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# Synthesis and Stereochemistry of Indolactam Congeners. Conformational Behavior of the Nine-membered Lactams.

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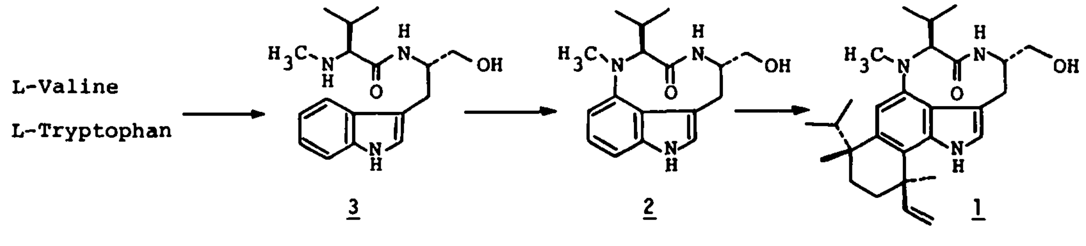
**Abstract:** The potent tumor promoters teleocidins and (-)-indolactam-V, which is a biologically active partial structure, exist in two conformational states (SOFA and TWIST forms) in solution. In order to examine the effect of the C-12 isopropyl group, a series of indolactams having a methyl, benzyl, isobutyl or tert-butyl group at the C-12 position instead of the isopropyl group have been synthesized. $^1$H-NMR measurements have shown that increasing bulkiness of the substituent on C-12 tends to increase the relative population of the SOFA conformer.

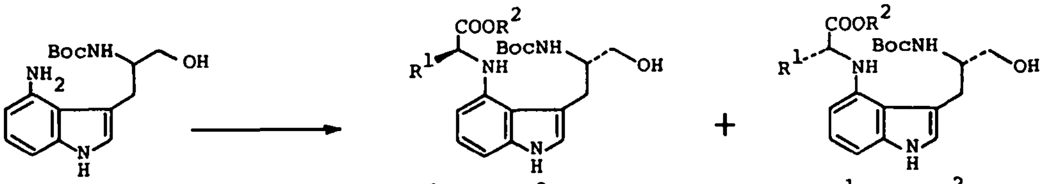
The two-stage initiation-promotion concept of tumor formation in mouse skin is now widely accepted.[1] Teleocidin derivatives such as teleocidin B-4 (**1**)[2] have been proved to be very potent skin tumor promoters.[3] (-)-Indolactam-V (**2**), which is an active fragment of teleocidins, has attracted much synthetic[4] and biological[5] interest. The teleocidins, including (-)-indolactam-V (**2**), bind strongly to the receptor of another tumor promoter, tetradecanoylphorbol acetate (TPA), and manifest a variety of very important epigenetic effects in vitro.[6]

Recently, we reported that teleocidins exist in two conformational states in solution.[7] The structures of the two conformers were deduced to be SOFA and TWIST forms, which are characterized by a trans and a cis amide bond, respectively. The relative stability of the two conformers seems to be affected by the bulkiness of the 12-isopropyl group. From the standpoint of biosynthesis, (-)-indolactam-V was isolated from Streptoverticillium blastmyceticum together with **1**,[8] and (-)-N-methylvalyltryptophanol (**3**: seco-compound of **2**) was isolated from Streptoverticillium olivoreticuli together with **1**,[9] which suggests that teleocidins are biosynthesized from L-tryptophan and L-valine through the route illustrated below. In this paper we describe a synthesis and conformational analysis of a series of indolactams having a substituent derived from other amino acids at the C-12 position in place of the isopropyl group.



We chose methyl, benzyl and isobutyl groups as the C-12 substituents as less bulky and hydrophobic groups similar to the isopropyl group. They can be derived from the amino acid, alanine, phenylalanine and leucine, respectively. We named the products indolactam-A (**4**), -F (**5**) and -L (**6**), respectively, using the IUPAC abbreviations of these amino acids. A tert-butyl group as the C-12 substituent was chosen as a bulkier group than isopropyl. It can be derived from a non-proteinous amino acid, tert-leucine, and was named indolactam-TL (**7**). Syntheses of these indolactams were carried out by essentially the same method as used for the synthesis of indolactam-V.[4,10]

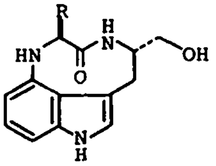
(±)-N-Boc-4-aminotryptophanol (**8**) was treated with ethyl pyruvate, and reduction of the product with sodium cyanoborohydride gave the diastereomeric methyl-substituted amino esters (**9**, 41%; **17**, 28%). Treatment of **8** with ethyl 2-bromophenylacetate gave the benzyl substituted amino esters (**10**, 36%; **18**, 28%). Condensation of **8** with methyl 2-oxoisocaproate, and followed by reduction with sodium cyanoborohydride gave the isobutyl-substituted amino esters (**11**, 43%; **19**, 26%). The amino esters (**9**, **10**, **11**) were hydrolyzed with aqueous KOH in methanol, and treated with N-hydroxysuccinimide-DCC in acetonitrile to give the activated esters (**13**, 52%; **14**, 60%; **15**, 55%), respectively. Condensation of **8** with ethyl 3,3-dimethyl-2-oxobutylate, followed by reduction gave the tert-butyl-substituted amino esters. The amino esters could not be hydrolyzed under various conditions because of the steric hindrance of the tert-butyl group. Thus, **8** was treated with benzyl 3,3-dimethyl-2-oxobutylate followed by reduction to give the amino esters (**12**, 15%; **20**, 27%). Hydrogenolysis of the benzyl ester of **12** with $H_2$/Pd-charcoal followed by treatment with N-hydroxysuccinimide-DCC gave the activated ester (**16**, 36%).



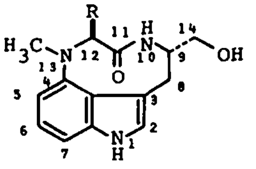
8

9 $R^1=CH_3$, $R^2=C_2H_5$
10 $R^1=CH_2C_6H_5$, $R^2=C_2H_5$
11 $R^1=CH_2CH(CH_3)_2$, $R^2=CH_3$
12 $R^1=C(CH_3)_3$, $R^2=CH_2C_6H_5$
13 $R^1=CH_3$, $R^2$=succinimide
14 $R^1=CH_2C_6H_5$, $R^2$=succinimide
15 $R^1=CH_2CH(CH_3)_2$, $R^2$=succinimide
16 $R^1=C(CH_3)_3$, $R^2$=succinimide

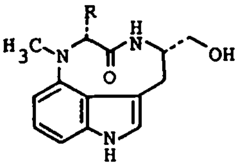
17 $R^1=CH_3$, $R^2=C_2H_5$
18 $R^1=CH_2C_6H_5$, $R^2=C_2H_5$
19 $R^1=CH_2CH(CH_3)_2$, $R^2=CH_3$
20 $R^1=C(CH_3)_3$, $R^2=CH_2C_6H_5$



21 R $=CH_3$
22 R $=CH_2C_6H_5$
23 R $=CH_2CH(CH_3)_2$
24 R $=C(CH_3)_3$



4 R $=CH_3$
5 R $=CH_2C_6H_5$
6 R $=CH_2CH(CH_3)_2$
7 R $=C(CH_3)_3$



25 R $=CH_3$
26 R $=CH_2C_6H_5$
27 R $=CH_2CH(CH_3)_2$
28 R $=C(CH_3)_3$

The activated esters (**13**, **14**, **15**, **16**) were treated with trifluoroacetic acid and then with weak aqueous alkali to give the corresponding lactams (**21**, 45%; **22**, 36%; **23**, 46%; **24**, 52%). N-Methylation of the lactams employing methyl iodide gave (±)-indolactam-A (**4**, 91%), -F (**5**, 77%), -L (**6**, 93%) and -TL (**7**, 75%). The diastereomeric esters (**17**, **18**, **19**, **20**) prepared from **8** were converted into (±)-epi-indolactam-A (**25**), -F (**26**), -L (**27**) and -TL (**28**) in a manner similar to that used for the preparation of the indolactams.

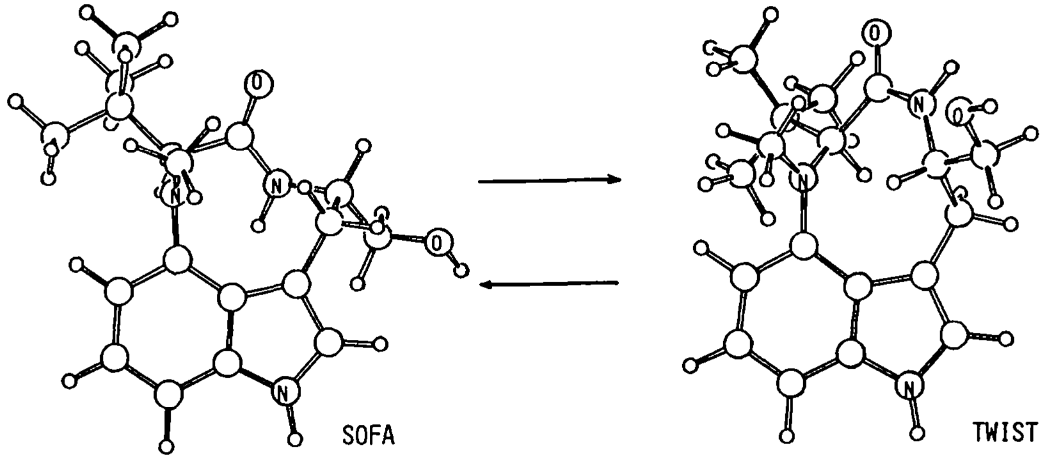
The $^1$H-NMR spectral data of indolactams in $CD_3OD$ are summarized in Table 1. Indolactam-V (**2**) exists as two conformers, SOFA and TWIST, in a ratio of 1:2.[7,10] The signals in the NMR spectra of indolactam-A (**4**) and indolactam-F (**5**) were not split, which indicates that a single conformer predominates. Detailed examination of the $^1$H-NMR spectrum of indolactam-L (**6**) in $CD_3OD$ led us to conclude that **6** exists as two conformers in a ratio of about 1:35. On the other hand, the $^1$H-NMR spectra of indolactam-TL (**7**) clearly indicated the existence of the two conformers in a ratio of 1:1 in $CD_3OD$ and 1:2 in $(CD_3)_2CO$. All the signals except for those of the C-12 substituents in the NMR spectra of **4**, **5**, the major conformer of **6** and one of the conformers of **7** could be assigned in accordance with those of the TWIST conformer of **2**. For example, the TWIST conformers were characterized by peaks at 6.43-6.62 ppm (assigned to H-5) and peaks at 4.48-5.00 ppm (assigned to H-12). The conformation of these signals were confirmed by the nuclear Overhauser effect (NOE) difference spectra. Saturation of the H-12 proton resulted in characteristic enhancement of the H-8a signal in all of **4**, **5**, the major conformer of **6** and one of the conformers of **7**. The extremely minor conformer of **6** and one of the conformers of **7** showed $^1$H-NMR signals consistent with those of the SOFA conformer of **2**. Although some peaks of the minor conformer of **6** were overlapped by the peaks of the major conformer, the chemical shifts and coupling constants of the peaks of the aromatic protons (H-2, H-6, H-7), H-8, H-14 and H-15 were similar to those of the SOFA conformer of **2**. All the peaks in the $^1$H-NMR spectrum of the conformer of **7** except for the tert-butyl proton at C-12 correspond to those of the SOFA conformer of **2**. The peaks of the protons on C-15 of both conformers of **7** were subject to low-field shielding in comparison with those of the two conformers of **2** because of the steric hindrance of the tert-butyl group. A conformational conversion of the two conformers was observed in the indolactam-TL acetate (**29**), which has quite similar chemical shifts to the two conformers of **2**; and the ratio of the two conformers was 1:1 in $CDCl_3$. When the $^1$H-NMR spectrum of **29** was recorded at -30°C by dissolving crystalline **29** (crystallized from ethanol) in $CDCl_3$ previously cooled to -40°C, only the peaks assigned to the SOFA conformer were detectable. When the solution was warmed to 23°C for 5 min and the spectrum was again recorded at -30°C, an equilibrated spectrum (SOFA:TWIST = 1:1) was obtained. The thermodynamic parameters of the conversion between the two conformers were determined by NMR measurements of the conversion rates from the SOFA conformer to the TWIST conformer. The rates were determined by the usual kinetic method of following the time-course at two temperature points, i.e. -10°C and +2°C, by a procedure similar to that used for the kinetic measurement of indolactam-V acetate. The rate constants of the conversion from the SOFA conformer to the TWIST conformer were $2.21 \times 10^{-4}$ $sec^{-1}$ at -10°C and $1.57 \times 10^{-3}$ $sec^{-1}$ at +2°C. This corresponds to a free energy of activation $\Delta G^{\#}$ of 19.7 kcal/mol at -10°C and 19.6 kcal/mol at +2°C. The enthalpy of activation $\Delta H^{\#}$ and the entropy of activation $\Delta S^{\#}$ were calculated to be 23.1 kcal/mol and +12.8 cal/K·mol, respectively. The thermodynamic parameters of

Table 1. $^1$H-NMR Chemical Schifts of (±)-Indolactam-V (2), -A (4), -F (5), -L (6) and -TL (7) in CD$_3$OD Solution at 23°C.*

| proton | indolactam-V | indolactam-A | indolactam-F | indolactam-L | indolactam-TL |
|---|---|---|---|---|---|
| TWIST:SOFA | 2:1 | | | 35:1 | 1:1 |
| TWIST | | | | | |
| $H_2$ | 6.94 (s) | 6.92-7.03 (m) | 6.88-6.98 (m) | 6.94-6.98 (m) | 6.93 (s) |
| $H_6$ | 6.95 (t,J=8.0) | | | | 6.95 (t,J=8.0) |
| $H_7$ | 6.88 (dd,J=8.0,1.1) | | | | 6.88 (dd,J=8.0,1.0) |
| $H_5$ | 6.44 (dd,J=8.0,1.1) | 6.62 (dd,J=6.0,2.0) | 6.43 (dd,J=7.3,2.0) | 6.52 (dd,J=5.9,2.6) | 6.57 (dd,J=8.0,1.1) |
| $H_8$ | 3.05 (dd,J=15.1,3.7) | 2.96 (dd,J=14.2,4.0) | 2.90 (dd,J=16.1,3.3) | 3.01 (dd,J=17.1,3.0) | 3.04-3.08 (m) |
| | 3.11 (dd,J=15.1,2.0) | 3.11 (dd,J=14.2,4.0) | 3.03 (dd,J=16.1,4.2) | 3.12 (dd,J=17.1,4.2) | |
| $H_9$ | 4.23 (m) | 4.81 (m) | 4.60 (m) | 4.64 (m) | 4.13 (m) |
| $H_{12}$ | 4.48 (d,J=10.5) | 4.51 (q,J=7.0) | 5.00 (dd,J=9.8,3.7) | 4.70 (t,J=7.0) | 4.74 (s) |
| $H_{14}$ | 3.45 (dd,J=11.3,9.0) | 3.53 (dd,J=11.2,8.0) | 3.47 (dd,J=11.2,8.0) | 3.50 (dd,J=11.4,5.0) | 3.45 (dd,J=11.1,8.8) |
| | 3.62 (dd,J=11.3,4.1) | 3.66 (dd,J=11.2,8.0) | 3.63 (dd,J=11.2,4.3) | 3.63 (dd,J=11.4,5.0) | 3.60 (dd,J=1.1,4.4) |
| N-C$\underline{H}_3$ | 2.88 (s) | 2.76 (s) | 2.87 (s) | 2.78 (s) | 3.11 (s) |
| C-12 substituent | 0.61 (d,3H,J=6.9) | 1.28 (s,3H) | 2.87 (dd,1H,J=13.7,3.9) | 0.59 (d,3H,J=6.8) | 1.02 (s,9H) |
| | 0.89 (d,3H,J=6.9) | | 3.34 (dd,1H,J=13.7,9.8) | 0.71 (d,3H,J=6.8) | |
| | 2.55 (dsept,1H,J=10.5,6.9) | | | 1.53 (m) | |
| | | | | 1.64 (ddd,1H) | |
| | | | | 1.77 (ddd,1H) | |
| SOFA | | | | | |
| $H_2$ | 7.11 (s) | | | 7.10 (s) | 7.11 (s) |
| $H_5$ | 6.95 (dd,J=8.0,1.1) | | | ? | 7.01-7.06 (m) |
| $H_6$ | 7.05 (t,J=8.0) | | | 7.07 (t,J=8.1) | |
| $H_7$ | 7.28 (dd,J=8.0,1.1) | | | 7.29 (dd,J=8.1,1.9) | 7.26 (dd,J=8.0,1.1) |
| $H_8$ | 2.87 (dd,J=15.0,1.8) | | | 2.88 (dd,J=14.5,2.3) | 2.90 (dd,J=12.6,3.0) |
| | 3.02 (dd,J=15.0,4.1) | | | ? | 3.04 (dd,J=12.6,5.0) |
| $H_9$ | 4.26 (m) | | | ? | 4.23 (m) |
| $H_{12}$ | 3.08 (d,J=12.0) | | | ? | 3.23 (s) |
| $H_{14}$ | 3.22 (dd,J=10.9,6.5) | | | 3.23 (dd,J=11.9,7.0) | 3.22 (dd,J=11.0,8.0) |
| | 3.30 (dd,J=10.9,7.9) | | | ? | 3.29 (dd,J=11.0,8.0) |
| N-C$\underline{H}_3$ | 2.77 (s) | | | 2.73 (s) | 2.96 (s) |
| C-12 substituent | 0.90 (d,3H,J=6.9) | | | 1.04 (d,6H,J=6.8) | 1.22 (s,9H) |
| | 1.24 (d,3H,J=6.9) | | | ? | |
| | 2.31 (dsept,1H,J=12.0,6.9) | | | | |

*Chemical shifts are shown by δ values from TMS. Coupling constants [Hz] are shown in parentheses.

the conversion between the two conformers of **29** were quite similar to those of indolactam-V acetate. The optimized structures obtained by empirical force field calculation using Allinger's MM2 program[11] for indolactam-TL (7) are illustrated in the Figure.



Indolactam-V (2) and teleocidins exist in two stable conformational states in solution. The two conformers, SOFA and TWIST forms, are characterized by the trans amide bond and cis amide bond, respectively. The free energy of activation for the conversion of SOFA and TWIST conformers of indolactam-V acetate was calculated to be 19.2 kcal/mol at -10°C by the usual kinetic method employing $^{1}$H-NMR measurements at low temperature.[10] A conformational analysis of a simple nine-membered lactam (azacyclononanone) has been done on the basis of IR[12] and NMR[13] studies. Azacyclononanone exists as an equilibrium mixture of cis and trans conformers in solution, and the free energy of activation for the conversion of the conformers was found to be 17 kcal/mol from the coalescence temperature of the carbonyl peaks. The presence of the C-12 substituent on indolactam-V as well as the fixation of four bondings by the indole ring seems to play a major role in the maintenance of the conformations. For instance, indolactam-G (no substituent on C-12) has been found in a conformational state other than TWIST and SOFA forms by X-ray crystallography and NMR spectroscopy (data mot shown). The relative amounts of the conformers and the conversion rates seem to be affected by the C-12 substituent. The present synthesis of indolactam-A, -F, -L, -TL shows experimentally that increasing bulkiness of the substituent on C-12 tends to increase the relative population of the SOFA conformer. The difference between the energy values for the SOFA form and the TWIST form ($\Delta$H(SOFA-TWIST)) was calculated to 0.92 kcal/mol for indolactam-A, 0.48 kcal/mol for indolactam-V and -0.82 kcal/mol for indolactam-TL by force field calculation using MM2, with torsional barriers of 20 kcal/mol and 9.5 kcal/mol for the amide bond and N-13 - C-4 bond, respectively. A detailed comparison of energy calculations in the gaseous state (MM2) with experimental measurements in solution would not be appropriate. However, the calculation shows a tendency for increase in the population of SOFA conformer when a bulky substituent is present at the C-12 position.

The conformation of biologically active compounds plays a critically important role in the appearance of the biological activity. Several classes of tumor promoters, diterpene esters (including TPA and 3TI), teleocidins and aplysiatoxins, appear to act by binding to the phorbol ester receptor, although their chemical structures are quite different. Recently, two computer modeling studies of the phorbol ester receptor have been described, based on the the similarity in the relative positions of certain heteroatoms and a hydrophobic group in the three chemical classes of tumor promoters.[14,15] In both reports, the X-ray conformation (corresponding to TWIST) was taken to be the active conformation of teleocidin. However, the free energy difference between the two conformers and the free energy of activation in the conversion of the two conformers indicate that the conformers are able to convert easily at room temperature. Thus, the possibility of two active conformers, the SOFA form and the TWIST form, of teleocidin should be considered in receptor mapping studies.[16]

## Experimental

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; IR spectra, JASCO DS-402G. NMR spectra were recorded with tetramethylsilane as an internal standard and the chemical shifts are given $\delta$ values from TMS. The IR data are presented in $cm^{-1}$. Column chromatography was performed on silica gel (Merck 7734 or 9385) and on aluminium oxide (Merck aluminium oxide 90 (neutral, activity II-III)).

**Methyl substituted amino esters (9 and 17)** A mixture of 2.01 g (6.58 mmol) of N-Boc-4-aminotryptophanol[10] and 1.54 g (13.2mmol) of ethyl pyruvate in 20 ml of chloroform was heated to reflux for 70 min under an Ar atmosphere. After removal of the solvent and excess ethyl pyruvate, the resulting brownish residue was dissolved in 30 ml of THF. Then, 1.33 g (21.1 mmol) of $NaBH_3CN$ was added portionwise with stirring at room temperature. The reaction mixture was stirred at room temperature for 12 h, poured into ice-water, acidified with 0.5 M aqueous citric acid and extracted with $CH_3COOC_2H_5$. The organic layer was dried over $MgSO_4$ and concentrated. Separation by column chromatography on silica gel using $CHCl_3$-$CH_3COOC_2H_5$ (3:2) as eluent gave two isomers. The less polar isomer was the ester 9 (1.09 g, 41%) and the more polar isomer was 17 (0.76 g, 28%). 9; yellow oil; IR (KBr) 1725 ($COOC_2H_5$), 1690 (NHCOO-), $^1$H-NMR ($CDCl_3$) 1.24 (t, 3H, J=7 Hz, $-CH_2-CH_3$), 1.45 (s, 9H, $-C(CH_3)_3$), 1.55 (d, J= 7 Hz, $-CH_3$), 3.14 (m, 2H, Ar-$CH_2$), 3.5-3.9 (m, 3H, $-CH_2$-OH and -CH), 4.12 (q, 1H, J=7 Hz, Ar-NH-CH), 4.20 (q, 2H, J=7 Hz,-O-$CH_2$-$CH_3$), 5.42 (bd, 1H, -NH-COO-), 6.11 (dd, 1H, J= 7.0, 1.3 Hz, 5-CH), 6.82 (dd, J= 7.0, 1.3 Hz, 7-CH), 6.9-7.1 (m, 2H, 2-CH, 6-CH), 8.16 (bs, 1H, 1-NH). 17; pale yellow oil; IR (KBr) 1725 ($COOC_2H_5$), 1690 (NHCOO-), $^1$H-NMR ($CDCl_3$) 1.24 (t, 3H, J=7 Hz, $-CH_2-CH_3$), 1.42 (s, 9H, $-C(CH_3)_3$), 1.57 (d, J= 7 Hz, $-CH_3$), 3.44-3.68 (m, 2H, Ar-$CH_2$), 3.68-3.92 (m, 3H, $-CH_2$-OH and -CH), 4.11 (q, 1H, J=7 Hz, Ar-NH-CH), 4.21 (q, 2H, J=7 Hz,-O-$CH_2$-$CH_3$), 5.30 (bd, 1H, -NH-COO-), 6.24 (dd, 1H, J= 7.0, 1.3 Hz, 5-CH), 6.84 (dd, J= 8.0, 1.3 Hz, 7-CH), 6.90 (bs, 1H, 2-CH), 7.00 (dd, 1H, J= 8.0, 7.0 Hz, 6-CH), 8.15 (bs, 1H, 1-NH).

**Benzyl substituted amino esters (10 and 18)** A mixture of 1.55 g (5.1 mmol) of 8 and 2.61 g (10.2 mmol) of ethyl 2-bromo-3-phenylpropionate and 1.27 g (15.3 mmol) of $NaHCO_3$ in 15 ml of ethanol was heated to reflux for 48 h under an Ar atmosphere. Then, 1.30 g of the bromoester and 0.5 g of $NaHCO_3$ was added and refluxed for 24 h. After removal of the solvent, the mixture was partitioned between $CH_3COOC_2H_5$ and water, and the organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent and separation by chromatography on silica gel using $CHCl_3$-$CH_3COOC_2H_5$ (4:1) as eluent gave two isomers. The less porlar isomer was the ester 10 (884 mg, 36%) and the more polar isomer was the ester 18 (690 mg, 28%). 10; pale yellow oil; $^1$H-NMR ($CDCl_3$) 1.16 (t, 3H, J=7 Hz, $-CH_2-CH_3$), 1.48 (s, 9H, $-C(CH_3)_3$), 3.0-3.3 (m, 4H, Ar-$CH_2$ X 2), 3.5-3.9 (m, 3H, $-CH_2$-OH and CH), 4.13 (q, 2H, J=7 Hz, -O-$CH_2$-$CH_3$), 4.44 (bt, 1H, Ar-NH-CH-), 5.25(bs, 1H, NH-COO-), 6.20 (d, 1H, J= 7 Hz, 5-CH), 6.7-7.1 (m, 3H, 2-CH, 6-CH, 7-CH), 7.25 (s, 5H, Ph), 8.13 (bs, 1H, 1-NH). 18; pale yellow oil; $^1$H-NMR ($CDCl_3$) 1.16 (t, 3H, J=7 Hz, $-CH_2-CH_3$), 1.40 (s, 9H, $-C(CH_3)_3$), 3.0-3.35 (m, 4H, Ar-$CH_2$ X 2), 3.4-3.6 (m, 2H, $-CH_2$-OH), 3.6-4.0 (m, 1H, -CH), 4.12 (q, 2H, J=7 Hz, -O-$CH_2$-$CH_3$), 4.45 (bt, 1H, Ar-NH-CH-), 5.10 (bs, 1H, NH-COO-), 6.22 (d, 1H, J= 7 Hz, 5-CH), 6.7-7.1 (m, 3H, 2-CH, 6-CH, 7-CH), 7.24 (s, 5H, Ph), 8.08 (bs, 1H, 1-NH).

**Isobutyl substituted amino esters (11 and 19)** The procedure was the similar as that used for the preparation of 9 and 17. After condensation of 8 (1.80 g, 5.9 mmol) with methyl 2-oxoisocaproate (2.5 g, 16.8 mmol) for 9 h and reduction with $NaBH_3CN$, the crude product was separated by column chromatography on silica gel using $CHCl_3$-$CH_3COOC_2H_5$ (3:1) as eluent to give a less polar isomer (11, 1.09 g, 43%) and a more polar isomer (19, 0.67 g, 26%). 11; pale yellow oil; IR (KBr) 1730 ($-COOCH_3$), 1690 (-NHCOO-), $^1$H-NMR ($CDCl_3$) 0.97 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.03 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.45 (s, 9H, $-C(C\underline{H}_3)_3$), 1.5-1.8 (m, 3H, $-C\underline{H}_2-C\underline{H}(CH_3)_2$), 2.8-3.2 (m, 2H, $Ar-C\underline{H}_2-$), 3.4-3.7 (m, 3H, $-C\underline{H}_2-OH$ and $-C\underline{H}$), 3.72 (s, 3H, $-COOC\underline{H}_3$), 4.22 (bt, 1H, J=6 Hz, $Ar-NH-C\underline{H}-$), 5.3 (bs, 1H, $-N\underline{H}COO-$), 6.16 (dd, 1H, J=7.0, 1.0 Hz 5-C$\underline{H}$), 6.76 (dd, 1H, J=7.0, 1.0 Hz, 7-C$\underline{H}$), 6.93 (d, 1H,J= 2.0 Hz, 2-C$\underline{H}$), 6.96 (t, 1H, J=7.0 Hz, 6-C$\underline{H}$), 9.10 (bs, 1H, 1-N$\underline{H}$). 19; pale yellow oil; IR (KBr) 1730 ($-COOCH_3$), 1690 (-NHCOO-), $^1$H-NMR ($CDCl_3$) 0.97 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.03 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.42 (s, 9H, $-C(C\underline{H}_3)_3$), 1.5-1.9 (m, 3H, $-C\underline{H}_2-C\underline{H}(CH_3)_2$), 2.8-3.3 (m, 2H, $Ar-C\underline{H}_2-$), 3.3-3.6 (m, 2H, $-C\underline{H}_2-OH$), 3.72 (s, 3H, $-COOC\underline{H}_3$), 3.8-4.0 (m, 1H, $-C\underline{H}$), 4.20 (bt, 1H, J=6 Hz, $Ar-NH-C\underline{H}-$), 5.1 (bs, 1H, $-N\underline{H}COO-$), 6.21 (d, 1H, J=7.0 Hz 5-C$\underline{H}$), 6.80 (d, 1H, J=7.0 Hz, 7-C$\underline{H}$), 6.87 (d, 1H,J= 2.0 Hz, 2-C$\underline{H}$), 7.00 (t, 1H, J=7.0 Hz, 6-C$\underline{H}$), 8.10 (bs, 1H, 1-N$\underline{H}$).

**Tert-butyl substituted amino esters (12 and 20)** The procedure was similar to that used for the preparation of 9 and 17. After condensation of 8 (2.50 g, 8.20 mmol) with benzyl 3,3-dimethyl-2-oxo-butyrate (5.41 g, 24.9 mol) for 4 days and reduction with $NaBH_3CN$, the crude product was separated by column chromatography on silica gel using $CHCl_3$-$CH_3COOC_2H_5$ (3:1) as eluent to give a less polar isomer (12, 0.61 g, 15%) and a more polar isomer (20, 1.11 g, 27%). 12; pale yellow oil; IR (KBr) 1720 ($COOCH_2Ph$), 1695 (NHCOO-), $^1$H-NMR ($CDCl_3$) 1.13 (s, 9H, $-C(C\underline{H}_3)_3$), 1.44 (s, 9H, Boc-$C(C\underline{H}_3)_3$), 3.1-3.3 (m, 2H, $Ar-C\underline{H}_2-$), 3.5-3.65 (m,2H, $-C\underline{H}_2-OH$), 3.7-3.8 (m, 1H, aliphatic C$\underline{H}$), 4.03 (bs, 1H, $Ar-NH-C\underline{H}-$), 5.13 (bs, 1H, $N\underline{H}COO-$), 5.15 (s, 2H, $-O-C\underline{H}_2-Ph$), 6.24 (d, 1H, J=8 Hz, 5-C$\underline{H}$), 6.7-7.1 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$), 7.32 (s, 5H, $-O-CH_2-\underline{Ph}$), 8.03 (bs, 1H, 1-N$\underline{H}$). 20; pale yellow oil; IR (KBr) 1720 ($COOCH_2Ph$), 1695 (NHCOO-), $^1$H-NMR ($CDCl_3$) 1.12 (s, 9H, $-C(C\underline{H}_3)_3$), 1.38 (s, 9H, Boc-$C(C\underline{H}_3)_3$), 3.1-3.3 (m, 2H, $Ar-C\underline{H}_2-$), 3.5-3.7 (m,2H, $-C\underline{H}_2-OH$), 3.8-4.0 (m, 1H, aliphatic C$\underline{H}$), 4.03 (bs, 1H, $Ar-NH-C\underline{H}-$), 5.00 (bs, 1H, $N\underline{H}COO-$), 5.12 (s, 2H, $-O-C\underline{H}_2-Ph$), 6.28 (d, 1H, J=8 Hz, 5-C$\underline{H}$), 6.7-7.1 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$), 7.29 (s, 5H, $-O-CH_2-\underline{Ph}$), 8.05 (bs, 1H, 1-N$\underline{H}$).

**Activated ester (13)** A mixture of a solution of 690 mg (1.70 mmol) of 9 in 25 ml of methanol and 8 ml of 2N aqueous KOH solution was kept at room temperature for 12 h. Methanol was evaporated off in vacuo and the residue was diluted with 5 ml of ice-water. The aqueous solution was acidified with 0.5 M cidric acid aq. solution at 0°C, and extracted with $CH_3COOC_2H_5$. The extract was washed twice with water and dried over $MgSO_4$ and concentrated to give the crude acid. The acid and 350 mg (3.04 mmol) of N-hydroxysuccinimide were dissolved in 2 ml of $CH_3CN$, and then a solution of 562 mg (2.73 mmol) of dicyclohexylcarbodiimide (DCC) in 3.5 ml of $CH_3CN$ was added at 0 °C with stirring. Stirring was continued for 90 min at 0°C, then the solvent was removed in vacuo and the residue was dissolved in $CH_3COOC_2H_5$. A precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated. The residue was dissolved in $CH_2Cl_2$ and the solution was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using n-hexane-$CH_2Cl_2$-$CH_3COO_2H_5$ (1:1:3) as eluent to give the activated ester (13) (445 mg, 52%). 13; pale yellow oil; IR (KBr) 1735 (-COOSu), 1695 (-NHCOO-); $^1$H-NMR ($CDCl_3$) 1.45 (s, 9H, $-CH(C\underline{H}_3)_3$), 1.76 (d, 3H, J=7 Hz, $-C\underline{H}_3$), 2.76 (s, 4H, $-CO-C\underline{H}_2-C\underline{H}_2-CO-$), 3.0-3.2 (m, 2H, $Ar-C\underline{H}_2-$), 3.4-3.8 (m, 3H, $-C\underline{H}_2-OH$ and $-C\underline{H}$), 4.60 (bq, 1H, $Ar-NH-C\underline{H}-$), 5.30 (bd, 1H, $-N\underline{H}-COO-$), 6.32 (dd, 1H, J=8, 3 Hz, 5-C$\underline{H}$), 6.74-7.12 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$), 8.12 (bs, 1H, 1-N$\underline{H}$).

**Activated ester (14)** The procedure was the same as that used for the preparation of 13, employing 797 mg (1.66 mmol) of 10, 25 ml of methanol, and 8 ml of 2 N aqueous KOH solution. An acid was isolated and converted to the activated ester (14), using 382 mg (3.32 mmol) of N-hydroxysuccinimide, 5 ml of $CH_3CN$ and 513 mg (2.49 mmol) of DCC, to give 548 mg (60%) of the activated ester (14); IR (KBr) 1730 ($-COOC_2H_5$), 1690 (-NHCOO-); $^1$H-NMR ($CDCl_3$) 1.48 (s, 9H, $-CH(C\underline{H}_3)_3$), 2.80 (s, 4H, $-CO-C\underline{H}_2-C\underline{H}_2-CO-$), 2.9-3.2 (m, 2H, $Ar-C\underline{H}_2-$), 3.35-3.8 (m, 5H, $-C\underline{H}_2-OH$, $-C\underline{H}$ and $-C\underline{H}_2Ph$), 4.8 (bs, 1H, $Ar-NH-C\underline{H}-$), 5.10 (bd, 1H, $-N\underline{H}-COO-$), 6.32 (d, 1H, J=8 Hz, 5-C$\underline{H}$), 6.85-6.95 (m, 2H, 2-C$\underline{H}$, 7-C$\underline{H}$), 7.04 (t,1H,J=8 Hz, 6-C$\underline{H}$), 7.2-7.5 (m, 5H, $-CH_2-\underline{Ph}$), 8.04 (bs, 1H, 1-N$\underline{H}$).

**Activated ester (15)** The procedure was the same as that used for the preparation of 13, employing 1.06 g (2.45 mmol) of 11, 25 ml of methanol, and 6 ml of 2 N aqueous KOH solution for 48 h. An acid was isolated and converted to the activated ester (15), using 432 mg (3.76 mmol) of N-hydroxysuccinimide, 8 ml of $CH_3CN$ and 763 mg (3.70 mmol) of DCC, to give 720 mg (55%) of the activated ester (15); IR (KBr) 1735 ($-COOCH_3$), 1695 (-NHCOO-); $^1$H-NMR ($CDCl_3$) 0.99 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.06 (d, 3H, J=7 HZ, $-CH(C\underline{H}_3)_2$), 1.48 (s, 9H, $-CH(C\underline{H}_3)_3$), 1.96-2.3 (m, 3H, $-C\underline{H}-C\underline{H}-(CH_3)_2$), 2.76 (s, 4H, $-CO-C\underline{H}_2-C\underline{H}_2-CO-$), 3.0-3.3 (m, 2H, $Ar-C\underline{H}_2-$), 3.4-3.9 (m, 3H, $-C\underline{H}_2-OH$, $-C\underline{H}$ ) 4.52 (bs, 1H, $Ar-NH-C\underline{H}-$), 5.30 (bd, 1H, $-N\underline{H}-COO-$), 6.36 (dd, 1H, J=7, 1 Hz, 5-C$\underline{H}$), 6.81 (dd, 1H, J=7, 1 Hz, 7-C$\underline{H}$), 6.91 (d, 1H, J=2 Hz, 2-C$\underline{H}$), 7.05 (t,1H,J=7 Hz, 6-C$\underline{H}$), 8.10 (bs, 1H, 1-N$\underline{H}$).

**Activated ester (16)** 587 mg (1.15 mmol) of 12 was dissolved in 120 ml of $CH_3COOC_2H_5$ containing 1 % water and was added 700 mg of 10 % Pd-charcoal. The suspension was vigorously stirred under 1 atm of $H_2$ at room temperature for 2 h, then filtered. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue (422 mg, 1.01 mmol) and 174 mg (1.51 mmol) of N-hydroxysuccinimide were dissolved in 2 ml of $CH_3CN$ and then a solution of 260 mg (1.26 mmol) of DCC in 2 ml of $CH_3CN$ was added at 0°C with stirring. Stirring was continued for 8 h at room temperature, then the solvent was removed *in vacuo* and the residue was dissolved in $CH_3COOC_2H_5$. A precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated. The residue was dissolved in $CH_2Cl_2$ and the solution was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using n-hexane-$CH_3COOC_2H_5$ (1:3) as eluent to give the activated ester (16) (206 mg, 36%). IR (KBr) 1735 (-$COOCH_3$), 1700 (-NHCOO-); $^1$H-NMR ($CDCl_3$-DMSO-$d_6$) 1.27(s, 9H, CH-C(C$\underline{H}_3$)$_3$), 1.44 (s, 9H, -O-CH(C$\underline{H}_3$)$_3$), 2.81 (s, 4H, -CO-C$\underline{H}_2$-C$\underline{H}_2$-CO-), 3.1-3.3 (m, 2H, Ar-C$\underline{H}_2$-), 3.4-3.7 (m, 3H, -C$\underline{H}_2$-O$\underline{H}$), 3.7-3.9 (m, 1H, -C$\underline{H}$), 4.24 (bd, 1H, Ar-NH-C$\underline{H}$-), 5.36 (bd, 1H, -N$\underline{H}$-COO-), 5.48 (bd, 1H, Ar-N$\underline{H}$), 6.42 (d, 1H, J=7 Hz, 5-C$\underline{H}$), 6.76-7.12 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$), 9.02 (bs, 1H, 1-N$\underline{H}$).

**Lactam (21)** Trifluoroacetic acid (4 ml) was added to a solution of 421 mg (0.873 mmol) of 13 in 4 ml of $CH_2Cl_2$ at 0°C with stirring. The mixture was stirred for 2 h, at 0°C under Ar atmosphere, then the trifluoroacetic acid was removed *in vacuo* at below 30°C. The residue was dissolved in 200 ml of $CH_3COOC_2H_5$, then 5 ml of saturated aqueous $NaHCO_3$ solution was adedd and the mixture was stirred for 5 h at room temperature. The organic layer was separated , washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on neutral aluminium oxide using $CH_3COOC_2H_5$-$CH_3OH$ (17:3) as eluent to afford 100 mg (45%) of the lactam (21). mp 224-227°C (from $C_2H_5OH$); IR (KBr) 1640 (CONH); $^1$H-NMR ($CD_3OD$) 1.54 (d, 3H, J=7 Hz, -C$\underline{H}_3$), 2.90-3.16 (m, 2H, Ar-C$\underline{H}_2$-), 3.5-3.9 (m, 3H, -C$\underline{H}$-C$\underline{H}_2$-OH), 4.11 (q, 1H, J=7 Hz, Ar-NH-C$\underline{H}$), 6.63 (dd, 1H, J= 7, 2Hz, 5-C$\underline{H}$), 6.82-7.10 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$); MS 259 ($M^+$);

**Lactam (22)** The procedure was the same as that used for the preparation of 21, employing 538 mg (0.98 mmol) of 14, 5 ml of $CH_2Cl_2$ and 5 ml of trifluoroacetic acid. After work-up, a residue was treated with 300 ml of $CH_3COOC_2H_5$ and 10 ml of saturated aqueous $NaHCO_3$ solution at refluxing temperature for 30 min and purified by column chromatography on aluminium oxide using $CHCOOC_2H_5$-$CH_3OH$ (23:2) as eluent to give 118 mg (36%) of the lactam (22). mp 220-223°C (from $C_2H_5OH$); IR (KBr) 1630 (CONH); $^1$H-NMR ($CD_3OD$) 2.8-3.2 (m, 4H, Ar-C$\underline{H}_2$- X 2), 3.4-3.7 (m, 2H, -CH-C$\underline{H}_2$-OH), 4.10 (t, 1H, J=8 Hz, Ar-NH-C$\underline{H}$), 5.08-5.4 ( m,1H, -C$\underline{H}$), 6.39 (dd, 1H, J= 7, 2Hz, 5-C$\underline{H}$), 6.7-7.1 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$), 7.1-7.5 (m, 5H, -CH$_2$-$\underline{Ph}$); MS 335 ($M^+$);

**Lactam (23)** The procedure was the same as that used for the preparation of 21, employing 700 mg (1.32 mmol) of 15, 5 ml of $CH_2Cl_2$ and 5 ml of trifluoroacetic acid. After work-up, a residue was treated with 350 ml of $CH_3COOC_2H_5$ and 10 ml of saturated aqueous $NaHCO_3$ solution at refluxing temperature for 3 h and purified by column chromatography on silica gel using $CH_3COOC_2H_5$ as eluent to give 181 mg (46%) of the lactam (23). mp 220.5-221.5°C (from $CH_3COOC_2H_5$); IR (KBr) 1620 (CONH); $^1$H-NMR ($CD_3OD$) 0.93 (d, 3H, J=7 Hz,-CH(C$\underline{H}_3$)$_2$), 1.01 (d, 3H, J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 1.70-1.95 (m, 3H, -C$\underline{H}$-C$\underline{H}_2$(CH$_3$)$_2$), 2.9-3.15 (m, 2H, Ar-C$\underline{H}_2$-), 3.5-3.8 (m, 2H, -CH-C$\underline{H}_2$-OH), 4.03 (t, 1H, J=7 Hz, Ar-NH-C$\underline{H}$), 5.1-5.4 ( m,1H, -C$\underline{H}$), 6.64 (dd, 1H, J= 7, 1Hz, 5-C$\underline{H}$), 6.8-7.1 (m, 3H, 2-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$); MS 301 ($M^+$);

**Lactam (24)** The procedure was the same as that used for the preparation of 21, employing 197 mg (0.38 mmol) of 16, 3 ml of $CH_2Cl_2$ and 3 ml of trifluoroacetic acid. After work-up, a residue was treated with 150 ml of $CH_3COOC_2H_5$ and 5 ml of saturated aqueous $NaHCO_3$ solution at refluxing temperature for 3 h and purified by column chromatography on silica gel using $CH_3COOC_2H_5$ as eluent to give 60 mg (60%) of the lactam (24). mp 225-228°C (from $CH_3COOC_2H_5$); IR (KBr) 1645 (CONH); $^1$H-NMR ($CD_3OD$) 1.21 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.76-3.22 (m, 2H, Ar-C$\underline{H}_2$-), 3.6-3.8 (m, 2H, -CH-C$\underline{H}_2$-OH), 4.10-4.30 (m, 1H, Ar-NH-C$\underline{H}$), 6.5-7.3 (m, 4H, 2-C$\underline{H}$, 5-C$\underline{H}$, 6-C$\underline{H}$, 7-C$\underline{H}$); MS 301 ($M^+$);

**Indolactam-A (4)** A mixture of 24.6 mg (0.095 mmol) of 21, 67 mg (0.80 mmol) of $NaHCO_3$ and 6 ml of $CH_3I$ in 2 ml of $CH_3OH$ was heated to reflux for 9 h under an Ar atmosphere. The solvent was removed *in vacuo* and the residual solid was partitioned betwen $CH_3COOC_2H_5$ and water. The organic layer was dried over $MgSO_4$ and concentrated to give crude 4. Purification by column chromatography on silica gel using $CH_3COOC_2H_5$ as eluent gave (±)-indolactam-A (4). (23.3 mg, 90%); mp 204-207°C (from $CH_3COOC_2H_5$- n-hexane); $^1$H-NMR ($CD_3OD$) signals are given in the text; MS 273 ($M^+$); Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. found: C, 65.64; H, 7.13; N, 15.11.

**Indolactam-F (5)** The procedure was the same as that used for the preparation of 4 employing 78 mg (0.23 mmol) of 22, 58 mg (0.69 mmol) of $NaHCO_3$, 5 ml of $CH_3I$ and 2 ml of $CH_3OH$ for 24 h at refluxing temperature. The yield of (±)-indolactam-F (5) was 53 mg (66%): mp 196-198°C (from $CH_3COOC_2H_5$- n-hexane); $^1$H-NMR ($CD_3OD$) signals are described in the text; MS m/e 349.1772, calcd. for $C_{21}H_{23}N_3O_2$ 349.1787.

**Indolactam-L (6)** The procedure was the same as that used for the preparation of 4 employing 92 mg (0.31 mmol) of 23, 78 mg (0.93 mmol) of $NaHCO_3$, 5 ml of $CH_3I$ and 2 ml of $CH_3OH$ for 40 h at refluxing temperature. The yield of (±)-indolactam-L (6) was 90 mg (93%): mp 230-233°C (from benzene); $^1$H-NMR ($CD_3OD$) signals are described in the text; MS 315 ($M^+$); Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.54; H, 8.05; N, 13.32.

**Indolactam-TL (7)** The procedure was the same as that used for the preparation of 4 employing 50 mg (0.17 mmol) of 24, 43 mg (0.51 mmol) of $NaHCO_3$, 5 ml of $CH_3I$ and 2 ml of $CH_3OH$ for 6 days at refluxing temperature. The yield of (±)-indolactam-TL (7) was 40 mg (70%): mp 245-247°C (from benzene); $^1$H-NMR ($CD_3OD$) signals are described in the text; MS 315 ($M^+$); Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.82; H, 8.16; N, 13.09.

**Indolactam-TL acetate (29)** A mixture of 13 mg (0.041 mol) of 7 and 1 ml of acetic anhydride in 1 ml of pyridine was allowed to react at room temperature for 18 h. After removal of the solvent *in vacuo*, the residue was dissolved in 10 ml of $CH_3COOC_2H_5$ and the solution was washed with water, dried and concentrated. Purification by column chromatography on silica gel using $CH_2Cl_2$-$CH_3COOC_2H_5$ (9:1) gave 12.8 mg (82%) of indolactam-TL acetate (29). mp 191-193°C (from $C_2H_5OH$).

**Epi-indolactam-A (25), F (26), L (27) and TL (28)** The procedure was the same as that used for the preparation of indolactams. 25: mp 212-215°C (from $CH_3COOC_2H_5$- n-hexane); $^1$H-NMR ($CD_3OD$); Two conformers existed in a ratio of 3:1. Signals due to the major conformer were assigned as follows. 1.21 (d, 3H, J=7 Hz, $-C\underline{H}_3$), 2.78 (s, 3H, $N-C\underline{H}_3$), 2.83 (dd, 1H, J=15, 4Hz, $Ar-C\underline{H}_2-$), 3.34 (dd, 1H, $Ar-C\underline{H}_2-$), 3.65-3.75 (m, 3H, $-C\underline{H}-C\underline{H}_2-OH$), 4.27 (q, 1H, J=7 Hz, $Ar-N-C\underline{H}$), 6.80 (d, 1H, J= 7 Hz, $5-C\underline{H}$), 6.9-7.15 (m, 3H, $2-C\underline{H}$, $6-C\underline{H}$, $7-C\underline{H}$); MS 273 ($M^+$); Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.64; H, 7.05; N, 15.23. 26: mp 218-220°C (from benzene); $^1$H-NMR ($CD_3OD$) 2.87 (dd, 1H, J=16.9, 4.9 Hz, $Ar-C\underline{H}_2-$), 2.94(dd, 1H, J=16.9, 4.9 Hz, $Ar-C\underline{H}_2-$) 2.94 (s, 3H, $N-C\underline{H}_3$), 3.30 (dd, 1H, J=16.9, 3.9 Hz, $Ar-C\underline{H}_2-$), 3.42 (dd, 1H, J=16.9, 10.0 Hz, $Ar-C\underline{H}_2-$), 3.42 (m, 1H, $-C\underline{H}$), 3.54-3.63 (m, 2H, $-CH-C\underline{H}_2-OH$), 4.41 (dd, 1H, J=10.0, 4.9 Hz, $Ar-N-C\underline{H}$), 6.80 (dd, 1H, J= 7.3,1.0 Hz, $5-C\underline{H}$), 6.90-6.95 (m, 3H, $2-C\underline{H}$, $6-C\underline{H}$, $7-C\underline{H}$), 7.00-7.11 (m, 5H, $-CH_2-\underline{Ph}$); Anal. Calcd. for $C_{21}H_{23}N_3O_2\cdot 1/2C_6H_6$: C, 74.20; H, 6.75; N, 10.82. Found: C, 74.30; H, 6.81; N, 10.61. MS m/e 349.1773, Calcd. for $C_{21}H_{23}N_3O_2$ 349.1787. 27: mp 163-165°C (from benzene-n-hexane); $^1$H-NMR ($CD_3OD$) 0.61 (d, 3H, J=7 Hz,$-CH(C\underline{H}_3)_2$), 0.74 (d, 3H, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.29-1.43 (m, 2H, $-C\underline{H}_2-C\underline{H}(CH_3)_2$), 2.04 (dd, 1H, J=10.0, 8.0 Hz, $-C\underline{H}_2CH(CH_3)_2$), 2.83 (s, 3H, $N-C\underline{H}_3$), 2.87 (dd, 1H, J=14, 3 Hz, $Ar-C\underline{H}_2-$), 3.2-3.4 (m, 1H, $Ar-C\underline{H}_2$), 3.65-3.78 (m, 3H, $-C\underline{H}-C\underline{H}_2-OH$), 4.24 (dd, 1H, J=10, 3 Hz, $Ar-N-C\underline{H}$), 6.73 (d, 1H, J= 7 Hz, $5-C\underline{H}$), 6.94 (s, 1H, $2-C\underline{H}$), 6.98 (t, 1H, J=7 Hz, $6-C\underline{H}$), 7.03(d, 1H, J=7 Hz, $7-C\underline{H}$); MS 315 ($M^+$); Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.31; H, 8.13; N, 13.25.28: mp 171-173°C (from benzene); $^1$H-NMR ($CD_3OD$) 0.95(s, 9H, $-C(C\underline{H}_3)_3$), 2.94 (dd, 1H, J=15, 2 Hz, $Ar-C\underline{H}_2-$), 3.03 (dd, 1H, J=15, 3 Hz, $Ar-C\underline{H}_2-$), 3.29 (s, 3H, $N-C\underline{H}_3$), 3.69-3.77 (m, 3H, $-C\underline{H}-C\underline{H}_2-OH$), 4.41 (s, 1H, $Ar-N-C\underline{H}$), 6.78 (m, 1H, $5-C\underline{H}$), 6.92-6.97 (m, 3H, $2-C\underline{H}$, $6-C\underline{H}$, $7-C\underline{H}$); MS 315 ($M^+$); Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.83; H, 7.97; N, 13.03.

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16) A study entitled "A receptor model for tumor promoters. Superposition of phorbol esters and teleocidins" will shortly be published by Itai, A. et al.