Synthesis, Conformation, and Biological Activity of Teleocidin Mimics, Benzolactams. A Clarification of the Conformational Flexibility Problem in Structure−Activity Studies of Teleocidins

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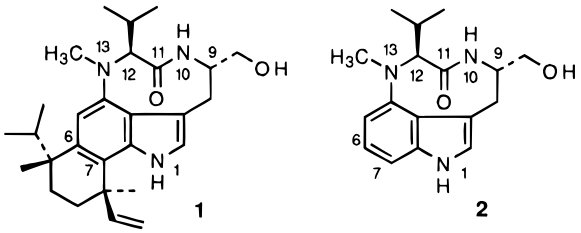
Abstract: Tumor-promoter teleocidins and their active congeners (indolactams) are known to exist in an equilibrium between at least two conformational states in solution, the twist and sofa form, due to *cis*−*trans* isomerization of the amide bond and the steric effects of substituents on the nine-membered lactam ring. Benzolactam-Vs, in which the indole ring of indolactams is replaced with a benzene ring, were designed and synthesized in an attempt to reproduce the active conformation of teleocidins. Among these benzolactams, eight-membered lactams (benzolactam-V8) can only exist in the twist form, and 9- and 10-membered lactams (benzolactam-V9 and -V10) exist exclusively in the sofa form in solution. The stronger biological activity of benzolactam-V-8-310 than that of indolactam-V (IL-V) and the inactivity of benzolactam-V-9-310 for differentiation inducing activity of HL-60 clearly indicated that the twist form is close to the active conformation of teleocidins.

Introduction

The teleocidins (teleocidin B-4, **1**) are a family of TPA-type tumor promoters[1] which includes diterpene esters represented by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and aplysiatoxins. (−)-Indolactam-V (IL-V, **2**), which lacks the hydrophobic group at the 6,7-position of the indole ring of teleocidins, was synthesized by us[2] and was later isolated from *Streptoverticillium blastmyceticum*.[3] IL-V is considered to be the minimum-sized structure exhibiting tumor-promoter activity,[4] and the synthesis of IL-V has become of interest in recent years.[5]

All teleocidins including IL-V exist in an equilibrium of two conformational states, twist and sofa forms,[6] as shown in Figure 1. On the other hand, in the crystalline state, a single conformation has been found for several teleocidin congeners: for example, teleocidin B-4 was found as the twist form[7] and olivoretin B as the sofa form.[8] The twist form is characterized by the *cis*-amide bond, whereas the sofa form is characterized by the *trans*-amide bond.



A kinetic study of the equilibrium has been performed by means of low-temperature NMR experiments on indolactam-V acetate.[9] The low energy barrier between the two conformers (the observed free energy of activation was $\Delta G^{\ddagger} = 19.2$ kcal/mol at −10 °C) and the short half-life of interconversion (estimated to be 1.2 s at 37 °C) make it difficult to interpret the interaction of these promoters with common macromolecular targets (i.e., protein kinase C (PKC) and tumor-promoter binding protein). It is particularly important to determine the active ring conformation of teleocidins in order to explain the relationships between the structures and activities of several classes of TPA-type tumor promoters with various skeletal structures.[10]

Relations between the conformational features of teleocidin derivatives in solution and their biological activities have also been examined.[11] For investigation of the active conformation of teleocidins, several congeners of indolactam-V, which have various alkyl groups at C-12, were synthesized,[12] and their conformations and biological activities[13] were investigated. All

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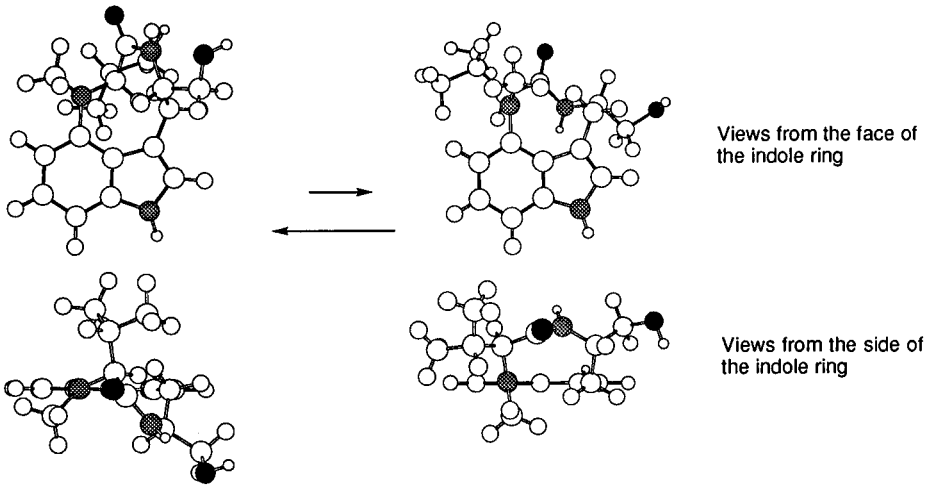

Figure 1. Equilibrium between the twist (left) and the sofa (right) forms in IL-V.

these congeners exist in different equilibria of two or more conformers, as judged from NMR studies. In studies on the prediction and interpretation of the conformational status of the indolactams by using molecular dynamics,[14,15] we have suggested the importance of the sofa form for the biological activity in terms of the existence ratio of the sofa form. However, conclusive evidence as to which conformer of teleocidin is the active form has not been obtained. Synthesis of molecules in which the lactam ring is restricted to either the twist or sofa form should lead to a solution to the problem. It might also allow the development of strategies for analyzing the mechanism of tumor promotion and for designing anti-tumor-promoting substances.

We report herein the synthesis of compounds with a new skeletal structure, benzolactam-Vs, in which the indole ring of IL-V is replaced with a benzene ring, and which have an 8-, 9-, or 10-membered lactam moiety. Conformational analysis indicated that the 8-membered lactam exists only in the twist form and the 9- and 10-membered lactams exist only in the sofa form in solution. 8-Membered derivatives having a sufficiently hydrophobic moiety exhibited biological activities similar to that of teleocidin B-4.[16]

Results and Discussion

Molecular Design of Benzolactams. The *cis*−*trans* isomerization of the amide bond is the major factor influencing the conformational interconversions of indolactams. Conformational analyses of simple lactams have been conducted by using several kinds of measurements.[17] These studies clearly indicate that the 5- to 8-membered lactams have the *cis* conformation and the 10-membered and larger lactams have the *trans* conformation. The 9-membered lactam, azacyclononanone, exists as an equilibrium mixture of *cis* and *trans* conformers, the relative amounts of which depend on solvent. Williamson and Roberts[18] observed the ^{13}C-NMR of crystalline *trans*-azacyclononanone, and the free energy of activation for the interconversion of *cis* and *trans* forms was found to be 17 kcal/mol at 64 °C from the coalescence temperature of the carbonyl peaks. This value is comparable to that of indolactam-V acetate, in which five atoms on the ring are fixed in the plane of the indole ring. Alteration of the ring-size of the lactams seems to be effective for the restriction of conformation to the twist (*cis*-amide) or sofa (*trans*-amide) form.

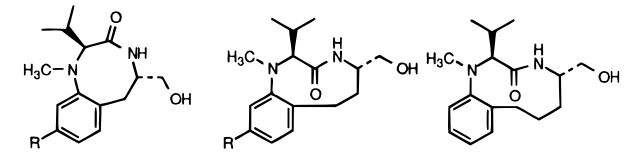

Figure 2. Structures of benzolactam-Vs (BL-Vs).

On the other hand, structure−activity relationships of indolactams give useful information for this molecular design. The presence of the hydrogen at N-1 of indolactam-V is not important for the activity, though N-methylation of indolactam-V slightly diminished the biological activity and N-prenylation and N-geranylation increased the activity.[19] Thus, we speculated that the indole ring of teleocidins could be replaced with a benzene ring.

On the basis of the above considerations, benzolactam-V-8 (BL-V8, **3**) was designed as a twist-restricted analog. Benzolactam-V9 (BL-V9, **4**) and benzolactam-V10 (BL-V10, **5**) were designed as sofa-restricted analogs (Figure 2). In the case of **3**, the energy difference between the most stable twist conformation and the sofa conformation was calculated to be more than 6 kcal/mol by a high-temperature molecular dynamics (HTMD) method.[14,20] The energy differences between the most stable sofa conformation and the twist conformation of **4** and **5** were also calculated to more than 10 kcal/mol. Superposition

(11) The importance of the twist form of teleocidins has been referred to in: Irie, K.; Hayashi, H.; Arai, M.; Koshimizu, K. *Agric. Biol. Chem.* **1986**, *50*, 2679−2680. Although 5-chloroindolactam-V exists in the sofa form predominantly, the activity of the compound is 0.1 of that of indolactam-V in our differentiation assay of HL-60 cells.

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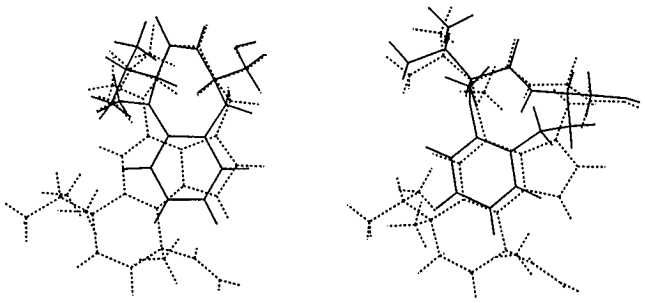

Figure 3. Left: superposition of the structures of BL-V8 (**3**) (solid) and the twist form of teleocidin B-4 (dashed). Right: superposition of the structures of BL-V9 (**4**) (solid) and the sofa form of teleocidin B-4 (dashed).

of the twist form of BL-V8 (**3**) and the twist form of teleocidin B-4 by MM-2 calculations, as well as the sofa form of BL-V9 (**4**) and the sofa form of teleocidin B-4, is illustrated in Figure 3. This figure shows that the atomic positions of the functional groups and the shapes of the molecules (**3** and **4**) coincided well with those of the twist and the sofa forms of teleocidin B-4, respectively.

The hydrophobic moiety on the indole ring of teleocidins plays a critical role in increasing the biological potency. The activity of teleocidin B-4 is 50−100 times higher than that of IL-V, which lacks the hydrophobic moiety.[4] On the other hand, the terpenoid side chain in teleocidin B-4 can be substituted by a simple linear alkyl group without loss of activity.[21,22] Figure 3 also suggests that introduction of an alkyl group at the *para* position of the $(CH_2)_n$ group may be effective in increasing the activity of these benzolactams. Therefore, benzolactam-V8-310, (**6**) and benzolactam-V9-310 (BL-V9-310, **7**), which have a hydrophobic decyl group on the benzene nucleus, were also designed.

Syntheses of Benzolactams. Syntheses of the benzolactams were carried out in a manner similar to that of IL-V.[6] The 8-membered lactam, BL-V8 (**3**) was prepared starting from 2-nitrobenzyl bromide as shown in Figure 4. The benzyl bromide was reacted with diethyl acetamidomalonate in DMF to afford the diester **8** (71%). Alkaline hydrolysis followed by decarboxylation gave a carboxylic acid, which was converted to the ethyl ester. Acid-catalyzed removal of the acetyl group yielded an amine, which was protected by Boc to give **9**. Reduction of the ester group of **9** using $LiBH_4$ in THF (96%), followed by reduction of the aromatic nitro group by catalytic hydrogenation (96%), yielded the amino alcohol **11**. The amine was condensed with methyl 2-oxoisovalerate, and the resulting imine was immediately reduced with $NaBH_3CN$. The crude mixture contained a small amount of enamine, which was also reduced by catalytic hydrogenation using 10% Pd/C. Separation of the diastereomeric esters **12** was difficult (60%, 1:1). In the construction of the 8-membered lactam structure, the succinimide-activated ester method was adopted. The methyl ester of **12** was hydrolyzed to a carboxylic acid, which was condensed with *N*-hydroxysuccinimide using DCC to give the activated ester (**13**, 81%). After deprotection of the Boc group using CF_3-COOH, cyclization was carried out under diluted conditions to avoid intermolecular condensation. Two cyclized diastereomers (**14** and **15**) were easily separated by column chromatography. Both lactams were methylated with CH_3I in MeOH to give BL-V8 (**3**, 65%) and *epi*-BL-V8 (**16**, 55%), respectively.

The 9-membered lactam BL-V9 (**4**) was also synthesized similarly by using 2-nitrophenethyl bromide, prepared from methyl 2-nitrophenylacetate (Figure 4). The phenethyl bromide was condensed with diethyl acetamidomalonate in DMF to give the diester **17** (81%). Acid-catalyzed hydrolysis followed by decarboxylation gave an amino acid, which was protected as the ethyl ester for the carboxyl group and with Boc for the amine to give **18**. The mixture of diastereomeric esters **21** was synthesized through five steps from **18**. The cyclization of the 9-membered ring was performed by the activated ester method using *N*-hydroxysuccinimide. In general, 9- and 10-membered rings are more difficult to cyclize than an 8-membered one. In the case of IL-V, the cyclization yields were above 60% because of the fixation of five atoms in the same plane by the indole ring. However, in the case of BL-V9, the cyclization yield was 30% (isomer ratio 2:3) because the benzene ring was less effective in fixing the other atoms in the same plane. The diastereomeric lactams produced (**23** and **24**) were separated by column chromatography. Each lactam was methylated with CH_3I in MeOH to give BL-V9 (**4**, 94%) and *epi*-BL-V9 (**25**, 98%), respectively.

The 10-membered lactam BL-V10 (**5**) was synthesized starting from 3-(2-nitrophenyl)propyl bromide, which was prepared from methyl 2-nitrocinnamate (Figure 4). The phenylpropyl bromide was reacted with diethyl acetamidomalonate in DMF to give the diester **26** (69%). The diester was converted by the same procedure described above to give the *N*-Boc amino ester **27** (80%). With the same procedure as used for BL-V9, cyclization of the 10-membered lactam was ineffective (below 10% yield). Therefore, the synthetic route was modified as follows. The nitro group of **27** was converted into a methylamino group in three steps, and the resultant **29** was reduced to the amino alcohol **30** with $LiBH_4$ (99%). For the introduction of the valine building block, the triflate of benzyl DL-α-hydroxyisovalerate was prepared from DL-valine. The triflate was reacted with the *N*-methylaniline **30** to give a mixture of diastereomers (53%, 1:1). A similar method has been used by Kogan et al. in the synthesis of IL-V.[23] The diastereomeric mixture **31** was converted to BL-V10 (**5**) and *epi*-BL-V10 (**33**) through four steps by the activated ester method. The yield of the cyclization step was 32% (isomer ratio 1:1). Because of the difficulty in the separation of the isomers, the lactams were acetylated and separated by column chromatography. BL-V10 acetate (**34**) and *epi*-BL-V10 acetate (**35**) were hydrolyzed by KOH in MeOH to give pure **5** (83%) and **33** (75%), respectively.

The alkylated analog of BL-V8 (BL-V8-310) was synthesized as shown in Figure 5. Reaction of 4-(bromomethyl)-3-nitrobenzaldehyde with diethyl acetamidomalonate without protection of the aldehyde group, followed by Wittig reaction employing nonylphosphonium ylide, gave **36** (55%). Deprotection and decarboxylation gave the amino acid, which was protected with ethyl ester for the carboxylic acid group and with Boc for the amine group, and the ester group was reduced with LiBH4 to afford **38** (59%). The nitro alcohol **38** was converted into the methylamino alcohol (**40**, 75%) by catalytic hydrogenation and formylation, followed by reduction with BH_3. Reaction of **40** with the triflate of benzyl DL-α-hydroxyisovalerate gave diastereomeric esters **41** (88%). After hydrogenolysis of the benzyl ester, condensation with *N*-hydroxysuccinimide using DCC gave the activated esters **42** (96%). After removal of the Boc group using CF_3COOH, cyclization was carried out under dilute conditions to give **6** (48%) and the epimer **43** (43%), which were isolated at this stage.

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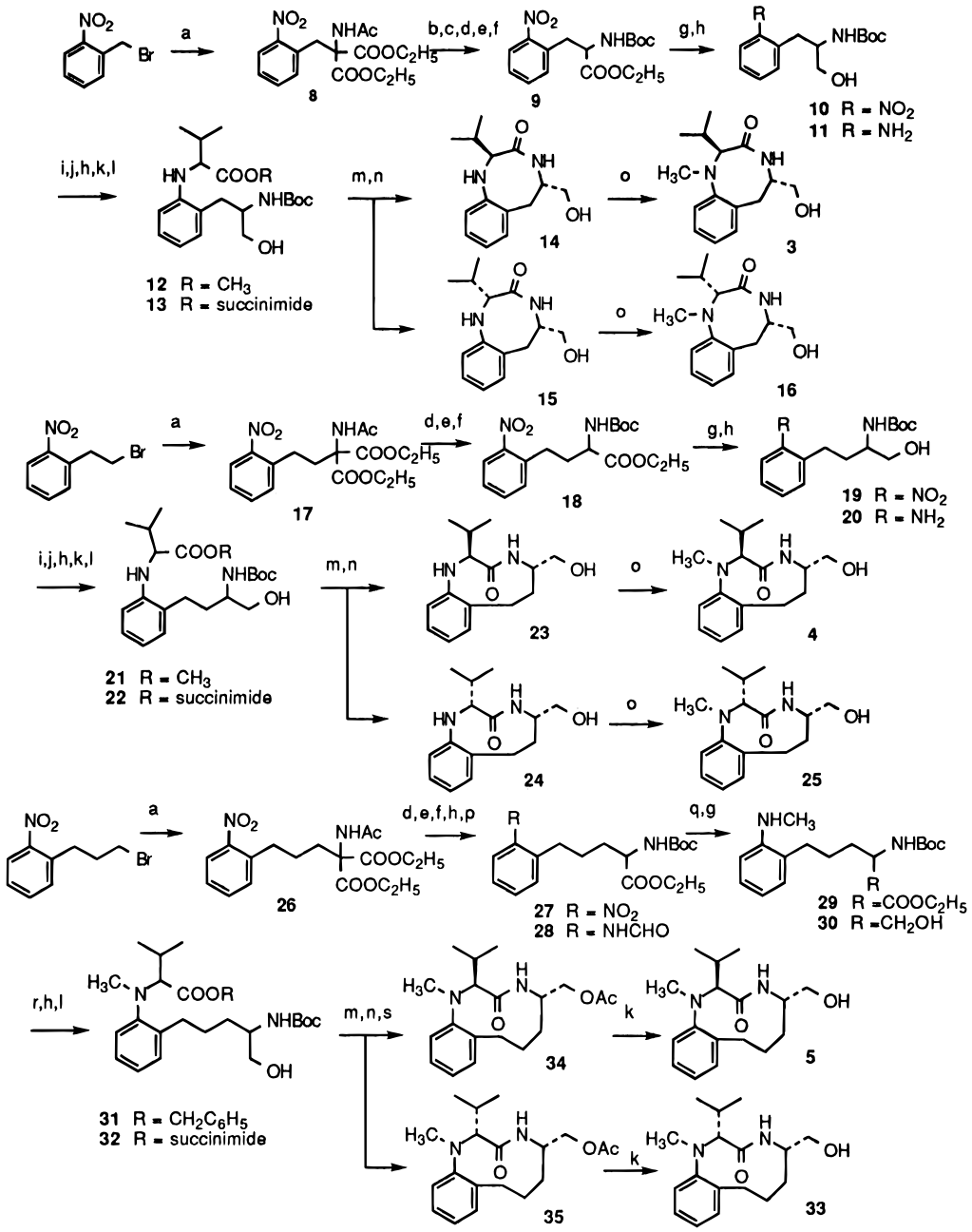


Figure 4. Synthesis of benzolactams (BL-V8: **3**, BL-V9: **4** and BL-V10: **5**). Key: (a) $CH_3CONHCH(COOC_2H_5)_2$, NaH/DMF, (b) KOH/H_2O; (c) HCl/H_2O; (d) HCl/AcOH; (e) $SOCl_2$/EtOH; (f) Boc_2O/CH_2Cl_2; (g) $LiBH_4$/THF; (h) H_2, Pd−C/$CH_3COOC_2H_5$−H_2O; (i) methyl 2-oxoisovalerate; (j) $NaBH_3CN$, THF; (k) KOH/CH_3OH−H_2O; (l) *N*-hydroxysuccinimide, DCC/CH_3CN; (m) CF_3COOH/CH_2Cl_2; (n) $NaHCO_3$(aq)/CH_3COOEt; (o) CH_3I, $NaHCO_3/CH_3OH$; (p) HCOOH, Ac_2O; (q) BH_3/THF; (r) triflate of benzyl DL-α-hydroxyisovalerate, 2,6-lutidine/CH_2ClCH_2Cl; (s) Ac_2O/pyridine.

The 9-membered lactam, BL-V9-310, was also synthesized from 4-(bromomethyl)-3-nitrobenzaldehyde. After protection of the aldehyde group with acetal, the benzyl bromide **44** was converted into the phosphonium salt **45**. The aldehyde **46** derived from DL-serine was reacted with the ylide generated from **45** to give **47** (57%, *cis:trans* 2:3). After deprotection of the acetal, the alkyl chain was introduced by the same procedure as described above to give a mixture of four stereoisomers **49** (48%). Catalytic hydrogenation of **49** gave a single amine **50**, which was converted to **51** (84%), and **51** was further converted into **7** and the epimer **54** in the same manner as described for the synthesis of **6**, in similar yields except for the cyclization step (20% for **7** and 17% for **54**).

Conformational Analysis of Benzolactams. The conformational analysis of indolactam-V and its acetate has been well investigated[4] by ^{1}H-NMR spectroscopy and nuclear Overhauser effect (NOE) experiments. Significant differences of chemical shifts between the twist form and the sofa form have been observed. Molecular dynamics (MD) calculation of possible ring conformations of indolactams has been conducted, and the resulting structures were classified into 10 ring conformations, including the twist and sofa forms of indolactam-V, on the basis of similarity of the nine torsion angles along the lactam ring.[14] Two indolactams, indolactam-G[15] and epi-indolactam-V,[15] were concluded from ^{1}H-NMR data to exist in solution only as the fold form and the *r-cis*-sofa form, respectively.

Each of the benzolactams was proven to exist in a single conformation in solution by ^{1}H-NMR spectral examination even at −60 °C. The absence of line broadening with increasing temperature shows the absence of any other conformer which may be discriminated on the NMR time scale. The ^{1}H-NMR spectral data for BL-V8 (**3**), BL-V9 (**4**), and BL-V10 (**5**) in

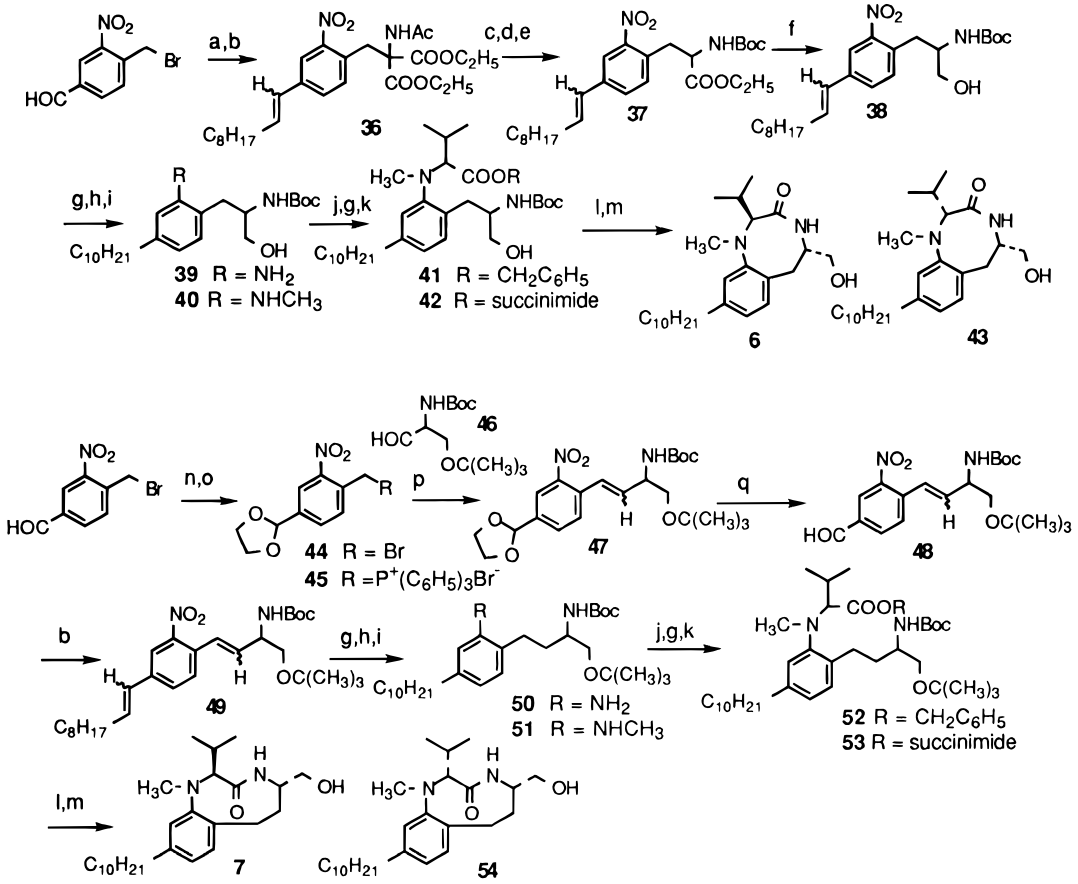


Figure 5. Synthesis of benzolactams (BL-V8-310: **6** and BL-V9-310: **7**). Key: (a) $CH_3CONHCH(COOC_2H_5)_2$, NaH/DMF; (b) $C_9H_{19}P^+Ph_3Br^-$, *n*-BuLi/THF; (c) HCl/AcOH; (d) $SOCl_2$/EtOH; (e) Boc_2O/CH_2Cl_2; (f) $LiBH_4$/THF; (g) H_2, Pd−C/EtOH; (h) HCOOH, Ac_2O; (i) BH_3/THF; (j) triflate of benzyl DL-α-hydroxyisovalerate, 2,6-lutidine/CH_2ClCH_2Cl; (k) *N*-hydroxysuccinimide, DCC/CH_3CN; (l) CF_3COOH/CH_2Cl_2; (m) $NaHCO_3$(aq)/CH_3COOEt; (n) $HOCH_2CH_2OH$, TsOH/toluene; (o) PPh_3/toluene; (p) **46**, K_2CO_3/DMF; (q) pyridinium *p*-toluenesulfonate/acetone, H_2O.

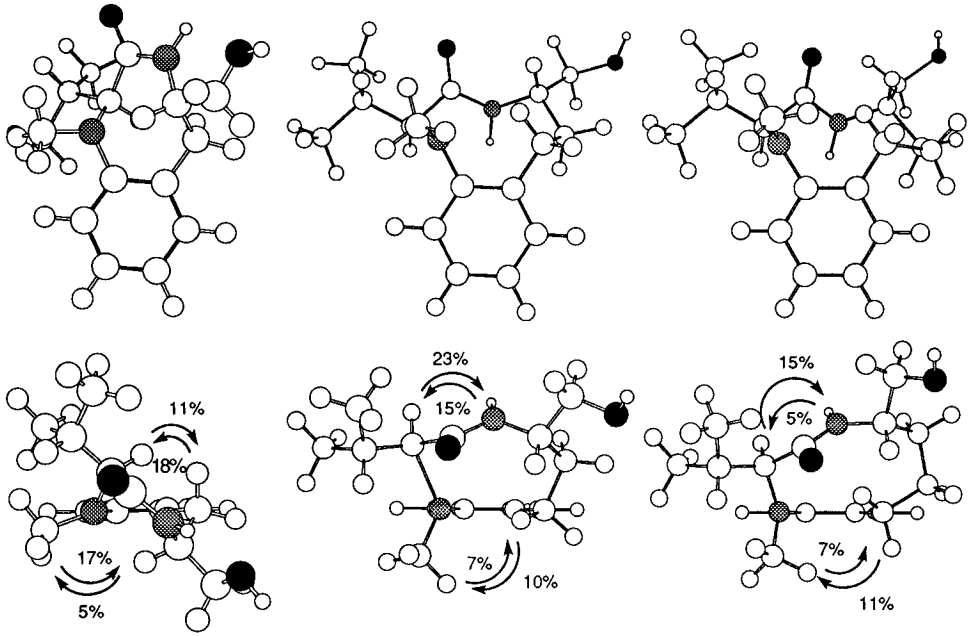
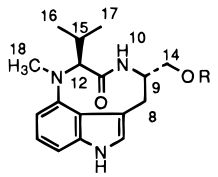
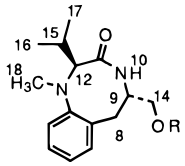
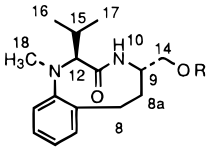
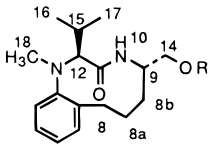


Figure 6. Stable conformations of BL-V8 (**3**; left), BL-V9 (**4**; center), and BL-V10 (**5**; right). The arrows indicate typical NOE enhancements in the acetates of the BL-Vs in $CDCl_3$. Top: views from the face of the benzene ring. Bottom: views from the side of the benzene ring.

CD_3OD along with those for the sofa and twist forms of indolactam-V are shown in Table 1. The chemical shifts in $CDCl_3$ of O-acetylated derivatives of these compounds are also compared with those of the sofa and twist forms of indolactam-V acetate in Table 1. The conformational structures of the benzolactams were deduced from ^{1}H-NMR spectra and NOE experiments by considering the comparability of the data with all 10 possible conformers, including the twist and sofa forms (Figure 6).

Though the chemical shifts of BL-V8 (**3**) took intermediate values between those of the twist and sofa forms of indolactam-V, perhaps due to molecular size difference, the NOE observa-

Table 1. ^{1}H NMR Chemical Shifts of Indolactam-V and Benzolactams[a]

	IL-V (sofa form)	IL-V (twist form)	BL-V8	BL-V9	BL-V10
H9	4.26 (m)	4.23 (m)	4.49 (bs)	4.29 (hex, $J = 6$)	3.34 (m)
H10					6.47 (bd, $J = 7$)
H12	3.08 (d, $J = 12$)	4.48 (d, $J = 11$)	3.44 (d, $J = 7$)	2.86 (d, $J = 11$)	2.89 (d, $J = 11$)
H14	3.30 (dd, $J = 8, 11$)	3.62 (dd, $J = 4, 11$)	3.60 (dd, $J = 5, 11$)	3.41 (m)	3.23 (dd, $J = 7, 11$)
	3.22 (dd, $J = 7, 11$)	3.45 (dd, $J = 7, 11$)	3.50 (dd, $J = 7, 11$)		3.31 (m)
H15	2.31 (dsept, $J = 7, 11$)	2.55 (dsept, $J = 7, 11$)	2.40 (oct, $J = 7$)	2.22 (m)	2.24 (m)
H16	1.24 (d, $J = 7$)	0.89 (d, $J = 7$)	1.09 (d, $J = 7$)	1.16 (d, $J = 7$)	1.17 (d, $J = 7$)
H17	0.90 (d, $J = 7$)	0.61 (d, $J = 7$)	0.94 (d, $J = 7$)	0.88 (d, $J = 7$)	0.88 (d, $J = 7$)
H18	2.77 (s)	2.88 (s)	2.76 (s)	2.73 (s)	2.79 (s)
Ar	7.11 (s)	6.94 (s)	6.93 (dt, $J = 2, 7$)	7.05−7.16 (m)	7.04−7.15 (m)
	6.95 (dd, $J = 1, 8$)	6.44 (dd, $J = 1, 8$)	7.06 (d, $J = 7$)		7.30 (dd, $J = 2, 7$)
	7.05 (t, $J = 8$)	6.95 (t, $J = 8$)	7.17 (m)		
	7.28 (dd, $J = 1, 8$)	6.88 (dd, $J = 1, 8$)			
H8α	3.02 (dd, $J = 4, 15$)	3.11 (dd, $J = 2, 15$)	3.03 (dd, $J = 9, 17$)	2.41 (dd, $J = 10, 14$)	2.55 (m)
H8β	2.87 (dd, $J = 2, 15$)	3.05 (dd, $J = 4, 15$)	2.89 (dd, $J = 9, 17$)	2.64 (dd, $J = 8, 14$)	
H8aα				1.67 (dd, $J = 11, 15$)	2.24 (m)
H8aβ				2.33 (m)	1.83 (dt, $J = 4, 14$)
H8bα					1.04 (m)
H8bβ					1.67 (dt, $J = 4, 15$)

	IL-V acetate (sofa)	IL-V acetate (twist)	BL-V8 acetate	BL-V9 acetate	BL-V10 acetate
H9	4.60 (m)	4.50 (m)	4.56 (bs)	4.60 (m)	4.18 (m)
H10	4.73 (d, $J = 12$)	6.08 (s)	5.75 (bd, $J = 3$)	4.46 (bd, $J = 11$)	4.35 (bd, $J = 9$)
H12	2.98 (d, $J = 11$)	4.36 (d, $J = 10$	3.44 (d, $J = 7$)	2.72 (d, $J = 11$)	2.74 (d, $J = 11$)
H14	3.83 (m)	3.99 (dd, $J = 8, 12$)	3.98 (dd, $J = 8, 11$)	3.90 (dd, $J = 4, 11$)	3.80 (dd, $J = 6, 11$)
	3.85 (m)	4.20 (dd, $J = 3, 12$)	4.20 (dd, $J = 4, 11$)	4.08 (dd, $J = 5, 11$)	3.97 (dd, $J = 7, 11$)
H15	2.39 (dsept, $J = 7, 10$)	2.61 (dsept, $J = 7, 10$)	2.43 (oct, $J = 7$)	2.31 (m)	2.31 (m)
H16	1.24 (d, $J = 7$)	0.93 (d, $J = 7$)	1.08 (d, $J = 7$)	1.16 (d, $J = 6$)	1.16 (d, $J = 7$)
H17	0.94 (d, $J = 7$)	0.64 (d, $J = 7$)	0.94 (d, $J = 7$)	0.90 (d, $J = 6$)	0.88 (d, $J = 7$)
H18	2.75 (s)	2.92 (s)	2.79 (s)	2.76 (s)	2.80 (s)
OAc	2.02 (s)	2.09 (s)	2.11 (s)	1.98 (s)	1.99 (s)
Ar	6.99 (s)	6.90 (s)	6.93 (dt, $J = 1, 8$)	7.15 (m)	7.06−7.18 (m)
	7.05 (d, $J = 8$)	6.52 (d, $J = 8$)	7.04 (d, $J = 6$)		
	7.17 (t, $J = 8$)	7.07 (t, $J = 8$)	7.06 (d, $J = 7$)		
	7.27 (d, $J = 8$)	6.91 (d, $J = 8$)	7.21 (dt, $J = 1, 8$)		
H8α	3.12 (dd, $J = 4, 16$)	3.09 (dd, $J = 3, 16$)	3.00 (bd, $J = 9$)	2.48 (dd, $J = 11, 14$)	2.63 (dt, $J = 4, 15$)
H8α	3.12 (dd, $J = 4, 16$)	3.09 (dd, $J = 3, 16$)	3.00 (bd, $J = 9$)	2.48 (dd, $J = 11, 14$)	2.63 (dt, $J = 4, 15$)
H8β	2.78 (d, $J = 16$)	3.24 (d, $J = 16$)		2.64 (dd, $J = 8, 14$)	2.53 (dt, $J = 4, 15$)
H8aα				1.68 (m)	2.15 (m)
H8aβ				2.33 (m)	1.91 (m)
H8bα					1.02 (m)
H8bβ					1.55 (dt, $J = 4, 15$)

[a] Top: IL-V (**2**), BL-V8 (**3**), BL-V9 (**4**), and BL-V10 (**5**) in CD_3OD. Bottom: IL-V acetate, **3**-acetate, **4**-acetate, and **5**-acetate in $CDCl_3$. Chemical shifts are shown by δ values from TMS. Coupling constants (Hz) are shown in parentheses. Numbering of the benzolactams is assigned as shown for convenience of comparison with the two conformers of IL-V.

tions were consistent with twist structure. In the NOE spectra, saturation of the H-8α proton resulted in 18% enhancement of the H-12 signal, and saturation of H-18 (*N*-methyl) caused 17% enhancement of the H-9 signal. These NOE enhancements are characteristic of the twist form of IL-V,[6] and no other conformation would show these NOE enhancements. Therefore, BL-V8 (**3**) exists in the twist form in solution. The benzolactam having a hydrophobic alkyl chain on the aromatic nucleus, BL-V8-310 (**6**), gave ^{1}H-NMR signals similar to those of **3**. NOE experiments confirmed the twist form of **6**.

The spectra data of BL-V9 (**4**) and BL-V10 (**5**) showed values similar to each other and resembled those of the sofa form of indolactam-V. In the sofa form of indolactam-V, typical features are (1) high-field shift of H-10 and H-12, which are shielded by aromatic current anisotropy, (2) low-field shielding of the aromatic proton H-5 and H-7, which shows the lack of planarity of the lone-pair electrons of nitrogen with the aromatic π electrons, and (3) the large coupling constant between H-9 and H-10 which indicates a dihedral angle between these protons close to 180°. These characteristic features were also recognized in the spectra of **4** and **5**. Furthermore, NOE enhancement of H-12 upon saturation of H-10 protons (NH) in the acetate of **4** and **5** was observed, as in the sofa form of IL-V.[6] The above experimental results demonstrate that the conformation of **4** and **5** in solution is the sofa form. The benzolactam having a hydrophobic alkyl chain on the aromatic nucleus, BL-V9-310 (**7**), gave ^{1}H-NMR signals similar to those of **4**. The sofa form of **7** was confirmed by NOE experiments.

In addition, the ^{1}H-NMR spectrum of BL-V10 (**5**) showed two characteristic phenomena. One is the high-field shielding of the H-8bα proton (1.04 ppm), which was caused because of the location of this proton above the benzene ring. The other

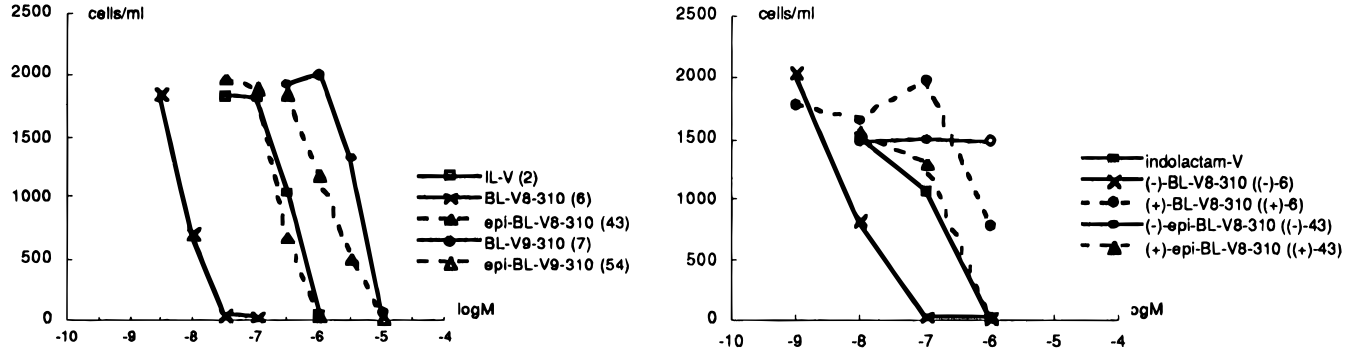


Figure 7. Inhibition of HL-60 cell growth by IL-V and BL-Vs.

was that the amide proton did not exchange in CD_3OD. Only partial exchange of the NH proton was observed during incubation at 40 °C for 40 min in CD_3OD. The proton is surrounded by the benzene ring and the hindered alkyl group, which would make it difficult to exchange. The sofa structure of **5** is also supported by these results.

The conformations of the *epi*-benzolactams were also investigated. The ^{1}H-NMR spectral data of *epi*-BL-V8 (**16**) and *epi*-BL-V9 (**25**) in CD_3OD resembled those of *epi*-IL-V, which exists predominantly in the *r-cis*-sofa form.[15,16] Strong NOE enhancement between H-9 and H-12 was observed, which is characteristic of the *r-cis*-sofa form. *epi*-BL-V10 (**33**) gave broadened signals at room temperature, which showed neither splitting nor sharpening even at −90 °C in CD_2Cl_2. Thus, **33** exists in at least two conformational states in solution, and their interconversion is too fast to be observable on the NMR time scale.

Active Conformation of Benzolactams. One of the most important, sensitive, and specific biological activities of the TPA-type tumor promoters is induction of growth inhibition, cell adhesion, and differentiation to monocytes of human promyelocytic leukemia cells (HL-60).[1,24] IL-V shows the activity at effective concentrations of 100−500 times lower than that of teleocidin B-4. Introduction of hydrophobic groups increases the potency. Recently, Kozikowski *et al*. reported the synthesis of a simplified analog of IL-V,[25] which resembles our simple 9-membered benzolactam. The compound showed no agonistic or antagonistic activity for PKC. This, however, may not cast light on the active conformation of teleocidins because their compound lacked a hydrophobic group. In fact, among the simple 8-, 9-, and 10-membered benzolactams without a hydrophobic group (**3**, **4**, and **5**), the 8-membered lactam **3** showed the activity at concentrations of 10^{-5} M order, and the other lactams did not show notable activity at concentrations below 10^{-5} M in the HL-60 differentiation assay. We thought that this result was not enough to identify the active conformation of teleocidins. However, the alkylated analogs of the 8- and 9-membered benzolactams (**6** and **7**) gave clear results in the HL-60 test (Figure 7). The twist-restricted BL-V8-310 (**6**) caused growth inhibition and differentiation of HL-60 cells at a concentration of 10^{-8} M. The potency of **6** was 30 times stronger than that of IL-V. In contrast, the sofa-restricted BL-V9-310 (**7**) proved to be inactive at concentrations below 10^{-5} M.

Optically pure BL-V8-310 was also investigated. The potency of (−)-BL-V8-310 was strong as expected from that of racemic **6**. (+)-BL-V8-310 proved to be inactive at concentrations below 10^{-6} M. Interestingly, (+)-*epi*-BL-V8-310 shows a significant potency, as strong as that of IL-V.[26]

Tumor-promoting activity is generally explained in terms of binding to and activation of protein kinase C (PKC). So we investigated the inhibition of [^{3}H]TPA binding to PKC by the benzolactams (**6** and **7**). Percentage inhibition in the presence of the compounds (1000-fold) was as follows: 88% for teleocidin B-4, 3% for IL-V, 44% for **6**, and 11% for **7**. Percentage inhibition in the presence of optically pure BL-V8-310 (1000-fold) was as follows: 59% for (−)-**6** and 6% for (+)-**6**.

Activation of PKC by the benzolactams was also investigated. Percentage phosphorylation in the presence of the compounds (10 mM) was as follows: 100% for TPA (control), 83% for teleocidin B-4, 43% for IL-V, 34% for **6**, and 16% for **7**.

Hashimoto and Shudo reported a cytosolic-nuclear tumor promoter-specific binding protein (CN-TPBP).[27] CN-TPBP binds TPA with the association constant of 1.4×10^{10} M^{-1} and also binds teleocidin B-4, debromoaplysiatoxin, and thapsigargin in a mutually competitive manner. The binding affinity order of various indolactams correlated with the adhesion-inducing potency order of the compounds toward HL-60. More interestingly, CN-TPBP was proven to move into the nucleus after the binding of TPA, in a way similar to nuclear receptors of glucocorticoid. These findings suggested that CN-TPBP may act as a possible nuclear receptor for tumor promoters and that tumor promoters may exert their biological effects by binding to CN-TPBP. We investigated the inhibition of [^{3}H]TPA binding to CN-TPBP by the benzolactams (**6** and **7**).

Percentage inhibition of [^{3}H]TPA binding in the presence of the compounds (1000-fold) was as follows (errors are estimated to be within 10%): 84% for teleocidin B-4, 37% for IL-V, 66% for **6**, and −5% for **7**. Percentage inhibition in the presence of optically pure BL-V8-310 (1000-fold) was as follows: 59% for (−)-**6** and 6% for (+)-**6**. Differentiating activity of these compounds in HL-60 cells correlated better to the binding potency than to PKC binding or activation.

Above all, BL-V8-310 shows a strong potency and BL-V9-310 is inactive. Further, (−)-BL-V8-310 shows strong potency,

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(25) Kozikowski, A. P.; Ma, D.; Pang, Y.-P.; Shum, P.; Likic, V.; Mishra, P. K.; Basu, A.; Lazo, J. S.; Ball, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 3957−3965.

(26) From the viewpoint of the conformational conversion, it is possible that the active conformation of (+)-**43** is also the twist form, since the conversion of the *r-cis*-sofa form of (+)-**43** to the twist form does not involve a high energy barrier. The conformational analysis and X-ray studies were carried out using racemic epi-IL-V.[15] Similarly, in the case of (+)-**43**, the energy differences between the most stable *r-cis*-sofa form and the next most stable conformations (the twist, fold, and r-twist forms) are greater than 4.5 kcal/mol by MD calculation. The relative atomic positions of the amide bond and hydroxymethyl group of the stable *r-cis*-sofa form of (+)-**43** are close to those of the twist form of (−)-**6**. The remarkable stability of the *r-cis*-sofa form of (+)-**43** and the difference of activity between (−)-**6** and (+)-**43** suggested that the two compounds interact with the macromolecular receptor as the twist form and *r-cis*-sofa form, respectively.

(27) Hashimoto, Y.; Shudo, K. *Jpn. J. Cancer Res. (Gann)* **1991**, *82*, 665−668.

but (+)-BL-V8-310 does not. BL-V9-310 exists exclusively in the sofa form in solution. It is possible that conformational conversion occurs upon binding to the receptor. BL-V8-310, however, is very difficult to convert into *trans*-amide form because of the lactam ring tension. Therefore, we conclude that the active conformation of teleocidin is not the sofa form, but the twist form (or a near twist form which has the *cis*-amide bonding). Irie *et al*. recently reported a twist-restricted C5−C13-bridged IL-V, which was formed from *N*-desmethyl-*N*-alkyl-IL-V by aza-Cope rearrangement, and its activity is comparable to that of IL-V.[28]

We have reported a molecular superposition study of the twist and the sofa forms of teleocidin B-4 onto TPA independently in order to extract common structural features.[29] The molecules were superposed in terms of physical and chemical properties, but not the atomic positions as employed in conventional methods.[10] The two superposing models showed equally good fit in terms of molecular shape and in the correspondence of two pairs of hydrogen-bonding groups, the carbonyl group at C-11 of teleocidin and at C-3 of TPA (as acceptor), and the CH_2OH at C-9 of teleocidin and at C-6 of TPA (as donor). We have concluded the superposition of the sofa form is somewhat better than that of the twist form, owing to the possibility of a third hydrogen bonding. However, the above experimental results confirmed the active conformation is the twist form.

Recently, a crystallographic study revealed direct interaction of phorbol 13-acetate with PKCδ Cys2 domain.[30] The binding sites clarified by the study can only bind with the twist form, but not the sofa form of teleocidins: this is in good agreement with the present conclusion. The X-ray study gave us an opportunity to consider the common hydrogen bonding sites of teleocidins and TPA. According to the crystal structure of phorbol 13-acetate and PKCδ Cys2 complex, we propose two binding mode of teleocidins and PKCδ. One possible interpretation is that the twist form of teleocidins require only two hydrogen bonds to PKC, as in the superposing model for twist form of teleocidin and TPA in the previous paper.[29] Though the assignments for phorbol 13-acetate hydrogen-bonding sites are reported, it may not be necessary for teleocidins to use all three hydrogen-bondings. This is consistent with the experimental result that 4-deoxyphorbol ester exhibits PKC activation in the range of nM order.[31] Although hydrogen bonding is an important factor for recognition of a biologically active molecule to a receptor, other favorable interactions such as good complimentarity in shape with the binding site (van der Waals interaction) can compensate for the lack of a hydrogen bond. Another possible explanation is that the twist form of teleocidins require three hydrogen bonds to PKC, as with phorbol 13-acetate in the complex crystal structure. The amide NH of teleocidins is also able to form a hydrogen bond at the carbonyl oxygen of Gly253 in the PKCδ Cys2 domain without conformational change of the main chain of the peptide, though it may cause some decrease of the fitness of whole molecular shapes.

Conclusion

Benzolactam-Vs, with a variable-sized lactam ring and a benzene ring instead of the indole ring of indolactam or teleocidin, were designed and synthesized as conformationally restricted analogs of teleocidins. (−)-BL-V8-310 ((−)-**6**), which exists only in the twist form with *cis*-amide in solution, exhibits biological activity at 10^{-8} M concentration in the HL-60 assay. It was only 10 times less potent than teleocidin B-4 and was 30 times more potent than IL-V in the HL-60 assay. On the other hand, BL-V9-310 (**7**) with *trans*-amide was inactive. Therefore, we concluded that the twist form of teleocidin is the biologically active form. This finding appears to solve the conformational flexibility problem that has bedeviled structure−activity studies of teleocidins. Synthesis of molecules having different skeletons with rigid conformation might allow us to identify the active conformation on the receptor. The present finding should be helpful in the design of such molecules and the development of strategies for analyzing the mechanism of tumor promotion.

Experimental Section

General Remarks. Melting points were obtained on Yanagimoto micro hot stage apparatus and are uncorrected. Spectra were recorded with the following instruments: ^{1}H-NMR spectra, JEOL JMN-FX-400 (400 MHz); mass spectra, JEOL JMN-DX 303; IR spectra, JASCO DS-402G; optical rotational spectra, JASCO DIP-181. NMR spectra were recorded with tetramethylsilane as an internal standard, and the chemical shifts are given δ values from TMS. The IR data are presented in cm^{-1}. Column chromatography was performed on silica gel (Merck 9385).

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-3-(2-nitrophenyl)propanoate (8). Sodium hydride (60% in oil; 5.0 g, 0.125 mol) was washed with *n*-hexane, dried under reduced pressure, and suspended in 100 mL of DMF under Ar atmosphere. A solution of 27.0 g (0.124 mol) of diethyl acetamidomalonate in 50 mL of DMF was added to it, followed by a solution of 27.0 g (0.125 mol) of *o*-nitrobenzyl bromide in 50 mL of DMF, and the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure. The residue was poured into ice−water, and the mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Recrystallization from CH_2Cl_2/*n*-hexane gave 31.1 g of **8** (71%) as pale yellow needles: mp 103−104 °C; ^{1}H-NMR ($CDCl_3$) 1.30 (t, 6H, J = 7 Hz, $-CH_2CH_3$), 1.98 (s, 3H, $COCH_3$), 4.08 (s, 2H, $ArCH_2$), 4.24 (dq, 4H, J = 1, 7 Hz, $-CH_2CH_3$), 6.47 (bs, 1H, NH), 7.24 (dd, 1H, J = 2, 7 Hz, ArH), 7.40 (dd, 1H, J = 2, 7 Hz, ArH), 7.82 (dd, 1H, J = 2, 7 Hz, ArH). Anal. Calcd for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.75; N, 7.95. Found: C, 54.66; H, 5.64; N, 8.06.

Ethyl 2-(Acetylamino)-3-(2-nitrophenyl)propanoate. A solution of 30.5 g of **8** (86.6 mmol) and 17.3 g of NaOH (0.43 mol) in 150 mL of water was refluxed for 70 min. The reaction mixture was cooled to room temperature and acidified with concentrated HCl. The precipitate was collected, washed with brine, and dried under reduced pressure at 80 °C for 4 h. The crude diacid was heated with 100 mL of water at 100 °C for 3 h. After being cooled with ice, the precipitate was collected and dried at 80 °C under reduced pressure over P_2O_5 for 6 h. The crude monoacid was added to a solution of 23 mL of $SOCl_2$ in 100 mL of dry ethanol (prepared at −10 °C) with stirring at −10 °C. The mixture was stirred for 1 h at room temperature and 3 h at 60 °C and then concentrated under reduced pressure to remove most of the ethanol. The residue was poured into saturated $NaHCO_3$(aq) and extracted with AcOEt. The organic layer was washed with 2 N Na_2CO_3, water, and brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in ethanol and treated with activated charcoal. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/AcOEt = 8/1 to afford 14.8 g of *N*-acetyl-2-nitrophenylalanine ethyl ester (61%): mp 72−74 °C; ^{1}H-NMR ($CDCl_3$) 1.22 (t, 3H, J = 7 Hz, $-CH_2CH_3$), 1.93 (s, 3H, $COCH_3$, 3.30 (dd, 1H, J = 8, 13 Hz, $ArCH_2$), 3.50 (dd, 1H, J = 6, 13 Hz, $ArCH_2$), 4.15 (dq, 2H, J = 1, 7 Hz, $-CH_2CH_3$), 4.89 (ddd, 1H, J = 1, 8, 8 Hz, $ArCH_2CH$), 6.21 (bd, 1H, J = 8 Hz, NH), 7.28−7.64 (m, 3H, ArH), 7.90 (m, 1H, ArH). Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.83; H, 5.70; N, 9.99.

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Ethyl 2-[(*tert*-Butoxycarbonyl)amino]-3-(2-nitrophenyl)propanoate (9). A solution of 14.5 g (51.8 mmol) of the *N*-acetylamino ester in 200 mL of ethanol saturated with HCl was refluxed for 48 h. The reaction mixture was cooled with ice−water, and ether was added. The precipitate was collected and dried; 12.3 g (86%) of the HCl salt of 2-nitrophenylalanine ethyl ester was obtained as colorless needles (mp 204 °C dec). The HCl salt (12.0 g) was suspended in water, neutralized with $NaHCO_3$, and extracted with AcOEt. The organic layer was dried and concentrated at below 40 °C under reduced pressure to give 9.8 g of amine. To a solution of 9.06 g (38.0 mmol) of the amine in 80 mL of dioxane−water (1.1), 8.0 g of $NaHCO_3$, (95.2 mmol), and 10.9 g (76 mmol) of *tert*-butoxycarbonyl azide were added. The mixture was heated at 40−50 °C for 40 h. After addition of Boc-N_3 (5.4 g, 38 mmol), the reaction mixture was stirred for another 24 h. Most of the solvent was removed under reduced pressure, and the residue was poured into 200 mL of water and extracted with AcOEt. The organic layer was washed with 0.5 M $NaHCO_3$(aq), 0.5 M citric acid, and water and then dried and concentrated. Recrystallization from benzene afforded 10.7 g of **9** as pale yellow needles (83%): mp 97.5−99 °C; ^{1}H-NMR ($CDCl_3$) 1.25 (t, 3H, J = 7 Hz, $-CH_2CH_3$), 1.37 (s, 9H, Boc), 3.24 (dd, 1H, J = 8, 14 Hz, $ArCH_2$), 3.52 (dd, 1H, J = 6, 14 Hz, $ArCH_2$), 4.19 (dq, 2H, J = 7 Hz, $-CH_2CH_3$), 4.66 (ddd, 1H, J = 6, 8, 8 Hz, CH_2CH), 5.20 (bd, 1H, J = 8 Hz, NH), 7.30−7.64 (m, 3H, ArH), 7.96 (bd, 1H, J = 8 Hz, ArH). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.60; H, 6.56; N, 8.40.

2-[(*tert*-Butoxycarbonyl)amino]-3-(2-nitrophenyl)propanol (10). To a solution of 1.5 g (70.0 mmol) of $LiBH_4$ in 150 mL of THF was added 10.5 g (60.3 mmol) of **9**. The solution was stirred for 1 h at 0 °C and 3 h at room temperature and concentrated. The residue was poured carefully into ice−water and extracted with AcOEt. The extract was washed with 10% aqueous citric acid, water, and brine and dried over $MgSO_4$. Evaporation and recrystallization afforded 8.73 g of **14** (96%) as colorless needles: mp 102−103 °C; ^{1}H-NMR ($CDCl_3$) 1.35 (s, 9H, Boc), 2.50 (bs, 1H, OH), 3.00 (dd, 1H, J = 8, 13 Hz, $ArCH_2$), 3.24 (dd, 1H, J = 5, 13 Hz, $ArCH_2$), 3.6−3.8 (m, 2H, CH_2OH), 3.97 (m, 1H, $ArCH_2CH$), 5.03 (bd, 1H, J = 8 Hz, NH), 7.20−7.64 (m, 3H, ArH), 7.92 (bd, 1H, J = 8 Hz, ArH). Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.72; H, 6.80; N, 9.24.

2-[(*tert*-Butoxycarbonyl)amino]-3-(2-aminophenyl)propan-1-ol (11). A mixture of 4.5 g (15.2 mmol) of **10** and 2.5 g of 10% Pd−C in 400 mL of AcOEt containing 1% water was vigorously stirred under 1 atm of H_2 at room temperature for 2 h and then filtered. The filtrate was concentrated and crystallized from benzene to afford 3.9 g of **11** as colorless leaflets (96%): mp 130.5−131.5 °C; ^{1}H-NMR ($CDCl_3$) 1.46 (s, 9H, Boc), 2.67 (dd, 1H, J = 10, 14 Hz, $ArCH_2$), 2.86 (dd, 1H, J = 5, 14 Hz, $ArCH_2$), 3.4−3.6 (m, 2H, CH_2OH), 3.70 (m, 1H, $ArCH_2CH$), 5.16 (bd, 1H, J = 8 Hz, NH), 6.65 (d, 1H, J = 9 Hz, ArH), 6.75 (d, 1H, J = 9 Hz, ArH), 6.99 (bd, 2H, J = 9 Hz, ArH). Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.44; H, 8.17; N, 10.34.

Diastereomeric Esters 12. A mixture of 3.6 g (13.5 mmol) of **11** and 4.4 g (33.8 mmol) of methyl 2-oxoisovalerate[6] in 80 mL of benzene was refluxed for 24 h with a Dean−Stark trap under an Ar atmosphere. Then 1.6 g (12.3 mmol) of methyl 2-oxoisovalerate was added, and the reaction mixture was refluxed for another 18 h. After removal of the solvent under reduced pressure, the residue was dissolved in 120 mL of THF. Then 1.7 g (26.9 mmol) of $NaBH_3CN$ was added with stirring at room temperature. The mixture was stirred at room temperature for 12 h, and the solvent was removed. The residue was poured into ice−water and extracted with CH_2Cl_2. The extract was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent afforded a crude oil. The residue includes the enamine, which was dissolved in 100 mL of AcOEt (containing 1% water) and hydrogenated over Pd−C in an H_2 atmosphere. After filtration and evaporation of the solvent, the crude product was purified by column chromatography on silica gel to give 4.13 g of **12** as a colorless liquid (80%): ^{1}H-NMR ($CDCl_3$) 1.04 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.04 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.08 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.12 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.45 (s, 9H, Boc), 1.47 (s, 9H, Boc), 2.18 (m, 2H, $CH(CH_3)_2$), 2.6−3.1 (m, 4H, $ArCH_2$), 3.4−3.7 (m, 4H, CH_2OH), 3.69 (s, 3H, $COOCH_3$), 3.71 (s, 3H, $COOCH_3$), 3.7−3.9 (m, 2H, NHCHCO), 4.15 (m, 1H, $ArCH_2CH$), 5.04 (bd, 1H, J = 8 Hz, NH), 5.22 (bd, 1H, J = 8 Hz, NH), 6.4−6.8 (m, 4H, ArH), 6.9−7.2 (m, 4H, ArH).

Activated Esters 13. A mixture of a solution of 4.05 g (10.7 mmol) of **12** in 25 mL of methanol and 25 mL of 2 N KOH(aq) was stirred for 24 h at room temperature. After removal of the solvent, the residue was acidified with 10% citric acid and extracted with AcOEt. The extract was washed twice with brine and dried over $MgSO_4$. Evaporation of the solvent afforded the carboxylic acid as a colorless oil. The acid and 2.45 g (21.3 mmol) of *N*-hydroxysuccimide were dissolved in 30 mL of CH_3CN, and then a solution of 3.29 g (15.9 mmol) of DCC in 10 mL of CH_3CN was added at 0 °C with stirring. Stirring was continued for 1 h at 0 °C and 2 h at room temperature, and then the solvent was removed under reduced pressure. The residue was suspended in AcOEt, and insoluble urea was filtered off. The filtrate was concentrated and purified by column chromatography on silical gel using AcOEt/*n*-hexane = 1/1 to give 4.09 g of **13** (81%) as a colorless liquid: ^{1}H-NMR ($CDCl_3$) 1.19 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), 1.24 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), 1.43 (s, 18H, Boc), 2.45 (m, 2H, $CH(CH_3)_2$), 2.78 (s, 4H, $COCH_2CH_2CO$), 2.80 (s, 4H, $COCH_2CH_2CO$), 2.7−3.0 (m, 4H, $ArCH_2$), 3.6−3.7 (m, 4H, CH_2OH), 3.70 (m, 2H, NHCHCO), 4.15 (m, 2H, $ArCH_2CH$), 5.04 (d, 1H, J = 7 Hz, NH), 5.16 (d, 1H, J = 7 Hz, NH), 5.35 (d, 1H, J = 8 Hz, NH), 5.81 (d, 1H, J = 8 Hz, NH), 6.6−6.8 (m, 4H, ArH), 6.7−7.2 (m, 4H, ArH).

***N*-Desmethylbenzolactam-V8 (14) and *N*-Desmethyl-*epi*-benzolactam-V8 (15).** Trifluoroacetic acid (30 mL) was added to a solution of 4.0 g (8.62 mmol) of **13** in 30 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 1 h at room temperature, and then the solvent was removed under reduced pressure at below 30 °C. The residue was dissolved in 80 mL of AcOEt, and then 80 mL of saturated $NaHCO_3$(aq) was added and the mixture was refluxed for 1 h with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was separated by column chromatography with AcOEt/CH_2Cl_2 = 4/1 to give 676 mg of **14** and 644 mg of **15**. **14**: colorless cubes (from $CHCl_3$); mp 187.5−188.5 °C; ^{1}H-NMR ($CDCl_3$) 0.94 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.14 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 2.02 (sept, 1H, J = 7 Hz, $CH(CH_3)_2$), 2.49 (d, 1H, J = 16 Hz, $ArCH_2$), 3.23 (t, 1H, J = 6 Hz, NHCHCO), 3.48 (dd, 1H, J = 8, 16 Hz, $ArCH_2$), 3.5−3.8 (m, 2H, CH_2OH), 3.87 (d, 1H, J = 9 Hz, NH), 4.00 (m, 1H, $ArCH_2CH$), 6.52−7.12 (m, 5H, ArH, NH). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.81; H, 8.15; N, 11.22. **15**: colorless cubes (from EtOH); mp 191−193 °C; ^{1}H-NMR ($CDCl_3$) 1.04 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.15 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 2.21 (sept, 1H, J = 7 Hz, $CH(CH_3)_2$), 2.88 (dd, 1H, J = 6, 16 Hz, $ArCH_2$), 2.92 (t, 1H, J = 6 Hz, NHCHCO), 3.18 (dd, 1H, J = 10, 16 Hz, $ArCH_2$), 3.32 (m, 1H, NH), 3.6−3.9 (m, 2H, CH_2OH), 4.20 (m, 1H, $ArCH_2CH$), 6.50 (bd, 1H, J = 8 Hz, NH), 6.7−7.2 (m, 4H, ArH). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.42; H, 8.09; N, 11.32.

Benzolactam-V8 (3). A mixture of 300 mg (1.21 mmol) of **14**, 500 mg of $NaHCO_3$, 10 mL of methanol, and 12 mL of CH_3I was refluxed for 85 h. The solvent was removed under reduced pressure, and the residual solid was dissolved in $CHCl_3$. This solution was washed twice with brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel using AcOEt/*n*-hexane = 3/1 and recrystallization from diisopropyl ether gave 174 mg of **3** as colorless cubes (55%): ^{1}H-NMR ($CDCl_3$) 0.89 (d, 3H, J = 6 Hz, $CH(CH_3)_2$), 1.06 (d, 3H, J = 6 Hz, $CH(CH_3)_2$), 2.42 (m, 1H, $CH(CH_3)_2$), 2.80 (s, 3H, N-CH_3), 2.80 (dd, 1H, J = 3, 16 Hz, $ArCH_2$), 3.09 (dd, 1H, J = 8, 16 Hz, $ArCH_2$), 3.46 (d, 1H, J = 10 Hz, NCHCO), 3.53 (t, 1H, J = 6 Hz, CH_2OH), 3.64 (m, 1H, CH_2OH), 4.05 (m, 1H, CH_2CH), 6.75−7.20 (m, 5H, ArH, NH); ^{1}H-NMR (CD_3OD) signals are given in the text. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.61; H, 8.57; N, 10.72.

***epi*-Benzolactam-V8 (16).** The procedure was the same as that used for the preparation of **3**, employing 300 mg (1.21 mmol) of **15**. The yield of **16** was 206 mg (65%): ^{1}H-NMR ($CDCl_3$) 0.88 (d, 3H, J = 6 Hz, $CH(CH_3)_2$), 0.97 (d, 3H, J = 6 Hz, $CH(CH_3)_2$), 2.40 (m, 1H, $CH(CH_3)_2$), 2.93 (s, 3H, NCH_3), 2.88 (m, 2H, $ArCH_2$), 3.19 (d, 1H, J = 11 Hz, NCHCO), 3.77 (m, 3H, CH_2OH, $ArCH_2CH$), 6.90 (m, 1H,

NH), 7.00−7.20 (m, 4H, ArH); ^{1}H-NMR (CD_3OD) 0.85 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 0.98 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 2.37 (m, 1H, CH(CH$_3$)$_2$), 2.76 (dd, 1H, J = 7, 15 Hz, ArCH_2), 2.91 (s, 3H, NCH_3), 2.92 (d, 1H, J = 15 Hz, ArCH_2), 3.24 (d, 1H, J = 11 Hz, NCHCO), 3.64 (m, 2H, CH_2OH), 3.72 (m, 1H, ArCH$_2$CH), 6.90−6.95 (m, 2H, ArH), 7.10−7.15 (m, 2H, ArH). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.68; H, 8.69; N, 10.62.

Benzolactam-V8 Acetate. To a solution of 65 mg (0.25 mmol) of **3** in 4 mL of pyridine was added 1 mL of acetic anhydride. The solution was left to stand for 4 h at room temperature, and the solvent was removed under reduced pressure. The residue was poured into 2 N HCl and extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on silica gel and by recrystallization from CH_2Cl_2−hexane afforded 71 mg of benzolactam-V8 acetate as a colorless oil (94%): IR (KBr) 3350 (NH), 1740 (C═O), 1640 (NHCO), 760, 740 (Ar); ^{1}H-NMR ($CDCl_3$) signals are given in the text; HRMS calcd for $C_{17}H_{24}N_2O_3$ 304.1787, found 304.1791.

***epi*-Benzolactam-V8 Acetate.** The procedure was the same as that used for the preparation of **3**-acetate employing 69 mg (0.26 mmol) of **16**, giving 78 mg of *epi*-benzolactam-V8 acetate (98%) as colorless prisms: mp 107 °C; IR (KBr) 3350 (NH), 1740 (C═O), 1655 (NHCO), 770, 750 (Ar); ^{1}H-NMR ($CDCl_3$) 0.89 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 0.96 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 2.11 (s, 3H, COCH_3), 2.44 (m, 1H, CH(CH$_3$)$_2$), 2.92 (s, 3H, NCH_3), 2.96 (m, 2H, ArCH_2), 3.19 (d, 1H, J = 11 Hz, NCHCO), 3.92 (m, 1H, ArCH$_2$CH), 4.15 (m, 2H, CH_2OH), 6.05 (m, 1H, NH), 6.94 (t, 1H, J = 7 Hz, ArH), 7.08 (t, 2H, J = 9 Hz, ArH), 7.19 (t, 1H, J = 8 Hz, ArH). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.36; H, 8.20; N, 9.31.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-4-(2-nitrophenyl)butanoate (17). 1-Bromo-2-(2-nitrophenyl)ethane was prepared according to Portoghese's procedure.[32] The procedure was the same as that used for the preparation of **8**, employing 7.3 g (0.18 mol) of NaH, 350 mL of DMF, 40.1 g (0.185 mol) of diethyl acetamidomalonate, and 39.1 g (0.17 mol) of 1-bromo-2-(2-nitrophenyl)ethane for 20 h at room temperature. The crude product was purified by column chromatography on silica gel, and crystallization from CH_2Cl_2/*n*-hexane gave 50.4 g of **17** (81%) as colorless needles: mp 75−76 °C; IR (KBr) 3250 (NH), 1755 (ester), 1740 (amide), 1540, 1345 (NO_2), 735 (Ar); ^{1}H-NMR ($CDCl_3$) 1.28 (t, 6H, J = 7 Hz, −CH$_2$CH_3), 2.10 (s, 3H, COCH_3), 2.71 (m, 4H, ArCH$_2$CH$_2$), 4.28 (dq, 4H, J = 1, 7 Hz, −CH_2CH$_3$), 7.35 (m, 2H, ArH), 7.52 (dt, 1H, J = 1, 8 Hz, ArH), 7.92 (dd, 1H, J = 1, 8 Hz, ArH). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.60; H, 6.06; N, 7.57. Found: C, 55.73; H, 6.05; N, 7.65.

Ethyl 2-[(*tert*-Butoxycarbonyl)amino]-4-(2-nitrophenyl)butanoate (18). A mixture of 5.16 g (14.1 mmol) of **17**, 12 mL of acetic acid, and 10 mL of concentrated HCl was refluxed gently for 9 h. The mixture was cooled to room temperature and added to 200 mL of ice−water. The aqueous layer was washed twice with 50 mL of CH_2Cl_2 and then concentrated to dryness. The residue was dried under reduced pressure over P_2O_5 to give 3.7 g of amino acid as a white solid. The crude monoacid was added to a solution of 6 mL of $SOCl_2$ in 15 mL of dry ethanol (prepared at −10 °C) with stirring at −40 °C. The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure to remove most of the ethanol. The residue was poured into saturated $NaHCO_3$(aq) and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$(aq), water, and brine. The solution was dried over $MgSO_4$ and then concentrated, and the residue was redissolved in 50 mL of CH_2Cl_2. To this solution was added 5.14 g (23.6 mmol) of Boc_2O at 0 °C. The mixture was stirred for 36 h at room temperature and concentrated. Purification by column chromatography on silica gel afforded 4.83 g of **18** (97%) as a pale yellow oil: IR (neat) 3350 (NH), 1735 (ester), 1700 (Boc), 1525, 1350 (NO_2), 740, 780 (Ar); ^{1}H-NMR ($CDCl_3$) 1.30 (t, 3H, J = 7 Hz, −CH$_2$CH_3), 1.46 (s, 9H, Boc), 2.00−2.07 (m, 1H, ArCH$_2$CH$_2$), 2.61−2.25 (m, 1H, CH$_2$CH$_2$), 2.91−3.00 (m, 2H, CH$_2$CH$_2$), 4.22 (dq, 2H, J = 7 Hz, −CH_2CH$_3$), 4.37 (m, 1H, CH$_2$CH), 7.37 (m, 2H, ArH), 7.53 (dt, 1H, J = 1, 8 Hz, ArH), 7.92 (dd, 1H, J = 1, 8 Hz, ArH); HRMS calcd for $C_{17}H_{24}N_2O_6$ 352.1634, found 352.1624.

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2-[(*tert*-Butoxycarbonyl)amino]-4-(2-nitrophenyl)butan-1-ol (19). The procedure was the same as that used for the preparation of **10**, employing 1.0 g (46.6 mmol) of $LiBH_4$, 50 mL of THF, and 4.83 g of **18** (13.7 mmol) for 1 h at 0 °C and 48 h at room temperature. Recrystallization from AcOEt/*n*-hexane afforded 2.67 g of **19** as pale yellow needles (63%): mp 109−109.5 °C; IR (KBr) 3500 (NH), 3300 (OH), 1530, 1360 (NO_2), 790, 755, 745, 710 (Ar); ^{1}H-NMR ($CDCl_3$) 1.46 (s, 9H, Boc), 1.78−1.92 (m, 2H, CH$_2$CH$_2$), 2.89−2.93 (m, 1H, CH$_2$CH$_2$), 3.00−3.04 (m, 1H, CH$_2$CH$_2$), 3.63−3.72 (m, 3H, CH$_2$CH, CH$_2$OH), 7.37 (m, 2H, ArH), 7.53 (dd, 1H, J = 1, 9 Hz, ArH), 7.93 (dd, 1H, J = 1, 9 Hz, ArH). Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.14; N, 9.03. Found: C, 58.27; H, 7.11; N, 8.97.

2-[(*tert*-Butoxycarbonyl)amino]-4-(2-aminophenyl)butan-1-ol (20). A mixture of 2.9 g (9.3 mmol) of **19** and 0.3 g of 10% Pd−C in 300 mL of ethanol was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and then filtered. The filtrate was concentrated, and the residue was crystallized from benzene to afford 2.57 g of **20** as colorless needles (98%): mp 79−80 °C; IR (KBr) 3300 (OH), 3350 (NH_2), 1675 (Boc), 745 (Ar); ^{1}H-NMR ($CDCl_3$) 1.46 (s, 9H, Boc), 1.71−1.92 (m, 2H, CH$_2$CH_2CH), 2.52−2.60 (m, 2H, ArCH_2), 3.61−3.73 (m, 3H, CH$_2$CH, CH$_2$OH), 6.68−6.77 (m, 2H, ArH), 7.02−7.05 (m, 2H, ArH); HRMS calcd for $C_{15}H_{24}N_2O_3$ 280.1787, found 280.1760.

Diastereomeric Esters 21. The amino alcohol **20** (2.57 g, 9.17 mmol) was converted into 1.92 g (52%) of **21** by the same method as that used for the preparation of **12**. **21**: IR (neat) 3350 (OH), 1730, 1715 (COOEt), 1700, 1685 (Boc), 750 (Ar); ^{1}H-NMR (CDCl3) 0.85−1.10 (m, 12H, CH(CH_3)$_2$), 1.48 (ds, 18H, Boc), 1.62−2.00 (m, 4H, ArCH$_2$CH_2), 2.10−2.23 (m, 2H, CH(CH$_3$)$_2$), 2.60−2.67 (m, 4H, ArCH_2), 3.58−3.78 (m, 4H, CH$_2$OH), 3.71 (ds, 6H, COOCH_3), 3.90−3.98 (m, 2H, NHCHCO), 4.16−4.28 (m, 2H, CH_2OH), 4.92 (bs, 1H, NHCOO), 5.07 (bs, 1H, NHCOO), 6.58 (d, 2H, NH), 6.68−6.86 (m, 2H, ArH), 7.04−7.11 (m, 4H, ArH).

Activated Esters 22. The diastereomeric esters **21** (1.72 g, 4.36 mmol) were converted into 1.61 g (77%) of **22** by the same method as that used for the preparation of **13**. The product was unstable and was used without further purification.

***N*-Desmethylbenzolactam-V9 (23) and *N*-Desmethyl-*epi*-benzolactam-V9 (24).** Trifluoroacetic acid (5 mL) was added to a solution of 1.61 g (8.62 mmol) of **22** in 30 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 30 min at 0 °C and 50 min at room temperature, and then the solvent was removed under reduced pressure below 30 °C. The residue was dissolved in 1 L of AcOEt, and then 300 mL of saturated $NaHCO_3$(aq) was added and the mixture was refluxed for 68 h with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was separated by column chromatography and PTLC with AcOEt/CH_2Cl_2 to give 108 mg of **23** and 158 mg of **24**. **23**: colorless prisms (from AcOEt−hexane); mp 147−148 °C; IR (KBr) 3350 (OH), 3280 (NH), 1625 (NHCO), 755 (Ar); ^{1}H-NMR (CD_3OD) two conformers (1:1) existed. Signals due to the conformers were assigned as follows: 0.90 (d, 1.5H, J = 7 Hz, CH(CH_3)$_2$), 1.05 (d, 1.5H, J = 7 Hz, CH(CH_3)$_2$), 1.26 (m, 3H, CH(CH3)2), 1.40 (m, 0.5H, ArCH$_2$CH_2), 1.80 (m, 0.5H, ArCH$_2$CH_2), 1.93 (m, 0.5H, ArCH$_2$CH_2), 2.10 (m, 0.5H, ArCH$_2$CH_2), 2.21 (m, 0.5H, CH(CH$_3$)$_2$), 2.42 (m, 0.5H, ArCH$_2$CH_2), 2.50−2.68 (m, 2H, ArCH$_2$), 3.17 (m, 0.5H, CH_2OH), 3.35−3.50 (m, 2H, CH_2OH, NHCHCO), 3.75 (d, 0.5H, J = 10 Hz, NHCHCO), 4.24 (m, 0.5H, CHCH$_2$OH), 4.35 (m, 0.5H, CHCH$_2$-OH), 6.80 (m, 0.5H, ArH), 6.94 (m, 0.5H, ArH), 7.03−7.20 (m, 3H, ArH). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.96; H, 8.50; N, 10.98. **24**: colorless needles (from MeOH); mp 130−131 °C; IR (KBr) 3450 (OH), 3300 (NH), 1655 (NHCO), 745 (Ar); ^{1}H-NMR (CD_3OD) 0.95 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.23 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.78 (m, 1H, ArCH$_2$CH_2), 1.99 (m, 1H, ArCH$_2$CH_2), 2.12 (m, 1H, ArCH$_2$CH_2), 2.78 (m, 1H, ArCH$_2$), 2.85 (m, 1H, ArCH$_2$0, 3.47 (m, 2H, CH_2OH), 3.75 (bs, 2H, NHCHCO, CHCH2OH), 6.89 (m, 2H, ArH), 6.99 (m, 1H, ArH), 7.10 (m, 1H, ArH). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.37; H, 8.43; N, 10.87.

Benzolactam-V9 (4). The procedure was the same as that used for the preparation of **3**, employing 84 mg (0.32 mmol) of **23** for 7 days. The yield of **16** was 65 mg (74%). **4**: colorless oil; IR (KBr) 3350

(OH), 1645 (NHCO), 760, 740 (Ar); ^{1}H-NMR ($CDCl_3$) 0.90 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.16 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.75 (dd, 1H, J = 12, 25 Hz, $ArCH_2CH_2$), 2.30 (m, 2H, $CH(CH_3)_2$, $ArCH_2CH_2$), 2.49 (dd, 1H, J = 11, 24 Hz, $ArCH_2$), 2.65 (m, 1H, $ArCH_2$), 2.74 (d, 1H, J = 17 Hz, NCHCO), 2.76 (s, 3H, N-CH_3), 3.43 (dd, 1H, J = 5, 11 Hz, CH_2OH), 3.61 (dd, 1H, J = 4, 11 Hz, CH_2OH), 4.44 (m, 1H, CH_2CH), 4.54 (d, 1H, J = 12 Hz, NH), 7.10 (s 1H, ArH), 7.14 (s, 3H, ArH); ^{1}H-NMR (CD_3OD) signals are given in the text; HRMS calcd for $C_{16}H_{24}N_2O_2$ 276.1838, found 276.1825.

***epi*-Benzolactam-V9 (25).** The procedure was the same as that used for the preparation of **4**, employing 70 mg (0.27 mmol) of **24** for 7 days to afford 69 mg of **25** (93%) as colorless needles from AcOEt−hexane: mp 164−165 °C; IR (KBr) 3400 (NH), 3300 (OH), 1645 (NHCO), 755, 745 (Ar); ^{1}H-NMR ($CDCl_3$) 0.82 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.19 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.58 (m, 1H, $ArCH_2CH_2$), 1.92 (m, 1H, $ArCH_2CH_2$), 2.49 (m, 1H, $CH(CH_3)_2$), 2.58 (m, 1H, $ArCH_2$), 2.71 (dd, 1H, J = 3, 7 Hz, $ArCH_2$), 2.76 (s, 3H, NCH_3), 3.17 (d, 1H, J = 10 Hz, NCHCO), 3.26 (bs, 1H, CH_2CH), 3.45 (dd, 1H, J = 6, 11 Hz, CH_2OH), 3.54 (dd, 1H, J = 4, 11 Hz, CH_2OH), 6.32 (bd, 1H, J = 11 Hz, NH), 7.15−7.27 (m, 4H, ArH); ^{1}H-NMR (CD_3OD) 0.84 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.21 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.64 (tt, 1H, J = 3, 13 Hz, $ArCH_2CH_2$), 1.76 (tt, 1H, J = 3, 12 Hz, $ArCH_2CH_2$), 2.44 (m, 1H, $CH(CH_3)_2$), 2.58 (dt, 1H, J = 3, 13 Hz, $ArCH_2$), 2.69 (dd, 1H, J = 3, 13 Hz, $ArCH_2$), 2.73 (s, 3H, NCH_3), 3.20 (bs, 1H, CH_2CH), 3.24 (d, 1H, J = 18 Hz, NCHCO), 3.38 (m, 2H, CH_2OH), 7.14−7.26 (m, 4H, ArH). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.27; H, 8.83; N, 9.84. Found: C, 69.53; H, 8.75; N, 10.14.

Benzolactam-V9 Acetate. The procedure was the same as that used for the preparation of **3**-acetate, employing 65 mg (0.24 mmol) of **4** to afford 71 mg of benzolactam-V9 acetate (98%) as colorless plates (94%): mp 127−128 °C; IR (KBr) 3350 (NH), 1740 (Ac), 1640 (NHCO), 760, 740 (Ar); ^{1}H-NMR ($CDCl_3$) 0.90 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.16 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.68 (m, 1H, $ArCH_2CH_2$), 1.98 (s, 3H, $COCH_3$), 2.31 (m, 2H, $CH(CH_3)_2$, $ArCH_2CH_2$), 2.48 (dd, 1H, J = 11, 14 Hz, $ArCH_2$), 2.64 (dd, 1H, J = 8, 14 Hz, $ArCH_2$), 2.72 (d, 1H, J = 11 Hz, NCHCO), 2.76 (s, 3H, NCH_3), 3.90 (dd, 1H, J = 4, 11 Hz, CH_2OH), 4.08 (dd, 1H, J = 5, 11 Hz, CH_2OH), 4.46 (bd, 1H, J = 11 Hz, NH), 4.60 (m, 1H, CH_2CH), 7.15 (s, 4H, ArH). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.82; H, 8.37; N, 8.63.

***epi*-Benzolactam-V9 Acetate.** The procedure was the same as that used for the preparation of **4**-acetate, employing 69 mg (0.25 mmol) of **25** to afford 78 mg of *epi*-benzolactam-V9 acetate as a colorless oil (98%): IR (KBr) 3350 (NH), 1740 (Ac), 1655 (NHCO), 770, 750 (Ar); ^{1}H-NMR ($CDCl_3$) 0.84 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.21 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.61 (m, 1H, $ArCH_2CH_2$), 1.82 (m, 1H, $ArCH_2CH_2$), 2.01 (s, 3H, $COCH_3$), 2.54 (m, 1H, $CH(CH_3)_2$), 2.60 (m, 1H, $ArCH_2$), 2.74−2.79 (m, 1H, $ArCH_2$), 2.77 (s, 3H, N-CH_3), 3.11 (d, 1H, J = 10 Hz, NCHCO), 3.46 (bs, 1H, CH_2CH), 3.89 (dd, 1H, J = 4, 12 Hz, CH_2OH), 3.99 (dd, 1H, J = 4, 12 Hz, CH_2OH), 5.62 (bd, 1H, J = 8 Hz, NH), 7.17−7.28 (m, 4H, ArH); HRMS calcd for $C_{18}H_{26}N_2O_3$ 318.1943, found 318.1964.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-5-(2-nitrophenyl)pentanoate (26). 1-Bromo-2-(2-nitrophenyl)propane was prepared from 2-nitrocinnamic acid.[32] The procedure was the same as that used for the preparation of **8**, employing 1.7 g (42.5 mmol) of NaH, 110 mL of DMF, 8.54 g (39.4 mmol) of diethyl acetamidomalonate, and 9.23 g (37.8 mmol) of 1-bromo-2-(2-nitrophenyl)ethane for 20 h at room temperature. The crude product was purified by column chromatography on silica gel to give 9.99 g of **26** (69%) as a pale yellow oil: IR (neat) 3400 (NH), 1735−1760 (ester), 1520, 1350 (NO_2), 740 (Ar); ^{1}H-NMR ($CDCl_3$) 1.26 (t, 6H, J = 7 Hz, $-CH_2CH_3$), 1.49 (m, 2H, $ArCH_2CH_2CH_2$), 2.04 (s, 3H, $COCH_3$), 2.45 (m, 2H, $ArCH_2CH_2CH_2$), 2.89 (t, 2H, J = 8 Hz, $ArCH_2CH_2CH_2$), 4.25 (m, 4H, $-CH_2CH_3$), 7.35 (m, 2H, ArH), 7.52 (dt, 1H, J = 1, 8 Hz, ArH), 7.90 (dd, 1H, J = 1, 8 Hz, ArH); HRMS calcd for $C_{18}H_{24}N_2O_7$ 380.1584, found 380.1546.

Ethyl 2-[(*tert*-Butoxycarbonyl)amino]-5-(2-nitrophenyl)pentanoate (27). The diester **26** (10.0 g, 26.3 mmol) was converted into 7.66 g (80%) of **27** by the same method as that used for the preparation of **18**. **27**: pale yellow oil; IR (neat) 3350 (NH), 1370 (ester), 1700 (Boc), 1525, 1345 (NO_2), 735 (Ar); ^{1}H-NMR ($CDCl_3$) 1.27 (t, 3H, J = 7 Hz, $-CH_2CH_3$), 1.44 (s, 9H, Boc), 1.64−1.74 (m, 4H, $ArCH_2CH_2CH_2$), 2.90 (t, 2H, J = 7 Hz, $ArCH_2$), 4.20 (q, 2H, J = 7 Hz, $-CH_2CH_3$), 4.34 (bs, 1H, CH_2CH), 5.05 (bs, 1H, NH), 7.35 (m, 2H, ArH), 7.52 (t, 1H, J = 8 Hz, ArH), 7.89 (dd, 1H, J = 1, 9 Hz, ArH); HRMS calcd for $C_{18}H_{26}N_2O_6$ 366.1791, found 366.1762.

Ethyl 2-[(*tert*-Butoxycarbonyl)amino]-5-[2-(formylamino)phenyl]-propanoate (28). A mixture of 4.17 g (9.3 mmol) of **27** and 620 mg of 10% Pd−C in 200 mL of ethanol was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and then filtered. The filtrate was concentrated, and the residue was redissolved in THF (10 mL). The amine solution was added at 0 °C to a mixed anhydride solution (prepared by addition of 3.16 g of formic acid to 5.52 g of acetic anhydride at 0 °C, followed by heating for 2.5 h at 50−60 °C). The mixture was stirred for 4.5 h at room temperature and then concentrated under reduced pressure. The residue was poured into saturated $NaHCO_3$(aq) and extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel afforded 4.05 g of **28** (87%) as a viscous oil: IR (KBr) 3330 (NH), 1735 (COOEt), 1700 (NHCHO), 1680 (Boc), 750 (Ar); ^{1}H-NMR ($CDCl_3$), two conformers exist in a ratio of 2:3, 1.28 (t, 1.2H, J = 7 Hz, $-CH_2CH_3$), 1.31 (t, 1.8H, J = 7 Hz, $-CH_2CH_3$), 1.45 (s, 9H, Boc), 1.60−1.98 (m, 4H, $ArCH_2CH_2CH_2$), 2.45−2.65 (m, 1H, $ArCH_2$), 2.72−2.84 (m, 0.4H, $ArCH_2$), 2.90−3.00 (m, 0.6H, $ArCH_2$), 4.22 (m, 2H, $-CH_2CH_3$), 4.40 (m, 0.4H, CH_2CH), 4.48 (m, 0.6H, CH_2CH), 5.20 (bd, 0.4H, J = 8 Hz, NH), 5.32 (bd, 0.6H, J = 8 Hz, NH), 7.10−7.25 (m, 4H, ArH), 8.07 (bd, 0.6H, J = 8 Hz, NHCHO), 8.47 (bs, 0.4H, NHCHO), 8.52 (m, 1H, NHCHO); HRMS calcd for $C_{19}H_{28}N_2O_5$ 364.1998, found 364.1955.

Ethyl 2-[(*tert*-Butoxycarbonyl)amino]-5-[2-(methylamino)phenyl]-propanoate (29). To a solution of 3.55 g (9.7 mmol) of **28** in 100 mL of THF was added dropwise 20 mL of 1.0 M BH_3 in THF solution at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of 10 mL of 10% citric acid, and the whole was extracted with AcOEt. After concentration, the residue was poured into brine and extracted with AcOEt. The organic layer was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel gave 3.00 g of **29** (88%) as colorless needles: mp 65−67 °C; IR (KBr) 3400, 3340 (NH), 1730 (COOEt), 1695 (BOC), 740 (Ar); ^{1}H-NMR ($CDCl_3$) 1.27 (t, 3H, J = 7 Hz, $-CH_2CH_3$), 1.45 (s, 9H, Boc), 1.60−1.90 (m, 4H, $ArCH_2CH_2CH_2$), 2.49 (m, 1H, $ArCH_2$), 2.62 (m, 1H, $ArCH_2$), 2.89 (s, 3H, NCH_3), 4.19 (m, 2H, $-CH_2CH_3$), 4.36 (m, 1H, CH_2CH), 5.10 (bd, 1H, NHCOO), 6.73 (m, 3H, NH, ArH), 7.04 (d, 1H, J = 6 Hz, ArH), 7.16 (t, 1H, J = 8 Hz, ArH). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.12; H, 8.65; N, 7.99.

2-[(*tert*-Butoxycarbonyl)amino]-5-[2-(methylamino)phenyl]propan-1-ol (30). The procedure was the same as that used for the preparation of **10**, employing 1.50 g (70.0 mmol) of $LiBH_4$, 200 mL of THF, and 6.84 g of **29** (19.5 mmol) for 1 h at 0 °C and 4 h at room temperature. Purification by silica gel column chromatography afforded 5.99 g of **30** as colorless needles (99%): mp 100 °C; IR (KBr) 3350 (NH), 3250 (OH), 1680 (Boc), 745 (Ar); ^{1}H-NMR ($CDCl_3$) 1.45 (s, 9H, Boc), 1.52−1.70 (m, 4H, $ArCH_2CH_2CH_2$), 2.46 (m, 1H, $ArCH_2$), 2.56 (m, 1H, $ArCH_2$), 2.88 (s, 3H, NCH_3), 3.55 (dd, 1H, J = 5, 10 Hz, CH_2OH), 3.68 (d, 1H, J = 10 Hz, CH_2OH), 3.70 (bs, 1H, CH_2CH), 4.70 (bs, 1H, NHCOO), 6.66 (m, 2H, ArH), 7.03 (dd, 1H, J = 1.5, 7 Hz, ArH), 7.15 (dt, 1H, J = 1.5, 7 Hz, ArH). Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08. Found: C, 66.34; H, 9.25; N, 8.99.

Diastereomeric Esters 31. A mixture of 3.37 g (10.9 mmol) of **30**, benzyl DL-α-[[(trifluoromethyl)sulfonyl]oxy]isovalerate[23] (6.09 g, 17.9 mmol), and 2,6-lutidine (4.26 g, 39.8 mmol) in 100 mL of CH_2ClCH_2Cl was refluxed for 2 days, and then the solvent was removed by evaporation. The residue was chromatographed on silica gel to give 2.91 g of a diastereomeric mixture of **31** as a pale yellow oil (53%): IR (KBr) 3400 (OH), 1720, 1710 (COOBn), 1690, 1685 (Boc), 745, 695 (Ar); ^{1}H-NMR ($CDCl_3$) 0.89 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), 1.13 (m, 6H, $CH(CH_3)_2$), 1.43 (two of s, 18H, Boc), 1.52 (m, 2H, $ArCH_2CH_2CH_2$), 1.65 (m, 2H, $ArCH_2CH_2CH_2$), 2.25 (m, 2H, $CH(CH_3)_2$), 2.40 (m, 2H, $ArCH_2CH_2CH_2$), 2.51 (m, 2H, $ArCH_2CH_2CH_2$), 2.78 (two of s, 6H, NCH_3), 2.82 (m, 4H, $ArCH_2$), 3.22 (two of d, 2H, $CHCH(CH_3)_2$), 3.52 (br, 2H, CH_2CH), 3.62 (br, 4H, CH_2OH), 4.58 (br, 2H, NHCOO),

4.99 (m, 4H, CH_2C$_6$H$_5$), 7.02 (m, 4H, ArH), 7.11 (m, 6H, ArH), 7.27 (m, 6H, ArH), 7.37 (m, 8H, ArH).

Activated Esters 32. A mixture of diastereomeric esters **31** (2.91 g, 5.84 mmol) and 530 mg of 10% Pd−C in 400 mL of methanol was vigorously stirred under 1 atm of H_2 at room temperature for 2 h and then filtered. The filtrate was concentrated, and the residue was crystallized from benzene to afford the carboxylic acid. The acid and 1.84 g (16.0 mmol) of *N*-hydroxysuccinimide were dissolved in 60 mL of CH_3CN, and then a solution of 1.65 g (8.17 mmol) of DCC in 10 mL of CH_3CN was added at 0 °C with stirring. Stirring was continued for 4 h at room temperature, and then the solvent was removed under reduced pressure. The residue was suspended in AcOEt, and insoluble urea was filtered off. The filtrate was concentrated and purified by column chromatography on silica gel to give 2.05 g of **32** (77%) as a colorless liquid. This product was unstable and was used without further purification.

Benzolactam-V10 Acetate (34) and *epi*-Benzolactam-V10 Acetate (35). Trifluoroacetic acid (15 mL) was added to a solution of 2.05 g (4.06 mmol) of **32** in 10 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 4 h at room temperature, and then the solvent was removed under reduced pressure below 30 °C. The residue was dissolved in 50 mL of AcOEt, and 10 mL of saturated $NaHCO_3$(aq) was added. The mixture was refluxed for 2 days with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was separated by column chromatography to give 436 mg (37%) of a mixture of BL-V10 (**5**) and *epi*-BL-V10 (**33**). The mixture of BL-V10 in 10 mL of pyridine was treated with 2 mL of acetic anhydride for 2 h at room temperature, and the solvent was removed under reduced pressure. The residue was poured into 2 N HCl and extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel and PTLC afforded 206 mg of benzolactam-V10 acetate (**34**) as colorless plates (41%) and 205 mg of *epi*-V10 acetate (**35**) as colorless plates (41%). **34**: colorless plates; mp 130.5−131.5 °C; IR (KBr) 3300 (NH), 1740 ($COCH_3$), 1645 (NHCO), 765, 710, 675 (Ar); ^{1}H-NMR ($CDCl_3$) 0.89 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.02 (m, 1H, ArCH$_2$CH$_2$CH_2), 1.16 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.55 (dt, 1H, J = 4, 15 Hz, ArCH$_2$CH$_2$CH_2), 1.91 (m, 1H, ArCH$_2$CH_2CH$_2$), 1.99 (s, 1H, OCOCH_3), 2.15 (m, 1H, ArCH$_2$CH_2CH$_2$), 2.31 (m, 1H, CH(CH$_3$)$_2$), 2.53 (dt, 1H, J = 4, 15 Hz, ArCH_2), 2.63 (dt, 1H, J = 4, 15 Hz, ArCH_2), 2.74 (d, 1H, J = 11 Hz, NCHCO), 2.80 (s, 3H, NCH_3), 3.80 (dd, 1H, J = 6, 11 Hz, CH$_2$OH), 3.97 (dd, 1H, J = 5, 11 Hz, CH$_2$OH), 4.18 (m, 1H, CH$_2$CH), 4.35 (bd, 1H, J = 9 Hz, NH), 7.06−7.18 (m, 3H, ArH), 7.27 (m, 1H, ArH). Anal. Calcd for $C_{19}H_{28}N_2O_3$; C, 68.65; H, 8.49; N, 8.43. Found: C, 68.47; H, 8.57; N, 8.33. **35**: colorless plates; mp 102−102.5 °C; IR (KBr) 3350 (NH), 1730 ($COCH_3$), 1655 (NHCO), 760, 750, 670 (Ar); *epi*-benzolactam-V10 acetate gave broadened ^{1}H-NMR signals even at −90 °C in CD_2Cl_2. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.39; H, 8.70; N, 8.62.

Benzolactam-V10 (5). To a solution of 53 mg (0.16 mmol) of **34** in 6 mL of MeOH was added 3 drops of 4 N KOH, and the mixture was stirred for 100 min at room temperature. After removal of the solvent under reduced pressure, the residue was poured into 2 N HCl and extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration, purification by column chromatography on silica gel, and recrystallization from AcOEt/*n*-hexane afforded 38 mg of benzolactam-V10 (**5**) as colorless plates (83%): mp 124−126 °C; IR (KBr) 3350 (NH), 1640 (NHCO), 760, 720 (Ar); ^{1}H-NMR ($CDCl_3$) 0.93 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.10 (m, 1H, ArCH$_2$CH$_2$CH_2), 1.15 (d, 3H, J = 7 Hz, CH(CH_3)$_2$), 1.56 (m, 1H, ArCH$_2$CH$_2$CH_2), 1.90 (m, 1H, ArCH$_2$CH_2CH$_2$), 2.14 (m, 1H, ArCH$_2$CH_2CH$_2$), 2.30 (m, 1H, CH(CH$_3$)$_2$), 2.63 (m, 2H, ArCH_2), 2.76 (s, 3H, NCH_3), 2.87 (d, 1H, J = 10 Hz, NCHCO), 3.39 (dd, 1H, J = 6, 11 Hz, CH$_2$OH), 3.46 (dd, 1H, J = 5, 11 Hz, CH$_2$OH), 3.85 (m, 1H, CH$_2$CH), 4.96 (bd, 1H, J = 8 Hz, NH), 7.12 (m, 1H, ArH), 7.27 (m, 1H, ArH); ^{1}H-NMR (CD$_3$OD) signals are given in the text. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.20; H, 9.01; N, 9.54.

***epi*-Benzolactam-V10 (33).** The procedure was the same as that used for the preparation of **5**, employing 32 mg (0.096 mmol) of **35** to afford 21 mg of **33** as colorless needles (83%): mp 157−158 °C; IR (KBr) 3400 (NH), 1655 (NHCO), 770, 690 (Ar); *epi*-benzolactam-V10 gave broadend ^{1}H-NMR signals even at −90 °C in CD_2Cl_2. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.22; H, 9.31; N, 9.61.

4-(Bromomethyl)-2-nitrobenzaldehyde. A mixture of 25.0 g (0.186 mol) of telephthalaldehyde and 220 mg of 10% Pd−C in 100 mL of ethanol−water (4:1) was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and then filtered. The filtrate was concentrated to give 25.2 g of 4-(hydroxymethyl)benzaldehyde. A mixture of the alcohol in 100 mL of toluene and 50 mL of 48% HBr was refluxed for 2 h with stirring. The mixture was poured into ice−water and extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Concentration and recrystallization from *n*-hexane afforded 37.5 g of 4-(bromomethyl)benzaldehyde as colorless needles (82%): mp 97.5−98.0 °C; IR (KBr) 1685 (CHO), 765 (Ar); ^{1}H-NMR ($CDCl_3$) 4.52 (s, 2H, CH_2), 7.56 (d, 2H, J = 8 Hz, ArH), 7.87 (d, 2H, J = 8 Hz, ArH), 10.02 (s, 1H, CHO). Anal. Calcd for C_8H_7OBr: C, 48.27; H, 3.54. Found: C, 48.19; H, 3.49. The bromide (22.3 g, 0.112 mol) was added at 0 °C to a solution of KNO_3 (11.65 g, 0.115 mol) in 200 mL of H_2SO_4, and the mixture was stirred for 4 h at room temperature, poured into ice−water, and extracted with CH_2Cl_2. The extract was washed with water, saturated $NaHCO_3$(aq), water, and brine and dried over $MgSO_4$. Concentration and recrystallization from AcOEt/*n*-hexane afforded 20.14 g of 4-(bromomethyl)-2-nitrobenzaldehyde as colorless needles (74%): mp 77.5−78 °C; IR (KBr) 1700 (CHO), 1525, 1345 (NO_2); ^{1}H-NMR ($CDCl_3$) 4.87 (s, 2H, $ArCH_2$), 7.79 (d, 1H, J = 8 Hz, ArH), 8.13 (dd, 1H, J = 2, 8 Hz, ArH), 8.52 (d, 1H, J = 2 Hz, ArH), 10.09 (s, 1H, CHO). Anal. Calcd for $C_8H_5NO_3Br$: N, 5.74; C, 39.37; H, 2.48. Found: N, 5.46; C, 39.53; H, 2.44.

Diester 36. The nitrobenzyl bromide (9.93 g, 40.7 mmol) was converted into ethyl 2-(acetylamino)-2-(ethoxycarbonyl)-3-(4-formyl-2-nitrophenyl)propanoate by employing 1.61 g (40.3 mmol) of NaH, 9.00 g (41.5 mmol) of diethyl acetamidomalonate, and 140 mL of DMF for 2.5 h at room temperature under an Ar atmosphere. Purification by column chromatography on silica gel with CH_2Cl_2 gave 14.95 g of ethyl 2-(acetylamino)-2-(ethoxycarbonyl)-3-(4-formyl-2-nitrophenyl)-propanoate as a pale yellow powder (98%): ^{1}H-NMR ($CDCl_3$) 1.28 (t, 6H, J = 7 Hz, −CH$_2$CH_3), 2.08 (s, 3H, $COCH_3$), 4.14 (s, 2H, ArCH_2) 4.20−4.30 (m, 4H, J = 1, 7 Hz, −CH_2CH$_3$), 7.50 (d, 1H, J = 8 Hz, ArH), 8.00 (dd, 1H, J = 1, 8 Hz, ArH), 8.32 (d, 1H, J = 1 Hz, ArH), 10.04 (s, 1H, CHO); HRMS calcd for $C_{17}H_{20}N_2O_8$ 380.1220, found 380.1217. A solution of the Wittig ylide was prepared as follows. A solution of nonyltriphenylphosphonium bromide[33] (4.47 g, 9.53 mmol) in 30 mL of THF was treated with 9.52 mmol of *n*-BuLi at 0 °C, and the mixture was stirred for 90 min under an Ar atmosphere. To the ylide solution was added a solution of 2.18 g (5.73 mmol) of the aldehyde in 10 mL of THF at −78 °C. The mixture was stirred for 90 min at −78 °C and 2 h at 0 °C. The reaction was quenched by the addition of 5 mL of 2 N HCl, and then the solvent was evaporated. The residue was poured into 2 N HCl and extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/1 afforded 1.07 g of **36** as a yellow viscous liquid (56%): ^{1}H-NMR ($CDCl_3$) (*cis*−*trans* isomers exist in a ratio of 1:3) 0.87 (m, 3H, (CH$_2$)$_7$CH_3), 1.28 (m, 16H, −(CH_2)$_5$CH$_3$, OCH$_2$CH_3), 1.45 (m, 2H, CH_2(CH$_2$)$_5$CH$_3$), 1.97 (2s, 3H, $COCH_3$), 2.20−2.34 (m, 2H, CH═CHCH_2), 4.02 (s, 0.5H, $ArCH_2$), 4.04 (s, 1.5H, $ArCH_2$), 4.26 (m, 4H, OCH_2CH$_3$), 5.80 (dd, 1H, J = 4, 12 Hz, ArCH═CH), 6.33 (br, 1H, ArCH═CH), 6.49 (br, 1H, NH), 7.14 (d, 0.25H, J = 8 Hz, ArH), 7.19 (d, 0.75H, J = 8 Hz, ArH), 7.36 (dd, 0.75H, J = 1, 8 Hz, ArH), 7.41 (dd, 0.25H, J = 1, 8 Hz, ArH), 7.72 (d, 1H, J = 1 Hz, ArH).

Nitro Alcohol 38. The diester **36** (4.42 g, 9.02 mmol) was converted into the nitro alcohol **38** by the same method as that used for the preparation of **19** from **17**. Purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/1 afforded 2.32 g of **38** as a colorless oil (59%): ^{1}H-NMR ($CDCl_3$) (*cis*−*trans* isomers exist in a

(33) Massy-Westropp, R. A.; O. Warren, R. F. *Aust. J. Chem.* **1984**, *37*, 1969−1977.

ratio of 1:3) 0.87 (m, 3H, $(CH_2)_7CH_3$), 1.20−1.40 (br, 12H, $-(CH_2)_6CH_3$), 1.62 (s, 9H, Boc), 2.20−2.30 (m, 2H, CH=CHCH_2), 3.04 (m, 1H, $ArCH_2$), 3.19 (m, 1H, $ArCH_2$), 3.69 (m, 1H, CH_2OH), 3.73 (m, 1H, CH_2OH), 3.99 (m, 1H, CH_2CH), 5.03 (br, 1H, ArCH=CH), 5.79 (dt, 1H, J = 7, 12 Hz, ArCH=CH), 6.36 (bd, 1H, J = 12 Hz, NH), 7.3−7.5 (m, 2H, ArH), 7.85 (bs, 1H, ArH); HRMS calcd for $C_{24}H_{42}N_2O_3$ 406.3195, found 406.3179.

Amino Alcohol 39. The procedure was the same as that used for the preparation of **20**, employing 2.32 g (5.7 mmol) of **38**, 200 mg of 10% Pd−C, and 20 mL of ethanol for 7 h at room temperature under H_2. Recrystallization from *n*-hexane afforded 2.04 g of **39** as colorless prisms (94%): mp 72−73 °C; ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, J = 7Hz, $(CH_2)_7CH_3$), 1.25 (br, 14H, $-(CH_2)_7CH_3$), 1.46 (s, 9H, Boc), 1.57 (m, 2H, $CH_2(CH_2)_7CH_3$), 2.66 (dd, 1H, J = 10, 14 Hz, $ArCH_2$), 2.84 (dd, 1H, J = 5, 14 Hz, $ArCH_2$), 2.49 (t, 2H, J = 8 Hz, $CH_2(CH_2)_8CH_3$), 3.58 (m, 2H, CH_2OH), 3.73 (m, 1H, CH_2CH), 5.13 (bd, 1H, J = 8 Hz, NH), 6.54 (s, 1H, ArH), 6.58 (d, 1H, J = 8 Hz, ArH), 6.93 (d, 1H, J = 8 Hz, ArH); HRMS calcd for $C_{24}H_{42}N_2O_3$ 406.3195, found 406.3179.

***N*-(Methylamino) Alcohol 40.** A solution of **39** (2.04 g, 5.02 mmol) in 30 mL of THF was added at 0 °C to a mixed anhydride solution (prepared by addition of 1.21 g of formic acid to 2.60 g of acetic anhydride at 0 °C, followed by heating for 2 h at 60−70 °C). After having been stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was poured into saturated $NaHCO_3$(aq), and the whole was extracted with AcOEt. The extract was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/1 afforded 1.75 g of the *N*-formate as a pale yellow oil (80%). To a solution of 1.61 g (3.71 mmol) of the formate in 100 mL of THF was added dropwise 16 mL of 1.0 M BH_3 in THF solution at 0 °C, and the mixture was stirred for 4 h at 0 °C. The reaction was quenched by the addition of 10 mL of 10% citric acid, and the whole was extracted with AcOEt. After concentration, the residue was poured into brine and extracted with AcOEt. The organic layer was washed with water and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1:2 gave 1.30 g of **40** as colorless prisms (89%): ^{1}H-NMR ($CDCl_3$) 0.86 (t, 3H, J = 7 Hz, $(CH_2)_7CH_3$), 1.24 (br, 14H, $-(CH_2)_7CH_3$), 1.44 (s, 9H, Boc), 1.56 (m, 2H, $CH_2(CH_2)_7CH_3$), 2.52 (t, 2H, J = 8 Hz, $CH_2(CH_2)_8CH_3$), 2.61 (dd, 1H, J = 10, 14 Hz, $ArCH_2$), 2.78 (dd, 1H, J = 4, 14 Hz, $ArCH_2$), 2.85 (s, 3H, NCH_3), 3.60 (m, 2H, CH_2OH), 3.67 (m, 1H, CH_2CH), 5.08 (br, 1H, NH), 6.45 (bs, 1H, ArH), 6.49 (d, 1H, J = 7 Hz, ArH), 6.88 (d, 1H, J = 7 Hz, ArH); HRMS calcd for $C_{25}H_{44}N_2O_3$ 420.3352, found 420.3315.

Diastereomeric esters 41. The *N*-methylamino alcohol **40** (1.27 g, 3.02 mmol) was converted into a diastereomeric mixture of esters **41** by the same method as that used for the preparation of **31** from **30**, using 1.84 g of the triflate and 1.05 g of 2,6-lutidine in 30 mL of CH_2ClCH_2Cl. Purification by column chromatography on silica gel with CH_2Cl_2/AcOEt = 20/3 gave 1.62 g of diastereomeric esters **41** as a colorless oil (80%). To confirm the structure, a small portion of the mixture was separated by using PTLC. **41A** (the stereochemistry corresponds to that of BL-V8-310): colorless oil; ^{1}H-NMR ($CDCl_3$) 0.87 (t, 3H, J = 7 Hz, $(CH_2)_7CH_3$), 0.91 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.16 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.23 (bs, 14H, $-(CH_2)_7CH_3$), 1.45 (s, 9H, Boc), 1.50 (bs, 2H, $CH_2(CH_2)_7CH_3$), 2.27 (m, 1H, $CH(CH_3)_2$), 2.45 (t, 2H, J = 8 Hz, $CH_2(CH_2)_8CH_3$), 2.76 (dd, 1H, J = 6, 13 Hz, $ArCH_2$), 2.84 (s, 3H, NCH_3), 2.97 (dd, 1H, J = 10, 13 Hz, $ArCH_2$), 3.27 (bd, 1H, CH_2OH), 3.33 (d, 1H, J = 10 Hz, NC*H*CO), 3.44 (bd, 1H, CH_2OH), 3.76 (bs, 1H, $CHCH_2OH$), 4.82 (d, 1H, J = 12 Hz, $ArCH_2O$), 4.95 (d, 1H, J = 12 Hz, $ArCH_2O$), 5.40 (bd, 1H, J = 8 Hz, NHCOO), 6.92 (bd, 2H, J = 8 Hz, ArH), 7.00 (m, 2H, ArH), 7.16 bd, 1H, J = 8 Hz, ArH), 7.25 (m, 3H, ArH); HRMS calcd for $C_{37}H_{58}N_2O_5$ 610.4346, found 610.4335. **41B** (the stereochemistry corresponds to that of *epi*-BL-V8-310): colorless oil; ^{1}H-NMR ($CDCl_3$) 0.87 (m, 6H, $(CH_2)_7CH_3$, $CH(CH_3)_2$), 1.15 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.23 (s, 14H, $-(CH_2)_7CH_3$), 1.37 (s, 9H, Boc), 1.50 (m, 2H, $CH_2(CH_2)_7CH_3$), 2.29 (m, 1H, $CH(CH_3)_2$), 2.45 (t, 2H, J = 8 Hz, $CH_2(CH_2)_8CH_3$), 2.59 (dd, 1H, J = 4, 13 Hz, $ArCH_2$), 2.87 (s, 3H, NCH_3), 2.91 (d, 1H, J = 13 Hz, $ArCH_2$), 3.25 (d, 1H, J = 10 Hz, NC*H*CO), 3.50−3.67 (br, 2H, CH_2OH), 3.72 (m, 1H, $CHCH_2OH$), 4.87 (d, 1H, J = 12 Hz, $ArCH_2O$), 4.99 (d, 1H, J = 12 Hz, $ArCH_2O$), 6.04 (bd, 1H, J = 3 Hz NH), 6.92 (m, 2H, ArH), 7.01 (m, 2H, ArH), 7.09 (m, 1H, ArH), 7.26 (m, 3H, ArH); HRMS calcd for $C_{37}H_{58}N_2O_5$ 610.4346, found 610.4332.

Activated esters 42. The diastereomeric esters **41** (950 mg, 1.56 mmol) were converted into 917 mg (96%) of **42** by the same method as that used for the preparation of **31**. The product was unstable and was used without further purification.

Benzolactam-V8-310 (6) and *epi*-Benzolactam-V8-310 (43). Trifluoroacetic acid (18 mL) was added to a solution of 1.28 g (8.62 mmol) of **42** in 35 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 2 h at room temperature, and then the solvent was removed under reduced pressure below 30 °C. The residue was dissolved in 2 L of AcOEt, and then 120 mL of saturated $NaHCO_3$(aq) was added and the mixture was refluxed for 6 h with vigorous stirring. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was separated by column chromatography with AcOEt to give 394 mg of **4** (48%) and 359 mg of **43** (43%). **4**: colorless needles (from AcOEt/*n*-hexane); mp 107−108 °C; IR (KBr) 1660 (NHCO); ^{1}H-NMR ($CDCl_3$) 0.88 (m, 6H, $(CH_2)_7CH_3$, $CH(CH_3)_2$), 1.05 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.26 (br, 14H, $-(CH_2)_7CH_3$), 1.57 (bs, 2H, $CH_2(CH_2)_7CH_3$), 2.41 (m, 1H, $CH(CH_3)_2$), 2.52 (br, 2H, $CH_2(CH_2)_8CH_3$), 2.77 (d, 1H, J = 17 Hz, $ArCH_2$), 2.79 (s, 3H, N-CH_3), 3.04 (dd, 1H, J = 8, 17 Hz, $ArCH_2$), 3.46 (d, 1H, J = 9 Hz, NC*H*CO), 3.52 (m, 1H, CH_2OH), 3.69 (m, 1H, CH_2OH), 4.03 (bs, 1H, CH_2CH), 6.81 (s, 1H, NH), 6.83 (bs, 1H, ArH), 6.90 (d, 1H, J = 7 Hz, ArH), 6.94 (d, 1H, J = 7 Hz, ArH); ^{1}H-NMR (CD_3OD) 0.89 (t, 6H, $(CH_2)_7CH_3$), 0.94 (d, 3H, $CH(CH_3)_2$), 1.09 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.27 (br, 14H, $-(CH_2)_7CH_3$), 1.57 (bs, 2H, $CH_2(CH_2)_7CH_3$), 2.39 (m, 1H, $CH(CH_3)_2$), 2.53 (dd, 2H, J = 6, 8 Hz, $CH_2(CH_2)_8CH_3$), 2.75 (s, 3H, NCH_3), 2.85 (dd, 1H, J = 9, 16 Hz, $ArCH_2$), 2.99 (dd, 1H, J = 4, 16 Hz, $ArCH_2$), 3.44 (d, 1H, J = 7 Hz, NC*H*CO), 3.49 (dd, 1H, J = 7, 11 Hz, CH_2OH), 3.59 (dd, 1H, J = 5, 11 Hz, CH_2OH), 4.48 (bs, 1H, CH_2CH), 6.76 (dd, 1H, J = 1, 7 Hz, ArH), 6.95 (d, 1H, J = 7 Hz, ArH), 6.96 (d, 1H, J = 1 Hz, ArH). Anal. Calcd for $C_{25}H_{42}N_2O_2$ C, 74.58; H, 10.51; N, 6.96; found, C, 74.57; H, 10.68, N, 7.14. **43**: colorless flakes (from AcOEt/*n*-hexane); mp 117−118 °C; IR (KBr) 1660 (NHCO); ^{1}H-NMR ($CDCl_3$) 0.88 (m, 6H, $(CH_2)_7CH_3$, $CH(CH_3)_2$), 0.97 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.26 (br, 14H, $-(CH_2)_7CH_3$), 1.57 (bs, 2H, $CH_2(CH_2)_7CH_3$), 2.42 (m, 1H, $CH(CH_3)_2$), 2.55 (m, 2H, $CH_2(CH_2)_8CH_3$), 2.83 (d, 1H, J = 16 Hz, $ArCH_2$), 2.90 (dd, 1H, J = 6, 16 Hz, $ArCH_2$), 2.93 (s, 3H, N-CH_3), 3.19 (d, 1H, J = 9 Hz, NC*H*CO), 3.73 (m, 3H, CH_2CH, CH_2OH), 6.66 (bd, 1H, J = 4 Hz, NH), 6.76 (dd, 1H, J = 1, 8 Hz, ArH), 6.91 (d, 1H, J = 1 Hz, ArH), 6.98 (d, 1H, J = 8 Hz, ArH); ^{1}H-NMR (CD_3OD) 0.89 (t, 3H, J = 7 Hz, $(CH_2)_7CH_3$), 0.85 (t, 3H, J = 7 Hz, $CH(CH_3)_2$), 0.98 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.27 (br, 14H, $-(CH_2)_7CH_3$), 1.57 (bs, 2H, $CH_2(CH_2)_7CH_3$), 2.37 (m, 1H, $CH(CH_3)_2$), 2.53 (m, 2H, $CH_2(CH_2)_8CH_3$), 2.71 (dd, 1H, J = 7, 16 Hz, $ArCH_2$), 2.88 (d, 1H, J = 16 Hz, $ArCH_2$), 2.90 (s, 3H, NCH_3), 3.23 (d, 1H, J = 11 Hz, NC*H*CO), 3.69 (m, 3H, CH_2CH, CH_2OH), 6.75 (dd, 1H, J = 1, 8 Hz, ArH), 6.94 (d, 1H, J = 1 Hz, ArH), 7.01 (d, 1H, J = 8 Hz, ArH). Anal. Calcd for $C_{25}H_{42}N_2O_2$ C, 74.58; H, 10.51; N, 6.96. Found: C, 74.33; H, 10.68; N, 7.11.

Benzolactam-V8-310 Acetate. The procedure was the same as that used for the preparation of **3**-acetate, employing 60 mg (0.15 mmol) of **6** to afford 54 mg of benzolactam-V8-310 acetate (82%) as a colorless oil: IR (neat) 1740 (Ac), 1660 (NHCO); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, J = 7 Hz, $(CH_2)_7CH_3$), 0.93 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.07 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.26 (m, 14H, $-(CH_2)_7CH_3$), 1.56 (m, 2H, $CH_2(CH_2)_7CH_3$), 2.10 (s, 3H, $COCH_3$), 2.43 (m, 1H, $CH(CH_3)_2$), 2.53 (m, 2H, $CH_2(CH_2)_8CH_3$), 2.77 (s, 3H, N-CH_3), 2.96 (d, 2H, J = 6 Hz, $ArCH_2$), 3.43 (d, 1H, J = 8 Hz, NC*H*CO), 3.96 (dd, 1H, J = 8, 12 Hz, CH_2OH), 4.20 (dd, 1H, J = 4, 12 Hz, CH_2OH), 4.56 (bs, 1H, CH_2CH), 5.68 (bd, J = 5 Hz, NH), 6.75 (dd, 1H, J = 1, 8 Hz, ArH), 6.87 (d, 1H, J = 1 Hz, ArH), 6.93 (d, 1H, J = 8 Hz, ArH); HRMS calcd for $C_{27}H_{44}N_2O_3$ 444.3352, found 444.3331.

***epi*-Benzolactam-V8-310 Acetate.** The procedure was the same as that used for the preparation of **3**-acetate, employing 94 mg (0.23 mmol) of **43** to afford 92 mg of *epi*-benzolactam-V8-310 acetate (98%) as a colorless oil: IR (neat) 1740 (Ac), 1665 (NHCO); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, $(CH_2)_7CH_3$), 0.89 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 0.96 (d, 3H, J = 7 Hz, $CH(CH_3)_2$), 1.26 (br, 14H, $-(CH_2)_7CH_3$), 1.57 (m, 2H, $CH_2(CH_2)_7CH_3$), 2.11 (s, 3H, $COCH_3$), 2.45 (m, 1H, $CH(CH_3)_2$),

2.54 (m, 2H, CH_2(CH_2)$_8$$CH_3$), 2.89 (d, 1H, J = 16 Hz, ArCH_2), 2.91 (s, 3H, NCH_3), 2.92 (dd, 1H, J = 8, 16 Hz, ArCH_2), 3.19 (d, 1H, J = 11 Hz, NC*H*CO), 3.91 (m, 1H, C*H*CH_2OH), 4.13 (m, 2H, CHCH_2-OH), 5.98 (bd, 1H, J = 7 Hz, NH), 6.74 (dd, 1H, J = 1, 8 Hz, ArH), 6.89 (d, 1H, J = 1 Hz, ArH), 6.97 (d, 1H, J = 8 Hz, ArH); HRMS calcd for $C_{27}H_{44}N_2O_3$ 444.3352, found 444.3316.

(−)-Benzolactam-V8-310 ((−)-6) and (−)-*epi*-Benzolactam-V8-310 ((−)-43). The procedure was the same as that used for the preparation of racemic **41**, employing **40** (154 mg, 0.37 mmol) and (+)-benzyl α-[[(trifluoromethyl)sulfonyl]oxy]isovalerate[23] (prepared from (*R*)-valine) to afford 205 mg of the diastereomeric ester **41A** (90%). The diastereomeric esters were converted to 55 mg of (−)-BL-V8-310 (**(−)-6**, 42%) and 43 mg of (−)-*epi*-BL-V8-310 (**(−)-43**, 33%). **(−)-6**: colorless oil; $[\alpha]^{22}_D = -278.2°$ (c = 0.64, $CHCl_3$). **(−)-43**: colorless oil; $[\alpha]^{22}_D = -140.3°$ (c = 0.75, $CHCl_3$).

(+)-Benzolactam-V8-310 ((+)-6) and (+)-*epi*-Benzolactam-V8-310 ((+)-43). The procedure was the same as that used for the preparation of racemic **41**, employing **40** (168 mg, 0.42 mmol) and (−)-benzyl α-[[(trifluoromethyl)sulfonyl]oxy]isovalerate (prepared from (*S*)-valine) to afford 184 mg of the diastereomeric ester **41B** (75%). The diastereomeric esters were converted to 52 mg of (−)-BL-V8-310 (**(+)-6**, 49%) and 51 mg of (−)-*epi*-BL-V8-310 (**(+)-43**, 48%). **(+)-6**: colorless oil; $[\alpha]^{22}_D$ = +280.3° (c = 0.61, $CHCl_3$). **(+)-43**: colorless oil; $[\alpha]^{22}_D$ +137.1° (c = 0.70, $CHCl_3$).

Phosphonium Salt 45. A mixture of 10.19 g (41.9 mmol) of 4-(bromomethyl)-2-nitrobenzaldehyde, 7.41 g of 1,2-ethanediol, and 10 mg of TsOH in 100 mL of toluene was refluxed with a Dean−Stark trap for 3.5 h. The mixture was cooled to room temperature and diluted with AcOEt. The organic layer was washed with saturated $NaHCO_3$(aq), water, and brine and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with CH_2Cl_2 afforded 11.64 g of the acetal **44** as a colorless oil (97%). A mixture of 6.90 g (24.0 mmol) of the acetal and 6.90 g (26.3 mmol) of triphenylphosphine in 60 mL of toluene was refluxed for 2 days. The precipitate was collected and washed with a small portion of toluene to give 8.35 g of **45** as a white powder (63%): mp 230−235 °C; ^{1}H-NMR (DMSO-d_6) 3.94−4.06 (m, 4H, OCH_2CH_2O), 5.46 (d, 2H, J = 15 Hz, CH_2P), 5.85 (s, 1H, OCHO), 7.43 (dd, 1H, J = 2, 8 Hz, ArH), 7.62 (m, 6H, ArH), 7.72 (m, 7H, ArH), 7.90 (m, 3H, ArH), 8.01 (s, 1H, ArH). Anal. Calcd for $C_{28}H_{25}NO_4PBr$: C, 61.10; H, 4.58; N, 2.58. Found: C, 61.30; H, 4.57; N, 2.40.

2-[(*tert*-Butoxycarbonyl)amino]-3-*tert*-butoxypropanal (46). To a solution of 2.96 g (12.7 mmol) of DL-*N*-Boc-*O*-*tert*-butylserine methyl ester in 140 mL of dry toluene was added 16 mL of 1.5 M diisobutylaluminum hydride in toluene, and the mixture was stirred for 1 h at −60 °C. The reaction was quenched by the addition of 10% citric acid, and the whole was warmed to room temperature and poured into 100 mL of 10% citric acid. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/2 to gave 2.03 g of the aldehyde as a colorless oil (77%): IR (neat) 3400 (NH), 1720 (CHO), 1705 (Boc); ^{1}H-NMR ($CDCl_3$) 1.18 (s, 1H, O-*t*-Bu), 1.47 (s, 9H, Boc), 3.60 (dd, 1H, J = 4, 9 Hz, CH_2OH), 3.92 (dd, 1H, J = 2, 9 Hz, CH_2OH), 4.24 (m, 1H, CH_2C*H*), 5.38 (bd, 1H, J = 4 Hz, NH), 9.62 (s, 1H, CHO); HRMS calcd for $C_{12}H_{23}NO_4$ 245.1627, found 245.1614.

Nitrostyrene (47). To a solution of 7.49 g (13.6 mmol) of **45** in 50 mL of DMF was added 1.80 g (18.2 mmol) of K_2CO_3, and the mixture was stirred for 1.5 h at room temperature. A solution of 2.99 g (12.2 mmol) of the aldehyde **46** in 20 mL of DMF was added to the ylide solution, and the whole was heated for 7 h at 95 °C. After removal of the solvent under reduced pressure, the residue was poured into 10% citric acid and extracted with AcOEt. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/3 gave 1.91 g of *cis*-**47** and 3.00 g of *trans*-**47** (total yield 92%). *cis*-**47**: pale yellow needles; mp 71−72 °C; IR (KBr) 3340 (NH), 1705 (Boc), 1525, 1360 (NO_2); ^{1}H-NMR ($CDCl_3$) 1.14 (s, 9H, O-*t*-Bu), 1.41 (s, 9H, Boc), 3.29 (m, 2H, CH_2O), 4.05−4.15 (m, 4H, OCH_2CH_2O), 4.33 (m, 1H, CH_2C*H*), 4.92 (bs, 1H, NH), 5.82 (dd, 1H, J = 9, 12 Hz, ArCH=C*H*), 5.89 (s, 1H, OCHO), 6.80 (d, 1H, J = 12 Hz, ArC*H*=CH), 7.71 (d, 1H, J = 7 Hz, ArH), 7.78 (bs, 1H, ArH), 8.17 (d, 1H, J = 1 Hz, ArH). Anal. Calcd for $C_{22}H_{32}N_2O_7$: C, 60.54; H, 7.39; N, 6.42. Found: C, 60.32; H, 7.45; N, 6.33. *trans*-**47**: pale yellow oil; IR (neat) 3300 (NH), 1710 (Boc), 1525, 1360 (NO_2); ^{1}H-NMR ($CDCl_3$) 1.18 (s, 9H, O-*t*-Bu), 1.47 (s, 9H, Boc), 3.55 (m, 2H, CH_2O), 4.02−4.14 (m, 4H, OCH_2CH_2O), 4.41 (bs, 1H, CH_2C*H*), 5.04 (bs, 1H, NH), 5.85 (s, 1H, OCHO), 6.24 (dd, 1H, J = 6, 15 Hz, ArCH=C*H*), 7.04 (d, 1H, J = 15 Hz, ArC*H*=CH), 7.59 (d, 1H, J = 8 Hz, ArH), 7.64 (dd, 1H, J = 1, 8 Hz, ArH), 8.03 (d, 1H, J = 1 Hz, ArH); HRMS calcd for $C_{22}H_{32}N_2O_7$ 436.2210, found 436.2254.

Aldehyde *cis*-48. A mixture of 2.85 g (6.53 mmol) of acetal *cis*-**47** and 0.98 g of pyridinium *p*-toluenesulfonate in 40 mL of acetone and 3 mL of H_2O was refluxed for 15 h. After concentration, the residue was diluted with AcOEt, washed with water and brine, and dried over $MgSO_4$. Concentration and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/2 gave 2.03 g of the aldehyde, *cis*-**48** (79%): pale yellow prisms; mp 103−104 °C; IR (KBr) 3300 (NH), 1700 (Boc), 1535, 1360 (NO_2), 750 (Ar); ^{1}H-NMR ($CDCl_3$) 1.15 (s, 9H, O-*t*-Bu), 1.40 (s, 9H, Boc), 3.32 (m, 2H, CH_2O), 4.31 (m, 1H, CH_2C*H*), 4.92 (bs, 1H, NH), 5.91 (dd, 1H, J = 9, 12 Hz, ArCH=C*H*), 6.84 (d, 1H, J = 12 Hz, ArC*H*=CH), 8.00 (bd, 1H, J = 8 Hz, ArH), 8.12 (dd, 1H, J = 1, 8 Hz, ArH), 8.53 (d, 1H, J = 1 Hz, ArH), 10.07 (s, 1H, CHO). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.22; H, 7.29; N, 7.07.

Aldehyde *trans*-48. The procedure was the same as that used for the preparation of *cis*-**48**, employing 3.0 g (6.88 mmol) of **43** to afford 1.78 g of the aldehyde *trans*-**48** as a pale yellow oil (66%): IR (neat) 3400 (NH), 1700 (CHO), 1680 (Boc), 1525, 1360 (NO_2); ^{1}H-NMR ($CDCl_3$) 1.19 (s, 9H, O-*t*-Bu), 1.48 (s, 9H, Boc), 3.55 (m, 2H, CH_2O), 4.55 (bs, 1H, CH_2C*H*), 5.12 (bs, 1H, NH), 6.42 (dd, 1H, J = 6, 16 Hz, ArCH=C*H*), 7.08 (d, 1H, J = 16 Hz, ArC*H*=CH), 7.78 (bd, 1H, J = 8 Hz, ArH), 8.05 (dd, 1H, J = 1, 8 Hz, ArH), 8.39 (d, 1H, J = 1 Hz, ArH), 10.04 (s, 1H, CHO); HRMS calcd for $C_{20}H_{28}N_2O_6$ 392.1947, found 392.1956.

Nitrostyrene *cis*-49. The procedure was the same as that used for the preparation of **36**, employing 589 mg (1.50 mmol) of *cis*-**48**, 1.97 g (4.20 mmol) of nonyltriphenylphosphonium bromide, and 4.0 mmol of *n*-BuLi to afford 758 mg of *cis*-**49** as a pale yellow oil (48%): IR (neat) 3400 (NH), 1710 (Boc), 1525, 1360 (NO_2); ^{1}H-NMR ($CDCl_3$) (*cis*−*trans* isomers exist in a ratio of 1:3) 0.88 (t, 3H, J = 7 Hz, (CH_2)$_7$CH_3), 1.14 (s, 9H, O-*t*-Bu), 1.26 (br, 10H, (CH_2)$_5$$CH_3$), 1.41 (s, 9H, Boc), 1.46 (m, 2H, CH_2(CH_2)$_5$$CH_3$), 2.23 (m, 0.5H, C$H_2$($CH_2$)$_6$-$CH_3$), 2.33 (m, 1.5H, C$H_2$($CH_2$)$_6$$CH_3$), 3.31 (m, 2H, CH_2O), 4.39 (m, 1H, CH_2C*H*), 4.39 (bs, 1H, NH), 5.80 (m, 2H, ArCH=C*H*), 6.37 (m, 1H, ArC*H*=CH), 6.89 (m, 1H, ArC*H*=CH), 7.50 (dd, 0.75H, J = 2, 7 Hz, ArH), 7.55 (dd, 0.25H, J = 2, 7 Hz, ArH), 7.69 (bs, 1H, ArH), 7.94 (d, 0.75H, J = 2 Hz, ArH), 7.99 (d, 0.25H, J = 2 Hz, ArH).

Nitrostyrene *trans*-49. The procedure was the same as that used for the preparation of **36**, employing 1.78 g (4.54 mmol) of *trans*-**48**, 5.32 g (11.35 mmol) of nonyltriphenylphosphonium bromide, and 11.0 mmol of *n*-BuLi to afford 1.10 g of *trans*-**49** as a pale yellow oil (48%): IR (neat) 3400, 3300 (NH), 1715, 1705 (Boc), 1545, 1360 (NO_2); ^{1}H-NMR ($CDCl_3$) (*cis*−*trans* isomers exist in a ratio of 1:2) 0.87 (t, 3H, J = 7 Hz, (CH_2)$_7$CH_3), 1.19 (s, 9H, O-*t*-Bu), 1.26 (br, 10H, (CH_2)$_5$$CH_3$), 1.44 (m, 2H, C$H_2$($CH_2$)$_5$$CH_3$), 1.47 (s, 9H, Boc), 2.23 (dd, 0.7H, J = 6, 15 Hz, CH_2(CH_2)$_6$$CH_3$), 2.31 (dd, 1.3H, J = 6, 15 Hz, CH_2(CH_2)$_6$$CH_3$), 3.53 (m, 2H, CH_2O), 4.42 (m, 1H, CH_2CH), 5.05 (bs, 1H, NH), 5.78 (dt, 0.3H, J = 7, 12 Hz, ArCH=C*H*), 6.26 (m, 0.7H, ArCH=C*H*), 6.35 (m, 2H, ArC*H*=C*H*), 7.00 (d, 0.3H, J = 15 Hz, ArC*H*=CH), 7.02 (d, 0.7H, J = 15 Hz, ArC*H*=CH), 7.43 (dd, 0.7H, J = 1, 8 Hz, ArH), 7.49 (m, 0.6H, ArH), 7.54 (d, 0.7H, J = 8 Hz, ArH), 7.80 (d, 0.7H, J = 1 Hz, ArH), 7.84 (d, 0.3H, J = 1 Hz, ArH).

Amine 50. A mixture of 758 mg (1.50 mmol) of *cis*-**49** and 110 mg of 10% Pd−C in 100 mL of methanol was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and then filtered. The filtrate was concentrated and crystallized from benzene to afford 713 mg of **50** as a yellow viscous liquid (100%). *trans*-**49** was also converted into **50** by the same procedure: IR (neat) 3350, 3400 (NH), 1700 (Boc), 735 (Ar); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, J = 7 Hz, (CH_2)$_7$CH_3), 1.17 (s, 9H, O-*t*-Bu), 1.26 (br, 14H, (CH_2)$_7$$CH_3$), 1.45 (s, 9H, Boc), 1.56 (m, 2H, CH_2(CH_2)$_7$$CH_3$), 1.80 (m, 2H, Ar$CH_2CH_2$), 2.48 (m, 4H, Ar$CH_2$), 3.43 (m, 2H, CH_2O), 3.72 (bS, 1H, CH_2C*H*), 4.83 (bd, 1H, *J*

= 8 Hz, NH), 6.50 (bs, 1H, ArH), 6.55 (dd, 1H, *J* = 7 Hz, ArH), 6.95 (bd, 1H, *J* = 7 Hz, ArH); HRMS calcd for $C_{25}H_{44}N_2O_3$ 420.3352, found 420.3396.

***N*-Methylamine 51.** The amine **50** (713 mg, 1.50 mmol) was converted into the *N*-methylamine **51** by the same methods as used for the preparation of **40** from **39**. The *N*-formate (674 mg, 89%) was isolated and purified by column chromatography on silica gel with AcOEt/*n*-hexane = 1/2 as a colorless oil: IR (neat) 3300 (NH), 1700 (Boc), 1680 (CHO), 730 (Ar); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 1.17 (s, 9H, O-*t*-Bu), 1.26 (br, 14H, $(CH_2)_7CH_3$), 1.47 (s, 9H, Boc), 1.59 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.70−1.90 (m, 2H, $ArCH_2CH_2$), 2.57 (t, 2H, *J* = 8 Hz, $ArCH_2$), 2.62 (t, 2H, *J* = 8 Hz, $ArCH_2$), 3.37 (m, 2H, CH_2O), 3.55 (m, 0.4H, CH_2CH), 3.65 (m, 0.6H, CH_2CH), 4.95 (m, 1H, NH), 6.93 (dd, 0.6H, *J* = 1, 8 Hz, ArH), 6.94 (s, 1H, ArH), 7.00 (dd, 0.4H, *J* = 1, 8 Hz, ArH), 7.08 (d, 0.6H, *J* = 8 Hz, ArH), 7.15 (d, 0.4H, *J* = 8 Hz, ArH), 7.79 (d, 0.6H, *J* = 1 Hz, NHCHO), 8.00 (bs, 0.4H, NHCHO), 8.43 (d, 0.4H, *J* = 2 Hz, CHO), 8.49 (d, 0.6H, *J* = 11 Hz, CHO); HRMS calcd for $C_{30}H_{52}N_2O4$ 504.3927, found 504.3938. Reduction of the formate with BH_3 and purification by column chromatography on silica gel with AcOEt/*n*-hexane = 1/3 afforded 786 mg of **51** as a colorless oil (94%): IR (neat) 3400 (NH), 1700 (Boc); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 1.17 (s, 9H, O-*t*-Bu), 1.26 (br, 14H, $(CH_2)_7CH_3$), 1.46 (s, 9H, Boc), 1.60 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.79 (m, 2H, $ArCH_2CH_2$)), 2.50 (m, 2H, $ArCH_2$), 2.54 (t, 2H, *J* = 8 Hz, $ArCH_2$), 2.88 (s, 3H, N-CH_3), 3.41 (m, 2H, CH_2O), 3.68 (bs, 1H, CH_2CH), 4.85 (m, 1H, NH), 6.53 (m, 2H, ArH), 6.96 (d, 1H, *J* = 8 Hz, ArH); HRMS calcd for $C_{30}H_{54}N_2O_3$ 490.4134, found 490.4120.

Diastereomeric Esters 52. The *N*-methylamine **51** (913 mg, 1.86 mmol) was converted into a diasteromeric mixture of esters **52** by the same methods as that used for the preparation of **41** from **40**, using 974 mg (2.86 mmol) of the triflate and 1.02 g of 2,6-lutidine in 30 mL of CH_2ClCH_2Cl. Purification by column chromatography on silica gel with CH_2Cl_2/AcOEt = 20/1 gave 1.20 g of diastereomeric esters **41** as a colorless oil (95%) (331 mg of starting material was recovered): ^{1}H-NMR ($CDCl_3$) 0.87 (m, 6H, $(CH_2)_7CH_3$, $CH(CH_3)_2$), 1.13 (s, 9H, O-*t*-Bu, 1.17 (d, 6H, *J* = 7 Hz, $CH(CH_3)_2$), 1.23 (m, 14H, $(CH_2)_7CH_3$), 1.4 (s, 9H, Boc), 1.4−1.5 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.7−1.8 (br, 1H, CH_2-CH), 1.8−1.9 (m, 1H, CH_2CH), 2.24 (m, 1H, $CH(CH_3)_2$), 2.43 (t, 2H, *J* = 8 Hz, $ArCH_2$), 2.45−2.62 (m, 1H, $ArCH_2$), 2.73−2.90 (m, 1H, $ArCH_2$), 2.70 (s, 1.5H, NCH_3), 2.80 (s, 3H, N-CH_3), 3.21 (d, 0.5H, *J* = 7 Hz, NCHCO), 3.23 (d, 0.5H, *J* = 7 Hz, NCHCO), 3.33 (bd, 2H, *J* = 11 Hz, CH_2OH), 3.68 (bs, 1H, CH_2CH), 4.75 (br, 2H, NH), 4.93 (d, 0.5H, *J* = 12 Hz, OCH_2Ar), 4.94 (d, 0.5H, *J* = 12 Hz, OCH_2Ar), 5.03 (d, 2H, *J* = 12 Hz, OCH_2Ar), 6.88 (m, 2H, ArH), 7.10 (m, 3H, ArH), 7.26 (m, 3H, ArH).

Activated Esters 53. The diastereomeric esters **52** (1.40 g, 2.73 mmol) were converted into 1.11 g (78%) of **53** by the same method as that used for the preparation of **42**. The product was unstable and was used without further purification.

Benzolactam-V9-310 (7) and *epi*-Benzolactam-V9-310 (54). Trifluoroacetic acid (6 mL) was added to a solution of 1.11 g (8.62 mmol) of **53** in 12 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 1 h at 0 °C and for 5 h at room temperature, and then the solvent was removed under reduced pressure at below 30 °C. The residue was dissolved in 1.1 L of AcOEt, and then 100 mL of saturated $NaHCO_3$(aq) was added and the mixture was refluxed for 18 h with vigorous stirring. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was separated by column chromatography with AcOEt to give 134 mg of **7** (20%) and 112 mg of **54** (17%). **7**: colorless oil; IR (KBr) 1660 (NHCO); ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 0.91 (t, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.17 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.26 (m, 14H, $(CH_2)_7CH_3$), 1.58 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.71 (m, 1H, $ArCH_2CH_2$), 2.22−2.32 (m, 2H, $CH(CH_3)_2$, $ArCH_2CH_2$), 2.45 (t, 1H, *J* = 14 Hz, $ArCH_2$), 2.52 (t, 2H, *J* = 8 Hz, $CH_2(CH2)_8CH_3$), 2.63 (dd, 1H, *J* = 8, 14 Hz, $ArCH_2$), 2.72 (d, 1H, *J* = 11 Hz, NCHCO), 2.75 (s, 3H, NCH_3), 3.43 (dd, 1H, *J* = 6, 11 Hz, CH_2OH), 3.61 (dd, 1H, *J* = 4, 11 Hz, CH_2OH), 4.44 (bs, 1H, $CHCH_2OH$), 4.58 (bd, 1H, *J* = 11 Hz, NH), 6.88 (d, 1H, *J* = 1 Hz, ArH), 6.97 (dd, 1H, *J* = 1, 8 Hz, ArH), 7.03 (d, 1H, *J* = 8 Hz, ArH); ^{1}H-NMR (CD_3OD) 0.88 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 0.89 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 1.17 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.29 (br, 14H, $(CH_2)_7CH_3$), 1.58 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.66 (m, 1H, $ArCH_2CH_2$), 2.22 (m, 1H, $CH(CH_3)_2$), 2.30 (m, 1H, $ArCH_2CH_2$), 2.37 (dd, 1H, *J* = 10, 14 Hz, $ArCH_2$), 2.61 (dd, 1H, *J* = 7, 14 Hz, $ArCH_2$), 2.72 (s, 3H, NCH_3), 2.84 (d, 1H, *J* = 11 Hz, NCHCO), 3.41 (m, 2H, CH_2OH), 4.28 (hextet, 1H, *J* = 6 Hz, CH_2CH), 6.88 (d, 1H, *J* = 2 Hz, ArH), 6.98 (dd, 1H, *J* = 2, 8 Hz, ArH), 7.06 (d, 1H, *J* = 8 Hz, ArH); HRMS calcd for $C_{30}H_{52}N_2O_2$ 416.3402, found 416.3442. **54**: colorless needles (from AcOEt/*n*-hexane); mp 146.5 °C; ^{1}H-NMR ($CDCl_3$) 0.87 (m, 6H, $CH(CH_3)_2$, $(CH_2)_7CH_3$), 1.21 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.27 (m, 14H, $(CH_2)_7CH_3$), 1.55−1.65 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.80 (m, 1H, $ArCH_2CH_2$), 1.80 (m, 1H, $ArCH_2CH_2$), 2.55 (m, 4H, $ArCH_2CH_2(CH_2)_7CH_3$, $CH(CH_3)_2$, $ArCH_2$), 2.72 (dt, 1H, *J* = 3, 13 Hz, $ArCH_2$), 2.77 (s, 3H, N-CH_3), 3.14 (d, 1H, *J* = 11 Hz, NCHCO), 3.31 (m, 1H, $CHCH_2OH$), 3.44 (dd, 1H, *J* = 6, 11 Hz, CH_2-OH), 3.54 (dd, 1H, *J* = 4, 11 Hz, CH_2OH), 5.47 (bd, 1H, *J* = 12 Hz, NH), 6.98 (dd, 1H, *J* = 1, 8 Hz, ArH), 7.05 (d, 1H, *J* = 1 Hz, ArH), 7.07 (d, 1H, *J* = 8 Hz, ArH); ^{1}H-NMR (CD_3OD) 0.84 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 0.89 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 1.21 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.29 (m, 14H, $(CH_2)_7CH_3$), 1.58 (m, 2H, $CH_2(CH_2)_7$-CH_3), 1.63 (m, 1H, $ArCH_2CH_2$), 1.72 (m, 1H, $ArCH_2CH_2$), 2.46 (m, 1H, $CH(CH_3)_2$), 2.54 (m, 3H, $ArCH_2CH_2(CH_2)_7CH_3$, $ArCH_2$), 2.65 (dt, 1H, *J* = 3, 13 Hz, $ArCH_2$), 2.72 (s, 3H, NCH_3), 3.20 (bs, 1H, $CHCH_2$-OH), 3.21 (d, 1H, *J* = 11 Hz, NCHCO), 3.39 (m, 2H, CH_2OH), 6.98 (dd, 1H, *J* = 1, 8 Hz, ArH), 7.05 (d, 1H, *J* = 1 Hz, ArH), 7.11 (d, 1H, *J* = 8 Hz, ArH). Anal. Calcd for $C_{30}H_{52}N_2O_2$: N, 6.72; C, 74.95; H, 10.64. Found: N, 6.87; C, 75.02; H, 10.87.

Benzolactam-V9-310 Acetate. The procedure was the same as that used for the preparation of **6**-acetate, employing 40 mg (0.096 mmol) of **7** to afford 40 mg of benzolactam-V9-310 acetate (90%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) 0.89 (m, 6H, $CH(CH_3)_2$, $(CH_2)_7CH_3$), 1.17 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.26 (m, 14H, $(CH_2)_7CH_3$), 1.60 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.64 (m, 1H, $ArCH_2CH_2$), 1.99 (s, 3H, $COCH_3$), 2.30 (m, 2H, $CH(CH_3)_2$, $ArCH_2CH_2$), 2.44 (dd, 1H, *J* = 11, 14 Hz, $ArCH_2$), 2.54 (t, 2H, *J* = 8 Hz, $ArCH_2CH_2(CH_2)_7CH_3$), 2.61 (dd, 1H, *J* = 7, 14 Hz, $ArCH_2$), 2.70 (d, 1H, *J* = 11 Hz, NCHCO), 2.74 (s, 3H, N-CH_3), 3.99 (dd, 1H, *J* = 5, 11 Hz, CH_2OH), 4.09 (dd, 1H, *J* = 5, 11 Hz, CH_2OH), 4.45 (bd, 1H, *J* = 11 Hz, NH), 4.46 (m, 1H, $CHCH_2OH$), 6.89 (d, 1H, *J* = 1 Hz, ArH), 6.97 (dd, 1H, *J* = 1, 8 Hz, ArH), 7.02 (d, 1H, *J* = 8 Hz, ArH); HRMS calcd for $C_{28}H_{46}N_2O_3$ 458.3508, found 458.3494.

***epi*-Benzolactam-V9-310 Acetate.** The procedure was the same as that used for the preparation of **7**-acetate, employing 59 mg (0.142 mmol) of **54** to afford 52 mg of *epi*-benzolactam-V9-310 acetate (80%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) 0.84 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 0.88 (t, 3H, *J* = 7 Hz, $(CH_2)_7CH_3$), 1.21 (d, 3H, *J* = 7 Hz, $CH(CH_3)_2$), 1.27 (m, 14H, $(CH_2)_7CH_3$), 1.56 (m, 3H, $CH_2(CH_2)_7CH_3$, $ArCH_2CH_2$), 1.78 (m, 1H, $ArCH_2CH_2$), 2.02 (s, 3H, $COCH_3$), 2.55 (m, 4H, $ArCH_2$-$CH_2(CH_2)_7CH_3$, $CH(CH_3)_2$, $ArCH_2$), 2.72 (dd, 1H, *J* = 3, 14 Hz, $ArCH_2$), 2.77 (s, 3H, NCH_3), 3.09 (d, 1H, *J* = 10 Hz, NCHCO), 3.48 (bs, 1H, $CHCH_2OH$), 3.89 (dd, 1H, *J* = 4, 11 Hz, CH_2OH), 4.01 (dd, 1H, *J* = 7, 11 Hz, CH_2OH), 5.36 (bd, 1H, *J* = 12 Hz, NH), 6.99 (dd, 1H, *J* = 1, 8 Hz, ArH), 7.06 (d, 1H, *J* = 1 Hz, ArH), 7.08 (d, 1H, *J* = 8 Hz, ArH); HRMS calcd for $C_{28}H_{46}N_2O_3$ 458.3508, found 458.3460.

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