Synthesis of Viscumamide and Its Analogs

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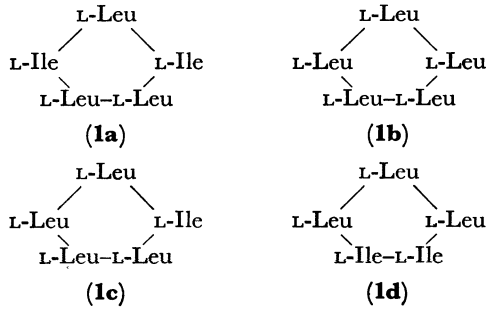
Viscumamide, cyclo(–L-Leu–L-Ile–L-Leu–L-Ile–L-Leu–) (**1a**) and its three analogs, cyclo(–L-Leu–L-Leu–L-Leu–L-Leu–L-Leu–), cyclo(–L-Leu–L-Ile–L-Leu–L-Leu–L-Leu–), and cyclo(–L-Ile–L-Ile–L-Leu–L-Leu–L-Leu–) were synthesized by the *N*-hydroxysuccinimide ester method. The yields in the cyclization step were low due to a strong intermolecular association even at high dilution, which causes cyclodimerization and other polymerization. Chromatographic and spectroscopic comparison of synthetic **1a** with natural viscumamide showed their identity. The structure of viscumamide was confirmed to be **1a**.

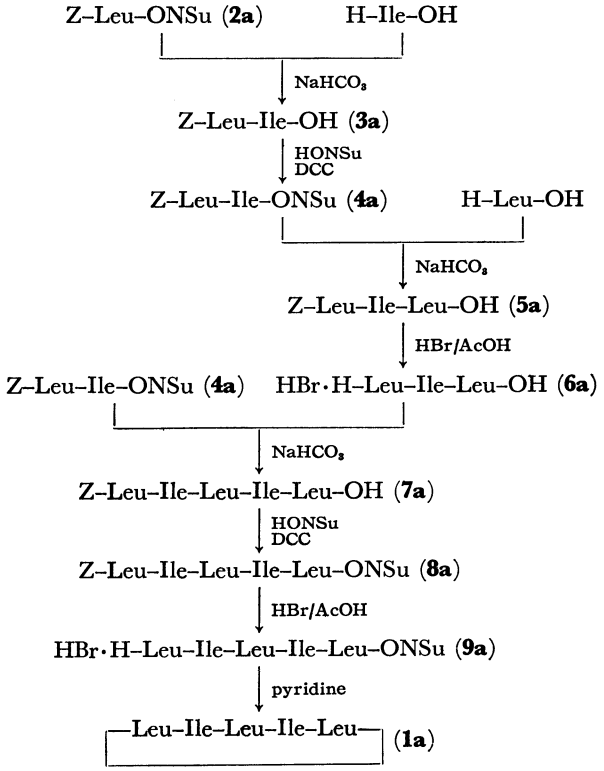
In a paper on the constituents of the mistletoe, *Viscum album* Linn. *var. coloratum* Ohwi, we reported on the isolation and structure of viscumamide, a new cyclic pentapeptide, which was assigned to be cyclo(-L-leucyl-L-isoleucyl-L-leucyl-L-isoleucyl-L-leucyl) (**1a**).[1]

In order to confirm the structure of viscumamide, we attempted to synthesize the cyclic peptide **1a** and three analogous cyclic peptides which consist of L-leucine and L-isoleucine.

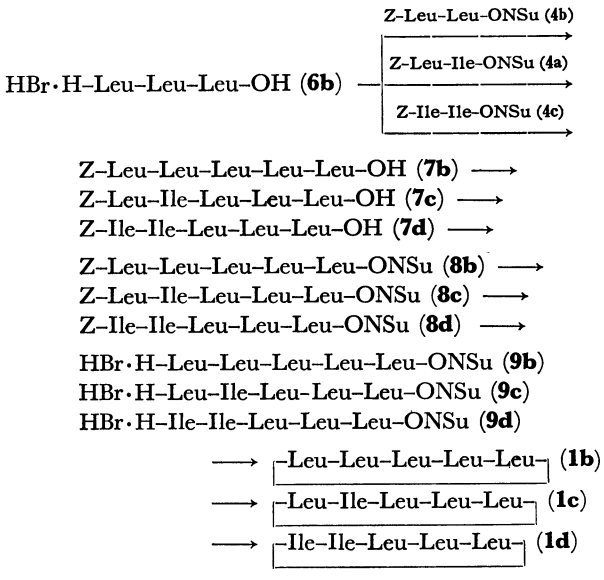
This paper deals with the synthesis of these cyclic pentapeptides, and the chromatographic and spectroscopic comparison of synthetic **1a** with natural viscumamide.



The synthesis of **1a** is outlined in Scheme 1. The *N*-hydroxysuccinimide ester method[2] was employed throughout the coupling reactions, the removal of benzyloxycarbonyl (Z) groups of the intermediates being performed by the action of hydrogen bromide in acetic acid.[3] Z-L-Leucine *N*-hydroxysuccinimide ester (–ONSu) (**2a**)[2] was coupled with L-isoleucine in the presence of sodium hydrogencarbonate to yield needles of Z-L-leucyl-L-isoleucine (**3a**) in 92% yield. Z-Dipeptide **3a** was then transformed into Z-L-leucyl-L-isoleucine *N*-hydroxysuccinimide ester (**4a**) as an oil by treatment with *N*-hydroxysuccinimide (HONSu) and dicyclohexylcarbodiimide (DCC) in dioxane. Purification of the substance by crystallization was unsuccessful. Z-Dipeptide ester **4a** was coupled with L-leucine in the same way as described above to yield Z-L-leucyl-L-isoleucyl-L-leucine (**5a**) as fine crystals in 67% yield based on **3a**. After removal of the Z group of the Z-tripeptide **5a** by the action of hydrogen bromide in acetic acid, the resulting tripeptide hydrobromide (**6a**) was coupled with Z-dipeptide ester **4a** to yield Z-L-leucyl-L-isoleucyl-L-leucyl-L-isoleucyl-L-leucine (**7a**) as fine crystals in 56% yield. Z-Pentapeptide **7a** was transformed into the corresponding *N*-hydroxysuccinimide ester (**8a**) as fine



Scheme 1.



Scheme 2.

crystals in 71% yield by the reaction with *N*-hydroxysuccinimide and dicyclohexylcarbodiimide in *N*,*N*-dimethylformamide (DMF) followed by separation from *N*,*N'*-dicyclohexylurea (DCU) by extraction with ethyl acetate. After removal of the Z group of the Z-pentapeptide ester **8a** in the same way as described above, the pentapeptide hydrobromide (**9a**) thus obtained was cyclized in pyridine at 40 °C by the high dilution method.[4] Purification through silica gel column, followed by chromatography on alumina, gave cyclo(-L-leucyl-L-isoleucyl-L-leucyl-L-isoleucyl-L-leucyl) (**1a**) as colorless needles in 6.5% yield.

Cyclic pentapeptides (**1b**, **1c**, and **1d**) were synthesized in the same way as described for the preparation of **1a** (Scheme 2). **2a** was chosen as the starting material and the peptide chains were extended stepwise to yield Z-L-leucyl-L-leucyl-L-leucine (**5b**). After removal of the Z group, the resulting tripeptide hydrobromide (**6b**) was coupled with the Z-dipeptide esters **4b**, **4a**, and **4c** to yield Z-pentapeptides **7b**, **7c**, and **7d**, respectively. The Z-pentapeptides were transformed into the corresponding *N*-hydroxysuccinimide esters **8b**, **8c**, and **8d**. After removal of the Z-groups, the resulting pentapeptide ester hydrobromides (**9b**, **9c**, and **9d**) were respectively cyclized and purified in the same way as described for the preparation of **1a** affording cyclic pentapeptides **1b**, **1c**, and **1d** as colorless needles in 6.5%, 4.5%, and 4.4% yields, respectively.

Cyclodimerization has been shown to occur predominantly with tripeptides and with pentapeptides.[5-7] Significant differences in the yield of cyclization have been observed to depend on the configuration of the amino acids in the open peptide chain.[8-10]

The yields in the cyclization step were low due to dimerization and other polymerization, since the pentapeptide esters (**9a**, **9b**, **9c**, and **9d**) consist of five L-amino acids, undergoing strong intermolecular association even at high dilution.

Racemization during this synthesis seems negligible, since the specific rotation value of synthetic **1a** is −56° which is identical with that of natural viscumamide.[11] Synthetic **1a** was identical with natural viscumamide in the infrared absorption spectrum (Fig. 1), the proton magnetic resonance spectrum (Fig. 2), and thin layer

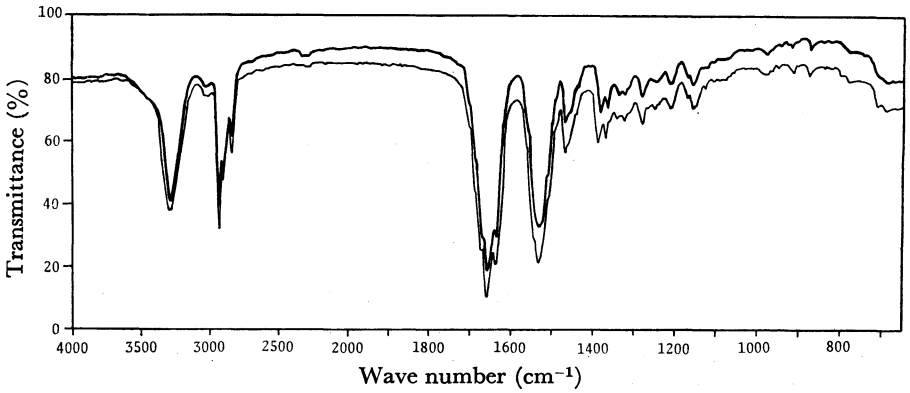


Fig. 1. Infrared absorption spectra of synthetic **1a** (heavy line) and natural viscumamide (light line) in KBr disk.

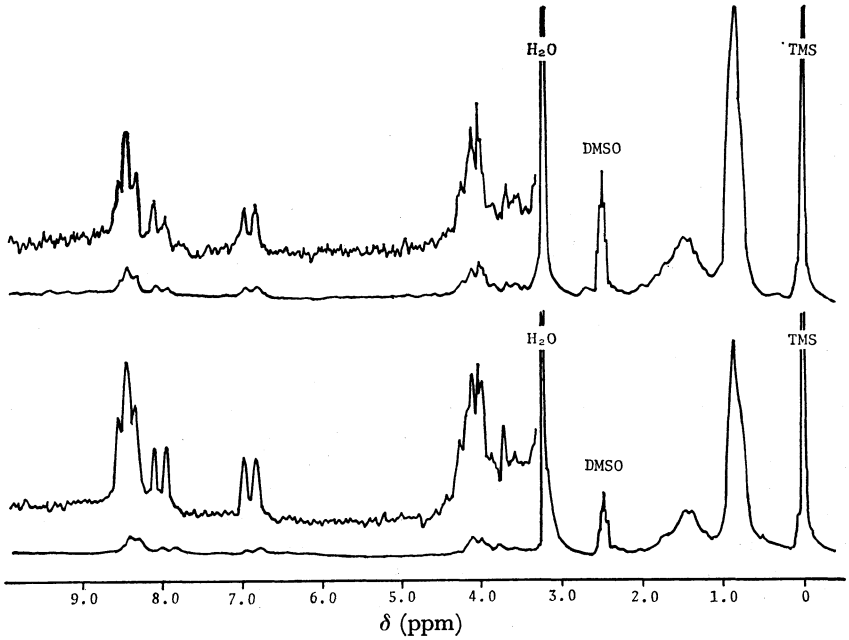


Fig. 2. Proton magnetic resonance spectra of synthetic **1a** (lower) and natural viscumamide (uper) in DMSO-d_6 at 30 °C.

chromatography with various solvent systems (Table 1). The results indicate that the structure of viscumamide is confirmed to be cyclo(–L-leucyl–L-isoleucyl–L-leucyl–L-isoleucyl–L-leucyl) (**1a**).

Experimental

All melting points are uncorrected. The proton magnetic resonance spectra were measured with a JEOL JNM PFT-60 NMR spectrometer at 60 MHz with tetramethylsilane as an internal standard. The infrared absorption spectra were measured with a Hitachi EPI-G3 recording spectrophotometer. The optical rotations were measured with a Union PM-101 polarimeter. Thin layer chromatography (TLC) was carried out on silica gel (Wakogel B-10).

Z-L-Leu-L-Lle-OH (3a). A solution of Z-L-Leu-ONSu[2] (**2a**) (72.5 g, 0.2 mol) in ethanol (1 l) was added to a solution of L-isoleucine (26.4 g, 0.2 mol) and sodium hydrogencarbonate (33.6 g, 0.4 mol) in water (1 l). After being stirred at room temperature overnight, the solution was acidified with 2M hydrochloric acid, and then ethanol was removed under reduced pressure below 40 °C. The precipitate separated from aqueous solution was dissolved in ethyl acetate (300 ml), and the solution was washed with water and dried over sodium sulfate. Hexane (300 ml) was added and the solution was chilled in a refrigerator. **3a** was obtained as colorless needles: mp 125—126 °C (lit,[9] 101—101.5 °C); yield, 62.8 g (83%); $[\alpha]_D^{25}$ $-5.0\pm0.2°$ (*c* 1.0, EtOH). (Found: C, 63.53; H, 8.19; N, 7.37%).

Z-L-Leu-L-Leu-OH (3b). **3b** was obtained in the same way as described above from **2a** (72.5 g, 0.2 mol) and L-leucine (26.4 g, 0.2 mol); colorless needles: mp 117—118 °C (lit,[9] 97.5—98.5 °C); yield, 63.5 g (88%); $[\alpha]_D^{25}$ $-25.0\pm0.2°$ (*c* 1.0, EtOH). (Found: C, 63.51; H, 8.22; N, 7.34%).

Z-L-Ile-L-Ile-OH (3c). **3c** was obtained in the same way as described above from Z-L-Ile-ONSu[3] (**2b**) (18.9 g, 50 mmol) and L-isoleucine (6.6 g, 50 mmol); colorless needles: mp 128—129 °C; yield, 16.7 g (88%); $[\alpha]_D^{25}$ $-8.9\pm0.2°$ (*c* 1.0, EtOH). (Found: C, 63.54; H, 8.20; N, 7.37%).

Z-L-Leu-L-Ile-ONSu (4a). DCC (30.9 g, 0.15 mol) was added at 0 °C to a solution of **3a** (56.8 g, 0.15 mol) and HONSu (17.3 g, 0.15 mol) in dry dioxane (300 ml). After being stirred at 0 °C for 4 h and then at room temperature overnight, DCU separated was filtered off and washed with dioxane. The combined filtrate and washings were evaporated to dryness under reduced pressure. **4a** was obtained as a colorless oil: yield, 67.8 g (95%); IR 1815 and 1785 (succinimide), and 1740 cm^{-1} (ester C=O).

Z-L-Leu-L-Leu-ONSu (4b). **4b** was obtained in the same way as described above from **3b** (62.5 g, 0.17 mol), HONSu (19.0 g, 0.17 mol), and DCC (34.0 g, 0.17 mol); colorless oil: yield, 76.9 g (98%); IR 1817 and 1787 (succinimide), and 1743 cm^{-1} (ester C=O).

Z-L-Ile-L-Ile-ONSu (4c). **4c** was obtained in the same way as described above from **3c** (15.1 g, 40 mmol), HONSu (4.6 g, 40 mmol), and DCC (8.3 g, 40 mmol); colorless oil: yield, 18.1 g (95%); IR 1817 and 1787 (succinimide), and 1742 cm^{-1} (ester C=O).

Z-L-Leu-L-Ile-L-Leu-OH (5a). L-Leucine (5.2 g, 40 mmol) and **4a** (15.0 g, 40 mmol) were treated in the same way as described for the preparation of **3a**. Concentration of the mixture under reduced pressure followed by chilling in a refrigerator gave the precipitate, which was collected and washed with water. Recrystallization from ethanol gave 13.2 g (67%) of **5a** as colorless fine crystals: mp 182—183 °C; $[\alpha]_D^{25}$ $-53.4\pm0.4°$ (*c* 0.5, EtOH). Found: C, 63.25; H, 8.52; N, 8.36%. Calcd for $C_{26}H_{41}N_3O_6$: C, 63.52; H, 8.41; N, 8.55%.

Z-L-Leu-L-Leu-L-Leu-OH (5b). **5b** was obtained in the same way as described above from **4b** (59.4 g, 0.13 mol) and L-leucine (16.4 g, 0.13 mol); colorless fine crystals: mp 102—104 °C; yield, 39.9 g (65%); $[\alpha]_D^{25}$ $-51.0\pm0.4°$ (*c* 0.5, EtOH). Found: C, 63.53; H, 8.63; N, 8.24%. Calcd for $C_{26}H_{41}N_3O_6$: C, 63.52; H, 8.41; N, 8.55%.

Z-L-Leu-L-Ile-L-Leu-L-Ile-L-Leu-OH (7a). **5a** (12.3 g, 25 mmol) was treated with 30% hydrogen bromide in acetic acid (25 g) at room temperature for 1 h, dry ether (100 ml) and dry hexane (200 ml) being added to the solution. Chilling of the solution gave the precipitate which was collected by filtration, washed with dry hexane, and dried in a desiccator over sodium hydroxide overnight; yellowish powder **6a**: yield, 11.9 g.

To a solution of **4a** (11.9 g, 25 mmol) in ethanol was added a solution of the tripeptide hydrobromide (**6a**) (11.9 g) and sodium hydrogencarbonate (6.3 g, 75 mmol) in a mixture of water (250 ml) and ethanol (200 ml). The mixture was treated in the same way as described for the preparation of **5a**. Recrystallization from 2-propanol gave **7a** as colorless fine crystals: mp 262—265 °C (dec); yield, 10.1 g (56%, based on **5a**); $[\alpha]_D^{25}$ $-57\pm2°$ (*c* 0.1, EtOH). Found: C, 63.39; H, 9.04; N, 9.63%. Calcd for $C_{38}H_{63}N_5O_8$: C, 63.57; H, 8.85; N, 9.76%.

Z-L-Leu-L-Leu-L-Leu-L-Leu-L-Leu-OH (7b). **7b** was obtained as colorless fine crystals in the same way as described above from the tripeptide hydrobromide (**6b**) prepared from **5b** (12.3 g, 25 mmol) and **4b** (11.9 g, 25 mmol): mp 263—266 °C (dec); yield, 12.4 g (69%, based on **5b**); $[\alpha]_D^{25}$ $-67\pm2°$ (*c* 0.1, EtOH). Found: C, 63.29; H, 9.08; N, 9.58%. Calcd for $C_{38}H_{63}N_5O_8$: C, 63.57; H, 8.55; N, 9.76%.

Z-L-Leu-L-Ile-L-Leu-L-Leu-L-Leu-OH (7c). **7c** was obtained as colorless fine crystals in the same way as described above from the tripeptide hydrobromide (**6b**) prepared from **5b** (12.3 g, 25 mmol) and **4a** (11.9 g, 25 mmol): mp 243—246 °C (dec); yield, 9.7 g (54%, based on **5b**); $[\alpha]_D^{25}$ $-31\pm2°$ (*c* 0.1, EtOH). Found: C, 63.33; H, 9.07; N, 9.61%. Calcd for $C_{38}H_{63}N_5O_8$: C, 63.57; H, 8.55; N, 9.76%.

Z-L-Ile-L-Ile-L-Leu-L-Leu-L-Leu-OH (7d). **7d** was obtained as colorless fine crystals in the same way as described above from the tripeptide hydrobromide (**6b**) prepared from **5b** (12.3 g, 25 mmol) and **4c** (11.9 g, 25 mmol): mp 256—258 °C (dec); yield, 9.5 g (53%, based on **5b**); $[\alpha]_D^{25}$ $-42\pm2°$ (*c* 0.1, EtOH). Found: C, 63.13; H, 9.13; N, 9.62%. Calcd for $C_{38}H_{63}N_5O_8$: C, 63.57; H, 8.55; N, 9.76%.

Z-L-Leu-L-Ile-L-Leu-L-Ile-L-Leu-ONSu (8a). DCC (2.7 g, 13 mmol) was added at 0 °C to a solution of **7a** (8.6 g, 12 mmol) and HONSu (1.7 g, 15 mmol) in DMF (500 ml). After being stirred at 0 °C for 8 h and then at room temperature for 16 h, deposited DCU was filtered off and washed with DMF. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was extracted twice with hot ethyl acetate (150 ml) to remove DCU and then recrystallized from 2-propanol. **8a** was obtained as colorless fine crystals: mp 249—250 °C (dec); yield, 6.9 g (71%); $[\alpha]_D^{25}$ $-55\pm2°$ (*c* 0.1, EtOH); IR (Nujol) 1819 and 1789 (succinimide), and 1746 cm^{-1} (ester C=O). Found: C, 67.67; H, 8.41; N, 10.04%.

Calcd for $C_{42}H_{66}N_6O_{10}$: C, 61.89; H, 8.16; N, 10.31%.

Z-L-Leu-L-Leu-L-Leu-L-Leu-L-Leu-ONSu (8b). **8b** was obtained as colorless fine crystals in the same way as described above from **7b** (8.6 g, 12 mmol), HONSu (1.7 g, 15 mmol), and DCC (2.7 g, 13 mmol): mp 237—238 °C (dec); yield, 6.4 g (65%); $[\alpha]_D^{25}$ $-67\pm2°$ (*c* 0.1, EtOH); IR (Nujol) 1817 and 1790 (succinimide), and 1746 cm^{-1} (ester C=O).

Found: C, 61.75; H, 8.55; N, 10.13%.

Calcd for $C_{42}H_{66}N_6O_{10}$: C, 61.89; H, 8.16; N, 10.31%,

Z-L-Leu-L-Ile-L-Leu-L-Leu-L-Leu-ONSu (8c). **8c** was obtained as colorless fine crystals in the same way as described above from **7c** (8.6 g, 12 mmol), HONSu (1.7 g, 15 mmol), and DCC (2.7 g. 13 mmol): mp 248—250 °C (dec); yield, 6.7 g (69%); $[\alpha]_D^{25}$ −69±2° (*c* 0.1, EtOH); IR (Nujol) 1819 and 1790 (succinimide), and 1742 cm^{-1} (ester C=O). Found: C, 61.82; H, 8.49; N, 10.14%. Calcd for $C_{42}H_{66}N_6O_{10}$: C, 61.89; H, 8.16; N, 10.31%.

Z-L-Ile-L-Ile-L-Leu-L-Leu-L-Leu-ONSu (8d). **8d** was obtained as colorless fine crystals in the same way as described above from **7d** (8.6 g, 12 mmol), HONSu (1.7 g, 15 mmol), and DCC (2.7 g, 13 mmol): mp 243—245 °C (dec); yield, 6.8 g (70%); $[\alpha]_D^{25}$ −51±2° (*c* 0.1, EtOH); IR (Nujol) 1817 and 1788 (succinimide), and 1745 cm^{-1} (ester C=O). Found: C, 61.80; H, 8.41; N, 10.20%. Calcd for $C_{42}H_{66}N_6O_{10}$: C, 61.89; H, 8.16; N, 10.31%.

Cyclo(-L-Leu-L-Ile-L-Leu-L-Ile-L-Leu-) (1a). **8a** (5.7 g, 7 mmol) was treated with 20% hydrogen bromide in acetic acid (15 g) in the same way as described for the preparation of **6a**. The pentapeptide ester hydrobromide (**9a**) (yellowish powder; yield, 5.1 g (96%)) thus obtained was dissolved in DMF (1 l), and the solution was added dropwise into pyridine (2 l) with stirring at 40 °C over a period of 12 h; stirring at room temperature was then continued for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in hot chloroform (250 ml). The solution was subject ed to chromatography on a column of silica gel (100 g). After the column had been eluted with chloroform (400 ml), elution with a mixture of ethyl acetate and ethanol (19: 1) (400 ml) gave the desired product, as determined by TLC. The effluent was evaporated to dryness under reduced pressure, giving a brownish powder which was dissolved in chloroform (100 ml) and then further purified by column chromatography on alumina (100 g). The column was washed with chloroform (200 ml) and successively with ethyl acetate (200 ml). Elution with a mixture of ethyl acetate and ethanol (19: 1) (200 ml) followed by recrystallization from ethanol gave 257 mg (6.5 %) of cyclic pentapeptide (**1a**) as colorless needles: mp >300 °C; $[\alpha]_D^{20}$ −56±2° (*c* 0.1, EtOH); MS (70 eV), M^+ *m/e* 565; PMR (DMSO-d_6, amide protons, at 30 °C) δ=8.68 (1H, d, *J*=6.6 Hz), 8.58 (2H, d, *J*=7.2 Hz), 8.15 (1H, d, *J*=9.0 Hz), and 6.97 ppm (1H, d, *J*=9.0 Hz); IR (KBr) 3300, 3050, and 1535 (amide NH), 1680, 1661, and 1638 cm^{-1} (amide C=O). Found: C, 63.39; H, 9.89; N, 12.22%. Calcd for $C_{30}H_{55}N_5O_5$: C, 63.68; H, 9.80; N, 12.38%.

Cyclo(-L-Leu-L-Leu-L-Leu-L-Leu-L-Leu-) (1b). **1b** (238 mg, 6.0% based on **8b**) was obtained and purified in the same way as described above *via* HBr·H-L-Leu-L-Leu-L-Leu-L-Leu-L-Leu-ONSu (**9b**) (yellowish powder; 5.2 g (98%)) from **8b** (5.7 g, 7 mmol); colorless needles: mp >300 °C; $[\alpha]_D^{20}$ −67 ±2° (*c* 0.1, EtOH); MS (70 eV), M^+ *m/e* 565; PMR (DMSO-d_6, amide protons, at 30 °C) δ=8.71 (1H, d, *J*=7.2 Hz), 8.53 (1H, d, *J*=6.6 Hz), 8.18 (1H, d, *J*=6.6 Hz), 7.63 (1H, d, *J*=9.0 Hz), and 7.23 ppm (1H, d, *J*=9.0 Hz); IR (KBr) 3290, 3060, and 1540 (amide NH), and 1659, 1651, and 1640 cm^{-1} (amide C=O). Found: C, 63.85; H, 9.68; N, 12.40%. Calcd for $C_{30}H_{55}N_5O_5$: C, 63.68; H, 9.80; N, 12.38%.

Cyclo(-L-Leu-L-Ile-L-Leu-L-Leu-L-Leu-) (1c). **1c** (178 mg, 4.5% based on **8c**) was obtained and purified in the same way as described above *via* HBr·H-L-Leu-L-Ile-L-Leu-L-Leu-L-Leu-ONSu (**9c**) (yellowish powder; yield, 5.1 g (95%)) from **8c** (5.7 g, 7 mmol); colorless needles: mp >300 °C; $[\alpha]_D^{15}$ −71 ±2° (*c* 0.1, EtOH); MS (70 eV), M^+ *m/e* 565; PMR (DMSO-d_6, amide protons, at 30 °C) δ=8.59 (1H, d, *J*=7.8 Hz), 8.40 (1H, d, *J*=8.4 Hz), 8.33 (1H, d, *J*=7.8 Hz), 8.04 (1H, d, *J*=8.4 Hz), and 7.19 ppm (1H, d, *J*=8.4 Hz); IR (KBr) 3350, 3310, 3050, and 1520 (amide NH), and 1658 and 1652 cm^{-1} (amide C=O). Found: C, 63.59; H, 10.03; N, 11.98%. Calcd for $C_{30}H_{55}N_5O_5$: C, 63.68; H, 9.80; N, 12.38%.

Cyclo(-L-Ile-L-Ile-L-Leu-L-Leu-L-Leu-) (1d). **1d** (175 mg, 4.4% based on **8d**) was obtained and purified in the same way as described above *via* HBr·H-L-Ile-L-Ile-L-Leu-L-Leu-L-Leu-ONSu (**9d**) (yellowish powder; yield, 5.3 g (99%)) from **8d** (5.7 g, 7 mmol); colorless needles: mp >300 °C; $[\alpha]_D^{15}$ −52 ±2° (*c* 0.1, EtOH); MS (70 eV), M^+ *m/e* 565; PMR (DMSO-d_6, amide protons, at 30 °C) δ=8.53 (1H, d, *J*=7.8 Hz), 8.33 (1H, d, *J*=7.8 Hz), 8.11 (1H, d, *J*=9.0 Hz), 8.06 (1H, d, *J*=7.8 Hz), and 7.67 ppm (1H, d, *J*=9.0 Hz); IR (KBr) 3300, 3050, and 1530 (amide NH), and 1658 and 1650 cm^{-1} (amide C=O). Found: C, 63.66; H, 10.01; N, 12.26%. Calcd for $C_{30}H_{55}N_5O_5$: C, 63.66; H, 9.80; N, 12.38%.

Comparison of Viscumamide with Synthetic Cyclopentapeptides. The specific rotation value, mass spectrum, proton magnetic resonance spectrum, and infrared absorption spectrum of synthetic viscumamide **1a** were identical with those of the authentic sample. A thin layer chromatographic comparison of viscumamide with the synthetic cyclopentapeptides is given in Table 1.

Table 1. Thin layer chromatography of cyclopentapeptides

Solvents[a]	Substances				
	Viscumamide	**1a**	**1b**	**1c**	**1d**
I	0.36	0.36	0.36	0.38	0.44
II	0.50	0.50	0.55	0.57	0.58

a) Solvents: I=chloroform–methanol (95: 5), II=ethyl acetate.

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11) The specific rotation value of this substance has been recorded as $[\alpha]_D^{25}$ −49.1° (*c* 0.2, EtOH) by the use of an ORD spectrophotometer.[1] This value was recorded as $[\alpha]_D^{20}$ −54 ±2° (*c* 0.1, EtOH) by the use of a polarimeter under the same conditions as those of synthetic **1a**.