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Tuning of α-Silyl Carbocation Reactivity into Enone Transposition: Application to the Synthesis of Peribysin D, *E*-Volkendousin, and *E*-Guggulsterone

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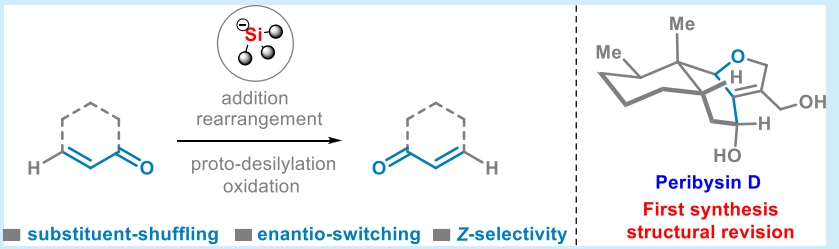

ABSTRACT: A reliable method for enone transposition has been developed with the help of silyl group masking. Enantio-switching, substituent shuffling, and *Z*-selectivity are the highlights of the method. The developed method was applied for the first total synthesis of peribysin D along with its structural revision. Formal synthesis of *E*-guggulsterone and *E*-volkendousin was also claimed using a short sequence.

The multidirectional reactivity of the enone moiety makes it an attractive functional group in organic synthesis. All three carbon atoms and the oxygen present in the enone system can be manipulated as per the requirement.[1] Transposition of both the carbonyl group and the olefinic bond further enhances the synthetic utility of the enone synthons and thereby offers a high degree of opportunity in organic synthesis. On the contrary, dealing with these types of compounds becomes difficult.[2] Over the past few decades, enones served as vital intermediates in natural product synthesis.[3] One such type of enone rearrangement was attempted by our group during the synthesis of peribysin family natural products.[4] We wanted to achieve an enone transposition reaction from compound **1** to compound **2** (Figure 1A). However, after screening a few conditions, we settled for a six-step sequence with poor yields. The most studied transformation of this kind is the oxidative rearrangement of *ter*-alcohols to enones using Cr^{VI}-based reagents,[5] but the main drawback of this transformation is that the group added to enone carbonyl is not detachable after rearrangement (Figure 1B). Apart from this, there are a few known methods in the literature; each has certain advantages and limitations.[6] One such type of reaction is Wharton reaction, wherein α,β-epoxy ketone is rearranged to the corresponding allylic alcohol using hydrazine.[7] With this background, we decided to develop a transposition method using a silicon-based masking group (Figure 1C) because a silyl lithium reagent can be easily prepared and added to the carbonyl group, wherein an α-silyl tertiary carbocation can be generated in situ. If a double bond is present in conjugation, then it can undergo rearrangement because of the favored tertiary to secondary carbocation rearrangement and silicon α-effect (Figure 1D).[8]

In addition, the silyl groups are reactive toward various nucleophiles such as hydroxides, alkoxides, and fluorides, which make them easy to detach from the substrate. A similar kind of rearrangement of α-silyl alcohols was reported by Honda and co-workers during the synthesis of allyl ethers.[9] A few more useful rearrangements of α-silyl alcohols were reported by Sakaguchi et al., and a Cr(VI)-mediated oxidative rearrangement was reported by Song et al.[10] With this background, we first prepared the $PhMe_2SiLi$ reagent as described by Fleming et al. and added it to a model substrate 4,4-dimethyl-2-cyclohexen-1-one (**3a**).[11] The reaction gave an 84% yield of the desired 1,2-addition product **3b** (Scheme 1). The next task was to perform the rearrangement of compound **3b** to obtain compound **3c**. Here, we used acetonitrile and H_2O as a mixture of solvents (in a 1:1 ratio), and a few drops of TFA was added. The rearranged product was observed in 55% yield. Further tweaking the ratio of solvents (9:1 CH_3CN/H_2O) gave a 95% yield of the rearranged alcohol (Scheme 1). In addition, for proto-desilylation of compound

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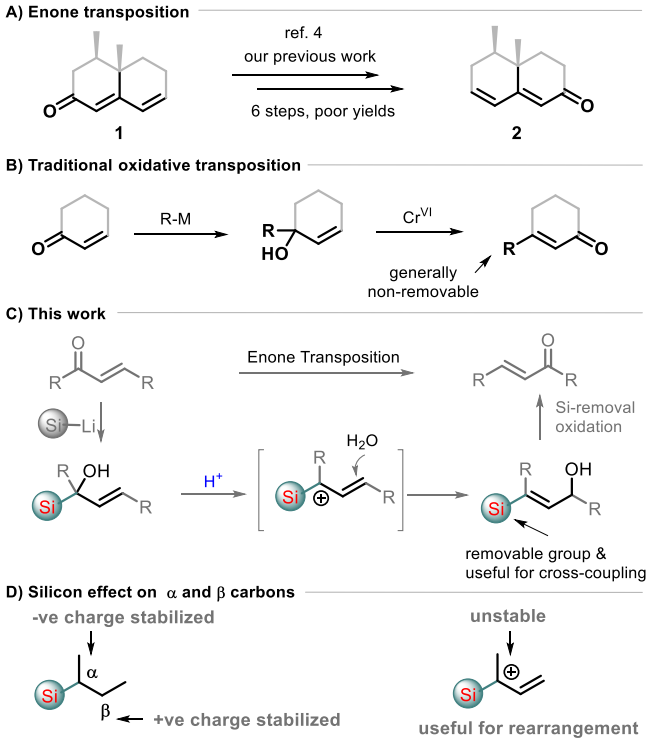
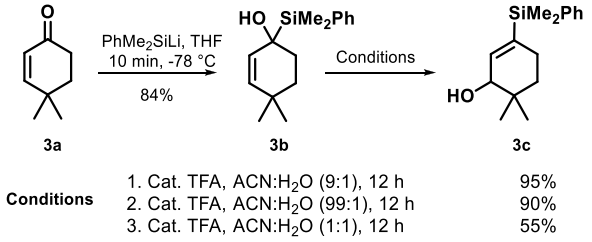


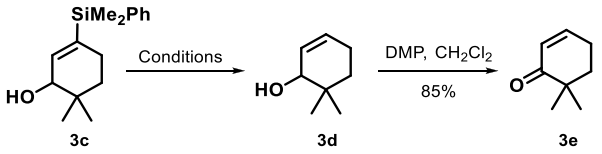
Figure 1. (A) Our previous work. (B) Traditional oxidative transposition. (C) This work. (D) Silicon α and β effects.

Scheme 1. Optimization of Silyl Addition and Transposition Reaction



3c to obtain compound **3d** (Scheme 2), reaction with TFA, BF_3·MeOH, or BF_3·AcOH did not give the desired product **3d**.

Scheme 2. Optimization of Proto-desilylation



Instead, the starting material was recovered completely (Table 1, entries 1−3). Reaction with HI resulted in partial decomposition of the starting material. In addition, fluoride- and alkoxide-based reagents were unsuccessful in the desilylation reaction (Table 1, conditions 5−7).[12] The use of HMPA along with TBAF as reported by Muraoka et al. gave an ∼20% yield of the desired product.[13] Capperucci et al. have reported a condition under which TBAF and KOH were used in combination for the proto-desilylation of the triphenyl silyl group.[14] Under the same condition, we observed successful removal of the phenyl dimethyl silyl group, which furnished product **3d** in 64% yield when refluxed in THF for 16 h. The

Table 1. Optimization of Proto-desilylation

	reagent[a]	solvent	temp	time (h)	observation
1	TFA	CH_2Cl_2	reflux	12	NR
2	BF_3·MeOH	CH_2Cl_2	0 °C to rt	10	NR
3	BF_3·AcOH	AcOH	rt	10	NR
4	HI	THF/H_2O	rt to 70 °C	4	decomposed
5	TBAF	THF	reflux	5	NR
6	KF	DMF	80 °C	2	NR
7	NaOMe	MeOH	reflux	6	NR
8	TBAF/HMPA	DMSO	80 °C	2	∼20%
9	TBAF, KOH	THF	reflux	16	64%[b]
10	TBAF, KOH	THF	85 °C, MW	0.5	98%[b]

[a]Reaction performed on a 100 mg scale. NR indicates no reaction, and MW indicates microwave irradiation. [b]Isolated yield.

reaction time was significantly decreased when the reaction was carried out in a microwave at 85 °C with an excellent yield of 98% (Table 1, entry 10). The mechanism of proto-desilylation is the replacement of the phenyl ring on silicon with the hydroxide to give silanol.[15] In addition, the silanol intermediate on reaction with fluoride ions gives the desilylated alcohol **3d**.

Finally, the allylic alcohol was oxidized using DMP to give rearranged enone **3e** in 85% yield. The whole sequence can be performed with only two purification steps after rearrangement and after a final oxidation step with an overall yield of 66%. It is interesting to note that, when the reaction was started with 4,4-dimethyl cyclohexenone, the end product is 6,6-dimethyl cyclohexenone (an example of substituent shuffling). After having the optimized reaction sequence in hand, we first screened substituted cyclohexenones. The reaction of 2,6-cyclohexenone of 2,4-dimethyl cyclohexenone. Similarly, 4-*tert*-butyl cyclohexenone was transformed into 6-*tert*-butyl cyclohexenone in 53% overall yield. Chiral substrate **5a** gave compound **5e** in 28% overall yield. Here it is clear from these four examples that when the substituent is present at positions 4 and 6 on cyclohexenones, in the end, the positions of these substituents are exchanged. Next, we prepared two bicyclic enones **7a** and **8a**. Enone **7a** was derived from (+)-3-carene in two steps that under the optimized conditions gave two different enones, **7e** and **7h**. The structure of *E*-enone **7e** was confirmed by single-crystal X-ray diffraction during the alcohol stage. These two enones and their intermediates can be utilized as building blocks for natural product synthesis. Bicyclic enone **8a** underwent smooth rearrangement to give enone **8e** in 39% overall yield. The structure of intermediate **8d** of enone **8e** was confirmed via single-crystal X-ray diffraction, where the equatorial hydroxyl group was observed after the rearrangement reaction (Scheme 3). In addition, we tested the method on our original target compound (conversion of compound **1** to **2**) but it failed to give the desired product.

Next, we tested the commercially available enone **9a**, which gave a 56% overall yield of **9e**. Here, interestingly, the *Z*-enone was observed as the major product. The selectivity arose during the rearrangement reaction where the bulky silyl group prefers the less sterically crowded side to give alcohol **9c** having *E*-geometry. After deprotection, the geometry remained unchanged to give the *Z*-enone. Hydrocinnamaldehyde-derived enone **10a** furnished the desired rearranged enone **10e** with a 92:8 *Z*:*E* selectivity, whereas the corresponding

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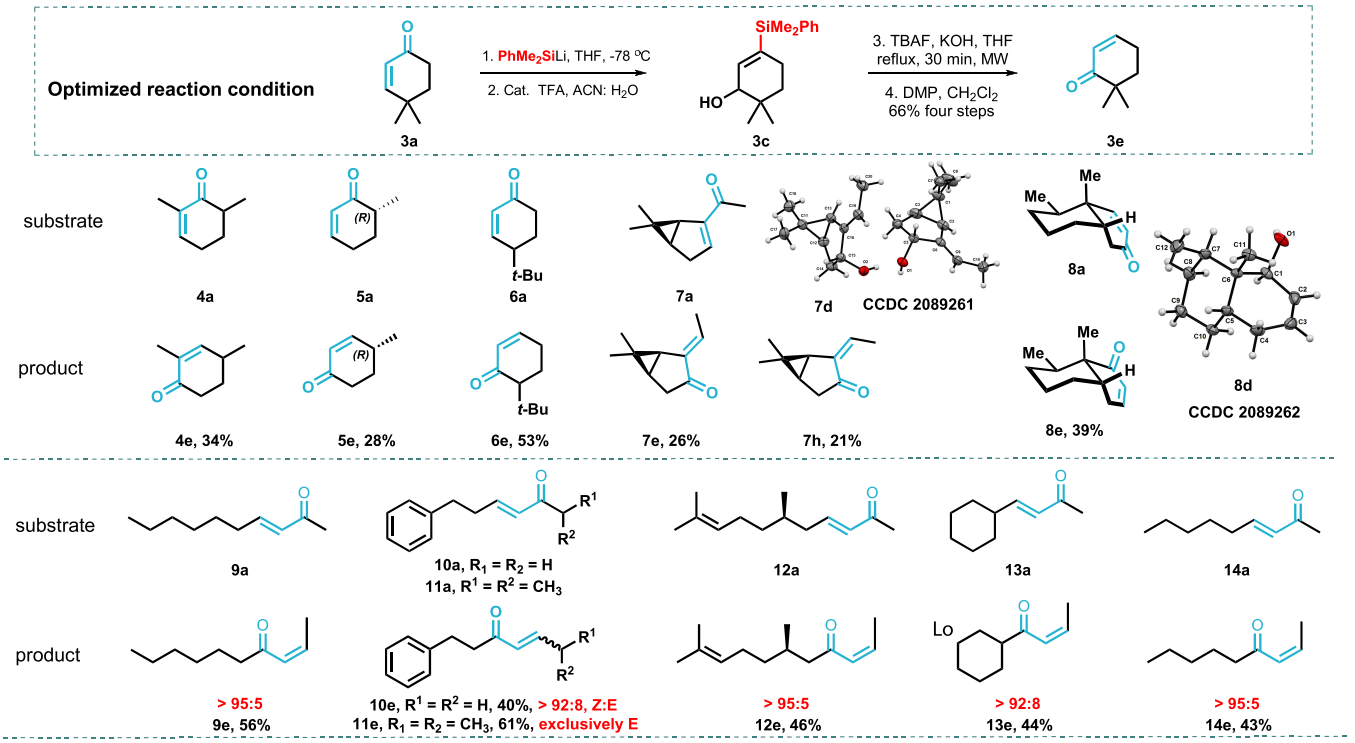
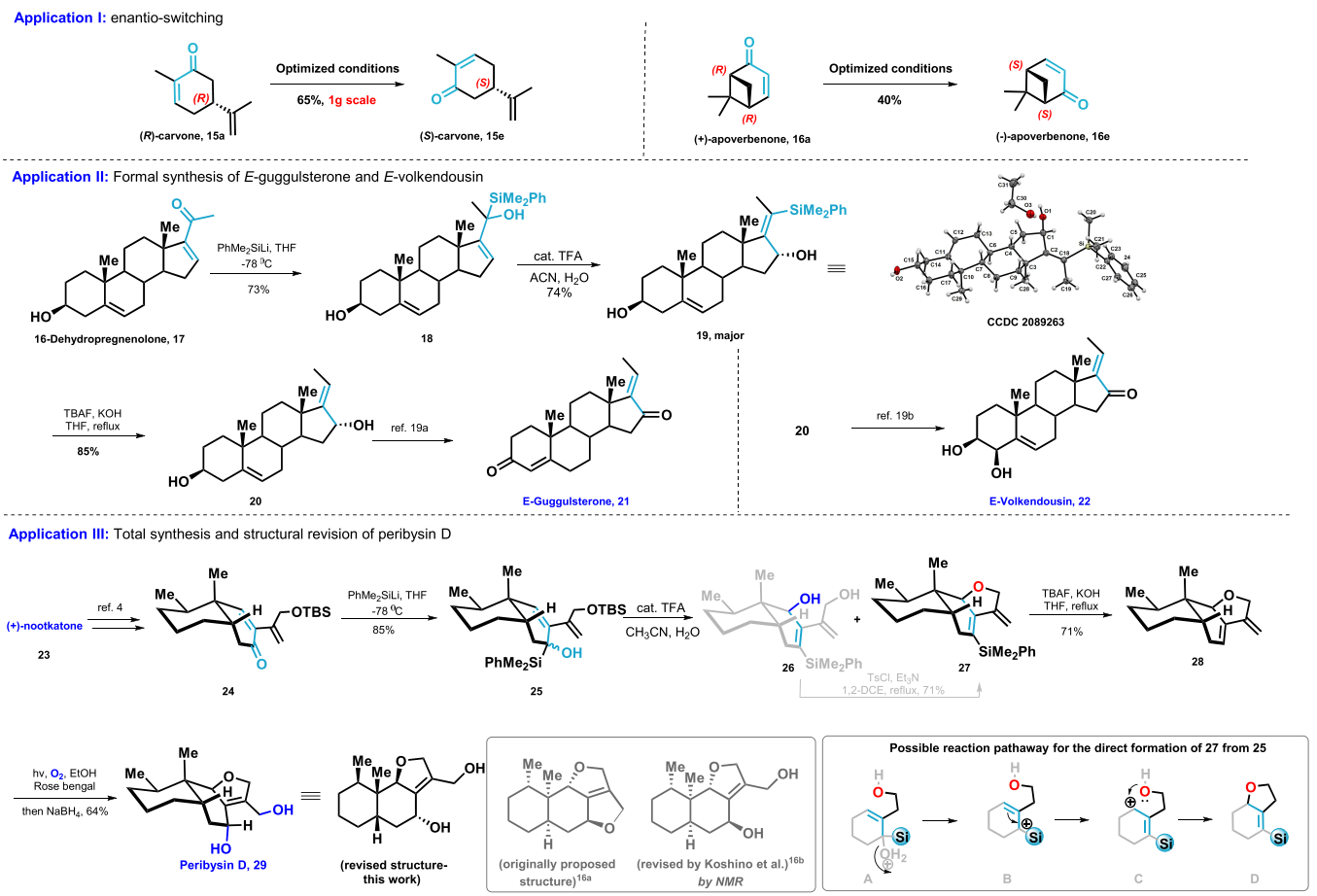
Scheme 3. Substrate Scope of Enone Transposition



Scheme 4. Various Applications of the Developed Method



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isopropyl ketone **11a** exclusively provided *E*-enone **11e**. Here the steric bulk of the isopropyl group was responsible for the exclusive *E*-selectivity. Next, three more enones (**12a−14a**) derived from *R*-citronellal, cyclohexane carboxaldehyde, and hexanal were converted to their corresponding *Z*-enones (**12e−14e**, respectively) in 46%, 44%, and 43% yields, respectively. In the literature, few other metal-based methods are available such as the Rh(I)-catalyzed reaction reported by Zhuo et al. for *Z*-enone synthesis.[16] Also, several other methods of olefin isomerization are available, the majority of which gives *E*-alkenes.[17] Thus, we believe that the current method will be more useful for accessing the *Z*-enones, which are difficult to access by other methods.

During the synthesis of substrates, we have generated a library of functional building blocks having a silicon handle. These vinyl silanes can be used for various purposes in organic synthesis.[12] Furthermore, the silicon-incorporated organic compounds can be used in medicinal chemistry programs because of the unique properties of the silicon-incorporated compounds.[18] Access to the enantiopure starting materials is one of the key factors in the chiral pool synthesis of natural products. Sometimes, it is difficult to access a particular enantiomer for the synthesis because some compounds exist in nature in only one enantiomeric form, or one of the isomers is costly in most of the cases. Here we have demonstrated an exciting application of the developed method for the interconversion of *R*-carvone to *S*-carvone with an overall yield of 65%. Similarly, the enantio-switching of (+)-apoverbenone to (−)-apoverbenone gave a 40% overall yield (Scheme 4). To further expand the scope of the method, we focused on the synthesis of two bioactive steroidal natural products guggulsterone (having mineralocorticoid, androgen, estrogen, etc., receptor antagonist and activities) and volkendousin (having anticancer activity).[19] We treated 16-dehydropregnenolone with $PhMe_2SiLi$, which gave a 90% yield of silyl addition product **18**. Treatment of compound **18** with catalytic TFA in a CH_3CN/H_2O mixture furnished **19** as a major product. The structure of compound **19** was confirmed by single-crystal X-ray diffraction, which helped us to fix the double bond geometry and the newly generated chiral center. Proto-desilylation of compound **19** furnished alcohol **20**. All of the data for compound **20** were in agreement with the reported data. Compound **20** was previously transformed into *E*-guggulsterone and *E*-volkedousin in one step each.[19] Thus, here, we have accomplished the formal synthesis of *E*-guggulsterone and *E*-volkedousin using a short sequence. Recently, we accomplished the synthesis and structural revision of five peribysin family natural products isolated from *Periconia byssoides* OUPS-N133 by Yamada and co-workers.[4,20a] The most potent member from this series is peribysin D having an IC_{50} value of 0.1 μM.

The originally proposed structure (tetracyclic) of peribysin D was revised by Koshino et al. to a tricyclic structure on the basis of the NMR studies.[20b] In addition to the impressive biological activity, the structure of peribysin D was also associated with some ambiguity, which necessitates the total synthesis of the same. In our previous attempts to synthesize peribysin D, we encountered challenges in installing the oxygen functionality at the carbon next to the quaternary methyl center. Here, we envisioned installing the oxygen functionality at the desired position by using the method presented here (Scheme 4, application III). Thus, we synthesized compound **24** by our previously developed protocol.[4] To compound **24** was added $PhMe_2SiLi$ to give addition product **25**, which was then subjected to catalytic TFA in CH_3CN/H_2O, which gave the desired product **26**. In addition to diol **26**, a nonpolar compound observed in the same reaction mixture after characterization was found to be compound **27**. In addition, the structure of compound **27** was confirmed by conversion of **26** to **27** using TsCl and Et_3N. Mechanistically, the TBS group in compound **25** first is deprotected to give free alcohol. Protonation of *ter*-alcohol followed by elimination of a H_2O molecule generates α-silyl carbocation **B**, which rearranges to give intermediate **C** (Scheme 4). Subsequent trapping of the carbocation by free alcohol offers cyclized product **D**. Here, H_2O and free alcohol compete as nucleophiles to provide two different products, **26** and **27**. Compound **27** after desilylation using TBAF and KOH furnished diene **28** in 80% yield. Finally, diene **28** upon reaction with molecular oxygen in the presence of Rose Bengal in EtOH resulted in cyclic peroxide, which was reduced in situ with $NaBH_4$ to give peribysin D.[21] All of the spectral data, including ^1H and ^{13}C NMR data, were in agreement with the literature report.[17] It was clear from our previous work that the structure of peribysin D may need to be stereochemically revised (see ref 4). Thus, CD spectra were recorded, which matched those reported by Yamada et al.[20,22] On the basis of all of these observations, spectral data, CD spectra, and our previous work, the structure of peribysin D was revised.

In summary, we have developed a method for enone transposition having potentially high synthetic utility. A silyl-based masking group was chosen for in situ generation and rearrangement of α-silyl carbocation species. The developed method was successfully tested with a variety of substrates with exciting outcomes such as substituent shuffling, enantio-switching, and *Z*-selectivity. A library of vinyl silanes having potentially high synthetic utility were generated during the course of making the substrates. Using the developed method, the first synthesis of peribysin D was achieved along with its structural revision. Additionally, formal synthesis of two bioactive natural products, *E*-guggulsterone and *E*-volkendousin, was accomplished in a short sequence. Further applications of the method are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02173.

General and experimental procedures, compound characterization data, single-crystal X-ray data of compounds **7d**, **8d**, and **19** and NMR spectra of selected compounds (PDF)

Accession Codes

CCDC 2089261−2089263 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(22) The specific optical rotation for synthetic peribysin D was found to be −1.8 in EtOH (the reported optical rotation for natural peribysin D is +4.6 in EtOH). Because the magnitude of the rotation was very small and close to zero, it was difficult to comment on the structural revision of peribysin D. Thus, CD spectra was recorded to confirm the stereochemistry.

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