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# Chemoenzymatic synthesis of both enantiomers of α-tocotrienol

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**Abstract**—The stereoselective acylation of the achiral chromanedimethanol derivative **1** by vinyl acetate in the presence of *Candida antarctica* lipase B gave the (*S*)-monoester **2** in high enantiomeric purity (ee ⩾ 98%). Enzymatic hydrolysis of diesters of compound **1** failed to give (*R*)-monoester **2** in good yield and high ee. Thus, both enantiomers of α-tocotrienol were synthesized from the (*S*)-monoester **2**.


## 1. Introduction

The term vitamin E is the generic descriptor for all tocopherol and tocotrienol derivatives that qualitatively exhibit the biological activity of α-tocopherol.[1] This vitamin occurs naturally in eight main isoforms: α, β, γ, and δ-tocopherols, and four corresponding tocotrienols (Fig. 1). Tocotrienols differ from tocopherols by possessing a farnesyl (three double bonds) rather than a saturated phytyl side chain. The α, β, γ, and δ-homologues are defined by the methylation patterns of the aromatic ring. Natural tocopherols and tocotrienols share the same 2*R* configuration. The chiral 2-methylchroman moiety is found in several natural products such as clusifoliol,[2] rhododaurichromanic acid A,[3] garcinoic acid,[4] cystoseirol,[5] polyalthidin,[6] siccanin,[7] and δ-*trans*-tocotrienoloic acid.[8] Also, synthetic 2-methylchromans have significant biological activities; for example, troglitazone is an antidiabetic agent[9] and trolox derivatives show antioxidant, antiarrhythmic, and anti-inflammatory activities.[10–12]

Tocotrienols are plant constituents particularly abundant in palm oil and cereal seeds.[13,14] A variety of biological activities have been recently ascribed to tocotrienols.[15] They are lipid-soluble antioxidants that protect membranes and cell components from the oxidative stress mediated by free radicals.[16,17] Tocotrienols down-regulate cholesterol biosynthesis by increasing HMG-CoA reductase degradation as well as decreasing the efficiency of the translation of HMG-CoA reductase mRNA.[18,19] They also inhibit the oxidation of low density lipoproteins associated with cardiovascular diseases.[20] In addition, they have been shown to have anticancer[21,22] and neuroprotective properties.[23,24]

Compared with tocopherols, the synthesis of tocotrienols has received little attention. A stereoselective synthesis of α-tocotrienol via fractional crystallization of an intermediate acid with (*S*)-α-methylbenzyl amine[25] and a few syntheses of the racemic compounds have been reported.[26–28] Herein, we report the synthesis of both enantiomers of α-tocotrienol via the enzymatic desymmetrization of the achiral chromanedimethanol **1**.[29]

## 2. Results and discussion

The substrate **1** (Scheme 1) was readily prepared on the basis of the protocol described by Harada et al.[30] A modified procedure using $Bu_3SnCH_2OCH_2OCH_3$ as a hydroxymethyl anion equivalent[31] gave a better overall yield. Esterification of **1** with vinyl acetate in the presence of *Candida antarctica* lipase B (CAL-B) in diethyl ether gave monoester (*S*)-**2** (60% yield, ee ⩾ 98%) and the corresponding achiral diester **3** (27% yield).[32] Replacement of diethyl ether by acetonitrile provided a better yield of monoester (*S*)-**2** (**2**, 87% yield; **3**, 12% yield) but a lower 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 (MTPA) in the presence of 1-[3-(dimethylamino)propyl]-3-ethyl-car-

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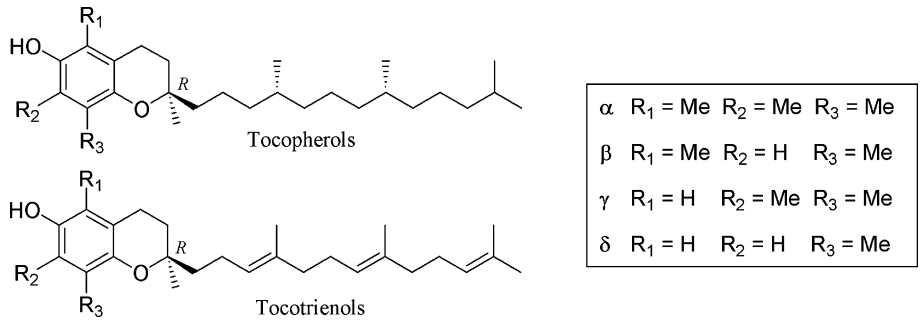
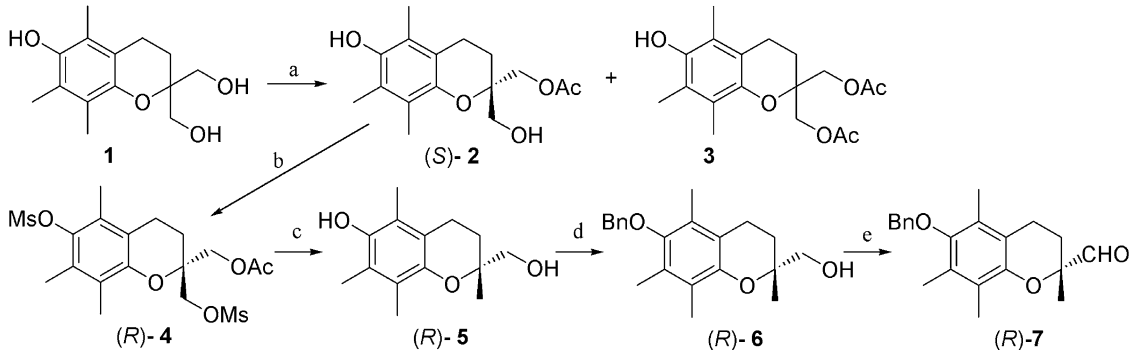



**Figure 1.** Structures of vitamin E natural main isoforms.



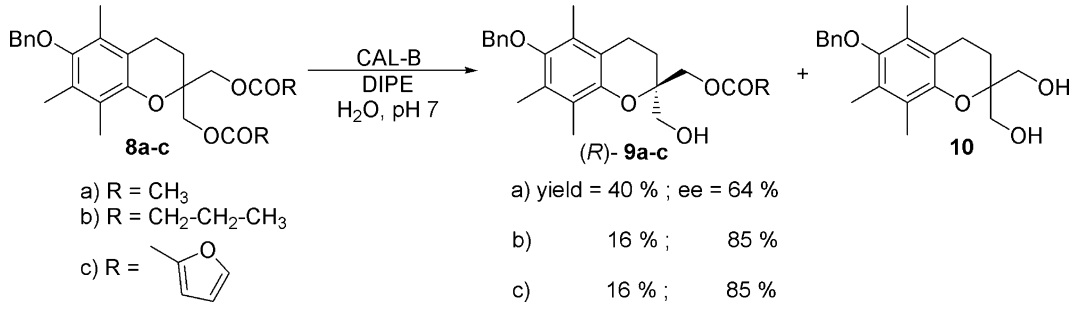

**Scheme 1.** Reagents and conditions: (a) *Candida antarctica* lipase B, vinyl acetate, $Et_20$, 2 h; (b) MsCl, $Et_3N$, $CH_2Cl_2$; (c) $NaBH_4$, DMSO, 115 °C; (d) NaH, BnBr, THF; (e) $(COC1)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C.

bodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP), followed by $^{19}F$ NMR (376 MHz) analysis of the resulting diastereoisomeric esters (Mosher's ester). The next step is the conversion of the primary alcohol to a methyl group. Sodium borohydride in polar aprotic solvents provides an effective source of nucleophilic hydride for the reductive displacement of functional leaving groups. Thus, 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 1). Reduction of (*R*)-**4** with $NaBH_4$ in DMSO provided chromanol (*R*)-**5** in 82% yield. Selective benzylation of the phenol function with benzyl bromide afforded (*R*)-**6** in 80% yield. The enantiomeric excess of (*R*)-**6** was further checked by $^{19}F$ NMR analysis of the MTPA derivative. This procedure proved that there is complete retention of configuration (ee $\geqslant$ 98%) 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.[33–35] This chemical correlation proved that the enzymatic acylation of **1** provided monoester **2** with the (*S*) configuration.

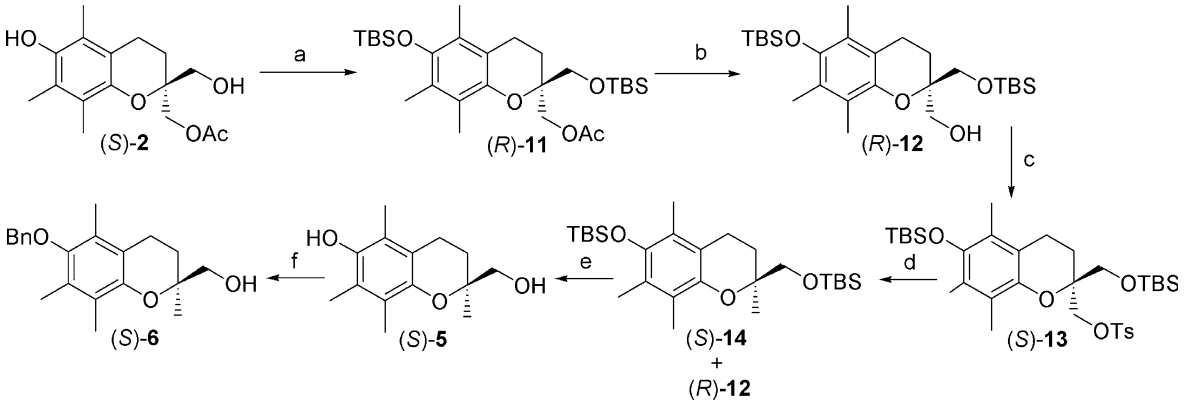
Chromane derivative (*R*)-**6** leads to (*S*)-α-tocotrienol, the non-natural enantiomer, after the introduction of the side chain. As enzymes usually show the same enantioselectivity for acylation and deacylation reactions, the hydrolysis of diesters **8a**–**c** (Scheme 2) appeared attractive since it would produce the monoesters **9a**–**c** of opposite configuration. However, the hydrolysis of diesters **8a**–**c** proved to be inefficient in terms of yield and enantioselectivity under various conditions. This enzymatic hydrolysis, like many desymmetrizations, is coupled with a subsequent kinetic resolution.[36] Thus, hydrolysis of **8a**–**c** first give the chiral monoesters **9a**–**c** but these products are also substrates for the hydrolase, resulting in the production of achiral diol **10**. This second hydrolysis lowers the yield of monoesters but increases their ee by kinetic resolution. The diesters and the monoesters are similar substrates and the enzymes usually have a preference for the same stereogenic center, thus removing the minor enantiomer. For instance, the hydrolysis of esters **8b**,**c** in water-saturated diisopropyl ether (DIPE) in the presence of CAL-B gave monoesters with fair ee (85%) but the yield was low (16%) and the main product was the achiral diol **10**.

Thus, the opposite enantiomer (*S*)-**6** leading to the naturally occurring (*R*)-α-tocotrienol was synthesized from the same starting material (*S*)-**2** (Scheme 3). Protection of both hydroxyl groups of (*S*)-**2** with *tert*-butyldimethylsilyl ethers followed by the removal of the acetate moiety of (*R*)-**11** with ethylmagnesium bromide provided (*R*)-**12** in high yield. Preparation and reduction of tosylate (*S*)-**13** gave protected chromanol (*S*)-**14**. Deprotection of silyl ethers with TBAF and selective benzylation of (*S*)-**5** provided (*S*)-**6**. The enantiomeric purity of (*S*)-**6** (ee $\geqslant$ 98%) was confirmed by $^{19}F$ NMR analysis of the MTPA derivative.

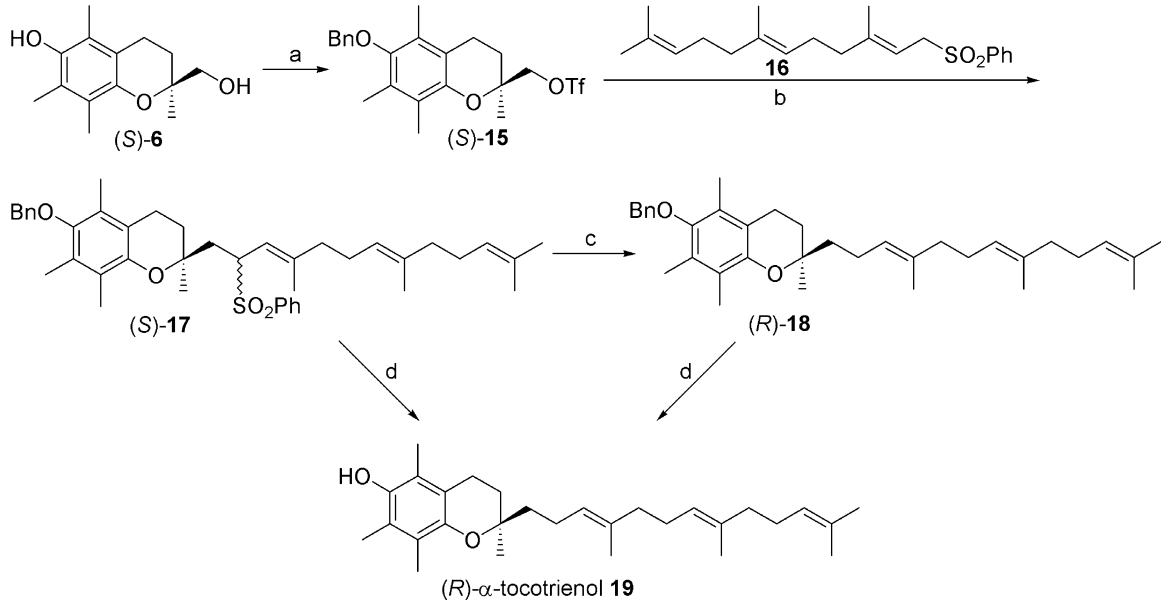
The coupling of chromanol (*S*)-**6** with the farnesyl side chain was accomplished using the reaction sequence depicted in Scheme 4. The anion of known sulfone




**Scheme 2.**




**Scheme 3.** Reagents: (a) TBSCl, imidazole, $CH_2Cl_2$; (b) EtMgBr, THF; (c) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$; (d) $LiEt_3BH$, THF; (e) TBAF, AcOH, THF; (f) BnBr, NaH, DMF.




**Scheme 4.** Reagents and conditions: (a) $Tf_2O$, $Et_3N$, $CH_2Cl_2$, −10 °C; (b) *n*BuLi, THF/HMPA, −78 °C; (c) $PdCl_2$(dppp), $LiBHEt_3$, THF, −10 °C; (d) Li, $EtNH_2/Et_20$, −78 °C.

**16**[37,38] generated by treatment with *n*-butyllithium in the presence of hexamethylphosphoramide (HMPA) was subjected to alkylation with triflate (*S*)-**15** to give product (*S*)-**17** as a mixture of diastereoisomers in 60% yield. No attempt was made to separate these diastereoisomers since the newly formed stereogenic center is eliminated in the next step. In a previous paper, we reported the removal of the phenylsulfonyl and benzyl groups in one step via dissolving-metal reduction with lithium in ethylamine. Unfortunately, we have since discovered that this method leads to some loss of the stereochemical integrity of the double bonds. The contaminant isomers

are not easily separable by standard chromatographic techniques. In an alternative method, desulfonylation of the allylic sulfone (*S*)-**17** with $LiBHEt_3$ catalyzed by $PdCl_2$(dppp) proceeded without migration of the double bond.[39–41] Natural α-tocotrienol (*R*)-**19** was obtained by debenzylation of (*R*)-**18**. Though this second method is longer by one step, it provides pure α-tocotrienol. The same sequence was applied for the transformation of (*R*)-**6** into non-natural (*S*)-α-tocotrienol. The preparation and chiral phase HPLC analysis of α-tocotrienol methyl ethers according to a known procedure confirmed the stereochemical (*RS*, *E*/*Z*) purity of the synthetic enantiomers.[42]

In conclusion, both enantiomers of α-tocotrienol **19** have been prepared from the same starting material (*S*)-**2**, which was obtained by enzymatic desymmetrization of prochiral chromanedimethanol **1**.[43,44]

## 4. Experimental

### 4.1. General methods

Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (c as g of compounds per 100 mL). Flash chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. NMR spectra were recorded at 400 MHz ($^1$H), 376 MHz ($^{19}$F), and 100 MHz ($^{13}$C) on a Varian Inova AS400 spectrometer. *Candida antarctica* lipase B was purchased from Boehringer–Mannheim (Chirazyme® L-2, c.-f. C2; 5 U/mg).

### 4.2. Enzymatic desymmetrization of chromanedimethanol 1

Compound **1** (216 mg, 0.86 mmol) was dissolved in diethyl ether (30 mL) on powdered molecular sieves (3A, 200 mg). Lipase B from *Candida antarctica* (26 mg) and vinyl acetate (400 μL, 4.30 mmol) were then added and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography and quenched by filtration of the enzyme (2 h). The volatiles were evaporated and the crude product was purified by flash chromatography ($CH_2Cl_2$/ethyl acetate, 9:1) to give monoacetate (*S*)-**2** (150 mg, 60%) and diacetate **3** (114 mg, 39%) as white solids.

Compound (*S*)-**2**: mp 139 °C; $[\alpha]_D^{22}$ −15.6 (*c* 1.53, $CHCl_3$); IR (KBr) 3400, 2920, 2900, 1700, 1400, 1250, 1040, 930, 800 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.93 (m, 2H), 2.09 (s, 3H), 2.10 (s, 6H), 2.15 (s, 3H), 2.22 (br s, 1H), 2.63 (t, *J* = 6.4 Hz, 2H), 3.67 (m, 2H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.22 (d, *J* = 11.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 11.11, 11.63, 12.02, 19.50, 20.68, 24.08, 63.64, 64.49, 75.52, 117.31, 118.54, 121.37, 122.48, 144.17, 145.32, 170.96; HRMS (EI) calcd for $C_{16}H_{22}O_5$ ($M^+$) 294.1467. Found 294.1470.

Compound **3**: mp 111 °C; IR (KBr) 3550, 2960, 1730, 1455, 1390, 1240, 1040, 940, 910, 850 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.95 (t, *J* = 6.9 Hz, 2H), 2.07 (s, 3H), 2.08 (s, 6H), 2.09 (s, 3H), 2.15 (s, 3H), 2.63 (t, *J* = 6.9 Hz, 2H), 4.14 (d, *J* = 11.4 Hz, 2H), 4.23 (d, *J* = 11.4 Hz, 2H), 4.25 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 11.08, 11.50, 12.00, 19.41, 20.65, 24.56, 64.26, 73.94, 116.88, 118.29, 121.31, 122.75, 144.09, 145.31, 170.48; HRMS (CI, $NH_3$) calcd for $C_{18}H_{24}O_6$ ($M^+$) 336.1573. Found 336.1577.

### 4.3. Mesylate (*R*)-4

Monoacetate (*S*)-**2** (91 mg, 0.31 mmol) was dissolved in anhydrous dichloromethane (5 mL) cooled to 0 °C under a dry argon atmosphere. Anhydrous triethylamine (130 μL, 0.933 mmol) and methanesulfonyl chloride (70 μL, 0.904 mmol) were added and the solution was stirred at room temperature for 1 h. The solution was diluted with ethyl acetate and washed successively with 3 N aq HCl, sat. aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography ($CH_2Cl_2$/ethyl acetate, 97:3) to give mesylate (*R*)-**4** (133 mg, 94%) as a white solid. Mp. 125 °C; $[\alpha]_D^{23}$ −1.39 (*c* 1.52, $CHCl_3$); IR (KBr) 3000, 2920, 1730, 1450, 1340, 1220, 1160, 1040, 955, 815 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 2.00 (dd, *J* = 12.7 and 6.8 Hz, 2H), 2.07 (s, 3H), 2.10 (s, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 2.65 (t, *J* = 6.8 Hz, 2H), 3.02 (s, 3H), 3.24 (s, 3H), 4.16 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 10.9 Hz, 1H), 4.31 (d, *J* = 10.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 11.79, 13.53, 14.34, 19.14, 20.59, 23.63, 37.40, 38.67, 63.47, 68.82, 74.45, 117.44, 123.93, 127.47, 129.53, 140.39, 148.30, 170.18; HRMS (CI, $NH_3$) calcd for $C_{18}H_{26}O_9S_2$ ($M^+$) 450.1018. Found 450.1021.

### 4.4. Compound (*R*)-5

Mesylate (*R*)-**4** (69.5 mg, 0.152 mmol) and sodium borohydride (54.4 mg, 1.438 mmol) were dissolved in anhydrous dimethylsulfoxide (2 mL) under dry argon atmosphere. The solution was stirred at 115 °C for 20 h. The solution was cooled to 0 °C, water was added (1 mL), and the solution was stirred for 15 min. Then, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added and the mixture was stirred for 10 min. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography ($CH_2Cl_2$/ethyl acetate, 95:5) to give (*R*)-**5** (29.4 mg, 82%) as a white solid. Mp. 126.5–127.5 °C, lit.[33] 127–129 °C; $[\alpha]_D^{23}$ −1.8 (*c* 1.45, EtOH); lit.[33] $[\alpha]_D$ 1.54 (*c* 1.89, EtOH) for the *S* enantiomer; IR (KBr) 3400, 2900, 1440, 1405, 1245, 1155, 1080, 1030, 885 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.74 (dt, *J* = 13.3 and 5.5 Hz, 1H), 2.01 (dt, *J* = 13.3 and 8.4 Hz, 1H); 2.13 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 2.30 (t, *J* = 6.1 Hz, 1H), 2.67 (m, 2H), 3.65 (m, 2H), 4.72 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 11.22, 11.74, 12.13, 20.16, 20.32, 27.76, 69.21, 74.94, 117.20, 118.91, 121.50, 122.39, 144.79, 145.00.

### 4.5. Compound (*R*)-6

To a solution of (*R*)-**5** (425.0 mg, 1.798 mmol) in anhydrous THF (20 mL) cooled to 0 °C under dry argon atmosphere was added sodium hydride (62.7 mg,

2.613 mmol) and the mixture was stirred for 10 min. Benzyl bromide (300 μL, 2.522 mmol) was added and the mixture was allowed to reach room temperature and stirred for 20 h. The mixture was diluted with diethyl ether (60 mL) and washed successively with 3 N aq HCl, saturated aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and the solvents were removed in vacuo. The crude product was purified by flash chromatography (petroleum ether/diethyl ether 65:35) to give (*R*)-**6** (470.0 mg, 80%) as a white solid. Mp 72–74 °C (lit.[33] mp 66–69.5 °C); $[\alpha]_D^{22}$ 1.1 (*c* 1.05, $CHCl_3$); IR (KBr) 3380, 2900, 1440, 1400, 1360, 1245, 1145, 1075, 1040, 895 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (s, 3H), 1.75 (m, 1H), 1.93 (br s, 1H), 2.03 (m, 1H), 2.12 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 2.67 (m, 2H), 3.61 (d, $J$ = 11.3 Hz, 1H), 3.67 (d, $J$ = 11.3 Hz, 1H), 4.70 (s, 2H), 7.37 (m, 3H), 7.51 (d, $J$ = 7.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.80, 11.92, 12.78, 20.09, 20.49, 27.62, 69.25, 74.67, 75.27, 117.52, 122.83, 126.12, 127.63, 127.73, 128.15, 128.38, 137.82, 147.21, 148.57.

### 4.6. Compound (*R*)-7

To a solution of oxalyl chloride (200 μL, 2.29 mmol) in dichloromethane (2 mL) was added dimethylsulfoxide (250 μL, 3.52 mmol) at −78 °C under dry argon atmosphere. After stirring for 15 min, alcohol (*R*)-**6** (115 mg, 0.35 mmol) in dichloromethane (3 mL) was added and, after 90 min, triethylamine (650 μL, 4.66 mmol). After stirring for an additional 3 h at −78 °C, the solution was allowed to warm to room temperature. Ethyl acetate was added and the organic layer was washed with 3 N aq HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated. Flash chromatography (hexane/ethyl acetate, 95:5) afforded aldehyde (*R*)-**7** (110.7 mg, 97%) as a white solid. Mp 58–59 °C, lit.[33] 56–61 °C; $[\alpha]_D^{22}$ −13.5 (*c* 1.21, $CHCl_3$), lit.[34] −10.9 (*c* 0.39, $CHCl_3$, *R* enantiomer), lit.[45] 12.5 (*c* 2.8, $CHCl_3$, *S* enantiomer). The spectroscopic data of **7** were identical to those reported in the literature.[33–35]

### 4.7. Compound (*R*)-11

To a solution of monoacetate (*S*)-**2** (446 mg, 1.52 mmol) in dry dimethylformamide (10 mL) were added *tert*-butyl-dimethylsilyl chloride (701 mg, 4.65 mmol) and imidazole (528 mg, 7.75 mmol) and the mixture was stirred at room temperature for 24 h. The mixture was diluted with water and the aqueous phase was extracted with diethyl ether (3× 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (hexane/ethyl acetate, 85:15) afforded compound (*R*)-**11** (755 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ 6.03 (*c* 7.16, $CHCl_3$); IR (neat) 2954, 2929, 2885, 2857, 1748, 1462, 1252, 1094, 947, 837 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, 3H), 0.05 (s, 3H), 0.13 (s, 6H), 0.89 (s, 9H), 1.05 (s, 9 H), 1.84–2.02 (m, 2H), 2.06 (s, 6H), 2.09 (s, 3H), 2.10 (s, 3H), 2.57 (t, $J$ = 6.8 Hz, 2H), 3.60 (d, $J$ = 10.0 Hz, 1H), 3.71 (d, $J$ = 10.0 Hz, 1H), 4.19 (d, $J$ = 11.2 Hz, 1H), 4.23 (d, $J$ = 11.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −5.35, −5.33, −3.12, −3.09, 12.15, 13.63, 14.55, 18.40, 18.83, 19.99, 21.17, 24.21, 26.02, 26.32, 63.58, 65.54, 75.92, 117.80, 122.96, 123.77, 126.42, 144.77, 145.44, 171.16; HRMS (CI, $NH_3$) calcd for $C_{28}H_{50}O_5Si_2$ ($M^+$), 522.3197. Found 522.3203.

### 4.8. Compound (*R*)-12

To a solution of (*R*)-**11** (716 mg, 1.369 mmol) in dry THF (36 mL) was added ethylmagnesium bromide (1 M solution in THF, 6.85 mL, 6.85 mmol) and the solution was stirred at room temperature for 1.5 h. A saturated aqueous solution of $NH_4Cl$ (20 mL) was slowly added and the mixture was extracted with ethyl acetate (3× 30 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 85:15) to give (*R*)-**12** (636 mg, 97%) as a colorless oil. $[\alpha]_D^{23}$ 8.13 (*c* 6.16, $CHCl_3$); IR (neat) 3468, 2983, 2955, 2928, 2857, 1641, 1257, 1091, 835 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.05 (s, 3H), 0.07 (s, 3H), 0.12 (s, 6H), 0.91 (s, 9H), 1.05 (s, 9H), 1.93–1.97 (m, 2H), 2.05 (s, 1H), 2.07 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.50–2.65 (m, 2H), 3.59 (d, $J$ = 9.6 Hz, 1H), 3.69–3.76 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −5.35, −3.10, 12.35, 13.66, 14.55, 18.37, 18.83, 20.09, 24.11, 26.04, 26.32, 64.96, 66.34, 76.58, 118.16, 122.68, 123.99, 126.40, 144.86, 145.37; HRMS (CI, $NH_3$) calcd for $C_{26}H_{48}O_4Si_2$ ($M^+$) 480.3091. Found 480.3082.

### 4.9. Compound (*S*)-13

To a solution of (*R*)-**12** (616 mg, 1.323 mmol), triethylamine (1.29 mL, 9.26 mmol) and 4-dimethylaminopyridine (50 mg) in dry dichloromethane (45 mL) was added *p*-toluenesulfonyl chloride (1.26 g, 6.61 mmol) and the solution was stirred at room temperature for 12 d. The solution was diluted with diethyl ether (100 mL) and the organic phase was washed with 1 N aq HCl, saturated aq $NaHCO_3$, and brine. The organic phase was then dried over $MgSO_4$ and evaporated. Flash chromatography (hexane/ethyl acetate, 75:25) provided (*S*)-**13** (719 mg, 86%) as a colorless oil. $[\alpha]_D^{23}$ −1.49 (*c* 4.47, $CHCl_3$); IR (neat) 3431, 3065, 3031, 2857, 1598, 1462, 1367, 1253, 1178, 1095, 835 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ −0.007 (s, 3H), −0.01 (s, 3H), 0.11 (s, 6H), 0.84 (s, 9H), 1.04 (s, 9H), 1.82-1.89 (m, 2H), 1.98 (s, 3H), 2.00 (s, 3H), 2.07 (s, 3H), 2.43 (s, 3H), 2.45-2.48 (m, 2H), 3.56 (d, $J$ = 10.0 Hz, 1H), 3.62 (d, $J$ = 10.0 Hz, 1H), 4.06 (s, 2H), 7.29 (d, $J$= 7.6 Hz, 2H), 7.75 (d, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −5.38, −5.34, −3.13, 12.16, 13.57, 14.53, 18.34, 18.83, 19.67, 21.86, 23.75, 25.98, 26.31, 63.41, 69.96, 75.69, 117.41, 122.96, 123.79, 126.52, 128.18, 129.97, 132.90, 144.91, 145.02; HRMS (CI, $NH_3$) calcd for $C_{33}H_{54}O_6SSi_2$ ($M^+$) 634.3179. Found 634.3187.

### 4.10. Compound (*S*)-14

To a solution of (*S*)-**13** (272 mg, 0.428 mmol) in dry THF (15 mL) was added lithium triethylborohydride (1 M solution in THF, 1 mL, 1 mmol) at 0 °C under a dry argon atmosphere. The solution was stirred at room temperature for 4 h and then at reflux for 12 h. Then,

after mixture was allowed to cool down at room temperature, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was stirred for 10 min. The solution was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography (hexane/ethyl acetate, 9:1) provided alcohol (*R*)-**12** (95 mg, 46%) and (*S*)-**14** (71 mg, 36%) as a yellow oil. $[\alpha]_D^{23}$ 1.46 (*c* 1.41, $CHCl_3$); IR (neat) 2955, 2928, 2896, 2857, 1462, 1413, 1252, 1092, 946, 836 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.04 (s, 3H), 0.07 (s, 3H), 0.13 (s, 6H), 0.91 (s, 9H), 1.06 (s, 9H), 1.26 (s, 3H), 1.73–1.80 (m, 1H), 1.92–1.99 (m, 1H), 2.07 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.54–2.58 (m, 2H), 3.53 (d, $J$ = 9.6 Hz, 1H), 3.59 (d, $J$ = 9.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −5.23, −5.19, −3.11, −3.09, 12.23, 13.66, 14.56, 18.48, 18.84, 20.77, 22.43, 26.10, 26.35, 28.49, 68.61, 75.34, 117.94, 122.77, 123.77, 126.11, 144.37, 146.11; HRMS (CI, $NH_3$) calcd for $C_{26}H_{48}O_3Si_2$ ($M^+$) 464.3142. Found 464.3148.

### 4.11. Compound (*S*)-5

To a solution of (*S*)-**14** (409 mg, 0.881 mmol) in dry THF (15 mL) was added glacial acetic acid (0.416 mL, 7.27 mmol) and the solution was stirred for 5 min under a dry argon atmosphere. Then, *n*-tetrabutylammonium fluoride (2.04 g, 7.8 mmol) was added and the solution was stirred for 72 h at room temperature. The reaction was quenched by addition of brine (10 mL) and the product was extracted with ethyl acetate (3× 30 mL). The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography ($CH_2Cl_2$/ethyl acetate, 9:1) to give (*S*)-**5** (208 mg, quantitative). $[\alpha]_D^{23}$ 1.61 (*c* 2.25, EtOH). The spectroscopic data were identical for both enantiomers.

### 4.12. Compound (*S*)-6

Benzylation of (*S*)-**5** gave (*S*)-**6** in 80% yield according to the procedure described above. $[\alpha]_D^{23}$ −1.55 (*c* 2.09, $CHCl_3$). The spectroscopic data of (*S*)-**6** were identical for both enantiomers.

### 4.13. Compound (*S*)-15

To a solution of (*S*)-**6** (152.3 mg, 0.467 mmol) and anhydrous triethylamine (100 μL, 0.718 mmol) in dry dichloromethane (4.6 mL) cooled to −10 °C under argon atmosphere was added trifluoromethanesulfonic anhydride (100 μL, 0.594 mmol). The solution was stirred at −10 °C for 30 min. The solution was diluted with ethyl acetate and washed with 3 N aq HCl, saturated aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and the solvents were removed in vacuo. The crude product was purified by flash chromatography (hexane/diethyl ether, 93:7) to give (*S*)-**15** (131.9 mg, 62%) as a white solid. Mp 90–92 °C; $[\alpha]_D^{23}$ −3.56 (*c* 2.14, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.38 (s, 3H), 1.87 (m, 1H), 2.01 (m, 1H), 2.12 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 2.68 (t, $J$ = 6.8 Hz, 2H), 4.45 (d, $J$ = 10.2 Hz, 1H), 4.51 (d, $J$ = 10.2 Hz, 1H), 4.71 (s, 2H), 7.40 (m, 3H), 7.52 (d, $J$ = 6.9 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.61, 11.89, 12.76, 19.62, 20.96, 27.66, 72.77, 74.65, 79.46, 116.50, 120.68, 123.32, 126.05, 127.63, 127.76, 128.38, 128.68, 137.69, 146.40, 148.95; HRMS (CI, $NH_3$) calcd for $C_{22}H_{25}F_3O_5S$ ($M^+$) 458.1375. Found 458.1367.

### 4.14. Compound (*S*)-17

To a solution of sulfone **16** (676 mg, 2.0 mmol) in THF (6 mL) and HMPA (1.7 mL) cooled to −78 °C under a dry argon atmosphere was added dropwise a solution of *n*-butyllithium (1.6 M in hexane, 0.95 mL, 1.50 mmol) and the mixture was stirred for 30 min. A solution of triflate (*S*)-**15** (560 mg, 1.22 mmol) in dry THF (9 mL) was added dropwise and the solution was stirred at −78 °C for 8 h, then at room temperature for 10 h. The solution was diluted in diethyl ether, washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified first by flash chromatography on silica gel (hexane/ethyl acetate, 9:1), then by column chromatography on C-18 reverse-phase (acetonitrile/water, 95:5) to give the mixture of diastereoisomers (*S*)-**17** (0.786 g, 60%) as a yellow oil. IR (neat) 3030, 2925, 2855, 1453, 1373, 1304, 1254, 1146, 1085, 999, 854 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13 (s, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 1.58 (s, 6H), 1.66 (s, 3H), 1.70–2.07 (m, 30 H), 2.10 (s, 3H), 2.13 (s, 3H), 2.18–2.19 (s, 3H), 2.49–2.59 (m, 4H), 4.04–4.08 (m, 1H), 4.12–4.16 (m, 1H), 4.66 (s, 4H), 4.99–5.08 (m, 4H), 5.16 (d, $J$ = 9.6 Hz, 2H), 7.23–7.55 (m, 14 H), 7.60 (t, $J$ = 7.4 Hz, 2H), 7.75 (d, $J$ = 7.2 Hz, 2H), 7.83 (d, $J$ = 7.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 12.12, 12.19, 13.08, 13.10, 16.23, 16.75, 17.93, 20.59, 20.71, 24.32, 24.43, 25.94, 26.28, 26.90, 32.13, 32.41, 37.20, 37.65, 39.92, 40.03, 40.07, 61.33, 61.81, 74.04, 74.19, 74.91, 117.23, 117.28, 119.06, 119.10, 122.84, 123.15, 123.70, 123.74, 124.41, 126.30, 127.91, 127.95, 128.02, 128.04, 128.32, 128.68, 128.77, 128.92, 129.20, 129.68, 131.62, 133.50, 133.63, 135.82, 135.87, 137.84, 137.95, 138.11, 138.14, 144.46, 145.14, 147.26, 147.46, 148.64, 148.73; HRMS (CI, $NH_3$) calcd for $C_{42}H_{54}O_4S_1$ ($M^+$) 654.3743. Found 654.3752.

### 4.15. Compound (*R*)-18

To a solution of sulfone (*S*)-**17** (1.684 g, 2.56 mmol) and $PdCl_2$(dppp) (151 mg, 0.256 mmol) in dry THF (70 mL) cooled to 0 °C under dry argon atmosphere was added dropwise a solution of lithium triethylborohydride (1 M in THF, 7.7 mL, 7.7 mmol). The mixture was stirred at 0 °C for 5 h and then at room temperature overnight. The mixture was diluted with ether and washed successively with 1 M aq KCN, brine, and water. The organic layer was dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (pure hexane to hexane/AcOEt, 95:5) to give (*R*)-**18** (1.00 g, 76%) as a colorless oil. $[\alpha]_D^{23}$ 4.76 (*c* 0.63, $CHCl_3$); IR (neat) 3089, 3065, 3033, 2968, 2924, 2855, 1458, 1368, 1248, 1159, 1090 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (s, 3H), 1.53–1.65 (m, 11H), 1.67 (s, 3H), 1.73–1.87 (m, 2H), 1.93–1.99 (m, 4H), 2.01–2.07 (m, 4H), 2.10–2.16 (m, 8H), 2.21 (s, 3H), 2.59 (t, $J$ = 6.74 Hz, 2H), 4.68 (s, 2H), 5.05–5.17 (m, 3H), 7.33 (t, J = 7.03 Hz, 1H), 7.39

(t, $J = 7.03$ Hz, 2H), 7.90 (d, $J = 7.03$ Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 12.06, 12.22, 13.09, 16.11, 16.23, 17.92, 20.90, 22.45, 24.08, 25.95, 26.82, 26.98, 31.60, 39.91, 39.93, 39.95, 74.80, 74.93, 117.77, 123.18, 124.42, 124.59, 124.63, 126.21, 127.93, 127.99, 128.18, 128.68, 131.48, 135.18, 135.33, 138.26, 148.08, 148.39; HRMS (CI, $NH_3$) calcd for $C_{36}H_{51}O_2$ $(MH)^+$ 515.3889. Found 515.3882.

### 4.16. (*R*)-α-Tocotrienol 19

To a solution of (*R*)-**18** (219 mg, 0.426 mmol) in diethyl ether (11 mL) cooled to −78 °C under a dry argon atmosphere was added ethyl amine (11 mL) and then lithium (81 mg, 11.65 mmol). The mixture was stirred at −78 °C for 3 h. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (3 mL) and methanol (3 mL). The solvents were evaporated and the residue was dissolved in diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The crude material was purified by flash chromatography (hexane/ethyl acetate, 95:5) to yield (*R*)-α-tocotrienol (0.150 g, 83%) as a solid. Mp 30–31 °C; $[\alpha]_D^{23}$ −4.12 (*c* 2.47, $CHCl_3$); IR (neat) 3465, 2968, 2925, 2855, 1450, 1376, 1257, 1166, 1088, 928 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (s, 3H), 1.48–1.67 (m, 14H), 1.80 (m, 2H), 1.96 (m, 4H), 2.02–2.16 (m, 12H), 2.21 (s, 3H), 2.61 (t, $J = 6.74$ Hz, 2H), 4.17 (br s, 1H), 5.13 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.49, 11.99, 12.42, 16.10, 16.21, 17.90, 20.95, 22.43, 23.93, 25.92, 26.80, 26.96, 31.77, 39.72, 39.90, 39.92, 74.49, 117.51, 118.68, 121.22, 122.84, 124.41, 124.60, 131.48, 135.16, 135.25, 144.77, 145.68.

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