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NEW PROBES FOR RECEPTOR ANALYSIS OF TUMOR PROMOTERS SYNTHESIS OF FLUORESCENT DERIVATIVES OF (-)-INDOLACTAM V, THE BASIC RING-STRUCTURE OF TELEOCIDINS

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Abstract: A biologically active fluorescent compound, (-)-7-(2-N-dansylaminoethyl)indolactam V (13), was synthesized from (-)-indolactam V (1) in 6 steps together with an inactive fluorescent derivative, (-)-7-(2-N-dansylaminoethyl)-14-O-methylindolactam V (20). (-)-Indolactam V (1) exists as two stable conformers in solution at room temperature. The effect of substituents and substitution positions of the indole ring on these two conformational states of (-)-indolactam V (1) were discussed in detail.

Teleocidins (teleocidin A-1, A-2, B-1 - B-4)[1] are new potent tumor promoters[2] produced by Actinomycetes. Smaller in molecular weight and of higher stability than the other potent tumor promoters, phorbol esters,[3] aplysiatoxins[4] and palytoxin,[5] they are particularly convenient for studying the mechanism of tumor promotion because many derivatives are easily obtainable by organic synthesis. Hitherto, structure-activity studies on a wide range of teleocidin derivatives[6] have elucidated the structural requirements for tumor-promoting activity and the structural similarity of the several potent tumor promoters mentioned above, and have provided a basis for designing a TPA antagonist. In addition to this indirect approach, however, direct identification of the putative receptor site of tumor promoters using photolabile and fluorescent derivatives is indispensable to reveal the mechanism of tumor promotion. In this paper, we report the synthesis of fluorescent compounds, (-)-7-(2-N-dansylaminoethyl)indolactam V (13)[7] and (-)-7-(2-N-dansylaminoethyl)-14-O-methylindolactam V (20), from (-)-indolactam V (1), which is obtainable in large quantities from natural resources[8] and by organic synthesis.[9] Further, the effect of substituents and substitution positions of the indole ring on the two conformational states of 1 is also discussed.

Our newest structure-activity study[6g] indicated that large substituents at positions 2 or 5 of the indole ring of 1 conspicuously lowered activity, and that hydrophobic substituents at position 7 enhanced the activity. Furthermore, the structural requirement at position 7 of 1 proved quite low. These results suggest that position 7 of 1 is most suitable for introducing a fluorescent group without decreasing activity. The dansyl group was chosen because of its relatively small molecular size and stability.

Several methods of the introduction of alkyl or acyl substituents onto position 7 of an indole ring has been reported.[10] However, direct introduction of substituents onto position 7 of 1 is more desirable from the view point of synthesizing many kinds of fluorescent, photolabile or radioactive probes. Lately, 7-alkylindolactam Vs have been synthesized starting from indolactam V by two methods, Friedel-Crafts alkylation and palladium catalyzed vinyl coupling reaction.[11]

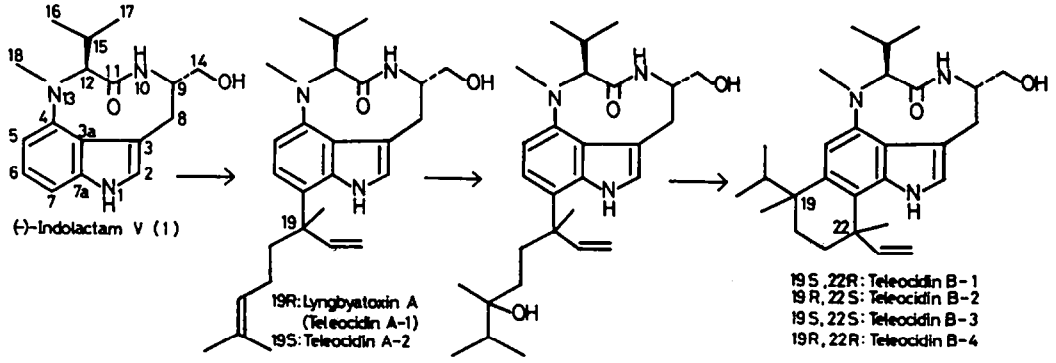
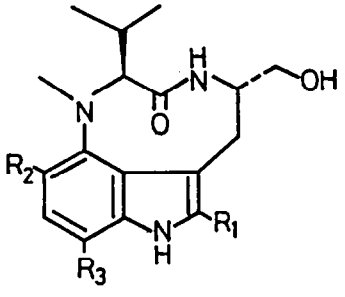
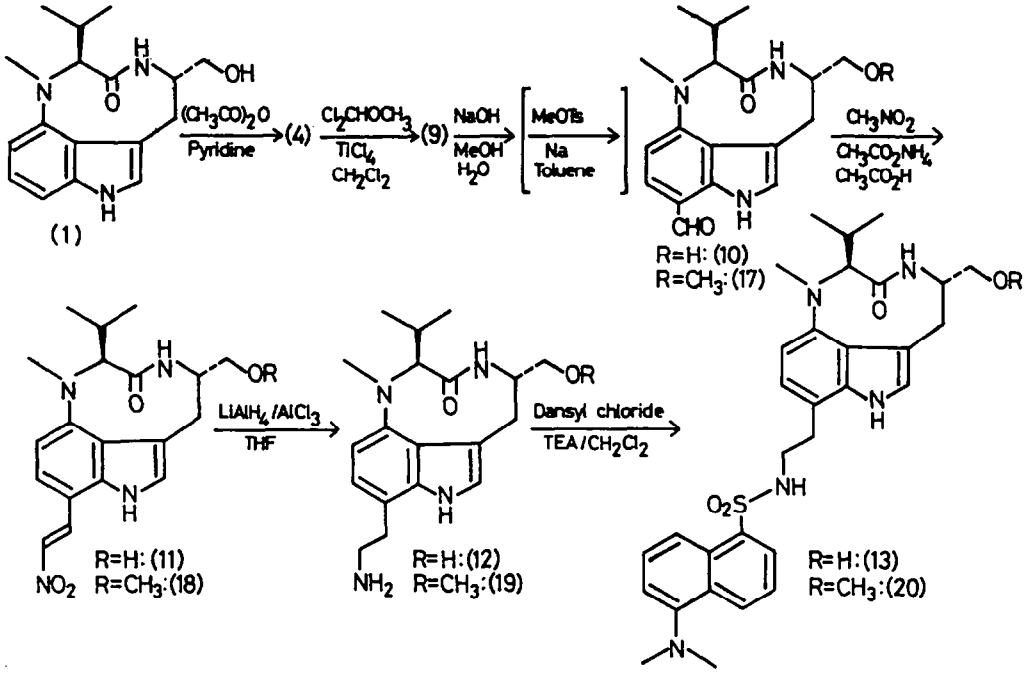


Fig. 1 Possible biosynthetic pathway of teleocidins

First, the reactivity at position 7 of 1 was examined.[12] Halogenation of 1 using bromine and iodine in dioxane-pyridine gave mainly (-)-7-bromoindolactam V (2) and (-)-7-iodoindolactam V (3) in 25 % and 35 % yield, respectively. The Friedel-Crafts acylation of (-)-14-O-acetylindolactam V (4)[8a] using acetic anhydride and butyric anhydride in aluminum chloride and nitrobenzene, followed by hydrolysis, afforded principally (-)-7-acetylindolactam V (5) and (-)-7-butanoylindolactam V (6) in 45 % and 29 % yield, respectively. 2,7-Diacyl derivatives (7 and 8) were obtained as minor products, which were found to fluoresce strongly in ethanol [λ_{max} (excitation): 400 nm, λ_{max} (emission): 515 nm]. However, these were completely inactive.[6g] Friedel-Crafts alkylation using aluminum chloride and alkyl chloride in nitrobenzene was unsuccessful. Maybe introduction of the first alkyl substituent increases the reactivity of the indole ring toward further substitution and polymerization. Direct introduction of alkyl substituents into 1 was attained under a quite mild reaction condition. For example, treatment of 1 with prenylbromide in acetic acid and sodium acetate[13] gave (-)-7-prenylindolactam V in 10 % yield, $[\alpha]_D^{25}$ -143° (c=0.35, EtOH). This reaction, however, was not so selective as Friedel-Crafts acylation and halogenation mentioned above, 2 or 5 substituted and disubstituted derivatives of 1 being obtained. Recently, 7-prenylindolactam V has been synthesized by Friedel-Crafts alkylation of 1-acetyl-14-O-TBDMS-indolactam V using prenylchloride and trifluoroacetic acid silver salt in nitromethane.[11] These results indicate that position 7 of 1 is most active in the electrophilic aromatic substitution, and that introduction of electron-withdrawing groups results in a good yield and selectivity because they deactivate the indole ring to prevent further reaction. (-)-Indolactam V (1) is believed to be a biosynthetic intermediate of teleocidins. High reactivity at position 7 of 1 is compatible with the biosynthetic pathway (Fig 1).[14]



R_1	R_2	R_3	
H	H	Br	(2)
H	H	I	(3)
H	H	$COCH_3$	(5)
H	H	$CO(CH_2)_2CH_3$	(6)
$COCH_3$	H	$COCH_3$	(7)
$CO(CH_2)_2CH_3$	H	$CO(CH_2)_2CH_3$	(8)
H	Cl	H	(21)
H	$COCH_3$	H	(22)



On the basis of these considerations, position 7 of (-)-14-O-acetylindolactam V (4) was formylated. Treatment of 4 with titanium tetrachloride and dichloromethyl methyl ether in dry methylene chloride afforded (-)-7-formyl-14-O-acetylindolactam V (9) in 25 % yield along with unreacted 4 (30 %). Compound 9 was hydrolized by alkaline treatment to 10. Condensation of 10 with nitromethane was achieved in ammonium acetate and acetic acid to give 11 in 76 % yield. In this reaction, large excess of nitromethane was necessary to obtain sufficient yield. Reduction of 11 was accomplished by use of lithium aluminum hydride and aluminum chloride in tetrahydrofuran. The resultant primary amine (12) was extracted and was used in the next reaction without further purification. Treatment of 12 with dansyl chloride in triethylamine and methylene chloride gave 13 in 50 % yield from 11. The overall yield of 13 was 10 %. This synthetic method is also available for photolabile and other fluorescent indolactam derivatives using 12 as an intermediate. Compound 12 can also be bound to agarose gel for affinity chromatography.

The possible tumor-promoting activity of 13 was estimated by Epstein-Barr virus early antigen-inducing activity[15] and inhibition of specific binding of [^{3}H]TPA to a mouse epidermal particulate fraction.[16] The results suggested that 13 is about 10 times stronger a tumor promoter than (-)-indolactam V (1).

An inactive fluorescent derivative which has a quite similar structure to the active one is necessary as a reference in the experiment employing fluorescent probes. Recent studies have indicated that the hydroxyl group at C-14 of teleocidins must be free for the appearence of tumor-promoting activity.[6b,c,e,f] Thus a 14-O-methyl derivative of 13 was synthesized. As there exist three positions (imino group at N-1, amido group at N-10 and hydroxyl group at C-14) which can be methylated by Williamson ether synthesis in 1, the selective methylation at C-14 was investigated. Methyl p-toluene sulfonate (MeOTs) was used as a methylating reagent. Treatment of 1 with MeOTs in sodium hydride and tetrahydrofuran did not show any selectivity and gave mainly (-)-1,14-O-dimethyl-

indolactam V (14). When a less polar solvent, benzene, was used instead of tetrahydrofuran, a little selectivity was observed and (-)-14-O-methylindolactam V (15)[6c] was obtained in 9 % yield. Further, treatment of 1 with MeOTs in sodium and toluene gave 15 in 15 % yield.[6c] The reactivity at position 10 was very low and this position was methylated only when 1 was heated with MeOTs in sodium hydride and tetrahydrofuran. Next, the same reaction in sodium and toluene was carried out with (-)-7-formylindolactam V (10), whose imino group at N-1 is deduced to be less reactive than 1 because of the intramolecular interaction between formyl group and the imino group, to give 17 in 29 % yield. (-)-7-(2-N-dansylaminoethyl)-14-O-methylindolactam V (20) was synthesized from 17 by the same method as was used in the synthesis of 13. The overall yield of 20 was 3 %. The possible tumor-promoting activity of 20, estimated by the above mentioned two bioassays, was quite absent.

Table 1 ^{1}H NMR chemical shifts of 1, 4 and 15 in $CDCl_3$ at room temperature[a]

	1		4		15	
Conformer	A	B	A	B	A	B
H-5	NI[b]	6.50 (d,J=7.6)	7.04 (d,J=7.5)	6.53 (d,J=7.6)	NI[b]	6.51 (d,J=7.6)
H-10	4.74 (d,J=11.6)	7.37 (br.s)	4.65 (d,J=12.0)	6.01 (br.s)	NI[b]	6.14 (br.s)
H-12	NI[b]	4.40 (d,J=10.4)	2.98 (d,J=10.7)	4.36 (d,J=10.4)	NI[b]	4.36 (d,J=10.4)
H-16	0.93 (d,J=6.4)	0.63 (d,J=6.7)	0.94 (d,J=6.1)	0.64 (d,J=6.7)	0.92 (d,J=6.4)	0.62 (d,J=6.7)
H-17	1.25 (d,J=6.7)	0.93 (d,J=6.4)	1.24 (d,J=6.7)	0.93 (d,J=6.1)	1.24 (d,J=7.0)	0.92 (d,J=6.4)
H-18	2.75 (s)	2.92 (s)	2.75 (s)	2.93 (s)	2.76 (s)	2.93 (s)

[a]The ratio of the two conformers are as follows; 1, conformer A:B=1:4.4; 4, 1:2.6; 15, 1:7.2.
[b]The signals could not be identified because of its low intensity.

Table 2 ^{1}H NMR chemical shifts of 5, 8, 9, 18, 21 and 22 in $CDCl_3$ at r.t.

	5	8	9	18	21[a]	22[a]
H-5	6.48 (d,J=8.2)	6.46 (d,J=8.6)	6.58 (d,J=8.2)	6.57 (d,J=8.2)	----	----
H-10	7.12 (br.s)	7.35 (br.s)	6.11 (br.s)	6.23 (br.s)	4.77 (d,J=10.7)	4.89 (d,J=10.4)
H-12	4.56 (d,J=10.4)	4.48 (d,J=10.3)	4.54 (d,J=10.4)	4.48 (d,J=10.4)	3.09 (d,J=10.4)	2.93 (d,J=10.7)
H-16	0.58 (d,J=6.7)	0.52 (d,J=7.0)	0.59 (d,J=6.7)	0.57 (d,J=6.7)	0.97 (d,J=6.4)	0.84 (d,J=6.4)
H-17	0.94 (d,J=6.1)	0.94 (d,J=6.2)	0.95 (d,J=6.1)	0.94 (d,J=6.4)	1.36 (d,J=6.7)	1.03 (d,J=7.0)
H-18	2.98 (s)	2.99 (s)	3.01 (s)	2.98 (s)	2.75 (s)	2.74 (s)

[a]The ratio of the two conformers are as follows; 21, conformer A:B=10:1; 22, 30:1.

It is known that teleocidins and (-)-indolactam V (1) exist as two stable

conformers in solution at room temperature: conformer A of the SOFA type and B of the TWIST type.[10a] Introduction of an electron-withdrawing group into position 7 will increase the resonance among the lone-pair electrons on N-13, aromatic electrons and the substituent at position 7, fixing the molecule in conformer B, in which the lone-pair electrons on N-13 are more delocalizable onto the indole ring. As was expected, 5, 6, 7, 8, 9, 10, 11, 17 and 18 existed only as conformer B in chloroform-d or methanol-d_4 at room temperature. This was determined by comparison of their chemical shifts with those of the two conformers of 1, 4 or 15 (Table 1). Large differences in chemical shifts between conformer A and B is observed chiefly at H-5, 10, 12, 16, 17 and 18. The chemical shifts of these protons of 5, 8, 9 and 18 are summarized in Table 2, indicating that the fixed conformer of these compounds is conformer B. The other compounds also showed chemical shifts similar to those of conformer B (see the experimental section). Compound 13 and 20, on the other hand, which has an electron-donating substituent at position 7, existed as the two conformers.

While introduction of a substituent into position 5 of 1 will hinder the resonance by a steric interaction between the substituent and the N-methyl group, to fix the molecule in conformer A. Thus 5-substituted derivatives of 1 were synthesized. Radical reaction of 1 with N-chlorosuccinimide in dioxane gave predominantly (-)-5-chloroindolactam V (21) in 40 % yield. Friedel-Crafts acetylation by use of a large excess of acetic anhydride gave (-)-5-acetylindolactam V (22) as a biproduct in 7 % yield. In the ^{1}H NMR of 21 and 22 in chloroform-d, the signals ascribable to conformer A are almost exclusively observed as was shown in Table 2.

Until now, very little has been known about conformation-activity relationship. Endo *et al.* proposed that the free energy difference between the two conformers and the free energy of activation in the conversion of the two conformers are calculated to be so small that the conformers convert easily at room temperature.[10a] As there exists a large difference in conformation between the two conformers, one of them is likely responsible for the biological activity. Compounds 5, 6, 10 and 11 had high activity comparable to (-)-indolactam V (1), and 22 was inactive,[6g] indicating that conformer B may play a significant role for tumor-promoting activity.

Recently, cellular uptake and localization of fluorescent derivatives of phorbol ester-type tumor promoters have been reported.[17] Compounds 13 and 20 might give a clue to the mechanism of tumor promotion in combination with these fluorescent phorbol esters. Cellular uptake and localization of 13 and 20 in several cells are in progress.

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EXPERIMENTAL SECTION

All melting points are uncorrected. The following spectroscopic and analytical instruments were used: UV, Shimadzu UV-200; IR, Shimadzu Model 435; ^{1}H NMR, JEOL GX 400 (400 MHz, ref. TMS); MS, JEOL JMS-DX 300 (70 eV, 300 μA); ORD, Jasco Model J-5; HPLC, 655A pump equipped with 655A-11 variable wave length UV monitor (Hitachi, LTD., Tokyo, Japan). HPLC was carried out on NOVAPAK C_{18} (Waters Associates). Wako C-100 and C-200 gel (Silica gel, Wako Pure Chemical Industries) and YMC I-40/64 gel (ODS, Yamamura Chemical Laboratory) were used for column chromatography.

(-)-Indolactam V (1) (-)-Indolactam V (1) was obtained from culture broth of *Streptoverticillium blastmyceticum* NA34-17 by the method reported previously.[8a]

(-)-7-Bromoindolactam V (2) (-)-Indolactam V (1) (80 mg) was dissolved in dioxane (2 ml) and pyridine (0.1 ml). To the solution, Br_2 (8 μl) was added, and stirred at room temperature for 2 hr. After partitioning between EtOAc and water, the EtOAc extract was purified by column chromatography on Wako C-200 gel, eluting with toluene containing increasing amounts of acetone. The eluates with 20, 25 and 30 % acetone were combined and chromatographed on YMC I-40/64 gel with 65 % MeOH in water to give 2 (25 mg, 25 % yield). Colorless rods from EtOH-water, mp 198°C dec., $[\alpha]_D^{22}$ -210° (c=0.11, EtOH). UV λ_{max} (EtOH) nm (ε): 314 (9400), 310 (9700), 287.5 (7600), 230.5 (28,000). IR ν_{max} (KBr) cm^{-1}: 3370, 3300, 2940, 2870, 1655, 1622, 1607, 1500, 1445, 1038, 865, 792. ^{1}H NMR δ ($CDCl_3$) ppm: conformer A:B=1:6.3; conformer B, 0.62 (3H,d,J=6.7Hz), 0.93 (3H,d,J=6.1Hz), 2.59 (1H,m), 2.89 (3H,s), 3.03 (1H,dd,J=17.7Hz,3.7Hz), 3.17 (1H,br.d,J=17.7Hz), 3.56 (1H,dd,J=11.0Hz,8.6Hz). 3.74 (1H,dd,J=11.0Hz,4.0Hz), 4.24 (1H,br.s), 4.33 (1H,d,J=10.1Hz), 6.40 (1H,d,J=8.2Hz), 6.95 (1H,s), 7.03 (1H,br.s), 7.18 (1H,d,J=8.2Hz), 8.19 (1H,br.s); conformer A, 0.94 (d,J=6.4Hz), 1.23 (d,J=6.7Hz), 2.40 (m), 2.73 (s). Other peaks had weak intensities and overlapped those of the major conformer. EIMS m/z 379 (M^+). Anal. Calcd. for $C_{17}H_{22}N_3O_2Br$: C, 53.69; H, 5.83; N, 11.05. Found: C, 53.75; H, 5.61; N, 10.94.

(-)-7-Iodoindolactam V (3) (-)-Indolactam V (1) (96.5 mg) was dissolved in dioxane (2 ml) and pyridine (0.1 ml). To the solution, I_2 (46 mg) was added and stirred at room temperature for one day. The reaction mixture was worked up in the same way as above to give 48.5 mg (35 % yield) of 3, which was recrystallized from MeOH-water to give pale yellow platelets, mp 202°C dec., $[\alpha]_D^{29}$ -240° (c=0.13, EtOH). UV λ_{max} (EtOH) nm (ε): 315.5 (10,800), 311.5 (11,200), 288 (8700), 233 (30,800). IR ν_{max} (KBr) cm^{-1}: 3420, 3320, 3200, 2900, 2870, 1630, 1595, 1535, 1492, 1440, 1342, 1060, 1038, 800, 790. ^{1}H NMR δ (CD_3OD) ppm: conformer A:B=1:2.2; conformer B, 0.61 (3H,d,J=6.7Hz), 0.89 (3H, d,J=6.4Hz), 2.54 (1H,m), 2.87 (3H,s), 3.08 (2H,m), 3.46 (1H,dd,J=11.0Hz,8.9Hz), 3.61 (1H,dd, J=11.0Hz,4.6Hz), 4.16 (1H,m), 4.43 (1H,d,J=10.4Hz), 6.32 (1H,d,J=8.2Hz), 7.03 (1H,s), 7.30 (1H,d, J=8.2Hz); conformer A, 0.89 (d,J=6.4Hz), 1.22 (d,J=6.7Hz), 2.30 (m), 2.71 (s), 4.26 (m), 6.76 (d, J=7.9Hz), 7.20 (s), 7.46 (d,J=7.9Hz). Other peaks had weak intensities and overlapped those of the major conformer. EIMS m/z 427 (M^+). Anal. Calcd. for $C_{17}H_{22}N_3O_2I$: C, 47.79; H, 5.19; N, 9.83. Found: C, 47.78; H, 5.18; N, 9.75.

(-)-7-Acetylindolactam V (5) Acetic anhydride (70 μl) was treated with 14-O-acetate of 1 (4, 200 mg) and $AlCl_3$ (110 mg) in nitrobenzene (2 ml) at room temperature for one day. After adding water and MeOH, the products were hydrolyzed with NaOH at room temperature for 30 min. The reaction mixture was partitioned between EtOAc and water. The EtOAc extract was purified by column chromatography on Wako C-200 gel with 0.8 % MeOH in $CHCl_3$ to give 5 (90 mg, 45 % yield). Pale yellow rods from EtOH-water, mp 219-222°C. $[\alpha]_D^{24}$ -670° (c=0.18, EtOH). UV λ_{max} (EtOH) nm (ε): 370 (20,900), 258 (15,500). IR ν_{max} (KBr) cm^{-1}: 3390, 2950, 1660, 1645, 1575, 1502, 1281, 1165, 1048, 795. ^{1}H NMR δ ($CDCl_3$) ppm: conformer B only, 0.58 (3H,d,J=6.7Hz), 0.94 (3H,d,J=6.1Hz), 2.60 (1H,m), 2.61 (3H,s), 2.98 (3H,s), 3.07 (1H,dd,J=17.4Hz,3.4Hz), 3.18 (1H,br.d,J=17.4Hz), 3.59 (1H,m), 3.75 (1H,m), 4.10 (1H,m), 4.56 (1H,d,J=10.4Hz), 6.48 (1H,d,J=8.2Hz), 7.00 (1H,s), 7.12 (1H,br.s), 7.70 (1H,d,J=8.2Hz), 10.80 (1H,br.s). EIMS m/z 343 (M^+). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.46; H, 7.35; N, 12.16.

(-)-7-Butanoylindolactam V (6) Butyric anhydride (100 µl) was treated with 4 (107 mg) and $AlCl_3$ (113 mg) in nitrobenzene (1.5 ml) at 50°C for 2 hr. The reaction mixture was worked up in the same way above to give 34 mg (29 % yield) of 6. Pale yellow leaflets from MeOH, mp 207-209°C, $[\alpha]_D^{20}$ -546° (c=0.90, EtOH). UV λ_{max} (EtOH) nm (ε): 370 (19,300), 258.5 (14,300). IR ν_{max} (KBr) cm^{-1}: 3460, 3280, 2960, 1660, 1630, 1572, 1502, 1157. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.57 (3H,d,J=6.7Hz), 0.93 (3H,d,J=6.4Hz), 1.02 (3H,t,J=7.6Hz), 1.80 (2H,sextet,J=7.6Hz), 2.55 (1H,m), 2.95 (3H,s), 2.96 (2H,m), 3.10 (1H,dd,J=17.7Hz,3.4Hz), 3.15 (1H,br.d,J=17.7Hz), 3.60 (1H,m), 3.73 (1H,m), 4.12 (1H,m), 4.56 (1H,d,J=10.1Hz), 6.45 (1H,d,J=8.5Hz), 6.99 (1H,s), 7.72 (1H,d,J=8.5Hz), 7.86 (1H,br.s), 10.87 (1H,br.s). EIMS m/z 371 (M^+). Anal. Calcd. for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.31. Found: C, 68.06; H, 7.94; N, 11.40.

(-)-2,7-Diacetylindolactam V (7) Amorphous powder, $[\alpha]_D^{23}$ -655° (c=0.74, EtOH). UV λ_{max} (EtOH) nm (ε): 398 (22,200), 319 (15,900), 258 (16,200). IR ν_{max} (KBr) cm^{-1}: 3370, 2920, 1665, 1650, 1575, 1515, 1505, 1280. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.51 (3H,d,J=6.6Hz), 0.94 (3H,d, J=6.2Hz), 2.55 (1H,m), 2.63 (3H,s), 2.65 (3H,s), 2.99 (3H,s), 3.05 (1H,dd,J=19.1Hz,3.3Hz), 3.64 (2H,m), 4.10 (1H,br.s), 4.29 (1H,dd,J=19.1Hz,3.7Hz), 4.47 (1H,d,J=10.3Hz), 6.46 (1H,d,J=8.4Hz), 7.49 (1H,br.s), 7.82 (1H,d,J=8.4Hz), 11.46 (1H,br.s). HR-EIMS m/z 385.2000 (M^+, Calcd. for $C_{21}H_{27}N_3O_4$, 385.2002).

(-)-2,7-Dibutanoylindolactam V (8) Amorphous powder, $[\alpha]_D^{18}$ -527° (c=0.61, EtOH). UV λ_{max} (EtOH) nm (ε): 398 (20,300), 320 (14,300), 258.5 (14,900). IR ν_{max} (KBr) cm^{-1}: 3370, 2950, 2870, 1665, 1573, 1513, 1265, 1170. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.52 (3H,d,J=7.0Hz), 0.94 (3H,d,J=6.2Hz), 1.05 (6H,m), 1.82 (4H,m), 2.56 (1H,m), 2.99 (3H,s), 2.92-3.07 (5H,m), 3.63 (2H,m), 4.09 (1H,m), 4.34 (1H,dd,J=19.2Hz,3.5Hz), 4.48 (1H,d,J=10.3Hz), 6.46 (1H,d,J=8.6Hz), 7.35 (1H,br.s), 7.86 (1H,d,J=8.6Hz), 11.59 (1H,br.s). HR-EIMS m/z 441.2621 (M^+, Calcd. for $C_{25}H_{35}N_3O_4$, 441.2628).

(-)-7-Formyl-14-O-acetylindolactam V (9) Compound 4 (340 mg) was dissolved in dry CH_2Cl_2 (2 ml) and cooled by acetone-ice. To the reaction mixture, $TiCl_4$ (100 µl) and Cl_2CHOCH_3 (150 µl) was added and stirred at room temperature for 20 hr. After partitioning between CH_2Cl_2 and water, the CH_2Cl_2 layer was chromatographed on Wako C-100 gel eluting with toluene containing increasing amounts of acetone. The eluates with 10, 15 and 20 % acetone were combined and chromatographed on YMC I-40/64 gel with 30 % CH_3CN in water to give 9 as amorphous powder (91.6 mg, 25 % yield). $[\alpha]_D^{21}$ -447° (c=2.15, EtOH). UV λ_{max} (EtOH) nm (ε): 371 (17,400), 261.5 (11,100). IR ν_{max} (KBr) cm^{-1}: 3320, 2960, 1740, 1665, 1650, 1587, 1500, 1240, 1142, 1042. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.59 (3H,d,J=6.7Hz), 0.95 (3H,d,J=6.1Hz), 2.10 (3H,s), 2.62 (1H,m), 3.01 (3H,s), 3.17 (1H,dd,J=17.7Hz,3.7Hz), 3.23 (1H,br.d,J=17.7Hz), 4.00 (1H,dd,J=12.2Hz,9.2Hz), 4.22 (1H,dd, J=12.2Hz,3.7Hz), 4.24 (1H,m), 4.54 (1H,d, J=10.4Hz), 6.11 (1H,br.s), 6.58 (1H,d,J=8.2Hz), 7.03 (1H,s), 7.51 (1H,d,J=8.2Hz), 9.85 (1H,s), 10.42 (1H,br.s). HR-EIMS m/z 371.1835 (M^+, Calcd. for $C_{20}H_{25}N_3O_4$, 371.1845).

(-)-7-Formylindolactam V (10) Treatment of 9 with MeOH and water (pH 11) gave 10 quantitatively, which was recrystallized from EtOH. Pale yellow rods, mp 246-248°C, $[\alpha]_D^{21}$ -558° (c=0.25, EtOH). UV λ_{max} (EtOH) nm (ε): 372 (18,600), 262 (11,900). IR ν_{max} (KBr) cm^{-1}: 3480, 3390, 2960, 1660, 1650, 1585, 1498, 1365, 1295, 1242, 1142, 1043. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.58 (3H,d, J=6.7Hz), 0.95 (3H,d,J=6.1Hz), 2.60 (1H,m), 3.00 (3H,s), 3.08 (1H,dd,J=17.7Hz,3.7Hz), 3.18 (1H,br.d,J=17.7Hz), 3.58 (1H,m), 3.76 (1H,m), 4.07 (1H,m), 4.58 (1H,d,J=10.1Hz), 6.56 (1H,d, J=8.2Hz), 6.98 (1H,br.s), 7.02 (1H,s), 7.51 (1H,d,J=8.2Hz), 9.83 (1H,s), 10.41 (1H,br.s). EIMS m/z 329 (M^+). Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.48; H, 6.91; N, 12.64.

(-)-7-Nitrovinylindolactam V (11) Compound 10 (35 mg) was dissolved in AcOH (0.1 ml) and CH_3NO_2 (0.9 ml). $AcONH_4$ (90 mg) was added to the solution and refluxed for 30 min. The reaction mixture was evaporated to dryness with toluene and partitioned between EtOAc and water. The EtOAc extracts

were chromatographed on Wako C-200 gel with 0.75 % MeOH in $CHCl_3$ to give 11 (30 mg, 76 % yield). Amorphous powder, $[\alpha]_{650}^{26}$ -1085° (c=0.21, EtOH). UV λ_{max} (EtOH) nm (ε): 476 (20,500), 285 (10,000), 233 (19,200). IR ν_{max} (KBr) cm^{-1}: 3360, 2950, 1655, 1615, 1567, 1512, 1430, 1260, 1212, 1150. ^1H NMR δ (CD_3OD) ppm: conformer B only, 0.57 (3H,d,J=7.0Hz), 0.91 (3H,d,J=6.4Hz), 2.55 (1H,m), 2.95 (3H,s), 3.10 (1H,br.d,J=17.7Hz), 3.17 (1H,dd,J=17.7Hz,3.4Hz), 3.48 (1H,dd,J=11.3Hz,8.9Hz), 3.61 (1H,dd,J= 11.3Hz.4.6Hz), 4.08 (1H,m), 4.61 (1H,d,J=10.4Hz), 6.60 (1H,d,J=8.5Hz), 7.08 (1H,s), 7.47 (1H, d,J=8.5Hz), 7.88 (1H,d,J=13.4Hz), 8.47 (1H,d,J=13.4Hz). HR-EIMS m/z 372.1781 (M^+, Calcd. for $C_{19}H_{24}N_4O_4$, 372.1798).

(-)-7-(2-N-dansylaminoethyl)indolactam V (13) Compound 11 (31 mg) was dissolved in THF (0.5 ml). $AlCl_3$ (28 mg) and $LiAlH_4$ (13 mg) in THF (1 ml) was added to the solution and refluxed for 1.5 hr. The reaction mixture was extracted with water (PH 1, HCl), followed by partitioning between EtOAc and water (PH 14, NaOH), to give 12 [EIMS m/z 344 (M^+)] which gave a characteristic coloration with ninhydrin and was used in the next reaction without further purification. Compound 12 was treated with dansyl chloride (46 mg) in CH_2Cl_2 (2 ml) and $N(CH_2CH_3)_3$ (1 ml) for 40 min at room temperature. After partitioning between EtOAc and water, the EtOAc extract was chromatographed on Wako C-200 gel with 1 % MeOH in $CHCl_3$ to give 13 as an amorphous powder (24 mg, 50 % yield from 11). $[\alpha]_D^{22}$ -80° (c=0.26, MeOH). UV λ_{max} (EtOH) nm (ε): 335 (4700), 305.5 (11,200), 288.5 (10,200), 250 (17,500), 218.5 (62,000). IR ν_{max} (KBr) cm^{-1}: 3370, 2940, 2880, 1650, 1588, 1507, 1315, 1141, 1075. ^1H NMR δ ($CDCl_3$) ppm: conformer A:B=1:3.5; conformer B, 0.61 (3H,d,J=6.4Hz), 0.92 (3H,d,J=6.4Hz), 2.58 (1H,m), 2.86 (3H,s), 2.88 (6H,s), 2.90-3.25 (6H,m), 3.54 (1H,m), 3.73 (1H,m), 4.24 (1H,br.s), 4.34 (1H,d,J=10.3Hz), 5.01 (1H,br.s), 6.36 (1H,d,J=8.1Hz), 6.68 (1H,d,J=8.1Hz), 6.92 (1H,s), 7.04 (1H,br.s), 7.18 (1H,d,J=7.7Hz), 7.51 (2H,m), 8.20 (1H,d,J=8.6Hz), 8.24 (1H,d,J=7.3Hz), 8.54 (1H,d,J=8.5Hz), 8.68 (1H,br.s); conformer A, 1.22 (d,J=6.8Hz), 2.37 (m), 2.71 (s), 4.70 (d,J=11.1Hz), 9.04 (br.s). Other peaks had weak intensities and overlapped those of the major conformer. HR-in-beam-EIMS m/z 577.2740 (M^+, Calcd. for $C_{31}H_{39}N_5O_4S$, 577.2723).

(-)-1,14-O-Dimethylindolactam V (14) (-)-Indolactam V (1) (24.5 mg) was dissolved in THF (1 ml). To the solution, NaH (20 mg) in THF (1 ml) was added and stirred at 0 °C for 20 min. MeOTs (39 mg) was added to the above reaction mixture and stirred at room temperature for 30 min. This reaction mixture was treated with n-BuOH and partitioned between EtOAc and water. The EtOAc layer was chromatographed on Wako C-100 gel with toluene containing increasing amount of acetone. The eluates with 10 and 15 % acetone was collected and recrystallized from MeOH to give 14 as colorless needles (16.5 mg, 62 % yield). mp 203-204°C, $[\alpha]_D^{25}$ -171° (c=0.14, EtOH). UV λ_{max} (EtOH) nm (ε): 315 (8900), 307 (9100), 286 (6700), 230 (29,800). IR ν_{max} (KBr) cm^{-1}: 3425, 3225, 2925, 1670, 1600, 1560, 1495, 1120. ^1H NMR ($CDCl_3$) ppm: conformer A:B=1:8.5; conformer B, 0.62 (3H,d, J=6.7Hz), 0.91 (3H,d,J=6.4Hz), 2.61 (1H,m), 2.91 (1H,dd,J=17.4Hz,3.7Hz), 2.92 (3H,s), 3.18 (1H,br.d,J=17.4Hz), 3.31 (3H,s), 3.33 (1H,m), 3.38 (1H,dd,J=9.8Hz,4.3Hz), 3.69 (3H,s), 4.37 (1H,m), 4.38 (1H,d,J=10.1Hz), 6.13 (1H,br.s), 6.52 (1H,d,J=7.6Hz), 6.73 (1H,d,J=1.2Hz), 6.83 (1H,d, J=8.2Hz), 7.10 (1H,dd,J=8.2Hz,7.6Hz); conformer A, 1.24 (d,J=6.7Hz), 2.74 (s). EIMS m/z 329 (M^+). Anal. Calcd. for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.75; Found: C, 69.01; H, 8.43; N, 12.69.

(-)-1,10,14-O-Trimethylindolactam V (16) The reaction mixture of 1 (25 mg), NaH (20 mg) and MeOTs (77.5 mg) in THF (2 ml) was refluxed for 4 hr and stood at room temperature for 12 hr. This was worked up by the same method as above and chromatographed on Wako C-200 gel with 2 % Acetone in toluene, followed by HPLC using NOVAPAK C_{18} with 55 % CH_3CN in water to give 16 as viscous oil (7.2 mg, 26 % yield). $[\alpha]_D^{25}$ -93° (c=0.35, EtOH). UV λ_{max} (EtOH) nm (ε): 316 (7800), 307 (8400), 289 (6500), 231 (29,200). IR ν_{max} (KBr) cm^{-1}: 3425, 2950, 1625, 1600, 1570, 1495, 1325, 1280, 1120, 1110, 975. ^1H NMR δ ($CDCl_3$) ppm: Major conformer, 0.49 (3H,d,J=6.7Hz), 0.66 (3H,d,J=6.7Hz), 2.59 (1H,m), 2.9-4.0 (17H,m), 4.06 (1H,d,J=10.4Hz), 6.57 (1H,d,J=7.6Hz), 6.76 (1H,s), 6.81 (1H,d, J=7.6Hz), 7.06 (1H,t,J=7.6Hz). HR-EIMS m/z 343.2244 (M^+, Calcd. for $C_{20}H_{29}N_3O_2$, 343.2260).

(-)-7-Formyl-14-O-methylindolactam V (17) Compound 10 (30 mg) was refluxed with MeOTs (40 μl) and

Na (100 mg) in toluene (2 ml) for 30 min. After filtration, the reaction mixture was partitioned between EtOAc and water. The EtOAc extracts were chromatographed on Wako C-200 gel with toluene containing increasing amounts of acetone. The 15 and 20 % acetone eluates were collected and chromatographed on YMC I-40/64 gel with 57 % MeOH in water to give 17 (9 mg, 29 % yield). Pale yellow rods from MeOH, mp 271-273°C, $[\alpha]_D^{26}$ -719° (c=0.44, $CHCl_3$). UV λ_{max} (EtOH) nm (ε): 372 (24,100), 262 (15,300). IR ν_{max} (KBr) cm^{-1}: 3400, 3250, 2900, 1670, 1638, 1585, 1500, 1297, 1247, 1143, 1112, 1040. ^1H NMR δ ($CDCl_3$) ppm: conformer B only, 0.57 (3H,d,J=6.7Hz), 0.94 (3H,d, J=6.4Hz), 2.61 (1H,m), 3.00 (3H,s), 3.01 (1H,dd,J=17.4Hz,3.4Hz), 3.19 (1H,br.d,J=17.4Hz), 3.33 (3H,s), 3.33 (1H,m), 3.41 (1H,dd,J=9.5Hz,4.3Hz), 4.13 (1H,m), 4.55 (1H,d,J=10.1Hz), 6.21 (1H,br.s), 6.56 (1H,d,J=8.2Hz), 7.00 (1H,s), 7.50 (1H,d,J=8.2Hz), 9.83 (1H,s), 10.41 (1H,br.s). EIMS m/z 343 (M^+). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.49; H, 7.41; N, 12.09.

(-)-7-Nitrovinyl-14-O-methylindolactam V (18) Compound 17 (10 mg) in AcOH (0.1 ml) and CH_3NO_2 (1 ml) was mixed with $AcONH_4$ (50 mg). After reflux for 1 hr, the reaction mixture was evaporated in vacuo with toluene to dryness. The residue was partitioned between EtOAc and water, and the EtOAc layer was chromatographed on Wako C-200 gel with $CHCl_3$, followed by HPLC on NOVAPAK C_{18} with 67 % MeOH in water to give 18 (7.2 mg, 65 % yield). Dark red rods from EtOH, mp 229°C dec., $[\alpha]_{650}^{27}$ -1068° (c=0.029, $CHCl_3$). UV λ_{max} (EtOH) nm (ε): 474.5 (19,700), 282 (9700), 232.5 (18,100). IR ν_{max} (KBr) cm^{-1}: 3260, 2920, 1660, 1610, 1565, 1507, 1330, 1268, 1200, 1148, 1115. ^1H NMR δ ($CDCl_3$) ppm: comformer B only, 0.57 (3H,d,J=6.7Hz), 0.94 (3H,d,J=6.4Hz), 2.61 (1H,m), 2.98 (3H,s), 3.02 (1H,dd,J=17.7Hz,3.4Hz), 3.20 (1H,br.d,J=17.7Hz), 3.35 (3H,s), 3.35 (1H,m), 3.42 (1H,dd, J=9.5Hz,4.3Hz), 4.17 (1H,m), 4.48 (1H,d,J=10.4Hz), 6.23 (1H,br.s), 6.57 (1H,d,J=8.2Hz), 7.01 (1H,s), 7.38 (1H,d,J=8.2Hz), 7.64 (1H,d,J=13.4Hz), 8.33 (1H,d,J=13.4Hz), 8.70 (1H,br.s). EIMS m/z 384 (M^+). Anal. Calcd. for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.02; H, 6.73; N, 14.41.

(-)-7-(2-N-Dansylaminoethyl)-14-O-methylindolactam V (20) Compound 20 was obtained from 18 (20 mg) by the same method as was used in the synthesis of 13. Amorphous powder (9.1 mg, 30 % yield), $[\alpha]_D^{28}$ -66° (c=0.46, EtOH). UV λ_{max} (EtOH) nm (ε): 335 (4000), 304.5 (9200), 289 (8400), 250 (14,500), 218.5 (51,700). IR ν_{max} (KBr) cm^{-1}: 3370, 2930, 2870, 1648, 1588, 1575, 1507, 1452, 1315, 1141. ^1H NMR δ ($CDCl_3$) ppm: comformer A:B=1:5; conformer B, 0.61 (3H,d,J=6.7Hz), 0.92 (3H,d,J=6.4Hz), 2.60 (1H,m), 2.89 (9H,s), 2.92-3.22 (6H,m), 3.33 (3H,s), 3.33 (1H,m), 3.42 (1H,dd,J=9.8Hz,4.3Hz), 4.32 (1H,d,J=10.4Hz), 4.36 (1H,m), 4.77 (1H,t,J=6.4Hz), 6.14 (1H,br.s), 6.38 (1H,d,J=7.9Hz), 6.69 (1H,d,J=7.9Hz), 6.94 (1H,s), 7.19 (1H,d,J=7.6Hz), 7.53 (2H,m), 8.19 (1H,d,J=8.6Hz), 8.26 (1H,d,J=7.3Hz), 8.56 (1H,d,J=8.6Hz), 8.64 (1H,br.s); conformer A, 1.21 (d,J=6.7Hz), 2.73 (s). Other peaks had weak intensities and overlapped those of the major conformer. HR-EIMS m/z 591.2856 (M^+, Calcd. for $C_{32}H_{41}N_5O_4S$, 591.2879).

(-)-5-Chloroindolactam V (21) A mixture of 1 (106 mg) and N-chlorosuccinimide (66 mg) in dioxane (6 ml) was stirred at room temperature for 10 min. After adding water and EtOH, this reaction mixture was evaporated to dryness and partitioned between EtOAc and water. EtOAc extracts were purified by column chromatography on Wako C-200 gel with 22.5 % acetone in toluene, followed by on YMC I-40/64 gel with 65 % MeOH in water to give 21 as amorphous powder (47 mg, 40 % yield). $[\alpha]_D^{29}$ +46° (c=0.15, EtOH). UV λ_{max} (EtOH) nm (ε): 298 (5900), 233 (26,000). IR ν_{max} (KBr) cm^{-1}: 3290, 2960, 2930, 1642, 1490, 1462, 1040. ^1H NMR δ ($CDCl_3$) ppm: conformer A:B=10:1; conformer A, 0.97 (3H,d,J=6.4Hz), 1.36 (3H,d,J=6.7Hz), 2.62 (1H,m), 2.75 (3H,s), 2.79 (1H,dd,J=14.7Hz,1.8Hz), 3.09 (1H,d,J=10.4Hz), 3.18 (1H,dd,J=14.7Hz,4.3Hz), 3.35 (2H,m), 4.46 (1H,m), 4.77 (1H,d,J=10.7Hz), 7.06 (1H,d,J=2.1Hz), 7.18 (1H,d,J=8.6Hz), 7.27 (1H,d,J=8.6Hz), 8.38 (1H,br.s); conformer B, 1.07 (d,J=6.7Hz), 1.27 (d,J=6.4Hz). Other peaks had weak intensities and overlapped those of the major conformer. HR-EIMS m/z 335.1418 (M^+, Calcd. for $C_{17}H_{22}N_3O_2Cl$, 335.1401).

(-)-5-Acetylindolactam V (22) Amorphous powder, $[\alpha]_D^{19}$ +57° (c=0.40, EtOH). UV λ_{max} (EtOH) nm

(ε): 290 (4800), 248sh (9000), 227 (18,000). IR ν_{max} (KBr) cm^{-1}: 3370, 3290, 2960, 2930, 2880, 1675, 1655, 1605, 1500, 1465, 1350, 1140. ^1H NMR δ ($CDCl_3$) ppm: conformer A:B=30:1; conformer A, 0.84 (3H,d,J=6.4Hz), 1.03 (3H,d,J=7.0Hz), 2.45 (1H,m), 2.52 (3H,s), 2.74 (3H,s), 2.78 (1H,d, J=14.4Hz), 2.93 (1H,d,J=10.7Hz), 3.16-3.27 (3H,m), 4.38 (1H,br.m), 4.89 (1H,d,J=10.4Hz), 6.90 (1H,d,J=8.2Hz), 7.05 (1H,d,J=2.1Hz), 7.25 (1H,d,J=8.2Hz), 8.93 (1H,br.s). HR-EIMS m/z 343.1890 (M^+, Calcd. for $C_{19}H_{25}N_3O_3$, 343.1896).

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