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Novel Synthesis of (S)-(-)-Chroman-2-carboxylic Acid, Vitamin E Precursor

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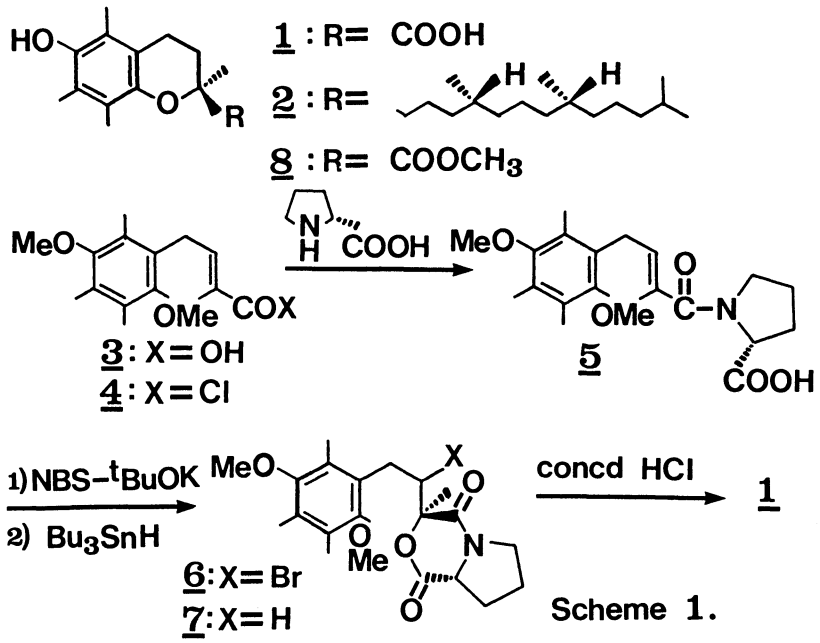
A new strategy to the synthesis of (S)-(-)-chroman-2-carboxylic acid, a pivotal intermediate possessing the absolute configuration required for the construction of α-tocopherol, was disclosed by utilizing asymmetric halolactonization of acylproline. Debromination followed by acidic hydrolysis directly afforded the title compound in 98% enantiomeric excess.

Among a variety of optically active naturally occuring compounds possessing a biological activity, α-tocopherol (2) and closely related substances being potent antioxidants and radical scavengers in chemical and biological systems have been receiving considerable attention with respect to clinical and nutritional applications in human health.[1)]

In a recent continuation of our work on the total synthesis of α-tocopherol (2), we have revealed an efficient synthetic method of the optically active chromanmethanol using Sharpless epoxidation.[2)] Although other several approaches for the synthesis of optically active chroman moiety of 2 have been elaborated up to date,[1b,3)] relatively little attention has been devoted to the development of processes for the synthesis of chroman carboxylic acid (1), mainly prepared so far by classical resolution of that counterpart.[4)] With these considerations in mind, this paper describes short and novel synthesis of highly optical active (S)-(-)-1 by utilizing asymmetric halolactonization of (R)-acylproline (5) starting from (R)-proline and (E)-trisubstituted carboxylic acid (3).



Scheme 1.

As shown in Scheme, acid chloride (4) prepared from 3, which was obtained

according to the recently exploited alkylation of amide[5] followed by hydrolysis of its N-t-Boc derivative,[6] was treated with (R)-proline as a chiral source under Schotten-Baumann condition to give 5[7] in quantitative yield. Asymmetric bromolactonization, developed by Terashima and Koga[8] using potassium salts of 5, was carried out by stirring with NBS at -20 °C for 2 h, and then r.t. for 2 days under N_2. Crude 6 thus obtained was successively submitted to debromination with Bu_3SnH in benzene at 90 °C for 10 h to afford crucial intermediate 7[9] in 85% yield based on 5 as a diastereomeric mixture. At this point, the ratio of the two diastereomers could not be determined although one would be highly predominant.

Fortunately, when hydrolysis of 7 was effected by refluxing with concd HCl for 10 h, the target substance (S)-(-)-1[10] ($[\alpha]_D^{26}$-64.8°(c 1.01, EtOH)) was directly obtained in 98% yield through the three steps of successive hydrolysis, deprotection and cyclization to the chroman ring. Esterification of 1 afforded its methyl ester (S)-(-)-(8) ($[\alpha]_D^{24}$-60.5°(c 1.02, MeOH)) in 91% yield. Since the highest reported optical rotation of 8 is $[\alpha]_D^{25}$-61.85°(c 5, MeOH),[4] the ratio of the two enantiomers and optical purity of acid (S)-(-)-(1) can be calculated as 99:1 and 98%, respectively.

In view of our results, the synthetic strategy to optically active 1 in Scheme 1 offers versatile and stereodefined introduction of the chroman chiral center of α-tocopherol.

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7) 5: Pale yellow caramel, $[\alpha]_D^{25}$+18.7°(c 1.15, MeOH); IR ($CHCl_3$): 3690-2450, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.85-2.35 (4H, m), 2.00 (3H, s), 2.17 (9H, s), 3.35-3.81 (4H, m), 3.64 (6H, s), 4.50 (1H, t, J=7.0 Hz), 5.50-5.86 (1H, m), 9.22 (1H, s).
8) S-s. Jew, S. Terashima, and K. Koga, Tetrahedron, 35, 2337(1979); S-s. Jew, S. Terashima, and K. Koga, ibid., 35, 2345(1979), and references quoted therein.
9) 7: White crystals, $[\alpha]_D^{24}$+58.7°(c 1.09, MeOH); mp 159-160 °C; IR ($CHCl_3$): 1750, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.70 (3H, s), 1.90-2.36 (6H, m), 2.16 (9H, s), 2.40-2.93 (2H, m), 3.45-3.83 (2H, m), 3.63 (6H, s), 4.67 (1H, t, J=7.0 Hz).
10) The optical rotation, $[\alpha]_D^{25}$+66.1°(c 1, EtOH) of the unnatural R-antipode (1) is only reported in the literature.[4]

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