Abstract

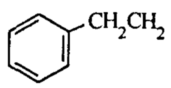
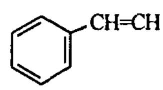
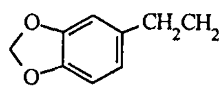
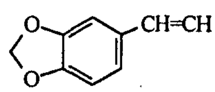
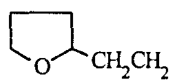
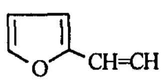
Selectivity is a goal towards synthetic efficiency. In order to achieve that goal, several transformations proceeding with high degree of selectivity were carried out with the help of enzymes and small molecules as catalysts.

The presence of some kind of hindrance in the form of a 'gate' in the active-site of PLE as proposed by Jones' *et al.* prompted us to study the kinetics of hydrolysis of flexible or saturated esters and locally inflexible α, β-unsaturated or cyclopropane carboxylic esters. In line with our expectations, the saturated esters underwent hydrolysis at a rate much faster compared to the α, β-unsaturated or cyclopropane counterparts. Treatment of an equimolar mixture of the two pairs of esters with PLE at pH 7.4 effected the hydrolysis of only the saturated ester functionality; the unsaturated esters remaining intact (**Table 1**).

Scheme 1

$$\underset{\mathbf{1\ (a\text{-}d)}}{R^1COOMe} + \underset{\mathbf{2\ (a\text{-}d)}}{R^2COOMe} \xrightarrow[\text{pH 7.4}]{\text{PLE / Acetone-buffer}} \underset{\mathbf{3\ (a\text{-}d)}}{R^1COOH} + \underset{\mathbf{2\ (a\text{-}d)}}{R^2COOMe}$$

Table 1

R^1	R^2	Time of Reaction	% of yield of saturated acid
$CH_3CH_2CH_2$ **1 a**	$CH_3CH{=}CH$ **2 a**	4h	98 (**3 a**)
 **1 b**	 **2 b**	6h	95 (**3 b**)
 **1 c**	 **2 c**	20h	96 (**3 c**)
 **1 d**	 **2 d**	16h	95 (**3 d**)

Hydrolysis of substrates where both the saturated and α, β-unsaturated or cyclopropane carboxylic ester functionalities are present in the same molecule, also proceeded with high degree of selectivity; the saturated ester underwent complete hydrolysis (**Table 2, 3, 4**).

Scheme 2

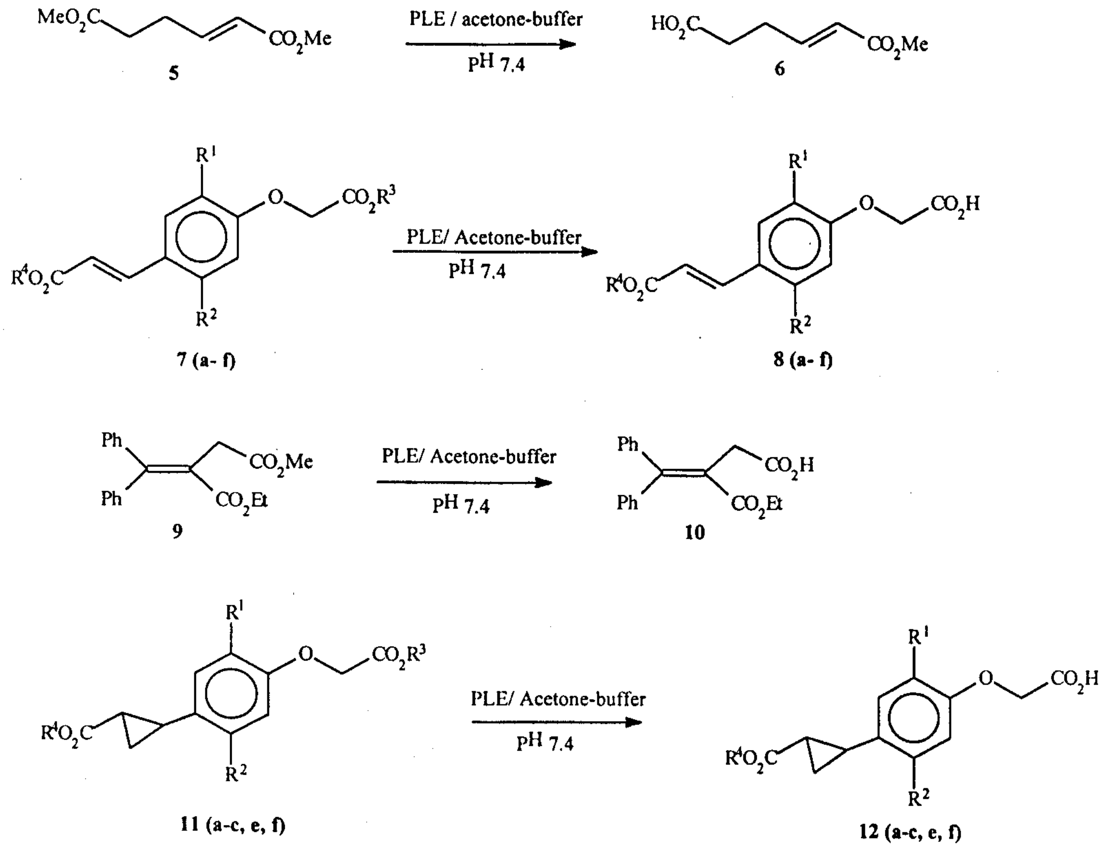


Table 2

Substrate	Product	Yield (%)
Dimethyl 2-hexenedioate **5**	**2-Hexenedioic acid 1-methyl ester** **6**	**91**
Methyl 3-ethoxycarbonyl-4, 4-diphenyl-3-butenoate **9**	**3-Ethoxycarbonyl-4, 4-diphenyl-3-butenoic acid** **10**	**95**

Table 3

Reactant	R^1	R^2	R^3	R^4	Product (Yield)
7 a	H	H	Me	Me	8 a (91%)
7 b	OMe	H	Me	Me	8 b (92%)
7 c	OMe	Br	Me	Me	8 c (95%)
7 d	H	H	Et	Et	8 d (93%)
7 e	H	H	Me	Et	8 e (93%)
7 f	OMe	H	Me	Et	8 f (93%)

Table 4

Reactant	R^1	R^2	R^3	R^4	Product (Yield)
11 a	H	H	Me	Me	12 a (95%)
11 b	OMe	H	Me	Me	12 b (92%)
11 c	OMe	Br	Me	Me	12 c (93%)
11 e	H	H	Me	Et	12 e (96%)
11 f	OMe	H	Me	Et	12 f (96%)

Regioselectivity was also observed during the PLE-catalyzed hydrolysis (**Table 5**) of substrates containing an acetate on a saturated arm and another one attached onto a β, γ-unsaturated system in the same molecule. These results confirmed definite role of binding on the observed selectivity.

Scheme 3

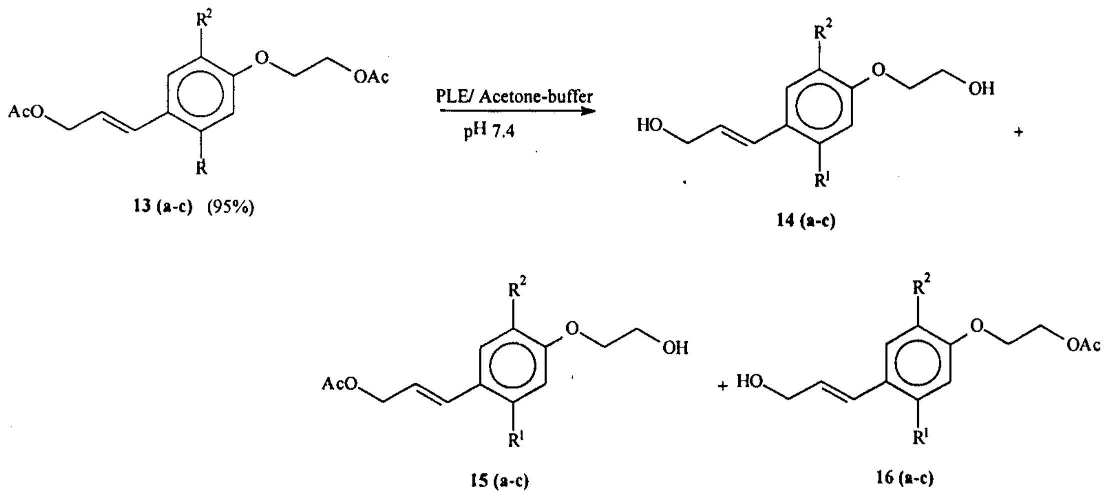
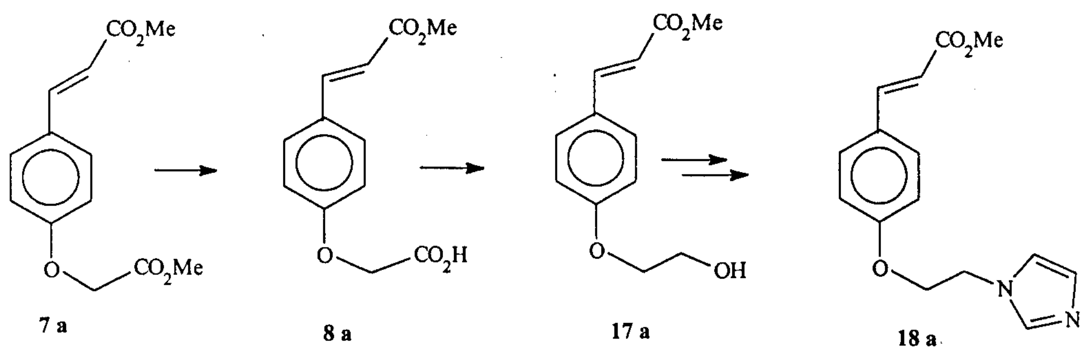


Table 5

Substrate	R^1	R^2	% of dialcohol 14 (a-c)	% monoacetate 15 (a-c)	% monoacetate 16 (a-c)
13 a	H	H	20	~80	Trace
13 b	OMe	H	20	60	20
13 c	OMe	Br	40	40	20

The observed selectivity has been applied to the synthesis of an intermediate (**17a**) for the thromboxane synthetase inhibitor **18a** as shown in **Scheme 4.** This is an example of using the methyl ester as a selective protecting group.

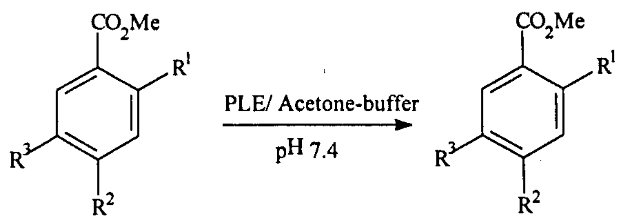
Scheme 4



7 a 8 a 17 a 18 a

Other transformatinos proceeding with high degree of selectivity include the chemoselective hydrolysis of phenolic acetates in the presence of aromatic esters or saturated esters over aromatic esters (**Table 6, 7**).

Scheme 5

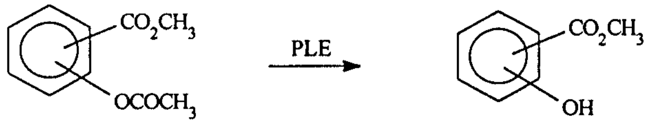


19 (a-d) 20 (a-d)

Table 6

Substrate	Reaction time (h)	Product	Yield (%)
$R^1 = R^3 = H$, $R^2 = OCH_2CO_2Me$ **19 a**	18	$R^1 = R^3 = H$, $R^2 = OCH_2CO_2H$ **20 a**	100
$R^1 = OCH_2CO_2Me$, $R^2 = R^3 = H$ **19 b**	20	$R^1 = OCH_2CO_2H$, $R^2 = R^3 = H$ **20 b**	96
$R^1 = OCH_2CO_2Me$, $R^2 = H$, $R^3 = Br$ **19 c**	24	$R^1 = OCH_2CO_2H$, $R^2 = H$, $R^3 = Br$ **20 c**	98
$R^1 = H$, $R^3 = Br$, $R^2 = OCH_2CO_2Me$ **19 d**	24	$R^1 = H$, $R^3 = Br$, $R^2 = OCH_2CO_2H$ **20 d**	99

Scheme 6



21 (a-f) **22 (a-e)**

Table 7

Substrate	Time (min)	Product	Yield (%)
Methyl 4-acetoxybenzoate (21 a)	15	Methyl 4-hydroxybenzoate (22 a)	90
Methyl 2-acetoxybenzoate (21 b)	15	Methyl 2-hydroxybenzoate (22 b)	92
Methyl 3-acetoxybenzoate (21 c)	20	Methyl 3-hydroxybenzoate (22 c)	85
Methyl 3-bromo 4-acetoxybenzoate (21 d)	20	Methyl 3-bromo-4-hydroxybenzoate (22 d)	84
Methyl 5-bromo 2-acetoxybenzoate (21 e)	20	Methyl 5-bromo-2-hydroxybenzoate (22 e)	85
Methyl 3-methyl 2-acetoxybenzoate (21 f)	240	---	---

PLE along with the lipase enzyme PPL have been used to catalyze hydrolytic reactions in an attempt to achieve high degree of stereoselectivity. The substrates, in these cases, are the β-lactam esters (**23 a-d**). For the 3-ethoxycarbonyl β-lactam (**23 a-d**), while PPL produced almost no selectivity, moderate enantioselectivities were observed [for R = furyl or thienyl (**23 b,c**)] for reactions catalyzed by PLE. On the other hand, hydrolysis of β-lactam acetates (**25 a-f**) by PPL proceeded with high degree of enantioselectivity (**Table 8**). In this case, PLE was ineffective in terms of the desired selectivity. Incidentally, the chiral β-lactams (**26 a-f**) can be used as side chain variants of the anticancer agent *taxol*.

Scheme 7

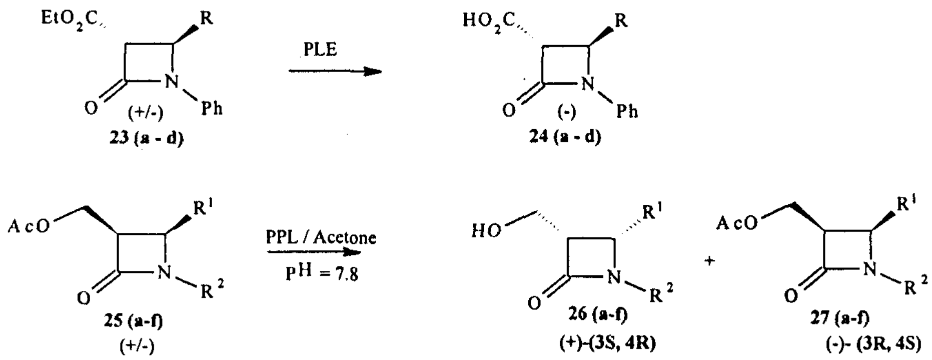
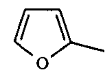
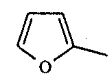
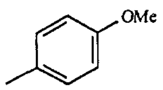
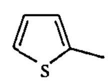
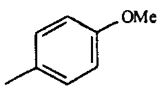
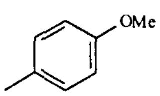
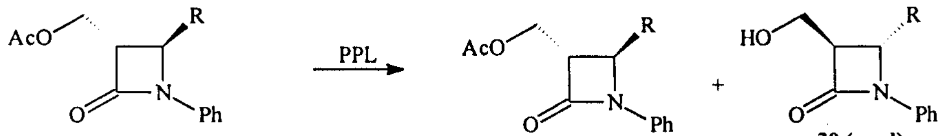


Table 8

R1	R2	% ee of Alcohol	$[\alpha]_D^{27}$	% ee of Acetate	$[\alpha]_D^{27}$
Ph	Ph	83	(+)-91.42⁰	20	(-)-24.5⁰
	Ph	84	(+)-69.66⁰	63	(-)-73.0⁰
		85	(+)-127.88⁰	40	(-)-34.16⁰
	Ph	90	(+)-172.98⁰	50	(-)-70.23⁰
Ph		92	(+)-156.75⁰	60	(-)-37.68⁰
	Ph	>98	(+)-117.4⁰	58	(-)-37.71⁰

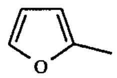
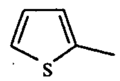
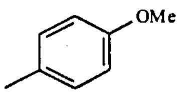
In the case of *trans*-β-lactam acetates (**28 a-d**), PLE again failed to show any enantioselectivity. The enantioselectivity shown by PPL, unlike in the case of *cis*-β-lactam acetates (**25 a-f**), ranged from poor to moderate as shown in **Table 9**. Moreover, the conversion was also poor showing that the *trans* acetates are inferior substrates for PPL.

Scheme 8



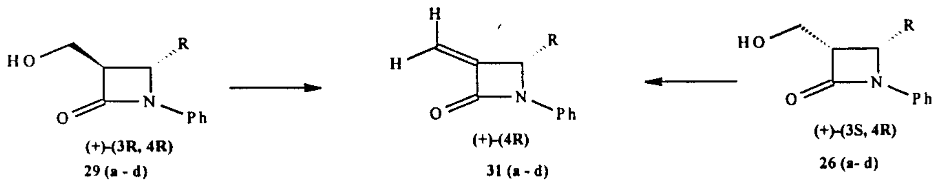
28 (a - d) (+/-) → **29 (a - d)** (-)-(3S, 4S) + **30 (a - d)** (+)-(3R, 4R)

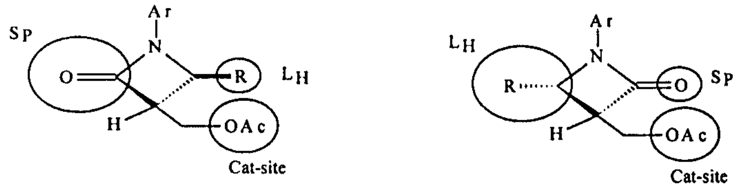
Table 9

Substrate	R¹	Reaction Time (h)	Extent of Conversion/ % Yield of Alcohol	% ee
28 a	Ph	30	45	50
28 b		28	30	33
28 c		30	20	10
28 d		30	20	10

One interesting aspect of the above hydrolysis is that the exomethylene-β-lactams (**31 a-d**) obtained from the hydrolysed alcohols from the *cis* and *trans* acetates have the same sign of rotation and hence same absolute configuration at C-4 . This is only possible if the stereochemically preferable isomers from *cis* and *trans*-β-lactam acetates undergoing hydrolysis have mirror image configurations at C-4. The *cis*-β-lactam acetates have been shown to bind according to Jones' model. This necessitates the preferential binding mode of the *trans*-β-lactam acetates to be according to Seebach's model which is enantiomeric to the Jones' model. Thus the adjacent chirality in the large hydrophobic group (in this case C-4 with the substituent) can dictate the mode of binding (**Figure 1**).

Scheme 9





Jones' Model **Figure 1** **Seebach's Model**

Attempted enantioselective synthesis of β-lactam alcohols (**33 a-d**) using natural chiral bases like (+) cinchonine or (+) cinchonidine met with moderate success (**Table 10**).

Scheme 10

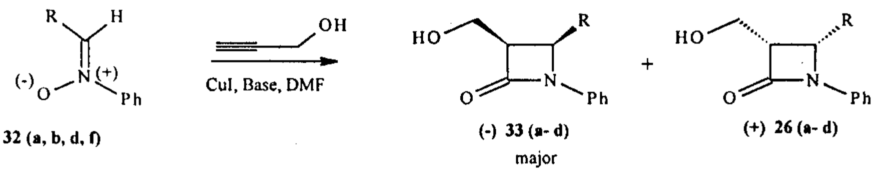


Table 10

Substituent (R)	Substrate	Base	Product-ratio (enantiomeric ratio)
Phenyl	32 a	(+)cinchonine	1:1
	32 a	(+)cinchonidine	5:2
2-Furyl	32 b	(+)cinchonine	1:1
	32 b	(+)cinchonidine	2:1
2-Thienyl	32 d	(+)cinchonine	1:1
	32 d	(+) cinchonidine	1:1
4-Methoxyphenyl	32 f	(+) cinchonine	1:1
	32 f	(+) Cinchonidine	1.2:1

Apart from biologically important β-lactams, we have also attempted the stereo and regioselective synthesis of aromatic fused 1,4-dioxanes which have, in recent years, drawn considerable attention because of their physiological activities. The key step in the synthesis is the Pd-mediated C-O bond formation in propargyloxy phenol or napthol systems (**Scheme11**). The results depicted in **Table 11**, show the involvement of high degree of regio and **Z**-selectivity in the reaction. Incidentally, the benzodioxane (**36 a**) has been reduced to the saturated analogue (**40 a**) which is an intermediate for the antidepressant drug *azaloxan* (**41, Scheme 12**).

Scheme 11

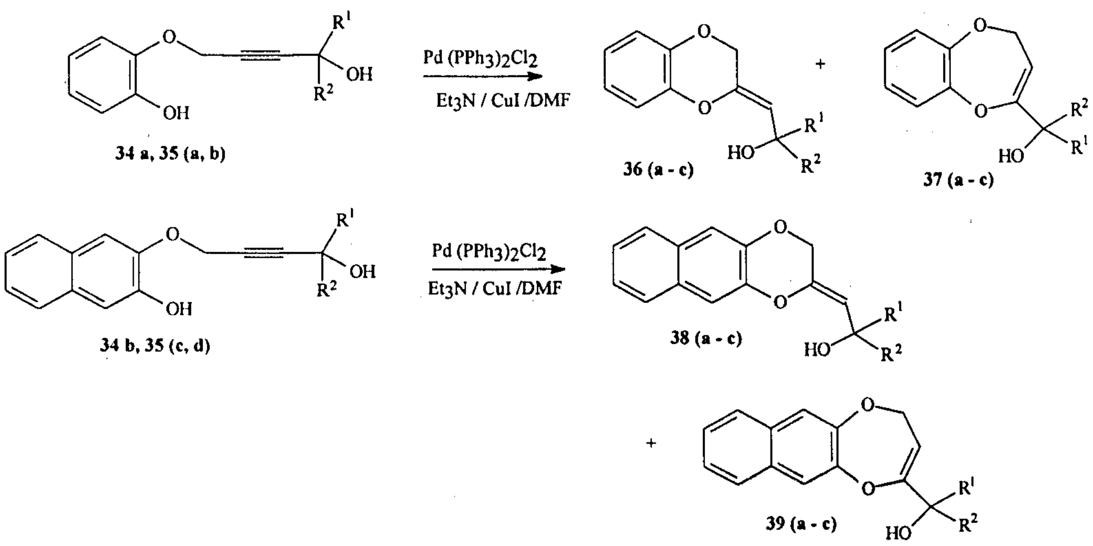
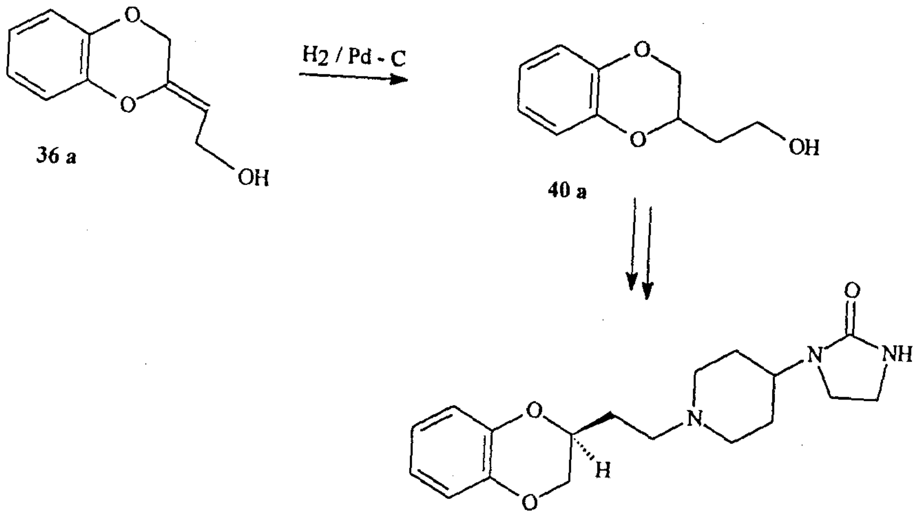


Table 11

Substrates	Product - exo(%)	(% Yield - endo)
$R^1 = R^2 = H$ (34 a)	71	7.5
$R^1 = R^2 = Me$ (35 a)	80	---
$R^1 = Me, R^2 = Et$ (35 b)	73	---
$R^1 = R^2 = H$ (34 b)	75	---
$R^1 = R^2 = Me$ (35 c)	78	---
$R^1 = Et, R^2 = Me$ (35 d)	82	---

x

Scheme 12



36 a

40 a

41