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One-Handed Helical Screw Direction of Homopeptide Foldamer Exclusively Induced by Cyclic α-Amino Acid Side-Chain Chiral Centers

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Abstract: Chiral cyclic α,α-disubstituted amino acids, (3*S*,4*S*)- and (3*R*,4*R*)-1-amino-3,4-(dialkoxy)cyclopentanecarboxylic acids ((*S*,*S*)- and (*R*,*R*)-Ac_5c^{dOR}; R: methyl, methoxymethyl), were synthesized from dimethyl L-(+)- or D-(−)-tartrate, and their homochiral homoligomers were prepared by solution-phase methods. The preferred secondary structure of the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide was a left-handed (*M*) 3_{10} helix, whereas those of the (*S*,*S*)-Ac_5c^{dOMe} octa- and decapeptides were left-handed (*M*) α helices, both in solution and in the crystal state. The octa- and decapeptides can be well dissolved in pure water and are more α helical in water than in 2,2,2-trifluoroethanol solution. The left-handed (*M*) helices of the (*S*,*S*)-Ac_5c^{dOMe} homochiral homopeptides were exclusively controlled by the side-chain chiral centers, because the cyclic amino acid (*S*,*S*)-Ac_5c^{dOMe} does not have an α-carbon chiral center but has side-chain γ-carbon chiral centers.

Keywords: amino acids · chirality · conformation analysis · helical structures · peptides

Introduction

Helices are life-science-related three-dimensional structures. For instance, they are found in proteins as helical secondary structures and in DNA as a double-helical structure. Recently, de novo designed helical structures of foldamers, such as β peptides,[1] peptoids,[2] oligoarenes,[3] and urea oligomers,[4] have attracted the attention of organic, medicinal, and peptide chemists, and some have been used to design biologically active molecules and organocatalysts. Helices are chiral, and their helical screw senses result in two directions, right handedness (*P*) and left handedness (*M*). The α helices in proteins almost always have a right-handed (*P*) screw sense. This right handedness is believed to result from the asymmetric center at the α-carbon atom of proteinogenic L-α-amino acids, because if peptides composed of L-α-amino acids formed left-handed (*M*) helical structures, steric repulsion would arise between the carbonyl group and the side-chain β-carbon atom of one residue.[5]

Among the L-α-amino acids, threonine and isoleucine exclusively have an additional chiral center at the side-chain β-carbon atom, as well as at the α-carbon atom; however, only a little physiochemical attention has been paid to the influence of side-chain asymmetric centers on the secondary structure of peptides.[6,7] Scientists have believed that the α-carbon chiral centers of L-α-amino acids affect the helical screw bias of their peptides but that side-chain chiral centers do not, and the physiochemical role of side-chain chiral centers has been overlooked. Herein, we describe the design and synthesis of chiral cyclic α,α-disubstituted amino acids in which chiral centers exist at the side-chain γ-carbon atoms but not at the α-carbon atoms, and we reveal that the side-chain chiral centers of cyclic amino acid homochiral homopeptides can control the helical screw direction into one handedness in organic solvent, in water, and also in the crystal state.

Results and Discussion

Design and synthesis of chiral cyclic α,α-disubstituted α-amino acids: We designed chiral cyclic α,α-disubstituted α-amino acids, 1-amino-3,4-(dialkoxy)cyclopentanecarboxylic acids (Ac_5c^{dOR}; R: methyl (Me) or methoxymethyl (MOM)), having chiral centers at the side-chain γ-carbon atoms but

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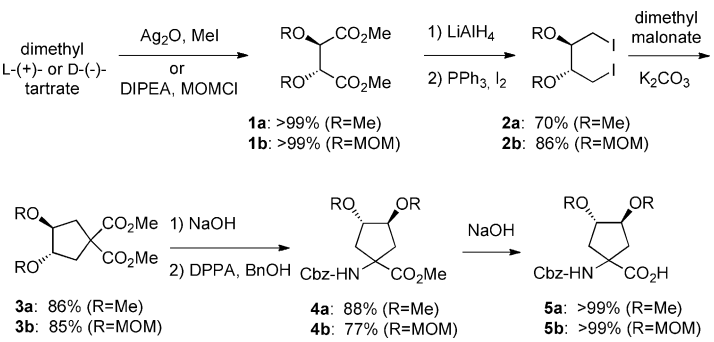
not at the α-carbon atoms.[8,9] The α-carbon atom of the cyclic amino acid does not affect the screw direction of the helix formed by the peptides because the α-carbon atom is not an asymmetric center. Thus, we reasoned that the helical screw sense of the Ac_5c^{dOR} homochiral homopeptides would be exclusively affected by the side-chain chiral centers.[10–12]

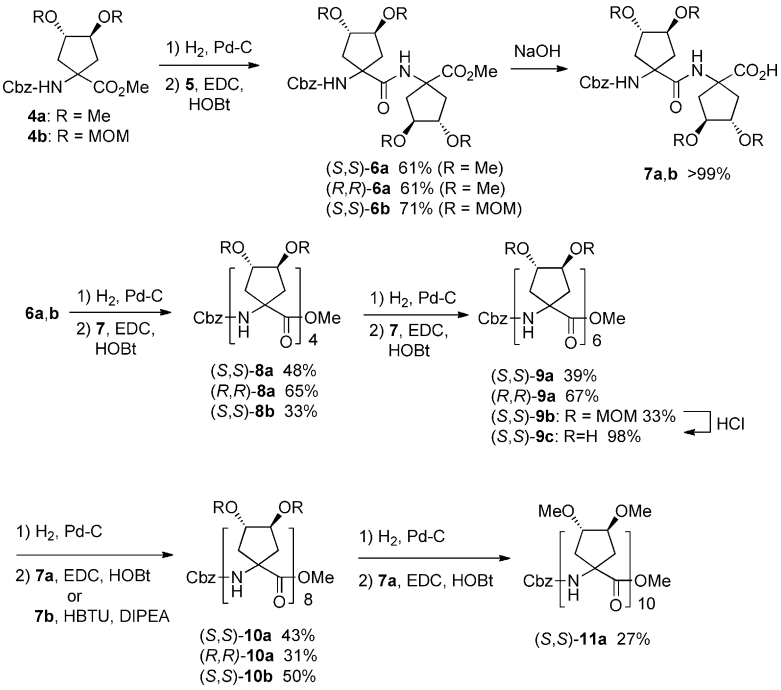
We efficiently synthesized both enantiomers of the optically active cyclic amino acid[13] (*S*,*S*)- and (*R*,*R*)-Ac_5c^{dOMe} by starting from dimethyl L-(+)- or D-(−)-tartrate (Scheme 1).[14] Dimethyl tartrate was converted into diiodide



Scheme 1. Synthesis of the cyclic amino acids Cbz-(Ac_5c^{dOR})-OMe (R: Me, MOM). DIPEA: *N*,*N*-diisopropylethylamine; DPPA: diphenylphosphoryl azide; Bn: benzyl; Cbz: benzyloxycarbonyl.

2a in 70% yield through a three-step sequence of methylation of the secondary alcohols with MeI/Ag_2O, reduction of the methyl esters with $LiAlH_4$, and substitution of the primary alcohols with iodide. Dialkylation of dimethylmalonate with the diiodide **2a** by KO*t*Bu in dimethylsulfoxide (DMSO) at room temperature gave cyclic diester **3a** in 53% yield. Later, the yield of product **3a** was improved to 86% by using K_2CO_3 in *N*,*N*-dimethylformamide (DMF) at 75°C. Monohydrolysis of an ester, followed by Curtius rearrangement with DPPA[15] and work up with benzyl alcohol produced the Cbz-protected cyclic amino acid Cbz-(Ac_5c^{dOMe})-OMe (**4a**) in 88% yield. The synthesis from dimethyl L-(+)-tartrate afforded Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]-OMe ((*S*,*S*)-**4a**), whereas that from dimethyl D-(−)-tartrate gave the enantiomeric Cbz-[(*R*,*R*)-Ac_5c^{dOMe}]-OMe ((*R*,*R*)-**4a**) on the gram scale. By a similar procedure, the cyclic amino acid Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]-OMe (**4b**), with two MOM substituents at the γ-position of the cyclic side chain, was synthesized from dimethyl L-(+)-tartrate with protection of the secondary alcohols as the MOM ethers (Scheme 1). Alkaline hydrolysis of the ester in the cyclic amino acids **4a**,**b** produced the free-C-terminal amino acids Cbz-(Ac_5c^{dOR})-OH (**5a**,**b**) in >99% yield. The spectroscopic data of all compounds supported their structures.

Preparation of homochiral homo-oligopeptides composed of the cyclic amino acids (*S*,*S*)- and (*R*,*R*)-Ac_5c^{dOMe} and (*S*,*S*)-Ac_5c^{dOMOM}: Homochiral homopeptides (up to decapeptide **11a** for (*S*,*S*)-Ac_5c^{dOMe} and octapeptides **10a**,**b** for (*R*,*R*)-Ac_5c^{dOMe} and (*S*,*S*)-Ac_5c^{dOMOM}, respectively) were prepared by solution-phase methods, with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride and 1-hydroxybenzotriazole (HOBt), or *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), employed as the coupling reagents,[16] as illustrated in Scheme 2. After removal of the Cbz protecting group in Cbz-(Ac_5c^{dOR})-OMe (**4a**,**b**) by hydrogenolysis with H_2/5% Pd-C, the resulting free-N-terminal amino acid was coupled with the free-C-terminal amino acids Cbz-(Ac_5c^{dOR})-OH (**5a**,**b**) by EDC and HOBt to produce the dipeptides Cbz-(Ac_5c^{dOR})$_2$-OMe (**6a**,**b**) in 61–71% yield. Alkaline hydrolysis of **6a**,**b** afforded free-C-terminal dipeptide acids **7a**,**b** in quantitative yields. After removal of the Cbz-protecting group in the dipeptides **6a**,**b** by hydrogenolysis, the resulting free-N-terminal dipeptides were coupled with the dipeptide acids **7a**,**b** to give tetrapeptides **8a**,**b** in 33–65% yield. Hexapeptides **9a**,**b**, octapeptides **10a**,**b**, and decapeptide (*S*,*S*)-**11a** were prepared by two amino acid elongations in a similar manner to that used for the preparation of tetrapeptides



Scheme 2. Synthesis of the homopeptides Cbz-(Ac_5c^{dOR})$_n$-OMe (R: Me, MOM; n=2–10).

8a,**b**. Interestingly, the octapeptides **10a**,**b** and decapeptide **11a** could be dissolved in water because of the presence of the ether functional groups. Removal of the MOM protecting groups from hexapeptide **9b** by treatment with concentrated HCl in MeOH gave a hexapeptide with twelve hydroxy groups, Cbz-[(*S*,*S*)-Ac_5c^{dOH}]$_6$-OMe (**9c**), which was well dissolved in pure water.

Conformation analysis in solution: The dominant conformations of the Ac_5c^{dOR} homopeptides in solution were studied by using IR, ^{1}H NMR, and CD spectroscopies. Figure 1

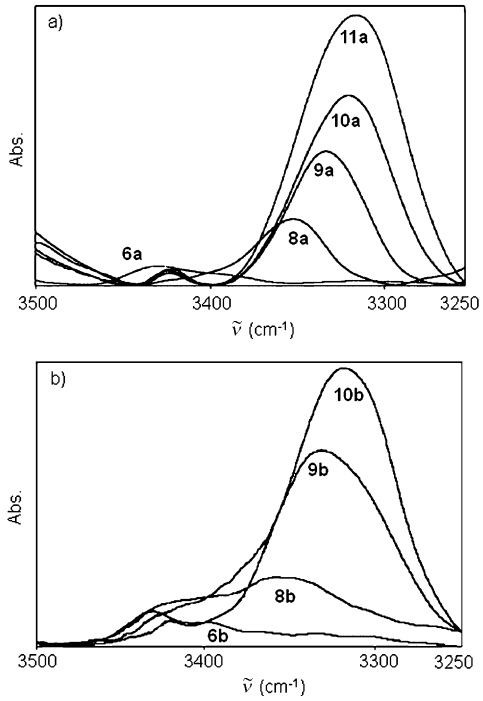


Figure 1. IR absorption spectra of a) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_n$-OMe (n=2: **6a**; 4: **8a**; 6: **9a**; 8: **10a**, 10: **11a**) and b) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_n$-OMe (n=2: **6b**; 4: **8b**; 6: **9b**; 8: **10b**) in $CDCl_3$ solution. Peptide concentration: 1.0 mM.

shows the IR absorption spectra of Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_n$-OMe (n=2 (**6a**), 4 (**8a**), 6 (**9a**), 8 (**10a**), 10 (**11a**)) and Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_n$-OMe (n=2 (**6b**), 4 (**8b**), 6 (**9b**), 8 (**10b**)) in the 3500–3250 cm^{-1} region at a peptide concentration of 1.0 mM in $CDCl_3$ solution. In the IR absorption spectra of Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_n$-OMe (Figure 1a), the weak bands at 3420–3440 cm^{-1} region are assigned to free (solvated) peptide NH groups and the strong bands at 3320–3360 cm^{-1} are assigned to peptide NH groups with N−H···O=C intramolecular hydrogen bonds of different strengths. As the peptide chain length increases, the strong band observed at 3360 cm^{-1} in **8a** shifts to slightly lower wavenumbers (3320 cm^{-1} in **11a**) and the relative intensity of the bands in the 3320–3360 cm^{-1} region gradually increases. These IR absorption spectra are very similar to those of achiral 1-aminocyclopentanecarboxylic acid (Ac_5c) homopeptides[17] and α-aminoisobutyric acid (Aib) homopeptides,[18] which form 3_{10} helices in solution, and are very different from the spectra of diethylglycine (Deg)[19] and (*S*)-butylethylglycine[20] homochiral homopeptides, which assume fully extended planar C_5 conformations. The IR absorption spectra of homochiral homopeptides composed of (*S*,*S*)-Ac_5c^{dOMOM} (Figure 1b) show similar absorption spectra to those of (*S*,*S*)-Ac_5c^{dOMe} homochiral homopeptides, but the absorption bands in the 3320–3360 cm^{-1} region in the (*S*,*S*)-Ac_5c^{dOMOM} peptides are slightly wider than those of the (*S*,*S*)-Ac_5c^{dOMe} peptides.

To obtain more detailed information on the preferred conformation, the ^{1}H NMR spectra of the Ac_5c^{dOR} hexapeptides (*S*,*S*)-**9a**,**b** and octapeptides (*S*,*S*)-**10a**,**b** were measured in $CDCl_3$ solution. In the ^{1}H NMR spectra of Ac_5c^{dOMe} homopeptides **9a** and **10a**, the N(1)H signals at the N terminus could be unambiguously determined by their high-field positions at δ=5.54 ppm (brs, 1H) in **9a** and δ=5.53 ppm (brs, 1H) in **10a**, due to their urethane structure,[21] but the remaining five or seven NH protons could not be assigned at this stage. Also, the N(1)H signals at the N terminus of **9b** and **10b** were assigned as signals at δ=6.66 ppm (brs, 1H) in **9b** and δ=6.51 ppm (brs, 1H) in **10b** by their high-field positions. Figure 2 and Figure 3 illustrate the results of solvent perturbation experiments by 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-yloxyl (TEMPO; 0–5×10^{-2}% w/v).[18a,b] Two NH chemical shifts of **9a**,**b** and **10a**,**b** were sensitive (solvent-exposed NH group) to the addition of the perturbing reagent DMSO, although one NH signal of **10b** could not be analyzed perfectly because of overlapping with the signals of the Cbz protecting group. Also, with the addition of the TEMPO radical, the

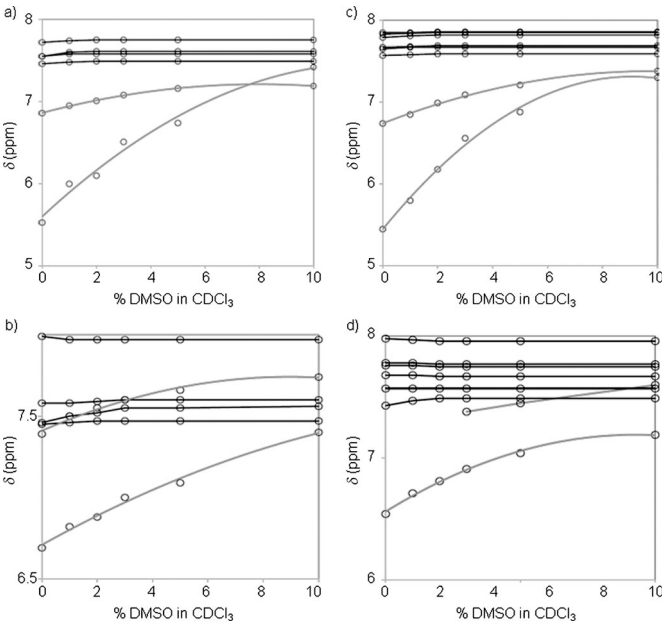


Figure 2. Plots of N−H chemical shifts in the ^{1}H NMR spectra of the homopeptides a) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_6$-OMe (**9a**), b) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_6$-OMe (**9b**), c) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_8$-OMe (**10a**), and d) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_8$-OMe (**10b**) as a function of increasing percentage of DMSO added to the $CDCl_3$ solution.

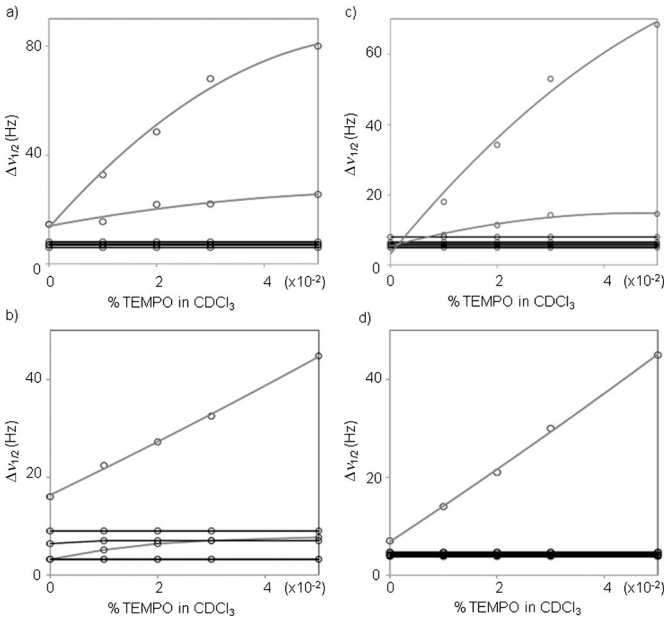


Figure 3. Plots of bandwidth of the N–H protons of the homopeptides a) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_6$-OMe (**9a**), b) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_6$-OMe (**9b**), c) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_8$-OMe (**10a**), and d) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_8$-OMe (**10b**) as a function of increasing percentage of TEMPO added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

bandwidth of two NH signals broadened in the case of **9a**, **9b**, and **10a**, although one NH signal of **10b** overlapped with the signals of the Cbz protecting group. These results mean that two NH protons are solvent exposed, which suggests that two NH protons are not intramolecularly hydrogen bonded. These data are in accordance with a 3_{10}-helical structure, in which two NH groups at the N terminus of the peptide are freely solvated (not intramolecularly hydrogen-bonded) peptide NH groups.

Figure 4 shows the 2D ROESY ^{1}H NMR spectra of hexapeptides **9a** and **9b** in $CDCl_3$ solution. Both ROESY ^{1}H NMR spectra show 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, respectively. Sequential NH ($i\rightarrow i+1$) dipolar interactions are used to diagnose helical structures; however, these interactions alone do not enable assessment of whether a 3_{10}- or α-helical conformation is present. In L-α-amino acid peptides and proteins, two NOE constraints [$d_{\alpha N}$ ($i\rightarrow i+2$)] and [$d_{\alpha N}$ ($i\rightarrow i+4$)] are believed to be characteristic of the 3_{10}- and α-helical structures, respectively;[22] however, these interactions do not occur in the case of the Ac_5c^{dOR} homopeptides because the cyclic α,α-disubstituted amino acids lack an α-hydrogen atom. The NH ($i\rightarrow i+1$) interactions of octapeptide **10a** could not be analyzed with the 2D ROESY ^{1}H NMR spectrum because significant NH proton signals overlapped and showed poor signal dispersion.

The CD spectra of (*S*,*S*)-Ac_5c^{dOMe} peptides **9a**, **10a**, and **11a** in 2,2,2-trifluoroethanol (TFE) show positive maxima at approximately 208 and 222 nm (207, 223 nm for **9a**; 208, 225 nm for **10a**; 210, 225 nm for **11a**), which indicates that

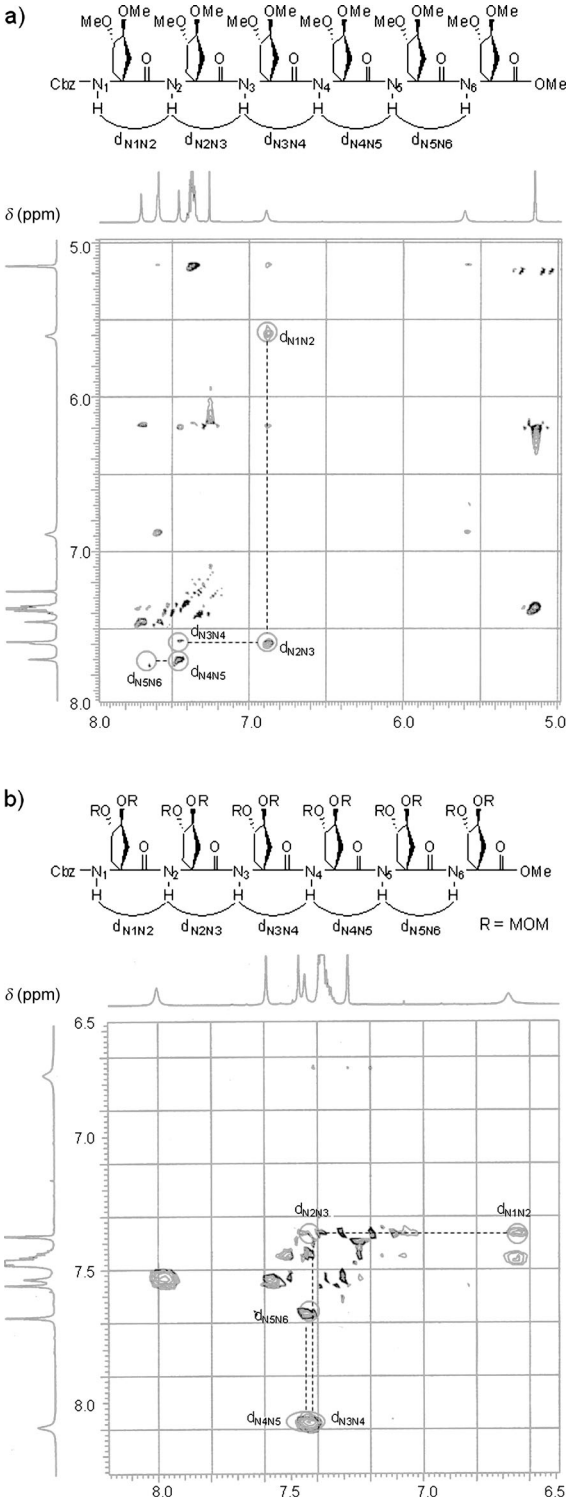


Figure 4. Rotating-frame nuclear Overhauser effect spectroscopy (ROESY) ^{1}H NMR spectra of a) Cbz-[(*S*,*S*)-Ac_5c^{dOMe}]$_6$-OMe (**9a**) and b) Cbz-[(*S*,*S*)-Ac_5c^{dOMOM}]$_6$-OMe (**9b**).

the helical screw sense is left handed (*M*), although hexapeptide **9a** lacks the negative maximum at approximately 200 nm (Figure 5a). The *R* ratios ($\theta_{222}/\theta_{208}$) suggest that the secondary structure of hexapeptide **9a** ($R=0.4$) is a 3_{10} helix

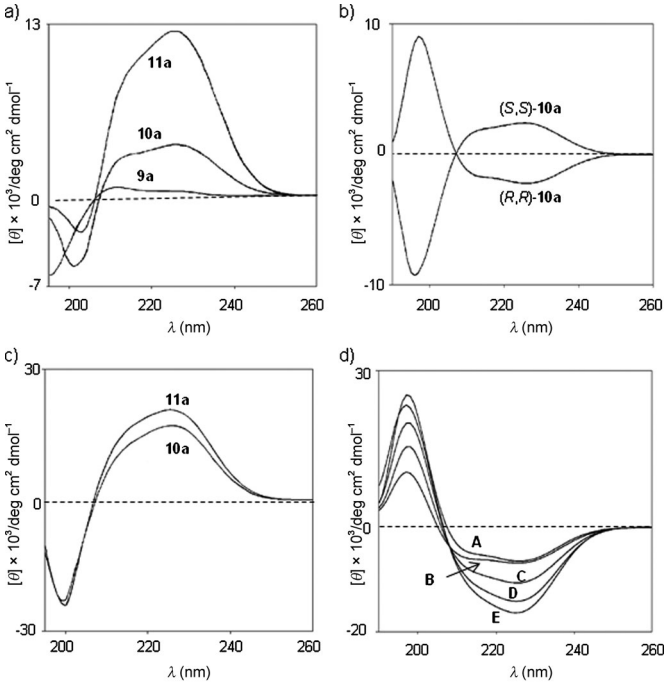


Figure 5. CD spectra of (*S*,*S*)- and (*R*,*R*)-Ac_5c^{dOMe} homochiral homopeptides: a) (*S*,*S*)-Ac_5c^{dOMe} homochiral homopeptides (**9a**, **10a**, and **11a**) in TFE solution (0.50 mM), b) (*S*,*S*)-Ac_5c^{dOMe} and (*R*,*R*)-Ac_5c^{dOMe} homochiral octapeptides ((*S*,*S*)- and (*R*,*R*)-**10a**) in TFE solution (0.50 mM), c) (*S*,*S*)-Ac_5c^{dOMe} homochiral octa- and decapeptides (**10a** and **11a**) in pure water (0.50 mM), and d) (*R*,*R*)-Ac_5c^{dOMe} homochiral octapeptide (*R*,*R*)-**10a** in various solutions (0.5 mM; A: TFE; B: MeCN; C: MeCN/H_2O (10/90); D: MeCN/H_2O (50/50); E: H_2O).

and that those of octapeptide **10a** ($R=1.4$) and decapeptide **11a** ($R=1.5$) are α helices.[23] The CD spectrum of the enantiomeric (*R*,*R*)-Ac_5c^{dOMe} octapeptide (*R*,*R*)-**10a** shows negative maxima at 208 nm and 225 nm, which indicates a right-handed (*P*) α helix (Figure 5b). Measurement of the CD spectra of (*R*,*R*)-**10a** at different temperatures (30–70 °C) in TFE solution did not change the shape (maxima at 208 nm and 225 nm), although the intensities of the maxima slightly decreased. These results indicated that the right-handed α-helical structure of **10a** is stable even at high temperature (70 °C).[24] Interestingly, the intensity of the maxima at 210 nm and 225 nm in the CD spectra of the (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a** and decapeptide **11a** were stronger in water than in TFE solution, which indicates that these peptides are more α helical in water (Figure 5c). Figure 5d shows the CD spectra of the (*R*,*R*)-Ac_5c^{dOMe} octapeptide (*R*,*R*)-**10a** in a variety of solvents. These spectra also indicate that the α-helical structure is more stable in water than in organic solvents.

The CD spectra of (*S*,*S*)-Ac_5c^{dOMOM} peptides **9b** and **10b**, with the MOM ether, in TFE showed similar patterns to those of (*S*,*S*)-Ac_5c^{dOMe} peptides **9a** and **10a**, which indicates that the helical screw sense is left handed (Figure 6a). Figure 6b shows the CD spectra of (*S*,*S*)-Ac_5c^{dOH} hexapeptide **9c** with 12 deprotected hydroxy groups. On the basis of the CD spectra, the (*S*,*S*)-Ac_5c^{dOH} peptide **9c** does not form a helical structure in TFE solution but instead seems to have a random-chain conformation. However, in water, positive maxima are shown at 208 and 225 nm ($R>1.0$) in the CD spectrum, although the intensities are weak, which suggests a left-handed (*M*) α-helical structure as a partially occurring conformation in water.

Conformations of (*S*,*S*)-Ac_5c^{dOMe} homochiral homopeptides in the crystal state: X-ray crystallographic analyses unambiguously revealed the molecular structures and conformations of the terminally protected (*S*,*S*)-Ac_5c^{dOMe} peptides in the crystal state. The (*S*,*S*)-Ac_5c^{dOMe} peptides formed good crystals for X-ray crystallographic analysis upon slow evaporation of the solvent at room temperature (**9a**: EtOH/H_2O; **10a**: MeOH/H_2O; **11a**: $CHCl_3$/*i*PrOH). The crystal and diffraction parameters of hexapeptide **9a**, octapeptide **10a**, and decapeptide **11a** are summarized in Table 1.[25–27] The molecular structures are illustrated in Figures 7–11. Relevant backbone and side-chain torsion angles[24] and the intra- and intermolecular hydrogen-bond parameters are listed in Table 2 and Table 3, respectively.

Three crystallographically independent molecules, *A*, *B*, and *C*, existed in the asymmetric unit of (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a**. Three methoxy groups, that is, an ether oxygen atom of the methoxy group at residues 3 and 6 in molecule *B* and the methoxy group at residue 4 in molecule *C*, were disordered. Molecules *A*–*C* were all folded into left-handed (*M*) 3_{10}-helical structures and, thus, displayed positive signs of the φ and ψ torsion angles at each amino acid residue, as illustrated in Figure 7. The average values of torsion angles φ and ψ are +57.8°, +28.9° in molecule *A*, +58.5°, +32.1° in molecule *B*, and +59.2°, +30.5° in mole-

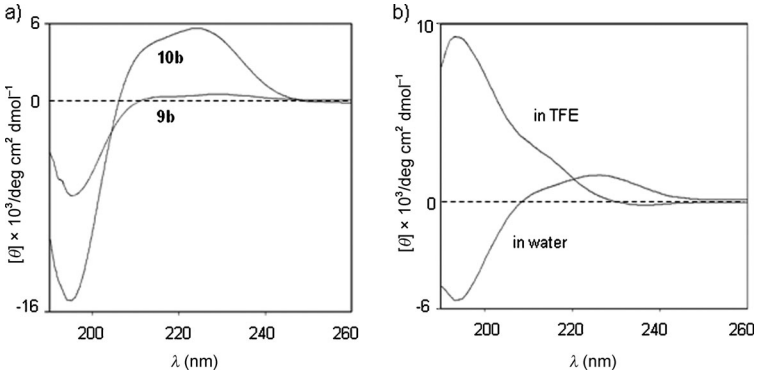


Figure 6. CD spectra of a) (*S*,*S*)-Ac_5c^{dOMOM} homochiral homopeptides **9b** and **10b** in TFE (0.50 mM) and b) (*S*,*S*)-Ac_5c^{dOH} hexapeptide **9c** in TFE (0.50 mM) and water (0.50 mM).

Table 1. Crystal and diffraction parameters of the (*S*,*S*)-Ac_5c^{dOMe} peptides **9a**, **10a**, and **11a**.

	Hexapeptide **9a**	Octapeptide **10a**	Decapeptide **11a**
empirical formula	$C_{57}H_{88}O_{21}N_6$	$C_{73}H_{114}O_{27}N_8 \cdot 3H_2O$	$C_{89}H_{140}O_{33}N_{10}$
M_r	1193.34	1589.77	1878.11
crystal dimensions [mm]	0.50×0.30×0.15	0.60×0.40×0.30	0.30×0.25×0.15
crystal system	monoclinic	monoclinic	monoclinic
a, *b*, *c* [Å]	22.854, 11.880, 33.632	15.639, 16.431, 15.989	14.480, 20.886, 16.904
α, β, γ [°]	90, 91.995, 90	90, 95.85, 90	90, 111.64, 90
V [Å^3]	9182.0	4087.2	4751.9
space group	$P2_1$	$P2_1$	$P2_1$
Z value	6	2	2
D_{calcd} [g cm^{-3}]	1.295	1.292	1.313
μ ($Mo_{K\alpha}$) [cm^{-1}]	0.99	1.00	1.00
no. of observations ($I>-10.0\sigma I$)	31196	16850	15457
no. of variables	2300	1023	357
R_1, R_w	0.075, 0.1972	0.0579, 0.140	0.1469, 0.2848
solvent	$EtOH/H_2O$	$MeOH/H_2O$	$CHCl_3$/*i*PrOH

Table 2. Selected torsion angles ω, φ, and ψ [°] for **9a** (*A*–*C*), **10a**, and **11a**, as determined by X-ray crystallographic analysis.

Torsion angle	**9a** *A*	**9a** *B*	**9a** *C*	**10a**	**11a**
θ_0	178.6	175.1	175.1	180.0	−170.8
ω_0	170.0	169.9	164.8	168.1	160.0
φ_1	56.4	61.4	66.1	60.5	60.1
ψ_1	42.0	35.9	25.3	43.7	46.6
ω_1	171.7	178.5	−179.1	173.5	173.2
φ_2	64.8	58.1	54.7	57.0	63.5
ψ_2	17.4	27.8	34.0	50.1	43.4
ω_2	−175.1	175.4	175.0	172.8	177.6
φ_3	57.2	63.1	58.4	60.7	55.4
ψ_3	25.6	21.3	27.4	47.1	53.1
ω_3	178.5	179.4	174.9	175.5	174.5
φ_4	60.0	56.6	53.5	59.5	60.5
ψ_4	17.6	27.5	33.2	46.8	47.4
ω_4	−176.8	176.9	173.1	174.8	173.8
φ_5	59.6	58.6	67.4	58.4	59.8
ψ_5	22.8	29.7	17.1	46.7	48.8
ω_5	179.6	167.5	177.0	176.9	171.9
φ_6	48.7	53.1	55.1	65.6	63.0
ψ_6	47.8	50.1	46.2	49.4	43.7
ω_6	−179.0	172.9	178.2	171.3	179.3
φ_7	–	–	–	64.8	56.8
ψ_7	–	–	–	43.7	46.1
ω_7	–	–	–	−171.9	175.8
φ_8	–	–	–	−54.2	56.2
ψ_8	–	–	–	−43.9	45.7
ω_8	–	–	–	−174.2	173.8
φ_9	–	–	–	–	60.5
ψ_9	–	–	–	–	48.2
ω_9	–	–	–	–	173.2
φ_{10}	–	–	–	–	−63.7
ψ_{10}	–	–	–	–	−14.6[a]
ω_{10}	–	–	–	–	−172.0[a]

[a] Disorder of the torsion angles (ψ_{10}=166.8, ω_{10}=−148.5) of **11a** was observed.

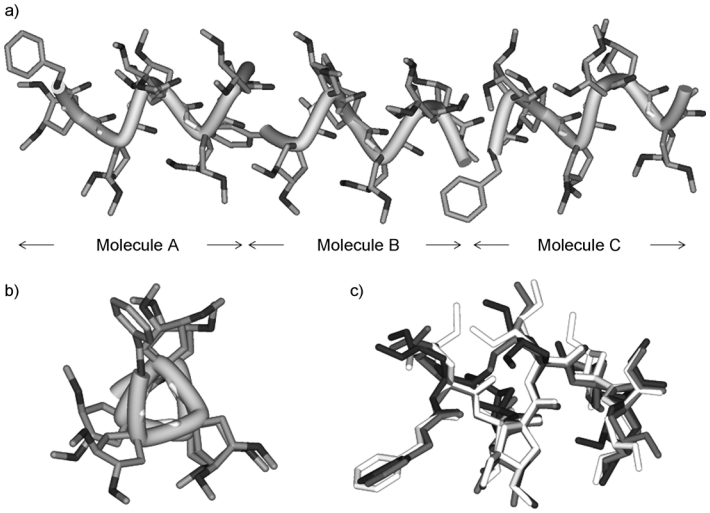


Figure 7. Secondary structure of (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a**, as determined by X-ray crystallographic analysis: a) The three crystallographically independent molecules (*A*–*C*), as viewed perpendicular to the 3_{10}-helical axis, b) the structure of molecule *A*, as viewed along the 3_{10}-helical axis, and c) the superimposed structures of molecules *A*–*C*.

cule *C*. These torsion angles are in good agreement with the ideal torsion angles (+60°, +30°) of the (*M*) 3_{10}-helical structure.[28] The three molecules have generally similar secondary structures but show small differences in the conformation of the side chain and the peptide backbone, as shown in the superimposed structures in Figure 7c. Four successive intramolecular hydrogen bonds of the $i \leftarrow i+3$ type, which correspond to the 3_{10}-helical structure, are found in each molecule. Molecule *A* shows four intramolecular hydrogen bonds between H–N(3a) and the C(0a)=O(0a) oxygen atom of the Cbz group (with an N(3a)···O(0a) distance of 3.03 Å), between H–N(4a) and C(1a)=O(1a) (N(4a)···O(1a): 2.98 Å), between H–N(5a) and C(2a)=O(2a) (N(5a)···O(2a): 3.04 Å), and between H–N(6a) and C(3a)=O(3a) (N(6a)···O(3a): 2.99 Å). Molecule *B* similarly shows four intramolecular hydrogen bonds between H–N(3b) and C(0b)=O(0b) (N(3b)···O(0b): 2.98 Å), between H–N(4b) and C(1b)=O(1b) (N(4b)···O(1b): 3.08 Å), between H–N(5b) and C(2b)=O(2b) (N(5b)···O(2b): 3.15 Å), and between H–N(6b) and C(3b)=O(3b) (N(6b)···O(3b): 3.09 Å). Also, molecule *C* shows four intramolecular hydrogen bonds between H–N(3c) and C(0c)=O(0c) (N(3c)···O(0c): 3.00 Å), between H–N(4c) and C(1c)=O(1c) (N(4c)···O(1c): 3.00 Å), between H–N(5c) and C(2c)=O(2c) (N(5c)···O(2c): 3.19 Å), and between H–N(6c) and C(3c)=O(3c) (N(6c)···O(3c): 2.98 Å). In packing mode, molecules *A*–*C* are connected by two intermolecular hydrogen bonds, respectively, to form a head-to-tail alignment of (*M*) 3_{10} helices of molecules *A*, *B*, and *C*, that is, ···*A*···*B*···*C*···*A*···*B*···*C*··· chains.[24]

In the asymmetric unit of (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a**, only one conformer of peptide molecule existed, together with three water molecules. Although it has been reported that α,α-disubstituted α-amino acid containing homopeptides prefer to form a 3_{10} helix over an α helix (3.6_{13} helix),[29]

Table 3. Intra- and intermolecular H-bond parameters for **9a**, **10a**, and **11a**.

Peptide[a]	Donor, D–H	Acceptor, A	Distance [Å], D···A	Angle [°], D–H···A	Symmetry operations
9a:					
A (*M*)	N_{3a}–H	O_{0a}	3.03	153.6	*x*,*y*,*z*
	N_{4a}–H	O_{1a}	2.98	164.2	*x*,*y*,*z*
	N_{5a}–H	O_{2a}	3.04	165.2	*x*,*y*,*z*
	N_{6a}–H	O_{3a}	2.99	170.2	*x*,*y*,*z*
B (*M*)	N_{3b}–H	O_{0b}	2.98	149.1	*x*,*y*,*z*
	N_{4b}–H	O_{1b}	3.08	159.9	*x*,*y*,*z*
	N_{5b}–H	O_{2b}	3.15	165.5	*x*,*y*,*z*
	N_{6b}–H	O_{3b}	3.09	171.4	*x*,*y*,*z*
C (*M*)	N_{3c}–H	O_{0c}	3.00	155.1	*x*,*y*,*z*
	N_{4c}–H	O_{1c}	3.00	156.9	*x*,*y*,*z*
	N_{5c}–H	O_{2c}	3.19	160.9	*x*,*y*,*z*
	N_{6c}–H	O_{3c}	2.98	167.1	*x*,*y*,*z*
	N_{1b}–H	O_{5a}	2.75	170.6	*x*,*y*,*z*
	N_{2b}–H	O_{6a}	2.93	159.4	*x*,*y*,*z*
	N_{1c}–H	O_{5b}	2.87	165.7	*x*,*y*,*z*
	N_{2c}–H	O_{6b}	3.00	146.7	*x*,*y*,*z*
	N_{1a}–H	$O_{5c'}$	2.81	173.1	$x+1,y,z-1$
	N_{2a}–H	$O_{6c'}$	3.08	164.8	$x+1,y,z-1$
10a (*M*):	N_4–H	O_0	3.10	167.4	*x*,*y*,*z*
	N_5–H	O_1	2.95	164.6	*x*,*y*,*z*
	N_6–H	O_2	3.08	164.2	*x*,*y*,*z*
	N_7–H	O_3	2.87	162.5	*x*,*y*,*z*
	N_8–H	O_4	2.98	166.8	*x*,*y*,*z*
	N_1–H	$O_{8'}$	2.91	156.3	$x,y+1,z$
	N_2–H	$O_{w(a)}$	2.92	169.6	*x*,*y*,*z*
	$O_{w(b)}$–H[b]	O_{m5}[b]	2.78	177.8	*x*,*y*,*z*
	$O_{w(a)}$–H	$O_{w(c')}$	2.83	165.8	$-x+2,y+1/2,-z$
	$O_{w(c)}$–H	$O_{6'}$	2.89	171.5	$-x+2,y+1/2,-z$
	$O_{w(a)}$–H	$O_{7'}$	2.89	175.9	$x,y+1,z$
	$O_{w(c)}$–H	$O_{w(b')}$	2.81	174.2	$x,y,z-1$
	$O_{w(b)}$–H	$O_{m2'}$	2.84	174.4	$-x+2,y-1/2,z+1$
11a (*M*):	N_4–H	O_0	3.04	165.7	*x*,*y*,*z*
	N_5–H	O_1	3.00	165.2	*x*,*y*,*z*
	N_6–H	O_2	2.96	160.0	*x*,*y*,*z*
	N_7–H	O_3	3.03	166.5	*x*,*y*,*z*
	N_8–H	O_4	3.07	161.7	*x*,*y*,*z*
	N_9–H	O_5	3.21	156.3	*x*,*y*,*z*
	N_{10}–H	O_6	3.18	162.5	*x*,*y*,*z*
	N_1–H	$O_{8'}$	2.92	170.7	$x,y,z-1$
	N_2–H	$O_{9'}$	3.00	152.3	$x,y,z-1$

[a] The number of the amino acid residues begins at the *N* terminus of the peptide chain. [b] O_w: water (a, b, c); O_m: methoxy.

the homochiral (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a** was folded into a left-handed (*M*) α helix in the crystal state. A reversal of the C-terminal torsion angles occurred, that is, the signs (negative) of the φ and ψ torsion angles (−54.2°, −43.9°) of the C-terminal residue (residue 8) were opposite to those (positive) of the preceding residues (1–7). This phenomenon is frequently observed in the 3_{10}-helical peptides of 2-amino-isobutyric acid.[30] The mean values of the φ and ψ torsion angles of amino acid residues 1–7 are +60.9° and +46.8°, values that are close to those for the ideal left-handed (*M*) α helix (+60° and +45°).[28a] Figure 8 shows the secondary structure of the (*M*) α-helical molecule perpendicular to and along the α-helical axis. Five intramolecular hydrogen bonds, in which each hydrogen bond forms a 13-membered (atom) pseudo-ring of the $i \leftarrow i+4$ type, existed in the α-helical molecule of **10a**. These are shown between H–N(4) and the C(0)=O(0) oxygen atom of the Cbz group (with an N(4)···O(0) distance of 3.10 Å), between H–N(5) and C(1)=O(1) (N(5)···O(1): 2.95 Å), between H–N(6) and C(2)=O(2) (N(6)···O(2): 3.08 Å), between H–N(7) and C(3)=O(3) (N(7)···O(3): 2.87 Å), and between H–N(8) and C(4)=O(4) (N(8)···O(4): 2.98 Å). In packing mode, the chains of the intermolecularly hydrogen-bonded (*M*) α helices are formed in a head-to-tail alignment along the *b*-axis direction (Figure 9).[24]

The (*S*,*S*)-Ac_5c^{dOMe} decapeptide **11a**, which has a molecular weight of 1878, crystallized in space group $P2_1$ to form one left-handed (*M*) α-helical conformer in the asymmetric unit (Figure 10). We could not obtain good reflection data because of the high molecular weight and conformational flexibility of the methoxy groups. Thus, least-squares refinement of the crystal structure was performed by using reflection data at the maximal value of 1.2 Å resolution, and the carbon atoms were refined as isotropic displacement factors. The signs (negative) of the φ and ψ torsion angles (−63.7°, −14.6°) of the C-terminal residue (residue 10) are opposite to those (positive) of the preceding residues (1–9), that is, a reversal of the C terminus was observed. The mean values of the φ and ψ torsion angles of amino acid residues 1–9 are +59.5° and +47.0°. There are seven intramolecular hydrogen bonds of the $i \leftarrow i+4$ type, which corresponds to an α-helical structure; these hydrogen bonds were between H–N(4) and the C(0)=O(0) oxygen atom of the Cbz group (with an N(4)···O(0) distance of 3.04 Å), between H–N(5) and C(1)=O(1) (N(5)···O(1): 3.00 Å), between H–N(6) and C(2)=O(2) (N(6)···O(2): 2.96 Å), between H–N(7) and C(3)=O(3) (N(7)···O(3): 3.03 Å), between H–N(8) and C(4)=O(4) (N(8)···O(4): 3.07 Å), between H–N(9) and C(5)=O(5) (N(9)···O(5): 3.21 Å), and between H–N(10) and C(6)=O(6) (N(10)···O(6): 3.18 Å). In packing mode, two intermolecular hydrogen bonds are formed between the H–N(1)

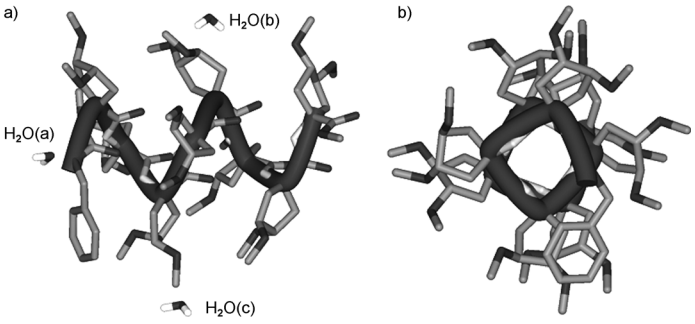


Figure 8. α-Helical secondary structure of the (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a**, as determined by X-ray crystallographic analysis: a) View perpendicular to the α-helical axis and b) view along the α-helical axis.

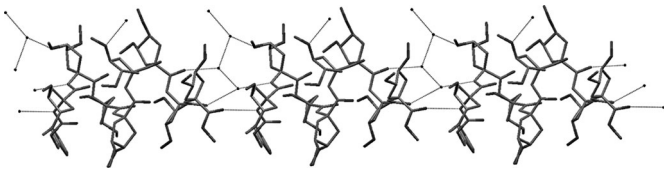


Figure 9. Packing of **10a** in the crystalline state. Intermolecular hydrogen bonds are indicated as dashed lines.

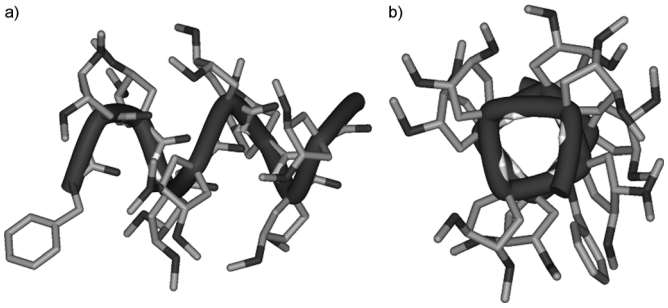


Figure 10. α-Helical secondary structure of the (*S*,*S*)-Ac_5c^{dOMe} decapeptide **11a**, as determined by X-ray crystallographic analysis: a) View perpendicular to the α-helical axis and b) view along the α-helical axis.

peptide donor and C(8′)=O(8′) of a symmetry-related molecule (x, y, $z-1$; N(1)···O(8′): 2.91 Å), and between the H–N(2) peptide donor and C(9′)=O(9′) of a symmetry-related molecule (x, y, $z-1$; N(2)···O(9′): 3.00 Å), to form the chains

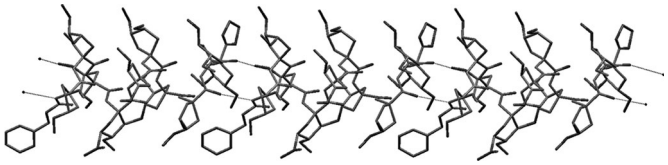


Figure 11. Packing of **11a** in the crystalline state. Intermolecular hydrogen bonds are indicated as dashed lines.

of intermolecularly hydrogen-bonded left-handed (*M*) α helices in a head-to-tail alignment (Figure 11).

Computational analysis of the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide and octapeptide: Conformational search calculations were performed with the MacroModel Ver. 8.1 package (Schrodinger, Inc.) on an SGI workstation. The Monte Carlo multiple minimum method and an AMBER* force field were used for finding the global and local minimum-energy conformations. As initial structures, extended, (*P*), and (*M*) 3_{10}-helical and α-helical structures were used, and more than 50000 conformers were optimized.

The calculation for the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a** produced an (*M*) α helix as a global minimum-energy conformation (0 kcal mol^{-1}), and an (*M*) 3_{10} helix was obtained as a local minimum-energy conformation, which exhibited an energy of +3.22 kcal mol^{-1}. The peptide main-chain structure of the calculated (*M*) 3_{10}-helical conformer was similar to those of the conformers in the crystal state, as

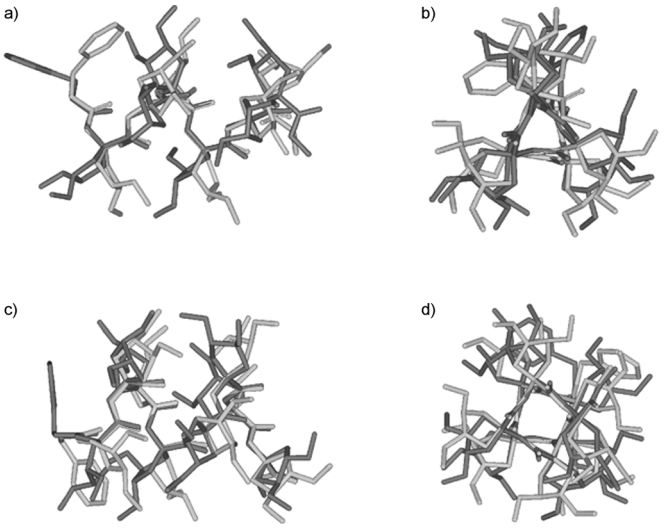


Figure 12. Superimposed structures determined by X-ray crystallographic analysis (black) and the calculated minimum-energy conformation (light gray): a, b) 3_{10} helix of the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a** and c, d) α helix of the (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a**.

shown by the superimpositions in Figure 12. A right-handed (*P*) 3_{10} helix (+2.03 kcal mol^{-1}) and a right-handed (*P*) α helix (> +15.00 kcal mol^{-1}) were obtained as local minimum-energy conformations.

The calculation for the (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a** afforded a left-handed (*M*) α helix as a global minimum-energy conformation. The main-chain structure of the calculated (*M*) α helix matches the structure determined by X-ray crystallographic analysis (Figure 12), although some differences in the side-chain cyclopentane ring and protecting group were observed. A left-handed (*M*) 3_{10} helix (+4.16 kcal mol^{-1}), a right-handed (*P*) α helix (> +15.00 kcal mol^{-1}), and a (*P*) 3_{10} helix (+4.06 kcal mol^{-1}) were produced as local minimum-energy conformations.

Discussion: The preferred secondary structure of the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a** was a left-handed (*M*) 3_{10} helix and those of the (*S*,*S*)-Ac_5c^{dOMe} octa- and decapeptides **10a** and **11a** were left-handed (*M*) α helices, both in solution and in the crystalline state. Empirically, the increasing percentage of α,α-disubstituted amino acid in the peptide sequence and the decreasing length of the peptide preferentially induces the formation of a 3_{10} helix, and α,α-disubstituted amino acid homochiral homopeptides usually prefer a 3_{10} helix over an α helix.[18d,31] Toniolo and co-workers recently reported that interconversion between α and 3_{10} helices might be allowed, even in a homochiral homo-heptapeptide amide exclusively composed of the chiral α,α-disubstituted amino acid L-αMeVal, by the selection of the solvent MeOH or the strong hydrogen-bonding donor 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP).[29] They reported a 3_{10}-helical structure recrystallized from MeOH and an α-helical structure from HFIP by X-ray crystallographic analysis. Herein, both the (*S*,*S*)-Ac_5c^{dOMe} octapeptide **10a** and the decapeptide **11a** formed α helices, even in TFE or water, without

being dissolved in the strong hydrogen-bonding solvent HFIP. Furthermore, X-ray crystallographic analyses showed α-helical structures recrystallized from $MeOH/H_2O$ or $CHCl_3$/*i*PrOH. Thus, the chiral cyclic amino acids (*S*,*S*)-Ac_5c^{dOR} have a stronger propensity to form α helices than L-αMeVal. The α-helical properties of the (*S*,*S*)-Ac_5c^{dOR} homopeptides were also supported by the computational analysis.

The cyclic amino acid (*S*,*S*)-Ac_5c^{dOR} homochiral homopeptides do not have α-carbon chiral centers, but they formed left-handed (*M*) helices. Thus, the one-handed helical screw sense was exclusively controlled by the side-chain chiral centers. One of the factors that controls the helical screw direction of the (*S*,*S*)-Ac_5c^{dOR} homochiral homopeptides to form the left handedness might be steric repulsions among the side-chain substituents. If the (*S*,*S*)-Ac_5c^{dOMe} homopeptides formed right-handed (*P*) 3_{10} helices, unfavorable contact between an alkoxy group of amino acid residue *i* and an alkoxy group of residue *i*+3 would arise because these two residues are positioned one on top of each other in the ternary helix, although a bicyclic amino acid homo-hexapeptide showed both diastereomeric right-handed (*P*) and left-handed (*M*) 3_{10} helices.[11] The one-handed helical screw sense was also found in the α-helical (*S*,*S*)-Ac_5c^{dOMe} octapeptide and decapeptide. These results may be attributed to the existence of an equilibrium between the α helix and 3_{10} helix. The right-handed (*P*) 3_{10} helices of the (*S*,*S*)-Ac_5c^{dOMe} peptides, which are in equilibrium with the (*P*) α helix, may be unfavorable, and then the left-handed (*M*) helix may be preferred. Furthermore, a one-handed helical screw sense was also found with the hydroxy substituent on the cyclopentane ring; the OH group is small enough to eliminate large steric repulsion between two substituents. Thus, besides the steric repulsion between the substituents at the two amino acid residues *i* and *i*+3, the absolute configuration of the substituent chiral centers at the cyclopentane ring of amino acid residue *i* would affect the φ and ψ torsion angles of residue *i* through bond and/or space effects and would control the homochiral homopeptides in a one-handed helical screw direction. Furthermore, the measurement of CD spectra of (*S*,*S*)-Ac_5c^{OH} **9c** in different solvents indicated that the hydrogen bonding of solvents may be crucial for the formation of the secondary structure, including helical screw control.

Conclusions

We synthesized chiral cyclic α,α-disubstituted α-amino acids (*S*,*S*)- and (*R*,*R*)-Ac_5c^{dOR} from L-(+)- or D-(−)-dimethyl tartrate and prepared the homochiral homopeptides up to the decamer. The dominant conformation of the (*S*,*S*)-Ac_5c^{dOMe} hexapeptide **9a** was an (*M*) 3_{10}-helical structure and those of octapeptide (*S*,*S*)-**10a** and decapeptide (*S*,*S*)-**11a** were (*M*) α-helical structures, both in solution and in the crystal state. We demonstrated that chiral centers at the side chain γ-carbon atoms of the cyclic α-amino acid exclusively controlled the helical screw sense of the peptides, without an α-carbon chiral center. Although it is already known that side-chain chiral centers affect the helical screw direction of polymers such as poly(alkylisocyanates), and poly(alkylsilanes),[32] no detailed research on the relationship between the helical screw handedness of polymers and asymmetric centers in the side chains of the monomers with high-resolution analysis has been reported so far. Furthermore, these results imply that the chiral center at the side-chain β-carbon atom of isoleucine and threonine would affect the secondary structure of their peptides, although these residues also exhibit a strong screw sense bias due to their chiral α-carbon atom and they are poorly helicogenic residues.[6,7] The design of new chiral cyclic amino acids and their foldamers as well as the application of such molecules as asymmetric catalysts or biologically active molecules are currently underway in our group.[14,33]

Experimental Section

The cyclic amino acids (*S*,*S*)-Ac_5c^{dOMe} ((*S*,*S*)-**4a**), (*R*,*R*)-Ac_5c^{dOMe} ((*R*,*R*)-**4a**), and (*S*,*S*)-Ac_5c^{dOMOM} (**4b**) were synthesized from dimethyl L-(+)- or D-(−)-tartrate. The syntheses of the homochiral homopeptides were carried out according to solution-phase segment condensation methods, by using EDC and HOBt, or HBTU, as coupling reagents. All compounds were purified by column chromatography on silica gel. Full experimental details are available in the Supporting Information.

Acknowledgements

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