Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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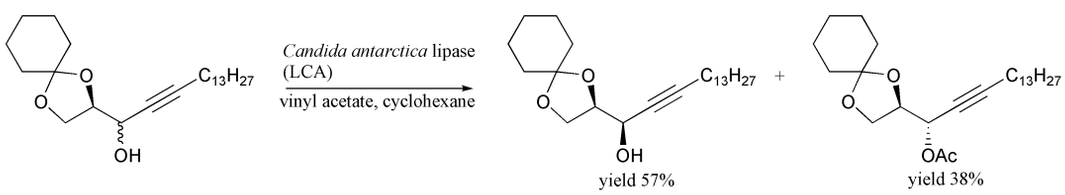
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

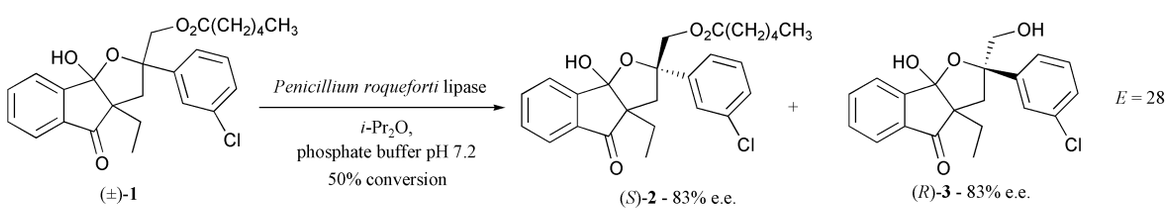
Resolution of a diastereomeric mixture of propargylic alcohols ***Lipase***



F. Compostella, L. Franchini, G.B. Giovenzana, L. Panza, D. Prosperi and F. Ronchetti, *Tetrahedron: Asymmetry*, 2002, **13**, 867.

The alcohol was obtained in a syn/anti ratio of 4:6 and treatment of the mixture with LCA gave the *anti* acetyl derivative and *syn* alcohol in diastereomerically pure forms, with no trace of the *syn* acetylated derivative observed. The *anti* derivative was deacetylated and inverted by Mitsunobu reaction with acetic acid to give the *syn* acetylated derivative.

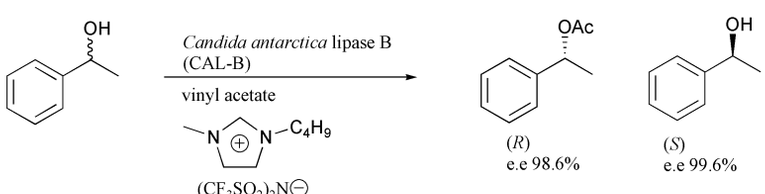
Kinetic resolution of a diol ***Lipase***



K. Tanaka, K. Yoshida, C. Sasaki and Y. T. Osano, *J. Org. Chem.*, 2002, **67**, 3131.

The use of an isobutyrate ester of (±)-**1** gave excellent selectivity [(*R*)-**3** - 96% e.e.) at 46% conversion, *E* =125], however, the poor reaction rate rendered the hydrolysis impractical.

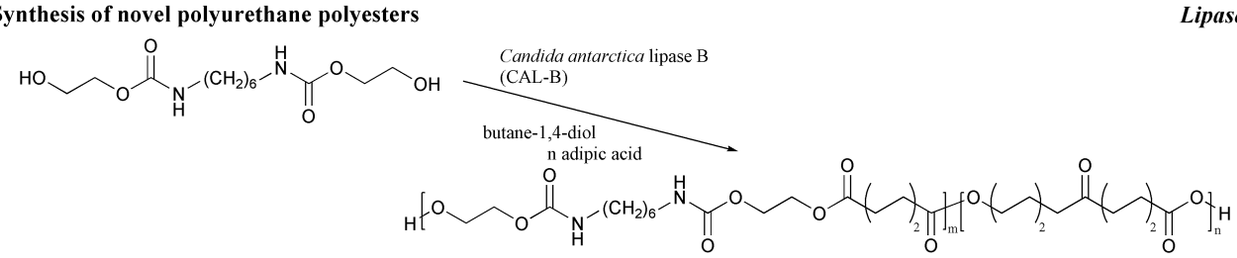
Biocatalysis in ionic liquids using supercritical carbon dioxide as the mobile phase ***Lipase***



M. T. Reetz, W. Wiesenhöfer, G. Franciò and W. Leitner, *Chem. Commun.*, 2002, 992.

The kinetic resolution of 1-phenylethanol in the ionic liquid solvent 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonimide) [BMIM][BTA] using super critical CO_2 as the mobile phase to isolate the products was studied. The reaction was carried out in a batchwise process and after 4 consecutive runs there was a 51.4% conversion of the alcohol and e.e.s as shown. The acylation of octan-1-ol in a similar system, but with a continuous type process was also studied and found be effective.

Synthesis of novel polyurethane polyesters ***Lipase***

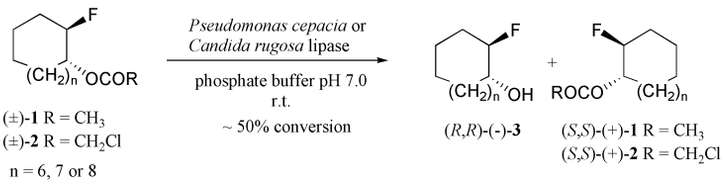


R. W. McCabe and A. Taylor, *Chem. Commun.*, 2002, 934.

The biscarbamate was dissolved in butane-1,4-diol at 90°C and then, after cooling to 60°C, adipic acid was added portionwise in the presence of the CAL-B giving the polyester polyurethane with molecular weight of 9350 Daltons. Various other biscarbamates were synthesised and reacted in this way, giving other unusual polyester polyurethanes. This method allows the synthesis of these polyurethanes without employing the usual toxic isocyanate intermediates

Synthesis of optically active vicinal fluorohydrins by lipase-catalysed deracemisation

Lipase



(±)-**1** R = CH_3
(±)-**2** R = CH_2Cl
n = 6, 7 or 8

(*R*,*R*)-(-)-**3**

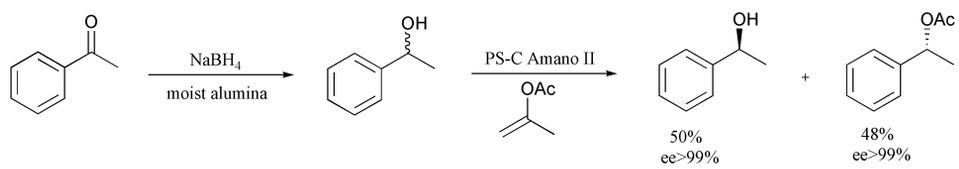
(*S*,*S*)-(+)-**1** R = CH_3
(*S*,*S*)-(+)-**2** R = CH_2Cl

D. Wölker and G. Haufe, *J. Org. Chem.*, 2002, **67**, 3015.

Pseudomonas cepacia lipase was most selective for the six- and seven-membered ring compounds (±)-**1** and **2** ($E > 65$), while the lipase from *Candida rugosa* was most useful for the eight-membered ring compounds.

Lipase catalysed synthesis of enantiopure secondary alcohols

Lipase

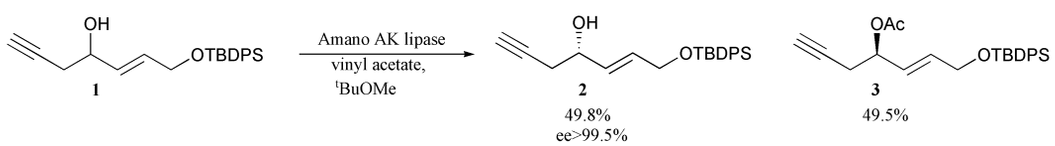


A. Kamal, M. Sandbhor and K. V. Ramana, *Tetrahedron*: *Asymmetry*, 2002, **13**, 815.

The reduction of carbonyl compounds with alumina assisted sodium borohydride followed by lipase catalysed transesterification of the corresponding secondary alcohol in a one-pot process is reported.

Asymmetric synthesis of enantiomerically enriched 12-(*S*)-HETE

Lipase

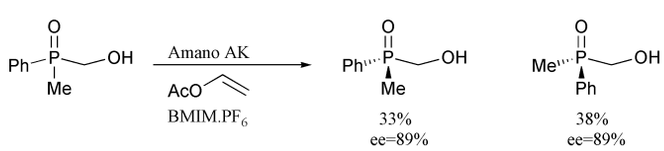


Y.-G. Suh, K.-H. Min, Y.-S. Lee, S.-Y. Seo, S.-H. Kim and H.-J. Park, *Tetrahedron Lett.*, 2002, **43**, 3825.

A novel and efficient asymmetric synthesis of (*S*)- and (*R*)-12-HETE using a combination of enzymatic and chemical processes is reported. The key enzymatic step involved kinetic resolution of **1** to give the desired intermediates, **2** and **3**, in high yield and excellent enantiomeric excess.

Kinetic resolution of *P*-chiral hydroxymethanephosphinates and hydroxymethylphosphine oxides

Lipase

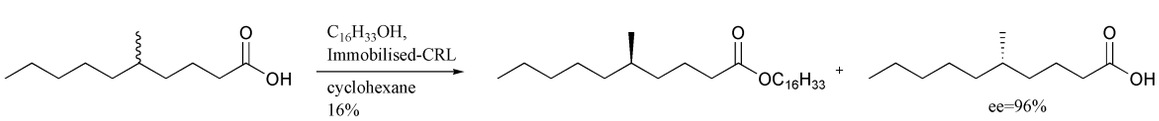


P. Kielbasinski, M. Albrycht, J. Luczak and M. Mikolajczyk, *Tetrahedron*: *Asymmetry*, 2002, **13**, 735.

A study of lipase mediated kinetic resolution of racemic *P*-chiral hydroxymethanephosphinates and a hydroxymethylphosphine oxide in ionic liquid media is reported. The enantioselectivity of this process was found to be far better than in organic media.

Lipase catalysed esterification of 2- to 8-methyldecanoic acids

Lipase

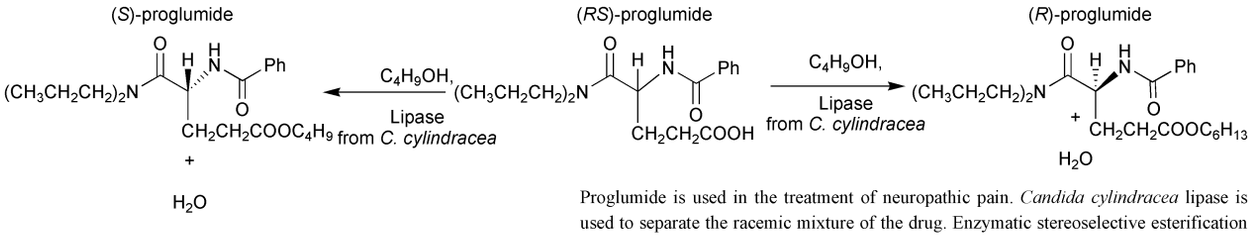


E. Hedenström, B.-V. Nguyen and L.A. Silks, *Tetrahedron*: *Asymmetry*, 2002, **13**, 835.

An investigation of lipase catalysed esterification of the racemic 2- to 8-methyldecanoic acids is reported. *Candida rugosa* lipase (CRL) was found to be a highly enantioselective catalyst for this process even when the methyl group was positioned at carbon 8 in the alkyl chain.

Lipase catalysed resolution of (*RS*)-proglumide

Lipase

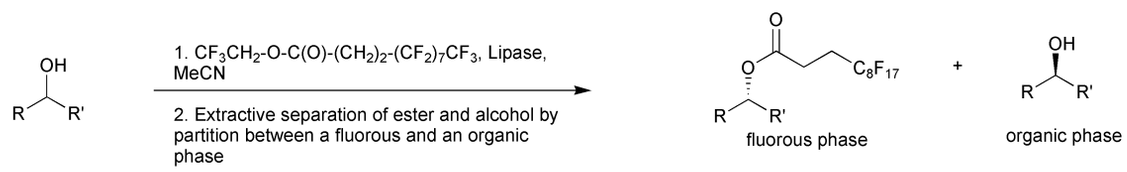


Proglumide is used in the treatment of neuropathic pain. *Candida cylindracea* lipase is used to separate the racemic mixture of the drug. Enzymatic stereoselective esterification was carried out in organic solvents. Butanol and hexanol were found to be suitable for formation of *S* and *R* esters respectively. Hexane was the best solvent for the esterification and the optimum temperature was found to be 30°C.

R. V. Muralidhar, R. R. Chirumamilla, V. N. Ramachandran, R. Marchant and P. Nigam, *Bioorg. Med. Chem.*, 2002, **10**, 1471.

Separation of enantiomers by lipase-catalysed fluorous-phase delabeling

Lipase

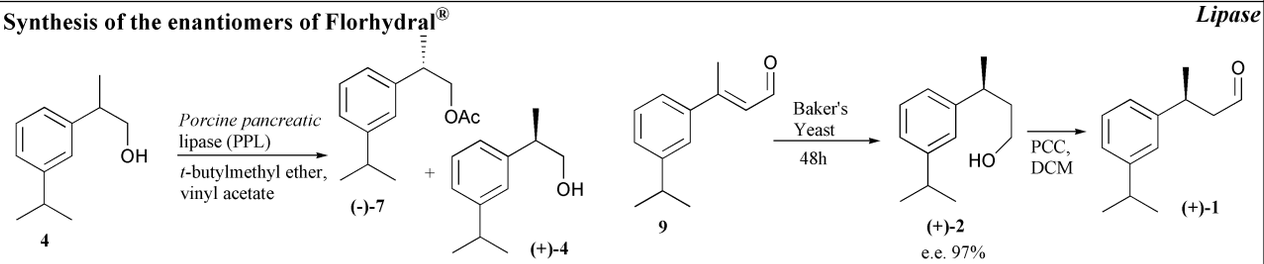


Simultaneous enantiomer-selective fluorous-phase delabeling and kinetic resolution was achieved by lipase-catalysed alcoholysis of highly fluorinated esters of racemic alcohols. The separation of the fast-reacting delabeling enantiomers and the slow-reacting fluorous-phase labeled enantiomers was performed very efficiently by partition in an organic–fluorous biphasic solvent system.

S. M. Swaleh, B. Hungerhoff, H. Sonnenschein and F. Theil, *Tetrahedron*, 2002, **58**, 4085.

Synthesis of the enantiomers of Florhydral®

Lipase

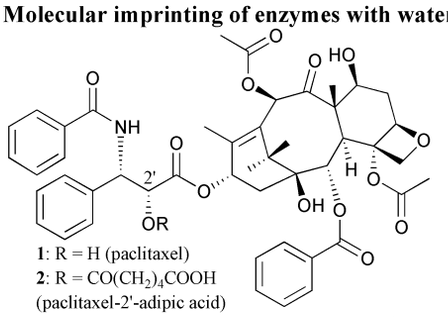


The enantiomers of Florhydral® **1** were obtained. Lipase resolution of **2** proved to be ineffective and so the enzymatic transesterification of the similar alcohol **4** was carried out. High e.e.'s (99%) were achieved after 96h. In the case of **(-)-7** the acetate was hydrolysed to the alcohol and re-treated with the lipase (48h). Subsequent steps gave each enantiomer of **1**. A route to the more potent enantiomer, **(+)-1** was developed, where **9** was reduced to **(+)-2** using baker's yeast.

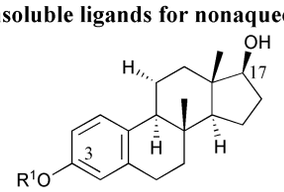
A. Abate, E. Brenna, C. D. Negri, C. Fuganti and S. Serra, *Tetrahedron: Asymmetry*, 2002, **13**, 899.

Molecular imprinting of enzymes with water-insoluble ligands for nonaqueous biocatalysis

Lipase, protease, subtilisin Carlsberg



1: R = H (paclitaxel)
2: R = $CO(CH_2)_4COOH$ (paclitaxel-2'-adipic acid)



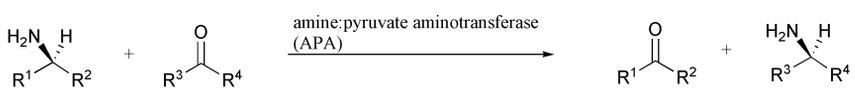
3: R^1 = H (17β-estradiol)
4: R^1 = SO_3 (17β-estradiol 3-sulfate)
5: R^1 = CH_2COOH (17β-estradiol 3-carboxymethyl ether)

By modifying imprinters **1** or **3** to increase their water solublity, the catalytic activity of thermolysin or subtilisin and lipase TL imprinted with **2** or **4** and **5** respectively, was greatly increased (8.8 -fold or 10-fold and 26-fold respectively). Alternatively, by modifying the medium to increase its ability to dissolve the hydrophobic imprinter **1** or **3**, for example by using *tert*-butyl alcohol or 1,4-dioxane as co-solvents, the catalytic activity of all three enzymes could be increased.

J. O. Rich, V. V. Mozhaev, J. S. Dordick, D. S. Clark and Y. L. Khmelnitsky, *J. Am. Chem. Soc.*, 2002, **124**, 5254.

Exploring an active site on the basis of the substrate structure – reactivity relationship.

Aminotransferase

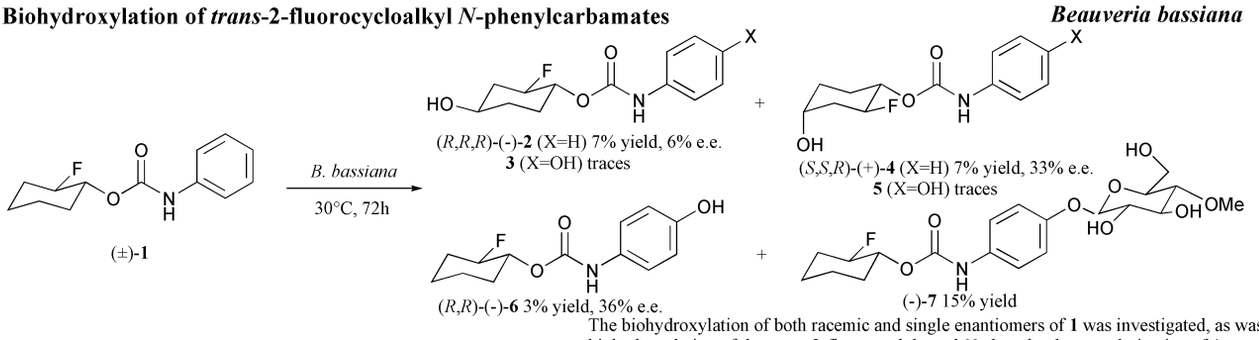


An active site model of the APA from *Vibrio fluvialis* JS17 was constructed on the basis of the substrate structure and reactivity relationship. Various amino donors (containing/not containing aryl group and amino acids and their derivatives) and amino acceptors (keto acids, keto esters, aldehydes and ketones) were analysed for reactivity. The binding site was discussed in detail and found to consist of two pockets, one large and the other small.

J.-S. Shin and B.-G. Kim, *J. Org. Chem.*, 2002, **67**, 2848.

Biohydroxylation of *trans*-2-fluorocycloalkyl *N*-phenylcarbamates

Beauveria bassiana

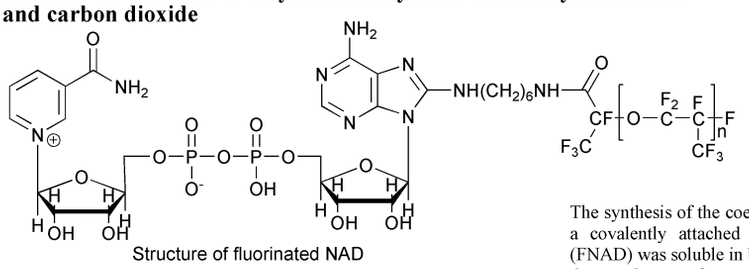


G. Haufe, D. Wölker and R. Fröhlich, *J. Org. Chem.*, 2002, **67**, 3022.

The biohydroxylation of both racemic and single enantiomers of **1** was investigated, as was biohydroxylation of the *trans*-2-fluorocycloheptyl *N*-phenylcarbamate derivative of **1**.

Fluorinated NAD as a soluble coenzyme for enzymatic chemistry in fluorous solvents and carbon dioxide

Dehydrogenase

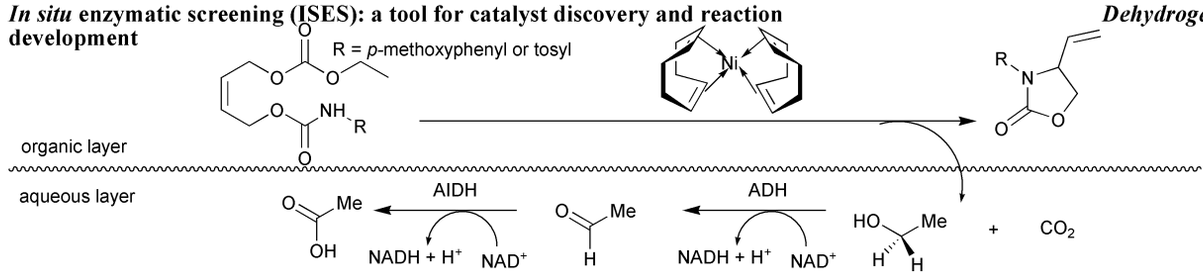


J. L. Panza, A. J. Russell and E. J. Beckman, *Tetrahedron*, 2002, **58**, 4091.

The synthesis of the coenzyme nicotinamide adenine dinucleotide (NAD) with a covalently attached fluorinated polymer is reported. Fluorinated NAD (FNAD) was soluble in both fluorous solvents and liquid carbon dioxide due to the attachment of a perfluoropolyether. In both solvent types, the activity of horse liver alcohol dehydrogenase using FNAD was greater than the same molar amount of unmodified (insoluble) NAD.

In situ enzymatic screening (ISES): a tool for catalyst discovery and reaction development

Dehydrogenase

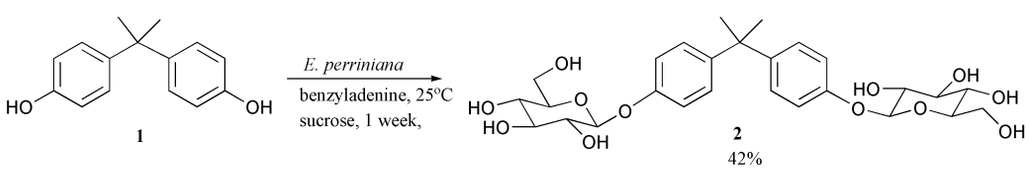


D. B. Berkowitz, M. Bose and S. Choi, *Angew. Chem., Int. Ed.*, 2002, **41**, 1603.

Six non-palladium transition metal catalysts were simultaneously monitored for intramolecular allylic amination with model substrates. The organic reaction is coupled to an enzymatic reaction that allows continuous UV spectroscopic monitoring of the reaction.

Phytoremediation of bisphenol A by cells of *Eucalyptus perriniana*

Eucalyptus perriniana

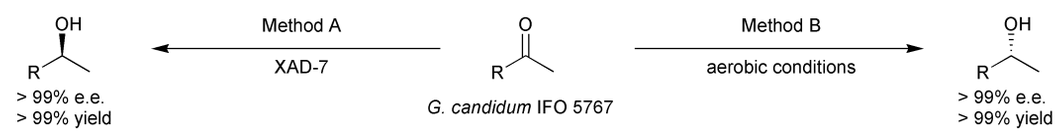


H. Hamada, R. Tomi, Y. Asada and T. Furuya, *Tetrahedron Lett.*, 2002, **43**, 4087.

A study of the biotransformation of bisphenol A **1** by cultured suspension cells of *Eucalyptus perriniana* is reported. These biotransformations resulted in regioselective hydroxylation and glycosylation of **1**, giving products such as **2** in good yield.

Asymmetric synthesis of both enantiomers of secondary alcohols by reduction with a single microbe

Microbial

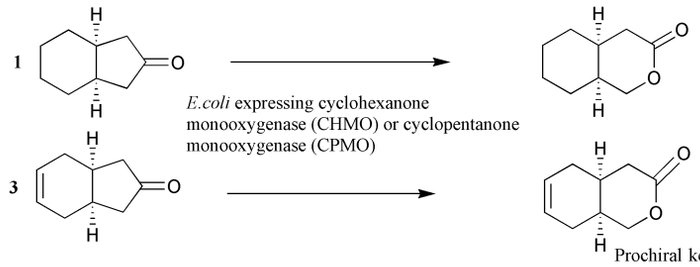


K. Nakamura, K. Takenaka, M. Fujii and Y. Ida, *Tetrahedron Lett.*, 2002, **43**, 3629.

Reduction of aromatic ketones with *Geotrichum candidum* IFO 5767 afforded the corresponding (*S*)-alcohols with e.e.s > 99% when amberlite^{TM} XAD-7, a hydrophobic polymer was added to the reaction system. The same microbe afforded (*R*)-alcohols also in excellent e.e.s when the reaction was conducted under aerobic conditions.

Baeyer-Villiger oxidation of bicyclic [4.3.0] ketones

Recombinant E. coli

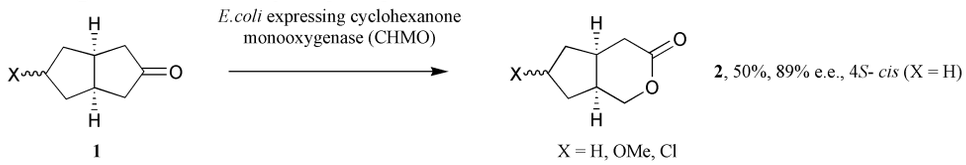


M. D. Mihovilovic, B. Müller, M. M. Kayser and P. Stanetty, *Synlett*, 2002, 700.

Prochiral ketones **1** and **3** were oxidised to chiral lactones **2** and **4** respectively using *E. coli* expressing cyclopentanone monooxygenase from *Pseudomonas* sp. Another strain of *E. coli* expressing the widely used cyclohexanone monooxygenase from *Acinetobacter* sp. gave lactones of low optical purity.

Baeyer-Villiger oxidation of bicyclic [3.3.0] ketones

Recombinant E. coli



1

X = H, OMe, Cl

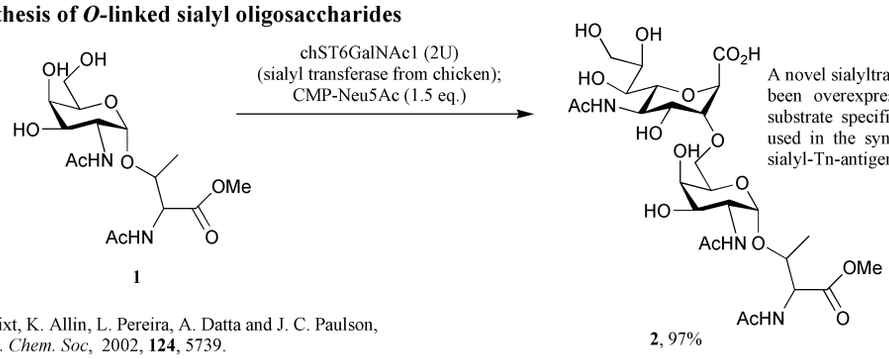
X = H, OMe, Cl

M. D. Mihovilovic, B. Muller, M. M. Kayser, J. D. Stewart and P. Stanetty, *Synlett*, 2002, 703.

Prochiral bicyclic [3.3.0] series ketones **1** were oxygenated to lactones **2** using a recombinant strain of *E. coli* expressing cyclohexanone monooxygenase from *Acinetobacter calcoaceticus* NCIMB 9871. Where X = MeO, addition of cyclodextrin was necesary to achieve acceptable levels of bioconversion. The stereochemistry at the subsituent position X influenced the enantioselectivity of CHMO *e.g. exo* chloro and methoxy ketones were oxidised with excellent enantioselectivities compared to their *endo* analogs.

Synthesis of *O*-linked sialyl oligosaccharides

Sialyltransferase



1

O. Blixt, K. Allin, L. Pereira, A. Datta and J. C. Paulson, *J. Am. Chem. Soc*, 2002, **124**, 5739.

A novel sialyltransferase from chicken, chSTGalNac1, has been overexpressed and detailed studies made on its substrate specificity. In addition, the enzyme has been used in the synthesis of all four possible sialyl-T- and sialyl-Tn-antigens including **2**.