An Extended Planar C_5 Conformation and a 3_{10}-Helical Structure of Peptide Foldamer Composed of Diverse α-Ethylated α,α-Disubstituted α-Amino Acids

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Abstract: Optically active peptide foldamers Tfa-[(S)-(αEt)Leu]-[(S)-(αEt)Nva]-Deg-[(S)-(αEt)Nle]-OEt (**10**) and Tfa-[(S)-(αEt)Val]-[(S)-(αEt)Leu]-[(S)-(αEt)-Nva]-Deg-[(S)-(αEt)Nle]-OEt (**11**) composed of diverse α-ethylated α,α-disubstituted α-amino acids were synthesized. The dominant conformation of these peptides in solution was an unusual, fully extended planar conformation, and that in the crystal state was both right-handed (*P*) and left-handed (*M*) 3_{10}-helical structures in **10** and a *P* 3_{10}-helical structure in **11**, respectively. The preferred planar C_5 conformation of the peptides prepared from chiral α-ethylated α,α-disubstituted α-amino acids was drastically different from the 3_{10}-helical structure of the peptides prepared from chiral α-methylated α,α-disubstituted α-amino acids.

Keywords: amino acids · conformation analysis · helical structures · peptidomimetics

Introduction

Foldamers, which were named by Gellman,[1] are oligomers having well-defined secondary structural preferences. Within the past decade, many unnatural oligomers bearing interesting conformational properties have been reported, because control of the folding pattern leads to new types of molecules with useful properties. In particular, peptide-foldamers such as β-peptides,[2] which are made from β-amino acids, and the peptides prepared from α,α-disubstituted α-amino acids[3] have been focused on by organic, peptide, and medicinal chemists.

It has been well known that the homopeptides prepared from achiral 2-aminoisobutyric acid (Aib) form a 3_{10}-helical structure,[4] whereas those from diethylglycine [Deg: 2-ethyl-2-aminobutyric acid ((αEt)Abu)],[5a] dipropylglycine (Dpg),[5b,c] and diphenylglycine form a fully extended planar C_5 conformation.[5] Recently, the Toniolo and the Seebach groups concentrated on the conformation of oligopeptides prepared from optically active α,α-disubstituted α-amino acids, because proteinogenic α-amino acids are chiral molecules except for glycine. They reported that the homo- and heteropeptides prepared from chiral α-methylated α,α-disubstituted α-amino acids [(αMe)AAs] formed the 3_{10}-helical structures in the crystal state and in solution, and the screw sense of helicity, right-handed (*P*) or left-handed (*M*) helicity, depended on the chiral center of the quaternary carbon of (αMe)AAs.[3e,f, 6, 7] On the other hand, we reported that the conformation of homopeptides prepared from a chiral α-ethylated α,α-disubstituted α-amino acid [(αEt)AA]; (*S*)-butylethylglycine [(*S*)-Beg,α-ethylnorleucine, (*S*)-(αEt)Nle] was the fully planar C_5 conformation both in the crystal state and in solution.[8] The fully extended conformation was formed in the case of unusual homopeptides prepared from glycine,[9] Deg, Dpg, or (*S*)-(αEt)Nle (Beg), and also was observed in the case of unusual heteropentapeptides containing one chiral α-amino acid as a guest molecule in the sequences of Deg residues.[10, 11] We herein describe for the first time the synthesis of heteropentapeptide Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**), in which each of the amino acid residues is a different α-ethylated α,α-disubstituted α-amino acid, and also report its 3_{10}-helical and planar C_5 conformation in the crystal state and in solution.

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Results and Discussion

Design of heteropentapeptide: As an (αEt)AA heteropeptide, we designed pentapeptide Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**),

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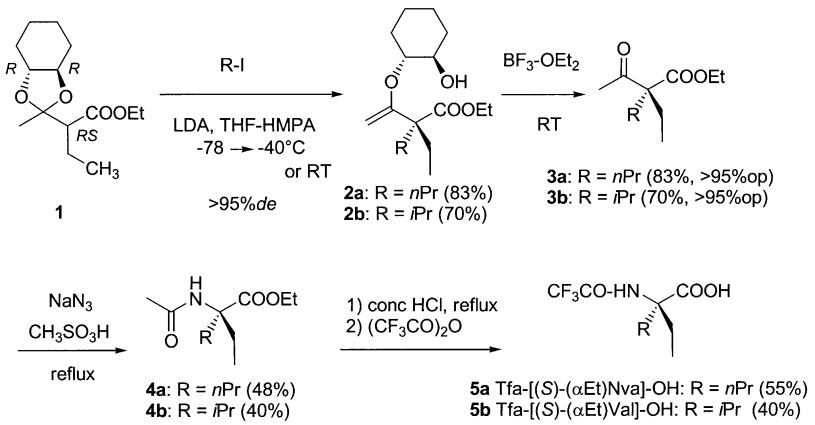
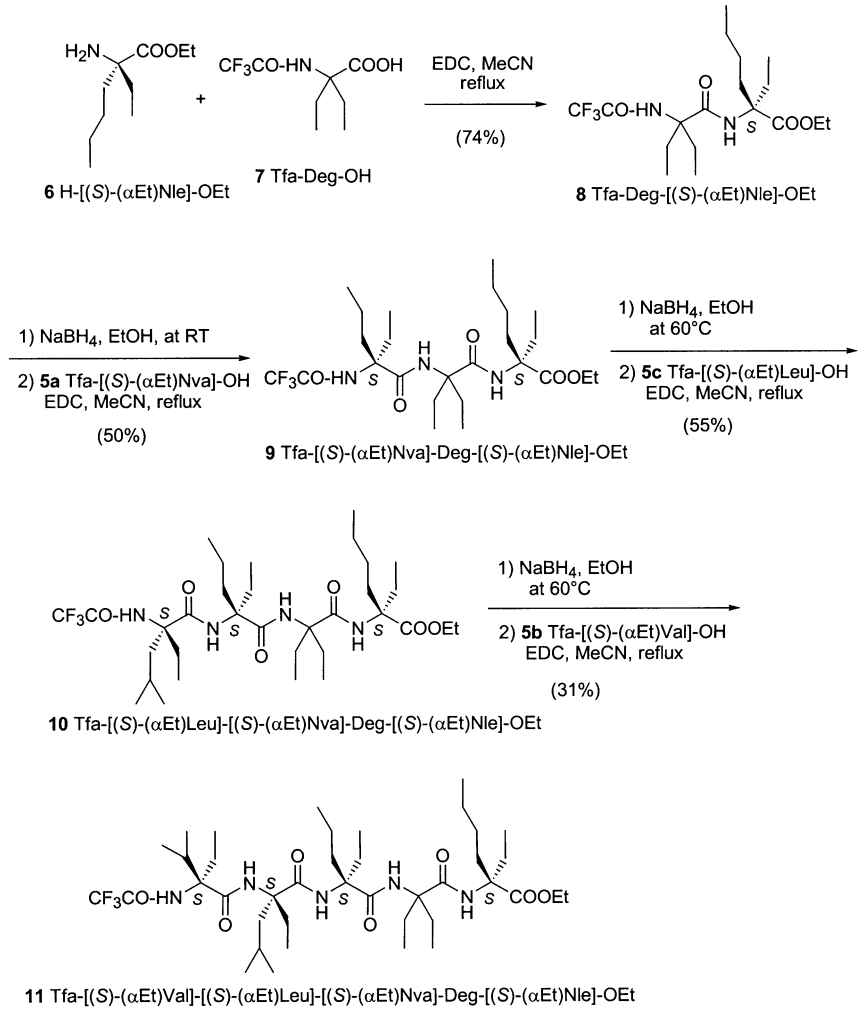
which has different (αEt)AAs as the individual amino acid residues, and the structure is very different from those of the Deg and (*S*)-(αEt)Nle homopeptides,[8] which preferentially form the planar C_5 conformation.

Asymmetric synthesis of (*S*)-α-ethylated α,α-disubstituted α-amino acids: We synthesized the optically active (αEt)AAs by an asymmetric alkylation of the β-keto ester by using (*R*,*R*)-cyclohexane-1,2-diol as a chiral auxiliary, and subsequent Schmidt rearrangement, as shown in Scheme 1.[12, 13] That is to say, chiral **1**, which consists of (*R*,*R*)-cyclohexane-1,2-diol and ethyl 2-ethylacetoacetate, was alkylated with LDA (5 equiv), Pr-I (5 equiv), and HMPA (5 equiv) in THF at -78 to $-40\,^{\circ}C$ or room temperature to give enol ethers **2a** and **2b** in 83 and 70% yield, respectively. The cyclohexane-1,2-diol moiety in **2** was removed by treatment with $BF_3\cdot OEt_2$ in EtOH/H_2O to afford β-keto esters **3a** (83%) and **3b** (70%). The optical purities (>95% op) and absolute configurations of **3a** and **3b** were determined by comparison with the reported specific rotations.[13] The obtained β-keto esters **3a** and **3b** could be converted into the α,α-disubstituted α-amino acids **4a** in 48% and **4b** in 40% yield by Schmidt rearrangement. The protecting group in **4** was removed by hydrolysis with concentrated HCl, and then the N terminus was protected as a trifluoroacetyl group to produce Tfa-[(*S*)-(αEt)Nva]-OH **5a** in 55% and Tfa-[(*S*)-(αEt)Val]-OH **5b** in 40% yield, respectively.



Scheme 1. Synthesis of the optically active (αEt)AAs.



Scheme 2. Preparation of heteropentapeptide **11**. Yields are based on recovered materials.

Preparation of heteropentapeptide Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt: We prepared the heteropentapeptide Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**) by the solution-phase methods, employing an ethyl ester as the C terminus and a trifluoroacetyl group as the N terminus (Scheme 2). At first, the dipeptide **8** was prepared in 74% yield by the coupling of H-(*S*)-(αEt)Nle-OEt (**6**) and Tfa-Deg-OH (**7**) by using 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC). Removal of the trifluoroacetyl group in **8** by $NaBH_4$ reduction followed by coupling with Tfa-[(*S*)-(αEt)Nva]-OH (**5a**) by treatment with EDC in refluxing MeCN gave tripeptide **9** in 50% yield based on the

recovered material. Tetra- and pentapeptides **10** (55%) and **11** (31%) were synthesized in a manner similar to that described for **9**. The spectroscopic data of all compounds supported their structures.

Crystal-state conformational analysis: We determined the molecular and crystal structures of the three terminally protected tri-, tetra-, and pentapeptides **9**, **10**, and **11** by X-ray crystallographic analysis.[14] Crystals of good quality for X-ray analysis were obtained by slow evaporation of an EtOH or EtOH/$CHCl_3$ solution at room temperature. The molecular structures of **9**, **10**, and **11** with atomic-numbering schemes are given in Figures 1–4. Relevant backbone and side-chain torsion angles are summarized in Table 1. The intra- and intermolecular hydrogen-bond parameters are listed in Table 2.

The structure of tripeptide **9** was solved in the space group $P2_12_12_1$. Two intramolecular hydrogen bonds are observed, that is to say, intramolecularly hydrogen-bonded C_5 conformations of the residues (*S*)-(αEt)Nva[1] and (*S*)-(αEt)Nle[3] are formed in the crystal state. The set of torsion angles ϕ,ψ for the residue are $+177.6$, -179.8° for (*S*)-(αEt)Nva[1] and $+177.0$, $+177.5^\circ$ for (*S*)-(αEt)Nle[3]. The N1$\cdots$O1 distance is 2.54 Å and the N3$\cdots$O3 is 2.60 Å. The torsion angles of Deg[2] are -59.5, -42.8°. In the packing mode, one intermolecular hydrogen bond is shown between the H–N2 peptide donor and the C2′=O2′ carbonyl oxygen atom of the peptide of a symmetry-related molecule ($-x+\frac{1}{2}$, $-y$, $z+\frac{1}{2}$), with an N2$\cdots$O2′ distance of 2.93 Å. The conformation of **9** in the crystal state is a bent planar C_5 conformation, which is very similar to that of homotripeptide Tfa-$(Deg)_3$-OEt prepared from diethylglycine[5d] and that of homotripeptide Tfa-[(*S*)-(αEt)Nle]$_3$-OEt prepared from (*S*)-butylethylglycine (Figure 1).[8]

Table 1. Selected torsion angles ω, ϕ, ψ, and χ[a] [°] for the peptides **9**, **10**, and **11** as determined by X-ray crystallographic analysis.

Torsion angle	Tripeptide **9**	Tetrapeptide **10** molecule **A** (*M*)	Tetrapeptide **10** molecule **B** (*P*)	Pentapeptide **11**
ω_0	−173.1	176.5	−174.6	−170.6
ϕ_1	177.6	53.7	−58.2	−58.3
ψ_1	−179.8	37.1	−34.9	−37.5
ω_1	−172.8	169.6	−178.4	−173.9
ϕ_2	−59.5	56.0	−48.4	−57.4
ψ_2	−42.8	26.0	−34.5	−19.1
ω_2	−171.2	177.8	−175.8	176.3
ϕ_3	177.0	53.7	−52.0	−48.7
ψ_3	177.5	33.6	−39.7	−32.1
ω_3	−176.7	179.0	−177.2	−175.1
ϕ_4	–	−48.6	46.9	−52.8
ψ_4	–	−53.0	56.2	−37.5
ω_4	–	−175.1	174.0	−178.9
ϕ_5	–	–	–	47.2
ψ_5	–	–	–	52.7
ω_5	–	–	–	174.9
χ_1^e	−53.2	−176.1	58.7	30.3
χ_1^a	52.3	−66.5	179.6	−71.0[b]
χ_2^e	65.7	176.3	64.7	66.2
χ_2^a	−177.1	−61.4	−178.4	81.0
χ_3^e	−58.5	−177.1	60.8	63.3
χ_3^a	57.7	−49.5	177.5	179.2
χ_4^e	–	65.2	−175.1	60.1
χ_4^a	–	−175.8	−66.9	179.6
χ_5^e	–	–	–	−174.9
χ_5^a	–	–	–	−65.3

[a] The superscripts e and a refer to the ethyl and the alkyl side chains, respectively. [b] The angle $\chi_1^a = 165.8^\circ$ also exists because the substituent of the side chain is an isopropyl group.

Table 2. Intra- and intermolecular hydrogen bond parameters for the peptides **9**, **10**, and **11**.[a]

Donor D–H	Acceptor A	Distance [Å] D$\cdots$A	Angle [°] D–H$\cdots$A	Symmetry operations
Tfa-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**9**)				
N_1–H	O_1	2.54	110	x,y,z
N_3–H	O_3	2.60	108	x,y,z
N_2–H	$O_{2'}$	2.93	173	$-x+\frac{1}{2},-y,z+\frac{1}{2}$
Tfa-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**10**)				
A (*M*)				
N_{3a}–H	O_{0a}	3.18	164	x,y,z
N_{4a}–H	O_{1a}	3.06	166	x,y,z
B (*P*)				
N_{3b}–H	O_{0b}	3.01	161	x,y,z
N_{4b}–H	O_{1b}	3.00	150	x,y,z
N_{1a}–H	$O_{4b'}$	2.92	172	x,y,z
N_{2a}–H	$O_{5b'}$	3.34[b]	135	x,y,z
N_{1b}–H	$O_{4a'}$	2.87	179	$x-1,y-1,z-1$
N_{2b}–H	$O_{5a'}$	3.25[b]	141	$x-1,y-1,z-1$
Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**)				
N_3–H	O_0	3.10	168	x,y,z
N_4–H	O_1	3.12	162	x,y,z
N_5–H	O_2	3.13	179	x,y,z
N_1–H	$O_{4'}$	2.91	172	$x,y,z-1$
N_2–H	$O_{5'}$	3.47[b]	158	$x,y,z-1$

[a] The number of the amino-acid residues begins at the N terminus of the peptide chain. [b] The distance of D$\cdots$A is somewhat long for a hydrogen bond.

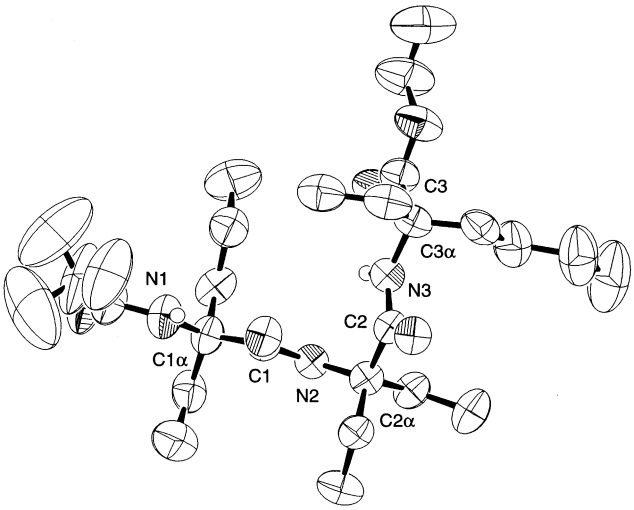


Figure 1. ORTEP drawing of the molecular structure of Tfa-[(*S*)-(αEt)-Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**9**) with atom numbering (ellipsoids at 50% probability).

Tetrapeptide **10** crystallizes in the triclinic space group *P*1. Two crystallographically independent molecules **A** and **B** exist in the asymmetric unit of **10**. Both molecules **A** and **B** are folded into the 3_{10}-helical structure: molecule **A** has a left-handed (*M*) structure and molecule **B** is right-handed (*P*), as shown in Figure 2. The corresponding ϕ,ψ torsion angles

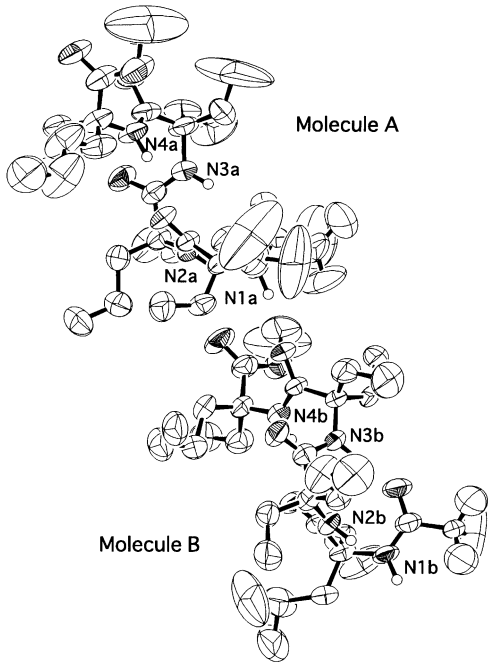


Figure 2. ORTEP drawing of the molecular structure of Tfa-[(*S*)-(αEt)-Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**10**) with atom numbering (ellipsoids at 50% probability).

between two molecules of opposite helicity are different by sign, but the absolute values are similar. The relationship of the two molecules **A** and **B** is not enantiomeric but diastereomeric because the chiral centers of amino acid residues in both molecules **A** and **B** are the same *S* configuration. In molecule **A**, the signs of the ϕ and ψ torsion angles (-48.6, -53.0°) of the (*S*)-(αEt)Nle^{4a} residue at the C terminus are opposite to those of the preceding residues (*S*)-(αEt)Leu^{1a}, (*S*)-(αEt)Nva^{2a} and Deg^{3a} (positive signs); also, in molecule **B**, the signs of the torsion angles ($+46.9$, $+56.2^\circ$) of the (*S*)-(αEt)Nle^{4b} residue are opposite to those of the preceding residues (negative signs); this phenomenon is frequently observed in the 3_{10}-helical peptides of Aib.[4] Molecule **A** shows two intramolecular hydrogen bonds between the H–N3a and C0a=O0a oxygen atom of the trifluoroacetyl group with an N3a$\cdots$O0a distance of 3.18 Å and between H–N4a and C1a=O1a (N4a$\cdots$O1a = 3.06 Å), and molecule **B** similarly shows two intramolecular hydrogen bonds between H–N3b and C0b=O0b (N3b$\cdots$O0b = 3.01 Å) and between H–N4b and C1b=O1b (N4b$\cdots$O1b = 3.00 Å). In the packing mode, two intermolecular hydrogen bonds are formed between the H–N1a peptide donor and C4b′=O4b′ O atom (N1a$\cdots$O4b′ = 2.92 Å), and between H–N1b and C4a′=O4a′ of a symmetry-related molecule ($x-1$, $y-1$, $z-1$) (N1b$\cdots$O4a′ = 2.87 Å). Moreover, two weak intermolecular hydrogen bonds are observed between H–N2a and C5b′=O5b′ (N2a$\cdots$O5b′ = 3.34 Å) and also between H–N2b and C5a′=O5a′ of a symmetry-related molecule ($x-1$, $y-1$, $z-1$) (N1b$\cdots$O5a′ = 3.25 Å). The chains of intermolecularly hydrogen-bonded molecules are formed in a head-to-tail alignment of *P* 3_{10}-helix (molecule **B**) and *M* 3_{10}-helix (molecule **A**), that is, $\cdots P\cdots M\cdots P\cdots M\cdots$ chains of the 3_{10}-helical molecules **A** and **B** are formed.

The structure of heteropentapeptide **11** was solved in the monoclinic space group $P2_1$. Only one 3_{10}-helical structure exists in the asymmetric unit (Figure 3). The screw sense of helicity is a right-handed (*P*) helix, but a flip of the torsion

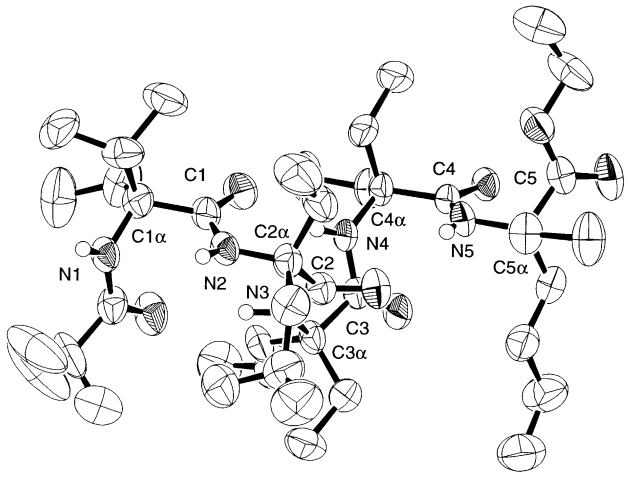


Figure 3. ORTEP Drawing of the molecular structure of Tfa-[(*S*)-(αEt)-Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**) with atom numbering (ellipsoids at 50% probability).

angles at the C terminus occurs, that is, the signs of the ϕ and ψ torsion angles ($+47.2$, $+52.7^\circ$) of the (*S*)-(αEt)Nle^5 residue are opposite to those of the preceding residues (*S*)-(αEt)Val^1, (*S*)-(αEt)Leu^2, (*S*)-(αEt)Nva^3 and Deg^4 (negative signs), corresponding to a change (*M*) in the handedness of the helix at the C terminus. The mean values of the ϕ and ψ torsion angles for the sequence (*S*)-(αEt)Val^1 to Deg^4 are $\phi = -54.3$ and $\psi = -31.6^\circ$, close to the ideal right-handed (*P*) 3_{10}-helix (-49 and -26°).[3d] Figure 4 shows the ORTEP drawing of the

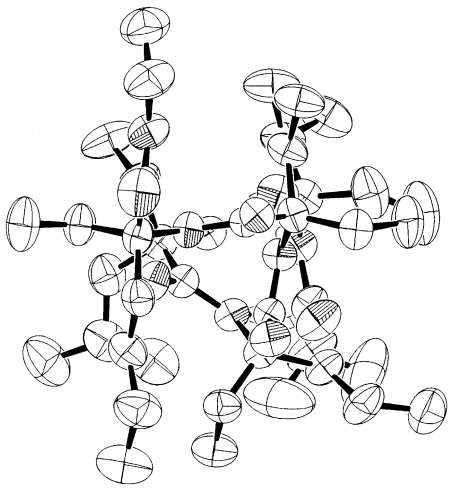


Figure 4. ORTEP Drawing of **11** as view along the helix axis (ellipsoids at 50% probability).

P 3_{10}-helical structure along the helix axis. There are three intramolecular hydrogen bonds between H–N3 and the C0=O0 oxygen atom of the trifluoroacetyl group with an N3$\cdots$O0 distance of 3.10 Å, between H–N4 and C1=O1 (N4$\cdots$O1 = 3.12 Å), and between H–N5 and C2=O2 (N5$\cdots$

O2 = 3.13 Å). In the packing mode, one intermolecular hydrogen bond is observed between H–N1 and the C4′=O4′ O atom of a symmetry-related molecule (x, y, $z-1$) (N1 ··· O4′ = 2.91 Å), and the N2 ··· O5′ distance of 3.47 Å is somewhat long for a hydrogen bond between H–N2 and C5′=O5′ carbonyl oxygen atom. As a result, the chains of intermolecularly hydrogen-bonded 3_{10}-helices are formed in the $\cdots P \cdots P \cdots P \cdots P \cdots$ mode of the head-to-tail alignment, along the c direction.

Solution conformational analysis: At first, the preferred conformation of the heteropeptides in $CDCl_3$ solution was studied by FT-IR spectroscopy. The IR spectra of tetra- and pentapeptides **10** and **11** remain essentially unchanged at the concentration range of 1.0 – 10.0 mM. These results mean that the concentration of the peptide does not affect the strength of the intermolecular hydrogen bonds. Figure 5 shows the IR

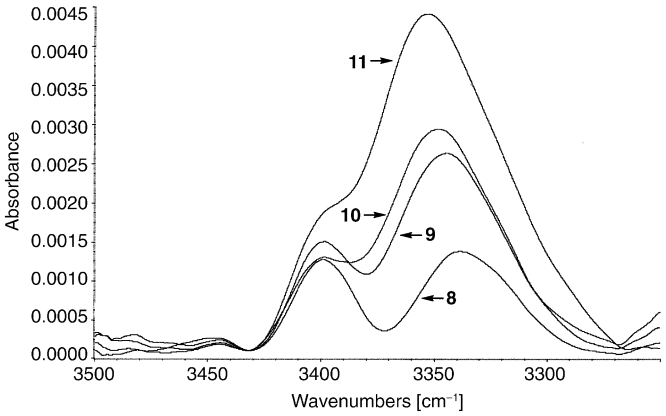


Figure 5. FT-IR Absorption spectra (3500 – 3250 cm^{-1} region) of the heteropeptides **8**, **9**, **10**, and **11** in $CDCl_3$ solution. Peptide concentration 1.0 mM.

absorption of the di- to pentapeptides **8** – **11** in the 3250 – 3500 cm^{-1} region at a peptide concentration of 1.0 mM. The band at 3380 – 3420 cm^{-1} is assigned to amide NH groups with a relatively strong C–F ··· H(N) ··· O=C intramolecular hydrogen bond, and that at 3340 – 3360 cm^{-1} to peptide NH groups with N–H ··· O=C intramolecular hydrogen bonds of different strength. With increasing the peptide main-chain length, the relative intensity of the absorption band at 3340 – 3360 cm^{-1} region increases, and also the absorption observed at 3340 cm^{-1} in the dipeptide **8** shifts to higher wave numbers (3360 cm^{-1} in the pentapeptide **11**). These IR spectra are very similar to those of the Deg and (*S*)-(αEt)Nle homopeptides that form the extended planar C_5 conformation in solution,[5d, 8a] but very different from those of Aib homopeptides and heteropeptides which form the 3_{10}-helical structure.[4, 8a, 10]

Next, we measured the ^{1}H NMR spectra of the tetrapeptide **10** and the pentapeptide **11** under various conditions. In the ^{1}H NMR spectra of **10** and **11** in $CDCl_3$, the signals of the trifluoroacetamide NH at the N terminus are unambiguously determined by their high-field position at $\delta = 6.78$ ppm (br s, 1H) both in **10** and **11**, and those of the amide NH at the C terminus are assigned by their low-field position to $\delta = 8.10$ (br s, 1H) in **10** and 8.17 ppm (br s, 1H) in **11**, on analogy of the N- and C-terminal NH signals of dipeptide **8**. The precise assignments of the two remaining internal NH protons in **10** and three NH protons in **11** cannot be made, and these signals appear in a narrow region of $\delta = 7.35 – 7.49$ ppm. The chemical shifts of all NH protons in **10** were essentially independent of the concentration at the examined range of 1.0 – 10.0 mM in **10**. The additional effects of the strong hydrogen-bonding acceptor solvent, DMSO or the paramagnetic free radical 2,2,6,6-tetramethyl-1-piperidyloxyl (TEMPO), on the chemical shifts of NH signals were measured for the tetrapeptide **10** and pentapeptide **11**. Figure 6 shows the results that all NH signals both in **10** and **11** are almost insensitive to the addition of the two perturbing agents DMSO (0 – 10% (v/v)) and TEMPO ($0 – 5 \times 10^{-2}$% (w/v)); this means that no solvent-exposed NH protons exist in the peptides. It has been known that two NH protons forming intermolecular hydrogen bonds of the 3_{10}-helical structures are sensitive to addition of the perturbing agents, but all NH protons of the fully planar C_5 conformation are insensitive.[6, 10] These ^{1}H NMR experiments of the heteropeptides **10** and **11** are the same as those of the Deg and (*S*)-(αEt)Nle homopeptides, which form the fully planar C_5 conformation in solution.[5d, 8a]

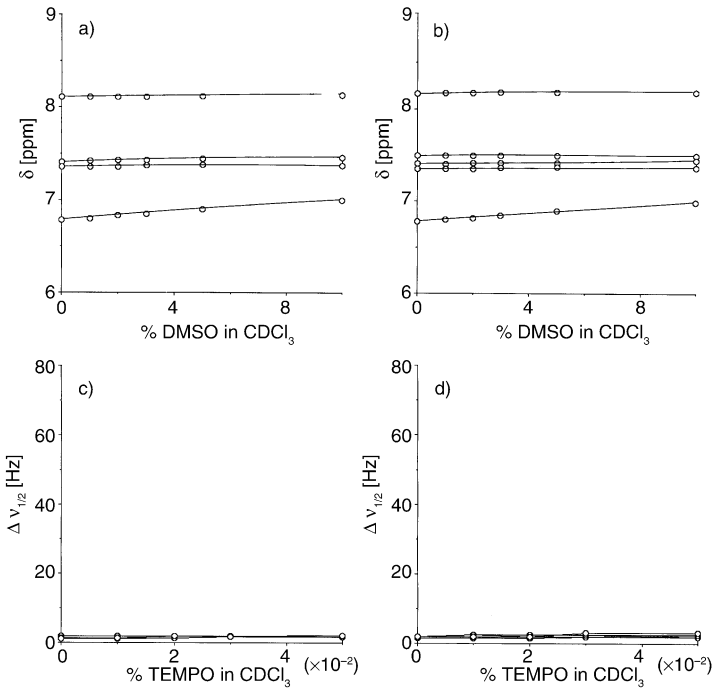


Figure 6. a) Plots of NH chemical shifts in the ^{1}H NMR spectra of Tfa-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**10**; 1.0 mM), and b) of Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt (**11**; 1.0 mM) as a function of increasing percentages of DMSO (v/v) added to the $CDCl_3$ solution; c) plots of the bandwidth of the NH protons of **10** (1.0 mM), and d) of **11** (1.0 mM) as a function of increasing percentages of TEMPO (w/v) added to the $CDCl_3$ solution.

We also measured the CD spectra of the heteropeptides **8**, **9**, **10**, and **11** in 2,2,2-trifluoroethanol (CF_3CH_2OH). It is known that the negative and positive maxima and intensity of two bands at 222 nm and 208 nm, and a band at 192 nm in the CD spectra, indicates the screw sense of helicity and also a 3_{10}- or α-helical structure of peptides that contain chiral α-

methylated α,α-disubstituted α-amino acids.[15] The CD spectra of **10** and **11** are quite different from those of the 3_{10}-helical peptides. This may be attributed to the fact that the peptides **10** and **11** form the fully planar C_5 conformation in solution, albeit the main-chain length of peptide is too short for the precise analysis of conformation by the CD spectra (not shown).

Computational analysis:[16] The conformational search calculation with MacroModel was applied to the heteropentapeptide **11**. AMBER* and MMFF were used as a force field. The calculated torsion angles are summarized in Table 3. The calculation by AMBER* produced the *P* 3_{10}-helical structure (conformation A) as a global minimum-energy conformation. The conformational search starting from the extended structure as an initial conformation by the Monte Carlo method[17] did not afford the *M* 3_{10}-helical structure or the planar C_5 conformation. Therefore, the calculation was performed starting from the typical *M* 3_{10}-helix ($\phi = 60$, $\psi = 30^\circ$), and the *M* 3_{10}-helical structure (conformation B) obtained as a local minimum-energy conformation which exhibits an energy of $+1.90$ kcal mol^{-1}. The energy of the planar C_5 conformation (conformation C) in which the torsion angles of the peptide main-chain were constrained as the planar conformation, was estimated to be $+25.4$ kcal mol^{-1} by AMBER*.

Table 3. Selected calculated (MacroModel and MMFF) torsion angles ω, ϕ, ψ, and χ[a] [°] for the heteropentapeptides **11**.

	AMBER*			MMFF			
	A[b]	B[c]	C[d]	D[e]	E[c]	F[d]	G[d]
energy [kcal mol^{-1}]	0	+1.90	+25.4	+1.80	+2.27	+1.08	0
ω_0	−179.5	178.1	−178.8	−167.4	167.0	−178.8	−178.8
ϕ_1	−51.3	51.5	−177.2	−57.7	50.9	−177.7	−177.7
ψ_1	−25.5	28.8	159.4	−28.1	31.8	171.9	171.9
ω_1	−174.4	−175.4	177.7	−177.2	174.7	177.0	177.0
ϕ_2	−51.0	45.7	173.6	−49.9	54.1	−174.2	−174.2
ψ_2	−20.1	33.4	−173.3	−28.4	32.8	−172.1	−171.8
ω_2	172.6	−178.9	−173.1	−170.9	172.3	−173.9	−174.1
ϕ_3	−42.8	54.2	179.1	−61.7	60.0	−172.9	−172.6
ψ_3	−36.8	18.7	−172.6	−35.9	21.8	176.8	176.3
ω_3	−178.6	−169.9	−177.0	−178.8	176.0	178.2	178.1
ϕ_4	−54.1	44.7	178.7	68.6	62.4	176.8	176.9
ψ_4	−23.0	41.7	−179.2	−45.9	32.8	−178.4	−177.3
ω_4	−177.7	175.2	−177.1	−176.0	178.5	−179.1	−177.5
ϕ_5	−45.0	46.7	179.7	179.7	−62.9	−179.0	−178.3
ψ_5	−35.9	51.9	−179.8	−6.5	−19.4	−179.9	−1.0
ω_5	178.3	179.9	179.9	−176.0	−175.5	179.6	−179.7
χ_1^e	31.1	−46.9	−52.4	58.9	174.9	−42.3	−42.4
χ_1^{ip}	−174.4	−37.7	49.6	−173.9	−59.9	52.7	52.9
χ_1^{ip}	48.1	−161.0	173.7	60.7	64.9	−179.9	-179.8
χ_2^e	45.8	−48.4	63.5	−65.9	176.2	−54.3	−54.5
χ_2^{ib}	64.3	−49.7	59.8	−81.5	−43.0	77.3	77.3
χ_3^e	61.3	68.8	−46.9	59.4	175.2	−49.1	−49.1
χ_3^p	−172.4	−30.7	46.6	−176.7	−59.2	54.3	54.0
χ_4^e	−68.9	−56.6	52.1	−65.0	173.8	−57.1	−56.7
χ_4^e	33.1	178.9	−53.0	−60.6	−57.4	53.9	53.8
χ_5^e	52.1	176.8	−60.3	−56.1	62.0	−61.5	−61.0
χ_5^b	67.4	−58.5	62.0	54.8	66.1	62.9	62.6

[a] The superscripts e, b, p, ip, and ib refer to the ethyl, butyl, propyl, isopropyl, and isobutyl side chains, respectively. [b] *P* 3_{10}-helix. [c] *M* 3_{10}-helix. [d] Planar. [e] *P* distorted 3_{10}-helix.

In the conformational search starting from the extended structure by the Monte Carlo method, the calculation by MMFF produced the planar C_5 conformation (conformation G), in which the torsion angles ($\phi = -178.3$, $\psi = -1.0^\circ$) at the (*S*)-(αEt)Nle[5] residue were planar, but not with the C_5 conformation as the global minimum-energy conformation. The fully extended C_5 planar structure (conformation F) for which five consecutive C_5 conformations were formed, was obtained as a local minimum-energy conformation ($+1.08$ kcal mol^{-1}). The 3_{10}-helical structure was not given by MMFF when the extended structure was used as an initial structure of the conformational search. Therefore, the conformations A and B, which were produced as the minimum-energy conformations by AMBER*, were used as the initial structure of the conformational search by the Monte Carlo method and MMFF. The MMFF calculation afforded the *P* 3_{10}-helical structure (conformation D, $+1.80$ kcal mol^{-1}) with distorted torsion angles at Deg[4] and (*S*)-(αEt)Nle[5] residues, and the (*M*) 3_{10}-helical structure (conformation E, $+2.27$ kcal mol^{-1}) with the flip of torsion angles at the C terminus as the local minimum-energy conformations, respectively.

Conformation A is similar to that determined by the X-ray crystallographic analysis, except for the C-terminal structure. Figure 7 shows the pentapeptide **11** as determined by X-ray

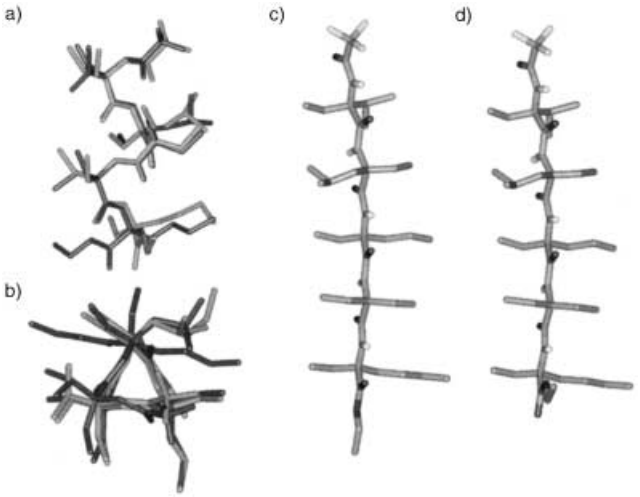


Figure 7. a), b) Superimposition of the conformation determined by X-ray analysis (in dark) and of the calculated (MacroModel, AMBER*) minimum-energy conformation A (in light) of the heteropentapeptide **11**; c) the calculated (MacroModel, MMFF) minimum-energy conformation F of **11**; d) the calculated (MacroModel, MMFF) minimum-energy conformation *G* of **11**.

crystallographic analysis, superimposed on the minimum-energy conformation A calculated by AMBER*, and the conformations F and G as the minimum-energy conformation calculated by MMFF of MacroModel, which may preferentially be formed in solution.

Conclusion

We have synthesized chiral α-ethylated amino acids, (*S*)-(αEt)Val and (*S*)-(αEt)Nva, by using (*R*,*R*)-cyclohexane-1,2-diol as a chiral auxiliary, and we have also prepared the heteropeptides **10** and **11** composed of diverse chiral (αEt)AAs. The overall yield of pentapeptide was not satisfactory because of the steric hindrance of (αEt)AAs, but for the first time the heteropentapeptide containing different (αEt)AAs was prepared. The X-ray crystallographic analysis revealed that the preferred conformation of the tetrapeptide **10**, which has three chiral centers, in the crystal state was both *P* and *M* 3_{10}-helical structures in a 1:1 ratio, and that of the pentapeptide **11**, which has four chiral centers of *S* configuration, was the right-handed *P* 3_{10}-helical structure. This may be attributed to the fact that three chiral quaternary carbons of (αEt)AAs are too weak to govern the screw sense of the 3_{10}-helical structure, and four chiral centers of *S* configuration may regulate the screw sense of helicity to the right-handed (*P*) helix, or perhaps the *P* 3_{10}-helical structure of **11** crystallized out by chance. The relationship between the screw sense of helicity and the chiral center of the (αEt)AAs seems to be that the *S* configuration of amino acid induces the right-handed (*P*) helix, as natural L-α-amino acids (*S* configuration) induce the right-handed (*P*) α-helix. The calculation by MacroModel also suggested that the *P* 3_{10}-helical structure of **11** was more stable than the *M* helical structure. In solution, the dominant conformation of **10** and **11** was not the 3_{10}-helical structure shown in the crystal state, but the fully planar C_5 conformation; similarly the Deg homopeptide and the Deg heteropeptide with an (*S*)-(αEt)Nle residue have different conformations in the crystal state and in solution.[5d, 10] We speculate that two intermolecular hydrogen bonds exist in the 3_{10}-helical structure, but no intermolecular hydrogen bonds in the planar C_5 conformation. Therefore, the intermolecular hydrogen bonds in a minor 3_{10}-helical structure existing in solution affect the nucleation events, and the 3_{10}-helical structure was preferentially induced in the crystal state. The conformation of (*S*)-(αEt)Nle homotetrapeptide was the fully planar C_5 conformation both in solution and in the crystal state,[8a] but those of **10**, **11**, and the Deg homopeptide have different conformations in solution and in the crystal state. It is not clear why the different conformations in the crystal state were formed from the similar dominant planar conformations of **10**, **11**, and (*S*)-(αEt)Nle homopeptide in solution. The Toniolo and the Seebach groups independently reported that the homo- and heteropeptides prepared from chiral (αMe)AAs would form the 3_{10}-helical structure.[6, 7] However, the results presented here and previously by us[8] establish for the first time that the homopeptides and heteropeptides **10** and **11** prepared from chiral (αEt)AAs preferentially form the fully extended planar C_5 conformation. The fully planar conformation built of (αEt)AAs will be used as a novel structure for the design of molecular devices and catalysts.[18]

Experimental Section

General: Ethyl (2*RS*)-3,3-[(1*R*,2*R*)-cyclohexane-1,2-dioxy]-2-ethylbutanoate (**1**), (*S*)-(αEt)Leu (**5c**), (*S*)-(αEt)Nle (**6**), and Deg **11** were prepared according to our previous reports[5d, 8, 10, 13]. Optical rotations $[\alpha]_D$ were measured with a Jasco DIP-316 polarimeter with 1.0 dm cell. Circular dichroism spectra (CD) were measured with a Jasco J-720 W spectropolarimeter with a 1.0 mm path length cell. Infrared spectra (IR) were recorded on a Nicolet Avatar-320 spectrometer for conventional measurement (KBr), and the solution ($CDCl_3$) method used an NaCl cell with a 0.1 mm path length. ^{1}H NMR spectra were determined at 270 MHz (Jeol GX-270). FABMS spectra were taken on a Jeol JMS 610H or Jeol JMS-SX 102 spectrometer. Elemental analyses were performed at the Analytical Center of the Faculty of Sciences, Kyushu University.

Ethyl (2*R*)-2-ethyl-2-propyl-3-[(1*R*,2*R*)-2-hydroxycycloheyloxy]-3-butenoate (2a):[13] *n*BuLi (3.1 mL, 47.8 mmol, 1.5 M in hexane) was added dropwise to a stirred solution of diisopropylamine (6.8 mL, 47.8 mmol) in THF (40 mL) at $-78\,^\circ$C; the solution was warmed to $0\,^\circ$C and then stirred for 30 min at $0\,^\circ$C. The solution was cooled to $-78\,^\circ$C, HMPA (8.3 mL, 47.8 mmol) was added, and then **1** (2.48 g, 9.56 mmol) in THF (5 mL) was added dropwise. The solution was stirred at $-78\,^\circ$C for 30 min, and then 1-iodopropane (4.63 mL, 47.8 mmol) was added dropwise to the stirred solution. The solution was stirred at $-78\,^\circ$C for 3 h, $-40\,^\circ$C for 2 h, and diluted with saturated aqueous NH_4Cl. This was then extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane gave enol ether **2a** (2.37 g, 83%) as a colorless oil: $[\alpha]_D^{23} - 60.5$ ($c = 1.00$ in $CHCl_3$).

Ethyl (2*R*)-2-ethyl-2-isopropyl-3-[(1*R*,2*R*)-2-hydroxycycloheyloxy]-3-butenoate (2b):[13] Compound **2b** was prepared from **1** in a manner similar to that described for the preparation of **2a**: 70%; a colorless oil; $[\alpha]_D^{28} - 43.1$ ($c = 1.10$, $CHCl_3$).

Ethyl (2*R*)-2-ethyl-2-propylacetoacetate (3a):[13] $BF_3 \cdot OEt_2$ (10 mL, 83.9 mmol) was added dropwise to a stirred solution of **2a** (2.50 g, 8.39 mmol) in EtOH (125 mL) and H_2O (50 mL) at room temperature. After being stirred for 1 h, the solution was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (10% EtOAc in hexane) to give β-keto ester **3a** (1.4 g, 83%) as a colorless oil: $[\alpha]_D^{27} - 1.1$ ($c = 1.40$ in $CHCl_3$).

Ethyl (2*R*)-2-ethyl-2-isopropylacetoacetate (3b):[13] Compound **3b** was prepared from **2b** in a manner similar to that described for the preparation of **3a**: 70%; a colorless oil; $[\alpha]_D^{28} + 13.8$ ($c = 1.08$ in $CHCl_3$).

(*S*)-*N*-Acetyl-α-ethylnorvaline ethyl ester (4a):[13] Methansulfonic acid (5.0 mL, 70.0 mmol) was added dropwise to a stirred solution of β-keto ester **3a** (1.40 g, 6.97 mmol) in $CHCl_3$ (35 mL) at $0\,^\circ$C; NaN_3 (1.81 g, 27.8 mmol) was then added. After refluxing for 6 h, the reaction mixture was cooled to room temperature, diluted with H_2O, neutralized with diluted aqueous NH_3, extracted with diethyl ether, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (50% EtOAc in hexane) to give **4a** (719 mg, 48%): colorless crystals: m.p. 49–50 °C (recryst. from $CHCl_3$); $[\alpha]_D^{30} + 12.0$ ($c = 0.99$ in $CHCl_3$).

(*S*)-*N*-Acetyl-α-ethylvaline ethyl ester (4b):[13] Compound **4b** was prepared from **3b** in a manner similar to that described for the preparation of **4a**: 40%; a colorless oil; $[\alpha]_D^{30} + 12.2$ ($c = 1.92$ in $CHCl_3$).

(*S*)-*N*-Trifluoroacetyl-α-ethylnorvaline (Tfa-[(*S*)-(αEt)Nva]-OH; 5a): A mixture of **4a** (1.08 g, 5.06 mmol) in concentrated aqueous HCl (5 mL) was refluxed for 48 h, and then the solution was evaporated. The residue was dissolved in $(Tfa)_2O$ (2.0 mL), and the solution was stirred at room temperature for 24 h. The mixture was poured into 5% aqueous $NaHCO_3$, and the solution washed with Et_2O and then acidified with citric acid. The solution was extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded **5a** (676 mg, 55%). The acid **5a** was used in the next reaction without purification: colorless crystals. M.p. 75–76 °C; $[\alpha]_D^{27} + 11.6$

($c = 0.91$ in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.26$ (br s, 1H), 2.80 (br, 1H), 2.41–2.58 (m, 2H), 1.78–1.95 (m, 2H), 0.96–1.32 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.81 ppm (t, $J = 7.3$ Hz, 3H); IR (KBr): $\tilde{\nu} = 3349$, 3120 (br), 1740, 1708, 1543 cm^{-1}; MS (FAB): m/z: 242 $[M+H]^+$.

(*S*)-*N*-Trifluoroacetyl-α-ethylvaline (Tfa-[(*S*)-(αEt)Val]-OH 5b): Compound **5b** was prepared from **4b** in a manner similar to that described for the preparation of **5a**: 40% yield; colorless crystals; m.p. 99–101 °C; $[\alpha]_D^{22} + 12.1$ ($c = 0.98$ in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.29$ (br s, 1H), 4.00 (br, 1H), 2.61–2.71 (m, 2H), 2.09 (m, 1H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.82 ppm (t, $J = 7.3$ Hz, 3H); IR (KBr): $\tilde{\nu} =$ 3339, 3118, 1736, 1714, 1548 cm^{-1}; MS (FAB): m/z: 242 $[M+H]^+$.

Ethyl trifluoroacetyldiethylglycyl-(*S*)-α-ethylnorleucinate (Tfa-Deg-[(*S*)-(αEt)Nle]-OEt; 8): A solution of **6** (500 mg, 2.66 mmol), **7** (402 mg, 2.21 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC; 508 mg, 2.66 mmol) in MeCN (12 mL) was refluxed for 24 h, and the solution was then evaporated. The residue was diluted with $CHCl_3$, washed with 3% HCl, 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to afford **8** (645 mg, 74%). Colorless crystals: m.p. 69–70 °C (recryst. from EtOH); $[\alpha]_D^{29} + 5.4°$ ($c = 1.12$ in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.95$ (br s, 1H), 6.80 (br s, 1H), 4.28 (q, $J = 7.3$ Hz, 2H), 2.59–2.75 (m, 2H), 2.36–2.52 (m, 2H), 1.61–1.90 (m, 4H), 1.32 (t, $J = 7.3$ Hz, 3H), 1.14–1.26 (m, 2H), 0.88–1.05 (m, 2H), 0.72–0.88 ppm (m, 12H); IR (KBr): $\tilde{\nu} = 3350$, 3322, 1718, 1663, 1518 cm^{-1}; MS (FAB): m/z: 419 $[M+Na]^+$, 397 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{31}F_3N_2O_4$: C 54.53, H 7.88, N, 7.07; found C 54.25, H 7.79, N 6.84.

Ethyl trifluoroacetyl-(*S*)-α-ethylnorvalyldiethylglycyl-(*S*)-α-ethylnorleucinate (Tfa-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt; 9): $NaBH_4$ (400 mg, 10.6 mmol) was added portionwise to a stirred solution of **8** (800 mg, 2.02 mmol) in EtOH (50 mL) at room temperature. After being refluxed for 2 h, the mixture was poured into 1% aqueous HCl (50 mL), and then EtOH was evaporated. The residue was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column choromatography on silica gel (2% MeOH in $CHCl_3$ to give H-Deg-[(*S*)-(αEt)Nle]-OEt (280 mg, 46%, 79% based on recovered material). The solution of H-Deg-[(*S*)-(αEt)Nle]-OEt (325 mg, 1.08 mmol), **5a** (217 mg, 0.903 mmol), and EDC (206 mg, 1.08 mmol) in MeCN (17 mL) was refluxed for 24 h. After evaporation, the residue was diluted with $CHCl_3$, washed with 3% aqueous HCl, and 5% aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent afforded the white solid, which was purified by column choromatography on silica gel. The fraction eluted with 50% EtOAc in hexane gave **9** (356 mg, 63%). Colorless crystals: m.p. 162–163 °C (recryst. from EtOH); $[\alpha]_D^{26} + 15.7$ ($c = 0.93$ in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 8.00$ (br s, 1H), 7.39 (br s, 1H), 6.78 (br s, 1H), 4.28 (q, $J = 7.3$ Hz, 2H), 2.34–2.72 (m, 6H), 1.58–1.90 (m, 6H), 1.31 (t, $J = 7.3$ Hz, 3H), 1.00–1.27 (m, 4H), 0.85–1.00 (m, 2H), 0.73–0.92 ppm (m, 18H); IR (KBr): $\tilde{\nu} = 3390$, 3328, 3295, 1731, 1655 cm^{-1}; MS (HR-FAB(+)): m/z calcd for $C_{25}H_{44}O_5N_3F_3$ $[M+H]^+$: 524.3311; found 524.3297.

Ethyl trifluoroacetyl-(*S*)-α-ethylleucyl-(*S*)-α,α-ethylnorvalyldiethylglycyl-(*S*)-α-ethylnorleucinate (Tfa-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt; 10): Compound **10** was prepared from **9** and **5c** in a manner similar to that described for the preparation of **9**: 31% (55% based on recovered material); colorless crystals; m.p. 136–137 °C (recryst. from $CHCl_3$/EtOH); $[\alpha]_D^{24} + 14.5$ ($c = 1.48$ in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 8.10$ (br s, 1H), 7.42 (br s, 1H), 7.36 (br s, 1H), 6.78 (br s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.43–2.68 (m, 8H), 1.59–1.84 (m, 8H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.00–1.34 (m, 5H), 0.73–1.00 ppm (m, 29H); IR (KBr): $\tilde{\nu} = 3399$, 3348 (br), 3312, 1728, 1679, 1660, 1492 cm^{-1}; MS (FAB): m/z: 687 $[M+Na]^+$, 665 $[M+H]^+$; elemental analysis calcd (%) for $C_{33}H_{59}F_3N_4O_6$: C 59.62, H 8.94, N 8.43; found C 59.62, H 8.94, N 8.34.

Ethyl trifluoroacetyl-(*S*)-α-ethylvalyl-(*S*)-α-ethylleucyl-(*S*) α,α-ethylnorvalyl-diethylglycyl-(*S*)- α-ethylnorleucinate (Tfa-[(*S*)-(αEt)Val]-[(*S*)-(αEt)Leu]-[(*S*)-(αEt)Nva]-Deg-[(*S*)-(αEt)Nle]-OEt; 11): Compound **11** was prepared from **10** and **5b** in a manner similar to that described for the preparation of **9**: 5% (31% based on recovered material); colorless crystals; m.p. 152–153 °C (recryst. from $CHCl_3$/EtOH); $[\alpha]_D^{22} + 11.7$ ($c = 0.33$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3336$ (br), 3228, 1725, 1709, 1681, 1666, 1644, 1529 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 8.17$ (br s, 1H), 7.49 (br s, 1H), 7.41 (br s, 1H), 7.35 (br s, 1H), 6.78 (br s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.35–2.90 (m, 11H), 1.55–1.95 (m, 8H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.15–1.35 (m, 5H), 1.10 (d, $J = 6.9$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.73–1.00 ppm (m, 32H); MS (HR-FAB(+)): m/z calcd for $C_{40}H_{73}O_7N_5F_3$ $[M+H]^+$: 792.5462; found 792.5545.

X-ray crystal structure determination: The crystals of **9** and **10** were grown from EtOH, and **11** from $CHCl_3$/EtOH. Data collection was performed on a Rigaku-RAXIS-RAPID Imaging Plate diffractometer, equipped with graphite-monochromated $Mo_{K\alpha}$ radiation. Indexing was performed from 1 oscillation which was exposed for 10 min. The camera radius was 127.4 mm. Readout was performed in the 0.10 mm pixel mode. A total of 44 images, corresponding to 220° oscillation angles, were collected with two different goniometer settings. Exposure time was 4.0 min deg^{-1} for **9**, and 5.0 min deg^{-1} for **10** and **11**. Data were processed by the PROCESS-AUTO program package. 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[19] and expanded by Fourier techniques.[20] All non-H atoms were given anisotropic thermal parameters, some H atoms were refined isotropically, and the remaining H atoms included in calculated positions given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of **9** gave an R factor of 0.139 ($R_w = 0.184$) based on 3875 $[I > -10.00\sigma(I)]$ reflections and an R_1 factor of 0.063 based on 971 $[I > 2.0\sigma(I)]$ reflections, and the largest peak and hole in the final difference Fourier map were 0.29 and -0.22 e $Å^{-3}$. The R factor of **10** was 0.176 ($R_w = 0.240$) based on 8924 $[I > -10.00\sigma(I)]$ reflections and an R_1 factor of 0.106 based on 4803 $[I > 2.0\sigma(I)]$ reflections, and the largest peak and hole in the final difference Fourier map were 0.71 and -0.30 e $Å^{-3}$. The R factor of **11** was 0.099 ($R_w = 0.154$) based on 5289 $[I > -10.00\sigma(I)]$ reflections and an R_1 factor of 0.062 based on 2822 $[I > 2.0\sigma(I)]$ reflections, and the largest peak and hole in the final difference

Table 4. Crystal and diffraction parameters of the peptides **9**, **10**, and **11**.

	9	**10**	**11**
formula	$C_{25}H_{44}O_5N_3F_3$	$C_{33}H_{59}O_6N_4F_3 \times 2$	$C_{40}H_{72}O_7N_5F_3$
Mr	523.6	664.8×2	792.0
crystal dimensions [mm]	$0.40 \times 0.10 \times 0.10$	$0.50 \times 0.30 \times 0.15$	$0.30 \times 0.30 \times 0.30$
T [°C]	23	23	23
crystal system	orthorhombic	triclinic	monoclinic
a [Å]	15.490	10.852	11.637
b [Å]	18.264	19.179	18.071
c [Å]	10.759	10.564	12.222
α [°]	90	101.40	90
β [°]	90	113.53	115.76
γ [°]	90	89.25	90
V [Å^3]	3043.9	1970.9	2314.8
space group	$P2_12_12_1$	$P1$	$P2_1$
Z	4	1	2
ρ_{calcd} [g cm^{-3}]	1.143	1.120	1.136
$F(000)$	1128	720	860
μ ($Mo_{K\alpha}$) [cm^{-1}]	0.91	0.86	0.85
$2\theta_{max}$ [°]	54.9	55	55
observed reflections $[I > -10.0\sigma(I)]$	3875	8924	5289
parameters	327	830	518
R/R_w	0.139/0.184	0.176/0.240	0.099/0.154
reflections used for R_1 $[I > 2.0\sigma(I)]$	971	4803	2822
R_1	0.063	0.106	0.062
GOF	0.90	2.07	1.32
solvent	EtOH	EtOH	$CHCl_3$/EtOH

Fourier map were 0.25 and -0.21 e Å^{-3}. All calculations were performed by means of the teXsan[21] crystallographic package.

Molecular mechanics calculations: Conformational search calculations were performed with the package of MacroModel Ver. 6.5[17] on an SGI O_2 workstation. The parameters used were as follows: conformational search, Monte Carlo method; force field, AMBER* or MMFF; more than 15000 structures were minimized; solvent: water for AMBER* and $CHCl_3$ for MMFF. The fully extended conformation of **11** was used as the initial conformation for the calculations.

The calculation by AMBER* afforded the conformation A [0 kcal mol^{-1}; *P* 3_{10}-helix] as the global minimum-energy conformation, but neither *M*-helix nor planar conformation. The calculation by AMBER* starting from the typical *M* 3_{10}-helical structure ($\phi = 60$, $\psi = 30^\circ$) as an initial conformation gave the conformation B (+1.90 kcal mol^{-1}; *M* 3_{10}-helix) as a local minimum-energy conformation. The energy of the conformation C (planar C_5 conformation) was estimated to be +25.4 kcal mol^{-1} by the AMBER* calculation. The calculation by MMFF afforded the conformations F (+1.08 kcal mol^{-1}; planar conformation) and G (0 kcal mol^{-1}; planar conformation) as the global minimum-energy conformations of **11** within 3.0 kcal mol^{-1}, but not 3_{10}-helical structures. By using the conformations A and B as the initial conformations, the calculation by MMFF produced the conformation D (+1.80 kcal mol^{-1}; *P* distorted 3_{10}-helix) and the conformation E (+2.27 kcal mol^{-1}; *M* 3_{10}-helix) as the local minimum-energy conformations.

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