Preparative biotransformations

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1 Introduction and background information

This Review summarizes novel, preparatively useful biotransformations that have featured in a wide cross-section of organic chemistry Journals[1] and some specialist periodicals[2] during 1997. Specifically excluded from this Review are papers dealing with enzyme mechanisms and those reporting studies on enzyme inhibition.

There were more than 300 relevant papers in the above-mentioned Journals. The most popular areas of study involved hydrolysis reactions (25% of total), mainly ester hydrolysis, and esterification reactions (23%). Enzyme-catalysed amide formation has been a less popular area of study (5%). Reduction reactions, largely the reduction of ketones, accounted for 13% of the total; a similar fraction described a range of oxidation reactions (12.5%). Carbon–carbon bond formation (5%) and the use of catalytic antibodies and other enzyme mimetics (6%) represent small but significant areas of investigation. One noteworthy area of growth over the past year has been the enzymatic synthesis of complex carbohydrates and surrogates (10% of total), with workers taking advantage of the increased availability of key enzymes. In this document attention has been paid to reporting preparative yields and the optical purity of products whenever possible.

Several interesting reviews were published in 1997. Stecher and Faber described biocatalysed deracemization techniques, including dynamic resolutions and stereoinversions[3] (in a complementary review Somfai details non-enzymatic methods for the resolution of secondary alcohols).[4] An up-to-date survey of lipases was published[5] and the use of enzymes for the synthesis of amino acids, peptides and carbohydrates has been described.[6] The effect of the incorporation of one or more fluorine atoms into substrates for enzyme-catalysed reactions has been discussed.[7] Sheldon and co-workers have reviewed the current use of peroxidases[8] while Griengl *et al*. summarized the present knowledge concerning the formation and cleavage of cyanohydrins.[9] The asymmetric protonation of enols as well as the asymmetric decarboxylation of α-aryl-α-methylmalonic acids and related reactions have been the topics of another survey.[10]

2 Hydrolysis reactions

2.1 Ester hydrolysis

The advantage of using enzyme-removable blocking groups in phosphopeptide chemistry is clearly advantageous. For example *Aspergillus niger* lipase-catalysed cleavage of heptyl esters under mild conditions (pH 7, 37 °C, phosphate buffer, acetone) has been employed in the preparation of sensitive, base labile serine/threonine phosphopeptides.[11,12] 2-Methoxyethyl esters have been recommended for the protection of peptides and glycopeptides since the 2-methoxyethanol moiety is easily removed under mild conditions using lipase A6 (again from *Aspergillus niger*) or lipase N (from *Rhizopus niveus*).[13] Regioselective hydrolyses of saturated acyclic esters in the presence of α,β-unsaturated or cyclopropane carboxylates has been achieved using pig liver esterase (ple). The weaker binding of the latter species was explained using the Jones model.[14]

The kinetic resolution of esters of the type $R^1CH(R^2)CO_2R^3$ is a standard procedure of biocatalysis. Examples published in 1997 include those illustrated in Table 1. The ester unit undergoing hydrolysis may also be attached to a ring system as illustrated in Scheme 1. Enantioselective hydrolysis of esters with the chiral centre at the β-position are also successful. For example ethyl (±)-6-benzyloxy-3-hydroxyhexanoate was resolved in a synthetic route to (−)-cassine.[23] The optically active ester **1** was obtained from the racemate using the protease from *Aspergillus oryzae*.[24]

The use of enzymes for the stereoselective hydrolysis of *meso* and prochiral diesters is popular methodology in synthetic organic chemistry and a couple of new results using prochiral compounds are given in Scheme 2. For mixed diesters of type **2**, lipase AK in methyl *tert*-butyl ether containing methanol is preferred for hydrolysis of some compounds (**2**, R = methoxymethyl) affording the (*S*)-acid (63% ee). Lipase PS works better for the compound (**2**, R = H) giving the (*R*)-acid in 70% ee.[27]

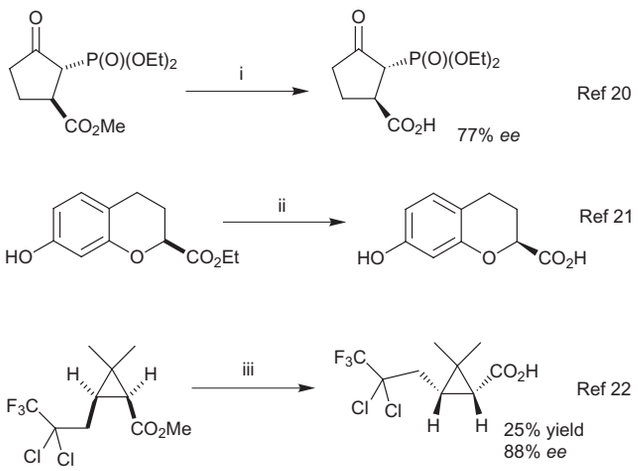
α-Methylene lactones [**3**, R = CH_3 or $CH(CH_3)_2$] may be resolved using *Candida antarctica* lipase (E = 200).[28]

The potential power of the error-prone polymerase chain reaction (pcr) for the optimization of biocatalytic activity is well-illustrated by the hydrolysis of compounds $RCH(CH_3)$-CO_2-*p*-nitrophenyl, using *Ps. aeruginosa* PAO1. The wild-type

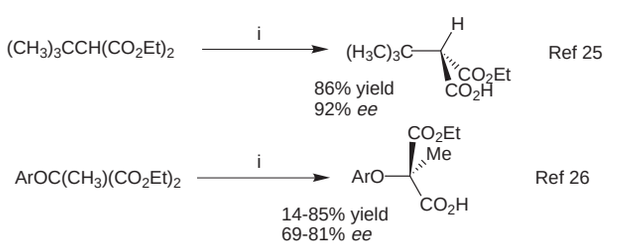
Table 1 Biocatalytic enantioselective hydrolysis of esters of the type $R^1CH(R^2)CO_2R^3$

$$R^1CH(R^2)CO_2R^3 \xrightarrow[H_2O]{cat.} R^1CH(R^2)CO_2H + R^3OH$$

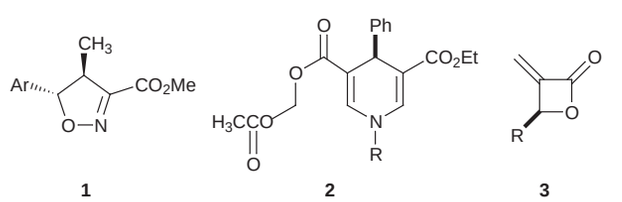
Ref.	R^1	R^2	R^3	Catalyst	Acid yield; ee or *E*
15	Various	CH_3	CH_3	Esterase from *Ps. putida*	(*S*); E ≥ 500
16	EtO_2CCH_2	$CH_2CH(CH_3)_2$	Et	Subtilisin	(*R*); 47% 99% ee
17	$ArCH_2$	$NHCOCF_3$	CH_3	Subtilisin	(*S*); >99% ee
18	Alkyl or aryl	NH_2	^{i}Bu	*A. oryzae*	E ~ 150
19	Aryl or benzyl	$NHCOCH_3$	CH_3	Rice bran lipase	≥94% ee



Scheme 1 *Reagents and conditions*: i) α-chymotrypsin, H_2O; ii) lipase PS 30, H_2O; iii) porcine pancreatic lipase (ppl), pH 8.



Scheme 2 *Reagents and conditions*: i) ple, phosphate buffer, pH 7.



enzyme gave low (2%) enantioselectivity. Random mutagenesis using error-prone pcr gave clones with hydrolase activity. Repeated mutagenesis, using the most active species in each case, gave protein with high selectivity (81% ee) for the (*S*)-ester after 4 cycles.[29] In a more conventional study subtilisin from *Bacillus lentus* was modified in a selected way to incorporate cysteine residues. These residues were modified with methanethiosulfonate reagents to produce hydrolase catalysts with k_{cat}/K_m enhanced over that of the wild-type enzyme.[30]

The enantioselective hydrolysis of esters of the type $R^1CH(R^2)$ $OCOR^3$ has continued to be investigated. Results of recent studies are listed in Table 2.

Regio- and stereo-selective hydrolysis of the primary acetate unit in diacetates of the type $RSCH(OCOCH_3)CH_2OCOCH_3$ using *Pseudomonas fluorescens* lipase† in *tert*-butyl methyl ether and pH 7 buffer gave the (*S*)-alcohols with *E* 7→100 in

† *Candida rugosa* and *Candida cylindracea* are two names used for the same organism; similarly *Pseudomonas cepacia* is also known as *Pseudomonas fluorescens*. The name given in the relevant paper will be the one used in this Review.

Table 2 Hydrolysis of esters of the type $R^1CH(R^2)OCOR^3$

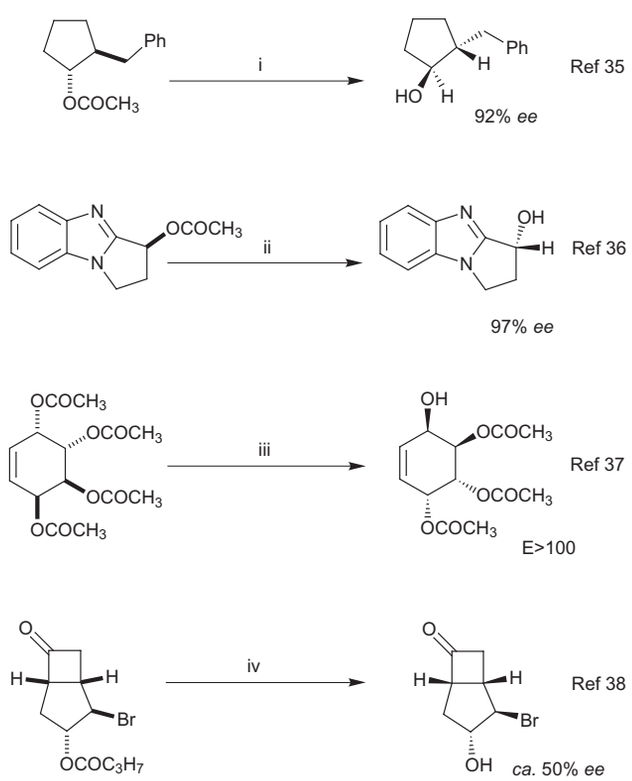
$$R^1CH(R^2)OCOCH_3 \xrightarrow[H_2O]{cat.} R^1CH(R^2)OH + CH_3CO_2H$$

Ref.	R^1	R^2	Catalyst	Alcohol configuration; yield; ee
31	XCH_2	$P(O)(O^iPr)_2$	Lipase AP6	(*S*); 44%; 86% ee
32	$CH_3CH(Cl)$	CO_2Me	Amano P lipase	(*S*); 40%; 89% ee

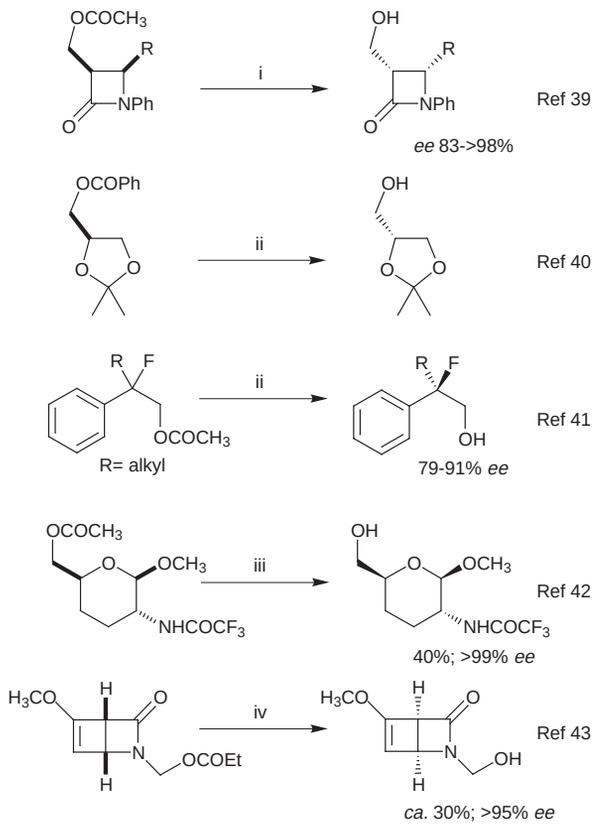
studies related to the synthesis of the optically active antiviral lamivudine.[33] [Note that for calculation of *E* values from enantiomeric excesses (and conversions) the Sih method or Ratels Modification is recommended over other methods.[34]]

The acetate unit may be appended to a ring system (Scheme 3) or adjacent to a ring system (Scheme 4), with good to excellent optical activities being observed for products in both cases. The resolution of (±)-4-acetoxy[2.2]paracyclophane was effected using *Candida cylindracea* lipase (ccl)† to afford the (±)-(*R*)-phenol **4**.[44] Note that ccl and porcine pancreatic lipase effect deacetylation of peracetates of polyphenolics: regioselective hydrolysis occurs if an ethyl ester group is present in the molecule, leaving the CO_2Et unit intact.[45]

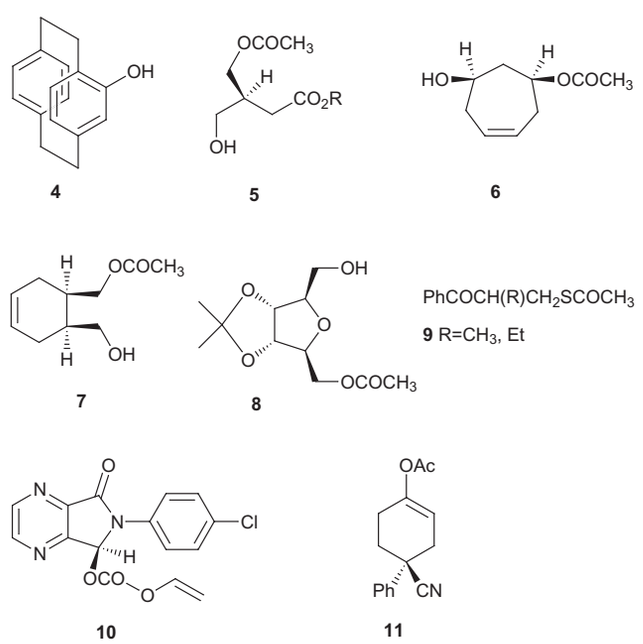
The hydrolysis of prochiral and *meso*-diacetates has been employed to gain access to various acetoxy alcohols, for



Scheme 3 *Reagents and conditions*: i) *Candida cylindracea* lipase; ii) *Candida antarctica* lipase; iii) *Mucor miehei* lipase (Lipozyme) *n*-BuOH, *tert*-BuOMe; iv) *Humicola lanuginosa* lipase, s.c. CO_2.



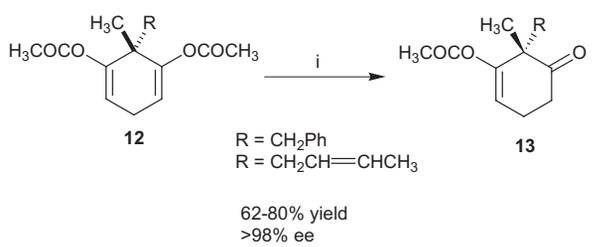
Scheme 4 *Reagents and conditions*: i) porcine pancreatic lipase, pH 8; ii) Amano PS, pH 7 buffer; iii) porcine pancreatic lipase, phosphate buffer–acetone; iv) Amano PS, i-Pr_2O saturated with H_2O.



example the diester **5**,[46] the cyclic secondary alcohol **6**[47] and the primary alcohols **7**[48] and **8**[49] using *Pseudomonas fluorescens* lipase as the catalyst in the majority of cases; the yields ranged from 72–94% and ees were >90%.

The selective hydrolysis of the α,α-diacetate $PhCH(CH_3)CH(OCOCH_3)_2$ gave (*R*)-2-phenylpropanal (25% conversion, 72% ee) using *Candida rugosa* lipase.[50] Hydrolysis of the thioacetate **9** gave the (*R*)-thiol (25–43% yield; ≥95% ee) using *P. cepacia* lipase or *Alcaligenes* lipase.[51] Extension of earlier work on the hydrolysis of cyclic carbonates has now given (*S*)-12-benzyloxydodecane-1,2-diol and congeners, useful for the synthesis of (*S*)-8-hydroxyhexadecanoic acid, a spore inhibitor of some fungi.[52] *Candida antarctica* lipase-catalysed hydrolysis of the corresponding racemic material gave (+)-carbonate **10** which was readily converted into the hypnotic agent zopiclone.[53]

There has been some interesting work published on the enzyme-catalysed hydrolysis of enol acetates. For example *Pseudomonas fluorescens* lipase-catalysed hydrolysis of the relevant racemate furnished the enol ester **11** (33% yield; >99% ee) and 4-cyano-4-phenylcyclohexanone which could be recycled.[54] Hydrolysis of achiral enol acetates derived from 2-alkylcyclohexanones gave the corresponding (*S*)-2-alkylcycloalkanone for short-chain alkyl groups (for example 2-methylcyclohexanone was obtained in >99% optical purity) while for longer chains (*e.g.* pentyl) the (*R*)-enantiomer is obtained, albeit in lower optical purity (50% ee).[55] The prochiral compounds **12** are hydrolysed by *Candida cylindracea* lipase to give ketones **13** with excellent enantiomeric excesses (Scheme 5).[56]



Scheme 5 *Reagents and conditions*: i) *Candida cylindracea* lipase, H_2O, pH 7 buffer, 35 °C.

In an attempt to allow more predictability in all enzyme-catalysed ester hydrolysis reactions Jones and Kazlauskas have continued to develop preference guidelines for some of the more popular biocatalysts. For lipase-catalysed hydrolyses of the simple esters of secondary alcohols the faster reacting enantiomer is shown as compound A (Fig. 1). For esters of chiral carboxylic acids, a simple rule based on the size of substituents at the adjacent stereocentre works for *Candida rugosa* lipase [the faster reacting enantiomer is shown as formula B in Fig. 1] but not for *Aspergillus niger* lipase (Anl). For the latter enzyme a rule can be formulated for α-amino acids whereby the enzyme has high selectivity for enantiomers of type **14**. The charged group influences the enantioselectivity significantly. Note that commercial Anl has a contaminating hydrolase which may complicate matters.[57]

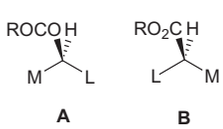
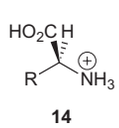
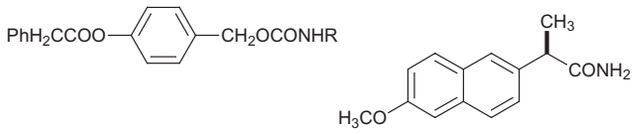


Fig. 1

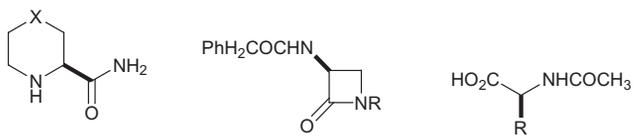


2.2 Amide hydrolysis

The phenacetyl ($PhCH_2CO$) group has been used to protect amine functions during the synthesis of phosphopeptides: the protecting group is readily removed using penicillin acylase.[12] A similar strategy has been used to prepare complex nucleotides and nucleopeptides.[58] It has also been developed further for phosphorylated and glycosylated peptides by the introduction of the amine protecting group shown in formula **15**, which on



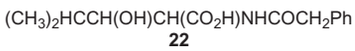
15 **16**



17 X = NH
18 X = CH_2

19 R = H, CH_2Ph, $CH{=}CHCH_3$

20 R = $CH_2CH_2SCH_3$
21 R = CH_2ferrocenyl



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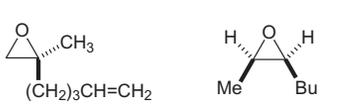
treatment with penicillin-G acylase breaks down to release the amine and generate phenylacetic acid, CO_2 and methylidene quinone.[59]

Hydrolysis of the amide (±)-**16** with *Rhodococcus erythropolis* MP5O in organic solvents containing a trace of water yielded (*S*)-naproxan (42%, >99% ee) on a preparative scale.[60] The amide (±)-**17** is resolved to give the (*S*)-acid (41%, >99% ee) using *Klebsiella* sp. DSM 9174 and the (*R*)-acid (22%, 99% ee) using *Burkholdia* sp. DSM 9925. The analogous piperidine derivative **18** is enantioselectively hydrolysed by *Pseudomonas* sp. DSM 9924 to give the (*S*)-acid (20%, 97% ee).[61] Penicillin-G acylase catalyses the hydrolysis of the amides **19** to produce the (*S*)-aminolactams.[62]

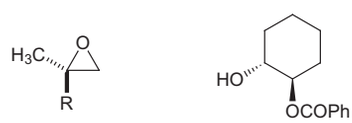
Enzyme-catalysed hydrolysis of amides continues to be a valuable method for the production of amino acids. *Aspergillus* acylase has been used for the enantioselective hydrolysis of the amides **20**[63] and **21**[64] to afford the corresponding (*S*)-amino acids (35–45% yield; >99% ee). Finally the phenacetyl group is removed from the (*S*,*S*)-enantiomer of the amide **22** to furnish optically active 3-hydroxy leucine (29%, >99% ee).[65]

2.3 Epoxide hydrolysis

An authoritative review of this area has been published by Archelas and Furstoss,[66] and further research has been published by Faber and co-workers. For example the Austrian team has used *Rhodococcus equi* for the hydrolysis of epoxide **23** to give (*S*)-2-methylhept-6-ene-1,2-diol (13%, $E = 39$), an intermediate to (−)-frontalin.[67] Deracemization of 2,3-disubstituted oxiranes (such as the epoxide **24**) may be effected using lyophilized whole cells of *Nocardia* sp EH1 to form the (*R*,*R*)-diol (79%; 91% ee). The kinetics of this enantioconvergent process were examined.[68] Treatment of epoxides **25** with *Nocardia* sp. EH1 furnished the (*S*)-diol and recovered (*R*)-epoxide: addition of acid to this mixture gave (*S*)-diol (>90%; >90% ee) in a one-pot process[69] reminiscent of earlier work by Widdowson.[69b]



23 **24**



25 R=CH_2Ph or $^nC_5H_{11}$ **26**

At the same time Jacobsen has been developing salen–cobalt complexes for stereoselective ring-opening of epoxides. For example use of the organometallic catalyst with benzoic acid and cyclohexene epoxide gave the hydroxy ester **26** (98%, 77% ee).[70]

2.4 Nitrile hydrolysis

Meth-Cohn and Wang have made an extensive study of the hydrolysis of dinitriles of the type $NC(CH_2)_nX(CH_2)_nCN$ (where $n = 1$–4, X = CH_2, O, S, NR) using *Rhodococcus* sp. AJ270. For such aliphatic dinitriles (dicyanoalkanes) with short chains (adiponitrile and lower molecular weight species) the mono acid is formed; for longer chains the diacid is produced. On inclusion of a heteroatom in the chain, the regioselectivity of the hydrolysis is dependent on the position of the heteroatom in the chain. For example mono acids are produced when an oxygen atom is placed β, γ or δ to the nitrile group, or when a sulfur substituent is present in the β or γ position.[71]

The boronic acid $(HO)_2BCH{=}CHCH_2CN$ is hydrolysed to the amide (75%) using *Rhodococcus rhodochrous* IFO 15564. Subsequent Suzuki–Miyaura cross-coupling provided the dienes $ArCH{=}CH{-}CH{=}CCH_2CONH_2$ which gave the corresponding acid (87%) on re-treatment with the same organism. The inactivity of the amidase in the first transformation was due, it was mooted, to the presence of the boronic acid moiety in the substrate.[72]

3 Esterification reactions

Enzyme-catalysed esterification using lipases (or occasionally esterases) in organic solvents containing limited amounts of water (*i.e.* low water activity) is an area of considerable current interest. Studies aimed at achieving the best enzyme activity in non-aqueous systems have shown that suitable pairs of crystalline solids (*e.g.* lysine with lysine hydrochloride) can control acid–base conditions in low-water organic media and hence the catalytic activity of enzymes. Thus using this strategy immobilized subtilisin Carlsberg shows a four-fold enhancement for ethyl to isopropyl exchange in *N*-acetylphenylalanine esters using hexane as solvent.[73] Dendritic poly(benzyl ether)s have been used as second generation, versatile acid/base buffers for biocatalysis in non-polar solvents.[74] It has also been shown that addition of methanol can substantially increase the rate of serine protease (*e.g.* subtilisin or α-chymotrypsin) activity under anhydrous conditions.[75]

Lipases immobilized in organic–inorganic hybrid materials with the help of a sol–gel process rightly earned Reetz the Fluka Reagent Prize for 1997. Increased enzyme activity, conservation of enantioselectivity, long-term stability and convenient recovery procedures are some of the advantages.

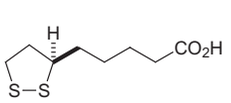
Most enzyme-catalysed esterifications involve the coupling of a chiral alcohol to a simple acyl unit; more rarely it is necessary to couple a simple alcohol to a chiral carboxylic acid. In one of the rare examples in the latter category immobilized *Rhizomucor miehei* lipase effects enantioselective esterification of 2-arylpropanoic acids. The enzyme shows (*S*)-enantiorecognition (except for ketoprofen) and an active site model has been described.[76]

The carboxylic acid **27** is enantioselectively esterified using *Candida cylindracea* lipase in hexane containing *n*-hexanol to furnish the (*R*)-acid and the (*S*)-hexyl ester ($E = 7.5$).[77]

The regio- or stereoselective esterification of chiral primary alcohols is often very successful. For example selective acylation of the primary hydroxy group in compounds **28** was observed (95–100% selectivity) in studies aimed at the synthesis of D-allosamine derivatives.[78] The pyranose **29** may be coupled with straight chain C_{10}–C_{18} fatty acids to give 6-O monoesters in 85–90% yield *en route* to cationic surfactants with antimicrobial activity.[79] Regioselective acylation of a spiroketal diol using Amano P lipase and vinyl acetate furnished the monoacetate (90%) contaminated with a small amount of diester (5%) in

Table 3 Enzyme-catalysed mono-esterification of diols of the type $RCH(CH_2OH)_2$

Ref.	R	Catalyst	Acylating agent (solvent)	Product		
				Config.	Yield (%)	Optical purity (ee, %)
89	C_2H_5	Freeze-dried *C. oxydans*	vinyl acetate	(−)	—	90
90	Ar (various)	Porcine pancreatic lipase	vinyl acetate (ether)	*R*	*ca.* 80	>99
91	2- or 4-Pyridyl	Porcine pancreatic lipase on Celite	vinyl acetate	*R*	81	>97
92	Ar (protected polyphenolic)	Lipase AL	vinyl acetate (ether)	*S*	72	89
93	*p*-Tolyl	Porcine pancreatic lipase	vinyl acetate (ether)	*R*	84	99
94	Ar (*o*-nitro *p*-benzyloxy)	Porcine pancreatic lipase	vinyl acetate	*R*	92	92
95	$CH_2C(OH)(C_6H_3F_2)$-triazole	Nova 435	vinyl acetate	*S*	83	97



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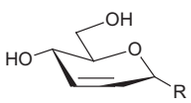
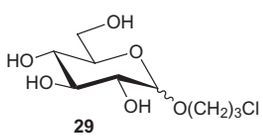


28 R=H or *p*-methoxyphenoxy



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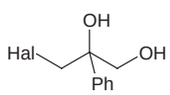

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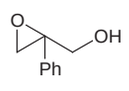

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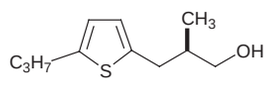

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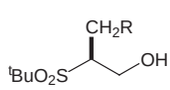
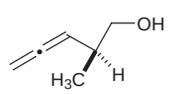


33 R=H or Ph



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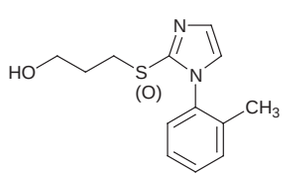

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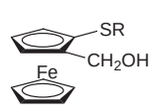
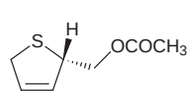


36 R=CH_3, Ph, ^{t}Bu



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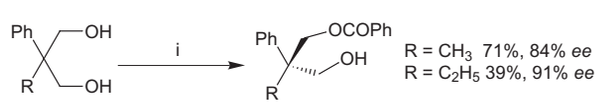


38 R = CH_3, C_2H_5

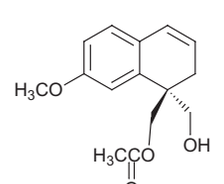
Scheme 6 *Reagents and conditions*: i) Amano AY lipase, $CH_2C(OEt)$-OCOPh, diisopropyl ether, 18 h–3 d.

work aimed at the preparation of the C_5–C_{16} fragment of tautomycin.[80]

Optically active esters may be obtained on acetylation of the corresponding racemic primary alcohols. For example the diol **30** and the epoxyalcohol **31** are enantioselectively acetylated ($E = 69$, 153 respectively) using lipase AK in isopropyl acetate.[81] In a related study (±)-methyl 2-hydroxy-2-hydroxymethyl-hexadecanoate acid furnished (*S*)-methyl 2-acetoxymethyl-2-hydroxyhexadecanoate acid ($E = 19$) on treatment with *Pseudomonas fluorescens* lipase in *tert*-butyl methyl ether containing vinyl acetate. The unreacted (*R*)-diol was converted into the (*R*)-epoxide, a potent hypoglycaemic agent.[82] Similarly the thiophene derivative **32** gives the (*S*)-acetate ($E > 100$) using Amano PS lipase in chloroform or *tert*-butyl methyl ether containing vinyl acetate. Subsequent Raney nickel-catalysed hydrogenation yields optically active esters of long chain 2-methylalkanols.[83] Likewise the alcohols **33** were resolved ($E = 18$–49) using *Candida antarctica* lipase and vinyl acetate.[84] By employing *Pseudomonas cepacia* lipase in tetrahydrofuran containing vinyl acetate the alcohol **34** was converted into the (*R*)-acetate (23% yield; 96% ee) and recovered (*S*)-alcohol (26% yield; 99% ee).[85] Lipase AL in a mixture of ethyl acetate and isopropenyl acetate acetylates the (*S*)-enantiomer of the sulfoxide **35** (*ca.* 50% ee at *ca.* 50% conversion).[86] The ferrocene derivative **36** was enantioselectively acylated ($E \sim 30$) using lipozyme or Novozyme in vinyl acetate.[87] A full paper has been published on the synthesis of optically active ester **37** using a trans-esterification procedure.[88]

The monoacetylation of prochiral or *meso* primary diols is a well-trodden pathway to obtain optically active materials in high yields. A selection of recently investigated substrates is shown in Table 3.

The diols **38** were selectively acylated as described in Scheme 6 using Amano AY as the catalyst.[96] Similarly the acetate **39** was obtained (93% ee) on treatment of the corresponding diol with immobilized *Pseudomonas cepacia* lipase in *tert*-butyl methyl ether containing vinyl acetate. The hydroxy ester **39** is a key intermediate to (−)-aphanorphine and (+)-eptazocine.[97] The tetraol **40** reacts with vinyl acetate in tetrahydrofuran, under catalysis by *Pseudomonas fluorescens* lipase to give the (*R*,*R*)-diester (78%; >95% ee and de).[98] The polyfunctional hydroxy ester **41** is prepared from the diol by utilizing *Pseudomonas fluorescens* lipase and vinyl acetate as the acyl transfer agent (86% yield; 98% ee).[99] Finally an intermediate to (−)-curcumanolide **42** has been prepared from the corresponding diol (56%; >99% ee) using *Pseudomonas fluorescens* lipase and vinyl acetate in *n*-octane.[100]



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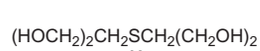

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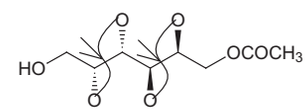

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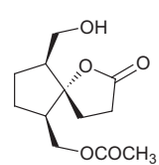


42

Lipase-catalysed resolution of racemic secondary alcohols $R^1CH(OH)R^2$ where R^1 is a large group and R^2 is a small entity

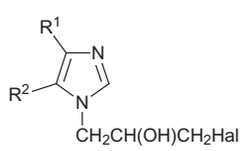
Table 4 Resolution of secondary alcohols of the type $CH_3CH(OH)R$

Ref.	R	Catalyst	Acylating agents (solvent)	Config.	Product yield (%)	Optical purity
101	CH_2Hal	*Candida antarctica*	vinyl butyrate	—	—	$E > 160$
102	6-Methoxy-2-naphthyl	Rabbit gastric lipase	vinyl acetate	*R*	—	$E > 500$
103	Ph	*Candida antarctica* (immobilized)	*p*-chlorophenyl acetate	*R*	~99[a]	~99% ee
104	CHCHPh	Porcine pancreatic lipase	vinyl acetate (*tert*-butyl methyl ether)	*R*	—	$E = 156$
105	$H_9C_4C{\equiv}C$	*Candida antarctica*	vinyl acetate (hexane)	*S*	41	93% ee
106	3-Pyridyl	Amano PS	vinyl acetate	*R*	45	96% ee
107	$TBSO-(CH_2)_7$	*Candida rugosa* lipase	trifluoroethyl butanoate	*R*	30	93% ee
108	$C(Hal)(CH_3)_2$	*Pseudomonas* lipase	vinyl acetate	*S*	—	E = 180

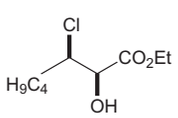
[a] Using a binuclear ruthenium catalyst to effect dynamic resolution.

must now be regarded as standard practice in biotransformations. Eight examples of resolutions of alcohols of the type $CH_3CH(OH)R$ are collected together in Table 4. Note that the rate of kinetic resolutions of alcohols $RCH(OH)CH_3$ using pig liver esterase (ple) and vinyl propanoate in toluene may be increased by co-lyophilization of the enzyme with methoxypolyethyleneglycol (MPEG) with no loss in enantioselectivity. The ple–MPEG combination may be immobilized on an ultrafiltration membrane.[109]

Changing the methyl group for another small unit does not cause problems usually. For example the halomethyl compounds **43** have been resolved using Amano PS and vinyl acetate to give the (*S*)-acetates (92–98% ee).[110] Similarly 4-chloro-2-(4-fluorophenyl)propanol forms the (*R*)-acetate (44%; 97% ee) on treatment with vinyl acetate and Amano lipase PS in hexane.[111] Polar groups can be accommodated next to the alcohol unit: the cyanohydrin obtained from formylferrocene is acetylated to give the (*R*)-ester (50%; 84% ee) using Amano *Pseudomonas cepacia* lipase in vinyl acetate.[112] Similarly 2-cyano-1-pentafluorophenylethanol gives the (*R*)-ester ($E >$ 100%) using a lipase from the Toyobo Company in diisopropyl ether containing vinyl acetate.[113]



43 R^1, R^2=H or NO_2



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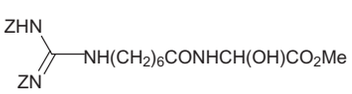

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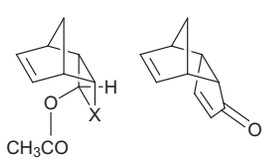
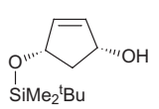
2-Hydroxy esters may also be resolved; for instance the halohydrin **44** gives the (*R*,*R*) diester on reaction with vinyl acetate catalysed by Amano PS lipase.[114] Lipase AK effects the resolution of the hydroxy ester **45** using isopropenyl acetate (in toluene) as the acylating agent, furnishing the diester in 46% yield (98% ee).[115] Methyl 3-hydroxytetradecanoate gives the optically active acetate (49%; 70% ee) using lipase PS and vinyl acetate in tetrahydrofuran. The enantiomeric excess of the product was raised to >99% by recrystallization.[116] 2-Arylprop-3-enols furnish the (*R*)-acetate (40–44%; 85–97% ee) on Amano AK lipase-catalysed acetylation employing vinyl acetate in hexane.[117]

Much of the other work on enzyme-catalysed esterification processes has focused on the resolution of cycloalkanols, principally cyclobutanol, cyclopentanol and cyclohexanol derivatives. Two papers describe the preparation of the keto ester **46** in optically active form (*ca.* 40% yield; 97% ee) using lipase PS (immobilized on Celite) in vinyl acetate and tetrahydrofuran containing triethylamine.[118] The conversion of **46** into the



46 X=CO
48 X=CH_2

47



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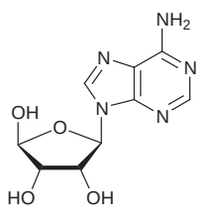
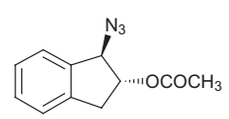


50

optically active enone **47** was described also. The ester **48** is available using a similar procedure (40%; 89% ee).[119]

A new method has been described for the preparation of partially protected cyclopent-2-ene *cis* 1,4-diols (*e.g.* compound **49**) avoiding the use of cyclopentadiene. The corresponding racemic alcohol is readily prepared from furfuryl alcohol and is resolved using pancreatin in tetrahydrofuran and vinyl acetate containing triethylamine (>45%; 95% ee).[120] Compounds of this type have been used to make 5′-noradenosine **50** which displays potent activity against Trypanosomes.[121]

Indanol derivatives **51**[122] and **52**[123] are available from the corresponding racemic alcohols. In the first process immobilized Amano lipase PS was used in a 1 : 1 mixture of dimethoxyethane and isopropenyl acetate (44% yield of ester; >96% ee) while in the second procedure immobilized *Candida antarctica* lipase was the catalyst of choice with vinyl acetate as the acylating agent (35% yield of ester; 93% ee). It has now been found that the most convenient way of preparing the useful diol **53** in optically active form (98.5% ee) is to resolve the racemic diol using Amano lipase PS and vinyl acetate in tetrahydrofuran or *tert*-butyl methyl ether (44% yield of recovered diol).[124]



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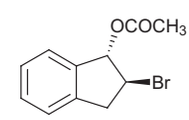

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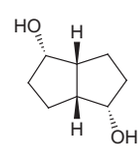
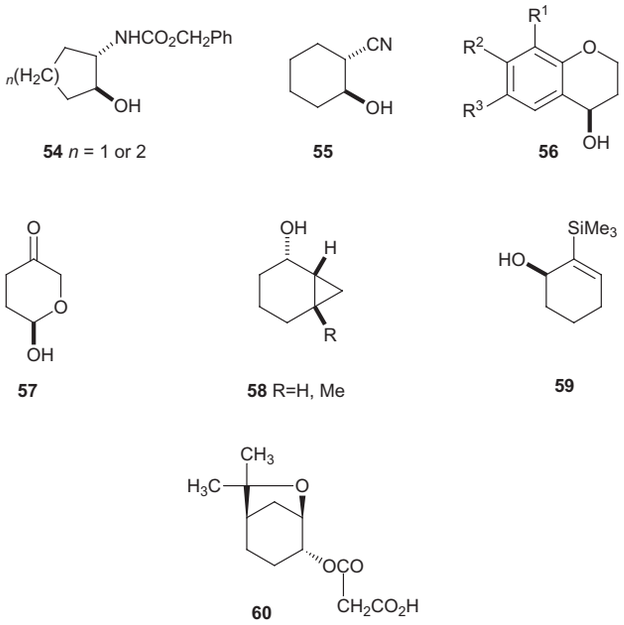


53

Cyclic amino alcohol derivatives such as **54** are readily resolved in almost quantitative yield using *Pseudomonas cepacia* lipase and vinyl acetate in 1,4-dioxane ($E > 100$).[125] The *trans*-cyanohydrin **55** is efficiently resolved using a similar procedure.[126] Chroman-4-ols **56** may be resolved using Amano PS lipase and vinyl acetate in *n*-hexane yields are virtually quantitative while ees vary according to the substitution pattern. High ees for ester and recovered alcohol are recorded for $R^1 = CH_3$; $R^2 = R^3 = H$.[127] Lipase PS-catalysed esterification of 6-hydroxypyranone **57** using vinyl acetate gave the (*S*)-acetate (76% ee) at >99% conversion due to *in situ* epimerization.[128] The bicycloalkanol **58** is easily resolved to give (2*R*)-acetoxybicyclo-[3.1.0]heptane ($E = 50$–80) using *Candida antarctica* lipase and isopropyl acetate in methyl *tert*-butyl ether.[129] Another enzyme, a lipase from *Burkholderia* sp. (Chirazyme) was the preferred

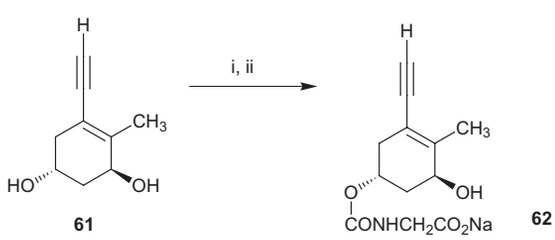


54 *n* = 1 or 2 **55** **56**

57 **58** R=H, Me **59**

60

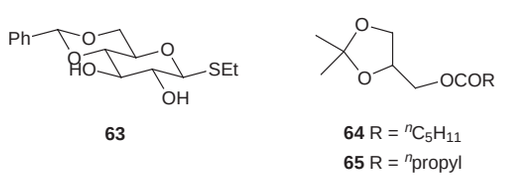
catalyst for acetylation of the allylic alcohol **59** using vinyl acetate to afford the (*R*)-acetate ($E > 200$).[130] The microorganism *Glomeralla cingulata* converts the appropriate racemic alcohol into malonic ester **60** and recovered alcohol, both enantiopure. The malonic acid is produced in the medium as part of the metabolism of the microorganism.[131] Regioselective alkoxycarbonylation of the diol **61** gave the carbamate **62** which was utilized in the synthesis of 1α,25-dihydroxyvitamin-D_3 (Scheme 7).[132] For the diol **63** regioselective acetylation at the C-3 OH group (94% selectivity) can be obtained using lipase P and vinyl acetate.[133] Thermolysin catalyses the esterification of the paclitaxel side-chain using divinyl adipate in *tert*-amyl alcohol. The adipic acid moiety was further modified by exchange of the remaining vinyl unit for glucose (through esterification of the C-6 OH group) to give water-soluble paclitaxel derivatives.[134]



61 **62**

Scheme 7 *Reagents and conditions*: i) $OC(OCH{=}CH_2)_2$, *Candida antarctica* lipase, toluene; ii) $H_2NCH_2CO_2Na$.

A two-stage resolution of the ester **64** was effected by, first, treatment with lipase AK in methanol to give (*S*)-alcohol (80% ee at 46% conversion) and recovered ester. Esterification of this alcohol with vinyl butanoate using the same catalyst gave the ester **65** (86% yield; 95% ee).[135] (Note that 1-ethoxyvinyl acetate has also been recommended as an irreversible acyl transfer agent for lipase catalysed reactions in organic solvents: the reaction leads to innocuous ethyl acetate as the by-product.[136])



63 **64** R = $^n C_5H_{11}$

65 R = ^{n}propyl

Useful active site models of one of the most widely-used lipases, *Pseudomonas cepacia* lipase have been published.[137] Using this (and other) lipases under ideal conditions should lead to no change in the E value on progression of the reaction. Strangely *Pseudomonas cepacia* catalysed esterification of sulcatol gave increasing E values as a function of substrate conversion when using dichloromethane or dichloroethane as solvents.[138] Note that in some cases the E value may be improved by substantially lowering the reaction temperature (*e.g.* to −40 °C).[139] 1,4,8,11-Tetrathiacyclotetradecane enhances the selectivity of acylation of 5-phenylpent-1-en-3-ol using small acylating agents, for example vinyl acetate.[140]

An improvement in the efficiency of measurement of *E* values for lipases and esterases can be achieved by measuring initial rates of reaction of pure enantiomers *versus* a reference compound.[141] The relationship of structure, stability and activity of adsorbed enzymes with respect to E values has been reviewed[142] as has the advantages presented by CLECs (cross-linked enzyme crystals).[143]

Isoamyl acetate has been synthesized (90% yield) *via* a lipase-catalysed acylation of the alcohol using ammonium acetate in super-critical CO_2. The yield was almost independent of the pressure and temperature of the CO_2.[144]

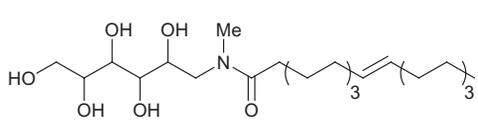
Aspergillus acylase 1 is known to effect hydrolysis of *N*-acyl-amino acids (see section 2.2). It has now been shown to be an effective catalyst for transesterification reactions using vinyl esters as acyl donors.[145]

4 Preparation of amides

The preparation of polypeptides using enzymes is established technology. Coupling of Boc-Phe-Gly-Gly-OGp and H-Ala-Phe-Ala-Ala-Gly-OH has been accomplished in 98% yield using the cysteine protease clostripain as the catalyst. The Gp[4-guanidinophenylester] group provides a recognition site for the enzyme and a good leaving group.[146] Clostripain (and also chymotrypsin) has been used to prepare the highly functionalized tetrapeptide H-Lys-Tyr-Arg-Ser-OH.[147] Trypsin (from *Streptomyces griseus*) has been shown to couple N^{α}-Boc-α,α-dialkylamino acid *p*-guanidino- and *p*-guanidinomethyl phenyl esters to alanine *p*-nitroanilide.[148] The formation of amide bonds by intramolecular cyclization of resin bound amino acids using trypsin forms a key element in a new approach to screening libraries of linear compounds for enzymatic cyclisation.[149] Microperoxidase-9 (a nonapeptide covalently attached to a haem) has been coupled to amino acids using trypsin in 50% dimethylformamide in water to give a series of novel haem-peptides.[150]

Subtilisin–sodium dodecyl sulfate in ethanol catalyses peptide bond formation; for example Z-Ala-Ala-Leu-OMe couples to HPhe-*p*-nitroanilide in 80% yield.[151] Immobilized subtilisin catalysed acylation of amino alcohols [*e.g.* $H_2NCH(CH_2Ph)$-CH_2OH] and peptide methyl esters (*e.g.* Z-Ala-Ala-OMe) in yields 37–77%; subsequent mild oxidation to peptide aldehydes furnished some potent serine protease inhibitors.[152]

Lipases are also commonly employed to catalyse the formation of amide bonds. Thus *Candida antarctica* lipase catalysed regioselective aminolyses (using propylamine) of *N*-protected L-glutamic acid diethyl esters. The product [$RHNCH(CONH$-$CH_2CH_2CH_3)CH_2CH_2CO_2Et$] was obtained most efficiently when R = Cbz or Boc.[153] The same lipase catalysed the formation of oleoyl-*N*-methylglucamide **66** from *N*-methyl glucamine and oleic acid in the first report of such amide bond synthesis from hydroxylated secondary amines and carboxylic acids or esters. Yields reach 97% in some instances.[154]



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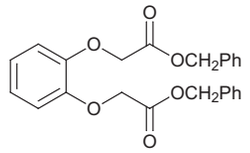
A library of amide products is produced on coupling the diester **67** with a mixture of amines $H_2N(CH_2)_nNHBoc$



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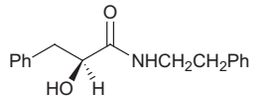
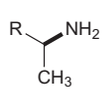


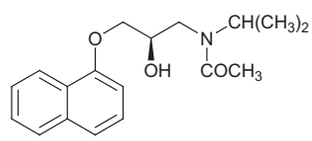
68

(n = 2,3,5,6) followed by treatment with trifluoroacetic acid.[155] The same enzyme has been shown to couple benzyl phenoxyacetate and the partially protected polyamine $BocHN(CH_2)_3NH(CH_2)_3NH_2$ through the reaction of primary amine function, with excellent regioselectivity and in high yield.[156] The α-hydroxy ester $PhCH_2CH(OH)CO_2CH_2Ph$ has been resolved using phenethylamine and *Pseudomonas cepacia* lipase, giving the amide **68** in 86% ee at 49% conversion; the methyl and ethyl esters react more slowly.[157]

The resolution of amines can be effected in a complementary fashion. For example chiral amines of type **69** are resolved using *Candida antarctica* lipase in ethyl acetate (E = 31–100). In this case the (*R*)-enantiomer forms the amide product more rapidly.[158] Similarly racemic propranolol may be resolved into (*R*)-propranolol and (*S*)-*N*-acetylpropranolol **70** (E = 21) using *Candida antarctica* lipase in diisopropyl ether containing isopropenyl acetate.[159]



69 R= 2-thienyl, 2-furyl or 2-pyridyl



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5 Reduction reactions

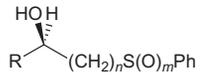
5.1 Reduction of ketones

Bakers' yeast alcohol dehydrogenase and horse liver alcohol dehydrogenase catalyse the reduction of compounds $RCOCH_3$ (R = Ph, $PhOCH_2$, CO_2H) with ees close to 100% using NADH as cofactor. Cofactor recycling was effected using methyl viologen and electrolysis.[160]

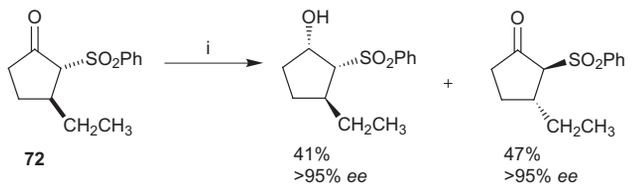
Improved enantioselectivity has been obtained for bioreduction of compounds $RCOCH_2OCOCH_3$ (R = Me, Ph, *n*-Bu) to give the (*S*)-alcohol (ee 67–>99%) by addition of L-cysteine or phenyl vinyl sulfide. The rate of reduction is accelerated by the additive while the rate of hydrolysis of the ester group is decreased.[161]

There has been a good deal of interest in the reduction of keto sulfides and keto sulfones. The keto sulfide $PhS(CH_2)_3COCH_3$ is reduced by bakers' yeast to give the (*S*)-alcohol (97%; 97% ee) which was converted into a bee pheromone.[162] Ohta and co-workers have shown that various keto sulfides and sulfones are reduced by *Pichia farinosa* IAM 4682 to give alcohols **71** (72–94%; 88–97% ee) with anti-Prelog selectivity. If the ee of the product was somewhat low it could be improved by treatment of the material with *Rhodococcus rhodochrous*, which preferentially oxidizes the minor component.[163] Maguire *et al.* have demonstrated that keto sulfones $RCOCH_2SO_2CH_3$ (R = butyl or higher alkyl or phenylbutyl) are reduced to the (*S*)-alcohols with ees as high as 87%.[164] Similarly the keto sulfone $PhSO_2CH_2CH_2COCH_2Cl$ afforded the (*R*)-alcohol (85%; 88% ee) on reduction with bakers' yeast over a period of 5 days.[165] More complex keto sulfones are reduced just as efficiently; for example the cyclic keto sulfone **72** is transformed with high enantio- and stereo-selectivity (Scheme 8).[166]

In contrast both enantiomers of the ketone **73** are reduced by bakers' yeast to give two diastereomers (yield 30–35%; de >97%), both possessing the (*S*)-configuration at the newly-formed stereogenic centre. The products were converted into nonactic acid and analogues.[167] Bakers' yeast reduction of the



71 R = CH_3, C_2H_5, CF_3
n = 1 or 2
m = 0 or 2



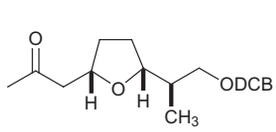
72

41%
>95% *ee*

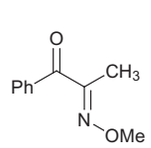
47%
>95% *ee*

Scheme 8 *Reagents and conditions*: i) bakers' yeast, H_2O.

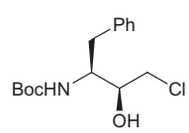
ketone **74** furnished the (*R*)-alcohol (79%; 97% ee), a key intermediate to (−)-norephedrine,[168] while protected amino alcohol **75** is available (75% yield, >99% de) by reduction of the corresponding (*S*)-Boc-amino ketone with *Streptomyces nodolus* SC 13149.[169]



73 DCB = dichlorobenzyl



74

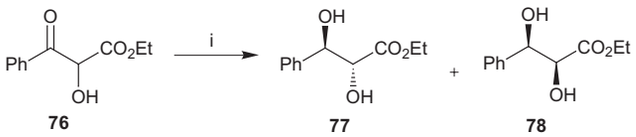


75

Reduction of 5-oxohexanoic acid with *Yamadazyma furinosa* IFO 10896 furnished (*R*)-5-hydroxyhexanoic acid in 98% yield and 97% ee.[170] (*R*)-2-Hydroxyhex-5-enoic acid (99% ee) was obtained from ethyl 2-oxohex-5-enoate by a double biotransformation, first hydrolysis of the ester function under mild conditions using *Candida rugosa* lipase (Crl) and then employing a dehydrogenase from *Lactobacillus delbrueckii* subspecies *bulgarius* using NADH and FDH as cofactors. The (*S*)-enantiomer of 2-hydroxyhex-5-enoic acid was obtained (99% ee) by a similar two-step strategy, again using Crl in the first step to provide the keto acid and then reduction using *Bacillus stearothermophilus* dehydrogenase, lactate dehydrogenase, NADH and FDH. In both cases yields were excellent (≤94%) and the procedure was appropriate for the multi-gram scale.[171]

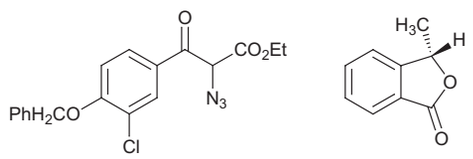
The classic bakers' yeast reduction of ethyl 3-oxobutanoate (ethyl acetoacetate) gave a better ee for the (*S*)-alcohol on addition of resins such as DOW 24D or Amberlite XAD1, XAD7 or XAD 1180. The yield was not affected. The effect of the resin was believed to be through control of substrate concentration.[172] Other work involving reduction of β-keto esters in aqueous solution has concentrated on 2-substituted β-keto esters. For example reduction of ethyl 2-methyl-3-oxobutanoate with *Geotrichum candidum* yielded *syn*-(2*R*,2*S*) and *anti*-(2*S*,3*S*) hydroxy esters in about equal proportions. However addition of methyl vinyl ketone (mvk) or chloroacetone gave the *anti* compound exclusively. Mvk is believed to deactivate "*syn*-enzymes" selectively, while chloroacetone is the preferred substrate for "*syn*" but not the "*anti*"-dehydrogenases.[173] The 2-hydroxy compound **76** furnished the diastereoisomeric diols **77** and **78** in the ratio 10:1 and 82% yield: both diols were essentially optically pure (Scheme 9). Note that the pH of the reaction must be kept at a low value; if raised benzoic acid is a major product.[174] A similar result is obtained for the azide **79**.[175] The lactone **80** is produced (92%; >99% ee) on *Geotrichum candidum* reduction of methyl 2-acetylbenzoate over one day at 30 °C.[176]

Following on from earlier work, Smallridge *et al.* have shown that yeast reduction of alkyl 3-oxobutanoates in petroleum ether afforded the corresponding (*S*)-alcohol (57–96% yield; 94–>99% ee) irrespective of the ester alkyl group.[177] Similarly, reduction of ethyl 4-chloro-3-oxobutanoate furnished the (*R*)-



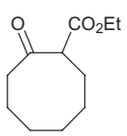
76 **77** **78**

Scheme 9 *Reagents and conditions*: i) calcium alginate immobilized bakers' yeast, citrate buffer, pH 4.0, glucose.



79 **80**

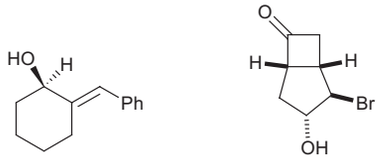
alcohol (98% conversion; 73% ee). By way of comparison reduction of the latter substrate in water gives the (*S*)-alcohol in low optical purity.[178] Bakers' yeast reduction of the keto ester **81** is not very productive; more success was achieved with *Beauvaria bassiana* which gave the *cis*-(*S*)-alcohol in low yield and 98% ee and with *Mucor griseocyanus* which furnished the *trans*-(*S*)-alcohol in 88% ee.[179] Reduction of ketoamides of the type $R^1COCH_2CONHR^2$ using *Mortierella isabellina* proceed according to Prelog's Rule, more often than not. Thus when R^1 is small (*e.g.* CH_3) then the (*S*)-alcohol is formed (ee 89–>99% when R^2 = H, CH_2Ph) while when R^1 is large (*e.g.* Ph) then the reduction takes place in the opposite mode [*i.e.* the (*S*)-alcohol (43–92% ee) is formed; note the switch due to the operation of the Sequence Rule].[180]



81

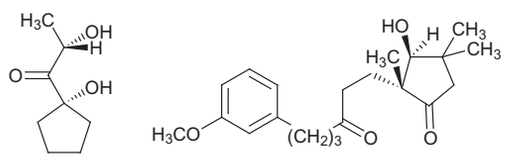
A little work has been carried out on the bio-reduction of simple cyclic ketones. For example 2-nitroethylcyclohexanone, and the 4-thia and 4-oxa analogues, were reduced by bakers' yeast to provide the *cis*-(*S*)-alcohols (48–58% conversion; 70–>99% ee).[181] The alcohol **82** is available from the corresponding ketone (40% yield) in high optical purity using *Candida lipolytica*. In contrast reduction of the same ketone with *Mucor subtilissimus* gave (1*S*,2*R*)-2-benzylcyclohexan-1-ol (97% ee) as a major product.[182] 3-Nitromethyl-, 3-phenylsulfonyl- and 3-phenylsulfonylmethyl-cyclohexanone all gave the corresponding (1*S*,3*S*)- and (1*S*,3*R*)-products (80% yields; 90–>99% ee) on reduction with bakers' yeast.[183]

The bromohydrin **83** was reduced enantioselectively by bakers' yeast over six hours to give the (2*S*,3*S*,6*S*)-diol and (2*R*,3*R*)-hydroxy ketone in quantitative crude yield. Both diol and hydroxy ketone were essentially optically pure and were used in the construction of chiral ligands for rhodium-catalysed asymmetric hydrogenation reactions.[184]



82 **83**

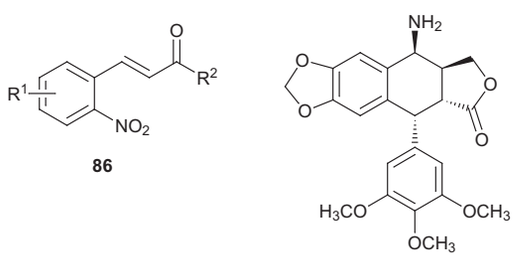
A series of acyclic diketones $RCOCH_2COCH_2Cl$ (where R = methyl through pentyl) have been reduced with bakers' yeast in the presence of allyl alcohol or organic solvent or, alternatively, after heat-treatment. All of the modifications gave enhanced (*S*)-selectivity (66–96% ee) and moderate to good yields (41–70%) of products.[185] The diol **84** has been manufactured on a large scale from the corresponding hydroxydione by bakers' yeast reduction.[186] Diacetyl reductase from *Bacillus stearothermophilus* has been isolated, characterized and shown to reduce 1,2-diones (*e.g.* cyclohexane-1,2-dione) to give the (*S*,*S*)-diols (80% yield; 95% ee for the above dione). The cofactor, NADH, was recycled using bicyclo[3.2.0]heptanone (a co-substrate) or, more conventionally, glucose-6-phosphate/glucose-6-phosphate dehydrogenase. The methodology may be utilized to form (*S*)-hydroxy ketones when unsymmetrical diketones are used as substrates.[187] The hydroxydione **85** is produced as the major component (37%) of a mixture when the appropriate trione is reduced by *Schizosaccharomyces pombe* NRRL Y-164 over 78 h.[188]



84 **85**

5.2 Miscellaneous reduction reactions

The reduction of aromatic *N*-oxides to the corresponding heteroaromatic compounds using bakers' yeast and aqueous sodium hydroxide over 2–8 h (*ca.* 90% yield) has been reported.[189] The same research group has disclosed that nitrobenzene derivatives **86** afford quinoline derivatives (*via* the quinoline *N*-oxides) using yeast in hot, aqueous sodium hydroxide.[190] However such reductions of nitrocompounds with bakers' yeast under extreme conditions have been re-investigated by Turner *et al.* who proved that the transformations are, in fact, non-enzymatic.[191]



86 **87**

Aromatic azido compounds have been reduced to the corresponding amines (in the presence of ester groups) in high yield using bakers' yeast in phosphate buffer containing ethanol (pH 7.2) over 1–2 days. The same paper describes the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines using chemo-selective bakers' yeast reduction of an azide moiety in the presence of an aldehyde group.[192] In a further application of this methodology, a mixture of 4α- and 4β-*cis* azidopodophyllotoxins were reduced to 4β-aminopodophyllotoxin **87** in 88% yield using bakers' yeast at pH 7.2 over 4 h. The predominance of the β-epimer of the amine was believed to be due to the isomerization of the substituent *via* Schiff's base formation.[193]

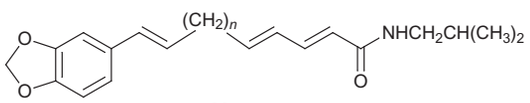
In an extension of earlier work it has now been shown that substrates of the type $CH_3CH(OR)COCO_2CH_3$ may be transformed into amino acids $CH_3CH(OR)CH(NH_2)CO_2H$ using a two-step, dual-enzyme transformation involving, initially *Candida cylindracea* lipase to produce the keto acid and then amino acid dehydrogenase in the presence of ammonium formate, FDH and NADH.[194]

Stereoselective deoxygenation of racemic alkyl aryl sulfoxides can be accomplished using *Rhodobacter sphaeroides*. The (*R*)-sulfoxide (40–47%; >99% ee) is recovered.[195]

Seleno-subtilisin is available by a three-step protocol from

subtilisin, involving modification of serine-221 in the active site. This semi-synthetic peroxidase can catalyse the rapid, enantioselective reduction of hydroperoxide $PhCH(OOH)CH_2OH$ yielding the (*S*)-hydroperoxide and the (*R*)-alcohol (both 98% ee).[196] Comparison of the resolution of compounds $R^1CH(OOH)C[Si(CH_3)_3]CHR^2$ using horseradish peroxidase and guaiacol as opposed to lipases led to the conclusion that the lipase-based methodology was, in fact, more successful.[197]

In an interesting carbon–carbon double bond reduction, Das *et al.* have shown that the alkene unit adjacent to the aromatic ring in compounds **88** is reduced using bakers' yeast (yield *ca.* 60%) over 48 h at room temperature.[198]



88

6 Oxidation reactions

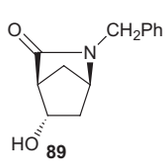
6.1 Hydroxylation reactions

2-Aminopyrimidines are hydroxylated at C-5 using *Beauvaria bassiana* and at C-2 and/or C-4 using *Rhodococcus erythropolis* and *Agrobacterium* sp. in yields often 70% or more.[199]

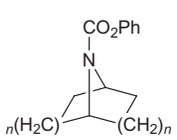
The particulate methanemonooxygenase from *Methylococcus capsulatus* gave the (2*R*)-alkanol from butane and pentane (46% and 80% ee respectively). Propylene gave (*S*)-propylene oxide (15% ee). The oxidations using this enzyme are limited to straight-chain hydrocarbons with five carbon atoms or less.[200]

2-Ethylbenzoic acid was converted into the lactone **80** (80%; 99% ee) using *Pseudomonas putida* (induced with σ-toluic acid) over 3 days at 30 °C and at pH 6.8.[201]

Racemic *N*-benzyl-2-azabicyclo[2.2.1]heptan-3-one is hydroxylated to give the alcohol **89** (30%), derived from the (−)-lactam. The (−)-enantiomer of the substrate is hydroxylated at four times the rate of the (+)-enantiomer.[202] A series of *N*-substituted bridgehead azabicycloalkanes were oxidized using the fungi *Beauvaria bassiana*, *Rhizopus nigricans*, *Aspergillus ochraceus* and *Rhizopus arrhizus*. In a typical example the 7-azabicycloheptanone **90** was transformed by *B. bassiana* to give the 2-*endo*-alcohol (46%, 51% ee); more surprisingly the corresponding azabicyclononane **91** gave the *exo*-3-hydroxy derivative (26%) using the same organism.[203] The oxidation of *N*-benzoyl tetrahydroisoquinolines using *C. elegans* led to hydroxylation in the saturated heterocyclic ring system.[204]



89



90 *n* = 1
91 *n* = 2

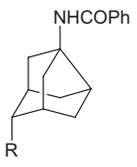
1-Azidoadamantane gave mainly the 3-hydroxy derivative (9%) and the *cis*-4-hydroxy derivative (8%) when oxidized using *B. bassiana*. The same organism converted the noradamantane **92** into the alcohol **93** in 58% yield.[205]

7*a*-Hydroxy- and 7*a*,15-dihydroxyaromadendrane were hydroxylated by *Mucor plumbus* over 6 days to give the diol and triol **94** respectively in 58–61% yield.[206]

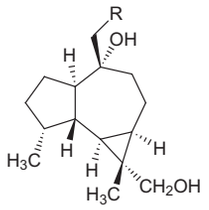
Penta-acylated taxadiene **95** was hydroxylated in the positions indicated, by the fungus *Absidia coerula* (65% combined yield).[207]

6.2 Dihydroxylation

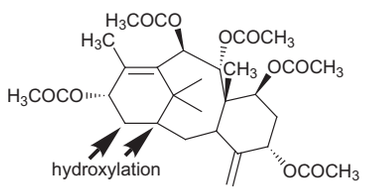
Optically active 3-substituted cyclohexa-3,5-diene-1,2-diols continue to be employed in multi-step syntheses of natural products and analogues. For example the 3-chlorodienediol



92 R=H
93 R=OH

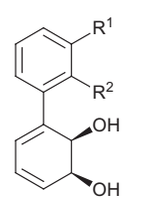


94 R=H or OH

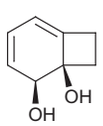


95

has been converted into 2-deoxy-2-fluoro-D-glucose in eight steps.[208] The 3-bromoethyldienediol has been employed in routes to *ent*-morphinans.[209] Along the same lines the availability of the 3-methyl and 3-phenyl derivatives has given rise to new approaches to morphine itself.[210] *E. coli* JM 109 (pDTG 601) (a recombinant microorganism introduced by Gibson *et al.* that over-expresses genetic information for the enzyme toluene dioxygenase from several Pseudomonads) yields the dihydroxy-compounds **96** from the corresponding biphenyl on a multigram scale.[211] Benzocyclobutane gave the diols **97** (18%) and **98** (13%) as well as (*S*)-benzocyclobutanol (33%) on incubation with *Pseudomonas putida* UV4.[212] Another pseudomonad, *P. testosteroni* A3C produced the diol **99** (81%) from 2-naphthoic acid.[213] *m*-Xylene-induced cells of *Sphingomonas yanoikuyae* convert chrysene into the diol **100** in low yield.[214]



96 R^1, R^2= H, OMe



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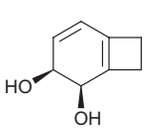

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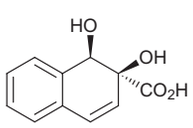

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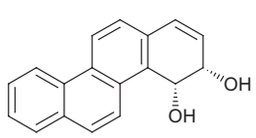


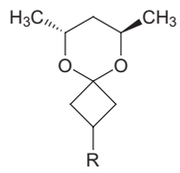
100

6.3 Baeyer–Villiger oxidation

The work of Furstoss and co-workers is predominant in this area. For example the French group converted 3-(4-chlorophenyl)cyclobutanone into the (*S*)-γ-lactone using *Acinetobacter calcoaceticus* (85% ee) and the (*R*)-γ-lactone using *Cunninghamella echinulata* (30%, >99% ee). The latter compound is a precursor of (*R*)-(−)-baclofen, a GABA agonist.[215] Resting cells of *C. echinulata* converted 3-benzyloxymethylcyclobutanone into the (*R*)-γ-lactone (30%; >97% ee) *en route* to (*S*)- and (*R*)-proline.[216] *C. echinulata* also converted (±)-bicyclohept-2-en-6-one into (−)-(1*R*,5*S*)-3-oxabicyclo[3.3.0]-oct-6-en-2-one (35%; >98% ee) a synthetic intermediate for both cyclosarkomycin[217] and multifidene.[218]

(*S*)-(−)-5-Methyloxepan-2-one has been prepared from 4-methylcyclohexane using cyclohexanone monooxygenase from *Acinetobacter calcoaceticus* and a modified formate dehydrogenase re-designed to accommodate NADPH as the cofactor. The transformation was carried out in a repetitive batch reactor.[219]

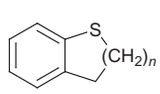
Alternatives to stereoselective Baeyer–Villiger oxidations by microorganisms are now provided by aerobic oxidations catalysed by chiral copper complexes.[220] In addition *m*-chloroperbenzoic acid oxidation of the chiral acetal **101** provided up to 89% ee of the corresponding 4-substituted γ-lactone.[221]



101

6.4 Heteroatom oxidation

A review has appeared focusing on the biotransformations catalysed by peroxidases (including heteroatom oxidation).[222] A comparison has been made between the chloroperoxidase (cpo) from *Caldariomyces fumago* and the cyclohexanone monooxygenase (cmo) from *Acinetobacter calcoaceticus* for their abilities stereoselectively to oxidize dialkyl sulfides (R^1-S-R^2) to the corresponding sulfoxides. For $R^1 = CH_3$, R^2 = isopropyl, allyl, pentyl or cyclopentyl, cpo gives >98% ee (*R*)-enantiomer at 75–>98% conversion. Cmo gives equal efficiency and stereoselectivity for $R^1 = CH_3$, R^2 = isopropyl, *tert*-butyl, allyl, cyclopentyl, cyclohexyl. It was concluded that, overall, cpo was the more convenient biocatalyst to use, being commercially available, using H_2O_2 as a cheap oxidant and not requiring co-factor regeneration.[223] The cyclic sulfides **102** were converted into the (*S*)-sulfoxides (90% ee at 84–99% conversion) using the vanadium-dependent bromoperoxidase from *Corallina officinalis*. The slow addition of hydrogen peroxide was essential for successful biotransformations.[224]



102 *n* = 1, 2

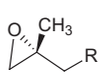
A predictive model for *Helminthosporium* sp.-catalysed oxidation of benzyl alkyl sulfides [to (*S*)-sulfoxides] has been proposed.[225]

Sperm whale myoglobin has been modified to provide a peroxygenase capable of converting methyl phenyl sulfide into the (*S*)-sulfoxide (85% ee); styrene was converted into the (*R*)-epoxide (68% ee) using the same catalyst.[226]

The modified Sharpless–Kagan methodology[227] provides an alternative way to convert sulfides into optically active sulfoxides.

6.5 Miscellaneous oxidations

Two papers have been published on the employment of the chloroperoxidase from *Caldariomyces fumago* to convert the appropriate alkenes into optically active epoxides **103** (82% yield; 92% ee) and **104** (33–93% yields; 50–95% ee).[228]



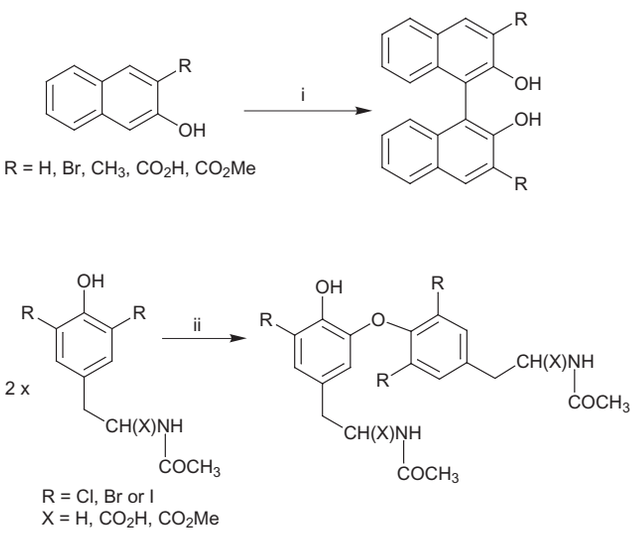
103 R= $NHCO_2CH_3$
104 R= $(CH_2)_nBr$; *n* =1-4

Metal-free chloroperoxidases from *Pseudomonas pyrrocinia* and *Streptomyces aureofacius* exhibit oxidizing activity due to an unusual hydrolase activity, namely the formation of peracetic acid from acetate and H_2O_2.[229]

Permeabilized, metabolically inactive forms of the methylotrophic yeasts, *Hansenula polymorpha* and *Pichia pastoris* contain glycolate oxidase which was used (in combination with catalase T from *Saccharomyces cerevisiae*) to convert glycolic acid into glyoxylic acid. The latter compound was coupled with aminomethylphosphonic acid and reduced to give the broad spectrum herbicide glyphosate, $HO_2CCH_2NHCH_2PO_3H$.[230] Glycolate oxidase from spinach (available in spinach acetone powder from Sigma) has been used to resolve α-hydroxy acids $RCH(OH)CO_2H$ [R = *n*-alkyl up to *n*-heptyl, alkenyl, isopropyl, $(CH_2)_2O(CH_2)_4CH_3$]. The (*S*)-enantiomer of the substrate was converted into the keto acid leaving unreacted (*R*)-enantiomer ee 86–>99% at *ca.* 50% conversion (over 22–60 h).[231]

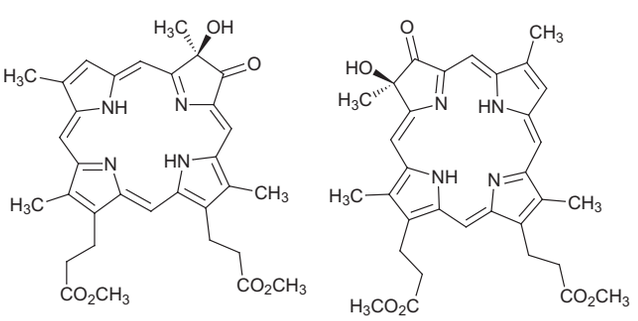
The primary hydroxy group in *O*-methylgalactoside was converted into an aldehyde group using purified galactose oxidase.[232]

Horseradish peroxidase and peroxide in pH 6 buffer has been used in two different phenol oxidative coupling procedures (Scheme 10). In the first, binaphthols were formed in 60–80% yield and modest to good (38–64% ee) enantiomeric excess.[233] In the second, phenethylamine and phenylalanine derivatives have been coupled in 45–65% yield.[234]



Scheme 10 *Reagents and conditions*: i) horseradish peroxidase (hrp), 5% H_2O_2 (slow addition) pH 6.0 buffer, CH_3CN; ii) hrp, H_2O_2, pH 6.0 buffer, <1 h; $NaHSO_3$, NaOH, H_2O.

Horseradish peroxidase and glutathione convert deuteroporphyrin into two novel chlorins **105** and **106** after methylation of the carboxylic acid groups.[235]

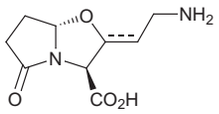


105 **106**

Clavaminic acid synthase isozymes from *Streptomyces clavuligerus* have been used to make small amounts of bicyclic lactams **107** from (2*S*,3*R*)-5-amino-3-hydroxy-2-(2-oxopyrrolidin-1-yl)pentanoic acid.[236]

Linoleic acid has been converted into the (*R*)-hydroxy keto acid $H_{11}C_5CH(OH)CH{=}CHCO(CH_2)_8CO_2H$ in four steps. In the first step lipoxygenase is employed to prepare an alkenylhydroperoxide as previously described. In the last step lipase PS is used to hydrolyse a macrocyclic lactone under mild conditions.[237]

Yeast has been used to oxidize podophyllotoxone to dehydropodophyllotoxin **108** on a small (50 mg) scale.[238]



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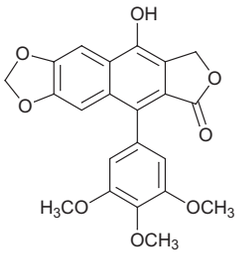


108

7 Carbon–carbon bond formation

7.1 Preparation of cyanohydrins

A comparison of apple, apricot, cherry and plum meal suggested the apple preparation was best for producing (*R*)-cyanohydrins from hindered aldehydes. For example pivalaldehyde gave (*R*)-cyanohydrin (99% conversion; 90% ee) over 24 h.[239] Such (*R*)-cyanohydrins are converted into (*S*)-amino acids quite readily.[240] Apple or almond meal also provide (*R*)-cyanohydrins from alkyl methyl ketones; for example methyl *n*-pentyl ketone gave (*R*)-cyanohydrin (76% conversion; 98% ee). Increasing the size of the methyl group is counter-productive.[241]

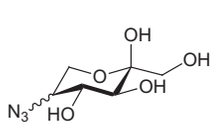
(*R*)-Oxynitrilase-catalysed addition of HCN to aromatic aldehydes (ArCHO) has provided intermediates to (*S*)-amphetamines,[242] (*R*)-terbutaline and a late-stage intermediate to salbutamol.[243]

(*S*)-Selective hydroxynitrile lyases are available[9] and have been used to prepare the (*S*)-cyanohydrin $H_3C(CH_2)_4CH$-$CHCH(OH)CN$ a precursor to (15*S*)-hydroxyoctadecadienoic acid.[244]

Alternative non-enzymic methods for the preparation of optically active cyanohydrins have been reported. These include the bismuth(III) chloride addition of trimethylsilyl cyanide to aldehydes in the presence of diethyl L-tartrate [for example benzaldehyde gave (*S*)-cyanohydrin (72% ee) in 0.5 h][245] and use of the Binol–$Ti(CN)_2$ complex.[246]

7.2 Aldol reactions

Dihydroxyacetone monophosphate (dhap) and 2-azido-3-hydroxypropanal afford the azidotetraol **109** in an aldol reaction catalysed by rabbit muscle aldolase (rma). The latter azide was converted into novel cyclic imine sugars which acted as α-fucosidase inhibitors.[247] Similarly rma catalysed the coupling of dhap to (5*Z*)-3,8-dioxadec-5-enedial to provide the triol **110** after removal of the residual phosphate group using potato acid phosphatase (40% yield).[248] Note that dhap is conveniently prepared from L-α-glycerophosphate using co-immobilized L-α-glycerophosphate oxidase and catalase. The coupled enzyme system may be recovered and re-used without loss in activity.[249]



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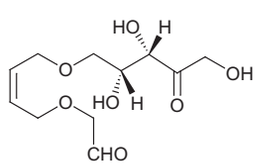


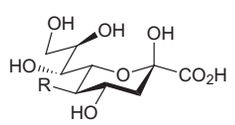
110

L-Threonine aldolase from *Escherichia coli* and D-threonine aldolase from *Xanthomonus oryzae* have been cloned and overexpressed. The enzymes work well in aqueous dimethyl sulfoxide solution (up to 40% DMSO) using pyridoxal phosphate (to activate glycine). A wide range of aldehydes are accepted as substrates.

Several β-hydroxy-α-amino acid derivatives, hydroxyleucines, γ-benzyloxythreonines and polyoxamic acids have been prepared on a preparative scale. For example 2-methylpropanal gave (*S*)-hydroxy-(*R*)-leucine in 65% yield after recrystallization.[250]

The increased availability of sialic acid aldolase has promoted research aimed at the preparation of sialic acids and related compounds. The enzyme catalyses the aldol reaction between (methyl) pyruvate and 2-deoxymannose,[251] 2-azidomannose[251] and 2-mannosamine derivatives[252] to furnish compounds (**111**, R = H, N_3, NHCOR respectively). Excess pyruvate may be removed at the end of the reaction by means of pyruvate decarboxylase from bakers' yeast.

A multiple-enzyme-based synthesis of the amino acid moiety of nikkomycins and analogues **112** has been reported. The first step involves an aldol reaction between the requisite aldehyde and pyruvate or fluoropyruvate using KDPG-aldolase. The next transformation utilized phenylalanine dehydrogenase (from *Bacillus sphaericus* and over-expressed in *E. coli*) and NADH, recycling the NADH using yeast formate dehydrogenase and formate. The overall yields for the two steps were as high as 75%.[253]



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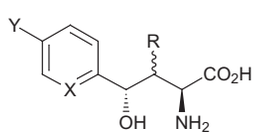


112

8 Carbohydrate chemistry

There has been much-increased activity in this area. In addition to the aldolase work (documented above) the use of glycosidases and glycosyltransferases is becoming more popular.

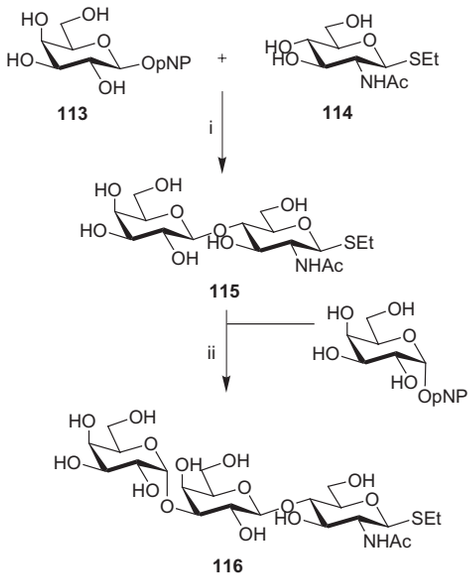
In a simple procedure β-galactosidase from *Bacillus circulans* has been used to couple compounds **113** and **114** to give the disaccharide **115**. The latter compound was reacted with *p*-nitrophenylgalactoside using α-galactosidase II from *Aspergillus oryzae* to give compound **116**, a receptor for toxin A from *Clostridium difficule* (Scheme 11).[254] A very similar procedure, published almost simultaneously, was described by Nilsson.[255] *N*-Acetyllactosamine is available by *B. circulans* β-galactosidase-catalysed transfer of a galactose unit from D-lactose to *N*-acetylglucosamine.[256] Coffee bean galactosidase has been used to prepare compound **117** in 20% yield, an improvement on Nilsson's earlier procedure. Compound **117** was used in a chemical synthesis of Galα1-3Galβ1-4GlcNAc.[257]

β-Galactosidase from *E. coli* featured in a three-enzyme synthesis of fluorescence-labelled tetrasaccharide **118** (Scheme 12). The other enzymes involved were lipase PS (to protect the reactive C-6 hydroxy group of the starting material) and β-glucuronidase (to couple glucuronic acid in the final step).[258]

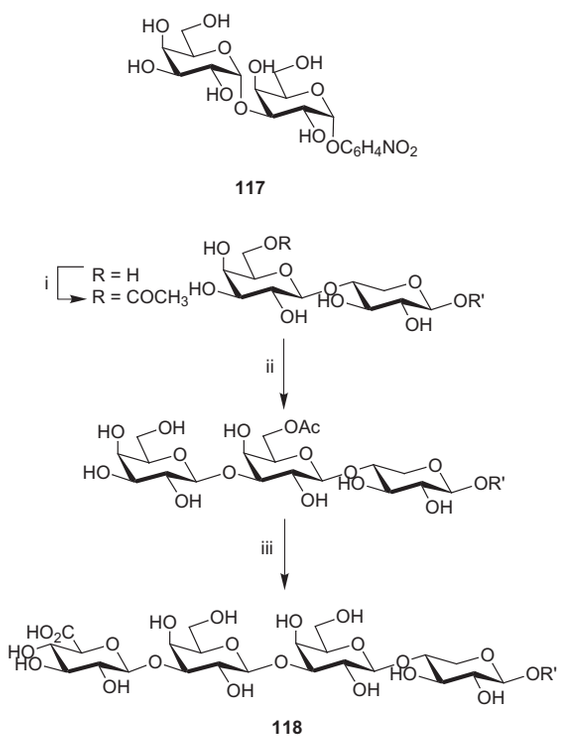
N-Acetyllactosamine is available from *o*-nitrophenylgalactoside and *N*-acetylglucosamine in 61% yield after 30 min using a thermophilic glycosidase.[259] The thermophilic bacterium *Sulfolobus solfactaricus* contains a β-glycosidase activity allowing compounds **119** derived from rengyosides to be derivatized using *p*-nitrophenyl-β-D-glucopyranoside in 15–44% yield.[260] α-Glucosidase from yeast catalyses the transfer of a glucopyranosyl unit from maltose to the C-4 hydroxy group of 5-azido-5-deoxyfructopyranose (6% yield) *en route* to glucosylated derivatives of a glucosidase inhibitor.[261]

A more unusual use of the galactosidase from *E. coli* is the resolution of the diastereoisomeric sulfoxides **120**. The (*S*)-sulfoxide is hydrolysed to galactose over 20 h leaving the (*R*)-sulfoxide relatively unscathed.[262]

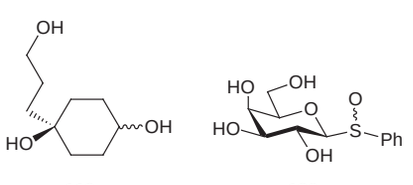
Various lipid-coated glycoside hydrolases (*e.g.* α- and β-mannosidases, β-D-galactosidase) act as catalysts for the transglycosylation of, for example, α-D- and β-D-mannoside as well



Scheme 11 *Reagents and conditions*: i) β-galactosidase from *B. circulans*; ii) α-galactosidase II from *A. oryzae.*

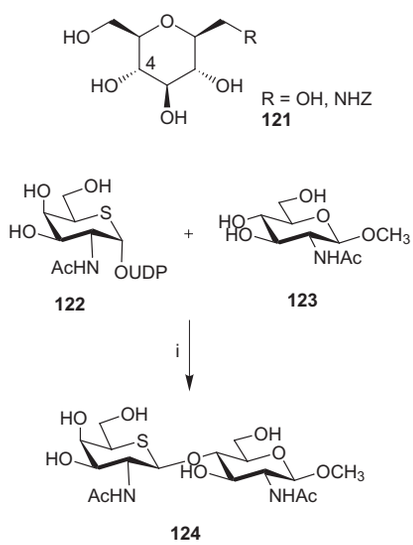


Scheme 12 *Reagents and conditions*: i) lipase PS, vinyl acetate, 89%; ii) *E. coli* β-galactosidase, galactose, pH 7.3, 37 °C, 16%; iii) K_2CO_3 in MeOH then β-glucuronidase, glucuronic acid, pH 5, 37 °C, 12%.

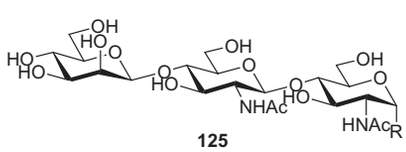


as β-D-galactoside to hydrophobic acceptor alcohols such as 5-phenylpentan-1-ol. The lipid coating acts to solubilize the enzymes in organic solvents such as diisopropyl ether.[263] Thermostable glycosidase-catalysed reversed hydrolysis and transglycosidations are faster (complete reaction in typically 2–3 h) when performed in a dry system (water activity 0.8) using focused microwave irradiation and at 95 °C. The hydrolytic side reaction is limited to *ca.* 10%. The dry conditions are obtained by co-immobilization of enzyme donor and acceptor on a support such as neutral alumina.[264] β-Galactosidase from *Aspergillus oryzae* remains active at −7 °C in, for example, the coupling of vinyl-β-D-galactoside and methyl α-galactoside.[265]

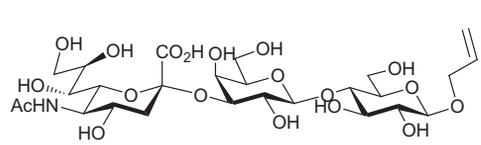
β-1,4-Galactosyl transferase from bovine colostrum catalyses the coupling of UDP glucose to the C-4 OH-group of C-glucosides **121** (37–68% yield) when the reaction is run in the presence of UDP glucose epimerase and other selected ingredients.[266] Bovine 1,4-galactosyl transferase catalyses the regioselective transfer of galactose (from UDP-galactose) to kaurane glycosides stevioside and steviolbioside, adding the new unit to give the β-D-gal-(1→4)-β-D-glu moiety at the glycosylated terminus of the molecule.[267] The thiasugar **122** has been coupled to the glucosamine derivative **123** to give the compound **124** in 47% yield using lactose synthase (a complex of galactosyl transferase and lactalbumin) (Scheme 13).[268] Highly stereo- and regio-selective formation of the β-1,4-mannoside bond in the trisaccharide **125** is accomplished by a modified yeast β-mannosyltransferase overexpressed in *E. coli*. Immobilization on a nickel(II) affinity column appeared to stabilize the enzyme.[269]

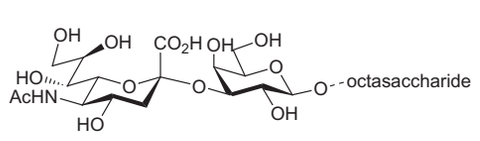


Scheme 13 *Reagents and conditions*: i) lactose synthase.

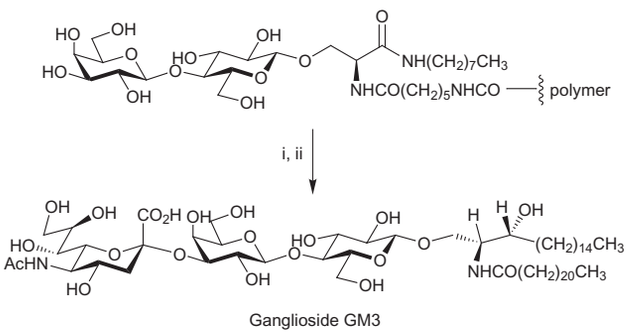


An investigation into the donor substrate specificity of α-2,3-sialyl transferase has been conducted and the utility of the enzyme for the synthesis of oligosaccharides that contain derivatized sialic acids **126** has been demonstrated.[270]



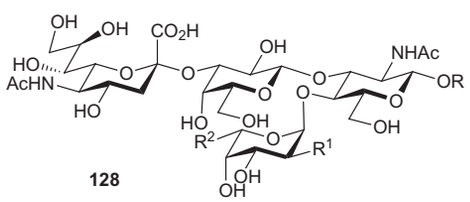


The synthesis of a biantennary core-fucosylated dodecasaccharide has been achieved by adding the disaccharide unit **127** to the preformed octasaccharide using β-galactoside-α-2,6-sialyltransferase.[271] Ganglioside GM3 has been prepared using a lactose/water soluble polymer adduct and the enzyme α-2,3-sialyltransferase in the first step. The polymer assisted enzymatic process afforded the desired product in an overall yield of 56% (Scheme 14).[272] GM3, Lewis X and sialyl Lewis X are available in ^{13}C enriched form. The use of recombinant *Trypanosoma cruzi trans*-sialidase to convert Gal-β-1,4-Glc into NeuNAc-α-2,3-Gal-β-1,4-Glc is noteworthy.[273]



Scheme 14 *Reagents and conditions*: i) CMP-NeuAc, α-2,3-sialyltransferase, BSA, pH 7.5 buffer, 37 °C, 3 days, calf intestinal phosphatase; ii) ceramide, ceramide transferase, citrate buffer, pH 6.

Two cloned fucosyl transferases Fuc-t III and Fuc-t VI catalyse the addition of non-natural GDP-linked donor sugars to trisaccharide acceptors to give products **128** and **129** respectively. The Fuc-t III showed a broader substrate range tolerating changes at C-2 (R^1 = OH, NH_2, F) and C-6 (R^2 = H, CH_3, CH_2OH) (yields 48–97%); in contrast Fuc-t VI allowed changes only at C-6 (R^1 = OH; R^2 = H, CH_3, CH_2OH) (yields 58–82%).[274] Fuc-t VI has been used to glycosylate non-natural acceptors (*e.g.* compound **130**) with non-natural GDP-activated donor sugars to create sialyl-Lewis X libraries.[275] The new versatile procedure for the synthesis of nucleotide-activated donor sugars is useful in this connection.[276]



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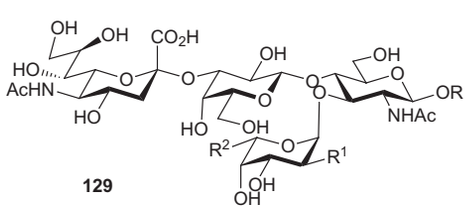

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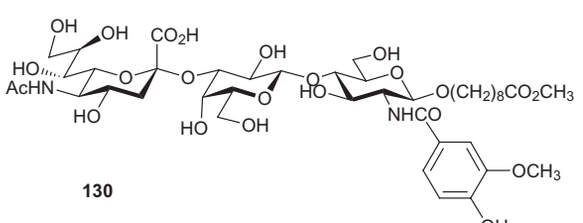
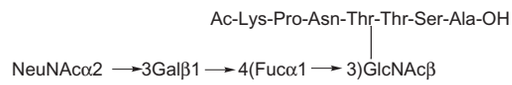


130

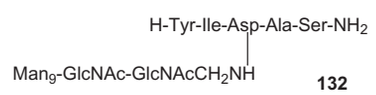
The synthesis of glycopeptide **131** possessing an *O*-glycosidically linked sialyl Lewis X structure has been accomplished by using fucose transferase to extend the glycan unit, by appending the fucose moiety to the glycopeptide substrate in solution or on a solid support.[277]



131

Ribonuclease B has been treated with *endo*-glycosidase H to leave a variant of ribonuclease possessing a single *N*-acetylglucosamine at Asn 34 of the 124-amino acid sequence. A new ribonuclease glycoform, containing the branched oligosaccharide sialyl Lewis X, was synthesized using glycosyl transferases *e.g.* β-1,4-galactosyl transferase. Thus galactosyl transferases also accept glycoproteins as good substrates.[278]

The synthesis of high-mannose type *N*-glycopeptides has been achieved by chemical synthesis of GlcNAc-containing peptides and by transferring $Man_9GlcNAc$ to the terminal GlcNAc in 26% yield using *endo*-β-*N*-acetyl glucosaminidase from *Arthrobacter protophormiae* in aqueous organic solvents. Thus, in contrast to using a host of glycosyl transferases, this approach allows the installation of a complex oligosaccharide chain into glycoconjugates to give products such as **132** in one step using one enzyme.[279] Transglycosylation to Fmoc-Asn-(GlcNAc)-NH-β-cyclodextrin by *endo*-β-*N*-acetylglucosaminidase from *Mucor hiemalis* gave three species of natural oligosaccharide branched cyclodextrins, for example compound **133**, in 6–12% yield.[280]



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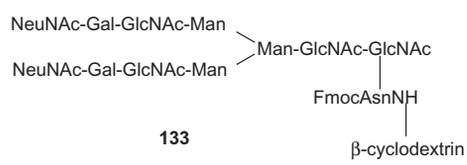
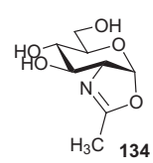


133

Using chitinase (from a *Bacillus* sp.) in citrate buffer (pH 7.8) the oxazoline **134** as the glycosyl donor and *N*-acetylglucosamine as the acceptor, *N*,*N*′-diacetylchitobiose **135** has been prepared in 43% yield.[281] Recombinant 1,3-1,4β-D-glucanase from *Bacillus licheniformis* has been used to prepare methyl 4-*O*-β-laminaribiosyl-β-laminaribioside **136** from β-laminaribiosyl fluoride and methyl β-laminaribioside.[282]



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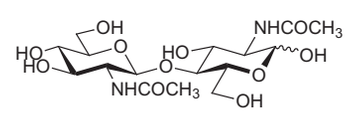

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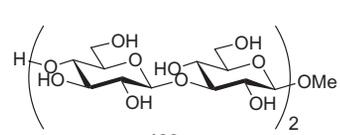


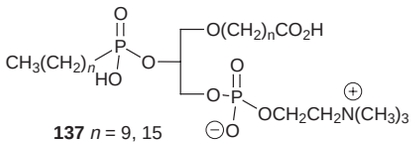
136

9 Enzyme mimetics

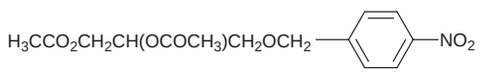
9.1 Catalytic antibodies

This section will be structured such that hydrolases will be considered first, then carbon–carbon bond-forming antibodies; finally a selection of catalytic antibodies showing other activities will be described.

A phospholipase A_2-like catalytic antibody has been isolated using the quaternary ammonium compound **137** as the hapten.[283] The racemate **138** is hydrolysed enantioselectively, generating the (*R*)-primary alcohol (36% yield; 80% ee), using IgG 2D10 raised to phosphonate **139**.[284] An antibody raised to the achiral hapten **140** shows different rates of hydrolysis for the



137 n = 9, 15



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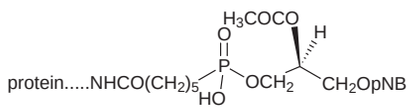

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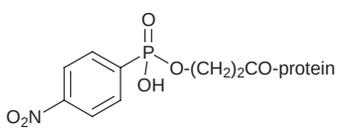

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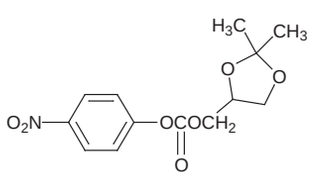

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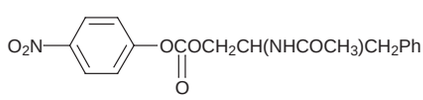


142

two enantiomers of compound **141** with $k^s_{cat}/k^r_{cat} \sim 4$ with $k_{cat}/k_{uncat} \geq 14$ for both enantiomers.[285] An acyl intermediate has been observed for this antibody during hydrolysis of carbonate **142**.[286]

The aryl carbamate **143** is hydrolysed using antibodies raised to haptens **144** conjugated to keyhole limpet haemocyanin. The usually disfavoured $B_{AC}2$ mechanism is promoted, indicating the antibody overcomes an energy barrier ≥13 kcal mol^{-1}.[287]

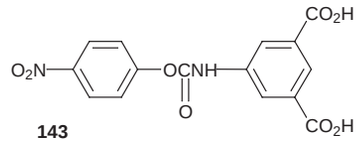
There have been two reports concerning the use of positively charged twist-boat haptens, for example the iminocyclitol **145**, to generate antibodies *in vitro* and *in vivo* capable of catalysing the hydrolysis of *p*-nitrophenyl glucopyranoside and *p*-nitrophenyl galactopyranoside with $k_{cat}/k_{uncat} \geq 2 \times 10^4$.[288]

The concept of "reactive immunization" (in this case utilizing a labile phosphonate diester hapten) has been employed to generate a library of hydrolases. The most active catalysts (raised to BSA-linked hapten **146**) increased the rate of hydrolysis of naproxen ester **147** by up to 10^5. Five of the monoclonal antibodies showed good selectivity for the hydrolysis of the (*S*)-ester (90% ee naproxen acid at 26% conversion).[289]

It has been shown previously that antibody 16G3 can catalyse the synthesis of dipeptides; it has now been shown that this protocol may be extended to allow the preparation of tri- and tetra-peptides in yields of 80%.[290]

A polyclonal catalytic antibody raised to hapten **148** showed a modest rate enhancement for the Diels–Alder reaction depicted in Scheme 15.[291]

Catalytic antibody 38C2 (now available from Aldrich) has been used previously for the catalysis of a wide range of inter-



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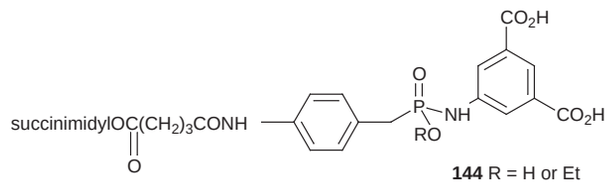
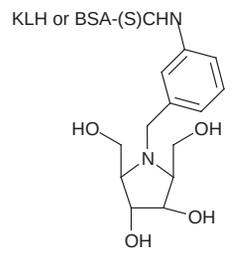


144 R = H or Et



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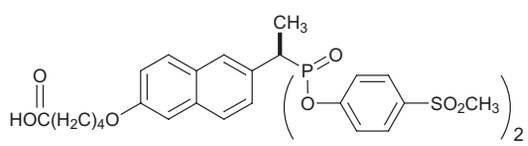

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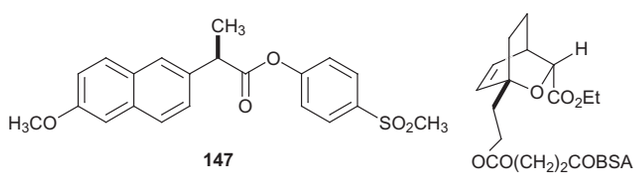

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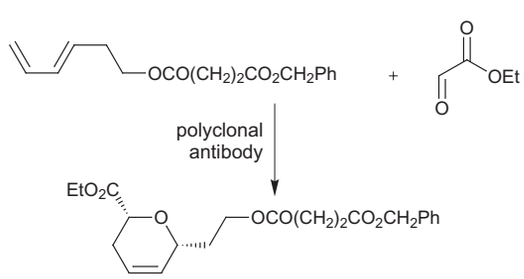
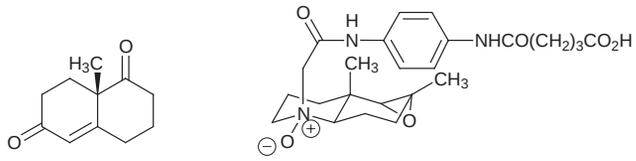


Scheme 15

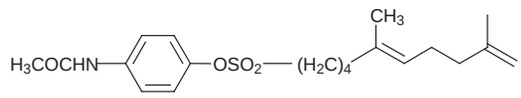
molecular aldol reactions. It has recently been used to catalyse both steps of the Robinson annulation of 2-methyl-2-(oxobutyl)-cyclohexane-1,3-dione to the bicyclic dione **149** (96% ee) with $k_{cat}/k_{uncat} = 3.6 \times 10^6$. Indeed the whole sequence from 2-methylcyclohexane-1,3-dione and methyl vinyl ketone can be catalysed using the same antibody![292]

Antibody catalysed cationic reactions have been reviewed.[293] Further studies on tandem ring-forming reactions at neutral pH have featured catalytic antibodies raised to hapten **150** which enhance the cyclization of diene **151** to give the bicyclodec-2-ene, the bicyclodec-3-ene and the exomethylene compound (summarized in formula **152**) in the ratio 2 : 3 : 1 with a rate enhancement of *ca.* 2×10^3.[294] Similarly the antibody raised to the hapten **153** is known to catalyse the cyclization of alkene **154**. Theoretical data show that antibodies that are able to bind and stabilize a perturbed cation intermediate amplify intrinsic structural biases.[295]

The hapten **155** has been coupled to carrier proteins and used to raise antibodies capable of promoting a pericyclic elimin-



149 150



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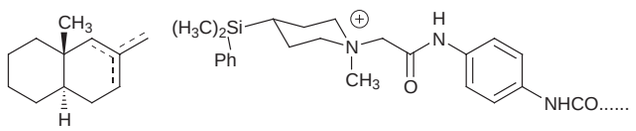

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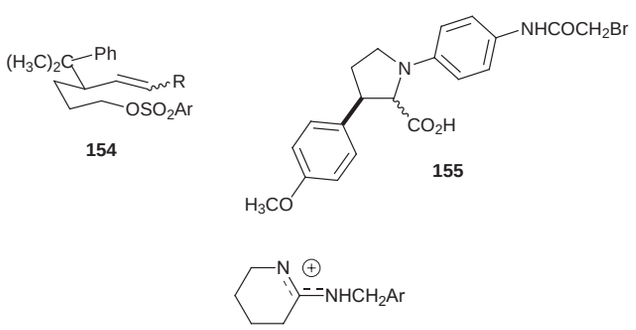
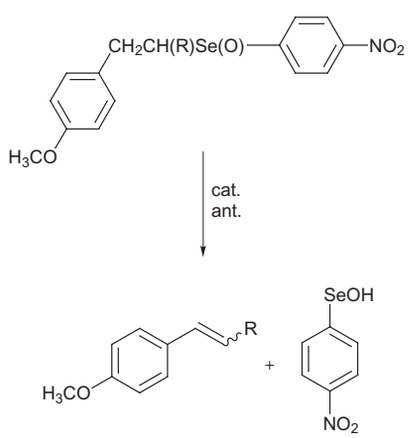


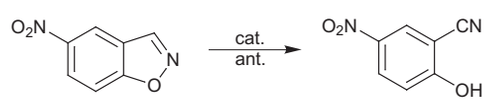
154 155 156

ation $k_{cat}/k_{uncat} \geq 10^3$ (Scheme 16) for which natural enzymes are unavailable.[296]



Scheme 16

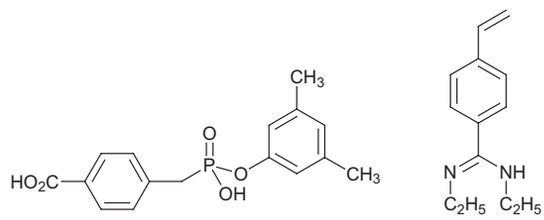
An antibody raised to the cationic hapten **156** in an unsuccessful effort to raise glycosidase activity showed adventitious catalysis of the reaction described in Scheme 17 ($k_{cat}/k_{uncat} = 1.8 \times 10^4$).[297]



Scheme 17

9.2 Other enzyme mimetics

Polymers possessing an imprint of the phosphonate **157** and having catalytically active groups, by incorporation of the styrene derivative **158** into the matrix, show strong catalytic activity and typical enzyme properties (*e.g.* Michaelis–Menten kinetics, competitive inhibition, substrate selectivity *etc.*).[298]



157 **158**

KO-42 is a polypeptide with 42 amino acid residues that has been designed to fold into a hairpin helix-loop-helix motif that dimerizes to form a four-helix bundle. KO-42 catalyses the hydrolysis of mono-*p*-nitrophenyl fumarate at pH 4.1 and 27 °C at a rate $>10^3$ times that of the conventional imidazole-catalysed reaction.[299]

Adipocyte-lipid-binding protein, modified by attachment of a 1,10-phenanthroline unit to a unique cysteine residue, catalyses the enantioselective hydrolysis of several unactivated amino acid esters at rates 32–280 times the background reaction. Ala-O^{i}Pr is one of the best substrates with a rate enhancement of 130 and showing reasonable enantioselectivity (ee 86% for the L-enantiomer). Unactivated amides are also hydrolysed.[300]

Stereoselective reduction of acetophenone was accomplished by using sodium borohydride in the presence of β-cyclodextrin and triethylamine through formation of a three-component complex.[301]

A review on the use of polyamino acids for the stereoselective epoxidation of α,β-unsaturated ketones has appeared.[302] The substrate range for this curious biomimetic reaction has been enlarged[303] and the methodology has been used to make diltiazem and taxol side-chain.[304] Note that Jackson and co-workers have developed a method involving modified lithium and magnesium *tert*-butyl peroxides for similar stereoselective epoxidations of chalcones.[305]

The cyclic α-MePhe-His dipeptide shows the same propensity as the Inoue (cyclo Phe-His) dipeptide for the asymmetric addition of HCN to aldehydes. For example benzaldehyde and HCN at −40 °C combine to give (*R*)-mandelonitrile (98%; 99% ee).[306] However *N*-methyl derivatives of cyclo Phe-His catalyse the formation of **racemic** cyanohydrins indicating that both CONH units are essential for effecting asymmetric catalysis.[307]

In a continuation of work on semi-synthetic transaminases derived from fatty acid-binding proteins it has been shown that rate, enantioselectivity and substrate specificity can be altered by site-directed mutagenesis to alter the position of attachment of the pyridoxamine cofactor.[308]

10 Miscellaneous biotransformations

It has been shown that bovine adenosine deaminase is effective in converting a 2,6-diaminoadenosine residue into a guanosine unit in 3′-desoxyribo-, 2′-desoxy-, 2′-aminoarabino- and thiaarabino-systems.[309]

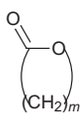
Labelled nucleoside phosphates are available from labelled glucose using enzymes from the pentose phosphate pathway. Using these new methods one gram of nucleoside monophosphate can be prepared from one gram of glucose.[310]

Phospholipase D (for example from *Streptomyces antibioticus*, from cabbage or from peanut) allows the interchange of the choline "head-group" in compounds of the type $RCOOCH_2CH(OCOR)CH_2OP(O)OCH_2CH_2N^+(CH_3)_3$ for other residues such as ethanolamine, glycerol and L-serine.[311]

But-3-enyl diphosphate is a substrate for the thermostable farnesyl diphosphate synthase from *Bacillus stearothermophilus* affording norgeranyl and norfarnesyl diphosphate.[312]

Halogenases isolated from *Pseudomonas fluorescens* have been shown to be capable of converting L-tryptophan into 7-chloro-L-tryptophan.[313]

The employment of enzymes in polymer-forming reactions has been reviewed.[314] Kobayashi has continued to publish significant work in this area. For example, the Japanese group has recently shown that diols, such as octane-1,8-diol, and diacids, such as decanedioic acid, may be coupled by *Ps. cepacia* lipase in water in up to 50% yield (mol wt *ca.* 1600 daltons; M_w/M_n 1.6).[315] Immobilized *Candida antarctica* lipase catalyses very fast ring-opening polymerization of lactones **159**. Addition of an alcohol as an initiator further increased the rate of polymerization. In this way 1 mmol of ε-caprolactone was polymerized in 1 h using 10 mg of catalyst.[316] Acylation of polyester terminal alcohol groups has been achieved by enzyme-catalysed ring-opening polymerization of 12-dodecanolide in the presence of acrylic vinyl esters, for example vinyl methacrylate.[317]



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11 Conclusions

Enzymes, traditionally used in food processing, have found increasing use during the past twenty years in the manufacture of chemicals. Enzymatic reactions are currently used to produce *ca.* 1800 kilotonnes per year of intermediates for the pharmaceutical industry. An additional 1500 tonnes of aspartame are also produced using an enzymatic process. Further opportunities and recent developments, as illustrated in this Review, will ensure that biocatalysis will find increasing application for the synthesis of chiral intermediates and ethical drug substances.[318]

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