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Facile Synthesis of (2*R*,3*R*)-Phenylalanine-2,3-d_2 and NMR Study on Deuterated Gramicidin S[1)]

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(2*R*,3*R*)-Phenylalanine-2,3-d_2 (D-Phe*) was synthesized through catalytic reduction of *cyclo*(-(*Z*)-2,3-dehydrophenylalanyl-D-alanyl-) under an atmosphere of $^2H_2$ and successive acid hydrolysis in the yield of 80% in high chiral induction. The D-Phe* thus obtained was used for synthesis of [D-Phe*$^{4,4'}$] gramicidin S (GS*). The ^{1}H NMR spectrum of GS* in DMSO-d_6 showed a sharp singlet at 2.98 ppm for the (3*S*)-proton of D-Phe* residue. It has been proposed that among rotamers of D-Phe aromatic side chain in GS the one with κ_1=180° is predominant. The present observation provides sound evidence for assignments of D-Phe β-protons based on the proposal.

Selectively deuterated amino acid is important for studying conformations of biologically active peptides and proteins. Kirby and Michael[2)] synthesized 3-deuterated aromatic amino acids by catalytic hydrogenation of *trans*-α-acylaminocinnamic acid-β-*d* derivatives and subsequent deacylation with acylase. Kainosho and Ajisaka[3)] synthesized selectively deuterated L-amino acids by use of enzyme and studied conformations of the amino acids in aqueous solutions. Nagai and Kobayashi[4)] used α-chymotrypsin instead of acylase and obtained both diastereomers, (2*S*,3*R*)-*N*-acetyl-L-phenylalanine-3-*d* and (2*R*,3*R*)-*N*-acetyl-D-phenylalanine-3-*d* ethyl ester in the yield of 6% each. The prefixes L and D are used here to clarify configuration at the α-center. These deuterated amino acids were used to the synthesis and conformational studies of [Met^5]enkephalin.[5,6)] In every case, optical resolution was inevitable at the final stage in the amino acid synthesis, lowering the yields of deuterated products.

Izumiya *et al.*[7,8)] recently developed a new method for synthesizing optically active amino acids, that is, catalytic hydrogenation of dipeptide anhydrides containing a dehydroamino acid residue and an L- or D-amino acid residue. They observed that the condensation of *cyclo*(-*N*-acetyl-glycyl-*N*-acetyl-L-alanyl-) with benzaldehyde exclusively yielded *cyclo*(-2,3-dehydrophenylalanyl-*N*-acetyl-L-alanyl-) of *Z* configuration. Deacetylation with hydrazine, catalytic hydrogenation in the presence of Pd black, and successive acid hydrolysis yielded L-phenylalanine in high chiral inductiction, 97.0%.[9)]

This paper deals with the synthesis of (2*R*,3*R*)-phenylalanine-2,3-d_2 as an example of facile synthesis of the selectively deuterated and optically active aromatic amino acid. We also report the synthesis and ^{1}H NMR analysis of gramicidin S containing two residues of the deuterated D-phenylalanine.

Results and Discussion

Synthesis of (2R,3R)-Phenylalanine-2,3-d$_2$ (D-Phe).* (2*R*,3*R*)-Phenylalanine-2,3-d_2 was synthesized in a manner similar to that described for L-phenylalanine.[9)] *cyclo*(-ΔPhe-D-Ala-) (**3**)[10)] was catalytically reduced under an atmosphere of $^2H_2$ to give *cyclo*(-(2*R*,3*R*)-Phe-2,3-d_2-D-Ala-) (**4**) in an excellent yield. Chiral induction was estimated as 98.8% by HPLC. Compound **4** was hydrolyzed to give (2*R*,3*R*)-phenylalanine-2,3-d_2 (D-Phe*) (**5**); no L-isomer was detected by the modified Manning-Moore method.[11,12)] Content of deuterium was estimated to be 90%±10% by use of ^{1}H NMR spectroscopy. As the chirality at α-center was so high, H–D exchange at the α-center should be, if any, negligible. Therefore, some 10% hydrogen observed in ^{1}H NMR spectrum was attributed to contamination in the course of deuteration. Stereochemistry of β-center was assigned to be *R* according to the literature[2)] and results of previous experiments.[7-9)] Kirby and Michael showed that hydrogenation of *trans*-α-acylaminocinnamic acid derivatives proceeded in *cis* configuration insensitive to variation of substituents and catalysts with at least 95% chirality.[2)] In case of dehydrodipeptide anhydrides, rigid planar structure of the substrates favored highly chiral hydrogenation.[7-9)] The ^{1}H NMR spectrum of D-Phe* (**5**) in TFA-*d* showed a singlet at δ=3.37 with an intensity of 1 H and another singlet at 3.58 with 0.1 H. The latter signal was attributed to βCH proton contaminated in deuteration. Exact chiral induction at the β-center was not determined.

Synthesis of [(2R,3R)-D-Phe-2,3-d$_2$$^{4,4'}$]gramicidin S (GS).* The deuterated D-phenylalanine thus obtained was used for the synthesis of gramicidin S (GS). ^{1}H NMR study on the synthetic deuterio-GS should give useful information on confirming the conformation of GS. Figure 1 shows the route for the synthesis. Boc-pentapeptide acid (**13**) was converted to the active ester, which was treated with TFA to remove the Boc group. The pentapeptide active ester thus obtained was subjected to cyclization in pyridine to give a mixture of desired [L-Orn(Z)$^{2,2'}$, D-Phe*$^{4,4'}$]gramicidin S (Z_2GS*) (**14**) and a by-product (cyclic monomer) which was removed by Sephadex LH-20 column chromatography. Compound **14** was hydrogenolyzed to give [D-Phe*$^{4,4'}$]-gramicidin S (GS*) (**15**). A part of **15** was used to prepare [L-Orn-(Boc)$^{2,2'}$, D-Phe*$^{4,4'}$]gramicidin S ((Boc)$_2$GS*) (**16**).

^{1}H NMR Study on Gramicidin S and Related Peptides. Figure 2 shows 90 MHz ^{1}H NMR spectra of **14** (a), Z_2GS (b), **15**·2HCl (c), and GS·2HCl (d). In Fig. 2 (a) and (c), each βCH signal in D-Phe* resonates as a sharp singlet. This indicates that highly stereoselective deuteration proceeded not only at α-center but also at β-center.

In regard to side chain conformation of GS, Dygert

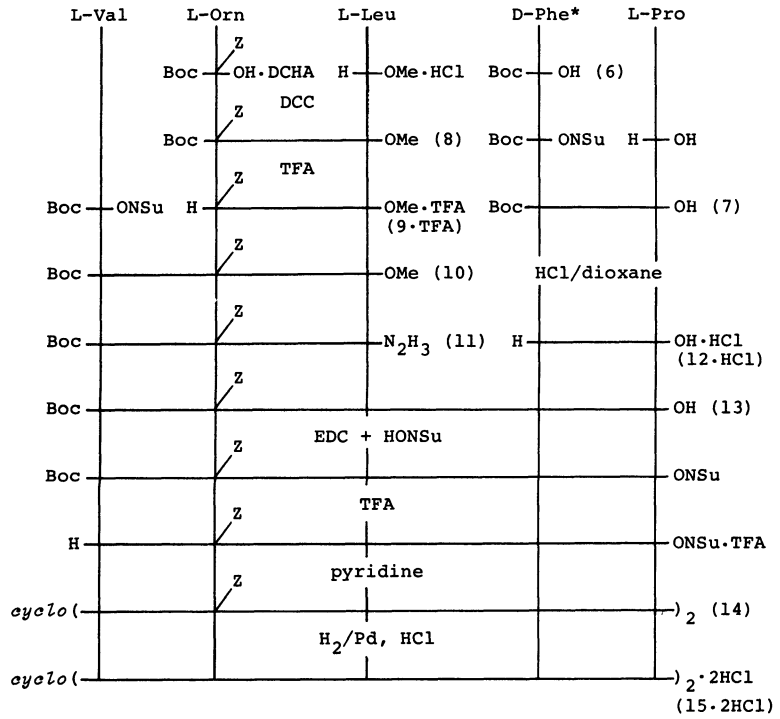

Fig. 1. Synthesis of deuterated gramicidin S.

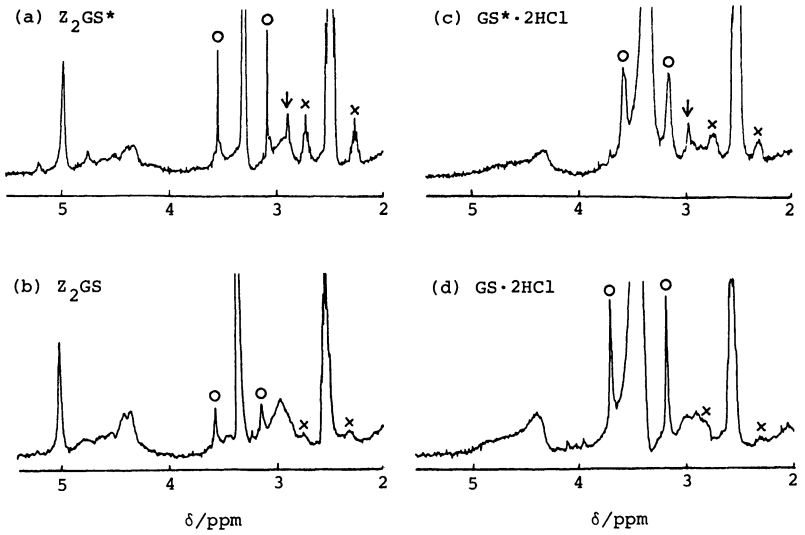

Fig. 2. 90 MHz ^{1}H NMR spectra of gramicidin S and related derivatives. Satelite of HDO (O); satelite of DMSO (×). Arrows in (a) and (c) indicate (3*S*)-proton signals.

et al.[13] proposed the D-Phe side chain conformation with $\kappa_1=180°$ to be most stable conformation as shown in Fig. 3. Rae and Scheraga[14] supported this proposal on the basis of ^{1}H NMR results. Assuming this D-Phe side chain conformation, Jones *et al.*[15] assigned the chemical shifts of D-Phe $H_{\beta 1}$ and $H_{\beta 2}$ protons in GS in CD_3OD solution as $\delta=3.04$ and 2.96, respectively. Krauss and Chan[16] also assigned them as $\delta=3.10$ and 2.96 in CD_3OD, and 2.97 and 2.88 in DMSO-d_6 solution. Figure 2 (c) shows that the (3*S*)-proton in GS* resonated at $\delta=2.98$ in DMSO-d_6 solution. As the protons named $H_{\beta 1}$ and $H_{\beta 2}$ correspond to *pro-S* and *pro-R*, respectively, this result agreed quite well with the assignments by Jones *et al.*[15] and by Krauss and

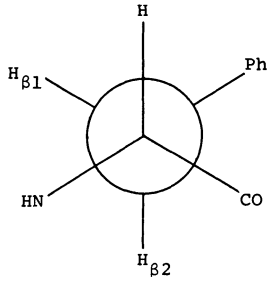

Fig. 3. Conformation for D-Phe side chain with $\kappa_1=180°$.

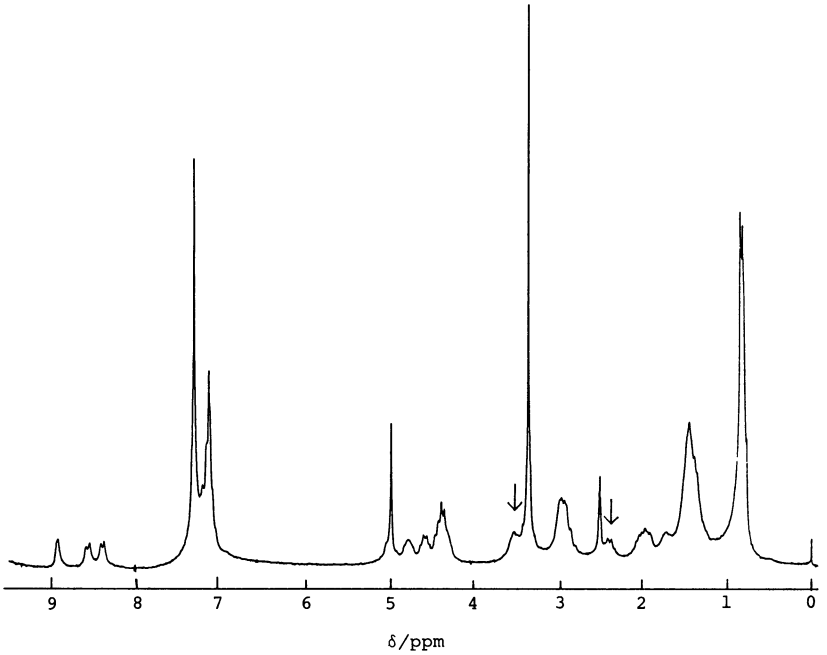

Fig. 4. 200 MHz ^{1}H NMR spectrum of bis(benzyloxycarbonyl)gramicidin S. Arrows indicate δCH_2-proton signals in L-Pro residues.

Chan.[16] Thus, our experimental results provided sound evidence for their assignments and the conformation of D-Phe side chain in GS with $\kappa_1=180°$.

Figures 2 (b) and (d) show that signals of L-Orn δ CH_2 and D-Phe βCH_2 overlap and appear as broad multiplets at about δ=2.9—3.0. The shape of the multiplets in (b) differs from that in (d), suggesting some chemical shift change between GS and Z_2GS. Similarly, the sharp singlet of D-Phe* (3S)-proton in Fig. 2 (a) resonates at δ=2.90 but the same singlet resonates at 2.98 in Fig. 2 (c). Benzyloxycarbonylation of GS* induced some 0.08 upfield shift of the (3S)-proton signal. Krauss and Chan[16] proposed the conformation of GS with intramolecular hydrogen bonds between L-Orn δNH and D-Phe C=O. If Z_2GS holds the same conformation, steric crowding around the D-Phe-L-Pro peptide bonds may be expected because bulky Z groups approach D-Phe side chains. However, 200 MHz ^{1}H NMR spectrum of Z_2GS (Fig. 4) showed that a δCH signal of L-Pro resonates at δ=2.40, indicating proximity of the D-Phe side chain to the pyrrolidine ring.[14] This means that the D-Phe side chain in Z_2GS maintains the orientation with $\kappa_1=180°$ in spite of possible steric crowding. The upfield shift of (3S)-proton of D-Phe* in Z_2GS* should be explained in terms of shielding effect due to the near-by Z group. Interestingly, the D-Phe* (3S)-proton in $(Boc)_2$GS* resonates at δ=2.93, showing minute difference between the aromatic and alkyl urethane groups in inducing chemical shift change of D-Phe (3S)-signal.

Experimental

All the melting points are uncorrected. TLC was carried out on silica gel G (Merck) with following solvent systems, the ratio in parentheses after each system being shown by volume: R_f^1, $CHCl_3$–MeOH (5:1); R_f^2, *n*-BuOH–AcOH–pyridine–water (4:1:1:2); R_f^3, $CHCl_3$–MeOH–AcOH (50:10:2). Optical rotations were measured on a Union high sensitivity polarimeter PM-71. HPLC was carried out on a Hitachi 635A liquid chromatograph and samples were detected at 210 nm absorption.

Synthesis of (2R,3R)-Phenylalanine-2,3-d_2. cyclo*(-ΔPhe-D-Ala-) (3)*: Z-Gly-D-Ala-OMe (**1**) was synthesized from Z-Gly-OH and H-D-Ala-OMe·HCl following the procedure for L-isomer;[8] yield of **1**, 86%; mp 91—93 °C; $[\alpha]_D^{23}$+20.6° (*c* 1, DMF). Reported values for L-isomer, mp 64—69 °C; $[\alpha]_D^{20}$ −21.0° (*c* 1, DMF).[8] Compound **1** in a mixture of MeOH and AcOH was hydrogenolyzed and then the filtrate was evaporated. The residue in *s*-BuOH which contains AcOH (0.1 M(1 M=1 mol dm^{-3})) was treated as described in the literature;[17] yield of *cyclo*(-Gly-D-Ala-) (**2**), 96%; mp 241—242 °C (dec); $[\alpha]_D^{21}$+21.4 (*c* 0.5, DMF). Reported values for L-isomer, mp 228—230 °C; $[\alpha]_D^{20}$−21.3° (*c* 1, DMF).[8] Possible polymorphism may explain high melting points of **1** and **2** compared to those of L-isomer. Compound **2** was converted to *cyclo*(-(*Z*)-ΔPhe-D-Ala-) (**3**) as described for L-isomer;[9] yield, 61%; mp 241—245 °C (dec); $[\alpha]_D^{21}$+18.0° (*c* 1, DMF). Reported values for L-isomer, mp 246—248 °C; $[\alpha]_D^{20}$−19.2° (*c* 1, DMF).

cyclo*(-(2R, 3R)-Phe-2, 3-*d_2*-D-Ala-) (4)*: Compound **3** (864 mg, 4 mmol) dissolved in DMF (150 ml) was deuterated in the presence of Pd black under an atmosphere of $^2H_2$ for 3d at 0° and *ca.* 1 atm. Crystals precipitated in the course of reduction were crushed occasionally and dissolved in DMF with short-time heating. After filtration of Pd black, the solution was evaporated and the residue was collected with the aid of ether; yield, 845 mg (97%); R_f^1 0.82. The extent (98.8%) of chiral induction was determined by HPLC as described in the later section.

(2R,3R)-Phenylalaine-2,3-d_2 *(D-Phe*) (5)*: Compound **4** (437 mg, 2 mmol) was hydrolyzed in 6 M HCl (8 ml) at 110 °C for 4.5 h and the solution was evaporated. The residue was dissolved in water (100 ml) and the solution was treated for 90 min at room temperature with charcoal (9 g) which had been treated with 5% AcOH (120 ml) for 90 min.[18] After filtration, the charcoal was extracted with an aqueous solution (100 ml) containing 5% phenol and 20% AcOH, and

the extraction was repeated twice more. Combined extract was thoroughly washed with ether,diluted with water, and the solution was applied to a column of Dowex 50 (H^+ form) (0.9×8 cm). The column was washed with water, eluted with 1 M NH_4OH, and the eluate was evaporated. The residue (D-Phe*) was recrystallized from hot water-acetone; yield, 264 mg (80%); mp 240—243 °C; R_f^2 0.60. Optical purity was ascertained by the modified Manning-Moore procedure;[10,11] no L-phenylalanine was detected. Content of deuterium was estimated to be 90%±10% by the comparison of signal intensity of ^1H NMR spectra.

Separation of cyclo(-Phe-Ala-) Diastereomers with HPLC. The extent of chiral induction after deuteration of **3** was determined by the HPLC. Experimental conditions for separation of the diastereomers were as follows: Column, Li-Chrosorb RP-18 (4×150 mm); solvent, water-CH_3CN (8:1); flow rate, 1.2 ml/min; pressure, 180 kg/cm²; elution time, 7.5 min for *cyclo*(-L-Phe-D-Ala-) and 10.2 min for *cyclo*(-D-Phe-D-Ala-).

Synthesis of [(2R,3R)-Phe-2,3-$d_2^{4,4'}$]gramicidin S (GS).*

Boc-D-Phe-OH·DCHA (6·DCHA)*: Compound **5** was treated with $(Boc)_2O$[19] and the oily **6** was converted to crystalline DCHA salt; yield, 97%; mp 210—215 °C (dec); $[\alpha]_D^{26}$—26.9 (*c* 1, MeOH). Reported values for protio L-isomer, mp 210—212 °C; $[\alpha]_D^{27}$+29.2 (*c* 1, MeOH).[20]

Boc-D-Phe-L-Pro-OH (7)*: An oily Boc-D-Phe*-OH obtained from **6**·DCHA was converted to Boc-D-Phe*-ONSu by treatment with DCC and HONSu. This Boc-D-Phe*-ONSu was coupled with H-L-Pro-OH in the usual manner; yield, 74%; mp 167—170 °C; R_f^1 0.55. Reported value for protio **7**, R_f^1 0.54.[21]

Boc-L-Orn(Z)-L-Leu-OMe (8): To a chilled solution of Boc-L-Orn(Z)-OH·DCHA (3.83 g, 7 mmol) and H-L-Leu-OMe·HCl (1.27 g, 7 mmol) in CH_2Cl_2 (28 ml), was added DCC (1.44 g, 7 mmol), and the mixture was stirred at 0 °C overnight. After filtration, the solution was evaporated. The residue was dissolved in EtOAc, and the solution was washed with water, 10% citric acid, 4% $NaHCO_3$, and water, and dried (Na_2SO_4). After evaporation, the residue was crystallized by the addition of ether and petroleum ether; yield, 3.17 g (92%); mp 85—88 °C; $[\alpha]_D^{21}$—12.4 (*c* 1, DMF); R_f^1 0.79.

Found: C, 61.01; H, 8.04; N, 8.59%. Calcd for $C_{25}H_{39}O_7N_3$: C, 60.83; H, 7.96; N, 8.51%.

H-L-Orn(Z)-L-Leu-OMe·TFA (9·TFA): Compound **8** (2.96 g, 6 mmol) was treated with TFA (30 ml) at 0 °C for 20 min and the solution was evaporated. The oily residue was treated with ether and petroleum ether. Crystals were collected and washed with ether; yield, 2.49 g (83%); R_f^2 0.82. This was used to the next step without further purification.

Boc-L-Val-L-Orn(Z)-L-Leu-OMe (10): Into a solution of **9**·TFA (1.77 g, 3.5 mmol) in a mixture of tetrahydrofuran (7 ml) and NEt_3 (0.49 ml, 3.5 mmol), was added Boc-L-Val-ONSu (1.77 g, 3.5 mmol) at 0 °C. The mixture was stirred at room temperature overnight, evaporated, and diluted with EtOAc. The solution was treated as described for **8**; yield, 1.88 g (91%); mp 147—149 °C; $[\alpha]_D^{20}$—16.0° (*c* 1, DMF); R_f^1 0.71.

Found: C, 60.89; H, 8.25; N, 9.66%. Calcd for $C_{30}H_{48}O_8N_4$: C, 60.79; H, 8.16; N, 9.45%.

Boc-L-Val-L-Orn(Z)-L-Leu-N_2H_3 (11). Into a solution of **10** (1.78 g, 3 mmol) in DMF (6 ml), was added hydrazine hydrate (1.5 ml, 30 mmol). The mixture was left to stand at room temperature overnight. After the addition of water, precipitated crystals were collected, washed with water, and dried. Recrystallization from DMF-ether gave 1.40 g (79%); mp 199—200 °C; $[\alpha]_D^{20}$—15.2° (*c* 1, DMF); R_f^1 0.67.

Found: C, 58.66; H, 8.23; N, 14.37%. Calcd for $C_{29}H_{48}O_7N_6$: C, 58.76; H, 8.16; N, 14.18%.

H-D-Phe-L-Pro-OH·HCl (12·HCl)*: Compound **7** (176 mg, 0.48 mmol) was treated with 3.6 M HCl in dioxane (2.6 ml, 9.6 mmol) for 1 h and the solution was evaporated. The product was collected with the aid of ether; yield, 146 mg (100%); R_f^3 0.26. This was used to the next step without further purification.

Boc-L-Val-L-Orn(Z)-L-Leu-D-Phe-L-Pro-OH (13)*: Compound **11** (237 mg, 0.4 mmol) was changed to Boc-tripeptide azide with isopentyl nitrite following the literature.[22] The azide was coupled with **12**·HCl (146 mg, 0.48 mmol) in the usual manner; yield, 66 mg (20%); R_f^2 0.82. Reported value for protio **13**, R_f^2 0.82.[23]

cyclo(-L-Val-L-Orn(Z)-L-Leu-D-Phe-L-Pro-)₂ (Z_2GS*) (14)*: Into a chilled solution of **13** (105 mg, 0.11 mmol) in a mixture of DMF (0.5 ml) and CH_2Cl_2 (0.5 ml), were added HONSu (30 mg, 0.26 mmol) and EDC·HCl (50 mg, 0.26 mmol) at 0 °C. After being stirred at room temperature overnight, the solution was treated with cold water, and the precipitate (Boc-pentapeptide-ONSu) was collected. After drying, the precipitate was treated with TFA (1.3 ml) for 30 min and then evaporated. The residue (H-pentapeptide-ONSu·TFA) was dissolved in DMF (3 ml) and the solution was added dropwise into pyridine (40 ml) at room temperature. After 3 d, the mixture was evaporated and the residue was dissolved in MeOH. The solution was passed through Amberlyst 15 and A27 columns (1.8×3.5 cm each), washed with MeOH, and evaporated. Crude product (56 mg) was dissolved in MeOH and the solution was applied on a Sephadex LH-20 column (2×84 cm) and eluted with MeOH. Fractions containing **14** were evaporated; yield, 25.5 mg (28%); R_f^2 0.96. Reported value for protio Z_2GS, R_f^2 0.96.[24]

cyclo(-L-Val-L-Orn-L-Leu-D-Phe-L-Pro-)₂·2HCl (GS*·2HCl) (15·2HCl)*: A portion (5 mg) of **14** was dissolved in MeOH (4 ml) containing 40 µl of 0.3 M HCl in dioxane, the solution was hydrogenolyzed, and the filtrate was evaporated to give 4.0 mg of **15**·2HCl; R_f^1 0.74.

cyclo(-L-Val-L-Orn(Boc)-L-Leu-D-Phe-L-Pro-)₂ ($(Boc)_2GS$*) (16)*: A portion (3.0 mg) of **15**·2HCl was dissolved in a mixture of DMF (0.3 ml) and NEt_3 (2.0 µl) and treated with $(Boc)_2O$ (1.3 mg, 0.006 mmol) for 2 h. The mixture was evaporated and diluted with EtOAc. The solution was washed with water, dried, and evaporated to remain 2.8 mg of **16**; R_f^1 0.76.

^1H NMR spectroscopy. ^1H NMR spectra were recorded in DMSO-d_6 solution on a JEOL FX-90Q spectrometer or a JEOL FX-200 spectrometer at 29 °C. Tetramethylsilane was used as an internal reference; sample concentration, 10—30 mg/ml. The spectra obtained are shown in Figs. 2 and 4.

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10) Abbreviations according to IUPAC-IUB Commission, *Pure Appl. Chem.*,**40**, 217 (1974), are used throughout. Other abbreviations: DCC, dicyclohexylcarbodiimide; DCHA, dicyclohexylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EDC·HCl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HONSu, *N*-hydroxysuccinimide; HPLC, high performance liquid chromatography; ΔPhe, 2,3-dehydrophenylalanine; TFA, trifluoroacetic acid.
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