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Synthesis of 7-Substituted Indolactam-V. An Introduction of Hydrophobic Moieties on the Indole Ring. †

Yasuyuki Endo, Yasuo Sato and Koichi Shudo*

Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Tokyo, 113, Japan.

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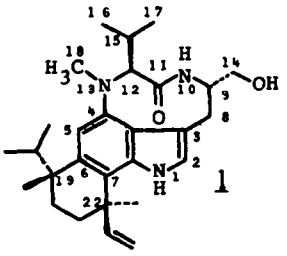
Abstract: (-)-Indolactam-V, which shares the same partial structure of teleocidins A and B, shows a weak promoting activity compared to teleocidins. It suggests that the hydrophobic moieties substituted on the 6,7-positions of teleocidins play a role in increasing the biological activity. 7-Substituted indolactam-Vs have been synthesized starting from indolactam-V by two methods for preparation, which consisted of Friedel-Crafts alkylation and palladium catalyzed vinyl coupling reaction.

Teleocidins (e.g. teleocidin B-4,[1] 1, teleocidin A-1,[2] 2) are potent skin tumor-promoters.[3] (-)-Indolactam-V (3)[4] which is a common portion of the teleocidin molecule has attracted synthetic[5] and stereochemical[6] interest. (-)-Indolactam-V (3) itself shows a weak tumor promoting activity compared to teleocidins in a two-stage carcinogenesis experiment on mouse skin.[7]



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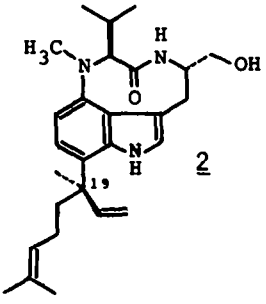

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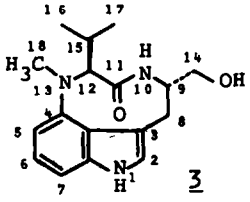

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3 shows about two orders weaker activitiy compared to teleocidins for the biological and biochemical activities related to a tumor promoting activity, such as induction of ornithine decarboxylase on mouse skin, HL-60 cell adhesion and inhibition of specific [^{3}H]TPA binding to a mouse particulate fraction.[8] The difference of the activities between 3 and teleocidins may be interpreted in terms of the absence or presence of the terpenoid hydrocarbon chain. On the other hand, four teleocidin B isomers (diastereomeric at C-19 and C-20 for 1) and two teleocidin A isomers (diastereomeric at C-19 for 2)[9] show similar potencies in a two-stage carcinogenesis experiment and the other biological tests.[10] Therefore, the activity of these teleocidins seems to be independent on a specific structure of the hydrocarbon moiety. The substituent on 6, 7-position of the indole ring seems to

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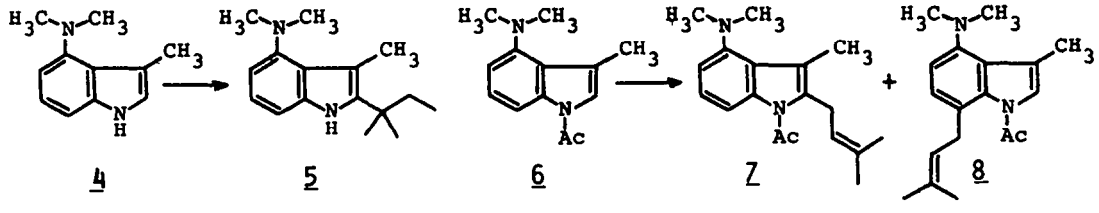
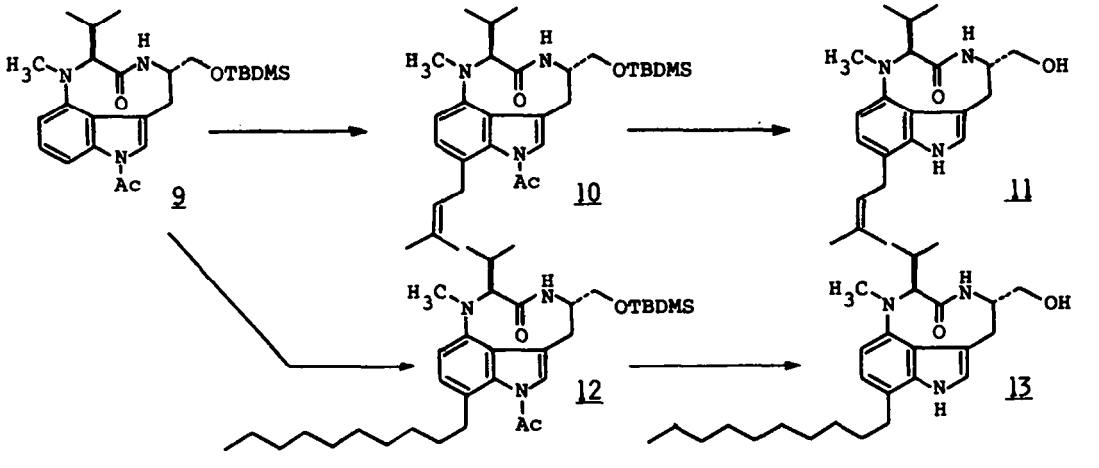
exert simply as a part of hydrophobic domain on the molecule in relation to the putative receptor. In this paper we describe a synthesis of 7-substituted inolactam-Vs which contain effective hydrophobicity for the appearance of the activities.

A new method for an introduction of terpenoid chain to 6,7-position has been presented by Nakatsuka et al. during a study of synthesis of teleocidin Bs.[11] We have already synthesized (-)-indolactam-V-tetramethylene, which contains 6,7-substituted hydrocarbon moiety by a method similar to that was used in the synthesis of 3 starting from 6,7,8,9-tetrahydrobenzo[g]indole.[12] However, particularly with a view to synthesize a number of derivatives for structure-activity studies, a much more direct synthetic method was required, and for this purpose, a method starting from indolactam-V seemed ideally suited, in spite of the difficulty in introduction of alkyl group onto the indole nuclei. Recently, 7-alkyl derivatives of indolactam-V were prepared by Irie et al. employing Friedel-Crafts acylation of indolactam-V acetate and following reduction.[13]

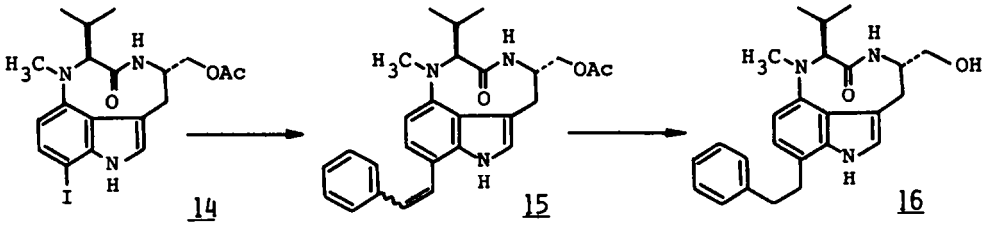
In our model experiment, 4-dimethylamino-3-methylindole (4) was alkylated by 2-chloro-2-methylbutane in the presence of $AgClO_4$ to give 2-(1',1'-dimethylpropyl)-4-dimethylamino-3-methylindole (5) in 35 % yield. And no 7-alkylated product was obtained. This is because electron density on the 2-position of the indole ring is relatively high. Whereas 1-acetyl-4-dimethylamino-3-methylindole (6) was alkylated by 1-chloro-3-methyl-2-butene in the presence of $AgOCOCF_3$ in nitromethane to give 2- (7, 12 %) and 7-(3',3'-dimethylallyl)-4-dimethylamino-3-methylindole (8, 16 %).



Indolactam-V (3) was converted to 1-acetyl-14-O-TBDMS-indolactam-V (9) in 89 % yield by the usual way. 9 was reacted with 1-chloro-3-methyl-2-butene in the presence of $AgOCOCF_3$ in nitromethane to give 1-acetyl-7-(3',3'-dimethylallyl)-14-O-TBDMS-indolactam-V (10) in 21 % yield. Deprotection of 10 employing aqueous K_2CO_3 solution followed by tetrabutylammonium fluoride in THF gave 7-(3',3-dimethylallyl)-indolactam-V (11). A similar treatment of 9 with 1-chloro-2-decene in the presence of $AgOCOCF_3$ and hydrogenation of the product afforded 1-acetyl-7-decyl-14-O-TBDMS-indolactam-V (12) in 18 % yield. Deprotection of 12 gave 7-decylindolactam-V (13).



Another method for a synthesis of 7-substituted indolactam-V was carried out employing palladium catalyzed coupling of halogenated indolactam-V with olefin. 3 was selectively iodinated on 7-position of the indole ring by the method of Koshimizu et al.[13] 14-O-Acetyl-7-iodoindolactam-V (14) was heated at 100 C with styrene in the presence of $Pd(OAc)_2$ in triethylamine and acetonitrile to give a cis-trans mixture of 14-O-acetyl-7-styrylindolactam-V (15) in 73 % yield. 15 was hydrogenated and hydrolyzed to give 7-phenethylindolactam-V (16) in 86 % yield.



14 15 16

Teleocidins, including indolactam-V (3) exist in two stable conformational states; SOFA form and TWIST form in solution.[5,12] For example, the ratio of the two conformers of teleocidin B-4 were 1:7 in $CDCl_3$, 3:5 in CD_3OD by NMR spectra. The 7-substituted indolactam-V (11, 13, 16) exist in the two conformers in CD_3OD in ratios of 7:6, 8:7 and 4:5, respectively. All the signals except for 7-substituents in the NMR spectra of 11, 13 and 16, could be assigned in accordance with those of the two conformers of teleocidins. These compounds (11, 13, 16) were found to exhibit much stronger activities than 3. Details of the biological activities of them will be reported elsewhere. The two methods for introduction on to 7-position of the indole nuclei of indolactam-V will be useful tools in preparation of indolactam-V derivatives for structure-activity studies.

Experimental Section

General Remarks. Melting points were obtained on a Yanagimoto micro hot stage and are uncorrected. Spectra were recorded with the following instruments: ^{1}H-NMR spectra, JEOL JMN-FX-100 (100MHz) and JEOL JMN-FX-400 (400MHz); mass spectra, JEOL JMN-DX-300; HPLC, SHIMADZU LC-3A liquid chromatography with a SPD-2A UV detector. NMR spectra were recorded with tetramethylsilane as an internal standard and the chemical shifts are given δ values from TMS. Column chromatography was performed on silica gel (Merck 7734 or 9385).

Reaction of 4-dimethylamino-3-methylindole (4) A mixture of 87 mg (0.5 mmol) of 4, 138 mg (1 mmol) of K_2CO_3 and 1 ml of 2-chloro-2-methylbutane in 5 ml of nitromethane was added 172 mg (1 mmol) of $AgClO_4$ with stirring at room temperature. The mixture was heated to reflux for 2.5 h. under Ar atmosphere. The mixture was poured into water, and extracted with CH_2Cl_2. Dryness over $MgSO_4$, evaporated concentration gave a crude product. Purification by column chromatography on silica gel using n-hexane-CH_2Cl_2 (2:3) gave 43 mg (35%) of 2-(1',1'-dimethylpropyl)-4-dimethylamino-3-methylindole (5). 5:colorless viscous liquid; ^{1}H-NMR ($CDCl_3$) 0.78 (t, 3H, J= 6.5 Hz, $-CH_2-CH_3$), 1.42 (s, 6H, $-C(CH_3)_2-$), 1.78 (q, 2H, J= 6.5 Hz, $-CH_2-CH_3$), 2.65 (s, 3H, 3-CH_3), 2.80 (s, 6H, $-N(CH_3)_2$), 6.68 (m, 1H, 5-CH), 6.94-7.00 (m, 2H, 6,7-CH), 7.82 (bs, 1H, 1-NH); MS 244 (M^+).

Reaction of 1-acetyl-4-dimethylamino-3-methylindole (6) A mixture of 108 mg (0.5 mmol) of 6 and 3.1 ml (30 mmol) of 1-chloro-3-methyl-2-butene in 5 ml of nitromethane was added 59.7 mg (1.5 mmol) of MgO and 126 mg (1.5 mmol) of $NaHCO_3$. To the suspension, a solution of 331 mg (1.5 mmol) of $AgOCOCF_3$ in 5 ml of nitromethane was added dropwise with stirring at room temperature. After stirring for 1 h, 126 mg (1.5 mmol) of $NaHCO_3$ and a solution of 331 mg (1.5 mmol) of $AgOCOCF_3$ in 5 ml of nitromethane was added to the mixture. After further stirring for 30 min, the mixture was poured into aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. Dryness over $MgSO_4$, evaporated concentration gave a crude product. Purification by column chromatography on silica gel using n-

hexane-$CH_3COOC_2H_5$ (8:1) gave 17.3 mg (12%) of 1-acetyl-2-(3',3'-dimethylallyl)-4-dimethylamino-3-methylindole (7) and 22.9 mg (16%) of 1-acetyl-7-(3',3'-dimethylallyl)-4-dimethylamino-3-methylindole (8). 7: colorless viscous liquid; ^{1}H-NMR ($CDCl_3$) 1.71 (d, 3H, J=1.0 Hz, $=C(CH_3)_2$), 1.77 (d, 3H, J=1.0 Hz, $=C(CH_3)_2$), 2.50 (s, 3H, 3-CH_3),2.72 (s, 3H, $-COCH_3$), 2.77 (s, 6H, $-N(CH_3)_2$), 3.68 (bd, 2H, J= 6.0 Hz, $-CH_2$-CH), 5.15 (tt, 1H, $-CH_2$-CH), 6.89 (dd, 1H, J= 8.1, 1.0 Hz, 5-CH), 7.15 (t, 1H, J= 8.1 Hz, 6-H), 7.60 (dd, 1H, J= 8.1, 1.0 Hz, 7-CH); MS 284 (M^+). 8: colorless viscous liquid; ^{1}H-NMR ($CDCl_3$) 1.70 (d, 6H, J=1.0 Hz, $=C(CH_3)_2$), 2.47 (d, 3H, J= 1.1 Hz, 3-CH_3),2.56 (s, 3H, $-COCH_3$), 2.74 (s, 6H, $-N(CH_3)_2$), 3.35 (bd, 2H, J= 6.0 Hz, $-CH_2$-CH), 5.12 (tt, 1H, J= 6.0, 1.0 Hz, $-CH_2$-CH), 6.88 (d, 1H, J= 8.1 Hz, 5-CH), 7.04 (d, 1H, J= 1.1 Hz, 2-H), 7.05 (d, 1H, J= 8.1 Hz, 6-CH); MS 284 (M^+).

1-Acetyl-14-O-TBDMS-indolactam-V (9) 301 mg (1 mmol) of indolactam-V and 680 mg (10 mmol) of imidazole was added to a solution of TBDMS chloride (752 mg, 5 mmol) in 1 ml of DMF. The mixture was stirred for 1 h at 30°C. Removal of the solvent under reduced pressure at 50°C and purification by column chromatography on silica gel using CH_2Cl_2-$CH_3COOC_2H_5$ (30:1) as eluent gave 14-O-TBDMS-indolactam-V (403 mg, 97 %). 52mg (1.3 mmol) of NaH (60 % in oil) was washed with n-hexane and suspended in 2 ml of DMF, and 360 mg (0.87 mmol) of 14-O-TBDMS-indolactam-V was added to the suspension at 0°C. After vigorous stirring for 10 min at 0°C, a solution of 1.8 ml of acetic anhydride in 2 ml of DMF was added, and the whole was stirred for 30 min at 0°C. Then, the solvent was removed under reduced pressure at room temperature and partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (5:2) gave 359 mg (91 %) of 1-acetyl-14-O-TBDMS-indolactam-V (9): mp 174-176°C (ethanol-n-hexane); ^{1}H-NMR ($CDCl_3$) Conformers TWIST and SOFA ratio was 15:1. Signals due to the major (TWIST) conformer were assigned as follows. 0.04 (s, 3H, Si-CH_3), 0.06 (s, 3H, -Si-CH_3), 0.60 (d, 3H, J= 7.0Hz, $-C(CH_3)_2$), 0.87 (s, 9H, -Si-$C(CH_3)_3$), 0.92 (d, 3H, J= 7.0 Hz, $-CH(CH_3)_2$), 2.5 (m, 1H, $-CH(CH_3)_2$), 2.60 (s, 3H, $-COCH_3$), 2.7-3.2 (m, 2H, Ar-CH_2), 2.90 (s, 3H, N-CH_3), 3.48 (dd, 1H, J= 11.2, 10.3 Hz, $-CH_2$-OH), 3.67 (dd, 1H, J= 11.2, 5.0 Hz, $-CH_2$-OH), 4.13 (d, 1H, J= 10.5 Hz, 12-CH), 4.2 (m, 1H, 9-CH), 6.11 (s, 1H, 10-NH), 6.76 (d, J=8.0 Hz, 5-CH), 7.09 (s, 1H, 2-CH), 7.23 (t, 1H, J=8.0 Hz, 6-CH), 8.07 (d, 1H, J=8.0 Hz, 7-CH). MS 457 (M^+); Anal. ($C_{25}H_{39}N_3O_3Si$) C,H,N.

1-Acetyl-7-(3',3'-dimethylallyl)-14-O-TBDMS-indolactam-V (10) A mixture of 140 mg (0.31 mmol) of 9 and 3.2 ml (31 mmol) of 1-chloro-3-methyl-2-butene in 5 ml of nitromethane was added 61.7 mg (1.55 mmol) of MgO and 515 mg (6.2 mmol) of $NaHCO_3$. To the suspension, a solution of 1.35 g (6.2 mmol) of $AgOCOCF_3$ in 5 ml nitromethane was added dropwise with stirring at room temperature. After stirring for 1 h, 772 mg (9.3 mmol) of $NaHCO_3$ and a solution of 2.03 g (9.3 mmol) of $AgOCOCF_3$ in 8 ml of nitromethane was added to the mixture. After further stiring for 30 min, the mixture was poured into aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. Dryness over $MgSO_4$, evaporated concentration gave a crude product. Purification by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (4:1) gave 33.3 mg (21%) of 1-acetyl-7-(3',3'-dimethylallyl)-14-O-TBDMS-indolactam-V (10) and starting material (9, 41%). 10: mp 122-124°C (CH_2Cl_2-n-hexane); ^{1}H-NMR ($CDCl_3$) Conformers TWIST and SOFA ratio was 18:1. Signals due to the major (TWIST) conformer were assigned as follows. 0.04 (s, 3H, Si-CH_3), 0.06 (s, 3H, -Si-CH_3), 0.66 (d, 3H, J= 7.0Hz, $-C(CH_3)_2$), 0.89 (s, 9H, -Si-$C(CH_3)_3$), 0.90 (d, 3H, J= 7.0 Hz, $-CH(CH_3)_2$), 1.71 (d, 6H, J=1.1 Hz, $-CHC(CH_3)_2$) 2.4 (m, 1H, $-CH(CH_3)_2$), 2.56 (s, 3H, $-COCH_3$), 2.7-3.2 (m, 2H, Ar-CH_2), 2.89 (s, 3H, N-CH_3), 3.6-3.8 (m, 4H, $-CH_2$-OH, Ar-CH_2-$CHC(C_3)_2$), 4.10 (d, 1H, J= 10.5 Hz, 12-CH), 4.25 (bs, 1H, 9-CH), 5.07 (t, 1H, $-CHC(CH_3)_2$), 6.12 (s, 1H, 10-NH), 6.72 (d, J=8.0 Hz, 5-CH), 7.04 (s, 1H, 2-CH), 7.04 (d, 1H, J=8.0 Hz, 6-CH). MS 525 (M^+); Anal. ($C_{30}H_{47}N_3O_3Si$) C,H,N.

7-(3',3'-Dimethylallyl)-indolactam-V (11) To a solution of 30 mg (0.057mol) of 10 in 2 ml of methanol, a solution of 40 mg (0.288 mmol) of K_2CO_3 in 0.5 ml of water was added. The mixture was allowed to stand at room temperature for 1 h. Removal of the solvent under reduced pressure at room temperature, and partition between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (4:1) gave 22 mg (80%) of 7-(3',3'-dimethylalyl)-14-O-TBDMS-indolactam-V. The TBDMS ether (20 mg (0.041 mmol) was dissolved in 0.5 ml of THF, and to the solution, 108 mg (0.41 mmol) of tetra-n-butylammonium fluoride in 0.21 ml of THF was added. After stirring the mixture for 30 min at room temperature, the solvent was removed under reduced pressure at room temperature to give a residual oil. The crude product was partitioned between CH_2Cl_2 and water, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (1:2) gave 10.4 mg (74 %) of 7-(3',3'-dimethylallyl)-indolactam-V (11): mp 227-229°C

(ethanol); ^{1}H-NMR (CD_3OD) Conformers TWIST and SOFA ratio was 6:7 in this solution; TWIST conformer: 0.63 (d, 3H, J= 6.8 Hz, $-CH(C\underline{H}_3)_2$), 0.89 (d, 3H, J= 6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.75 (s, 6H, $CHC(C\underline{H}_3)_2$), 2.53 (dsept, 1H, J= 6.8, 10.4 Hz, $-C\underline{H}(CH_3)_2$), 2.87 (s, 3H, $N-C\underline{H}_3$), 3.05 (dd, 1H, J= 3.8, 17.2 Hz, $Ar-C\underline{H}_2-$), 3.11 (d, 1H, J= 17.2 Hz, $Ar-C\underline{H}_2-$), 3.45 (dd, 1H, J=9.2, 11.2 Hz, $-C\underline{H}_2-OH$), 3.52 (d, 2H, J= 7.3 Hz, $Ar-C\underline{H}_2-CHC(CH_3)_2$), 3.62 (dd, 1H, J= 4.6, 11.2 Hz, $-C\underline{H}_2-OH$), 4.25 (m, 1H, 9-C$\underline{H}$), 4.42 (d, 1H, J= 10.4 Hz, 12-C$\underline{H}$), 5.41 (m, 1H, $-C\underline{H}C(CH_3)_2$), 6.39 (d, 1H, J= 7.8 Hz, 5-C$\underline{H}$), 6.73 (d, 1H, J= 8.7 Hz, 6-C$\underline{H}$), 6.95 (s, 1H, 2-C$\underline{H}$) SOFA conformer: 0.89 (d, 3H, J= 6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.23 (d, 3H, J= 6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.75 (s, 6H, $CHC(C\underline{H}_3)_2$), 2.29 (dsept, 1H, J= 6.8, 11.0 Hz, $-C\underline{H}(CH_3)_2$), 2.70 (s, 3H, $N-C\underline{H}_3$), 2.89 (dd, 1H, J= 1.5, 14.3 Hz, $Ar-C\underline{H}_2-$), 3.00 (dd, 1H, J= 4.6, 14.3 Hz, $Ar-C\underline{H}_2-$), 3.04 (d, 1H, J= 11.0 Hz, 12-C$\underline{H}$), 3.23 (dd, 1H, J= 7.0, 11.0 Hz, $-C\underline{H}_2-OH$), 3.31 (d, 1H, J= 11.0 Hz, $-C\underline{H}_2-OH$), 3.43 (d, 2H, J= 6.4 Hz, $Ar-C\underline{H}_2-CHC(CH_3)_2$), 4.25 (m, 1H, 9-C$\underline{H}$), 5.41 (m, 1H, $-C\underline{H}C(CH_3)_2$), 6.85 (d, 1H, J= 7.8 Hz, 5-C$\underline{H}$), 6.89 (d, 1H, J= 8.7 Hz, 6-C$\underline{H}$), 7.11 (s, 1H, 2-C$\underline{H}$) MS m/e 369.2394, calcd. for $C_{22}H_{31}N_3O_2$ 369.2416.

1-Acetyl-7-decyl-14-O-TBDMS-indolactam-V (12) The procedure was similar to that used for the preparation of 10, employing 95 mg (0.21 mmol) of 9 and 3.625 g (21 mmol) of 1-chloro-2-decene. After work-up, the reaction mixture was chromatographed on silica gel using benzene-$CH_3COOC_2H_5$ (5:1) to give 25 mg (20 %) of 1-acetyl-7-(2'-decenyl)-14-O-TBDMS-indolactam-V and 20 mg (21 %) of starting material (9). The allylated product (20 mg, 0.034 mmol) was hydrogenated in the presence of 20 mg of Pd-charcoal in 3 ml of ethanol under 1 atm H_2 at room temperature for 2 h, then the mixture was filtered. The filtrate was concentrated under reduced pressure and separated by column chromatography on silica gel (n-hexane-$CH_3COOC_2H_5$ 5:1) to give 1-acetyl-7-decyl-14-O-TBDMS-indolactam-V (12) as a viscous liquid (18 mg, 90 %). ^{1}H-NMR ($CDCl_3$) TWIST conformer was predominate in this solution. 0.06 (s, 6H, $-Si-C\underline{H}_3$), 0.65 (d, 3H, J= 7.0Hz, $-C(C\underline{H}_3)_2$), 0.89 (s, 12H, $-Si-C(C\underline{H}_3)_3$, $-(CH_2)_9-C\underline{H}_3$), 0.91 (d, 3H, J= 7.0 Hz, $-CH(C\underline{H}_3)_2$), 1.1-1.6 (m, 18H, $-(C\underline{H}_2)_9-$), 2.35 (m, 1H, $-C\underline{H}(CH_3)_2$), 2.60 (s, 3H, $-COC\underline{H}_3$), 2.7-3.1 (m, 2H, $Ar-C\underline{H}_2$), 2.88 (s, 3H, $N-C\underline{H}_3$), 3.6-3.8 (m, 2H, $-C\underline{H}_2-OH$), 4.05 (d, 1H, J= 10.5 Hz, 12-C$\underline{H}$), 4.26 (bs, 1H, 9-C$\underline{H}$), 6.11 (s, 1H, 10-N$\underline{H}$), 6.71 (d, J=8.0 Hz, 5-C$\underline{H}$), 7.03 (s, 1H, 2-C$\underline{H}$), 7.04 (d, 1H, J=8.0 Hz, 6-C$\underline{H}$). MS 597 (M^+)

7-Decylindolactam-V (13) The procedure was similar to that used for the preparation of 11 employing 18 mg (0.03 mmol) of 12. After deprotection of N-acetyl and TBDMS group of 12, the crude product was purified by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (1:2) as eluent. Further purification by HPLC (polygocil 60-$_5C_{18}$, 4.5 mm X 250 mm, methanol-water 88:12) and freeze-drying gave 7.0 mg (63 %) of 7-decylindolactam-V as amorphous powder. ^{1}H-NMR (CD_3OD) Conformers TWIST and SOFA ratio was 7:8 in this solution; TWIST conformer: 0.63 (d, 3H, J= 6.7 Hz, $-CH(C\underline{H}_3)_2$), 0.89 (d, 3H, J= 6.7 Hz, $-CH(C\underline{H}_3)_2$), 0.84-0.96 (m, 3H, $-(CH_2)_8-C\underline{H}_3$), 1.17-1.75 (m, 16H, $-(C\underline{H}_2)_8-$), 2.54 (dsept, 1H, J= 6.7, 10.3 Hz, $-C\underline{H}(CH_3)_2$), 2.82 (t, 3H, J= 7.6 z, $Ar-C\underline{H}_2-(CH_2)_8-$), 2.87 (s, 3H, $N-C\underline{H}_3$), 3.04-3.15 (m, 2H, $Ar-C\underline{H}_2-$), 3.45 (dd, 1H, J=8.9, 11.2 Hz, $-C\underline{H}_2-OH$), 3.62 (dd, 2H, J= 4.4, 11.2 Hz, $-C\underline{H}_2-OH$), 4.25 (m, 1H, 9-C$\underline{H}$), 4.43 (d, 1H, J= 10.3 Hz, 12-C$\underline{H}$), 6.40 (d, 1H, J= 7.8 Hz, 5-C$\underline{H}$), 6.75 (d, 1H, J= 8.7 Hz, 6-C$\underline{H}$), 6.94 (s, 1H, 2-C$\underline{H}$) SOFA conformer: 0.89 (d, 3H, J= 6.7 Hz, $-CH(C\underline{H}_3)_2$), 0.84-0.96 (m, 3H, $-(CH_2)_8-C\underline{H}_3$), 1.24(d, 3H, J= 6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.17-1.75 (m, 16H, $-(C\underline{H}_2)_8-$), 2.30 (dsept, 1H, J= 6.7, 11.0 Hz, $-C\underline{H}(CH_3)_2$), 2.70 (s, 3H, $N-C\underline{H}_3$), 2.74 (t, 3H, J= 7.5 Hz, $-(CH_2)_8-C\underline{H}_3$), 2.87 (dd, 1H, J= 1.6, 14.4 Hz, $Ar-C\underline{H}_2-$), 3.00 (dd, 1H, J= 4.7, 14.4 Hz, $Ar-C\underline{H}_2-$), 3.06 (d, 1H, J= 11.0 Hz, 12-C$\underline{H}$), 3.23 (dd, 1H, J= 6.8, 11.0 Hz, $-C\underline{H}_2-OH$), 3.31 (dd, 1H, J= 7.8, 11.0 Hz, $-C\underline{H}_2-OH$), 4.25 (m, 1H, 9-C$\underline{H}$), 6.86 (d, 1H, J= 7.8 Hz, 5-C$\underline{H}$), 6.89 (d, 1H, J= 8.7 Hz, 6-C$\underline{H}$), 7.10 (s, 1H, 2-C$\underline{H}$) MS m/e 441.3360, calcd. for $C_{27}H_{43}N_3O_2$ 441.33529.

7-Iodoindolactam-V A 100 mg (0.33 mmol) of 3 was dissolved in 2 ml of pyridine and 2 ml of 1,4-dioxane. To the solution, 127 mg (1.0 mmol) of iodine was added with stirring at 0°C. After stirring for 1 h at 0°C, 43 mg (0.33 mmol) of iodine was added. The mixture was allowed to stand for 1 h. Removal of the solvent under reduced pressure and the residue was dissolved in $CH_3COOC_2H_5$ and washed with 3 % $Na_2S_2O_3$ solution. The organic layer was dried over $MgSO_4$ and concentrated to give a crude product. Purification by column chromatography on silica gel using $CH_2Cl_2-CH_3COOC_2H_5$ (1:1) to give 126 mg (89 %) of 7-iodoindolactam-V: mp 210°C (dec.)(methanol).

14-O-Acetyl-7-iodoindolactam-V (14) A mixture of 100 mg (0.23 mmol) of 7-iodoindolactam-V and 2 ml of acetic anhydride in 3 ml of pyridine was allowed to react at room temperature for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in 20 ml of $CH_3COOC_2H_5$ and the solution was washed with water, dried and concentrated. Purification by column chromatography on silica gel using $CH_2Cl_2-CH_3COC_2H_5$ (6:1) gave 99 mg (90 %) of 14-O-acetyl-7-iodoindolactam-V (14): colorless fine needles (ethanol-n-hexane), mp 178°C (dec.); ^{1}H-NMR ($CDCl_3$) Conformer TWIST and SOFA ratio was 4:1 in this solution. TWIST conformer: 0.64 (d, 3H, J=6.8, -

$CH(C\underline{H}_3)_2$), 0.93 (d, 3H, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 2.10 (s, 3H, $-COC\underline{H}_3$), 2.65 (dsept, 1H, J= 6.8, 10.0 Hz, $-C\underline{H}(CH_3)_2$), 2.92 (s, 3H, N-$C\underline{H}_3$), 3.10 (dd, 1H, J= 3.7 16.0 Hz, Ar-$C\underline{H}_2$-), 3.22 (d, 1H, J= 16.0 Hz, Ar-$C\underline{H}_2$-), 3.97 (dd, 1H, J=8.1, 11.6 Hz, $-C\underline{H}_2$-OH), 4.21 (dd, 1H, J= 3.6, 11.6 Hz, $-C\underline{H}_2$-OH), 4.25 (d, J=10.0 Hz, 12-C$\underline{H}$), 4.50 (m, 1H, 9-C$\underline{H}$), 6.04 (s, 1H, 10-N$\underline{H}$), 6.38 (d, 1H, J=8.1 Hz, 5-C$\underline{H}$), 6.97 (s, 1H, 2-C$\underline{H}$), 7.34 (d, 1H, J= 8.1 Hz, 6-C$\underline{H}$), 8.10 (s, 1H, 1-N$\underline{H}$) SOFA conformer: 0.94 (d, 3H, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.24 (d, 3H, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 2.01 (s, 3H, $-COC\underline{H}_3$), 2.40 (dsept, 1H, J= 6.8, 10.7 Hz, $-C\underline{H}(CH_3)_2$), 2.75 (s, 3H, N-$C\underline{H}_3$), 2.78 (d, 1H, J= 16.2 Hz, Ar-$C\underline{H}_2$-), 2.98 (d, 1H, J= 10.7 Hz, 12-C$\underline{H}$), 3.12 (dd, 1H, J= 3.6, 16.2 Hz, Ar-$C\underline{H}_2$-), 3.83-3.85 (m, 2H, $-C\underline{H}_2$-OH), 4.60 (m, 1H, 9-C$\underline{H}$), 4.70 (d, 1H, J=11.2 Hz, 10-N$\underline{H}$), 6.92 (d, 1H, J=8.1 Hz, 5-C$\underline{H}$), 7.04 (s, 1H, 2-C$\underline{H}$), 7.51 (d, 1H, J= 8.1 Hz, 6-C$\underline{H}$), 8.30 (s, 1H, 1-N$\underline{H}$); MS 469 (M^+); Anal. ($C_{19}H_{24}IN_3O_2$) C,H,N.

14-O-Acetyl-7-styrylindolactam-V (15) A mixture of 80 mg (0.17 mmol) of 14, 178 mg (1.7 mmol) of styrene, 2.8 mg (0.017 mmol) of $Pd(OCOCH_3)_2$, 10.4 mg (0.034 mmol) of tris(o-tolyl)phosphine and 86 mg (0.85 mmol) of triethylamine in 0.2 ml of acetonitrile was heated at 100°C in a sealded tube for 24 h. After removal of the solvent under reduced pressure , the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel using n-hexane-$CH_3COOC_2H_5$ (1:3) gave 55.2 mg (73 %) of a cis-trans mixture of 14-O-acetyl-7-styrylindolactam-V (15). MS (M^+) 445

7-Phenethylindolactam-V (16) A mixture of 40 mg (0.09 mmol) of 15 and 60 mg of 10 % Pd-charcoal in 10 ml of ethanol was stirred under 1 atm of H_2 at room temperature for 2.5 h, then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane-$CH_3COOC_2H_5$ 1:1) to give 37 mg (92 %) of 14-O-acetyl-7-phenethylindolactam-V : colorless needles, mp 170-172°C (ethanol-n-hexane); MS (M^+) 447. 35 mg (0.078 mol) of the acetate was dissolved in 10 ml of methanol. To the solution, 3.1 ml of 2N aqueous KOH solution was added with stirring. After stirring under Ar atmosphere for 1 h at room temperature, the solvent was removed under reduced pressure and the residue was dissolved in $CH_3COOC_2H_5$ and washed with water. The organic layer was dried over $MgSO_4$, concentrated and chromatographed on silica gel using n-hexane-$CH_3COOC_2H_5$ (1:2) to give 26 mg (82 %) of 7-phenethylindolactam-V: colorless fine needles, mp 221-222°C (ethanol-n-hexane); ^{1}H-NMR (CD_3OD) Conformers TWIST and SOFA ratio was 5:4 in this solution; TWIST conformer: 0.63 (d, 3H, J= 6.6 Hz, $-CH(C\underline{H}_3)_2$), 0.89 (d, 3H, J= 6.6 Hz, $-CH(C\underline{H}_3)_2$), 2.55 (dsept, 1H, J= 6.6, 10.2 Hz, $-C\underline{H}(CH_3)_2$), 2.87 (s, 3H, N-$C\underline{H}_3$), 2.80-3.17 (m, 6H, Ar-$C\underline{H}_2$-, Ar-$(C\underline{H}_2)_2$-Ar), 3.46 (dd, 1H, J=9.3, 11.0 Hz, $-CH_2$-OH), 3.63 (dd, 1H, J= 4.3, 11.0 Hz, $-C\underline{H}_2$-OH), 4.25 (m, 1H, 9-C$\underline{H}$), 4.43 (d, 1H, J= 10.2 Hz, 12-C$\underline{H}$), 6.37 (d, 1H, J= 7.7 Hz, 5-C$\underline{H}$), 6.70 (d, 1H, J= 7.7 Hz, 6-C$\underline{H}$), 6.95 (s, 1H, 2-C$\underline{H}$), 7.06-7.34 (m, 5H, phenyl) SOFA conformer: 0.89 (d, 3H, J= 6.6 Hz, $-CH(C\underline{H}_3)_2$), 1.24 (d, 3H, J= 6.6 Hz, $-CH(C\underline{H}_3)_2$), 2.30 (dsept, 1H, J= 6.6, 11.1 Hz, $-C\underline{H}(CH_3)_2$), 2.70 (s, 3H, N-$C\underline{H}_3$), 2.80-3.17 (m, 7H, Ar-$C\underline{H}_2$-, Ar-$(C\underline{H}_2)_2$-Ar, 12C$\underline{H}$), 3.23 (dd, 1H, J= 6.9, 11.1 Hz, $-CH_2$-OH), 3.31 (dd, 1H, J= 7.6, 11.1 Hz, $-C\underline{H}_2$-OH), 4.25 (m, 1H, 9-C$\underline{H}$), 6.89 (s, 2H, 5-C$\underline{H}$, 6-C$\underline{H}$), 7.11 (s, 1H, 2-C$\underline{H}$), 7.06-7.34 (m, 5H, phenyl); MS m/e 405.2400, Calcd. for $C_{25}H_{31}N_3O_2$ 405.2416.

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