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Lipase Catalyzed Formation of Lactones *via* Irreversible Intramolecular Acyltransfer

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Abstract: The lipase catalyzed formation of lactones is greatly facilitated, if the conditions of irreversible acyltransfer are employed. While only insignificant amounts of lactones are obtained from hydroxy carboxylic acids (±)-**1a-f** or their methyl esters (±)-**2a-f**, considerable yields can be obtained, if the corresponding vinyl esters (±)-**3a-f** are used as substrates. Due to the enantioselectivities, displayed by the lipase from *Pseudomonas sp.*, optically active products are formed.

Esterhydrolase (esterase, lipase) catalyzed preparations of monolactones **4a-f** and dilactones **5a-f** could be attempted *via* three different routes (scheme 1):

(1) Intramolecular esterification, using the hydroxy carboxylic acids (±)-**1a-f**;
(2) Reversible intramolecular acyltransfer, using the hydroxy carboxylic acid esters (±)-**2a-f**;
(3) Irreversible intramolecular acyltransfer, using the hydroxy carboxylic acid vinyl esters (±)-**3a-f**.

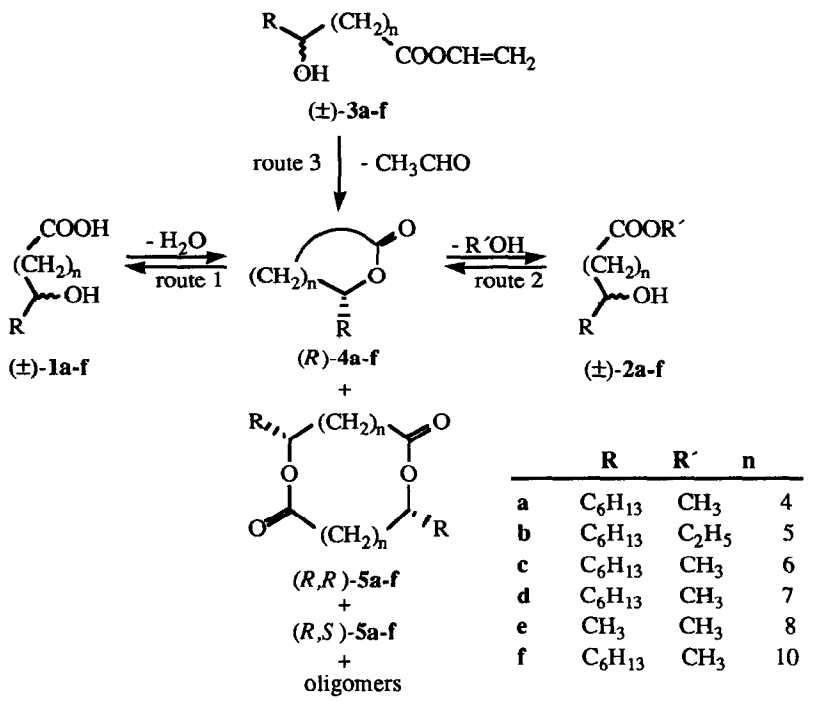
While routes 1 and 2 employ reversible transformations in which the released nucleophiles (H_2O, MeOH, EtOH) can participate in back reactions, route 3 provides an irreversible approach due to the spontaneous tautomerisation of the liberated vinyl alcohol into the non nucleophilic acetaldehyde.[1,2] It was to be expected, therefore, that considerably higher rates of transformations and product yields should be observed, if vinyl esters (±)-**3a-f** are employed as substrates in these enzymatic reactions.[3]

This was indeed observed. In typical experiments 2.5 mmol of the corresponding substrates (±)-**1a-f** and (±)-**2a-f**, (±)-**3a-f** were each dissolved in 500 ml tert.-butyl methyl ether or hexane, respectively. After the addition of 20 g molecular sieves 3 Å [(±)-**1a-f**] or 5 g molecular sieves 4 Å [(±)-**2a-f**, (±)-**3a-f**] together with 2.5 g of an immobilized lipase from *Pseudomonas sp.* (SAM II)[5] the mixtures were shaken in stoppered Erlenmeyer flasks at room temperature with 250 r.p.m. while the product formation was monitored by TLC[6]. The results - products and their yields - are summarized in table 1.

Even after 34 d no products at all were observed in the lipase catalyzed transformations employing (±)-**1a-f** (route 1). Equally, no traces of cyclic products were found in the corresponding transformations of the methyl and ethyl esters (±)-**2a-e** (route 2), although small quantities of oligomers were produced. Only from the reaction of (±)-**2f**, next to 11 % of a dimer, 21 % of the dilactones (*R,R*)- and (*R,S*)-**5f** were isolated as an unseparable mixture (table 1). In contrast to (±)-**3a**, which proved to be no substrate for the employed lipase from *Pseudomonas sp.*, all other vinyl esters (±)-**3b-f** indeed produced variable amounts of lactones next to a wide variety of oligomers (table 1). From the transformation of (±)-**3b** the 8-membered monolactone (*R*)-**4b** was isolated for the first time in low yield together with a trimer and the dilactones (*R,R*)- and (*R,S*)-**5b**, which were successfully separated by column chromatography (100 g silica gel; eluents: hexane/^{t}BuOMe = 9:1, followed by hexane/^{t}BuOMe = 3:1). In contrast - and somewhat expectedly - no mediocyclic monolactones (*R*)-**4c-e** with 9 to 11-membered rings were isolated from the transformations of (±)-**3c-e**, while considerable amounts of the dilactones (*R,R*)- and (*R,S*)-**5c-e** were isolated, purified and characterized. From (±)-**3f** the 13-

membered monolactone (*R*)-**4f** was formed in fair yield together with considerable quantities of the dilactones (*R,R*)- and (*R,S*)-**5f**, which, unfortunately, could not be separated by column chromatography.

Scheme 1



	R	R´	n
a	C_6H_{13}	CH_3	4
b	C_6H_{13}	C_2H_5	5
c	C_6H_{13}	CH_3	6
d	C_6H_{13}	CH_3	7
e	CH_3	CH_3	8
f	C_6H_{13}	CH_3	10

Table 1. Products and yields in the enzymatic transformations of (±)-**2f** and (±)-**3a-f**.

substrate	reaction time [h]	isolated yields in [%]								
		mono-lactone *R*	dilactone *R,R*	dilactone *R,S*	tri-lactone	educt	dimer	trimer	tetramer	poly-mer
3b	152	11	17	4				22[a]		
3c	152		20	9				7[a]	6[a]	
3d	152		16	4	8[b]				2[a]	55[a]
3e	152		18	9						51[c]
3f	26	17	53[d]							
2f	75		21[d]			51[a]	11[e]			

a) $[\alpha]_D^{20} = 0$ (c=1, $CHCl_3$)

b) Mixture of (*R,R,R*), (*R,R,S*), and (*R,S,S*); $[\alpha]_D^{20} = -2.7$ (c=0.8, $CHCl_3$)

c) $[\alpha]_D^{20} = +2.2$ (c=1, $CHCl_3$)

d) Mixture of (*R,R*) and (*R,S*)

e) $[\alpha]_D^{20} = -1.8$ (c=1, $CHCl_3$)

Based on literature reports[4,7-10] it was not surprising to find that the formation of the mono- and dilactones proceeded with distinct enantioselectivities and all chiral cyclic products showed optical rotations (table 2).

Table 2. Chiroptical data of mono- and dilactones

substrate	optical rotation in $CHCl_3$							
	monolactone		dilactone					
	(*R*)		(*R,R*)		(*R,S*)		(*R,R*) and (*R,S*)	
	$[\alpha]_D^{20}$	c	$[\alpha]_D^{20}$	c	$[\alpha]_D^{20}$	c	$[\alpha]_D^{20}$	c
3b	-2.4	0.5	-6.2	0.5	0	1		
3c			-3.8	1	0	1		
3d			-7.9	0.9	0	1		
3e			-4.7	1.7	0	1		
3f	-5.5	1					-7.0	1
2f							-3.3	1

Only lactones (*R*)-**4b,f** and (*R,R*)-**5b-f** next to the optically inactive *meso*-derivatives (*R,S*)-**5b-f** were resulting from the (*R*)-configurated acyldonors (*R*)-**2f** and (*R*)-**3b-f**.[11] These observations could be interpreted exemplified for (±)-**3b** as outlined in scheme 2.

If indeed, as expected, the (*R*)-configurated acyldonors are preferentially accepted as substrates by the lipase, the intermediate acyl-enzyme could react in the following ways:

(1) *Intramolecular* displacement leading to the monolactone (*R*)-**4b**;

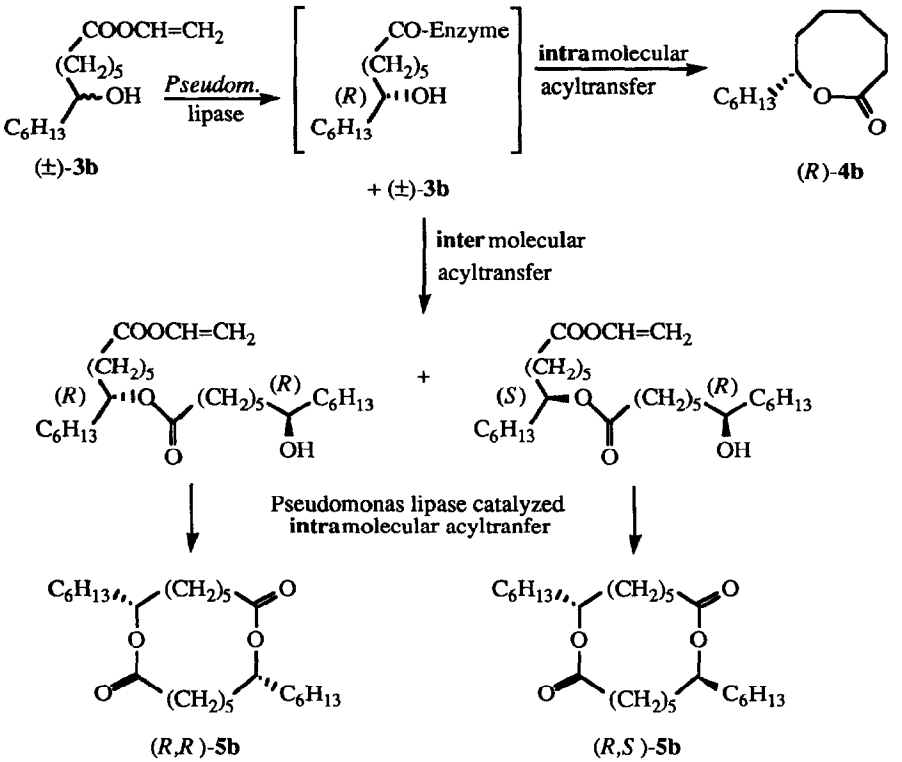
(2) *Intramolecular* transfer of the acylgroup from the intermediate acyl-enzyme onto the *racemic* nucleophile (±)-**3b**, thus leading to a mixture of diastereomeric (*R,R*)- and (*R,S*)-dimers, which could cyclize *via* another intramolecular step to the isolated dilactones (*R,R*)- and (*R,S*)-**5b**.

It was observed previously[4,10] that the proportions of formed mono- and dilactones are to a certain degree dependent on the reaction temperature, with higher temperatures favouring the monolactone production. This fact, together with the advantages resulting from the use of vinyl esters as substrates was employed successfully for the production of enantiomerically pure (*R*)-**4f** in high yield.

Thus, 818 mg (2.5 mmol) of (±)-**3f**[12] was dissolved in 500 ml of hexane and the mixture heated to 66°C. Then 5 g molecular sieves 4 Å were added together with 1.25 g of immobilized lipase from *Pseudomonas sp.* (SAM II)[5] and the mixture stirred at 66°C for 24 h. The product formation was monitored by TLC[6]. The formed monolactone (*R*)-**4f** was successfully separated from a mixture of the diastereomeric dilactones (*R,R*)- and (*R,S*)-**5f** by column chromatography (100 g silica gel; eluent: hexane/^{t}BuOMe = 19:1). Isolated were 224 mg (32 %) of (*R*)-**4f** [$[\alpha]_D^{20}$= -5.5 (c=1, $CHCl_3$); identical with the optical rotation reported by Yamada, Otha *et al.*[4]] together with 127 mg (18 %) of the diastereomeric dilactones (*R,R*)- and (*R,S*)-**5f** [optical rotation of the mixture: $[\alpha]_D^{20}$= -4.2 (c=1, $CHCl_3$)].

In summary, due to the recent synthetic availability of hydroxy carboxylic acid vinyl esters[12], a series of previously unknown mono- and dilactones [(*R*)-**4b**, (*R,R*)- and (*R,S*)-**5b-f**] could be synthesized for the first time in an enantioselective way from their racemic precursors. The known (*R*)-**4f** was obtained enantiomerically pure and in 34 % yield (68 % based on the converted enantiomer).

Scheme 2



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5. On kieselgur immobilized lipase from *Pseudomonas sp.* was obtained from Amano Pharmaceutical Co.; activity: 1500 U/g, standard: tributyrine.
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11. The absolute configurations of all products were assigned tentatively based on the known[4] (*R*)-**4f** and the fact that all optical rotations show identical signs. With the exception of (*R*)-**4f** no optical purities can be assigned to the obtained products at this time.
12. Lobell, M.; Schneider, M. P.; in preparation.