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# Rare earth triflate catalysts in the synthesis of Vitamin E and its derivatives

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Dedicated to Professor W.F. Hölderich on the occasion of his 60th birthday.

## Abstract

Vitamin E is known as the most important fat-soluble antioxidant in biological systems. The scale for commercially produced (all-*rac*)-α-tocopherol reaches over 25,000 tonnes per year. The known processes for the synthesis of α-tocopherol suffer from disadvantages like formation of by-products and waste-water problem. To overcome these drawbacks, new types of catalysts have been developed. These are rare earth metal triflates, e.g. $Bi(OTf)_3$, $Ga(OTf)_3$, $Tm(OTf)_3$ or $Hf(OTf)_4$. This new approach to Vitamin E or derivatives thereof has several advantages, based on high yields (above 94%) and selectivities.

*Keywords:* Vitamin E; α-Tocopherol; Antioxidant; Metal triflates; Rare earth metal triflates

## 1. Introduction

Vitamin E covers a class of compounds derived from 6-chromanol. The eight naturally occurring substances are divided in the group of tocopherols **1–4** (with a saturated $C_{16}$-side chain), and tocotrienols **5–8** (possessing a triply unsaturated $C_{16}$-side chain), and are all single isomer compounds, i.e. characterized by their ($2R,4'R,8'R$) and ($2R,3'E,7'E$) stereochemistry, respectively (Scheme 1) [1,2].

The eight ($2R,4'R,8'R$)-tocopherols and ($2R,3'E,7'E$)-tocotrienols are widely distributed in nature. High amounts in various compositions are found in plant oils, e.g. from sunflower, corn, or palm fruits. The highest biological activity is found for α-tocopherol. Vitamin E is the most important lipid-soluble biological antioxidant [3]. For the radical scavenger effects see Ref. [4]. The relative biological activity of tocopherol stereoisomers and homologues was studied by Weiser and Vecci [5]. The economically most important sales form is the acetate derivative of (all-*rac*)-α-tocopherol (**11**), a mixture of eight stereoisomers, mainly applied to animal nutrition. The world market of this product is around 30,000 tons/annum. Producers are DSM Nutritional Products, BASF, and companies located in China [6].

As pointed out the main market of (all-*rac*)-α-tocopherol (**11**) is the application in the feed market (74%). An example exhibiting the antioxidant properties of Vitamin E used in animal nutrition for improvement of meat quality is shown in Fig. 1.

Other applications are in cosmetics (3%), pharmaceuticals (24%), and the food market. The main application form (98%) of tocopherol is the acetate form [2].

The total synthesis of (all-*rac*)-α-tocopherol (**11**), the compound of highest commercial interest due to its biological and antioxidant properties, is based on the reaction of trimethylhydroquinone (**9**) with isophytol (**10**), phytol or phytyl halides [2,7] (Scheme 2).

In this article we will describe the most recent results from our research laboratories on new catalyst types and procedures for the preparation of **11** and some of its derivatives.

## 2. Results and discussion

In general, the development and application of catalytic reactions is one of the fundamental issues in fine chemical industry, e.g. in the synthesis of vitamins like Vitamin E. The

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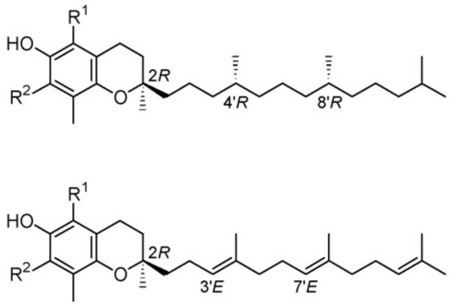


| $R^1$ | $R^2$ | (2R,4'R,8'R) | |
|---|---|---|---|
| $CH_3$ | $CH_3$ | α-tocopherol | **1** |
| $CH_3$ | H | β-tocopherol | **2** |
| H | $CH_3$ | γ-tocopherol | **3** |
| H | H | δ-tocopherol | **4** |

| $R^1$ | $R^2$ | (2R,3'E,7'E) | |
|---|---|---|---|
| $CH_3$ | $CH_3$ | α-tocotrienol | **5** |
| $CH_3$ | H | β-tocotrienol | **6** |
| H | $CH_3$ | γ-tocotrienol | **7** |
| H | H | δ-tocotrienol | **8** |

Scheme 1. Naturally occurring Vitamin E compounds.

aim of these activities is to reduce waste and to achieve an economical and ecological benefit. Here catalysis is one of the most important technology platforms. This statement is not only connected to the production of vitamins. Also for other fine chemical products this is a key factor for success. For an overview about new catalytic processes developed in Europe during the 1980s see [8].

Key-factors that determine the economic success of industrial research and development are based on the criteria:

- availability and costs of raw materials,
- technology,
- environmental aspects,
- selectivity,
- yield,
- turn over number, and
- reduction of numbers of steps and unit operations.

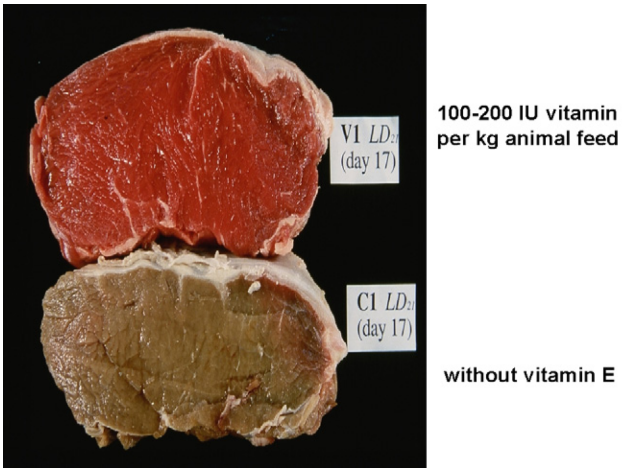
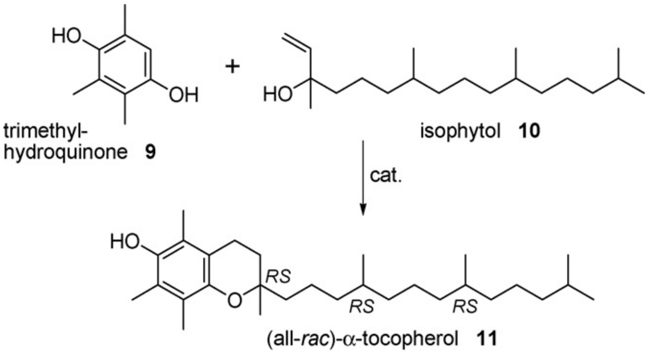


Fig. 1. Example for application of Vitamin E in animal nutrition.



Scheme 2. Synthesis of (all-*rac*)-α-tocopherol.

Scope of process research and development is the integrated approach of reaction, separation, and product formulation. Future trends are the combination of unit operations, continuous processing, processing with high productivity, with the focus on high yields and selectivity [9].

According to Sheldon's classification of ranking by the e-factor (Table 1 [10]), most vitamins are typical fine chemicals with prices above US\$ 10 $kg^{-1}$ and production volumes of about 1000–10,000 tons/annum. A few vitamins can be placed in the class of bulk chemicals.

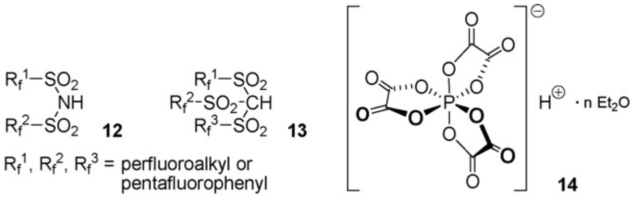
As already mentioned, the strategy of Vitamin E [(all-*rac*)-α-tocopherol, **11**] synthesis is based on the preparation of TMHQ (**9**), IP (**10**), and the Friedel-Crafts type reaction (Scheme 2) followed by acylation to the commercial form.

The pioneering work of Karrer and Isler on the condensation reaction of **9** with **10** [11] resulted in the first Vitamin E production at Roche in Basel in the early 1950ies. Several classical Lewis and Brønsted acids, or combinations thereof, work well in this reaction. Typical examples are $ZnCl_2$/HCl, $BF_3$, or $AlCl_3$, applied in various organic solvents. For large-scale production, however, corrosion problems and contamination of waste-water, in particular with zinc and halide ions, are major drawbacks of such procedures. Further disadvantages are the high, often near stoichiometric amounts of "catalysts", necessary for obtaining satisfying results.

During the last years several approaches to find environmentally friendly procedures were investigated. The main focus was on reactions in supercritical fluids, or in two-phase or multi-phase solvent systems, and the use of

Table 1
e-Factor in various segments of industry [10]

| Industry segment | Product tonnage | e-Factor (kg by-product/kg product) |
|---|---|---|
| Oil refining | $10^6$–$10^8$ | <0.1 |
| Bulk chemicals | $10^4$–$10^6$ | 1–5 |
| Fine chemicals | $10^2$–$10^4$ | 5–50 |
| Pharmaceuticals | $10^1$–$10^3$ | 25 to >100 |

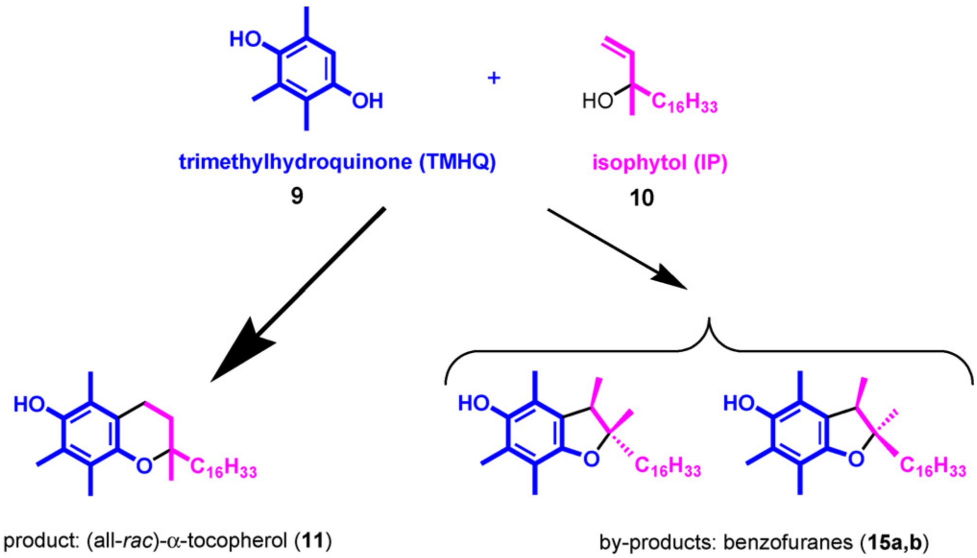


Scheme 3. Strongly acidic compounds used in Friedel-Crafts-type preparations of Vitamin E.

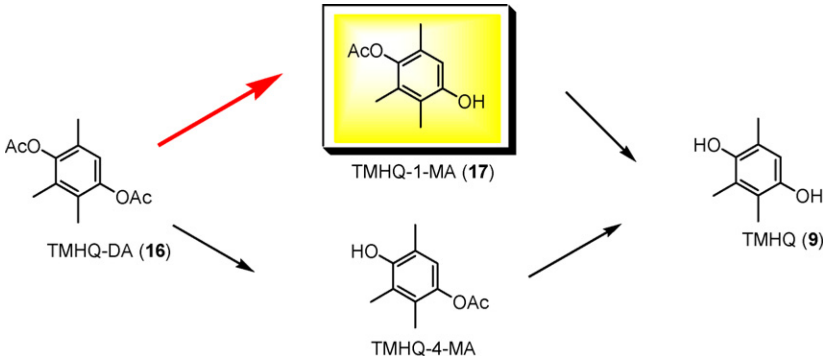
new types of catalysts [12–23]. Especially Nafion® based systems or micro-encapsulated catalysts were used as substitutes for mineral acids [20,23,24]. New developments of modern catalysts include the work on the combined use of boric and oxalic (tartaric, citric) acid [21], and the application of various new types of efficient Friedel-Crafts mediators in truly catalytic amounts, i.e. below 1 mol%. Examples of such catalysts are rare earth metal triflates, e.g. $Sc(OTf)_3$ [25,26], heteropolytungsten acids [27], polyfluorinated compounds of type **12/13** [28–30], and phosphate **14** [31] (Scheme 3).

Remarkable features of these systems are not only the high chemical yield, but in particular the extremely high selectivity of the overall condensation reaction of trimethylhydroquinone (**9**) with isophytol (**10**): The formation of isomeric products, e.g. benzofuran compounds **15a**,**b** [25] (Scheme 4), is considerably reduced, thus facilitating the purification of the final product.

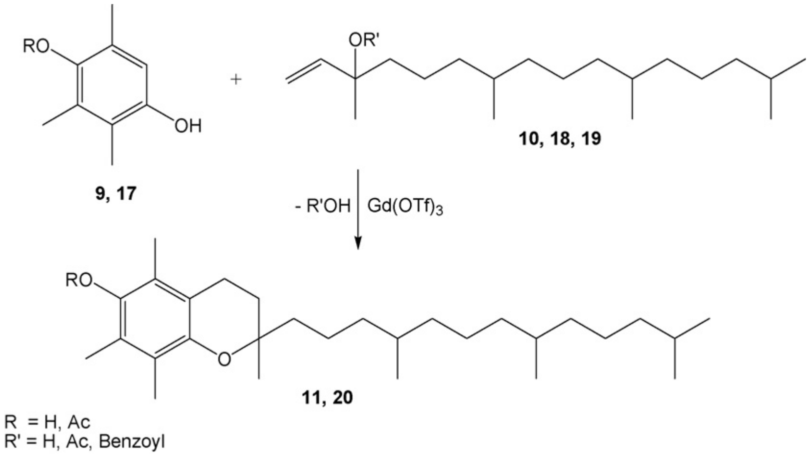
We started our investigation with the aim to find an efficient procedure for the condensation reaction to (all-*rac*)-α-tocopherol (**11**). In particular, the disadvantages of existing procedures should be addressed, which are, e.g. waste formation or the fact that high yield and selectivity could be achieved only with an excess of (expensive) isophytol [25,26]. Another goal was the use of trimethylhydroquinone-1-monoacetate (TMHQ-1-MA, **17**) as an alternative aromatic starting material. The latter can be prepared efficiently by highly selective enzyme catalyzed saponification of trimethylhydroquinone diacetate **16** [32] (Scheme 5). It would be advantageous, if the condensation reaction could be performed by starting from TMHQ-1-MA (**17**), since the synthesis of tocopheryl acetate is then achieved in a direct manner.



Scheme 4. Selective formation of chroman ring.



Scheme 5. Synthesis of TMHQ-1-MA.



Scheme 6. Rare earth metal triflate catalyzed synthesis of tocopherol and its derivatives.

Additionally the acylation reaction of tocopherol was investigated.

We found that TMHQ (**9**) or its mono-acetate derivative (**17**) can be easily transferred into tocopherol (**11**) or tocopheryl acetate (**20**) using rare earth metal triflates, e.g. $Gd(OTf)_3$ (Scheme 6) [33]. The reaction can be carried out in several solvent systems, e.g. bi-phasic systems especially systems based on ethylene or propylene carbonate and hexane, heptane or octane. The preferred reaction temperature is in the range from 80 to 160 °C. Beneficial of this catalyst system is the high selectivity at low catalyst loading. The reaction can be carried out at a substrate–catalyst-ratio (s/c) of 1000, and the product can be isolated in 95% yield after bulb to bulb distillation.

Table 2
Rare earth metal triflate catalyzed Friedel-Craft alkylation of trimethylhydroquinone-1-monoacetate

| Catalyst | Yield[a] (%) **20** | Selectivity (%) |
|---|---|---|
| $Bi(OTf)_3$ | 91.0 | 96.0 |
| $Ga(OT)_3$ | 92.0 | 97.0 |
| $Hf(OTf)_4$ | 93.3 | 98.0 |
| $Sc(OTf)_3$ | 92.3 | 97.5 |
| $Gd(OTf)_3$ | 94.0 | 98.0 |

[a] Isolated after bulb to bulb distillation, s/c = 1000, saponification < 2%, reaction temperature 140 °C, and reaction time 60 min, all reactions in ethylene carbonate heptane mixture.

Table 3
Rare earth metal catalyzed ring closure reaction of phytyltrimethyl-hydroquinone acetate

| Catalysed | Yield (%)[a] **20** | Selectivity (%) |
|---|---|---|
| $Bi(OTf)_3$ | 99.2 | 99.2 |
| $Ga(OT)_3$ | 98.9 | 99.5 |
| $Hf(OTf)_4$ | 99.9 | 99.9 |
| $Sc(OTf)_3$ | 99.4 | 99.9 |
| $Gd(OTf)_3$ | 94.0 | 99.0 |

[a] Isolated after bulb to bulb distillation, s/c = 10,000, saponification < 0.5%, reaction temperature 140 °C, and reaction time 60 min, all reactions in ethylene carbonate heptane mixture.

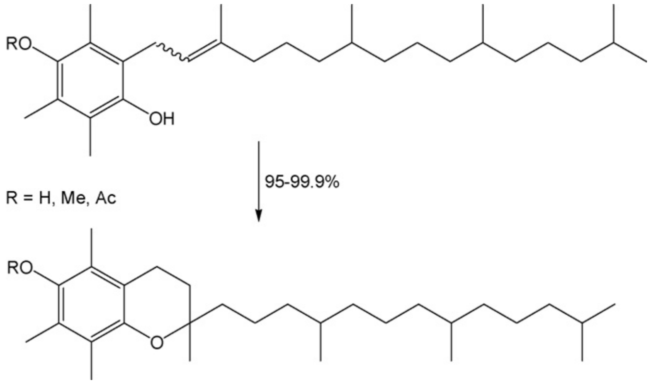
Under similar conditions, $Bi(OTf)_3$ is also a very efficient catalyst. Even at a s/c of 5000 a 98% yield of product was obtained after distillation of the product [34]. Another advantage of these catalysts is their independence from the reaction mode. Several feed modes can be used, e.g. continuous feed of the allyl alcohol or its derivatives to a mixture of the catalyst the aromatic starting material in the solvent (or solvent mixture).

Furthermore we found that $Hf(OTf)_4$ or $Sc(OTf)_3$ catalyze the reaction of **10** and **9** or **17** very efficiently. The chroman compounds **11** and **20** can be isolated in >92% yield at s/c of 10,000. Main advantage of these catalysts is their selectivity, because the saponification of the ester derivatives (starting material and product) under the reaction conditions is not observed (less than 0.3%).

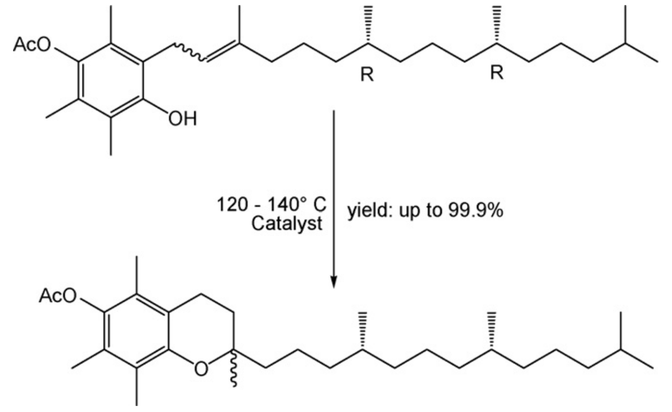
In Table 2 the main achievements are summarized [34,35].

Furthermore it was found that the ring closure reaction can be achieved in several solvent systems, e.g. polar solvents like γ-butyrolactone or ethylene carbonate, and non-polar solvents, e.g. heptane. The ring closure reaction is independent from the solvent polarity (Table 3) (Scheme 7).

Here it can be pointed out that the ring closure reaction of derivatives of phytyltrimethylhydroquinone, e.g. the methyl ether, can also be achieved [36].



Scheme 7. Rare earth catalyzed ring closure reaction.



Scheme 8. Influence of triflate catalyzed ring closure reaction on stereochemistry in the chroman ring formation.

In a detailed study we investigated the influence of the catalyst-solvent system on the stereochemical outcome of the reaction when starting from optically active phytyltrimethylhydroquinone. Starting from natural phytol ((*R*,*R*)-configuration) and TMHQ we synthesized (4′*R*,8′*R*)-phytyltrimethylhydroquinone and studied the ring closure reaction (Scheme 8).

It was observed that the application of triflate catalysts in various solvent systems, e.g. polar system, e.g. γ-butyrolactone, non-polar solvent systems, e.g. heptane or toluene or two-phase solvent systems, e.g. ethylene carbonate or propylene carbonate and heptane, in the ring closure reaction no epimerization on the stereocenters 4′ and 8′ occurs. In s/c ratio was up to 10,000 and the reaction temperature 120–140 °C. (2*RS*,4′*R*,8′*R*)-α-tocopheryl acetate (2-ambo-tocopheryl acetate) could be synthesized in excellent yield.

The tocopherol (**11**) synthesized by the presented methods can easily transferred into tocopheryl acetate (**20**) using a continuous acylation reaction [7].

## 3. Conclusions

In summary we have shown that:

- Triflates, especially rare earth triflates, can be used in the synthesis of (all-*rac*)-α-tocopherol or its acetate.
- Selectivity and yield could be increased by 3% compared to state of the art systems by increased temperature and pressure (2–6 bar).
- These improvements can be realized with several Friedel-Crafts type catalysts and solvents and have a broad value in Friedel-Crafts type reaction in general, and an economic benefit in the synthesis of Vitamin E.
- A further advantage is the easier purification of the final product due to the lower content of by-products.

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