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BIOCATALYTIC RESOLUTION OF LONG-CHAIN 3-HYDROXYALKANOIC ESTERS

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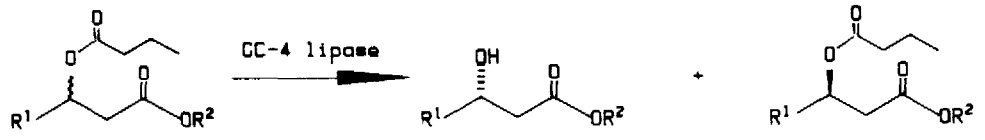
Summary: Enzymatic resolution of 3-butanoyloxyalkanoates of various chain length using *Geotrichum candidum* lipase led to optically active 3-hydroxyalkanoates.

Chiral hydroxyalkanoic acids and derivatives have been shown to be versatile tools for EPC-synthesis[1]. Furthermore, long-chain 3-hydroxyacids are structural elements of bacterial endotoxins with potential therapeutic significance, such as lipid A[2]. Although several methods for the synthesis of the lower homologs are available[1,3,4], optically active long-chain 3-hydroxy-acids have only been obtained by asymmetric reduction of the corresponding 3-oxoacids using baker's yeast[5] - in low yield - or by means of chiral modified hydrogenation catalysts[6]. Therefore, we studied the biocatalytic preparation of long-chain 3-hydroxyalkanoates. A very recent publication[4] on the enzymatic resolution of (ω-1)-acyloxyalkanoates prompts us to report some of the results of our approach which makes use of a biocatalytic resolution of methyl 3-acyloxyalkanoates by *Geotrichum candidum* (GC-4) lipase[7] applying a two-step process described earlier[8].



rac-1a-5a (S)-1b-5b (R)-1a-5a

	1a,b	2a,b	3a,b	4a,b	5a,b
R^1	n-C_7H_{15}	n-$C_{11}H_{23}$	n-$C_{15}H_{31}$	$(CH_2)_4CH(n\text{-}C_4H_9)_2$	n-$C_{11}H_{23}$
R^2	CH_3	CH_3	CH_3	CH_3	t-Bu

Substrate	Conversion 40%		Conversion 60%	
	Product[a]	e.e. [%][b]	Product[a]	e.e. [%][b]
rac-1a	(*S*)-1b	74	(*R*)-1a	42
rac-2a	(*S*)-2b	84	(*R*)-2a	75
rac-3a	(*S*)-3b	84	(*R*)-3a	32
rac-4a	(*S*)-4b	92	(*R*)-4a	50
rac-5a[c]	(*S*)-5b	19	(*R*)-5a	<10

[a] The absolute configuration was correlated by comparison of $[\alpha]_D^{20}$ values with literature data (1b[8], 2b[8], 3b[5], 5b[9]) or by LIS-^{1}H-nmr experiments of the MTPA ester of 4b[10]. [b] Determined by ^{1}H-nmr spectroscopy using Eu(hfc)$_3$, butanoates (*R*)-1a-5a were transformed into alcohols (*R*)-1b-5b for measurement (cat.NaOMe /MeOH, r.t.). [c] Lipase AY-30 from *Candida cylindracea* was used[7].

A variation of the 3-acyloxy moiety (acetate, chloroacetate, octanoate, butanoate) on *rac*-2b revealed the latter to be best suited with GC-4 lipase in terms of enantioselection, although in all cases some undesired cleavage of the methyl ester was observed. An attempt, to block this side reaction by employing a *t*-butyl ester (*rac*-5a) resulted in non-acceptance by GC-4 lipase. Lipase AY-30[7], however, could hydrolyse *rac*-5a, but with low enantioselection. To evaluate the applicability of this method, methyl 3-butanoyloxyalkanoates with various chain length (C-10, C-14, C-18) and a branched derivative (*rac*-4a) were resolved with GC-4 lipase, leading to 3-hydroxyalkanoates with moderate to good e.e.'s. Since it has been shown that optical purities of 3-hydroxyalkanoic acids can easily be brought to 100% by recrystallisation of the corresponding dicyclohexylammonium salts[6], we believe that the method described is a valuable tool for the preparation of enantiomerically pure long-chain 3-hydroxyalkanoic acids.

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