

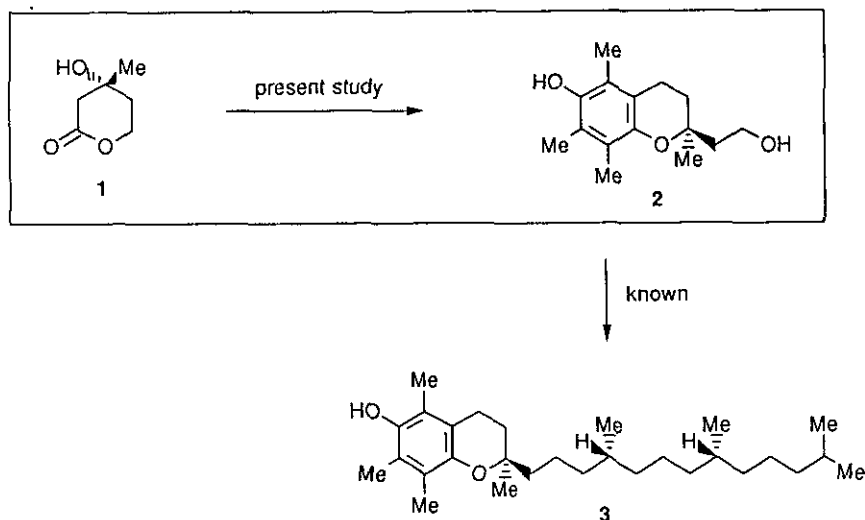
A FACILE CONVERSION OF NATURAL (*R*)-MEVALONOLACTONE INTO A VITAMIN E KEY INTERMEDIATE

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Abstract—— Natural (*R*)-mevalonolactone (1) produced by fermentation has been facilely converted into a vitamin E key synthetic intermediate (2).

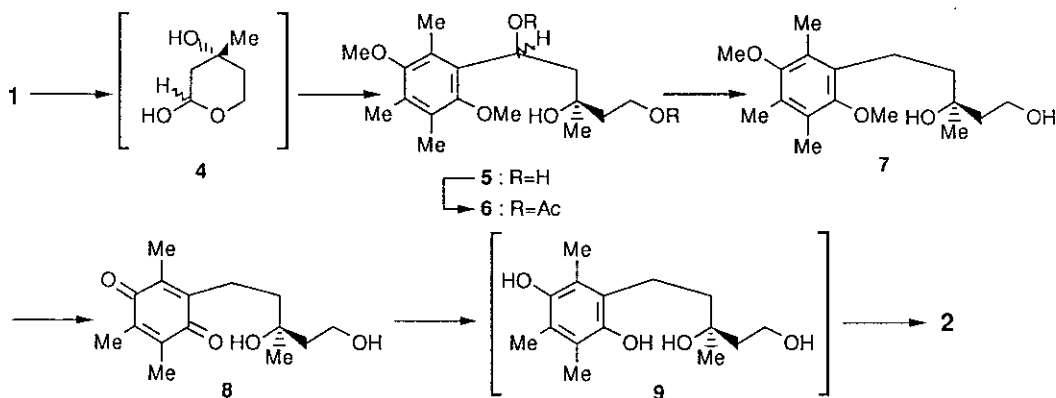
It has been reported that physiological activity of vitamin E (3) mostly owes to the chirality of 2 position of its chroman moiety.¹ Enantioselective construction of the 2-position² is, therefore, the most important. We report herein facile and efficient incorporation of (*R*)-mevalonolactone (1), available by fermentation,^{3,4} into a key intermediate^{2b,5} (2) of vitamin E (3) with complete preservation of the original chiral integrity (Scheme 1).



Scheme 1

Treatment of natural (*R*)-mevalonolactone (**1**) produced by fermentation^{3,6} with diisobutylaluminum hydride (1.2 equiv.), followed by the Grignard reagent prepared from 2,5-dimethoxy-3,4,6-trimethylbromobenzene (9 equiv.),⁷ in the same flask at $-30\text{ }^{\circ}\text{C}$ furnished a 1:1 mixture of the triol (**5**) in 80% yield. After acetylation of the mixture, the diacetate (**6**) obtained in 92% yield was treated with lithium (9 equiv.) in liq. ammonia to give the diol (**7**) in 76% yield. On exposure to cerium(IV) ammonium nitrate (CAN) (4 equiv.) in acetonitrile,^{2c} **7** afforded the benzoquinone (**8**) in 81% yield. Catalytic hydrogenation of **8** yielded the air-sensitive hydroquinone (**9**) which was immediately refluxed with a catalytic amount of *p*-toluenesulfonic acid in benzene^{2k,8} to give rise to the key intermediate (**2**) in 71% overall yield from **8** with retention of the chirality. Preservation of the original chiral integrity was confirmed by ^1H nmr measurement (500 MHz) of the bis-MTPA (both enantiomers) esters derived from **2** which revealed **2** to be optically pure (>98% ee) as the starting material.^{5c,6}

Since natural (*R*)-mevalonolactone (**1**) could have been produced in a large quantity by fermentation,³ the present method may have great practical value for the production of vitamin E itself as well as the related antioxidants.^{5b}



Scheme 2

EXPERIMENTAL SECTION

All reactions except reduction were carried out under argon. Ir spectra were measured with a JASCO A-102 spectrophotometer. ^1H Nmr spectra were recorded on JEOL-FX90R and JEOL-JNM-

GX500 spectrometers. Ms spectra were measured with a JEOL-O1SG-2 instrument. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

(3*R*,5*R*/*S*)-5-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methylpentane-1,3,5-triol (5)

— To a stirred solution of (–)-mevalonolactone (1) $[[\alpha]_D^{27} -22.16^\circ$ (*c* 1.17, EtOH), ~100% ee] (89 mg, 0.68 mmol) in THF (3 ml) is added diisobutylaluminum hydride in CH₂Cl₂ (0.9 M, 0.9 ml, 0.81 mmol) dropwise at –30 °C. Then, to the mixture is added the Grignard reagent, prepared from 2,5-dimethoxy-3,4,6-trimethylbromobenzene (1.6 g, 6.15 mmol) and magnesium (114 mg, 7 m atom) in THF (11 ml), at the same temperature and the stirring is continued for 3 h at room temperature. After treating the reaction mixture with 30% NH₄OH (3 ml), the mixture is diluted with Et₂O (20 ml) and filtered through Celite. The organic layer separated is washed with brine (5 ml), dried over MgSO₄, and evaporated under reduced pressure. The residue is purified by chromatography on a silica gel column (30 g) using AcOEt as eluent to give the pure triol (5) as a colorless oil; yield: 180 mg (80%). Ir (neat): ν_{\max} : 3370 cm⁻¹; ¹H nmr (CDCl₃): δ 5.45 (m, 2H), 4.90 (m, 2H), 4.25 – 3.60 (m, 8H), 2.40 – 2.10 (m, 9H), 1.85 – 1.50 (m, 4H), 1.50 (s, 1.5H), 1.32 (s, 1.5H); ms (*m/z*): 312 (M⁺), 209 (100%). Calcd for C₁₇H₂₈O₅: 312.1937. Found: 312.1926 (M⁺). As a less polar fraction 1,4-dimethoxy-2,3,6-trimethylbenzene (878 mg, 89%) is recovered and is recycled after bromination.

(3*R*,5*R*/*S*)-1,5-Diacetoxy-5-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-methyl-3-hydroxypentane (6)

— To a stirred solution of 5 (1.3 g, 4.17 mmol) in CH₂Cl₂ (15 ml) is added Ac₂O (1.89 ml, 20 mmol), triethylamine (3.48 ml, 25 mmol), and 4-*N,N*-dimethylamino-pyridine (50 mg) and mixture is stirred at room temperature for 1 h. The mixture is diluted with CH₂Cl₂ (50 ml) and washed with sat. aq. NaHCO₃ (20 ml x 2), brine (20 ml), and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (50 g) using Et₂O-hexane (1:1 v/v) as eluent to give the diacetate (6) as a colorless oil; yield: 1.55 g (92%). Ir (neat): ν_{\max} : 3450, 1720 cm⁻¹; ¹H nmr (CDCl₃): δ 6.50 (m, 1H), 4.20 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.38 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H), 2.05 (s, 6H), 2.50 – 1.20 (m, 5H), 1.29 (s, 1.5H), 1.20 (s, 1.5H); ms (*m/z*): 396 (M⁺), 206 (100%). Calcd for C₁₇H₂₈O₄: 396.2148. Found: 396.2159.

(3*S*)-5-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methylpentane-1,3-diol (7) — To a stirred solution of 6 (132 mg, 0.33 mmol) in a mixture of THF (3 ml) and liq. NH₃ (ca. 15 ml) was

added lithium metal (20 mg, 2.86 m atom) portionwise at $-33\text{ }^{\circ}\text{C}$. After stirring at the same temperature for 10 min, the mixture is treated with NH_4Cl (ca. 0.5 g) and most of NH_3 is evaporated at room temperature. The residue is extracted with Et_2O (30 ml) and the extract is washed with sat. aq. NaHCO_3 , brine, and dried over MgSO_4 . After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (5 g) using Et_2O -hexane (2:3 v/v) as eluent to give pure **7** as a colorless oil; yield: 75 mg (76%); $[\alpha]_{\text{D}}^{25} +3.80^{\circ}$ (c 1.50, CHCl_3). Ir (neat) ν_{max} : 3350 cm^{-1} ; ^1H nmr (CDCl_3): δ 3.93 (t, $J=7.0$ Hz, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 2.60 (m, 4H), 2.26 (s, 3H), 2.18 (s, 6H), 1.33 (s, 3H); ms (m/z): 296 (M^+), 193 (100%). Calcd for $\text{C}_{17}\text{H}_{28}\text{O}_4$: 296.1987. Found: 296.2003.

(S)-2-(3,5-Dihydroxy-3-methylpentyl)-3,5,6-trimethyl-1,4-benzoquinone (8) ——— To a stirred solution of **7** (650 mg, 2.20 mmol) in MeCN (20 ml) is added $\text{Ce}(\text{NH}_4)_2(\text{NO}_2)_6$ (2.97 g, 8.78 mmol) in H_2O (20 ml) dropwise at room temperature. After stirring for 10 min, the mixture is diluted with Et_2O (30 ml) and sat. aq. NaHCO_3 (20 ml) and the organic layer is separated. The organic layer is washed with brine, dried over MgSO_4 , and evaporated under reduced pressure. The residue is purified by chromatography on a silica gel column (30 g) using Et_2O -hexane (5:1 v/v) as eluent to give pure **8** as a yellow oil; yield: 471 mg (81%); $[\alpha]_{\text{D}}^{27} +6.33^{\circ}$ (c 1.12, CHCl_3). Ir (neat) ν_{max} : $3350, 1650\text{ cm}^{-1}$; ^1H nmr (CDCl_3): δ 3.95 (t, $J=7.0$ Hz, 2H), 2.58 (m, 4H), 2.05 (s, 3H), 2.00 (s, 6H), 1.90 – 1.45 (m, 4H), 1.33 (s, 3H); ms (m/z): 266 (M^+), 178 (100%). Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4$: 266.1518. Found: 266.1498.

(S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-ethanol (2) ——— The benzoquinone (**8**) (471 mg, 1.77 mmol) in AcOEt (7 ml) is hydrogenated over 10% Pd-C (50 mg) at atmospheric pressure for 2 h at room temperature. After removal of the catalyst, the solvent is removed under reduced pressure to leave the air-sensitive hydroquinone (**9**) which is immediately refluxed with *p*-toluenesulfonic acid (20 mg) in benzene (15 ml) for 1 h. The mixture is washed with sat. aq. NaHCO_3 (5 ml), dried over MgSO_4 , and evaporated under reduced pressure. The residue is purified by chromatography on a silica gel column (20 g) using Et_2O -hexane (1:1 v/v) as eluent to give the pure chromanethanol (**2**) as colorless needles (CH_2Cl_2 -hexane); yield: 310 mg (71%); mp $137 - 138\text{ }^{\circ}\text{C}$ (lit.:^{2d} $136.5 - 137.5\text{ }^{\circ}\text{C}$); $[\alpha]_{\text{D}}^{27} -4.06^{\circ}$ (c 0.70, MeOH). Ir (Nujol) ν_{max} : 3400 cm^{-1} ; ^1H nmr (CDCl_3): δ 4.70 (br s, 1H, exchangeable with D_2O), 3.90 (t, $J=7.0$ Hz, 2H), 2.66 (t, $J=7.0$ Hz, 2H), 2.16 (s, 3H), 2.10 (s, 6H), 2.20 – 1.70 (m, 4H), 1.28 (s, 3H); ms (m/z): 250 (M^+), 164 (100%).

Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1567. Bis-MTPA (both enantiomers) esters of **2** do not show any detectable signals (>98% ee) of enantiomeric impurity in their 1H nmr spectra (500 MHz).

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6. Optically pure material, $[\alpha]_D^{27} -22.16^\circ$ (*c* 1.17, EtOH) (>98% ee), was used. Optical purity was determined by analysis of 1H nmr spectra (500 MHz) of MTPA (both enantiomers) esters derived from *N,N*-dimethylmevalonic amide prepared from the natural product.
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