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ENANTIOSELECTIVE EPOXIDATION USING LIPOSOMISED m-CHLORO-PERBENZOIC ACID (LIP MCPBA)

Atul Kumar[1] and Vinod Bhakuni[2]*

[1] Division of Pharmacokinetics and Metabolism and
[2] Division of Membrane Biology,
Central Drug Research Institute, Lucknow, India

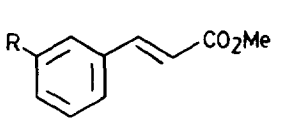
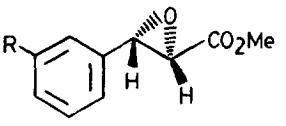
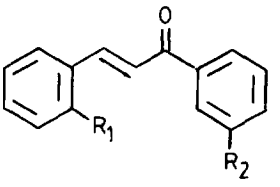
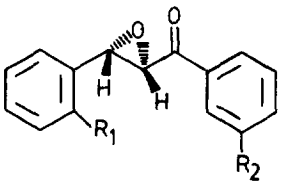
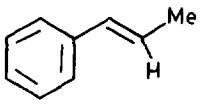
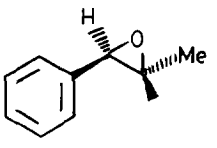
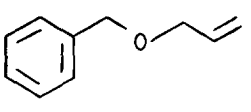
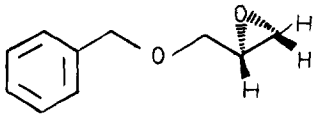
SUMMARY: *A highly enantioselective epoxidation of functionalized and unfunctionalized olefins using m-chloroperbenzoic acid in liposomised form (LIP MCPBA) has been demonstrated.* Copyright © 1996 Published by Elsevier Science Ltd

The asymmetric epoxidation of functionalized and unfunctionalized olefins is emerging as a very versatile and important synthetic transformation in organic chemistry[1]. Currently there are three major approaches to asymmetric epoxidation[2] viz. enzymatic which uses chloroperoxidase enzyme, purely synthetic using catalysts like (salen)Mn complex and chiral metalloporphyrins, and catalytic antibodies. Using these approaches moderate to high enantioselectivity can be obtained but they suffer from a major drawback that there is a high degree of substrate specificity as well as extreme reaction conditions associated with them[2].

We report here an entirely new strategy for enantioselective epoxidation of functionalized and unfunctionalized olefines using m-CPBA incorporated in liposomes (LIP MCPBA).

Egg phosphatidylcholine (EYPC) was isolated and purified according to the published procedure[3] m-CPBA containing EYPC liposomes were prepared as described earlier and were found to be intact by electron microscopic analysis and permeability studies[5]. The localization of m-CPBA in the liposomal bilayer was studied by ^{1}H-NMR nuclear overhauser enhancement (nOe) difference spectroscopic technique[6]. The only nOe that was observed was a negative nOe (-1.93%) between the aromatic protons of m-CPBA and the acyl chain protons of the phospholipid molecules. This suggests that m-CPBA molecules in the liposomised form are intercalated in the acyl chain region of the liposomal bilayer and not dispersed in the aqueous compartment[6] and that, there is a specific interaction between the aromatic ring protons of m-CPBA and the fatty acyl chain protons of the phospholipid molecules.

Table 1: Conversion of olefins to epoxides using LIP MCPBA

Entry	Olefin	Epoxide	%ee	% yield
1.				
	a. R=H		92	75
	b. R=OMe		95	70
2.				
	a. R_1=H; R_2=H		70	65
	b. R_1=Cl; R_2=H		68	63
	c.R_1=H; R_2=Cl		62	67
3.				
			82	76
4.				
			95	82

Note: Absolute configuration assumed by comparision of optical rotation and NMR spectroscopy[8].

LIP MCPBA on reaction with a variety of functionalized and unfunctionalized olefins yielded enantioselective epoxide products[7] (summarized in Table 1).

Phospholipid molecules, because of the amphipathic nature, when dispersed in water form closed bilayer shells known as liposomes or vesicles[9]. Owing to their nature, liposomes can accommodate a remarkable array of molecules at different sites[10]. Highly polar and relatively small molecules are trapped in the aqueous compartments whereas non polar molecules are intercalated in the fatty acyl chains of the phospholipid bilayers. The hydrophobic part of the amphipathic molecules gets inserted in the bilayer, and the hydrophilic part extends into the aqueous compartment or exposed in the outer surface of the liposomes. These specific intereactions between the lipid and the guest molecule in a liposomal configurations restrict the orientation of guest molecule at a specific sites, depending on its nature. This property of liposome-guest molecule has been exploited in stereospecific synthesis due to the fact that control of conformation of reagent and reacting molecule is essential for achieving a high degree of stereospecificity of the product.

In conclusion, the strategy for stereospecific synthesis using liposomised reagent, as described here, should be general and applicable to a large number of reactions. The work described here is the first step twoards defining the use of liposomised reagents in stereospecific reactions. The success of this basic study should encourage the application of liposomised reagents in stereospecific synthesis.

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4. Bhakuni, V.; Gupta, C.M. *Biochim. Biophys Acta.*, **1989**, *982*, 216- 222. Briefly; 100 mg of EYPC was dissolved in small quantity of chloroform and to it was added 25 mg of m-chloroperbenzoic acid and solution evaporated resulting into the formation of a thin film. The film was dried under vacuum for 30 mins. This was suspended in 2 mL of triple distilled water and vortexed vigrously. The suspension was sonicated at 4°C for 15 mins and centrifuged at 5000 rpm for 15 mins. The supernatent containing LIP MCPBA was passed through sepharose 6B for separating free m- CPBA from liposomised. The LIP MCPBA thus obtained was used for further reaction. The maximum incorporation of m-CPBA in liposomes that was

achieved was EYPC: m-CPBA, 4:1 (*wt/wt*).

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7. 0.35 m mole of desired reacting molecule was dissolved in 80 ul of ethanol. To it was added 1 ml of LIP MCPBA; the concentration of ethanol should not be more than 15% in the reaction mixture as higher concentrations disrupted the liposomes. The reaction mixture was stirred at room temperature (25°C) for 2 hrs. The product, epoxide in the present case, was extracted from the reaction mixture using ethyl acetate by phase separation. The combined ethyl acetate layers were dried over anhydrous sodium sulfate and evaporated to yield the epoxide. For completion of reaction the ratio of reacting molecule to m-CPBA in LIP MCPBA should be 1:1:4. (*mole /mole*).

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