THE SYNTHESIS OF C-13 LABELED VITAMIN E, [2a-^{13}C]all-rac-α-TOCOPHEROL[1]

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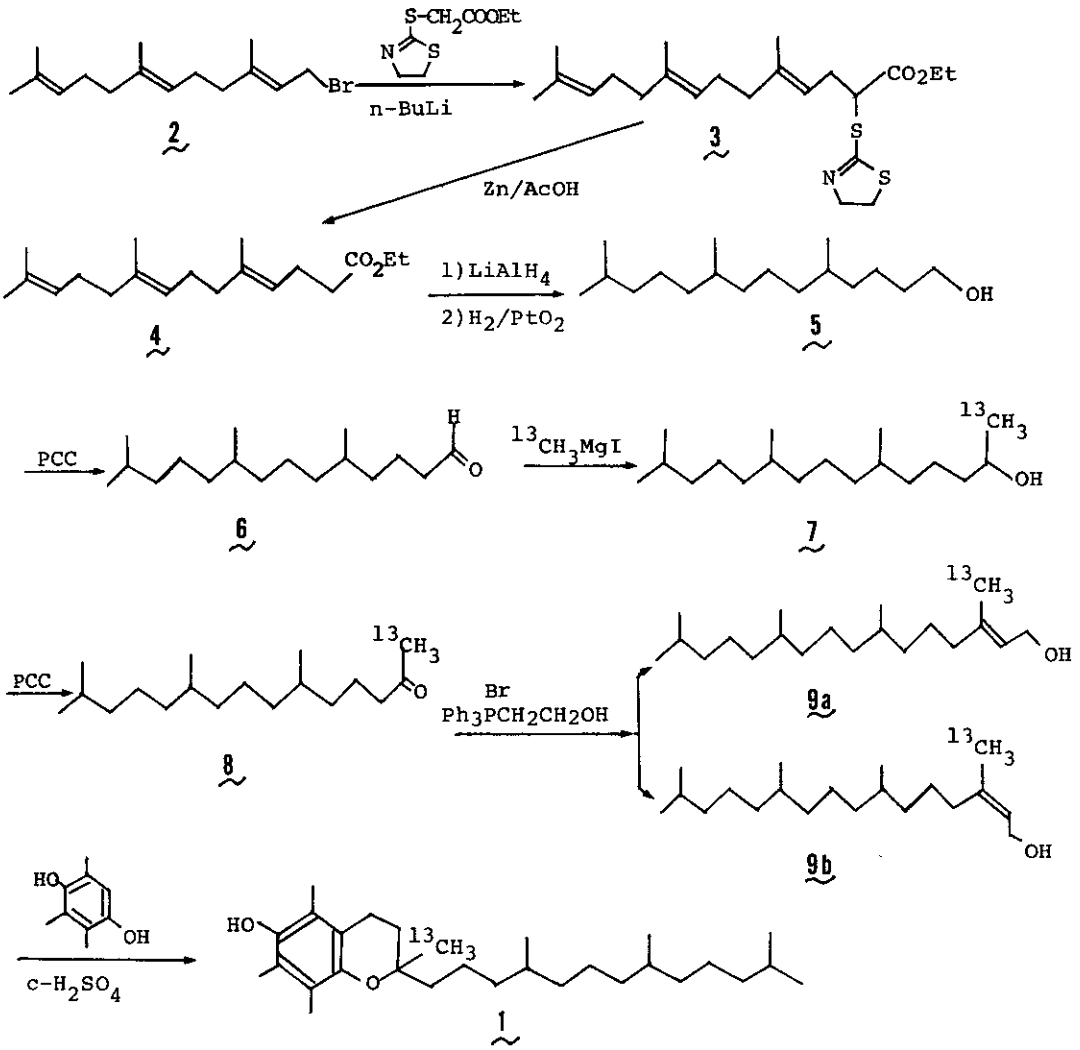
Abstract- Vitamin E with a ^{13}C-labeled isoprenoid side chain, [2a-^{13}C]all-rac-α-tocopherol (1), was synthesized by condensation of trimethylhydroquinone with a mixture of [3a-^{13}C]phytol (9a) and its geometrical isomer (9b). The ^{13}C-labeled phytol was prepared using 5,9,13-trimethyltetradecan-1-al (6) as an intermediate and [^{13}C]methyl iodide as a ^{13}C source. The total yield of the labeled α-tocopherol was 65.4% on the basis of [^{13}C]methyl iodide.

A commonly accepted explanation for the role of vitamin E is that it serves as a biological antioxidant and radical scavenger protecting unsaturated lipids from oxidation by free radical chain reaction *in vivo*.[2] On the other hand, Lucy et al.[3] proposed that vitamin E might stabilize biomembrane through an anchoring effect of its isoprenoid side chain on the fatty acyl, particularly arachidoyl, chains of polyunsaturated phospholipids. This theory, however, is still unproved. To the elucidation of the vitamin E-lipid interaction in biomembrane, it is presumably advantageous to measure the ^{13}C-relaxation times of carbon atoms of its isoprenoid side chain in biomembrane. Vitamin E with a ^{13}C-labeled isoprenoid side chain is necessary to the ^{13}C-NMR study. We have recently established a new route for the synthesis of C-13 labeled α-tocopherol (1).[4] We now wish to report the preparation of [2a-^{13}C]all-rac-α-tocopherol (1). A starting material, farnesyl bromide (2) was treated with ethyl 2-mercaptothiazolinylacetate in the presence of n-butyl lithium to give ethyl 2-mercaptothiazolinyl-5,9,13-trimethyltetradecanoate (3) in 82.1% yield. With zinc powder



3 was desulfurized in acetic acid at room temperature. The product yielded was reduced with $LiAlH_4$ and, successively, under 20 atm of hydrogen in the presence of platinum oxide to give 5,9,13-trimethyltetradecanol (5) in 76.0% yield from 3. With pyridinium chlorochromate (PCC) 5 was converted to 5,9,13-trimethyltetradecan-1-al (6) in 89.2% yield. The Grignard reaction of 6 with [^{13}C]methylmagnesium iodide in dry ether afforded [1-^{13}C]6,10,14-trimethyl-2-pentadecanol (7).[5] On oxidation of 7 with PCC, [1-^{13}C]6,10,14-trimethyl-pentasecan-2-one (8)[6] was produced in 81.7% yield from 6. Treatment of 8 with (2-hydroxyethyl)triphenylphosphonium bromide in dry THF gave a mixture of [3a-^{13}C]phytol (9a) and its geometrical isomer (9b) in 87.4%, of which ratio was 2:3, respectively.[7] A mixture of both compounds was refluxed with tri-

methylhydroquinone in ethyl acetate containing a small amount of sulfuric acid to obtain the desired [2a-^{13}C]all-rac-α-tocopherol (1) in 91.6% yield. The ^{13}C-labeling of C-2a in 1 was proved on the basis of the marked enhancement of a signal due to C-2a (23.8 ppm) and the coupling between C-2a and C-2 (J_{C-C}=40.8 Hz) in ^{13}C-NMR ($CDCl_3$). The total yield of 1 based on [^{13}C]methyl iodide was 65.4%.

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5. Mass 271 (M^+); IR (neat) 3410 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 1.17 (dd, 3H, J_{C-H}= 126.0 Hz, J_{H-H}=8.0 Hz, -$^{13}CH_3$), 3.83 (m, 1H, -CH-OH); ^{13}C-NMR ($CDCl_3$) δ, 68.1 (d, J_{C-C}=38.4 Hz), 23.5 (q, ^{13}C-enriched).

6 Mass 269 (M^+); IR (neat) 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 2.16 (d, 3H, J_{C-H}= 126.0 Hz, -$^{13}CH_3$); ^{13}C-NMR ($CDCl_3$) δ, 209.0 (d, J_{C-C}=39.7 Hz), 29.8 (q, ^{13}C-enriched).

7. (9a); Mass 297 (M^+); IR (neat) 3415 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 1.68 (d, 3H, J_{C-H}=126.0 Hz, -$^{13}CH_3$), 4.16 (bd, 2H, J=7.5 Hz, -CH_2-OH), 5.46 (bt, 1H, J= 7.5 Hz, =C-H); ^{13}C-NMR ($CDCl_3$) δ, 123.6 (d, J_{C-C}=40.9 Hz), 16.2 (q, ^{13}C-enriched). (9b): Mass 297 (M^+); IR (neat) 3415 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, 1.76 (d, 3H, J_{C-H}=126.0 Hz, -$^{13}CH_3$), 4.14 (bd, 2H, J=7.5 Hz, -CH_2-OH), 5.42 (bt, 1H, J=7.5 Hz, =C-H); ^{13}C-NMR ($CDCl_3$) δ, 123.6 (d, J_{C-C}=40.9 Hz), 23.4 (q, ^{13}C-enriched).

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