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Synthesis of (*S*)-α-tocotrienol via an enzymatic desymmetrization of an achiral chroman derivative

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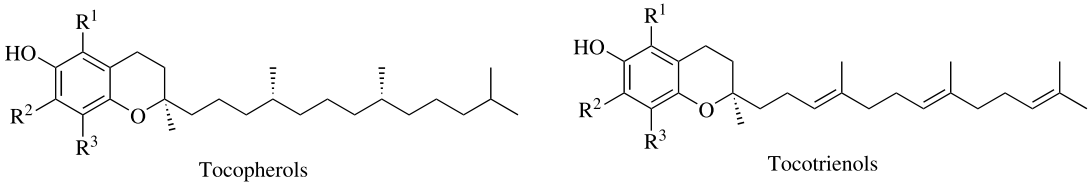
Abstract—The stereoselective acylation of an achiral chromandimethanol derivative by vinyl acetate in the presence of *Candida antarctica* lipase in organic media gave the corresponding (*S*)-monoester in high enantiomeric purity (ee = 98%). (*S*)-α-Tocotrienol was synthesized in 19% overall yield over six steps from this (*S*)-monoester.

Vitamin E occurs naturally in eight main isoforms: α, β, γ and δ-tocopherols and four corresponding tocotrienols[1] (Fig. 1). The α, β, γ and δ-homologues are determined by the methylation patterns of the common chromanol moiety. Tocotrienols differ from tocopherols by possessing a farnesyl (three double bonds) rather than a phytyl (saturated) side chain. Natural tocotrienols have the (2*R*),3′-trans,7′-trans configuration. The chiral chromanol subunit is found in several other natural products such as polyalthidin,[2] cystoseirol,[3] and garcinoic acid.[4] This structural element is also found in synthetic bioactive compounds such as the antidiabetic drug troglitazone.[5]

Tocotrienols are found in high concentration in palm oil and rice bran and in lower concentrations in several other natural sources (soybeans, barley, wheat germ).[6] Tocotrienols inhibit cholesterol biosynthesis by post-transcriptional suppression of β-hydroxy-β-methyl-glutaryl-coenzyme A reductase activity.[6–8] Also, tocotrienols are effective antioxidants and inhibit the oxidation of low density lipoproteins associated with coronary heart disease. In addition, they have been shown to have anticarcinogenic and neuroprotective properties.[9,10] Saucy et al. reported a stereoselective synthesis of α-tocotrienol via fractional crystallization of an intermediate acid with (*S*)-α-methylbenzyl amine



α R1 = Me R2 = Me R3 = Me

β R1 = Me R2 = H R3 = Me

γ R1 = H R2 = Me R3 = Me

δ R1 = H R2 = H R3 = Me

Figure 1. Vitamin E main isoforms.

Keywords: α-tocotrienol; desymmetrization; lipase; asymmetric synthesis.

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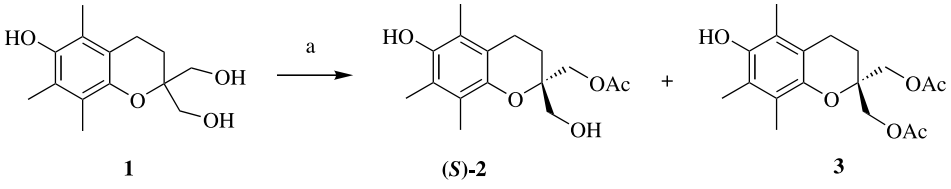
as a resolving agent.[11] A few syntheses of racemic α-tocotrienol have been reported.[12–14]

We report here the enzymatic desymmetrization of achiral chromanedimethanol **1** and the use of the corresponding enantiomerically enriched monoester **2** in the synthesis of (*S*)-α-tocotrienol.

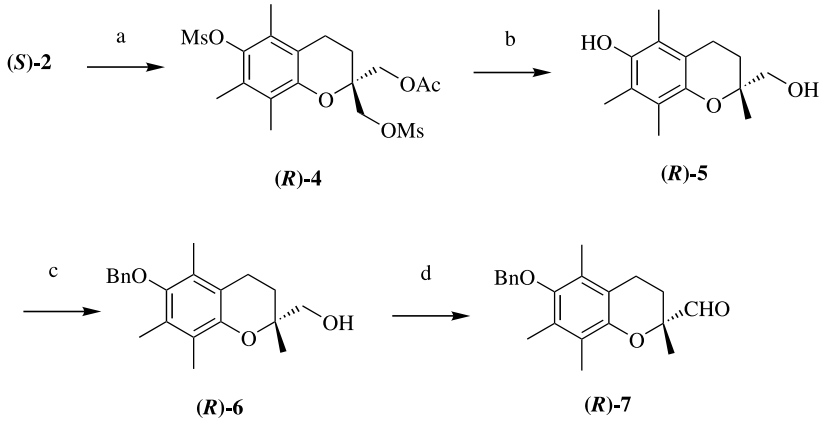
Triol **1** was first prepared according to the procedure reported by Oku et al.[15] A modified procedure using tributyl[(methoxymethoxy)methyl]-stannane[16] as a hydroxymethyl anion equivalent gave a better overall yield. Next, we did some screening to find enzymes which are able to distinguish the enantiotopic groups of compound **1**. Of the enzymes and conditions studied,[17] the esterification of triol **1** with vinyl acetate in the presence of *Candida antarctica* lipase in Et_2O (Scheme 1) gave enantiomerically pure (ee ≥ 98%) monoester **2** (60% yield) and the corresponding achiral diester **3** (27%). Replacement of ether by acetonitrile provided a better yield of monoester **2** (**2**, yield = 87%; **3**, yield = 12%) but a lower enantiomeric excess (ee = 90%). Diester **3** is easily recovered and recycled by chemical hydrolysis of the ester groups. The enantiomeric composition of **2** was determined by reaction with (+)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDC) and dimethylaminopyridine (DMAP), followed by ^{19}F NMR (282 MHz) analysis of the resulting diastereomeric esters (MTPA, Mosher's ester). A variety of strategies based on enzymatic kinetic resolutions have been developed for the asymmetric synthesis of related heterocyclic compounds.[18–24]

Monoester (*S*)-**2** was treated with two equivalents of mesyl chloride in the presence of triethylamine to give dimesylate (*R*)-**4** in 87% yield (Scheme 2). Reduction of (*R*)-**4** with $NaBH_4$ in DMSO provided chromanol (*R*)-**5** in 82% yield. Selective benzylation of the phenol function (NaH, benzyl bromide, THF, 80%) afforded (*R*)-**6**. The enantiomeric purity of (*R*)-**6** was further checked by ^{19}F NMR analysis of the MTPA derivative (ee ≥ 98%). This procedure proved that there is complete retention of configuration in the previous steps. The absolute configuration of (*R*)-**6** was determined by its transformation (Swern's oxidation, 97% yield) into known chroman-2-carboxaldehyde (*R*)-**7** ($[\alpha]_D^{23}$ − 13.5 (*c* 1.21, $CHCl_3$); lit.[21] $[\alpha]_D$ −10.9 (*c* 0.39, $CHCl_3$) for *R* configuration; lit.[25] $[\alpha]_D$ 12.78 (*c* 5, $CHCl_3$) for *S* configuration.

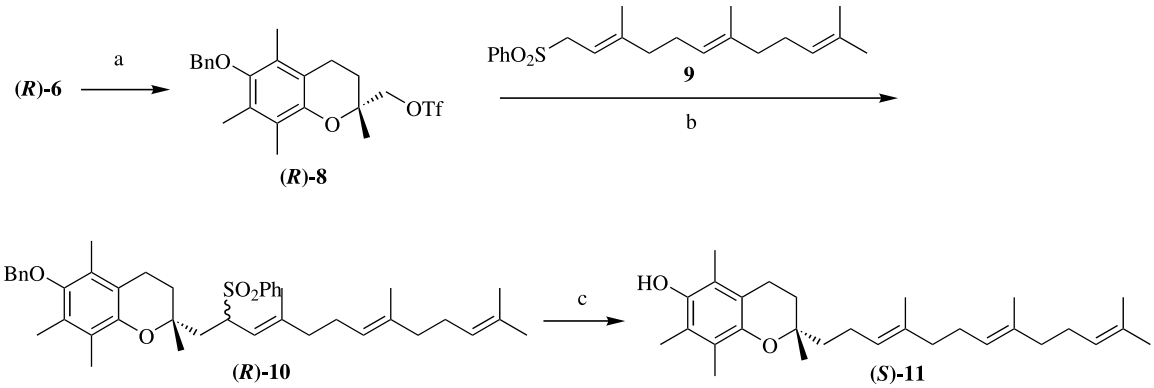
The coupling of chromanol (*R*)-**6** with the farnesyl side chain was accomplished using the reaction sequence depicted in Scheme 3. The anion of sulfone **9**[26,27] generated by treatment with butyllithium in the presence of hexamethylphosphoramide (HMPA) was subjected to alkylation with the triflate (*R*)-**8** to give the coupling product (*R*)-**10** as a mixture of diastereoisomers in 60% yield. Reductive cleavage of (*R*)-**10** provided α-tocotrienol (*S*)-**11** in 83% yield. The spectroscopic and physical data of synthetic (*S*)-α-tocotrienol were identical to those reported in the literature.[11–14,28,29]



Scheme 1. *Reagents and conditions*: (a) *Candida antarctica* lipase, vinyl acetate, Et_2O, 2 h.



Scheme 2. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 87%; (b) $NaBH_4$, DMSO, 82%; (c) NaH, BnBr, THF, 80%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 97%.



Scheme 3. *Reagents and conditions*: (a) Tf_2O, Et_3N, CH_2Cl_2, −10°C, 65%; (b) BuLi, THF/HMPA, −78°C, 60%; (c) Li, $EtNH_2$, Et_2O, −78°C, 83%.

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