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CHEMOENZYMATIC SYNTHESIS OF OPTICALLY ACTIVE α-TOCOPHEROL SIDE CHAIN

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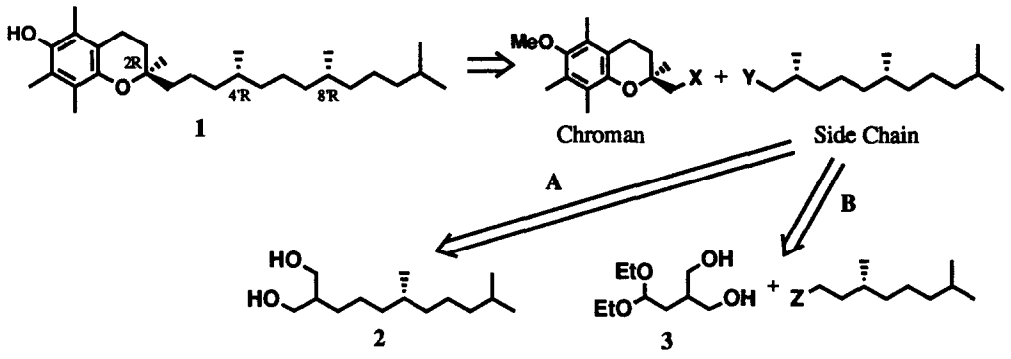
Abstract: Chemoenzymatic synthesis of (2R,6R)-2,6,10-trimethylundecanol and (3R,7R)-3,7,11-trimethyldodecanol, which are key intermediates in the total synthesis of natural α-tocopherol, *via* Lipase-catalyzed asymmetric induction to prochiral 1,3-propanediol derivatives is described.

(2R,4R',8'R)-α-Tocopherol (**1**) and closely related substances being potent antioxidants and radical scavengers in biological and chemical 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 synthesis[2] of **1**, we have revealed efficient synthetic methods of some key intermediates of **1**, the chroman and the side chain, using asymmetric isomerization[3a], Sharpless oxidation[3b] and asymmetric halolactonization.[3c] In the last years many reports[4] have appeared describing that enzymes are particularly attractive catalysts having the ability to discriminate between two enantiotopic groups of a symmetrical substrate.

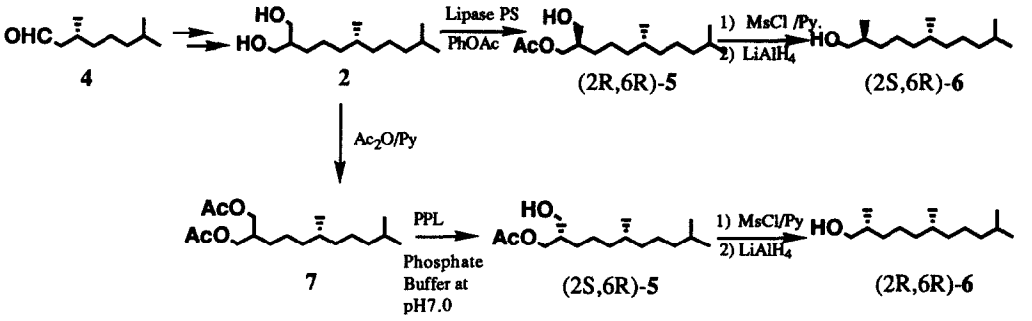
With these considerations in mind, this paper describes an efficient chemoenzymatic aproach to the enantioselective synthesis of the α-tocophrol side chains. Our strategy, the route A or B, is based on the Lipase-catalyzed asymmetric induction to the readily accessible prochiral 1,3-propanediol derivatives, **2** and **3**.



(R)-6,10-Dimethyl-2-(hydroxymetyl)undecanol (**2**), which was easily prepared from (R)-citronellal (**4**) by the modified method reported by Oku et al.,[2b] was treated with phenylacetate in the presence of Lipase PS[5] at 15°C

for 3 hours to afford the monoester **5** (86% e.e.)[6] in 85% yield as shown in Scheme 1. The absolute configuration at C-2 position of **5** was determined to be **R** by its conversion into the known (2S,6R)-2,6,10-trimethylundecanol (**6**)[7,8](85% e.e.[9]). In order to synthesize (2R,6R)-**6**, the natural α-tocopherol C_{14}-side chain, the enzymatic hydrolysis of the diester **7** was also examined, i.e. *porcine pancreatic lipase*(PPL)-catalyzed hydrolysis of **7** in phosphate buffer at pH 7.0 gave the monoester **5**[10](53% yield, 88% e.e.[6b]), which was treated with mesyl choride-pyridine, followed by $LiAlH_4$ to afford (2R,6R)-**6** (88% e.e.) in 89% yield.[11]

Scheme 1.



Moreover, to obtain the optically active C_{15}-side chain of **1**, the route B was also investigated as shown in Scheme 2. The diol **9**, which was easily prepared by the treatment of diethyl malonate anion with the bromoketal **8**, followed by $LiAlH_4$ was subjected to Lipase PS-catalyzed transesterification to give the monoester **10** (88% yield, 98% e.e.).[12,13] The absolute configuration of **10** was determined as follows; the monoester **10** was treated with Jones Reagent to give directly (S)-3-acetoxymethylbutanolide (**11**)[14,15] in 63% yield. On the basis of this result, the absolute configuration of **10** was identified to be **R**.

As an useful chiral building block was obtained in hand, the following approach for the conversion of **10** into the C_{15}-side chain was examined. The monoester **10** was treated with mesyl chloride-pyridine, followed by $LiAlH_4$ to afford the alcohol **12**[16] (87% yield, 98% e.e.[17]). The treatment of **12** with tosyl chloride-pyridine gave the tosylate **13**[18] (85% yield), which was then treated with (R)-3,7-dimethyloctanylmagnesium bromide in the presence of Li_2CuCl_4 [19] to afford the C-15 ketal **14**[20] in 85% yield. Deprotection of **14** by hydrochloric acid gave the aldehyde **15**[21] (99% yield), which was reduced by $NaBH_4$ to afford (3R,7R)-3,7,11-trimethyldodecanol (**16**) in 94% yield.[22-24]

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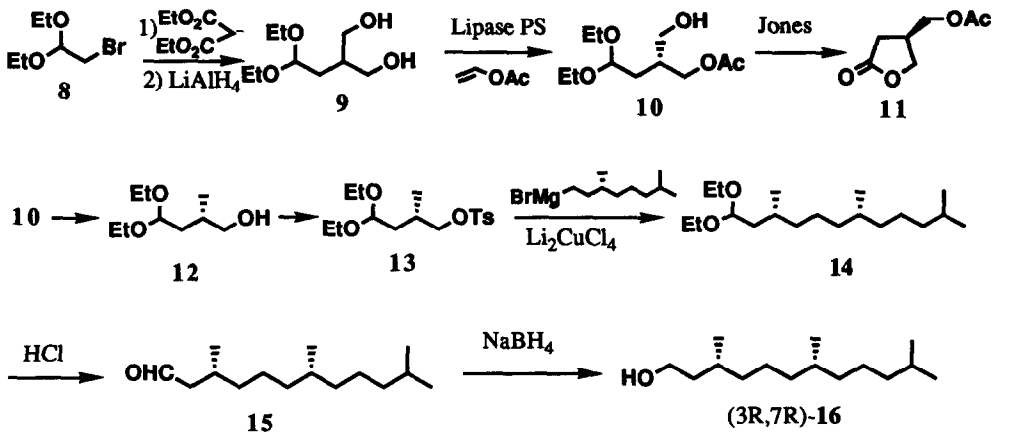
Scheme 2.



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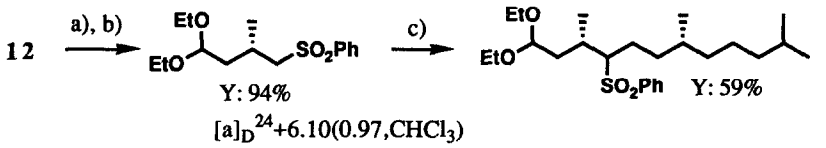
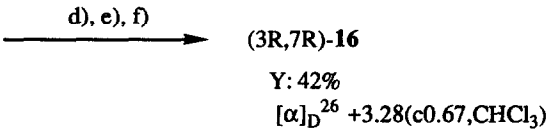
5. *Pseudomonas fluorescens lipase.* (Amano Pharmaceutical Co., Ltd., Nagoya, Japan)
6. a) (2R,6R)-**5**: $[\alpha]_D^{20}$ +8.57°(c1.14,$CHCl_3$), b) E.e. was determined by HPLC (Chiralcel OD, hexane-2-propanol=95:5, 0.5 ml/min).
7. a) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, 64, 1158-1173, b) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.*, **1982**, 23, 2825-2828.

8. (2S,6R)-**6**: $[\alpha]_D^{22}$-7.21°(c1.08,hexane), [Lit.[7a] $[\alpha]_D^{25}$-9.21°(c2,hexane)].
9. E.e. was determined by HPLC (Chiralcel OD, hexane-ethanol=95:5, 0.2 ml/min).
10. (2S,6R)-**5**: $[\alpha]_D^{22}$ -9.43°(c1.17, $CHCl_3$).
11. (2R,6R)-**6**:$[\alpha]_D^{22}$+7.67°(c1.02,hexane) [Lit.$[\alpha]_D^{25}$+9.02(c0.665,hexane)[2b],$[\alpha]_D^{25}$+9.13(c2,hexane)[7a]]
12. Presented at the 21st Annual Meeting of UCRS in Chubu area, Nagoya, October1990, Abstr. 146-147. Recently Achiwa et al. reported similar results independently: Terao, Y.; Akamatsu, M.; Achiwa, K., *Chem. Pharm. Bull.* **1991**, 39, 823-824.
13. a) $[\alpha]_D^{21}$+13.1°(c1.22,CCl_4), b) E.e. was determined by HPLC: Chiralcel OJ, hexane-2-propanol=95:5, 0.7ml/min.
14.. Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1989**, 957-962.
15. (S)-**11**: $[\alpha]_D^{22}$+37.0°(c1.28,$CHCl_3$) [Lit.[14] $[\alpha]_D^{24}$-25.3°(c0.96,$CHCl_3$) for (R)-**11**].
16. **12**: $[\alpha]_D^{24}$-12.8°(c1.15, CCl_4).
17. E.e. was determined by HPLC analysis of the (S)-(-)-MTPA ester obtained from **12** (Chiralcel OJ, hexane-2-propanol=95:5, 0.2 ml/min).
18. **13**: $[\alpha]_D^{22}$+5.0°(c1.20,$CHCl_3$).
19. Murata, K.; Kochi, J. K. *Synthesis*, **1971**, 957-962.
20. **14**: $[\alpha]_D^{15}$+3.04°(c1.21, $CHCl_3$),
21. **15**: $[\alpha]_D^{22}$+8.38°(c1.37, octane) [Lit.[3a] $[\alpha]_D^{25}$+8.7°(c0.85, octane)],
22. a) Fujiwara, J; Fukutani, Y.; Hasegawa, M; Maruoka, K.; Yamamoto, H. *J. Amer. Chem. Soc.*, **1984**, 106, 5004-5005, b) Koreeda, M.; Brown, L. *J. Org. Chem.*, **1983**, 48, 2122-2124.
23. (3R,7R)-**16**: $[\alpha]_D^{21}$+3.26°(c1.09, $CHCl_3$) [Lit. $[\alpha]_D^{18}$+3.49°(c1.09,$CHCl_3$)[22a],$[\alpha]_D^{23}$+3.35°(c0.955, $CHCl_3$)[22b].:
24. The following conversion of **12** into (4R,7R)-**16** was also examined.





a) $(PhS)_2$ / Ph_3P, b) mcpba, c)BuLi,  , d) Li /$EtNH_2$
e) HCl, f)$NaBH_4$