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Asymmetric synthesis of aryloxypropanolamines via OsO_4-catalyzed asymmetric dihydroxylation

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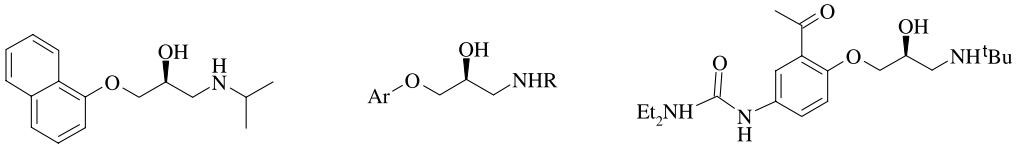
Abstract—A simple and effective procedure for the enantioselective synthesis of several β-adrenergic blocking agents incorporating the first asymmetric synthesis of celiprolol, is described. The key steps are (i) sharpless asymmetric dihydroxylation of aryl allyl ethers to introduce chirality into the molecules and (ii) conversion of cyclic sulfates into the corresponding epoxides using a three-step procedure.

1. Introduction

β-Adrenergic blocking agents (β-blockers) are important drugs widely used for the treatment of hypertension, angina pectoris, glaucoma, anxiety and obesity. The discovery of propranolol (**1a**), the first successful drug having antianginal and antihypertensive effects, prompted the synthesis of many thousands of compounds containing an aryloxypropanolamine moiety.[1] The three fundamental goals of cardiovascular drugs are: lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[2] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[3] Blocking of the β-receptor system reduces the overall activity of the sympathetic nervous system. β-Blockers are thus used to increase life expectancy after heart attack. Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic. Although (*S*)-isomers are known to be much more effective (100–500-fold) than the (*R*)-isomer,[4] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some cases toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is desirable.

In the literature, there are several reports available for the synthesis of β-blockers (**1a–g**)[5] (Fig. 1) which include classical resolution via diastereomers, chromatographic



1a : (S)-Propranolol

1b: Ar = 2-methoxyphenyl, R=^{i}Pr, (S)-Moprolol
1c: Ar = 3-methylphenyl, R=^{i}Pr, (S)-Toliprolol
1d: Ar = 2-cyanophenyl, R=^{t}Bu, (S)-Bunitrolol
1e: Ar = 4-acetamidophenyl, R=^{i}Pr, (S)-Practolol
1f: Ar = 2,3-dimethylphenyl, R=^{t}Bu,(S)-Xibenolol

1g : (S)-Celiprolol

Figure 1.

Keywords: Antihypertensive; Asymmetric dihydroxylation; Epoxides; Cyclic sulfates.
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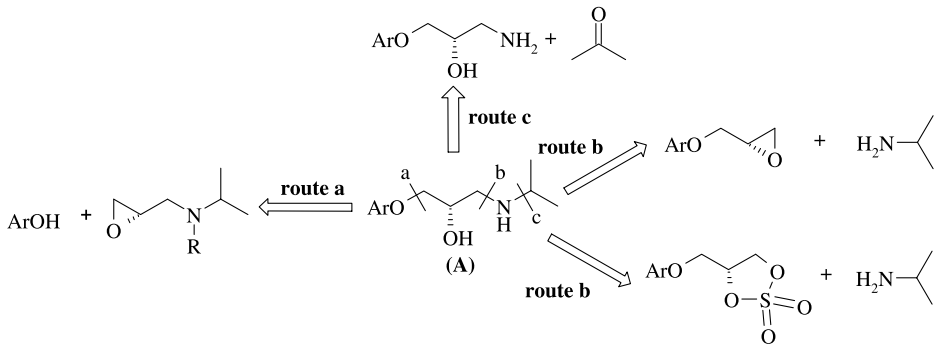


Figure 2. Retrosynthetic analysis of β-adrenergic blocking agents (**A**).

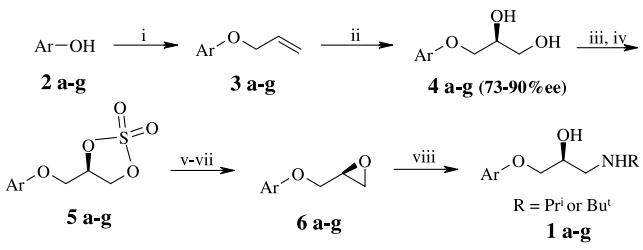
separation of enantiomers, enzymatic resolution, kinetic resolution and asymmetric synthesis via chiral pool strategy. Furthermore, many of these methods suffer from disadvantages such as low overall yields, use of expensive enzymes and resolving agents, low optical purity, the need for separation of diastereomers and the use of expensive chiral catalysts. In order to develop a new general route for the asymmetric synthesis of β-adrenergic blockers with good optical purity and yield, we decided to make use of sharpless asymmetric dihydroxylation (AD) and chemistry of chiral 1,2- cyclic sulfates.[6] Herein, we report catalytic enantioselective synthesis of seven such β-blockers (**1a–g**) from readily available starting materials (Fig. 1).

2. Results and discussion

Retrosynthetic analysis of these β-adrenergic blocking agents (**A**) is shown in Figure 2. There are three possible disconnections at the a, b and c bonds. Most of the previous synthetic routes are based on the disconnection of bonds at either a or b.

The general synthetic scheme we have employed for the synthesis of (*S*)-propranolol (**1a**), (*S*)-moprolol (**1b**), (*S*)-toliprolol (**1c**), (*S*)-bunitrolol (**1d**), (*S*)-practolol (**1e**), (*S*)-xibenolol (**1f**) and (*S*)-celiprolol (**1g**) is presented in Scheme 1.

Allylation of phenols **2a–g** (**2a**=α-naphthol, **2b**=2-methoxyphenol, **2c**=3-methylphenol, **2d**=2-cyanophenol, **2e**=4-acetamidophenol, **2f**=2,3-dimethylphenol, **2g**=2-hydroxy, 4-nitro- acetophenone) with allyl bromide gave allyl ethers **3a–g** in >97% yield.



Scheme 1. (i) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux, 12 h, 97–99%; (ii) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 12 h, 94–98%, 73–90% ee; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 40 min. 96–99%; (iv) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min. 94–98%; (v) LiBr, THF 25 °C, 2–3 h; (vi) 20% H_2SO_4, Et_2O, 25 °C, 10 h; (vii) K_2CO_3, MeOH, 0 °C, 2 h, 80–85% overall in three steps; (viii) R-NH_2, H_2O (cat.), reflux, 2 h, 99%.

These allylic ethers **3a–g** were then subjected for the Os-catalyzed sharpless asymmetric dihydroxylation (AD) using $(DHQD)_2$-PHAL (hydroquinidine 1,4-phthalazinediyl diether) as chiral ligand in the presence of $K_3Fe(CN)_6$/K_2CO_3 as co-oxidant to give the enantiomerically enriched diols **4a–g**. The diols **4a–g** were then treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0 °C to afford cyclic sulfites in 96–99% yield as 1:1 diastereomeric mixture. The formation of cyclic sulfite was clearly evident from the appearance of multiplets at δ 4.00–5.50 in its ^1H NMR spectrum. The cyclic sulfites of the corresponding diols were then converted into cyclic sulfates **5a–g** in 94–98% yield using $RuCl_3$-catalyzed oxidation. The ^1H NMR spectrum of cyclic sulfates **5a–g** showed the disappearance of several multiplets at δ 4.25–4.32, 4.72–4.86 and at 5.22–5.26 due to diastereomeric mixtures of cyclic sulfites. Finally, the cyclic sulfates **5a–g** were subjected to nucleophilic displacement with appropriate amine nucleophiles followed by hydrolysis of the resulting salts to afford the corresponding β-blockers **1**(**a–g**), respectively. However, these reactions resulted in very low yields of the final β-blockers (yields were often less than 30%). Hydrolysis of the salts of cyclic sulfates using various reaction conditions such as 20% H_2SO_4 in ether, 50% H_2SO_4 in ether, concd HCl, 20% aq NaOH and 50% aq NaOH was conducted but all of them failed to improve the yields of the final products. Hence, we decided to convert these cyclic sulfates **5a–g** into the corresponding epoxides **6a–g** using a three-step procedure. Thus, cyclic sulfates **5a–g** were first treated with anhydrous LiBr, followed by treatment with 20% aq H_2SO_4 in ether to give the corresponding bromoalcohols. These were then treated with anhydrous K_2CO_3 in MeOH at 0 °C to afford the corresponding epoxides **6a–g** in high overall yields (80–85% in three steps).[7]

Finally the epoxides **6a–g** were then subjected to regiospecific nucleophilic opening with the respective amines to furnish the corresponding β-blockers **1**(**a–g**) in excellent yields and enantiomeric excess (up to 99%). In case of celiprolol, the nitro group was hydrogenated at 20 psi H_2 pressure with 10% Pd/C as catalyst at room temperature to get the amine which was condensed with diethyl carbomyl chloride (DECC) to afford the corrosponding (*S*)-celiprolol.