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Stereoselective Synthesis of 2,4-Diamino Acids by Asymmetric Hydrogenation

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A stereoselective synthesis of unusual basic amino acids, ornithine, 2,4-diaminopentanoic acid, and 2,4-diamino-6-methylheptanoic acid, was achieved by the hydrogenation of cyclic α,β-dehydro dipeptides obtained by the condensation of cyclo(-Gly-L(or D)-aminoacyl-) and protected linear or chiral amino aldehydes. The degree of chiral induction greatly depended on the bulkiness of the side chains of α,β-dehydro amino acids. The R_f values on paper chromatography of (2*S*,4*S* or 2*R*,4*S*)-diaminopentanoic acid prepared by the present method were different from the reported values of a compound which had been obtained from metabolic products of *Clostridium sticklandii* and estimated to be 2,4-diaminopentanoic acid.

In any study on the design, synthesis and structure-function of bioactive peptides, the use of unusual amino acids as starting materials is often important. We have established a synthetic method of optically active α-amino acids by asymmetric hydrogenation of cyclic α,β-dehydro dipeptides and successfully prepared lots of α-amino acids.[1–4] However, the method was applied only for the preparation of neutral amino acids. It seems interesting how the chiral induction in hydrogenation would be influenced by a functional and/or chiral side chain in cyclic α,β-dehydro dipeptides. We selected in the present study ornithine (**3**) with a functional side chain, and 2,4-diaminopentanoic acid (**1**) and 2,4-diamino-6-methylheptanoic acid (**2**) with a chiral side chain as target materials (Fig. 1).

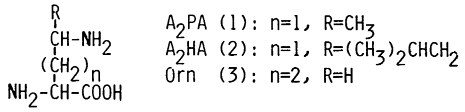

Fig. 1. Structure of synthetic amino acids.

Among compounds **1**—**3**, **1** was reported to be a metabolic intermediate in the an aerobic oxidation of ornithine in *Clostridium sticklandii*.[5] The structure was estimated merely from the behavior on paper chromatography and the metabolic pathway because of the scarce presence of the intermediate in the cells. Since the isolation and identification of the intermediate have not yet been carried out, its chemical and optical identification is attractive. Compound **2** was previously synthesized as a diastereoisomer by catalytic hydrogenation of ethyl 3-propyl-5-pyrazolinecarboxylate, but not obtained as an optically active one.[6] Hence, the stereoselective synthesis of the optically active diastereoisomer is also of interest.

Results and Discussion

The synthetic route for **1** and **2** is shown in Fig. 2. We previously reported that when L-amino acid[7] was used in cyclic α,β-dehydro dipeptide as a chiral source,

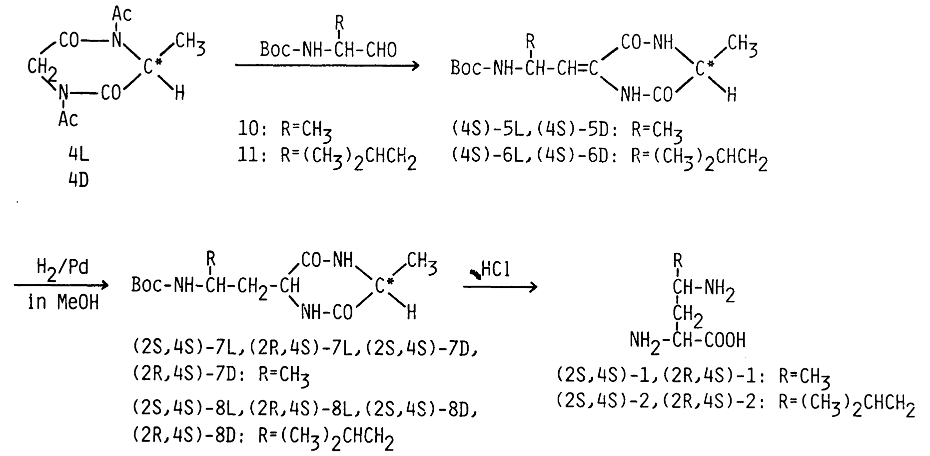

Fig. 2. Synthetic route for 2,4-diamino acids (**1** and **2**).

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asymmetric hydrogenation exclusively gave L-amino acid.[1] If the asymmetric hydrogenation of cyclic α,β-dehydro dipeptides (**5** and **6**) proceeds stereospecifically, it is able to synthesize stereoselectively two optical isomers of **1** and those of **2**, respectively, via the condensation of **4L** and **4D** with the protected (2*S*)-2-amino aldehyde (**10** or **11**) followed by hydrogenation. As an asymmetric source, we chose neutral L- or D-alanine because of the easy separation of alanine from basic amino acids, i.e., final products.

In the synthesis of **1**, the condensation of **4L** with Boc-(2*S*)-alaninal (**10**)[8] in the presence of *t*-BuOK[9] gave cyclic acetyl-α,β-dehydro dipeptide, which was then deacetylated by the action of 1-(2-aminoethyl)piperazine to afford cyclic α,β-dehydro dipeptide, (4*S*)-**5L**. A mixture of (2*S*,4*S*)-**7L** and (2*R*,4*S*)-**7L** was obtained by hydrogenation of (4*S*)-**5L** in the presence of Pd-black. In order to determine the formation ratio of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1**, the hydrogenated mixture was subjected to acid hydrolysis and then amino acid analysis. The elution pattern of the hydrolysate is shown in Fig. 3. The stereochemistry in this amino acid was deduced as follows: the main product should be (2*S*,4*S*)-**1**, based on the previously proposed mechanism for the asymmetric hydrogenation of cyclic α,β-dehydro dipeptides.[1] The peak ratio of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** in the hydrolysate was 3:2. The color yield of the purified optical isomers, (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1**, for ninhydrin was determined to be ca. 1:1. Thus, the chiral induction of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** in hydrogenation was calculated to be 3:2, as shown in Table 1. After the isomers were separated with AG 50WX8 using a sodium citrate buffer (pH 5.28) as an eluent, the final products were purified by recrystallization. Their purity was confirmed by thin-layer chromatography and elemental analysis. The preparation of **1** from (4*S*)-**5D** was also carried out similarly (Fig. 2). The use of **4D** instead of **4L** gave highly stereoselectively (2*R*,4*S*)-**1** (Table 1). Compound **2** was obtained from **4L** or **4D** and Boc-(2*S*)-leucinal (**11**)[8] in the same manner as described above. The ^{1}H NMR spectra of (4*S*)-**6L** and (4*S*)-**6D** obtained (Fig. 4) showed that the signal peaks corresponding to each functional group were observed. It is suggested that the *Z*- or *E*-isomer was formed stereoselectively without racemization in the condensation reaction. To determine the geometric isomers of *Z*- or *E*-isomer, we measured the NOESY spectrum by 2D NMR spectroscopy. The correlation between the amide proton of piperazinedione ($-\overset{|}{C}=\overset{|}{C}-NH-$) and proton of asymmetric carbon ($-\overset{|}{N}-\overset{|}{C}H-\overset{|}{C}=$) in the NOESY spectrum indicates that these proton are closely located. Consequently, (4*S*)-**6L** and (4*S*)-**6D** are not *E*-isomer but *Z*-isomer. Compounds (4*S*)-**5L** and (4*S*)-**5D** also showed NMR spectra similar to those of (4*S*)-**6L** and (4*S*)-**6D**, respectively (data not shown). Compounds (4*S*)-**6L** and (4*S*)-**6D** were not obtained in good yields. The low yields can probably be attributable to slow reaction, because the TLC of the reaction mixture showed main spots of the product and the starting materials, including some minor spots. The condensation of **4L** with **11** gave selectively (2*S*,4*S*)-2,4-diamino-6-methylheptanoic acid (**2**). In the case of **4D**, the product was a mixture of (2*S*,4*S*)-**2** and (2*R*,4*S*)-**2**, although the formation of (2*R*,4*S*)-**2** was fairly preferential. In the case of **3**, Boc-3-aminopropionaldehyde was obtained from Boc-3-amino-1-propanol by oxidation with pyridium dichromate,[10] and diethylamine was used instead of 1-(2-aminoethyl)piperazine in the step of deacetylation. Compound **3** was obtained in good optical yield from cyclo(-ΔOrn(Boc)-L-Ala-) (**9**), which was derived from **4L** and Boc-3-aminopropionaldehyde.

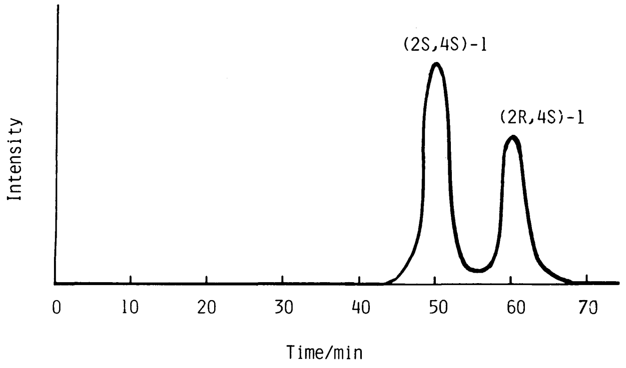

Fig. 3. Elution pattern of A_2PA.

We previously presented a presumptive mechanism on the asymmetric hydrogenation of cyclic α,β-dehydro dipeptide; the rigid planar structure of cyclic α,β-dehydro dipeptide, which is induced when the peptide is absorbed on the catalyst, has an important effect on asymmetric hydrogenation.[11] However, if there is a group which makes adsorption of the ring structure on the catalyst disadvantageous, the chiral induction in hydrogenation will decrease. The fact that L-ornithine (**3**) was obtained in good optical yield indicates that, when L-alanine was used as a chiral source, the

Table 1. Chiral Induction in Hydrogenation of Cyclic Dehydrodipeptides

Cyclic dehydrodipeptide	Amino acid	Chiral induction
(4*S*)-**5L**	A_2PA	3:2 (2*S*,4*S*:2*R*,4*S*)
(4*S*)-**5D**	A_2PA	1:5 (2*S*,4*S*:2*R*,4*S*)
(4*S*)-**6L**	A_2HA	95:5 (2*S*,4*S*:2*R*,4*S*)
(4*S*)-**6D**	A_2HA	2:3 (2*S*,4*S*:2*R*,4*S*)

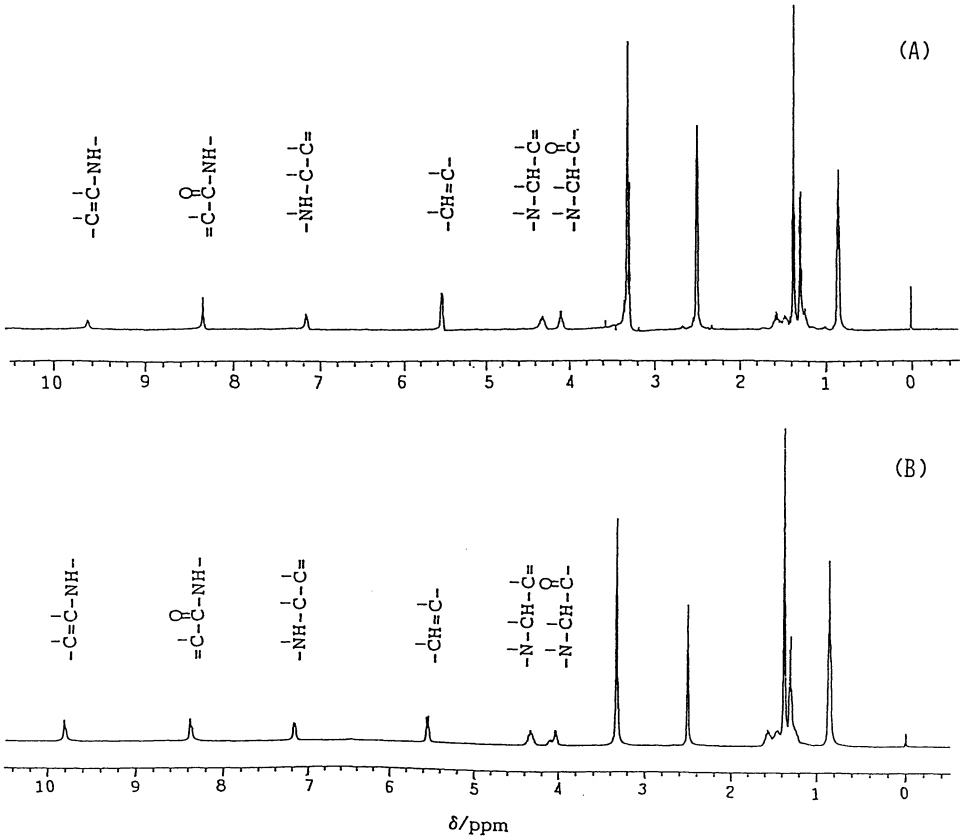

Fig. 4. ${}^1H$ NMR spectra of dehydro compounds (4*S*)-**6L** (A) and (4*S*)-**6D** (B).

Table 2. Comparison of the Chromatographic Property of Synthetic Compounds **1**, L-Ornithine, and Reported Compound[a)]

Solvent	(2*S*,4*S*)-**1**	(2*R*,4*S*)-**1**	L-Orn	Reported compound	L-Orn
MeOH:H_2O:pyridine (20:5:1)	0.08	0.12	0.13	0.46[b)]	0.16[b)]
1-Propanol:pyridine:H_2O (1:1:1)	0.10	0.22	0.23	0.42[b)]	0.22[b)]

a) Paper chromatography was carried out on Whatmann 3MM paper. b) Cited from Ref. 5.

adsorption of the urethane group on a catalytic surface had no effect on the optical yield. In the case of (4*S*)-**5L**, (4*S*)-**5D**, and (4*S*)-**6D**, the optical yields were relatively low. It is considered from the CPK model that free rotation between β- and γ-carbon atoms in the dehydro moiety is hindered because of collision of urethane NH and α-NH in the dehydroamino acid residue. Consequently, the side chain (CH_3 or $(CH_3)_2CHCH_2$) and the Boc group project to the upper and lower side, respectively, of the piperazinedione ring or vice versa. This indicates that the extent of chiral induction is not necessarily determined only by the methyl side chain in the Ala residue, i.e., chiral source. Interestingly, (4*S*)-**6L** could be highly selectively hydrogenated, although we can not now explain the reason.

The R_f values on paper chromatography of synthetic (2*S*,4*S*)-**1** and (2*S*,4*R*)-**1** were quite different from those of the reported compound which was estimated previously as 2,4-diaminopentanoic acid (see Table 2). Therefore, the structure of the metabolic intermediate should be reexamined. To date, the intermediates in the similar reactions in the lysine fermentation have been identified as 3,6-diaminohexanoic acid (β-lysine),[12)] 3,5-diaminohexanoic acid,[13,14)] and 5-amino-3-oxohexanoic acid.[15)] Another amino acid has been tentatively identified as 2,5-diaminohexanoic acid.[16)]

We tried to develop our asymmetric synthesis for the preparation of unusual basic amino acids. Further work along this line is in progress in order to obtain stereoselectively complicated amino acid, such as ones containing two or more asymmetric centers.

Experimental

Thin-layer chromatography was performed on silica gel G (Merck) with the following solvent systems: R_f^1 *n*-BuOH-AcOH-pyridine-H_2O (4:1:1:2, v/v); R_f^2, $CHCl_3$-MeOH (5:1, v/v); R_f^3, $CHCl_3$-EtOAc (1:1, v/v); R_f^4, *n*-BuOH-AcOH-H_2O (1:1:2, v/v). Optical rotations were measured on a Union high-sensitivity polarimeter PM-71. Amino acid analyses were performed with a Hitachi KLA-5 amino acid analyzer after the hydrolysis in 6 M HCl (1 M=1 mol dm^{-3}) in sealed tubes at 110 °C for 24 h. ^{1}H NMR spectra were determined at 25 °C with JEOL JNN-GX-400 spectrometer (400 MHz) using Me_4Si as the internal standard in DMSO-d_6.

Cyclo(-Ac-Gly-Ac-L-Ala-) (4L) and Cyclo(-Ac-Gly-Ac-D-Ala-) (4D). Compound **4L** and **4D** were synthesized by the same procedure as that described in the literature.[1]

Cyclo(-ΔA$_2$PA(Boc)-L-Ala-) ((4*S*)-5L). To a chilled solution of **4L** (2.2 g, 10.5 mmol) in DMF (15 ml) were added a solution of *t*-BuOK (1.2 g, 10.5 mmol) in *t*-BuOH (20 ml) and **10** (1.82 g, 10.5 mmol)[8] at 0 °C. The mixture was stirred at 0 °C for 2 h and at 25 °C for 3 h. After evaporation in vacuo, the residue was dissolved in EtOAc, washed with water, dried over Na_2SO_4 and evaporated. Oily cyclo(-ΔA$_2$PA-N-Ac-L-Ala-) was dissolved in DMF (5 ml), and to the solution was added 1-(2-aminoethyl)piperazine (2.6 ml) at 0 °C. The solution was stirred at 0 °C for 1 h and at 25 °C for 2 h and evaporated in vacuo. The residue was dissolved in EtOAc, washed with 10% citric acid and aq. NaCl, dried over Na_2SO_4 and evaporated. The residual oil was crystallized by the addition of MeOH-ether. Yield, 600 mg (28%); mp 215—220 °C; $[\alpha]_D^{20}$ +106° (*c* 1.0, MeOH); R_f^2 0.73. Found: C, 54.81; H, 7.34; N, 14.70%. Calcd for $C_{13}H_{21}O_4N_3$: C, 55.11; H, 7.47; N, 14.83%. Compound (4*S*)-**5D** was prepared similarly from **4D** and **10**. Yield, 59%; mp 210—214 °C; $[\alpha]_D^{20}$ +104° (*c* 1.0, MeOH); R_f^2 0.68. Found: C, 55.22; H, 7.47; N, 14.55%.

Cyclo(-ΔA$_2$HA(Boc)-L-Ala-) ((4*S*)-6L). Compound (4*S*)-**6L** was synthesized by the same procedure as that described above using **4L** (1.7 g, 7.9 mmol) and **11** (2.36 g, 10.5 mmol).[8] Yield, 475 mg (19%); mp 187—191 °C; $[\alpha]_D^{20}$ +106° (*c* 1.0, MeOH); R_f^3 0.34. Found: C, 58.66; H, 8.39; N, 12.65%. Calcd for $C_{16}H_{27}O_4N_3$: C, 59.06; H, 8.39; N, 12.91%. Compound (4*S*)-**6D** was prepared similarly from **4D** and **11**. Yield 19%; mp 179—185 °C; $[\alpha]_D^{20}$ +108° (*c* 1.0, MeOH); R_f^3 0.33. Found: C, 58.78; H, 8.39; N, 12.76%.

Cyclo(-A$_2$PA(Boc)-L-Ala-). Compound (4*S*)-**5L** (567 mg, 2 mmol) was dissolved in MeOH (20 ml) and hydrogenated at 1 atm pressure of H_2 in the presence of Pd black (20 mg) for 5 h at 25 °C. The filtrate was evaporated and the residue was crystallized by the addition of ether-petroleum ether. The hydrogenated compound was observed to show two spots by R_f^3, owing to the presence of diastereomers ((2*S*, 4*S*)-**7L** and (2*R*,4*S*)-**7L**). Yield of the diastereomers, 525 mg (92%), R_f^3 0.27 and 0.15. Cyclo(-A$_2$PA(Boc)-D-Ala-) was prepared similarly. Yield of the diastereomers ((2*S*,4*S*)-**7D** plus (2*R*,4*S*)-**7D**), 90%; R_f^3 0.25 and 0.15.

Cyclo(-A$_2$HA(Boc)-L-Ala-). This compound was synthesized by the same procedure as described above using (4*S*)-**6L** (423 mg, 1.3 mmol). The yield of the diastereomers ((2*S*, 4*S*)-**8L** plus (2*R*,4*S*)-**8L**), 362 mg (85%); R_f^3 0.38 and 0.36. Cyclo(-A$_2$HA(Boc)-D-Ala-) was prepared similarly. The yield of the diastereomers ((2*S*,4*S*)-**8D** plus (2*R*,4*S*)-**8D**) was 93%; R_f^3 0.37 and 0.34.

2,4-Diaminopentanoic Acid ((2*S*,4*S*)-1 and (2*R*,4*S*)-1). Cyclo(-A$_2$PA(Boc)-L-Ala-) (428 mg, 1.5 mmol) was hydrolyzed with 6 M HCl at 110 °C for 24 h. The solution was evaporated several times by the addition of water. The residue dissolved in water was put on a column of Dowex 50WX8 (200—400 mesh, H$^+$ form). The column was washed with water, 1 M pyridine, and eluted with 2 M aq. ammonia. The eluate was evaporated several times by the addition of water. The enantiomeric ratio of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** was determined using a portion of the residue as 3:2 with an amino acid analyzer. The yield of (2*S*,4*S*)-**1** plus (2*R*,4*S*)-**1** was 172 mg (87%); R_f^1 0.33 and 0.25. The ratio of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** from cyclo(-A$_2$PA(Boc)-D-Ala-) was 1:5. The yield of (2*S*,4*S*)-**1** plus (2*R*,4*S*)-**1** in a 1.5 mmol scale was 163 mg (82%); R_f^1 0.33 and 0.25. The residue was solidified from H_2O-acetone as its monohydrochloride by the addition of an equivalent hydrochloric acid.

2,4-Diamino-6-methylheptanoic Acid ((2*S*,4*S*)-2 and (2*R*, 4*S*)-2). Hydrolysis of cyclo(-A$_2$HA(Boc)-L-Ala-) and cyclo(-A$_2$HA(Boc)-D-Ala-) (327 mg, 1 mmol each) was performed by the same procedure as that described above. The ratios of (2*S*,4*S*)-**2** and (2*R*,4*S*)-**2** were determined as 95:5 from cyclo(-A$_2$HA(Boc)-L-Ala-) and 2:3 from cyclo(-A$_2$HA(Boc)-D-Ala-), respectively. Yields of (2*S*,4*S*)-**2** plus (2*R*,4*S*)-**2** from cyclo(-A$_2$HA(Boc)-L-Ala-) and from cyclo(-A$_2$HA(Boc)-D-Ala-) were 194 mg (92%) and 169 mg (80%), respectively; R_f^1 0.64 and 0.25.

Separation of (2*S*,4*S*)-1 and (2*R*,4*S*)-1. Diastereomeric 2,4-diaminopentanoic acid (**1**) from cyclo(-A$_2$PA(Boc)-L-Ala-) (68 mg 0.4 mmol) was separated into its diastereoisomers by chromatography using a colum (1.8×150 cm) of AG 50WX8 (200—400 mesh, H$^+$ from). Diastereomers were eluted with a 0.35 M sodium citrate buffer of pH 5.28. The component of the fraction from 1850 to 2000 ml was confirmed to be (2*S*,4*S*)-**1** and that of the fraction from 2300 to 2450 ml to be (2*R*,4*S*)-**1**, using an amino acid analyzer. Each of the fractions containing (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** was concentrated. The concentrated solution was desalted using Dowex 50WX8 (200—400 mesh, H$^+$ form). After washing with water, the basic amino acid was eluted with 2 M aq. ammonia. The eluate was evaporated several times in order to remove excess ammonia by the addition of water. The residue was recrystallized from H_2O-acetone as its monohydrochloride. Recoveries of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1** were 32 mg (77%) and 16 mg (59%), respectively. (2*S*,4*S*)-**1**; mp 185—191 °C (decomp); $[\alpha]_D^{20}$ +7.2° (*c* 0.3, H_2O); R_f^1 0.33. Found: C, 35.90; H, 7.65; N, 16.21%. Calcd for $C_5H_{12}O_2N_2 \cdot HCl$: C, 35.61; H, 7.77; N, 16.61%. (2*R*,4*S*)-**1**; mp 198—202 °C (decomp); $[\alpha]_D^{20}$ −5.0° (*c* 1.0, H_2O); R_f^1 0.25. Found: C, 35.77; H, 7.78; N, 16.03%. Diastereomeric **1** (68 mg, 0.4 mmol) from cyclo(-A$_2$PA(Boc)-D-Ala-) was also treated similarly. Recoveries of (2*S*,4*S*)-**1** and (2*R*,4*S*)-**1**, 6 mg (45%) and 40 mg (72%).

Separation of (2*S*,4*S*)-2 and (2*R*,4*S*)-2. Diastereoisomeric 2,4-diamino-6-methylheptanoic acid from cyclo (-A$_2$HA(Boc)-L-Ala-) (105 mg, 0.5 mmol) was separated into its diastereoisomers by chromatography using a column (1×30 cm) of AG 50WX8 (200—400 mesh, H$^+$ form). Diastereoisomers were eluted with a 0.35 M sodium citrate buffer of pH 5.28. The component of the fraction from 350 to 500 ml was confirmed to be (2*S*,4*S*)-**2**, and that of the fraction from 650 ml to 800 ml to be (2*R*,4*S*)-**2**, and worked up as described above. Recoveries of (2*S*,4*S*)-**2** and (2*R*,4*S*)-**2** were 82 mg (82%) and 4 mg (74%), respectively. (2*S*,4*S*)-**2**; mp 235—240 °C (decomp); $[\alpha]_D^{20}$ +7.6° (*c* 0.5, H_2O); R_f^1 0.63. Found: C, 45.28; H, 9.02; N, 13.30%. Calcd for $C_8H_{18}O_2N_2\cdot HCl$: C, 45.60; H, 9.09; N, 13.30%. (2*R*,4*S*)-**2**; mp 245—248 °C (decomp); $[\alpha]_D^{20}$ −5.3° (*c* 0.5, H_2O); R_f^1 0.55. Found: C, 45.35; H, 9.25; N, 13.15%. Diastereomeric **2** (105 mg) from cyclo(-A₂HA(Boc)-D-Ala-) was also treated similarly. Recoveries of (2*S*,4*S*)-**2** and (2*R*,4*S*)-**2** were 32 mg (76%) and 53 mg (83%), respectively.

Cyclo(-ΔOrn(Boc)-L-Ala-) (9). To a solution of Boc-$NH(CH_2)_3OH$ (9.58 g, 54.7 mmol) in CH_2Cl_2 (200 ml) was added pyridium dichromate (43.76 g, 109 mmol). The mixture was stirred at room temperature for 24 h. After evaporation in vacuo, the residue dissolved in EtOAc was put on a column of silica gel and the portion containing aldehyde was collected. After evaporation in vacuo, crude aldehyde (6.31 g, 12.2 mmol) was obtained. To a solution of crude aldehyde in DMF (40 ml) were added a solution of *t*-BuOK (1.64 g, 12.2 mmol) in *t*-BuOH (30 ml) and **4L** (2.63 g, 12.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, at 25 °C for 24 h and evaporated in vacuo. The residue was dissolved in EtOAc, washed with water, dried over Na_2SO_4 and evaporated. The residue was dissolved in DMF (6 ml) and was added to $NH_2NH_2\cdot H_2O$ (0.97 ml, 12.2 mmol). The mixture was stirred at 25 °C for 2 h and evaporated. The residue was crystallized by the addition of ether. Yield, 1.85 g (54%); mp 233—235 °C; $[\alpha]_D^{20}$ −12.4° (*c* 1.0, DMF); R_f^2 0.69. Found: C, 55.03; H, 7.56; N, 14.78%. Calcd for $C_{13}H_{21}O_4N_3$: C, 55.11; H, 7.47; N, 14.83%.

Cyclo(-Orn(Boc)-L-Ala-). This compound was synthesized from **9** (220 mg, 0.78 mmol) by the same procedure as described for the preparation of cyclo(-A₂PA(Boc)-L-Ala-). The yield was 208 mg (94%).

L-Ornithine (3). The hydrolysis of cyclo(-Orn(Boc)-L-Ala-) (460 mg, 1.6 mmol) was performed by the same procedure described for the preparation of **1**. This compound was confirmed to be L-Orn, as compared with authentic L-Orn by thin-layer chromatography and polarimetry. The yield was 130 mg (62%); R_f^1 0.03, R_f^4 0.54; $[\alpha]_D^{20}$ +17.1° (*c* 1.0, H_2O) (lit,[17] $[\alpha]_D^{20}$ +16.8° (*c* 1, H_2O)).

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