Helical Structures of Bicyclic α-Amino Acid Homochiral Oligomers with the Stereogenic Centers at the Side-Chain Fused-Ring Junctions

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 75th birthday

Chiral bicyclic α-amino acid (*R*,*R*)-$Ab_{5,6=}c$ with stereogenic centers at the γ-position of fused-ring junctions, and its enantiomer (*S*,*S*)-$Ab_{5,6=}c$, were synthesized. The CD spectra of (*R*,*R*)-$Ab_{5,6=}c$ oligomers indicated that the (*R*,*R*)-$Ab_{5,6=}c$ hexapeptide formed a mixture of right-handed (*P*)- and left-handed (*M*)-3_{10}-helices, while, in the (*R*,*R*)-$Ab_{5,6=}c$ nonapeptide, a right-handed (*P*)-3_{10}-helix slightly dominated over the (*M*)-helix. X-Ray crystallographic analyses of (*S*,*S*)-tripeptide and (*R*,*R*)-hexapeptide revealed that both the tripeptide and hexapeptide formed a mixture of (*P*)- and (*M*)-3_{10}-helices, respectively. These results indicated that the side-chain environments around the stereogenic centers are particularly important to control the helical-screw handedness of foldamers.

Introduction. – Helices are chiral, and, therefore, two helical screw senses, right-handed (*P*) and left-handed (*M*), are possible. The relationship between (*P*)- and (*M*)-helices is enantiomeric with regard to the helical backbone structure. The α-helices in proteins almost always form a right-handed (*P*) screw sense, but not a left-handed (*M*) screw sense. This is because α-L-amino acids have stereogenic α-C-atoms and, therefore, right-handed (*P*)- and left-handed (*M*)-helices of peptides become diastereoisomers. If proteinogenic α-L-amino acid peptides formed left-handed (*M*)-helices, there would be steric repulsion between the C=O group and the side-chain β-C-atom, and, therefore, right-handed (*P*)-helices are preferred [1].

Among α-L-amino acids, isoleucine and threonine possess an additional stereogenic center at the side-chain β-position besides a stereogenic center at the α-position; however, little attention has been paid as to how the stereogenic centers of the side chain affect the secondary structure of their oligomers [2]. We have previously reported that chiral cyclic α,α-disubstituted α-amino acid (Ac_5c^{dOM}) [3], in which stereogenic centers are only the side-chain γ-C-atoms, controls the helical-screw sense of its homochiral oligomers (*Fig. 1*) [4][5]; however, it is not clear how strongly the side-chain stereogenic centers affect the screw sense of helical oligomers. Thus, herein we designed a chiral bicyclic α,α-disubstituted α-amino acid with stereogenic centers at the γ-side-chain fused-ring junctions, *i.e.*, (1*R*,6*R*)-8-aminobicyclo[4.3.0]non-3-ene-8-car-

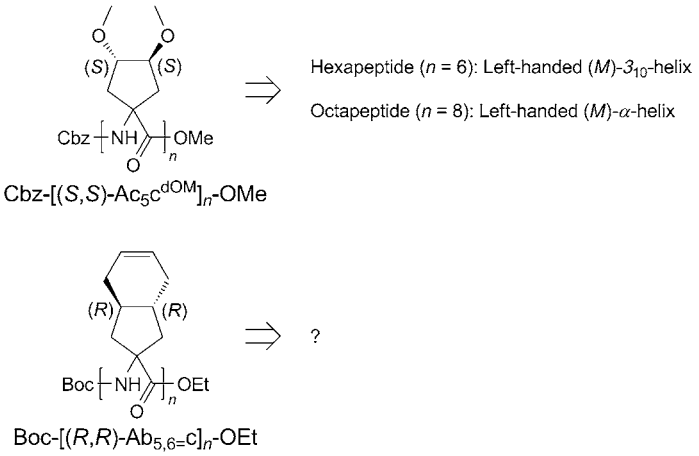

Fig. 1. *Homochiral oligomers Cbz-[(*S,S*)-Ac$_5$c^{dOM}]$_n$-OMe and Boc-[(*R,R*)-Ab$_{5,6=}$c]$_n$-OEt, in which stereogenic centers are only the side-chain γ-C-atoms*

boxylic acid ((*R*,*R*)-Ab$_{5,6=}$c)[1]) and its enantiomer (*S*,*S*)-Ab$_{5,6=}$c, and studied the effect of side-chain stereogenicity on the secondary structure of their homochiral oligomers in solution and in the crystal state. Furthermore, we demonstrated the chemical modifications of olefin in amino acid (*R*,*R*)-Ab$_{5,6=}$c and its oligomer [6].

Results. – *Synthesis of Optically Active Bicyclic Amino Acid.* The optically active bicyclic amino acid Boc-[(*R*,*R*)-Ab$_{5,6=}$c]-OEt ((*R*,*R*)-**4**) was synthesized from (*S*,*S*)-cyclohex-4-ene-1,2-dicarboxylic acid ((*S*,*S*)-**1**) [7] as follows: reduction of the dicarboxylic acid (*S*,*S*)-**1** gave diol (*S*,*S*)-**2**, followed by replacement of OH groups with I, to afford (*S*,*S*)-**3**. Bisalkylation of ethyl isocyanoacetate ($CNCH_2COOEt$) with (*S*,*S*)-**3** [8], followed by hydrolysis of isocyanate under acidic conditions and protection with Boc_2O, gave the bicyclic amino acid ester Boc-[(*R*,*R*)-Ab$_{5,6=}$c]-OEt ((*R*,*R*)-**4**). For the peptide preparation, the N-terminal-free amino acid ester H-[(*R*,*R*)-Ab$_{5,6=}$c]-OEt ((*R*,*R*)-**5**) was prepared by acidic deprotection, and the C-terminal-free amino acid Boc-[(*R*,*R*)-Ab$_{5,6=}$c]-OH ((*R*,*R*)-**6**) was obtained by alkaline hydrolysis from (*R*,*R*)-**4**. Also, we synthesized the enantiomer of bicyclic amino acid, Boc-[(*S*,*S*)-Ab$_{5,6=}$c]-OEt ((*S*,*S*)-**4**), starting from (*R*,*R*)-**1** in the same manner described for the synthesis of (*R*,*R*)-**4** (*Scheme 1*).

Modification of Bicyclic Amino Acid. We reasoned that the olefin function at the side chain of the bicyclic amino acid could be converted to several functional groups. Actually, after ozonolysis of the olefin in (*R*,*R*)-**4**, reduction with $NaBH_4$ gave a dihydroxy amino acid ester (*R*,*R*)-**7**, oxidation with *Oxone*® afforded a dicarboxy amino acid ester (*R*,*R*)-**8**, and reductive amination with $BnNH_2$ afforded a bicyclic seven-membered ring amino acid ester (*R*,*R*)-**9**. Moreover, hydrogenation of the olefin in (*R*,*R*)-**4** furnished a saturated bicyclic amino acid ester Boc-[(*R*,*R*)-Ab$_{5,6}$c]-OEt (**10**).

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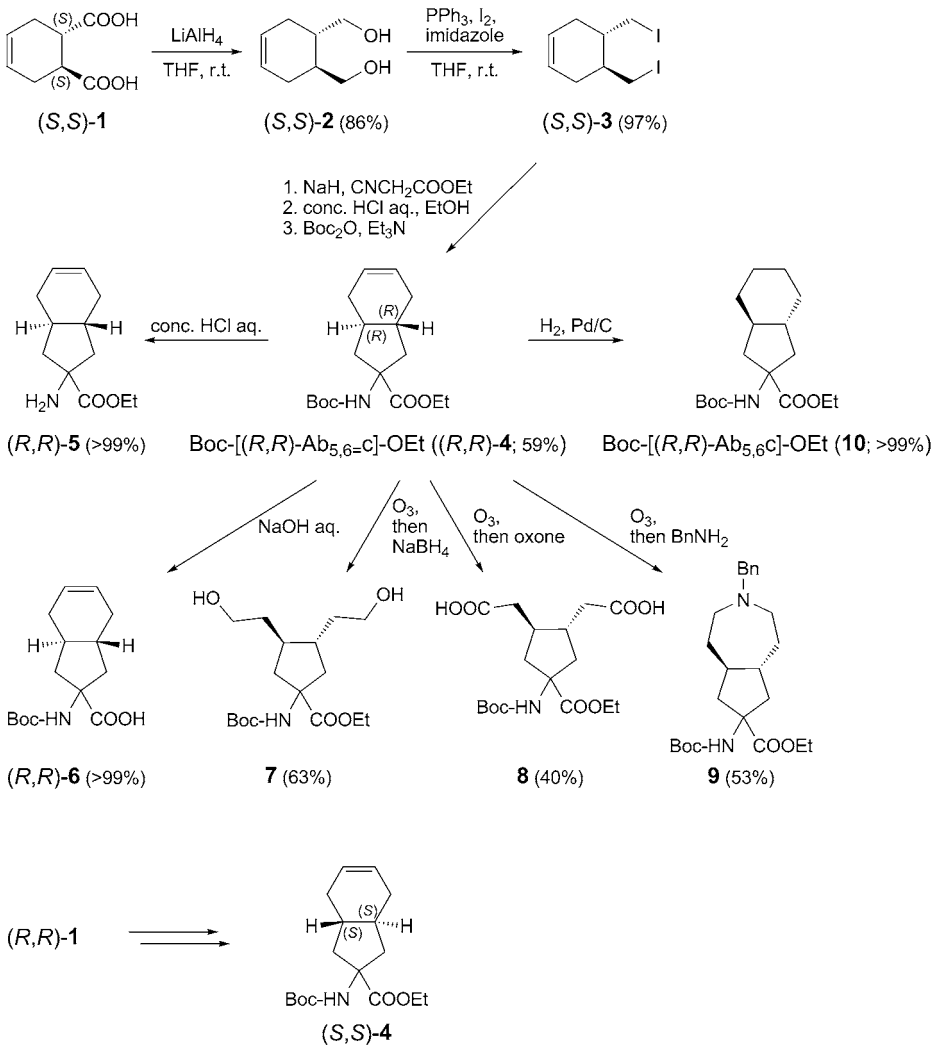
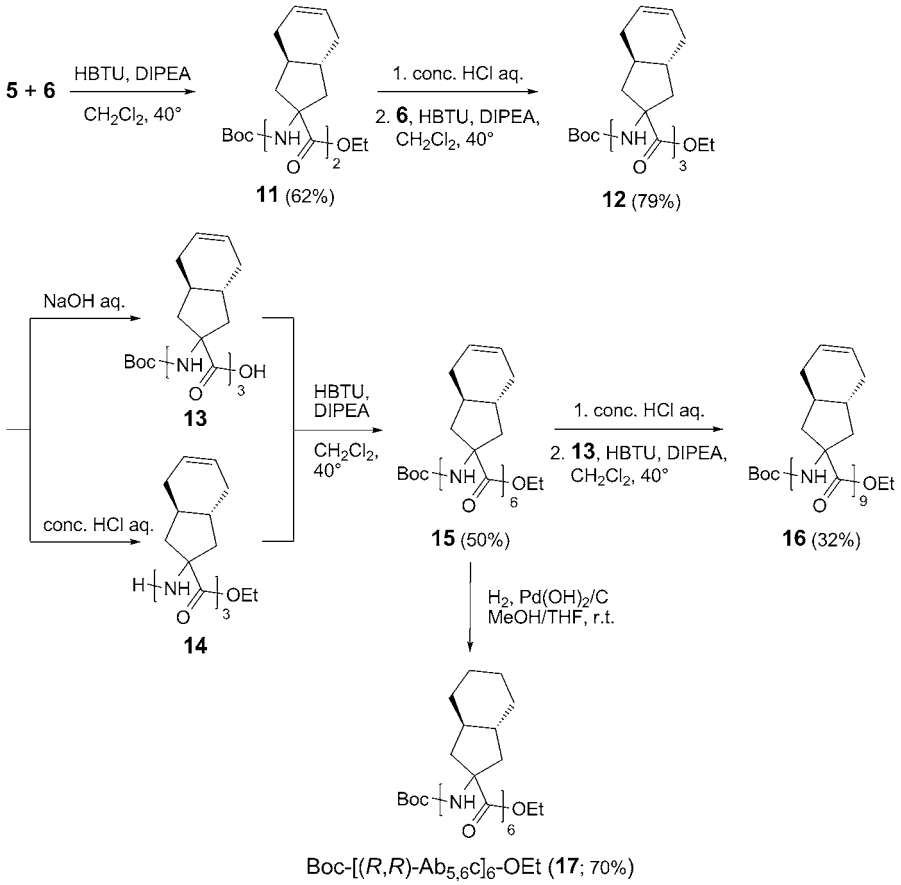
[1]) The descriptor '5,6 =' represents five-membered ring, six-membered ring, and olefin.

Scheme 1. *Synthesis and Modification of Bicyclic Amino Acid Boc-[(*R,R*)-Ab$_{5,6=}$c]-OEt* ((*R*,*R*)-**4**), *and Its Enantiomer (*S,S*)-***4***



Preparation of Ab$_{5,6=}$c Homochiral Oligomers and Modification. Homochiral oligomers Boc-(Ab$_{5,6=}$c)$_n$-OEt (up to nonapeptide; $n = 9$ for (*R*,*R*)-enantiomer, and hexapeptide; $n = 6$ for (*S*,*S*)-enantiomer) were prepared by solution-phase methods (*Scheme 2*); that is, coupling between H-[(*R*,*R*)-Ab$_{5,6=}$c]-OEt ((*R*,*R*)-**5**) and Boc-[(*R*,*R*)-Ab$_{5,6=}$c]-OH ((*R*,*R*)-**6**) using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and EtN^{i}Pr$_2$ (DIPEA) led to a dipeptide Boc-[(*R*,*R*)-Ab$_{5,6=}$c]$_2$-OEt ((*R*,*R*)-**11**) in 62% yield. Removal of the Boc group in **11**, followed by coupling with (*R*,*R*)-**6**, afforded a tripeptide Boc-[(*R*,*R*)-Ab$_{5,6=}$c]$_3$-OEt ((*R*,*R*)-**12**) in 79% yield. Hydrolysis of C-teminal ester in **12** under alkaline conditions

Scheme 2. *Synthesis and Modification of* (R,R)-*Ab*$_{5,6=}$*c Homochiral Oligomers*



gave C-terminal-free tripeptide Boc-[(*R*,*R*)-Ab$_{5,6=}$c]$_3$-OH ((*R*,*R*)-**13**). Removal of the Boc group in **12** and subsequent coupling with the C-terminal free tripeptide (*R*,*R*)-**13** using HBTU and DIPEA produced a hexapeptide (*R*,*R*)-**15** in 50% yield. The (*R*,*R*)-Ab$_{5,6=}$c nonapeptide (*R*,*R*)-**16** was prepared by coupling between N-terminal-free hexapeptide and the C-terminal-free tripeptide (*R*,*R*)-**13** in 32% yield. The enantiomeric (*S*,*S*)-Ab$_{5,6=}$c hexapeptide (*S*,*S*)-**15** was also prepared in a manner similar to that described for (*R*,*R*)-**15**.

The six olefins in (*R*,*R*)-Ab$_{5,6=}$c hexapeptide **15** could be hydrogenated by H_2/20% $Pd(OH)_2$-C in one step to give the saturated peptide Boc-[(*R*,*R*)-Ab$_{5,6}$c]$_6$-OEt (**17**) in 70% yield.

Conformational Study of Homochiral Oligomers in Solution. The preferred conformation of homochiral oligomers in solution was studied by FT-IR, ^{1}H-NMR, and CD spectroscopy. In the FT-IR spectra of oligomers Boc-[(*R*,*R*)-Ab$_{5,6=}$c]$_n$-OEt ($n = 1, 2, 3, 6, 9$) in the NH-stretching region (amide A 3250 – 3500 cm^{-1}, in $CDCl_3$

solution), the weak bands around the 3430 cm^{-1} region were assigned to free (solvated) peptide NH groups, and the strong bands around the 3320–3360 cm^{-1} region were assigned to peptide NH groups with N–H ··· O=C intramolecular H-bonds of different strength (data are not shown; see [6]). As the peptide-chain length increases, the band at 3360 cm^{-1} in tripeptide **12** ($n=3$) shifts to a slightly lower wavenumber (3320 cm^{-1} in nonapeptide **16** ($n=9$)), and the relative intensity of the bands in the 3320–3360 cm^{-1} region gradually increases. These IR spectra were very similar to those of helical peptides, such as aminocyclopentanecarboxylic acid (Ac_5c) [9] and α-aminoisobutyric acid (Aib) homopeptides [10], but different from those of peptides such as diethylglycine (Deg) [11] and (*S*)-butylethylglycine [12] homopeptides, which form the fully extended planar C_5-conformation.

To obtain further conformational information on homochiral oligomers, the ^{1}H-NMR spectra of (*R*,*R*)-$Ab_{5,6=}c$ hexapeptide **15** and nonapeptide **16**, and saturated (*R*,*R*)-$Ab_{5,6}c$ hexapeptide **17** were recorded in $CDCl_3$ solution (data are not shown; see [6]). In the ^{1}H-NMR spectra of **15**, **16**, and **17**, N(1)H signals of the urethane type at the N-terminus were unambiguously assigned by their high-field positions, but the remaining NH H-atoms could not be attributed at this stage. Solvent-perturbation experiments involving the addition of the strong H-bond acceptor solvent DMSO (0–10% (*v*/*v*)) or the paramagnetic free radical (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO; $0-5\times10^{-2}$% (*w*/*v*)) were performed [10a][10b]. Two NH chemical shifts in hexapeptides **15** and **17**, and nonapeptide **16** were sensitive to the addition of the perturbing reagent DMSO. Also, the addition of the TEMPO broadened the bandwidth of the two NH signals. These two NH H-atoms were those of the first two N-terminal residues, as demonstrated by 2D-NMR experiments. These results revealed that the two NH H-atoms are solvent-exposed, suggesting that they are not intramolecularly H-bonded. These results are in accord with a 3_{10}-helical structure, in which two NH groups at the N-terminus of the peptide are freely solvated (not intramolecularly H-bonded).

The nuclear *Overhauser* effect spectroscopy (NOESY) ^{1}H-NMR spectra of helical peptides show a series of strong sequential NH($i\rightarrow i+1$) dipolar interactions. Furthermore, in peptides and proteins based on coded α-amino acids, there are two NOE constraints, [$d_{\alpha N}$ ($i\rightarrow i+2$)] and [$d_{\alpha N}$ ($i\rightarrow i+4$)], which are characteristic of the 3_{10}- and the α-helical structure, respectively [13]. Unfortunately, these latter interactions do not occur in homopeptides composed of α,α-disubstituted α-amino acids, because their residues lack α-CH H-atoms. *Fig. 2* shows the ROESY ^{1}H-NMR spectra of hexapeptides **15** (*a*), **17** (*b*), and nonapeptide **16** (*c*) in $CDCl_3$ solution. The spectra of **15** and **17** displayed a complete series of sequential NH($i\rightarrow i+1$) dipolar interactions from the *N*-terminal N(1)H to the *C*-terminal N(6)H, which is characteristic of a helical secondary structure (*Fig. 2*, *a* and *b*), while the spectrum of nonapeptide **16** showed only a partial series of sequential NH($i\rightarrow i+1$) cross-peaks from NH(1) to NH(5) and from NH(6 or 7) to NH(8 or 9) (*Fig. 2*, *c*).

The CD spectra of (*R*,*R*)- and (*S*,*S*)-$Ab_{5,6=}c$ hexapeptides, (*R*,*R*)- and (*S*,*S*)-**15** respectively, (*R*,*R*)-$Ab_{5,6}c$ hexapeptide **17**, and (*R*,*R*)-$Ab_{5,6=}c$ nonapeptide **16** were recorded in 2,2,2-trifluoroethanol (TFE) solution to obtain information about their helical screw senses. The spectrum of (*R*,*R*)-**15** does not show characteristic maxima for a helical structure (208 and 222 nm), suggesting the existence of roughly equal amounts

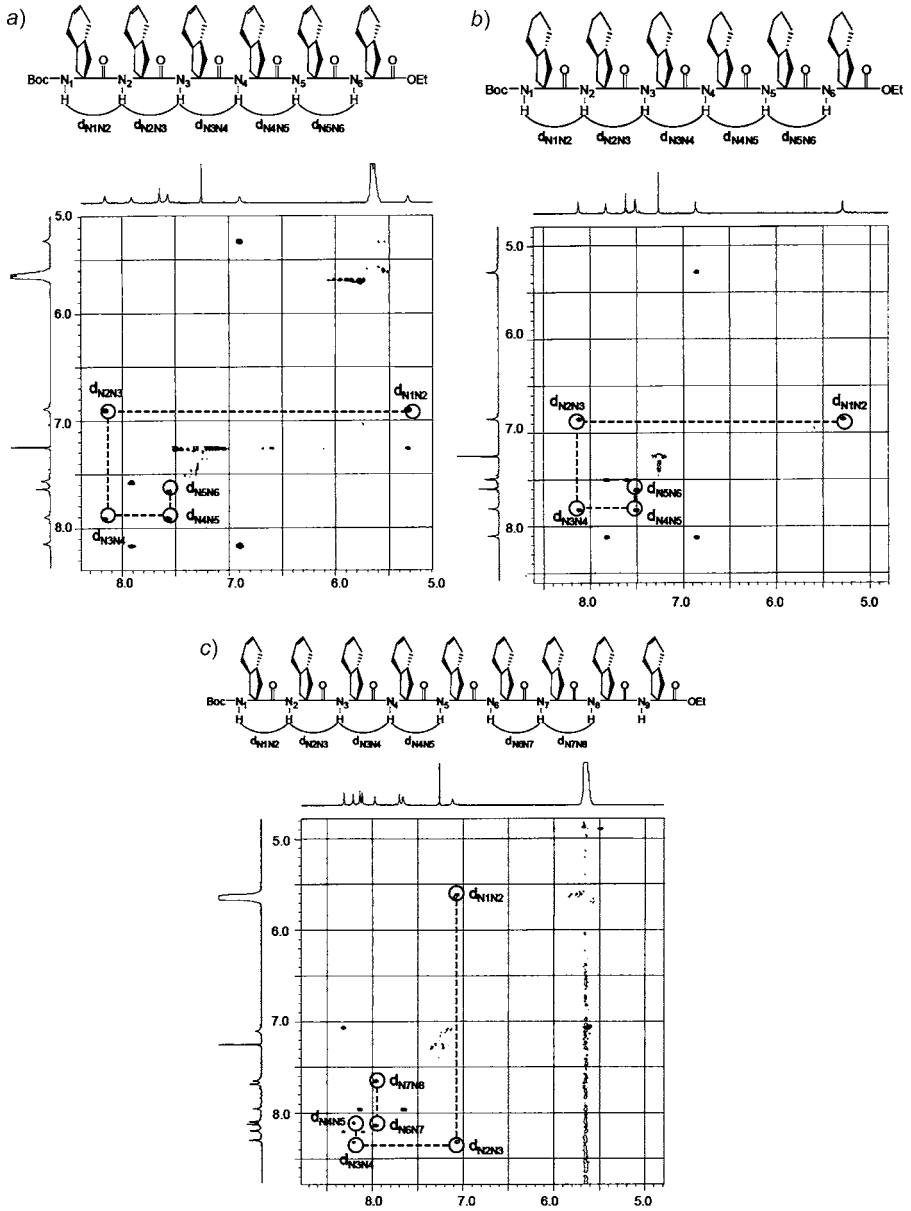


Fig. 2. *ROESY* ^{1}*H-NMR* ($CDCl_3$) *Spectra of hexapeptides* **15** (*a*) *and* **17** (*b*), *and nonapeptide* **16** (*c*). Peptide concentration: 5.0 mM.

of both (*P*)- and (*M*)-helices (*Fig. 3*). The CD spectrum of the enantiomeric (*S*,*S*)-**15** shows the mirror image shape of the CD spectrum of (*R*,*R*)-**15**. These results suggest that the (*R*,*R*)- and (*S*,*S*)-**15** form enantiomeric global secondary structures. The

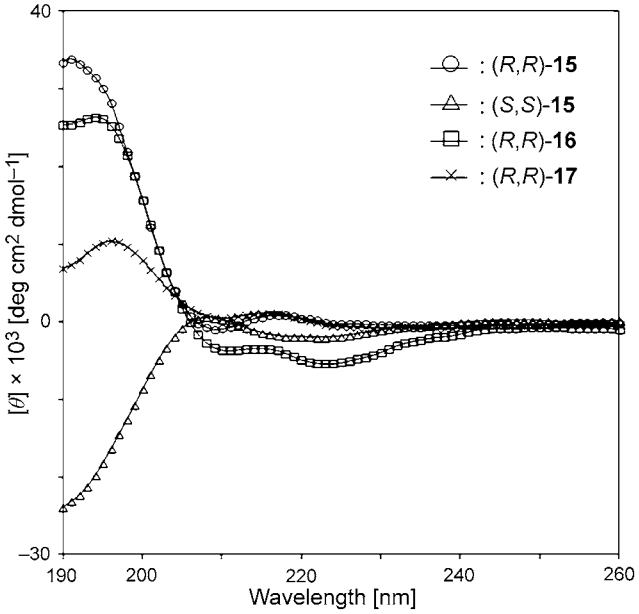


Fig. 3. *CD Spectra of Boc-[(*R,R*)-Ab$_{5,6=}$c]$_n$-OEt* ((*R*,*R*)-**15**: $n=6$ (circle), (*R*,*R*)-**16**: $n=9$ (square)), *enantiomeric Boc-[(*S,S*)-Ab$_{5,6=}$c]$_6$-OEt* ((*S*,*S*)-**15** (triangle)), *and Boc-[(*R,R*)-Ab$_{5,6}$c]$_6$-OEt* ((*R*,*R*)-**17** (cross)) *in TFE soln.* Peptide concentration: 50 μM.

spectrum of nonapeptide **16** shows weak negative maxima at 208 and 222 nm, and a positive maximum at 192 nm, indicating that the (*P*)-helix would be slightly predominant. The conversion of **15** to the saturated (*R*,*R*)-Ab$_{5,6}$c hexapeptide **17** by hydrogenation changed the shape of the CD spectrum, suggesting that the dominant conformation may slightly be changed.

X-Ray Crystallographic Analyses. X-Ray crystallographic analyses unambiguously revealed the secondary structures of (*S*,*S*)-Ab$_{5,6=}$c tripeptide (*S*,*S*)-**12** and (*R*,*R*)-Ab$_{5,6=}$c hexapeptide (*R*,*R*)-**15** in the crystal state. Both the tripeptide (*S*,*S*)-**12** and the hexapeptide (*R*,*R*)-**15** provided suitable crystals for X-ray crystallographic analyses by slow evaporation of $CHCl_3$/EtOH solutions at room temperature. X-Ray data collections were performed using *RIGAKU VariMax* with *Saturn* (confocal) for (*S*,*S*)-**12**, and *RIGAKU RAPID* and graphite-monochromated MoK_α radiation for (*R*,*R*)-**15**. The structures of the peptides were solved using the SHELXS 97 direct method [14] and expanded using the *Fourier* technique [15]. All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the remaining H-atoms were placed at the calculated positions. Relevant backbone and side-chain torsion angles and the intra- and intermolecular H-bond parameters are compiled in *Tables 1–4*, respectively.

The (*S*,*S*)-Ab$_{5,6=}$c tripeptide (*S*,*S*)-**12** crystallized in space group *P*1 to form four β-turn conformers (3_{10}-helices) **A**, **B**, **C**, and **D** in the asymmetric unit. Two molecules **A** and **D** were (*P*)-β-turns, and two molecules **B** and **C** were (*M*)-β-turns (*Fig. 4*). In four

Table 1. *Selected Torsion Angles ω, ϕ, and ψ* [°] *for Tripeptide (*S,S*)-***12***, as Determined by X-Ray Crystallographic Analysis*

Torsion angle	**A**	**B**	**C**	**D**
ω_0	– 171.1	171.6	170.1	– 171.9
ϕ_1	– 64.6	62.5	63.4	– 60.6
ψ_1	– 26.0	29.1	26.2	– 30.1
ω_1	– 178.5	179.6	– 177.9	– 179.2
ϕ_2	– 48.2	48.8	48.1	– 46.1
ψ_2	– 47.5	47.9	47.8	– 45.6
ω_2	– 174.7	– 179.5	178.3	– 178.1
ϕ_3	43.9	– 56.7	– 43.2	55.4
ψ_3	46.5	– 36.6	– 47.1	35.2
ω_3	– 174.0	– 175.5	175.6	174.8

Table 2. *Intra- and Intermolecular H-Bond Parameters for Tripeptide (*S,S*)-***12***

Peptide[a])	Donor	Acceptor	Distance [Å]	Angle [°]	Symmetry operations
Molecule **A**	N_{3a}–H	O_{0a}	3.13	139.9	x, y, z
	N_{1a}–H	O_{1b}'	2.87	164.2	$1+x, y, z$
Molecule **B**	N_{3b}–H	O_{0b}	3.11	133.2	x, y, z
	N_{1b}–H	O_{1a}	2.89	168.0	x, y, z
Molecule **C**	N_{3c}–H	O_{0c}	3.09	135.5	x, y, z
	N_{1c}–H	O_{1d}'	2.91	163.0	$-1+x, -1+y, z$
Molecule **D**	N_{3d}–H	O_{0d}	3.06	140.9	x, y, z
	N_{1d}'–H	O_{1c}	2.82	164.0	$x, 1+y, z$

[a]) The number of amino acid residues begins at the N-terminus of the peptide chain.

β-turn conformers, the ϕ and ψ torsion angle signs at the C-terminus residue (3) were opposite of those of the preceding residues (1 and 2). The peptide-backbone structures of (*P*)-β-turns **A** and **D**, and also (*M*)-β-turns **B** and **C** were similar, respectively (*Fig. 5*).

In the β-turn structures **A** – **D**, one intramolecular H-bond of the $i \leftarrow i+3$ type was observed between H–N(3) and C(0) = O(0) (3.13 Å (a), 3.11 Å (b), 3.09 Å (c), 3.06 Å (d)), respectively. In the packing mode, the β-turn structures of $\cdots$**A**(*P*)$\cdots$**B**(*M*)$\cdots$ **A**(*P*)$\cdots$**B**(*M*)$\cdots$ and $\cdots$**C**(*M*)$\cdots$**D**(*P*)$\cdots$**C**(*M*)$\cdots$**D**(*P*)$\cdots$ were formed, by one intermolecular H-bond, respectively.

In the asymmetric unit of (*R*,*R*)-$Ab_{5,6=}$c hexapeptide (*R*,*R*)-**15**, there were four crystallographically independent molecules **E**, **F**, **G**, and **H**, along with two EtOH molecules. Two molecules **E** and **H** were (*P*)-3_{10}-helices, and two molecules **F** and **G** were (*M*)-3_{10}-helices (*Fig. 6*). The main-chain backbone structures of (*P*)-helical molecules **E** and **H**, and also (*M*)-helical molecules **F** and **G** were well matched, respectively, except for small differences in the conformations of their side chains (*Fig. 7*). The mean values of the ϕ, ψ torsion angles of the amino acid residues (1 – 5)

Table 3. *Selected Torsion Angles ω, ϕ, and ψ* [°] *for Hexapeptide (*R,R*)-***15***, as Determined by X-Ray Crystallographic Analysis*

Torsion angle	**E**	**F**	**G**	**H**
ω_0	– 176.1	172.7	172.5	– 171.8
ϕ_1	– 61.1	66.1	61.8	– 66.8
ψ_1	– 25.2	19.0	26.7	– 19.9
ω_1	– 179.5	178.8	178.7	179.4
ϕ_2	– 60.9	59.1	56.8	– 59.1
ψ_2	– 17.2	20.7	19.0	– 19.9
ω_2	176.0	– 178.3	– 178.8	174.9
ϕ_3	– 58.4	53.7	56.3	– 56.2
ψ_3	– 20.6	29.4	23.6	– 24.8
ω_3	177.2	177.5	– 179.2	179.9
ϕ_4	– 59.9	59.2	54.1	– 59.8
ψ_4	– 23.8	22.2	27.1	– 25.2
ω_4	175.4	– 178.7	179.2	– 179.0
ϕ_5	– 55.7	52.9	59.1	– 53.9
ψ_5	– 32.7	37.5	27.4	– 37.7
ω_5	– 175.3	171.5	170.2	– 173.4
ϕ_6	51.2	– 48.4	– 54.6	48.6
ψ_6	46.6	– 47.7	– 44.3	45.1
ω_6	157.9	179.4	179.6	179.8

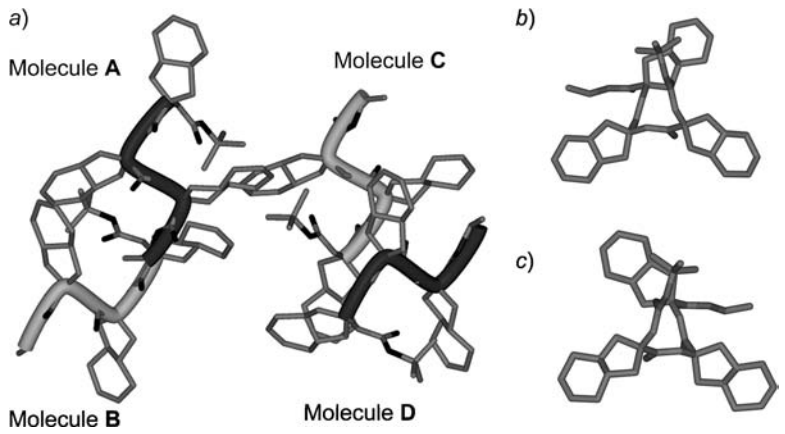


Fig. 4. a) *X-Ray diffraction structure of Boc-[(*S,S*)-Ab*$_{5,6=}$*c]*$_3$*-OEt* ((*S,S*)-**12**)*;* b) *the structure of molecule* **A***, and* c) *molecule* **C***, as viewed along the helical axis*

were $-59.3°$, $-23.9°$ for **E**, $+58.2°$, $+25.8°$ for **F**, $+57.6°$, $+24.8°$ for **G**, and $-59.2°$, $-25.5°$ for **H**, respectively, which are close to those for an ideal 3_{10}-helical structure ($\pm 60°$ and $\pm 30°$) [16]. Reversal of the torsion angle signs at the C-terminus residue occurred, *i.e.*, the values of the ϕ, ψ torsion angles of the residue (6) were $+51.2°$, $+46.6°$ for **E**, $-48.4°$, $-47.7°$ for **F**, $-54.6°$, $-44.3°$ for **G**, and $+48.6°$, $+45.1°$ for **H**.

Table 4. *Intra- and Intermolecular H-Bond Parameters for Hexapeptide (*R,R*)-***15**

Peptide[a])	Donor	Acceptor	Distance [Å]	Angle [°]	Symmetry operations
Molecule **E**	N_{3e}–H	O_{0e}	2.99	167.2	*x*, *y*, *z*
	N_{4e}–H	O_{1e}	3.03	173.3	*x*, *y*, *z*
	N_{5e}–H	O_{2e}	2.95	157.8	*x*, *y*, *z*
	N_{6e}–H	O_{3e}	2.93	155.6	*x*, *y*, *z*
	N_{1e}–H	O_{5f}	2.98	168.2	*x*, *y*, *z*
	N_{2e}–H	O_{6f}	2.96	149.5	*x*, *y*, *z*
Molecule **F**	N_{3f}–H	O_{0f}	3.16	171.8	*x*, *y*, *z*
	N_{4f}–H	O_{1f}	2.96	166.1	*x*, *y*, *z*
	N_{5f}–H	O_{2f}	2.93	159.5	*x*, *y*, *z*
	N_{6f}–H	O_{3f}	3.05	158.0	*x*, *y*, *z*
	N_{1f}–H	O_{5e}'	2.87	167.6	*x*, *y*, $-1+z$
	N_{2f}–H	O_{6e}'	3.15[b])	131.7	*x*, *y*, $-1+z$
Molecule **G**	N_{3g}–H	O_{0g}	3.01	169.1	*x*, *y*, *z*
	N_{4g}–H	O_{1g}	3.01	172.3	*x*, *y*, *z*
	N_{5g}–H	O_{2g}	2.95	163.9	*x*, *y*, *z*
	N_{6g}–H	O_{3g}	2.92	167.4	*x*, *y*, *z*
	N_{1g}–H	O_{5h}'	3.03	171.5	*x*, *y*, $1+z$
	N_{2g}–H	O_{6h}'	2.95	147.5	*x*, *y*, $1+z$
Molecule **H**[c])	N_{3h}–H	O_{0h}	3.12	167.7	*x*, *y*, *z*
	N_{4h}–H	O_{1h}	2.93	165.1	*x*, *y*, *z*
	N_{5h}–H	O_{2h}	2.95	158.9	*x*, *y*, *z*
	N_{6h}–H	O_{3h}	3.06	152.8	*x*, *y*, *z*
	N_{1h}–H	O_{5g}	2.85	160.1	*x*, *y*, *z*

[a]) The number of amino acid residues begins at the N-terminus of the peptide chain. [b]) The D ··· A distance is slightly long for an intermolecular H-bond. [c]) The D ··· A distance of $N_{2h} \cdots O_{6g}$ (3.48 Å) is too long for an intermolecular H-bond.

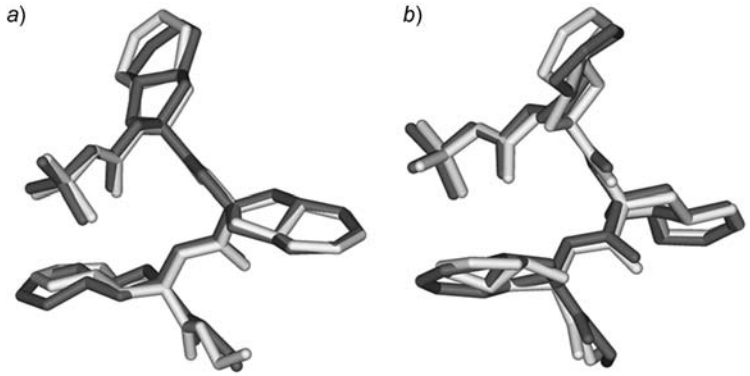


Fig. 5. *Overlaid structures of Boc-[(*S,S*)-Ab*$_{5,6=}$*c]*$_3$*-OEt* ((*S*,*S*)-**12**). *a*) Molecules **A** (dark) and **B** (bright), and *b*) molecules **C** (dark) and **D** (bright).

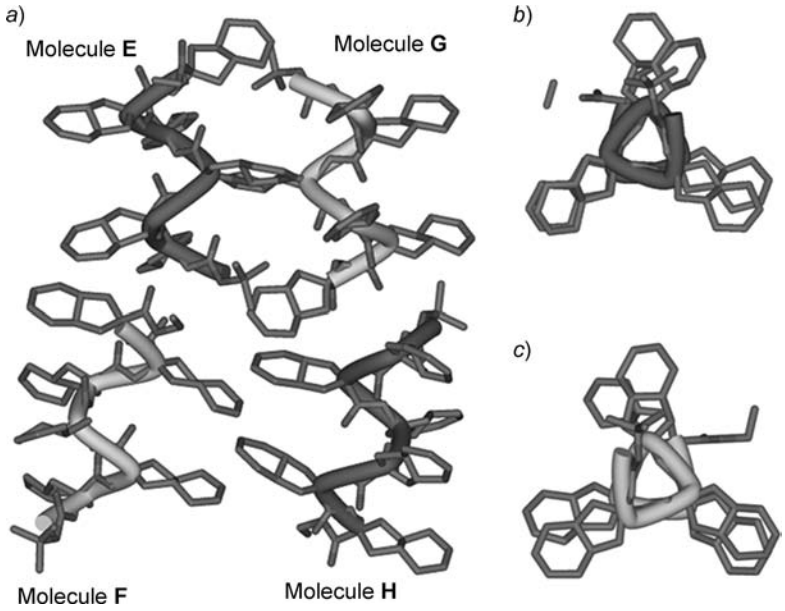


Fig. 6. *X-Ray diffraction structure of* a) *Boc-[(*R,R*)-Ab*$_{5,6=}$*c]*$_6$*-OEt* ((*R*,*R*)-**15**) (EtOH molecules are omitted)*; b*) *the structure of molecule* **E** *and* c) *molecule* **F***, as viewed along the helical axis*

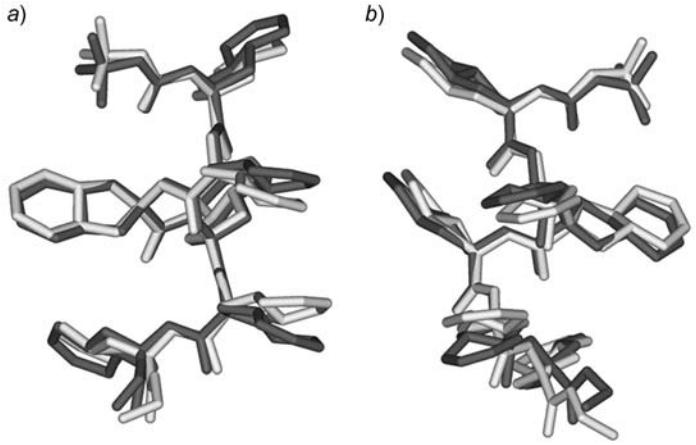


Fig. 7. *Overlaid structures of Boc-[(*R,R*)-Ab*$_{5,6=}$*c]*$_6$*-OEt* ((*R*,*R*)-**15**). *a*) Molecules **E** (dark) and **H** (bright), and *b*) molecules **F** (dark) and **G** (bright)

In the 3_{10}-helical molecules **E** – **H**, four consecutive H-bonds of the $i \leftarrow i+3$ type were observed between H–N(3) and C(0)=O(0) (N(3)$\cdots$O(0) 2.99 (e), 3.16 (f), 3.01 (g), and 3.12 Å (h); N–H$\cdots$O 167.2° (e), 171.8° (f), 169.1° (g), and 167.7° (h)), H–N(4) and C(1)=O(1) (N(4)$\cdots$O(1) 3.03 (e), 2.96 (f), 3.01 (g), and 2.93 Å (h); N–H

$\cdots$O 173.3° (e), 166.1° (f), 172.3° (g), and 165.1° (h)), H–N(5) and C(2)=O(2) (N(5) $\cdots$O(2) 2.95 (e), 2.93 (f), 2.95 (g), and 2.95 Å (h); N–H$\cdots$O 157.8° (e), 159.5° (f), 163.9° (g), and 158.9° (h)), and H–N(6) and C(3)=O(3) (N(6)$\cdots$O(3) = 2.93 (e), 3.05 (f), 2.92 (g), and 3.06 Å (h); N–H$\cdots$O 155.6° (e), 158.0° (f), 167.4° (g), and 152.8° (h)).

In the packing mode, the 3_{10}-helical chains of $\cdots$**E**(P)$\cdots$**F**(M)$\cdots$**E**(P)$\cdots$**F**(M)$\cdots$ and $\cdots$**G**(M)$\cdots$**H**(P)$\cdots$**G**(M)$\cdots$**H**(P)$\cdots$ mode were formed in head-to-tail alignment. Four intermolecular H-bonds between molecules **E** and **F**, *i.e.*, H–N(1e) and C(5f)=O(5f), H–N(2e) and C(6f)=O(6f), H–N(1f) and C(5e′)=O(5e′), and H–N(2f) and C(6e′)=O(6e′) were observed, and three intermolecular H-bonds between molecules **G** and **H**, *i.e.*, H–N(1g) and C(5h′)=O(5h′), H–N(2g) and C(6h′)=O(6h′), and H–N(1h) and C(5g)=O(5g) were observed, as shown in *Table 4* and *Fig. 8*.

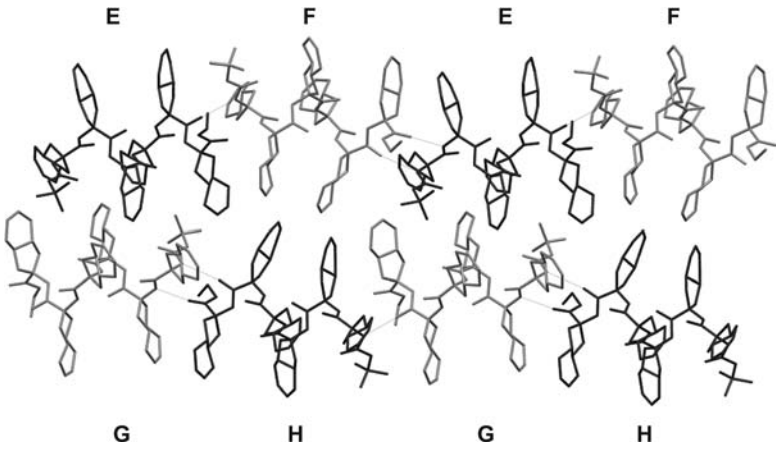


Fig. 8. *Packing of hexapeptide* **15** (dark color for molecules **E** and **H**, and bright color for molecule **F** and **G**) *in the crystalline state.* Intermolecular H-bonds are indicated as dashed lines.

Molecular-Mechanics Calculation. A conformational search calculation of (*R*,*R*)-$Ab_{5,6=}c$ hexapeptide (*R*,*R*)-**15** was performed using the Monte Carlo Multiple Minimum (MCMM) method of MacroModel (v. 8.1, *Schrödinger*, *Inc.*) with the AMBER* force field. As initial structures, extended, 3_{10}- and α-helical structures were used, and more than 50,000 structures were optimized. The calculated structure of (*R*,*R*)-**15** produced a (*P*)-3_{10}-helix as the global minimum-energy conformation (0 kcal/mol), and an (*M*)-3_{10}-helix was obtained as a local minimum-energy conformation, which exhibited an energy of +1.60 kcal/mol. The peptide main-chain structures of (*P*)- and (*M*)-3_{10}-helical conformers produced by the calculations were similar to those observed in the crystalline state, with some differences in the side-chain and the C-terminal ester conformations, as depicted by their superimposition in *Fig. 9*.

Discussion. – The dominant conformations of (*R*,*R*)- and (*S*,*S*)-$Ab_{5,6=}c$, and saturated (*R*,*R*)-$Ab_{5,6}c$ homopeptides in solution were found to be 3_{10}-helical structures by FT-IR and ^{1}H-NMR analyses. Judging from the CD spectra in TFE solution, roughly

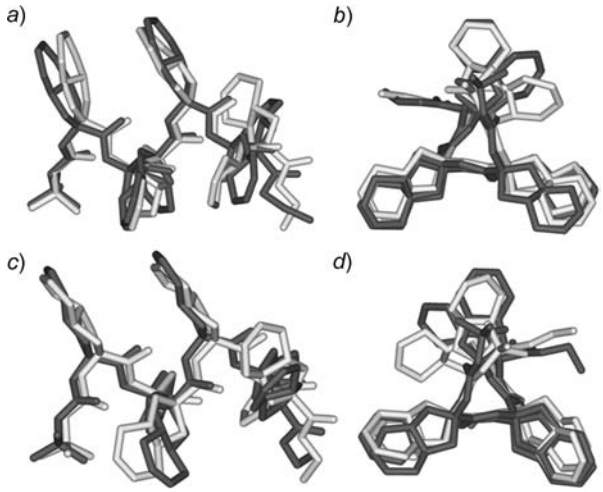


Fig. 9. *Superimposition of the conformation determined by X-ray crystallographic analysis and of the calculated minimum-energy conformation of (*R,R*)-***15***.* Overlaid X-ray (dark) and calculated (bright) structure of right-handed (*P*)-helix as viewed *a*) perpendicular to and *b*) along the helical axes. Overlaid X-ray (dark) and calculated (bright) structure of left-handed (*M*)-helix as viewed *c*) perpendicular to and *d*) along the helical axes.

equal amounts of both (*P*)- and (*M*)-helices seemed to occur of two (*R*,*R*)-$Ab_{5,6=}c$ and (*R*,*R*)-$Ab_{5,6}c$ hexapeptides **15** and **17**, respectively, while the enantiomeric (*R*,*R*)-$Ab_{5,6=}c$ and (*S*,*S*)-$Ab_{5,6=}c$ hexapeptides showed the mirror images of the CD spectra, suggesting that one enantiomeric global structure may be slightly predominant. Furthermore, the CD spectrum of the (*R*,*R*)-$Ab_{5,6=}c$ nonapeptide **16** showed characteristic maxima at 192, 208, and 222 nm for the right-handed (*P*)-helical structure, although the intensities of ellipticity were weak. These results might be attributed to the fact that, by the increase of the number of stereogenic centers (eighteen) in **16**, the (*P*)-helical conformer would become more stable than the (*M*)-conformers.

In the crystalline state, X-ray crystallographic analyses of (*S*,*S*)-**12** and (*R*,*R*)-**15** revealed the existence of both diastereoisomeric (*P*)- and (*M*)-β-turns, or 3_{10}-helical conformations in a 1:1 ratio, respectively.

We have reported that the chiral cyclic α-amino acid (*S*,*S*)-Ac_5c^{dOM}, in which stereogenic centers are only at the side-chain γ-C-atoms, controls the helical screw sense of its homopeptides [4]. That is to say, the (*S*,*S*)-Ac_5c^{dOM} hexapeptide forms a (*M*)-3_{10}-helix, and the (*S*,*S*)-Ac_5c^{dOM} octapeptide and decapeptide form (*M*)-α-helices both in solution and in the crystalline state.

The γ-side-chain stereogenic centers in bicyclic α-amino acid (*R*,*R*)-$Ab_{5,6=}c$ are less flexible than those in monocyclic α-amino acid (*S*,*S*)-Ac_5c^{dOM} because the stereogenic centers exist at the fused-ring junctions, and thus, the helical-screw handedness of (*R*,*R*)-$Ab_{5,6=}c$ hexapeptide (*R*,*R*)-**15** would not be controlled.

Fig. 10 shows the mean values of torsion angles (C^{α}–C^{β}–C^{γ}–C^{δ}) of (*R*,*R*)-$Ab_{5,6=}c$ and those of torsion angles (C^{α}–C^{β}–C^{γ}–O) of (*S*,*S*)-Ac_5c^{dOM} in their crystalline states. In (*S*,*S*)-Ac_5c^{dOM}, the MeO substitutents occupy the vertical region of the cyclopentane

ring and would strongly affect the peptide-backbone conformation. On the other hand, in (*R*,*R*)-$Ab_{5,6=}c$, the cyclohexane substituent occupies the horizontal region of the cyclopentane ring, and might slightly affect the peptide-backbone conformation. Taking these results into account, the side-chain stereogenic centers of α-amio acids affect the secondary structure of oligomers, and the side-chain environments around the stereogenic centers, such as bulkiness and flexibility, are important to control the screw sense of their helical oligomers.

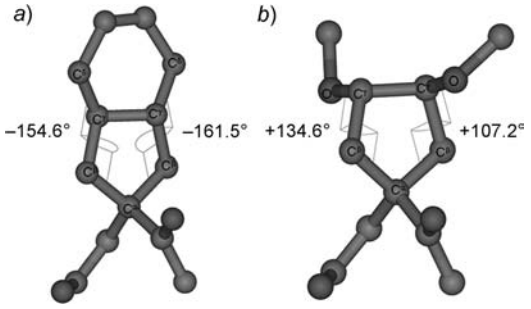


Fig. 10. *Torsion angles of side chain at the γ-position. a*) Mean values of torsion angles (C^{α}–C^{β}–C^{γ}–C^{δ}) of (*R*,*R*)-$Ab_{5,6=}c$, and *b*) those of torsion angles (C^{α}–C^{β}–C^{γ}–O) of (*S*,*S*)-Ac_5c^{dOM}.

Conclusions. – We have synthesized chiral bicyclic α-amino acids (*R*,*R*)- and (*S*,*S*)-$Ab_{5,6=}c$, and modified them to various cyclic α,α-disubstituted amino acids. The (*R*,*R*)-$Ab_{5,6=}c$ homochiral hexapeptide (*R*,*R*)-**15**, having twelve stereogenic centers at the side-chain bicyclic skeleton formed both diastereoisomeric right-handed (*P*)- and left-handed (*M*)-3_{10}-helices. These results indicate that the side-chain stereogenic centers affect the secondary structure of their peptides, but the side-chain environments of the stereogenic centers (bulkiness and flexibility) are important to control the screw sense of helical oligomers (foldamers).

Experimental Part

General. (*S*,*S*)- and (*R*,*R*)-cyclohex-4-ene-1,2-dicarboxylic acids (**1**) were prepared according to the methods described in [7]. Optical rotations: *Jasco DIP-316* polarimeter, with a 1.0-dm cell. Circular dichroism (CD) spectra: *Jasco J-720W* spectropolarimeter, with 1.0-mm path length cell. IR Spectra: *Nicolet Avatar-320* spectrometer for conventional measurement (KBr, or neat), and the soln. ($CDCl_3$) method with 0.1-mm path length of NaCl cells. ^{1}H-NMR Spectra: at 400 or 500 MHz (*Varian Unity*). EI-MS and FAB-MS spectra: *Jeol JMS 610 H* or *Jeol JMS-SX 102* spectrometer. Elemental analyses were performed at the Analytical Center of the Faculty of Sciences, Kyushu University.

Synthesis and Modification of Bicyclic Amino Acids.

(1S,2S)*-Cyclohex-4-ene-1,2-dicarboxylic Acid* ((*S*,*S*)-**1**) [7]. *Data of* (*S*,*S*)-**1**. Colorless crystals. M.p. 147–148°. $[\alpha]_D^{26} = +142.0$ ($c = 1.10$, EtOH) ([7]: $[\alpha]_D = +160.0$ ($c = 2.70$, EtOH)). IR (KBr): 3100 (br.), 2933, 1698, 1215. ^{1}H-NMR ($CDCl_3$): 10.17 (br., 2 H); 5.73 (*m*, 2 H); 2.83 (*m*, 2 H); 2.45 (*m*, 2 H); 2.28 (*m*, 2 H). FAB-MS: 171 ($[M+H]^+$). Anal. calc. for $C_8H_{10}O_4$ (170.16): C 56.47, H 5.92; found: C 56.49, H 5.83.

Data of (*R*,*R*)-**1**. $[\alpha]_D^{23} = -149.0$ ($c = 0.97$, EtOH).

*(4*S,5S*)-4,5-Bis(hydroxymethyl)cyclohexene* (*=(1*S,2S*)-Cyclohex-4-ene-1,2-diyldimethanol*; (*S*,*S*)-**2**). The carboxylic acid (*S*,*S*)-**1** (3.6 g, 21.2 mmol) was added portionwise to a rigorously stirred

suspension of $LiAlH_4$ (1.80 g, 46.5 mmol) in THF (160 ml) at 0°. After stirring at r.t. for 12 h, the reaction was quenched with 15% aq. NaOH, and the resulting suspension was filtered off through *Celite*. The filtrate was dried ($MgSO_4$), and evaporated *in vacuo* to leave a white solid, which was purified by CC (SiO_2). The fraction eluted with 5% MeOH in $CHCl_3$ afforded diol (*S*,*S*)-**2** (2.60 g, 86%). Colorless crystals. M.p. 53–54°. $[\alpha]_D^{26} = +66.5$ ($c = 1.00$, EtOH). IR (KBr): 3300 (br.), 3025, 2959, 2916. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.65 (*m*, 2 H); 3.83 (br., 2 H); 3.70 (*d*, $J = 11.0$, 2 H); 3.56 (*dd*, $J = 5.0, 11.0$, 2 H); 2.02 (*m*, 2 H); 1.85 (*m*, 2 H); 1.68 (br. *s*, 2 H). FAB-MS: 143 ($[M+H]^+$). Anal. calc. for $C_8H_{14}O_2$ (142.20): C 67.57, H 9.92; found: C 67.12, H 9.94.

Data of (*R*,*R*)-**2** Yield: 92%. M.p. 55–56°. $[\alpha]_D^{25} = -66.7$ ($c = 1.02$, EtOH).

*(4*S*,5*S*)-4,5-Bis(iodomethyl)cyclohexene* ((*S*,*S*)-**3**). A soln. of (*S*,*S*)-**2** (2.50 g, 17.6 mmol), PPh_3 (18.4 g, 70.3 mmol), 1*H*-imidazole (7.2 g, 105.5 mmol), and I_2 (22.3 g, 87.9 mmol) in THF (200 ml) was stirred at r.t. for 3 h. The soln. was diluted with AcOEt, washed with H_2O, sat. aq. $Na_2S_2O_3$, aq. 1N HCl, 5% aq. $NaHCO_3$, brine, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by CC (SiO_2; hexane) to give (*S*,*S*)-**3** (6.20 g, 97%). Colorless crystals. M.p. 39–40°. $[\alpha]_D^{26} = +49.4$ ($c = 1.13$, EtOH). IR (KBr): 3023, 2951, 2898, 2833, 1257, 1202, 1173. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.62 (*m*, 2 H); 3.37 (*dd*, $J = 4.3$, 10.3, 2 H); 3.28 (*d*, $J = 10.3$, 2 H); 2.02–2.08 (*m*, 4 H); 1.42 (*m*, 2 H). FAB-MS: 362 ($[M+H]^+$). Anal. calc. for $C_8H_{12}I_2$ (361.99): C 26.54, H 3.34; found: C 26.52, H 3.27.

Data of (*R*,*R*)-**3** Yield: 91%. M.p. 39–40°. $[\alpha]_D^{25} = -54.2$ ($c = 0.81$, EtOH).

*Ethyl (1*R,*6*R*)-8-[(*tert*-Butoxycarbonyl)amino]bicyclo[4.3.0]non-3-ene-8-carboxylate* (= *Ethyl (3a*R,*7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate*; Boc-[(*R*,*R*)-$Ab_{5,6=}$c]-OEt; (*R*,*R*)-**4**). A soln. of $CNCH_2COOEt$ (756 µl, 6.92 mmol) and (*S*,*S*)-**3** (2.27 g, 6.29 mmol) in Et_2O/DMF (10 ml; 9:1) was added dropwise to the stirred suspension of NaH (423 mg, 17.61 mmol) in Et_2O/DMF (40 ml) at 0°. After stirring at 0° for 3 h, the soln. was diluted with H_2O, extracted with Et_2O, and dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by CC (SiO_2; 30% AcOEt in hexane) to give the alkylated isonitrile (882 mg, 64%). Colorless oil. $[\alpha]_D^{26} = +98.8$ ($c = 1.25$, EtOH). IR (neat): 3023, 2980, 2895, 2836, 2135, 1744, 1443, 1275, 1195. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.70–5.71 (*m*, 2 H); 4.27 (*q*, $J = 7.1$, 2 H); 2.75 (*dd*, $J = 7.7, 13.0$, 1 H); 2.46 (*dd*, $J = 11.8, 18.0$, 1 H); 2.27–2.34 (*m*, 2 H); 1.71 (*m*, 1 H); 1.80–1.98 (*m*, 5 H); 1.34 (*t*, $J = 7.1$, 3 H). FAB-MS: 219 ($[M+H]^+$).

A soln. of the alkylated isonitrile (1.70 g, 7.75 mmol) and conc. aq. HCl (4 ml) in EtOH (50 ml) was stirred at 0° for 3 h. Then, the soln. was neutralized with 5% aq. $NaHCO_3$, and EtOH was evaporated. The aq. residue was extracted with AcOEt and dried ($MgSO_4$). Removal of the solvent afforded a crude amine, which was solved in dioxane (80 ml), and then $(Boc)_2O$ (2.03 g, 9.30 mmol) and Et_3N (1.3 ml, 9.32 mmol) were added. After stirring at r.t. for 24 h, the soln. was evaporated, and diluted with AcOEt. The soln. was washed with 1N aq. HCl, 5% aq. $NaHCO_3$, brine, and dried ($MgSO_4$). After removal of the solvent, the oily residue was purified by CC (SiO_2). The fraction eluted with 30% AcOEt in hexane afforded (*R*,*R*)-**4** (2.21 g, 92%). Colorless crystals. M.p. 101–103°. $[\alpha]_D^{26} = +60.8$ ($c = 0.99$, EtOH). IR (KBr): 3350 (br.), 3021, 2981, 1712, 1216. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.63–5.66 (*m*, 2 H); 5.01 (br. *s*, 1 H); 4.16 (*q*, $J = 7.0$, 2 H); 2.62 (*dd*, $J = 6.0, 13.3$, 1 H); 2.22–2.26 (*m*, 2 H); 2.10 (*m*, 1 H); 1.79–1.93 (*m*, 5 H); 1.49 (*m*, 1 H); 1.42 (*s*, 9 H); 1.24 (*t*, $J = 7.0$, 3 H). FAB-MS: 310 ($[M+H]^+$). HR-FAB-MS: 310.2006 ($[M+H]^+$, $C_{17}H_{28}NO_4^+$; calc. 310.2013). Anal. calc. for $C_{17}H_{27}NO_4$ (309.40): C 65.99, H 8.80, N 4.53; found: C 65.90, H 8.73, N 4.50.

Data of (*S*,*S*)-**4** Yield: 77%. M.p. 101–103°. $[\alpha]_D^{28} = -62.1$ ($c = 0.975$, EtOH).

*Ethyl (1*R,*6*R*)-8-Aminobicyclo[4.3.0]non-3-ene-8-carboxylate* (= *Ethyl (3a*R,*7a*R*)-2-Amino-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate*; H_2N-[(*R*,*R*)-$Ab_{5,6=}$c]-OEt; (*R*,*R*)-**5**}. A soln. of (*R*,*R*)-**4** (190 mg, 0.615 mmol) in conc. aq. HCl (3 ml) and AcOEt (9 ml) was stirred at r.t. for 5 h. The soln. was neutralized with 5% aq. $NaHCO_3$, extracted with AcOEt, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by CC (SiO_2; 10% MeOH in $CHCl_3$) to give (*R*,*R*)-**5** (127 mg, > 99%). Colorless oil. $[\alpha]_D^{29} = +93.3$ ($c = 0.30$, EtOH). IR (neat): 3370 (br.), 3302, 3020, 2958, 2906, 2832, 1727, 1441, 1266, 1189. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.68–5.69 (*m*, 2 H); 4.17 (*q*, $J = 7.1$, 2 H); 2.50 (*dd*, $J = 7.3, 12.9$, 1 H); 2.24–2.29 (*m*, 2 H); 1.68–1.89 (*m*, 8 H); 1.28 (*t*, $J = 7.1$, 3 H); 1.21 (*m*, 1 H). HR-FAB-MS: 210.1530 ($[M+H]^+$, $C_{12}H_{20}NO_2^+$; calc. 210.1489).

Data of (*S*,*S*)-**5** Yield: > 99%. $[\alpha]_D^{28} = -102.7$ ($c = 1.60$, EtOH).

*(1*R,*6*R*)-8-[(*tert-*Butoxycarbonyl)amino]bicyclo[4.3.0]non-3-ene-8-carboxylic Acid* (=*(3a*R,*7a*R*)-2-[(*tert-*Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H-*indene-2-carboxylic Acid*; Boc-[(*R*,*R*)-$Ab_{5,6=}$c]-OH; (*R*,*R*)-**6**). A soln. of (*R*,*R*)-**4** (186 mg, 0.602 mmol) and 1N aq. NaOH (2.0 ml, 2.0 mmol) in MeOH (12 ml) was stirred at r.t. for 12 h. Then, the soln. was neutralized with 1N aq. HCl, and MeOH was evaporated. The aq. soln. was extracted with AcOEt and dried (Na_2SO_4). Removal of the solvent afforded (*R*,*R*)-**6** (170 mg, >99%). Colorless crystals, which were used for the next reaction without further purification.

Data of (*R*,*R*)-**6**. M.p. 88–90°. $[\alpha]_D^{24} = +49.0$ ($c = 1.02$, EtOH). IR (KBr): 3333, 3023, 2981, 1710, 1681, 1529, 1172. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.65–5.68 (*m*, 2 H); 5.09 (br. *s*, 1 H); 2.74 (*m*, 1 H); 2.29 (*m*, 1 H); 2.25 (*m*, 1 H); 2.13 (*m*, 1 H); 1.99 (*m*, 1 H); 1.76–1.84 (*m*, 4 H); 1.44 (br., 1 H); 1.44 (*s*, 9 H). HR-FAB-MS: 282.1747 ($[M+H]^+$, $C_{15}H_{24}O_4N^+$; calc. 282.1705).

Data of (*S*,*S*)-**6** Yield: >99%. M.p. 90–91°. $[\alpha]_D^{29} = -53.1$ ($c = 0.91$, EtOH).

*Ethyl (3*R,*4*R*)-1-[(*tert-*Butoxycarbonyl)amino]-3,4-bis(2-hydroxyethyl)cyclopentanecarboxylate* (**7**). Ozone gas was bubbled into a soln. of (*R*,*R*)-**4** (60 mg, 0.194 mmol) in MeOH (4 ml) and CH_2Cl_2 (6 ml) at −78°, and the reaction was monitored by TLC. $NaBH_4$ (32 mg, 0.86 mmol) was added portionwise to the soln. at −78°. After stirring at −78° for 30 min, the soln. was gradually warmed to r.t. and neutralized with 1N aq. HCl. After evaporation of MeOH and CH_2Cl_2, the aq. soln. was extracted with $CHCl_3$ and dried ($MgSO_4$). Removal of the solvent afforded a colorless oil, which was purified by CC (SiO_2). The fraction eluted with 5% MeOH in $CHCl_3$ gave **7** (59 mg, 63%). Colorless oil. $[\alpha]_D^{25} = -35.3$ ($c = 1.00$, EtOH). IR (neat): 3350 (br.), 2977, 2932, 1720, 1699, 1519, 1168, 1050. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.18 (br. *s*, 1 H); 4.17 (*q*, *J* = 7.1, 2 H); 3.59–3.74 (*m*, 4 H); 2.57 (*dd*, *J* = 8.1, 13.7, 1 H); 1.81–2.20 (*m*, 9 H); 1.58 (*m*, 1 H); 1.48 (*m*, 1 H); 1.43 (*s*, 9 H); 1.26 (*t*, *J* = 7.1, 3 H). HR-FAB-MS: 346.2199 ($[M+H]^+$, $C_{17}H_{32}NO_6^+$; calc. 346.2224).

*2,2′-[(1*R,*2*R*)-4-[(*tert-*Butoxycarbonyl)amino]-4-(ethoxycarbonyl)cyclopentane-1,2-diyl]diacetic Acid* (**8**). Ozone gas was bubbled into a soln. of (*R*,*R*)-**4** (50 mg, 0.162 mmol) in MeOH (9 ml) and CH_2Cl_2 (1 ml) at −78°, and the reaction was monitored by TLC. Me_2S (0.2 ml) was added to the soln. at −78°, and the soln. was warmed to r.t. Removal of the solvent afforded a crude dialdehyde. The crude dialdehyde and *Oxone*® (104 mg, 0.169 mmol) in DMF (4 ml) was stirred at r.t. for 5 h. The soln. was acidified with 1N aq. HCl, extracted with AcOEt, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by CC (SiO_2; 5% MeOH in $CHCl_3$) to give **8** (24 mg, 40%). Colorless oil. $[\alpha]_D^{25} = -16.9$ ($c = 0.72$, $CHCl_3$). IR (neat): 3368 (br.), 2980, 1713, 1369, 1167. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.13 (br., 1 H); 4.19 (*q*, *J* = 7.1, 2 H); 1.45–2.61 (*m*, 12 H); 1.43 (*s*, 9 H); 1.27 (*t*, *J* = 7.1, 3 H). EI-MS: 300.3 (4, $[M-{}^t\text{BuO}]^+$), 241.2 (19), 149.1 (15), 83.0 (100).

*Ethyl (1*R,*7*R*)-*N*-*Benzyl-9-[(*tert-butoxycarbonyl)amino]-4-azabicyclo[5.3.0]decane-9-carboxylate* (=*Ethyl (5a*R,*8a*R*)-3-Benzyl-7-[(*tert-butoxycarbonyl)amino]decahydrocyclopenta[*d*]azepine-7-carboxylate*; **9**). Crude aldehyde, which was prepared from (*R*,*R*)-**4** (50 mg, 0.162 mmol) by the same procedure, was dissolved in CH_2Cl_2 (3 ml) and MeOH (3 ml). $BnNH_2$ (44 µl, 0.40 mmol) was added to the soln., and the soln. was stirred at r.t. for 30 min, and then $NaBH_3CN$ (25 mg, 0.40 mmol) was added. After stirring at r.t. for 12 h, the soln. was diluted with H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by CC (SiO_2 (10% AcOEt in hexane) to give **9** (35 mg, 53%). Colorless oil. $[\alpha]_D^{24} = -6.90$ ($c = 0.17$, $CHCl_3$). IR (neat): 3366 (br.), 3026, 2976, 2930, 1716 (br.), 1495, 1453, 1366, 1170. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.21–7.35 (*m*, 5 H); 4.95 (br. *s*, 1 H); 4.18 (*q*, *J* = 7.1, 2 H); 3.65 (*s*, 2 H); 2.54–2.74 (*m*, 5 H); 1.82–2.12 (*m*, 7 H); 1.55 (*m*, 1 H); 1.44 (*s*, 9 H); 1.36 (*m*, 1 H); 1.27 (*t*, *J* = 7.1, 3 H). HR-FAB-MS: 417.2767 ($[M+H]^+$, $C_{24}H_{37}N_2O_4^+$; calc. 417.2753).

*Ethyl (1*R,*6*R*)-8-[(*tert-*Butoxycarbonyl)amino]bicyclo[4.3.0]nonane-8-carboxylate* (=*Ethyl (3a*R,*7a*R*)-2-[(*tert-*Butoxycarbonyl)amino]octahydro-1*H-*indene-2-carboxylate*; Boc-[(R,R)-$Ab_{5,6}$c]-OEt; **10**). A suspension of (*R*,*R*)-**4** (23 mg, 0.074 mmol) and 5% Pd/C (50 mg) in MeOH (5 ml) was stirred at r.t. under H_2 for 24 h. Then, the catalyst was filtered off, and the filtrate was evaporated. The residue was purified by CC (SiO_2; 10% AcOEt in hexane) to give **10** (24 mg, >99%). Colorless crystals. M.p. 53–54°. $[\alpha]_D^{26} = -6.35$ ($c = 1.14$, EtOH). IR (KBr): 3346, 2977, 2930, 2851, 1728, 1686, 1522, 1289, 1183. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.01 (br. *s*, 1 H); 4.18 (*q*, *J* = 7.1, 2 H); 2.51 (*m*, 1 H); 1.71–2.00 (*m*, 7 H); 1.43 (*s*, 9 H); 1.35–1.42 (*m*, 2 H); 1.26 (*t*, *J* = 7.1, 3 H); 1.15–1.25 (*m*, 2 H); 0.98–1.15 (*m*, 2 H).

FAB-MS: 312 ($[M+H]^+$). Anal. calc. for $C_{17}H_{29}NO_4$ (311.42): C 65.57, H 9.39, N 4.50; found: C 65.52, H 9.31, N 4.42.

Synthesis and Modification of Homochiral Oligomers.

*Ethyl (3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate* (Boc-[(*R*,*R*)-$Ab_{5,6=}c]_2$-OEt; (*R*,*R*)-**11**). A mixture of (*R*,*R*)-**5** (100 mg, 0.50 mmol), (*R*,*R*)-**6** (170 mg, 0.60 mmol), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU; 228 mg, 0.60 mmol), and EtN^iPr_2 (DIPEA; 174 µl, 1.00 mmol) in CH_2Cl_2 (5 ml) was stirred at 40° for 5 h. Then, the soln. was diluted with AcOEt, washed with 1N aq. HCl, 5% aq. $NaHCO_3$, and brine, and dried ($MgSO_4$). Removal of the solvent afforded white solids, which were purified by CC (SiO_2; 1% MeOH in $CHCl_3$) to give (*R*,*R*)-**11** (148 mg, 62%). Colorless crystals. M.p. 209–210°. $[\alpha]_D^{22} = +85.3$ ($c = 0.38$, $CHCl_3$). IR ($CDCl_3$): 3437 (br.), 3024, 2914, 2836, 1718, 1684, 1161. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.26 (br. *s*, 1 H); 5.60–5.67 (*m*, 4 H); 4.92 (br. *s*, 1 H); 4.17 (*q*, $J = 7.2$, 2 H); 2.80 (*m*, 1 H); 2.61 (*m*, 1 H); 2.17–2.24 (*m*, 5 H); 1.30–2.05 (*m*, 13 H); 1.44 (*s*, 9 H); 1.24 (*t*, $J = 7.2$, 3 H). FAB-MS: 473 ($[M+H]^+$). Anal. calc. for $C_{27}H_{40}N_2O_5$ (472.62): C 68.62, H 8.53, N 5.93; found: C 68.32, H 8.45, N 6.05.

Data of (*S*,*S*)-**11** Yield: 68%. M.p. 210–211°. $[\alpha]_D^{26} = -79.5$ ($c = 0.67$, $CHCl_3$).

*Ethyl (3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate* (Boc-[(*R*,*R*)-$Ab_{5,6=}c]_3$-OEt; (*R*,*R*)-**12**). A mixture of (*R*,*R*)-**11** (156 mg, 0.330 mmol) in conc. aq. HCl (2 ml) and AcOEt (6 ml) was stirred at r.t. for 5 h. The soln. was neutralized with 5% aq. $NaHCO_3$, extracted with AcOEt, and dried ($MgSO_4$). After removal of the solvent, the residue was filtered through a short SiO_2 column (10% MeOH in $CHCl_3$) to leave an amine (114 mg). A soln. of the amine (114 mg, 307 mmol), (*R*,*R*)-**6** (103 mg, 0.367 mmol), HBTU (140 mg, 0.370 mmol), and DIPEA (0.10 ml, 0.60 mmol) in CH_2Cl_2 (10 ml) was stirred at 40° for 48 h. Then, the soln. was diluted with $CHCl_3$, washed with 1N aq. HCl, 5% aq. $NaHCO_3$, and brine, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by CC (SiO_2; 5% MeOH in $CHCl_3$) to give (*R*,*R*)-**12** (165 mg, 85%). Colorless crystals. M.p. 238–239° (recryst. from $CHCl_3$). $[\alpha]_D^{24} = +70.6$ ($c = 0.85$, $CHCl_3$). IR ($CDCl_3$): 3433 (br.), 3365 (br.), 3024, 2913, 2835, 1720, 1706, 1521, 1271, 1160. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.66 (br. *s*, 1 H); 6.59 (br. *s*, 1 H); 5.63–5.66 (*m*, 6 H); 5.07 (br. *s*, 1 H); 4.10–4.17 (*m*, 2 H); 2.72–2.87 (*m*, 3 H); 2.20–2.38 (*m*, 7 H); 1.50–2.17 (*m*, 17 H); 1.47 (*s*, 9 H); 1.20–1.31 (*m*, 6 H). HR-FAB-MS: 636.4017 ($[M+H]^+$, $C_{37}H_{54}N_3O_6^+$; calc. 636.4013).

Data of (*S*,*S*)-**12**: 68%. M.p. 237–238° (recryst. from $CHCl_3$/EtOH). $[\alpha]_D^{24} = -81.0$ ($c = 0.85$, $CHCl_3$).

*(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylic Acid* (Boc-[(*R*,*R*)-$Ab_{5,6=}c]_3$-OH; (*R*,*R*)-**13**). A soln. of (*R*,*R*)-**12** (35 mg, 55 µmol) in 1N aq. NaOH (2.0 ml, 2.0 mmol) and MeOH (6 ml) was stirred at 60° for 12 h. Then, the soln. was neutralized with 1N aq. HCl, and MeOH was evaporated. The aq. residue was extracted with AcOEt and dried (Na_2SO_4). Removal of the solvent gave crude (*R*,*R*)-**13**, which was used for the next reaction without purification. M.p. 148–149°. $[\alpha]_D^{23} = +112.6$ ($c = 0.88$, $CHCl_3$). IR (KBr): 3323 (br.), 3021, 2907, 1684 (br.), 1520, 1167. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.0 (br., 1 H); 7.77 (br. *s*, 1 H); 6.88 (br. *s*, 1 H); 5.63–5.66 (*m*, 6 H); 5.31 (br. *s*, 1 H); 2.80–2.93 (*m*, 3 H); 2.46 (*m*, 1 H); 2.21–2.29 (*m*, 7 H); 1.60–2.09 (*m*, 15 H); 1.46 (*s*, 9 H); 1.10–1.30 (*m*, 4 H). HR-FAB-MS: 608.3693 ($[M+H]^+$, $C_{35}H_{50}N_3O_6^+$; calc. 608.3700).

*Ethyl (3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate* (Boc-[(*R*,*R*)-$Ab_{5,6=}c]_6$-OEt; (*R*,*R*)-**15**). Aq. conc. HCl (0.7 ml) was added dropwise to the stirred soln. of (*R*,*R*)-**12** (30 mg, 47 µmol) in AcOEt (2 ml) at 0°. After stirring at r.t. for 5 h, the soln. was neutralized with 5% aq. $NaHCO_3$, extracted with AcOEt, and dried ($MgSO_4$). Removal of the solvent afforded a residue, which was purified by short CC (SiO_2; 10% MeOH in $CHCl_3$) to give an N-terminal-free tripeptide (*R*,*R*)-**14**. A mixture of (*R*,*R*)-**13**

(33 mg, 55 μmol), HBTU (21 mg, 55 μmol), and DIPEA (16 μl, 94 μmol) in CH_2Cl_2 (2 ml) was added to the stirred soln. of the N-terminal-free tripeptide (*R*,*R*)-**14** in CH_2Cl_2 (3 ml) at r.t. After stirring at 40° for 48 h, the soln. was diluted with $CHCl_3$, washed with 1N aq. HCl, 5% aq. $NaHCO_3$, and brine, and dried ($MgSO_4$). Removal of the solvent afforded white solids, which were purified by CC (SiO_2; 5% MeOH in $CHCl_3$) to give (*R*,*R*)-**15** (27 mg, 50%). Colorless crystals. M.p. 240° (dec.). $[\alpha]_D^{24} = +215.3$ ($c = 0.64$, $CHCl_3$). IR ($CDCl_3$): 3426 (br.), 3332 (br.), 2913, 2835, 1725, 1698, 1525, 1280, 1158. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.16 (br. *s*, 1 H); 7.91 (br. *s*, 1 H); 7.65 (br. *s*, 1 H); 7.57 (br. *s*, 1 H); 6.90 (br. *s*, 1 H); 5.60 – 5.70 (*m*, 12 H); 5.32 (br. *s*, 1 H); 4.11 – 4.18 (*m*, 2 H); 3.10 – 3.23 (*m*, 4 H); 2.85 (*m*, 1 H); 2.48 – 2.70 (*m*, 3 H); 2.05 – 2.30 (*m*, 13 H); 1.56 – 1.95 (*m*, 33 H); 1.48 (*s*, 9 H); 1.20 – 1.42 (*m*, 9 H). FAB-MS: 1126 ($[M+H]^+$). HR-FAB-MS: 1147.6840 ($[M+Na]^+$, $C_{67}H_{92}N_6NaO_9^+$; calc. 1147.6823.

Data of (*S*,*S*)-**15** Yield: 29%. M.p. 240° (dec.). $[\alpha]_D^{25} = -202.0$ ($c = 0.395$, $CHCl_3$).

*Ethyl (3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl}carbonyl)amino]-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2-carboxylate* (Boc-[(*R*,*R*)-$Ab_{5,6=}c]_9$-OEt; (*R*,*R*)-**16**). Conc. aq. HCl (2 ml) was added to the stirred soln. of (*R*,*R*)-**15** (90 mg, 80 μmol) in AcOEt (5 ml) at 0°. After stirring at r.t. for 12 h, the soln. was neutralized with 5% aq. $NaHCO_3$, extracted with $CHCl_3$, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by short CC (SiO_2; 10% MeOH in $CHCl_3$) to leave an N-terminal-free hexapeptide (45 mg, 44 μmol). A soln. of the hexapeptide amine (45 mg, 44 μmol), (*R*,*R*)-**13** (33 mg, 54 μmol), HBTU (21 mg, 54 μmol), and DIPEA (15 μl, 86 μmol) in CH_2Cl_2 (5 ml) was stirred at 40° for 48 h. The soln. was diluted with $CHCl_3$, washed with 1N aq. HCl, 5% aq. $NaHCO_3$, and brine, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by CC (SiO_2). The fraction eluted with 5% MeOH in $CHCl_3$ afforded (*R*,*R*)-**16** (42 mg, 32%). White powder. M.p. 250° (dec.). $[\alpha]_D^{26} = +247.1$ ($c = 0.20$, $CHCl_3$). IR ($CDCl_3$): 3424 (br.), 3314 (br.), 3023, 2912, 2890, 1724, 1697, 1650, 1528, 1281. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.29 (br. *s*, 1 H); 8.17 (br. *s*, 1 H); 8.12 (br. *s*, 1 H); 8.09 (br. *s*, 1 H); 7.96 (br. *s*, 1 H); 7.68 (br. *s*, 1 H); 7.64 (br. *s*, 1 H); 6.97 (br. *s*, 1 H); 5.34 (br. *s*, 1 H); 5.60 – 5.67 (*m*, 18 H); 4.10 – 4.18 (*m*, 2 H); 3.09 – 3.24 (*m*, 8 H); 2.57 – 2.92 (*m*, 8 H); 2.05 – 2.25 (*m*, 20 H); 1.52 – 1.94 (*m*, 45 H); 1.48 (*s*, 9 H); 1.26 – 1.35 (*m*, 12 H). FAB-MS: 1638 ($[M+Na]^+$).

*Ethyl (3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[({(3a*R*,7a*R*)-2-[(*tert*-Butoxycarbonyl)amino]octahydro-1*H*-inden-2-yl}carbonyl)amino]octahydro-1*H*-inden-2-yl}carbonyl)amino]octahydro-1*H*-inden-2-yl}carbonyl)amino]octahydro-1*H*-inden-2-yl}carbonyl)amino]octahydro-1*H*-inden-2-yl}carbonyl)amino]octahydro-1*H*-indene-2-carboxylate* (Boc-[(*R*,*R*)-$Ab_{5,6}c]_6$-OEt; (*R*,*R*)-**17**). A suspension of (*R*,*R*)-**15** (50 mg, 0.044 mmol) and 20% $Pd(OH)_2$/C (50 mg) in MeOH (9 ml) and THF (1 ml) was stirred under H_2 for 24 h. Then, the catalyst was filtered off, and the filtrate was evaporated. The residue was purified by CC (SiO_2; 5% MeOH in $CHCl_3$) to give (*R*,*R*)-**17** (36 mg, 70%). Colorless crystals. M.p. 272 – 273°. $[\alpha]_D^{26} = +132.1$ ($c = 0.315$, $CHCl_3$). IR ($CDCl_3$): 3426 (br.), 3336 (br.), 2925, 2853, 1723, 1699, 1661, 1522, 1448, 1287. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.12 (br. *s*, 1 H); 7.83 (br. *s*, 1 H); 7.61 (br. *s*, 1 H); 7.51 (br. *s*, 1 H); 6.86 (br. *s*, 1 H); 5.29 (br. *s*, 1 H); 4.09 – 4.19 (*m*, 2 H); 2.97 – 3.10 (*m*, 4 H); 2.78 (*m*, 1 H); 2.34 – 2.58 (*m*, 3 H); 1.62 – 1.86 (*m*, 33 H); 1.51 (*s*, 9 H); 0.80 – 1.45 (*m*, 46 H). FAB-MS: 1138 ($[M+H]^+$). HR-FAB-MS: 1159.7736 ($[M+Na]^+$, $C_{67}H_{104}O_9N_6Na^+$; calc. 1159.7762).

*Crystal Data for (*S,S*)-*12 *and (*R,R*)-*15. (*S,S*)-**12**: 4($C_{37}H_{53}N_3O_6$); M_r 2543.3; Triclinic; *P*1, $a = 11.586$ Å, $b = 12.450$ Å, $c = 25.295$ Å; $\alpha = 92.82°$, $\beta = 102.85°$, $\gamma = 90.50°$; $V = 3552.0$ Å^3; $Z = 4$; $D_{calc} = 1.189$ g/cm^3; $\mu(MoK_\alpha) = 0.80$ cm^{-1}; No. of observations ($I > 2\sigma(I)$) = 14441; No. of variables, 1657; $R_1 = 0.0685$, and $R_w = 0.1466$.

(R,R)-**15**: 4($C_{67}H_{92}N_6O_9$) · 2 EtOH; M_r 4594.0; Triclinic; *P*1, $a = 15.765$ Å, $b = 16.535$ Å, $c = 26.90$ Å; $\alpha = 74.22°$, $\beta = 82.32°$, $\gamma = 75.39°$; $V = 6514$ Å^3; $Z = 4$; $D_{calc} = 1.171$ g/cm^3; $\mu(MoK_\alpha) = 0.78$ cm^{-1}; No. of observations ($I > 2\sigma(I)$) = 29059; No. of variables, 3045; $R_1 = 0.0589$, and $R_w = 0.1373$. CCDC-892764 for **12** and CCDC-284623 for **15** contain the supplementary crystallographic data for this paper. These data

can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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