1.1 INTRODUCTION

The simplest β-amino acid is β-aminopropionic acid (β-alanine, 1), which is not a proteinogenic amino acid, but it is an essential component of many relevant, biologically active compounds, such as vitamin B₃ (pantothenic acid, 2). Furthermore, chiral derivatives of β-amino acid are useful precursors of chiral, enantiomerically pure β-amino acids; see, for example, β-alanine derivatives 3–6²–⁵ (Scheme 1.1).

There are three general types of open-chain chiral β-amino acids, depending on whether the substitution takes place at the carbon bearing the carboxyl group (α-position), the carbon bearing the amino group (β-position), or at both positions (α,β-disubstitution) (Fig. 1.1a).⁶ In addition, cyclic β-amino acids may present the amino acid and the carboxylic groups as substituents of a carbocyclic ring or may incorporate the amino group in a heterocyclic ring (Fig. 1.1b).

Recently, Seebach and co-workers⁷,⁸ proposed the terms β²⁻ and β³⁻ amino acid, where the numbers indicate the position of the side chains, in order to distinguish positional isomers (Scheme 1.2).

The following sections in this chapter are arranged following the Seebach β²⁻/β³⁻ convention and present illustrative examples of relevant β-amino acids in each category. No attempt is made to include an exhaustive list of compounds or contributing authors.
β-Alanine, 1

(R)-(−)-Pantothenic acid, 2

3, ref 2

4, ref 3

5, ref 4

6, ref 5

Scheme 1.1

α-substituted

β-substituted

(a) Linear β-amino acids

α,β-substituted

(b) Cyclic β-amino acids

Figure 1.1

β²-amino acid, R³ = H

β³-amino acid, R² = H

cyclic β-amino acid, R²−R³ = (CH₂)ₙ

Scheme 1.2
1.2 $\beta^2$-ALKYL-$\beta$-AMINO ACIDS

$(R)$-2-Methyl-3-aminopropionic acid $(R)$-7 is a prototype of $\beta^2$-alkyl-$\beta$-amino acids and is a residue present in cryptophycin 1 (8), a potent antitumor depsipeptide$^9$ (Scheme 1.3).

![Scheme 1.3](image)

Enantiopure $\beta^2$-phenylalanine $(S)$-9 and $\beta^2$-homovaline $(R)$-10 were recently synthesized by Gellman and co-workers$^{10}$ to provide access to new $\beta$-peptides with specific conformations and particular functions (Scheme 1.4).

![Scheme 1.4](image)

1.3 $\beta^3$-ALKYL-$\beta$-AMINO ACIDS

Among $\beta$-amino acids that exhibit interesting pharmacological properties in free form, emeriamine $(R)$-11 has shown activity as a hypoglycemic and antiketogenic agent$^{11}$ (Scheme 1.5). In this context, iturinic acid $(R)$-12 is a component of biologically relevant peptide iturin,$^{12}$ and synthetic antibiotic TAN-1057 A (13) is a dipeptide containing a $\beta^3$-arginine fragment$^{13}$ (Scheme 1.5).
1.4 \( \beta^{2,2}\)-DISUBSTITUTED \( \beta\)-AMINO ACIDS

\( \alpha,\alpha\)-Dialkylated derivatives of proteinogenic amino acids are efficient inhibitors of those enzymes that metabolize the natural substrates.\(^{14}\) Furthermore, synthetic peptides incorporating \( \alpha,\alpha\)-dialkylated \( \alpha\)-amino acids adopt modified backbone conformations,\(^{15}\) exhibiting increased lipophilicity\(^{16}\) and increased resistance to both enzymatic and chemical hydrolysis.\(^{17}\) It may be anticipated that incorporation of \( \alpha,\alpha\)-disubstituted \( \beta\)-amino acids into unnatural peptides will confer peculiar conformational and chemical properties. Not surprisingly, several reports describing the enantioselective synthesis of \( \beta^{2,2}\)-dialkylated \( \beta\)-amino acids have recently appeared,\(^{18-20}\) and Scheme 1.6 presents four examples taken from Ref. 19.

\[ \text{Scheme 1.5} \]

\[ \text{Scheme 1.6} \]

1.5 \( \beta^{2,3}\)-DISUBSTITUTED \( \beta\)-AMINO ACIDS

Dolastatin 11 (16) is a natural product which exhibits activity against lymphocytic leukemia and contains a 2-methyl-3-aminopentanoic acid reside within a cyclic depsipeptide.\(^{21}\) (Scheme 1.7). Majusculamide C is a related depsipeptide which is cytotoxic and exhibits fungicidial activity against several plant pathogens.\(^{22}\) Very recently, Kimura and co-workers\(^{23}\) reported the isolation and structural
elucidation of kulokekahilide-1 (17), a cytotoxic cyclic bidepsipeptide which contains the β^{2,3}-disubstituted β-amino acid residue 3-amino-2-methylhexanoic acid (Scheme 1.7).

The relevance of β^{2,3}-dialkyl-β-amino acids is not limited to their biological occurrence, as several cases have proved their usefulness in the development of sheet-forming β-peptides.24

1.6 β^{3,3}-DISUBSTITUTED β-AMINO ACIDS

While oligomers of the achiral β^{2,2}-gem-disubstituted β-amino acids 1-(aminomethyl)cyclopropane and 1-(aminomethyl)cyclohexane carboxylic acid have already been shown to form 8- and 10-membered hydrogen-bonded rings,25 significant work is presently being conducted with analogous peptides containing β^{3,3}-disubstituted β-amino acids.20,26

Scheme 1.8 presents the structures of achiral β^{3,3}-cyclobutane aminocarboxylic acid 1826 and chiral open-chain compounds 19 and 2027 as illustrative examples of this type of β-amino acid.
2,3-Alkylated aspartic acids \( 21–24 \) are both \( \alpha,\alpha \)-disubstituted \( \alpha \)-amino acids and \( \beta,\beta \)-disubstituted \( \alpha \)-amino acids\(^\text{28} \) (Scheme 1.9). Aspartic acid derivatives such as \( 21–24 \) are specially interesting subjects for study owing to their relevant biological properties.

\[
\text{H}_2\text{N} - \text{CO}_2\text{H}
\]

\( (S)-19, R = \text{CH}_3, \text{ref 27} \)

\( (S)-20, R = \text{n-Bu}, \text{ref 27} \)

\[
\text{H}_2\text{N} - \text{R} - \text{O} - \text{Ph}
\]

\( (S)-18, \text{ref 26} \)

\( \text{Scheme 1.8} \)

\( \beta^{2,3} \)-Alkylated aspartic acids \( 21–24 \) are both \( \alpha,\alpha \)-disubstituted \( \alpha \)-amino acids and \( \beta,\beta \)-disubstituted \( \alpha \)-amino acids\(^\text{28} \) (Scheme 1.9). Aspartic acid derivatives such as \( 21–24 \) are specially interesting subjects for study owing to their relevant biological properties.

\[
\text{H}_2\text{N} - \text{CO}_2\text{H}
\]

\( (S)-21, R = \text{CH}_3 \)

\( (S)-22, R = \text{CH}_2\text{CH}_3 \)

\( (S)-23, R = \text{n-C}_4\text{H}_9 \)

\( (S)-24, R = \text{CH}_2\text{Ph} \)

\[
\text{H}_2\text{N} - \text{R} - \text{CO}_2\text{H}
\]

\( (S)-26, R = \text{Ph} \)

\( (R)-27, R = 1\text{-naphthyl} \)

\( (R)-28, R = \text{C}_6\text{H}_{13} \)

\[
\text{H}_2\text{N} - \text{R} - \text{CO}_2\text{H}
\]

\( (+)-\text{NSL-95301, (R)-25} \)

\( \text{Scheme 1.9} \)

1.7 \( \beta^{2,2,3} \)-TRISUBSTITUTED \( \beta \)-AMINO ACIDS

\( (R)-(+)\)-3-Amino-3-phenyl-2,2-dimethylpropionyl derivative NSL-95301, \( (R)-25 \), is a novel trisubstituted \( \beta \)-amino acid exhibiting potent inhibition of platelet aggregation, which makes it a promising antithrombotic agent\(^\text{29} \) (Scheme 1.10). From the synthetic point of view, both catalytic enantioselective\(^\text{30} \) and stoichiometric diastereoselective\(^\text{31,32} \) procedures afford \( \beta^{2,2,3} \)-amino acids \( 26–28 \) in good enantiomeric excess (Scheme 1.10).

\[
\text{H}_2\text{N} - \text{R} - \text{O} - \text{Ph}
\]

\( (R)-26, R = \text{Ph} \)

\( (R)-27, R = 1\text{-naphthyl} \)

\( (R)-28, R = \text{C}_6\text{H}_{13} \)

\[
\text{H}_2\text{N} - \text{R} - \text{CO}_2\text{H}
\]

\( \text{Scheme 1.10} \)
1.8 $\beta^{2,2,3,3}$-TETRASUBSTITUTED $\beta$-AMINO ACIDS

Tetrasubstituted $\beta^{2,2,3,3}$-amino acids may be capable of acting as secondary-structure breakers when incorporated into $\beta$-peptides. $\beta$-Lactamas 29 and 30 are two examples of suitable precursors of $\beta^{2,2,3,3}$-amino acids$^{33}$ (Scheme 1.11).

![Scheme 1.11]

29, $R^1 = R^2 = R^3 = R^4 = CH_3$
30, $R^1 = R^2 = (CH_2)_5; R^3 = R^4 = (CH_2)_5$

1.9 $\beta^2$-ARYL-$\beta$-AMINO ACIDS

(S)-3-Amino-2-phenylpropionic acid, (S)-31, is an $\alpha$-aryl-$\beta$-amino acid present in the side chain in the structure of penicillin betaine, whereas its ethyl ester derivative has neurological activity.$^{34}$ Tryptophan analog (R)-32 has recently been synthesized by Arvanitis and co-workers$^{35}$ (Scheme 1.12).

![Scheme 1.12]

1.10 $\beta^3$-ARYL-$\beta$-AMINO ACIDS

$\beta$-Tyrosine is a $\beta$-aryl-$\beta$-amino acid present in jasplakinolide (33), a sponge metabolite of considerable interest because of its insecticidal, anthelminthic, and
antifungal properties.\textsuperscript{36,37} Similarly, \((R)-3\text{-amino-3-phenylpropionic acid is present in cyclic peptide astins 34–36, natural products with antitumor properties}\textsuperscript{38} (Scheme 1.13).

More recently, \(\beta^3\text{-quinoline-}\beta\text{-alanine derivative RWJ-53033 (37) was considered for development as a potent nonpeptide integrin antagonist,}\textsuperscript{39} whereas \(\text{para-substituted 3-aryl-3-aminopropionic acid derivative 38 is actually a broad-spectrum carbapenem drug}\textsuperscript{40} (Scheme 1.13).

Recently, von Nussbaum and co-workers\textsuperscript{41} discovered the new natural \(\beta^3\text{-amino acid (R)-}\beta-(3,4\text{-dihydroxyphenyl})-\beta\text{-alanine [(R)-}\beta^3\text{-Dopa, (R)-39 in the mushroom}}

\begin{verbatim}
[CH3]
\text{H}_{3}N_{2}O_{3}N_{4}S_{5}CO_{2}H
38
\end{verbatim}
Cortinarius violaceus. Actually (R)-39 is present in the mushroom as the Fe(III) complex, which gives the fruit its peculiar blue-violet color. (R)-β3-Dopa was also obtained by enzymatic conversion of tyrosine via β3-(4-hydroxyphenyl)-β-alanine precursor (R)-40 (Scheme 1.14).

1.11 OLEFINIC AND ALKYNYL-β-AMINO ACIDS

α,β-Unsaturated β-amino acid derivatives have found widespread use in the synthesis of naturally occurring compounds such as alkaloids and antibiotics, and they have also been employed as precursors to derivatives with relevant pharmacological properties. Furthermore, unsaturated (3S)-aminopentynoic acid is the key pharmacophore in the antithrombotic agent xemilofiban (41). Two interesting natural products containing unsaturated β-amino acids are onchidin (42) and mutoporin (43). Onchidin is a potent protein phosphatase-1 inhibitor. Very recently, the novel α,β-unsaturated β-amino acid–containing molecule CJ-15,801 (44) was reported as an inhibitor of multiple-drug-resistant Staphylococcus aureus strains (Scheme 1.15).

γ-Unsaturated β-amino acids represent an interesting subclass of compounds. For example, unsaturated α-methyl-β-amino acid ADDA (45) is present in the antibiotics cyanovirin RR, nodularin, and microcystin LR. Very recently, Lurain and Walsh have developed a method for the enantioselective synthesis of γ-unsaturated β-amino acids such as 46–49 (Scheme 1.16).

Special mention deserves also the synthetic procedure recently developed by Adam et al. that provides a route to α-methylene-β-alkyl-β-amino acids 50 and 51 (Scheme 1.16).
Scheme 1.15

Xemilofiban, 41

Onchidin, 42

Motuporin, 43

CJ-15,801 (44)
1.12 \( \alpha,\beta \)-DIAMINO ACIDS

\( \alpha,\beta \)-Diaminopropionic acid (52) is the prototype for this type of \( \beta \)-amino acids. This diamine is a structural component of several natural products, such as bleomycin,\(^5\) sulfazecin,\(^4\) and capreomycin (53).\(^5\) By the same token, (2S,3S)-diaminobutanoic acid is a common component of the linear heptapeptide antibiotics antrimycins (54a–h)\(^5\) (Scheme 1.17). Modified taxol side chain 55 has been coupled to the taxane ring system to increase water solubility of the corresponding taxol analogs.

\[\text{Scheme 1.16}\]

\[\text{Scheme 1.17}\]
1.13 **α-HYDROXY-β-AMINO ACIDS**

α-Hydroxy-β-amino acids are probably the most important members of the β-amino acid family. They are the essential moiety of many well-known natural products endowed with significant biological activity. The best known example is the potent neoplastic agent taxol\textsuperscript{57,58} but also remarkable are bestatin (56), a well-known immune response modifier containing (2S,3R)-3-amino-2-hydroxy-4-phenylbutanoic acid,\textsuperscript{59} aminopeptidase inhibitors amastatin (57)\textsuperscript{60} and phebestin (58),\textsuperscript{61} and microginin (59),\textsuperscript{62} which inhibits angiotensin-converting enzyme (Scheme 1.18).

![Structural formula of Bestatin, Amastatin, and Phebestin](image1)

Scheme 1.18

1.14 **β-AMINO-γ-HYDROXY ACIDS**

β-Amino-γ-hydroxy acids are relevant compounds because they are components of peptides of pharmacological interest.\textsuperscript{63} One example is (2S,4R)-2-amino-4-hydroxy-adipic acid (60), which is a constituent of theonellamide F, a powerful cytotoxic...
agent against P388 leukemia cells \( \text{64} \) (Scheme 1.19). A second example is the metabolite oryzoxymycin \( \text{61} \), isolated in 1968 by Hashimoto et al. \( \text{65} \)

![Scheme 1.19](image)

1.15 CARBOCYCLIC \( \beta \)-AMINO ACIDS

Cispentacin \( \text{62} \) is an antifungal antibiotic, \( \text{66} \) whereas other carbocyclic \( \beta \)-amino acids are useful intermediates for the enantioselective synthesis of alkaloids. \( \text{67} \) For example, \((2S)-(1R)\)-cyclohexanecarboxylic acid \( \text{63} \) has found many applications in the synthesis of natural products and peptide mimetics. \( \text{68} \) By contrast, nonnatural cyclic \textit{trans}-cyclohexyl and \textit{trans}-cyclopentyl \( \beta \)-amino acids \((\text{64} \text{ and } \text{65}, \text{ respectively})\) have been incorporated into \( \beta \)-peptide foldamers \( \text{69} \) (Scheme 1.20).

![Scheme 1.20](image)

Conformationally restricted peptidomimetics frequently exhibit increased biological activity as well as enhanced stability. Incorporation of cyclic \( \beta \)-amino acids into such unnatural peptides confers the desired rigidity characteristics. \( \text{69} \text{– } \text{71} \) A salient example of conformationally constrained \( \beta \)-amino acids is phenylalanine analog \( \text{66} \) \( \text{72} \) (Scheme 1.20).

1.16 HETEROCYCLIC \( \beta \)-AMINO ACIDS

Methylphenidate \( \text{67} \) is the most frequently used medication for the treatment of hyperactive children with attention-deficit disorder. \( \text{73} \) RWJ-50042 \( \text{68} \) is an effective antagonist of the platelet fibrinogen receptor, containing a nipecotic acid scaffold \( \text{74} \) (Scheme 1.21).

![Scheme 1.21](image)
β-Proline 69 (3-carboxypyrrolidine) has been synthesized in both enantiomeric forms and used to study structure–activity relationships between receptors and natural amino acids. Also interesting is the recent synthesis of all four stereoisomers of β-amino acid 70 containing an aziridine heterocycle (Scheme 1.21).

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REFERENCES
