Pergamon

Tetrahedron, Vol. 52, No. 11, pp. 3769-3826, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01021-1

TETRAHEDRON REPORT NUMBER 392

Enantioselective Synthesis Through Enzymatic Asymmetrization

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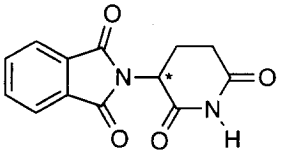
1. INTRODUCTION

During the last few decades almost no other aspect of organic synthesis has received as much attention as the preparation of enantiomerically pure compounds. The synthesis of optically active materials is an important task and represents a challenge to academic and industrial chemists alike. An increasing interest in understanding biological processes and the general recognition that chirality plays a crucial role in nature fostered a tremendous effort in enantioselective synthesis. In the course of synthesizing natural products and designing new target compounds, chemists had to acknowledge the fact that enantiopurity is related to biological properties.[1,2] Opposite enantiomers interact differently within an organism and can display various activities. Some differences are enormous, ranging from distinguishable smells and flavors to teratogenic effects. Between 1958 and 1962, the worldwide use of the racemic drug thalidomide (**1**) by pregnant women resulted in severe birth defects in approximately 10,000 children. The lesser sedating enantiomer had the teratogenic side effect. Events like this have stimulated drug regulation legislation including highly restrictive guidelines for the marketing of synthetic chiral drugs. The 1962 amendments required that adequate information be provided to establish the effectiveness and safety of a new drug. The United States Food and Drug Administration (FDA) does not prohibit the marketing of racemates. However, the choice of a racemic synthesis over the development of an enantiopure drug must be justified. The FDA requires investigations on the bioavailability and pharmacological effect of a chiral drug and its final approval is based on complete background information on each enantiomer and, possibly, the racemic mixture. There is a strong emphasis on the development of single stereoisomers for the marketing of new drugs. In contrast, the fate of already marketed racemic drugs and those under development seems uncertain. What is clear is that there is considerable interest by the pharmaceutical industry in re-marketing former racemic drugs in enantiopure forms. With industry adjusting to a changing regulatory climate, the control of stereochemistry and the design of new methodologies for asymmetric synthesis has become increasingly important.



1 Thalidomide

Asymmetric synthesis[3] has contributed to the determination of relative configurations and reaction mechanisms, and is widely used in natural product synthesis and in industrial preparations of pharmaceuticals, flavors, fragrances, pesticides, etc. One can resort to a variety of methods to accomplish the synthesis of enantiomerically pure compounds, and among those, the application of enzymes has become accepted as a routine procedure.[4-14] Although the concept of enzyme application to asymmetric synthesis has been long recognized, it is only recently that these catalysts are attracting the attention of the non-specialist.

1.1. Turmoil in the discovery of a new science

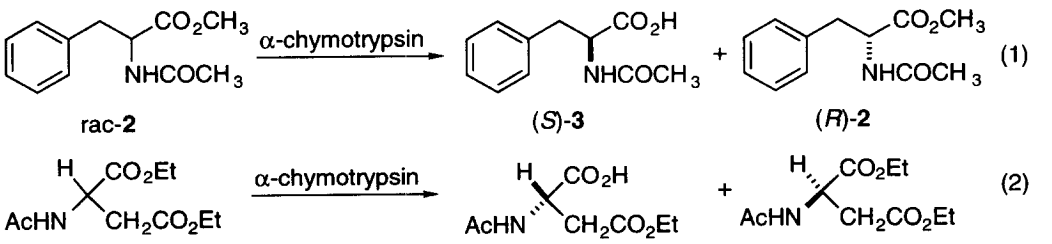
Enzymes have valuable industrial[4] and medical applications. The fermentation of wine, leavening of bread, curdling of cheese, and the brewing of beer have been known for eons. It was not until the 19th century that scientists began to investigate the nature of these processes.[15] Payen and Perzon discovered the first enzyme in 1833, when they observed a precipitation from an aqueous malt extract. Three years later, Schwann extracted the active component of gastric juice and called it pepsin. The discovery of enzymes preceeded the idea of catalysis, which was put forward by Berzelius in 1837. The following years were marked by a scientific dispute that evolved with discussions about the nature of fermentation. Liebig, often referred to as the founder of biochemistry, explained fermentation on the basis of enzyme action. He did not

believe that living cells were essential for fermentation and became Pasteur's chief opponent. In 1848, Pasteur reported his remarkable work on optical activity of tartrates and turned his attention to the resolution of racemates. Using a microorganism, he performed a kinetic separation for the first time, and his studies in succeeding years led him to believe in the necessity of vital forces. The term "enzyme" was coined by Kühne (1876), and it was Emil Fischer who carried out the first asymmetric synthesis when he applied the cyanohydrin reaction to L-arabinose (1894). He also noticed that enzymes have a high degree of substrate specificity and proposed a lock and key model for enzyme-substrate interaction during catalysis. In 1897, Buchner extracted a cell-free juice from yeast and demonstrated that fermentation can occur without living cells. He therefore ended the long controversy about fermentation. Based on symmetry principles, Marckwald published the first, historically important definition of asymmetric synthesis in 1904; a modern definition was proposed by Morrison and Mosher almost seventy years later.[3] By 1920, about a dozen enzymes were known, none of which had been isolated. In 1926, Sumner succeeded in first crystallizing an enzyme; with the improvement in instrumentation, the isolation and purification of new enzymes was accelerated. At present, more than 3000 enzymes have been catalogued[16] and several hundred can be obtained commercially. By far, the best asymmetric syntheses are achieved in nature by enzymes. Organic chemists, however, have put forward great effort to achieve comparable results by various means. Although many non-enzymatic methods have emerged for enantioselective synthesis, biotransformations are likely to play an increasingly important role in aiding organic chemists to meet a wide range of synthetic challenges.

1.2. Enzymes as synthetic tools

Even though enzymes may show a high degree of substrate-specificity in catalyzing transformations of natural substrates, they often accept a wide range of structurally related compounds. For this reason, enzymes have become extremely important in the preparation of enantiomerically pure, unnatural compounds. For almost every type of chemical reaction there exists an enzyme-catalyzed equivalent. A variety of reactions can be mediated, such as oxidations, reductions, hydrolyses, condensations, and isomerizations. Enzymes can also be involved in carbon-carbon and carbon-heteroatom bond formation. The Enzyme Commisson has classified enzymes in six main groups according to the type of reaction they catalyze:[17] (1) Oxidoreductases; (2) Transferases; (3) Hydrolases; (4) Lyases; (5) Isomerases; (6) Ligases. Enzymes from groups 1 through 4, especially hydrolytic enzymes, have found broad application in organic transformations.

Enzymes are chiral host molecules and their ability to discriminate between enantiomers of a racemic substrate is of well-recognized preparative value. The resolution of racemic mandelate by pig liver esterase was published by Dakin as early as 1903.[18] α-Chymotrypsin isolated from bovine pancreas, was one of the earliest enzymes to be investigated preparatively and has been widely used for the resolution of amino acids.[19] Its catalytic activity illustrates some of the advantages of biotransformations. The enzyme *chemo-* and *enantioselectively* hydrolyzes the ester group of **2** to afford the enantiopure *N*-acetyl L-phenylalanine (**3**) (eq 1).[20] The regioselectivity is exemplified in the hydrolysis of diethyl L-*N*-acetyl aspartate, in which only one of the ester groups is processed (eq 2).[21]



An enzymatic resolution[9] gives access to both enantiomers, which is desirable if both are required for pharmacokinetics, drug-receptor interaction studies, or other uses. However, if only one enantiomer is needed, a 50% conversion constitutes the maximum yield. Enzymes are also capable of differentiating enantiotopic groups of prochiral and *meso*-compounds. In contrast to the kinetic resolution of a racemic material, the theoretical yield of these conversions is 100%. The enzymatic asymmetrization of *meso*-compounds has gained popularity in recent years and constitutes an elegant approach for the synthesis of enantiomerically pure compounds. Based on a three point attachment rule, the enzymatic conversion of *meso*-substrates was discussed by Ogston in 1948.[22] Pioneering work was accomplished by Cohen who investigated thoroughly the requirements for stereospecificity in chymotrypsin-mediated hydrolyses and published his initial work on diethyl acetamidomalonate in 1959.[23]

Due to low cost, high stability, and substrate tolerance, hydrolases,[10,11] such as pig liver esterase (PLE),[12] porcine pancreatic lipase (PPL), and α-chymotrypsin, have been frequently used. Lipases are designed by nature to function at a water-lipid interface involving the enzyme in aqueous solution and the insoluble lipid substrate. The use of lipases in organic solvents simply "inverts" this interface — the enzyme and its associated water of hydration is insoluble and the substrate is in solution. It is logical, then, that lipases are particuliarly useful for transformations in organic solvents.[24] Oxidoreductases are not as frequently applied because of expensive cofactors that are required and the constraints associated with sensitivity and cofactor regeneration. Despite those drawbacks, there have been numerous reports on the use of horse liver alcohol dehydrogenase.[7h] Jones and several other groups have applied this enzyme to the oxidation of *meso*-diols and reduction of *meso*-ketones. Baker's yeast is commonly used as a "cocktail" of dehydrogenases and its application is fairly simple, lacking all the technical difficulties that are usually associated with handling oxidoreductases in pure form.[8a]

Most asymmetrization substrates bear common functionalities such as alcohols, ketones and esters. However, in order to maximize the use of enzymes as tools in synthetic chemistry, it is important to broaden the choice of functional classes effective as substrates. Hydrolases for epoxides[25] and nitriles,[26] as well as redox enzymes used in Baeyer-Villiger oxidations[27] open up new opportunities in asymmetric synthesis. A very rare approach to asymmetrization is the application of glycosidases (galactosidase[28] from *Escherichia coli* or *Aspergillus oryzae*), to yield mono-β-D-galactosides with de values up to 96% (Figure 1).

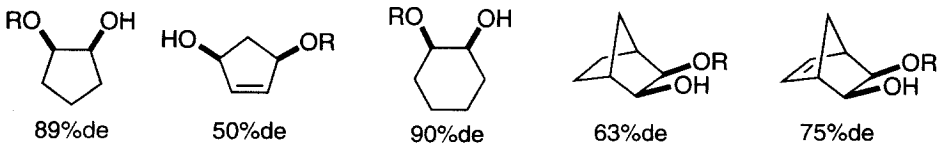
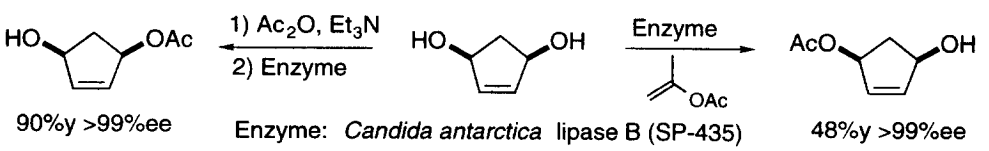


Figure 1. Asymmetric glycosylation of cyclic *meso*-diols by β-galactosidase (R=β-D-gal).

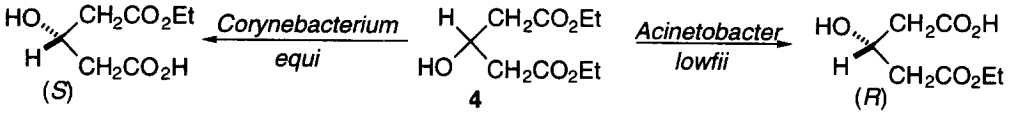
Regardless of the enantiomeric outcome of the enzymatic asymmetrization, it is usually possible to enter either enantiomeric series by modification of subsequent reaction steps or of the reaction conditions of the enzymatic transformation. Generally lipases operate at the same prochiral center regardless of media, thus one can choose between enantiocomplementary hydrolysis or synthesis pathways as illustrated in Scheme 1.[29]

Scheme 1



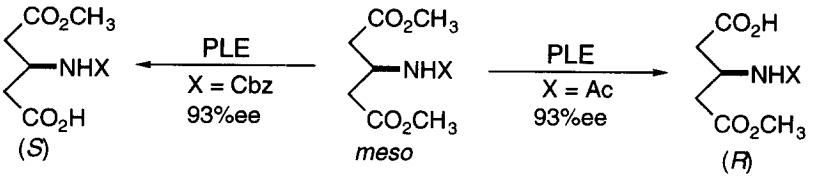
With the increasing availability of biocatalysts, one can take advantage of those that exhibit opposite enantioselectivity. The prochiral diester **4** was hydrolyzed with different microorganisms; by use of *Acinetobacter lowfii* the hydrolysis yielded the (*R*) acid, whereas *Corynebacterium equi* sp. gave rise to the (*S*) enantiomer (Scheme 2).[30]

Scheme 2

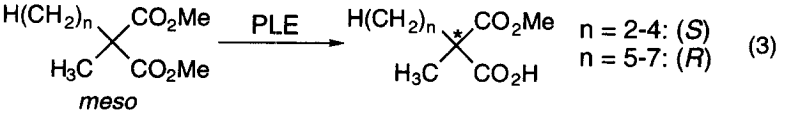


Certain substrate modifications can cause a reversal of enantioselectivity. The nature of the protection of the amino functionality not only improved the stereoselectivity[31] but also determined the configuration of the product (Scheme 3).[32]

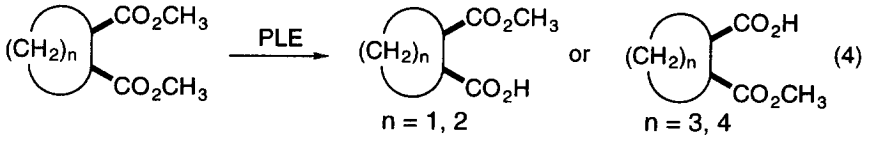
Scheme 3



Enantioselectivity can also be influenced by chain length or ring size of certain *meso*-substrates. Various ethyl malonates upon treatment with pig liver esterase gave rise to different product configurations (eq 3).[33]

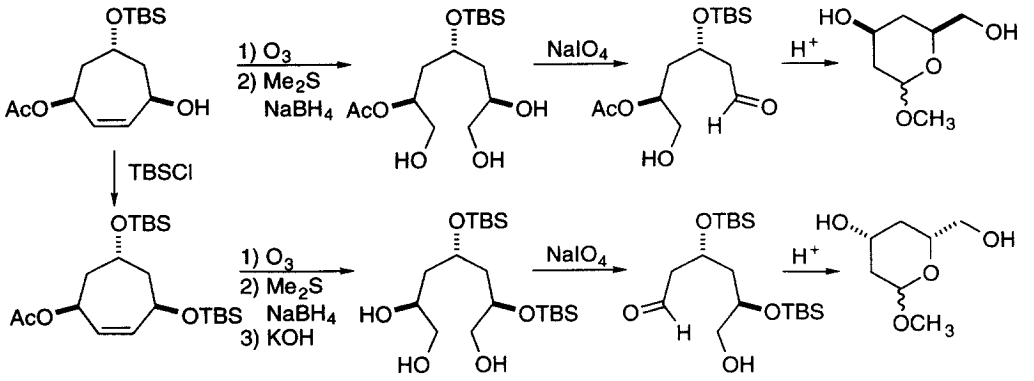


In the case of cyclic *meso*-diesters, pig liver esterase cleaved the ester group at the (*S*)-stereogenic center of small ring diesters; when the ring size was increased, the enzyme exhibited a reversed enantiotopic specificity by processing the ester group at the (*R*)-center (eq 4).[34]

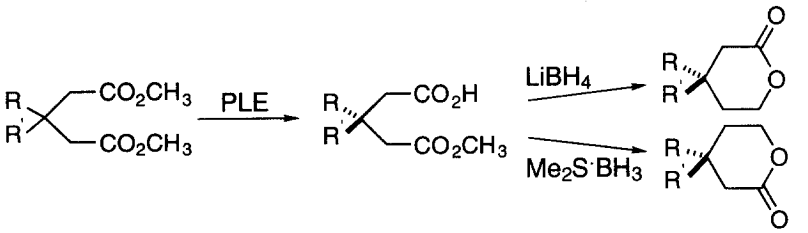


The use of simple protective group manipulation was exploited in the synthesis of all possible methyl 2,4-dideoxyhexopyranosides. Asymmetrization of the starting *meso*-cycloheptanediol gave rise to an enantiopure monoacetate by use of *Pseudomonas cepacia* lipase (Amano P-30) in the presence of isopropenyl acetate. The latter compound was converted to both hexopyranoside enantiomers by similar reaction sequences (Scheme 4).[35] A similar approach is depicted in Scheme 5. After enzymatic transformation of the diester, both lactone enantiomers can be obtained by choice of different reagents in subsequent steps.[36]

Scheme 4



Scheme 5



In recent years, enzyme applications especially in the asymmetrization of *meso*-compounds have become very common, and their importance is reflected by numerous reports in the literature including their use in drug syntheses.[13] Many comprehensive reviews have appeared that discuss the use and practicality of biotransformations in organic synthesis.[4-24] Reviews on the asymmetrization of prochiral substrates are not as common and are often dealt with in connection with general enzyme applications. It should be mentioned, a recent detailed review by Danieli *et al.* has appeared on enzymatic asymmetrization and covers the literature until the middle of 1991.[14] The versatility of 2-methyl-1,3-propanediol derivatives and its equivalents has also been recognized, and a review entirely dedicated to their preparation and application is available.[37] This Report will emphasize the application of enantiopure intermediates that are obtained *via* enzymatic asymmetrization of prochiral substrates with enantiotopic groups and *meso*-compounds and includes many publications through Fall 1995. We will focus on those intermediates that can be isolated in high chemical yields and enantiopurities and on their use in organic synthesis. A discussion based on enzyme classification does not seem useful for such purposes. Thus, this Report has been organized according to the synthetic equivalent that can be "built into" the desired target molecule. Based on the substrate framework, chain length, and ring size, we differentiate between acyclic (2.1) and cyclic (2.2) *meso*-and prochiral compounds, and discuss them separately from borderline examples (2.3), namely *meso*-cycloalkane diesters and dimethanols. A fourth segment (2.4) describes the use of polycyclic substrates, and the final segment (2.5) deals with asymmetrization of metalloorganic and miscellaneous compounds that do not fit into any of the other categories. Table 1 lists common abbreviations for enzymes featured in this review and as denoted by authors.

Table 1. Commonly Used Enzyme Abbreviations

α-CT	α-Chymotrypsin
ACE	Acetyl cholinesterase
Amano P-30	*Pseudomonas fluorescens* (=*cepacia*) lipase
Amano PS	*Pseudomonas fluorescens* (=*cepacia*) lipase
ANL	*Aspergillus niger* lipase
APL	Amano lipase AP
AY	*Candida cylindracea* (=*rugosa*) lipase
CAL-B	*Candida antarctica* lipase B
CCL	*Candida cylindracea* (=*rugosa*) lipase
CE	Cholesterol esterase
CEH	cytosolic epoxide hydrolase
CRL	*Candida rugosa* (=*cylindracea*) lipase
CVL	*Chromobacterium viscosum* lipase
EEL	Electric eel cholinesterase
GCL	*Geotrichum candidum* lipase
HLADH	Horse liver alcohol dehydrogenase
lipase AH	*Pseudomonas* sp. lipase
lipase AK	*Pseudomonas* sp. lipase
lipase AY	*Candida cylindracea* (=*rugosa*) lipase
lipase MY	*Candida cylindracea* (=*rugosa*) lipase
lipase OF	*Candida cylindracea* (=*rugosa*) lipase
lipase B	*Candida antarctica* lipase B
lipase P	*Pseudomonas fluorescens* (=*cepacia*) lipase
lipase PS	*Pseudomonas fluorescens* (=*cepacia*) lipase
LPL	lipoprotein lipase fr. *Pseudomonas* sp.
LPL-800	*Pseudomonas cepacia* lipase (purified)
LMJ	*Mucor javanicus* lipase
MEH	microsomal epoxide hydrolase
Mucor sp.	*Mucor miehei* lipase
PAN	Pancreatin, pancreatic lipases (also contains esterases, proteases or their zymogens, and amylases)
PCL	*Pseudomonas cepacia* (=*fluorescens*) lipase
PFL	*Pseudomonas fluorescens* (=*cepacia*) lipase
PGL	recombinant cutinase fr. *Fusarium solani pisi*
PLE	Pig liver esterase
PPL	Porcine pancreatic lipase
Protease P6	protease fr. *Aspergillus melleus*
PS	*Pseudomonas fluorescens* (=*cepacia*) lipase
PSL	*Pseudomonas cepacia* (=*fluorescens*) lipase
RDL	*Rhizopus delemar* lipase
SAM II	*Pseudomonas* sp. lipase
Sp.382	*Candida* sp. lipase
SP435	recombinant *Candida antarctica* B lipase
Seaprose S	protease fr. *Aspergillus melleus*
Sub.	Subtilisin (bacterial proteinase)

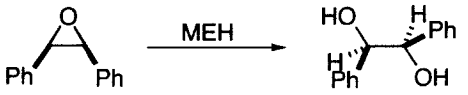
2. ENZYMATIC ASYMMETRIZATION

2.1. Acyclic *meso*-and prochiral substrates

2.1.a. *Vicinal* diols

Only a few *meso*-derivatives of acyclic *vicinal* diols have been asymmetrized successfully.[38] Often a mixture of all possible stereoisomers was subjected to biocatalysis. The results are generally not synthetically

useful owing to low chemical or optical yields. The erosion of enantiopurity might be due to facile 1,2-acyl migration. The asymmetrization of *meso*-epoxides by enantioselective hydrolysis constitutes another approach to the preparation of optically active *vicinal* diols (eq 5).[25]



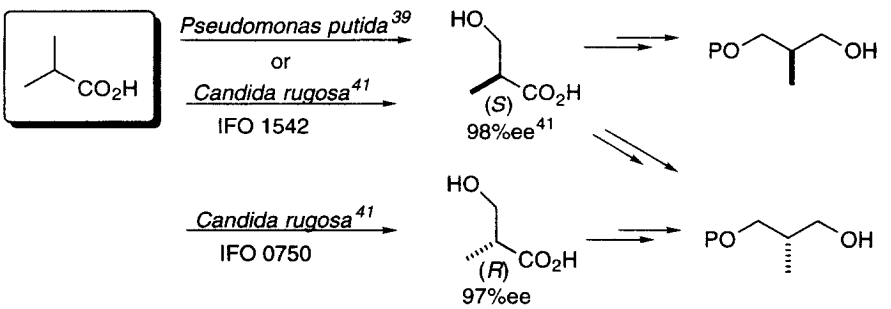
(5)

2.1.b. 2-Substituted-1,3-propanediols, 1,3-diesters, and 1,3-dichlorides

The enantioselective preparation and synthetic elaboration of 2-methyl-1,3-propanediol and its synthetic equivalents were recently reviewed.[37] In this section we reiterate known asymmetrization methods of this compound and its synthetic applications. Asymmetrizations of other 2-substituted 1,3-propanediols and malonates, as well as of 1,3-dichloro-2-propanol, will also be presented.

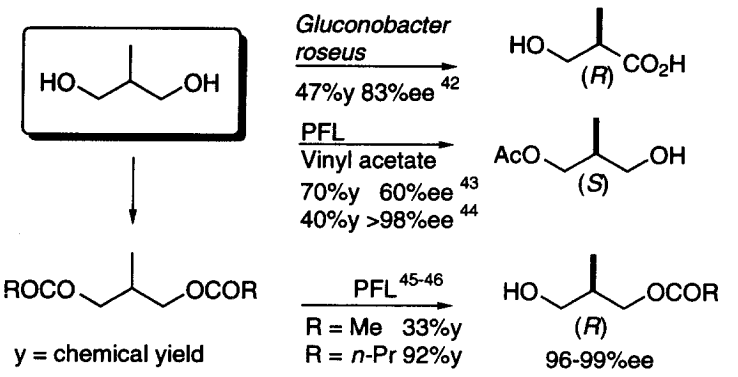
The first enzymatic synthesis of chiral derivatives of 2-methyl-1,3-propanediol was achieved by microbiological oxidation of isobutyric acid. Treatment of isobutyric acid with *Pseudomonas putida* provided enantiopure (*S*)-3-hydroxy-2-methylpropanoic acid on a multigram scale,[39] allowing for the preparation of both enantiomers by protective group manipulation.[40a] It was found later that either enantiomer of the hydroxy acid could be obtained by choice of the strain of *Candida rugosa* (Scheme 6).[41]

Scheme 6



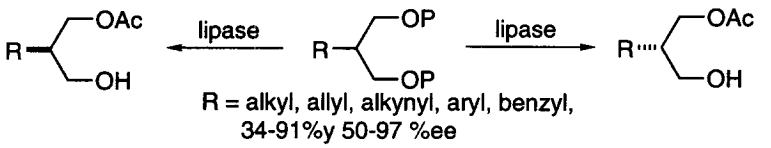
(*R*)-3-Hydroxy-2-methylpropanoic acid can also be obtained *via* microbiological oxidation of 2-methyl-1,3-propanediol (Scheme 7).[42] Enzymatic acetylation of the same diol led to the (*S*)-monoacetate with good chemical but moderate optical yield.[43] Santaniello *et al.* substantially improved the enantiopurity of the product by allowing a subsequent enzymatic resolution to occur.[44] When the reaction was stopped before the diacetate started to form, 40% of the diol and 52% monoacetate of only 60%ee were isolated. However, when the reaction was continued until the diol was consumed, 60% of the diacetate formed and the monoacetate, which did not react in the second esterification step, was obtained in 40% yield with high enantiopurity (>98%ee). These findings were confirmed when racemic monoacetate was subjected to enzymatic acetylation using PFL. Again, enantiopure (*S*)-monoacetate and the diacetate were isolated. This indicates that a resolution of the racemate occured rather than asymmetrization of a *meso*-substrate. The enantiomeric (*R*)-monoacetate was obtained through PFL-mediated hydrolysis of the diacetate[44,45] or dibutyrate.[46] Enantiopure C_4-building blocks derived from isobutyric acid or 2-methyl-1,3-propanediol have been employed in the synthesis of α-tocopherol,[40a] (*R*)- and (*S*)-muscone,[40b,45] (-)-maysine,[40c,d] and calcimycin.[40g]

Scheme 7



The enzymatic hydrolysis of 2-substituted-1,3-propane diacetates was reported by several groups (Scheme 8).[45-54] In most cases the enzyme of choice was porcine pancreatic lipase; it gave the asymmetrized monoacetate in good chemical yield and enantiopurity. Empirical models for the interpretation of the results obtained with this enzyme were proposed.[51] An extensive study by Guanti and co-workers on the effect of unsaturation adjacent to the prochiral center of these diacetates confirmed the suggested beneficial effect of a π-system in that position. A dramatic effect of the double bond geometry on the absolute configuration of the enzymatic reaction products was observed.[53]

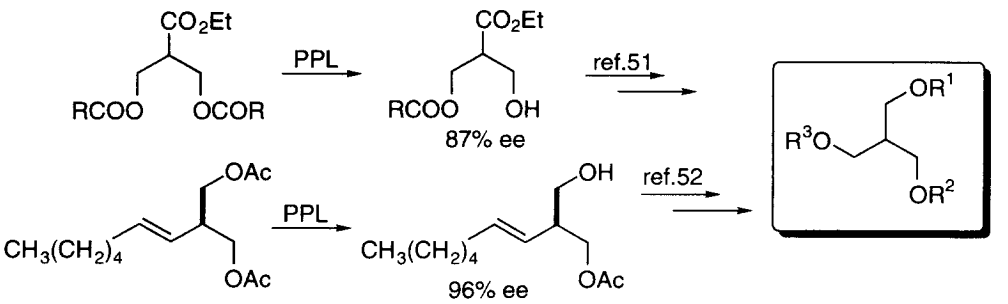
Scheme 8



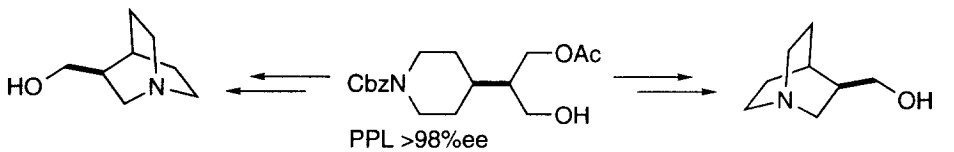
In the course of these studies, Guanti and co-workers investigated the asymmetrization of an interesting C_{3v}-symmetric triol.[52,54] The corresponding triacetate was successfully converted to prochiral diacetates (R^1 = R^2 = Ac; R^3 = various protecting groups) by use of a PPL-mediated hydrolysis for the selective deprotection of just one hydroxyl group. However, various 1,3-diacetoxy-2-alkoxymethylpropanes were either unreactive or afforded poor yields and ee's in a subsequent enzymatic monohydrolysis. A different approach was chosen; the use of (E)-1,3-diacetoxyl-2-alkenylpropanes provided an efficient entry into a series of "asymmetrized tris(hydroxymethyl)methanes", since the double bond can be cleaved *via* ozonolysis and represents a synthetic equivalent to the desired hydroxymethyl group. The authors reported detailed studies on enantiodivergent transformations of various monoacetates into a number of chiral building blocks.[52,54-58] Seebach and Ehrler applied a similar approach by testing 3-acyloxy-2-(acyloxymethyl)propanoates as substrates.[51] Subsequent transformations gave rise to tris(hydroxymethyl)methane derivatives; the absolute configuration was not established (Scheme 9).

Complementary synthetic methods for the asymmetrization of 2-substituted-1,3-propanediols led to enantiomeric monoacetates[43,44,48,58-62] and provide preferred routes for the preparation of both enantiomers of 3-hydroxymethylquinuclidine (Scheme 10).[59]

Scheme 9

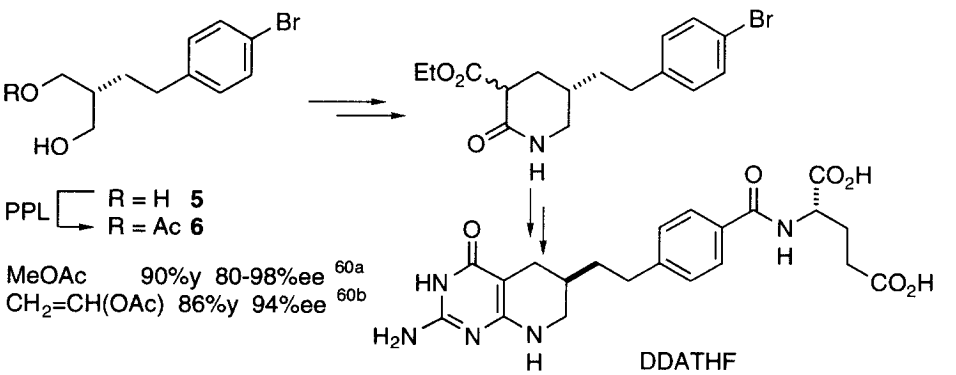


Scheme 10



An interesting asymmetrization protocol has been applied to the synthesis of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, Scheme 11). Initially the diol **5** was treated with methyl acetate in the presence of immobilized PPL to afford the monoacetate **6** in 90% yield but of variable enantiopurity. This step was improved by the use of PPL and vinyl acetate in THF/hexane.[60]

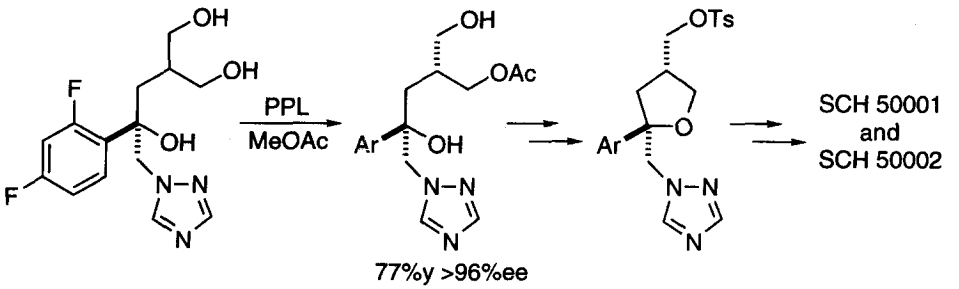
Scheme 11



An effective use of porcine pancreatic lipase catalysis was reported in the total synthesis of antifungal compounds SCH 50001 and SCH 50002. The fairly complex substrate, bearing a distal triazole ring and a chiral carbinol center, was acetylated diastereoselectively in the presence of methyl acetate as transfer reagent. (Scheme 12).[63]

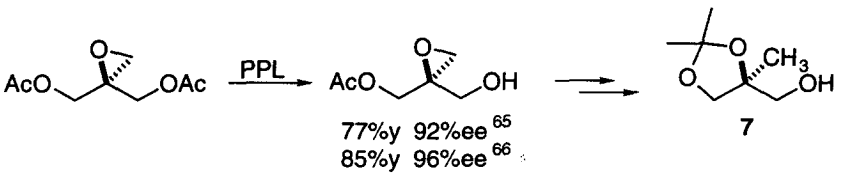
Aliphatic nitro compounds are synthetically useful derivatives and can be processed by use of enzymatic catalysis. Seebach and co-workers have studied the saponification of *meso*-2-nitro-1,3-propanediols, which are readily available from nitroalkanes and aldehydes (eq 6).[64]

Scheme 12



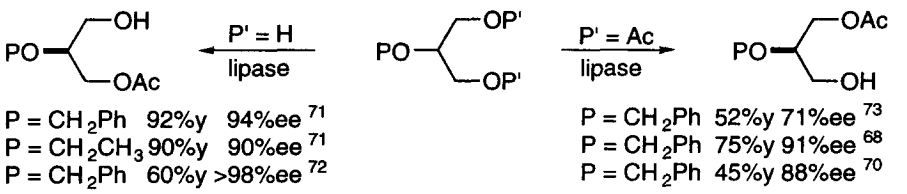
The synthesis of acetonide **7** links the asymmetrization of 2-substituted 1,3-propanediols to glycerols. Asymmetric hydrolysis of a geminally disubstituted achiral diacetate with PPL gave rise to enantiopure (*R*)-2-acetoxymethylglycidol, which is a versatile *tertiary*-alcohol building block. The use of lipase OF afforded the (*S*)-enantiomer but with substantially lower optical yields (56%, Scheme 13).[65,66]

Scheme 13



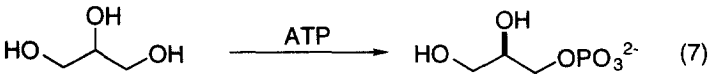
The first successful enzymatic asymmetrization of glycerol was described by Leuthardt an co-workers in a study of HLADH-mediated oxidations of this triol. L-Glyceraldehyde, formed enantioselectively, combined with phosphodihydroxyacetone mediated by either rabbit muscle or liver aldolase; the single product was identified as L-sorbose-1-phosphate.[67] Alternative syntheses of enantiopure glycerol derivatives utilizing hydrolytic enzymes have been studied by many research groups. The products were obtained in good chemical yields and enantiopurities (Scheme 14).[68-73]

Scheme 14



Related compounds such as *N*-Cbz-serinol served as good substrates in this type of asymmerization. PPL-catalyzed transesterification of this diol with vinyl pentanoate gave rise to (2*R*)-2-*N*-(benzyloxycarbonyl)-3-*O*-pentanoylserinol in 77% yield (after 60% conversion) and 97% ee.[73]

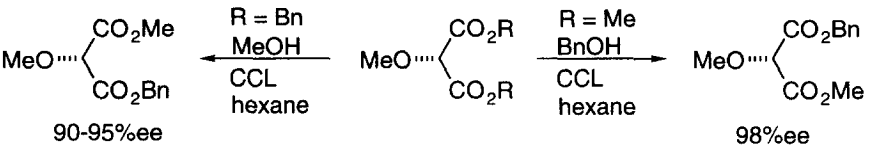
A practical single-step procedure for the preparation of L-glycerol-3-phosphate, an important intermediate in the synthesis of phospholipids, was reported by Whitesides and Rios-Mercadillo.[74] Enantioselective enzymatic phosphorylation of glycerol using ATP, immobilized glycerol kinase, and acetate kinase was achieved in 76% chemical yield (eq 7)



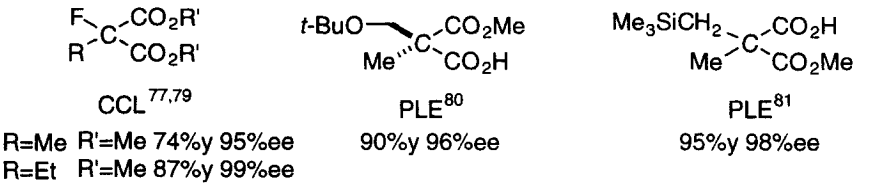
(7)

Early attempts to asymmetrize monosubstituted malonates under aqueous conditions failed, because the activated C-H in the half ester undergoes fast exchange accompanied by racemization.[75] Gutman and co-workers reported the use of enzymes in organic solvents, which allowed for the efficient preparation of such optically labile compounds and their subsequent conversion into the corresponding, configurationally stable, hydroxy-esters (Scheme 15).[76]

Scheme 15

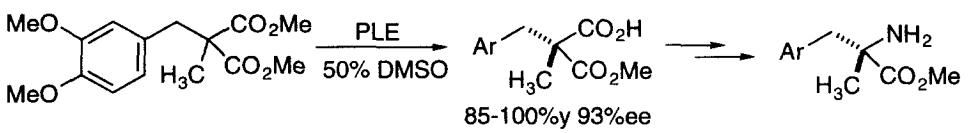


The problem of optical instability does not exist for 2,2-disubstituted malonates, which have been studied by several research groups.[76-82] Selected examples are shown.



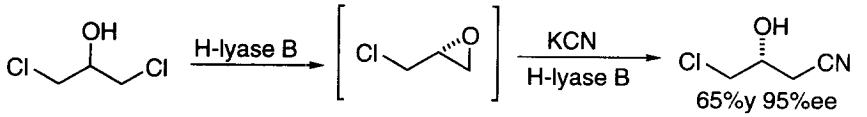
A synthetic application is given in Scheme 16, outlining the synthesis of (*S*)-α-methyl-3,4-dihydroxyphenylalanine (L-α-methyl DOPA).[33,78a] A dramatic effect of the reaction medium on the enantiomeric excess during PLE-catalysis was observed. When a pure aqueous buffer system was employed the product displayed only 16%ee. Upon variation of the solvent system (50% DMSO) the selectivity was drastically increased (93%ee). Stereoselective degradation of the chiral hemiester *via* Curtius-rearrangement of an acyl azide intermediate allowed for the introduction of the amino functionality.

Scheme 16



A new method for the asymmerization of 1,3-dichloro-2-propanol was recently described by Nakamura and co-workers (Scheme 17).[83] A new enzyme, H-lyase B, was found in the *Corynebacterium* sp. strain N-1074,[84] and the expression of the cloned enzyme was accomplished in *Escherichia coli*.[85]

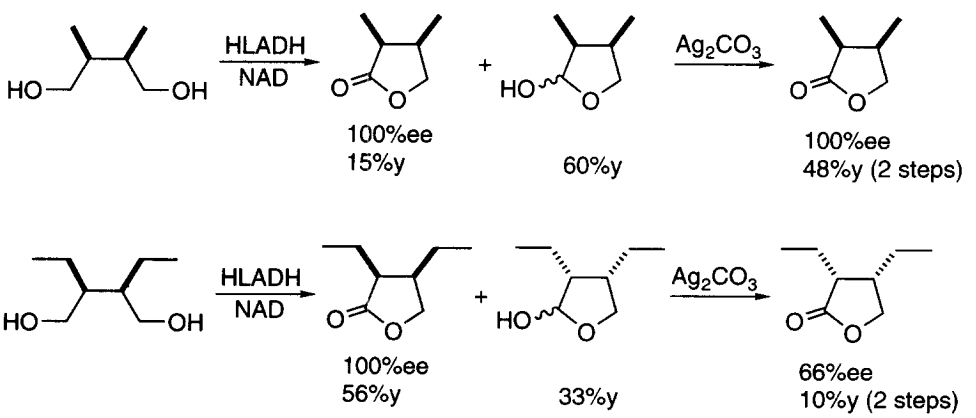
Scheme 17



2.1.c.*meso*-2,3-Disubstituted butane-1,4-diols and succinates

The HLADH-catalyzed conversion of 2,3-dimethyl- and 2,3-diethyl-1,4-butanediol was described by Jones and co-workers. These substrates are stereoselectively oxidized to hydroxyaldehyde intermediates which undergo further *in situ* oxidation affording the corresponding lactones. For each substrate the enzyme preferentially operates on the hydroxymethyl group at the (*S*)-stereogenic center. For 2,3-dimethyl-1,4-butanediol the stereoselection occurs in the initial oxidation of the *meso*-diol to hemiacetals with (3*S*) chirality only. For the corresponding homologue the stereodiscrimination is most profound in the second oxidation as indicated by low ee values of the enantiomeric lactone after oxidation with Ag_2CO_3 (Scheme 18).[86]

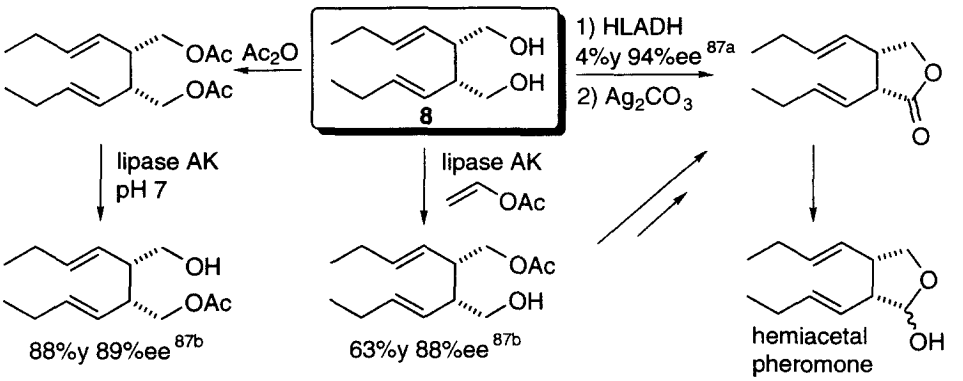
Scheme 18



Recently Mori and co-workers reported the synthesis of the optically active hemiacetal pheromone of the spined citrus bug *Biprorulus bibax*.[87] In their first approach,[87a] the HLADH oxidation of *meso*-diol **8** was tested, but the chemical yield was poor, and the crude product was obtained as a 1:1 *cis* /*trans* mixture of acetals. A subsequent oxidation-reduction protocol was needed in order to remove the unwanted *trans*-isomer. The absolute configuration was assigned on an empirical rule basis and proved to be incorrect. In a subsequent article, a lipase-catalyzed acetylation of the same *meso*-diol was described.[87b] The enantiopurity of the final product, (3*R*,4*S*)-3,4-bis[(*E*)-1'-butenyl]tetrahydrofuran-2-ol, was improved to 100% *via* formation of a diastereoisomeric salt and crystallization (Scheme 19).

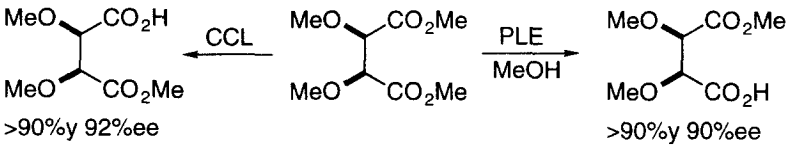
Unlike the optically active (*R*,*R*) or (*S*,*S*)-tartaric acid, its *meso*-form is rarely used in organic synthesis. An early study on the enzymatic hydrolysis of the dimethyl ester led to the monomethyl ester with moderate ee value (48%);[88] substantial improvements have been reported by Bestmann and Philipp.[89a] The *meso*-dimethyl

Scheme 19



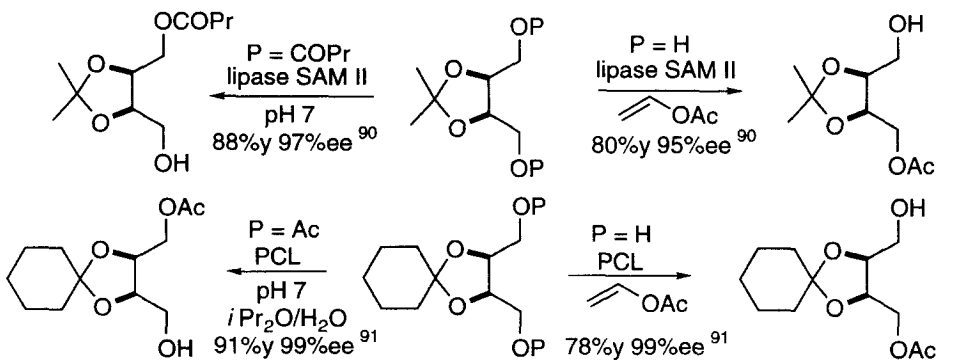
2,4-dimethoxysuccinate was hydrolyzed by pig liver esterase, which processes the ester group at the (*S*)-stereogenic center; in contrast, the lipase from *Candida cylindracea* (Sigma type VII) attacks the ester group at the (*R*)-center in the absence of methanol (Scheme 20).[89]

Scheme 20

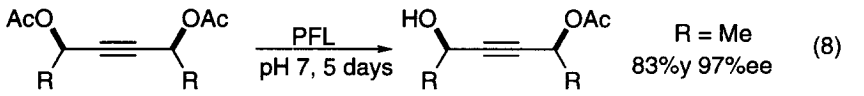


The asymmetrization of 2,3-diprotected erythritols was studied by Bestmann,[89] Vandewalle,[90] Gais,[91] and Burgess.[92a] The use of lipase SAM II or PCL gave access to either enantiomeric series in good chemical yields and enantiopurities (Scheme 21). Biocatalysis was equally successful with ethylidene (lipase PS) and methoxymethyl (PPL or PAN) protected erythritols as substrates[89] but not sufficient for practical applications when the corresponding 2,3-dibenzyl ether derivative was employed.[92a]

Scheme 21

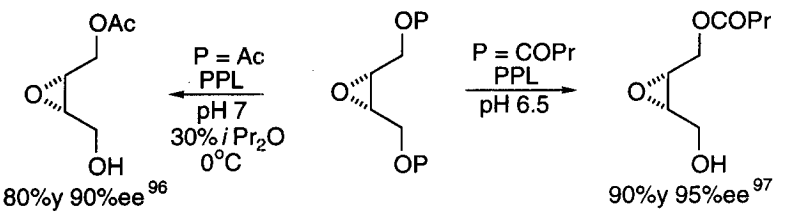


Recently, Uguen and co-workers reported the enzymatic asymmetrization of *meso*-acetylenic diacetates. Unfortunately, bisacetate derivatives that bear substituents other than methyl reacted much more slowly and were not useful as substrates (eq 8).[93]



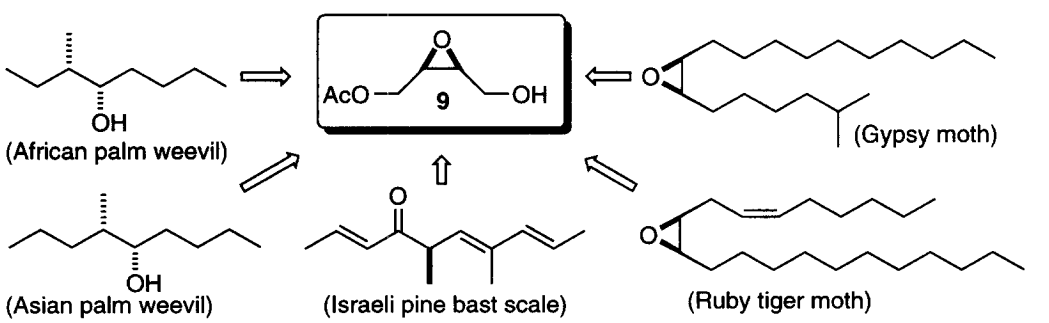
cis-Epoxysuccinic acid is another potentially useful *meso* C_4-building block. The enzymatic discrimination between the carboxylate groups of the diester was not completely successful, possibly due to a competitive spontaneous hydrolysis.[34b,94,95] The enzymatic asymmetrization of structurally related *meso-cis*-2,3-epoxybutane 1,4-diol diesters was reported by several research groups and proved to be most successful in the hydrolysis pathway (Scheme 22).[96-98] PPL was the most efficient enzyme, and lower ee values (51%) of the isolated mono acetates were improved by addition of cosolvents (88-90%ee).[96a] Enantioselectivity was also influenced by temperature and ester chain length; the use of dibutyrates was advantageous. The reaction was scaled up to 50 g and afforded (2*S*,3*R*)-4-butanoyloxy-2,3-epoxybutan-1-ol with ee in the range of 90%; the product was converted to optically pure material after a single recrystallization.[97] When the enzymatic transesterification of the *meso*-diol with vinyl butyrate was attempted, the (+)-enantiomer was isolated with low yield and low enantiopurity (50%ee).[98] The monobutyrate was also obtained *via* a PPL-catalyzed resolution of the racemic 4-hydroxy-2,3-epoxybutyl butyrate with 2,2,2-trifluoroethyl butyrate (93%ee).[99]

Scheme 22



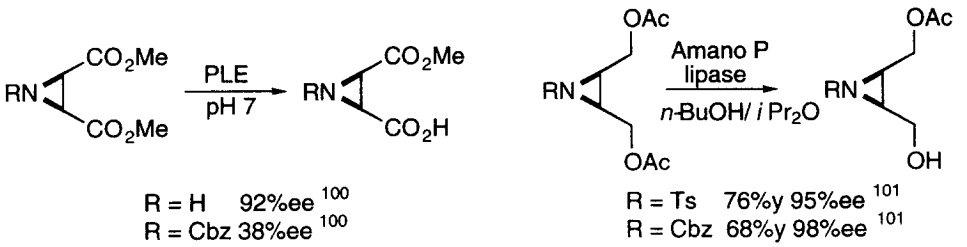
The *meso*-diacetate derived alcohol **9** was used by Mori and co-workers as a common precursor in the total synthesis of a number of pheromones (Scheme 23).[96b]

Scheme 23



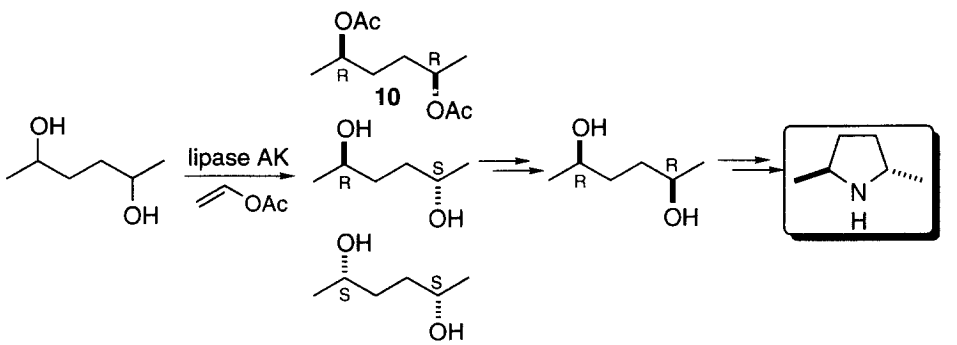
meso-Dimethyl aziridine-2,3-dicarboxylates, which can be synthesized from the *cis*-epoxysuccinate, have been successfully asymmetrized by use of PLE.[100] Biocatalytic processing of related *meso*-aziridines, prepared from *cis*-2-butene-1,4-diol, was reported by Fuji and co-workers (Scheme 24).[101]

Scheme 24



A practical synthesis of optically active (*R,R*)-2,5-dimethylpyrrolidine, reported by Kim *et al.*,[102] used an enzymatic asymmetrization to afford its precursor. The procedure starts with a mixture of all three stereoisomers of 2,5-hexanediol, which are converted to a mixture of diacetate, monoacetate, and diol (1:2:1). Subsequent inversion of all alcohol functionalities in the latter two compounds provided, after hydrolysis, enantiomerically and diastereomerically enriched (*R,R*)-2,5-hexanediol (>98%ee, 72%de). Its repeated enzyme-catalyzed trans-esterification afforded the diacetate **10** in high optical purity (ee and de >98%, Scheme 25). Enantiomeric (*S,S*)-2,5-hexanediol and (2*R*,5*R*)-2,5-dimethylpyrrolidine were prepared from 2,5-hexanedione *via* enantioselective reduction with baker's yeast (57%y, >95%ee).[103]

Scheme 25

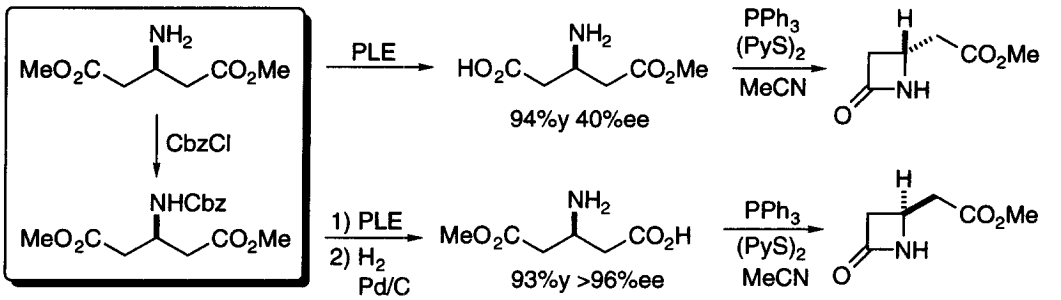


2.1.d.Glutaric acid derivatives and *meso*-pentanols

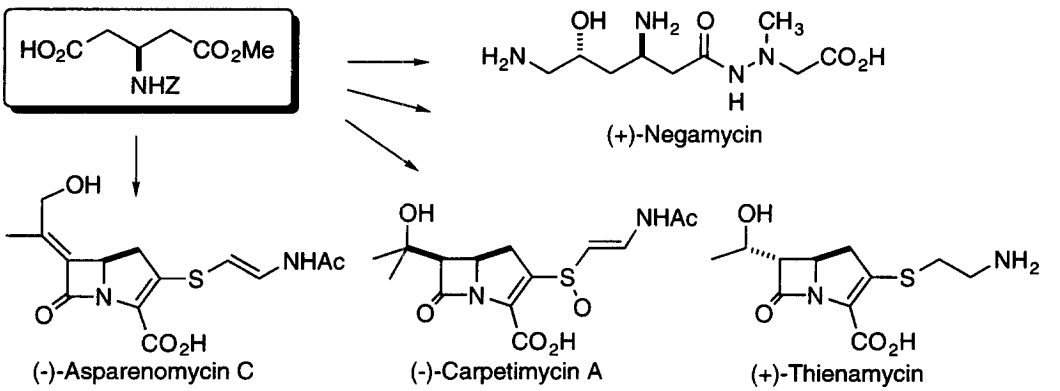
Enzymatic transformations of various substituted glutaric acid derivatives have been studied by many research groups.[104-123] Diethyl β-acetamidoglutarate was the first compound studied; α-chymotrypsin-catalyzed hydrolysis led to the corresponding enantiopure monoester.[23c] Reports on 3-mono and 3,3-disubstituted glutarates followed including contributions from the laboratories of Ohno, Sih, Tamm, Jones, Seebach, and others.[105] Asymmetrization of dimethyl β-aminoglutarate has been extensively studied by researchers from the Ohno laboratory. The enzyme as well as the protective group were varied in order to control enantioselectivity during asymmetrization. The synthesis of both enantiomers of 4-substituted-2-azetidinones nicely illustrates the applicability of this protocol (Scheme 26).[106]

The same monoester was employed in the synthesis of (+)-negamycin and various carbapenems; all have the *R* configuration at the bridgehead carbon (Scheme 27).[106]

Scheme 26

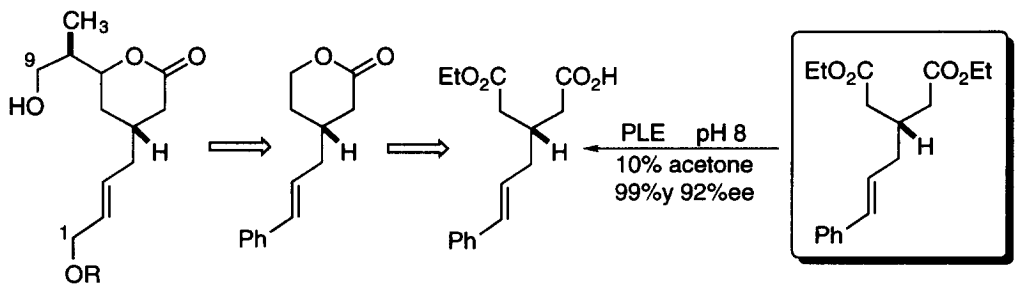


Scheme 27



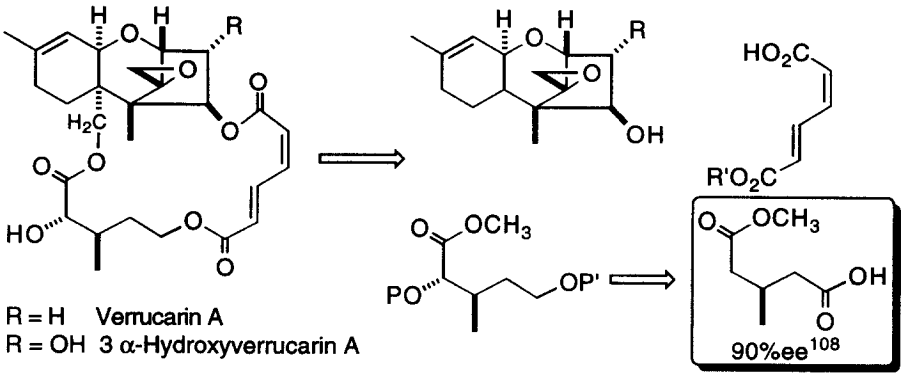
The Ohno laboratory has also achieved the enantioselective synthesis of the right-half segment (C_1-C_9) of the macrolide antibiotic rhizoxin.[107] An enzymatic asymmetrization of a 3-substituted glutarate provided the key transformation (Scheme 28).

Scheme 28

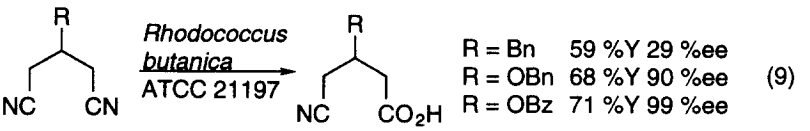


Optically active dimethyl 3-methylglutarate was employed in the synthesis of a verrucarin segment. Tamm *et al.* obtained the key intermediate after reduction of the carboxyl group, protection of the primary alcohol, and α-hydroxylation (Scheme 29).[108]

Scheme 29

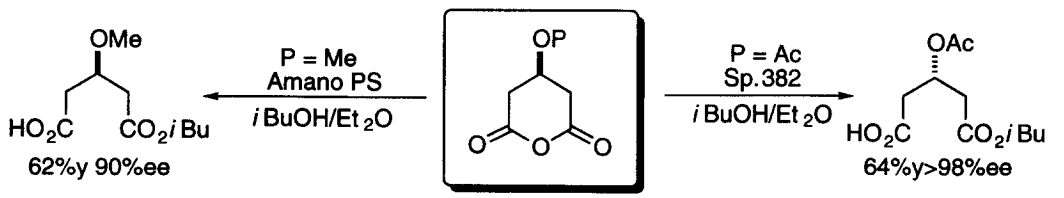


Rhodococcus butanica ATCC 21197 operates on nitrogen-containing functional groups such as nitriles and preferentially hydrolyzes the cyano group at the (*S*)-stereogenic center of 3-substituted glutaronitriles (eq 9);[26a] *Rhodococcus butanica* SP361 was found to display slightly lower enantioselectivity.[26b]



The influence of various enzymes, alcohols, and solvents on the stereochemical outcome of the asymmetrization of 3-substituted pentanedioic anhydrides was investigated by Ozegowski and Oda. The appropriate choice of protective group and enzyme allowed access to either enantiomer of protected 3-hydroxy pentanedioates (Scheme 30).[111]

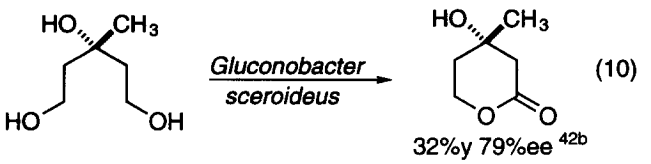
Scheme 30



Dimethyl β-hydroxyglutarate was studied in enzyme-catalyzed polymerizations. A chiral polymer was obtained with modest enantioselectivity (30-37 % ee).[115a]

PFL-catalyzed hydrolysis of a prochiral 1,3,5-pentanetriol derivative gave rise to enantiopure (*R*)-3-*t*-butyldimethylsilyloxy-5-acetoxy-1-pentanol (55%y, >98%ee) which was applied to the synthesis of a cyanobacterial heterocyst glycolipid.[115b]

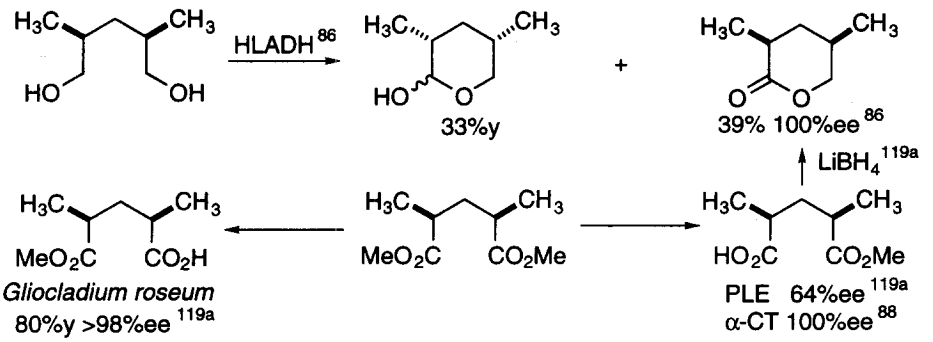
Enzymatic[116] and microbial[42b,117] enantioselective oxidations of 3-substituted-1,5-pentanediols have been observed, for example oxidation of 3-methyl-1,3,5-pentanetriol afforded unnatural (+)-(*S*)-mevalonolactone (eq 10),[42b,116a] which has also been prepared from dimethyl glutarate derivatives.[117]



(10)

meso-2,4-Pentanediol served as substrate for oxidoreductases and lipases. Lipase P catalyzed a transesterification in vinyl acetate to afford (2*R*,4*S*)-1-hydroxy-2,4-dimethylpentyl acetate in high enantiopurity (82%y, 98%ee).[43] Jones and co-workers prepared 2,4-dimethyl-δ-valerolactone from the same substrate using HLADH.[86] The initial oxidation of the *meso*-2,4-dimethyl-1,5-pentanediol was non-selective, while the enzyme processed only one hemiacetal enantiomer in the second step. Both lactone enantiomers were prepared from dimethyl 2,4-dimethylglutarate *via* chemoenzymatic synthesis (Scheme 31).[88,119a]

Scheme 31

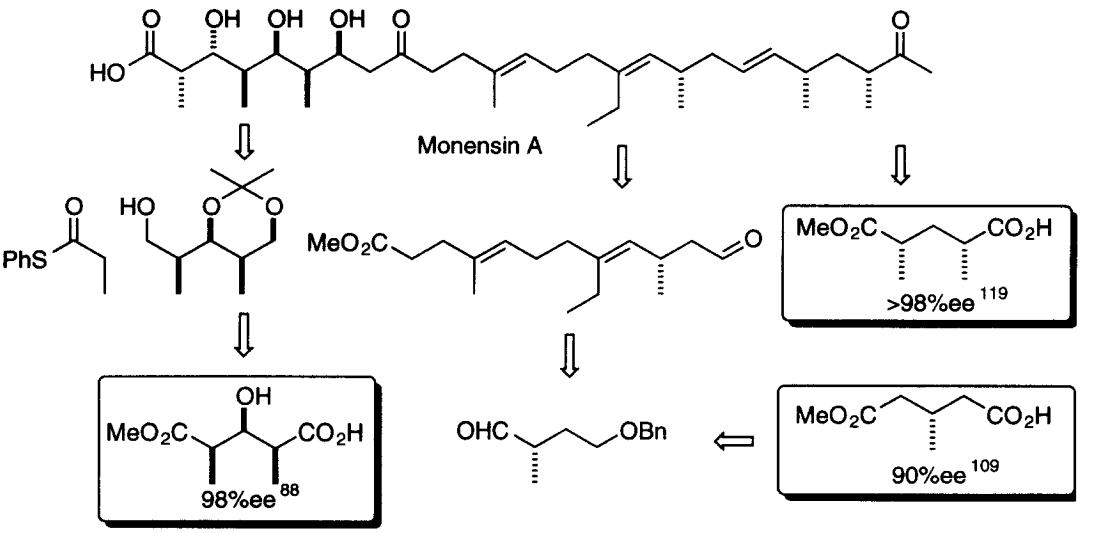


Enantiopure building blocks derived from substituted glutaric acid derivatives proved to be convenient starting materials in the synthesis of macrolides.[119b,120-123] The synthesis of the putative biosynthetic precursor of monensin A, reported by Sih and co-workers,[119b] illustrates the application of enzymatically prepared glutarates in the design of complex, polyfunctional target molecules. All three important fragments were prepared *via* biocatalysis, *e.g.*, both enantiomers of the 2,4-dimethylpentanedioic acid monoester are available, either through enzymatic hydrolysis of the diester [88,119] or alcoholysis of *meso*-2,4-dimethylglutaric anhydride[111,118](Scheme 32). A similar disconnection strategy was followed in Robinson's synthesis of the same molecule.[120]

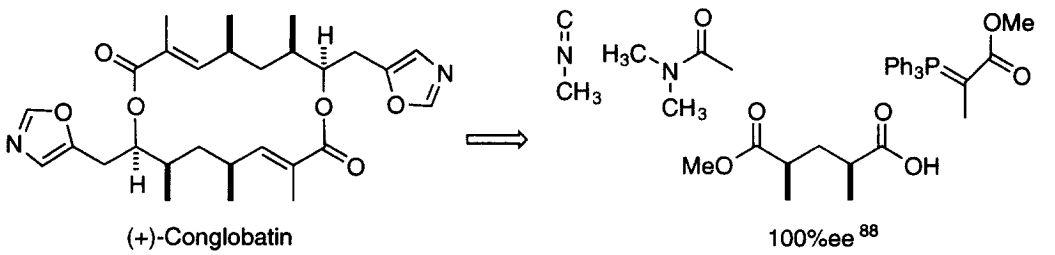
The 2,4-dimethylglutaric acid, half ester, as obtained by Tamm's chymotrypsin-based procedure,[88] was also used by Schregenberger and Seebach in the total synthesis of (+)-conglobatin, a C_2-symmetrical 16-membered macrolide isolated from a culture of *Streptomyces conglobatus* (Scheme 33).[121]

Tamm and co-workers reported a highly enantioselective pig liver esterase-catalyzed asymmetrization of dimethyl 3-hydroxy-2,4-dimethylglutarate. This enzyme hydrolyzes diesters carrying more substituents with higher stereoselectivity than their less substituted counterparts.[88] The chiral mono-ester was used in the total synthesis of the C_{19}-C_{27} segment of rifamycin *S*. The complex structure of this microbial secondary metabolite reveals a local symmetry element at C_{23}, and the use of a *meso*-building block facilitates the synthetic process (Scheme 34).[122]

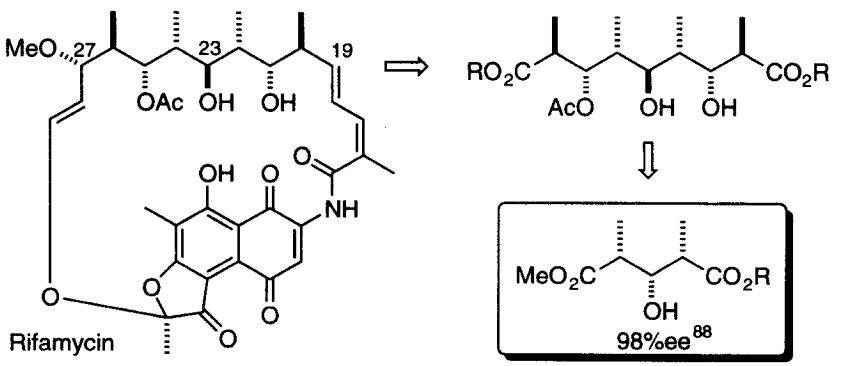
Scheme 32



Scheme 33

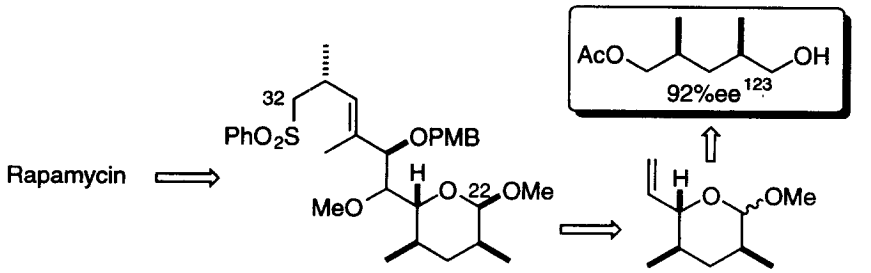


Scheme 34



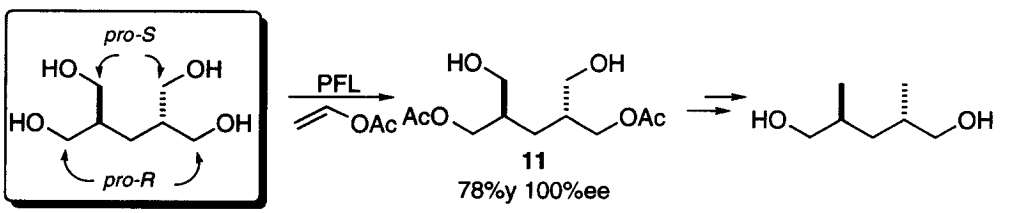
Ley and co-workers enzymatically asymmetrized 2,4-dimethyl-1,5-pentanediol using crude porcine pancreatic lipase suspended on Celite in the presence of methyl acetate. The monoacetate was employed in the synthesis of the C_{22}-C_{32} fragment of rapamycin (Scheme 35).[123]

Scheme 35



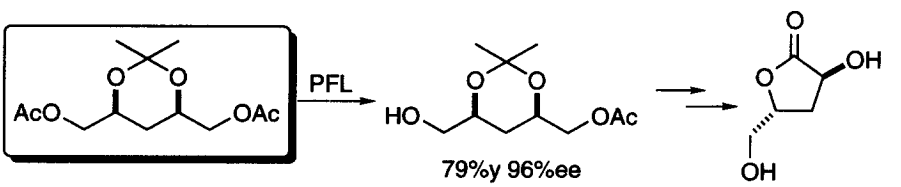
Enzymatic asymmetrization of an interesting, "double-*meso*" tetraol was recently reported by Uguen and co-workers. *Pseudomonas fluorescens* lipase (SAM II from Fluka) effectively catalyzed acetylation to afford an inseparable mixture of acetate **11** and its *meso*-diastereoisomer. The free hydroxyl groups were transformed into phenyl sulfides, allowing for the separation of the bis-sulfide mixture. The absolute configuration and optical purity were established by correlation to the known 2,4-dimethyl-1,5-pentanediol (Scheme 36).[124]

Scheme 36



Sakai *et al.* reported on the *Pseudomonas fluorescens* lipase-mediated asymmetrization of *meso*-4,6-diacetoxymethyl-2,2-dimethyl-1,3-dioxane. The hydrolysis product was subsequently transformed into 2-hydroxy-4-hydroxymethyl-4-butanolide, which displays hunger modulating activities (Scheme 37).[125]

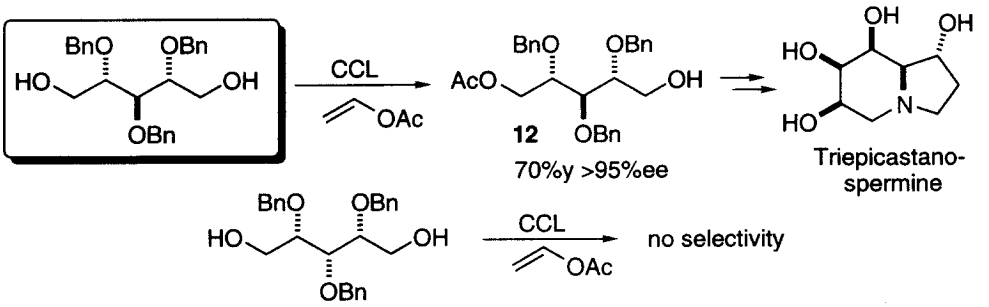
Scheme 37



The biocatalytic differentiation of enantiotopic groups in *meso*-substrates such as ribitol and xylitol was studied by Burgess and Henderson. The *ribo*-derivative was successfully asymmetrized with *Candida cylindracea*; however, when the *xylo*-pentitol derivative was employed as substrate, the acyl transfer occurred

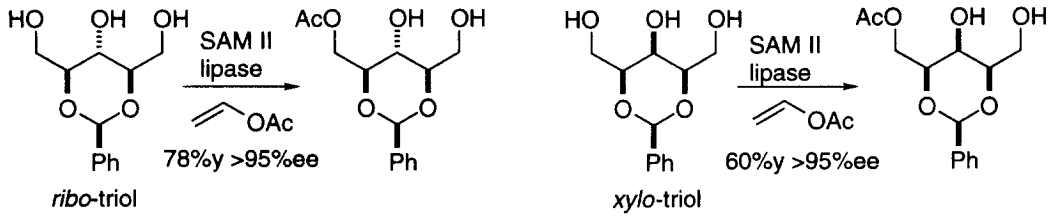
in a stereorandom fashion. The corresponding optically active xylitol was obtained through asymmetric allylation and carried on in the synthesis of a castanospermine stereoisomer. Monoacetate **12**, obtained *via* biocatalysis, was converted to 1,6,8-triepicastanospermine (Scheme 38).[92a]

Scheme 38



Earlier problems associated with the asymmetrization of xylitols were recently solved. Both *ribo*- and *xylo*-triol were converted to their corresponding 2,4-*O*-benzylidene derivatives; the latter derivatives were found to be excellent substrates for SAM II lipase-catalyzed transesterifications (Scheme 39).[126]

Scheme 39



2.1.e. Adipic acid derivatives

The *meso*-dimethyl 3,4-epoxyadipate was rapidly hydrolyzed by pig liver esterase with excellent selectivity. The absolute configuration and optical purity of the half-ester were determined by transformation into the unsaturated hydroxy diester (Scheme 40).[113]

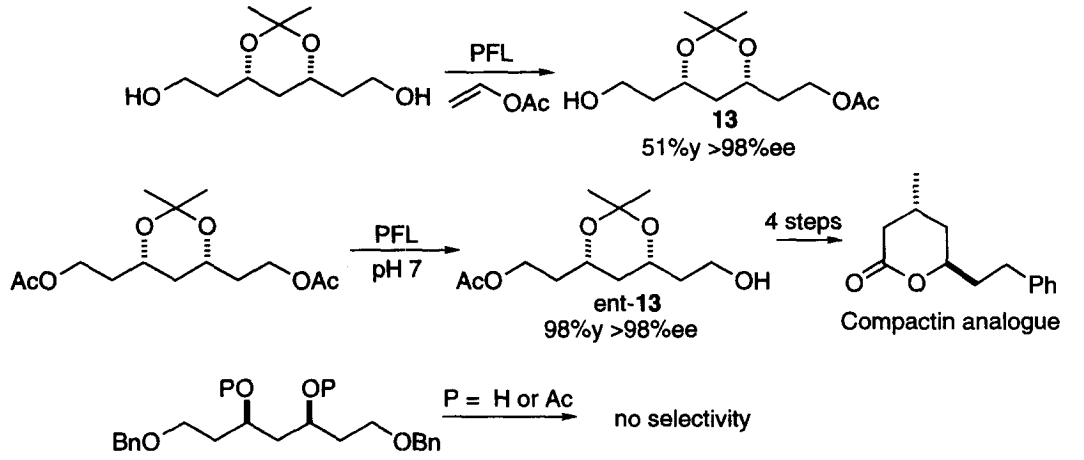
Scheme 40

2.1.f. 1,7-Heptanediols and heptanedioic acids

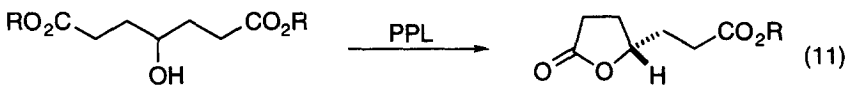
The enzymatic synthesis of seven-carbon polyhydroxylated chiral building blocks was reported by Bonini *et al.*[127] Among various hydrolases, *Pseudomonas fluorescens* lipase (PFL) was found to be the most selective enzyme leading to monoacetates **13** and ent-**13** with excellent enantioselectivity. However, neither

the enzymatic hydrolysis of a related diacetate nor the transesterification of the corresponding diol displayed encouraging selectivity (Scheme 41).

Scheme 41



Porcine pancreatic lipase catalyzed enantioselectively the hydrolyses of prochiral γ-hydroxypimelates, the best result being obtained for the faster reacting ethyl and benzyl esters. The intermediate half-esters were not isolated because of spontaneous lactonization in the presence of the enzyme (eq 11).[128]



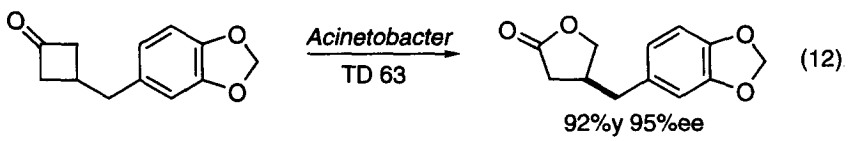
(11)

R =CH_2CH_3 >98%ee; R =$CH(CH_3)_2$ 46%ee; R =CH_2Ph >95%ee

2.2. Cyclic *meso*- and prochiral substrates

2.2.a. 3-Substituted-cyclobutanones

Furstoss and co-workers successfully employed a prochiral cyclobutanone in an asymmetric Baeyer-Villiger oxidation using a strain of *Acinetobacter* (eq 12).[129]

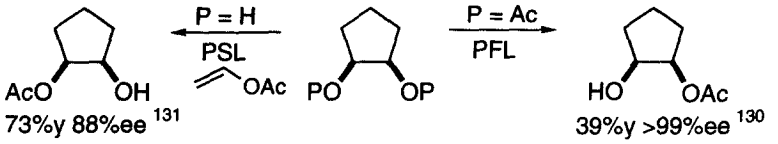


(12)

2.2.b. *meso*-Cyclopentanediols and cyclopentanediones

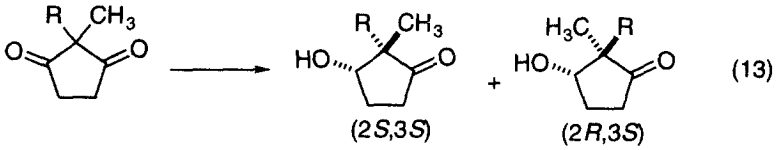
Meso-cyclopentanediols play an important role in the chemoenzymatic synthesis of prostaglandins, prostacyclins, and other natural compounds, such as cyclitols, carbohydrates, azasugars, and indolizidine alkaloids. This list can easily be expanded, and the abundance of papers in the literature is no surprise.

Scheme 42



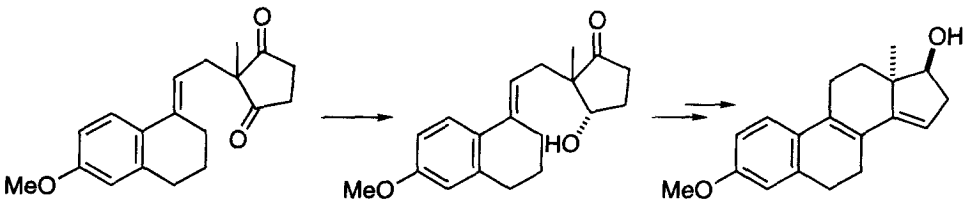
Pseudomonas fluorescens lipase was found to be effective in the hydrolysis of the *cis*-1,2-diacetoxypentane to afford the corresponding monoacetate with high optical purity (Scheme 42).[130] This result is in contrast to the findings with 4-, 5-, and 6-membered ring *cis*-1,2-diacetoxycycloalkanes, which were hydrolyzed to optically inactive monoacetaes with PLE.[132] Higher chemical yields but lower optical purity were observed during PSL-catalyzed transesterification of the same substrate.[131]

Several 2,2-disubstituted 1,3-diones have been subjected to microbial reductions.[133,134] In most cases, the asymmetrization of cyclopentanediones affords the (2*S*,3*S*)-stereoisomer with high enantioselectivity (eq 13).



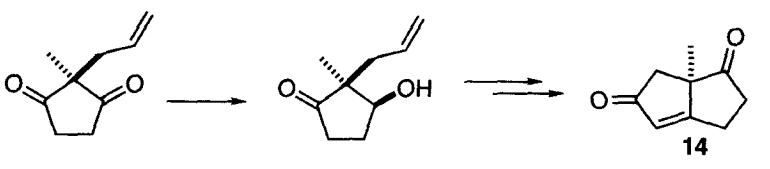
An early approach to the asymmetric synthesis of steroid precursors was undertaken by Kosmol *et al.* using microorganisms such as *Bacillus* spp. and *Saccharomys* spp. (Scheme 43).[133]

Scheme 43



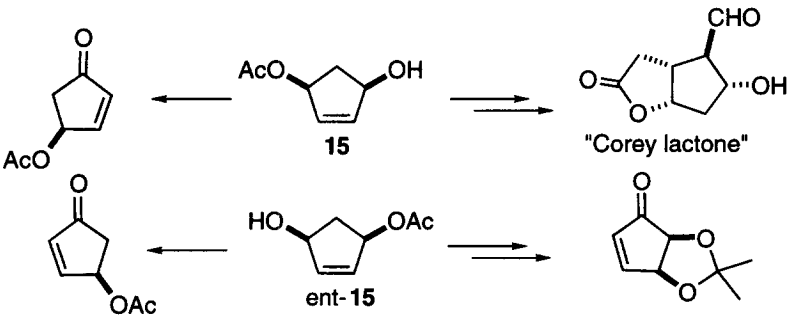
Brooks and co-workers studied the series 2-propyl, 2-allyl, and 2-propynyl-2-methyl-1,3-cyclopentanedione using baker's yeast. In all cases the microbial ketol products were produced in enantiopure form (>98%ee). The utility of these readily available chiral intermediates was exemplified by the preparation of (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione **14**, a key intermediate in the total synthesis of coriolin (Scheme 44).[134]

Scheme 44



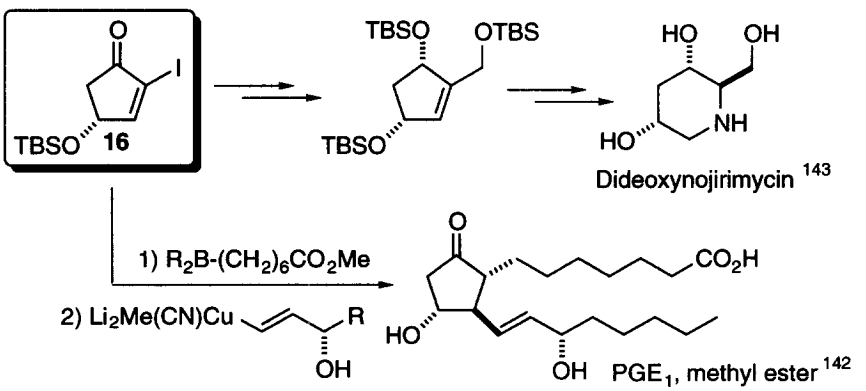
The first attempts to asymmetrize *cis*-3,5-diacetoxycyclopentene employed microbial hydrolysis;[135] however (1*S*,4*R*)-4-hydroxy-2-cyclopentenyl acetate (**15**) was formed with modest optical purity The use of well-defined enzymes for the same reaction led to either enantiomer in high yield (59-94%) and enantiopurity (86-99%) depending on the choice of enzyme.[136-138] The best results were obtained with relatively expensive electric eel acetylcholinesterase (94%y, 96%ee).[136] Lipase B from *Candida antarctica* (Novo SP-435) was found to be an effective alternative.[29] Monoacetate ent-**15** was also obtained *via* enzymatic acetylation of the corresponding diol in organic media.[26,138,139a] The use of a catalytic antibody for enantioselective hydrolysis of *cis*-3,5-diacetoxycyclopentene was reported by Danishefsky *et al.*,[139b] and a related substrate, 4,4-dimethyl-3,5-diacetoxycyclopentene, was subjected to enzymatic catalysis.[140a] The preparation of optically active 4-hydroxy-2-cyclcpentyl acetate and related molecules has been studied by several research groups. These compounds have attracted enormous attention due to their versatility; they are important precursors to functionalized cyclopentenones and have been used in prostaglandin synthesis (Scheme 45).[141]

Scheme 45



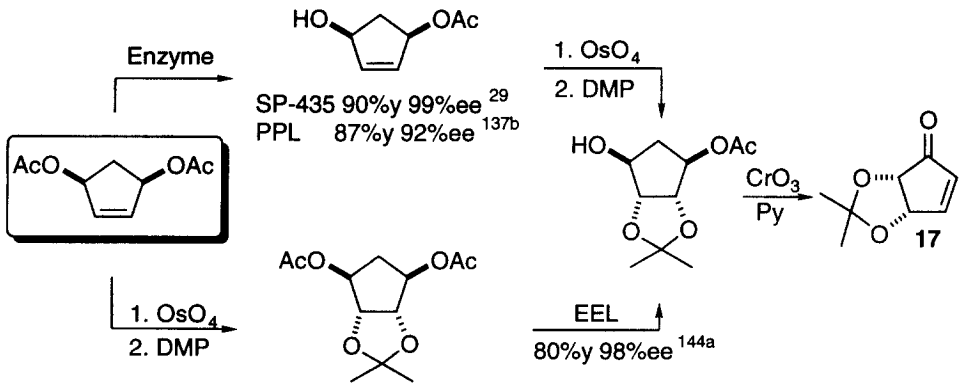
Monoacetate **15** was utilized as starting material in the preparation of enantiopure α-iodoenone **16**. Scheme 46 illustrates its application in a two-step, three-component coupling synthesis of prostaglandins.[142] It was also applied in the synthesis of 1,3-dideoxynojirimycin. The enone was reduced and subjected to Pd(0)-mediated carbon monoxide coupling; subsequent ozonolysis and reductive amination furnished the desired piperidine derivative.[143]

Scheme 46

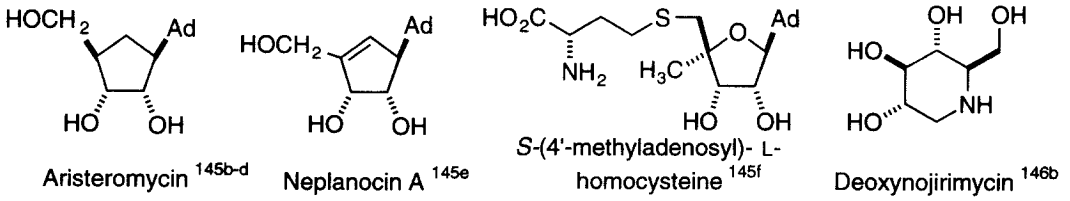


The enzymatic asymmetrization protocol was applied to the synthesis of 4-methyl-2,3-(isopropylidenedioxy)-1-cyclopentanol, which proved to be a useful starting material in the synthesis of PGE_2, methyl ester *via* enone **17** (Scheme 47).[144]

Scheme 47

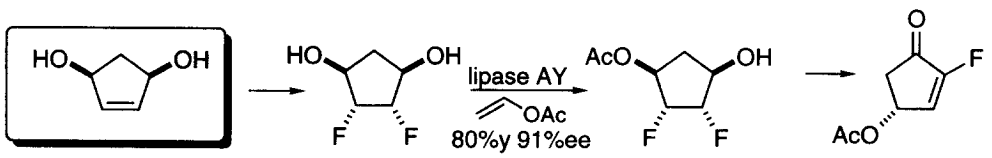


Some recent applications of the same enone **17** or its enantiomer in the synthesis of polyhydroxylated natural products include the preparation of aristeromycin, neplanocin A, the 4-substituted ribonucleoside analogue *S*-(4'-methyladenosyl)-L-homocysteine, and various nojrimycins.[145,146]



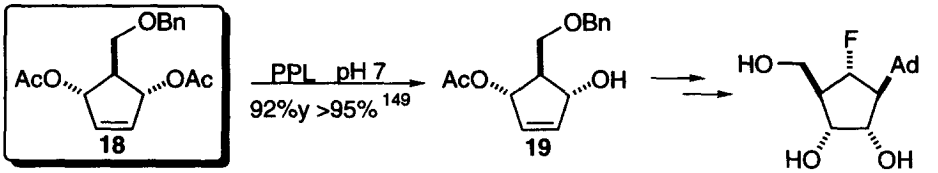
The introduction of fluorine substituents is of particular interest in the field of medicinal chemistry. Sato and co-workers accomplished the addition of molecular fluorine to the *meso*-diol with high stereoselectivity. Enzymatic asymmetrization, followed by oxidation and elimination of hydrogen fluoride provided (*R*)-4-acetoxy-2-fluoro-2-cyclopenten-1-one, an attractive building block (Scheme 48).[147]

Scheme 48

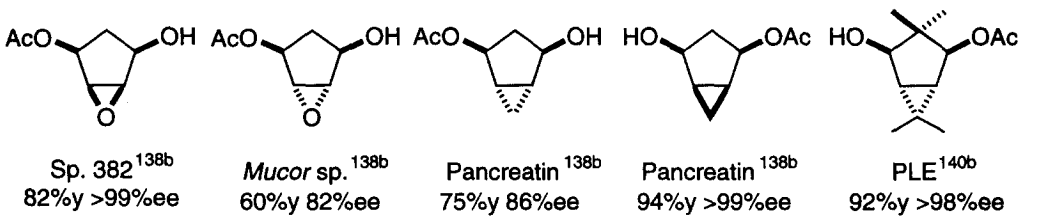


meso-Diacetate **18** prepared from cyclopentadiene in three steps was hydrolyzed by porcine pancreatic lipase[148] or acetylcholinesterase[149] and afforded 3-hydroxy-2-[(phenylmethoxy)methyl]-4-cyclopentenyl acetate (**19**), which was converted to a fluorinated nucleoside analogue (Scheme 49). A misassignment of the absolute stereochemistry of **19** was corrected by LeGrand and Roberts; both PPL and acetylcholinesterase gave rise to the same monoester.[150]

Scheme 49

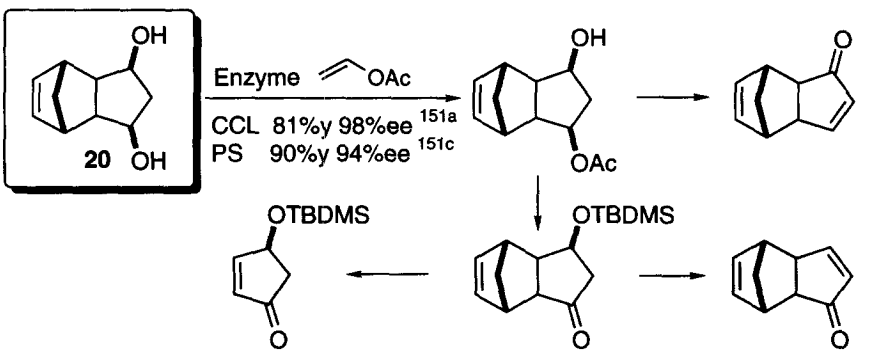


Theil and co-workers have investigated the lipase-catalyzed transesterification of various *meso*-cyclopentenediols with vinyl acetate in tetrahydrofuran/triethylamine as standard conditions. In most cases, the lipase processed the hydroxyl group at the (*S*)-site. However, in the case of the *syn*-cyclopropane diol, all enzymes preferentially acetylated the hydroxyl group at the (*R*)-center.[138b] A similar, sterically encumbered substrate has been examined by Krief *et al.*[140b]



The bicyclic diol **20**, which served as a masked chemical equivalent of *cis*-2-cyclopentene-1,3-diol, was asymmetrized by use of *Candida cylindracea* lipase[151a] or lipase PS (Amano)[151c]. Straightforward protective group manipulation gave access to either enantiomeric series of a tricyclic enone. A retro-Diels-Alder reaction was used to fragment the adduct to enantiopure 4-(*tert*-butyldimethylsilyloxy)-2-cyclopenten-1-one (Scheme 50).

Scheme 50

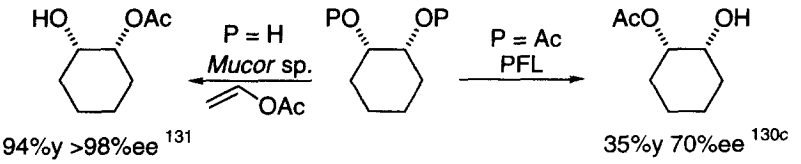


2.2.c. Prochiral and *meso*- cyclohexanediols, cyclohexanones, and related heterocycles

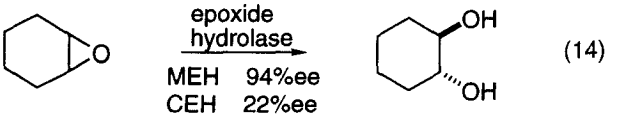
The asymmetrization of *meso*-cyclohexanols led to a variety of synthetically interesting chiral building blocks. Unlike *vicinal* cyclopentanediols,[130] *Pseudomonas fluorescens* lipase was less efficient for asymmetrization. Lower selectivity as well as a reversal in product configuration were attributed to PFL-

catalyzed acyl-migration. This effect was even more profound for the seven-membered ring *vic*-diol (2%ee). However, the enantiocomplementary synthesis route was more successful. Among various *cis*-1,2-dihydroxycycloalkanes tested, Nicolosi *et al.* reported that the six membered ring substrate was the most efficiently asymmetrized during esterification (Lipozyme® IM, *Mucor miehei* lipase) giving rise to the monoacetate with high yield and enantiopurity (Scheme 51).[131] They also investigated the asymmetrization of *cis*-1,2-dihydroxycyclohexa-3,5-diene employing the same enzyme.[152]

Scheme 51



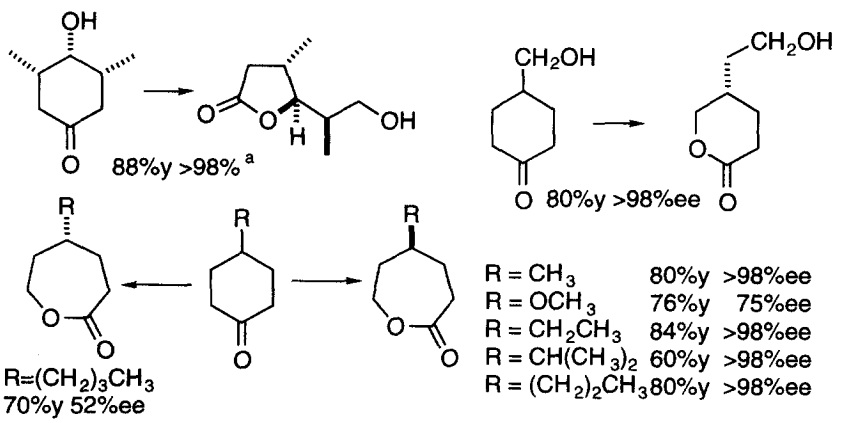
(*R,R*)-cyclohexane-*trans*-1,2-diol was formed as a product of cyclohexene oxide hydrolysis by rabbit liver microsomal (MEH) and cytosolic (CEH) epoxide hydrolase. However, this protocol suffers from low conversion rates and decreasing ee values with increasing incubation time (eq 14).[25c]



(14)

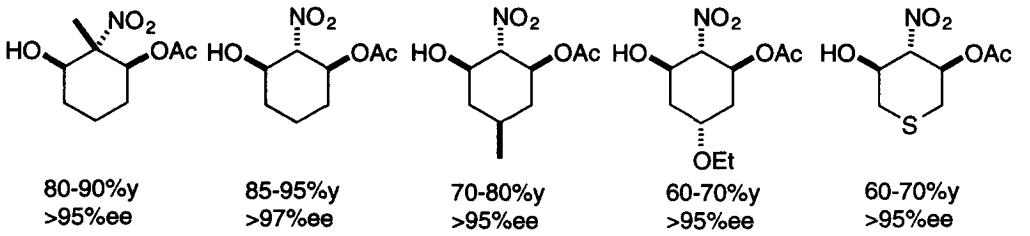
A series of enzymatic Baeyer-Villiger oxidations of prochiral cyclohexanones was reported by Taschner *et al.*[27] Various substrate patterns were studied with use of cyclohexanone oxygenase, isolated from *Acinetobacter* NCIB 9871; and in most cases *R*-selectivity prevailed to afford the corresponding lactones in high yields and ee's.

Scheme 52

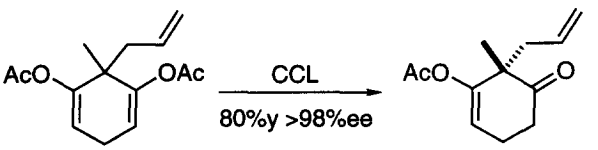


[a] absolute configuration unknown

Seebach *et al.* have studied the PLE-catalyzed hydrolysis of six-membered ring *meso*-nitrodiol diacetates analoguous to aliphatic *meso*-2-nitro-1,3-propanediols.[64]



An asymmetric synthesis of enantiopure ketoenol acetate **21** by enzymatic hydrolysis of a prochiral dienol diacetate was reported (eq 15).[153]

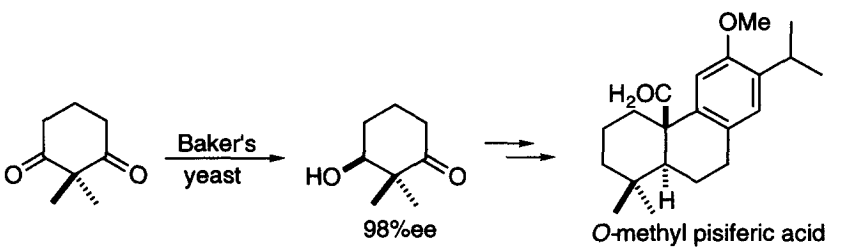


(15)

21

(*S*)-3-Hydroxy-2,2-dimethylcyclohexanone is a versatile intermediate and is readily available in high enantiopurity *via* reduction of the corresponding 1,3-dione with *Kloeckera magna* ATCC 20109[154] or baker's yeast.[155] This ketol has been utilized in the synthesis of various terpenes, such as both enantiomers of *O*-methyl pisiferic acid (Scheme 53).[156]

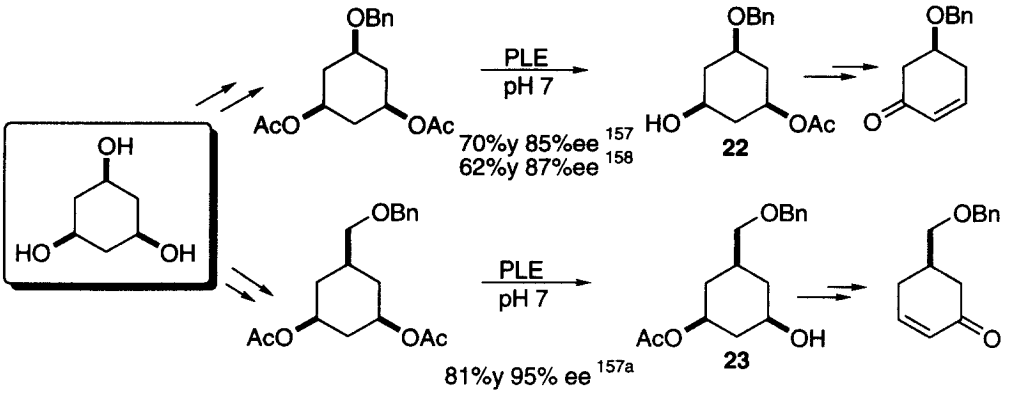
Scheme 53



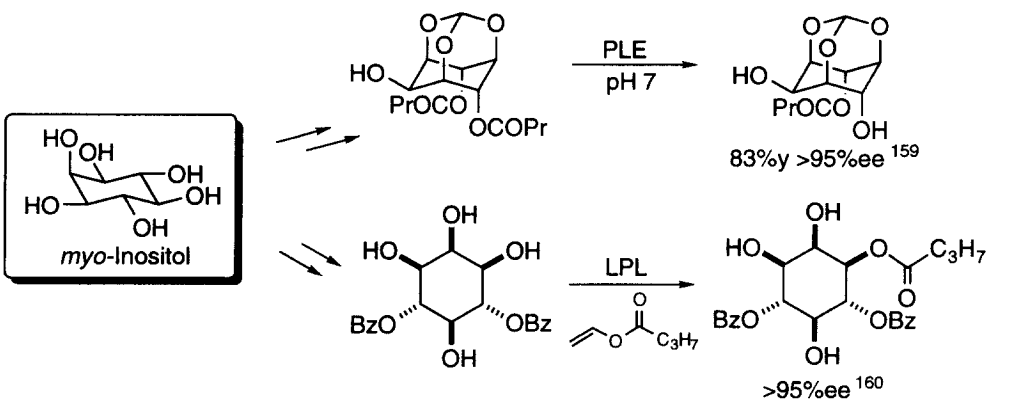
Several *cis*-1,3,5-cyclohexanetriol derivatives were the subject of enzymatic asymmetrization studies in the laboratories of Vandewalle[157] and Sakai.[158] The early misassignment[157a] of the absolute configuration of monoacetate **22** was corrected later.[157b] Interestingly, the opposite asymmetric induction was observed during enzymatic hydrolysis to monoacetate **23** (Scheme 54).

The enzymatic asymmetrization was also used for highly oxygenated ring systems such as *myo*-inositol derivatives.[159,160] The use of inexpensive *myo*-inositol in connection with the asymmetrization protocol gives easy access to various enantiopure inositol phosphates and phospholipids (Scheme 55).

Scheme 54

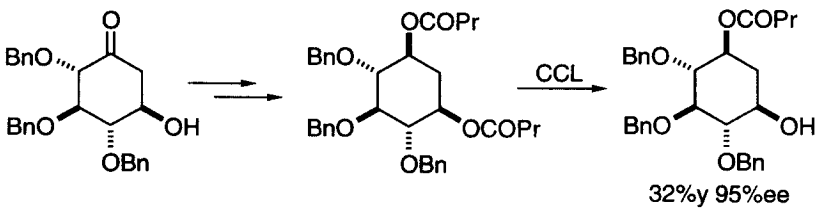


Scheme 55



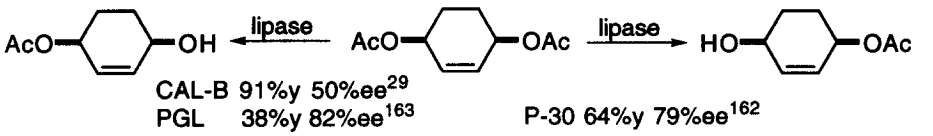
The asymmetrization procedure was also applied to 1-deoxy-*scyllo*-inositol derivatives; the *meso*-substrate, however, was derived from chiral α-D-glucopyranoside (Scheme 56).[161]

Scheme 56



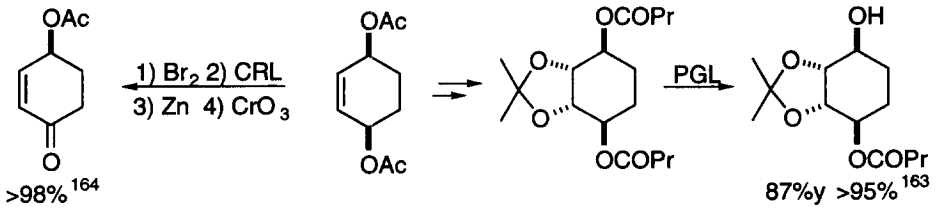
Compared with other *meso*-2-cycloalken-1,4-diols, the enzymatic asymmetrization of the six membered ring system was the most challenging.[29,162,163] With various lipases the hydrolysis took place with low to moderate selectivity. An improvement in selectivity was only accomplished with decreased chemical yields. Presumably the -CH=CH- and -CH_2CH_2- in this case are too similar in size and cannot be fully distinguished by the enzyme (Scheme 57).

Scheme 57



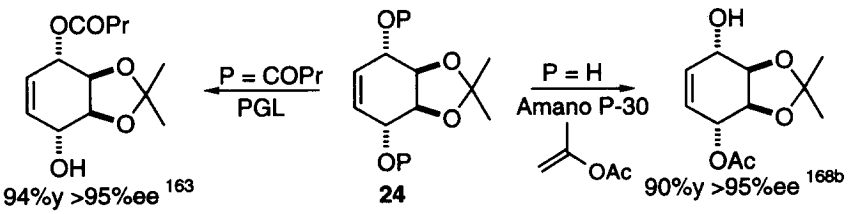
In order to optimize the selectivity, bromine was added to the alkene, thus increasing the size of the substituents and improving enzyme catalysis. The bromine was subsequently eliminated with zinc dust, and the olefinic alcohol was oxidized to the enantiopure enone.[164] An interesting application of the intermediary allyl alcohol in palladium-catalyzed transformations was reported by Bäckvall and co-workers.[165] The selectivity also increased when the alkene was transformed to the acetonide-protected diol, affording the monoester in 87% yield after hydrolysis (Scheme 58).[163]

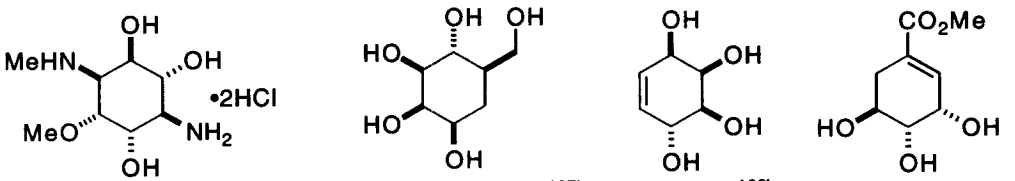
Scheme 58



meso-3,5-Cyclohexadiene-1,2-diol, available *via* oxidation of benzene by mutants of *P. putida*,[166] was transformed into a functionalized cyclohexene derivative **24**. The diol is a substrate for enzymatic acetylation,[168a] and its diester is suitable for lipase-catalyzed hydrolysis (Scheme 59).[163,167a] Enantiopure allylic alcohols were converted into a wide spectrum of natural products, *e.g.*, (+)-fortamine dihydrochloride,[168a,c] carbasugars,[168b,c] conduritols,[163,168b] conduramines,[168a] (+)- and (-)-methyl shikimate.[168c]

Scheme 59



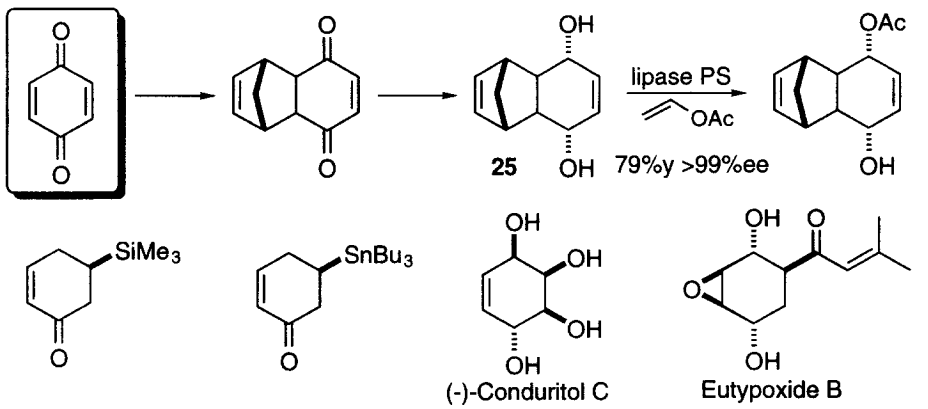


(+)-Fortamine•2HCl[167a] 5a-Carba-α-D-mannose[167b] (-)-Conduritol[168b] (+)-Methyl shikimate[168c]

Efficient asymmetrization of the *meso*-diol **25** derived from the 1,4-benzoquinone-cyclopentadiene adduct was developed by Takano *et al.* Enzymatic acetylation afforded an enantionpure mono-acetate, and its regio- and diastereoselective functionalization gave rise to valuable intermediates for the synthesis of

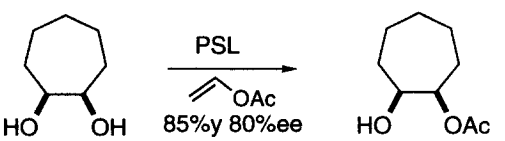
eutypoxide B and conduritol C. The cyclopentadiene moiety was removed *via* a thermolytic *retro*-Diels-Alder cleavage. Other useful intermediates, such as 5-tributylstannyl- and 5-trimethylsilyl-2-cyclohexenones, were obtained. (Scheme 60). Analogous chemistry was applied to related tricyclohexanoids prepared from 1,3-cyclohexadiene and benzoquinone.[169]

Scheme 60



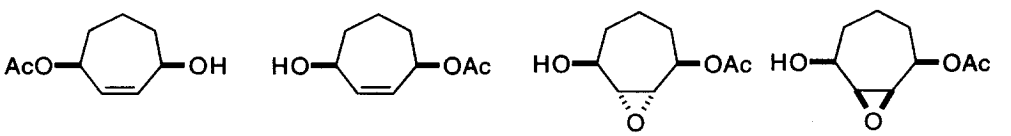
2.2.d. *meso*-Cycloheptanediols and derivatives

cis-1,2-Diacetoxycycloheptane is not a suitable substrate for PFL-catalyzed hydrolysis. In contrast to the fndings of the corresponding *meso*-cyclopentane derivative (>99%ee) the product was isolated with opposite configuration with only 2%ee, 67% of the substrate being recovered.[130] PSL-catalyzed transesterification of the *meso*-diol was much more successful (eq 16)[131]



(16)

Regio- and diastereoselective transformations of 1,3-cycloheptadiene and cycloheptatriene led to a variety of *meso*-diols and diacetates.[170-174] All of them were successfuly asymmetrized either in the hydrolysis or synthesis routes, or both. In almost all cases, the *meso*-diol system was synthesized from related dienes either *via* singlet oxygen cycloaddition or Bäckvall's palladium-catalyzed diacetoxylation. Selected examples are illustrated below.

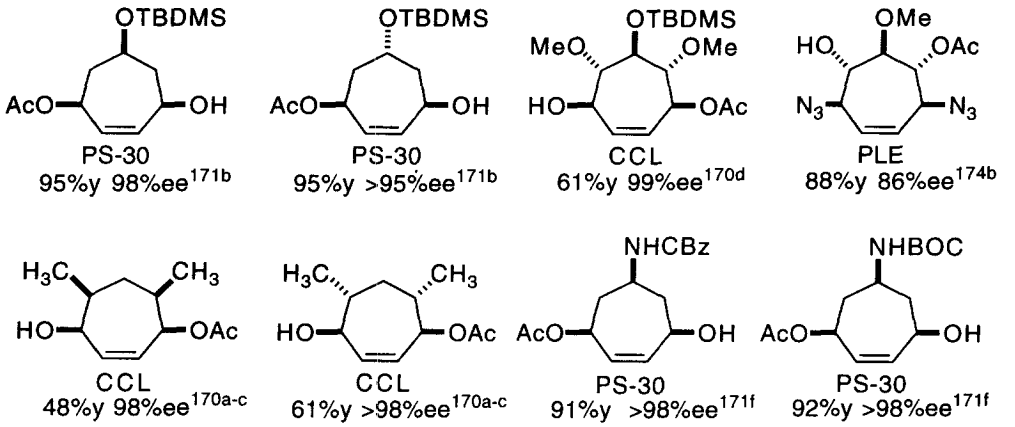


CAL-B
92%y >99%ee[29]

SP-435
81%y >99%ee[29]

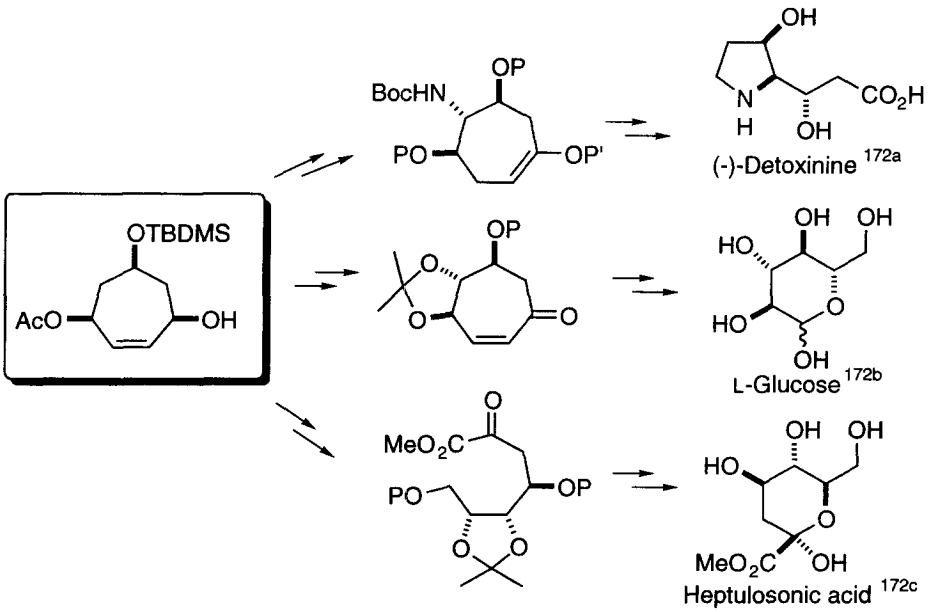
LPL-800
89%y >98%ee[171f]

P-30
92%y 80%ee[171f]

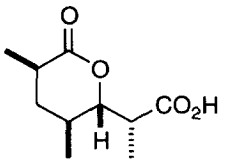


Scheme 61 illustrates transformations of a cycloheptatriene derived monoacetate into detoxinine,[172a] L-glucose,[172b] and 3-deoxy-D-*arabino*-heptulosonic acid.[172c]

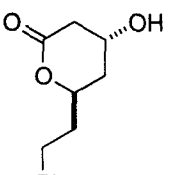
Scheme 61



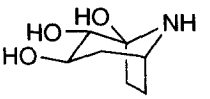
Other optically pure seven-membered ring intemediates obtained from enzymatic reactions have been transformed into a variety of synthetically useful building blocks and polyhydroxylated natural compounds. Some examples are shown below, including the Prelog-Djerassi lactone,[170a-c] a compactin analogue,[171a] and the tropane alkaloid calystegine A_3.[171f]



(+)-Prelog-Djerassi lactone

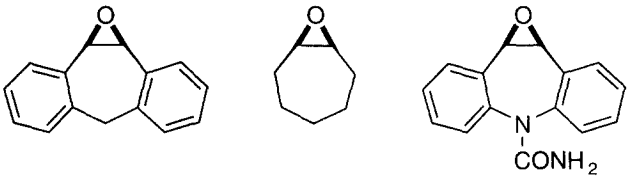


Compactin analogue



Calystegine A 3

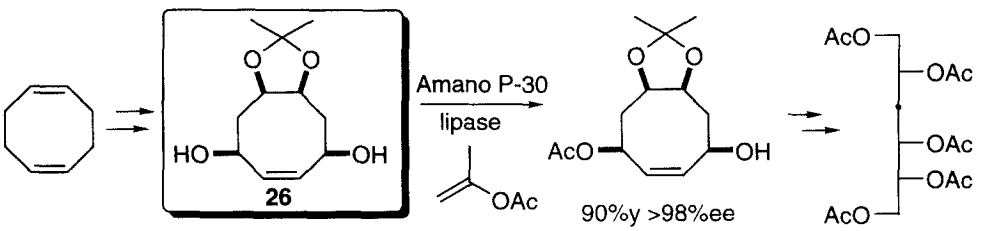
The three variously structured seven membered ring substrates shown below have been subjected to microsomal epoxide hydrolases, which open the epoxide ring to form *trans*-1,2-diols.[25]



2.2.e. 1,4-Cyclooctanediol

In the only reported enzymatic asymmetrization of an eight-membered ring system *meso*-diol **26** was treated with lipase from *Pseudomonas cepacia* (Amano P-30) in isopropenyl acetate at 50°C for four days and gave the monoacetate in 90% yield and 98% ee. The relative and absolute configurations were confirmed by chemical correlation to the known 3-deoxy-D-*ribo*-hexitol pentaacetate (Scheme 62).[175]

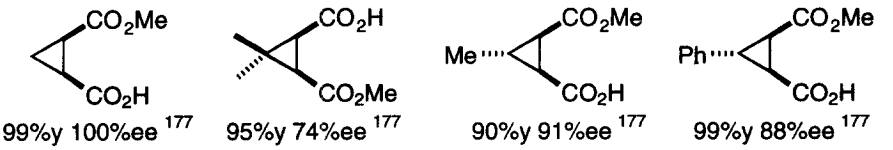
Scheme 62



2.3. *meso*-Cycloalkanediesters and cycloalkanedimethanols

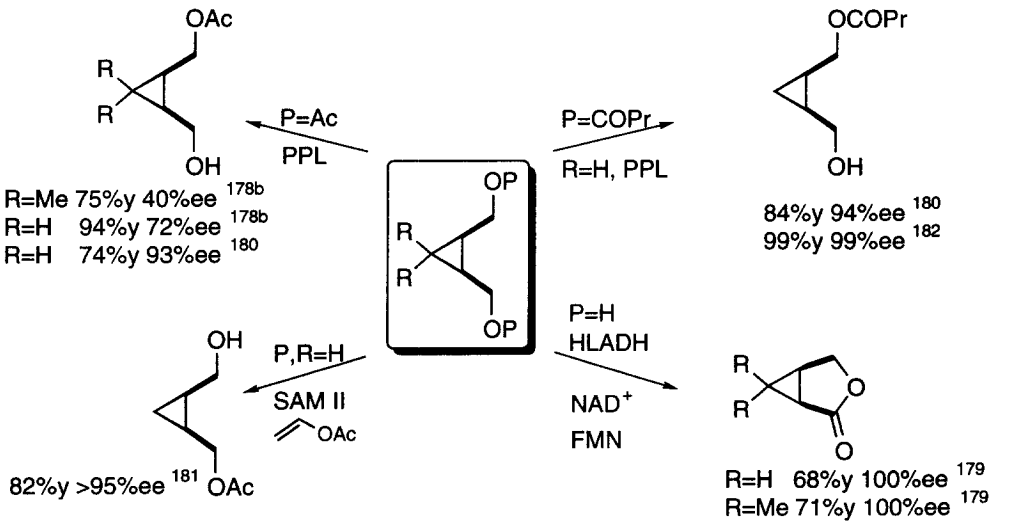
2.3.a. Cyclopropanedicarboxylates and cyclopropanedimethanols

Enzymatic asymmetrization gives a fast and realiable entry to optically active cyclopropanes and complements chemical resolutions and enantioselective syntheses.[176] PLE-catalyzed hydrolyses of substituted cyclopropanedicarboxylates have been studied by the Jones,[34] Tamm,[88,177] and Schneider[178] research groups. Jones and also Schneider reported the highly enantioselective hydrolysis of *cis*-cyclopropanedicarboxylates, but they assigned opposite absolute configurations to the product. This issue was addressed in subsequent studies.[34b,177]



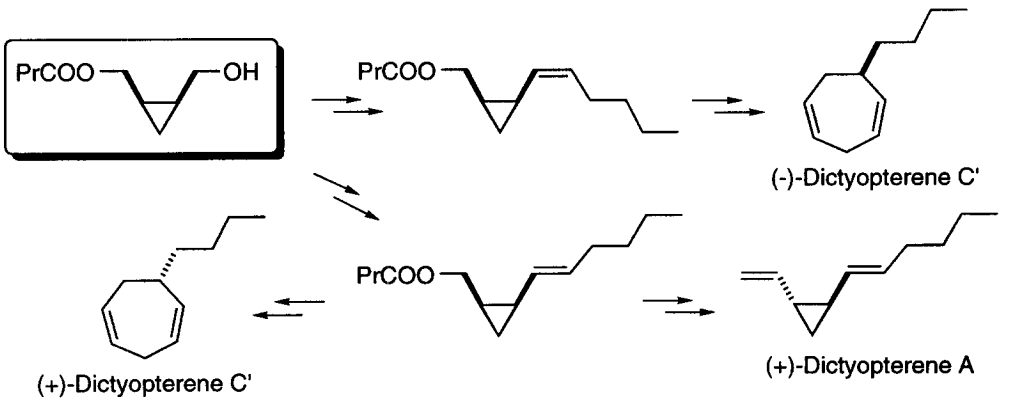
Various cyclopropanedimethanols and related diesters have been subjected to enzymatic asymmetrization; Scheme 63 summarizes the results.[178-182]

Scheme 63



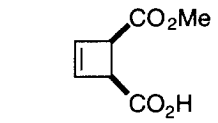
The recent total synthesis of enantiopure seaweed pheromones dictyopterenes A and C' exemplifies the versatility of such cyclopropyl building blocks (Scheme 64).[182]

Scheme 64

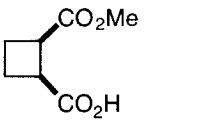


2.3.b. Cyclobutanedicarboxylates and cyclobutanedimethanols

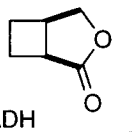
Various optically active cyclobutane systems have been derived *via* enzymatic processing of *meso*-dicarboxylates or *meso*-dimethanols. Typical products are listed below.



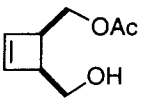
PLE 92%y 86%ee [184]
PLE 96%y 86%ee [185]



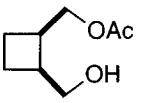
PLE 98%y 86%ee [178]
PLE 87%y >97%ee [34]



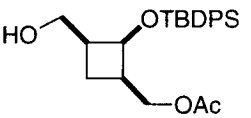
HLADH
90%y 100%ee [179]



Amano P
75%y 97%ee [185]



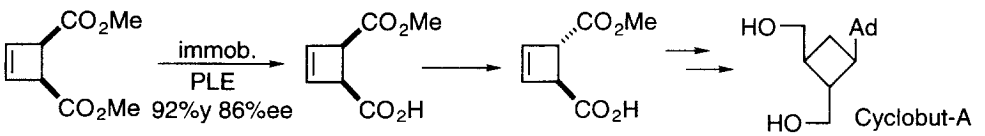
PPL 78%y 96%ee [180]
SAM II 87%y >95%ee [181]



lipase MY
96%y 95%ee [183]

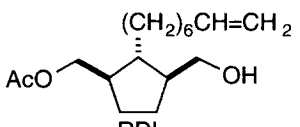
An application of one of those compounds in the synthesis of the potent antiviral agent cyclobut-A (Scheme 65) was reported by Jung and Sledeski.[184]

Scheme 65

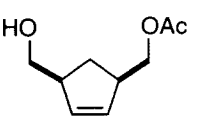


2.3.c. 1,2- and 1,3-Cyclopentanedicarboxylates, 1,3-cyclopentanedimethanols, and related heterocycles

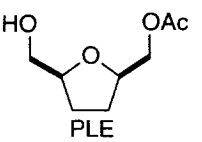
Products of enzymatic asymmetrization of branched *meso*-cyclopentane systems are depicted below, along with heterocyclic analogues.[47,186-197]



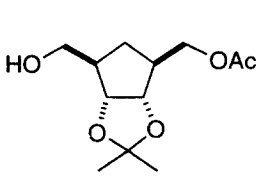
RDL
69%y >99%ee [188a]



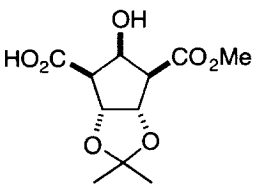
CCL
68%y 97%ee [195]



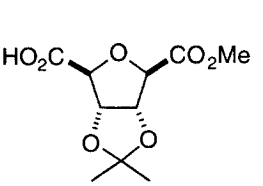
PLE
65%y 51%ee [190b]



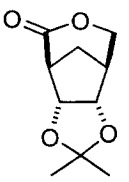
PFL
69%y >99%ee [188b]



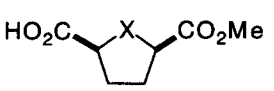
PLE
43-81%y >95%ee [193]



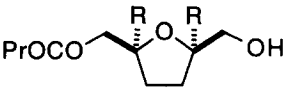
PLE
86%y 72%ee [186c]



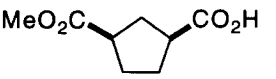
HLADH
25%y 100%ee [197]



PLE
X = O 98%y 42%ee[186b]
X = S 83%y 46%ee[186b]

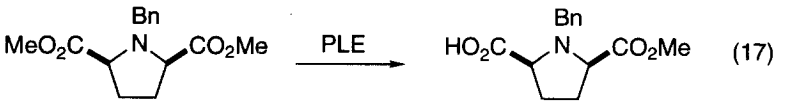


LMJ
R=H 75%y >99%ee[194]
R=Me 60%y >99%ee[194]



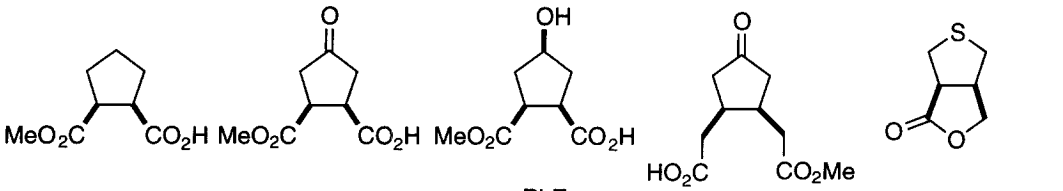
PLE 82%y 34%ee[186b]
PCL 97%y 90%ee[196]
Sub. 98%y 90%ee[196]
CE 92%y 91%ee[196]

Norin, Hult, and co-workers investigated an enantioselective route to (*R*)-proline derivatives *via* enzymatic hydrolysis of *cis*-*N*-benzyl-2,5-bis(methoxycarbonyl)pyrrolidine. Initial attempts afforded the half ester with only 17%ee; addition of 25% DMSO as cosolvent dramatically increased enantioselectivity to 100% (eq 17).[187]



(17)

Enzymatic hydrolysis of *meso*-1,2-cyclopentanedicarboxylates and derivatives thereof proved to be the most troublesome. This problem received much attention from the Jones,[34,86] Tamm,[191] and Gais[192] research groups and to some extent was succesfully solved.



PLE
92%y 17%ee [34]

PLE
30%y 72%ee [192b]

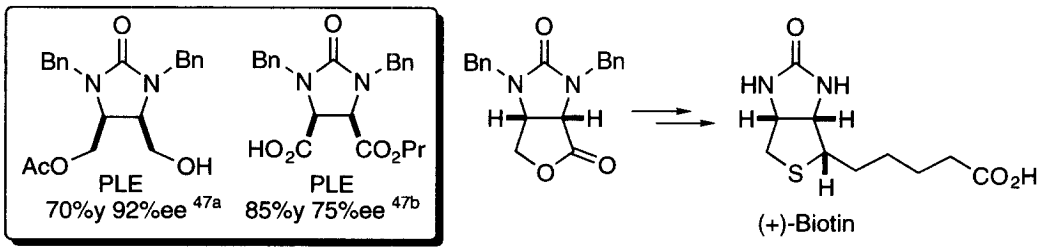
PLE
76%y 80%ee [192b]

PLE
94%y 87%ee [192b]

HLADH
81%y 100%ee [86]

Various *meso*-1,3-dibenzylimidazolidin-2-one derivatives have been subjected to PLE-catalysis. Enantioselectivity of the *cis*-acetates was higher than for the corresponding *cis*-diesters; the value was improved by a switch from a methyl (71%y, 38%ee) to a propyl (85%y, 75%ee) ester. Both systems can be transformed into a bicyclic lactone, which is a known precursor to (+)-biotin (Scheme 66).[47]

Scheme 66



PLE
70%y 92%ee [47a]

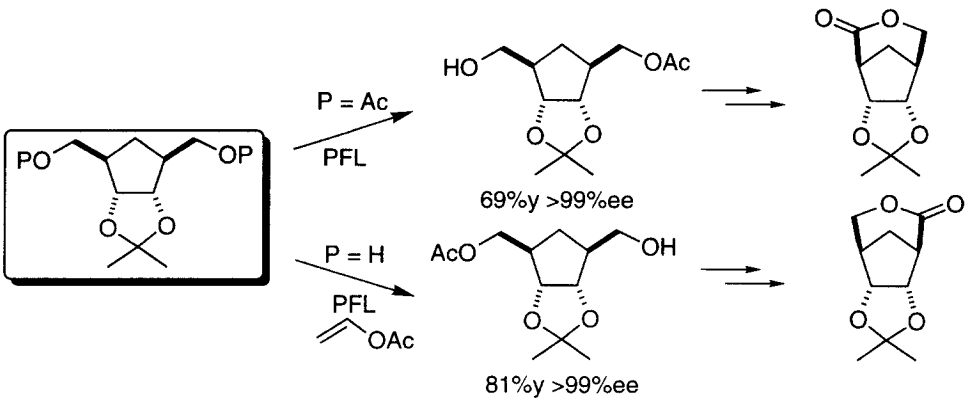
PLE
85%y 75%ee [47b]

(+)-Biotin

Enantiopure compounds, prepared from a *meso*-1,3-bis(acetoxymethyl)cyclopentane derivative, were used in the total syntheses of carbocyclic nucleosides, carbacyclins, prostaglandins, and polyether antibiotics. Scheme 67 presents a recent preparation of Ohno's lactone intermediate for (-)-aristeromycin and (-)-

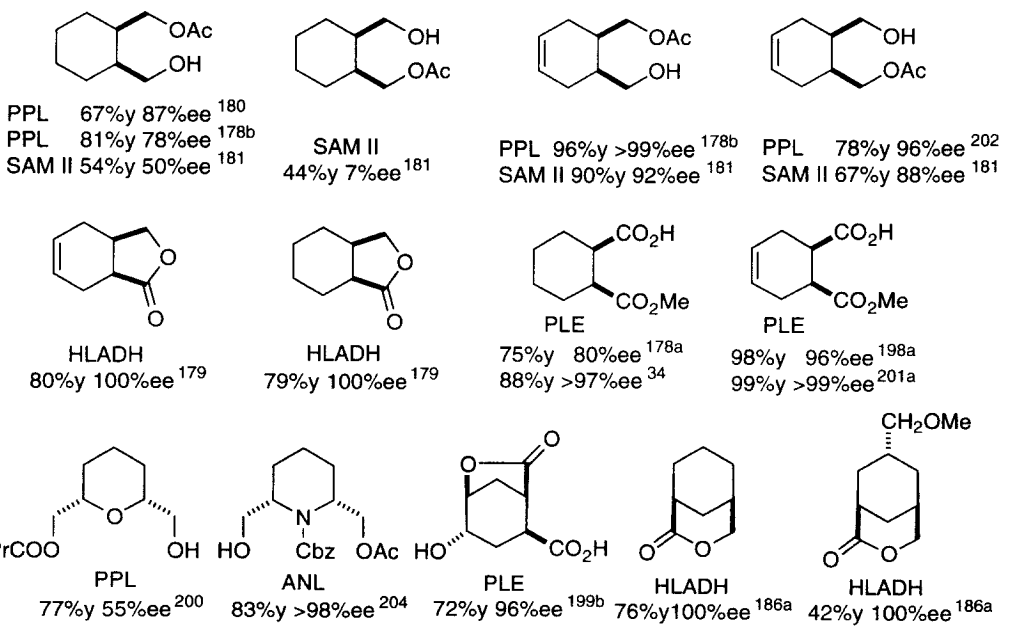
neplanocin A.[188] This approach to the lactone, together with the classic Ohno method,[209b] nicely illustrates the diversity of possible routes in an enzymatic asymmetrization protocol.

Scheme 67



2.3.d. Cyclohexanedicarboxylates, cyclohexanedimethanols, and related heterocycles

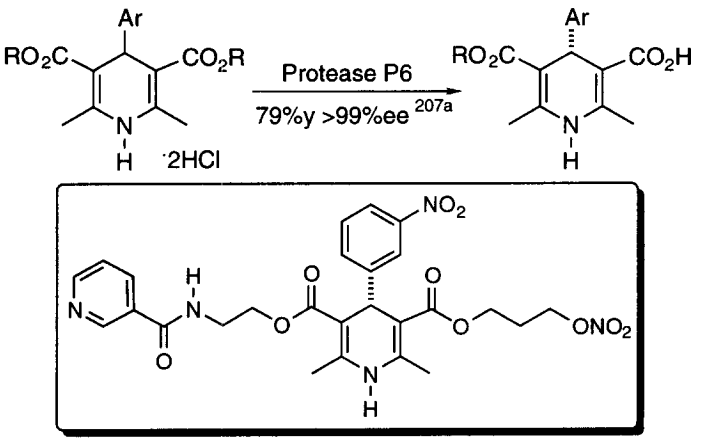
Selected cyclohexane building blocks and related heterocyclic systems obtained *via* enzymatic asymmetrizations are illustrated below.[198-208]



Considerable attention has been given to the asymmetric hydrolysis and transesterification of various prochiral 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylates.[207] These materials belong to an

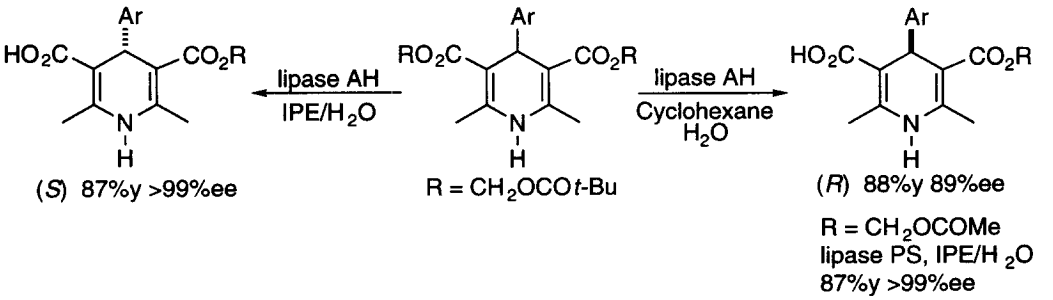
important class of calcium antagonists and have been widely used for the treatment of cardiovascular diseases. Selected proteases (Protease P, Seaprose S) and lipases (AH, PS) provided the corresponding monoesters with high enantioselectivity. Protease-catalyzed hydrolysis afforded (4*R*)-3-[2-(nicotinoylamino)-ethoxycarbonyl]-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylic acid, which was converted to the desired product (see box in Scheme 68) by esterification with 3-nitrooxypropyl bromide. The same product was obtained through enzymatic transesterification with 3-nitrooxypropanol (77%y, >99%ee).[207a] Proteases also hydrolyzed activated esters such as the corresponding bis(cyanoethyl) and bis[2-(methylsulfonyl)ethyl]-dicarboxylates that were not processed by PLE or lipase AK.[207b]

Scheme 68



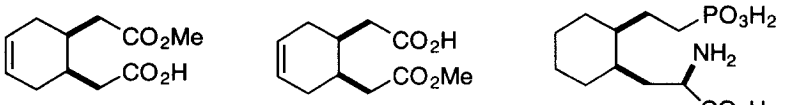
Initial studies revealed that lipases and esterases were not effective in hydrolyzing simple ester derivatives (R = Me, Et, Ph) due to steric hindrance or inactivity.[207c] This problem was solved by introducing acyloxymethyl moieties as activating groups.[207d] Numerous 1,4-dihydropyridinedicarboxylates were investigated by Achiwa *et al.* Lipase AH and lipase PS displayed opposite enantioselectivity; the latter enzyme showed best results when the ester group was changed from *tert.*-butyl to methyl or ethyl. The same laboratory reported a drastic solvent effect on enantioselectivity when lipase AH was employed. Opposite enantiomers were isolated by simple change of solvent from diisopropyl ether to cyclohexane (Scheme 69).[207e]

Scheme 69



Homologues of cyclohexenedicarboxylates were asymmetrized by use of PLE, PPL, or α-chymotrypsin. The monoesters can be isolated in good chemical yields and enantiopurities and serve as interesting building

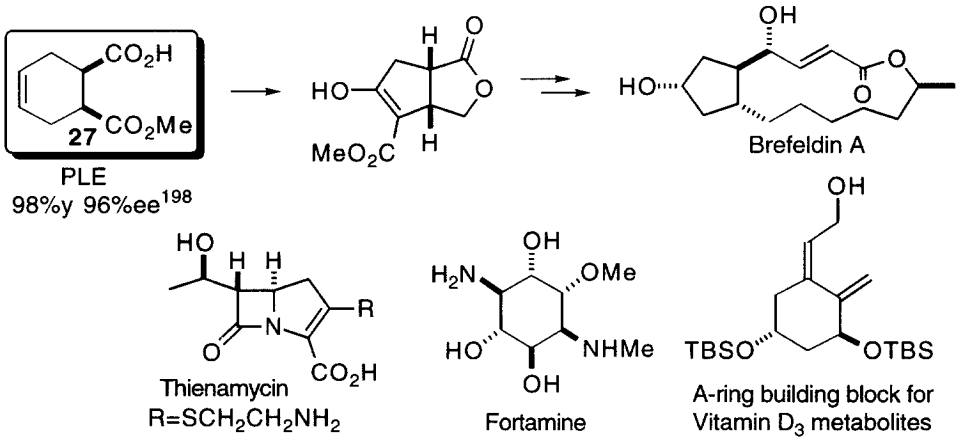
blocks. Hamilton *et al.* reported the synthesis of a potent and selective NMDA antagonist starting with (1*R*,2*S*)-methyl hydrogen *cis*-cyclohex-4-ene-1,2-diacetate.[205]



PLE 84%y 68%ee [192b]
PLE 91%y 76%ee [189]
PPL 97%y 97%ee [189]
α-CT 90%y 86%ee [192b]
NMDA antagonist

Many enzymatic syntheses have been published to date,[198-208] but it was Ohno and co-workers, who first established the full potential and usefulness of the asymmetrization concept in many synthetic applications.[198] Monoester **27** was transformed into numerous target molecules such as carbapenem antibiotics and fortamine, as well as into the A-ring building block for vitamin D_3 metabolites. Extensive studies towards the synthesis of cyclopentanoid natural products have been performed by Gais and co-workers.[201] The preparation of a bicyclic lactone allowed facile access to brefeldin A (Scheme 70).

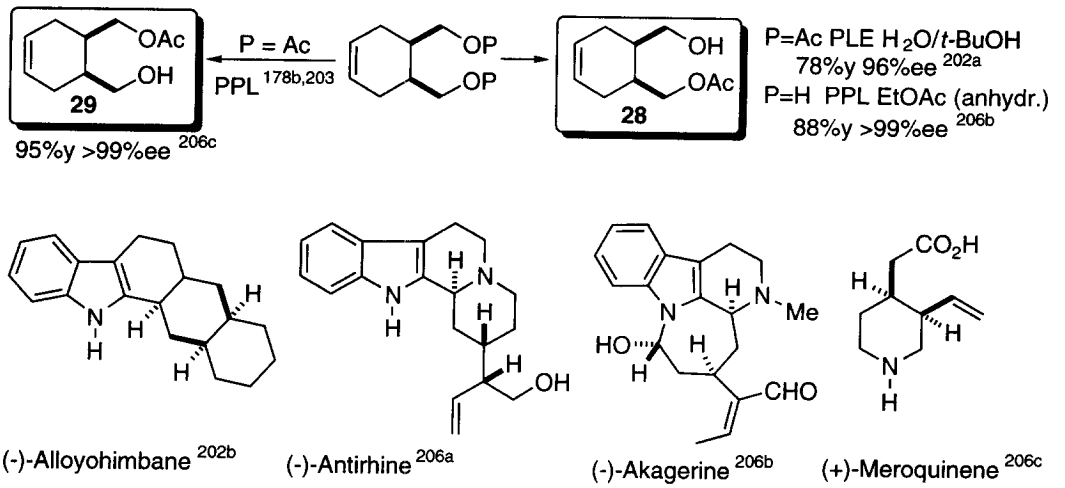
Scheme 70



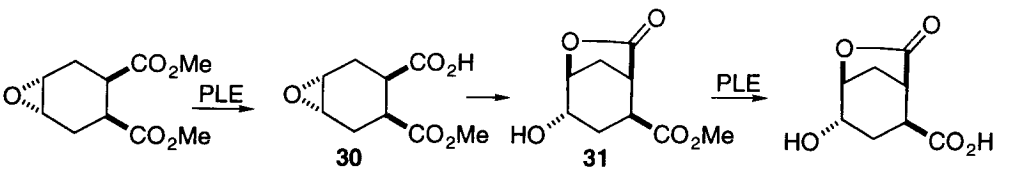
Access to cyclohex-4-ene-1,2-dimethanol monoacetate can be achieved by either enzyme-mediated hydrolysis of the *meso*-diacetate or acetylation of the corresponding 1,2-dimethanol.[203] Enantiopure monoacetate **28** was used as a key intermediate in the synthesis of several indole alkaloids, namely (-)-antirhine[206a] and (-)-alloyohimbane.[202b] Danieli and co-workers employed the same substrate in the first enantioselective total synthesis of (-)-akagerine. However, the enzyme-mediated key step was modified from the initial protocol[202a] in order to find a reproducible methodology on a multigram scale. The best results were obtained with porcine pancreatic lipase in anhydrous ethyl acetate.[206b] The enantiomer **29** was also used by the same laboratory in the preparation of (+)-meroquinene,[206c] a key intermediate in the synthesis of *Cinchona* alkaloids (Scheme 71).

The PLE-catalyzed asymmetrization of dimethyl 4,5-epoxy-1,2-*cis*-cyclohexanedicarboxylate was reported by Tamm *et al.* and gave rise to an interesting lactone.[199a] The proposed mechanism is depicted in Scheme 72, the first step being the hydrolysis of the equatorial ester to afford the monocarboxylic acid **30**. An intramolecular epoxide ring opening provided hydroxy-δ-lactone **31** and was followed by PLE-mediated hydrolysis of the second ester group.

Scheme 71

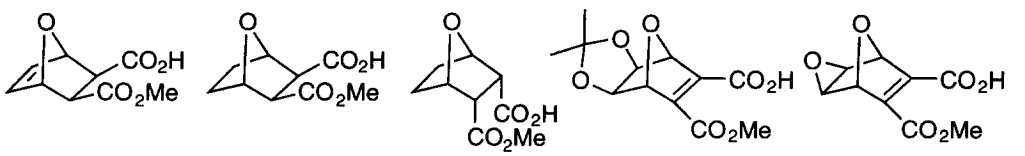


Scheme 72



2.4. Polycyclic *meso*-substrates[174,209-221]

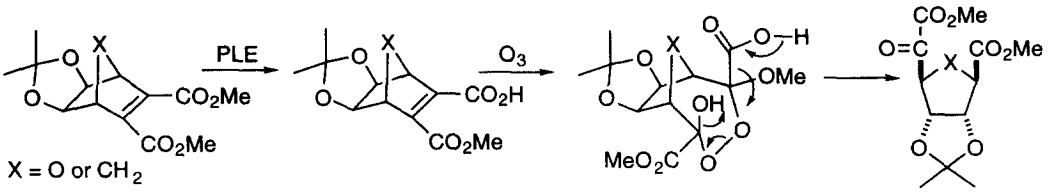
A tandem [4+2] cycloaddition-enzymatic asymmetrization, providing an enantioselective Diels-Alder reaction equivalent, has been studied in many variations. In almost all cases the catalysis products were obtained with good chemical yields and enantiopurities. Pig liver esterase was employed to hydrolyze various *meso*-dicarboxylates.[209,214]



86%y 75%ee [214] 82%y 98%ee [214] 87%y 64%ee [214] 96%y 77%ee [209c] 100%y 77%ee [209a]

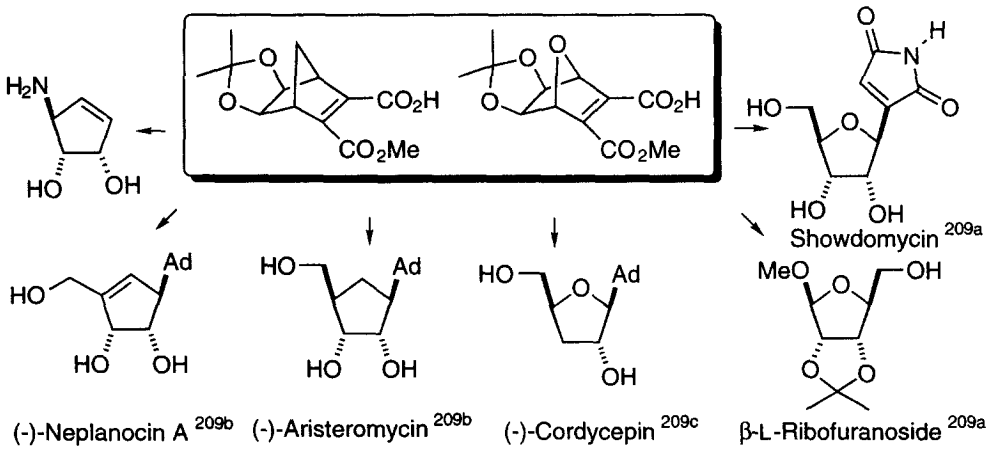
Ohno *et al.* subjected various monoesters to decarboxylative ozonolysis to unveil the ribose skeletons. The mechanism is illustrated in Scheme 73.[209]

Scheme 73

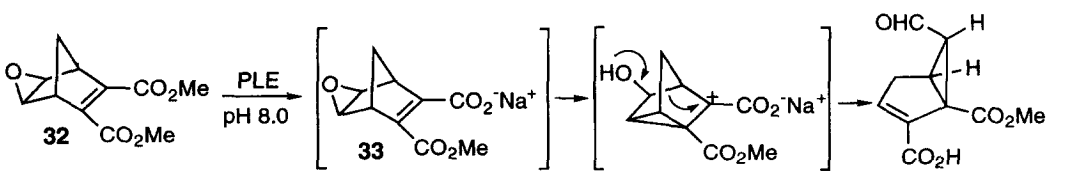


The same laboratory applied this methodology to the synthesis of several nucleosides as shown in Scheme 74.[209] In connection with this study, a new regio- and stereoselective asymmetric rearrangement of *meso*-dicarboxylate **32** was discovered during enzymatic hydrolysis The monoester **33**, generated *in situ* in this reaction, undergoes an extremely facile Meinwald-type rearrangement to afford the bicyclo product in quantitative yield but only 47% ee (Scheme 75).[209d-f]

Scheme 74

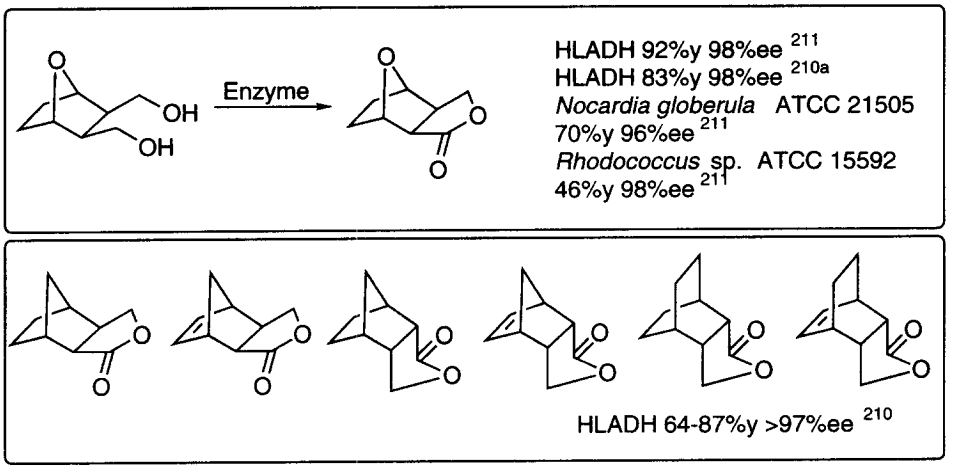


Scheme 75

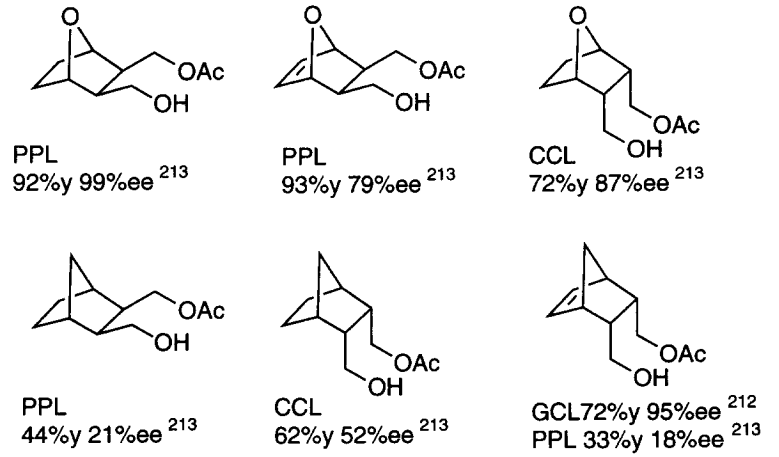


HLADH-catalyzed oxidations (Scheme 76) of *meso*-bicyclic diols have also been used as asymmetrization procedures.[210,211]

Scheme 76

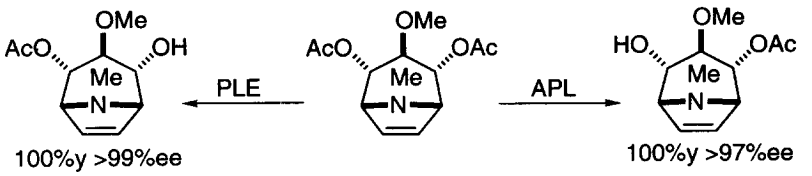


Related compounds are also accessible by lipase processing of *meso*-diols, diacetates, or diesters.[212-214]



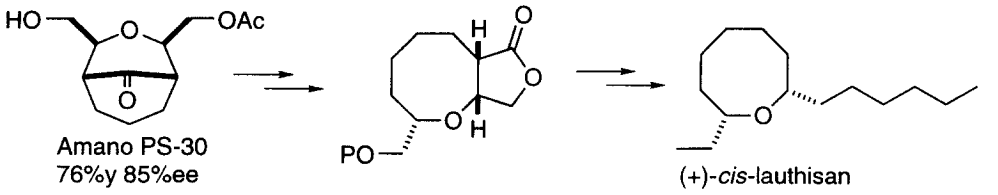
The *meso*-azabicyclo[3.2.1]diacetate shown in Scheme 77 has been subjected to enzymatic hydrolysis. It was found that esterases and lipases exert opposite enantioselectivities and allow for the isolation of either enantiomer with excellent yields and very good ee values.[174a,b]

Scheme 77



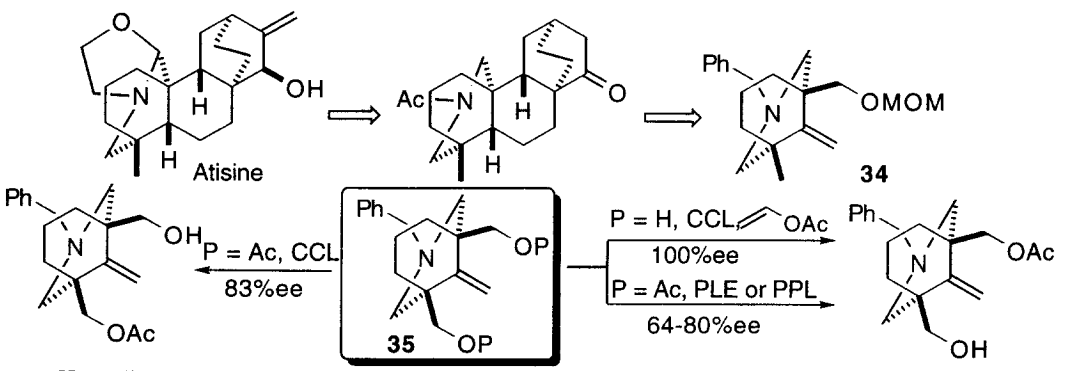
Kim *et al.* reported a new [4+3] cycloaddition approach to *cis*-2,8-disubstituted oxocanes. The key intermediate in the synthesis of (+)-*cis*-lauthisan was prepared by treatment of the *meso*-diol with crude Amano PS-30 lipase in isopropenyl acetate (Scheme 78).[215]

Scheme 78

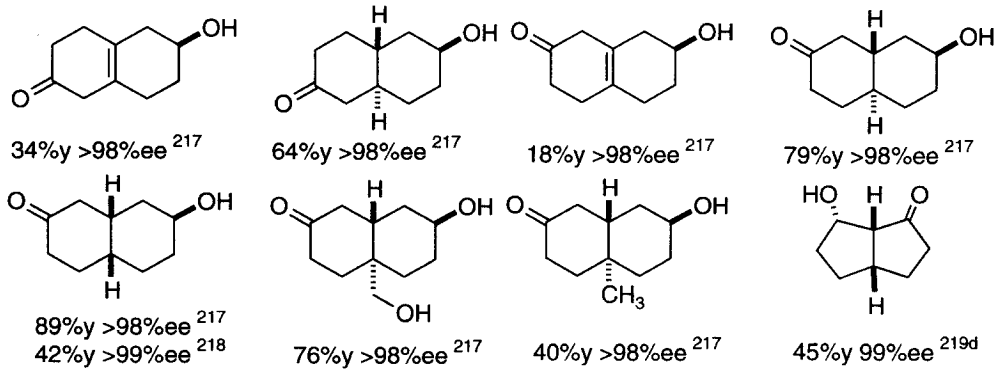


Fukumoto and co-workers reported the total synthesis of atisine, the predominant alkaloid of *Aconitum heterophyllum*. The key intermediate **34** was obtained *via* enzymatic asymmetrization of *meso*-diol **35** (P = H) or the corresponding diacetate (P = Ac). Both enantiomeric monoacetates were transformed into the natural enantiomer of atisine (Scheme 79).[216]

Scheme 79

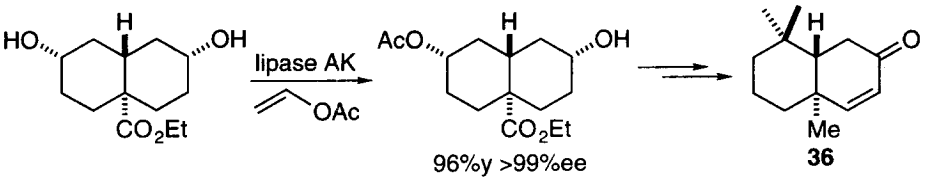


Horse liver alcohol dehydrogenase-catalyzed asymmetrizations of *meso*-decalindiones were studied by the Jones[217] and the Nakazaki[218] research groups. Baker's yeast catalyzed reductions of prochiral bicyclic diketones, *e.g.*, bicyclo[2.2.1]heptane-2,5-dione, bicyclo[2.2.2]octane-2,6-dione, and bicyclo[3.3.0]octane-2,8-dione, were also reported.[219] Regio- and stereoselective reactions afforded the enantiopure keto-alcohols shown:

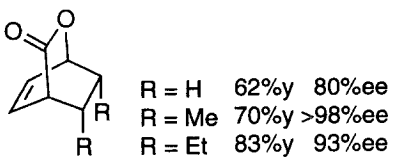


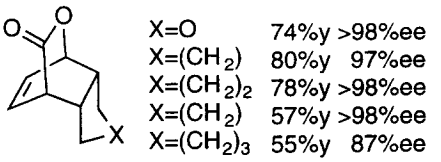
The lipase-catalyzed asymmetrization of a *meso*-decahydronaphthalenediol has served as an alternative route in the preparation of hydroxy-ketone **36**, a pivotal intermediate in the synthesis of (-)-polygodial, (-)-warburganal, and (-)-drimenin (Scheme 80).[220]

Scheme 80



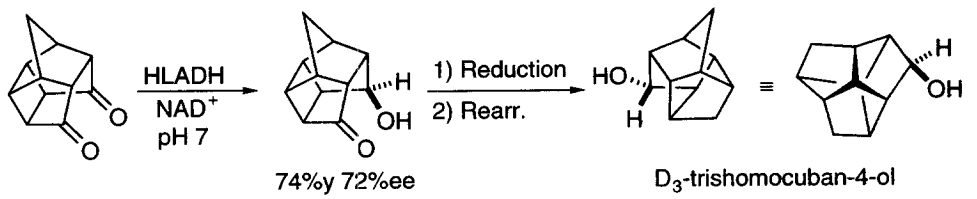
Taschner and Peddada reported the enzymatic Baeyer-Villager oxidation of a series of bicyclo[2.2.1]hept-2-en-7-ones utilizing cyclohexanone oxygenase, an enzyme isolated from the bacterium *Actinebacter* NCIB 9871. Most lactone products were obtained in high enantiopurity as determined by conversion of the lactones into the corresponding Mosher esters.[27c]





Horse liver alcohol dehydrogenase was used in the enantioselective reduction of a caged-shaped *meso*-diketone. The keto-alcohol was efficiently transformed into optically active (+)-D_3-trishomocuban-4-ol (Scheme 81).[221]

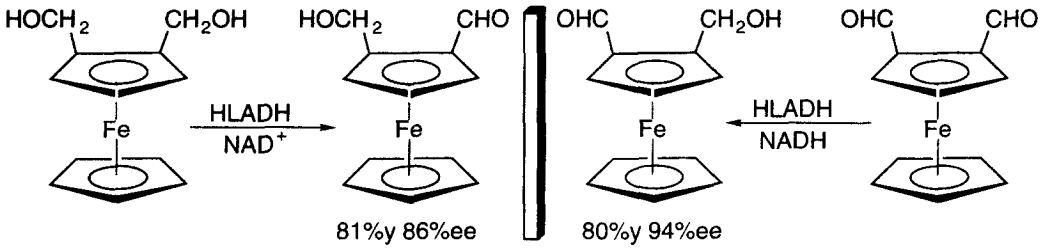
Scheme 81



2.5.a. Organometallic *meso*-substrates

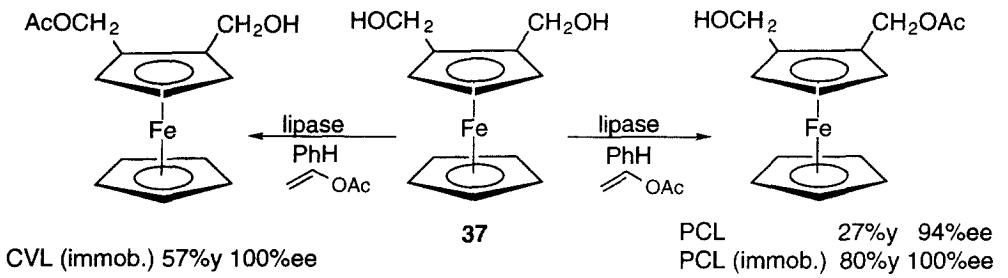
Enzymatic asymmetrization of organometallic *meso*-compounds has been recognized as a convenient method for the synthesis of enantiopure transition metal complexes. Yamazaki and Hosono reported the HLADH- catalyzed asymmetrization of 1,2-bis(hydroxymethyl)- and 1,2-diformylferrocene. The absolute configuration and enantiopurity were established by chemical correlation to the known aldehyde, 1-formyl-2-methylferrocene. The reported biocatalysis constitutes the first example for the enzymatic generation of planar chirality in organometallic compounds (Scheme 82).[222]

Scheme 82



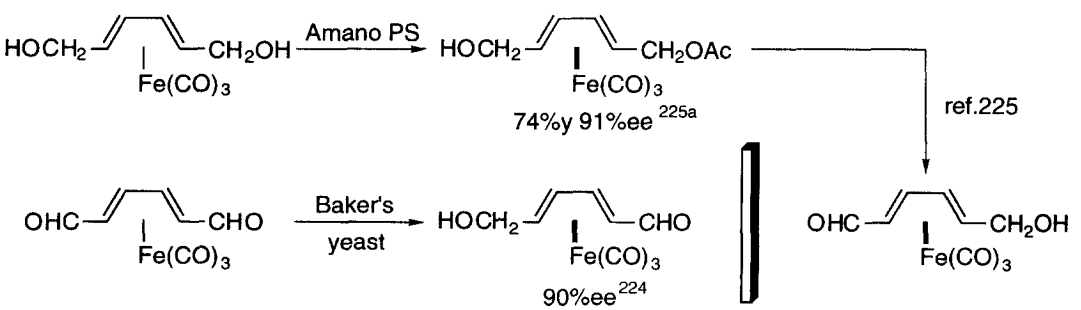
The asymmetrization of *meso*-diol **37** was also achieved with *Pseudomonas cepacea* lipase, which showed best results in an immobilized form. The antipode of the monoacetate was obtained with *Chromobacterium viscosum* (Scheme 83).[223a] Subsequently, Nicolosi and co-workers reported on the enzymatic acetylation of a *meso*, *dl*-mixture of 1,1'-bis(α-hydroxyethyl)ferrocene.[223b]

Scheme 83



The methodology of enzymatic asymmetrization of transition metal complexes was recently broadened by transformations of diene-$Fe(CO)_3$ complexes (Scheme 84).[224,225]

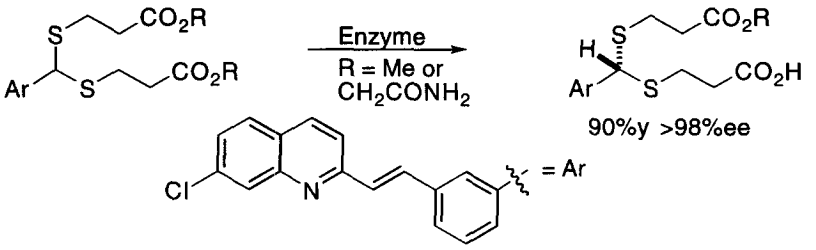
Scheme 84



2.5.b. Miscellaneous

Aryl and alkyl dithioacetals of mercaptopropionic acid derivatives are known to be potent receptor antagonists of leukotriene D_4. Various prochiral substrates have been studied by researchers at Merck Laboratories (Scheme 85).[226]

Scheme 85



Despite the remoteness of the prochiral, center enzymatic hydrolyses of the diesters proceeded with high enantioselectivity in the presence of purified *Pseudomonas* lipase from Sigma, giving the (*S*) enantiomer in each case. Both enantiomers of the LTD_4 antagonist MK-0571 were prepared from the same monoester.

3. CLOSING REMARKS

Nature's catalysts — the enzymes — should be considered by synthetic chemists in the same context as man-made catalysts; their use in a synthetic sequence may provide unique advantages of efficiency, stereoselectivity, and enviromental friendliness. Although enzymes are designed by nature to carry out a specific molecular transformation on a specific substrate, when encouraged to do so they can be remarkably promiscuous in regard to substrates and, yet, remain exquisitely chemo-, regio-, and enantioselective.

Biotransformations of interest in organic synthesis can be brought about under a variety of conditions. The most appealing to synthetic chemists are those than can be carried out with readily available, isolated enzymes requiring no added cofactors. Foremost among these are the various esterases which catalyze the hydrolysis or formation of esters. Among this group, the microbially-produced lipases are especially attractive in that they are readily available and can be easily enticed to work in the hydrolytic direction in the presence of water or in the synthetic direction in organic solvents. The latter can often offer the great advantage of wide-rangeing substrate solubility.

Those enzyme systems that require cofactors, especially the oxidoreductases can be handled by coupling enzymatic or non-enzymatic cofactor recycling. The organic chemist may prefer to use naturally coupled enzyme systems and tackle such transformations using whole cell techniques. Other than the simplest baker's yeast reductions, the novice may wish to seek counsel of a microbiologist in such instances.

Although enzymes can and are often called upon for their chemo- and regioselectivity, their most frequent use is in resolutions and asymmetric syntheses. This review has focused on the asymmetrization of prochiral molecules bearing enantiotopic groups and *meso*-compounds. Enzymes reach their maximum advantage with such substrates which can be processed entirely to a single enantiomer. (Another class of substrates that share this advantage — those with enantiotopic faces, *e.g.*, unsymmetrical ketones — is beyond the scope of the present review).

A number of the examples of useful, enantiopure intermediates derived from *meso*-substrates and included in this review have come from our laboratory. Given the past research activities of our laboratory, the success of this chemistry in itself should provide adequate encouragement to those chemists who have been reluctant to cross the unnatural barrier between organic synthesis and the biological sciences.

4. ACKNOWLEDGMENTS

This review and work from the author's laboratory quoted herein has been made possible by a grant from the National Science Foundation (CHE 9223011). We thank Dr. David L. Coffen (ArQule) and Prof. Romas J. Kazlauskas (McGill) for their helpful input.

5. REFERENCES AND NOTES

1. For stereochemistry and biological activity of drugs see: (a) Ariëns, E. J. *Med. Res. Rev.* **1986**, *6*, 451-466. (b) Beckett, A. H. *Biochem. Soc. Trans.* **1991**, *19*, 443-446. (c) Campbell, D. B.; Wilson, K. *Biochem. Soc. Trans.* **1991**, *19*, 472-475. (d) Simonyi, M. *Med. Res. Rev.* **1984**, *4*, 359-413. (e) Ariëns, E. J.; Wuis, E. W.; Veringa, E. J. *Biochem. Pharmacol.* **1988**, *37*, 9-18. (f) Grigg, W. *FDA Consum.* **1987**, *21*, 14-17. (g) Brown, C. Ed. *Chirality in Drug Design and Synthesis* Academic Press: New York, 1990. (h) Wainer, I. W.; Drayer, D. E. Eds. *Drug Stereochemistry: Analytical Methods and Pharmacology* Marcel Dekker, Inc.: New York, 1988. (i) Ariëns, E. J.; Van Rensen, J. J. S.; Welling, W. Eds. *Stereoselectivity of Pesticides. Biological and Chemical Problems* Elsevier: Amsterdam, 1988. (j) Ariëns, E. J.; Soudijn, W.; Timmermans, P. B. M. W. M. Eds. *Stereochemistry and Biological Activity of Drugs* Blackwell Scientific Publications: Oxford, 1983.

2. For industrial aspects on the development of optically active compounds see: (a) Sheldon, R. A. *Chemistry and Industry* **1990**, 212-219. (b) Sheldon, R. A. *Chirotechnology: Indutrial Syntheses of Optically Active Compounds* Marcel Dekker, Inc.: New York, 1993.

3. Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions* American Chemical Society: Washington, D. C., 1971.

4. For the use of enzymes in industry see: (a) Gerhartz W. Ed. *Enzymes in Industry* VCH: Weinheim, 1990. (b) Elferink, V. H. M.; Breitgoff, D.; Kloosterman, M.; Kamphuis, J.; van den Tweel, W. J. J.; Meijer, E. M. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 63-74

5. For specialized books see 4a and: (a) Wong, C.-H.; Whitesides, G. M. *Tetrahedron Organic Chemistry Series Vol. 12: Enzymes in Synthetic Organic Chemistry* Elsevier Science Ltd.: Oxford, 1994. (b) Davies, H. G.; Green, R. H.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry* Academic Press Ltd.: London, 1989. (c) Faber, K. *Biotransformations in Organic Chemistry* Springer-Verlag: Berlin Heidelberg, 1995. (d) Faber, K.; Griengl, H. in *Chirality - From Weak Bosons to the α-Helix* Janoschek, R. Ed.; Springer-Verlag: Berlin Heidelberg, 1991, 103-140. (e) Porter, R.; Clark, S. Eds. *Enzymes in Organic Synthesis, CIBA Foundation Symposium 111* Pitman: London, 1985. (f) Schneider, M. P. Ed. *Enzymes as Catalysts in Organic Synthesis* NATO ASI Series C, Reidel, Dordrecht, 1986. (g) Servi, S. *Microbial Reagents in Organic Synthesis* NATO ASI Series C, Kluwer, Dordrecht, 1992. (h) Abramowicz, D. A. Ed. *Biocatalysis* Van Nostrand Reinhold: New York, 1990. (i) Drauz, K.; Waldmann, H. Eds. *Enzyme Catalysis in Organic Synthesis Vol. 1 & 2* VCH: Weinheim, 1995.

6. For special issues of periodicals see: (a) Crout, D. H. G.; Griengl, H.; Faber, K.; Roberts, S. M. Eds. *Proceedings of the European Symposium on Biocatalysis, Graz 1993, Biocatalysis* special issue, 1994, Vol 9 (1-4). (b) Kieslich, K.; Leuenberger, H. G. W.; Seebach, D. Eds. *Proceedings of the International Bioorganic Symposium "Biotransformations in Organic Chemistry: Principles and Applications", Interlaken 1993, Chimia* special issue, 1993, Vol 47 (4). (c) Crout, D. H. G.; Roberts, S. M.; Jones, J. B. Eds. *Enzymes in Organic Synthesis, Tetrahedron: Asymmetry* special issue, 1993, Vol 4 (5-6). (d) Meijer, E. M. Ed. *Biocatalysis in Organic Chemistry, Recl. Trav. Chim. Pays-Bas* special issue, 1991, Vol 110 (5). (e) Azerad, R.; Sih, C. J. Eds. *Enantioselective Synthesis using Biological Systems, Biocatalysis* special issue, 1990, Vol 3 (1-2).

7. For general reviews see: (a) Azerad, R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 17-51. (b) Wong, C.-H.; Halcomb, R. L.; Ichikawa, Y.; Kajimoto, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 412-432; 521-546. (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071-

1140; (d) Drueckhammer, D. G.; Hennen, W. J.; Pederson R. L.; Barbas, III, C. F.; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499-525. (e) Leuenberger, H. G. W. *Pure Appl. Chem.* **1990**, *62*, 753-768. (f) Wong, C.-H. *Science* **1989**, *244*, 1145-1152. (g) Turner, N. J. *Nat. Prod. Rep.* **1989**, *6*, 625-644. (h) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351-3403. (i) Whitesides, G. M.; Wong, C.-W. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638. (j) Ohno, M. In: *Organic Syntheses, An Interdisciplinary Challenge, Proc. 5th IUPAC Symposium Syn. Org. Synth.*, Streith, J.; Prinzbach, H.; Shill, H. Eds.; Blackwells: Oxford, 1984, 189-204. (k) Yamada, H.; Shimizu, S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 622-642. (l) Sariaslani, F. S.; Rosazza, J. P. N. *Enzyme Microb. Technol.* **1984**, *6*, 242-253. (m) Butt, S.; Roberts, S. M. *Chem. Br.* **1987**, 127-134. (n) Akiyama, A.; Bednarski, M.; Kim, M.-J.; Simon, E. S.; Waldmann, H.; Whitesides, G. M. *Chem. Br.* **1987**, 645-654. For enzymatic protecting group techniques see: (o) Waldmann, H.; Sebastian, D. *Chem. Rev.* **1994**, *94*, 911-937. (p) Waldmann, H. *Kontakte (Darmstadt)* **1991** (2) 33-54.

8. (a) For a review on baker's yeast see: Csuk, R. Glänzer, B. I. *Chem. Rev.* **1991**, 49-97. (b) For a review on biocatalytic reductions see: Simon, H.; Bader, J.; Günther, H.; Neumann, S.; Thanos, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 539-553.
9. For a review on biocatalytic resolution see: Sih, C. J.; Wu, S.-H. *Topics in Stereochemistry Vol. 19* ; Eliel, E. L; Wilen, S. H. Eds.; John Wiley & Sons, Inc.: New York, 1989, 63-125.
10. For reviews on hydrolytic enzymes see: (a) Boland, W.; Fröβl, C.; Lorenz, M. *Synthesis* **1991**, 1049-1072. (b) Faber, K.; Riva, S. *Synthesis* **1992**, 895-910.
11. For a review on PFL see: Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 773-750.
12. For reviews on PLE see: (a) Ohno, M.; Otsuka, M. *Org. React. N. Y.* **1989**, *37*, 1-55. (b) Zhu, L.-M.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587-6611.
13. For a review on enzymes in the synthesis of chiral drugs see: Margolin, A. L. *Enzyme Microb. Technol.* **1993**, *15*, 266-280.
14. Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. *Chiral Synthons via Enzyme-Mediated Asymmetrization of Meso Compounds* in *Advances in the Use of Synthons in Organic Chemistry* Dondoni, A.; Padwa, A. Eds.; JAI Press Ltd.: London, 1993, 143-219.
15. For historical aspects see: Fruton, J. S. *Molecules and Life* Wiley-Interscience: New York, 1972, 22-86.
16. *Enzyme Nomenclature* Academic Press, Inc.: New York, 1992.
17. International Union of Biochemistry *Enzyme Nomenclature* Academic Press: Orlando, 1984.
18. Dakin, H. D. *Proc. Chem. Soc. London* **1903**, *19*, 161.
19. Jones, J. B.; Sih, C. J.; Perlmann, D. *Tech. Chem. (Prague)* **1976**, *10*, 107.
20. Clement, G. E.; Potter, R. *J. Chem. Educ.* **1971**, *48*, 695-696.
21. Cohen, S. G.; Crossley, J.; Khedouri, E. *Biochemistry* **1963**, *2*, 820-823.
22. Ogston, A. G. *Nature* **1948**, *162*, 963.
23. (a) Cohen, S. G.; Altschul, L. *Nature* **1959**, *183*, 1678. (b) Cohen, S. G.; Klee, L. H. *J. Am. Chem. Soc.* **1960**, *82*, 6038-6042. (c) Cohen, S. G.; Khedouri, E. *J. Am. Chem. Soc.* **1961**, *83*, 1093-1096. (d) Cohen, S. G.; Khedouri, E. *J. Am. Chem. Soc.* **1961**, *83*, 4228-4233.
24. (a) Chen, C.-S.; Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695-707. (b) Klibanov, A. M. *Trends Biochem. Sci.* **1989**, *14*, 141-144. (c) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120. (d) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 3192-3196. (e) Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Enzyme Microb. Technol.* **1993**, *15*, 367-382.
25. (a) Bellucci, G.; Berti, G.; Chiappe, C.; Fabri, F.; Marioni, F. *J. Org. Chem.* **1989**, *54*, 968-970. (b) Bellucci, G.; Capitani, I.; Chiappe, C.; Marioni, F. *J. Chem. Soc., Chem. Commun.* **1989**, 1170-1171. (c) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Chem. Soc. Perkin Trans. I* **1989**, 2369-2373.
26. (a) Kakeya, H.; Sakai, N.; Sano, A.; Yokoyama, M.; Sugai, T.; Ohta, H. *Chem. Lett.* **1991**, 1823-1824. (b) Beard, T.; Cohen, M. A.; Parratt, J. S.; Turner, N. J.; Crosby, J.; Moilliet, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1085-1104.

27. (a) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892-6893. (b) Taschner, M. J.; Black, D. J.; Chen, Q.-Z. *Tetrahedron: Asymmetry* **1993**, *4*, 1387-1390. (c) Taschner, M. J.; Peddada, L. *J. Chem. Soc., Chem. Commun.* **1992**, 1384-1385.
28. (a) Gais, H. J.; Zeissler, A.; Maidonis, P. *Tetrahedron Lett.* **1988**, *29*, 5743-5744. (b) Crout, D. H. G.; MacManus, D. A.; Critchley, P. *J. Chem. Soc., Chem. Commun.* **1991**, 376-378.
29. Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287-7290.
30. Gopalan, A. S.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 5235-5238.
31. Ohno, M.; Kobayashi, S.; Limori, T.; Wang, Y.-F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405-2406.
32. Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *40*, 311-314.
33. Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347-1352.
34. (a) Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 236-238. (b) Sabbioni, G.; Jones, J. B. *J. Org. Chem.* **1987**, *52*, 4564-4570.
35. Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 3931-3932.
36. (a) Francis, C. J.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 579-580. (b) Lam, L. K. P.; Hui, R. A, H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047-2050.
37. For preparation and synthetic application of asymmetrized 2-methyl-1,3-propanediol and its equivalents see: Banfi, L.; Guanti, G. *Synthesis*, **1993**, 1029-1056.
38. (a) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1994**, *5*, 283-288. (b) Bisht, K. S.; Parmar, V. S.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1993**, *4*, 957-958. (c) Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1993**, *4*, 925-930.
39. Goodhue, C. T.; Schaeffer, J. R. *Biotech. Bioeng.* **1971**, *13*, 203-214.
40. For functionalization and synthetic application of (*S*)-3-hydroxy-2-methylpropanoic acid see: (a) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505-3511. (b) Branca, Q.; Fischl, A. *Helv. Chim. Acta.* **1977**, *60*, 925-944. (c) Meyers, A. I.; Babiak, K. A.; Campbell, A. L; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015-5024. (d) Meyers, A. I.; Hudspeth, J. P. *Tetrahedron Lett.* **1981**, *22*, 3925-3928. (e) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343-4346. (f) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4347-4350. (g) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789-6791.
41. (a) Hasegawa, J.; Ogura, M.; Hamaguchi, S.; Shimazaki, M.; Kawaharada, H.; Watanabe, K. *J. Ferment. Technol.* **1981**, *59*, 203. (b) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541-546.
42. (a) Ohta, H.; Tetsukawa, H. *Chem. Lett.* **1979**, 1379-1380. (b) Ohta, H.; Tetsukawa, H.; Noto, N. *J. Org. Chem.* **1982**, *47*, 2400-2404.
43. Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189-6192.
44. Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Tetrahedron Lett.* **1990**, *31*, 5657-5660.
45. Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1638-1639.
46. Wirz, B.; Schmid, R.; Walther, W. *Biocatalysis* **1990**, *3*, 159-167.
47. (a) Wang, Y.-F.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 4999-5002. (b) Iriuchijima, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907-1910.
48. (a) Tombo, G. M. R.; Schär, H.-P.; Fernandez, X.; Busquets, I.; Ghisalba, O. *Tetrahedron Lett.* **1986**, *27*, 5707-5710. (b) Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941-4958.
49. Morgan, B.; Bydlinsky, G.; Dodds, D. R. *Tetrahedron: Asymmetry* **1995**, *6*, 1765-1772.
50. Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1989**, 957-962.
51. Ehrler, J.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 379-388.

52. Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 2697-2698.
53. (a) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081-7092. (b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron: Asymmetry* **1990**, *1*, 721-724.
54. Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *57*, 1540-1554.
55. Guanti, G.; Banfi, L.; Riva, R.; Zannetti, M. T. *Tetrahedron Lett.* **1993**, *34*, 5483-5486.
56. Guanti, G.; Banfi, L.; Zannetti, M. T. *Tetrahedron Lett.* **1993**, *34*, 5487-5490.
57. Guanti, G.; Banfi, L.; Merlo, V.; Narisano, E.; Thea, S. *Tetrahedron* **1993**, *49*, 9501-9516.
58. (a) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymmetry* **1994**, *5*, 9-12. (b) Banfi, L.; Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1345-1356.
59. Guanti, G.; Banfi, L.; Brusco, S.; Narisano, E. *Tetrahedron: Asymmetry* **1994**, *5*, 537-540.
60. (a) Barnett, C. J.; Wilson, T. M. *Tetrahedron Lett.* **1989**, *30*, 6291-6294. (b) Barnett, C. J.; Wilson, T. M.; Wendel, S. R.; Winningham, M. J.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 7038-7045.
61. Atsuumi, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Ohkubo, M.; Yonezawa, T.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Tetrahedron Lett.* **1990**, *31*, 1601-1604.
62. Terao, Y.; Akamatsu, M.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 823-825.
63. Lovey, R. G.; Saksena, A. K.; Girijavallabhan, V. M. *Tetrahedron Lett.* **1994**, *35*, 6047-6050.
64. (a) Eberle, M.; Missbach, M.; Seebach, D. *Organic Syntheses* **1993**, *8*, 332-338. (b) Eberle, M.; Egli, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1-23. (c) Seebach, D.; Eberle, M. *Chimia* **1986**, *40*, 315-318.
65. Seu, Y.-B.; Kho, Y.-H. *Tetrahedron Lett.* **1992**, *33*, 7015-7016.
66. Itoh, T.; Ohara, H.; Takagi, Y.; Kanda, N.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 4215-4218.
67. (a) Hadorn, B.; Leuthardt, F.; Ménard, E.; Vischer, D. *Helv. Chim. Acta* **1963**, *46*, 2003-2008. (b) Bally, C.; Leuthardt, F. *Helv. Chim. Acta* **1970**, *53*, 732-738.
68. Breitgoff, D.; Laumen. K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523-1524.
69. Suemune, H.; Mizuhara, Y.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *34*, 3440-3444.
70. Kerscher, V; Kreiser, W. *Tetrahedron Lett.* **1987**, *28*, 531-534.
71. Terao, Y.; Murata, M.; Achiwa, K. *Tetrahedron Lett.* **1988**, *29*, 5173-5176.
72. (a) Lattmann, R.; Ghisalba, O.; Gygax, D.; Schär, H. P.; Schmidt, E. *Biocatalysis* **1990**, *3*, 137-144. (b) Ghisalba, O.; Lattmann, R.; Gygax, D. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 263-264.
73. Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200-7205.
74. Rios-Mercadillo, V. M.; Whitesides, G. M *J. Am. Chem. Soc.* **1979**, *101*, 5828-5829.
75. Kosmol, H.; Kieslich, K.; Gibian, H. *Liebigs Ann. Chem.* **1968**, *711*, 38-41.
76. (a) Gutman, A. L.; Shapira, M.; Boltanski, A. *J. Org. Chem.* **1992**, *57*, 1063-1065. (b) Shapira, M.; Gutman, A. L. *Tetrahedron: Asymmetry* **1994**, *5*, 1689-1700.
77. Kitazume, T.; Sato, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1811-1814.
78. (a) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T. *Tetrahedron Lett.* **1985**, *26*, 4957-4958. (b) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry*, **1995**, *6*, 893-900.
79. Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J. T. *J. Org. Chem.* **1986**, *51*, 1003-1006.
80. Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250-1254.
81. De Jeso, B.; Belair, N.; Deleuze, H.; Rascle, M.-C.; Maillard, B. *Tetrahedron Lett.* **1990**, *31*, 653-654.
82. Gutman, A. L.; Shapira, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1467-1468.
83. Nakamura, T.; Nagasawa, T.; Yu, F.; Watanabe, I.; Yamada, H. *Tetrahedron* **1994**, *50*, 11821-11826.

84. (a) Nakamura, T.; Yu, F.; Mizunashi, W.; Watanabe, I. *Appl. Environ. Microbiol.* **1993**, *59*, 227-230. (b) Nakamura, T.; Nagasawa, T.; Yu, F.; Watanabe, I.; Yamada, H. *J. Bacteriol.* **1992**, *174*, 7613-7619.

85. Yu, F.; Nakamura, T.; Mizunashi, W.; Watanabe, I. *Biosci. Biotech. Biochem.*, **1994**, *58*, 1551-1457.

86. Ng, G. S. Y.; Yuan, L.-C.; Jakovac, I. J.; Jones, J. B. *Tetrahedron* **1984**, *40*, 1235-1243.

87. (a) Mori, K.; Amaike, M.; Oliver, J. E. *Liebigs. Ann. Chem.* **1992**, 1185-1190. (b) Mori, K.; Amaike, M.; Watanabe, H. *Liebigs. Ann. Chem.* **1993**, 1287-1294.

88. Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501-2511.

89. (a) Bestmann, H. J.; Philipp, U. C. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 86-88. (b) Bestmann, H. J.; Bauriegel, L. *Tetrahedron Lett.* **1995**, *36*, 853-856.

90. Pottie, M.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron: Asymmetry* **1991**, *2*, 329-330.

91. Gais, H.-J.; Hemmerle, H.; Kossek, S. *Synthesis* **1992**, 169-173.

92. (a) Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1991**, *32*, 5701-5704. (b) Burgess, K.; Chaplin, D. A.; Henderson, I. *J. Org. Chem.* **1992**, *57*, 1103-1109.

93. Adjé, N.; Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4631-4634.

94. Häbich, D.; Hartwig, W. *Tetrahedron Lett.* **1987**, *28*, 781-784.

95. Crout, D. H. G.; Gaudet, V. S. B.; Hallinan, K. O. *J. Chem. Soc. Perkin Trans. 1* **1993**, 805-812.

96. (a) Brevet, J.-L.; Mori, K. *Synthesis* **1992**, 1007-1012. (b) Mori, K. *Pure Appl. Chem.* **1994**, *66*, 1991-1998. (c) Mori, K.; Amaike, M. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2727-2733.

97. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1991**, *32*, 3043-3046.

98. Corser, D. A.; Dart, R. K.; Marples, B. A. *J. Chem. Research (S)* **1992**, 66.

99. Vänttinen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1992**, *3*, 1529-1532.

100. Reñold, P.; Tamm, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2295-2298.

101. Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Tetrahedron Lett.* **1990**, *31*, 6663-6666.

102. (a) Kim, J.-J.; Lee, I. S. *Synlett* **1993**, 767-768. (b) Kim, M.-J.; Lee, I. S. *J. Org. Chem.* **1993**, *58*, 6483-6485.

103. (a) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765-767. (b) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755-1756.

104. (a) For the use of β-aminoglutarates see: 23c, 106. (b) For the use of 3-alkyl substituted glutarate derivatives see: 107-110, 111b, 112. (c) For the use of 3-hydroxyglutarate derivatives see: 111a, 113-115. (d) For the use of 2,4-dimethylglutarate derivatives see: 118-122.

105. For publications from specific laboratories see: (a) Jones *et al.* see ref. 116. (b) Ohno *et al.* see refs. 31, 32, 106, 107. (c) Seebach *et al.* see ref. 121. (d) Sih *et al.* see refs. 109, 117, 119. (e) Tamm *et al.* see ref. 88, 108, 113, 122, and references cited therein.

106. For the use of β-aminoglutarates in the synthesis of (+)-negamycin and various carbapenems see refs. 31, 32, and: (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465-6466. (b) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659-1660. (c) Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217-220.

107. For synthetic studies on rhizoxin using glutarates see: (a) Nakada, M; Kobayashi, S.; Ohno, M.; Iwasaki, S; Okuda, S. *Tetrahedron Lett.* **1988**, *29*, 3951-3954. (b) Kobayashi, S.; Nakada, M.; Ohno, M. *Pure Appl. Chem.* **1992**, *64*, 1121-1124.

108. For the synthesis of verrucarin and related compounds see: (a) Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, C. *Helv. Chim. Acta* **1982**, *65*, 1412-1417. (b) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744-754.

109. (a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299. (b) VanMiddlesworth, F.; Wang, Y. F.; Zhou, B.; DiTullio, D.; Sih, C. J. *Tetrahedron Lett.* **1985**, *26*, 961-964.

110. Genicot, C.; Ley, S. V. *Synthesis* **1994**, 1275-1277.

111. For alkoholysis of pentanedioic anhydrides see: (a) Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1993**, 805-808. (b) Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087-3092. (c) also see ref.118.

112. For hydrolysis of various glutarate diesters see ref. 88.

113. Mohr, P.; Rösslein, L.; Tamm, C. *Helv. Chim Acta* **1987**, *70*, 142-152.

114. (a) Roy, R.; Rey, A. W. *Tetrahedron Lett.* **1987**, *28*, 4935-4938. (b) Santaniello, E.; Chiari, M.; Ferraboschi, P.; Trave, S. *J. Org. Chem.* **1988**, *53*, 1567-1569. (c) Brooks, D. W.; Palmer, J. T. *Tetrahedron Lett.* **1983**, *24*, 3059-3062.

115. (a) Gutman, A. L.; Bravdo, T. *J. Org. Chem.* **1989**, *54*, 5645-5646. (b) Soriente, A.; Laudisio, G.; Giordano, M.; Sodano, G. *Tetrahedron: Asymmetry* **1995**, *6*, 859-862.

116. For HLADH-catalyzed oxidation of substituted 1,5-pentanediols see: (a) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556-561. (b) Jones, J. B.; Lok, K. P *Can. J. Chem.* **1979**, *57*, 1025-1032.

117. (a) Huang, F.-C.; Hsu Lee, L. F.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J.; Caspi, E.; Eck, C. R. *J. Am. Chem. Soc.* **1975**, *97*, 4144-4145. (b) Also see ref. 30.

118. Ozegowski, R.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1993**, *4*, 695-698.

119. (a) Chen, C.-S.; Fujimoto, Y.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 3580-3582. (b) VanMiddlesworth, F.; Patel, D. V.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2996-2997.

120. Holmes, D. S.; Sherringham, J. A.; Dyer, U. C.; Russell, S. T.; Robinson, J. A. *Helv. Chim. Acta* **1990**, *73*, 239-259.

121. (a) Schregenberger, C.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 5881-5884. (b) Schregenberger, C.; Seebach, D. *Liebigs Ann. Chem.* **1986**, 2081-2103.

122. (a) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621-625. (b) Born, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 2242-2250.

123. Anderson, J. C.; Ley, S. V.; Marsden S. P. *Tetrahedron Lett.* **1994**, *35*, 2087-2090.

124. Breuilles, P.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4205-4208.

125. (a) Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1650-1652. (b) Xie, Z.-F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 973-980.

126. Vandewalle, M.; Deprez, L.; Pottie, M.; Vanhessche, K. *Carbohydrates as Organic Raw Materials II*; G. Descotes Ed.; VCH: Weinheim, 1992, 39-57.

127. (a) Bonini, C.; Racioppi, R.; Righi, G.; Viggiani, L. *J. Org. Chem.* **1993**, *58*, 802-803. (b) Bonini, C.; Racioppi, R.; Viggiani, L.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1993**, *4*, 793-805.

128. Gutman, A. L.; Bravdo, T. *J. Org. Chem.* **1989**, *54*, 4263-4265.

129. Alphand, V.; Lebreton, J.; Furstoss, R. personal communication

130. For PFL-catalyzed asymmetrization see: (a) Xie, Z.-F.; Suemune, H.; Nakamura, I.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 4454-4459. (b) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838-839. (c) Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966-967.

131. Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1995**, *6*, 519-524.

132. Crout, D. H. G.; Gaudet, V. S. B.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 808-809.

133. For reduction of disubstituted cyclopentanediones in steroid synthesis see: (a) Gibian, H.; Kieslich, K.; Koch, H.-J.; Kosmol, H.; Rufer, C.; Schröder, E.; Vössing, R. *Tetrahedron Lett.* **1966**, 2321-2329. (b) Kosmol, H.; Kieslich, K.; Vössing, R.; Koch, H.-J.; Petzoldt, K.; Gibian, H. *Liebigs*

Ann. Chem. **1967**, *701*, 199-205. (c) Rufer, C.; Kosmol, H.; Schröder, E.; Kieslich, K.; Gibian, H. *Liebigs Ann. Chem.* **1967**, *702*, 141-148. (d) Dai, W.-M.; Zhou, W.-S. *Tetrahedron* **1985**, *41*, 4475-4482. (e) Schwarz, S.; Truckenbrodt, G.; Meyer, M.; Zepter, R.; Weber, G.; Carl, C.; Wentzke, M. *J. Prakt. Chem.* **1981**, *323*, 729-736. (f) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, *25*, 1241-1244.

134. (a) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820-2821. (b) Brooks, D. W.; Grothaus, P. G.; Palmer, J. T. *Tetrahedron Lett.* **1982**, *23*, 4187-4190. (c) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472-4473. (d) Brooks, D. W.; Woods, K. W. *J. Org. Chem.* **1987**, *52*, 2036-2039. (e) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223-3232.

135. (a) Takano, S.; Tanigawa, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1976**, 189-190. (b) Miura, S.; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Matsubara, S.; Ishimoto, S *Tetrahedron* **1976**, *32*, 1893-1898.

136. (a) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255-1256. (b) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Organic Syntheses* **1995**, *73*, 25-35.

137. (a) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875-5878. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298-1299. (c) Laumen, K.; Reimerdes, E. H.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 407-410. (d) Sugai, T.; Mori, K. *Synthesis* **1988**, 19-22.

138. (a) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Häfner, B.; Schwarz, S. *Synthesis* **1988**, 540-541. (b) Theil, F.; Schick, H.; Winter, G.; Reck, G. *Tetrahedron* **1991**, *47*, 7569-7582. (c) Theil, F.; Schick, H.; Lapitskaya, M. A.; Pivnitsky, K. K. *Liebigs Ann. Chem.* **1991**, 195-200. (d) Theil, F.; Schick, H. *J. Prakt. Chem.* **1991**, 497-499. (e) Theil, F. *Tetrahedron: Asymmetry* **1995**, *6*, 1693-1698.

139. (a) Jommi, G.; Orsini, F.; Sisti, M.; Verotta, L. *Gazz. Chim. Ital.* **1988**, *118*, 863-864. (b) Ikeda, S.; Weinhouse, M. I.; Janda, K. D.; Lerner, R. A. Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 7763-7764.

140. (a) Miyakoda, H.; Sagawa, S.; Nagaoka, H.; Yamada, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 587-594. (b) Krief, A.; Surleraux, D.; Ropson, N. *Tetrahedron: Asymmetry* **1993**, *4*, 289-292.

141. (a) For a review on 4-oxo-2-cyclopentenyl acetate as synthetic intermediate see: Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 480-492. For the preparation of enantiopure 4-*tert.*-butyldimethylsiloxy-2-cyclopent-1-one see: (b) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Organic Syntheses* **1995**, *73*, 36-43. (c) Paquette, L. A.; Heidelbaugh, T. M. *Organic Syntheses* **1995**, *73*, 44-49.

142. Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.

143. Johnson, C. R.; Golebiowski, A.; Braun, M. P.; Sundram, H. *Tetrahedron Lett.* **1994**, *35*, 1833-1834.

144. For chemoenzymatic synthesis of prostaglandins see: (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655-5656. (b) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726-4735. (c) Johnson C, R.; Chen, Y.-F. *J. Org. Chem.* **1991**, *56*, 3352-3357.

145. (a) For application of enzymes in the synthesis of bioactive polyols see: Johnson, C. R.; Adams, J. P.; Bis, S. J.; De Jong, R. L.; Golebiowski, A.; Medich, J. R.; Penning, T. D.; Senanayake, C. H.; Steensma, D. H.; Van Zandt, M. C. *Pure Appl. Chem.* **1992**, *64*, 1115-1120. (b) Parry, R. J.; Haridas, K.; De Jong, R.; Johnson, C. R. *Tetrahedron Lett.* **1990**, *31*, 7549-7552. (c) Parry, R. J.; Haridas, K.; De Jong, R.; Johnson, C. R. *J. Chem. Soc., Chem. Commun.* **1991**, 740-741. (d) De Jong, R. L. *Synthesis of Aristeromycin and Carbocyclic Analogues of Oxetanocin*, Wayne State University, 1990. (e) Medich, J. R.; Kunnen, K.; Johnson, C. R. *Tetrahedron Lett.*, **1987**, *36*, 4131-4134. (f) Johnson, C. R.; Esker, J. L.; Van Zandt, M. C. *J. Org. Chem.* **1994**, *59*, 5854-5855.

146. (a) Johnson, C. R.; Golebiowski, A.; Schoffers, E.; Sundram, H.; Braun, M. P. *Synlett* **1995**, 313-314. (b) Johnson, C. R.; Nerurkar, B. M.; Golebiowski, A.; Sundram, H.; Esker, J. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1139-1140.

147. Sato, M.; Hirokawa, T.; Hattori, H.; Toyota, A.; Kaneko, C. *Tetrahedron: Asymmetry* **1994**, *5*, 975-980.

148. Cotterill, I. C.; Cox, P. B.; Drake, A. F.; Le Grand, D. M.; Hutchinson, E. J.; Latouche, R.; Pettman, R. B.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3071-3075.

149. Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863-5864.

150. LeGrand, D. M.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1751-1752.

151. (a) Liu, Z.-Y.; He, L.; Zheng, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2277-2278. (b) Zhang, L.; Yang, J.-Y.; Liu, Z. Y. *Chin. Chem. Lett.* **1992**, *3*, 787. (c) Sato, M.; Hattori, H.; Murakami, M.; Kaneko, C. *Chem. Lett.* **1993**, 1919-1922.

152. (a) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron Lett.* **1995**, *36*, 6545-6546. (b) Also see ref. 28b.

153. Duhamel, P.; Renouf, P.; Cahard, D.; Yebga, A.; Poirier, J.-M. *Tetrahedron: Asymmetry* **1993**, *4*, 2447-2450.

154. Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. D.; Duax, W.L.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 4549-4554.

155. Yanai, M.; Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2373-2377.

156. (a) For the synthesis of pisiferic acid see: Mori, K.; Mori, H. *Tetrahedron* **1986**, *42*, 5531-5538.
For further applications see: (b) Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487-5493. (c) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273-281. (d) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 283-290. (e) Mori, K.; Mori, H.; Yanai, M. *Tetrahedron* **1986**, *42*, 291-294. (f) Mori, K.; Tamura, H. *Tetrahedron* **1986**, *42*, 2643-2646.

157. (a) Carda, M.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 17-20. (b) Dumortier, L.; Carda, M.; Van der Eycken, J.; Snatzke, G.; Vandewalle, M. *Tetrahedron: Asymmetry* **1991**, *2*, 789-792.

158. Suemune, H.; Takahashi, M.; Maeda, S.; Xie, Z.-F.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 425-428.

159. Baudin, G.; Glänzer, B. I.; Swaminathan, K. S.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 1367-1378.

160. (a) Andersch, P.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2135-2138. (b) Andersch, P. Ger. Offen. DE 4,243,867; *Chem. Abstr.* **1994**, *121*, 180121p.

161. Hönig, H.; Seufer-Wasserthal, P.; Stütz, A. E.; Zenz, E. *Tetrahedron Lett.* **1989**, *30*, 811-812.

162. Harris, K. J.; Gu, Q.-M.; Shih, Y.-E.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3941-3944.

163. Dumortier, L.; Liu, P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243-245.

164. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656-2665.

165. Bäckvall, J.-E.; Gatti, R.; Schink, H. E. *Synthesis* **1993**, 343-348.

166. Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653.

167. (a) Pingli, L.; Vandewalle, M. *Tetrahedron Lett.* **1993**, *34*, 3625-2628. (b) Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228-230. (c) Liu, P.; Vandewalle, M. *Tetrahedron* **1994**, *50*, 7061-7074.

168. (a) Johnson, C. R.; Plé, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388-390. (b) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006-1007. (c) Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1-2.

169. (a) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 177-178. (b) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**,

948-950. (c) Takano, S.; Moriya, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 614-615. (d) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 788-789. (e) Ogasawara, K. *Pure Appl. Chem.* **1994**, *66*, 2119-2122. (f) Moriya, M.; Kamikubo, T.; Ogesawara, K. *Synthesis* **1995**, 187-190.

170. (a) Pearson, A. J.; Bansal, H. S.; Lai, Y.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 519-520. (b) Pearson, A. J.; Lai, Y.-S. *J. Chem. Soc., Chem. Commun.* **1988**, 442-443. (c) Pearson, A. J.; Lai, Y.-S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem.* **1989**, *54*, 3882-3893. (d) Pearson, A. J.; Srinivasan, K. *J. Org. Chem.* **1992**, *57*, 3965-3973. (e) Pearson, A. J.; Chang, K. *J. Org. Chem.* **1993**, *58*, 1228-1237.

171. (a) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 736-738. (b) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597-2600. (c) Also see ref. 35. (d) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *58*, 7185-7194. (e) Scialdone, M. A.; Johnson, C. R. *Tetrahedron Lett.* **1995**, *36*, 43-46. (f) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615-623.

172. (a) Whitaker, D. T. *Chemoenzymatic Synthesis of (-)-Detoxinine from Cycloheptatriene*, Wayne State University, 1994. (b) Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414-9418. (c) Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910-2912.

173. For enzymatic asymmetrization studies in aqueous and organic media see: (a) Bis, S. J.; Whitaker, D. T.; Johnson, C. R. *Tetrahedron: Asymmetry* **1993**, *4*, 875-878. (b) For 5,6, and 7-membered ring systems see refs. 29 and 145a.

174. (a) Falk-Heppner, M.; Keller, M.; Prinzbach, H. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1253-1255. (b) Hoenke, C.; Klüwer, P.; Hugger, U.; Krieger, R.; Prinzbach, H. *Tetrahedron Lett.* **1993**, *34*, 4761-4764. (c) Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, *36*, 4185-4188.

175. Johnson, C. R.; Harikrishnan, L. S.; Golebiowski, A. *Tetrahedron Lett.* **1994**, *35*, 7735-7738.

176. Salaün, J. *Chem. Rev.* **1989**, *89*, 1247-1270.

177. Walser, P.; Renold, P.; N'Goka, V.; Hosseinzadeh, F.; Tamm, C. *Helv. Chim. Acta* **1991**, *74*, 1941-1952.

178. (a) Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Gorisch, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 67-68. (b) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073-2076.

179. Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659-4665.

180. Kasel, W.; Hultin, P. G.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1985**, 1563-1564.

181. Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E.; Schneider, M. P. *Tetrahedron Lett.* **1989**, *30*, 1793-1796.

182. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215-1230.

183. Sato, M.; Ohuchi, H.; Abe, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 313-328.

184. Jung, M. E.; Sledeski, A. W. *J. Chem. Soc., Chem. Commun.* **1993**, 589-591.

185. Harvey, J.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1993**, *4*, 807-812.

186. (a) Bridges, A. J.; Raman, P. S.; Ng, G. S. Y.; Jones, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 1461-1467. (b) Jones, J. B.; Hinks, R. S.; Hultin, P. G. *Can. J. Chem.* **1985**, *63*, 452-456. (c) Hultin, P. G.; Mueseler F.-J.; Jones, J. B. *J. Org. Chem.* **1991**, *56*, 5375-5380. (d) Also see refs. 34 and 86.

187. Björkling, F.; Boutelje, J.; Hjalmarsson, M.; Hult, K.; Norin, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1041-1042.

188. (a) Suemune, H.; Okana, K.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 1741-1747. (b) Tanaka, M.; Yoshioka, M.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 981-996. (c) Tanaka, M.; Yoshioka, M.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1454-1455. (d) Also see ref. 197.

189. Nagao, Y.; Kume, M.; Wakabayashi, R. C. *Chem. Lett.* **1989**, 239-242.

190. (a) Naemura, K.; Takahashi, N.; Chikamatsu, H. *Chem. Lett.* **1988**, 1717-1720. (b) Naemura, K.; Fukuda, R.; Takahashi, N.; Konishi, M.; Hirose, Y.; Tobe, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 911-918.

191. Renold, P.; Tamm, C. *Tetrahedron: Asymmetry* **1993**, *4*, 1047-1050.

192. (a) Hemmerle, H.; Gais, H.-J. *Tetrahedron Lett.* **1987**, *28*, 3471-3474. (b) Gais, H.-J.; Bülow, G.; Zatorski, A.; Jentsch, M.; Maidonis, P.; Hemmerle, H. *J. Org. Chem.* **1989**, *54*, 5115-5122.

193. Zemlicka, J.; Craine, L. E. *J. Org. Chem.* **1988**, *53*, 937-942.

194. Estermann, H.; Prasad, K.; Shapiro, M. J.; Repic, O.; Hardtmann, G. E.; Bolsterli, J. J.; Walkinshaw, M. D. *Tetrahedron Lett.* **1990**, *31*, 445-448.

195. Mekrami, M.; Sicsic, S. *Tetrahderon: Asymmetry* **1992**, *3*, 431-436.

196. Chênevert, R.; Lavoie, M.; Courchesne, G.; Martin, R. *Chem. Lett.* **1994**, 93-96.

197. Mohar, B.; Stimac, A.; Kobe, J. *Tetrahedron: Asymmetry* **1994**, *5*, 863-878.

198. (a) Kobayashi, S.; Kamiyama, K.; Iimori, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 2557-2560. (b) Kurihara, M.; Kamiyama, K.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1985**, *26*, 5831-5834. (c) Kamiyama, K.; Kobayashi, S.; Ohno, M. *Chem. Lett.* **1987**, 29-32. (d) Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 1057-1060. (e) Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 113-116. (f) Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577-1580. (g) Kobayashi, S.; Kamiyama, K.; Ohno, M. *J. Org. Chem.* **1990**, *55*, 1169-1117. (h) For more cyclohexane building blocks and related heterocyclic systems see refs. 178-181, 189, and 192.

199. (a) Kuhn, T.; Tamm, C.; Riesen , A.; Zehnder, M. *Tetrahedron Lett.* **1989**, *30*, 693-696. (b) Also see ref. 88.

200. Jones, J. B.; Hinks, R. S. *Can J. Chem.* **1987**, *65*, 704-707.

201. (a) Gais, H.-J.; Lukas, K. L. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 142-143. (b) Gais, H.-J.; Lied, T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 145-146. (c) Gais, H.-J.; Lied, T.; Lukas, K. L. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 511-512. (d) Gais, H.-J.; Lukas, K. L.; Ball, W. A.; Braun, S.; Lindner, H. J. *Liebigs Ann. Chem.* **1986**, 687-716. (e) Gais, H.-J.; Lindner, H. J.; Lied, T.; Lukas, K. L.; Ball, W. A.; Rosenstock, B.; Sliwa, H. *Liebigs Ann. Chem.* **1986**, 1179-1212.

202. (a) Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *27*, 4639-4642. (b) Riva, R.; Banfi, L.; Danieli, B.; Guanti, G.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1987**, 299-300.

203. For enzymatic preparation of enantiopure cyclohex-4-enedimethanol monoacetates see refs. 58, 178b, 181, 202, 206.

204. Chênevert, R.; Dickman, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1021-1024.

205. Hamilton, G. S.; Huang, Z.; Yang, X.-J.; Patch, R. J.; Narayanan, B. A.; Ferkany, J. W. *J. Org. Chem.* **1993**, *58*, 7263-7270.

206. (a) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *29*, 8837-8852. (b) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506-2513. (c) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron: Asymmetry* **1990**, *1*, 793-800.

207. For protease-catalyzed hydrolysis of 1,4-dihydropyridine dicarboxylates see: (a) Adachi, T.; Ishii, M.; Ohta, Y.; Ota, T.; Ogawa, T.; Hanada, K. *Tetrahedron: Asymmetry* **1993**, *4*, 2061-2068. (b) Hirose, Y.; Kariya, K.; Sasakik, I.; Kurono, Y.; Achiwa, K. *Tetrahedron Lett.* **1993**, *34*, 3441-3444. For lipase-catalyzed hydrolysis of 1,4-dihydropyridine dicarboxylates see: (c) Holdgrün, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3465-3468. (d) Ebiike, H.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1991**, *32*, 5805-5808. (e) Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, *33*, 7157-7160. (f) Hirose, Y.; Kariya, K.; Nakanishi, Y.; Kurono, Y.; Achiwa, K. *Tetrahedron Lett.* **1995**, *36*, 1063-1066. (g) Hirose, Y.; Sasaki, S.; Achinami, K. Jpn. Kokai Tokkyo Koho JP 06,107,636 [94,107,636]; *Chem. Abstr.* **1994**, *121*, 108531e.

208. Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1332-1335.

209. (a) Ito, Y.; Shibata, T.; Arita, M.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 6739-6741. (b) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049-4055. (c) Ohno, M.; Ito, Y.; Arita, M.; Shibata, T.; Adachi, K.; Sawai, H. *Tetrahedron* **1984**, *40*, 145-152. (d) Niwayama, S.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 6313-6316. (e) Niwayama, S.; Noguchi, H.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1993**, *4*, 665-668. (f) Niwayama, S.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1994**, *116*, 3290-3295.

210. (a) Jones, J. B.; Francis, C. J. *Can. J. Chem.* **1984**, *62*, 2579-2584. (b) Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521-2526.

211. (a) Patel, R. N.; Liu, M.; Banerjee, A.; Thottathil, J. K.; Kloss, J.; Szarka, L. J. *Enzyme Microb. Technol.* **1992**, *14*, 778-784. (b) Patel, R. N.; Liu, M.; Banerjee, A.; Szarka, L. *Indian J. Chem.* **1992**, *31B*, 832-836.

212. Murata, M.; Ikoma, S.; Achiwa, K. *Chem. Pharm. Bull.* **1990**, *38*, 2329-2331.

213. (a) Andreu, C.; Marco, J. A.; Asensio, G. *J. Chem. Soc. Perkin Trans. 1* **1990**, 3209-3210. (b) Asensio, G.; Andreu, C.; Marco, J. A. *Chem. Ber.* **1992**, *125*, 2233-2238.

214. Bloch, R.; Guibe-Jampel, E.; Girard, C. *Tetrahedron Lett.* **1985**, *26*, 4087-4090.

215. Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792-793.

216. (a) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164-1171. (b) Ihara, M.; Suzuki, M.; Hirabayashi, A.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2053-2058.

217. (a) Dodds, D. R.; Jones, J. B.; *J. Chem. Soc., Chem. Commun.* **1982**, 1080-1081. (b) Dodds, D. R.; Jones, J. B.; *J. Am. Chem. Soc.* **1988**, *110*, 577-583.

218. Nakazaki, M.; Chikamatsu, H.; Taniguchi, M. *Chem. Lett.* **1982**, 1761-1764.

219. (a) Kitahara, T.; Miyake, M.; Kido, M.; Mori, K. *Tetrahedron: Asymmetry* **1990**, *1*, 775-782. (b) Watanabe, H.; Mori, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2919-2934. (c) Mori, K.; Nagano, E. *Biocatalysis* **1990**, *3*, 25. (d) Inoue, T.; Hosomi, K.; Araki, M.; Nishide, K.; Node, M *Tetrahedron: Asymmetry* **1995**, *6*, 31-34.

220. Toyooka, N.; Nishino, A.; Momose, T. *Tetrahedron Lett.* **1993**, *34*, 4539-4540.

221. Naemura, K.; Fujii, T.; Chikamatsu, H. *Chem. Lett.* **1986**, 923-926.

222. Yamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1988**, *29*, 5769-5770.

223. (a) Nicolosi, G.; Morrone, R.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1992**, *3*, 753-758. (b) Lambusta, D.; Nicolosi, G.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1993**, *4*, 919-924.

224. Howell, J. A. S.; Palin, M. G.; Jaouen, G.; Top, S.; El Hafa, H.; Cense, J. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1241-1252.

225. (a) Uemura, M.; Nishimura, H.; Yamada, S.; Nakamura, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 6581-6582. (b) Uemura, M.; Nishimura, H.; Yamada, S.; Hayashi, Y.; Nakamura, K.; Ishihara, K.; Ohno, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1673-1682.

226. (a) Hughes, D. L.; Bergan, J. J.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 1787-1788. (b) Hughes, D. L.; Bergan, J. J.; Amato, J. S.; Bhupathy, M.; Leazer, J. L.; McNamara, J. M.; Sidler, D. R.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1990**, *55*, 6252-6259. (c) Hughes, D. L.; Song, Z.; Smith, G. B.; Bergan, J. J.; Dezeny, G. C.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1993**, *4*, 865-874.

(*Received* 4 *August* 1995)