Preparations of Bicyclic Chiral Lactone Synthons *via* Stereospecific Pig Liver Esterase-catalysed Hydrolyses of *meso*-Diesters. Ring-size induced Reversal of Stereospecificity

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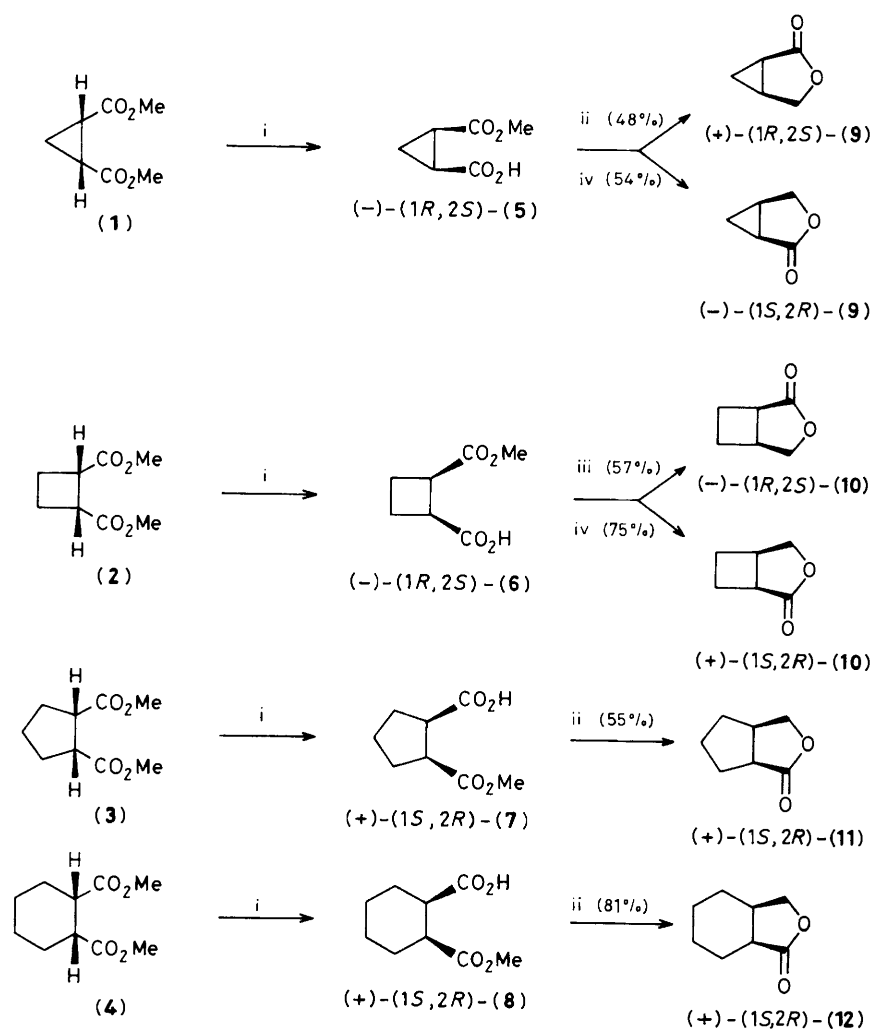
Stereospecific pig liver esterase-catalysed hydrolysis of monocyclic *meso*-1,2-diesters provides a convenient preparative route to both enantiomers of useful chiral lactones and demonstrates a sharply defined and unprecedented ring-size-mediated reversal of stereospecificity.

The ability of enzymes to catalyse stereospecific transformations of *meso*-compounds into valuable chiral synthons is now established as a method of considerable value in asymmetric synthesis.[1—3] For the preparation of useful[4] chiral bicyclic lactones such as (**9**)—(**12**), the most versatile enzyme so far documented is horse liver alcohol dehydrogenase.[1] However, alcohol dehydrogenases suffer from the disadvantage that expensive and unstable nicotinamide coenzymes are required.[5] We now report that the coenzyme problem can be avoided in bicyclic lactone preparation by exploiting a cofactor-independent hydrolase such as pig liver esterase (PLE).[3] In addition a very clearly defined and novel reversal



Scheme 1. i, PLE, 20 °C, pH 7, 2—6 h; ii, $BH_3{\cdot}Me_2S$; iii, (a) $ClCO_2Et$, NEt_3, (b) $NaBH_4$; iv, $LiBH_4$. The products [except (+)-(1*S*,2*R*)-(**11**), 17% e.e.] were obtained in >97% e.e.

of stereospecificity has been observed. PLE-catalysed hydrolyses of the *meso*-diesters (**1**)—(**4**) give the corresponding half acid esters (**5**)—(**8**) (Scheme 1). These chiral intermediates may then be converted into either lactone enantiomer of the compounds (**9**)—(**12**) *via* selective reduction of the carboxy[6,7] or ester[8] group.

Preparative-scale (up to 3 g of substrate) PLE-catalysed hydrolyses of the *meso*-diesters (**1**)—(**4**)[9] were effected at pH 7.† For the diesters (**1**) and (**2**), the hydrolyses were enantiotopically specific for the *pro-S* methoxycarbonyl group. The ease with which either lactone enantiomer can be obtained from such acid–ester products was demonstrated by the conversion of (−)-(1*R*,2*S*)-(**5**) and (−)-(1*R*,2*S*)-(**6**) into (+)-(1*R*,2*S*)- and (−)-(1*S*,2*R*)-(**9**) and (−)-(1*R*,2*S*)- and (+)-(1*S*,2*R*)-(**10**), respectively.

With the cyclopentyl substrate (**3**), the enzyme's stereospecificity changed, with a marginal *pro-R* enantiotopic specificity of ester group hydrolysis being manifest in a 17% enantiomeric excess (e.e.) of the product lactone (+)-(1*S*, 2*R*)-(**11**). The reversal of stereospecificity became complete for the cyclohexyl diester (**4**), with the optically pure lactone (+)-(1*S*,2*R*)-(**12**) being isolated after the reduction step. The e.e.s. of the lactones (**9**)—(**12**) were established by n.m.r. spectroscopy[10] and are considered accurate to within ±3%. The absolute configurations were assigned by comparisons with authentic samples obtained previously.[1]

In addition to extending the synthetic value of pig liver esterase-catalysed hydrolyses to an important group of chiral synthons, the reversal of stereospecificity that these data reveal represents a fascinating and highly significant new aspect of the enzyme's properties. While some inversions of enzyme stereospecificity within structurally related series of substrates are known,[5,11] the dramatic ring-size mediated reversal reflected by the current data is, to our knowledge, unprecedented. Further investigation of the factors controlling this stereospecificity reversal are in progress.

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† The results of <100% enantiomeric excess obtained in other PLE-catalysed *meso*-diester hydrolyses performed at pH 8 were due, at least in part, to competing chemical hydrolyses at the higher pH (ref. 3).

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References

1 R. Mislin, Ph.D. Thesis, ETH, Zurich, 1968; D. R. Dodds and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 1982, 1080; I. J. Jakovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659; G. S. Y. Ng, L.-C. Yuan, I. J. Jakovac, and J. B. Jones, *Tetrahedron*, in the press.

2 D. M. Jerina, H. Ziffer, and J. W. Daly, *J. Am. Chem. Soc.*, 1970, **92**, 1056; G. Bellucci, G. Berti, G. Catelani, and E. Mastrorilli, *J. Org. Chem.*, 1981, **46**, 5148; G. Bellucci, G. Berti, R. Bianchini, P. Cetera, and E. Mastrorilli, *ibid.*, 1982, **47**, 3105; M. Ohno, *Fermentn. Ind. (Jpn.)*, 1979, **37**, 836.

3 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, *ibid.*, p. 6739; S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, 1982, **46**, 1907.

4 J. B. Jones, M. A. W. Finch, and I. J. Jakovac, *Can. J. Chem.*, 1982, **60**, 2007.

5 W. H. Baricos, R. P. Chambers, and W. Cohen, *Anal. Lett.*, 1976, **9**, 257; J. B. Jones and J. F. Beck, *Tech. Chem. (N.Y.)*, 1976, **10**, 107; C.-H. Wong and G. M. Whitesides, *Aldrichimica Acta*, 1983, **16**, 27.

6 C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, 1974, **39**, 3052.

7 K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492.

8 J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.

9 L. L. McCoy, *J. Am. Chem. Soc.*, 1958, **80**, 6558; E. R. Buchmann, A. O. Reims, T. Skei, and M. J. Schlatter, *ibid.*, 1942, **64**, 2696; L. N. Owens and A. G. Petro, *J. Chem. Soc.*, 1955, 2383; A. Cambon and R. Jullien, *Bull. Soc. Chim. Fr.*, 1973, 2003.

10 I. J. Jakovac and J. B. Jones, *J. Org. Chem.*, 1979, **44**, 2165.

11 H. L. Boter and A. J. Ooms, *Biochem. Pharmacol.*, 1967, **16**, 1563; H. M. Schwartz, W.S. Wu, P. W. Marr, and J. B. Jones, *J. Am. Chem. Soc.*, 1978, **100**, 5199.