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AN EFFICIENT SYNTHESIS OF (S)-CHROMANMETHANOL, A VITAMIN E PRECURSOR

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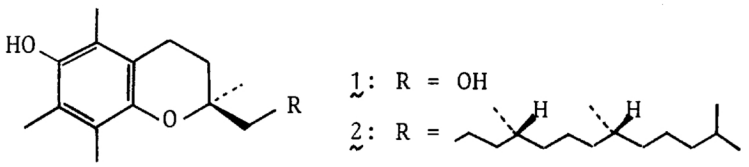
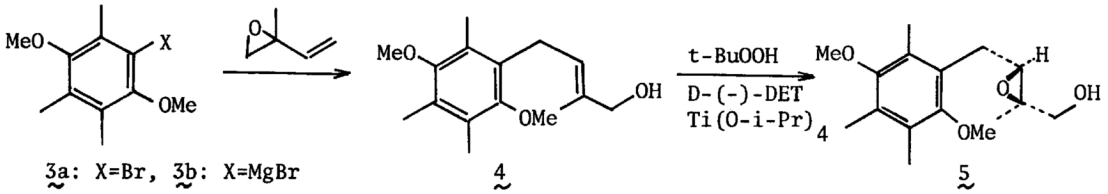
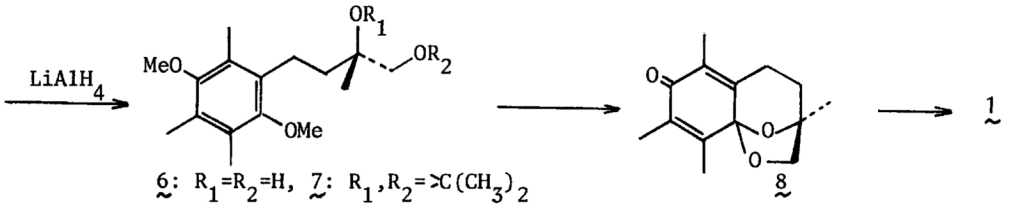
The (S)-chromanmethanol, a key intermediate for the synthesis of optically active α-tocopherol was synthesized by a reaction sequence which utilized the asymmetric epoxidation of the (E)-allylic alcohol to the (2R,3R)-epoxyalcohol in high enantiomeric excess.

In recent years much attention has been paid on the efficient synthesis of the natural form of α-tocopherol (2), whose framework has been built up via the C-C bond formation between an optically active chroman moiety and a chiral acyclic terpene chain. The optically active chromanyl group was until now mainly prepared through the optical resolution of the corresponding carboxylic acid,[1] or synthesized from an optically active precursor.[2] Recently Sakito[3] and Solladie[4] reported the asymmetric synthesis of the chroman moiety (1) in high enantiomeric excess.

We here describe a simple and efficient approach to the optically active (S)-chromanmethanol (1) by utilizing the asymmetric epoxidation[5] of the (E)-allylic alcohol (4).







The Grignard reagent (3b). prepared from the bromide (3a) and magnesium in THF, was treated with a mixture of isoprene oxide and copper(I) iodide[6] in THF at -25 °C under nitrogen atmosphere to afford the (E)-allylic alcohol (4)[7] (60%). The asymmetric epoxidation[5] of 4 with anhydrous tert-butyl hydroperoxide, D-(-)-diethyl tartrate, and titanium tetraisopropoxide at -20 °C in CH_2Cl_2 gave the (2R,3R)-epoxyalcohol (5)[8] (87%). Reduction of 5 with lithium aluminum hydride in ether provided the (S)-diol (6)[9] quantitatively. 6 was then converted to the chromanmethanol (1)[10] by the method reported by Barner and Schmid.[2b]

The ^{1}H-NMR spectrum of the chromanmethanol (1) in the presence of Eu(hfbc)$_3$ indicated a single enantiomer peak and the optical purity was assumed to be more than 95% e.e.

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7) 4: mp 67-70 °C; IR(KBr) 3300cm^{-1}; ^{1}H NMR(CCl_4) δ 1.20(1H,s), 1.70(3H,s), 2.02 (9H,s), 3.20(2H,d,J=7 Hz), 3.45(6H,s), 3.75(2H,s), and5.10(1H,t,J=7 Hz); MS Found: m/z 264.1714. Calcd for $C_{16}H_{24}O_3$: M, 264.1723.

8) 5: $[\alpha]_D^{23}$ +17.69°(c2.2,$CHCl_3$); ^{1}H NMR($CDCl_3$) δ 1.30(3H,s), 2.08(6H,s), 2.15(3H, s), 2.40-3.10(4H,m), 3.42(2H,s), 3.52(6H,s); MS Found: m/z 280.1673. Calcd for $C_{16}H_{24}O_4$: M, 280.1673.

9) The optical purity was established as follows. 6 was converted to the acetonide (7) by the method described in Ref. 3, and the ^{1}H NMR spectrum of 7 in the presence of Eu(hfbc)$_3$ showed a single enantiomer peak. Therefore, the e.e. seems to be over 95%. 6: $[\alpha]_D^{20}$ +3.07(c2.2, CH_2Cl_2).

10) Oxidation of 6 with ceric ammonium nitrate followed by ketalization with 1 mol dm^{-3} HCl afforded the (3S)-ketal (8) (64%), along with (S)-2-methyl-4-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)butan-1,2-diol (ca. 30%) which was converted to 8 with 1 mol dm^{-3} HCl. Hydrogenation of 8 over a catalytic amount of Pd-C at room temperature gave the (S)-chromanmethanol (1) (68%). $[\alpha]_D^{23}$ -2.80°(c1.1, CH_2Cl_2). The spectral data were identical with those reported by Barner and Schmid.[2b]

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