An Expeditious Synthesis of Methyl Jasmonate

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Dedicated to the memory of Dr. *Günther Ohloff* [1])

We present an efficient three-step, two-pot synthesis of methyl jasmonate (*trans*-**1**) based on *Diels–Alder* cycloaddition of cyclopent-2-enone (**2**) and chloroprene (=2-chlorobuta-1,3-diene; **3d**) in either $CHCl_3$ or CH_2Cl_2, catalyzed by $SnCl_4$ (0.2 mol-equiv.) at 20° (75% yield). Subsequent ozonolysis of a *cis*/*trans* 55:45 mixture of the cycloadduct **4d** in either CH_2Cl_2 or AcOEt at −78°, followed by addition of Me_2S and MeOH in the presence of $NaHCO_3$, afforded, in 64% yield, a *cis*/*trans* 40:60 mixture of the known aldehyde **5c**. The latter was reacted at −50° under salt-free conditions with the propyl *Wittig* reactant to furnish **1** as a *cis*/*trans* 20:80 mixture ((*E*/*Z*) 3:97). Alternatively, a *cis*/*trans* 7:93 mixture ((*E*/*Z*) 4:96) was obtained in 88% yield from epimerized **5c** (AcOH, H_2O, 40°; 99%) under usual *Wittig* conditions at −20°.

Introduction. – We recently presented a new synthesis of methyl jasmonate (*trans*-**1**) based on a cascade *Baylis–Hillman* reaction in combination with an ortho-ester *Claisen* rearrangement [1]. During our initial literature search, previous approaches were studied in detail, and we were attracted by the *Diels–Alder* methodology reported by *Tanaka* and *Torii* [2]. Indeed, their strategy based on cycloaddition of commercially available cyclopent-2-enone (**2**)[2]) to buta-1,3-diene (**3a**) had been earlier reported to afford, under thermal conditions (autoclave, 110°, 12 d; or 210°, 1 d [4]), an epimerized mixture of *cis*/*trans*-**4a** in 22–29% yield (for structures, see the *Scheme* below). This strategy necessitates, after a 75-cm spinning-band distillation (48% yield), eleven further synthetic steps towards methyl epijasmonate (*cis*-**1**). Alternatively, *Fringuelli* and *Wenkert* and co-workers reported that [4+2] cycloaddition to either butadiene (**3a**) or isoprene (**3b**) may be conducted in the presence of 0.9 to 0.2 mol-equiv. of $AlCl_3$ in toluene at 70–50° to afford a *cis*/*trans*-epimeric mixture of **4a**,**b** in *ca.* 74–85% isolated yield, respectively [5][3]). This latter intermediate, also obtained in 74% yield after column-chromatographic purification by *Hailes et al.* [6] *via* a cationic *Diels–Alder* reaction of cyclopent-2-enone acetal [7], followed by deprotection, necessitates, after reduction, protection, ozonolysis, and *Wittig* reaction, a haloform degradation prior to the last three steps, to transform the methyl ketone into a methyl carbox-

[1]) Deceased on 9th November, 2005.
[2]) For synthetic accesses from either cyclopentanone or cyclopentadiene, see [3].
[3]) When this cycloaddition was conducted in the presence of 0.9 mol-equiv. of $AlCl_3$ in toluene at −10°, a *cis*/*trans* 94:6 mixture of **4a** was obtained in 52% yield [5c].

ylate. This cationic [4+2] cycloaddition catalyzed by camphorsulfonic acid (CSA) in the presence of 4M $LiClO_4$ in Et_2O (*Braun–Sauer* conditions [8]) may also be catalyzed by either *NafionH* [9] or $InCl_3$ [10].

Unfortunately, when a chiral acetal was used, a 1:1 mixture of diastereoisomers was obtained [11]. More elegantly, the use of 2-silyloxy- or 2-alkoxybuta-1,3-dienes such as **3c** potentially gives access directly to the desired ester oxidation state [12]. In fact, prone to polymerization under catalytic conditions[4]), the thermal cycloaddition afforded, in 27–72% yield, mixtures of epimers such as **4c**[5]) as well as *meta*/*para* regioisomers, in addition to a double-bond-migration product[6]) [14], so that the overall yield was only *ca*. 5% after chromatographic purification[7]). Alternatively, cycloaddition of dienophile **2** to 2-[(diethylphosphoryl)oxy]buta-1,3-diene catalyzed by $SnCl_4$ gave rise to yields not higher than 12% [16][8]).

Results and Discussion. – Our synthetic protocol is outlined in the *Scheme*. We reasoned that chloroprene (=2-chlorobuta-1,3-diene; **3d**), possessing the appropriate oxidation state, would be at least as reactive as buta-1,3-diene proper (**3a**), and as regioselective as isoprene (**3b**), but much more stable than 2-methoxybuta-1,3-diene (**3c**) in the presence of *Lewis* acid catalysts[9]). Our hypothesis was corroborated by theoretical calculations at the B3LYP/6-31G** level of theory [18]. Both the differences in energy between the LUMO of cyclopent-2-enone (**2**) and the HOMO of the appropriate dienes **3a**–**d** and their s-*cis*/s-*trans* conformations, as well as the relative coefficients of atomic orbitals at C(1), C(2), C(3), and C(4), are reported in the *Table*. These calculations indicate that, for dienophile **2**, the most important LUMO coefficient at C(3) should 'interact' with the C(1)-prominent coefficient of the HOMO of **3**, leading to the desired *para* regioisomers **4**, in accord with our expectations based upon frontier-orbital theory [19]. The presence of the Cl-atom at C(2) decreases the HOMO energy and, hence, the electronic reactivity of **3d**, but, at the same time, thermodynamically increases the amount of the reactive s-*cis* conformer as compared to **3a**–**c**. Finally, stability calculations demonstrate that the transient *cis* isomer **4d** is thermodynamically higher in energy by 0.33 kcal/mol than its *trans* isomer, which would, thus, be accessible by epimerization under typical reaction or workup conditions [20].

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[4]) For recent advances in the catalyzed homo-*Diels–Alder* reaction with analogues of **3c**, see [13].

[5]) Data of *cis*-2,3,3a,4,7,7a-hexahydro-5-methoxy-1*H*-inden-1-one (*cis*-**4c**): ^{1}H-NMR: 1.82 (*m*, 2 H); 2.05 (*m*, 1 H); 2.15–2.35 (*m*, 5 H); 2.5 (*m*, 1 H); 2.65 (*m*, 1 H); 3.48 (*s*, 3 H); 4.55 (br. *t*, *J*=3, 1 H). ^{13}C-NMR: 20.4 (*t*); 26.4 (*t*); 28.7 (*t*); 33.4 (*d*); 34.2 (*t*); 47.0 (*d*); 53.9 (*q*); 90.9 (*d*); 153.6 (*s*); 219.2 (*s*). MS: 166 (100, M^+), 151 (16), 137 (29), 133 (26), 122 (62), 109 (98), 91 (23), 79 (23), 77 (24), 43 (21), 39 (20).

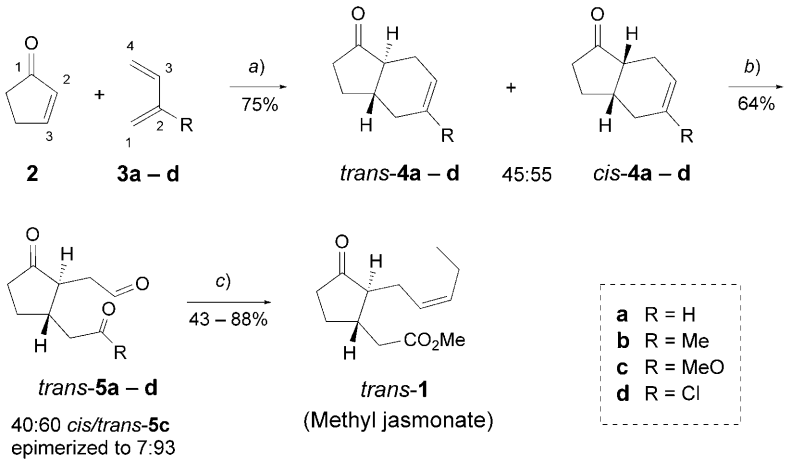
[6]) Data of *cis*-2,3,3a,6,7,7a-hexahydro-5-methoxy-1*H*-inden-1-one (1.77 kcal/mol lower in energy than *trans*-**4c**): ^{1}H-NMR: 1.73 (*m*, 1 H); 1.81 (*m*, 1 H); 1.98 (*m*, 1 H); 2.10 (*m*, 2 H); 2.20 (*m*, 2 H); 2.32 (*m*, 1 H); 2.48 (*m*, 1 H); 3.04 (*m*, 1 H); 3.50 (*s*, 3 H); 4.52 (br. *d*, *J*=3, 1 H). ^{13}C-NMR: 20.3 (*t*); 24.4 (*t*); 28.6 (*t*); 35.6 (*d*); 35.9 (*t*); 47.3 (*d*); 54.0 (*q*); 95.7 (*d*); 156.8 (*s*); 221.0 (*s*). MS: 166 (57, M^+), 137 (47), 110 (100), 109 (65), 95 (24), 79 (21), 67 (18), 39 (17).

[7]) Cycloadduct **4c** is also an intermediate for the synthesis of prostacyclin analogues [15].

[8]) For the natural occurrence and earlier syntheses of methyl jasmonate (*trans*-**1**), see references cited in [1]. For a recent review on methyl epijasmonate (*cis*-**1**), see [17].

[9]) Furthermore, **3d** is very inexpensive since it is being used on a multi-ton scale by the plastic industry.

Scheme



a) 0.2 mol-equiv. $SnCl_4$, CH_2Cl_2 or $CHCl_3$. *b*) 1. O_3, CH_2Cl_2 or AcOEt, $-78°$; 2. Me_2S; 3. MeOH, $NaHCO_3$. *c*) $[Ph_3PPr]^+Br^-$, $NaNH_2$, ^{t}BuOK, toluene, $-50°$ (or $[Ph_3PPr]^+Br^-$, BuLi, toluene, $-20°$).

Table. *HOMO/LUMO and* cis/trans *Energy Differences as well as Relative Atomic-Orbital Coefficients of Compounds* **2**–**4**. At the B3LYP 6-31G** level of theory.

Compound	$\Delta E_{HOMO/LUMO}$ [eV]	Orbital coefficient				ΔE [kcal/mol]	
		C(1)	C(2)	C(3)	C(4)	s-*cis*-**3a**–**d**	*cis*-**4a**–**d**
2	–	−0.19	−0.13	+0.25	+0.26[a])	–	–
3a	4.99	+0.22	+0.16	−0.16	−0.22	3.85	0.44
3b	4.98	+0.22	+0.17	−0.13	−0.18	3.12	0.25
3c	4.64	+0.25	+0.15	−0.08	−0.14	2.75	0.47
3d	5.47	+0.22	+0.17	−0.13	−0.17	2.57	0.33

[a]) O-atom.

The most-efficient conditions involve 0.2 mol-equiv. of $SnCl_4$ in $CHCl_3$[10]) in the presence of 1.5 mol-equiv. of a 50% soln. of chloroprene (**3d**) in xylene. After 18 h at

[10]) Anhydrous toluene is unsuitable, and $CHCl_3$ or CH_2Cl_2 (SDS quality) should not be dried (P_2O_5), but used without further purification, otherwise very low yields are obtained. This suggests that traces of H_2O (0.01%) or stabilizing EtOH (*ca.* 0.5–1.0%) modify the catalyst for the *Diels–Alder* reaction. With 0.2 mol-equiv. of $SnCl_4$ in anhydrous CH_2Cl_2, the cycloaddition works much better in the presence of additional trace amounts (1%) of EtOH (58% yield), rather than traces (0.01% or 1%) of H_2O (10 and 5% yield, resp.). A 63:37 *cis*/*trans*-**4d** mixture was obtained in 43–51% yield after 18 h in $CHCl_3$ at either 20° with 0.1 mol-equiv. of $SnCl_4$, or at 0° with 0.2 mol-equiv. $SnCl_4$ or $BF_3 \cdot OEt_2$. Alternatively, a 53:47 mixture was obtained in 38–42% yield after 18 h at 20° with either 0.2 mol-equiv. of $InCl_3$ or CF_3SO_3H in $CHCl_3$, or with 0.01 mol-equiv. of CSA in 4M $LiClO_4$ in Et_2O (1% ee). The cycloaddition was unsuccessful in $CHCl_3$, when catalyzed with one of the following reagents: 0.01 or 0.2 mol-equiv. of conc. HCl, CSA, *Filtrol*®, *NafionH*, $TiCl_4$, $TiCl_2(O^iPr)_2$, $ZrCl_4$, $ZrCl_3(OEt)$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $BiCl_3$, $CeCl_3$ hydrate, or $ZnCl_2$.

20°, a 55:45 mixture of *cis*/*trans*-**4d** was obtained in 75% yield after bulb-to-bulb distillation[11]). In order to reduce further condensation or polymerization, ozonolysis of the C=C bond was performed by modifying the protocol described by *Keul* and *Griesbaum* [22]. Accordingly, an excess of O_3 was bubbled at −78° through an AcOEt soln. of *cis*/*trans*-**4d**. Then, Me_2S was added, followed by MeOH and $NaHCO_3$[12]), before the mixture was allowed to come to ambient temperature. The known aldehyde **5c** [1][2][23][24][13]) was obtained after bulb-to-bulb distillation in 64% yield as a *cis*/*trans* 40:60 mixture, which was then quantitatively epimerized under acidic conditions (AcOH, H_2O, 40°) [1] to a *cis*/*trans* 7:93 mixture. Finally, *Wittig* reaction, as reported before [24] ($[Ph_3PPr]^+Br^-$, BuLi, toluene, −20 → 20°)[14]), afforded methyl jasmonate (*trans*-**1**) as a *cis*/*trans* 7:93 mixture ((*E*/*Z*) 4:96; 88% yield). Alternatively, the crude 40:60 *cis*/*trans* aldehyde **5c** was treated under filtered (*Chromafil P-20*/*25*; 0.2 μm)[15]) salt-free modified conditions [26] ($[Ph_3PPr]^+Br^-$, $NaNH_2$, ^{t}BuOK, toluene, −50°; 43% yield) to afford a 20:80 *cis*/*trans* mixture ((*E*/*Z* 3:97).

Conclusion. – We have worked out a new, efficient, three-step synthesis of methyl jasmonate (*trans*-**1**). The protocol is based on regioselective [4+2] cycloaddition of commercial cylopent-2-enone (**2**) and industrially available chloroprene (**3d**), catalyzed by a *Brønsted*/*Lewis* acid, followed by an ozonolysis–esterification–epimerization domino process and a final stereoselective *Wittig* reaction[16]).

Experimental Part

General. See [28].

cis/trans-*5-Chloro-2,3,3a,4,7,7a-hexahydro-1*H-*inden-1-one* (*cis*/*trans*-**4d**). A mixture of **2** (1.86 g, 22.7 mmol) and **3d** (5.99 g, 34 mmol; 50% in xylene) was added at 20° to a soln. of $SnCl_4$ (1.20 g, 4.6 mmol) in either $CHCl_3$ or CH_2Cl_2 (20 ml). After 18 h at 20°, the mixture was diluted, and then extracted with H_2O, washed with sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), filtered, concentrated, and pre-purified by

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[11]) For thermal homo-type [4+2] cycloadditions of **3d**, see [21].

[12]) Like for the initial MeONa/MeOH ozonolysis conditions (37% yield), extensive epimerization (15:85 to 10:90 mixtures of *cis*/*trans*-**4d**; 58–60% yield) was observed when a homogeneous organic base such as pyridine or Et_3N was used in CH_2Cl_2, while a 40:60 mixture was obtained (60% yield) in the presence of K_2CO_3 in CH_2Cl_2. With $NaHCO_3$, a one-pot cycloaddition–ozonolysis–esterification–epimerization process in CH_2Cl_2 afforded a *cis*/*trans* 10:90 mixture of **5c** in 47–51% global yield. Alternatively, when performed in $CHCl_3$, the corresponding known methyl *trans*-2-(2,2-dimethoxyethyl)-3-oxocyclopentylacetate [1] was obtained in 21% yield during a one-pot procedure in the presence of 1.0 mol-equiv. of MeOH/K_2CO_3.

[13]) In addition, the corresponding unreported acid *trans*-**5** (R=OH) was obtained in 30% yield when MeOH was replaced by H_2O during the ozonolysis of **4d**. IR: 3200, 2921, 2852, 1777, 1708, 1463, 1405, 1377, 1220, 1068, 923, 721. ^{1}H-NMR: 1.59 (*m*, 1 H); 1.9–2.5 (*m*, 6 H); 2.55–2.8 (*m*, 2 H); 2.95 (*dd*, *J*=7, 16, 1 H); 8.7 (br. *s*, 10 H); 9.77 (*s*, 1 H). ^{13}C-NMR: 27.6 (*t*); 37.0 (*t*); 38.1 (*d*); 38.5 (*t*); 42.3 (*t*); 49.1 (*d*); 177.4 (*s*); 200.1 (*d*); 217.9 (*s*). MS: 184 (0, M^+), 166 (4), 156 (8), 142 (39), 97 (100), 83 (62), 70 (18), 55 (35), 41 (21), 39 (20).

[14]) For alternative conditions (such as $[Ph_3PPr]^+Br^-$, $NaN(SiMe_3)_2$, THF/DMF, 20°), see [1][2][25].

[15]) We are indebted to Dr. *C. Margot* (*Firmenich SA*) for this suggestion.

[16]) The asymmetric [4+2] cycloaddition of **2** to **3c**,**d** using *Corey*'s (S. *Zhang*, *Firmenich SA*) or *Yamamoto*'s conditions (as a *Lewis* acid assisted *Brønsted* acid catalyst in dried or non-purified, reagent-grade $SnCl_4/CH_2Cl_2$, using chiral diols or amino alcohols) [27], will be reported in due course.

bulb-to-bulb distillation to afford a 55:45 to 57:43 mixture of *cis*/*trans*-**4d** in 75% yield. Further purification by column chromatography (CC) (SiO_2; CH_2Cl_2/hexane 6:4) afforded the pure stereoisomers in anal. quantities. B.p. 80°/0.2 mbar.

Data of trans-**4d**. IR: 2920, 1737, 1639, 1458, 1437, 1404, 1351, 1310, 1279, 1167, 1139, 1123, 1070, 991, 959, 932, 887, 815, 792. ^{1}H-NMR: 0.89 (*m*, 1 H); 1.28 (*m*, 1 H); 1.60 (*m*, 1 H); 1.96 (*m*, 1 H); 2.0 (*m*, 1 H); 2.2 (*m*, 1 H); 2.3 (*m*, 1 H); 2.43 (*m*, 2 H); 2.61 (*m*, 1 H); 5.88 (*m*, 1 H). ^{13}C-NMR: 25.1 (*t*); 27.2 (*t*), 37.6 (*t*); 38.8 (*d*); 39.8 (*t*); 50.0 (*d*); 123.7 (*d*); 131.7 (*s*); 216.6 (*s*). MS: 172 (10), 170 (20, M^+), 135 (100), 117 (20), 91 (60), 79 (45), 77 (40).

Data of cis-**4d**. IR: 2940, 1737, 1663, 1459, 1437, 1407, 1350, 1334, 1263, 1122, 1000, 988, 960, 933, 788, 695. ^{1}H-NMR: 0.88 (*m*, 2 H); 1.24 (*m*, 1 H); 1.84 (*m*, 1 H); 2.04 (*m*, 1 H); 2.29 (*m*, 2 H); 2.44 (*dd*, *J* = 4, 7, 1 H); 2.69 (*m*, 1 H); 5.77 (*m*, 1 H). ^{13}C-NMR: 22.7 (*t*); 26.1 (*t*); 33.4 (*t*); 33.7 (*t*); 33.9 (*d*); 45.8 (*d*); 122.2 (*d*); 129.8 (*s*); 217.8 (*s*). MS: 172 (7), 170 (20, M^+), 135 (100), 117 (24), 91 (65), 79 (40), 77 (43).

Methyl trans-*[3-Oxo-2-(2-oxoethyl)cyclopentyl]acetate* (*trans*-**5c**). *Method 1*. A soln. of *cis*/*trans*-**4d** (0.58 g, 3.41 mmol; *cis*/*trans* 44:56) in AcOEt (10 ml) was subjected to ozonolysis at −78°, until saturation of the blue-colored soln. was observed. Me_2S (2.5 ml, 34.1 mmol) was then added, followed, after 1 h at −78°, by MeOH (1.4 ml, 34.1 mmol) and $NaHCO_3$ (0.29 g, 3.41 mmol). Then, the temp. was allowed to reach 20° within 1 h, and the mixture was stirred at this temp. for 2 h. Evaporation under vacuum gave a crude residue, which was diluted with AcOEt, washed neutral with H_2O, dried (Na_2SO_4), filtered, concentrated, and purified by bulb-to-bulb distillation to afford a 38:62 mixture[17]) of *cis*/*trans*-**5c** in 64% yield. This mixture was treated with AcOH/H_2O at 40° [1] to afford quantitatively the known *trans* epimer **5c** as a *cis*/*trans* 7:93 mixture after bulb-to-bulb distillation.

Method 2. A mixture of **2** (5.0 g, 61 mmol) and **3d** (16.1 g, 91 mmol; 50% in xylene) was added at 20° to a soln. of $SnCl_4$ (3.17 g, 12.2 mmol) in CH_2Cl_2 (50 ml). After 18 h at 20°, the mixture was cool to −78°, and saturated with O_3 during 90 min. Then, Me_2S (37.2 g, 600 mmol) was added, followed, after 2 h at −78°, by $NaHCO_3$ (5.04 g, 60 mmol) and MeOH (19.2 g, 600 mmol). Then, the temp. was allowed to reach 20° within 1 h, and the mixture was stirred at this temp. for 18 h. Concentration under vacuum gave a crude residue, which was diluted with CH_2Cl_2, washed neutral with H_2O, dried (Na_2SO_4), filtered, concentrated, and purified by bulb-to-bulb distillation to afford a 10:90 mixture of *cis*/*trans*-**5c** in 47% yield. In the presence of 2.0 mol-equiv. of $NaHCO_3$ and 20 mol-equiv. of MeOH, the yield could be raised to 51%. B.p. 140°/0.29 mbar. For anal. data, see [1].

Methyl Jasmonate (= *Methyl* trans-*3-Oxo-2-[(2Z)-pent-2-enyl]cyclopentylacetate*; *trans*-**1**). *Method 1*. BuLi (1.6M soln. in hexane; 3.75 ml, 1.35 mmol) was added dropwise at 0° to a suspension of triphenyl(propyl)phosphonium bromide (540 mg, 1.4 mmol) in toluene (3 ml). After 1 h at 20°, the mixture was cooled down to −20°, and a soln. of **5c** (250 mg, 1.26 mmol; *cis*/*trans* 38:62) in toluene (4 ml) was added dropwise. After 2 h at −20°, and 1 h at +20°, H_2O/hexane was added. After filtration and concentration, the residue was purified by bulb-to-bulb distillation to afford **1** in 88% yield as a *cis*/*trans* 7:93 and (*E*/*Z*) 4:96 mixture.

Method 2. Triphenyl(propyl)phosphonium bromide (980 mg, 2.56 mmol) was added to a suspension of $NaNH_2$ (180 mg, 2.32 mmol; 50% in toluene) in toluene (10 ml). After 5 min, ^{t}BuOK (23.5 mg, 0.21 mmol) was added, and after 60 min, the suspension was cooled to −20°, and filtered (*Chromafil P-20*/*25*; 0.2 μm) with a syringe. The clear soln. was cooled to −50°, and a soln. of **5c** (500 mg, 2.53 mmol; *cis*/*trans* 36:64) in toluene (5 ml) was added dropwise. After 5 h at this temp., sat. aq. NH_4Cl soln. was added, the mixture was allowed to equilibrate, and then extracted with Et_2O. The org. phase was dried, concentrated, and purified by bulb-to-bulb distillation to afford **1** in 43% yield as a *cis*/*trans* 20:80 and (*E*/*Z*) 3:97 mixture. B.p. 175°/0.1 mbar. For anal. data, see [1].

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[17]) A 40:60 mixture (60% yield) was obtained when CH_2Cl_2 was used as a solvent instead of AcOEt.

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