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HIGHLY REGIOSELECTIVE RING-OPENING OF α- SUBSTITUTED CYCLIC ACID ANHYDRIDES CATALYZED BY LIPASE

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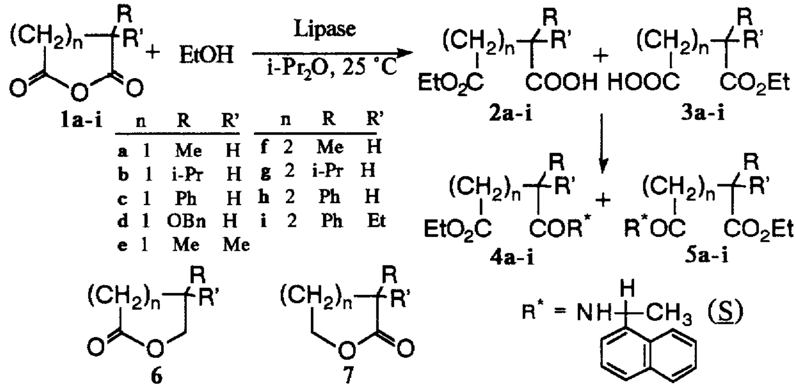
Summary: Lipase Amano P irreversibly catalyzed a ring-opening of α-substituted cyclic acid anhydrides 1 preferentially at the less hindered carbonyl goup to give monoesters with high regioselectivity.

Potential of lipases as an acylation-catalyst for organic synthesis in non-aqueous media is of considerable current interest.[1] In particular, a regioselective transformation of a functional group is, as well as a stereoselective one, an important factor which must be controlled in synthesis. In this regard lipases have been used for regioselective acyl-exchange of sugars[2] and glycols;[3] however, regioselective transformations of carboxyl groups are limited.[4] We reported in the previous paper that a microbial lipase well catalyzed the stereoselective ring-opening of prochiral cyclic acid anhydrides in an organic solvent.[5] Some lipases have been reported to have a preference for carboxylic acids without α-substituents.[6] Therefore, if cyclic anhydrides with an alkyl substituent at the α-position are used, a preferential ring-opening at the less hindered carbonyl group would be anticipated.

On this basis we wish to report a regioselective ring-opening of racemic cyclic acid anhydrides 1 with ethanol catalyzed by a lipase from *Pseudomonas fluorescens* (Amano P) in diisopropyl ether. After the ring-opening of 1, the two compounds was obtained: the monoester 2 and 3. The ratios 2 : 3 were measured by converting them into the corresponding amide-esters 4 and 5[7] followed by HPLC analyses[8] of them. This method allowed the ratios of the four isomers (2, 3 and their enantiomers) to be determined precisely.



1a-i

	n	R	R'		n	R	R'
a	1	Me	H	f	2	Me	H
b	1	i-Pr	H	g	2	i-Pr	H
c	1	Ph	H	h	2	Ph	H
d	1	OBn	H	i	2	Ph	Et
e	1	Me	Me				

2a-i 3a-i 4a-i 5a-i 6 7

The results of the lipase-catalyzed reaction together with those of non-enzymatic ethanolysis of 1 are listed in Table 1. The lipase irreversibly catalyzed the ring-opening at the less hindered side of all the anhydrides 1 except for 1e and 1i, yielding racemic monoesters 2 in high chemical yields. The di-substituted anhydrides 1e and 1i were, however, poor substrates for the lipase presumably because of bulkiness of the substituents. The product mixture 2 and **3** was converted to a mixture of the lactones **6** and **7** by functional group-selective reduction.[9] As shown in Table 1, either of the lactones **6** and **7** was obtained from the same product mixture **2** and **3** in good chemical yields; the ratios of **6** and **7** agreed well with those of **2** and **3**.

Table Regioselective Ring-Opening of **1** with Ethanol Catalyzed by Lipase Amano P and Functional Group-selective Reduction of Product **2** and **3**[a]

	Anhydride 1			Time	Yield of	Ratios	Ratios[b]	Reduction	Yield of	Ratios
	n	R	R'	(h)	2,3 (%)	2 : 3	(2 : 3)	Method[c]	6,7 (%)	6 : 7
a	1	Me	H	17	100	92 : 8	(57 : 43)	BH_3-SMe_2	87	93 : 7
b	1	i-Pr	H	6 days	100	99 : 1	(79 : 21)	BH_3-SMe_2	88	99 : 1
								$LiBH_4$	96	2 : 98
c	1	Ph	H	24	100	100 : 0	(69 : 31)	BH_3-SMe_2	70	100 : 0
								LiBH4	94	0 : 100
d	1	OBn	H	67	100	48 : 52	(9 : 91)	BH_3-SMe_2	80	49 : 51
e	1	Me	Me	13 days	100	82 : 18	(75 : 25)	BH_3-SMe_2	83	82 : 18
f	2	Me	H	24	100	80 : 20	(49 : 51)	BH_3-SMe_2	70	83 : 17
g	2	i-Pr	H	25	100	100 : 0	(82 : 18)	BH_3-SMe_2	76	100 : 0
								LiBH4	74	0 : 100
h	2	Ph	H	22	100	93 : 7	(46 : 54)	BH_3-SMe_2	74	95 : 5
i	2	Ph	Et	no reaction		-	-	-	-	-

[a] Reaction conditions: **1** (10 mmol), EtOH (11 mmol), lipase Amano P (1.0 g), dry i-Pr_2O (100 mL), 25 °C. Spontaneous ethanolysis was not observed without the lipase in this condition. [b] Results of the reaction without the lipase: **1** (10 mmol), EtOH (170 mmol), 25 °C, 1 week. [c] See reference 9.

The regioselectivity, i.e. the ratios **2** : **3**, improved by increasing the size of the substituent R, almost complete regioselection was achieved for **1b**, **c**, and **g**. The anhydride **1d**, however, gave almost 1:1 mixture of the monoesters **2d** and **3d**. This result can be explained as follows: the carbonyl group near the oxygen atom is more reactive to the nucleophilic attack of ethanol than the other (**2d** : **3d** = 9 : 91 for spontaneous ethanolysis), whereas the lipase catalyzes the reaction preferentially at the less hindered side; hence, the electronic and the steric factors compensated with each other in the lipase-catalyzed reaction of **1d**.

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7. Product mixture **2** and **3** (0.1 mmol), $SOCl_2$ (0.12 mmol), (*S*)-(-)-1-(1-naphthyl)ethylamine (0.11 mmol), NEt_3 (0.3 mmol), dry toluene (2 mL), 0°C, 1 hr.
8. Silica gel column (NUCLEOSIL 50-5, 4 mm x 25 cm); eluent, hexane-AcOEt (5 : 2); 280 nm. The four isomers (**4**, **5** and their diastereomers) were base-line separated except for the diastereomers **5f**.
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