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Additional and Supplementary Volumes to the 4th Edition

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TO THE 4TH EDITION

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Preface

As we approach the 100th anniversary of Emil Fischer's first synthesis of peptides, we bring together in a new presentation the wide variety of topics which demonstrate how far our field has grown and indicate the challenges that lie ahead. These five volumes cover the core of peptide and peptidomimetic chemistry and bring to peptide scientists, comprehensive and critical presentations in the *Houben–Weyl* tradition. Thus, the chapters are not encyclopedic, but rather focused on the most effective routes for peptide and peptidomimetic synthesis.

In 1974, Professor Erich Wünsch edited two *Houben–Weyl* volumes on the Synthesis of Peptides. That was a monumental undertaking and provided a resource widely used by chemists to prepare peptides and their derivatives with maximum attention to yield and purity of products. The current volumes continue these principles but encompass a much larger effort in the area of the organic chemistry of peptides and peptidomimetics. We as editors followed the *Houben–Weyl* concept of emphasizing protocols and reactions. Procedures for the often-used protections, deprotections, activations, and peptide and peptidomimetic bond formations remain the critical theme in all of the chapters. In addition, we make certain that there is a continuity that joins ongoing productivity in research to the accomplishments of the pioneers of our field. This format sets the stage for future scientists to undertake important research.

The founders of the field of peptide research paid great attention to methodology and isolation of products. The development of analytical and spectroscopic tools has enabled peptide scientists to create molecules of incredible variety and purity. Current researchers are in many ways mainly concerned with the interface between organic and biological chemistry. Thus, there is a strong emphasis on biologically interesting peptides and peptidomimetics in our volumes. However, the protocols and methodology covered in these volumes can also be applied to design novel materials, nanostructures, liquid crystals, and molecular sensors. Peptides and peptidomimetics represent structures applicable to broad vistas of molecular designs.

Recent developments in nucleic acids and protein sciences have allowed researchers to unravel the mechanisms of the biological action of many peptide ligands. As a consequence, many analogues and mimetics of natural ligands have been designed and synthesized. In these volumes we have paid substantial attention to these advances. With the exciting developments in genomics, proteomics, and pharmaconomics, the field of peptide and peptidomimetic research is expanding into new areas of molecular diversity. As a result, peptides remain a key component of the molecules of life.

The five volumes simultaneously represent a tribute to the pioneers in our field led by Emil Fischer and to the key figures who guided us more recently including Vincent du Vigneaud and Bruce Merrifield. We also acknowledge the hard work and creativity of all the scientists who have made substantial contributions to the chemistry of peptides and peptidomimetics. They are too numerous to name here. Nearly one hundred authors wrote chapters to create these volumes. Finally, the volumes are a challenge for future scientists to continue to make exciting discoveries as the new century unfolds.

The volumes are divided into sections covering a broad spectrum of reactions involved in peptide chemistry, synthesis of building blocks and target structures. Volume E 22a covers the protection of main-chain and side-chain functional groups, methods of peptide bond formation, and aspects of peptide synthesis in solution and on solid supports. Volume E 22b includes synthesis of large peptides and proteins. Specific methods are illustrated for the preparation of cysteine peptides, peptidomimetics, and conjugates such as glycopeptides, lipopeptides, phosphopeptides, and sulfated peptides. Cyclic peptides are extensively treated in this section. Volume E 22b concludes with a section on purification, analysis, and spec-

trometry of peptidic structures. Quality standards and comparative syntheses are also presented. Volume E 22c deals with peptidomimetic structures including side-chain-modified and main-chain-altered structures. In this volume, secondary structure inducing mimetics and scaffolds are treated. The synthesis of peptide nucleic acid (PNA) structures is also contained in this volume. Volume E 22d deals with *de novo* designed peptide-like molecules including template-assisted formation of helices, sheets, and loops. In addition, coiled coils are covered. Reactive peptides are presented. These molecules are composed of peptidic structures containing a wide variety of reactive groups for biologically important targets. The series concludes with a chapter on peptide natural products which are illustrative of nature's formulation of biologically active peptides and peptidomimetics. These are points of departure for peptide chemists to design and synthesize analogues and mimetics. The final volume of the series, E22e is an index volume containing an authors' index, substance index and preparation index

This series on the synthetic aspects of peptides and peptidomimetics could not have come about without the dedication and commitment of my three coeditors, Arthur Felix, Luis Moroder, and Claudio Toniolo. Each brought a wealth of experience, insight, and knowledge to formulate the scope of the volumes and critically review each of the chapters. In addition, the coeditors and I wish to thank Dr. Guido F. Herrmann for his unflagging support throughout the project. The professional staff of Thieme, led by Dr. Fiona Shortt, have worked tirelessly to ensure that the volumes appear with great attention to detail consistent with the *Houben–Weyl* tradition.

As a final note, the success of this venture rests with you the scientists throughout the world. We will know if we have created a useful set of volumes by the attention paid to them. If we have succeeded, there can be no greater satisfaction.

Murray Goodman
Editor-in-Chief
San Diego, USA
May 2004

Contents to all Volumes

Volume E 22a

Synthesis of Peptides

- 1 Scope of the Volumes**
- 2 Protection of Functional Groups**
- 3 Peptide Bond Formation**
- 4 Synthesis of Peptides**

Volume E 22b

- 5 Methods for Protein Synthesis**
- 6 Specific Methods**
- 7 Analytics of Synthetic Peptides**

Volume E 22c

Synthesis of Peptidomimetics

- 8 Introduction to the Synthesis of Peptidomimetics**
- 9 Side-Chain-Modified Peptides**
- 10 Main-Chain-Modified Peptides**
- 11 Combined Side-Chain- and Main-Chain-Modified Peptides**
- 12 Peptides Incorporating Secondary Structure Inducers and Mimetics**

Volume E 22d

- 13 De Novo Peptide Structures**
- 14 Macropeptide Structures**
- 15 Reactive Peptides**
- 16 Synthesis of Peptide Natural Products**

Volume E 22e

- 17 Authors' Index**
- 18 Keyword Index**
- 19 Preparation Index**

Table of Contents

Volume E 22c

8	Introduction to the Synthesis of Peptidomimetics	1
	(<i>C. Toniolo and M. Goodman</i>)	
9	Side-Chain-Modified Peptides	3
	(<i>A. M. Felix</i>)	
9.1	Synthesis of Side-Chain Conformationally Restricted α-Amino Acids	5
	(<i>V. J. Hruby, G. Han, and P. M. Gitsu</i>)	
9.1.1	β -Methylphenylalanine	6
9.1.1.1	Asymmetric Epoxide Ring Opening	6
9.1.1.2	Asymmetric Aziridine Ring Opening	10
9.1.1.3	Through Chiral Auxiliary Oxazolidinone	10
9.1.2	β ,2,6-Trimethyltyrosine	10
9.1.2.1	Through Chiral Auxiliary Oxazolidinone	12
9.1.3	β -Methylnaphthylalanine	21
9.1.3.1	Asymmetric Aziridine Ring Opening	21
9.1.3.2	Through Chiral Auxiliary Oxazolidinone	23
9.1.4	1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid	23
9.1.4.1	Cyclization of Phenylalanine with Formaldehyde	24
9.1.4.2	Alkylation Followed by Resolution Using Menthol	24
9.1.4.3	Resolution Using Mandelic Acid	26
9.1.5	Substituted Phenylglycine	28
9.1.5.1	The Chiral Strecker Reaction	28
9.1.5.2	Evans Electrophilic Azidation	29
9.1.6	Substituted Glutamic Acid	31
9.1.6.1	γ -Monosubstituted Glutamic Acid	32
9.1.6.1.1	Alkylation of Glutamic Acid	32
9.1.6.1.2	Alkylation of Pyroglutamic Acid	33
9.1.6.2	β , γ -Disubstituted Glutamic Acid	34
9.1.6.2.1	Asymmetric Diels–Alder Reaction	34
9.1.6.2.2	Simmons–Smith Cyclization	38
9.1.6.3	γ , γ -Disubstituted Glutamic Acid	40
9.1.6.3.1	Asymmetric Simmons–Smith Cyclization	40
9.1.7	Substituted Cysteine	42
9.1.7.1	β -Methylcysteine	43
9.1.7.1.1	Nucleophilic Substitution	43
9.1.7.2	β -Phenylcysteine	45
9.1.7.2.1	Oxazoline Ring Opening	45
9.1.7.2.2	Through Auxiliary Oxazolidinone	45

9.2	Synthesis of Peptides Containing Proline Analogues	52
	<i>(P. Thamm, H.-J. Musiol, and L. Moroder)</i>	
9.2.1	Aziridine-2-carboxylic Acid	55
9.2.1.1	Synthesis of Aziridine-2-carboxylic Acid	56
9.2.1.2	Protected Aziridine-2-carboxylic Acid Derivatives	59
9.2.1.3	Synthesis of Aziridine-2-carboxylic Acid Peptides	60
9.2.1.3.1	Acylation with N-Protected Aziridine-2-carboxylic Acid	60
9.2.1.3.2	2-Carbonylaziridine Peptides from N-Terminal Serine/Threonine Peptides	60
9.2.1.3.3	Acylation of 2-Carbonylaziridine Peptides	60
9.2.1.3.4	Deprotection of Aziridine-2-carboxylic Acid Peptides	61
9.2.2	Azetidine-2-carboxylic Acid	62
9.2.2.1	Synthesis of Azetidine-2-carboxylic Acid	62
9.2.2.2	Synthesis of Azetidine-2-carboxylic Acid Peptides	63
9.2.3	Five-Membered Proline Analogues	64
9.2.3.1	Hydroxyproline	64
9.2.3.2	Proline Analogues Derived from Hydroxyproline	67
9.2.3.3	Azaprolines	68
9.2.3.3.1	Pyrazolidine-2-carboxylic Acid	68
9.2.3.3.1.1	Synthesis of Pyrazolidine-2-carboxylic Acid Derivatives	69
9.2.3.3.1.2	Synthesis of Pyrazolidine-2-carboxylic Acid Peptides	69
9.2.3.3.2	Imidazolidine-2-carboxylic Acid	70
9.2.3.3.3	Pyrazolidine-3-carboxylic Acid	71
9.2.3.3.3.1	Synthesis of Pyrazolidine-3-carboxylic Acid and Related Derivatives .	71
9.2.3.3.3.2	Synthesis of Pyrazolidine-3-carboxylic Acid Peptides	72
9.2.3.4	Oxaprolines	72
9.2.3.4.1	Oxazolidine-4-carboxylic Acid	72
9.2.3.4.1.1	Synthesis of Oxazolidine-4-carboxylic Acid Peptides	73
9.2.3.4.1.2	Synthesis of Side-Chain-Substituted Oxazolidine-4-carboxylic Acid Peptides	73
9.2.3.4.2	Isoxazolidine-3-carboxylic Acid	73
9.2.3.4.2.1	Synthesis of Isoxazolidine-3-carboxylic Acid Peptides	74
9.2.3.5	Thiaprolines	74
9.2.3.5.1	Thiazolidine-2-carboxylic Acid	74
9.2.3.5.1.1	Synthesis of Thiazolidine-2-carboxylic Acid Peptides	74
9.2.3.5.2	Thiazolidine-4-carboxylic Acid	75
9.2.3.5.2.1	Synthesis of Thiazolidine-4-carboxylic Acid and Related Analogues .	75
9.2.3.5.2.2	Synthesis of Thiazolidine-4-carboxylic Acid Peptides	76
9.2.4	Six-Membered Proline Analogues	77
9.2.4.1	Pipecolic Acid	77
9.2.4.1.1	Synthesis of Pipecolic Acid	77
9.2.4.1.2	Synthesis of Pipecolic Acid Peptides	77
9.2.4.2	Azapipecolic Acids	78
9.2.4.2.1	Piperazine-2-carboxylic Acid	78
9.2.4.2.1.1	Synthesis of Piperazine-2-carboxylic Acid Peptides	79
9.2.4.2.2	Piperidazine-3-carboxylic Acid (Piperazic Acid)	79
9.2.4.2.2.1	Synthesis of Piperidazine-3-carboxylic Acid (Piperazic Acid) Peptides	79
9.2.4.3	Oxapipecolic Acids	80
9.2.4.3.1	Synthesis of Oxapipecolic Acid Peptides	81
9.2.4.4	Thiapipecolic Acids	81

9.3	Synthesis of Photoreactive Peptides	87
	(<i>A. Bisello and M. Chorev</i>)	
9.3.1	Peptides Containing Phenyl Azides (Azidoarenes)	89
9.3.1.1	Synthesis of 4-Azidophenylalanine and Its Protected Derivatives . .	91
9.3.1.2	Strategies for the Synthesis of Peptides Containing 4-Azidophenylalanine	93
9.3.1.3	Synthesis of Protected 4-Aminophenylalanine Derivatives	99
9.3.1.4	Synthesis of Tritiated 4-Azidophenylalanine and Its Protected Derivatives	100
9.3.1.5	Biochemical, Site-Specific Incorporation of <i>N</i> ^ε -(5-Azido-2-nitrobenzoyl)lysine into Proteins	102
9.3.2	Nitrophenyl-Containing Peptides	103
9.3.3	Peptides Containing Arenediazoniums	104
9.3.4	[3-(Trifluoromethyl)-3 <i>H</i> -diazirin-3-yl]aryl-Containing Peptides	105
9.3.4.1	Synthesis of N-Protected 4-[3-(Trifluoromethyl)-3 <i>H</i> -diazirin-3-yl]-L-phenylalanine	106
9.3.4.2	Methods of Incorporating 4-[3-(Trifluoromethyl)-3 <i>H</i> -diazirin-3-yl]arenes into Peptides	112
9.3.4.3	Biochemical, Site-Specific Incorporation of 4-[3-(Trifluoromethyl)-3 <i>H</i> -diazirin-3-yl]phenylalanine into Proteins by Phe(4-Tmd)-tRNA ^{Phe} . .	114
9.3.5	Peptides Containing Aryl Ketones	116
9.3.5.1	Strategies for the Synthesis of Peptides Containing Benzophenone Derivatives	117
9.3.5.2	Side Reactions of the Benzophenone Moiety during Peptide Synthesis	120
9.3.5.3	Synthesis of Protected Amino Acids Containing Benzophenone Derivatives	121
9.3.5.4	Radiolabeled Benzophenone-Containing Photophores	125
9.3.6	Photocaged Peptides	129
9.3.6.1	Synthesis of 2-Nitrobenzyl-Protected Amino Acids	130
9.3.6.2	Synthesis of Desyl-Protected Amino Acids	135
9.3.6.3	4-Hydroxyphenacyl-Protected Amino Acids	139
9.3.6.4	Synthesis of Photocaged Peptides	140
9.4	Synthesis of Peptides as Receptors and Devices	153
	(<i>N. Voyer</i>)	
9.4.1	Crown Ether Peptides	153
9.4.1.1	Synthesis of 3-(3,4-Dihydroxyphenyl)alanine Crown Ethers	153
9.4.1.2	Synthesis of Crown Ether Lysine and Glutamic Acid Derivatives . .	155
9.4.1.3	Crown Ether at the C- or N-Terminal Position	157
9.4.2	Cyclodextrin Peptides	158
9.4.3	Porphyrin Peptides	159
9.4.4	Peptides with Metal Binding Sites	162
9.4.4.1	Pyridyl, Bipyridyl, and Related Metal Ligand Peptides	162
9.4.4.2	Peptides with Phosphine Ligands	165
9.4.4.3	Peptides with Coenzyme Chimeras	167
9.4.4.4	Peptides with a Ligand at Terminal Positions	170
9.4.5	Ferrocenyl Peptides	171
9.4.5.1	Preparation of Ferrocenylalanine via Resolution	171
9.4.5.2	Enantioselective Synthesis of Ferrocenylalanine	173
9.4.5.3	Ferrocenyl Modification of Peptide Side Chains	175
9.4.6	Peptides with Aminodiacetic Acid and Ethylenediaminetetraacetic Acid Side Chains	176
9.4.6.1	Peptides with Aminodiacetic Side Chains	176

9.4.6.2	Peptides with Ethylenediaminetetraacetic Acid Side Chains	178
9.4.7	Peptides with Nucleobase Side Chains	180
9.4.7.1	Nucleo Ethylglycines	181
9.4.7.2	Nucleo Alanines	182
9.4.8	Peptides with Miscellaneous Side Chains	184
9.4.8.1	Peptides with Diazobenzene Alanine	185
9.4.8.2	Peptides with Diazobenzene Aspartic Acid	187
9.4.8.3	Peptides with Pyrenylalanine	187
9.4.8.4	Peptides with Side-Chain-Modified Cysteine	189
9.4.8.5	Peptides with Boronic Acid Side Chains	191
9.5	Synthesis of Cycloisodityrosine Peptides	194
	(<i>D. L. Boger and S. L. Castle</i>)	
9.5.1	Cycloamidation	195
9.5.2	Intramolecular Thallium Trinitrate Oxidative Coupling	197
9.5.3	Intramolecular Ullmann Reaction	199
9.5.4	Intramolecular Nucleophilic Aromatic Substitution	203
9.6	Tryptathionine Peptides	207
	(<i>A. Fontana</i>)	
10	Main-Chain-Modified Peptides	213
	(<i>C. Toniolo</i>)	
10.1	Synthesis of N-Alkylated Peptides	215
	(<i>C. Gilon, M. A. Dechantsreiter, F. Burkhart, A. Friedler, and H. Kessler</i>)	
10.1.1	Synthesis of <i>N</i> -Alkyl Amino Acids as Building Blocks for N-Alkylated Peptides	218
10.1.1.1	N-Alkylation of Protected Amino Acids	220
10.1.1.1.1	N-Alkylation of <i>N</i> ^α -Arylsulfonyl Amino Acids	220
10.1.1.1.2	N-Alkylation of Benzyloxycarbonyl- and <i>tert</i> -Butoxycarbonyl-Protected Amino Acids	223
10.1.1.2	N-Alkylation of Urethane-Protected Amino Acids with Aldehydes	225
10.1.1.2.1	N-Alkylation of Fmoc-Protected α -Amino Acids	226
10.1.1.2.2	N-Alkylation of Benzyloxycarbonyl-Protected α -Amino Acids	227
10.1.1.3	Reductive Alkylation of Amino Acids and Their Derivatives	229
10.1.1.3.1	Direct N-Monoalkylation of Zwitterionic Amino Acids	229
10.1.1.3.2	Reductive Alkylation of Amino Acid Esters	230
10.1.1.3.3	Reductive Alkylation of Temporarily <i>N</i> -Alkyl Protected Amino Acids	232
10.1.1.4	Synthesis of <i>N</i> ^α -(ω -Functionalized Alkyl) Amino Acids in Solution	233
10.1.1.4.1	Synthesis by Nucleophilic Substitution	234
10.1.1.4.2	Synthesis by Reductive Alkylation	238
10.1.1.4.2.1	Reductive Alkylation Reaction of Zwitterionic Amino Acids	238
10.1.1.4.3	Synthesis by 1,4-Michael Addition to Amino Acid <i>tert</i> -Butyl Esters	240
10.1.1.5	Miscellaneous Methods for the Synthesis of <i>N</i> -Alkyl Amino Acids	241
10.1.2	N-Alkylation of Peptides on Solid Supports	243
10.1.2.1	Site Specific N-Alkylation of Amino Acids and Peptides on Solid Support	244
10.1.2.1.1	Reductive Methylation of 4,4'-Dimethoxybenzhydryl-Protected Amino Acids	244
10.1.2.1.2	On-Resin Reductive Alkylation in Trimethyl Orthoformate	245
10.1.2.1.3.	On-Resin Alkylation of Nitrophenylsulfonyl-Protected Peptides	245
10.1.2.1.4	On-Resin Formation of <i>N</i> -Alkylglycines	246
10.1.2.2	Nonspecific N-Alkylation of Peptides	246
10.1.3	Synthesis of N-Alkylated Peptides	247

10.1.3.1	Preventing Piperazine-2,5-dione Formation	247
10.1.3.2	Acylation of <i>N</i> -Alkyl Amino Acids during Peptide Synthesis	252
10.1.3.3	Lability of <i>N</i> -Alkylated Peptides to Acids	257
10.1.3.4	Peptoids: Peptides Based on <i>N</i> -Alkylated Glycines	259
10.1.3.4.1	Synthesis of Peptoid Monomers in Solution	263
10.1.3.4.2	Submonomer SPPS of Peptoids	264
10.2	Synthesis of Depsipeptides	272
	(<i>V. T. Ivanov and I. I. Mikhaleva</i>)	
10.2.1	Formation of the Ester Bond	274
10.2.1.1	Mixed Anhydrides	274
10.2.1.2	Carbodiimides with or without Additives	277
10.2.1.3	1,1'-Carbonyldiimidazole Method and Related Approaches	280
10.2.1.4	Activation of the Hydroxy Group	281
10.2.1.5	Active Esters	283
10.2.1.6	Acid Chlorides	284
10.2.1.7	Other Synthetic Approaches	285
10.3	Synthesis of Peptides Based on C^α-Tetrasubstituted	
	α-Amino Acids	292
	(<i>F. Formaggio, Q. B. Broxterman and C. Toniolo</i>)	
10.3.1	Peptides with Non-consecutive C ^α -Tetrasubstituted α-Amino Acids	293
10.3.1.1	Synthesis in Solution	293
10.3.1.1.1	<i>N</i> -[3-(Dimethylamino)propyl]- <i>N'</i> -ethylcarbodiimide Hydrochloride/ 7-Aza-1,2,3-benzotriazol-1-ol Activation	294
10.3.1.1.2	Symmetrical Anhydride Activation	295
10.3.1.2	Synthesis on Solid Support	296
10.3.2	Peptides with Consecutive C ^α -Tetrasubstituted α-Amino Acids	297
10.3.2.1	Synthesis in Solution	298
10.3.2.1.1	Oxazol-5(4 <i>H</i>)-one Activation	298
10.3.2.1.2	<i>N</i> -[3-(Dimethylamino)propyl]- <i>N'</i> -ethylcarbodiimide Hydrochloride/ 7-Aza-1,2,3-benzotriazol-1-ol Activation	299
10.3.2.1.3	Symmetrical Anhydride Activation	300
10.3.2.1.4	Amino Acyl Fluoride Activation	300
10.3.2.2	Synthesis on Solid Support	301
10.3.3	Peptides Containing C ^α -Trifluoromethylated α-Amino Acids	301
10.3.3.1	Synthesis in Solution	301
10.3.3.1.1	C ^α -Tetrasubstituted α-Amino Acids as Acyl Donors	302
10.3.3.1.2	C ^α -Tetrasubstituted α-Amino Acids as Nucleophiles	302
10.3.3.2	Synthesis on Solid Support	303
10.3.4	Peptides Containing TOAC Residues	303
10.3.4.1	Synthesis in Solution	304
10.3.4.1.1	<i>N</i> -[3-(Dimethylamino)propyl]- <i>N'</i> -ethylcarbodiimide Hydrochloride/ 1,2,3-Benzotriazol-1-ol Activation	305
10.3.4.1.2	Symmetrical Anhydride Activation	305
10.3.4.1.3	<i>N</i> -[3-(Dimethylamino)propyl]- <i>N'</i> -ethylcarbodiimide Hydrochloride/ 7-Aza-1,2,3-benzotriazol-1-ol Activation Activation	306
10.3.4.1.4	Amino Acyl Fluoride Activation	306
10.3.4.2	Synthesis on Solid Support	306
10.4	Synthesis of Azapeptides	311
	(<i>J. Gante[†], H. Kessler, and C. Gibson</i>)	
10.4.1	Addition of Hydrazine Derivatives to Isocyanates	312
10.4.2	Reaction of Activated Esters of <i>N</i> -Carboxylic Acids with Amino Groups	313

10.4.3	Reaction of <i>N</i> -Azolides with Amino Groups	316
10.4.4	Reaction of <i>N</i> -Carboxylic Acid Chlorides with Amino Groups	318
10.4.5	Ring Opening of 1,3,4-Oxadiazol-2(3 <i>H</i>)-ones by Amino Groups . . .	320
10.4.6	Reaction of Hydrazides with Carbonic Acid Derivatives or Isocyanic Acid	321
10.5	Synthesis of Peptides Containing Carbaamide Bond Replacements .	324
	(<i>D. Tourwé, K. Iterbeke, and E. Mannekens</i>)	
10.5.1	ψ [CH ₂ –CH ₂] Peptides	324
10.5.1.1	Arndt–Eistert Homologations	327
10.5.1.2	Wittig Alkenation of β -Amino Aldehydes	328
10.5.1.3	Piperidin-2-one Enolate Alkylation	329
10.5.1.4	Chiral Enolate Addition to Acrylonitrile	330
10.5.1.5	Reduction of ψ [CH=CH] Dipeptides	331
10.5.2	ψ [CX=CY] Peptides	332
10.5.2.1	ψ [<i>E</i> , CH=CH] Isosteres	336
10.5.2.1.1	Curtius Rearrangement	336
10.5.2.1.2	Alkenation Reactions	337
10.5.2.1.2.1	Wittig Type	337
10.5.2.1.2.2	Julia Type	339
10.5.2.1.2.3	β -Elimination	341
10.5.2.1.2.4	Silane Elimination: S _E Reaction	342
10.5.2.1.3	S _N 2' Displacements	346
10.5.2.1.3.1	Allylic Mesylates	346
10.5.2.1.3.2	Allylic Aziridines	350
10.5.2.1.3.3	Trost Alkylation of Allylic Acetates	353
10.5.2.1.4	Sigmatropic Rearrangements	355
10.5.2.1.4.1	[2,3]-Wittig–Still Rearrangement	355
10.5.2.1.4.2	Orthoester Claisen Rearrangement	357
10.5.2.1.4.3	Overman Rearrangement	358
10.5.2.2	ψ [<i>Z</i> , CH=CH] Isosteres	360
10.5.2.2.1	Ring-Closing Metathesis	360
10.5.2.2.2	Wittig–Still Sigmatropic Rearrangement	362
10.5.2.3	ψ [<i>E</i> , CX=CY] Isosteres	363
10.5.2.3.1	Overman Rearrangement	363
10.5.2.3.2	Substitution of a 1,4-Dibromobut-2-ene	364
10.5.2.3.3	S _N 2' Substitutions	365
10.5.3	ψ [C≡C] Peptides	367
10.5.3.1	Mitsunobu Reaction	367
10.5.3.2	Acetylide Addition to Oxirane	368
10.6	Synthesis of Peptides Containing C/O Amide Bond Replacements . .	373
	(<i>S. Ro</i>)	
10.6.1	ψ [CH ₂ O] (Methyleneoxy) Peptides	373
10.6.2	ψ [CH(OH)CH ₂] (1-Hydroxyethylene) Peptides	376
10.6.2.1	Synthesis by Addition of a Grignard Reagent	384
10.6.2.2	Synthesis and Alkylation of the Lactone Intermediate	386
10.6.3	ψ [CH ₂ CH(OH)] (2-Hydroxyethylene) Peptides	387
10.6.3.1	Synthesis of 2-Hydroxyethylene Peptides	387
10.6.4	ψ [CH(OH)CH(OH)] (1,2-Dihydroxyethylene) Peptides	390
10.6.5	ψ [C(=O)CH ₂] (1-Oxoethylene) Peptides	392
10.6.5.1	Synthesis by Reaction of a Halomethyl Ketone	394
10.6.6	ψ [CH(O)CH] (Oxirane) Peptides	396

10.7	Synthesis of Peptides Containing C/N Amide Bond Replacements . .	400
	(M. AMBLARD, M. ROLLAND, J.-A. FEHRENTZ, and J. MARTINEZ)	
10.7.1	ψ [CH ₂ NH] (Methyleneamino) (Reduced Amide) Peptides	400
10.7.1.1	Condensation of a N ^α -Urethane Protected α-Amino Aldehyde with a Free Amino Component	401
10.7.1.1.1	Preparation of a N ^α -Urethane Protected α-Amino Aldehyde by Reductive Methods	402
10.7.1.1.1.1	Reduction of α-Amino Acid Halides and Esters	403
10.7.1.1.1.2	Reduction of 3,5-Dimethylpyrazole Derivatives or Weinreb Amides .	404
10.7.1.1.2	Preparation of a N ^α -Urethane Protected α-Amino Aldehyde by Oxidative Methods	406
10.7.1.1.3	Preparation of a N ^α -Urethane Protected α-Amino or Peptide Aldehyde on a Solid Support	407
10.7.1.1.4	Reductive Amination	409
10.7.1.1.4.1	Reductive Amination in Solution	409
10.7.1.1.4.2	Reductive Amination on Solid Support	409
10.7.1.2	Reduction of a Peptide or Thioamide Bond	410
10.7.1.2.1	Amide Bond Reduction	411
10.7.1.2.2	Thioamide Bond Formation and Reduction	411
10.7.2	ψ [CH(CN)NH] [(Cyano)methyleneamino] Peptides	412
10.7.2.1	Synthesis of ψ [CH(CN)NH] Pseudopeptides in Solution	412
10.7.2.2	Solid Phase Synthesis of ψ [CH(CN)NH] Pseudopeptides	414
10.7.2.3	Assignment of Configuration in ψ [CH(CN)NH] Pseudopeptides . . .	415
10.7.3	ψ [NHCH ₂] (Aminomethylene) (Reduced Retro-amide) Peptides . .	415
10.7.3.1	Synthesis of ψ [NHCH ₂] Pseudopeptides	416
10.7.4	ψ [CH=NNH] (Iminoaza) Peptides	416
10.7.4.1	Synthesis of Iminoaza Peptides	417
10.7.5	ψ [CH ₂ NHNH] (Reduced Iminoaza) Peptides	419
10.7.5.1	Synthesis of Reduced Iminoaza Peptides	419
10.8	Peptides Containing C/N/O Amide Bond Replacements	423
	(M. Marraud and R. Vanderesse)	
10.8.1	(Nitrono) Peptides	423
10.8.2	[Methyleneamino(hydroxy)] or (N-Hydroxy reduced amide) Peptides	424
10.8.3	(N-Hydroxyamide) Peptides	425
10.8.3.1	Synthesis of α-Hydroxyamino Acids and Derivatives	425
10.8.3.1.1	Halogen Substitution	426
10.8.3.1.2	Oxime Reduction	426
10.8.3.1.3	Oxaziridine or Imidazolidine-4-one Hydrolysis	427
10.8.3.1.4	α-Amino Acid Oxidation	428
10.8.3.2	(N-Hydroxyamide) Peptide Synthesis	429
10.8.3.2.1	C-Coupling of N-Benzyloxy α-Amino Acids	429
10.8.3.2.2	N-Coupling of N-Benzyloxy α-Amino Acid Derivatives	430
10.8.3.2.3	Cleavage of the O-Benzyl Group	431
10.8.3.2.4	Methodologies for (N-Hydroxyamide) Peptide Synthesis	431
10.8.4	(N-Aminoamide) Peptides	434
10.8.4.1	Synthesis of α-Hydrazino Acids	434
10.8.4.1.1	Asymmetric Synthesis	434
10.8.4.1.2	Shestakov Rearrangement	436
10.8.4.1.3	N-Amination of α-Amino Acids	437
10.8.4.2	(N-Aminoamide) Peptide Synthesis	437
10.8.4.2.1	Regioselective N-Protection of α-Hydrazino Acid Derivatives	438
10.8.4.2.2	C- and N ^α -Coupling of N ^β -Protected α-Hydrazino Acid Derivatives .	438

10.8.4.2.3	Strategies for (<i>N</i> -Aminoamide) Peptide Synthesis	439
10.8.4.3	(<i>N</i> -Aminoamide) Peptide Synthesis by Ugi's Reaction	440
10.8.5	(Hydrazide) Peptides	441
10.8.5.1	(Hydrazide) Peptide Synthesis in Solution	441
10.8.5.2	Solid-Phase (Hydrazide) Peptide Synthesis	442
10.8.5.3	(Hydrazide) Polypeptide Synthesis	443
10.8.6	(Amidoxy) Peptides	444
10.8.6.1	Synthesis of α -Aminoxy Acid Derivatives	444
10.8.6.2	(Amidoxy) Peptide Synthesis	444
10.8.7	(Oxomethyleneamino) Peptides	445
10.8.7.1	Modified Dakin–West Reaction	446
10.8.7.2	From Chloromethyl Ketones	446
10.8.8	[(Hydroxy)ethyleneamino] Peptides	447
10.8.8.1	From (Oxomethyleneamino) Peptides	447
10.8.8.2	Stereoselective Opening of Epoxides	448
10.8.9	(Ethyleneamino) Peptides	449
10.8.10	(Oxime) Peptides	450
10.8.11	(But-2-enamide) Peptides [(Vinylogous amide) Peptides]	451
10.8.11.1	(<i>E</i>)-4-Aminobut-2-enoic Acids	452
10.8.11.2	(<i>Z</i>)-4-Aminobut-2-enoic Acids	453
10.8.11.3	(But-2-enamide) Peptide Synthesis	453
10.9	Synthesis of Peptides with Sulfur-Containing Amide Bond Replacements	458
	(<i>A. F. Spatola, K. Darlak, and P. Romanovskis</i>)	
10.9.1	$\psi[\text{C}(=\text{S})\text{--NH}]$ (Thioamide) Peptides	458
10.9.1.1	Selective Thionylation	459
10.9.1.2	Thioacylation with <i>N</i> -Protected Amino Monothioacids	460
10.9.1.3	Thioacylation with a Benzimidazolone Derivative	461
10.9.2	$\psi[\text{CH}_2\text{--S}]$ (Methylenethio) Peptides	463
10.9.2.1	Synthesis of $\psi[\text{CH}_2\text{--S}]\text{Gly}$ Peptides	464
10.9.2.2	Synthesis of $\psi[\text{CH}_2\text{--S}]\text{Xaa}$ ($\text{Xaa} \neq \text{Gly}$) Peptides	465
10.9.2.3	Solid-Phase Synthesis of $\psi[\text{CH}_2\text{--S}]$ Peptides	467
10.9.3	$\psi[\text{CH}_2\text{--SO}]$ Sulfinyl Peptides	469
10.9.4	$\psi[\text{CH}_2\text{--SO}_2]$ and $\psi[\text{SO}_2\text{--CH}_2]$ (Sulfonyl and Retro-sulfonyl) Peptides	469
10.9.5	$\psi[\text{C}(=\text{O})\text{--S}]$ (Thioester) Peptides	469
10.9.5.1	Solution Synthesis of Thioester Peptides	470
10.9.5.2	Solid-Phase Synthesis of Thioester Peptides	471
10.9.6	$\psi[\text{C}(=\text{S})\text{--S}]$ (Dithioester) Peptides	474
10.9.6.1	Preparation of Dithioesters via the Pinner Reaction	475
10.9.6.2	Preparation of Dithioesters Using Lawesson's Reagent	476
10.9.7	$\psi[\text{SO}\text{--NH}]$ and $\psi[\text{CH}_2\text{--SO}\text{--NH}]$ (Sulfinamide and Methylene Sulfonamide) Peptides, and $\psi[\text{SO}_2\text{--NH}]$ and $\psi[\text{CH}_2\text{--SO}_2\text{--NH}]$ (Sulfonamide and Methylene Sulfonamide) Peptides	478
10.9.7.1	Preparation of an α -Aminosulfonic Acid	478
10.9.7.2	Synthesis of Protected α -Aminosulfonamides	479
10.9.7.3	Synthesis of Taurine-Containing Analogues	481
10.9.7.4	Synthesis of Methylene Sulfonamides Through Methylene Sulfinyl Derivatives	483
10.9.8	$\psi[\text{NH}\text{--SO}_2]$ (Retro-sulfonamide) Peptides	486
10.9.9	$\psi[\text{C}\equiv\text{C}\text{--SO}_2\text{NH}]$ (Vinylogous Sulfonamide) Peptides	487

10.10	Synthesis of Peptides with Phosphorus-Containing Amide Bond Replacements	492
	(P. A. Bartlett, J. E. Hanson, B. P. Morgan, and B. A. Ellsworth)	
10.10.1	Phosphorus Analogues of α -Amino Acids	492
10.10.1.1	Synthesis of Phosphonate Amino Acid Analogues	493
10.10.1.1.1	Strecker-Type Synthesis of α -Aminoalkylphosphonic Acids	493
10.10.1.1.2	Phosphonic Amino Acids and Their Derivatives via <i>N</i> -Acyliminium Ion Intermediates	494
10.10.1.1.2.1	Condensation with Triaryl Phosphites	494
10.10.1.1.2.2	Condensation with Amino Derivatives	495
10.10.1.1.3	Alkylation of Protected Aminomethylphosphonic Acids	496
10.10.1.1.4	Amination of Alkyl- and Acylphosphonates	498
10.10.1.1.5	Reaction of α -Iminoalkylphosphonates with Nucleophiles	499
10.10.1.1.6	Preparation of Optically Active α -Aminoalkylphosphonic Acids via Separation of Covalent Diastereomers	500
10.10.1.1.7	Asymmetric Synthesis of α -Aminoalkylphosphonic Acids	502
10.10.1.2	Synthesis of Hydrogen Phosphinate Amino Acid Analogues	504
10.10.1.2.1	Strecker-Type Condensation	504
10.10.1.2.2	Alkylation of Protected Aminomethylphosphinic Acid	505
10.10.1.2.3	Resolution of α -Aminoalkylphosphinic Acids via Crystallization of Diastereomeric Salts	508
10.10.2	Compounds Containing Phospha-Peptide Linkages: P–N, P–O, and P–C Bonds	510
10.10.2.1	Synthesis of Phosphonamidate Peptide Analogues	510
10.10.2.1.1	Formation of Phosphonic Acid Monoesters	510
10.10.2.1.2	Synthesis of Phosphonamidates from Phosphonic Acid Monoesters	511
10.10.2.1.3	Synthesis of Phosphonamidates from H-Phosphinates	513
10.10.2.2	Synthesis of Phosphonate Peptide Analogues	514
10.10.2.2.1	Synthesis via Electrophilic, Activated Phosphonates	514
10.10.2.2.2	Synthesis of Phosphonates via Mitsunobu Displacement	514
10.10.2.3	Synthesis of Phosphinate Peptide Analogues	515
10.10.2.3.1	Reactions Involving Nucleophilic Phosphorus	515
10.10.2.3.1.1	Conjugate Addition of Alkyl Phosphonites to Acrylates	515
10.10.2.3.1.2	Addition of Alkyl Phosphonites to Carbonyl Compounds and Imines	517
10.10.2.3.2	Reactions Involving Electrophilic Phosphorus	519
10.10.3	Peptides Containing Deprotected Phosphorus	519
10.10.3.1	P–O Cleavage: Acid- and Base-Catalyzed Deprotection	521
10.10.3.2	O–C Cleavage by Nucleophilic Reagents	521
10.10.3.2.1	Bromotrimethylsilane	522
10.10.3.2.2	Lithium Propanethiolate	523
10.10.3.3	Oxidation of H-Phosphinates	524
10.11	Synthesis of <i>retro-inverso</i>-Peptides	528
	(L. Scheibler and M. Chorev)	
10.11.1	Synthesis in Solution	534
10.11.1.1	Preparation of <i>gem</i> -Diaminoalkyl Derivatives	534
10.11.1.2	Coupling Procedures Leading to <i>gem</i> -Diaminoalkyl Derivatives	539
10.11.1.3	Preparation of C2-Substituted Malonyl Derivatives	540
10.11.2	Solid-Phase Synthesis of Partially Modified <i>retro-inverso</i> Peptides	544
10.11.2.1	On-Resin Generation of <i>gem</i> -Diaminoalkyl Moieties	544
10.11.2.2	Synthesis by Incorporation of Partially Modified <i>retro-inverso</i> Dipeptide Synthons	546

10.12	Synthesis of Peptides Based on β-Amino Acids	552
	(<i>J. L. Matthews</i>)	
10.12.1	Peptides Containing a Single β -Amino Acid	552
10.12.1.1	Synthesis by Silver Alkanoate Activation	553
10.12.1.2	Synthesis by Light Activation	554
10.12.2	β^3 -Peptides	555
10.12.2.1	Peptide Coupling via an Activated Ester	555
10.12.3	β^2 -Peptides	557
10.12.3.1	Synthesis via Evans Methodology	557
10.12.4	$\beta^{2,3}$ -Peptides	558
10.12.4.1	$\beta^{2,3}$ -Peptides Bearing Protein Amino Acid Side Chains	559
10.12.4.1.1	Synthesis via Alkylation of β^3 -Amino Acids	559
10.12.4.2	$\beta^{2,3}$ -Peptides from Cycloalkyl-Substituted Amino Acids	560
10.12.4.2.1	Coupling of Cycloalkyl-Substituted Amino Acids	560
10.12.4.3	$\beta^{2,3}$ -Peptides Bearing Allyl Substituents	562
10.12.4.3.1	Iterative Free Radical C-Allylation Reactions	562
10.12.4.3.2	One-Pot Triallylation Reaction	564
10.12.5	β -Peptide Polymers	564
10.12.5.1	Polymerization of α -Protected Aspartic Acid	565
10.12.6	Cyclo- β -peptides	565
10.12.6.1	Synthesis via a Pentafluorophenyl Ester	566
10.12.7	Applications of Solid-Phase Peptide Synthesis to β -Peptides	567
10.12.7.1	Fmoc Strategy	567
10.13	Synthesis of Peptides Based on γ-Amino Acids	570
	(<i>P. Jouin</i>)	
10.13.1	γ -Amino- β -hydroxy Acids	571
10.13.1.1	Aldol Condensation of Amino Aldehydes with Ester Enolates	571
10.13.1.1.1	Substrate Control in the Aldol Reaction	572
10.13.1.1.2	Reagent Control in the Aldol Reaction	572
10.13.1.2	Allylation of Amino Aldehydes	573
10.13.1.3	Reduction of γ -Amino- β -oxo Esters	575
10.13.1.3.1	Diastereoselectivity during Borohydride Reduction	575
10.13.1.3.2	Asymmetric Hydrogenation of β -Oxo Esters	576
10.13.1.4	4-Hydroxy Lactam Intermediates	576
10.13.1.4.1	Chiral Tetramic Acids via Meldrum's Acid Condensation	577
10.13.1.4.2	Chiral Tetramic Acids via Cyclization of γ -Amino- β -oxo Esters	577
10.13.1.4.3	Stereoselective Reduction of Tetramic Acids	578
10.13.2	Other γ -Amino Acids	578
10.13.2.1	Synthesis of N/O-Methylated γ -Amino- β -hydroxy Acids	578
10.13.2.1.1	Synthesis from <i>N</i> -Methyl Amino Acids or Amino Aldehydes	579
10.13.2.1.2	Methylation of N-Protected γ -Amino- β -hydroxy Acids	579
10.13.2.1.3	Methylation of Allylic Derivatives	580
10.13.2.2	Synthesis of α -Substituted γ -Amino- β -hydroxy Acids	580
10.13.2.2.1	α -Heterosubstituted γ -Amino- β -hydroxy Acids	580
10.13.2.2.2	α,α -Dihalogenated γ -Amino- β -hydroxy Acids	581
10.13.2.2.3	α -Alkylated γ -Amino- β -hydroxy Acids	582
10.13.2.3	Synthesis of β,γ -Diamino Acids	583
10.13.3	Peptides Containing γ -Amino- β -hydroxy Acids	584
10.13.4	Stereochemical Determination	584
10.13.4.1	Determination of Enantiomeric Purity	584
10.13.4.1.1	γ -Amino Derivatization	585
10.13.4.1.2	β -Hydroxy Derivatization	585

10.13.4.2	Absolute Configurations of γ -Amino- β -hydroxy Acids	586
10.13.4.2.1	Stereochemistry Determined from Oxazolidinones	586
10.13.4.2.2	Stereochemistry Determined from Pyrrolidinones	587
10.14	Synthesis of Peptides Containing Ureine and Urethane Linkages	590
	(<i>M. E. Wilson and J. S. Nowick</i>)	
10.14.1	Ureine Peptides	590
10.14.1.1	Ureine Linkages from Amines and Isocyanates	591
10.14.1.1.1	Available Isocyanates	591
10.14.1.1.2	Isocyanates Prepared with Phosgene or Triphosgene	593
10.14.1.1.3	Isocyanates Prepared by the Curtius Rearrangement	594
10.14.1.2	Ureine Linkages by Coupling Amines with Carbonic Acid Derivatives	595
10.14.1.2.1	Carbamoyl Chlorides	595
10.14.1.2.2	Carbonyl Diimidazole	597
10.14.1.2.3	Aryl Carbamates	597
10.14.1.3	Coupling Urea-Containing Segments to Amino Acids or Peptides . .	599
10.14.2	Urethane Peptides	600
10.14.2.1	Urethane Linkages by Coupling Amines and Alcohols with Carbonic Acid Derivatives	601
10.14.2.2	Coupling Urethane-Containing Segments to Amino Acids or Peptides	603
10.15	Synthesis of Peptides Containing an Aromatic Spacer	606
	(<i>D. Tourwé, J. Van Hemel, and J. Piron</i>)	
10.15.1	Aminobenzoic Acid Peptides	606
10.15.1.1	Synthesis of Aminobenzoyl Peptides	608
10.15.1.1.1	Acylation with Unprotected Aminobenzoic Acid Active Esters . . .	608
10.15.1.1.2	Acylation with Isatoic Anhydride	609
10.15.1.1.3	Coupling of Nitrobenzoic Acid	609
10.15.1.1.4	Coupling with Urethane-Protected Aminobenzoic Acid	610
10.15.1.2	Synthesis of Peptidyl-Aminobenzoic Acid	611
10.15.1.2.1	Acylation of Unprotected Aminobenzoic Acid	612
10.15.1.2.2	Coupling of Hindered Amino Acids to Aminobenzoic Acid Esters .	612
10.15.2	(Aminophenyl)acetic Acid Peptides	613
10.15.2.1	Synthesis of (Aminophenyl)acetyl Peptides	613
10.15.3	(Aminomethyl)benzoic Acid Peptides	614
10.15.3.1	Synthesis of (Aminomethyl)benzoic Acid Peptides: Construction and Protection of (Aminomethyl)benzoic Acid	615
10.15.3.1.1	3- and 4-(Aminomethyl)benzoic Acid From Cyanobenzoic Acid . . .	617
10.15.3.1.2	2-(Aminomethyl)benzoic Acid From Phthalimidine	617
10.15.3.1.3	N-Protection of (Aminomethyl)benzoic Acid	617
10.15.3.1.4	(Aminomethyl)benzoic Acid from (Chloromethyl)benzoic Acid . . .	618
10.15.3.1.5	α -Substituted 3-(Aminomethyl)benzoic Acid Derivatives	619
10.15.3.2	Synthesis of (Aminomethyl)benzoyl Peptides	619
10.15.3.3	(Aminomethyl)benzoic Acid: Coupling of Amino Acids or Peptides to (Aminomethyl)benzoic Acid	620
10.15.4	(Aminomethylphenyl)acetic Acid Peptides	620
10.15.4.1	Synthesis of (Aminomethylphenyl)acetic Acid Isomers	621
10.15.4.1.1	2-(Aminomethylphenyl)acetic Acid From (2-Methylphenyl)acetic Acid	622
10.15.4.1.2	2-(Aminomethylphenyl)acetic Acid From δ -Lactams	622
10.15.4.1.3	Preparation of α - and δ -Substituted 2-(Aminomethylphenyl)acetic Acid	622
10.15.4.1.4	Synthesis of 3-(Aminomethylphenyl)acetic Acid	624

10.15.4.1.5	Synthesis of 4-(Aminomethylphenyl)acetic Acid	625
10.15.5	(Aminomethyl)biphenylcarboxylic Acid Peptides	625
10.15.5.1	Synthesis of Derivatives of (Aminomethyl)biphenylcarboxylic Acids .	627
10.15.6	(Aminomethyl)thienylcarboxylic Acid Peptides	628
10.15.6.1	Synthesis of Derivatives of (Aminomethyl)thienylcarboxylic Acids .	628
10.15.7	(Aminomethyl)pyrrolicarboxylic Acid Peptides	629
10.15.7.1	Synthesis of Derivatives of (Aminomethyl)pyrrolicarboxylic Acids .	630
11	Combined Side-Chain- and Main-Chain-Modified Peptides	635
	(<i>C. Toniolo</i>)	
11.1	Synthesis of Peptides Based on α,β-Didehydro-α-amino Acids	636
	(<i>R. M. Joshi and V. S. Chauhan</i>)	
11.1.1	α,β -Didehydro- α -amino Acids	637
11.1.1.1	General Methods of Synthesis of α,β -Didehydro- α -amino Acids . . .	638
11.1.1.1.1	<i>N</i> -Acyl α,β -Didehydro- α -amino Acids Via Azlactones [Oxazol-5(4 <i>H</i>)-ones]	638
11.1.1.1.1.1	Erlenmeyer Synthesis	638
11.1.1.1.1.2	Bergmann–Stern Synthesis	639
11.1.1.1.1.3	Azlactone Formation from β -Hydroxy- α -amino Acids	639
11.1.1.1.1.4	Oxidation of Saturated Azlactones	640
11.1.1.1.2	Synthesis of α,β -Didehydro- α -amino Acid Derivatives by Condensation of Amides or Nitriles with α -Oxo Acids	641
11.1.1.1.2.1	Condensation of Amides	641
11.1.1.1.2.2	Condensation of Nitriles	643
11.1.1.1.3	Synthesis of α,β -Didehydro- α -amino Acids by Elimination Reactions	644
11.1.1.1.3.1	Elimination Reactions from β -Hydroxy- α -amino Acid Derivatives . .	644
11.1.1.1.3.2	β -Elimination Reactions from Serine Side-Chain Derivatives	645
11.1.1.1.3.3	β -Elimination Reactions from Cysteine Side-Chain Derivatives . . .	646
11.1.1.1.4	α,β -Didehydro- α -amino Acid Derivatives by <i>N</i> -Chlorination/ Dehydrochlorination	647
11.1.1.2	Synthesis of Aromatic α,β -Didehydro- α -amino Acids	648
11.1.1.2.1	Synthesis of α,β -Didehydrophenylalanine Derivatives	648
11.1.1.2.2	Synthesis of α,β -Didehydrotyrosine Derivatives	649
11.1.1.2.3	Synthesis of α,β -Didehydrotryptophan Derivatives	650
11.1.1.3	Synthesis of Aliphatic α,β -Didehydro- α -amino Acids	650
11.1.1.3.1	Synthesis of α,β -Didehydroalanine and α,β -Didehydroaminobutanoic Acid Peptides	650
11.1.1.3.2	Synthesis of α,β -Didehydrovaline, α,β -Didehydroleucine, and α,β - Didehydroisoleucine Peptides	651
11.1.1.3.3	Synthesis of α,β -Didehydroglutamic Acid and α,β -Didehydroaspartic Acid Peptides	652
11.1.1.3.4	Synthesis of α,β -Didehydroornithine and α,β -Didehydrolysine Peptides	653
11.1.2	α,β -Didehydropeptides	655
11.1.2.1	Synthesis of α,β -Didehydropeptides in Solution	655
11.1.2.2	Synthesis of α,β -Didehydropeptides on Solid Support	657
11.1.3	Bioactive Peptides Containing α,β -Didehydro- α -amino Acids	657
11.1.3.1	Synthesis and Structure–Function Analysis of Bioactive Peptides Containing α,β -Didehydro- α -amino Acids	657
11.2	Synthesis of Peptides Based on Aromatic Heterocycles	663
	(<i>C. P. Miller and P. Wipf</i>)	
11.2.1	Pyrrole-Based Peptides	663

11.2.2	Imidazole-Based Peptides	665
11.2.3	Oxazole-, Dihydrooxazole-, and Oxazolidine-Based Peptides	666
11.2.3.1	Peptide-Based Dihydrooxazoles as Precursors to Peptide-Based Oxazoles	666
11.2.3.2	Oxidation of Peptide-Based Dihydrooxazoles to Peptide-Based Oxazoles	669
11.2.3.3	Peptide-Based Oxazoles from Glycine Acylation and Cyclodehydration	669
11.2.3.4	Peptide-Based Oxazoles by Oxidation and Cyclodehydration of Threonine and β -Phenylserine Residues	671
11.2.3.5	Peptide-Based Oxazoles by Rhodium-Mediated Carbenoid Insertion of Diazocarbonyl Compounds into an Amide N–H Bond Followed by Cyclodehydration	674
11.2.4	Thiazole-, Dihydrothiazole-, and Thiazolidine-Based Peptides	676
11.2.4.1	Peptide-Based Dihydrothiazoles as Precursors to Peptide-Based Thiazoles: The Interconversion of Peptide-Based Dihydrooxazoles to Peptide-Based Dihydrothiazoles	676
11.2.4.2	Peptide-Based Dihydrothiazoles from Condensation of an Imidate and a β -Amino Thiol	678
11.2.4.3	Oxidation of Peptide-Based Dihydrothiazoles to Peptide-Based Thiazoles	679
11.2.4.4	Peptide-Based Thiazoles via the Condensation of β -Halo- α -oxo Esters with Thioamides: A Modified Hantzsch Synthesis	679
11.2.4.5	Peptide-Based Thiazoles from the Synthesis and Oxidation of Peptide-Based Thiazolidines	680
11.2.5	Oxadiazole-Based Peptides	682
11.2.5.1	Peptide-Based 1,2,4-Oxadiazoles by the Reaction of Amino Acid Anhydrides with Amidoximes	682
11.2.5.2	Peptide-Based 1,3,4-Oxadiazoles by the Preparation and Reaction of Diacylhydrazines	684
11.2.6	Triazole-Based Peptides	685
11.2.6.1	Peptide-Based 1,2,4-Triazoles by the Preparation and Reaction of Acylamidrazones	686
11.2.7	Tetrazole-Based Peptides	688
11.2.7.1	Peptide-Based Tetrazoles from the Reaction of Imidoyl Chlorides and Hydrazoic Acid	688
12	Peptides Incorporating Secondary Structure Inducers and Mimetics (<i>C. Toniolo</i>)	693
12.1	Synthesis of Peptides Incorporating β-Turn Inducers and Mimetics (<i>M. KAHN and M. EGUCHI</i>)	695
12.1.1	β -Turn Inducers	696
12.1.1.1	C $^{\alpha}$ -Alkyl α -Amino Acids	696
12.1.1.2	α,β -Didehydro- α -amino Acids	697
12.1.1.3	N $^{\alpha}\leftrightarrow$ C $^{\alpha}$ and C $^{\alpha}\leftrightarrow$ C $^{\alpha}$ Cyclized α -Amino Acids and Dipeptide Units	697
12.1.2	β -Turn Mimetics and Their Incorporation into Peptide Sequences	700
12.2	Synthesis of Peptides Incorporating γ-Turn Inducers and Mimetics (<i>M. Kahn and M. Eguchi</i>)	741
12.2.1	Peptides Incorporating γ -Turn Inducers and Mimetics	741
12.2.1.1	Synthesis of γ -Turn Inducers and Mimetics	744
12.2.1.2	Synthesis of Peptides Containing γ -Turn Inducers and Mimetics	755

12.3	Synthesis of Peptides Incorporating Helix Inducers and Mimetics . . .	759
	<i>(E. Doval Santos and A. C. Satterthwait)</i>	
12.3.1	Helix Inducers	760
12.3.1.1	Helix Induction Resulting from the Peptide Sequence	760
12.3.1.1.1	Proteinogenic Amino Acids	760
12.3.1.1.2	Nonproteinogenic α -Amino Acids	761
12.3.1.1.2.1	C $^{\alpha,\alpha}$ -Disubstituted Glycines	761
12.3.1.1.2.2	α,β -Didehydrophenylalanine	763
12.3.1.1.3	Helix End Capping	763
12.3.1.1.4	Helix Stabilization by Side-Chain Interactions	767
12.3.1.2	Other Factors Affecting Helix Stability	768
12.3.2	Helix Mimetics	769
12.3.2.1	Synthetic Templates	769
12.3.2.1.1	Kemp's Templates: Restricted Analogues of Oligoproline	769
12.3.2.1.2	Bartlett's Templates: Derivatives of 3,6-Dimethyl-4-oxo-2,3,4,5,6,7-hexahydro-1 <i>H</i> -indole-3,6-dicarboxylic Acid	770
12.3.2.1.3	Tetrahydronaphthalene-Based Templates	772
12.3.2.1.4	Other Templates	773
12.3.2.2	Covalent Main-Chain Links	773
12.3.2.2.1	Hydrogen Bond Mimic: α -Helix Nucleation from the N-Terminus	773
12.3.2.2.2	N-Terminal Extension of a Nucleated Helix	776
12.3.2.3	Covalent Side-Chain Links	777
12.3.2.3.1	Lactams	777
12.3.2.3.2	Disulfides	779
12.3.2.3.3	Alkanediyl Links	780
12.3.2.3.4	[(4-Aminomethyl)phenyl]acetic Acid Bridged Peptides: Single or Overlapping <i>i, i + 7</i> Side-Chain Bridges	782
12.3.2.4	Metal-Chelated Side-Chain Cross-links	785
12.3.2.4.1	Chelation with Metal Ions	786
12.3.2.4.2	Chelation with Metal Complexes	786
12.3.2.4.3	Incorporation of Metal-Binding Ligands in a Peptide Chain	788
12.4	Synthesis of β-Sheet Peptides and Proteins Incorporating Templates . . .	793
	<i>(P. Chitnumsub, S. Deechongkit, R. Kaul, J. P. Schneider, K. Y. Tsang, A. Moretto, H. Bekele, S. R. LaBrenz, H. A. Lashuel, and J. W. Kelly)</i>	
12.4.1	β -Sheet Peptides Incorporating Templates via Solution-Phase Synthesis	793
12.4.1.1	Incorporation of the Dibenzofuran-2,8-dipropanoic Acid Template	793
12.4.1.2	Incorporation of the Dibenzofuran-4,6-dipropanoic Acid Template	796
12.4.1.3	Incorporation of the Dibenzofuran-4,6-dipropanoic Acid Template with Intervening Ethylene Glycol Units Between the Template and Peptide Strands	797
12.4.2	β -Sheet Peptides and Proteins Incorporating Templates via Solid-Phase Peptide Synthesis	799
12.4.2.1	Incorporation of the 4-(2-Aminoethyl)dibenzofuran-6-propanoic Acid Template	799
12.4.2.2	Incorporation of the 4-(2-Aminoethyl)-2,8-bis(2-carboxyethyl)-dibenzofuran-6-propanoic Acid Template	801
12.4.2.3	Incorporation of the 6,6'-Bis(acylamino)-2,2'-bipyridine-Based Template	802
12.4.3	β -Sheet Peptides Incorporating Templates via a Combination of Solution- and Solid-Phase Peptide Synthesis	803
12.4.3.1	Incorporation of the Dibenzofuran-4,6-dipropanoic Acid Template	803

12.5	Synthesis of Peptides with Sugar Amino Acids	807
	(<i>E. Gräfin von Roedern, M. A. Born, M. Stöckele, and H. Kessler</i>)	
12.5.1	Sugar Amino Acids as Peptidomimetics	807
12.5.1.1	Sugar Amino Acid Building Blocks	810
12.5.1.1.1	Synthesis of 2-Amino-2-deoxy-1- <i>O</i> -methyl- α/β -D-glucopyranuronic Acid	810
12.5.1.1.2	Synthesis of 7-Amino-2,6-anhydro-7-deoxy-L- <i>glycero</i> -L- <i>gulo</i> -heptonic Acid	811
12.5.1.1.3	Synthesis of 7-Amino-2,6-anhydro-3,4,5-tri- <i>O</i> -benzyl-7-deoxy-L- <i>glycero</i> -L- <i>gulo</i> -heptonic Acid	813
12.5.1.1.4	Synthesis of 3-Amino-2,6-anhydro-4,5,7-tri- <i>O</i> -benzyl-3-deoxy-D- <i>glycero</i> -D- <i>gulo</i> -heptonic Acid	815
12.5.1.2	Peptides with Sugar Amino Acid Building Blocks	816
12.5.1.2.1	Solution-Phase Synthesis of Peptides Based on 2-Amino-2-deoxy-1- <i>O</i> -methyl- α -D-glucopyranuronic Acid	817
12.5.1.2.2	Solid-Phase Synthesis of Peptides Based on 3-Amino-2,6-anhydro-3-deoxy-D- <i>glycero</i> -D- <i>gulo</i> -heptonic Acid	818
12.6	Peptide Nucleic Acids	822
	(<i>A. Püschl and P. E. Nielsen</i>)	
12.6.1	Peptide Nucleic Acid Monomers	824
12.6.1.1	Synthesis of the <i>N</i> -[2-(<i>tert</i> -Butoxycarbonylamino)ethyl]glycine Backbone	824
12.6.1.2	Synthesis of the Pseudoisocytosine Peptide Nucleic Acid Monomer	825
12.6.1.3	Synthesis of the 2,6-Diamino-9 <i>H</i> -purine Peptide Nucleic Acid Monomer	826
12.6.1.4	Synthesis of the D-Lysine Peptide Nucleic Acid Monomer	827
12.6.2	Peptide Nucleic Acid Oligomers	829
12.6.2.1	<i>tert</i> -Butoxycarbonyl/Benzyloxycarbonyl Method	829
12.6.2.2	9-Fluorenylmethoxycarbonyl/Benzhydryloxycarbonyl Method	831
12.6.3	Peptide Nucleic Acid–Peptide Conjugates	832
12.6.4	Labeled Peptide Nucleic Acid Oligomers	833
12.6.4.1	Radioactive Labeling	833
12.6.4.2	Non-radioactive Labeling	833

8 Introduction to the Synthesis of Peptidomimetics

C. TONIOLO and M. GOODMAN

The discovery of a multitude of naturally occurring, bioactive peptides has generated a rich source of pharmacophores from which medicinal chemists are developing new useful therapeutic drugs. After binding to an enzyme, or a membrane receptor, peptide-based inhibitors, neurotransmitters, immunomodulators, and hormones influence cell-to-cell communications and control a variety of vital functions such as metabolism, immune defense, digestion, respiration, sensitivity to pain, reproduction, and behavior.

As a result of intense research, a wealth of protection strategies and coupling methods is available for synthesis in solution and on solid supports. Peptides of up to almost fifty amino acid residues can now be prepared in sufficient quantities for pharmacological and clinical assays, and for clinical drugs and diagnostics. Thus, in the last few years new peptide-based treatments for a series of diseases have been established.^[1,2]

Though naturally occurring peptides based on coded amino acids have been widely used as drugs, there are problems with the use of peptides as therapeutic agents. The problems mainly arise from their rapid metabolism by proteolysis, and their interactions at multiple receptors. As a result, peptide researchers have sought modifications of peptide structures to create more stable and bioavailable molecules.^[3-27]

Given the extensive biology associated with peptides, it is not surprising that considerable effort has been devoted to the synthesis of *peptidomimetics* to overcome the unfavorable properties and therapeutic deficiencies of peptides. In particular, since the advent of solid-phase synthesis and, more recently, combinatorial chemistry, interest in peptidomimetic design and preparation has exploded. In theory, the peptide chemist is only limited by their imagination in the novel modifications that can be tailored for synthetic peptide analogues.

Peptidomimetics have found wide application as biostable, bioavailable, and often potent surrogates of naturally occurring peptides. They form the basis of important families of enzyme inhibitors and they act as receptor agonists and antagonists. Peptide chemists are also gaining a deeper understanding of the structural features of this class of compounds that influence their ability to permeate biological membranes and their pharmacokinetic properties.

Nanomolar affinity for a protein receptor can be achieved by a peptide having a few, appropriately oriented side chains. This implies that the peptide backbone is not an absolute requirement for this high affinity, thus justifying the search for peptidomimetics. These compounds imitate the topology of a peptide, but may partly, or completely, lack its amide backbone characteristics. It is the rationale for the use of peptidomimetics that the backbone scaffold places the amino acid side chains in a particular 3D-position to allow contact with the enzyme or receptor protein. The 3D-relationship of the side-chain groups in the peptide (topology) determines its binding and biological messages.

However, it was immediately recognized by peptide chemists that, even in the cases where a direct (backbone)peptide···protein(backbone) interaction is not operative, the backbone conformation may dramatically influence the biological response. It is evident that the introduction of new, promising peptidomimetics is based primarily on the combined knowledge of the complementary conformational, topochemical, and electronic properties of the native peptide and of its address (in other words, of the receptor or the active site of the enzyme with which it interacts). Then, the design of peptidomimetics as potential bioactive compounds must take into particular account two structural factors: (i) a favorable fit (tertiary structure) with respect to the corresponding complementary spatial situation at the active site; (ii) the placement of structural elements (e.g., functional groups, polar and

hydrophobic regions) in well-defined positions so that the required interactions (e.g., hydrogen bonds, electrostatic or hydrophobic interactions) can occur.

A major problem in this area of research is represented by the conformational flexibility of most peptides, the high dependence of their conformation on environment, and the relationship between the conformation in solution and the receptor-bound conformation. To overcome these difficulties, a successful approach involves the preparation of conformationally constrained analogues. Synthetic, bioactive peptidomimetics specifically designed for this approach are characterized either by cyclization (main-chain-to-main-chain; side-chain-to-main-chain; or, side-chain-to-side-chain) or by the incorporation of amino acid or dipeptide building blocks that can explore only a very limited portion of conformational space. Corollary, useful properties of these systems often include prolonged biological activity as a result of an increased stability to proteolytic enzymes. By combining computer-assisted molecular modeling, modern spectroscopic and NMR techniques, and X-ray diffraction analysis it is now possible to design peptidomimetic drugs, the structural spectrum of which lies between that of slightly modified peptides and that of pure nonpeptide molecules. The preparation of such compounds requires the utilization of the complete arsenal of modern, synthetic organic chemistry in addition to the methodologies developed by peptide chemists.

This volume brings together most of these critical issues by highlighting recent advances in a number of core areas of peptidomimetic synthesis. Section 9 focuses on side-chain-modified peptides, Section 10 describes the preparation and use of a variety of peptide main-chain modifications. Combined side-chain- and main-chain-modified peptides are covered in Section 11. Finally, Section 12 provides chemistry leading to peptides incorporating secondary structure (β - and γ -turns, helices, β -sheets) mimetics and inducers.

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9 Side-Chain-Modified Peptides

A. M. FELIX

The biological function of peptides and proteins depends on their native conformation. The side-chain functionalities of the α -amino acids that comprise peptides and proteins have profound effects on their properties. These functionalities reside in the 20 naturally occurring α -amino acids, which have different propensities for formation of the three major secondary structural conformations.^[1] In addition to these naturally occurring α -amino acids whose primary structure enables the polypeptide to fold into a predictable secondary and tertiary structure, the incorporation of unnatural amino acids has opened important areas of research.

The large number of theoretically possible conformational states for a linear peptide is significantly reduced when the side chain of the peptide is modified with conformationally restricted α -amino acids. Conformationally restricted analogues of biologically active peptides may be more resistant to enzymatic degradation, or may be locked into a biologically active preferred conformation. Conformationally restricted peptides may result in other potential advantages including enhanced receptor selectivity, prolonged receptor binding, or increased hydrophobicity that may improve absorption and serve as important models for peptide design.^[2]

The introduction of β -substituted analogues of natural amino acids into biologically important peptides enables their use as templates for peptidomimetics. Procedures for the synthesis of β -substituted analogues have been devised for several naturally occurring amino acids including β -substituted phenylalanines, 2',6'-dimethyltyrosines, naphthylalanines, and cysteines, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids, and substituted phenylglycines, and glutamic acids (Section 9.1).

The pyrrolidine ring structure of proline is unique and places it in a special category among the natural α -amino acids since it leads to conformational restriction and a high probability of a *cis*-peptide bond preceding the proline residue in a polypeptide.^[3] Proline and analogues of proline can play important roles in the *de novo* design of biologically important peptides and proteins. Procedures have been reported for the synthesis of nitrogen-containing three-membered rings (aziridine-2-carboxylic acids), four-membered rings (azetidine-2-carboxylic acids), five-membered rings (prolines), and six-membered rings [pipercolic acids (piperidine-2-carboxylic acids)], as well as those containing other heteroatoms (Section 9.2).

The incorporation of photoreactive amino acids into peptides (either during stepwise synthesis of the peptide or postsynthetically) enables the generation of a photoaffinity reagent that can bind to a receptor through carbene or nitrene intermediates. These peptides also contain tags (fluorophores, radionuclei, or biotin functions) which enable the identification of ligand-contact sites.^[4] The synthesis of a variety of side-chain-modified phenylalanine- and benzophenone-containing photophores, and their use in the synthesis of the corresponding peptides (substance P, angiotensins, vasopressins, enkephalins), are reported (Section 9.3). The preparation of benzophenone-containing peptides using solid-phase methods either by direct insertion during synthesis or post-insertion after assemblage is described (Section 9.3.5.1).

Synthetic peptides containing side-chain modification have also been used as molecular scaffolds for the preparation of multiple receptors and molecular devices.^[5] These include the use of crown ethers, cyclodextrins, porphyrins, and peptides with metal-binding sites (including ferrocenyl and EDTA side chains) (Section 9.4). Cyclization procedures have been developed to prepare biologically active cycloisodityrosine peptides which contain 14- or 17-membered rings (Section 9.5). The use of tryptathionine, a cross-linking dipeptide consisting of side-chain-to-side-chain linked L-Trp-L-Cys that is present in phallotoxins,^[6] a family of cyclic heptapeptides, is also described (Section 9.6).

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9.1 Synthesis of Side-Chain Conformationally Restricted α -Amino Acids

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The side-chain groups of the 20 naturally occurring α -amino acids, which are found in peptides and proteins that are the products of genes, have a wide range of chemical functionalities which make them readily adaptable as acids, bases, nucleophiles, electrophiles, chelators, charged groups, hydrophobes, hydrophiles, proton acceptors, proton donors, etc. These also tend to be quite conformationally flexible with energy barriers to rotation about their torsional angles χ^1 (α - β bond), χ^2 (β - γ bond), etc. generally less than $8 \text{ kcal} \cdot \text{mol}^{-1}$ and, therefore, they readily interconvert at physiological temperatures. The exception is proline which has a five-membered ring which restricts the conformation; even so, proline readily interconverts between envelope-like conformations rapidly on the NMR timescale. Why nature has chosen 19 amino acid side-chain groups (Gly has no side-chain group) that are so flexible is not known, but it has great significance.

In order to understand peptide-protein, peptide-nucleic acid, peptide-peptide, peptide-lipid, and peptide-sugar interactions, binding, and information transduction in biological systems, side-chain conformational restriction can provide a very powerful tool for design.^[1-3] Of course, of the 20 naturally occurring amino acids found in proteins, three have β -disubstitutions; namely, valine which has β -dimethyl substitution and hence is prochiral at the β -carbon atom, threonine which can be viewed as β -methylserine and hence is chiral at the β -carbon atom, and isoleucine which has β -methyl and β -ethyl substitution, and hence has a β -chiral center, and can be viewed as a β -methyl derivative of α -aminopentanoic acid. The presence of a β -substitution for these amino acids does lead to additional torsional constraint about the χ^1 (C_α - C_β) torsional angle. Undoubtedly this has been exploited by nature in some way, but surprisingly little has been undertaken by peptide and protein chemists to examine this question, and to systematically evaluate the effect of β -substitution on protein folding or molecular recognition, until quite recently.

It has been known for many years, however, that the β -branched amino acids, especially valine and isoleucine, cause problems in synthesis,^[4,5] and special care and additional reaction time are required when β -substituted amino acids are added to a growing peptide chain in synthesis. For example, in the synthesis of [2,4-diisoleucine]oxytocin efforts to couple the isoleucine to isoleucine by the azide method failed and only the rearranged product was obtained.^[6] Also, it is much more difficult to hydrolyze peptide bonds formed between two or more contiguous β -substituted amino acids using standard 6 M HCl conditions. For example, in the hydrolysis of [2,4-diisoleucine]oxytocin (3 isoleucine residues adjacent to each other) complete hydrolysis takes 60 hours.

Synthetic Side-Chain Conformationally Constrained α -Amino Acids

Because β -substituted analogues of the naturally occurring amino acids and their analogues can lead to novel amino acids with conformationally restricted side-chain groups, they provide unique opportunities to explore (a) the topographical requirements [$g(-)$, *trans*, or $g(+)$] for molecular recognition with a particular conformational scaffold (α -helix, β -turn, etc.), (b) the stereostructural requirements for information transduction for specific pharmacophore elements, (c) the dynamic requirements for binding and induction of conformational changes accompanying binding, (d) the effects of topographical constraint on peptide stability against proteolysis on bioavailability, and on peptide-membrane permeability, and (e) their use as templates for the preparation of peptidomimetics. Thus, their design, synthesis, and incorporation into bioactive peptides and/or peptides designed to

explore topographical properties is an increasingly important area of research. In this section we examine a few of the various modes of side-chain topographical constraints which have been examined to date, with specific applications to the design of biologically active peptides.

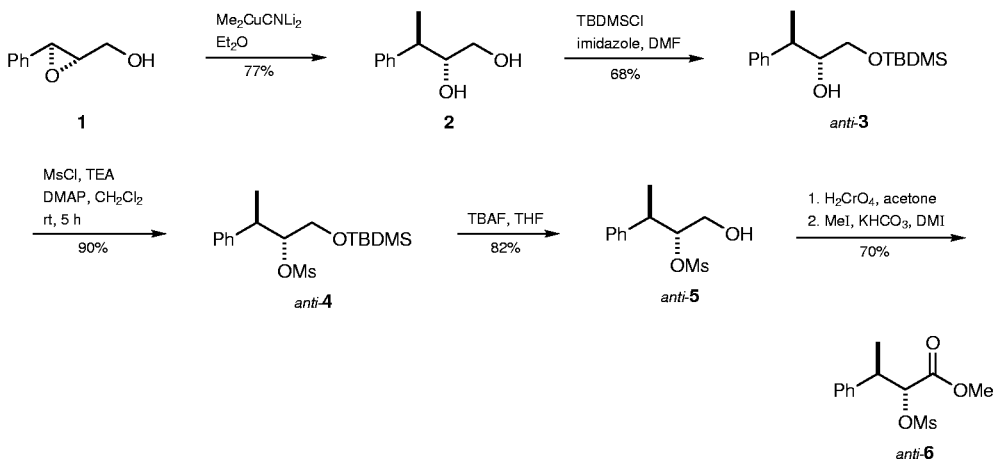
9.1.1 β -Methylphenylalanine

There is increasing evidence^[3,7–19] demonstrating the important impact on bioactivity that β -methylphenylalanines can have when incorporated into bioactive peptides. Asymmetric synthesis of these compounds with well-established chemistry and economic starting materials has become well developed. Among the reported syntheses, the chiral auxiliary assisted asymmetric pathway^[20–22] remains the most well-developed approach, while other pathways have only been briefly explored, because either too many steps were involved^[23] or poor stereoselectivity was obtained.^[24]

9.1.1.1 Asymmetric Epoxide Ring Opening

N $^{\alpha}$ -Boc-protected β -methylphenylalanines can be prepared from diastereoselective ring opening of epoxide derivatives, followed by selective protection, oxidation, and functional group substitutions (Schemes 1–5). Low yields in some steps limit the applications of this method.^[23]

Scheme 1 Synthesis of the *anti*-Intermediate^[23]



Scheme 2 Improved Synthesis of the *anti*-Intermediate^[23]

