

Preparations of Chiral Hydroxyester Synthons via Stereoselective Porcine Pancreatic Lipase-catalysed Hydrolyses of *meso*-Diesters

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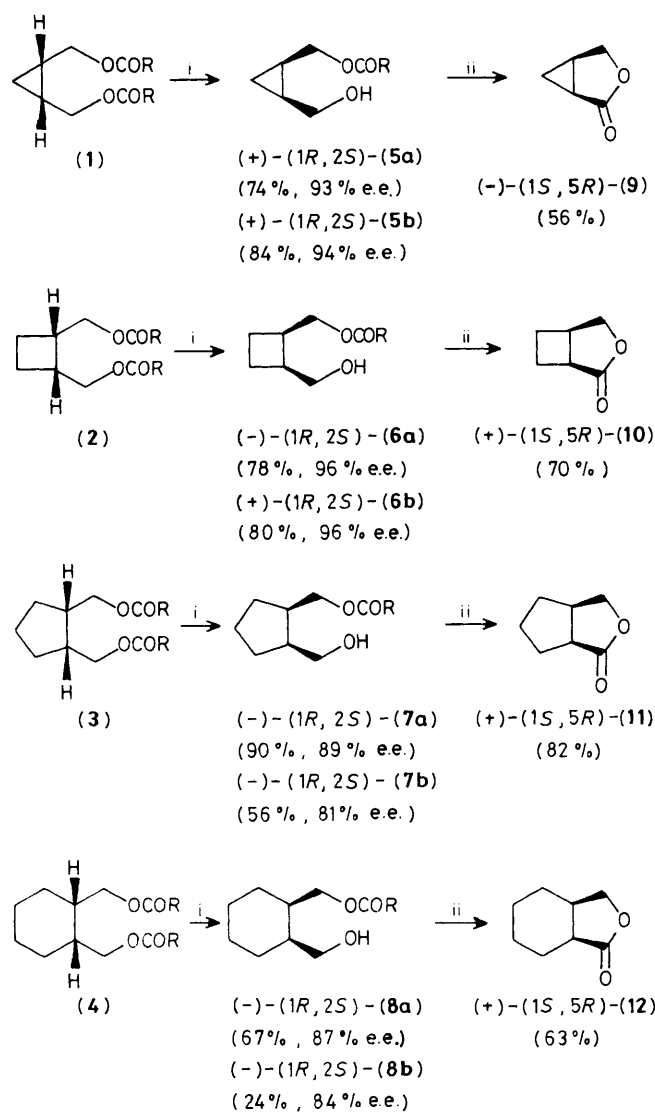
Stereoselective porcine pancreatic lipase-catalysed hydrolyses of monocyclic *meso*-1,2-diesters provides a flexible and convenient preparative route to chiral hydroxyesters and lactones of asymmetric synthetic value.

The abilities of enzymes to catalyse stereospecific transformations of *meso*-compounds into chiral synthons of asymmetric synthetic value are becoming increasingly well documented.¹ Horse liver alcohol dehydrogenase (HLADH)^{2,3} and pig liver esterase (PLE)^{4,5} have proven particularly valuable in this regard. In view of the increasing interest in this area, and the exciting results reported by other groups^{6,7} using porcine pancreatic lipase (PPL, EC 3.1.1.3), we have evaluated the stereospecificity of PPL-catalysed hydrolyses of the monocyclic *meso*-diesters (1)—(4).† We

now report that these hydrolyses are highly stereoselective, giving the synthetically useful hydroxyesters (5)—(9) in good yields and of very high enantiomeric excesses (e.e.s) (Scheme 1).

Preparative-scale (up to 2 g of substrate) PPL-catalysed hydrolyses of (1)—(4) were performed at pH 7. In each case the hydrolyses were enantiotopically specific for the (*S*)-centre ester group, giving the corresponding hydroxyesters (5)—(8) in good yields and of very high e.e.s. The lower yields in the hydrolyses of the more lipophilic diesters (7b), and (8b) are due to hydrolysis of the hydroxyester products to the corresponding diols in these cases. Whether this subsequent reaction is enzyme-catalysed has not yet been established. The hydroxyesters (5)—(8) were readily converted into the lac-

† The substrate diesters (1)—(4) were readily prepared from their known precursor diols.³ All new compounds gave satisfactory spectral and elemental analytical data.



Scheme 1. i, PPL, 20 °C, pH 7, 0.02 M KH_2PO_4 , 0.4 M Na or KCl, 0.005 M CaCl_2 , 4–20 h; ii, (a) CrO_3 , (b) $-\text{OH}$, (c) H^+ .

tones (9)–(12) respectively. The e.e.s of (5)–(8) were determined on their derivative lactones by n.m.r. spectroscopy⁸ using the racemic lactones for calibration and are considered accurate to within $\pm 3\%$. The absolute configurations were assigned by comparisons of (9)–(12) with authentic samples.³

These results extend the asymmetric synthetic utility of PPL considerably. The method complements other similar enzymic approaches, with the chiral synthons (5)–(8) being of different oxidation states to the products of HLADH- or PLE-catalysed transformations of analogous *meso*-substrates. Furthermore, in contrast to PLE,⁵ PPL is consistently (*S*)-centre specific in its catalyses of this diester series.⁷ It also retains the flexibility of esterase-catalysed reactions^{4,5} in that no expensive coenzyme is needed and that hydroxyesters (5)–(8) or lactones (9)–(12) of potential⁹ or demonstrated^{3,4,10,11} chiral synthon value can be prepared at will by

the Scheme 1 methods, or by trivial chemical modifications thereof. The lactones (9)–(12) permit elaboration to either *cis* or *trans* (after controlled epimerisation) substituted target molecules. Optimisation of the e.e. levels of Scheme 1 *via* reaction condition manipulation is now in progress.[‡]

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References

- C. J. Suckling and H. C. S. Wood, *Chem. Br.*, 1979, **15**, 2343; A. Fischli in 'Modern Synthetic Methods,' ed. R. Scheffold, Salle/Sauerlander, Frankfurt, 1980, pp. 259 ff; J. B. Jones in 'Enzymic and Nonenzymic Catalysis,' eds. P. Dunnill, A. Wiseman, and N. Blakeborough, Ellis Horwood/Wiley, Chichester/New York, 1980, pp. 54–83; in 'Asymmetric Synthesis,' vol. 5, ed. J. A. Morrison, Academic, New York, 1985, in the press; C.-H. Wong and G. M. Whitesides, *Aldrichimica Acta*, 1983, **16**, 27; *Angew. Chem., Int. Ed. Engl.*, 1985, in the press; A. M. Klivanov, *Science*, 1983, **219**, 722; A. R. Battersby, *Chem. Br.*, 1984, **20**, 611.
- D. R. Dodds and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 1982, 1080; K. P. Lok, I. J. Jakovac, and J. B. Jones, *J. Am. Chem. Soc.*, 1985, **107**, 2521 and references therein.
- I. J. Jakovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659; T. Ikeda and C. R. Hutchinson, *J. Org. Chem.*, 1984, **49**, 2837.
- C.-S. Chen, Y. Fujimoto, and C. J. Sih, *J. Am. Chem. Soc.*, 1981, **103**, 3580; Y. Ito, T. Shibata, M. Arita, H. Sawai, and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 6739; S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, 1982, **46**, 1907; P. Mohr, N. W. Sarcevic, C. Tamm, K. Gawronska, and J. C. Gawronski, *Helv. Chim. Acta*, 1983, **66**, 2501; M. Schneider, N. Engel, P. Honicke, G. Heinemann, and H. Gorisch, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 67; H. J. Gais and T. Lied, *Angew. Chem.*, 1984, **96**, 143; Y. F. Wang and C. J. Sih, *Tetrahedron Lett.*, 1984, **24**, 4999; J. B. Jones, R. S. Hinks, and P. G. Hultin, *Can. J. Chem.*, 1985, **63**, 452; F. Bjorkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, and P. Szmulik, *Tetrahedron*, 1985, **41**, 1347.
- G. Sabbioni, M. L. Shea, and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 1984, 236.
- Y.-F. Wang, C.-S. Chen, G. Girduakas, and C. J. Sih, *J. Am. Chem. Soc.*, 1984, **106**, 3695; B. Cambou and A. M. Klivanov, *Appl. Biochem. Biotech.*, 1984, **9**, 255; *J. Am. Chem. Soc.*, 1984, **106**, 2687.
- W. E. Ladner and G. M. Whitesides, *J. Am. Chem. Soc.*, 1984, **106**, 7250.
- I. J. Jakovac and J. B. Jones, *J. Org. Chem.*, 1979, **44**, 2165.
- A. Cervantes and A. Guzman, *Tetrahedron Lett.*, 1972, 1123; T. Kitihara and K. Mori, *Tetrahedron*, 1984, **40**, 2935; P. Crabbe, M. R. Barbachyn, C. R. Johnson, and M. D. Glick, *J. Org. Chem.*, 1984, **49**, 2748.
- J. B. Jones, M. A. W. Finch, and I. J. Jakovac, *Can. J. Chem.*, 1982, **60**, 2007.
- P. D. Kennell, S. S. Matharu, J. B. Taylor, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2553; T. Ikeda and C. R. Hutchinson, *J. Org. Chem.*, 1984, **49**, 2837.
- K. Laumen and M. Schneider, *Tetrahedron Lett.*, 1985, **26**, 2073.

[‡] After submission of this manuscript we learned of similar results, but of undetermined absolute configurations, for PPL-catalysed hydrolyses of the acetates (1a)–(4a).¹² Also, we have now established that the absolute configuration of the cyclohexenyl analogue of (8a) prepared by Ladner and Whitesides⁷ is of the same type as shown for (8a).