q, 1, H-5). Found: C, 64.12; H, 8.56%. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

DL-*1, 3, 4, 5, 6-Penta-*O*-acetyl-2-deoxy-1-*C*-methyl*-chiro-*inositol* (**13**). Compound **14** (120 mg) was heated in 80% aqueous acetic acid (10 ml) under reflux for 19 h. The solution was evaporated and the residue was acetylated with acetic anhydride and pyridine at 80—90 °C for 20 h. The acetate was purified on a silica gel column in 2-butanone–toluene (1:8 v/v). Fractions showing a single spot at R_f 0.38 on TLC in 2-butanone–toluene (1:6, v/v) were combined and evaporated to give 87 mg (56%) of **13** as a colorless syrup. PMR: δ 1.50 (s, 3, CH_3 at C-1), 1.96 (s, 3, OAc), 2.00 (s, 6, 2OAc), 2.11 (s, 3, OAc), 2.15 (s, 3, OAc), 2.22—2.91 (m, 2, CH_2 at C-2), 4.79—5.56 (m, 4, ring protons). Found: C, 52.86; H, 6.27%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.

DL-*2, 3-*O*-Cyclohexylidene-6-deoxy-4, 5-*O*-isopropylidene-1-*C*-methyl*-myo-*inositol* (**15**). Compound **6** (600 mg) was treated with lithium aluminum hydride (0.37 g) in tetrahydrofuran (25 ml) as in the preparation of **14**, to give 567 mg (94%) of **15** as an amorphous solid, mp 86—88 °C. PMR: δ 1.30 (s, 3, CH_3 at C-1), 1.41 (s, 6, $2CH_3$), 1.51—1.80 (m, 10, C_6H_{10}). Found: C, 64.72; H, 8.67%. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

DL-*1, 2, 3, 4, 5-Penta-*O*-acetyl-6-deoxy-1-*C*-methyl*-myo-*inositol* (**16**). Compound **15** (560 mg) was heated in 80% aqueous acetic acid (20 ml) under reflux for 20 h. The solution was evaporated and the residue was acetylated. The acetate was purified on a silica gel column in 2-butanone–toluene (1:8, v/v). Fractions showing a single spot at R_f 0.32 on TLC in 2-butanone–toluene (1:6, v/v) were combined and evaporated to give 407 mg (56%) of **16** as a syrup. PMR: δ 1.69 (s, 3, CH_3 at C-1), 1.94 (s, 3, OAc), 1.99 (s, 6, 2OAc), 2.03 (s, 3, OAc), 2.15 (s, 3, OAc), 2.25—2.56 (m, 2, CH_2 at C-6), 4.76—5.55 (m, 4, ring protons). Found: C, 52.82; H, 6.35%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.

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