THE SYNTHESIS OF C-13 LABELED VITAMIN E, [6'-^{13}C]all-rac-α-TOCOPHEROL[1]

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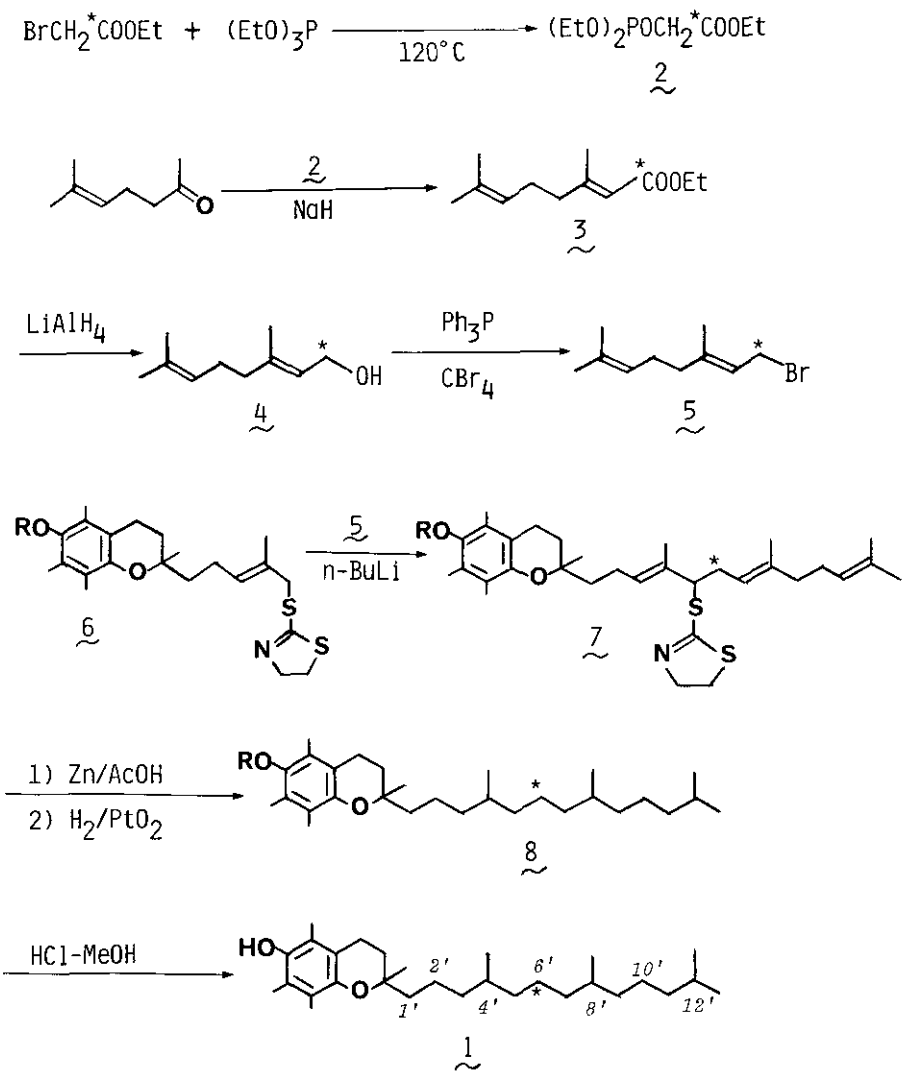
Abstract- Vitamin E with a ^{13}C-labeled isoprenoid side chain, [6'-^{13}C]all-rac-α-tocopherol (1), was synthesized using 6-methoxymethoxy-2,5,7,8-tetramethyl-2-[(E)-4-methyl-5-(thiazolin-2-yl)thio-3-penten-1-yl]chroman (6) as a key intermediate and ethyl [1-^{13}C]bromoacetate as a ^{13}C source. The overall yield of 1 based on ethyl [1-^{13}C]bromoacetate was 19.2%.

Vitamin E, especially α-tocopherol, seems to act as an antioxidant in the matrix of biomembranes in which it is mostly located.[2] In addition, vitamin E has been proposed to act as its structural component, which stabilizes biomembranes containing polyunsaturated lipids. This membrane-stabilizing effect is presumed to arise from a physicochemicalinteraction between the isoprenoid side chain of α-tocopherol and the polyunsaturated fatty acid, particularly arachidonic acid, moieties of the phospholipids in biomembranes.[3] However, no evidence has been obtained to show that this physicochemical interaction exists in biomembranes. One of possible techniques for the verification of the above hypothesis would be the measurement of ^{13}C-relaxation time (T_1) on vitamin E in biomembranes. For these T_1 measurement, α-tocopherol having a ^{13}C-labeled isoprenoid side chain is very useful. We have recently reported the synthesis of α-tocopherol having a ^{13}C-labeled methyl group in its isoprenoid side chain.[4] Using this ^{13}C-labeled α-tocopherol, we are studying the motional property of methyl groups of the isoprenoid side chain in biomembrane lipid core containing polyunsaturated lipids. Further, we ecxpect to determine the segmental motion of the isoprenoid side chain in biomembrane lipid core on the basis of the T_1 values of the ^{13}C-labeled methylene carbon atoms in the isoprenoid side chain of α-tocopherol in polyunsaturated lipids core.

We now wish to report the preparation of [6'-^{13}C]all-rac-α-tocopherol, which is necessary for the T_1 measurement of a ^{13}C-labeled methylene in its isoprenoid side chain.

Ethyl [1-^{13}C]bromoacetate was treated with an equivalent of triethyl phosphite at 120 °C for 2 h to give triethyl [1-^{13}C]phosphonoacetate (2) in 98.5% yield. In the presence of sodium hydride, 2 reacted with 2-methyl-2-hepten-6-one in dry tetrahydrofuran at 0 °C for 2 h to give ethyl [1-^{13}C]3,7-dimethyl-2,6-octadienoate (3) in 60.6% yield.[5] With $LiAlH_4$, 3 was reduced in dry ether at 0 °C to give [1-^{13}C]geraniol (4) in 73.7% yield.[6]



*C: ^{13}C, R: CH_2OCH_3

By a treatment with carbon tetrabromide and triphenyl phosphine in dry benzene under reflux, 4 was converted into [1-^{13}C]geranyl bromide (5). Because of its instability, 5 was used in the next step without further purification. As previously reported,[4a] 6-methoxymethoxy-2,5,7,8-tetramethyl-2-[(E)-4-methyl-5-(thiazolin-2-yl)thio-3-penten-1-yl]chroman (6) was reacted with 5 in the presence of n-butyllithium to give a coupling product, 6-methoxymethoxy-2,5,7,8-tetramethyl-2-[[6-^{13}C](3E,7E,11E)-4,8,12-trimethyl-5-(thiazolin-2-yl)thio-3,7,11-tridecatrien-1-yl]chroman (7) in 78.0% yield from 5.[7] With zinc powder, 7 was desulfurized in acetic acid at room temperature, and then the product obtained was reduced under 50 atm of hydrogen in the presence of platinum oxide to give 6-methoxymethoxy-2,5,7,8-tetramethyl-2-([6-^{13}C]4,8,12-trimethyltridec-1-yl)chroman (8) in 56.0% yield from 7.[8] Finally, the methoxymethyl group was removed by the use of methanolic hydrogen chloride to give the desired [6'-^{13}C]all-rac-α-tocopherol in nearly quantitative yield. The labeled position was confirmed on the basis of the marked enhancement of a signal at 24.5 ppm and the coupling of a labeled carbon atom at 6' position to two carbon atoms at 5' and 7' positions (J_{C-C}=35.7 Hz) in the ^{13}C-NMR spectrum. The overall yield of 1 based on [1-^{13}C]ethyl bromoacetate was 19.2%.

REFERENCES AND NOTES

1. TMIG-I No. 70

2. (a) P. M. McCay and M. M. King, "Vitamin E", ed. by L. J. Machlin, Marcel Dekker, Inc. New York, 1980.

(b) A. L. Tappel, "Free Radical in Biology", vol.4, ed. by W. A. Pryor, Academic Press, New York, 1980.

3. J. A. Lucy and J. T. Dilgle, Nature, 1964, 204, 156.

4. (a) S. Urano, S. Nakano and M. Matsuo, Chem. Pharm. Bull., 1983, 31, 4341;

(b) S. Urano, K. Tokuzawa and M. Matsuo, Heterocycles, 1984, 22, 257;

(c) S. Urano, S. Nakano and M. Matsuo, J. Labelled Compounds & Radiopharmaceuticals, 1984, 21, 313;

(d) S. Urano and M. Matsuo, Heterocycles, 1984, 22, 1975;

(e) S. Urano, S. Nakano and M. Matsuo, Chem. Pharm. Bull., 1985, 33, 1266;

(f) S. Urano, R. Muto and M. Matsuo, J. Labelled Compounds & Radiopharmaceuticals, 1985, in press.

5. Mass 197 (M^+); IR (neat) 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ, 1.26 (t, 3H, J=8.0 Hz, $-CH_3$), 1.61, 1.69 (each s, 3H, $=C-CH_3$), 4.14 (q, 2H, J=8.0 Hz, $O-CH_2$), 5.08 (bt, 1H, C=C-H), 5.66 (bs, 1H, C=C-H); ^{13}C-NMR ($CDCl_3$) δ, 166.9 (s, ^{13}C-enriched), 116.1 (dd, J_{C-C}=76.1 Hz).

6. Mass 155 (M^+); IR (neat) 3340 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 1.60 (s,3H,$-CH_3$), 1.66 (s, 6H, $-CH_3$ x 2), 2.10 (bt, 4H, $-CH_2$ x 2), 3.66 (dd, 2H, J_{C-H}=142.0 Hz, $^{13}CH_2$-OH), 5.13 (bt, 1H, C=C-H), 5.44 (bt, 1H, C=C-H); ^{13}C-NMR ($CDCl_3$) δ, 124.1 (dd, J_{C-C}=54.0 Hz), 59.3 (t, ^{13}C-enriched).

7. Mass 586 (M^+); IR (neat) 1570 cm^{-1}; UV (methanol) 278 (ε:2600), 288 (3400) nm; ^{1}H-NMR ($CDCl_3$) δ, 1.24 (s, 3H, $-CH_3$), 1.60, 1.66, 1.69 (each, s, 3H, $-CH_3$), 2.10, 2.16, 2.20 (each s, 3H, $-CH_3$), 3.34 (t, 2H, J=8.0 Hz, $S-CH_2$), 3.62 (s, 3H, $O-CH_3$), 4.21 (t, 2H, J=8.0 Hz, $N-CH_2$); ^{13}C-NMR ($CDCl_3$) δ,55.8 (dd, J_{C-C}=33.5 Hz), 32.4 (t, ^{13}C-enriched).

8 Mass 475 (M^+); IR (neat) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 0.85 (d, 12H, J=8.0 Hz, $-CH_3$ x 4), 2.08, 2.14, 2.18 (each s, $-CH_3$), 2.58 (t, 2H, J=7.5 Hz, $=C-CH_2$), 3.60 (s, 3H, $-O-CH_3$), 4.86 (s, 2H, $O-CH_2-O$); ^{13}C-NMR ($CDCl_3$) δ, 37.4 (dt, J_{C-C}=36.4 Hz), 24.5 (t, ^{13}C-enriched).

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