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Zr-Catalyzed Carboalumination: A New Route to Tocotrienols

Thomas Netscher,[a] Robert K. Müller,[a] Heinz Schneider,[a] Ei-ichi Negishi[b]

[a]DSM Nutritional Products, Research and Development, P.O. Box 2676, CH-4002 Basel, Switzerland; E-mail: thomas.netscher@dsm.com

[b]Brown Laboratory of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084, USA

Abstract. Vitamin E, consisting of the groups of tocotrienols and tocopherols, is the biologically most important fat-soluble antioxidant. In the context of total synthesis of these compounds, the Zr-mediated carbometalation methodology was applied. (*E*)-Geranylacetone was converted into the corresponding terminal alkyne which furnished the (all-*E*)-alkenyl iodide by carboalumination/ iodonolysis. Treatment with butyl lithium delivered the (all-*E*)-vinyl lithium compound for the coupling with (enantiomerically pure) benzyl *O*-protected chroman acetaldehydes. Reductive deoxygenation of the protected 2'-hydroxy-tocotrienols yielded various stereochemically defined homologous trienols.

Keywords. Vitamin E, tocopherols, tocotrienols, trisubstituted olefins, stereoselectivity, polyprenoids

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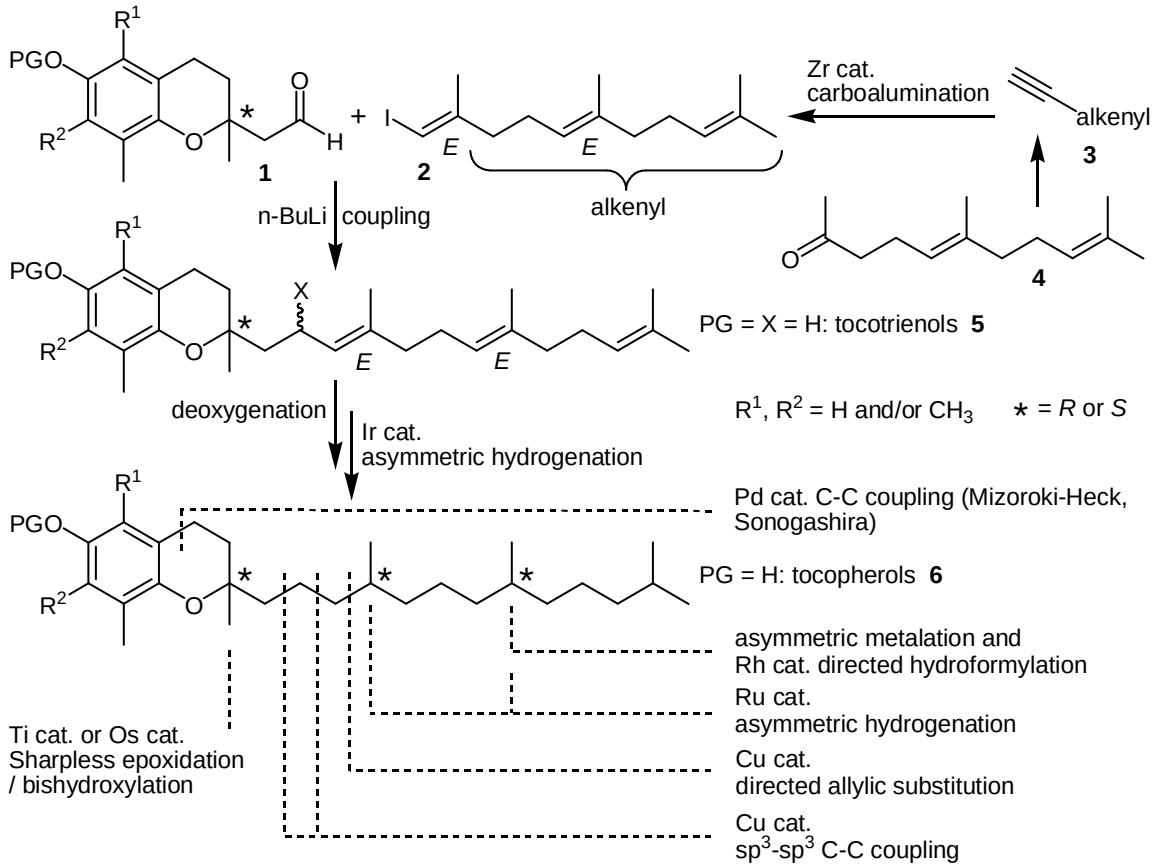
Introduction

Tocotrienols **5** and tocopherols **6** are members of the group of vitamin E compounds, which represent the most important lipid-soluble antioxidant in nature.[1] During our activities in this field, we have developed a variety of routes towards naturally occurring tocopherols, mostly containing metal-catalyzed transformations as the key steps. An overview is sketched in **Scheme 1**[2]. An extraordinary approach to tocopherols **6** was found by application of the highly stereoselective Ir-catalyzed asymmetric hydrogenation, starting from derivatives of (all-*E*)-tocotrienols **5**.[3] In this regard, the access to tocotrienols is of increasing importance. Isolation of pure tocotrienols from natural sources is troublesome, and only a few synthetic routes have been developed to date[2b].

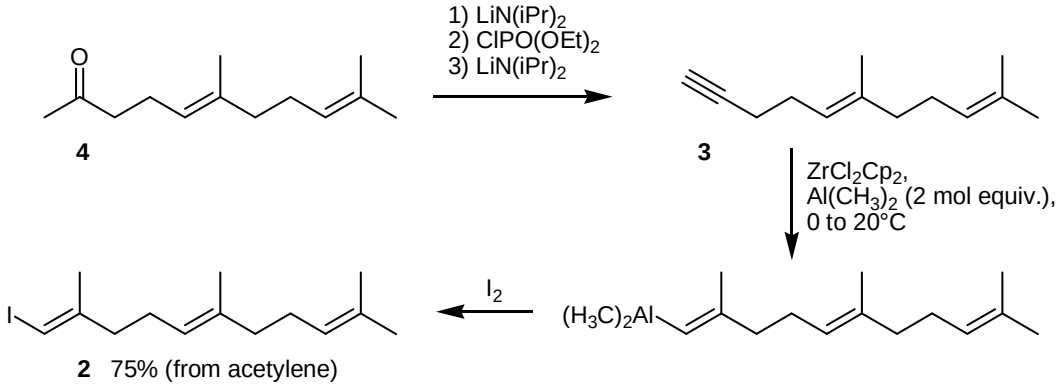


Scheme 1. Overview on known routes to tocopherols (**6**) and stereoselective total synthesis of tocotrienols (**5**) described in this work.

We therefore envisioned the pathway shown in **Scheme 1**. Starting from easily available (*E*)-geranylacetone (**4**), alkyne **3** should be used as the starting material for the zirconium-catalyzed carboalumination methodology[4], thus delivering the stereodefined trienyl building block **2** for coupling with chroman compounds of type **1**.

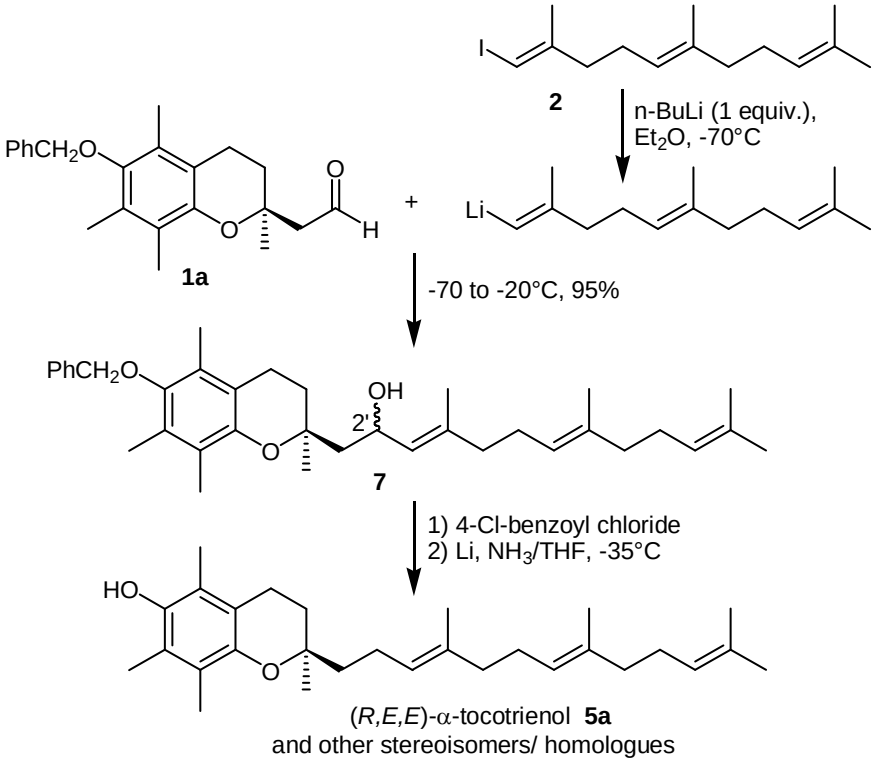
Results

The conversion of methyl ketone **4** into the terminal acetylene **3** was achieved by the two-step, but one-pot procedure via the diethyl enolphosphate[5] (**Scheme 2**) in 45% isolated yield. For such transformations in polyprenoid chemistry, more suitable alternative methods are still not available. Best results for the carboalumination-iodonolysis sequence (**3**→**2**) were obtained by treatment of alkyne **3** with 2 mol equiv. trimethylaluminum in presence of 1 mol equiv. $ZrCl_2Cp_2$ (0°C to room temp.). After addition of iodine and work-up, (all-*E*)-alkenyl iodide **2** was isolated in 75%.



Scheme 2. Transformation of (*E*)-geranylacetone (**4**) to (all-*E*)-alkenyl iodide **2** by Zr-catalyzed carboalumination and iodonolysis.

For the coupling step with the chroman unit, iodine-lithium exchange with n-BuLi (-70°C, Et_2O) delivered the vinyl-lithium compound which was reacted with the benzyl protected enantiomerically pure chroman acetaldehyde **1a**. Alcohol **7** was obtained in up to 95% isolated yield as a 3:1 epimeric mixture.



Scheme 3. Final steps of tocotrienol synthesis by coupling and reductive deoxygenation/ deprotection.

Deoxygenation and concomitant benzyl ether cleavage were achieved by esterification of the 2'-hydroxy function with 4-chlorobenzoyl chloride and subsequent reduction with 10 mol equiv. Li in NH_3/THF (-35°C), thus yielding (*R*,*E*,*E*)-α-tocotrienol (**5a**). Spectroscopic data of **5a** and its acetate derivative were identical with the values published, and the optical purity (generally >99.5%) was analyzed by chiral-phase HPLC. By applying the same methodology, various other stereochemically defined tocotrienols, i.e. enantiomers and homologous [e.g. by using (all-*E*)-farnesylacetone (C_{18}) instead of (*E*)-geranylacetone (C_{13})], were prepared.

Conclusions

The Zr-catalyzed carbometalation methodology was applied successfully to the preparation of various isomeric and homologous tocotrienols and their derivatives. While this sequence is not applicable to large-scale synthesis due to the high amounts of reagents necessary, it serves as a reliable laboratory method for the preparation of stereochemically defined tocotrienols in gram amounts for analytical, synthetic, and biological studies.

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