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Synthesis of (2*R*,8′*S*,3′*E*)-δ-tocodienol, a tocoflexol family member designed to have a superior pharmacokinetic profile compared to δ-tocotrienol

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ABSTRACT

A group of side chain partially saturated tocotrienol analogues, namely tocoflexols, have been previously designed in an effort to improve the pharmacokinetic properties of tocotrienols. (2*R*,8′*S*,3′*E*)-δ-Tocodienol (**1**) was predicted to be a high value tocoflexol for further pharmacological evaluation. We now report here an efficient eight-step synthetic route to compound **1** utilizing naturally-occurring δ-tocotrienol as a starting material (24% total yield). The key step in the synthesis is oxidative olefin cleavage of δ-tocotrienol to afford the chroman core of **1** with retention of chirality at the C-2 stereocenter.

1. Introduction

Tocotrienol, and its tocopherol counterpart belong to the vitamin E family. Both tocotrienol and tocopherol have α-, β-, γ-, and δ-homologues and share a common 6-hydroxychroman moiety, with tocotrienol having an unsaturated farnesyl side chain that differs from the saturated phytyl side chain in tocopherol (Fig. 1). Tocotrienols have been shown to have many bioactivities that are often not observed with tocopherols.[1] Both tocopherols and tocotrienols have been investigated for their use as potential radiation protectors. Among them, γ- and δ-tocotrienol exhibit the most significant radioprotective effects.[2] However, both γ- and δ-tocotrienol have low bioavailability and short plasma elimination half-lives[3] that limit their exposure in systemic circulation and require that they be administered in large doses.[2] The low bioavailability and short half-live of γ- and δ-tocotrienol are, at least in part, caused by their weak binding affinity to α-tocopherol transfer protein (α-TTP). α-TTP is a specific transport protein responsible for transferring the vitamin E compounds out of the liver, where they are subject to metabolism, into the systemic circulation.[4] α-Tocopherol is rapidly secreted from the liver into plasma because it has the highest affinity for α-TTP out of all vitamin E homologues.[5] In contrast, γ- and δ-tocotrienol are restrained in the liver due to

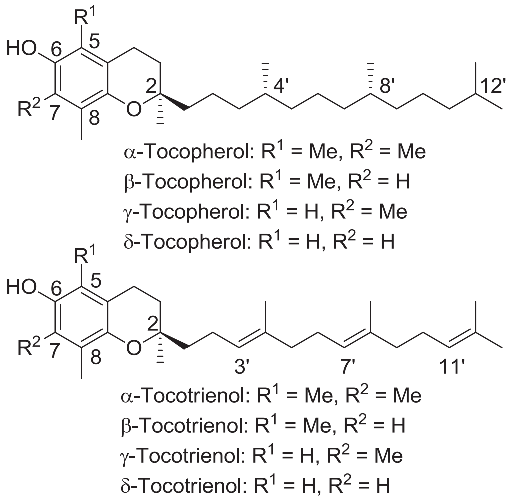

Fig. 1. Structures of naturally occurring tocopherols and tocotrienols.

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their low affinity for α-TTP. As a result, the estimated apparent elimination half-lives of γ-tocotrienol ($t_{1/2}$=4.3 h) and δ-tocotrienol ($t_{1/2}$=2.3 h) in humans are 4.5- and 8.7-fold shorter, respectively, than α-tocopherol ($t_{1/2}$=20 h).[3]

The crystal structures of naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol bound to α-TTP reveal that the C4′–C9′ fragment of the saturated phytyl side chain in the α-tocopherol molecule is bent into a U-shape.[6] It is difficult for the C4′–C9′ fragment in the farnesyl chain of tocotrienol to take up the same shape because of the relatively high rigidity caused by the presence of the Δ3′ and Δ7′ double bonds, which compromises the incorporation of tocotrienols into the binding pocket of α-TTP. These observations prompted us to design more flexible analogues with enhanced bendability in their side chains by saturating Δ3′ and/or Δ7′ double bonds in the δ-tocotrienol molecule. This group of 'flexible' δ-tocotrienol analogues was collectively termed tocoflexols, from which (2*R*,8′*S*,3′*E*)-δ-tocodienol (**1**, Fig. 2) was identified as a compound with the highest affinity for α-TTP through a vigorous molecular dynamics-based screening program.[7] Herein, we describe the synthesis of compound **1** from naturally-occurring δ-tocotrienol.

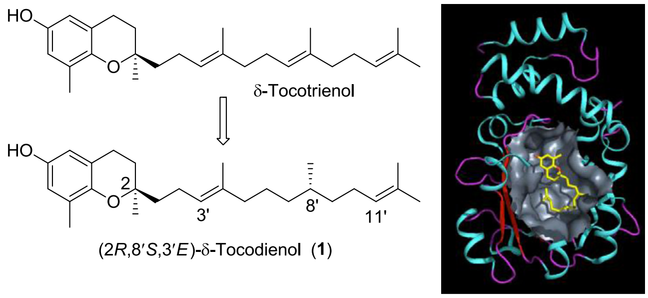
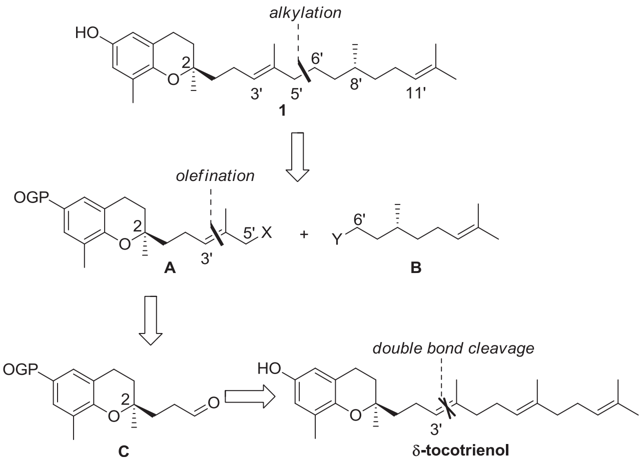


Fig. 2. Structures of δ-tocotrienol and (2*R*,8′*S*,3′*E*)-δ-tocodienol (**1**) (left); and simulated docking of **1** in the binding cavity of α-TTP (right).

2. Results and discussion

Our retrosynthetic strategy is outlined in Scheme 1. A disconnection at the C5′–C6′ bond of (2*R*,8′*S*,3′*E*)-δ-tocodienol (**1**) would lead to segments **A** and **B**, which can be coupled through various alkylation methods. Segment **B** can be derived from commercially available *R*-(+)-citronellol, while segment **A** can be derived from aldehyde **C** via a Horner–Wadsworth–Emmons (HWE) olefination reaction to form the *E*-double bond.



Scheme 1. Retrosynthetic approach to (2*R*,8′*S*,3′*E*)-δ-tocodienol (**1**).

The syntheses of aldehyde **C** (3-chromanylpropanals) type building blocks, including the corresponding 3-chromanylpropanols and 3-chromanylpropanoic acids, in optically pure forms have been reported.[8] There are also a variety of reported enantioselective approaches to the synthesis of the chiral chroman core of vitamin E, i.e., chromanylmethanols,[9] which could serve as a precursor for the synthesis of aldehyde **C**. However, most of these syntheses are low-yielding, multistep procedures. Given the potential utility of **C** as a key intermediate for the synthesis of δ-tocotrienol analogues with modifications on the side chain, we decided to search for an alternative but simpler and more efficient method to this compound. As δ-tocotrienol is readily available from natural sources, we envisioned that **C** could be synthesized by oxidative cleavage of the double bonds of naturally occurring optical pure δ-tocotrienol.

Commercially available DeltaGold®, a tocopherol free vitamin E supplement obtained in an enriched form from annatto oil, contains 67% δ-tocotrienol and 7.5% γ-tocotrienol, and was used as the source of δ-tocotrienol. The isolation of δ-tocotrienol from DeltaGold® using silica gel based flash column chromatography was straightforward and afforded 3.5 g of δ-tocotrienol in a pure form from 6.0 g of the mixture.[10]

The 6-OH group of δ-tocotrienol was then protected as a silyl ether moiety and the resulting TBS-protected product **2** was submitted to olefin oxidative cleavage (Table 1). Compound **2** was treated with OsO_4 (5 mol %) and $NaIO_4$ (9 equiv) in THF/H_2O at room temperature; the consumption of the starting material and intermediates was monitored by GC–MS and TLC. Initial screening of reaction conditions revealed that the ratio of the two solvents, THF and H_2O, was an important factor for the progress of the reaction, and a 3:1 ratio of THF/H_2O afforded the best result (Table 1, entry 1). A relatively low reaction concentration (0.05–0.1 M) of **2** was necessary for the progress of the reaction, likely due to the low solubility of both **2** and $NaIO_4$ in the solvent mixture. Disappointingly, only low yields of aldehyde **3** (10–17% yield) were obtained from these reactions.[11] No improvement was seen in the yield of **3** using various solvents (1,4-dioxane, diethyl ether, acetone, and *t*-butanol were examined) or by adding 2,6-lutidine.[12]

When the ratio of THF/H_2O was changed to 1:1, a significant amount of unreacted starting material (**2**) still remained (TLC and GC–MS analyses) after 48 h, likely due to the low solubility of **2** in the solvent mixture (Table 1, entry 2). A decrease in the proportion of H_2O in the solvent mixture by changing the ratio of THF/H_2O to 10:1 resulted in a relatively rapid disappearance of **2**. However, only trace amounts of **3** were detected and the major product was the olefin dihydroxylation product (with three pairs of 1,2-diols) due to the low solubility of $NaIO_4$ in the reaction mixture (entry 3). We reasoned that the sluggish reaction was caused by the very different solubilities of **2** and $NaIO_4$ in the reaction media, and the low yields were probably caused by the long reaction time and the relatively unstable nature of aldehyde **3** in the reaction mixture. The dihydroxylation step was completed in 24 h when the reaction was conducted in a 10:1 ratio of THF/H_2O (entry 3). Olefin dihydroxylation of **2** afforded three pairs of 1,2-diols, which should provide sufficient solubility in a polar solvent system that can dissolve $NaIO_4$. We envisaged that such homogeneous or near homogeneous reaction mixture would result in rapid cleavage of the 1,2-diol products. Thus, we tried the reaction in a two-step one-pot fashion by initial treatment of **2** with OsO_4 (5 mol %) and *N*-methylmorpholine-*N*-oxide (NMO, 4 equiv) in a 10:1 ratio mixture of THF/H_2O to form the tris-dihydroxylation product, followed by addition of H_2O (to a final 1:1 ratio of THF/H_2O) and $NaIO_4$ to the reaction mixture. Under these conditions, compound **3** was obtained in a significantly improved conversion (38% after conversion to the alcohol) (entry 4). Further investigation of the reaction revealed that a procedure developed by Nicolaou et al.,[13] involving $PhI(OAc)_2$ as an oxidative cleaving agent of 1,2-diols, afforded the

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