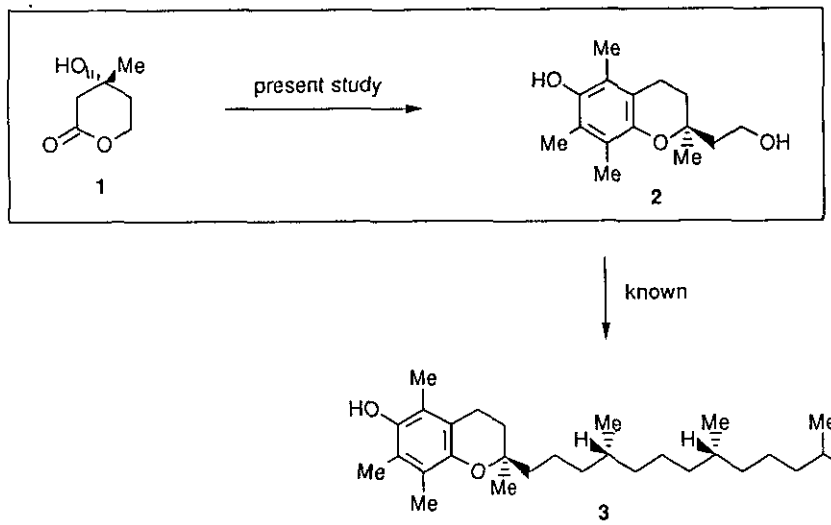
A FACILE CONVERSION OF NATURAL (*R*)-MEVALONOLACTONE INTO A VITAMIN E KEY INTERMEDIATE

Seiichi Takano,* Youichi Shimazaki, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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

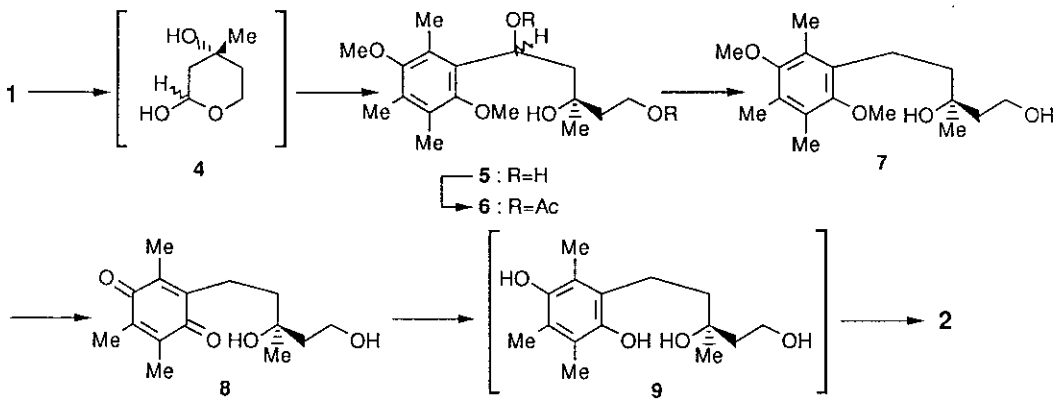
It has been reported that physiological activity of vitamin E (**3**) mostly owes to the chirality of 2 position of its chroman moiety.[1] Enantioselective construction of the 2-position[2] is, therefore, the most important. We report herein facile and efficient incorporation of (*R*)-mevalonolactone (**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 °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 ^{1}H 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. ^{1}H 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° (*c* 1.17, EtOH), ~100% ee] (89 mg, 0.68 mmol) in THF (3 ml) is added diisobutylaluminum hydride in CH_2Cl_2 (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% NH_4OH (3 ml), the mixture is diluted with Et_2O (20 ml) and filtered through Celite. The organic layer separated is washed with brine (5 ml), dried over $MgSO_4$, 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 ($CDCl_3$): 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 $C_{17}H_{28}O_5$: 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 CH_2Cl_2 (15 ml) is added Ac_2O (1.89 ml, 20 mmol), triethylamine (3.48 ml, 25 mmol), and 4-*N*,*N*-dimethylaminopyridine (50 mg) and mixture is stirred at room temperature for 1 h. The mixture is diluted with CH_2Cl_2 (50 ml) and washed with sat. aq. $NaHCO_3$ (20 ml x 2), brine (20 ml), and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (50 g) using Et_2O-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 ($CDCl_3$): 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 $C_{17}H_{28}O_4$: 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. NH_3 (ca. 15 ml) was

added lithium metal (20 mg, 2.86 m atom) portionwise at –33 °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%); $[\alpha]_D^{25}$ +3.80° (*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 $C_{17}H_{28}O_4$: 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 $Ce(NH_4)_2(NO_2)_6$ (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%); $[\alpha]_D^{27}$ +6.33° (*c* 1.12, $CHCl_3$). Ir (neat) ν_{max}: 3350, 1650 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 $C_{15}H_{22}O_4$: 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 °C (lit.:[2d] 136.5 – 137.5 °C); $[\alpha]_D^{27}$ –4.06° (*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).

ACKNOWLEDGMENTS

We thank Asahi Denka Co., Tokyo, for the donation of a large quantity of (*R*)-mevalonolactone produced by fermentation.

REFERENCES AND NOTE

1. Cf. E. Niki, *J. Syn. Org. Chem.*, 1989, **47**, 902.
2. Enantiocontrolled construction of the chroman moiety, see: (a) H. Mayer, P. Schudel, R. Ruegg, and O. Isler, *Helv. Chim. Acta*, 1963, **46**, 650; (b) J. W. Scott, F. T. Bizzarro, D. R. Parrish, and G. Saucy, *ibid.*, 1976, **59**, 290; (c) R. Barner and M. Schmidt, *ibid.*, 1979, **62**, 2384; (d) N. Cohen, R. J. Lopresti, and G. Saucy, *J. Am. Chem. Soc.*, 1979, **101**, 6710; (e) J. M. Akkerman, H. de Koning, and H. O. Huisman, *Heterocycles*, 1981, **15**, 797; (f) C. Fuganti and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, **1982**, 205; (g) Y. Sakito and G. Suzukamo, *Tetrahedron Lett.*, 1982, **23**, 4953; (h) G. Solladie and G. Moine, *J. Am. Chem. Soc.*, **1984**, 106, 6097; (i) K. Takabe, K. Okisaka, Y. Uchiyama, T. Katagiri, and H. Yoda, *Chemistry Lett.*, **1985**, 561; (j) T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, 1987, **109**, 527; (k) S. Inoue, H. Ikeda, S. Sato, K. Horie, T. Ota, O. Miyamoto, and K. Sato, *J. Org. Chem.*, 1987, **52**, 5495; (l) H. Yoda and K. Takabe, *Chemistry Lett.*, **1989**, 465.
3. A. Endo and S. Koike, Japan Kokai Patent, 63-2164847 (1988).
4. (*R*)-Mevalonolactone may also be obtained by enantiocontrolled synthesis, for example, see: S. Takano, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1984**, 82; F. Bonadies, G. Rossi, and C. Bonini, *Tetrahedron Lett.*, 1984, **25**, 5431; S. V. Frye and E. Eliel, *J. Org. Chem.*, 1985, **50**, 3402; K. Mori and K. Okada, *Tetrahedron*, 1985, **41**, 557; S. Takano, Y. Shimazaki, Y. Iwabuchi, and K. Ogasawara, to be submitted.
5. (a) N. Cohen, B. L. Banner, and C. Neukom, *Synth. Commun.*, 1982, **12**, 57; (b) Y. Fujita, M. Shiono, K. Ejiri, and K. Saita, *Chemistry Lett.*, **1985**, 1399; (c) N. Cohen, W. S. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, *J. Org. Chem.*, 1986, **41**, 3505.
6. Optically pure material, $[\alpha]_D^{27}$ –22.16° (*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.
7. 1,4-Dimethoxy-2,3,5-trimethylbenzene generated from surplus of the Grignard reagent could be recovered and recycled after bromination.
8. N. Cohen, R. J. Lopresti, and C. Neukom, *J. Org. Chem.*, 1981, **46**, 2445.

Received, 23rd March, 1990