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AN ASYMMETRIC SYNTHESIS OF α-TOCOPHEROL SIDE CHAIN

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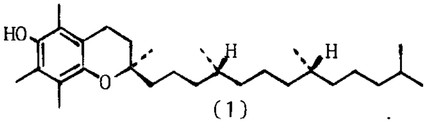
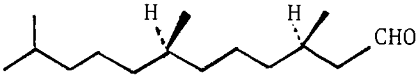
Abstract: A stereospecific synthesis of (3R,7R)-3,7,11-trimethyldodecanal (2) with highly optical purity was achieved by utilizing the coupling reaction of the amino sulfone (9) with (R)-3,7-dimethyloctyl magnesium bromide (7), and the asymmetric isomerization of the resulting (E)-allylic amine (10).

α-Tocopherol (1) has been receiving much attention with regard to a potent antioxidant and radical scavenger in chemical and biological systems. Therefore, there is an increasing need for an efficient and stereocontrolled method[1-3] for the synthesis which feasible for a large scale production.

In this communication we wish to report a convenient and simple route to a chiral acyclic terpene chain (2) of α-tocopherol, by utilizing cationic rhodium(I) complex-catalyzed asymmetric isomerization [4] of N,N-dialkyl allylic amine.



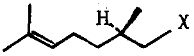
(1)



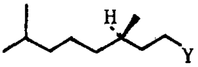
(2)

Optically pure (R)-citronellal (3) was used as a starting material. Sodium borohydride reduction of (3) and subsequent Pd-catalyzed hydrogenation of (4) gave (R)- 3,7-dimethyloctanol (5) in 96% yield. Treatment[3] of (5) with hydrogen bromide afforded (R)- 3,7-dimethyloctyl bromide (6) in 82% yield.[5]

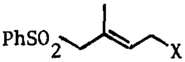
The optically active Grignard reagent (7), prepared from (6) and Mg in THF, was treated with the (E)-aminosulfone (9)[6] in the presence of copper(II) acetylacetonate[7] in THF at room temperature for 24 hrs to afford the (E)-allylic amine (10)[8] in 48% yield.[9] The asymmetric isomerization of (10) with a catalytic amount of $Rh[(-)\text{-}BINAP]_2ClO_4$ in THF at 100°C for 15 hrs gave the optically active (3R)-enamine (11) in 95% yield. Hydrolysis of (11) with aqueous sulfuric acid (20%) in toluene at 0°C for 1 hr afforded (3R,7R)-3,7,11-trimethyldodecanal (2).[10] Its optical purity was established by HPLC analysis[11] of the amide (12), which was prepared[12] from (2), to be 97.4% e.e.[13]



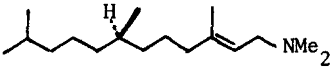
(3): X=CHO
(4): X=CH$_2$OH



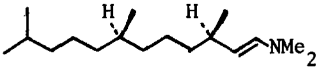
(5): Y=OH
(6): Y=Br
(7): Y=MgBr



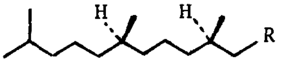
(8): X=Cl
(9): X=NMe$_2$



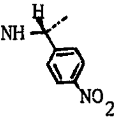
(10)



(11)



(12): R= -CONH



References and Footnotes

1) For recent syntheses of optically active chroman part, see: Y. Sakito and G. Suzukamo, Tetrahedron Lett., 23, 4953 (1982), G. Solladie and G. Moine, J. Am. Chem. Soc., 106, 6097 (1984), K. Takabe, K. Okisaka, Y. Uchiyama, T. Katagiri and H. Yoda, Chem. Lett., 1985, 561.

2) For recent syntheses of optically active side chain, see: C. H. Heathcock and E. T. Jarvi, Tetrahedron Lett., 23, 2825 (1982), G. Helmchen and R. Schmierer, ibid., 24, 1235 (1983), M. Koreeda and L. Brownm, J. Org. Chem., 48, 2122 (1983), J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka and H. Yamamoto, J. Am. Chem. Soc., 106, 5004 (1984) and references cited therein.

3) T. Fujisawa, T. Sato, T. Kawara and K. Ohashi, Tetrahedron Lett., 22, 4823 (1981).

4) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita and R. Noyori, J. Chem. Soc. Chem. Commun., 1982, 600.

5) $[\alpha]_D^{28}$ -6.66°(neat), Lit.^{3} $[\alpha]_D^{23}$ -6.56°(neat).

6) (9) was easily prepared by the reaction of (E)-chloro-2-methyl-1-phenylsulfonyl-2-butene (8) with dimethylamine. For the synthesis of (8) see: W. E. Truce, C. T. Goralsky, L. W. Christensen and R. H. Bavry, J. Org. Chem., 35, 4217 (1970).

7) M. Julia and J-N. Verpeaux, Tetrahedron, 39, 3289 (1983).

8) (10): $[\alpha]_D^{20}$ -1.25°(c: 2.2, EtOH), MS(m/z) 253.2764 (calcd. for $C_{17}H_{35}N$ 253.2761), IR(cm^{-1}, neat) 1670 and 1030, ^{1}H-NMR(δ, CDCl$_3$) 0.80(9H,d,J=7Hz), 0.95-1.45(12H,m), 1.55(3H,s), 1.70-2.03(2H,m), 2.11(6H,s), 2.66(2H,d,J=7Hz), 5.15(1H,t,J=7Hz).

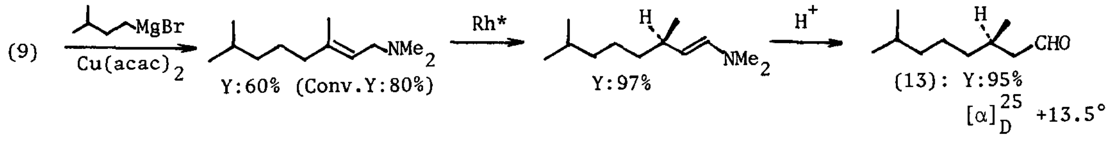
9) The conversion yield was 85%.

10) (2): $[\alpha]_D^{25}$ +8.7°, Lit.*, $[\alpha]_D$ +9.0, ^{1}H-NMR(δ, CDCl$_3$) 0.82(2H,d,J=7Hz), 1.00-1.40(15H,m), 2.30(2H,dd), 9.15(1H,t,J=3.5Hz). (* O. Isler, Helv. Chim. Acta, 46, 976 (1963))

11) Unicil NQ C$_{18}$ 5μ, 4 id 300mm, Mobile phase: CH$_3$CN/H$_2$O=70/30.

12) D. Valentine Jr., K. K. Chan, C. G. Scott, K. K. Johnson, K. Toth and G. Saucy, J. Org. Chem., 41, 62 (1976).

13) (R)-3,7-dimethyloctanal (13) (97.5% e.e.), a precursor of (5) was also synthesized through the reaction sequence as follows:



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