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Note

Synthesis of 2,3-*O*-isopropylidene- and 3-*O*-benzoyl-2-*O*-benzyl-2-*C*-methyl-L-glyceraldehyde

MASANORI YAMAURA, TSUNEJI SUZUKI, YUJI TAGAMI, HIRONOBU HASHIMOTO*, AND JUJI YOSHIMURA
Department of Life Science, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama, 227 (Japan)

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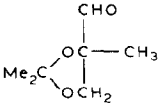
2-*C*-Methylglyceraldehyde derivatives are among the simplest branched-chain chiral synthons and both the (*R*)-enantiomer and the (*S*)-enantiomer (**1**) of the corresponding 2,3-*O*-isopropylidene derivative were used for the synthesis of such natural products as vitamin E (ref. 1) and bicyclomycin[2], respectively. The synthon **1** (ref. 3) was recently prepared from 2-methyl-2-propan-1-ol *via* Sharpless asymmetric epoxidation, and the pure (*R*)-enantiomer[3] of **1** was derived *via* optical resolution of ethyl 2-(benzyloxy)-2-methylmalonate. On the other hand, we had synthesized[4] 2,3-di-*O*-benzyl-2-*C*-methyl-L-glyceraldehyde (**2**) from D-glucose.



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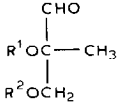

2 $R^1 = R^2 = Bn$

3 $R^1 = Bn, R^2 = Bz$

Bn = PhCH
Bz = PhCO

The synthesis of the optically pure synthon **1** and of a new synthon, *i.e.*, the 3-*O*-benzoyl-2-*O*-benzyl derivative **3**, is now described, together with an interesting 1→4 *O*-benzoyl migration occurring during reduction with sodium borohydride.

As a starting material for the synthesis of **1** was used 4-*O*-benzoyl-2-*O*-benzyl-2-*C*-methyl-D-erythritol[4] (**4**), which was obtained in 76% yield from 5-*O*-benzoyl-3-*O*-benzyl-3-*C*-methyl-D-ribofuranose by periodate oxidation and successive reduction of the branched tetrose **8** with sodium borohydride in methanol at† 0°. The

*To whom correspondence should be addressed.
†The temperature reported in ref. 4 must be revised.

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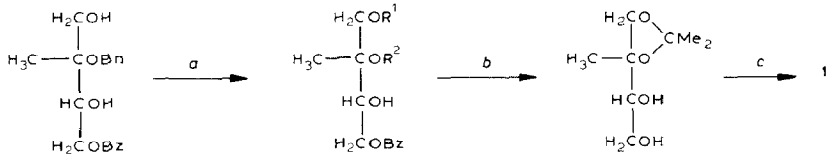
O-debenzylated derivative (**5**) of **4** was acetalated with 2-methoxypropene and pyridinium *p*-toluenesulfonate to give the 1,2-*O*-isopropylidene derivative **6**, and a mixture of the corresponding 1,3- and 2,3-acetals in 59 and 38% yield, respectively. The latter mixture could be separated after acetylation, to give the unreacted 1,3-acetal and 1-*O*-acetyl-2,3-acetal in 45 and 51% yield, respectively. The *O*-debenzoylated derivative (**7**) of **6** was oxidized with periodate to give **1** in 67% yield.



4 5 $R^1 = R^2 = H$ 6 $R^1, R^2 = Me_2C$ 7

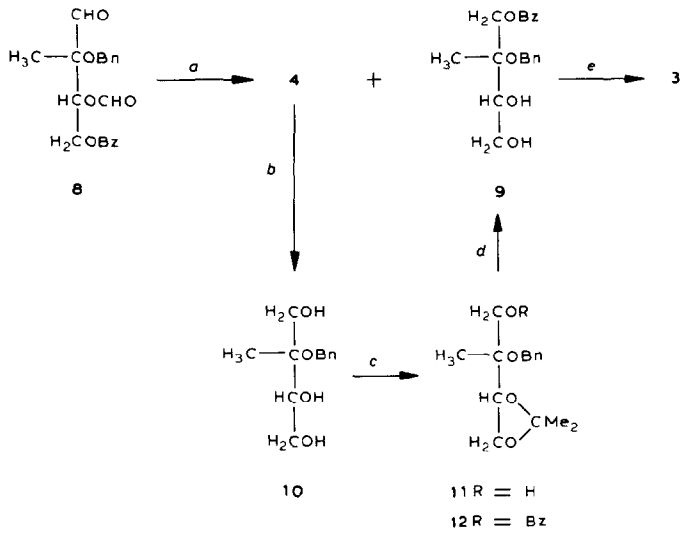
(*a*) H_2, Pd–C–EtOH; 5 ⟶ 6 : $Me_2C(OMe)_2$, PPTS/acetone,

(*b*) NaOMe–MeOH, (*c*) $NaIO_4$–MeOH–H_2O.

In the preparation of **4**, it was found that the aforementioned reduction of **8** for 93 h at ambient temperature gave the *O*-debenzoylated derivative **10** exclusively. It is noteworthy that, after 3 h under the same conditions the 1-*O*-benzoyl derivative **9** was obtained in 38% yield, together with the expected 4-*O*-benzoyl derivative **4** (37%). After 6 h, the ratio of **4** to **9** remained unchanged, indicating an equilibrium between **4** and **9** *via* *O*-benzoyl migration. Because this 1⟶4-migration *via* a 7-membered-ring intermediate was not observed under general basic conditions, such as M sodium hydroxide, pyridine, and triethylamine, participation of the sodium borohydride may be considered. In addition to ^1H-n.m.r. data, the structure of **9** was further confirmed by the following chemical conversions. Treatment of **10** (ref. 4) with acetone–sulfuric acid gave the 3,4-*O*-isopropylidene derivative **11** in 70% yield, and its 1-benzoate **12** was converted into **9** by acid hydrolysis. In the latter step, reaction with 70% acetic acid at room temperature gave **9** in 76% yield, together with a small proportion of the benzoyl-migrated product **4**, the yield of which increased at a higher reaction temperature. Finally, oxidative cleavage of **9** with periodate gave another new chiral synthon, **3**, in 96% yield.

EXPERIMENTAL

General methods. — Melting points were measured with a Mel-Temp apparatus, and are uncorrected. Optical rotations were measured on either a Carl Zeiss LEP-Al or a JASCO DIP-4 polarimeter. Chromatography was performed on



(*a*) $NaBH_4$–MeOH–H_2O, (*b*) NaOMe–MeOH, (*c*) acetone, H_2SO_4; **11** → **12**: BzCl–pyridine, (*d*) 70% AcOH, (*e*) $NaIO_4$–MeOH–H_2O.

Wakogel C-200 (Wako Pure Chem. Ind.), flash chromatography on either Wakogel C-300 or Kieselgel 60 (230–400 mesh, Merck), and thin-layer chromatography on Kieselgel 60. I.r. spectra were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H-N.m.r. spectra were recorded at 100 MHz with a JEOL JMN PS-100 spectrometer, with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C-N.m.r. spectra were recorded at 22.6 MHz with a JEOL FX-90Q spectrometer. Chemical shifts are reported in p.p.m. downfield from internal Me_4Si.

*2,3-O-Isopropylidene-2-C-methyl-*L*-glyceraldehyde* (**1**). — A mixture of **7** (630 mg, 3.58 mmol) and sodium periodate (800 mg, 3.74 mmol) in methanol (20 mL) and water (20 mL) was sonicated for 10 min, and further stirred for 20 min at room temperature. Crystalline materials were filtered off, and washed with a small amount of ether. The filtrate was mixed with water (50 mL) and extracted with ether. The extract was washed with saturated, aqueous NaCl solution, dried, and evaporated at the normal pressure, and the syrupy residue was distilled to give **1** (369 mg, 72%), b.p. 50–53°/4.27 kPa; $[\alpha]_D^{25}$ −7.0° (*c* 1.0, MeOH), $[\alpha]_D^{25}$ −13.3° (*c* 0.1, $CHCl_3$); ν_{max}^{NaCl} 1725 cm^{-1}; ^{1}H-n.m.r.: δ 9.64 (s, H-1), 3.75 and 4.27 (ABq, 2 H, *J* 9.0 Hz, H-3), 1.36 (s, 3 H, CMe), and 1.47 (s, 6 H, CMe_2); ^{13}C-n.m.r.: δ 202.1 (d, C-1), 111.3 (s, CMe_2), 86.6 (s, C-2), 70.9 (t, C-3), 26.8 and 26.4 (each q, C*Me*), and 19.3 (q, C*Me*).

Anal. Calc. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.27; H, 8.34.

*3-O-Benzoyl-2-O-benzyl-2-C-methyl-*L*-glyceraldehyde* (**3**). — Compound **9** (485 mg, 1.47 mmol) and sodium periodate (377 mg, 1.76 mmol) were dissolved in 1:1 methanol–water (80 mL). After stirring for 3 h, methanol was evaporated. The aqueous solution was diluted with water and extracted with CH_2Cl_2. The syrupy

residue obtained by the usual workup of the extract was purified on a column of silica gel with 3:1 hexane–ethyl acetate, to give **3** as a syrup (425 mg, 96%); $[\alpha]_D^{22}$ +6.0° (*c* 0.5, $CHCl_3$); ν_{max}^{NaCl} 1740 and 1725 cm^{-1}; ^{1}H-n.m.r.: δ 9.79 (s, H-1), 8.1–8.0 and 7.6–7.3 (m, 5 H, Bz), 7.37 (s, 5 H, CH_2Ph), 4.68 and 4.51 (ABq, 2 H, *J* 6.0 Hz, H-3), 4.65 (s, 2 H, CH_2Ph), and 1.46 (s, Me); ^{13}C-n.m.r.: δ 202.1 (d, C-1), 165.8 (s, CO), 137.8 (s, Ph), 133.2, 129.7, 128.5, 127.9, and 127.5 (each d, Ph), 81.6 (s, C-2), 66.5 and 65.3 (each t, C-3 and CH_2Ph), and 16.7 (q, C*Me*).

Anal. Calc. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.23; H, 6.04.

$NaBH_4$ reduction of **8** *at room temperature.* — To a solution of **8** (ref. 4; 32.8 g, 92 mmol) in 2:1 methanol–water (450 mL) was added sodium borohydride (19 g, 0.5 mol) at 0°. The solution was for 3 h kept at room temperature, made neutral with 0.1M hydrochloric acid, concentrated to half volume, and then extracted with chloroform. The residue obtained by evaporation of the extract was fractionated on a column with ethyl acetate–hexane (4:1→1:0), to give **4** (12.2 g, 37%), **9** (12.4 g, 37.5%), and **10** (1.8 g, 8.2%). Compounds **4** and **10** were identified by their ^{1}H-n.m.r. spectra in comparison with those reported previously[4]. Compound **9** had $[\alpha]_D^{15}$ +4.0° (*c* 1.0, MeOH); ^{1}H-n.m.r.: δ 8.1–7.9 and 7.6–7.3 (m, 5 H, Bz), 7.29 (s, 5 H, Ph), 4.57 and 4.49 (each s, 4 H, 2 H-1 and CH_2Ph), 3.96–3.50 (m, 3 H, H-3,4), and 1.35 (s, CMe); ^{13}C-n.m.r.: δ 155.7 (s, CO), 131.1 (s, Ph), 126.3, 123.3, 123.2, 122.1, 122.0, and 121.1 (each d, Ph), 78.1 (s, C-2), 73.6 (d, C-3), 66.4, 65.8 and 64.1 (each t, C-1, C-4, and CH_2Ph), and 22.6 (q, C*Me*).

Anal. Calc. for $C_{19}H_{22}O_5$: C, 67.09; H, 6.71. Found: C, 67.03; H, 6.79.

*4-O-Benzoyl-2-C-methyl-*D*-erythritol* (**5**). — Compound **4** (ref. 4; 1.5 g, 4.55 mmol) was hydrogenolyzed in ethanol (60 mL) in the presence of 10% palladium-on-charcoal (150 mg) and acetic acid (1 drop) for 24 h at room temperature. The solid residue obtained by the usual workup was recrystallized from ethanol, to give **5** in 96% yield (1.05 g); m.p. 116–117° (prisms, EtOH), $[\alpha]_D^{25}$ +26.5° (*c* 1.0, MeOH); ν_{max}^{KBr} 3440 and 1700 cm^{-1}; ^{1}H-n.m.r. (CD_3OD): δ 8.2–8.0 and 7.8-7.3 (m, 5 H, Bz), 4.0–3.4 (m, 5 H, 2 H-1,3,4), and 1.17 (s, CMe).

Anal. Calc. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.91; H, 6.63.

*4-O-Benzoyl-1,2-O-isopropylidene-2-C-methyl-*D*-erythritol* (**6**). — To a solution of **5** (640 mg, 2.67 mmol) in dry acetone (30 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) and then, dropwise at −30°, a solution of 2-methoxypropene (2.0 mL, 17 mmol) in acetone (10 mL). The temperature was maintained for 5 h, and then gradually raised to room temperature. After 2 h, the solution was poured into ice–water and extracted with ethyl acetate. The extract was successively washed with saturated $NaHCO_3$ and NaCl solution, dried, and evaporated. The syrupy residue was fractionated on a column with 7:3 hexane–ethyl acetate, to give **6** (611 mg, 82%) and a mixture of the corresponding 1,2- and 1,3-acetals (108 mg, 15%). Compound **6** had m.p. 65–67° (needles, cyclohexane), $[\alpha]_D^{25}$ −4.1° (*c* 1.1, $CHCl_3$), $[\alpha]_D^{25}$ −4.3° (*c* 2.0, MeOH); ^{1}H-n.m.r.: δ 8.2–8.0 and 7.7–7.3 (m, 5 H, Bz), 4.61 (dd, H-4b), 4.37 (dd, $J_{4a,4b}$ 11.5 Hz, H-4a), 4.22 and 3.74 (ABq, 2 H, *J* 8.5 Hz, H-1), 3.96 (dd, $J_{3,4a}$ 3.0, $J_{3,4b}$ 7.0 Hz, H-3), 2.9 (bs, OH), and

1.37 (s, CMe); ^{13}C-n.m.r.: δ 167.0 (s, CO), 133.1, 129.6 and 128.4 (each d, Ph), 129.8 (s, Ph), 109.6 (s, CMe_2), 81.9 (s, C-2), 73.6 (d, C-3), 72.0 and 66.2 (each t, C-1 and C-4), 27.0 and 26.9 (each q, CMe_2), and 20.5 (q, C*Me*).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.23.

The same acetalation carried out in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid (instead of PPTS) for 10 h at 0° gave **6** and a mixture of the 1,3- and 2,3-acetals in 59 and 38% yield, respectively. Furthermore, this mixture (360 mg, 150 mmol) was separated after treatment with acetic anhydride (0.4 mL) in pyridine (5 mL) for 1 h at room temperature. The usual workup, and flash chromatography with hexane–ethyl acetate (4:1→1:1) gave the 1,3-acetal (163 mg, 45%) and the 1-*O*-acetyl-2,3-acetal (248 mg, 51%), $[\alpha]_D^{15}$ +51.8° (*c* 1.0, MeOH).

4-O-Benzoyl-1,3-O-isopropylidene-2-C-methyl-D-erythritol had ^{1}H-n.m.r.: δ 8.2–8.0 and 7.7–7.4 (m, 5 H, Bz), 4.72 and 4.35 (each q, 2 H, $J_{4a,4b}$ 11.6 Hz, H-4), 4.15 (q, $J_{3,4a}$ 2.0, $J_{3,4b}$ 8.0 Hz, H-3), 3.80 and 3.56 (ABq, 2 H, *J* 11.8 Hz, H-1), 3.24 (bs, OH), 1.50 and 1.44 (each s, CMe_2), and 1.38 (s, CMe); ^{13}C-n.m.r.: δ 166.8 (s, CO), 133.0 (s, Ph), 130.0, 129.9, and 128.3 (each d, Ph), 99.4 (s, CMe_2), 74.8 (d, C-3), 70.9 and 64.0 (each t, C-1,4), 67.1 (s, C-2), 28.5 (q, C*Me*), and 19.5 and 19.3 (each q, CMe_2).

1-O-Acetyl-4-O-benzoyl-2,3-O-isopropylidene-2-C-methyl-D-erythritol had ^{1}H-n.m.r.: δ 8.3–8.0 and 7.8–7.3 (m, 5 H, Bz), 4.62 and 4.30 (each dd, $J_{4a,4b}$ 12.0 Hz, H-4), 4.56 (t, $J_{3,4a} = J_{3,4b}$ 6.0 Hz, H-3), 4.13 and 4.09 (ABq, 2 H, *J* 11.2 Hz, H-1), 2.06 (s, Ac), 1.48 (s, CMe), and 1.44 (s, 6 H, CMe_2); ^{13}C-n.m.r.: δ 170.9 (s, Ac), 165.9 (s, CO), 133.1 (s, Ph), 129.6 and 128.4 (each d, Ph), 108.1 (s, CMe_2), 80.6 (d, C-3), 80.0 (s, C-2), 65.6 and 62.2 (each t, C-1,4), 28.1 (q, Ac), 26.6 (s, C*Me*), and 22.2 and 20.7 (each q, CMe_2).

1,2-O-Isopropylidene-2-C-methyl-D-erythritol (**7**). — To a solution of **6** (300 mg, 1.07 mmol) in absolute methanol (8 mL) was added 0.1M NaOMe (0.5 mL) at room temperature. The solution was kept for 30 min, made neutral with Amberlite IR-45 ion-exchange resin, and the residue obtained by evaporation of the filtrate was purified on a column of silica gel with hexane–ethyl acetate (1:1→1:3), to give **7** (175 mg, 93%); $[\alpha]_D^{15}$ +7.6° (*c* 1.5, MeOH); ^{1}H-n.m.r.: δ 4.12 and 3.70 (ABq, 2 H, *J* 9.0 Hz, H-1), 3.9–3.4 (m, 5 H, H-3,4 and 2 HO), 1.41 (s, 6 H, CMe), and 1.29 (s, CMe).

Anal. Calc. for $C_8H_{16}O_4$: C, 54.33; H, 9.15. Found: C, 54.37; H, 9.06.

2-O-Benzyl-3,4-O-isopropylidene-2-C-methyl-D-erythritol (**11**). — To a solution of **10** (5.5 g, 24.3 mmol) in dry acetone (60 mL) was added a solution of conc. sulfuric acid (1 mL) in acetone (20 mL). After 2 days at room temperature, the usual workup followed by chromatography on a column of silica gel with 8:1 benzene–acetone gave **11** as a syrup which crystallized in a refrigerator; m.p. 42–43° (prisms, methanol–hexane), $[\alpha]_D^{22}$ +13.2° (*c* 1.0, $CHCl_3$), ^{1}H-n.m.r.: δ 7.3 (m, 5 H, Ph), 4.62 and 4.56 (ABq, *J* 11.0 Hz, CH_2Ph), 4.26 (dd, $J_{3,4a}$ 6.0, $J_{4a,4b}$ 7.6 Hz, H-4a), 4.1–3.9 (m, 2 H, H-3,4b), 3.65 (s, 2 H, H-1), 2.21 (bs, OH), 1.45 (s, CMe), and 1.35 and 1.24 (each s, CMe_2).

Anal. Calc. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.86; H, 8.44.

*1-O-Benzoyl-2-O-benzyl-3,4-O-isopropylidene-2-C-methyl-*D*-erythritol* (**12**). — Compound **11** (778 mg, 2.92 mmol) was treated with benzoyl chloride (500 mg, 3.50 mmol) in pyridine (4 mL), and the syrupy product obtained by the usual workup was purified on a column of silica gel with 7:3 hexane–ethyl acetate, to give **12** (1.06 g, 99%); $[\alpha]_D^{15}$ −4.3° (*c* 2.0, MeOH); ^{1}H-n.m.r.: δ 8.3–8.0 and 7.7–7.4 (m, 5 H, Bz), 7.30 (s, 5 H, Ph), 4.64 and 4.30 (ABq, *J* 12.0 Hz, H-1), 4.64 (s, CH_2Ph), 4.37 (A part of AB_2, H-3), 4.12 (B part of AB_2, *J* 8.7 Hz, H-4), 1.46 (s, Me), and 1.31 (s, 6 H, 2 Me); ^{13}C-n.m.r.: δ 166.1 (s, CO), 138.9 (s, Ph), 130.3, 129.6, 128.4, 128.2, and 127.2 (each d, Ph), 109.4 (s, CMe_2), 77.5 (d, C-3), 77.0 (s, C-2), 65.9, 65.1, and 65.0 (each t, C-1,4 and CH_2Ph), 26.2 and 24.7 (each q, CMe_2), and 15.3 (q, C*Me*).

Anal. Calc. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.47; H, 7.01.

O-Deisopropylidenation of **12**. — *Method A.* A solution of **12** (700 mg, 1.9 mmol) in 70% acetic acid (10 mL) was kept for 30 h at room temperature, diluted with water, and extracted with chloroform. The crude product obtained by the usual workup of the extract was purified by flash chromatography with 7:3 hexane–ethyl acetate, to give **9** (475 mg, 76%), whose ^{1}H-n.m.r. data were identical with those reported[4].

Method B. A solution of **12** (2.4 g, 6.48 mmol) in 70% acetic acid (30 mL) was heated for 3 h at reflux temperature. The same workup as in A gave **9** (1.17 g, 55%), **4** (0.63 g, 12%), and 4-*O*-acetyl-1-*O*-benzoyl-2-*O*-benzyl-2-*C*-methyl-D-erythritol (0.25 g, 26%). The last compound was characterized by the following data: ^{1}H-n.m.r.: δ 8.2–8.0 (m, 2 H, Bz), 7.7–7.1 (m, 8 H, CH_2*Ph* and part of Bz), 4.61 and 4.56 (each s, H-1 and CH_2Ph), 4.6–4.0 (m, H-3,4), 3.2 (bd, OH), 2.05 (s, Ac), and 1.36 (s, CMe); ^{13}C-n.m.r.: δ 171.4 (s, Ac), 166.4 (s, CO), 138.4 (s, Ph), 133.1, 129.7, 128.4, 128.3, and 121.4 (each d, Ph), 77.9 (s, C-2), 71.7 (d, C-3), 65.7 (t, C-4), 64.7 (t, C-1 and CH_2Ph), 20.8 (q, Ac), and 15.1 (q, C*Me*); and further as the corresponding 3,4-diacetate, ^{1}H-n.m.r.: δ 8.2–7.9 and 7.6–7.2 (m, 5 H, Bz), 7.28 (s, 5 H, Ph), 5.54 (dd, $J_{3,4a}$ 2.5, $J_{3,4b}$ 8.0 Hz, H-3), 4.60 and 4.23 (ddd, *J* 12.0 Hz, H-4), 4.54 and 4.38 (ABq, *J* 12.0 Hz, H-1), 2.09 and 2.03 (each s, Ac), and 1.40 (s, CMe); ^{13}C-n.m.r.: δ 170.6 and 170.0 (each s, Ac), 166.0 (s, CO), 138.3 (s, Ph), 133.1, 129.7, 128.5, 128.3, 127.4, and 127.3 (each d, Ph), 77.7 (s, C-2), 71.7 (d, C-3), 64.8 (t, 2 C, C-1,4), 62.9 (t, CH_2Ph), 20.8 and 20.7 (each q, Ac), and 16.7 (q, C*Me*).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.59; H, 6.38.

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