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THE SYNTHESIS OF E-(2S,3S)-3-TRIMETHYLSILYLGLYCIDOL AND ITS CONVERSION TO (-)-PROPRANOLOL

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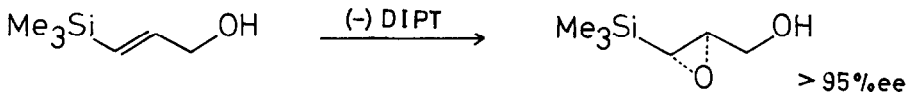
Summary: (-)-Propranolol was synthesized in a highly enantio- and regio-selective manner by using titanium mediated asymmetric epoxidation via the key intermediate, E-(2S,3S)-3-trimethylsilylglycidol.

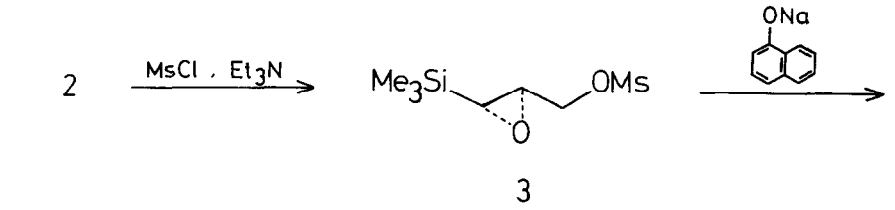
Chiral glycidol and its derivatives are versatile intermediates in the synthesis of the natural products.[1] However, glycidol is so unstable that it is difficult to obtain the pure substance.[1a] It would, therefore, be advantageous to prepare a stable synthetic equivalent of glycidol in optically pure form. Chan et al reported that α-trimethylsilyl epoxide was desilylated by treatment with fluoride anion without contacting the oxirane ring.[2] We would like to report here the synthesis of homochiral E-3-trimethylsilyl-glycidol using titanium mediated asymmetric epoxidation[3] and its conversion to (-)-propranolol which is a β-adrenergic receptor antagonist.[4]

E-3-Trimethylsilylallyl alcohol (1) which was prepared from 3-trimethyl-silylpropagyl alcohol by LAH reduction, was submitted to asymmetric epoxidation with (-)-diisopropyl tartrate to give the (2S,3S)-epoxy alcohol (2>95%ee) in 60% yield.[3),5]



1 2

Epoxy alcohol (2) was treated with methanesulfonyl chloride and triethylamine in dichloromethane at -20°C to afford the mesylate (3) in 89% yield. The mesyloxy group was substituted with the sodium salt of 1-naphtol in DMF to give the naphthyl ether (4) in 79% yield. Epoxy ether (4) was desilylated with tetrabutylammonium fluoride[2] in DMSO-THF to give 5 in 92% yield. Treatment of 5 with aqueous isopropylamine[6] at 60°C gave only one isomer, Propranolol (6), mp 72°C, $[\alpha]_D^{23}$=-9.2 (c=0.11, EtOH); Lit. mp 73°C, $[\alpha]_D^{23}$=-10.2, (c=1.02, EtOH)[4].



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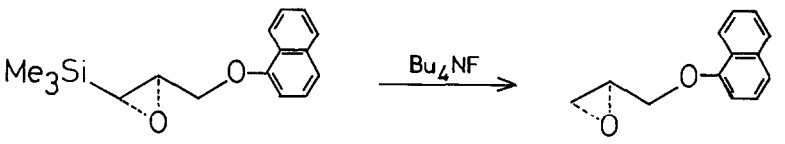

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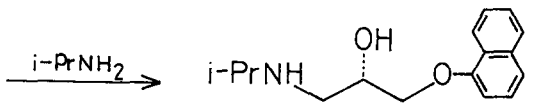

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References and Footnotes

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1. a) J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, J. Org. Chem., 43, 4876(1978). b) D. E. McClure, B. H. Arison, and J. J. Baldwin, J. Am. Chem. Soc., 101, 3666(1979).
2. T. H. Chan, P. W. K. Lau, and M. P. Li, Tetrahedron Lett., 2667(1976).
3. T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974(1980).
4. R. Howe and R. G. Shanks, Nature, 210, 1336(1966).
5. Epoxy alcohol 2 was sensitive to acid. The improved work-up procedure shown below was essential to isolate 2.

   After the reaction was completed, the reaction mixture was poured into a solution of acetonitrile and water saturated with NaF (1:1). The mixture was stirred for 1h at room temperature and extracted with dichloromethane. The organic layer was dried and concentrated. The residue was chromatographed on silica gel to give 2.

   Another improved procedure has been reported; L. A. Reed III, Y. Ito, S. Masamune, and K. B. Sharpless, J. Am. Chem. Soc., 104, 6468(1982).
6. H. Tucker, J. Org. Chem., 44, 2944(1979).

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