Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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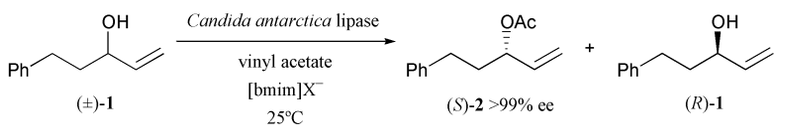
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

Enantioselective acylation in an ionic liquid solvent system

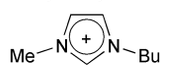
Lipase



(±)-**1** (*S*)-**2** >99% ee (*R*)-**1**

solvent	time/h	yield 2	rate	*E*
$bmimPF_6$	5	45	9.4	>580
$bmimBF_4$	3.5	44	14	>640
iPr_2O	3	47	17	>1000

bmim = butylmethylimidazolium

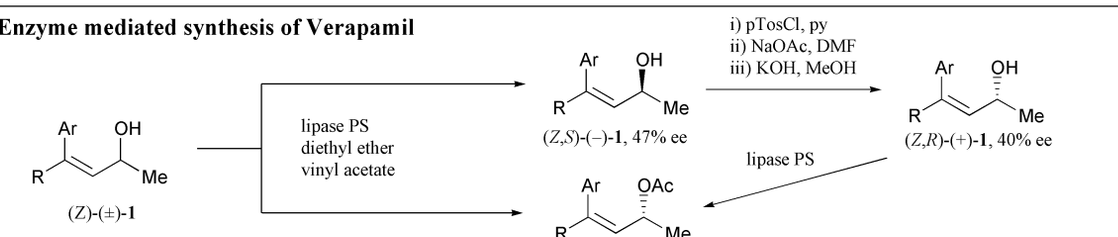


Other enzymes and counter ions were employed without success. $BmimPF_6$ was chosen as the most suitable solvent due to its insolubility in water and ether therefore allowing easy recovery. It was found that the enzyme was anchored in the ionic liquid after work-up facilitating a reasonably efficient enzyme recycling system.

T. Itoh, E. Akasaki, K. Kudo and S. Shirakami, *Chem. Lett.*, 2001, 262.

Enzyme mediated synthesis of Verapamil

Lipase



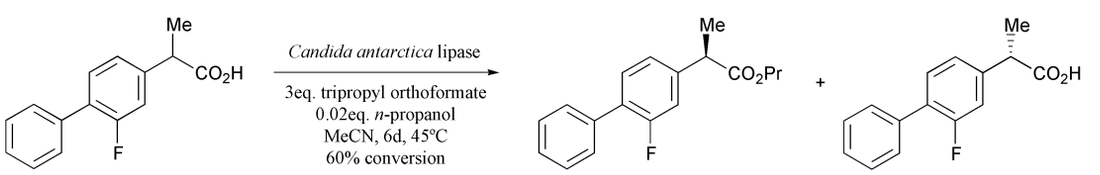
Ar = 3,4-dimethoxyphenyl
R = isopropyl

Compound **2** was used to synthesise both enantiomers of the title compound.

E. Brenna, C. Fuganti, P. Grasselli and S. Serra, *Eur. J. Org. Chem.*, 2001, 1349.

Irreversible lipase catalysed esterification in organic solvents

Lipase



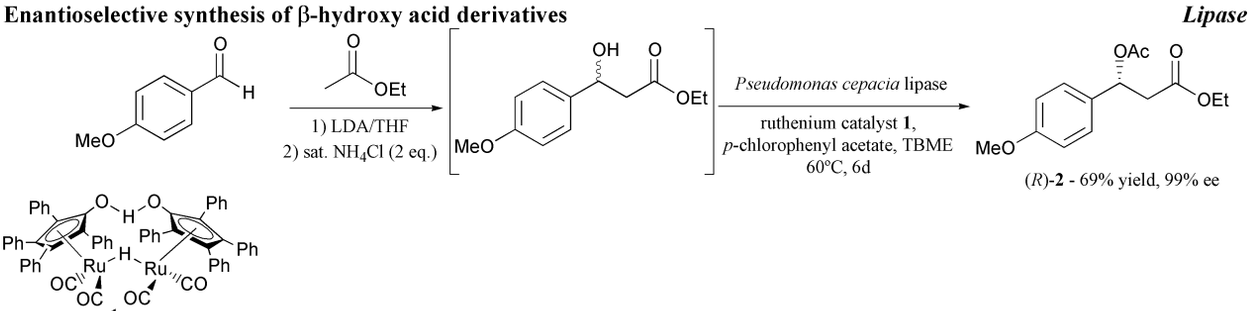
(±)-**1** (*R*)-**2**, 58%, 64% ee (*S*)-**1**, 39%, >98% ee

Hydrolysis of the orthoformate by the water produced in the esterification effectively stops the backwards reaction, and provides the nucleophile for the forward reaction. The new system was also effectively employed in the resolution of (*RS*)-2-methylvaleric acid.

R. Morrone, M. Piattelli and G. Nicolosi, *Eur. J. Org. Chem.*, 2001, 1441.

Enantioselective synthesis of β-hydroxy acid derivatives

Lipase



(*R*)-**2** - 69% yield, 99% ee

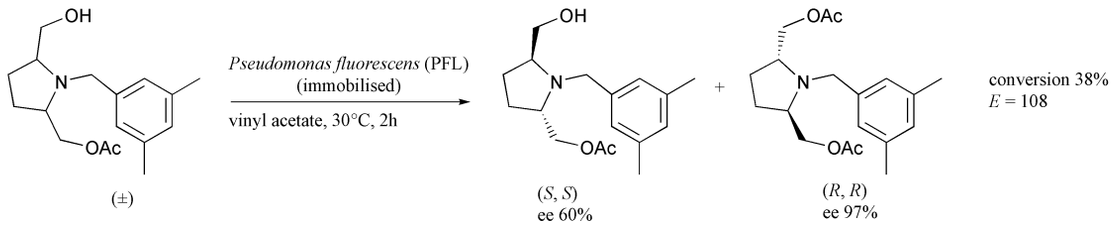
1

Dynamic kinetic resolution was combined with an aldol reaction to produce (*R*)-**2** in a one-pot procedure.

F. F. Huerta and J.-E. Bäckvall, *Org. Lett.*, 2001, **3**, 1209.

Substituent effect on resolution of *trans*-2,5-disubstituted pyrrolidines

Lipase

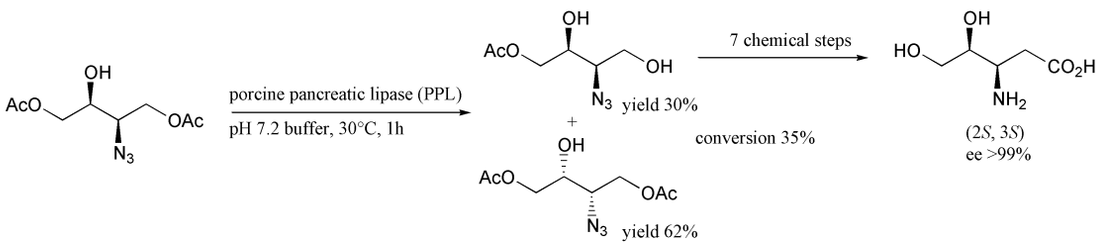


Various other substitution patterns around the aromatic ring, including 0 and 1 methyl groups were studied, for various enzymes. Highest enantioselectivities were observed for the substrate with the 3,5-dimethylbenzyl group. Further studies using this and 4 immobilised lipases revealed that PFL immobilised in sol-gel-AK resulted in the highest enantioselectivity.

Y. Kawanami, N. Iizuna, K. Maekawa, K. Maekawa, N. Takahashi and T. Kawada, *Tetrahedron*, 2001, **57**, 3349.

Synthesis of enantiomerically pure (2*S*,3*R*)-3-azido-2,4-dihydroxybutyl acetate

Lipase

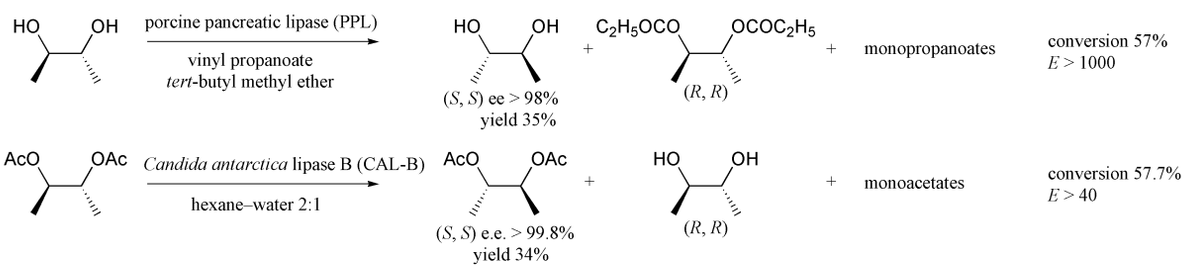


The *syn* enzyme substrate was obtained in 3 chemical steps from *cis*-butene-1,4-diol. The final product, (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid is an important synthetic intermediate in the syntheisis of antibiotics and phytosiderophores.

N. W. Fadnavis, M. Sharfuddin and S. K. Vadivel, *Tetrahedron: Asymmetry*, 2001, **12**, 691.

Resolution of butane-2,3-diol

Lipase

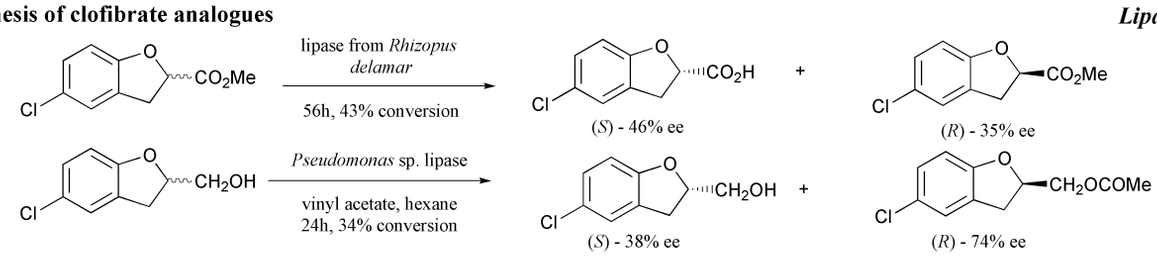


The *meso*-diol was converted to the *d,l*-diol by an epimerisation reaction in a ratio of >99.5:<0.5 after recrystallisation. Other lipases were tested for suitability, and those shown deemed to be most effective.

R. Liu and H.-E. Högberg, *Tetrahedron: Asymmetry*, 2001, **12**, 771.

Synthesis of clofibrate analogues

Lipase

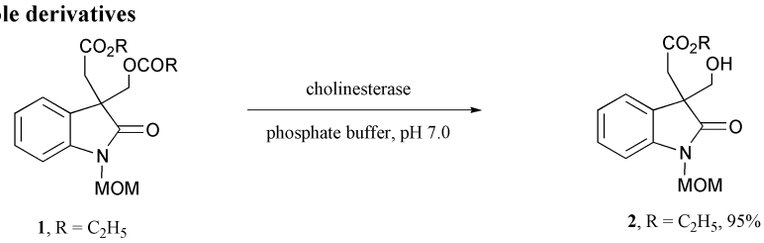


An extensive study into the enzymatic hydrolysis, transesterification and acylation of a series of rigid clofibrate analogues was reported (examples shown). Highest *E* value for resolutions was 4.5.

S. Ferorelli, C. Franchini, F. Loiodice, M. G. Perrone, A. Scilimati, M. S. Sinicropi, and P. Tortorella, *Tetrahedron: Asymmetry*, 2001, **12**, 853.

Hydrolysis of oxindole derivatives

Lipase



1, R = C_2H_5

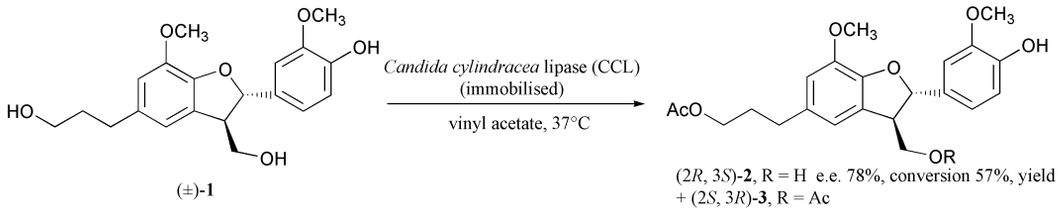
2, R = C_2H_5, 95% ee

Four enzymes were assessed for the transformation of analogues of **1** where R = Me, Et, *n*-Pr, *n*-Bu and Ph. Cholinesterase catalysed the transformation of **1** (R = Et) in 38% yield to give (+)- **2** with an ee of 95%.

K. Nakazawa, M. Hayashi, M. Tanaka, M. Aso and H. Suemune, *Tetrahedron: Asymmetry*, 2001, **12**, 897.

Resolution of a dihydrobenzofuran-type neolignan

Lipase



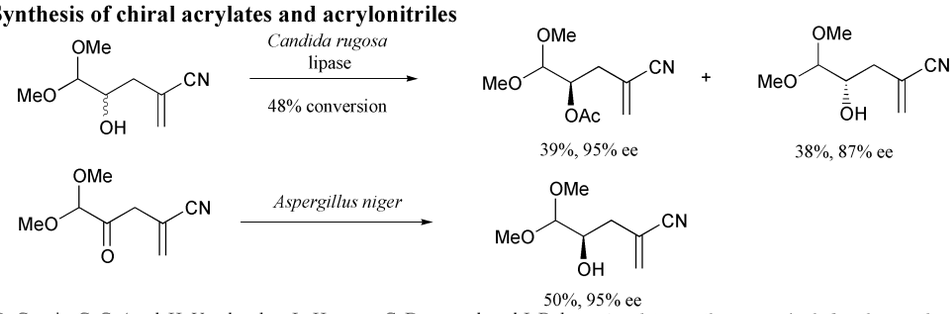
(2*R*, 3*S*)-**2**, R = H e.e. 78%, conversion 57%, yield 38%
+ (2*S*, 3*R*)-**3**, R = Ac

Various other lipases were also tested for suitability. The diacetylated species was only observed for *Candida* lipases, with a fast non enantioselective first acetylation, followed by a slow moderately enantiospecific second acetylation. Ees as high as 61% were observed for the product species (**2**, or **3**, depending on the lipase type), *via* reactions with lower conversion.

S. M. O. Van Dyck, G. L. F. Lemière, T. H. M. Jonckers, R. Dommisse, L. Pieters and V. Buss, *Tetrahedron*: *Asymmetry*, 2001, **12**, 785.

Synthesis of chiral acrylates and acrylonitriles

Lipase/Aspergillus niger

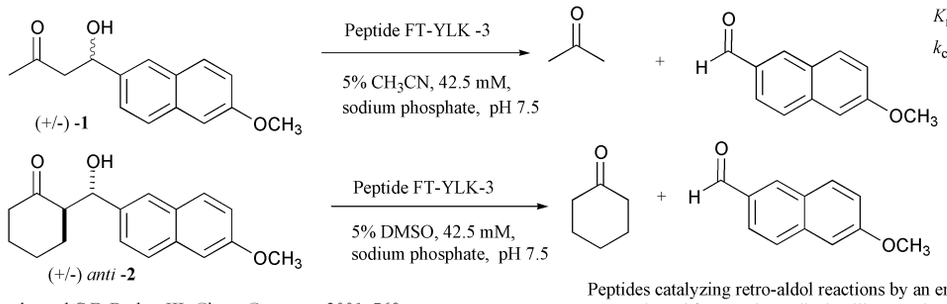


D. Crestia, C. Guérard, H. Veschambre, L. Hecquet, C. Demuynck and J. Bolte, *Tetrahedron: Asymmetry*, 2001, **12**, 869.

Acrylate synthons required for the synthesis of 3-deoxy-2-ulusonic acid were prepared using either lipase-catalysed esterification or whole cell reduction as shown.

Phage display selection of peptides possessing aldolase activity

Aldolase



K_m = 1.8mM, k_{cat}= 5.6x10^{-4} min^{-1},
k_{cat}/k_{uncat} = 1400

FT-YLK-3 = YKLLKELLAKLKWL LRKLLGPTCL-NH$_2$

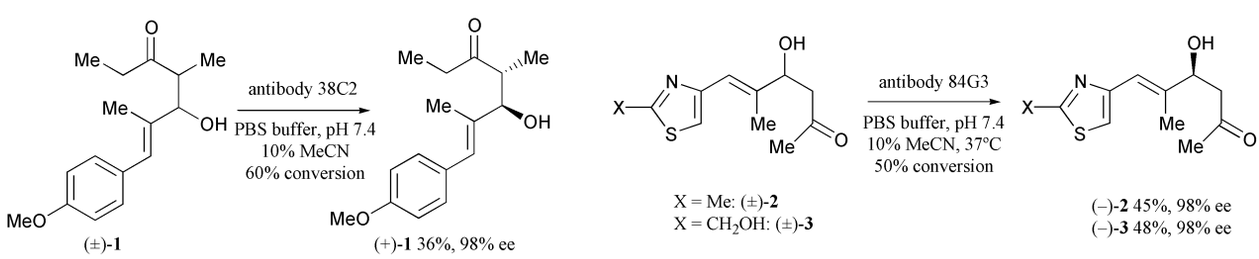
K_m = 1.1mM, k_{cat}= 1.2x10^{-3} min^{-1},
k_{cat}/k_{uncat} = 500

Peptides catalyzing retro-aldol reactions by an enamine-based reaction mechanism were selected from a phage display library using 1,3-diketones.

F. Tanaka and C.F. Barbas III, *Chem. Commun.*, 2001, 769.

Catalytic antibody route to naturally occurring epothilones

Aldolase antibodies

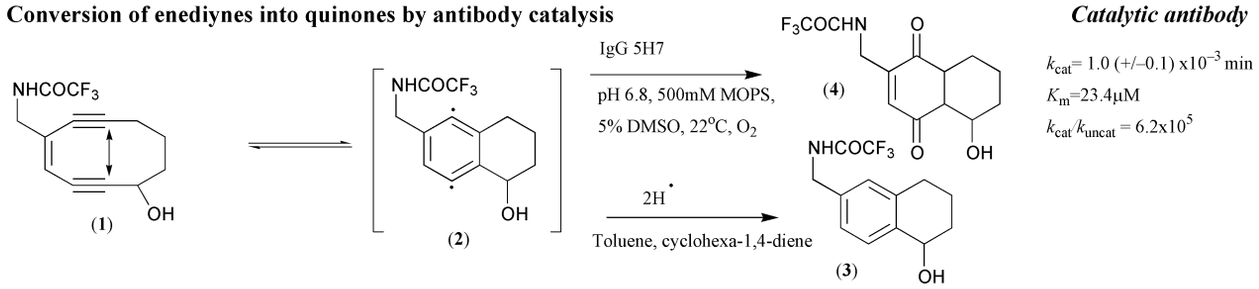


S. C. Sinha, J. Sun, G. P. Miller, M. Wartmann and R. A. Lerner, *Chem. Eur. J.*, 2001, **7**, 1691.

Compounds **1-3** prepared by aldolase antibody catalysed resolution, were used as enantiopure starting materials in the synthesis of epothilones A–F.

Conversion of enediynes into quinones by antibody catalysis

Catalytic antibody



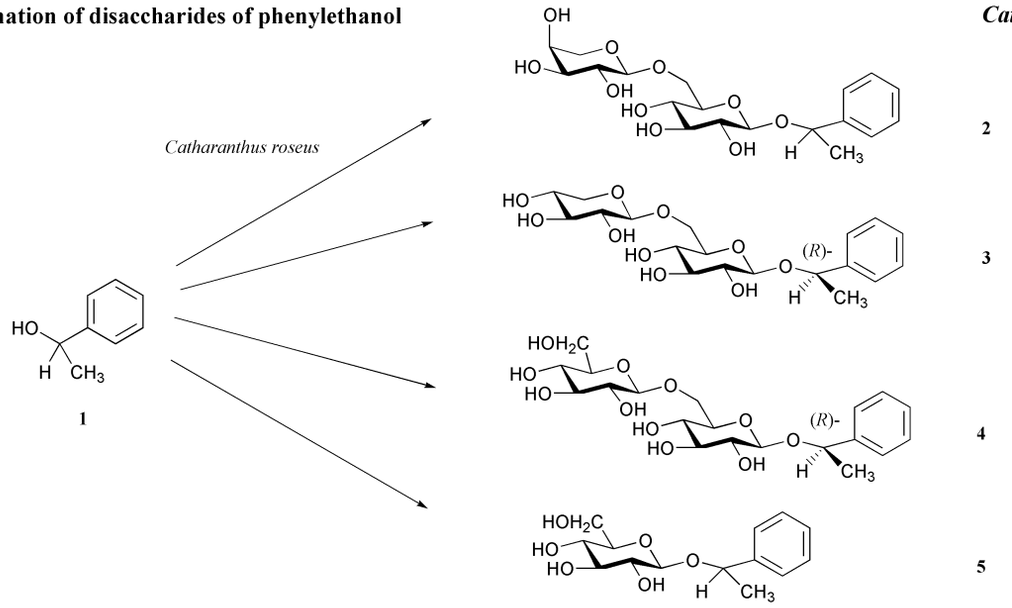
k_{cat}= 1.0 (+/–0.1) x10^{-3} min
K_m=23.4μM
k_{cat}/k_{uncat} = 6.2x10^5

L. H. Jones, C. W. Harwig, P. Wentworth, Jr., A. Simeonov, A. D. Wentworth, S. Py, J. A. Ashley, R. A. Lerner and K. D. Janda, *J. Am. Chem. Soc.*, 2001, **123**, 3607.

In toluene (with cyclohexa-1,4-diene), enediynol (**1**) cycloaromatizes to give tetralin (**3**). However, in aqueous buffer quinone (**4**) was formed. Two antibodies 5H7 and 3H3 significantly enhanced the observed rate of formation of (**4**).

Formation of disaccharides of phenylethanol

Catharanthus roseus

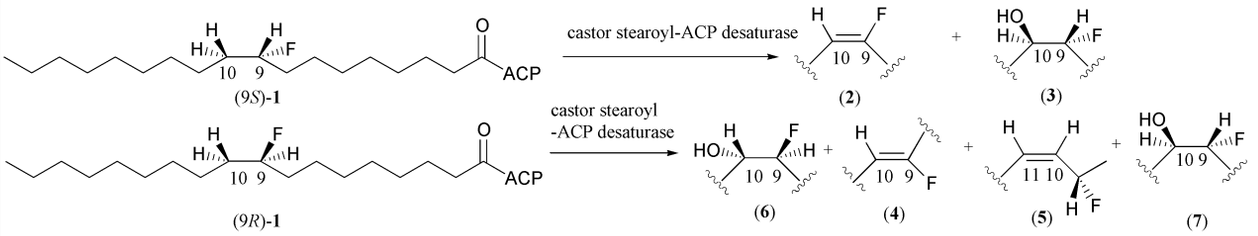


T. Hirata, K. Shimoda, T. Fujino, S. Yamune and S. Ohta, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 539.

The biotransformation of (*R*,*S*)-**1** by *Catharanthus roseus* gave disaccharides vicianoside **2**, primeveroside **3** and gentiobioside **4** *via* the corresponding glucoside **5**. **3** and **4** consisted only of (*R*)-phenylethanol in the aglycone moiety, indicating a measure of diastereoselectivity in the second reaction.

Desaturation of (*S*) and (*R*)-9-fluorostearoyl-ACP

Desaturase

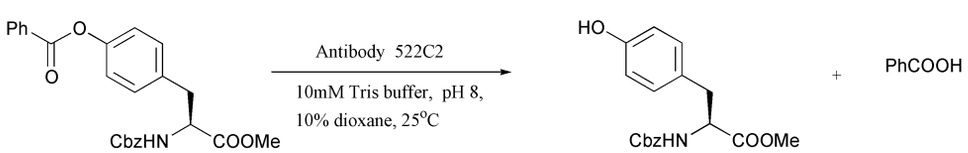


B. Behrouzain, B. Dawson, P. H. Buist and J. Shanklin, *Chem. Commun.*, 2001, 765.

The major product formed in the desaturation of (9*S*)-**1** was, after reductive workup, (*E*)-9-fluorooctadec-9-en-1-ol (**2**) accompanied by a small amount of *threo*-9,10-fluorohydrin (**3**). Desaturation of (9*R*)-**1** yielded two major fluorinated olefinic products (**4**) and (**5**) and a mixture of stereoisomeric hydroxylated products, *threo*-(**6**) and *erythro*-9,10-fluorohydrin (**7**).

Antibody catalysed hydrolysis of tyrosine benzoate

Esterase

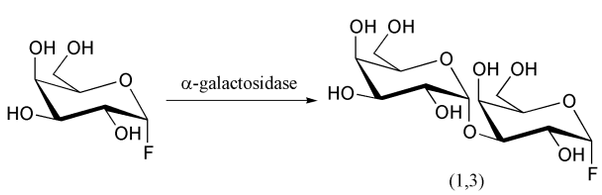


F. Benedetti, F. Berti, A. Colombatti, M. Flego, L. Gardossi, P. Linda and S. Peressini, *Chem. Commun.*, 2001, 715.

Antibody 522C2 is highly specific for the *S*-enantiomer of tyrosine benzoate and also displays activity against *p*-nitrophenyl benzoates and dipeptides containing tyrosine benzoate.

Studies into the self-condensation of some α-D-aldohexopyranosyl fluorides

Glycosidase

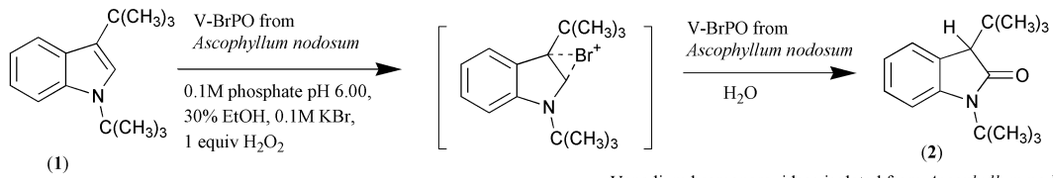


C. André, P. Spangenberg, E. Gentil and C. Rabiller, *Tetrahedron: Asymmetry*, 2001, **12**, 779.

The enzymatic self-condensation reactions of some α-D-aldohexopyranosyl fluorides were studied using ^{19}F NMR. In addition to α-galactosidase from green coffee beans, α-galactosidase Aga B from *Bacillus stearothermophilus* was tested and in both cases the (1,3) and (1,6) isomers were the major product with traces of the (1,2) product also observed. The study was also performed using α-D-glucopyranosyl fluoride, with α-glucosidase from *Saccharomyces cerevisiae*. The production of self-condensation disaccharides was found to be reduced compared to similar reactions using 4-nitrophenyl-α-galactoside.

Regiospecificity of vanadium bromoperoxidase

Haloperoxidase

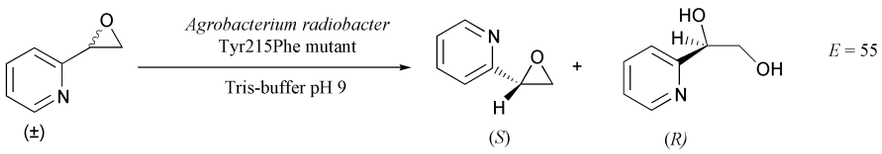


J. S. Martinez, G. L. Carroll, R. A. Tschirret-Guth, G. Altenhoff, R. D. Little and A. Butler, *J. Am. Chem. Soc.*, 2001, **123**, 3289.

Vanadium bromoperoxidase isolated from *Ascophyllum nodosum* or *Corallina officinalis* catalyses the regiospecific oxidation of (**1**) to produce the unbrominated product (**2**), in near quantitative yield. By contrast, the reaction with controlled addition of aqueous bromine produces three monobromo and one dibromoindolin-2-one products.

Enantioselective biohydrolysis of 2-, 3- and 4-pyridyloxirane

Hydrolase

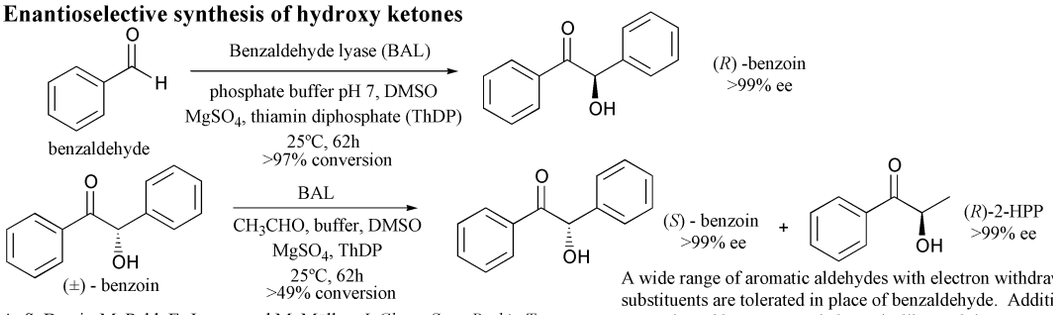


Y. Genzel, A. Archelas, J. H. L. Spelberg, D. B. Janssen and R. Furstoss, *Tetrahedron*, 2001, **57**, 2775.

Epoxide hydrolases from *A. radiobacter* AD1 wild type and its Tyr215Phe mutant were compared. The regioselectivity of the oxirane ring opening, the substrate concentration limit and the inhibitory effect of the diol were studied.

Enantioselective synthesis of hydroxy ketones

Lyase

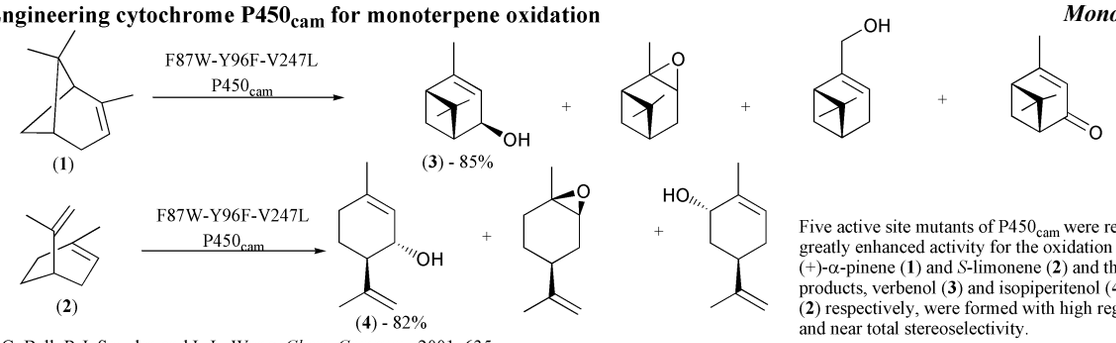


A. S. Demir, M. Pohl, E. Janzen and M. Müller, *J. Chem. Soc., Perkin Trans. 1*, 2001, 633.

A wide range of aromatic aldehydes with electron withdrawing and releasing substituents are tolerated in place of benzaldehyde. Additionally, different aromatic and heteroaromatic benzoin-like acyloins are accepted for resolution *via* C–C bond cleavage.

Engineering cytochrome $P450_{cam}$ for monoterpene oxidation

Monooxygenase

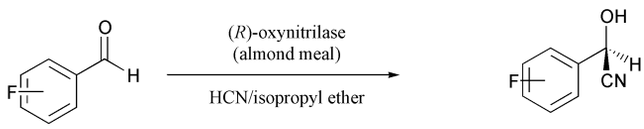


S.G. Bell, R.J. Sowden and L-L. Wong, *Chem. Commun.*, 2001, 635.

Five active site mutants of $P450_{cam}$ were reported to have greatly enhanced activity for the oxidation of (+)-α-pinene (**1**) and *S*-limonene (**2**) and the major products, verbenol (**3**) and isopiperitenol (**4**) from (**1**) and (**2**) respectively, were formed with high regioselectivity and near total stereoselectivity.

Synthesis of fluorinated mandelonitriles

Oxynitrilase

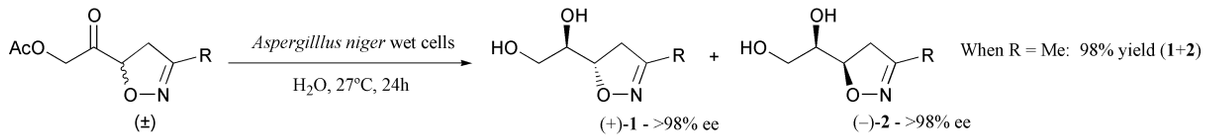


S. Han, P. Chen, G. Lin, H. Huang and Z. Li, *Tetrahedron: Asymmetry*, 2001, **12**, 843.

A series of fluorinated aromatic aldehydes were assessed as substrates for oxynitrilase from almonds. The *para*-fluoro derivative was obtained in 90% yield and 94% ee Ee's were lower for *para* and *ortho* substitutions or difluorinated aldehydes. Racemic products were obtained for polyfluorinated aldehydes.

Microbial reduction of 5-acylisoxazolines

Reductase

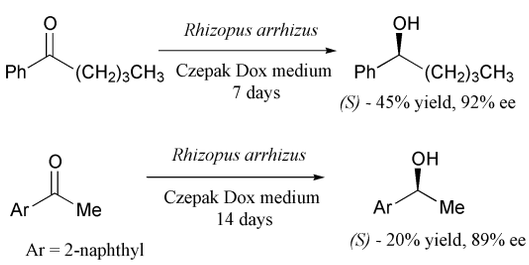


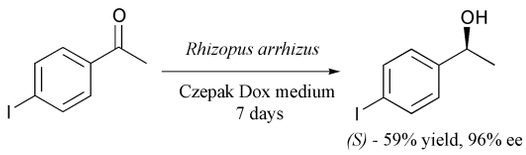
T. Gefflaut, C. Martin, S. Delor, P. Besse, H. Veschambre and J. Bolte, *J. Org. Chem.*, 2001, **66**, 2296.

Other R substituents were screened with similar yields and enantioselectivities.

Enantioselective reduction of arylalkanones

Reductase



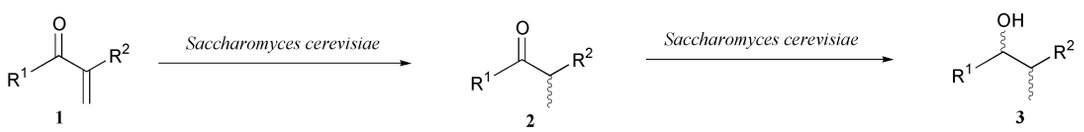


N. A. Salvi and S. Chattopadhyay, *Tetrahedron*, 2001, **57**, 2833.

The effect of substitution on the biotransformation of various arylalkanones was investigated. Increasing the size of the groups flanking the carbonyl function and the electron withdrawing capacity of the substituents in the aromatic ring improved the enantioselectivity of the reaction.

Reduction of α-methylene ketones

Saccharomyces cerevisiae

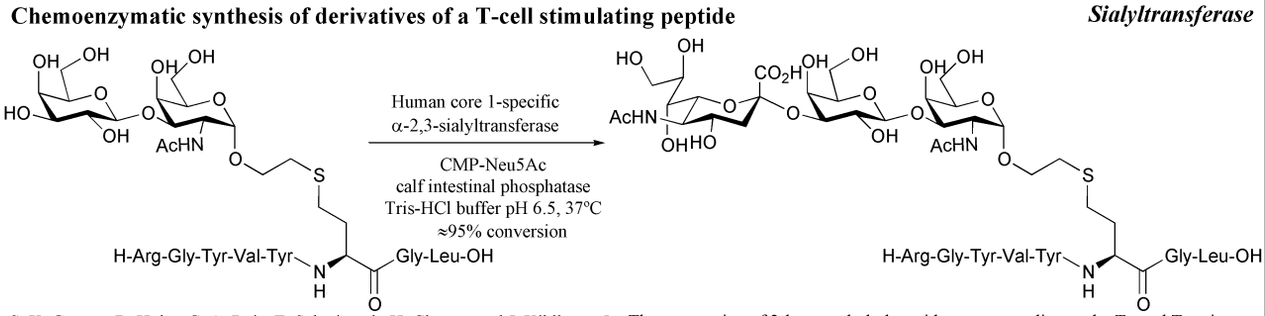


E. P .S. Filho, J. A. R Rodrigues and P. J. S. Moran, *Tetrahedron: Asymmetry*, 2001, **12**, 847.

α-Methylene ketones **1** where R^1 = Me; R^2 = alkyl/aryl were reduced at the C=C bond within 2h to yield (*R*)-α-methyl ketones with ee's of 88-99%. When incubated for a period of days, reduction to the α-methylalcohols was observed, with good de's when R^1 = Me.

Chemoenzymatic synthesis of derivatives of a T-cell stimulating peptide

Sialyltransferase

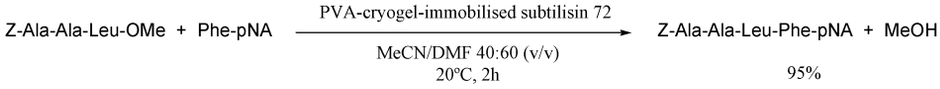


S. K. George, B. Holm, C. A. Reis, T. Schwientek, H. Clausen and J. Kihlberg, *J. Chem. Soc., Perkin Trans. 1*, 2001, 880.

The preparation of 2-bromoethyl glycosides corresponding to the Tn and T antigens starting from *N*-acetylgalactosamine is described.

Peptide synthesis in organic media

Subtilisin



A. V. Bacheva, F. M. Plieva, E. N. Lysogorskaya, I. Y. Filippova and V. I. Lozinsky, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1005.

Yield of peptide diminished at higher DMF concentrations. The immobilised subtilisin was an efficient catalyst for the peptide synthesis over at least three cycles, indicating a reserve of water in the cryoPVAG supramolecular matrix.
The immobilised subtilisin was also shown to accept tripeptides with a free carboxy group as the acyl donor, as well as tripeptides with non-protected C-terminal basic and acidic amino acid residues.