THE SYNTHESIS OF C-13 LABELED VITAMIN E,
[8'a-13C]all-rac-α-TOCOPHEROL

Shiro Urano*, Kumiko Tokuzawa, Shun-ichiro Nakano
and Mitsuyoshi Matsuo

Tokyo Metropolitan Institute of Gerontology, 35-2 Sakae-cho,
Itabashi-ku, Tokyo 173, Japan

Abstract — Vitamin E with a 13C-labeled isoprenoid side chain,
[8'a-13C]all-rac-α-tocopherol (1), was synthesized using 6-methoxymethoxy-
2,5,7,8-tetramethyl-2-(5-mercaptothiazolyl-4-methyl-3-penten-1-yl)-
chroman (8) as a key intermediate and [13C]methyl iodide as a 13C source.
The total yield of the labeled tocopherol based on [13C]methyl iodide
was 51.2%.

Recently, considerable attention has been focused on the action of α-tocopherol (vitamin E),
which is considered to prevent organs from oxidative lesion, especially peroxidative damage
of lipids in membrane. However, the mode of vitamin E action in biomembrane is still unclear.
For the elucidation of interaction between α-tocopherol and lipids in biomembrane, α-tocopherol
with a 13C-labeled isoprenoid side chain is presumed to be very useful. In order to obtain
the α-tocopherol, we have developed a new route for the synthesis of α-tocopherol using a key
intermediate, 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolyl-4-methyl-3-
penten-1-yl)chroman (8). We now wish to report the preparation of [8'a-13C]all-rac-
α-tocopherol (1).

3-Methyl-2-buten-1-ol (2) was brominated with phosphorus tribromide in dry ether at 0°C
for 15 min. The reaction product was allowed to react with methyl acetoacetate in
tetrahydrofuran at 0°C in the presence of equimolar amounts of sodium hydride and n-butyl lithium
to afford methyl 3-oxo-7-methyl-6-octenoate (4) in 79.0%. For protection of a ketonic group
of 4 as a ketal group, 4 and ethylene glycol were refluxed in dry benzene with a catalytic
amount of p-toluenesulfonic acid. Methyl 3,3-ethylendioxy-7-methyl-6-octenoate resulted was
reduced with lithium aluminium hydride in dry ether to give the corresponding alcohol (6). By a
treatment of 6 with carbon tetrabromide and triphenylphosphine in dry benzene under reflux for

- 257 -
30 min, 3,3-ethyldioxy-7-methyl-6-octenyl bromide \((\text{7})\) was obtained in 52.0% yield from \(\text{6}\).  

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\begin{align*}
\text{OH} & \xrightarrow{\text{PBr}_3} \underset{\text{Br}}{\text{OH}} \xrightarrow{\text{CH}_3\text{COCH}_2\text{CO}_2\text{Me}} \underset{\text{MnH/n-BuLi}}{\text{CH}} \xrightarrow{\text{COOMe}} \\
\text{(2)} & \quad \text{(3)} \quad \text{(4)}
\end{align*}
\]

6-Methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman \((\text{8})\), which was prepared previously, \(^3\) was allowed to react with \(\text{7}\) and n-butyl lithium in a mixture of tetrahydrofuran and hexamethylphosphoramide (24:1 v/v) in a dry ice-acetone bath to afford 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(4,12-dimethyl-8,8-ethyldioxy-5-5-mercaptothiazolinyl-3,11-tridecadien-1-yl)chroman \((\text{9})\) in 77.1% yield. \(^7\) With zinc \(\text{9}\) was desulfurized in acetic acid, and then the product obtained was converted into 6-hydroxy-2,5,7,8-tetramethyl-2-(4,12-dimethyl-8-oxo-3,11-tridecadien-1-yl)chroman \((\text{10})\) in hydrogen chloride-saturated methanol in 87.2% yield. \(^8\) The reaction of \(\text{10}\) with trityl[\(^{13}\)C]methylphosphonium iodide, which was derived from \([^{13}\text{C}]\text{methyl iodide (}^{13}\text{C} 90 \text{ atom }\%)\text{, Merck Sharp and Dohme, Montreal, Canada},\) in the presence of n-butyl lithium in dry tetrahydrofuran gave 6-hydroxy-2,5,7,8-tetramethyl-2-(4,12-dimethyl-8-[methylene-\(^{13}\)C]-3,11-tridecadien-1-yl)chroman \((\text{11})\) in 60.1% yield. \(^9\) On reduction of \(\text{11}\) under 50 atmospheres of hydrogen at room temperature in the presence of platinum dioxide, the desired \([8'a-^{13}\text{C}]\text{all-rac-}\alpha\text{-tocopherol (}\text{1}\) was obtained in 87.2% yield. The \(^{13}\text{C}\)-labeling of C-8' in \(\text{1}\) was proved spectroscopically; in the \(^1\text{H}-\text{NMR} \text{ spectrum (CDCl}_3\text{)}\text{ a signal at 0.86 ppm is split with a coupling constant of 124.0 Hz (}J_{\text{C-H}}\text{) and in the }^{13}\text{C}-\text{NMR} \text{ spectrum (CDCl}_3\text{) the intensity of a signal at 19.7 ppm is extremely increased and a signal at 32.7 ppm is split with a coupling constant of 35.4 Hz (}J_{\text{C-C}}\text{). The total yield of }\text{1}\text{ based on }^{[13}\text{C}]\text{methyl iodide was 51.2%}.\)
REFERENCES AND NOTES

1) TMIG-I No. 55.


4) Mass 184 (M+); IR (neat) 1709, 1745 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\), 1.63, 1.68 (each s, 3H, -CH₃), 2.27 (m, 2H, -C=CH₂-), 2.57 (t, 2H, J=8.0 Hz, -CH₂CO-), 3.84 (s, 2H, -CO-CH₂-CO₂Me), 3.74 (s, 3H, -O-CH₃), 5.07 (bt, 1H, J=8.0 Hz, =C-H); \(^{13}\)C-NMR (CDCl\(_3\)) 6, 202.3 (s), 167.6 (s), 133.1 (s), 52.3 (q), 49.1 (t), 43.1 (t), 25.6 (q), 22.3 (t), 17.6 (q).

5) Mass 200 (M+); IR (neat) 3500 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\), 1.61, 1.68 (each s, 3H, -CH₃), 1.70 (bt, 2H, -CH₂-CO), 1.96 (t, 2H, J=8.0 Hz, -CH₂-CO₂O), 3.78 (bd, 2H, -CH₂OH), 4.05 (s, 4H, -O-CH₂-CH₂-O-), 5.12 (t, 1H, J=8.0 Hz, =C-H); \(^{13}\)C-NMR (CDCl\(_3\)) 6, 131.8 (s), 123.8 (d), 111.9
Because this brominated compound is very unstable, it was used in the next step without purification.

7) Mass 645 (M⁺); UV (methanol) 284 (ε:4900), 280 (ε:4300) nm; ¹H-NMR (CDCl₃) δ, 1.29 (s, 3H, -CH₃), 1.62, 1.66, 1.68 (each s, 3H, =C-CH₃), 2.10, 2.15, 2.19 (each s, 3H, =C-CH₃), 3.35 (t, 2H, J=8.0 Hz, -S-CH₂⁻), 3.92 (s, 4H, -O-CH₂-CH₂-O⁻), 4.21 (m, 3H, -N-CH⁻, -S-CH⁻); ¹³C-NMR (CDCl₃) δ, 148.0 (s), 146.9 (s), 133.3 (s), 129.0 (d), 128.2 (s), 126.2 (s), 124.2 (d), 123.0 (s), 117.5 (s), 111.3 (s), 98.0 (t), 74.5 (s), 65.5 (t), 64.4 (t), 55.9 (d), 23.8 (q).

8) Mass 426 (M⁺); IR (neat) 3500, 1710 cm⁻¹; ¹H-NMR (CDCl₃) δ, 1.60, 1.62, 1.69 (each s, 3H, -CH₃), 2.11 (s, 6H, -CH₃), 2.18 (s, 3H, -CH₃), 2.26, 2.40 (each m, 2H, -CH₂-CO⁻), 5.12 (bt, 2H, =C-H); ¹³C-NMR (CDCl₃) δ, 210.7 (s), 145.5 (s), 144.7 (s), 132.6 (d), 122.9 (d), 122.6 (s), 121.2 (s), 118.7 (s), 76.1 (s), 42.9 (t).

9) Mass 425 (M⁺); IR (neat) 3450 cm⁻¹; UV (methanol) 281 (ε:4600) nm; ¹H-NMR (CDCl₃) δ, 4.76 (d, 2H, J=152.6 Hz, ¹³CH₂=C); ¹³C-NMR (CDCl₃) δ, 108.9 (t, ¹³C-enriched).

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