Conformation of Peptides Containing a Chiral α-Ethylated α,α-Disubstituted α-Amino Acid: (*S*)-α-Ethylleucine (= (2*S*)-2-Amino-2-ethyl-4-methylpentanoic Acid) within Sequences of Dimethylglycine and Diethylglycine Residues

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

[a]) Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan (tel: +81-92-642-6604; fax: +81-92-642-6545; e-mail: mtanaka@phar.kyushu-u.ac.jp; suemune@phar.kyushu-u.ac.jp)

[b]) Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

An optically active (*S*)-α-ethylleucine ((*S*)-αEtLeu) as a chiral α-ethylated α,α-disubstituted α-amino acid was synthesized by means of a chiral acetal auxiliary of (*R*,*R*)-cyclohexane-1,2-diol. The chiral α-ethylated α,α-disubstituted amino acid (*S*)-αEtLeu was introduced into the peptides constructed from 2-aminoisobutyric acid (=dimethylglycine, Aib), and also into the peptide prepared from diethylglycine (Deg). The X-ray crystallographic analysis revealed that both right-handed (*P*) and left-handed (*M*) 3_{10}-helical structures exist in the solid state of CF_3CO-$(Aib)_2$-[(*S*)-αEtLeu]-$(Aib)_2$-OEt (**14**) and CF_3CO-[(*S*)-αEtLeu]-$(Deg)_4$-OEt (**18**), respectively. The IR, CD, and ^{1}H-NMR spectra indicated that the dominant conformation of pentapeptides **14** and CF_3CO-[(*S*)-αEtLeu]-$(Aib)_4$-OEt (**16**) in solution is a 3_{10}-helical structure, and that of **18** in solution is a planar C_5 conformation. The conformation of peptides was also studied by molecular-mechanics calculations.

Introduction. – Foldamers [1], especially, peptides constructed from nonproteinogenic amino acids, such as β-amino acid, γ-amino acid, and α,α-disubstituted amino acid have attracted much attention among organic, peptide, and medicinal chemists, because some peptide-foldamers form unique secondary structures, show novel biological activities [2], and can be used as a ruler for the design of molecular devices and catalysts [3].

Some α,α-disubstituted α-amino acids have been known as biologically active α-amino acids, components of peptaibol antibiotics, and meteoritic amino acids [4]. For the conformational studies of peptides containing α,α-disubstituted α-amino acids, 2-aminoisobutyric acid (=dimethylglycine, Aib) has been extensively used because its structure is very simple and achiral, and it is also found in natural antibiotics. Now, the Aib peptide is known to form a 3_{10}-helical structure [5]. On the other hand, the peptides derived from diethylglycine (Deg), and dipropylglycine are known to form a fully planar C_5 conformers [6]. Very recently, the groups of *Toniolo* and *Seebach* independently reported the conformation of peptides prepared from chiral α-methylated α,α-disubstituted α-amino acids (αMeAAs) [7]. They concluded that the conformation of peptides prepared from αMeAAs is the 3_{10}-helical structure both in solution and in the solid state, and the screw sense of helicity would be determined by the chiral quaternary C-atom of αMeAAs.

We have studied the conformation of peptides prepared from the chiral α-ethylated α,α-disubstituted amino acid (*S*)-butylethylglycine ((*S*)-Beg), and reported that (*S*)-Beg homopeptides form the fully planar C_5 conformers [8], and that heteropeptides containing an (*S*)-Beg within a sequence of Aib adopt the 3_{10}-helical structure both in solution and in the solid state [9]. In this paper, we describe the synthesis of heteropeptides containing the chiral α-ethylated α,α-disubstituted α-amino acid (*S*)-α-ethylleucine (=(*S*)-isobutylethylglycine = (2*S*)-2-amino-2-ethyl-4-methylpentanoic acid; (*S*)-αEtLeu) within sequences of Aib residues and Deg residues, and their conformational analyses[1]).

Results. – *Asymmetric Synthesis of (*S*)-α-Ethylleucine.* We synthesized (*S*)-α-ethylleucine by an asymmetric alkylation of the corresponding β-keto ester with (*R*,*R*)-cyclohexane-1,2-diol as a chiral auxiliary [11], and subsequent *Schmidt* rearrangement (*Scheme*) [12][13]. The chiral acetal **1**, derived from (*R*,*R*)-cyclohexane-1,2-diol and ethyl 2-ethylacetoacetate, was treated with LDA (5 equiv.), i-BuI (5 equiv.), and HMPA (5 equiv.) in THF at $-78°$ to room temperature to afford ethylated enol ether **2** in 63% yield. Removal of the cyclohexane-1,2-diol moiety in **2** by treatment with $BF_3 \cdot OEt_2$ in EtOH/H_2O gave β-keto ester **3** in 88% yield. The enantiomeric excess of **3** was determined to be $>95\%$ ee by ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$. The *Schmidt* rearrangement of **3** with NaN_3 and $MeSO_3H$ in refluxing $CHCl_3$ afforded α,α-disubstituted α-amino acid (+)-**4** in 40% yield, 20% of starting material was recovered. With respect to consumed **3**, the yield of (+)-**4** was 50%. The enantiomeric excess of (+)-**4** was confirmed to be $>95\%$ ee by the ^{1}H-NMR spectroscopy with the chiral shift reagent (+)-Eu(hfc)$_3$, with racemic (±)-**4** as a reference standard. The compound (+)-**4** was converted to the trifluoroacetyl αEtLeu **6** in 70% yield by hydrolysis with concentrated HCl and subsequent acylation with $(CF_3CO)_2O$. Also, the C-terminal protected αEtLeu **5** was obtained in 68% yield by treatment of (+)-**4** with concentrated HCl and subsequent esterification with H_2SO_4 in refluxing EtOH. For the determination of the absolute configuration of (+)-**4**, the N-protected αEtLeu **6** was coupled with (*S*)-Beg-OEt **7** [8] by means of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDC) in refluxing MeCN to afford dipeptide **8** in 36% yield. The X-ray crystallographic analysis of **8** provided the absolute configuration of (+)-**4** to be (*S*) [13] (*cf. Fig. 1*).

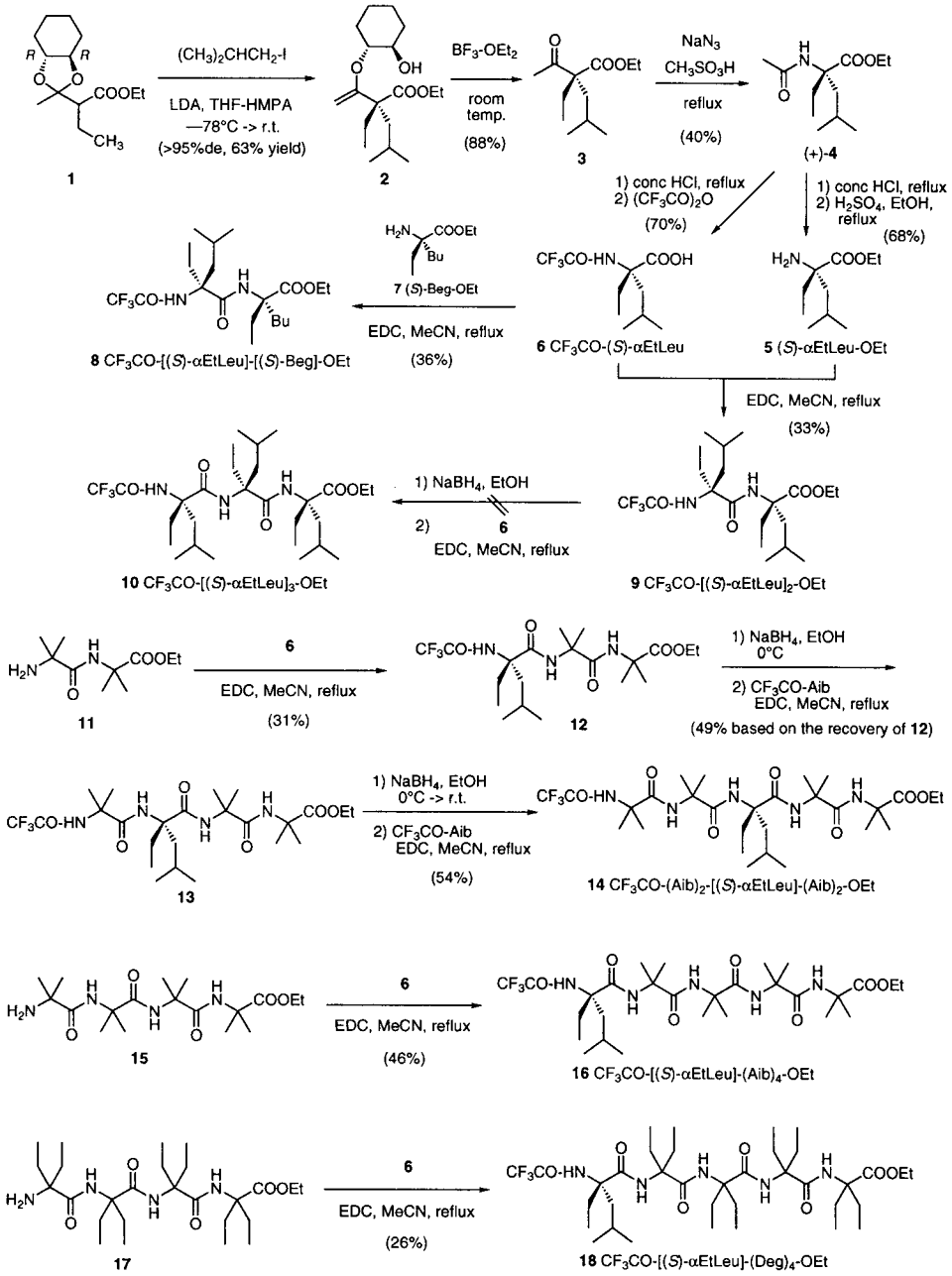
*Preparation of Peptides Bearing an (*S*)-αEtLeu within Sequences of Aib and Deg Residues.* First, we attempted to synthesize (*S*)-αEtLeu homopeptides. Dipeptide CF_3CO-[(*S*)-αEtLeu]$_2$-OEt (**9**) was easily prepared by coupling of **5** and **6** by treatment with EDC in refluxing MeCN in 33% yield. After deprotection of the CF_3CO group in **9** by $NaBH_4$ reduction, the coupling of the amine obtained and the acid **6** was attempted with EDC in refluxing MeCN. Unfortunately, no tripeptide **10** was isolated because of the steric hindrance of αEtLeu [8].

Next, we tried to synthesize heteropeptides containing an (*S*)-αEtLeu within Aib and Deg residues. We prepared three pentapeptides CF_3CO-(Aib)$_2$-[(*S*)-αEtLeu]-(Aib)$_2$-OEt (**14**), CF_3CO-[(*S*)-αEtLeu]-(Aib)$_4$-OEt (**16**), and CF_3CO-[(*S*)-αEtLeu]-

---

[1]) For reviews on the conformation of peptides prepared from α,α-disubstituted α-amino acids, see [5a–c][10].

Scheme



1 **2** **3** (+)-**4**

8 CF_3CO-[(*S*)-αEtLeu]-[(*S*)-Beg]-OEt

6 CF_3CO-(*S*)-αEtLeu **5** (*S*)-αEtLeu-OEt

10 CF_3CO-[(*S*)-αEtLeu]$_3$-OEt **9** CF_3CO-[(*S*)-αEtLeu]$_2$-OEt

11 **12**

13 **14** CF_3CO-(Aib)$_2$-[(*S*)-αEtLeu]-(Aib)$_2$-OEt

15 **16** CF_3CO-[(*S*)-αEtLeu]-(Aib)$_4$-OEt

17 **18** CF_3CO-[(*S*)-αEtLeu]-(Deg)$_4$-OEt

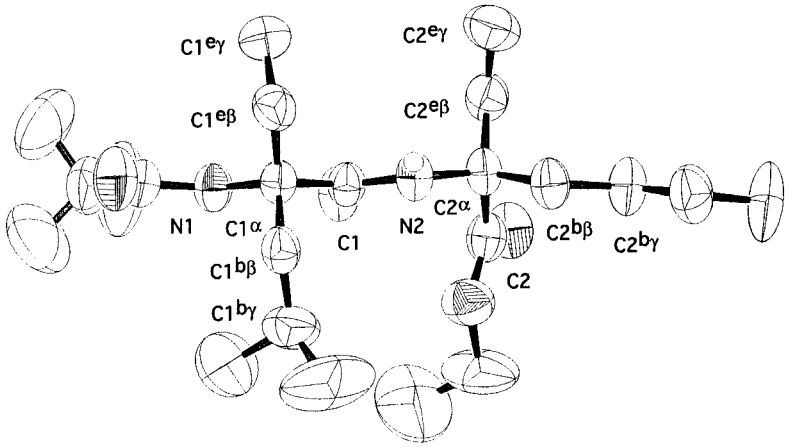


Fig. 1. *ORTEP Drawing of the molecular structure of CF_3CO-[(S)-αEtLeu]-[(S)-Beg]-OEt* (**8**) *with atom numbering* (ellipsoids at 50% probability)

$(Deg)_4$-OEt (**18**) by solution-phase methods. The heteropentapeptide CF_3CO-$(Aib)_2$-[(*S*)-αEtLeu]-$(Aib)_2$-OEt (**14**) was prepared starting from Aib dipeptide **11** [9]. Coupling of **11** and CF_3CO-(*S*)-αEtLeu (**6**) afforded tripeptide **12** in 31% yield. Deprotection of the CF_3CO group in **12** by $NaBH_4$ reduction at room temperature afforded complex mixtures, including an alcohol due to the reduction of the C-terminal ester function. Therefore, $NaBH_4$ reductive deprotection was carried out at 0° to give the desired amine, but large amounts of **12** were recovered. The coupling of the amine with CF_3CO-Aib gave tetrapeptide **13** in 49% yield. In a similar manner, the heteropentapeptide **14** was prepared from **13** and CF_3CO-Aib in 54% yield. The heteropentapeptide CF_3CO-[(*S*)-αEtLeu]-$(Aib)_4$-OEt (**16**) was prepared by coupling Aib tetrapeptide **15** [9] and CF_3CO-(*S*)-αEtLeu (**6**) by EDC in 46% yield, and CF_3CO-[(*S*)-αEtLeu]-$(Deg)_4$-OEt (**18**) was obtained from Deg tetrapeptide **17** [6d] in 26% yield.

Conformational Analysis in the Solid State. We determined the molecular and crystal structures of four terminally protected peptides, two dipeptides **8** and **9**, and two pentapeptides **14** and **18**, by X-ray crystallography. Crystals of good quality for X-ray analysis were obtained by slow evaporation of $CHCl_3$/MeOH at room temperature. The molecular structures with atomic-numbering schemes are shown in *Figs. 1–5*. Relevant backbone and side-chain torsion angles are given in *Table 1*, and the intra- and intermolecular H-bond parameters are listed in *Table 2*.

The heterodipeptide CF_3CO-[(*S*)-αEtLeu]-[(*S*)-Beg]-OEt (**8**) crystallizes in the space group $P2_12_12_1$[2]) (*Fig. 1*). One intramolecular H-bond in the αEtLeu[1] residue is observed. This means that intramolecularly H-bonded C_5 conformer of αEtLeu[1] is formed in the solid state. The set of ϕ, ψ torsion angles of αEtLeu[1] are −175.3°, +177.1°, and those of (*S*)-Beg[2] are −50.3°, −45.6°. In the packing mode, one intermolecular H-bond is seen between the H−N(2) and the C(2′)=O(2′) carbonyl

[2]) The X-ray crystallographic analysis of **8** has been briefly reported in [13].

Table 1. *Selected Torsion Angles* ω, ϕ, ψ, *and* χ[a]) [°] *for the Peptides* **8**, **9**, **14**, *and* **18** *as Determined by X-Ray Crystal-Structure Analysis*

Torsion angle	CF_3CO-[(*S*)-αEtLeu]-[(*S*)-Beg]-OEt (**8**)	CF_3CO-[(*S*)-αEtLeu]$_2$-OEt (**9**)	CF_3CO-(Aib)$_2$-[(*S*)-αEtLeu]-(Aib)$_2$-OEt (**14**)		CF_3CO-[(*S*)-αEtLeu]-(Deg)$_4$-OEt (**18**)	
			Molecule **A** (*M*)	Molecule **B** (*P*)	Molecule **A** (*M*)	Molecule **B** (*P*)
ω_0	175.4	176.3	−179.8	−177.0	172.3	−174.0
ϕ_1	−175.3	−177.6	56.3	−55.7	50.4	−55.7
ψ_1	177.1	178.0	31.2	−35.5	44.4	−40.9
ω_1	−174.9	−172.2	174.6	−170.1	171.5	−172.6
ϕ_2	−50.3	−47.7	53.6	−53.7	54.2	−54.4
ψ_2	−45.6	−51.1	33.5	−38.8	24.5	−26.6
ω_2	−170.1	−176.3	176.4	−173.5	179.1	−174.4
ϕ_3	–	–	53.5	−53.5	47.4	−50.7
ψ_3	–	–	33.8	−36.2	35.8	−37.8
ω_3	–	–	175.2	−173.5	176.2	−173.8
ϕ_4	–	–	60.6	−62.9	60.7	−56.2
ψ_4	–	–	32.9	−22.1	28.1	−25.7
ω_4	–	–	174.7	178.9	−178.2	−178.7
ϕ_5	–	–	54.5	−48.5	−43.8	44.3
ψ_5	–	–	46.9	−45.3	−51.7	51.5
ω_5	–	–	−177.1	175.8	−175.5	179.5
χ_1^e	−52.8	−52.3	–	–	179.9	57.5
χ_1^b	62.8	66.8	–	–	−52.6	−166.6
χ_2^e	65.4	64.0	–	–	176.4	178.4
χ_2^b	175.4	−173.2	–	–	−62.9[b])	62.5[b])
χ_3^e	–	–	−177.2	61.3	60.7	63.2
χ_3^b	–	–	−75.5	−168.1	179.6[b])	−177.8[b])
χ_4^e	–	–	–	–	−63.5	71.6
χ_4^e	–	–	–	–	−56.6	61.5
χ_5^e	–	–	–	–	68.0	−174.8
χ_5^e	–	–	–	–	178.2	−68.9

[a]) The subscripts e and b refer to the Et and Bu side chains, respectively. [b]) χ_2^e and χ_3^e.

Table 2. *Intra- and Intermolecular H-Bond Parameters for the Peptides* **8**, **9**, **14**, *and* **18**

Peptide [a])	Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operations
CF_3CO-[(*S*)-αEtLeu]-[(*S*)-Beg]-OEt (**8**)					
	N(1)–H	O(1)	2.57	117	*x*, *y*, *z*
	N(2)–H	O(2′)	2.99	158	$x+1/2,\ -y+3/2,\ -z+1$
CF_3CO-[(*S*)-αEtLeu]$_2$-OEt (**9**)					
	N(1)–H	O(1)	2.55	115	*x*, *y*, *z*
	N(2)–H	O(2′)	3.00	171	$x+1/2,\ -y+3/2,\ -z+1$
CF_3CO-(Aib)$_2$-[(*S*)-αEtLeu]-(Aib)$_2$-OEt (**14**)					
A (*M*)	N(3a)–H	O(0a)	3.16	162	*x*, *y*, *z*
	N(4a)–H	O(1a)	2.97	160	*x*, *y*, *z*
	N(5a)–H	O(2a)	3.01	154	*x*, *y*, *z*
B (*P*)	N(3b)–H	O(0b)	3.30[b])	165	*x*, *y*, *z*
	N(4b)–H	O(1b)	3.00	152	*x*, *y*, *z*
	N(5b)–H	O(2b)	3.04	159	*x*, *y*, *z*
	N(1a)–H	O(4b′)	2.75	153	$-x+1/2,\ -y+1,\ z+1/2$
	N(2a)–H	O(5b′)	3.42[b])	128	$-x+1/2,\ -y+1,\ z+1/2$
	N(1b)–H	O(4a′)	2.84	135	$-x+1/2,\ -y+1,\ z+1/2$
	N(2b)–H	O(5a′)	3.21[b])	127	$-x+1/2,\ -y+1,\ z+1/2$
CF_3CO-[(*S*)-αEtLeu]-(Deg)$_4$-OEt (**18**)					
A (*M*)	N(3a)–H	O(0a)	2.99	158	*x*, *y*, *z*
	N(4a)–H	O(1a)	3.15	171	*x*, *y*, *z*
	N(5a)–H	O(2a)	2.91	152	*x*, *y*, *z*
B (*P*)	N(3b)–H	O(0b)	3.04	159	*x*, *y*, *z*
	N(4b)–H	O(1b)	3.14	164	*x*, *y*, *z*
	N(5b)–H	O(2b)	2.96	159	*x*, *y*, *z*
	N(1a)–H	O(4b′)	2.82	165	$x, y, z+1$
	N(1b)–H	O(4a)	2.88	169	*x*, *y*, *z*

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

O-atom of a symmetry-related molecule ($x+1/2,\ -y+3/2,\ -z+1$), with a N(2)···O(2) distance of 2.99 Å.

The homodipeptide CF_3CO-[(*S*)-αEtLeu]$_2$-OEt (**9**) also crystallizes in the space group $P2_12_12_1$ (*Fig. 2*). One intramolecularly H-bonded C_5-conformer of αEtLeu[1] is formed in the solid state, and one intermolecular H-bond is observed between the H–N(2) and the C(2′)=O(2′) carbonyl O-atom of a symmetry-related molecule ($x+1/2,\ -y+3/2,\ -z+1$), with a N(2)···O(2) distance of 3.00 Å. The set of ϕ, ψ torsion angles of αEtLeu[1] are $-177.6°$, $+178.0°$, and those of αEtLeu[2] are $-47.7°$, $-51.1°$. Therefore, the conformations of dipeptides **8** and **9** are very similar.

The structure of CF_3CO-(Aib)$_2$-[(*S*)-αEtLeu]-(Aib)$_2$-OEt (**14**, *Fig. 3*) was also solved in the orthorhombic space group $P2_12_12_1$. There are two crystallographically independent molecules **A** and **B** in the asymmetric unit. Molecule **A** is folded into a left-handed (*M*) 3_{10}-helical structure, and molecule **B** is folded into a right-handed (*P*) 3_{10}-helical structure (*Fig. 4*), *i.e.*, the two molecules **A** and **B** are in a diastereoisomeric relationship, and they are connected by intermolecular H-bonds. Molecule **A** shows

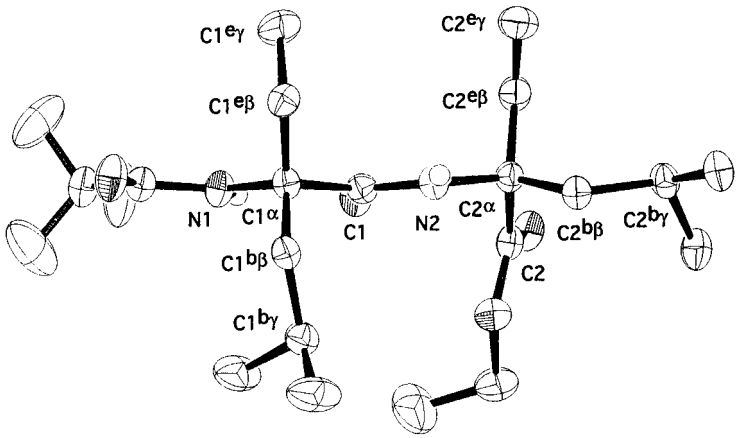


Fig. 2. *ORTEP Drawing of the molecular structure of CF_3CO-[(S)-αEtLeu]$_2$-OEt* (**9**) *with atom numbering* (ellipsoids at 50% probability)

three intramolecular H-bonds between H−N(3a) and the C(0a)=O(0a) O-atom of the CF_3CO group (N(3a)···O(0a) 3.16 Å), between H−N(4a) and C(1a)=O(1a) (N(4a)···O(1a) 2.97 Å), and between H−N(5a) and C(2a)=O(2a) (N(5a)···O(2a) 3.01 Å). In molecule **B**, two intramolecular H-bonds are observed between H−N(4b) and C(1b)=O(1b) (N(4b)···O(1b) 3.00 Å), and between H−N(5b) and C(2b)=O(2b) (N(5b)···O(2b) 3.04 Å), and also one weak intramolecular H-bond is shown between H−N(3b) and the C(0b)=O(0b) (N(3b)···O(0b) 3.30 Å). All signs of the ϕ and ψ torsion angles in molecule **A** are positive average values being $\phi = +55.7°$, $\psi = +35.7°$, while in molecule **B**, all signs of torsion angles are negative with average values $\phi = -54.9°$, $\psi = -35.6°$, respectively. The corresponding torsion angles in the molecules **A** and **B** differ by sign, but the absolute values are similar. Although the flip of torsion angles in the C-terminal Aib residue is often observed in the 3_{10}-helical structure of Aib peptides [5], these phenomena are not seen in molecules **A** and **B**. In the packing mode, two intermolecular H-bonds are observed between H−N(1a) and C(4b′)=O(4b′) O-atom of a symmetry-related molecule $(-x+1/2, -y+1, z+1/2)$ with N(1a)···O(4b′) distance of 2.75 Å, and also between H−N(1b) and C(4a′)=O(4a′) of a symmetry-related molecule $(-x+1/2, -y+1, z+1/2)$ with N(1b)···O(4a′) distance of 2.84 Å. Moreover, one weak intermolecular H-bond is observed between H−N(2b) and the C(5a′)=O(5a′) O-atom of a symmetry-related molecule $(-x+1/2, -y+1, z+1/2)$ with N(2b)···O(5a′) distance of 3.21 Å. The distance of N(2a)···O(5b′) is 3.42 Å, and is too long for an intermolecular H-bond. The head-to-tail alignment of right-handed (*P*) 3_{10}-helical molecule **B** and left-handed (*M*) 3_{10}-helical molecule **A** forms (···(*P*)···(*M*)···(*P*)···(*M*)···) chains of intermolecularly H-bonded molecules **A** and **B**.

The heteropentapeptide CF_3CO-[(*S*)-αEtLeu]-(Deg)$_4$-OEt (**18**, *Fig. 5*) crystallizes in the monoclinic $P2_1$ space group. Two crystallographic independent molecules **A** and **B**, which are diastereoisomeric (*M*)- and (*P*)-3_{10}-helical structures, exist in the asymmetric unit. In molecule **A**, three intramolecular H-bonds are observed between H−N(3a) and the C(0a)=O(0a) O-atom of the CF_3CO group with N(3a)···O(0a)

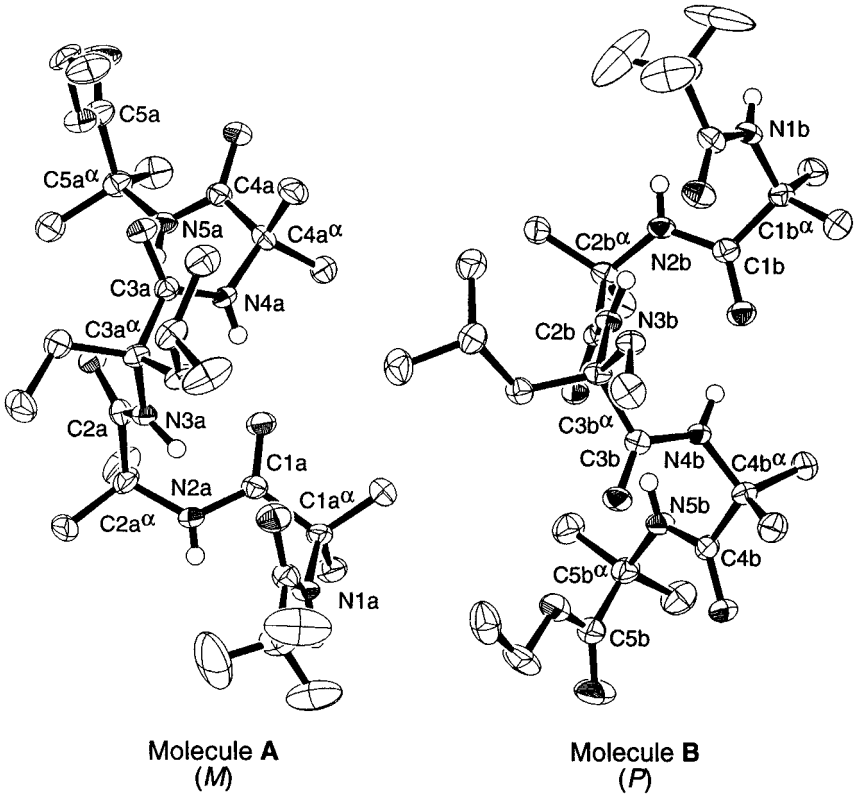


Fig. 3. *ORTEP Drawing of the molecular structure of CF_3CO-(Aib)$_2$-[(S)-αEtLeu]-(Aib)$_2$-OEt* (**14**) *with atom numbering* (ellipsoids at 50% probability)

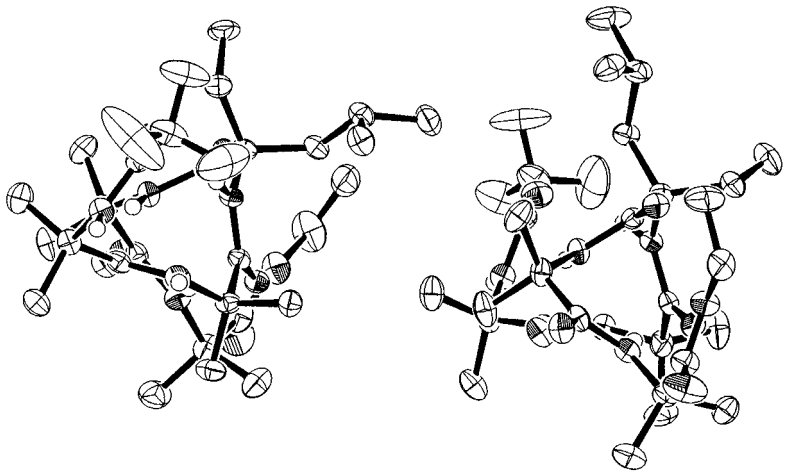


Fig. 4. *ORTEP Drawing of* **14** *viewed along the helix axis* (ellipsoids at 50% probability)

distance of 2.99 Å, between H–N(4a) and C(1a)=O(1a) (N(4a)···O(1a) 3.15 Å), and between H–N(5a) and C(2a)=O(2a) (N(5a)···O(2a) 2.91 Å). Similarly, three intramolecular H-bonds are observed in molecule **B** between H–N(3b) and C(0b)=O(0b) (N(3b)···O(0b) 3.04 Å), between H–N(4b) and C(1b)=O(1b) (N(4b)···O(1b) 3.14 Å), and between H–N(5b) and C(2b)=O(2b) (N(5b)···O(2b) 2.96 Å). The absolute values of the corresponding ϕ and ψ torsion angles in the molecules **A** and **B** are similar, but the signs of torsion angles are opposite. Furthermore, the signs of torsion angles (ϕ, $\psi = -43.8°$, $-51.7°$ in **A**, $+44.3°$, $+51.5°$ in **B**) of the Deg[5] residues at the C-terminus are opposite to those of the preceding residues (*S*)-αEtLeu[1], Deg[2], Deg[3], and Deg[4] (plus signs in **A**, and minus signs in **B**) in both molecules. These phenomena are often observed in the 3_{10}-helical structures of Aib peptides [5] and also in the 3_{10}-helical structures of Deg homopeptides [6d], and are known as the 3_{10}-helix-terminating structure. The average values of the ϕ and ψ torsion angles for the sequence (*S*)-αEtLeu[1] to Deg[4] are $\phi = +53.2°$, $\psi = +33.2°$ in molecule **A** and $\phi = -54.3°$, $\psi = -32.7°$ in molecule **B**, *i.e.*, close to the ideal torsion angles for the 3_{10}-helical structure are $\phi = 49°$ and $\psi = 26°$. In the packing mode of **18**, two intermolecular H-bonds are observed between the H–N(1a) and the C(4b′)=O(4b′) O-atom of a symmetry-related molecule (x, y, $z+1$) (N(1a)···O(4b′) 2.82 Å), and also between the H–N(1b) and the C(4a)=O(4a) of a symmetry-related molecule (x, y, z) (N(1b)···O(4a) 2.88 Å). Thus, the chains of intermolecular H-bonded molecules **A** and **B** are of the (···(*P*)···(*M*)···(*P*)···(*M*)···) mode in the head-to-tail alignment. No intermolecular H-bond is formed between N(2a)···O(5b′) and N(2b)···O(5a), as the distances of 3.54 Å and 3.64 Å are too long.

Solution Conformation Analysis. Fig. 6 shows the FT-IR absorption spectra of the pentapeptides **14**, **16**, and **18** in the 3500–3250 cm^{-1} region (peptide concentration of 1.0 mM). In both Aib heteropeptides **14** and **16**, the bands in the 3420–3440 cm^{-1} region, are assigned to free (solvated) peptide NH groups or to weak intramolecular H-bonded amide NH groups of the C–F···H–N type, and the strong bands in 3350–3370 cm^{-1}, are assigned to peptide NH groups with N–H···O=C intramolecular H-bonds of different strength. The relative intensity of the bands in the 3420–3440 cm^{-1} region increases gradually with decreasing peptide concentration (10.0–1.0 mM). These IR spectra are very similar to those of Aib homopeptides and Aib heteropeptides having an (*S*)-Beg. In Deg heteropeptide **18**, the bands at 3390 cm^{-1} region is assigned to amide NH groups with relatively strong C–F···H(N)···O=C intramolecular H-bond at the N-terminus, and those at 3340–3360 cm^{-1} to peptide NH groups with N–H···O=C intramolecular H-bonds of different strength. The concentration of **18** does not essentially affect the IR spectra, *i.e.*, the strength of the intermolecular H-bonds does not change with concentration (10.0–1.0 mM). The behavior of IR spectra of **18** is very similar to those of Deg homopeptides [6d] and (*S*)-Beg homopeptides [8].

To obtain more useful information, we recorded the ^{1}H-NMR spectra of pentapeptides **14**, **16**, and **18** under various conditions. In the ^{1}H-NMR ($CDCl_3$) spectra of **14** and **16**, only the trifluoroacetamide NH signals at the N-terminus could be unambiguously determined by their high-field positions (δ 6.56 (br. *s*, 1 H) in **14**, and δ 6.18 (br. *s*, 1 H) in **16**), and the remaining four NH protons could not be assigned. In the ^{1}H-NMR spectrum of **18**, the CF_3CONH signal at the N-terminus could be identified by its high-field position (δ 6.77 (br. *s*, 1 H)), and the amide NH signal at the C-

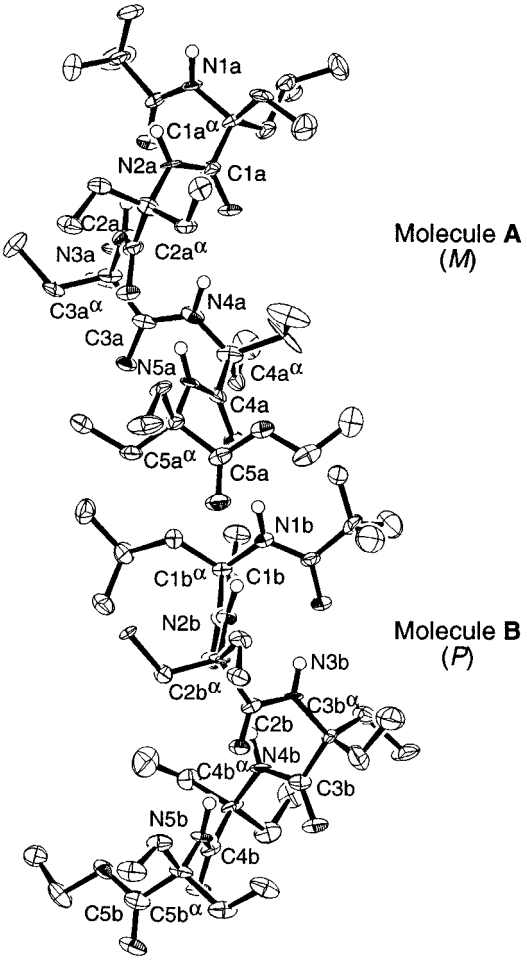


Fig. 5. *ORTEP Drawing of the molecular structure of CF_3CO-[(S)-αEtLeu]-(Deg)$_4$-OEt* (**18**) *with atom numbering* (ellipsoids at 50% probability)

terminus could be assigned by its low-field position (δ 8.11 (br. *s*, 1 H)), but the remaining three NH protons (Deg^2 to Deg^4) could not be assigned. The chemical shifts of Aib heteropeptides **14** and **16** were shifted to higher fields on dilution in $CDCl_3$ solution (concentration 10.0–1.0 mM), but those of Deg heteropeptide **18** were independent of the concentration in the examined range (10.0–1.0 mM). *Fig. 7* shows the solvent perturbation experiments by addition of the strong H-bond acceptor solvent DMSO (0–10% (*v*/*v*)), or the paramagnetic free radical 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO; $0-5\cdot10^{-2}$% (*w*/*v*)). In Aib heteropeptides **14** and **16**, two NH signals (Aib^1 and Aib^2 in **14**, and α$EtLeu^1$ and Aib^2 in **16**) were very sensitive (solvent-exposed NH group), and these results suggest that two intermolecular H-bonds between 3_{10}-helical structures might be disrupted by addition of the perturbing agents.

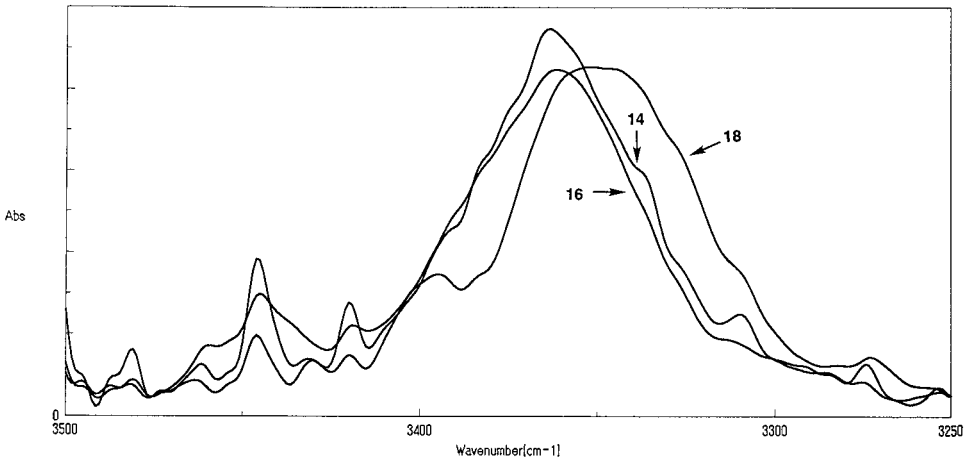


Fig. 6. *FT-IR Absorption spectra* (3500–3250 cm^{-1} region) *of the* CF_3CO-*(Aib)*$_2$-*[(*S*)-αEtLeu]-(Aib)*$_2$-*OEt* (**14**), CF_3CO-*[(*S*)-αEtLeu]-(Aib)*$_4$-*OEt* (***16***), *and* CF_3CO-*[(*S*)-αEtLeu]-(Deg)*$_4$-*OEt* (**18**) *in* $CDCl_3$ *solution.* Peptide concentration 1.0 mM.

In contrast, the NH signals of Deg heteropeptide **18** were insensitive to the addition of DMSO and TEMPO, *i.e.*, all NH signals might be involved in intramolecular H-bonds, that is to say, the heteropeptide **18** might form the planar C_5 conformation.

The CD spectra of heteropeptides **14**, **16**, and **18** were recorded in CF_3CH_2OH to obtain the information of global secondary structure[3]). *Toniolo* and co-workers reported that the screw sense of a helix and also a 3_{10}- and an α-helical structure of peptides constructed from chiral α-methylated α,α-disubstituted amino acids could be determined by the CD spectra [14], *i.e.*, the negative and positive maxima, and intensity of two bands at 222 and 208 nm, and a band at 192 nm in the CD spectra. The CD spectrum of Aib heteropeptide **14** exhibits the positive maxima at 220 and 212 nm, and a minimum at 203 nm, and that of **16** shows the positive maxima at 217 and 208 nm, and the minimum at 199 nm (*Fig. 8*). These CD spectra indicate that the (*M*)-3_{10}-helical structure is dominant, but they are different from the typical CD spectrum of 3_{10}-helical peptides containing chiral α-methylated α,α-disubstituted amino acids, which show one screw sense (*P*) or (*M*) of helicity. The ellipticity in the 190–250 nm region is positive. This may be attributed to the fact that both (*P*)- and (*M*)-3_{10}-helical structures exist in CF_3CH_2OH solution [7e], as those of **14** existed in the solid state, or that the main-chain length of the peptides would be too short for conformational analysis by CD spectra. The CD spectrum of Deg heteropeptide **18** is very different from the typical CD spectrum of chiral 3_{10}-helical peptides (*Fig. 8*).

Computational Analysis [15]. Molecular-mechanics calculations with *MacroModel* (force field, AMBER*) [16] were applied to the conformational analysis of the pentapeptides **14**, **16**, and **18** (*Table 3*). In the case of **14**, four different conformations, *i.e.*, a (*P*) distorted 3_{10}-helix (conformer *A*; 0 kcal/mol), a (*P*)-3_{10}-helix (conformer *B*; +1.16 kcal/mol), a (*M*) distorted 3_{10}-helix (conformer *C*; +1.27 kcal/mol), and a (*M*)-

[3]) *Errors:* In our previous papers [8][9], the unit [× 10] must be added to the *y*-axis of the CD spectra.

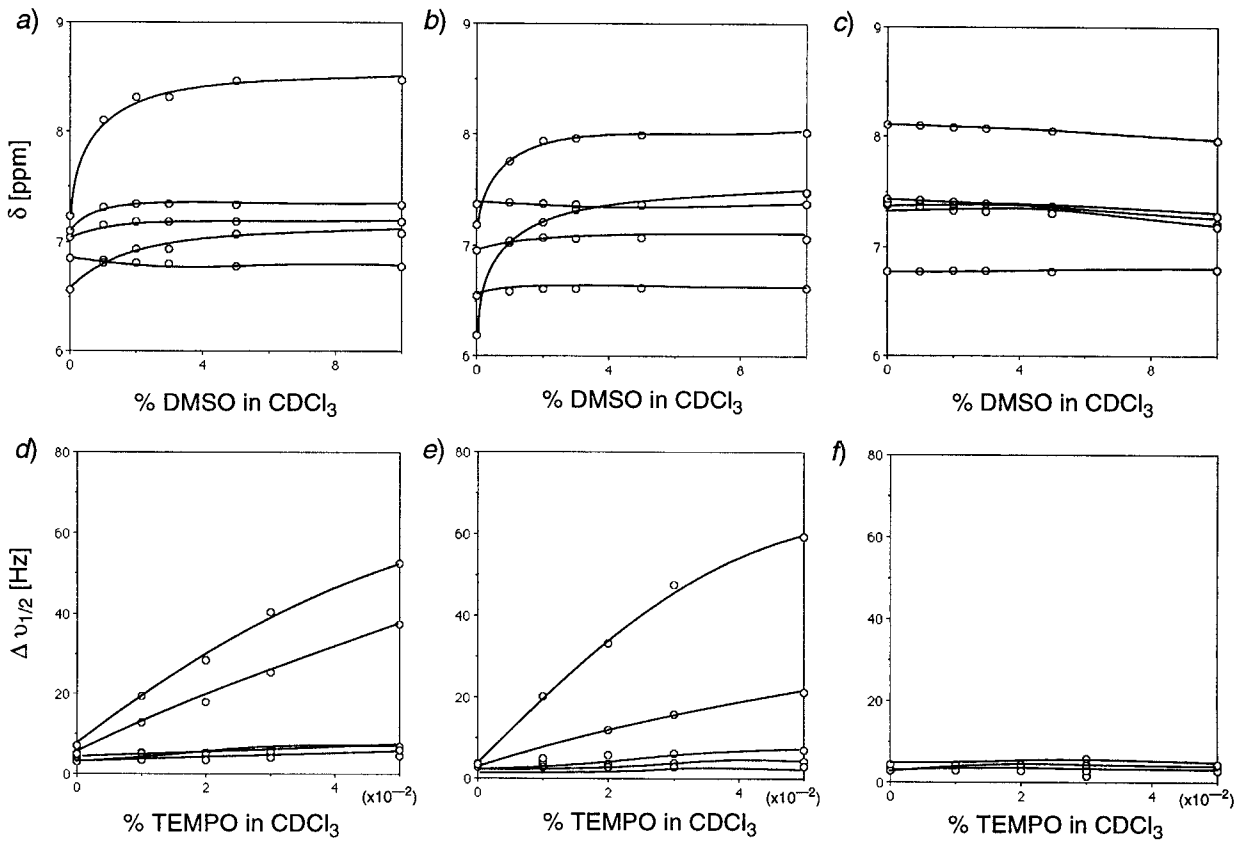


Fig. 7. a) *Plots of NH chemical shifts in the ^{1}H-NMR spectra of CF_3CO-(Aib)$_2$-[(S)-αEtLeu]-(Aib)$_2$-OEt* (**14**; 1.0 mM), b) *of CF_3CO-[(S)-αEtLeu]-(Aib)$_4$-OEt* (**16**; 1.0 mM), *and* c) *of CF_3CO-[(S)-αEtLeu]-(Deg)$_4$-OEt* (**18**; 1.0 mM) *as a function of increasing percentages of DMSO* (*v*/*v*) *added to the $CDCl_3$ solution*; d) *plots of the bandwidth of the NH H-atoms of CF_3CO-(Aib)$_2$-[(S)-αEtLeu]-(Aib)$_2$-OEt* (**14**; 1.0 mM), e) *of CF_3CO-[(S)-αEtLeu]-(Aib)$_4$-OEt* (**16**; 1.0 mM), *and* f) *of CF_3CO-[(S)-αEtLeu]-(Deg)$_4$-OEt* (**18**; 1.0 mM) *as a function of increasing percentages of TEMPO* (*w*/*v*) *added to the $CDCl_3$ solution*

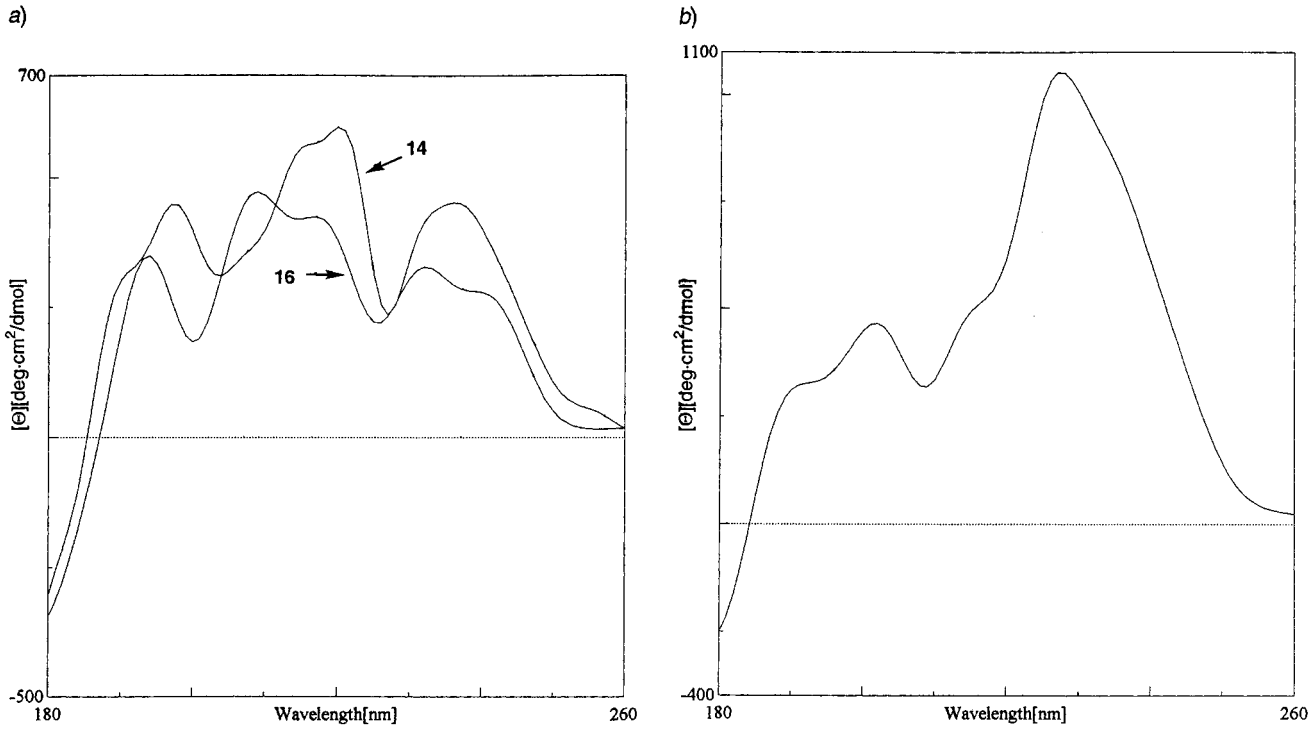


Fig. 8. *CD Spectra of* a) *CF_3CO-(Aib)$_2$-[(S)-αEtLeu]-(Aib)$_2$-OEt* (**14**) *and CF_3CO-[(S)-αEtLeu]-(Aib)$_4$-OEt* (**16**), *and* b) *CF_3CO-[(S)-αEtLeu]-(Deg)$_4$-OEt* (**18**) *in CF_3CH_2OH solution*. Peptide concentration 1.0 mM.

3_{10}-helix (conformer *D*; +1.82 kcal/mol) are observed with relative energies less than 3.0 kcal/mol of the global minimum energy. In the distorted 3_{10}-helical conformations *A* and *C*, the C_5 conformation of Aib[1] residues is observed, due to the existence of (*S*)-αEtLeu[3]. The conformers *B* and *D* are very similar to those determined for **14** by the X-ray crystal-structure analysis, as shown by their superimposition in *Fig. 9*,*a* and *b*. The main differences between the calculated conformations and crystal structures are the torsion angles in the C-terminal Aib[5] residue. The calculated conformations show that the flip of torsion angles in the C-terminal Aib[5] residue are opposite to those of the preceding residues, but the crystal structures show that all signs of the ϕ and ψ torsion angles are consistent in the molecules. In the case of **16**, the calculations afforded two minimum-energy conformers of 3_{10}-helical structures within 3.0 kcal/mol of the global minimum-energy. A (*P*)-3_{10}-helix (conformer *E*) is more stable than a (*M*)-3_{10}-helix (conformer *F*) by 1.42 kcal/mol. The calculations of **18** also produced two minimum-energy conformers of 3_{10}-helical structures. One is a right-handed (*P*)-3_{10}-helix (conformer *G*; 0 kcal/mol), and the other is a (*M*)-3_{10}-helix (conformer *H*; +1.45 kcal/mol). The conformers *G* and *H* are very similar to those determined for **18** by the X-ray crystal-structure analysis. *Fig. 9*,*c* and *d* show that the molecules **A** and **B** of **18** as determined by X-ray crystallographic analysis, superimposed on the minimum-energy conformations *G* and *H* calculated by *MacroModel*.

Discussion. – The X-ray crystallographic analysis of homodipeptide **9** shows that the αEtLeu[1] at the N-terminus forms the planar C_5 conformer ($\phi = -177.6^\circ$, $\psi = +178.0^\circ$), and this result suggests that the propensity of (*S*)-αEtLeu homopeptide is to form the planar C_5 conformer, as the propensity of (*S*)-Beg homopeptide is to the fully planar C_5 conformation [8][9]. The conformation of heteropentapeptide **14** containing an (*S*)-αEtLeu within a sequence of Aib residues is proved to be both (*P*)- and (*M*)-3_{10}-helical structures in the solid state. Four Aib residues strongly affect the secondary structure of the peptide and induce the 3_{10}-helical structure, and one (*S*)-αEtLeu within four Aib residues are not able to change the 3_{10}-helical structure into the other conformers, just as the introduction of an (*S*)-Beg within a sequence of Aib residues could not change [9]. The FT-IR and ^{1}H-NMR experiments revealed that, in solution, the Aib heteropeptides **14** and **16** containing an (*S*)-αEtLeu induce 3_{10}-helical structure, as well as in the solid state of **14**. The chirality of the quaternary C-atom of one (*S*)-αEtLeu within the sequences of Aib residues could not govern the screw sense of the 3_{10}-helical structure in the solid state, and, therefore, both (*P*)- and (*M*)-3_{10}-helical structures existed. The CD spectra of **14** and **16** suggest that the (*M*)-3_{10}-helical structure may be dominant in CF_3CH_2OH solution, but the CD spectra are different from the typical CD spectra of 3_{10}-helical peptides that have one screw sense of helicity [14]. It may be attributed to the existence of both the diastereoisomeric (*P*)- and (*M*)-3_{10}-helical structures in solution. The conformation of heteropentapeptide **18** containing an (*S*)-αEtLeu within a sequence of Deg residues is proved to be both (*P*)- and (*M*)-3_{10}-helical structures in the solid state. The propensity of Deg is known to form the fully planar C_5 conformer [6a], but even homopeptides prepared from Deg are apt to form 3_{10}-helical structures in the solid state when an ethyl ester is used as the protecting group at C-terminus [6d]. The conformational analysis by the FT-IR and ^{1}H-NMR spectra reveal that the heteropeptide **18** prefers the C_5 conformation in solution. The

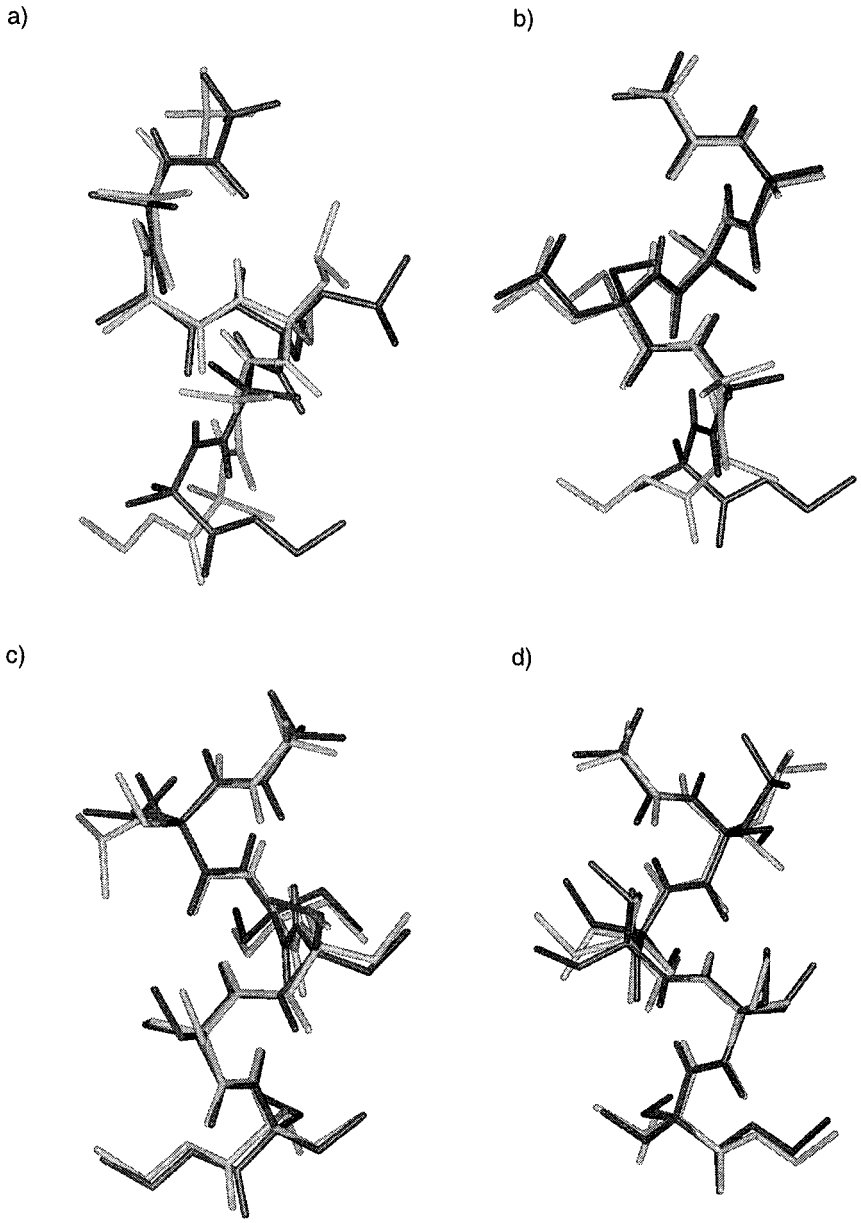


Fig. 9. *Superimposition of the conformation determined by X-ray analysis* (in light) *and of the calculated* (MacroModel) *minimum-energy conformations* (in dark): a) *molecule* **B** (P) *of* CF_3CO-$(Aib)_2$-[(S)-αEtLeu]-$(Aib)_2$-*OEt* (**14**) *and calculated conformation* B; b) *molecule* **A** (M) *of* **14** *and calculated conformation* D; *and* c) *molecule* **B** (P) *of* CF_3CO-[(S)-αEtLeu]-$(Deg)_4$-*OEt* (**18**) *and calculated conformation* G; d) *molecule* **A** (M) *of* **18** *and calculated conformation* H

Table 3. *Selected Calculated* (*MacroModel*) *Torsion Angles* ω, ϕ, ψ, *and* χ[a]) [°] *for the Heteropeptides* **14**, **16**, *and* **18**

	CF_3CO-$(Aib)_2$-[(*S*)-αEtLeu]-$(Aib)_2$-OEt (**14**)				CF_3CO-[(*S*)-αEtLeu]-$(Aib)_4$-OEt (**16**)		CF_3CO-[(*S*)-αEtLeu]-$(Deg)_4$-OEt (**18**)	
	Conf. *A* (*P*) distorted 3_{10}-helix	Conf. *B* (*P*)-3_{10}-helix	Conf. *C* (*M*) distorted 3_{10}-helix	Conf. *D* (*M*)-3_{10}-helix	Conf. *E* (*P*)-3_{10}-helix	Conf. *F* (*M*)-3_{10}-helix	Conf. *G* (*P*)-3_{10}-helix	Conf. *H* (*M*)-3_{10}-helix
Energy	0 kcal/mol	+1.16 kcal/mol	1.27 kcal/mol	+1.82 kcal/mol	0 kcal/mol	+1.42 kcal/mol	0 kcal/mol	+1.45 kcal/mol
ω_0	−179.1	−179.1	179.6	−178.5	−178.9	−179.9	−179.1	177.6
ϕ_1	178.7[b])	−46.9	−178.6[b])	47.2	−51.9	52.2	−50.6	55.9
ψ_1	−161.3b)	−31.6	167.3b)	34.8	−25.2	25.5	−27.3	18.4
ω_1	179.7	177.0	−179.3	179.6	174.5	−174.3	174.8	−171.9
ϕ_2	−47.6	−43.1	49.5	48.1	−45.7	45.1	−39.2	42.5
ψ_2	−34.1	−33.0	30.4	28.1	−32.6	32.6	−39.8	35.3
ω_2	−179.6	−178.4	−178.2	−179.0	178.4	−178.2	−171.6	179.5
ϕ_3	−51.5	−51.9	49.3	50.0	−48.6	48.4	−54.8	51.8
ψ_3	−23.0	−23.8	26.3	26.5	−26.3	26.7	−19.8	23.8
ω_3	171.4	171.5	−175.2	−175.3	174.0	−174.2	174.0	−176.2
ϕ_4	−44.7	−43.5	46.8	46.1	−45.9	45.8	−48.1	51.6
ψ_4	−34.3	−35.2	33.0	33.1	−33.5	33.7	−34.1	32.5
ω_4	−170.9	−171.2	170.6	170.8	−170.9	171.1	−171.6	165.2
ϕ_5	45.1	44.8	−44.8	−45.0	45.0	−44.7	42.5	−44.4
ψ_5	41.9	42.2	−42.1	−42.1	42.1	−42.3	35.5	−35.4
ω_5	−179.1	−178.9	179.0	178.9	−179.1	179.0	−179.2	−177.6
χ_1^e	–	–	–	–	53.3	−63.5	58.2	−67.2
χ_1^b	–	–	–	–	71.6	−65.3	73.0	−65.3
χ_2^e	–	–	–	–	–	–	−177.9	−56.7
χ_2^e	–	–	–	–	–	–	65.0	−48.0
χ_3^e	49.8	51.5	−65.7	−70.4	–	–	56.6	69.1
χ_3^b	63.7	69.5	−66.5	−67.2	–	–	74.4[c])	−31.4[c])
χ_4^e	–	–	–	–	–	–	59.3	−32.3
χ_4^e	–	–	–	–	–	–	66.1	72.7
χ_5^e	–	–	–	–	–	–	−60.4	66.8
χ_5^e	–	–	–	–	–	–	−64.6	54.4

[a]) The subscripts e and b refer to the Et and Bu side chains, 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 *A* and *C* of **14**. [c]) χ_3^e.

CD spectrum shows no characteristic bands for 3_{10}-helix formed by the homopeptides prepared from α-methylated α,α-disubstituted α-amino acids. The CD spectrum of **18** might be attributed to the existence in solution of several conformers, including the dominant C_5 conformer, and the (*P*)- and (*M*)-3_{10}-helical structures observed in the solid state.

Molecular-mechanics calculations with *MacroModel* can build the (*P*)- and (*M*)-3_{10}-helical structures of peptides, which are very similar to those formed in the solid state. In the case of the heteropeptide **14**, the (*P*) distorted 3_{10}-helix (conformer *A*) having C_5 conformation at Aib[1] residue was calculated as the global minimum-energy conformation. The (*S*)-αEtLeu[3] residue at the center position of pentapeptide affects the torsion angles (ϕ, ψ) of the Aib[1] residue at the N-terminus. However, X-ray-analysis revealed that this calculated distorted 3_{10}-helical structure was not observed, but that a perfect 3_{10}-helical structure was formed in the solid state. Also, the calculations estimated that the (*P*)-3_{10}-helical structures of heteropeptides containing a (*S*)-αEtLeu residue were more stable than the (*M*)-3_{10}-helical structures by only *ca.* 1 kcal/mol. The calculation by AMBER* could produce the (*P*)- and (*M*)-3_{10}-helical structures, but could not produce the fully planar C_5 conformer of the heteropeptide **18**, which was observed in solution, within 3.0 kcal/mol of the global minimum-energy.

Conclusions. – The (*S*)-α-ethylleucine **4** could be synthesized from (*R*,*R*)-cyclohexane-1,2-diol as a chiral acetal auxiliary, and could be introduced into the sequences of Aib and Deg peptides. The preparation of (*S*)-αEtLeu homotripeptide **10** could not be completed. This would be attributed to the steric hindrance, especially the bulkiness of substituent at the γ-position of the side chain, because the formation of (*S*)-Beg homopeptides could be achieved under the same reaction conditions [8].

The conformational analysis revealed that the propensity of (*S*)-αEtLeu is to form the planar C_5 conformer, but the introduction of one (*S*)-αEtLeu into the Aib peptides does not change the 3_{10}-helical structures formed by Aib residues, just as the introduction of (*S*)-Beg could not change it [9]. The Deg heteropeptide **18** containing an (*S*)-αEtLeu forms the (*P*)- and (*M*)-3_{10}-helical structures in the solid state, and the planar C_5 conformation is dominant in solution, as the Deg homopeptide showed the different conformations in the solid state and in solution [6d].

Experimental Part

General. (*R*,*R*)-Cyclohexane-1,2-diol acetal **1**, Aib peptides **11** and **15**, and Deg tetrapeptide **17** were prepared according to our previous reports [6d][9]. Optical rotations $[\alpha]_D$ were measured with a *Jasco DIP-316* polarimeter with a 1.0-dm cell. CD Spectra were recorded with a *Jasco J-720W* spectropolarimeter by using 10.0-mm path length cell. IR Spectra were recorded on a *Jasco A-100* spectrometer for conventional measurement (KBr and neat), and a *Jasco FT-IR 420* spectrophotometer for the soln. ($CDCl_3$) method with 0.1-mm path length of NaCl cell. ^{1}H-NMR Spectra were determined at 270 MHz (*Jeol GX-270*) or 500 MHz (*Varian Unity-500P*). FAB-MS Spectra were taken on a *Jeol JMS 610 H* or *Jeol JMS-SX 102* spectrometer. Elemental analyses were performed at the Analytical Center of the Faculty of Science at Kyushu University.

*Ethyl (2*R*)-2-Ethyl-3-[(1*R,2R*)-2-hydroxycyclohexyloxy]-2-(1-methylpropyl)but-3-enoate* (**2**) [13]. BuLi (52 ml, 80 mmol, 1.5M in hexane) was added dropwise to the stirred soln. of $(i\text{-}Pr)_2NH$ (8.28 g, 80 mmol) in THF (70 ml) at $-78°$, the soln. was warmed to 0°, and stirred for 30 min, and then cooled to $-78°$. HMPA (15.2 g, 80 mmol) and then acetal **1** (4.1 g, 16 mmol) in THF (10 ml) were added dropwise, and the soln. was stirred at $-78°$ for 30 min. i-BuI (15.1 g, 80 mmol) was added dropwise to the stirred soln. at $-78°$, and then the soln. was

gradually warmed to r.t. for 12 h. The soln. was diluted with sat. aq. NH_4Cl soln., extracted with AcOEt, and the extract was dried ($MgSO_4$), evaporated, and the residue was purified by CC (SiO_2; 10% AcOEt/hexane): **2** (3.14 g, 63%). Colorless oil. $[\alpha]_D^{27} = -47.7$ ($c = 0.99$, $CHCl_3$). IR (neat): 3500, 1730, 1645, 1610. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.03–4.24 (*m*, 4 H); 3.77 (*m*, 1 H); 3.50 (*m*, 1 H); 2.87 (br. *s*, 1 H), 2.00–2.23 (*m*, 2 H); 1.55–1.90 (*m*, 7 H); 1.13–1.36 (*m*, 4 H); 1.24 (*t*, $J = 7.0$, 3 H); 0.90 (*d*, $J = 6.4$, 3 H); 0.87 (*d*, $J = 6.4$, 3 H); 0.81 (*t*, $J = 7.4$, 3 H). FAB-MS: 313.5 ($[M + H]^+$).

*Ethyl (*R*)-2-Acetyl-2-ethyl-4-methylpentanoate* (**3**) [13]. $BF_3 \cdot OEt_2$ (4.63 g, 32.6 mmol) was added dropwise to the stirred soln. of **2** (1.02 g, 3.26 mmol) in H_2O (5 ml) and EtOH (20 ml) at r.t., and the soln. was stirred for 1 h. The soln. was diluted with brine, extracted with $CHCl_3$, and the extract was dried ($MgSO_4$), and evaporated, and the residue was purified by CC (SiO_2; 10% AcOEt/hexane): **3** (619 mg, 88%, >95% ee). Colorless oil. $[\alpha]_D^{26} = +9.20$ ($c = 1.15$, $CHCl_3$). IR (neat): 1740, 1710. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.22 (*q*, $J = 7.0$, 2 H); 2.12 (*s*, 3 H); 1.92–2.50 (*m*, 2 H); 1.78–1.90 (*m*, 2 H); 1.55 (*m*, 1 H); 1.26 (*t*, $J = 7.0$, 3 H); 0.87 (*d*, $J = 6.6$, 3 H); 0.85 (*d*, $J = 6.6$, 3 H); 0.75 (*t*, $J = 7.6$, 3 H). FAB-MS: 215.2 ($[M + H]^+$).

*Ethyl (*S*)-*N*-Acetyl-α-ethylleucinate* (**4**) [13]. MsOH (2.01 ml, 27.6 mmol) was added dropwise to the stirred soln. of **3** (592 mg, 2.76 mmol) in $CHCl_3$ (15 ml) at 0°, and then NaN_3 (898 mg, 13.8 mmol) was added. After reflux for 24 h, the mixture was cooled to r.t., diluted with H_2O, neutralized with dil. aq. NH_3 soln., and extracted with Et_2O, and the extract was dried ($MgSO_4$). After evaporation, the residue was purified by CC (SiO_2; 20% AcOEt/hexane): **4** (253 mg, 40%). Colorless crystals. M.p. 42–43° (from hexane). $[\alpha]_D^{25} = +21.2$ ($c = 1.09$, $CHCl_3$). IR (KBr): 3300 (br), 1720, 1645. ^{1}H-NMR (270 MHz, $CDCl_3$): 6.53 (br. *s*, 1 H); 4.17–4.28 (*m*, 2 H); 2.46–2.57 (*m*, 2 H); 2.02 (*s*, 3 H); 1.52–1.73 (*m*, 3 H); 1.31 (*t*, $J = 7.1$, 3 H); 0.89 (*d*, $J = 6.6$, 3 H); 0.77 (*d*, $J = 6.6$, 3 H); 0.70 (*t*, $J = 7.3$, 3 H). FAB-MS: 230.3 ($[M + H]^+$). The β-keto ester **3** was recovered in 20% yield.

*Ethyl (*S*)-α-Ethylleucinate* ([(*S*)-αEtLeu]-OEt; **5**). A mixture of **4** (896 mg, 3.91 mmol) in conc. aq. HCl soln. (5 ml) was refluxed for 2 d, and then evaporated. The residue and conc. H_2SO_4 (1 ml) in EtOH (10 ml) were refluxed for 3 d. After removal of EtOH, the oily residue was neutralized with 5% aq. $NaHCO_3$ soln., extracted with $CHCl_3$, and the extract was dried ($MgSO_4$) and evaporated: crude **5** (499 mg, 68%), which was used in the next reaction without purification. Colorless oil. $[\alpha]_D^{18} = +14.2$ ($c = 1.00$, $CHCl_3$). IR (neat): 3360*w*, 1710. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.08–4.22 (*m*, 2 H); 1.71–1.86 (*m*, 4 H); 1.69 (br. *s*, 2 H); 1.53 (*m*, 1 H); 1.28 (*t*, $J = 7.3$, 3 H); 0.95 (*d*, $J = 6.3$, 3 H); 0.833 (*t*, $J = 7.6$, 3 H); 0.832 (*d*, $J = 6.3$, 3 H). FAB-MS: 188.2 ($[M + H]^+$).

*Trifluoroacetyl-(*S*)-α-ethylleucine* (CF_3CO-[(*S*)-αEtLeu]; **6**). A mixture of **4** (690 mg, 3.01 mmol) in conc. aq. HCl soln. (5 ml) was refluxed for 2 d, and then evaporated. The residue was dissolved in $(CF_3CO)_2O$ (5 ml), and the soln. was stirred at r.t. for 2 d. The mixture was poured into 5% aq. $NaHCO_3$ soln., and the soln. was washed with Et_2O and then acidified with citric acid. The soln. was extracted with AcOEt, and the extract was dried ($MgSO_4$), and evaporated: **6** (540 mg, 70%), which was used in the next reaction without purification. Colorless oil. $[\alpha]_D^{23} = +4.2$ ($c = 0.91$, $CHCl_3$). IR (neat): 3300 (br.), 1720 (br). ^{1}H-NMR (270 MHz, $CDCl_3$): 7.35 (br. *s*, 1 H); 3.80 (br., 1 H); 2.46–2.60 (*m*, 2 H); 1.76–1.94 (*m*, 2 H); 1.58 (*sept.*, $J = 6.6$, 1 H); 0.91 (*d*, $J = 6.6$, 3 H); 0.86 (*d*, $J = 6.6$, 3 H); 0.80 (*t*, $J = 7.6$, 3 H). FAB-MS: 278.1 ($[M + Na]^+$), 256.1 ($[M + H]^+$).

*Ethyl Trifluoroacetyl-(*S*)-α-ethylleucyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-αEtLeu]-[(*S*)-Beg]-OEt; **8**) [13]. A soln. of **6** (50 mg, 0.196 mmol), **7** (55 mg, 0.294 mmol) [8], and *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC; 75 mg, 0.392 mmol) in MeCN (5 ml) was refluxed for 2 d, and then evaporated. The residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$). After evaporation, the residue purified by CC (SiO_2; 10% AcOEt/hexane): **8** (30 mg, 36%). Colorless crystals. M.p. 106–107° ($CHCl_3$/MeOH). $[\alpha]_D^{25} = +15.3$ ($c = 0.23$, $CHCl_3$). IR (KBr): 3370, 3320, 1730, 1710. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.05 (br. *s*, 1 H); 6.76 (br. *s*, 1 H); 4.28 (*q*, $J = 6.9$, 2 H); 2.33–2.72 (*m*, 4 H); 1.72–1.91 (*m*, 2 H); 1.50–1.68 (*m*, 3 H); 1.32 (*t*, $J = 7.1$, 3 H); 1.05–1.35 (*m*, 4 H); 0.90 (*d*, $J = 6.6$, 6 H); 0.88 (*t*, $J = 6.9$, 3 H); 0.763 (*t*, $J = 7.4$, 3 H); 0.756 (*t*, $J = 7.4$, 3 H). FAB-MS: 425.4 ($[M + H]^+$). Anal. calc. for $C_{20}H_{35}F_3N_2O_4$: C 56.59, H 8.31, N 6.60; found: C 56.64, H 8.28, N 6.57.

*Ethyl Trifluoroacetyl-(*S*)-α-ethylleucyl-(*S*)-α-ethylleucinate* (CF_3CO-[(*S*)-αEtLeu]-[(*S*)-αEtLeu]-OEt; **9**). A soln. of **5** (125 mg, 0.668 mmol), **6** (255 mg, 1.00 mmol), and EDC (192 mg, 1.00 mmol) in MeCN (10 ml) was refluxed for 2 d. After evaporation, the residue was diluted $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (SiO_2; 5% AcOEt/hexane): **9** (30 mg, 36%). Colorless crystals. M.p. 80–81° ($CHCl_3$/MeOH). $[\alpha]_D^{21} = -92.2$ ($c = 0.125$, $CHCl_3$). IR (KBr): 3390, 3370, 3320, 1730, 1710, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.03 (br. *s*, 1 H); 6.91 (br. *s*, 1 H); 4.11–4.33 (*m*, 2 H); 2.35–2.75 (*m*, 4 H); 1.50–1.88 (*m*, 6 H); 1.34 (*t*, $J = 7.3$, 3 H); 0.87–0.92 (*m*, 9 H); 0.71–0.80 (*m*, 9 H). Anal. calc. for $C_{20}H_{35}F_3N_2O_4$: C, 56.59; H 8.31; N 6.60; found: C 56.67, H 8.27, N 6.60.

*Ethyl Trifluoroacetyl-(*S*)-α-ethylleucyl-dimethylglycyl-dimethylglycinate* (CF_3CO-[(*S*)-αEtLeu]-Aib-Aib-OEt; **12**). A soln. of **6** (607 mg, 2.38 mmol), **11** (617 mg, 2.85 mmol), and EDC (547 mg, 2.85 mmol) in MeCN (20 ml) was refluxed for 2 d. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (SiO_2; 40% AcOEt/hexane): **12** (398 mg, 31%). Colorless crystals. M.p. 98–99° ($CHCl_3$/MeOH). $[\alpha]_D^{17} = +11.7$ ($c = 1.18$, $CHCl_3$). IR ($CHCl_3$): 3320 (br.), 1715 (br.), 1650. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.07 (br. *s*, 1 H); 7.12 (br. *s*, 1 H); 6.55 (br. *s*, 1 H); 4.22 (*q*, *J* = 7.3, 2 H); 2.55–2.65 (*m*, 2 H); 1.42–1.68 (*m*, 3 H); 1.65 (*s*, 3 H); 1.64 (*s*, 3 H); 1.60 (*s*, 3 H); 1.59 (*s*, 3 H); 1.28 (*t*, *J* = 7.1, 3 H); 0.89 (*d*, *J* = 6.6, 3 H); 0.84 (*d*, *J* = 6.3, 3 H); 0.73 (*t*, *J* = 7.4, 3 H). FAB-MS: 476 ($[M + Na]^+$), 454 ($[M + H]^+$).

*Ethyl Trifluoroacetyl-dimethylglycyl-(*S*)-2-α-ethylleucyl-dimethylglycyl-dimethylglycinate* (CF_3CO-Aib-[(*S*)-αEtLeu]-Aib-Aib-OEt; **13**). $NaBH_4$ (64 mg, 1.70 mmol) was added portionwise to the stirred soln. of **12** (385 mg, 0.849 mmol) in EtOH (10 ml) at 0°. After stirring at 0° for 8 h, the mixture was poured into 1% HCl soln. (40 ml), and then evaporated. The residue was diluted with 5% aq. $NaHCO_3$ soln., extracted with AcOEt, and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (SiO_2; 2% MeOH/$CHCl_3$): amine (81 mg, 69% based on 61% recovery). The soln. of the amine (81 mg, 0.227 mmol), CF_3CO-Aib (68 mg, 0.340 mmol), and EDC (65 mg, 0.340 mmol) in MeCN (5 ml) was refluxed for 2 d. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (SiO_2; 60% AcOEt/hexane): **13** (98 mg, 80%). Colorless crystals. M.p. 185–186° (from $CHCl_3$/MeOH). $[\alpha]_D^{25} = +4.3$ ($c = 0.97$, $CHCl_3$). IR (KBr): 3370, 3310, 3210, 3050, 1720, 1710, 1665, 1650. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.86 (br. *s*, 1 H); 7.46 (br. *s*, 1 H); 7.05 (br. *s*, 1 H); 6.63 (br. *s*, 1 H); 4.21 (*q*, *J* = 7.1, 2 H); 2.45–2.54 (*m*, 2 H); 1.73 (*s*, 3 H); 1.71 (*s*, 3 H); 1.43–1.62 (*m*, 3 H); 1.62 (*s*, 6 H); 1.58 (*s*, 6 H); 1.27 (*t*, *J* = 7.1, 3 H); 0.89 (*d*, *J* = 6.4, 3 H); 0.84 (*d*, *J* = 6.4, 3 H); 0.71 (*t*, *J* = 7.4, 3 H). Anal. calc. for $C_{24}H_{41}F_3N_4O6$: C 53.52, H 7.67, N 10.40; found: C 53.52, H 7.57, N 10.33.

*Ethyl Trifluoroacetyl-dimethylglycyl-dimethylglycyl-(*S*)-α-ethylleucyl-dimethylglycyl-dimethylglycinate* (CF_3CO-Aib-Aib-[(*S*)-αEtLeu]-Aib-Aib-OEt; **14**). $NaBH_4$ (19 mg, 0.501 mmol) was added portionwise to the stirred soln. of **13** (135 mg, 0.251 mmol) in EtOH (5 ml) at 0°, and the mixture was stirred for 8 h. The mixture was warmed to r.t., and stirred for 12 h, and then poured into 1% HCl soln. (20 ml), and the soln. was evaporated. The residue was diluted with 5% aq. $NaHCO_3$ soln., extracted with AcOEt, and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by short CC (SiO_2; 5% MeOH/$CHCl_3$): amine (80 mg, 72%). The soln. of amine (80 mg, 0.181 mmol), CF_3CO-Aib (54 mg, 0.271 mmol), and EDC (52 mg, 0.271 mmol) in MeCN (5 ml) was refluxed for 2 d. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (SiO_2; AcOEt): **14** (85 mg, 73%). Colorless crystals. M.p. 219–220° ($CHCl_3$/MeOH). $[\alpha]_D^{25} = -15.6$ ($c = 0.77$, EtOH). IR ($CDCl_3$): 3360, 3319, 3206, 1713, 1662. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.27 (br. *s*, 1 H); 7.13 (br. *s*, 1 H); 7.05 (br. *s*, 1 H); 6.84 (br. *s*, 1 H); 6.56 (br. *s*, 1 H); 4.16 (*q*, *J* = 7.3, 2 H); 1.88–2.12 (*m*, 2 H); 1.41–1.77 (*m*, 3 H); 1.65 (*s*, 3 H); 1.64 (*s*, 3 H); 1.56 (*s*, 6 H); 1.53 (*s*, 12 H); 1.24 (*t*, *J* = 7.1, 3 H); 0.91 (*d*, *J* = 6.6, 3 H); 0.88 (*d*, *J* = 6.6, 3 H); 0.77 (*t*, *J* = 7.4, 3 H). Anal. calc. for $C_{28}H_{48}F_3N_5O_7$: C 53.92, H 7.76, N 11.23; found: C 53.33, H 7.29, N 11.23.

*Ethyl Trifluoroacetyl-(*S*)-α-ethylleucyl-dimethylglycyl-dimethylglycyl-dimethylglycyl-dimethylglycinate* (CF_3CO-[(*S*)-αEtLeu]-Aib-Aib-Aib-Aib-OEt; **16**). The soln. of amine **15** (148 mg, 0.384 mmol) [9], **6** (98 mg, 0.384 mmol), EDC (88 mg, 0.461 mmol) in MeCN (5 ml) was refluxed for 2 d. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$), and evaporated, and the residue was purified by CC (SiO_2; 60% AcOEt/hexane): **16** (111 mg, 46%). Colorless crystals. M.p. 179–180° ($CHCl_3$/MeOH). $[\alpha]_D^{21} = -0.504$ ($c = 3.14$, $CHCl_3$). IR ($CDCl_3$): 3357, 1730, 1675, 1520. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.37 (br. *s*, 1 H); 7.18 (br. *s*, 1 H); 6.95 (br. *s*, 1 H); 6.54 (br. *s*, 1 H); 6.18 (br. *s*, 1 H); 4.14 (*q*, *J* = 7.3, 2 H); 2.21–2.36 (*m*, 2 H); 1.86 (*m*, 1 H); 1.55–1.76 (*m*, 2 H); 1.53 (*s*, 3 H); 1.52 (*s*, 6 H); 1.51 (*s*, 6 H); 1.49 (*s*, 3 H); 1.47 (*s*, 3 H); 1.46 (*s*, 3 H); 1.23 (*t*, *J* = 7.1, 3 H); 0.96 (*d*, *J* = 5.6, 3 H); 0.93 (*d*, *J* = 5.6, 3 H); 0.85 (*t*, *J* = 7.3, 3 H). Anal. calc. for $C_{28}H_{48}F_3N_5O_7$: C 53.92, H 7.76, N 11.23; found: C 53.65, H 7.74, N 10.77.

*Ethyl Trifluoroacetyl-(*S*)-α-ethylleucyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycinate* (CF_3CO-[(*S*)-αEtLeu]-Deg-Deg-Deg-Deg-OEt; **18**). A soln. of amine **17** (131 mg, 0.263 mmol) [6d], **6** (80 mg, 0.315 mmol), EDC (76 mg, 0.394 mmol) in MeCN (5 ml) was refluxed for 7 d. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% HCl and 5% aq. $NaHCO_3$ solns., and the extract was dried ($MgSO_4$) and evaporated. The residue was purified by CC (SiO_2; 50% AcOEt/hexane): **18** (50 mg, 26%). Colorless crystals. M.p. 197–198° ($CHCl_3$/MeOH). $[\alpha]^{25}{}_D = +9.0$ ($c = 1.40$, $CHCl_3$). IR ($CDCl_3$): 3353, 1720, 1675, 1652. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.11 (br. *s*, 1 H); 7.43 (br. *s*, 1 H); 7.40 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 6.77 (br. *s*, 1 H);

4.28 (q, $J = 7.3$, 2 H); 2.38–2.69 (m, 10 H); 1.60–1.91 (m, 11 H); 1.32 (t, $J = 7.3$, 3 H), 0.74–0.91 (m, 33 H). Anal. calc. for $C_{36}H_{64}F_3N_5O_7$: C 58.75, H 8.77, N 9.52; found: C 58.60, H 8.69, N 9.52.

X-Ray Crystal-Structure Determination[4]). All crystals of **8**, **9**, **14**, and **18** were grown from $CHCl_3$/MeOH. Data collection was performed on a *Rigaku-RAXIS-RAPID* imaging plate diffractometer, graphite-monochromated MoK_α radiation. Crystal and collection parameters are listed in *Table 4*. All crystals remained stable during the X-ray-data collection. The structures were solved by direct methods with SIR92 [17] and expanded by *Fourier* techniques [18]. All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the rest H-atoms included in calculated positions were given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of **8** gave an R factor of 0.120 ($R_w =$ 0.187) based on 3187 ($I > -10.00\,\sigma(I)$) reflections and R_1 factor of 0.065 based on 1829 ($I > 2.0\,\sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.35 and -0.29 eÅ^{-3}. The R factor of **9** was 0.073 ($R_w = 0.098$) based on 3089 ($I > -10.00\,\sigma(I)$) reflections and R_1 factor of 0.041 based on 1917 ($I > 2.0\,\sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.28 and -0.23 eÅ^{-3}. The R factor of **14** was 0.081 ($R_w = 0.124$) based on 8389 ($I > -10.00\,\sigma(I)$) reflections and R_1 factor of 0.047 based on 4219 ($I > 2.0\,\sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.50 and -0.45 eÅ^{-3}. The R factor of **18** was 0.130 ($Rw = 0.185$) based on 9306 ($I > -10.00\,\sigma(I)$) reflections and R_1 factor of 0.067 based on 5152 ($I > 2.0\,\sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.75 and -0.56 eÅ^{-3}, resp. All calculations were performed by means of the teXsan [19] crystallographic package.

Table 4. *Crystal and Diffraction Parameters of the Peptides* **8**, **9**, **14**, *and* **18**

	8	**9**	**14**	**18**
Empirical formula	$C_{20}H_{35}O_4N_2F_3$	$C_{20}H_{35}O_4N_2F_3$	$C_{28}H_{48}O_7N_5F_3$	$C_{36}H_{64}O_7N_5F_3$
M_r	424.5	424.5	623.71	735.93
Crystal dimensions [mm]	$0.40 \times 0.40 \times 0.40$	$0.25 \times 0.20 \times 0.20$	$0.30 \times 0.30 \times 0.10$	$0.20 \times 0.15 \times 0.10$
Data collection temp.	23°	−150°	−150°	−150°
Crystal system	orthorhombic	orthorhombic	orthorhombic	monoclinic
Lattice parameters:				
a, b, c [Å]	11.301, 11.318, 19.284	11.768, 18.060, 11.224	18.884, 22.285, 16.010	15.017, 11.562, 23.981
β [°]	90	90	90	92.416
V [Å^3]	2466.5	2385.6	6737.6	4160.2
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Z Value	4	4	8	4
D_{calc} [g/cm^3]	1.143	1.182	1.230	1.175
μ(MoK_α) [cm^{-1}]	0.93	0.96	0.99	0.90
No. of observations	3187 ($I > -10.0\,\sigma(I)$)	3089 ($I > -10.0\,\sigma(I)$)	8389 ($I > -10.0\,\sigma(I)$)	9306 ($I > -10.0\,\sigma(I)$)
No. of variables	272	404	817	920
R, R_w	0.120, 0.187	0.073, 0.098	0.081, 0.124	0.130, 0.185
No. of reflections to calc R_1	1829 ($I > 2.0\,\sigma(I)$)	1917 ($I > 2.0\,\sigma(I)$)	4219 ($I > 2.0\,\sigma(I)$)	5152 ($I > 2.0\,\sigma(I)$)
R_1	0.065	0.041	0.047	0.067
Solvent of crystallization	$CHCl_3$/MeOH	$CHCl_3$/MeOH	$CHCl_3$/MeOH	$CHCl_3$/MeOH

Molecular-Mechanics Calculations. Conformational-energy calculations were performed with the package of MacroModel Ver. 6.5 [16] on a *SGI* O_2 workstation. The parameters used were as follows: conformational search, MonteCarlo method; force field, AMBER*; more than 15000 structures were minimized; solvent, H_2O. The fully planar C_5 conformations of heteropeptides **14**, **16**, and **18** were used as the initial conformations for the calculations. The four conformations A (0 kcal/mol), B (+1.16 kcal/mol), C (+1.27 kcal/mol), and D (+1.82 kcal/mol) were obtained as the global minimum-energy conformations of **14** within 3.0 kcal/mol. The two conformations E (0 kcal/mol) and F (+1.42 kcal/mol) were calculated within 3.0 kcal/mol as the global

[4]) 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-180264, 180265, 180266, and 180267. 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) 336033; e-mail: deposit@ccdc.cam.ac.uk).

minimum-energy conformations of **16**. The conformational calculations of **18** afforded the two helical conformations *G* (0 kcal/mol) and *H* (+1.45 kcal/mol) as the global minimum-energy conformations, and no planar C_5 conformation was observed within 3.0 kcal/mol of the global minimum energy.

This work was partly supported by a *Grant-in-Aid for Scientific Research* (C) from *Japan Society for the Promotion of Science*.

REFERENCES

[1] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219.

[2] K. Gademann, M. Ernst, D. Hoyer, D. Seebach, *Angew. Chem., Int. Ed.* **1999**, *38*, 1223; E. A. Porter, X. Wang, H. S. Lee, B. Weisblum, S. H. Gellman, *Nature* **2000**, *404*, 565; T. S. Yokum, P. H. Elzer, M. L. McLaughlin, *J. Med. Chem.* **1996**, *39*, 3603.

[3] P. Rossi, F. Felluga, P. Tecilla, F. Formaggio, M. Crisma, C. Toniolo, P. Scrimin, *J. Am. Chem. Soc.* **1999**, *121*, 6948; C. Sissi, P. Rossi, F. Felluga, F. Formaggio, M. Palumbo, P. Tecilla, C. Toniolo, P. Scrimin, *J. Am. Chem. Soc.* **2001**, *123*, 3169; T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem., Int. Ed.* **2000**, *39*, 3635.

[4] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem., Int. Ed.* **1996**, *35*, 2708; C. Cativiela, M. D. D.-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517; C. Cativiela, M. D. D.-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645; R. Nagaraji, P. Balaram, *Acc. Chem. Res.* **1981**, *14*, 356; J. R. Cronin, S. Pizzarello, *Science* **1997**, *275*, 951.

[5] a) B. V. V. Prasad, P. Balaram, *Crit. Rev. Biochem.* **1984**, *16*, 307; b) I. L. Karle, P. Balaram, *Biochemistry* **1990**, *29*, 6747; c) I. L. Karle, *Acc. Chem. Res.* **1999**, *32*, 693; d) R. Kaul, P. Balaram, *Bioorg. Med. Chem.* **1999**, *7*, 105; e) R. Improta, V. Barone, K. N. Kudin, G.E. Scuseria, *J. Am. Chem. Soc.* **2001**, *123*, 3311.

[6] a) E. Benedetti, V. Barone, A. Bavoso, B. D. Blasio, F. Lelj, V. Pavone, C. Pedone, G. M. Bonora, C. Toniolo, M. T. Leplawy, K. Kaczmarek, A. Redlinski, *Biopolymers* **1988**, *27*, 357, 373; b) P. M. Hardy, I. N. Lingham, *Int. J. Peptide Protein Res.* **1983**, *21*, 392; c) E. Benedetti, C. Toniolo, P. Hardy, V. Barone, A. Bavoso, B. D. Blasio, P. Grimaldi, F. Lelj, V. Pavone, C. Pedone, G. Maria, and I. Lingham, *J. Am. Chem. Soc.* **1984**, *106*, 8146, 8152; d) M. Tanaka, N. Imawaka, M. Kurihara, H. Suemune, *Helv. Chim. Acta* **1999**, *82*, 494.

[7] a) C. Toniolo, M. Crisma, F. Formaggio, G. Valle, G. Cavicchioni, G. Precigoux, A. Aubry, J. Kamphuis, *Biopolymers* **1993**, *33*, 1061; b) F. Formaggio, M. Crisma, G. M. Bonora, M. Pantano, G. Valle, C. Toniolo, A. Aubry, D. Bayeul, J. Kamphuis, *Pept. Res.* **1995**, *8*, 6; c) A. Polese, F. Formaggio, M. Crisma, G. Valle, C. Toniolo, G. M. Bonora, Q. B. Broxterman, J. Kamphuis, *Chem.–Eur. J.* **1996**, *2*, 1104; d) S. Mammi, M. Rainaldi, M. Bellanda, E. Schievano, E. Peggion, Q. B. Broxterman, F. Formaggio, M. Crisma, C. Toniolo, *J. Am. Chem. Soc.* **2000**, *122*, 11735; e) B. Jaun, M. Tanaka, P. Seiler, F. N. M. Kühnle, C. Braun, D. Seebach, *Liebigs Ann./Recueil* **1997**, 1697.

[8] N. Imawaka, M. Tanaka, H. Suemune, *Helv. Chim. Acta* **2000**, *83*, 2823.

[9] M. Tanaka, M. Oba, N. Imawaka, Y. Tanaka, M. Kurihara, H. Suemune, *Helv. Chim. Acta* **2001**, *84*, 32.

[10] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, *30*, 238; C. Toniolo, E. Benedetti, *Macromolecules* **1991**, *24*, 4004; E. Benedetti, *Biopolymers (Peptide Science)* **1996**, *40*, 3; C. L. Wysong, T. S. Yokum, M.L. McLaughlin, R. P. Hammer, *Chemtech* **1997**, 26; M. Tanaka, *J. Synth. Org. Chem., Jpn.* **2002**, *60*, 125.

[11] K. Sakai, H. Suemune, *Tetrahedron: Asymmetry* **1993**, *4*, 2109; K. Kato, K. Sakai, H. Suemune, *Tetrahedron Lett.* **1992**, *33*, 247; K. Kato, K. Sakai, H. Suemune, *Tetrahedron* **1994**, *50*, 3315.

[12] G. I. Georg, X. Guan, J. Kant, *Tetrahdron Lett.* **1988**, *29*, 403.

[13] M. Tanaka, M. Oba, K. Tamai, H. Suemune, *J. Org. Chem.* **2001**, *66*, 2667.

[14] C. Toniolo, F. Formaggio, M. Crisma, H. E. Schoemaker, J. Kamphuis, *Tetrahedron: Asymmetry* **1994**, *5*, 507; C. Toniolo, A. Polese, F. Fornando, M. Crisma, J. Kamphuis, *J. Am. Chem. Soc.* **1996**, *118*, 2744; G. Yoder, A. Polese, R. A. G. D. Silva, F. Formaggio, M. Crisma, Q. B. Broxterman, J. Kamphuis, C. Toniolo, T. A. Keiderling, *J. Am. Chem. Soc.* **1997**, *119*, 10278.

[15] M. Kurihara, M. Tanaka, N. Imawaka, H. Suemune, N. Miyata, *JCPE Journal Jpn.* **1999**, *11*, 185.

[16] C. W. Still, Department of Chemistry, Columbia University.

[17] A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, G. Polidori, *J. Appl. Crystallogr.* **1994**, *27*, 435.

[18] P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel, J. M. M. Smits, the DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.
[19] Molecular Structure Corporation, 3200 Research Forest Drive, The Woodlands, TX 77381, USA, teXsan: Crystal Structure Analysis Package, 1985 and 1992.

Received March 22, 2002