CONFORMATIONAL STATES OF INDOLACTAMS. STRUCTURES OF 13-*N*-DESMETHYLINDOLACTAM-V AND 13-*O*-INDOLACTAM-V

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Abstract- Tumor-promoting teleocidins are known to exist in an equilibrium between two conformational states, the twist and the sofa form, in solution. 13-*O*-Indolactam-V, takes the fold form in solution and in the crystal, indicating that the conformation of the nine-membered lactam ring of indolactams is influenced by the nature of the group at position 13.

Teleocidins are tumor promoters as potent as 12-*O*-tetradecanoylphorbol-13-acetate (TPA).[1] Teleocidins and their active congeners (indolactam-V(**1**)s)[2] exist in solution in an equilibrium between at least two conformational states, the twist (**2**) and the sofa (**3**) forms[3] (Fig. 1) and this conformational equilibrium is mainly attributed to a *cis-trans* isomerization of the amide bond.

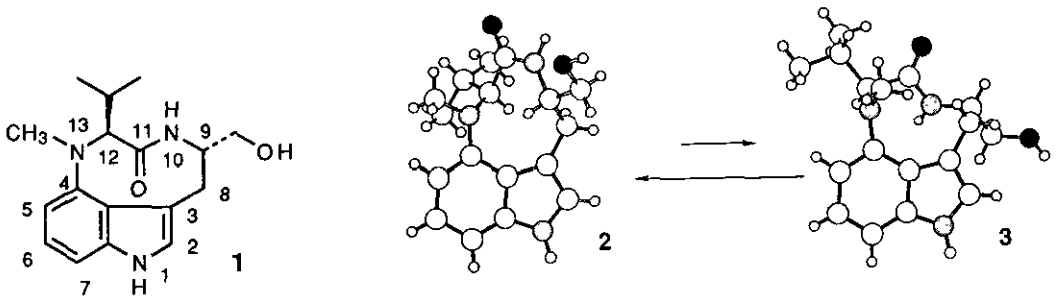


Figure 1. Conformation of indolactam-V in the twist (left) and sofa (right) forms

Recently, we have reported the design and synthesis of two conformationally restricted molecules, benzolactam-Vs, reproducing each of the two conformations. The biological activity of the benzolactam-Vs indicated that the active conformation for tumor-promoting activity of teleocidins is close to the twist form.[4] In addition to the *cis-trans* isomerization of the amide bond, the steric effects of substituents on the nine-membered lactam influence the equilibrium and the conformational features. To examine the effect of the C-12 substituent, we have synthesized a series of indolactams having a hydrogen,[5] methyl, benzyl, *iso*-butyl or *tert*-butyl group at the C-12 position instead of the isopropyl group of indolactam-V[6] and we have analyzed their conformations.[7] ^{1}H-Nmr experiments have shown that increasing bulkiness of the substituent on C-12 tends to increase the relative population of the sofa form.[6] However, a new ring conformation was observed in the crystal and in solution in the case of indolactam-G (**4**), which has no substituent on C-12. The ^{1}H-nmr experiments on indolactam-G at -30°C revealed the coexistence of two conformers in CD_3OD, in the ratio of 5:1. The major conformer was concluded to be the fold form (**5**). (Figure 2)

Here, we describe the steric effect of substituents on N-13, based on conformational analysis of 13-*N*-desmethylindolactam-V (**7**) and the synthesis and conformational analysis of 13-*O*-indolactam-V (**6**).

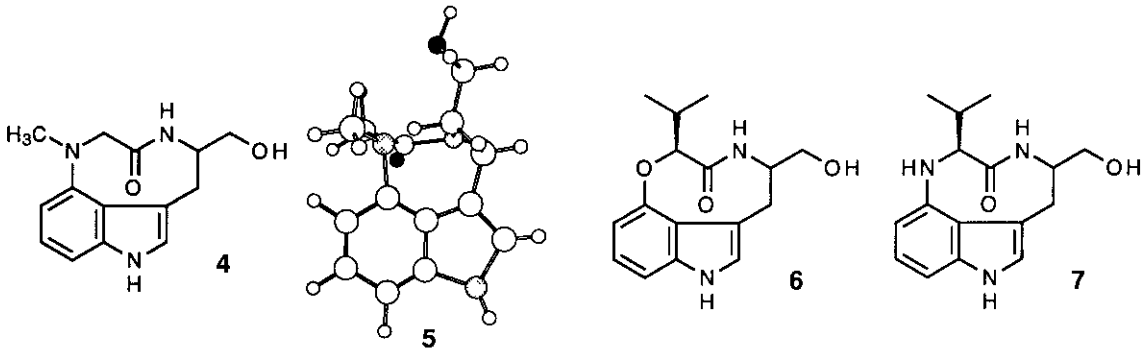
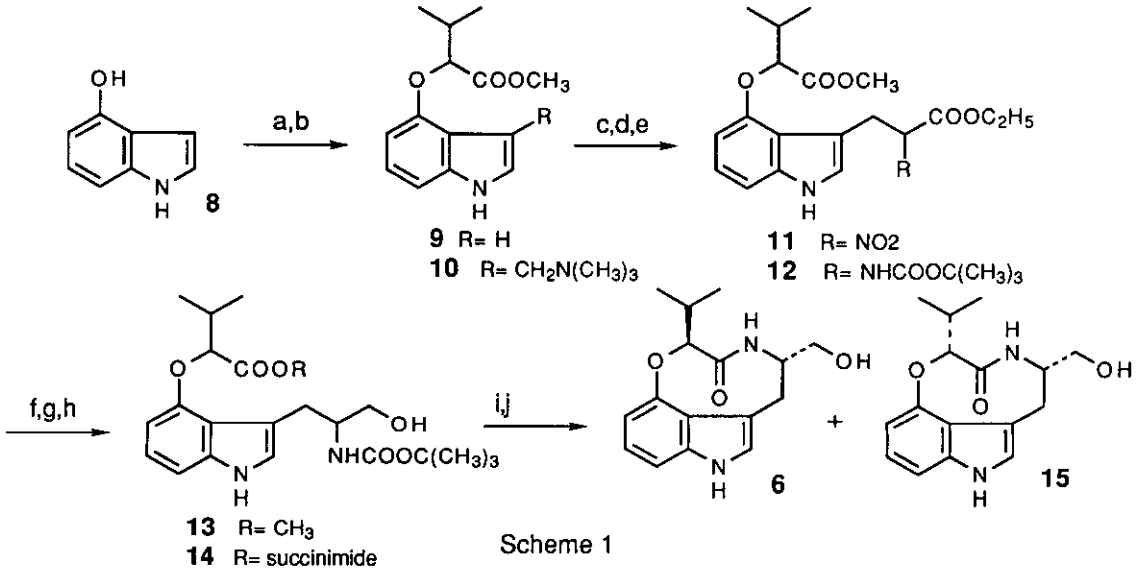


Figure 2

13-*O*-Indolactam-V was synthesized from 4-hydroxyindole (**8**) in the following way (Scheme 1). 4-Hydroxyindole (**8**) was *O*-alkylated with methyl 2-bromoisovalerate to afford methyl 2-(indol-4-yloxy)isovalerate (**9**) in 49 % yield. After conversion of **9** to a gramine derivative (**10**) by treatment with formaldehyde and *N,N*-dimethylamine, reaction with ethyl nitroacetate afforded the diastereomeric nitroester (**11**) in 74 % yield. Catalytic hydrogenation of the nitro group over platinum oxide in ethanol followed by protection with a Boc group gave **12** (63 %). Selective reduction of the two ester groups of **12** with sodium borohydride[8] gave diastereomeric alcohols (**13**) in 45 % yield. Then **13** was hydrolyzed with 2 N aq. KOH in methanol, and treated with *N*-hydrosuccinimide-DCC in acetonitrile to give the activated esters (**14**). (74 %) Deprotection of

the Boc group of **14** with trifluoroacetic acid followed by treatment with weak aqueous alkali in ethyl acetate afforded a diastereomeric mixture of lactams (**6** and **15**), which were separated by silica gel column chromatography. The determination of the relative configuration of the two lactams was difficult because of the complicated conformational features of this series of compounds. Spectral analysis of the 13-*O*-epi-indolactam-V (**15**) was helpful. The ^{1}H-nmr spectrum of the less polar isomer at 23°C showed broadening of peaks and the spectrum at -10°C revealed the coexistence of two conformers in $CDCl_3$ in a ratio of 13:1. In the nuclear Overhauser effect (NOE) measurements of the isomer, a strong enhancement of the H-12 signal was observed upon saturation of the H-9 proton. The short distance between H-12 and H-9 clearly indicates that this isomer is 13-*O*-epi-indolactam-V (**15**). Because it is impossible for H-9 and H-12 to be close in any conformation of 13-*O*-indolactam-V (**6**), it was concluded that the more polar isomer is **6**.



Scheme 1

a) NaH, methyl 2-bromoisovalerate/ DMF b) 37% HCHO, $(CH_3)_2NH$/ AcOH c) $O_2NCH_2COOC_2H_5$/ toluene d) H_2, PtO_2/ C_2H_5OH e) $(Boc)_2O$, $(C_2H_5)_3N$/ THF f) $NaBH_4$/ C_2H_5OH g) KOH aq/ CH_3OH h) *N*-hydroxysuccinimide, DCC/ CH_3CN i) CF_3COOH/ CH_2Cl_2 j) aq. $NaHCO_3$ / $CH_3COOC_2H_5$

The ^{1}H-nmr spectral data of **4**, **6**, and **7** (which was obtained as an intermediate in the synthesis of indolactam-V[2,3]) in CD_3OD are summarized in Table 1. The signals in the ^{1}H-nmr spectra of **6** at 23°C were not split, which indicates that a single conformer predominates. The chemical shifts and coupling constants of **6** were close to those of the fold form of **4** and were distinct from those of the twist form of indolactam-V (Table 1). In particular, the H-9 signal exhibited a low-field shift owing to the effect of the lone pair electrons on the nitrogen

atom or oxygen atom at the 13-position. The H-9 signal is ordinarily observed at 4.3 ppm in the case of the other conformations, the twist and sofa forms of indolactam-V. In the NOE experiments, saturation of the H-9 proton resulted in characteristic enhancement of the H-15 signal.

Table 1. ^{1}H-Nmr spectral data for **4**, **6** , **7** and the twist conformer of **1** in CD_3OD[a)]

Proton	Major conformer of **4** [b)]	**6**	Major conformer of **7**	Twist conformer of **1**
2-H	6.94 (s)	6.99 (d, 0.7)	6.95 (s)	6.94 (s)
5-H	6.91 (d, 7.6)	6.69 (dd, 7.7, 0.7)	6.66 (dd, 7.5, 1.0)	6.44 (dd, 8.0, 1.1)
6-H	7.03 (t, 7.6)	7.03 (dd, 8.1, 7.7)	6.94 (t, 7.5)	6.95 (t, 8.0)
7-H	7.08 (dd, 7.6, 0.7)	7.13 (dd, 8.1, 0.7)	7.02(dd, 7.5, 1.0)	6.88 (dd, 8.0, 1.1)
8α-H	3.17 (dd, 15.4, 8.3)	3.05 (ddd, 15.8, 6.0, 1.7)	3.14 (dd, 15.0, 6 5)	3.05 (dd, 15.1, 3.7)
8β-H	2.78 (dd, 15.4, 8.3)	2.90 (dd, 15.8, 11.7)	2.99 (dd, 15.0, 9.5)	3 11 (dd, 15 1, 2.0)
9-H	5.06 (m)	5.35 (m)	5.11 (m)	4.23 (m)
12-H	3.51 (d, 13.5)	3.95 (d, 9.5)	3.57 (d, 9.5)	4.48 (d, 10.5)
	3.94 (d, 13.5)			
14-H	3.57 (dd, 11.3, 8.6)	3.60 (dd, 11.4, 7.0)	3.62 (dd, 11.0, 7.0)	3.45 (dd, 11 3, 9.0)
	3.69 (11.3, 4.1)	3.69 (dd, 11.4, 4.6)	3.70 (dd, 11.0, 5.1)	3.62 (dd, 11.3, 4.1)
15-H		2.40 (m)	2.28 (m)	2.25 (m)
16-H		1.05 (d, 6.9)	1.04 (d, 6.5)	0.69 (d, 6.9)
17-H		1.34 (d, 6.9)	1.24 (d, 6.5)	0.89 (d, 6.9)

a) Chemical shifts are shown in δ, and coupling constants J in Hz are given in parentheses.
b) These spectral data were measured at -30°C.

The theoretically possible conformations of indolactams have been classified into 10 independent ring conformations by high-temperature molecular dynamics calculation.[9] On the basis of the above observation and exhaustive examination of molecular models considering the 10 possible conformations, the conformation of **6** is concluded to be the fold form in solution, like that of **4**. Crystallographic analysis, also revealed the fold form, as shown in Figure 3.

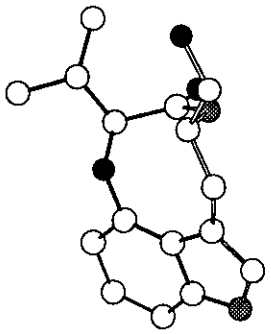


Figure 3. Chem 3D Drawing Obtained from X-Ray Diffraction Studies of 13-O-Indolactam-V (**6**).

On the other hand, the ^{1}H-nmr spectrum of 13-*N*-desmethylindolactam-V (**7**) clearly showed the existence of two conformers in a ratio of 4:1 at 23°C. The spectral data of the major conformer of **7** were close to those of **6** except for the protons on the carbon adjacent to the nitrogen at the 13-position. The fold conformers were characterized by a signal at 5.06-5.35 ppm and the assignment was confirmed by NOE experiments. Analogously with the case of **6**, strong enhancements were observed between the H-9 and H-12 protons.[10] The major conformation of **7** in solution is presumed to be the fold form.[11]

The predominance of the fold form in the cases of **4**, **6** and **7** shows that the methyl group on the nitrogen at the 13-position plays an important role in the maintenance of the characteristic conformational features of indolactam-V. Tumor-promoting activity of **6** and **7** was evaluated by assay of growth inhibition and differentiation of human promyelocytic leukemia cells (HL-60).[12] Compounds **6** and **7**, which exist in the fold form, were inactive below the concentration of 10^{-5} M, while indolactam-V is active at the concentration of 10^{-7} M.

EXPERIMENTAL

General Remarks Melting points were obtained on a Yanagimoto micro hot stage apparatus without correction. ^{1}H-Nmr spectra were measured with a JEOL JMN-GX-400 spectrometer (400 MHz), with TMS as an internal standard, and the chemical shifts are given in ppm as δ values from TMS. Mass spectra were recorded on a JEOL JMS-D-300 instrument for DI-Mass and JMS-DX-300 for high-resolution analysis. Ir spectra were recorded with a Shimadzu IR-408 and the data are presented in cm^{-1}. Flash column chromatography was performed on silica gel (Merck 9385).

Methyl 2-(Indol-4-yl)isovalerate (9) A 3.30 g (82.5 mmol) portion of NaH (60% in oil) was washed with n-hexane and suspended in 30 ml of dimethylformamide, and **8** (10.0 g, 75.1 mmol) was added to the suspension at 0°C. After vigorous stirring for 30 min at 23°C, methyl 2-bromoisovalerate (20.0 g, 103 mmol) was added and the whole was stirred for 1 h at 70°C. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (CH_2Cl_2) to give **9** (9.10 g, 49.0%). Colorless viscous liquid, ^{1}H-nmr ($CDCl_3$); 1.11 (d, 3H, J= 6.6 Hz), 1.17 (d, 3H, J= 6.6 Hz), 2.37 (m, 1H), 3.75 (s, 3H), 4.53 (d, 1H, J= 15.5 Hz), 6.38 (dd, 1H, J= 8.1, 5.9 Hz), 6.73 (t, 1H, J= 2.75 Hz), 7.04 (dd, 1H, J= 5.9 Hz), 7.13 (dd, 1H, J= 2.6, 2.4 Hz), 7.44 (d, 1H, J= 8.1 Hz), 8.16 (br s, 1H). Ir (KBr): 1740 (s, C=O). HRms: Calcd for $C_{14}H_{17}NO_3$: 247.2965; found: 247.2933.

Nitroester 11 A mixture of 8.0 g (32.4 mmol) of **9**, 50% aqueous dimethylamine (4.0 g, 44.4 mmol), formalin (3.7 g, 44.4 mmol), acetic acid (30 ml) and dioxane (30 ml) was stirred for 8 h at room temperature.

The mixture was poured into 15% aq. KOH solution with ice cooling and stirring, and the whole was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave **10** quantitatively. The crude **10** was dissolved in toluene (50 ml) and the solution was heated with ethyl nitroacetate (7.0 g, 52.6 mmol) at refluxing temperature under N_2. After cooling, the mixture was poured into CH_2Cl_2 (200 ml) and was washed with 1 N hydrochloric acid, brine, 5% aq. KOH then brine. The organic layer was dried over Na_2SO_4 and concentrated to afford an orange viscous liquid. The crude product was purified by silica gel column chromatography (CH_2Cl_2) to give 9.37 g (73.9%) of **11**. Dark red viscous liquid; ^{1}H-nmr ($CDCl_3$); isomer A; 1.08 (d, 3H, J= 6.9 Hz), 1.13 (d, 3H, J= 6.9 Hz), 1.22 (t, 3H, J= 7.1 Hz), 2.33 (m, 1H), 3.65 (dd, 1H, J= 14.6, 11.3 Hz), 3.70 (s, 3H), 3.91 (dd, 1H, J= 14.6, 4.0 Hz), 4.30 (q, 2H, J= 7.1 Hz), 4.67 (d, 1H, J= 5.8 Hz), 6.11 (dd, 1H, J= 11.3, 4.0 Hz), 6.41 (d, 1H, J= 8.0 Hz), 6.93 (s, 1H), 6.97 (d, 1H, J= 8.0 Hz), 7.04 (t, 1H, J= 8.0 Hz), 8.04 (br s, 1H). Isomer B; 1.07 (d, 3H, J= 6.9 Hz), 1.14 (d, 3H, J= 6.9 Hz), 1.30 (t, 3H, J= 7.1 Hz), 2.33 (m, 1H), 3.72 (s, 3H), 3.84 (dd, 1H, J= 14.8, 7.2 Hz), 4.22 (dd, 1H, J= 14.8, 7.2 Hz), 4.30 (q, 2H, J= 7.1 Hz), 4.64 (d, 1H, J= 7.0 Hz), 6.18 (m,1H), 6.41 (d, 1H, J= 8.0 Hz), 6.9 (s, 1H), 6.97 (d, 1H, J= 8.0 Hz), 7.04 (t, 1H, J= 8.0 Hz), 8.04 (bs, 1H). Ms m/z: 362 (M^+). Ir (KBr): 1745 (br, 2xC=O),1565 (s, NO_2), 1365 (s, NO_2). HRms: Calcd for $C_{19}H_{24}N_2O_7$: 392.4123; found: 392.4107.

N-Boc-aminoester 12 A mixture of 7.75 g (19.7 mmol) of **11** and 1.0 g of platinum oxide in 40 ml of dry ethanol was vigorously stirred under 1 atm of H_2 for 22 h at room temperature, then filtered. The filtrate was concentrated and chromatographed on silica gel (CH_2Cl_2: ethanol 9:1) to give the aminoester (5.13 g, 71.7%). Pale orange viscous liquid; ^{1}H-nmr ($CDCl_3$); isomer A; 1.12 (d, 3H, J= 7.0 Hz), 1.18 (d, 3H, J= 7.0 Hz), 1.23 (t, 3H, J= 7.0 Hz), 2.41 (m, 1H), 3.10 (dd, 1H, J= 13.9, 9.5 Hz), 3.50 (dd, 1H, J= 13.9, 5.3 Hz), 3.71 (s, 3H), 3.85 (dd, 1H, J= 9.5, 5.3 Hz), 4.18 (q, 2H, J= 7.0 Hz), 4.66 (d, 1H, J= 5.5 Hz), 6.33 (d, 1H, J= 7.3 Hz), 6.92 (d, 1H, J= 2.2 Hz), 6.97 (d, 1H, J= 8.0 Hz), 7.01 (dd, 1H, J= 8.0, 7.3 Hz), 8.25 (br s, 1H). Isomer B; 1.10 (d, 3H, J= 7.0 Hz), 1.18 (d, 3H, J= 7.0 Hz), 1.27 (t, 3H, J= 7.3 Hz), 2.41 (m, 1H), 2.91 (dd, 1H, J= 13.9, 9.2 Hz), 3.64 (dd, 1H, J= 13.9, 4.4 Hz), 3.71 (s, 3H), 4.10 (dd, 1H, J= 9.2, 4.4 Hz), 4.20 (q, 2H, J= 7.3 Hz), 4.58 (d, 1H, J= 6.2 Hz), 6.33 (d, 1H, J= 7.3 Hz), 6.92 (d, 1H, J= 2.2 Hz), 6.97 (d, 1H, J= 8.0 Hz), 7.01 (dd, 1H, J= 8.0, 7.3 Hz), 8.25 (br s, 1H). The aminoester (4.67 g, 12.9 mmol) and triethylamine (1.30 g, 12.9 mmol) were dissolved in 30 ml of THF, and *tert*-butoxycarbonyl anhydride (3.00 g, 13.7 mmol) was added with stirring. Stirring was continued for 24 h at room temperature, then the mixture was concentrated to dryness, and the residue was dissolved in 500 ml of CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$ and concentrated to give a crude product. Crystallization from ethanol gave 5.26 g (88.3%) of **12**.

Colorless fine needles, mp 164-166°C; ^{1}H-nmr signals of **12** showed broadening at -60-+40°C. Ms m/z: 462 (M^+), 362 (-Boc). Anal. Calcd for $C_{24}H_{34}N_2O_7$: C; 62.32, H; 7.41, N; 6.06. Found: C; 62.15, H; 7.39, N; 5.79.

N-Boc-aminoalcohol 13 To a solution of **12** (700 mg, 1.51 mmol) in 30 ml of ethanol, $NaBH_4$ (1.28 g, 33.8 mmol)) was added with stirring during 2 h at room temperature, and the whole was heated for 2 h at 50°C. The whole was poured into 500 ml of brine and extracted with CH_2Cl_2 (2 x 500 ml). The solution was dried over Na_2SO_4 and concentrated to give a residue. The crude product was chromatographed on silica gel (CH_2Cl_2: $CH_3COOC_2H_5$ 9:1) to give 288 mg (45.3%) of **13**. Colorless viscous liquid, ^{1}H-nmr ($CDCl_3$) ; isomers A and B; 1.06-1.12 (2x d, 2x 3H), 1.15-1.20 (2x d, 2x 3H), 1.27, 1.31 (2x s, 2x 9H), 2.25-2.43 (2x m, 2x 1H), 2.85-3.45 (2x m, 2x 2H), 3.57-3.67 (2x m, 2x 2H), 3.71, 3.75 (2x s, 2x 3H), 3.85-4.04 (m), 4.30-4.42 (2x m, 2x 1H), 4.62, 4.70 (2x br d, 2x 1H), 5.32, 5.68 (2x br s, 2x 1H), 6.36, 6.51 (2x d, 2x 1H, J= 8.0 Hz), 6.92-7.08 (m, 2x 3H), 8.16, 8.20 (2x br s, 2x 1H). Ms m/z: 420 (M^+). Ir (KBr): 1740 (s, $COOCH_3$), 1720 (s, $NHCOOC(CH_3)_3$. HRms: Calcd for $C_{22}H_{32}N_2O_6$: 420.5101; found: 420.5078.

Activated ester 14 A mixture of a solution of 288 mg (0.68 mmol) of **13** in 50 ml of methanol and 3.5 ml (70 mmol) of 2 N aq. KOH solution was kept at room temperature for 10 h. Methanol was evaporated off under reduced pressure and the residue was diluted with 200 ml of ice-water. The aqueous solution was acidified with 0.5 M aq. citric acid solution at 0°C, and extracted with $CH_3COOC_2H_5$ (2x 200 ml). The extract was dried over Na_2SO_4 and concentrated to give the crude product. The acid and 85 mg (0.74 mmol) of *N*-hydroxysuccinimide were dissolved in 5 ml of acetonitrile, and then a solution of 152 mg (0.74 mmol) of dicyclohexylcarbodiimide in 2 ml of acetonitrile was added at 0°C with stirring. Stirring was continued for 1 h at room temperature, then the solvent was removed and the residue was dissolved in 50 ml of $CH_3COOC_2H_5$. A precipitate was removed by filtration, and the filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel ($CH_3COOC_2H_5$) to give 255 mg (73.9 %) of the activated ester (**14**). Colorless viscous liquid, ^{1}H-nmr ($CDCl_3$) ; The signals of the **14** showed broadening owing to the presence of stereoisomers A and B in several conformational states. Major peaks were observed as follows; 1.23-1.28 (2x d, 2x 3H), 1.29 (2x s, 2x 9H), 3.06-3.29 (2x dd, 2x 2H), 3.56-3.78 (2x dd, 2x 2H), 5.00-5.02 (2x br d, 2x 1H), 6.53 (2x d, 2x 1H, J= 8.0 Hz), 6.99-7.01 (2x d, 2x 1H, J= 8.0 Hz), 7.08 (2X t, 2x 1H, J= 8.0 Hz), 8.36 (2x br s, 2x 1H). Ms m/z: 503 (M^+).

13-O-Indolactam-V (6) and 13-O-epi-indolactam-V (15) Trifluoroacetic acid (5 ml) was added to a solution of 255 mg (0.51 mmol) of **14** in 5 ml of CH_2Cl_2 at 0°C with stirring. The mixture was stirred for 5 h

at 0°C under an Ar atmosphere, then the trifluoroacetic acid was removed under reduced pressure at below 30°C. The residue was dissolved in $CH_3COOC_2H_5$ (10 ml), then 1 ml of saturated aq. $NaHCO_3$ solution was added and the mixture was stirred for 3 h at room temperature. The mixture was diluted with 50 ml of $CH_3COOC_2H_5$ and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was separated by preparative thin layer chromatography on silica gel (CH_2Cl_2: $CH_3COOC_2H_5$ 1:1) to afford 44.5 mg (30.5%) of **6** and 40.9 mg (28.0%) of **15**. The less polar isomer was **15** and the more polar isomer was **6**. **6**; colorless needles (ethanol), mp 214°C. Ir (KBr): 1640 (s, NHCO). ^{1}H-Nmr(CD_3OD) signals are given in the text. Ms *m/z*; 288 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C; 66.65, H; 6.99, N; 9.72. Found: C; 66.28, H; 7.01, N; 9.63. **15**; Colorless needles ($CH_3COOC_2H_5$), mp 208-210°C. Ir (KBr): 1640 (s, NHCO). ^{1}H-Nmr (CD_3OD) 0.95 (d, 3H, J= 7.0 Hz, 16- or 17-H), 1.37 (d, 3H, J= 7.0 Hz, 16- or 17-H), 2.29 (m, 1H, 15-H), 2.67 (dd, 1H, J= 14.3, 10.7 Hz, 8β-H), 3.13 (d, 1H, J= 14.3 Hz, 8α-H), 3.47 (d, 1H, J= 10.3 Hz, 12-H), 3.67 (dd, 1H, J= 11.0, 7.0 Hz, 14-H), 3.74 (dd, 1H, J= 11.0, 5.5 Hz, 14-H), 3.88 (m, 1H, 9-H), 6.71 (d, 1H, J= 7.7 Hz, 5-H), 7.03 (dd, 1H, J= 8.0, 7.7 Hz, 6-H), 7.07 (s, 1H, 2-H), 7.16 (d, 1H, J= 8.0 Hz, 7-H). Ms *m/z*; 288 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C; 66.65, H; 6.99, N; 9.72. Found: C; 66.32, H; 7.08, N; 9.60.

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10. A saturation transfer between the two conformers of *N*-desmethylindolactam-V (**7**) was observed in NOE measurements. This means that an equilibrium between the two conformers exists in the nmr time scale.

11. The minor conformation of **7** is neither the twist, sofa nor fold form. It could not be identified, because some peaks overlap with peaks of the major conformer.

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Received, 8th February, 1994