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Eco-Friendly and Industrially-Scalable Synthesis of the Sex Pheromone of *Lobesia botrana*. An Important Progress for the Eco-Protection of Vineyard

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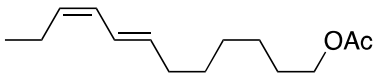
Graphic for Table of Contents



New Scalable Synthesis of the Sex Pheromone of *Lobesia Botrana*

ABSTRACT

A one-pot synthesis of the pheromone of *Lobesia botrana* is described. The procedure allows an efficient and economical access to this product which is used for the protection of vineyards.

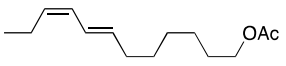
KEYWORDS: Sex pheromones, *Lobesia Botrana*, iron-catalyzed cross-coupling, dienol phosphates, trapping of dienolates

INTRODUCTION

Pheromones[1] are very promising for the eco-friendly protection of a wide range of crops such as grape, banana, apple, etc.[2] Contrary to classical pesticides, pheromones are specific to one species of pest, other insects, and especially pollinator insects, are unaffected. Furthermore, pheromones are biodegradable and have no effect upon human's health.[3] Those properties make pheromones ideal candidates for modern eco-friendly crop protection.

In our continued effort to develop efficient and large-scale procedures, we became interested in developping a new industrial access to the sex pheromone of the European grapevine moth *Lobesia botrana* **1**.

Figure 1. Sex pheromone of the European grapevine moth *Lobesia botrana:* (7*E*,9*Z*)-dodecadien-1-yl acetate

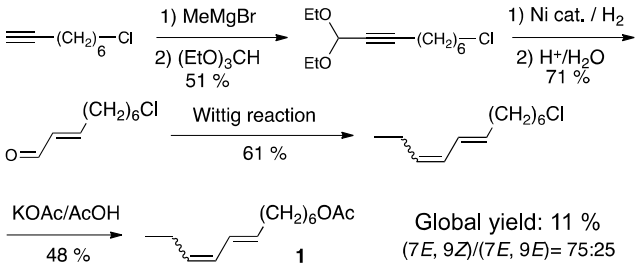


1

Despite its outstanding environmental benefits, few European countries are currently using this pheromone for the protection of vineyards on a large scale due to its relatively high cost.[4] However, in Germany or Switzerland where the government provides wine producers with financial support, 60 to 65 % of the surface of vineyards is successfully treated with the pheromone **1**.[5] In this context, it appears clearly that the search for an economically viable synthesis of the pheromone is a pre-requisite for a global use.

The current industrial process leading to the sex pheromone of *Lobesia botrana* is a linear and multi-step procedure starting from a not easily accessible chlorinated alkyne (Scheme).[6]

Scheme 1. Current industrial synthesis of the pheromone of *Lobesia botrana*



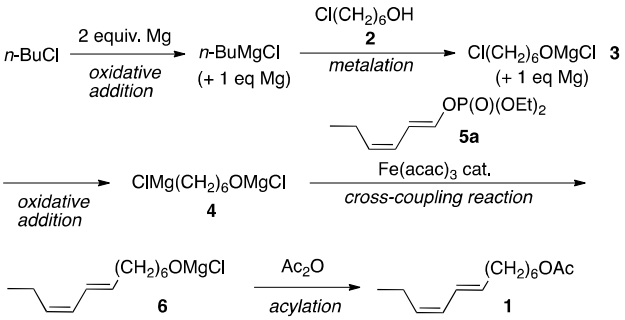
This relatively short synthesis requires the isolation of four intermediates, which is economically unfavorable. Furthermore, the pheromone **1** is isolated in only 11 % yield and 75 % of isomeric purity.

Other groups[7] also reported the synthesis of **1**. However, all the procedures are unattractive for an industrial production since they are too long and linear, poorly efficient, difficult to scale-up and require expensive reagents. Moreover, all intermediates have to be isolated.

RESULTS AND DISCUSSION

Previously,[8] we described an efficient and stereoselective iron-catalyzed cross-coupling reaction between dienol phosphates[9] and Grignard reagents. These results prompted us to explore a new economical and scalable synthesis of the pheromone of *Lobesia botrana* using this coupling reaction as a key step. Our project is based on a strategy described in Scheme 2; (*i*) preparation of the Grignard reagent ω-alcoholate **4** derived from 6-chlorohexanol **3**, and (*ii*) iron-catalyzed cross-coupling reaction of **4** with dienol phosphate **5a**, followed by an *in-situ* acylation of the resulting alcoholate **6** to give the desired pheromone **1** (Scheme 2).

Scheme 2. Strategy for one-pot synthesis of the pheromone of *Lobesia botrana* **1**

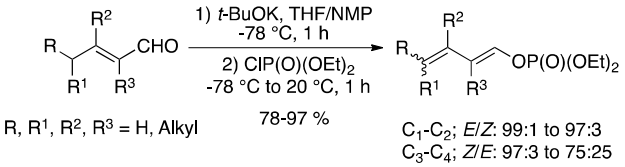


This project was ambitious since our goal was to perform the entire synthesis in a one-pot procedure.

*Stereoselective preparation of dienol phosphate **5** from trans-2-hexenal*

In 2008, our group reported a convenient method for a stereoselective preparation of dienol phosphates (Scheme 3).[9] It should be noted that the stereoisomeric purity of the C_3-C_4 double bond decreases when the length of the R alkyl group increases.

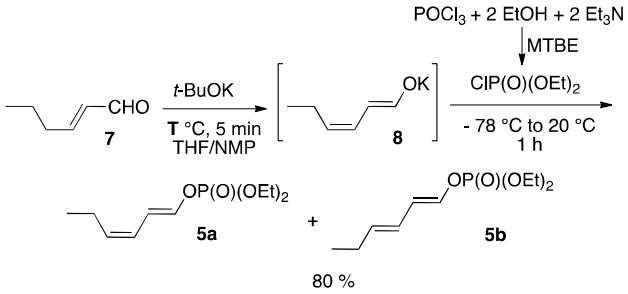
Scheme 3. Stereoselective synthesis of dienol phosphates



To prepare the pheromone of *Lobesia botrana* according to the strategy disclosed above (Scheme 2) we needed the dienol phosphate **5** derived from *trans*-2-hexenal **7** (Table 1). **7** was first treated with *t*-BuOK in a mixture of THF/NMP at -78 °C (Table 1, entry 1). The resulting dienolate **8** was then reacted with $ClP(O)(OEt)_2$ to give dienol phosphate **5** in 80 % yield (3*E*/3*Z*= 85:15).[10] It shoud be noted that on a large scale, $ClP(O)(OEt)_2$ is advantageously prepared from $POCl_3$ and EtOH (see supporting information).

For industrial applications, it is not very convenient to work at -78 °C. We have thus tried to perform the enolization step at a higher temperature (Table 1). It is important to recall that the commercial product **1** has a stereochemical purity of 75 % (1*E*,3*Z*/1*E*,3*E*= 3:1)[6] Thus, it is interesting to note that the dienol phosphate **5** can be obtained in a similar stereochemical ratio **5a**/**5b**= 73:24 at only -10 °C (Table 1, entry 4). On the other hand, the enolate **8** has to be trapped with $ClP(O)(OEt)_2$ rapidly to avoid the isomerisation of the C_3-C_4 double bond (Table 1, entries 4 and 5).

Table 1. Stereoselective synthesis of dienolphosphate **5**: Influence of the temperature.



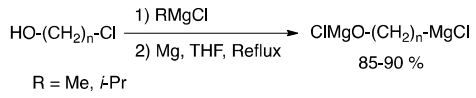
Entry	T (°C)	Ratio[a] (3Z, 1Z)	(3E, 1Z)	(3Z, 1E)	(3E, 1E)
1	-78	<1	<1	85	14
2	-50	<1	<1	82	16
3	-30	<1	<1	76	22
4	-10	<1	2	73	24
5	-10[b]	5	8	66	21
6	0	2	3	70	25
7	20	7	13	58	22

a/ Determined by GC. b/ Enolization time: 1h

Preparation of Grignard reagent $ClMgO(CH_2)_6MgCl$

In 1978, the group of Normant reported the preparation in good yields of alkyl Grignard reagents bearing an alcoholate in the ω-position (Scheme 4).[11] These functionalized Grignard reagents are readily obtained in a two-step procedure starting from an ω-chloroalcan-1-ol: (*i*) metallation of the alcohol with MeMgCl or *i*-PrMgCl (*ii*) insertion of magnesium (oxidative addition) into the carbon-chlorine bond of the chloroalcoholate $ClMgO(CH_2)_nCl$. On a large scale, the weak point of this procedure is the second step. Indeed, it is not always easy to activate the magnesium which is added to the chloroalcoholate solution and the yield ranges from 85 to 90%.

Scheme 4. Preparation of alkyl Grignard reagent $ClMgO(CH_2)_nMgCl$

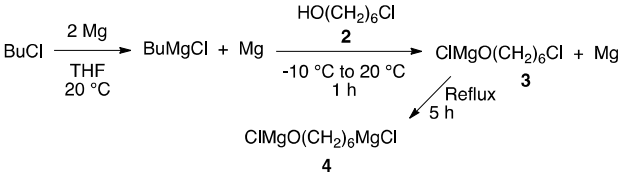


Our search of efficiency prompted us to develop a new one-pot procedure (Scheme 5). At first, butyl chloride reacts with two equivalents of magnesium to give BuMgCl + 1 equiv of Mg. Then, addition of chloroalcohol **2** between -10 to r.t. leads to the quantitative formation of the magnesium alcoholate **3**. By heating at reflux, this one undergoes an oxidative addition with the second equivalent of magnesium, to give the Grignard alcoholate **4** in 97 % yield. It should be noted that the conversion of **2** to **3** then of **3** to **4** can be performed sequentially only by adjusting the temperature of the reaction mixture.

Let us remark that this one-pot procedure allows to prepare $ClMgO(CH_2)_6MgCl$ much easier than the previous one depicted in Scheme 4. Indeed, the insertion of magnesium into the C-Cl bond of **3** occurs easily since the second equivalent of magnesium present

in the reaction mixture is already activated and very reactive. The expected Grignard reagent **4** was then obtained reproducibly in 97 % yield.

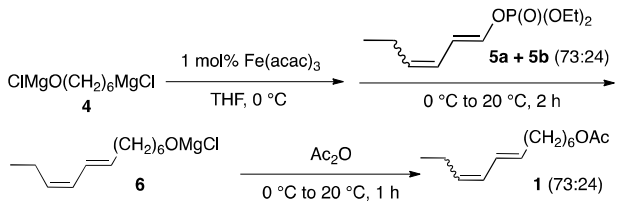
Scheme 5. One-pot preparation of $ClMgO(CH_2)_6MgCl$ **4**



*Fe-catalyzed cross-coupling reaction between Grignard reagent **4** and dienol phosphate **5***

To continue the development of our one-pot procedure, we have added at 0 °C, to the solution of $ClMgO(CH_2)_6MgCl$ **4** previously prepared (Scheme 5), a catalytic amount of $Fe(acac)_3$ and the dienol phosphate **5**[12]. The reaction mixture was stirred at room temperature for 2 h and the resulting alcoholate **6** was then acylated with acetic anhydride to give the pheromone **1** (Table 2). The first experiment was performed with 1 % of $Fe(acac)_3$. However, we have shown that the amount of catalyst can be decreased until 0.05 % (Table 2, entry 4). This result clearly evidences the high efficiency of iron catalysis.

Table 2. Iron-catalyzed cross-coupling reaction between Grignard reagent **4** and dienol phosphate **5** then acylation of **6** (one-pot procedure)



Entry	Amount of catalyst (mol %)	Isolated yield of **1** (%)
1	1	85
2	0.5	82
3	0.1	83
4	0.05	81

Conclusions

In this article, we describe a very short and efficient one-pot synthesis of the pheromone of *Lobesia botrana*. The key step of this procedure is an iron-catalyzed cross-coupling reaction between a dienol phosphate and a Grignard reagent alcoholate $ClMgO(CH_2)_6MgCl$. This procedure is currently used on an industrial scale for the production of the pheromone of *Lobesia botrana*.[10]

EXPERIMENTAL SECTION

General. Gas Chromatography analyses (GC) were performed on a Shimadzu Chromatograph 2010 Plus apparatus equipped with a flame ionization detector.

- Stereochemical ratio of dienol phosphates **5** was determined using a column Zebron ZB-5MS (length: 10 m, I.D.: 0.10 mm, film thickness: 0.10 μm. 5 % Polysilarylene / 95 % polydimethylsiloxane). Hydrogen was used as a carrier gas (1.07 mL/min, ratio split: 80). Standard analysis conditions: 80 °C to 200 °C (hold 4 min), heating rate: 20 °C/min.

- Stereochemical ratio of the pheromone **1** was determined using a column HP Innowax (length: 30 m, I.D.: 0.25 mm, film thickness: 0.25 μm). Hydrogen was used as a carrier gas (0.73 mL/min, ratio split: 100). Standard analysis conditions: 150 °C (hold 10 min) to 200 °C (hold 7.5 min), heating rate: 20 °C/min.

Thin layer chromatography (TLC) was carried out on silica gel plates (Carlo Erba 60 F254). Spots were detected with UV light and revealed with a potassium permanganate solution ($KMnO_4$: 6 g, K_2CO_3: 40 g, acetic acid: 0.5 mL, water: 600 mL).

Flash chromatography was performed on silica gel columns (Carlo Erba, spherical, neutral, 40-60 μm).

^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$) and ^{31}P NMR (121 MHz, H_3PO_4 external standard) were recorded on a Brucker Avance 300 instrument. Coupling constants (*J*) are given in Hz. The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Mass spectra were recorded on a Hewlett-Packart HP 5973 mass spectrometer *via* a GC/MS coupling with a Hewlett-Packart HP 6890 Chromatograph equipped with a capillary column HP-5MS (length: 50 m, I.D.: 0.25 mm, film thickness: 0.25 μm). Ionisation was performed by electronic impact (EI, 70 eV). Mass spectra are reported as *m*/*z* (% of relative intensity).

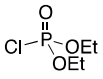
ESI-MS experiments were carried out using a LTQ-Orbitrap XL from Thermo Scientific and operated in positive ionization mode, with a spray voltage at 3.6 kV. Sheath and auxiliary gas were set at a flow rate of 45 and 15 arbitrary units (a.u.), respectively. Applied voltages were 20 and 70 V for the ion transfer capillary and the tube lens, respectively. The ion transfer capillary was held at 275 °C. Detection was achieved in the Orbitrap with a resolution set to 60,000 (at *m/z* 400) and a *m/z* range between 110-1200 in profile mode. Spectrum was analyzed using the acquisition software XCalibur 2.1 (Thermo Fisher Scientific). The

automatic gain control (AGC) allowed accumulation of up to 2.105 ions for FTMS scans. Maximum injection time was set to 300 ms and 1 µscan was acquired. 5 µL was injected using a Thermo Finnigan Surveyor HPLC system (Thermo Fisher Scientific) with a continuous infusion of methanol at 100 µL/min.

Purification of solvents and reagents. THF (Acros, 99.8 %, extra dry, stabilized), iron(III) acetylacetonate (Acros, 99 %), magnesium (nonferrum metal powders GmbH, 99.8 %, turnings, 3-4 mm), 6-chlorohexanol (Acros, 95 %), 2,2-biquinoline (Alfa Aesar, 98 %), ethyl bromide (Sigma-Aldrich, 98 %), *n*-butyl chloride (Acros, 99 %) acetic anhydride (Acros, 98 %), 1-methyl-2-pyrrolidinone (Acros, 99 %, extra pure), *trans*-2-hexenal, (Acros, 99 %), phosphorus oxychloride (Acros, 99 %), ethanol (absolute, Carlo Erba, for HPLC), potassium *tert*-butoxide (Acros, 98 %) were used without purification. Triethylamine was dried over potassium hydroxide and distilled under argon. *Tert*-butyl methyl ether was distilled under argon and stored under argon over activated 3Å molecular sieves.[13]

All reactions were performed under an argon atmosphere. Titration of Grignard reagents were performed according to the procedure reported by Watson[14] by using a 1 M solution of *sec*-butyl alcohol in toluene, 1 mL of the THF solution of the Grignard reagent and 1-2 mg of 2,2-biquinoline.

Diethyl chlorophosphate (CAS n°814-49-3)[15]

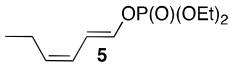


Preparative Procedure. In a dry four-neck 250 mL round-bottom flask equipped with a mechanical stirrer, a thermometer and an argon inlet, were introduced at 20 °C triethylamine (21.3 g, 210 mmol), *tert*-butyl methyl ether (75 mL) and ethanol (9.67 g, 210 mmol). Phosphorus oxychloride (15.3 g, 100 mmol) was added dropwise in 10 min *via* a syringe, the

temperature was maintained below -5 °C. Then, the cooling bath was removed and the white suspension was vigorously stirred during 5 h at 20 °C. The mixture was filtered and the solid was rinsed with 3x100 mL of diethyl ether. The solvents were removed under vacuo. The resulting crudez product was distilled under reduced pressure to afford 15.4 g (89 % yield) of diethyl chlorophosphate containing 3 % of triethylphosphate.

Eb_3 = 51 °C (litt.:[15] Eb_{10} = 85-87 °C). ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.37 (6H, t, *J* = 6.0 Hz), 4.16-4.30 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 15.6 (d, *J* = 7.5 Hz), 65.7 (d, *J* = 6.8 Hz). ^{31}P RMN ($CDCl_3$, 121 MHz, δ): 4.5.

Diethyl (1E,3Z)-hexa-1,3-dienyl phosphate[16]

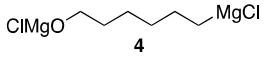


Preparative Procedure. In a dry four-neck 500 mL round-bottom flask equipped with a mechanical stirrer, a thermometer and an argon inlet, were introduced at 20 °C potassium *tert*-butoxide (12.6 g, 110 mmol), THF (150 mL) and NMP (100 mL). The purple solution was stirred at -10 °C and *trans*-hexenal (9.81 g, 100 mmol) was added dropwise in 5 minutes at 0 °C. After 5 minutes, diethyl chlorophosphate (20 g, 110 mmol) was added dropwise in 10 minutes at -10 °C. The mixture was stirred for 30 minutes then quenched by adding 150 mL of an aqueous solution of HCl (1 M). The aqueous layer was extracted with 3x50 mL of diethyl ether. The combined organic layers were dried over magnesium sulphate, filtrated and concentrated under vacuo. The product was distilled under reduced pressure to afford 19.9 g (84 %) of a yellow oil (1*E*,3*Z*/1*E*,3*E* = 74/26). The product can alternatively be purified by chromatography on a silica gel column using heptane/EtOAc 9:1 as eluent.

TLC, Rf = 0.53 (Heptane/EtOAc 1:1). GC: t_R(3*Z*, 1*Z*) = 2.93 min, t_R (3*E*, 1*Z*) = 3.01 min, t_R(3*Z*, 1*E*) = 3.14 min, t_R(3*E*, 1*E*) = 3.22 min. $Eb_{0.01}$ = 70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.95 (3H, t, *J* = 6.0 Hz), 1.32 (6H, t, *J* = 6.0 Hz), 2.0-2.14 (2H, m), 4.07-4.18 (4H, m), 5.39

(1H, dt, *J* = 12 Hz, 6 Hz), 5.78 (1H, t, *J* = 12 Hz), 6.24 (1H, t, *J* = 12 Hz), 6.63 (1H, dd, *J* = 12 Hz, 6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 14.0, 16.0 (d, *J* = 6.8 Hz), 20.9, 64.3 (d, *J* = 6.0 Hz), 113.2 (d, *J* = 11.3 Hz), 121.4, 133.9, 139.1 (d, *J* = 6.0 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz, δ): -4.5.

Grignard reagent 4 prepared from 6-chlorohexanol[17]



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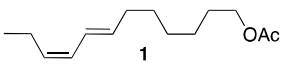
Preparative Procedure. In a dry four-neck 500 mL round-bottom flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, a condenser and an argon inlet, were introduced at 20 °C magnesium (17.8 g, 732 mmol) and THF (50 mL). Ethyl bromide (1.31 g, 12 mmol) was added instantaneously under vigorous stirring. After less than 1 min, the mixture became greenish and the temperature rose to 28-30 °C. The reaction mixture was then stirred at 50 °C and a solution of *n*-butyl chloride (30.8 g, 333 mmol) in THF (200 mL) was added dropwise in 20 to 30 min. After the end of the addition, stirring was continued for 3 h at 45 °C. The reaction mixture was cooled to -10 °C and 6-Chlorohexanol (41 g, 300 mmol) was added dropwise in 10 min *via* a syringe. The cooling bath was removed and the reaction mixture was stirred for 1 h. The product was then heated to reflux for 5 hours. After cooling to 20 °C, the expected Grignard reagent $ClMgO(CH_2)_6MgCl$ was obtained in 95-97 % yield.

(7E, 9Z)-Dodecadien-1-yl acetate[18]



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Preparative Procedure. To 82.5 mmol of $ClMgO(CH_2)_6MgCl$ prepared as described above were added , at 0 °C, THF (80 mL) and iron(III) acetylacetonate (26.5 mg, 0.1 mol%) in one portion. To the dark mixture thus obtained was added diethyl (1*E*,3*Z*)-hexa-1,3-dienyl phosphate **5** (17.6 g, 75 mmol) in 10 min *via* a syringe. The reaction mixture was then stirred for 2 h at 20 °C, cooled to 0 °C and acetic anhydride (14 mL, 150 mmol) was added dropwise at 5 °C in 5 min *via* a syringe. After 1 h of stirring at 20 °C, 150 mL of an aqueous solution of

HCl (1 M) was added to the reaction mixture. After decantation, the aqueous layer was extracted with 3x20 mL of petroleum ether. The combined organic layers were dried over magnesium sulphate, filtrated and concentrated under *vacuo*. The product was purified by distillation under reduced pressure affording 14.0 g (83 %) of a slightly yellow oil (7*E*,9*Z*/7*E*,9*E* = 74/26).

TLC, Rf = 0.4 (100 % Petroleum ether). GC: t_R(7*Z*, 9*Z*) = 13.04 min, t_R(7*E*, 9*Z*) = 13.24 min, t_R(7*Z*, 9*E*) = 13.33 min, t_R(7*E*, 9*E*) = 13.52 min. $Eb_{0.06}$ = 90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.98 (3H, t, *J* = 6.0 Hz), 1.27-1.41 (6H, m), 1.56-1.65 (2H, m), 2.02 (3H, s), 2.05-2.21 (4H, m), 4.04 (2H, t, *J* = 6.0 Hz), 5.29 (1H, td, *J* = 9.0 Hz, 6.0 Hz), 5.62 (1H, td, *J* = 15.0 Hz, 6.0 Hz), 5.89 (1H, t, *J* = 9.0 Hz), 6.28 (1H, dd, *J* = 15.0 Hz, 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 14.2, 20.88, 20.93, 25.7, 28.5, 28.7, 29.2, 32.7, 64.5, 125.6, 127.9, 131.7, 134.2, 171.0. HRMS: Calculated for $C_{14}H_{24}O_2Na$: 247.1669. Found: 247.1669.

ASSOCIATED CONTENT

† Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:

1-H, 13-C and MS spectra.

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Author Contributions

G.C., N.L. and A.M. contributed equally to this work. O.G. and S.D. participated to fruitful discussions.

Notes

The authors declare no competing financial interest.

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