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 intermediate2b,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\textsuperscript{3,6} with diisobutylaluminum hydride (1.2 equiv.), followed by the Grignard reagent prepared from 2,5-dimethoxy-3,4,6-trimethyl-bromobenzene (9 equiv.),\textsuperscript{7} in the same flask at \(-30^\circ\text{C}\) 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,\textsuperscript{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\textsuperscript{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 \(^1\text{H}\) 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.\textsuperscript{5c,6}

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

\textbf{EXPERIMENTAL SECTION}

All reactions except reduction were carried out under argon. Ir spectra were measured with a JASCO A-102 spectrophotometer. \(^1\text{H}\) 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.

(3R,5R/S)-5-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methylpentane-1,3,5-triol (5) —— To a stirred solution of (-)-mevalonolactone (1) [[α]D27 -22.16° (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 mmol) 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 C17H24O5: 312.1937. Found: 312.1926 (MC).

As a less polar fraction 1,4-dimethoxy-2,3,6-trimethylbenzene (878 mg, 89%) is recovered and is recycled after bromination.

(3R,5R/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: 180 mg (80%). 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, 3H), 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.

(3S)-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, 0.26 m atom) portionwise at −33 °C. After stirring at the same
temperature for 10 min, the mixture is treated with NH₄Cl (ca. 0.5 g) and most of NH₃ is evaporated
at room temperature. The residue is extracted with Et₂O (30 ml) and the extract is washed with sat.
aq. NaHCO₃, brine, and dried over MgSO₄. After evaporation of the solvent under reduced
pressure, the residue is purified by chromatography on a silica gel column (5 g) using Et₂O-hexane
(2:3 v/v) as eluent to give pure 7 as a colorless oil; yield: 75 mg (76%); [a]D²⁵ +3.80° (c 1.50,
CHCl₃). IR (neat) νmax: 3350 cm⁻¹; ¹H nmr (CDCl₃): 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

(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(NH₄)₂(NO₃)₆ (2.97 g, 8.78
mmol) in H₂O (20 ml) dropwise at room temperature. After stirring for 10 min, the mixture is diluted
with Et₂O (30 ml) and sat. aq. NaHCO₃ (20 ml) and the organic layer is separated. The organic
layer is washed with brine, dried over MgSO₄, and evaporated under reduced pressure. The
residue is purified by chromatography on a silica gel column (30 g) using Et₂O-hexane
(5:1 v/v) as eluent to give pure 8 as a yellow oil; yield: 471 mg (81%); [a]D²⁷ +6.33° (c 1.12, CHCl₃).
IR (neat) νmax: 3350, 1650 cm⁻¹; ¹H nmr (CDCl₃): 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 C₁₅H₂₂O₄:
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.
NaHCO₃ (5 ml), dried over MgSO₄, and evaporated under reduced pressure. The residue is
purified by chromatography on a silica gel column (20 g) using Et₂O-hexane (1:1 v/v) as eluent to
give the pure chromanethanol (2) as colorless needles (CH₂Cl₂-hexane); yield: 310 mg (71%); mp
137 – 138 °C (lit.: 2nd 136.5 – 137.5 °C); [α]D²⁷ −4.06° (c 0.70, MeOH). IR (Nujol) νmax: 3400 cm⁻¹; ¹H
nmr (CDCl₃): δ 4.70 (br s, 1H, exchangeable with D₂O), 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\textsubscript{15}H\textsubscript{22}O\textsubscript{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 \textsuperscript{1}H nmr spectra (500 MHz).

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REFERENCES AND NOTE

6. Optically pure material, [\alpha]_D^{27} +22.16^o (c 1.17, EtOH) (>98% ee), was used. Optical purity was determined by analysis of \textsuperscript{1}H nmr spectra (500 MHz) of MTPA (both enantiomers) esters derived from N,N-dimethylmevalonicamide 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.

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