Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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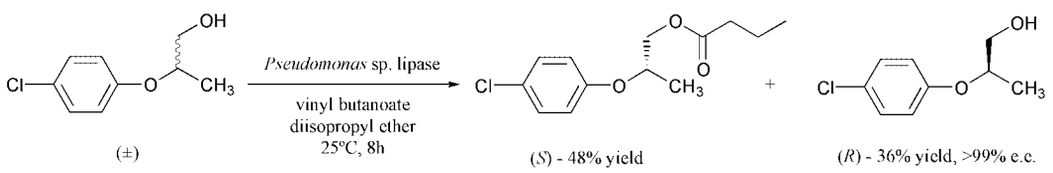
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

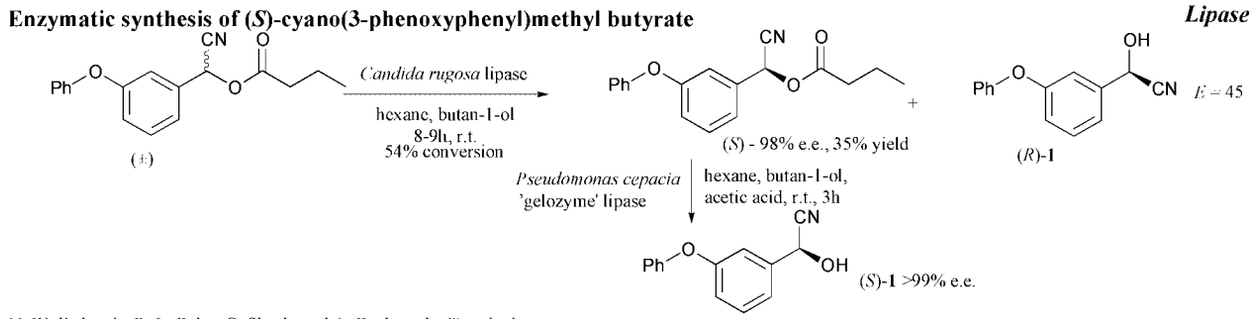
Resolution of 2-aryloxypropan-1-ols ***Lipase***



T. Miyazawa, T. Yukawa, T. Koshiba, H. Sakamoto, S. Ueji, R. Yanagihara and T. Yamada, *Tetrahedron: Asymmetry*, 2001, **12**, 1595.

Various factors affecting enantioselectivity were examined. The acyl donor and temperature were found to affect the enantioselectivity considerably.

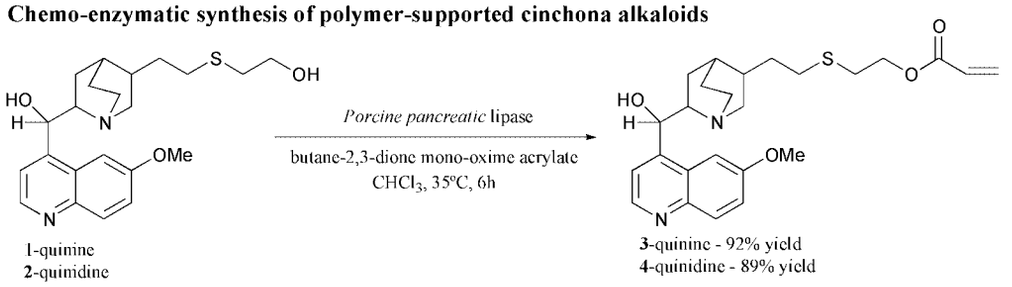
Enzymatic synthesis of (*S*)-cyano(3-phenoxyphenyl)methyl butyrate ***Lipase***



N. W. Fadnavis, R. L. Babu, G. Sheelu and A. Deshpande, *Tetrahedron: Asymmetry*, 2001, **12**, 1695.

(*R*)-**1** was decomposed in 1M imidazole solution and removed by vacuum distillation. This overcomes the problem of separation of the unwanted (*R*)-ester from the (*S*)-**1**.

Chemo-enzymatic synthesis of polymer-supported cinchona alkaloids ***Lipase***



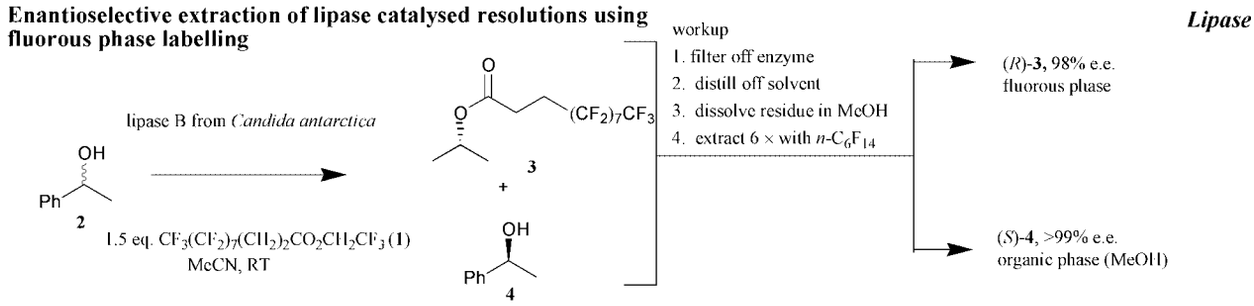
1-quinine
2-quinidine

3-quinine - 92% yield
4-quinidine - 89% yield

V. Athawale and N. Manjrekar, *Tetrahedron Lett.*, 2001, **42**, 4541.

Various solvents and temperatures were tested to optimise the yield of **3** and **4**.

Enantioselective extraction of lipase catalysed resolutions using fluorous phase labelling ***Lipase***

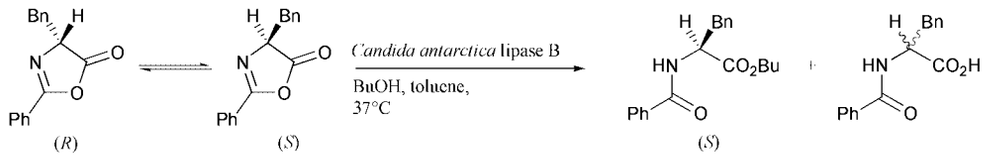


B. Hungerhoff, H. Sonnenschein and F. Theil, *Angew. Chem., Int. Ed.*, 2001, **40**, 2492.

Chromatographic separation of ester and alcoholic products of the CAL-B catalysed resolution of **2** is avoided by the use of a fluorous acyl donor **1**, which can be selectively extracted after reaction by a fluorous phase.

Effect of changing the protonated state of a lipase on enantioselectivity

Lipase

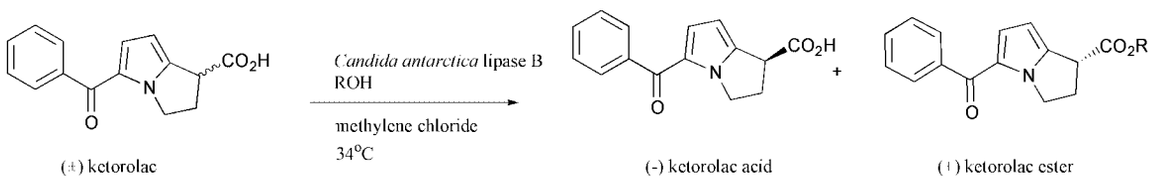


This dynamic resolution was used to study the effect of changing the protonation state of an enzyme on catalytic activity and enantioselectivity. A range of bases differing in pK_a were screened and Et_3N found to give the greatest increase in reaction rate and enantioselectivity. Since base solubility is solvent dependent and base strength is dependent on solvent polarity and protic/non protic nature a selection of solid state buffers were used to provide a range of pK_a's. Again, higher pK_a resulted in greater catalytic activity and enantioselectivity.

M. Quirós, M.-C. Parker and N. J. Turner, *J. Org. Chem.*, 2001, **66**, 5074.

Kinetic resolution of ketorolac using lipase B from *Candida antarctica*

Lipase



(-) ketorolac acid

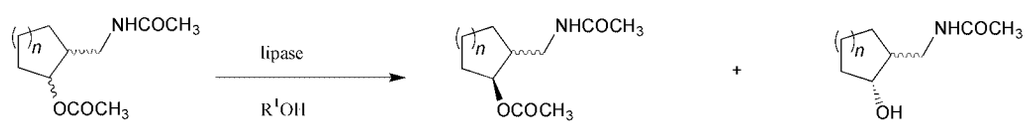
(+) ketorolac ester

Ketorolac was resolved into each of its enantiomers by reacting the acid with various alcohols using lipase B from *Candida antarctica*. Enantioselectivity was improved by optimising temperature, solvent and reaction time. >99% ee was achieved with esterification with octanol.

Y. H. Kim, C. S. Cheong, S. H. Lee and K. S. Kim, *Tetrahedron: Asymmetry*, 2001, **12**, 1865.

Kinetic resolution of *N,O*-diacetyl derivatives of cyclic 1,3-amino alcohols

Lipase



n = 1,2

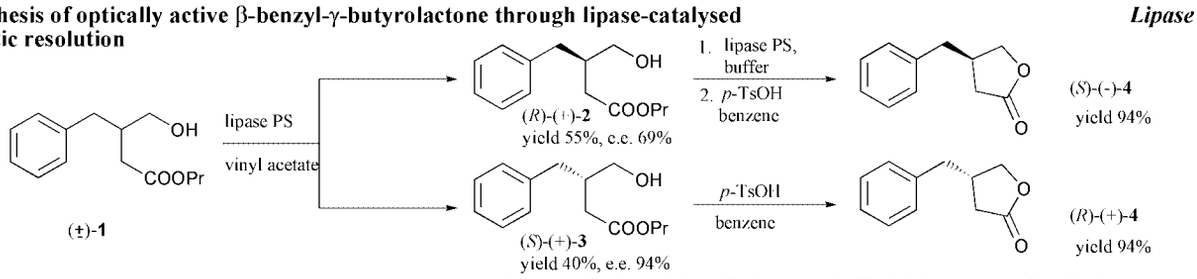
R^1 = Me, Et or ^{n}Bu

Asymmetric *O*-deacylation at the 1*R* stereogenic centre from the racemate enabled resolution of *N,O*-diacetyl derivatives. Gram scale resolutions were performed in ethanol in diisopropyl ether in the presence of Novozym 435 (lipase).

J. Kámán, E. Forró and F. Fülöp, *Tetrahedron: Asymmetry*, 2001, **12**, 1881.

Synthesis of optically active β-benzyl-γ-butyrolactone through lipase-catalysed kinetic resolution

Lipase

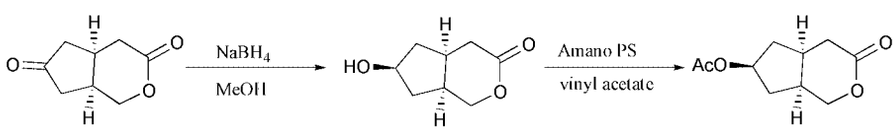


Lipase-catalysed acetylation of hydroxyester **1** afforded the acetate (+)-**2** and hydroxyester (+)- **3** which were separated. Lipase catalysed hydrolysis of the acetate group in (+)- **2** and subsequent acid mediated cyclisation of the hydroxyesters resulted in the formation of the desired products (+)-**4** and (−)-**4** in good yield.

Y. Caro, C. F. Masaguer and E. Raviña, *Tetrahedron: Asymmetry*, 2001, **12**, 1723.

Enantioselective synthesis of isoprostane and iridoid lactone intermediates by enzymatic transesterification

Lipase

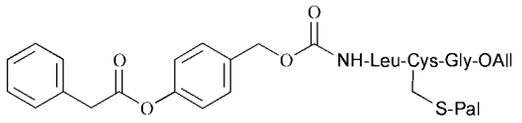


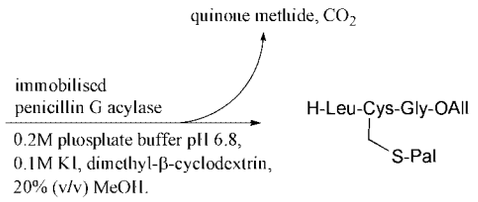
Lipase Amano PS-catalysed kinetic resolution provided synthetically useful building block lactones such as **3**.

G. Zanoni, F. Agnelli, A. Meriggi and G. Vidari, *Tetrahedron: Asymmetry*, 2001, **12**, 1779.

Peptide deprotection

Acylase



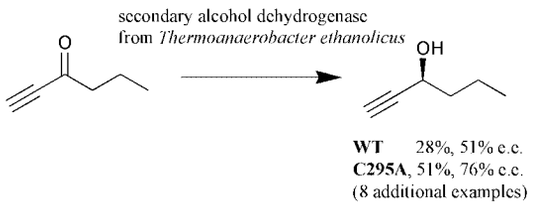


Enzymatic deprotection occurred with elimination of quinone methide, and suitable nucleophiles to remove this were found (*e.g.* KI or DMB). In other cases, penicillin G acylase cross-linked enzyme crystals were superior. However, peptides containing too many hydrophobic components were unsuitable for enzymatic transformation.

R. Machauer and H. Waldmann, *Chem. Eur. J.*, 2001, **7**, 2940.

Site-directed mutagenesis of alcohol dehydrogenase

Alcohol dehydrogenase

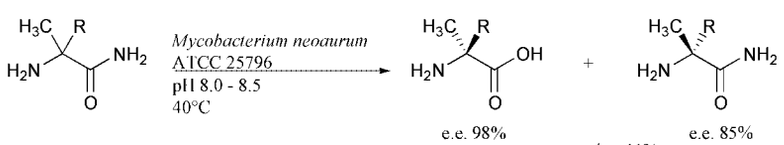


The activity of wild type secondary alcohol dehydrogenase (SAD) from *Thermoanaerobacter ethanolicus* toward ethynyl ketones is denatured by the reaction between an active site nucleophilic residue and the substrate triple bond. Molecular modelling studies using the structure of SAD from *Thermoanaerobacter brockii* showed the reactive residue to be Cys-295. When Cys-295 was mutated to alanine in *T. ethanolicus* SAD, the yield and enantioselectivity of reductions was in some cases improved. Cys-295 was suggested to be part of a small alkyl group binding pocket, the size of which regulates the binding orientation of the ethynyl ketone substrates.

C. Heiss, M. Laivenieks, J. G. Zeikus and R. S. Phillips, *Bioorg. Med. Chem.*, 2001, **9**, 1659.

Resolution of some C^{α}-tetrasubstituted α-amino acids

Amidase



R = CH_2-C(CH_3)–CH_2

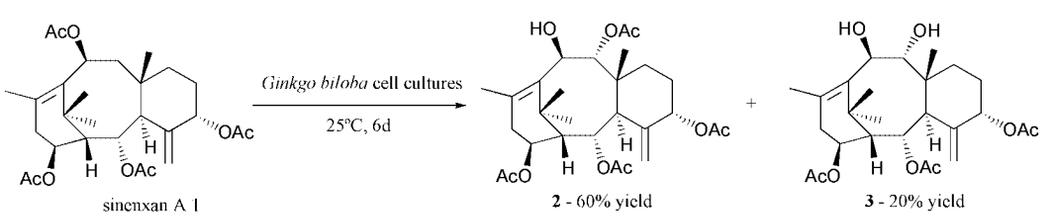
conversion 46%
E > 250

4 substrates (with variations in the sidechain, R) were resolved in this way. In each case the transformation was also carried out using *Ochrobactrum anthropi* NCIMB 40321. *M. neoaurum* was found to be more stereoselective than *O. anthropi*. Incorporation of these amino acids into peptides allowed ring closing metathesis reactions to be performed.

B. Kaptein, Q. B. Broxterman, H. E. Schoemaker, F. P. J. T. Rutjes, J. J. N. Veerman, J. Kamphuis, C. Peggion, F. Formaggio and C. Toniolo, *Tetrahedron*, 2001, **57**, 6567.

Biotransformation of 2α,5α,10β,14β-tetraacetoxy-4(20),11-taxadiene

Ginkgo biloba

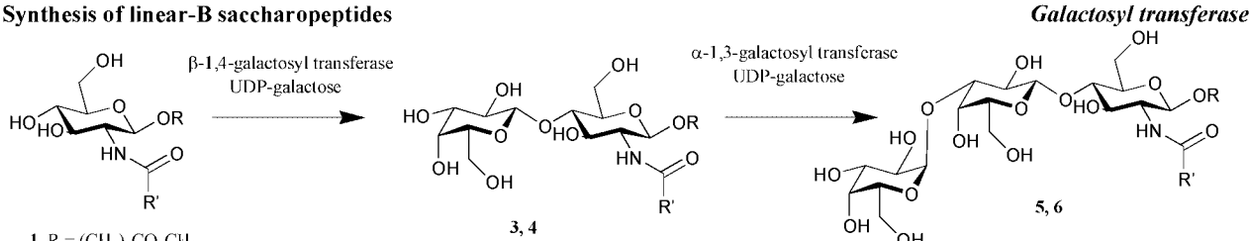


Sinenxan A **1** was used as a substrate for the bioconversion by *Ginkgo* cell cultures, yielding the hydroxylated products **2** and **3**.

J. Dai, H. Guo, D. Lu, W. Zhu, D. Zhang, J. Zheng and D. Guo, *Tetrahedron Lett.*, 2001, **12**, 4677.

Synthesis of linear-B saccharopeptides

Galactosyl transferase



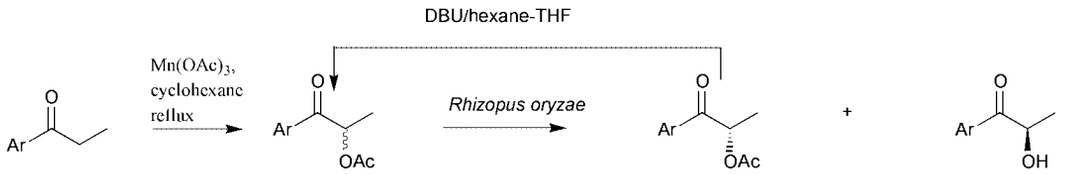
1, R = $(CH_2)_8CO_2CH_3$
2, R = $(CH_2)_3NHZ$

Linear β-saccharopeptides of type **5** and **6** were synthesised using sequential galactosyl transfer reactions catalysed by β-1,4-galactosyl transferase and α-1,3-galactosyl transferase. The enzymes tolerate the replacement of small N-acetyl groups with bulky, polar glycuronamides. Yields of up to 75% and 96% were observed for the first and second steps respectively with a series of eleven monosaccharide substrates.

O. Schwardt, G. Baisch and R. Öhrlein, *Bioorg. Med. Chem.*, 2001, **9**, 1857.

Chemoenzymatic access to enantiopure (*R*)-2-hydroxypropiophenones

Hydrolase

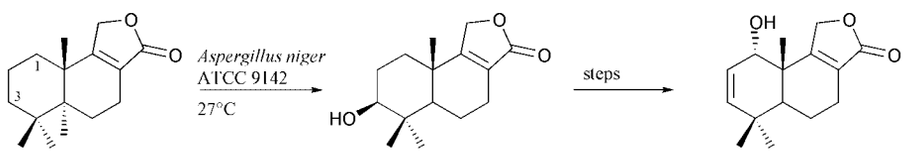


Manganese(III) acetate-mediated acetoxylation of an aryl ketone, followed by treatment with *Rhizopus oryzae*, yielded selective hydrolysis of the (*R*)-enantiomer. Impure acetoxy ketones can be epimerised using DBU in hexane/THF to afford the racemate.

A. S. Demir, H. Hamamci, O. Sesenoglu, F. Aydogan, D. Capanoglu and R. Neslihanoglu, *Tetrahedron: Asymmetry*, 2001, **12**, 1953.

Hydroxylation of confertifolin

Hydroxylase



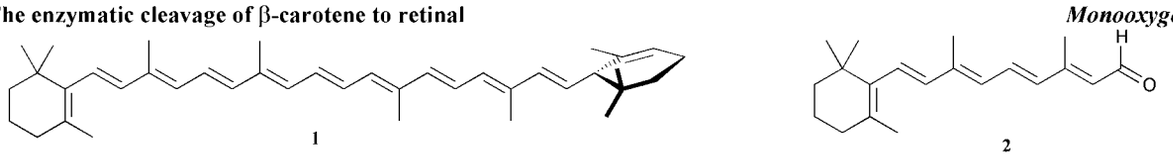
confertifolin yield 80-90%

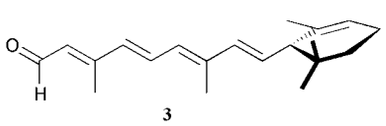
20 microorganisms were screened for their effectiveness in the biotransformation and *A. niger* was found to be the best. Subsequent chemical steps gave the 1α-hydroxy species.

G. Aranda, L. Moreno, M. Cortés, T. Prangé, M. Maurs and R. Azerad, *Tetrahedron*, 2001, **57**, 6051.

The enzymatic cleavage of β-carotene to retinal

Monooxygenase



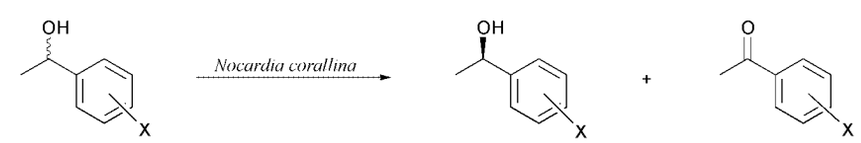


The mechanism of the enzymatic cleavage of β-carotene has been studied using analogue **1**. Derivatives of cleavage products **2** and **3** from reaction mixtures using 85% $^{17}O_2$ and 95% $H_2{}^{18}O$ and **3** were analysed by mass spectrometry. Products showed that one O atom derives from oxygen and one from water. This points to a cleavage mechanism initiated by a monooxygenase, rather than a dioxygenase, as previously thought.

M. G. Leuenberger, C. Engeloch-Jarret and W. D. Woggon, *Angew Chem., Int. Ed.*, 2001, **40**, 2614.

Resolution of methylarylmethanols *via* oxidation with *Nocardia corallina*

Nocardia corallina



X = H, Br, Cl, OMe, OPh

28%, ee>99% for X = H

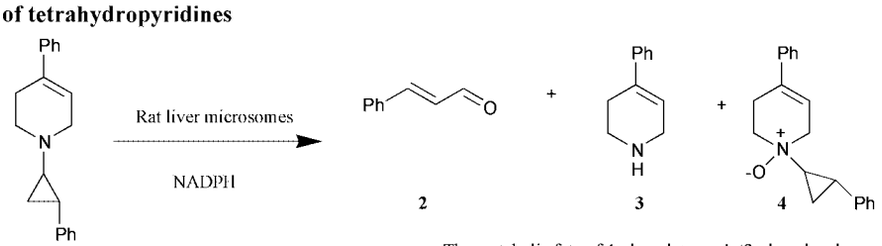
72%

Enantioselective enzymatic oxidation of a variety of racemates of methylarylmethanols with *Nocardia corallina* gave the ketone and unreacted (*R*)-alcohol. Greater reactivity was observed for *m*- and *p*-substituted methylarylmethanols. The lower reactivity of *o*- substituted compounds was attributed to steric hindrance.

H. I. Pérez, H. Luna, N. Manjarrez and A. Solís, *Tetrahedron: Asymmetry*, 2001, **12**, 1709.

Oxidation of tetrahydropyridines

Rat liver microsomal oxidase

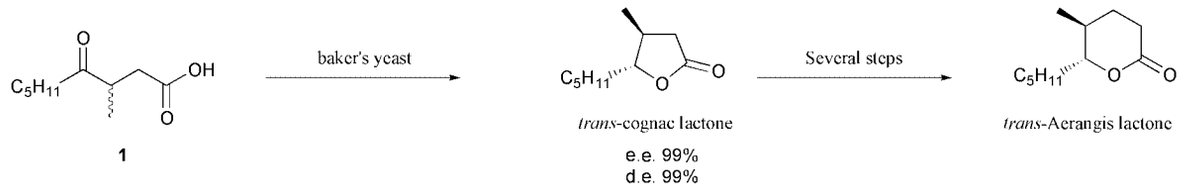


1 **2** **3** **4**

The metabolic fate of 4-phenyl-*trans*-1-(2-phenylcyclopropyl)-1,2,3,6-tetrahydropyridine **1** was analysed by biotransformation with rat liver microsomes supplemented with NADPH. In addition to oxidation products **3** (by *N*-dealkylation) and *N*-oxide **4**, cinnamaldehyde **2** was observed. **2** was thought to arise from a cytochrome P450 catalysed single electron tranfer (SET) reaction *via* an intermediate cyclopropylaminyl radical cation.

S. Kuttab, J. Shang and N. Castagnoli Jr., *Bioorg. Med. Chem.*, 2001, **9**, 1685.

Enantioselective synthesis of Aerangis lactone by baker's yeast-mediated reduction ***Reductase***



1

trans-cognac lactone

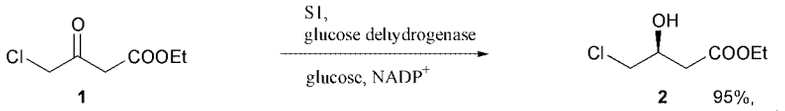
e.e. 99%
d.e. 99%

trans-Aerangis lactone

E. Brenna, C. D. Negri, C. Fuganti and S. Serra, *Tetrahedron: Asymmetry*, 2001, **12,** 1871.

trans-Aerangis lactone was synthesised by baker's yeast reduction of the 1,4-ketoacid **1** with subsequent synthetic steps. The *cis*-isomer was also selectively synthesised using baker's yeast followed by synthetic modification.

Stereoselective reduction of alkyl 3-oxobutanoate by carbonyl reductase from *Candida magnoliae* ***Reductase***



1 **2** 95%, ee>99%

Y. Yasohara, N. Kizaki, J. Hasegawa, M. Wada, M. Kataoka and S. Shimizu, *Tetrahedron: Asymmetry*, 2001, **12**, 1713.

Carbonyl reductase S1 from *Candida magnoliae* reduced ethyl 4-chloro-3-oxobutanoate **1** to the corresponding (*S*)-enantiomer alcohol **2**. Reductions of alkyl 2-substituted-3-oxobutanoates were also investigated but were found to be less efficient.