

Stereoselective Synthesis of Conjugated Bisallenols as Precursors of Novel Bis(2,5-dihydrofuran) Derivatives

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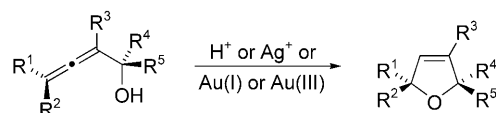
Abstract: A stereoselective synthesis of conjugated bis(α -hydroxyallenes) by copper-mediated S_N2' -substitution is described. Their silver- or gold-catalyzed cycloisomerization affords highly functionalized 2-allenyl-substituted 2,5-dihydrofurans and bis(2,5-dihydrofurans) under axis-to-center chirality transfer.

Keywords: bisallenols; chirality transfer; cycloisomerization; gold catalysis; silver catalysis

The rich and fascinating chemistry of conjugated bisallenols,^[1] a species containing one conjugated and two cumulated diene systems, has inspired chemists in the past decades. Ever since the isolation of the parent 1,2,4,5-hexatetraene (bisallenyl) by Hopf,^[2] these have been used as 4π components in $[4+2]$ cycloaddition reactions furnishing a wide variety of substituted carbo- and heterocyclic products.^[3] These reactions turned out to be an attractive method of preparing [2.2]paracyclophanes as well.^[4] The first iron(0)-catalyzed $[4+1]$ cycloaddition^[5] reaction was also reported using conjugated bisallenols and carbon monoxide furnishing cyclopentenones under mild conditions. Although the chemistry of (unfunctionalized) conjugated bisallenols is very rich, there are only few reports on functionalized derivatives,^[3f,6] and no systematic study on the synthesis and transformation of functionalized bisallenols has been reported to date. This is quite intriguing since the development of new methods for the synthesis of functionalized conjugated bisallenol derivatives can provide precursors for highly complex carbo- and heterocycles, employing efficient and atom-economical routes.

Herein, we disclose a novel, convenient and stereoselective approach to conjugated bis(α -hydroxyallenes), as well as their cyclization to bis(2,5-dihydrofuran) derivatives and 2-allenyl-substituted 2,5-dihydrofurans.

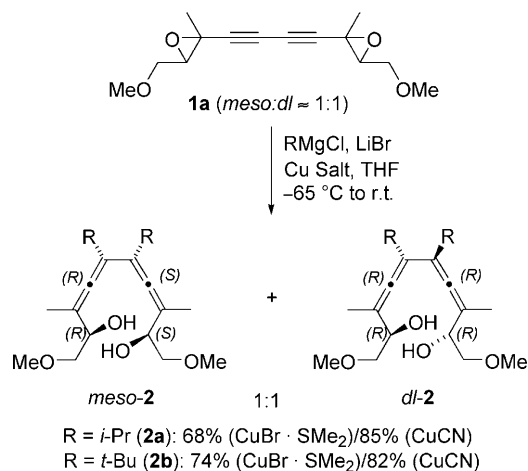
We take advantage of the cycloisomerization of α -hydroxyallenes^[7] to 2,5-dihydrofurans which is known to occur with axis-to-center chirality transfer when catalyzed by (anhydrous) acid,^[8] silver,^[9] or gold salts^[10,11] – the latter method is often superior in terms of efficiency and functional group tolerance (Scheme 1).



Scheme 1. Cycloisomerization of α -hydroxyallenes to 2,5-dihydrofurans.

We started our approach to bis(α -hydroxyallenes) from (*E*)-3-methylpent-2-en-4-yn-1-ol which was converted into the bisoxiranes **1a–c** by protection, Glaser–Hay coupling (CuCl/TMEDA/O_2)^[12] and epoxidation with *m*CPBA. Whereas the NMR spectra show a single set of signals, a slight splitting and/or broadening observed in the HPLC seems to indicate that the bisoxiranes **1** were formed as a mixture of the *meso*- and *dl*-diastereomers.^[13] All attempts to separate these isomers failed, so that the subsequent reactions were carried out with the mixture. For the allene formation by S_N2' -substitution of propargyloxiranes, various transition metals can be used.^[7] Whereas the iron-catalyzed reaction of bisoxiranes **1** with Grignard reagents,^[14] as well as the rhodium-catalyzed S_N2' -substitution with arylboronic acids^[15] did not afford any of the desired bisallenol, we were pleased to observe a smooth conversion of the bisoxiranes **1** into the bis(α -hydroxyallenes) **2** by reaction with magnesium cuprates in THF.^[7d,16] Thus, treatment of the *O*-methylated bis(propargyloxirane) **1a** with the cuprate obtained from isopropyl or *tert*-butylmagnesium chloride and $\text{CuBr}\cdot\text{SMe}_2$ at -65°C and warming of the reaction mixture to room temperature gave the

conjugated bisallenols **2a** and **2b** in 68% and 74% yield, respectively (Scheme 2). When CuCN was used as copper salt, the yields were improved to 85% (**2a**)



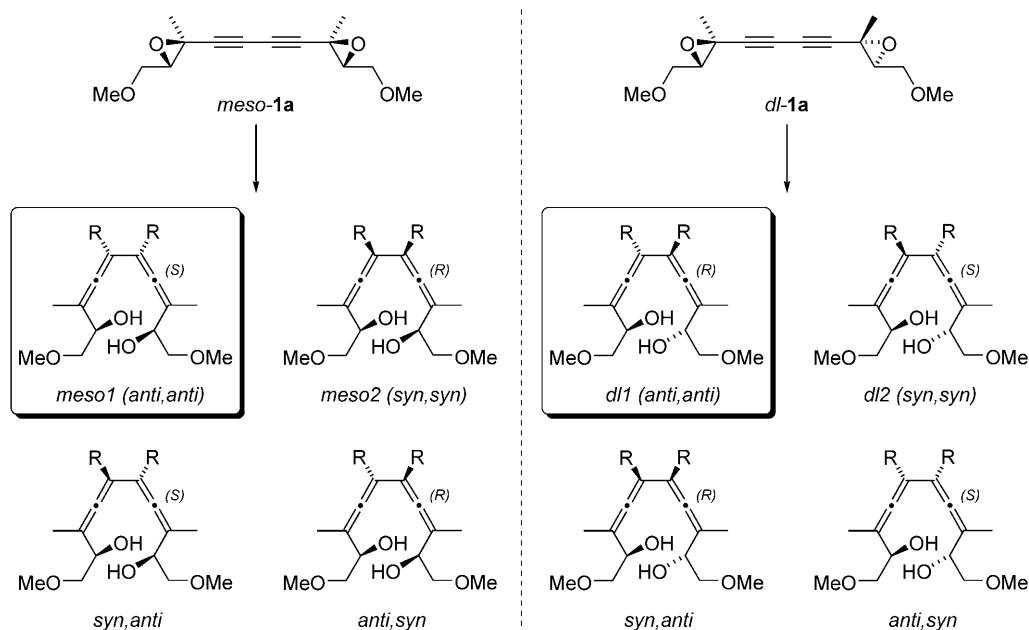
Scheme 2. Copper-mediated S_N2'-substitution of bisoxirane **1a** to bisallenols **2a/b**.

and 82% (**2b**). Both bisallenols were obtained as a 1:1 mixture of diastereomers which were separated by flash column chromatography; the relative configuration was determined with the X-ray structures of *meso*-**2a**,^[17] *meso*-**2b**,^[18] and *dl*-**2b**.^[19]

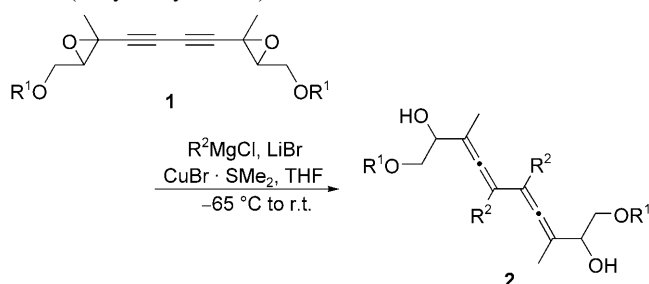
In principle, each propargyloxirane unit of bisoxiranes **1** can undergo a *syn*- or *anti*-selective S_N2'-substitution, so that 8 diastereomeric bisallenols can be formed (Scheme 3). It is very interesting to note that

out of these diastereomers, only the *meso1*- and *dl1*-isomers were obtained in a 1:1 ratio. The copper-mediated S_N2'-substitution of propargyloxiranes is known to proceed with high *anti*-selectivity in most cases, and it is often accompanied by epimerization of the allenic chirality axis (induced by single electron transfer from the cuprate or other reactive copper species present in the reaction mixture).^[7d,20] In the present case, both the *meso*- and *dl*-isomer of **1a** react in an *anti,anti*-manner. Moreover, epimerization processes can be excluded since these would probably lead to the formation of a statistical mixture of all diastereomeric bis(α-hydroxyallenes). Rather, it seems that *meso*-**1a** gives *meso*-**2a/b**, and *dl*-**1a** affords *dl*-**2a/b**.^[21]

Under the above reaction conditions, only a single diastereomer of bisallenols **2c** and **2d** was obtained with low yield when **1a** was treated with the magnesium cuprate derived from EtMgBr or PhMgCl and CuBr·SMe₂ (Table 1, entries 1 and 2). Moreover, bis(propargyloxiranes) **1b** and **1c** bearing benzyl or TBS protecting groups also furnished a single diastereomer of the corresponding bisallenol when treated with various magnesium cuprates (entries 4–7). This observation along with the fact that the yield of some bisallenols is higher than 50% (entries 4–6) indicates that the bis(propargyloxiranes) **1b** and **1c** are not exactly 1:1-*meso*/*dl*-mixtures, but rather enriched in one diastereomer.^[13] Only the reaction of **1b** with *i*-PrMgCl and CuBr·SMe₂ gave two diastereomeric bis(α-hydroxyallenes) **2f** (entry 3). Since the products **2c–i** are not crystalline, we were unable to determine their relative configuration. In contrast to **1a**, reaction of bisox-



Scheme 3. Possible diastereomers of bis(α-hydroxyallenes).

Table 1. Copper-mediated S_N2' -substitution of bisoxiranes **1** to bis(α -hydroxyallenes) **2**.

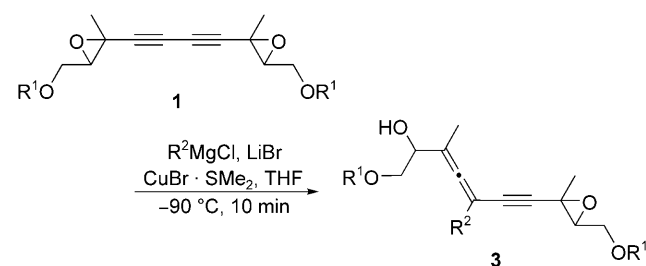
Entry	1	R^1	R^2	2	Yield [%]
1	1a	Me	Et	2c	12
2	1a	Me	Ph	2d	33
3	1b	Bn	<i>i</i> -Pr	2e	55 ^[a]
4	1b	Bn	<i>t</i> -Bu	2f	54
5	1c	TBS	<i>i</i> -Pr	2g	57
6	1c	TBS	<i>t</i> -Bu	2h	58
7	1c	TBS	Bn	2i	21

^[a] Mixture of 2 diastereomers in a ratio of 54:46 (55% combined yield).

irane **1c** with magnesium cuprates derived from $CuCN$ gave only complex product mixtures.

Further experimentation revealed that the reaction of the propargyloxirane units of **1** with magnesium cuprates occurs stepwise with quite different rates. Whereas the first S_N2' -substitution was found to be extremely fast even at $-90^\circ C$, the second substitution requires higher temperatures ($-20^\circ C$ to $0^\circ C$). An exception is the phenylmagnesium cuprate which requires rather higher temperatures (*ca.* $-10^\circ C$) already for the first substitution step. For $R^2 \neq Ph$, the monosubstitution products **3** can be isolated with 49–59% yield by quenching the reaction mixture at $-90^\circ C$ (Table 2).

With various bis(α -hydroxyallenes) **2** at hand, we examined their cycloisomerization to bis(2,5-dihydrofurans). Unfortunately, the use of various gold(I) or gold(III) salts in non-polar (dichloromethane, toluene) or polar solvents (THF, acetonitrile) did not afford any dihydrofuran product, but resulted in no conversion ($Ph_3PAuCl + AgOTf$ or $AgSbF_6$; $AuCl_3 + 2,2'$ -bipyridine^[10c]) or decomposition of the starting material ($AuCl$; $AuCl_3$; $AuBr_3$; $AuCl_3 + CuCl_2$ ^[22]). In the presence of *p*-toluenesulfonic acid in dichloromethane,^[8] an extremely slow formation of monocyclized products was observed. In contrast to this, treatment of the bisallenols **2a/e/g** bearing two isopropyl groups with substoichiometric amounts (0.25 equiv.) of silver nitrate in acetone at room temperature^[9] induced a rapid monocyclization to afford the corresponding 2-allenyl-substituted 2,5-dihydrofurans **4** with excellent yield (Scheme 4). In each case, a single diastereomer was obtained, indicating that the cyclization takes

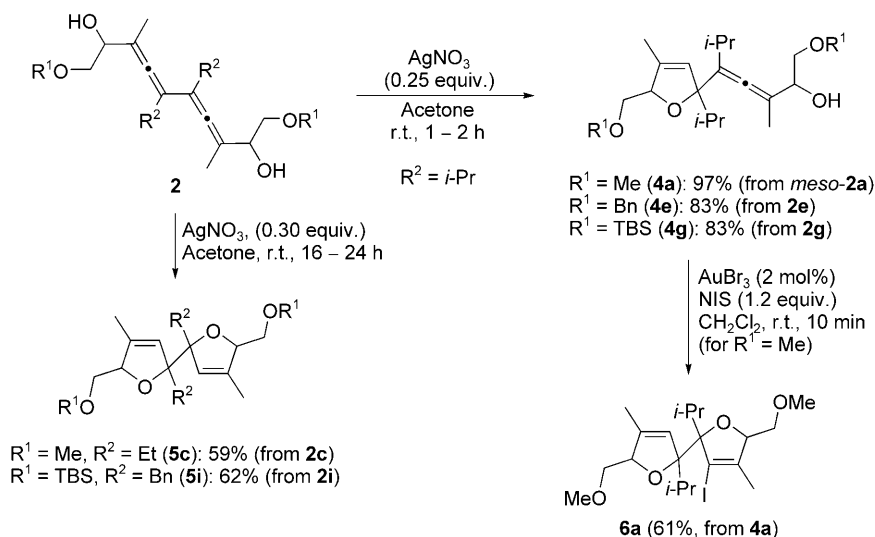
Table 2. Synthesis of monosubstitution products **3** from bisoxiranes **1**.

Entry	1	R^1	R^2	3	Yield [%]
1	1a	Me	<i>i</i> -Pr	3a	49
2	1a	Me	<i>t</i> -Bu	3b	53
3	1b	Bn	<i>i</i> -Pr	3c	49
4	1c	TBS	<i>n</i> -Bu	3d	57
5	1c	TBS	<i>i</i> -Pr	3e	54
6	1c	TBS	<i>t</i> -Bu	3f	59

place with axis-to-center chirality transfer. As observed previously for simple α -hydroxyallenes,^[9c] the presence of water in the reaction mixture should be avoided since it strongly decelerates the cyclization.

A second cyclization of the 2-allenyl-substituted 2,5-dihydrofurans **4** to the corresponding bis(2,5-dihydrofurans) could not be achieved with gold or silver salts alone. This is probably due to the steric hindrance at the allene caused by two adjacent isopropyl groups. In accordance with this assumption, treatment of the ethyl- or benzyl-substituted bisallenols **2c** and **2i** with 0.3 equiv. of $AgNO_3$ afforded the bis(2,5-dihydrofurans) **5c** and **5i** with good yield after prolonged reaction times (16–24 h; Scheme 4). In the case of $R^2 = i$ -Pr, the second cyclization step was realized by taking advantage of the accelerating effect of *N*-iodosuccinimide (NIS) on gold-catalyzed transformations.^[23] Thus, treatment of **4a** (obtained from *meso*-**2a**) with 2 mol% of gold(III) bromide in the presence of 1.2 equiv. of NIS in CH_2Cl_2 afforded the richly functionalized bis(2,5-dihydrofuran) **6a** with 61% yield after just 10 min at room temperature (Scheme 4).

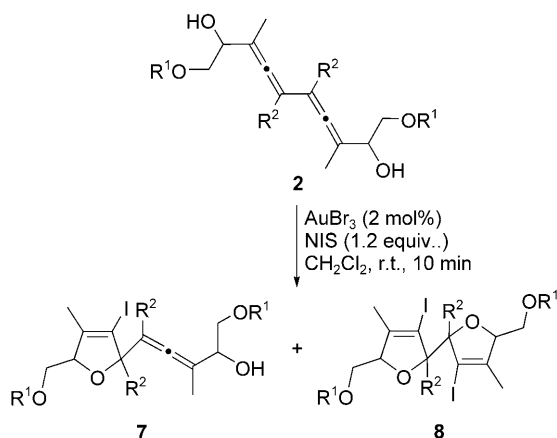
Unfortunately, all attempts to extend the silver-mediated cycloisomerization to bis(α -hydroxyallenes) **2** bearing very bulky substituents R^2 (*t*-Bu, Ph) failed even at higher temperatures or under microwave conditions. In the presence of NIS, however, the previously unsuccessful gold-catalyzed cyclization of the bis(α -hydroxyallenes) **2** could be achieved (Table 3). Thus, treatment of *meso*- or *dl*-**2a** with 2 mol% of $AuBr_3$ and 1.2 equiv. of NIS in CH_2Cl_2 provided the iodinated monocyclization products **7a** and **7a'** with 60% and 78% yield, respectively, after just 10 min reaction time (entries 1 and 2). Even the particularly bulky *tert*-butyl-substituted bisallenols **2b/f** were con-



Scheme 4. Silver- and gold-catalyzed cycloisomerization of bis(α -hydroxyallenes) **2**.

verted into the corresponding 2,5-dihydrofurans **7** with high yield under these conditions (entries 3 and 5). In contrast to these substrates, the diphenyl-substituted bisallene **2d** afforded not only the monocyclization product **7d** (38%), but also traces of the sterically crowded bis(2,5-dihydrofuran) **8d** (3% yield, entry 4). In this case, use of AgNO_3 in acetone instead of AuBr_3 caused a slight shift of the product ratio from **7d** (25%) to **8d** (9% yield). All heterocyclic products

Table 3. Gold-catalyzed cycloisomerization of bis(α -hydroxyallenes) **2** in the presence of *N*-iodosuccinimide (NIS).



Entry	2	R^1	R^2	7 (Yield [%])	8 (Yield [%])
1	<i>meso</i> - 2a	Me	<i>i</i> -Pr	7a (60)	–
2	<i>dl</i> - 2a	Me	<i>i</i> -Pr	7a' (78)	–
3	<i>meso</i> - 2b	Me	<i>t</i> -Bu	7b (81)	–
4 ^[a]	2d	Me	Ph	7d (38)	8d (3)
5	2f	Bn	<i>t</i> -Bu	7f (69)	–

^[a] Treatment of **2c** with AgNO_3 (10 mol%) and NIS (1.2 equiv.) in acetone for 15 min at room temperature afforded 25% of **7d** and 9% of **8d**.

were obtained as a single diastereomer, indicating that also these cyclizations take place with complete axis-to-center chirality transfer. In contrast to the bisallenes **2**, the monosubstitution products **3** failed to deliver a cycloisomerization product when subjected to silver or gold catalysis (with or without NIS), but furnished complex product mixtures.

In conclusion, we have developed an efficient and stereoselective access to previously unknown bis(α -hydroxyallenes) **2** by *anti*-selective $\text{S}_{\text{N}}2'$ -substitution of bis(propargyloxiranes) **1** with magnesium cuprates. It was found that the bisallenol formation takes place in two steps allowing the isolation of the monosubstitution products **3** at very low temperatures. In some cases only one diastereomer of the bis(α -hydroxyallene) was isolated. The isopropyl-substituted bisallenols **2a/e/g** undergo a facile silver-mediated monocyclization to 2-allenyl-substituted 2,5-dihydrofurans **4**, whereas the less bulky substrates **2c/i** afford the bis(dihydrofurans) **5**. A gold-catalyzed cyclization of the bisallenes **2** or the monocyclization products **4** is possible in the presence of *N*-iodosuccinimide, giving rise to the formation of the iodinated heterocycles **6–8**. All cyclizations proceed with complete chirality transfer from the allenic chirality axis to the new stereogenic center(s). At this point, it should be noted that the bis-tetrahydrofurandiols structure of the type **5** is found in Annonaceous acetogenins^[24] (ACGs) possessing high anticancer activities. Thus, by taking advantage of combined coinage-metal catalysis, our method may provide an alternative access to these highly interesting natural products. Moreover, the introduction of iodine into the dihydrofurans broadens the opportunities for subsequent transformations. Further studies on the synthesis and application of functionalized bisallenes are currently underway.

Experimental Section

Synthesis of Conjugated Bisallenol *meso*-**2b** and *dl*-**2b**; Representative Procedure

Anhydrous LiBr (416 mg, 4.8 mmol) was quickly weighed and transferred into a three-neck round-bottom flask. The flask was evacuated, heated with a heat gun and then cooled to room temperature under an argon atmosphere. CuBr·SMe₂ (985 mg, 4.8 mmol) and dry THF (18 mL) were added and the suspension was vigorously stirred until it became homogeneous and was then cooled to −25 °C. *tert*-Butylmagnesium chloride (2.0 M solution in THF, 2.4 mL, 4.8 mmol) was added dropwise. After stirring the mixture for 30 min at −25 °C, it was cooled to −65 °C, and a THF solution of the bis(propargyloxirane) **1a** (200 mg, 0.79 mmol in 2 mL THF) was added dropwise. The mixture was stirred for 10 min at −65 °C and slowly warmed up to room temperature. The completion of the reaction was proved by the TLC. The reaction was quenched by the addition of aqueous saturated NH₄Cl (3 mL) and stirred for 30 min at room temperature. It was then filtered through Celite and dried with sodium sulfate. After removal of the solvent, the residue was subjected to flash chromatography on silica gel using cyclohexane-ethyl acetate (2:1) as eluent to afford the conjugated bisallenols *meso*-**2b** (yield: 107 mg, 36.5%) and *dl*-**2b** (yield: 110 mg, 37.5%) as colorless solids.

The same procedure was used for the synthesis of the monoallenol adduct **3b** with the only change that **1a** was added at −90 °C and the mixture was stirred for 10 min at −90 °C before being quenched with methanol at the same temperature.

Synthesis of 2-Allenyl-Substituted 2,5-Dihydrofuran **4a**; Representative Procedure

The bisallene *meso*-**2a** (50 mg, 0.15 mmol) was dissolved in acetone (2 mL), AgNO₃ (6.3 mg, 0.04 mmol) was added, and the mixture was stirred for 2 h in the dark. After TLC control indicated complete consumption of the starting material, the reaction mixture was passed through a short pad of Celite and the solvent was removed. The residue was subjected to flash chromatography on silica gel using cyclohexane-ethyl acetate (2:1) as eluent to afford **3a** as a colorless viscous liquid; yield: 48 mg (97%).

Synthesis of Bis(2,5-dihydrofuran) **6a**; Representative Procedure

Dihydrofuran **4a** (50 mg, 0.15 mmol) was dissolved in dry dichloromethane (3 mL), and *N*-iodosuccinimide (40 mg, 0.18 mmol) as well as AuBr₃ (1.3 mg, 3 μmol) were added. After 10 min stirring at room temperature, TLC control indicated complete consumption of the starting material. The reaction mixture was passed through a short pad of Celite and the solvent was removed. The residue was subjected to flash chromatography on silica gel using cyclohexane-ethyl acetate (10:1) as eluent to afford **4a** as a brownish-red liquid; yield: 42 mg (61%).

Synthesis of 2-Allenyl-3-iodo-2,5-dihydrofuran **7b**; Representative Procedure

The bisallene *meso*-**2b** (50 mg, 0.14 mmol) was dissolved in dry dichloromethane (3 mL) and *N*-iodosuccinimide (37 mg, 0.17 mmol) as well as AuBr₃ (1.1 mg, 3 μmol) were added. After 10 min stirring at room temperature, TLC control indicated complete consumption of the starting material. The reaction mixture was passed through a short pad of Celite and the solvent was removed. The residue was subjected to flash chromatography on silica gel using cyclohexane-ethyl acetate (4:1) as eluent to afford the **7b** as a brownish-red liquid; yield: 54 mg (81%).

Supporting Information

General remarks, characterization data and NMR spectra are given in the Supporting Information.

Acknowledgements

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