

Lipase-Supported Synthesis of Biologically Active Compounds

Fritz Theil

Institut für Angewandte Chemie Berlin-Adlershof e.V., Rudower Chaussee 5, D-12484 Berlin, Germany

Received January 27, 1995 (Revised Manuscript Received April 26, 1995)

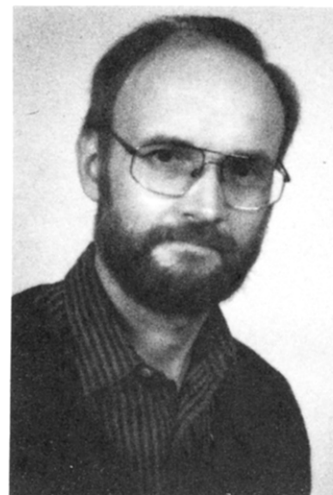
Contents

I. Introduction	2203
II. Prostanoids	2204
A. <i>cis</i> -Cyclopent-2-ene-1,4-diol Derivatives	2204
B. Kinetic Resolution of Bicyclo[3.2.0]heptanones	2205
C. Asymmetrization or Resolution of Further Cyclopentane Building Blocks	2205
D. Resolution of Bicyclo[3.3.0]octanone Derivatives	2206
E. Resolution of Further Intermediates	2207
III. Nucleosides	2207
A. Asymmetrization of Prochiral Cyclopentane Precursors	2207
B. Asymmetrization of Aliphatic Building Blocks	2208
C. Kinetic Resolution of Cyclopentane Derivatives	2209
D. Kinetic Resolution of Cyclobutane Intermediates	2209
E. Resolution of Bicyclic Precursors	2210
IV. Alkaloids	2210
V. Terpenoids	2211
VI. Monosaccharides and Cyclitols	2212
VII. Antibiotics	2213
VIII. β -Adrenergic Agents	2214
IX. Pesticides	2216
A. Pheromones	2216
1. Asymmetrization of <i>meso</i> -Intermediates	2216
2. Resolution of Racemic Building Blocks	2216
3. Lipase-Supported Lactonization	2217
4. Resolution of Racemic Pheromones	2217
5. Further Applications	2218
B. Miscellaneous Pesticides	2218
X. Miscellaneous Compounds	2219
A. Natural Products and Their Synthetic Analogs	2219
B. Synthetic Biologically Active Compounds	2222
XI. Summary and Outlook	2222
XII. Note Added in Proof	2224
XIII. References	2224

I. Introduction

The synthesis of organic compounds with one or several chirality centers is one of the most challenging tasks in modern organic synthesis. Among the possibilities to achieve asymmetric induction or to carry out kinetic resolution, biocatalytical processes have been established as unrenounceable methods in contemporary organic synthesis.

The number of publications utilizing enzymatic or whole cell biotransformations was explosively growing up in the last decade. This exciting field was



Fritz Theil was born in 1951. He studied chemistry at the University of Leipzig and received his diploma degree in 1974. Then he moved to the former "Zentralinstitut für Molekularbiologie der Akademie der Wissenschaften der DDR" in Berlin-Buch and received his Dr. rer. nat. in 1979. From 1979 to 1991 he was scientific co-worker at the "Zentralinstitut für Organische Chemie" at the same Academy in Berlin-Adlershof and from 1992 to 1993 at the "Zentrum für Selektive Organische Synthese", Berlin-Adlershof. Since 1994 he is scientific co-worker at the "Institut für Angewandte Chemie Berlin-Adlershof." Fritz Theil has been recipient of the "Förderpreis der Deutschen Akademie der Naturforscher - Leopoldina" in 1992. His current research interest is focused on the use of biocatalytic transformations for the synthesis of enantiomerically pure building blocks and biologically active compounds.

covered in reviews and monographs.^{1–6} The use of biocatalysts in the protecting group techniques was reviewed very recently and is therefore excluded in this review.^{7,8}

Among the biocatalysts used in organic synthesis, lipases (triacylglycerol acyl hydrolases, EC 3.1.1.3) are the most frequently used biocatalysts. Lipases are able to discriminate between enantiotopic groups and between the enantiomers of a racemate. This type of enzyme is very easy to handle and stable at higher temperatures (up to 100 °C) and toward organic solvents. Most of the lipases used are able to accept a broad range of substrates due to their ability to change their conformation depending on the substrate structure (induced fit enzyme). This type of biocatalysts can be used to perform enantioselective hydrolytic reactions and the formation of ester and amide bonds.^{9–13} These reviews and monographs usually do not focus their interest on the target molecule but on the substrate structure.

The aim of this review is to cover the literature from 1984 until October/November 1994 in which lipase-catalyzed reactions have been utilized in the synthesis of selected types of biologically active compounds.

Some lipases used are known under different names in the literature. This can be confusing if one compares different papers. Especially, in two cases of microbial lipases the organisms producing these enzymes have been reidentified and the lipases are recalled now. The former lipase P from *Pseudomonas fluorescens* supplied by Amano was reidentified as lipase from *Pseudomonas cepacia* and is called now lipase PS. Lipase from *Candida cylindracea* (CCL) was reidentified as lipase from *Candida rugosa*. At present the old and new names are used simultaneously. In other cases the trade name of the lipase depends on the supplier. In order to avoid further confusion, in this review the names of the lipases are the same as those which were utilized by the authors in their original papers.

II. Prostanoids

Prostaglandins, prostacyclins, thromboxanes, and their synthetic analogs play an important role as bioregulators in human and animal organisms. These natural compounds and particularly their metabolically more stable synthetic analogs have great importance as pharmaceuticals.¹⁴⁻¹⁶ The two main strategies of prostaglandin synthesis are shown in Figure 1. Starting from cyclopentadiene (1) via the

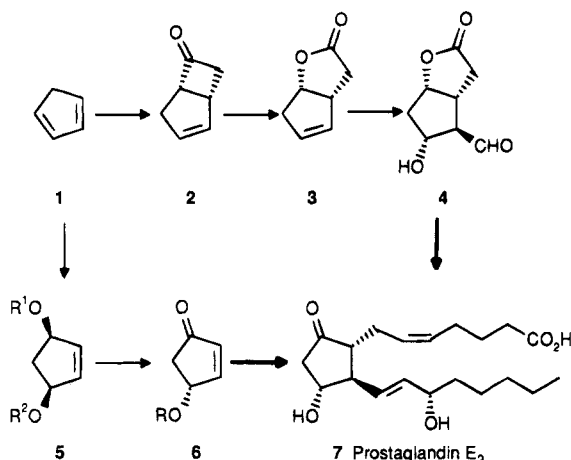


Figure 1.

bicyclo[3.2.0]heptenone (2), the lactone 3, and the Corey aldehyde 4 can be obtained. Starting from the key aldehyde 4 both side chains can be successively introduced building up the complete molecule. The second approach utilizing the cyclopentenone 6, prepared via the diol derivative 5 as a key intermediate, represents the most convergent route and is characterized by the successive one-pot introduction of both side chains (three-component coupling).

Due to their biological activities many efforts have been made to synthesize prostanoids in an enantiomerically pure state using biocatalysts including lipases as chiral catalysts. Attempts to introduce chirality into a suitable building block have been made on different stages of synthetic schemes used. It is the goal of any asymmetric synthesis to introduce chirality in as an early stage of a synthetic scheme as possible for example either by asymmetric resolution of a prochiral intermediate or by kinetic

resolution of a racemic building block. Lipases of different origin have been successfully applied on the synthesis of enantiomerically pure building blocks for prostaglandins and related compounds as demonstrated by numerous examples.

A. *cis*-Cyclopent-2-ene-1,4-diol Derivatives

The *meso*-configured cyclopentenediol derivatives 8 and 10 (Figure 2) have been the subject of many

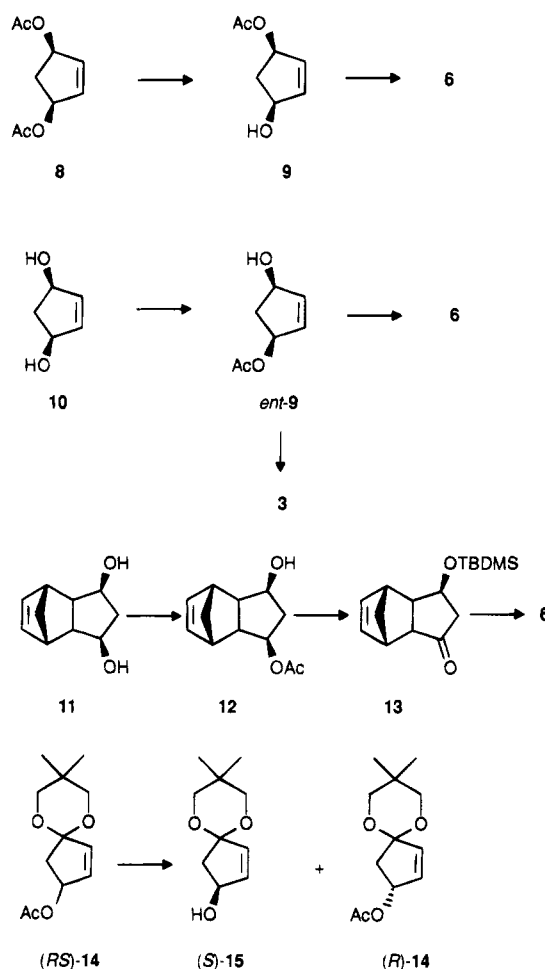


Figure 2.

efforts to asymmetrically synthesize these compounds by lipase-catalyzed hydrolysis of the diacetate 8 and other diesters¹⁷⁻²⁰ or enantioselective esterification of the diol 10¹⁹⁻²⁷ to afford the chiral monoacetates 9 and *ent*-9, respectively. Both of these enantiomeric monoacetates can be used in different approaches in the synthesis of prostaglandins and can be transformed into one common chiral intermediate, such as 6, by functional group interconversion. The first approach utilizes an orthoester-Claisen reaction of *ent*-9 affording the lactone 3 which can be converted into the Corey aldehyde 4, a key intermediate for the prostaglandin synthesis. The second very elegant approach is based on the conversion of the monoacetates *ent*-9 or 9 into the protected hydroxy cyclopentenone 6, an intermediate for the synthesis of prostaglandins, by the one-pot three-component coupling procedure introducing both side chains simultaneously,²⁸ as was very recently demonstrated by

Johnson.²⁷ Theoretically, both compounds **8** and **10** can be converted up to 100% into one enantiomerically pure monoacyl derivative. The lipases are operating enantioselectively, which means hydrolysis or esterification occurs at the same (*S*)-configured stereocenter. Hydrolysis leads to the formation of the monoacyl derivative **9** and the lipase-catalyzed transesterification leads to the corresponding enantiomer *ent*-**9**. In lipase-catalyzed hydrolysis the best results have been achieved by converting the corresponding diacetate into **9** in a chemical yield of 90% with 97% ee by using lipase from *Mucor miehei*¹⁸ or with the B lipase from *Candida antarctica* (SP 435) in a chemical yield of 90% with >99% ee.²⁰ The corresponding enantiomeric monoacetate *ent*-**9** has been obtained in most suitable cases in yields between 50–65% with >99% ee using pancreatin and vinyl acetate or trichloroethyl acetate in THF/NEt₃ mixtures^{21,22} or using lipase SP 435 and isopropenyl acetate in *tert*-butyl methyl ether.²⁰ The byproduct in these reactions is the diacetate **8** which can be recycled after saponification.

Compounds **9** or *ent*-**9** can be interconverted into the corresponding enantiomeric alcohol by simple functional group interconversion representing a further advantage of this type of compounds. The main disadvantage of the application of *cis*-cyclopentene-1,4-diol derivatives in large-scale synthesis is their insufficient way of preparation.²⁹ This is a problem that needs a solution because this versatile building block has been also used for the synthesis of further biologically active compounds as demonstrated in following sections.

In an additional attempt a 1:1 mixture of **8** with its *trans* diastereoisomer was subjected to a porcine pancreas lipase (PPL)-catalyzed hydrolysis or alcoholysis to give **9**.³⁰

Chiral cyclopentenone derivatives, such as **6**, can also be prepared by starting from the tricyclic *meso*-diol **11** which was asymmetricized with vinyl acetate in the presence of lipase from *Candida cylindracea* (CCL) in five steps including a pyrolytic transformation³¹ via the monoacetate **12** and the ketone **13** (Figure 2). Kinetic resolution of the cyclopentenol acetate (*RS*)-**14** with lipase P to give the (*S*)-alcohol (*S*)-**15** and the (*R*)-acetate (*R*)-**14a** offers a further access to enantiomerically pure cyclopentenone derivatives.³²

B. Kinetic Resolution of Bicyclo[3.2.0]heptanones

The bicyclo[3.2.0]heptane derivatives **16**–**22** (Figure 3) are intermediates in the synthesis of prostaglandins via the Corey aldehyde **4**. Therefore, intensive investigations have been made to resolve these compounds using lipases as biocatalysts. The synthetic strategy includes diastereoselective reduction of a racemic cyclobutanone followed by kinetic resolution of cyclobutanols, such as **16**–**22**, and finally reoxidation to furnish an optically active cyclobutanone derivative. The *endo*-acetate **16** was a much better substrate in hydrolyses in the presence of PPL, CCL, or lipase from *Mucor miehei* than the corresponding *exo*-acetate **17**.³³ Hydrolysis of **16** on treatment with these lipases furnished the corresponding

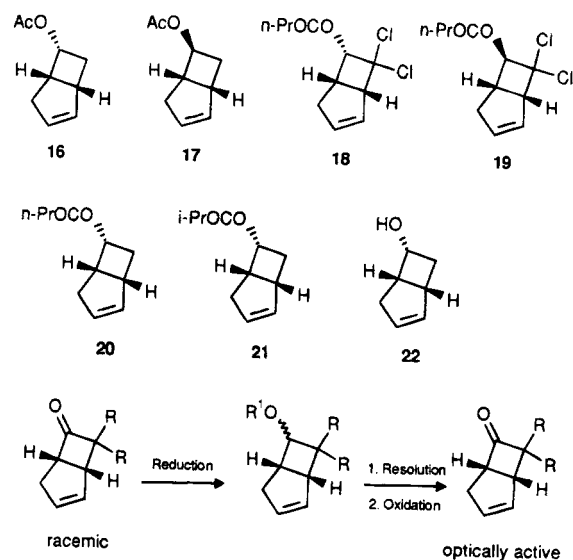


Figure 3.

alcohol in 23–29% yield with >94% ee. In contrast, reaction of **17** under identical conditions yielded the corresponding alcohol in only 7–12% yield with low ee. The derivatives **16** and **18**–**21** showed distinct behavior toward lipases of different origin.³⁴ The substrates of choice for a highly efficient resolution are the *endo* derivatives **20** and **16** using the lipases AK, SAM-II, or P. The *exo* derivative **19** could be resolved with lipase P in a sufficient manner as well. Esterification and interesterification of **22** and **16**, respectively, with various carboxylic acids showed that the most efficient processes are the interesterifications of **16** with cyclohexanecarboxylic acid or benzoic acid catalyzed by the commercial immobilized enzyme preparation Lipozyme (commercial preparation of lipase from *Mucor miehei* on a polymeric resin).³⁵ Interesterification of **16** with cyclohexanecarboxylic acid in hexane furnished the corresponding ester in 48% yield with 94% ee.

C. Asymmetricization or Resolution of Further Cyclopentane Building Blocks

Figure 4 demonstrates further examples of prostaglandin building blocks which have been converted into optically active derivatives using lipases. The asymmetricization of the *meso*-diester **23** was carried out using an asymmetric hydrolysis catalyzed by lipase from *Rhizopus delemar* affording the corresponding enantiomerically pure (*S*)-hydroxymethyl compound in 69% yield which was converted into 11-deoxyprostaglandin precursors **24**.³⁶ The racemic diacetate **25** was subjected to a lipase-catalyzed reaction to achieve both regio- and enantioselective hydrolysis simultaneously. The selectivity for both desired reactions using PPL was only moderate but the product could be converted into the known intermediate **26** leading to prostaglandin A₂.³⁷ The cyclopentenol derivatives **27** and **28** are precursors for the Corey lactone **3**. The derivatives **27** and **28** could be resolved by a lipase-catalyzed hydrolysis with lipase P or PS to give both enantiomers with

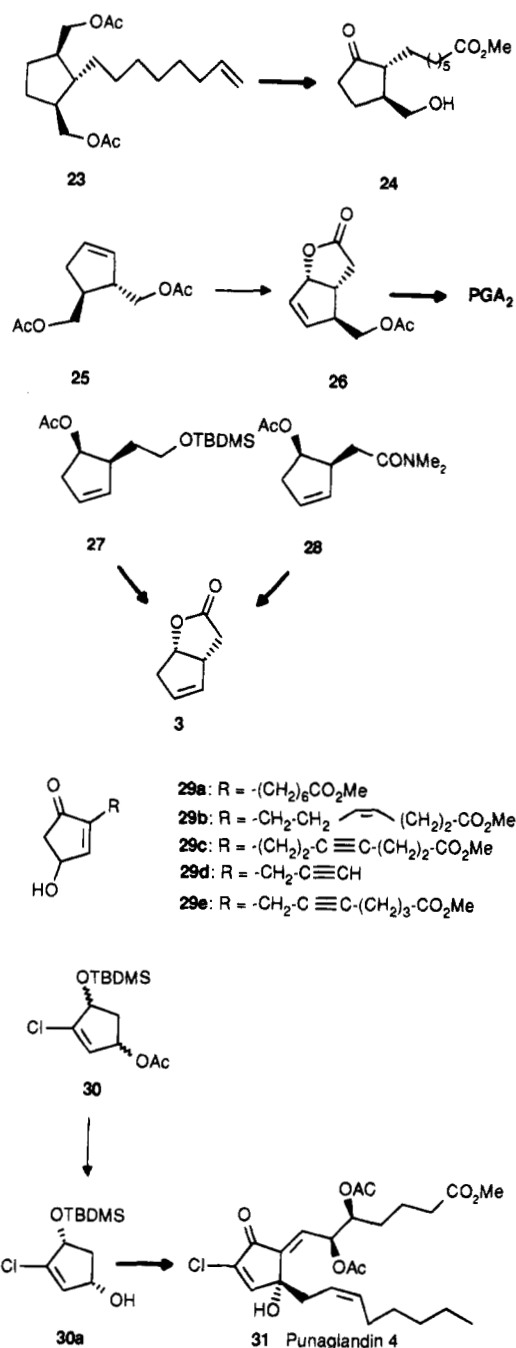


Figure 4.

high ee, whereas in the latter case the enantiomeric purity of the products was slightly diminished.³⁸ The racemic cyclopentenone derivatives **29a–e** bearing more or less complete upper prostaglandin side chains were suitable substrates for highly enantioselective PPL-catalyzed resolutions in the presence of vinyl acetate.²⁶ For example, in the case of **29b** the corresponding acetate was obtained in 43% yield with 92% ee. The remaining alcohol could be isolated in 35% yield with >99% ee. The racemic *cis/trans* mixture of the chloro derivative **30**, a building block for the marine prostanoid punaglandin **4** (**31**) with antitumor activity, has been resolved by hydrolysis with PPL yielding the enantiomerically pure *cis*-silyloxy alcohol **30a** which was converted in several steps into the desired biomolecule **31**.³⁹

D. Resolution of Bicyclo[3.3.0]octanone Derivatives

To this type of compounds belong the intermediates **32–36** (Figure 5) precursors of the Corey aldehyde or its carbocyclic analogs leading to metabolically stable carbacyclins, such as Iloprost (**37**).

The kinetic resolution of 1,3-diols without using additional protecting groups by a lipase-catalyzed transesterification includes two kinds of selectivity problems, regio- and enantioselectivity. In the case of the racemic diol **32** lipase PS⁴⁰ or lipase AK⁴¹ have been used as catalysts. The transesterification with vinyl acetate showed almost complete regioselectivity and very high enantioselectivity leading to the unchanged diol (+)-**32** and the primary monoacetate

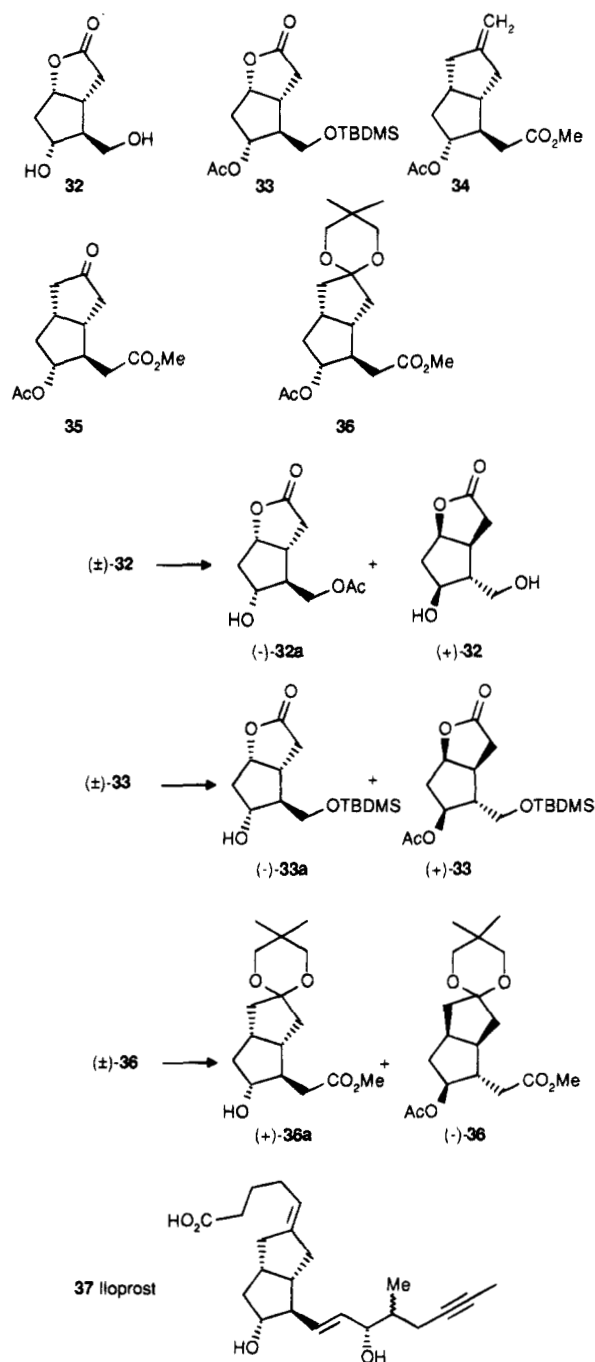


Figure 5.

(-)-**32a**, whereas the latter can be transformed into prostaglandins with natural configuration. This high selectivity in both cases is caused by the bicyclic structure of **32** as demonstrated by comparison with related 1,3-diols.⁴² The protected derivative **33** bearing two different protecting groups could be separated into its enantiomers using lipase PS by hydrolysis with very high enantioselectivity affording (+)-**33** and (-)-**33a**.⁴¹ The carbacyclin derivatives **34**⁴³ and **35**⁴⁴ have been subjected to enantioselective hydrolysis that affects its acetate group by using lipase from *Pseudomonas fluorescens* (lipase P). The Schering group reported on a highly efficient resolution of the Iloprost (**37**) intermediate **36** with lipase PL from *Alcaligenes* yielding 44% of (+)-**36a** in an enantiomerically pure form.⁴⁵ In the cases of the intermediates **34**–**36** the carboxylic methyl ester functions are not affected under the reaction conditions proving, in addition, the high chemoselectivity of the lipases used.

E. Resolution of Further Intermediates

Figure 6 depicts more examples of prostaglandin building blocks which have been asymmetrized or separated into their enantiomers. The prochiral *meso*-diol **38** could be efficiently asymmetrized by a transesterification using lipase from *Geotrichum candidum*. The corresponding chiral monoacetate,

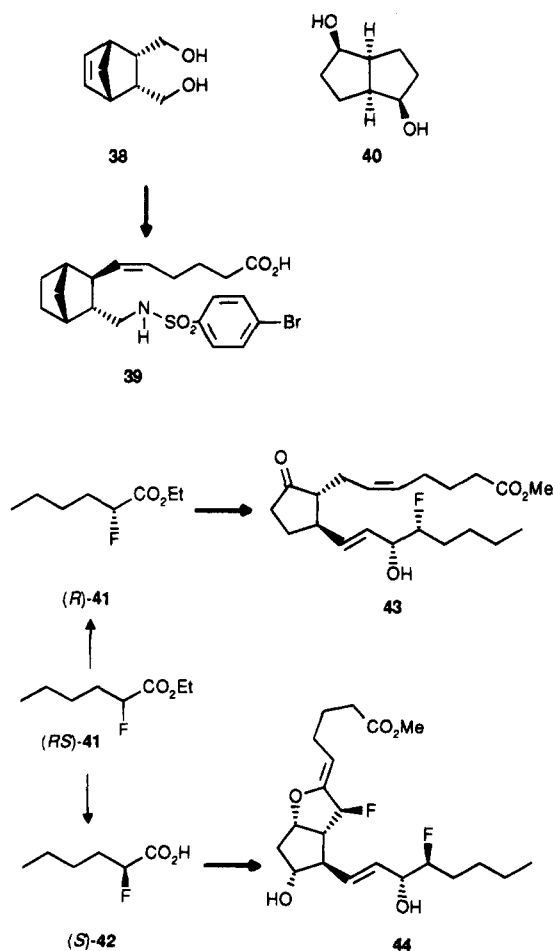


Figure 6.

obtained in 72% yield with 95% ee, was the basis for the synthesis of the thromboxane A₂ analog **39** exhibiting antagonistic activities compared with its natural counterpart.⁴⁶

Pancreatin-catalyzed transesterification of the racemic C₂-symmetric diol **40** afforded one of the enantiomeric diacetates in 32% yield almost enantiomerically pure. The remaining diol exhibited a lower ee. But repeated exposure of the enantiomerically enriched diol to the transesterification conditions yielded the unchanged diol with an enantiomeric purity of 90% which could be enhanced by recrystallization. Both enantiomers of **40** could be transformed by enantioconvergent routes into enantiomerically pure prostaglandins of natural configuration.⁴⁷ The enantiomerically pure 2-fluorohexanoates (*R*)-**41** and (*S*)-**42** are valuable building blocks in the synthesis of lower and upper side chain-modified prostaglandin analogs and have been resolved hydrolytically in the presence of lipase P-30. Racemic (*RS*)-**41** yielded after 60% conversion enantiomerically pure (*2R*)-ethyl 2-fluorohexanoate [(*R*)-**41**]. The corresponding acid (*S*)-**42** in enantiomerically enriched form (68% ee) furnished after reesterification and a second lipase-catalyzed hydrolysis with the same lipase the (*S*)-acid in finally enantiomerically pure form. Both of the enantiomers (*R*)-**41** and (*S*)-**42** are useful for the synthesis of the 16-fluoroprostaglandin **43** and the prostacyclin analog **44**, respectively.⁴⁸

III. Nucleosides

Due to their biological activity, *e.g.* antitumor and antiviral properties including their activity against the human immunodeficiency virus (HIV), there is an increasing interest in the synthesis of nucleoside analogs. Very recently, particular carbocyclic nucleosides with their antiviral activity associated with their higher metabolic stability and lower toxicity, when compared with the natural sugar containing parent compounds, have been found, and attention is now focused on the synthesis of enantiomerically pure derivatives.^{49,50}

Chemoenzymatic approaches including the use of lipases are among the favored methods to prepare enantiomerically pure nucleoside analogs starting from various types of prochiral or racemic building blocks.

A. Asymmetrization of Prochiral Cyclopentane Precursors

Figure 7 illustrates the types of prochiral cyclopentane starting materials used for the synthesis of enantiomerically pure nucleoside analogs. Roberts and his group hydrolyzed the trisubstituted *meso*-diacetate **45** with PPL into the monoacetate **45a** in a yield of 92% with >95% ee. The enantiomerically pure monoacetate **45a** has been used to synthesize various carbocyclic nucleoside analogs, *e.g.* the adenine derivative **46**,⁵¹ precursors for both enantiomers of aristeromycin (**47**),⁵² and neplanocin-A

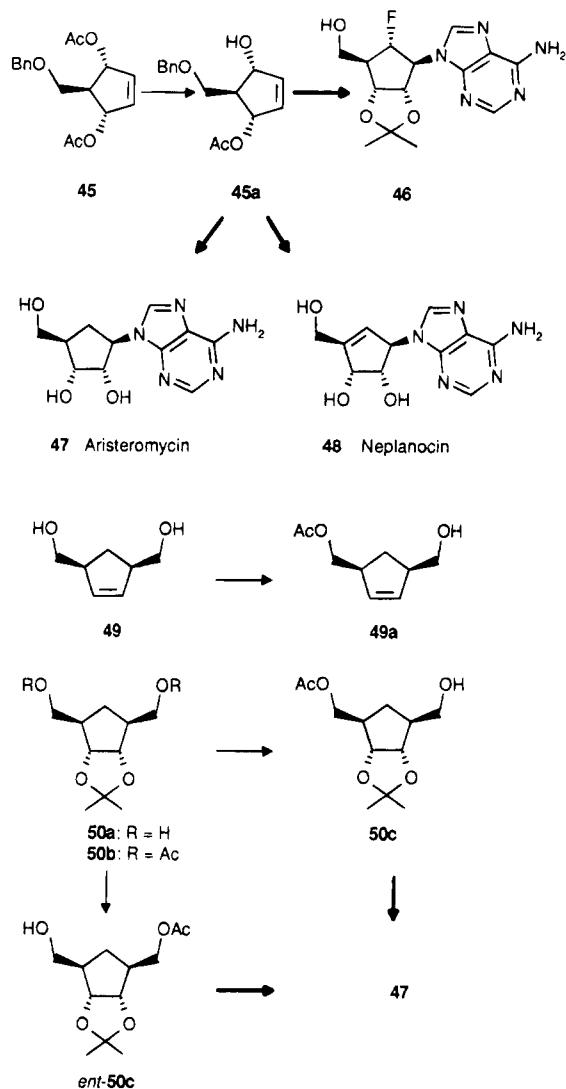


Figure 7.

(48).⁵³ The *cis*-diol **49** was asymmetrically converted by a lipase-catalyzed transesterification furnishing the corresponding chiral monoacetate **49a** with vinyl acetate in toluene in the presence of CCL in a yield of 68% with 97% ee. It is worth mentioning that other lipases were tested, and lipase-mediated hydrolysis of the corresponding diacetate showed a much lower enantioselectivity.⁵⁴ The latter results could be confirmed by other authors.⁵⁵ The prochiral diol **50a** was asymmetrically converted to furnish the monoacetate **50c** by a lipase-catalyzed transesterification in the presence of lipase P in a yield of 81% with >99% ee. On the other hand, hydrolysis of the corresponding diacetate **50b** with the same lipase yielded the enantiomeric monoacetate *ent*-**50c** in a yield of 69% with >99% ee. Furthermore, both have been transformed in an enantioconvergent way into (–)-aristeromycin (**47**).^{55,56} Additional attempts have been made to optimize the reaction conditions for the transesterification of **50a** as well as the hydrolysis of the corresponding diesters, such as **50b**, with the result that both enantiomeric monoesters are available now in almost quantitative chemical yield and in enantiomerically pure form.⁵⁷

The enantiomeric monoacetates **9** and *ent*-**9** (Figure 8) already used for the synthesis of prostaglandins have been utilized in the synthesis of enantiomerically

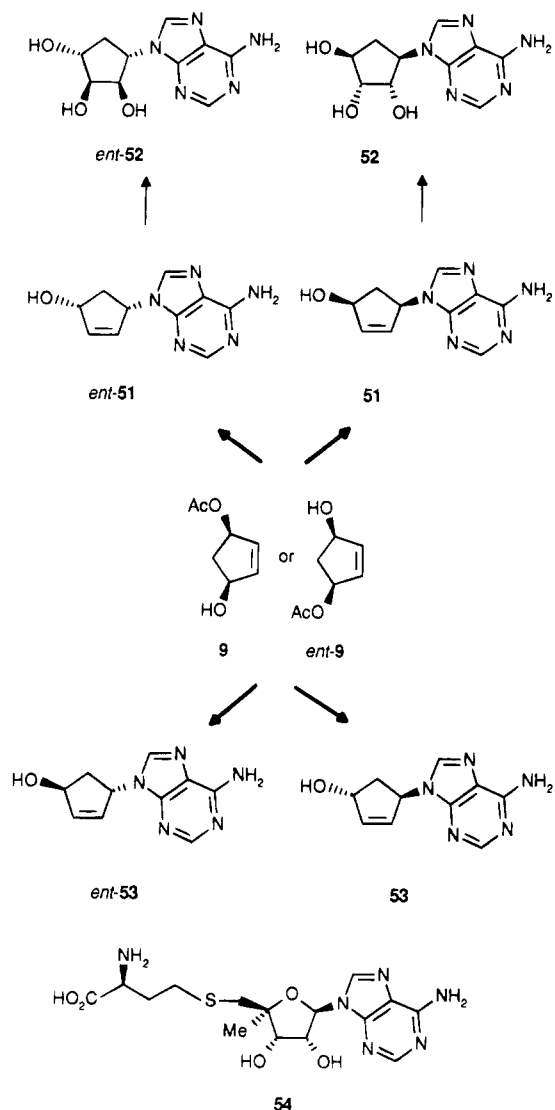


Figure 8.

ally pure 5'-nornucleoside analogs. Both enantiomers **51** and *ent*-**51** and the corresponding dihydroxy derivatives **52** and *ent*-**52**, respectively, have been prepared from the monoacetate **9**.^{58,59} A similar enantiodivergent approach was developed by switching functional groups and the type of nucleophilic substitution leading to the four possible isomeric 2',3'-dideoxy-2',3'-dideoxy-5'-noradenosins **51**, *ent*-**51**, **53**, and *ent*-**53** starting from the common enantiomer *ent*-**9**.^{60,61} A synthesis of neplanocin A (**48**) starting from **9** was reported as well.⁶² Furthermore, beginning with **9** the 4'-substituted adenosine derivative **54** was prepared.⁶³

B. Asymmetrization of Aliphatic Building Blocks

The prochiral 1,3-diol **55** (Figure 9) has been transformed by a lipase-catalyzed transesterification with lipase P enantioselectively into the (*R*)-monoacetate **55a** in a yield of 95% with 98% ee. Nucleoside analogs derived from 2,3-dideoxyribose *e.g.* **56** have been prepared.^{64,65} Enantioselective hydrolysis of the similar building block **57** with CCL yielded the (*S*)-monoacetate **57a** almost enantiomerically pure in

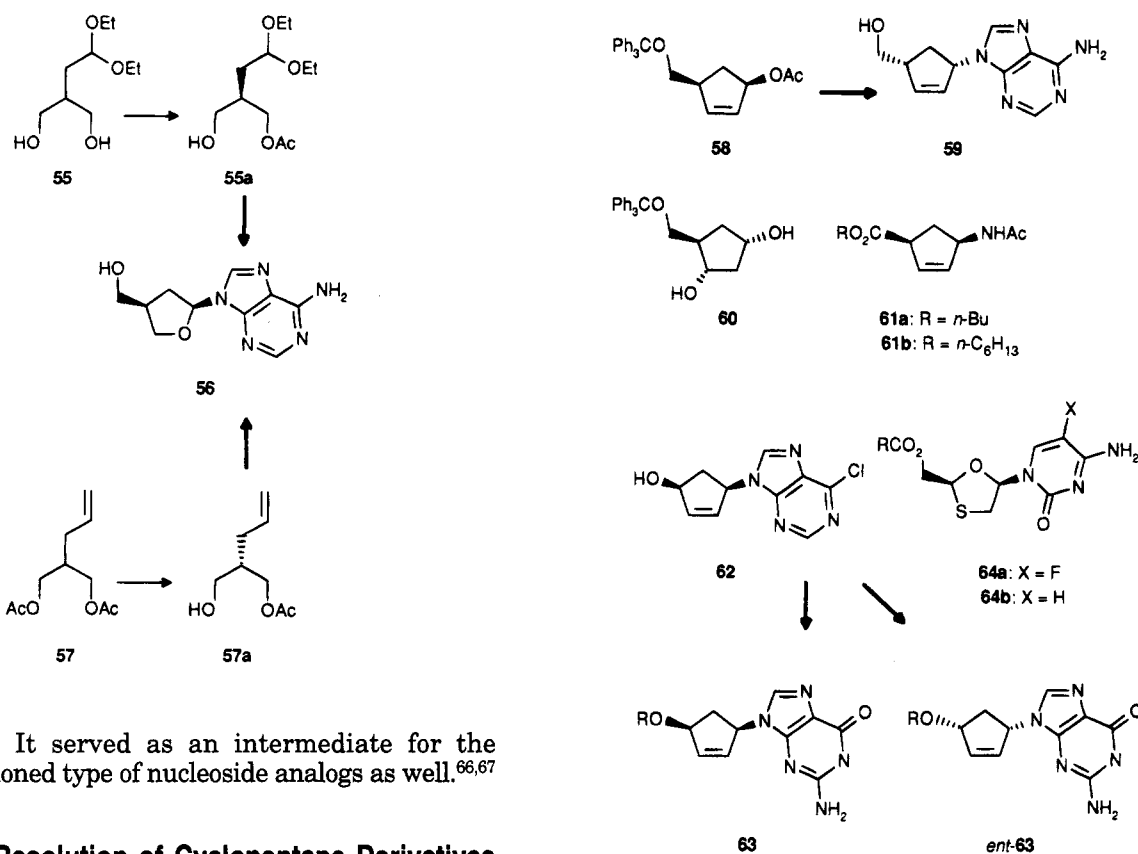


Figure 9.

50% yield. It served as an intermediate for the above-mentioned type of nucleoside analogs as well.^{66,67}

C. Kinetic Resolution of Cyclopentane Derivatives

Hydrolysis of the racemic *cis* compound **58** (Figure 10) in the presence of lipase P gave both enantiomers with >95% ee. The corresponding enantiomers have been converted into various nucleoside analogs including (+)-carbovir (**59**).^{68,69} The intermediate **58** represents a very attractive starting material. But its preparation by Prins reaction of cyclopentadiene with formaldehyde seems to be difficult due to the expenditure of its separation from the other diastereo- and regioisomers formed.^{70,71} The cyclopentanediol **60** was separated into its antipodes by transesterification with vinyl acetate in the presence of lipase P with high efficiency to give the two possible regioisomeric monoacetates which are enantiomeric to each other in almost enantiomerically pure form. Each enantiomer is acylated but with a completely different regioselectivity. The enantioselectivity of this reaction strongly depends on the protecting group at the primary hydroxy group, indicating that the trityl residue is superior to other substituents.⁷² The butyl and hexyl ester of the cyclopentyl amines **61a,b** have been resolved by hydrolysis with CCL to furnish both enantiomers almost enantiomerically pure.⁷³ Finally, kinetic resolution of complete nucleoside analogs has been demonstrated. Lipase P-supported resolution of the racemic *cis* analog **62** could be successfully carried out^{74,75} followed by conversion of both enantiomers into the corresponding guanosine derivatives **63** and *ent*-**63**. Surprisingly, the diphosphorylphosphonate of the "unnatural" enantiomer *ent*-**63** showed a higher activity against HIV reverse transcriptase than its enantiomer which corresponds to the D-sugar series.⁷⁵ The racemic nucleoside analogs **64a,b** were separated into their antipodes by enantioselective

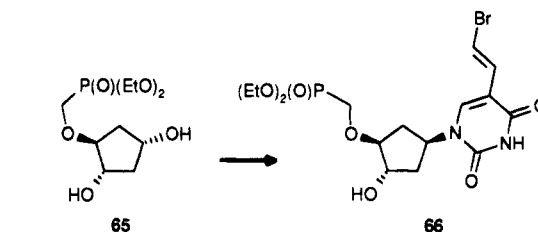


Figure 10.

hydrolysis in the presence of lipase PS-800.⁷⁶ Enantioselective transesterification of the dihydroxycyclopentane phosphonate **65** with vinyl acetate in the presence of lipase PS furnished two regioisomeric monoacetates with high ee. Using the corresponding pure enantiomer, nonracemic 5-bromovinyl-2'-deoxyuridine derivative **66** could be synthesized.⁷⁷

D. Kinetic Resolution of Cyclobutane Intermediates

The naturally occurring oxetanocin A (**67**, Figure 11) possessing antiviral properties initiated the synthesis of cyclobutane carbocyclic nucleoside analogs. As an intermediate in the synthesis of the carbocyclic analog **69** in enantiomerically pure form, the trisubstituted cyclobutane **68** was used as a substrate in a kinetic resolution by hydrolysis with lipase PS. Both enantiomers have been obtained in enantiomerically pure form.⁷⁸ The racemic cyclobutanediol **70** was subjected to a lipase P-catalyzed transesterification to give a complex reaction mixture consisting of the unchanged diol, two regioisomeric monoacetates, and a trace of the corresponding diacetate with moderate ee of all the products. Despite these problems,

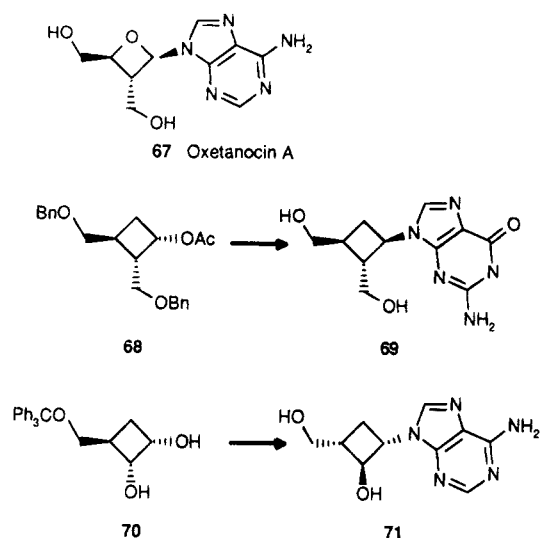


Figure 11.

enantiomerically enriched (60% ee) diol was subjected to a second resolution to furnish the diol with 93% ee which finally was converted into the nucleoside analog **71**.⁷⁹

E. Resolution of Bicyclic Precursors

The bicyclic compounds **72**, *ent*-**74**, and **76** (Figure 12) are versatile intermediates in the synthesis of

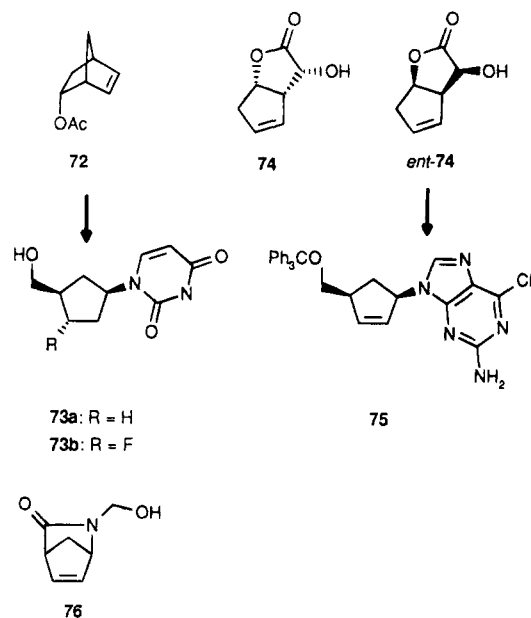


Figure 12.

nucleoside analogs. The *endo*-borneol acetate (**72**) was separated into its enantiomers by hydrolysis in the presence of CCL or lipase from *Pseudomonas* sp. furnishing both antipodes with >90% ee.^{80,81} Starting from these intermediates for instance the carbocyclic thymidine analogs **73a** and **73b** in enantiomerically pure form have been prepared.^{82,83} The racemic bicyclic hydroxylactone **74**, which is structurally related to prostaglandin intermediates, has

been resolved by transesterification or hydrolysis of its acetate or butanoate catalyzed by lipase P. One of its enantiomers, *ent*-**74**, was transformed into **75**, a known intermediate of the anti-HIV agent carbovir.^{84,85} The hydroxy lactone **74** represents a very potent intermediate for the synthesis of further bioactive compounds as very recently demonstrated by Roberts *et al.*⁸⁵ (compare sections VII and X.A). The kinetic resolution of the bicyclic lactam **76** by transesterification with vinyl acetate in the presence of the lipases PS or AK afforded a known building block for nucleoside analogs with ~90% ee.⁸⁶

IV. Alkaloids

Alkaloids are, due to their physiological properties, of interest in organic synthesis. Figure 13 shows building blocks which have been brought into enantiomerically pure state using lipase-catalyzed asymmetric resolutions or kinetic resolutions. The *meso*-diol **77a** was converted into an enantiomerically pure monoacetate by transesterification with vinyl acetate in benzene in the presence of CCL in a chemical yield of 32%. This building block has been transformed further realizing a formal total synthesis of the diterpene alkaloid atisine (**78**). The enzymatic hydrolysis of the corresponding diacetate **77b** in the presence of PPL, CCL or porcine liver esterase was less successful.⁸⁷ The 2-cyclohexen-1-ols **79a,b** are intermediates in the synthesis of eburnane alkaloids, for example (+)-vincamine (**80**). Kinetic resolution of **79a** and **79b** by lipase-catalyzed transesterification has been investigated under various reaction conditions. The success strongly depends on the origin of the lipase and the nature of the solvent.⁸⁸ The best results were obtained by reaction of **79a** with vinyl acetate in the presence of lipase from *Mucor miehei* to yield after 15% conversion the corresponding ester with 97% ee. The bicyclic *meso* derivatives **81a,b** are attractive starting materials for the synthesis of piperidin-3-ol alkaloids, such as cassine and spectaline. Their asymmetric resolution was most successfully carried out by transesterification of the diol **81a** with vinyl acetate in the presence of lipase CE or by hydrolysis of the diacetate **81b** using the same enzyme to furnish both enantiomers in yields of 85% with >99% ee. The optically pure intermediates have been converted into the known building block **82**.⁸⁹ The *cis*-2,6-disubstituted piperidine moiety represents a structural unit in numerous alkaloids. Asymmetric resolution of the prochiral *meso*-diacetate **83**, exhibiting this structure, by hydrolysis in the presence of lipase from *Aspergillus niger* yielded the corresponding chiral monoacetate with >95 or 98% ee and with a chemical yield of 73 or 83%, respectively, depending on the reaction conditions.⁹⁰ Resolution of pipercolic acid esters **84** by lipase from *Aspergillus niger* could efficiently be achieved by hydrolysis of the corresponding *n*-octyl ester, whereas the high enantioselectivity was achieved only after purification of the crude lipase preparation. This amino acid

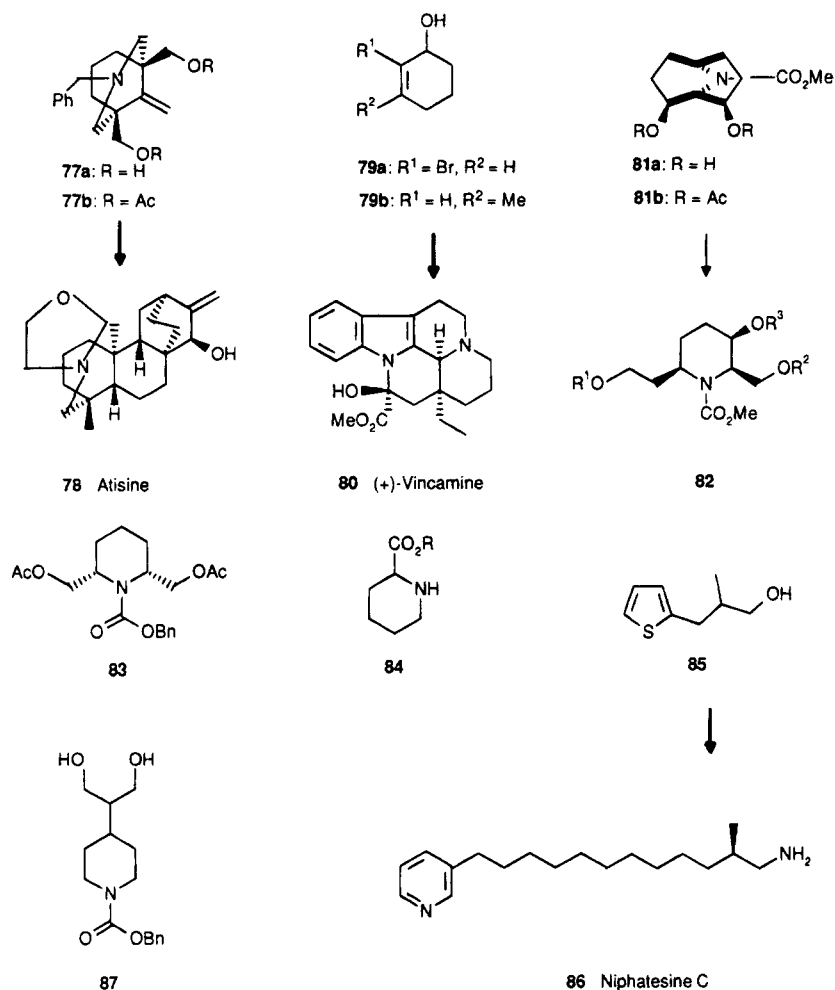


Figure 13.

is a precursor of numerous bioactive compounds particularly alkaloids.⁹¹ Niphatesine C (**86**) belongs to a group of pyridine alkaloids isolated from sponges. The synthesis of the optically active precursor by a lipase-mediated transesterification of the racemic thiophene derivative **85** by lipase PS and vinyl acetate gave the corresponding (*S*)-alcohol in 42% yield with 96% ee.⁹² The asymmetrization of the piperidine derivative **87** by lipase-catalyzed transesterification or hydrolysis of its corresponding diacetate served as the key step to synthesize both enantiomers of quinuclidine derivatives.⁹³ A chiral monoacetate in 52% yield with >98% ee was obtained by transesterification with vinyl acetate in the presence of PPL.

V. Terpenoids

Figure 14 depicts examples of lipase-catalyzed reactions useful for the synthesis of terpenoids. The racemic *trans*-alcohol **88** was separated into its enantiomers by a lipase-mediated transesterification in the presence of lipases of different origin. The most efficient lipase found was PS in the presence of vinyl acetate or vinyl butanoate. The resulting almost enantiomerically pure products were trans-

formed via oxidation and subsequent selenium oxide elimination into enantiomerically pure 2-cyclohexen-1-ol, a versatile intermediate for the synthesis of terpenes and other natural products.⁹⁴ Best results in the enantioselective transesterification of the *meso*-diol **89** were achieved with immobilized lipase AK in diisopropyl ether. The corresponding chiral monoacetate was obtained enantiomerically pure in almost quantitative yield. This building block serves as an intermediate in the synthesis of highly functionalized sesquiterpenes.⁹⁵ Bicyclo[2.2.1]heptene derivatives, such as **90**, are important building blocks in the synthesis of iridoids. They have been resolved efficiently by hydrolysis in the presence of lipase SAM-II.⁹⁶ The racemic drug *trans*-sobrerol (**91**) was separated into its antipodes by acylation with vinyl acetate in the presence of lipase PS. The enantioselectivity of this resolution depends on the solvent used.⁹⁷ When the enzyme was immobilized on Hyflo Super Cell and with *tert*-amyl alcohol as solvent both antipodes were obtained in optically pure form. Although amino acids are not covered in this paper, the lipase-mediated resolution of the 3-phenylisoserine precursors **92** and **93–95** should be mentioned because this amino acid represents the C-13 side chain of the very important tetracyclic diterpene taxol (**97**). Hönig *et al.* resolved the azido alcohol **92** and its further stereo- and regioisomers to give for instance **92** in enantiomerically pure form which was

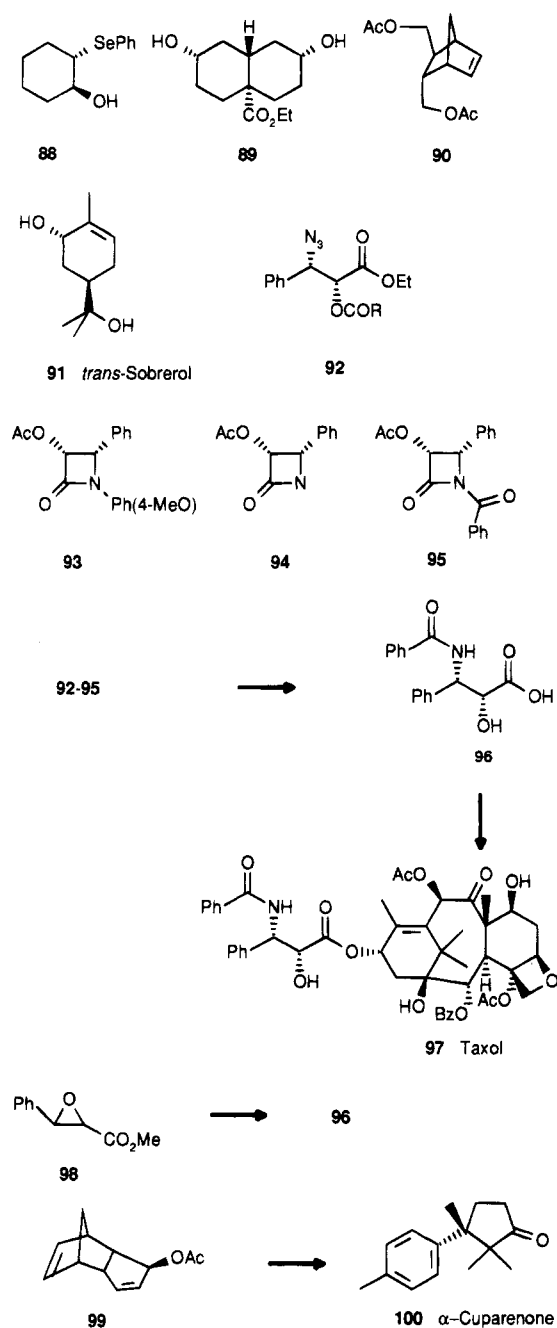


Figure 14.

subsequently transformed into the desired amino acid **96**.⁹⁸ Sih and co-workers used the β -lactams **93**–**95** as substrates in lipase-catalyzed resolutions. Variation of the lipase and addition of cosolvents allowed to prepare enantiomers of all three lactams in almost enantiomerically pure form. The corresponding enantiomerically pure products were converted into the phenylisoserine derivative **96**.⁹⁹ A highly selective large scale resolution of **94** using 1.5 kg of racemic substrate in the presence of lipases was reported as well.¹⁰⁰ Kinetic resolution of the *trans*- β -phenylglycidate **98** by transesterification with isobutyl alcohol in the presence of lipase MAP-10 yielded the enantiomers with high ee. Both enantiomers could be transformed into the taxol side chain **96** in an enantioconvergent manner.¹⁰¹ Optical resolution of 1-acetoxycyclopentadiene (**99**) by hydrolysis with lipase from *Candida cylindracea* was utilized to

synthesize the enantiomerically pure sesquiterpene α -cuparenone (**100**).¹⁰²

VI. Monosaccharides and Cyclitols

Figure 15 summarizes building blocks useful for the synthesis of monosaccharides and cyclitols which have been asymmetricized or resolved with the aid of lipases. Vandewalle and co-workers synthesized various conduritols, such as (–)-conduritol C (**104**),¹⁰³ and other cyclohexane polyols, such as **105**^{104,105} and (+)-fortamine **106**,¹⁰⁵ on the basis of lipase-catalyzed asymmetricizations of the prochiral diesters **101**–**103**. A lipase from *Fusarium solani pisi* was successfully used to asymmetricize the *meso*-diester **103** by hydrolysis furnishing the corresponding chiral monoester in 94% yield with >95% ee. Johnson and co-workers have utilized the corresponding diol of **103** as a substrate for an enantioselective transesterification by lipase from *Pseudomonas cepacia* as their key step on the route to enantiomerically pure polyhydroxylated cyclohexane derivatives, such as conduritols and conduramines.^{106,107} Asymmetricization of the prochiral monosubstituted cycloheptene triol **107** was carried out by transesterification with isopropenyl acetate in the presence of lipase from *Pseudomonas cepacia*.¹⁰⁸ The corresponding enantiomerically pure monoacetate obtained in 95% chemical yield with >95% ee was transformed into unnatural L-glucose (**108**)¹⁰⁹ and 3-deoxy-D-*arabino*-heptulosonic acid (**109**).¹¹⁰ The monoacetate *ent*-**9** was used furthermore to synthesize 1,3-dideoxynojirimycin (**110**).¹¹¹ Inositol derivatives have been target compounds which have been prepared in optically active form using lipase-mediated reactions. Deoxyinositols have been prepared on the basis of the resolution of **111** by the lipase from *Candida cylindracea*.¹¹² The selectively protected racemic *myo*-inositol derivatives **112** and **113** were separated into their enantiomers utilizing esterification with acetic anhydride or other acyl donors by a lipase in organic solvents.^{113–115} In the case of the diol **112**, the use of lipase AY instead of lipase P in the esterification with various acyl donors gave rise to an altered regioselectivity under retention of the enantioselectivity.¹¹⁵ Schneider and Andersch¹¹⁶ took advantage of two lipase-supported steps in the synthesis of enantiomerically pure *myo*-inositol derivatives. The triol **114** was acylated regioselectively and the tetrol **115** was asymmetricized. Both transformations were performed by lipoprotein lipase using vinyl acetate in the former and vinyl butanoate in the latter case. Racemic glycals, such as **116**,¹¹⁷ the furan derivative **117**,¹¹⁸ the azidopropane **119**,¹¹⁹ and the *meso*-pentitol **118**¹²⁰ were separated into their enantiomers or asymmetricized by lipase catalysis. The enantiomerically pure building block **119** was used by Wong and co-workers¹¹⁹ to prepare a substrate for aldolase-catalyzed C–C bond formation to furnish monosaccharides, such as 1-deoxynojirimycin (**120**), demonstrating the advantageous use of two different biotransformations.

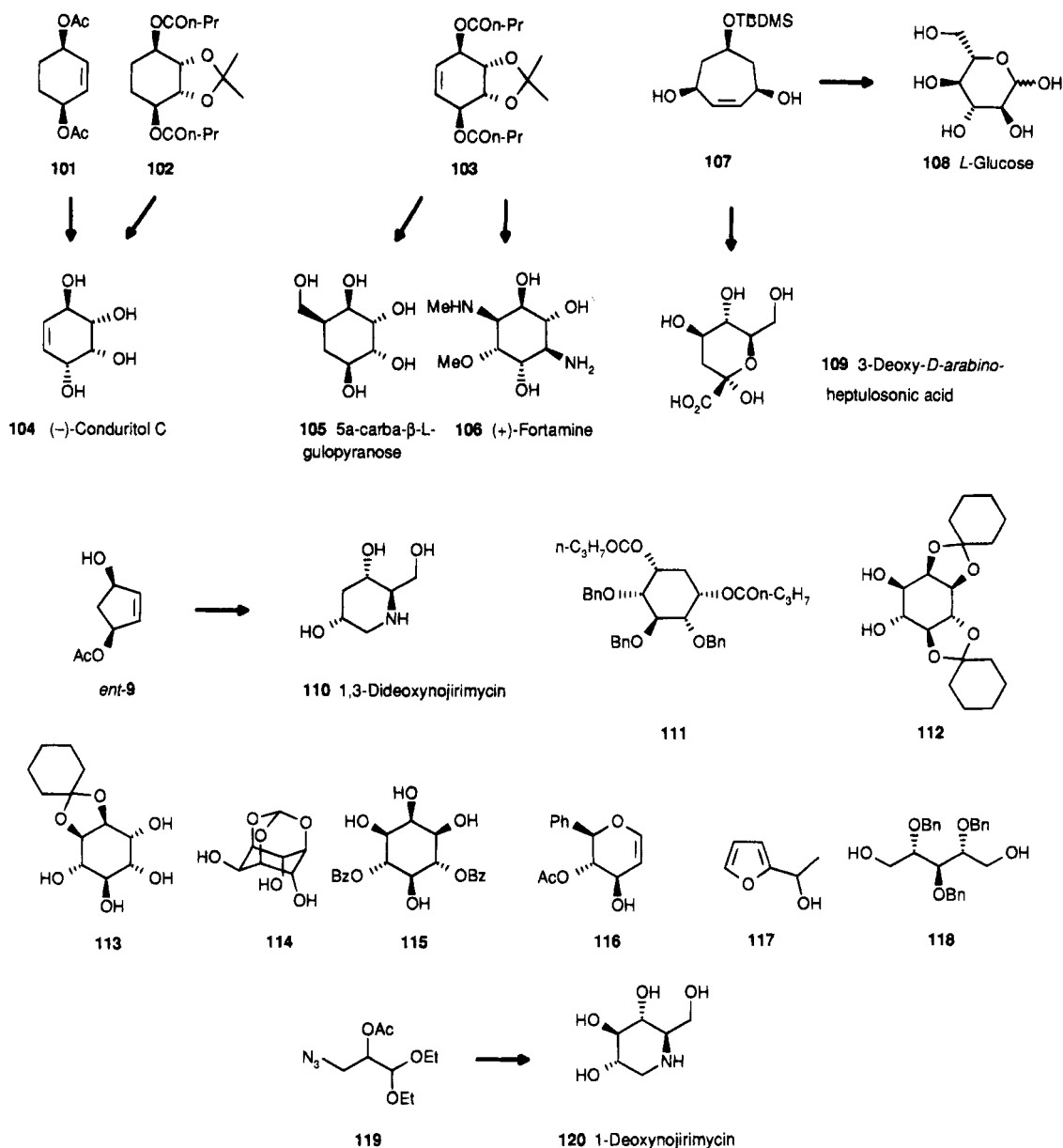


Figure 15.

VII. Antibiotics

Several approaches in the synthesis of antibiotics of different structure took advantage of biocatalytic lipase-mediated enantioselective steps to introduce chirality in precursors. Examples are depicted in Figure 16. The prochiral diacetate **121** could be converted with only low enantioselectivity into the corresponding chiral monoacetate using various lipases. Therefore, esterase from electric eels was utilized to prepare the desired chiral precursor for the antibiotic (-)-malyngolide (**122**).¹²¹ The diastereoisomerically pure but racemic acetate **123** was used by Sih and co-workers to synthesize a biosynthetic monensin A precursor **124**. For this purpose **123** was resolved by hydrolysis in the presence of PPL,^{122,123} *meso*-2,4-Dimethylglutaric anhydride (**125**) was asymmetrically resolved by alcoholysis with 2-methylpropanol in the presence of lipase SP 382 to give a

monoester with high ee which is a starting material for **124** and other biomolecules as well.^{124,125} Ene-diyne antibiotics, such as calicheamicins, are due to their biological properties attractive targets for contemporary organic synthesis. Danishefsky and co-workers utilized lipase-mediated resolutions on substrates, e.g. the tetrol **126** or related intermediates on their route to calicheamicinone (**127**), the aglycon of calicheamicin.^{126,127} The synthesis of the β -lactone antibiotic 1233A **129** was based on the lipase-catalyzed asymmetric resolution of the prochiral diacetate **128** to afford a chiral monoacetate in 86% yield with 90% ee.¹²⁸ Oudemansins **134**, antibiotics with strong antifungal activities, were the subject of several enantioselective syntheses using the diastereoisomerically pure but racemic intermediates **130–133** as substrates in lipase-catalyzed hydrolyses^{129,130} or transesterification.¹³¹ In the cases of the hydrolytic separations of compounds **130** and **131** the methyl ester function was unaffected by lipases. Chiral building blocks of type **130** were precursors for

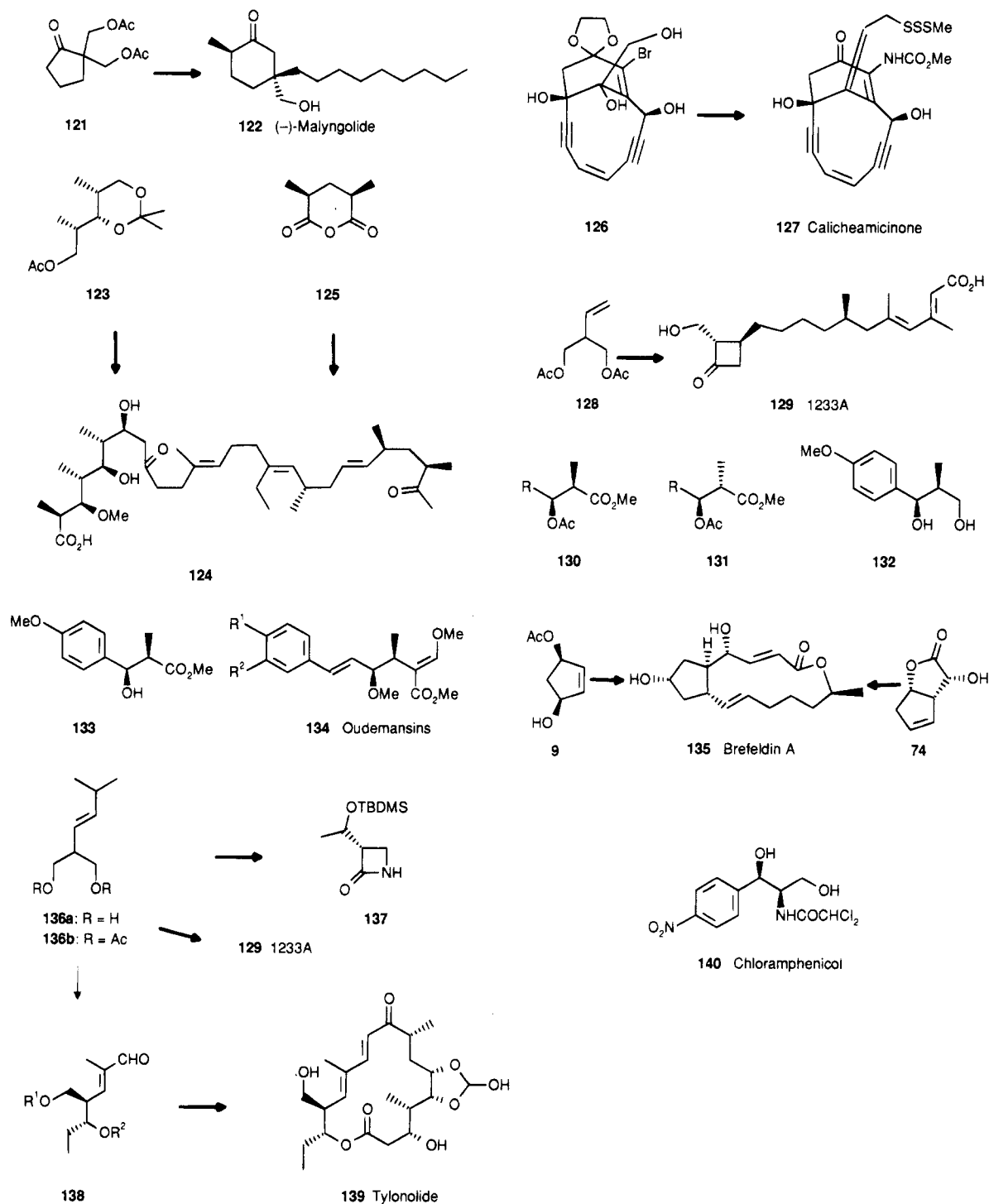


Figure 16.

erythronolide A as well.¹²⁹ Brefeldin A (**135**) exhibits besides its antibiotic properties also antiviral, cytostatic, and antimetabolic activity. This attractive target molecule was synthesized with the versatile intermediate **9**¹³² (compare sections II.A, III.A, and X.A) and the bicyclic hydroxylactone **74**, which has also been used for other purposes¹³³ (compare sections III.E and X.A) as the starting material. The diol **136a** and the corresponding diacetate **136b** are valuable synthetic intermediates developed by Guanti *et al.* Hydrolysis of **136b** with porcine pancreatic lipase yielded the corresponding (*S*)-monoacetate with 97% ee which was the basis for the synthesis of the carbapenem antibiotic building block **137**¹³⁴ or

138, an intermediate for the macrolide antibiotic tylonolide (**139**).¹³⁵ The antibiotic 1233A **129** was synthesized on the basis of the PPL-catalyzed transesterification of the diol **136a** with vinyl acetate furnishing the corresponding (*R*)-monoacetate with 96% ee.¹³⁶ Enantiomerically pure chloramphenicol (**140**) was the substrate for the regioselective introduction of various acyl substituents at the primary hydroxy group by lipases.¹³⁷

VIII. β -Adrenergic Agents

This type of cardiovascular drug (Figure 17) with the general structure **141** exhibits its biological

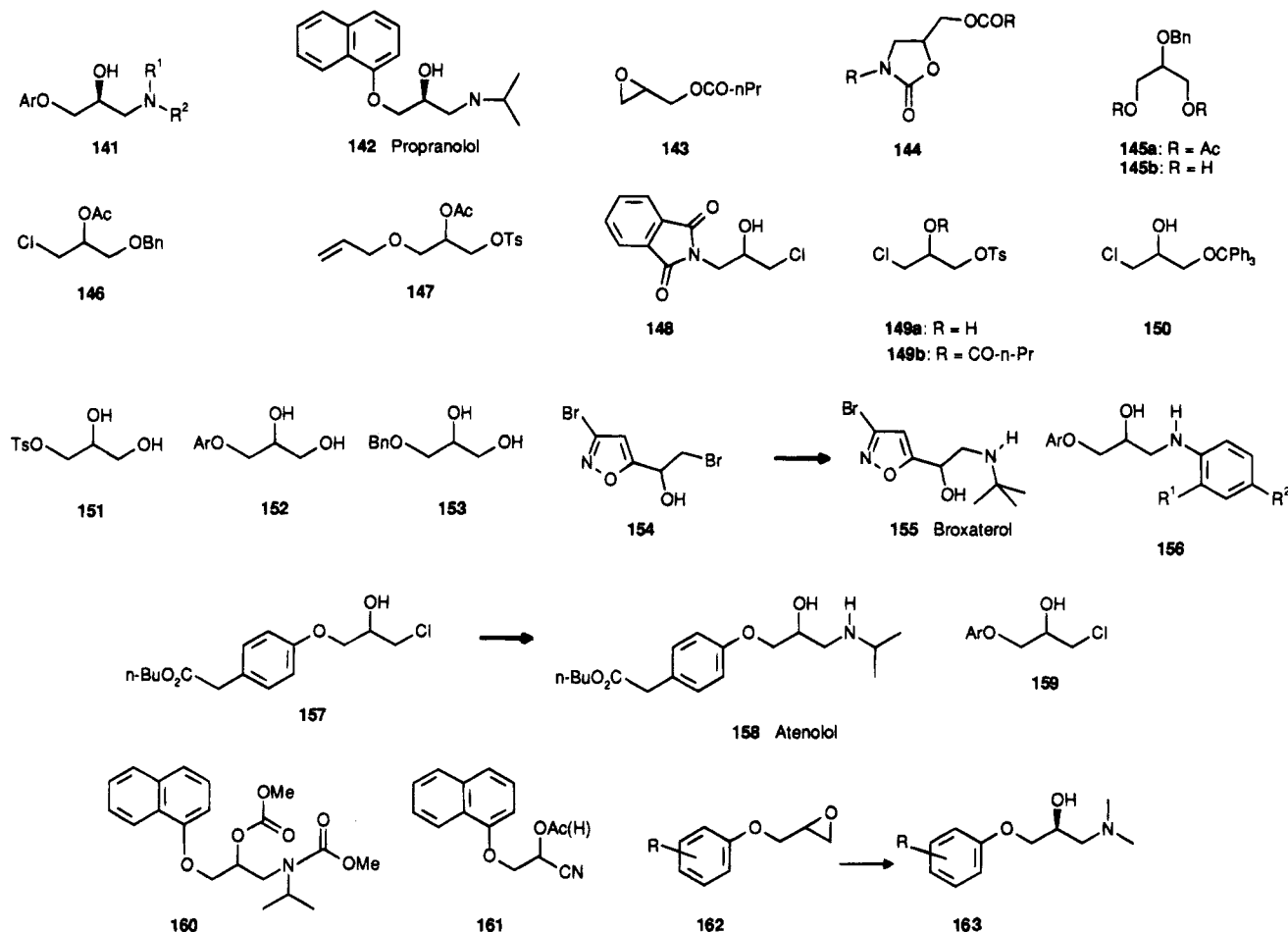


Figure 17.

activity in the (*S*) enantiomer. Many efforts have been made to synthesize such compounds in enantiomerically pure form.¹³⁸ A typical example for a β -adrenergic blocking agent is propranolol (**142**). Some approaches utilize lipase-catalyzed steps to prepare building blocks and complete drugs. Figure 17 depicts C_3 -building blocks with various substituents in 1- and 3-position which can or have been used to synthesize β -blockers.

Ladner and Whitesides resolved racemic glycidol butanoate (**143**) by hydrolysis using lipase from porcine pancreas.¹³⁹ The lipase-mediated kinetic resolution of the oxazolidinone esters **144** were the subject of intensive investigations by Hamaguchi *et al.* to furnish C_3 -building blocks with high ee.^{140–143} Asymmetrization of the prochiral glycerol derivatives **145a,b** were achieved by hydrolysis of the diacetate **145a** using lipase from porcine pancreas^{144,145} or by transesterification of the diol **145b** using a lipase from *Pseudomonas* sp. or lipase P.^{146,147} In the latter case,¹⁴⁷ the chiral monoacetate was obtained in 92% yield with 94% ee by reaction with vinyl acetate in the presence of lipase P. Terao *et al.*¹⁴⁷ have completed the synthesis of propranolol (**142**). The resolution of the 2-propanol derivatives **146**, **147**,¹⁴⁸ and **148**¹⁴⁹ could be more effectively carried out by hydrolysis than by transesterification of the corresponding alcohols. The 1-chloro-3-(tosyloxy)-2-propanols **149a,b** could be resolved either by

transesterification or by hydrolysis supported by lipase P-30.¹⁵⁰ The corresponding 3-trityloxy derivative **150** also was a suitable substrate for a highly enantioselective transesterification in the presence of lipase PS to afford the corresponding alcohol in 43% yield with >98% ee.¹⁵¹ Lipase-mediated transesterification of the 3-substituted 1,2-propanediols **151**,¹⁵² **152**,^{153,154} and **153**¹⁵⁵ have been executed using an one-pot two-step procedure. In the first step regioselective acylation afforded a racemic primary monoacetate which was kinetically resolved in the subsequent acylation step at the secondary hydroxy group. In the case of the aryloxy derivatives **152** the enantioselectivity of the sequential transesterification catalyzed by lipase PS strongly depends on the position of the substituent at the aryl residue and of the solvent used. The kinetic resolution of the bromohydrin **154** was followed by the synthesis of both enantiomers of broxaterol (**155**).¹⁵⁶ A variety of 2-propanol amines **156** were acylated in the presence of PPL with moderate enantioselectivity.¹⁵⁷ On the other hand, resolution of the atenolol precursor **157** proceeded with high enantioselectivity to give both almost enantiomerically pure chlorohydrins which were transformed into the corresponding drug **158**.¹⁵⁸ Chlorohydrins **159** leading to propranolol (**142**) and other derivatives were separated into their enantiomers by lipase-catalyzed transesterification or hydrolysis of their corresponding acetates.^{159,160} In both cases the synthesis of propranolol was completed. The

resolution of the propranolol derivative **160** by hydrolysis with PPL proceeded with moderate enantioselectivity.¹⁶¹ The cyanohydrin **161** was separated by transesterification with vinyl acetate by lipase from *Pseudomonas* sp.¹⁶² or by hydrolysis of the corresponding acetate with the same enzyme.¹⁶³ Although in both cases moderate enantioselectivity was observed, the transformation into propranolol was completed.

An unusual lipase-mediated reaction was reported by Kamal *et al.* very recently. Addition of amines to the glycidol derivatives **162** in the presence of lipases or subtilisin gave rise to a kinetically controlled enantioselective formation of the corresponding (*S*)-amino alcohols **163**.^{164,165}

IX. Pesticides

A. Pheromones

Pheromones act as semiochemicals between the members of the same species. They are well studied in insects. Insect pheromones are not *a priori* pesticides but their main field of application is insect pest control. Therefore, they are classified here as pesticides.

1. Asymmetrization of meso-Intermediates

Figure 18 shows *meso*-diesters or -diols used as building blocks for pheromones. The epoxydiacetate **164** was enantioselectively hydrolyzed in the presence of PPL which was the lipase of choice among several others tested to yield a chiral monoacetate in a chemical yield of 80% with 90% ee.¹⁶⁶ On the basis of this intermediate disparlure (**165**), the hecicosene derivative **167**,¹⁶⁶ the C₅₁ compound **168**,¹⁶⁷ and its antipode, both pheromones of the nymphs of the cockroach *Nauphoeta cinerea*, have been prepared by Mori *et al.* Furthermore, the main pheromone of the Israeli pine bast scale **166** and its antipode have been synthesized on the basis of the asymmetrization of the potent *meso* compound **164**.¹⁶⁸ The diacetate **169** asymmetrized by hydrolysis with lipase AK was the starting material to synthesize the pheromone **170**.¹⁶⁹ (+)-*endo*-Brevicomin (**172**) was obtained after asymmetrization of the *meso*-diol **171** with vinyl acetate in the presence of lipase AK. The corresponding chiral monoacetate was prepared by this procedure in 96% yield with 98.5% ee.¹⁷⁰ Asymmetric hydrolysis of the cyclopropane dibutanoate **173** under well-defined conditions yielded a chiral monobutanoate in quantitative chemical yield in enantiomerically pure state. This intermediate was transformed into the dictyopterenes A (**174**) and C (**175**) isolated from brown algae.¹⁷¹

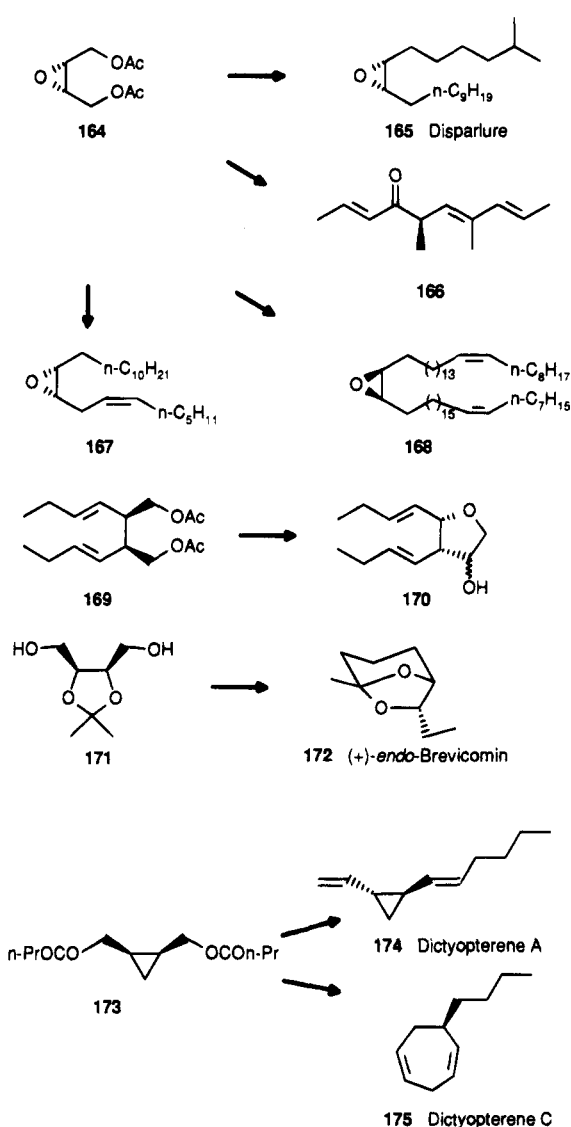


Figure 18.

2. Resolution of Racemic Building Blocks

Figure 19 shows racemic intermediates used for the synthesis of pheromones after kinetic resolution by lipases. The racemic cyanohydrin **176** and further alkyl chain-modified cyanohydrins have been resolved by a lipase-catalyzed transesterification in the presence of lipase PS. Subsequent microbial hydrolysis of the optically active cyanohydrin yielded the corresponding α -hydroxy acid which was transformed into (*R*)-4-dodecanolide (**177**), a pheromone of rove beetles.¹⁷² The resolution of (*E*)- γ -hydroxy- α,β -unsaturated phenyl sulfones, such as **178**, using lipase-mediated acylations which were very effective for this class of alcohols furnished the basis for the preparation of the aggregation pheromone **179**.¹⁷³ Treatment of the alcohol **178** with vinyl acetate and lipase PS in diisopropyl ether afforded after 50% conversion both antipodes with >95% ee. The synthesis of the enantiomerically pure spiroketal **181**, a beetle pheromone and its enantiomer, was realized after separation of the unsaturated alcohol **180** by transesterification with trifluoroethyl butanoate in the presence of PPL.¹⁷⁴ The epoxy alcohol **182**, a

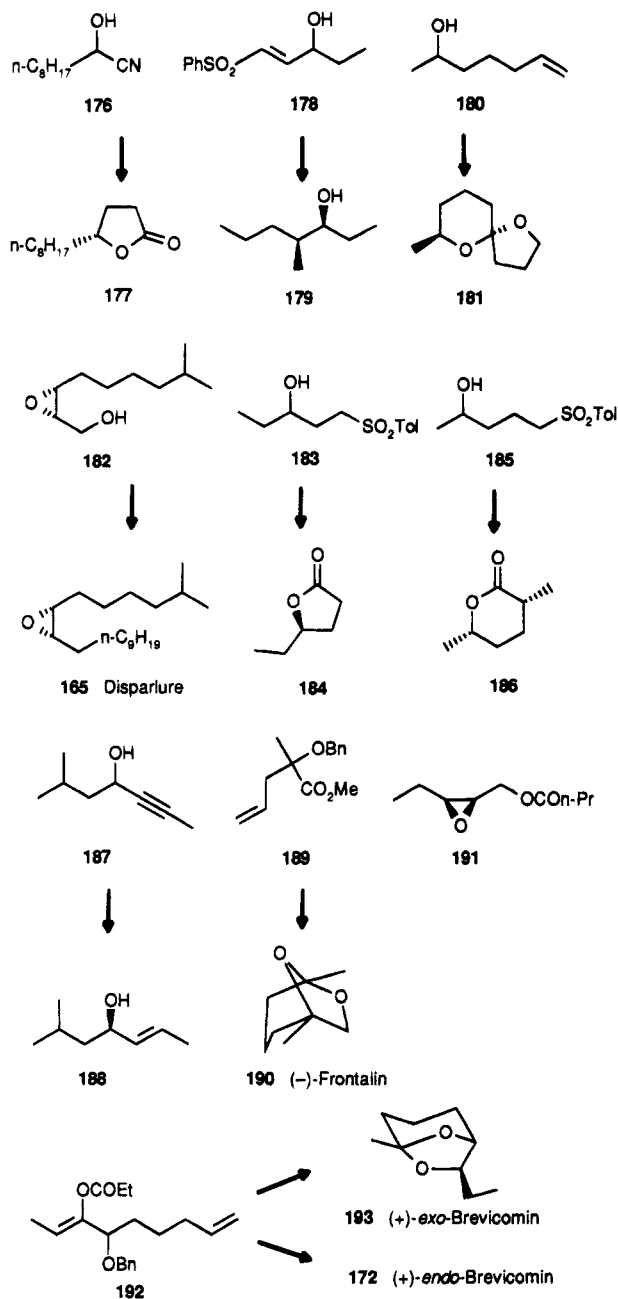


Figure 19.

precursor in the synthesis of disparlure (**165**), was resolved by transesterification with ethyl acetate in the presence of PPL. Further similar precursors have been used as substrates.¹⁷⁵ The hydroxy sulfones **183** and **185** in their optically active form obtained by a lipase PS-supported acylation were converted into the pheromones **184** and **186**, respectively.¹⁷⁶ The secondary allylic alcohol **188**, a pheromone of the American palm weevil, was prepared by resolution of the corresponding propargylic alcohol **187** as its acetate by hydrolysis in the presence of lipase A and subsequent hydrogenation.¹⁷⁷ Enantioselective hydrolysis of the protected α -hydroxy carboxylic ester **189** with lipase OF allowed the preparation of the aggregation pheromone (-)-frontalin (**190**).¹⁷⁸ Kinetic resolution of epoxy esters, such as **191**, with PPL and subsequent ring opening offers an access to *erythro*- and *threo*-1,2,3-pentanetriol

building blocks for *exo*- and *endo*-brevicomin (**193** and **172**, respectively).¹⁷⁹ In addition, (+)-*endo*- and (+)-*exo*-Brevicomin (**172** and **193**, respectively) have been prepared on the basis of the kinetic resolution of the enol ester **192** by hydrolysis with lipase OF.¹⁸⁰

3. Lipase-Supported Lactonization

Figure 20 depicts some pheromones with lactone structure which were obtained either by a direct lipase-catalyzed lactonization or by resolution of its open-chain hydroxy ester precursor. Mori and Tomioka¹⁸¹ obtained the macrocyclic lactones **194**, **196**, and **197** by direct enantioselective lactonization of the corresponding racemic hydroxy esters or in the cases of **195** and **198** by resolution of the corresponding hydroxy esters and subsequent chemical lactonization. For example the 12-membered lactone **194** was obtained in the presence of lipase P in 17% yield with >99% ee. (-)-Massoialactone (**200**) was synthesized via a PPL-catalyzed lactonization of the corresponding *syn*-dihydroxy ester yielding the β -hydroxy lactone **199** in 25% yield with 86% ee followed by a subsequent dehydration.¹⁸² The synthesis of the Japanese beetle pheromone **202** was a subject of intensive investigations using lipase-catalyzed steps.^{183,184} Attempts were focused on the enantioselective lactonization of its precursor **201** under various conditions. Most successful however were not the experiments which intended direct lactonization but enantioselective acylation of the corresponding hydroxy ester with carboxylic acid anhydrides in the presence of lipase PS.¹⁸⁴

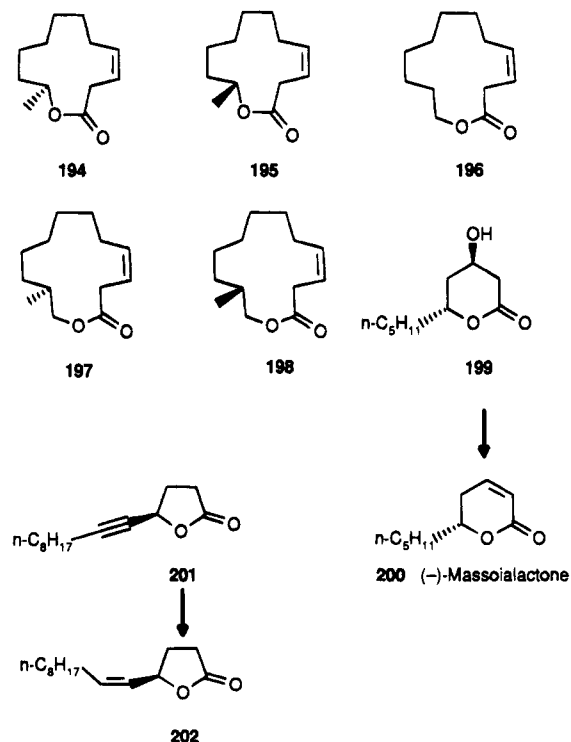


Figure 20.

4. Resolution of Racemic Pheromones

Many pheromones are relatively simple secondary alcohols which have been prepared in racemic form

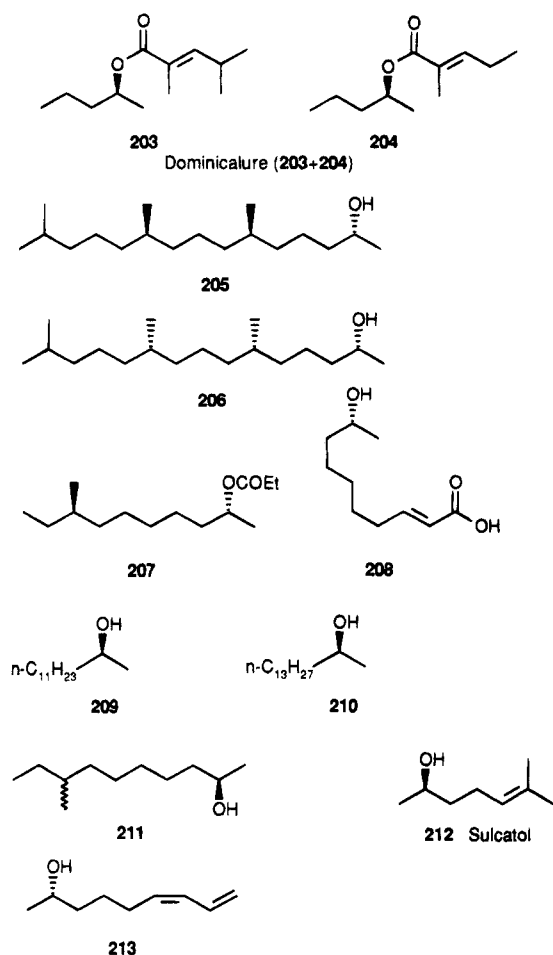


Figure 21.

and resolved by a lipase-catalyzed enantioselective hydrolysis or acylation. Figure 21 shows these pheromones. The mixture of the chiral esters **203** and **204** is called dominicalure and has been identified as aggregation pheromone of the lesser grain borer. The alcoholic component of these pheromones, 2-pentanol, was resolved by acylation with trifluoroethyl laurate catalyzed by PPL. Esterification of enantiomerically pure 2-pentanol with the corresponding acid components furnished both enantiomers of each ester.¹⁸⁵ The long-chain secondary alcohol **205** bearing three asymmetric centers was synthesized by a stereocontrolled construction of the alkyl chain with defined relative configuration at the asymmetric carbon atoms bearing methyl groups. Finally, the resulting diastereoisomeric mixture was resolved by lipase PS to give the sex pheromone of *Corcyra cephalonica*.¹⁸⁶ The corresponding diastereoisomer **206** was prepared in a similar manner.¹⁸⁷ The propanoate **207** represents a component of the sex pheromone of *Diabrotica species*. It was prepared in almost enantiomerically pure form by two lipase-catalyzed steps. First, the trichloroethyl carbonate of the corresponding racemic alcohol was hydrolyzed in the presence of lipase from *Pseudomonas fluorescens*. The resulting enantiomerically enriched alcohol was transformed again into the carbonate and hydrolyzed once more in the presence of the same lipase affording the corresponding alcohol with 99.5% ee.¹⁸⁷ The pheromone **208** was resolved by a PPL-catalyzed acylation with trifluoroethyl propanoate.¹⁸⁸

Both long-chain secondary alcohols **209** and **210**, pheromones of *Drosophila mulleri* and *D. busckii*, respectively, were separated into their enantiomers by hydrolysis of their corresponding acetates with lipase PS with very high enantioselectivity.¹⁸⁹ Separation of the diastereoisomeric mixture of **211** yielded a pheromone which was stereochemically homogeneous at the stereocenter bearing the secondary hydroxy group.¹⁹⁰ Both enantiomers of sulcatol (**212**) are known to be pheromones, therefore some efforts have been made to resolve the corresponding racemate under various conditions.^{186,191-193} The dienol **213**, a pheromone of the leafminer *Nepticula malella*, was obtained in enantiomerically pure form by resolution of its corresponding acetate in the presence of lipase AK.¹⁹⁴

5. Further Applications

The synthesis of the Japanese beetle pheromone **202** was the subject of a further investigation using a regioselective lipase-catalyzed acylation starting from the racemic diol **214** (Figure 22) which afforded the corresponding primary monoacetate. Oxidation of the latter compound furnished the corresponding ketone. The subsequent enantioselective reduction of the latter ketone with bakers' yeast and hydrolysis yielded the nonracemic chiral intermediate (*R*)-**215** which could be transformed into the beetle pheromone **202** and into the mosquito pheromone **216**.¹⁹⁵ A further application using a lipase in the synthesis of pheromones took advantage of their chemo- and diastereoselective properties. Due to its low stereochemical purity the synthetic aggregation pheromone (–)-sitophilate (**218**) (Figure 22) was converted into its chloroacetate **217** and subsequently hydrolyzed in the presence of a lipase from *Pseudomonas* to enhance the stereochemical purity.¹⁹⁶

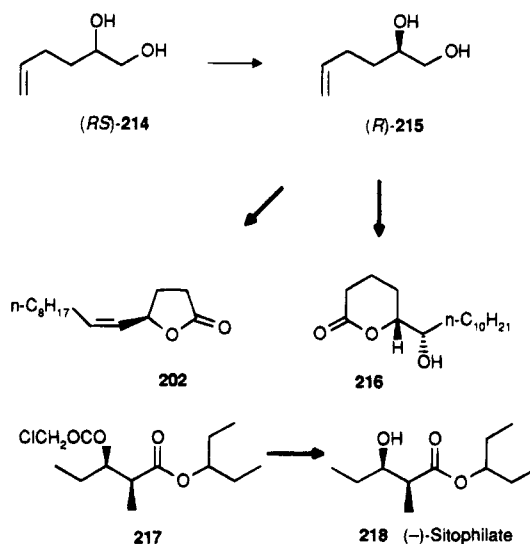


Figure 22.

B. Miscellaneous Pesticides

Apart from pheromones other building blocks of synthetic or natural pesticide analogs depicted in

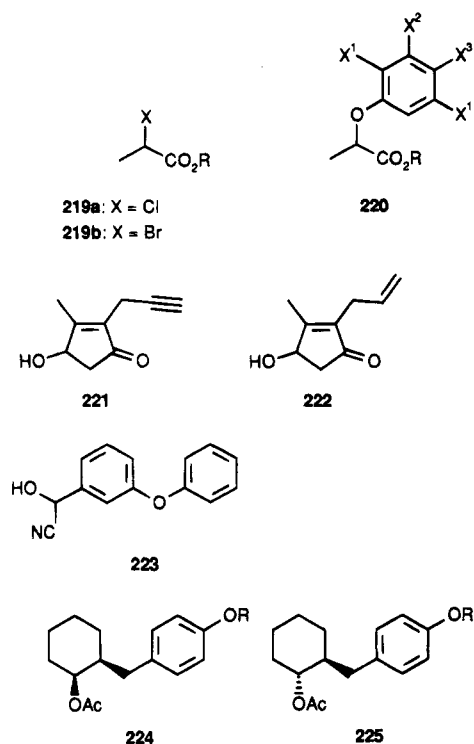


Figure 23.

Figure 23 have been prepared in enantiomerically pure or enriched form utilizing lipase-catalyzed biotransformations. Halogenated 2-(aryloxy)propanoic acids are widely used as herbicides. It is known that only the (*R*) enantiomer is biologically active. Therefore many efforts have been made to resolve their precursors 2-chloro-¹⁹⁷⁻¹⁹⁹ or 2-bromo propanoic acid (**219a** and **219b**)¹⁹⁸ as well as the phenoxy derivatives **220**^{198,200-204} by hydrolysis of their esters or by esterification in organic solvents in the presence of lipases. The most suitable way to resolve this type of compounds seems to be the esterification of 2-chloro- or 2-bromopropanoic acid with 1-butanol in organic solvents in the presence of lipase from *Candida cylindracea* as reported by Klibanov.¹⁹⁸ The chiral alcohols **221-223**, building blocks for enantiomerically pure synthetic pyrethroids, could be resolved by a lipase-supported hydrolysis of their corresponding acetates.^{205,206} In the cases of the cyclopentenol **221** and the cyanohydrin **223** the resolution using a lipase from *Arthrobacter* sp. was very effective, yielding both enantiomers in high enantiomeric purity. Furthermore, in case of **221** the configuration of the undesired alcohol was inverted by Mitsunobu reaction.²⁰⁶ Finally, racemic *cis* and *trans* juvenile hormone precursors **224** and **225** were resolved by hydrolysis in the presence of PPL or lipase from *Geotrichum candidum*.²⁰⁷

X. Miscellaneous Compounds

A. Natural Products and Their Synthetic Analogs

Figure 24 depicts synthetic intermediates related to mevinic acid, such as mevinolin (**226**) or meva-

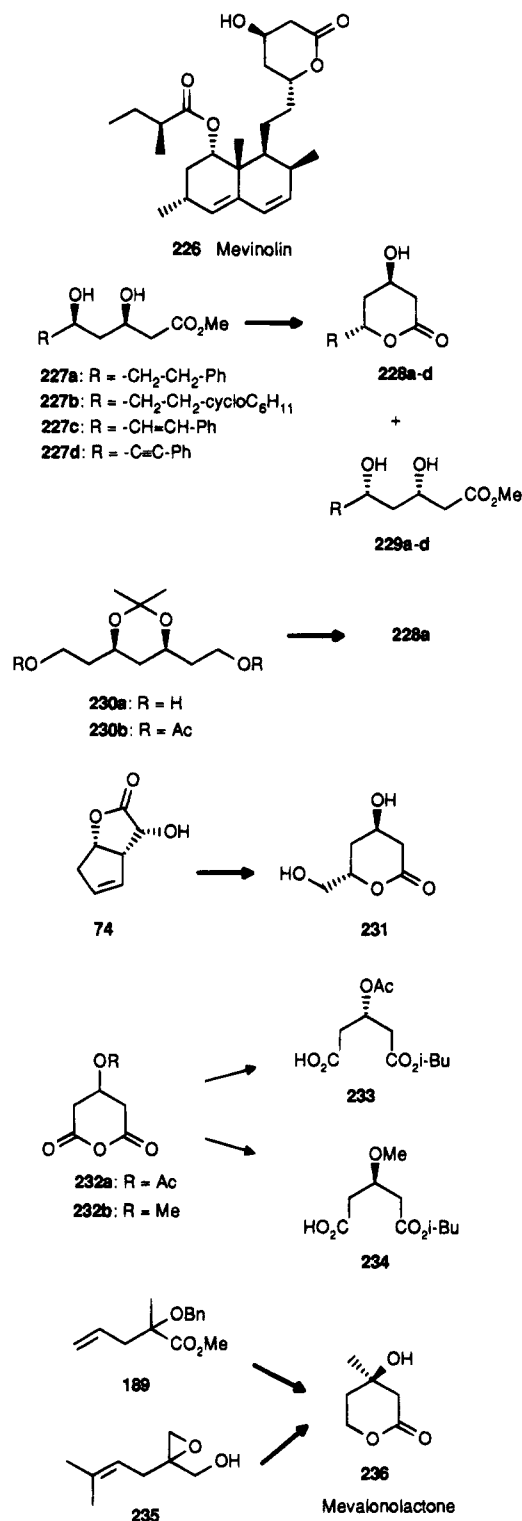


Figure 24.

lonolactone (**236**), which have been synthesized by lipase-supported steps. The lipase-catalyzed lactonization of the *syn*-3,5-dihydroxy carboxylic esters **227a-d** has been utilized for the synthesis of the lactone moieties **228a-d** of mevinic acid.²⁰⁸⁻²¹¹ Enantioselectivity and reaction rate of this intramolecular reaction strongly depend on the substituent R and the lipase used. The mevinic acid analog **228a** and its enantiomer have been synthesized using a lipase-catalyzed asymmetrization of the *meso*-diol **230a**²¹² or the diacetate **230b**.²¹³ The bicyclic α -hydroxy

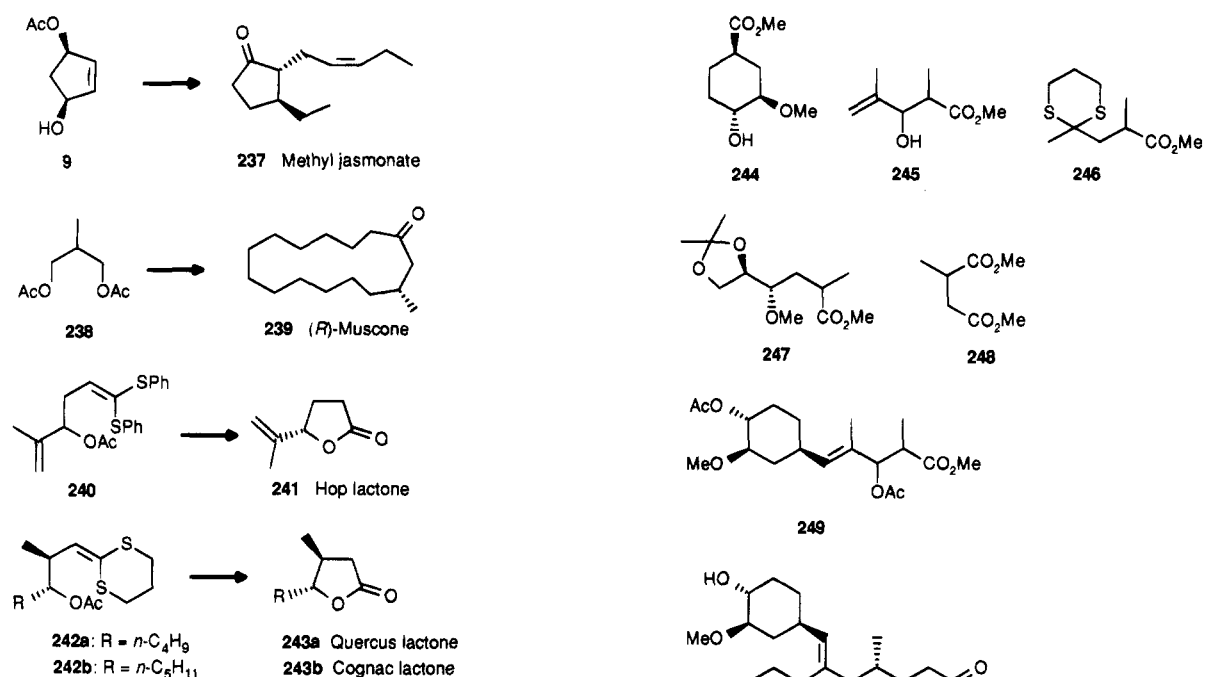


Figure 25.

lactone **74** obtained in enantiomerically pure form by a lipase-supported resolution was utilized as a starting material for the mevinic acid building block **231**.^{85,214} The monoesters **233** and **234**, building blocks for mevinic acid derivatives, have been prepared with high ee by enantioselective alcoholysis of the prochiral anhydrides **232a** or **232b** with 2-methylpropanol. The acetyl derivative **232a** yielded in the presence of lipases SP 382 the monoester **233** in 64% yield with >98% ee. The anhydride **232b** furnished in the presence of lipase PS the monoester **234** in 80% yield with 90% ee.²¹⁵ The enantioselectivity of this reaction was mainly influenced by the protecting group of the 3-hydroxy function of the anhydride. Mevalonolactone (**236**) was prepared either on the basis of the building block **189**,²¹⁶ also used for the synthesis of a pheromone (compare section IX.A.2), or by resolution of the oxiranemethanol **235** using a lipase-catalyzed transesterification.²¹⁷

Figure 25 shows examples for the synthesis of compounds with sensoric properties. Starting from the versatile enantiomerically pure monoacetate **9** both enantiomers of methyl jasmonate (**237**) and their corresponding diastereoisomers have been prepared.²¹⁸ Asymmetrization of the 1,3-propanediol diacetate (**238**) by hydrolysis with lipase from *Pseudomonas fluorescens* gave the corresponding enantiomerically pure chiral monoacetate in 33% yield which was transformed into (*R*)-muscone (**239**).²¹⁹

The resolution of a multitude of homoallylic alcohols containing dithioketene acetal functionalities with various lipases by hydrolysis of acetates, such as **240**, **242a**, and **242b**, or transesterification of the corresponding alcohols was intensively investigated.²²⁰ Using these resolved substrates, among others, hop lactone (**241**), quercus lactone (**243a**), and cognac lactone (**243b**), respectively, have been synthesized.

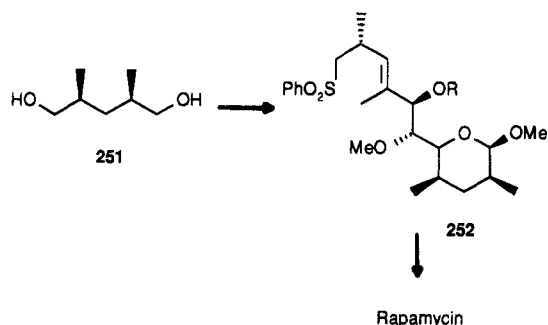


Figure 26.

Figure 26 shows building blocks for the synthesis of the immunosuppressive compounds FK 506 (**250**) and the structurally similar rapamycin which have been prepared in enantiomerically pure form by lipase catalysis. It was the aim of Sih and Gu to use as much as possible biocatalytic steps in their synthesis directed toward FK 506. The building blocks **244–249** have been prepared with high enantiomeric purity using lipase-catalyzed steps.^{221–223} Ley and co-workers²²⁴ utilized the enantioselective acylation of the *meso*-diol **251** in the presence of PPL as a key step in their approach directed toward the synthesis of rapamycin a macrolide with similar properties like FK 506 via the intermediate **252**.

The synthesis of autoregulators from *Streptomyces* sp. (Figure 27), such as the A-factor **254a**, based on the enzymatic asymmetrization of the prochiral diacetates **55b**,⁶⁴ **57**,^{225,226} and **253**,²²⁵ have been realized. Resolution of the racemic regulators **254b–e**

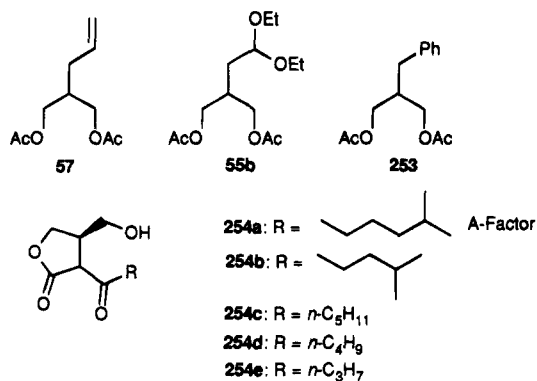


Figure 27.

by acylation with acetic anhydride was investigated using lipase L-10 or olipase-4SD.²²⁷

Figure 28 summarizes further building blocks which have been asymmetrically or kinetically resolved mediated by lipases. In the synthesis of (*R*)-carnitine chloride (**256**) two enzyme-catalyzed steps were used. The epoxy butanoate **255** was resolved by enantioselective hydrolysis with the lipase steapsin to give the corresponding unchanged ester with high enantiomeric purity. The latter was hydrolyzed nonstereoselectively with the protease alcalase furnishing the corresponding acid which subsequently was transformed into (*R*)-carnitine chloride (**256**).²²⁸ (–)-Avenaciolide (**258**), a natural antifungal agent, was synthesized using the resolution of the chloro derivative **257** by hydrolysis with lipase P.²²⁹ The long-chain hydroxy fatty acid **260** and its enantiomer, called coriolic acid, exhibit different biological func-

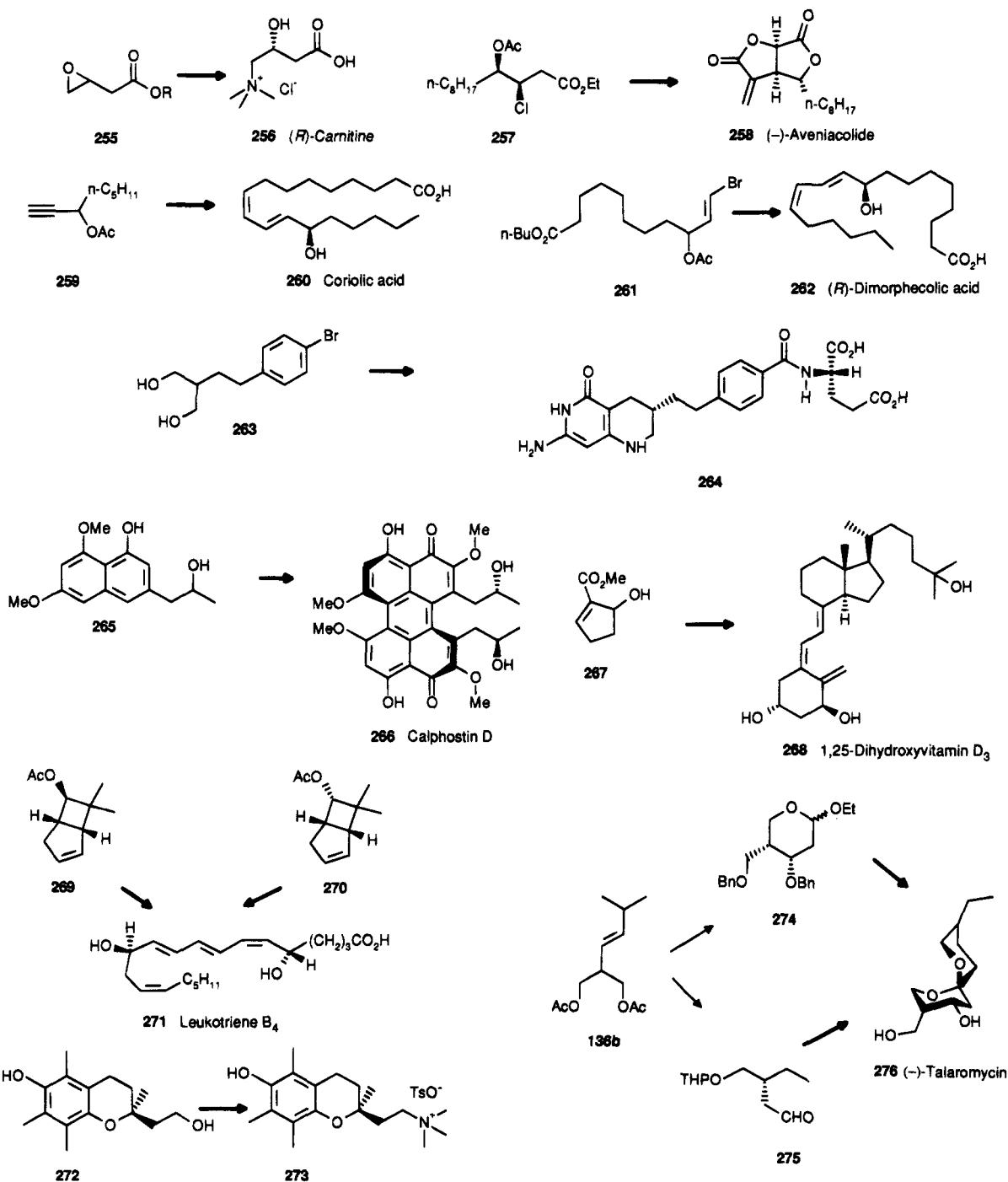


Figure 28.

tions. The latter isolated from rice plants has been shown to act as a self-defence substance against a special plant disease. Both enantiomers have been prepared by utilizing the lipase-catalyzed hydrolysis of the alkynol acetate **259**.²³⁰ Another self-protecting substance of rice plants, called (*R*)-dimorphecolic acid (**262**), has been prepared on the basis of the resolution of the 8-acetoxy carboxylic ester **261** with CCL. Surprisingly, hydrolysis occurred at the carboxylic ester function and not at the asymmetric center bearing the acetate group.²³¹ The lipase-catalyzed asymmetric resolution of the 1,3-propanediol derivative **263** on treatment with methyl acetate and PPL gave an enantiomerically enriched monoacetate (88% ee) in 90% yield which was converted into the tetrahydrofolic acid derivative **264** with oncolytic properties.²³² The protein kinase C¹-inhibitor calphostin D (**266**) was synthesized after separation of the racemic naphthol derivative **265** by transesterification with vinyl acetate in the presence of lipase from *Pseudomonas fluorescens* furnishing the corresponding acetate in 42% yield with >99% ee.²³³ The cyclopentenol **267** was resolved with high enantioselectivity by transesterification with vinyl acetate in the presence of lipase PS. The corresponding (*R*)-alcohol obtained enantiomerically pure was transformed into a known building block of 1,25-dihydroxyvitamin D₃ (**268**).²³⁴ An enantiocomplementary synthesis of the leukotrienes-B₄ (**271**) and -B₃ has been realized by resolution of the bicyclic acetates **269** and **270** using porcine pancreatic lipase or lipase from *Mucor miehei*.²³⁵ The α -tocopherol analog MDL-73404 **273** was prepared on the basis of the resolution of the primary alcohol **272** by transesterification with vinyl acetate in the presence of lipase B from *Pseudomonas* sp.²³⁶ The prochiral diacetate **136b**, already applied to the synthesis of substances with antibiotic properties (compare section VII), has been used for the synthesis of (-)-talaromycin A (**276**) intermediates **274** and **275**.²³⁷

B. Synthetic Biologically Active Compounds

Figure 29 depicts synthetic drugs or their precursors. Ketorolac (**277**), an antiinflammatory agent, was resolved by hydrolysis of its methyl ester with lipases and proteases.²³⁸ Lipase from *Mucor miehei* yielded the corresponding acid with 94% ee and the remaining ester with 90% ee. The use of proteases was superior in this case showing higher enantioselectivity. Dihydropyridines are widely used as calcium antagonists to regulate cardiovascular disorders. Their derivatives **278**²³⁹ and **279**²⁴⁰ have been asymmetrically resolved by lipase-catalyzed hydrolysis using lipases of different origin. The glycidic ester **280**, a building block of the calcium antagonist diltiazem (**281**), was separated into its enantiomers by lipases from *Candida cylindracea* or porcine pancreas with moderate selectivity.^{241,242} The prochiral tetrahydrofurans **282** and **283**, intermediates for platelet-activating factor antagonists, were asymmetrically resolved by hydrolysis with the lipase from *Mucor javanicus* to

give the corresponding monobutanoates in enantiomerically pure form.²⁴³ The carboxylic ester **284** was resolved to be an intermediate for the antihypertensive agent capoten (**285**).²⁴⁴ Best results were achieved utilizing a lipase from *Aspergillus niger*. Enantioselective transesterification of the prochiral diol **253a** on treatment with vinyl acetate and lipase P yielded a chiral monoacetate in a yield of 95% with 90% ee which was the basis for the synthesis of renin inhibitors.^{245,246} Dropropizine (**286**) is an antitussive agent and was separated into its enantiomers by alcoholysis of its corresponding diacetate in the presence of lipase from *Pseudomonas cepacia*.²⁴⁷ Mephesisin (**287**),²⁴⁸ a muscle relaxant, chlorphenesin (**288**), an antimycotic agent, and guaiphenesin (**289**), a muscle relaxant and tranquilizer, have been resolved by sequential transesterification with lipase PS.^{153,154} Resolution of the chloroacetate **290** by hydrolysis with lipase from *Pseudomonas fluorescens* yielded both enantiomers with 97 and 99% ee which are precursors of the antidepressants tomoxetine (**291a**), fluoxetine (**291b**), and nisoxetine (**291c**) which finally have been prepared in enantiomerically pure form.²⁴⁹ Enantioselective hydrolysis of the prochiral diester **292** with lipases was the prerequisite for the synthesis of enantiomerically pure leukotriene D₄-antagonists.²⁵⁰ By utilizing a lipase from *Pseudomonas* a chiral monoacetate was obtained in 90% yield with 98.5% ee. The resolution of the chloro alcohols **293a-c**, precursors for the antipsychotic agents **294a,b** or the antihistamine agent **295**, were successfully performed by transesterification of the alcohols or hydrolysis of the corresponding acetates by lipase from *Pseudomonas cepacia*.^{251,252} Furthermore, the separation of the enantiomers of the antipsychotic compound **294b** by transesterification or hydrolysis of the corresponding acetate was investigated using a variety of lipases.²⁵¹ Lipase P-30 is a suitable catalyst for the enantioselective hydrolysis of the α -hydroxy carboxylic ester **296**, a known intermediate for the synthesis of the angiotensin-converting enzyme inhibitor **297**, and of the dihydropyran carboxylic ester **298**, a precursor for the leukotriene antagonist **299**.⁴⁸ Finally, the synthesis of the hunger-modulating disubstituted lactone **301** based on the asymmetric resolution of the *meso*-diacetate **300** by hydrolysis with lipase from *Pseudomonas fluorescens* furnished a chiral monoacetate in 70% yield with 96% ee.²⁵³

XI. Summary and Outlook

Lipase-catalyzed transformations show high selectivity, especially enantioselectivity which is demonstrated by their applications in kinetic resolutions of racemic alcohols or their esters as well as in asymmetric resolutions of the corresponding prochiral derivatives. As shown in this review numerous building blocks have been prepared and used in the synthesis of biologically active natural and synthetic compounds.

Lipase-catalyzed hydrolysis or ester formation are becoming standard procedures for organic chemists due to their simple feasibility and high efficiency.

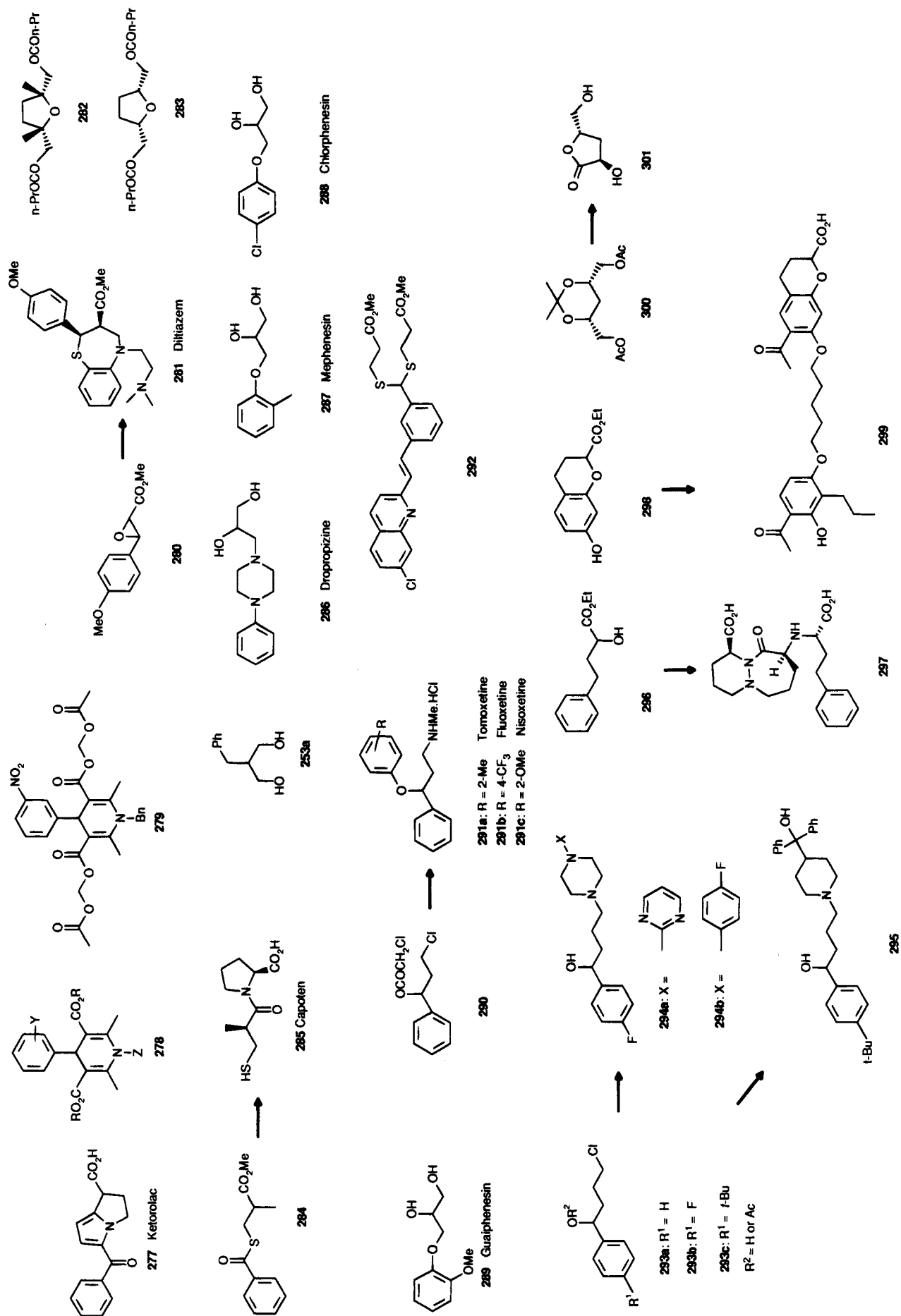


Figure 29.

Furthermore, lipases are inexpensive and in many cases able to fit a wide range of substrate structures which are far removed from their natural substrates. The selectivity of a reaction can be easily improved either by variation of the biocatalyst, the reaction medium, or the structure of the substrate. In addition, lipases are ecologically beneficial natural catalysts. Due to these advantages, it can be expected that lipase-catalyzed reactions will play an increasing role first of all in the preparation of nonracemic chiral biologically active compounds in the laboratory scale as well as in the industrial production.

In the future more insight into the active sites of lipases, the structural requirements of the substrates and the physicochemical properties of the reaction medium will be known. Then, the current often high expenditure required for the screening of lipases, suitable substrates and medium to find optimal conditions should be significantly shortened.

XII. Note Added in Proof

After submission of the original manuscript several relevant papers appeared or came to the knowledge of the author. These are concerning the sections II.E,²⁵⁴ III.C,²⁵⁵ IV,²⁵⁶⁻²⁵⁹ V,²⁶⁰⁻²⁶² VI,²⁶³ VII,²⁶⁴ IX.A.1,²⁶⁵ IX.A.2,^{266,267} IX.A.4,²⁶⁸⁻²⁷¹ X.A,²⁷²⁻²⁷⁴ and X.B.²⁷⁵⁻²⁷⁹

XIII. References

- Jones, J. B. *Tetrahedron* **1986**, *42*, 3351-3403.
- Davies, H. G., Green, R. H., Kelly, D. R., Roberts, S. M., Eds. *Biotransformations in Preparative Organic Chemistry*; Academic Press: London, 1989.
- Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Heidelberg, 1992.
- Poppe, L.; Novák, L. *Selective Biocatalysis*; VCH: Weinheim, 1992.
- Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
- Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071-1140.
- Reidel, A.; Waldmann, H. *J. Prakt. Chem.* **1993**, *335*, 109-127.
- Waldmann, H.; Sebastian, D. *Chem. Rev.* **1994**, *94*, 911-937.
- Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695-707; *Angew. Chem.* **1989**, *101*, 711-724.
- Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049-1072.
- Faber, K.; Riva, S. *Synthesis* **1992**, 895-910.
- Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Enzyme Microb. Technol.* **1993**, *15*, 367-382.
- Theil, F. *Catal. Today* **1994**, *22*, 517-536.
- Szántay, C.; Novák, L. *Synthesis of Prostaglandins*; Akadémiai Kiadó: Budapest, 1978.
- Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977.
- Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533-1566.
- Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875-5878.
- Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298-1299.
- Theil, F.; Schick, H.; Weichert, D.; Tannenberger, K.; Klappach, G. *J. Prakt. Chem.* **1991**, *333*, 497-499.
- Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287-7290.
- Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Häfner, B.; Schwarz, S. *Synthesis* **1988**, 540-541.
- Theil, F.; Schick, H.; Lapitskaya, M. A.; Pivnitsky, K. K. *Liebigs Ann. Chem.* **1991**, 195-200.
- Theil, F.; Schick, H.; Winter, G.; Reck, G. *Tetrahedron* **1991**, *47*, 7569-7582.
- Knoll, A.; Böhme, M.; Merker, S.; Fabian, G.; Häfner, B.; Theil, F. *Chimia* **1991**, *45*, 195-198.
- Jommi, G.; Orsini, F.; Sisti, M.; Verotta, L. *Gazz. Chim. Ital.* **1988**, *118*, 863-864.
- Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377-3381.
- Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.
- Noyori, R.; Suzuki, M. *Angew. Chem.* **1984**, *96*, 854-882; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847-875.
- Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876-877.
- Sugai, T.; Mori, K. *Synthesis* **1988**, 19-22.
- Liu, Z.-Y.; He, L.; Zheng, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2277-2278.
- Washausen, P.; Grebe, H.; Kieslich, K.; Winterfeldt, E. *Tetrahedron Lett.* **1989**, *30*, 3777-3778.
- Cotterill, I. C.; Macfarlane, E. L. A.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3387-3389.
- Klempier, N.; Geymayer, P.; Stadler, P.; Faber, K.; Griengl, H. *Tetrahedron: Asymmetry* **1990**, *1*, 111-118.
- Macfarlane, E. L. A.; Roberts, S. M.; Turner, N. J. *J. Chem. Soc., Chem. Commun.* **1990**, 569-571.
- Suemune, H.; Okano, H.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 1741-1747.
- Suemune, H.; Tanaka, M.; Obaishi, H.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 15-21.
- Sakai, T.; Iida, Y.; Kikuyama, S.; Tsuboi, S.; Utaka, M. *Chem. Lett.* **1991**, 1651-1652.
- Mori, K.; Takeuchi, T. *Tetrahedron* **1988**, *44*, 333-342.
- Weidner, J.; Theil, F.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1991**, 1301-1303.
- Sugahara, T.; Satoh, I.; Yamada, O.; Takano, S. *Chem. Pharm. Bull.* **1991**, *39*, 2758-2760.
- Weidner, J.; Theil, F.; Schick, H. *Tetrahedron: Asymmetry* **1994**, *5*, 751-754.
- Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966-967.
- Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838-839.
- Petzoldt, K.; Dahl, H.; Skuballa, W.; Gottwald, M. *Liebigs Ann. Chem.* **1990**, 1087-1091.
- Murata, M.; Ikoma, S.; Achiwa, K. *Chem. Pharm. Bull.* **1990**, *38*, 2329-2331.
- Djadchenko, M. A.; Pivnitsky, K. K.; Theil, F.; Schick, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2001-2002.
- Kalaritis, P.; Regenye, R. W.; Partridge, J. J.; Coffen, D. L. *J. Org. Chem.* **1990**, *55*, 812-815.
- Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623.
- Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670.
- 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.
- Le Grand, D. M.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1751-1752.
- Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1483-1487.
- Mekrami, M.; Sicsic, S. *Tetrahedron: Asymmetry* **1992**, *3*, 431-436.
- Tanaka, M.; Yoshioka, M.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 981-996.
- Tanaka, M.; Yoshioka, M.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1454-1455.
- Mohar, B.; Štimac, A.; Kobe, J. *Tetrahedron: Asymmetry* **1994**, *5*, 863-878.
- Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267-278.
- Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551-554.
- Dyatkina, N.; Costisella, B.; Theil, F.; von Janta-Lipinski, M. *Tetrahedron Lett.* **1994**, *35*, 1961-1964.
- Dyatkina, N.; Theil, F.; von Janta-Lipinski, M. *Tetrahedron* **1995**, *51*, 761-772.
- Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. *Synlett* **1994**, 491-493.
- Johnson, C. R.; Esker, J. L.; Van Zandt, M. C. *J. Org. Chem.* **1994**, *59*, 5854-5855.
- Terao, Y.; Akamatsu, M.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 823-825.
- Ohsawa, K.; Shiozawa, T.; Achiwa, K.; Terao, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1906-1909.
- Sells, T. B.; Nair, V. *Tetrahedron Lett.* **1992**, *33*, 7639-7642.
- Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117-138.
- Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2605-2607.
- Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 589-592.
- Saville-Stones, E. A.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Ford, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2603-2604.
- Saville-Stones, E. A.; Turner, R. M.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Carver, D. S. *Tetrahedron* **1994**, *50*, 6695-6704.
- Henly, R.; Elie, C. J. J.; Buser, H. P.; Ramos, G.; Moser, H. E. *Tetrahedron Lett.* **1993**, *34*, 2923-2926.
- Csuk, R.; Dörr, P. *Tetrahedron: Asymmetry* **1994**, *5*, 269-276.
- Merlo, V.; Reece, F. J.; Roberts, S. M.; Gregson, M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1717-1718.

- (75) Merlo, V.; Roberts, S. M.; Storer, R.; Bethell, R. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1477–1481.
- (76) Hoong, L. K.; Strange, L. E.; Liotta, D. C.; Koszalka, G. W.; Burns, C. L.; Schinazi, R. F. *J. Org. Chem.* **1992**, *57*, 5563–5565.
- (77) Coe, D. M.; Garofalo, A.; Roberts, S. M.; Storer, R.; Thorpe, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3061–3063.
- (78) Chen, X.; Siddiqui, S. M.; Schneller, S. W. *Tetrahedron Lett.* **1992**, *33*, 2249–2252.
- (79) Baschang, G.; Inderbitzin, W. *Tetrahedron: Asymmetry* **1992**, *3*, 193–196.
- (80) Eichberger, G.; Penn, G.; Faber, K.; Griengl, H. *Tetrahedron Lett.* **1986**, *27*, 2843–2844.
- (81) Oberhauser, T.; Bodenteich, M.; Faber, K.; Penn, G.; Griengl, H. *Tetrahedron* **1987**, *43*, 3931–3944.
- (82) Baumgartner, H.; Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1988**, *29*, 5745–5746.
- (83) Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1986**, *27*, 4291–4292.
- (84) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Palmer, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 313–314.
- (85) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Taylor, S. J. C.; Xiong, H. *Bioorg. Med. Chem.* **1994**, *2*, 387–394.
- (86) Nakano, H.; Okuyama, Y.; Iwasa, K.; Hongo, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1155–1156.
- (87) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164–1171.
- (88) Carrea, G.; Danieli, B.; Palmisano, G.; Riva, S.; Santagostino, M. *Tetrahedron: Asymmetry* **1992**, *3*, 775–784.
- (89) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett.* **1992**, *33*, 5389–5390.
- (90) Chênevert, R.; Dickman, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1021–1024.
- (91) Ng-Youn-Chen, M. C.; Serreqi, A. N.; Huang, Q.; Kazlauskas, R. J. *J. Org. Chem.* **1994**, *59*, 2075–2081.
- (92) Bracher F.; Papke T. *Tetrahedron: Asymmetry* **1994**, *5*, 1653–1656.
- (93) Guanti, G.; Banfi, L.; Brusco, S.; Narisano, E. *Tetrahedron: Asymmetry* **1994**, *5*, 537–540.
- (94) Izumi, T.; Nakamura, T.; Eda, Y. *J. Chem. Tech. Biotechnol.* **1993**, *57*, 175–180.
- (95) Toyooka, N.; Nishino, A.; Momose, T. *Tetrahedron Lett.* **1993**, *34*, 4539–4540.
- (96) Van der Eycken, J.; Vandewalle, M.; Heinemann, G.; Laumen, K.; Schneider, M. P.; Kredel, J.; Sauer, J. *J. Chem. Soc., Chem. Commun.* **1989**, 306–308.
- (97) Bovara, R.; Carrea, G.; Ferrara, L.; Riva, S. *Tetrahedron: Asymmetry* **1991**, *2*, 931–938.
- (98) Höning, H.; Seuffer-Wasserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841–3850.
- (99) Brievara, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068–1075.
- (100) Patel, R. N.; Banerjee, A.; Ko, R. Y.; Howell, J. M.; Li, W.-S.; Comezoglu, F. T.; Partyka, R. A.; Szarka, L. *Biotechnol. Appl. Biochem.* **1994**, *20*, 23–33.
- (101) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287–1289.
- (102) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271–272.
- (103) Dumortier, L.; Liu, P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243–245.
- (104) Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228–230.
- (105) Pingli, L.; Vandewalle, M. *Tetrahedron* **1994**, *50*, 7061–7074.
- (106) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006–1007.
- (107) Johnson, C. R.; Plé, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388–390.
- (108) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597–2600.
- (109) Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414–9418.
- (110) Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910–2912.
- (111) Johnson, C. R.; Golebiowski, A.; Braun, M. P.; Sundram, H. *Tetrahedron Lett.* **1994**, *35*, 1833–1834.
- (112) Höning, H.; Seuffer-Wasserthal, P.; Stütz, A. E.; Zenz, E. *Tetrahedron Lett.* **1989**, *30*, 811–812.
- (113) Ling, L.; Watanabe, Y.; Akiyama, T.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 1911–1914.
- (114) Ling, L.; Ozaki, S. *Tetrahedron Lett.* **1993**, *34*, 2501–2504.
- (115) Ling, L.; Li, X.; Watanabe, Y.; Akiyama, T.; Ozaki, S. *Bioorg. Med. Chem.* **1993**, *1*, 155–159.
- (116) Andersch, P.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2135–2138.
- (117) Berkowitz, D. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 5497–5500.
- (118) Drueckhammer, D. G.; Barbas, C. F., III; Nozaki, K.; Wong, C.-H.; Wood, C. Y.; Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607–1611.
- (119) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F., III; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924–3927.
- (120) Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1991**, *32*, 5701–5704.
- (121) Suemune, H.; Harabe, T.; Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 4345–4354.
- (122) VanMiddlesworth, F.; Patel, D. V.; Donaubaauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2996–2997.
- (123) Patel, D. V.; VanMiddlesworth, F.; Donaubaauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603–4614.
- (124) Ozegowski, R.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1993**, *4*, 695–698.
- (125) Ozegowski, R.; Kunath, A.; Schick, H. *J. Prakt. Chem.* **1994**, *336*, 544–546.
- (126) Rocco, V. P.; Danishefsky, S. J.; Schulte, G. K. *Tetrahedron Lett.* **1991**, *32*, 6671–6674.
- (127) Yamashita, D. S.; Rocco, V. P.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 6667–6670.
- (128) Mori, K.; Takahashi, Y. *Liebigs Ann. Chem.* **1991**, 1057–1065.
- (129) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5241–5244.
- (130) Akita, H.; Chen, C. Y.; Nagumo, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1207–1210.
- (131) Akita, H.; Umezawa, I.; Nozawa, M.; Nagumo, S. *Tetrahedron: Asymmetry* **1993**, *4*, 757–760.
- (132) Nokami, J.; Ohkura, M.; Dan-Oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409–2412.
- (133) Casy, G.; Gorins, G.; McCague, R.; Olivo, H. F.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1085–1086.
- (134) Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron* **1993**, *49*, 7385–7392.
- (135) Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267–270.
- (136) Guanti, G.; Banfi, L.; Schmid, G. *Tetrahedron Lett.* **1994**, *35*, 4239–4242.
- (137) Ottolina, G.; Carrea, G.; Riva, S. *J. Org. Chem.* **1990**, *55*, 2366–2369.
- (138) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437–475.
- (139) Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250–7251.
- (140) Hamaguchi, S.; Hasegawa, J.; Kawaharada, H.; Watanabe, K. *Agric. Biol. Chem.* **1984**, *48*, 2055–2059.
- (141) Hamaguchi, S.; Yamamura, H.; Hasegawa, J.; Watanabe, K. *Agric. Biol. Chem.* **1985**, *49*, 1509–1511.
- (142) Hamaguchi, S.; Asada, M.; Hasegawa, J.; Watanabe, K. *Agric. Biol. Chem.* **1985**, *49*, 1661–1667.
- (143) Hamaguchi, S.; Asada, M.; Hasegawa, J.; Watanabe, K. *Agric. Biol. Chem.* **1984**, *48*, 2331–2337.
- (144) Breitgoff, D.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523–1524.
- (145) Kerscher, V.; Kreiser, W. *Tetrahedron Lett.* **1987**, *28*, 531–534.
- (146) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200–7205.
- (147) Terao, Y.; Murata, M.; Achiwa, K.; Nishio, T.; Akamatsu, M.; Kamimura, M. *Tetrahedron Lett.* **1988**, *29*, 5173–5176.
- (148) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897–4901.
- (149) Gelo, M.; Šunjić, V. *Synthesis* **1993**, 855–857.
- (150) Chen, C.-S.; Liu, Y.-C.; Marsella, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2559–2561.
- (151) Kim, M. J.; Choi, Y. K. *J. Org. Chem.* **1992**, *57*, 1605–1607.
- (152) Bosetti, A.; Bianchi, D.; Cesti, P.; Golini, P.; Spezia, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2395–2398.
- (153) Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *Tetrahedron Lett.* **1993**, *34*, 305–306.
- (154) Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388–393.
- (155) Hérradón, B.; Cueto, S.; Mercuende, A.; Valverde, S. *Tetrahedron: Asymmetry* **1993**, *4*, 845–864.
- (156) De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646–2650.
- (157) Kamal, A.; Rao, M. V. *Tetrahedron: Asymmetry* **1991**, *2*, 751–754.
- (158) Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1992**, *57*, 6003–6005.
- (159) Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1991**, *56*, 5372–5375.
- (160) Ader, U.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 521–524.
- (161) Shieh, W.-R.; Gou, D.-M.; Chen, C.-S. *J. Chem. Soc., Chem. Commun.* **1991**, 651–653.
- (162) Wang, Y.-F.; Chen, S.-T.; Liu, K. K.-C.; Wong, C.-H. *Tetrahedron Lett.* **1989**, *30*, 1917–1920.
- (163) Matsuo, N.; Ohno, N. *Tetrahedron Lett.* **1985**, *26*, 5533–5534.
- (164) Kamal, A.; Damayanthi, Y.; Rao, M. V. *Tetrahedron: Asymmetry* **1992**, *3*, 1361–1364.
- (165) Kamal, A.; Rao, M. V. *Tetrahedron: Asymmetry* **1994**, *5*, 1881–1882.
- (166) Brevet, J.-L.; Mori, K. *Synthesis* **1992**, 1007–1012.

- (167) Mori, K.; Argade, N. P. *Liebigs Ann. Chem.* **1994**, 695–700.
- (168) Mori, K.; Amaike, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2727–2733.
- (169) Mori, K.; Amaike, M.; Watanabe, H. *Liebigs Ann. Chem.* **1993**, 1287–1294.
- (170) Mori, K.; Kiyota, H. *Liebigs Ann. Chem.* **1992**, 989–992.
- (171) Grandjean, D.; Pale, P.; Chucho, J. *Tetrahedron* **1991**, 47, 1215–1230.
- (172) Kakeya, H.; Sakai, N.; Sugai, T.; Ohta, H. *Agric. Biol. Chem.* **1991**, 55, 1877–1881.
- (173) Dominguez, E.; Carretero, J. C.; Fernandez-Mayoralas, A.; Conde, S. *Tetrahedron Lett.* **1991**, 32, 5159–5162.
- (174) Ramaswamy, S.; Oehlschlager, A. C. *Tetrahedron* **1991**, 47, 1157–1162.
- (175) Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Rama, F. *Tetrahedron Lett.* **1988**, 29, 2455–2458.
- (176) Jacobs, H. K.; Mueller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, 48, 8891–8898.
- (177) Mori, K.; Ishigami, K. *Liebigs Ann. Chem.* **1992**, 1195–1198.
- (178) Sugai, T.; Kakeya, H.; Ohta, H. *J. Org. Chem.* **1990**, 55, 4643–4647.
- (179) Classen, A.; Wershofen, S.; Yusufoglu, A.; Scharf, H.-D. *Liebigs Ann. Chem.* **1987**, 629–632.
- (180) Matsumoto, K.; Suzuki, N.; Ohta, H. *Tetrahedron Lett.* **1990**, 31, 7163–7166.
- (181) Mori, K.; Tomioka, H. *Liebigs Ann. Chem.* **1992**, 1011–1017.
- (182) Bonini, C.; Pucci, P.; Raccioppi, R.; Viggiani, L. *Tetrahedron: Asymmetry* **1992**, 3, 29–32.
- (183) Sugai, T.; Ohsawa, S.; Yamada, H.; Ohta, H. *Synthesis* **1990**, 1112–1114.
- (184) Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T. *Tetrahedron* **1991**, 47, 6223–6230.
- (185) Morgan, B.; Oehlschlager, A. C.; Stokes, T. M. *J. Org. Chem.* **1992**, 57, 3231–3236.
- (186) Naoshima, Y.; Kamezawa, M.; Tachibana, H.; Munakata, Y.; Fujita, T.; Kihara, K.; Raku, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 557–561.
- (187) Naoshima, Y.; Munakata, Y.; Yoshida, S.; Funai, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 549–553.
- (188) Morgan, B.; Oehlschlager, A. C.; Stokes, T. M. *Tetrahedron* **1991**, 47, 1611–1620.
- (189) Kamezawa, M.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *J. Chem. Ecol.* **1994**, 20, 1057–1061.
- (190) Sonnet, P. E.; Baillargeon, M. W. *J. Chem. Ecol.* **1987**, 13, 1279–1292.
- (191) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *J. Org. Chem.* **1987**, 52, 256–260.
- (192) Stokes, T. M.; Oehlschlager, A. C. *Tetrahedron Lett.* **1987**, 28, 2091–2094.
- (193) Bovara, R.; Carrea, G.; Ottolina, G.; Riva, S. *Biotechnol. Lett.* **1993**, 15, 169–174.
- (194) Mori, K.; Ogita, H. *Liebigs Ann. Chem.* **1994**, 1065–1068.
- (195) Ramaswamy, S.; Oehlschlager, A. C. *Tetrahedron* **1991**, 47, 1145–1156.
- (196) Sugai, T.; Sakuma, D.; Kobayashi, N.; Ohta, H. *Tetrahedron* **1991**, 35, 7237–7244.
- (197) Cambou, B.; Klivanov, A. M. *Appl. Biochem. Biotechnol.* **1984**, 9, 255–260.
- (198) Kirchner, G.; Scollar, M. P.; Klivanov, A. M. *J. Am. Chem. Soc.* **1985**, 107, 7072–7076.
- (199) Holmberg, E.; Hult, K. *Biocatalysis* **1992**, 5, 289–296.
- (200) Cambou, B.; Klivanov, A. M. *Biotechnol. Bioeng.* **1984**, 26, 1449–1454.
- (201) Deroncour, R.; Azerad, R. *Tetrahedron Lett.* **1987**, 28, 4661–4664.
- (202) Wu, S.-H.; Chu, F.-Y.; Wang, K.-T. *Bioorg. Med. Chem. Lett.* **1991**, 1, 339–342.
- (203) Chênevert, R.; D'Astous, L. *Can. J. Chem.* **1988**, 66, 1219–1222.
- (204) Guo, Z.-W.; Sih, C. J. *J. Am. Chem. Soc.* **1989**, 111, 6836–6841.
- (205) Hirohara, H.; Mitsuda, S.; Ando, E.; Komaki, R. In *Biocatalysts in Organic Syntheses*; Tramper, J., van der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985; pp 119–134.
- (206) Danda, H.; Furukawa, Y.; Umemura, T. *Synlett* **1991**, 441–442.
- (207) Rejzek, M.; Wimmer, Z.; Zarevúcka, M.; Šaman, D.; Pavlik, M.; Ricániková, M. *Tetrahedron: Asymmetry* **1994**, 5, 1501–1512.
- (208) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, 56, 4050–4052.
- (209) Henkel, B.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1992**, 809–811.
- (210) Henkel B.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1993**, 4, 153–156.
- (211) Henkel, B.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1994**, 5, 17–18.
- (212) Bonini, C.; Raccioppi, R.; Viggiani, L.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1993**, 4, 793–805.
- (213) Bonini, C.; Raccioppi, R.; Righi, G.; Viggiani, L. *J. Org. Chem.* **1993**, 58, 802–803.
- (214) McCague, R.; Olivo, H. F.; Roberts, S. M. *Tetrahedron Lett.* **1993**, 34, 3785–3786.
- (215) Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1993**, 805–808.
- (216) Sugai, T.; Kakeya, H.; Ohta, H. *Tetrahedron* **1990**, 46, 3463–3468.
- (217) Ferraboschi, P.; Grisenti, P.; Casati, S.; Santaniello, E. *Synlett* **1994**, 754–756.
- (218) Montforts, F.-P.; Gesing-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, 72, 1852–1859.
- (219) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1638–1639.
- (220) Pai, Y. C.; Fang, J.-M.; Wu, S.-H. *J. Org. Chem.* **1994**, 59, 6018–6025.
- (221) Sih, C. J.; Gu, R.-L. In *Microbial Reagents in Organic Synthesis*; Servi, S., Ed.; Kluwer Academic Publishers: Dordrecht, 1992; pp 79–92.
- (222) Gu, R.-L.; Sih, C. J. *Tetrahedron Lett.* **1990**, 31, 3283–3286.
- (223) Gu, R.-L.; Sih, C. J. *Tetrahedron Lett.* **1990**, 31, 3287–3290.
- (224) Anderson, J. C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, 35, 2087–2090.
- (225) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1989**, 957–962.
- (226) Wang, Y.-F.; Sih, C. J. *Tetrahedron Lett.* **1984**, 25, 4999–5002.
- (227) Mizuno, K.; Sakuda, S.; Nihira, T.; Yamada, Y. *Tetrahedron* **1994**, 50, 10849–10858.
- (228) Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Ricci, M. *J. Org. Chem.* **1988**, 53, 104–107.
- (229) Tsuboi, S.; Sakamoto, J.-I.; Sakai, T.; Utaka, M. *Chem. Lett.* **1989**, 1427–1428.
- (230) Chan, C.; Cox, P. B.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1988**, 971–972.
- (231) Bhalerao, U. T.; Dasaradhi, L.; Neelakantan, P.; Fadnavis, N. W. *J. Chem. Soc., Chem. Commun.* **1991**, 1197–1198.
- (232) Barnett, C. J.; Wilson, T. M. *Tetrahedron Lett.* **1989**, 30, 6291–6294.
- (233) Hauser, F. M.; Sengupta, D.; Corlett, S. A. *J. Org. Chem.* **1994**, 59, 1967–1969.
- (234) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Synlett* **1992**, 410–412.
- (235) Cotterill, I. C.; Dorman, G.; Faber, K.; Jaouhari, R.; Roberts, S. M.; Scheinmann, F.; Spreitz, J.; Sutherland, A. G.; Winders, J. A.; Wakefield, B. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1661–1663.
- (236) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1994**, 929–930.
- (237) Guanti, G.; Banfi, L.; Narisano, E.; Zannetti, M. T. *J. Org. Chem.* **1993**, 58, 1508–1514.
- (238) Fülling, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, 109, 2845–2846.
- (239) Ebiike, H.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1991**, 32, 5805–5808.
- (240) Holdgrün, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, 32, 3465–3468.
- (241) Gentile, A.; Giordano, C.; Fuganti, C.; Ghirotto, L.; Servi, S. *J. Org. Chem.* **1992**, 57, 6635–6637.
- (242) Kanerva, L. T.; Sundholm, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1385–1389.
- (243) Estermann, H.; Prasad, K.; Shapiro, M. J.; Repic, O.; Hardtmann, G. E.; Bolsterli, J. J.; Walkinshaw, M. D. *Tetrahedron Lett.* **1990**, 31, 445–448.
- (244) Gu, Q.-M.; Reddy, D. R.; Sih, C. J. *Tetrahedron Lett.* **1986**, 27, 5203–5206.
- (245) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, 30, 6189–6192.
- (246) Atsuami, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Ohkubo, M.; Yonezawa, T.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Tetrahedron Lett.* **1990**, 31, 1601–1604.
- (247) Bianchi, D.; Bosetti, A.; Cesti, P.; Golini, P. *Tetrahedron Lett.* **1992**, 33, 3231–3234.
- (248) Theil, F.; Ballschuh, S.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1991**, 2, 1031–1034.
- (249) Schneider, M. P.; Goergens, U. *Tetrahedron: Asymmetry* **1992**, 3, 525–528.
- (250) 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. Org. Chem.* **1990**, 55, 6252–6259.
- (251) Hanson, R. L.; Banerjee, A.; Comezoglu, F. T.; Mirfakhrae, K. D.; Patel, R. N.; Szarka, L. J. *Tetrahedron: Asymmetry* **1994**, 5, 1925–1934.
- (252) Bianchi, D.; Moraschini, P.; Bosetti, A.; Cesti, P. *Tetrahedron: Asymmetry* **1994**, 5, 1917–1920.
- (253) Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1989**, 37, 1650–1652.
- (254) Node, M.; Inoue, T.; Araki, M.; Nakamura, D.; Nishide, K. *Tetrahedron Lett.* **1995**, 36, 2255–2256.
- (255) Csuk, R.; Dörr, P. *Tetrahedron* **1995**, 51, 5789–5798.
- (256) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, 60, 615–623.
- (257) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, 60, 2506–2513.
- (258) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, 36, 3715–3718.
- (259) Palmisano, G.; Santagostino, M.; Riva, S.; Sisti, M. *Tetrahedron: Asymmetry* **1995**, 6, 1229–1232.
- (260) Witschel, M. C.; Bestmann, H. J. *Tetrahedron Lett.* **1995**, 36, 3325–3328.

- (261) Johnson, C. R.; Xu, Y.; Nicolaou, K. C.; Yang, Z.; Guy, R. K.; Dong, J. G.; Berova, N. *Tetrahedron Lett.* **1995**, *36*, 3291–3294.
- (262) Yamane, T.; Takahashi, M.; Ogasawara, K. *Synthesis* **1995**, 444–448.
- (263) Johnson, C. R.; Nerurkar, B. M.; Golebiowski, A.; Sundram, H.; Esker, J. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1139–1140.
- (264) Guanti, G.; Riva, R. *Tetrahedron Lett.* **1995**, *36*, 3933–3936.
- (265) Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1995**, 697–698.
- (266) Kamezawa, M.; Raku, T.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 598–599.
- (267) Högberg, H.-E.; Berglund, P.; Edlund, H.; Fägerhaag, J.; Hedenström, E.; Lundh, M.; Nordin, O.; Servi, S.; Vörde, C. *Catal. Today* **1994**, *22*, 591–606.
- (268) Naoshima, Y.; Munakata, Y.; Funai, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 999–1000.
- (269) Kamezawa, M.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1962–1963.
- (270) Pawar, A. S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1995**, *6*, 463–468.
- (271) Henkel, B.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1995**, 921–923.
- (272) Barnett, C. J.; Wilson, T. M.; Wendel, S. R.; Winningham, M. J.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 7038–7045.
- (273) Bauermeister, H.; Riechers, H.; Schomburg, D.; Washausen, P.; Winterfeldt, E. *Angew. Chem.* **1991**, *103*, 207–208; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 191–192.
- (274) Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, *36*, 4185–4188.
- (275) Colton, I. J.; Ahmed, S. N.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 212–217.
- (276) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 505–508.
- (277) Patel, R. N.; Banerjee, A.; McNamee, C. G.; Szarka, L. J. *Tetrahedron: Asymmetry* **1995**, *6*, 123–130.
- (278) Hirose, Y.; Kariya, K.; Nakanishi, Y.; Kurono, Y.; Achiwa, K. *Tetrahedron Lett.* **1995**, *36*, 1063–1066.
- (279) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Wang, H.; Ganguly, A. K.; Morgan, B.; Zaks, A.; Puar, M. S. *Tetrahedron Lett.* **1995**, *36*, 1787–1790.

CR9411233