Tetrahedron Letters,Vol.28,No.33,pp 3861-3864,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ENZYMATIC LACTONISATION OF γ-HYDROXYESTERS IN ORGANIC SOLVENTS. SYNTHESIS OF OPTICALLY PURE γ-METHYLBUTYROLACTONES AND γ-PHENYLBUTYROLACTONE.

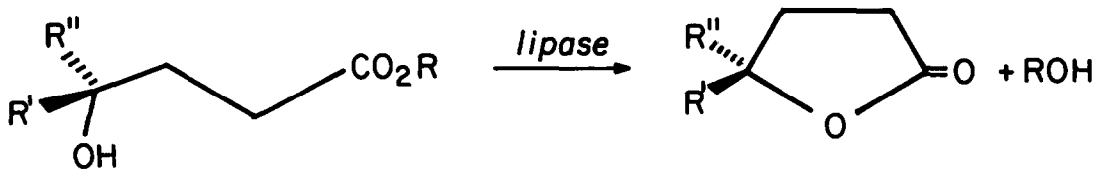
Arie L. Gutman*, Kheir Zuobi, and Aviv Boltansky
Department of Chemistry
Technion - Israel Institute of Technology,
Haifa 32000, Israel.

Summary: Porcine pancreatic lipase in anhydrous organic solvents catalyses the lactonisation of a number of esters of γ-hydroxyacids in nearly quantitative yields. This enzymatic process was used for the highly stereoselective synthesis of (S)-(-)-γ-methylbutyrolactone, (R)-(+)- γ-methylbutyrolactone and of optically active γ-phenylbutyrolactone.

Biocatalysis in nonaqueous media is a new and rapidly expanding field which has thus far been successfully applied to several preparatively important synthetic transformations[1]. A.M. Klibanov et al.[2] have reported that yeast lipase and porcine pancreatic lipase function in nearly anhydrous organic solvents and catalyze esterification and transesterification stereoselectively. Recently, Yamada et al.[3] reported that lipases can catalyze lactonisation of long-chain ω-hydroxyacids methyl esters in highly diluted solutions.

We now wish to report the facile and highly stereoselective enzymatic intramolecular transesterification for preparation of γ-lactones in organic solvents. Since γ-hydroxyacids themselves undergo spontaneous lactonisation, we investigated the behaviour of their methyl esters (1,2,3), which were obtained either by acid catalysed alcoholysis[4] or via the silver salt[5] from the corresponding commercially available lactones. Porcine pancreatic lipase (E.C.3.1.1.3.) was chosen because it is relatively inexpensive[6], does not require cofactors, has a broad substrate specificity[7] and has been shown to be effective in transesterification reactions.[2]

In a typical experiment (Scheme 1) the powdered commercial preparation of porcine pancreatic lipase was added to a solution of γ-hydroxyester in dry ether, and the suspension[8] was vigorously shaken at 26°C in a conical flask equipped with a drying tube. Aliquots were withdrawn periodically and their IR and/or NMR spectra measured. Progress was monitored (to within ± 5% accuracy) by comparing the 1770 cm^{-1} lactone carbonyl absorption of product and the 1730cm^{-1} ester carbonyl absorption of the starting material for reactions of 1 and 3, and by comparing NMR integration of the γ-methyl protons for reaction of 2. The enzyme catalysed the above reactions also in other anhydrous solvents. The initial rate of the enzymatic process in hexane was double of that in ether or THF and four times higher than that in chloroform.



1: R'=H, R''=H
2a:R'=CH_3, R''=H
2b:R'=H, R''=CH_3
3a:R'=Ph, R''=H
3b:R'=H, R''=Ph

4: R'=H, R''=H
5a:R'=CH_3, R''=H
5b:R'=H, R''=CH_3
6a:R'=Ph, R''=H
6b:R'=H, R''=Ph

Scheme 1

The kinetic profile of the enzymatic lactonisation of 1 and of the racemic 2 in ether (Fig 1) revealed, that although at low conversions the secondary hydroxyester 2 reacted faster than the primary hydroxyester 1, the lactonisation of 2 was considerably retarded near 45% conversion (e.g. 40% conversion after 23 hr and 60% conversion after an additional 100 hr). Since only minor inactivation of the enzyme was observed during the reaction[9], evidently the lipase-catalysed lactonisation of one enantiomer is much more effective than that of the other. Indeed, as illustrated in Fig. 1, the less favoured (R)-(-)- γ-hydroxy- γ-methylbutyrate 2b[10] reacted approximately 13 times more slowly than racemic 2 and some 26 times more slowly than (S)-(+)-(2a).

The general theory of enzyme-catalysed kinetic resolutions[11] suggests that with the increase in the degree of conversion of the racemic hydroxyester, the optical purity of the lactone formed decreases and that of the remaining hydroxyester increases. Accordingly, in order to optimise the production of the optically active lactone (5a), the reaction was stopped (by filtering out the enzyme) at 36% conversion, and in order to optimise the production of the optically active hydroxyester (2b), the reaction was terminated at 60% conversion. The reaction was very "clean" in that no byproducts were detected. The lactone was separated from the unreacted hydroxyester by chromatography on silica-gel.

The 36% conversion experiment afforded the optically active (S)-(-)- γ - methylbutyrolactone (5a), $[\alpha]_D = -32.2^\circ$ (c=16.0, CH_2Cl_2). The 60% conversion experiment gave optically active (R)-(-)- γ-hydroxy- γ-methylbutyrate (2b), $[\alpha]_D = -15.3^\circ$ (c=19.6, CH_2Cl_2). As expected, acid-catalysed lactonisation[12] of the latter gave (R)-(+)- γ-methylbutyrolactone 5b, $[\alpha]_D = +31.6^\circ$ (c=23.1, CH_2Cl_2). Both (S)- and (R)- enantiomers of this lactone 5 have been synthesised from the corresponding optically-pure glutamic acids[13]. Their reported specific rotations are $[\alpha]_D = -29.6^\circ$ (c=1.29, CH_2Cl_2) and $[\alpha]_D = +30.1^\circ$ (c=0.85, CH_2Cl_2), respectively. Comparison with the published figures and the illustrated kinetic profile suggest that both of our lactones 5a and 5b, and hence the hydroxyester 2b, were optically pure (ee > 94%).

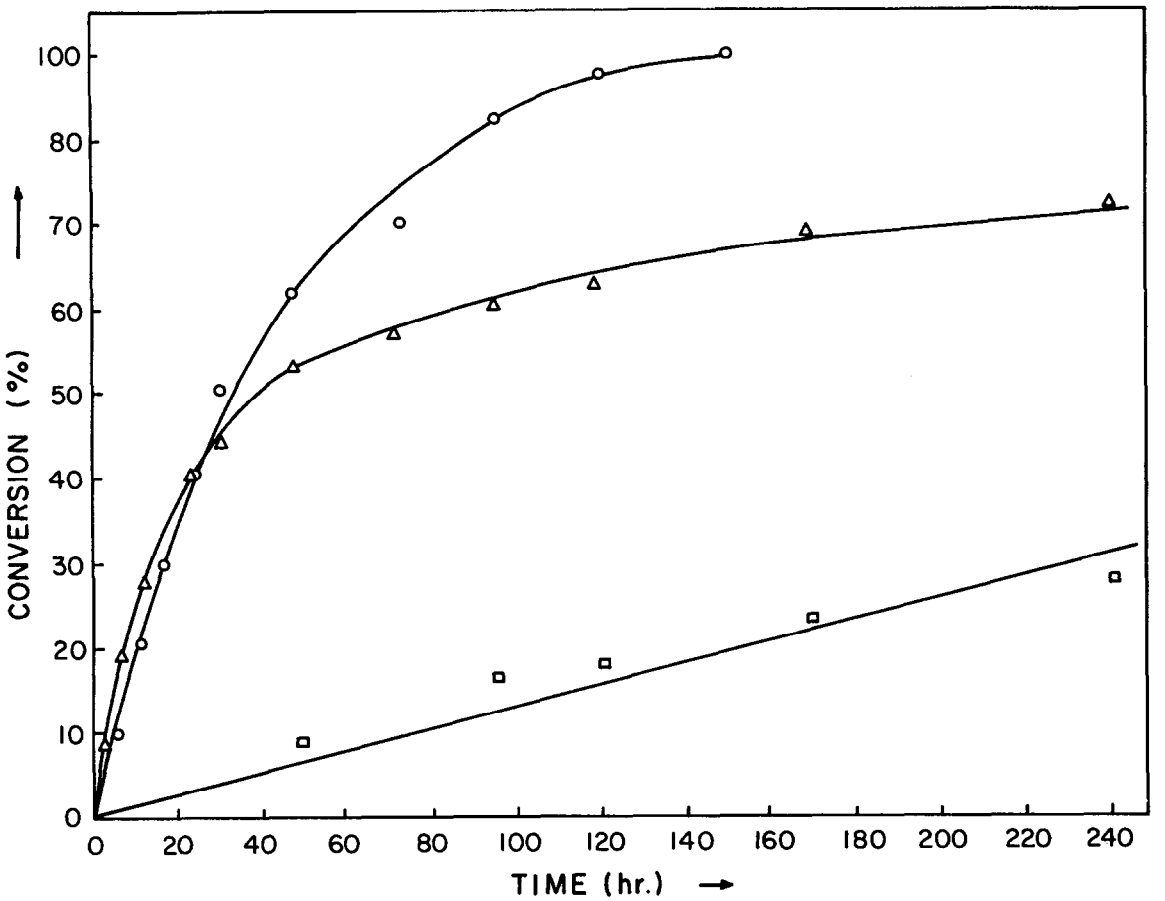


Figure 1. Time dependence of the porcine pancreatic lipase catalysed lactonisation of γ-hydroxyesters in ether.

(a) o-γ-hydroxybutyric acid methyl ester.
(b) Δ -(+)-γ-hydroxy- γ-methylbutyric acid methyl ester.
(c) □-(R)-(-)- γ-hydroxy- γ-methylbutyric acid methyl ester.
Conditions: 6 mmol hydroxyester, 0.9 g enzyme, 30 ml dry ether, shaking at 100rpm at 25°C under dry air.

Several other α and γ substituted γ-hydroxyesters were prepared and submitted to the action of porcine pancreatic lipase. It was found that α-substituted γ-hydroxyesters are very poor substrates for the enzyme. Thus, the initial rates of lactonisation of α-bromo- γ-hydroxybutyrate and of α-methyl- γ-hydroxybutyrate were respectively 200 and 50 times lower than that of the unsubstituted 1. On the other hand racemic γ-phenyl- γ-hydroxybutyrate (3) was lactonised at a rate only 5 times lower than 1. The kinetic profile of the reaction of 3 was similar to that of 2 and the (+)-γ-phenylbutyrolactone was formed preferentially. When the reaction was stopped at 35% conversion the isolated lactone 6 had an optical rotation of $[\alpha]_D = +7.8^\circ$ (c=12.0, CH_2Cl_2). Since optically active 6 was not reported in the literature[14] its absolute configuration and therefore the stereochemical course of the lactonisation remains unkown. However, the kinetic profile of the reaction indicated a very high ee value.

In conclusion, it was shown that porcine pancreatic lipase can act as a practical, highly stereoselective catalyst for lactonisation of some γ-hydroxyesters in organic solvents. Such a reaction is not feasible in aqueous solutions, where hydrolysis dominates. We have prepared optically active γ-methylbutyrolactones and γ-phenylbutyrolactone on a gram scale. The enzymatic preparation of other optically pure γ-lactones containing one or two assymetric carbon atoms is being investigated.

Acknowledgement: The research was supported by the fund for the promotion of research at the Technion.

REFERENCES

1. A.M. Klibanov, Chemtech, 354 (1986).
2. G. Kirchner, M.P. Scollar, and A.M. Klibanov, J.Am. Chem. Soc., 107, 7072 (1985).
3. A. Makita, T. Nihira, and Y. Yamada, Tetrahedron Lett., 28, 805 (1987).
4. H.C. Brown and K.A. Keblys, J. Org. Chem., 31, 485 (1966).
5. H. Machleift, Annalen, 655, 70 (1962).
6. Crude porcine pancreatic lipase was obtained from Sigma Chemical Co.
7. P. Desnuelle, "The Enzymes", 3rd ed.; Vol. 7, pp 575-616, Ed. P.D. Boyer, Academic Press: New-York, 1972; H. Brockerhoff, R.G. Jensen, "Lipolytic Enzymes", Academic Press: New York, 1974.
8. The enzyme is insoluble in ether and other organic media used.
9. The enzyme was recovered by filtration and was shown to be active in repeated lactonisation of a new batch of (3).
10. This enantiomer was obtained from the 60% conversion experiments described above.
11. C.S. Chen, Y. Fujimoto, G. Girdaukas, and C.J. Sih, J. Am. Chem. Soc., 104, 7294 (1982).
12. W.H. Pirkle, D.L. Sikkenga, and M.S. Pavlin, J. Org. Chem., 42, 384 (1977).
13. K. Mori, Tetrahedron, 31, 3011 (1975).
14. I.J. Jakovac and J.B. Jones, J. Org. Chem., 44, 2165 (1979).

(Received in UK 27 May 1987)