PERKIN 1 ABSTRACTS

Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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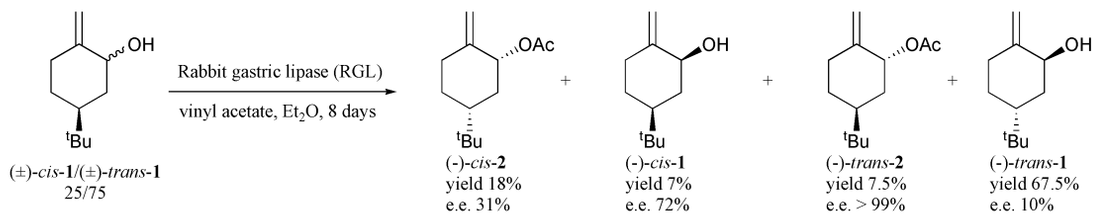
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

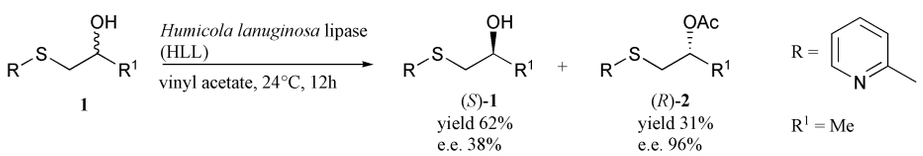
Resolution of diastereomeric mixtures of 2-methylene-5-*tert*-butylcyclohexanols ***Lipase***



Initial experiments used pure *cis*- or *trans*- substrates and the difference in rate of conversion suggested that the acylation may be diastereoselective. The enantioenriched *trans*-**2** was readily separated from the unreacted alcohols and *cis*-**2**. The corresponding hydrolysis experiments were also carried out and the mixture of racemic *cis*-**2** and *trans*-**2** afforded (+)-*cis*-**1** in 26% yield and 94% e.e.

C. Bidjou, L. Aribi-Zouioueche and J.-C Fiaud, *Tetrahedron Lett.*, 2002, **43**, 3025.

Resolution of heteroaryl β-hydroxy sulfides ***Lipase***

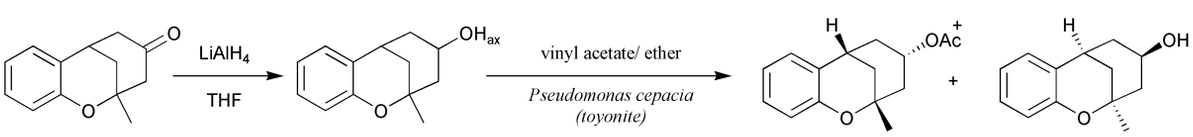


conversion 33%
E = 71

The conversion, and therefore product e.e.'s could be tailored by varying reaction time. Other heteroaryl β-hydroxy sulfides (variations in R and R^1) were tested and enantiomeric ratios found to range from 14 to 71.

S. S. Chimni, S. Singh, S. Kumar and S. Mahajan, *Tetrahedron: Asymmetry*, 2002, **13**, 511.

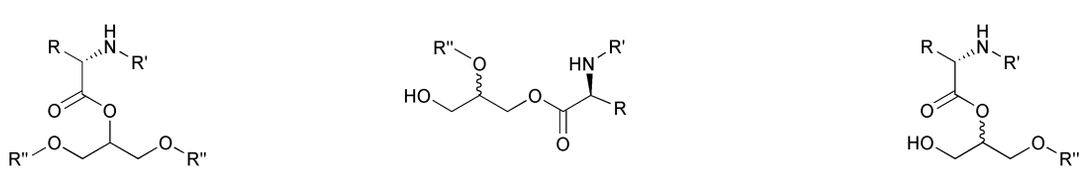
Resolution of 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocine derivatives ***Lipase***



Chemical resolutions of 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4-one have been performed with the configurational assignment by X-ray analysis and chemical correlation of its ketal synthesised with (2*R*, 3*R*)-butane-2,3-diol. Kinetic resolution of the hydroxy derivative was carried out by lipase from *Pseudomonas cepacia*.

T. Kurtán, E. Baitz-Gács, Z. Májer, A. Bényei and S. Antus, *J. Chem. Soc., Perkin Trans. 1*, 2002, 888.

Lipase catalysed resolution of glycerol derivatives ***Lipase***

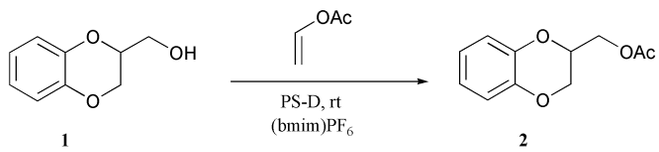


Lipase catalysed esterification of one or two hydroxy groups of amino acid glyceryl ester derivatives by lauric acid produced mono- and dilauroylated amino acid glyceride conjugates. The reaction was carried out in solvent free media with the continuous removal of water.

C. Morán, M. R. Infante and P. Clapés. *J. Chem. Soc., Perkin Trans. 1,* 2002, 1124.

Lipase catalysed transesterification in ionic liquids and organic solvents

Lipase



1 **2**

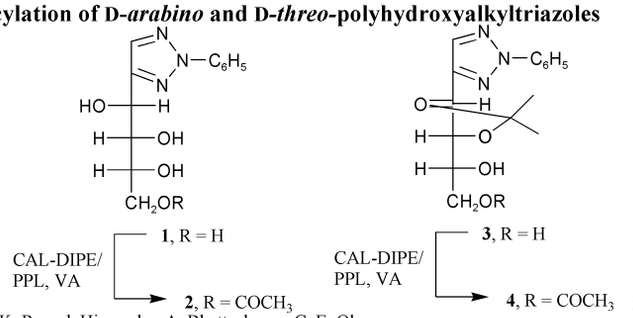
70%

S. J. Nara, J. R. Harjani and M. M. Salunkhe, *Tetrahedron Lett.*, 2002, **43**, 2979.

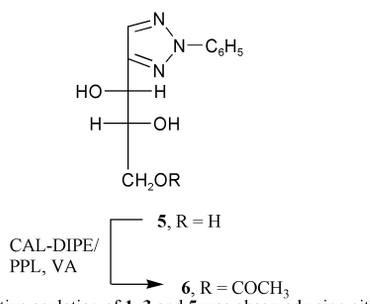
A comparative study of the transesterification of 2-hydroxymethyl-1,4-benzodioxane, **1**, catalysed by a number of lipases in ionic liquids and organic solvents is reported. It was found that ionic liquids act as an alternative, recyclable media for lipase-catalysed transesterification without inhibiting the catalytic activity of the lipase.

Acylation of D-*arabino* and D-*threo*-polyhydroxyalkyltriazoles

Lipase



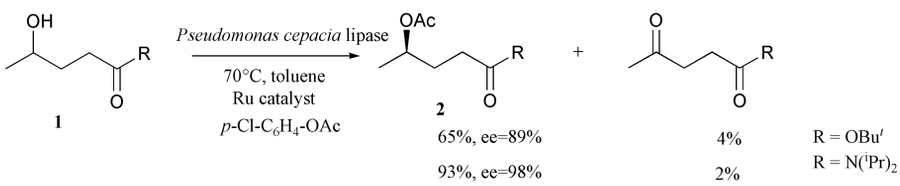
A. K. Prasad, Himanshu, A. Bhattacharya, C. E. Olsen and V. S. Parmar, *Bioorg. Med. Chem.*, 2002, **10**, 947.



Selective acylation of **1**, **3** and **5** was observed using either *Candida antarctica* lipase (CAL) in diisopropyl ether (DIPE) or porcine pancreatic lipase (PPL) using vinyl acetate as acyl donors.

Dynamic kinetic resolution of γ-hydroxy acid derivatives

Lipase

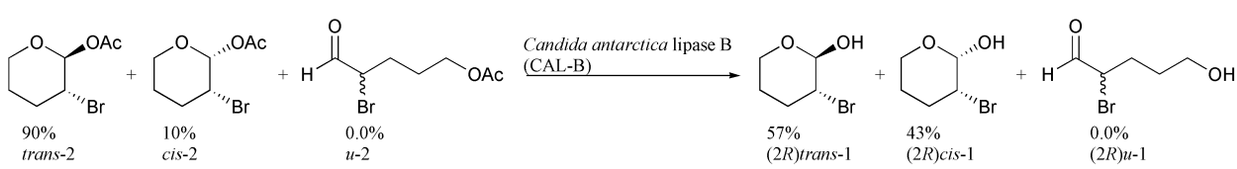


A.-B. L. Runmo, O. Pàmies, K. Faber and J.-E. Bäckvall, *Tetrahedron Lett.*, 2002, **43**, 2983.

The synthesis of enantiomerically enriched γ-hydroxy acid derivatives, such as **2**, in a high yielding, single step reaction, from ruthenium- and enzyme-catalysed dynamic kinetic resolution of substrate **1** is reported.

Resolution and decyclisation of hemiacetals

Lipase

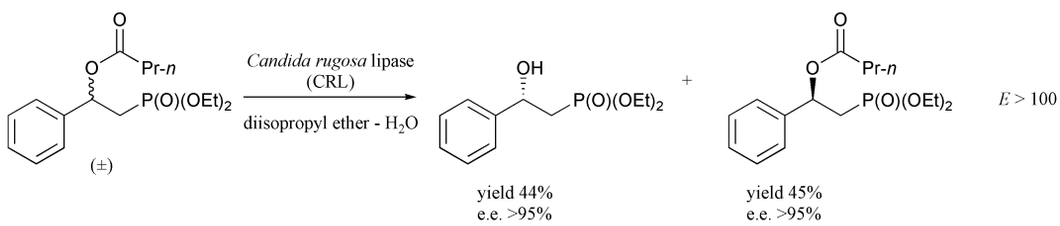


L. Villo, A. Metsala, O. Parve and T. Pehk, *Tetrahedron Lett.*, 2002, **43**, 3203.

The acetate substrates were obtained by reaction of the corresponding alcohols with acetic anhydride. After the resolution, treatment with LiOH and methanol caused only the *trans*- hemiacetal anomer to react, giving *trans*-2-methoxytetrahydropyran-3-ol with 98% optical purity. The furan equivalents were also tested as substrates, and in each case the corresponding enzymatic acetylation was carried out. Acetylation tended to result in decyclisation.

Preparation of optically pure 2-hydroxy-2-arylethanephosphonates

Lipase

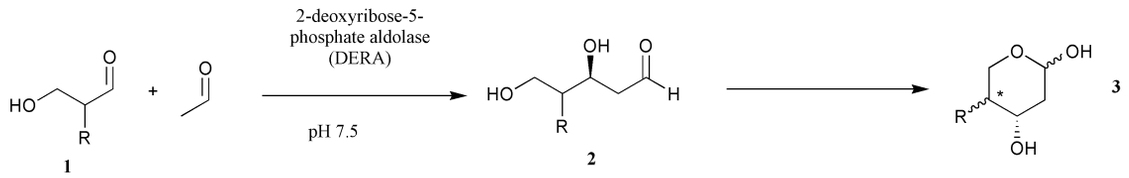


Y. Zhang, Z. Li and C. Yuan, *Tetrahedron Lett.*, 2002, **43**, 3247.

Substrates varying in the aryl group and the ethyl group were tested and similar results observed. Diisopropyl ether equilibrated with 0.5% 1.2 M $MgCl_2$ was found to be the most effective solvent.

Synthesis of novel pyranose synthons

Aldolase

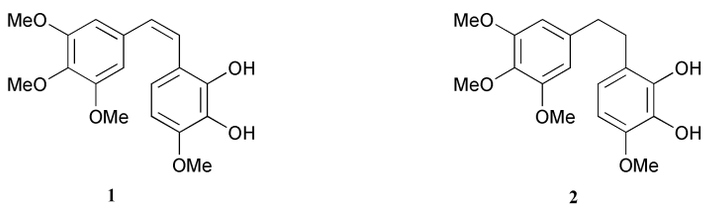


J. Liu and C-H. Wong, *Angew. Chem., Int. Ed.*, 2002, **41**, 1404.

2-Deoxyribose-5-phosphate aldolase (DERA) was used to condense a series of β-hydroxyaldehydes **1** to chiral C5 units **2**. These were then cyclized to form the stable hemiacetals **3**. D isomers were preferred enzyme substrates when R was polar (*e.g.* OH; N_3), but L isomers when R was hydrophobic (R = Me; MeO). 1,3-Polyols **3** could be converted to lactones for further synthetic elaboration.

Biooxidation of arenes to corresponding catechols

Dioxygenase

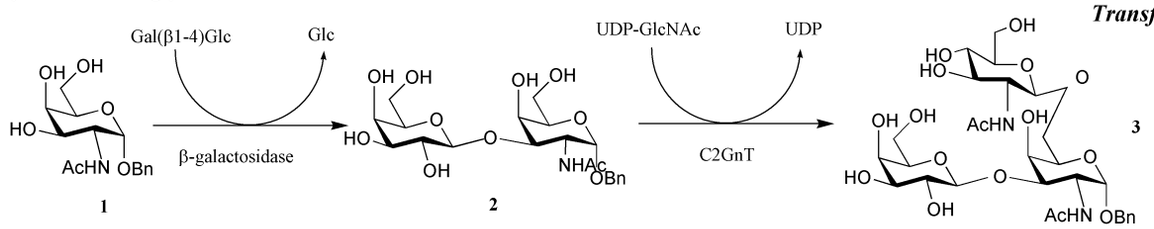


V. P. Bui, T. Hudlicky, T. V. Hansen and Y. Stenstrom, *Tetrahedron Lett.*, 2002, **43**, 2839.

The convergent synthesis of two related combretastatins, **1** and **2**, is reported. This was achieved by coupling biocatalytically generated starting material *p*-bromomethoxycatechol with trimethoxyphenylacetylene.

Synthesis of *O*-glycan core structure

Galactosidase/ Transferase

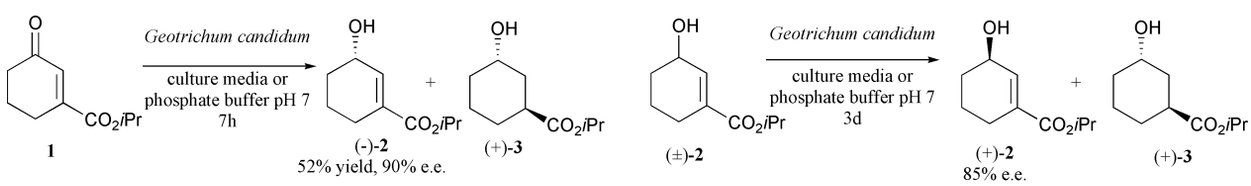


C. Hoh, G. Dudziak and A. Liese, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1031.

A genetic algorithm was developed using the GALOP software to optimise reaction conditions (temperature, pH, [substrate], [enzyme]) for the two-step conversion of GalNac-α1-OBn **1** to the OBn derivative of the Core 2 *O*-glycan **3**. Galactose was transferred to **1** using β-galactosidase to form intermediate **2**, onto which GlcNAc was transferred using C2Gn Transferase.

Chemoenzymatic synthesis of isopropyl (3*R*)- and (3*S*)-3-hydroxycyclohex-1-ene-1-carboxylates

Geotrichum candidum

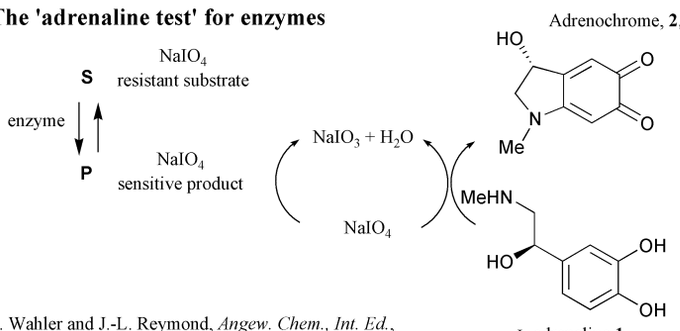


L. Fonteneau, S. Rosa and D. Buisson, *Tetrahedron: Asymmetry*, 2002, **13**, 579.

Subsequent chemical reduction of the double bonds of (-)- and (+)-**2** afforded all isomers of the corresponding cyclohexanols.

The 'adrenaline test' for enzymes

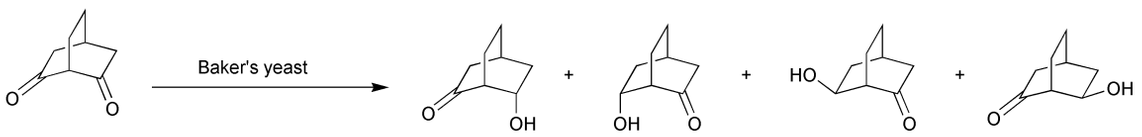
Hydrolases



D. Wahler and J.-L. Reymond, *Angew. Chem., Int. Ed.*, 2002, **41**, 1229.

A new colorimetric assay of enzyme activity based on the quantification of periodate-sensitive reaction products by back-titration was reported. Periodate reacts with enzyme products such as 1,2-diols (epoxide hydrolases, lipases). Any unreacted periodate was assayed by reaction with L-adrenaline **1** to form the red dye adrenochrome **2**. The assay was demonstrated with phytases, lipases and epoxide hydrolases and would be amenable to miniaturisation for high-throughput screening applications.

Stereoselective reduction of bicyclo[2.2.2]octane-2,6-dione *Microbial*

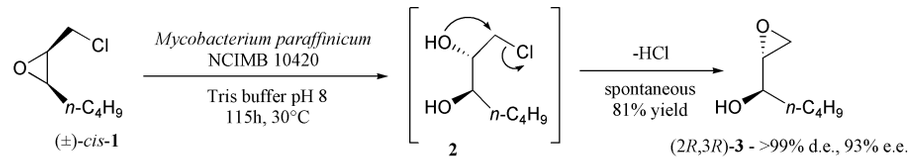


Possible products from mono reduction of the diketone

A. L. Botes, D. Harvig, M. S. van Dyk, I. Sarvary, T. Frejd, M. Katz, B. Hahn-Hägerdal and M. F. Gorwa-Grausland, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1111.

Yeast strains were screened for the enantioselective reduction of bicyclo[2.2.2]-octane-2,6-dione. Reducing activity was found in 80% of the screened yeasts.

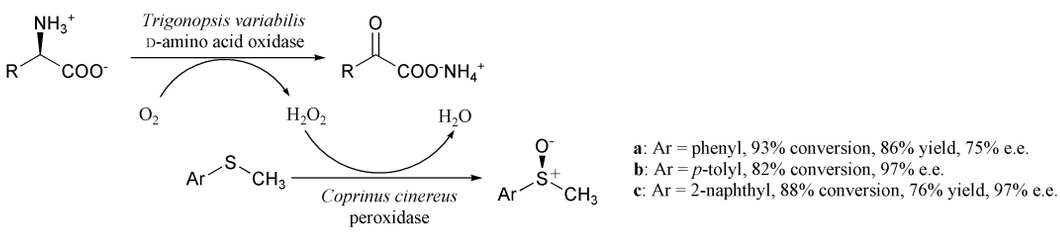
Enantioconvergent enzyme-triggered cascade reaction of chloroalkyloxirane *Mycobacterium paraffinicum*



S. F. Mayer, A. Steinreiber, M. Goriup, R. Saf and K. Faber, *Tetrahedron: Asymmetry*, 2002, **13**, 523.

(2*R*,3*R*)-**3** is an intermediate in the synthesis of a constituent of Jamaican rum and of (+)-Pestalotin.

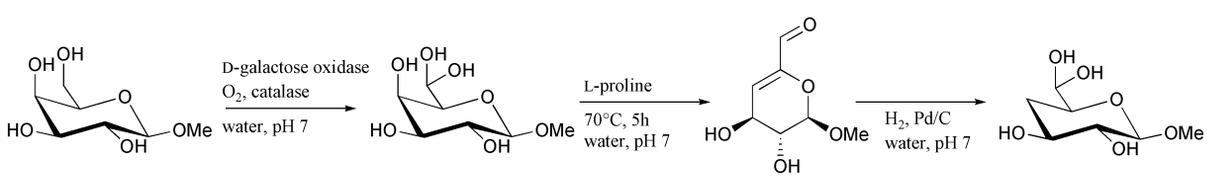
Enantioselective synthesis of sulfoxides *Oxidase*



K.Okrasa, A. Falcimaigne, E. Guibé-Jampel and M. Therisod, *Tetrahedron: Asymmetry*, 2002, **13**, 519.

Various conditions were studied to optimise the bi-enzymatic system including enzyme ratios.

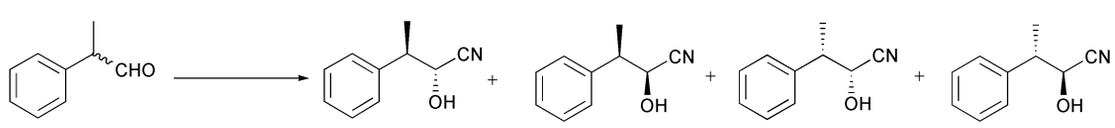
One-pot preparation of 4-deoxy-6-aldehydo-β-D-glucoside from methyl β-D-galactoside *Oxidase*



R. Schoevaart and T. Kieboom, *Tetrahedron Lett.*, 2002, **43**, 3399.

Using three different types of catalyst in sequence, in one pot, the modification of methyl β-D-galactoside into a 4-deoxy-D-glucose derivative was achieved quantitatively

Selectivity of (*S*)-oxynitrilase towards α– and β-substituted aldehydes *Oxynitrilase*



1 **1a,** (2*R*,3*R*) 0.4% **1b**, (2*S*,3*R*) 49.5% **1c**, (2*R*,3*S*) 3.3% **1d**, (2*S*,3*S*) 46.8%

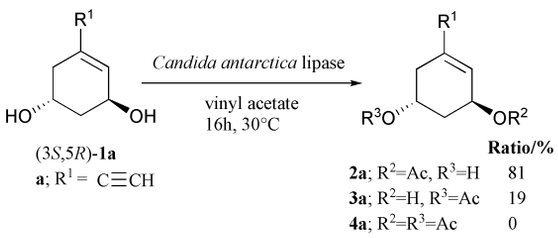
d.e. 3*R* = 98.3% d.e. 3*S* = 86.8%

G. Roda, S. Riva, B. Danieli, H. Griengl, U. Rinner, M. Schmidt and A. M. Zabelinskaja, *Tetrahedron*, 2002, **58**, 2979.

A study on the effect of stereocentres situated close to the carbonyl function in enzyme catalysed cyanuration of alkyl substituted aldehydes is reported. The d.e. of products from these reactions were found to be strongly dependent on the configuration of the stereocentre already existing in the starting molecule.

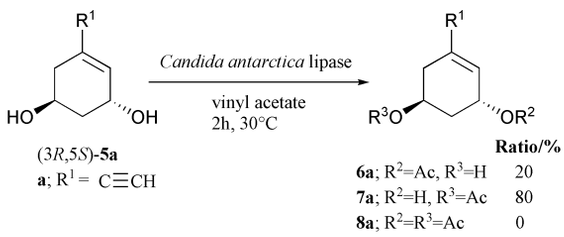
Chemoenzymatic synthesis of 6-*s*-*cis* locked 1α,25-dihydroxyvitamin D_3 analogues

Lipase



(3*S*,5*R*)-**1a**
a; R^1 = C≡CH

	Ratio/%
2a; R^2=Ac, R^3=H	81
3a; R^2=H, R^3=Ac	19
4a; R^2=R^3=Ac	0



(3*R*,5*S*)-**5a**
a; R^1 = C≡CH

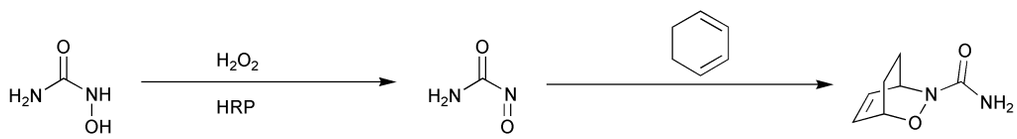
	Ratio/%
6a; R^2=Ac, R^3=H	20
7a; R^2=H, R^3=Ac	80
8a; R^2=R^3=Ac	0

M. Díaz, M. Ferrero, S. Fernández and V. Gotor, *Tetrahedron: Asymmetry*, 2002, **13**, 539.

The opposing selectivity of **1a** and **5a** should be noted; (3*S*,5*R*)-**1a** showed preference for acylation of the C-3 hydroxy group whereas (3*R*,5*S*)-**5a** was acylated at C-5.

Horseradish peroxidase catalyzed nitric oxide formation from hydroxyurea

Peroxidase

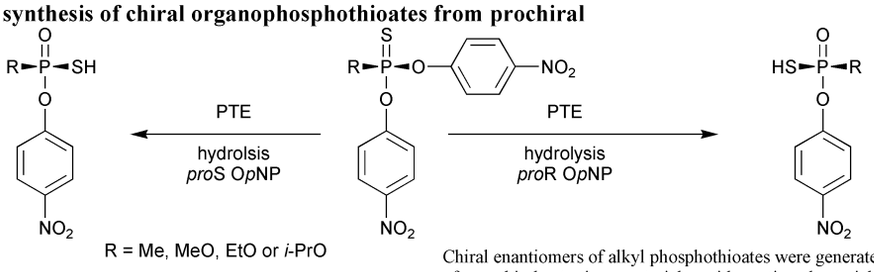


J. Huang, E. M. Sommers, D. B. Kim-Shapiro and S. B. King, *J. Am. Chem. Soc.*, 2002, **124**, 3473.

Horseradish peroxidase catalyses the formation of nitric oxide from hydroxyurea in the presence of hydrogen peroxide. Gas chromatographic and infrared spectroscopy revealed the presence of nitroxyl, the one electron reduced form of nitric oxide. Electron paramagnetic resonance spectroscopy and trapping studies show the intermediacy of a nitroxide radical and a *C*-nitroso species during the reaction.

Enzymatic synthesis of chiral organophosphothioates from prochiral precursors

Phosphotriesterase

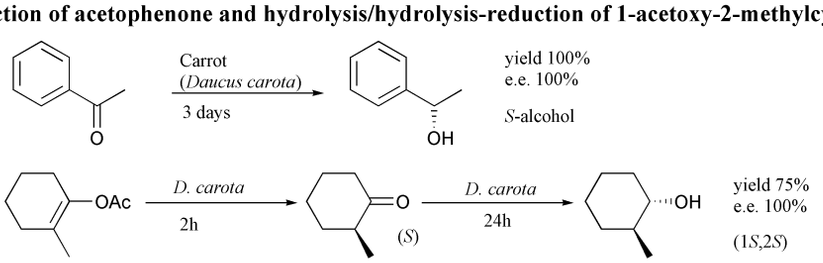


W.-S. Li, Y. Li, C. M. Hill, K. T. Lum and F. M. Raushel, *J. Am. Chem. Soc.*, 2002, **124,** 3498.

Chiral enantiomers of alkyl phosphothioates were generated by the stereoselective hydrolysis of prochiral starting materials with native bacterial phosphotriesterase (PTE) from *Pseudomonas diminuta*. The prochiral selectivity of the PTE wild-type enzyme can be manipulated by specific modifications to the substrate binding domain with the active site of the protein.

Reduction of acetophenone and hydrolysis/hydrolysis-reduction of 1-acetoxy-2-methylcyclohexene

Plant

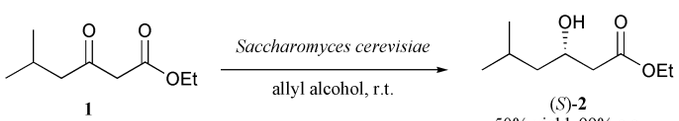


R. Bruni, G. Fantin, A. Medici, P. Pedrini and G. Sacchetti, *Tetrahedron Lett.*, 2002, **43**, 3377.

Other plants screened for the reduction of acetophenone were found to be lower yielding or failed to convert after 5 days. Various plants were screened for the hydrolysis of 1-acetoxy-2-methylcyclohexene, and in some cases the subsequent reduction. Yields were generally high for the hydrolysis. For some plants the *cis*-alcohols were also obtained.

Chemoenzymatic synthesis of (*R*)- and (*S*)-2-methyloctan-4-ol

Saccharomyces cerevisiae



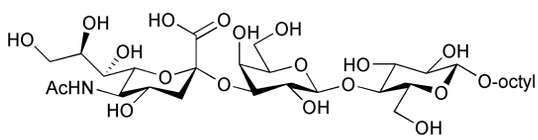
1

(*S*)-**2**
50% yield, 99% e.e.

P. T. Baraldi, P. H. G. Zarbin, P. C. Vieira and A. G. Corrêa, *Tetrahedron: Asymmetry*, 2002, **13**, 621.

Different strains of *S. cerevisiae* and inhibitors were tested to improve the e.e. and yield. (*R*)-**2** was prepared from (*S*)-**2** using Mitsunobu chemistry.

Synthesis of α-2,3-sialylated octyl β-lactoside ***Sialidase***

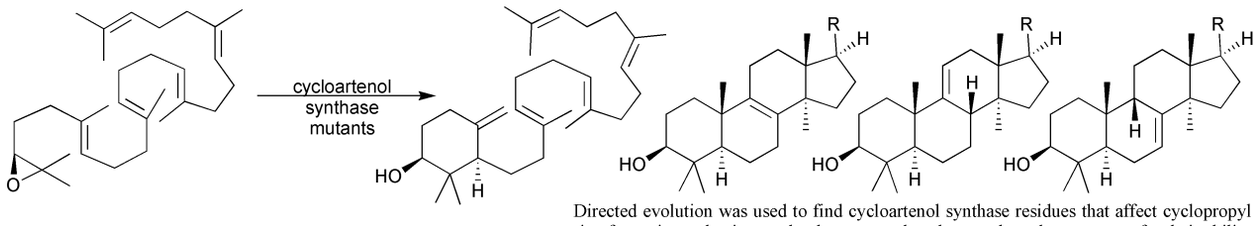


1

A comparison of chemical and chemoenzymatic approaches to the synthesis of α-2,3-sialylated octyl β-lactoside, **1** is reported. Chemoenzymatic synthesis was found to be a far more efficient route, requiring fewer steps, less chromatographic purification and giving a similar yield to a chemical synthesis.

W. B. Turnbull, J. A. Harrison, K. P. R. Kartha, S. Schenkman and R. A. Field, *Tetrahedron*, 2002, **58**, 3207.

Directed evolution to generate cycloartenol synthase mutants that produce lanosterol ***Synthase***



Directed evolution was used to find cycloartenol synthase residues that affect cyclopropyl ring formation, selecting randomly generated cycloartenol synthase mutants for their ability to genetically complement a yeast strain lacking lanosterol synthase. To increase the likelihood of finding novel mutants, *Dictyostelium discoideum* cycloartenol synthase was used for the mutagenesis.

M. M. Meyer, R. Xu and S. P. T. Matsuda, *Org. Lett.*, 2002, **4**, 1395.