Conformational Study of Heteropentapeptides Containing an α-Ethylated α,α-Disubstituted Amino Acid: (*S*)-Butylethylglycine (=2-Amino-2-ethylhexanoic Acid) within a Sequence of Dimethylglycine (=2-Aminoisobutyric Acid) Residues

by **Masakazu Tanaka**[a])*, **Makoto Oba**[a]), **Naoto Imawaka**[a]), **Yoshitsugu Tanaka**[a]), **Masaaki Kurihara**[b]), and **Hiroshi Suemune**[a])*

[a]) Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[b]) Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan

Heteropentapeptides containing the α-ethylated α,α-disubstituted amino acid (*S*)-butylethylglycine and four dimethylglycine residues, *i.e.*, CF_3CO-[(*S*)-Beg]-$(Aib)_4$-OEt (**4**) and CF_3CO-$(Aib)_2$-[(*S*)-Beg]-$(Aib)_2$-OEt (**7**), were synthesized by conventional solution methods. In the solid state, the preferred conformation of **4** was shown to be both a right-handed (*P*) and a left-handed (*M*) 3_{10}-helical structure, and that of **7** was a right-handed (*P*) 3_{10}-helical structure. IR, CD, and ^{1}H-NMR spectra revealed that the dominant conformation of both **4** and **7** in solution was the 3_{10}-helical structure. These conformations were also supported by molecular-mechanics calculations.

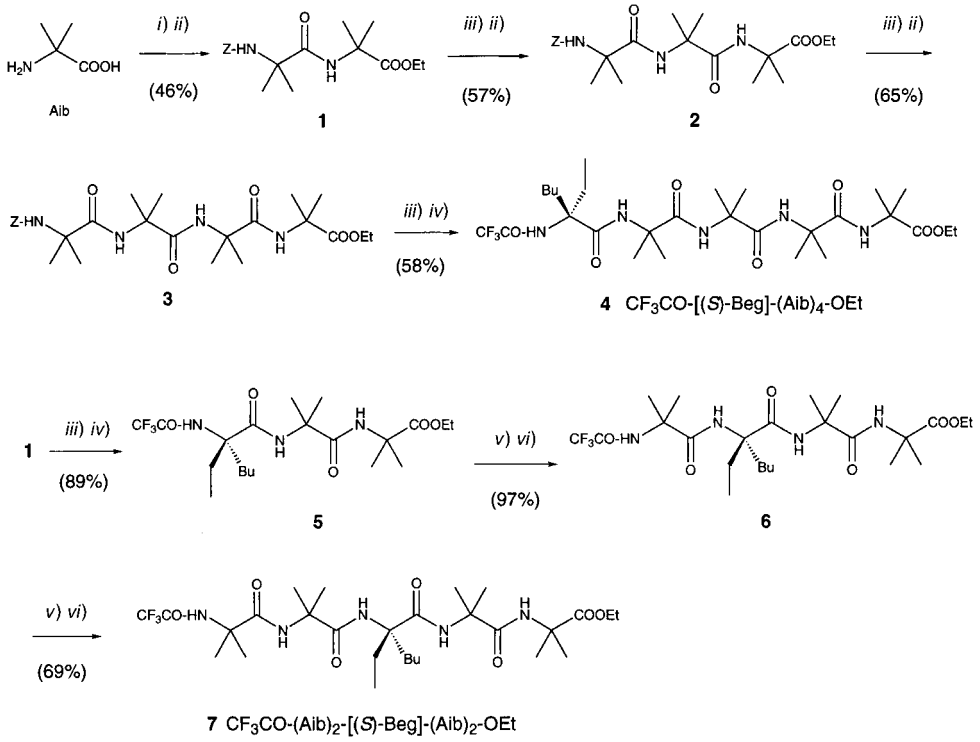
Introduction. – α,α-Disubstituted amino acids and their peptides have attracted considerable attention since these amino acids and peptides show unique biological activities [1] and very stable secondary structures [2]. The conformation of homopeptides constituted from achiral α,α-disubstituted amino acids, such as 2-aminoisobutyric acid (=dimethylglycine; Aib), diethylglycine, dipropylglycine, and alicyclic glycine (Ac(*n*)c), has been extensively studied because synthesis of the achiral amino acids could be easily achieved, even by peptide chemists. The conformation of Aib and Ac(*n*)c is known to be a 3_{10}-helical structure [3][4], and that of diethylglycine [5] and dipropylglycine [6] is a fully planar C_5 conformation. Recently, some methods for the asymmetric synthesis of chiral α,α-disubstituted amino acids have been reported by several groups, including us [7]. Although various chiral α,α-disubstituted amino acids were enantioselectively synthesized, only a few papers on the conformation of peptides containing the chiral α,α-disubstituted amino acids are published, except for α-methylated α,α-disubstituted amino acids [8][9]. The α-methylated α,α-disubstituted amino acids could be easily prepared by enzymatic resolution of racemic amino acids [10], and the conformation of α-methylated α,α-disubstituted amino acids, such as isovaline, α-methylvaline, or α-methylleucine, is known to be a 3_{10}-helical structure [8][9]. Furthermore, the sense of the 3_{10}-helical structure dependent on the chirality of a quaternary C-atom in the α-methylated α,α-disubstituted amino acids, has been reported by *Toniolo* and co-workers [8] and *Seebach* and co-workers [9].

Previously, we prepared homopeptides containing the chiral α-ethylated α,α-disubstituted amino acid (*S*)-butylethylglycine (=(2*S*)-2-amino-2-ethylhexanoic acid; (*S*)-Beg), and reported that these homopeptides adopted a fully planar C_5 conformation, both in $CDCl_3$ solution and in the solid state [11]. In this paper, we wish to report

the conformation of heteropeptides containing (*S*)-Beg as a guest amino acid in the Aib sequence because the propensity of Aib is to form a strong 3_{10}-helical structure while that of (*S*)-Beg seems to take a planar C_5 conformation. This method to study the propensity of α,α-disubstituted amino acids to adopt a certain conformation was reported by *Toniolo* and co-workers [12] and seemed to be very useful for obtaining information on the conformational property of the guest amino acid [13].

Results. – *Heteropentapeptides CF_3CO-[(S)-Beg]-$(Aib)_4$-OEt and CF_3CO-$(Aib)_2$-[(S)-Beg]-$(Aib)_2$-OEt.* The preparation of optically active (*S*)-Beg according to the methods of *Liu et al.* [14], *i.e.* of *N*-(trifluoroacetyl)-protected butylethylglycine (CF_3CO-Beg) and of butylethylglycine ethyl ester (Beg-OEt), has already been reported by us [11]. The Aib dipeptide and tetrapeptide were prepared by conventional solution-phase methods, employing an ethyl ester as the C-terminus and a Z-protecting group as the N-terminus [15]. We prepared Aib homotetrapeptide **3** step-by-step from the C-terminus *via* **1** and **2** by means of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC) as a coupling reagent and hydrogenolysis for deprotection of the Z-protecting group (*Scheme*). The heteropentapeptide CF_3CO-[(*S*)-Beg]-$(Aib)_4$-OEt (**4**) was obtained from **3** on removal of the Z-protecting group

Scheme



i) $SOCl_2$, EtOH, reflux. *ii*) Z-Aib, EDC, HOBt. *iii*) H_2, Pd/C. *iv*) CF_3CO-(*S*)-Beg, EDC, MeCN, reflux. *v*) $NaBH_4$, EtOH. *vi*) CF_3CO-Aib, EDC, MeCN, reflux.

by hydrogenolysis (H_2, Pd/C) and subsequent coupling with CF_3CO-(*S*)-Beg by treatment with EDC in refluxing MeCN. The heteropentapeptide CF_3CO-$(Aib)_2$-[(*S*)-Beg]-$(Aib)_2$-OEt (**7**) was prepared from Aib dipeptide **1** by hydrogenolysis followed by coupling with CF_3CO-(*S*)-Beg, affording the intermediate tripeptide **5** in 89% yield. Removal of the trifluoroacetyl group by $NaBH_4$ reduction followed by coupling with CF_3CO-Aib gave tetrapeptide **6** (97%), which was transformed similarly to the heteropentapeptide **7** (69%).

Solid-State Conformational Analysis. We determined the molecular and crystal structures of the two terminally blocked heteropentapeptides **4** and **7** by X-ray crystallographic analysis. Crystals of good quality for X-ray analysis were easily obtained by slow evaporation of $CHCl_3$/MeOH solutions at room temperature, whereas no suitable crystals have yet been obtained in the case of the (*S*)-Beg homopentapeptide [11]. The molecular structures of **4** and **7** with atomic numbering schemes are shown in *Figs. 1–3*. Relevant backbone and side-chain torsion angles are given in *Table 1*. The intra- and intermolecular H-bond parameters are listed in *Table 2*.

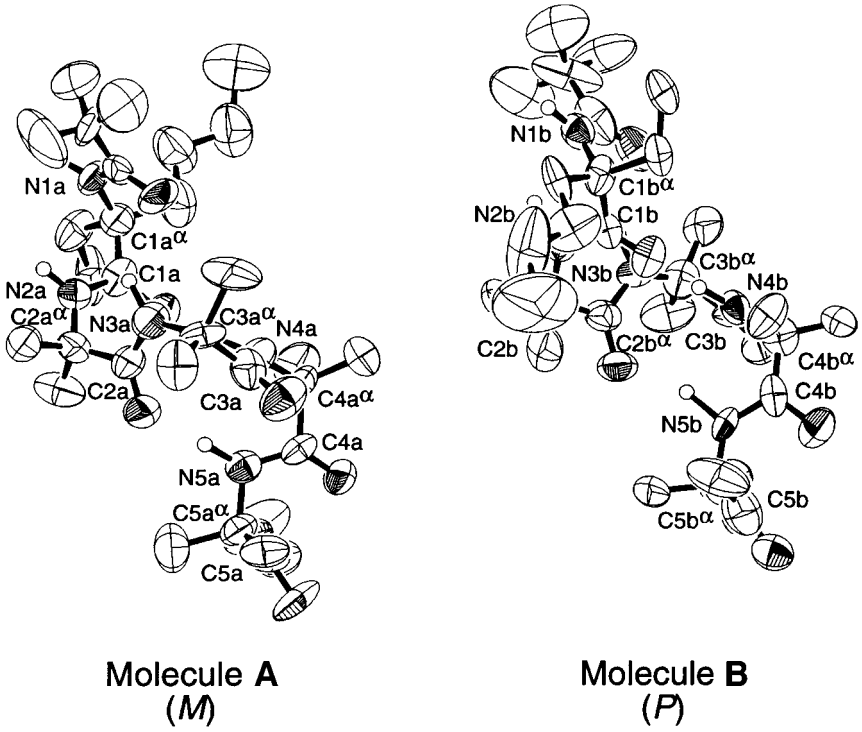


Fig. 1. *ORTEP Drawing of the crystal structure of CF_3CO-[(S)-Beg]-$(Aib)_4$-OEt* (**4**) *with atom numbering* (ellipsoids at 50% probability)

The heteropeptide CF_3CO-[(*S*)-Beg]-$(Aib)_4$-OEt (**4**) crystallizes in the monoclinic space group $P2_1$. Two crystallographically independent molecules **A** and **B** occur in the

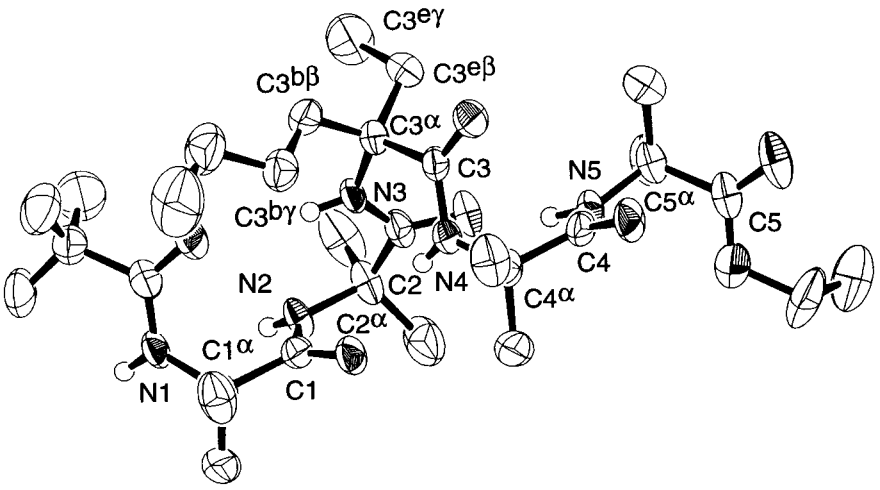


Fig. 2. *ORTEP Drawing of the crystal structure of* CF_3CO-(Aib)$_2$-[(S)-Beg]-(Aib)$_2$-OEt (**7**) *with atom numbering* (ellipsoids at 50% probability)

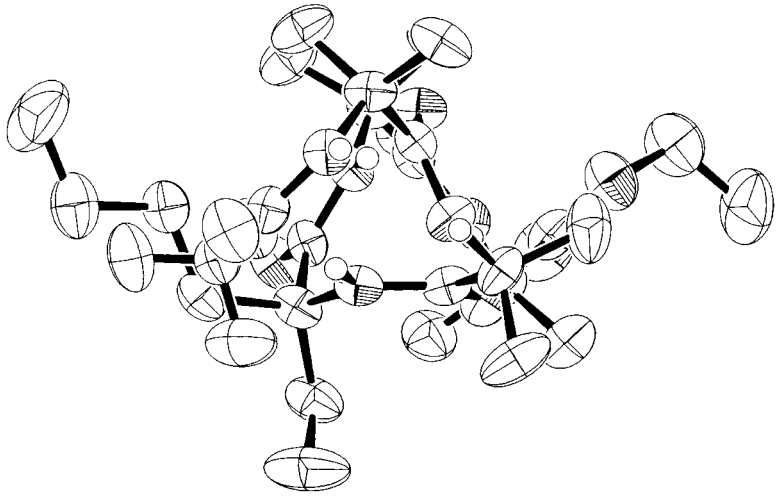


Fig. 3. *ORTEP Drawing of* **7**, *viewed along the helix axis* (ellipsoids at 50% probability)

asymmetric unit of **4**. Both molecules **A** and **B** are folded in the distorted 3_{10}-helical structure, **A** displaying a left-handed (*M*) and **B** a right-handed (*P*) 3_{10}-helical structure, which are connected by intermolecular H-bonds. Molecule **A** shows three intramolecular H-bonds between H–N(3a) and the C(0a)=O(0a) O-atom of the CF_3CO group with a N(3a)$\cdots$O(0a) distance of 3.12 Å, between H–N(4a) and C(1a)=O(1a) (N(4a)$\cdots$O(1a) = 3.05 Å), and between H–N(5a) and C(2a)=O(2a) (N(5a)$\cdots$O(2a) = 2.93 Å). Similarly, three intramolecular H-bonds are observed in molecule **B**, between H–N(3b) and C(0b)=O(0b) (N(3b)$\cdots$O(0b) = 3.10 Å), between H–N(4b) and C(1b)=O(1b) (N(4b)$\cdots$O(1b) = 3.01 Å), and between H–N(5b) and

Table 1. *Selected Torsion Angles ω, ϕ, ψ, and χ*[a]) [°] *for the Heteropentapeptides* **4** *and* **7** *as Determined by X-Ray Crystal-Structure Analysis*

	CF_3CO-[(*S*)-Beg]-$(Aib)_4$-OEt (**4**)		CF_3CO-$(Aib)_2$-[(*S*)-Beg]-$(Aib)_2$-OEt (**7**)
	Molecule **A** (*M*)	Molecule **B** (*P*)	(*P*)
ω_0	– 179.8	179.5	– 171.5
ϕ_1	57.2	– 43.0	– 54.9
ψ_1	40.4	– 47.8	– 34.4
ω_1	176.0	– 166.1	– 176.2
ϕ_2	54.8	– 52.9	– 53.8
ψ_2	36.6	– 31.8	– 27.6
ω_2	176.5	– 174.5	– 173.9
ϕ_3	48.0	– 58.2	– 61.5
ψ_3	36.0	– 32.0	– 15.5
ω_3	174.6	– 178.7	174.9
ϕ_4	56.4	– 64.1	– 49.9
ψ_4	28.9	– 23.9	– 36.4
ω_4	– 178.5	178.6	169.8
ϕ_5	– 53.1	47.8	57.9
ψ_5	– 47.6	49.3	50.7
ω_5	179.3	166.0	167.8
χ_1^e	– 176.0	45.0	–
χ_1^b	– 67.8	176.0	–
χ_3^e	–	–	57.0
χ_3^b	–	–	73.3

[a]) The subscripts e and b refer to the ethyl and butyl side chains, respectively.

Table 2. *Intra- and Intermolecular H-Bond Parameters for the Heteropeptides* **4** *and* **7**[a])

Peptide: conformation	Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operations
CF_3CO-[(*S*)-Beg]-$(Aib)_4$-OEt (**4**): **A** (*M*)	N(3a)–H	O(0a)	3.12	135	*x*,*y*,*z*
	N(4a)–H	O(1a)	3.05	171	*x*,*y*,*z*
	N(5a)–H	O(2a)	2.93	172	*x*,*y*,*z*
B (*P*)	N(3b)–H	O(0b)	3.10	147	*x*,*y*,*z*
	N(4b)–H	O(1b)	3.01	143	*x*,*y*,*z*
	N(5b)–H	O(2b)	3.13	155	*x*,*y*,*z*
	N(1a)–H	O(4b′)	2.82	149	*x*,*y*,*z* – 1
	N(2a)–H	O(5b′)	3.27[b])	138	*x*,*y*,*z* – 1
	N(1b)–H	O(4a′)	2.84	161	*x* + 1,*y*,*z*
	N(2b)–H	O(5a′)	3.30[b])	–	*x* + 1,*y*,*z*
CF_3CO-$(Aib)_2$-[(*S*)-Beg]-$(Aib)_2$-OEt (**7**): (*P*)	N(3)–H	O(0)	3.09	147	*x*,*y*,*z*
	N(4)–H	O(1)	3.01	143	*x*,*y*,*z*
	N(5)–H	O(2)	3.08	167	*x*,*y*,*z*
	N(1)–H	O(4′)	2.95	166	*x*,*y*,*z* + 1
	N(2)–H	O(5′)	3.10	157	*x*,*y*,*z* + 1

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

C(2b)=O(2b) (N(5b)···O(2b) = 3.13 Å). The average absolute values of the ϕ and ψ torsion angles are $\phi = 53.9°$ and $\psi = 37.9°$ in molecule **A**, and $\phi = 53.2°$ and $\psi = 37.0°$ in molecule **B**, whereas, in general, the ideal torsion angles for the 3_{10}-helical structure are $\phi = 49°$ and $\psi = 26°$, and those for the α-helical structure are $\phi = 57°$ and $\psi = 47°$. The relationship between the two conformations **A** and **B** is that of diastereoisomeric (*M*) and (*P*) helices. The corresponding torsion angles in the molecules of opposite helicity differ by sign, but the absolute values are almost the same. The signs of the ϕ and ψ torsion angles of the Aib-5a residue at the C-terminus (−53.1 and −47.6°, resp.) are opposite to those of the preceding residues (*S*)-Beg-1a, Aib-2a, Aib-3a, and Aib-4a (positive angles); also in molecule **B**, the signs of the torsion angles of the Aib-5b residue (+47.8 and +49.3°, resp.) are opposite to those of the preceding residues. These phenomena are often observed in the 3_{10}-helical structures of homo- and heteropeptides containing Aib, and are known as the 3_{10}-helix-terminating structure [3]. In the packing mode of heteropeptide **4**, two intermolecular H-bonds are observed between the H−N(1a) peptide donor and the C(4b′)=O(4b′) O-atom of a symmetry-related molecule (x, y, $z-1$) with a N(1a)···O(4b′) distance of 2.82 Å, and also between the H−N(1b) and C(4a′)=O(4a′) of a symmetry-related molecule ($x+1$, y, z) with a N(1b)···O(4a′) distance of 2.84 Å. Moreover, two weak intermolecular H-bonds are observed between the H−N(2a) peptide donor and the C(5b′)=O(5b′) O-atom of a symmetry-related molecule (x, y, $z-1$) with a N(2a)···O(5b′) distance of 3.27 Å, and also between H−N(2b) and C(5a′)=O(5a′) of a symmetry-related molecule ($x+1$, y, z) with a N(2b)···O(5a′) distance of 3.30 Å. The chains of intermolecularly H-bonded molecules are formed in a head-to-tail alignment of right-handed (*P*) 3_{10}-helical molecules **B** and left-handed (*M*) 3_{10}-helical molecules **A**, *i.e.*, they are (···*P*···*M*···*P*···*M*···) chains of the molecules **A** and **B**.

The structure of heteropeptide CF_3CO-$(Aib)_2$-[(*S*)-Beg)]-$(Aib)_2$-OEt (**7**) was also solved in the space group of $P2_1$. Only one molecule exists in the asymmetric unit of the heteropeptide **7**. The molecule is folded in the 3_{10}-helical structure, and the sense of helicity is a right-handed (*P*) helix. Three intramolecular H-bonds are observed, *i.e.* between H−N(3) and the C(0)=O(0) O-atom of the CF_3CO group (N(3)···O(0) = 3.09 Å), between H−N(4) and C(1)=O(1) (N(4)···O(1) = 3.01 Å), and between H−N(5) and C(2)=O(2) (N(5)···O(2) = 3.08 Å). The mean values of the ϕ and ψ torsion angles for the sequence Aib-1 to Aib-4 are $\phi = -55.0°$ and $\psi = -28.5°$, close to those expected for a right-handed (*P*) 3_{10} helix (−49 and −26°). The signs of the ϕ and ψ torsion angles of the Aib-5 residue at the C-terminus (+57.9 and +50.7°, resp.) are opposite to those of the preceding residues Aib-1, Aib-2, Aib-4, and (*S*)-Beg-3, as it is often the case for a 3_{10}-helix-terminating structure of the Aib peptides. In the packing mode of **7**, two intermolecular H-bonds are observed between the H−N(1) peptide donor and the C(4′)=O(4′) O-atom of a symmetry-related molecule (x, y, $z+1$) with a N(1)···O(4′) distance of 2.95 Å, and also between H−N(2) and C(5′)=O(5′) of a symmetry-related molecule (x, y, $z+1$) with a N(2)···O(5′) distance of 3.10 Å along the *c* direction. Thus, the chains of intermolecular H-bonded molecules are of the (···*P*···*P*···*P*···) mode in the head-to-tail alignment.

Solution Conformational Analysis. First, the preferred conformations of the heteropeptides **4** and **7** were analyzed by FT-IR spectroscopy at various concentrations in the range 0.5–10.0 mM ($CDCl_3$). In the case of the 3_{10}-helical structure, the two NH

groups of the residues at the N-terminus are free or intermolecularly H-bonded to another molecule, whereas all NH functional groups are intramolecularly H-bonded to the carbonyl groups of the same amino-acid residues in the planar C_5 conformation. *Fig. 4* shows the IR absorption spectra in the 3500–3250 cm^{-1} region at a peptide concentrations of 1.0 mM. In both heteropeptides **4** and **7**, the bands in the 3420–3450 cm^{-1} region, which are assigned to free (solvated) peptide NH groups or to amide NH groups with a weak intramolecular H-bond of the C–F···H–N type, and the strong bands at 3350–3375 cm^{-1}, which are assigned to peptide NH groups with N–H···O=C intramolecular H-bonds of different strength, are observed, but the band at 3380–3415 cm^{-1}, which is typical for the planar C_5 conformation, is not observed. The relative intensity of the bands in the 3420–3450 cm^{-1} region increases gradually with decreasing peptide concentration. The solution IR spectra of **4** and **7** are very similar to those of homopeptides CF_3CO-(Aib)$_n$-OEt with the 3_{10}-helical structure, but differ from those of homopeptide CF_3CO-(Deg)$_n$-OEt [5] or CF_3CO-[(*S*)-Beg)]$_n$-OEt [11] with the fully planar C_5 conformation.

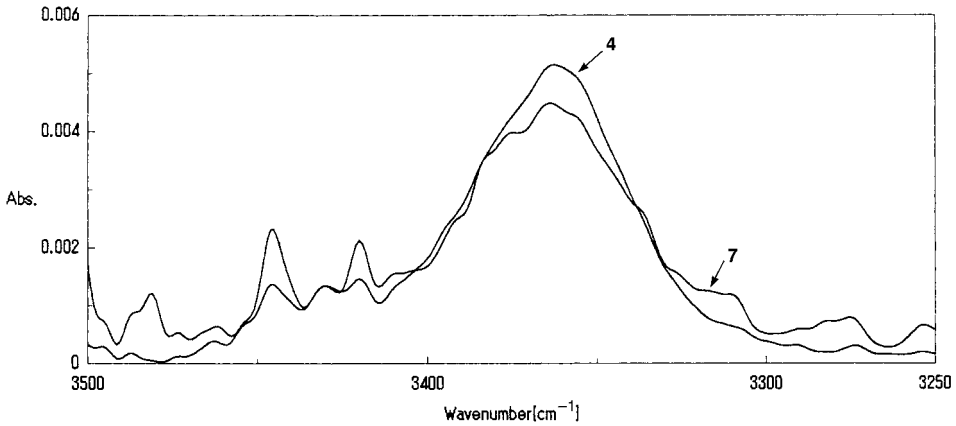


Fig. 4. *FT-IR Absorption spectra* (3500–3250 cm^{-1} region) *of the* CF_3CO-*[(*S*)-Beg]-(Aib)$_4$-OEt* (**4**) *and* CF_3CO-*(Aib)$_2$-[(*S*)-Beg]-(Aib)$_2$-OEt* (**7**) *in* $CDCl_3$ *solution*. Peptide concentration 1.0 mM.

Also, the CD spectra were measured to determine the global secondary structure. At a 1.0 mM concentration of heteropeptide **4** or **7** in 2,2,2-trifluoroethanol, the CD spectra exhibit the characteristic peaks for the helix, *i.e.* the positive maxima at 219 and 211 nm and the negative maximum at 197 nm [16] (*Fig. 5*). Surprisingly, these CD spectra seem to suggest that the dominant conformation of the heteropeptides is a left-handed (*M*) helix in CF_3CH_2OH solution (*vide supra:* the sense of helicity in **4** was both (*P*) and (*M*) in the solid state, and that in **7** was (*P*)). These CD spectra are slightly different from the typical CD spectrum of the 3_{10}-helical peptides prepared from chiral α-methylated α,α-disubstituted amino acids [16]. This may be attributed to the fact that the main-chain length of the peptides was insufficient for the examination of conformation by CD spectra, or that several conformations exist in CF_3CH_2OH solution, including a left-handed (*M*) helical structure.

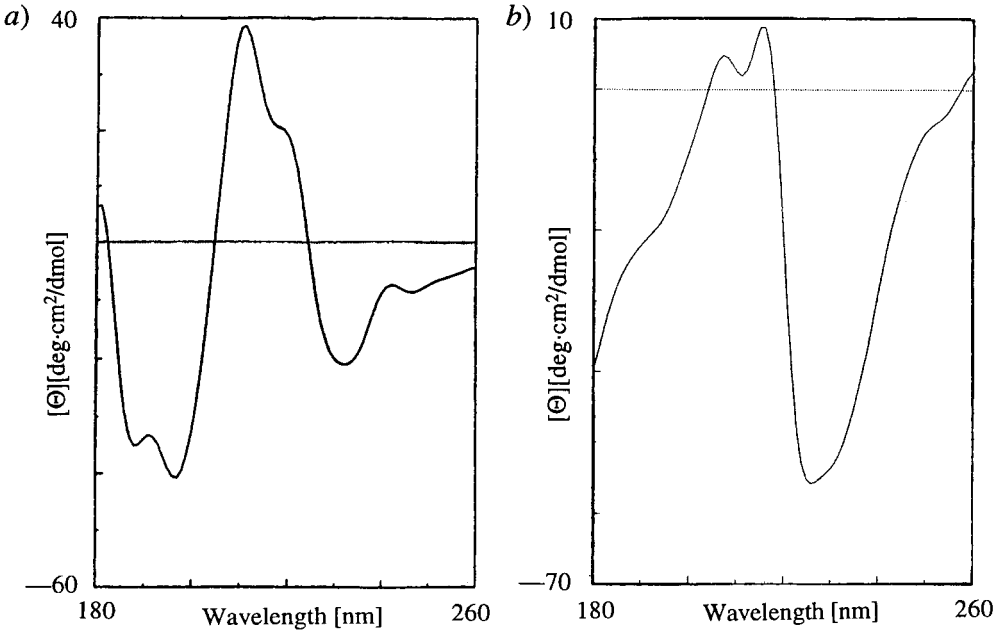


Fig. 5. *CD Spectra of* a) CF_3CO-[(S)-*Beg*]-$(Aib)_4$-*OEt* (**4**) *and* b) CF_3CO-$(Aib)_2$-[(S)-*Beg*]-$(Aib)_2$-*OEt* (**7**) *in* CF_3CH_2OH *solution*. Peptide concentration 1.0 mM.

We then measured the ^{1}H-NMR spectra to obtain more detailed information on the conformation of the heteropeptides **4** and **7**. In the ^{1}H-NMR spectra of both peptides **4** and **7** in $CDCl_3$, only the trifluoroacetamide NH signals at the N-terminus are unambiguously determined by their high-field positions (δ 6.57 (br. *s*, 1 H) in **4**, and δ 6.43 (br. *s*, 1 H) in **7**). The precise assignments of the remaining four NH protons can not be made. The NH chemical shifts of heteropeptides **4** and **7** are shifted to higher fields on dilution in $CDCl_3$ (concentration 10.0 to 0.5 mM). Solvent perturbation experiments were carried out by addition of the strong H-bond acceptor solvent DMSO (0–10% (*v*/*v*); *Fig. 6*, *a* and *b*) or the paramagnetic free radical 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO; $0-5\cdot10^{-2}$% (*w*/*v*); *Fig. 6 c* and *d*). In both heteropeptides **4** and **7**, two NH proton signals are very sensitive (solvent-exposed NH protons) to the addition of DMSO and TEMPO. These results are in agreement with the finding that the two intermolecular H-bonds of the 3_{10}-helical structure formed by these peptides are disrupted on addition of DMSO or TEMPO.

At room temperature, the ^{1}H-NMR spectra of both peptides **4** and **7** exhibit the number of signals expected for either a single dominant conformation or for several conformations in fast exchange. However, the X-ray analysis of heteropeptide **4** revealed that two conformations, *i.e.*, a (*P*) helix and a (*M*) helix, exist in the solid state. Therefore, we measured the ^{1}H-NMR spectra of **4** and **7** at lower temperatures. As the temperature is lowered from 30 to $-55°$, broadening of all signals of **7** occurs (*Fig. 7*) *i.e.*, several different conformations of **7** exist in $CDCl_3$ solution. No peak splitting is observed at $-55°$, as the exchange between the conformations is too fast for detection

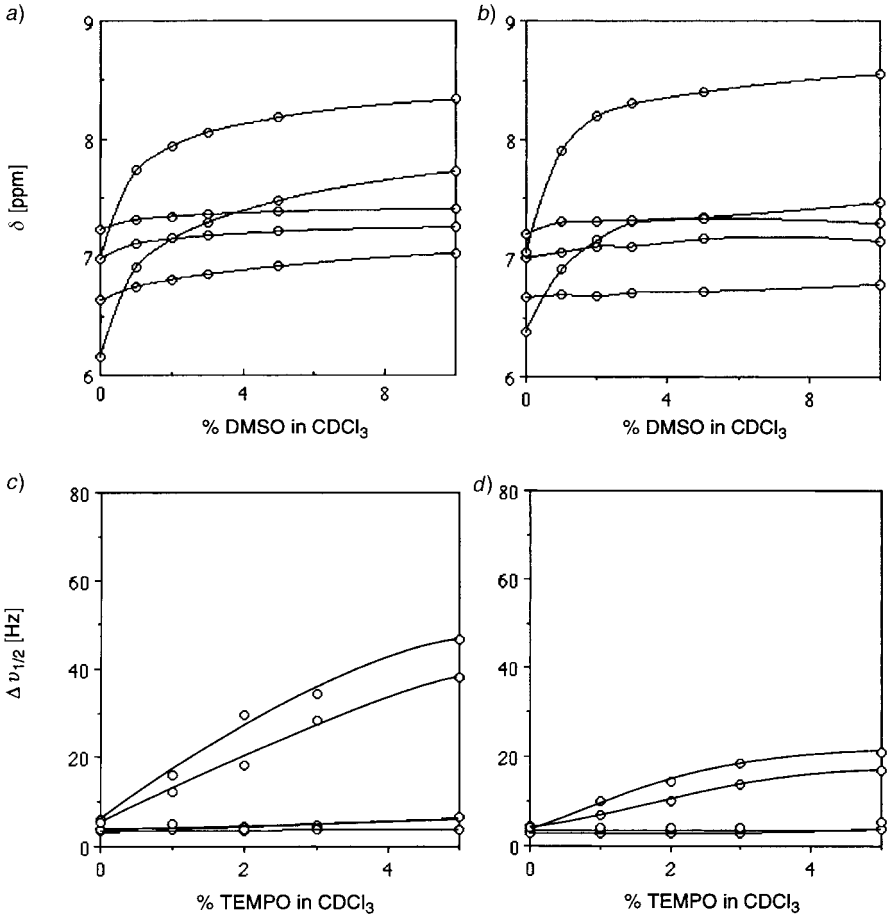


Fig. 6. a) *Plots of NH chemical shifts in the ^{1}H-NMR spectra of CF_3CO-[(S)-Beg]-$(Aib)_4$-OEt* (**4**; 1.0 mM) *and* b) *of CF_3CO-$(Aib)_2$-[(S)-Beg]-$(Aib)_2$-OEt* (**7**; 1.0 mM) *as a function of increasing percentages of DMSO* (*v*/*v*) *added to the $CDCl_3$ solution*; c) *plots of the bandwidth of the NH protons of CF_3CO-[(S)-Beg]-$(Aib)_4$-OEt* (**4**; 2.0 mM), *and* d) *of CF_3CO-$(Aib)_2$-[(S)-Beg]-$(Aib)_2$-OEt* (**7**; 2.0 mM) *as a function of increasing percentages of TEMPO* (*w*/*v*) *added to the $CDCl_3$ solution*

by 600-MHz ^{1}H-NMR. Measurements at lower temperatures than $-55°$ or elongation of the peptide main-chain by the addition of more Aib residues might provide evidence for the existence of several conformations [9]. The ^{1}H-NMR spectra of **4** at lower temperatures ($30° \rightarrow -55°$) also exhibit signal broadening.

Computational Analysis [17]. We also studied the conformations by molecular-mechanics calculations with MacroModel [18]. In the case of heteropeptide **4**, the minimum-energy conformations are the 3_{10}-helical structures. Two different conformations, *i.e.* a (*P*) 3_{10} helix (conformation *A*; 0 kcal/mol) and a (*M*) 3_{10} helix (conformation *B*; +0.46 kcal/mol) are within 3.0 kcal/mol of the global minimum energy. These conformations are very similar to those determined for **4** by the X-ray crystal-structure analyses, as shown by their superimposition in *Fig. 8*, *a* and *b*. In the case of **7**, the

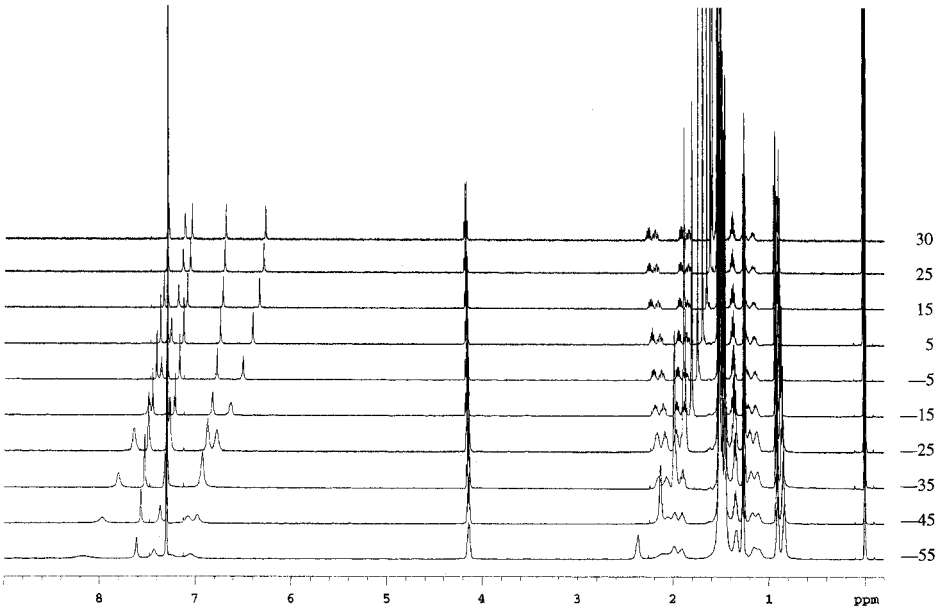


Fig. 7. *^{1}H-NMR Spectra* (600 MHz, $CDCl_3$) *of heteropeptide* **7** *at ten different temperatures* (30 to −55°)

calculations afforded four minimum-energy conformations with relative energies less than 3.0 kcal/mol. The most stable conformation calculated is not a precise (*P*) 3_{10} helix (conformation *D*), but a distorted (*P*) 3_{10} helix (conformation *C*). Conformation *C* is more stable than conformation *D* by 1.27 kcal/mol. The torsion angles ϕ_1 and ψ_1 of the Aib-1 residue at the N-terminus in the conformations *C* and *E* display not a 3_{10} helix but a C_5 conformation due to the existence of (*S*)-Beg at the center of peptide **7** (*Table 3*).

Fig. 8. *Superimposition of the conformations determined by X-ray analysis* (in red) *and of the calculated* (MacroModel) *minimal-energy conformations* (in green): a) *molecule* **B** (*P*) *of* CF_3CO-[(S)-*Beg*]-$(Aib)_4$-*OEt* (**4**) *and calculated conformation* A; b) *molecule* **A** (*M*) *of* **4** *and calculated conformation* B; *and* c) CF_3CO-$(Aib)_2$-[(S)-*Beg*]-$(Aib)_2$-*OEt* (**7**) *and calculated conformation* D

The calculation of the heteropeptide **7** reveals that the right-handed (*P*) helices are more stable than the left-handed (*M*) helix. The conformations *C* and *E* are very similar, but the orientation of the ester function at the *C*-terminus is different. The conformation *D* (*P*) 3_{10} helix) is more stable than conformation *F* ((*M*) 3_{10} helix) by 1.03 kcal/mol. Superimposition of the (*P*) 3_{10}-helical structure of **7** determined by the X-ray analysis and the calculated conformation *D* shows that these two conformations are very similar (*Fig. 8,c*).

Table 3. *Selected Calculated* (MacroModel) *Torsion Angles* ω, ϕ, ψ, *and* χ[a]) [°] *for the Heteropeptides* **4** *and* **7**

	CF_3CO-[(*S*)-Beg]-(Aib)$_4$-OEt (**4**)		CF_3CO-(Aib)$_2$-[(*S*)-Beg]-(Aib)$_2$-OEt (**7**)			
	Conformation *A* (*P*) 3_{10} helix	Conformation *B* (*M*) 3_{10} helix	Conformation *C* (*P*) distorted 3_{10} helix	Conformation *D* (*P*) 3_{10} helix	Conformation *E* (*P*) distorted 3_{10} helix	Conformation *F* (*M*) 3_{10} helix
Energy	0 kcal/mol	+0.46 kcal/mol	0 kcal/mol	+1.27 kcal/mol	+1.38 kcal/mol	+2.30 kcal/mol
ω_0	−178.9	178.6	178.8	179.6	179.6	−179.3
ϕ_1	−52.1	52.4	179.0[b])	−47.1	178.4[b])	47.0
ψ_1	−26.1	25.6	−170.6[b])	−35.0	−166.2[b])	34.3
ω_1	174.7	−174.1	−179.9	179.7	178.1	−179.8
ϕ_2	−45.4	45.1	−47.8	−45.7	−48.2	45.7
ψ_2	−32.5	33.0	−34.5	−32.4	−34.0	31.9
ω_2	178.4	−178.6	−179.5	−177.7	−179.9	178.1
ϕ_3	−48.5	48.7	−50.4	−51.8	−50.4	51.5
ψ_3	−26.6	26.6	−25.8	−25.2	−23.4	25.2
ω_3	174.2	−174.3	175.1	−174.6	172.6	−174.4
ϕ_4	−46.0	46.1	−47.6	−46.3	−43.5	46.0
ψ_4	−33.4	33.4	−32.3	−33.1	−37.6	33.2
ω_4	−170.7	170.8	−170.4	−170.5	179.6	170.8
ϕ_5	45.0	−44.8	44.9	44.9	168.0	−44.9
ψ_5	42.1	−42.0	42.1	42.1	−66.2	−42.2
ω_5	−179.1	178.8	−179.0	−179.0	−179.0	179.1
χ_1^e	51.5	−62.4	–	–	–	–
χ_1^b	63.6	−51.0	–	–	–	–
χ_3^e	–	–	51.1	52.8	51.6	−70.5
χ_3^b	–	–	66.0	73.3	66.9	−52.2

[a]) The subscripts e and b refer to the ethyl and butyl side chain, respectively. [b]) The torsion angles ϕ_1 and ψ_1 of the Aib-1 residue are typical for a C_5 conformation in the case of conformations *C* and *E* of **7**.

Discussion. – The conformations of heteropeptides **4** and **7** containing (*S*)-Beg in Aib sequences are 3_{10}-helical structures both in the solid state and in solution, although the homopeptide prepared from (*S*)-Beg shows a fully planar C_5 conformation [11]. Both right-handed (*P*) and left-handed (*M*) 3_{10}-helical structures exist in a 1:1 ratio with the (···*P*···*M*···*P*···*M*···) mode in the head-to-tail alignment in the crystals of **4**, and only the right-handed (*P*) 3_{10}-helical structure exists in the crystals of **7**. In solution, both heteropeptides seem to be folded into the 3_{10}-helical structure because the IR spectra and the results of ^{1}H-NMR experiments with DMSO or TEMPO are similar to those of helical peptides. The sense of the helicity dominantly formed in solution is left-handed (*M*) because the CD spectra of **4** and **7** show positive maxima at 219 and 211 nm and the negative maximum at 197 nm. The dominant conformation in solution

seems to be different from that in the solid state determined by X-ray analysis; this is confirmed by variable-temperature ^{1}H-NMR spectra. The broadening of the ^{1}H-NMR signals at low temperature means that several conformations, probably (*P*) and (*M*) 3_{10}-helical structures, exist as stable conformations in equilibrium, and at room temperature they undergo a fast exchange. The molecular-mechanics calculations of **4** and **7** support the existence of both (*P*) and (*M*) 3_{10} helices. The calculated energy differences of these two structures are *ca.* 0.5 kcal/mol in **4** and *ca.* 1 kcal/mol in **7**.

Conclusions. – The preferred conformation of the heteropentapeptides **4** and **7** containing an (*S*)-Beg in Aib sequences is a 3_{10}-helical structure, whereas the conformation of (*S*)-Beg homopeptides is a fully planar C_5 conformation. The ^{1}H-NMR measurements and molecular-mechanics calculations suggest that several stable conformations exist in solution. The results presented here show that the propensity of (*S*)-Beg is to adopt a planar C_5 conformation in the homopeptides, but the introduction of one (*S*)-Beg into Aib pentapeptides does not drastically change the 3_{10}-helical structure formed by Aib residues, just as the introduction of diethylglycine or dipropylglycine could not change it [19].

Experimental Part

General. Aib was purchased from *Tokyo Kasei Co.*, and the derivatives of (*S*)-Beg were prepared according to our previous report [11]. Optical rotations $[\alpha]_D$: *Jasco DIP-316* polarimeter, 1.0-dm cell. Circular dichroism (CD) spectra: *Jasco J-720W* spectropolarimeter; 10.0-mm cell. IR Spectra: *Jasco-A-100* spectrometer for conventional measurement (KBr and neat), and *Jasco FT-IR-420* spectrophotometer for the soln. ($CDCl_3$) method, 0.1-mm NaCl cell. ^{1}H-NMR Spectra: at 270 MHz (*Jeol GX-270*), 500 MHz (*Varian Unity-500P*), or 600 MHz (*Varian Unity-600P*). EI-MS and FAB-MS: *Jeol JMS-610 H* or *Jeol JMS-SX-102* spectrometer; in *m*/*z*. Elemental analyses were performed in the Analytical Center of the Faculty of Science at Kyushu University.

Ethyl [(Benzyloxy)carbonyl]-dimethylglycyl-dimethylglycinate (= *Ethyl 2-{[2-{[(Benzyloxy)carbonyl]-amino}-2-methyl-1-oxopropyl]amino}-2-methylpropanoate*; Z-Aib-Aib-OEt; **1**) [15]. A mixture of Aib (6.0 g, 58.3 mmol) and $SOCl_2$ (6.32 ml, 87.5 mmol) in EtOH (200 ml) was refluxed for 12 h. After removal of EtOH, the residue was diluted with 5% aq. $NaHCO_3$ soln., the soln. extracted with $CHCl_3$, and the extract dried (Na_2SO_4) and evaporated: crude Aib-OEt (9.85 g, quant.). IR (neat): 3400, 3320, 1730. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.16 (*q*, *J* = 7.1, 2 H); 1.71 (br. *s*, 2 H); 1.34 (*s*, 6 H); 1.28 (*t*, *J* = 7.1, 3 H).

A mixture of Aib-OEt (1.27 g, 9.71 mmol), Z-Aib (2.77 g, 11.7 mmol), and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDC; 2.24 g, 11.7 mmol) in MeCN (30 ml) was stirred at 50° for 12 h. After evaporation of MeCN, the residue was diluted with $CHCl_3$, the org. phase washed with 5% aq. $NaHCO_3$ soln, 3% HCl soln. and brine, dried ($MgSO_4$), and evaporated, and the oily residue purified by CC (SiO_2): **1** (1.55 g, 46%). Colorless crystals. M.p. 96.0 – 97.0° (from $CHCl_3$/hexane). IR (KBr): 3350, 3290, 3260, 1700, 1640. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.30 – 7.36 (*m*, 5 H); 6.91 (br. *s*, 1 H); 5.34 (br. *s*, 1 H); 5.10 (*s*, 2 H); 4.17 (*q*, *J* = 7.1, 2 H); 1.52 (*s*, 6 H); 1.51 (*s*, 6 H); 1.25 (*t*, *J* = 7.1, 3 H). FAB-MS: 351 ($[M+H]^+$).

Ethyl [(Benzyloxy)carbonyl]-dimethylglycyl-dimethylglycyl-dimethylglycinate (= *Ethyl 2-{[2-{[2-{[(Benzyloxy)carbonyl]amino}-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl]amino}-2-methylpropanoate*; Z-Aib-Aib-Aib-OEt; **2**) [15]. A mixture of **1** (1.00 g, 2.86 mmol) and 5% Pd/C (400 mg) in MeOH (40 ml) was vigorously stirred under H_2 for 5 h. The Pd-catalyst was filtered off, the filtrate evaporated, and the oily residue purified by CC (SiO_2, 5% MeOH/$CHCl_3$): amino derivative (593 mg, 96%). IR (neat): 3350, 1740, 1670. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.03 (br. *s*, 1 H); 4.18 (*q*, *J* = 7.1, 2 H); 1.55 (br. *s*, 2 H); 1.53 (*s*, 6 H); 1.34 (*s*, 6 H); 1.26 (*t*, *J* = 7.1, 3 H). FAB-MS: 217 ($[M+H]^+$).

The soln. of the amino derivative (593 mg, 2.75 mmol), Z-Aib (782 mg, 3.30 mmol), EDC (303 mg, 3.30 mmol), and HOBt (446 mg, 3.30 mmol) in CH_2Cl_2 (40 ml) was stirred at r.t. for 36 h. The soln. was diluted with $CHCl_3$, washed with cold 3% HCl soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the white solid purified by CC (SiO_2, 30% AcOEt/hexane): **2** (681 mg, 57% from **1**). Colorless crystals. M.p.

125.0–126.0° (from $CHCl_3$/hexane). IR (KBr): 3400, 3370, 3320, 1710, 1690, 1650. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.33–7.39 (*m*, 5 H); 7.21 (br. *s*, 1 H); 6.37 (br. *s*, 1 H); 5.19 (br. *s*, 1 H); 5.11 (*s*, 2 H); 4.16 (*q*, *J* = 7.1, 2 H); 1.50 (*s*, 6 H); 1.48 (*s*, 6 H); 1.43 (*s*, 6 H); 1.25 (*t*, *J* = 7.1, 3 H). FAB-MS: 458 ($[M+Na]^+$), 436 ($[M+H]^+$).

Ethyl [(Benzyloxy)carbonyl]-dimethylglycyl-dimethylglycyl-dimethylglycyl-dimethylglycinate (= *Ethyl 2-{{2-{{2-{{2-{[(Benzyloxy)carbonyl]amino}-2-methyl-1-oxopropyl}amino}-2-methyl-1-oxopropyl}amino}-2-methyl-1-oxopropyl]amino}-2-methylpropanoate*; Z-Aib-Aib-Aib-Aib-OEt; **3**) [15]. Tetrapeptide **3** was prepared similarly as described for **2**. Purification by CC (SiO_2, 5% MeOH/$CHCl_3$) afforded **3** (65% from **2**). Colorless crystals. M.p. 133.0–134.0° (from $CHCl_3$/hexane). IR (KBr): 3340, 1710, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.37 (br. *s*, 1 H); 7.34–7.36 (*m*, 5 H); 7.15 (br. *s*, 1 H); 6.43 (br. *s*, 1 H); 5.73 (br. *s*, 1 H); 5.11 (*s*, 2 H); 4.12 (*q*, *J* = 7.1, 2 H); 1.50 (*s*, 6 H); 1.47 (*s*, 6 H); 1.46 (*s*, 6 H); 1.33 (*s*, 6 H); 1.21 (*t*, *J* = 7.1, 3 H). FAB-MS: 543 ($[M+Na]^+$), 521 ($[M+H]^+$).

*Ethyl (Trifluoroacetyl)-(*S*)-2-butyl-2-ethylglycyl-dimethylglycyl-dimethylglycyl-dimethylglycyl-dimethylglycinate* (= *Ethyl 2-{{2-{{2-{{2-{{(2*S*)-2-Ethyl-1-oxo-2-[(trifluoroacetyl)amino]hexyl}amino}-2-methyl-1-oxopropyl}amino}-2-methyl-1-oxopropyl}amino}-2-methyl-1-oxopropyl}amino}-2-methylpropanoate* CF_3CO-[(*S*)-Beg]-Aib-Aib-Aib-Aib-OEt; **4**). A mixture of **3** (159 mg, 306 μmol) and 5% Pd/C (50 mg) in MeOH (15 ml) was vigorously stirred under H_2 for 16 h. The Pd-catalyst was filtered off, the filtrate evaporated, and the oily residue passed through a short silica-gel column: amino derivative. A soln. of the latter, CF_3CO-(*S*)-Beg (76 mg, 298 μmol), and EDC (72 mg, 372 μmol) in MeCN (15 ml) was refluxed for 3 days. After evaporation, the residue was diluted with $CHCl_3$, the soln. washed with 3% HCl soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the white solid purified by CC (SiO_2, 60% AcOEt/hexane): **4** (107 mg, 69%). Colorless crystals. M.p. 201–202° (from MeOH). $[\alpha]_D^{24} = +0.41$ (*c* = 1.05, $CHCl_3$). IR (KBr): 3300, 1700, 1650, 1630. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.46 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 7.13 (br. *s*, 1 H); 6.73 (br. *s*, 1 H); 6.57 (br. *s*, 1 H); 4.13 (*q*, *J* = 7.1, 2 H); 2.06–2.23 (*m*, 2 H); 1.77–1.98 (*m*, 2 H); 1.51 (*s*, 6 H); 1.49 (*s*, 12 H); 1.45 (*s*, 6 H); 1.23 (*t*, *J* = 7.1, 3 H); 1.12–1.43 (*m*, 4 H); 0.84–0.94 (*m*, 6 H). FAB-MS: 646 ($[M+Na]^+$), 624 ($[M+H]^+$). Anal. calc. for $C_{28}H_{48}F_3N_5O_7$: C 53.92, H 7.76, N 11.23; found: C 53.83, H 7.70, N 10.83.

*Ethyl (Trifluoroacetyl)-(*S*)-2-butyl-2-ethylglycyl-dimethylglycyl-dimethylglycinate* (= *Ethyl 2-{{2-{{(2*S*)-2-Ethyl-1-oxo-2-[(trifluoroacetyl)amino]hexyl}amino}-2-methyl-1-oxopropyl}amino}-2-methylpropanoate*; CF_3CO-[(*S*)-Beg]-Aib-Aib-OEt; **5**). Tripeptide **5** was prepared from **1** and CF_3CO-(*S*)-Beg similarly as described for **4**. Purification by CC (SiO_2, 30% AcOEt/hexane) afforded **5** (89%). Colorless crystals. M.p. 114.0–115.0° (from $CHCl_3$/hexane). $[\alpha]_D^{28} = +12.5$ (*c* = 1.03, $CHCl_3$). IR (Kbr): 3370, 3240, 1710, 1690, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.94 (br. *s*, 1 H); 7.08 (br. *s*, 1 H); 6.58 (br. *s*, 1 H); 4.22 (*q*, *J* = 7.1, 2 H); 2.53–2.69 (*m*, 2 H); 1.49–1.70 (*m*, 2 H); 1.64 (*s*, 3 H); 1.63 (*s*, 3 H); 1.59 (*s*, 6 H); 0.98–1.35 (*m*, 4 H); 1.28 (*t*, *J* = 7.1, 3 H); 0.85 (*t*, *J* = 7.3, 3 H); 0.77 (*t*, *J* = 7.4, 3 H). FAB-MS: 476 ($[M+Na]^+$), 454 ($[M+H]^+$). Anal. calc. for $C_{20}H_{34}F_3N_3O_5$: C 52.97, H 7.56, N 9.27; found: C 52.99, H 7.50, N 9.26.

*Ethyl (Trifluoroacetyl)-dimethylglycyl-(*S*)-2-butyl-2-ethylglycyl-dimethylglycyl-dimethylglycinate* (= *Ethyl 2-{{2-{{(2*S*)-2-Ethyl-2-{{2-methyl-1-oxo-2-[(trifluoroacetyl)amino]propyl}amino}-1-oxohexyl}amino}-2-methyl-1-oxopropyl}amino}-2-methylpropanoate*; CF_3CO-Aib-[(*S*)-Beg]-Aib-Aib-OEt; **6**). $NaBH_4$ (54 mg, 1.41 mmol) was added portionwise to the stirred soln. of **5** (319 mg, 704 μmol) in EtOH (10 ml) at 0°, and the mixture was stirred for 8 h. The reaction was quenched with 1% HCl soln. (35 ml), and then EtOH was evaporated. The mixture was diluted with 5% aq. $NaHCO_3$ soln., extracted with AcOEt, the extract dried ($MgSO_4$) and evaporated, and the residue purified by CC (SiO_2, 1% MeOH/$CHCl_3$): amino derivative (120 mg, 99% based on 52% recovery of **5**). A soln. of the amino derivative (120 mg, 271 μmol), CF_3CO-Aib (145 mg, 728 μmol), and EDC (140 mg, 730 μmol) in MeCN (10 ml) was refluxed for 36 h. After evaporation, the residue was diluted with $CHCl_3$, the soln. washed with 3% HCl soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the white solid purified by CC (SiO_2, 3% MeOH/$CHCl_3$): **6** (256 mg, 98%). Colorless crystals. M.p. 186.0–187.0° (from $CHCl_3$/hexane). $[\alpha]_D^{26} = +4.00$ (*c* = 1.00, $CHCl_3$). IR (KBr): 3400, 3350, 1720, 1680, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.78 (br. *s*, 1 H); 6.98 (br. *s*, 1 H); 6.96 (br. *s*, 1 H); 6.79 (br. *s*, 1 H); 4.19 (*q*, *J* = 7.1, 2 H); 2.26–2.41 (*m*, 2 H); 1.70 (*s*, 3 H); 1.69 (*s*, 3 H); 1.59 (*s*, 3 H); 1.58 (*s*, 3 H); 1.56 (*s*, 6 H); 1.45–1.79 (*m*, 2 H); 1.26 (*t*, *J* = 7.1, 3 H); 1.00–1.33 (*m*, 4 H); 0.86 (*t*, *J* = 7.3, 3 H); 0.76 (*t*, *J* = 7.4, 3 H). FAB-MS: 561 ($[M+Na]^+$), 539 ($[M+H]^+$). Anal. calc. for $C_{24}H_{41}F_3N_4O_6$: C 53.52, H 7.67, N 10.40; found: C 53.46, H 7.62, N 10.37.

*Ethyl (Trifluoroacetyl)-dimethylglycyl-dimethylglycyl-(*S*)-2-butyl-2-ethylglycyl-dimethylglycyl-dimethylglycinate* (= *Ethyl 2-{{2-{{(2*S*)-2-Ethyl-2-{{2-methyl-2-{{2-methyl-1-oxo-2-[(trifluoroacetyl)amino]propyl}amino}-1-oxopropyl}amino}-1-oxohexyl}amino}-2-methyl-1-oxopropyl}amino}-2-methylpropanoate*; CF_3CO-Aib-Aib-[(*S*)-Beg]-Aib-Aib-OEt; **7**). Pentapeptide **7** was prepared from **6** and CF_3CO-Aib, similarly as described for **6**. Purification by CC (SiO_2, 3% MeOH/$CHCl_3$) afforded **7** (69%). Colorless crystals. M.p. 227–228° (from

$CHCl_3$/hexane). $[\alpha]_D^{29} = +15.01$ ($c = 1.06$, $CHCl_3$). IR (KBr): 3350, 1720, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.41 (br. *s*, 1 H); 7.30 (br. *s*, 1 H); 7.07 (br. *s*, 1 H); 6.69 (br. *s*, 1 H); 6.43 (br. *s*, 1 H); 4.13 (*q*, $J = 7.1$, 2 H); 1.81–1.98 (*m*, 2 H); 1.63 (*s*, 3 H); 1.62 (*s*, 3 H); 1.51 (*s*, 12 H); 1.50 (*s*, 6 H); 1.45–1.67 (*m*, 2 H); 1.23 (*t*, $J = 7.1$, 3 H); 1.08–1.33 (*m*, 4 H); 0.87 (*t*, $J = 7.1$, 3 H); 0.79 (*t*, $J = 7.4$, 3 H). FAB-MS: 646 ($[M + Na]^+$), 624 ($[M + H]^+$). Anal. calc. for $C_{28}H_{48}F_3N_5O_7$: C 53.92, H 7.76, N 11.23; found: C 53.83, H 7.74, N 11.04.

X-Ray Crystal-Structure Determination[1]). Both crystals **4** and **7** were grown from $CHCl_3$/MeOH. Data collection was performed on a *Rigaku-AFC5R* diffractometer, Ni-foil-filtered CuK_α radiation. Crystal and collection parameters are listed in *Table 4*. Both crystals remained stable at r.t. during the X-ray data collection. The structures were solved by direct methods with SIR92 [20] and expanded by *Fourier* techniques [21]. All non-H-atoms were given anisotropic thermal parameters and H-atoms included in calculated positions given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of **4** gave an *R* factor of 0.065 ($R_w = 0.048$) based on 3202 ($I > 2.0\ \sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.15 and -0.16 eÅ^{-3}. The *R* factor of **7** was 0.046 ($R_w = 0.044$) for 2425 data ($I > 3.0\ \sigma(I)$), and the largest peak and hole in the final difference *Fourier* map were 0.13 and -0.12 eÅ^{-3}. All calculations were performed by means of the teXsan [22] crystallographic package.

Table 4. *Crystal and Diffraction Parameters of the Heteropeptides* **4** *and* **7**

	CF_3CO-[(*S*)-Beg]-(Aib)$_4$-OEt (**4**)	CF_3CO-(Aib)$_2$-[(*S*)-Beg]-(Aib)$_2$-OEt (**7**)
Empirical formula	$C_{56}H_{96}F_6N_{10}O_{14}$	$C_{28}H_{48}F_3N_5O_7$
M_r	1247.42	623.71
Crystal dimensions [mm]	$0.30 \times 0.20 \times 0.20$	$0.30 \times 0.20 \times 0.20$
Crystal system	monoclinic	monoclinic
Lattice parameters		
a, *b*, *c* [Å]	9.821, 17.599, 20.517	10.879, 13.296, 12.111
α, β, γ [°]	90, 91.67, 90	90, 104.610, 90
V [Å^3]	3544.7	1695.1
Space group	$P2_1$	$P2_1$
Z value	2	2
D_{calc} [g/cm^3]	1.169	1.222
μ (CuK_α) [cm^{-1}]	7.95	8.32
No. of observations	3202 ($I > 2.0\ \sigma(I)$)	2425 ($I > 3.0\ \sigma(I)$)
No. of variables	776	410
R, R_w	0.065, 0.048	0.046, 0.044
Solvent of crystallization	$CHCl_3$/MeOH	$CHCl_3$/MeOH

Molecular-Mechanics Calculations. Conformational-energy calculations were performed with the package of *MacroModel* Ver. 6.5 [18] on a *SGI O$_2$* workstation. The parameters used were as follows: conformational search, Monte Carlo Method; force field, AMBER*; more than 15000 structures were minimized; solvent, water. The fully planar C_5 conformations of the heteropeptides **4** and **7** were used as the initial conformations for the calculations. The two conformations *A* (0 kcal/mol) and *B* (+0.46 kcal/mol) were obtained as the global minimum-energy conformations of **4** within 3.0 kcal/mol. The four conformations *C* (0 kcal/mol), *D* (+1.27 kcal/mol), *E* (+1.38 kcal/mol), and *F* (+2.30 kcal/mol) were calculated within 3.0 kcal/mol as the global minimum-energy conformations of **7**.

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[1]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-147462 and 147463. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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