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SHARPLESS ASYMMETRIC DIHYDROXYLATION OF ARYLOXY ALLYL ETHERS: A SIMPLE ROUTE TO CHIRAL β-BLOCKERS

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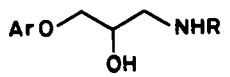
Summary: Sharpless asymmetric dihydroxylations of aryloxy allyl ethers are described.

The general awareness of the synthesis of enantiomerically pure compounds in the context of their biological properties has expanded in recent years[1]. It is reckoned that in the near future all new drugs containing asymmetric center(s) may be required to be used in enantiomerically pure forms[2]. As a consequence, an array of new reagents and methods has been developed, a particularly interesting reaction being the Sharpless asymmetric cis-dihydroxylation of olefins in the presence of cinchona alkaloid derivatives[3]. The commercial viability of this method holds tremendous potential for two principal reasons: A) the adaptability of this procedure for industrial applications and B) economic considerations, as valuable reagents can be used in catalytic amounts and more importantly they are recoverable. The Sharpless asymmetric dihydroxylations of terminal olefins in the presence of cinchona alkaloids has been shown to afford the corresponding diols with moderate ee (40-70%). We felt that it would be interesting to study Sharpless asymmetric dihydroxylation of allyloxyethers (**2**) and observe the influence of oxygen on the stereochemical outcome of this reaction. Moreover, this protocol would also provide a new synthetic route to chiral substituted glycerol derivative (**3**), valuable intermediates for the synthesis of chiral β-blocker drugs (**1**). Although racemic β-blockers have been used over two decades, there is now a great deal of concern[4] about their safety, and efforts are being made to introduce enantiomerically pure (S)-β-blockers (higher affinity to the β-receptors) in the consumer market. (S)-Propranolol (**6**) forms the representative example of the present study.



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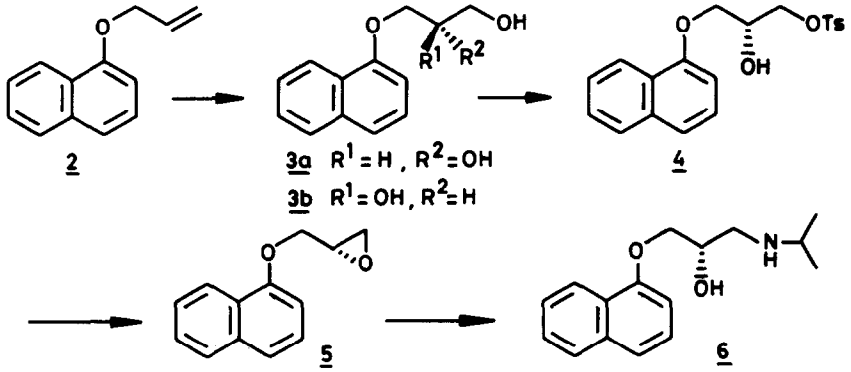
1-Naphthalenoxy allyl ether (**2**) was prepared[5] from 1-naphthol and allyl bromide in the presence of potassium carbonate in refluxing acetone in 85% yield. Subsequent dihydroxylation of (**2**) (slow addition, 8 h) in the presence of 0.025 equivalents of osmium tetroxide and 1.5 equivalents of N-methylmorpholine-N-oxide (NMO) with dihydroquinidine-p-chlorobenzoate (DHQDPCB) as chiral ligand in a 4:1 mixture of acetone:water at 0° gave the (S)-diol (**3a**) (80%) with 40% enantiomeric excess (ee)[6]. In accordance with recent observation, the above reaction was also conducted at -30°, however, the ee of the (S)-diol (**3a**) increased to only 48%. Similarly, with dihydroquinine-p-chlorobenzoate (DHQPCB) as the chiral ligand, the dihydroxylation of (**2**) gave the (R)-diol (**3b**) (44% ee) at -30°.

The recent modification[7] of employing potassium ferricyanide instead of NMO is a fascinating observation. Recently Sharpless's group[8] noted that the combination of OsO_4-$K_3Fe(CN)_6$ in the presence of cinchona alkaloid derivatives considerably improved the ee of the dihydroxylation reaction. Therefore **2** was subjected to dihydroxylation (without slow addition) at room temperature by using OsO_4-$K_3Fe(CN)_6$ and DHQDPCB in a 1:1 t-butanol:water mixture. The ee of the corresponding (S)-diol (**3a**) was found to be 60%. The diol (**3a**) was transformed further into (S)-propranolol (**6**).



The diol (**3a**) was converted into the monotosylate (**4**) and subsequently transformed into the epoxide (**5**) with methanolic sodium methoxide. The ring opening reaction of the epoxide (**5**) with excess of boiling isopropylamine gave (S)-propranolol (**6**) isolated as the hydrochloride (60% ee).

The Sharpless asymmetric dihydroxylation of 2-methoxyphenyloxy allyl ether and 4-(2-methoxyethyl)phenyloxy allyl ether leading to the formation of (S)-guaifensin, a muscle relaxant and expectorant, and (S)-metoprolol, a β-blocker were also carried out in 50-60% ee. It is pertinent to mention that future studies to enhance the ee of the diol (**3a**) along the lines suggested above by using some newly introduced[9] chiral ligands will be a worthwhile proposition.

References and foot notes:

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6. The ee of these diols were determined by HPLC and ^1H NMR studies of the derived Mosher esters and subsequently confirmed by comparison of the optical rotations. **3a** $[\alpha]_D^{26}$ +4.01° (c 1.1, MeOH), lit. [G D Ogg, D G Neilson, I H Stevenson and G A Lyles, J Pharm Pharmacol., **39**, 378 (1987)], $[\alpha]_D^{26}$ +6.7° (MeOH).
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