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Conformational heterogeneity of tripeptides containing Boc–Leu–Aib as corner residues in the solid state

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Abstract—A critical analysis of single crystal X-ray diffraction studies on a series of terminally protected tripeptides containing a centrally positioned Aib (α-aminoisobutyric acid) residue has been reported. For the tripeptide series containing Boc–Ala–Aib as corner residues, all the reported peptides formed distorted type II β-turn structures. Moreover, a series of Phe substituted analogues (tripeptides with Boc–Phe–Aib) have also shown different β-turn conformations. However, the Leu-modified analogues (tripeptides with Boc–Leu–Aib) disrupt the concept of β-turn formation and adopt various conformations in the solid state. X-ray crystallography sheds some light on the conformational heterogeneity at atomic resolution.

1. Introduction

Creation of a β-turn—a region of a protein involving four consecutive residues where the polypeptide chain reverses by nearly 180 degrees to maintain a 10-membered ring hydrogen bond between the backbone CO(*i*) and NH(*i*+3) groups—in small synthetic peptides with non-coded amino acids is an interesting area of peptidomimetics (Fig. 1).[1] Originally, three distinct β-turn conformations depending on backbone torsion angles ϕ and ψ were first recognized through molecular modeling studies by Venkatachalam in 1968.[2] Up to now, there are 10 different types of β-turns, which have been identified and classified, comprising up to 25% of folded proteins and peptides.[3] In particular, β-turns play an important role in stabilizing protein tertiary structures, initiating folding, facilitating intermolecular recognition, and interstrand interactions.[4] Recent interest in the conformational properties of foldamers[5] formed by conformationally constrained and conformationally flexible amino acid analogues has been stimulated by the knowledge that new classes of folded structures can be formed by backbone homologation.[1b,6] Specifically, incorporation of hybrid sequences containing α- and ω-amino acids is interesting in the rational design of secondary structures.[7] Grison et al. introduced a cis- or trans-vinylogous residue into modified peptides to mimic β-turn structure and studied their heterogeneity using X-ray diffraction in the solid state.[8] Fasman and co-workers have presented X-ray models of Piv–Pro-Ser–$NHCH_3$ and Boc–Val-Ser–$NHCH_3$ that adopt almost identical backbone conformations, which are very close to the expected backbone torsional angles of a type I β-turn.[9] Balaram and co-workers have reported a dramatic consequence upon backbone homologation in the crystal structure where Piv–Pro-Gly–NHMe adopts a type II β-turn conformation while Piv–Pro-βGly–NHMe is an open structure with a fully extended β-residue.[10] From our previous report, it has been observed that the short synthetic terminally blocked peptides with a centrally positioned Aib residue can form either β-turn[11] or open conformations.[12] Our group also has reported some model peptides containing β and γ

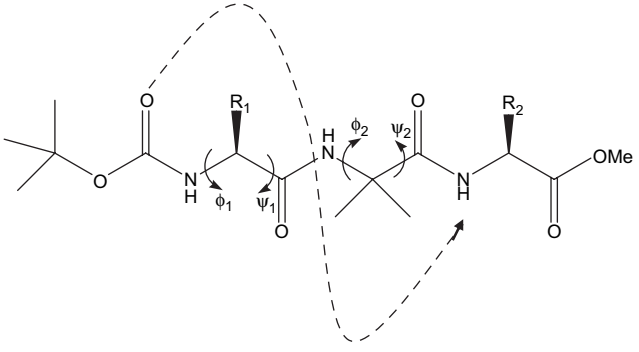

Figure 1. Schematic presentation of β-turn conformation in a terminally protected tripeptide molecule.

Keywords: β-Turn; S-shape structure; Conformational heterogeneity; Tripeptides; X-ray crystallography.
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amino acids that incorporate unusual turns instead of a natural β-turn in the peptide backbone conformations.[13] Recently we have demonstrated that the incorporation of α-aminoisobutyric acid (Aib) in the central hydrophobic core of an amyloid β-peptide residue 17–20 disrupts the β-sheet structure and switches over to a consecutive β-turn conformation.[14] Studies on β-turns have mostly focused on the prime source of folding, which is main chain (backbone) conformational preference. However, in peptides and proteins, side-chain–side-chain interactions within and between helices and β-sheets are also key to the stabilization of the folded structures.[15] Here, we are presenting an example of attractive side-chain–side-chain interactions in a series of tripeptides containing Boc–Leu–Aib as a corner residue. Specifically, the result shows that intrastrand side-chain–side-chain interactions have an important role and can introduce conformational heterogeneity for closely related peptides in the solid state.

2. Results and discussion

The schematic presentations of the tripeptides reported in this study (compounds **1**–**7**) are shown in Figure 2. The relevant backbone torsion angles and conformations of the tripeptides with some previously reported other tripeptides containing centrally positioned Aib are given in Table 1. All the reported tripeptides contain an Aib residue at the central position and it is well established that Aib is helicogenic and induced a 3_{10} helical nature in a peptide backbone. However, from X-ray crystallography, the tripeptides Boc–Ala–Aib–Val–OMe **5**,[11a] Boc–Ala–Aib–Ile–OMe **6**,[11a] and Boc–Ala–Aib–βAla–OMe **7**[11c] containing Boc–Ala–Aib as corner residue had no significant change in the peptide backbone conformations with the variation of the C-terminal residues (Table 1). Figure 3 reveals that peptides **5**, **6**, and **7** adopt folded conformations corresponding to the distorted type II β-turn structure. Peptides **5** and **6** contain comparatively bulky Val and Ile residues, respectively, and peptide **7** has a conformationally flexible βAla residue at the C-terminus. For peptides **5**, **6**, and **7** there exists a weak 4→1 hydrogen bond between Boc–CO and NH of C-terminal residue (N···O, 3.61, 3.48, and 3.17 Å for **5**, **6**, and **7**, respectively). The β-turn backbones of tripeptides **5**, **6**, and **7** are strikingly similar. It is also interesting to note that another previously reported tripeptide Boc–Ala–Aib–Ala–OMe adopts a similar β-turn structure (Table 1).[16]

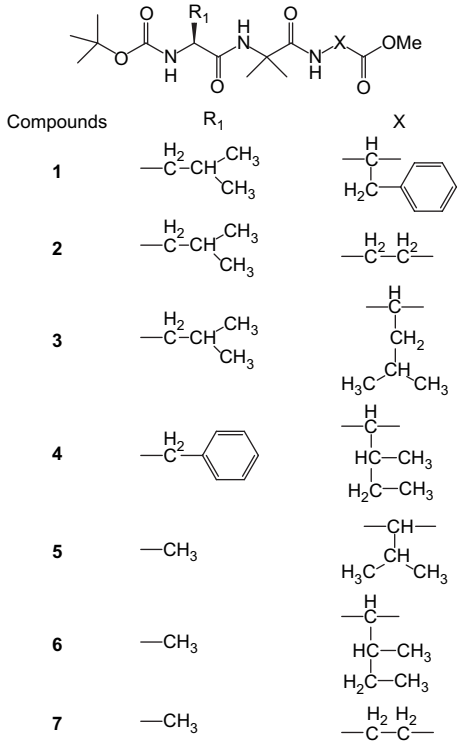

Figure 2. The schematic presentation of tripeptides **1**–**7**.

The single crystal X-ray diffraction studies on a Phe substituted analogue of the terminally protected tripeptides, i.e., the peptide having Boc–Phe–Aib as corner residues also exhibits similar 10-membered intramolecular hydrogen bonded turn forming conformation in the solid state. The crystal structure of the tripeptide Boc–Phe–Aib–Ilu–OMe **4**[13b] reveals that the peptide adopts a folded conformation corresponding to a slightly distorted type II β-turn structure with Phe and Aib occupying the *i*+1 and *i*+2 positions, respectively (Fig. 4). Backbone torsion angles for tripeptide **4** are listed in Table 1. In ideal type II β-turns, the torsion angles are $\phi_1=-60°$, $\psi_1=120°$, $\phi_2=80°$, and $\psi_2=0°$. The previously reported tripeptides Boc–Phe–Aib–Leu–OMe[17] and Boc–Phe–Aib–*m*-ABA–OMe[18] (*m*-ABA: *m*-aminobenzoic acid) also have a similar β-turn structure in the solid state (Table 1). The most interesting feature of the tripeptides containing Boc–Phe–Aib as corner residues is that irrespective of the C-terminal residues they share a common backbone conformation.

However, the Leu-modified analogues, i.e., the tripeptides with Boc–Leu–Aib as corner residues disrupt the concept of β-turn forming structure and adopt various conformations in the solid state for different peptides. Most of the ϕ and ψ values of the constituent amino acid residues of tripeptide Boc–Leu–Aib–Phe–OMe **1**[12a] fall within the helical region of the Ramachandran map. The torsion angles ϕ_1 (−62.91) and ψ_1 (−41.20) are in the right-handed helical region whereas the ϕ_2 (58.15) and ψ_2 (46.24) are in the left-handed helical region, which prevents the peptide from forming any intramolecular hydrogen bonded folded structures. Hence, the overall backbone conformation is an S-shape structure (Fig. 5a). Interestingly, for tripeptide Boc–Leu–Aib–βAla–OMe **2**,[11b] there are two molecules A and B in the asymmetric unit, which are joined together by one intermolecular hydrogen bond to form a molecular dimer of two conformers, which are for the most part equivalent. However, both molecules A and B in the asymmetric unit form a 10-membered intramolecular hydrogen bond between Boc–CO and NH of C-terminal βAla residue (N···O, 3.01 Å) to obtain a distorted type II β-turn structure (Fig. 5b for molecule A). For each conformer in the asymmetric unit of peptide **2**, backbone torsions are listed in Table 1. The molecular conformation of the tripeptide Boc–Leu–Aib–Leu–OMe **3**[12b] in the crystal (Fig. 5c) reveals that this peptide does not form any intramolecular hydrogen bonded β-turn structure even though the ϕ and ψ values of the majority of the constituent amino acid residues fall within the helical region of the Ramachandran map (Table 1). It was found that the torsion angles ϕ_1

Table 1. Conformation of tripeptides Boc–X–Aib–Y–OMe in the solid state with torsion angles (°)

Compound	ϕ_1	ψ_1	ϕ_2	ψ_2	Structure	Reference
Boc–Leu–Aib–Phe–OMe **1**	−62.8	−41.5	58.6	46.2	S-shape	12a
Boc–Leu–Aib–βAla–OMe **2** A	−57.1	128.3	66.0	18.1	Turn	11b
Boc–Leu–Aib–βAla–OMe **2** B	−57.9	126.5	70.7	13.1	Turn	11b
Boc–Leu–Aib–Leu–OMe **3**	−78.2	−27.6	60.5	49.5	S-shape	12b
Boc–Leu–Aib–*m*-ABA–OMe	−71.9	142.4	55.8	33.3	Turn	18
Boc–Phe–Aib–Ile–OMe **4**	−59.2	154.2	62.5	30.9	Turn	13b
Boc–Phe–Aib–Leu–OMe	−62.0	127.5	61.5	26.6	Turn	17
Boc–Phe–Aib–*m*-ABA–OMe	−61.6	142.0	63.6	22.6	Turn	18
Boc–Ala–Aib–Val–OMe **5**	−58.1	146.7	60.1	30.8	Turn	11a
Boc–Ala–Aib–Ile–OMe **6**	−54.6	147.1	60.0	30.0	Turn	11a
Boc–Ala–Aib–βAla–OMe **7**	−58.0	134.7	62.9	23.9	Turn	11c
Boc–Ala–Aib–Ala–OMe	−65	140	67	25	Turn	16

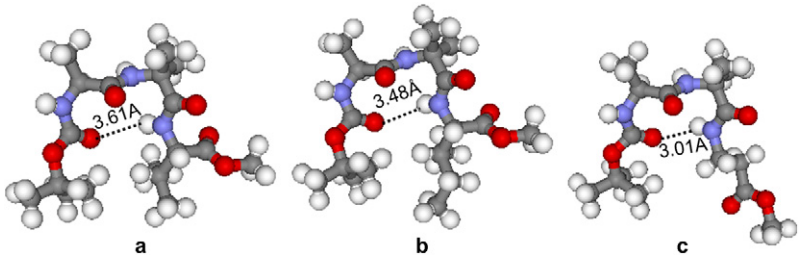

Figure 3. The solid state conformations of tripeptides (a) Boc–Ala–Aib–Val–OMe **5**, (b) Boc–Ala–Aib–Ile–OMe **6**, and (c) Boc–Ala–Aib–βAla–OMe **7**. The intramolecular hydrogen bonds are shown as dotted lines. Nitrogen atoms are blue, oxygen atoms are red, and carbon atoms are gray.

(−78.2) and ψ_1 (−27.6) are in the right-handed helical region whereas ϕ_2 (60.5) and ψ_2 (49.5) are in the left-handed helical region. The overall backbone conformation is an S-shape structure although it has significant differences from that of tripeptide **1**. It is also interesting to note that another previously reported tripeptide Boc–Leu–Aib–*m*-ABA–OMe adopted a folded conformation corresponding to a slightly distorted type II β-turn structure where the torsion angles were found to be deviated as ϕ_1=−71.9°, ψ_1=142.4°, ϕ_2=55.8°, and ψ_2=33.3° (Table 1).[18] As a consequence a very weak 4→1 intramolecular hydrogen bond between Boc–CO and NH of *m*-ABA (N···O, 3.89 Å) appeared. Marshall et al. have reported another tripeptide Boc–Leu–Aib–Pro–OH where the backbone conformation can best be described as a chain reversal with the Leu and Aib residues at the corners of the bend with the torsion angles ϕ_1=−84.4°, ψ_1=163.1°, ϕ_2=53.3°, and ψ_2=37.3°.[19] Since proline is the (*i*+3)th residue, an intramolecular hydrogen bond across the bend is not possible. The superposition of the backbone of tripeptides **1**, **2**, and **3** clearly demonstrates the conformational heterogeneity of these tripeptides containing Boc–Leu–Aib as corner residues in the solid sate

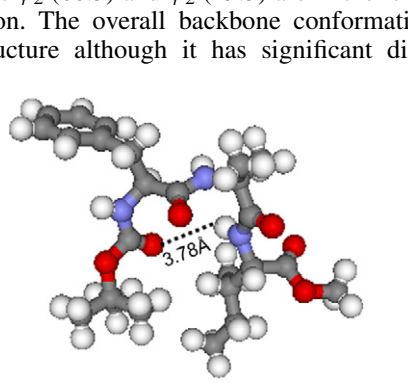

Figure 4. The molecular structure of tripeptide Boc–Phe–Aib–Ile–OMe **4** in crystal. The hydrogen bond is shown as dotted line. Nitrogen atoms are blue, oxygen atoms are red, and carbon atoms are gray.

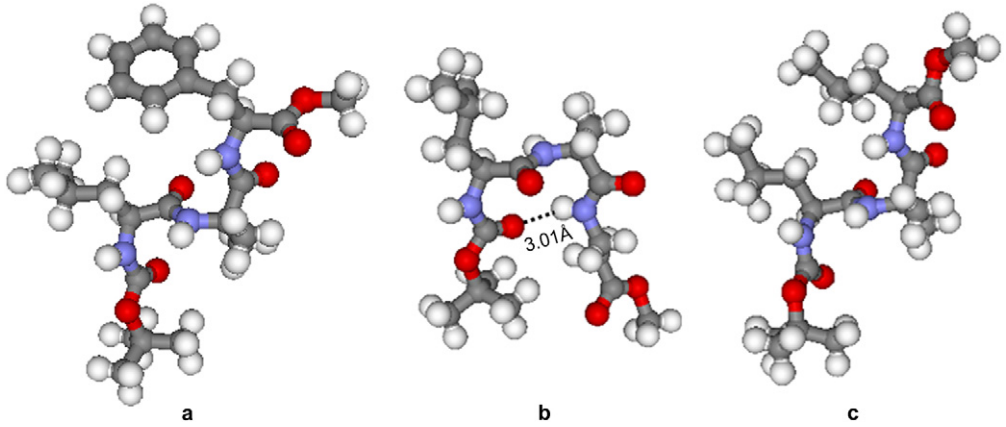

Figure 5. The X-ray structures of tripeptides (a) Boc–Leu–Aib–Phe–OMe **1**, (b) Boc–Leu–Aib–βAla–OMe **2**, and (c) Boc–Leu–Aib–Leu–OMe **3**. Intramolecular hydrogen bond in peptide **2** is shown as dotted line. Nitrogen atoms are blue, oxygen atoms are red, and carbon atoms are gray.

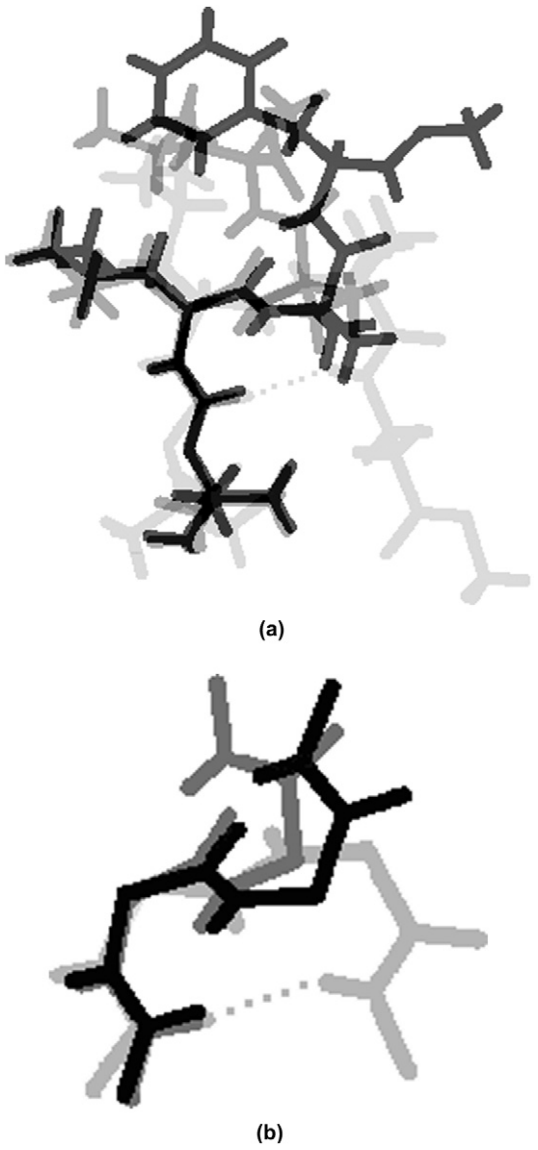

Figure 6. (a) The superposition of the tripeptides **1** (black), **2** (light gray), and **3** (gray) clearly exhibits the conformational heterogeneity in the solid sate and (b) the superposition of the closely related tripeptides **1** (black), **2** (light gray), and **3** (gray) backbone (ϕ_1, ψ_1, ϕ_2, and ψ_2) where the side chains and protecting groups are omitted for clarity.

(Fig. 6). Crystal data for peptides **1**, **2**, and **3** are listed in Table 2. The interaction with the Leu secondary butyl group in the tripeptide molecules may induce deviations from their more usual arrangements. Particularly, the necessary condition for β-turn formation is overall molecular planarity, which is lost due to interactions between the bulky substitutents of Boc–Leu–Aib containing tripeptides and the conformations of strained molecules are far from the standard one.[20]

3. Conclusion

Single crystal X-ray diffraction analysis of a terminally protected tripeptide series containing a centrally positioned helicogenic α-aminoisobutyric acid residue has been reported. The tripeptide series with Boc–Ala–Aib as corner residues has shown distorted type II β-turn structures. Moreover, a series of Phe substituted analogues (tripeptides with Boc–Phe–Aib) also formed closely related β-turn conformations. However, the Leu-modified analogues (tripeptides with Boc–Leu–Aib) disrupt the concept of β-turn structure formation and adopt various conformations in the solid state. It is not surprising that a short peptide of this nature exists in different conformations of similar energies with the crystal structure being considered as a snapshot of one of the many possible conformations.[23] X-ray crystallography sheds some light on the conformational heterogeneity of tripeptides containing Boc–Leu–Aib as corner residues at atomic resolution. This study may be useful for protein modification and rational design in peptidomimetic and crystal engineering studies.

Table 2. Crystal and data collection parameters of peptides **1**, **2**, and **3**

	Peptide **1**	Peptide **2**	Peptide **3**
Empirical formula	$C_{25}H_{39}N_3O_6$	$C_{19}H_{35}N_3O_6$	$C_{22}H_{41}N_3O_6$
Crystallizing solvent	DMSO	Methanol–water	Methanol–water
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a(Å)	6.023(3)	10.210(14)	10.010(14)
b(Å)	10.311(3)	10.373(14)	10.580(14)
c(Å)	43.051(7)	44.00(6)	25.250(3)
α(°)	90	90	90
β(°)	90	90	90
γ(°)	90	90	90
v(Å^3)	2673.6	4660	2674
μ(Mo Kα)/mm	0.085	0.085	0.080
Z	4	8	4
Mol. wt	477.59	401.50	443.58
Density (calcd, Mg/mm^3)	1.186	1.145	1.102
F(000)	1032	1744	968
T(°)	293	293	293
Tot., uniq. data	4509, 4179	20,026, 5936	13,560, 4802
Observed reflns. $I>2\sigma(I)$	2887	4795	2812
R	0.0577	0.086	0.0863
wR	0.1983	0.224	0.2439
S	1.22	1.01	0.89
λ(Å) (Mo Kα)	0.71073	0.71073	0.71073
No. of param	340	522	291

4. Experimental

4.1. Synthesis of the peptides

4.1.1. Boc–Leu–OH 8. See Ref. 21.

4.1.2. Boc–Leu–Aib–OMe 9. See Ref. 22.

4.1.3. Boc–Leu–Aib–OH 10. See Ref. 22.

4.1.4. Boc–Leu–Aib–Phe–OMe 1. See Ref. 14.

4.1.5. Boc–Leu–Aib–βAla–OMe 2. Boc–Leu–Aib–OH (3.03 g, 10 mmol) in DMF (10 mL) was cooled in an ice-water bath and H–βAla–OMe was isolated from the corresponding methyl ester hydrochloride (2.81 g, 20 mmol) by neutralization with saturated $NaHCO_3$ solution, subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 5 mL. It was added to the reaction mixture, followed immediately by DCC (2.10 g, 10 mmol) and HOBt (1.40 g, 10 mmol). The reaction mixture was stirred

for 3 days. The residue was taken in ethyl acetate (50 mL) and the DCU was filtered off. The organic layer was washed with 2 M HCl (3×50 mL), brine, 1 M sodium carbonate (3×50 mL), brine (2×50 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to yield 3.45 g (8.6 mmol) of white solid. The final compound was purified on a silica gel column (100–200 mesh size) using ethyl acetate and toluene mixture (3:1) as eluent. Single crystals were obtained from methanol–water solution by slow evaporation.

Yield=86% (3.45 g, 8.6 mmol). Mp 111–113 °C. IR (KBr): 1661, 1695, 3327, 3321 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.99 (t, J=8.4, 1H), 6.53 (s, 1H), 4.92 (d, J=6.75, 1H), 3.96 (m, 1H), 3.68 (s, 3H), 3.46–3.50 (m, 2H), 2.54–2.56 (m, 2H), 1.58–1.65 (m, 3H), 1.50–1.52 (s, 6H), 1.45 (s, 9H), 0.92–0.96 (m, 6H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 11.28, 11.47, 15.23, 17.98, 22.30, 24.18, 25.02, 27.89, 31.25, 37.14, 51.12, 56.06, 58.23, 80.17, 170.03, 169.81, 171.69 ppm. $[\alpha]_D^{27.8}$ +6.3 (c 2.12, $CHCl_3$). Mass spectral data $(M+Na+H)^+$=425.6, M_{calcd}=401.5. Elemental analysis calcd for $C_{19}H_{35}N_3O_6$ (401): C, 56.86; H, 8.73; N, 10.47. Found: C, 56.32; H, 8.9; N, 10.29.

4.1.6. Boc–Leu–Aib–Leu–OMe 3. Compound **3** was prepared from acid **10** (1.22 g, 5 mmol) and H–Leu–OMe (isolated from the corresponding methyl ester hydrochloride 1.82 g, 10 mmol) to yield 1.73 g (3.9 mmol) of white solid using a procedure comparable to that of the preparation of **2**. Purification was achieved by silica gel column (100–200 mesh) using ethyl acetate and toluene mixture (3:1) as eluent. Single crystals were grown from methanol–water mixture by slow evaporation.

Yield=1.73 g (3.9 mmol, 78%). Mp 117–119 °C. IR (KBr): 1669, 1684, 3321, 3350 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.05 (d, J=8.04, 1H), 6.58 (s, 1H), 4.87 (d, J=5.2, 1H), 4.55–4.59 (m, 1H), 3.98 (m, 1H), 3.71 (s, 3H), 1.61–1.67 (m, 6H), 1.53–1.56 (s, 6H), 1.44 (s, 9H), 0.91–0.96 (m, 12H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 11.31, 15.00, 21.76, 22.76, 24.38, 24.09, 40.27, 51.44, 56.26, 80.08, 156.81, 170.85, 171.74, 173.52 ppm. $[\alpha]_D^{27.8}$ −15.9 (c 2.12, $CHCl_3$). Mass spectral data $(M+Na)^+$=466.6, M_{calcd}=443. Elemental analysis calcd for $C_{22}H_{41}N_3O_6$ (443): C, 59.59; H, 9.25; N, 9.48. Found: C, 59.54; H, 9.18; N, 9.52.

4.1.7. Boc–Phe–Aib–Ile–OMe 4. See Ref. 13b.

4.1.8. Boc–Ala–Aib–Val–OMe 5. See Ref. 11a.

4.1.9. Boc–Ala–Aib–Ile–OMe 6. See Ref. 11a.

4.1.10. Boc–Ala–Aib–βAla–OMe 7. See Ref. 11c.

4.2. NMR experiments

All NMR studies were carried out on Brüker DPX 300 MHz spectrometer at 300 K in $CDCl_3$. Peptide concentrations were in the range 1–10 mM.

4.3. Mass spectrometry

Mass spectra of peptides were recorded on a Micromass Zabspec Hybrid Sector-TOF by positive mode electronspray ionization using a 1% solution of acetic acid in methanol–water as liquid carrier.

4.4. Single crystal X-ray diffraction studies

For tripeptides **1**–**3**, intensity data were collected with Mo Kα radiation using the MARresearch Image Plate System. For all peptides, the crystals were positioned at 70 mm from the Image Plate. Selected details of the structure solutions and refinements are given in Table 2. With a counting time of 2 min 100 frames were measured at 28 intervals. Data analyses were carried out with the XDS program.[24] The structures were solved using direct methods with the (SHELXL)[25] program. All non-H atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to nitrogen and carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times to those of the atom to which they were attached. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre reference CCDC-176329 (peptide **1**), CCDC 191375 (peptide **2**), and CCDC 208708 (peptide **3**).

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