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Lipase Catalysed Kinetic Resolution of Racemic (±)2,2-Dimethyl-3-(2-Methyl-1-Propenyl)-cyclopropane Carboxyl esters+

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Abstract : Optically active (1R)(-) and (1S)(+)-trans-Chrysanthemic acid and its esters were prepared from corresponding racemic methyl ester by lipase mediated enantioselective hydrolysis, is described.

Enzymes are exceptional biocatalysts which have recently become an effective tool in organic synthesis in introducing centres of chirality which is otherwise difficult to introduce purely by chemical methods[1,2]. The hydrolytic enzymes are the most actively exploited group of enzymes and have found industrial applications in preparation of chiral compounds[3]. Cis, trans-substituted derivatives of cyclopropane carboxylic acids are abundent in nature and are commercially used as insecticides in agriculture[5,6]. In contrast to well documented asymmetric synthesis and resolution of racemic mixtures of these cyclopropane anologues[4,5] the application of hydrolytic enzymes such as lipases in stereoselective synthesis has never been studied. So the attention was directed towards the synthesis of enantiomerically pure chrysanthemic acid which is an important intermediate for several synthetic household pyrethroids.

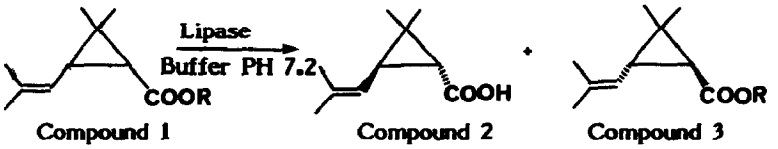
We now report a successful enzymatic kinetic resolution of racemic 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxylic esters, using lipases (Scheme 1). The racemic trans-2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane carboxylic esters were synthesised as reported in the literature[7]. To the substrate (a-d, 0.2 g) dissolved in 0.1M phosphate buffer (pH 7.2) or organic solvent, added 0.5 g of lipase[8] and the mixture is incubated at 37°C. The pH of the medium was maintained constant by pH stat method. The reaction was followed by monitoring the product ratio using HPLC[9]. Finally the products were purified by column chromatography and the structures are characterised by spectral data.

The higher enantioselectivity was observed in the reaction carried out in surfactant phosphate buffer (2% Triton x 100) using Candida cyclindracea lipase, when compared to non-polar organic solvent medium (Table 1). From the reaction kinetics (Fig.1), the rate constants K_m and V_{max} were greater in the aqueous surfactant buffer compared to non-aqueous medium[11]. It is presumed that the surfactant increased the catalytic efficiency by insertion of substrate molecules into micelles, thus increasing the molecular hydrophobicity and flexibility, at a particular topology of enzyme active site to facilitate the binding of substrate in catalytic vacuole for measurable stereoselective activity.

In conclusion the lipase catalysed asymmetric hydrolysis of racemic 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxylate esters, gave the products (-) and (+)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxylic acid and its esters of biological interest with

good optical purity. Further application of this methodology is in progress.

Scheme I



Compound 1 Compound 2 Compound 3

Ia = R-CH_3; Ib = R-C_2H_5; Ic = R-$C(CH_3)_2$; Id = R-CH_2CCl_3

Table 1 : Results of the lipase catalysed hydrolysis of Racemic (±)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxyl esters by candida cylindracea.

Sub-strate	Medium	Reaction conditions		Optically active acid			Optically active ester		
		time(hr)	conversion %	Yield %	ee%	configu-ration *	Yield %	ee%	Configu-ration *
Ia.	i) 0.1M buffer PH 7.2	12	25	30	72	R	20	65	S
	ii) Triton x 100 0.1M buffer PH 7.2	8	40	40	90	R	45	88	S
	iii) Cyclohexane	20	8	5	15	R	10	15	S
	iv) Isopropanol	16	10	18	29	R	15	20	S
Ib.	i) 0.1M buffer PH 7.2	12	30	35	75	R	30	65	S
	ii) Triton x 100 0.1M buffer PH 7.2	8	45	42	96	R	42	91	S
	iii) Cyclohexane	20	16	10	15	R	15	18	S
	iv) Isopropanol	16	20	26	45	R	16	30	S
Ic.	i) Triton x 100 0.1M buffer PH 7.2	18	20	15	40	R	15	68	S
	ii) Cyclohexane	20	10	12	15	R	19	30	S
	iii) Isopropanol	16	15	10	20	R	10	35	S
Id.	i) Triton x 100 0.1M buffer PH 7.2	10	35	22	38	R	15	25	S
	ii) Cyclohexane	20	15	25	15	R	8	18	S
	iii) Isopropanol	18	18	10	16	R	16	16	S

The reaction conditions are described in the text given. Enantiomeric excess (ee) and stereochemical assignments confirmed to literature values[10].

* Configuration of the carbon (C_3) in the cyclopropane ring with the -COOR group involved in selectivity.

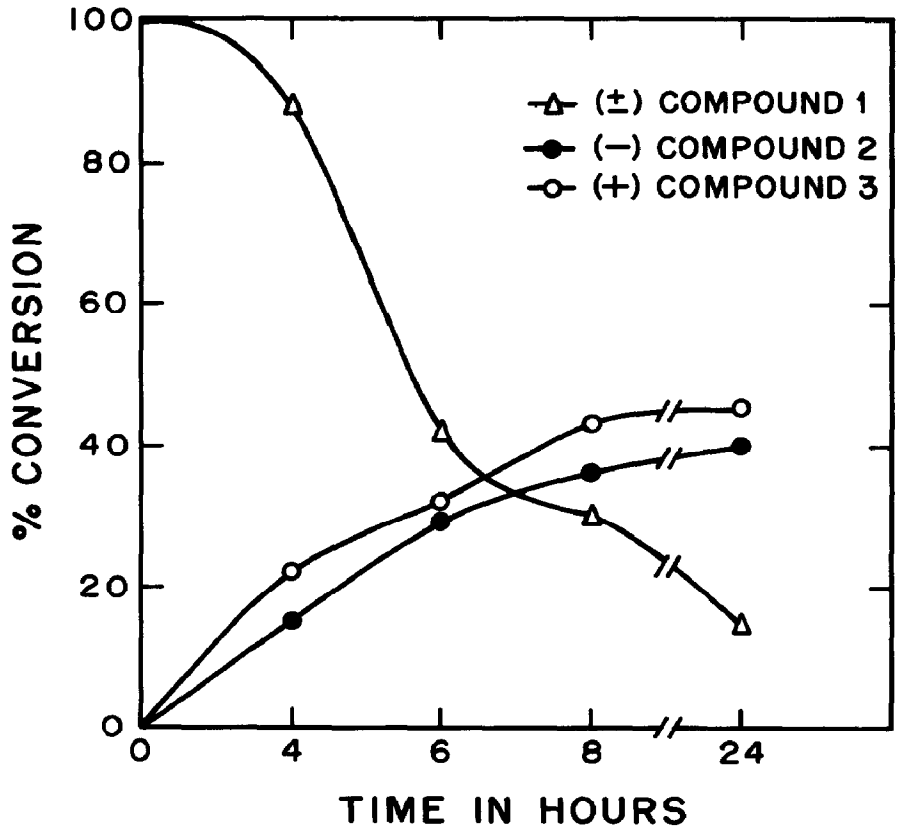


Fig. 1 : **Progress curves of stereospecific hydrolysis of compound Ia in 2% Triton x 100, 0.1 M sodiumphosphate buffer pH 7.2.**

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8. Lipase from Candida cyclindracea Type VII, Specific activity 900 units per mg Protin (Biuret). Sigma Chemical Co., USA.

9. Time course of the reaction of compound I incubated with lipase obtained from Candida cylindracea Type VII in 0.1 M phosphate surfactant buffer pH 7.2 (2% Triton x 100) at 37° at different time intervels, showing relative concentration of acid and its ester. Reaction is followed by HPLC Schmidazu C-R4A using TSK ODS-120A, 5 um column (4.6x25 cm) in Acetonitrile : Water (70:30) system at 254 nm.

10. Eanantiomeric excess (ee) of
i) (-)-R-,2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxylic acid, optical rotation $[\alpha]_D$ = -15 (conc=1.0 methanol), ii) (+)-S-2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropane carboxylate ethyl ester, optical rotation $[\alpha]_D$ = +18 (conc=1.0 methanol), compared with Roussel Uclaf Fr. Pat.No.1,536,458 (**1967**).

11. Values of kinetic parameters K_m and V_{max} of lipase catalysed reaction are calculated as reported by M. Dixon and E. Webb (1964) Enzyme, 2nd Edition, p 84, Academic Press, New York.

	Medium	K_m mol min^{-1}	V_{max} mol min^{-1} mg^{-1}
a)	0.1M sodiumphosphate buffer pH 7.2	20	60
b)	0.1M sodiumphosphate surfactant buffer pH 7.2	32	85
c)	Isopropanol	20	25
d)	Cyclohexane	15	20

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