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Kinetic resolution of 1-acenaphthenol and 1-acetoxynaphthene through lipase-catalyzed acylation and hydrolysis

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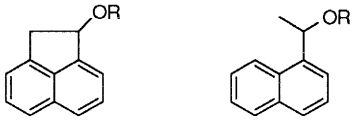
Abstract

Acenaphthenyl acetate and acenaphthenol are resolved through *Pseudomonas fluorescens* lipase (PFL)-catalyzed hydrolysis and acylation, respectively. By contrast, the structurally related 1-(1-naphthyl)ethyl acetate and 1-(1-naphthyl)ethanol are inactive under the same reaction conditions.

Keywords: kinetic resolution; enzyme; catalysis; enantioselective; acylation; hydrolysis.

Enantiomerically pure 1-arylethanols and their derivatives are compounds of interest in transition metal-catalyzed organic synthesis. Noteworthy, 1-(1-naphthyl)ethyl acetate and carbonate have been used as chiral, optically active substrates in palladium-catalyzed substitutions.[1] In this context, we have been interested in the preparation of optically active 1-acenaphthenol to investigate the behaviour of its esters in Pd-catalyzed substitutions. (−)-1-Acenaphthenol **1**, a benzylic alcohol which is an early metabolite of oxidation of acenaphthene, has already been obtained by fractional crystallization of the diastereomeric camphanic esters and its configuration shown to be *R* by X-ray diffraction.[2]



1 R = H
2 R = $COCH_3$
3 R = $OCOCH_3$

4 R = H
5 R = $COCH_3$

Since the first assays for lipase-catalyzed acylation of **1** were disappointing[3] we turned to investigations on the resolution of (±)-**1** by enzymatic hydrolysis of the corresponding acetate and methyl carbonate (Scheme 1). Two lipases were examined: a microbial lipase from *Pseudomonas fluorescens* (PFL) and

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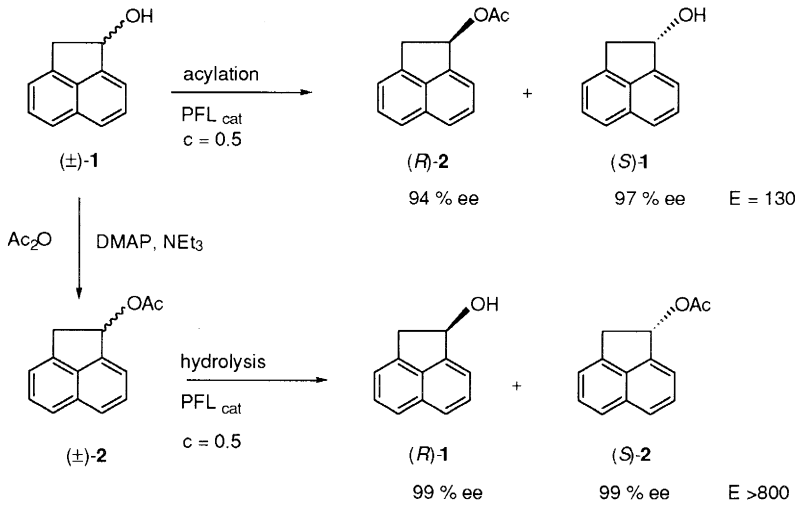
a mammalian, the rabbit gastric lipase (RGL),[4] since this latter showed good enantioselectivities in the kinetic resolution of secondary benzylic alcohols through acylation.[3] Moreover, we wished to compare both the activity and the selectivity displayed by these lipases in the kinetic resolution of **4** and **5**, which may be regarded as the flexible counterparts of rigid **1** and **2**. The results for lipase-catalyzed hydrolyses of **2**, **3** and **5** are shown in Table 1.



Scheme 1.

Table 1
Lipase-catalyzed hydrolyses of **2**, **3** and **5**

Substrate[a]	Lipase (mg)	Reaction time (h)	Conversion[b] (%)	Recovered Ester ee(%) (% yield)[c]	Alcohol ee(%)[d] (% yield)[c]	E[b]
(±)- **3**	PFL (50)	90	41	62[e)] (17)	89 (13)	30
(±)- **3**	RGL (80)	120	42	8[e)] (22)	10 (17)	1.3
(±)- **2**	PFL (50)	90	50	99[f)] (31)	99 (35)	>800
(±)- **2**	RGL (100)	24	61	81[f)] (32)	51 (40)	8
(±)- **5**	PFL (50)	120	< 5	-	-	-
(±)- **5**	RGL (50)	120	< 5	-	-	-

[a] 2 mmol, 30°C. [b] c and E were calculated from $ee_{substrate}$ and $ee_{product}$ using standard equations [5]; [c] yields given for isolated products after silica gel chromatography (hexane / ethyl acetate 80 / 20). [d)] measured by chiral hplc on Chiralcel® OD-H column, hexane/isopropanol 97/3, flow 0.5 mL.min^{-1}. [e)] measured by chiral hplc on Regis® (*S*,*S*)-WHELK-01 column, hexane/isopropanol 9/1, flow 0.5 mL.min^{-1}. [f)] measured by chiral hplc on Chiralcel® OD-H column, hexane/isopropanol 9/1, flow 0.5 mL.min^{-1}

RGL was inactive for hydrolysis of **5**, and moderately selective for hydrolysis of **2**. By contrast, although inactive for hydrolysis of **5**, PFL displayed both good activity and enantioselectivity (*E*>800) in hydrolysis of **2**.

An analogous investigation was carried out for acylation of **1** and **4**. The results are shown in Table 2.

Table 2
Lipase-catalyzed acylation of alcohols **1** and **4** with isopropenyl acetate

Substrate[a)]	Lipase (mg)	Reaction time (h)	Conversion[b] (%)	Recovered alcohol ee(%)[c] (% yield)[d]	Ester ee(%)[e] (% yield)[d]	E[b]
(±)- **1**	PFL (50)	24	50	97 (34)	94 (41)	130
(±)- **1**	RGL (80)	24	90	77 (22)	8	2.2
(±)- **4**	PFL (50)	90	- [f)]	-	-	-
(±)- **4**	RGL (100)	120	20	19	78	11

[a] 2 mmol, 30°C; 3 mmol isopropenyl acetetate. [b] c and E were calculated from $ee_{substrate}$ and $ee_{product}$ using standard equations[5]; [c] measured by chiral hplc on Chiralcel® OD-H column, hexane/isopropanol 97/3, flow 0.5 mL. min $^{-1}$. [d] yields given for isolated products after silica gel chromatography. [e] measured by chiral hplc on Chiralcel® OD-H column, hexane/isopropanol 9/1, flow 0.5 mL. min $^{-1}$. [f] very low conversion: less than 1 % ester produced.

Here again, both **1** and **4** were acylated with isopropenyl acetate in the presence of RGL with poor (*E*=1.8) to moderate (*E*=14) selectivity. The same trend as for hydrolysis was observed in PFL-catalyzed acylation: PFL was found to be inactive for acylation of **4**, but both active and enantioselective in acylation of **1**.

The chiroptical properties of **1** and **2** are reported in Table 3.

Table 3
Chiroptical properties of **1** and **2**, obtained through acylation and hydrolysis, respectively[a]

Compound	$[\alpha]_D^{20}$	c (g.100mL^{-1})	% ee[b]	Compound	$[\alpha]_D^{20}$	c (g.100mL^{-1})	% ee[b]
(*S*)-**1**	+ 1.34	2.6	97	(*R*)-**1**	- 1.38	2.1	99
(*R*)-**2**	+ 81.6	3.4	94	(*S*)-**2**	- 85.2	2.2	99

[a] optical rotations measured with a Perkin Elmer 241 polarimeter, in $CHCl_3$ solvent.

[b] see Tables 1 and 2.

RGL was neither satisfactory in acylation of **1** and **4**, nor in hydrolysis of **2**, **3** and **5**. PFL was inactive in acylation of **4** and hydrolysis of **5**, but showed excellent enantiocomplementarity, since it was both active and enantioselective in acylation of **1** and hydrolysis of the corresponding esters **2** and **3**. Both enantiomers of **1** and **2** were thus obtained directly with the same enzyme.

The high *E* value recorded for PFL-catalyzed hydrolysis of **2** indicates that the spatial structure of the *R*-configurated rigid substrate fits nicely in the active site of the enzyme for acylation. The same trend holds for acylation of **1**, where (*R*)-**1** should have the ideal shape for nucleophilic attack of the acylenzyme.

Rigid **1** and **2** can be regarded as resembling particular conformations of **4** and **5**, respectively. Since **4** and **5** are inactive, we may conclude that the active conformation of **4** and **5** for enzyme-mediated acylation and hydrolysis cannot be reached, or is too poorly populated. This sounds reasonable since in such a conformation, the methyl group of **4** and **5** would suffer severe steric interactions with the *peri*-H atom attached to the C-8 naphthalenic carbon atom. Such results could help in designing the shape of the active site of the enzyme and the steric and spatial requirements for activity and selectivity in PFL-catalyzed acylations and hydrolysis of secondary alcohols. Work is in progress along this line.

In summary, acenaphthenyl acetate and acenaphthenol are resolved and obtained in >97% *ee* through *Pseudomonas fluorescens* lipase (PFL)-catalyzed hydrolysis and acylation, respectively. (*R*)-Acenaphtol has the required structure for a nice fit with the enzyme active site. By contrast, the structurally related 1-(1-naphthyl)ethyl acetate and 1-(1-naphthyl)ethanol are inactive under the same reaction conditions, indicating that the active conformation of the (*R*)-enantiomer is of too high an energy.

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