

# Helical L-Leu-Based Peptides Having Chiral Five-Membered Carbocyclic Ring Amino Acids with an Ethylene Acetal Moiety

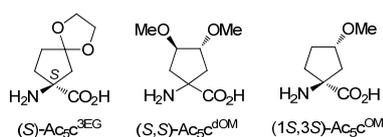
Yurie Koba,<sup>[a]</sup> Atsushi Ueda,<sup>[a]</sup> Makoto Oba,<sup>[a]</sup> Mitsunobu Doi,<sup>[b]</sup> Yosuke Demizu,<sup>[c]</sup> Masaaki Kurihara,<sup>[d]</sup> Masakazu Tanaka\*<sup>[a]</sup>

**Abstract:** L-Leu-based heteropeptides having (*R*)- or (*S*)-chiral five-membered carbocyclic ring amino acids ( $\text{Ac}_5\text{C}^{3\text{EG}}$ ) with an ethylene acetal moiety were prepared. A conformational analysis using FT-IR absorption,  $^1\text{H}$  NMR, and CD spectra revealed that L-Leu-based hexapeptides and nonapeptides having (*R*)- or (*S*)- $\text{Ac}_5\text{C}^{3\text{EG}}$  formed right-handed (*P*) helical structures in solution. An X-ray crystallographic analysis of nonapeptides **5a** and **5b** showed similar right-handed (*P*)  $\alpha$ -helical structures, without an intramolecular hydrogen bond of the peptide N–H $\cdots$ –O– (acetal) type.

## Introduction

L-Amino acid-based heteropeptides having  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids (dAAs) have been reported to form helical secondary structures.<sup>[1–6]</sup> As a dAA,  $\alpha$ -aminoisobutyric acid (Aib) has widely been used to induce helical structures. A right-handed (*P*)  $3_{10}$ -helix is induced in relatively shorter L-amino acid-based peptides having a high Aib content; however, a right-handed (*P*)  $\alpha$ -helix is preferentially formed in relatively longer L-amino acid-based peptides having a low Aib content.<sup>[7]</sup> Besides Aib, we incorporated cyclic dAAs such as achiral 1-aminocyclopentanecarboxylic acid ( $\text{Ac}_5\text{C}$ ),<sup>[8,9]</sup> chiral (*S,S*)-1-amino-3,4-(dimethoxy)cyclopentanecarboxylic acid  $\{(\text{S,S})\text{-Ac}_5\text{C}^{\text{dOM}}\}$ ,<sup>[8–11]</sup> and (1*S*,3*S*)-1-amino-3-methoxycyclopentanecarboxylic acid  $\{(1\text{S},3\text{S})\text{-Ac}_5\text{C}^{\text{OM}}\}$ <sup>[12,13]</sup> into L-Leu-based heteropeptides  $-(\text{L-Leu-L-Leu-dAA})_n-$  as model peptides. The amino acid (*S,S*)- $\text{Ac}_5\text{C}^{\text{dOM}}$  has two chiral centers exclusively at the side chain without an  $\alpha$ -chiral center, and the (1*S*,3*S*)- $\text{Ac}_5\text{C}^{\text{OM}}$  has chiral centers both at the  $\alpha$ -carbon and at the side chain. We reported that these cyclic amino acid-containing L-Leu-based peptides induced right-handed (*P*)  $\alpha$ -helical structures. Furthermore, the cyclic amino acid-containing L-amino acid-based heteropeptides may be used as chiral organocatalysts<sup>[13–15]</sup> and cell-penetrating peptides.<sup>[16–19]</sup>

We previously reported the synthesis of a chiral five-membered carbocyclic ring dAA: (*R*)- or (*S*)-amino-3,3-(ethylenedioxy)cyclopentanecarboxylic acid ( $\text{Ac}_5\text{C}^{3\text{EG}}$ ) with an ethylene acetal moiety, in which the  $\alpha$ -carbon atom was a chiral center, and the helical structures of its homo-chiral homopeptides.<sup>[20]</sup> In the present study, to reveal the influence of (*S*)- or (*R*)- $\text{Ac}_5\text{C}^{3\text{EG}}$  on its heteropeptide conformation, we prepared L-Leu-based heteropeptides having (*S*)- or (*R*)- $\text{Ac}_5\text{C}^{3\text{EG}}$ ; Cbz-[L-Leu-L-Leu- $\{(S)\text{- or } (R)\text{-Ac}_5\text{C}^{3\text{EG}}\}_n\text{-OMe}$  ( $n = 1, 2, \text{ and } 3$ ), and examined their preferred conformations in solution and in a crystal state (Figure 1).



**Figure 1.** Chemical structures of chiral five-membered carbocyclic ring  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids: (*S*)- $\text{Ac}_5\text{C}^{3\text{EG}}$ , (*S,S*)- $\text{Ac}_5\text{C}^{\text{dOM}}$  and (1*S*,3*S*)- $\text{Ac}_5\text{C}^{\text{OM}}$  reported by us.

[a] Y. Koba, Dr. A. Ueda, Dr. M. Oba, Prof. M. Tanaka  
Graduate School of Biomedical Sciences  
Nagasaki University  
1-14 Bunkyo-machi, Nagasaki 852-8521, Japan  
E-mail: matanaka@nagasaki-u.ac.jp

[b] Prof. M. Doi  
Osaka University of Pharmaceutical Sciences  
Osaka 569-1094, Japan

[c] Dr. Y. Demizu  
Division of Organic Chemistry  
National Institute of Health Sciences  
Tokyo 158-8501, Japan

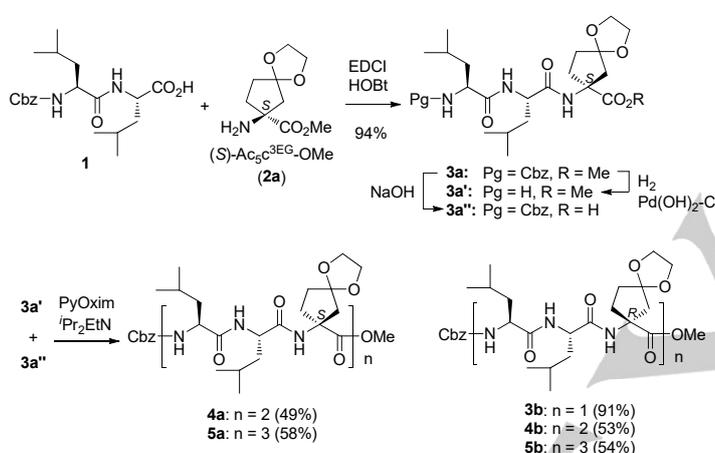
[d] Prof. M. Kurihara  
Graduate School of Pharmaceutical Sciences  
International University of Health and Welfare  
Ohtawara 324-8501, Japan

## Results and Discussion

Preparation of (S)- and (R)-Ac<sub>5</sub>C<sup>3EG</sup>-Containing L-Leu-Based Heteropeptides

We prepared Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**a**) and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**b**) ( $n = 1, 2,$  and  $3$ ) using the following solution-phase methods (Scheme 1). Tripeptide Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]-OMe (**3a**) was prepared by coupling between Cbz-(L-Leu-L-Leu)-OH (**1**) and (S)-Ac<sub>5</sub>C<sup>3EG</sup>-OMe (**2a**)<sup>[20]</sup> using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling reagents in 94% yield. The hydrolysis of the C-terminal methyl ester in **3a** under alkaline conditions (NaOH/H<sub>2</sub>O-THF) proceeded to give a tripeptide carboxylic acid, and the N-terminal-protecting group in **3a** was removed by hydrogenolysis using H<sub>2</sub>/Pd(OH)<sub>2</sub>-C to produce a tripeptide amine. The coupling between them using [ethyl cyano(hydroxyimino)acetato-O<sup>2</sup>]tri-1-pyrrolidinylphosphonium hexafluorophosphate (PyOxim)<sup>[21]</sup> and *N,N*-diisopropylethylamine (*i*Pr<sub>2</sub>EtN) gave the hexapeptide Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>2</sub>-OMe (**4a**) in 49% yield. Similarly, nonapeptide (**5a**) was prepared in 58% yield from the hexapeptide amine and tripeptide carboxylic acid.

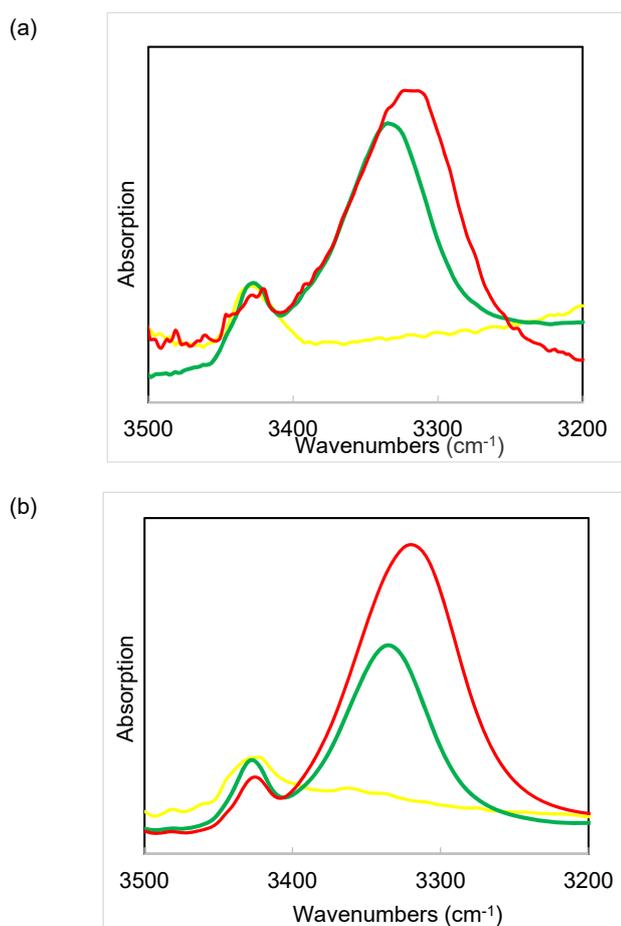
(R)-Ac<sub>5</sub>C<sup>3EG</sup>-containing L-Leu-based peptides Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**b**) ( $n = 1$  (**3b**),  $2$  (**4b**), and  $3$  (**5b**)) were prepared in a similar manner to those of (S)-Ac<sub>5</sub>C<sup>3EG</sup>-containing peptides. The spectroscopic data of heteropeptides supported their chemical structures.



Scheme 1. Preparation of (S)- and (R)-Ac<sub>5</sub>C<sup>3EG</sup>-containing L-Leu-based peptides.

## Conformational Analysis in Solution

Figure 2 shows the FT-IR absorption spectra of peptides Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**a**) and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**b**) in CDCl<sub>3</sub> solution (5.0 mM). In the N-H stretching region (amide A) of peptides **4a, 5a** and **4b, 5b** ( $n = 2$  and  $3$ ), strong bands were noted at 3310–3340 cm<sup>-1</sup> and these bands may have been derived from the peptide N–H groups with N–H⋯O=C intramolecular hydrogen bonds. On the other hand, weak bands were observed at approximately 3430 cm<sup>-1</sup> and these bands may have been derived from the free solvated N–H groups.<sup>[22]</sup> No band at approximately 3370–3390 cm<sup>-1</sup>, which may have been derived from the intramolecular hydrogen bonds of the N–H⋯O– (acetal) type, was observed.<sup>[23,24]</sup> In tripeptides **3a** and **3b**, no band or a very weak band was observed at approximately 3350 cm<sup>-1</sup>. These results suggest that the β-turn structure (the peptide N–H group with N–H⋯O=C intramolecular hydrogen bond) was not formed or unstable in the CDCl<sub>3</sub> solution of **3**.

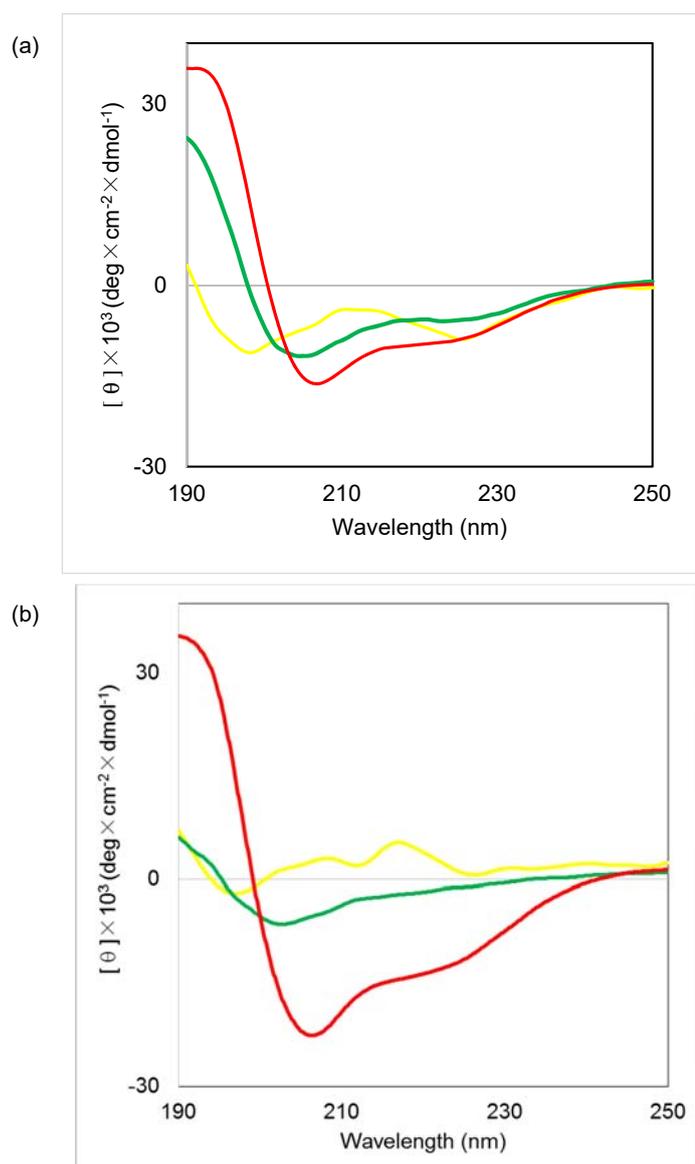


**Figure 2.** FT-IR absorption spectra of heteropeptides (a) Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**3a–5a**;  $n = 1–3$ ) and (b) Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>n</sub>-OMe (**3b–5b**;  $n = 1–3$ ) in CDCl<sub>3</sub>. Peptide concentration: 5.0 mM. Triptides (**3a**, **3b**): yellow, hexapeptides (**4a**, **4b**): green, and nonapeptides (**5a**, **5b**): red.

The nuclear Overhauser effect spectroscopy (NOESY) NMR spectra of hexapeptides **4a** and **4b** were measured in CDCl<sub>3</sub> solution at room temperature (Data are not shown). The spectrum of Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>2</sub>-OMe **4a** showed partial NH ( $i \rightarrow i+1$ ) dipolar interactions, from N(1)H to N(3)H; however, the NOE constraint NH ( $i \rightarrow i+1$ ;  $i = 3, 4, 5$ ) was not analyzed because of the overlap of signals. Unfortunately, we were unable to analyze the NOE constraints [ $d_{\alpha N}$  ( $i \rightarrow i+2$ )] or [ $d_{\alpha N}$  ( $i \rightarrow i+4$ )] due to signal overlaps.<sup>[25]</sup> The spectrum of Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>2</sub>-OMe **4b** also showed only partial NH ( $i \rightarrow i+1$ ) dipolar interactions from N(1)H to N(3)H; no other information was obtained because of signal overlaps.

The CD spectra of peptides **3a–5a** and **3b–5b** in 2,2,2-trifluoroethanol (TFE) solution are shown in Figure 3.<sup>[8,9,26,27,28]</sup> Triptides **3a** and **3b** show no characteristic maxima (222 nm and 208 nm) for helical structures, and these results are attributed to the peptide-main chain length not being sufficiently long to form helical secondary structures.

In contrast, the CD spectra of hexapeptides **4a**, **4b** and nonapeptides **5a**, **5b** showed negative maxima at approximately 222 nm and 208 nm, respectively, and a markedly stronger positive maximum at approximately 192 nm; however, the intensities of the maxima of **4b** were relatively weak. The chiral centers of L-Leu residues may control the helical-screw sense of peptides into right-handedness because 66% content of L-Leu exists in heteropeptides **4** and **5**, and the propensity of the helical-screw control of cyclic amino acid (S)-Ac<sub>5</sub>C<sup>3EG</sup> is relatively weak.<sup>[20]</sup> The intensities of maxima in (S)-Ac<sub>5</sub>C<sup>3EG</sup> hexapeptide **4a** were stronger than those of (R)-Ac<sub>5</sub>C<sup>3EG</sup> hexapeptide **4b**. This may be attributed to the chiral centers of L-Leu matching that of (S)-Ac<sub>5</sub>C<sup>3EG</sup> and mismatching that of (R)-Ac<sub>5</sub>C<sup>3EG</sup>; however, the (S)-Ac<sub>5</sub>C<sup>3EG</sup> homopeptides preferentially formed left-handed (*M*)-helices.<sup>[20]</sup> However, the effects of chiral (S)- and (R)-Ac<sub>5</sub>C<sup>3EG</sup> on the right-handed (*P*) helical structures of L-Leu-based peptides currently remains unclear because the CD spectra of (S)- and (R)-Ac<sub>5</sub>C<sup>3EG</sup>-containing nonapeptides **5a** and **5b** showed similar shapes.



**Figure 3.** CD spectra of heteropeptides (a) Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>n</sub>-OMe (**3a–5a**; n = 1–3) and (b) Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>n</sub>-OMe (**3b–5b**; n = 1–3) in TFE solution (0.05 mM). Tripeptides (**3a**, **3b**): yellow, hexapeptides (**4a**, **4b**): green, and nonapeptides (**5a**, **5b**): red.

### X-Ray Crystallographic Analysis of (S)- and (R)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Nonapeptides

Nonapeptides Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe **5a** and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe **5b** provided suitable crystals for an X-ray crystallographic analysis due to the slow evaporation of <sup>t</sup>PrOH/H<sub>2</sub>O (**5a**) and MeOH/H<sub>2</sub>O (**5b**) at room temperature. The crystal and diffraction parameters of **5a** and **5b** are summarized in Table 1, and the relevant backbone and side-chain torsion angles as well as the intra- and intermolecular hydrogen bond parameters are listed in Tables 2 and 3. Molecular structures are shown in Figures 4 and 5.<sup>[29]</sup>

**Table 1.** Crystal and diffraction parameters of Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>3</sub>-OMe **5a** and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>3</sub>-OMe **5b**.

	Cbz-[L-Leu-L-Leu-((S)-Ac <sub>5</sub> C <sup>3EG</sup> )] <sub>3</sub> -OMe <b>5a</b>	Cbz-[L-Leu-L-Leu-((R)-Ac <sub>5</sub> C <sup>3EG</sup> )] <sub>3</sub> -OMe <b>5b</b>
empirical formula	C <sub>69</sub> H <sub>109</sub> N <sub>9</sub> O <sub>18</sub> ·H <sub>2</sub> O	C <sub>69</sub> H <sub>109</sub> N <sub>9</sub> O <sub>18</sub> ·CH <sub>4</sub> O·H <sub>2</sub> O
<i>M</i> r	1370.67	1402.72
crystal dimensions [mm]	0.50×0.28×0.08	0.28×0.20×0.10
crystal system	orthorhombic	monoclinic
temperature [K]	100	100
lattice parameters:		
<i>a</i> , <i>b</i> , <i>c</i> [Å]	11.729, 15.658, 41.277	10.697, 23.417, 15.281
$\alpha$ , $\beta$ , $\gamma$ [°]	90, 90, 90	90, 90.23, 90
<i>V</i> [Å <sup>3</sup> ]	7581	3827.7
space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	<i>P</i> 2 <sub>1</sub>
<i>Z</i> value	4	2
<i>D</i> <sub>calc</sub> [g/cm <sup>3</sup> ]	1.201	1.217
$\mu$ (CuK $\alpha$ ) [cm <sup>-1</sup> ]	0.718	0.732
no. of observations ( <i>I</i> > -10.0 $\sigma$ <i>I</i> )	7092	13752
no. of variables	874	903
<i>R</i> <sub>1</sub> , <i>R</i> <sub>w</sub>	0.1087, 0.3792	0.0809, 0.2524
solvent	<sup>t</sup> PrOH/H <sub>2</sub> O	MeOH/H <sub>2</sub> O

**Table 2.** Selected torsion angles  $\omega$ ,  $\phi$ ,  $\psi$ , and  $\chi$  [°] of Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>3</sub>-OMe **5a** and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)]<sub>3</sub>-OMe **5b**.<sup>[a,b]</sup>

Torsion Angle	(S)-Ac <sub>5</sub> C <sup>3EG</sup> nonapeptide <b>5a</b>	(R)-Ac <sub>5</sub> C <sup>3EG</sup> nonapeptide <b>5b</b>
$\omega_0$	-173.3	-179.5
$\phi_1$	-66.4	-74.5
$\psi_1$	-48.1	-26.1
$\omega_1$	-177.4	172.2
$\phi_2$	-54.1	-71.8
$\psi_2$	-46.1	-40.2
$\omega_2$	-173.3	173.2
$\phi_3$	-56.6	-54.0
$\psi_3$	-47.1	-45.3
$\omega_3$	177.7	-179.6
$\phi_4$	-61.6	-63.2
$\psi_4$	-48.4	-42.9
$\omega_4$	-176.7	178.4

$\phi_5$	-59.7	-56.9
$\psi_5$	-39.9	-44.9
$\omega_5$	-178.3	-177.0
$\phi_6$	-55.3	-58.0
$\psi_6$	-45.3	-40.4
$\omega_6$	-176.9	178.9
$\phi_7$	-74.8	-67.2
$\psi_7$	-40.9	-44.6
$\omega_7$	-177.0	-170.6
$\phi_8$	-64	-88.0
$\psi_8$	-42	-38.9
$\omega_8$	-173	-177.2
$\phi_9$	49	36.2
$\psi_9$	50	58.5
$\omega_9$	178	176.9
$\chi_1$	178.8	-66.6
$\chi_2$	173.7	-173.3
$\chi_3$	-88.7	86.0
$\chi_3'$	76.0	-77.3
$\chi_4$	174.7	-173.5
$\chi_5$	-58.1	-176.8
$\chi_6$	-101.9	82.9
$\chi_6'$	78.9	-77.3
$\chi_7$	-73	-74.9
$\chi_8$	-171	-67.5
$\chi_9$	-115	163.7
$\chi_9'$	90	-156.9

[a] The number of amino acid residues begins at the *N* terminus of the peptide chain. [b]  $\chi_n$ : N-C(1) $\alpha$ -C(2) $\beta$ -C(3) $\gamma$ (acetal);  $\chi_n'$ : N-C(1) $\alpha$ -C(5) $\beta'$ -C(4) $\gamma'$  (Numbering of cyclopentane).

**Table 3.** Intra- and intermolecular H-bond parameters for Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>C<sup>3EG</sup>)<sub>3</sub>-OMe **5a** and Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>C<sup>3EG</sup>)<sub>3</sub>-OMe **5b**.

Peptide	Donor D-H	Acceptor A	Distance [Å] D...A	Angle [°] D-H...A	Symmetry operations
Cbz-[L-Leu-L-Leu-((S)-Ac <sub>5</sub> C <sup>3EG</sup> ) <sub>3</sub> -OMe ( <b>5a</b> )					
	N <sub>4</sub> -H	O <sub>0</sub>	3.45 <sup>[a]</sup>	168	x,y,z
	N <sub>5</sub> -H	O <sub>1</sub>	3.00	171	x,y,z
	N <sub>6</sub> -H	O <sub>2</sub>	2.86	161	x,y,z
	N <sub>7</sub> -H	O <sub>3</sub>	3.52 <sup>[a]</sup>	159	x,y,z
	N <sub>8</sub> -H	O <sub>4</sub>	2.94	162	x,y,z
	N <sub>9</sub> -H	O <sub>5</sub>	2.89	159	x,y,z
	N <sub>1</sub> -H	O <sub>8</sub>	2.85	136	x, -1+y, z

O <sub>w</sub> -H <sup>[b]</sup>	O <sub>7</sub>	2.86	164	x,y,z
N <sub>3</sub> -H	O <sub>w</sub>	3.05	160	x, 1+y, z
O <sub>w</sub> -H <sup>[b]</sup>	O <sub>3'(acetal)</sub>	2.82	157	x, 1+y, z
Cbz-[L-Leu-L-Leu-((R)-Ac <sub>3</sub> C <sup>3EG</sup> )] <sub>3</sub> -OMe ( <b>5b</b> )				
N <sub>4</sub> -H	O <sub>0</sub>	3.04	156	x,y,z
N <sub>5</sub> -H	O <sub>1</sub>	2.91	157	x,y,z
N <sub>6</sub> -H	O <sub>2</sub>	2.96	162	x,y,z
N <sub>7</sub> -H	O <sub>3</sub>	3.23	158	x,y,z
N <sub>8</sub> -H	O <sub>4</sub>	2.96	153	x,y,z
N <sub>9</sub> -H	O <sub>5</sub>	2.85	163	x,y,z
N <sub>1</sub> -H	O <sub>8</sub>	2.82	133	x,y,1+z
N <sub>3</sub> -H	O <sub>w</sub>	3.05	163	x,y,-1+z
O <sub>M</sub> -H <sup>[b]</sup>	O <sub>1</sub>	2.87	166	x,y,z
O <sub>w</sub> -H <sup>[b,c]</sup>	O <sub>7</sub>	2.86	136	x,y,z

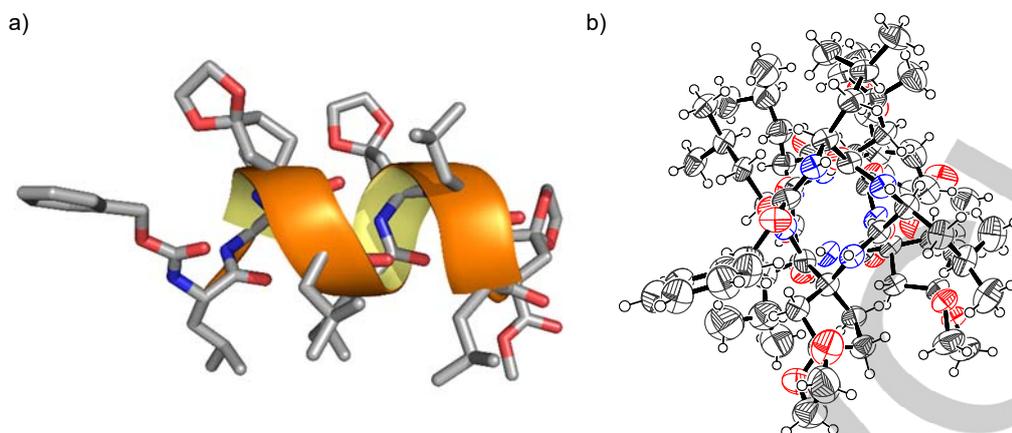
[a] The distance is slightly long for an intramolecular hydrogen bond. [b] O<sub>M</sub>: O atom of MeOH; O<sub>w</sub>: O atom of water. [c] Disordered.

Nonapeptide **5a** was solved in the space group  $P2_12_12_1$  to give a right-handed (*P*)  $\alpha$ -helical structure along with one water molecule in the asymmetric unit. The average  $\phi$  and  $\psi$  torsion angles of residues (1–8) were  $-61.6^\circ$  and  $-44.7^\circ$ , respectively, which were consistent with those of the ideal (*P*)  $\alpha$ -helix ( $-57^\circ$  and  $-47^\circ$ ).<sup>[30–33]</sup> However, the signs of the  $\phi$  and  $\psi$  torsion angles of the (S)-Ac<sub>3</sub>C<sup>3EG</sup> residue (9) at the C-terminus were positive, and opposite to those of the preceding residues. The reversal of the signs of the C-terminal residue torsion angles are frequently observed in helical Aib and related peptides, and known as the helix-terminating structure.<sup>[34,35]</sup>

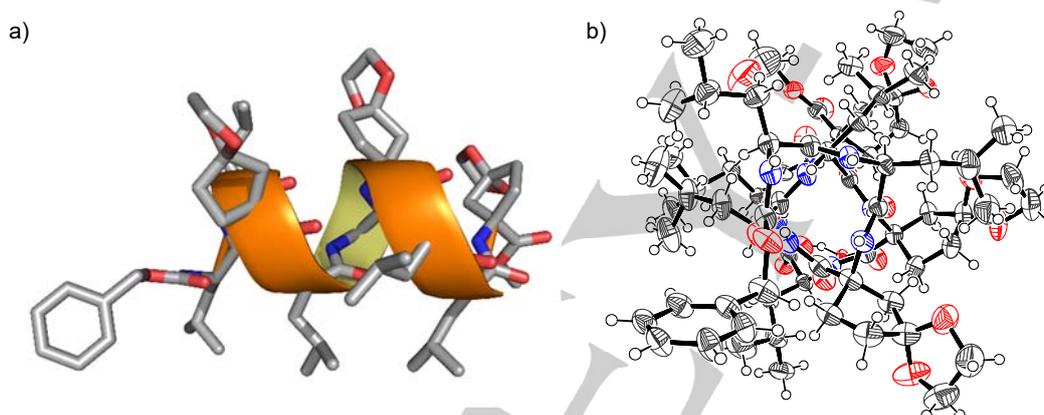
Four intramolecular hydrogen bonds of the  $i-i+4$  type N–H $\cdots$ O=C ( $\alpha$ -helix) were observed between H–N( $i+4$ ) and C( $i$ )=O( $i$ ) ( $i = 1, 2, 4, 5$ ), and two weak intramolecular hydrogen bonds of the  $i-i+4$  type ( $\alpha$ -helix) were observed between H–N( $i+4$ ) and C( $i$ )=O( $i$ ) ( $i = 0, 3$ ). In the packing mode, an intermolecular hydrogen bond was observed between the H–N(1) peptide donor and C(8')=O(8') [N(1) $\cdots$ O(8') = 2.85 Å] of a symmetry-related ( $x, -1+y, z$ ) molecule. Furthermore, the peptide H–N(3') donor of the symmetry-related ( $x, 1+y, z$ ) molecule was intermolecularly hydrogen-bonded to a water O<sub>w</sub>, and the water H–O<sub>w</sub> donor formed hydrogen bonds with C(7)=O(7) [O<sub>w</sub> $\cdots$ O(7) = 2.86 Å] and with O<sub>3'</sub> of acetal oxygen [O<sub>w</sub> $\cdots$ O<sub>acetal</sub>(3') = 2.82 Å] of the symmetry-related ( $x, 1+y, z$ ) molecule.

Diastereomeric nonapeptide **5b** crystallized in the space group  $P2_1$  to form a right-handed (*P*)  $\alpha$ -helical structure, along with one methanol and one water molecule in the asymmetric unit. In the (*P*)  $\alpha$ -helical structure of **5b**, a reversal of the C-terminal torsion angle signs also occurred, *i.e.*, the signs of the  $\phi$  and  $\psi$  torsion angles of the C-terminal residue (9) were opposite to those of the preceding residues (1–8). The average values of the torsion angles  $\phi$  and  $\psi$  of residues (1–8) were  $-66.7^\circ$  and  $-40.4^\circ$ , respectively.

Six consecutive intramolecular hydrogen bonds of the  $i-i+4$  type N–H $\cdots$ O=C ( $\alpha$ -helix) were observed between ( $i+4$ ) and C( $i$ )=O( $i$ ) ( $i = 0\sim5$ ). In the packing mode, similar to those of **5a**, an intermolecular hydrogen bond was observed between the H–N(1) peptide donor and C(8')=O(8') [N(1) $\cdots$ O(8') = 2.82 Å] of a symmetry-related ( $x, y, 1+z$ ) molecule. Furthermore, the peptide H–N(3') donor of the symmetry-related ( $x, y, -1+z$ ) molecule was intermolecularly hydrogen-bonded to a water O<sub>w</sub>, and the water H–O<sub>w</sub> donor formed hydrogen bonds with C(7)=O(7) [O<sub>w</sub> $\cdots$ O(7) = 2.86 Å]. An intermolecular hydrogen bond between the methanol H–O<sub>M</sub> donor and O atom of the C(1)=O(1) acceptor was formed; however, no hydrogen bond was observed between the O atom of acetal oxygen and H–O<sub>w</sub> of water.

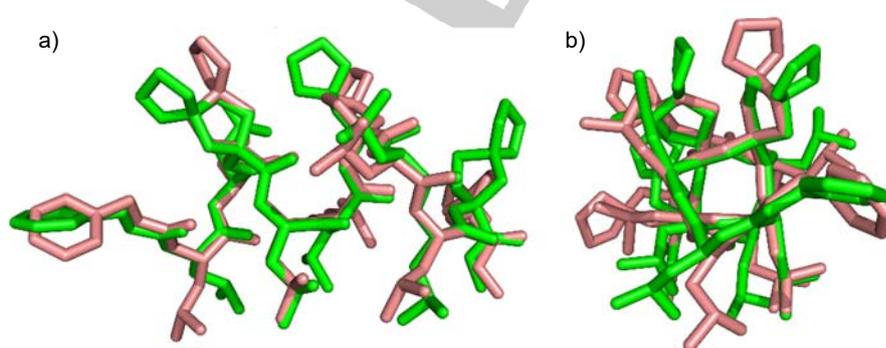


**Figure 4.** Right-handed (*P*)  $\alpha$ -helical structure of Cbz-[L-Leu-L-Leu-((*S*)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe **5a** by an X-ray crystallographic analysis. (a) View perpendicular to the helical axis (Water omitted for clarity), and (b) an ORTEP drawing as viewed along the helical axis.



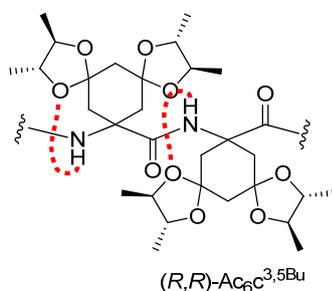
**Figure 5.** Right-handed (*P*)  $\alpha$ -helical structure of Cbz-[L-Leu-L-Leu-((*R*)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe **5b** by an X-ray crystallographic analysis. (a) View perpendicular to the helical axis (Solvents omitted for clarity), and (b) an ORTEP drawing as viewed along the helical axis.

The superimposed structures of helices **5a** and **5b** are shown in FIGURE 6. Although the conformation of the side chain of L-Leu residues and the cyclopentane ring of the C-terminal Ac<sub>5</sub>c<sup>3EG</sup> are different, the peptide-backbone structures of **5a** and **5b** are well superimposed.



**Figure 6.** Superimposed structures of (*S*)-Ac<sub>5</sub>c<sup>3EG</sup>-containing nonapeptide **5a** (green) and (*R*)-Ac<sub>5</sub>c<sup>3EG</sup>-containing nonapeptide **5b** (Salmon pink).

We previously reported that short homopeptides (up to a tetrapeptide) composed of the six-membered carbocyclic ring amino acid (*R,R*)-Ac<sub>6</sub>C<sup>3,5Bu</sup> bearing two  $\gamma$ -acetal moieties preferentially formed helical structures with intramolecular hydrogen bonds of the N(*i*)-H $\cdots$ O- (*i*, acetal) type both in solution and in the crystal state (Figure 7).<sup>[23]</sup> On the other hand, homopeptides (hepta- and octapeptides) composed of the five-membered carbocyclic ring amino acid (*R*)-Ac<sub>5</sub>C<sup>3EG</sup> with an acetal moiety at the  $\gamma$ -position showed left-handed (*M*) helical structures in solution without the N(*i*)-H $\cdots$ O- (*i*, acetal)-type intramolecular hydrogen bond.<sup>[20]</sup> The carbocyclic ring size difference of dAAs may affect the distance of N(*i*)-H and -O- (*i*, acetal), and the intramolecular hydrogen bond pattern may be different.



**Figure 7.** Hydrogen bonding pattern of (*R,R*)-Ac<sub>6</sub>C<sup>3,5Bu</sup> homopeptide.

L-Leu-based hetero-nonapeptides having three (*S*)- or (*R*)-Ac<sub>5</sub>C<sup>3EG</sup> both preferentially formed similar right-handed (*P*) helical structures in solution and in the crystal state. There was no intramolecular hydrogen bond of the N(*i*)-H $\cdots$ O- (*i*, acetal) type, which was observed in the (*R,R*)-Ac<sub>6</sub>C<sup>3,5Bu</sup> homopeptides; however, the H-O<sub>w</sub> donor of water formed a hydrogen bond with O<sub>3'</sub> of acetal oxygen [O<sub>w</sub> $\cdots$ O<sub>acetal</sub>(3') = 2.82 Å] in the crystal state of **5a**.

## Conclusions

L-Leu-based hexapeptides and nonapeptides having (*R*)- or (*S*)-Ac<sub>5</sub>C<sup>3EG</sup> formed right-handed (*P*) helical structures in solution. In the crystal state, L-Leu-based nonapeptides **5a** and **5b** having (*R*)- or (*S*)-Ac<sub>5</sub>C<sup>3EG</sup> both showed similar right-handed (*P*)  $\alpha$ -helical structures. The -L-Leu-L-Leu- sequence worked as a determinant of direction of helix in the predominant  $\alpha$ -helix formation. The effects of chiral five-membered carbocyclic ring amino acids (*R*)- or (*S*)-Ac<sub>5</sub>C<sup>3EG</sup> on the preferred structures of their L-Leu-based -(L-Leu-L-Leu-Ac<sub>5</sub>C<sup>3EG</sup>)<sub>n</sub>- peptides were very weak.

## Experimental Section

### General Experimental Methodology

Optical rotations [ $\alpha$ ]<sub>D</sub> were measured using a 1.0 dm cell. Circular dichroism spectra (CD) were measured using a 1.0-mm path length cell. Infrared absorption spectra (IR) were recorded for conventional measurements (KBr), and the solution (CDCl<sub>3</sub>) method using the 0.1-mm path length of an NaCl cell. <sup>1</sup>H NMR spectra were obtained at 400 or 500 MHz. FAB-HRMS spectra were taken in the dual-focusing sector field mode, and ESI-HRMS spectra were measured in the ToF mode.

### Preparation of Peptides.

#### (*S*)-Ac<sub>5</sub>C<sup>3EG</sup>-Containing Tripeptide; Cbz-L-Leu-L-Leu-((*S*)-Ac<sub>5</sub>C<sup>3EG</sup>)-OMe (**3a**).

*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI·HCl, 296 mg, 1.54 mmol) and 1-hydroxybenzotriazole hydrate (HOBT·H<sub>2</sub>O, 278 mg, 1.82 mmol) were added to a solution of Cbz-(L-Leu)<sub>2</sub>-OH **1** (582 mg, 1.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. A solution of amine (*S*)-Ac<sub>5</sub>C<sup>3EG</sup>-OMe **2a** (281 mg, 1.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added dropwise to the reaction mixture at 0 °C. The resultant solution was gradually warmed to room temperature and stirred overnight. After the removal of CH<sub>2</sub>Cl<sub>2</sub>, the residue was diluted with EtOAc and washed successively with 1 M aqueous HCl, water, 5% aqueous NaHCO<sub>3</sub>, and brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc in *n*-hexane) to give tripeptide **3a** (751 mg, 96%) as colorless crystals: mp 67–69 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -38.4 (c 1.24, CHCl<sub>3</sub>); IR (KBr)  $\nu$  3314 (br), 2955, 2874, 1744, 1701, 1651, 1539, 1261, 1238, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.37 (m, 5H), 7.01 (br s, 1H), 6.56 (br s, 1H), 5.34 (br s, 1H), 5.07–5.12 (m, 2H), 4.44 (m, 1H), 4.18 (br m, 1H), 3.85–3.92 (m, 4H), 3.68 (s, 3H), 2.53 (d, *J* = 14.5 Hz, 1H), 2.37 (m, 1H), 2.15 (d, *J* = 14.5 Hz, 1H), 1.91–2.09 (m, 3H), 1.58–1.76 (m, 4H), 1.43–1.56 (m, 2H), 0.85–0.97 (m, 12H); ESI-HRMS: *m/z* [M+H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>44</sub>N<sub>3</sub>O<sub>8</sub> 562.3128, found 562.3159.

**(R)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Tripeptide; Cbz-L-Leu-L-Leu-((R)-Ac<sub>5</sub>c<sup>3EG</sup>)-OMe (3b).**

Tripeptide **3b** was prepared from **1** and **2b** in a similar manner to that described for the preparation of **3a**. 91%; colorless crystals; mp 75–76 °C;  $[\alpha]_D^{26} -51.1$  (c 1.00, CHCl<sub>3</sub>); IR (KBr)  $\nu$  3310 (br), 2955, 1744, 1701, 1651, 1535, 1261, 1238, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.38 (m, 5H), 6.88 (br s, 1H), 6.37 (br s, 1H), 5.08–5.18 (m, 3H), 4.42 (dd, *J* = 6.8, 11.5 Hz, 1H), 4.17 (br m, 1H), 3.86–3.92 (m, 4H), 3.69 (s, 3H), 2.46 (d, *J* = 14.4 Hz, 1H), 2.41 (m, 1H), 1.96–2.14 (m, 4H), 1.59–1.72 (m, 4H), 1.49–1.53 (m, 2H), 0.89–0.95 (m, 12H); ESI-HRMS: *m/z* [M+H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>44</sub>N<sub>3</sub>O<sub>8</sub> 562.3128, found 562.3150.

**(S)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Hexapeptide; Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>2</sub>-OMe (4a).**

A suspension of tripeptide **3a** (117 mg, 0.208 mmol) and 20% Pd(OH)<sub>2</sub>-C (23 mg) in THF (4 mL) was vigorously stirred for 1.5 h under a H<sub>2</sub> atmosphere at room temperature. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with THF. Evaporation of the filtrate afforded crude amine **3a'** as a brown amorphous, which was used for the next step without purification. On the other hand, 0.2 M aqueous NaOH (1.02 mL, 0.204 mmol) was added dropwise to the stirred solution of tripeptide **3a** (57.2 mg, 0.102 mmol) in THF (1 mL) at 0 °C and the reaction mixture was gradually warmed to room temperature. After being stirred for 24 h, the reaction mixture was cooled to 0 °C, acidified with 1 M aqueous citric acid, and extracted with EtOAc. The EtOAc extracts were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave crude carboxylic acid **3a''** in quantitative yield as a white amorphous, which was used for the next step without purification. PyOxim (132 mg, 0.250 mmol) and 'Pr<sub>2</sub>EtN (72.3  $\mu$ L, 0.416 mmol) were added to the stirred mixture of amine **3a'** (0.208 mmol) and carboxylic acid **3a''** (114 mg, 0.208 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C, and the reaction mixture was gradually warmed to room temperature. After being stirred for 48 h, the reaction mixture was diluted with EtOAc and washed with 5% aqueous NaHCO<sub>3</sub> and brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (75% EtOAc in *n*-hexane containing 0.25% Et<sub>3</sub>N) to provide hexapeptide **4a** (97.4 mg, 49% in 2 steps from **3a**) as an off-white solid: mp 209–210 °C;  $[\alpha]_D^{25} -0.48$  (c 1.01, CHCl<sub>3</sub>); IR (KBr)  $\nu$  3310(br), 2959, 2855, 1744, 1651, 1535, 1339, 1270, 1220, 1140, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.36–7.40 (m, 5H), 7.34 (br s, 1H), 7.33 (br s, 1H), 7.29 (br s, 1H), 7.25 (br s, 1H), 6.59 (br s, 1H), 5.22 (br s, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 4.37 (m, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.96 (m, 1H), 3.67–3.91 (m, 8H), 3.67 (s, 3H), 2.80 (m, 1H), 2.73 (d, *J* = 14.9 Hz, 1H), 2.24–2.35 (m, 3H), 2.23 (m, 1H), 2.00–2.09 (m, 3H), 1.96 (m, 1H), 1.62–1.87 (m, 12H), 1.53–1.47 (m, 2H), 0.85–0.99 (m, 24H); FAB-HRMS: *m/z* [M]<sup>+</sup> calcd for C<sub>49</sub>H<sub>76</sub>N<sub>6</sub>O<sub>13</sub> 956.5470, found 956.5463.

**(R)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Hexapeptide; Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>2</sub>-OMe (4b).**

Hexapeptide **4b** was prepared from **3b** in a similar manner to that described for the preparation of **4a**. 53%; colorless crystals; mp 190–192 °C;  $[\alpha]_D^{23} +2.99$  (c 1.01, CHCl<sub>3</sub>); IR (KBr)  $\nu$  3337 (br), 2959, 1740, 1713, 1667, 1528, 1258, 1215, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.46 (br s, 1H), 7.36–7.40 (m, 5H), 7.28–7.33 (m, 3H), 6.57 (br s, 1H), 5.54 (br s, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.36 (m, 1H), 4.23 (m, 1H), 3.92–3.99 (m, 2H), 3.80–3.90 (m, 8H), 3.67 (s, 3H), 3.19 (m, 1H), 2.93 (d, *J* = 14.8 Hz, 1H), 2.73 (d, *J* = 14.8 Hz, 1H), 2.25–2.39 (m, 2H), 2.16–2.24 (m, 2H), 2.04–2.13 (m, 3H), 1.95 (m, 1H), 1.58–1.82 (m, 11H), 1.54 (m, 1H), 1.44 (m, 1H), 0.82–0.99 (m, 24H); FAB-HRMS: *m/z* [M]<sup>+</sup> calcd for C<sub>49</sub>H<sub>76</sub>N<sub>6</sub>O<sub>13</sub> 956.5470, found 956.5464.

**(S)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Nonapeptide; Cbz-[L-Leu-L-Leu-((S)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe (5a).**

Nonapeptide **5a** was prepared from **4a** in a similar manner to that described for the preparation of **4a**. 58%; colorless crystals; mp 204–206 °C;  $[\alpha]_D^{26} +24.6$  (c 0.87, CHCl<sub>3</sub>); IR (CDCl<sub>3</sub>)  $\nu$  3323 (br), 2961, 1717, 1655, 1526, 1339, 1271, 1217, 1125, 1074, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.80 (br s, 1H), 7.69–7.72 (m, 2H), 7.49–7.58 (m, 4H), 7.35–7.43 (m, 5H), 6.98 (br s, 1H), 5.90 (br s, 1H), 5.20 (s, 2H), 4.34 (m, 1H), 4.18–4.26 (m, 4H), 4.03 (m, 1H), 3.86–3.98 (m, 12H), 3.65 (s, 3H), 2.92 (m, 1H), 2.77 (d, *J* = 14.8 Hz, 1H), 2.62 (d, *J* = 14.8 Hz, 1H), 2.42 (m, 1H), 2.21–2.28 (m, 3H), 1.48–2.16 (m, 19H), 1.22–1.47 (m, 10H), 1.19–0.83 (m, 36H); FAB-HRMS: *m/z* [M]<sup>+</sup> calcd for C<sub>69</sub>H<sub>109</sub>N<sub>9</sub>O<sub>18</sub> 1351.7891, found 1351.7893.

**(R)-Ac<sub>5</sub>c<sup>3EG</sup>-Containing Nonapeptide; Cbz-[L-Leu-L-Leu-((R)-Ac<sub>5</sub>c<sup>3EG</sup>)]<sub>3</sub>-OMe (5b).**

Nonapeptide **5b** was prepared from **4b** in a similar manner to that described for the preparation of **4a**. 54%; colorless crystals; mp 224–226 °C;  $[\alpha]_D^{24} +8.13$  (c 1.00, CHCl<sub>3</sub>); IR (CDCl<sub>3</sub>)  $\nu$  3321 (br), 2959, 2361, 1709, 1659, 1531, 1339, 1261, 1215, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (br d, *J* = 8.7 Hz, 1H), 7.69 (br s, 1H), 7.57 (br s, 1H), 7.56 (br s, 1H), 7.48 (br s, 1H), 7.46 (br s, 1H), 7.37–7.42 (m, 5H), 7.35 (br s, 1H), 7.07 (br s, 1H), 6.23 (br s, 1H), 5.20 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.31 (m, 1H), 4.21 (m, 1H), 4.04 (m, 1H), 3.90–3.97 (m, 3H), 3.78–3.88 (m, 12H), 3.65 (s, 3H), 3.04 (d, *J* = 14.5 Hz, 1H), 2.97 (d, *J* = 14.5 Hz, 1H), 2.70 (d, *J* = 13.6 Hz, 1H), 2.45 (m, 1H), 2.24–2.40 (m, 4H), 1.98–2.22 (m, 10H), 1.59–1.96 (m, 17H), 1.52 (m, 1H), 0.78–1.04 (m, 36H); FAB-HRMS: *m/z* [M+Na]<sup>+</sup> calcd for C<sub>69</sub>H<sub>109</sub>N<sub>9</sub>O<sub>18</sub>Na 1374.7788, found 1374.7782.

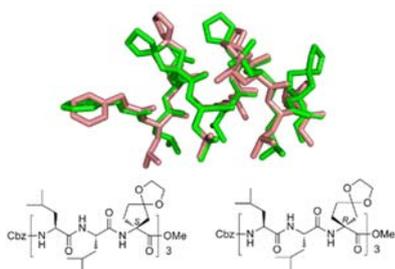
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**Keywords:** amino acids • helical structures • peptides • peptidomimetics • conformation analysis

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## Entry for the Table of Contents



L-Leu-based nonapeptides having (*R*)- or (*S*)-chiral five-membered carbocyclic ring amino acids with an ethylene acetal moiety were prepared. An X-ray crystallographic analysis revealed the nonapeptides formed similar right-handed (*P*)  $\alpha$ -helical structures, without an intramolecular hydrogen bond of the peptide N-H $\cdots$ O- (acetal) type.