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Enzymatic resolution of (±)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropane carboxylate †,‡

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Abstract: A novel biocatalytic kinetic resolution of a chemically labile racemic *cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropane carboxylate ester is studied.
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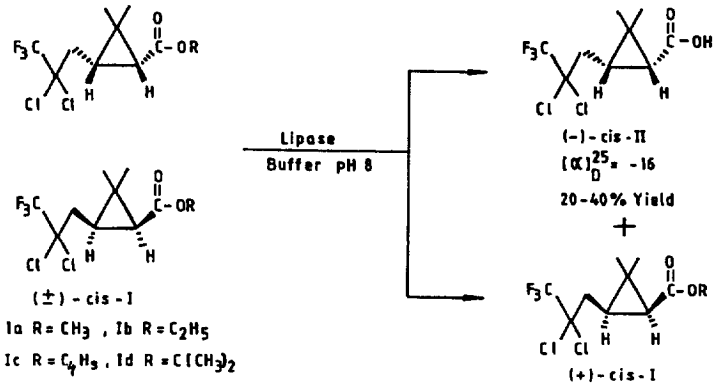
In today's world where the population is constantly on the increase, there is a requirement for augmenting the food production, which has promoted the exploration of new effective and non polluting insecticides for protecting the cultivation of crops and in controlling the pests in stored food products.[1] Pyrethroids are a class of powerful insecticides structurally related to the naturally occurring insecticides chrysanthemates.[2] The physiological activities of the pyrethroid insecticides are closely related to their absolute (R)-(−)-configuration at C-3 of the *cis*-cyclopropane ring.[3] The potential use of enzymes to instil the asymmetry in the synthesis of enantiomericically pure biologically active molecules is well documented.[4] Nevertheless, relatively few stereospecific synthesis of new unnatural pyrethroids as potent household insecticides have been studied.

We now report the stereospecific hydrolysis of chemically labile racemic (±)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropanecarboxyl esters (**1**) using hydrolytic enzymes (see scheme below).



The diastereomeric mixture of (±)-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropanecarboxyl esters was synthesized as reported in the literature.[5] After separation, the racemic *cis*-compound was selectively hydrolysed using different hydrolytic enzymes.[6] The products were purified by column chromatography with gradient solvent system of hexane:ethyl acetate and the yields are given in Table 1. The structural elucidation of the compounds were determined using the spectral data.[7] Values of kinetic parameters were calculated as reported in our earlier studies.[8] The enantioselectivity of the reaction using different incubation mediums and enzymes, obtained from

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‡ IICT Communication No. 3801.
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Table 1. Selective hydrolysis of racemic (±)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropane carboxyl esters

Substrate	Reaction conditions		Product Optically Active acid		Remaining Optically Active ester	
	Time hr	Conversion %	Yield	ee %	Yield	ee %
1a	8	26	25	88	30	65
1b	8	35	30	90	25	60
1c	18	30	20	40	20	60
1d	20	32	25	60	20	55

General Procedure : Racemic esters (0.5 mmol), PPL (100-200 mg), 0.1 M trisbuffer pH 8.0 (20 ml) incubated at 25-30°C for respective hours. The products are quantified by GC., enantiomeric excess (ee) determined by NMR studies.

different sources were shown in Table 2. The reaction has shown high enantioselectivity in aqueous medium compared to organic medium. From the reaction kinetics (Figure 1) it is observed that the optimum conversion and ee% was achieved at 8 hours of incubation time. The rate constants Km and V_{max} were greater in the aqueous surfactant and polar medium compared to non-polar medium.[9] This may be due to an increase in hydrophilicity of the substrate facilitating the interaction of the enzyme at its catalytic active site, whereas in non-polar solvent medium the binding of the compound to the enzyme active site is less significant. Chemically the reaction is so labile that the compound is readily gets hydrolysed and dehydrohalogenated to 3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethyl-cyclopropane carboxylic acid, even under mild basic conditions. Whereas by using lipases we have shown the catalytic efficiency of the enzyme in hydrolysing the labile cyclopropane esters enantioselectively. We presume that the absolute configuration of the products obtained by selective hydrolysis of substituted (±)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropane analogs by lipases are similar to as reported in our earlier studies[7] i.e., lipases hydrolyse selectively the (R)-(−)-enantiomer of the racemic compounds (±) **1**.

In conclusion, the enzymes are used for the first time in enantiospecific hydrolysis of chemically labile (±)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropane carboxylate ester to give stereoselectively the products R-(−)-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropanecarboxylic acid and its S-(+)-esters, as new pyrethroid intermediates of biological interest in high enantiomeric purity.

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Table 2. Hydrolysis of (+)-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropane carboxylate ester (ethyl) by lipases obtained from different sources

Source of Enzyme lipase	Reaction medium	Reaction		Product Optically Active acid		Remaining Optically active ester	
		Time hr	Conversion	Yield %	ee %	Yield %	ee %
Candida cylindreacea	a) 0.1M Tris+2% Tritonx100 buffer pH8.0	8	40	30	80	40	90
	b) Ethanol	10	30	20	55	25	65
	c) Cyclohexane	24	05	-ND-	-ND-	-ND-	-ND-
	d) Isopropanol	18	03	-ND-	-ND-	-ND-	-ND-
Pseudomonas fluorescens	a) 0.1M Tris+2% Tritonx100 buffer pH8.0	8	30	25	55	25	80
	b) Ethanol	12	20	20	40	18	50
	c) Cyclohexane	16	05	-ND-	-ND-	-ND-	-ND-
	d) Isopropanol	18	05	-ND-	-ND-	-ND-	-ND-
Procince pancreas lipase (crude	a) 0.1M Tris+2% Tritonx100 buffer pH8.0	8	35	30	90	25	60
	b) Ethanol	16	20	15	60	20	45
	c) Cyclohexane	20	15	05	30	08	25
	d) Isopropanol	18	10	07	35	12	40

The reaction conditions are described in table 1. All the solvents used are of analytical grade. Values are average of three experiments. -ND- - Not detectable due to low % conversion.

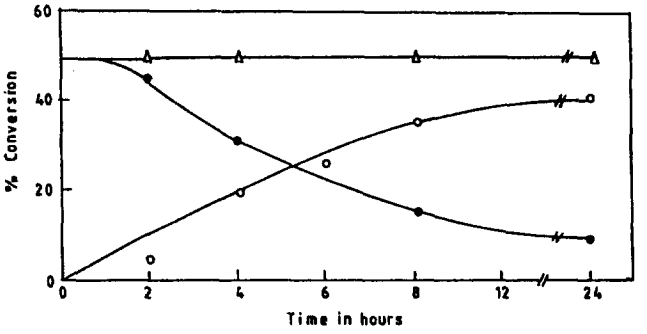

Figure 1. Time course stereospecific hydrolysis of compound Ib. △ (±) *cis* Ib ester (substrate), • (+) *cis* Ib ester (substrate), ○ (−) *cis* IIb acid (product).

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6. Lipase obtained from Candida cylindreacea, Type VII; Pseudomonas fluorescens Type II and Procine pancreatic lipase (PPL) Type II obtained from Sigma Chemical Co., USA. Specific activity of the enzymes ranges from 75U–175U/mg protein (Biuret).
7. Enantiomeric excess (ee) is calculated by NMR studies. NMR (200 MHz): 0.9 (m, 1H), 1.1–1.4 (2s, $2CH_3$), 1.6 (m, 1H), 2.3 (m, 2H). Specific rotation i) (−)-R-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropane carboxylic acid, $[\alpha]_D$ −16 (conc.=1.0 methanol), (+)-S-*cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl cyclopropane carboxylate ethyl ester, $[\alpha]_D$=+10 (conc=1.0 methanol).
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9. Time course of reaction (compound Ib) at different time intervals showing relative concentration of acid and its ester quantified by GC (Hewlett Packard 5890 Mixed Column OV 17 and OV 1 (8 feet × 1/8 inch dia).

	Medium	**Km mol min^{-1}**	**V_{max} mol min^{-1} mg^{-1}**
a)	0.1 M Tris-HCl buffer pH 8.0	15	48
b)	0.1 M Tris surfactant buffer pH 8.0	25	56
c)	Cyclohexane	18	20
d)	Isopropanol	23	28

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