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Design of a stabilized short helical peptide and its application to catalytic enantioselective epoxidation of (*E*)-chalcone

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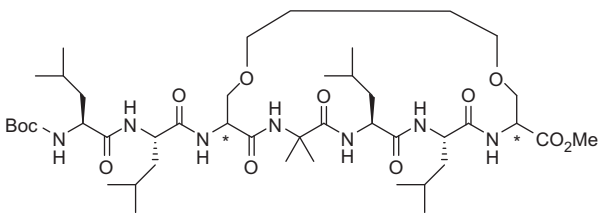
ABSTRACT

Stabilized short helical heptapeptides containing a combination of an α-aminoisobutyric acid as a helical promoter and L/D-serine derivatives to produce cross-linked units were synthesized. The cyclic peptide ***R*$_{3,7}$*R*-2**, which had D-serine derivatives at its 3rd and 7th positions, formed a stable right-handed (*P*) α-helix in solution and the crystalline state. Furthermore, its N-terminal free helical peptide catalyzed the enantioselective epoxidation of (*E*)-chalcone to afford the epoxide in a high yield and moderate enantioselectivity.

The de novo design of peptides that fold into well-defined secondary structures is of extreme importance to a wide variety of fields such as organic chemistry and biological and material sciences. A number of approaches for stabilizing the secondary structures of peptides have been reported.[1] As conformationally restricted amino acids, α,α-disubstituted α-amino acids have been widely used,[2] and α-aminoisobutyric acid (Aib) has been found to be particularly useful as a helical promoter.[3] On the other hand, for covalent helix-stabilization, disulfide, lactam, and hydrocarbon bridge methods have been reported.[4] Thus, we speculated that stable helical structures could be constructed using a combination of α,α-disubstituted α-amino acids and a covalent cross-linking system. Herein, we have designed and synthesized four L-leucine (L-Leu) based heptapeptides, ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2**, containing an α-aminoisobutyric acid at the 4th position as a helical promoter and L/D-serine derivatives[5] at the 3rd and 7th positions to produce a cross-linked subunit (Fig. 1).[6] Their dominant conformations were studied using their CD spectra in solution and X-ray crystallographic analysis in the crystalline state. In addition, N-terminal free peptides were prepared and used for enantioselective epoxidation of (*E*)-chalcone, which is known as the Juliá–Colonna asymmetric reaction.[7]

L/D-Serine derivatives **A** were synthesized starting from Boc-L/D-Ser.[5] The linear heptapeptides ***S*$_{3,7}$*S*-1**, ***S*$_{3,7}$*R*-1**, ***R*$_{3,7}$*S*-1**, and ***R*$_{3,7}$*R*-1** were prepared by conventional solution-phase methods with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) as coupling reagents (Scheme 1).[8] An intramolecular ruthenium catalyzed ring-closing metathesis reaction of ***S*$_{3,7}$*S*-1**, ***S*$_{3,7}$*R*-1**, ***R*$_{3,7}$*S*-1**, and ***R*$_{3,7}$*R*-1** gave cyclic peptides as a mixture of olefin isomers (*E*/*Z* ratio of isomers was not determined), and subsequent hydrogenation afforded saturated cyclic peptides ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2** in good yields.[9]

The CD spectra of the eight peptides (***S*$_{3,7}$*S*-1**, ***S*$_{3,7}$*R*-1**, ***R*$_{3,7}$*S*-1**, ***R*$_{3,7}$*R*-1**, ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2**) were measured in



***S*$_{3,7}$*S*-2, *S*$_{3,7}$*R*-2, *R*$_{3,7}$*S*-2, *R*$_{3,7}$*R*-2**

Figure 1. Chemical structures of heptapeptides ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2**. The nomenclature ***S*$_{3,7}$*R*** refers to a peptide with an *S* configuration at the 3rd position and an *R* configuration at the 7th position.

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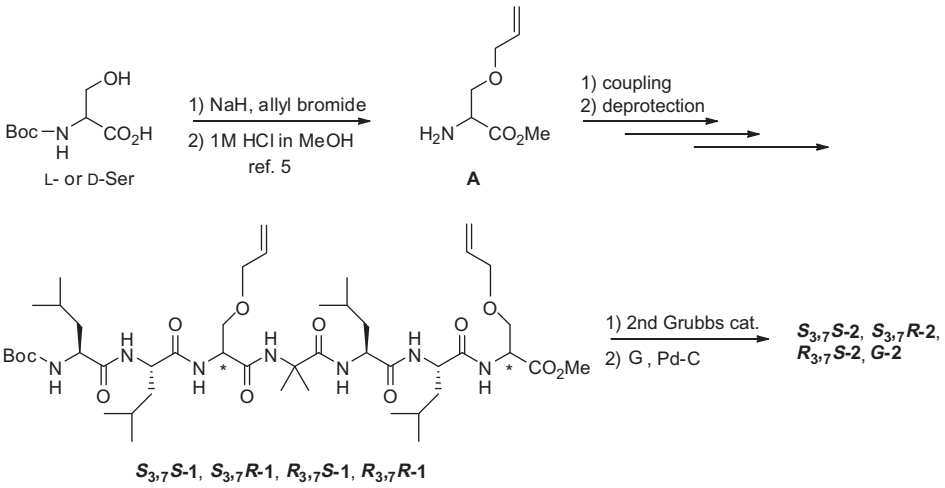


Scheme 1. Synthesis of heptapeptides ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2**.

2,2,2-trifluoroethanol (TFE) solution to obtain information about their secondary structures. The CD spectra of all eight peptides showed negative maxima at around 208 and 222 nm, indicating that they displayed a right-handed helical-screw sense (*P*).[10] Their ($\theta_{222}/\theta_{208}$) *R* values suggested that the dominant secondary structure of the linear peptides ***S*$_{3,7}$*S*-1**, ***S*$_{3,7}$*R*-1**, and ***R*$_{3,7}$*S*-1** was a 3_{10}-helix ($R = 0.3$).[11,12] The CD spectra of the cyclic molecules ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, and ***R*$_{3,7}$*S*-2** were similar to those of the linear peptides.[12] However, the CD spectrum of the cyclic ***R*$_{3,7}$*R*-peptide** was dynamically changed. These spectra indicate that cyclization changes the dominant secondary structure from a 3_{10}-helix ($R = 0.3$ for ***R*$_{3,7}$*R*-1**[13]) to an α-helix ($R = 0.8$ for ***R*$_{3,7}$*R*-2**) (Fig. 2).[10]

The peptide ***R*$_{3,7}$*R*-2** formed suitable crystals for X-ray crystallographic analysis after slow evaporation of the solvent $CHCl_3$/*n*-hexane at room temperature.[14] The relevant backbone and side-chain torsion angles and the intra- and intermolecular hydrogen-bond parameters are listed in Tables 1 and 2, respectively.

Only one conformer of the peptide molecule was found in the asymmetric unit of the ***R*$_{3,7}$*R*-2** peptide, a right-handed (*P*) α-helix containing a chloroform molecule. The mean values of the φ and ψ torsion angles of the amino acid residues (1–6) were −67.2° and −46.9°, 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 ($\varphi = 65.0°$, $\psi = -170.5°$). Figure 3 shows the X-ray structure of the (*P*) α-helical wheel as viewed from positions perpendicular to (A) and along (B) the helical axis. Three intramolecular hydrogen bonds of the *i*←*i*+4 type were observed between the H–N(4) and C(0) = O(0) [N(4)···O(0) = 2.92 Å; N–H···O 158.2°], the H–N(5) and C(1) = O(1) [N(5)···O(1) = 3.17 Å; N–H···O 150.7°], and the H–N(7) and C(3) = O(3) [N(7)···O(3) = 2.92 Å; N–H···O 140.3°], and one weak intramolecular hydrogen bond was found between the H–N(6) and C(2) = O(2) [N(6)···O(2) = 3.26 Å; N–H···O 143.0°]. In packing mode, three intermolecular hydrogen bonds were observed among the α-helical conformers; that is, between the H–N(1) and O(4') [N(1)···O(4') = 3.04 Å; N–H···O 161.7°], the H–N(2) and O(5') [N(2)···O(5') = 3.03 Å; N–H···O 151.3°], and the H–N(3) and O(6') [N(3)···O(6') = 2.96 Å; N–H···O 154.6°]. The helical molecules were connected by intermolecular hydrogen bonds forming head-to-tail aligned chains.

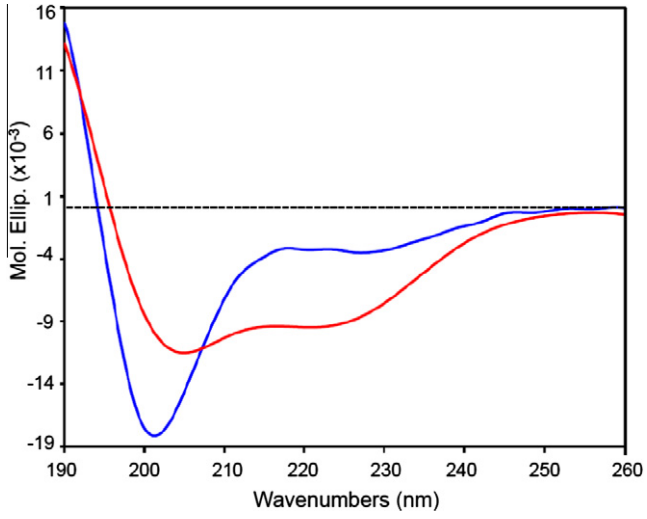


Figure 2. CD spectra in the 190–260 nm region of the linear peptide ***R*$_{3,7}$*R*-1** (blue) and the cyclic peptide ***R*$_{3,7}$*R*-2** (red) in TFE solution. Peptide concentration: 0.5 mM.

Table 1
Selected torsion angles ω, φ, ψ, and χ (°) for peptide ***R*$_{3,7}$*R*-2**

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 2
Intra- and intermolecular H-bond parameters for peptide ***R*$_{3,7}$*R*-2**[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*

[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.

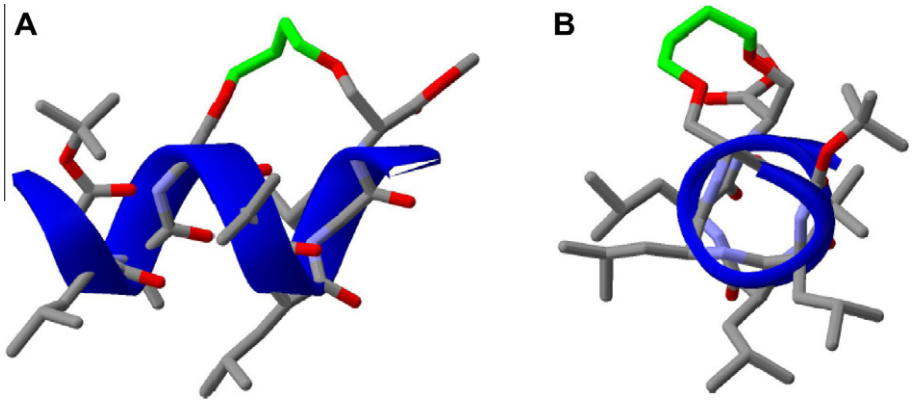
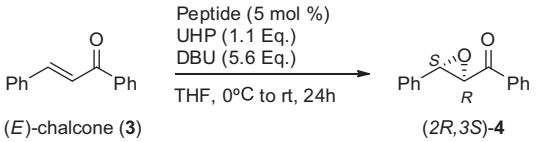


Figure 3. X-ray diffraction structure of ***R*$_{3,7}$*R*-2**, as viewed from positions (A) perpendicular to and (B) along the helical axis. The chloroform molecule has been omitted. The linker is shown in green.

Table 3
Asymmetric epoxidation of (*E*)-chalcone using the N-terminal free peptides **H-*S*$_{3,7}$*S*-1**, **H-*S*$_{3,7}$*R*-1**, **H-*R*$_{3,7}$*S*-1**, **H-*R*$_{3,7}$*R*-1**, **H-*S*$_{3,7}$*S*-2**, **H-*S*$_{3,7}$*R*-2**, **H-*R*$_{3,7}$*S*-2**, and **H-*R*$_{3,7}$*R*-2**



Entry	Peptide	Yield (%)	ee (%)
1	**H-*S*$_{3,7}$*S*-1**	90	58
2	**H-*S*$_{3,7}$*S*-2**	89	65
3	**H-*S*$_{3,7}$*R*-1**	91	57
4	**H-*S*$_{3,7}$*R*-2**	89	64
5	**H-*R*$_{3,7}$*S*-1**	82	35
6	**H-*R*$_{3,7}$*S*-2**	86	37
7	**H-*R*$_{3,7}$*R*-1**	93	30
8	**H-*R*$_{3,7}$*R*-2**	89	69

Next, we used the N-terminal free peptides[17] **H-*S*$_{3,7}$*S*-1**, **H-*S*$_{3,7}$*R*-1**, **H-*R*$_{3,7}$*S*-1**, **H-*R*$_{3,7}$*R*-1**, **H-*S*$_{3,7}$*S*-2**, **H-*S*$_{3,7}$*R*-2**, **H-*R*$_{3,7}$*S*-2**, and **H-*R*$_{3,7}$*R*-2** as catalysts for the enantioselective epoxidation of (*E*)-chalcone (**3**).[18] The epoxidation of **3** (0.3 mmol) using 5 mol % of peptides was carried out in THF (2 mL) containing urea-H_2O_2 (UHP, 0.33 mmol) and DBU (1.68 mmol) under aerobic conditions with the temperature gradually increasing from 0 °C to room temperature over 24 h.[19] In all cases, the epoxidation proceeded smoothly to afford the product (2*R*,3*S*)-**4** in high yield (Table 3). The use of the linear and cyclic **H-*S*$_{3,7}$*S*-** and **H-*S*$_{3,7}$*R*-**peptides afforded the epoxide (2*R*,3*S*)-**4** with moderate enantiomeric excess (entries 1, 2, 3, and 4), but that involving **H-*R*$_{3,7}$*S*-**peptides gave (2*R*,3*S*)-**4** in a poor enantiomeric excess (entries 5 and 6). On the other hand, the enantioselectivity of (2*R*,3*S*)-**4** was improved by the use of a stabilizing **H-*R*$_{3,7}$*R*-2** α-helical peptide (entries 7 and 8). Whether linear or cyclic peptides (entries 1–6) were used barely affected the enantiomeric excess of (2*R*,3*S*)-**4**. However, in the case of **H-*R*$_{3,7}$*R*-**peptides, the enantiomeric product excess was strongly affected by cyclization (entries 7 and 8); that is, the linear ***R*$_{3,7}$*R*-1** peptide forming the 3_{10}-helix gave a poor enantiomeric excess, but the cyclic ***R*$_{3,7}$*R*-2** peptide forming the α-helix gave a moderate enantiomeric excess. Since the ***R*$_{3,7}$*R*-2** peptide has a much stronger tendency to form α-helix than the other peptides, it worked more as an effective catalyst.[18b,20]

In summary, we have synthesized four linear heptapeptides, ***S*$_{3,7}$*S*-1**, ***S*$_{3,7}$*R*-1**, ***R*$_{3,7}$*S*-1**, and ***R*$_{3,7}$*R*-1**, and four cyclic peptides, ***S*$_{3,7}$*S*-2**, ***S*$_{3,7}$*R*-2**, ***R*$_{3,7}$*S*-2**, and ***R*$_{3,7}$*R*-2**, containing Aib as a helical promoter and serine derivatives as a cross-linking system. The dominant conformation of the linear peptide ***R*$_{3,7}$*R*-1** was a (*P*) 3_{10}-helix. Through the cyclization of ***R*$_{3,7}$*R*-1** into ***R*$_{3,7}$*R*-2**, its dominant conformation was changed to a (*P*) α-helical structure. In addition, its N-terminal free peptide was successfully used as a catalyst for the enantioselective epoxidation of (*E*)-chalcone. The design of further stabilized short helical peptides and their application to asymmetric reactions is currently underway.

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8. Spectroscopic data for ***R*$_{3,7}$*R*-1**: Foam; $[\alpha]_D^{24} = +1.0$ (*c* 0.5, $CHCl_3$); IR (in $CDCl_3$) 3432, 3327, 2960, 2872, 1666, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.45 (d, *J* = 8.4 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); [HR-ESI(+)]: *m*/*z* calcd for $C_{46}H_{81}N_7O_{12}Na$ $[M+Na]^+$ 946.5835: found 946.5834.
9. Procedure for the synthesis of peptide ***R*$_{3,7}$*R*-2**: Under an inert atmosphere, a solution of ***R*$_{3,7}$*R*-1** (155 mg, 0.17 mmol) and Grubbs catalyst 2nd generation (72 mg, 0.09 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 20 h. The solution was then poured into water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a cyclic peptide, which was used for the next reaction without further purification. A solution of the above peptide and $Pd(OH)_2$ (10 mg) in MeOH (10 mL) was vigorously stirred under an H_2 atmosphere for 2 h. The Pd-catalyst was then filtered off, and the filtrate was concentrated in vacuo, before being purified by silica gel column chromatography (*n*-hexane/AcOEt = 1:4) to afford ***R*$_{3,7}$*R*-2** (93 mg, 62% yield). Colorless crystals; mp 206–208 °C (recryst. from $CHCl_3$/*n*-hexane); $[\alpha]_D^{24} = -11.4$ (*c* 0.5, $CHCl_3$); IR (in $CDCl_3$) 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), 7.00 (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, 3H), 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); [HR-ESI(+)]: *m*/*z* calcd for $C_{44}H_{79}N_7O_{12}Na$ $[M+Na]^+$ 920.5679: found 920.5671.
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12. The CD spectra showed that the right-handed helicity of ***S*$_{3,7}$*S*-**, ***S*$_{3,7}$*R*-**, and ***R*$_{3,7}$*S*-**peptides was stronger than that of ***R*$_{3,7}$*R*-**peptides.
13. The IR and ^1H NMR spectra also indicated that the dominant conformation of ***R*$_{3,7}$*R*-1** in solution was a 3_{10}-helical structure.
14. X-ray data collection was performed using Bruker AXS SMART APEX imaging plate diffractometers and graphite-monochromated Mo Kα radiation. The structures of the peptides were solved using the SHELXS 97 direct method[15] and expanded using the Fourier technique.[16] All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the remaining H-atoms were placed at the calculated positions. *Crystal data for* ***R*$_{3,7}$*R*-2**: $C_{44}H_{79}O_{12}N_7$,$CHCl_3$; M_r = 1017.51; Monoclinic; *P*2$_1$, *a* = 10.728, *b* = 18.340, *c* = 14.943 Å; α = 90, β = 105.782, γ = 90°; *V* = 2829.3 Å^3; *Z* = 2; D_{calcd} = 1.194 g/cm^3; μ (Mo Kα) = 0.22 cm^{-1}; No. of observations ($I > 2\sigma(I)$) = 4202; No. of variables = 604; R_I = 0.0719, and R_w = 0.2165. CCDC-797487 for ***R*$_{3,7}$*R*-2** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
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17. Trifluoroacetic acid (0.2 mL) was added to a solution of ***R*$_{3,7}$*R*-2** (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 the removal of the solvent, the N-terminal free peptide **H-*R*$_{3,7}$*R*-2** (358 mg, 90%) was obtained, which was used as a catalyst for enantioselective epoxidation without further purification.
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19. General procedure for peptide-catalyzed asymmetric epoxidation of chalcone; THF (2 mL) was added to a mixture of peptide **H-*R*$_{3,7}$*R*-2** (12 mg, 0.015 mmol) and chalcone (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, the 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*)-**4** (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).[18e]
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