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Chemoenzymatic Synthesis of (R) - and (S) - Atenolol and Propranolol employing Lipase Catalyzed Enantioselective Esterification and Hydrolysis

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Abstract : Chemoenzymatic synthesis of (R) - and (S) - atenolol and propranolol employing lipase catalyzed enantioselective esterification and hydrolysis is described.

In a drug molecule the stereochemistry plays an important role in biological activity[1]. In case of 2 - propanolamines e. g. atenolol and propranolol, the β - blockers, the activity is associated with the (S) - isomer. On the contrary the opposite (R) - enantiomer may be responsible for the side effects[2]. There have been considerable efforts done in the preparation of enantiomerically pure(S) - propanolamines by employing biocatalytic processes[3,4]. There are several reports regarding the chiral O - acyl derivatives of aryloxypropanolamines served as prodrugs[5-7].

The synthesis of (R) - and (S) - atenolol have been achieved by lipase catalyzed hydrolysis[3] of the intermediate O - acetyl esters. The synthesis of (R) - and (S) -

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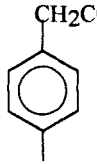
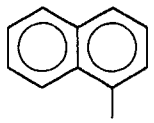
propranolol have been achieved by using lipase catalyzed hydrolysis[2,8] of the intermediate O - acetyl esters and also by using lipase catalyzed acylation[9,10] of the intermediate secondary alcohols. *Rhizopus arrhizus*[11,12] have been employed for enantioselective hydrolysis of acid esters and also its lipase[13] was employed for enantioselective hydrolysis of the secondary alcohol esters. Lipase of *Pseudomonas cepacia* (PS) was used for enantioselective O- esterification of secondary alcohol function[2,3,8,9]. The above advantages of lipases to catalyze the enantioselective reactions (e. g. esterification, hydrolysis) and also the importance of the chiral drugs prompted us to develop a methodology for the synthesis of chirally pure atenolol and propranolol. In present methodology we report here the direct resolution of (±) - atenolol and (±) - propranolol using lipase catalysed enantioselective synthesis, by employing enantioselective esterification and hydrolysis.

The methodology consists of esterification of (±) - atenolol and (±) - propranolol with vinyl acetate [Table - 1, Scheme - 1] or succinic anhydride [Table-2, Scheme - 2] in the presence of lipase PS - D to give (S) - alcohol and (R) - ester. The products were separated by column chromtography and the intermediate (R) - ester [confirmed by co-TLC with authentic sample], was hydrolyzed [using K_2CO_3-MeOH] to give (R) - alcohol. Further the corresponding O - acetyl ester of (±) - atenolol and (±) - propranolol were subjected to enantioselective hydrolysis [Table -3, Scheme -3] using lipase of *Rhizopus arrhizus* to produce (R) - alcohol and (S) - ester. The products were separated by column chromtography and the intermediate (S) - ester [confirmed by co -TLC with authentic sample], was hydrolyzed [using K_2CO_3-MeOH] to give (S) - alcohol. The compounds were obtained in good optical purity and isolated yields (35 - 45 %).

Table 1 :

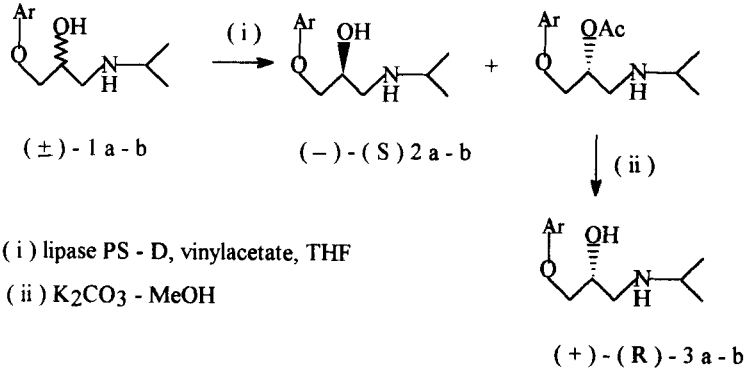
Substrate 1	Ar -	Product 2 : conf.[n], ee, (yield[♣])	Product 3 : conf.[n], ee, (yield[♣])
a		a* : (S), 94 %,(42 %) [a]$_D$ = - 15.0 (0.5, EtOH), Lit.[4] [a]$_D$ = - 16.0 (1, EtOH)	a : (R), 82 %,(40 %) [a]$_D$ = + 13.0 (1, EtOH), Lit.[4] [a]$_D$ = + 16.0 (1, EtOH)
b		b** : (S), 98%,(45%) [a]$_D$ = - 10.0 (1, EtOH), Lit.[3] [a]$_D$ = - 10.2 (1.02,EtOH)	b : (R), 88 %,(43 %) [a]$_D$ = + 9.0 (0.5, EtOH), Lit.[3] [a]$_D$ = + 10.2 (1.02,EtOH)

♣ The yields are isolated yields. conf.[n] = configuration

* ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 6H), 2.5 (m,1H), 2.6-2.8 (m,2H), 3.4 (s,2H), 3.8 (s,2H), 3.9 (m,1H), 5.0 (s,4H), 6.8(d,2H), 7.2 (d,2H).

** ^{1}H NMR ($CDCl_3$) : δ 1.1-1.2 (d, 6H), 2.8-3.1 (m, 3H), 4.1-4.3 (d,3H), 6.8-8.3 (m,7H).

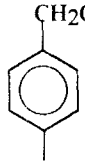
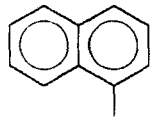
Scheme 1 :



(i) lipase PS - D, vinylacetate, THF

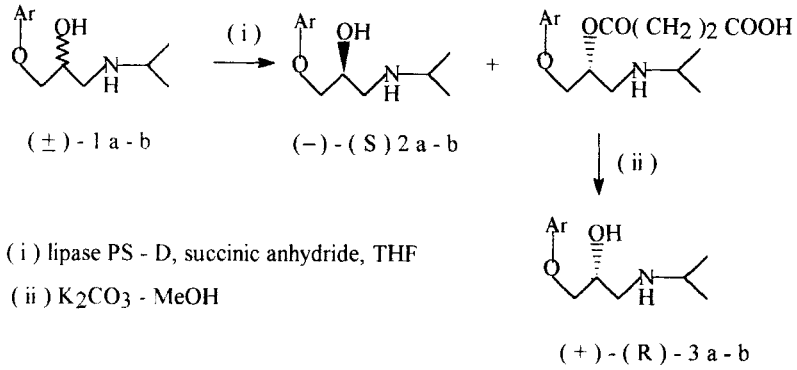
(ii) K_2CO_3 - MeOH

Table 2 :

Substrate 1	Ar -	Product 2 : conf.^{n}, ee, (yield$^\clubsuit$)	Product 3 : conf.^{n}, ee, (yield$^\clubsuit$)
a		a : (S), 94 %,(40%) [a]$_D$ = - 15.0 (1, EtOH), Lit.[4] [a]$_D$ = - 16.0 (1, EtOH)	a : (R), 88 %, (38 %) [a]$_D$ = + 14.0 (2, EtOH), Lit.[4] [a]$_D$ = + 16.0 (1, EtOH)
b		b : (S), 98 %, (45 %) [a]$_D$ = - 10.0 (1, EtOH), Lit.[3] [a]$_D$ = - 10.2 (1.02,EtOH)	b : (R), 88 %, (38 %) [a]$_D$ = + 9.0 (1, EtOH), Lit.[3] [a]$_D$ = + 10.2 (1.02,EtOH)

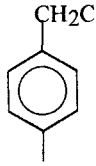
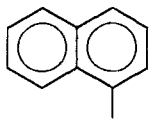
$\clubsuit$ The yields are isolated yields. conf.^{n} = configuration

Scheme 2 :



In order to optimise the reaction on larger scale, esterification of (±) - atenolol (25 mmol, 6.65 g) was carried by lipase PS - D (2.25 g) by usual procedure to give (S) - atenolol (94 % ee, 42 % yield$^\clubsuit$) along with (R) - atenolol (after hydrolysis of the correspounding ester) (82 % ee, 40 % yield$^\clubsuit$). This reaction was completed after 12h as

Table 3 :

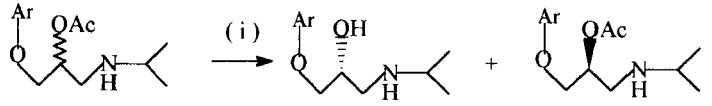
Substrate l	Ar -	Product 2 : conf.[n], ee, (yield[♣])	Product 3 : conf.[n], ee, (yield[♣])
a		a* : (R), 82 %,(37%) [a]$_D$ = + 13.0 (2, EtOH), Lit.[4] [a]$_D$ = + 16.0 (1, EtOH)	a : (S), 69 %,(44%) [a]$_D$ = - 11.0 (1, EtOH), Lit.[4] [a]$_D$ = - 16.0 (1, EtOH)
b		b** : (R), 98 %,(35%) [a]$_D$ = + 10.0 (0.5, EtOH), Lit.[3] [a]$_D$ = +10.2 (1.02,EtOH)	b : (S), 78 %,(43 %) [a]$_D$ = - 8.0 (1, EtOH), Lit.[3] [a]$_D$ = - 10.2 (1.02,EtOH)

♣ The yields are isolated yields. conf.[n] = configuration

* ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 6H), 2.5 (m,1H), 2.6-2.8 (m,2H), 3.4 (s,2H), 3.8 (s,2H), 3.9 (m,1H), 5.0 (s,4H), 6.8(d,2H), 7.2 (d,2H).

** ^{1}H NMR ($CDCl_3$) : δ 1.1-1.2 (d, 6H), 2.8-3.1 (m, 3H), 4.1-4.3 (d,3H), 6.8-8.3 (m,7H).

Scheme 3 :



compared to the same recation performed on a small scale which required 10h for completion.

Experimental :

THF was dried over sodium wire. All reactions were monitored by TLC [thin layer chromatography] on glass plates coated with 0.25 mm layer of silica gel. Compounds visualized by iodine vapours or in UV light. Column chromtography was done with silica gel 60 - 120 mesh, Merck. The substrate (±) - atenolol[15], (±) - propranolol[16] and their corresponding O - acetyl esters were prepared by literature procedure[6]. Lipase 'PS - D' [lipase PS immobilized on " diatomite "] was obtained from ' Amano Pharmaceutical Co., Ltd. Japan.' The *Rhizopus arrhizus* lipase was obtained from Fluka. ^{1}H NMR spectra were recorded on (MSL) 300 MHz spectrometer, using $CDCl_3$ or DMSO - d_6 as solvents. Optical rotation measurments were done on JASCO - 360 polarimeter.

General procedure for the Enantioselective Esterification of (±) - atenolol and (±) - propranolol with vinyl acetate [or succinic anhydride] :

A mixture of 5 mmol (±) - atenolol / (±) - propranolol, 6 mmol vinyl acetate/ 5 mmol succinic anhydride in 10 ml THF and 0.75 mg lipase PS - D was stirred at room temperature for 10 h. [reaction progress was monitored by TLC]. The reaction mixture was filtered through celite pad to remove the enzyme, washed with MeOH / $CHCl_3$. The combined organic solvent was dried over Na_2SO_4 and evaporated under reduced pressure. The products were separated by column chromtography. [atenolol - $CHCl_3$: MeOH 8 : 2 / propranolol - $CHCl_3$: MeOH 9.8 : 0.2] or [atenolol - Ethyl acetate : MeOH 9.5 : 0.5 / propranolol - Ethyl acetate].

General procedure for the Enantioselective Hydrolysis of (±) - O - acetyl ester of atenolol and propranolol :

A mixture of 1 g (±) - O - acetyl ester of atenolol / propranolol, 10 ml THF,

10 ml 0.1M phosphate buffer (pH 7) and 0.5 g lipase *Rhizopus arrhizus* were stirred at room temperature for 20 h. [reaction progress was monitored by TLC]. The reaction mixture was filtered through celite pad to remove the enzyme, washed with n - BuOH or $CHCl_3$. Aqueous phase was extracted with n - BuOH (for atenolol) or $CHCl_3$ (for propranolol). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The products were separated by column chromtography. [atenolol - $CHCl_3$: MeOH 8 : 2 / propranolol - $CHCl_3$: MeOH 9.8 : 0.2].

In summary, we have developed a direct method to synthesize both the enantiomers of the two important β - blockers. As other important β - blockers like practolol, oxprenolol, metaprolol, acebutolol, moprolol, etc. are all closely related to atenolol and propranolol[17], our present route should serve as a protocol for all these chiral drugs.

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