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Enantioselective epoxidation of α,β-unsaturated ketones catalyzed by stapled helical L-Leu-based peptides

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ABSTRACT

Stapled helical L-leucine-based heptapeptides were synthesized and used as catalysts for the enantioselective epoxidation of α,β-unsaturated ketones. All N-terminal free stapled peptides were successfully used as chiral catalysts. Among them, the use of **H-*hS*$_{3,7}$*hS*-10** gave epoxide products with high enantioselectivities of up to 99% ee. Furthermore, the dominant conformations of the N-terminal protected stapled peptides ***R*$_{3,7}$*R*-10** and ***hS*$_{3,7}$*hS*-10** were investigated by ^{1}H NMR, IR, CD spectra, and X-ray crystallographic analysis. The peptide ***R*$_{3,7}$*R*-10** formed a right-handed (*P*) α-helix in solution and in the crystalline state, while ***hS*$_{3,7}$*hS*-10** formed a right-handed (*P*) 3_{10}-helix in solution.

1. Introduction

The de novo design of peptides and proteins is of extraordinary importance in the fields of organic chemistry, nanotechnology, and medicinal chemistry. A variety of approaches to controlling the conformations of peptides have been investigated,[1] and the incorporation of α,α-disubstituted α-amino acids[2] and cross-linked side chains[3] into peptide sequences is of vital importance for constructing stable helical structures. Recently, we have reported that the L-leucine (L-Leu) rich stapled heptapeptide ***R*$_{3,7}$*R*-10**, which contains an α-aminoisobutyric acid (Aib)[4] at its fourth position as a helical promoter and D-serine derivatives at its third (***R*$_3$**) and seventh (***$_7$R*$_{3,7}$*R*-10**) positions as a cross-linked subunit,[5] formed a stable right-handed (*P*) α-helix (Fig. 1).[6] Furthermore, its N-terminal free **H-*R*$_{3,7}$*R*-10** was successfully used as a chiral catalyst for the enantioselective epoxidation of (*E*)-chalcone.[7] However, the enantioface discrimination by **H-*R*$_{3,7}$*R*-10** was not so succesful.[6] As part of our ongoing research, we prepared stapled peptides with different side-chain lengths at the third and seventh positions and used them for the catalytic enantioselective epoxidation of α,β-unsaturated ketones.

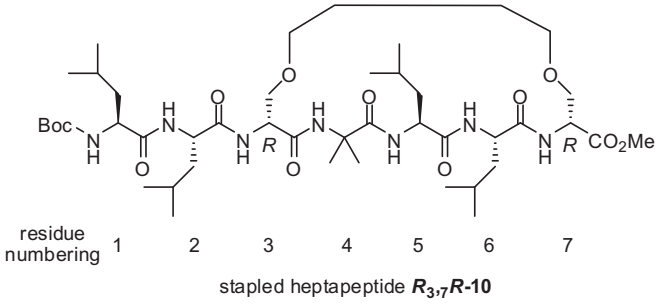

Fig. 1. Chemical structure of the stapled heptapeptide ***R*$_{3,7}$*R*-10**. The nomenclature ***R*$_{3,7}$*R*** refers to a peptide with an *R* configuration at its third position and an *R* configuration at its seventh position.

2. Results and discussion

Stapled peptides were synthesized as follows (Scheme 1). First, the hydroxy group of Boc-L/D-Ser or Boc-L-homoserine (Boc-L-Hse) was allylated, and then treatment with 1 M HCl in MeOH afforded the amino acid esters (*S*)-**3**, (*R*)-**3**, and (*S*)-**4**. The linear heptapeptides ***S*$_{3,7}$*S*-9**, ***S*$_{3,7}$*R*-9**, ***R*$_{3,7}$*S*-9**, ***R*$_{3,7}$*R*-9**, ***hS*$_{3,7}$*S*-9**, ***hS*$_{3,7}$*R*-9**, and ***hS*$_{3,7}$*hS*-9** were prepared by conventional solution-phase methods

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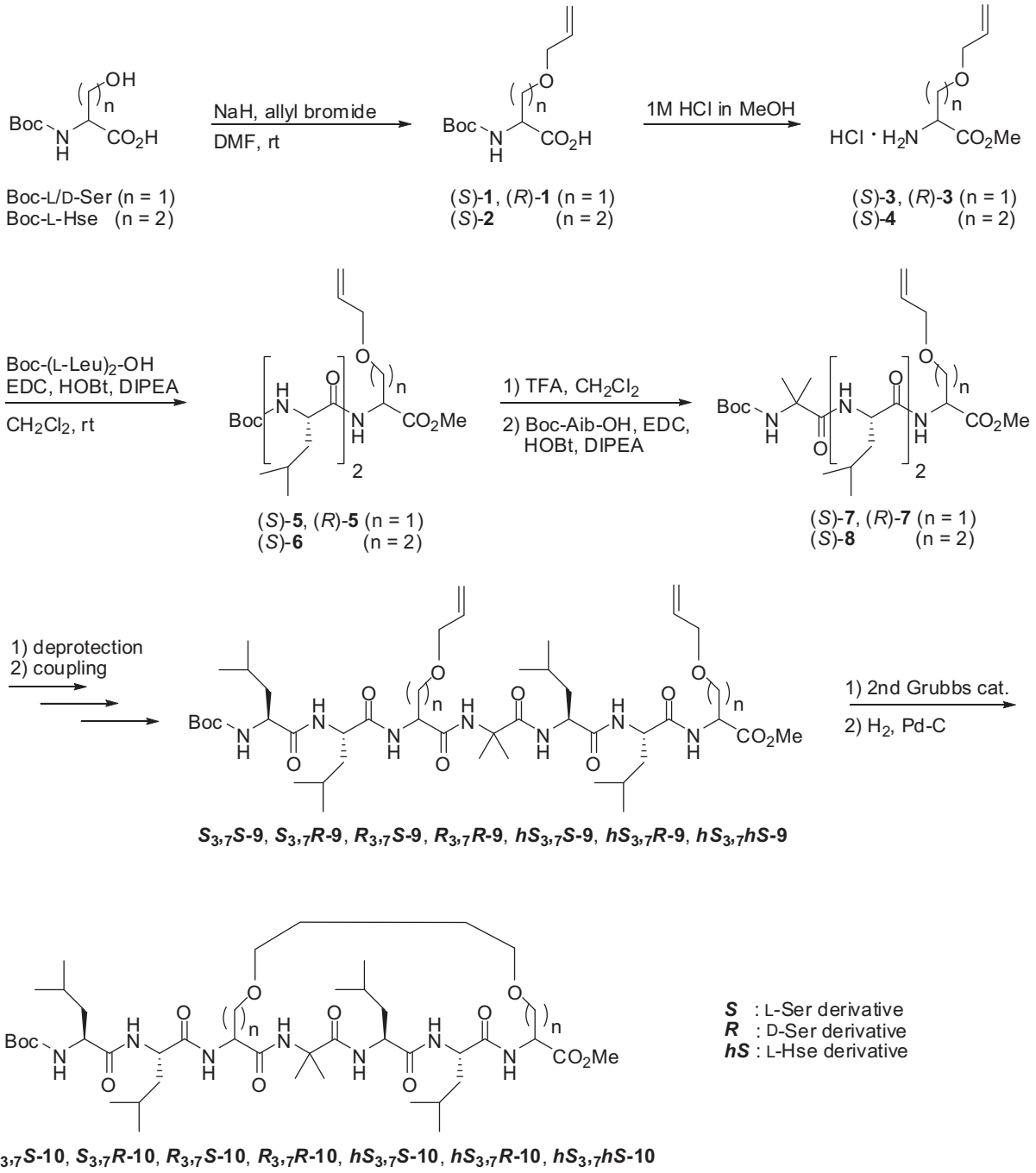
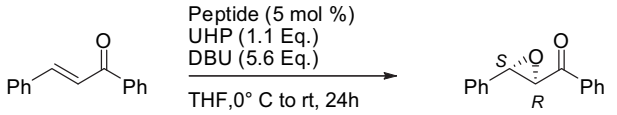


Scheme 1. Synthesis of the stapled heptapeptides ***S***$_{3,7}$***S*-10**, ***S***$_{3,7}$***R*-10**, ***R***$_{3,7}$***S*-10**, ***R***$_{3,7}$***R*-10**, ***hS***$_{3,7}$***S*-10**, ***hS***$_{3,7}$***R*-10**, and ***hS***$_{3,7}$***hS*-10**. The nomenclature ***hS*** indicates an L-homoserine (L-Hse) derivative.

with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents. Then, intramolecular ruthenium-catalyzed ring-closing metathesis reactions involving the linear peptides gave stapled peptides as a mixture of olefin isomers (the *E*/*Z* ratio of isomers was not determined). The subsequent hydrogenation of the olefin mixtures afforded the saturated stapled peptides ***S***$_{3,7}$***S*-10**, ***S***$_{3,7}$***R*-10**, ***R***$_{3,7}$***S*-10**, ***R***$_{3,7}$***R*-10**, ***hS***$_{3,7}$***S*-10**, ***hS***$_{3,7}$***R*-10**, and ***hS***$_{3,7}$***hS*-10**.

We examined the enantioselective epoxidation of (*E*)-chalcone (**11a**) using N-terminal free peptides (Table 1).[8,9] The epoxidation of **11a** using 5 mol % of peptides was carried out in THF containing urea-H_2O_2 (UHP) and DBU under aerobic conditions with the temperature gradually increasing from 0 °C to room temperature over 24 h. In all cases, the epoxidation proceeded smoothly to afford the (2*R*,3*S*)-epoxidated chalcone **12a** in high yield. The use of the stapled peptides gave (2*R*,3*S*)-**12a** with higher enantioselectivity than those produced using the linear peptides (entries 1–14). Among the stapled peptides **H-*S***$_{3,7}$***S*-10**, **H-*S***$_{3,7}$***R*-10**, **H-*R***$_{3,7}$***S*-10**, and **H-*R***$_{3,7}$***R*-10** (entries 2, 4, 6, 8) with the same-length linker, the reaction by **H-*R***$_{3,7}$***R*-10** proceeded with the most enantioselective efficiency.[6] Among **H-*S***$_{3,7}$***S*-10**, **H-*hS***$_{3,7}$***S*-10**, and **H-*hS***$_{3,7}$***hS*-10** (entries 2, 10, 14), which have the different side-chain lengths, the use of **H-*hS***$_{3,7}$***hS*-10** afforded (2*R*,3*S*)-**12a** with the highest enantiomeric excess (87% ee). Furthermore, using 10 mol % **H-*hS***$_{3,7}$***hS*-10** (entry 15), (2*R*,3*S*)-**12a** was obtained in almost complete enantioselectivity (99% ee).

Table 1
Asymmetric epoxidation of (*E*)-chalcone (**11a**) using the N-terminal free peptides



(*E*)-chalcone (**11a**) (2*R*,3*S*)-**12a**

Entry	Peptide	Yield (%)	ee (%)
1	**H-*S*$_{3,7}$*S*-9**	90	58
2	**H-*S*$_{3,7}$*S*-10**	89	65
3	**H-*S*$_{3,7}$*R*-9**	91	57
4	**H-*S*$_{3,7}$*R*-10**	89	64
5	**H-*R*$_{3,7}$*S*-9**	82	35
6	**H-*R*$_{3,7}$*S*-10**	86	37
7	**H-*R*$_{3,7}$*R*-9**	93	30
8	**H-*R*$_{3,7}$*R*-10**	89	69
9	**H-*hS*$_{3,7}$*S*-9**	94	77
10	**H-*hS*$_{3,7}$*S*-10**	96	79
11	**H-*hS*$_{3,7}$*R*-9**	96	71
12	**H-*hS*$_{3,7}$*R*-10**	95	75
13	**H-*hS*$_{3,7}$*hS*-9**	97	79
14	**H-*hS*$_{3,7}$*hS*-10**	93	87
15[a]	**H-*hS*$_{3,7}$*hS*-10**	99	>99

[a] Catalyst (10 mol %) was used.

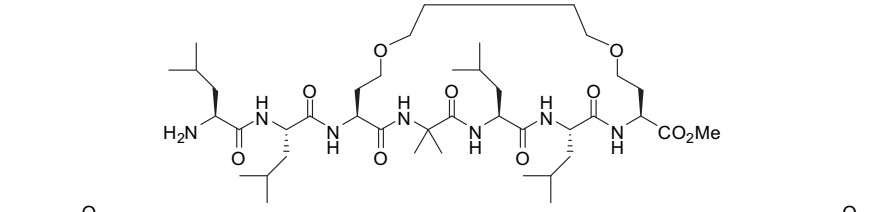
Next, we examined the asymmetric epoxidation of several acyclic α,β-unsaturated ketones (**11a**–**h**) using 10 mol % **H-*hS*$_{3,7}$*hS*-10** (Table 2).[10,11] The substrates were converted to the corresponding epoxides in high yield (87–99%; entries 1, 5–8) although the yields of the substrates containing an alkyl substituent as the R^2 were low (entries 2–4). The epoxide in which R^1=Ph and R^2=2-furanyl was obtained with excellent enantiomeric excess (99% ee, entry 5), while the enantioselectivities of other epoxides were moderate to high (72–88% ee, entries 2–4, 6–8).

Next, the preferred conformations of **$R_{3,7}$*R*-10** and **$hS_{3,7}$*hS*-10** were studied in $CDCl_3$ solution using ^{1}H NMR spectroscopy. Fig. 3 shows a solvent perturbation experiment involving the addition of the strong H-bond acceptor solvent DMSO (0–10% (v/v)). Three NH [N(1)–H, N(2)–H, and N(3)–H] chemical shifts in **$R_{3,7}$*R*-10** were sensitive to the addition of the perturbing reagent DMSO (Fig. 3A). These results demonstrate that the three NH protons are solvent-exposed, suggesting that they are not intramolecularly hydrogen-bonded and are in accord with an α-helical structure. In the peptide **$hS_{3,7}$*hS*-10**, two NH [N(1)–H and N(2)–H] chemical shifts were sensitive to the addition of the perturbing reagent DMSO (Fig. 3B), indicating a 3_{10}-helical structure.[4d]

The CD spectra of the N-terminal protected linear peptides **$R_{3,7}$*R*-9** and **$hS_{3,7}$*hS*-9** and the stapled peptides **$R_{3,7}$*R*-10** and **$hS_{3,7}$*hS*-10** were measured in 2,2,2-trifluoroethanol (TFE) solution. The CD spectra of all four peptides showed negative maxima at around 204 and 222 nm, indicating a right-handed helical-screw sense (*P*) (Fig. 4).[13] The *R* ratio ($\theta_{222}/\theta_{204}$) suggested that the dominant secondary structure of the linear **$R_{3,7}$*R*-9** peptide was a 3_{10}-helix (*R*=0.3)[13,14] and that of the corresponding stapled **$R_{3,7}$*R*-10** peptide was an α-helix (*R*=0.8, Fig. 4A).[13] The dominant secondary structures of both the linear peptide **$hS_{3,7}$*hS*-9** and the stapled peptide **$hS_{3,7}$*hS*-10** were 3_{10}-helices (*R*=0.3, Fig. 4B).[14] The intensity of the CD spectrum for the stapled peptide **$hS_{3,7}$*hS*-10** was increased compared with that of the linear peptide **$hS_{3,7}$*hS*-9**, indicating that the stapled peptide **$hS_{3,7}$*hS*-10** formed a more helical structure than the linear peptide **$hS_{3,7}$*hS*-9**.[14]

The stapled peptide **$R_{3,7}$*R*-10** formed good crystals for X-ray crystallographic analysis by slow evaporation of the solvent $CHCl_3$/*n*-hexane at room temperature. The crystal and diffraction parameters of **$R_{3,7}$*R*-10** are summarized in Table 3, and the relevant

Table 2
Asymmetric epoxidation of α,β-unsaturated ketones (**11a**–**h**) using **H-*hS*$_{3,7}$*hS*-10**



11a-11h **12a-12h**

Entry	Substrate	Yield (%)	ee (%)
1	**11a**: R^1=Ph, R^2=Ph	98	99
2	**11b**: R^1=Ph, R^2=Me	49	72
3	**11c**: R^1=Ph, R^2=^{i}Pr	78	86
4	**11d**: R^1=Ph, R^2=^{t}Bu	60	88
5	**11e**: R^1=Ph, R^2=2-furanyl	99	99
6	**11f**: R^1=Me, R^2=Ph	99	72
7	**11g**: R^1=4-Cl–Ph, R^2=Ph	99	85
8	**11h**: R^1=4-MeO–Ph, R^2=Ph	87	74

To obtain information on the preferred conformations of the N-terminal protected stapled peptides **$R_{3,7}$*R*-10** and **$hS_{3,7}$*hS*-10**, the FT-IR spectra of the NH-stretching region (amide A: 3250–3500 cm^{-1}) were measured in $CDCl_3$ solution (Fig. 2, peptide concentration: 1.0 mM). The weak bands around the 3430 cm^{-1} region were assigned to free (solvated) peptide NH groups, and the strong bands around the 3330 cm^{-1} region were assigned to peptide NH groups with N–H···O=C intramolecular H-bonds. The IR spectra of both **$R_{3,7}$*R*-10** and **$hS_{3,7}$*hS*-10** were very similar to those of helical peptides in solution.[12]

backbone and side-chain torsion angles, and intra- and intermolecular hydrogen-bond parameters are listed in Tables 4 and 5, respectively. Data collection was performed on Bruker AXS SMART APEX imaging plate diffractometers using graphite-monochromated Mo Kα radiation. All crystals remained stable during the X-ray-data collection. The structure of **$R_{3,7}$*R*-10** was solved using the SHELXS 97 direct method[15] and expanded by the Fourier technique.[16] All non-H-atoms were given anisotropic

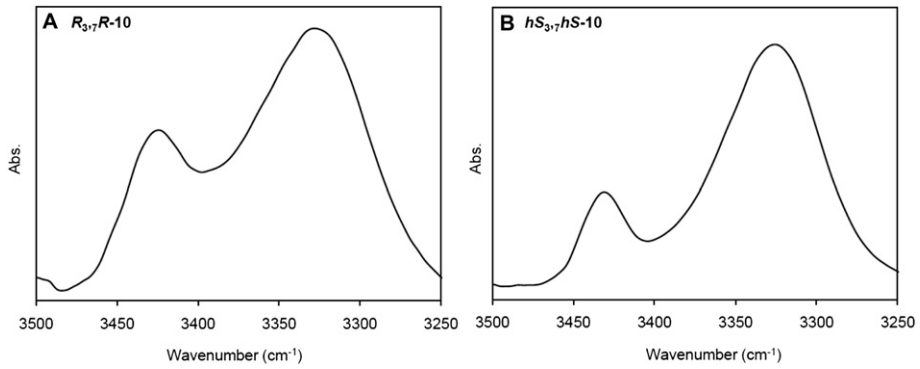


Fig. 2. FT-IR spectra (3250–3500 cm^{-1} region) of (A) ***R***$_{3,7}$***R*-10** and (B) ***hS***$_{3,7}$***hS*-10** in $CDCl_3$ solution. Peptide concentration: 1.0 mM.

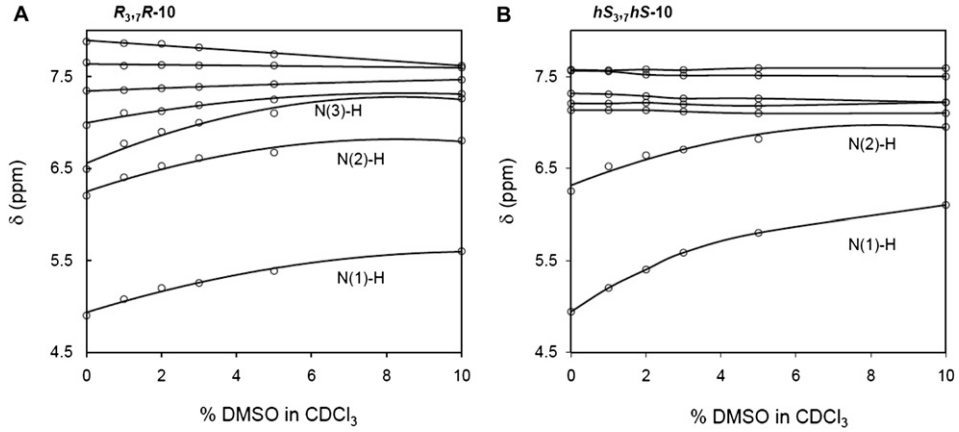


Fig. 3. ^{1}H NMR experiment involving the addition of DMSO to the $CDCl_3$ solution of (A) ***R***$_{3,7}$***R*-10** and (B) ***hS***$_{3,7}$***hS*-10**. Plots of NH chemical shifts in the ^{1}H NMR spectra of ***R***$_{3,7}$***R*-10** and ***hS***$_{3,7}$***hS*-10** as a function of increasing concentrations of DMSO (v/v) being added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

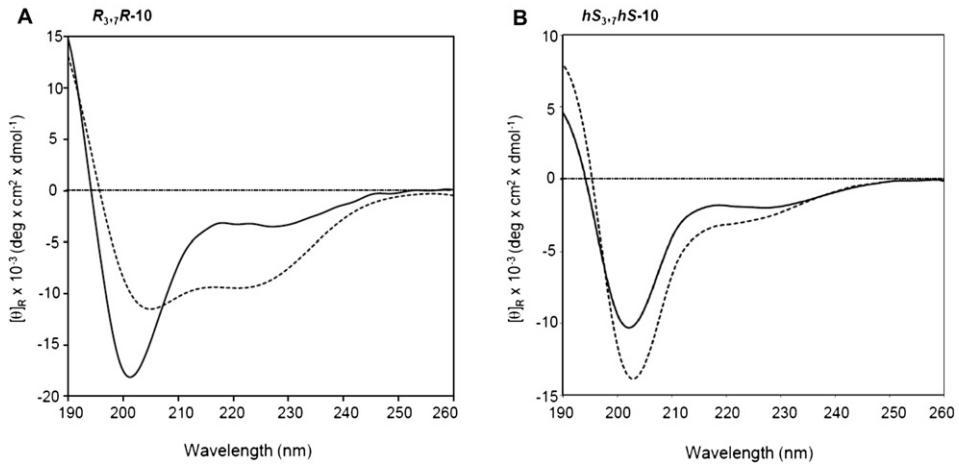


Fig. 4. 190–260 nm Region of the CD spectra of (A) the linear peptide ***R***$_{3,7}$***R*-9** (solid line) and the stapled peptide ***R***$_{3,7}$***R*-10** (dashed line), and (B) the linear peptide ***hS***$_{3,7}$***hS*-9** (solid line) and the stapled peptide ***hS***$_{3,7}$***hS*-10** (dashed line) in TFE solution. Peptide concentration: 0.5 mM.

thermal parameters, some H-atoms were refined isotropically, and the remaining H-atoms were placed at the calculated positions. The final cycle of full-matrix least-squares refinement of ***R***$_{3,7}$***R*-10** gave an R_1 factor of 0.0719 on the basis of 4202 ($I>2\sigma(I)$) reflections and an *Rw* factor of 0.2165 for all data.[17]

In the asymmetric unit of the stapled peptide ***R***$_{3,7}$***R*-10**, only one right-handed (*P*) α-helical conformer of the peptide molecule was detected, together with a chloroform molecule. The mean values of the ϕ and ψ torsion angles of amino acid residues (1–6) were −67.2° and −46.9°, respectively, which are close to the values for an ideal right-handed (*P*) α-helix (−60° and −45°), and the torsion angles of D-Ser (7) were distorted (ϕ=65.0°, ψ=−170.5°). Fig. 5 shows the X-ray structure of the (*P*) α-helical wheel as viewed from positions perpendicular to and along the helical axis. Three intramolecular hydrogen bonds, which formed a 13-membered (atoms) pseudo ring of the $i\leftarrow i+4$ type, were observed between the H–N(4) and C(0)=O(0) [N(4)···O(0)=2.92 Å], the H–N(5) and C(1)=O(1) [N(5)···O(1)=3.17 Å], and the H–N(7) and C(3)=O(3) groups

Table 3
Crystal and diffraction parameters for ***R***$_{3,7}$***R*-10**

Formula	$C_{44}H_{79}O_{12}N_7$, $CHCl_3$
M_r	1017.51
Crystal dimensions [mm]	0.40×0.30×0.01
T [K]	240
Crystal system	Monoclinic
a, b, c [Å]	10.728, 18.340, 14.943
α, β, γ [°]	90, 105.782, 90
V [Å^3]	2829.3
Spacer group	$P2_1$
Z	2
D calcd [g/cm^3]	1.194
μ (Mo Kα) [cm^{-1}]	0.22
No. of observations	4202 ($I>2\sigma(I)$)
No. of variables	604
R_1, R_w	0.0719, 0.2165
Solvent	$CHCl_3$/*n*-hexane

Table 4
Selected torsion angles (ω, ϕ, ψ, and χ [°]) for ***R***$_{3,7}$***R*-10**

Residue	Torsion angle			
	ϕ	ψ	ω	χ
L-Leu(1)	−75.2	−50.5	176.3	−70.0
L-Leu(2)	−62.2	−38.5	176.5	−172.9
D-Ser(3)	−52.6	−52.3	−177.9	165.6
Aib(4)	−57.7	−37.4	−178.9	—
L-Leu(5)	−67.8	−28.7	179.1	−62.7
L-Leu(6)	−87.9	−74.2	−176.7	−65.5
D-Ser(7)	65.0	−170.5	−176.1	−69.9

Table 5
Intra- and intermolecular H-bond parameters for ***R***$_{3,7}$***R*-10**[a]

Donor D—H	Acceptor A	Distance D···A	Angle [°] D—H···A	Symmetry operations
N_4—H	O_0	2.92	158.2	*x*, *y*, *z*
N_5—H	O_1	3.17	150.7	*x*, *y*, *z*
N_6—H	O_2	3.26[b]	143.0	*x*, *y*, *z*
N_7—H	O_3	2.92	140.3	*x*, *y*, *z*
N_1—H	$O_{4'}$	3.04	161.7	1+*x*, *y*, *z*
N_2—H	$O_{5'}$	3.03	151.3	1+*x*, *y*, *z*
N_3—H	$O_{6'}$	2.96	154.6	1+*x*, *y*, *z*
CCl_3—H	$O_{5'}$	3.12	172.9	1+*x*, *y*, *z*

[a] The amino acid numbering begins at the N-terminus of the peptide chain.
[b] The distance is a bit long for a hydrogen bond.

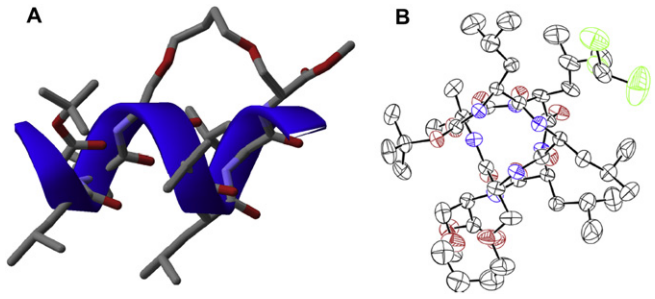


Fig. 5. X-ray diffraction structure of ***R***$_{3,7}$***R*-10**, (A) as viewed perpendicular to the helical axis and (B) an ORTEP drawing as viewed along the helical axis.

[N(7)···O(3)=2.92 Å], and one weak intramolecular hydrogen bond was detected between the H—N(6) and C(2)=O(2) groups [N(6)···O(2)=3.26 Å]. In packing mode, three intermolecular hydrogen bonds were formed between the H—N(1) and O(4′) [N(1)···O(4′)=3.04 Å], the H—N(2) and O(5′) [N(2)···O(5′)=3.03 Å], and the H—N(3) and O(6′) [N(3)···O(6′)=2.96 Å] groups. Furthermore, the chloroform molecule was held in place by a weak hydrogen bond between H—CCl_3 and O(5′) [Cl_3C···O(5′)=3.12 Å].[18] The helical molecules were connected by intermolecular hydrogen bonds, forming head-to-tail aligned chains, as shown in Fig. 6.

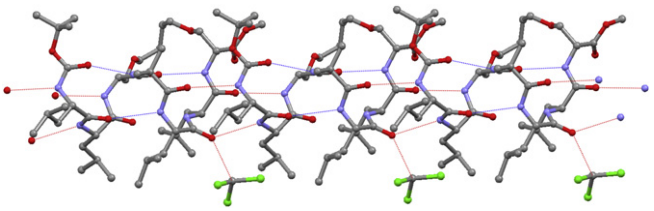


Fig. 6. Packing of ***R***$_{3,7}$***R*-10** in the crystalline state. The intramolecular (blue) and intermolecular (red) hydrogen bonds are indicated as dashed lines.

The dominant conformations of the stapled heptapeptides ***R***$_{3,7}$***R*-10** and ***hS***$_{3,7}$***hS*-10** in solution were found to be helical structures. Judging from *R* values of their CD spectra in TFE solution, the peptide ***hS***$_{3,7}$***hS*-10**, which contained cross-linked L-homoserine derivatives at its third and seventh positions, formed a stable right-handed (*P*) 3_{10}-helix, as reported by O'Leary and Grubbs.[5] On the other hand, the peptide ***R***$_{3,7}$***R*-10**, which is tethered by D-serine derivatives at the third and seventh positions, formed a (*P*) α-helix. These results might be attributed to the fact that the *R* configurations of the third and seventh D-serine residues and the length of C—C tether stabilize α-helices more than 3_{10}-helices.

The N-terminal free stapled peptides catalyzed the enantioselective epoxidation of α,β-unsaturated ketones to afford epoxides with higher enantioselectivities than those produced using the linear peptides. Among the stapled peptides, the use of **H-*hS***$_{3,7}$***hS*-10** gave epoxides with the highest enantioselectivity, even though the corresponding N-terminal protected peptide ***hS***$_{3,7}$***hS*-10** formed a 3_{10}-helix. According to Roberts' model, the three N-terminal protons in α-helical peptides without an N-terminal N(1)—H proton, N(2)—H, N(3)—H, and N(4)—H, are crucial for asymmetric induction.[9b,19] In addition, 3_{10}-helical peptides possess less catalytic activity than α-helical peptides.[9e,20] Taking these points into account, N-terminal free **H-*hS***$_{3,7}$***hS*-10** might form a mixture of α/3_{10}-helices under our reaction conditions.[21] Although ***R***$_{3,7}$***R*-10** was folded into a right-handed (*P*) α-helix, the enantioselectivity of the epoxychalcone **11a** produced using N-terminal free **H-*R***$_{3,7}$***R*-10** was lower than that produced using **H-*hS***$_{3,7}$***hS*-10**. This can be attributed to the fact that having a third D-serine residue with an *R* configuration, which results in the formation of a hydrogen bond with the chalcone peroxide enolate, is less favorable than the *S* configuration produced by a third L-homoserine residue.[9b,19]

3. Conclusion

We have synthesized L-Leu-rich peptides that are tethered by L-serine, D-serine, and L-homoserine derivatives at their third and seventh positions. All N-terminal free stapled peptides were successfully used as chiral catalysts for the enantioselective epoxidation of (*E*)-chalcone. In addition, the use of **H-*hS***$_{3,7}$***hS*-10** gave epoxide products of α,β-unsaturated ketones with high enantioselectivities. Our results provide valuable information for the design of stabilized short helical peptides, which can be applied to asymmetric reactions.

4. Experimental

4.1. General methods

Optical rotations $[\alpha]_D$ were measured with JASCO P-2200 polarimeter using a 1.0 dm cell in $CHCl_3$. ^{1}H NMR spectra were

recorded on a Varian AS 400 spectrometer in $CDCl_3$ with tetramethylsilane used as an internal standard. FT-IR spectra were recorded on a JASCO FT-IR-4100 spectrometer at 1 cm^{-1} resolution, with an average of 128 scans used for the solution ($CDCl_3$) method and a 0.1 mM path length for NaCl cells. ESI-MS spectra were taken on a SHIMADZU LCMS-IT-TOF spectrometer. CD spectra were recorded with a Jasco J-720 W spectropolarimeter using a 1.0 mm path length cell. 2,2,2-Trifluoroethanol (TFE) was used as a solvent.

(***S***)-**1**, (***R***)-**1**, and (***S***)-**2** were synthesized in accordance with Ref. 22.

*4.1.1. O-Allyl-L-serine methyl ester (L-Ser(O-allyl)-OMe) hydrochloride [(**S**)-**3**].* Compound (***S***)-**1** (24 mmol, 5.9 g) in 1 M HCl in MeOH (100 mL) was stirred at room temperature for 12 h. The solution was then evaporated to give (***S***)-**3** (4.7 g, quant.) as colorless crystals, which were used next reaction without further purification. Colorless crystals; mp 99–101 °C; $[\alpha]_D^{24}$ +14.8 (*c* 0.30, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.91 (m, 1H), 5.21–5.35 (m, 2H), 4.30 (m, 1H), 4.04–4.08 (m, 2H), 3.93 (d, *J*=4.4 Hz, 1H), 3.91 (d, *J*=4.8 Hz, 1H), 3.85 (s, 3H), ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 135.1, 118.3, 73.3, 67.9, 54.4; [HR-ESI(+)]: *m*/*z* calcd for $C_7H_{13}NO_3Na$ $[M+Na]^+$ 182.0793: found 182.0794.

*4.1.2. O-Allyl-D-serine methyl ester (D-Ser(O-allyl)-OMe) hydrochloride [(**R**)-**3**].* Compound (***R***)-**3** was prepared using a similar method to that described for the preparation of (***S***)-**3**. $[\alpha]_D^{24}$ −14.2 (*c* 0.30, MeOH).

*4.1.3. O-Allyl-L-homoserine methyl ester (L-Hse(O-allyl)-OMe) hydrochloride [(**S**)-**4**].* Compound (***S***)-**4** was prepared using a similar method to that described for the preparation of (***S***)-**3**. Yellow oil; $[\alpha]_D^{24}$ +24.8 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.91 (m, 1H), 5.19–5.30 (m, 2H), 4.17 (m, 1H), 4.00 (d, *J*=1.2 Hz, 1H), 3.94 (d, *J*=1.2 Hz, 1H), 3.83 (s, 3H), 3.70–3.74 (m, 2H), 2.17–2.24 (m, 2H), ^{13}C NMR (100 MHz, CD_3OD) δ 170.7, 135.8, 117.5, 73.0, 66.7, 53.7, 52.5, 31.2; [HR-ESI(+)]: *m*/*z* calcd for $C_8H_{15}NO_3Na$ $[M+Na]^+$ 196.0950: found 196.0948.

*4.1.4. Boc-L-Leu-L-Leu-L-Ser(O-allyl)-OMe [(**S**)-**5**].* A mixture of Boc-(L-Leu)$_2$-OH (12.2 g, 35.5 mmol), (***S***)-**3** (6.9 g, 35.5 mmol), EDC (8.2 g, 42.6 mmol), HOBt (5.8 g, 42.6 mmol), and DIPEA (13.6 mL, 78.1 mmol) in CH_2Cl_2 (300 mL) was stirred at room temperature for 12 h. The solution was then evaporated, diluted with AcOEt (300 mL), washed with 3% aqueous HCl, 5% $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a white solid, which was purified by column chromatography on silica gel (*n*-hexane/AcOEt=2:1) to give (***S***)-**5** (16.4 g, 95%) as colorless crystals. Mp 120–121 °C; $[\alpha]_D^{24}$ −23.8 (*c* 0.80, $CHCl_3$); IR (in $CDCl_3$): ν 3432, 3342, 2960, 2872, 1672, 1506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J*=8.8 Hz, 1H), 6.48 (d, *J*=8.8 Hz, 1H), 5.83 (m, 1H), 5.18–5.26 (m, 2H), 4.84 (br s, 1H), 4.69 (m, 1H), 4.50 (m, 1H), 4.11 (m, 1H), 3.98 (m, 2H), 3.87 (m, 1H), 3.76 (s, 3H), 3.63 (q, *J*=4.4 Hz, 1H), 1.66–1.71 (m, 6H), 1.44 (s, 9H), 0.90–0.94 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 170.4, 134.0, 117.6, 117.4, 72.3, 72.2, 69.3, 52.9, 52.6, 51.5, 41.1, 41.0, 40.9, 28.3, 24.8, 24.7, 24.6, 23.0, 22.8, 22.0, 21.9, 21.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{24}H_{43}N_3O_7Na$ $[M+Na]^+$ 508.2999: found 508.2991.

*4.1.5. Boc-L-Leu-L-Leu-D-Ser(O-allyl)-OMe [(**R**)-**5**].* Tripeptide (***R***)-**5** was prepared using a similar method to that described for the preparation of (***S***)-**5**. 57% yield; Colorless crystals; mp 121–122 °C; $[\alpha]_D^{24}$ −59.3 (*c* 0.20, $CHCl_3$); IR (in $CDCl_3$) ν 3431, 3344, 2960, 2874, 1678, 1501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J*=8.8 Hz, 1H), 6.46 (d, *J*=8.8 Hz, 1H), 5.82 (m, 1H), 5.26–5.17 (m, 2H), 4.83 (br s, 1H), 4.69 (m, 1H), 4.51 (m, 1H), 4.10 (br s, 1H), 3.96 (d, *J*=8.8 Hz, 2H), 3.84 (d, *J*=8.8 Hz, 1H), 3.75 (s, 3H), 3.65 (d, *J*=8.8 Hz, 1H) 1.55–1.71 (m, 6H), 1.44 (s, 9H), 0.91–0.96 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.6, 170.4, 134.0, 117.6, 117.5, 72.2, 72.2, 69.3, 52.6, 52.5, 51.6, 41.2, 40.9, 40.7, 28.2, 24.8, 24.7, 24.6, 23.0, 22.8, 22.0, 21.9, 21.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{24}H_{43}N_3O_7Na$ $[M+Na]^+$ 508.2999: found 508.2996.

*4.1.6. Boc-L-Leu-L-Leu-L-Hse(O-allyl)-OMe [(**S**)-**6**].* Tripeptide (***S***)-**6** was prepared using a similar method to that described for the preparation of (***S***)-**5**. 63% yield; Colorless crystals; mp 113–115 °C; $[\alpha]_D^{24}$ −39.5 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$) ν 3326, 2960, 2872, 1676, 1502 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J*=7.2 Hz, 1H), 6.50 (d, *J*=7.6 Hz, 1H), 5.90 (m, 1H), 5.20–5.31 (m, 2H), 4.85 (br s, 1H), 4.65 (m, 1H), 4.46 (m, 1H), 4.11 (br s, 1H), 3.94 (d, *J*=5.6 Hz, 2H), 3.73 (s, 3H), 3.72 (m, 1H), 3.49–3.57 (m, 3H), 2.06–2.19 (m, 2H), 1.64–1.70 (m, 4H), 1.46 (s, 9H), 0.92–0.95 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 172.0, 171.5, 134.3, 117.3, 72.1, 66.6, 66.4, 52.3, 51.5, 50.9, 41.5, 40.9, 31.2, 28.3, 24.7, 24.6, 22.9, 22.0; [HR-ESI(+)]: *m*/*z* calcd for $C_{25}H_{45}N_3O_7Na$ $[M+Na]^+$ 522.3155: found 522.3152.

*4.1.7. Boc-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe [(**S**)-**7**].* Trifluoroacetic acid (15 mL) was added to a solution of (***S***)-**5** (6.2 g, 12.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the whole was stirred at room temperature for 1 h. Removal of the solvent afforded a crude amine, which was used without further purification. A mixture of EDC (11.3 g, 59 mmol), HOBt (8.0 g, 59 mmol), and Boc-Aib (10.0 g, 49.2 mmol) in CH_2Cl_2 (280 mL) was stirred at 0 °C for 30 min, then, a solution of amine in CH_2Cl_2 (50 mL) and DIPEA (14.7 mL, 84.4 mmol) was added. After being stirred at room temperature for 12 h, the solution was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give tetrapeptide (***S***)-**7** (5.8 g, 81%). Foam; $[\alpha]_D^{24}$ −24.3 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3439, 3335, 2961, 2874, 1677, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (br s, 1H) 7.10 (d, *J*=7.2 Hz, 1H), 6.56 (d, *J*=6.4 Hz, 1H), 5.85 (m, 1H), 5.14–5.26 (m, 2H), 4.92 (br s, 1H), 4.85 (m, 1H), 4.52 (m, 1H), 4.31 (m, 1H), 3.95–3.99 (m, 2H), 3.83 (m, 1H), 3.75 (s, 3H), 3.71 (m, 1H), 1.48–1.83 (m, 6H), 1.48 (s, 6H), 1.44 (s, 9H), 0.87–0.99 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 172.1, 172.0, 170.6, 155.2, 134.3, 117.1, 80.9, 72.0, 69.3, 56.9, 52.8, 52.6, 52.4, 51.7, 40.2, 40.1, 28.2, 28.2, 26.4, 25.0, 24.7, 23.1, 23.0, 21.5, 21.4; [HR-ESI(+)]: *m*/*z* calcd for $C_{28}H_{50}N_4O_8Na$ $[M+Na]^+$ 593.3526: found 593.3519.

*4.1.8. Boc-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe [(**R**)-**7**].* Tetrapeptide (***R***)-**7** was prepared using a similar method to that described for the preparation of (***S***)-**7**. 85% yield; Colorless crystals; mp 132–133 °C; $[\alpha]_D^{24}$ −33.3 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3429, 3334, 2961, 2874, 1673, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 7.16 (d, *J*=7.2 Hz, 1H), 6.56 (d, *J*=6.4 Hz, 1H), 5.86 (m, 1H), 5.15–5.27 (m, 2H), 4.87 (br s, 1H), 4.69 (m, 1H), 4.49 (m, 1H), 4.27 (m, 1H), 4.00 (d, *J*=6.4 Hz, 2H), 3.85 (m, 1H), 3.74 (m, 1H), 3.72 (s, 3H), 1.65–1.83 (m, 6H), 1.51 (s, 6H), 1.45 (s, 9H), 0.88–0.97 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 172.3, 172.1, 170.7, 155.3, 134.4, 117.1, 81.1, 72.2, 72.1, 69.1, 57.0, 53.1, 52.8, 52.6, 52.4, 52.2, 52.1, 51.9, 40.3, 40.0, 28.3, 28.2, 26.6, 25.1, 25.0, 24.8, 24.4, 24.2, 23.1, 23.0, 22.9, 21.6, 21.2; [HR-ESI(+)]: *m*/*z* calcd for $C_{28}H_{50}N_4O_8Na$ $[M+Na]^+$ 593.3526: found 593.3520.

*4.1.9. Boc-Aib-L-Leu-L-Leu-L-Hse(O-allyl)-OMe [(**S**)-**8**].* Tetrapeptide (***S***)-**8** was prepared using a similar method to that described for the preparation of (***S***)-**7**. 60% yield; Colorless crystals; mp 108–110 °C; $[\alpha]_D^{24}$ −29.0 (*c* 1.00, $CHCl_3$); IR (in $CDCl_3$): ν 3427, 3340, 2961, 2875, 1675, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (br s, 1H), 7.19 (br s, 1H), 6.52 (d, *J*=6.0 Hz, 1H), 5.88 (m, 1H), 5.13–5.26 (m, 2H), 4.95 (br s, 1H), 4.62 (m, 1H), 4.52 (m, 1H), 4.30 (m, 1H), 3.93–3.95 (m, 2H), 3.71 (s, 3H), 3.49 (t, *J*=7.2 Hz, 2H), 2.06–2.17 (m, 2H), 1.53–1.86 (m, 6H), 1.48 (s, 6H), 1.47 (s, 9H), 0.89–0.98 (m, 12H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 174.8, 172.2, 171.8, 155.4, 134.9, 116.8, 81.2, 71.9, 66.5, 57.0, 53.2, 52.2, 51.7, 50.1, 40.3, 40.1, 31.6, 28.2, 26.8, 25.2, 24.8, 23.2, 23.1, 21.5, 21.3; [HR-ESI(+)]: *m*/*z* calcd for $C_{29}H_{52}N_4O_8Na$ $[M+Na]^+$ 607.3683: found 607.3684.

Linear heptapeptides ***S***$_{3,7}$***S*-9**, ***S***$_{3,7}$***R*-9**, ***R***$_{3,7}$***S*-9**, ***R***$_{3,7}$***R*-9**, ***hS***$_{3,7}$***S*-9**, ***hS***$_{3,7}$***R*-9**, and ***hS***$_{3,7}$***hS*-9** were synthesized by conventional solution-phase methods by EDC and HOBt as coupling reagents.

*4.1.10. Boc-L-Leu-L-Leu-L-Ser(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (**S**$_{3,7}$**S*-9).* Foam; $[\alpha]_D^{24}$ −32.5 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3432, 3327, 2960, 2872, 1666, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.43 (br s, 1H), 7.36 (br s, 1H), 7.34 (br s, 1H), 7.10 (d, *J*=5.6 Hz, 1H), 6.74 (d, *J*=4.4 Hz, 1H), 5.77–5.92 (m, 2H), 5.11–5.27 (m, 4H), 4.87 (d, *J*=4.0 Hz, 1H), 4.72 (m, 1H), 4.46 (m, 1H), 4.25 (m, 1H), 4.07 (m, 1H), 3.92–4.03 (m, 7H), 3.76–3.83 (m, 2H), 3.74 (s, 3H), 3.69 (m, 1H), 1.44–1.84 (m, 27H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.2, 173.5, 173.1, 173.0, 170.8, 170.5, 156.7, 134.7, 133.9, 117.1, 116.9, 81.4, 72.3, 72.1, 69.5, 67.9, 57.3, 56.9, 54.1, 53.5, 52.7, 52.3, 52.0, 40.2, 39.9, 39.6, 39.5, 28.2, 27.2, 25.3, 24.9, 24.8, 23.4, 23.2, 22.9, 22.8, 22.6, 21.8, 21.5, 21.1, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 946.5841: found 946.5834.

*4.1.11. Boc-L-Leu-L-Leu-L-Ser(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (**S**$_{3,7}$**R*-9).* Foam; $[\alpha]_D^{24}$ −32.6 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3430, 3327, 2960, 2871, 1665, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=6.0 Hz, 1H), 7.48 (d, *J*=4.8 Hz, 1H), 7.38 (br s, 1H), 7.34 (d, *J*=5.6 Hz, 1H), 7.15 (d, *J*=6.0 Hz, 1H), 6.78 (d, *J*=4.0 Hz, 1H), 5.77–5.93 (m, 2H), 5.12–5.30 (m, 4H), 4.96 (d, *J*=4.0 Hz, 1H), 4.69 (m, 1H), 4.41 (m, 1H), 4.18 (m, 1H), 3.93–4.13 (m, 9H), 3.79–3.86 (m, 2H), 3.70 (s, 3H), 1.47–1.89 (m, 27H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.75.7, 174.2, 173.6, 173.3, 173.2, 171.1, 170.5, 134.7, 133.9, 117.1, 116.9, 81.5, 72.1, 71.8, 69.2, 67.9, 57.3, 56.9, 54.1, 53.7, 52.8, 52.4, 52.0, 40.2, 39.8, 39.7, 39.5, 28.3, 28.2, 27.3, 25.3, 25.0, 24.9, 24.8, 23.3, 23.1, 22.9, 22.8, 22.7, 21.8, 21.4, 21.0, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 946.5841: found 946.5830.

*4.1.12. Boc-L-Leu-L-Leu-D-Ser(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (**R**$_{3,7}$**S*-9).* Foam; $[\alpha]_D^{24}$ −6.3 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3429, 3327, 2960, 2872, 1667, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.38 (d, *J*=7.3 Hz, 1H), 7.33 (d, *J*=6.0 Hz, 1H), 7.21 (br s, 1H), 7.03 (br s, 1H), 5.76–5.91 (m, 2H), 5.13–5.26 (m, 4H), 4.94 (br s, 1H), 4.72 (m, 1H), 4.50 (m, 1H), 4.24 (m, 1H), 4.08 (m, 1H), 3.94–4.05 (m, 9H), 3.56 (m, 2H), 3.74 (s, 3H), 1.44–1.83 (m, 27H), 0.88–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 174.0, 172.9, 172.8, 172.7, 170.7, 169.8, 156.7, 134.6, 134.1, 117.4, 117.0, 81.5, 72.2, 72.0, 69.4, 68.0, 57.2, 54.6, 54.4, 53.7, 53.6, 52.7, 52.3, 51.8, 40.3, 40.0, 39.8, 39.6, 29.7, 28.3, 28.2, 27.0, 25.2, 24.9, 24.8, 24.7, 23.4, 23.3, 22.8, 21,8, 21.7, 21.2, 21.0; [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 946.5841: found 946.5837.

*4.1.13. Boc-L-Leu-L-Leu-D-Ser(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (**R**$_{3,7}$**R*-9).* Foam; $[\alpha]_D^{24}$ +1.0 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3432, 3327, 2960, 2872, 1666, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.45 (d, *J*=6.4 Hz, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.22 (br s, 1H), 7.14 (br s, 1H), 6.61 (d, *J*=4.8 Hz, 1H), 5.76–5.93 (m, 2H), 5.11–5.30 (m, 4H), 4.96 (br s, 1H), 4.69 (m, 1H), 4.46 (m, 1H), 4.21 (m, 1H), 4.09 (m, 1H), 3.80–4.04 (m, 10H), 3.70 (s, 3H), 1.44–1.82 (m, 27H), 0.91–0.99 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 174.1, 173.2, 172.8, 171.0, 169.8, 134.6, 134.2, 117.3, 117.0, 81.6, 72.1, 72.0, 69.1, 57.1, 54.6, 54.4, 53.8, 53.7, 52.9, 52.1, 40.2, 39.9, 39.8, 39.5, 28.3, 25.2, 24.9, 24.8, 24.7, 23.4, 23.3, 23.3 22.8, 21.8, 21.7, 21.0, 20.9; [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 946.5841: found 946.5834.

*4.1.14. Boc-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (**hS**$_{3,7}$**S*-9).* Foam; $[\alpha]_D^{24}$ −33.2 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3427, 3328, 2960, 2872, 1666, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=4.4 Hz, 1H), 7.47 (d, *J*=4.8 Hz, 1H), 7.38 (br s, 1H), 7.36 (d, *J*=6.0 Hz, 1H), 7.18 (d, *J*=6.4 Hz, 1H), 6.90 (br s, 1H), 5.81–5.91 (m, 2H), 5.11–5.27 (m, 4H), 5.07 (br s, 1H), 4.71 (m, 1H), 4.45 (m, 1H), 4.23 (m, 1H), 3.91–4.00 (m, 6H), 3.77 (d, *J*=5.2 Hz, 1H), 3.74 (s, 3H), 3.47–3.60 (m, 4H), 2.12 (m, 1H), 1.96 (m, 1H), 1.46–1.86 (m, 27H), 0.86–0.99 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.1, 173.4, 173.1, 173.0, 172.3, 170.8, 156.7, 134.7, 134.3, 117.6, 116.9, 81.4, 72.0, 71.9, 69.5, 67.4, 57.1, 55.2, 54.3, 53.8, 53.5, 52.7, 52.3, 51.9, 40.1, 39.7, 39.6, 39.4, 30.4, 28.3, 28.2, 27.3, 25.2, 24.9, 24.8, 23.4, 23.3, 23.2, 22.9, 22.8, 21.8, 21.4, 21.1, 20.7; [HR-ESI(+)]: *m*/*z* calcd for $C_{47}H_{84}N_7O_{12}$ $[M+H]^+$ 938.6178: found 938.6168.

*4.1.15. Boc-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (**hS**$_{3,7}$**R*-9).* Foam; $[\alpha]_D^{24}$ −27.0 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3431, 3327, 2960, 2871, 1666, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=4.4 Hz, 1H), 7.51 (d, *J*=6.0 Hz, 1H), 7.34 (d, *J*=7.2 Hz, 1H), 7.20 (d, *J*=7.2 Hz, 1H), 6.83 (br s, 1H), 5.84–5.93 (m, 2H), 5.12–5.29 (m, 4H), 4.89 (br s, 1H), 4.69 (m, 1H), 4.41 (m, 1H), 4.18 (m, 1H), 3.93–4.04 (m, 6H), 3.78–3.85 (m, 2H), 3.70 (s, 3H), 3.49–3.64 (m, 4H), 1.61–2.14 (m, 14H), 1.45–1.55 (m, 15H), 0.87–1.00 (m, 24H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.4, 173.7, 173.5, 173.3, 172.5, 171.0, 156.7, 134.6, 134.4, 117.5, 116.9, 81.3, 72.1, 72.0, 69.1, 67.2, 57.1, 55.0, 54.4, 54.1, 53.7, 52.9, 52.5, 52.0, 40.1, 39.7, 39.4, 30.5, 28.3, 28.2, 27.2, 25.2, 24.9, 24.8, 24.7, 23.5, 23.3, 23.1 22.9, 22.7, 21.8, 21.4, 21.1, 29.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{47}H_{83}N_7O_{12}Na$ $[M+Na]^+$ 938.6178: found 938.6177.

*4.1.16. Boc-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-L-Hse(O-allyl)-OMe (**hS**$_{3,7}$**hS*-9).* Foam; $[\alpha]_D^{24}$ −32.9 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3426, 3327, 2960, 2871, 1665, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=4.4 Hz, 1H), 7.48 (br s, 1H), 7.46 (br s, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.23 (d, *J*=6.0 Hz, 1H), 7.06 (br s, 1H), 5.80–5.91 (m, 2H), 5.42 (br s, 1H), 5.08–5.25 (m, 4H), 4.62 (m, 1H), 4.40 (m, 1H), 4.18 (m, 1H), 3.89–4.03 (m, 7H), 3.69 (s, 3H), 3.48–3.58 (m, 4H), 1.96–2.21 (m, 4H), 1.53–1.84 (m, 12H), 1.48 (s, 6H), 1.45 (s, 9H), 0.85–0.97 (s, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.5, 173.7, 173.2, 173.0, 172.7, 172.5, 135.0, 134.3, 117.4, 16.6, 81.3, 72.0, 71.8, 67.1, 66.3, 57.0, 54.9, 54.4, 54.2, 53.7, 52.2, 52.1, 49.8, 40.1, 39.7, 39.6, 39.3, 31.6, 39.5, 28.2, 27.2, 25.2, 24.8, 24.7, 23.4, 23.3, 23.0, 22.9, 22.7, 21.8, 21.5, 21.0, 20.7; [HR-ESI(+)]: *m*/*z* calcd for $C_{48}H_{86}N_7O_{12}$ $[M+H]^+$ 952.6334: found 952.6333.

*4.1.17. Stapled heptapeptide **S**$_{3,7}$**S*-10.* Under inert atmosphere, a solution of ***S***$_{3,7}$***S*-9** (73 mg, 0.08 mmol) and Grubbs catalyst second generation (24 mg, 0.03 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 20 h. The solution was poured in water and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford a stapled peptide, which was used for the next reaction without further purification. A solution of above peptide and $Pd(OH)_2$ (5 mg) in MeOH (4 mL) was vigorously stirred under an H_2 atmosphere for 2 h. The Pd-catalyst was filtered off, and the filtrate was concentrated in vacuo, which was purified by silica gel column chromatography (*n*-hexane/AcOEt=1:3) to afford a ***S***$_{3,7}$***S*-10** (54 mg, 76% yield). Foam; $[\alpha]_D^{24}$ −19.5 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3429, 3321, 2959, 2874, 1666, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=9.2 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 1H), 7.37 (d, *J*=7.6 Hz, 1H), 7.32 (br s, 1H), 6.81 (d, *J*=3.6 Hz, 1H), 6.69 (d, *J*=6.8 Hz, 1H), 5.06 (d, *J*=4.4 Hz, 1H), 4.80 (m, 1H), 4.60 (m, 1H), 4.34 (m, 1H), 4.03 (m, 1H), 3.84 (m, 1H), 3.78 (s, 3H), 3.66–3.76 (m, 5H), 3.36–3.56 (m, 4H), 1.45–1.83 (m, 31H), 0.86–1.00 (m, 24H); ^{13}C (100 MHz, $CDCl_3$) δ 174.5, 174.4, 173.2, 172.9, 171.1, 170.4, 156.9, 81.3, 71.3, 70.3, 70.1, 68.2, 57.4, 55.4, 54.5, 54.1, 53.3, 53.2, 52.5, 52.4, 41.3, 40.1, 40.0, 39.9, 28.3, 28.2, 26.6, 25.4, 25.3, 25.2, 24.9, 24.8, 24.6, 23.9, 23.3, 22.8,

22.7, 21.9, 21.5, 21.3, 21.0, 19.1; [HR-ESI(+)]: *m*/*z* calcd for $C_{44}H_{79}N_7O_{12}Na$ $[M+Na]^+$ 920.5684: found 920.5681.

4.1.18. Stapled heptapeptide ***S***$_{3,7}$***R*-10**. Stapled peptide ***S***$_{3,7}$***R*-10** was prepared using a similar method to that described for the preparation of ***S***$_{3,7}$***S*-10**. 62%; Foam; $[\alpha]_D^{24}$ −29.1 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3439, 3327, 2961, 2872, 1665, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.87 (d, *J*=7.2 Hz, 1H), 7.65 (d, *J*=8.8 Hz, 1H), 7.41 (br s, 1H), 7.28 (br s, 1H), 6.97 (br s, 1H), 6.63 (d, *J*=8.0 Hz, 1H), 5.01 (d, *J*=5.6 Hz, 1H), 4.61 (m, 1H), 4.37 (m, 1H), 4.32 (m, 1H), 4.06–4.16 (m, 1H), 3.74–3.86 (m, 4H), 3.70 (s, 3H), 3.40–3.49 (m, 6H), 1.44–1.86 (m, 31H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.5, 174.1, 173.5, 172.9, 172.4, 170.8, 70.9, 69.6, 66.9, 57.5, 54.2, 53.7, 53.0, 52.9, 52.1, 40.2, 40.1, 39.9, 39.4, 28.2, 26.4, 25.2, 25.0, 24.9, 24.8, 24.6, 24.5, 24.1, 23.3, 23.2, 22.9, 22.7, 22.2, 21.7, 21.3, 21.1, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{44}H_{79}N_7O_{12}Na$ $[M+Na]^+$ 920.5684: found 920.5681.

4.1.19. Stapled heptapeptide ***R***$_{3,7}$***S*-10**. Stapled peptide ***R***$_{3,7}$***S*-10** was prepared using a similar method to that described for the preparation of ***S***$_{3,7}$***S*-10**. 58%; Foam; $[\alpha]_D^{24}$ −35.0 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3439, 3328, 2960, 2873, 1667, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.41 (d, *J*=8.4 Hz, 1H), 7.33 (br s, 1H), 7.23 (d, *J*=7.3 Hz, 1H), 7.10 (br s, 1H), 6.69 (br s, 1H), 6.63 (d, *J*=6.0 Hz, 1H), 4.92 (br s, 1H), 4.70 (m, 1H), 4.33 (m, 1H), 4.21 (m, 1H), 4.03 (m, 1H), 3.52–3.81 (m, 9H), 3.40–3.51 (m, 4H), 1.45–1.90 (m, 31H), 0.85–0.10 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.7, 174.5, 173.9, 173.1, 170.3, 170.2, 157.2, 80.6, 74.1, 71.3, 71.2, 70.5, 57.3, 57.0, 54.9, 54.2, 53.8, 53.1, 52.9, 52.5, 40.1, 39.7, 28.2, 26.8, 26.5, 25.4, 25.1, 24.7, 24.3, 23.5, 23.3, 23.2, 23.1, 22.7, 22.6, 22.5, 21.9, 21.6, 21.3, 21.0, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{44}H_{79}N_7O_{12}Na$ $[M+Na]^+$ 920.5684: found 920.5673.

4.1.20. Stapled heptapeptide ***R***$_{3,7}$***R*-10**. Stapled peptide ***R***$_{3,7}$***R*-10** was prepared using a similar method to that described for the preparation of ***S***$_{3,7}$***S*-10**. 62%; Colorless crystals; mp 206–208 °C (recryst from $CHCl_3$/*n*-hexane); $[\alpha]_D^{24}$ −11.4 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3421, 3326, 2960, 2872, 1699, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.88 (br s, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.33 (br s, 1H), 6.54 (d, *J*=5.6 Hz, 1H), 6.35 (br s, 1H), 4.92 (br s, 1H), 4.67 (m, 1H), 4.50 (m, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 4.13 (m, 1H), 3.91–4.00 (m, 2H), 3.67–3.79 (m, 4H), 3.36–3.57 (m, 4H), 2.24 (t, *J*=7.2 Hz, 1H), 2.13 (m, 1H), 1.91 (m, 1H), 1.45–1.80 (m, 31H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.1, 173.5, 173.4, 173.1, 171.9, 170.6, 80.6, 70.9, 69.9, 68.4, 57.0, 54.7, 53.3, 53.0, 52.9, 52.6, 52.5, 52.3, 40.4, 40.3, 40.0, 38.6, 28.2, 25.8, 25.0, 25.2, 24.9, 24.7, 24.6, 24.5, 24.4, 23.3, 23.2, 22.9, 22.8, 21.7, 21.1, 21.0; [HR-ESI(+)]: *m*/*z* calcd for $C_{44}H_{79}N_7O_{12}Na$ $[M+Na]^+$ 920.5684: found 920.5671.

4.1.21. Stapled heptapeptide ***hS***$_{3,7}$***S*-10**. Stapled peptide ***hS***$_{3,7}$***S*-10** was prepared using a similar method to that described for the preparation of ***S***$_{3,7}$***S*-10**. 79%; Foam; $[\alpha]_D^{24}$ −14.5 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3428, 3327, 2960, 2871, 1665, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.67 (d, *J*=8.4 Hz, 1H), 7.58 (d, *J*=4.8 Hz, 1H), 7.41 (d, *J*=8.0 Hz, 1H), 7.19 (br s, 1H), 7.11 (d, *J*=7.6 Hz, 1H), 6.64 (d, *J*=4.0 Hz, 1H), 5.23 (br s, 1H), 4.87 (m, 1H), 4.53 (m, 1H), 4.36 (m, 1H), 4.03–4.08 (m, 2H), 3.91–3.98 (m, 2H), 3.78 (s, 3H), 3.51–3.56 (m, 2H), 3.36–3.49 (m, 4H), 2.43 (t, *J*=7.6 Hz, 1H), 2.02 (m, 1H), 1.44–1.87 (m, 32H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.9, 174.2, 173.7, 173.3, 172.8, 170.2, 157.1, 81.5, 70.5, 70.3, 69.9, 65.7, 57.1, 55.4, 54.8, 54.1, 53.0, 52.8, 52.5, 41.2, 40.3, 40.1, 40.0, 31.5, 28.3, 27.3, 25.9, 25.6, 25.2, 25.0, 24.8, 24.4, 23.5, 23.4, 23.1, 22.9, 22.7, 22.6, 21.8, 21.6, 21.1, 20.9; [HR-ESI(+)]: *m*/*z* calcd for $C_{45}H_{82}N_7O_{12}$ $[M+H]^+$ 912.6021: found 912.6014.

4.1.22. Stapled heptapeptide ***hS***$_{3,7}$***R*-10**. Foam; $[\alpha]_D^{24}$ −11.9 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3430, 3328, 2960, 2871, 1665, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.70 (br s, 1H), 7.66 (br s, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.52 (br s, 1H), 7.11 (d, *J*=7.2 Hz, 1H), 6.66 (d, *J*=4.8 Hz, 1H), 5.17 (br s, 1H), 4.44 (m, 1H), 4.32 (m, 1H), 4.01–4.09 (m, 2H), 3.97 (m, 1H), 3.88 (d, *J*=4.4 Hz, 1H), 3.79 (m, 1H), 3.71 (s, 3H), 3.60–3.63 (m, 3H), 3.46–3.51 (m, 2H), 3.33–3.39 (m, 2H), 1.43–2.18 (m, 33H), 0.88–1.00 (m, 24H) ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.2, 174.4, 174.0, 173.7, 173.5, 173.3, 170.5, 157.3, 80.6, 72.1, 69.8, 69.3, 65.5, 57.0, 55.4, 55.2, 54.3, 54.0, 53.3, 53.1, 52.0, 40.9, 40.2, 39.8, 39.6, 31.2, 28.3, 28.2, 27.1, 26.8, 25.1, 24.8, 24.6, 24.3, 23.4, 23.3, 23.2, 23.1, 23.0, 22.8, 22.6, 21.7, 21.6, 21.4, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{45}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 912.6021: found 912.6013.

4.1.23. Stapled heptapeptide ***hS***$_{3,7}$***hS*-10**. Stapled peptide ***hS***$_{3,7}$***hS*-10** was prepared using a similar method to that described for the preparation of ***S***$_{3,7}$***S*-10**. 87%; Colorless crystals; mp 105–107 °C; $[\alpha]_D^{24}$ −16.1 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3430, 3326, 2960, 2871, 1665, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.59 (d, *J*=2.4 Hz, 1H), 7.56 (br s, 1H), 7.31 (d, *J*=9.2 Hz, 1H), 7.22 (br s, 1H), 7.16 (d, *J*=6.8 Hz, 1H), 6.55 (d, *J*=4.4 Hz, 1H), 5.09 (br s, 1H), 4.73 (m, 1H), 4.53 (m, 1H), 4.23 (m, 1H), 3.05 (m, 1H), 4.00 (m, 1H), 3.94 (m, 1H), 3.74 (s, 3H), 3.61–3.67 (m, 2H), 3.47–3.57 (m, 2H), 3.35–3.44 (m, 4H), 1.65–2.26 (m, 20H), 1.48–1.60 (m, 15H), 0.87–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.0, 174.4, 173.7, 173.4, 173.3, 172.6, 172.3, 157.1, 81.3, 70.5, 70.3, 66.8, 66.0, 56.9, 55.3, 54.9, 54.1, 53.7, 52.4, 52.1, 49.3, 40.3, 40.2, 40.0, 39.5, 32.2, 31.2, 28.3, 28.2, 27.2, 25.4, 25.3, 25.1, 24.9, 24.8, 24.6, 23.5, 23.4, 23.1, 22.8, 22.7, 21.7, 21.6, 21.0, 20.9, 20.7; [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{84}N_7O_{12}$ $[M+H]^+$ 926.6178: found 926.6171.

*4.1.24. H-L-Leu-L-Leu-L-Ser(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (****H*-*S***$_{3,7}$***S*-9**).* Trifluoroacetic acid (0.2 mL) was added to a solution of ***S***$_{3,7}$***S*-9** (448 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the solution was stirred at room temperature for 1 h. Then, the solution was neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, N-terminal free peptide **H**-***S***$_{3,7}$***S*-9** (358 mg, 90%) was obtained, which was used as catalyst for enantioselective epoxidation without further purification. Foam; $[\alpha]_D^{24}$ −30.1 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3427, 3329, 2959, 2872, 1666, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.01 (d, *J*=3.6 Hz, 1H), 7.47 (br s, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.02 (d, *J*=6.8 Hz, 1H), 6.97 (d, *J*=5.2 Hz, 1H), 5.80–5.92 (m, 2H), 5.12–5.30 (m, 4H), 4.72 (m, 1H), 4.45 (m, 1H), 4.24 (m, 1H), 3.96–4.09 (m, 6H), 3.58–3.84 (m, 9H), 3.42 (m, 1H), 1.24–1.85 (m, 18H), 0.87–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.4, 173.5, 173.1, 173.0, 170.9, 170.5, 134.6, 133.8, 117.1, 117.0, 72.0, 71.9, 69.4, 67.8, 57.3, 56.0, 53.9, 53.5, 53.2, 52.7, 52.4, 52.0, 43.3, 39.9, 39.6, 39.5, 29.7, 27.1, 25.2, 25.1, 24.8, 24.7, 23.4, 23.3, 23.2, 22.9, 21.4, 21.3, 21.1, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{41}H_{74}N_7O_{10}$ $[M+H]^+$ 824.5497: found 824.5482.

*4.1.25. H-L-Leu-L-Leu-L-Ser(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (****H*-*S***$_{3,7}$***R*-9**).* N-Terminal free peptide **H**-***S***$_{3,7}$***R*-9** was prepared using a similar method to that described for the preparation of **H**-***S***$_{3,7}$***S*-9**. 99%; Foam; $[\alpha]_D^{24}$ −35.4 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3428, 3328, 2960, 2872, 1666, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.02 (d, *J*=4.0 Hz, 1H), 7.49 (br s, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.32 (d, *J*=4.8 Hz, 1H), 7.04 (d, *J*=5.6 Hz, 1H), 7.00 (br s, 1H), 5.80–5.92 (m, 2H), 5.14–5.28 (m, 4H), 4.70 (m, 1H), 4.42 (m, 1H), 4.19 (m, 1H), 4.08 (m, 1H), 3.98–4.04 (m, 6H), 3.81–3.86 (m, 2H), 3.69–3.80 (m, 5H), 3.40–3.43 (m, 2H), 1.50–1.87 (m, 18H), 0.87–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 177.4, 175.6, 173.6, 173.3, 173.1, 171.1, 170.5, 134.6, 133.8, 117.3, 117.0, 72.1, 71.8, 69.1, 67.8, 57.2, 55.8, 53.9, 53.7, 53.1, 52.8, 52.3, 52.1, 43.4, 40.0, 39.7, 39.5, 29.7, 27.0, 25.2, 25.1, 24.8, 24.7, 23.3, 23.2, 23.1, 22.9, 21.4, 21.2, 21.0, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{41}H_{74}N_7O_{10}$ $[M+H]^+$ 824.5497: found 824.5592.

*4.1.26. H-L-Leu-L-Leu-D-Ser(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (****H*-*R***$_{3,7}$***S*-9**).* N-Terminal free peptide **H**-***R***$_{3,7}$***S*-9** was prepared

using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 76%; Foam; $[\alpha]_D^{24}$ −7.9 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3425, 3326, 2960, 2872, 1664, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.97 (d, *J*=4.8 Hz, 1H), 7.56 (br s, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.25 (br s, 1H), 7.04 (br s, 1H), 6.63 (br s, 1H), 5.80–5.88 (m, 2H), 5.14–5.30 (m, 4H), 4.71 (m, 1H), 4.44 (m, 1H), 4.36 (m, 1H), 4.27 (m, 1H), 3.92–4.04 (m, 6H), 3.82 (m, 1H), 3.74 (s, 3H), 3.70–3.73 (m, 3H), 3.60 (m, 1H), 3.38 (m, 1H), 1.25–1.79 (m, 18H), 0.89–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.9, 172.8, 170.8, 170.2, 134.3, 133.6, 118.3, 117.2, 72.3, 72.0, 69.2, 68.7, 57.2, 54.1, 53.6, 53.3, 53.1, 52.7, 52.4, 52.0, 43.5, 39.9, 39.6, 29.7, 26.3, 25.0, 24.8, 24.7, 24.6, 23.8, 23.3, 23.2, 22.5, 22.1, 21.4, 21.2, 21.1; [HR-ESI(+)]: *m*/*z* calcd for $C_{41}H_{74}N_7O_{10}$ $[M+H]^+$ 824.5497: found 824.5576.

*4.1.27. H-L-Leu-L-Leu-D-Ser(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (**H-*R*$_{3,7}$*R*-9**).* N-Terminal free peptide **H-*R*$_{3,7}$*R*-9** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 99%; Colorless crystals; mp 186–188 °C; $[\alpha]_D^{24}$ −4.5 (*c* 1.00, $CHCl_3$); IR (in $CDCl_3$): *ν* 3424, 3326, 2960, 2872, 1666, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.97 (d, *J*=4.8 Hz, 1H), 7.56 (br s, 1H), 7.45 (d, *J*=8.0 Hz, 1H), 7.28 (d, *J*=6.8 Hz, 1H), 6.92 (d, *J*=6.8 Hz, 1H), 6.61 (d, *J*=6.4 Hz, 1H), 5.79–5.92 (m, 2H), 5.14–5.30 (m, 4H), 4.68 (m, 1H), 4.45 (m, 1H), 4.39 (m, 1H), 4.21 (m, 1H), 3.94–4.06 (m, 6H), 3.74–3.86 (m, 4H), 3.71 (s, 3H), 3.59 (m, 1H), 3.39 (m, 1H), 1.25–1.84 (m, 18H), 0.89–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.4, 173.0, 172.9, 172.8, 170.9, 170.2, 134.4, 133.7, 118.2, 117.2, 72.3, 72.1, 69.0, 68.7, 57.2, 54.1, 53.7, 53.5, 53.2, 52.8, 52.3, 52.2, 43.1, 39.9, 39.8, 39.6, 29.7, 26.4, 25.0, 24.9, 24.8, 24.7, 23.7, 23.3, 23.2, 23.1 22.6, 22.0, 21.5, 21.1; [HR-ESI(+)]: *m*/*z* calcd for $C_{41}H_{74}N_7O_{10}$ $[M+H]^+$ 824.5497: found 825.4487.

*4.1.28. H-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-L-Ser(O-allyl)-OMe (**H-*hS*$_{3,7}$*S*-9**).* N-Terminal free peptide **H-*hS*$_{3,7}$*S*-9** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 99%; Foam; $[\alpha]_D^{24}$ −24.1 (*c* 0.70, $CHCl_3$); IR (in $CDCl_3$): *ν* 3330, 2959, 2872, 1663, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.01 (d, *J*=4.0 Hz, 1H), 7.64 (d, *J*=4.8 Hz, 1H), 7.62 (br s, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.16 (d, *J*=6.0 Hz, 1H), 5.82–5.95 (m, 2H), 5.11–5.33 (m, 4H), 4.72 (m, 1H), 4.46 (m, 1H), 4.24 (m, 1H), 4.07 (m, 1H), 3.94–4.02 (m, 7H), 3.76–3.81 (m, 2H), 3.74 (s, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.40 (m, 1H), 2.05–2.08 (m, 2H), 1.24–1.83 (m, 18H), 0.87–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.9, 173.8, 173.7, 173.6, 173.4, 172.4, 171.2, 134.4, 134.2, 117.7, 117.1, 72.2, 72.0, 69.1, 67.7, 57.0, 55.7, 54.6, 53.9, 53.2, 52.9, 52.5, 52.4, 42.2, 40.0, 39.8, 39.6, 29.9, 26.9, 25.2, 25.1, 24.9, 24.8, 24.7, 24.6, 23.3, 23.2, 22.8, 22.7, 21.6, 21.0, 20.9; [HR-ESI(+)]: *m*/*z* calcd for $C_{42}H_{76}N_7O_{10}$ $[M+H]^+$ 838.5654: found 838.5668.

*4.1.29. H-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-D-Ser(O-allyl)-OMe (**H-*hS*$_{3,7}$*R*-9**).* N-Terminal free peptide **H-*hS*$_{3,7}$*R*-9** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 79%; Foam; $[\alpha]_D^{24}$ −20.2 (*c* 1.30, $CHCl_3$); IR (in $CDCl_3$): *ν* 3330, 2959, 2874, 1664, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.05 (d, *J*=3.2 Hz, 1H), 7.70 (d, *J*=4.8 Hz, 1H), 7.65 (br s, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 7.38 (d, *J*=7.6 Hz, 1H), 7.23 (d, *J*=6.0 Hz, 1H), 5.81–5.95 (m, 2H), 5.14–5.33 (m, 4H), 4.69 (m, 1H), 4.40 (m, 1H), 4.18 (m, 1H), 4.11 (m, 1H), 4.03 (d, *J*=5.6 Hz, 2H), 3.95–4.01 (m, 5H), 3.80–3.86 (m, 2H), 3.71 (s, 3H), 3.58 (m, 1H), 3.52 (m, 1H), 3.41 (m, 1H), 2.05 (m, 2H), 1.26–1.88 (m, 18H), 0.87–1.01 (m, 24H) ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.9, 173.7, 173.5, 173.4, 172.1, 171.1, 134.5, 134.1, 117.8, 117.1, 72.3, 72.1, 69.0, 68.0, 57.1, 55.7, 54.2, 53.8, 52.8, 52.5, 52.3, 43.1, 40.1, 39.7, 39.5, 29.6, 27.0, 25.1, 25.0, 24.8, 24.7, 23.3, 23.1, 22.9, 22.8, 21.4, 21.3, 21.0, 20.8; [HR-ESI(+)]: *m*/*z* calcd for $C_{42}H_{76}N_7O_{10}$ $[M+H]^+$ 838.5654: found 838.5640.

*4.1.30. H-L-Leu-L-Leu-L-Hse(O-allyl)-Aib-L-Leu-L-Leu-L-Hse(O-allyl)-OMe (**H-*hS*$_{3,7}$*hS*-9**).* N-Terminal free peptide **H-*hS*$_{3,7}$*hS*-9** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 89%; Foam; $[\alpha]_D^{24}$ −31.6 (*c* 1.00, $CHCl_3$); IR (in $CDCl_3$): *ν* 3329, 2959, 2872, 1663, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.01 (d, *J*=3.6 Hz, 1H), 7.67 (br s, 1H), 7.63 (d, *J*=4.8 Hz, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.30 (d, *J*=8.8 Hz, 1H), 7.19 (d, *J*=5.6 Hz, 1H), 5.83–5.95 (m, 2H), 5.10–5.34 (m, 4H), 4.62 (m, 1H), 4.46 (m, 1H), 4.21 (m, 1H), 4.08 (m, 1H), 3.96–4.01 (m, 5H), 3.93 (d, *J*=5.6 Hz, 2H), 3.71 (s, 3H), 3.59 (m, 1H), 3.51 (t, *J*=6.8 Hz, 3H), 3.41 (m, 1H), 2.16–2.23 (m, 2H), 2.03–2.12 (m, 2H), 1.25–1.84 (m, 18H), 0.87–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.0, 173.7, 173.4, 173.2, 172.6, 172.2, 135.0, 134.1, 117.8, 116.6, 72.3, 71.8, 68.0, 66.3, 57.1, 55.9, 54.3, 53.8, 53.0, 52.2, 49.8, 43.0, 40.1, 39.7, 39.4, 31.5, 29.7, 27.1, 25.1, 25.0, 24.8, 24.7, 23.4, 23.3, 23.1, 23.0, 22.8, 21.4, 21.3, 20.9, 20.7; [HR-ESI(+)]: *m*/*z* calcd for $C_{43}H_{78}N_7O_{10}$ $[M+H]^+$ 852.5810: found 852.5809.

*4.1.31. N-Terminal free stapled peptide **H-*S*$_{3,7}$*S*-10**.* N-Terminal free stapled peptide **H-*S*$_{3,7}$*S*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 88%; Foam; $[\alpha]_D^{24}$ −25.8 (*c* 0.20, $CHCl_3$); IR (in $CDCl_3$): *ν* 3422, 3326, 2960, 2872, 1667, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.94 (d, *J*=4.4 Hz, 1H), 7.49 (br s, 1H), 7.38 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 1H), 6.54 (d, *J*=6.8 Hz, 1H), 4.75 (m, 1H), 4.46–4.52 (m, 2H), 4.36 (m, 1H), 4.16 (m, 1H), 4.00–4.07 (m, 3H), 3.67–3.82 (m, 5H), 3.38–3.51 (m, 5H), 3.34 (m, 1H), 1.26–2.05 (m, 22H), 0.85–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.9, 173.5, 173.2, 173.1, 171.2, 171.1, 171.0, 71.2, 70.4, 69.8, 68.2, 57.1, 55.1, 54.6, 53.7, 53.6, 53.3, 53.0, 52.7, 41.7, 40.7, 40.2, 39.8, 29.7, 29.3, 25.8, 25.5, 25.4, 24.9, 24.7, 24.4, 24.3, 23.1, 22.6, 22.5, 21.9, 21.6, 21.4, 21.3; [HR-ESI(+)]: *m*/*z* calcd for $C_{39}H_{72}N_7O_{10}$ $[M+H]^+$ 798.5341: found 798.5329.

*4.1.32. N-Terminal free stapled peptide **H-*S*$_{3,7}$*R*-10**.* N-Terminal free peptide **H-*S*$_{3,7}$*R*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 93%; Foam; $[\alpha]_D^{24}$ −50.9 (*c* 0.25, $CHCl_3$); IR (in $CDCl_3$): *ν* 3424, 3330, 2960, 2872, 1666, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.92 (d, *J*=4.8 Hz, 1H), 7.53 (br s, 1H), 7.50 (br s, 1H), 7.44 (br s, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 6.52 (d, *J*=7.2 Hz, 1H), 4.48–4.55 (m, 2H), 4.33–4.40 (m, 2H), 4.21 (m, 1H), 4.04 (m, 1H), 3.85 (m, 1H), 3.75 (d, *J*=6.0 Hz, 2H), 3.71 (s, 3H), 3.55 (m, 1H), 3.43–3.51 (m, 4H), 3.32–3.37 (m, 2H), 1.24–1.86 (m, 22H), 0.86–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.7, 173.6, 173.2, 173.1, 171.1, 171.0, 170.8, 71.1, 70.1, 69.6, 67.5, 57.2, 54.9, 54.1, 53.6, 53.4, 53.3, 53.1, 52.3, 42.4, 41.2, 40.4, 39.8, 29.7, 25.7, 25.3, 25.1, 25.0, 24.9, 24.7, 24.5, 23.2, 23.1, 22.8, 22.7, 21.7, 21.5, 21.2, 20.9; [HR-ESI(+)]: *m*/*z* calcd for $C_{39}H_{72}N_7O_{10}$ $[M+H]^+$ 798.5341: found 798.5311.

*4.1.33. N-Terminal free stapled peptide **H-*R*$_{3,7}$*S*-10**.* N-Terminal free peptide **H-*R*$_{3,7}$*S*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 82%; Foam; $[\alpha]_D^{24}$ −18.8 (*c* 1.00, $CHCl_3$); IR (in $CDCl_3$): *ν* 3425, 3324, 2960, 2872, 1665, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.88 (d, *J*=5.6 Hz, 1H), 7.53 (d, *J*=6.8 Hz, 1H), 7.52 (br s, 1H), 7.38 (d, *J*=13.2 Hz, 1H), 7.16 (d, *J*=8.8 Hz, 1H), 6.53 (br s, 1H), 4.66 (m, 1H), 4.50 (m, 1H), 4.34 (m, 1H), 4.15 (m, 1H), 4.04 (m, 1H), 3.90 (m, 1H), 3.78–3.84 (m, 2H), 3.74 (s, 3H), 3.57–3.72 (m, 2H), 3.34–3.52 (m, 6H), 1.24–1.96 (m, 22H), 0.87–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.9, 174.1, 173.6, 173.4, 173.1, 171.0, 170.7, 71.5, 71.4, 70.5, 70.3, 57.5, 57.3, 53.9, 53.6, 53.4, 53.2, 52.8, 52.6, 43.8, 40.2, 40.0, 39.4, 26.5, 26.2, 25.3, 25.1, 25.0, 24.6, 23.5, 23.4, 23.1, 22.8, 22.7, 22.2, 21.8, 21.6, 21.5, 21.4; [HR-ESI(+)]: *m*/*z* calcd for $C_{39}H_{72}N_7O_{10}$ $[M+H]^+$ 798.5341: found 798.5338.

*4.1.34. N-Terminal free stapled peptide **H-*R*$_{3,7}$*R*-10**.* N-Terminal free peptide **H-*R*$_{3,7}$*R*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 96%; Foam; $[\alpha]_D^{24}$ −22.0 (*c* 0.50, $CHCl_3$); IR (in $CDCl_3$): *ν* 3423, 3330, 2960, 2872, 1668,

1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=6.8 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.52 (br s, 1H), 7.06 (d, J=7.2 Hz, 1H), 6.41 (d, J=7.6 Hz, 1H), 6.10 (d, J=7.2 Hz, 1H), 4.63 (m, 1H), 4.46–4.54 (m, 2H), 4.28–4.37 (m, 2H), 4.11–4.22 (m, 2H), 4.00 (m, 1H), 3.78–3.86 (m, 2H), 3.70 (s, 3H), 3.44–3.52 (m, 5H), 3.33 (m, 1H), 1.24–2.19 (m, 22H), 0.90–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.9, 173.6, 173.3, 172.8, 171.2, 171.0, 71.3, 70.6, 70.5, 69.9, 57.5, 56.8, 54.7, 53.8, 53.5, 53.3, 52.7, 52.5, 40.4, 40.1, 29.9, 29.8, 25.4, 25.3, 25.1, 25.0, 23.6, 23.5, 23.4, 23.3, 23.2, 23.0, 22.0, 21.8, 21.7, 21.4, 21.3, 21.2; [HR-ESI(+)]: m/z calcd for $C_{39}H_{71}N_7O_{10}Na$ $[M+Na]^+$ 820.5160: found 820.5152.

4.1.35. N-Terminal free stapled peptide ***H-hS$_{3,7}$S-10***. N-Terminal free peptide **H-*hS*$_{3,7}$*S*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 99%; Foam; $[\alpha]_D^{24}$ −19.1 (c 1.00, $CHCl_3$); IR (in $CDCl_3$): ν 3322, 2958, 2874, 1663, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.78 (br s, 1H), 7.55 (br s, 1H), 7.41 (br s, 1H), 7.24 (br s, 1H), 7.21 (br s, 1H), 4.83 (m, 1H), 4.41 (m, 1H), 4.26 (m, 1H), 4.15 (m, 1H), 4.08 (m, 1H), 3.86 (m, 1H), 3.77 (s, 3H), 3.75 (d, J=6.8 Hz, 2H), 3.56–3.58 (m, 2H), 3.39–3.50 (m, 6H), 2.02–2.05 (m, 2H), 1.26–1.92 (m, 22H), 0.86–1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 174.9, 174.7, 174.1, 173.5, 173.4, 170.9, 70.5, 69.8, 69.4, 65.8, 56.6, 54.7, 54.1, 53.7, 53.4, 53.0, 52.7, 52.4, 43.1, 43.0, 40.8, 40.0, 26.5, 25.7, 25.6, 24.9, 24.8, 24.7, 24.6, 24.4, 23.2, 23.1, 22.9, 22.5, 21.8, 21.7, 21.2, 21.1; [HR-ESI(+)]: m/z calcd for $C_{40}H_{74}N_7O_{10}$ $[M+H]^+$ 812.5497: found 812.5496.

4.1.36. N-Terminal free stapled peptide ***H-hS$_{3,7}$R-10***. N-Terminal free peptide **H-*hS*$_{3,7}$*R*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 61%; Foam; $[\alpha]_D^{24}$ −34.8 (c 0.50, $CHCl_3$); IR (in $CDCl_3$): ν 3328, 2959, 2874, 1664, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=4.4 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.52 (br s, 1H), 7.41 (br s, 1H), 7.22 (br s, 1H), 6.57 (br s, 1H), 4.42 (m, 1H), 4.34 (m, 1H), 4.23 (m, 1H), 4.11 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 3.71 (s, 3H), 3.60 (m, 1H), 3.55 (m, 1H), 3.41–3.51 (m, 7H), 3.35 (m, 1H), 1.93–2.14 (m, 2H), 1.25–1.88 (m, 22H), 0.87–1.02 (m, 24H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.3, 174.3, 173.8, 173.3, 171.5, 171.0, 71.7, 70.4, 69.0, 66.4, 57.4, 56.8, 54.7, 54.3, 54.1, 53.9, 53.8, 52.6, 43.1, 40.5, 40.2, 40.1, 31.1, 26.7, 26.2, 25.6, 25.1, 24.9, 24.8, 24.0, 23.5, 23.4, 23.3, 23.2, 22.9, 21.9, 21.8, 21.6, 21.5; [HR-ESI(+)]: m/z calcd for $C_{40}H_{74}N_7O_{10}$ $[M+H]^+$ 812.5497: found 812.5478.

4.1.37. N-Terminal free stapled peptide ***H-hS$_{3,7}$hS-10***. N-Terminal free peptide **H-*hS*$_{3,7}$*hS*-10** was prepared using a similar method to that described for the preparation of **H-*S*$_{3,7}$*S*-9**. 74%; Foam; $[\alpha]_D^{24}$ −33.8 (c 0.82, $CHCl_3$); IR (in $CDCl_3$): ν 3329, 2958, 2874, 1664, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=4.4 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H), 7.30 (d, J=6.8 Hz, 1H), 7.28 (br s, 1H), 7.09 (d, J=4.8 Hz, 1H), 6.82 (d, J=7.2 Hz, 1H), 4.66 (m, 1H), 4.49 (m, 1H), 4.26 (m, 1H), 4.17 (m, 1H), 4.09 (m, 1H), 3.73 (s, 3H), 3.57 (m, 1H), 3.37–3.54 (m, 10H), 2.18–2.25 (m, 2H), 1.91–2.11 (m, 2H), 1.25–1.85 (m, 22H), 0.87–1.02 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 174.6, 174.4, 173.8, 173.1, 173.0, 70.7, 70.6, 66.8, 66.4, 56.9, 55.0, 54.8, 54.3, 53.6, 52.9, 52.7, 49.9, 42.9, 40.4, 40.1, 40.0, 31.9, 31.4, 26.8, 25.7, 25.6, 25.2, 25.1, 24.9, 24.8, 23.6, 23.5, 23.4, 23.2, 22.9, 21.9, 21.8, 21.2, 21.1; [HR-ESI(+)]: m/z calcd for $C_{41}H_{76}N_7O_{10}$ $[M+H]^+$ 826.5654: found 826.5651.

4.2. General procedure for peptide-catalyzed asymmetric epoxidation of chalcone

THF (2 mL) was added to the mixture of peptide **H-*R*$_{3,7}$*R*-2** (12 mg, 0.015 mmol) and (*E*)-chalcone (**11a**) (63 mg, 0.3 mmol) in a screw vial equipped with a magnetic stirring bar. Urea hydrogen peroxide (31 mg, 0.33 mmol) and DBU (11.3 μL, 1.68 mmol) were added at 0 °C, and the mixture was gradually warmed to room temperature. After being stirred for 24 h, the reaction mixture was diluted with AcOEt, and washed with saturated aqueous $Na_2S_2O_3$. Then, organic layer was evaporated to give an oily residue, which was purified by silica gel column chromatography (*n*-hexane/AcOEt=20:1) to afford a (2*R*,3*S*)-**12a** (60 mg, 89% yield, 69% ee). Colorless crystals; $[\alpha]_D^{23}$ −183.6 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–8.02 (m, 2H), 7.36–7.62 (m, 8H), 4.29 (d, J=1.6 Hz, 1H), 4.08 (d, J=1.6 Hz, 1H). HPLC (DAICEL Chiralpak AD column, 4.6 mmϕ×250 mm; 10% EtOH in hexane; flow rate, 1.0 mL/min): retention time (t_R)=19.1 min (2*R*,3*S*-enantiomer, major), 26.4 min (2*S*,3*R*-enantiomer, minor).[9e]

*4.2.1. (3**R**,4**S**)-trans-Epoxy-4-phenylbutan-2-one (**12b**).* Colorless oil: $[\alpha]_D^{26}$ −56.7 (c 1.00, $CDCl_3$) [lit.,[23] −73.3° (c 1.00, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.40 (m, 3H), 7.27–7.29 (m, 2H), 4.00 (d, J=1.6 Hz, 1H), 3.49 (d, J=1.6 Hz, 1H), 2.19 (s, 3H). HPLC (DAICEL Chiralpak IA 4.6 mmϕ×250 mm, 1% ^{i}PrOH in hexane, flow rate is 0.5 mL/min): t_R=14.9 min (2*S*,3*R*-enantiomer, minor), 16.7 min (2*R*,3*S*-enantiomer, major).

*4.2.2. (4**R**,5**S**)-trans-Epoxy-2-methyl-5-phenylpentan-3-one (**12c**).* Colorless crystals: $[\alpha]_D^{26}$ −141.4 (c 1.00, $CDCl_3$) [lit.,[24] −208° (c 1.00, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5H), 3.92 (d, J=2.0 Hz, 1H), 3.60 (d, J=2.0 Hz, 1H), 1.17 (q, J=5.2 Hz, 6H). HPLC (DAICEL Chiralcal OD-H 4.6 mmϕ×250 mm, 5% EtOH in hexane, flow rate is 1.0 mL/min): t_R=5.34 min (2*R*,3*S*-enantiomer, major), 5.65 min (2*S*,3*R*-enantiomer, minor).

*4.2.3. (1**S**,2**R**)-trans-Epoxy-4,4-dimethyl-1-phenylpentan-3-one (**12d**).* Colorless crystals: $[\alpha]_D^{26}$ −150.9 (c 1.0, $CDCl_3$) [lit.,[25] −194° (c 1.00, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.39 (m, 5H), 3.86 (s, 2H), 1.24 (s, 9H). HPLC (DAICEL Chiralcal OD-H 4.6 mmϕ×250 mm, 5% EtOH in hexane, flow rate is 1.0 mL/min): t_R=5.5 min (2*R*,3*S*-enantiomer, major), 5.9 min (2*S*,3*R*-enantiomer, minor).

*4.2.4. (2**R**,3**S**)-trans-Epoxy-3-phenyl-1-(2-furyl)propan-1-one (**12e**).* Colorless crystals: $[\alpha]_D^{26}$ −191.9 (c 1.00, $CDCl_3$) [lit.,[26] −200° (c 1.00, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.46 (d, J=4.0 Hz, 1H), 6.59–6.60 (m, 5H), 4.20 (m, 2H). HPLC (DAICEL Chiralcal OD-H 4.6 mmϕ×250 mm, 5% EtOH in hexane, flow rate is 1.0 mL/min): t_R=59.5 min (2*R*,3*S*-enantiomer, major), 39.1 min (2*S*,3*R*-enantiomer, minor).

*4.2.5. (2**R**,3**S**)-trans-Epoxy-3-methyl-1-phenylpropan-1-one (**12f**).* Colorless crystals: $[\alpha]_D^{26}$ −5.0 (c 1.00, $CDCl_3$) [lit.,[27] −10.0° (c 0.60, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–8.26 (m, 2H), 7.61 (m, 1H), 7.48–7.52 (m, 1H), 3.97 (s, 1H), 3.23 (m, 1H), 1.52 (d, J=4.4 Hz, 3H). HPLC (DAICEL Chiralcal OD-H 4.6 mmϕ×250 mm, 1% ^{i}PrOH in hexane, flow rate is 1.0 mL/min): t_R=15.2 min (2*R*,3*S*-enantiomer, major), 17.1 min (2*S*,3*R*-enantiomer, minor).

*4.2.6. (2**R**,3**S**)-trans-Epoxy-3-(4-chlorophenyl)-1-phenylpropan-1-one (**12g**).* Thin yellow crystals: $[\alpha]_D^{26}$ −202.4 (c 1.00, $CDCl_3$) [lit.,[26] −233° (c 1.00, CH_2Cl_2)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–8.01 (m, 2H), 7.61–7.65 (m, 2H), 7.48–7.52 (m, 2H), 7.38 (d, J=8.4 Hz, 2H), 7.31 (d, J=8.4 Hz, 2H), 4.24 (d, J=1.6 Hz, 1H), 4.06 (d, J=1.6 Hz, 1H). HPLC (DAICEL Chiralcal OD-H 4.6 mmϕ×250 mm, 1% ^{i}PrOH in hexane, flow rate is 1.0 mL/min): t_R=30.0 min (2*S*,3*R*-enantiomer, minor), 32.3 min (2*R*,3*S*-enantiomer, major).

*4.2.7. (2**R**,3**S**)-trans-Epoxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**12h**).* Thin yellow crystals: $[\alpha]_D^{26}$ −169.1 (c 1.00, $CDCl_3$) [lit.,[28] another 2*S*,3*R*-enantiomer, +131° (c 0.70, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J=7.2 Hz, 2H), 7.61 (m, 1H), 7.47–7.52 (m, 2H), 7.30 (d, J=8.8 Hz, 2H), 6.92–6.94 (m, 2H), 4.28 (d, J=1.6 Hz, 1H), 4.03 (d, J=1.6 Hz, 1H), 3.83 (s, 3H). HPLC (DAICEL Chiralcal OD-

H 4.6 mmϕ×250 mm, 1% ^{i}PrOH in hexane, flow rate is 0.5 mL/min): t_R=27.1 min (2*R*,3*S*-enantiomer, major), 29.0 min (2*S*,3*R*-enantiomer, minor).

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