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Enzyme Catalyzed Stereoselective Synthesis of (S)-Propanolamines

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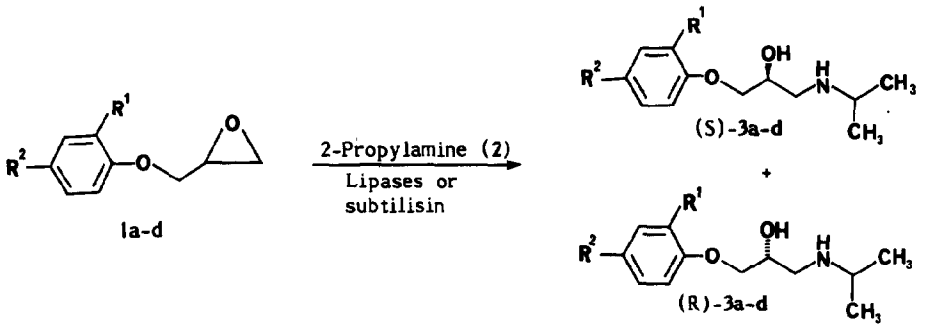
Abstract: Stereoselective synthesis of (S)-propanolamines has been carried out by the ring opening of racemic epoxides with 2-propylamine in presence of lipases and subtilisin. The effect of solvent towards selectivity has also been studied.

Synthesis of optically active beta-adrenergic blocking agents is of growing interest.[1,2] In recent years, a large number of methodologies including asymmetric synthesis[3] and bioconversions[4] have been described for the preparation of 2-propanolamines. The classical route in the production of beta-adrenergic blockers is by the opening of the epoxides with the corresponding amines. We recently investigated for the first time the opening of epoxides with amines in presence of enzymes. This study has led to the stereoselective synthesis of 2-propanolamines in presence of biocatalysts such as liver microsomes[5] and porcine pancreatic lipase (PPL).[6] There has also been a report on the enzyme catalyzed asymmetric opening of an epoxide by azide.[7] As a part of our continuing investigation of the biotransformations, we have examined the opening of epoxides with amines in presence of other lipases and subtilisin[8] in different organic solvents for optimization of the biocatalytic process. The lipases employed were from Candida cylindracea[9] (CCL) and lipozyme[8] (a fungal lipase from Mucor miehei immobilized on a macroporous synthetic resin, actual activity=49 BIU/g).

In a general experimental procedure; to epoxide, (1) (50 mg) dissolved in organic solvents (30-50 ml, sufficient enough for the dissolution of the substrate), the enzyme CCL (100 mg) or lipozyme (200 mg) or subtilisin (100 mg) was added and stirred for 5 minutes at room temperature. To this was added slightly more than half a molar equivalent amount of 2-propylamine (2) in 2-3 batches. After being stirred at 20-40°C for 2 to 3 days, the enzyme is filtered and the resulting solution was evaporated. The residue was immediately subjected to column chromatography (silica), chloroform-methanol (9.8:0.2) to recover the unreacted epoxide. After the complete recovery of the epoxide the eluent was changed to chloroform-methanol (9.5:0.5) for obtaining the propanolamine (3a). The reactions were monitored by TLC.

The enzymatic opening of epoxides with 2-propylamine was carried out in various organic solvents such as hexane, THF, toluene and ethylacetate. It is observed that



the enantiomeric excess of the (S)-propanolamine was excellent when lipozyme lipase was employed, particularly in toluene as a solvent. The absolute configuration was obtained by the correlation studies as described earlier.[6]

In summary, we have described a simple procedure for the synthesis of biologically important propanolamines accompanied by their kinetic resolution.

Table 1. Lipozyme-catalyzed opening of epoxides with 2-propylamine in toluene

Entry	R^1	R^2	Conversion (%)	(S)3, ee (%)[a]
1a	H	H	29	90
1b	H	Cl	43	92
1c	OCH_3	H	36	99
1d	H	$NHCOCH_3$	41	80

[a]Compounds **3** were derivatized to oxazolidones[10] and enantiomeric excesses were determined by HPLC[6].

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