Lipase-catalysed Enantioselective Ring-opening of Oxazol-5(4*H*)-ones coupled with Partial *in situ* Racemisation of the Less Reactive Isomer

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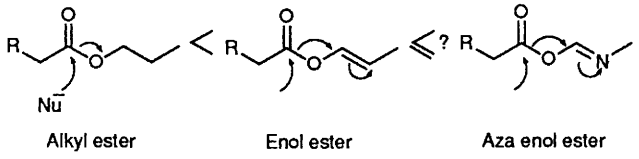
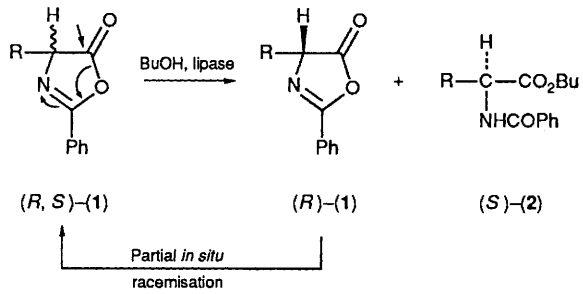
2-Phenyl-4-methyl-oxazol-5(4*H*)-one undergoes lipase-catalysed enantioselective ring-opening with butan-1-ol in di-isopropyl ether; the less reactive isomer of the oxazolone further undergoes partial *in situ* racemisation under the reaction conditions to afford, after quantitative conversion, butyl *N*-benzoylalaninate enriched in one isomer.

Oxazol-5(4*H*)-ones, commonly known as azlactones, form a class of highly versatile intermediates for the synthesis of α-amino acids and peptides.[1] They undergo ring-opening with various nucleophiles like water, alcohols, amines, amino acid esters, hydrazines, hydrazoic acid, and phosphate anions to furnish α-amino acid derivatives.[1] Owing to the ease with which azlactones racemise,[1a] they make excellent substrates for enantioselective ring-opening studies. The unreactive isomer can be racemised and recycled so as to allow, in principle, quantitative conversion of a racemic azlactone to a single isomer of the product.

The behaviour of azlactones towards a variety of hydrolytic



Scheme 1



Scheme 2

enzymes has been extensively studied.[1c] Because azlactones undergo spontaneous hydrolysis in the presence of water, previous attempts to cleave them enantioselectively using enzymes[2a—c] or cyclodextrins[2c,d] as catalysts have met with little success. Exploiting the recent discovery of enzymic activity in anhydrous organic solvents,[3] we herein report the first successful enzyme-catalysed enantioselective ring-opening of an azlactone, 2-phenyl-4-methyloxazol-5(4*H*)-one (**1**; R = Me), using butan-1-ol in di-isopropyl ether (DIPE).[4]

Azlactones were considered as the cyclic aza analogues of the highly reactive enol esters recently reported by Wong *et al.*, in their lipase-catalysed transesterification studies.[5] If enol esters, due to an irreversible reaction, can undergo transesterification much faster than the simple alkyl esters, then aza enol esters (cyclic in this work) should behave in the same way, owing to a similar reaction mechanism, yielding stable amides (Scheme 1).

To test our theory, we subjected 2-phenyl-4-oxazol-5(4*H*)-one[6] (**1**, R = H), one of the simplest azlactones known, to lipase-catalysed transesterification with n-butanol in DIPE.[4†] Both the lipases used, porcine pancreatic lipase (PPL) and *Candida cylindracea* (CCL), led to quantitative conversion of the azlactone to butyl hippurate (Scheme 2). We then tested the stereoselectivity of this reaction using alanine derived azlactone (**1**; R = CH_3), readily prepared from alanine (PhCOCl–NaOH followed by Ac_2O dehydration). Reaction of (**1**) with n-butanol under similar conditions with PPL or CCL, after about 45% conversion, gave (*R*)-butyl *N*-benzoylalaninate (**2**) in low optical purity [10 and 3% enantiomeric excess (e.e.) with PPL and CCL respectively]. However, lipase from *Mucor miehei* (Lipozyme)‡ showed better selectivity for the (*S*)-isomer; under identical conditions,† after 45% conversion (45 min), (*S*)-(**2**) was obtained in 57% e.e.

Interestingly, a single recrystallisation of this compound in DIPE afforded (*S*)-(**2**) in >99% optical purity. Hexane, however, though suitable for recrystallisation, did not lead to any optical enrichment. A similar recrystallisation technique for the enantiomeric enrichment of other amino acid derivatives has been reported recently.[7] Choosing the right solvent might hold the key to the success of such recrystallisations.

While the butyl ester products of these reactions all showed optical activity, no optical rotation was found for any of the isolated unreacted azlactones [lit.[2d] for (*S*)-(**1**), $[\alpha]_D^{25}$ −72.5° (*c* 0.25, dioxane)]. This suggests *in situ* racemisation of the unreacted azlactone under the reaction conditions. To confirm this, we allowed the Lipozyme-catalysed reaction to attain 100% conversion (*ca.* 6 h) and isolated (*S*)-(**2**) in 34% e.e.

In summary, our preliminary findings show that azlactones can be enantioselectively cleaved by nucleophiles under lipase catalysis in organic solvents. There is scope for *in situ* racemization of the less reactive isomer which can lead to quantitative conversion of the racemic azlactone to a single isomer of the product. This discovery should pave the way to a new method of preparing important chiral α-amino acids and peptides using readily available enzymes and easily prepared azlactones.

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† A mixture of azlactone (20 mmol), n-butanol (40 mmol), and 4 g PPL/YL (Sigma) (or alternatively 1 g Lipozyme) in 40 ml DIPE was stirred at ambient temperature until the required conversion was achieved. Filtration, removal of solvent, and separation/purification on a silica-gel column (dichloromethane) afforded the product in >90% of the theoretical yield. The absolute configuration and e.e. of product (**2**) were determined by chiral HPLC analysis (Pirkle, DNBPG-column) and by comparison of the optical rotation with that of an authentic sample prepared from (*S*)-alanine: $[\alpha]_D^{25}$ +39° (*c* 4.4, $CHCl_3$); observed $[\alpha]_D^{25}$ for product with PPL, −3.96° (*c* 9, $CHCl_3$); CCL, −1.23° (*c* 3.6, $CHCl_3$); Lipozyme, +22.2° (*c* 8.8, $CHCl_3$) and +13.3° (*c* 3.7, $CHCl_3$) for 45 and 100% conversion respectively.

‡ Lipozyme™ (31 BIU g^{-1}), a commercially available lipase from the fungus *Mucor miehei*, immobilised on a macroporous anion exchange resin, was kindly provided by NOVO.

References

1 For reviews on this topic, see: (a) Y. S. Rao and R. Filler, in 'Oxazoles,' ed. I. J. Turchi, vol. 45, Wiley, New York, 1986, ch. 3, pp. 361—730; (b) B. E. Maryanoff, *ibid.*, ch. 5, p. 988; (c) R. Filler and Y. S. Rao, in 'Advances in Heterocyclic Chemistry,' vol. 21, ed. A. R. Katritzky, Academic Press, New York, 1977, pp. 175—206; (d) R. Filler, *ibid.*, vol. 4, 1965, pp. 75—106; pp. 188—9.

2 (a) J. de Jersey and B. Zerner, *Biochemistry*, 1969, **8**, 1967; (b) J. de Jersey, *ibid.*, 1970, **9**, 1761; (c) V. Daffe, and J. Fastrez, *J. Am. Chem. Soc.*, 1980, **102**, 3601; (d) *J. Chem. Soc., Perkin Trans. 2*, 1983, 789.

3 A. M. Klibanov, *Chemtech.*, 1986, 354; C. S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 695.

4 H. S. Bevinakatti, A. A. Banerji, and R. V. Newadkar, *J. Org. Chem.*, 1989, **54**, 2453; H. S. Bevinakatti, and R. V. Newadkar, *Biotechnol. Lett.*, 1989, **11**, 785.

5 Y. F. Wang, J. J. Lalonde, M. Momangan, D. E. Bergbreiter, and C. H. Wong, *J. Am. Chem. Soc.*, 1988, **110**, 7200.

6 Prepared from hippuric acid following the known method: G. E. Vandenberg, J. B. Harrison, H. E. Carter, and B. J. Magerlin, *Org. Synth., Coll. Vol. V*, 1973, 946.

7 M. J. O'Donnell, W. D. Bennett, and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353.