

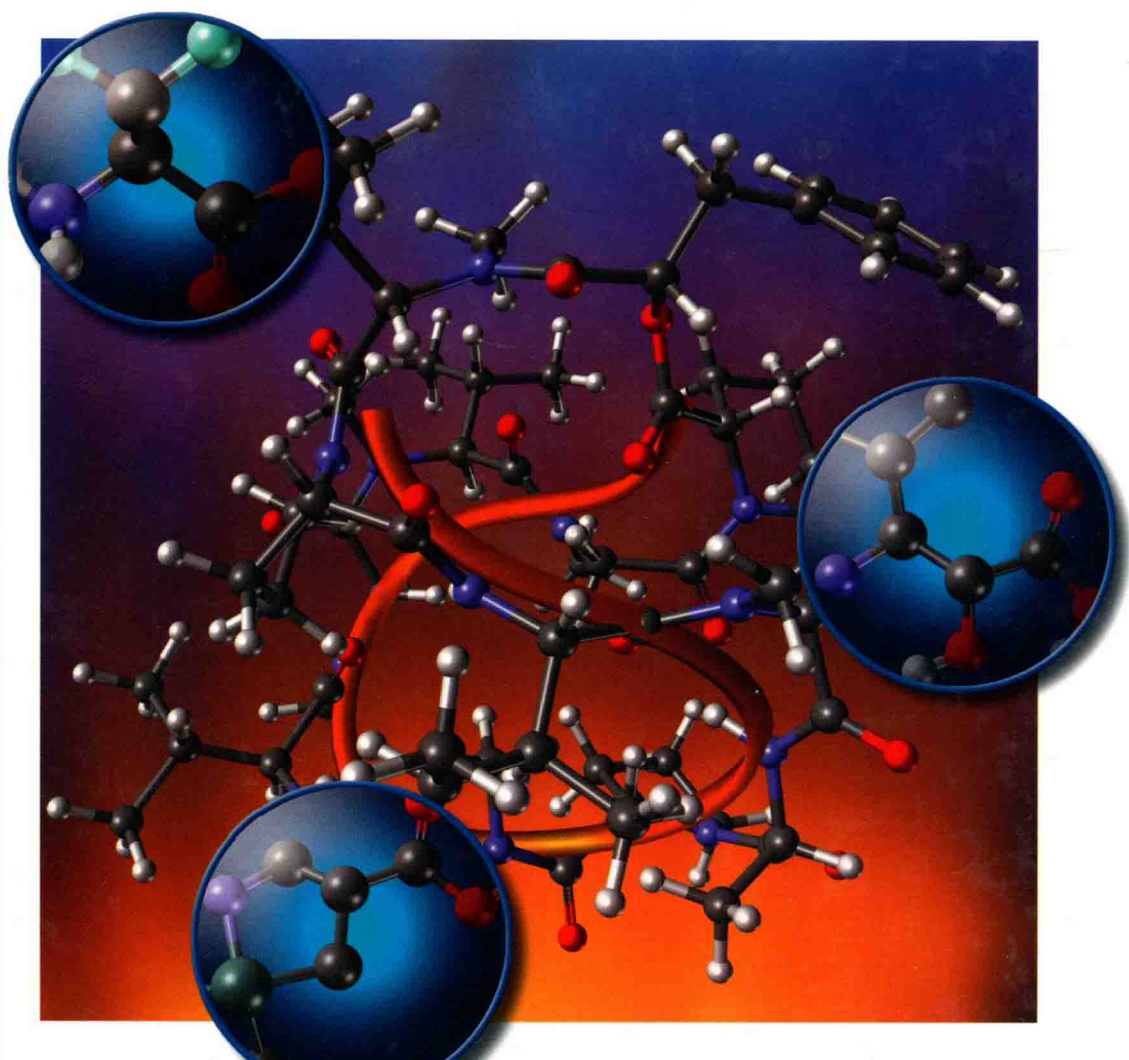
Edited by Andrew B. Hughes

 WILEY-VCH

# Amino Acids, Peptides and Proteins in Organic Chemistry

Volume 2

Modified Amino Acids, Organocatalysis  
and Enzymes



# Amino Acids, Peptides and Proteins in Organic Chemistry

Volume 2 - Modified Amino Acids, Organocatalysis  
and Enzymes

*Edited by*  
*Andrew B. Hughes*



WILEY-  
VCH

WILEY-VCH Verlag GmbH & Co. KGaA

#### **The Editor**

##### **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** Betz-Druck GmbH, Darmstadt

**Bookbinding** Litges & Dopf GmbH, Heppenheim

**Cover Design** Schulz Grafik Design, Fußgönheim

Printed in the Federal Republic of Germany

Printed on acid-free paper

**ISBN:** 978-3-527-32098-1

**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

### **Neil Audsley**

The Food and Environment  
Research Agency  
Sand Hutton  
York YO41 1LZ  
UK

### **Sonia Barberis**

Universidad Nacional de San Luis,  
Chacabuco y Pedernera  
Faculty of Chemistry, Biochemistry and  
Pharmacy  
San Luis  
Argentina

### **Annette G. Beck-Sickinger**

Leipzig University  
Institute of Biochemistry  
Brüderstraße 34  
04103 Leipzig  
Germany

### **Karen Brand**

Leipzig University  
Institute of Biochemistry  
Brüderstraße 34  
04103 Leipzig  
Germany

### **Keith Brocklehurst**

Queen Mary, University of London  
School of Biological and Chemical  
Sciences  
Fogg Building, Mile End Road  
London E1 4NS  
UK

### **Arwen J. Cross**

University of Sydney  
School of Molecular and Microbial  
Biosciences  
G08 Biochemistry Building  
NSW 2006  
Sydney  
Australia

### **Valery M. Dembitsky**

The Hebrew University of Jerusalem  
School of Pharmacy  
Department of Medicinal Chemistry  
and Natural Products  
PO Box 12065  
Jerusalem 91120  
Israel

**Marc Devocelle**

Royal College of Surgeons in Ireland  
Centre for Synthesis & Chemical  
Biology  
Department of Pharmaceutical &  
Medicinal Chemistry  
123 St. Stephens Green  
Dublin 2  
Ireland

**Sean Doyle**

National University of Ireland  
Maynooth  
Department of Biology  
Maynooth, Co. Kildare  
Ireland

**Nicholas Gathergood**

Dublin City University  
School of Chemical Sciences and  
National Institute for Cellular  
Biotechnology  
Glasnevin, Dublin 9  
Ireland

**Giovanna Ghirlanda**

Arizona State University  
Department of Chemistry and  
Biochemistry  
Tempe, AZ 85287-1604  
USA

**Darren Griffith**

Royal College of Surgeons in Ireland  
Centre for Synthesis & Chemical  
Biology  
Department of Pharmaceutical &  
Medicinal Chemistry  
123 St. Stephens Green  
Dublin 2  
Ireland

**Sheraz Gul**

European ScreeningPort GmbH  
Schnackenburgallee 114  
22525 Hamburg  
Germany

**Fanny Guzmán**

Pontificia Universidad Católica de  
Valparaíso  
Institute of Biology  
Avenida Brasil 2950  
Valparaíso  
Chile

**R. Elwyn Isaac**

University of Leeds  
Institute of Integrative and Comparative  
Biology  
Faculty of Biological Sciences  
Leeds LS2 9JT  
UK

**Thomas Hayes**

Dublin City University  
School of Chemical Sciences and  
National Institute for Cellular  
Biotechnology  
Glasnevin  
Dublin 9  
Ireland

**Usama M. Hegazy**

Uppsala University  
Biomedical Center  
Department of Biochemistry and  
Organic Chemistry  
Box 576  
751 23 Uppsala  
Sweden

**Andrés Illanes**

Pontificia Universidad Católica de  
Valparaíso  
School of Biochemical Engineering  
Avenida Brasil 2147  
Valparaíso  
Chile

**Uli Kazmaier**

Universität des Saarlandes  
Institut für Organische Chemie  
Im Stadtwald  
66123 Saarbrücken  
Germany

**Valery P. Kukhar**

National Academy of Sciences of  
Ukraine  
Institute of Bioorganic Chemistry and  
Petrochemistry  
Murmanskaya Street  
Kiev 94  
Ukraine

**Joel P. Mackay**

University of Sydney  
School of Molecular and Microbial  
Biosciences  
G08 Biochemistry Building  
NSW 2006  
Sydney  
Australia

**Robyn E. Mansfield**

University of Sydney  
School of Molecular and Microbial  
Biosciences  
G08 Biochemistry Building  
NSW 2006  
Sydney  
Australia

**Bengt Mannervik**

Uppsala University  
Biomedical Center  
Department of Biochemistry and  
Organic Chemistry  
Box 576  
751 23 Uppsala  
Sweden

**Celine J. Marmion**

Royal College of Surgeons in Ireland  
Centre for Synthesis and Chemical  
Biology  
Department of Pharmaceutical and  
Medicinal Chemistry  
123 St. Stephens Green  
Dublin 2  
Ireland

**Jacqueline M. Matthews**

University of Sydney  
School of Molecular and Microbial  
Biosciences  
G08 Biochemistry Building  
NSW 2006  
Sydney  
Australia

**Javier Narváez-Vásquez**

University of California Riverside  
Department of Botany and Plant  
Sciences  
3401 Watkins Dr.  
Riverside, CA 92521  
USA

**Martha L. Orozco-Cárdenas**

University of California Riverside  
Department of Botany and Plant  
Sciences  
3401 Watkins Dr.  
Riverside, CA 92521  
USA



and

University of California Riverside  
Plant Transformation Research Center  
Riverside, CA 92521  
USA

**Gregory Pearce**

Washington State University  
Institute of Biological Chemistry  
Pullman, WA 99164  
USA

**Richard W. Pickersgill**

Queen Mary, University of London  
School of Biological and Chemical  
Sciences  
Joseph Priestley Building  
Mile End Road  
London E1 4NS  
UK

**Leonard J. Prins**

University of Padova  
Padova Section  
Department of Chemical Sciences and  
ITM-CNR  
Via Marzolo 1  
35131 Padova  
Italy

**Yingmei Qi**

Temple University  
Department of Chemistry  
1901 N. 13th Street  
Philadelphia, PA 19122  
USA

**Vadim D. Romanenko**

National Academy of Sciences of  
Ukraine  
Institute of Bioorganic Chemistry and  
Petrochemistry  
Murmanskaya Street  
Kiev 94  
Ukraine

**Paolo Scrimin**

University of Padova  
Padova Section  
Department of Chemical Sciences and  
ITM-CNR  
Via Marzolo 1  
35131 Padova  
Italy

**Scott McN. Sieburth**

Temple University  
Department of Chemistry  
1901 N. 13th Street  
Philadelphia, PA 19122  
USA

**Morris Srebnik**

The Hebrew University of Jerusalem  
School of Pharmacy  
Department of Medicinal Chemistry  
and Natural Products  
PO Box 12065  
Jerusalem 91120  
Israel

**Joëlle Vidal**

Université de Rennes 1  
CNRS UMR 6510, Chimie et  
Photonique Moléculaires  
Campus de Beaulieu, case 1012  
35042 Rennes Cedex  
France

**Haibo Xie**

Dublin City University  
School of Chemical Sciences and  
National Institute for Cellular  
Biotechnology  
Glasnevin, Dublin 9  
Ireland

## Contents

### List of Contributors XIX

### Part One Synthesis and Chemistry of Modified Amino Acids 1

<b>1</b>	<b>Synthesis and Chemistry of <math>\alpha,\beta</math>-Didehydroamino Acids</b>	<b>3</b>
	<i>Uli Kazmaier</i>	
1.1	Introduction	3
1.2	Synthesis of DDAAAs	3
1.2.1	DDAAAs via Eliminations	3
1.2.1.1	DDAAAs via $\beta$ -Elimination	3
1.2.1.1.1	From $\beta$ -Hydroxy Amino Acids	3
1.2.1.1.2	From $\beta$ -Thio- and Selenoamino Acids	5
1.2.1.2	Elimination from <i>N</i> -Hydroxylated and -Chlorinated Amino Acids and Peptides	6
1.2.1.3	DDAAAs from $\alpha$ -Oxo Acids and Amides	6
1.2.1.4	DDAAAs from Azides	7
1.2.2	DDAAAs via C=C Bond Formation	7
1.2.2.1	DDAAAs via Azlactones [5(4H)-Oxazolones]	7
1.2.2.2	DDAAAs via Horner–Emmons and Wittig Reactions	8
1.2.2.3	DDAAAs via Enolates of Nitro- and Isocyano- and Iminoacetates	10
1.2.3	DDAAAs via C–C Bond Formation	12
1.2.3.1	DDAAAs via Heck Reaction	12
1.2.3.2	DDAAAs via Cross-Coupling Reactions	13
1.3	Reactions of DDAAAs	14
1.3.1	Additions to the C=C Bond	14
1.3.1.1	Nucleophilic Additions	14
1.3.1.2	Radical Additions	15
1.3.1.3	Cycloadditions	17
1.3.1.3.1	[3+2] Cycloadditions	18

1.3.1.3.2	[4+2] Cycloadditions	19
1.3.1.4	Catalytic Hydrogenations	19
1.3.2	Halogenations of DDAAAs	21
1.4	Conclusions	21
1.5	Experimental Procedures	22
1.5.1	General Procedure for the Two-Step Synthesis of Dehydroisoleucine Derivatives	22
1.5.2	General Procedure for the Synthesis of $\alpha,\beta$ -Didehydroamino Acid Esters by the Phosphorylglycine Ester Method using DBU	22
1.5.3	General Procedure for the Synthesis of $\alpha$ -Chloroglycine Derivatives	23
1.5.4	General Procedure for the Synthesis of Homomeric Dimers	23
1.5.5	General Procedure for the Synthesis of (Z)- $\gamma$ -Alkyl- $\alpha,\beta$ -Didehydroglutamates from Imino Glycinates	24
1.5.6	Palladium-Catalyzed Trifold Heck Coupling	25
1.5.7	General Experimental Procedure for Conjugate Addition of Alkyl iodides to Chiral $\alpha,\beta$ -Unsaturated Amino Acid Derivatives	25
1.5.8	Bromination of <i>N</i> -tert-Butyloxycarbonyldehydroamino Acids	26
	References	26
<b>2</b>	<b>Synthesis and Chemistry of <math>\alpha</math>-Hydrazino Acids</b>	<b>35</b>
	<i>Joëlle Vidal</i>	
2.1	Introduction	35
2.1.1	$\alpha$ -Hydrazino Acids are Potent Inhibitors of Pyridoxal Phosphate Enzymes	35
2.1.2	Natural Products Containing the N–N–C–C=O Fragment	36
2.1.3	Synthetic Bioactive Products Containing the N–N–C–C=O Fragment	39
2.1.4	The CO–N–N–C–CO–NH Fragment is a Turn Inducer in Pseudopeptides	40
2.2	Synthesis	41
2.2.1	Disconnection 1a: Reaction of Hydrazine Derivatives with Carbon Electrophiles	41
2.2.1.1	Reaction of Hydrazine Derivatives with Enantiopure $\alpha$ -Halogeno Acids	42
2.2.1.2	Reaction of Hydrazine Derivatives with Enantiopure Activated $\alpha$ -Hydroxy Esters	42
2.2.1.3	Mitsunobu Reaction of Aminophthalimide Derivatives with Enantiopure $\alpha$ -Hydroxy Esters	43
2.2.1.4	Reaction of Hydrazine Derivatives with Nonracemic Epoxides	43
2.2.1.5	Enantioselective Conjugate Addition of Hydrazines to $\alpha,\beta$ -Unsaturated Imides	44
2.2.2	Disconnection 1b: Stereoselective Synthesis using Azodicarboxylates	44
2.2.2.1	Stereoselective $\alpha$ -Hydrazination of Chiral Carbonyl Compounds using Azodicarboxylates	45

2.2.2.2	Catalytic Enantioselective $\alpha$ -Hydrazination of Carbonyl Compounds using Azodicarboxylates	46
2.2.2.3	Stereoselective $\alpha$ -Hydrazination of Chiral $\alpha,\beta$ -Unsaturated Carboxylates using Azodicarboxylates	50
2.2.3	Disconnection 2: Synthesis from Chiral Nonracemic $\alpha$ -Amino Acids	52
2.2.3.1	Schestakow Rearrangement of Hydantoic Acids Prepared from $\alpha$ -Amino Acids	52
2.2.3.2	Reduction of <i>N</i> -Nitroso- $\alpha$ -Amino Esters	52
2.2.3.3	Amination of $\alpha$ -Amino Acids by Hydroxylamine Derivatives	52
2.2.3.4	Amination of $\alpha$ -Amino Acids by Oxaziridines	53
2.2.4	Disconnections 3, 4, and 5: Syntheses from Hydrazones or $\alpha$ -Diazoesters	55
2.2.4.1	Catalytic Enantioselective Hydrogenation of Hydrazones	56
2.2.4.2	Stereoselective and Catalytic Enantioselective Strecker Reaction	56
2.2.4.3	Stereoselective Addition of Organometallic Reagents to Hydrazones	57
2.2.4.4	Stereoselective or Catalytic Enantioselective Mannich-Type Reaction with Hydrazones	58
2.2.4.5	Enantioselective Friedel–Crafts Alkylations with Hydrazones	59
2.2.4.6	Diastereoselective Zinc-Mediated Carbon Radical Addition to Hydrazones	59
2.2.4.7	Catalytic Enantioselective Reaction of $\alpha$ -Diazoesters with Aldehydes and Subsequent Stereoselective Reduction	59
2.2.5	Piperazic Acid and Derivatives by Cycloaddition Reactions	61
2.2.5.1	Diels–Alder Cycloaddition	61
2.2.5.2	1,3-Dipolar Cycloaddition	62
2.3	Chemistry	63
2.3.1	Cleavage of the N–N Bond	63
2.3.2	Reactivity of the Hydrazino Function	67
2.3.2.1	Reaction of Unprotected $\alpha$ -Hydrazino Acid Derivatives with Acylating Reagents	67
2.3.2.2	Reaction of <i>N</i> <sup>1</sup> -Substituted $\alpha$ -Hydrazino Acid Derivatives with Acylating Reagents	69
2.3.2.3	Reaction of <i>N</i> <sup>2</sup> -Protected $\alpha$ -Hydrazino Acid Derivatives with Acylating Reagents	69
2.3.2.4	Reaction with Aldehydes and Ketones	69
2.3.3	Reactivity of the Carboxyl Function	73
2.3.4	Synthesis of Heterocycles	74
2.3.4.1	Cyclization Leading to Piperazic Acid Derivatives	74
2.3.4.2	Other Heterocycles	75
2.4	Conclusions	78
2.5	Experimental Procedures	79
2.5.1	( <i>S</i> )-2-hydrazinosuccinic Acid Monohydrate	79

- 2.5.2 (–)-(R)-*N*<sup>1</sup>,*N*<sup>2</sup>-dibenzoyloxycarbonyl-2-hydrazino-2-phenyl Propionic Acid, Methyl Ester 80
- 2.5.3 (+)-(R)-*N*<sup>1</sup>,*N*<sup>2</sup>-Bis(benzoyloxycarbonyl)-1-hydrazino-2-oxocyclopentane Carboxylic Acid, Ethyl Ester 81
- 2.5.4 (–)-L-*N*-Aminovaline 81
- 2.5.5 (+)-L-*N*-benzyl-*N*-(tert-butoxycarbonylamino)tryptophan, Hexylamine Salt 82
- 2.5.6 (R)-2-(*N*<sup>2</sup>-benzoylhydrazino)-2-(4-dimethylaminophenyl) Acetonitrile 83
- 2.5.7 *tert*-Butoxycarbonylamino-(4-dimethylamino-2-methoxy-phenyl)-acetic Acid Ethyl Ester by Reduction using SmI<sub>2</sub> 84
- 2.5.8 (R)-1,2-bis(benzoyloxycarbonyl)piperazine-3-carboxylic Acid 84
- References 86

### 3 Hydroxamic Acids: Chemistry, Bioactivity, and Solution- and Solid-Phase Synthesis 93

*Darren Griffith, Marc Devocelle, and Celine J. Marmion*

- 3.1 Introduction 93
- 3.2 Chemistry, Bioactivity, and Clinical Utility 93
  - 3.2.1 Chemistry 93
  - 3.2.2 Bioactivity and Clinical Utility 95
    - 3.2.2.1 Hydroxamic Acids as Siderophores 95
    - 3.2.2.2 Hydroxamic Acids as Enzyme Inhibitors 97
      - 3.2.2.2.1 MMP Inhibitors 98
      - 3.2.2.2.2 HDAC Inhibitors 102
      - 3.2.2.2.3 PGHS Inhibitors 104
  - 3.3 Solution-Phase Synthesis of Hydroxamic Acids 106
    - 3.3.1 Synthesis of Hydroxamic Acids Derived from Carboxylic Acid Derivatives 106
      - 3.3.1.1 From Esters 107
      - 3.3.1.2 From Acid Halides 108
      - 3.3.1.3 From Anhydrides 109
      - 3.3.1.4 From [1.3.5]Triazine-Coupled Carboxylic Acids 110
      - 3.3.1.5 From Carbodiimide-Coupled Carboxylic Acids 111
      - 3.3.1.6 From Acyloxyphosphonium Ions 111
      - 3.3.1.7 From Carboxylic Acids Coupled with other Agents 113
    - 3.3.2 Synthesis of Hydroxamic Acids from *N*-acyloxazolidinones 114
    - 3.3.3 Synthesis of Hydroxamic Acids from *gem*-Dicyanoepoxides 115
    - 3.3.4 Synthesis of Hydroxamic Acids from Aldehydes 115
    - 3.3.5 Synthesis of Hydroxamic Acids from Nitro Compounds 116
    - 3.3.6 Synthesis of Hydroxamic Acids via a Palladium-Catalyzed Cascade Reaction 116
    - 3.3.7 Synthesis of *N*-Formylhydroxylamine (Formohydroxamic Acid) 117
    - 3.3.8 Synthesis of Reverse or Retro-Hydroxamates 117
    - 3.3.9 Synthesis of Acylhydroxamic Acids 120

3.4	Solid-Phase Synthesis of Hydroxamic Acids	121
3.4.1	Acidic Cleavage	122
3.4.1.1	O-Tethered Hydroxylamine	122
3.4.1.1.1	Cleavage with 30–90% TFA	122
3.4.1.1.2	Super Acid-Sensitive Linkers	124
3.4.1.2	N-Tethered Hydroxylamine	126
3.4.1.3	Other Methods of Solid-Phase Synthesis of Hydroxamic Acids based on an Acidic Cleavage	126
3.4.2	Nucleophilic Cleavage	128
3.4.2.1	Other Methods	129
3.5	Conclusions	130
3.6	Experimental Procedures	130
3.6.1	Synthesis of 3-Pyridinehydroxamic Acid	130
3.6.2	Synthesis of O-benzylbenzohydroxamic Acid	131
3.6.3	Synthesis of N-methylbenzohydroxamic Acid	131
3.6.4	Synthesis of Isobutyrohydroxamic Acid	132
3.6.5	Synthesis of O-benzyl-2-phenylpropionohydroxamic Acid	132
3.6.6	Synthesis of Methyl 3-(2-quinolinylmethoxy)benzeneacetohydroxamic Acid	133
3.6.7	Synthesis of the Chlamydocin Hydroxamic Acid Analog, <i>cyclo</i> (L-Asu(NHOH)–Aib-L-Phe–D-Pro)	133
3.6.8	Synthesis of O-benzyl-4-methoxybenzohydroxamic Acid	134
3.6.9	Synthesis of O-benzylbenzohydroxamic acid	134
3.6.10	Synthesis of a 4-chlorophenyl Substituted- $\alpha$ -bromohydroxamic acid	134
3.6.11	Synthesis of 4-Chlorobenzohydroxamic Acid	135
3.6.12	Synthesis of Acetohydroxamic Acid	135
3.6.13	Synthesis of N-hydroxy Lactam	136
3.6.14	Synthesis of O- <i>tert</i> -butyl-N-formylhydroxylamine	136
3.6.15	Synthesis of Triacetylsalicylhydroxamic Acid	137
	References	137

#### **4 Chemistry of $\alpha$ -Aminoboronic Acids and their Derivatives** 145

*Valery M. Dembitsky and Morris Srebnik*

4.1	Introduction	145
4.2	Synthesis of $\alpha$ -Aminoboronic Acids	146
4.3	Synthesis of $\alpha$ -Amidoboronic Acid Derivatives	146
4.4	Asymmetric Synthesis via $\alpha$ -Haloalkylboronic Esters	151
4.5	Synthesis of Glycine $\alpha$ -Aminoboronic Acids	154
4.6	Synthesis of Proline $\alpha$ -Aminoboronic Acids	155
4.7	Synthesis of Alanine $\alpha$ -Aminoboronic Acids	162
4.8	Synthesis of Ornithine $\alpha$ -Aminoboronic Acids	164
4.9	Synthesis of Arginine $\alpha$ -Aminoboronic Acids	167
4.10	Synthesis of Phenethyl Peptide Boronic Acids	170
4.11	Synthesis via Zirconocene Species	172

4.12	Synthesis and Activity of Amine-Carboxyboranes and their Derivatives	174
4.13	Synthesis of Boron Analogs of Phosphonoacetates	179
4.14	Conclusions	183
	References	183
<b>5</b>	<b>Chemistry of Aminophosphonic Acids and Phosphonopeptides</b>	<b>189</b>
	<i>Valery P. Kukhar and Vadim D. Romanenko</i>	
5.1	Introduction	189
5.2	Physical/Chemical Properties and Analysis	191
5.3	Synthesis of $\alpha$ -Aminophosphonic Acids	193
5.3.1	Amidoalkylation in the "Carbonyl Compound–Amine–Phosphite" Three-Component System	193
5.3.2	Kabachnik–Fields Reaction	195
5.3.3	Direct Hydrophosphonylation of C=N Bonds	199
5.3.4	Syntheses using C–N and C–C Bond-Forming Reactions	206
5.4	Synthesis of $\beta$ -Aminophosphonates	212
5.5	Synthesis of $\gamma$ -Aminophosphonates and Higher Homologs	219
5.6	Phosphono- and Phosphinopeptides	227
5.6.1	General Strategies for the Phosphonopeptide Synthesis	229
5.6.2	Peptides Containing P-terminal Aminophosphonate or Aminophosphinate Moiety	230
5.6.3	Peptides Containing an Aminophosphinic Acid Unit	233
5.6.4	Peptides Containing a Phosphonamide or Phosphinamide Bond	236
5.6.5	Phosphonodepsipeptides Containing a Phosphonoester Moiety	239
5.6.6	Peptides Containing a Phosphonic or Phosphinic Acid Moiety in the Side-Chain	240
5.7	Remarks on the Practical Utility of Aminophosphonates	240
5.8	Conclusions	245
5.9	Experimental Procedures	246
5.9.1	Synthesis of N-Protected $\alpha$ -aminophosphinic Acid 10 ( $R^1 = \text{EtOCOCH}_2$ , $R^2 = \text{Me}$ )	246
5.9.2	Synthesis of Phosphonomethylaminocyclopentane-1-carboxylic Acid (17)	246
5.9.3	General Procedure for Catalytic Asymmetric Hydrophosphonylation. Synthesis of $\alpha$ -Aminophosphonate 39 ( $R^1 = \text{C}_5\text{H}_{11}$ , $R^2 = \text{Ph}_2\text{CH}$ )	247
5.9.4	General Procedure of the Asymmetric Aminohydroxylation Reaction: Synthesis of $\beta$ -Amino- $\alpha$ -hydroxyphosphonates 87	247
5.9.5	Dimethyl ( <i>S,S</i> )-(–)-3- <i>N,N</i> -bis( $\alpha$ -Methylbenzyl) amino-2-oxopropylphosphonate ( <i>S,S</i> )-100 and Dimethyl 3-[( <i>S,S</i> )- <i>N,N</i> -bis( $\alpha$ -methylbenzylamino)-(2 <i>R</i> )-hydroxypropylphosphonate ( <i>R,S,S</i> )-101	248
5.9.6	General Procedure for the Preparation of Dialkyl Phenyl(4-pyridylcarbonylamino) methyl-phosphonates 126	249

- 5.9.7 Synthesis of 1-[(Benzyloxy) carbonyl] propyl-N1-[[1,1'-biphenyl-4-yl-methyl](methoxy) phosphoryl] methyl}leucinamide (159a) 249  
References 249

## 6 Chemistry of Silicon-Containing Amino Acids 261

*Yingmei Qi and Scott McN. Sieburth*

- 6.1 Introduction 261  
6.1.1 Stability of Organosilanes 261  
6.1.2 Sterics and Electronics 262  
6.2 Synthesis of Silicon-Containing Amino Acids 263  
6.2.1 Synthesis of  $\alpha$ -Silyl Amino Acids and Derivatives 263  
6.2.2 Synthesis of  $\beta$ -Silylalanine and Derivatives 263  
6.2.3 Synthesis of  $\omega$ -Silyl Amino Acids and Derivatives 267  
6.2.4 Synthesis of Silyl-Substituted Phenylalanines 269  
6.2.5 Synthesis of Amino Acids with Silicon  $\alpha$  to Nitrogen 269  
6.2.6 Synthesis of Proline Analogs with Silicon in the Ring 269  
6.3 Reactions of Silicon-Containing Amino Acids 271  
6.3.1 Stability of the Si-C Bond 272  
6.3.2 Functional Group Protection 272  
6.3.3 Functional Group Deprotection 272  
6.4 Bioactive Peptides Incorporating Silicon-Substituted Amino Acids 272  
6.4.1 Use of  $\beta$ -Silylalanine 272  
6.4.2 Use of *N*-Silylalkyl Amino Acids 274  
6.4.3 Use of Silaproline 274  
6.5 Conclusions 275  
6.6 Experimental Procedures 276  
6.6.1 L- $\beta$ -Trimethylsilylalanine 23 276  
6.6.2 ( $\pm$ )- $\beta$ -Trimethylsilylalanine 23 276  
6.6.3 L- $\beta$ -Trimethylsilylalanine 23 277  
6.6.4 ( $\pm$ )-*p*-Trimethylsilylphenylalanine 60 277  
6.6.5 L-4-Dimethylsilaproline 100 278  
References 278

## Part Two Amino Acid Organocatalysis 281

### 7 Catalysis of Reactions by Amino Acids 283

*Haibo Xie, Thomas Hayes, and Nicholas Gathergood*

- 7.1 Introduction 283  
7.2 Aldol Reaction 285  
7.2.1 Intramolecular Aldol Reaction and Mechanisms 285  
7.2.1.1 Intramolecular Aldol Reaction 285  
7.2.1.2 Mechanisms 287  
7.2.2 Intermolecular Aldol Reaction and Mechanisms 289  
7.2.2.1 Intermolecular Aldol Reaction 289



7.2.2.2	Mechanisms	292
7.2.3	Carbohydrate Synthesis	294
7.2.3.1	Carbohydrate Synthesis	294
7.2.3.2	Synthesis of Amino Sugars	297
7.3	Mannich Reaction	298
7.3.1	$\alpha$ -Aminomethylation	298
7.3.2	Direct Mannich Reaction	298
7.3.3	Indirect Mannich Reaction using Ketone Donors	303
7.3.4	anti-Mannich Reactions	303
7.4	$\alpha$ -Amination Reaction	306
7.5	Michael Reaction	308
7.5.1	Mechanism for Iminium Ion-Catalyzed Michael Reaction	309
7.5.1.1	Iminium Ion-Catalyzed Intermolecular Michael Reactions	309
7.5.2	Mechanism for the Enamine-Catalyzed Michael Reaction	313
7.5.2.1	Enamine-Catalyzed Intramolecular Michael Reactions	313
7.5.2.2	Enamine-Catalyzed Intermolecular Michael Reactions	313
7.6	Morita–Baylis–Hillman Reaction and Its Aza-Counterpart	319
7.6.1	Morita–Baylis–Hillman Reactions	319
7.6.2	Aza-Morita–Baylis–Hillman Reactions	320
7.7	Miscellaneous Amino Acid-Catalyzed Reactions	321
7.7.1	Diels–Alder Reaction	322
7.7.2	Knoevenagel Condensation	322
7.7.3	Reduction and Oxidation	323
7.7.4	Rosenmund–von Braun Reaction	326
7.7.5	Activation of Epoxides	326
7.7.6	$\alpha$ -Fluorination of Aldehydes and Ketones	327
7.7.7	$S_N2$ Alkylation	328
7.8	Sustainability of Amino Acid Catalysis	328
7.8.1	Toxicity and Ecotoxicity of Amino Acid Catalysis	328
7.8.2	Amino Acid Catalysis and Green Chemistry	329
7.9	Conclusions and Expectations	330
7.10	Typical Procedures for Preferred Catalysis of Reactions by Amino Acids	330
	References	333

### Part Three Enzymes 339

8	<b>Proteases as Powerful Catalysts for Organic Synthesis</b>	341
	<i>Andrés Illanes, Fanny Guzmán, and Sonia Barberis</i>	
8.1	Enzyme Biocatalysis	341
8.2	Proteolytic Enzymes: Mechanisms and Characteristics	345
8.3	Proteases as Process Catalysts	348
8.4	Proteases in Organic Synthesis	350