Tetrahedron Letters,Vol.23,No.47,pp 4953-4954,1982 0040-4039/82/474953-02$03.00/0
Printed in Great Britain

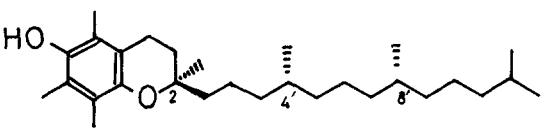
ASYMMETRIC SYNTHESIS OF A CHROMAN DERIVATIVE (VITAMIN E PRECURSOR)

Yoji Sakito* and Gohfu Suzukamo

Central Research Laboratory, Sumitomo Chemical Co., Ltd.
Takatsuki, Osaka 569, Japan

Summary. Chromanmethanol 2, a chiral intermediate for the synthesis of α-tocopherol 1, is prepared from α-hydroxy aldehyde 5, which is obtained by an asymmetric synthesis in over 95% ee.

In recent years much attention has been paied on a synthesis of optically active α-tocopherol 1 (vitamin E).[1)]



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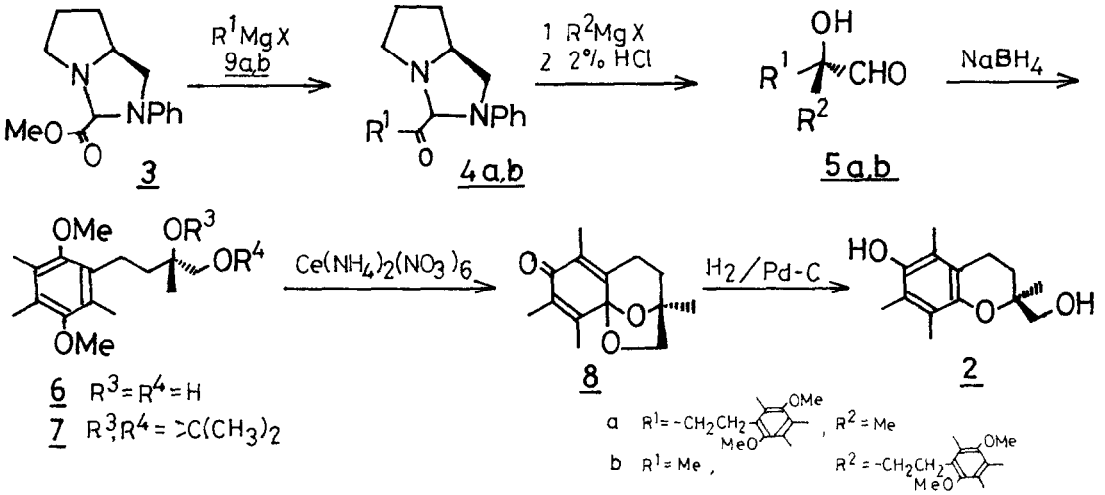
Bioassay of stereoisomers of α-tocopheryl acetate showed that the biopotency is affected by the chirality at the carbon atom on chroman skeleton (C-2).[2)] Several methods for the synthesis of optically active chroman moiety so far reported involve optical resolution or microbial treatment of appropriate precursors.[3)]

In this communication we describe a new approach to optically active chromanmethanol 2 [4)] by applying an asymmetric synthesis of α-hydroxy aldehydes reported previously [5)]



The method is capable of controlling the absolute configuration by choosing the order of introduction of two substituents originated from the Grignard reagents. Desired (S)-α-hydroxy aldehyde 5a, a precursor of natural α-tocopherol (2R,4'R,8'R), is obtained by the addition of methylmagnesium iodide to keto aminal 4a.[6]

Methoxycarbonyl aminal 3, prepared from (S)-2-anilinomethylpyrrolidine and methyl hydroxymethoxyacetate,[5] was treated with the Grignard reagent 9a [7] at -100°C to afford keto aminal 4a (55%). Reaction of keto aminal 4a with methylmagnesium iodide at -100°C followed by hydrolysis with 2% hydrochloric acid at 0°C gave (S)-α-hydroxy aldehyde 5a[8] (54%) The chiral auxiliary, (S)-2-anilinomethylpyrrolidine, was easily recovered from the hydrolysate. Reduction of α-hydroxy aldehyde 5a with $NaBH_4$ afforded (S)-diol 6,[9] whose optical purity was estimated as follows.

Diol 6 was converted to acetonide 7 [10] by treatment with 2,2-dimethoxypropane/p-TsOH. The ^1H NMR spectrum of acetonide 7 in the presence of $Eu(hfc)_3$ showed a single enantiomer peak and the optical purity was assumed to be more than 95%.[11]

Oxidation of (S)-diol 6 with ceric ammonium nitrate afforded (3S)-ketal 8 (64%)[10] along with (S)-2-methyl-4-(3,5,6-trimehtyl-1,4-benzoquinon-2-yl)-butane-1,2-diol (20%), which was converted to (3S)-ketal 8 by treatment with hydrochloric acid. Catalytic hydrogenation of (3S)-ketal 8 gave (S)-chromanmethanol 2 (76%).[3b]

The ^1H NMR spectrum of (S)-chromanmethanol thus obtained, when run in the presence of $Eu(hfc)_3$, indicated the presence of a single enantiomer peak.

Acknowledgement: We thank Prof. T. Mukaiyama for his interest and advice.

References and Notes

1) N. Cohen, C. G. Scott, C. Neukom, R. J. Lopresti, G. Weber, and G. Saucy, Helv. Chim. Acta, 64, 1158 (1981), and references cited therein.
2) S. R. Ames, J. Assoc. Off. Anal. Chem., 55, 625 (1972).
3) a) N. Cohen, R. J. Lopresti, and G. Saucy, J. Am. Chem. Soc., 101, 6710 (1979) b) R. Barner and H. Schmidt, Helv. Chim. Acta, 62, 2384 (1979) c) N. Cohen, J. W. Scott, F. T. Bizzaro, R. J. Lopresti, W. F. Eichel, and G. Saucy, ibid, 61, 837 (1978) d) J. W. Scott, F. T. Bizzaro, D. R. Parrish, and G. Saucy, ibid, 59, 290 (1976) e) H. Mayer, P. Schudel, R. Ruegg, and O. Isler, ibid, 46, 650 (1963)
4) Conversion of (S)-chromanmethanol 2 into (2R)-α-tocopherol has been reported in reference 3a).
5) T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 705 (1979).
6) Addition of the Grignard reagent 9a to keto aminal 4b followed by hydrolysis gave (R)-α-hydroxy aldehyde 5b in 93% ee.
7) L. I. Smith and H. C. Miller, J. Am. Chem. Soc., 64, 440 (1942)
8) $[\alpha]_D$ +39.6° (c 0.53, benzene) NMR(CCl_4) δ= 1.20 (3H, s), 1.56-1.85 (2H, m), 2.05 (9H, s), 2.16-2.80 (2H, m), 3.40 (1H, s), 3.46 (3H, s), 3.51 (3H, s), 9.25 (1H, s).
9) $[\alpha]_D$ +3.1° (c 1.14, CH_2Cl_2) NMR(CCl_4) δ= 1.17 (3H, s), 1.50 (2H, m), 2.08 (6H, s), 2.13 (3H, s), 2.67 (4H, m), 3.37 (2H, s), 3.55 (3H, s), 3.62 (3H,s).
10) The NMR spectrum was identical with that reported in reference 3b).
11) The observed specific rotation ($[\alpha]_D$ +4.3° (c 2.1, $CHCl_3$)) corresponds to 96% ee (S) by comparison with the reported value ($[\alpha]_D$ +4.5° (c 2.2, $CHCl_3$)) in reference 3b).

(Received in Japan 31 July 1982)