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# Three-Dimensional Structural Control of Diastereomeric Leu-Leu-Aib-Leu-Leu-Aib Sequences in the Solid State

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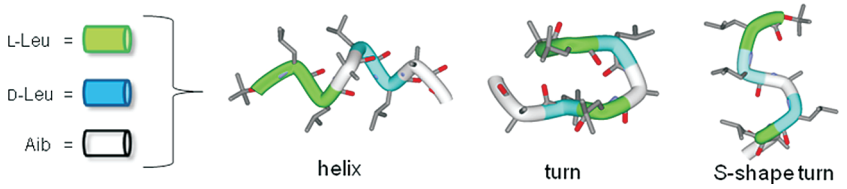


Three diastereomeric -Leu-Leu-Aib-Leu-Leu-Aib- peptides composed of the same numbers of L-Leu, D-Leu, and Aib residues were synthesized: Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (**1**), Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**), and Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**). The crystals of the three peptides were characterized by X-ray crystallographic analysis as follows: (**1**) orthorhombic, $P2_12_12_1$, $a$ = 21.383 Å, $b$ = 11.070 Å, $c$ = 19.560 Å, $Z$ = 4, $R_1$ = 0.0527, and $R_w$ = 0.1562; (**2**) monoclinic, $P2_1$, $a$ = 9.391 Å, $b$ = 21.278 Å, $c$ = 11.662 Å, $\beta$ = 99.125, $Z$ = 2, $R_1$ = 0.0507, and $R_w$ = 0.1447; and (**3**) triclinic, $P1$, $a$ = 12.545 Å, $b$ = 14.913 Å, $c$ = 15.330 Å, $\alpha$ = 77.622, $\beta$ = 66.601, $\gamma$ = 78.839, $Z$ = 2, $R_1$ = 0.0775, and $R_w$ = 0.1971. The three diastereomeric peptides, **1**, **2**, and **3**, showed unique conformations. That is to say, **1** was folded into a left-handed (*M*) $3_{10}$-helical structure, **2** was folded into a distorted $\beta$-hairpin nucleated by a type II′ $\beta$-turn-like structure, and **3** was folded into an S-shape turn structure based on two type II/III $\beta$-turns.

## Introduction

The *de novo* design of peptides that fold into well-defined secondary structures is crucially important in a wide variety of fields such as organic chemistry and biological and material sciences. Approaches to controlling the conformations of peptides have been studied by several groups.[1] As templates for stabilizing the secondary structures of peptides, α,α-disubstituted α-amino acids have been widely used,[2] and α-aminoisobutyric acid (Aib) has been found to be particularly useful as a helical promoter.[3] We have recently reported that the placement of Aib residues in a L-leucine-based hexapeptide (L-Leu-L-Leu-Aib-L-Leu-L-Leu-Aib) stabilized its right-handed (*P*) $3_{10}$-helical structure.[4] Incidentally, the placement of L-amino acids in a helical sequence containing enantiomeric D-amino acids generally destabilizes the helical structure.[5] However, the accurate design of hybrid peptides with an effective combination of L- and D-amino acids is useful for constructing novel specific conformations.[6] Therefore, we speculated that new secondary structures could be built by appropriate design of Leu-based

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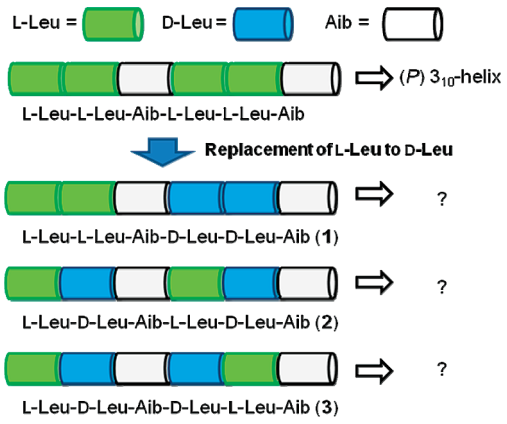


**FIGURE 1.** Design of peptides **1**, **2**, and **3**.

hexapeptides with a primary structure of Leu-Leu-Aib-Leu-Leu-Aib containing two L-Leu, two D-Leu, and two Aib residues in various combinations (Figure 1). Therefore, we designed and synthesized three diastereomeric peptides, Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (**1**), Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**), and Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**), and studied their preferred conformations in the crystalline state (Figure 2).

## Results and Discussion

**Synthesis of Peptides.** Peptides **1**, **2**, and **3** were synthesized by conventional solution-phase methods according to a fragment condensation strategy using *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and 1-hydroxybenzotriazole (HOBT) as coupling reagents.[4]

**Crystal-State Conformational Analysis.** Peptides **1**, **2**, and **3** formed good crystals for X-ray crystallographic analysis by slow evaporation of the solvents (MeCN/MeOH) at room temperature. The crystal and diffraction parameters of **1**, **2**, and **3** are summarized in Table 1. Data collection was performed on Bruker AXS SMART APEX imaging plate diffractometers using graphite-monochromated Mo Kα radiation. All crystals remained stable during the X-ray data collection. The structures of the peptides were solved using the SHELXS 97 direct method[7] and expanded by the Fourier technique.[8] All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the remaining H-atoms were placed at the calculated positions. The final cycle of full-matrix least-squares refinement of **1** gave an $R_1$ factor of 0.0527 on the basis of 5633 ($I > 2\sigma(I)$) reflections and an $R_w$ factor of 0.1562 for all data. The $R_1$ factor of **2** was 0.0507 on the basis of 5187 ($I > 2\sigma(I)$) reflections, and the $R_w$ factor was 0.1447 for all data. The $R_1$ factor of **3** was 0.0775 based on 9915 ($I > 2\sigma(I)$) reflections, and the $R_w$ factor was 0.1971 for all data.[9] The relevant backbone and side-chain torsion angles and the intra- and intermolecular hydrogen-bond parameters are listed in Tables 2 and 3.

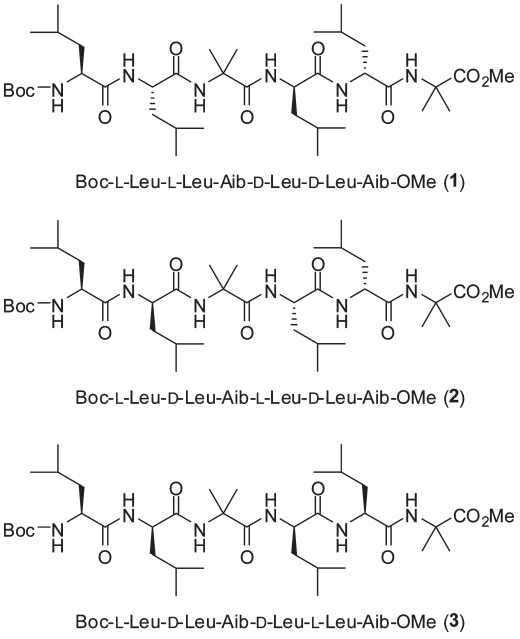


**FIGURE 2.** Chemical structures of the three diastereomeric peptides **1**, **2**, and **3**.

X-ray analysis of Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (**1**) showed a left-handed (*M*) 3$_{10}$-helical structure with flipping of the N-terminal L-Leu(1) and C-terminal Aib(6) residues, which was solved with the space group $P2_12_12_1$ (Figure 3). The mean values of the $\phi$ and $\psi$ torsion angles of the residues [L-Leu(2) to D-Leu(5)] were +57.3° and +31.2°, respectively, which are close to those of an ideal left-handed (*M*) 3$_{10}$-helical structure (+60° and +30°). The flipped torsion angles ($\phi$ and $\psi$) at the N- and C-termini were negative, i.e., −101.9° and −24.7° for L-Leu(1), and −48.7° and −49.1° for Aib(6), respectively. Three consecutive hydrogen bonds of the $i \leftarrow i + 3$ type were observed between H−N(4) and C(1)═O(1) [N(4)···O(1) = 2.97 Å;

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(9) CCDC-768211, 768212, and 768213 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax (+44) 1223-336-033 or deposit@ccdc.cam.ac.uk).

**TABLE 1. Crystal and Diffraction Parameters of Peptides 1, 2, and 3**

| | 1 | 2 | 3 |
|---|---|---|---|
| formula | $C_{38}H_{70}O_9N_6$ | $C_{38}H_{70}O_9N_6$ | $C_{38}H_{70}O_9N_6 \cdot C_2H_3N$ |
| $M_r$ | 755.00 | 755.00 | 796.05 |
| crystal dimensions [mm] | 0.40 × 0.40 × 0.25 | 0.50 × 0.25 × 0.20 | 0.50 × 0.35 × 0.08 |
| $T$ [K] | 240 | 240 | 240 |
| crystal system | orthorhombic | monoclinic | triclinic |
| $a$ [Å] | 21.383 | 9.391 | 12.545 |
| $b$ [Å] | 11.070 | 21.278 | 14.913 |
| $c$ [Å] | 19.560 | 11.662 | 15.330 |
| α [deg] | 90 | 99.125 | 77.622 |
| $\beta$ [deg] | 90 | 90 | 66.601 |
| $\gamma$ [deg] | 90 | 90 | 78.839 |
| $V$ [Å$^3$] | 4629.9 | 2300.9 | 2552.1 |
| space group | $P2_12_12_1$ | $P2_1$ | $P1$ |
| $Z$ | 4 | 2 | 2 |
| $D_{calc}$ [g/cm$^3$] | 1.083 | 1.090 | 1.036 |
| $\mu$ (Mo Kα) [cm$^{-1}$] | 0.77 | 0.77 | 0.73 |
| no. of observations | 5633 ($I > 2\sigma(I)$) | 5187 ($I > 2\sigma(I)$) | 9915 ($I > 2\sigma(I)$) |
| no. of variables | 478 | 478 | 1011 |
| $R_1$, $R_w$ | 0.0527, 0.1562 | 0.0507, 0.1447 | 0.0775, 0.1971 |
| solvent | MeCN/MeOH | MeCN/MeOH | MeCN/MeOH |

**TABLE 2. Selected Torsion Angles [deg] for Peptides 1, 2, and 3**

| | | | 3 | |
|---|---|---|---|---|
| torsion angle | 1 | 2 | molecule **A** | molecule **B** |
| $\omega_0$ | −173.7 | 177.4 | −176.4 | −176.7 |
| $\phi_1$ | −101.9 | −87.6 | −51.4 | −59.4 |
| $\psi_1$ | −24.7 | 69.8 | 129.9 | 125.9 |
| $\omega_1$ | 177.7 | −175.9 | 167.5 | 172.1 |
| $\phi_2$ | 57.8 | 45.8 | 86.2 | 86.8 |
| $\psi_2$ | 35.1 | −133.1 | 8.3 | 7.6 |
| $\omega_2$ | −179.8 | −174.1 | −165.7 | −160.8 |
| $\phi_3$ | 51.7 | −63.0 | −51.6 | −56.6 |
| $\psi_3$ | 33.1 | −23.6 | −42.9 | −36.5 |
| $\omega_3$ | 176.0 | −178.1 | −171.4 | −175.2 |
| $\phi_4$ | 63.6 | −73.1 | −61.2 | −62.1 |
| $\psi_4$ | 19.5 | −25.2 | −16.1 | −15.6 |
| $\omega_4$ | 173.5 | −178.6 | 179.6 | 178.4 |
| $\phi_5$ | 56.2 | 78.9 | −87.8 | −85.4 |
| $\psi_5$ | 37.1 | −118.6 | −20.1 | −18.2 |
| $\omega_5$ | −168.7 | 178.6 | −175.1 | −172.2 |
| $\phi_6$ | −48.7 | 52.3 | 46.6 | 53.7 |
| $\psi_6$ | −49.1 | 41.4 | −140.4 | −143.6 |
| $\omega_6$ | −179.3 | 179.0 | −176.9 | −179.6 |
| $\chi_1$ | −64.2 | −68.8 | −175.0 | −178.0 |
| $\chi_2$ | −50.1 | −177.2 | 60.4 | 63.1 |
| $\chi_4$ | 62.5 | −179.9 | 65.0 | 62.1 |
| $\chi_5$ | 74.3 | 69.6 | −51.8 | −53.0 |

N−H···O 154.9°], H−N(5) and C(2)═O(2) [N(5)···O(2) = 2.95 Å; N−H···O 159.7°], and H−N(6) and C(3)═O(3) [N(6)···O(3) = 3.02 Å; N−H···O 132.0°]. The N-terminus was flipped away from the helix, thereby preventing the formation of the N(3)···O(O) hydrogen bonds usually observed in $3_{10}$-helical peptides.[10] In the packing mode, two intermolecular hydrogen bonds were observed between the H−N(1) donor and the C(4′)═O(4′) acceptor [N(1)···O(4′) = 2.84 Å; N−H···O 141.4°] of a symmetry-related molecule ($x$, $-1 + y$, $z$) and the H−N(2) donor and the C(5′)═O(5′) acceptor [N(2)···O(5′) = 2.81 Å; N−H···O 137.6°] of a symmetry-related molecule ($x$, $-1 + y$, $z$). The helical molecules were connected by two hydrogen bonds, forming chains with a head-to-tail alignment, as shown in Figure 4. The flipping of L-Leu(1) may occur because of repulsion of the side chains between L-Leu(1) and D-Leu(5′)

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**TABLE 3. Intra- and Intermolecular H-Bond Parameters for Peptides 1, 2, and 3**[a]

| donor D−H | acceptor A | distance D···A [Å] | angle D−H···A [deg] | symmetry operations |
|---|---|---|---|---|
| | | Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (**1**) | | |
| $N_4$−H | $O_1$ | 2.97 | 154.9 | $x, y, z$ |
| $N_5$−H | $O_2$ | 2.95 | 159.7 | $x, y, z$ |
| $N_6$−H | $O_3$ | 3.02 | 132.0 | $x, y, z$ |
| $N_1$−H | $O_{4'}$ | 2.84 | 141.4 | $x, -1 + y, z$ |
| $N_2$−H | $O_{5'}$ | 2.81 | 137.6 | $x, -1 + y, z$ |
| | | Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**) | | |
| $N_1$−H | $O_5$ | 2.83 | 173.3 | $x, y, z$ |
| $N_4$−H | $O_1$ | 2.93 | 138.9 | $x, y, z$ |
| $N_5$−H | $O_2$ | 3.23[b] | 154.7 | $x, y, z$ |
| $N_3$−H | $O_{6'}$ | 3.00 | 164.5 | $2 - x, -1/2 + y, 1 - z$ |
| $N_6$−H | $O_{0'}$ | 3.02 | 167.8 | $-1 + x, y, z$ |
| | | Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**) | | |
| | | molecule **A** | | |
| $N_{3A}$−H | $O_{0A}$ | 3.25[b] | 133.4 | $x, y, z$ |
| $N_{5A}$−H | $O_{2A}$ | 2.98 | 164.9 | $x, y, z$ |
| $N_{6A}$−H | $O_{3A}$ | 2.98 | 157.3 | $x, y, z$ |
| $N_{1A}$−H | $O_{1B'}$ | 2.96 | 157.4 | $x, y, -1 + z$ |
| $N_{2A}$−H | $O_{5B'}$ | 2.95 | 167.6 | $x, -1 + y, -1 + z$ |
| $N_{4A}$−H | $O_{6B'}$ | 2.77 | 137.5 | $x, -1 + y, -1 + z$ |
| | | molecule **B** | | |
| $N_{3B}$−H | $O_{0B}$ | 3.27[b] | 134.4 | $x, y, z$ |
| $N_{5B}$−H | $O_{2B}$ | 2.98 | 164.4 | $x, y, z$ |
| $N_{6B}$−H | $O_{3B}$ | 2.99 | 164.3 | $x, y, z$ |
| $N_{1B}$−H | $O_{4A'}$ | 2.92 | 166.1 | $x, 1 + y, z$ |
| $N_{2B}$−H | $O_{5A'}$ | 2.78 | 139.8 | $x, 1 + y, z$ |

[a]The numbering of the amino acid residues begins at the N-terminus of the peptide. [b]The distance D···A is quite long for a hydrogen bond.

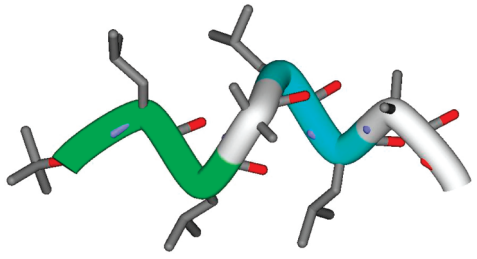

**FIGURE 3.** X-ray diffraction structure of Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (**1**).

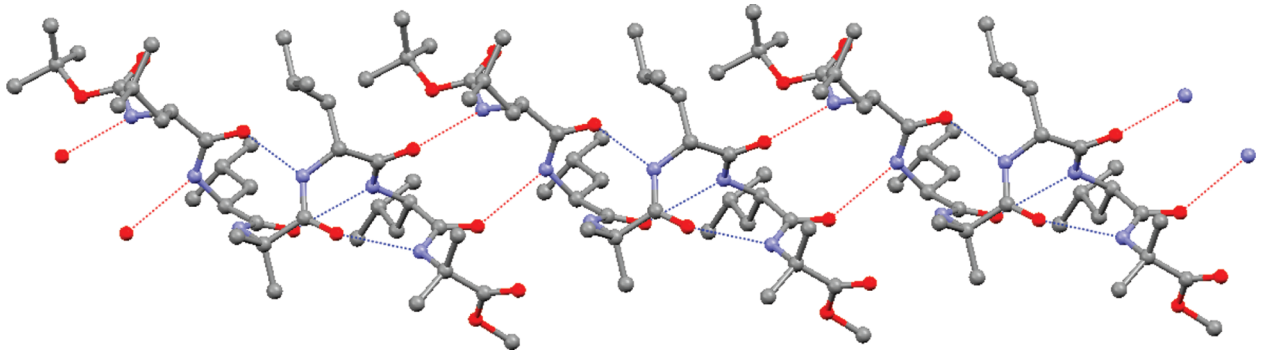

**FIGURE 4.** Packing of **1** in the crystalline state. Intramolecular (blue) and intermolecular (red) hydrogen bonds are indicated as dashed lines.

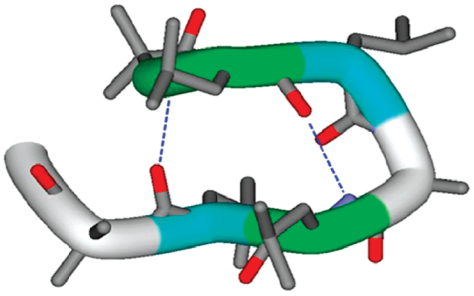

**FIGURE 5.** X-ray diffraction structure of Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**).

in the packing mode when the torsion angles of L-Leu(1) are positive. Peptide **1** demonstrated only a left-handed screw sense in the crystalline state even though it contained the same number of L-Leu and D-Leu residues. It is not exactly clear why a left-handed screw sense was produced over a right-handed screw sense in this peptide. C-Terminal D-Leu chirality seems to exert more control over the torsion angles of the N-terminal direction than N-terminal L-Leu chirality, and a slightly energetically favorable conformer might be preferentially packed into the crystalline conformer.

On the other hand, the crystal structure of Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**), which was solved with the space group $P2_1$, was a distorted $\beta$-hairpin nucleated by a type II′ $\beta$-turn-like structure (Figure 5). The $\beta$-turn was formed between D-Leu(2) and Aib(3), and the values of the $\phi$ and $\psi$ torsion angles of the D-Leu(2) residue were +45.8° and −133.1°, respectively, and those of the Aib(3) residue were −63.0° and −23.6°, respectively [backbone torsion angles of ideal type II′ $\beta$-turn: $\phi(i+1) = 60°$, $\psi(i+1) = -120°$, and $\phi(i+2) = +80°$, $\psi(i+2) = 0°$].[11] Two different types of intramolecular hydrogen bond were found, one hydrogen bond of the $i+4 \leftarrow i$ type between H−N(1) and C(5)═O(5) [N(1)···O(5) = 2.83 Å; N−H···O 173.3°] and another of the $i \leftarrow i+3$ type between H−N(4) and C(1)═O(1) [N(4)···O(1) = 2.93 Å; N−H···O 138.9°]. Furthermore, one weak intramolecular hydrogen bond was observed between H−N(5) and C(2)═O(2) [N(5)···O(2) = 3.23 Å; N−H···O 154.7°]. In the packing mode, two intermolecular hydrogen bonds were observed between the H−N(3) donor and the C(6′)═O(6′) acceptor [N(3)···O(6′) = 3.00 Å; N−H···O 164.5°] of a symmetry-related molecule $(2-x, -1/2+y, 1-z)$, and the H−N(6) donor and the C(0′)═O(0′) acceptor [N(6)···O(0′) = 3.02 Å; N−H···O 167.8°] of a symmetry-related molecule $(-1+x, y, z)$ (Figure 6). This structure was formed by two processes, extension and bending of parts of the peptide backbone. That is to say, a combination of L-amino acid ($i$) and D-amino acid ($i+1$) residues, L-Leu(1)-D-Leu(2) and L-Leu(4)-D-Leu(5), formed a semiextended conformations[12] and the Aib(3) residue acted as a bent scaffold to form a distorted $\beta$-hairpin structure.

The structure of Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**) was solved with the space group $P1$. Two crystallographically independent molecules, **A** and **B**, were found in the asymmetric unit of **3** together with an acetonitrile molecule. Molecules **A** and **B** were folded into different types of $\beta$-turn structures to form an S-shape turn (Figure 7).[6c] The conformations of molecules **A** and **B** were well matched except for small differences in the conformations of their side chain, as shown by their superimposition in Figure 8. In the S-shape turn, a type II $\beta$-turn was found at the L-Leu(1A) and D-Leu(2A) residues ($\phi1 = -51.4°$, $\psi1 = +129.9°$, and $\phi2 = +86.2°$, $\psi2 = +8.3°$), and a type III $\beta$-turn (ideal backbone torsion angles, $\phi = -60°$, $\psi = -30°$)[11] was demonstrated at the D-Leu(4A) and L-Leu(5A) ($\phi = -74.5°$, $\psi = -18.1°$), as shown in Figure 9. In molecule **A**, two consecutive hydrogen bonds of the $i \leftarrow i+3$ type were observed between H−N(5A) and C(2A)═O(2A) [N(5A)···O(2A) = 2.98 Å; N−H···O 164.9°] and between H−N(6A) and C(3A)═O(3A) [N(6A)···O(3A) = 2.98 Å; N−H···O 157.3°]. Furthermore, one weak intramolecular hydrogen bond was observed between H−N(3A) and C(0A)═O(0A) [N(3A)···O(0A) = 3.25 Å; N−H···O 133.4°]. Molecule **B** similarly contained two intramolecular hydrogen bonds between H−N(5B) and C(2B)═O(2B) [N(5B)···O(2B) 2.98 Å; N−H···O 164.4°] and between H−N(6B) and C(3B)═O(3B) [N(6B)···O(3B) 2.99 Å; N−H···O 164.3°], and one weak intramolecular hydrogen bond between H−N(3B) and C(0B)═O(0B) [N(3B)···O(0B) = 3.27 Å; N−H···O 134.4°]. In the packing mode, five intermolecular hydrogen bonds were observed between the H−N(1A) donor and the C(1B′)═O(1B′) acceptor [N(1A)···O(1B′) = 2.96 Å; N−H···O 157.4°] of a symmetry-related molecule $(x, y, -1+z)$, the H−N(2A) donor and the C(5B′)═O(5B′) acceptor [N(2A)···O(5B′) = 2.95 Å; N−H···O 167.6°] of a symmetry-related molecule $(x, -1+y, -1+z)$, the H−N(4A) donor and the C(6B′)═O(6B′) acceptor [N(4A)···O(6B′) = 2.77 Å;

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(12) (a) Doi, M.; In, Y.; Ikuma, K.; Inoue, M.; Ishida, T. *Acta Crystallogr.* **1993**, *C49*, 1530–1532. (b) Murali, R.; Lalitha, V.; Subramanian, E.; Parthasarathy, R. *Int. J. Pept. Protein Res.* **1986**, *27*, 160–164.

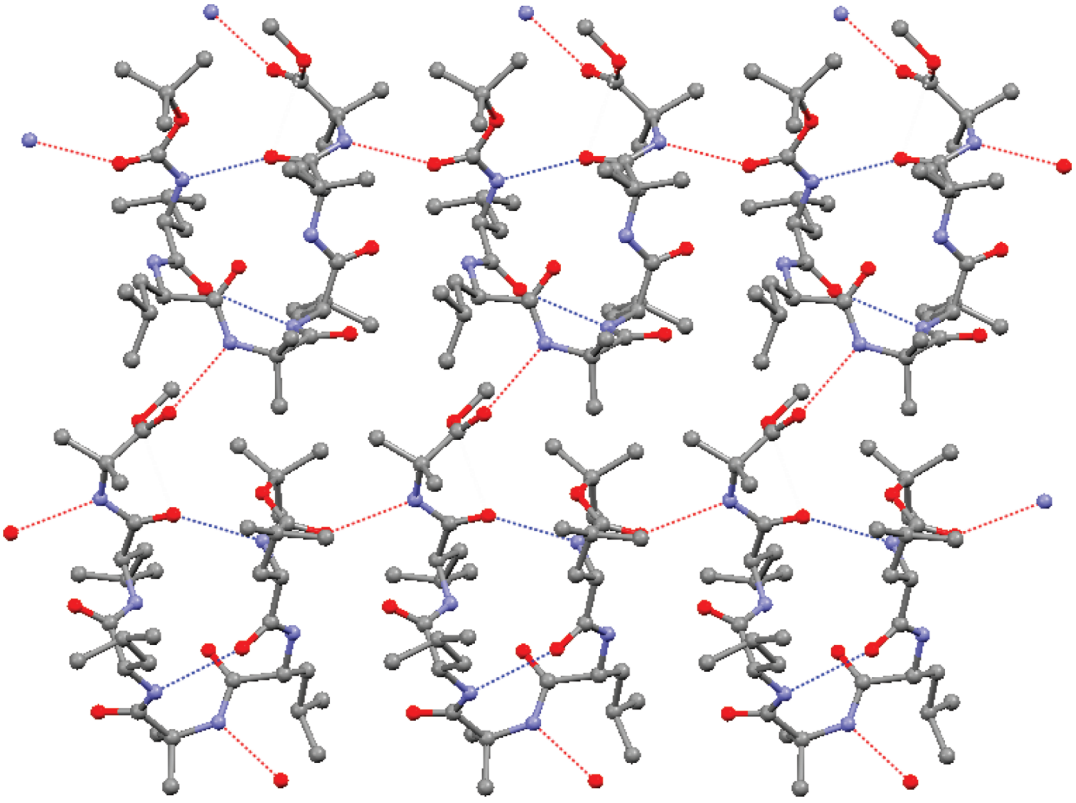

**FIGURE 6.** Packing of **2** in the crystalline state. Intramolecular (blue) and intermolecular (red) hydrogen bonds are indicated as dashed lines.

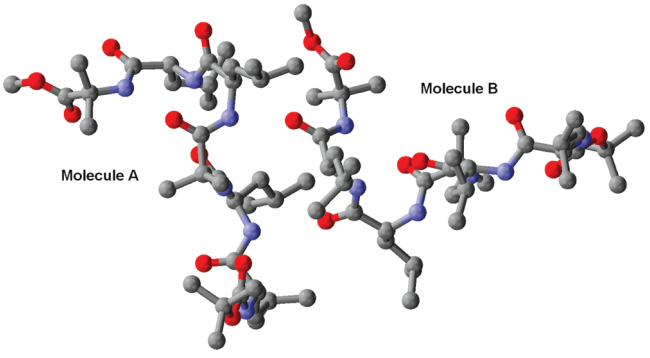


**FIGURE 7.** X-ray diffraction structure of Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**). The acetonitrile molecule has been omitted.

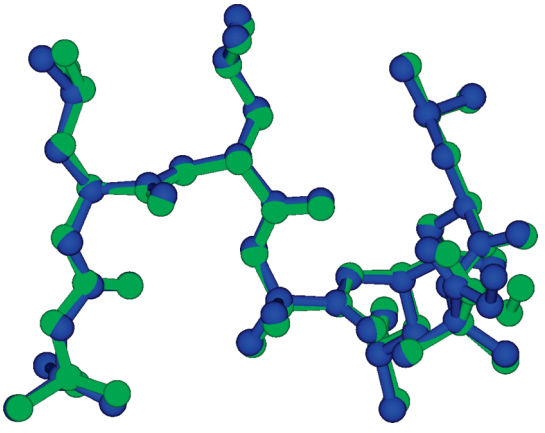

**FIGURE 8.** Overlay of the structures of molecules **A** (green) and **B** (blue).

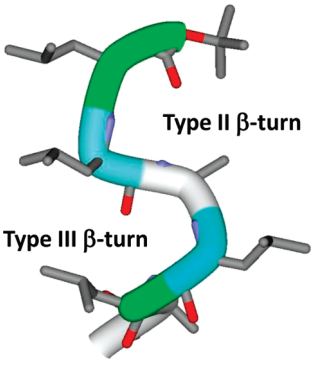


**FIGURE 9.** S-Shape turn structure of **3** (molecule **A**).

N−H···O 137.5°] of a symmetry-related molecule ($x$, $-1+y$, $-1+z$), the H−N(1B) donor and the C(4A′)═O(4A′) acceptor [N(1B)···O(4A′) = 2.92 Å; N−H···O 166.1°] of a symmetry-related molecule ($x$, $1+y$, $z$), and the H−N(2B) donor and the C(5A′)═O(5A′) acceptor [N(2B)···O(5A′) = 2.78 Å; N−H···O 139.8°] of a symmetry-related molecule ($x$, $1+y$, $z$). Molecules **A** and **B** were alternately connected by five intermolecular hydrogen bonds, as shown in Figure 10. The S-shape turn structure was formed by the Aib(3) residue acting as a bent scaffold and the L-Leu(1)-D-Leu(2) and D-Leu(4)-L-Leu(5) sequences forming semiextended conformations.

## Conclusion

We have synthesized the three diastereomeric -Leu-Leu-Aib-Leu-Leu-Aib- peptides Boc-L-Leu-L-Leu-Aib-D-Leu-D-

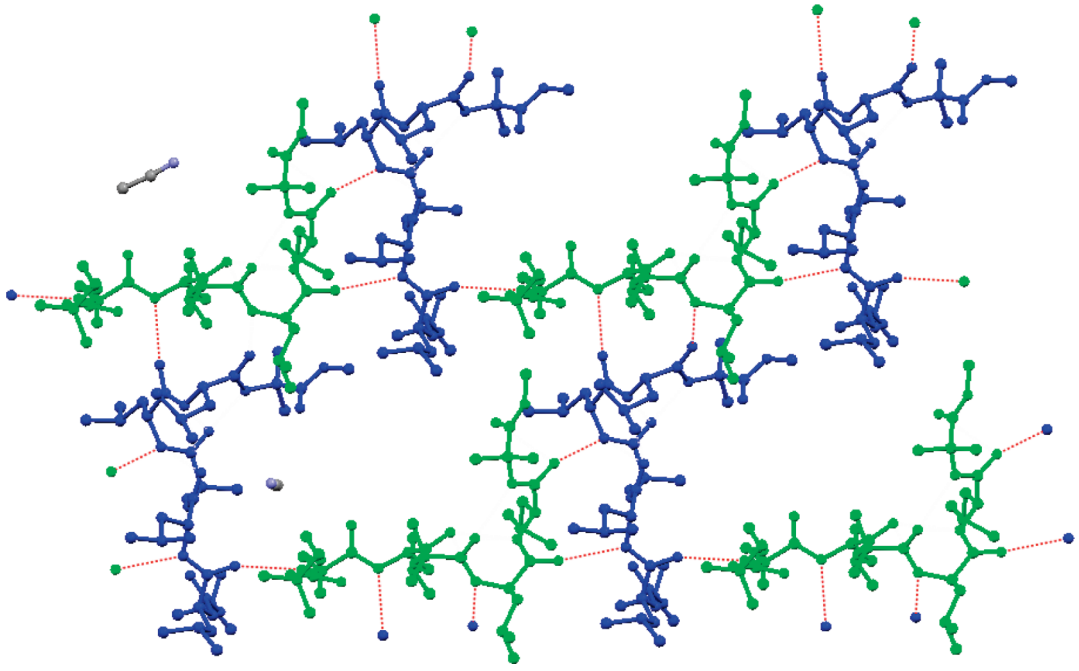

**FIGURE 10.** Packing of **3** (green, molecule **A**; blue, molecule **B**) in the crystalline state. Intermolecular (red) hydrogen bonds are indicated as dashed lines.

Leu-Aib-OMe (**1**), Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (**2**), and Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (**3**) and studied their preferred conformations by X-ray crystallographic analysis. The preferred conformation of **1** was a left-handed (*M*) $3_{10}$-helical structure, that of **2** was a distorted $\beta$-hairpin nucleated by a type II′ $\beta$-turn-like structure, and that of **3** was an S-shape turn structure nucleated by two type II/III $\beta$-turns. The appropriate incorporation of L-Leu(*i*)-L-Leu($i+1$),[4] D-Leu(*i*)-D-Leu($i+1$), L-Leu(*i*)-D-Leu($i+1$), and D-Leu(*i*)-L-Leu($i+1$) next to Aib residues produced novel secondary structures that have not previously been identified. These results are valuable for the design of peptides with well-defined secondary structures and may also be relevant for the *de novo* design of peptides/proteins.

## Experimental Section

**Synthesis of Peptides 1, 2, and 3.** The synthesis of peptides **1**, **2**, and **3** was carried out according to the stepwise solution-phase method using HBTU and HOBT as coupling reagents. All compounds were purified by column chromatography on silica gel.

**Boc-L-Leu-L-Leu-Aib-D-Leu-D-Leu-Aib-OMe (1).** Colorless crystals; mp 246−248 °C (recryst from MeCN/MeOH); $[\alpha]^{22}_{D}$ − 13.4 (*c* 0.5, MeOH); IR (in $CDCl_3$) 3370, 3280, 2956, 1780, 1657, 1530, 1374 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.6 Hz, 1H), 7.37 (d, $J$ = 6.0 Hz, 1H), 7.19 (br s, 1H), 7.15 (br s, 1H), 6.94 (br s, 1H), 5.05 (d, $J$ = 5.2 Hz, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 3.94 (m, 1H), 3.82 (m, 1H), 3.69 (s, 3H), 1.50−1.82 (m, 24H), 1.45 (s, 9H), 0.86−1.01 (m, 24H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.1, 175.8, 174.1, 173.7, 172.9, 172.4, 156.3, 80.9, 57.1, 56.2, 54.4, 54.0, 53.6, 52.6, 52.4, 39.8, 39.5, 38.3, 28.5, 27.5, 25.4, 25.2, 25.0, 24.4, 23.6, 23.4, 21.5, 21.3, 21.1; ESI(+)-MS $m/z$ 778 $[M + Na]^+$.

**Boc-L-Leu-D-Leu-Aib-L-Leu-D-Leu-Aib-OMe (2).** Colorless crystals; mp 162−164 °C (recryst from MeCN/MeOH); $[\alpha]^{22}_{D}$ − 7.2 (*c* 0.5, MeOH); IR (in $CDCl_3$) 3372, 3260, 2952, 1782, 1661, 1529, 1220 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (br s, 1H), 7.13 (br s, 1H), 7.11 (br s, 1H), 6.81 (br s, 1H), 6.56 (br s, 1H), 6.20 (br s, 1H), 4.33 (m, 1H), 4.00−4.19 (m, 3H), 3.72 (s, 3H), 1.47−1.81 (m, 24H), 1.45 (s, 9H), 0.90−0.99 (m, 24H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 175.3, 175.0, 174.1, 173.3, 173.1, 175.1, 80.3, 57.2, 56.6, 53.5, 53.2, 52.9, 40.0, 39.6, 39.4, 39.2, 28.5, 26.9, 25.2, 25.0, 24.9, 24.0, 23.3, 23.2, 23.1, 22.1, 21.8, 21.7, 21.5; ESI(+)-MS $m/z$ 778 $[M + Na]^+$.

**Boc-L-Leu-D-Leu-Aib-D-Leu-L-Leu-Aib-OMe (3).** Colorless crystals; mp 176−178 °C (recryst from MeCN/MeOH); $[\alpha]^{22}_{D}$ − 2.5 (*c* 0.5, MeOH); IR (in $CDCl_3$) 3300, 2955, 1765, 1656, 1527, 1375 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (br s, 1H), 7.21 (br s, 1H), 7.13 (br s, 1H), 7.11 (br s, 1H), 6.81 (br s, 1H), 5.22 (br s, 1H), 4.22−4.29 (m, 2H), 4.03 (m, 1H), 3.83 (m, 1H), 3.69 (s, 3H), 1.43−1.91 (m, 33H), 0.88−1.00 (m, 24H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.7, 175.4, 175.1, 173.9, 173.8, 173.5, 156.2, 80.5, 57.4, 56.1, 55.3, 54.1, 53.6, 52.5, 52.4, 39.9, 39.8, 39.5, 28.5, 26.7, 25.6, 25.2, 25.1, 25.0, 24.9, 24.7, 24.1, 23.8, 23.4, 23.2, 23.0, 21.9, 21.8, 21.6, 21.1; ESI(+)-MS $m/z$ 778 $[M + Na]^+$.

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**Supporting Information Available:** The crystallographic data and copies of the $^1H$ NMR and $^{13}C$ NMR spectra of all new compounds are available free of charge via the Internet at http://pubs.acs.org.