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# A new route to Vitamin E key-intermediates by olefin cross-metathesis

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**Abstract**

The ruthenium-catalyzed olefin cross-metathesis has been successfully applied to the synthesis of derivatives of phytyltrimethylhydroquinone. These products, containing a trisubstituted olefinic double bond, are useful intermediates for an alternative route to α-tocopheryl acetate (Vitamin E acetate). Using the second generation Grubbs' catalyst $RuCl_2(C_{21}H_{26}N_2)(CHPh)PCy_3$ (Cy = cyclohexyl) and Hoveyda–Grubbs' catalyst $RuCl_2(C_{21}H_{26}N_2)\{CH\text{-}C_6H_4(O\text{-}iPr)\text{-}2\}$, the reactions were performed with various *C*-allylated and *O*-allylated derivatives of trimethylhydroquinone-1-acetate as substrates. 2,6,10,14-Tetramethylpentadec-1-ene and derivatives of phytol were employed as olefin partners for the cross-metathesis reactions. The Vitamin E precursors could be prepared in up to 83% isolated yields as mixtures of E and Z stereoisomers.


*Keywords:* Ruthenium-catalysis; Tocopherols; Isoprenoids; E/Z selectivity; Homo-coupling

## 1. Introduction

Vitamin E is an essential food ingredient and is of high economic importance due to its biological activity and antioxidant properties. From the family of Vitamin E compounds, naturally occurring α-tocopherol with (2R,4′R,8′R) configuration is the biologically most valuable one [1,2]. Synthetic all-racemic α-tocopherol ((all-rac)-**3a**) is produced on a scale of over 25,000 tons per year worldwide, mainly for application in feed industry, followed by the pharmaceutical, food and cosmetic markets. (all-rac)-α-Tocopheryl acetate (**3b**) is the major sales form [3]. It is usually produced by the condensation reaction of trimethylhydroquinone with isophytol, phytol or a derivative thereof in the presence of a Lewis or Brønsted acid catalyst, followed by an acetylation reaction [4].

Such procedures, however, have often the disadvantage of the formation of salts (waste material) and by-products, such as benzofurans or other impurities, which are rather difficult to separate from final products **3a** or **3b**. Regarding the construction of the tocopherol skeleton, it has been reported that phytylhydroquinones (2′E,7′R,11′R)-**2a** and (2′EZ,all-rac)-**2a** are open-chain precursors in biosynthetic [5] as well as chemical [6] routes to tocopherols, respectively (Scheme 1). Furthermore, we have shown that phytyl ether **1c** can be transformed into the Vitamin E precursor **2c** by a [1,3]-rearrangement reaction, finally leading to **3c** after cyclization [7]. Compounds **1** and **2** (particularly **1a**,**b** and **2a**,**b**) are, therefore, considered as Vitamin E key-intermediates for an alternative route to Vitamin E (**3a**,**b**), circumventing the formation of by-products accumulated by conventional procedures.

Olefin metathesis has become a powerful tool for C–C bond formation in organic chemistry in recent years [8]. In line with our continual effort to develop alternative methods in the field of tocopherol chemistry, we would like to describe here the successful application of the ruthenium-catalyzed olefin cross-metathesis (CM) reaction for the synthesis of the Vitamin E key-intermediates **1b**, **2b**, and related compounds [9].

## 2. Results and discussion

The commercially available ruthenium alkylidenes **8a** (second generation Grubbs' catalyst) and **8b** (Hoveyda–Grubbs' catalyst) have been applied as efficient catalysts for the preparation of alkenes. From the many applications reported, most examples deal with ring closing metathesis (RCM, [10]) and the formation of more or less unhindered olefinic double bonds [11]. For the synthesis of sterically more crowded olefins, like tri- or even tetrasubstituted alkenes with such ruthenium catalysts, however, we did not find many

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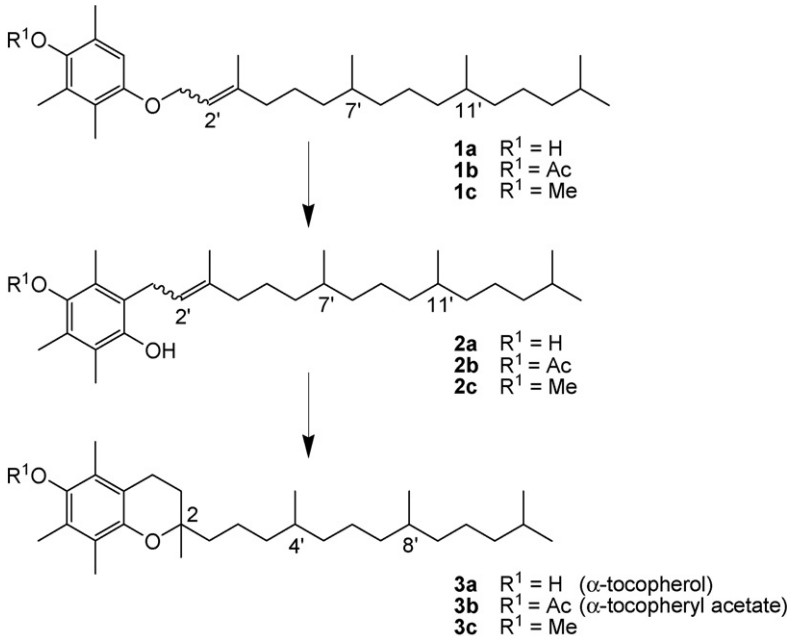



Scheme 1. Synthesis of tocopherols from open-chain precursors.

examples when we started our project. We decided to investigate catalysts **8a**,**b** in the synthesis of compounds **1b**, **2b** (=**6a**) and **6b–d** (Scheme 2) which contain a trisubstituted carbon–carbon double bond.

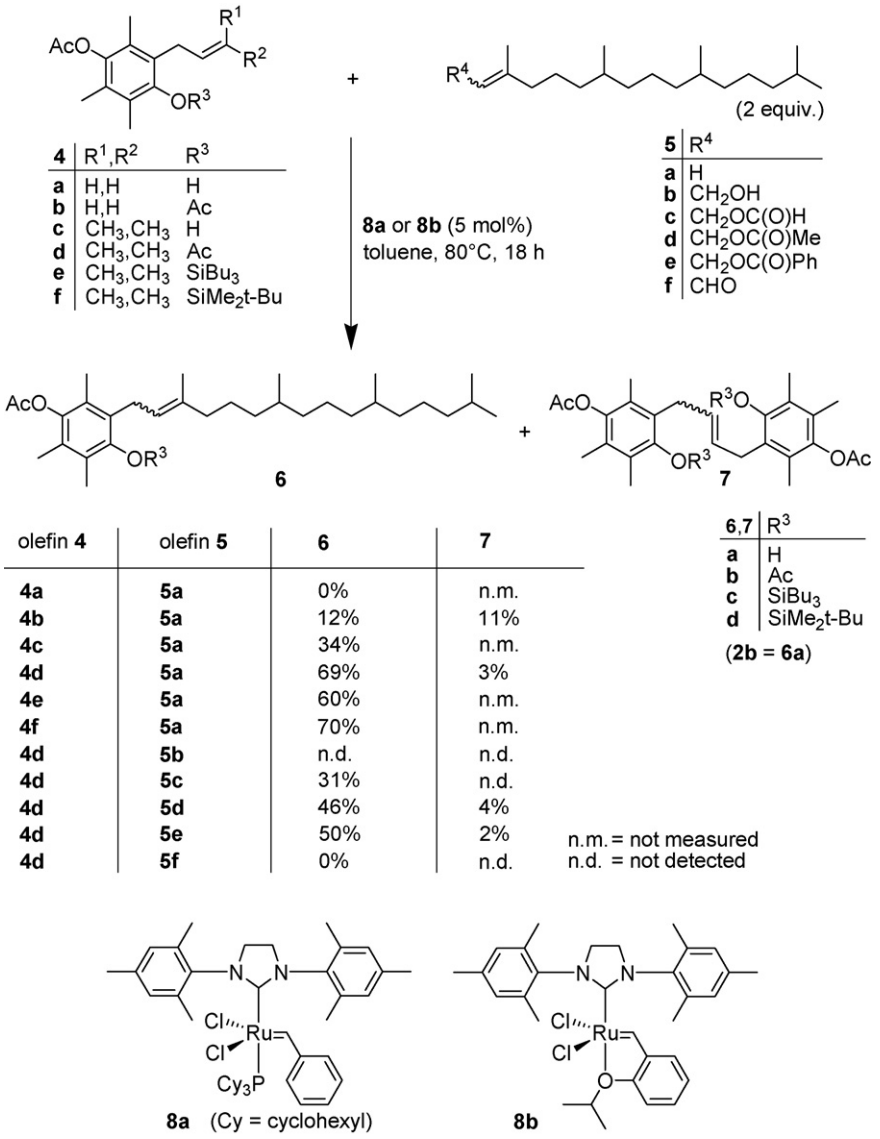
We started our experiments with the *C*-allylated (**4a–f**) derivatives of 2,3,6-trimethylhydroquinone-1-acetate as substrates for the synthesis of **6a–d** (Scheme 2). The disubstituted terminal olefin 2,6,10,14-tetramethylpentadec-1-ene (**5a**) and compounds **5c–f**, easily derived from 3,7,11,15-tetramethylhexadec-2-en-1-ol (phytol, **5b**), were used as the CM partners. The reactions were carried out under an inert atmosphere in toluene (other solvents like dichloromethane or tetrahydrofuran gave low yields) at 80° using the ruthenium complex **8a** or **8b** (5 mol% based on substrates **4**) as catalyst, with a ratio **4**/**5** of 1:2. Tridecane (same amount as **4**) was used as an internal standard for GLC determination of reactants and products. The results obtained for the synthesis of compounds **6a–d** is summarized in Scheme 2.

In the CM reaction of **4a**, possessing a terminal olefin moiety, with the terminal disubstituted olefin **5a**, no expected product **6a** (=**2b**) could be found. When starting from **4b**, **6b** was formed in low yield (12%) only. In both reactions, the homo-dimerization (self-metathesis) of the starting substrates **4a** and **4b** to the disubstituted products **7a** and **7b**, respectively, was detected. The formation of the dimers **7a** and **7b** points to the high reactivity of these terminal olefins towards CM, which may be a possible explanation for the low yields obtained when the monosubstituted terminal olefins **4a** or **4b** were used as substrates. The preparation of dimers **7a** and **7b** (81 and 77%, respectively) for reference could be achieved by starting from **4a** and **4b** in toluene at room temperature. Remarkably, **7b** can be isolated easily from the reaction mixture by precipitation with diethyl ether. For both dimers, the stereochemistry could not be determined, since NMR, GLC, and HPLC analyses did not provide any information about a separation of the signals or peaks of E and Z isomers.

The (unwanted) formation of homo-dimers prompted us to test the strategy of Grubbs and co-workers for avoiding undesired self-metathesis products, i.e. going via a homo-dimerization of one of the olefins [12]. Therefore, dimers **7a** and **7b** were also used as starting materials (not shown in Scheme 2). Compound **7a** did not lead to the formation of the desired product **6a**, but dimer **7b** gave **6b** with an even better yield than in the case when monomer **4b** was used as substrate (26% instead of 12%).

Due to this fact, we started to investigate the potential of trisubstituted olefins as more convenient substrates because they should not undergo self-metathesis easily, that is, the formation of the tetrasubstituted 2,3-dimethylbut-2-ene as by-product is surely disfavored. Indeed, no or only traces of dimer were detected when using compounds **4c–f** in the CM reactions. The isolated yields (between 34 and 70%) with these four substrates were always higher compared to the results with **4a** and **4b**. When **4c** is used as the starting material, the low yield of 34% could be due to a chelation of the hydroxyl moiety of **4c** to ruthenium, resulting in a deactivation of the catalyst [13]. The application of allylic alcohol **5b** (in the reaction with olefin **4d**) failed (**4d** remained in solution after the reaction).

The O-protected olefins **4d–f** bearing a trisubstituted olefinic double bond were the best substrates especially when the terminal olefin **5a** was used as the CM partner, resulting in isolated yields of **6** between 60 and 70%. Furthermore, allylic esters **5c–e** of phytol (**5b**) proved to be much better starting olefins than phytol itself. In reactions with **4d** the CM product **6b** was obtained in yields of 31, 46, and 50%, respectively. The corresponding α,β-unsaturated aldehyde phytal (**5f**) gave no conversion.



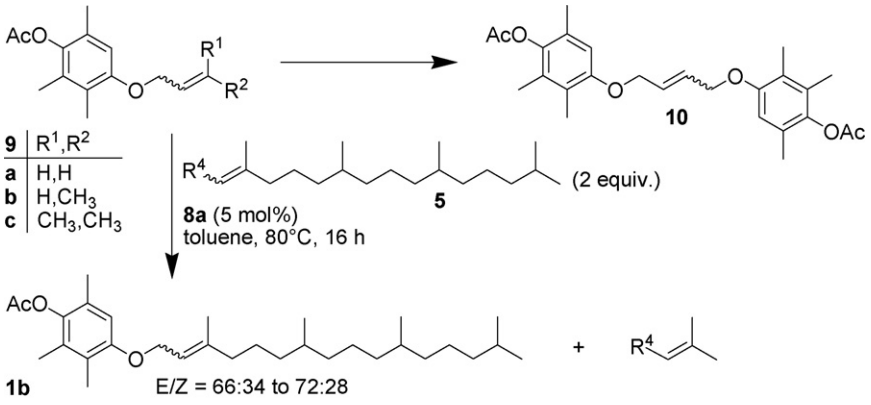

| olefin **4** | olefin **5** | **6** | **7** |
|---|---|---|---|
| **4a** | **5a** | 0% | n.m. |
| **4b** | **5a** | 12% | 11% |
| **4c** | **5a** | 34% | n.m. |
| **4d** | **5a** | 69% | 3% |
| **4e** | **5a** | 60% | n.m. |
| **4f** | **5a** | 70% | n.m. |
| **4d** | **5b** | n.d. | n.d. |
| **4d** | **5c** | 31% | n.d. |
| **4d** | **5d** | 46% | 4% |
| **4d** | **5e** | 50% | 2% |
| **4d** | **5f** | 0% | n.d. |

Scheme 2. Cross-metathesis reactions of olefins **4** and **5**.

On the basis of the results outlined in Scheme 2, we also applied the ruthenium-catalyzed cross-metathesis reaction to the synthesis of the Vitamin E key-intermediate **1b** (Scheme 3). The reaction conditions were the same as those described above, with toluene as solvent, tridecane as internal standard, and **8a** (5 mol%) as a catalyst. We employed three different *O*-allylated substrates **9** possessing a mono-(**9a**, $R^1 = R^2 = H$), a di-(**9b**, $R^1 = CH_3$, $R^2 = H$), and a trisubstituted (**9c**, $R^1 = R^2 = CH_3$) olefin moiety. The same CM partners as before were used, except the allylic alcohol **5b** which proved to be inefficient (vide supra). The ratio **9/5** was 1:2. Reaction between allyl ether **9a** and olefin **5a** led to the phytyl ether **1b** in only 29% yield, probably due to the concomitant formation of dimer **10** (ca. 33% determined by GLC). Dimeric compound **10** was also prepared for reference from **9a** in toluene at room temperature (yield 30%) in presence of catalyst **8a** (5 mol%). Product **10** is a mixture of two isomers (63:37, determined by GLC), presumably corresponding to the E and Z stereoisomers (not confirmed).

When the disubstituted olefin **9b** was employed, the yield increased to 51% while the formation of **10** was low (6%), and a large amount of unreacted starting substrate (ca. 50%) remained in the reaction mixture. As expected, allyl ether **9c**, containing a trisubstituted olefinic double bond, proved to be the best substrate in the reaction with olefin **5a**, since it did not dimerise (**10** < 1%), affording the desired product with 73% yield. Increasing the amount of catalyst to 10 mol%, or the overall concentration of the reaction mixture by a factor 4 did not afford better yields (68% in both cases). We also reacted **9c** with the other derivatives of phytol. When starting from **5c** to **5e**, yields in a range from 58 to 67% were achieved. Here, again, the formation of dimer **10** was not observed, and this probably explains the favored formation of **1b**.

Test reactions were also carried out both solvent-free and in vacuo, conditions already employed successfully by Grubbs and co-workers for the synthesis of symmetrical disubstituted olefins [14]. Performing the experiment under vacuum should have the benefit of removing the stoichiometric gaseous




| $R^1$ | $R^2$ | $R^4$ | isolated yields CM-product **1b** | dimer **10** | solvent; remarks |
|---|---|---|---|---|---|
| H | H | H | 29% | 33% | toluene |
| $CH_3$ | H | H | 51% | 6% | toluene |
| $CH_3$ | $CH_3$ | H | 73% | <1% | toluene |
| $CH_3$ | $CH_3$ | H | 68% | n.d. | toluene; 10 mol% **8a** |
| $CH_3$ | $CH_3$ | H | 68% | 2% | toluene; 4-fold conc. |
| $CH_3$ | $CH_3$ | H | 67% | n.d. | solvent-free |
| $CH_3$ | $CH_3$ | H | 83% | n.d. | solvent-free; 33 mbar |
| $CH_3$ | $CH_3$ | $CH_2OC(O)H$ | 67% | n.d. | toluene |
| $CH_3$ | $CH_3$ | $CH_2OC(O)Me$ | 59% | n.d. | toluene |
| $CH_3$ | $CH_3$ | $CH_2OC(O)Ph$ | 58% | n.d. | toluene |

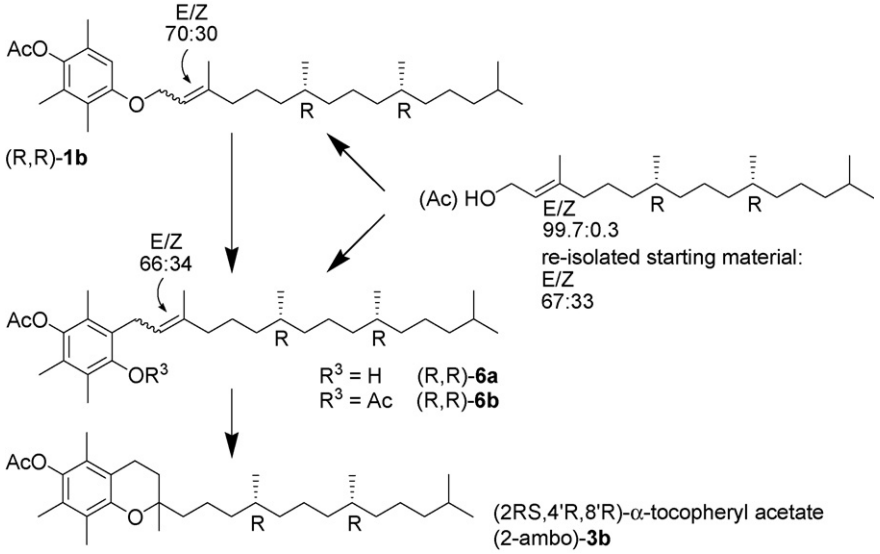
n.d. = not detected

Scheme 3. Cross-metathesis reactions of *O*-allyl precursors **9**.

by-product of the reaction, isobutene, and therefore pushing the reaction toward completion. When starting from **9c** and **5a**, a yield of 67% was reached by performing the reaction without solvent, and the isolated yield could be improved up to 83% by applying vacuum (33 mbar), while no dimerisation product (**10**) was detected. This result is of particular interest from an industrial point of view, since it gives not only higher yields, but also reduces the expenditure of time and material in handling and recycling of solvents.

The optimized coupling conditions resulting from the experiments described above were also used for the synthesis of optically active building blocks. Starting from natural (E,R,R)-phytol, which is readily available as a major degradation product of green plant's chlorophyll by extraction, we prepared the corresponding olefins (R,R)-**1b/6a/6b/3b**, possessing a (R,R)-configurated side chain (Scheme 4).

In addition to the value of the optically active intermediates, e.g. for the preparation of (2RS,4′R,8′R)-α-tocopheryl acetate




Scheme 4. Synthesis of (2-ambo)-**3b** by olefin cross-metathesis.

((2-ambo)-**3b**), we obtained information about the E/Z selectivity [15] of the cross-metathesis reactions. Independent of the E/Z ratio of the trisubstituted olefin used, mixtures of E/Z isomers in very similar ratios (around 2:1) were always obtained. A 66:34 mixture of E- and Z-products resulted even when starting from isomerically highly pure (E,R,R)-phytol (E/Z = 99.7:0.3). The E/Z ratio of starting material re-isolated (remaining in solution after 18 h of reaction time) was in the same range (E/Z = 67:33), corresponding roughly to the thermodynamic equilibrium. This suggests that E/Z isomerisation (via metathesis equilibrium) is faster than the cross-metathesis reaction.

## 3. Conclusion

In conclusion, ruthenium-catalyzed cross-metathesis has been applied successfully to the synthesis of key-intermediates in Vitamin E chemistry. The results from our studies may be of general interest for other areas of natural product synthesis, where compounds containing sterically congested and trialkyl-substituted C=C bonds are involved.

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