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Stereocontrolled Generation of the (2*R*) Chroman Core of Vitamin E: Total Synthesis of (2*R*,4′*RS*,8′*RS*)-α-Tocopherol

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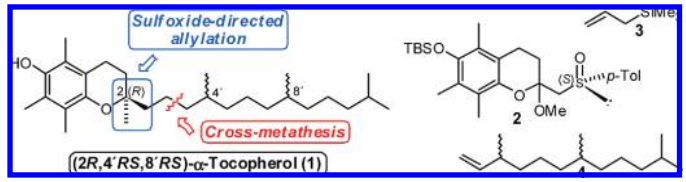
ABSTRACT



(2*R*,4′*RS*,8′*RS*)-α-Tocopherol (1) was prepared using, as the two key steps, a novel diastereoselective $TiCl_4$-promoted (*S*)-sulfoxide-directed allylation of ketal 2 with allyl trimethyl silane 3 to efficiently generate the challenging (2*R*) stereocenter of the chroman moiety and a cross-metathesis reaction with olefin 4 to efficiently join the lipophilic alkyl chain present in the final target.

(*R*,*R*,*R*)-α-Tocopherol (**1**) is the biologically most active member of the vitamin E family as a natural lipophilic antioxidant and radical scavenger.[1] In particular, **1** protects polyunsaturated fatty acids, other components of the cell membrane, and low-density lipoproteins (LDL) by capturing highly reactive free radicals formed in the body as byproduct of natural oxidative metabolism.[2,3]

Tocopherols possess a shikimate-derived aromatic moiety and a terpenoid side chain leading to a 6-chromanol framework with a (*R*) stereogenic center at C-2 and two (*R*) stereocenters at the saturated chain (Figure 1). Industrially, α-tocopherol is produced on a large scale as a mixture of all eight possible stereoisomers, (*all-rac*)-**1**.[4] Recent studies have shown that (2*S*)-configured tocopherols have no antioxidant effect in biological systems because they are not accepted as substrates by the α-tocopherol transfer protein (TTP), which is responsible for the transport of vitamin E into the tissue.[5] On the other hand, the configuration of the stereogenic centers in the side chain appears to have no influence on the antioxidant effect.[5] As a result, (*all-rac*)-**1** exhibits a maximum of 50% of the biological activity of (*R*,*R*,*R*)-**1**. Therefore, there is considerable interest in devel-

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oping processes for the enantioselective synthesis of vitamin E with special attention to the construction of the (*R*) stereogenic center at C-2, which is the more challenging task.

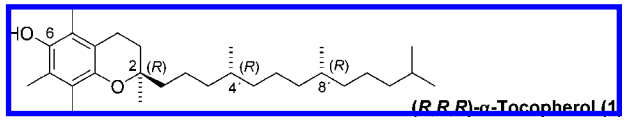


Figure 1. Structure of (*R*,*R*,*R*)-α-tocopherol (**1**).

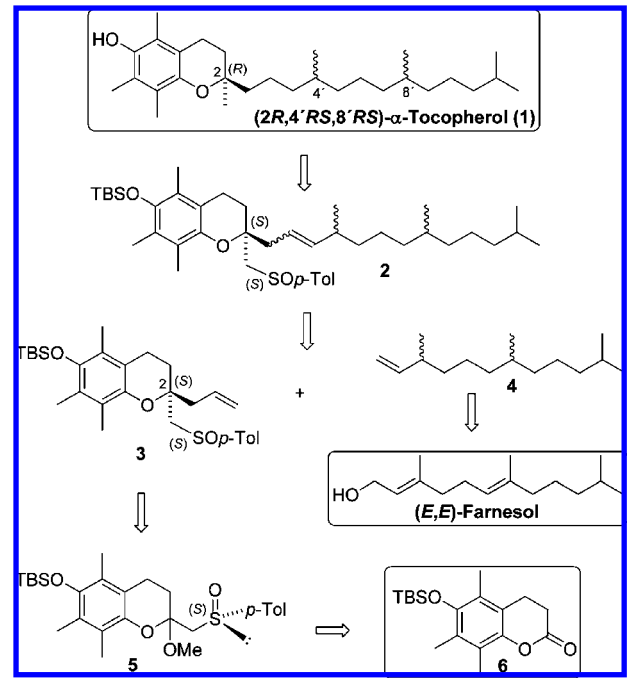
Concerning the overall synthetic strategy, the three major problems of the total synthesis of (*R*,*R*,*R*)-**1** are the formation of the chiral chroman ring,[6] the introduction of the two chiral centers in the aliphatic side chain, and the coupling of chroman and side chain building blocks.[7a] General routes have used classical optical resolutions, biocatalysis, chiral-pool starting materials, the application of chiral auxiliaries, and asymmetric catalysis.[7]

Among the many types of transition-metal-catalyzed carbon−carbon bond-forming reactions, olefin metathesis has attracted widespread attention from the synthetic community in recent years and has become a powerful tool for organic chemists.[8] Nevertheless, to the best of our knowledge, the only example described in the literature for the olefin cross-metathesis (CM) reaction applied to the synthesis of vitamin E intermediates has been recently reported by Netscher et al.[9]

Herein, we describe a short synthesis of (2*R*,4′*RS*,8′*RS*)-α-tocopherol (**1**) using a novel diastereoselective (*S*)-sulfoxide-directed[10] allylation to generate the challenging (*R*) stereogenic center at C-2 of the chroman unit and a cross-metathesis reaction to join the alkyl chain present in the final target.

As can be seen in the retrosynthetic Scheme 1, (2*R*,4′*RS*,8′*RS*)-**1** could be obtained from an advanced

Scheme 1. Retrosynthesis towards (2*R*,4′*RS*,8′*RS*)-α-Tocopherol (**1**)



intermediate such as **2**, after desulfinylation, double bond reduction, and OTBDMS deprotection. The assembly of the full carbon skeleton of **2** would be possible after a cross-metathesis reaction between allyl sulfinyl chroman **3** and olefin **4**, which in turn could be available from (*E*,*E*)-farnesol after simple transformations. Compound **3**, showing the correct absolute configuration at the C-2 stereogenic center, would be formed by a diastereoselective sulfoxide-directed allylation of ketal **5**, which could be obtained from 3,4-dihydrocoumarin **6**.

The stereoselective synthesis of the chroman moiety of α-tocopherol (**1**), (*S*,*SS*)-**3**, is depicted in Scheme 2 and started with known OTBS-protected 3,4-dihydrocoumarin **6**,[11] which was submitted to reaction with the LDA-generated lithium anion of (*S*)-methyl *p*-tolyl sulfoxide[12] to afford sulfinyl chromanol **7**, in 73% yield. After ketalization of **7** [$CH(OMe)_3$, *p*-TsOH, 87%], the resulting 2-methoxy-3,4-dihydro-benzopyran **5**, obtained as mixture of stereoisomers at C-2, was submitted to the key step formation of the C-2 stereogenic center of the chroman unit through a sulfoxide-directed Lewis acid promoted nucleophilic substitution reaction.[13] After trying several nucleophiles (Me_3Al, $Me_3SiCH_2CH{=}CH_2$), Lewis acids (TBDMSOTf, $TiCl_4$, $ZrCl_4$), and experimental conditions, we found that the best results, in terms of diastereoselectivity and yield, were achieved from reaction of **5** with allyl trimethyl silane (3

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(11) Compound **6** was prepared in two steps (see Supporting Information) from commercially available trimethyl hydroquinone following a modification of a previously described procedure:Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527–532.

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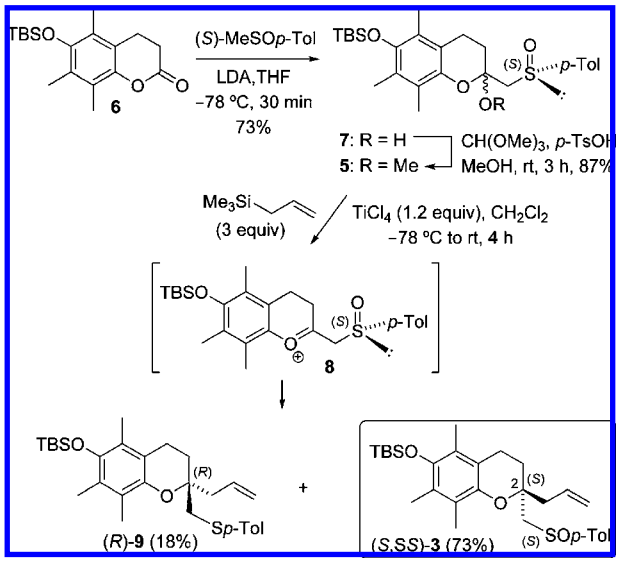
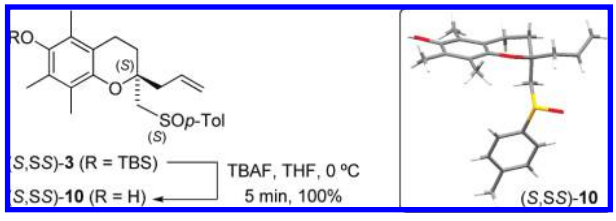
Scheme 2. Diastereoselective Synthesis of Chroman (*S*,*SS*)-**3**



equiv) in the presence of $TiCl_4$ (1.2 equiv) in CH_2Cl_2 at −78 °C. Under these conditions, a difficult to separate 81:19 mixture of (*S*,*SS*)-**3** and the corresponding epimer at C-2 was obtained. Fortunately, when the reaction mixture was allowed to warm to rt, a mixture of allyl sulfinyl chroman (*S*,*SS*)-**3** and thioether (*R*)-**9**[14] was obtained, from which (*S*,*SS*)-**3** could be isolated in a remarkable 73% yield. The stereoselective (*S*)-sulfoxide-directed addition of the allylsilane to the upper face of oxocarbenium intermediate **8**, formed after the $TiCl_4$-promoted elimination of the methoxy group present in the starting material **5**, explains the formation of (*S*,*SS*)-**3**.

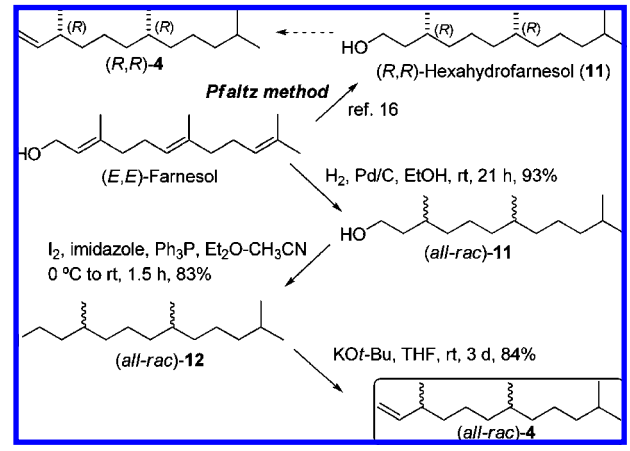
Thus, we have performed the stereoselective synthesis of the chroman fragment of (2*R*,4′*RS*,8′*RS*)-α-tocopherol (**1**), (*S*,*SS*)-**3**, in only three steps from known starting material **6**, with 49% overall yield.

Scheme 3. Synthesis and X-ray ORTEP of Sulfinyl Chroman (*S*,*SS*)-**10**



The absolute configuration of the newly created stereogenic center at C-2 of chroman (*S*,*SS*)-**3** could not be determined at this stage, but after transformation into the OH free derivative (*S*,*SS*)-**10** (TBAF, THF, 0 °C, 5 min, 100%), suitable crystals were collected for X-ray analysis[15] (Scheme 3).

Scheme 4. Synthesis of Olefin (*all-rac*)-**4** from (*E*,*E*)-Farnesol



With the appropriately substituted (2*S*)-chroman moiety in hand, we turned our attention to the synthesis of the lipophilic alkyl chain present in the final target. Very recently, Pfaltz et al.[16] have reported an enantioselective hydrogenation protocol to efficiently transform (*E*,*E*)-farnesol into (*R*,*R*)-hexahydrofarnesol (**11**), with 91% yield and 99% ee (Scheme 4), which could serve us as starting material for the synthesis of natural (*R*,*R*,*R*)-α-tocopherol via (*R*,*R*)-**4**. Nevertheless, taking into account that the necessary chiral catalyst is not commercially available, we decided to validate our initially proposed CM strategy by using a racemic analogue. Thus, (*E*,*E*)-farnesol was fully hydrogenated (H_2, Pd/C, EtOH, rt, 21 h, 93%)[17] into hexahydrofarnesol (*all-rac*)-**11**, which was converted into iodide (*all-rac*)-**12**, by treatment with iodine in the presence of imidazole and triphenyl phosphine (Et_2O-CH_3CN, 0 °C to rt, 1.5 h), with 83% yield. Finally, dehydroiodination of **12** with potassium *tert*-butoxide furnished olefin (*all-rac*)-**4**, in 84% yield (Scheme 4). Thus, we could prepare the alkyl chain of (2*R*,4′*RS*,8′*RS*)-α-tocopherol (**1**), (*all-rac*)-**4**, in only three steps from commercially available (*E*,*E*)-farnesol, with 65% overall yield.

Having efficiently synthesized the two main fragments of (2*R*,4′*RS*,8′*RS*)-α-tocopherol (**1**), sulfinyl chroman **3**, and alkyl chain **4**, we undertook their coupling using a cross-metathesis approach (Scheme 5). After trying several experimental conditions, we found that the best yield was achieved by heating, under microwave irradiation,[18] a mixture of allyl chroman (*S*,*SS*)-**3** and 2.9 equiv of olefin

(14) (*R*)-**9** was shown to proceed from the reduction of a small percentage of the sulfoxide epimer at C-2 of (*S*,*SS*)-**3**, probably produced by the presence of the Lewis acid $TiCl_4$.

(15) CCDC 730815 for (*S*,*SS*)-**10** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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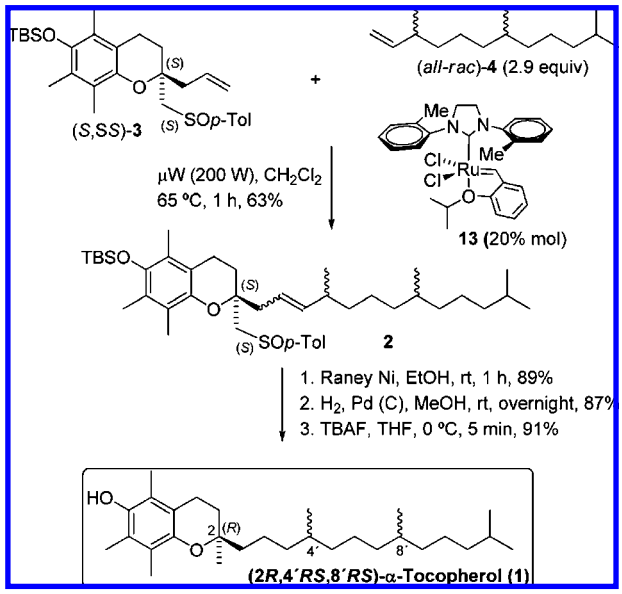
Scheme 5. Completion of Synthesis of (2*R*,4′*RS*,8′*RS*)-α-Tocopherol (**1**)



(*all-rac*)-**4** in the presence of 20 mol % of the commercially available modified second-generation Grubbs−Hoveyda ruthenium catalyst **13**. Under these conditions, compound (*S*,*SS*)-**2**, bearing the full carbon skeleton of α-tocopherol (**1**), was isolated in 55% yield, after chromatographic purification (63% yield based on recovered starting material).[19] To the best of our knowledge, this is the first example described in the literature for a successful cross-metathesis reaction of a sulfoxide-containing olefin.[20] Finally, (2*R*,4′*RS*,8′*RS*)-**1** could be obtained from **3** after desulfinylation (Raney Ni, EtOH, rt, 1 h, 89%), double bond reduction [H_2, Pd (C), MeOH, rt, overnight, 87%], and OTBS deprotection (TBAF, THF, 0 °C, 5 min, 91%), with >99% ee.[21]

In conclusion, we have reported a new, short and efficient total synthesis of (2*R*,4′*RS*,8′*RS*)-α-tocopherol (**1**) in only seven steps for the longest linear sequence and 10 total steps, starting from a known 3,4-dihydrocoumarin and commercially available (*E*,*E*)-farnesol, with 24.4% overall yield. The two key features of our synthetic approach were a novel homochiral sulfoxide-directed ionic allylation of a 2-chromanol derivative to create the challenging stereogenic center at C-2, and a cross -metathesis reaction to efficiently couple the lipophilic alkyl chain present in the final target. To the best of our knowledge, the described synthesis is one of the shortest procedures reported to date for the preparation of a (2*R*)-configured tocopherol. Moreover, our methodology represents a new access to natural (*R*,*R*,*R*)-α-tocopherol by combining with the enantioselective hydrogenation protocol reported by Pfaltz.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all compounds, and X-ray data in CIF format for (*S*,*SS*)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) When the same reaction was performed in absence of microwave irradiation, compound **2** was isolated pure in 48% yield.

(20) For an unsuccessful attempt, see:(a) Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R.; Grela, K. *Tetrahedron* **2003**, *59*, 4525–4531. For a few examples of ring-closing metathesis chemistry applied to sulfoxides, see: (b) Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem*. **2004**, *69*, 2750–2754. (c) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2002**, 1987–1990. (d) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett*. **2001**, *3*, 703–706.

(21) The optical purity was determined by HPLC allowing separation of the C-2 diastereoisomers [Daicel Chiralpack IB, 1% *i*-PrOH in hexane, 1.0 mL/min, 254 nm, $t_{(2R,4'RS,8'RS)} = 12.2$ min, $t_{(2S,4'RS,8'RS)} = 13.4$ min].