

# Biocatalysis in Organic Synthesis 1

Preface .....	V
Volume Editors' Preface .....	IX
Abstracts .....	XIII
Table of Contents .....	XXV
<b>1.1 Introduction .....</b>	<b>1</b>
<b>1.1.1 Historical Perspectives: Paving the Way for the Future</b> S. Servi, D. Tessaro, and F. Hollmann .....	1
<b>1.1.2 Enzyme Classification and Nomenclature and Biocatalytic Retrosynthesis</b> A. Liese and L. Pesci .....	41
<b>1.1.3 Enzyme Sources and Selection of Biocatalysts</b> R. Lauchli and D. Rozzell .....	75
<b>1.2 Strategies and Methods in Biocatalysis</b> A. Díaz-Rodríguez and I. Lavandera .....	95
<b>1.3 Hydrolysis and Transacylation: Esterases, Lipases, Phosphatases, and Phosphoryl Transferases</b> M. Bertau and G. E. Jeromin .....	129
<b>1.3.1 Resolution of Alcohols, Acids, and Esters by Hydrolysis</b> M. Bertau and G. E. Jeromin .....	129
<b>1.3.2 Resolution of Alcohols, Amines, Acids, and Esters by Nonhydrolytic Processes</b> M. Rodríguez-Mata and V. Gotor-Fernández .....	189
<b>1.3.3 Transphosphorylation</b> R. Wever, L. Babich, and A. F. Hartog .....	223
<b>1.4 Nitrile and Amide Hydrolysis and Enzymatic Synthesis of Amides and Peptides .....</b>	<b>255</b>
<b>1.4.1 Hydrolysis of Nitriles to Amides</b> Y. Asano .....	255
<b>1.4.2 Hydrolysis of Nitriles to Carboxylic Acids</b> L. Martínková and A. B. Veselá .....	277

<b>1.4.3</b>	<b>Hydrolysis of Amides</b>	303
M. Hall, K. Faber, and G. Tasnádi	.....	
<b>1.4.4</b>	<b>Enzymatic Synthesis of Amides</b>	329
J. W. Schmidberger, L. J. Hepworth, A. P. Green, and S. L. Flitsch	.....	
<b>1.4.5</b>	<b>Hydrolysis of Hydantoins, Dihydropyrimidines, and Related Compounds</b>	373
C. Slomka, U. Engel, C. Syldatk, and J. Rudat	.....	
<b>1.5</b>	<b>Isomerizations: Racemization, Epimerization, and <i>E/Z</i>-Isomerization</b>	415
K. Faber and S. M. Glueck	.....	
<b>1.6</b>	<b>Glycosides</b>	483
<b>1.6.1</b>	<b>Glycosidases and Glycosynthases</b>	483
B. Cobucci-Ponzano and M. Moracci	.....	
<b>1.6.2</b>	<b>Glycosyltransferases</b>	507
J. Voglmeir and S. L. Flitsch	.....	
<b>Keyword Index</b>	.....	543
<b>Author Index</b>	.....	575
<b>Abbreviations</b>	.....	603

## Table of Contents

<b>1.1</b>	<b>Introduction</b>	
<b>1.1.1</b>	<b>Historical Perspectives: Paving the Way for the Future</b>	
	S. Servi, D. Tessaro, and F. Hollmann	
<b>1.1.1</b>	<b>Historical Perspectives: Paving the Way for the Future</b>	1
<b>1.1.1.1</b>	The Chiral-Synthon Era, Dominated by Hydrolytic Enzymes	2
<b>1.1.1.2</b>	Beyond Chiral Synths	5
<b>1.1.1.2.1</b>	Large-Scale Processes	5
<b>1.1.1.2.2</b>	Processes with Cofactor Recycling	8
<b>1.1.1.2.2.1</b>	L- <i>tert</i> -Leucine	9
<b>1.1.1.2.2.2</b>	2-Hydroxy-4-phenylbutanoic Acid	9
<b>1.1.1.2.2.3</b>	Baeyer–Villiger Monooxygenase Catalyzed Oxyfunctionalizations	10
<b>1.1.1.2.2.4</b>	Transaminase-Catalyzed Reductive Aminations	11
<b>1.1.1.2.3</b>	Reverse Hydrolysis Conditions	13
<b>1.1.1.2.3.1</b>	β-Lactam Antibiotic Synthesis	13
<b>1.1.1.2.3.2</b>	Aspartame	15
<b>1.1.1.2.3.3</b>	Lipase-Catalyzed Esterification	15
<b>1.1.1.2.3.4</b>	Phosphate-Transferring Enzymes	17
<b>1.1.1.3</b>	Microbial Reagents	20
<b>1.1.1.3.1</b>	Training with Baker's Yeast	21
<b>1.1.1.3.1.1</b>	Reduction of β-Keto Esters	21
<b>1.1.1.3.1.2</b>	Reduction of C=C Bonds	24
<b>1.1.1.3.1.3</b>	Acyloin Condensation and Other C–C Bond Forming Reactions	27
<b>1.1.1.3.1.4</b>	Kinetic Resolution of Esters	29
<b>1.1.1.4</b>	Enzyme-Catalyzed C–C Bond Forming Reactions	30
<b>1.1.1.4.1</b>	Cyanohydrins through Enzyme Catalysis	30
<b>1.1.1.4.1.1</b>	Oxynitrilase (Hydroxynitrile Lyase)	30
<b>1.1.1.4.1.2</b>	Kinetic Resolution of Cyanohydrins	32
<b>1.1.1.4.2</b>	Aldolases	33
<b>1.1.1.5</b>	Conclusions	33
<b>1.1.2</b>	<b>Enzyme Classification and Nomenclature and Biocatalytic Retrosynthesis</b>	
	A. Liese and L. Pesci	
<b>1.1.2</b>	<b>Enzyme Classification and Nomenclature and Biocatalytic Retrosynthesis</b>	41
<b>1.1.2.1</b>	Recommended, Systematic Names and EC Numbers of Enzymes	41
<b>1.1.2.1.1</b>	Structure of the Classification and Nomenclature Systems	41
<b>1.1.2.2</b>	Braunschweig Enzyme Database (BRENDA): A Comprehensive Web Platform for Enzyme-Based Research	45

<b>1.1.2.3</b>	Possible Retrosynthetic Approaches .....	48
<b>1.1.2.3.1</b>	Substrate Promiscuity .....	49
<b>1.1.2.3.2</b>	Alkanes .....	49
<b>1.1.2.3.3</b>	Alkenes .....	50
<b>1.1.2.3.4</b>	Amines .....	50
<b>1.1.2.3.5</b>	Alcohols .....	52
<b>1.1.2.3.6</b>	Aldehydes and Ketones .....	54
<b>1.1.2.3.7</b>	Epoxides .....	55
<b>1.1.2.3.8</b>	Carboxylic Acids .....	55
<b>1.1.2.3.9</b>	Esters and Amides .....	57
<b>1.1.2.3.10</b>	Imines .....	58
<b>1.1.2.3.11</b>	Amino Acids .....	58
<b>1.1.2.3.12</b>	$\alpha$ -Hydroxy Acids .....	59
<b>1.1.2.3.13</b>	$\alpha$ -Hydroxy Ketones .....	60
<b>1.1.2.3.14</b>	$\beta$ -Hydroxy Aldehydes, $\beta$ -Hydroxy Ketones, and $\beta$ -Hydroxy Carboxylic Acids .....	61
<b>1.1.2.3.15</b>	Cyanohydrins, Hemithioacetals, and Hemiaminals .....	62
<b>1.1.2.3.16</b>	Sulfoxides and Sulfones .....	62
<b>1.1.2.3.17</b>	Halides .....	62
<b>1.1.2.3.18</b>	Functionalization of Arenes .....	63
<b>1.1.2.3.19</b>	Vicinal Diols .....	64
<b>1.1.2.3.20</b>	Cyclic Compounds .....	65
<b>1.1.2.3.21</b>	Carbohydrates .....	65
<b>1.1.2.3.22</b>	Peroxides .....	66
<b>1.1.2.3.23</b>	Polymers .....	67
<b>1.1.2.3.24</b>	Isomerization .....	67
<b>1.1.2.3.25</b>	Example: Biocatalytic Retrosynthesis for the <i>syn</i> -3,5-Dihydroxy Acid Side Chain of Atorvastatin .....	68

---

**1.1.3 Enzyme Sources and Selection of Biocatalysts**

R. Lauchli and D. Rozzell

<b>1.1.3</b>	<b>Enzyme Sources and Selection of Biocatalysts .....</b>	75
<b>1.1.3.1</b>	Enzyme Suppliers .....	75
<b>1.1.3.2</b>	Natural Biocatalyst Diversity .....	78
<b>1.1.3.3</b>	Biocatalyst Engineering .....	82
<b>1.1.3.3.1</b>	Sitagliptin Synthesis .....	83
<b>1.1.3.3.2</b>	Telaprevir and Boceprevir Synthesis .....	84
<b>1.1.3.3.3</b>	Odanacatib Synthesis .....	85
<b>1.1.3.4</b>	Strategies for Selecting Enzymes .....	85
<b>1.1.3.5</b>	Future Outlook .....	86
<b>1.1.3.6</b>	Tables of Biocatalyst Suppliers and Biocatalyst Engineering Companies .....	87
<b>1.1.3.6.1</b>	European Companies .....	87
<b>1.1.3.6.2</b>	North American Companies .....	89
<b>1.1.3.6.3</b>	Asian Companies .....	91

**1.2 Strategies and Methods in Biocatalysis**

A. Díaz-Rodríguez and I. Lavandera

---

<b>1.2</b>	<b>Strategies and Methods in Biocatalysis</b>	95
<b>1.2.1</b>	Stereoselective Transformations	96
<b>1.2.1.1</b>	Starting from Prochiral and <i>meso</i> -Compounds: Desymmetrizations	97
<b>1.2.1.2</b>	Starting from Racemates	98
<b>1.2.1.2.1</b>	Kinetic Resolutions	99
<b>1.2.1.2.2</b>	Parallel Kinetic Resolutions	102
<b>1.2.1.2.3</b>	Deracemizations	103
<b>1.2.1.2.4</b>	Enantioconvergent Processes	105
<b>1.2.1.2.5</b>	Dynamic Systems	107
<b>1.2.1.3</b>	Other Asymmetric Transformations	113
<b>1.2.2</b>	Shortening the Routes: One-Pot Cascade and Tandem Systems	114
<b>1.2.2.1</b>	Multienzymatic Protocols	115
<b>1.2.2.2</b>	Combining Enzymes with Organocatalysts or Metal Catalysts	119
<b>1.2.3</b>	Conclusions and Outlook	123

**1.3 Hydrolysis and Transacylation: Esterases, Lipases, Phosphatases, and Phosphoryl Transferases****1.3.1 Resolution of Alcohols, Acids, and Esters by Hydrolysis**

M. Bertau and G. E. Jeromin

---

<b>1.3.1</b>	<b>Resolution of Alcohols, Acids, and Esters by Hydrolysis</b>	129
<b>1.3.1.1</b>	The Catalytic Triad	129
<b>1.3.1.2</b>	The Oxyanion Hole	133
<b>1.3.1.3</b>	Characteristics of Hydrolases and Their Fields of Application	134
<b>1.3.1.3.1</b>	Differences between Esterases and Lipases	134
<b>1.3.1.3.2</b>	Interfacial Activation of Lipases	135
<b>1.3.1.3.3</b>	Esterases	136
<b>1.3.1.3.3.1</b>	Porcine Liver Esterase	136
<b>1.3.1.3.3.2</b>	Horse Liver Esterase	136
<b>1.3.1.3.3.3</b>	Acetylcholinesterase	138
<b>1.3.1.3.3.4</b>	Cholesterol Esterase	139
<b>1.3.1.3.3.5</b>	Penicillin Acylase	141
<b>1.3.1.3.3.6</b>	Microbial Esterases and Whole-Cell Biotransformations	141
<b>1.3.1.3.4</b>	Lipases	143
<b>1.3.1.3.4.1</b>	Porcine Pancreatic Lipase	144
<b>1.3.1.3.4.2</b>	<i>Candida rugosa</i> Lipase	144
<b>1.3.1.3.4.3</b>	<i>Rhizomucor miehei</i> Lipase	144
<b>1.3.1.3.4.4</b>	<i>Candida antarctica</i> Lipase B	144
<b>1.3.1.3.4.5</b>	<i>Pseudomonas cepacia</i> Lipase	144
<b>1.3.1.3.4.6</b>	Lipases in Glyceride Chemistry	144
<b>1.3.1.3.4.7</b>	Industrial Applications	147
<b>1.3.1.3.5</b>	Further Hydrolases	147

<b>1.3.1.3.6</b>	Formate Dehydrogenase .....	148
<b>1.3.1.4</b>	Stereochemistry of Hydrolases .....	151
<b>1.3.1.4.1</b>	Stereoselectivity Model for Esterases .....	151
<b>1.3.1.4.2</b>	Kazlauskas' Rule .....	153
<b>1.3.1.4.3</b>	Stereochemistry of Triacyl Glycerides .....	154
<b>1.3.1.5</b>	<i>meso</i> -Trick and Desymmetrization .....	154
<b>1.3.1.6</b>	Resolution of Racemates .....	157
<b>1.3.1.6.1</b>	Kinetic Resolution .....	157
<b>1.3.1.6.2</b>	Dynamic Kinetic Resolution .....	158
<b>1.3.1.7</b>	Kinetic Resolution of Racemic Carboxylic Acid Esters to Chiral Alcohols and Chiral Carboxylic Acid Esters .....	159
<b>1.3.1.7.1</b>	Racemic Carboxylic Acid Esters of Monovalent Alcohols .....	159
<b>1.3.1.7.1.1</b>	Synthesis of Chiral Primary Alcohols .....	159
<b>1.3.1.7.1.1.1</b>	Enantioselective Kinetic Resolution of Esters of Primary Alcohols by <i>Pseudomonas cepacia</i> Lipase .....	160
<b>1.3.1.7.1.1.2</b>	Enantioselective Kinetic Resolution of Esters of Chiral Primary Alcohols by Porcine Pancreatic Lipase .....	161
<b>1.3.1.7.1.1.3</b>	Enantioselective Kinetic Resolution of Esters of Chiral Primary Alcohols by Penicillin Acylase .....	163
<b>1.3.1.7.1.2</b>	Synthesis of Chiral Secondary Alcohols .....	164
<b>1.3.1.7.1.3</b>	Synthesis of Chiral Tertiary Alcohols .....	168
<b>1.3.1.7.2</b>	Racemic Esters of Chiral Diols .....	170
<b>1.3.1.7.2.1</b>	Synthesis of Chiral 1,2-Diols .....	170
<b>1.3.1.7.2.1.1</b>	Enantioselective Kinetic Resolution of Esters of Chiral 1,2-Diols with One Chiral Center .....	170
<b>1.3.1.7.2.1.2</b>	Enantioselective Kinetic Resolution of Esters of Chiral 1,2-Diols with Two Chiral Centers .....	173
<b>1.3.1.7.3</b>	Prochiral Esters of 1,3-Diols .....	174
<b>1.3.1.7.3.1</b>	Synthesis of Chiral Esters of Propane-1,3-diols .....	174
<b>1.3.1.7.3.2</b>	Synthesis of Chiral Esters of Cyclic <i>meso</i> -1,3-Diols .....	176
<b>1.3.1.8</b>	Kinetic Resolution of Lactones .....	177
<b>1.3.1.9</b>	Kinetic Resolution of Racemic Carboxylic Acid Esters to Chiral Carboxylic Acids and Chiral Carboxylic Acid Esters .....	178
<b>1.3.1.9.1</b>	Deracemization of Monocarboxylic Acid Esters .....	178
<b>1.3.1.9.2</b>	Deracemization of Dicarboxylic Acid Esters .....	180
<b>1.3.1.9.2.1</b>	Desymmetrization of Substituted Malonate and Glutarate Dialkyl Esters .....	180
<b>1.3.1.9.2.2</b>	Deracemization of Cyclic Dicarboxylic Acid Esters .....	182
<b>1.3.1.9.3</b>	Deracemization of $\beta$ -Amino Carboxylic Acid Esters .....	183
<b>1.3.2</b>	<b>Resolution of Alcohols, Amines, Acids, and Esters by Nonhydrolytic Processes</b>	
	M. Rodríguez-Mata and V. Gotor-Fernández	
<b>1.3.2</b>	<b>Resolution of Alcohols, Amines, Acids, and Esters by Nonhydrolytic Processes</b> .....	189
<b>1.3.2.1</b>	Resolution of Alcohols .....	192
<b>1.3.2.1.1</b>	Classical Kinetic Resolution .....	193
<b>1.3.2.1.1.1</b>	Ester Synthesis .....	193

---

---

<b>1.3.2.1.1.2</b>	Amino Alcohol Transformation .....	198
<b>1.3.2.1.2</b>	Dynamic Kinetic Resolution .....	200
<b>1.3.2.2</b>	Resolution of Amines .....	202
<b>1.3.2.2.1</b>	Classical Kinetic Resolution .....	202
<b>1.3.2.2.1.1</b>	Amide Synthesis .....	203
<b>1.3.2.2.1.2</b>	Carbamate Synthesis .....	205
<b>1.3.2.2.1.3</b>	Amino Alcohol Transformation .....	206
<b>1.3.2.2.2</b>	Dynamic Kinetic Resolution .....	208
<b>1.3.2.2.2.1</b>	Dynamic Kinetic Resolution of Primary Amines .....	208
<b>1.3.2.2.2.2</b>	Dynamic Kinetic Resolution of Secondary Amines .....	211
<b>1.3.2.3</b>	Resolution of Acids .....	213
<b>1.3.2.3.1</b>	Classical Kinetic Resolution .....	213
<b>1.3.2.4</b>	Resolution of Esters .....	214
<b>1.3.2.4.1</b>	Classical Kinetic Resolution .....	214
<b>1.3.2.4.1.1</b>	Transesterification .....	214
<b>1.3.2.4.1.2</b>	Interestesterification .....	216
<b>1.3.2.4.1.3</b>	Aminolysis .....	217
<b>1.3.2.4.1.4</b>	Ammonolysis .....	217
<b>1.3.2.5</b>	Conclusions .....	218

---

### **1.3.3 Transphosphorylation**

R. Wever, L. Babich, and A. F. Hartog

---

<b>1.3.3</b>	<b>Transphosphorylation</b> .....	223
<b>1.3.3.1</b>	Applications of Phosphate Esters .....	223
<b>1.3.3.2</b>	Classical Synthesis versus Biocatalytic Procedures .....	224
<b>1.3.3.3</b>	Transphosphorylation by Kinases .....	225
<b>1.3.3.3.1</b>	Phosphorylation by Kinases Using ATP and ATP Regenerating Systems .....	225
<b>1.3.3.3.1.1</b>	Phosphorylation of Glucose and Analogues by Hexokinase .....	226
<b>1.3.3.3.1.2</b>	Phosphorylation of Nucleotides and Nucleosides .....	230
<b>1.3.3.3.1.3</b>	Phosphorylation of Glycerol by Glycerol Kinase .....	230
<b>1.3.3.3.2</b>	Polyphosphate-Dependent Kinases .....	231
<b>1.3.3.3.2.1</b>	Synthesis of Phosphorylated Aldohexoses by Polyphosphate-Dependent Kinases .....	231
<b>1.3.3.4</b>	Transphosphorylation by Phosphate-Hydrolyzing Enzymes .....	232
<b>1.3.3.4.1</b>	Alkaline Phosphatases .....	232
<b>1.3.3.4.1.1</b>	Phosphorylation of Glycerol and (Poly)alcohols by Alkaline Phosphatases .....	232
<b>1.3.3.4.2</b>	Acid Phosphatases and Transphosphorylation Mechanism .....	233
<b>1.3.3.4.2.1</b>	Synthesis of Phosphorylated Nucleosides .....	234
<b>1.3.3.4.2.2</b>	Phosphorylation of Carbohydrates by Pyrophosphate .....	235
<b>1.3.3.4.2.3</b>	Phosphorylation of (Poly)alcohols by Acid Phosphatases .....	237
<b>1.3.3.4.2.4</b>	Phosphorylation of 1,3-Dihydroxyacetone Using Pyrophosphate .....	238
<b>1.3.3.4.3</b>	Phosphorylases .....	238
<b>1.3.3.4.3.1</b>	Synthesis of $\alpha$ -D-Glucose 1-Phosphate and $\alpha$ -D-Galactose 1-Phosphate Using Sucrose Phosphorylase and Lactose Phosphorylase .....	239
<b>1.3.3.4.3.2</b>	Nucleoside Phosphorylases .....	240

<b>1.3.3.5</b>	One-Pot Cascade Reactions Involving Transphosphorylation Reactions .....	241
<b>1.3.3.5.1</b>	Synthesis of (Phosphorylated) Carbohydrates via Intermediate	
	Formation of Glyceraldehyde 3-Phosphate .....	242
<b>1.3.3.5.2</b>	Synthesis of (Phosphorylated) Carbohydrates via Intermediate	
	Formation of 1,3-Dihydroxyacetone Phosphate .....	243
<b>1.3.3.6</b>	Outlook .....	250
<b>1.4</b>	<b>Nitrile and Amide Hydrolysis and Enzymatic Synthesis of Amides and Peptides</b>	
<b>1.4.1</b>	<b>Hydrolysis of Nitriles to Amides</b>	
	Y. Asano	
<b>1.4.1</b>	Hydrolysis of Nitriles to Amides .....	255
<b>1.4.1.1</b>	Hydrolysis of Aromatic and Arylalkyl Nitriles .....	258
<b>1.4.1.2</b>	Hydrolysis of $\alpha$ -Substituted Nitriles .....	261
<b>1.4.1.3</b>	Hydrolysis of Dinitriles and Related Compounds .....	263
<b>1.4.1.4</b>	Hydrolysis of Aminonitriles .....	267
<b>1.4.1.5</b>	Hydrolysis of $\beta$ -Substituted Nitriles .....	271
<b>1.4.2</b>	<b>Hydrolysis of Nitriles to Carboxylic Acids</b>	
	L. Martíková and A. B. Veselá	
<b>1.4.2</b>	Hydrolysis of Nitriles to Carboxylic Acids .....	277
<b>1.4.2.1</b>	Synthesis of Achiral Carboxylic Acids or Carboxamides .....	278
<b>1.4.2.1.1</b>	Synthesis of (Hetero)cyclic Carboxamides .....	278
<b>1.4.2.1.1.1</b>	By Chemoenzymatic Synthesis from Aldehydes .....	278
<b>1.4.2.1.2</b>	Synthesis of 3-Oxo Amides .....	279
<b>1.4.2.1.2.1</b>	By Nitrile Hydratase .....	279
<b>1.4.2.1.3</b>	Synthesis of Cyano Carboxamides or Cyano Carboxylic Acids .....	281
<b>1.4.2.1.3.1</b>	From Dinitriles by Nitrile Hydratase and Amidase .....	281
<b>1.4.2.1.3.2</b>	From Dinitriles by Nitrilase .....	281
<b>1.4.2.2</b>	Synthesis of Enantiopure 2-Substituted Carboxylic Acids or Carboxamides .....	283
<b>1.4.2.2.1</b>	From Racemic Nitriles by Nitrilase .....	283
<b>1.4.2.2.2</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	283
<b>1.4.2.2.3</b>	From Disubstituted Malononitriles by Nitrile Hydratase and Amidase .....	285
<b>1.4.2.2.4</b>	Synthesis of 2-Hydroxy Carboxylic Acids and Carboxamides from Aldehydes by Hydroxynitrile Lyase and Nitrilase .....	286
<b>1.4.2.2.5</b>	Synthesis of 2-Hydroxy Carboxylic Acids and Carboxamides from Aldehydes by Hydroxynitrile Lyase, Nitrile Hydratase, and Amidase .....	286
<b>1.4.2.3</b>	Synthesis of Enantioenriched 3-Substituted Carboxylic Acids or Carboxamides .....	287
<b>1.4.2.3.1</b>	From Racemic Nitriles by Nitrilase .....	287
<b>1.4.2.3.2</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	288
<b>1.4.2.3.3</b>	From 3-Oxo Nitriles by Carbonyl Reductase and Nitrilase .....	289
<b>1.4.2.3.4</b>	From 3-Substituted Glutaronitriles by Nitrilase .....	290
<b>1.4.2.3.5</b>	From 3-Substituted Glutaronitriles by Nitrile Hydratase and Amidase .....	290

---

<b>1.4.2.4</b>	Synthesis of 3-Substituted 2-Methylene Carboxylic Acids and 2-Methylene Carboxamides .....	291
<b>1.4.2.4.1</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	291
<b>1.4.2.5</b>	Synthesis of ( <i>E</i> )- $\alpha,\beta$ -Unsaturated Carboxylic Acids .....	291
<b>1.4.2.5.1</b>	From ( <i>E/Z</i> )- $\alpha,\beta$ -Unsaturated Nitriles by Nitrilase .....	291
<b>1.4.2.6</b>	Synthesis of Enantioenriched (Hetero)cyclic Carboxylic Acids or Carboxamides .....	292
<b>1.4.2.6.1</b>	Synthesis of Three-Membered-Ring Carboxylic Acids or Carboxamides .....	292
<b>1.4.2.6.1.1</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	292
<b>1.4.2.6.2</b>	Synthesis of Four-Membered-Ring Carboxylic Acids and Their Corresponding Amides and Esters .....	295
<b>1.4.2.6.2.1</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	295
<b>1.4.2.6.3</b>	Synthesis of (Hetero)cyclic $\beta$ - or $\gamma$ -Amino Carboxylic Acids or Their Corresponding Carboxamides .....	295
<b>1.4.2.6.3.1</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	295
<b>1.4.2.6.3.2</b>	From Racemic Nitriles by Nitrilase .....	296
<b>1.4.2.6.4</b>	Synthesis of 2,3-Dihydro-1,4-benzodioxin-2-carboxylic Acid Derivatives .....	297
<b>1.4.2.6.4.1</b>	From Racemic Nitriles by Nitrile Hydratase and Amidase .....	297
<b>1.4.2.6.5</b>	Synthesis of Cyclitols .....	298
<b>1.4.2.6.5.1</b>	From Racemic Nitriles by Lipase, Nitrile Hydratase, and Amidase .....	298

---

**1.4.3** **Hydrolysis of Amides**

M. Hall, K. Faber, and G. Tasnádi

---

<b>1.4.3</b>	<b>Hydrolysis of Amides</b> .....	303
<b>1.4.3.1</b>	Synthesis of Amino Acids .....	304
<b>1.4.3.1.1</b>	Kinetic Resolution of $\alpha$ -Amino Acid Amides .....	304
<b>1.4.3.1.1.1</b>	Enantiopure $\alpha$ -Monosubstituted Amino Acids .....	305
<b>1.4.3.1.1.1.1</b>	Preparation Using Aminopeptidase from <i>P. putida</i> ATCC 12633 .....	305
<b>1.4.3.1.1.1.2</b>	Preparation Using Acylase I from <i>Aspergillus melleus</i> .....	307
<b>1.4.3.1.1.2</b>	Enantiopure $\alpha,\alpha$ -Disubstituted Amino Acids .....	307
<b>1.4.3.1.1.2.1</b>	Preparation Using Amino Amidase from <i>M. neoaurum</i> ATCC 25795 .....	307
<b>1.4.3.1.1.2.2</b>	Preparation Using Amidase from <i>O. anthropi</i> NCIMB 40321 .....	309
<b>1.4.3.1.2</b>	Kinetic Resolution of <i>N</i> -Acyl Amino Acids .....	310
<b>1.4.3.1.2.1</b>	Enantiopure $\alpha$ -Amino Acids .....	310
<b>1.4.3.1.2.1.1</b>	Preparation Using Acylase I .....	310
<b>1.4.3.1.2.2</b>	Enantiopure $\beta$ -Amino Acids and Esters .....	313
<b>1.4.3.1.2.2.1</b>	Preparation Using Penicillin G Acylase .....	313
<b>1.4.3.2</b>	Synthesis of Aliphatic Carboxylic Acids .....	315
<b>1.4.3.2.1</b>	Kinetic Resolution of $\alpha$ -Substituted Phenylacetamides with Amidases .....	315
<b>1.4.3.3</b>	Synthesis of Chiral Aliphatic Amines .....	316
<b>1.4.3.3.1</b>	Kinetic Resolution of <i>N</i> -Acetyl (Arylalkyl)amines .....	316
<b>1.4.3.4</b>	Hydrolysis of Lactams .....	317

<b>1.4.4</b>	<b>Enzymatic Synthesis of Amides</b>	
	J. W. Schmidberger, L. J. Hepworth, A. P. Green, and S. L. Flitsch	
<hr/>		
<b>1.4.4</b>	<b>Enzymatic Synthesis of Amides</b>	329
<b>1.4.4.1</b>	Lipases	331
<b>1.4.4.1.1</b>	Amide Formation without Stereochemical Considerations	332
<b>1.4.4.1.1.1</b>	Chemoselectivity toward Amino Alcohols	335
<b>1.4.4.1.2</b>	Solvent-Free Aminolysis	336
<b>1.4.4.1.3</b>	Aminolysis in Ionic Liquids	338
<b>1.4.4.1.4</b>	Exploring the Chemical Scope of Aminolysis Reactions	339
<b>1.4.4.1.5</b>	Aminolysis Involving Lactams	342
<b>1.4.4.1.2</b>	Amide Generation through Kinetic Resolution	343
<b>1.4.4.1.2.1</b>	Kinetic Resolution of Amines	344
<b>1.4.4.1.2.2</b>	Kinetic Resolution of Esters with Amine Nucleophiles	347
<b>1.4.4.1.2.3</b>	Transamidation Reactions	349
<b>1.4.4.1.3</b>	Dynamic Kinetic Resolution	350
<b>1.4.4.1.3.1</b>	Metal-Catalyzed Racemization	351
<b>1.4.4.1.3.2</b>	Metal-Free Dynamic Kinetic Resolution	353
<b>1.4.4.1.4</b>	Enantioselective Enzymatic Desymmetrization	354
<b>1.4.4.1.4.1</b>	Desymmetrization of Prochiral Diesters and Diamines	354
<b>1.4.4.1.4.2</b>	Carbamate Formation via Aminolysis of Dialkyl Carbonates	355
<b>1.4.4.2</b>	Penicillin Acylases	356
<b>1.4.4.3</b>	Proteases	358
<b>1.4.4.4</b>	Nitrile Hydratases	360
<b>1.4.4.4.1</b>	Synthesis of Nonchiral Amides from an Industrial Perspective	361
<b>1.4.4.4.1.1</b>	Industrial Synthesis of Acrylamide	362
<b>1.4.4.4.1.2</b>	Industrial Synthesis of Nicotinamide	362
<b>1.4.4.4.2</b>	Challenges Associated with Nitrile Hydratases	363
<b>1.4.4.4.3</b>	Regioselective Hydration of Nitriles	363
<b>1.4.4.4.3.1</b>	5-Cyanovaleramide	363
<b>1.4.4.4.4</b>	Kinetic Resolution of Nitriles	364
<b>1.4.4.4.4.1</b>	Enantioselective Nitrile Hydratases	364
<b>1.4.4.4.4.2</b>	Nitrile Hydratase–Amidase Systems	365
<b>1.4.4.4.5</b>	Dynamic Kinetic Resolution of Nitriles	366
<b>1.4.4.4.6</b>	Desymmetrization of Dinitriles	366
<b>1.4.4.5</b>	Future Outlook	367
<hr/>		
<b>1.4.5</b>	<b>Hydrolysis of Hydantoins, Dihydropyrimidines, and Related Compounds</b>	
	C. Slomka, U. Engel, C. Syldatk, and J. Rudat	
<hr/>		
<b>1.4.5</b>	<b>Hydrolysis of Hydantoins, Dihydropyrimidines, and Related Compounds</b>	373
<b>1.4.5.1</b>	Hydantoins and Related Compounds	373
<b>1.4.5.1.1</b>	Occurrence and Relevance in Nature	373
<b>1.4.5.1.2</b>	Chemical Synthesis of Hydantoins	374
<b>1.4.5.1.3</b>	Chemical Properties of Hydantoins	377

---

<b>1.4.5.2</b>	Hydrolysis of Hydantoins, Dihydropyrimidines, and Related Compounds:	
<b>1.4.5.2.1</b>	The Superfamily of Cyclic Amidohydrolases .....	377
<b>1.4.5.2.2</b>	Functions and Properties of Cyclic Amidohydrolases .....	377
<b>1.4.5.2.3</b>	Representative Cyclic Amidohydrolases .....	378
<b>1.4.5.2.3.1</b>	Hydantoinases .....	379
<b>1.4.5.2.3.2</b>	Classification and Evolutionary Relationship .....	379
<b>1.4.5.2.3.3</b>	Biochemical and Structural Properties .....	380
<b>1.4.5.3</b>	Enantioselectivity .....	381
<b>1.4.5.3.1</b>	Hydrolysis of <i>N</i> -Carbamoyl amino Acids .....	381
<b>1.4.5.3.1.1</b>	<i>N</i> -Carbamoyl- $\alpha$ -amino Acid Hydrolases .....	381
<b>1.4.5.3.1.2</b>	$\beta$ -Ureidopropionases and L- <i>N</i> -Carbamoylases .....	382
<b>1.4.5.3.1.2</b>	D- <i>N</i> -Carbamoylases .....	382
<b>1.4.5.4</b>	Synthesis of Selected Amino Acids by Hydantoinases and Related Enzymes ..	383
<b>1.4.5.4.1</b>	The Hydantoinase Process .....	383
<b>1.4.5.4.1.1</b>	Synthesis of D-Amino Acids .....	384
<b>1.4.5.4.1.1.1</b>	Various Approaches for the Synthesis of D-4-Hydroxyphenylglycine .....	386
<b>1.4.5.4.1.1.1.1</b>	D-4-Hydroxyphenylglycine Synthesis Using Wild-Type Strains .....	386
<b>1.4.5.4.1.1.2</b>	D-4-Hydroxyphenylglycine Synthesis Using Recombinantly Expressed Enzymes in Resting Cells of <i>E. coli</i> .....	387
<b>1.4.5.4.1.1.3</b>	D-4-Hydroxyphenylglycine Synthesis Using Isolated Enzymes .....	389
<b>1.4.5.4.1.1.2</b>	Synthesis of D-Methionine .....	391
<b>1.4.5.4.1.2</b>	Synthesis of L-Amino Acids .....	392
<b>1.4.5.4.1.2.1</b>	Synthesis of L-Homophenylalanine .....	394
<b>1.4.5.4.1.2.2</b>	Synthesis of L-Methionine .....	395
<b>1.4.5.4.1.2.3</b>	Synthesis of L-Tryptophan .....	396
<b>1.4.5.4.1.2.4</b>	Synthesis of L-Phenylalanine .....	397
<b>1.4.5.4.1.2.5</b>	Synthesis of L-2-Amino-3-(2-oxocyclopentyl)propanoic Acid .....	398
<b>1.4.5.4.1.3</b>	Synthesis of $\beta$ -Amino Acids .....	401
<b>1.4.5.4.1.3.1</b>	Synthesis of L- $\beta$ -Phenylalanine .....	403
<b>1.4.5.4.1.3.2</b>	Synthesis of D- $\alpha$ -Methyl- $\beta$ -alanine .....	405
<b>1.4.5.5</b>	Approaches To Improve the Hydantoinase Process .....	407
<b>1.4.5.5.1</b>	Methods for Screening and Isolation of Hydantoinases .....	407
<b>1.4.5.5.2</b>	Enzyme Engineering of Hydantoinases and Related Enzymes .....	407
<b>1.4.5.5.2.1</b>	Construction of Fusion Enzymes as an Alternative to Separately Expressed and Coexpressed Enzymes .....	407
<b>1.4.5.5.2.2</b>	Directed Evolution for Process Optimization .....	408
<b>1.4.5.5.2.3</b>	Enzyme Immobilization .....	408
<b>1.5</b>	<b>Isomerizations: Racemization, Epimerization, and E/Z-Isomerization</b>	
	K. Faber and S. M. Glueck	
<hr/>		
<b>1.5</b>	<b>Isomerizations: Racemization, Epimerization, and E/Z-Isomerization</b> .....	415
<b>1.5.1</b>	Racemization and Epimerization .....	415
<b>1.5.1.1</b>	Racemization of Secondary Alcohols .....	416
<b>1.5.1.1.1</b>	Using Whole Microbial Wild-Type Cells .....	416
<b>1.5.1.1.2</b>	Using (Semi)purified Recombinant Overexpressed Enzymes .....	417

---

<b>1.5.1.2</b>	Racemization of $\alpha$ -Hydroxy Ketones (Acyloins) .....	420
<b>1.5.1.2.1</b>	Using Whole Microbial Cells .....	420
<b>1.5.1.3</b>	Racemization of $\alpha$ -Hydroxy Carboxylic Acids .....	423
<b>1.5.1.3.1</b>	Mandelate Racemase .....	423
<b>1.5.1.3.2</b>	Lactate Racemase .....	426
<b>1.5.1.3.3</b>	Racemization of $\alpha$ -Hydroxy Carboxylic Acids Using Whole Microbial Cells .....	427
<b>1.5.1.4</b>	Racemization of $\alpha$ -Amino Acids .....	428
<b>1.5.1.4.1</b>	PLP Independent Amino Acid Racemases .....	428
<b>1.5.1.4.1.1</b>	Glutamate Racemase .....	429
<b>1.5.1.4.1.2</b>	Proline Racemase .....	432
<b>1.5.1.4.1.3</b>	Aspartate Racemase .....	433
<b>1.5.1.4.2</b>	PLP Dependent $\alpha$ -Amino Acid Racemases .....	434
<b>1.5.1.4.2.1</b>	Isoleucine 2-Epimerase .....	436
<b>1.5.1.4.2.2</b>	Arginine Racemase .....	437
<b>1.5.1.4.2.3</b>	Amino Acid Racemase .....	438
<b>1.5.1.5</b>	Racemization of $\alpha$ -Amino Acid Derivatives .....	441
<b>1.5.1.5.1</b>	Racemization of N-Acylamino Acids .....	441
<b>1.5.1.5.2</b>	Racemization of Hydantoins .....	443
<b>1.5.1.5.3</b>	Racemization of $\alpha$ -Amino Lactams .....	445
<b>1.5.1.5.4</b>	Racemization of Amino Acid Amides .....	446
<b>1.5.1.6</b>	Racemization of Amines .....	447
<b>1.5.1.7</b>	Epimerization of Carbohydrates and Derivatives .....	449
<b>1.5.1.7.1</b>	N-Acylglucosamine 2-Epimerase .....	452
<b>1.5.1.7.2</b>	Cellobiose 2-Epimerase .....	453
<b>1.5.1.7.3</b>	D-Psicose 3-Epimerase .....	455
<b>1.5.1.7.4</b>	D-Tagatose 3-Epimerase .....	455
<b>1.5.1.7.5</b>	Mannobiose 2-Epimerase .....	456
<b>1.5.2</b>	cis-trans-Isomerases .....	456
<b>1.5.2.1</b>	Linoleate cis-trans-Isomerase .....	457
<b>1.5.3</b>	Intramolecular Oxidoreductases .....	458
<b>1.5.3.1</b>	Isomerization of C3-Sugars .....	459
<b>1.5.3.1.1</b>	Triose Phosphate Isomerase .....	459
<b>1.5.3.2</b>	Isomerization of C5- and C6-Sugars .....	461
<b>1.5.3.2.1</b>	L-Arabinose Isomerase .....	461
<b>1.5.3.2.2</b>	D-Arabinose Isomerase .....	464
<b>1.5.3.2.3</b>	D-Lyxose Isomerase .....	465
<b>1.5.3.2.4</b>	D-Xylose Isomerase .....	467
<b>1.5.3.2.5</b>	L-Rhamnose Isomerase .....	471
<b>1.5.4</b>	Mutases .....	473
<b>1.5.4.1</b>	Aminomutases .....	473
<b>1.5.4.1.1</b>	PLP Dependent Aminomutases .....	473
<b>1.5.4.1.2</b>	MIO Dependent Aminomutases .....	476
<b>1.5.5</b>	Conclusions and Outlook .....	478

**1.6****Glycosides****1.6.1****Glycosidases and Glycosynthases**

B. Cobucci-Ponzano and M. Moracci

**1.6.1****Glycosidases and Glycosynthases** ..... 483**1.6.1.1**

Glycoside Hydrolases ..... 484

**1.6.1.1.1**

Classification ..... 484

**1.6.1.1.2**

Hydrolytic Reaction Mechanism ..... 484

**1.6.1.1.3**

Glycoside and Oligosaccharide Synthesis ..... 485

**1.6.1.2**

Glycosynthases ..... 486

**1.6.1.2.1**

Approaches for the Construction of a Glycosynthase ..... 486

**1.6.1.3**

Applications of Glycoside Hydrolases and Glycosynthases in Glycoside Synthesis ..... 488

**1.6.1.3.1**

Applications of Glycoside Hydrolases ..... 488

**1.6.1.3.1.1**

Glycoside Synthesis by Reverse Hydrolysis ..... 488

**1.6.1.3.1.2**

Glycoside Synthesis by Transglycosylation ..... 489

**1.6.1.3.1.3**

Comparison of Glycoside Synthesis by Reverse Hydrolysis and Transglycosylation ..... 492

**1.6.1.3.2**

Applications of Glycosynthases ..... 493

**1.6.1.3.2.1**

Glycosyl Fluorides as Glycosynthase Substrates ..... 494

**1.6.1.3.2.1.1**Synthesis of Mechanism-Based Inhibitors and Precursors of Cell Antigens by exo- $\beta$ -Glycosynthase ..... 494**1.6.1.3.2.1.2**

Synthesis of Glycosylated Flavonoids ..... 496

**1.6.1.3.2.2**

Glycosyl Azides as Glycosynthase Substrates ..... 498

**1.6.1.3.2.2.1**Synthesis of Precursors of Cell Antigens by exo- $\alpha$ -Fucosynthase ..... 498**1.6.1.3.2.3**

Aryl Glycosides as Glycosynthase Substrates ..... 499

**1.6.1.3.2.3.1**Synthesis of Branched  $\beta(1 \rightarrow 3)/\beta(1 \rightarrow 6)$  Glucosides by exo- $\beta$ -Glycosynthase ..... 499**1.6.1.3.2.4**

Dihydrooxazoles as Glycosynthase Substrates ..... 501

**1.6.2****Glycosyltransferases**

J. Voglmeir and S. L. Flitsch

**1.6.2****Glycosyltransferases** ..... 507**1.6.2.1**

Sugar Nucleotides as Glycosyl Donors ..... 508

**1.6.2.1.1**

Commonly Known Nucleotide-Activated Sugars ..... 509

**1.6.2.1.2**

Unusual Nucleotide-Activated Sugars ..... 514

**1.6.2.2**

Other Sugar Donors ..... 516

**1.6.2.2.1**

Glycosyl Phosphates ..... 516

**1.6.2.2.2**

Di- and Oligosaccharides ..... 518

**1.6.2.2.3**

Glycosyl Lipids ..... 518

**1.6.2.2.4**

Other Sugar Donors ..... 519

<b>1.6.2.3</b>	Glycoconjugate Products .....	520
<b>1.6.2.3.1</b>	Free Oligosaccharides .....	520
<b>1.6.2.3.1.1</b>	Galactosylation .....	520
<b>1.6.2.3.1.2</b>	Fucosylation .....	521
<b>1.6.2.3.1.3</b>	Sialylation .....	523
<b>1.6.2.3.2</b>	Glycolipid Oligosaccharides .....	526
<b>1.6.2.3.2.1</b>	Globosides .....	526
<b>1.6.2.3.2.2</b>	Gangliosides .....	528
<b>1.6.2.3.3</b>	Glycopeptides and Glycoproteins .....	528
<b>1.6.2.3.3.1</b>	<i>N</i> -Glycopeptides and Glycoproteins .....	528
<b>1.6.2.3.3.2</b>	<i>O</i> -Glycopeptides and Glycoproteins .....	530
<b>1.6.2.3.4</b>	Glycosaminoglycans .....	533
<b>1.6.2.3.4.1</b>	Poly- <i>N</i> -acetyllactosamines .....	533
<b>1.6.2.3.4.2</b>	Heparosan .....	533
<b>1.6.2.3.5</b>	Homoglycan Extensions .....	534
<b>1.6.2.3.6</b>	Glycosylated Natural Products .....	536
<b>1.6.2.4</b>	Conclusions and Outlook .....	538
<b>Keyword Index</b> .....		543
<b>Author Index</b> .....		575
<b>Abbreviations</b> .....		603