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

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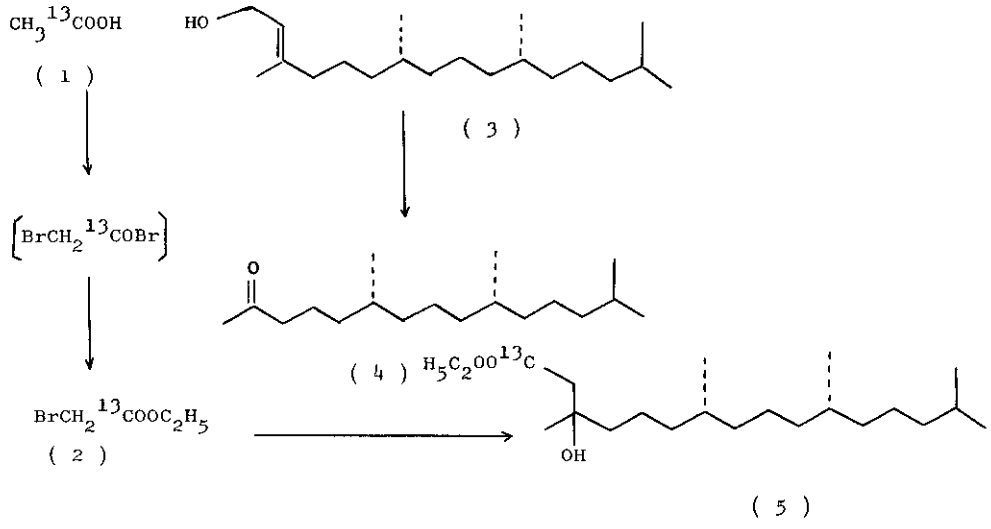
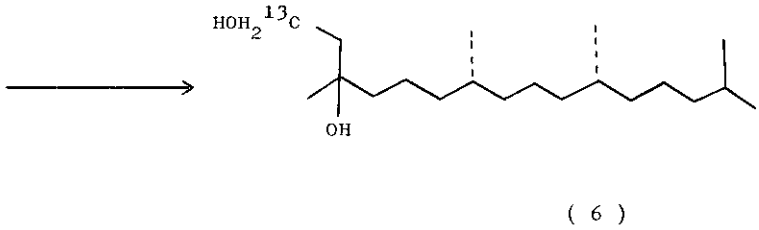
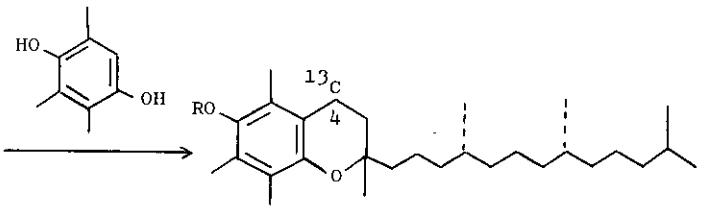
Summary: A convenient procedure for the synthesis of regiospecifically ^{13}C-labeled α-tocopheryl acetate of high enrichment is described.

The wide applications of ^{13}C-N.M.R. spectroscopy to the study of natural products biosynthesis and metabolic pathway are well established[1]. 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 Biàha's method[2] 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 procedure[4]. 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

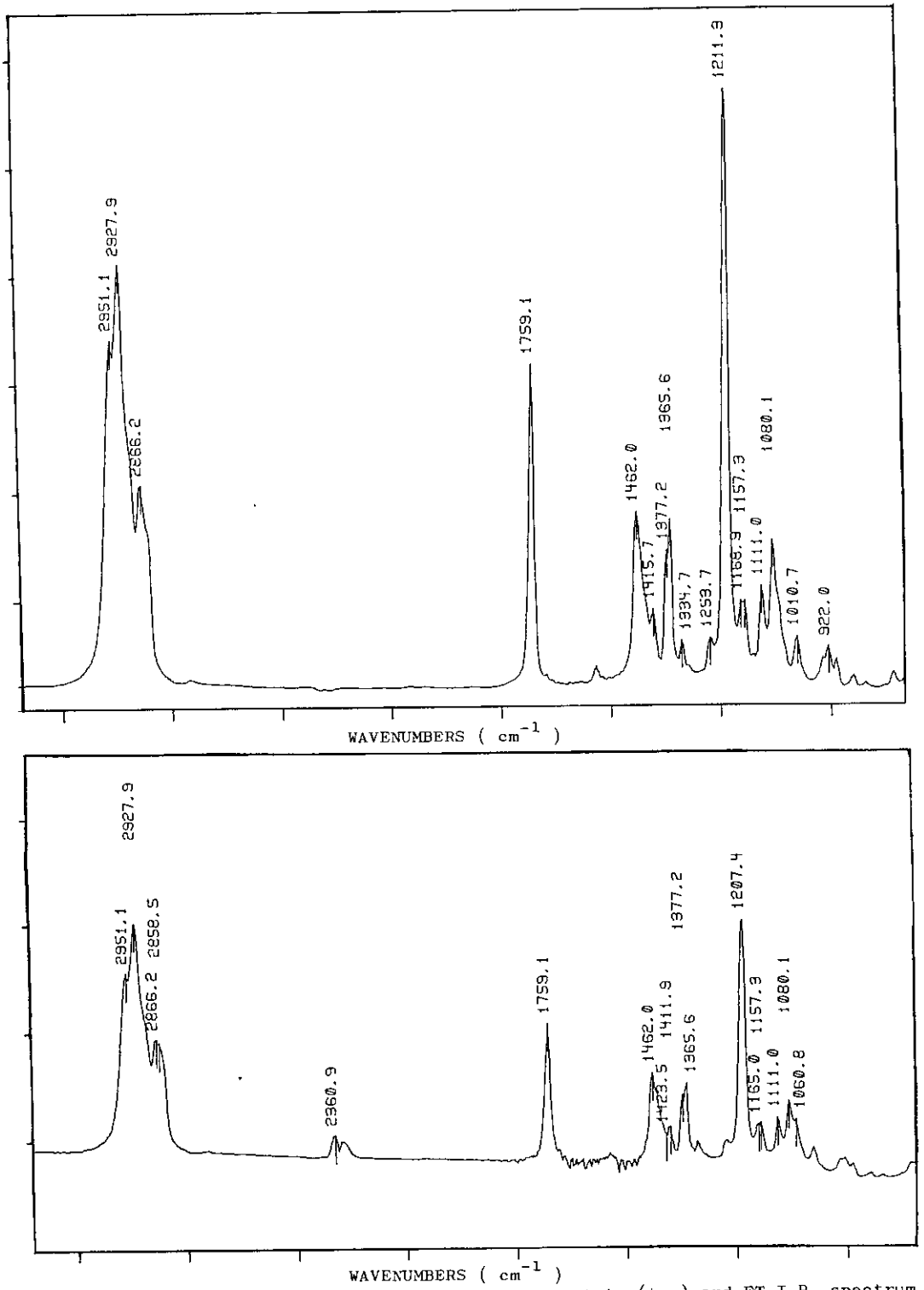


Figure 1. FT-I.R. spectrum of dl-α-tocopheryl acetate (top) and FT-I.R. spectrum of ^{13}C-enriched 2-(RS)-α-tocopheryl acetate-4-^{13}C (bottom).

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 method[5] 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}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-$C_{16}H_{33}$, 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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