

THE SYNTHESIS OF REGIOSPECIFICALLY ^{13}C -LABELED α -TOCOPHERYL ACETATE

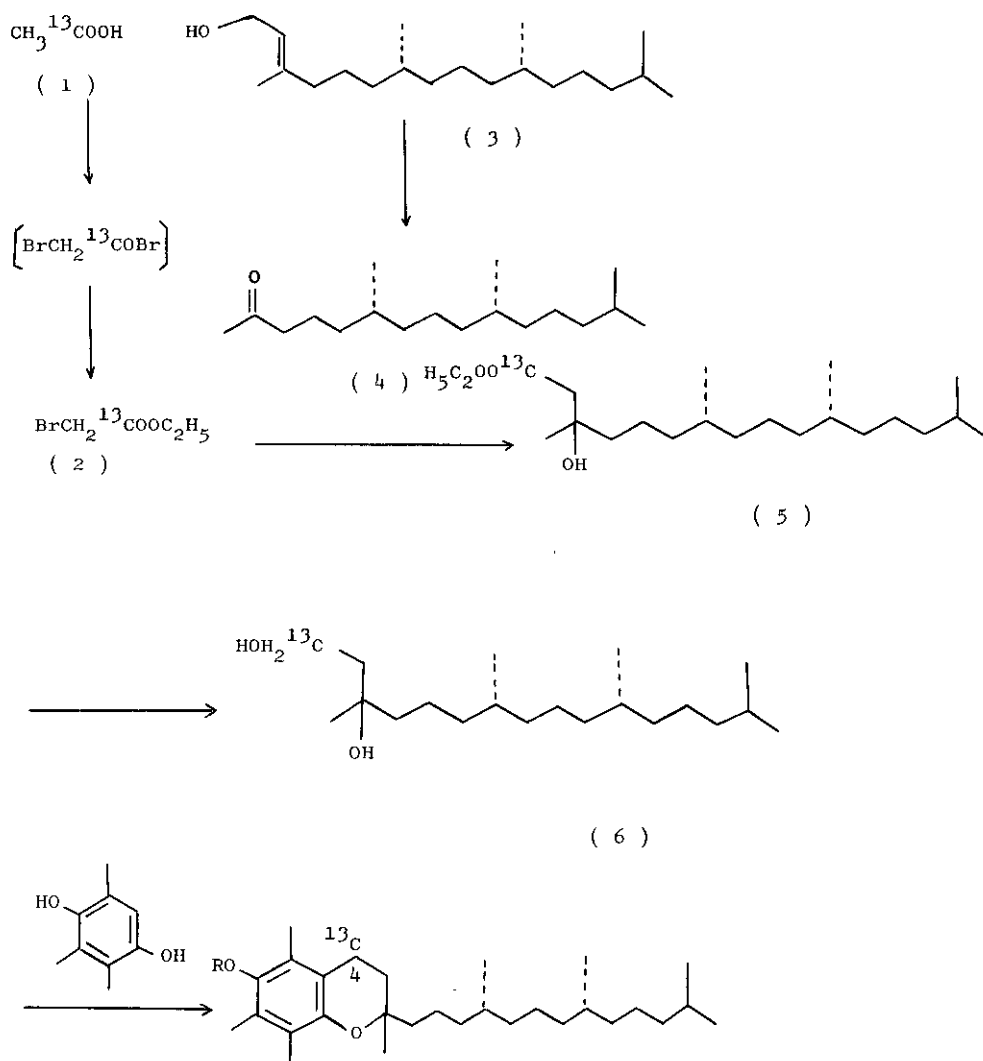
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Summary: A convenient procedure for the synthesis of regiospecifically ^{13}C -labeled α -tocopheryl acetate of high enrichment is described.

The wide applications of ^{13}C -N.M.R. spectroscopy to the study of natural products biosynthesis and metabolic pathway are well established¹. The importance of α -tocopheryl acetate as the pharmaceutical substances and antioxidant reagents prompted us to undertake this study. ^{13}C -labeled chroman ring compounds serve as key substances in mechanistic studies of the biological metabolic pathway and the mechanism of the antioxidation. To our surprise; however, there exist no literature reports which describe ^{13}C -labeled tocopherol, one of the most fundamental compounds. Here we report a convenient synthesis of α -tocopheryl acetate-4- ^{13}C , which is useful to study the metabolic pathway of the animals and the mechanism of the antioxidation, from the acetic acid-1- ^{13}C in four steps (Scheme 1).

An adaptation of Bláha's method² was used to prepare α -tocopheryl acetate-4- ^{13}C . The carefully dried acetic acid-1- ^{13}C (2.0 g; 90 atom %- ^{13}C) (1) was treated with dried red phosphorus and dried bromine, and then followed by absolute ethyl alcohol, so ethyl bromoacetate-1- ^{13}C (2) was obtained in 74% isolated yield after usual workup and by distillation at 152-158° C.³ Phytone (4) was converted from natural phytol (3) by the reported procedure⁴. Reformatsky reaction of the resulting 4.1g of ethyl bromoacetate-1- ^{13}C (2) with (4) and copper-zinc in a mixture of benzene and ethyl ether gave 3-hydroxyester (5). Ethyl tetramethyl-3-hydroxy-hexadecanoate (4.03 g; 5) was converted into the corresponding 1,3-diol (6) by lithium aluminum hydride reduction to yield 1,3-diol-1- ^{13}C (3.5 g; 6) quantitatively. α -Tocopherol-4- ^{13}C was prepared by the condensation of (6) and trimethylhydroquinone in xylene containing p-toluene sulfonic acid.



(7) R= H

(8) R= COCH_3

Scheme 1

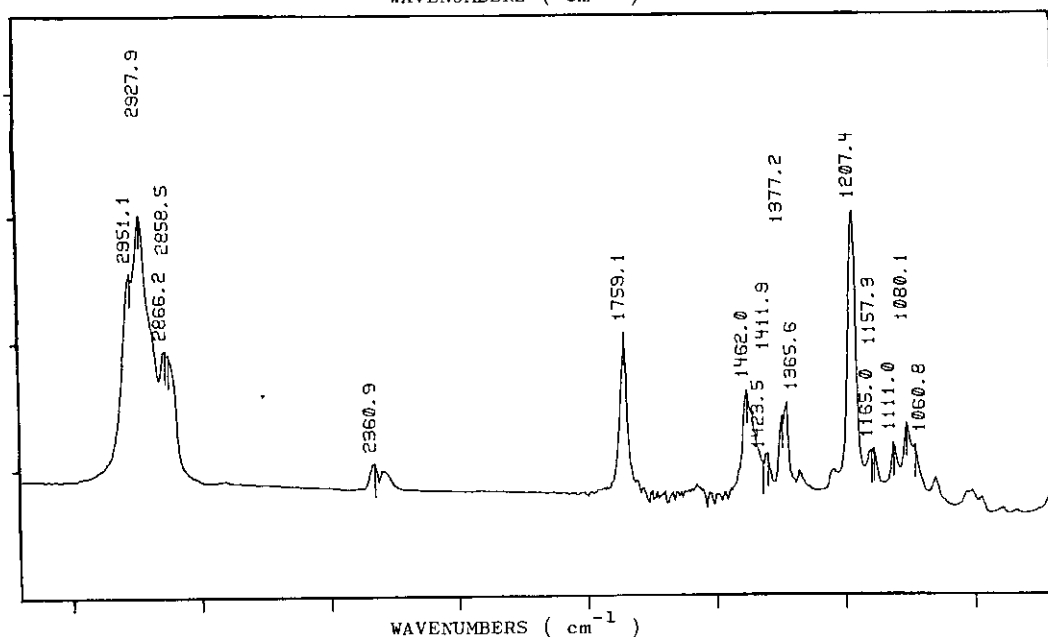
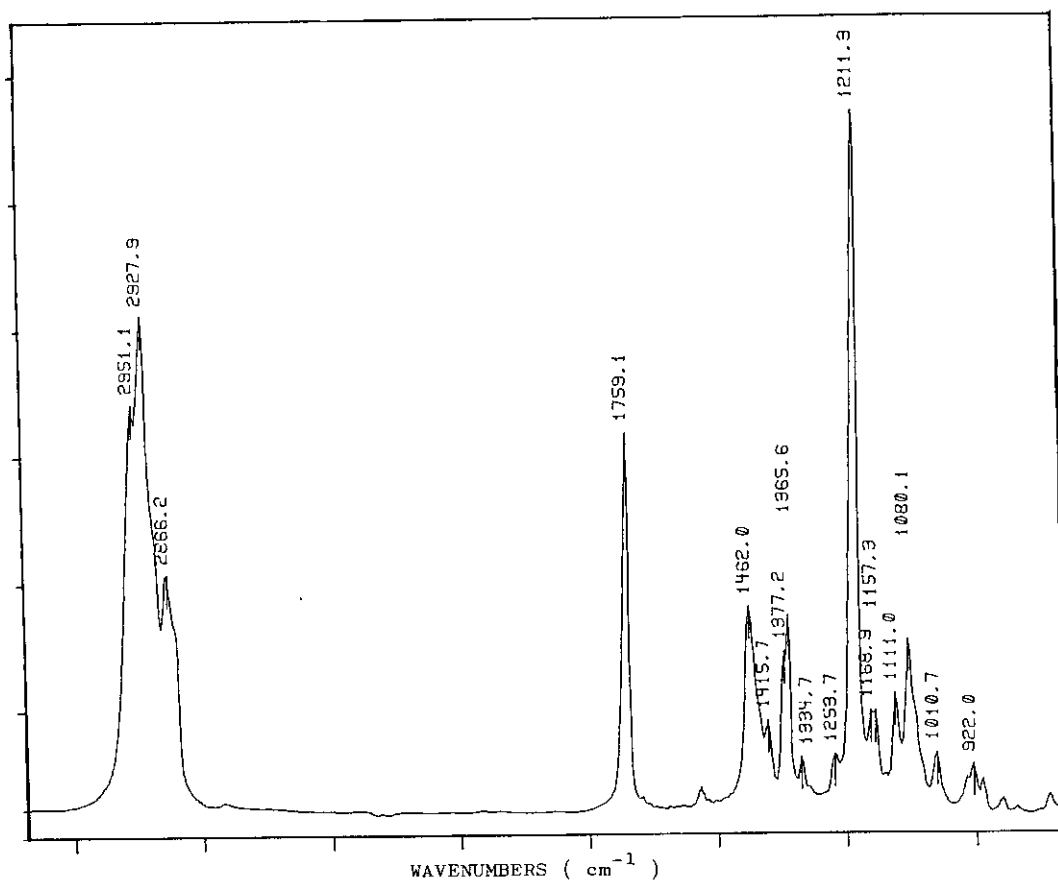


Figure 1. FT-I.R. spectrum of dl-α-tocopheryl acetate (top) and FT-I.R. spectrum of ¹³C-enriched 2-(RS)-α-tocopheryl acetate-4-¹³C (bottom).

For preventing formation of the colored material by autoxidation, the α -tocopherol-4- ^{13}C was acetylated with anhydrous acetic acid and pyridine at room temperature, and the α -tocopheryl acetate-4- ^{13}C (8), which was purified by silica gel chromatography, obtained in 67% yield from (6). Also (7) can be prepared by described method⁵ from (8).

The I.R. spectroscopy absorptions of ^{13}C -labeled α -tocopheryl acetate (8) exhibited the enrichment signal at C-4, which was shown at 2859 cm^{-1} ($^{13}\text{C-H}$), 1759 cm^{-1} (OCOCH_3), 1207 cm^{-1} and 1061 cm^{-1} (^{13}C -chroman ring). The results are given in figure 1. ^{13}C -labeled (8) was also confirmed by M.S. spectroscopy, with the peaks shown at m/e 473 (M^+ , 10%), m/e 431 (M^+-42 , 100%), m/e 208 (M^+-265 , 18%), m/e 206 ($431-\text{C}_{16}\text{H}_{33}$, 10%), m/e 166 (206-40, 99%), and by ^{13}C -N.M.R. spectroscopy shown at C-4 methylene carbon (20.6 ppm).

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