

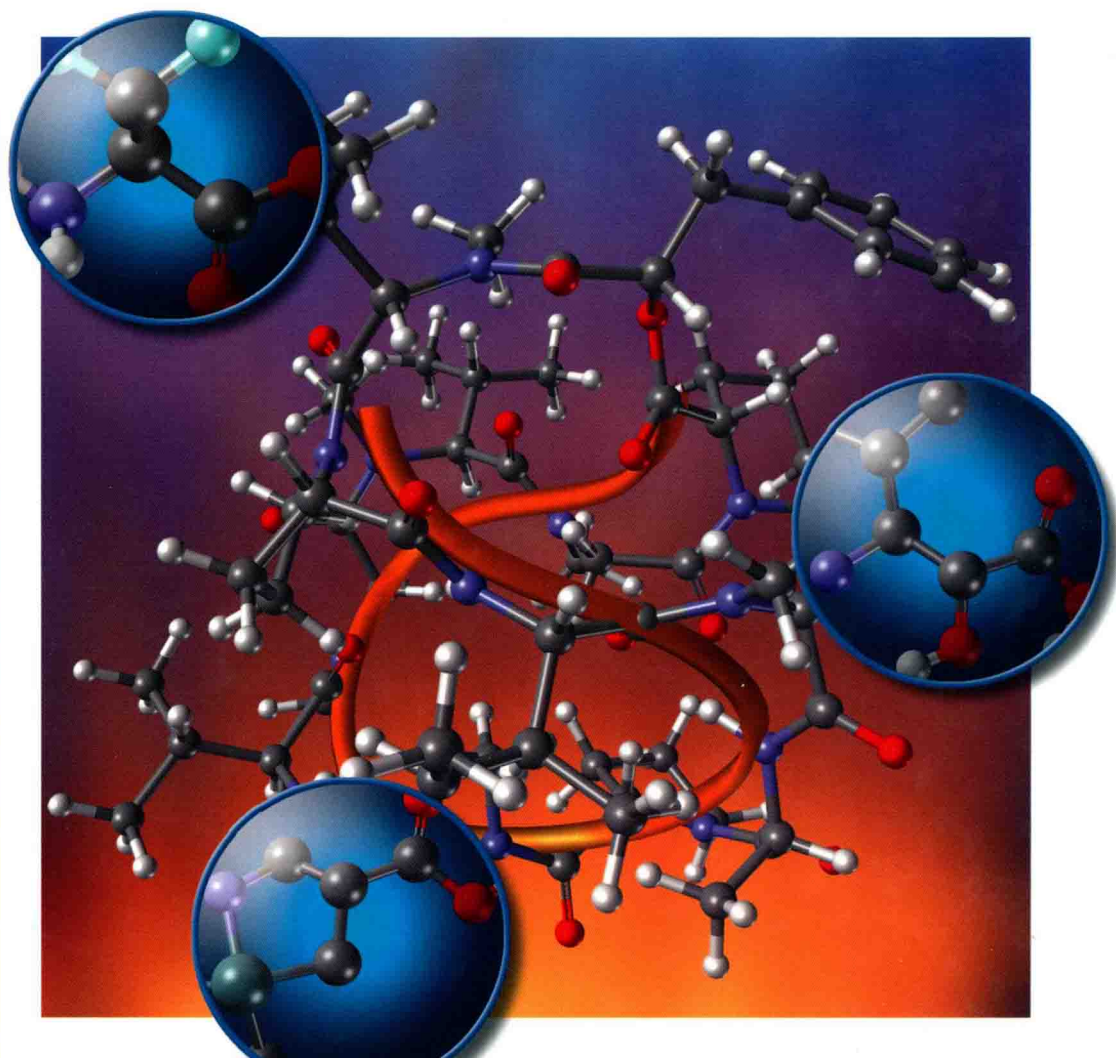
Edited by Andrew B. Hughes

 WILEY-VCH

Amino Acids, Peptides and Proteins in Organic Chemistry

Volume 1

Origins and Synthesis of Amino Acids



Amino Acids, Peptides and Proteins in Organic Chemistry

Volume 1 - Origins and Synthesis of Amino Acids

Edited by
Andrew B. Hughes



WILEY-VCH Verlag GmbH & Co. KGaA

The Editor

Dr. Andrew B. Hughes
La Trobe University
Department of Chemistry
Victoria 3086
Australia

■ All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

© 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Composition Thomson Digital, Noida, India

Printing Strauss GmbH, Mörlenbach

Bookbinding Litges & Dopf GmbH, Heppenheim

Cover Design Schulz Grafik Design, Fußgönheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32096-7

**Amino Acids, Peptides and Proteins
in Organic Chemistry**

Edited by
Andrew B. Hughes

Further Reading

Fessner, W.-D., Anthonsen, T.

Modern Biocatalysis

**Stereoselective and Environmentally
Friendly Reactions**

2009

ISBN: 978-3-527-32071-4

Sewald, N., Jakubke, H.-D.

Peptides: Chemistry and Biology

2009

ISBN: 978-3-527-31867-4

Lutz, S., Bornscheuer, U. T. (eds.)

Protein Engineering Handbook

2 Volume Set

2009

ISBN: 978-3-527-31850-6

Aehle, W. (ed.)

Enzymes in Industry

Production and Applications

2007

ISBN: 978-3-527-31689-2

Wiley-VCH (ed.)

Ullmann's Biotechnology and Biochemical Engineering

2 Volume Set

2007

ISBN: 978-3-527-31603-8

Budisa, N.

Engineering the Genetic Code

**Expanding the Amino Acid Repertoire
for the Design of Novel Proteins**

2006

ISBN: 978-3-527-31243-6

Demchenko, A. V. (ed.)

Handbook of Chemical Glycosylation

**Advances in Stereoselectivity and
Therapeutic Relevance**

2008

ISBN: 978-3-527-31780-6

Lindhorst, T. K.

Essentials of Carbohydrate Chemistry and Biochemistry

2007

ISBN: 978-3-527-31528-4

List of Contributors

David J. Ager

DSM Pharma Chemicals
PMB 150
9650 Strickland Road, Suite 103
Raleigh, NC 27615
USA

Luigi Aurelio

Monash University
Department of Medicinal Chemistry
Victorian College of Pharmacy
381 Royal Parade
Parkville, Victoria 3052
Australia

Yamir Bandala

Centro de Investigación y de Estudios
Avanzados del Instituto Politécnico
Nacional
Departamento de Química
Apartado Postal 14-740
07000 México DF
México

A. Richard Chamberlin

University of California, Irvine
Departments of Chemistry
Pharmaceutical Sciences, and
Pharmacology
Irvine, CA 92697
USA

Roberto Fernández de la Pradilla

CSIC
Instituto de Química Orgánica
Juan de la Cierva 3
28006 Madrid
Spain

Enikő Forró

University of Szeged
Institute of Pharmaceutical Chemistry
Eötvös u. 6
6720 Szeged
Hungary

Stephen Freeland

University of Maryland
Baltimore County
Department of Biological Sciences
1000 Hilltop Circle,
Baltimore, MD 21250
USA

Ferenc Fülöp

University of Szeged
Institute of Pharmaceutical Chemistry
Eötvös u. 6
6720 Szeged
Hungary

Antonio Guarna

Università degli Studi di Firenze
Polo Scientifico e Tecnologico
Dipartimento di Chimica Organica
"Ugo Schiff"
Via della Lastruccia 13
50019 Sesto Fiorentino
Firenze
Italy

Stephen A. Habay

University of California, Irvine
Department of Chemistry
Irvine, CA 92697
USA

Jane R. Hanrahan

University of Sydney
Faculty of Pharmacy
Sydney, NSW 2006
Australia

Graham A.R. Johnston

University of Sydney
Adrien Albert Laboratory of Medicinal
Chemistry
Department of Pharmacology
Faculty of Medicine
Sydney, NSW 2006
Australia

Andrew B. Hughes

La Trobe University
Department of Chemistry
Victoria 3086
Australia

Eusebio Juaristi

Centro de Investigación y de Estudios
Avanzados del Instituto Politécnico
Nacional
Departamento de Química
Apartado Postal 14-740
07000 México DF
México

Bernard Kaptein

DSM Pharmaceutical Products
Innovative Synthesis & Catalysis
PO Box 18
6160 MD Geleen
The Netherlands

Steven M. Kennedy

University of California, Irvine
Department of Chemistry
Irvine, CA 92697
USA

Loránd Kiss

University of Szeged
Institute of Pharmaceutical Chemistry
Eötvös u. 6
6720 Szeged
Hungary

Z. Martins

Imperial College London
Department of Earth Science and
Engineering
Exhibition Road
London SW7 2AZ
UK

Gloria Menchi

Università degli Studi di Firenze
 Polo Scientifico e Tecnologico
 Dipartimento di Chimica Organica
 "Ugo Schiff"
 Via della Lastruccia 13
 50019 Sesto Fiorentino
 Firenze
 Italy

Steve S. Park

University of California, Irvine
 Department of Chemistry
 Irvine, CA 92697
 USA

Caroline M. Reid

University of Glasgow, WestChem
 Department of Chemistry
 The Joseph Black Building
 University Avenue
 Glasgow G12 8QQ
 UK

M.A. Sephton

Imperial College London
 Department of Earth Science and
 Engineering
 Exhibition Road
 London SW7 2AZ
 UK

Hans E. Schoemaker

DSM Pharmaceutical Products
 Innovative Synthesis & Catalysis
 PO Box 18
 6160 MD Geleen
 The Netherlands

Theo Sonke

DSM Pharmaceutical Products
 Innovative Synthesis & Catalysis
 PO Box 18
 6160 MD Geleen
 The Netherlands

Peter Spiteller

Technische Universität München
 Institut für Organische Chemie und
 Biochemie II
 Lichtenbergstraße 4
 85747 Garching bei München
 Germany

Madeleine Strickland

University of Bristol
 School of Chemistry
 Cantock's Close
 Bristol BS8 1TS
 UK

Andrew Sutherland

University of Glasgow, WestChem
 Department of Chemistry
 The Joseph Black Building
 University Avenue
 Glasgow G12 8QQ
 UK

Andrea Trabocchi

Università degli Studi di Firenze
 Polo Scientifico e Tecnologico
 Dipartimento di Chimica Organica
 "Ugo Schiff"
 Via della Lastruccia 13
 50019 Sesto Fiorentino
 Firenze
 Italy

Alma Viso

CSIC
 Instituto de Química Orgánica
 Juan de la Cierva 3
 28006 Madrid
 Spain

Christine L. Willis

University of Bristol
 School of Chemistry
 Cantock's Close
 Bristol BS8 1TS
 UK

Contents

List of Contributors XVII

Part One Origins of Amino Acids 1

1	Extraterrestrial Amino Acids 3
	<i>Z. Martins and M.A. Sephton</i>
1.1	Introduction 3
1.2	ISM 6
1.2.1	Formation of Amino Acids in the ISM via Solid-Phase Reactions 6
1.2.2	Formation of Amino Acids in the ISM via Gas-Phase Reactions 8
1.3	Comets 9
1.4	Meteorites 11
1.4.1	Sources of Meteoritic Amino Acids (Extraterrestrial versus Terrestrial Contamination) 17
1.4.1.1	Detection of Amino Acids that are Unusual in the Terrestrial Environment 17
1.4.1.2	Determination of the Amino Acid Content of the Meteorite Fall Environment 17
1.4.1.3	Determination of Enantiomeric Ratios 18
1.4.1.4	Determination of Compound-Specific Stable Isotope Ratios of Hydrogen, Carbon, and Nitrogen 18
1.4.2	Synthesis of Meteoritic Amino Acids 19
1.5	Micrometeorites and IDPs 23
1.6	Mars 23
1.7	Delivery of Extraterrestrial Amino Acid to the Earth and its Importance to the Origin of Life 24
1.8	Conclusions 26
	References 27
2	"Terrestrial" Amino Acids and their Evolution 43
	<i>Stephen Freeland</i>
2.1	Introduction 43

2.2	What are the 20 “Terrestrial” Amino Acids?	44
2.2.1	The 21st and 22nd Genetically Encoded Amino Acids	45
2.2.2	Do other Genetically Encoded Amino Acids Await Discovery?	46
2.2.3	Genetic Engineering can Enlarge the Amino Acid Alphabet	47
2.2.4	Significance of Understanding the Origins of the Standard Alphabet	48
2.3	What do We Know about the Evolution of the Standard Amino Acid Alphabet?	49
2.3.1	Nonbiological, Natural Synthesis of Amino Acids	50
2.3.2	Biosynthetic Theories for the Evolutionary Expansion of the Standard Amino Acid Alphabet	53
2.3.3	Evidence for a Smaller Initial Amino Acid Alphabet	55
2.3.4	Proteins as Emergent Products of an RNA World	56
2.3.5	Stereochemical Rationale for Amino Acid Selection	57
2.4	Amino Acids that Life Passed Over: A Role for Natural Selection?	58
2.4.1	Were the Standard Amino Acids Chosen for High Biochemical Diversity?	60
2.4.2	Were the Standard Amino Acids Chosen for “Cheap” Biosynthesis?	62
2.4.3	Were the Standard Amino Acids Chosen to Speed Up Evolution?	62
2.5	Why Does Life Genetically Encode L-Amino Acids?	64
2.6	Summary, Synthesis, and Conclusions	64
	References	66

Part Two Production/Synthesis of Amino Acids 77

3	Use of Enzymes in the Synthesis of Amino Acids	79
	<i>Theo Sonke, Bernard Kaptein, and Hans E. Schoemaker</i>	
3.1	Introduction	79
3.2	Chemo-Enzymatic Processes to Enantiomerically Pure Amino Acids	80
3.3	Acylase Process	81
3.4	Amidase Process	83
3.4.1	Amidase Process for α,α -Disubstituted α -Amino Acids	86
3.5	Hydantoinase Process	88
3.6	Ammonia Lyase Processes	90
3.6.1	Aspartase-Catalyzed Production of L-Aspartic Acid	91
3.6.2	Production of L-Alanine from Fumaric Acid by an Aspartase–Decarboxylase Cascade	92
3.6.3	Phenylalanine Ammonia Lyase-Catalyzed Production of L-Phenylalanine and Derivatives	93
3.7	Aminotransferase Process	94
3.7.1	Aminotransferase-Catalyzed Production of D- α -H- α -Amino Acids	97

3.8	AADH Process	99
3.9	Conclusions	102
	References	103
4	β-Amino Acid Biosynthesis	119
	<i>Peter Spiteller</i>	
4.1	Introduction	119
4.1.1	Importance of β -Amino Acids and their Biosynthesis	119
4.1.2	Scope of this Chapter	119
4.2	Biosynthesis of β -Amino Acids	120
4.2.1	Biosynthesis of β -Alanine and β -Aminoisobutyric Acid	120
4.2.1.1	β -Alanine	120
4.2.1.2	β -Aminoisobutyric Acid	122
4.2.2	Biosynthesis of β -Amino Acids by 2,3-Aminomutases from α -Amino Acids	122
4.2.2.1	β -Lysine, β -Arginine, and Related β -Amino Acids	124
4.2.2.2	β -Phenylalanine, β -Tyrosine, and Related β -Amino Acids	127
4.2.2.3	β -Glutamate and β -Glutamine	132
4.2.2.4	β -Leucine	132
4.2.2.5	β -Alanine	132
4.2.3	Biosynthesis of α,β -Diamino Acids from α -Amino Acids	132
4.2.3.1	General Biosynthesis of α,β -Diamino Acids	132
4.2.3.2	Structures and Occurrence of α,β -Diamino Acids in Nature	132
4.2.3.3	Biosynthesis of Selected α,β -Diamino Acids	135
4.2.3.3.1	Biosynthesis of β -ODAP	135
4.2.3.3.2	Biosynthesis of the α,β -Diaminopropanoic Acid Moiety in the Bleomycins	136
4.2.3.3.3	Biosynthesis of the Penicillins	137
4.2.3.3.4	Biosynthesis of the Capreomycinide Moiety in Viomycin	137
4.2.3.3.5	Biosynthesis of the Streptolidine Moiety in Streptothricin F	137
4.2.4	Biosynthesis of α -Keto- β -Amino Acids from α -Amino Acids	139
4.2.5	<i>De Novo</i> Biosynthesis of β -Amino Acids by PKSs	139
4.2.5.1	Introduction	139
4.2.5.2	General Biosynthesis of Polyketide-Type β -Amino Acids	141
4.2.5.3	Structures and Occurrence of Polyketide-Type β -Amino Acids in Nature	142
4.2.5.4	Biosynthesis of Selected Polyketide-Type β -Amino Acids	149
4.2.5.4.1	Long-Chain β -Amino Acids Occurring as Constituents of the Iturins	149
4.2.5.4.2	Biosynthesis of the Ahda Moiety in Microginin	151
4.2.5.4.3	Biosynthesis of the Ahpa Residue in Bestatin	151
4.2.5.4.4	Biosynthesis of the Adda Residue in the Microcystins	152
4.2.6	β -Amino Acids Whose Biosynthesis is Still Unknown	152
4.3	Conclusions and Future Prospects	154
	References	155

5	Methods for the Chemical Synthesis of Noncoded α-Amino Acids found in Natural Product Peptides	163
	<i>Stephen A. Habay, Steve S. Park, Steven M. Kennedy, and A. Richard Chamberlin</i>	
5.1	Introduction	163
5.2	Noncoded CAAs	164
5.3	Noncoded Amino Acids by Chemical Modification of Coded Amino Acids	185
5.4	Noncoded Amino Acids with Elaborate Side-Chains	205
5.5	Conclusions	226
	References	226
 6	 Synthesis of <i>N</i>-Alkyl Amino Acids	 245
	<i>Luigi Aurelio and Andrew B. Hughes</i>	
6.1	Introduction	245
6.2	<i>N</i> -Methylation via Alkylation	246
6.2.1	S_N2 Substitution of α -Bromo Acids	246
6.2.2	<i>N</i> -Methylation of Sulfonamides, Carbamates, and Amides	249
6.2.2.1	Base-Mediated Alkylation of <i>N</i> -Tosyl Sulfonamides	249
6.2.2.2	Base Mediated Alkylation of <i>N</i> -Nitrobenzenesulfonamides	250
6.2.2.3	<i>N</i> -Methylation via Silver Oxide/Methyl Iodide	252
6.2.2.4	<i>N</i> -Methylation via Sodium Hydride/Methyl Iodide	253
6.2.2.5	<i>N</i> -Methylation of Trifluoroacetamides	257
6.2.2.6	<i>N</i> -Methylation via the Mitsunobu Reaction	257
6.3	<i>N</i> -Methylation via Schiff's Base Reduction	259
6.3.1	Reduction of Schiff's Bases via Transition Metal-Mediated Reactions	259
6.3.2	Reduction of Schiff's Bases via Formic Acid: The Leuckart Reaction	260
6.3.3	Quaternization of Imino Species	261
6.3.4	Reduction of Schiff's Bases via Borohydrides	263
6.3.5	Borane Reduction of Amides	264
6.4	<i>N</i> -Methylation by Novel Methods	265
6.4.1	1,3-Oxazolidin-5-ones	265
6.4.2	Asymmetric Syntheses	272
6.4.3	Racemic Syntheses	277
6.5	<i>N</i> -Alkylation of Amino Acids	280
6.5.1	Borohydride Reduction of Schiff's Bases	280
6.5.1.1	Sodium Borohydride Reductions	281
6.5.1.2	Sodium Cyanoborohydride Reductions	281
6.5.1.3	Sodium Triacetoxyborohydride Reductions	282
6.5.2	<i>N</i> -Alkylation of Sulfonamides	282
6.5.2.1	Base-Mediated Alkylation of Benzene Sulfonamides	282
6.5.3	Reduction of <i>N</i> -Acyl Amino Acids	283
6.5.3.1	Reduction of Acetamides	284

6.5.4	Novel Methods for <i>N</i> -Alkylating α -Amino Acids	284
6.5.4.1	Asymmetric Synthesis of <i>N</i> -Alkyl α -Amino Acids	284
6.5.4.2	<i>N</i> -Alkylation of 1,3-Oxazolidin-5-ones	284
	References	286
7	Recent Developments in the Synthesis of β-Amino Acids	291
	<i>Yamir Bandala and Eusebio Juaristi</i>	
7.1	Introduction	291
7.2	Synthesis of β -Amino Acids by Homologation of α -Amino Acids	291
7.3	Chiral Pool: Enantioselective Synthesis of β -Amino Acids from Aspartic Acid, Asparagine, and Derivatives	298
7.4	Synthesis of β -Amino Acids by Conjugate Addition of Nitrogen Nucleophiles to Enones	300
7.4.1	Achiral β -Amino Acids	300
7.4.2	Enantioselective Approaches	304
7.4.2.1	Addition of "Chiral Ammonia" Equivalents to Conjugated Prochiral Acceptors	304
7.4.2.2	Addition of a Nitrogen Nucleophile to a Chiral Acceptor	306
7.4.2.3	Asymmetric Catalysis	308
7.5	Synthesis of β -Amino Acids via 1,3-Dipolar Cycloaddition	312
7.6	Synthesis of β -Amino Acids by Nucleophilic Additions	316
7.6.1	Aldol- and Mannich-Type Reactions	316
7.6.2	Morita–Baylis–Hillman-Type Reactions	321
7.6.3	Mannich-Type Reactions	324
7.7	Synthesis of β -Amino Acids by Diverse Addition or Substitution Reactions	328
7.8	Synthesis of β -Amino Acids by Stereoselective Hydrogenation of Prochiral 3-Aminoacrylates and Derivatives	330
7.8.1	Reductions Involving Phosphorus-Metal Complexes	331
7.8.2	Reductions Involving Catalytic Hydrogenations	333
7.9	Synthesis of β -Amino Acids by use of Chiral Auxiliaries: Stereoselective Alkylation	334
7.10	Synthesis of β -Amino Acids via Radical Reactions	338
7.11	Miscellaneous Methods for the Synthesis of β -Amino Acids	340
7.12	Conclusions	347
7.13	Experimental Procedures	348
7.13.1	Representative Experimental Procedure: Synthesis of (<i>S</i>)-3-(<i>tert</i> -Butyloxycarbonylamino)-4-phenylbutanoic Acid	348
7.13.2	Representative Experimental Procedure: Synthesis of (<i>S</i>)-2-(Aminomethyl)-4-phenylbutanoic Acid, (<i>S</i>)-19	350
7.13.3	Representative Experimental Procedure: Synthesis of β^3 -Amino Acids by Conjugate Addition of Homochiral Lithium <i>N</i> -Benzyl- <i>N</i> -(α -methylbenzyl)amide	352
7.13.4	Representative Experimental Procedure: Synthesis of Cyclic and Acyclic β -Amino Acid Derivatives by 1,3-Dipolar Cycloaddition	353

- 7.13.5 Representative Experimental Procedure: Synthesis of (*R*)-3-*tert*-Butoxycarbonylamino-3-phenylpropionic Acid Isopropyl Ester using a Mannich-Type Reaction 354
- 7.13.6 Representative Experimental Procedure: General Procedure for the Hydrogenation of (*Z*)- and (*E*)- β -(Acylamino) acrylates by Chiral Monodentate Phosphoramidite Ligands 354
- 7.13.7 Representative Experimental Procedure: Synthesis of Chiral α -Substituted β -Alanine 355
- 7.13.8 Representative Experimental Procedure: Synthesis of Chiral β -Amino Acids by Diastereoselective Radical Addition to Oxime Esters 357
- References 358

8 Synthesis of Carbocyclic β -Amino Acids 367

Loránd Kiss, Enikő Forró, and Ferenc Fülöp

- 8.1 Introduction 367
- 8.2 Synthesis of Carbocyclic β -Amino Acids 368
 - 8.2.1 Synthesis of Carbocyclic β -Amino Acids via Lithium Amide-Promoted Conjugate Addition 369
 - 8.2.2 Synthesis of Carbocyclic β -Amino Acids by Ring-Closing Metathesis 371
 - 8.2.3 Syntheses from Cyclic β -Keto Esters 372
 - 8.2.4 Cycloaddition Reactions: Application in the Synthesis of Carbocyclic β -Amino Acids 375
 - 8.2.5 Synthesis of Carbocyclic β -Amino Acids from Chiral Monoterpene β -Lactams 377
 - 8.2.6 Synthesis of Carbocyclic β -Amino Acids by Enantioselective Desymmetrization of *meso* Anhydrides 378
 - 8.2.7 Miscellaneous 379
 - 8.2.8 Synthesis of Small-Ring Carbocyclic β -Amino Acid Derivatives 383
- 8.3 Synthesis of Functionalized Carbocyclic β -Amino Acid Derivatives 385
- 8.4 Enzymatic Routes to Carbocyclic β -Amino Acids 393
 - 8.4.1 Enantioselective *N*-Acylation of β -Amino Esters 394
 - 8.4.2 Enantioselective *O*-Acylation of *N*-Hydroxymethylated β -Lactams 394
 - 8.4.3 Enantioselective Ring Cleavage of β -Lactams 395
 - 8.4.4 Biotransformation of Carbocyclic Nitriles 396
 - 8.4.5 Enantioselective Hydrolysis of β -Amino Esters 396
 - 8.4.6 Analytical Methods for the Enantiomeric Separation of Carbocyclic β -Amino Acids 397
- 8.5 Conclusions and Outlook 398
- 8.6 Experimental Procedures 399
 - 8.6.1 Synthesis of Hydroxy Amino Ester Ethyl (1*R**,2*S**,4*S**)-2-(Benzyloxycarbonylamino)-4-hydroxycyclohexanecarboxylate (205a) by Oxirane Ring Opening of with Sodium Borohydride 399

- 8.6.2 Synthesis of Bicyclic β -Lactam (1*R**,5*S**)-6-azabicyclo[3.2.0]hept-3-en-7-one (223) by the Addition of Chlorosulfonyl Isocyanate to Cyclopentadiene 399
- 8.6.3 Synthesis of β -Amino Ester Ethyl *cis*-2-aminocyclopent-3-enecarboxylate Hydrochloride (223a) by Lactam Ring-Opening Reaction of Azetidinone 223 400
- 8.6.4 Synthesis of Epoxy Amino Ester Ethyl (1*R**,2*R**,3*R**,5*S**)-2-(*tert*-butoxycarbonylamino)-6-oxabicyclo[3.1.0]hexane-3-carboxylate (225) by Epoxidation of Amino Ester 224 400
- 8.6.5 Synthesis of Azido Ester Ethyl (1*R**,2*R**,3*R**,4*R**)-4-Azido-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclopentanecarboxylate (229) by Oxirane Ring Opening of with Sodium Azide 401
- 8.6.6 Isomerization of Azido Amino Ester to Ethyl (1*S**,2*R**,3*R**,4*R**)-4-Azido-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclopentanecarboxylate (230) 401
- 8.6.7 Lipase-Catalyzed Enantioselective Ring Cleavage of 4,5-Benzo-7-azabicyclo[4.2.0]octan-8-one (271), Synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Hydrochlorides (307 and 308) 402
- 8.6.8 Lipase-Catalyzed Enantioselective Hydrolysis of Ethyl *trans*-2-aminocyclohexane-1-carboxylate (298), Synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-2-Aminocyclohexane-1-carboxylic Acid Hydrochlorides (309 and 310) 404
- References 405

9 Synthetic Approaches to α,β -Diamino Acids 411

Alma Viso and Roberto Fernández de la Pradilla

- 9.1 Introduction 411
- 9.2 Construction of the Carbon Backbone 411
 - 9.2.1 Methods for the Formation of the C_b–C_c Bond 411
 - 9.2.1.1 Reaction of Glycinates and Related Nucleophiles with Electrophiles 411
 - 9.2.1.2 Dimerization of Glycinates 416
 - 9.2.1.3 Through Cyclic Intermediates 417
 - 9.2.2 Methods in Which the C_a–C_b Bond is Formed 420
 - 9.2.2.1 Nucleophilic Synthetic Equivalents of CO₂R 420
 - 9.2.2.2 Electrophilic Synthetic Equivalents of CO₂R and Other Approaches 423
 - 9.2.3 Methods in Which the C_bC_{b'} or C_cC_{c'} Bonds are Formed 424
- 9.3 Introduction of the Nitrogen Atoms in the Carbon Backbone 425
 - 9.3.1 From Readily Available α -Amino Acids 425
 - 9.3.2 From Allylic Alcohols and Amines 427
 - 9.3.3 From Halo Alkanoates 428
 - 9.3.4 From Alkenoates 429
 - 9.3.5 Electrophilic Amination of Enolates and Related Processes 431
 - 9.3.6 From β -Keto Esters and Related Compounds 433
- 9.4 Conclusions 433

9.5	Experimental Procedures	434
9.5.1	(<i>S</i> ₅ ,2 <i>R</i> ,3 <i>S</i>)-(+)-Ethyl-2- <i>N</i> -(diphenylmethyleneamino)-3- <i>N</i> -(<i>p</i> -toluenesulfinyl)-amino-3-phenylpropanoate (14b)	434
9.5.2	Synthesis of Ethyl (2 <i>R</i> ,3 <i>R</i>)-3-amino-2-(4-methoxyphenyl)aminopentanoate 32a via Asymmetric aza-Henry Reaction	434
	References	435
10	Synthesis of Halogenated α-Amino Acids	441
	<i>Madeleine Strickland and Christine L. Willis</i>	
10.1	Introduction	441
10.2	Halogenated Amino Acids with a Hydrocarbon Side-Chain	442
10.2.1	Halogenated Alanines and Prolines	442
10.2.2	Halogenated α -Amino Acids with Branched Hydrocarbon Side-Chains	445
10.2.2.1	Halogenated Valines and Isoleucines	445
10.2.2.2	Halogenated Leucines	451
10.3	Halogenated Amino Acids with an Aromatic Side-Chain	457
10.3.1	Halogenated Phenylalanines and Tyrosines	457
10.3.2	Halogenated Histidines	460
10.3.3	Halogenated Tryptophans	462
10.4	Halogenated Amino Acids with Heteroatoms in the Aliphatic Side-Chain	463
10.4.1	Halogenated Aspartic and Glutamic Acids	463
10.4.2	Halogenated Threonine and Lysine	465
	References	466
11	Synthesis of Isotopically Labeled α-Amino Acids	473
	<i>Caroline M. Reid and Andrew Sutherland</i>	
11.1	Introduction	473
11.2	Enzyme-Catalyzed Methods	473
11.3	Chiral Pool Approach	477
11.4	Chemical Asymmetric Methods	483
11.5	Conclusions	488
11.6	Experimental Procedures	489
11.6.1	Biocatalysis: Synthesis of [¹⁵ N]L-amino Acids from α -Keto Esters using a One-Pot Lipase-Catalyzed Hydrolysis and Amino Acid Dehydrogenase-Catalyzed Reductive Amination	489
11.6.2	Chiral Pool: Preparation of Aspartic Acid Semi-Aldehydes as Key Synthetic Intermediates; Synthesis of Methyl (2 <i>S</i>)- <i>N</i> , <i>N</i> -di- <i>tert</i> -butoxycarbonyl-2-amino-4-oxobutanoate from L-aspartic Acid	489
11.6.3	Asymmetric Methods: Asymmetric Alkylation Using the Williams' Oxazine and Subsequent Hydrogenation to Give the α -Amino Acid	490
	References	491

12	Synthesis of Unnatural/Nonproteinogenic α-Amino Acids	495
	<i>David J. Ager</i>	
12.1	Introduction	495
12.2	Chemical Methods	497
12.2.1	Resolution Approaches	497
12.2.2	Side-Chain Methods	497
12.2.2.1	Introduction of the Side-Chain	497
12.2.2.2	Modifications of the Side-Chain	500
12.2.3	Introduction of Functionality	502
12.2.3.1	Nitrogen Introduction	502
12.2.3.2	Carboxylic Acid Introduction	503
12.2.3.2.1	Strecker Reaction	503
12.2.4	Hydrogenation	504
12.2.5	Other Chemical Methods	508
12.3	Enzymatic Methods	508
12.3.1	Acyases	509
12.3.2	Hydantoinases	510
12.3.3	Ammonia Lyases	510
12.3.4	Transaminases	511
12.3.5	Dehydrogenases	513
12.3.6	Amino Acid Oxidases	514
12.3.7	Decarboxylases	515
12.4	Conclusions	516
12.5	Experimental Procedures	516
12.5.1	Side-Chain Introduction with a Phase-Transfer Catalyst	516
12.5.2	Introduction of Nitrogen Through an Oxazolidinone Enolate with a Nitrogen Electrophile	517
12.5.3	Asymmetric Hydrogenation with Knowles' Catalyst	518
12.5.4	Asymmetric Hydrogenation with Rh(DuPhos) Followed by Enzyme-Catalyzed Inversion of the α -Center	519
	References	520
13	Synthesis of γ- and δ-Amino Acids	527
	<i>Andrea Trabocchi, Gloria Menchi, and Antonio Guarna</i>	
13.1	Introduction	527
13.2	γ -Amino Acids	528
13.2.1	GABA Analogs	528
13.2.2	α - and β -Hydroxy- γ -Amino Acids	534
13.2.3	Alkene-Derived γ -Amino Acids	539
13.2.4	SAAAs	541
13.2.5	Miscellaneous Approaches	542
13.3	δ -Amino Acids	547
13.3.1	SAAAs	547
13.3.1.1	Furanoid δ -SAA	547