THE SYNTHESIS OF C-13 LABELED VITAMIN E, [8'a-^{13}C]all-rac-α-TOCOPHEROL[1]

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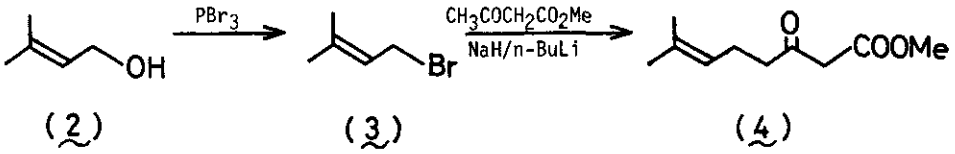
Abstract —— Vitamin E with a ^{13}C-labeled isoprenoid side chain, [8'a-^{13}C]all-rac-α-tocopherol (1), was synthesized using 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)-chroman (8) as a key intermediate and [^{13}C]methyl iodide as a ^{13}C source. The total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

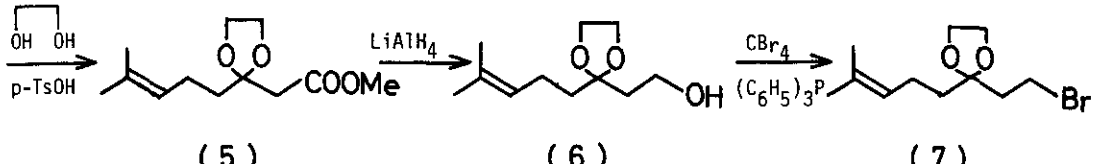
Recently, considerable attention has been focused on the action of α-tocopherol (vitamin E), which is considered to prevent organs from oxidative lesion, especially peroxidative damage of lipids in membrane.[2] However, the mode of vitamin E action in biomembrane is still unclear. For the elucidation of interaction between α-tocopherol and lipids in biomembrane, α-tocopherol with a ^{13}C-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-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (8).[3] We now wish to report the preparation of [8'a-^{13}C]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%.[4] 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 ehter to give the corresponding alcohol (6).[5] By a treatment of 6 with carbon tetrabromide and triphenylphosphine in dry benzene under reflux for

30 min, 3,3-ethylendioxy-7-methyl-6-octenyl bromide (7) was obtained in 52.0% yield from 4.[6]

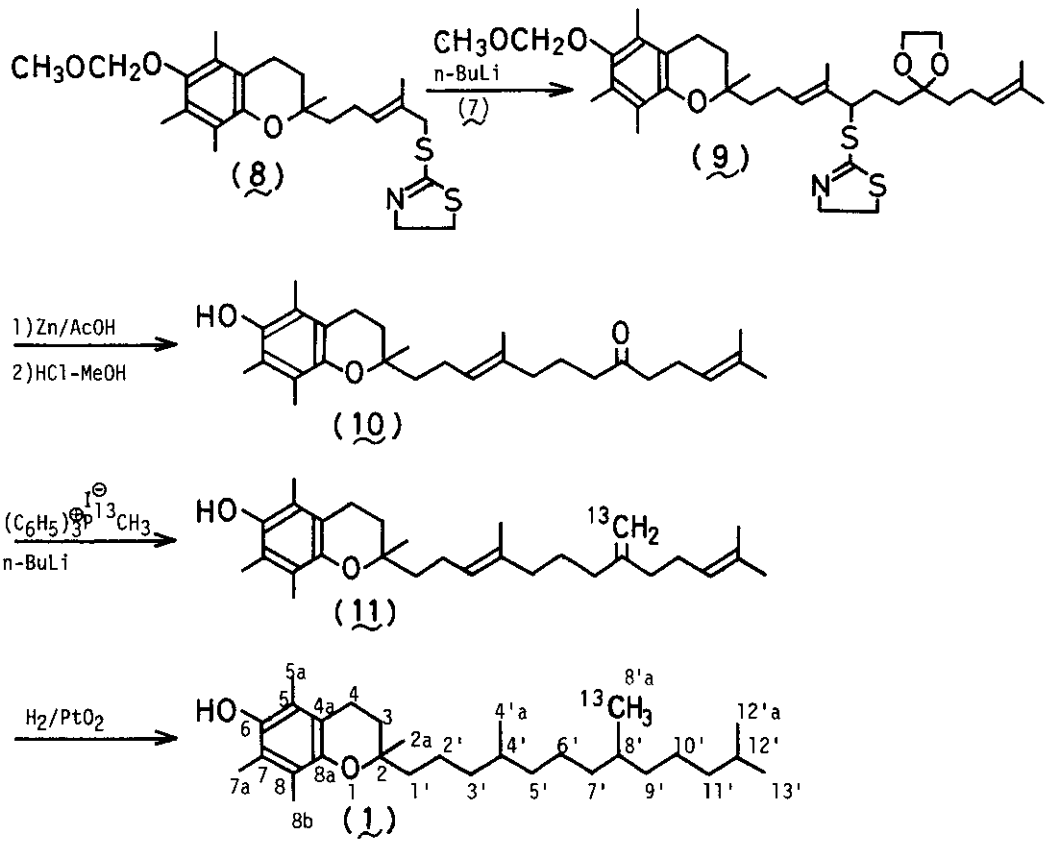


(2) (3) (4)



(5) (6) (7)

6-Methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (8), which was prepared previously,[3] was allowed to react with 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-ethylendioxy-5-5-mercaptothiazolinyl-3,11-tridecadien-1-yl)chroman (9) in 77.1% yield.[7] With zinc 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 (10) in hydrogen chloride-saturated methanol in 87.2% yield.[8] The reaction of 10 with triphenyl[^{13}C]methylphosphonium iodide, which was derived from [^{13}C]methyl iodide (^{13}C 90 atom %; 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 (11) in 60.1% yield.[9] On reduction of 11 under 50 atmospheres of hydrogen at room temperature in the presence of platinum dioxide, the desired [8'a-^{13}C]all-rac-α-tocopherol (1) was obtained in 87.2% yield. The ^{13}C-labeling of C-8' in 1 was proved spectroscopically; in the ^{1}H-NMR spectrum ($CDCl_3$) a signal at 0.86 ppm is split with a coupling constant of 124.0 Hz (J_{C-H}) and in the ^{13}C-NMR spectrum ($CDCl_3$) 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_{C-C}). The total yield of 1 based on [^{13}C]methyl iodide was 51.2%.



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1) TMIG-I No. 55.

2) P. P. Nair and H. J. Kayden, Ann. N. Y. Acad. Sci.,1972, 203, 1 ; J. B. Bieri and Anderson, Arch. Biochem. Biophys., 1960, 90, 105.

3) S. Urano, S. Nakano and M. Matsuo, Chem. Pharm. Bull., 1983, 31, 4341.

4) Mass 184 (M^+); IR (neat) 1709, 1745 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 1.63, 1.68 (each s, 3H, $-CH_3$), 2.27 (m, 2H, $=C-CH_2-$), 2.57 (t, 2H, J=8.0 Hz, $-CH_2CO-$), 3.84 (s, 2H, $-CO-CH_2-CO_2Me$), 3.74 (s, 3H, $-O-CH_3$), 5.07 (bt, 1H, J=8.0 Hz, =C-H); ^{13}C-NMR ($CDCl_3$) δ, 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 ($CDCl_3$) δ, 1.61, 1.68 (each s, 3H, $-CH_3$), 1.70 (bt, 2H, $-CH_2-C<^{O}_{O}$), 1.96 (t, 2H, J=8.0 Hz, $-CH_2-C<^{O}_{O}$), 3.78 (bd, 2H, $-CH_2OH$), 4.05 (s, 4H, $-O-CH_2-CH_2-O-$), 5.12 (t, 1H, J=8.0 Hz, =C-H); ^{13}C-NMR ($CDCl_3$) δ, 131.8 (s), 123.8 (d), 111.9

(s), 64.8 (t), 58.7 (t), 38.5 (t), 37.3 (t), 25.6 (q), 22.5 (t), 17.6 (q).

6) 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; ^{1}H-NMR ($CDCl_3$) δ, 1.29,(s, 3H, $-CH_3$), 1.62, 1.66, 1.68 (each s, 3H, $=C-CH_3$), 2.10, 2.15, 2.19 (each s, 3H, $=C-CH_3$), 3.35 (t, 2H, J=8.0 Hz, $-S-CH_2-$), 3.92 (s, 4H, $-O-CH_2-CH_2-O-$), 4.21 (m, 3H, $-N-CH_2-$, -S-CH-); ^{13}C-NMR ($CDCl_3$) 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}; ^{1}H-NMR ($CDCl_3$) δ, 1.60, 1.62, 1.69 (each s, 3H, $-CH_3$), 2.11 (s, 6H, $-CH_3$), 2.18 (s, 3H, $-CH_3$), 2.26, 2.40 (each m, 2H, $-CH_2-CO-$), 5.12 (bt, 2H,=C-H); ^{13}C-NMR ($CDCl_3$) 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; ^{1}H-NMR ($CDCl_3$) δ, 4.76 (d, 2H, J_{C-H}=152.6 Hz, $^{13}CH_2=C$); ^{13}C-NMR ($CDCl_3$) δ, 108.9 (t, ^{13}C-enriched).

Received, 8th October, 1983