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Toward the Valorization of Cotton Wastes: Application of a Gossypol-Derived Ligand to an Asymmetric Diels–Alder Reaction

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ABSTRACT

Gossypol, a major metabolite of cotton plants, has been used for the first time as a source material for the preparation of derivatives employed in asymmetric catalysis. Specifically, the (R)-enantiomer of the 6,6',7,7'-O-tetramethyl derivative of apogossypol has been synthesized in five steps and 47% total yield from enantiopure (–)-(R)-gossypol. This axially chiral diol was used as a ligand in the enantioselective boron-catalyzed Diels–Alder reactions of 2'-hydroxychalcones and dienes, achieving high yields and moderate enantioselectivities. Considering the potentially high amounts of gossypol isolable from agricultural wastes of cotton crops, these results open the way for the introduction of a promising new class of biomass-derived asymmetric catalysts.

1 | Introduction

In line with the principles of sustainable development and circular economy, there is a growing need to use renewable energy sources or carbon-based feedstock in organic synthesis [1, 2]. In this context, an attractive strategy involves the design and preparation of organic catalysts and ligands using biomass as a raw material rather than fossil fuels, for example, through the valorization of agricultural wastes [3–6]. Since the advent of enantioselective catalysis, natural products have served as a foundation for the design and development of chiral auxiliaries and catalysts. However, the application of waste biomass-derived organocatalysts remains in its early stages. Moreover, to our knowledge, despite the central role played by C_2-symmetric biaryl diols as chiral catalysts and ligands in asymmetric synthesis (e.g., **1**-**5**, Figure 1), naturally occurring products featuring such structural motifs have never been used as source materials for their production [7].

Cotton (*Gossypium* spp.) is one of the major global agricultural crops, mainly intended for textile fiber manufacturing, with its seeds also used for both human and livestock food consumption [8]. The global cultivated area today exceeds 30 million ha, and the current production is > 20 million metric tons/year, with prospects for further growth in the next decade [9, 10]. All the parts of the cotton plants, but especially seeds (ca 1%, with peaks of up to 6% of the total weight), contain high amounts of both the enantiomeric forms of the axially chiral phytoalexin gossypol (**6**, Figure 1), featuring a functionalized 2,2′-bi-1-naphthol structure. Since gossypol is toxic to nonruminant animals and humans, and exhibits antifertility effects in males, it must be removed during the production of edible oil and cattle feed using various processing methods, such as fermentation and solvent extraction [11–13]. Nevertheless, gossypol and its derivatives sparked interest for the impressively wide range of potential biomedical applications, owing to anticancer, contraceptive, anti-inflammatory, antiviral, and cytotoxic activities among the others [14–16]. It

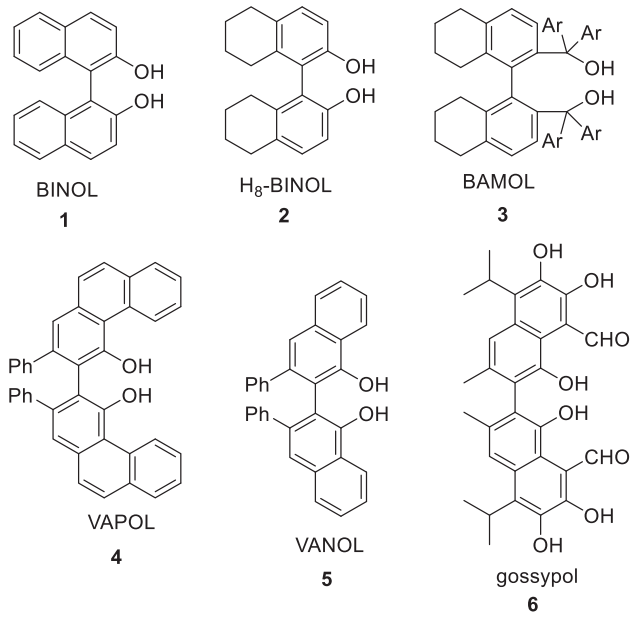


FIGURE 1 | Structure of C_2-symmetric chirally axial biaryl diols and gossypol.

must also be noted that, taking into account the large content of gossypol in whole cotton plants, including wastes produced during harvest and ginnery, this molecule could be regarded as one of the most intriguing and undervalued "unrecovered" products from agricultural biomass [17–19]. However, despite the similarity of gossypol's structure with axially chiral binaphthyl ligands and catalysts, applications in asymmetric synthesis have never been described so far. To fill this gap, we report herein the application of a C_2-symmetric gossypol-derived chiral ligand in the enantioselective Diels–Alder reaction of 2'-hydroxychalcones.

This reaction is effectively mediated by boron complexes with axially chiral biaryl diols, as demonstrated for the first time by Wulff, Lei, and coworkers, who used VANOL as a chiral ligand in stoichiometric amounts [20, 21]. The resulting Diels–Alder adducts have been used as key intermediates for the synthesis of cyclohexene-containing natural products. In a handful of later works, VANOL and other axially chiral diols have been used in catalytic protocols, leading to the desired adducts with good to excellent *endo*-diastereoselectivity and enantioselectivity [22–24].

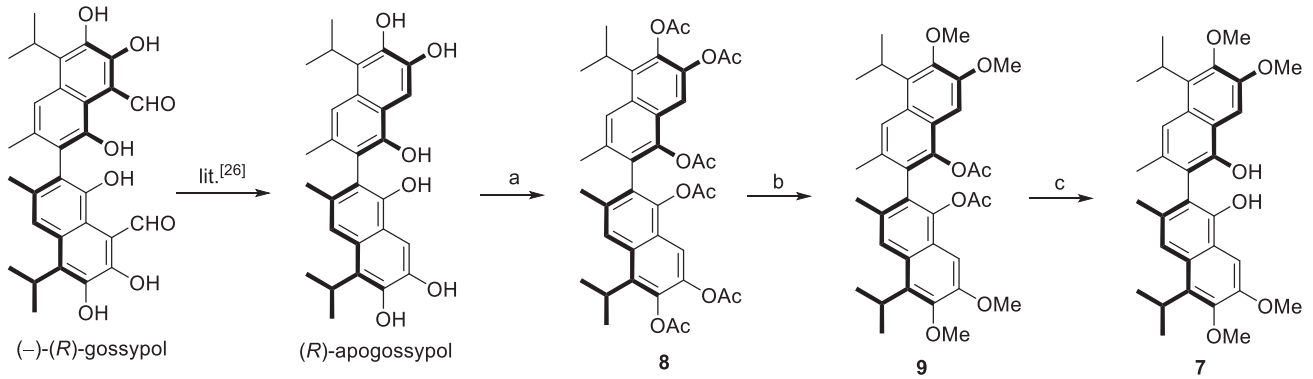
Considering the ready-made 2,2′-bi-1-naphthol framework of gossypol, similar to that of VANOL, we looked at this Diels–Alder reaction as an appropriate benchmark process for testing the potential of chiral gossypol-derived ligands in asymmetric catalysis.

2 | Results and Discussion

As an initial step in designing an appropriate derivative, we recognize the necessity of protecting the four phenolic groups at the 6,6',7,7' positions, while retaining free the 1,1'-hydroxyl groups proximal to the chiral axis, as the exclusive binding sites of the molecule. This strategy prevents multiple modes of coordination to boron. However, attempts to selectively protect 6,6',7,7'-hydroxy groups while preserving free 1,1'-hydroxy and 8,8'-formyl functionalities were hindered by the formation of a highly stable lactol ring. Therefore, we moved toward a chiral ligand candidate lacking the 8,8'-formyl groups. Since the synthesis of racemic 6,6'7,7'-*O*-tetramethylated apogossypol derivative **7** has recently been reported [25], we sought to adapt the pathway to obtain the compound in enantiopure form. Although this strategy finally worked, modifications of experimental conditions needed to be made in some steps to prevent erosion of the enantiomeric purity (Scheme 1).

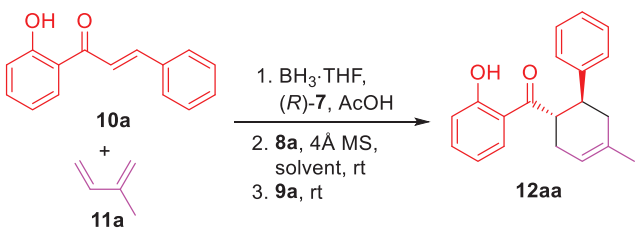
(−)-(*R*)-Gossypol was submitted to deformylation to provide (*R*)-apogossypol, as previously described [26–28]. Subsequent peracetylation proceeded smoothly, leading to **8**. The subsequent tetramethylation step revealed a crucial issue related to the reaction time, since this experimental detail was not specified in the reported *O*-methylation on the racemic compound [25]. The crude product we obtained after K_2CO_3-promoted methanolysis was tentatively subjected to full methylation by stirring the mixture overnight at room temperature. However, under those conditions, only low yields were achieved, accompanied by a partial loss of enantiomeric purity. Consequently, we decided to reduce reaction time to 2 h, with beneficial effects on both the yield and the configurational stability. Major issues were observed with the reductive deacetylation of chiral diester **9**. Under previously reported conditions (2.5 equiv. of $LiAlH_4$ at 0°C) [25], diol **7** was obtained quantitatively in 30 min, but with a substantial loss of enantiomeric purity (<60% ee). Fortunately, performing the reduction at −40°C with smaller amounts of $LiAlH_4$ (1.5 equiv.), ensured preservation of the enantiomeric purity (94% ee), still affording a good yield.

Once obtained, the axially chiral diol **7**, it was tested as a ligand in the enantioselective Diels–Alder reaction of hydroxychalcone **10a** with isoprene (**11a**) in the presence of borane-THF complex, using different solvents (Table 1). According to the procedure previously optimized with other ligands, stoichiometric amounts of diol-boron complex, preliminarily formed by mixing BH_3·THF with the ligand and acetic acid in THF, were used after removal of the solvent and re-dissolving in the appropriate solvent, to promote the cycloaddition [20]. Reaction performed in THF provided the expected product **12aa** in good e.r., but the conversion was incomplete even after a long time (Table 1, entry 1). A lower level of enantioselectivity was observed in toluene (Table 1, entry 2). Chlorinated solvents proved to be better, leading to the desired cycloadduct after 20 h, with a good enantioselectivity. A slightly better result was achieved in CH_2Cl_2 than in DCE (Table 1, cf. entries 3 and 4). Attempts to carry out the process using in situ-generated catalytic amounts of the diol-boron complex, according to literature procedures [23, 24], resulted in total conversion but required longer reaction times and led to significantly lower enantiomeric ratio (Table 1, entry 5). Recovery of the ligand after reaction revealed a decrease in its enantiomeric purity (70% ee), suggesting that its partial racemization negatively affects the enantioselectivity of the process. However, carrying out the reaction at 0°C, resulted in incomplete conversion even after enormously longer reaction time, with negligible increase of the ee (Table 1, entry 6). No conversion was observed in the absence of a catalyst, ruling out the involvement of the background reaction under optimized conditions (Table 1, entry 7).



SCHEME 1 | Synthesis of gossypol-derived chiral ligand **7**; (a) Ac_2O, DMAP, CH_2Cl_2, rt, 16 h, 86%; (b) i. K_2CO_3, $CH_3OH/CH_2Cl_2/H_2O$ 4:2:1, 65°C, 1 h; ii. K_2CO_3, DMF, 15 min, then CH_3I, rt, 2 h, 69%, 2 steps; (c) $LiAlH_4$ (1.5 equiv.), THF, −40°C, 80%, 94% ee.

TABLE 1 | Optimization of the Diels–Alder reaction with ligand **7**[a,b].



Entry	Solvent	Time (h)	Yield (%)	e.r.
1	THF	68	41	82:18
2	Toluene	20	44	76:24
3	DCE	20	99	86:14
4	CH_2Cl_2	20	99	88:12
5[c]	CH_2Cl_2	92	98	68:32
6[d]	CH_2Cl_2	168	74	90:10
7[e]	CH_2Cl_2	68	—	—

[a]Reaction conditions: i. BH_3•THF (0.027 mmol), **7** (0.027 mmol), AcOH (0.027 mmol), THF (0.5 mL), rt; 30 min; ii. **10a** (0.022 mmol), 4Å MS (100 mg), solvent (0.5 mL), rt, 1 h; iii. **11a** (0.44 mmol), rt.

[b]Enantiomeric ratios were measured by chiral HPLC analysis.

[c]Reaction performed with a catalytic amount of $B(O_iPr)_3$-**7** complex: $B(O_iPr)_3$ (0.010 mmol), **7** (0.012 mmol), **10a** (0.10 mmol), 4Å MS (100 mg), CH_2Cl_2 (1.0 mL), 40°C, 2 h, then **11a** (1.0 mmol), rt.

[d]Reaction performed at 0°C.

[e]Reaction performed without a catalyst.

Under all the conditions, **12aa** was obtained as a single regioisomer. As expected, the use of (*R*)-**7** favored the formation of the dextrorotatory enantiomer, in agreement with the stereochemical outcome observed with the structurally analogous ligand VANOL [20, 24]. It should be noted that, contrary to the original report [20, 24], the (*S*,*S*) configuration has been later demonstrated for (+)-**12aa** [23, 29]. This finding indicates a preference for an *endo*-(*Si*,*Si*) approach of diene **11a** to the (*R*)-**7**-B-**10a** complex (Figure 2).

The optimized conditions were then used to define the scope of this methodology (Scheme 2). Pleasingly, reaction of the parent 2'-hydroxychalcone **10a** with diversely substituted dienes

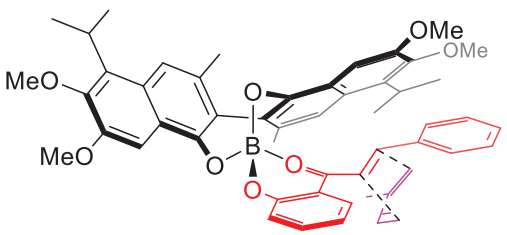
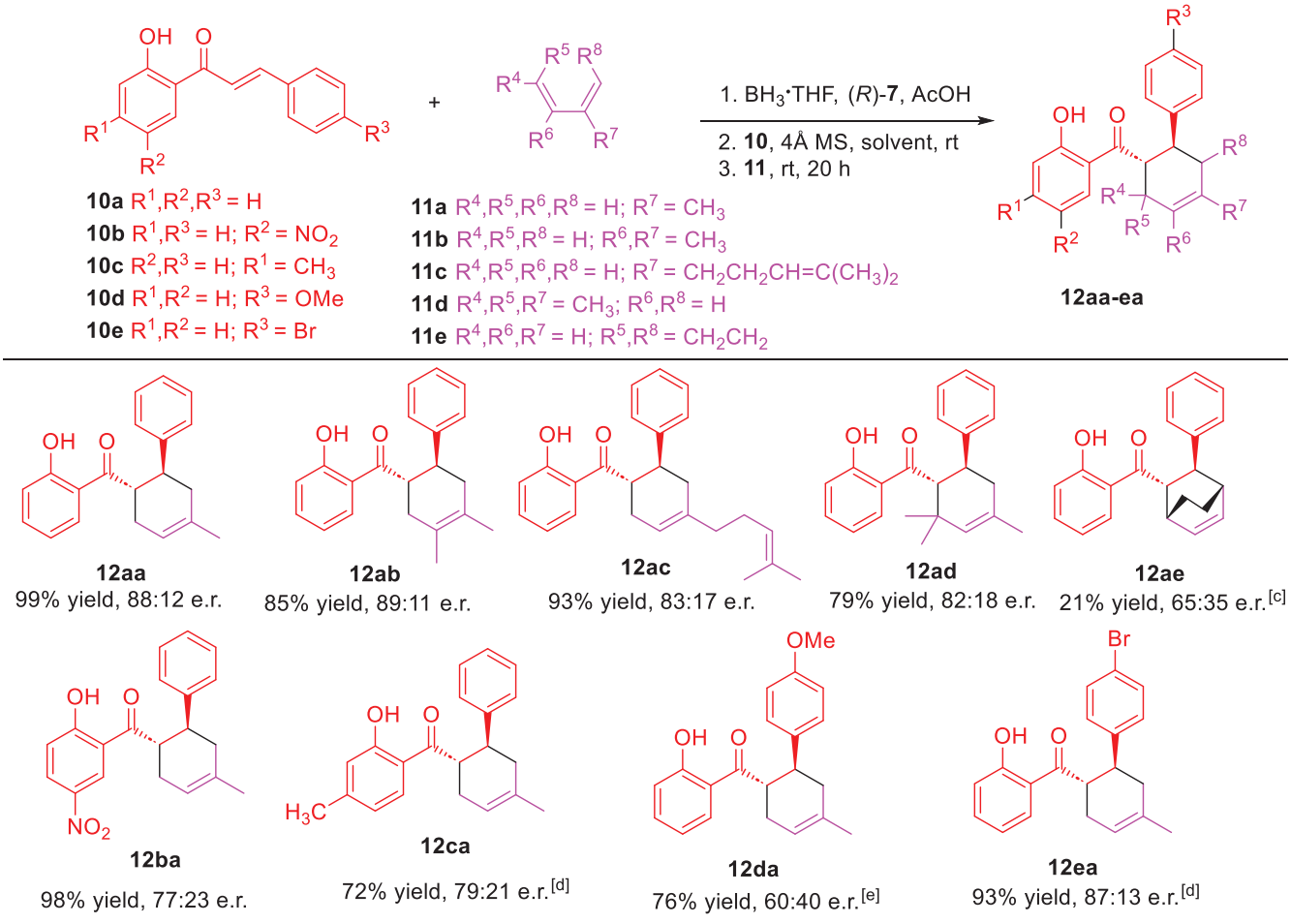


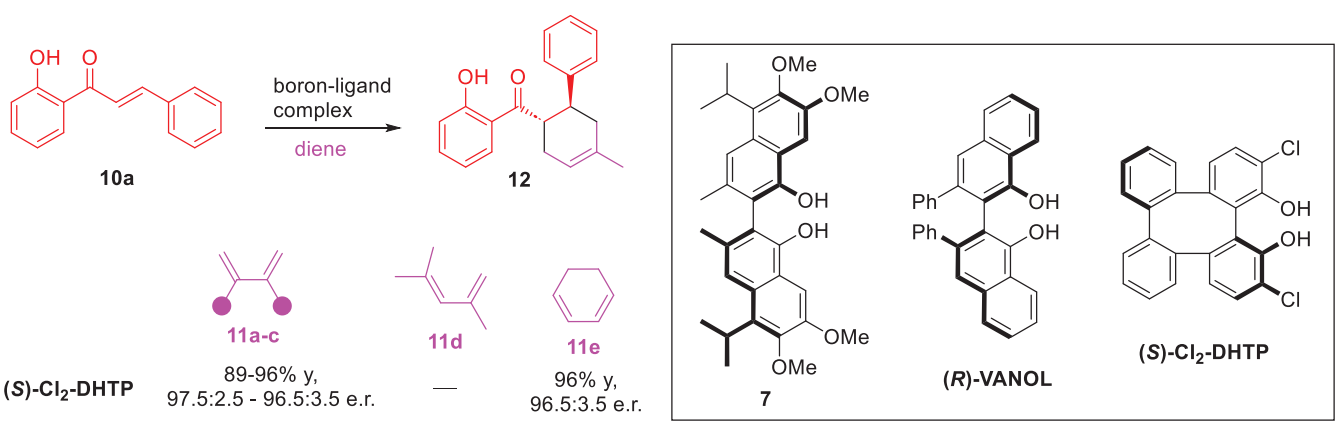
FIGURE 2 | Tentative model of the transition state.

11a–c proceeded at comparable rates as for isoprene, leading to the previously reported cycloadducts **12aa–ac** in high yields and good enantioselectivities (in the range 89:11–83:17). We observed that, in the enantioselective Diels–Alder reaction with 2'-hydroxychalcones, the impact of double substitution at a terminal carbon of the conjugated diene has not yet been investigated. Interestingly, the reaction of **10a** with the more hindered diene **11d** caused only a slight decrease in the yield and an e.r. value that was comparable to the other dienes. Cyclic diene **11e** led to a very long reaction time and poor conversion. The resulting product **12ae** was achieved exclusively as the *endo* isomer, although with disappointing enantiopurity. The scarce reactivity could be ascribed to the sterically demanding bridged bicyclic transition state involved, and the long reaction time may have led to substantial racemization of the chiral ligand. The next step was the investigation of the effect of the substituents in the dienophile. Substitution of the aryl ring attached to the carbonyl with both electron-withdrawing and electron-releasing groups resulted in a very small decrease in the enantiomeric ratios (products **12ba** and **12ca**). A slight extension of the reaction time was required for the methyl-substituted substrate **10c**, which also afforded lower conversion. Conversely, introduction of an electron-releasing group on the *β*-aryl ring affected the reactivity to a greater extent, requiring longer reaction time, and lowering both the conversion and the enantioselectivity (product **12da**). Replacement of the OMe group with a Br improved the performance of the substrate, in terms of reaction time, yield, and enantioselectivity (**12ea**). All the parameters with this substrate proved to be in line with the best entries.

A comparison of the efficiency of ligand **7** with the results previously reported for VANOL and Cl_2-DHTP in the Diels-



SCHEME 2 | Substrate scope with different 2'-hydroxychalcones and dienes; (a) Reaction conditions as reported in note [a] of Table 1, except where otherwise noted. (b) Enantiomeric ratios were measured by chiral HPLC analysis. (c) 168 h reaction time. (d) 48 h reaction time. (e) 120 h reaction time.



SCHEME 3 | Diels-Alder reaction of 2'-hydroxychalcone **10a** with dienes: comparison of **7** with previously reported axially chiral ligands [20, 23].

Alder reaction of **10a** with 2-monosubstituted and 2-disubstituted dienes **11a–c**, is provided in Scheme 3 [20, 23]. Our gossypol-derived ligand furnished comparable yields and significantly lower, though still good, levels of enantioselectivity. We also recorded an unprecedented and noteworthy reaction with 1,1,3-trisubstituted diene **11d**, which gave similar results. On the other hand, in comparison to the above-mentioned ligands, the results achieved with cyclic diene **11e** were disappointing both for yield and enantiomeric ratio. However, beyond the specific application we presented, the major accomplishment of this work was to have laid the foundation for designing and developing new chiral ligands and catalysts derived from the gossypol scaffold.

3 | Conclusion

In conclusion, in this contribution, we presented the first application of an enantiopure gossypol-derived ligand in asymmetric synthesis. Although past synthetic modifications of gossypol have been carried out using racemic starting material, we have demonstrated that enantiopure derivatives are accessible if reaction conditions are carefully controlled. Specifically, the selectively protected chiral diol **7** has been prepared in five steps from (–)-(*R*)-gossypol in 47% total yield. The synthetic procedure is advantageous both in terms of efficiency and sustainability, considering that the well-established synthetic analogue VANOL, widely employed in catalysis, is traditionally prepared in five steps and 48% total yield, based on a chromium carbene complex intermediate in the early stages, which is obtained employing the highly toxic and probable carcinogen $Cr(CO)_6$ [30]. The potential of this chiral derivative has been used for promoting an enantioselective benchmark process, namely the enantioselective Diels–Alder cycloaddition of 2'-hydroxychalcones to dienes, achieving generally high yields and moderate levels of enantioselectivity. The lower efficiency of this gossypol ligand compared to the structurally similar VANOL could be tentatively ascribed to a decreased configurational stability around the chiral axis, due to the smaller steric hindrance of 3,3'-Me groups in comparison to 3,3'-Ph. The present contribution clearly demonstrates that gossypol is a promising and readily available scaffold for the design and application of novel biomass-derived organocatalysts and ligands. Future work will be devoted to structural modification of this scaffold, especially directed to improve its configurational stability (Supporting Information).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

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The following files are available free of charge.

Experimental procedures, compound characterization

data, and NMR spectra for all compounds (PDF).

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