Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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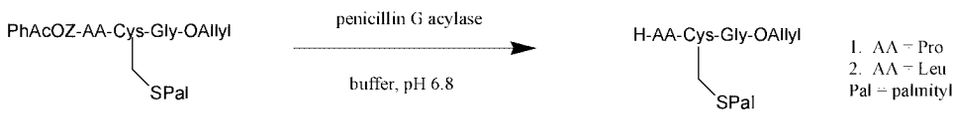
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst design and optimisation will also be included.

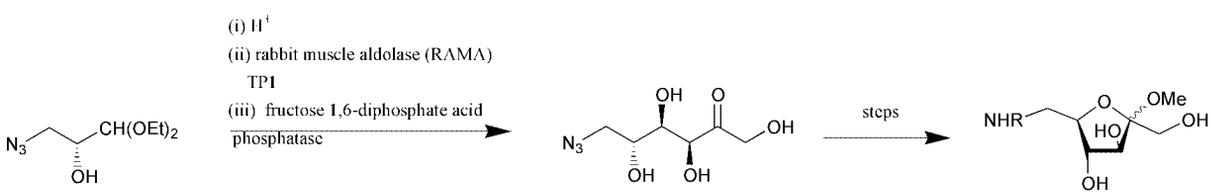
Deprotection of PhAcOZ protected peptides. ***Acylase***



Reactions performed in 20% methanol and 38 equivalents of dimethyl-β-cyclodextrin for substrate solubilisation. Longer peptides deprotected using cross-linked enzyme crystals (CLECS) of Penicillin G acylase. Products constitute fragments of the N-terminal undetrigintapeptide (29mer) of endothelial NO synthase.

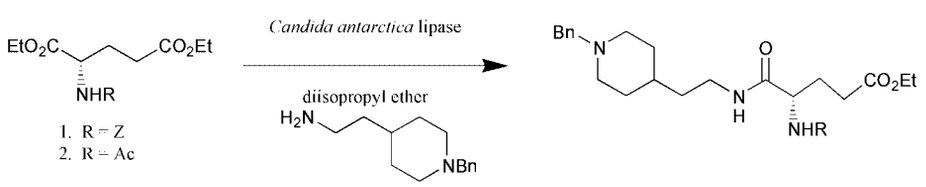
R. Machauer and H. Waldmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 1449.

Chemoenzymatic synthesis of fructose analogues. ***Aldolase***



L. Azéma, F. Bringaud, C. Blonski and J. Périé, *Bioorg. Med. Chem.*, 2000, **8**, 717. D-Fructose analogues were tested for activity against the glucose transporter of *Trypanosoma brucei*.

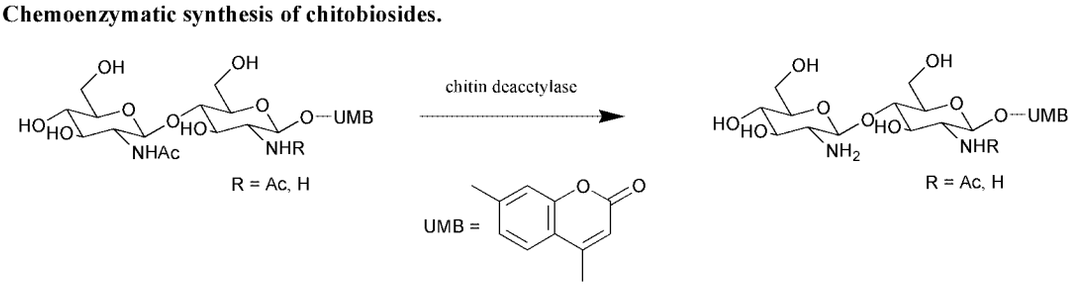
Synthesis of acetylcholinesterase inhibitors *via* lipase catalysed amidation. ***Lipase***



A. Martínez, C. Lanot, C. Perez, A. Castro, P. López-Serrano and S. Conde, *Bioorg. Med. Chem.*, 2000, **8**, 731.

Enzymatic amidation is regioselective for ω-esters. Products were evaluated for acetylcholinesterase (AChE) inhibition.

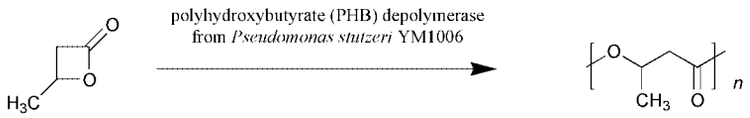
Chemoenzymatic synthesis of chitobiosides. ***Chitinase***



Y. Honda, S. Tanimori, M. Kirihata, S. Kaneko, K. Tokuyasu, M. Hashimoto and T. Watanabe, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 827.

Products used as fluorescent substrates to test for chitinase activity in *Bacillus circulans*.

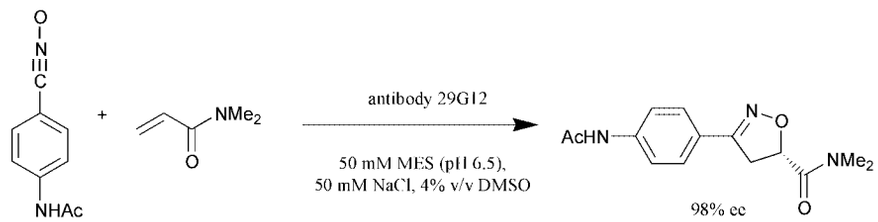
Polymerisation of β-butyrolactone. ***Depolymerase***



Y. Suzuki, T. Ohura, K. Kasuya, K. Toshima, Y. Doi and S. Matsumura, *Chem. Lett.* 2000, 318.

A comparison of activities of PHB depolymerase variants with (i) and without (ii) a substrate binding domain (SBD) is presented. The activity of (i) > (ii). SBD is not necessary for activity and may be responsible for the specific interaction of the growing poly 3-hydroxybutanoate chain.

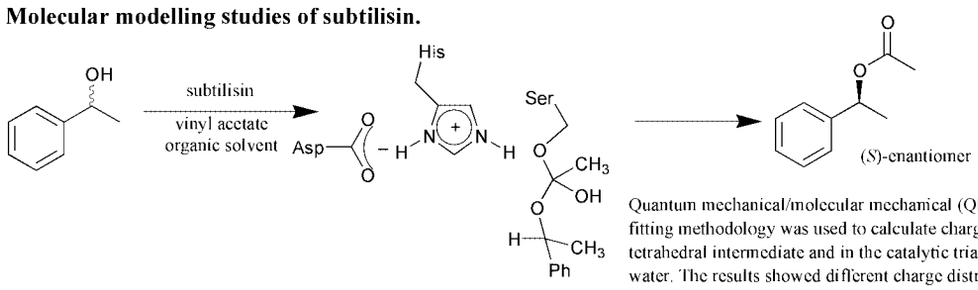
Asymmetric 1,3 dipolar cycloaddition. ***Antibody***



J. D. Toker, P. Wentworth, Jr., Y. Hu, K. N. Houk and K. D. Janda, *J. Am. Chem. Soc.*, 2000, **122**, 3244.

First example of an antibody catalysed [3+2] pericyclic reaction.

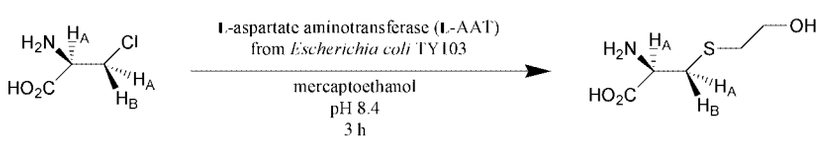
Molecular modelling studies of subtilisin. ***Protease***



G. Colombo, G. Ottolina, G. Carrea and K. M. Merz Jr., *Chem. Commun.*, 2000, 559.

Quantum mechanical/molecular mechanical (QM/MM) electrostatic potential fitting methodology was used to calculate charge distribution on atoms in the tetrahedral intermediate and in the catalytic triad residues, in both hexane and water. The results showed different charge distributions between the (*R*)- and (*S*)-enantiomers in the same solvent, due to the stereodifferentiating environment of the enzyme. Charge distributions between analogous atoms in different solvents were also different due to the different polarising characteristics of the solvent.

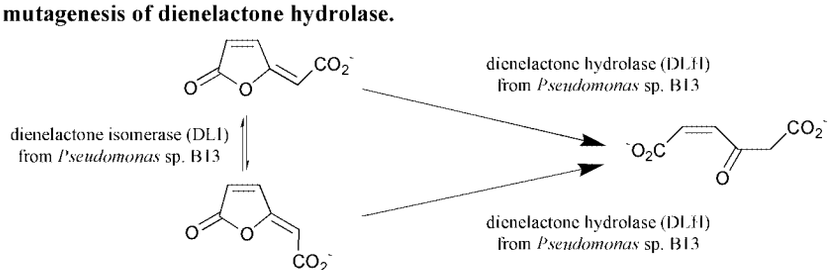
β-Substitution reaction by an aminotransferase. ***Aminotransferase***



B. Adams, K. J. M. Beresford, S. M. Whyte and D. W. Young, *Chem. Commun.*, 2000, 619.

Example of an aminotransferase performing a β-substitution reaction. Labelling studies were used to show that the reaction proceeds with retention of configuration at the β-center. This shows that the relationship between the α- and β-families of the pyridoxal phosphate enzymes may be closer than homology suggests.

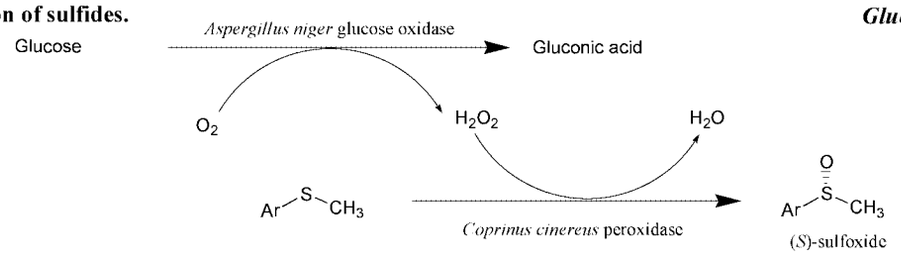
Site-directed mutagenesis of dienelactone hydrolase. ***Hydrolase/Isomerase***



L. Walker, C. J. Easton and D. L. Ollis, *Chem. Commun.*, 2000, 671.

Site-directed mutagenesis of cysteine to serine in the catalytic triad of DLH results in a change of catalytic character from a hydrolase to an isomerase. The inability of DLI to hydrolyse dienelactones is ascribed to the non-productive collapse of the tetrahedral intermediate.

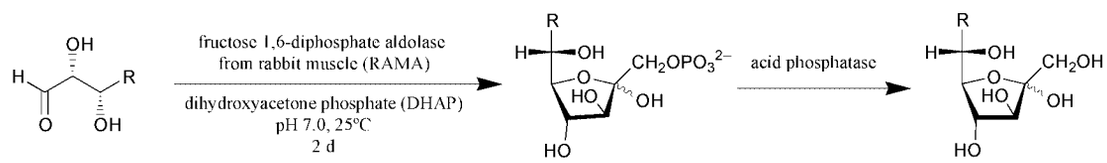
Oxidation of sulfides. ***Glucose Oxidase/ Peroxidase***



A one-pot glucose oxidase–peroxidase system was used in the enantioselective oxidation of thioanisole and its derivatives. Yields ranged from 65-95%, with ees of 57-90%. Electron-withdrawing and electron-donating groups at the *para*-position resulted in lower yields and ee.

K. Okrasa, E. Guibé-Jampel and M. Therisod, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1077.

Chemoenzymatic synthesis of perfluoroalkylated sugars. ***Aldolase***



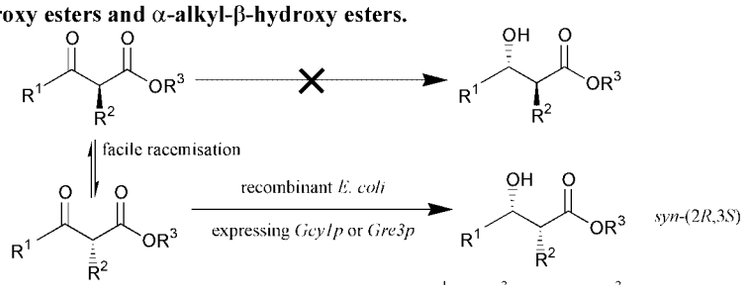
R = $Cl(CF_2)_4$, $Cl(CF_2)_6$, C_8F_{17}

30-35% yield

6-C-Perfluoroalkyl-D-fructoses are novel sugars and may be useful as biomedical surfactants.

W. Zhu and Z. Li, *J. Chem. Soc., Perkin Trans. 1*, 2000, **1105**.

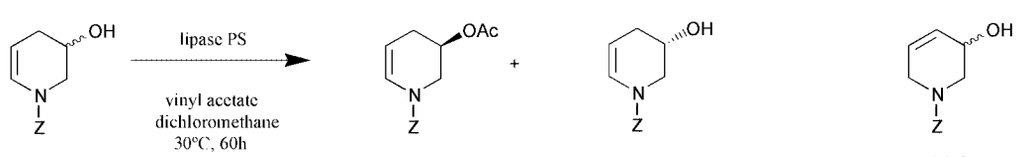
Synthesis of β-hydroxy esters and α-alkyl-β-hydroxy esters. ***Dehydrogenase***



R^1 an d R^3 = Me or Et, R^3 = H, Me, Et, allyl or propargyl. 87% yield and >98% ee and de obtained using recombinant *E. coli* expressing *Gre3p* when R^1 = Me, R^3 = Et and R^2 = propargyl.

S. Rodríguez, K. T. Schroeder, M. M. Kayser and J. D. Stewart, *J. Org. Chem.*, 2000, **65**, 2586.

Resolution of CBz protected hydroxy tetrahydropyridines ***Lipase***



(±)-**1**

(*R*)-, 47% yield
>99% ee

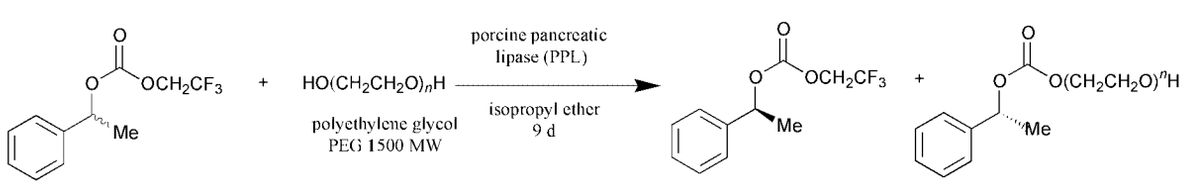
(*S*)-, 48% yield
>99% ee

(±)-**2**

The isomer **2** was resolved using an analogous approach.

H. Sakagami and K. Ogasawara, *Synthesis*, 2000, 521.

Resolution of carbonates. ***Lipase***



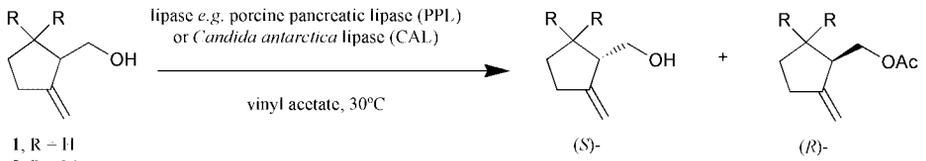
(*S*)-, 80% ee

(*R*)-, 96% ee

On completion, reaction was cooled to 0 °C. Filtration of the frozen PEG and acylated PEG yields the (*S*)-carbonate without chromatography. Some hydrolysis of the carbonate to *sec*-phenylethyl alcohol by PPL was observed.

L. J. Whalen and C. J. Morrow, *Tetrahedron: Asymmetry*, 2000, **11**, 1279.

Resolution of allylic(hydroxymethyl)methylenecyclopentanes. ***Lipase***



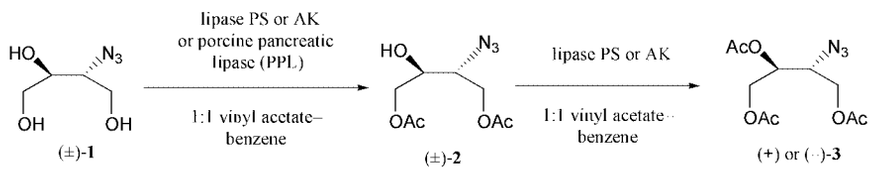
1, R = H
2, R = Me

(*S*)- (*R*)-

Best resolution of **1** was achieved using PPL, giving alcohol (72% ee) and acetate (31% ee) at 72% conversion. The resolution of **2** was best achieved using Amano AK lipase, giving (*S*)-alcohol of 96% ee and (*R*)-acetate of 62% ee. The resolution of substrate **2** was effected with complementary selectivity using PPL or CAL, but the enantioselectivity was poor.

G. Laval, G. Cardillo, H. Monti, A. Tolomelli, G. Audran and J. M. Galano, *Tetrahedron: Asymmetry*, 2000, **11**, 1289.

Resolution of *syn*-2-azido-1,3,4-trihydroxybutane and *syn*-2-azido-1,4-diacetoxy-3-hydroxybutane. ***Lipase***

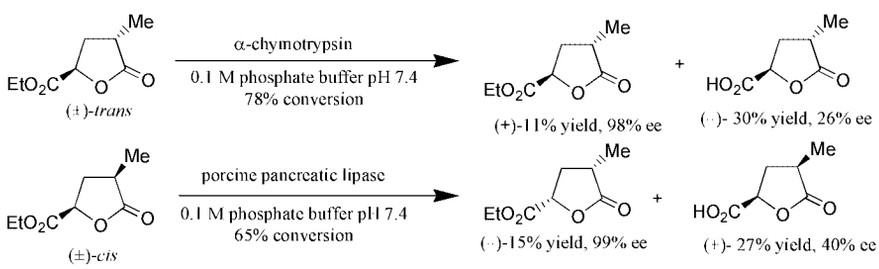


(±)-**1** (±)-**2** (+) or (−)-**3**

(2*S*,3*R*)-**2** is obtained in high ee (> 99%) and satisfactory yields using Amano or PS lipase and either triol **1** or diacetate **2** as substrates. A good yield and ee are obtained for (2*R*, 3*S*)-**3** when lipase AK and triol **1** are used.

G. Iacazio, D. Martini, S. Sanchez and B. Faure, *Tetrahedron: Asymmetry*, 2000, **11**, 1313.

Resolution of lactone esters. ***Hydrolase***



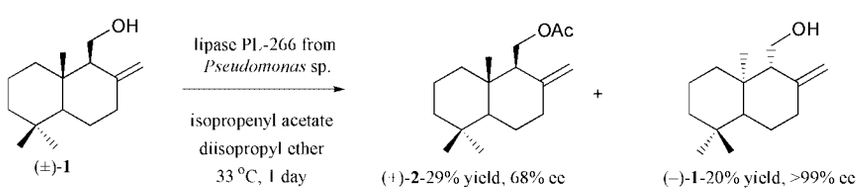
(±)-*trans* (+)-11% yield, 98% ee (−)- 30% yield, 26% ee

(±)-*cis* (−)-15% yield, 99% ee (+)- 27% yield, 40% ee

Other hydrolases were tested with decreased enantioselectivities. Products are precursors of (+)- and (−)-marmelo lactones A and B.

S. Drioli, C. Forzato, P. Nitti, G. Pitacco and E. Valentin, *Tetrahedron: Asymmetry*, 2000, **11**, 1353.

Enantioselective acetylation of albicanol and drimenol. ***Lipase***

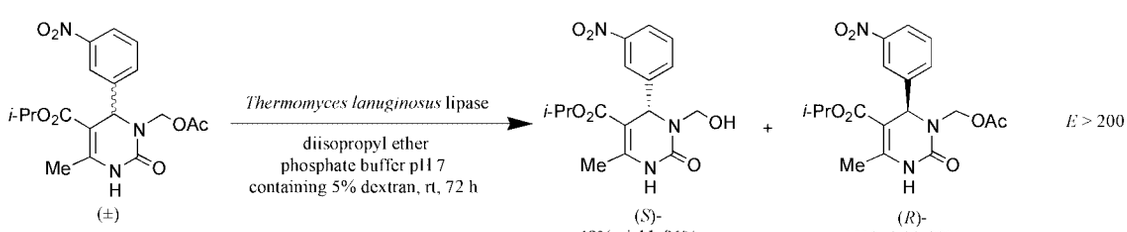


(±)-**1** (+)-**2**-29% yield, 68% ee (−)-**1**-20% yield, >99% ee

Various lipases with different enantioselectivities were screened. Conversion of (±)-**1** into (±)-drimenol followed by asymmetric acetylation using a range of lipases afforded (+)- and (−)-drimenol. Deprotection of (+)-**2** afforded the natural (+)-albicanol which was a precursor to the natural products (−)-albicanyl-3,4-dihydroxycinnamate, (−)-drimenol, (−)-drimenin and (−)-ambrox.

H. Akita, M. Nozawa, A. Mitsuda and H. Ohsawa, *Tetrahedron: Asymmetry*, 2000, **11**, 1375.

Resolution of 4-aryl-3,4-dihydro-pyrimid-2(1*H*)-one esters. ***Lipase***



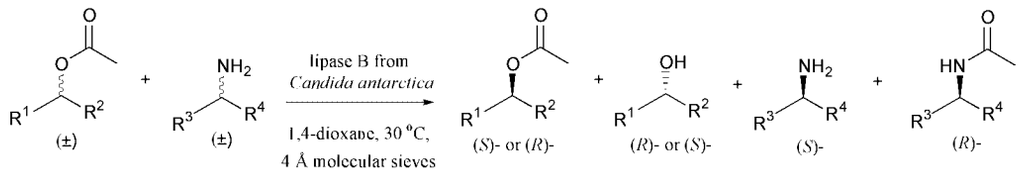
(±) (*S*)- 49% yield, 96% ee (*R*)- 45% yield, 98% ee *E* > 200

Product is a precursor to antihypertensive agent (*R*)-SQ 32926.

B. Schnell, U. T. Strauss, P. Verdino, K. Faber and C. O. Kappe, *Tetrahedron: Asymmetry*, 2000, **11**, 1449.

One-pot resolution of chiral alcohols and amines.

Lipase

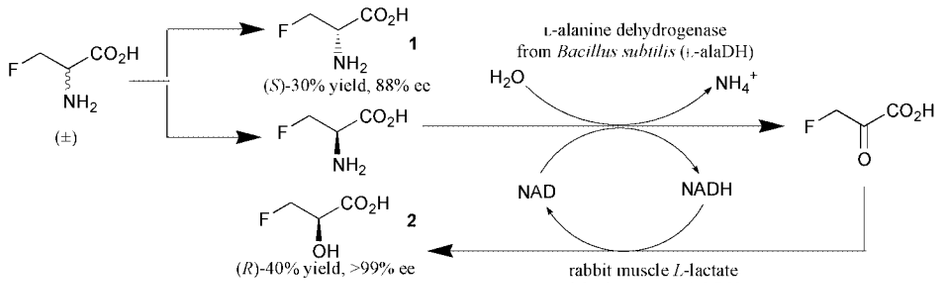


R^1 and R^3 = various aryl and alkyl groups, R^2 and R^4 = various alkyl and alkoxy substituents. Resolution of (±)-1-(phenyl)ethyl acetate with various aryl and alkyl amines as nucleophiles afforded excellent enantiomeric ratios for both the alcohol and the amine (E>200).

E. García-Urdiales, F. Rebolledo and V. Gotor, *Tetrahedron: Asymmetry*, 2000, **11**, 1459.

Synthesis of (*S*)-3-fluoroalanine and (*R*)-3-fluorolactic acid.

Dehydrogenase

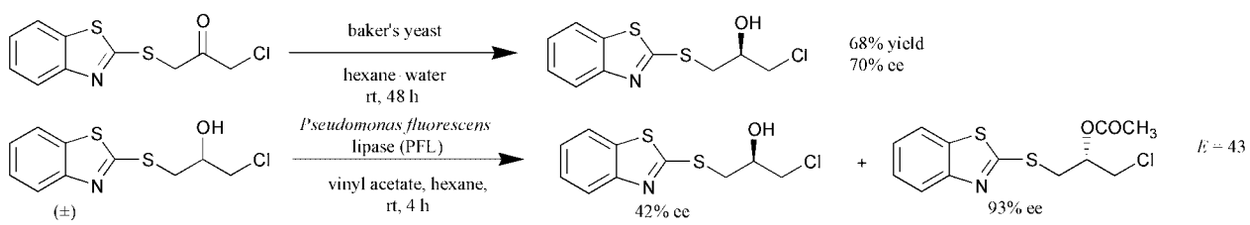


Coupled enzymatic system for the synthesis of 1 and **2**.

L. P. B. Gonçalves, O. A .C. Antunes, G. F. Pinto and E. G. Oestreicher, *Tetrahedron: Asymmetry*, 2000, **11**, 1465.

Synthesis of 1-(benzothiazol-2-ylsulfanyl)-3-chloropropan-2-ol.

Bakers Yeast/Lipase

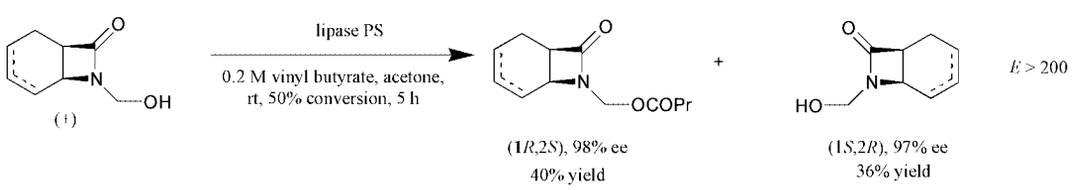


A chemical synthesis of optically active 1-(benzothiazol-2-ylsulfanyl)-3-chloropropan-2-ol was also described. Compounds are precursors to beta blockers.

L. Di Nunno, C. Franchini, A. Scilimati, M. S. Sinicropi and P. Tortorella, *Tetrahedron: Asymmetry*, 2000, **11**, 1571.

Resolution of alicyclic β-lactams.

Lipase

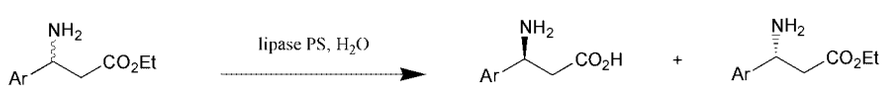


The resolution described was carried out on a gram scale. Enantiomerically pure alicyclic β-amino acids and β-lactams were formed from the resolved azetidinones.

J. Kámán, E. Forró and F. Fülöp, *Tetrahedron: Asymmetry*, 2000, **11**, 1593.

Resolution of aromatic β-amino acid esters.

Lipase



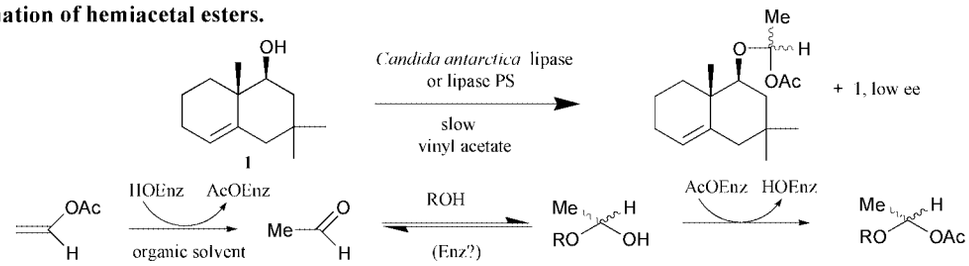
Ar = Ph, 2-Br-Ph, 3-Br-Ph, 4-Br-Ph
4-FPh, 1-naphthyl

Reactions were volume efficient, running at 200 g/L. The effect of pH on the reaction was found to be important. For hydrolysis of β -phenylalanine ethyl ester, the enantiomeric excess of the ester was 73% at pH 7 and 99% at pH 8 for the same percentage conversion.

S. J. Faulconbridge, K. E. Holt, L. G. Sevillano, C. J. Lock, P. D. Tiffin, N. Tremayne and S. Winter, *Tetrahedron Lett.*, 2000, **41**, 2679.

Formation of hemiacetal esters.

Lipase

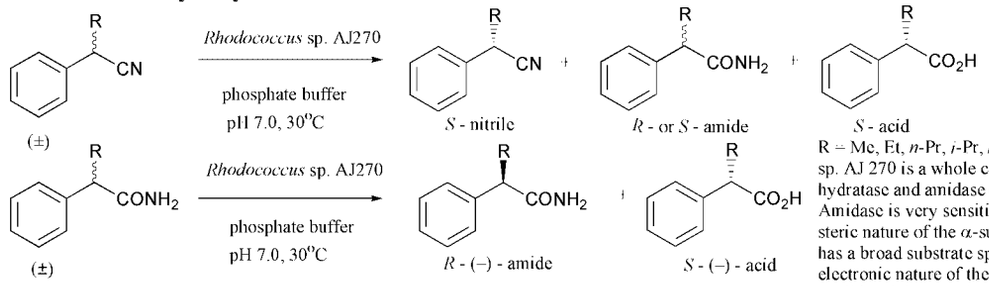


H. E. Hogberg, M. Lindmark, D. Isaksson, K. Sjodin, M. C. R. Franssen, H. Jongejan, J. B. P. A. Wijnberg and A. de Groot, *Tetrahedron Lett.*, 2000, **41**, 3193.

With some hindered secondary alcohols, the acetaldehyde resulting from vinyl acetate reacts with the alcohol to form a hemiacetal intermediate which is acetylated by the enzyme. Five additional structural examples.

Enantioselective hydrolysis of nitriles and amides

Nitrile hydratase/ Amidase

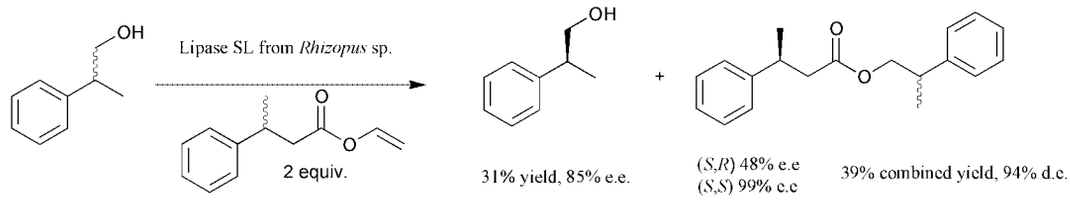


R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, MeO, MeS. *Rhodococcus* sp. AJ 270 is a whole cell system containing both nitrile hydratase and amidase enzymes.
Amidase is very sensitive to both the electronic and steric nature of the α-substituent while nitrile hydratase has a broad substrate spectrum irrespective of the electronic nature of the α-substituent. The amidase exhibits higher *R*-selectivity for amides than the nitrile hydratase.

M.-X. Wang, G. Lu, G.-J. Ji, Z.-T. Huang, O. Meth-Cohn and J. Colby, *Tetrahedron: Asymmetry*, 2000, **11**, 1123.

Resolution of primary alcohol using chiral acyl donor

Lipase

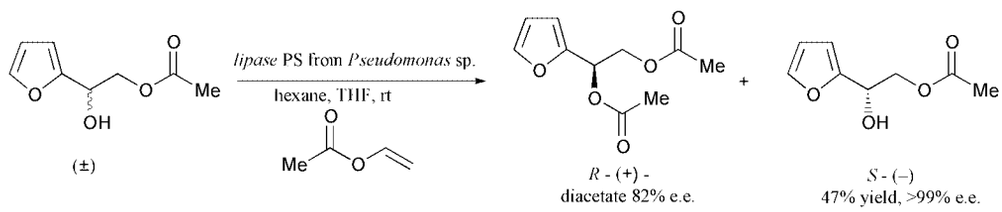


The use of a racemic acyl donor containing a stereogenic center β to the carbonyl group gave dramatic increases in enantioselectivity. Only one enantiomer of the acyl donor reacted allowing the use of racemic acyl donors. A variety of solvents, lipases and acyl donors were studied with *E* values ranging from 1 to 98.

K. Hirose, H. Naka, M. Yano, S. Ohashi, K. Naemura and Y.Tobe, *Tetrahedron: Asymmetry*, 2000, **11**, 1199

Resolution of 2-(2-furyl)-2-hydroxyethyl acetate

Lipase

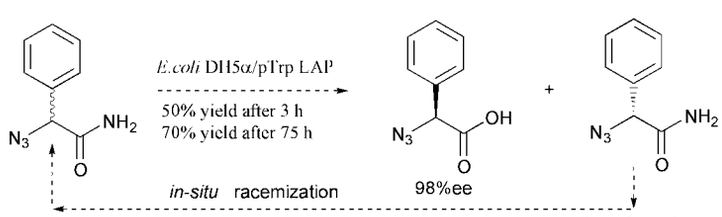


E.e. of diacetate was increased by deacetylation to the corresponding diol and *R*-acetylation with vinyl acetate in the presence of *Lipase* PS to give *R*-diacetate in 98% e.e.

J. E. Kaminska, K. Smigielski, D. Lobodzinska and J. Góra, *Tetrahedron: Asymmetry*, 2000, **11**, 1211.

Resolution of α-azido acids and amides

Aminopeptidase



Transformation performed using whole cells from *Escherichia. coli* containing the *Pseudomonas putida* L-aminopeptidase gene (*pepA*). Aliphatic substrates do not show *in-situ* racemisation *e.g.* hydrolysis of (+/-) 2-azidohexanoic acid gave 50% (*S*)-2-azidohexanoic acid after 20h (e.e.>99.8%).

C. W. Tornøe, T. Sonke, I. Maes, H. E. Schoemaker and M. Meldal *Tetrahedron: Asymmetry*, 2000, **11**, 1239.