A Stereoselective Route to Hydroxyethylamine Dipeptide Isosteres†

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An efficient synthesis of stereodefined hydroxyethylamine dipeptide isosteres has been developed, utilizing a *syn*-selective Grignard addition and reductive amination as the key reactions.

Extensive research toward finding potent enzyme inhibitors active against HIV protease has led to the development of various peptide isosteres, wherein the scissile peptide bond is replaced by hydrolytically more stable isosteric functional groups.[1] A useful approach in this regard has been the incorporation of a transition-state isostere, mimicking the tetrahedral transition-state of amide bond hydrolysis, into the designed inhibitors. In this context, hydroxyethylamine (HEA) dipeptide isosteres (Figure 1) constitute a useful class of HIV protease inhibitors.[2,3] Interestingly, studies regarding the effect of the absolute configuration of the structurally critical hydroxy group of these class of compounds have revealed that (i) the hydroxy configuration necessary for maximal protease inhibitory activity depends on the peptide framework and (ii) inhibitors may bind to the protease with either of the two possible configurations.[4] It appears that, in these inhibitors where binding interactions involve several sub-sites, substituents present in P_4-P_3 and $P_{3'}$ positions exert significant influence on the $P_1-P_{1'}$ binding interactions. Consequently, a number of methods have been reported for the synthesis of HEA peptide isosteres with either of the two possible hydroxy group configurations. Interestingly, in all the above methods, the key HEA peptide isostere structural core has been assembled via initial synthesis of a chiral α-aminoalkyl epoxide and subsequent opening of the epoxide with suitable amine nucleophiles.[4−10] We report herein an alternative approach toward building up the HEA dipeptide framework

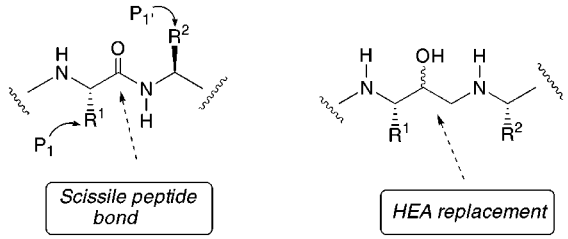

Figure 1. Hydrolytically stable hydroxyethylamine (HEA) dipeptide isosteric replacement for the scissile peptide bond.

via a stereoselective Grignard addition and a reductive amination as the key reaction steps.

Recent work from our laboratory has demonstrated the utility of chelation-controlled, *syn*-selective addition of Grignard reagents to chiral α-amino aldehydes for the stereoselective formation of structurally important 1,2-amino alcohol units.[11] In continuation of the above studies, we envisaged that (i) addition of vinylmagnesium bromide to phenylalaninal (derived from L-phenylalanine) forming the *syn*-*β*-amino alcohol fragment **4**, followed by (ii) utilization of the vinyl group as an aldehyde precursor and subsequent reductive amination with various amino acids **3** will provide a direct route to stereodefined hydroxyethylamine peptide isosteres **1** (Scheme 1). Results of the studies thus undertaken are described below.

In a one-pot reaction, L-phenylalanine was converted to the known *N*-Boc-phenylalaninol (**5**)[12] (Scheme 2) by sequential carboxylic acid reduction and Boc-protection of the amino group. Following a reported protocol,[13] Swern oxidation of the alcohol **5** to the corresponding aldehyde and its in-situ reaction with vinylmagnesium bromide afforded the *syn*-amino alcohol **4** as the major product (*syn:anti* = 87:13, diastereoisomers separated by column chromatography). The pivotal intermediate **4**, having the required stereodefined *β*-amino alcohol functionality and the strategic terminal alkene moiety, represents an ideal precursor for the proposed synthesis of the hydroxyethylamine isosteres. Subsequent acetonide protection of the amino alcohol functionality provided the oxazolidine derivative **6**, for which the

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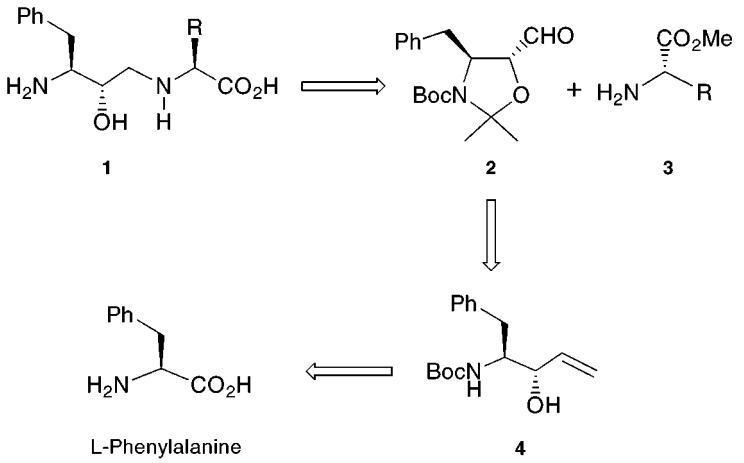
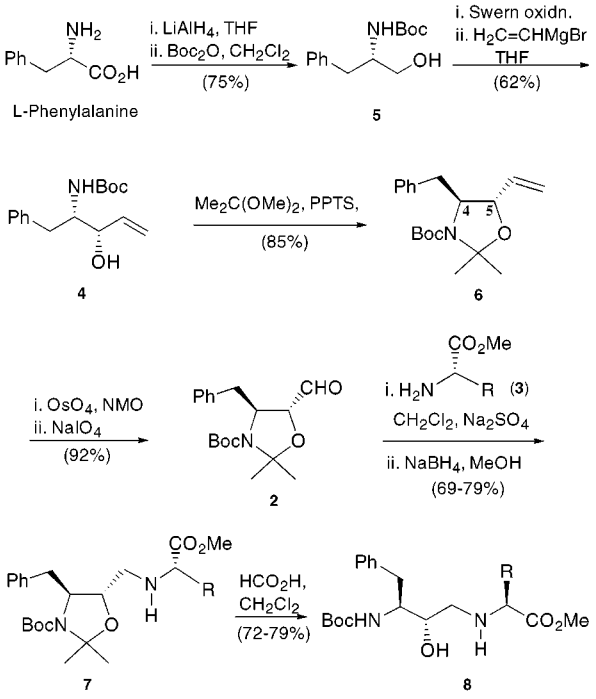
Scheme 1



Scheme 2



3,7,8, a. R = $MeSCH_2CH_2$
b. R = $PhCH_2$
c. R = Me
d. R = $(Me)_2CH$
e. R = $(Me)_2CHCH_2$

coupling constant between the two protons in the ring ($J_{4,5}$ = 6.3 Hz) is consistent with their trans-relationship, thereby also confirming the assigned stereochemistry.

Introduction of the second amino acid fragment via functionalization of the terminal double bond of oxazolidine **6** was next investigated. Thus, oxidative degradation of the alkene under standard conditions afforded the corresponding aldehyde **2**, which was then subjected to reductive amination with various amino acid esters **3**, affording uneventfully the expected diamino alcohol derivatives **7** in good overall yield. Enantiomeric purity of the products thus formed were verified by HPLC analysis. Finally, deprotection of the acetonide linkage resulted in the target hydroxyethylamine dipeptide isosteres **8** in good yields.

In conclusion, a new method, resulting in an efficient, stereoselective route to biologically important hydroxyethylamine dipeptide isosteres, has been developed following a relatively short and simple reaction sequence. The strategy and the approach described is of general applicability and can be easily extended to synthesize a large number of possible structural variants, utilizing different amino acid combinations to form the HEA dipeptide skeleton. It is hoped that the described method will be a useful addition to existing methodologies for synthesizing hydroxyethylamine peptide isosteres of potential biological importance.

Experimental Section[14]

(3*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-5-phenyl-1-pentene (4). To a stirred solution of oxalyl chloride (2.4 mL, 27.88 mmol) and CH_2Cl_2 (50 mL) at −78 °C under nitrogen atmosphere was added DMSO (2.26 mL, 31.86 mmol) dropwise. After stirring for 30 min, a solution of the amino alcohol **5**[12] (4 g, 15.93 mmol) in CH_2Cl_2 (100 mL) was added over 30 min. The mixture was warmed to −35 °C and stirred for 30 min at this temperature, followed by addition of diisopropylethylamine (19 mL, 111.55 mmol) over 5 min. The reaction mixture was then warmed to 0 °C in 15 min and transferred through a cannula to a room-temperature solution of vinylmagnesium bromide (1 M soln in THF, 100 mL, 100 mmol) over 30 min. After stirring for 2 h at room temperature, the reaction mixture was poured into aqueous saturated NH_4-Cl solution (100 mL) and acidified to pH 4 by adding 10% aqueous HCl solution. The organic layer was separated, the aqueous layer extracted with $CHCl_3$ (3 × 100 mL), and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4, solvent was removed under vacuum and the residual oil purified by flash column chromatography (ethyl acetate/hexane = 1/12) to yield the amino alcohol **4** (2.7 g, 62%) as a viscous semisolid: $[\alpha]^{22}_D$ = −43.4 (*c*=1, $CHCl_3$); IR (neat) 3364, 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (br s, 9H), 2.88 (d, J = 7.3 Hz, 2H), 3.76 (m, 1H), 4.07 (br s, 1H), 4.75 (d, J = 8.9 Hz, 1H), 5.22 (m, 2H), 5.89 (m, 1H), 7.23 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.1, 138.4, 129.3, 128.4, 128.3, 126.3, 116.0, 79.4, 72.8, 56.2, 38.1, 28.3; FABMS 278 (MH^+). Anal. Calcd for $C_{16}H_{23}NO_3$ (277.36): C, 69.29; H, 8.36; N, 5.05. Found: C, 69.61; H, 8.28; N, 4.78.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-(1-ethynyl)-1,3-oxazolidine (6). A solution of the amino alcohol **4** (3 g, 10.8 mmol), 2,2-dimethoxypropane (19.5 mL, 123.7 mmol), and a catalytic amount of pyridinium *p*-toluenesulfonate (50 mg) in toluene (35 mL) was stirred at 80 °C for 4 h. Removal of the solvent under vacuum and purification of the resulting residue by column chromatography (ethyl acetate/hexane = 1/19) afforded the pure oxazolidine derivative **6** (2.9

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g, 85%) as a light yellow viscous liquid: $[\alpha]^{22}_D = 11.5$ ($c = 1.1$, $CHCl_3$); IR (neat) 1697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 and 1.55 (2s, 15H), 3.13 (br s, 2H), 3.89 (m, 1H), 4.30 (dd, $J = 4.04$ and 6.3 Hz, 1H), 5.18 (m, 2H), 5.74 (m, 1H), 7.25 (m, 5H); FABMS 318 (MH^+). Anal. Calcd for $C_{19}H_{27}NO_3$ (317.42): C, 71.89; H, 8.57; N, 4.41. Found: C, 71.51; H, 8.57; N, 4.59.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-formyl-1,3-oxazolidine (2). To a stirred solution of the vinyl oxazolidine **6** (2.5 g, 7.88 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (4.61 g, 39.4 mmol) in acetone (15 mL) and water (3 mL) at room temperature was added a catalytic amount of OsO_4 solution in toluene (5% solution, 5 mol %). After stirring for 8 h, a saturated aqueous solution of Na_2SO_3 (5 mL) was added to the mixture and the resulting solution extracted with ethyl acetate (4 × 50 mL). The combined extracts were dried over Na_2SO_4, and the solvent was removed thoroughly under vacuum affording the crude dihydroxylated compound (2.7 g), which was dissolved in CH_2Cl_2 (40 mL) and added in one lot to a vigorously stirred suspension of $NaIO_4$ supported in silica gel (16 g, 20% $NaIO_4$)[15] in CH_2Cl_2 (25 mL) maintained at 0 °C. After stirring at the same temperature for 1 h, the solid was removed by filtration and washed with $CHCl_3$ (3 × 25 mL), and the combined filtrate was concentrated under vacuum. The resulting residue was filtered through a pad of silica gel yielding the pure aldehyde **2** (2.31 g, 92% two steps) as a viscous liquid: $[\alpha]^{22}_D = 6$ ($c = 1.0$, $CHCl_3$); IR (neat) 1728, 1691 cm^{-1}; ^1H NMR δ 1.5 (br s, 15H), 2.8 and 3.22 (2m, 2H), 4.12 (m, 1H), 4.40 (m, 1H), 7.23 (m, 5H), 9.62 (br s, 1H); MS (FAB+) 320 (MH^+). The aldehyde **2** was found to decompose on storage and was used immediately for the next reaction.

General Procedure for the Synthesis of 7a−e. To a stirred mixture of the aldehyde **2** (1 mmol) and anhydrous Na_2SO_4 (50 mg) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of the commercially available amino acid methyl ester **3** (1 mmol) in CH_2Cl_2 (5 mL) and stirring continued for 1 h while allowing the reaction mixture to warm to room temperature. The mixture was filtered, the solid residue washed with CH_2Cl_2 (2 × 5 mL), and the combined filtrate concentrated under reduced pressure. The syrupy residue thus obtained was dissolved in MeOH (15 mL) and cooled to − 15 °C, and $NaBH_4$ (1.2 mmol) was added to the solution in portions. After stirring the reaction mixture for 2 h at room temperature, water (15 mL) was added to the reaction mixture, and the resulting solution was extracted with ethyl acetate (4 × 25 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residual liquid was purified by column chromatography (ethyl acetate/hexane = 1/9) affording the product. Enantiomeric purity of the products formed were confirmed by HPLC analysis. HPLC conditions; column: CHIRALCEL (ODS); mobile phase: 90% acetonitrile + 10% water; flow rate: 1 mL/min; UV detection at 225 nm.

7a: colorless oil; 70% yield; $[\alpha]^{22}_D = -30.6$ (c=1.10, $CHCl_3$); IR (neat) 3315, 1748, 1697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 (br s, 15H), 1.75 (m, 2H), 2.05 (s, 3H), 2.11 (br s, 1H), 2.49 (t, $J = 7.3$ Hz, 2H), 2.59 (m, 3H), 3.20 (m, 2H), 3.59 (s, 3H), 3.62 (m, 1H), 3.98 (m, 1H), 7.23 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.9, 160.0, 137.7, 129.5, 128.5, 126.6, 91.3, 80.5, 78.4, 61.8, 60.2, 51.7, 51.5, 32.6, 30.4, 28.5, 27.3, 15.3; FABMS 467 (MH^+). Anal. Calcd for $C_{24}H_{38}N_2O_5S$ (466.63): C, 61.77; H, 8.21; N, 6.00; S, 6.87. Found: C, 61.61; H, 8.28; N, 6.38; S, 6.49.

7b: colorless oil; 74% yield; $[\alpha]^{22}_D = -12.9$ ($c = 1.51$, $CHCl_3$); IR (neat) 3402, 1742, 1686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.49 (br s, 15H), 2.18 (br s, 1H), 2.45−2.78 (m, 2H), 2.48 (m, 2H), 3.22−3.35 (m, 2H), 3.54 (s, 3H), 3.70−3.91 (m, 2H), 3.95 (m, 1H), 7.18 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.4, 161.0, 137.6, 137.1,129.3, 129.0, 128.3, 128.1, 126.5, 126.4, 91.8, 79.8, 78.3, 62.8, 61.5, 51.3, 39.6, 28.4, 27.1; FABMS 483 (MH^+). Anal. Calcd for $C_{28}H_{38}N_2O_5$ (482.61): C, 69.68; H, 7.94; N, 5.80. Found: C, 70.03; H, 8.15; N, 5.67.

7c: colorless oil; 69% yield; $[\alpha]^{22}_D = -27.8$ ($c = 1.20$, $CHCl_3$); IR (neat) 3353, 1751, 1692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, $J = 6.38$ Hz, 3H), 1.58 (br s, 15H), 2.14 (br s, 1H), 2.63−2.78 (m, 2H), 3.22 (m, 2H), 3.69 (s, 3H), 3.82 (m, 2H), 4.03 (m, 1H), 7.22 (m, 5H); FABMS 407 (MH^+). Anal. Calcd for $C_{22}H_{34}N_2O_5$ (406.52): C, 65.00; H, 8.43; N, 6.89. Found: C, 65.27; H, 8.70; N, 7.12.

7d: colorless oil; 72% yield; $[\alpha]^{22}_D = -25.2$ ($c = 1.20$, $CHCl_3$); IR (neat) 3353, 1746, 1693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, $J = 6.3$ Hz, 6H), 1.50 (br s, 15H), 1.8 (m, 1H), 2.17 (br s, 1H), 2.58−2.71 (m, 2H), 2.89−3.20 (m, 2H), 3.67 (s, 3H), 3.73 (m, 2H), 4.07 (m, 1H), 7.17 (m, 5H); FABMS 435 (MH^+). Anal. Calcd for $C_{24}H_{38}N_2O_5$ (434.57): C, 66.33; H, 8.81; N, 6.45. Found: C, 66.49; H, 8.53; N, 6.80.

7e: colorless oil; 79% yield; $[\alpha]^{22}_D = -28.7$ ($c = 1.22$, $CHCl_3$); IR (neat) 3448, 1752, 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (2d, 6H), 1.36 (m, 3H), 1.52 (br s, 15H), 2.56−2.74 (m, 2H), 3.01−3.33 (m, 2H), 3.65 (s, 3H), 3.82 (m, 2H), 3.99 (m, 1H), 7.20 (m, 5H); FABMS 449 (MH^+); Anal. Calcd for $C_{25}H_{40}N_2O_5$ (448.60): C, 66.94; H, 8.99; N, 6.24. Found: C, 67.23; H, 8.68; N, 6.57.

General Procedure for the Synthesis of 8a−e. To a well-stirred solution of **7** (1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 96% formic acid (10 mL) dropwise. After 30 min. the cooling bath was removed and stirring continued at room temperature for another 30 min. The reaction mixture was then concentrated under vacuum (below 40 °C), and the resulting residue was dissolved in $CHCl_3$ (20 mL), washed sequentially with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residual liquid was purified by column chromatography (ethyl acetate/hexane = 1/3), affording the product.

8a: light yellow oil; 79% yield; $[\alpha]^{22}_D = -35.9$ ($c = 0.80$, $CHCl_3$); IR (neat) 3453, 1736, 1688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (br s, 9H), 1.90 (m, 2H), 2.07 (s, 3H), 2.31 (br s, 1H), 2.53 (m, 4H), 2.88 (br d, $J = 7.4$ Hz, 2H), 3.33 (dd, J = 4.5 and 7.7 Hz, 1H), 3.52 (m, 1H), 3.69 (br s, 4H), 4.89 (d, J = 9.4 Hz,1H), 7.21 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.7, 155.5, 138.3, 129.4, 128.6, 128.4, 126.7, 79.2, 68.5, 59.4, 53.7, 52.0, 50.6, 45.3, 39.1, 32.2, 30.5, 29.6, 28.3, 15.4; FABMS 427 (MH^+). Anal. Calcd for $C_{21}H_{34}N_2O_5S$ (426.57): C, 59.13; H, 8.03; N, 6.57, S, 7.52. Found: C, 59.43; H, 8.16; N, 6.93; S, 7.18.

8b: light yellow oil; 73% yield; $[\alpha]^{22}_D = -19.8$ ($c = 0.70$, $CHCl_3$); IR (neat) 3440, 1752, 1692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (br s, 9H), 2.48 (m, 3H, 1H exchangeable with D_2O), 2.72 (d, $J = 6.6$ Hz, 2H), 2.98 (dd, $J = 5.5$ and 13.3 Hz, 2H), 3.40 (m, 2H), 3.62 (m, 1H), 3.68 (s, 3H), 4.83 (d, $J = 9.9$ Hz, 1H), 7.19 (m, 10H); FABMS 443 (MH^+). Anal. Calcd for $C_{25}H_{34}N_2O_5$ (442.55): C, 67.85; H, 7.74; N, 6.33. Found: C, 67.63; H, 8.07; N, 6.65.

8c: colorless oil; 72% yield; $[\alpha]^{22}_D = -13.3$ ($c = 0.73$, $CHCl_3$); IR (neat) 3411, 1743, 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.7$ Hz, 3H), 1.38 (s, 9H), 2.33 (m, 1H), 2.83 (m, 2H), 3.28 (m, 2H), 3.63 (m, 2H), 3.71 (s, 3H), 3.98 (m, 1H), 4.97 (m,1H), 7.22 (m, 5H); FABMS 367 (MH^+). Anal. Calcd for $C_{19}H_{30}N_2O_5$ (366.45): C, 62.27; H, 8.25; N, 7.64. Found: C, 62.12; H, 8.58; N, 7.91.

8d: colorless oil; 74% yield; $[\alpha]^{22}_D = -26.9$ ($c = 1.20$, $CHCl_3$); IR (neat) 3401, 1744, 1691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (br d, 6H), 1.41 (br s, 9H), 1.9 (m, 1H), 2.44 (dd, $J = 4.4$ and 13.3 Hz, 1H), 2.64 (m, 1H), 2.93 (m, 2H), 3.51 (m, 1H), 3.66 (br s, 1H), 3.72 (s, 4H), 4.88 (d, $J = 9.0$ Hz,1H), 7.24 (m, 5H); FABMS 395 (MH^+). Anal. Calcd for $C_{21}H_{34}N_2O_5$ (394.25): C, 63.93; H, 8.69; N, 7.10. Found: C, 64.21; H, 8.63; N, 7.42.

8e: colorless oil; 78% yield; $[\alpha]^{22}_D = -31.8$ ($c = 2.20$, $CHCl_3$); IR (neat) 3348, 1746, 1682 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, $J = 6.8$ Hz, 6H), 1.38 (br s, 10H), 1.69 (m, 2H), 2.43 (dd, $J = 4.0$ and 12.7 Hz, 1H), 2.5−2.63 (m, 1H), 2.88 (d, J = 7.6 Hz, 2H), 3.18 (br t, $J = 7.4$ Hz, 1H), 3.49 (m, 1H), 3.62 br (s, 1H), 3.67 (s, 3H), 4.83 (d, $J = 9.3$ Hz,1H), 7.23 (m, 5H); FABMS 409 (MH^+). Anal. Calcd for $C_{22}H_{36}N_2O_5$ (408.53): C, 64.68; H, 8.88; N, 6.86. Found: C, 64.85; H, 8.91; N, 7.07.

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