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Palladium and (or) ruthenium catalyzed synthesis of natural products

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Abstract : We describe successively acryloxypalladation as a key step in the synthesis of ring fused α-methylene-γ-butyrolactone, palladium induced cyclisation of vinyl-bicyclo[2,2,2]octene to form the tricyclo[4,3,1,$0^{3,7}$] skeleton of isocyanopupukeanane, and palladium as well as ruthenium catalyzed degradation reactions of the sclareol side chain in order to prepare ambergris derivatives such as Ambrox® and ambraketal.

It is now for several years that we have been interested in various metal catalyzed reactions such as acetoxypalladation (ref.1), acryloxypalladation (ref.2) or oxidations (ref.3). An advantage of these reactions is that they are often highly selective, and can also be run practically at room temperature. Natural products are the usual target molecules to test such metal catalyzed reactions which have to be included as a key step in new synthetic schemes in order to demonstrate their efficiency and versatility. We describe examples concerning three types of compound : α-methylene-γ-butyrolactones known for their biological activity (ref.4) ; isocyanopupukeananes which are members of an interesting class of marine compounds (ref.5), and ambergris derivatives which play an important role in fragrance industry (ref.6). We will discuss the advantages of the synthetic schemes proposed, without hiding their drawbacks.

We had reported earlier a new acryloxypalladation reaction of alkenes such as **1.** This reaction (Fig. 1) yields α-methylene-γ-butyrolactone in one step (ref.7), provided an intermediate π-allyl complex does not form. This reaction proceeds by the intermediacy of the double bond acryloxypalladation which yields π complex **2**, and insertion product **3** ; further insertion of the acrylic double bond into the carbon palladium bond thus formed, followed by ß-elimination yields the α-methylenic group of lactone **5b**. Unfortunately, this pathway competes with the formation of an intermediate π-allyl complex **6** which undergoes the nucleophilic attack of the acrylate to give rise to allylic acrylates **7**. As a consequence, acryloxypalladation only leads unequivocally to α-methylene-γ-butyrolactones with alkenes such as norbornene where the intermediate π-allyl complex similar to **6** cannot form. With cycloalkenes instead, the π-allyl complex **6** forms readily and yields allylic acrylates **7**, and not the ring fused α-methylene-γ-butyrolactones **5b** which are featured by numerous natural products possessing a wide range of biological activities (ref.4). This difficulty could be got round by preparing α-substituted acrylates **9** by known procedures (ref.7).

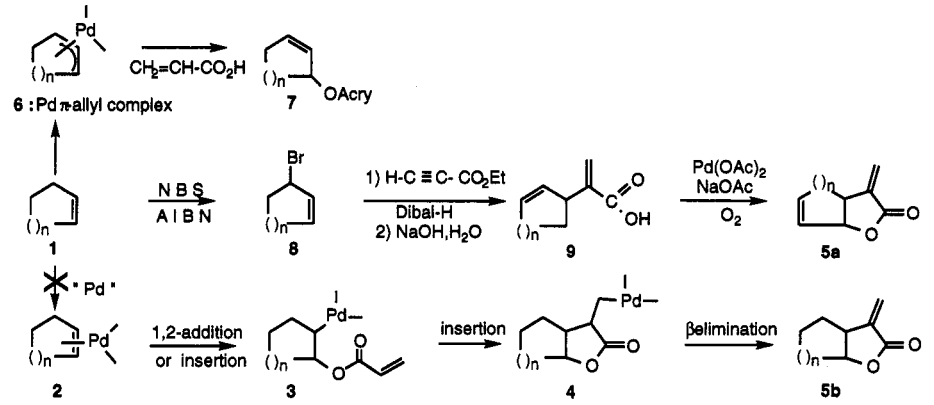

Fig.1 Formation of α-methylene-γ-butyrolactones **5** and allylic acrylates **7** by acryloxypalladation of cycloalkenes

Catalytic quantities of $Pd(OAc)_2$ readily (80% yield) induce a cyclization of **9** into **5a**, independent of the mechanism, which involves either a 1,2-addition, or an intramolecular nucleophilic attack of the carboxylate on an intermediate π-allyl complex. We are presently studying the intimate mechanism of this reaction and its extension to acrylates α-substituted by different cycloalkenes (bicyclo[4,4,0]decenes or bicyclo[5,4,0] undecenes) in order to have an access to the eudesmanolide or guainolide series (ref.4).

The second topic is related to the synthesis of 2-isocyanopupukeanane **11** (Fig. 2) which has been synthetized as 9-isocyanopupukeanane **12** using common intermediate **10** (ref.8). This molecule features a tricyclo[4,3,1,$0^{3,7}$] skeleton which can also be considered as a bicyclo[2,2,2]octane skeleton bridged with an ethano bridge. The latter formed by carbons 4 and 5, is substituted by an *endo* isopropyl group which sticks inside the "cavity" formed by the tricyclic system. Acetoxypalladation of **13a** readily gives rise (ref.1,9) to **14a** which features a tricyclic skeleton substituted by an acetoxy and a chlorine group in the 5- and 2- positions, respectively. This intermediate could possibly be used, as an intermediate for the synthesis of 2-isocyanopupukeanane **11**.

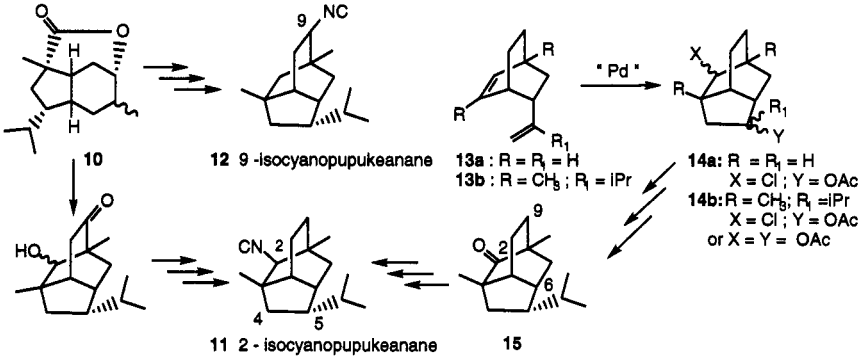

Fig. 2 General approach to 2- and 9-isocyanopupukeanane.

Unfortunately a more thorough study of the chloroacetoxypalladation cyclisation of **13a** showed that this reaction (ref.9) was neither chemo- nor stereoselective, as initially thought. As a consequence, it was not possible to use the cyclisation of **13b** into **14b** to prepare **15** and **11**. We therefore turned our attention to a palladium induced cyclisation of trimethylsilyl enol ethers (ref.10). The latter had the advantage to give the possibility to introduce properly the keto group on the tricyclic skeleton, which could then be transformed into the isonitrile, using a standard procedure. The use of a cycloaddition to synthesize the starting ester **17**, which looked straitghforward, turned out to be impossible because of the lack of selectivity.

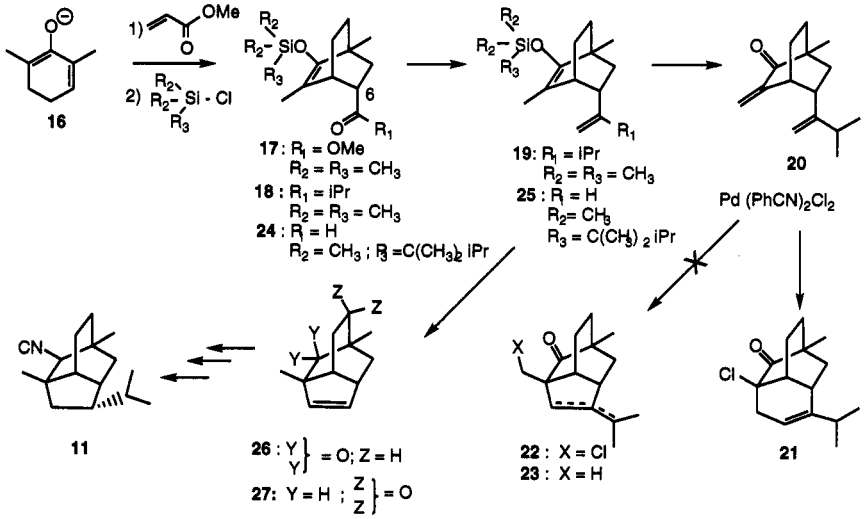

Fig. 3 Palladium induced cyclization of **25** into the tricyclic ketone **26** precursor of 2-isocyanopupukeanane

This problem could be solved by reacting enolate **16** with methyl acrylate in a Michael reaction (Fig.3), which nevertheless competes with a [2+2+2] MIMIRC annulation (ref.11). The transformation of ester

17 into the isopropyl substituted double bond of **19** via isopropyl ketone **18** is not easy. This is most likely due to epimerisation which can occur on carbon-6 in ester **17**, and to the low or moderate yields of Wittig type reactions used to transform **18** into **19**. Furthermore, when the latter product was reacted with palladium acetate in acetonitrile, the expected cyclization (ref.10b) into **23** did not occur, and dienone **20** is formed instead (ref.10a), probably via a β-elimination reaction. The reason for this failure probably lies in the difficulty of insertion of the sterically hindered isopropyl substituted double bond of **19** into the appropriate carbon-palladium bond of the oxo π-σ,palladium complex formed from the trimethylsilyl enol ether ; this cyclization would also lead to an increase of steric strain in the tricyclo[4,3,1,$0^{3,7}$] skeleton of **23**. Dienone **20** was submitted to a palladium induced cyclization (ref.10b) with equimolecular amounts of $Pd(PhCN)_2Cl_2$, to form **22**, which could then have been transformed into **23** and 2-isocyanopupukeanane **11**. Unfortunately this cyclization was not observed, but compound **21** featuring a tricyclo[5,3,1,$0^{3,8}$] skeleton was formed instead, because the chloropalladation of the *exo*-methylenic double bond of **20** occurs with a Markovnikov orientation.

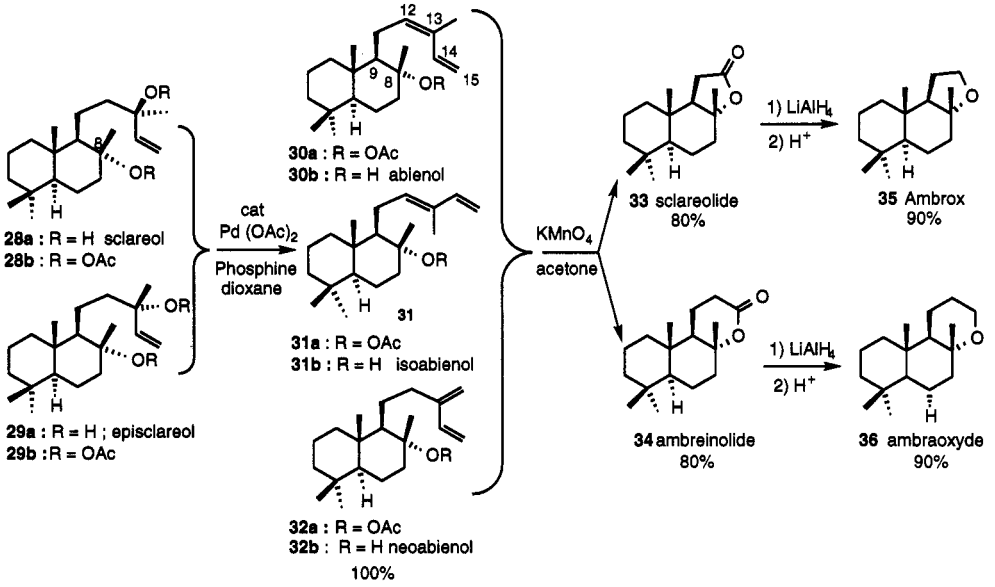

Fig. 4 Synthesis of Ambrox® **35** and Ambraoxyde **36** from Sclareol **28a** via the mixture of abienols **30b**, **31b** and **32b**.

To overcome these difficulties, compound **25**, with the unsubstituted double bond, was prepared from the corresponding aldehyde **24** where the silyl enol ether features the more resistant thexyl-dimethyl protecting group (ref.12). Now the palladium assisted cyclization of **25** yielded the unsaturated ketone **26.** As the isopropyl group had been introduced with the right configuration on the double bond of **27**, and the keto group further transformed into isonitrile (ref.8) to yield 9-isocyanopupukeanane **12,** the obtention of **26** can be considered as a formal synthesis (ref.8c,8d) of 2-isocyanopupukeanane (ref.11b). This example shows that the catalytic acetoxypalladation, which occurs readily, with good yields on unsubstituted vinylbicyclo[2,2,2]octene **13a**, can neither be used on **13b** because of its lack of selectivity, nor extrapolated to a functionalized starting material such as **19**, because of its lack of reactivity.

The third topic concerns ambergris - a metabolite of the blue sperm whale - derivatives. These compounds have been at the origin of intensive research as a consequence of the dwindling world supply of ambergris, and of their interest in perfume and fragrance industry (ref.6). Although several derivatives can be considered as target molecules featuring an interesting odour, Ambrox®* **35** (Fig. 4 and 5) and ambraketal **44** (Fig. 6) are the most attractive. Ambrox® and related derivatives have been prepared by total synthesis (ref.13). But semisyntheses using terpenes such as manool (ref.14) or sclareol (ref.15) as starting material present particular interest in this domain, as products thus obtained can still be considered as "natural fragrances". Sclareol **28a**** presents attractive structural features, especially the right configuration of the 8-hydroxyl group, which is the same as the one found in Ambrox® **35**. This is decisive, as it has been shown that there exists a close relationship (ref.16) between the ambergris

* : Ambrox® is a registred trade mark of the Firmenich Company, Geneva.
** : Commercial sclareol generally contains small amounts of episclareol **29a**.

fragrance intensity and the various possible configurations of the tetrahydrofuran ring function in **35**, as well as more generally speaking, with the structure of ambergris derivatives.

Although at first glance, the sclareol side chain degradation looks rather straightforward, this process turns out to be rather ticklish (ref.15) because of the reactivity of the two tertiary alcohols of sclareol, one of which is also allylic.

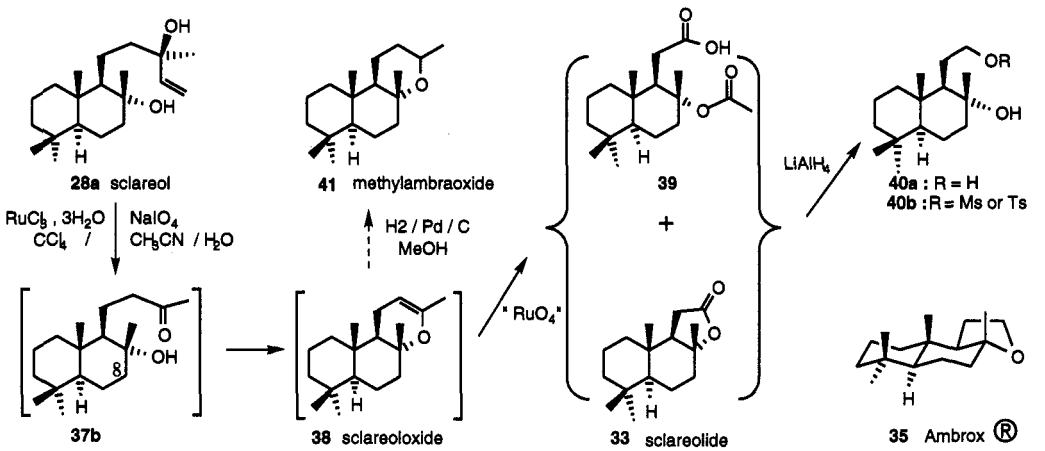

Fig 5 Synthesis of Ambrox® **35** by oxidative degradation of the sclareol **28a** side chain, with RuO_4 generated *in situ*

Our first approach involved the unequivocal preparation of the three abienol acetates **30a**, **31a**, **32a** using a selective and quantitative elimination, with a palladium catalyzed reaction carried out on sclareol acetate **28b**. Unfortunately neither these three abienol acetates, nor the corresponding abienols themselves, can easily be separated. Consequently, the latter mixture was oxidized with permanganate into sclareolide **33** and ambreinolide **34**, which could be easily separared, and transformed into Ambrox® **35** and ambraoxyde **36** (ref.17), respectively.

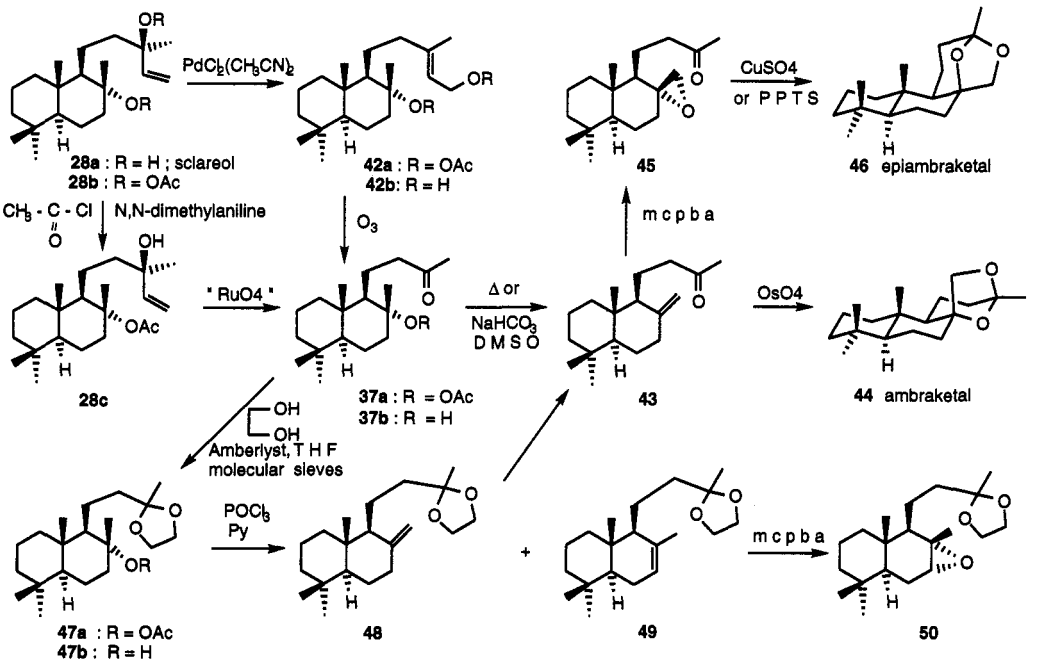

Fig 6 Different strategies for the synthesis of ambraketal **44** and epiambraketal **46** from sclareol **26a**

However a ruthenium catalyzed oxidative degradation (ref.18) of the sclareol **28a** side chain (Fig. 5), is much more efficient, as it allows the obtention of the mixture of the acid acetate **39** and sclareolide **33** (ref.19) without isolating the intermediate keto alcohol **37b** ; the latter cannot be isolated as it readily

cyclizes into sclareoloxide **38**, which immediately undergoes oxidative cleavage to **33** and **39**. This mixture is reduced by $LiAlH_4$ to diol **40a**, and transformed into the corresponding monomesylate **40b** (or tosylate) which is further cyclized into Ambrox® **35** in presence of sodium hydride (or pyridine). To our knowledge, this is by far, the fastest and most efficient way to transform sclareol into Ambrox®, reported in literature.

A similar problem of side chain degradation arises in the preparation of ambraketal **44** or epiambraketal **46** (Fig. 6), but it is now reduced to the selective transformation of the tertiary alcohol on carbon-8, into an exocyclic methylenic group in key intermediate **43**. We have reached this goal by using two different strategies. The first one (ref.17) involves a palladium catalyzed isomerisation of the side chain double bond of sclareyl acetate **28b** into isosclareyl acetate **42a**. Ozonolysis of the double bond of the latter, yields keto acetate **37a**.

Pyrolysis of this keto acetate, or much better, elimination with sodium bicarbonate in DMSO yields key intermediate **43**. The transformation of **43** into ambraketal **44** can be easily achieved by catalytic osmylation, whereas epiambraketal **46** is obtained by the intermediacy of epoxyde **45**, which is reacted either with copper sulfate or pyridinium paratoluenesulfonate (PPTS). It is interesting to note that if the ozonolysis is carried out on isosclareol itself **42b**, sclareoloxide **38** (Fig. 5) can now be isolated in excellent yield, and transformed into Ambrox **35** by furher ozonolysis into **39**, reduction into **40a** and cyclization via **40b**. Sclareoloxide can also be hydrogenated in methylambraoxyde **41** (Fig. 5).

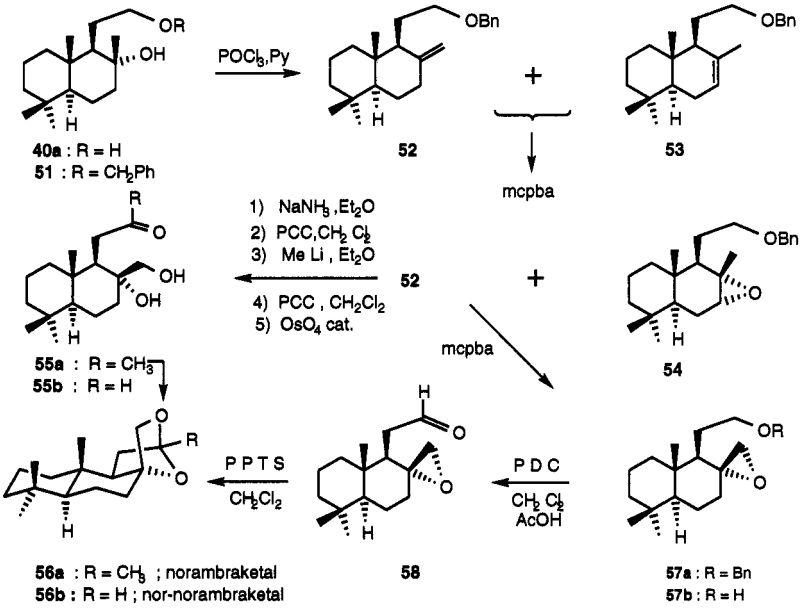

Fig. 7 Synthesis of norambraketal **56a** and nor-norambraketal **56b** from intermediate **40a** prepared in two steps from sclareol

There is another, but somewhat more lengthy pathway from **37a** to key intermediate **43** (Fig. 6) by protection of the keto group as in the ethylene ketal **47a** (ref.20). Elimination of the corresponding alcohol **47b** yields a mixture of **48** and **49**. The latter cannot be easily separated by chromatography, but the trisubstituted double bond of **49** undergoes selective epoxidation into **50** with *meta*-chloroperbenzoic acid, whereas **48** remains unchanged. Accordingly, compound **48** can now be easily separated from **50**, and the protection of the keto group can be removed to yield **43**.

The second strategy (ref.21) used to degrade the side chain of sclareol in order to obtain epiambraketal **46** and ambraketal **44** is by far the most efficient. It relies on the selective acetylation of the C-8 alcohol of sclareol into **28c**, which could be achieved with acetyl chloride in presence of N,N-dimethylaniline.Because of the presence of the acetate on the 8-carbon, the RuO_4 catalyzed oxidation now yields **37a** instead of **38** as in the sequence reported in Figure 5. This is because intermediate keto acetate **37a** cannot cyclise into sclareoloxide **38**, whereas alcohol **37b** does so readily. The transformation of **37a** into **44** and **46** has been reported above.

Norambraketal **56a** (ref.22), and nor-norambraketal **56b** (ref.23) have been synthetized using similar strategies (Fig. 7). Diol **40a** is chemio selectively benzylated into **51** which was transformed into the

mixture of alkenes **52** and **53** by treatment with $POCl_3$ in pyridine. Epoxidation of this mixture by *meta*-chloroperbenzoic acid gave epoxide **54**, but left **52** unchanged. The latter is then transformed into **55a** by the sequence of reactions reported in Figure 7. Contrary to what had been observed for the transformation of **43** into **44** (Fig. 6) the glycol **55a** can now be isolated, and requires the action of pyridinumparatoluenesulfonate (PPTS) to cyclize into norambraketal **56a**. As the glycol **55b** derived from γ-homofarnesylic aldehyde could not be prepared by catalytic osmylation, intermediate **52** was further epoxidized into **57a**. After deprotection and oxidation of the primary alcool **57b**, epoxy aldehyde **58** was obtained and cyclised into nor-norambraketal **56b** (Fig. 7).

We can conclude that in the synthetic scheme of 2-isocyanopupukeanane, the use of a transition metal catalyzed cyclization as a key step in the synthetic scheme, was not as satisfactory as expected. On the contrary the use of such reactions in the synthesis of α-methylene-γ-butyrolactones is quite promising, and most efficient in the synthesis of ambergris fragrances.

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