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Preparation of trialkyl-substituted olefins by ruthenium catalyzed cross-metathesis

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Abstract

A summary of the application of ruthenium catalyzed olefin cross-metathesis towards the synthesis of selected natural compounds is given. Recent examples for the preparation of intermediates on the way to tocopherols (vitamin E) are discussed. This group of biologically most important fat-soluble antioxidants is synthetically available by various routes, for which key-building blocks containing trialkyl-substituted olefinic double bonds can now be prepared efficiently (isolated yields up to 83%). The results presented may be of interest for the area of syntheses of isoprenoid natural products in general.

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

1. Introduction

Trisubstituted olefinic carbon–carbon bonds are widespread structural elements of many natural products. The *E*/*Z* stereochemistry of such olefins is an important feature in particular in the area of naturally occurring isoprenoid compounds, as they are predominantly not mixtures, but single-isomer products. Prominent examples, of which their unambiguous stereochemistry is defined by the biosynthetic pathway, are various plant *cis-trans*(*Z*,*E*)-polyprenols (**1**) and dolichols (**2**) [1], (all-*E*)-polyprenols (**3**), tocotrienols (**4**) [2], (all-*E*-)-coenzyme Q_{10} (**5**) [3], (*E*)-phytol (**6**) [4], and vitamin K_1 (**7**) [5] (Fig. 1). In addition, trialkyl-substituted olefins with defined *E*- or *Z*-stereochemistry are valuable building blocks for a large variety of synthetic applications.

Known synthetic methods leading efficiently to the selective, or even specific, formation of either *E*- or *Z*-stereoisomers of trisubstituted terpenoids are, however, limited. Modified Wittig procedures favour the *Z*-isomer, and classical Horner–Wadsworth–Emmons condensation protocols deliver mostly *E*-stereochemistry [6,7]. Exceptionally high stereoselectivities can be obtained with the Negishi-type zirconium catalyzed carboalumination of acetylenes [8–10] which has been applied e.g. for the synthesis of (*E*)-phytol, vitamin K_1, and coenzyme Q_{10} [11–13]. Other known coupling methods need the extensive (equimolar) use of protecting groups and metal–organic reagents, e.g. applied in routes via allyl sulfones. Efficient methods for the stereoselective homologation by a C_5 (isoprene) unit in the area of terpene chemistry are still lacking. The coupling of allylic electrophiles with allyl-type nucleophiles could be achieved in a stereoselective manner only in singular examples by using π-allylic palladium complexes in combination with strongly directing and activating leaving groups [14]. Truly catalytic synthetic strategies for such transformations are not known.

Recently, it has been demonstrated that metathesis has evolved to be a powerful tool in the synthesis of substituted olefins [15]. This methodology is, however, rather limited in the field of isoprenoids synthesis. In this article, some examples for the preparation of cyclic as well as open-chain trisubstituted C=C bonds are reviewed, and then the application of the ruthenium-catalyzed cross-metathesis for the

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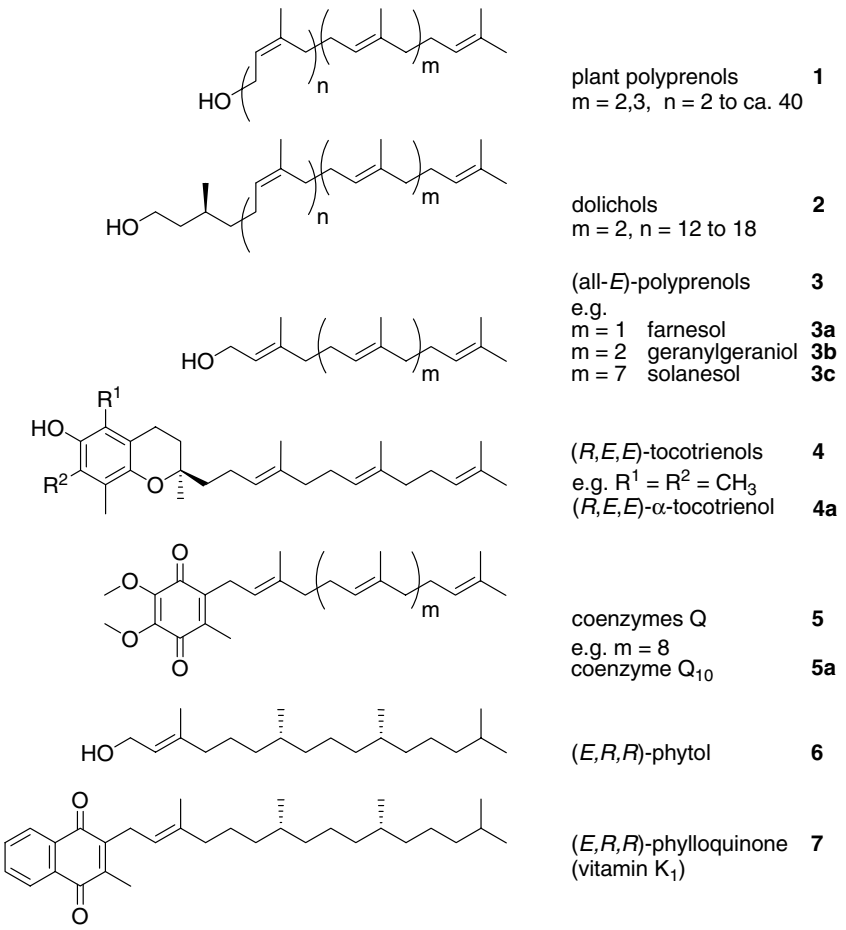


Fig. 1. Examples of isoprenoid natural products containing *E*- or *Z*-configurated trisubstituted C=C bonds.

preparation of key-intermediates in routes to the economically important vitamin E will be presented. The intention of this contribution is to summarize the results obtained in a recent study with respect to its application in the field of vitamin E chemistry and to draw the attention of the reader to the more general trends extracted from the examples on this rather specialized topic of natural product synthesis. It may also provide useful data regarding the applicability of the methodology to the synthesis of other biologically active compounds.

Vitamin E is essential for human and animal life due to its antioxidant and biological properties. Even though naturally occurring stereoisomerically pure (2*R*,4′*R*,8′*R*)-α-tocopherol (*R*,*R*,*R*-**8**) possesses the highest vitamin E activity, all-racemic α-tocopherol (all-*rac*)-**8** [16] (Fig. 2) is still

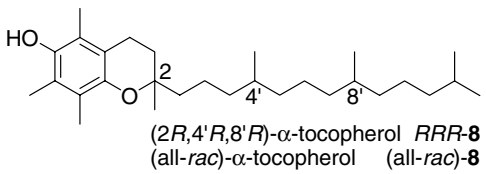


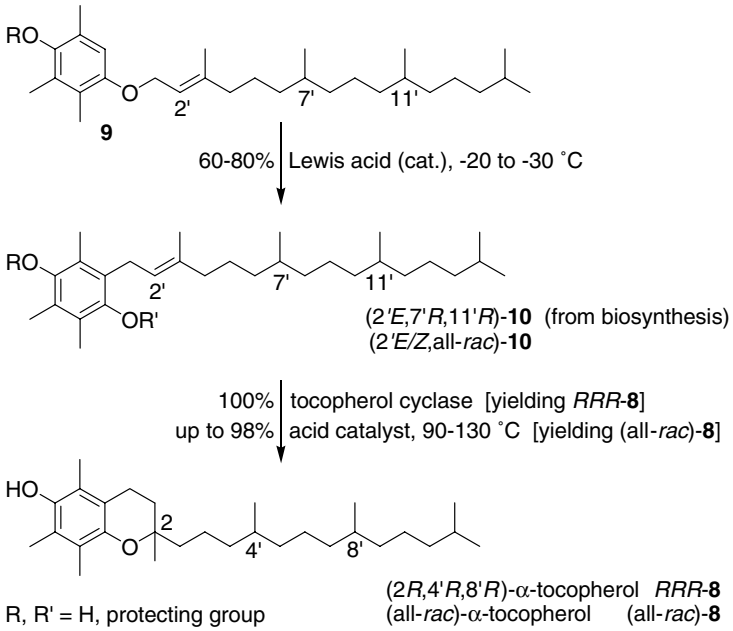
Fig. 2. Most important vitamin E compounds.

of enormous economical interest, i.e. over 25,000 tons per year are currently produced worldwide.

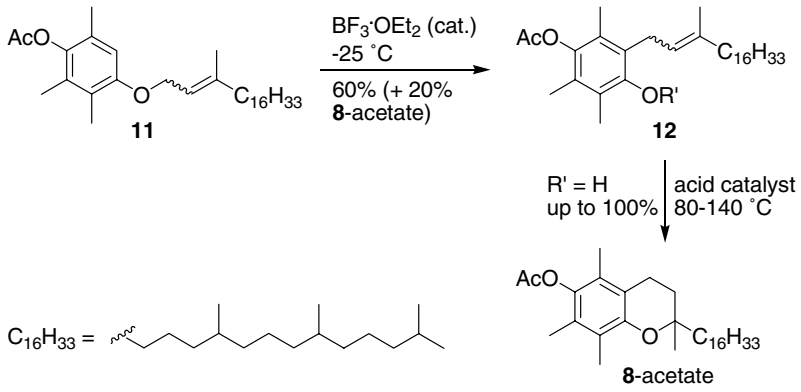
All-racemic α-tocopherol {(all-*rac*)-**8**} is prepared on industrial scale by the direct condensation reaction of trimethylhydroquinone with isophytol [16]. Regarding the construction of the tocopherol skeleton, it is known that phytylhydroquinones of type **10** are open-chain precursors in both the biosynthetic {(2′*E*,7′*R*,11′*R*)-**10**} and chemical synthetic routes {(2′*E*/*Z*,all-*rac*)-**10**} to tocopherols (Scheme 1). Hydroquinone (2′*E*,7′*R*,11′ *R*)-**10** (R = R′ = H) is an intermediate in the biosynthesis of (*R*,*R*,*R*)-**8** [17], and compound (2′*E*/*Z*,all-*rac*)-**10** can be converted chemically to (all-*rac*)-**8** [18].

Recently, it was found that allyl ethers (2′*E*/*Z*,all-*rac*)-**11**, as well as compounds **12** (R′ = H) can be used as precursors of (all-*rac*)-**8**-acetate [19] (Scheme 2).

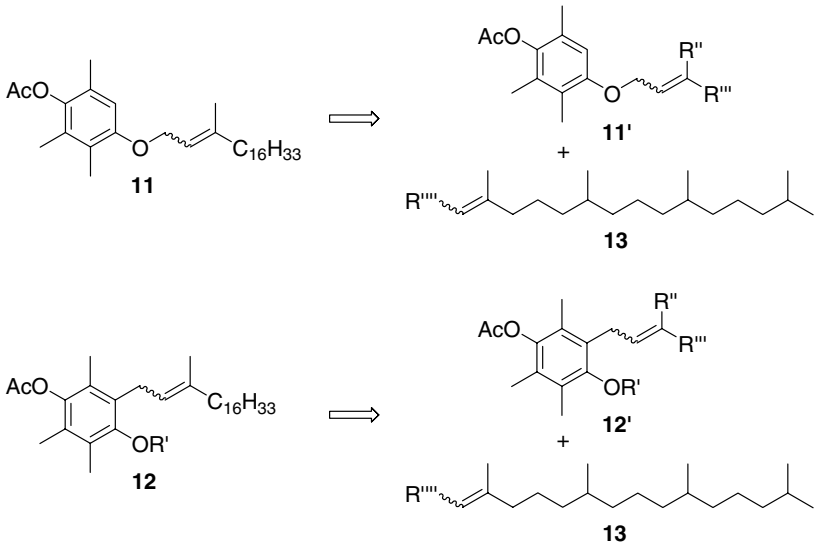
As efficient methods were investigated to convert compounds **9**/**10** and **11**/**12** into α-tocopherol **8** (or its corresponding acetate derivative) (Schemes 1 and 2), the access to olefins **11** and **12** by using olefin cross-metathesis methodology was envisaged from olefin **13** and olefins **11**′ and **12**′ (Scheme 3). Olefin metathesis has developed recently to a synthetically powerful method [15,20] for obtaining bioactive products [21].



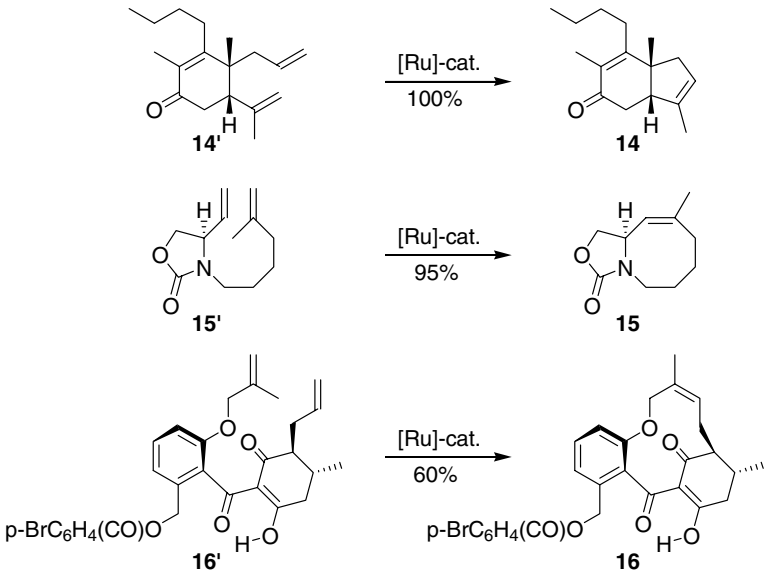
Scheme 1. Synthesis of tocopherols from open-chain precursors.



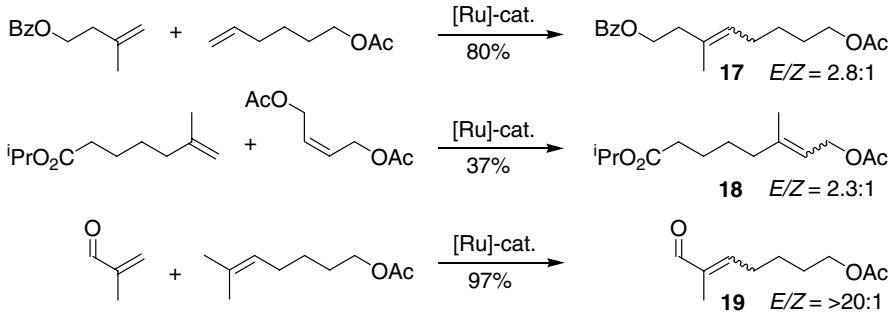
Scheme 2. Preparation of vitamin E acetate from open-chain precursors.



Scheme 3. Retrosynthetic scheme for the synthesis of open-chain precursors of vitamin E acetate.



Scheme 4. Examples of ring closing metathesis reactions yielding trisubstituted (hetero-)cycloalkenes.



Scheme 5. Examples of cross-metathesis reactions leading to trisubstituted olefins as *E*/*Z* mixtures.

The formation of trisubstituted olefins can be challenging, but ring closing metathesis (RCM) reactions have on the rare occasion been successfully used in the synthesis of functionalized intermediates during preparation of natural products, such as **14** [22], **15** [23], and **16** [24] (Scheme 4).

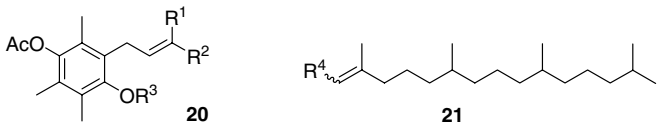
While RCM is be difficult to make trisubstituted cycloalkenes, the synthesis of open-chain trisubstituted olefins by metal-catalyzed cross-metathesis is even more difficult to achieve and, in general, poor *E*/*Z* selectivities are observed [25]. For example, trisubstituted olefins such as **17** [26], **18** [27], and **19** [28] were obtained as *E*/*Z* mixtures by using a cross-metathesis reaction (Scheme 5).

In this context it is worth noting, that cross-metathesis is applied in large-scale industrial processes (the Shell-Higher-Olefin-Process SHOP, the Further-Exploitation-of-Advanced-Shell-Technology FEAST, and the Phillips Triolefin Process) [15,20].

2. Results and discussion

Based on such information, a project using olefin cross-metathesis for the preparation of vitamin E key-intermediates such as compounds **11** and **12** was examined at DSM Nutritional Products (former Roche Vitamins) [29]. At first, cross-coupling reactions were examined between various olefins of type **20** and various olefins of type **21** in order to obtained compounds of type **12**, precursors of vitamin E (Fig. 3).

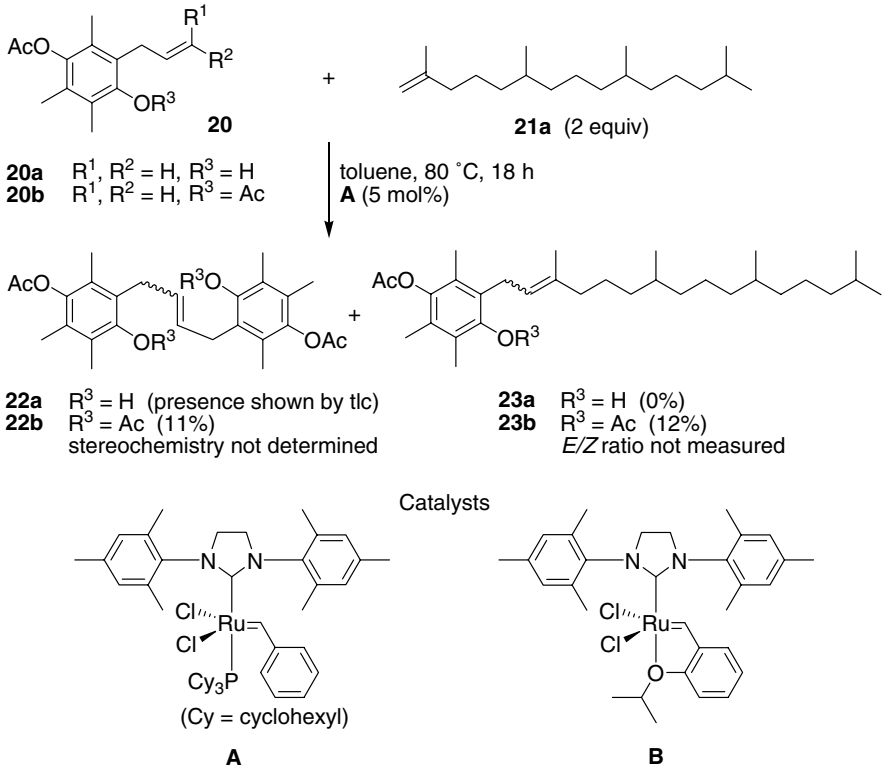
The cross-metathesis reaction was achieved under standard conditions [30], e.g. in toluene and in the presence of the second-generation Grubbs catalyst **A** or Hoveyda-Grubbs catalyst **B** (5 mol%), and in the presence of 2 equiv.



20a R^1, R^2 = H, R^3 = H
20b R^1, R^2 = H, R^3 = Ac
20c R^1, R^2 = CH_3, R^3 = H
20d R^1, R^2 = CH_3, R^3 = Ac
20e R^1, R^2 = CH_3, R^3 = $SiBu_3$
20f R^1, R^2 = CH_3, R^3 = $SiMe_2$t-Bu

21a R^4 = H
21b R^4 = CH_2OH
21c R^4 = $CH_2OC(O)H$
21d R^4 = $CH_2OC(O)Me$
21e R^4 = $CH_2OC(O)Ph$

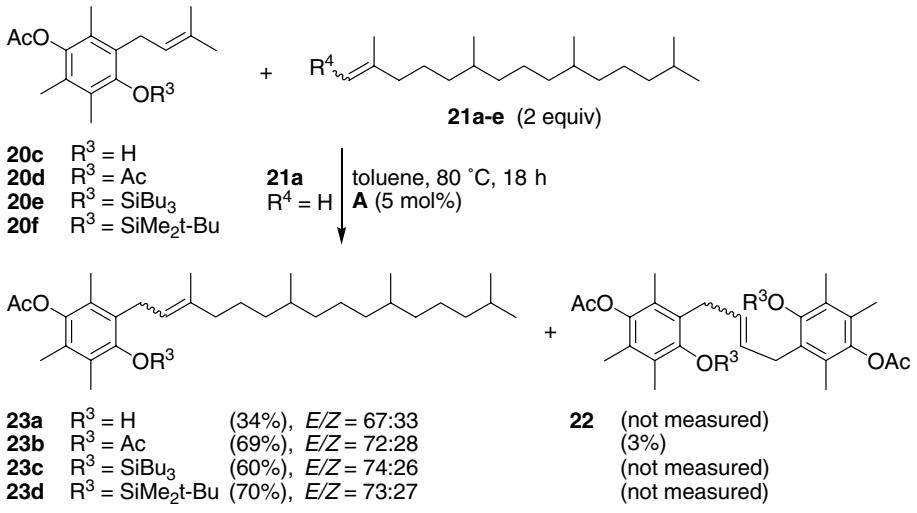
Fig. 3. Olefinic starting materials for cross-metathesis reactions on the way to vitamin E intermediates.



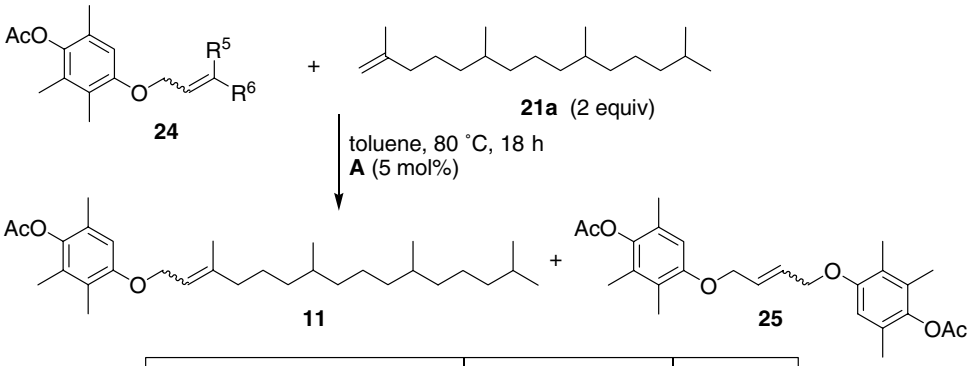
Scheme 6. Cross-metathesis reactions of terminal olefins **20a**,**b**.

of **21** (Scheme 6). With the terminal olefins **20a** and **20b**, the cross-metathesis is very slow or no reaction takes place. Furthermore, dimeric homo-coupling products **22** were isolated from the reaction mixtures, while the desired products **23** were obtained in disappointingly low yields (0% and 12%). Unexpectedly, dimers of type **22** could not be used as the starting materials, as a very slow reaction takes place and compounds of type **23** were not formed (Scheme 6).

The situation changed completely when dimethyl substituted olefins **20c**–**f** were used. Compounds of type **23** were isolated in 31–70% yield as a *E*/*Z* mixtures (66:34 to 74:26) and dimers of type **22** were found only in traces (0–4%) (Scheme 7). The functional groups R^4 in compounds of type **21** (see Fig. 3) have an influence on the outcome of the coupling reactions. For example, the allylic alcohol phytol **21b** ($R^4 = CH_2OH$) gave no conversion at all, in contrast to the protected alcohol derivatives **21c** {$R^4 = CH_2OC(O)H$}, **21d** {$R^4 = CH_2OC(O)Me$}, and **21e** {$R^4 = CH_2OC(O)Ph$}, which were transformed into the desired compounds **23** in yields of 31%, 46%, and 50%,



Scheme 7. Cross-metathesis reactions of *C*-dimethylallyl precursors **20c**–**f** (only selected examples with olefin **21a**, $R^4 = H$, are shown).

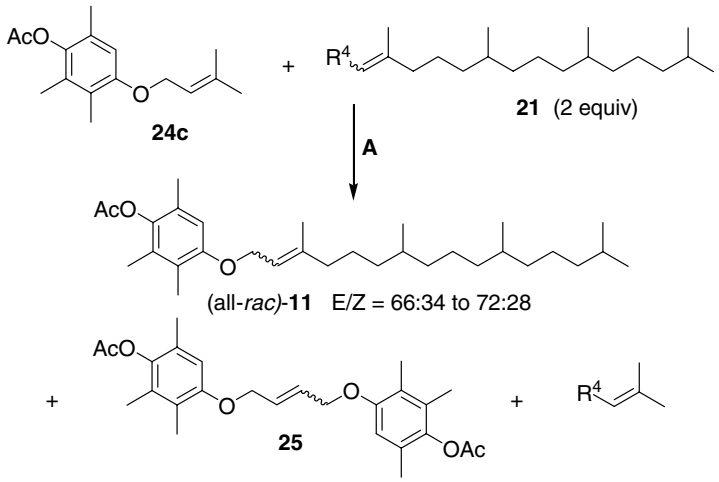


24		yield 11	E/Z	yield 25
24a	R^5 = H, R^6 = H	29%	72:28	33%
24b	R^5 = CH_3, R^6 = H	51%	66:34	6%
24c	R^5 = CH_3, R^6 = CH_3	73%	67:33	<1%

Scheme 8. Cross-metathesis reactions of *O*-allyl precursors **24**.

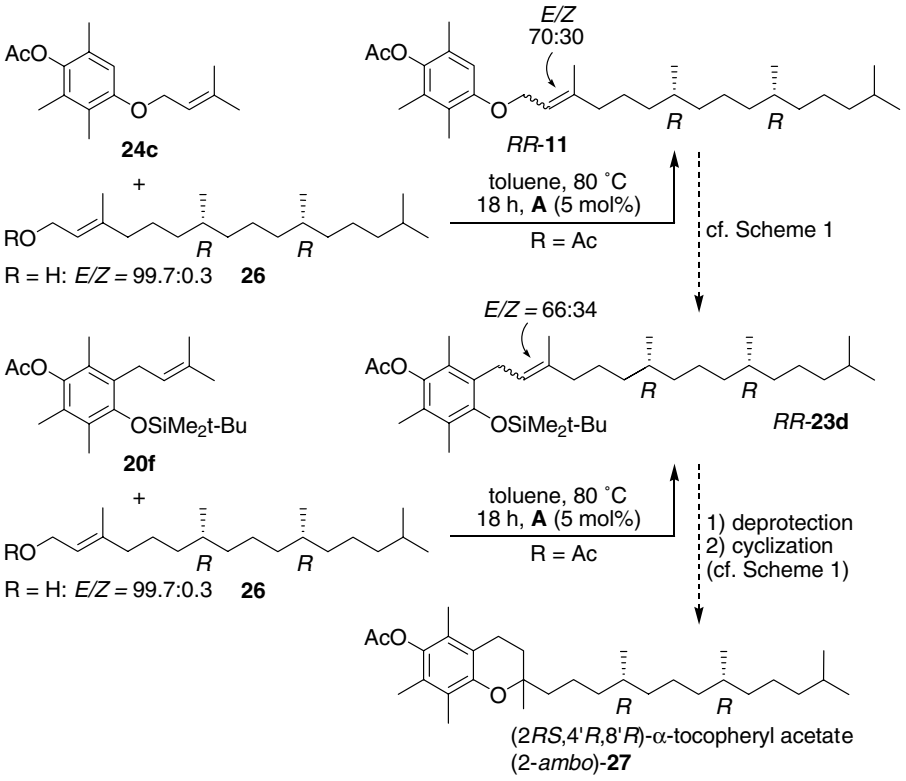
respectively. The catalyst, e.g. **A** or **B**, as well as the amount of the catalyst have no effect on the reaction as similar yields in compounds of type **23** were isolated. On the contrary, toluene is a better solvent than dichloromethane and tetrahydrofuran as by using these two latter solvents, the yields of **23** were decreased and are inferior to 20%.

Similar effects were observed in the preparation of *O*-allyl ethers of type **11** from different substituted olefins of type **24** and **21** (Scheme 8). Compounds of type **11** were obtained from the coupling of **21a** with **24a**, **24b**, **24c** in 29%, 51%, and 73%, respectively, accompanied by dimer **25** in 33% from **24a**, 6% from **24b**, and <1% from **24c**. It



21, R^4	solvent	conc. 24c	A	pressure	yield 11	yield 25
H	toluene	0.04 M	5 mol%	ambient	73%	<1%
H	toluene	0.04 M	10 mol%	ambient	68%	n.d.
H	toluene	0.16 M	5 mol%	ambient	68%	2%
H	none	ca. 2.5 M	5 mol%	ambient	67%	n.d.
H	none	ca. 2.5 M	5 mol%	33 mbar	83%	n.d.
$CH_2OC(O)H$	toluene	0.04 M	5 mol%	ambient	67%	n.d.
$CH_2OC(O)Me$	toluene	0.04 M	5 mol%	ambient	59%	n.d.
$CH_2OC(O)Ph$	toluene	0.04 M	5 mol%	ambient	58%	n.d.
						n.d. = not detected

Scheme 9. Optimization of the cross-metathesis reaction of substrate **24c**.



Scheme 10. Preparation of optically active vitamin E intermediates by olefin cross-metathesis.

can be easily deduced from these results, that the substitution pattern of olefin **24** has a dramatic impact on the formation of both products **11** (isolated yields) and dimer **25** (yields determined by GLC with tridecane as an internal standard). The best results were obtained with compound **24c**.

Screening of the various R^4 substituents present in compounds of type **21** did not result in a major change in the formation of **11**. The best results were obtained when solvent-free conditions were used, and by running the reaction under vacuum in order to eliminate isobutene which is formed during the reaction, and in consequence to shift the equilibrium of the reversible metathesis reaction towards the formation of product **11** (Scheme 9).

The optimized coupling conditions (5 mol% **A**, toluene, 80 °C, 18 h) were also applied to the synthesis of optically active building blocks. Based on the easy availability of natural (*E*,*R*,*R*)-phytol, which is the major degradation product coming from the extraction of green plants' chlorophyll, compound (*R*,*R*)-**11** was synthesized efficiently from (*R*,*R*)-**26** and **24c**, and (*R*,*R*)-**23d** from (*R*,*R*)-**26** and **20f** (Scheme 10). In addition to the efficient synthesis of the optically active (2*RS*,4′*R*,8′*R*)-α-tocopheryl acetate {(2-*ambo*)-**27**}, the results provide some insight into the stereoselectivity of the cross-metathesis reactions. Independently of the *E*/*Z* ratio of the trisubstituted olefin **26**, a mixture of *E*/*Z* isomers were always obtained in very similar ratios (66:34 to 70:30). Even when the isomerically highly pure (*E*,*R*,*R*)-phytol (**26**, R=H, *E*/*Z* = 99.7:0.3) is used, compounds (*R*,*R*)-**11** and (*R*,*R*)-**23d** were obtained as ca. 2:1 mixtures of (*E*)- and (*Z*)-isomers, and the *E*/*Z* ratio of the recovered olefin **26** is around 67:33 which corresponds roughly to the thermodynamic equilibrium. This is in agreement with the values obtained for the examples **17** and **18** (Scheme 5), and for trialkyl-substituted products obtained by other methods (cf. e.g. Refs. [5,18,19]).

In summary, preparatively useful conditions for the synthesis of key-intermediates for vitamin E chemistry by applying cross-metathesis catalyzed by ruthenium-complexes have been developed. The results presented here may find broader interest in other areas of natural products synthesis, in particular for the preparation of compounds containing sterically congested and trialkyl-substituted C=C bonds.

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