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THE RESOLUTION OF RACEMIC 1,2-DIOLS BY THE ESTERASE CATALYSED HYDROLYSIS OF THE CORRESPONDING CYCLIC CARBONATE

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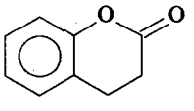
Abstract: Racemic 1-phenyl-1,2-ethane diol can be resolved by the pig liver esterase catalysed hydrolysis of the corresponding cyclic carbonate to give the (R) and (S) 1-phenyl-1,2-ethane diol with an ee of 97 and 78% respectively.

It has been stated that enzymes may catalyse different reactions provided that the overall electron density changes are of a similar nature.[1] For example, carboxypeptidases are known not only to catalyse the hydrolysis of peptides, but also to catalyse the enolisation of ketones.[2] Although pig liver esterase, PLE, (E.C.3.1.1.1) is usually considered to only catalyse the hydrolysis of esters[3] it has recently been shown that ß-lactams may also act as hydrolytic substrates.[4] This observation had been stimulated by some earlier experiments which had shown that PLE catalyses the hydrolysis of lactones, such as dihydrocoumarin 1, with the same efficiency it shows with phenolic esters such as phenyl acetate.



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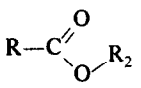
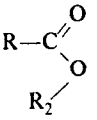
Lactones differ from acyclic esters in the conformation adopted around the carbonyl carbon - alcohol oxygen bond, esters exist predominantly in the **Z** conformation whereas small and medium sized lactones adopt the **E** conformer[5] (**scheme 1**). This difference in conformation may be expressed in the differential



Z trans



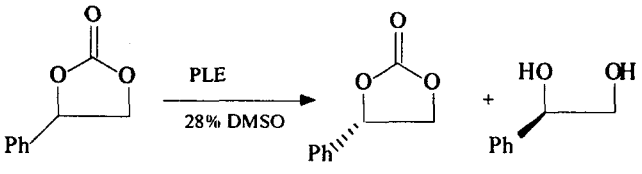
E cis

Scheme 1

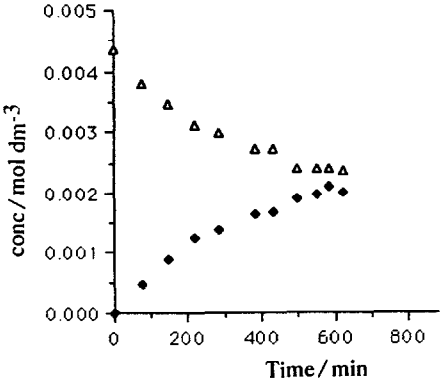
binding of the alcohol or carboxylic acid residues in the enzyme catalysed reactions of esters and lactones. We have therefore been exploring the possible differences in the molecular recognition shown by esterases towards cyclic and acyclic esters.

The resolution of 1,2-diols is of synthetic interest and herein we report a simple method based on our studies of the reactivity of cyclic structures. The hydrolysis of cyclic carbonates to diols is a synthetically and particularly clean reaction as the other product is carbon dioxide. For example, 1-phenyl-1,2-ethane diol cyclic carbonate **2** is hydrolysed selectively by PLE to give the (**R**) 1,2-diol **4** and the (**S**) carbonate **3** in both good optical and chemical yields. The unreacted (**S**) carbonate can then be easily hydrolysed to the (**S**) 1,2-diol **4** in aqueous alkali.

The carbonate **2** and the diol **4** are easily identified by HPLC using a LiChrosorb C18 reverse phase column and an eluent system containing acetonitrile-0.1% trifluoroacetic acid solution. The retention times are: **2**, 4.6 and **3**, 2.6 min. The second order rate constant, k_{cat}/K_m, for the PLE catalysed hydrolysis of the (**R**) carbonate is 1 x 10^2 mol^{-1} dm^3 s^{-1} at pH 7.4 and 20°C. The time course of the reaction (**scheme 2**), terminates at approximately 50% conversion, which is indicative of only one enantiomer being hydrolysed. The (**R**) 1,2-diol was isolated with a 97% ee and a 85% yield whereas the (**S**) 1,2-diol was obtained with an ee of 78% and a yield of 80%.



2 3 4



Scheme 2

Experimental

Synthesis of the 1-phenyl-1,2-ethanediol cyclic carbonate

Racemic 1-phenyl-1,2-ethanediol 5g (36mmol), was dissolved in 50 cm^3 of tetrahydrofuran (THF). Pyridine (1.5 cm^3) was then added and the resulting solution cooled to 0°C, Triphosgene, 2.5 g (8.4 mmol), was added and the solution refluxed for 2 hours. The THF was removed by rotary evaporation and the product obtained by trituration of the oil in water. The carbonate was recrystallised from toluene.

^1H nmr (270 MHz) $CDCl_3$: δ: 4.35 (1H,t,Hl); 4.80 (1H,t,H2); 5.25 (1H,t,H2); 7.40 (5H,m,Ph); IR (Nujol Mull): 1783 cm^{-1}; GC-MS: Only one peak in the chromatogram m/e = 164 m.pt. 53°C; Yield 73%

Resolution of (±) 1-phenyl-1,2-ethanediol cyclic carbonate with pig-liver esterase

1-Phenyl-1,2-ethanediol carbonate, 1g (6.1 mmol), was dissolved in 280 cm^3 of dimethylsulphoxide and made up to 1 dm^3 with pH 7.4 phosphate buffer. To this was then added 2 cm^3 of a stock solution of PLE (100 mg Protein/9.1 cm^3) and the reaction monitored to 50% conversion by HPLC. The unreacted (S) carbonate was extracted with ether (3 times) and purified by column chromatography using 1:1 hexane: ethyl acetate on Silica 60 in 80% yield. The (S) carbonate was then hydrolysed using aqueous sodium hydroxide and the (S) diol extracted using ethyl acetate, dried over magnesium sulphate and the solvent evaporated to give the product in 80% yield. The (R) diol was extracted from the reaction mixture using ethyl acetate and after a similar work-up was recovered in 85% yield. The specific optical rotations were $[\alpha]_D^{20}$ = -31.2° for the (R) 1-phenyl-1,2-ethanediol carbonate; $[\alpha]_D^{20}$ = -66.0° for the (R) 1-phenyl-1,2-ethanediol C = 1.0 $CDCl_3$ (Lit = 66.0°) and $[\alpha]_D^{20}$ = + 51.4° for (S) 1-phenyl-1,2-ethanediol C = 1.0 $CDCl_3$

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