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Research Article

A novel asymmetric synthesis of tritium and carbon-14 labeled (*R*)-ibuprofen

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Summary

An efficient asymmetric synthesis of tritium and carbon-14 labeled *R*-ibuprofen was achieved in good overall yield (15% and 47%, respectively) and excellent enantiomerical excess (> 98% e.e.), using (4*R*, 5S)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: *R*-ibuprofen; radioactive labeling; tritium; carbon-14; asymmetric synthesis; chiral auxiliary

Introduction

2-(4-isobutylphenyl)propionic acid (ibuprofen) is one of the most well-known non-steroidal anti-inflammatory agents. The metabolic transformations of ibuprofen include oxidation at both the methine and terminal methyl carbon of the isobutyl side-chain to give the hydroxy metabolite and carboxy metabolite. Most importantly, it has been also shown that ibuprofen undergoes metabolic chiral inversion at the 2-position of the propionic acid group from the *R*-enantiomer to the *S*-isomer.[1–3] Evidently, this *in vivo* bioactivation process leads to enhanced therapeutic and toxic effects of the drug. As the metabolic chiral inversion is an important reaction in the pharmacokinetics of some optically active drugs, the radioisotopic labeled ibuprofen was needed for fatty acid CoA lipases inhibition studies. The carbon-14 labeled (*R*)-ibuprofen was first synthesized, however, the specific activity of [^{14}C](*R*)-ibuprofen was not high enough for the assay, so tritium

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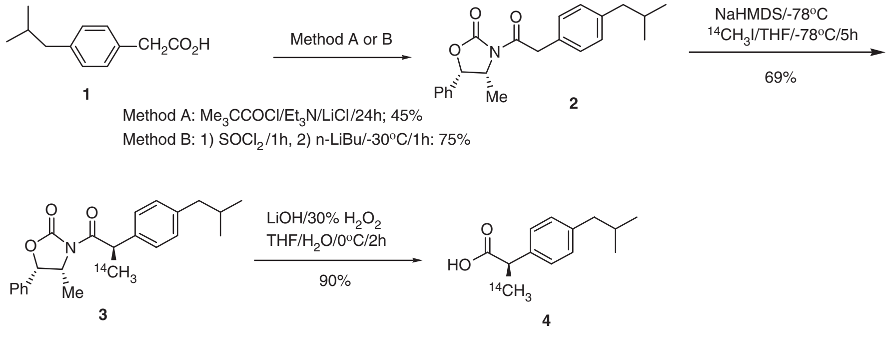
labeled ibuprofen was synthesized. In this paper, we would like to introduce a novel asymmetric synthesis of radio-labeled (*R*)-ibuprofen.

Results and discussion

The synthesis of racemic stable-isotope labeled ibuprofen has been reported in literatures.[4–6] The known seven-step synthetic approach could be adapted to prepare radiolabeled racemic ibuprofen. The desired *R*-enantiomer of ibuprofen could then be separated by chiral prep. HPLC. However, considering the long synthetic steps and the loss of half radioactive material, a more efficient asymmetric synthesis needed to be developed.

Unlabeled *S*-ibuprofen was synthesized in 95–96% e.e. using homochiral *N*-acylbornanesultam[7] or 4-isopropyl-2-oxazolidinone[8] as chiral auxiliaries. It was reported that an asymmetric methylation of 4-methyl-5-phenyl-2-oxazolidinone imide derivatives gave a higher diastereoselectivity (>95% d.e.) than 4-substituted 2-oxazolidinone imides.[9] Therefore, 4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone was applied as the chiral auxiliary to prepare both [^{14}C] and [^{3}H](*R*)-ibuprofen.

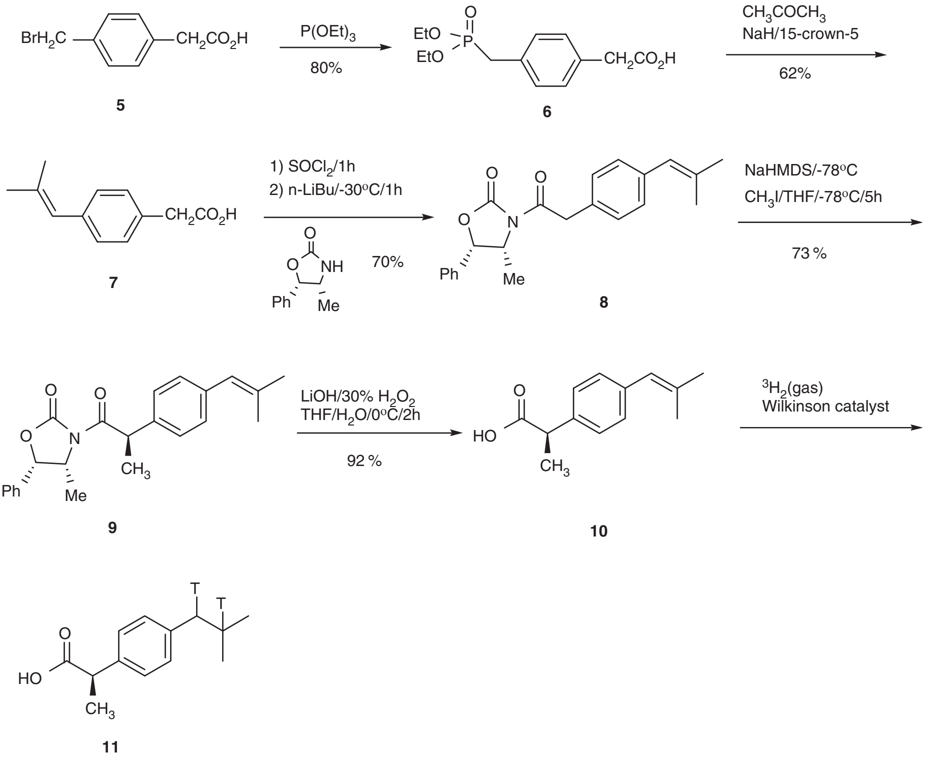
Carbon-14 labeled (*R*)-ibuprofen was synthesized in three steps (see Scheme 1) in an overall 47% yield (>98% e.e.). 4-Isobutylphenylacetic acid **1** was prepared from isobutylbenzene in two steps by adapting the known procedure.[4] Two methods, A and B, for the *N*-acylation of the oxazolidinone were applied.[8] Method B was preferred due to its higher yield and shorter reaction time. As expected, the asymmetric methylation of imide **2** with [^{14}C]MeI in the presence of NaHDMS gave the desired methylated product **3** with high diastereoselectivity (98.2% d.e. based on a chiral HPLC assay). Hydrolysis of the chiral auxiliary with standard reaction conditions (LiOH/30% H_2O_2) furnished the desired [^{14}C]*R*-ibuprofen **4** in 81%. The chemical and radiochemical purities of **4** were found to be >98% and specific activity was found to be 54.8 mCi/mmol by gravimetric assay.



Scheme 1. Asymmetric synthesis of [^{14}C]*R*-ibuprofen

The new synthetic approach was easily applied to the preparation of the chiral unsaturated precursor **10** of *R*-ibuprofen. Thus, the treatment of commercially available *p*-bromomethylphenylacetic acid with triethyl phosphine formed triethylphosphonium bromide **6**. Wadsworth-Emmons olefination gave olefin **7** in the presence of 15-crown-5 in 62% yield, but only 32% without the crown ether. Unsaturated phenylacetic acid **7** was converted to the corresponding acryl chloride with $SOCl_2$, followed by the *N*-acrylation of the 4-methyl-5-phenyl-2-oxazolidinone. The treatment of the chiral imide **8** with NaHMDS in THF afforded the enolate which was stereoselectively alkylated with methyl iodide to furnish the α-methyl intermediate **9** with >95% d.e. Removal of the chiral auxiliary using LiOH-H_2O_2 in THF/H_2O resulted in the formation of desired unsaturated chiral acid **10**. The enantiomeric excess (e.e.) of **3**, **4**, **9** and **10** were determined to be more than 97% from their 400 MHz ^{1}H-NMR and chiral HPLC analysis.

The tritiation of unsaturated precursor **10** of *R*-ibuprofen was completed in presence of Wilkinson's catalyst to form the desired [$^3H_2$] *R*-ibuprofen with 99.72% radiochemical purity and 98.5% enantiomeric purity. No racemization was found during the Wilkinson's catalytic reduction reaction (Scheme 2).



Scheme 2. Asymmetric synthesis of [$^3H_2$](*R*)-ibuprofen 11

Experimental

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or 400 MHz. Mass spectra was recorded on Waters Micromass ZQ 2050. Chemical purity of all labeled compounds was determined by HPLC and GC-MS or LC-MS. Purifications were done by flash column chromatography on a Biotage Flash 40 system. [^{14}C]CH_3I (100 mCi, 55 mCi/mmol) was purchased from American Radiolabeled Chemicals Inc (ARC). Tritium gas was purchased from ARC. Acid **1** was prepared by following Capponi's procedure starting with isobutylbenzene.[4]

(4R, 5S)-N-(4-isobutylphenyl acetyl)-4-methyl-5-phenyl-2-oxazolidinone **2**

A solution of 4-isobutylphenyl acetic acid **1** (1.55 g, 8.1 mmol) in $SOCl_2$ (1.5 ml, 17.3 mmol) was stirred at 100°C for 1 h. The excess $SOCl_2$ was removed with THF (2 × 5 ml) under reduced pressure. The residue was dissolved in THF (3 ml) to form solution A. To a solution of (4*R*, 5*S*)-4-methyl-5-phenyl-2-oxazolidinone (1.5 g, 8.5 mmol) in THF (5 ml) was added a solution of *n*-BuLi (2.5 M, 3.4 ml, 8.5 mmol) at −40°C. The mixture was stirred for 30 min at the same temperature. To this solution was added solution A at −40°C (CH_3CN/dry ice). The mixture was stirred at −40°C for 1.5 h, and then quenched with 1 N $NaHSO_4$ (60 ml). The aqueous layer was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, and concentrated to give crude **2**, which was purified by flash chromatography (silica gel, 5% EtOAc/hexane). The titled compound was obtained as a colorless oil (2.13 g, 75%). ^{1}H NMR ($CDCl_3$) δ 0.894 (d, $J = 6.59$ Hz, 6H), 0.883 (d, $J = 6.59$ Hz, 3H), 1.848 (m, 1H), 2.45 (d, $J = 7.24$ Hz, 2H), 4.27 (dd, $J = 5.82$ Hz, 2H), 4.754 (m, 1H), 5.65 (d, $J = 7.248$ Hz, 1H), 7.10 (d, $J = 7.90$ Hz, 2H), 7.22 (d, $J = 7.90$ Hz, 2H), 7.27–7.29 (m, 2H), 7.36–7.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 171.5, 138.2, 135.6, 132.3, 131.0, 129.6, 129.2, 129.0, 128.9, 125.9, 124.5, 78.7, 55.5, 43.4, 42.7, 30.1, 22.9, 18.3, 14.6; MS (CI) $[M + H^+]$: 352.

(4R, 5S)-N-(4-isobutylphenyl-α-[^{14}C]methylacetyl)-4-methyl-5-phenyl-2-oxazolidinone **3**

To a solution of compound **2** (0.60 g, 1.68 mmol) in THF (15 ml) was added a solution of 1 M NaHMDS in THF (2.0 ml, 2 mmol) at −78°C over 15 min. The resulting red yellow solution was stirred for 1 h. To this solution was added [^{14}C]CH_3I (100 mCi, 55 mCi/mmol, 1.8 mmol) at −78°C. The mixture was stirred at −78°C for 1 h and then at −40°C for 2 h which produced a cloudy mixture. The mixture was quenched with a solution of AcOH (0.40 g) in ether (15 ml). After stirring for 15 min, the mixture was filtered and the filtrate was concentrated by distillation. Purification by flash chromatography (silica gel, 5% EtOAc/hexane) gave the title compound **3** (0.460 g, 69 mCi, 69%). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H), 0.89 (d, $J = 6.59$ Hz, 6H), 1.49 (d, $J = 6.81$ Hz, 2H), 1.84 (m, 1H), 2.43 (d, $J = 7.15$ Hz, 2H), 4.67 (m, 1H), 5.10 (q, $J = 7.01$ Hz, 1H), 5.50 (d, $J = 7.02$ Hz, 1H), 7.09 (d, $J = 7.91$ Hz, 2H), 7.26–7.28 (m, 5H), 7.34–7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.6, 174.4, 138.1, 129.6, 128.9, 127.7, 125.8, 78.8, 55.6, 43.5, 42.8, 30.3, 22.7, 19.5, 18.5, 14.7. MS (CI) $[M + H^+]$: 366.

[^{14}C] (R)-ibuprofen **4**

To a solution of compound **3** (0.45 g, 67.5 mCi, 1.23 mmol) in THF (6 ml) and water (2.2 ml) was added a solution of LiOH (0.088 mg, 3.7 mmol) in water (2.3 ml) and H_2O_2 (30%, 1.65 ml) at 0°C. The resulting mixture was stirred at 0°C for 3 h. To this cold solution was added a solution of $NaHSO_3$ (0.35 g), Na_2SO_3 (0.62 g) in water (2.5 ml). The mixture was extracted with CH_2Cl_2 (5 × 20 ml). The combined organic layers were washed with brine (15 ml), dried over $MgSO_4$, and then concentrated to give an oily residue, which was purified by flash chromatography (silica gel MeOH/Et_2O/hexane = 5/30/65). Compound **4** was obtained as colorless oil (0.231 g, 61 mCi, 90%). Specific activity (SA) = 54.8 mCi/mmol; radiochemical purity: 98.7%; chiral purity: 98.1%; reverse phase HPLC conditions: column: Phenomenex LUNA C18(2), 3 μm, 4.6 × 150 mm; mobile phase: A = 0.01 M TEA, pH = 2.5 w/$HClO_4$, B = CH_3CN, 80% A linear gradient to 30% A over 10 min, hold at A:B = 30:70 for 10 min, flow rate: 1.0 ml/min, UV detection: 220 nm, retention time: 12.3 min; chiral HPLC conditions: column: Chiralcel OH-RH, 3 μm, 4.6 × 150 mm, mobile phase: Premix 25% H_2O, 75% MeOH + 0.1% acetic acid, flow rate: 1.0 ml/min, UV: 220 nm, retention time: 10.1 min.

[4-(Diethoxyphosphinyl)methyl]-phenylacetic acid **6**

A suspension of *p*-bromomethylphenylacetic acid **5** (5.0 g, 21.9 mmol) in triethylphosphite (20 ml, 117 mmol) was heated at 120°C for 18 h. After cooling to room temperature, the mixture was quenched with water (38 ml) and 2 N NaOH (48 ml). The aqueous layer was washed with EtOAc (5 × 25 ml) and then acidified with 1 N HCl (20 ml). The acidic solution was extracted with EtOAc (3 × 100 ml). The combined organic layers were washed with water (25 ml) and brine (20 ml), dried over $MgSO_4$, and concentrated by rotovap to give **6** as a colorless oil which solidified after stirring (5.0 g, 80%). ^{1}H NMR ($CDCl_3$) δ 7.25–7.23 (m, 4H), 4.03–3.96 (m, 4H), 3.59 (s, 2H), 3.13 (d, $J = 21.7$ Hz, 2H), 1.25–1.19 (m, 6H); MS (CI) $[M + H^+]$: 287.

4-Isobuteneyl-phenylacetic acid **7**

To a solution of compound **6** (4.1 g, 14.2 mmol) in THF (80 ml) and 15-crown-5 (3.6 g) at 5°C, was added NaH (60%, 2.3 g) in three portions. Then to this suspension was added acetone (10 ml). The resulting mixture was stirred at RT for 48 h. To the reaction mixture was added cold water (200 ml). The mixture was extracted with CH_2Cl_2 (3 × 80 ml). The aqueous layer was acidified with 1 N HCl (50 ml), extracted with CH_2Cl_2 (4 × 80 ml), washed with brine, and dried over $MgSO_4$. Concentration by rotovap gave crude product **7**, which was purified by flash chromatography (silica gel, MeOH/Et_2O/hexane/AcOH = 5/30/65/0.5). Compound **7** was obtained as a white solid (1.68 g, 62%). ^1H NMR ($CDCl_3$) δ 11.3 (bs, 1H), 2.25–7.17 (m, 4H), 6.24 (s, 1H), 3.62 (s, 2H), 1.89 (d, $J = 1.32$ Hz, 3H), 1.85 (d, $J = 1.31$ Hz, 3H). ^{13}C NMR ($CDC1_3$) δ 178.1, 135.1, 129.2, 127.3, 45.6, 41.5, 30.1, 19.3; MS (CI) [$M + H^+$]: 191.

(4R, 5S)-N-(4-isobutenylphenylacetyl)-4-methyl-5-phenyl-2-oxazolidinone **8**

A solution of compound **7** (1.55 g, 8.15 mmol) in $SOCl_2$ (1.5 ml, 17.3 mmol) was stirred at 100°C for 1 h. The excess $SOCl_2$ was removed with THF (2 × 5 ml) under reduced pressure. The residue was dissolved in THF (3 ml) to form solution A. To a solution of 4-methyl-5-phenyl-2-oxazolidinone (1.5 g, 8.5 mmol) in THF (5 ml) was added a solution of *n*-BuLi (2.5 M, 3.4 ml, 8.5 mmol) at −40°C. The mixture was stirred for 30 min at the same temperature. To this solution was added the solution A at −40°C (CH_3CN/dry ice). The mixture was stirred at −40°C for 1.5 h and then quenched with 1 N $NaHSO_4$ (60 ml). The aqueous layer was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, and concentrated to give a crude product, which was purified to flash chromatography (silica gel, 5% EtOAc/hexane). Compound **8** was obtained as a colorless oil (1.99 g, 70%). ^1H NMR ($CDCl_3$) δ 0.89 (d, $J = 7.59$ Hz, 3H), 1.85 (d, $J = 1.09$ Hz, 3H), 1.89 (d, $J = 1.09$ Hz, 3H), 4.28 (dd, $J = 5.6$ Hz, 2H), 4.75 (m, 1H), 5.65 (d, $J = 7.25$ Hz, 1H), 6.24 (s, 1H), 7.19 (d, $J = 7.12$ Hz, 2H), 7.28 (d, $J = 7.12$ Hz, 2H), 7.34–7.67 (m, 2H), 7.37–7.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 153.1, 138.1, 135.8, 132.5, 131.2, 129.5, 129.1, 129.0, 128.9, 125.8, 124.9, 79.2, 55.3, 41.6, 27.1, 19.7, 14.7; MS (CI) [$M + H^+$]: 350.

(4R, 5S)-N-[(4-(isobutenylphenyl)-α-methylacetyl]-4-methyl-5-phenyl-2-oxazolidinone **9**

To a solution of compound **8** (0.8 g, 2.3 mmol) in THF (12 ml) was added 1 M NaHMDS in THF (2.53 ml, 2.53 mmol) at −78°C to form a yellow solution, which was stirred for 1 h at −78°C. To this cold solution was added MeI (1.76 g, 12.5 mmol) at −78°C. The resulting mixture was stirred at −78°C for

1.5 h, then at −40°C for 2 h. The mixture was quenched with AcOH (0.41 g, 6.8 mmol) in ether (10 ml), and filtered through a Celite bed. The filtrate was concentrated by rotovap to give an oily residue, which was apurified by flash chromatography (silica gel, 3% EtOAc/hexane).

Compound **9** was obtained as a colorless oil (0.61 g, 73%). ^{1}H NMR ($CDCl_3$) δ 0.93 (d, $J = 6.59$ Hz, 3H), 1.50 (d, $J = 7.03$ Hz, 3H), 1.86 (d, $J = 1.09$ Hz, 3H), 1.88 (d, $J = 1.09$ Hz, 3H), 4.67 (m, 1H), 5.12 (q, $J = 6.80$ Hz, 1H), 5.50 (d, $J = 7.03$ Hz, 1H), 6.22 (s, 1H), 7.18 (d, $J = 8.34$ Hz, 2H), 7.26 (d, $J = 8.34$ Hz, 2H), 7.27–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 171.6, 152.8, 138.0, 133.6, 130.4, 129.2, 128.9, 127.9, 126.9, 125.8, 78.9, 55.6, 44.1, 27.2, 24.9, 19.5, 14.7; MS (CI) $[M + H^+]$: 364.

4-(Isobutenylphenyl)-α-methylacetic acid **10**

To a solution of compound **9** (0.3 g, 0.83 mmol) in THF (4 ml) and water (1.5 ml) was added a solution of LiOH (60 mg, 2.5 mmol) in water (1.5 ml) and H_2O_2 (30%, 1.1 ml) at 0°C. The resulting mixture was stirred at 0°C for 3 h. To this cold solution was added a solution of $NaHSO_3$ (0.235 g), Na_2SO_3 (0.416 g) in water (1.5 ml). The mixture was extracted with CH_2Cl_2 (15 ml × 5). The combined organic layers were washed with brine (15 ml), dried over $MgSO_4$, and then concentrated by rotovap to give an oily residue, which was purified by flash chromatography (silica gel, MeOH/Et_2O/hexane = 5/30/65). Compound **10** was obtained as colorless oil (0.156 g, 92%). ^{1}H NMR ($CDCl_3$) δ 1.50 (d, $J = 7.25$ Hz, 3H), 1.84 (d, $J = 1.09$ Hz, 3H), 1.88 (d, $J = 1.09$ Hz, 3H), 3.71 (q, $J = 6.93$ Hz, 1H), 6.22 (s, 1H), 7.17 (d, $J = 8.34$ Hz, 2H), 7.25 (d, $J = 8.34$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 179.9, 138.1, 137.3, 135.9, 130.8, 130.4, 129.2, 128.6, 128.1, 127.7, 124.8, 45.1, 27.1, 19.6, 18.3; MS (CI) $[M + H^+]$: 205.

[$^3H_2$]R-2-(4-Isobutylphenyl)propionic acid (R-ibuprofen) **11**

Compound **10** (1 mg, 4.9 μmol) was reduced with 600 mCi carrier free tritium gas and 1 mg Wilkinson's catalyst in 0.5 ml EtOH on a commercial tritiation manifold (TRI-SORBER ® Tritiation Manifold, IN/US Systems, Inc.) for 4 h. Labile products were removed by distillation in ethanol and the crude product was subjected to the reverse phase HPLC purification. The fractions containing pure product were pooled and reconstituted in ethanol to give 11 mCi of final product with the following specifications: specific activity (SA) = 54 Ci/mmol (by MS); radiochemical purity: 99.72%; chiral purity = 99.92%; reverse phase HPLC conditions: column: Phenomenex LUNA C18(2), 3 μm, 4.6 × 150 mm; mobile phase: A = 0.01 M TEA, pH = 2.5 w/$HClO_4$, B = CH_3CN, 80% A linear gradient to 30% A over 10 min, hold at A:B = 30:70 for 10 min, flow rate: 1.0 ml/min, UV detection:

220 nm, retention time: 12.1 min; chiral HPLC conditions: column: Chiralcel OH-RH, 3 μm, 4.6 × 150 mm, mobile phase: Premix 25% H_2O, 75% MeOH + 0.1% acetic acid, flow rate: 1.0 ml/min, UV: 220 nm, retention time: 10.0 min.

Conclusion

In conclusion, we have developed an efficient asymmetric synthesis of tritium and carbon-14 labeled (*R*)-ibuprofen with excellent enantiomeric excess and good overall yields.

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