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Tetrahedron: *Asymmetry* 17 (2006) 2511–2515

An alternative stereoselective synthesis of the macrocyclic fragrances (*R*)-12-methyltridecanolide and (*S*)-muscolide by means of an asymmetric catalytic conjugate addition/Baeyer–Villiger oxidation

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Received 1 August 2006; accepted 6 September 2006

Abstract—We show herein an alternative catalytic, highly enantioselective approach to (*R*)-12-methyltridecanolide and (*S*)-muscolide, that is, chiral macrocyclic lactones which are good musk odorants. In fact, they can be efficiently prepared by a sequence of reactions consisting of a catalytic asymmetric conjugated addition of dimethylzinc to suitable α,β-unsaturated enones followed by a Baeyer–Villiger oxidation. Interestingly, high enantiomeric excesses (up to 92%) are obtained in the asymmetric conjugate addition by means of the 'tropos' phosphoramidite **L1**.

1. Introduction

The musk odorants are an important class of fragrances having different chemical structures and are widely employed[1] in the perfume industry. Perhaps the most well known structure is the nitroarene one, such musk ambrette which was largely used in cosmetics, toiletries and other household products. However, the use of musk ambrette has been severely restricted since 1981 because of ecological concerns. On the contrary, macrocyclic lactones and ketones, that is, naturally occurring musk odorants, are environmentally safe, even if they are more expensive. In general they are characterized[2] by a ring having 15–17 members, lactones are stronger than ketones. As far as the chiral structures are concerned, even if often the two antipodes do not differ strongly in olfactory properties (e.g., (+)- and (−)-muscone, **1**), some cases are well known (e.g., (+)- and (−)-12-methyl-13-tridecanolide, **2**) for which a qualitative odor difference between the two enantiomers exists,[3] so a synthetic design aimed at efficiently preparing such valuable chiral molecules must be taken into account to necessarily involve a step concerning the asymmetric processes in the project. For instance, there are several types of synthetic approaches to (−)-**1**,[4,5] while in Ref. 6 we collect the most recent methods. Some attempts at efficiently preparing (+)- and (−)-**2** are also reported.[7] Therefore, the aim of this paper is to describe an alternative synthetic approach to (+)-**2** which follows the synthetic procedure reported in Scheme 1.

Our reasoning is as follows: the target lactone compound can be obtained by a Baeyer–Villiger oxidation of a suitable, optically active, saturated ketone, which in turn can be prepared by an asymmetric conjugate addition of Me_2Zn upon the corresponding α,β-unsaturated ketone. This last compound must be prepared by starting from commercially available and inexpensive compounds. The above scheme is founded on the fact that the Baeyer–Villiger oxidation is a simple transformation which requires inexpensive chemicals and, most importantly, occurs with complete retention of configuration.[8] In addition, much progress has been made in the catalytic enantioselective conjugate addition of organozinc compounds to α,β-unsaturated ketones by means of enantiopure phosphorous ligands[9] and our group recently succeeded in preparing (−)-muscone in high (84%) enantiomeric excess by means of a new, home-made,[10] 'tropos' phosphoramidite ligand[11] **L1** (Chart 1). We shall describe herein all the steps leading to (*R*)-**2**.

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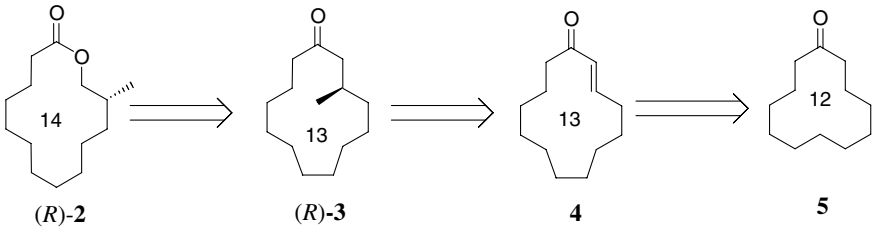
doi:10.1016/j.tetasy.2006.09.007



Scheme 1. Synthesis of macrocyclic lactone (*R*)-**2**.

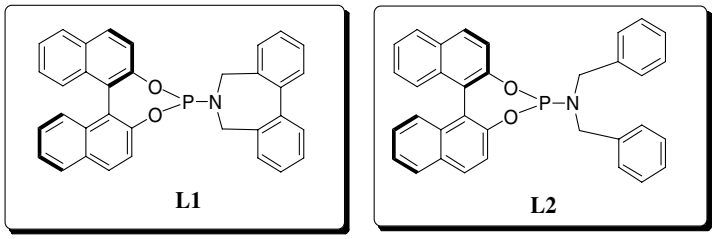


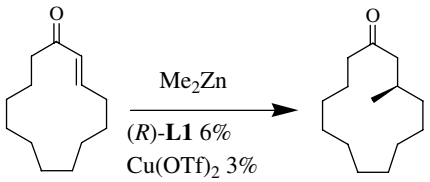
Chart 1.

2. Results and discussion

Following Scheme 1 it would appear obvious that for the synthesis of (*R*)-**2** the 13-membered ring α,β-unsaturated ketone **4** is necessary. This compound could be prepared by the same sequence employed previously for the synthesis of cyclopentadecenone[10] starting from cyclotridecanone. We decided to use cyclododecanone **5** as a starting material, carrying out a ring enlargement of a $-CH_2-$ unit, following a recent procedure of Ruedi and Hansen.[12] To this end, a solution of **5** in pentane was treated with anhydrous triethylamine, freshly distilled trimethylsilylchloride, NaI in anhydrous acetonitrile, forming the corresponding trimethylsilylether **6**[13] in quantitative yield. Simmons–Smith cyclopropanation of **6** using Zn–Cu and CH_2I_2 in boiling ether provided cyclopropane **7**[13] in 68% yield. Compound **7** and pyridine in DMF were added slowly to a solution of anhydrous $FeCl_3$ in DMF. Heating for 2 h at 80 °C afforded the required cyclotridec-2-en-1-one **4** chemically pure in 45% overall yield (Scheme 2).

The conjugate addition of Me_2Zn to cyclotridec-2-en-1-one **4**, performed under the same conditions used for (*R*)-muscone,[10] afforded the desired product in only 28% yield and 68% ee (Table 1, entry 1). The yield was lower than that observed in the alkylation of cyclopentadec-2-en-1-one (72% yield, 84% ee)[10] because of the formation of major by-products generated by attack of the in situ formed enolate on to another molecule of unreacted substrate. Increasing the temperature to 25 °C in order to lower the reaction time gave the same results (entry 2). Finally, when the reaction was performed at −10 °C product (*R*)-**2** was obtained in 68% yield and 92% ee (Fig. 1).

Table 1. Asymmetric conjugated addition of Me_2Zn to cyclotridec-2-en-1-one in presence of **L1**

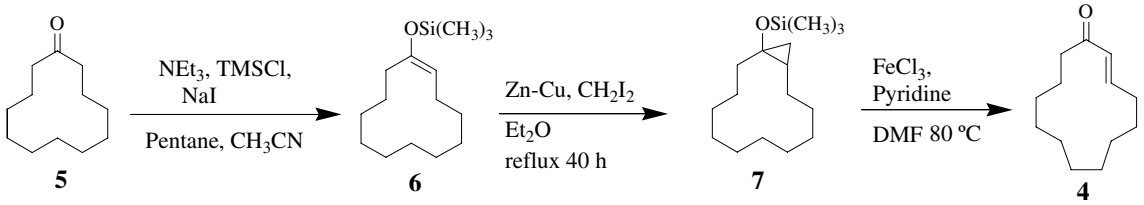


Entry[a]	*T* (°C)	Time (min)	Yield[d] (%)	ac[c]	ee[b] (%)
1	0	60	28	*R*	67
2	25	40	25	*R*	63
3	−10	90	68	*R*	92

[a] Carried out in toluene.
[b] Determined by GC analysis with Hydrodex-β-3P column.
[c] Assigned by the sign of optical rotatory power.[14]
[d] Calculated on the isolated and purified product.

By contrast, under the same experimental conditions, using the phosphoramidite ligand (*R*)-**L2**[9a] (Chart 1) compound (*R*)-**3** was obtained in 60% yield and 84% ee (Scheme 3).

The last step for the synthesis of (*R*)-**2** is the Baeyer–Villiger oxidation of (*R*)-**3**. Therefore, to a solution of



Scheme 2. Synthesis of cyclotridec-2-en-1-one.

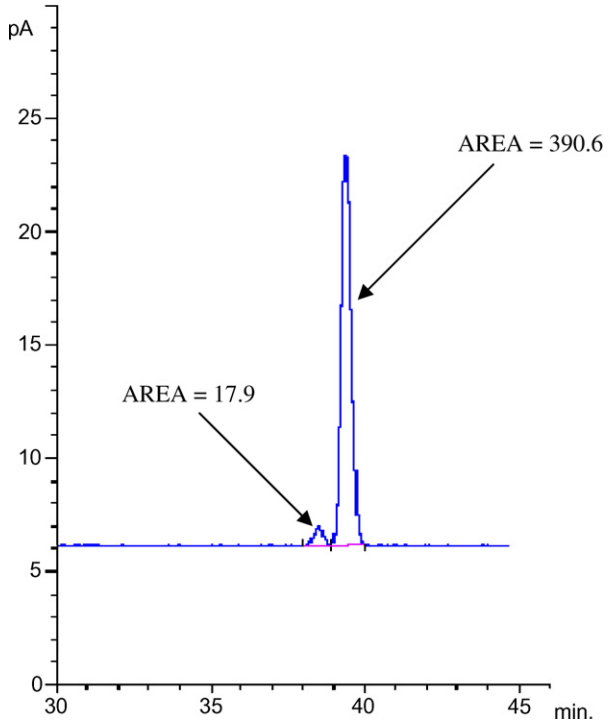
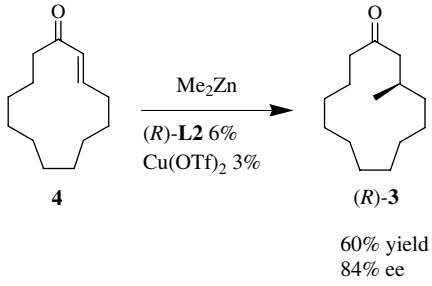
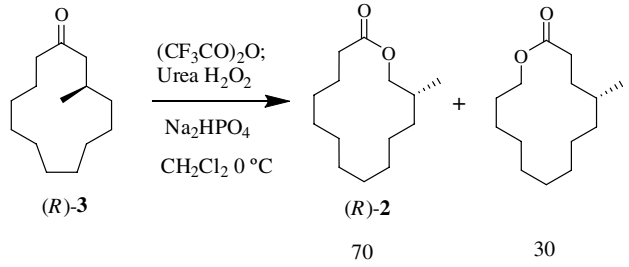


Figure 1. Chromatographic separation of (*R*)-**3**. Hydrodex–β-3P Column: N_2, 140 °C iso, FID 220 °C, split 25 mL/min.



Scheme 3. Asymmetric conjugate addition of Me_2Zn to cyclotridec-2-en-1-one in the presence of **L2**.

(*R*)-**3**, urea hydrogen peroxide and Na_2HPO_4 in CH_2Cl_2 trifluoroacetic anhydride was added at 0 °C for 6 h (Scheme 4).[8a] The reaction was monitored by GC–MS analysis that revealed the formation of two isomers in a ratio of 70:30. After complete conversion, the product (as a mixture 70:30 of regioisomers) was isolated in 86% yield and by ^1H NMR analysis it was possible to identify (*R*)-**2** as the main product. After purification by PLC on silica gel, a 90:10 regioisomeric ratio was obtained.



Scheme 4. Baeyer–Villiger oxidation of (*R*)-**3**.

By an analogous procedure, we synthesized (*S*)-muscolide starting from (*S*)-muscone obtained in 82% ee by asymmetric conjugate addition of dimethylzinc to 2-cyclopentadecenone.[10] The Baeyer–Villiger oxidation, performed under the same conditions used for (*R*)-**2**, gave the desired product in 80% yield and a better (80:20) regioisomeric ratio. Also in this case, after purification by PLC on silica gel, a 90:10 regioisomeric ratio was obtained (Scheme 5).

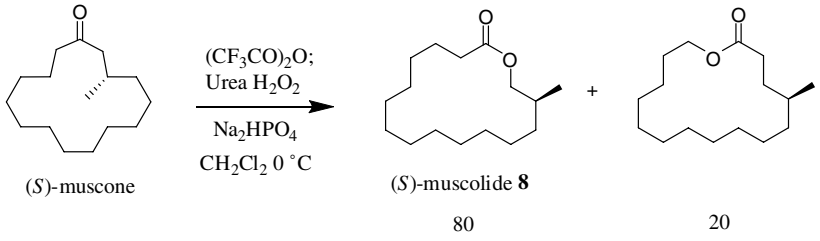
3. Conclusions

With this investigation we have shown that the sequence of catalytic asymmetric conjugate addition to a suitable macrocyclic enone/Baeyer–Villiger oxidation constitutes an efficient route to (*R*)-12-methyltridecanolide and (*S*)-muscolide, that is, valuable musk odorants largely employed in the perfume industry. Such a procedure is based on an efficient asymmetric conjugate addition of dimethylzinc to a 13-(or 15-) membered α,β-unsaturated enone. This result is guaranteed by the use of the 'tropos' phosphoramidite ligand **L1**, designed on the basis of the principle of 'asymmetric activation of flexible groups' due to Mikami and co-workers.[11] It is interesting to note that the results of this investigation clearly show that phosphoramidite **L1** constitutes a chiral ligand which provides high enantioselectivities in the conjugate addition of $ZnMe_2$ to macrocyclic ketones, a process which has not been studied in the past: to the best of our knowledge, only a report[14] describes asymmetric conjugate addition of organometallics to macrocyclic ketones, but in a stoichiometric manner.

4. Experimental

4.1. 1-Trimethylsilyloxycyclododec-1-ene 6

To a solution of cyclododecanone (25 g, 140 mmol) in anhydrous pentane (130 mL), under a nitrogen atmosphere,



Scheme 5. Baeyer–Villiger oxidation of (*S*)-muscone.

triethylamine (31 g, 308 mmol) and freshly distilled chlorotrimethylsilane (34 g, 313 mmol) were added, followed by a solution of anhydrous sodium iodide (46 g, 307 mmol) in anhydrous acetonitrile (250 mL). After 12 h of stirring at room temperature, the upper organic layer (pentane) was separated and transferred into a dry flask. The remaining mixture was extracted with anhydrous pentane until no trace of silylenolether was detected by TLC. The pentane phases were gathered and concentrated in vacuo to give the product as a colorless oil (35 g, 138 mmol, 98%). The silylenolether was used in the subsequent reaction without further purification. MS (EI): *m*/*z* 254 (M^+, 35), 143 (100), 73 (89), 130 (88), 183 (40), 75 (39), 115 (20).

4.2. 1-Trimethylsilyloxybicyclo[10.1.0]tridecane 7

Under a nitrogen atmosphere to a suspension of zinc–copper couple (28 g, 210 mmol) in anhydrous diethyl ether (270 mL) stirred at room temperature, methylene iodide (57 g, 200 mmol) and 1-trimethylsilyloxycyclododec-1-ene (35 g, 138 mmol) were added. The mixture was refluxed for 2 h, then cooled and stirred at room temperature for 12 h. After filtration the solution was washed successively with cold aqueous 10% NH_4Cl, aqueous 10% $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4 and the solvent removed in vacuo. Purification by fractional distillation to remove methylene iodide in excess gave product **7** as a yellow oil (25 g, 94 mmol, 68%). MS (EI): *m*/*z* 268 (M^+, 15), 143 (100), 130 (94), 73 (86), 75 (30), 155 (28). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.11 (s, 9H); 0.18 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 5.7$ Hz); 0.42 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 5.0$ Hz); 0.59–0.66 (m, 1H); 0.79–0.87 (m, 1H); 1.02–1.18 (m, 1H); 1.20–1.70 (m, 15H); 1.75–1.87 (m, 1H); 2.14–2.22 (m, 1H); 2.45–2.49 (m, 1H).

4.3. Cyclotridec-2-en-1-one 4

To a stirred mixture of anhydrous $FeCl_3$ (30 g, 185 mmol) in dry dimethylformamide (125 mL), a solution of 1-trimethylsilyloxybicyclo [10.1.0]tridecano (17 g, 63 mmol) and dry pyridine (5 g, 63 mmol) in dry dimethylformamide (100 mL) was added dropwise over 2 h at 0 °C under nitrogen atmosphere. The resultant brown solution was heated at 80 °C for 2 h and then cooled at room temperature. The reaction mixture was quenched with 10% HCl and extracted with chloroform. The organic phase was dried over Na_2SO_4 and the solvent removed in vacuo. Purification by column chromatography (SiO_2 petroleum ether/EtOAc 90:10) gave **4** as a yellow oil (8 g, 41 mmol, 65%). MS (EI): *m*/*z* 194 (M^+, 50), 81 (100), 109 (78), 95 (53), 68 (52), 41 (41). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.20–1.40 (m, 14H); 1.60–1.80 (m, 4H); 2.25–2.30 (m, 2H); 2.50–2.58 (m, 2H); 6.22 (d, 1H, $J = 15.7$ Hz); 6.80–6.90 (m, 1H).

4.4. Enantioselective conjugate addition of dimethylzinc to cyclotridec-2-en-1-one: synthesis of (*R*)-(−)-3-methylcyclotridecan-1-one (3) (representative procedure)

A solution of $Cu(OTf)_2$ (5.6 mg, 0.015 mmol) and chiral ligand (***R***)-**L1** (15.3 mg, 0.03 mmol) in dry toluene (5 mL) was stirred for 1 h at room temperature under a nitrogen atmosphere. After cooling to −10 °C, Me_2Zn (2.0 M in toluene, 0.4 mL, 1.5 equiv) was added followed by cyclotridec-2-en-1-one (97 mg, 0.5 mmol). The reaction was monitored by GC–MS analysis. After stirring for 2.5 h at −10 °C, 1 M HCl solution (10 mL) and diethyl ether (5 mL) were added and stirred for a few minutes. Then the mixture was extracted three times with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether/diethyl ether 95:5), affording (*R*)-(−)-3-methylcyclotridec-2-en-1-one **3** (68%) as a colorless oil.

The ee (92%) was determined by GC analysis with Hydrodex-β-3P column (25 m × 0.25 mm). $[\alpha]_D = -12.9$ (*c* 0.7, CH_3OH); MS (EI): *m*/*z* 210 (M^+, 36), 85 (100), 55 (89), 41 (70), 69 (67), 97 (59), 125 (35); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.98 (d, 3H, $J = 7.7$ Hz); 1.22–1.40 (m, 16H); 1.57–1.66 (m, 1H); 2.00–2.08 (m, 1H); 2.22 (dd, 1H, $J_1 = 15.0$ Hz, $J_2 = 3.8$ Hz); 2.36–2.46 (m, 2H); 2.50–2.58 (m, 1H).

4.5. (12*R*)-(+)-12-Methyl-13-tridecanolide 2

To a solution of (*R*)-(−)-3-methylcyclotridecan-1-one (ee = 92%) (23 mg, 0.10 mmol), urea hydrogen peroxide (57 mg, 0.61 mmol) and Na_2HPO_4 (100 mg, 0.70 mmol) in CH_2Cl_2 (5 mL), trifluoroacetic anhydride (139 mg, 93 μL, 0.66 mmol) was added at 0 °C. The reaction was monitored by GC–MS analysis. After stirring for 6 h at 0 °C the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, saturated $Na_2S_2O_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give the mixture of products (*R*)-**2** and its regioisomer as a yellow oil (86% overall yield) and 70:30 as a regioisomeric ratio. After purification by PLC (SiO_2, petroleum ether/ethyl acetate 98:2), a 90:10 regioisomeric ratio was obtained.

Compound (*R*)-**2** (major regioisomer): MS (EI): *m*/*z* 226 (M^+, 4), 208 (18), 165 (14), 153 (25), 139 (14), 124 (20), 111 (34), 98 (53), 83 (54), 69 (80), 55 (100), 41 (75). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.93 (d, 3H $J = 6.5$ Hz); 1.20–1.40 (m, 15H); 1.52–1.58 (m, 3H); 1.60–1.75 (m, 1H); 2.31–2.39 (m, 1H); 2.40–2.46 (m, 1H); 3.70 (dd, 1H, $J_1 = 8.5$ Hz $J_2 = 11.0$ Hz); 4.20 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 11.0$ Hz).

Minor regioisomer: MS (EI): *m*/*z* 226 (M^+, 5), 208 (5), 166 (68), 138 (18), 124 (23), 110 (34), 96 (53), 82 (68), 69 (80), 55 (100), 41 (75). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.96 (d, 3H, $J = 6.5$ Hz) 1.20–1.50 (m, 15H); 1.52–1.58 (m, 3H); 2.07–2.14 (m, 1H); 2.31–2.39 (m, 1H); 2.40–2.46 (m, 1H); 4.12–4.18 (m, 2H).

4.6. (*S*)-(+)-Muscolide 8

To a solution of (*S*)-muscone (ee = 84%) (39 mg, 0.16 mmol), prepared as reported,[10] urea hydrogen peroxide (100 mg, 1.00 mmol) and Na_2HPO_4 (160 mg, 1.12 mmol) in CH_2Cl_2, trifluoroacetic anhydride (216 mg, 145 μL, 1.07 mmol) was added at 0 °C. The reaction was monitored

by GC–MS analysis. After 6 h of stirring at 0 °C the reaction was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, saturated $Na_2S_2O_3$ solution and brine. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give the mixture of products (*S*)-**8** and its regioisomer as a yellow oil (60% overall yield) and 80:20 as a regioisomeric ratio. After purification by PLC (SiO_2; petroleum ether/ethyl acetate 98:2), a 90:10 regioisomeric ratio was obtained.

Compound (*S*)-**8** (major regioisomer): MS (EI): *m*/*z* 254 (M^+, 5), 236 (26), 194 (11), 111 (31), 97 (55), 83 (62), 69 (83), 55 (100), 41 (74); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (d, 3H, $J = 6.9$ Hz); 1.03–1.50 (m, 19H); 1.50–1.75 (m, 3H); 1.77–1.88 (m, 1H); 2.37 (t, 2H, $J = 6.0$ Hz); 3.80 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 8.0$ Hz); 4.10 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 3.8$ Hz).

Minor regioisomer: MS (EI): *m*/*z* 254 (M^+, 10), 236 (7), 194 (69), 166 (16), 110 (31), 96 (62), 82 (69), 69 (88), 55 (100), 41 (74); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.98 (d, 3H $J = 6.9$ Hz); 1.03–1.50 (m, 19H); 1.50–1.75 (m, 3H); 1.77–1.88 (m, 1H); 2.22 (d, 2H, $J = 7.2$ Hz); 4.06–4.10 (m, 1H); 4.18–4.22 (m, 1H).

Acknowledgement

Financial support from MIUR-COFIN 2004 'Aromi e fragranze' and Università degli Studi della Basilicata is gratefully acknowledged.

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