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Secondary Structures

Cyclic α,α-Disubstituted α-Amino Acids with Menthone in Their Side-Chains Linked through an Acetal Moiety and Helical Structures of Their Peptides

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Abstract: The chiral cyclic α,α-disubstituted α-amino acids, Hms[(–)-Men] and Hms[(+)-Men] with (–)- and (+)-menthones in their side-chains, respectively, were designed and synthesized. Hms[(–)-Men] homopeptides and Hms[(–)/(+)-Men]-containing L-Leu-based peptides were prepared in order to investigate the conformational properties of Hms[(–)/(+)-Men]. The preferred conformations of the Hms[(–)/(+)-Men]-containing peptides were determined by FTIR, ^{1}H NMR, and CD spectroscopy in solution, and by X-ray crystallographic analysis in the crystal state. Conformational analysis in solution revealed similar right-handed (*P*) 3_{10}-helical structures for the Hms[(–)/(+)-Men]-containing octapeptides. In the solid state of the hexapeptides, the peptide main-chain structures were mostly similar; however, some differences were observed in the side-chains. The Hms[(–)/(+)-Men] may function as helical inducers, but their side-chain chiralities had only a negligible effect on their helical-screw control of L-Leu-based peptides.

Introduction

Peptides composed of cyclic α,α-disubstituted α-amino acids (dAAs) are known to adopt helical structures;[1] they may be used as helical foldamers in functional peptides.[2] The helical-screw sense of homopeptides is in some cases controllable by the chiral centers in their side-chains. The number of chiral centers in the peptides and also their environments are important for controlling the helical-screw sense.[3] The presence of heteroatoms, such as oxygen, in the side-chains of dAAs also has a significant influence on the secondary structure; heteroatoms are capable of cleaving intramolecular hydrogen bonds between the amide N–H and carbonyl O=C in the peptide backbone, and forming new hydrogen bonds with the amide N–H.[4] Leplawy, Toniolo, and coworkers described *O*,*O*-isopropylidene-α-(hydroxymethyl)serine [Hms(Ipr)] (Figure 1), the peptides of which formed destabilized 3_{10}-helical structures as a result of newly observed intramolecular hydrogen bonds between the ether oxygen and the amide N–H.[4b] We recently synthesized a cyclic dAA with two chiral acetals [(*R*,*R*)-Ac_6c^{35dBu}], and analyzed the conformation of its peptides (Figure 1).[4d] The (*R*,*R*)-Ac_6c^{35dBu} tripeptide had intramolecular hydrogen bonds between the side-chain acetal oxygen and the amide N–H in the same amino-acid residues, and was not capable of controlling the helical-screw sense regardless of its twelve chiral centers. Therefore, extensive efforts have been devoted to designing and synthesizing new cyclic dAAs, and carrying out conformational analysis of their dAA-containing peptides.[5]

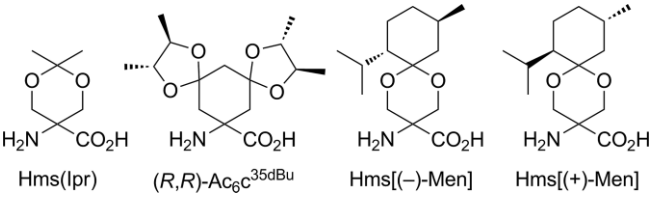

Figure 1. Structures of Hms(Ipr), (*R*,*R*)-Ac_6c^{35dBu}, Hms[(–)-Men], and Hms[(+)-Men].

In the work described in this paper, a cyclic dAA {Hms[(–)/(+)-Men]} with (–)- or (+)-menthone in the side-chain, attached through an acetal moiety, was designed and synthesized (Figure 1). We synthesized Hms[(–)/(+)-Men] homopeptides and heteropeptides in L-leucine (Leu) sequences, and were interested in the conformational properties of Hms[(–)/(+)-Men] from two points of view. One was whether Hms[(–)/(+)-Men]-containing peptides would adopt a helical structure in spite of the bulky menthone moiety and acetal oxygens in the side-chain. The other was whether the helical screw-sense of the peptides would be affected by the chirality of the (–)- or (+)-menthone moiety. Conformational analysis of Hms[(–)/(+)-Men] heteropeptides was carried out in solution using FTIR, ^{1}H NMR, and CD spectroscopic measurements, and in the crystal state by X-ray crystallographic analysis.

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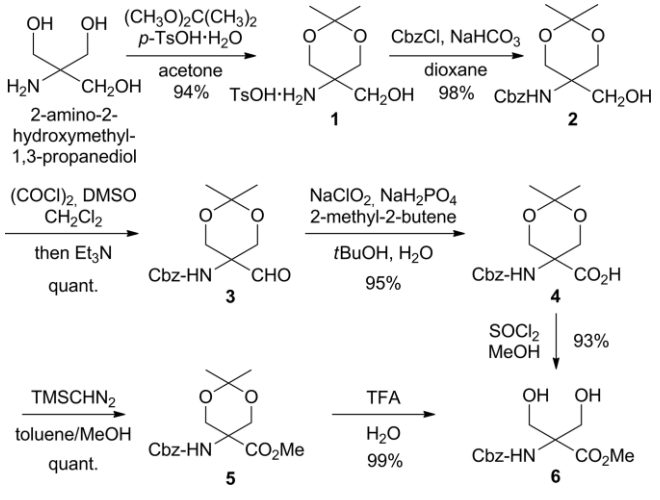
Results and Discussion

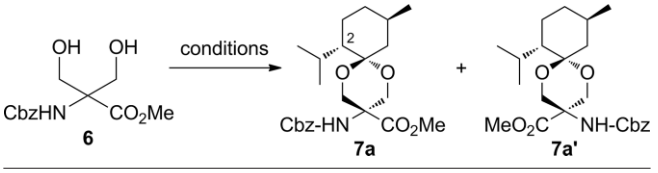
Synthesis of Chiral Hms[(–)/(+)-Men] with Menthone in the Side-Chain

A chiral dAA Hms[(–)-Men] was synthesized starting from 2-amino-2-hydroxymethyl-1,3-propanediol (Scheme 1). Treatment of 2-amino-2-hydroxy-1,3-propanediol with 2,2-dimethoxypropane and *p*TsOH·H_2O gave *O*,*O*-isopropylidene derivative **1** as a *p*TsOH salt in 94 % yield. Cbz (benzyloxycarbonyl) protection of the amino group was carried out using benzyl chloroformate to give **2**. Swern oxidation of alcohol **2** followed by Pinnick oxidation of the resulting aldehyde **3** gave Cbz-Hms(Ipr)-OH **4** in an excellent yield. Treatment of **4** with (trimethylsilyl)diazomethane quantitatively gave ester Cbz-Hms(Ipr)-OMe **5**, which was converted into diol Cbz-Hms-OMe **6** by acidic hydrolysis. Diol Cbz-Hms-OMe **6** was also obtained from Cbz-Hms(Ipr)-OH **4** by methyl esterification and *O*,*O*-isopropylidene deprotection by treatment with acidic MeOH. Acetalization using (–)-menthone was initially attempted by heating in refluxing toluene in the presence of *p*TsOH (Table 1, entry 1). Unfortunately, these acetalization conditions resulted in a low yield (20 %) and a moderate diastereomeric ratio (**7a**/**7a**′ = 83:17). The ratios of diastereomeric mixtures were determined based on the peak intensity ratio of the methyl ester protons in the ^{1}H NMR spectra (δ = 3.75 ppm for major product **7a**, and δ = 3.80 ppm for minor product **7a**′). The diastereomers were separated by column chromatography on silica gel (*n*-hexane/acetone). To improve the yield and diastereometic ratio, Noyori's conditions were examined.[6] Treatment of Cbz-Hms-OMe **6** with 1,1,1,3,3,3-hexamemethyldisiazane (HMDS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave a bis(trimethylsilyl) ether, which was used in a subsequent reaction without purification. The crude bis(trimethylsilyl) ether was treated with (–)-menthone and TMSOTf at –40 °C, giving Cbz-Hms[(–)-Men]-OMe **7** in a moderate yield (41 %) with a good diastereomeric ratio (**7a**/**7a'** = 93:7; Table 1, entry 2). Furthermore, at a lower temperature (–78 °C), the acetalization gave a good yield (84 %) and an excellent diastereomeric ratio (**7a**/**7a**′ = 98:2; Table 1, entry 3). The stereochemistry of the major product (i.e., **7a**) was determined by NOESY NMR spectroscopy (Figure S1). The NOESY NMR spectrum of **7a** showed a correlation between the amide proton and the *i*Pr methine proton, suggesting that the Cbz-amino group at the α position and the C-2 carbon in the *i*Pr group derived from (–)-menthone had a *syn* relationship. The stereochemistry of the major product (i.e., **7a**) was unambiguously confirmed by X-ray crystallographic analysis of its peptide derivatives (vide infra). Acetalization between diol Cbz-Hms-OMe **6** and (+)-menthone gave enantiomer Cbz-Hms[(+)-Men]-OMe **7b**.



Scheme 1. Synthesis of Cbz-Hms-OMe **6**; TFA = trifluoroacetic acid.

Table 1. Acetalization of the side-chain of Cbz-Hms-OMe **6** using (–)-menthone.

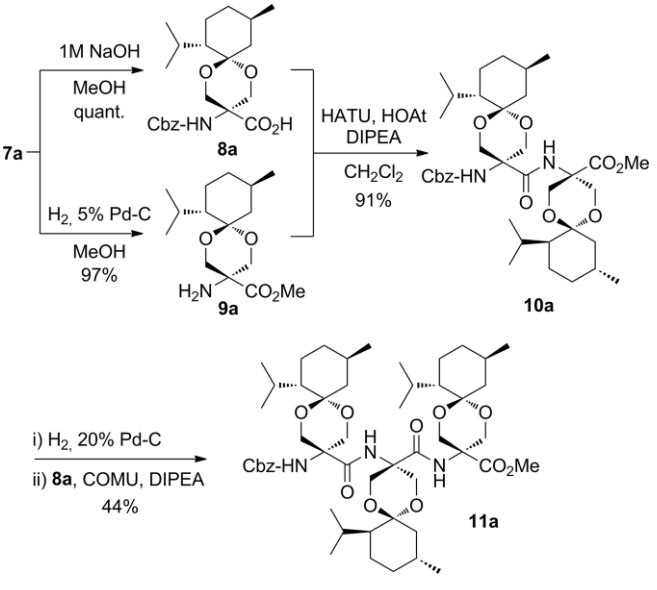


Entry	Conditions	Yield [%]	*dr* (**7a**/**7a**′)[a]
1	(–)-menthone, *p*TsOH, toluene, reflux	20	83:17
2	i. HMDS, TMSOTf, THF, 0 °C ii. (–)-menthone, TMSOTf, CH_2Cl_2, –40 °C	41	93:7
3	i. HMDS, TMSOTf, THF, 0 °C ii. (–)-menthone, TMSOTf, CH_2Cl_2, –78 °C	84	98:2

[a] *dr* was determined by ^{1}H NMR spectroscopy.

Preparation of Peptides

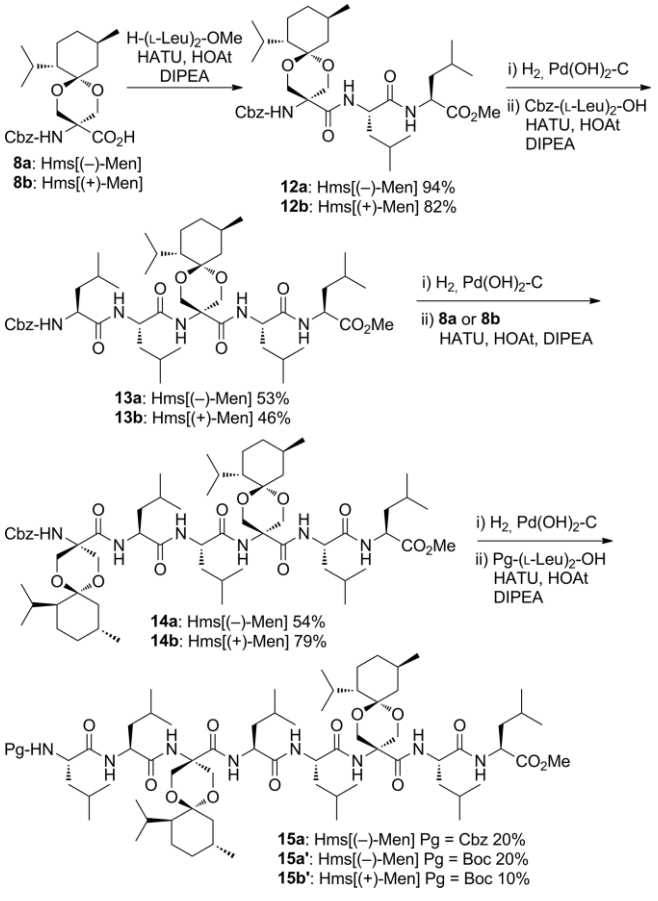
We initially attempted to synthesize Hms[(–)-Men] homopeptides (Scheme 2). The alkaline hydrolysis and hydrogenolysis of Cbz-Hms[(–)-Men]-OMe **7a** gave C-terminal-free carboxylic acid **8a** and N-terminal-free amine **9a**, respectively. Dipeptide **10a** was easily prepared in 91 % yield by coupling **8a** and **9a** by



Scheme 2. Synthesis of Hms[(–)-Men] homopeptides; DIPEA = diisopropylethylamine.

treatment with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt). Hydrogenolysis of **10a** followed by coupling with **8a** using HATU or (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylaminomorpholinocarbenium hexafluorophosphate (COMU) as a coupling reagent gave tripeptide **11a** in 27 or 44 % yield. After deprotection of the Cbz group in **11a**, coupling between the amine derived from **11a** and carboxylic acid **8a** was attempted using HATU or COMU. However, no tetrapeptide was isolated, which may have been due to the steric hindrance of the (–)-menthone moiety and the unfavorable conformation masking the N-terminal amine.

We subsequently synthesized heteropeptides having Hms-[(–)-Men] or Hms[(+)-Men] in L-Leu sequences (Scheme 3). The synthesis of octapeptides **15a**, **15a′**, and **15b′** was achieved using solution-phase methods with HATU and HOAt as the coupling reagents. Elongation of the peptide chain proceeded well by fragment coupling using an N-terminal-protected L-Leu dipeptide, or by stepwise addition of C-terminal-free carboxylic acid **8a** or **8b**.



Scheme 3. Synthesis of heteropeptides having Hms[(–)-Men] or Hms[(+)-Men] in L-Leu sequences. Only the structures of Hms[(–)-Men] and its peptides are shown.

Conformational Analysis in Solution

Figure 2 shows the FTIR absorption spectra of the Hms[(–)-Men]-containing peptides **13a**, **14a**, **15a**, and **15a′** (Figure 2, a), and Hms[(+)-Men]-containing peptides **13b**, **14b**, and **15b′** (Figure 2, b) in the 3250–3500 cm^{-1} region ($CDCl_3$). The weak bands in the 3420–3440 cm^{-1} region were assigned to free (solvated) peptide NH groups, the weak bands in the 3370–3400 cm^{-1} region were assigned to peptide NH groups with intramolecular hydrogen bonds to the acetal oxygens, and the strong bands in the 3300–3370 cm^{-1} region were assigned to peptide NH groups with intramolecular hydrogen bonds to the peptide O=C groups.[4b] The low-frequency band observed at 3340 cm^{-1} in pentapeptides **13a** and **13b** shifted to a lower wavenumber of 3320 cm^{-1} in octapeptides **15a**, **15a′**, and **15b′**, and its intensity increased with elongation of the peptide length. These shifts in wavelength and increases in intensity are similar to those observed for Ac_nc homopeptides.[1c] Hexapeptides **14a** and **14b** showed bands assigned to peptide NH groups intramolecularly hydrogen bonded to the acetal oxygens, and weak bands assigned to free peptide NH groups. The α-helical and 3_{10}-helical peptides have three and two intramolecular-hydrogen-bond-free peptide NH groups at the N-terminus, respectively. Accordingly, hexapeptides **14a** and **14b** did not form a complete and typical helical structure. The presence of Hms[(–)/(+)-Men] at the N-terminus of the hexapeptide affected the formation of hydrogen bonds between the N-terminal peptide N–H and the acetal oxygens.

The NOESY NMR spectra of hexapeptides **14a** and **14b** and octapepetides **15a**, **15a′**, and **15b′** were measured in $CDCl_3$ solution (Figure 3 and Figure S2) in order to investigate the effects of the chiralities of methone (**14a** and **14b**; **15a′** and **15b′**) and the N-terminal-protecting groups (**15a** and **15a′**) on the preferred conformation of peptides. Sequential NH ($i \rightarrow i+1$) dipolar interactions [d_{NN} ($i \rightarrow i+1$)] are generally used to diagnose helical structures, and the NOE constraints $d_{\alpha N}$ ($i \rightarrow i+2$) and $d_{\alpha N}$ ($i \rightarrow i+4$) are characteristics of 3_{10}-helical and α-helical structures, respectively.[7] The NOESY NMR spectrum of Hms[(–)-Men]-containing hexapeptide **14a** showed a complete series of sequential NH ($i \rightarrow i+1$) dipolar interactions from the N-terminal NH to C-terminal NH, together with the NOE constraint $d_{\alpha N}$ (2→4), suggesting the existence of a partial 3_{10}-helical structure (Figure S2a). In the NOESY spectrum of Hms[(+)-Men]-containing hexapeptide **14b**, four NH ($i \rightarrow i+1$) dipolar interactions [d_{NN} ($i \rightarrow i+1$); i = 1, 3, 4, and 5] were observed (Figure S2b); however, none of the NOE constraints $d_{\alpha N}$ useful for determining the types of helical structures were observed. The NOESY NMR spectra of Hms[(–)-Men]-containing octapeptides **15a** and **15a′** showed a series of sequential NH ($i \rightarrow i+1$) dipolar interactions from the N-terminal N(1)–H to N(7)–H, but did not show the dipolar interaction d_{NN} (7→8) (Figure S2c and Figure 3). Neither NOE constraints $d_{\alpha N}$ ($i \rightarrow i+2$) nor $d_{\alpha N}$ ($i \rightarrow i+4$) were observed. The preferred conformation of Hms[(–)-Men]-containing octapeptides **15a** and **15a′** in $CDCl_3$ may be similar, regardless of the N-terminal protecting groups. The NOESY spectrum of Hms[(+)-Men]-containing octapeptide **15b′** showed partial dipolar interactions [d_{NN} ($i \rightarrow i+1$); i = 1, 3–7], but not the dipolar interaction d_{NN} (2→3) (Figure S2d). However, neither NOE constraints $d_{\alpha N}$ ($i \rightarrow i+2$) nor $d_{\alpha N}$ ($i \rightarrow i+4$) were analyzed due to overlap of the proton signals. Most sequential NH ($i \rightarrow i+1$) dipolar interactions [d_{NN} ($i \rightarrow i+1$)] were observed in all of the peptides,

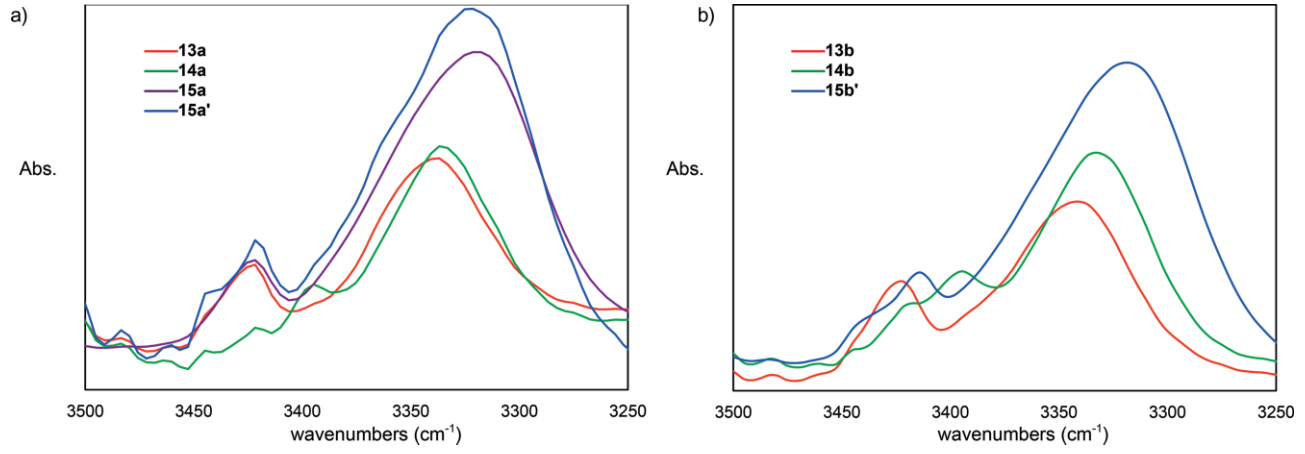
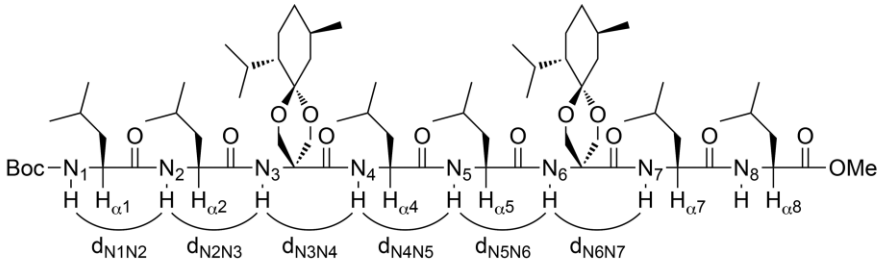


Figure 2. FTIR absorption spectra of a) Hms[(–)-Men]-containing peptides **13a**, **14a**, **15a**, and **15a′**, and b) Hms[(+)-Men]-containing peptides **13b**, **14b**, and **15b′**. The peptide concentration was 5 mM in $CDCl_3$.



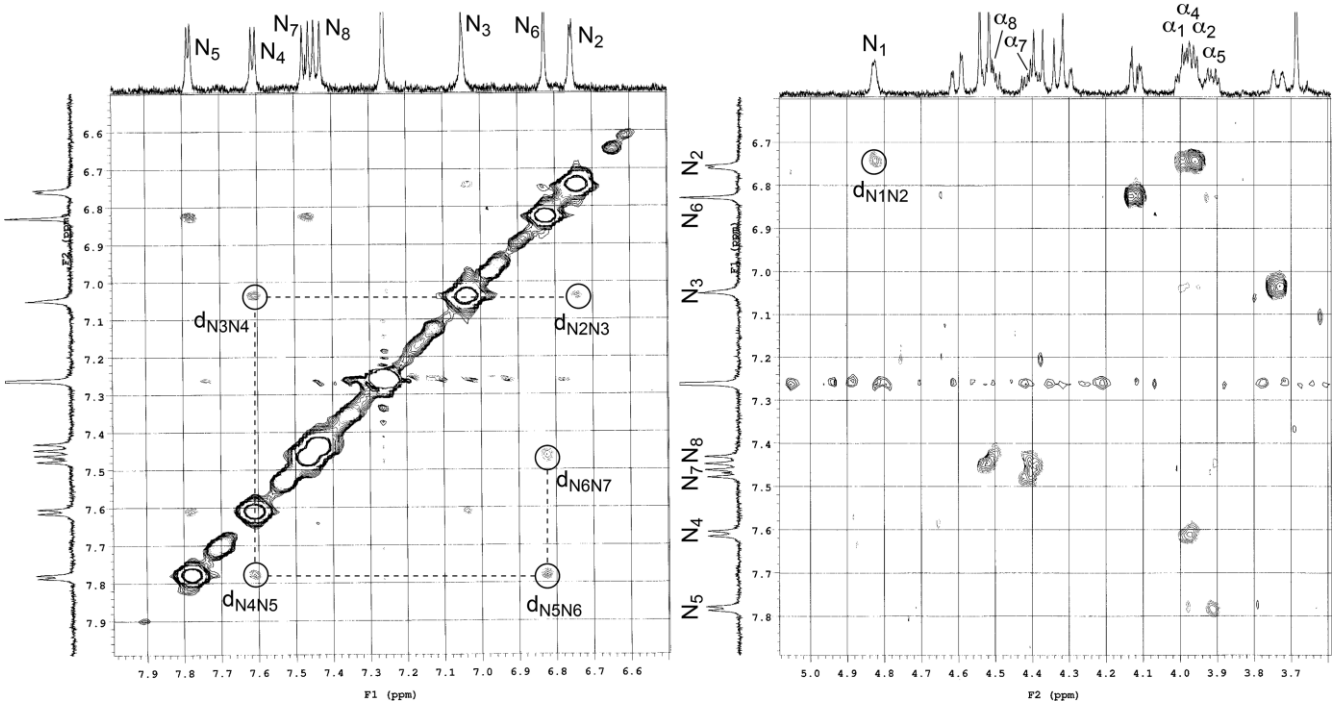


Figure 3. NOESY NMR spectra of Hms[(–)-Men]-containing octapepetide **15a′**.

which implies the existence of helical structures; however, it is difficult to deduce the preferred conformations based on these results alone.

The CD spectra of Hms[(–)-Men]-containing peptides **13a**, **14a**, **15a**, and **15a′** and Hms[(+)-Men]-containing peptides **13b**, **14b**, and **15b′** were measured in 2,2,2-trifluoroethanol (TFE) solution (Figure 4). Negative maxima at 205–209 nm ($\pi\rightarrow\pi^*$) and 222–225 nm ($n\rightarrow\pi^*$) are diagnostic of right-handed (*P*) helical structures.[8] The ratio of R ($\theta_{n\rightarrow\pi^*}/\theta_{\pi\rightarrow\pi^*}$) has been used as a parameter to distinguish α-helical from 3_{10}-helical structures

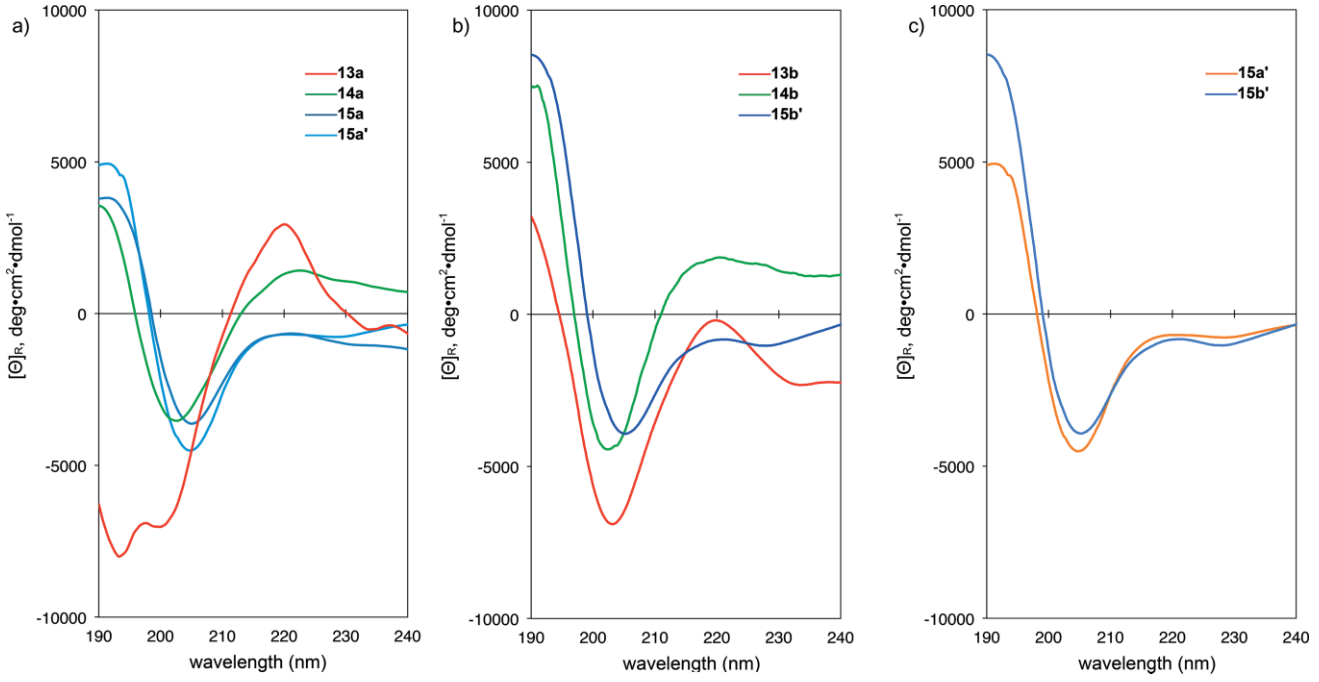


Figure 4. CD spectra of a) Hms[(–)-Men]-containing peptides **13a**, **14a**, **15a**, and **15a′**, b) Hms[(+)-Men]-containing peptides **13b**, **14b**, and **15b′**, and c) octapeptides **15a′** and **15b′**. The peptide concentration was 0.1 mM in TFE.

(i.e., $R \approx 1$: α-helix; $R \leq 0.4$: 3_{10}-helix). Hms[(–)-Men]-containing pentapeptide **13a** showed a negative maximum at 193–200 nm, and positive maximum at 220 nm, which is similar to a random structure. The spectra of pentapeptide **13b** and hexapeptides **14a** and **14b** did not show the maxima characteristic of a helical structure. These results imply that shorter peptides such as pentapeptides and hexapeptides do not have the ability to form complete helical structures and/or control the helical screw-sense in TFE solution. Although the existence of partial 3_{10}-helical structures was suggested from the NOESY NMR spectrum of hexapeptide **14a**, the CD spectrum of **14a** did not indicate a one-handed helical-screw sense. However, the different solvents used for the measurements ($CDCl_3$ for NMR spectroscopy, and TFE for CD spectroscopy) may affect the preferred conformation in solution. Furthermore, the results obtained from the different methods were not completely consistent with each other for other peptides; this may be due not only to the different solvents used, but also to direct information about peptide secondary structures not being obtained (FTIR: free or hydrogen-bonded N–H; NOESY spectrum: distance between hydrogen atoms). Octapeptides **15a**, **15a′**, and **15b′** showed negative maxima at approximately 208 nm and 222 nm, and a positive maximum at 192 nm; this shows the presence of right-handed (*P*) helical structures. The ratio of *R* ($\theta_{n\rightarrow\pi^*}/\theta_{\pi\rightarrow\pi^*}$) suggested that the dominant secondary structure of the octapeptides **15a** ($R = 0.222$), **15a′** ($R = 0.173$), and **15b′** ($R = 0.270$) was a 3_{10}-helix. However, the intensities of negative maxima at 205–209 nm ($\pi\rightarrow\pi^*$) and 222–225 nm ($n\rightarrow\pi^*$) were too weak for ideal helices. These results imply that the helical secondary structures and/or helical screw-sense of the octapeptides were not completely controlled. Figure 4 (a) indicates that N-terminal protecting groups do not markedly affect the ratio *R* (Cbz **15a**: 0.222; Boc **15a′**: 0.173) (Boc = *tert*-butoxycarbonyl). Comparisons between (–)- and (+)-menthone in the side-chains of dAAs in octapeptides **15a′** and **15b′** revealed that the values obtained at 222 nm were similar (Figure 4, c). The CD spectrum of homotripeptide **11** was also measured, but it did not show the characteristic maxima of a one-handed helical-screw structure (data not shown).

Conformational Analysis in the Crystal State

Hms[(–)-Men]-containing pentapeptide **13a**, hexapeptide **14a**, and octapeptide **15a′**, and Hms[(+)-Men]-containing hexapeptide **14b** formed good crystals for X-ray crystallographic analysis through slow evaporation of the solvent (**13a**: EtOH/MeOH; **14a**: DMF; **14b**: DMF; **15a′**: EtOAc/*n*-hexane) at room temperature.[9] The crystal and diffraction parameters of **13a**, **14a**, **14b**, and **15a′** are summarized in Table S1. The molecular structures of **13a**, **14a**, **14b**, and **15a′** are given in Figures 5, 6, 7, 8, and

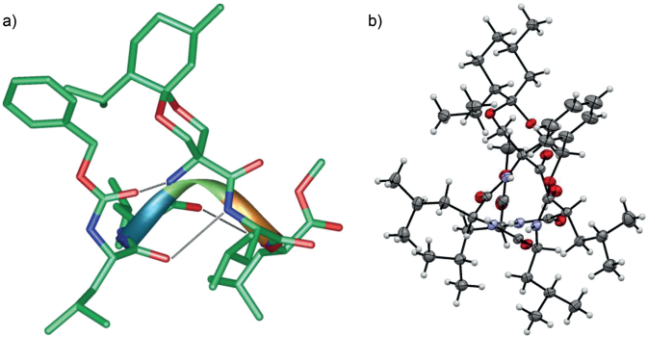


Figure 5. X-ray crystallographic structure of pentapeptide **13a** as viewed a) perpendicular to and b) along the helical axis.

9. The relevant backbone and side-chain torsion angles as well as intra- and intermolecular hydrogen-bond parameters are listed in Tables 2, 3, and S2.

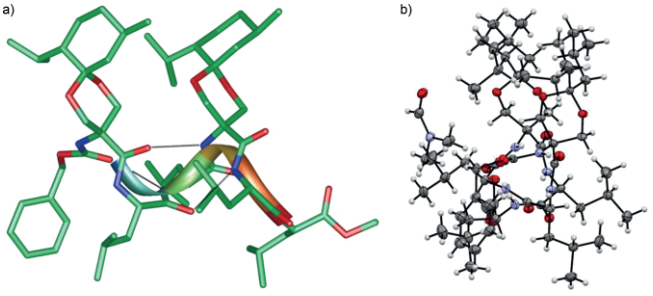


Figure 6. X-ray crystallographic structure of hexapeptide **14a** as viewed a) perpendicular to and b) along the helical axis. In a), the DMF molecule has been omitted.

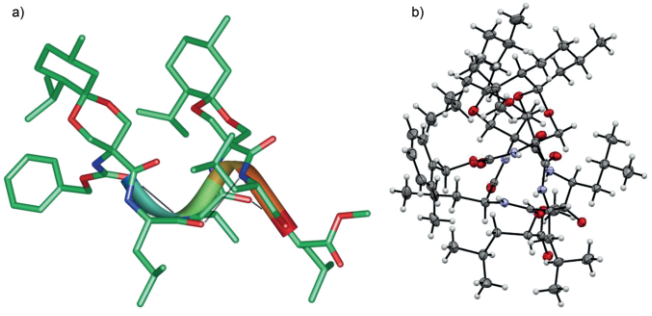


Figure 7. X-ray crystallographic structure of hexapeptide **14b** as viewed a) perpendicular to and b) along the helical axis.

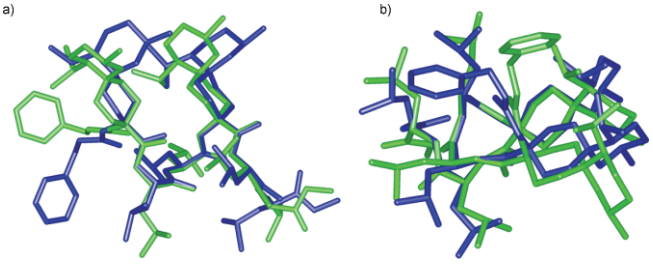


Figure 8. Overlaid structures of hexapepetides **14a** (blue) and **14b** (green), as viewed a) perpendicular to and b) along the helical axis.

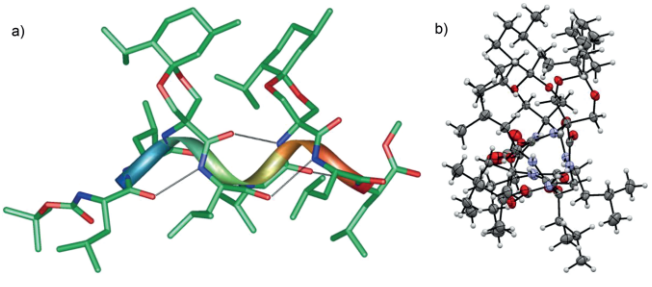


Figure 9. X-ray crystallographic structure of octapeptide **15a′** as viewed a) perpendicular to and b) along the helical axis. The EtOAc molecule has been omitted.

Pentapeptide **13a** was folded into a right-handed (*P*) 3_{10}-helical structure (Figure 5). The molecule showed negative signs for the ϕ and ψ torsion angles from the N-terminal residue to the C-terminal residue. The mean values of the ϕ and ψ torsion angles of the amino acid residues (1–5) were –61.8° and –32.6°, which are close to the ideal values for a right-handed (*P*) 3_{10}-helix (–60° and –30°). Three intramolecular hydrogen bonds were observed in the crystal state, with each hydrogen bond forming a 10-membered (atom) pseudoring of the *i*←*i*+3 type corresponding to a 3_{10}-helical conformation (Table 3). In the

Table 2. Average values of torsion angles ϕ and ψ [°] for pentapeptide **13a**, hexapeptides **14a** and **14b**, and octapeptide **15a′**, as determined by X-ray crystallographic analysis.

Peptide	ϕ [°]	ψ [°]	Secondary structure
pentapeptide **13a**	–61.8	–32.6	(*P*) 3_{10}-helix
hexapeptide **14a**[a]	–60.2	–25.6	distorted (*P*) 3_{10}-helix
hexapeptide **14b**[a]	–62.4	–30.3	distorted (*P*) 3_{10}-helix
octapeptide **15a**[b]	–63.5	–25.3	distorted (*P*) 3_{10}-helix

[a] Torsion angles of Leu(5) and Leu(6) were omitted. [b] Torsion angles of Leu(1) were omitted.

Table 3. Intra- and intermolecular hydrogen-bond parameters for pentapeptide **13a**, hexapeptides **14a** and **14b**, and octapeptide **15a′**.

Peptide[a]	Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operation
Pentapeptide **13a**					
	N(3)–H	O(0)	3.20	135	*x*, *y*, *z*
	N(4)–H	O(1)	3.07	156	*x*, *y*, *z*
	N(5)–H	O(2)	3.04	142	*x*, *y*, *z*
	N(1)–H	O(4′)	2.92	162	–1 + *x*, *y*, *z*
	N(2)–H	O(5′)	2.93	146	–1 + *x*, *y*, *z*
Hexapeptide **14a**					
	N(3)–H	O(0)	2.98	160	*x*, *y*, *z*
	N(4)–H	O(1)	3.05	140	*x*, *y*, *z*
	N(5)–H	O(2)	2.96	154	*x*, *y*, *z*
	N(6)–H	O(3)	3.08	161	*x*, *y*, *z*
	N(2)–H	O(DMF)	2.80	159	*x*, *y*, *z*
	N(1)–H	O(5′)	2.87	169	3/2 – *x*, 1 – *y*, –1/2 + *z*
Hexapeptide **14b**					
	N(3)–H	O(0)	3.02	141	*x*, *y*, *z*
	N(4)–H	O(1)	3.44[b]	128	*x*, *y*, *z*
	N(5)–H	O(2)	2.95	152	*x*, *y*, *z*
	N(6)–H	O(3)	3.04	162	*x*, *y*, *z*
	N(1)–H	O(6′)	2.95	142	– ×, –1/2 + *y*, 1/2 – *z*
	N(2)–H	O(5′)	2.98	137	–*x*, –1/2 + *y*, 1/2 – *z*
Octapeptide **15a′**					
	N(4)–H	O(1)	3.00	158	*x*, *y*, *z*
	N(5)–H	O(2)	3.01	156	*x*, *y*, *z*
	N(6)–H	O(3)	3.00	146	*x*, *y*, *z*
	N(7)–H	O(4)	3.02	165	*x*, *y*, *z*
	N(8)–H	O(5)	2.92	156	*x*, *y*, *z*
	N(1)–H	O(6′)	2.74	135	1/2 – *x*, 2 – *y*, –1/2 + *z*
	N(3)–H	O(7′)	2.98	176	1/2 – *x*, 2 – *y*, –1/2 + *z*

[a] The number of amino acid residues begins at the N-terminus of the peptide chain. [b] The distance of N(4)–H···O(1) (3.44 Å) in **14b** is too long for an intramolecular hydrogen bond.

packing mode, the molecule was connected by intermolecular hydrogen bonds between H–N(1) and C(4′)=O(4′), and between H–N(2) and C(5′)=O(5′) of a symmetry-related molecule (–1 + *x*, *y*, *z*), thereby forming a head-to-tail alignment of 3_{10}-helical chains. These results are different from those seen for the CD spectrum (random structure). This may be due to the fact that the single crystal for X-ray analysis was obtained by recrystallization from EtOH/MeOH, and that the CD spectrum was measured in TFE, or alternatively a minor right-handed (*P*) 3_{10}-helical structure existing in solution could be preferentially induced in the crystal state as a result of nucleation events.

The crystal structure of hexapeptide **14a** containing two (–)-menthone units was solved; this molecule crystallized together with a DMF molecule in the space group $P2_12_12_1$. The structure showed a distorted right-handed (*P*) 3_{10}-helix (Figure 6). The mean values of the ϕ and ψ torsion angles of the amino acid residues (1–4) were –60.2° and –25.6°, respectively, which are close to those of an ideal right-handed 3_{10}-helical structure. However, the torsion angles of Leu(5) (ϕ = –92.8°; ψ = –7.4°) and Leu(6) (ϕ = –69.1°; ψ = +142.8°) were different from the ideal helical values. Four consecutive intramolecular hydrogen bonds of the *i*←*i*+3 type were present (Table 3). In the packing mode, two intermolecular hydrogen bonds were observed between H–N(2) and O_{DMF} of DMF, and between H–N(1) and C(5)=O(5′) of a symmetry-related molecule (3/2 – *x*, 1 – *y*, –1/2 + *z*). The helical molecules were connected by intermolecular hydrogen bonds forming a head-to-tail alignment of chains. Conformational analysis of hexapeptide **14a** by NOESY NMR spectroscopy revealed the existence of a partial 3_{10}-helical structure, which is consistent with the results of the X-ray crystallographic analysis.

In the crystal structure of hexapeptide **14b**, two enantiomeric (+)-menthones exclusively crystallized into a distorted right-handed (*P*) 3_{10}-helical structure (Figure 7); however, compound **14b** did not show the characteristic CD spectrum of a helical structure (Figure 4, b). The mean values of the torsion angles ϕ and ψ of amino acid residues 1–4 were –62.4° and –30.3°, respectively, which are close to the ideal values for a right-handed (*P*) 3_{10}-helix; however, the torsion angles for Leu(5) (ϕ = –102.5°; ψ = +14.3°) and Leu(6) (ϕ = –50.2°; ψ = –42.9°) residues were different from the helical values. Three intramolecular hydrogen bonds of the *i*←*i*+3 type were observed (Table 3). The distance between H–N(4) and C(1)=O(1) (3.44 Å) was too long for an intramolecular hydrogen bond. In the packing mode, two intermolecular hydrogen bonds between H–N(1) and C(6′)=O(6′), and between H–N(2) and C(5′)=O(5′) of a symmetry-related molecule (–*x*, –1/2 + *y*, 1/2 – *z*) were observed. The 3_{10}-helical structures were packed to form a head-to-tail alignment of chains.

The peptide main-chain structure of hexapeptide **14a** was similar to that of hexapeptide **14b**, as shown by the superimpositions in Figure 8; however, some differences in the side-chains and protecting groups were observed. We identified marked differences, particularly in the acetal moieties derived from (–)- and (+)-menthones. Each isopropyl substituent occupied an equatorial position on a cyclohexane ring (in a chair conformation); this may have resulted in the the acetal moieties having slightly different structures. Nevertheless, the lack of a marked difference in the peptide main-chain structures between hexapeptides **14a** and **14b** may be due to the chiral centers being far from the α-carbon atoms[4c,4d] and/or the low flexibility of the side-chain structures.[3c,3e] Hydrogen bonds between the peptide N–H and acetal oxygens were not detected in the crystal state.

The X-ray crystallographic results for hexapeptides **14a** and **14b** were different from those from the CD spectra; this may be due to the different solvents used for recrystallization and for the CD measurements. Alternatively, several random structures were present in solution, and the helical structures were formed preferentially in the crystal state as a result of the nucleation events.

The structure of octapeptide **15a′**, with two (–)-menthone units, was solved in the space group $P2_12_12_1$ to give a distorted right-handed (*P*) 3_{10}-helical structure, along with an EtOAc molecule in an asymmetric unit (Figure 9). The Boc protecting group, the side-chain of the Leu(4) residue, and the methyl ester group were disordered. The mean values of the torsion angles ϕ and ψ of amino acid residues 2–8 were –63.5° and –25.3°, respectively, and are close to the ideal values for a right-handed (*P*) 3_{10}-helical structure. However, the torsion angles ϕ and ψ for the Leu(1) residue were +74.5° and +13.8°, respectively, which are different from those expected for a right-handed (*P*) helix, and closer to the values expected for a left-handed (*M*) helix. Five successive intramolecular hydrogen bonds of the *i*←*i*+3 type, corresponding to a 3_{10}-helical conformation, were observed (Table 3). However, an intramolecular hydrogen bond was not observed between H–N(3) and C(0)=O(0). In the packing mode, two intermolecular hydrogen bonds were observed between H–N(1) and C(6′)=O(6′) and between H–N(3) and C(7′)=O(7′) of a symmetry-related molecule (1/2 – *x*, 2 – *y*, –1/2 + *z*). The 3_{10}-helical structures were packed to form a head-to-tail alignment in a chain. The distorted right-handed (*P*) 3_{10}-helical structure in the crystal state is consistent with the results of the CD spectrum, which suggest a right-handed (*P*) 3_{10}-helical conformation in solution.

Conclusions

We synthesized the chiral cyclic dAAs Hms[(–)-Men] and Hms[(+)-Men] with high diastereomeric excesses, and prepared Hms[(–)-Men]- and Hms[(+)-Men]-containing L-Leu-based peptides. The dominant conformations of the Hms[(–)-Men]- and Hms[(+)-Men]-containing peptides with L-Leu sequences in solution appeared to be helical structures, based on FTIR and ^{1}H NMR spectra. Furthermore, CD spectra suggested that the dominant secondary structures were similar for Hms[(–)-Men]- and Hms[(+)-Men]-containing peptides, and demonstrated the existence of a right-handed (*P*) 3_{10}-helical structure for the octapeptides. The preferred conformations of Hms[(–)-Men]-containing peptides **13a**, **14a**, and **15a′** and Hms[(+)-Men]-containing peptide **14b** were determined to be a complete or partial right-handed (*P*) 3_{10}-helical structure by X-ray crystallographic analysis. All the cyclohexane rings of the methone moieties occupied chair structures with the methyl and isopropyl substituents in

equatorial positions. A comparison between hexapeptides **14a** and **14b** in order to evaluate the effect of menthone chirality on the peptide secondary structures revealed that the peptide main-chain structures were similar; however, some differences in the side-chains and protecting groups, particularly in the acetal moieties, were observed. These results imply that the influence of Hms[(–)/(+)-Men] residues on the secondary structures of L-Leu-based peptides incorporating such residues is weak, because the chiral centers are far from the α-carbon atoms, and/or because of the rigid inflexible nature of the side-chain structures. The acetal moiety in the dAAs designed here can be changed, and our results may be beneficial for the design of functional helical peptides.

Experimental Section

General Remarks: Optical rotations $[\alpha]_D^{r.t.}$ were measured with a Jasco DIP-370 polarimeter using a 0.5 dm cell. Infrared spectra (IR) were recorded with a Shimadzu IR Affinity-1 spectrometer for conventional measurement (KBr), or using the solution ($CDCl_3$) method with a 0.1 mm path-length NaCl cell. ^1H and ^{13}C NMR spectra were determined with JEOL AL 400 (400 MHz) and Varian NMR System 500PS SN type (500 MHz) spectrometers. FAB-MS spectra and DART-MS spectra were recorded with JEOL JMS-700N and JEOL JMS-T1000TD spectrometers, respectively. X-ray crystallographic analyses were measured with Rigaku Varimax Saturn/1200S and XtaLAB P200 MM007HF-DW instruments.

(5-Amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol *p*-Tosylate (1): 2,2-Dimethoxypropane (5.0 mL, 40 mmol) and 2-amino-2-hydroxymethyl-1,3-propanediol (1.0 g, 8.2 mmol) were added to a stirred solution of *p*-toluenesulfonic acid monohydrate (2.9 g, 15 mmol) in acetone (30 mL), and the mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration, washed with acetone and Et_2O, and then dried to give **1** (2.6 g, 94 %) as colorless crystals. This was used for the next reaction without further purification, m.p. 161–162 °C. IR (KBr): $\tilde{\nu}$ = 3306, 3148, 2990, 1616, 1524, 1454, 1373, 1226, 1165, 1123 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.99 (br. s, 3 H), 7.48 (d, J = 16 Hz, 2 H), 7.12 (d, J = 16 Hz, 2 H), 5.47 (t, J = 9.5 Hz, 1 H), 3.89 (d, J = 25 Hz, 2 H), 3.65 (d, J = 25 Hz, 2 H), 3.49 (d, J = 8.8 Hz, 2 H), 2.29 (s, 3 H), 1.38 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 145.7, 137.8, 125.9, 125.3, 98.7, 61.8, 59.7, 53.3, 26.3, 20.7, 19.7 ppm. HRMS (FAB^+): calcd. for $C_7H_{16}NO_3$ $[M + H]^+$ 162.1130; found 162.1133.

(5-Benzyloxycarbonylamino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (2): $NaHCO_3$ solution (5 % aq.; 120 mL) was added to a suspension of compound **1** (4.0 g, 12 mmol) in dioxane (60 mL). A solution of benzyl chloroformate (6.0 mL, 42 mmol) in dioxane (8 mL) was then added dropwise with stirring, and the mixture was kept at room temperature for 24 h. The dioxane was evaporated, and the residual mixture was diluted with Et_2O, washed with $NaHCO_3$ (5 % aq.), and brine, and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel (80 % EtOAc in hexane) to give compound **2** (3.5 g, 98 %) as colorless crystals, m.p. 64–66 °C. IR (KBr): $\tilde{\nu}$ = 3399, 3287, 2943, 1686, 1547, 1454, 1373, 1296, 1261, 1134, 1084 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.40 (m, 5 H), 5.62 (br. s, 1 H), 5.09 (s, 2 H), 3.75–3.91 (m, 6 H), 1.84 (br. s, 1 H), 1.44 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 135.9, 128.5, 127.5, 98.7, 67.0, 64.1, 64.0, 53.5, 26.0, 20.4 ppm. HRMS ($DART^+$): calcd. for $C_{15}H_{22}NO_5$ $[M + H]^+$ 296.1498; found 296.1519.

5-Benzyloxycarbonylamino-2,2-dimethyl-1,3-dioxan-5-carbaldehyde (3): DMSO (3.6 mL, 51 mmol) was added to a stirred solution of oxalyl chloride (2.1 mL, 25 mmol) in CH_2Cl_2 (40 mL) at –78 °C, and the mixture was stirred at –78 °C for 30 min. Compound **2** (2.5 g, 8.4 mmol) was then added, and stirring was continued for a further 30 min. Triethylamine (13 mL, 93 mmol) was added, and the mixture was stirred at –78 °C for 10 min, and then at room temperature for 30 min. The solution was diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with $NaHSO_4$ (saturated aq.), $NaHCO_3$ (5 % aq.), brine, and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel (20 % EtOAc in hexane) to give aldehyde **3** (1.48 g, 98 %) as colorless crystals, m.p. 86–89 °C. IR (KBr): $\tilde{\nu}$ = 3332, 2993, 1728, 1712, 1520, 1454, 1381, 1246, 1204, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 7.32–7.38 (m, 5 H), 5.81 (br. s, 1 H), 5.13 (s, 2 H), 4.00–4.15 (m, 4 H), 1.48 (m, 3 H), 1.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 155.9, 135.7, 128.6, 128.4, 128.2, 98.8, 67.4, 62.5, 60.1, 27.0, 19.7 ppm. HRMS (FAB^+): calcd. for $C_{15}H_{20}NO_5$ $[M + H]^+$ 294.1341; found 294.1386.

***N*-α-(Benzyloxycarbonyl)-*O,O*-isopropylidine-α-hydroxymethylserine [Cbz-Hms(Ipr)-OH 4]**. A solution of aldehyde **3** (2.6 g, 8.9 mmol) in *t*BuOH (80 mL) and 2-methyl-2-butene (20 mL) was added to a stirred solution of $NaCl_2O$ (7.8 g, 86 mmol) and NaH_2PO_3 (10 g, 74 mmol) in water over 10 min. The mixture was stirred at room temperature for 24 h. The solvent was removed, the residue was diluted with water, and the mixture was washed with *n*-hexane. The aqueous layer was acidfied with $NaHSO_4$, and extracted with EtOAc, and the organic extract was dried with $MgSO_4$. Removal of the solvent gave **4** (6.3 g, 95 %) as colorless crystals. This compound was used for the next reaction without further purification, m.p. 165–167 °C. IR (KBr): $\tilde{\nu}$ = 3433, 3321, 3020, 1735, 1539, 1334, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.38 (m, 5 H), 5.79 (br. s, 1 H), 5.13 (s, 2 H), 4.17 (s, 4 H), 1.80 (br. s, 1 H), 1.49 (s, 3 H), 1.48 (s, 3 H) ppm. HRMS (FAB^+): calcd. for $C_{15}H_{20}NO_6$ $[M + H]^+$ 310.1290; found 310.1241.

***N*-α-(Benzyloxycarbonyl)-*O,O*-isopropylidine-α-hydroxymethylserine Methyl Ester [Cbz-Hms(Ipr)-OMe 5]**. A solution of (trimethylsilyl)diazomethane (9.3 mL, 16.5 mmol) in toluene (10 mL) was added to a stirred solution of **5** (1.27 g, 4.1 mmol) in toluene (15 mL) and MeOH (10 mL). The mixture was stirred at room temperature for 15 min. The solvent was then removed. The residue was purified by column chromatography on silica gel (20 % EtOAc in hexane) to give methyl ester **5** (1.34 g, quant.) as colorless crystals, m.p. 78–79 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.36 (m, 5 H), 5.72 (br. s, 1 H), 5.11 (s, 2 H), 4.23 (d, J = 12 Hz, 2 H), 3.96 (d, J = 12 Hz, 2 H), 3.75 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 155.1, 136.0, 128.5, 128.2, 98.8, 67.1, 63.8, 60.4, 56.3, 52.7, 28.5, 18.2, 14.2, 4.3 ppm. HRMS ($DART^+$): calcd. for $C_{16}H_{22}NO_6$ $[M + H]^+$ 324.1447; found 324.1464.

***N*-α-(Benzylxycarbonyl)-α-hydroxymethylserine Methyl Ester (Cbz-Hms-OMe 6)**

Method 1: Compound **5** (2.0 g, 6.3 mmol) was added to a mixture of trifluoroacetic acid (1.8 mL) and H_2O (0.2 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The solvent was then removed. The residue was purified by column chromatography (50 % EtOAc in hexane) to give **6** (910 mg, 99 %) as colorless crystals.

Method 2: $SOCl_2$ (0.92 mL, 13 mmol) was added to a stirred solution of compound **4** (2.6 g, 8.5 mmol) in MeOH (320 mL). The mixture was stirred at 60 °C for 10 h. The reaction mixture was neutral-

ized with $NaHCO_3$ (5 % aq.), and then the MeOH was removed under vacuum. The residual mixture was extracted with $CHCl_3$ and dried with Na_2SO_4. The solvent was then removed. The residue was purified by column chromatography on silica gel (50 % EtOAc in hexane) to give **6** (2.2 g, 93 %) as colorless crystals, m.p. 65–67 °C. IR (KBr): $\tilde{\nu}$ = 3399, 3349, 3067, 2893, 2855, 2754, 2646, 2592, 2461, 2164, 1794, 1748, 1674, 1639, 1524, 1439, 1385, 1331, 1254, 1234, 1204, 1126, 1084, 1065, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.38 (m, 5 H), 5.91 (br. s, 1 H), 5.13 (s, 2 H), 4.04 (d, J = 12 Hz, 2 H), 3.94 (d, J = 12 Hz, 2 H), 3.80 (s, 3 H), 2.15 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 135.9, 128.6, 128.3, 128.1, 67.3, 64.1, 53.1 ppm. HRMS (DART$^+$): calcd. for $C_{13}H_{18}NO_6$ [M + H]$^+$ 284.1134; found 284.1128.

Cbz-Hms[(–)-Men]-OMe (7a)

Method 1: A mixture of *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol), **6** (0.80 g, 2.9 mmol), and (–)-menthone (0.70 mL, 4.1 mmol) in toluene was heated at reflux for 24 h. The mixture was then diluted with diethyl ether, washed with $NaHCO_3$ (5 % aq.), and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (90 % EtOAc in *n*-hexane) to give Cbz-Hms[(–)-Men]-OMe **7** (0.24 g, 20 %) as a colorless oil.

Method 2: 1,1,1,3,3,3-Hexamethyldisilazane (HMDS; 1.2 mL, 18 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf; 101 µL, 1.8 mmol) were added to a stirred solution of **6** (0.80 g, 9.1 mmol) in THF (30 mL). The reaction mixture was stirred at 0 °C for 90 min. The mixture was then diluted with Et_2O, washed with ice-cold water, and dried with $MgSO_4$. The solvent was removed to give crude TMS-**6** (1.2 g, 96 %), which was used in the next reaction without further purification.

TMSOTf (10 µL, 0.18 mmol) was added to a stirred solution of TMS-**6** (0.76 g, 1.8 mmol) and (–)-menthone (0.62 mL, 3.4 mmol) in CH_2Cl_2 (15 mL) at –40 or –78 °C, and the mixture was stirred at –40 or 78 °C for 24 h. NaOH (2 % in MeOH; 3 mL) was then added, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with ice-cold water, and extracted with Et_2O. The combined organic extracts were washed with H_2O and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (90 % EtOAc in hexane) to give Cbz-Hms[(–)-Men]-OMe (**7**) (0.63 g, 84 %) as a colorless oil.

Data for **7a**: $[\alpha]_D^{27}$ = –16.8 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3437, 2955, 1717, 1497, 1458, 1381, 1273, 1234, 1123, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.37 (m, 5 H), 5.06 (s, 2 H), 4.96 (br. s, 1 H), 4.29–4.37 (m, 2 H), 4.04–4.09 (m, 1 H), 3.87–3.92 (m, 1 H), 3.80 (br. s, 3 H), 2.69 (d, J = 12 Hz, 1 H), 2.38–2.48 (m, 1 H), 1.71–1.74 (m, 1 H), 1.33–1.55 (m, 3 H), 1.27 (d, J = 12 Hz, 1 H), 0.84–0.93 (m, 10 H), 0.72 (t, J = 11 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 155.1, 136.3, 128.44, 128.42, 128.0, 127.7, 101.2, 67.8, 63.0, 2.4, 58.4, 56.5, 52.6, 50.8, 35.7, 34.7, 29.0, 24.3, 23.7, 22.1, 21.5, 18.4 ppm. HRMS (DART$^+$): calcd. for C23H34NO6 [M + H]$^+$ 420.2386; found 420.2386.

Data for **7a'**: $[\alpha]_D^{21}$ = –10.1 (c = 0.23, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3341, 2956, 1735, 1506, 1459, 1279, 1229, 1161, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.36 (m, 5 H), 5.06 (s, 2 H), 4.98 (br. s, 1 H), 4.36 (d, J = 12 Hz, 1 H), 4.32 (d, J = 12 Hz, 1 H), 4.06–4.10 (m, 1 H), 3.85–3.93 (m, 1 H), 3.80 (s, 3 H), 2.68 (d, J = 12 Hz, 1 H), 2.32–2.35 (m, 1 H), 1.71–1.74 (m, 1 H), 1.38–1.57 (m, 3 H), 1.24–1.26 (m, 1 H), 0.83–0.92 (m, 10 H), 0.75 (t, J = 12 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 154.8, 135.7, 128.6, 128.4, 128.2, 101.0, 77.2, 67.2, 63.3, 62.9, 54.9, 52.7, 50.9, 36.4, 34.7, 29.2, 23.9, 23.7, 22.2, 21.7, 18.4 ppm. HRMS (DART$^+$): calcd. for $C_{23}H_{34}NO_6$ [M + H]$^+$ 420.2386; found 420.2386.

Data for **7b**: $[\alpha]_D^{29}$ = +17.9 (c = 1.0, $CHCl_3$).

Cbz-Hms[(–)-Men]-OH (8a): NaOH solution (1 M aq.; 1.5 mL, 1.5 mmol) was added dropwise to a stirred solution of Cbz-Hms-[(–)-Men]-OMe (**7a**) (0.63 g, 1.5 mmol) in MeOH (20 mL). The mixture was stirred at room temperature overnight. The MeOH was removed, and the aqueous layer was acidfied with citric acid to pH 3, and extracted with $CHCl_3$. The organic extract was dried with $MgSO_4$. Removal of the solvent gave crude carboxylic acid **8a** (0.60 mg, quant.) as a colorless oil, which was used in the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (br. s, 1 H), 7.33–7.35 (m, 5 H), 5.72 (br. s, 1 H), 5.15 (s, 2 H), 4.35 (d, J = 12 Hz, 1 H), 4.18 (d, J = 12 Hz, 1 H), 4.01 (d, J = 12 Hz, 1 H), 3.96 (d, J = 12 Hz, 1 H), 2.71 (d, J = 13 Hz, 1 H), 2.36–2.39 (m, 1 H), 1.74 (d, J = 12 Hz, 1 H), 1.36–1.54 (m, 3 H), 1.25–1.27 (m, 1 H), 0.86–0.93 (m, 10 H), 0.72 (t, J = 13 Hz, 1 H) ppm. MS (DART): m/z = 406 [M + H]$^+$.

H-Hms[(–)-Men]-OMe (9a): A mixture of Cbz-Hms[(–)-Men]-OMe (**7a**) (0.62 g, 1.5 mmol) and Pd/C (5 %; 300 mg) in MeOH (30 mL) was vigorously stirred under a hydrogen atmosphere at room temperature. After 2 h, the Pd/C catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give a crude amine **9a** (405 mg, 97 %), which was used for next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.40 (d, J = 12 Hz, 1 H), 4.18 (d, J = 12 Hz, 1 H), 3.76 (s, 3 H), 3.57–3.62 (m, 2 H), 2.72–2.75 (m, 1 H), 2.44–2.49 (m, 1 H), 1.99 (br. s, 2 H), 1.71–1.77 (m, 1 H), 1.43–1.53 (m, 3 H), 1.25–1.30 (m, 1 H), 0.85–0.96 (m, 10 H), 0.72 (t, J = 12 Hz, 1 H) ppm. MS (DART): m/z = 286 [M + H]$^+$.

Cbz-{Hms[(–)-Men]}$_2$-OMe (10a): Crude amine **8a** (0.30 g, 1.2 mmol) was added to a stirred solution of crude carboxylic acid **9a** (0.4 g, 0.98 mmol), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; 0.64 g, 1.3 mmol), 1-hydroxy-7-azabenzotriazole (HOAt; 0.40 g, 1.3 mmol), and diisopropylethylamine (162 µL, 1.3 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 40 °C for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with $NaHCO_3$ (5 % aq.), and brine, and dried with $MgSO_4$. The solvent was removed to give a white solid, which was purified by column chromatography on silica gel (10 % EtOAc in hexane) to give dipeptide **10a** (604 mg, 91 %) as colorless crystals, m.p. 168–170 °C. $[\alpha]_D^{27}$ = –32.2 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3421, 2951, 2873, 1744, 1667, 1554, 1504, 1381, 1304, 1269, 1153, 1118 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (br. s, 1 H), 7.31–7.36 (m, 5 H), 5.44 (br. s, 1 H), 5.16 (s, 2 H), 4.32–4.37 (m, 2 H), 4.24 (d, J = 12 Hz, 1 H), 4.01–4.13 (m, 2 H), 3.85–3.95 (m, 3 H), 3.72 (s, 3 H), 2.73 (t, J = 12 Hz, 2 H), 2.35–2.41 (m, 2 H), 1.69–1.77 (m, 2 H), 1.37–1.55 (m, 6 H), 1.26 (t, J = 8 Hz, 2 H), 0.82–0.94 (m, 20 H), 0.65–0.73 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 169.3, 156.2, 135.8, 128.5, 128.2, 128.0, 101.4, 101.1, 67.3, 63.0, 62.8, 62.7, 61.7, 57.4, 55.8, 52.5, 50.7, 35.8, 35.6, 34.7, 29.0, 24.3, 24.1, 23.8, 23.7, 22.1, 22.0, 21.62, 21.55, 18.9, 18.5 ppm. HRMS (DART$^+$): calcd. for $C_{37}H_{57}N_2O_9$ [M + H]$^+$ 673.4064; found 673.4064.

Cbz-{Hms[(–)-Men]}$_3$-OMe (11a): A mixture of Cbz-{Hms[(–)-Men]}$_2$-OMe **10a** (0.14 g, 0.21 mmol) and Pd/C (20 %; 30 mg) in MeOH (30 mL) was vigorously stirred under a hydrogen atmosphere at room temperature. After 17 h, the Pd/C catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give crude **10a**-amine (0.11 g, quant.).

The crude **10a**-amine (41 mg, 76 µmol) was added to a stirred solution of crude carboxylic acid **9a** (38 mg, 93 µmol), COMU (49 mg, 0.11 mmol), and diisopropylethylamine (16 µL, 0.11 mmol) in CH_2Cl_2

(15 mL). The mixture was stirred at 40 °C for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with $NaHCO_3$ (5 % aq.), and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (10 % EtOAc in hexane) to give dipeptide **11a** (31 mg, 44 %) as colorless crystals, m.p. 115–117 °C. $[\alpha]_D^{19}$ = –13.9 (*c* = 1.4, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3348, 2954, 1716, 1693, 1519, 1496, 1296, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.35–7.36 (m, 5 H), 6.88 (s, 1 H), 5.81 (s, 1 H), 5.26 (d, *J* = 12 Hz, 1 H), 5.11 (d, *J* = 12 Hz, 1 H), 4.06–4.41 (m, 9 H), 3.80–3.94 (m, 3 H), 3.71 (s, 3 H), 2.74–2.78 (m, 3 H), 2.46–2.49 (m, 1 H), 2.33–2.39 (m, 2 H), 1.25–1.74 (m, 15 H), 0.83–0.93 (m, 30 H), 0.66–0.74 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.8, 168.0, 156.7, 135.7, 128.6, 128.4, 128.0, 101.5, 101.2, 100.6, 67.7, 63.8, 63.4, 62.4, 61.8, 61.6, 61.2, 57.8, 56.6, 52.3, 50.9, 50.71, 50.67, 35.9, 35.8, 35.7, 34.8, 34.7, 29.1, 29.04, 29.00, 24.5, 24.3, 24.0, 23.83, 23.81, 23.7, 22.2, 22.0, 21.72, 21.70, 21.5, 19.2, 19.1, 18.5 ppm. HRMS (FAB^+): calcd. for $C_{51}H_{80}N_3O_{12}$ $[M + H]^+$ 925.5742; found 925.5755.

Cbz-Hms[(–)-Men]-(L-Leu)$_2$-OMe (12a): The amine H-(L-Leu)$_2$-OMe (0.44 g, 1.8 mmol) was added to a stirred solution of crude carboxylic acid **8a** (0.47 g, 1.1 mmol), HATU (0.78 g, 1.8 mmol), HOAt (0.28 g, 1.8 mmol), and diisopropylethylamine (358 µL, 1.8 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with $NaHCO_3$ (5 % aq.), and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (30 % EtOAc in hexane) to give tripeptide **12a** (665 mg, 94 %) as a colorless oil. $[\alpha]_D^{19}$ = –11.4 (*c* = 0.43, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3441, 3020, 2918, 2350, 1753, 1678, 1577, 1539, 1384, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.38 (m, 5 H), 7.08 (s, 1 H), 6.66 (d, *J* = 2.8 Hz, 1 H), 5.27–5.29 (m, 2 H), 5.01 (d, *J* = 14 Hz, 1 H), 4.48–4.51 (m, 2 H), 4.34–4.48 (m, 2 H), 3.93–4.03 (m, 1 H), 3.91–3.95 (m, 1 H), 3.68 (s, 3 H), 2.88 (*J* = 14 Hz, 1 H), 2.38–2.42 (m, 1 H), 1.51–1.75 (m, 12 H), 1.24–1.26 (m, 1 H), 0.85–1.01 (m, 20 H), 0.70 (t, *J* = 12 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 173.2, 172.6, 169.0, 135.5, 128.7, 128.6, 128.3, 100.9, 67.9, 64.1, 58.4, 55.0, 52.4, 52.0, 50.8, 40.2, 39.9, 39.5, 35.9, 34.8, 29.0, 25.1, 24.5, 24.0, 23.4, 23.1, 22.8, 22.1, 21.8, 21.5, 20.9, 19.5 ppm. HRMS (FAB^+): calcd. for $C_{35}H_{55}N_3O_8Na$ $[M + Na]^+$ 668.3887; found 668.3898.

Cbz-Hms[(+)-Men]-(L-Leu)$_2$-OMe (12b): Tripeptide **12b** was prepared from **8b** and H-(L-Leu)$_2$-OMe in a manner similar to that described for the preparation of tripeptide **12a**: 82 % yield, colorless crystals, m.p. 60–61 °C. $[\alpha]_D^{17}$ = –2.0 (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3325, 2955, 1732, 1651, 1535, 1454, 1269, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.37 (m, 5 H), 6.96 (d, *J* = 7.1 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 5.63 (s, 1 H), 5.23 (d, *J* = 12 Hz, 1 H), 5.09 (d, *J* = 13 Hz, 1 H), 4.46–4.56 (m, 2 H), 4.38–4.42 (m, 1 H), 4.26 (d, *J* = 12 Hz, 1 H), 3.97 (d, *J* = 12 Hz, 1 H), 3.84 (d, *J* = 13 Hz, 1 H), 3.71 (s, 3 H), 2.78 (d, *J* = 13 Hz, 1 H), 2.37–2.41 (m, 1 H), 1.24–1.79 (m, 13 H), 0.87–0.95 (m, 20 H), 0.69 (t, *J* = 12 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 171.4, 169.0, 156.2, 135.6, 128.5, 128.3, 127.8, 101.4, 67.3, 62.9, 62.0, 60.3, 57.9, 52.1, 51.8, 50.8, 50.6, 40.7, 40.0, 35.8, 34.6, 29.6, 28.9, 24.8, 24.1, 23.6, 23.0, 21.9, 21.6, 20.9, 18.6, 14.1 ppm. HRMS (FAB^+): calcd. for $C_{35}H_{56}N_3O_8$ $[M + H]^+$ 646.4067; found 646.4062.

Cbz-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-OMe (13a): A mixture of Cbz-Hms[(–)-Men]-(L-Leu)$_2$-OMe (**12a**) (0.31 g, 0.48 mmol) and Pd/C (20 %; 75 mg) in MeOH (50 mL) was vigorously stirred under a hydrogen atmosphere at room temperature. After being stirred for 17 h, the Pd/C catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give crude **12a**-amine (0.23 g, quant.).

The crude **12a**-amine (0.20 g, 0.38 mmol) was added to a stirred solution of carboxylic acid Cbz-(L-Leu)$_2$-OH (0.10 g, 0.38 mmol), HATU (0.18 g, 0.46 mmol), HOAt (64 mg, 0.46 mmol), and diisopropylethylamine (80 µL, 0.46 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with $NaHCO_3$ (5 % aq.), and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (60 % EtOAc in hexane) to give dipeptide **13a** (179 mg, 53 %) as colorless crystals, m.p. 230–231 °C. $[\alpha]_D^{26}$ = –35.2 (*c* = 1.2, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3363, 2958, 2360, 1716, 1670, 1508, 1269 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.41 (m, 7 H), 6.87 (s, 1 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 5.39 (d, *J* = 2.8 Hz, 1 H), 5.25 (d, *J* = 9.7 Hz, 1 H), 4.97 (d, *J* = 9.8 Hz, 1 H), 4.64 (d, *J* = 9.6 Hz, 1 H), 4.46–4.51 (m, 2 H), 4.31–4.39 (m, 1 H), 4.19 (d, *J* = 9.8 Hz, 1 H), 3.92–3.97 (m, 3 H), 3.66 (s, 3 H), 2.85 (d, *J* = 10 Hz, 1 H), 2.42–2.49 (m, 1 H), 1.49–1.88 (m, 14 H), 1.35–1.41 (m, 1 H), 1.28 (d, *J* = 12 Hz, 1 H), 0.89–1.10 (m, 35 H), 0.73 (t, *J* = 12 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 173.2, 172.6, 169.0, 157.0, 135.5, 128.6, 128.5, 128.3, 100.9, 67.9, 64.0, 61.0, 58.4, 55.0, 54.9, 52.4, 52.0, 51.0, 50.8, 40.23, 40.17, 39.8, 39.5, 35.9, 34.8, 29.0, 25.1, 25.0, 24.5, 24.4, 24.0, 23.4, 23.1, 22.8, 22.7, 22.1, 21.82, 21.76, 21.53, 21.47, 20.9, 19.4 ppm. HRMS (FAB^+): calcd. for $C_{47}H_{78}N_5O_{10}$ $[M + H]^+$ 872.5749; found 872.5741.

Cbz-(L-Leu)$_2$-Hms[(+)-Men]-(L-Leu)$_2$-OMe (13b): Pentapeptide **13b** was prepared from tripeptide **12b** and Cbz-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of tripeptide **12a**: 46 % yield, colorless crystals, m.p. 220–221 °C. $[\alpha]_D^{26}$ = –0.29 (*c* = 1.0, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3422, 3340, 2958, 1716, 1670, 1508, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.41 (m, 7 H), 6.88 (s, 1 H), 6.73 (d, *J* = 3.4 Hz, 1 H), 5.44 (d, *J* = 2.9 Hz, 1 H), 5.24 (d, *J* = 12 Hz, 1 H), 4.97 (d, *J* = 12 Hz, 1 H), 4.63 (d, *J* = 12 Hz, 1 H), 4.42–4.51 (m, 2 H), 4.35–4.40 (m, 1 H), 4.19 (d, *J* = 10 Hz, 1 H), 3.92–4.00 (m, 3 H), 3.65 (s, 3 H), 2.87 (d, *J* = 12.5 Hz, 1 H), 2.48 (q, *J* = 14 Hz, 1 H), 1.50–1.83 (m, 14 H), 1.31–1.42 (m, 1 H), 1.26–1.29 (m, 1 H), 0.73–1.02 (m, 35 H), 0.73 (t, *J* = 12 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 173.2, 172.8, 172.5, 168.8, 157.0, 135.6, 128.6, 128.5, 128.2, 100.6, 67.8, 64.5, 60.4, 58.4, 55.3, 52.3, 52.0, 51.0, 50.8, 40.4, 40.0, 39.9, 39.7, 36.0, 34.8, 29.1, 25.0, 24.9, 24.4, 23.8, 23.5, 23.4, 23.1, 22.6, 22.5, 22.0, 21.9, 21.8, 21.5, 21.4, 20.9, 19.1 ppm. HRMS (FAB^+): calcd. for $C_{47}H_{78}N_5O_{10}$ $[M + H]^+$ 872.5749; found 872.5751.

Cbz-Hms[(–)-Men]-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-OMe (14a): Hexapeptide **14a** was prepared from pentapeptide **13a** and carboxylic acid **8a** in a manner similar to that described for the preparation of pentapeptide **13a**: 54 % yield, colorless crystals, m.p. 236–237 °C. $[\alpha]_D^{25}$ = +7.9 (*c* = 1.0, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3337, 2959, 1712, 1670, 1523, 1269 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 4.3 Hz, 1 H), 7.33–7.38 (m, 7 H), 6.81 (s, 1 H), 6.52 (d, *J* = 4.9 Hz, 1 H), 5.97 (s, 1 H), 5.14–5.23 (m, 2 H), 4.48–4.56 (m, 3 H), 4.31–4.41 (m, 4 H), 3.91–4.11 (m, 4 H), 3.69 (s, 3 H), 3.48–3.51 (m, 1 H), 2.94 (d, *J* = 13 Hz, 1 H), 2.73 (d, *J* = 12 Hz, 1 H), 2.41–2.45 (m, 1 H), 2.28–2.32 (m, 1 H), 1.15–1.81 (m, 23 H), 0.65–1.01 (m, 45 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 173.2, 172.9, 170.6, 169.2, 157.0, 135.2, 128.7, 128.5, 127.8, 101.8, 100.7, 67.9, 64.7, 64.4, 60.7, 60.4, 60.2, 58.7, 57.8, 55.7, 54.1, 52.3, 52.0, 51.0, 50.7, 40.1, 40.0, 39.6, 39.1, 36.0, 35.8, 34.9, 34.6, 29.1, 29.0, 25.2, 25.1, 25.0, 24.8, 24.5, 23.9, 23.6, 23.1, 23.0, 22.8, 22.1, 21.54, 21.45, 21.0, 20.9, 19.3, 18.2 ppm. HRMS (FAB^+): calcd. for $C_{61}H_{100}N_6O_{13}Na$ $[M + Na]^+$ 1147.7246; found 1148.7339.

Cbz-Hms[(+)-Men]-(L-Leu)$_2$-Hms[(+)-Men]-(L-Leu)$_2$-OMe (14b): Hexapeptide **14b** was prepared from pentapeptide **13b** and carb-

oxylic acid **8b** in a manner similar to that described for the preparation of pentapeptide **13a**: 79 % yield, colorless crystals, m.p. 239–240 °C. $[\alpha]_D^{26}$ = –52.8 (*c* = 1.0, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3333, 2958, 1716, 1670, 1523, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 3.4 Hz, 1 H), 7.56 (dd, *J* = 7.8, 11.6 Hz, 1 H), 7.30–7.35 (m, 5 H), 7.15 (d, *J* = 3.9 Hz, 1 H), 6.61 (s, 1 H), 6.07 (s, 1 H), 5.70 (s, 1 H), 5.28 (d, *J* = 13 Hz, 1 H), 5.08–5.12 (m, 2 H), 4.67 (d, *J* = 12 Hz, 1 H), 4.17–4.40 (m, 4 H), 3.85–4.12 (m, 8 H), 3.83 (d, *J* = 12 Hz, 1 H), 3.70 (s, 3 H), 2.99 (d, *J* = 12 Hz, 1 H), 2.72 (d, *J* = 13 Hz, 1 H), 2.20–2.48 (m, 2 H), 0.73–1.81 (m, 65 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 173.6, 173.1, 173.0, 170.3, 169.1, 165.7, 156.6, 135.5, 128.5, 128.3, 128.2, 128.0, 127.5, 127.0, 101.3, 100.9, 100.5, 67.1, 64.4, 61.0, 58.4, 57.3, 55.9, 53.2, 52.2, 51.8, 51.1, 50.9, 50.6, 39.8, 39.4, 39.1, 38.4, 35.6, 34.8, 34.6, 28.8, 28.7, 24.9, 24.5, 24.2, 24.0, 23.6, 23.4, 22.9, 22.8, 22.4, 22.3, 21.9, 21.6, 21.4, 21.3, 20.9, 20.7, 19.7, 18.8, 18.3 ppm. HRMS (FAB^+): calcd. for $C_{61}H_{101}N_6O_{13}$ $[M + H]^+$ 1125.7227; found 1125.7440.

Cbz-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-OMe (15a): Octapeptide **15a** was prepared from hexapeptide **14a** and Cbz-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of pentapeptide **13a**: 20 % yield, colorless crystals, m.p. 241–242 °C. $[\alpha]_D^{24}$ = –3.5 (*c* = 1.3, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3321, 2985, 1708, 1223 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 3.1 Hz, 1 H), 7.58 (d, *J* = 4.6 Hz, 1 H), 7.50 (d, *J* = 9.9 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.38 (m, 6 H), 6.90 (s, 1 H), 6, 77 (s, 1 H), 5.42 (s, 1 H), 5.35 (d, *J* = 12 Hz, 1 H), 5.00 (d, *J* = 12 Hz, 1 H), 4.48–4.61 (m, 3 H), 4.30–4.42 (m, 4 H), 4.12–4.18 (m, 1 H), 3.92–4.08 (m, 5 H), 3.68–3.74 (m, 1 H), 3.67 (s, 3 H), 2.98 (d, *J* = 14 Hz, 1 H), 2.80–2.85 (m, 1 H), 2.42–2.50 (m, 2 H), 0.77–1.86 (m, 86 H) ppm. HRMS (FAB^+): calcd. for $C_{73}H_{123}N_8O_{15}$ $[M + H]^+$ 1351.9108; found 1351.9097.

Boc-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-Hms[(–)-Men]-(L-Leu)$_2$-OMe (15a′): Octapeptide **15a′** was prepared from hexapeptide **14a** and Boc-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of pentapeptide **13a**: 20 % yield, colorless crystals, m.p. 250–251 °C. $[\alpha]_D^{27}$ = –9.5 (*c* = 0.38, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3341, 2885, 1717, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 4.2 Hz, 1 H), 7.62 (d, *J* = 4.2 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.05 (s, 1 H), 6.83 (s, 1 H), 6.75 (d, *J* = 2.4 Hz, 1 H), 4.83 (d, *J* = 4.9 Hz, 1 H), 4.52–4.59 (m, 5 H), 4.32–4.41 (m, 2 H), 4.13 (d, *J* = 12 Hz, 1 H), 3.90–4.01 (m, 5 H), 3.72–3.78 (m, 1 H), 3.68 (s, 3 H), 2.95 (d, *J* = 12 Hz, 1 H), 2.80 (d, *J* = 12 Hz, 1 H), 2.45 (ddd, *J* = 6.7, 14, 20 Hz, 1 H), 2.31 (ddd, *J* = 6.7, 14, 21 Hz, 1 H), 1.49 (s, 9 H), 1.15–1.89 (m, 23 H), 0.62–1.03 (m, 63 H) ppm. HRMS (FAB^+): calcd. for $C_{70}H_{125}N_8O_{15}$ $[M + H]^+$ 1317.9264; found 1317.9276.

Boc-(L-Leu)$_2$-Hms[(+)-Men]-(L-Leu)$_2$-Hms[(+)-Men]-(L-Leu)$_2$-OMe (15b′): Octapeptide **15b′** was prepared from hexapeptide **14b** and Boc-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of pentapeptide **13a**: 20 % yield, colorless crystals, m.p. 250–251 °C. $[\alpha]_D^{23}$ = +27.7 (*c* = 0.29, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}$ = 3321, 2958, 1708, 1670, 1532, 1223 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 3.4 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 5.9 Hz, 1 H), 6.86 (s, 1 H), 6.74 (s, 1 H), 6.55 (s, 1 H), 4.78 (d, *J* = 4.9 Hz, 1 H), 4.28–4.49 (m, 5 H), 3.80–4.18 (m, 8 H), 3.68 (s, 3 H), 3.55–3.61 (m, 1 H), 2.83 (d, *J* = 14 Hz, 1 H), 2.58 (d, *J* = 14 Hz, 1 H), 2.18–2.34 (m, 2 H), 1.21–1.86 (m, 32 H), 0.72–1.04 (m, 63 H) ppm. HRMS (FAB^+): calcd. for $C_{70}H_{125}N_8O_{15}$ $[M + H]^+$ 1317.9264; found 1317.9277.

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[9] CCDC 1453020 (for **13a**), 1453021 (for **14a**), 1453022 (for **14b**), and 1453023 (for **15a′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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