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Synthesis of 3-Aminolactams as X-Gly Constrained Pseudodipeptides and Conformational Study of a Trp-Gly Surrogate

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3-Amino-δ-valerolactams *trans*-**11a**−**c** were synthesized through conjugate addition and Curtius rearrangement and converted into Fmoc-{Trp-Gly}, Fmoc-{Ile-Gly}, and Fmoc-{Phe-Gly} pseudodipeptides. Conformational analyses of tripeptide analogues Ac-{Trp-Gly}-Leu-NH_2 **17a** and **17b** by NMR experiments and molecular modeling calculations showed that diastereomer **17a** adopted a γ-turn/distorted type II β-turn structure, whereas diastereomer **17b** adopted mainly a γ-turn structure.

Introduction

In the context of our studies on the synthesis of functionalized 3-aminolactams as constrained surrogates of dipeptides,[1] we established a new synthetic method to obtain X-Gly pseudodipeptides based on the use of 3-benzyloxycarbonyl-5,6-dihydropyridin-2-one **1** as a starting compound (Figure 1).[2,3] This new methodology implied introduction of a substituent in position C4 by conjugate addition, and amination of C3 by subsequent Curtius rearrangement.

In principle, this method would allow us to thermodynamically control the relative stereochemistry of the ring substituents (see Figure 2). Thus, conformational equilibration and epimerization on C3 would lead to the most thermodynamically stable 3,4-trans isomers, and in this way we would be able to obtain only two isomers out of the four kinetic products.

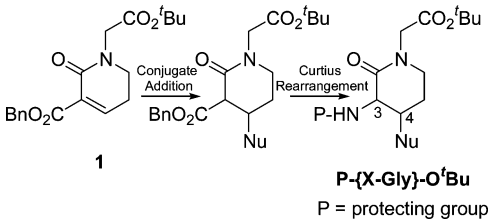

FIGURE 1. Synthesis of X-Gly pseudopeptides.

Our interest in β- and γ-turn conformations[1] and the fact that Trp is usually not involved in turns,[4] despite its relevant biological role in nature,[5] prompted us to study whether the integration of the indole nucleus on the piperidone backbone would still promote a turn.[6] Since the lactam backbone provides the i+1 and i+2 residues of the tetrapeptide that forms the β- or γ-turns (Figure 3), we chose to protect the *N*-terminus using an acetyl group, extend the *C*-terminus by introducing

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(2) For previous applications of 5,6-dihydropyridin-2-ones in Diels−Alder reactions, see: (a) Casamitjana, N.; Amat, M.; Llor, N.; Carreras, M.; Pujol, X.; Fernández, M.; López, V.; Molins, E.; Miravitlles, C.; Bosch, J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2033−39. (b) Casamitjana, N.; López, V.; Jorge, A.; Bosch, J.; Molins, E.; Roig, A. *Tetrahedron* **2000**, *56*, 4027−4042. (c) Casamitjana, N.; Jorge, A.; Pérez, C. G.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron Lett.* **1997**, *38*, 2295−2298.

(3) For the application of 5,6-dihydropyridin-2-ones in the synthesis of indole alkaloids by conjugate addition, see: (a) Forns, P.; Fernández, M. M.; Diez, A.; Rubiralta, M.; Cherrier, M.-P.; Bonin, M.; Quirion, J.-C. *Synthesis* **1999**, 258−263. (b) Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M.; *Tetrahedron* **1996**, *52*, 3563−3574. (c) Micouin, L.; Diez, A.; Castells, J.; López, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693−1696. (d) Diez, A.; Castells, J.; Forns, P.; Rubiralta, M.; Grierson, D. S.; Husson, H.-P.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1994**, *50*, 6585−6602.

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(5) For biological relevance of Trp see: http://www.acdlabs.com/publish/tryptophan/.

(6) It is well-known that Freidinger lactams induce turns: (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656−658. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104−109.

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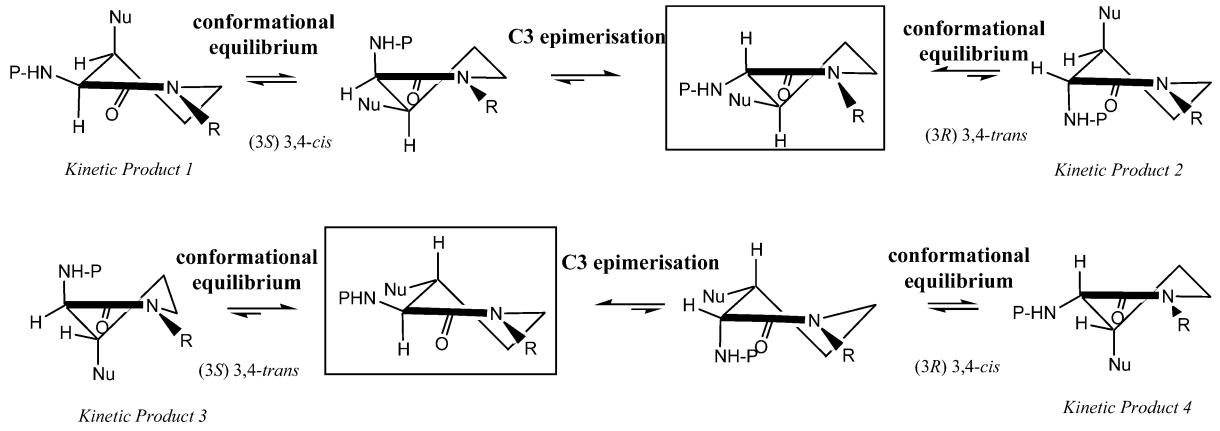

FIGURE 2. Thermodynamic control of the relative stereochemistry of C3 and C4 of 3,4-disubstituted piperidones **8**.

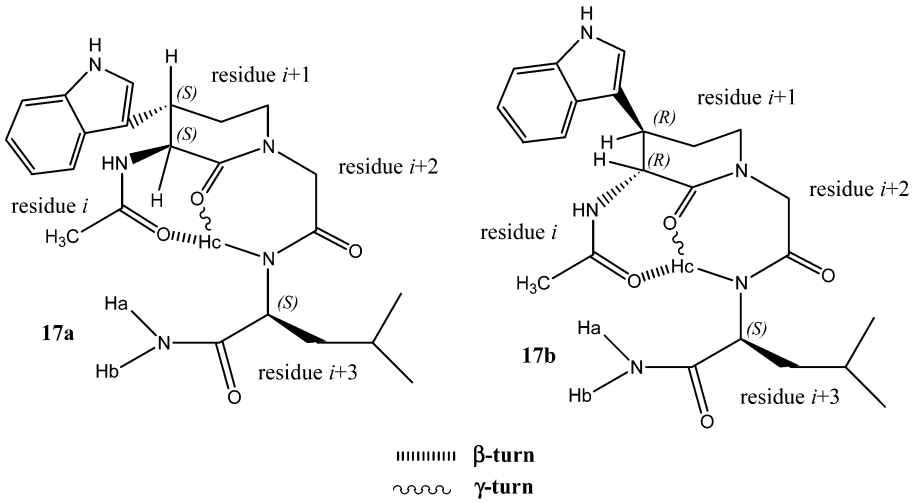

FIGURE 3. Hydrogen bonds stabilizing β- and γ-turns in Ac-{Trp-Gly}-Leu-NH_2 **17a** and **17b** .

a Leu-NH_2 residue, and study the conformational preferences of Ac-{Trp-Gly}-Leu-NH_2 **17a** and **17b**.

Trp-Gly-Leu is the *C*-terminus of a synthetic peptide corresponding to amino acids 400−429 of the gp21 envelope transmembrane glycoprotein.[7] This synthetic 30-residue peptide (peptide 400−429) strongly inhibits not only infection by cell-free Human T-Cell Leukemia Virus Type 1 (HTLV-1) but also syncytium formation induced by cocultivation with HTLV-1-producing cells. According to Jinno and co-workers, peptide 400−429 seems to be important for the envelope functions, not only in cell-to-cell but also in virus-to-cell infection. In addition, they report that six residues, including the terminal Leu, are necessary for the activity of gp21 peptide 400−429.

Results and Discussion

Synthesis and Structural Assignment. The synthesis of 3-benzyloxycarbonyl-5,6-dihydropyridin-2-one **1** was performed with our own methodology[2] and *N*-*tert*-butoxycarbonyl-2-piperidone (**2**)[8] as the initial substrate (Scheme 1). Thus, introduction of the benzyloxycarbonyl and phenylselanyl groups at position 3 was performed in a one-pot procedure, using LHMDS as base and $ClCO_2$-Bn and PhSeCl as electrophiles. *N*-Deprotection of piperidone **3** with 2,6-lutidine and TMSOTf[9] to give disubstituted piperidone **6**[10] followed by *N*-alkylation with *tert*-butyl bromoacetate, K_2CO_3, and TBAB in CH_3CN gave trisubstituted piperidone **7** in good yield. Finally, elimination of the phenylselanyl group with *m*-CPBA as oxidizing agent at 0 °C furnished dihydropyridone **1** in a 71% overall yield from compound **2**. When the phenylselanyl group elimination was performed prior to the *N*-deprotection and alkylation steps, intermediate dihydropyridone **4** was obtained as a crude product that was subsequently treated with TFA to yield *N*-deprotected dihydropyridone **5**, but the last alkylation step to furnish compound **1** was unsuccessful. Structure assignment of dihydropyridone **1** was based on the presence of two signals at δ 128.9 and 147.3 in the ^{13}C NMR spectra for the olephinic carbons and a multiplet at δ 7.25−7.45 in the ^1H NMR spectra for olephinic proton H-4.

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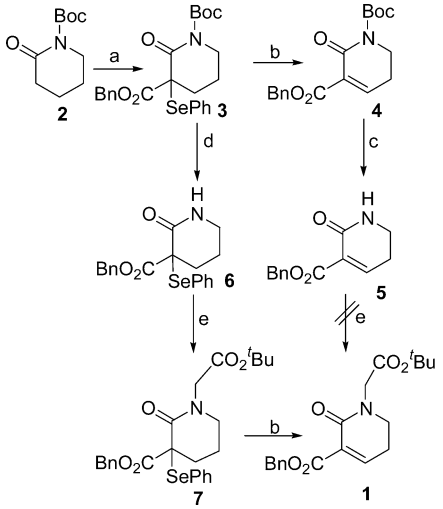
(9) (a) Zhang, A. J.; Russell, D. H.; Zhu, J.; Burguess, K. *Tetrahedron Lett.* **1998**, *39*, 7439−7442. (b) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876. This reagent is compatible with the presence of other functional groups, see: (c) Hamada, Y.; Shiori, T. *J. Org. Chem.* **1986**, *51*, 5489−5490.

(10) When *N*-deprotection was performed with TFA at 0 °C piperidone **6** was obtained in 63% yield accompanied by 3-(benzyloxycarbonyl)piperidin-2-one (13%) as a byproduct, see Experimental Section.

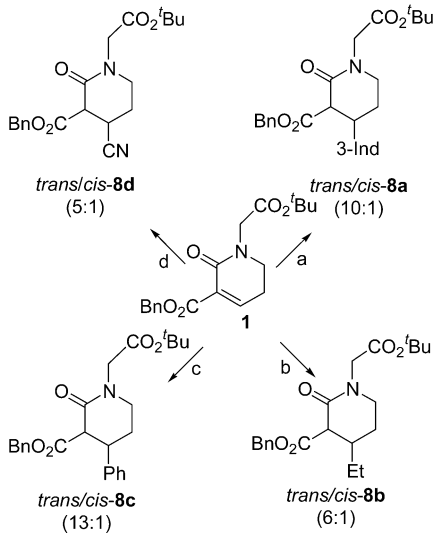
SCHEME 1. Synthesis of 5,6-Dihydropyridin-2(1*H*)-one 1[a]



[a] Reagents and conditions: (a) LHMDS, $ClCO_2Bn$, PhSeCl, dry THF, −78 °C, 93%; (b) *m*-CPBA, dry CH_2Cl_2, 0 °C to rt (not purified); (c) TFA, dry CH_2Cl_2, 0 °C (not purified); (d) TMSOTf, 2,6-lutidine, dry CH_2Cl_2, rt, 80%; (e) $BrCH_2CO_2{}^tBu$, K_2CO_3, TBAB, dry CH_3CN, rt, 96% for **7**.

Indole itself has been used in conjugate addition reactions with α,β-unsaturated carbonylic compounds in acidic media.[11] Nevertheless, to overcome the problem of acidity control when using acid catalysis, and to avoid polymerization side reactions, the use of nonprotonic acid catalysis by means of Montmorillonite clays has also been described for the alkylation of indoles with α,β-unsaturated ketones and esters.[12] In our case, the presence of the *tert*-butoxycarbonyl group made us choose this last method to avoid ester hydrolysis. Following the described procedure for conjugate additions with Montmorillonite KSF[13] as a catalyst, racemic 4-indolyl-2-piperidones *cis*- and *trans*-**8a** (1:10) were prepared in 80% yield from dihydropyridone **1** and indole in CH_2Cl_2 at room temperature for 24 h[12,14] (Scheme 2). As expected, the separation of the cis and trans isomers was not possible, since during the purification process the cis isomer was converted into the trans isomer. To investigate the potential of 5,6-dihydro-2(1*H*)-pyridones in conjugate addition reactions, other nucleophiles, such as Grignard reagents and cyanide, were also studied.[15] When using EtMgBr or Ph-

SCHEME 2. Conjugate Addition to Dihydropyridone 1[a]



[a] Reagents and conditions: (a) indole, Montmorillonite KSF, dry CH_2Cl_2, rt, 80%; (b) EtMgBr, CuBr·SMe_2, dry THF, −78 °C to rt, 83%; (c) PhMgBr, CuBr·SMe_2, dry THF, −78 °C to rt, 77%; (d) KCN, NH_4Cl, DMF/H_2O, 90 °C, 83%.

MgBr in the presence of the catalyst CuBr·Me_2S[16] and the solvent THF at −78 °C, 1,3,4-trisubstituted-2-piperidones *cis*- and *trans*-**8b** (1:6) and *cis*- and *trans*-**8c** (1:13) were obtained in 83% and 77% yield, respectively. Finally, the addition of the cyano group, which can be subsequently converted into other functions,[17] on the unsaturated pyridone **1** was achieved by reaction with KCN and NH_4Cl in DMF−H_2O to yield 4-cyano-2-piperidones *cis*- and *trans*-**8d** (1:5) in an 83% yield.

In all cases, the most favored diastereomer was trans, although proportions varied according to the nucleophile type. The most characteristic NMR data for 1,3,4-trisubstituted piperidones *trans*-**8** are the δ values for carbons C-3 and C-4, and the coupling constant between protons 3-H and 4-H (≈8−11 Hz).

As mentioned above, this method allowed us to thermodynamically control the relative stereochemistry of the ring substituents (Figure 2). Thus, conformational equilibration and epimerization on C3 led mainly to the most thermodynamically stable 3,4-trans isomers, and in this way we obtained the two trans isomers as major products out of the possible four kinetic products.

To achieve Trp-Gly, Ile-Gly, and Phe-Gly dipeptide analogues, 4-substituted 3−(benzyloxycarbonyl)piperidones *trans*- and *cis*-**8a**−**c** were hydrogenated and the resulting carboxylic acids were converted into carbamates **11a**−**c** through a modified Curtius rearrangement,[18,19] by treatment with Et_3N and DPPA, followed by BnOH[20] and dibutyltin dilaurate (Scheme 3).[21] When 4-cyanopi-

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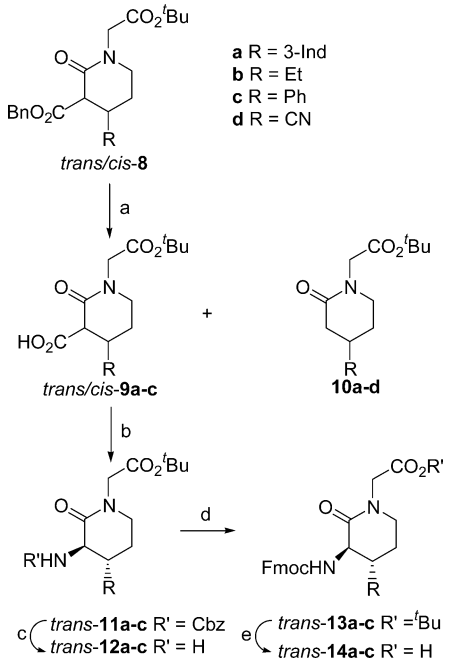
(19) The classical Curtius rearrangement with NaN_3 failed, see: Fukazawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1649−1658.

SCHEME 3. Synthesis of X-Gly Pseudodipeptides[a]

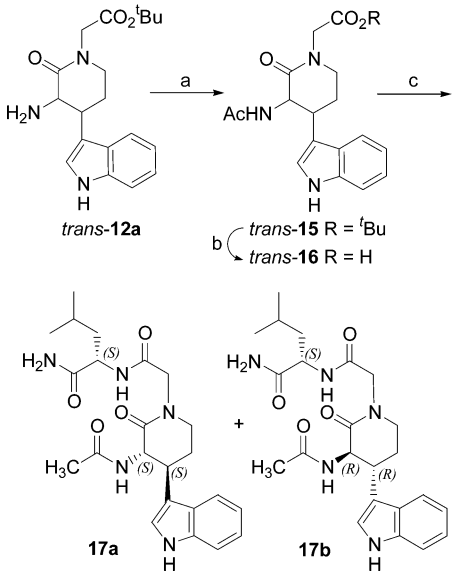


[a] Reagents and conditions: (a) H_2, Pd-C 10%, MeOH or AcOEt, rt, **9a**, **9b**, and **9c** were not purified, 61% for **10d**; (b) Et_3N, DPPA, dry benzene, 50 °C; then dry BnOH, dibutyltin dilaurate, 80 °C, 53% for *trans*-**11a**, 65% for *trans*/*cis*-**11b**, and 68% for *trans*-**11c**; (c) H_2, Pd-C 10%, MeOH or AcOEt, rt, *trans*-**12a** and *trans*-**12c** were not purified, 63% for *trans*-**12b**; (d) Fmoc-OSu, $NaHCO_3$, acetone or acetone−H_2O (4:1), rt, 63% for *trans*-**13a**, 61% for *trans*-**13b**, and 30% for *trans*-**13c** from *trans*-**11c**; (e) for *trans*-**14a**, AcOH−^{i}PrOH−H_2O (2:1:1), 100 °C, 91%; for *trans*-**14b**,**c**, 10% TFA−CH_2Cl_2, rt, 36% for *trans*-**14b** and quantitative for *trans*-**14c**.

peridone **8d** was hydrogenated in the same conditions, 3-decarboxylated piperidone **10d** was the only product obtained, together with unmodified starting material. In the other cases, the decarboxylation products were also obtained (traces for **10a** and variable amounts for **10b** and **10c**). However, the decarboxylation process could be avoided, in all cases except for the cyano derivative, when the products were not purified by chromatography with use of silica gel and the solvent evaporated without heating.[22]

Compounds *trans*-**11a**−**c** were derivatized to be used as Trp-Gly, Ile-Gly, and Phe-Gly surrogates in peptide synthesis. Thus, deprotection of the amino group by hydrogenolysis afforded 3-aminopiperidones *trans*-**12a**−**c**, and subsequent *N*-protection with Fmoc-OSu[23] gave Fmoc/O^{t}Bu derivatives *trans*-**13**a−**c**. Finally, *N*-Fmoc protected carboxylic acids *trans*-**14a**−**c** were prepared by mild acid hydrolysis[24] of the *tert*-butyl ester function.

SCHEME 4. Synthesis of Tripeptides 17a,b[a]



[a] Reagents and conditions: (a) AcCl, pyridine, dry CH_2Cl_2, rt, 85%; (b) AcOH−^{i}PrOH−H_2O (2:1:1), 100 °C, quantitative; (c) HCl·L-Leu-NH_2, Et_3N, DCC, HOBt, dry DMF, rt, 41%.

Once pseudodipeptide analogues were obtained, we proceeded to prepare tripeptides Ac-{Trp-Gly}-Leu-NH_2 **17a**,**b** to perform the corresponding structural studies. The required *N*-acetylated dipeptide *trans*-**16** was prepared from 3-aminopiperidone *trans*-**12a** by *N*-acetylation and hydrolysis of the resulting *tert*-butyl ester *trans*-**15** (Scheme 4). The coupling of *trans*-**16** with L-Leu-NH_2·HCl, using standard conditions[25] with Et_3N, DCC, and HOBt, yielded pseudotripeptides (2*S*,3′*S*,4′*S*)-**17a** and (2*S*,3′*R*,4′*R*)-**17b** in 41% yield. Addition of the extra chiral carbon of known configuration of the Leu residue on the molecule converted the pair of trans enantiomers into two diastereomers, so we should have been able to identify the absolute configurations of compounds **17a** and **17b** by X-ray crystallography and NMR. The two diastereomers were separated by column chromatography, but unfortunately, we could not suitably crystallize them.

Conformational Studies of Compounds 17a and 17b. To determine whether compounds **17a** and **17b** can promote a β- or a γ-turn conformation, we performed conformational studies using NMR experiments and molecular modeling calculations. β- and γ-turns are nonperiodic peptide segments that reverse the orientation of the peptide chain.[1a,26,27] The most general features of a β-[28,29] and a γ-turn[30] are described in the literature. The major types[31] of β-turns show a characteristic hydrogen

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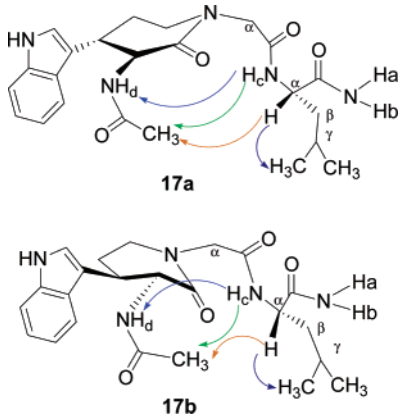

FIGURE 4. NOESY correlations in**17a**,**b**.

bond between the oxygen atom of the carbonyl function of the first amino acid (*i*) and the NH amide proton of the fourth (*i*+3). If the distance between the oxygen and the hydrogen atoms involved is less than 2.5 Å, a hydrogen bond might be present,[32] while if the distance is between 2.5 and 4 Å,[27c,33] there is a significant interaction between them (see Figure 3).

Since at that moment absolute configuration of diastereomers **17a** and **17b** was not known, in this study we refer to them as tripeptides or diastereomers I and II.

The first relevant observation was the splitting of some of the signals in the ^{1}H NMR spectra of each of the tripeptides I and II due to the presence of two slow-converting conformations in equilibrium in solution. The affected signals were Ha, Hb, Hα, Hβ, Hγ, and most of the indole nucleus.

NMR Studies. 1. NOESY. Different facts were observed for each diastereomer. Correlations showing the necessary approach to establish one of the two hydrogen bonds that would stabilize a β- or γ-turn were not observed in pseudotripeptide I. However, in its epimer II correlations between protons NHc and H-α-Leu with the acetyl methyl group protons and between protons NHc and NHd were observed. These correlations allowed us to establish a conformation in which the formation of an intramolecular hydrogen bond[32] would be possible, and this, as indicated in Figure 4, could happen in both diastereomers **17a** and **17b**. The formation of a hydrogen bond between NHc and the acetyl carbonyl group would stabilize a β-turn while the formation of a hydrogen bond between NHc and the lactam carbonyl group would stabilize a γ-turn.

2. Chemical Shift, Addition of a Competitive Solvent, and Temperature Coefficient. According to Scolastico criteria,[27c,34] which take into account NMR data indicated in Table 1, results seemed more conclusive. For diastereomer I, protons NHa and NHc were probably in equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state whereas protons NHb and NHd were non-hydrogen bonded. For diastereomer II, data suggested that protons NHa and NHd were in equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state, proton NHb was exposed to the solvent, and proton NHc was probably hydrogen bonded.

The overall NMR analysis suggested that proton NHa of both diastereomers I and II was in equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state, whereas proton NHb was clearly non-hydrogen bonded. Concerning protons NHc and NHd, the results suggested that in diastereomer I proton NHc was in equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state and proton NHd was non-hydrogen bonded, whereas in diastereomer II, proton NHc was clearly intramolecularly hydrogen-bonded and proton NHd was in equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state. These results were not conclusive and they were later evaluated together with those from the molecular model calculations.

Molecular Modeling. 1. Monte Carlo Calculations.[35] To determine the conformational space available to compounds **17a** and **17b**, we performed both Monte Carlo and molecular dynamics with iterative simulated annealing[36] calculations. For the Monte Carlo protocol, molecular models for compounds **17a** and **17b** were initially constructed by using the model-building facility implemented in Spartan 5.0. Coordinates for these structures were used as input for the Monte Carlo protocol.[37] Rotation was allowed around the dihedral angles, which constitute the main determinants of the structure (Figure 5). A conformational search of **17a** and **17b** was carried out with Spartan version 5.0,[1a,37] starting from different extended conformations. Structures corresponding to the energy minima (as calculated with the MMF94 force field[38]) within a 10-kcal/mol window above the global minimum were analyzed on the basis of all

(28) The most characteristic features of a β-turn are the distance R (<7 Å) between the Cα_i and Cα_{i+3} and the dihedral angle τ ($-90° < \tau < 90°$) formed by the four Cα atoms belonging to the tetrapeptide, see: Perczel, A.; McAllister, M. A.; Csaszar, P.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1993**, *115*, 4849−4858.

(29) The major β-turns are classified according to the torsion angles of the second (ϕ_1, ψ_1: $\phi_1 = -60 \pm 30°$ and $\psi_1 = 120 \pm 30°$) and third amino acids (ϕ_2, ψ_2: $\phi_2 = 80 \pm 30°$ and $\psi_2 = 0 \pm 45°$), see: (a) Rose, G. D.; Gierash, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1−109. (b) Ball, J. B.; Hughes, R. A.; Alewood, P. F.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467−3478. (c) Liskamp, R. M. J. *Recl. Trav. Chim. Pays Bas* **1994**, *113*, 1−63.

(30) The main features characterizing a classical γ-turn are the torsion angles of the second amino acid (ϕ_2, ψ_2: $\phi_2 = 70°/85°$ and $\psi_2 = -60°/-70°$) and the distance between the carbonyl carbon atom of the second amino acid (*i*+1) and the nitrogen atom of the amino group of the third residue (*i*+3) with a preferential value of 3 Å, see ref 27a.

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(33) Takeuchi, Y.; Marshall, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 5363−5372.

(34) The temperature coefficients in DMSO, according to Kessler criteria, suggested that in diastereomer I protons NHa and NHc ($|\Delta\delta/\Delta T| < 3$ ppb/K) were intramolecularly hydrogen bonded whereas protons NHb and NHd ($|\Delta\delta/\Delta T| \sim 4$ ppb/K) were exposed to the solvent. For diastereomer II, proton NHa ($|\Delta\delta/\Delta T| = 2.5$ ppb/K) was probably intramolecularly hydrogen bonded whereas other NH protons were exposed to the solvent (Table 1), see: Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−523.

(35) The above results were confirmed performing a parallel conformational search, using molecular dynamics with Iterative Simulated Annealing, see ref 36. This protocol was run five times, employing fully extended starting structures of both compounds (**17a** and **17b**) and AMBER (implemented in DISCOVER 3) as force field. The profiles for the main parameters characterizing γ- and β-turns were similar to those found with the Monte Carlo protocol (data not shown).

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(37) Hehre, W. J.; Huang, W. W.; Klunzinger, P. E.; Deppmeier, B. J.; Driessen, A. J. *A Spartan Tutorial;* Wavefunction, Inc.: Irvine, CA, 1997; pp 85−93.

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TABLE 1. Chemical Shifts, Δδ upon Addition of DMSO and Temperature Coefficients for Diastereomers I and II

	diastereomer I					diastereomer II				
	$CDCl_3$ (ppm)	δDMSO (ppm)	Δδ (ppm)	|Δδ/ΔT| (ppb/K)		δ$CDCl_3$ (ppm)	δDMSO (ppm)	Δδ (ppm)	|Δδ/ΔT| (ppb/K)	
				$CDCl_3$	DMSO				$CDCl_3$	DMSO
Ha	8.39	7.64	−0.75	3	2.6	8.51	7.63	−0.88	3.5	2.5
Hb	5.47	7.27	1.8	2.5	4	5.54	7.27	1.73	2.5	4
Hc	7.45	8.29	0.84	4	2	7.69	8.43	0.74	2.5	4
Hd	6.32	7.86	1.54	4.5	3.7	6.89	7.89	1	15.5	3.5

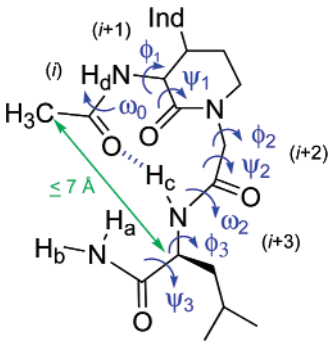

FIGURE 5. Dihedral angles for structures **17**.

TABLE 2. Percentages of Minima Energy Conformers of the Pseudopeptides Which Exhibit Different Features of β-II and/or γ-Turns (Monte Carlo Conformational Search)

	diastereomer	
	17a	**17b**
$R(C\alpha_i \cdots C\alpha_{i+3}) < 7$ Å	49[a]	40[a]
$-90° < \tau > +90°$	75[a]	70[a]
$NHc \cdots O_iC < 2.5$ Å	16[a]	17[a]
$+70° < \Phi_2 > +85°$	40[b]	61[b]
$-60° < \Psi_2 > -70°$	33[b]	31[b]
$NHc \cdots O_{i+1}C < 2.5$ Å	61[b]	64[b]
$-90° < \Phi_1 > -30°$	63[c]	
$+90° < \Psi_1 > +150°$	59[c]	
$+50° < \Phi_2 > +110°$	60[c]	
$-45° < \Psi_2 > +45°$	39[c]	31[d]
$90° < \Phi_1 > 30°$		68[d]
$-150° < \Psi_1 > -90°$		62[d]
$-45° < \Phi_2 > +45°$		69[d]
ω_0 trans/cis	100/0	93/7
ω_2 trans/cis	100/0	100/0

[a] Percentage of conformers with expected values for canonical β turns. [b] Percentage of conformers with expected values for canonical γ turns. [c] Percentage of conformers with expected values for canonical β-II turns. [d] Percentage of conformers with expected values for canonical β-II′ turns.

the geometric turn parameters, which are diagnostic for the presence of γ- and β-turns. The corresponding distribution profiles are summarized in Table 2 and the Supporting Information.

A general analysis of the Monte Carlo results (Table 2) showed that two of the characteristic geometric features of the β-turn (R and τ) were fulfilled by a considerable percentage of the stable conformer populations of **17a** and **17b** while the distance $CO_i \cdots NHc$ was not fulfilled by the main part of the conformer population of both diastereomers. On the other hand, in a considerable percentage of the population the distance between NHc and CO_{i+1} corresponded to that of a hydrogen bond, and the angles ϕ_2 and ψ_2 agreed well with the values expected for a γ-turn. Another hydrogen bond between $NHa \cdots CO_{i+2}$ (see the Supporting Information) was present in part of the population of conformers of both diastereomers. This last result was in agreement with the ^1H NMR observation that in both diastereomers proton NHa was in equilibrium between a hydrogen-bonded and non-hydrogen-bonded state.

To determine the presence of cis and trans conformers for the acetamide group, we analyzed the dihedral angles ω_0 and ω_2 (Figure 5). Most of the conformers of both diastereomers presented a trans disposition for the CO−N bond whereas for conformer **17b** a very low percentage of the conformer population had a cis disposition for ω_0 (Table 2).

A more detailed study of the conformers obtained in the Monte Carlo search allowed us to classify the minima energy conformers (with energies above 2.5 kcal/mol with respect to the global minimum) of each diastereomer into families (Table 3, Figure 6). Diastereomers **17a** and **17b** yielded two and five families of conformers, respectively. All conformers of both compounds met the general criteria (*R* and τ) for a β-turn. On the other hand, only conformers **17a$_1$** and **17b$_5$** showed distances allowing a hydrogen bond[39] between NHc and CO_i. An analysis of the dihedral angles Ψ_1, Φ_1, Ψ_2, and Φ_2 confirmed that family **17a$_1$** was a β-II′ turn while **17b$_5$** was a β-II turn. In addition, these conformers presented a supplementary hydrogen bond between NHa and CO_{i+1}.

Compound **17b** showed distances allowing a hydrogen bond[39] between NHc and CO_{i+1} for the families of conformations **17b$_1$**, **17b$_2$**, **17b$_3$**, and **17b$_4$** which corresponded to γ-turn conformations. A closer analysis of the dihedral angles Ψ_2 and Φ_2 confirmed that these families were γ-turn conformations. Conformers **17b$_1$**, **17b$_2$**, and **17b$_3$** presented one supplementary hydrogen bond between NHa and CO_i and, in addition, conformer **17b$_2$** had another hydrogen bond between NHb and CO_{i+2} (see Figure 6). Remarkably, conformer **17b$_4$** (which is 1.8 kcal higher in energy than the global minima) presented a cis disposition for the C−N bond belonging to the acetamide group ($\omega_0 = 0$) favoring the formation of an extra hydrogen bond between NHd and CO_{i+3}. This last result is in agreement with the observation in the ^1H NMR experiments that proton NHd in diasteromer II was in equilibrium between a hydrogen-bonded and non-hydrogen-bonded state.

We measured the distance between the lactam ring center (see the legend of Table 3) and the methine carbon of the isobutyl group from the Leu side chain to evaluate if the steric hindrance between this ring and the Leu side chain could explain the relative stabilities of the families of conformers. We observed that in the higher energy

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TABLE 3. Characteristics of Energy Minima Conformers (Monte Carlo) for Compounds 17

	17a, families =		**17b**, families =							
	1	2	1	2	3	4	5	β-II′[a]	β-II[a]	γ[a]
ΔE (kcal/mol)	0	1.9	0	0.7	1.2	1.8	2.0			
NHc···CO$_i$ (Å)	1.9	2.8	2.7	4.4	3.5	6.1	2.0	≤2.5 Å	≤2.5 Å	
NHc···CO$_{i+1}$ (Å)	2.7	2.2	2.2	2.0	2.1	1.9	2.7			≤2.5 Å
R(Cα_i···Cα_{i+3}) (Å)	5.1	6.1	5.9	5.6	6.3	5.9	5.2	≤7 Å	≤ 7 Å	
NHa···CO$_i$ (Å)	3.2	1.8	1.7	1.9	1.9	6.4	3.1			
NHa···CO$_{i+1}$ (Å)	2.1	3.3	3.9	4.2	2.9	5.9	2.1			
τ (deg)	−11	−27	24	3.4	14	−31	13	$-90 \le \tau \le 90$	$-90 \le \tau \le 90$	
Φ_1 (deg)	62	63	−63	−74	−64	164	−62	60 ± 30	−60 ± 30	
Ψ_1 (deg)	−140	−158	154	151	159	88	141	−120 ± 30	120 ± 30	
Φ_2 (deg)	−77	−87	87	75	83	81	76	−80 ± 30	80 ± 30	70/85
Ψ_2 (deg)	5	46	−54	−95	−80	−80	−4	0 ± 45	0 ± 45	−60/−70
lactam-C(CH$_3$)$_2$ (Å)[b]	6.26	5.20	6.38	7.21	6.74	6.65	5.58			

[a] Expected values for canonical β-II, β-II′, and γ-turns. [b] A pseudoatom was created in the mass center of the lactam ring. The distance is between this pseudatom and the methine atom belonging to the isobutyl group from the side chain of the Leu residue.

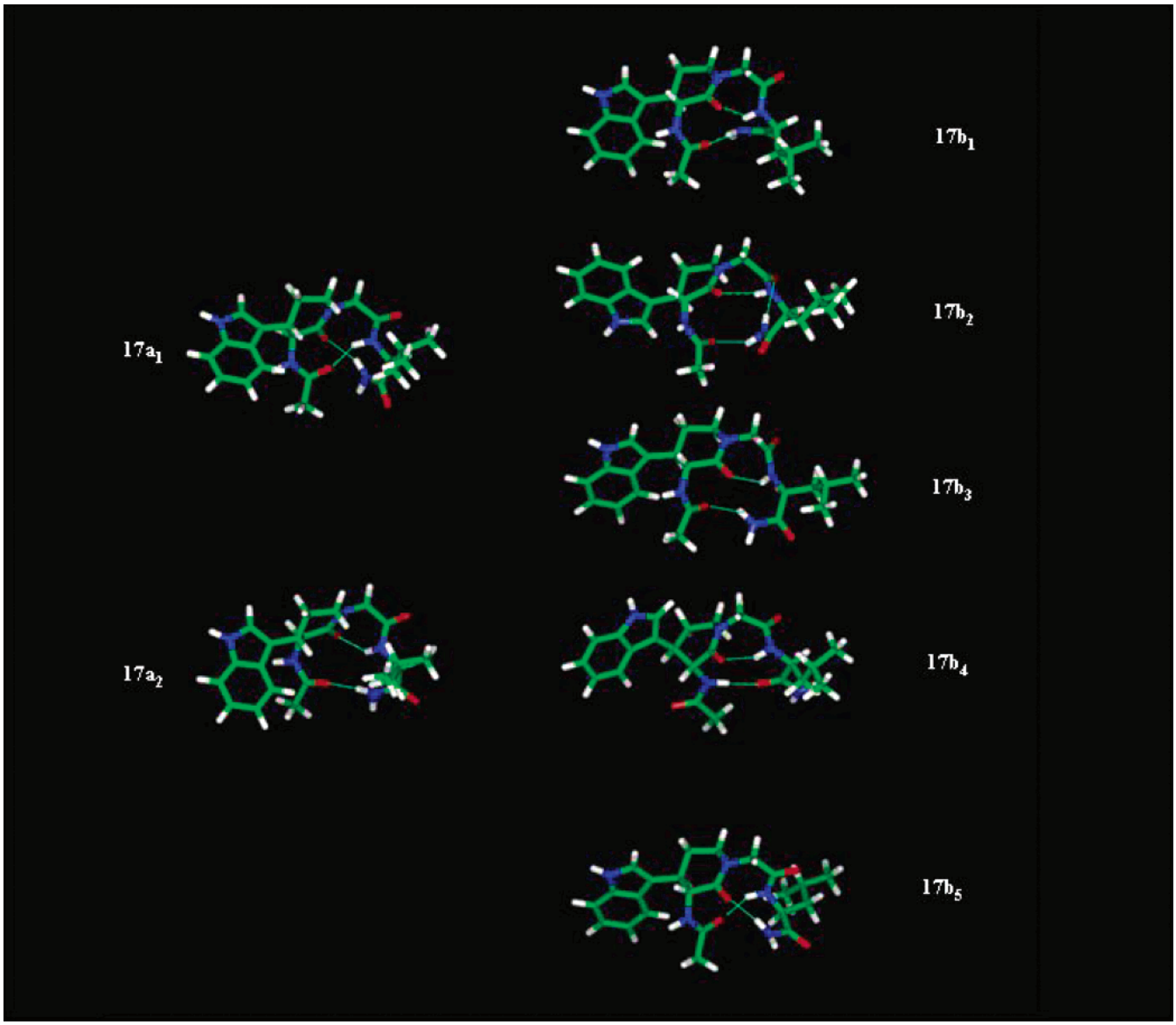

FIGURE 6. Stick conformational representation of minimum energy conformers of diastereomers **17a**,**b** obtained after the Monte Carlo conformational search.

conformers (approximately 2 kcal/mol above the global minima) of diastereomers **17a$_2$** and **17b$_5$** the distance was shorter than that observed for the other conformers (5.20 and 5.58 Å compared to approximately 6.26−7.21 Å). It is worth pointing out that the most energetic conformation for diastereomer **17a** was the γ-turn conformation,

TABLE 4. Percentages of Conformers of the Pseudopeptides Which Exhibit Different Features of β-II and/or γ-Turns from 1 ns, 300 K Molecular Dynamics

	conformer	
	17a$_1$	**17b$_1$**
R(Cα−Cα$_{i+3}$) < 7 Å	100[a]	98[a]
−90° < τ > +90°	100[a]	100[a]
NHc···O$_i$C < 2.5 Å	10[a]	2[a]
+70° < Φ$_2$ > +85°	0[b]	91[b]
−60° < Ψ$_2$ > −70°	8[b]	77[b]
NHc···O$_{i+1}$C < 2.5 Å	1[b]	100[b]
NHa···O$_i$C < 2.5 Å	90	85
NHa···O$_{i+1}$C < 2.5 Å	4	5
ω$_0$ trans/cis	100/0	100/0

[a] Percentage of conformers with expected values for canonical β turns. [b] Percentage of conformers with expected values for canonical γ turns.

whereas the most energetic conformation for diastereomer **17b** was the β-turn conformation. The shorter distance (5.20 Å) between the center of the lactam ring and the Leu side chain in **17a$_2$** could explain the lesser stability of this γ-turn family with respect to the family of conformer **17a$_1$**, which defines a β-turn. For the other diastereomer **17b**, the shorter distance between the center of the lactam ring and the Leu side chain was observed in the **17b$_5$** family of conformers. In this case, this corresponded to a β-turn conformation and the γ-turn conformation was more stable for this diastereomer.

In summary, our Monte Carlo calculations allowed us to conclude that isomer **17a** was a γ-turn/distorted type-II β-turn structure, whereas isomer **17b** was mainly a γ-turn structure. Moreover, steric hindrance can explain the different stabilities of both families of conformers.

2. Molecular Dynamics Calculations. To study the dynamic behavior of the most stable family of conformations of pseudopeptides **17a** and **17b**, the global minima conformers of both compounds (**17a$_1$** and **17b$_1$**) were taken as the starting points for molecular dynamics calculations. We analyzed the geometric β- and γ-turn diagnosis parameters of the structures generated during the molecular dynamics simulation for 1 ns at 300 K in $CDCl_3$ as an explicit solvent (Table 4).

In the family of conformers **17a$_1$** all distances R remained below 7 Å and no major dihedral angle τ fluctuations with respect to those of the starting structures were observed for the molecular dynamic simulations. The distances found for NHc···O$_i$C were not compatible with the presence of a hydrogen bond (involved in the formation of the β-turn), which was in contrast with the starting structure. Although the initial distances NHc···CO$_i$ and NHa···CO$_{i+1}$ of conformer **17a$_1$** (Table 3, 1.9 Å for NHc···CO$_i$ and 2.1 Å for NHa···CO$_{i+1}$) were appropriate for the formation of a hydrogen bond, most of the conformers found during the MD calculation did not establish a hydrogen bond while a new hydrogen bond was established between NHa and CO$_i$ (Table 4, 90% of the population). This was in agreement with the observation in the ^{1}H NMR experiments that proton NHa in both diastereomers was in equilibrium between a hydrogen-bonded and non-hydrogen-bonded state.

Similarly, in the family of conformers of the other diastereomer **17b$_1$**, all distances R remained below 7 Å, no major dihedral angle τ fluctuations with respect to those of the starting structures were shown for the molecular dynamic simulations, and the distances found for NHc···O$_i$C were not compatible with the presence of a hydrogen bond. Nevertheless, the distance values corresponding to NHc and CO$_{i+1}$ of this conformer indicated that these atoms established a hydrogen bond compatible with the presence of a γ-turn (100% of the population). The supplementary hydrogen bond between NHa and CO$_i$ also maintained the distance during the MD calculation in 85% of the population. The participation of proton NHc in an intramolecular hydrogen bond was evidenced by the ^{1}H NMR experiments (NOESY and temperature coefficients in $CDCl_3$ and in d_6-DMSO). Thus, this result would be in accordance with the fact that proton NHc in diastereomer II was clearly intramolecularly hydrogen bonded.

As was described above, the absolute configuration of both diastereomers I and II has not been established so far. Taking into account that ^{1}H NMR experiments (NOESY and temperature coefficients in $CDCl_3$ and in d_6-DMSO) evidenced that NHc participated in an intramolecular hydrogen bond in diastereomer II, but not in I, our molecular modeling results would allow us to assign the absolute configuration **17b** to diastereomer II, in which there is a hydrogen bond between NHc and CO$_{i+1}$ stabilizing the formation of a γ-turn. In contrast, absolute configuration **17a** would be assigned to diastereomer I, in which a hydrogen bond between NHc and CO$_{i+1}$ was not observed.

Experimental Section

3-(Benzyloxycarbonyl)-1-(*tert*-butoxycarbonyl)-3-(phenylselanyl)piperidin-2-one (3). A solution of LHMDS 1 M in dry THF (100 mL) was added dropwise to a solution of *N*-(*tert*-butoxycarbonyl)-2-piperidone **2** (8.7 g, 43.6 mmol) in dry THF (100 mL) under inert atmosphere at −78 °C. The resulting mixture was stirred at this temperature for 1 h, benzyl chloroformate (7.9 mL, 52.3 mmol) was added dropwise, and stirring was continued for 30 min. Next, a solution of phenylselanyl chloride (10.8 g, 56.7 mmol) in dry THF (80 mL) was added and stirring at −78 °C was continued for a further 30 min. The mixture was then allowed to warm to room temperature for 2 h and, after addition of 1 N HCl (200 mL), was extracted with AcOEt. The combined organic extracts were washed with aqueous saturated $NaHCO_3$ solution and brine, dried, and concentrated to furnish a crude product, that after purification by chromatography (hexane/AcOEt, 9/1) afforded piperidone **3** (19.8 g, 93%): IR (NaCl) 1719 cm^{-1}; ^{1}H NMR δ 1.59 (s, 9 H), 1.65 (m, 1 H), 1.81 (dqn, *J* = 14.3, 5.8 Hz, 1 H), 2.00 (ddd, *J* = 13.9, 10.1, 5.7 Hz, 1 H), 2.24 (dt, *J* = 13.7, 5.5 Hz, 1 H), 3.38 (dt, *J* = 13.2, 6.2 Hz, 1 H), 3.60 (ddd, *J* = 13.1, 8.2, 5.2 Hz, 1 H), 5.15 and 5.27 (2d, *J* = 12.4 Hz, 1 H each), 7.20−7.60 (m, 10 H); ^{13}C NMR δ 20.7, 27.8, 31.6, 45.2, 56.7, 67.6, 83.3, 126.3, 135.1, 127.9, 128.1, 128.3, 128.5, 128.6, 128.8, 129.1, 129.6, 131.3, 138.3, 152.6, 167.6, 169.2; EIMS *m*/*z* 489 (M$^+$ + 1, 8), 389 (6), 157 (10), 91 (100), 57 (84); mp (AcOEt) 55−57 °C. Anal. Calcd for $C_{24}H_{27}NO_5Se$: C, 59.02; H, 5.57; N, 2.87. Found: C, 59.28; H, 5.75; N, 2.91.

3-(Benzyloxycarbonyl)-1-(*tert*-butoxycarbonyl)-5,6-dihydropyridin-2(1*H*)-one (4). To a stirred solution of piperidone **3** (6.0 g, 13.5 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added dropwise a solution of *m*-CPBA (3.7 g, 20.4 mmol, 95.5%) in dry CH_2Cl_2 (80 mL). The resulting mixture was stirred at 0 °C for 15 min, then at room temperature for 1 h. The reaction mixture was then quenched with aqueous saturated $NaHCO_3$ solution (40 mL) and stirred for a further 10 min. The aqueous layer was extracted several times with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, and

concentrated to afford crude dihydropyridone **4** (4.3 g) that was used in the next step without further purification: ^{1}H NMR δ 1.52 (s, 9 H), 2.52 (td, J = 6.3, 4.4 Hz, 2 H), 3.87 (t, J = 6.2 Hz, 2 H), 5.27 (s, 2 H), 7.25−7.43 (m, 5 H), 7.52 (t, J = 3.8 Hz, 1H).

3-(Benzyloxycarbonyl)-5,6-dihydropyridin-2(1*H*)-one (5). To a solution of dihydropyridone **4** (3.5 g, 10.6 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added dropwise a solution of TFA (48.5 mL, 0.6 mol), and the resulting mixture was stirred for 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to afford dihydropyridone **5** (2.25 g), which was used in the next step without further purification: ^{1}H NMR δ 2.50 (td, J = 6.4, 4.8 Hz, 2 H), 3.43 (td, J = 6.4, 2.6 Hz, 2 H), 5.27 (s, 2 H), 6.34 (br s, 1 H), 7.25−7.41 (m, 5 H), 7.50 (t, J = 4.8 Hz, 1 H).

3-(Benzyloxycarbonyl)-3-(phenylselanyl)piperidin-2-one (6). Method A. To a solution of piperidone **3** (2.1 g, 4.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of TFA (9.4 mL, 0.12 mol), and the resulting mixture was stirred for 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (7 mL) and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give a crude product, which was purified by chromatography (hexane/ AcOEt 4/1) to afford piperidone **6** (1.01 g, 63%) and **3-(benzyloxycarbonyl)piperidin-2-one** (130 mg, 13%) as a byproduct.

Method B. TMSOTf (10 mL, 55.2 mmol) was added dropwise to a solution of piperidone **3** (16.4 g, 36.8 mmol) in dry CH_2Cl_2 (70 mL) and 2,6-lutidine (8.5 mL, 73.6 mmol) at room temperature. The resulting mixture was stirred for 15 min and the reaction was quenched by addition of aqueous saturated NH_4Cl solution (50 mL). The mixture was extracted several times with Et_2O, and the combined organic extracts were washed with water and brine, dried, and concentrated. The crude residue obtained was washed repeatedly with Et_2O to yield piperidone **6** as the unique product (10.4 g, 80%): IR (NaCl) 1720, 1656 cm^{-1}; ^{1}H NMR δ 1.54 (m, 1 H), 1.78 (m, 1 H), 1.94 (ddd, J = 13.7, 11.9, 3.4 Hz, 1 H), 2.16 (ddd, J = 13.7, 4.8, 3.7 Hz, 1 H), 3.24 (m, 2 H), 5.23 (s, 2 H), 6.50 (br s, 1 H), 7.22−7.57 (m, 10 H); ^{13}C NMR δ 20.1, 32.0, 41.9, 53.4, 67.4, 126.5, 135.4, 127.9, 128.1, 128.3, 128.6, 129.4, 138.2, 168.6, 170.4; EIMS m/z 389 (M^++1, 16), 157 (2), 91 (100), 77 (16), 65 (19). Anal. Calcd for $C_{19}H_{19}NO_3Se$: C, 58.77; H, 4.93; N, 3.61. Found: C, 58.46; H, 4.97; N, 3.65. **3-(Benzyloxycarbonyl)-piperidin-2-one**: IR (NaCl) 1736, 1669 cm^{-1}; ^{1}H NMR δ 1.73 (m, 1 H), 1.88 (m, 1 H), 2.08 (m, 2 H), 3.30 (m, 2 H), 3.43 (t, J = 7.2 Hz, 1 H), 5.20 (s, 2 H), 7.35 (m, 6 H); ^{13}C NMR δ 20.2, 24.7, 41.9, 48.5, 66.8, 127.9, 128.0, 128.3, 135.5, 167.9, 170.5; EIMS m/z 233 (M^+, 2), 142 (3), 99 (100), 91 (75). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.11; H, 6.48; N, 6.10.

3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-3-(phenylselanyl)piperidin-2-one (7). To a solution of piperidone **6** (13 g, 33.5 mmol) in dry CH_3CN (150 mL) was added TBAB (43.2 g, 134 mmol) and K_2CO_3 (46.3 g, 335 mmol) at room temperature under inert atmosphere. Then, *tert*-butylbromoacetate (7.4 mL, 50.2 mmol) was also added and the resulting mixture was vigorously stirred for 24 h at the same temperature. The mixture was filtered and the solvent was evaporated. Chromatography of the resulting residue (hexane/AcOEt, 9/1) furnished piperidone **7** (16.3 g, 96%): IR (NaCl) 1739, 1649 cm^{-1}; ^{1}H NMR δ 1.47 (s, 9 H), 1.63 (m, 1 H), 1.85 (dm, J = 14 Hz, 1 H), 1.99 (ddd, J = 13.4, 11.9, 3.6 Hz, 1 H), 2.15 (dt, J = 13.8, 4.4 Hz, 1 H), 3.27 (ddd, J = 11.6, 6.2, 4.0 Hz, 1 H), 3.33 (ddd, J = 11.7, 9.9, 5.3 Hz, 1 H), 3.87 and 4.13 (2d, J = 17.0 Hz, 1 H each), 5.22 (s, 2 H), 7.20−7.55 (m, 10 H); ^{13}C NMR δ 20.8, 28.0, 32.6, 48.9, 49.9, 53.7, 67.4, 81.9, 127.0, 127.9, 128.0, 128.2, 128.3, 128.5, 129.3, 135.5, 138.3, 166.7, 167.5, 170.3; CIMS m/z 502 (M^+, 6), 503 (M^+ + 1, 37), 520 (M^+ + 18, 6); mp (hexane) 83−85 °C. Anal. Calcd for $C_{25}H_{29}NO_5Se$: C, 59.76; H, 5.82; N, 2.79. Found: C, 59.29; H, 5.89; N, 2.74.

3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-5,6-dihydropyridin-2(1*H*)-one (1). To a solution of piperidone **7** (8.9 g, 17.7 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added dropwise a solution of *m*-CPBA (4.8 g, 26.6 mmol, 95.5%) in dry CH_2Cl_2 (90 mL) under inert atmosphere. The resulting mixture was stirred at 0 °C for 15 min and at room temperature for 1 h. The reaction was then quenched with aqueous saturated $NaHCO_3$ solution (50 mL) and stirred for 10 min. The organic layer was extracted several times with CH_2Cl_2, washed with brine, and dried. After evaporation of the solvent, the resulting crude dihydropyridone **1** (6.9 g) was used in the next reaction without further purification: IR (NaCl) 1739, 1661 cm^{-1}; ^{1}H NMR δ 1.47 (s, 9 H), 2.56 (td, J = 6.8, 4.5 Hz, 2 H), 3.50 (t, J = 6.9 Hz, 2 H), 4.13 (s, 2 H), 5.26 (s, 2 H), 7.25−7.45 (m, 6 H); ^{13}C NMR δ 24.3, 28.0, 45.8, 48.8, 66.8, 82.0, 128.1, 128.3, 128.5, 128.9, 135.7, 147.3, 161.0, 163.9, 168.2; CIMS m/z 345 (M^+, 2), 244 (24), 91 (100).

***trans*/*cis*-3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-4-(3-indolyl)piperidin-2-one (*trans*/*cis*-8a).** Indole (1.79 g, 15.3 mmol) was added to a solution of dihydropyridone **1** (5.3 g, 15.3 mmol) in dry CH_2Cl_2 (15 mL) and Montmorillonite KSF (3.06 g) under inert atmosphere. The resulting mixture was stirred at room temperature for 1 day. The clay was then filtered through a Celite pad and the filtrate was concentrated. The crude product was purified by chromatography (hexane/AcOEt, 9/1) to yield a mixture of diastereomers *trans*/*cis*-**8a** (10:1, 80%). The structure assignment was made with enriched samples of both diastereomers. *trans*-**8a**: IR (NaCl) 1739, 1733, 1650, 1640, 1634 cm^{-1}; ^{1}H NMR δ 1.46 (s, 9 H), 2.12 (m, 1 H), 2.30 (dq, J = 13.5 and 4 Hz, 1 H), 3.38 (ddd, J = 11.7, 5.5, and 4.0 Hz, 1 H), 3.57 (td, J = 11.5 and 4.5 Hz, 1 H), 3.85 (m, 2 H), 3.86 and 4.26 (2 d, J = 17.0 Hz, 1 H each), 5.02 and 5.08 (2 d, J = 12.4 Hz, 1 H each), 6.97 (d, J = 8.5 Hz, 2 H), 6.98 (d, J = 2.0 Hz, 1 H), 7.15−7.20 (m, 3 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 8.12 (br s, 1 H); ^{13}C NMR δ 28.0, 29.1, 34.2, 48.1, 49.4, 55.6, 66.7, 82.0, 111.4, 116.0, 118.6, 119.4, 121.2, 122.1, 125.9, 127.5, 127.6, 127.7, 128.0, 128.2, 135.4, 136.3, 166.5, 167.7, 170.1; EIMS m/z 462 (M^+, 7), 389 (4), 327 (3), 91 (96), 57 (100). Anal. Calcd for $C_{27}H_{30}N_2O_5 \cdot {}^1/_3H_2O$: C, 69.66; H, 6.02; N, 6.18. Found: C, 69.16; H, 6.64; N, 6.21. *cis*-**8a**: IR (NaCl) 1739, 1733, 1650, 1640, 1634 cm^{-1}; ^{1}H NMR δ 1.49 (s, 9 H), 2.12 (m, 1 H), 2.89 (qd, J = 12.7 and 5.3 Hz, 1 H), 3.46 (ddd, J = 11.7, 5.6, and 2.5 Hz, 1 H), 3.66 (td, J = 11.5 and 5.0 Hz, 1 H), 3.76 and 4.48 (2d, J = 17.1 Hz, 1 H each), 4.10 (dd, J = 3.9 and 0.6 Hz, 1 H), 4.69 and 4.76 (2d, J = 13 Hz, 1 H each), 6.65 (d, J = 7.2 Hz, 2 H), 6.84 (d, J = 2.0 Hz, 1 H), 7.07−7.20 (m, 5 H), 7.57 (d, J = 7.5 Hz, 1 H), 7.59 (d, J = 8 Hz, 1 H), 8.02 (br s, 1 H);[40] ^{13}C NMR δ 24.0, 28.1, 33.4, 48.6, 49.9, 53.4, 66.3, 82.0, 111.3, 114.8, 118.6, 119.6, 121.4, 122.2, 126.3, 127.6, 127.7, 128.0, 128.2, 135.2, 136.0, 166.1, 167.8, 169.5; EIMS m/z 462 ($M^{+\bullet}$, 7), 389 (4), 327 (3), 91 (96), 57 (100). Anal. Calcd for $C_{27}H_{30}N_2O_5 \cdot {}^1/_3H_2O$: C, 69.66; H, 6.02; N, 6.18. Found: C, 69.16; H, 6.64; N, 6.21.

***trans*/*cis*-3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-4-ethylpiperidin-2-one (*trans*/*cis*-8b).** A solution of dihydropyridone **1** (350 mg, 1.01 mmol) in dry THF (2 mL) was added dropwise to a mixture of EtMgBr (1.51 mL, 1.51 mmol) and CuBr·Me_2S (103 mg, 0.5 mmol) in dry THF (1.5 mL) at −78 °C under inert atmosphere. The mixture was stirred at this temperature during 15 min, then at 0 °C for 2 h, and finally at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted several times with Et_2O. The organic extracts were washed with brine and water, dried, and concentrated. The resulting residue was purified by chromatography (hexane/AcOEt, 3/2) to yield a mixture of diastereomers *trans*/*cis*-**8b**

(40) Proton 4-H could not be assigned because it is masked by signals corresponding to the major isomer *trans*-**9a**.

(6:1, 83%). The structure assignment was made with an enriched sample of diastereomer *trans*-**8b**: IR (NaCl) 1746, 1738, 1731, 1659, 1651, 1644 cm^{-1}; ^1H NMR δ 0.90 (t, $J = 7.5$ Hz, 3 H), 1.31−1.57 (m, 2 H), 1.45 (s, 9 H), 1.57 (m, 1 H), 2.02 (ddd, $J = 13.5$, 7.8, and 4.5 Hz, 1 H), 2.16 (m, 1 H), 3.23 (d, $J = 9.6$ Hz, 1 H), 3.38 (m, 2 H), 3.77 and 4.24 (2 d, $J = 16.9$ Hz, 1 H each), 5.20 (d, $J = 0.9$ Hz, 2 H), 7.36 (m, 5 H); ^{13}C NMR δ 10.6, 25.8, 26.4, 27.9, 37.7, 47.5, 49.3, 55.2, 66.7, 81.8, 127.9, 128.0, 128.3, 135.6, 166.1, 167.6, 170.3; EIMS *m*/*z* 375 (M^+, 2), 376 ($M^+ + 1$, 2), 319 (51), 302 (26), 274 (41), 228 (53), 210 (34), 184 (32), 166 (98), 91 (100), 57 (57). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.21; H, 7.75; N, 3.69.

***trans*/*cis*-3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-4-phenylpiperidin-2-one (*trans*/*cis*-8c).** Operating as above for the preparation of **8b**, from dihydropyridone **1** (1.05 g, 3.04 mmol) in dry THF (6 mL) and a mixture of PhMgBr (3.04 mL, 3.04 mmol) and CuBr·Me_2S (312 mg, 1.52 mmol) in dry THF (4.5 mL), a diastereomeric mixture of *trans*/*cis*-**8c** (13:1, 77%) was obtained after purification by chromatography (hexane/AcOEt, 3/2). The structure assignment was made with an enriched sample of diastereomer *trans*-**8c**: IR (NaCl) 1740 and 1650 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 2.11 (m, 2 H), 3.43 (ddd, $J = 11.8$, 4.9, and 2.7 Hz, 1 H and td, $J = 11.5$ and 3.7 Hz, 1 H), 3. 59 (td, $J = 11.4$ and 5.4 Hz, 1 H), 3. 67 (d, $J = 11.1$ Hz, 1 H), 3.91 and 4.21 (2 d, $J = 17.1$ Hz, 1 H each), 4.99 and 5.07 (2 d, $J = 12.4$ Hz, 1 H each), 7.03−7.28 (m, 10 H); ^{13}C NMR δ 28.0, 29.4, 42.6, 48.1, 49.1, 56.4, 66.5, 81.9, 126.7, 127.2, 127.6, 127.7, 128.1, 128.7, 135.4, 141.0, 166.0, 167.5, 169.3; EIMS *m*/*z* 423 (M^+, 3), 367 (53), 322 (31), 276 (63), 232 (38), 214 (86), 91 (100), 57 (59). Anal. Calcd for $C_{25}H_{29}NO_5 \cdot {}^1/_{15}H_2O$: C, 70.45; H, 6.93; N, 3.29. Found: C, 70.09; H, 6.87; N, 3.29.

***trans*/*cis*-3-(Benzyloxycarbonyl)-1-[(*tert*-butoxycarbonyl)methyl]-4-cyanopiperidin-2-one (*trans*/*cis*-8d).** NH_4Cl (116 mg, 2.17 mmol) and a solution of KCN (189 mg, 2.9 mmol) in H_2O (1.5 mL) were added to a solution of dihydropyridone **1** (0.5 g, 1.45 mmol) in DMF (12 mL). The resulting reaction mixture was stirred at 90 °C for 20 min. Then, H_2O (10 mL) was added and the aqueous phase was extracted several times with AcOEt. The organic extracts were washed with brine, dried, and concentrated to give a residue that after purification by chromatography (hexane/AcOEt, 4/1) yielded a diastereomeric mixture of *trans*/*cis*-**8d** (5:1, 83%). The structure assignment was made with an enriched sample of diastereomer *trans*-**8d**: IR (NaCl) 2245, 1744, 1666, 1650, 1644 $cm.^{-1}$; ^1H NMR δ 1.46 (s, 9 H), 2.18 (m, 1 H), 2.35 (ddd, $J = 14.1$, 8.7, and 5.2 Hz, 1 H), 3.51 (m, 3 H), 3.72 (d, $J = 8.4$ Hz, 1 H), 3.97 and 4.05 (2 d, $J = 17.1$ Hz, 1 H each), 5.26 (s, 2 H), 7.31−7.40 (m, 5 H); ^{13}C NMR δ 24.5, 27.7, 27.9, 46.4, 49.4, 50.9, 67.9, 82.4, 118.4, 128.0, 128.3, 128.5, 134.8, 162.5, 166.9, 167.3; EIMS *m*/*z* 299 (6), 271 (10), 181 (16), 91 (100), 57 (97); mp (hexane/AcOEt 3/2) 114−115 °C. Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.85; H, 6.54; N, 7.39.

***trans*/*cis*-1-[(*tert*-Butoxycarbonyl)methyl]-4-(3-indolyl)-2-oxopiperidine-3-carboxylic Acid (*trans*/*cis*-9a).** A mixture of esters *trans*/*cis*-**8a** (10:1, 5.3 g, 11.5 mmol) in MeOH (40 mL) containing 10% Pd-C (2 g) was hydrogenated at room temperature for 36 h. The resulting crude product was filtered through a Celite pad and the solvent was evaporated to furnish quantitatively a diastereomeric mixture of acids *trans*/*cis*-**9a,** which was used directly in the next step without further purification. An analytical sample of acids *trans*/*cis*-**9a** was obtained by chromatography (hexane): IR (NaCl) 3357, 1737, 1636, 1631 cm^{-1}; ^1H NMR δ 1.47 (s, 18 H), 2.07−2.39 (m, 4 H), 3.37 (m, 4 H), 3.80−4.42 (m, 8 H), 7.10−7.81 (m, 10 H), 8.25 (br s, 4 H); ^{13}C NMR δ 23.2 and 27.9, 27.9, 31.2 and 32.6, 47.5 and 47.7, 49.9, 47.8 and 57.7, 82.4 and 82.6, 111.6, 112.1 and 115.4, 118.4, 119.1, 119.2 and 121.1, 120.5 and 121.8, 125.8 and 126.1, 136.4, 166.9, 167.5, 168.1, 169.0 and 171.3; EIMS *m*/*z* 328 (33), 272 (68), 156 (35), 84 (23), 57 (100). Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.13; H, 6.89; N, 7.64.

***trans*/*cis*-[1-[(*tert*-Butoxycarbonyl)]methyl]-4-ethyl-2-oxopiperidine-3-carboxylic Acid (*trans*/*cis*-9b) and 1-[(*tert*-Butoxycarbonyl)methyl]-4-ethylpiperidin-2-one (10b).** Operating as above for the preparation of **9a**, a mixture of esters *trans*/*cis*-**8b** (660 mg, 1.76 mmol) in AcOEt (25 mL) containing 10% Pd-C (250 mg) was hydrogenated at room temperature for 2 h to yield a diastereomeric mixture of acids *trans*/*cis*-**9b** (2.8:1, 500 mg) that was used in the next step without further purification. Piperidone **10b** was obtained as a byproduct when the evaporation of the solvent was done while heating the water bath of the rotaevaporator. ^1H and ^{13}C NMR data were assigned from spectra of a crude sample of the diastereomeric mixture: IR (NaCl) 3458, 1738, 1650, 1618 cm^{-1}. *trans*-**9b**: ^1H NMR δ 0.97 (t, $J = 7.2$ Hz, 3 H), 1.35 (m, 1 H), 1.47 (s, 9 H), 1.67 (m, 1 H), 2.05 (m, 1 H), 2.29 (m, 1 H), 3.14 (d, $J = 7.8$ Hz, 1 H), 3.40 (m, 2 H), 3.83 and 4.23 (2 d, $J = 17.1$ Hz, 1 H each), 8.64 (br s, 1 H); ^{13}C NMR δ 10.8, 25.4, 26.5, 27.9, 36.0, 47.4, 49.9, 52.9, 82.3, 167.1, 168.2, 170.8. *cis*-**9b**: ^1H NMR δ 0.98 (t, $J = 7.3$ Hz, 3 H), 1.35 (m, 1 H), 1.47 (s, 9 H), 1.67 (m, 2 H), 2.05 (m, 1 H), 2.57 (m, 1 H), 3.40 (m, 2 H), 3.53 (td, $J = 12.0$ and 5.7 Hz, 1 H), 3.83 and 4.18 (2 d, $J = 17.2$ Hz, 1 H each), 8.64 (br s, 1 H); ^{13}C NMR δ 11.5, 20.8, 23.9, 27.9, 35.0, 46.5, 49.7, 48.9, 82.6, 166.8, 169.6, 171.1; EIMS *m*/*z* 270 (1), 185 (21), 140 (39), 112 (35), 57 (100). **10b**: IR (NaCl) 1742, 1651 cm^{-1}; ^1H NMR δ 0.93 (t, $J = 7.2$ Hz, 3 H), 1.37 (qn, $J = 7.2$ Hz, 2 H), 1.47 (s, 9 H), 1.55 (m, 1 H), 1.78 (m, 1 H), 1.93 (dm, $J = 12.9$ Hz, 1 H), 2.03 (dd, $J = 17.4$ and 10.8 Hz, 1 H), 2.56 (ddd, $J = 17.4$, 4.9, and 1.8 Hz, 1 H), 3.31 (m, 1 H), 3.37 (qd, $J = 11.4$ and 4.8 Hz, 1 H), 3.95 and 4.06 (2 d, $J = 17.1$ Hz, 1 H each); ^{13}C NMR δ 11.0, 28.0, 28.2, 28.6, 34.6, 38.1, 48.1, 49.0, 81.7, 168.1, 170.2; EIMS *m*/*z* 242 ($M^+ + 1$, 1), 185 (24), 168 (16), 140 (45), 112 (38), 57 (100).

***trans*-1-[(*tert*-Butoxycarbonyl)methyl]- 2-oxo-4-phenylpiperidin-3-carboxylic Acid (*trans*-9c) and 1-[(*tert*-Butoxycarbonyl)methyl]-4-phenylpiperidin-2-one (10c).** Operating as above for the preparation of **9a**, a mixture of esters *trans*/*cis*-**8c** (831 mg, 1.96 mmol) in AcOEt (35 mL) containing 10% Pd-C (300 mg) was hydrogenated at room temperature for 4 h to yield acid *trans*-**9c** (570 mg) as the unique diastereomer, which was used directly in the next step without further purification. Piperidone **10c** was obtained as a byproduct when the evaporation of the solvent was done while heating the water bath of the rotaevaporator. NMR experiments were performed with a crude sample of *trans*-**9c**: IR (KBr) 3432, 1740, 1604 cm^{-1}; ^1H NMR δ 1.49 (s, 9 H), 2.11 (m, 2 H), 3.39 (dt, $J = 12.6$ and 4.8 Hz, 1 H), 3.52 (ddd, $J = 12.1$, 8.4, and 5.1 Hz, 1 H), 3.68 (m, 2 H), 3.96 and 4.22 (2 d, $J = 16.8$ Hz, 1 H each), 7.27−7.36 (m, 5 H), 7.34 (tt, $J = 7.5$ and 1.2 Hz, 2 H); ^{13}C NMR δ 27.9, 29.4, 41.1, 47.8, 49.8, 53.8, 82.4, 126.9, 127.1, 128.7, 141.6, 167.1, 167.8, 170.2; EIMS *m*/*z* 289 (1), 233 (33), 188 (29), 91 (20), 57 (100). **10c**: IR (NaCl) 1740, 1650 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 1.96−2.14 (m, 2 H), 2.52 (dd, $J = 17.4$ and 11.4 Hz, 1 H), 2.75 (ddd, $J = 17.5$, 5.1, and 2.0 Hz, 1 H), 3.14 (m, 1 H), 3.36 (ddd, $J = 11.7$, 5.1, and 3.3 Hz, 1 H), 3.53 (td, $J = 11.1$ and 5.1 Hz, 1 H), 3.94 and 4.17 (2 d, $J = 17.1$ Hz, 1 H each), 7.19−7.35 (m, 5 H); ^{13}C NMR δ 27.9, 30.1, 38.6, 39.1, 48.1, 48.8, 81.7, 126.3, 126.6, 128.5, 143.2, 167.9, 169.5; EIMS *m*/*z* 289 (M^+, 2), 233 (82), 188 (59), 91 (22), 57 (100).

1-[(*tert*-Butoxycarbonyl)methyl]-4-cyanopiperidin-2-one (10d). Operating as above for the preparation of **9a**, a mixture of esters *trans*/*cis*-**8d** (300 mg, 0.8 mmol) in AcOEt (14 mL) containing 10% Pd-C (120 mg) was hydrogenated at room temperature for 1 night to yield cyanopiperidine **10d** (117 mg, 61%) after purification by chromatography (hexane/AcOEt, 4/1). Starting ester **8d** (60 mg) was also recovered. **10d**: IR (NaCl) 2241, 1738, 1652 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 2.09−2.28 (m, 2 H), 2.70 (dd, $J = 17.5$ and 7.8 Hz, 1 H), 2.76 (dd, $J = 17.4$ and 6 Hz, 1 H), 3.14 (tdd, $J = 8.2$, 6.0, and 3.6 Hz, 1 H), 3.41−3.57 (m, 2 H), 3.84 and 4.18 (2 d, $J = 17.2$ Hz, 1 H

each); ^{13}C NMR δ 24.3, 25.9, 27.9, 34.1, 46.2, 48.9, 82.1, 119.7, 165.7, 167.4; EIMS *m/z* 182 (11), 165 (1), 137 (34), 109 (21), 57 (100).

***trans*-3-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butoxycarbonyl)methyl]-4-(3-indolyl)piperidin-2-one (*trans*-11a).** To a solution of *trans*/*cis*-**9a** (1 g, 2.7 mmol) in dry benzene (15 mL) at room temperature was added Et_3N (0.94 mL, 6.7 mmol) and DPPA (1.48 mL, 6.7 mmol), and the mixture was stirred for 3.5 h at 50 °C. After the mixture was cooled to room temperature, dry BnOH (0.7 mL, 6.7 mmol) and dibutyltin dilaurate (0.16 mL, 0.26 mmol) were added and stirring at 80 °C was continued for 4 h. The reaction was then cooled to room temperature and diluted with Et_2O (70 mL). The resulting solution was washed with water and brine, and the organic layer was dried and concentrated. The crude residue was washed several times with Et_2O to yield *trans*-**11a** (678 mg, 53%) as the unique diastereomer: IR (NaCl) 3401, 1735, 1725, 1648 cm^{-1}; ^{1}H NMR δ 1.49 (s, 9 H), 2.22 (m, 2 H), 3.33 (dt, J = 14.3 and 4.8 Hz, 1 H), 3.58 (m, 2 H), 4.07 (s, 2 H), 4.37 (dd, J = 11.1 and 9.0 Hz, 1 H), 4.86 and 4.95 (2 d, J = 12 4 Hz, 1 H each), 5.28 (d, J = 8.4 Hz, 1 H), 7.00 (s, 1 H), 7.05 (t, J = 7.8 Hz, 1 H), 7.11 (m, 2 H), 7.16 (t, J = 6.9 Hz, 1 H), 7.23 (m, 3 H), 7.34 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 8.55 (br s, 1 H); ^{13}C NMR δ 28.1, 29.9, 36.1, 48.0, 49.6, 57.2, 66.6, 82.1, 111.4, 116.3, 118.4, 119.3, 121.1, 121.8, 126.6, 127.7, 128.2, 136.1 136.3, 156.6, 168.1, 169.5; CIMS *m/z* 478 (M^+ + 1, 30), 495 (M^+ + 18, 3). Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.8. Found: C, 67.68; H, 6.57; N, 9.1.

***trans*/*cis*-3-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butoxycarbonyl)methyl]-4-ethylpiperidin-2-one (*trans*/*cis*-11b).** Operating as above for the preparation of **11a**, from acids *trans*/*cis*-**9b** (450 mg, 1.6 mmol) in dry benzene (14 mL), Et_3N (0.5 mL, 3.9 mmol), DPPA (0.88 mL, 3.9 mmol), dry BnOH (0.41 mL, 3.9 mmol), and dibutyltin dilaurate (0.10 mL, 0.16 mmol) compounds *trans*- and *cis*-**11b** (321 mg and 82 mg respectively, 65%) were obtained after purification by chromatography (hexane/AcOEt, 4/1). *trans*-**11b**: IR (NaCl) 3304, 1728, 1662, 1650 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.93 (t, 3 H, J = 7.3 Hz), 1.26 (qnd, 1 H, J = 6.5 and 1.5 Hz), 1.43 (s, 9 H), 1.61−1.76 (m, 3 H), 2.05 (m, 1 H), 3.31 (ddd, J = 11.7, 5.5, and 3.5 Hz, 1 H), 3.37 (m, 1 H), 3.96 (t, J = 10.0 Hz, 1 H), 3.79 and 4.11, and 3.83 and 4.09 (4 d, J = 17.0 Hz, 1 H each two d),[41] 5.1 (s, 2 H), 5.15 and 5.52 (d, J = 8.2 Hz; 1 H), 7.23−7.33 (m, 5 H); ^{13}C NMR[41] δ 10.2 and 10.3, 24.9, 25.9 and 26.0, 27.8, 39.3 and 39.8, 47.3, 49.2, 56.1 and 56.3, 66.5, 81.6 and 81.7, 127.6 and 128.1, 136.2, 156.8 and 156.9, 167.6 and 167.7, 168.8 and 169.6; EIMS *m/z* 390 (M^+, 1), 334 (8), 289 (8), 199 (21), 91 (100), 57 (50). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 67.91; H, 6.54; N, 8.8. Found: C, 67.68; H, 6.57; N, 9.1. *cis*-**11b**: IR (NaCl) 3397, 1728, 1662, 1650 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (t, J = 7.5 Hz, 3 H), 1.25 (m, 1 H), 1.43 (s, 9 H), 1.56 (m, 1 H), 1.93 (m, 1 H), 2.03 (m, 1 H), 2.41 (m, 1 H), 3.24 (ddd, J = 12.0, 6.5, and 3.5 Hz, 1 H), 3.41 (td, J = 11.1 and 6.0 Hz, 1 H), 3.59 and 4.22 (2d, J = 17.2 Hz, 1 H each), 4.30 (t, J = 5.0 Hz, 1 H), 5.06 and 5.09 (2 d, J = 12.2 Hz, 1 H each), 5.80 (d, J = 4.0 Hz, 1 H), 7.27−7.34 (m, 5 H); ^{13}C NMR δ 11.5, 18.6, 23.5, 28.1, 36.3, 45.3, 49.6, 55.8, 66.6, 82.0, 127.8, 127.9, 128.4, 136.4, 156.0, 167.6, 169.1; EIMS *m/z* 390 (M^+, 3), 334 (24), 317 (9), 289 (18), 243 (11), 227 (8), 199 (36), 91 (100), 57 (60); HRMS calcd for $C_{21}H_{30}N_2O_5$ 390.2155, found 390.2138.

***trans*-3-[(Benzyloxycarbonyl)amino]-1-[(*tert*-butoxycarbonyl)methyl]-4-phenylpiperidin-2-one (*trans*-11c).** Operating as above for the preparation of *trans*-**11a**, from acids *trans*/*cis*-**9c** (570 mg, 1.71 mmol) in dry benzene (18 mL), Et_3N (0.59 mL, 4.27 mmol), DPPA (0.95 mL, 4.27 mmol), and then dry BnOH (0.44 mL, 4.27 mmol) and dibutyltin dilaurate (0.10 mL, 0.16 mmol) piperidone *trans*-**11c** (560 mg, 68%) was obtained as the unique product after purification by chromatography (hexane/AcOEt, 4/1): IR (NaCl) 3318, 1733, 1652 cm^{-1}; ^{1}H NMR δ 1.48 (s, 9 H), 2.14 (m, 1 H), 2.25 (qd, J = 11.7 and 5.7 Hz, 1 H), 3.27 (br t, J = 11.7 Hz, 1 H), 3.39 (m, 1 H), 3.58 (m, 1 H), 4.04 (s, 2 H), 4.29 (t, J = 10.3 Hz, 1 H), 4.99 (s, 2 H), 5.17 (d, J = 8.4 Hz, 1 H), 7.18−7.30 (m, 10 H); ^{13}C NMR δ 28.0, 30.0, 44.5, 47.9, 49.4, 57.2, 66.5, 82.0, 127.0, 127.2, 127.6, 127.7, 128.2, 128.5, 136.4, 141.2, 156.3, 167.9, 169.3; EIMS *m/z* 382 (2), 337 (2), 247 (7), 91 (100), 57 (74). Anal. Calcd for $C_{25}H_{30}N_2O_5 \cdot {}^1/_5H_2O$: C, 67.92; H, 6.93; N, 6.34. Found: C, 67.44; H, 6.87; N, 6.65.

***trans*-3-Amino-1-[(*tert*-butoxycarbonyl)methyl]-4-(3-indolyl)piperidin-2-one (*trans*-12a).** A solution of carbamate *trans*-**11a** (2.2 g, 1.13 mmol) in MeOH (100 mL) containing 10% Pd-C (0.8 g) was hydrogenated at room temperature overnight. The resulting mixture was then filtered through a Celite pad and the solvent was evaporated. The crude product was dissolved in CH_2Cl_2, washed with an aqueous saturated solution of $NaHCO_3$, and extracted several times with CH_2Cl_2. The organic layer was dried and concentrated to yield 3-aminopiperidone *trans*-**12a** (1.4 g). An analytical sample was obtained by crystallization from dry Et_2O: IR (NaCl) 3303, 1739, 1650 cm^{-1}; ^{1}H NMR δ 1.49 (s, 9 H), 2.17 (m, 3 H), 2.29 (qd, J = 13.8 and 5.7 Hz, 1 H), 3.24 (td, J = 11.4 and 2.8 Hz, 1 H), 3.37 (ddd, J = 11.8, 5.7, and 2.5 Hz, 1 H), 3.57 (td, J = 11.4 and 4.5 Hz, 1 H), 3.76 (d, J = 10.8 Hz, 1 H), 3.97 and 4.15 (2 d, J = 17.1 Hz, 1 H each), 6.99 (s, 1 H), 7.08 (t, J = 7.3 Hz, 1 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.37 (d, J = 8.1 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 8.98 (br s, 1 H); ^{13}C NMR δ 27.9, 28.7, 38.6, 48.4, 49.3, 56.8, 81.9, 111.6, 115.9, 118.6, 118.9, 121.5, 121.7, 125.9, 136.4, 167.9, 171.9; CIMS *m/z* 343 (M^+, 5), 344 (M^+ + 1, 16), 372 (M^+ + 29, 2); HRMS calcd for $C_{19}H_{25}N_3O_3$ 343.1896, found 343.1898.

***trans*-3-Amino-1-[(*tert*-butoxycarbonyl)methyl]-4-ethylpiperidin-2-one (*trans*-12b).** Operating as above for the preparation of *trans*-**12a**, a solution of carbamate *trans*-**11b** (216 mg, 0.55 mmol) in AcOEt (25 mL) containing 10% Pd-C (86 mg) was hydrogenated at room temperature for 4 h. The resulting crude product was purified by washing with hexane and dry Et_2O to yield 3-aminopiperidone *trans*-**12b** (90 mg, 63%): IR (NaCl) 3301, 1740, 1649 cm^{-1}; ^{1}H NMR δ 0.95 (t, 3 H, J = 7.2 Hz), 1.25 (m, 1 H), 1.46 (s, 9 H), 1.61 (m, 2 H), 1.86 (m, 1 H), 1.99 (m, 1 H), 2.10 (br s, 2 H, NH_2), 3.07 (d, J = 9.9 Hz, 1 H), 3.30 (ddd, J = 11.5, 5.4 ,and 3.0 Hz, 1 H), 3.38 (td, J = 11.1 and 4.8 Hz, 1 H), 3.98 (s, 2 H); ^{13}C NMR δ 10.4, 25.4, 25.7, 28.0, 41.4, 47.9, 49.4, 56.3, 81.8, 167.9, 172.8; EIMS *m/z* 256 (M^+, 1), 239 (8), 211 (1), 183 (7), 155 (5), 127 (9), 111 (16), 97 (34), 57 (100).

***trans*-3-Amino-1-[(*tert*-butoxycarbonyl)methyl]-4-phenylpiperidin-2-one (*trans*-12c).** Operating as above for the preparation of *trans*-**12a**, a solution of carbamate *trans*-**12c** (438 mg, 0.99 mmol) in AcOEt (40 mL) containing 10% Pd-C (175 mg) was hydrogenated at room temperature overnight to yield *trans*-**12c** (227 mg). The resulting product was used directly in the next step without further purification. An analytical sample was obtained when the crude product was treated with 1 N HCl and extracted with CH_2Cl_2. Then the aqueous layer was quenched with solid $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated to furnish pure *trans*-**12c**: IR (NaCl) 3380, 3317, 1739, 1650 cm^{-1}; ^{1}H NMR δ 1.49 (s, 9 H), 1.84 (m, 2 H), 2.06 (m, 1 H), 2.23 (qd, J = 13.4 and 4.8 Hz, 1 H), 2.93 (br t, J = 10.5 Hz, 1 H), 3.39 (ddd, J = 11.8, 5.7, and 1.8 Hz, 1 H), 3.59 (td, J = 11.7 and 4.8 Hz, 1 H), 3.59 (d, J = 11.7 Hz, 1 H), 3.97 and 4.11 (2 d, J = 17.1 Hz, 1 H each), 7.25−7.38 (m, 5 H); ^{13}C NMR δ 28.1, 29.2, 47.0, 48.4, 49.3, 57.1, 81.9, 127.0, 128.8, 142.2, 167.9, 171.8; EIMS *m/z* 304 (M^+, 6), 287 (5), 231 (20), 203 (8), 91 (24), 77 (8), 57 (100). Anal. Calcd for $C_{17}H_{24}N_2O_3 \cdot {}^1/_{10}H_2O$: C, 66.69; H, 7.97; N, 9.15. Found: C, 66.34; H, 7.92; N, 9.00.

***trans*-1-[(*tert*-Butoxycarbonyl)methyl]-3-{[(9-fluorenyl)-methoxycarbonyl]amino}-4-(3-indolyl)piperidin-2-one**

(41) Splitting of this signal and of the majority of signals in the ^{13}C NMR spectra indicated the presence of rotamers. This fact was not observed for the cis isomer.

(*trans*-13a). To a mixture of 3-aminopiperidone *trans*-**12a** (300 mg, 0.87 mmol) and $NaHCO_3$ (109 mg, 1.3 mmol) in acetone (12 mL) was added Fmoc-OSu (438 mg, 1.3 mmol). The resulting mixture was stirred overnight at room temperature. Then the solvent was evaporated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with aqueous 0.1 N HCl solution and water, dried, and concentrated to yield piperidone *trans*-**13a** (312 mg, 63%) after purification by chromatography (hexane/AcOEt, 7/3): IR (NaCl) 3415, 1747, 1725, 1618 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (s, 9 H), 2.18 (m, 1 H), 2.26 (m, 1 H), 3.40 (m, 1 H), 3.63 (m, 2 H), 3.97 and 4.57 (2 d, J = 17.0 Hz, 1 H each), 4.03−4.15 (m, 3 H), 4.41 (t, J = 9.5 Hz, 1 H), 5.23 (d, J = 7.5 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.04 (s, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 7.0 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.52 (d, J = 7.0 Hz, 1 H), 7.63 (d, J = 7.5 Hz, 2 H), 8.15 (br s, 1 H); ^{13}C NMR δ 27.9, 29.7, 35.9, 46.8, 47.9, 49.5, 57.2, 66.8, 81.9, 111.5, 116.0, 118.3, 119.1, 119.6, 121.1, 121.7, 125.1, 126.5, 126.8, 127.3, 136.1, 140.9, 143.7, 143.8, 156.6, 168.1, 169.5; EIMS *m*/*z* 179 (100). Anal. Calcd for $C_{34}H_{35}N_3O_5 \cdot {}^1/_5H_2O$: C, 71.74; H, 6.27; N, 7.38. Found: C, 71.44; H, 6.50; N, 7.66.

***trans*-1-[(*tert*-Butoxycarbonyl)methyl]-4-ethyl-3-{[(9-fluorenyl)methoxycarbonyl]amino}-piperidin-2-one (*trans*-13b).** Operating as above for the preparation of *trans*-**13a**, from aminopiperidone *trans*-**12b** (90 mg, 0.35 mmol) and $NaHCO_3$ (44 mg, 0.52 mmol) in acetone:H_2O (5 mL, 4:1), and then Fmoc-OSu (175 mg, 0.52 mmol), piperidone *trans*-**13b** (103 mg, 61%) was obtained after purification by chromatography (hexane/AcOEt, 4/1): IR (NaCl) 3316, 1727, 1654 cm^{-1}; ^1H NMR δ 0.91 (m, 3 H), 1.25 (m, 1 H), 1.46 (s, 9 H), 1.67−1.87 (m, 3 H), 2.06 (m, 1 H), 3.37 (m, 2 H), 3.98 (t, J = 9.9 Hz, 1 H), 3.85 and 4.13 (2 d, J = 17.1 Hz, 1 H each), 4.24 (t, J = 7.2 Hz, 1 H), 4.38 (dd, J = 7.5 and 2.4 Hz, 2 H), 5.24 and 5.32 (2 d, J = 9.3 and 8.4 Hz, 1 H), 7.30 (td, J = 7.3 and 1.0 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 2 H), 7.62 (t, J = 6.7 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H); ^{13}C NMR δ 10.5, 25.0, 26.1, 27.9, 40.1, 47.0, 47.4, 49.4, 56.4, 66.8, 81.8, 119.6, 125.0, 126.8, 127.4, 127.7, 128.2, 141.0, 143.6, 143.9, 157.0, 167.8, 169.7; EIMS *m*/*z* 256 (5), 239 (9), 200 (4), 178 (100), 152 (22), 127 (42), 98 (61), 84 (47), 57 (83); HRMS calcd for $C_{28}H_{34}N_2O_5$ 478.2468, found 478.2482.

***trans*-1-[(*tert*-Butoxycarbonyl)methyl]-3-{[(9-fluorenyl)-methoxycarbonyl]amino}-4-phenylpiperidin-2-one (*trans*-13c).** Operating as above for the preparation of *trans*-**13a**, from aminopiperidone *trans*-**12c** (227 mg, 0.74 mmol) and $NaHCO_3$ (93 mg, 1.11 mmol) in acetone:H_2O (5 mL, 4:1), and then Fmoc-OSu (374 mg, 1.11 mmol), *trans*-**13c** (157 mg, 30% from *trans*-**11c**) was obtained after purification by chromatography (hexane/AcOEt, 4/1): IR (NaCl) 3321, 1734, 1655 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 2.16 (m, 1 H), 2.27 (m, 1 H), 3.32 (m, 1 H), 3.39 (m, 1 H), 3.62 (m, 1 H), 4.06 (s, 2 H), 4.15 (d, J = 6.9 Hz, 1 H), 4.22−4.28 (m, 3 H), 5.25 (d, J = 6.9 Hz, 1 H), 7.22−7.29 (m, 7 H), 7.36 (t, J = 7.2 Hz, 2 H), 7.47 (t, J = 7.9 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 2 H); ^{13}C NMR δ 26.0, 29.8, 44.4, 46.9, 47.9, 49.4, 57.3, 66.8, 82.0, 119.7, 125.1, 126.8, 127.0, 127.2, 127.4, 128.5, 141.0, 141.3, 143.8, 156.2, 167.9, 169.3; EIMS *m*/*z* 196 (6), 178 (100), 57 (33).

***trans*-3-{[(9-Fluorenyl)methoxycarbonyl]amino}-4-(3-indolyl)-2-oxopiperidine-1-acetic Acid (*trans*-14a).** A solution of piperidone *trans*-**13a** (266 mg, 0.47 mmol) in ^{i}PrOH:H_2O:AcOH (1:1:2, 15 mL) was stirred for 72 h at 100 °C. The solvent was then evaporated and carboxylic acid *trans*-**14a** (219 mg, 91%) was obtained. An analytical sample was purified by chromatography (hexane): IR (KBr) 3400, 1712, 1640, 1246 cm^{-1}; ^1H NMR δ 2.13 (m, 2 H), 3.41 (m, 1 H), 3.61 (m, 2 H), 4.08−4.38 (m, 5 H), 4.42 (br t, J = 8.1 Hz, 1 H), 5.96 (d, J = 9.3 Hz, 1 H), 7.10 (br s, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.36 (m, 7 H), 7.60 (d, J = 7.2 Hz, 2 H), 7.70 (d, J = 7.2 Hz, 2 H), 8.25 (br s, 1 H); ^{13}C NMR δ 29.3, 35.7, 46.8, 48.2, 49.6, 56.8, 66.8, 111.4, 115.7, 118.2, 119.0, 119.6, 120.9, 121.1, 121.6, 125.0, 126.5, 126.8, 127.3, 135.9, 136.1, 140.8, 143.5, 143.6, 156.8, 170.4, 171.1; EIMS *m*/*z* 287 (4), 178 (100). Anal. Calcd for $C_{30}H_{27}N_3O_5 \cdot {}^1/_2H_2O$: C, 69.49; H, 5.44; N, 8.10. Found: C, 69.10; H, 5.71; N, 8.06.

***trans*-3-{[(9-Fluorenyl)methoxycarbonyl]amino}-4-ethyl-2-oxopiperidine-1-acetic Acid (*trans*-14b).** A solution of piperidone *trans*-**13b** (50 mg, 0.1 mmol) in TFA−CH_2Cl_2 (10%, 2 mL) was stirred at room temperature overnight. The solvent was then evaporated and the resulting residue was dissolved in CH_2Cl_2. The organic solution was washed with 5% $NaHCO_3$, acidified with 1 N HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to yield acid *trans*-**14b** (16 mg, 36%): IR (NaCl) 3319, 1723, 1650 cm^{-1}; ^1H NMR δ 0.94 (t, J = 6.9 Hz, 3 H), 1.25 (m, 1 H), 1.63−1.85 (m, 3 H), 2.08 (m, 1 H), 3.36 (m, 1 H), 3.57 (m, 1 H), 3.70 and 4.37 (2 d, J = 17.8 Hz, 1 H each), 4.05 (t, J = 10.2 Hz, 1 H), 4.24 (t, J = 7.0 Hz, 1 H), 4.36 (d, J = 7.8 Hz, 2 H), 6.12 (d, J = 9.6 Hz, 1 H), 7.29 (td, J = 7.2 and 0.9 Hz, 2 H), 7.39 (t, J = 6.9 Hz, 1 H), 7.62 (t, J = 6.9 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H); ^{13}C NMR δ 10.5, 25.0, 26.2, 39.8, 47.1, 48.8, 50.2, 56.4, 67.0, 119.8, 125.2, 126.9, 127.5, 141.1, 143.8, 143.9, 157.4, 171.3, 172.0; EIMS *m*/*z* 196 (17), 178 (100), 165 (56). Anal. Calcd for $C_{24}H_{26}N_2O_5 \cdot {}^1/_5TFA$: C, 65.82; H, 5.93; N, 6.29. Found: C, 65.35; H, 6.28; N, 6.12.

***trans*-3-{[(9-Fluorenyl)methoxycarbonyl]amino}-4-phenyl-2-oxopiperidine-1-acetic Acid (*trans*-14c).** Operating as above for the preparation of *trans*-**14b**, from piperidone *trans*-**13c** (50 mg, 0.09 mmol) and TFA−CH_2Cl_2 (10%, 2 mL) carboxylic acid *trans*-**14c** (45 mg, quantitative) was obtained: IR (NaCl) 3323, 1722, 1643 cm^{-1}; ^1H NMR δ 2.13 (m, 1 H), 2.24 (m, 1 H), 3.27 (m, 1 H), 3.66 (m, 1 H), 3.78 (m, 1 H), 3.92 and 4.24 (2 d, J = 17.1 Hz, 1 H each), 4.27−4.38 (m, 2 H), 4.98 (s, 2 H), 5.69 and 5.83 (2 d, J = 8.7 Hz, 1 H),[42] 7.17−7.31 (m, 12 H), 7.72 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 29.7, 44.3, 47.1, 48.2, 48.3, 56.9, 66.4, 119.6, 125.0, 127.0, 127.1, 127.4, 127.6, 128.2, 128.5, 136.3, 141.7, 143.7, 156.5, 170.1; EIMS *m*/*z* 248 (2), 196 (18), 178 (100), 165 (63), 57 (16).

***trans*-3-Acetamido-1-[(*tert*-butoxycarbonyl)methyl]-4-(3-indolyl)piperidin-2-one (*trans*-15).** To a solution of aminopiperidone *trans*-**12a** (200 mg, 0.58 mmol) in dry CH_2Cl_2 (0.4 mL), under inert atmosphere at room temperature, was added pyridine (62 μL, 0.87 mmol) and AcCl (93 μL, 1.16 mmol). The resulting mixture was stirred for 3 h and 0.1 N HCl was then added. The organic layer was washed with aqueous saturated $NaHCO_3$ solution and brine, dried, and concentrated to yield 3-acetamidopiperidone *trans*-**15** (190 mg, 85%): IR (KBr) 3448, 3289, 1741, 1640 cm^{-1}; ^1H NMR δ 1.49 (s, 9 H), 1.77 (s, 3 H), 2.16 (qd, J = 11.4 and 5.6 Hz, 1 H), 2.34 (dm, J = 10.5 Hz, 1 H), 3.37 (ddd, J = 11.7, 5.4, and 2.7 Hz, 1 H), 3.60 (td, J = 11.5 and 3.6 Hz, 1 H), 3.66 (td, J = 11.7 and 3.8 Hz, 1 H), 3.97 and 4.16 (2 d, J = 17.1 Hz, 1 H each), 4.71 (dd, J = 11.4 and 9.0 Hz, 1 H), 6.01 (d, J = 9.3 Hz, 1 H), 7.09 (t, J = 7.5 Hz, 1 H), 7.15 (s, 1 H), 7.18 (t, J = 6.9 Hz, 1 H), 7.37 (d, J = 8.1 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 8.62 (br s, 1 H); ^{13}C NMR δ 22.9, 28.1, 30.2, 36.0, 48.0, 49.6, 55.2, 82.1, 111.6, 116.2, 118.2, 119.2, 121.1, 121.8, 126.6, 136.2, 168.2, 169.6, 170.9; CIMS *m*/*z* 385 (M^+, 100), 386 ($M^+ + 1$, 25), 403 ($M^+ + 18$, 1). Anal. Calcd for $C_{21}H_{27}N_3O_4$: C, 65.44; H, 7.06; N, 10.90. Found: C, 65.11; H, 7.10; N, 10.85.

***trans*-3-Acetamido-4-(3-indolyl)-2-oxopiperidine-1-acetic Acid (*trans*-16).** A solution of acetamidopiperidone *trans*-**15** (429 mg, 1.11 mmol) in AcOH:^{i}PrOH:H_2O (2:1:1, 60 mL) was stirred for 24 h at 100 °C. The solvent was then evaporated and crude acid *trans*-**16** (358 mg, quantitative) was obtained. An analytical sample was purified by chromatography (CH_2Cl_2/MeOH, 94/6): IR (NaCl) 3359, 1648 cm^{-1}; ^1H NMR (MeOH) δ 1.74 (s, 3 H), 2.23 (m, 2 H), 3.38 (m, 1 H), 3.61 (m, 3 H, 6-H), 4.12 (s, 2 H), 4.59 (d, J = 11.4 Hz, 1 H), 6.99 (td, J = 7.2 and 1.0 Hz, 1 H), 7.07 (td, J = 7.5 and 1.2 Hz, 1 H), 7.11 (s, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.57 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (MeOH) δ 22.5, 30.6, 37.1, 49.0, 49.6, 56.9, 112.3, 117.0, 119.3, 119.7, 122.2, 122.3, 128.0, 137.9, 171.5, 172.5, 173.2; CIMS *m*/*z* 329 (M^+, 2), 330 ($M^+ + 1$, 100), 347 ($M^+ + 18$, 1).

(42) Rotamers were observed.

(2*S*)-2-{2-[(3*SR*, 4*SR*)-3-Acetamido-4-(3-indolyl)-2-oxo-1-piperidinyl]acetamido}-4-methylpentanamide (Tripeptides I and II or 17a and 17b). To a solution of carboxylic acid *trans*-**16** (108 mg, 0.34 mmol) in dry DMF (2 mL) at 0 °C was added DCC (85 mg, 0.41 mmol) and HOBt (63 mg, 0.41 mmol). The resulting mixture was stirred for 10 min at room temperature and HCl·L-Leu-NH_2 (62 mg, 0.37 mmol) and Et_3N (71 μL, 0.51 mmol) were added. Stirring was continued overnight at room temperature. The solvent was then evaporated and the residue was dissolved in toluene and washed several times with brine. The organic layer was dried and concentrated to afford a mixture of diastereomers I and II (**17a** and **17b**, 60 mg, 41%) after purification by chromatography (AcOEt/MeOH, 98/2). **Tripeptide I (17a):** IR (NaCl) 3286, 1632 cm^{-1}; ^1H NMR (600 MHz) δ 0.95 and 0.98 (2 d, J = 6.6 Hz, 3 H each), 1.58−1.68 (m, 3 H), 1.92 (s, 3 H), 2.20 (dq, J = 13.8 and 2.5 Hz, 1 H), 2.31 (qd, J = 13.3 and 4.4 Hz, 1 H), 3.42 (m, 1 H), 3.77 (ddd, J = 12.7, 10.5, and 3.4 Hz, 1 H), 3.82 (td, J = 12.0 and 3.6 Hz, 1 H), 3.87 (dd, J = 10.6 and 6.8 Hz, 1H), 4.51 (m, 1 H), 3.34 and 5.06 (2 d, 1 H each, J = 16.0 Hz), 5.47 (br s, 1 H), 6.32 (d, J = 6.8 Hz, 1 H), 7.06 (d, J = 2.2 Hz, 1 H), 7.11 (td, J = 7.0 and 0.9 Hz, 1 H), 7.21 (td, J = 8.1 and 0.9 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.52 (d, J = 7.9 Hz, 1 H), 8.15 (br s, 1 H), 8.38 (br s, 1 H). Some of the signals corresponding to a minor rotamer could be assigned: 0.90 and 0.92 (2 d, J = 6.1 Hz, 3 H each), 4.62 (m, 1 H), 5.33 (br s, 1 H), 6.78 (br s, 1 H). ^{13}C NMR δ 21.6, 22.2, 22.7, 23.0, 23.3, 24.5, 24.6, 32.9, 36.2, 40.1, 49.2, 52.1, 52.5, 52.7, 55.1, 111.6, 116.5, 118.6, 119.7, 121.0, 122.4, 126.2, 136.1, 168.5, 168.9, 170.9, 174.1, 175.1; EIMS *m*/*z* 319 (12), 276 (22), 194 (18), 156 (39), 98 (17), 55 (30). **Tripeptide II (17b):** IR (NaCl) 3294, 1641 cm^{-1}; ^1H NMR (600 MHz) δ 0.88 and 0.92 (2 d, J = 6.4 Hz, 3 H each), 1.20−1.85 (m, 3-H), 1.85 (s, 3 H), 2.23 (m, 1 H), 2.32 (m, 1 H), 3.42 (dm, J = 12.0 Hz, 1 H), 3.76 (dd, J = 10.2 and 6.7 Hz, 1 H), 3.85 (ddd, J = 13.3, 10.2, and 3.0 Hz, 1 H), 3.92 (td, J = 12.0 and 5.4 Hz), 4.51 (m, 1 H), 3.48 and 4.76 (2 d, J = 16.7 Hz, 1 H each), 5.54 (br s, 1 H), 6.89 (br s, 1 H), 7.05 (d, J = 2.2 Hz, 1 H), 7.11 (t, J = 7.1 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.39 (d, J = 8.2 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 1 H), 8.20 (br s, 1 H), 8.51 (br s, 1 H). Some of the signals corresponding to a minor rotamer could be assigned: 0.92 and 0.99 (2 d, J = 6.1 Hz, 3 H each), 5.77 (br s, 1 H), 6.89 (br s, 1 H), 7.27 (t, J = 6.6 Hz, 1 H), 7.27 (t, J = 6.6 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 1 H). ^{13}C NMR δ 21.1, 21.8, 22.6, 23.3, 24.3, 24.5, 24.9, 25.1, 32.8, 35.5, 39.1, 48.5, 50.3, 51.9, 52.3, 53.9, 110.8, 111.5, 116.7, 118.0, 118.4, 119.5, 120.8, 122.2, 124.3, 125.0, 126.3, 127.9, 136.2, 168.2, 171.0, 171.5, 174.8, 176.2; EIMS *m*/*z* 319 (7), 276 (15), 194 (17), 156 (36), 98 (53), 55 (100).

Molecular Modeling Studies: Conformational Search. All calculations were run on a SGI workstation (R4000, 128 MB RAM, 19 GB hard disk) under an Irix 5.3 operating system. Molecular mechanics calculations were carried out with Spartan v 5.0 and Insight II discover 3.0 v1997.

Optimized Monte Carlo Search and Energy Minimization. In this paper, we used the MMFF94 force field implemented in Spartan v 5.0. By default, atomic partial charges were calculated from data in the chosen molecular mechanics force field. The conformational search of diastereomers **17a** and **17b** was carried out with an optimized Monte Carlo method employing the MMFF94 force field as implemented in Spartan 5.0. Energy minimization used a conjugated gradient method, with a final gradient of 0.0001 kcal/Å mol as the convergence criteria. All conformers within a 10-kcal/mol window above the global minimum were used to determine the profiles. To determine the conformer families, atoms belonging to the lactam skeleton and peptide backbones were considered. We employed a similar protocol for the conformational search of compounds **17a** and **17b** starting from extended structures. Eight degrees of freedom were considered here (see Figure 5). Each run included 3000 steps. The structures obtained were clustered by conformation and energy. The resulting lowest energy conformations were the starting points for molecular dynamics studies.

Molecular Dynamics. The resulting lowest energy conformers of compounds $\mathbf{17a_1}$ and $\mathbf{17b_1}$ (resulting from the Monte Carlo search and Iterative simulated annealing) constituted the starting points for molecular dynamics studies with a distance dependent dielectric (4*r*) constant and an explicit solvent model in chloroform. NVT calculations at 300 K were performed by using cubic boxes of 48 Å side length and 433 chloroform molecules. Periodical bounded conditions were applied. After adequate heating and equilibration of the system for 50 ps, evolution times were 1 ns. One thousand structures were saved periodically from each profile distribution for further analyses. Profile distributions were analyzed for conformational preferences measuring the γ- and/or β-turn descriptors. For the β-turn, these are the distance R (R < 7 Å) between the Cα_i and the Cα_{i+1}, the dihedral angle τ ($-90 < \tau < 90$) formed by the four Cα atoms, and the distance between the carbonyl function of the first amino acid (i) and the amide group of the fourth (i+3). The major β-turns are classified according to the torsion angles of the second (ϕ_1, ψ_1: $\phi_1 = -60 \pm 30°$ and $\psi_1 = 120 \pm 30°$) and the third amino acids (ϕ_2, ψ_2: $\phi_1 = 80 \pm 30°$ and $\psi_1 = 0 \pm 45°$). For the γ-turn, they are the distance between the carbonyl function of the second amino acid (i+1) and the amide group of the fourth amino acid (i+3) and the torsion angles of the second amino acid (ϕ_2, ψ_2: ϕ_1 = 70°/85° and $\psi_1 = -60°/-70°$).

Iterative Simulated Annealing. The calculations were carried out within the molecular mechanics with use of the AMBER force field implemented in DISCOVER v 97. They were conducted under vacuum with a distant-dependent dielectric constant (4*r*) and a cutoff of 13 Å. Starting from extended structures of the diastereomers, the structure is minimized and subsequently heated to 900 K in a very short period of time. The structure is then cooled slowly to 100 K and minimized. In our case the heating was carried out in steps. At each step, the temperature was raised by 100 K in 0.1 ps, and then the system was allowed to stay 1 ps at the new temperature. The system was allowed to stand for 10 ps at 1000 K and then cooled in steps. At each step, the temperature was lowered by 100 K in 0.1 ps, and after cooling, the system was allowed to stay 10 ps at the new temperature. This structure is the starting conformation for another cycle, creating a library of conformations that are rank ordered by energy every 150 cycles. The procedure is repeated until no new conformations appear after a predetermined number of cycles (in our case 5 times) within a 5-kcal/mol energy range with respect to the lowest energy structure already found. Heating has to be carried out rapidly to make the molecule jump to a different region in the space. In contrast, cooling is slow to obtain the lowest energy minimum of the region. This protocol was run five times, employing fully extended starting structures of both diastereomers **17a** and **17b**.

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Supporting Information Available: Distribution profiles for Monte Carlo and molecular dynamics calculations of compounds **17a** and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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