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Lipase-Catalyzed Highly Enantioselective Macrolactonization of Hydroxyacid Esters in an Organic Solvent

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In the lipase-catalyzed macrolactonization of long chain hydroxy acid methyl esters, the presence of a double bond in the acyl part was found to favor the formation of the monomeric product.

Lipases have already been utilized for lactonization of long-chain hydroxyacid[1] and esters.[2] The yields of monomeric lactones are generally low and greatly depend on the size of the ring to be formed. In this study the effect of the structure of the substrate was examined in which the ring size is fixed.

When methyl 12-hydroxydodecanoate (**1a**) was incubated with lipase P[3] in anhydrous isooctane, no dodecanolide (**2a**) was detected; instead, oligo-lactones were formed.[4] On the other hand, 12-tridecanolide (**2b**) was resulted from methyl 12-hydroxytridecanoate (**1b**) when it was exposed to lipase P under the same conditions (6%). These results lead to an interesting hypothesis, i.e., the yield of monomeric lactones might depend on the total carbon numbers of the starting hydroxyesters when the ring size of the resulting lactones is the same. Thus, we tried further studies on the lactonization of various kinds of secondary hydroxyesters. To a solution of 100 mg of substrate in 100 ml of anhydrous isooctane was added 500 mg of lipase P and 1 g of molecular sieves 4A.[5] The suspension was stirred at 65 °C for 24 h. The products were isolated and purified by column chromatography on silica gel (eluent, chloroform:hexane=1:1). As shown in the Table 1, the yields of monomeric lactones were dependent on the chain length of R^1. While **1b** afforded the monomeric lactone **2b** in only 6% yield, the yield of the desired lactone **2c** raised to 14% when methyl 12-hydroxyoctadecanoate (**1c**) was used instead.

To ascertain the effect of structure of the acyl chain and the asymmetric nature of the lipase-catalyzed lactonization, we used racemic (E)- and (Z)-methyl 12-hydroxy-9-octadecenoate (**1d, 1e**) as substrates. As shown in the Table 1, both of unsaturated hydroxyesters afforded monomeric lactones **2** in higher yields than **1c**,[6] without regard to the configuration. Although the details are not clear, it is supposed that the presence of a double bond make such conformation of the enzyme-substrate complex thermodynamically favorable in which the hydroxyl group and acyl carbon are relatively nearer each other. In all cases, the enantiomeric

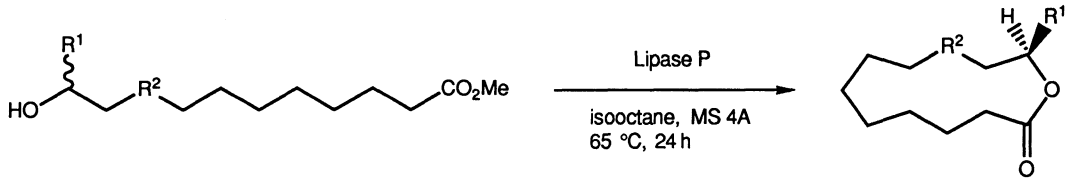

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Table 1. Lactonization of Hydroxy Esters with Lipase P

	R^1	R^2	Conversion/%	Yield/%	%e.e.[a]	$[\alpha]_D$/°[b]	Config.
a	H	CH_2CH_2	100	0	—	—	—
b	CH_3	CH_2CH_2	57	6	—	—	—
c	C_6H_{13}	CH_2CH_2	91	14	>99	-5.5	R
d	C_6H_{13}	CH=CH (E)	87	18	>99	+41.4	R
e	C_6H_{13}	CH=CH (Z)	70	20	98	+32.2	R

a) Determined by HPLC analysis of the corresponding (+)-MTPA esters of reduced diol.

b) Mesured in chloroform at room temperature (c 1).

excess of the resulting monomeric lactones were extremely high, and to our knowledge, this is the first example in such cases.[2] As the oligo-lactones and open-chain oligomeric esters are revealed to consist of (R)- and (S)-enantiomers of the starting compound, only the intramolecular cyclization step is considered to be a highly enantioselective reaction.

The enantiomeric excess of the products were determined by the sequence of reduction with $LiAlH_4$, hydrogenation, (for **2d**, **e**) derivation to (+)-MTPA esters, and HPLC analysis[7] of the esters. The absolute configuration was determined by comparing the sign of the optical rotation of the diol with the reported one.[8]

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References

1) G. Zhi-wei, T. K. Ngooi, A. Scilimati, G. Fulling, and C. J. Sih, Tetrahedron Lett., 29, 5583 (1988).
2) A. Makita, T. Nihira, and Y. Yamada, Tetrahedron Lett., 28, 805 (1987).
3) Lipase from Pseudomonas sp. (Amano Pharmaceutical Co.).
4) Products were compared with the authentic monomeric lactone, which was prepared via Baeyer-Villiger reaction, by TLC and ^{1}H-NMR analysis.
5) Molecular sieves 4A is thought to be effective for removal of methanol formed. No condensation products were obtained by the aid of only MS 4A in the absence of the lipase.
6) The products were identified by spectroscopic data (^{1}H-NMR, IR, MS) and determination of molecular weight by Rast's method.
7) Column, ZORBAX SIL(4.6 mm x 25 cm); eluent, hexane/AcOEt=200/1 (0.5 ml/min); retention time for racemic **2c**, 201, 210 min; **2d**, 280, 297 min; **2e**, 222, 233 min. Only the underlined peaks were observed for enzymatic reaction products.
8) T. H. Applewhite, R. G. Binder, and W. Gaffield, J. Org. Chem., 32, 1173 (1967).

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