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# β-Turn mimic in tripeptide with Phe(1)-Aib(2) as corner residues and β-strand structure in an isomeric tripeptide: an X-ray diffraction study

**Anita Dutt,[a] Roland Fröhlich[b] and Animesh Pramanik*[a]**

[a] *Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata, 700 009, India. E-mail: animesh_in2001@yahoo.co.in*

[b] *Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149, Münster, Germany*

***Received 6th October 2004, Accepted 29th November 2004***
***First published as an Advance Article on the web 21st January 2005***

A single crystal X-ray diffraction study of the tripeptide Boc-Phe-Aib-Leu-OMe (Aib = α-aminoisobutyric acid) reveals that it forms structurally one of the best type II β-turns so far reported in tripeptides, stabilized by 10 atom intramolecular hydrogen bonding. In contrast, the isomeric tripeptide Boc-Phe-Leu-Aib-OMe adopts a β-strand like conformation. Interestingly, a previously reported structure of another isomeric tripeptide, Boc-Leu-Aib-Phe-OMe, shows a double bend conformation without any intramolecular hydrogen bonding. These results demonstrate an example of the creation of structural diversities in the backbone of small peptides depending upon the co-operative steric interactions amongst the amino acid residues.

## Introduction

β-Turns were first recognized in the late 1960s by Venkatachalam.[1] To date, more than 10 different types of β-turns have been identified and classified.[2,3] They are now known to be common structural motifs comprising up to 25% of all residues in folded proteins and peptides.[4] β-Turns also appear to play important roles in stabilizing tertiary structures, initiating folding and facilitating intermolecular recognition.[4a] Recently, it has been shown that β-turn and extended β-strand like structures are subunits for supramolecular β-sheet assembles and amyloid-like fibrils in short model peptides.[5–8] The formation of amyloid-like fibrils is a causative factor in many neurodegenerative diseases including Alzheimer's disease, Huntington's disease and prion-related encephalopathies.[9] The therapeutic challenge in all forms of these fatal neurodegenerative diseases is to prevent amyloid fibril formation, a goal that requires a detailed understanding of the pathways of β-sheet aggregation as well as fibrillation. Because of their critical importance there has been considerable interest in designing β-turns and β-turn mimetics, as well as in the creation of β-strand like structures which promote β-sheet assemblage.

Creation of β-turns in small synthetic peptides with non-coded amino acids is an emerging aspect in the field of peptidomimetics. A list of various tripeptides with adopted type II β-turns and bend structures are presented in Table 1 (Fig. 1). Balaram *et al.* have established that the peptides Boc-Ala(1)-D*pg*(2)-Ala(3)-OMe and Boc-Ala(1)-D*bg*(2)-Ala(3)-OMe (where D*pg* = α,α-di-*n*-propylglycine and D*bg* = α,α-di-*n*-butylglycine) adopt distorted type II β-turn with Ala(1) and D*pg*/D*bg*(2) as the corner residues (Fig. 1).[10] In both peptides however, the observed (N---O) distances between the Boc CO and Ala(3) NH groups are far too long (3.44 and 3.63 Å) for an intramolecular 4→1 hydrogen bond (Table 1, Entry a, b). The same group have also demonstrated that peptides Boc-Ala-$Ac_6$c-Ala-OMe and Boc-Ala-$Ac_7$c-Ala-OMe (where $Ac_6$c = 1-aminocyclohexane-1-carboxylic acid and $Ac_7$c = 1-aminocycloheptane-1-carboxylic acid) form β-turns in solution phase (Table 1, Entry c, d).[11]

**Table 1** List of type II β-turns in tripeptides (Entry a–i, m) with torsion angles (°) of the residues at turn, intra-molecular hydrogen bond (HB) distance H---O=C (Å) and N–H---O angles (°)

| Entry | Peptides | $\phi_1$ | $\psi_1$ | $\phi_2$ | $\psi_2$ | H---O=C | N–H---O | Ref. |
|---|---|---|---|---|---|---|---|---|
| | Idealized type II β-turn | −60 | 120 | 80 | 0 | | | 1 |
| a. | Boc-Ala-D*pg*-Ala-OMe[a] | −56.1 | 139.9 | 66.2 | 19.3 | β-Turn without HB | | 10 |
| b. | Boc-Ala-D*bg*-Ala-OMe[a] | −61.5 | 143.3 | 66.5 | 21.1 | β-Turn without HB | | 10 |
| c. | Boc-Ala-$Ac_6$c-Ala-OMe[a] | | | | | β-Turn in solution phase | | 11 |
| d. | Boc-Ala-$Ac_7$c-Ala-OMe[a] | | | | | β-Turn in solution phase | | 11 |
| e. | Boc-Ala-Aib-Val-OMe[a] | −58.1 | 146.7 | 60.1 | 30.8 | 2.89 | 142.0 | 5 |
| f. | Boc-Ala-Aib-Ile-OMe | −54.6 | 147.1 | 60.0 | 30.0 | 2.77 | 141.0 | 5 |
| g. | Boc-Ala-Aib-β-Ala-OMe | −58.0 | 134.6 | 63.0 | 23.0 | 2.48 | 138.5 | 7 |
| h. | Boc-Ala-Gly-Val-OMe | −55.6 | 139.6 | 72.7 | 19.1 | 2.56 | 143.0 | 5 |
| i. | Boc-Leu-Aib-β-Ala-OMe[b] | −57.1 | 128.3 | 66.0 | 18.1 | 2.24 | 148.4 | 6 |
| | (Mol. A and B) | −57.9 | 126.5 | 70.7 | 13.1 | 2.17 | 153.2 | 6 |
| j. | Z-Aib-2Dpy-Aib-OMe[c] | | | | | Type III β-turn | | 14 |
| k. | Boc-Leu-Aib-Leu-OMe | −78.2 | −27.6 | 49.5 | 49.5 | Double bend structure | | 12 |
| l. | Boc-Leu-Aib-Phe-OMe | −62.8 | −41.5 | 58.6 | 46.2 | Double bend structure | | 13 |
| m. | Boc-Phe-Aib-Leu-OMe (**I**) | −62.0 | 127.5 | 61.5 | 26.6 | 2.35 | 158.0 | |
| n. | Boc-Phe-Leu-Aib-OMe (**II**) | −98.8 | 117.7 | −63.7 | 130.1 | β-Strand structure | | |
| | (Mol. A, B and C) | −117.5 | 128.1 | −86.7 | 131.7 | β-Strand structure | | |
| | | −125.2 | 134.7 | −80.7 | 130.5 | β-Strand structure | | |

[a] D*pg* = α,α-di-*n*-propylglycine and D*bg* = α,α-di-*n*-butylglycine, $Ac_6$c = 1-aminocyclo-hexane-1-carboxylic acid and $Ac_7$c = 1-aminocycloheptane-1-carboxylic acid, Aib = α-aminoisobutyric acid. [b] Two molecules in the asymmetric unit. [c] 2Dpy = α,α-di(2-pyridyl) glycine.

DOI: 10.1039/b415455j

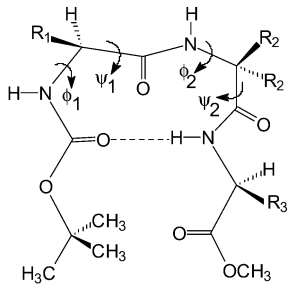

**Fig. 1** β-Turn conformation in a tripeptide.

Recently, Banerjee and co-workers have shown that the fragments such as Ala(1)-Aib(2), Ala(1)-Gly(2) can also induce β-turns stabilised by 10 atom intramolecular hydrogen bonding in tripeptides (Table 1, Entry e–h) (Fig. 1).[5,7] They have also demonstrated that the sequence Boc-Leu(1)-Aib(2)-βAla(3)-OMe, where Ala(1) has been replaced by Leu(1), can also preferentially adopt a β-turn conformation by intramolecular hydrogen bonding (Table 1, Entry i).[6] From these results it is evident that in tripeptides, a fragment of chiral amino acid (1) followed by an achiral amino acid (2) is necessary to nucleate a β-turn structure. However, this theory does not hold good owing to the observation that sequences such as Boc-Leu(1)-Aib(2)-Leu(3)-OMe and Boc-Leu(1)-Aib(2)-Phe(3)-OMe (Table 1, Entry k, l) adopt a double bend structure instead of a β-turn conformation, emphasising the role of third residue in β-turn formation.[12,13] Interestingly another tripeptide Z-Aib(1)-2Dpy(2)-Aib(3)-OMe (Z = benzyloxycarbonyl, 2Dpy = α,α-di(2-pyridyl)glycine), where all the three amino acids are achiral, has been reported to fold in a type III β-turn structure (Table 1, Entry j).[14] Therefore, it is apparent that various factors contributing to β-turn formation are not yet fully understood.[15]

To gain further insight regarding the role of various residues in the formation of β-turn and β-strand like structures in small peptides we have prepared two peptides, Boc-Phe(1)-Aib(2)-Leu(3)-OMe (**I**) and Boc-Phe(1)-Leu(2)-Aib(3)-OMe (**II**) (Table 1, Entry m, n) with the same amino acids as that of peptide Boc-Leu(1)-Aib(2)-Phe(3)-OMe, but at different positions in the sequence. In peptide **I** the incorporation of the fragment Phe(1)-Aib(2) is unprecedented. Moreover, the positioning of the sterically demanding Leu residue at the end of the peptide **I** may influence the adopted configuration. In addition to this, it is interesting to see whether peptide **II** prefers a double bend or extended β-strand like structure. Importantly this investigation will provide more information about the creation of structural diversities in the backbone of small peptides depending upon the co-operative steric interactions among the residues. Peptides **I** and **II** were prepared by conventional solution phase synthesis and their single crystal X-ray diffraction studies are described below.

## Results and discussion

The crystal structure of the tripeptide Boc-Phe(1)-Aib(2)-Leu(3)-OMe **I** (Fig. 2) reveals that it adopts a folded conformation corresponding to a slightly distorted type II β-turn structure with Phe(1) and Aib(2) occupying the $i + 1$ and $i + 2$ positions respectively. In ideal type II β-turns, torsion angles of $\phi_{i+1} = -60°$, $\psi_{i+1} = 120°$, $\phi_{i+2} = 80°$, $\psi_{i+2} = 0°$ have been observed.[1] As a consequence of the deviation of $\psi_{i+1}$ (127.5°), $\phi_{i+2}$ (61.5°) and $\psi_{i+2}$ (26.6°) from these values (Table 2), a weak 4→1 hydrogen bond between Boc-CO and Leu (3)-NH with an N25---O7 distance of 3.15Å (Table 3) resulted. The observed hydrogen bond (H---O=C)) distance 2.35 Å is well complimented by the N–H---C=O angle of 158°. The formation of a longer hydrogen bond is a characteristic of slightly distorted type II β-turns, as it has been exemplified by the structures of short synthetic peptides with non-coded amino acids. Nevertheless, peptide **I** produces one of the best type II β-turn structures so far reported in the literature (Table 1). There are two intermolecular hydrogen bonds (N8–H8---O32, N19–H19---O24) that are responsible for connecting individual peptide molecules to stabilize the supra-molecular assembly in crystals. In the first, the O---H separation of 2.35 Å and the N---O separation of 3.12 Å indicate a weak hydrogen bond when compared to the second, where the corresponding geometrical parameters are 2.15 Å and 2.99 Å, respectively. Fig. 3 shows the network of hydrogen bonds creating the self-assembly of peptide **I** in the β-turn conformation.

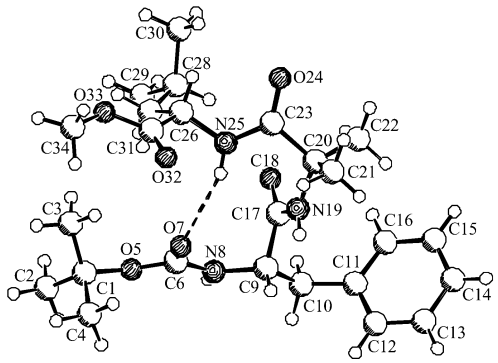

**Fig. 2** The SCHAKAL diagram of peptide **I** showing the atomic numbering scheme. The weak intramolecular hydrogen bond is shown as a dotted line.

Interestingly, the crystal structure of peptide **II** reveals that the asymmetric unit contains three independent molecules (mol. A, B, and C). The SCHAKAL diagram with the atom numbering scheme for one of the molecules of the peptide **II** is illustrated in Fig. 4. The backbone torsions are mostly

**Table 2** Selected torsion angles (°) for peptides **I** and **II**

| | | | | | |
|---|---|---|---|---|---|
| **Peptide I** | | | | | |
| C9–N8–C6–O5 | −177.4 | $\omega_0$ | N19–C20–C23–N25 | 26.6 | $\psi_2$ |
| C6–N8–C9–C17 | −62.0 | $\phi_1$ | C20–C23–N25–C26 | 179.0 | $\omega_2$ |
| N8–C9–C17–N19 | 127.5 | $\psi_1$ | C23–N25–C26–C31 | −129.0 | $\phi_3$ |
| C9–C17–N19–C20 | 176.0 | $\omega_1$ | N25–C26–C31–O33 | 15.2 | $\psi_3$ |
| C17–N19–C20–C23 | 61.5 | $\phi_2$ | | | |
| **Peptide II (mol. A, B, C)** | | | | | |
| C9–N8–C6–O5 | −178.4 | −177.6 | −165.8 | $\omega_0$ | |
| C6–N8–C9–C17 | −98.8 | −117.5 | −125.2 | $\phi_1$ | |
| N8–C9–C17–N19 | 117.7 | 128.1 | 134.7 | $\psi_1$ | |
| C9–C17–N19–C20 | 177.4 | 179.8 | 169.0 | $\omega_1$ | |
| C17–N19–C20–C25 | −63.7 | −86.7 | −80.7 | $\phi_2$ | |
| N19–C20–C25–N27 | 130.1 | 131.7 | 130.5 | $\psi_2$ | |
| C20–C25–N27–C28 | −179.1 | 178.4 | −170.9 | $\omega_2$ | |
| C25–N27–C28–C31 | −49.9 | −52.0 | −54.1 | $\phi_3$ | |
| N27–C28–C31–O33 | −43.2 | −40.7 | −43.7 | $\psi_3$ | |

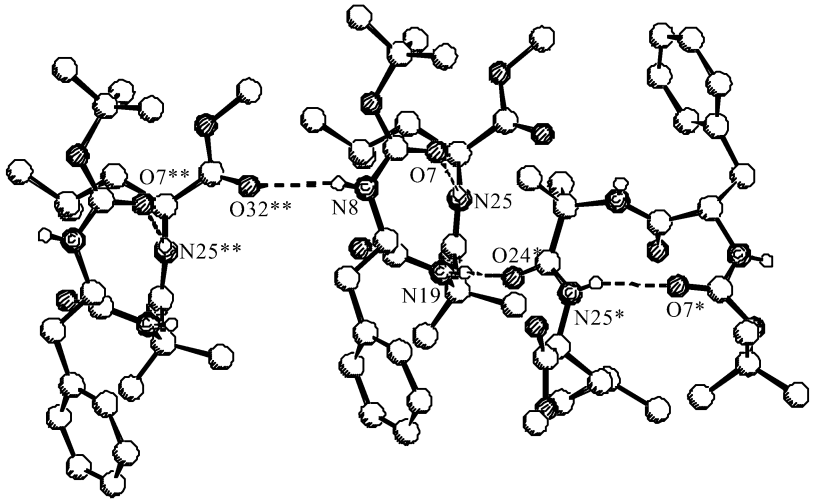


**Fig. 3** Hydrogen bonding scheme of peptide **I** (hydrogen atoms bonded to carbon atoms are omitted for clarity).

**Table 3** Intra- and intermolecular hydrogen bonding parameters of peptides **I** and **II**

| D–H---A | H---A/Å | D---A/Å | D–H---A/° |
|---|---|---|---|
| **Peptide I** | | | |
| N25–H25---O7 | 2.35 | 3.15 | 158 |
| N8–H8---O32[a] | 2.35 | 3.12 | 162 |
| N19–H19---O24[b] | 2.15 | 2.99 | 170 |
| **Peptide II** | | | |
| N8A–H8A---O26B | 2.39 | 3.02 | 169 |
| N19A–H19A---O18C | 1.95 | 2.75 | 165 |
| N27A–H27A---O7B | 2.15 | 3.22 | 179 |
| N8B–H8B---O26C[c] | 2.20 | 3.03 | 158 |
| N19B–H19B---O18A | 1.82 | 2.74 | 167 |
| N8C–H8C---O26A | 2.42 | 3.09 | 173 |
| N19C–H19C---O18B[d] | 2.02 | 2.84 | 177 |
| N27B–H27B---O101 | 1.98 | 2.86 | 159 |
| N27C–H27C---O201 | 2.05 | 2.84 | 152 |
| O201–H201---O7A | 2.21 | 2.83 | 131 |

[a] Symmetry equivalent $x + 1, y, z$. [b] Symmetry equivalent $-x, y + 1/2, -z$. [c] Symmetry equivalent $x, y + 1, z$. [d] Symmetry equivalent $x, y - 1, z$.

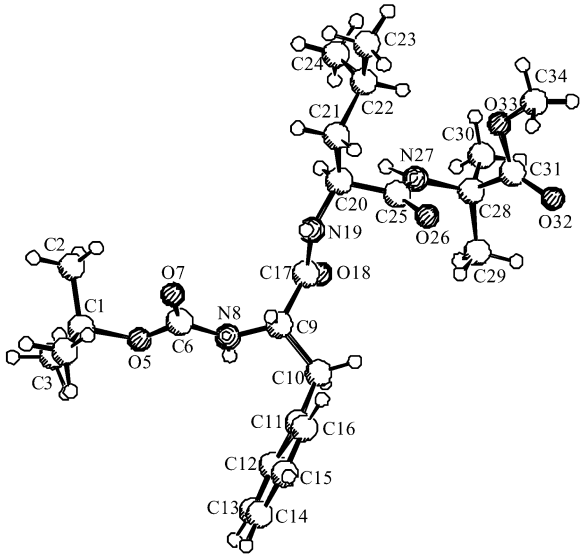


**Fig. 4** The SCHAKAL diagram of peptide **II** including the atom numbering scheme.

in the extended conformations (Table 2); a prerequisite for individual β-strand formation. The torsion angles at Phe ($\phi_1 = -98.8/-117.5/-125.2°$, $\psi_1 = 111.7/128.1/134.7°$) and Leu ($\phi_2 = -63.7/-86.7/-80.7°$, $\psi_2 = 130.1/131.7/130.5°$) indicate a fully extended conformation. The variations from extended values of torsions occur near the terminal position, which is occupied by the conformationally restricted α-aminoisobutyric acid (Aib) residue ($\phi_3 = -49.9/52.0/-54.1°$, $\psi_3 = -43.2/-40.7/-43.7°$). In case of peptide **II**, the hydrogen bonding scheme (Fig. 5) is more complex than in peptide **I** due to the three independent molecules in the asymmetric unit and the presence of solvent molecules (for details see Table 3). Seven of the nine possible hydrogen donors form hydrogen bonds between the different peptide molecules. The O---H separation varies between 1.82 and 2.42 Å and the N---O separation between 2.74 and 3.22 Å, showing a wide range of possible hydrogen bonds in the self-assembly. The remaining two hydrogen donors from the peptide molecules form hydrogen bonds with solvent molecules. In addition, there is a relatively weak hydrogen bond O–H---O7A where the water molecule acts as hydrogen donor.

It is also interesting to note that another previously reported isomeric tripeptide Boc-Leu(1)-Aib(2)-Phe(3)-OMe adopts a double bend structure without any intramolecular hydrogen bonding (Table 1).[13] Therefore, three isomeric tripeptides show totally different conformational preferences depending only upon the position of the constituent amino acids in the backbone.

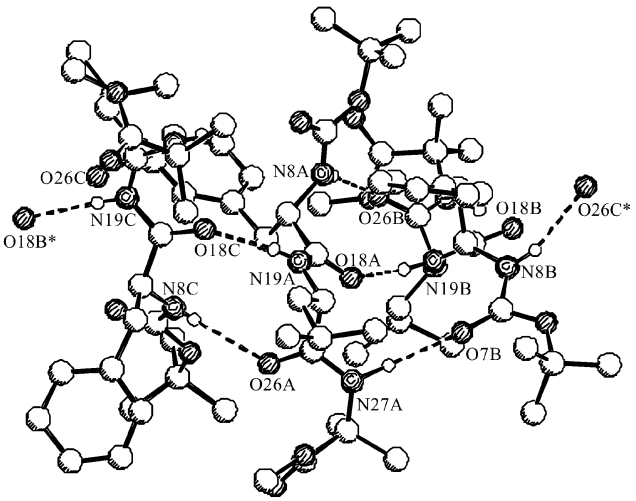


**Fig. 5** Hydrogen bonding scheme of peptide **II** (hydrogen atoms bonded to carbon atoms and solvent molecules are omitted for clarity).

## Conclusions

The peptide **I** adopts a remarkable type II β-turn structure in solid state, stabilized by 10 atom intra-molecular hydrogen bonding. These results demonstrate that the fragment Phe(1)-Aib(2) is equally effective in inducing β-turn like structures in tripeptides such as that of Ala(1)-Aib(2) and Leu(1)-Aib(2). Interestingly, peptide **II** where the position of the last two residues (Aib and Leu) of peptide **I** are interchanged, takes on a fully extended β-strand like structure. These two peptides may serve as subunits in the formation of supra-molecular β-sheet assemblage and amyloid-like fibrils.[5–8]

## Experimental

### Synthesis of peptides

The peptides were synthesised by conventional solution phase procedures. The *t*-butyloxycarbonyl and methyl ester group were used for amino and carboxyl protections and dicyclohexylcarbodiimide (DCC) or DCC 1-hydroxybenzotriazole (HOBT) as coupling agents. Methyl ester hydrochlorides of Aib and Leu were prepared by the thionyl chloride–methanol procedure. All the intermediates obtained were checked for purity by thin layer chromatography (TLC) on silica gel and used without further purification. All of the final peptides were purified by column chromatography using silica gel (100–200 mesh) as the stationary phase and an ethyl acetate and petroleum ether mixture as the eluent.

### Boc-Phe-Aib-Leu-OMe (I)

**Boc-Phe-Aib-OMe (1).** Boc-Phe-OH (1.33 g, 5 mmol) was dissolved in dimethylformamide (DMF, 3 mL). Aib-OMe (0.59 g, 5 mmol) obtained from its hydrochloride was added, followed by DCC (1.0 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 days. The precipitated dicyclohexylurea (DCU) was filtered and diluted with ethyl acetate (80 mL). The organic layer was washed with an excess of water, 1 N HCl (3 × 30 mL), 1 M $Na_2CO_3$ solution (3 × 30 mL) and again with water. The solvent was then dried over anhydrous $Na_2SO_4$ and evaporated in *vacuo*, giving a light yellow gum. Yield: 1.46 g (80.0%).

**Boc-Phe-Aib-OH (2).** Peptide **1** (0.84 g, 2.3 mmol) was dissolved in methanol (10 mL) and 4 N NaOH (3 mL) was added. The reaction mixture was stirred at room temperature for 2 days. The progress of the reaction was monitered by TLC. After completion of the reaction the methanol was evaporated. The residue obtained was diluted with water and washed with diethylether. The aqueous layer was cooled on ice, neutralised using 2 N HCl and extracted with ethyl acetate. The solvent was evaporated in *vacuo* to give a yellow gum. Yield: 0.63 g (78.0%).

**Boc-Phe-Aib-Leu-OMe (I).** Peptide **2** (0.35 g, 1 mmol) was dissolved in DMF (4 mL). Leu-OMe obtained from its hydrochloride (0.26 g, 2 mmol) was added, followed by DCC (0.2 g, 1 mmol) and HOBT (0.14 g). The reaction mixture was stirred at room temperature for 5 days. The work up of the reaction was carried out as in the case of **1**. Yield: 0.36 g (76.0%). Single crystals were grown from a methanol–water mixture by slow evaporation and were stable at room temperature. Mp = 116–118 °C; $[\alpha]_{578}^{25} = -21°$ ($c$ = 0.10 g per 100 ml; $CH_3OH$), (found: C, 62.95; H, 8.28; N, 8.85. $C_{25}H_{39}N_3O_6$ requires: C, 62.87; H, 8.23; N, 8.80%); IR (KBr): 3376, 3315, 2957, 1697, 1660, 1531 $cm^{-1}$; $^1H$ NMR 500 MHz ($CDCl_3$, $\delta$ ppm): 0.94 ($C^{\delta}H$ of Leu, 6H, m), 1.40 ($C^{\beta}H$ of Aib, 6H, s), 1.43 (Boc-$CH_3$s, 9H, s), 1.58 ($C^{\beta}H$ and $C^{\gamma}H$ of Leu, 2H, m), 3.07 ($C^{\beta}H$ of Phe, 2H, d), 3.70 (−$OCH_3$, 3H, s), 4.15–4.19 ($C^{\alpha}H$ of Leu, 1H, m), 4.53–4.57 ($C^{\alpha}H$ of Phe, 1H, q), 5.01 (Phe NH, 1H, d), 6.14 (Aib NH, 1H, s), 6.93 (Leu NH, 1H, d), 7.21–7.30 (phenyl ring protons).

### Boc-Phe-Leu-Aib-OMe (II)

Peptide **II** was synthesised following a similar procedure to that for peptide **I**. Single crystals were grown from a methanol–water mixture by slow evaporation and were stable at room temperature. Mp = 148–150 °C; $[\alpha]_{578}^{25} = -26°$ ($c$ = 0.10 g per 100 ml; $CH_3OH$), (found: C, 62.97; H, 8.29; N, 8.88. $C_{25}H_{39}N_3O_6$ requires: C, 62.87; H, 8.23; N, 8.80%); IR (KBr): 3312, 3069, 2958, 1746, 1650, 1536 $cm^{-1}$; $^1H$ NMR 500 MHz ($CDCl_3$, $\delta$ ppm): 0.91 ($C^{\delta}H$ of Leu, 6H, d), 1.41 (Boc-$CH_3$s, 9H, s), 1.51 ($C^{\beta}H$ of Aib, 6H, s), 1.60–1.62 ($C^{\beta}H$ and $C^{\gamma}H$ of Leu, 2H, m), 3.11 ($C^{\beta}H$ of Phe, 2H, m), 3.70 ($OCH_3$, 3H, s), 4.26 ($C^{\alpha}H$ of Leu, 1H, m), 4.36 ($C^{\alpha}H$ of Phe, 1H, m), 4.89 (Phe NH, 1H, d), 6.30 (Leu NH, 1H, d), 6.69 (Aib NH, 1H, s), 7.19–7.31 (phenyl ring protons).

### Crystal data

**Peptide I.** $C_{25}H_{39}N_3O_6$, $M$ = 477.59, monoclinic, space group $P2_1$ (No. 4), $a$ = 8.889(1), $b$ = 11.196(1), $c$ = 13.856(1) Å, $\beta$ = 92.09(1)°, $V$ = 1378.0(2) Å$^3$, $D_c$ = 1.151 g $cm^{-3}$, $\mu$ = 0.82 $cm^{-1}$, $Z$ = 2, $\lambda$ = 0.71073 Å, $T$ = 198 K, 11 001 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin$\theta$)/$\lambda$] = 0.66 Å$^{-1}$, 6281 independent ($R_{int}$ = 0.032) and 4504 observed reflections [$I \geq 2\sigma(I)$], 324 refined parameters, $R$ = 0.060, $wR^2$ = 0.109.

**Peptide II.** $(C_{25}H_{39}N_3O_6)_3 \cdot CH_3OH \cdot H_2O$, $M$ = 1482.84, monoclinic, space group $C2$ (No. 5), $a$ = 47.011(1), $b$ = 13.325(1), $c$ = 14.106(1) Å, $\beta$ = 95.26(1)°, $V$ = 8799.1(9) Å$^3$, $D_c$ = 1.119 g $cm^{-3}$, $\mu$ = 0.81 $cm^{-1}$, $Z$ = 4, $\lambda$ = 0.71073 Å, $T$ = 198 K, 35 335 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin$\theta$)/$\lambda$] = 0.65 Å$^{-1}$, 18 476 independent ($R_{int}$ = 0.045) and 12 183 observed reflections [$I \geq 2\sigma(I)$], 976 refined parameters, $R$ = 0.067, $wR^2$ = 0.155.†


## Acknowledgements

A. D. is grateful to the UGC, New Delhi for offering her a Junior research Fellowship. We are thankful to UGC, New Delhi and the University of Calcutta for providing financial support.


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3 Lewis *et al.*[2b] classified β-turns into 10 distinct types (I, I′, II, II′, III, III′, IV, V, VI and VII), while Richardson[2a] later reclassified β-turns into 6 distinct types (I, I′, II, II′, VIa and VIb) and a random category (IV).
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