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Synthesis of 6-Substituted Indolactams by Microbial Conversion

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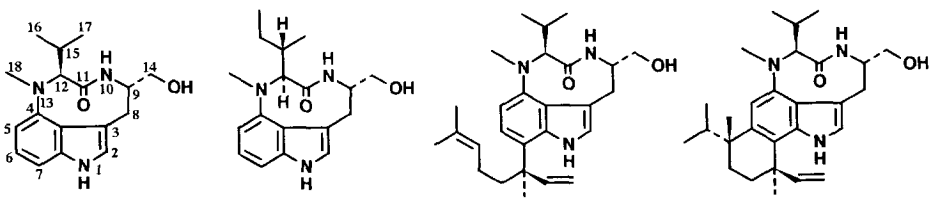
Abstract: New indolactam derivatives (**24-27**) with a fluorine, bromine, iodine or methyl group at position 6 of (-)-indolactam-V (**1**) were synthesized from corresponding *seco*-compounds (6-substituted *N*-methyl-L-valyl-L-tryptophanols) by the microbial conversion using *Streptoverticillium blastmyceticum* NA34-17. (-)-5-Fluoroindolactam-V (**23**) and (-)-7-methylindolactam-V (**28**) were similarly obtained by this method. (-)-6-Methylindolactam-V (**27**) had almost the same biological activities as (-)-7-methylindolactam-V (**28**), indicating that the substituent effect at position 6 of (-)-indolactam-V (**1**) is similar to that at position 7.

INTRODUCTION

(-)-Indolactam-V (**1**),[1,2] the core structure of tumor-promoting teleocidins (Fig. 1),[3] is a key compound for investigating the structure-activity relationship. Although about 100 indolactam derivatives have been synthesized during the last decade to reveal the structural factors responsible for tumor-promoting activity,[4] synthesis of a 6-substituted (-)-indolactam-V has not yet been reported. Since teleocidin B-4 with a monoterpenoid side chain at position 6 and 7 is a potent tumor promoter,[3] introduction of a substituent at position



(-)-Indolactam-V (**1**) (-)-Indolactam-I Teleocidin A-1 Teleocidin B-4

Fig. 1 Structure of naturally-occurring teleocidin-related compounds.

6 of **1** would result in new analogues with potent tumor-promoting activity and new photolabile or fluorescent probes for the receptor analysis of tumor promoters.

To synthesize 6-substituted indolactams, reactivity at both positions 4 and 6 of the indole ring should be properly regulated. However, the electrophilic aromatic substitution such as halogenation and Friedel-Crafts acylation of (-)-indolactam-V (**1**) resulted in the orientation at position 7.[5-7] No 6-substituted derivatives of **1** were obtained by these substitution reactions although the 2- or 5-substituted derivatives were reported as minor products.[8] It is, therefore, preferable to introduce a substituent into position 6 before introduction of the amino function into position 4 of the indole ring. There are several examples of the synthesis of 6-substituted indoles; nitration of gramine and methyl indole-3-carboxylate occurred at position 4 or 6,[5,9] and bromination of ethyl indole-3-carboxylate occurred at position 5 or 6.[10,11] These findings indicate that 6-substituted tryptophan derivatives can be easily synthesized by these methods.

Introduction of an amino function into position 4 of a 6-substituted indole derivative proved to be a very troublesome operation; nitration of methyl 6-ethyl-1-methylindole-3-carboxylate gave no 4-substituted product.[12] However, microbial conversion using teleocidin-producing micro-organisms would reduce the difficulty of this step.[13] We have recently shown that thirteen indolactam congeners with L-Ala, Abu, γ,δ-Δ-Nva, propargyl-Gly, Nva, Nle, *tert*-Leu, γ-methallyl-Gly, Leu, Ile, *allo*-Ile, 2-thienyl-Gly or Phg instead of L-Val in **1**, *e.g.* (-)-indolactam-I (Fig. 1), can be synthesized from their *seco*-compounds (*N*-methyl-L-amino acidyl-L-tryptophanols) by microbial conversion using *Streptoverticillium blastmyceticum* NA34-17.[13] We have applied a similar method to the synthesis of the 6-substituted indolactams; 6-substituted *N*-methyl-L-valyl-L-tryptophanols synthesized mainly from the 6-nitrotryptophan derivative (**2**)[14,15] and commercially available tryptophan derivatives have been metabolized by this Actinomycete. This paper describes the synthesis of several 6-substituted indolactams along with 5 or 7-substituted ones by this microbial conversion. The biological activities of (-)-6 or 7-methylindolactam-V are also mentioned.

RESULTS AND DISCUSSION

The 6-substituted *N*-methyl-L-valyl-L-tryptophanols (**6**, **7**, **8** and **11**) were synthesized from the 6-nitrotryptophan derivative (**2**) as shown in Fig. 2. Compound **2** obtained from L-tryptophan by 6 steps[14,15] was reduced by sodium borohydride in dimethylformamide (DMF) and water to give **3** in a 73% yield. Deprotection of the carbobenzyloxy (Z) group was accomplished by acid hydrolysis (85%), and the resultant amine (**4**) was condensed with *tert*-butoxycarbonyl (Boc) *N*-methyl-L-valine to give **5** in an 80% yield. Compound **5** served as a key intermediate of the following 6-substituted cyclization precursors (**6**, **7**, **8** and **11**).

N-Methyl-6-nitro-L-valyl-L-tryptophanol (**6**) was obtained by removal of the Boc group of **5** in an 87% yield. Catalytic hydrogenation of **6** with platinum oxide gave the amino derivative (**7**) in a 93% yield. The acetylamino derivative (**8**) was derived from **5** by the hydrogenation, acetylation and deprotection of the Boc group in a 75% yield. 6-Iodo-*N*-methyl-L-valyl-L-tryptophanol (**11**) was synthesized from **5** via diazotization. After protection of the hydroxyl group with an acetyl group (100%), the nitro group was reduced with sodium borohydride and nickel chloride in methanol[16] to yield the 6-amino derivative (**9**) in a 76% yield. This reduction is suitable for a large scale synthesis because the platinum oxide is very expensive. Since sodium nitrite in 80% aqueous acetic acid was shown to be a good diazotizing agent for unsubstituted aminoindoles,[17] **9** was treated

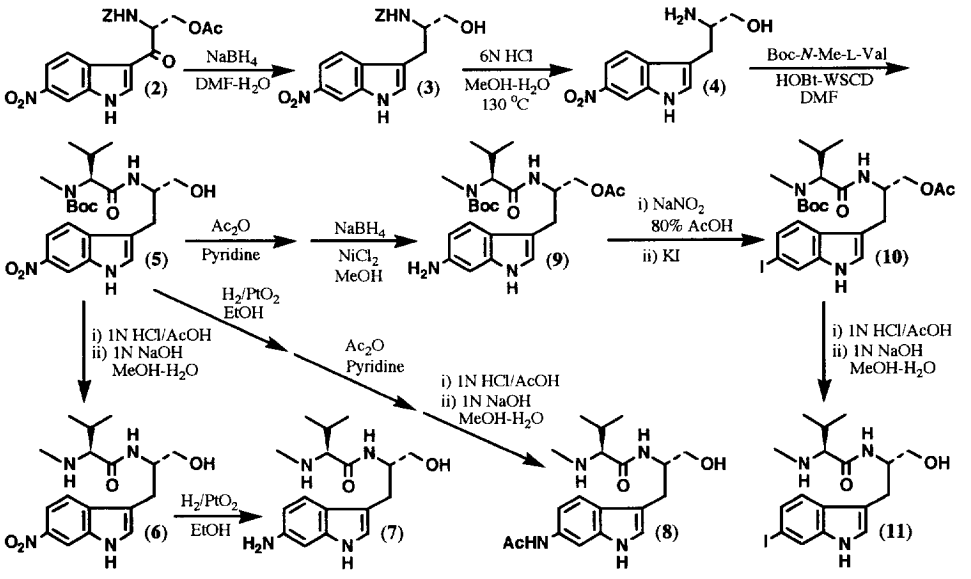


Fig. 2 Synthesis of the 6-substituted cyclization precursors from **2**.

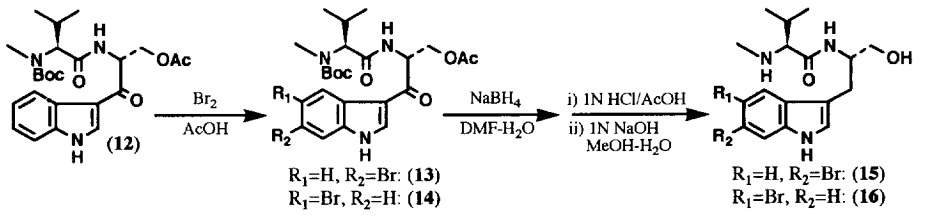


Fig. 3 Synthesis of 5- or 6-bromo-*N*-methyl-L-valyl-L-tryptophanol (**15** and **16**).

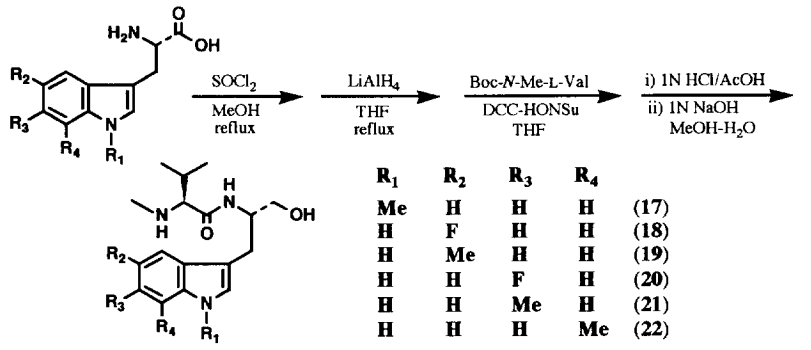


Fig. 4 Synthesis of the 1-, 5-, 6- or 7-substituted cyclization precursors from corresponding tryptophan derivatives.

with sodium nitrite in 80% acetic acid, followed by potassium iodide treatment. The desired iodo compound (**10**) was obtained in a 38% yield. Diazotization of **9** with 1N hydrogen chloride or sulfuric acid resulted only in the formation of a complex mixture. The Boc group of **10** was removed quantitatively to give 6-iodo-*N*-methyl-L-valyl-L-tryptophanol (**11**).

Since introduction of bromine via the above-mentioned diazotization was unsuccessful, direct bromination was attempted (Fig. 3). Compound **12** prepared from Boc-*N*-methyl-L-valyl-L-tryptophanol by the method of Kogan *et al.*[15] was treated with bromine in acetic acid. The 6-bromo derivative (**13**) was obtained in a 7% yield along with the 5-bromo derivative (**14**, 13%). Compound **13** was reduced and deprotected to give 6-bromo-*N*-methyl-L-valyl-L-tryptophanol (**15**) in a 40% yield. 5-Bromo-*N*-methyl-L-valyl-L-tryptophanol (**16**) was similarly obtained from **14** in a 50% yield. Other 6-substituted cyclization precursors (**20** and **21**) and 1-, 5- or 7-substituted ones (**17**, **18**, **19** and **22**) were synthesized from corresponding commercially available tryptophan derivatives by the method reported previously[13] as shown in Fig. 4.

The feeding experiment of these cyclization precursors with *S. blastmyceticum* NA34-17 was done by the method reported previously.[13] Since the initiation of the (-)-indolactam-V (**1**) production varied with the cultural conditions, the optimum time to add the cyclization precursors and to harvest the culture broth was guided by the pH of the medium; each precursor was added to the medium at the pH bottom (*ca.* 6.0) and the culture broth was harvested 12 hours after the pH recovered to 6.8.

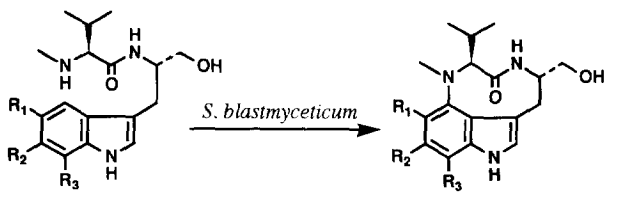
Table 1 and Fig. 5 summarize the results of the microbial conversion. Among the methyl substituted precursors (**17**, **19**, **21** and **22**), 6,*N*-dimethyl-L-valyl-L-tryptophanol (**21**) was most efficiently converted into the corresponding indolactam (**27**). The conversion yields of the 6-fluoro and 6-bromo derivatives (**20** and **15**) were higher, and comparable to that of the natural precursor, *N*-methyl-L-valyl-L-tryptophanol. 7-Methyl derivative (**22**) was moderately converted into the cyclized product (**28**). However, 1-methyl, 5-methyl and 5-bromo precursors (**17**, **19** and **16**) did not yield any cyclization products. These findings indicate that the steric requirement at positions 1 and 5 of *N*-methyl-L-valyl-L-tryptophanol is strict. Of course, it is probable that the imino group at position 1 participates in the hydrogen bonding at the enzyme surface. Although 6-methyl, 6-fluoro and 6-bromo precursors (**21**, **20** and **15**) efficiently cyclized, the cyclization yield of the 6-iodo derivative (**11**) was only 0.3%, and 6-nitro, 6-amino and 6-acetylamino derivatives (**6**-**8**) did not yield any cyclization products. An electronic effect is also deduced to be an important factor to affect the cyclization yield, but the fact that both 6-nitro and 6-amino precursors (**6** and **7**) with the electron-withdrawing and donating substituent, respectively, did not yield any cyclization products suggests that the steric factor and the hydrophobicitiy are more critical. The relatively high specificity of the cyclization enzyme to these substituted precursors is a strong circumstantial evidence of the biosynthetic pathway[18] that the cyclization at position 4 occurrs before the introduction of a monoterpenoid moiety at positions 6 and 7 of the indole ring.

Since bulkiness of a substituent at position 6 seems to decrease the efficiency of the microbial conversion, a precursor with a larger alkyl substituent than iodine could not be a substrate of the cyclization enzyme. However, the palladium catalized coupling reaction[7] of 6-halogenated indolactams as **25** and **26** with olefin would give a variety of 6-substituted indolactams. Thus, this microbial conversion is a convenient method to prepare various 6-substituted indolactams as well as 12-substituted ones because teleocidin-producing micro-organisms are very common.[4,19]

Table 1 Microbial conversion of the 1-, 5-, 6- or 7-substituted cyclization precursors

Compound	Cyclization yield (%)	Compound	Cyclization yield (%)
1-Me (**17**)	ND[a]	6-F (**20**)	8.1
5-F (**18**)	6.7	6-Br (**15**)	8.1
5-Br (**16**)	ND	6-I (**11**)	0.3
5-Me (**19**)	ND	6-NO_2 (**6**)	ND
6-Me (**21**)	4.1	6-NH_2 (**7**)	ND
7-Me (**22**)	1.9	6-NHAc (**8**)	ND
Control (*N*-Me-L-Val-L-Trp-ol)	8.5		

[a]Not detected (less than 0.1%).



R_1	R_2	R_3	
F	H	H	(**23**)
H	F	H	(**24**)
H	Br	H	(**25**)
H	I	H	(**26**)
H	Me	H	(**27**)
H	H	Me	(**28**)
H	H	H	(**1**)

Fig. 5 Synthesis of new indolactam analogues by microbial conversion.

Table 2 Biological activities of the indolactam derivatives (**1**, **27** and **28**)

Compound	Inhibition of specific [^{3}H]TPA binding[a] pIC_{50} (log1/M)	Incorporation of $^{32}P_i$ into phospholipids of HeLa cells[b] Relative cpm/mg protein 10^{-8}M	10^{-7}M	10^{-6}M	10^{-5}M
(-)-6-Methyl-indolactam-V (**27**)	5.92 (0.37)[c]	1.13 (0.14)	1.96 (0.11)	6.72 (0.27)	6.40 (0.19)
(-)-7-Methyl-indolactam-V (**28**)	5.81 (0.26)	1.26 (0.08)	1.74 (0.10)	6.76 (0.32)	5.98 (0.00)
(-)-Indolactam-V (**1**)	5.55 (0.13)	1.09 (0.01)	1.41 (0.03)	4.94 (0.10)	7.31 (0.42)

[a]This assay was carried out by the cold acetone filter method[20] using an epidermal particulate fraction prepared from dorsal epidermis of female ICR mice as reported previously.[21] The assay solution (1ml) consisted of 20mM Tris-HCl (pH 7.4), 4nM [^{3}H]TPA, 2mM 2-mercaptoethanol, the particulate fraction (100μg of protein) and various concentrations of an inhibitor. [b]This assay was done by the method reported previously[22] with slight modifications.[23] Final dimethyl sulfoxide (DMSO) concentration was 0.2%. Radioactivity of 0.2% DMSO was determined to be 1.00. [c]Standard deviation.

The tumor-promoting activity of (-)-6-methylindolactam-V (**27**) along with (-)-7-methylindolactam-V (**28**) and (-)-indolactam-V (**1**) was examined by two *in vitro* bioassays closely related to *in vivo* tumor promotion: binding affinity to the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) receptor in the mouse epidermal particulate fraction, and ability to enhance the incorporation of radioactive inorganic phosphate ($^{32}P_i$) into phospholipids of HeLa cells (Table 2). The binding affinity to the TPA receptor was evaluated by inhibition of the specific binding of [^{3}H]TPA to the mouse epidermal particulate fraction and expressed by the concentration required to cause 50% inhibition, IC_{50}. Compound **27** as well as **28** had a slightly stronger binding affinity than **1**. A similar tendency was observed in the incorporation of $^{32}P_i$ into HeLa cell phospholipids; **1** had a maximum increase of $^{32}P_i$ incorporation at 10^{-5}M, while both **27** and **28** at 10^{-6}M. (-)-6-Methylindolactam-V (**27**) existed as two stable

conformers, the sofa and the twist form,[24] as observed in (-)-indolactam-V (**1**) and (-)-7-methylindolactam-V (**28**). These findings indicate the similarity in the substituent effects at positions 6 and 7 of **1**.

In summary, we have synthesized new 6-substituted indolactams (**24-27**) by the microbial conversion using *S. blastmyceticum* NA34-17. Although introduction of a larger substituent than iodine into position 6 of (-)-indolactam-V (**1**) proved to be difficult because of the substrate specificity of the cyclization enzyme, a variety of 6-alkyl indolactams can be synthesized from the 6-halogenated derivatives as **25** and **26** by the palladium catalized coupling reaction with olefin.[7] Since nitration at position 4 of a 6-substituted indole derivative proved to be difficult,[12] and since Kogan's attempt to cyclize 8-oxo-*N*-methyl-L-valyl-L-tryptophanol by means of regiospecific thallation was disappointing,[15] this microbial conversion may be at present only one method to obtain a 6-substituted indolactam from a 6-substituted tryptophan derivative. The mechanism of the microbial conversion, therefore, needs to be revealed. Our recent experiment has shown that the cyclization enzyme is present in the mycelia, not in the culture broth. Precursors such as **15** and **20** are especially useful as substrates for isolation of the cyclization enzyme since the cyclization products do not occur naturally and their cyclization efficiency is very high.

ACKNOWLEDGMENTS

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EXPERIMENTAL

General remarks

Melting points are not corrected. The following spectroscopic and analytical instruments were used: UV, Shimadzu UV-200; Digital Polarimeter, Jasco DIP-4; ^{1}H NMR, JEOL GX400, Bruker ARX500 and AC300 (ref. TMS); HPLC, Waters Model 600E with Model 484 UV detector and Waters Model 625LC with Model 486 UV detector; MS, JEOL JMS-DX300 (for EI: 70eV, 300μA). HPLC was carried out on a YMC packed SH-342 (ODS, 20mm i.d. x 150mm), A-023 (silica gel, 10mm i.d. x 250mm), SH-043 (silica gel, 20mm i.d. x 250mm) column (Yamamura Chemical Laboratory) and μ-Bondasphere C_{18} (19mm i.d. x 150mm) column (Waters Associates). Wako C-100 and C-200 gel (silica gel, Wako Pure Chemical Industries) and YMC A60-350/250 gel (ODS, Yamamura Chemical Laboratory) were used for column chromatography. Radio-isotopes and 1-, 5-, 6- or 7-substituted tryptophans were purchased from NEN Research Products and Sigma, respectively.

*Boc-N-Methyl-6-nitro-L-valyl-L-tryptophanol (**5**)*

Compound **2** (10.2g, 24mmol) obtained from L-tryptophan by 6 steps[14,15] was dissolved in DMF (233ml) and H_2O (58ml). To the solution, $NaBH_4$ (3.8g, 96mmol) was added portionwise, and the reaction mixture was stirred at room temperature for 45 minutes. The mixture was partitioned between CH_2Cl_2 and water, and the CH_2Cl_2 layer was dried over Na_2SO_4. The CH_2Cl_2 extracts were purified by column chromatography on a Wako C-200 gel using hexane and EtOAc (1:1) to yield **3** (6.45g, 17.5mmol) in a 73% yield. Compound **3**, yellow needles from MeOH, mp. 171-174°C, $[\alpha]_D$ -45.9° (c=0.40, MeOH, 19.5°C). UV λ_{max} (MeOH) nm (ε): 372 (6,400), 326 (7,300), 267 (8,500), 252 (8,800). ^{1}H NMR δ (CD_3OD, 0.065M, 300K) ppm: 2.89 (1H, dd, J=14.6, 7.9Hz), 3.07 (1H, dd, J=14.6, 5.9Hz), 3.56 (2H, m), 3.92 (1H, m), 4.96 (1H, d, J=12.5Hz), 5.02 (1H, d, J=12.5Hz), 7.27 (5H, m), 7.43 (1H, s), 7.72 (1H, d, J=8.3Hz), 7.88 (1H, d, J=8.3Hz), 8.30 (1H, s). FAB-MS [3-nitro-benzylalcohol (NBA)] m/z: 370 (MH^+). Anal. Calcd. for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.97; H, 5.34; N, 11.29.

Compound **3** (1.40g, 3.79mmol) dissolved in 6N HCl containing 50% MeOH (43ml) was heated at 130°C in a sealed tube for 40 minutes. The reaction mixture was neutralized with 8N NaOH, and the MeOH was evaporated *in vacuo*. After the pH was adjusted to 10 using 1N NaOH, the concentrates were extracted with EtOAc. After drying over Na_2SO_4 and concentration, the EtOAc extracts were purified by column chromatography on a Wako C-100 gel using $CHCl_3$ containing increasing amounts of 2-PrOH to give **4** (760mg, 3.23mmol) in an 85% yield. Compound **4**, amorphous, $[\alpha]_D$ -26.7° (*c*=0.34, MeOH, 23.5°C). UV λ_{max} (MeOH) nm (ε): 369 (5,900), 324 (7,100), 263 (8,400), 252 (8,600). ^{1}H NMR δ (CD_3OD, 0.21M, 300K) ppm: 2.77 (1H, dd, *J*=14.4, 7.4Hz), 2.96 (1H, dd, *J*=14.4, 6.1Hz), 3.15 (1H, m), 3.43 (1H, dd, *J*=10.7, 6.7Hz), 3.58 (1H, dd, *J*=10.7, 4.6Hz), 7.48 (1H, s), 7.69 (1H, d, *J*=8.8Hz), 7.91 (1H, dd, *J*=8.8, 1.9Hz), 8.30 (1H, d, *J*=1.9Hz). FAB-MS (NBA) *m/z*: 236 (MH^+).

Compound **4** (1.51g, 6.42mmol) was stirred in anhydrous DMF (9ml) containing Boc-*N*-methyl-L-valine (1.49g, 6.45mmol), 1-hydroxybenzotriazole (HOBt, 0.92g, 6.79mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSCD·HCl, 1.30g, 6.79mmol). After 45 hours, the reaction mixture was extracted with EtOAc. After drying over Na_2SO_4 and concentration, the EtOAc extracts were purified by column chromatography on a Wako C-200 gel with hexane and EtOAc (4.5:5.5), followed on a YMC A60-350/250 gel with MeOH and water (stepwise) to yield **5** (2.30g, 5.13mmol) in an 80% yield. Compound **5**, amorphous, $[\alpha]_D$ -121.8° (*c*=0.90, MeOH, 26°C). UV λ_{max} (MeOH) nm (ε): 371 (7,500), 327 (8,900), 267 (10,000), 252 (10,100). ^{1}H NMR δ (CD_3OD, 0.098M, 300K) ppm: 0.80 (3H, d, *J*=6.4Hz), 0.90 (3H, d, *J*=6.4Hz), 1.40 (9H, s), 2.14 (1H, m), 2.58 (3H, s), 2.90 (1H, m), 3.09 (1H, m), 3.58 (2H, m), 4.06 (1H, d, *J*=11.0Hz), 4.28 (1H, m), 7.41 (1H, s), 7.71 (1H, d, *J*=8.9Hz), 7.92 (1H, dd, *J*=8.9, 2.1Hz), 8.30 (1H, d, *J*=2.1Hz). FAB-MS (NBA) *m/z*: 449 (MH^+).

*N-Methyl-6-nitro-L-valyl-L-tryptophanol (**6**)*

Compound **5** (507mg, 1.13mmol) was treated with 1N HCl-AcOH (23.2ml). After 30 minutes, the reaction mixture was evaporated with toluene *in vacuo* to dryness. The concentrates were then mixed with 1N NaOH containing 50% MeOH (36ml) for 30 minutes. After extraction with EtOAc, the EtOAc extracts were recrystallized from CH_3CN to yield **6** (342mg, 0.98mmol) in an 87% yield. Compound **6**, yellow rods, mp. 202-205°C, $[\alpha]_D$ -53.8° (*c*=0.18, MeOH, 24.9°C). UV λ_{max} (MeOH) nm (ε): 377 (7,200), 328 (8,400), 267 (9,600), 252 (9,700). ^{1}H NMR δ (CD_3OD, 0.085M, 300K) ppm: 0.84 (3H, d, *J*=7.0Hz), 0.86 (3H, d, *J*=7.3Hz), 1.78 (1H, m), 2.01 (3H, s), 2.66 (1H, d, *J*=6.4Hz), 2.93 (1H, dd, *J*=14.7, 8.9Hz), 3.12 (1H, dd, *J*=14.7, 5.8Hz), 3.59 (1H, dd, *J*=11.0, 5.5Hz), 3.63 (1H, dd, *J*=11.0, 5.5Hz), 4.32 (1H, m), 7.48 (1H, s), 7.78 (1H, d, *J*=8.9Hz), 7.93 (1H, dd, *J*=8.9, 2.1Hz), 8.29 (1H, d, *J*=2.1Hz). FAB-MS (NBA) *m/z*: 349 (MH^+). Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.08. Found: C, 58.86; H, 7.04; N, 16.12.

*6-Amino-N-methyl-L-valyl-L-tryptophanol (**7**)*

Compound **6** (190mg, 0.545mmol) dissolved in EtOH (6ml) was stirred in the presence of PtO_2 (20mg, 0.088mmol) under 1 atm of H_2 at room temperature for 40 minutes. The filtered reaction mixture was evaporated *in vacuo* to dryness. The concentrates were purified by HPLC on YMC SH-342 using 10% CH_3CN containing 0.3% trifluoroacetic acid (TFA) to give **7** (161mg, 0.506mmol) in a 93% yield. Compound **7**, amorphous, $[\alpha]_D$ -34.0° (*c*=0.62, MeOH, 17°C). UV λ_{max} (MeOH) nm (ε): 303.5 (3,300), 270.5 (4,100), 230 (23,200). ^{1}H NMR δ (CD_3OD, 0.12M, 300K) ppm: 0.88 (3H, d, *J*=6.8Hz), 0.89 (3H, d, *J*=6.8Hz), 1.83 (1H, m), 2.07 (3H, s), 2.74 (1H, d, *J*=6.3Hz), 2.83 (1H, dd, *J*=14.6, 8.3Hz), 2.99 (1H, dd, *J*=14.6, 5.7Hz), 3.58 (2H, m), 4.28 (1H, m), 6.57 (1H, dd, *J*=8.4, 2.0Hz), 6.72 (1H, d, *J*=2.0Hz), 6.88 (1H, s), 7.40 (1H, d, *J*=8.4Hz). HR-EIMS *m/z*: 318.2040 (M^+, calcd. for $C_{17}H_{26}N_4O_2$, 318.2055).

*6-Acetylamino-N-methyl-L-valyl-L-tryptophanol (**8**)*

Compound **5** (85mg, 0.19mmol) dissolved in EtOH (6ml) was stirred in the presence of PtO_2 (8mg, 0.032mmol) under 1 atm of H_2 at room temperature for 20 minutes. After filtration followed by evaporation, the concentrates were purified by HPLC on YMC SH-342 using 25% CH_3CN containing 0.3% TFA to give 6-

amino-Boc-*N*-methyl-L-valyl-L-tryptophanol (75mg, 0.18mmol) in a 95% yield. This amine (52mg, 0.12mmol) was treated with acetic anhydride (0.5ml) in pyridine (0.5ml). After 45 minutes, ice was added to the reaction mixture, which was evaporated with toluene *in vacuo* to dryness. The concentrates were partitioned between EtOAc and water, and the EtOAc layer was dried over Na_2SO_4. After evaporation, the EtOAc extracts (52mg) were treated with 1N HCl-AcOH (1.8ml) for 30 minutes. The reaction mixture was evaporated with toluene *in vacuo* to dryness. The concentrates were then treated with 1N NaOH containing 50% MeOH (2.8ml) for 30 minutes. After extraction with EtOAc, drying over Na_2SO_4 and concentration, the EtOAc extracts were purified by HPLC on YMC SH-342 using 15% CH_3CN containing 0.3% TFA to give **8** (35.6mg, 0.099mmol) in a 79% yield. Compound **8**, amorphous, $[\alpha]_D$ -13.6° (*c*=0.29, MeOH, 26°C). UV λ_{max} (MeOH) nm (ε): 291 (3,700), 243 (11,100). ^1H NMR δ (CD_3OD, 0.031M, 300K) ppm: 0.88 (3H, d, *J*=6.7Hz), 0.90 (3H, d, *J*=7.0Hz), 1.83 (1H, m), 2.03 (3H, s), 2.13 (3H, s), 2.77 (1H, d, *J*=6.4Hz), 2.87 (1H, dd, *J*=14.7, 8.6Hz), 3.05 (1H, dd, *J*=14.7, 5.5Hz), 3.59 (2H, m), 4.31 (1H, m), 6.98 (1H, dd, *J*=8.5, 1.8Hz), 7.06 (1H, s), 7.56 (1H, d, *J*=8.5Hz), 7.76 (1H, d, *J*=1.8Hz). HR-EIMS *m/z*: 360.2160 (M^+, calcd. for $C_{19}H_{28}N_4O_3$, 360.2161).

6-Iodo-N-methyl-L-valyl-L-tryptophanol (11)

Compound **5** (11.9g, 26.5mmol) was treated with acetic anhydride (60ml) in pyridine (60ml). After 30 minutes, ice was added to the reaction mixture, which was evaporated with toluene *in vacuo* to dryness. The concentrates were partitioned between EtOAc and water, and the EtOAc layer was dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The EtOAc extracts (13.0g) dissolved in MeOH (100ml) were mixed with $NiCl_2 \cdot 6H_2O$ (12.7g, 53.0mmol). The reaction mixture was cooled in ice-water, to which $NaBH_4$ (4.0g, 106mmol) was added carefully. After an additional 10 minutes of stirring, MeOH was evaporated from the mixture *in vacuo*. The residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to dryness. The concentrates were purified by column chromatography on a Wako C-200 gel with EtOAc and hexane (1:1) to yield **9** (9.24g, 20.1mmol) in a 76% yield as colorless oil, which crystallized after standing overnight. Compound **9**, colorless needles from EtOAc-hexane, mp. 97.5-99°C, $[\alpha]_D$ -88.2° (*c*=0.49, MeOH, 24.5°C). UV λ_{max} (MeOH) nm (ε): 302.5 (4,400), 278 (4,300), 270 (4,400), 230 (30,000). ^1H NMR δ ($CDCl_3$, 0.074M, 300K) ppm: 0.85 (3H, d, *J*=6.6Hz), 0.92 (3H, d, *J*=6.4Hz), 1.46 (9H, s), 2.06 (3H, s), 2.27 (1H, m), 2.76 (3H, s), 2.76 (2H, m), 2.92 (1H, dd, *J*=14.6, 5.8Hz), 4.03 (3H, m), 4.49 (1H, m), 6.42 (1H, br.d, *J*=6.9Hz), 6.57 (1H, dd, *J*=8.4, 1.9Hz), 6.62 (1H, d, *J*=1.9Hz), 6.83 (1H, s), 7.41 (1H, d, *J*=8.4Hz), 7.84 (1H, br.s). FAB-MS (NBA) *m/z*: 460 (M^+). Anal. Calcd. for $C_{24}H_{36}N_4O_5$: C, 62.59; H, 7.88; N, 12.16. Found: C, 62.41; H, 8.09; N, 12.11.

Compound **9** (651mg, 1.41mmol) dissolved in 80% AcOH (52ml) was cooled by ice-water. To the solution, a solution of $NaNO_2$ (108mg, 1.53mmol) in chilled water (1ml) was added slowly under argon. Immediately after, a solution of KI (259mg, 1.56mmol) in chilled water (1ml) was added to the reaction mixture, which was stirred for 10 minutes under cooling. After addition of sodium hydrogen sulfite (*ca.* 50mg), the mixture was evaporated with toluene *in vacuo* to dryness. The concentrates were partitioned between EtOAc and water, and the EtOAc layer was dried over Na_2SO_4. After evaporation, the EtOAc extracts were purified by column chromatography on a Wako C-200 gel with EtOAc and hexane (3:7), followed on a YMC A60-350/250 gel with 70% MeOH to give **10** (310mg, 0.54mmol) in a 38% yield. Compound **10**, amorphous, $[\alpha]_D$ -96.5° (*c*=0.15, MeOH, 22°C). UV λ_{max} (MeOH) nm (ε): 296 (6,200), 289 (7,300), 232 (47,700). ^1H NMR δ ($CDCl_3$, 0.029M, 300K) ppm: 0.85 (3H, d, *J*=6.6Hz), 0.92 (3H, d, *J*=6.4Hz), 1.44 (9H, s), 2.07 (3H, s), 2.26 (1H, m), 2.73 (3H, s), 2.84 (1H, dd, *J*=14.6, 7.8Hz), 2.94 (1H, dd, *J*=14.6, 6.2Hz), 3.98 (1H, d, *J*=10.9Hz), 4.03 (2H, m), 4.49 (1H,m), 6.42 (1H, br.d, *J*=6.6Hz), 6.99 (1H, s), 7.39 (1H, dd, *J*=8.4, 1.0Hz), 7.41 (1H, d, *J*=8.4Hz), 7.71 (1H, s), 8.09 (1H, br.s). FAB-MS (NBA) *m/z*: 571 (M^+).

Compound **10** (80mg, 0.14mole) was treated with 1N HCl-AcOH (23.2ml). After 30 minutes, the reaction mixture was evaporated with toluene *in vacuo* to dryness. The concentrates were then mixed with 1N NaOH containing 50% MeOH (2ml) for 30 minutes. After extraction with EtOAc and drying over Na_2SO_4, the EtOAc layer was concentrated *in vacuo* to yield **11** (60mg, 0.14mmol) quantitatively. Compound **11**, amorphous, $[\alpha]_D$ -20.4° (*c*=0.17, MeOH, 19.5°C). UV λ_{max} (MeOH) nm (ε): 297 (3,500), 288 (4,400), 232

(28,900). ^{1}H NMR δ (CD_3OD, 0.043M, 300K) ppm: 0.84 (3H, d, *J*=6.9Hz), 0.86 (3H, d, *J*=6.9Hz), 1.76 (1H, m), 2.02 (3H, s), 2.62 (1H, d, *J*=6.3Hz), 2.86 (1H, dd, *J*=14.6, 8.4Hz), 3.04 (1H, ddd, *J*=14.6, 5.9, 0.6Hz), 3.56 (1H, dd, *J*=10.9, 5.5Hz), 3.60 (1H, dd, *J*=10.9, 5.2Hz), 4.28 (1H, m), 7.05 (1H, s), 7.27 (1H, dd, *J*=8.3, 1.5Hz), 7.44 (1H, d, *J*=8.3Hz), 7.66 (1H, d, *J*=1.1Hz). HR-EIMS *m/z*: 429.0899 (M^+, calcd. for $C_{17}H_{24}N_3O_2I$, 429.0913).

*6-Bromo-N-methyl-L-valyl-L-tryptophanol (**15**) and 5-bromo-N-methyl-L-valyl-L-tryptophanol (**16**)*

Compound **12** (402mg, 0.88mmole) synthesized from Boc-*N*-methyl-L-valyl-L-tryptophanol[13] by the method of Kogan *et al.*[15] was dissolved in acetic acid (0.83ml). Bromine (0.045ml, 0.87mmole) dissolved in acetic acid (0.36ml) was added to the solution under cooling with ice-water. After 5 minutes of stirring, the mixture was partitioned between EtOAc and saturated $NaHSO_3$ aqueous solution. The EtOAc layer was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to dryness. The EtOAc extracts were purified by column chromatography on a YMC A60-350/250 gel with 70% MeOH, followed by HPLC on YMC SH-043 using hexane, $CHCl_3$ and 2-PrOH (80:17:3) to give the 6-bromo derivative (**13**, 31mg, 0.058mole) and the 5-bromo derivative (**14**, 61mg, 0.114mmole) in a 7% and a 13% yield, respectively. Compound **13**, amorphous, $[\alpha]_D$ +7.5° (*c*=0.99, MeOH, 19°C). UV λ_{max} (MeOH) nm (ε): 299 (11,200), 270 (16,200), 247 (16,500). ^{1}H NMR δ ($CDCl_3$, 0.011M, 318K) ppm: 0.91 (3H, d, *J*=6.6Hz), 1.02 (3H, d, *J*=6.5Hz), 1.45 (9H, s), 2.03 (3H, s), 2.31 (1H, m), 2.75 (3H, s), 4.10 (1H, dd, *J*=11.4, 7.9Hz), *ca.*4.2 (1H, br.s), 4.65 (1H, dd, *J*=11.4, 4.2Hz), 5.63 (1H, m), 7.38 (1H, dd, *J*=8.5, 1.4Hz), 7.57 (1H, d, *J*=1.4Hz), 8.18 (1H, d, *J*=8.5Hz), 8.20 (1H, d, *J*=3.1Hz), 9.16 (1H, br.s). FAB-MS *m/z*: 538 (MH^+). Compound **14**, amorphous, $[\alpha]_D$ +38.6° (*c*=0.58, MeOH, 19°C). UV λ_{max} (MeOH) nm (ε): 300 (11,300), 264 (10,000), 247.5 (13,900). ^{1}H NMR δ ($CDCl_3$, 0.028M, 318K) ppm: 0.92 (3H, d, *J*=6.6Hz), 1.03 (3H, d, *J*=6.5Hz), 1.47 (9H, s), 2.04 (3H, s), 2.31 (1H, m), 2.77 (3H, s), 4.11 (1H, dd, *J*=11.4, 7.8Hz), 4.23 (1H, br.s), 4.65 (1H, dd, *J*=11.4, 4.1Hz), 5.62 (1H, m), 7.24 (1H, d, *J*=8.6Hz), 7.36 (1H, dd, *J*=8.6, 1.9Hz), 8.20 (1H, d, *J*=3.2Hz), 8.46 (1H, d, *J*=1.9Hz), 9.50 (1H, br.s). FAB-MS *m/z*: 538 (MH^+).

Compond **13** (60mg, 0.11mmole) was dissolved in DMF (0.9ml) and H_2O (0.2ml). To the solution, $NaBH_4$ (17mg, 0.45mmol) was added portionwise, and the reaction mixture was stirred at room temperature for 2 hours. The mixture was partitioned between EtOAc and water, and the EtOAc layer was dried over Na_2SO_4. After evaporation, the EtOAc extracts were purified by column chromatography on a Wako C-100 gel using toluene and increasing amounts of acetone, followed by HPLC on μ-Bondasphere C_{18} to yield 6-bromo-Boc-*N*-methyl-L-valyl-L-tryptophanol (28mg, 0.058mmole) in a 52% yield. This product (25mg, 0.052mmole) was subjected to the Boc cleavage as mentioned above to give 6-bromo-*N*-methyl-L-valyl-L-tryptophanol (**15**, 15mg, 0.039mmole) in a 76% yield. Compound **15**, amorphous, $[\alpha]_D$ -36.0° (*c*=0.49, MeOH, 20°C). UV λ_{max} (MeOH) nm (ε): 295 (6,500), 287.5 (7,200), 280 (6,700), 228 (43,700). ^{1}H NMR δ (CD_3OD, 0.079M, 300K) ppm: 0.85 (3H, d, *J*=6.9Hz), 0.86 (3H, d, *J*=6.9Hz), 1.78 (1H, m), 2.02 (3H, s), 2.65 (1H, d, *J*=6.3Hz), 2.87 (1H, dd, *J*=14.6, 8.3Hz), 3.05 (1H, ddd, *J*=14.6, 5.9, 0.6Hz), 3.57 (1H, dd, *J*=10.9, 5.4Hz), 3.60 (1H, dd, *J*=10.9, 5.2Hz), 4.29 (1H, m), 7.10 (1H, s), 7.10 (1H, dd, *J*=8.4, 1.7Hz), 7.46 (1H, d, *J*=1.7Hz), 7.55 (1H, d, *J*=8.4Hz). HR-EIMS *m/z*: 381.1029 (M^+, calcd. for $C_{17}H_{24}N_3O_2Br$, 381.1052). 5-Bromo-*N*-methyl-L-valyl-L-tryptophanol (**16**) was similarly obtained from **14** in a 50% yield. Compound **16**, amorphous, $[\alpha]_D$ -51.5° (*c*=0.44, MeOH, 20°C). UV λ_{max} (MeOH) nm (ε): 298 (4,600), 290.5 (5,700), 284 (5,500), 228 (36,000). ^{1}H NMR δ (CD_3OD, 0.069M, 300K) ppm: 0.84 (3H, d, *J*=6.9Hz), 0.86 (3H, d, *J*=6.8Hz), 1.78 (1H, m), 2.02 (3H, s), 2.64 (1H, d, *J*=6.4Hz), 2.85 (1H, dd, *J*=14.7, 8.7Hz), 3.04 (1H, dd, *J*=14.7, 5.2Hz), 3.56 (1H, dd, *J*=10.9, 5.6Hz), 3.60 (1H, dd, *J*=10.9, 5.3Hz), 4.27 (1H, m), 7.13 (1H, s), 7.15 (1H, dd, *J*=8.6, 1.9Hz), 7.22 (1H, d, *J*=8.6Hz), 7.79 (1H, d, *J*=1.9Hz). HR-EIMS *m/z*: 381.1052 (M^+, calcd. for $C_{17}H_{24}N_3O_2Br$, 381.1052).

*1-, 5,- 6- or 7-Substituted N-methyl-L-valyl-L-tryptophanols (**17-22**)*

Synthesis of these compounds (**17-22**) was carried out from corresponding commercially available tryptophan derivatives by the method reported previously.[13]

1,*N*-Dimethyl-L-valyl-L-tryptophanol (**17**), a 7.2% yield from 1-methyl-DL-tryptophan, amorphous, $[\alpha]_D$ -35.3° (*c*=0.74, MeOH, 28°C). UV λ_{max} (MeOH) nm (ε): 290.5 (3,500), 282 (4,100), 276 (3,800), 222 (24,200). ^{1}H NMR δ (CD_3OD, 0.066M, 300K) ppm: 0.84 (3H, d, *J*=6.7Hz), 0.85 (3H, d, *J*=6.7Hz), 1.77 (1H, m), 2.02 (3H, s), 2.64 (1H, d, *J*=6.4Hz), 2.88 (1H, dd, *J*=14.6, 8.2Hz), 3.06 (1H, dd, *J*=14.6, 5.5Hz), 3.57 (1H, dd, *J*=10.7, 5.2Hz), 3.61 (1H, dd, *J*=10.7, 5.2Hz), 3.71 (3H, s), 4.29 (1H, m), 7.00 (1H, s), 7.02 (1H, ddd, *J*=7.9, 7.0, 0.9Hz), 7.13 (1H, dt, *J*=7.6, 1.2Hz), 7.28 (1H, d, *J*=8.2Hz), 7.63 (1H, dd, *J*=8.2, 0.9Hz). HR-EIMS *m/z*: 317.2076 (M^+, calcd. for $C_{18}H_{27}N_3O_2$, 317.2103).

5-Fluoro-*N*-methyl-L-valyl-L-tryptophanol (**18**), a 9.4% yield from 5-fluoro-DL-tryptophan, amorphous, $[\alpha]_D$ -17.0° (*c*=1.06, MeOH, 23°C). UV λ_{max} (MeOH) nm (ε): 287 (4,200), 222.5 (16,100). ^{1}H NMR δ (CD_3OD, 0.10M, 300K) ppm: 0.85 (3H, d, *J*=7.0Hz), 0.87 (3H, d, *J*=6.7Hz), 1.78 (1H, m), 2.03 (3H, s), 2.65 (1H, d, *J*=6.4Hz), 2.85 (1H, dd, *J*=14.7, 8.2Hz), 3.03 (1H, dd, *J*=14.7, 6.1Hz), 3.57 (1H, dd, *J*=10.7, 5.5Hz), 3.61 (1H, dd, *J*=10.7, 4.9Hz), 4.28 (1H, m), 6.82 (1H, dt, *J*=9.2, 2.4Hz), 7.15 (1H, s), 7.25 (1H, dd, *J*=8.9, 4.3Hz), 7.31 (1H, dd, *J*=10.1, 2.4Hz). HR-EIMS *m/z*: 321.1823 (M^+, calcd. for $C_{17}H_{24}N_3O_2F$, 321.1853).

5,*N*-Dimethyl-L-valyl-L-tryptophanol (**19**), a 7.2% yield from 5-methyl-DL-tryptophan, amorphous, $[\alpha]_D$ -30.7° (*c*=0.93, MeOH, 22°C). UV λ_{max} (MeOH) nm (ε): 290 (2,900), 288 (3,800), 277 (3,900), 225 (21,200). ^{1}H NMR δ (CD_3OD, 0.176M, 300K) ppm: 0.85 (3H, d, *J*=7.1Hz), 0.87 (3H, d, *J*=7.1Hz), 1.75 (1H, m), 2.05 (3H, s), 2.41 (3H, s), 2.64 (1H, d, *J*=6.4Hz), 2.87 (1H, dd, *J*=14.6, 8.3Hz), 3.04 (1H, dd, *J*=14.6, 6.1Hz), 3.58 (1H, dd, *J*=10.9, 5.3Hz), 3.61 (1H, dd, *J*=10.9, 5.3Hz), 4.29 (1H, m), 6.90 (1H, dd, *J*=8.3, 1.3Hz), 7.04 (1H, s), 7.18 (1H, d, *J*=8.3Hz), 7.42 (1H, d, *J*=0.7Hz). HR-EIMS *m/z*: 317.2097 (M^+, calcd. for $C_{18}H_{27}N_3O_2$, 317.2103).

6-Fluoro-*N*-methyl-L-valyl-L-tryptophanol (**20**), a 7.3% yield from 6-fluoro-DL-tryptophan, amorphous, $[\alpha]_D$ -35.6° (*c*=0.96, MeOH, 21°C). UV λ_{max} (MeOH) nm (ε): 283 (3,900), 220 (22,400). ^{1}H NMR δ (CD_3OD, 0.06M, 300K) ppm: 0.85 (3H, d, *J*=6.4Hz), 0.87 (3H, d, *J*=6.4Hz), 1.78 (1H, m), 2.04 (3H, s), 2.66 (1H, d, *J*=6.4Hz), 2.87 (1H, dd, *J*=14.7, 8.5Hz), 3.05 (1H, dd, *J*=14.7, 6.1Hz), 3.57 (1H, dd, *J*=11.0, 5.5Hz), 3.61 (1H, dd, *J*=11.0, 5.5Hz), 4.29 (1H, m), 6.78 (1H, ddd, *J*=9.8, 8.5, 2.4Hz), 6.99 (1H, dd, *J*=9.8, 2.4Hz), 7.08 (1H, s), 7.58 (1H, dd, *J*=8.5, 5.2Hz). HR-EIMS *m/z*: 321.1832 (M^+, calcd. for $C_{17}H_{24}N_3O_2F$, 321.1853).

6,*N*-Dimethyl-L-valyl-L-tryptophanol (**21**), a 3.6% yield from 6-methyl-DL-tryptophan, amorphous, $[\alpha]_D$ -32.1° (*c*=0.16, MeOH, 19°C). UV λ_{max} (MeOH) nm (ε): 292 (4,100), 282 (4,900), 224 (32,800). ^{1}H NMR δ (CD_3OD, 0.017M, 300K) ppm: 0.85 (3H, d, *J*=6.7Hz), 0.86 (3H, d, *J*=7.0Hz), 1.77 (1H, m), 2.04 (3H, s), 2.39 (3H, s), 2.63 (1H, d, *J*=6.4Hz), 2.87 (1H, dd, *J*=14.3, 7.6Hz), 3.03 (1H, dd, *J*=14.3, 6.1Hz), 3.56 (1H, dd, *J*=11.0, 5.5Hz), 3.60 (1H, dd, *J*=11.0, 5.5Hz), 4.29 (1H, m), 6.84 (1H, dd, *J*=8.2, 1.2Hz), 7.00 (1H, s), 7.09 (1H, d, *J*=1.2Hz), 7.50 (1H, d, *J*=8.2Hz). HR-EIMS *m/z*: 317.2097 (M^+, calcd. for $C_{18}H_{27}N_3O_2$, 317.2103).

7,*N*-Dimethyl-L-valyl-L-tryptophanol (**22**), a 7.3% yield from 7-methyl-DL-tryptophan, amorphous, $[\alpha]_D$ -27.5° (*c*=0.57, MeOH, 23°C). UV λ_{max} (MeOH) nm (ε): 290 (4,100), 280.5 (5,200), 275 (4,900), 222 (30,500). ^{1}H NMR δ (CD_3OD, 0.072M, 300K) ppm: 0.85 (3H, d, *J*=6.9Hz), 0.86 (3H, d, *J*=6.9Hz), 1.77 (1H, m), 2.05 (3H, s), 2.44 (3H, s), 2.63 (1H, d, *J*=6.3Hz), 2.89 (1H, dd, *J*=14.6, 8.3Hz), 3.06 (1H, ddd, *J*=14.6, 6.1, 0.6Hz), 3.57 (1H, dd, *J*=10.8, 5.3Hz), 3.60 (1H, dd, *J*=10.8, 5.3Hz), 4.30 (1H, m), 6.86 (1H, d, *J*=7.0Hz), 6.91 (1H, t, *J*=7.4Hz), 7.09 (1H, s), 7.46 (1H, d, *J*=7.4Hz). HR-EIMS *m/z*: 317.2090 (M^+, calcd. for $C_{18}H_{27}N_3O_2$, 317.2103).

Feeding experiment with cyclization precursors

S. blastmyceticum NA34-17 was innoculated to a 500ml flask containing 100ml of a medium consisting of 1% glucose, 1% polypeptone, 1% meat extract and 0.5% NaCl (pH 6.6). After the flask was shaken at 27°C for 72 hours, 2ml of this seed culture was transferred to a 500ml flask containing 100ml of a medium (2% glucose, 1% polypeptone, 1% meat extract, 0.5% NaCl), and the flask was shaken at 27°C. The pH of the culture broth was checked at 12-hour intervals. A cyclization precursor dissolved in DMSO (5mg/0.5ml) which was sterilized

with a membrane filter (0.45μm) was added to the flask at the pH bottom (*ca.* 6.0) approximately after 96 hours. The culture broth was harvested 12 hours after the pH had recovered to 6.8, and filtered to remove the mycelia. The filtrate was extracted three times with EtOAc. The EtOAc layer was dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The EtOAc extracts were purified by column chromatography on a Wako C-100 gel with toluene and increasing amounts of acetone. The 30-50% acetone eluates were further purified by HPLC on μ-Bondasphere C_{18} with 60-70% MeOH to give an indolactam derivative. The following indolactam derivatives were obtained by the microbial conversion.

(-)-5-Fluoroindolactam-V (**23**), amorphous, $[\alpha]_D$ +71.7° (*c*=0.10, MeOH, 26°C). UV λ_{max} (MeOH) nm (ε): 299 (7,600), 289 (8,100), 223.5 (25,800). ^{1}H NMR δ ($CDCl_3$, 0.013M, 300K, sofa > 95%) ppm: sofa conformer; 0.94 (3H, d, *J*=6.7Hz), 1.26 (3H, dd, *J*=6.7, 3.4Hz, through space coupling with fluorine), 2.46 (1H, m), 2.76 (3H, s), 2.82 (1H, dd, *J*=14.7, 1.5Hz), 2.90 (1H, d, *J*=11.0Hz), 3.10 (1H, dd, *J*=14.3, 4.3Hz), 3.43 (2H, m), 4.47 (1H, m), 4.72 (1H, d, *J*=11.0Hz), 7.01 (1H, dd, *J*=10.1, 8.6 Hz), 7.07 (1H, d, *J*=2.4Hz), 7.19 (1H, dd, *J*=8.6, 4.0Hz), 8.27 (1H, br.s). HR-EIMS *m/z*: 319.1693 (M+, calcd. for $C_{17}H_{22}N_3O_2F$, 319.1696).

(-)-6-Fluoroindolactam-V (**24**), amorphous, $[\alpha]_D$ -386.0° (*c*=0.11, MeOH, 18°C). UV λ_{max} (MeOH) nm (ε): 292 (11,000), 227 (28,000). ^{1}H NMR δ ($CDCl_3$, 0.015M, 300K, sofa:twist = 1:15) ppm: twist conformer; 0.64 (3H, d, *J*=6.7Hz), 0.93 (3H, d, *J*=6.4Hz), 2.59 (1H, m), 2.88 (3H, s), 3.01 (1H, dd, *J*=17.4, 3.7Hz), 3.15 (1H, br.d, *J*=17.4Hz), 3.57 (1H, dd, *J*=11.3, 8.5Hz), 3.75 (1H, dd, *J*=11.3, 3.7Hz), 4.22 (1H, br.s), 4.40 (1H, d, *J*=10.4Hz), 6.28 (1H, dd, *J*=12.2, 2.1Hz), 6.57 (1H, dd, *J*=8.5, 2.1Hz), 6.86 (1H, s), 7.18 (1H, br. s), 7.98 (1H, br. s): sofa conformer; 1.23 (3H, d, *J*=6.7Hz), 2.74 (3H, s). Other peaks of the sofa conformer had weak intensities and/or overlapped the peaks of the twist conformer. HR-EIMS *m/z*: 319.1683 (M+, calcd. for $C_{17}H_{22}N_3O_2F$, 319.1696).

(-)-6-Bromoindolactam-V (**25**), amorphous, $[\alpha]_D$ -236.1° (*c*=0.039, MeOH, 22°C). UV λ_{max} (MeOH) nm (ε): 311 (8,800), 302 (8,800), 235 (34,000). ^{1}H NMR δ ($CDCl_3$, 0.004M, 300K, sofa:twist = 1:7) ppm: twist conformer; 0.63 (3H, d, *J*=6.7Hz), 0.93 (3H, d, *J*=6.4Hz), 2.03 (1H, br.s, 14-OH), 2.59 (1H, m), 2.90 (3H, s), 2.99 (1H, dd, *J*=17.4, 3.6Hz), 3.16 (1H, br.d, *J*=17.4Hz), 3.54 (1H, m), 3.75 (1H, m), 4.19 (1H, m), 4.35 (1H, d, *J*=10.2Hz), 6.58 (1H, d, *J*=1.5Hz), 6.62 (1H, br.s), 6.86 (1H, s), 7.04 (1H, d, *J*=1.5Hz), 7.98 (1H, br.s): sofa conformer; 0.94 (3H, m), 1.24 (3H, d, *J*=6.7Hz), 2.39 (1H, m), 2.73 (3H, s), 2.82 (1H, dd, *J*=14.6, 1.4Hz), 2.97 (1H, d, *J*=10.8Hz), 3.07 (1H, dd, *J*=14.6, 4.8Hz), 3.41 (2H, m), 4.44 (1H, m), 4.64 (1H, br.d, *J*=10.8Hz), 7.02 (1H, d, *J*=2.2Hz), 7.16 (1H, d, *J*=1.7Hz), 7.44 (1H, d, *J*=1.7Hz), 8.26 (1H, br.s). HR-EIMS *m/z*: 379.0879 (M+, calcd. for $C_{17}H_{22}N_3O_2Br$, 379.0896).

(-)-6-Iodoindolactam-V (**26**), white powder, $[\alpha]_D$ -256.6° (*c*=0.13, MeOH, 18°C). UV λ_{max} (MeOH) nm (ε): 303 (8,300), 294.5 (7,900), 239 (45,000). ^{1}H NMR δ (CD_3OD, 0.018M, 300K, sofa:twist = 1:3.1) ppm: twist conformer; 0.61 (3H, d, *J*=6.7Hz), 0.89 (3H, d, *J*=6.3Hz), 2.54 (1H, m), 2.85 (3H, s), 3.07 (2H, m), 3.45 (1H, dd, *J*=11.1, 9.0Hz), 3.60 (1H, dd, *J*=11.1, 4.6Hz), 4.11 (1H, m), 4.45 (1H, d, *J*=10.2Hz), 6.66 (1H, d, *J*=1.4Hz), 6.90 (1H, s), 7.23 (1H, d, *J*=1.4Hz): sofa conformer; 0.90 (3H, d, *J*=6.5Hz), 1.21 (3H, d, *J*=6.7Hz), 2.30 (1H, m), 2.69 (3H, s), 2.86 (1H, dd, *J*=14.5, 1.7Hz), 2.98 (1H, dd, *J*=14.5, 4.5Hz), 3.07 (1H, d, *J*=11.1Hz), 3.21 (1H, dd, *J*=11.0, 6.8Hz), 3.26 (1H, dd, *J*=11.0, 8.0Hz), 4.24 (1H, m), 7.07 (1H, s), 7.24 (1H, d, *J*=1.6Hz), 7.63 (1H, d, *J*=1.6Hz). HR-EIMS *m/z*: 427.0753 (M+, calcd. for $C_{17}H_{22}N_3O_2I$, 427.0756).

(-)-6-Methylindolactam-V (**27**), amorphous. UV λ_{max} (MeOH) nm (ε): 295.5 (7,200), 294.5 (7,300), 230.5 (26,400). ^{1}H NMR δ ($CDCl_3$, 0.01M, 300K, sofa:twist = 1:2.5) ppm: twist conformer; 0.64 (3H, d, *J*=6.7Hz), 0.93 (3H, d, *J*=6.4Hz), 2.19 (1H, br.s, 14-OH), 2.39 (3H, s), 2.60 (1H, m), 2.91 (3H, s), 2.98 (1H, dd, *J*=17.4, 3.7Hz), 3.16 (1H, br.d, *J*=17.4Hz), 3.53 (1H, m), 3.74 (1H, m), 4.28 (1H, m), 4.38 (1H, d, *J*=10.1Hz), 6.32 (1H, s), 6.70 (1H, s), 6.77 (1H, br.s), 6.81 (1H, s), 7.84 (1H, br. s): sofa conformer; 0.94 (3H, d, *J*=6.4Hz), 1.25 (3H, d, *J*=6.7Hz), 2.42 (3H, s), 2.73 (3H, s), 6.88 (1H, s), 6.96 (1H, s), 7.07 (1H, s). Other peaks of the sofa conformer had weak intensities and/or overlapped the peaks of the twist conformer. HR-EIMS *m/z*: 315.1946 (M+, calcd. for $C_{18}H_{25}N_3O_2$, 315.1947).

(-)-7-Methylindolactam-V (**28**), amorphous, $[\alpha]_D$ -100.0° (*c*=0.37, MeOH, 22°C). UV λ_{max} (MeOH) nm (ε): 286.5 (7,400), 226.5 (26,200). ^{1}H NMR δ (CD_3OD, 0.013M, 300K, sofa:twist = 1:1) ppm: twist conformer; 0.62 (3H, d, *J*=6.7Hz), 0.88 (3H, d, *J*=6.4Hz), 2.36 (3H, s), 2.52 (1H, m), 2.86 (3H, s), 3.07 (2H, m), 3.45 (1H, dd, *J*=11.3, 9.2Hz), 3.62 (1H, dd, *J*=11.3, 4.6Hz), 4.25 (1H, m), 4.42 (1H, d, *J*=10.1Hz), 6.37 (1H, d, *J*=7.6Hz), 6.74 (1H, d, *J*=7.6Hz), 6.96 (1H, s); sofa conformer; 0.89 (3H, d, *J*=6.4Hz), 1.23 (3H, d, *J*=6.7Hz), 2.29 (1H, m), 2.45 (3H, s), 2.69 (3H, s), 2.88 (1H, m), 3.00 (1H, m), 3.05 (1H, d, *J*=11.0Hz), 3.22 (1H, dd, *J*=11.0, 7.0Hz), 4.25 (1H, m), 6.86 (2H, s), 7.12 (1H, s). Other peaks of the sofa conformer overlapped the peaks of the twist conformer and/or solvent. HR-EIMS *m/z*: 315.1944 (M^+, calcd. for $C_{18}H_{25}N_3O_2$, 315.1947).

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