A Novel Synthesis of a Branched-chain Amino Sugar, Methyl 2-Amino-2,3-dideoxy-3-*C*-formyl-α-D-xylofuranoside-3′*R*,5-hemiacetal

Kuniaki TATSUTA,* Satoru MIYASHITA, Kohji AKIMOTO, and Mitsuhiro KINOSHITA
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223
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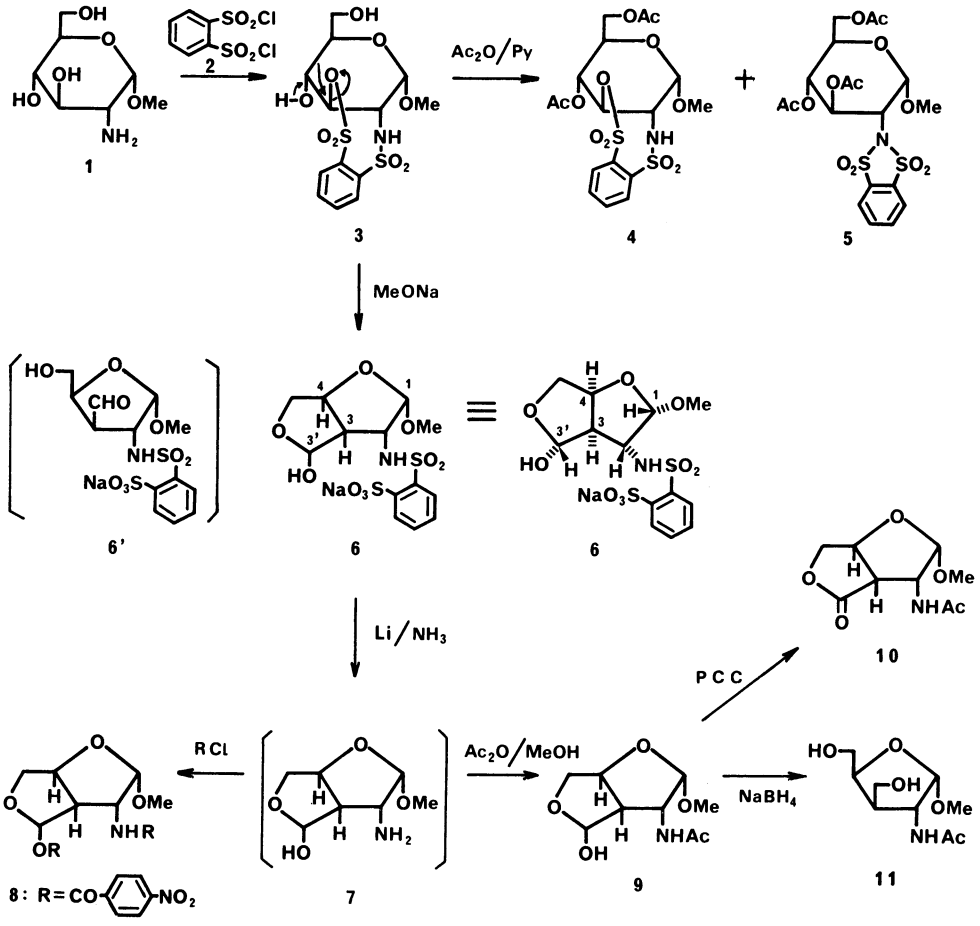
Methyl 2-amino-2*N*,3*O*-(*o*-benzenedisulfonyl)-2-deoxy-α-D-glucopyranoside, which was prepared from methyl 2-amino-2-deoxy-α-D-glucopyranoside and *o*-benzenedisulfonyl dichloride, was treated with sodium methoxide to afford exclusively a branched-chain amino sugar, methyl 2,3-dideoxy-3-*C*-formyl-2-(*o*-sulfobenzenesulfonyl)amino-α-D-xylofuranoside-3′*R*,5-hemiacetal sodium salt (**6**). Some derivatives were synthesized from **6**.

A variety of carbohydrates have been used for stereospecific syntheses of natural products as chiral sources.[1] However, little has been reported using amino sugars,[2] because of their scanty derivatives.

We now report a novel synthesis of branched-chain amino sugar, which may be useful for a suitably functionalized skeleton of alkaloids and β-lactam antibiotics. A noteworthy feature of this synthesis is that it does not require the use of extrinsic protecting groups. The key step was a skeletal rearrangement of the *N*,*O*-*o*-benzenedisulfonyl derivative **3**, where the *o*-benzenedisulfonyl group played simultaneously two roles as an *N*-protecting group and a leaving sulfonyl group. The reagent *o*-benzenedisulfonyl dichloride (**2**) was prepared from dipotassium *o*-benzenedisulfonate and phosphorus pentachloride in an 81% yield.[3] Methyl 2-amino-2-deoxy-α-D-glucopyranoside[4] (**1**) reacted with **2** to give exclusively methyl 2-amino-2*N*,3*O*-(*o*-benzenedisulfonyl)-2-deoxy-α-D-glucopyranoside (**3**) in an 87% yield. Acetylation of **3** gave the corresponding diacetate **4**, which, on longer reaction time, was gradually converted into the triacetate **5**. The ^{1}H-NMR of **5** showed no signal due to the NH group, supporting the *o*-benzenedisulfonimido structure **5**. The ^{1}H-NMR of **3** showed $J_{1,2}$=3.5 Hz, $J_{2,3}$=11.0 Hz and $J_{3,4}$=8.5 Hz, indicating that the chair form existed in the C_1^4 conformation, where the migrating C-4—C-5 bond can be *trans* coplanar to the C-3-benzenesulfonyloxy bond. Therefore, the sequential skeletal rearrangement of **3** seems to be facilitated by the breaking of parallel bonds to give, stereospecifically, a ring-contracted branched-chain furanoside **6**, through the aldehydo structure **6′**.[5] Furthermore, the ring



contraction of glycopyranosides through the possibly produced carbenium ion at their C-3 positions has been already reported to give stereospecifically 3-deoxy-3-*C*-formyl-xylo- or lyxo-furanosides.[5,6] When treated with sodium methoxide in methanol, **3** afforded a single product, methyl 2,3-dideoxy-3-*C*-formyl-2-(*o*-sulfobenzenesulfonyl)amino-α-D-xylofuranoside-3′*R*,5-hemiacetal sodium salt (**6**) in an 82% yield. Assignment of the absolute structure of **6** was based on the following aspects in addition to the aforesaid reaction mechanism: (i) the production of methyl 3-deoxy-3-*C*-formyl-α-D-xylofuranoside-3′,5-hemiacetal, for example, by solvolysis of methyl 3-*O*-(*p*-nitrobenzenesulfonyl)-α-D-glucopyranoside as reported by Austin *et al.*,[5] to support the stereochemistry at C-3 and C-4; (ii) the zero coupling constant between H-3 and H-3′ to show the dihedral angle to be approximately 90° supporting the *trans* configuration; (iii) the reasonable structure of the derivatives **7**—**11** as described later on. The characteristic signals (δ 101.72 ppm and 103.86 ppm) in the ^{13}C-NMR of **6** also supported the presence of two anomeric carbons. In the newly produced hemiacetal, however, an interconversion known as a mutarotation was not recognized at all even in H_2O or D_2O, indicating that the hydroxyl group at C-3′ was stereospecifically fixed in (*R*)-configuration.

Treatment of **6** with lithium in liquid ammonia afforded the crude amino furanoside (**7**), which was not purified because of its instability but characterized as the corresponding *p*-nitrobenzoyl derivative (**8**). Selective *N*-acetylation of the crude product **7** also gave crystalline methyl 2-acetamido-2,3-dideoxy-3-*C*-formyl-α-D-xylofuranoside-3′*R*,5-hemiacetal (**9**) in a 78% overall yield (from **6**). Compound **9** was oxidized with pyridinium chlorochromate to afford the γ-lactone, methyl 2-acetamido-2,3-dideoxy-3-*C*-carboxy-α-D-xylofuranoside-3′,5-lactone (**10**) in a 79% yield, and, on the other hand, reduced with sodium borohydride to yield the diol, methyl 2-acetamido-2,3-dideoxy-3-*C*-hydroxymethyl-α-D-xylofuranoside (**11**) in an 82% yield.

The application of these branched-chain derivatives to elaboration of *N*-containing natural products is an exciting prospect.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR was recorded on a Hitachi Perkin-Elmer 225 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS or D_2O with sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as internal standard on a Varian EM-390(90 MHz)or a Bruker WM 250 spectrometer (250 MHz), and ^{13}C-NMR spectra at 25.2 MHz or 62.9 MHz on a Varian XL 100 or a Bruker WM 250 spectrometer with TMS in $CDCl_3$ and dioxane in D_2O as internal standards. Optical rotations were measured on Carl Zeiss photoelectric polarimeter. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 and Wakogel C-200 or Kieselgel 60, respectively. In general, evaporation was carried out under reduced pressure below 30 °C.

Methyl 2-amino-2-deoxy-α-D-glucopyranoside[4b] (**1**) and *o*-benzenedisulfonyl dichloride[3] (**2**: mp 151—152 °C) were prepared according to the published procedures.

*Methyl 2-Amino-2*N,*3*O-*(o-benzenedisulfonyl)-2-deoxy-α-D-glucopyranoside (3).* To a stirred solution of **2** (10.0 g, 36 mmol) in pyridine (800 ml) was added dropwise a solution of monocarbonate of **1** (8.0 g, 31 mmol) in pyridine (80 ml) at room temperature over a period of 30 min, and stirring at this temperature was continued for another 30 min. After addition of ethanol (4.3 ml), the resulting solution was evaporated and co-evaporated with toluene to give a residue, which was chromatographed on silica gel (450 g) with 3 : 2 benzene–acetone to afford a solid. Recrystallization from ethyl acetate gave needles of **3** (10.7 g, 87%): R_f 0.37 (3 : 2 benzene–acetone); mp 131—132 °C; $[\alpha]_D^{18}$ +149° (*c* 1.0, acetone); IR (KBr): 1425, 1345, 1180, 1160 cm^{-1} (O–SO_2, N–SO_2); ^{1}H-NMR ($CDCl_3$): δ=3.44 (3H, s, OMe), 3.5—4.0 (5H, m, H-2,4,5 and 6), 4.88 (1H, d, H-1, $J_{1,2}$=3.5 Hz), 5.08 (1H, dd, H-3, $J_{2,3}$=11.0 Hz, $J_{3,4}$=8.5 Hz, *vice versa*), ≈5.7 (1H, a broad signal, NH), 7.6—7.9 (2H, m, aromatic), 8.2—8.3 (2H, m, aromatic).

Found: C, 39.84; H, 4.68; N, 3.23%. Calcd for $C_{13}H_{17}NO_9S_2$: C, 39.49; H, 4.33; N, 3.54%.

*Methyl 4,6-Di-*O*-acetyl-2-amino-2*N,*3*O-*(o-Benzenedisulfonyl)-2-deoxy-α-D-glucopyranoside (4) and Methyl 3,4,6-Tri-*O*-acetyl-2-amino-*N,N′*-(o-benzenedisulfonyl)-2-deoxy-α-D-glucopyranoside (5).* A solution of **3** (51.9 mg, 0.131 mmol) in pyridine (0.5 ml) was stirred with acetic anhydride (0.074 ml) at room temperature for 13 h. After addition of a few drops of ethanol, the resulting solution was evaporated to a residue, which was chromatographed on silica gel (5 g) with 3 : 1 benzene–ethyl acetate to give **4** (41 mg, 65%) and **5** (8.9 mg, 13%) having the R_f-values of 0.71 and 0.76 (3 : 2 benzene–acetone) respectively.

4: Cubics from ethyl acetate–hexane; mp 198—199 °C; $[\alpha]_D^{17}$ +135° (*c* 1.0, $CHCl_3$); IR (KBr) 1740, 1735, 1730 (OAc), 1425, 1360, 1345, 1185, 1175, 1145 cm^{-1} (O–SO_2, N–SO_2); ^{1}H-NMR ($CDCl_3$): δ=2.10 and 2.16 (each 3H, s, OAc), 3.49 (3H, s, OMe), 3.95—4.05 (2H, m, H-2 and 5), 4.15 (1H, dd, H-6, $J_{5,6}$=2.0 Hz, $J_{6,6'}$=12.5 Hz), 4.30 (1H, dd, H-6′, $J_{5,6'}$=4.5 Hz), 4.93 (1H, d, H-1, $J_{1,2}$=3.5 Hz), 5.21 (2H, m, H-3 and 4), 5.65 (1H, a broad signal, NH), 7.68 and 7.81 (each 1H, m, aromatic), 8.20 and 8.23 (each 1H, m, aromatic).

Found: C, 42.33; H, 4.41; N, 2.65; S. 13.19%. Calcd for $C_{17}H_{21}NO_{11}S_2$: C, 42.59; H, 4.41; N, 2.92; S, 13.37%.

5: Needles from benzene–hexane; mp 178—179 °C; $[\alpha]_D^{18}$ +118° (*c* 1.0, $CHCl_3$); IR (KBr): 1760, 1740, 1725, 1720 (OAc), 1430, 1365, 1190, 1180 cm^{-1} (N–SO_2); ^{1}H-NMR ($CDCl_3$): δ=2.09, 2.22 and 2.38 (each 3H, s, OAc), 3.50 (3H, s, OMe), 4.0—4.6 (3H, m, H-5 and 6), 4.84 (1H, dd, H-2, $J_{1,2}$=3.5 Hz, $J_{2,3}$=12 Hz), 5.02 (1H, d, H-1), 5.23 (1H, t, H-4, $J_{3,4}$=$J_{4,5}$=9.0 Hz), 6.38 (1H, dd, H-3), 7.9—8.1 (2H, m, aromatic), 8.5—8.7 (2H, m, aromatic).

Found: C, 43.65; H, 4.41; N, 2.84; S, 12.10%. Calcd for $C_{19}H_{23}NO_{12}S_2$: C, 43.76; H, 4.45; N, 2.69; S, 12.30%.

*Methyl 2,3-Dideoxy-3-*C*-formyl-2-(o-sulfobenzenesulfonyl)amino-α-D-xylofuranoside-3′*R*,5-hemiacetal Sodium Salt (6).* To a stirred and ice-cooled solution of **3** (5.76 g, 14.6 mmol) in dry methanol (115 ml) was added sodium methoxide (1.57 g, 29.2 mmol), and the solution was stirred at 50 °C overnight. After further addition of sodium methoxide (2.36 g, 43.7 mmol), stirring at 50 °C was continued for another 1 d. The resulting suspension was neutralized with Amberlite CG-50 (H type), filtered, and the filtrate evaporated to give a residue, which was chromatographed on silica gel (240 g) with 4 : 1 chloroform–methanol to give a solid of **6** (5.0 g, 82%): R_f 0.34 (4 : 1 chloroform–methanol); $[\alpha]_D^{19}$ +5° (*c* 1.0, MeOH); $[\alpha]_{365}^{19}$ −35° (*c* 1.0, MeOH); IR (KBr): 1340, 1170, 1140(N–SO_2, SO_3Na); ^{1}H-NMR (D_2O): δ=2.52 (1H, t, H-3, $J_{2,3}$=$J_{3,4}$≃7.5 Hz, $J_{3,3'}$=0 Hz), 3.08 (3H, s, OMe), 3.62 (1H, dd, H-2,

$J_{1,2}$=4.5 Hz), 3.84 (2H, broad s, H-5), 4.55 (1H, d, H-1), 4.77 (1H, m, H-4), 5.12 (1H, s, H-3′, $J_{3,3'}$=0 Hz), 7.55—7.80 (2H, m, aromatic), 8.05—8.20 (2H, m, aromatic); ^{13}C-NMR (62.9 MHz, D_2O) δ=55.24, 60.30 and 81.73 (C-2,3 and 4, *vice versa*), 55.70 (OMe), 71.61 (C-5), 101.72 and 103.86 (C-1 and 3′, *vice versa*), 130.97, 131.34, 132.94, 135.06, 136.37, and 141.69 (aromatic).

Found: C, 37.05; H, 3.89; N, 3.61%. Calcd for $C_{13}H_{16}NO_9S_2Na$: C, 37.41; H, 3.86; N, 3.36%.

*Methyl 2-Amino-2,3-dideoxy-3-C-formyl-α-D-xylofuranoside-3′R,5-hemiacetal (**7**).* A gaseous ammonia was introduced and trapped in a pre-cooled vessel containing **6** (2.17 g, 5.20 mmol) at −60 °C. To the resulting solution (about 60 ml) was added a piece of lithium metal (144 mg) by portions with stirring, and stirring at −50 °C was continued for 1 h. After careful addition of NH_4Cl (1.11 g), the mixture was allowed to evaporate to a residue, which was dried *in vacuo* to afford a crude solid (3.3 g) containing **7** with concomitant salts. As the product **7** was considerably labile, the solid was used for the next step without purification.

*Methyl 2,3-Dideoxy-3-C-formyl-2-(p-nitrobenzoyl)amino-3′-C-(p-nitrobenzoyl)-α-D-xylofuranoside-3′R,5-hemiacetal (**8**).* A crude solid of **7** (173 mg) was stirred with *p*-nitrobenzoyl chloride (400 mg) in pyridine (6.0 ml) at 70 °C overnight. After addition of ethanol, the resulting mixture was evaporated to give a residue, which was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to a residue, which was chromatcgraphed on silica gel (15 g) with 4 : 1 benzene–ethyl acetate to afford, after recrystallization from ethyl acetate-hexane, needles of **8** (57 mg, 44% from **6**): mp 208—210 °C; $[\alpha]_D^{21}$ 0° (*c* 1.0, $CHCl_3$); $[\alpha]_{405}^{21}$ −35° (*c* 1.0, $CHCl_3$); IR (KBr): 1730 (ester), 1660 (amide I), 1600 (aromatic), 1525 (amide II), 1345 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$): δ=3.05 (1H, t, H-3, $J_{2,3}$=$J_{3,4}$=7.5 Hz, $J_{3,3'}$=0 Hz), 3.50 (3H, s, OMe), 4.19 (2H, broad s, H-5), 4.56 (1H, dt, H-2, $J_{1,2}$=4.5 Hz, $J_{2,NH}$=7.5 Hz), 5.0 (1H, m, H-4), 5.08 (1H, d, H-1), 6.82 (1H, d, NH), 6.93 (1H, s, H-3′), 7.9—8.4 (8H, m, aromatic); ^{13}C-NMR (25.2 MHz, $CDCl_3$): δ=54.71 (OMe), 56.03 and 56.65 (C-2 and 3), 73.20 (C-5), 80.68 (C-4), 103.21 and 103.41 (C-1 and 3′, *vice versa*), 123.16, 123.41, 128.00, 130.40, 134.88, 138.88, 149.32 and 150.22 (aromatic), 162.92, 164.92 (C=O).

Found: C, 53.12; H, 4.20; N, 8.63%. Calcd for $C_{21}H_{19}N_3O_{10}$: C, 53.28; H, 4.05; N, 8.88%.

*Methyl 2-Acetamido-2,3-dideoxy-3-C-formyl-α-D-xylofuranoside-3′R,5-hemiacetal (**9**).* To a solution of a crude solid of **7** (1.0 g) in methanol (20 ml), were added triethylamine (0.22 ml) and, after 30 min, acetic anhydride (0.45 ml) with stirring at room temperature. After 1.5 h, the resulting solution was evaporated to a residue, which was chromatographed on silica gel (30 g) with 3 : 2 chloroform–acetone followed by recrystallization from acetone–hexane to give needles of **9** (267 mg, 78% from **6**): R_f 0.69 (3 : 1 ethyl acetate–methanol); mp 165 °C, $[\alpha]_D^{16}$ +58° (*c* 1.0, $CHCl_3$); IR (KBr): 1650 (amide I), 1550 cm^{-1} (amide II); ^{1}H-NMR ($CDCl_3$): δ=1.99 (3H, s, NAc), 2.55 (1H, t, H-3, $J_{2,3}$=$J_{3,4}$=7.5 Hz, $J_{3,3'}$=0 Hz); 3.48 (3H, s, OMe), 3.85—4.2 (3H, m, H-5 and OH), 4.21 (1H, dt, H-2, $J_{1,2}$=5.0 Hz, $J_{2,NH}$=7.5 Hz), 4.86 (1H, d, H-1), 4.7—4.9 (1H, m, H-4), 5.79 (1H, d, H-3′, $J_{3',OH}$=3.0 Hz, which collapsed to a singlet on addition of D_2O), 6.14 (1H, d, NH, which disappeared on addition of D_2O).

Found: C, 50.03; H, 6.87; N, 6.24%. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45%.

*Methyl 2-Acetamidc-2,3-dideoxy-3-C-carboxy-α-D-xylofuranoside-3′,5-lactone (**10**).* To a vigorously stirred solution of **9** (1.75 g, 8.06 mmol) in dry $CHCl_3$ (35 ml) was added pyridinium chlorochromate (3.47 g, 16.1 mmol) by portions at room temperature, and stirring at this temperature was continued for 2 d. The turbid supernatant was pipetted off, and the precipitated mass was triturated several times with dichloromethane. The combined supernatants were evaporated to a residue, which was chromatographed on silica gel (150 g) with 2 : 1 chloroform–acetone followed by recrystallization from ethyl acetate-hexane to afford needles of **10** (1.37 g, 79%): R_f 0.29 (2 : 1 chloroform–acetone); mp 192 °C; $[\alpha]_D^{17}$ +100° (*c* 1.0, $CHCl_3$); IR (KBr): 1760 (lactone), 1650 (amide I), 1555 cm^{-1} (amide II); ^{1}H-NMR ($CDCl_3$ with a drop of D_2O): δ=2.02 (3H, s, NAc), 3.10 (1H, dd, H-3, $J_{2,3}$=5.0 Hz, $J_{3,4}$=6.0 Hz), 3.44 (3H, s, OMe), 4.40 (2H, d, H-5, $J_{4,5}$=3.0 Hz), 4.77 (1H, t, H-2, $J_{1,2}$=5.0 Hz), 4.90 (1H, dt, H-4), 5.08 (1H, d, H-1).

Found: C, 50.39; H, 6.14; N, 6.31%. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51%.

*Methyl 2-Acetamido-2,3-dideoxy-3-C-hydroxymethyl-α-D-xylofuranoside (**11**).* To a stirred solution of **9** (80 mg) in methanol (0.8 ml) was added $NaBH_4$ (28 mg) by portions at room temperature. After 30 min, the resulting solution was neutralized with Amberlite CG-50 (H type), filtered and then evaporated to a residue, which was chromatographed on silica gel (7.5 g) with 15 : 1 chloroform–methanol followed by recrystallization from benzene–hexane to afford needles of **11** (66 mg, 82%): R_f 0.13 (1 : 1 benzene–acetone); mp 113—114°; $[\alpha]_D^{19}$ +100° (*c* 1.0, $CHCl_3$); IR (KBr): —1650, 1610, 1555 cm^{-1} (amide); ^{1}H-NMR ($CDCl_3$): δ=2.04 (3H, s, NAc), 2.34 (1H, m, H-3), 3.43 (3H, s, OMe), 3.7—4.0 (5H, m, H-3′, 5 and OH), 4.20 (1H, dt, H-4, $J_{3,4}$=9.0 Hz, $J_{4,5}$=3.0 Hz), 4.42 (1H, ddd, H-2, $J_{1,2}$=5.0 Hz, $J_{2,NH}$=8.5 Hz, $J_{2,3}$=11.5 Hz), 4.71 (1H, t, OH, $J_{CH_2,OH}$=7.0 Hz, which disappeared on addition of D_2O), 4.95 (1H, d, H-1), 6.23 (1H, broad d, NH, which disappeared on addition of D_2O).

Found: C, 49.40; H, 7.59; N, 6.28%. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39%.

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