Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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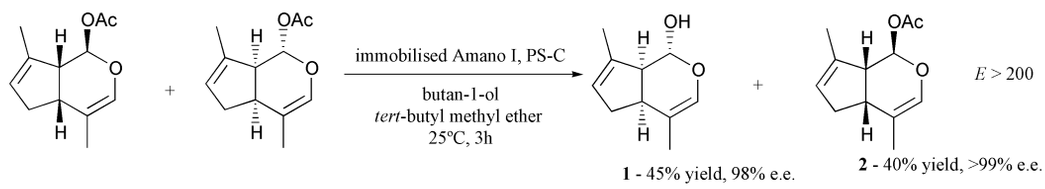
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

Chemo-enzymatic synthesis of gastrolactol ***Lipase***



1 - 45% yield, 98% e.e. **2** - 40% yield, >99% e.e.

E. M. Santangelo, D. Rotticci, I. Liblikas, T. Norin and C. R. Unelius, *J. Org. Chem.*, 2001, **66**, 5384.

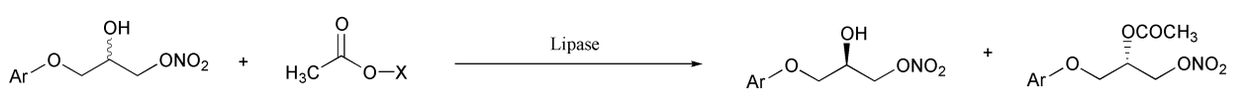
Compounds **1** and **2** are useful intermediates in the synthesis of biologically active iridoids.

Thermodynamic quantitative structure-activity relationship analysis for enzyme-ligand interactions in aqueous phosphate buffer and organic solvent ***Lipase***

A study of the thermodynamic QSAR for chymotrypsin-ligand binding and comparison of the effects of organic solvent on the substrate specificity of the enzymes to those in aqueous phosphate buffer is reported.

K. H. Kim, *Bioorg. Med. Chem.*, 2001, **9**, 1951

Resolution of 3-aryloxy-1-nitrooxypropan-2-ols ***Lipase***



(*R, S*) **1a-1g**

X = -CH=CH_2 or -C(CH_3)=CH_2

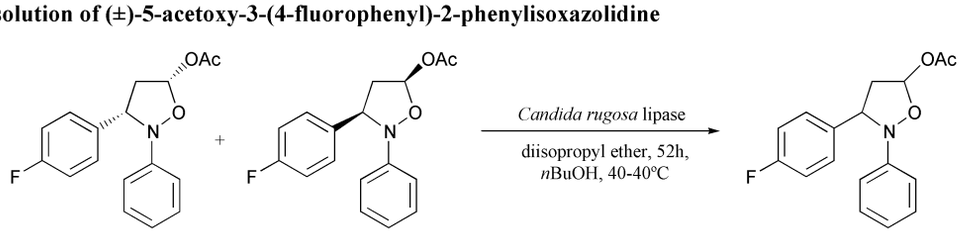
(*R*) **1a-1g** (*S*) **2a-2g**

a = C_6H_5-
b = 2-CH_3-C_6H_4-
c = 3-CH_3-C_6H_4-
d = 4-CH_3-C_6H_4-
e = 2-CH_3O-C_6H_4-
f = 4-Cl-C_6H_4-
g = 2,6-Cl-C_6H_3-

B. K. Pchelka, A. Loupy, J. Plenkiewicz, A. Petit and L. Blanco, *Tetrahedron: Asymmetry*, 2001, **12**, 2109.

An extensive study was carried out into the resolution of 3-aryloxy-1-nitrooxypropan-2-ols **1a-1g** using a series of lipases under different conditions of solvent, acyl donor and additives such as triethylamine. (*R*)-Alcohols and (*S*)-acetates were produced. Best results were obtained using lipase from *Pseudomonas cepacia* (Amano PS) or *Pseudomonas fluorescens* (Amano AK) with vinyl acetate in hexane at 4 or 22°C. Enantioselectivities (*E*) of 31-111 were observed.

Resolution of (±)-5-acetoxy-3-(4-fluorophenyl)-2-phenylisoxazolidine ***Lipase***



(±) (-) - >99% e.e., 43% yield

S. Mukherjee, A. K. Prasad, V. S. Parmar and O. W. Howarth, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2117.

First report of an enzymatic resolution of a highly substituted isoxazolidine.

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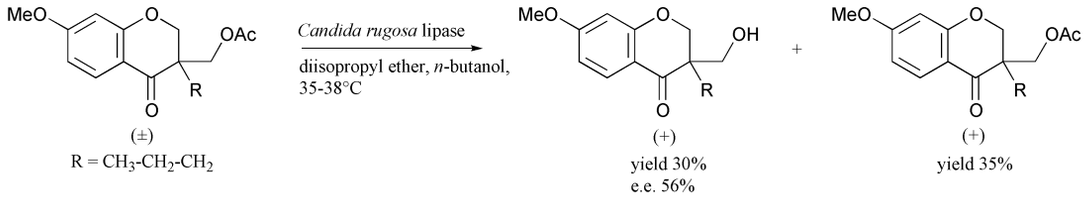
Stereoselective deacetylation

Lipase

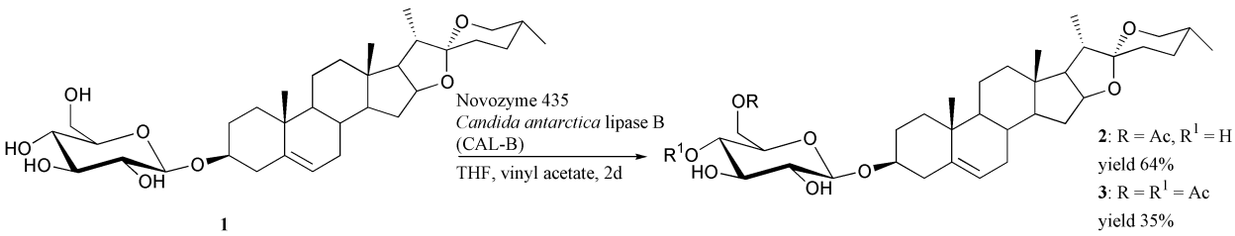


Poonam, A. K. Prasad, A. Azim, R. Kumar, S. C. Jain, V. S. Parmar, C. E. Olsen and W. Errington, *Tetrahedron*, 2001, **57**, 7395.

The corresponding acylation was found to be ineffective. In both cases 3 lipases were screened, and only the results shown were found to be satisfactory. 6 different R groups of varying chain length were tested. E.e.'s for the alcohol ranged from 14 to 56% and the rate of deacylation was found to depend on chain length. The (+) acetate was chemically deacylated giving the (-)-alcohol.

Regioselective acylation of saponins

Lipase

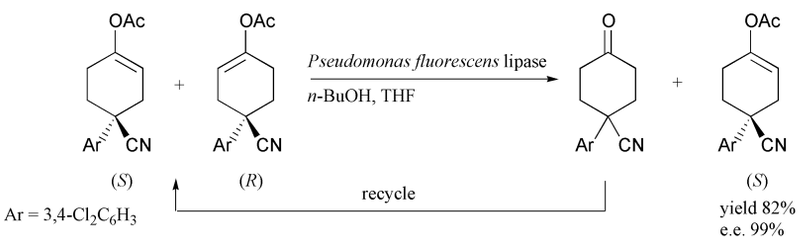


B. Yu, G. Xing, Y. Hui and X. Han, *Tetrahedron Lett.*, 2001, **42**, 5513.

Of 6 lipases screened, Novozyme 435 was found to be most effective. The amount of **2** and **3** depended on the reaction time. Other saponins (di and trisaccharides) treated in a similar way also gave the corresponding mono- and di-acetylated products. Other acylating agents were found to be less effective.

Deracemisation of an enol acetate

Lipase

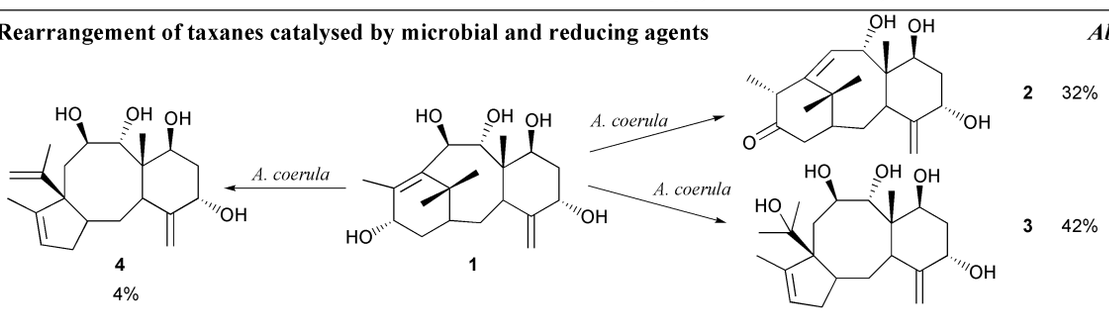


G. R. Allan, A. J. Carnell and W. Kroutil, *Tetrahedron Lett.*, 2001, **42**, 5959.

The ketone was converted back to the enol ester with potassium *tert*-butoxide and isopropenyl acetate. The e.e. and yield were achieved after 4 cycles.

Rearrangement of taxanes catalysed by microbial and reducing agents

Absidia coerula

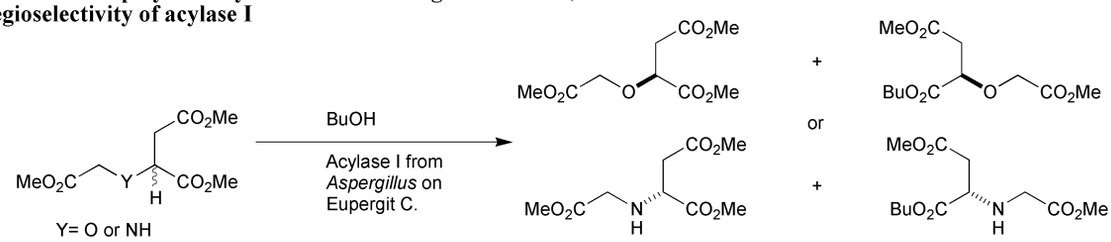


D. Sun, A. Nikolakakis, F. Sauriol, O. Mamer and L. O. Zamir, *Bioorg. Med. Chem.*, 2001, **9**, 1985.

Biotransformation of **1** with *Absidia coerula* gave a taxane, **2,** with a C-13 ketone and a C10-C11 double bond from oxidation-reduction processes. Two unexpected taxanes, **3** and **4**, were also obtained which were structurally similar to taxanes obtained from conditions where chemical reducing agents were used.

Resolution of polycarboxylic acid esters using the enantio-, chemo- and regioselectivity of acylase I

Acylase I



A. Liljeblad, R. Aksela and L. T. Kanerva, *Tetrahedron: Asymmetry,* 2001, **12,** 2059.

The most sterically hindered methyl ester group of a choice of three was converted to the butyl ester with Acylase I enantioselectively. Acylase I was shown to transform (±)-methyl *N*-acetylmethionine and (±)-valine to the corresponding (*S*)-amino acids.

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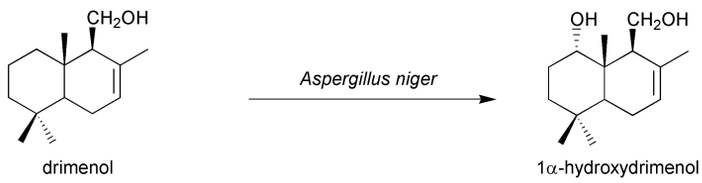
Microbiologically-assisted semisynthesis of 1α-hydroxydrimenol

Aspergillus niger

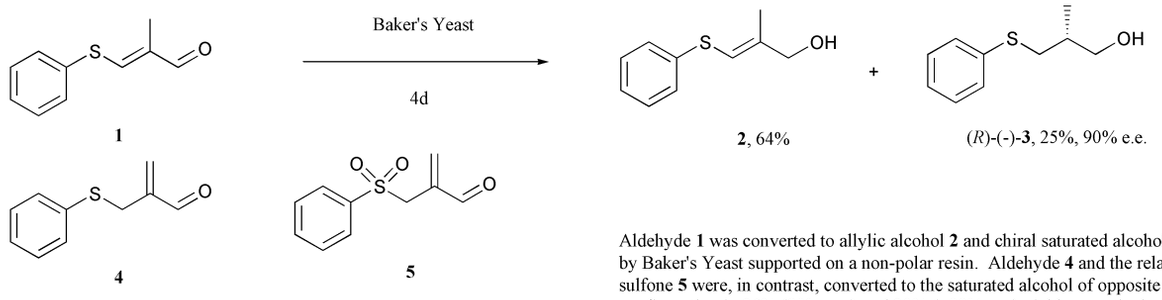


G. Aranda, M. Cortés, M. Maurs and R. Azerad, *Tetrahedron: Asymmetry,* 2001, **12**, 2013.

The semisynthesis of drimenol derivatives by microbial 3β-hydroxylation followed by a functionalised transfer to position 1 to generate a new potentially bioactive hydroxylated terpenic compound.

Reduction of substituted methacroleins

Baker's Yeast

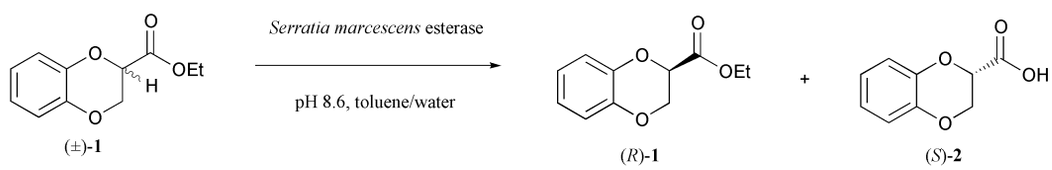


S. Serra and C. Fuganti, *Tetrahedron: Asymmetry*, 2001, **12**, 2191.

Aldehyde **1** was converted to allylic alcohol **2** and chiral saturated alcohol **3** by Baker's Yeast supported on a non-polar resin. Aldehyde **4** and the related sulfone **5** were, in contrast, converted to the saturated alcohol of opposite (*S*)-configuration in 36% (80% e.e.) and 20% (>98% e.e.) yield respectively.

Resolution of ethyl 1,4-benzodioxane-2-carboxylate

Esterase

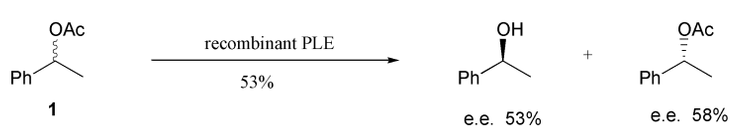


Q. K. Fang, P. Grover, Z. Han, F. X. McConville, R. F. Rossi, D. J. Olsson, D. W. Kessler, S. A. Wald and C. H. Senanayake, *Tetrahedron: Asymmetry*, 2001, **12**, 2169.

Ethyl 1,4-benzodioxane-2-carboxylate **1** was resolved using an esterase from *Serratia marcescens* in a pH stat system. An *E* value of 273 was observed for the resolution. Recovered substrate ***(R)*-1** was racemised with a catalytic amount of potassium *tert*-butoxide in toluene. Crude (*S*)-**2** was recovered with a yield of 41-43% and 98.4% e.e. (*S*)-**2** served as a synthon for the preparation of quinazoline drug (*S*)-dioxazin mesylate.

New aspects in the application of pig liver esterase

Esterase

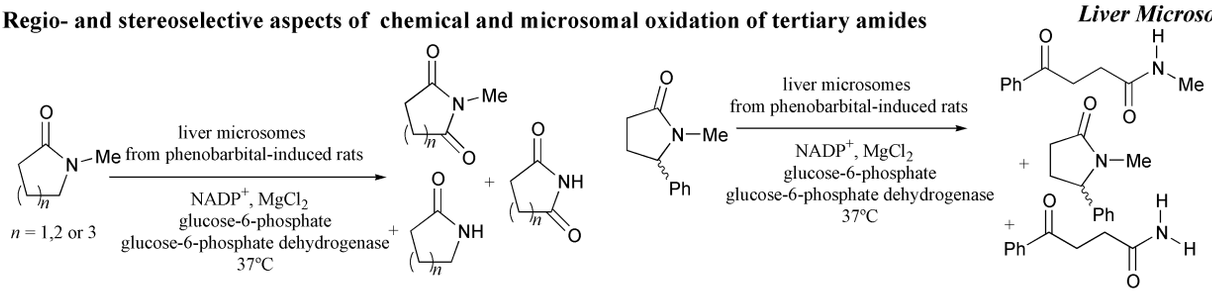


A. Musidlowska, S. Lange and U. T. Bornscheuer, *Angew. Chem., Int. Ed.,* 2001, **40**, 2851.

Production of stable recombinant pig liver esterase is reported from the overexpression of active PLE in the yeast *Pichia pastoris*. Significantly higher enantioselectivities were found in the hydrolysis of racemic 1-phenylethyl acetate, **1** , with recombinant PLE in comparison to reactions with a number of commercially available PLE preparations.

Regio- and stereoselective aspects of chemical and microsomal oxidation of tertiary amides

Liver Microsomes



J. Iley, R. Tolando and L. Constantino, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1299.

Microsomal dealkylation was found to be regioselective for the *Z* -alkyl group by calculating relative rates of isolated reactions and the stereochemical requirement of the phenobarbital-induced microsomes is low.

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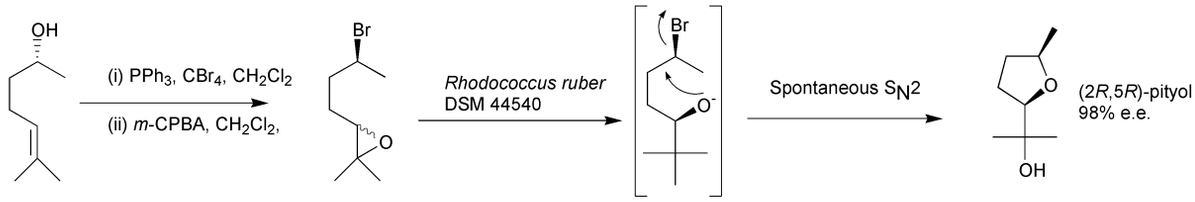
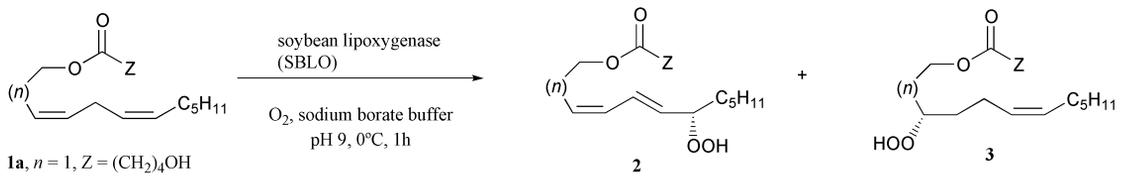
Enantio- and diastereo-convergent synthesis of (2*R*,5*R*) and (2*R*,5*S*)-pityol by enzyme catalysed ring closure ***Rhodococcus ruber***



A. Steinreiber, K. Edegger, S. F. Mayer and K. Faber, *Tetrahedron: Asymmetry*, 2001, **12**, 2067.

Kinetically resolved enantiomers of sulcatol obtained by *Candida antarctica* lipase B ester hydrolysis were the starting point for the preparative-scale biotransformation to the target (2*R*,5*R*)- and (2*R*,5*S*)-pityol. The chemoenzymatic synthesis was carried out with *Rhodococcus ruber* DSM 44540 to give (2*R*,5*R*)-pityol in 54% isolated yield and 65% d.e. at a conversion of >98% e.e.

Hydroxylation of non-natural alkenes ***Soybean lipoxygenase***



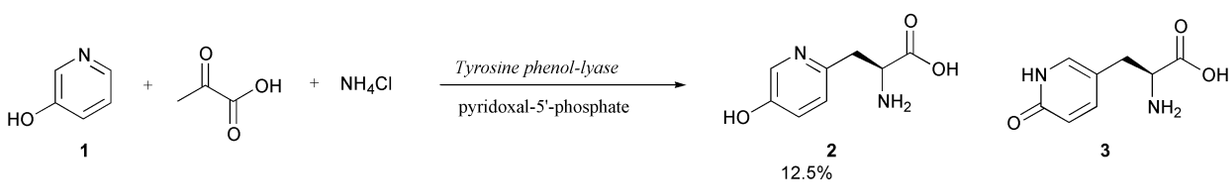
1a, *n* = 1, Z = $(CH_2)_4OH$
1b, *n* = 1, Z = $(CH_2)_3OH$
1c, *n* = 1, Z = $(CH_2)_2OH$

2 **3**

J. S. Yadav, S. Nanda and A. Bhaskar Rao, *Tetrahedron: Asymmetry*, 2001, **12**, 2129.

Chiral diols were derived from chiral hydroperoxides **2** and **3** themselves obtained from substrates **1a** to **1c** using soybean lipoxygenase (SBLO). In all cases hydroperoxides **2** were the major product (49:1). Regioselectivity was unaffected by pH (6-9). The results show that SBLO accepted substrates with non-polar 'Z' groups and that the regioselectivity of oxidation is strongly dependent on the hydrophobicity of the proximal unit.

Enzymatic synthesis of aza-L-tyrosines ***Tyrosine phenol-lyase***



1 **2** 12.5% **3**

E. B. Watkins and R. S. Phillips, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2099

Use of recombinant tyrosine phenol-lyase from *Citrobacter freundii* enabled the synthesis of 2-aza-L-tyrosine **2**, and 3-aza-L-tyrosine **3** from 2-hydroxypyridine, **1**, pyruvic acid and pyridoxal-5'-phosphate.

Enantioselective reduction of an azidoketone ***Yeast***

(*S*)
yield 94%
e.e. >98%

P. A. Procopiou, G. E. Morton, M. Todd and G. Webb, *Tetrahedron: Asymmetry*, 2001, **12**, 2005.

5 organisms were found to be effective for selective reduction. Of these, 3 preferentially gave the (*R*) enantiomer, and the others gave the (*S*). Subsequent chemical steps gave (*S*)-salmeterol.

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