Synthesis of chiral five-membered carbocyclic ring amino acids with an acetal moiety and helical conformations of its homo-chiral homopeptides

Yurie Koba,[1] Yoko Hirata,[1] Atsushi Ueda,[1] Makoto Oba,[1] Mitsunobu Doi,[2] Yosuke Demizu,[3] Masaaki Kurihara,[3] Masakazu Tanaka[1]*

[1]*Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*

[2]*Osaka University of Pharmaceutical Sciences, Osaka 569-1094, Japan*

[3]*Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan*

matanaka@nagasaki-u.ac.jp

*Chiral five-membered carbocyclic ring amino acids bearing various diol acetal moieties were synthesized starting from L-malic acid, and homo-chiral homopeptides composed of cyclic amino acid (*S*)-Ac_5c^{3EG} bearing an ethylene glycol acetal, up to an octapeptide, were prepared. A conformational analysis revealed that (*S*)-Ac_5c^{3EG} homopeptides formed helical structures. (*S*)-Ac_5c^{3EG} homopeptides, up to hexapeptides, formed helical structures without controlling the helical screw direction, while (*S*)-Ac_5c^{3EG} hepta- and octapeptides formed helical structures with a preference for the left-handed (*M*) helical-screw direction.*

Keywords: α,α-disubstituted amino acid; cyclic amino acid; conformation; helix; homopeptide

INTRODUCTION

Peptides composed of non-proteinogenic amino acids have attracted the attention of organic, peptide, and medicinal chemists because they preferentially form a variety of stable secondary structures.[1–3] Of these, α,α-disubstituted α-amino acid-containing peptides have been reported to form stable 3_{10}-helices, α-helices, and fully planar extended structures,[4–9] which are capable of using the design of chiral organocatalysts[10–14] and cell-penetrating peptides.[15–18]

We recently designed and synthesized the six-membered ring amino acid Ac_6c^{4Bu} with a changeable chiral acetal moiety,[19] as well as the cyclic amino acid $Ac_6c^{3,5Bu}$ with two chiral acetal moieties (FIGURE 1).[20] In these six-membered ring amino acids, the α-carbon atom was not a chiral center, whereas the side-chain acetal moiety had chiral centers. A conformational analysis of their homo-chiral peptides revealed that, they formed helical secondary structures in solution and in a crystal state, and the effects of the chiral centers of their homopeptides on helical-screw bias was very weak.

We designed a chiral five-membered carbocyclic ring α,α-disubstituted α-amino acid Ac_5c^{3EG} with an acetal moiety, in which the α-carbon atom was a chiral center.[21] The acetal moiety at the γ-position may be changeable and also removed to a carbonyl functional group. We also prepared its homo-chiral homopeptides, up to an octapeptide, and examined their preferred secondary structures. We already reported the preferred structures of chiral five-membered carbocyclic ring amino acid homopeptides: however, they had chiral centers at the α-carbon atom and on the side chain,[22] or exclusively on the side chain.[23–24] The chiral amino acid Ac_5c^{3EG} had a chiral center exclusively at the α-carbon atom. Furthermore, we investigated which type of intramolecular hydrogen bond, the N–H···O=C or N–H···–O– (acetal) type, was formed.

[**FIGURE 1**; here]

FIGURE 1 Chemical structures of chiral cyclic α,α-disubstituted α-amino acids with acetal moieties.

RESULTS AND DISCUSSION

Synthesis of Chiral Five-membered Carbocyclic Ring Amino Acids with an Acetal Moiety

Both enantiomers of five-membered carbocyclic ring amino acid (*S*)- and (*R*)-Ac_5c^{3EG} with an ethylene glycol acetal were synthesized starting from L-malic acid, as shown in SCHEME 1. L-Malic acid was converted into the MOM-protected diester **1** in 83% yield by a treatment with $SOCl_2$/MeOH, and the subsequent protection of a secondary alcohol as a MOM ether.[25] The diester **1** was then converted into the diiodide **2** in 51% yield by reduction of the ester with $LiAlH_4$, and substitution with iodide using I_2/PPh_3. The alkylation of dimethyl malonate with **2** produced the cyclic diester **3** in 82% yield. The monohydrolysis of **3** under alkaline conditions, followed by the Curtius rearrangement with diphenylphosphoryl azide (DPPA) and a work-up with BnOH gave the amino acid **4** in 62% yield. The amino acid **4** is a mixture of two diastereomers; however, we were unable to separate them using preparative TLC or column chromatography on silica gel. Deprotection of the MOM ether in **4** with $ZrCl_4$ gave the alcohols **5** in 92% yield.[26] The alcohols **5** were separated by column chromatography on silica gel to give two diastereoisomers, **5a** and **5b**, in the ratio of 7 (more polar) to 3 (less polar). The stereochemistry of **5a** was unambiguously determined to be 1*S*,3*S* by an X-ray crystallographic analysis.[27] The alcohols **5a** and **5b** were oxidized by pyridinium dichromate (PDC) to give amino acids (*S*)-**6** (95%) and (*R*)-**6** (85%), respectively, with a carbonyl functional group. The conversion of a carbonyl functional group into an ethylene glycol acetal by ethylenedioxybis(trimethylsilane) and TMSOTf gave Cbz-{Ac_5c^{3EG}}-OMe (*S*)-**7** (84%) and (*R*)-**7** (89%), respectively.

By using various kinds of alcohols, we synthesized chiral five-membered carbocyclic ring amino acids with different acetal moieties. For example, the reaction of (*S*)-**6** with propane-1,3-diol gave a cyclic amino acid (*S*)-**8** with a propane-1,3-dioxy moiety in 18% yield, while that with chiral (*R*,*R*)-butane-

2,3-diol gave a cyclic amino acid (*S*)-**9**, in which chiral centers existed at the α-carbon and side chain in 54% yield. Furthermore, in the reaction with trimethyl orthoacetate, the amino acid (*S*)-**6** was converted into the amino acid (*S*)-**10** with a dimethyl acetal moiety in 66% yield.

[**SCHEME 1**; here]

SCHEME 1 Synthesis of the five-membered carbocyclic ring amino acid (*S*)-Ac_5c^{3EG} and its analogues.

Preparation of (*S*)-Ac_5c^{3EG} Homopeptides

(*S*)-Ac_5c^{3EG} homo-chiral homopeptides, up to an octapeptide, were synthesized by solution-phase methods, as follows. The C-terminal free amino acid (*S*)-**11** was prepared by alkaline hydrolysis of the methyl ester in (*S*)-**7**, while the N-terminal free amino acid (*S*)-**12** was prepared by hydrogenolysis using H_2/Pd-C. Coupling between (*S*)-**11** and (*S*)-**12** using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 1-hydroxy-7-azabenzotriazole (HOAt), and $^{i}Pr_2NEt$ produced the dipeptide (*S*)-**13** in 95% yield. Deprotection of the N-terminal Cbz-protecting group in (*S*)-**14**, followed by coupling with (*S*)-**11** using HATU, HOAt, and $^{i}Pr_2NEt$ gave the tripeptide (*S*)-**14** in 81% yield. Similarly, elongation of the peptide length by stepwise one amino acid residues produced the tetrapeptide (*S*)-**15** (76%), pentapeptide (*S*)-**16** (37%), hexapeptide (*S*)-**17** (59%), heptapeptide (*S*)-**18** (44%), and octapeptide (*S*)-**19** (6%). Alternatively, the (*S*)-Ac_5c^{3EG} tetrapeptide (*S*)-**15** was prepared by coupling between the dipeptide acid and dipeptide amine derived from (*S*)-**13**; however, the yield was moderate (37%). The spectroscopic data of homopeptides supported their structures.

[**SCHEME 2**; here]

SCHEME 2 Preparation of (*S*)-Ac_5c^{3EG} homopeptides.

Conformational Analysis in Solution

The FT-IR absorption spectra of homopeptides Cbz-{(*S*)-Ac_5c^{3EG}}$_n$-OMe (**7** and **13**–**19**: n = 1–8) in $CDCl_3$ are shown in FIGURE 2. In the N-H stretching region (amide A) of peptides **14**–**19** (n = 3–8), weak bands were observed at approximately 3420–3430 cm^{-1} (free solvated N-H), whereas strong bands were noted at 3310–3360 cm^{-1} and may have been derived from the peptide NH groups with N–H···O=C intramolecular hydrogen bonds.[28] No band at approximately 3390-3370 cm^{-1} was observed in peptides **14**–**19**. This band was attributed to the peptide NH group with intramolecular hydrogen bonds between peptide N–H and acetal –O– (ether). This band was observed in the $Ac_6c^{3,5Bu}$ homopeptides having acetal moieties.[20,29]

[**FIGURE 2**; here]

FIGURE 2 FT-IR absorption spectra of homopeptides Cbz-{(*S*)-Ac_5c^{3EG}}$_n$-OMe (**7** and **13**–**19**: n = 1–8) in $CDCl_3$. Peptide concentration: 5 mM.

In the conformational analysis, distance-geometry methods in the ROESY NMR spectra could not be applied to the (*S*)-Ac_5c^{3EG} homopeptides because they had no hydrogen atom at the α-carbon of amino acid residues. Instead, we used solvent perturbation experiments in the ^{1}H NMR spectrum of (*S*)-**17** by adding the strong H-bond acceptor solvent DMSO-d_6 {0-10% (*v*/*v*)}, as shown in FIGURE 3. In the ^{1}H NMR spectrum of (*S*)-**17**, only the NH signal at the N-terminus was unambiguously determined by its high-field position {δ 5.62 (br s, 1H)}, while the remaining five NH protons could not be assigned. Two

NH signals were sensitive to the addition of DMSO-d_6; one (n = 1) was very sensitive, while the other was slightly sensitive (solvent-exposed NH group), and the FT-IR absorption spectra and these results suggested that a 3_{10}-helical structure was preferentially formed.[23,24,28] ^{1}H NMR experiments by the addition of the paramagnetic free radical 2,2,6,6-tetramethylpiperidin-1-yloxyl {TEMPO; 0-5x10^{-2}% (*w*/*v*)} did not give clear results due to the overlapping of NH signals.

[**FIGURE 3** here]

FIGURE 3 Plots of N-H chemical shifts in ^{1}H NMR spectra of Cbz-{(*S*)-Ac_5c^{3EG}}$_6$-OMe (*S*)-**17**, as a function of the increasing percentage of DMSO-d_6 (*v*/*v*) added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

The CD spectra of peptides (*S*)-**17**–**19** (n = 6–8) were measured in 2,2,2-trifluoroethanol (TFE) solution.[30,31] Up to hexapeptide (*S*)-**17**, no characteristic maxima (222 nm and 208 nm) for helical structures were observed, and this may be attributed to the peptide-main chain length not being sufficiently long to control the helical-screw direction to one-handedness.[22] In contrast, the CD spectra of heptapeptide (*S*)-**18** and octapeptide (*S*)-**19** showed positive maxima at 222 nm and 208 nm, and a much stronger negative maximum at 192 nm. These maxima of CD spectra were characteristic of a left-handed (*M*) helical structure.[22,31] The helical-screw direction may not have been perfectly controlled to left-handedness because the intensities of the 222 nm and 208 nm maxima were weak. The results of CD spectra depended on the peptide main-chain length and were similar to those of homopeptides composed of the chiral five-membered carbocyclic ring amino acid (1*S*,3*S*)-Ac_5c^{OM} with a 3-methoxy functional group.[22]

[**FIGURE 4**; here]

FIGURE 4 CD spectra of (*S*)-Ac_5c^{3EG} homopeptides Cbz-{(*S*)-Ac_5c^{3EG}}$_n$-OMe (**7** and **17**–**19**: n = 1 and 6–8) in TFE solution (0.05 mM).

X-ray Crystallographic Analysis of the (*R*)-Ac_5c^{3EG} Dipeptide

The Cbz-{(*R*)-Ac_5c^{3EG}}$_2$-OMe dipeptide (*R*)-**13** provided suitable crystals for an X-ray crystallographic analysis due to the slow evaporation of EtOH/H_2O at room temperature. The crystal and diffraction parameters of (*R*)-**13** are summarized in TABLE 1. The molecular structure is shown in FIGURE 5. The ϕ and ψ torsion angles of the N-terminal residue were −66.4° and −33.0°, which corresponded to those of a right-handed (*P*) β-turn, whereas the C-terminal residue torsion angles (ϕ and ψ: +52.1° and −142.5°) were indicative of a semi-extended conformation. An intramolecular hydrogen bond of the N–H···O=C or N–H···–O– (acetal) type was not observed, whereas an intermolecular hydrogen bond was detected between N(1)–H and O(1')=C(1') (N···O distance: 2.86 Å; N–H···O angle: 167°).

The preferred structure of peptides composed of the six-membered ring amino acid (*R*,*R*)-$Ac_6c^{3,5Bu}$ bearing acetal moieties at the γ-position was a helical structure with the intramolecular hydrogen bonds of the N(*i*)–H···–O– (*i*, acetal) type both in solution and a crystal state.[20,29] On the other hand, peptides composed of the five-membered carbocyclic ring amino acid (*R*)-Ac_5c^{3EG} with a γ-acetal moiety showed no intramolecular hydrogen bond of the N(*i*)–H···–O– (*i*, ether) type. These differences in the hydrogen-bond pattern may be attributed to the ring size difference of amino acids as well as the conformational differences of rings.

TABLE 1 Crystal and diffraction parameters of the Cbz-{(*R*)-Ac_5c^{3EG}}$_2$-OMe dipeptide (*R*)-**13**.

[**TABLE 1**; here]

[**FIGURE 5**; here]

FIGURE 5 An ORTEP drawing of the Cbz-{(*R*)-Ac_5c^{3EG}}$_2$-OMe dipeptide (*R*)-**13**.

CONCLUSION

Chiral five-membered carbocyclic ring amino acids with various acetal moieties were synthesized starting from L-malic acid. (*S*)-Ac_5c^{3EG} homo-chiral homopeptides, up to an octapeptide, were prepared. A conformational analysis revealed that (*S*)-Ac_5c^{3EG} homopeptides formed helical structures. CD spectra suggested that, up to a hexapeptide length, (*S*)-Ac_5c^{3EG} homopeptides might form both right-handed (*P*) and left-handed (*M*) helical structures at almost equal amounts. However, elongation of the peptide length to a heptapeptide and octapeptide resulted in the helical-screw direction being partially controlled to left-handedness. Left-handed (*M*) helical structures were controlled exclusively by the chiral α-carbon atoms of five-membered carbocyclic ring amino acids. We are now studying the preferred structures of peptides with these five-membered carbocyclic ring amino acids inserted into a L-Leu sequence.

This work was supported in part by a Grant-in-Aid for Young Scientists (A) (25713008) from JSPS (M. O.), a Grant-in-Aid for Scientific Research on Innovative Areas 'Advanced Molecular Transformations by Organocatalysts' (26105745) from MEXT (M. T.), and Special Coordination Funds for Promoting Science and Technology from JST (A. U.).

MATERIALS AND METHODS

General Experimental Methodology

Optical rotations $[\alpha]_D$ were measured using a 1.0 dm cell. Circular dichroism spectra (CD) were measured using a 1.0-mm path length cell. Infrared absorption spectra (IR) were recorded for conventional measurements (KBr), and the solution ($CDCl_3$) method using the 0.1-mm path length of an NaCl cell. ^1H NMR spectra were determined at 400 or 500 MHz. HRMS(FAB) spectra were taken in the dual-focusing sector field mode, and HRMS(ESI) spectra were measured in the ToF mode.

Synthesis of Cyclic Amino Acids

Dimethyl (2*S*)-2-(Methoxymethoxy)succinate (1)[25]

A solution of L-malic acid (20.0 g, 149 mmol) and $SOCl_2$ (24.0 mL, 328 mmol) in MeOH (360 mL) was stirred at room temperature for 48 h. The solution was then neutralized with 1M aqueous NaOH and evaporated. The aqueous solution was extracted with $CHCl_3$ and dried over $MgSO_4$. Removal of the solvent gave a diester (21.5 g), which was used without purification. Methoxymethyl chloride (MOMCl; 42.1 mL, 555 mmol) was added dropwise to the stirred solution of L-malic acid diester (21.5 g, 132 mmol) and $^iPr_2NEt$ (75.1 mL, 431 mmol) in CH_2Cl_2 (240 mL) at 0°C, and the solution was then stirred at room temperature for 24 h. The solution was diluted with saturated aqueous NH_4Cl, extracted with $CHCl_3$, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by short column chromatography on silica gel (30% EtOAc in *n*-hexane) to give **1** (25.6 g, 83%) as a colorless oil: $[\alpha]^{31}_D$ −73.0 (*c* 1.16, $CHCl_3$); IR (neat) 2957, 1740, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.70–4.77 (m, 2H), 4.56 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.39 (s, 3H), 2.81–2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 170.2, 96.2, 71.6, 55.9, 52.1, 51.8, 37.5.

(2*S*)-1,4-Diiodo-2-(methoxymethoxy)butane (2)

A solution of diester **1** (105 g, 509 mmol) was added dropwise to the stirred suspension of $LiAlH_4$ (23.2 g, 611 mmol) in THF (800 mL) at 0°C, and the mixture was warmed to room temperature. After being stirred for 24 h, the reaction was quenched with water, and the mixture was filtered through Celite. Evaporation of the filtrate gave a crude diol (60.5 g, 79%), which was used without purification. A mixture of crude diol (60.5 g, 403 mmol), PPh_3 (317 g, 1.21 mol), imidazole (82.4 g, 1.21 mol), and I_2 (307 g, 1.21 mol) in THF was stirred at 0°C, and the mixture was then warmed to room temperature. After being stirred for 5 h, the mixture was diluted with EtOAc, washed with water, saturated aqueous $Na_2S_2O_3$, 1M aqueous HCl, 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 5% EtOAc in *n*-hexane gave **2** (97.5 g, 65%) as a yellowish oil: $[\alpha]^{28}_D$ −39.3 (*c* 1.26, $CHCl_3$); IR (neat) 2947, 2889, 1145, 1096, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 2H), 3.54 (m, 1H), 3.45 (s, 3H), 3.25–3.41 (m, 4H), 2.04–2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.5, 76.1, 56.3, 39.1, 10.0, 1.4; ESI-HRMS: *m/z* $[M^+]$ calcd for $C_6H_{12}I_2O_2$ 369.8927, found 369.8955.

Dimethyl (3*S*)-3-(Methoxymethoxy)cyclopentane-1,1-dicarboxylate (3)

A mixture of **2** (18.2 g, 49.3 mmol), dimethyl malonate (5.60 mL, 49.0 mmol), and K_2CO_3 (17.0 g, 123 mmol) in DMF (150 mL) was stirred at 75°C under an Ar atmosphere. After being stirred for 50 h, the mixture was diluted with EtOAc, and K_2CO_3 was filtered off. The filtrate was evaporated, and the residue was purified by column chromatography on silica gel (30% EtOAc in *n*-hexane) to give **3** (9.92 g, 82%) as a colorless oil: $[\alpha]^{29}_D$ +6.21 (*c* 1.12, $CHCl_3$); IR (neat) 2955, 1734, 1437, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.60 (q, *J* = 6.8 Hz, 2H), 4.21 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.34 (s, 3H), 2.45–2.52 (m, 2H), 2.37 (m, 1H), 2.13 (m, 1H), 1.76–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 172.3, 95.0, 77.4, 58.6, 55.2, 52.7, 52.6, 40.4, 32.1, 31.8; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{11}H_{19}O_6$ 247.1182, found 247.1179.

Methyl (1*RS*,3*S*)-1-(Benzyloxycarbonyl)amino-3-(methoxymethoxy)cyclopentanecarboxylate (4)

A solution of **3** (49.3 g, 200 mmol) in MeOH (100 mL) and 0.5M aqueous NaOH (540 mL) was stirred at 0°C, and then the solution was warmed to room temperature. After being stirred at room temperature for 16 h, the solution was neutralized with 1M aqueous HCl, and MeOH was evaporated. The aqueous solution was extracted with EtOAc, dried over $MgSO_4$, and evaporated to give a crude monocarboxylic acid (37.6 g), which was used for the next reaction without purification. A solution of crude monocarboxylic acid (37.6 g), diphenylphosphoryl azide (DPPA; 38.4 mL, 178 mmol), and Et_3N (24.8 mL, 178 mmol) in toluene (500 mL) was refluxed for 1 h. Benzyl alcohol (18.5 mL, 178 mmol) was then added to the solution, and the solution was refluxed for 6 h. After removal of the solvent, the residue was diluted with EtOAc, washed with 1M aqueous HCl, 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by column chromatography on silica gel (25% EtOAc in *n*-hexane) to give **4** (41.9 g, 62%) as a colorless oil: IR (neat) 3348 (br), 2953, 1724, 1719, 1522, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 5.56 (br s, 0.2H), 5.30 (br s, 0.8H), 5.09 (s, 2H), 4.63 (s, 2H), 4.32 (m, 1H), 3.73 (br s, 3H), 3.35 (s, 2.0H), 3.33 (s, 1.0H), 2.28–2.44 (m, 3H), 2.10 (m, 1H), 1.70–2.20 (m, 2H); ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{17}H_{24}NO_6$ 338.1604, found 338.1588.

Methyl (1*S*,3*S*)- and (1*R*,3*S*)-1-(Benzyloxycarbonyl)amino-3-hydroxycyclopentanecarboxylate (5a and 5b)

A mixture of **4** (990 mg, 2.93 mmol) and $ZrCl_4$ (342 mg, 1.47 mmol) in MeOH (18 mL) was refluxed under an Ar atmosphere for 3 h. The solution was then evaporated to give the residue, which was purified by column chromatography on silica gel. The fraction eluted with 60% EtOAc in *n*-hexane gave **5a** (more polar, 558 mg, 65%) as colorless crystals and **5b** (less polar, 230 mg, 27%) as a colorless oil:

5a: mp 59–62 °C; $[\alpha]^{21}_{D}$ −3.66 (*c* 0.95, $CHCl_3$); IR (KBr) 3422, 3221, 3050, 1736, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 5.30 (br s, 1H), 5.09 (s, 2H), 4.47 (br s, 1H), 3.75 (br s, 3H), 2.37–2.56 (m, 3H), 2.28 (br m, 1H), 2.14 (m, 1H), 1.93 (br m, 1H), 1.88–1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 155.5, 136.2, 128.4, 128.1, 128.0, 72.8, 66.7, 65.0, 52.9, 46.7, 36.0, 34.7; FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{15}H_{20}NO_5$ 294.1341, found 294.1361; X-ray crystallographic parameter: solvent: EtOAc/*n*-hexane; empirical formula: $C_{15}H_{19}NO_5$; *M*r: 337.36; crystal dimensions [mm]: 0.15 x 0.10 x 0.02; crystal system: orthorhombic; *a*, *b*, *c* [Å]: 5.9160, 12.667, 22.091; *V* [$Å^3$]: 1655.5; space group: $P2_12_12_1$; *Z*: 4; D_{calc} [g/cm^3]: 1.354; μ (Mo$K\alpha$) [cm^{-1}]: 1.03; no. of observations ($I > -10.0\ \sigma I$): 1884; no. of variables: 245; R_1 0.0599; R_W 0.1646.

5b: $[\alpha]^{28}_{D}$ −7.02 (*c* 1.05, $CHCl_3$); IR (neat) 3356 (br), 2954, 1700 (br), 1520 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 6.10 (br s, 1H), 5.10 (s, 2H), 4.41 (br s, 1H), 4.21 (br s, 1H), 3.76 (br s, 3H), 2.52 (m, 1H), 2.41 (m, 1H), 1.90–2.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 155.2, 136.0, 128.5, 128.2, 128.1, 73.1, 66.8, 64.9, 52.9, 46.7, 35.6, 34.9; FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{15}H_{20}NO_5$ 294.1341, found 294.1375.

Methyl (*S*)-1-(Benzyloxycarbonyl)amino-3-oxocyclopentanecarboxylate {(*S*)-6} and (*R*)-6

A mixture of **5a** (200 mg, 0.682 mmol) and pyridinium dichromate **(**PDC; 641 mg, 1.70 mmol) in CH_2Cl_2 (10 mL) was stirred under an Ar atmosphere at room temperature for 84 h. The mixture was then filtered through Celite, and filtrate was evaporated. The residue was purified by column chromatography on silica gel (50% EtOAc in *n*-hexane) to give (*S*)-**6** (189 mg, 95%) as colorless crystals: mp 113–115 °C; $[\alpha]^{21}_{D}$ +5.03 (*c* 0.96, $CHCl_3$); IR (KBr) 3314 (br), 1744, 1717, 1528, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.42 (m, 5H), 5.48 (br s, 1H), 5.10 (s, 2H), 3.76 (br s, 3H), 2.94 (d, *J* = 18.5 Hz, 1H), 2.82 (br d, *J* = 18.5 Hz, 1H), 2.38–2.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0, 173.2, 155.4, 135.9, 128.5, 128.3, 128.1, 67.0, 62.5, 53.1, 47.8, 35.9, 32.6; ESI-

HRMS: *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}NO_5$ 292.1185, found 292.1204. Oxidation of **5b** with PDC gave (*R*)-**6** in 85% yield.

(*R*)-**6**: mp 115–117 °C; $[\alpha]^{20}_D$ −4.56 (*c* 0.84, $CHCl_3$).

Methyl (*S*)-1-(Benzyloxycarbonyl)amino-3,3-(ethylenedioxy)cyclopentanecarboxylate [Cbz-{(*S*)-Ac_5c^{3EG}}-OMe; (*S*)-7] and (*R*)-7

Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 80 μL) was slowly added to the stirred solution of ethylenedioxybis(trimethylsilane) (4.4 ml, 17.8 mmol) and (*S*)-**6** (2.59 g, 8.89 mmol) in CH_2Cl_2 (60 mL) at −35°C under an Ar atmosphere, and the solution was stirred for 35 h at the same temperature. The solution was then diluted with 5% aqueous $NaHCO_3$, extracted with $CHCl_3$, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by column chromatography on silica gel (60% EtOAc in *n*-hexane) to give (*S*)-**7** (2.53 g, 84%) as a colorless oil: $[\alpha]^{26}_D$ +19.7 (*c* 0.98, $CHCl_3$); IR (neat) 3340 (br), 2955, 1736, 1716, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 5.41 (br s, 1H), 5.10 (s, 2H), 3.86–3.94 (m, 4H), 3.74 (br s, 3H), 2.49 (d, *J* = 14.6 Hz, 1H) 2.40 (m, 1H), 1.90–2.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 155.3, 136.2, 128.3, 128.2, 128.0, 116.4, 66.6, 64.3, 64.2, 63.9, 52.5, 46.5, 34.6, 34.1; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_6$ 336.1447, found 336.1472. The enantiomeric (*R*)-**7** was also obtained from (*R*)-**6** in 89% yield by the same procedure as described above.

(*R*)-**7**: $[\alpha]^{26}_D$ −21.0 (*c* 1.02, $CHCl_3$).

Methyl (*R*)-1-(Benzyloxycarbonyl)amino-3,3-(propane-1,3-dioxy)cyclopentanecarboxylate {(*S*)-8}

A solution of (*S*)-**6** (100 mg, 0.343 mmol), propane-1,3-diol (50 μL, 0.692 mmol), and pyridinium *p*-toluenesulfonate (PPTS; 1.5 mg) in toluene (10 ml) was refluxed for 4 h, fixed with a Dean-Stark apparatus. The solution was then diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried

over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (60% EtOAc in *n*-hexane) to give (*S*)-**8** (22 mg, 18%) as a colorless oil: $[\alpha]^{22}_D$ +9.23 (*c* 1.00, $CHCl_3$); IR (neat) 3341 (br), 2955, 1717 (br), 1520, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.40 (m, 5H), 5.38 (br s, 1H), 5.05–5.13 (m, 2H), 3.80–3.95 (m, 4H), 3.73 (br s, 3H), 2.31–2.50 (m, 3H), 2.02–2.18 (m, 3H), 1.65–1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 155.3, 136.2, 128.4, 128.1, 108.2, 66.7, 64.1, 61.9, 61.3, 52.6, 45.7, 33.9, 25.3; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{18}H_{24}NO_6$ 350.1604, found 350.1629.

Methyl (*S*)-1-(Benzyloxycarbonyl)amino-3,3-{(2*R*,3*R*)-butane-2,3-dioxy}cyclopentanecarboxylate {(*S*)-9}

A solution of (*S*)-**6** (68.2 mg, 0.234 mmol), (2*R*,3*R*)-butane-2,3-diol (24 μL, 0.263 mmol), *p*-TsOH (4.6 mg, 0.024 mmol) in toluene (6 ml) was refluxed for 3 h, fixed with a Dean-Stark apparatus. The solution was then neutralized with Et_3N, diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (60% EtOAc in *n*-hexane) to give (*S*)-**9** (46 mg, 54%) as a colorless oil: $[\alpha]^{28}_D$ +15.6 (*c* 1.15, $CHCl_3$); IR (neat) 3348 (br), 2974, 1721, 1520, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.36 (m, 5H), 5.43 (br s, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 3.72 (br s, 3H), 3.51–3.56 (m, 2H), 2.45 (d, *J* = 14.6 Hz, 1H), 2.38 (m, 1H), 2.00–2.16 (m, 4H), 1.23 (t, *J* = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 155.4, 136.3, 128.4, 128.1, 128.0, 115.6, 78.5, 78.4, 66.7, 64.2, 52.6, 48.2, 36.3, 33.9, 16.8, 16.7; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_6$ 364.1760, found 364.1773.

Methyl (*S*)-1-(Benzyloxycarbonyl)amino-3,3-(dimethoxy)cyclopentanecarboxylate {(*S*)-10}

Compound (*S*)-**10** was prepared from (*S*)-**6** and trimethyl orthoacetate in a manner similar to that described for the preparation of (*S*)-**9**: 66%; a colorless oil; $[\alpha]^{28}_D$ +6.47 (*c* 1.04, $CHCl_3$); IR (neat)

3345 (br), 2951, 2820, 1724 (br), 1520, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.39 (m, 5H), 5.36 (br s, 1H), 5.09 (s, 2H), 3.73 (br s, 3H), 3.20 (s, 3H), 3.17 (s, 3H), 2.35–2.48 (m, 2H), 2.18 (br d, *J* = 14.2 Hz, 1H), 1.92–2.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 155.3, 134.2, 128.4, 128.0, 110.4, 66.7, 63.9, 52.6, 49.6, 49.0, 45.0, 34.2, 32.7; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{23}NNaO_6$, 360.1423 found 360.1425.

(*S*)-1-(Benzyloxycarbonyl)amino-3,3-(ethylenedioxy)cyclopentanecarboxylic Acid [Cbz-{(*S*)-Ac_5c^{3EG}}-OH; (*S*)-11] and (*R*)-11

0.1M aqueous NaOH (20 mL) was added to the stirred solution of (*S*)-**7** (310 mg, 0.925 mmol) in MeOH (5 mL) at 0°C, and the solution was warmed to room temperature. After being stirred for 24 h, the solution was acidified with citric acid, and evaporated. The residue was extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent gave a crude amino acid (*S*)-**11** (309 mg, quantitative) as a colorless oil, which was used for the next reaction without purification. $[\alpha]^{31}_D$ +21.5 (*c* 1.00, $CHCl_3$); IR (neat) 3327 (br), 3233, 1716 (br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (br, 1H), 7.30–7.36 (m, 5H), 5.62 (br s, 1H), 5.11 (br s, 2H), 3.86–3.93 (m, 4H), 2.07–2.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 155.8, 136.0, 128.5, 128.1, 128.0, 116.6, 67.0, 64.5, 64.4, 63.7, 46.2, 34.7, 34.1; FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}NO_6$ 322.1291, found 322.1306.

(*R*)-**11**: $[\alpha]^{30}_D$ −22.9 (*c* 1.00, $CHCl_3$).

Methyl (*S*)-1-Amino-3,3-(ethylenedioxy)cyclopentanecarboxylate [H-{(*S*)-Ac_5c^{3EG}}-OMe; (*S*)-12] and (*R*)-12

A mixture of (*S*)-**7** (538 mg, 1.61 mmol) and 10% Pd-C (130 mg) was rigorously stirred under a H_2 atmosphere at room temperature for 5 h. The Pd-catalyst was then filtered off, and the filtrate was evaporated to give (*S*)-**12** (313 mg, 97%), which was used for the next reaction without purification. $[\alpha]^{28}_D$ +0.98 (*c* 0.95, $CHCl_3$); IR (neat) 3368 (br), 2920, 1735, 1720 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ 6.55 (br s, 2H), 3.94–4.00 (m, 4H), 3.83 (s, 3H), 2.05–2.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 116.6, 64.5, 64.4, 62.9, 53.0, 46.4, 35.3, 34.8; FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_9H_{16}NO_4$ 202.1079, found 202.1107.

(*R*)-**12**: $[\alpha]^{22}_D$ −1.25 (*c* 1.02, $CHCl_3$).

Synthesis of (*S*)-Ac$_5$c^{3EG} Homopeptides

(*S*)-Ac$_5$c^{3EG} Dipeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_2$-OMe; (*S*)-13]

A solution of (*S*)-**11** (1.20 g, 3.73 mmol), (*S*)-**12** (633 mg, 3.14 mmol), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; 1.43 g, 3.76 mmol), 1-hydroxy-7-azabenzotriazole (HOAt; 512 mg, 3.76 mmol) and $^iPr_2NEt$ (1.3 mL) in MeCN (10 mL) was stirred at room temperature under a N_2 atmosphere for 26 h. The solution was then evaporated, diluted with EtOAc, washed with 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent afforded a white solid, which was purified by column chromatography on silica gel (80% EtOAc in *n*-hexane) to give (*S*)-**13** (1.50 g, 95%) as colorless crystals: mp 126–128 °C; $[\alpha]^{26}_D$ +9.97 (*c* 1.30, $CHCl_3$); IR (KBr) 3391 (br), 3298, 2955, 1724, 1708, 1655, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.27–7.38 (m, 5H), 6.03 (br s, 1H), 5.04–5.15 (m, 2H), 3.80–4.00 (m, 8H), 3.70 (s, 3H), 2.31–2.55 (m, 6H), 1.95–2.15 (m, 6H); FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{25}H_{33}N_2O_9$ 505.2186, found 505.2177.

(*R*)-Ac$_5$c^{3EG} Dipeptide (*R*)-**13**: mp 129–130 °C; $[\alpha]^{28}_D$ −12.2 (*c* 0.98, $CHCl_3$).

(*S*)-Ac$_5$c^{3EG} Tripeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_3$-OMe; (*S*)-14]

A mixture of (*S*)-**13** (760 mg, 1.50 mmol) and 20% $Pd(OH)_2$-C (70 mg) in MeOH (20 mL) was rigorously stirred under a H_2 atmosphere at room temperature. The Pd-catalyst was then filtered off, and the filtrate was evaporated to give a crude amine (593 mg). A solution of the crude amine (593 mg), (*S*)-**11** (578 mg, 1.80 mmol), HATU (684 mg, 1.80 mmol), HOAt (245 mg, 1.80 mmol), and $^iPr_2NEt$ (627

μL) in MeCN (20 mL) was stirred at room temperature under an Ar atmosphere. After being stirred for 22 h, the solution was evaporated, diluted with EtOAc, washed with 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent afforded a white solid, which was purified by column chromatography on silica gel. The fraction eluted with EtOAc gave (*S*)-**14** (820 mg, 81%) as colorless crystals: mp 70–72 °C; $[\alpha]^{22}_D$ +22.1 (*c* 0.85, $CHCl_3$); IR ($CDCl_3$) 3418 (br), 3360 (br), 2955, 1744, 1713, 1678, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (br s, 1H), 7.25–7.41 (m, 5H), 7.20 (br s, 1H), 5.91 (br s, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 3.82–3.98 (m, 12H), 3.71 (s, 3H), 1.93–2.67 (m, 18H); ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{33}H_{43}N_3NaO_{12}$ 696.2744, found 696.2736.

(*S*)-Ac$_5$c^{3EG} Tetrapeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_4$-OMe; (*S*)-15]

Tetrapeptide (*S*)-**15** was prepared from tripeptide (*S*)-**14** in a manner similar to that described for the preparation of (*S*)-**14**: 76%; colorless crystals; mp 90–92 °C; $[\alpha]^{20}_D$ +10.0 (*c* 0.96, $CHCl_3$); IR ($CDCl_3$) 3422, 3337 (br), 2954, 1747, 1682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (br s, 1H), 7.48 (br s, 1H), 7.32–7.40 (m, 5H), 7.17 (br s, 1H), 6.05 (br s, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 3.80–3.95 (m, 16H), 3.68 (s, 3H), 2.69 (d, *J* = 14.6 Hz, 1H), 2.50–2.59 (m, 3H), 2.20–2.49 (m, 8H), 1.85–2.18 (m, 12H); FAB-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{41}H_{54}N_4NaO_{15}$ 865.3483, found 865.3486.

(*S*)-Ac$_5$c^{3EG} Pentapeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_5$-OMe; (*S*)-16]

Pentapeptide (*S*)-**16** was prepared from tetrapeptide (*S*)-**15** in a manner similar to that described for the preparation of (*S*)-**14**: 37%; colorless crystals; mp 223–225 °C (decomp.); $[\alpha]^{28}_D$ −28.1 (*c* 1.00, $CHCl_3$); IR (KBr) 3333 (br), 2955, 2886, 1736, 1663, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.56 (br s, 1H), 7.52 (br s, 1H), 7.32–7.42 (m, 5H), 7.03 (br s, 1H), 5.88 (br s, 1H), 5.15 (s, 2H), 3.75–3.95 (m, 20H), 3.69 (s, 3H), 2.62–2.80 (m, 4H), 2.22–2.40 (m, 10H), 1.88–2.21 (m, 16H); FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{49}H_{66}N_5O_{18}$ 1102.4403, found 1102.4406.

(*S*)-Ac$_5$c^{3EG} Hexapeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_6$-OMe; (*S*)-17]

Hexapeptide (*S*)-**17** was prepared from pentapeptide (*S*)-**16** in a manner similar to that described for the preparation of (*S*)-**14**: 59%; colorless crystals; mp 129–132 °C (decomp.); $[\alpha]^{31}_{D}$ −54.2 (*c* 0.70, $CHCl_3$); IR ($CDCl_3$) 3333 (br), 2955, 1744, 1670, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (br s, 1H), 7.77 (br s, 1H), 7.70 (br s, 1H), 7.63 (br s, 1H), 7.30–7.42 (m, 5H), 7.04 (br s, 1H), 5.94 (br s, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 3.76–3.95 (m, 24H), 3.71 (s, 3H), 1.90–2.66 (m, 36H); FAB-HRMS: *m/z* $[M+H]^+$ calcd for $C_{57}H_{77}N_6O_{21}$ 1181.5142, found 1181.5159.

(*S*)-Ac$_5$c^{3EG} Heptapeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_7$-OMe; (*S*)-18]

Heptapeptide (*S*)-**18** was prepared from hexapeptide (*S*)-**17** in a manner similar to that described for the preparation of (*S*)-**14**: 44%; colorless crystals; mp 80–82 °C (decomp.); $[\alpha]^{29}_{D}$ −59.8 (*c* 1.27, $CHCl_3$); IR ($CDCl_3$) 3314 (br), 2955, 1748, 1663, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (br s, 1H), 7.78 (br s, 1H), 7.72 (br s, 1H), 7.67 (br s, 1H), 7.64 (br s, 1H), 7.32–7.42 (m, 5H), 6.93 (br s, 1H), 5.81 (br s, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 3.77–3.95 (m, 28H), 3.69 (s, 3H), 1.85–2.64 (m, 42H); FAB-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{65}H_{87}N_7NaO_{24}$ 1372.5700, found 1372.5699.

(*S*)-Ac$_5$c^{3EG} Octapeptide [Cbz-{(*S*)-Ac$_5$c^{3EG}}$_8$-OMe; (*S*)-19]

Octapeptide (*S*)-**19** was prepared from heptapeptide (*S*)-**18** in a manner similar to that described for the preparation of (*S*)-**14**: 6%; a white solid; $[\alpha]^{28}_{D}$ −62.1 (*c* 0.35, $CHCl_3$); IR ($CDCl_3$) 3310 (br), 2955, 1748, 1659, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.84 (m, 4H), 7.65 (br s, 1H), 7.58 (br s, 1H), 7.31–7.42 (m, 5H), 6.81 (br s, 1H), 5.63 (br s, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 3.76–3.96 (m, 32H), 3.69 (s, 3H), 1.89–2.65 (m, 48H); FAB-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{73}H_{98}N_8NaO_{27}$ 1541.6439, found 1541.6423.

REFERENCES

1. Gellman, S. H. Acc. Chem. Res. 1998, 31, 173–180.
2. Seebach, D.; Matthews, J. L. Chem. Commun. 1997, 2015–2022.
3. Fischer, L.; Guichard, G. Org. Biomol. Chem. 2010, 8, 3101–3117.
4. Heimgartner, H. Angew. Chem. Int. Ed. 1991, 30, 238–264.
5. Toniolo, C.; Crisma, M.; Formaggio, F.; Valle, G.; Cavicchioni, G.; Précigoux, G.; Aubry, A.; Kamphuis, J. Biopolymers 1993, 33, 1061–1072.
6. Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. Biopolymers (Pept. Sci.) 2001, 90, 396–419.
7. Tanaka, M. Chem. Pharm. Bull. 2007, 55, 349–358.
8. Crisma, M.; Toniolo, C. Biopolymers (Pept. Sci.) 2015, 104, 46–64.
9. Crisma, C.; De Zotti, M.; Formaggio, F.; Peggion, C.; Moretto, A.; Toniolo, C. J. Pept. Sci. 2015, 21, 148–177.
10. Nagano, M.; Doi, M.; Kurihara, M.; Suemune, H.; Tanaka, M. Org. Lett. 2010, 12, 3564–3566.
11. Yamagata, N.; Demizu, Y.; Sato, Y.; Doi, M.; Tanaka, M.; Nagasawa, K.; Okuda, H.; Kurihara, M. Tetrahedron Lett. 2011, 52,798–801.
12. Demizu, Y.; Yamagata, N.; Nagoya, S.; Sato, Y.; Doi, M.; Tanaka, M.; Nagasawa, K.; Okuda, H.; Kurihara, M. Tetrahedron 2011, 67, 6155–6165.
13. Licini, G.; Bonchio, M.; Broxterman, Q. B.; Kaptein, B.; Moretto, A.; Toniolo, C.; Scrimin, P. Biopolymers (Pept. Sci.) 2006, 84, 97–104.
14. Barrett, K. T.; Miller, S. J. J. Am. Chem. Soc. 2013, 135, 2963–2966.
15. Wada, S.; Hashimoto, Y.; Kawai, Y.; Miyata, K.; Tsuda, H.; Nakagawa, O.; Urata, H. Bioorg. Med. Chem. 2013, 21, 7669–7673.
16. Hsiao, Y.-C.; Lee, C.-Y.; Lin, Y.-J.; Tsai, S.-H.; Jeng, K.-C. G.; Chao, W.-T.; Lung, F.-Di T. Medicinal Chemistry Research 2013, 22, 5337–5343.

17. Kato, K.; Oba, M.; Nishida, K.; Tanaka, M. Bioconjugate Chem. 2014, 25, 1761–1768.

18. Yamashita, H.; Demizu, Y.; Shoda, T.; Sato, Y.; Oba, M.; Tanaka, M.; Kurihara, M. Bioorg. Med. Chem. 2014, 22, 2403–2408.

19. Oba, M.; Ishikawa, N.; Demizu, Y.; Kurihara, M.; Suemune, H.; Tanaka, M. Eur. J. Org. Chem. 2013, 7679–7682.

20. Tanda, K.; Eto, R.; Kato, K.; Oba, M.; Ueda, A.; Suemune, H.; Doi, M.; Demizu, Y.; Kurihara, M.; Tanaka, M. Tetrahedron 2015, 71, 3909–3914.

21. Hirata, Y.; Oba, M.; Fukudome, M.; Demizu, Y.; Kurihara, M.; Doi, M.; Tanaka, M. Peptide Science 2011 (Proceedings of the 48th Japanese peptide Symposium) 2012, 101–102.

22. Nagano, M.; Tanaka, M.; Doi, M.; Demizu, Y.; Kurihara, M.; Suemune, H. Org. Lett. 2009, 11, 1135–1137.

23. Tanaka, M.; Demizu, Y.; Doi, M.; Kurihara, M.; Suemune, H. Angew. Chem. Int. Ed. 2004, 43, 5360–5363.

24. Demizu, Y.; Doi, M.; Kurihara, M.; Maruyama, T.; Suemune, H.; Tanaka, M. Chem. Eur. J. 2012, 18, 2430–2439.

25. Hanaya, T.; Schurrle, K.; Yamamoto, H. Heterocycles 2006, 69, 283–294.

26. Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. Tetrahedron Lett. 2004, 45, 9229–9232.

27. CCDC-1416530 (**5a**) and 1416531 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif.

28. Crisma, M.; Bonora, G. M.; Toniolo, C.; Benedetti, E.; Bavoso, A.; Di Blasio, B.; Pavone, V.; Pedone, C. Int. J. Biol. Macromol. 1988, 10, 300–304.

29. Wolf, W. M.; Stasiak, M.; Leplawy, M. T.; Bianco, A.; Formaggio, F.; Crisma, M.; Toniolo, C. J. Am. Chem. Soc. 1998, 120, 11558–11566.

30. Toniolo, C.; Polese, A.; Formaggio, F.; Crisma, M.; Kamphuis, J. J. Am. Chem. Soc. 1996, 118, 2744–2745.

31. Yoder, G.; Polese, A.; Silva, R. A. G. D.; Formaggio, F.; Crisma, M.; Broxterman, Q. B.; Kamphuis, J.; Toniolo, C.; Keiderling, T. A. J. Am. Chem. Soc. 1997, 119, 10278–10285.

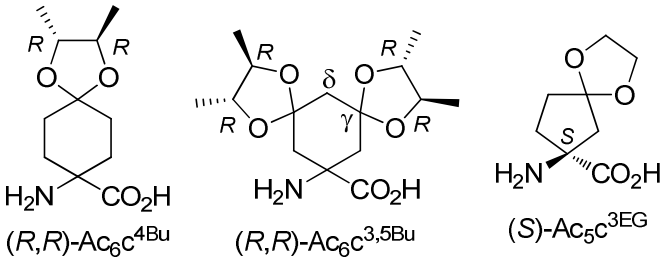
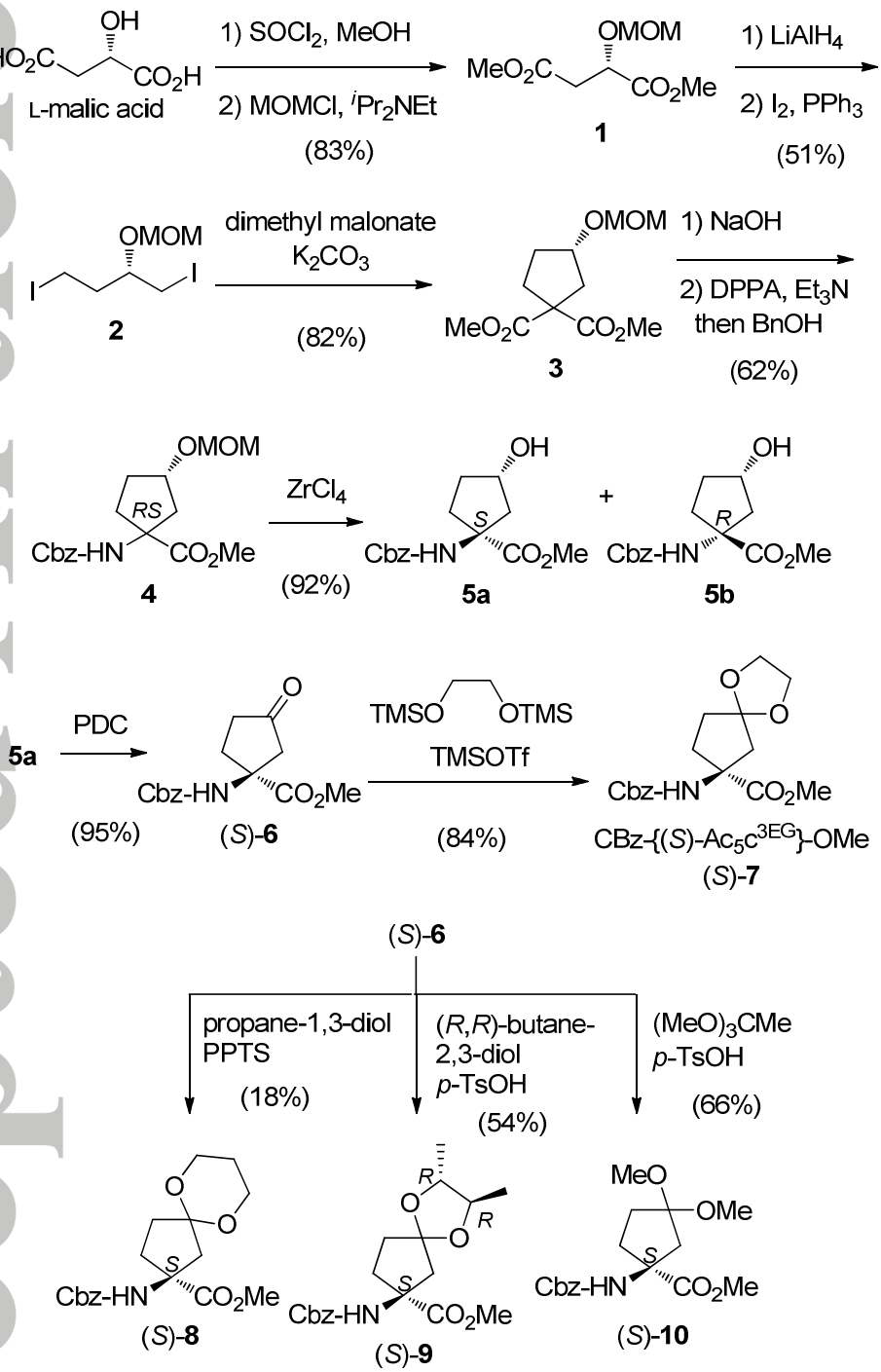
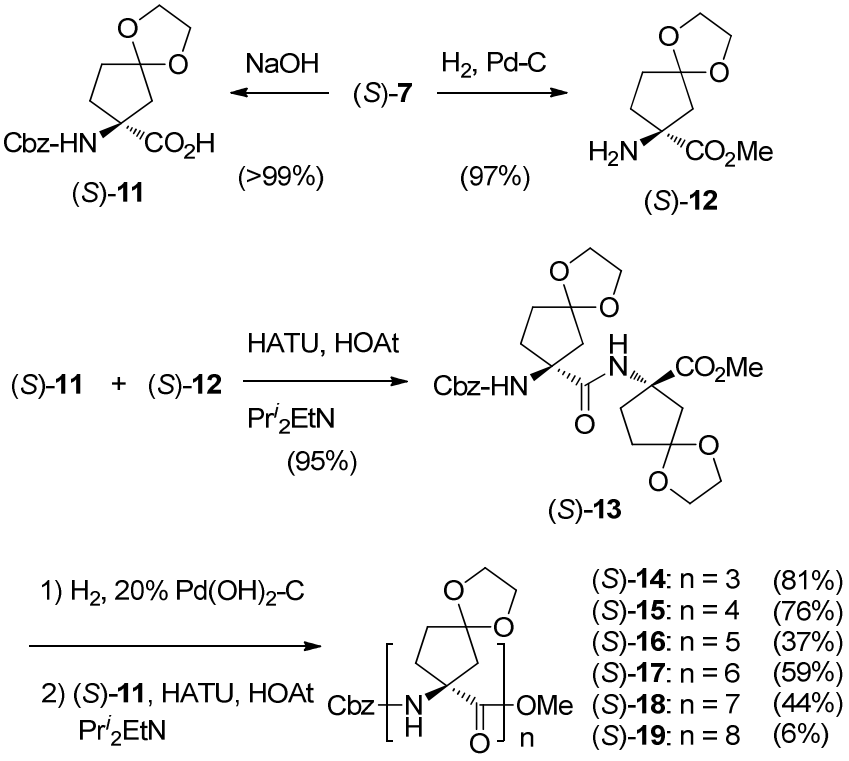


FIGURE 1 Chemical structures of chiral cyclic α,α-disubstituted α-amino acids with acetal moieties.



SCHEME 1 Synthesis of the five-membered carbocyclic ring amino acid (*S*)-Ac_5c^{3EG} and its analogues.



SCHEME 2 Preparation of (*S*)-Ac_5c^{3EG} homopeptides.

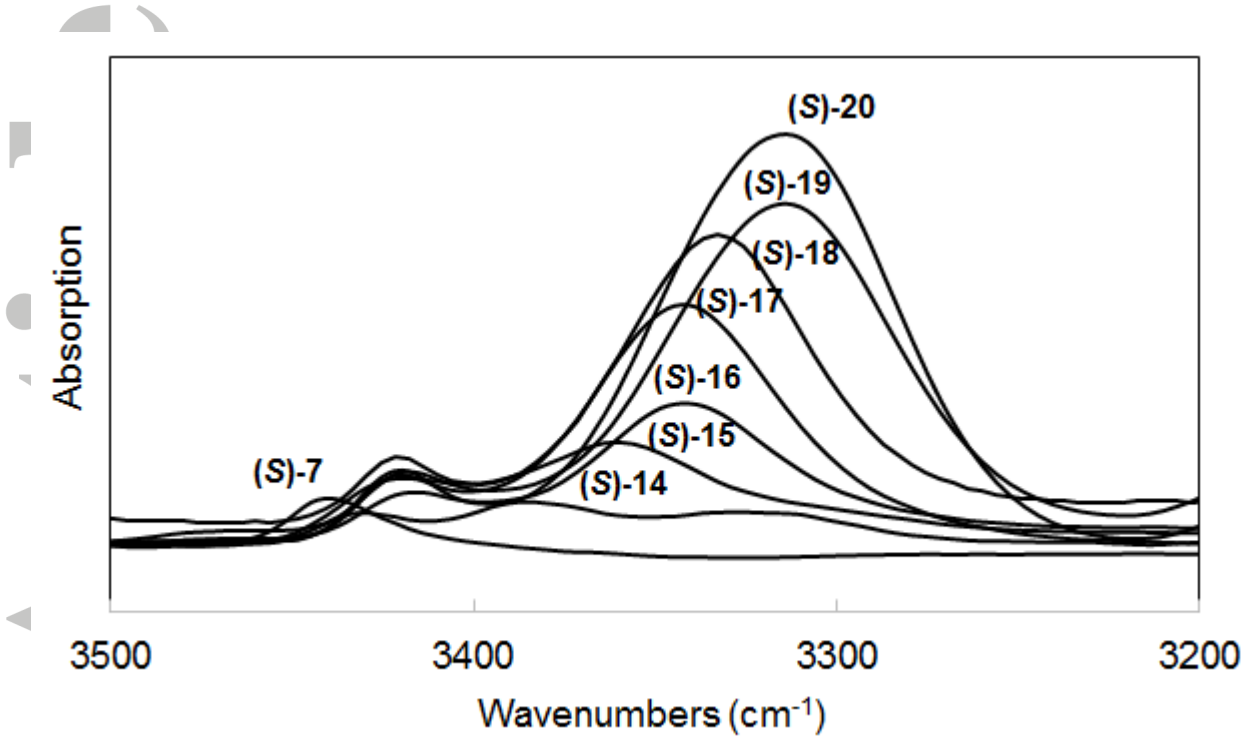


FIGURE 2 FT-IR absorption spectra of homopeptides Cbz-{(*S*)-Ac_5c^{3EG}}$_n$-OMe (**7** and **13**–**19**: n = 1–8) in $CDCl_3$. Peptide concentration: 5 mM.

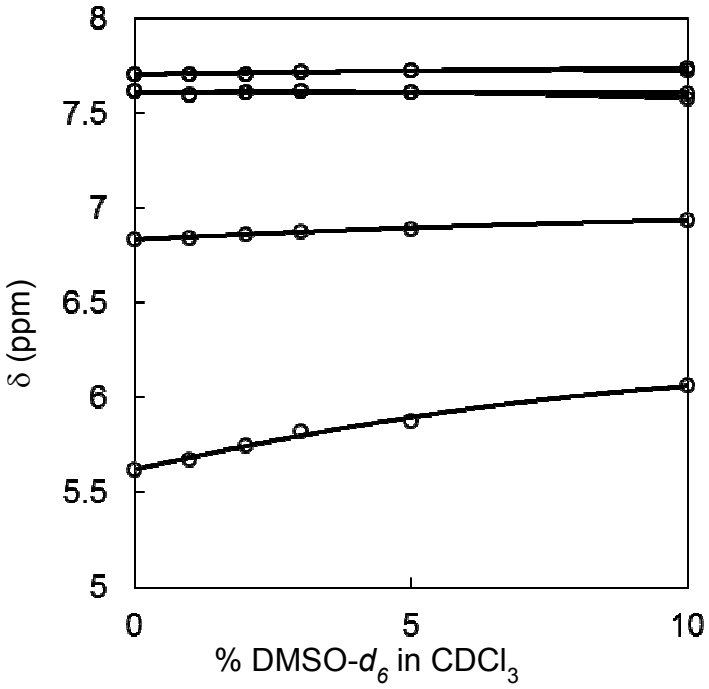


FIGURE 3 Plots of N-H chemical shifts in ^{1}H NMR spectra of Cbz-{(*S*)-Ac$_5$c^{3EG}}$_6$-OMe (*S*)-**17**, as a function of the increasing percentage of DMSO-d_6 (*v/v*) added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

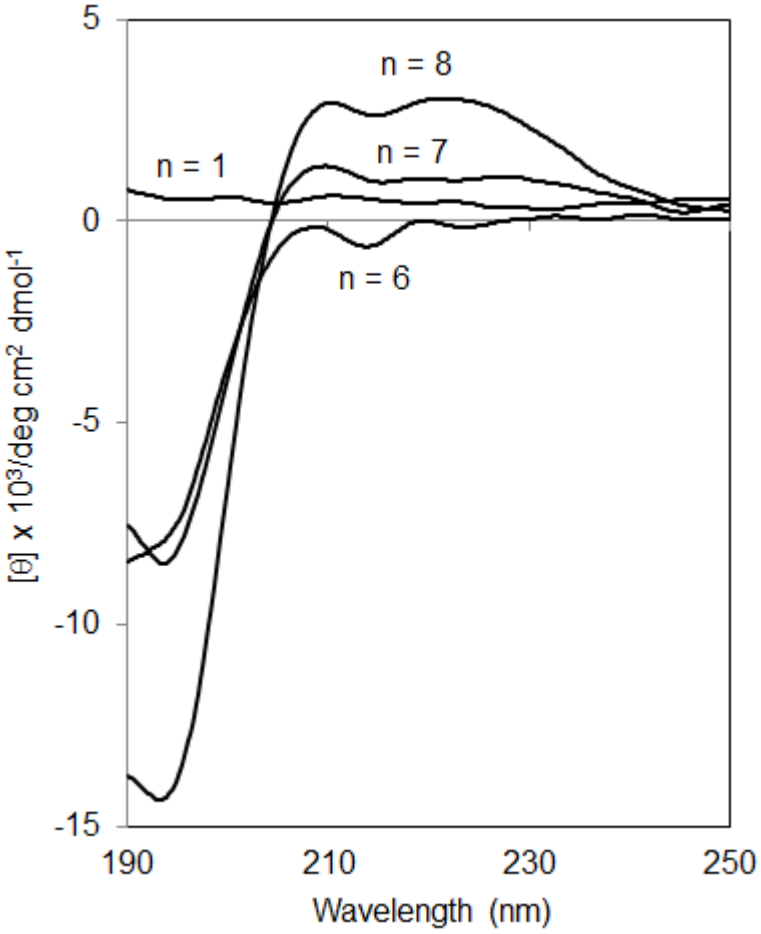


FIGURE 4 CD spectra of (*S*)-Ac_5c^{3EG} homopeptides Cbz-{(*S*)-Ac_5c^{3EG}}$_n$-OMe (**7** and **17**–**19**: n = 1 and 6–8) in TFE solution (0.05 mM).

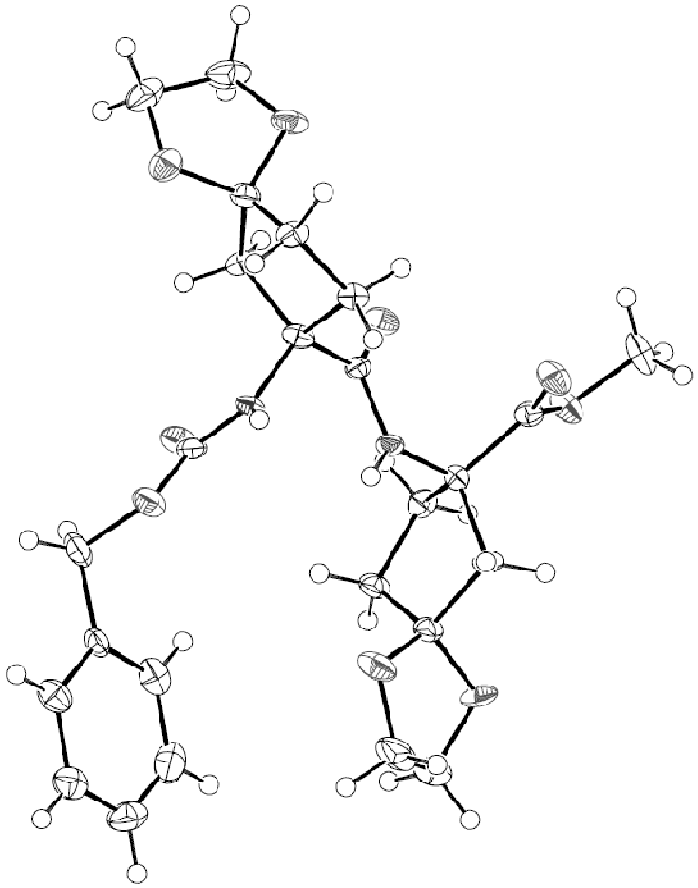


FIGURE 5 An ORTEP drawing of the Cbz-{(*R*)-Ac_5c^{3EG}}$_2$-OMe dipeptide (*R*)-**13**.

TABLE 1 Crystal and diffraction parameters of the Cbz-{(*R*)-Ac_5c^{3EG}}$_2$-OMe dipeptide (*R*)-**13**.

	(*R*)-Ac_5c^{3EG} dipeptide (*R*)-**13**
empirical formula	$C_{25}H_{32}N_2O_9$
*M*r	504.53
crystal dimensions [mm]	0.24×0.06×0.01
crystal system	monoclinic
lattice parameters:	
a, *b*, *c* [Å]	5.942, 24.15, 8.588
α, β, γ [°]	90, 94.419, 90
V [Å^3]	1228.7
space group	$P2_1$
Z value	2
D_{calc} [g/cm^3]	1.364
μ(Mo$K\alpha$) [cm^{-1}]	1.04
no. of observations ($I > -10.0\ \sigma I$)	1849
no. of variables	325
R_1, R_W	0.0739, 0.1709
solvent	EtOH/H_2O