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

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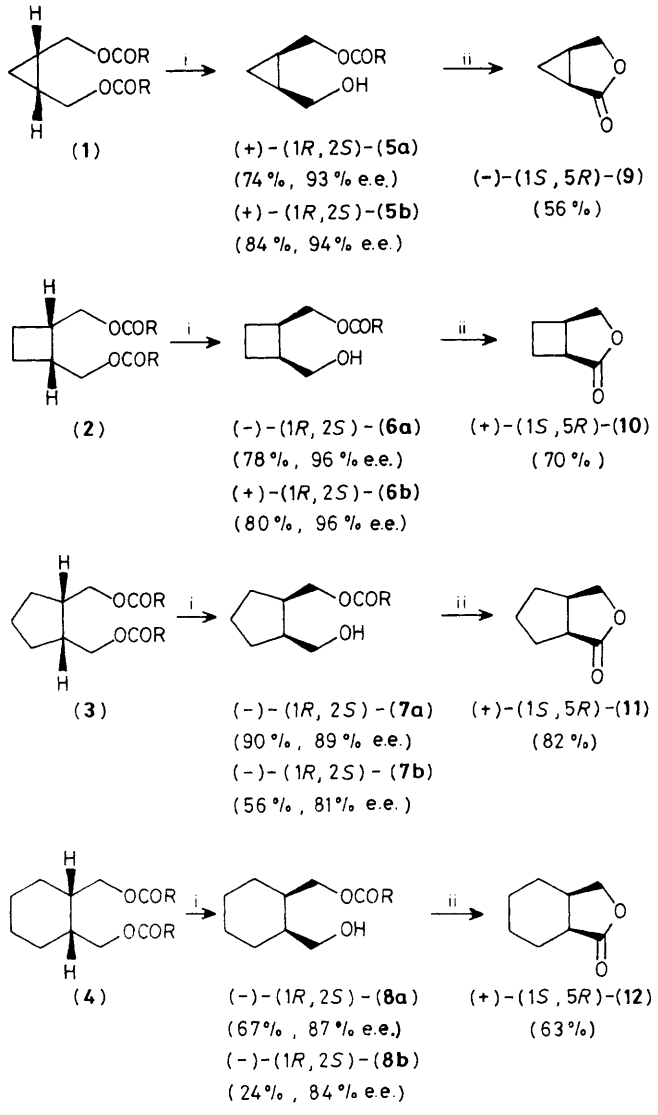
Stereoselective porcine pancreatic lipase-catalysed hydrolyses of monocyclic *meso*-1,2-diesters provides a flexible and convenient preparative route to chiral hydroxyesters and lactones of asymmetric synthetic value.

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) ^-OH, (c) H^+.

tones (**9**)—(**12**) respectively. The e.e.s of (**5**)—(**8**) were determined on their derivative lactones by n.m.r. spectroscopy[8] using the racemic lactones for calibration and are considered accurate to within ±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 potential[9] 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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‡ 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 Whitesides[7] is of the same type as shown for (**8a**).