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Organometallic chemistry in industrial vitamin A and vitamin E synthesis

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Abstract : This paper illustrates the concepts of short synthesis, high selectivity and reduce effluent for industrial processes in the field of vitamin A and E synthesis. We have selected four reactions to demonstrate how organometallic chemistry can improve industrial synthesis : isomerisation of methylbutynol 1 to prenal 2 ; Carbon - Carbon coupling and new access to geranylacetone ; Hydrogenation of α β-unsaturated aldehydes ; Oxidation and access to trimethylhydroquinone.

INTRODUCTION

The vitamin A and E are two of the main vitamins of industrial importance and the 3 major industrial producers are Hoffman-la-Roche, BASF. AG and Rhône-Poulenc Animal Nutrition.
The world market for vitamin A is around 3000 T/year and for vitamin E, around 10 000 T/year at a price of 40-50 $/kg for vitamin A acetate and 25-30 $/kg for Tocopherylacetate (ref. 2.)

For vitamin A 3, the chemical challenge in the synthesis is to solve a minimun of three problems : cyclisation, stereoselectivity (all trans > 95 % and 16 possibles stereoisomers) and stability due to the polyene system.

The syntheses used by the three manufacturers differ, firstly in the basic chemicals used to synthesize the key intermediate β-ionone 4, secondly in the type of intermediates used for chain extension and finally in the method of linkage employed to give the C_{20} final product :

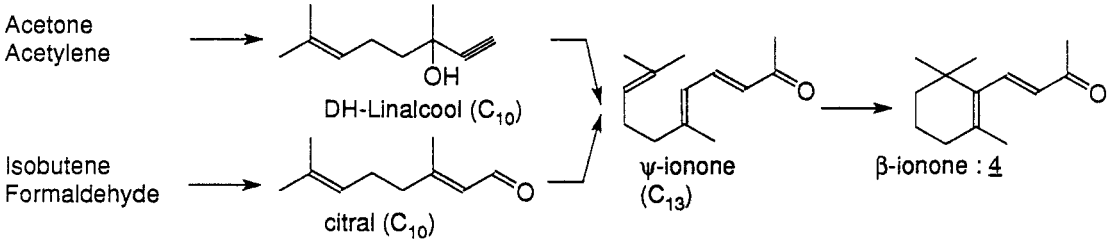


Fig. 1 : Synthesis of β-ionone from basic chemicals.

The polyene chain must be built up under particulary mild conditions - Hoffmann-La-Roche and Rhône-Poulenc achieve this by addition and elimination, the former by linking C_{14} and C_6 in a Grignard reaction and the latter by a Julia synthesis from C_{15} and C_5 (ref 3.). At BASF. AG, C_{15} is joined to C_5 in a one step Wittig reaction (ref. 1d.) [Fig. 2]

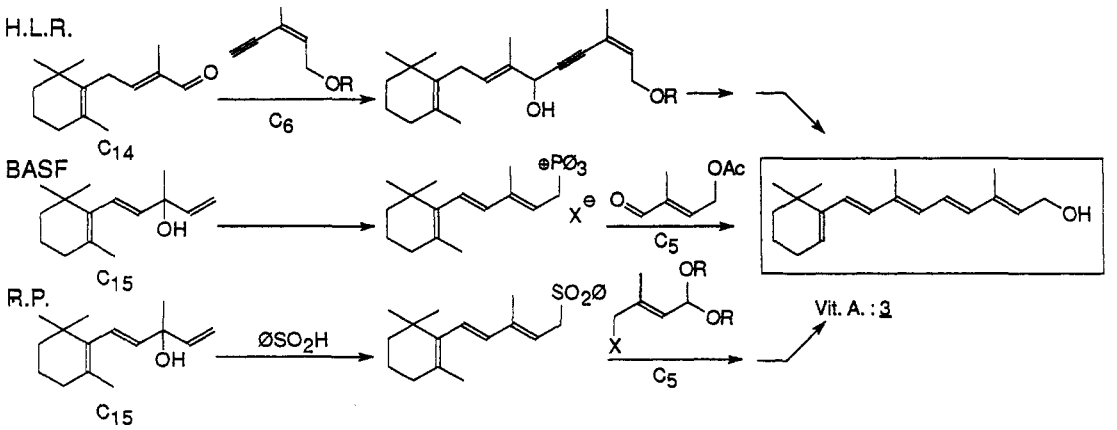


Fig. 2 : Technical synthesis of vitamin A

For vitamin E 6 (Tocopherol), the key intermediates are trimethylhydroquinone (TMHQ) 7 and isophytol 8 obtained from geranylacetone 9 (ref. 1c) [Fig. 3]

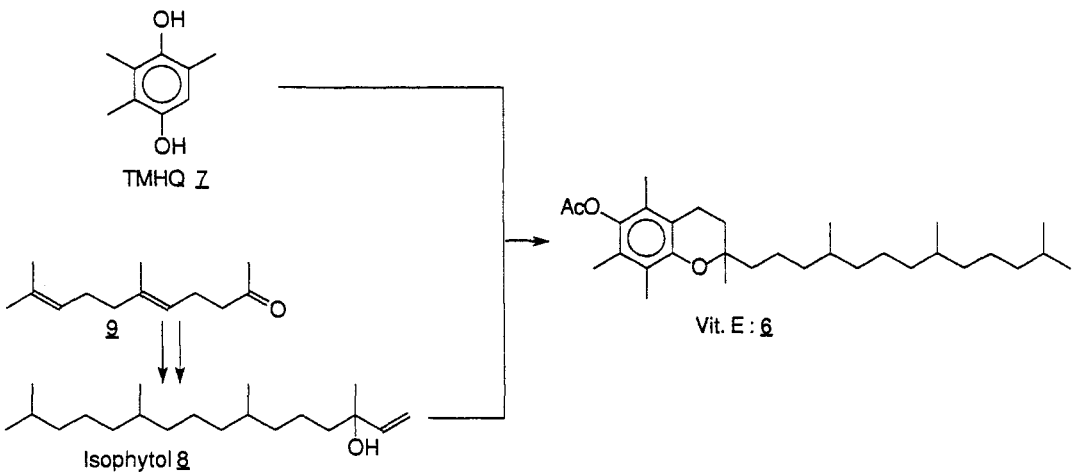


Fig. 3 : Technical synthesis of vitamin E.

Here, the syntheses used by the three manufacturers differ mainly in the basic chemicals used to synthesize geranylacetone 9 and TMHQ 7.

From the view point of organometallic and homogeneous catalysis, considerable efforts have been made by HLR and BASF on hydroformylation and oxidative addition of acetic acid to butadiene (ref. 4) in the synthesis of the aldehyde C_5 synthon. The aim of this report is to illustrate how organometallic chemistry can improve industrial synthesis (Chemioselectivity regioselectivity, yield and effluent) by looking in detail at four reactions used in the Rhône-Poulenc synthesis :

- *Isomerisation of 3-methyl-1-butyn-3-ol to 3-methyl-2-butene-1-al (key step of C_5 unit* Vit. A)
- Carbon - carbon coupling for an efficient access to geranyl acetone using Rhodium/TPPTS catalyst (water soluble)
- Chemoselective hydrogenation of prenal with Ru/TPPTS and of all-trans retinal with homogeneous supported Iridium catalyst.
- Oxidation and access to trimethylhydroquinone to illustrate influence of effluent on the choice of industrial process.

ISOMERISATION

The isomerisation of α-acetylenic alcohols into α, β-ethylenic carbonyl compounds - (versatile organic intermediates in the manufacture of fragrances, carotenoids etc)- has been studied extensively (ref. 5). Different catalysts have been proposed : acid catalysts which give rise to unselective rearrangements (ref. 6) ; or, more recently, oxo derivatives of vanadium, molybdenum or tungsten (ref. 7). Especially in the case of vanadates, good yields of isomerisation may be obtained with high dilution or with low transformation rate of substrate thus giving low productivity. We now propose new titanium/copper based catalysts which allow a simple, efficient, quick and selective isomerisation of α-acetylenic alcohols according to the following [Fig. 4] (ref. 8) single step process in a homogeneous liquid phase.

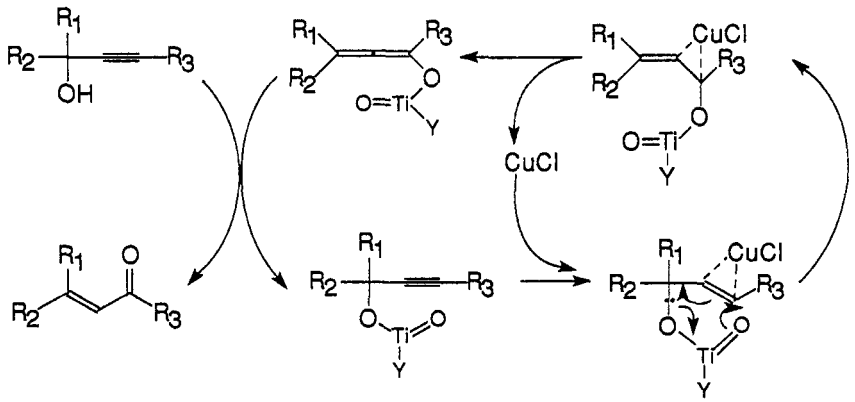
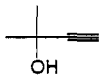
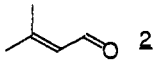
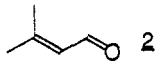
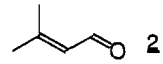
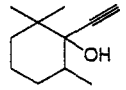
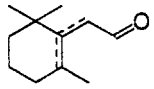
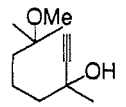
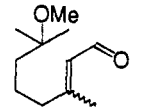
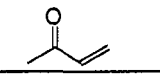


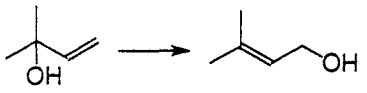
Fig. 4 : Isomerisation of acetylenic alcohols.

The use of a carboxylic acid as a co-catalyst allows a faster reaction and a better stability of both substrates and products, toluic or crotonic acids are among the best of those tested. The substrate is left unchanged when the reaction is performed either without the titanium or without the copper catalysts. The reaction is general and different acetylenic alcohols have been isomerized under similar conditions using the same $Ti(OR)_4$/CuCl catalyst, which is easy to recycle if high boiling point solvents like *o-dichlorobenzene or methyl benzoate are used (Table 1)*

Table 1 : Isomerisation of acetylenic alcohol, catalyzed by titanium/Cu catalysts.

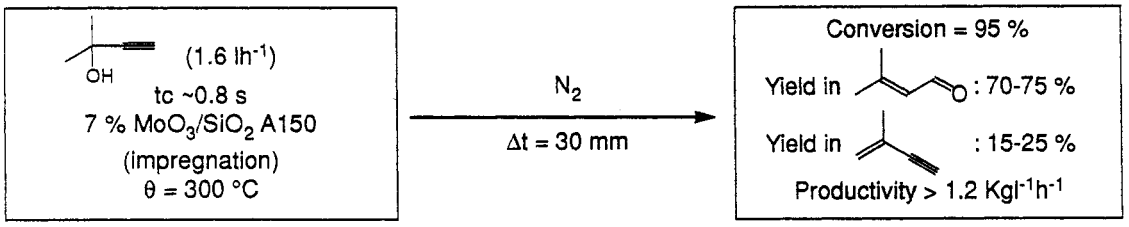
Alcohol (1 mole)	t°C	Time (h)	Catalyst (molar equivalent) $Ti(OR)_4$ R =	CuCl	Acid	Solvent (g)	Product	Yield %	Substrate Conversion %
 1	130	0,5	Bu 0.014	0.020	p.Toluic 0.171	O.$PhCl_2$ 150	 2	85	94
	130	0.5	Bu 0.014	0.020	O	O.$PhCl_2$ 150	 2	24	31
	130	1	iPr 0.0075	0.0081	crotonic 0.046	ØCO_2Me 200	 2	89	96
	130	4	Bu 0.013	0.018	p.Toluic 0.16	O.$PhCl_2$ 300		95	96
	130	2	Bu 0.0076	0.0081	crotonic 0.046	ØCO_2Me 230		71	98
	130	2.5	Bu 0.02	0.04	crotonic 0.122	O.$PhCl_2$ 605		47	70

The isomerisation of α-ethylenic alcohols to the corresponding allyl alcohols is very poor using the Ti/Cu catalyst whereas it is particulary efficient with the vanadate esters : (ref. 7a)



- $Ti(OR)_4$-CuCl : no reaction
- Orthovanadate : good yield

In heterogeneous catalytic conversion in the vapor phase, good results have been obtained with MoO_3-SiO_2 (ref. 7c). We were unable to reproduce these results and the best conditions in our hands for selectivity and productivity are, after optimisation (ref. 9).



The main advantages are a simple preparation and regeneration of the catalyst and also high productivity in a continuous heterogeneous vapor phase process. The main drawback is formation of 2-methyl-1-butyn leading to rapid deactivation of the catalyst by coking.

CARBON - CARBON COUPLING :

A new process was developped for the addition of active methylene compounds to conjugated dienes and used in a new industrial synthesis of geranylacetone by Rhône-Poulenc Animal Nutrition in 1988 (ref. 10)
In the literature, these types of additions have been catalyzed by homogeneous palladium, platinum, nickel or cobalt. In general, with neutral monodentate ligands (like triphenylphosphine), we obtained 1:2 addition compounds (1 mole of active methylene for 2 moles of dienes). In the presence of bidentate ligands (like bis 1,2-(diphenylphosphino)-ethane) the reaction give mainly 1:1 addition products but with regioselectivity less than 80 % (ref. 11).
In our new process, the addition is regioselective (≥ 99 %) and the isomers ratio is α/β ~45/55 (ref. 12) [Fig. 5]

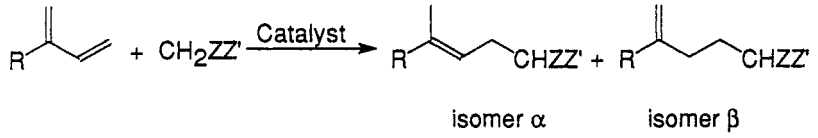


Fig 5 : Regioselective nucleophilic addition to 1,3 dienes.

The structure of final products (regioselectivity of addition) and the position of the double bond (isomer α and β) suggest a mecanism abstracted in Fig. 6. After the preparation of catalytic species :

$$1/2\ [RhCl(COD)]_2 + 3L + CH_2ZZ' \longrightarrow L_3Rh\text{-}CHZZ' + Cod + HCl$$

The addition of CH_2ZZ' is possible after activating the 1,3-diene by coordination to the rhodium atom. The origin of particular regioselectivity could be attributed to the formation of a Π-allyl intermediate which is followed by protonation in 1 or 3 position by transfert with an active methylene molecule.

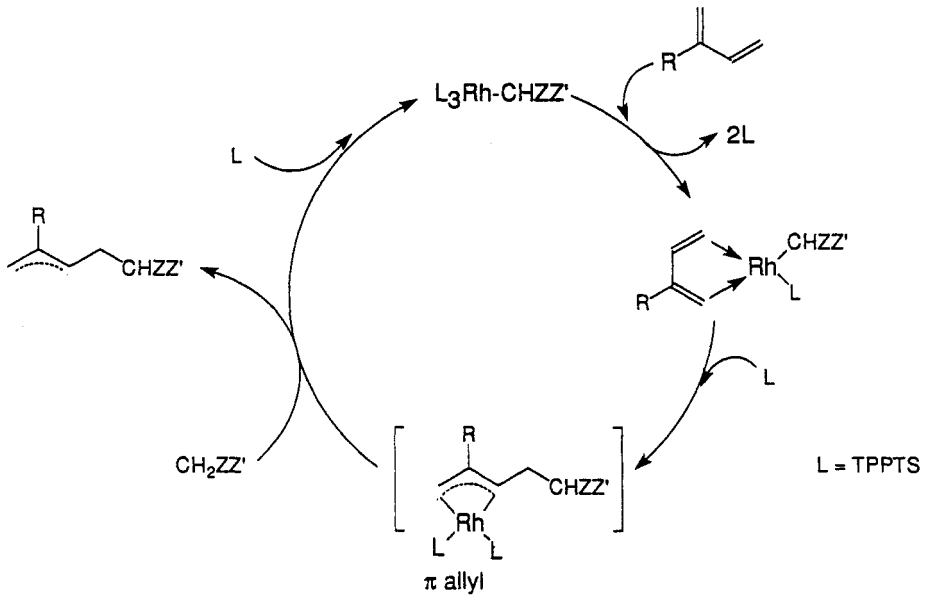


Fig. 6 : Mechanism of addition

Numerous susbtrates can be used : isoprene (R = CH_3), myrcene (R = C_6H_{11}), β-farnesene (R = $C_{11}H_{19}$) as dienes and see table 2 for examples of active methylene compounds (or nucleophiles)

Table 2 : Examples of products

CH_2ZZ' / 1,3-dienes	acetylacetone	OMe	$ØSO_2$	HO	NH
Isoprene		CO_2Me	$SO_2Ø$	OH (low yield)	
Myrcene		CO_2Me	$SO_2Ø$	No reaction	

The addition reaction is driven very selectively by using an aqueous soluble catalyst, based on a rhodium salt and a sulfonated phosphine, especially tris (m-sulfophenyl)-phosphine trisodium salt (TPPTS). This phosphine, easily obtained by sulfonation of triphenylphosphine, is very soluble in water (~1000 gl^{-1} at 20°C). The reaction proceeds in a biphasic liquid/liquid system where conversion is regulated by stirring time. The organic products are easily separated by simple decantation and the aqueous phase containing the catalyst can be recycled.

The excellent regioselectivity, the easy recovery and recycling of the aqueous rhodium catalyst permits industrialization to produce intermediates for vitamin E like geranylacetone in a short and economical process compared to the old chemistry which uses a more expensive raw material like linalool [Fig. 7] ; Futhermore the intermediate β-ketoester C_{15} is also a key compound to pseudoionone and vitamin A synthesis (ref. 18)

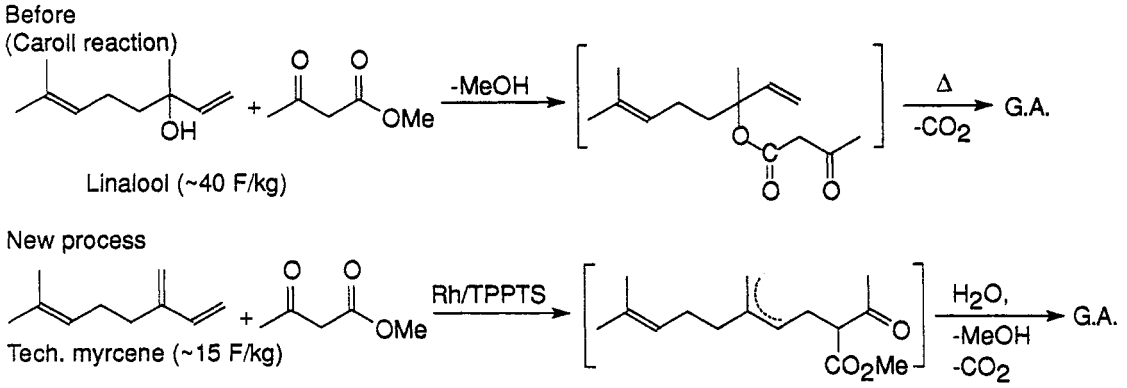


Fig 7 : Industrial geranylacetone production.

HYDROGENATION :

α, β - unsaturated aldehydes constitute important intermediates in the field of flavor and fragrance and vitamin chemistry. Catalytic and selective hydrogenation of α, β-unsaturated aldehydes to allylic alcohols is an attractive way to carry out the reduction with respect to economical and industrial process considerations. In previous papers, we have presented efficient homogeneous catalysts for this kind of hydrogenation (ref. 13).
In the case of aldehydes with a short carbon-chain lenght (3-methyl-2-butenal for instance), the catalyst recycling problem, the main drawback of homogeneous catalysis, had been overcome by the use of ruthenium complexes with sulfonated phosphines, especially tris (m-sulfophenyl)-phosphine trisodium salt (TPPTS).

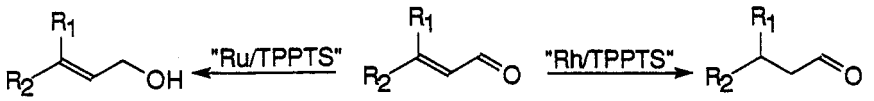
The data demonstrates clearly (Table 3) that extremely high selectivities at complete conversion are obtained. Interestingly the catalytic system is readily made from a mixture of $RuCl_3$ and TPPTS in water. The hydrogenation proceeds smoothly under moderate hydrogen pressure and temperature conditions. It requires an induction period which likely generates the active catalyst (in situ). In our system, the hydrogenation is a genuine two-phase reaction in which the complex remains in the aqueous phase. The two phases separate readily, allowing recycling of the aqueous catalytic phase. As can be seen from table 3 (runs 3,4 and 5) the selectivity did not decrease while recycling the catalyst.

Table 3 : Hydrogenation of α, β-unsaturated aldehydes with Ru-TPPTS [a)]

Run	Substrate	P_{H_2} (bar)	T (°C)	% conversion (hours)[b)]	% unsaturated alcohol	Selectivity %
1	cinnamaldehyde	20	35	99 (3)	97	98
2	crotonaldehyde	20	35	95 (4)	94	99
3	methyl-3-buten-2-al	20	35	100 (1)	97	97
4	first recycle	20	35	99 (0.5)	96	97
5	second recycle	20	35	99 (0.5)	96	97
6	citral	50	50	96 (15)	94	98

a) Reactions conditions : Catalyst prepared in situ $RuCl_3$/3 TPPTS ; Ru : 10^{-4} mol ; substrate : 20 mmol ; solvent : toluene/water = 5/5 ml.
b) Included induction period except runs 4 and 5.

We have also shown that it was possible to direct the hydrogenation by carefully choosing the nature of the metal, so that α, β-unsaturated aldehydes could be reduced either into the corresponding allylic alcohols with the "Ru/TPPTS" system (ref 13d) or into the saturated aldehydes with "Rh/TPPTS" (ref. 13e).



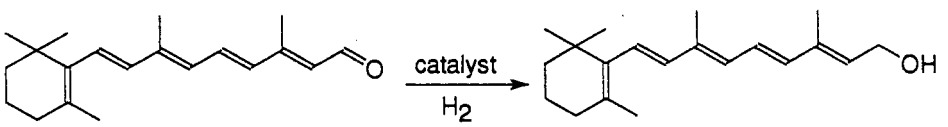
However, in the case of aldehydes with a long carbon-chain, (like vitamin A aldehyde), the use of a liquid - liquid biphasic system where the reactants are in the organic phase and the catalyst in water leads to poor results, probably because of the low solubility of the reactants in water. For instance, the chemioselective and stereoselective hydrogenation of hydroquinone all-trans retinal complex (RHQ) to all-trans retinol which is an important reaction in vitamin A synthesis, has been efficiently achieved with $RuH_2 (P\emptyset_3)_4$ in methanol whilst poor results were obtained in a biphasic system with $RuH_2 (TPPTS)_4$ (ref. 13a). In order to overcome the previous problem, we have studied the chemoselective hydrogenation of different aldehydes into allylic alcohols with two kinds of catalyst : (ref. 14.).

I) Supported aqueous-phase catalysts, similar to Rh catalysts recently developped for hydroformylation of long chain alkenes

II) Commercial supported homogeneous catalysts from DEGUSSA. AG.

Supported aqueous-phase catalysts $RuCl_2 (TPPTS)_3/SiO_2$ and $RuH_2 (TPPTS_{14}/SiO_2$ suffer from great drawbacks : their use seems limited to non polar solvents since in polar media such as methanol, we have observed the dissolution of a great part of the metal ; and difficulty in recycling them even in non polar media, because of the poisonous adsorption of organic compounds at the catalysts surface. Thus, it appears difficult to carry out the hydrogenation of unsaturated aldehydes on an industrial scale with this kind of catalyst.

Supported homogeneous catalysts based on phosphino-iridium compounds appear more promising. Thus, these catalysts are chemoselective and stereoconservative in the case of all-trans retinal and easy to recover and recycle. However their productivity (10-15 h^{-1}) has to be improved in order to offer a reasonable alternative.



All-trans retinal — all-trans retinol

Catalyst	Δt (h)	H_2 (bar) (%)	Conversion (%)	Yield [c] (%)	Turnover number (h^{-1})
RuH2 $(PPh_3)_4$ [a]	0,7	20	100	97	> 338
Ir 5 % RG 441 [b]	3,5	100	100	93,3	11

a) Conditions : Ru = $5{,}2.10^{-5}$ mole ; RHQ = $12.3.10^{-3}$ mole ; EtOH 95 = 50 ml ; 25 °C
b) Conditions : Ir = $7{,}5x10^{-5}$ mole ; RHQ = 3.10^{-3} mole ; EtOH 95 = 50 ml ; 50°C
c) In total retinol

Fig. 9 : Catalytic hydrogenation of retinal.

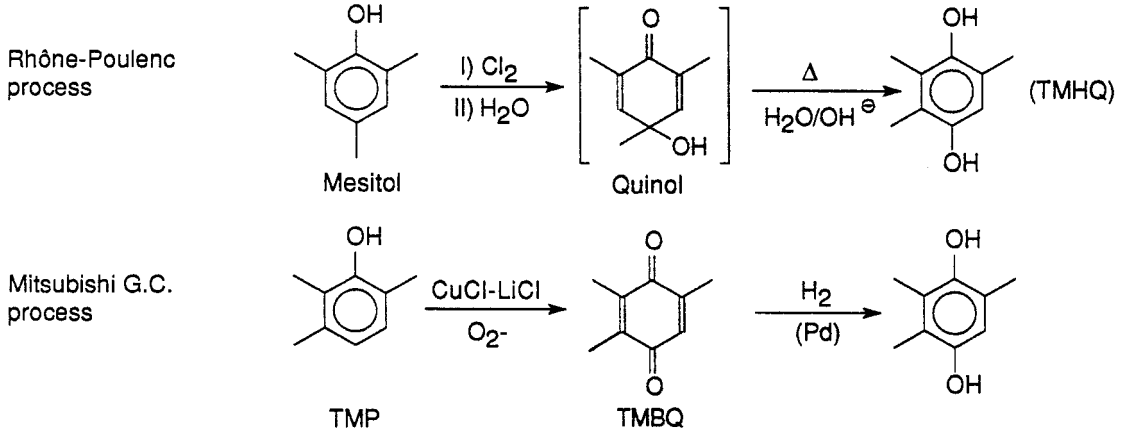
OXIDATION

In this paragraph, we want to compare two routes to trimethylhydroquinone to illustrate influence of effluent on the choice of industrial process (ref. 15). Trimethylhydroquinone (TMHQ) is a key intermediate for economy of the vitamin E process. The only industrial use of TMHQ is on the production of vitamin E, with a narrow market and only a few suppliers, often competitors on the final vitamin E. This is the reason why for fifteen years, Rhône-Poulenc Animal Nutrition have wanted their own internal TMHQ production.

Numerous ways of access have been studied, starting from differents raw materials. The last one, was based on oxidation by chlorine of 2,4,6-trimethylphenol (or mesitol). This process was attractive, because of the abondance and low price of the raw material. The only problem was an aqueous effluent problem, with a solution of salt in excessive quantity (> 50 kg/kgTMHQ), with an elevated C.O.D. and not biodegradable. This point killed the process.

At the same time, Mitsubishi Gaz Chem (MGC) licenced to Rhône-Poulenc Animal Nutrition a process using 2,3,6-trimethylphenol (TMP) as raw material with a first step using molecular oxygen as oxidant with a catalyst based on CuCl/LiCl. We obtained the trimethylbenzoquinone (TMBQ) which was hydrogenated with a special catalyst (1 % Pd/zeolithe) (ref. 16) in very smooth conditions (40°C atm. P.) at a very high selectivity (> 99 %) which permited isolation of pure TMHQ without any more purification. On the oxidation stage, the originality of the process is an easy recovery and recycling of the catalyst by simple decantation : The catalyst is in aqueous solution and the organic products (TMP and TMBQ) are dissolved in a heavy alcohol, with little solubility in water.

Finally, on the effluent point of view, the MGC process only produce 2,2 kg of aqueous effluent by kg of TMHQ with an important possibility of reduction
In conclusion, Rhône-Poulenc Animal Nutrition produce at the moment the TMHQ using the MGC process, since 1988 in a new plant on a scale of 1000 T/year [Fig. 10].



Process	Raw Material (cost, availability)	Simplicity of the process	Effluent	
RP	+++	++	---	
MGC	+	-	++	← Industrial process

Fig. 10 : Industrial process for TMHQ production

CONCLUSION

This article illustrates the concepts of short synthesis, high selectivity and no effluent for future industrial processes. Based on the examples coming from the recent development of vitamins A and E in Rhône-Poulenc Animal Nutrition, we saw the interest of developping new catalytic process to reach the goal of selectivity and economy. The most illustrative example is certainly the new vitamin E synthesis since 1988 with 2 major integrations on new raw materials using catalytic process with very high selectivity [Fig. 11.]

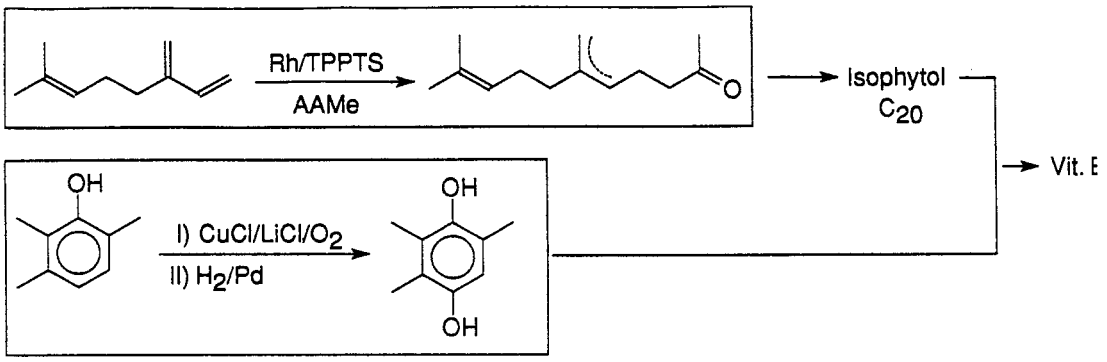


Fig. 11 : Rhône-Poulenc new process for vitamin E synthesis

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