Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Functionalization of Testosterone at Position 7α and Synthesis of 7α-(3-Methoxypropyl)-4-androsten-17β-ol-3-one

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Published online: 27 Apr 2009.

To cite this article: Dominic Bastien , Josée Nault & Gervais Bérubé (2009): Functionalization of Testosterone at Position 7α and Synthesis of 7α-(3-Methoxypropyl)-4-androsten-17β-ol-3-one, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:11, 1884-1892

To link to this article: http://dx.doi.org/10.1080/00397910802618430

Synthetic Communications®, 39: 1884–1892, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802618430

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Functionalization of Testosterone at Position 7α and Synthesis of 7α-(3-Methoxypropyl)-4-androsten-17β-ol-3-one

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Abstract: An efficient transformation of the terminal alkene function of 7α-allyltestosterone is reported along with the stereospecific synthesis of 7α-(3-methoxypropyl)-4-androsten-17β-ol-3-one.

Keywords: 7α-Allyltestosterone, hydroboration-iodation, steroids

Testosterone (**1**), a steroidal hormone, is mainly involved in the development and maintenance of male sexual characteristics. Structurally, beside the presence of a perhydrocylopentenophenantherene ring system, it has a ketone function at position 3 and a hydroxy function at position 17 of the steroidal nucleus Scheme 1.[1] These groups are essential for its biological activity.[2] Several structural modifications have been performed on the testosterone nucleus to get the desired antagonistic activity for the treatment of androgen-dependent disorders such as prostate cancer.[2,3]

The most interesting position on the testosterone nucleus for attachment of various substituents is position 7. This carbon is the position of choice because it is located halfway between the two groups (ketone and alcohol) that interact with the androgen receptor. These important

Received June 6, 2008.
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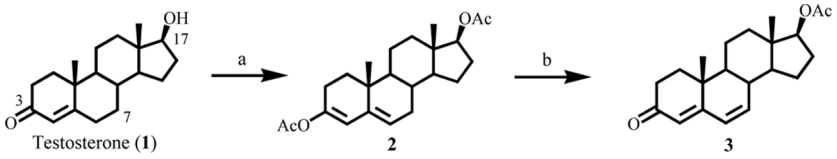


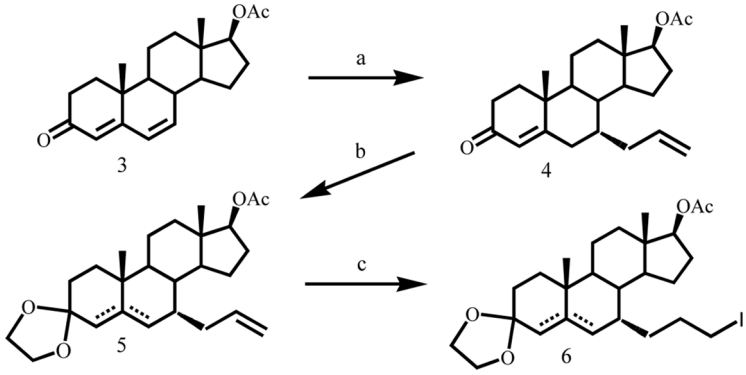
Scheme 1. (a) AcCl, Ac_2O, Pyr, reflux, 4 h; (b) 1, NBS, DMF, 0 °C, 50 min; 2, Li_2CO_3, LiBr, 92 °C, 4 h.

pharmacophores, the 3-ketone and the 17β-alcohol groups, are the key features for the activation of the receptor.[3] Thus, structural modification at position 7 should not affect greatly the steroid–receptor interaction and consequently can lead to compounds of biological importance.

However, the major drawback of this position is the absence of a useful functional group to perform chemical reactions. Consequently, it has to be introduced prior to further chemical transformations. First, the functionalization of position 7 on the steroid was done in a two-step process. Then, an iodoalkyl chain was introduced in a three-step reaction sequence. Finally, two nucleophiles were used to verify the ease of displacement of the terminal iodide.

As showed in Scheme 1, testosterone (**1**) was initially functionalized in a known two-step reaction sequence adapted from the reported procedure that used 19-nor-testosterone as the starting material.[4] For the first reaction, testosterone was treated with acetyl chloride and acetic anhydride in the presence of pyridine (Pyr). This reaction gave the diacetate **2** with 95% yield. The derivative **2** was further transformed into the dienone acetate **3** upon treatment with *N*-bromosuccinimide (NBS) for 50 min followed by Li_2CO_3 and LiBr at reflux for 2 h in dimethylformamide (DMF). Derivative **3** was obtained with 87% yield.

The next three steps led to the formation of an iodopropyl chain at 7α of the steroid nucleus (Scheme 2). The dienone **3** dissolved in dichloromethane was treated with $TiCl_4$ and allyltrimethylsilane in the presence of pyridine using a modified version of a reported protocol that used 19-nor-testosterone as the starting material.[5] This reaction was stereospecific. The alkyl chain was added on position 7α of the steroid nucleus. The 7α-allyl-enone **4** was obtained with 65% yield. Next, the ketone at position 3 was protected as an acetal. This protection was performed to avoid reduction of the ketone during the hydroboration step. Thus, derivative **4** was treated with ethylene glycol in benzene in the presence of p-toluenesulfonic acid (TsOH), which gave compound **5** in 80% yield.[6] As shown in Scheme 2, the acetal **5** is a mixture of two regioisomers having the double bond either in ring A (**5A**) or in ring B (**5B**), which are indicated by the dotted line. The ^{1}H NMR spectrum showed

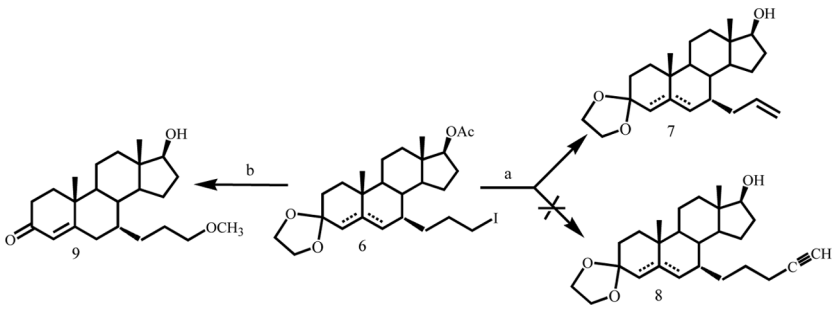


Scheme 2. (a) 1, $TiCl_4$, Pyr, DCM, −78 °C, 5 min; 2, allyltrimethylsilane, −30 °C, 1.5 h; (b) benzene, ethyleneglycol, TsOH, Dean–Stark, reflux, 24 h; (c) 1, BH_3-THF, THF, 30 min; 2. AcONa, NaI, chloramine-T, 5 min.

a split of several peaks corresponding to each regioisomer. The proportion of regioisomers evaluated by the ^{1}H NMR spectrum was about 1:2 (**5A**:**5B**).

To complete the three-step reaction sequence, hydroboration–iodation was performed.[7] Derivative **5** was treated with the borane (BH_3–THF) followed by sodium iodide in the presence of sodium acetate and chloramine-T. This reaction gave product **6** with 58% yield. For the characterization of that product (**6**), the pure regioisomer B was separated by flash chromatography. The ^{1}H NMR spectrum showed the disappearance of the allyl protons. The methylene near the iodide was expected to be a triplet. However, a multiplet was observed at 3.20 ppm instead. An electrostatic interaction between the double bond in ring B and the iodide is possible. This interaction limits the free rotation of the iodoalkyl chain. As a result, the protons near the iodide are not equivalent, which explains the complexity of the signal. To confirm this hypothesis, the ketal was removed with HCl 10% (data not shown) to obtain the free enone. In that case, the double bound migrated back into ring A. The electrostatic interaction between the iodide and the double bound was not possible any longer, and a triplet could be observed at 3.16 ppm for the methylene protons near the iodide.

Two nucleophilic substitution reactions were attempted (Scheme 3) on derivative **6**. First, the iodide **6** was treated with the sodium acetylide in a mixture of DMF and xylene.[8,9] The reaction was instantaneous, but the desired substitution product was not obtained. An elimination reaction occurred instead. The yield of this reaction was 74%. The ^{1}H NMR spectrum showed the presence of olefinic protons (located at



Scheme 3. (a) NaC≡CH/xylene, reflux, 2 h; (b) 1, MeOH, $NaOCH_3$, reflux, 12 h; 2, HCl 5 N, MeOH, reflux, 2 h.

5.00 and 5.68 ppm) as two doublets and a multiplet and the absence of the acetylenic protons. The infrared (IR) spectrum also showed the absence of the acetylenic bond. The substitution reaction with sodium monoalkoxide was also attempted. In this reaction, beside the nucleophilic substitution of the iodide by the alkoxide ion in compound **6**, deprotection at position 17 was anticipated. The iodide **6** was treated with an excess of sodium methoxide in methanol. The ^{1}H NMR spectrum showed the disappearance of the protons near the iodide (3.20 ppm). The new signals of the protons located at each side of the ether linkage were located at 3.31 ppm and 3.34 ppm as a singlet and multiplet. As expected, the acetate group on carbon 17 was removed to give compound **9** (as an acetal). The ^{1}H NMR spectrum showed the disappearance of the signal at 2.04 ppm (acetate). The enone was regenerated upon treatment with HCl to give derivative **9** with 93% yield.

In conclusion, the stereospecific synthesis of 7α-(3-methoxypropyl)-4-androsten-17β-ol-3-one (**9**) is reported. It was accomplished in six steps with 23% overall yield. The synthesis was done via the successful introduction of a 7α-(3-iodopropyl) side chain to the testosterone nucleus by a hydroboration–iodation reaction on an allyl chain to give derivative **6**. This reaction sequence could give access to a variety of 7α-substituted testosterone analogs of biological importance by the use of various nucleophiles.

EXPERIMENTAL

Anhydrous reactions were performed under an inert atmosphere; they were set up, assembled, and cooled under nitrogen. Unless otherwise noted, the starting material, reactant, and solvents were obtained commercially

and were used as such or purified and dried by standard means.[10] Organic solutions were dried over magnesium sulfate ($MgSO_4$), filtered, and evaporated on a rotary evaporator under reduced pressure. All reactions were monitored by ultraviolet (UV) fluorescence or staining with iodine. Commercial thin-layer chromatography (TLC) plates were Sigma T 6145 (polyester silica gel 60 Å, 0.25 mm). Preparative TLC was performed on 1-mm silica gel 60 Å, 20×20 plates (Whatman, 4861 840). Flash-column chromatography was performed according to the method of Still et al.[11] on Merck grade 60 silica gel, 230–400 mesh. All solvents used in chromatography had been distilled.

Melting points (mp) were recorded in open capillaries on an Electrothermal apparatus and are uncorrected. The infrared (IR) spectra were taken on a Nicolet Impact 420 Fourier transform–infrared (FT-IR) spectrophotometer. Mass spectral assays were obtained using a VG Micromass 7070 HS instrument using ionization energy of 70 eV.

Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker AMX-II-500 equipped with a reversed or QNP probe (Pharmacor) or (when indicated) on a Varian 200-MHz NMR apparatus. Samples were dissolved in deuterochloroform ($CDCl_3$) or deuteroacetone (acetone-d_6) for data acquisition using tetramethylsilane (TMS) or chloroform as internal standard (TMS, δ 0.0 ppm for ^{1}H NMR, and $CDCl_3$, δ 77.0 ppm for ^{13}C). Chemical shifts (δ) are expressed in parts per million (ppm), and the coupling constants (J) are expressed in hertz (Hz). Multiplicities are described by the following abbreviations: s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, m for multiplet, #m for several multiplets, and br s for broad singlet. Only the most characteristic signals are described for each compound.

Synthesis of 3,5-Androstadien-3,17β-diol Diacetate (2)

Acetyl chloride (10.9 mL, 153 mmol), acetic anhydride (3.4 mL, 42 mmol), and pyridine (1.1 mL, 13.6 mmol) were added to testosterone (3.4 g, 11.8 mmol). The solution was stirred 3.5 h at reflux and then 20 min at room temperature. The solvents were evaporated to dryness under vacuum. The steroid was dissolved in dichloromethane and filtered on silica gel. The solvent were evaporated again to obtain 4.2 g of diacetate **2** (crude yield 95%). No flash chromatography was needed for that step. The crude material was used as such for the next transformation. Mp: 143–147°C; IR (cm^{-1}): 1736 (C=O), 1666 (C=C), 1248 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 5.69 (1H, s, 4-CH), 5.39 (1H, m, 6-CH), 4.61 (1H, t, $J = 8.5$ Hz, 17-CH), 2.13 (3H, s, CH_3, C-3 acetate), 2.04 (3H, s, CH_3, C-17 acetate), 1.01 (3H, s, 19-CH_3), 0.83, (3H, s, 18-CH_3);

^{13}C NMR ($CDCl_3$, δ ppm): 171.2 (C=O, C-17 acetate), 169.3 (C=O, C-3 acetate), 147.1 (C-3), 139.5 (C-5), 123.5 (C-6), 116.9 (C-4), 82.7 (C-17). MS (m/e): 372 (M^+), 330 ($M^+ - C_2H_2O$). Exact mass calculated for $C_{23}H_{32}O_4 = 372.2300$; found = 372.2297.

Synthesis of 4,6-Androstadien-17β-ol-3-one Acetate (3)

Under a nitrogen atmosphere, DMF (3.9 mL) and water (0.08 mL) were combined with the diacetate **2** (1.3 g, 3.5 mmol) and cooled to 0°C. N-bromosuccinimide (NBS) was added over a period of 1 h and stirred for an additional 40 min at 0°C. Li_2CO_3 and LiBr were added to the mixture at room temperature. The mixture was heated for 3 h at 92°C and then poured in a water/ice solution containing 150 mL of water and 10 mL of acetic acid. The crude compound **3** was filtered, washed with water, and dried. Then, the crude material was purified by flash chromatography with a mixture of hexane/acetone (9:1) to give **3** in 87% yields (1.0 g). Mp: 144–147°C; IR (cm^{-1}): 1735 (C=O, acetate), 1664 (C=O, ketone), 1613 (C=C), 1252 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 6.11 (2H, m, 6-CH=CH-7), 5.68 (1H, s, 4-CH), 4.64 (1H, t, $J = 8.3$ Hz, 17-CH), 2.06 (3H, s, CH_3, acetate) 1.12 (3H, s, 19-CH_3), 0.86 (3H, s, 18-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 199.3 (C-3), 171.0 (C-O, acetate) 163.3 (C-5), 139.9 (C-7), 128.2 (C-4), 123.2 (C-6), 82.0 (C-17). MS (m/e): 328 (M^+), 286 ($M^+ - C_2H_2O$). Exact mass calculated for $C_{21}H_{28}O_3 =$ 328.2038; found = 328.2032.

Synthesis of 7α-Allyl-4-androsten-17β-ol-3-one Acetate (4)

Under an inert atmosphere of nitrogen, the steroid **3** was dissolved in dry dichloromethane and cooled to −78°C. Then, titanium(IV) chloride (3.8 mL, 34 mmol) and pyridine (0.7 mL, 8.5 mmol) were added to the solution. The mixture was stirred for 5 min; allyltrimethylsilane was added, and the mixture was stirred for 1.5 h at −78°C and 1.5 h at −30°C. °C. The black mixture was diluted with ether and washed with a 2% HCl solution (2 × 20 mL) and with water (4 × 20 mL). The organic phase was dried, filtered, and concentrated to a solid. The crude steroid was purified by flash chromatography with hexane/acetone (9:1) as the eluant. The crystalline compound **4** was obtained in good yield (1.5 g, 65%). Mp: 148–150°C; IR (cm^{-1}): 1720 (C=O, acetate), 1670 (C=O, ketone), 1630–1610 (C=C), 1220 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 5.71 (1H, s, 4-CH), 5.65 (1H, m, CH_2=CH), 5.00–5.02 (2H, 2d, $J = 10.3$ Hz and $J = 17.3$ Hz, CH_2=CH), 4.61 (1H, t, $J = 8.5$ Hz, 17-CH), 2.05 (3H, s, CH_3, acetate), 1.21 (3H, s, 19-CH_3), 0.85 (3H, s, 18-CH_3); ^{13}C NMR

($CDCl_3$, δ ppm): 198.7 (C-3), 170.8 (C=O, acetate), 168.9 (C-5), 136.6 (CH_2=CH), 126.0 (C-4), 116.6 (CH_2=CH), 82.2 (17-C). MS (m/e): 370 (M^+), 312 ($M^+ - C_2H_2O_2$). Exact mass: calculated for $C_{24}H_{34}O_3$ = 370.2508; found = 370.2505.

Synthesis of 7α-Allyl-5-androsten-17β-ol-3-one 3-Ethyleneketal Acetate (5)

The enone **4** (1.3 g, 3.5 mmol) in benzene (35 mL) was combined with ethylene glycol (0.56 g, 8.5 mmol) and *p*-toluenesulfonic acid (30 mg, 0.16 mmol). The mixture was heated at reflux with a Dean–Stark apparatus for 12 h. The compound was diluted with ether and washed with a 2% HCl solution (1 × 20 mL) and with water (4 × 20 mL). The organic phase was dried, filtered, and concentrated to a solid. The crude steroid was purified by flash chromatography (hexane/acetone, 85:15). The purification gave the product **5** with 80% yield (1.2 g) as a mixture of regioisomers. A and B indicate the position of the double bound, either in ring A or in ring B of the steroid nucleus. IR (cm^{-1}): 1730 (C=O, acetate), 1630–1610 (C=C), 1210 (C-O), 1090 (O-C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 5.68_A and 5.86_B (1H, 2 m, CH_2=CH), 5.19_A (1H, s, 4-CH), 5.39_B (1H, s, 6-CH), 5.01 (1H, m, CH_2=CH), 4.59–4.62 (1H, 2 t, J = 8.6 Hz, 17-CH), 3.86–4.01 (4H, m, O-CH_2-CH_2-O), 2.03_B and 2.04_A (1H, 2s, CH_3, acetate), 1.03_B and 1.05_A (1H, 2s, 19-CH_3), 0.80_B and 0.81_A (1H, 2s, 18-CH_3).

Synthesis of 7α-(3-Iodopropyl)-5-androsten-17β-ol-3-one 3-Ethyleneketal Acetate (6)

Ethyleneketal **5** (1.5 g, 3.6 mmol) was dissolved in dry THF (7 mL) and cooled to 0°C. BH_3-THF was added to the mixture and stirred for 30 min at 0°C. Then, sodium acetate 1 M in methanol (7 mL), an aqueous sodium iodide solution 1 M (7 mL), and chloramine-T (0.5 M) in methanol (14 mL) were added consecutively to the reaction mixture. The solution was heated at room temperature and stirred for 7 min. Aqueous sodium thiosulfate 1 M (7 mL) was added to stop the reaction. The reaction mixture was diluted in ether and washed with water (1 × 20 mL). The aqueous phase was recovered and washed with ether (2 × 20 mL). Then, the organic phases were combined, treated with a saturated sodium chloride aqueous solution, and washed with water (4 × 20 mL). The organic phase was dried, filtered, and concentrated. Flash chromatography (hexane/acetone, 9:1) gave **6** with 58% yield (1.1 g). Mp: 122–124°C; IR (cm^{-1}): 1720 (C=O, acetate), 1240 (CH_2I), 1240 (C-O, acetate), 1080 (O-C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 5.38 (1H, d, J = 4.2 Hz, 6-CH), 4.63

(1H, t, $J = 8.5$ Hz, 17-CH), 3.93 (4H, m, O-CH_2-CH_2-O), 3.20 (2H, m, CH_2I), 2.09 and 2.58 (2H, 2d, part A and B of system AB, $J = 13.9$ Hz, 4-CH_2), 2.04 (3H, s, CH_3, acetate), 1.03 (3H, s, 19-CH_3), 0.80 (3H, s, 18-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 171.1 (C-O, acetate), 140.3 (C-5), 125.7 (C-6), 109.3 (C-3), 82.6 (C-17), 64.2 (O-CH_2-CH_2-O), 7.5 (CH_2I). MS (m/e): 542 (M^+), 415 ($M^+ - I$). Exact mass calculated for $C_{26}H_{39}O_4I = 542.1893$; found = 542.1906.

Synthesis of 7α-Allyl-5-androsten-17β-ol-3-one 3-Ethyleneketal (7)

Under a nitrogen atmosphere, the iodide **6** (0.3 g, 0.55 mmol) was dissolved in a mixture of DMF/xylene anhydride (2:3) (3.5 mL) and excess sodium cyanide (0.46 g of sodium cyanide in oil). The reaction mixture was stirred for 2 h at room temperature. The product was extracted with ether and washed with water (4×5 mL). The organic phase was dried, filtered, and concentrated. The compound **7** was obtained with 74% yield (0.15 g) as a mixture of regioisomers. A and B indicate the position of the double bound, either in ring A or in ring B of the steroid nucleus. IR (cm^{-1}): 3420 (O-H), 1650 and 1620 (C=C), 1090 (O-C-O), 1030 (C-O, alcohol); ^{1}H NMR ($CDCl_3$, δ ppm): 5.69_A and 5.87_B (1H, 2 m, CH_2=CH), 5.30_B and 5.45_A (1H, 2s, OH), 5.39_B (1H, d, $J = 3.6$ Hz, 6-CH), 5.18_A (1H, s, 4-CH), 5.00 (2H, m, CH_2=CH), 3.93 (4H, m, O-CH_2-CH_2-O), 3.65 (1H, t, $J = 8.8$ Hz, 17-CH), 1.03_B and 1.06_A (3H, 2s, 19-CH_3), 0.75_B and 0.77_A (3H, 2s, 18-CH_3).

Synthesis of 7α-(3-Methoxypropyl)-4-androsten-17β-ol-3-one (9)

The iodide **6** (0.10 g, 0.18 mmol) was dissolved in dry methanol (3.5 mL). Then, sodium methoxide (0.042 g, 0.78 mmol) in excess was added to the steroid solution. The mixture was stirred at reflux for 12 h. The compound was extracted with ether and washed with water (3×2 mL). The ketal group was removed upon treatment with a 10% aqueous HCl solution for 1 h. Flash chromatography was needed (hexane–acetone, 9:1). The purification gave product **9** (0.070 g) with 93% yield. Mp: 134–135°C; IR (cm^{-1}): 3460 (O-H), 1650 (C=O), 1610 (C=C), 1060 (C-O-C), 1020 (C-O, alcohol); ^{1}H NMR ($CDCl_3$, δ ppm): 5.73 (1H, s, 4-CH), 3.66 (1H, t, $J = 8.6$ Hz, 17-CH), 3.34 (2H, m, -CH_2-O), 3.31 (3H, s, O-CH_3), 1.21 (3H, s, 19-CH_3), 0.80 (3H, s, 18-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 199.1 (C-3), 169.8 (C-5), 125.9 (C-4), 81.6 (C-17), 72.6 (-CH_2-O), 58.4 (O-CH_3). MS (m/e): 360 (M^+), 287 ($M^+ - C_4H_9O$). Exact mass calculated for $C_{23}H_{36}O_3 = 360.2664$; found = 360.2667.

ACKNOWLEDGMENTS

We are grateful to the Fonds de Recherche sur la Nature et les Technologies du Québec (FQRNT) for generous financial support. The authors thank Dr. Atul Gupta for his contribution in the preparation of this manuscript.

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