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PREPARATION OF OPTICALLY ACTIVE 1-ACETOXY-2-ARYLOXYPROPIONITRILES AND ITS APPLICATION TO A FACILE SYNTHESIS OF (S)-(-)-PROPRANOLOL

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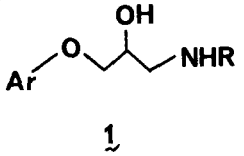
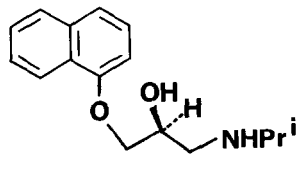
Summary: (S)-1-Acetoxy-2-aryloxypropionitriles were synthesized by an asymmetric hydrolysis of the racemates with an enzyme. (S)-Propranolol, a typical β-adrenergic blocker, was synthesized from (S)-1-acetoxy-2-α-naphthyloxypropionitrile in two steps.

Aryloxypropanolamines of general structure (1) are known to have hypotensive β-adrenergic blocking activity and it has already been established that the activity generally resides in the (S)-isomers.[1] Most of synthetic methods for (S)-isomer have been developed *via* (S)- or (R)-glycerol acetonide starting from D-mannitol [2] and Vitamin C [3] respectively, except for the one through asymmetric hydrolysis of 4-acetoxymethyloxazolidin-2-one.[4]

We report here a new and short practical synthesis of (S)-(-)-propranolol (2), a typical β-blocking agent, by an enzymatic method. The crucial step of the present synthesis is an enzyme-mediated asymmetric hydrolysis of a cyanoacetate (3).



1



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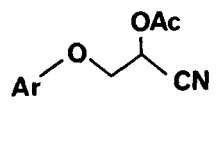


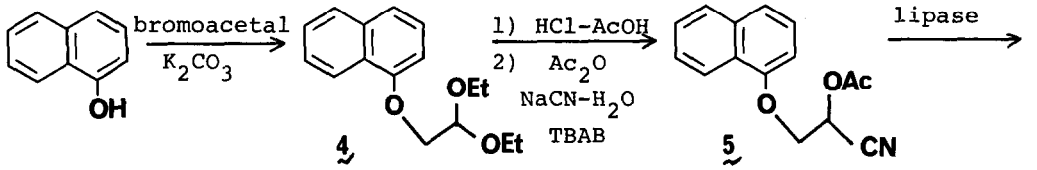
3

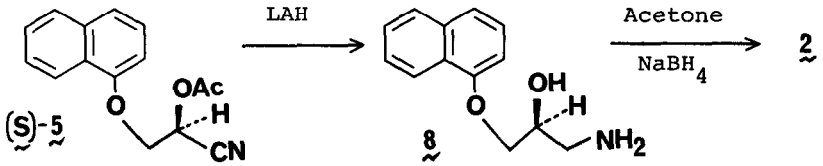
1-Naphthol was treated with bromoacetaldehyde diethyl acetal (K_2CO_3-DMF, 100°C, 10 hrs) to give the acetal (4) in 60 % yield. This was deprotected in conc.HCl-AcOH (1:10). Without any purification, the crude aldehyde in ether could be directly transformed into the cyanoacetate (5) [Ac_2O and NaCN with cat. TBAB, 57.6 % yield from (4)]. The acetate (5) was hydrolyzed in the presence of lipase produced by Pseudomonas sp. in pH 5 buffer solution (40°C, 24 hrs) to give the (S)-acetate, (S)-5 (79.4 % yield of the theoretical (S)-isomer), $[\alpha]_D^{23}$ = +36.1°(C=1.19, $CHCl_3$).

Related optically active aryloxyacetaldehyde cyanohydrin acetates [(6) (96.8 % e.e.) and (7) (73.8 % e.e.)][5] were prepared successfully by the same asymmetric hydrolysis.

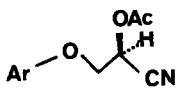
LAH reduction of the (S)-5 afforded the (S)-aminoalcohol (8), $[\alpha]_D^{23} = -7.3°$ (C=0.51, $CHCl_3$), in 81 % yield. The optical purity of 8 was determined to be 87.4 % e.e. by HPLC analysis of the 3,5-dinitrophenyl carbamate derivative (9).[6] Finally, treatment of 8 with acetone-$NaBH_4$ [1a] gave (S)-(-)-propranolol (2) (71 %), mp 71.0°C, $[\alpha]_D^{23} = -7.3°$ (C=0.57, EtOH) : Lit.[7] $[\alpha]_D^{21} = -8.1$.

Consequently, the absolute configuration of (S)-5 was rigorously confirmed.



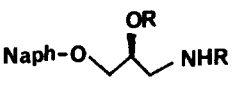


\+ (R)-cyanohydrin



6: Ar= 2-methylphenyl-

7: Ar= 3,5-dimethylphenyl-



9

R= (3,5-dinitrophenyl)NHCO-

References and Footnotes

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3) M.E. Jung and T.J. Shaw, J. Amer. Chem. Soc., 102, 6304 (1980).

4) S. Hamaguchi, J. Hasegawa, H. Kawaharada and K. Watanabe, Agr. Biol. Chem., 48, 2055 (1984).

5) The optical purity of 6 and 7 was determined by HPLC analysis of the corresponding 3,5-dinitrophenyl carbamate (see footnote 6).

6) 9 was analyzed on a Sumipax OA-1000 column (4mm x 25 cm, Sumika Chemical Analysis Service Ltd., Osaka, Japan) with $CHCl_3$-EtOH (10:1).

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