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Serine as Chiral Educt for the Practical Synthesis of Enantiopure N-Protected β-Hydroxyvaline†

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Abstract: *N-tert*-Butyloxycarbonyl- and *N*-benzenesulfonyl-β-hydroxyvalines **1a** and **1b** were, respectively, synthesized in enantiomerically pure form by a two-step protocol from their enantiomeric N-protected serine methyl esters **2a** and **2b**. The addition of CH_3MgBr to **2a** and **2b** provided diols **3a** and **3b**, respectively as major products in 83% and 81% yields. Selective oxidation of diols **3a** and **3b** was performed using a TEMPO, $NaClO_2$, NaOCl cocktail in 96% and 93% respective yields. This two-step process effectively furnished multigram amounts of enantiopure *N*-Boc-β-hydroxyvaline **1a**.

A rare example of a β,β-dialkyl-substituted β-hydroxy α-amino acid found in nature, β-hydroxyvaline was first isolated from the peptide antibiotic zorbamycin.[1] It has since been shown to be an important component in many biologically active molecules,[2−6] such as the aureobasidin[3] family of peptide antibiotics and the anti-HIV luzopeptins.[4] In addition, β-hydroxyvaline has served as an intermediate in the synthesis of monobactam antibiotics.[5,6]

Various syntheses have been proposed for the construction of β-hydroxyvaline and β-hydroxy-*N*-methylvaline; however, drawbacks including multiple steps, costly and toxic starting materials, and difficulties for scale-up all have restricted its production. Most procedures for the preparation of β-hydroxyvaline, produce the amino acid in racemic form and require crystallization with a chiral salt or enzymatic resolution to obtain enantiomerically enriched material.[5−7] Diastereoselective aldol condensations of acetone onto glycine enolate equivalents have provided β-hydroxyvaline of high enantiomeric purity in varying yields contingent on the chiral auxiliary.[8] For example, the diastereoselective condensation of lithiated bis-lactim ethers with acetone has provided access to β-hydroxyvaline on a hundred milligram scale after distillation from valine methyl ester.[8a] The diastereoselectivity of the condensation of acetone onto the sodium enolate, generated from treating the Ni(II) complex of the Schiff base from glycine and (*S*)-2-[*N*-(*N*′-benzylpropyl)-amino]benzophenone with NaH at 20 °C, was found to be time sensitive and decreased with longer reaction times.[8b,c] After 7 min, a 30/1 mixture of diastereomers was obtained.[8b,c] Removal of the auxiliary with 6 N HCl and ion-exchange chromatography provided (*S*)-β-hydroxyvaline of 99% enantiomeric purity in 80% overall yield from this two-step process.[8b,c] In addition, condensation of acetone onto the lithium enolate of (*R*)-1-benzoyl-2-*tert*-butyl-3-methyl-4-imidazolidinone at −100 °C followed by acid hydrolysis gave (*R*)-β-hydroxyvaline in 19% overall yield after purification by ion-exchange chromatography.[8d] From an industrial standpoint, the six-step ∼50% yielding synthesis from 3,3-dimethylacrylic acid provides 98% enantiopure material from an inexpensive achiral starting material by employing an enantioselective dihydroxylation.[9] Protection of the carboxylate of *N*-serine as its OBO (2,6,7-trioxabicyclio[2.2.2]octyl) ester followed by oxidations and nucleophilic additions at the β-carbon has provided access to a family of β,β-dialkyl-substituted serines; however, for the synthesis of β-hydroxyvaline, seven steps were required and provided **1a** in ∼58% yield.[10] At present, the most expedient synthesis of N-protected β-hydroxy-L-valine involves a three-step process from *N*-Boc-D-serine methyl ester in which the β-hydroxyl group was protected in an oxazolidine ring during nucleophilic addition to the carboxylate and deprotected during the final oxidation.[11] This route was claimed to provide *N*-Boc-L-β-hydroxyvaline in 50% overall yield; however, confusion exists concerning the characterization of the final protected amino acid.[11] Moreover, the oxidation step employed a toxic chromium reagent.[11]

In need of enantiopure β-hydroxyvaline suitably protected for our program on antimicrobial peptide synthesis, we have developed a two-step route to this β-hydroxy-α-amino acid by using chemistry based on Rapoport's methodology. The conversion of protected serine into enantiomeric amino acid counterparts without loss of

† Dedicated to the memory of Professor Henry Rapoport, deceased March 6, 2002.

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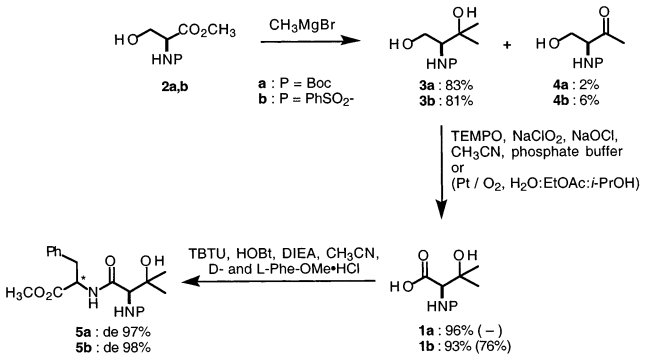
SCHEME 1. Synthesis and Enantiomeric Purity of *β*-Hydroxyvaline 1



configurational integrity was demonstrated by Rapoport in syntheses of D-isomers of norleucine, aminopimelate, DOPA (3-(3,4-dihydroxyphenyl)alanine), and allothreonine,[12] *β*-hydroxy analogues of glutamate, pipecolate, lysine, proline and methionine,[13] as well as the *γ*-alkyl-branched *β*-hydroxy-α-amino acid MeBmt.[14] Minimal use of alcohol protection has greatly enhanced the efficiency of this approach from serine, which employs amino acylation of a suitable organometallic reagent followed by selective oxidation of the *β*-hydroxyl group. To prepare *β*-hydroxyvaline, two amine protecting groups (Boc and $PhSO_2-$) were investigated in routes without alcohol protection from serine methyl ester consisting of addition of methylmagnesium bromide to the ester to generate diol **3** and selective oxidation of the primary alcohol to acid **1** (Scheme 1).

The *N*-Boc-[15] and *N*-$PhSO_2$-serine[12] methyl esters **2a**,**b** were initially synthesized by literature methods; *N*-Boc-D-serine methyl ester **2a** was later obtained commercially for the larger-scaled procedure. The addition of CH_3MgBr to methyl ester **2** provided diol **3** as well as ketone **4** (Scheme 1). Under our best conditions, CH_3MgBr was added to a solution of **2a** at −78 °C in diethyl ether, and a solution of **2b** was added to a suspension of CH_3MgBr in 3:1 toluene/THF at 0 °C. After purification by silica gel column chromatography, diols **3a** and **3b** were respectively isolated in 83% and 81% yields. The corresponding ketone **4** was isolated as a minor product from both reactions, and it was not observed in the larger scaled synthesis of **3a** in which overhead stirring was employed.

N-Protected *β*-hydroxyvaline was obtained from the selective oxidation of diol **3**. Employing TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) free radical, sodium chlorite, and sodium hypochlorite in a sodium phosphate buffered acetonitrile solution,[16] we obtained *β*-hydroxyvalines **1a** and **1b** in 96% and 93% yields, respectively. Oxidation with oxygen in the presence of Pt in a 21:5:4 water/2-propanol/EtOAc mixture also provided **1b** in 76% yield.[13,17]

To ascertain if any racemization had occurred during the synthesis of (*R*)-*β*-hydroxyvalines **1a** and **1b** from L-serine, their enantiomeric purity was investigated after conversion to diastereomeric dipeptides **5** (Scheme 1). Both (*R*)- and (*S*)-phenylalanine methyl ester hydrochloride were reacted respectively with acid **1** using benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and 1-hydroxybenzotriazole (HOBt) in acetonitrile. Observation of the 400 MHz ^1H NMR spectra of crude samples of **5a** and **5b** in $CDCl_3$ and respective measurement of the signals for the diastereotopic α-protons at 3.83 and 3.89 ppm for **5a** and the *γ*-protons at 0.94 and 1.03 ppm for **5b** demonstrated dipeptides **5** to be of >97% and >98% diastereomeric purity, respectively. Protected *β*-hydroxyvalines **1a** and **1b** are thus assumed to be of similarly high enantiomeric purity.

A two-step synthesis of enantiopure N-protected *β*-hydroxyvaline from L-serine methyl ester has been developed featuring a Grignard addition followed by a selective oxidation of the resulting diol. By nucleophilic addition in the presence of a primary alcohol and oxidation in the presence of a tertiary alcohol, short high-yielding processes have been developed that furnish, respectively, multigram amounts of enantiopure (>97%) *N*-Boc-*β*-hydroxyvaline **1a** and hundred milligram amounts of enantiopure (>98%) *N*-benzenesulfonyl-*β*-hydroxyvaline **1b** in 80% and 75% overall yields.

Experimental Section

General Methods. Reagent and solvent purification, spectroscopy, spectrometric analyses, and chromatography all were performed as described in the general section of the experimental details presented in a previous work.[18]

(2*S*)-2-*N*-(Boc)amino-3-methyl-1,3-butanediol (3a). To a solution of *N*-(Boc)-L-serine methyl ester **2a** (295 mg, 1.35 mmol) in Et_2O (13 mL) at −78 °C was added dropwise a solution of 3.0 M CH_3MgBr in Et_2O (600 mol %, 8.1 mmol, 2.7 mL). The dry ice bath was removed, and the reaction mixture was stirred for 1 h at rt, cooled to 0 °C, and treated dropwise with a solution of aqueous saturated NH_4Cl (10 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with brine, dried, filtered, and evaporated to a residue that was purified on a silica gel column using 1:1 EtOAc/hexanes as eluant. First to elute was ketone **4a** as an oil (5.5 mg, 2%): TLC $R_f = 0.45$ (70% EtOAc in hexanes); $[\alpha]^{20}_D$ 7.7 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD) *δ* 1.44 (s, 9 H), 2.20 (s, 3 H), 3.78 (m, 1 H), 3.87 (m, 1 H), 4.16 (s, 1 H); ^{13}C NMR (300 MHz, CD_3OD) *δ* 28.3, 29.5, 63.3, 64.5, 81.6 158.8, 209.4; HRMS calcd for $C_9H_{18}NO_4$ (MH^+) 204.1235, found 204.1231. Second to elute was diol **3a** as a white solid (246 mg, 83%): TLC $R_f = 0.35$ (70% EtOAc in hexanes); mp 87−89 °C; $[\alpha]^{20}_D$ −4.9 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD) *δ* 1.15 (s, 3 H), 1.22 (s, 3 H), 1.45 (s, 9 H), 3.49 (m, 1 H), 3.60 (m, 1 H), 3.79 (dd, 1 H, $J = 4.0, 11.2$); ^{13}C NMR (300 MHz, CD_3OD) *δ* 27.1, 28.6, 29.6, 61.9, 63.4, 74.4, 81.0, 159.5; HRMS calcd for $C_{10}H_{22}NO_4$ (MH^+) 220.1549, found 220.1547. Anal. Calcd for $C_{10}H_{21}NO_4$: C, 54.77; H, 9.65; N, 6.39. Found: C, 54.79; H, 10.62; N, 6.38.

(2*S*)-2-*N*-(Benzenesulfonyl)amino-3-methyl-1,3-butanediol (3b). To a 1.4 M solution of CH_3MgBr in 3:1 toluene/THF (600 mol %, 6 mmol, 52 mL) was added dropwise at 0 °C a solution of serine ester **2b** (247 mg, 1.0 mmol) in THF (10 mL). The ice bath was removed, and the reaction mixture was stirred for 1.5 h at rt. After workup and chromatography as described

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above for **3a**, first to elute was ketone **4b** as a white solid (14.5 mg, 6%): TLC $R_f = 0.45$ (70% EtOAc in hexanes); mp 142−144 °C; $[\alpha]^{20}_D$ 7.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 2.09 (s, 3 H), 3.61 (dd, 1 H, $J = 5.0, 11.3$), 3.77 (q, 2 H, $J = 4.2, 11.3$), 3.94 (t, 1 H, $J = 4.4$), 7.54 (m, 2 H), 7.59 (m, 1 H), 7.86 (m, 2 H); ^{13}C NMR (300 MHz, CD_3OD) δ 28.5, 64.2, 66.0, 128.9, 131.0, 134.6, 143.0, 208.2; HRMS calcd for $C_{10}H_{14}NO_4S$ (MH^+) 244.0643, found 244.0634. Second to elute was diol **3b** as an oil (210 mg, 81%): TLC $R_f = 0.40$ (70% EtOAc in hexanes); $[\alpha]^{20}_D$ −28.1 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.10 (s, 3 H), 1.18 (s, 3 H), 3.17 (t, 1 H, $J = 5.1$), 3.52 (m, 2 H), 7.53 (m, 2 H), 7.57 (m, 1 H), 7.9 (m, 2 H); ^{13}C NMR (300 MHz, CD_3OD) δ 27.0, 29.1, 63.6, 64.2, 74.7, 128.0, 131.1, 134.3, 144.2; HRMS calcd for $C_{11}H_{18}NO_4S$ (MH^+) 260.0957, found 260.0957. Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.44; H, 6.89; N, 5.24. On a larger scale, **2b** (3.0 g, 12.1 mmol) gave **3b** (2.55 g, 81%) and **4b** (70 mg, 2.5%).

(*R*)-β-Hydroxy-*N*-(Boc)valine (1a). A mixture of diol **3a** (439 mg, 2 mmol), sodium phosphate buffer (7.5 mL, 0.67 M, pH = 6.7), and TEMPO (10 mol %, 0.2 mmol, 31 mg) in MeCN (10 mL) was heated to 35 °C and treated dropwise simultaneously over 2 h (Caution! Do not mix bleach and sodium chlorite before adding to the reaction mixture)[16] with sodium chlorite ($NaClO_2$, 200 mol %, 4 mmol, 2 mL of solution: 5.71 g 80% w/w, 50.5 mmol in 25 mL in water) and diluted bleach (NaOCl, 2 mol %, 0.04 mmol, 1050 μL of solution: 0.66 mL commercial bleach 10.8% w/w in 25 mL of water). The mixture was stirred at 35 °C overnight, cooled to rt, treated with solid citric acid (pH = 3), and extracted with EtOAc (3 × 10 mL). The organic phases were combined and evaporated. The residue was dissolved in a solution of saturated Na_2CO_3 (20 mL) and washed with EtOAc (2 × 10 mL). The aqueous phase was acidified with H_3PO_4 1 M (pH = 3), saturated with NaCl, and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried, filtered, and evaporated to give a white solid **1a** (444 mg, 96%): mp 125−126 °C; $[\alpha]^{20}_D$ +2.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.25 (s, 3 H), 1.29 (s, 3 H), 1.45 (s, 9 H), 4.08 (s, 1 H); ^{13}C NMR (300 MHz, CD_3OD) δ 27.8, 27.9, 29.5, 64.1, 73.2, 81.6, 158.8, 175.1; HRMS calcd for $C_{10}H_{20}NO_5$ (MH^+) 234.1341, found 234.1337. Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 51.65; H, 9.00; N, 5.97.

(*R*)-β-Hydroxy-*N*-(benzenesulfonyl)valine (1b). The protocol described above for **1a** was employed with **3b** (130 mg, 0.5 mmol) and gave a white solid **1b** (127.5 mg, 93%). Alternatively, a solution of diol **3b** (134 mg, 0.512 mmol) in water (13 mL), EtOAc (4 mL), and *i*-PrOH (5 mL) was treated with freshly prepared PtO_2 (50 wt %, 67 mg, from reduction at 3 atm of H_2 in 8 mL of water).[19] Oxygen was bubbled through the suspension at 60 °C until all of the starting material had been consumed, usually 24 h. The reaction mixture was cooled to rt, and the catalyst was removed by filtration on Celite. The filtrate was saturated with NaCl and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried, filtered, and evaporated to give a white solid **1b** (106 mg, 76%): mp 164.4−165.5 °C; $[\alpha]^{20}_D$ −30.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.22 (s, 3 H), 1.26 (s, 3 H), 3.72 (s, 1 H), 7.52 (m, 2 H), 7.57 (m, 1 H), 7.84 (m, 2 H); ^{13}C NMR (300 MHz, CD_3OD) δ 27.1, 28.2, 66.4, 73.3, 129.2, 130.9, 134.6, 142.7, 173.8; HRMS calcd for $C_{11}H_{16}NO_5S$ (MH^+) 274.0758, found 274.0749. Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 48.20; H, 5.52; N, 5.11; S, 11.70. Found: C, 48.40; H, 5.60; N, 5.10; S, 11.92.

Enantiomeric Purity of (*R*)-β-Hydroxy-*N*-(Boc)valine (1a) and (*R*)-β-Hydroxy-*N*-(benzenesulfonyl)valine (1b). A solution of (*R*)-β-hydroxy-*N*-(Boc)valine **1a** (27 mg, 0.12 mmol) or (*R*)-β-hydroxy-*N*-(benzenesulfonyl)valine **1b** (32 mg, 0.12 mmol) in CH_3CN (1 mL) at 0 °C was treated with HOBt (100 mol %, 22 mg, 0.12 mmol) and TBTU (150 mol %, 58 mg, 0.18 mmol) and stirred for 30 min at 0 °C. The reaction mixture was treated with a premixed solution of (*R*)- or (*S*)-phenylalanine methyl ester hydrochloride (300 mol %, 78 mg, 0.36 mmol) and diisoprolyethylamine (DIEA) (400 mol %, 0.48 mmol, 62 mg, 84 μL) in CH_3CN (1 mL) at 0 °C. The reaction mixture was stirred 48 h at rt when TLC (EtOAc) showed complete disappearance of the starting acid **1**. The solvent was evaporated, and the solid residue was resuspended in CH_2Cl_2 (10 mL). The organic phase was washed with an aqueous saturated solution of $NaHCO_3$ (2 × 3 mL), 1 N NaH_2PO_4 (2 × 3 mL), and brine (3 mL), dried, filtered, and evaporated to give a residue that was directly examined by 400 MHz ^{1}H NMR spectroscopy in $CDCl_3$. Observation of the crude **5a** and **5b** and respective measurement of the diasterotopic α-protons at 3.83 and 3.89 ppm for **5a** and the γ-protons at 0.94 and 1.03 ppm for **5b** demonstrated that they were of >97% and >98% diastereomeric purity, respectively.

(*R,S*)-β-Hydroxy-*N*-(Boc)valinylphenylalanine methyl ester (*R,S*)-5a: ^{1}H NMR δ 1.03 (s, 3 H), 1.07 (s, 3 H), 1.35 (s, 9 H), 2.96 (dd, 1 H, $J = 5.9, 13.9$), 3.09 (dd, 1 H, $J = 5.3, 14$), 3.64 (s, 3 H), 3.83 (d, 1 H, $J = 9$), 4.78 (m, 1 H), 5.38 (br d, 1 H, $J = 8.9$), 6.92 (br d, 1 H, $J = 8$), 7.23−7.5 (m, 5 H).

(*R,R*)-β-Hydroxy-*N*-(Boc)valinylphenylalanine methyl ester (*R,R*)-5a: ^{1}H NMR δ 1.08 (s, 3 H), 1.19 (s, 3 H), 1.38 (s, 9 H), 3.04 (m, 2 H), 3.66 (s, 3 H), 3.89 (d, 1 H, $J = 9$), 4.79 (dd, 1 H, $J = 6.6, 13.6$), 5.41 (br d, 1 H, $J = 8.9$), 6.77 (br d, 1 H, $J = 7.9$), 7.0−7.26 (m, 5 H).

(*R,S*)-β-Hydroxy-*N*-(benzenesulfonyl)valinylphenylalanine methyl ester (*R,S*)-5b: ^{1}H NMR δ 1.03 (s, 3 H), 1.28 (s, 3 H), 2.90 (m, 2 H), 3.06 (m, 1 H), 3.67 (s, 3 H), 4.59 (m, 1 H), 6.7−7.8 (m, 10 H).

(*R,R*)-β-Hydroxy-*N*-(benzenesulfonyl)valinylphenylalanine Methyl Ester (*R,R*)-5b: ^{1}H NMR δ 0.94 (s, 3 H), 1.25 (s, 3 H), 2.8−3.1 (m, 3 H), 3.68 (s, 3 H), 4.62 (dd, 1 H, $J = 7.2, 13.6$), 6.8−7.8 (m, 10 H).

(*S*)-β-Hydroxy-*N*-(Boc)valine. A flame-dried, 1 L, three-necked, round-bottomed flask equipped with an overhead stirrer, thermometer, and glass stopper, under a nitrogen atmosphere, was charged with a solution of commercial *N*-Boc-D-serine methyl ester **2a** (9.0 g, 41.05 mmol) in Et_2O (425 mL), cooled to −78 °C, and treated dropwise with a 3.0 M solution of CH_3MgBr in Et_2O (3.0 M, 600 mol %, 246.3 mmol, 82 mL). The dry ice bath was removed, and the mixture was allowed to reach rt, stirred for 1 h, cooled to 0 °C, and treated dropwise with a solution of aqueous saturated NH_4Cl (400 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 400 mL). The organic phases were combined, washed with brine, dried with anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator with a bath at 40 °C to a white solid residue (8.37 g, 38.17 mmol) that was dissolved in MeCN (190 mL) and treated with sodium phosphate buffer (145 mL, 0.67 M, pH = 6.7) and TEMPO (10 mol %, 3.82 mmol, 597 mg), heated to 35 °C, and treated dropwise simultaneously over 2 h (Caution! Do not mix bleach and sodium chlorite before being added to the reaction mixture) with sodium chlorite ($NaClO_2$, 200 mol %, 76.34 mmol; 38 mL of solution: 22.84 g 80%, 202 mmol in 100 mL in water) and diluted bleach (NaOCl, 0.02 eq, 0.04 mmol, 1050 μL of solution: 2.64 mL commercial bleach 10.8% in 100 mL of water).[18] The mixture was stirred at 35 °C overnight, cooled to rt, and treated with solid citric acid (pH = 3), saturated with solid NaCl, and extracted with EtOAc (3 × 500 mL). The organic phases were combined and evaporated. The residue was dissolved in a solution of Na_2CO_3 2M (400 mL) and washed with EtOAc (2 × 100 mL). The aqueous phase was acidified with H_3PO_4 1M (pH = 3), saturated with NaCl, and extracted with EtOAc (3 × 200 mL). The organic phases were combined, dried, filtered, and evaporated to give a white solid (8.37 g). Recrystallization from a mixture of hexanes and EtOAc gave (*S*)-β-hydroxy-*N*-(Boc)valine as white crystals (7.43 g, 78%): mp 125−126 °C; $[\alpha]^{20}_D$ −2.5 (*c* 1.0, MeOH).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1** and **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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