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STEREOSELECTIVE HYDROLYSIS OF THE DIMETHYL 4,5-EPOXY-1,2-CIS-CYCLOHEXANEDICARBOXYLATES WITH PIG LIVER ESTERASE (PLE)

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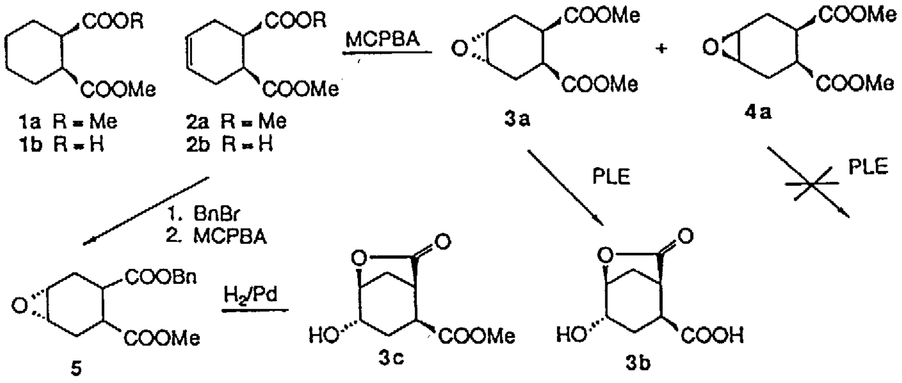
Abstract: The behaviour of dimethyl cis- and trans-4,5-epoxy-cis-1,2-cyclohexanedicarboxylate towards pig liver esterase (PLE) was studied. (1R, 2S, 4S, 5S)-4-Hydroxy-7-oxo-6-oxabicyclo[3.2.1]-octane-2-carboxylic acid was formed.

The recent years have witnessed the increasing importance of enzymes as chiral catalysts in asymmetric synthesis[1]. In this regard esterases such as pig liver esterase (PLE, EC 3.1.1.1.) have proved to be very attractive. The advantages of PLE are the stability, low cost, lack of the need for coenzymes and the fact that a wide spectrum of substrates is hydrolyzed. It has been shown that the commercially available preparations are mixtures of isozymes which exhibit essentially the same stereospecificity and can therefore be used in asymmetric synthesis as if they were a single species[2]. Not only *meso* and pro-chiral diesters can serve for the generation of a single enantiomer with high enantioselectivity, but also the resolution of racemic monoesters is possible[3]. Therefore the potential of PLE continues to receive undiminished attention[4]. Three models for the active site of PLE have been proposed[5], but they do not fully explain all results. Thus, some time ago we reported the hydrolysis of the *meso* diesters **1a** and **2a**[5a]. Surprisingly PLE hydrolyzed **2a** with higher enantioselectivity than **1a**. In order to gain more information about the active site of PLE allowing to explain this specific behaviour and with the aim of generating new chiral blocks, we introduced an epoxy group into dimethyl 1,2-cis-cyclohexanedicarboxylate (**1a**), because epoxides play an unique role in organic synthesis[6]. Treatment of **2a** with m-chloroperbenzoic acid (MCPBA) yielded the epoxy diesters **3a** and **4a** in a ratio of 3:1 (total yield 92%) after flash column chromatography (silicagel, ether/petroleum ether

55:45). **3a** was obtained in crystalline form (mp 50-51°). The relative configuration was determined by X-ray diffraction (Fig. 1). **3a** (2.3 mmol) was incubated with PLE (200 units, Boehringer, Mannheim GmbH, FRG), in KH_2PO_4 buffer at pH 7 and 24°. After consumption of one equiv. of 0.1 NaOH and usual work up, compound **3b** (yield 72%; mp 155-156°; $[\alpha]_D^{22} = -33.9°$ (c = 1.362, EtOH) was obtained. NMR spectroscopy did not allow to decide whether a γ or δ-lactone had been formed. An X-ray analysis clearly established



PLE-catalyzed hydrolyses:

Substrate	Product	%Yield	Abs. Config.	% e.e.
1a[a]	1b	98	(1R,2S)	75
2a	2b	95	(1R,2S)	85
3a	3b	72	(1R,2S,4S,5S)	96[b]
4a	no reaction after 24 h			

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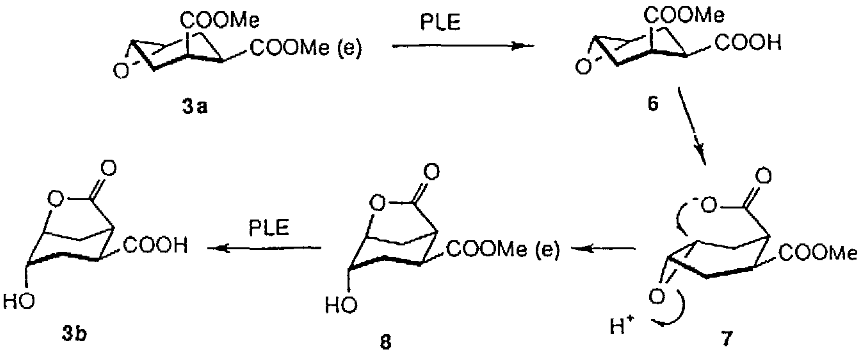
[a] For details see ref. 5a)

[b] The e.e. was determined by HPLC separation of the Mosher derivative of **3c**[7].

structure **3b** (1R, 2S, 4S, 5S)-4-hydroxy-7-oxo-6-oxabicyclo[3.2.1]octane-2-carboxylic acid) (Fig. 2). The absolute configuration was determined by comparison of the optical rotation of the methyl ester **3c** with synthetic material. **3c** from PLE hydrolysis: mp 85-87°; $[\alpha]_D^{22} = -39.5°$ (c = 1.362; EtOH) **3c** synthetic sample: mp 86-88°; $[\alpha]_D^{22} = -43.8°$. (c = 1.362; EtOH).

The unexpected isolation of a hydroxy acid with a δ-lactone group in place of the expected epoxy monoester can be rationalized by the following reaction mechanism: The first step is the hydrolysis of the equatorial ester group[5a,c] by PLE leading to the carboxylate **6**. After a conformational change to **7** an intramolecular S_N-reaction effects a cleavage of the epoxy group forming the hydroxy δ-lactone **8**. Because also the second ester group has now reached an equatorial orientation it is also hydrolyzed by PLE yielding the isolated acid **3b**. Compound **3b** represents an interesting polyfunctional synthon.



It is interesting to note that the epoxy ester **4a** was not hydrolyzed at all by PLE, probably due to high steric hindrance between the epoxy and the ester group.

As already mentioned the structures of **3a** (epoxide) (Fig. 1) and **3b** (lactone) (Fig. 2) were confirmed by X-ray diffraction analysis. Compound **3a** ($C_{10}H_{14}O_5$) crystallized in the monoclinic space group $P2_1/c$ with $a = 5.364(3)$, $b = 17.786(4)$, $c = 11.022(2)$ Å, $\beta = 96.53(3)°$, $Z = 4$. 2137 unique reflections were collected on a Enraf-Nonius diffractometer using graphite monochromated MoK_α ($\lambda = 0.71069$ Å) radiation and the $\omega/2\Theta$

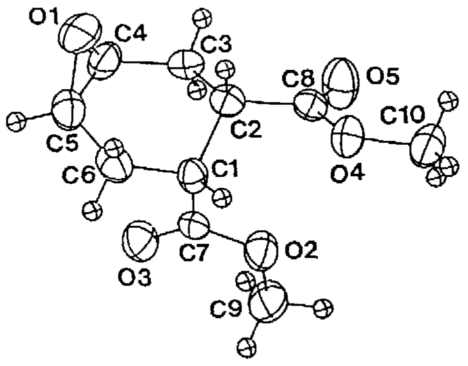


Fig. 1 ORTEP Plot of **3a**

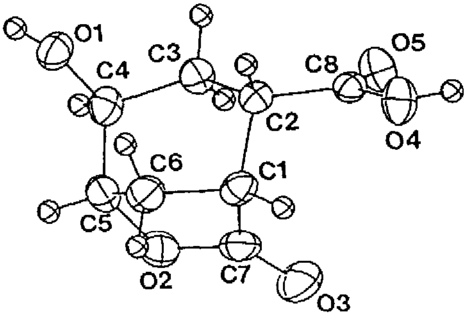


Fig. 2 ORTEP Plot of **3b**

scan technique. The raw data set was corrected for polarization effects. 1054 reflections were considered to be observed (Fo>2σ(Fo)). The structure was solved by direct methods using SHELXS-86 [8]. All non-hydrogen atoms were refined anisotropically, the hydrogen atoms were localized from Δ-F maps. Full matrix least-squares refinements of 192 parameters led to a R_w-value of 0.065 with $w = 0.862/(\sigma^2(F)+1.91\cdot10^{-3}F^2)$. Compound **3b** ($C_8H_{10}O_5$) crystallized in the orthorhombic space group $P2_12_12_1$ with a = 6.172(9), b = 9.205(1), c = 14.373(2) and Z = 4. For data collection and the structure determination the same techniques were used as for compound **3a**; Θ_{max}=27°, 1074 unique reflections, 837 used in refinements of 158 parameters, R_w = 0.037 with $w = 0.0850/(\sigma^2(F)+8.09\cdot10^{-4}F^2)$. [9]

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