Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 1047-1050, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

STEREOSELECTIVE HYDROLYSIS of SUBSTITUTED CYCLOPENTANE DIESTERS with PIG LIVER ESTERASE (PLE)

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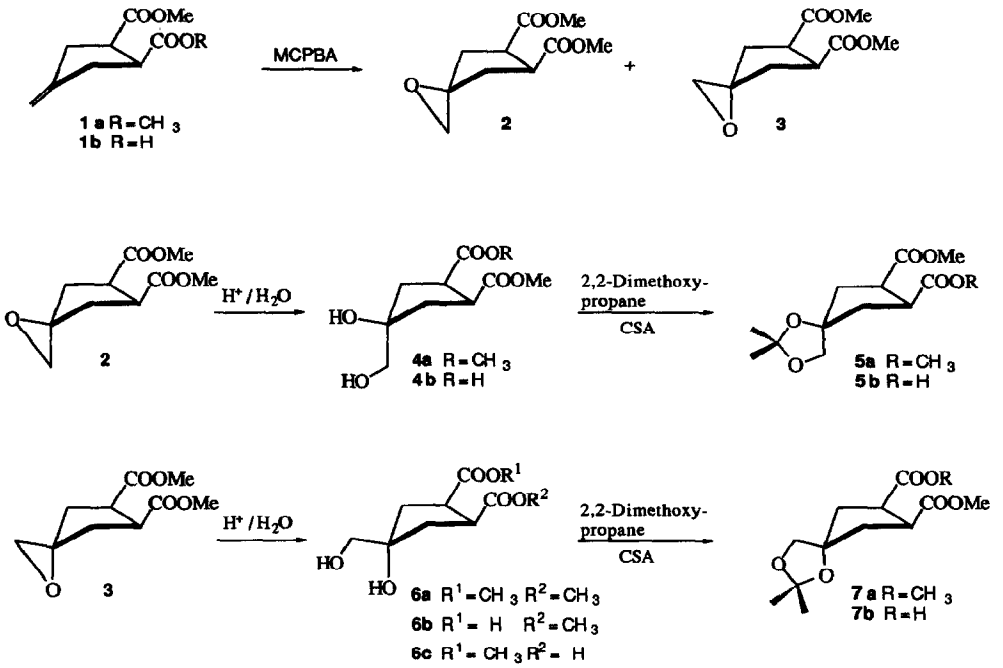
(*Received* 12 *February* 1993; *accepted* 26 *March* 1993)

Abstract: The hydrolysis of the dimethyl *meso* 1,2-cyclopentanedicarboxylates **1a**, **2**, **3**, **4a**, **5a**, **6a** and **7a**, containing various substituents at C(4) with pig liver esterase (PLE) is described.The stereoselectivity and absolute configurations of the resulting half esters were determined. In the case of substrate **2** the bicyclic lactone **10** was isolated as product.

The ability of serin-proteases to catalyse the hydrolysis of prochiral and *meso* diesters with high enantiomeric excess is now well established and is one of the valuable methods for the preparation of chiral synthons in natural product synthesis. In particular esterases, such as pig liver esterase (PLE, E.C. 3.1.1.1) a serin hydrolase, have been studied extensively in recent years [1]. Stability, low costs and the ability to hydrolyse stereoselectively a wide range of substrates are the additional advantages of this enzyme which operates without the need of a coenzyme. Recently *Jones* and coworkers [2] proposed a cubic active site model for PLE that reflects the topology of the enzyme pocket. This model is generally used to predict the specificity of PLE toward methyl ester substrates.

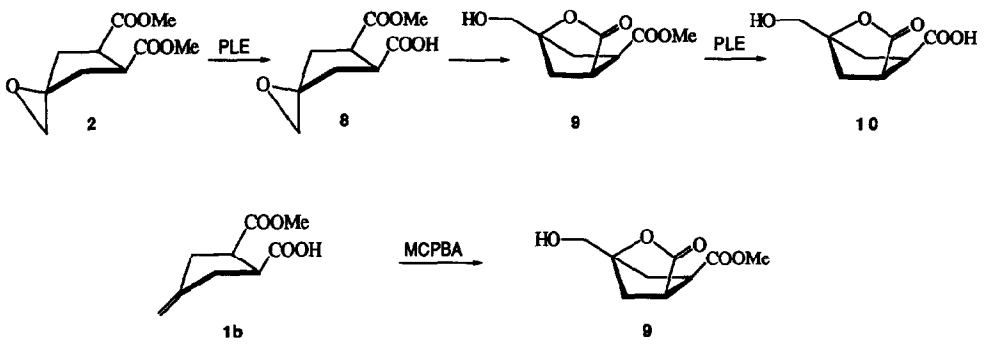
Here we report on the results of the hydrolysis of a series of structurally related dimethyl *meso* 1,2-cyclopentanedicarboxylates. They vary in the substituents in the C(4) position. The key intermediate **1a** has been prepared according to a procedure described by *Gais et al.* [3]. Treatment of diester **1a** with *m*-chloroperbenzoic acid (MCPBA) yielded the epoxy diesters **2** and **3** in a ratio of 3 : 2. The two isomeric compounds were separated by column chromatography on silicagel. The diols **4a** and **6a** were prepared by opening the epoxides **2** and **3** respectively, in H_2O at pH 4 in good yield. In a subsequent step the diols **4a** and **6a** were converted to the corresponding acetonides **5a** and **7a**, respectively, by treatment with 2,2-dimethoxypropane using 10-camphorsulphonic acid as catalyst [4].



In general, enzymatic hydrolyses with PLE of diesters take place in a 0.1 M phosphate buffer at pH 7.0. After consumption of 1 equiv. of base the solution was acidified to pH 2.5 and the resulting half esters were extracted with organic solvents [5]. In our case the products of the enzymatic hydrolysis were very polar compounds, especially **4b**, **6b**, **6c** and **10**, and could be extracted with organic solvents from the aqueous solution only in very moderate yields. Therefore we modified the method. Instead of 0.1 M phosphate buffer we used pure H_2O for the enzymatic reaction. After complete hydrolysis, indicated by the consumption of 1 equiv. of base, the free acid was formed by treatment with Dowex 50 W X 8 ion-exchange resin. Removal of the solvent by freeze drying and subsequent extraction of the residue with methanol yielded the half ester in almost pure form.

Enzymatic hydrolysis of the diesters **1a**, **4a**, **5a**, **6a** and **7a** yielded the corresponding half esters **1b**, **4b**, **5b**, **6c** and **7b** (see table 1). In the case of the spiro epoxide **2** the bicyclic lactone **10** was obtained after subsequent treatment with PLE and 1 equiv. of base. We [6] and others [7] have already reported the isolation of hydroxy acids containing an additional lactone group as a product of the PLE catalysed hydrolysis of epoxy *meso* diesters. The formation of a bicyclic lactone was explained by the following mechanism : In the first step PLE hydrolyses the pro-*S* ester group by forming the epoxy half ester **8**. After cleavage of the epoxide to the diol the carboxylate attacks the *tert* alcohol and forms the hydroxy γ-lactone **9**. The enzymatic hydrolysis of the pro-*R* ester group generates the isolated acid **10**.

Treatment of the isomeric spiro epoxide **3** with PLE led to the dihydroxy half ester **6b**. In this reaction the epoxide was cleaved to the diol. δ-Lactone formation was not observed. The enantioselectivity of the PLE catalysed hydrolysis of substrates **1a**, **3**, **4a**, **5a**, **6a** and **7a** was determined by the conversion of the resulting



half esters with (1*S*)-phenylethyl amine to the corresponding amides [8]. The absolute configurations of the half esters **1b**, **4b**, **5b**, **6b**, **6c** and **7b** were determined by chemical correlation. In a first step the acetonides were hydrolysed to the diols, which, in a second step were cleaved by $NaIO_4$ to the ketones of known absolute configuration [3]. Starting from the half ester **1b** the compound **10** was prepared by epoxidation with *m*-chloroperbenzoic acid (MCPBA) followed by spontanous lactonisation [9]. The resulting enantiomeric γ-lactones with known stereochemistry could be separated and analysed on a chiral column in GC. These results permitted the determination of the absolute configuration of the bicyclic lactone **10** after reesterification with diazomethane as well as the e.e. value of the enzymatic hydrolysis.

Table 1

Substrate	Product	t 1/2 (h)	% e.e.	Abs. Config.
1a	**1b**	1	63	1*S*, 2*R*
2	**11**	7	60	1*R*, 4*S*, 5*R*
3	**6b**	6.5	44	1*R*, 2*S*, 4*R*
4a	**4b**	9	73	1*R*, 2*S*, 4*S*
5a	**5b**	10	64	5*R*, 7*S*, 8*R*
6a	**6c**	21	21	1*S*, 2*R*, 4*S*
7a	**7b**	1.5	6	5*S*, 7*R*, 8*S*

The whole series of the cyclopentanoid diesters **1**, **2**, **3b**, **4a**, **5a**, **6a** and **7a** proved to be substrates for PLE. The half life time for the PLE catalysed hydrolysis of these substrates varies considerably and no obvious correlation exists between the $t_{1/2}$ value and the e.e. value of the half ester. Correlation with similar substrates reported by *Gais et al.* [3] shows that a *cis* ether function at C(4) attached to space-filling groups, e.g. *tert* butoxy or acetonide **5a**, leads to the preferential hydrolysis of the pro-*S* ester group by PLE. On the other hand the pro-*R* ester is preferentially hydrolysed in substrates containing a *cis* hydroxy group in C(4)-position, as for

instance in the case of diol **4a**. We explain these results by a H-bond fixation of the substrate in the catalytic pocket of the enzyme. The recent active site model for PLE [2] disregards such supplementary H-bond interactions between polar substituents and the protein surface of the active site in the case of *meso* diester substrates.

The compounds and derivatives therefrom were fully characterized by spectroscopic data.

Acknowledgment: We are grateful to the *Swiss National Science Foundation* for the financial support of these investigations.

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