Oxazolopiperidin-2-ones as Type II′ β-Turn Mimetics: Synthesis and Conformational Analysis

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We describe a straightforward synthesis of 9-substituted 3-aminooxazolidinopiperidin-2-ones **4**. Some derivatives were prepared for use in peptide synthesis as rigidified surrogates of the Ala-Pro dipeptide. Analysis of the amide derivatives **14** by NMR experiments and molecular mechanics/dynamics calculations shows that the major isomer **14a** has a stronger propensity than the minor isomer **14b** to adopt β-turn conformations, and the calculations indicate that in water **14a** adopts a stable βII′ turn conformation.

Introduction

A large number of bicyclic systems have been reported as β-turn mimetics, including the 6,5-bicyclic systems type **1**−**3** (Figure 1).[1] In particular, thiazolopiperidones **1**, first introduced as β-turn mimetics by Nagai and coworkers,[2] have been extensively used to study numerous bioactive peptides.[3−9] However, we have found that oxazolopiperidones **4** have not been studied as constrained pseudopeptides.

Despite the fact that **1a** induces a βII′ turn conformation in collaboration with the adjacent residues, this β-turn dipeptide seems not to be very useful for improving the activity of small peptides, where the β-turn position itself plays some role in interaction with the receptor site.[10] Interestingly, recent molecular modeling calculations on the tetrapeptide Ac-Ala-{**1a**}-Ala-NHMe indicate that the geometry of a turn induced by thiazolopiperidone **1a** differs significantly from that of an ideal β-turn.[11] In addition, the incorporation of each epimer **1a** or **1b** in a bioactive peptide has been shown to provoke distinct changes in its bioactivity.[8a]

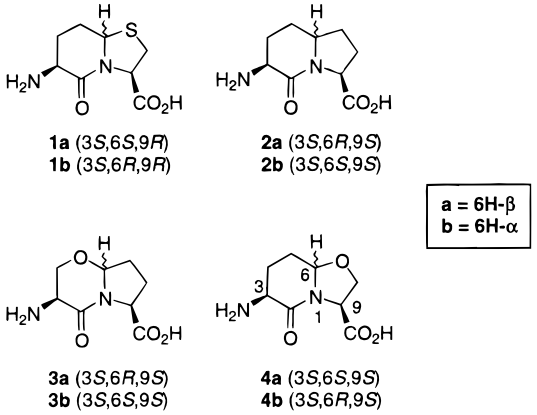

Figure 1.

We thought that the isosteric substitution of the sulfur in 7-position by an oxygen atom (Figure 1) might improve the binding properties of the β-turn dipeptide, since oxygen could act as a better hydrogen bond acceptor on the "external part" of the turn. With the aim of establishing the possible usefulness of oxazolopiperidones **4** as β-turn mimetics, we have prepared these bicyclic lactams

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(2) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647−650.

(3) For the use of **1a** in studies on gramicidin S, see: (a) Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1231−1234. (b) Bach, A. C., II.; Markwalder, J. A.; Ripka, W. C. *Int. J. Peptide Protein Res.* **1991**, *38*, 314−323. (c) Andreu, D.; Ruiz, S.; Carrero, C.; Alsina, J.; Albericio, F.; Jiménez, M. A.; de la Figuera, N.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Am. Chem. Soc.* **1997**, *119*, 10579−10586.

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(9) For studies on a zinc finger incorporating **1a** as an artificial β-turn, see: Viles, J. H.; Patel, S. U.; Mitchell, J. B. O.; Moody, C. M.; Justice, D. E.; Uppenbrink, J.; Doyle, P. M.; Harris, C. J.; Sadler, P. J.; Thornton, J. M. *J. Mol. Biol.* **1998**, *279*, 973−986. For more examples, see ref 10.

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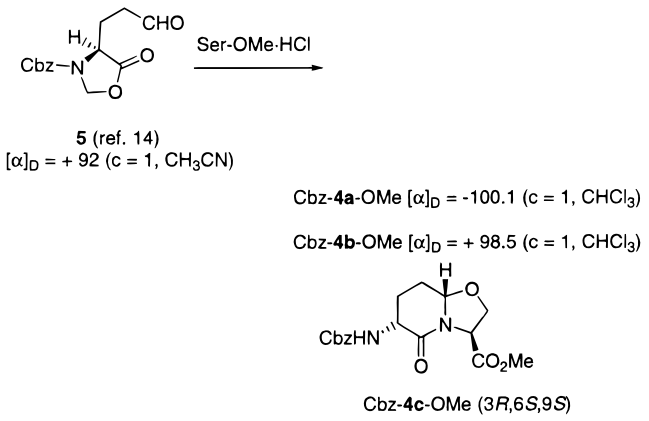

Figure 2.

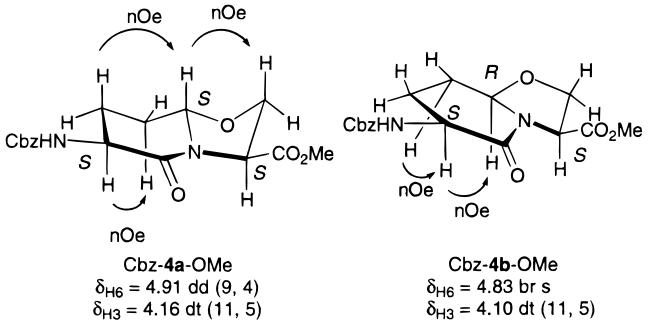

Figure 3. NOESY correlations and stereochemical assignment of oxazolopiperidones Cbz-**4a**-OMe and Cbz-**4b**-OMe.

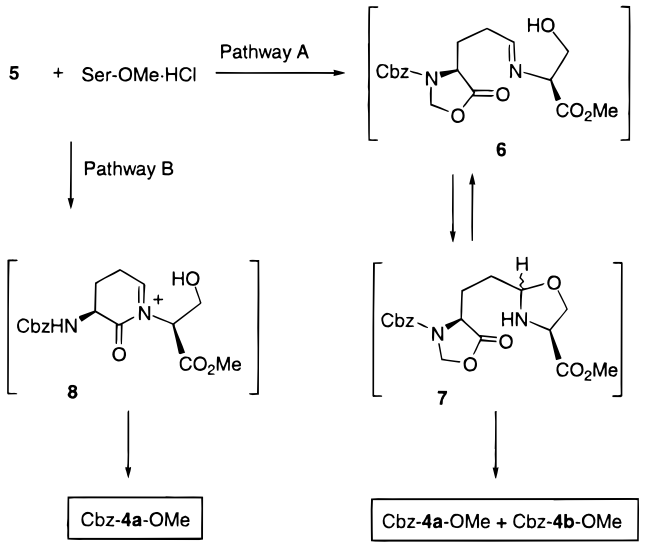

Figure 4.

and their derivatives **14** (Figure 6). The conformational analysis of **14**, both by NMR experiments and by molecular modeling calculations, indicates that oxazolopiperidone **14a** mimics a βII′ turn and that **14b** adopts a β-turn conformation that does not correspond to the classified types.[12]

(12) (a) Perczel, A.; McAllister, M. A.; Császár, P.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1993**, *115*, 4849−4858. (b) Richardson, J. *Adv. Prot. Chem.* **1981**, *34*, 167−339. (c) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Prot. Chem.* **1985**, *37*, 1−109. (d) Chou, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135−175. (e) Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425−1436.

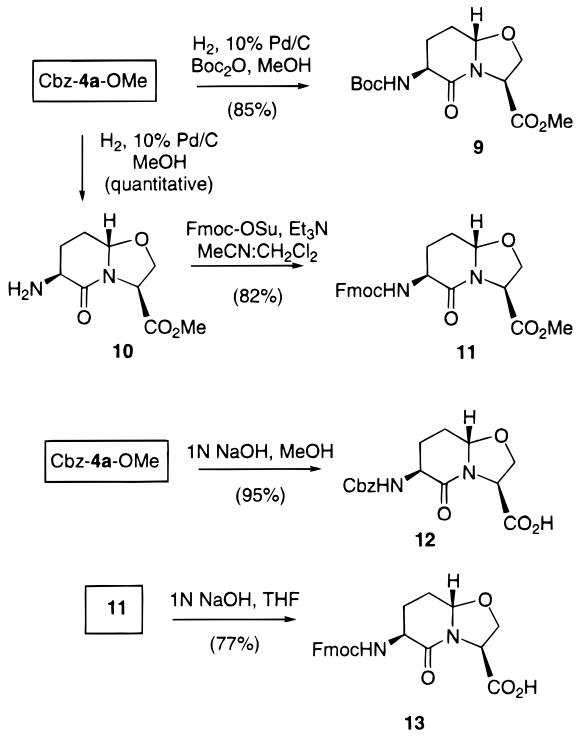

Figure 5.

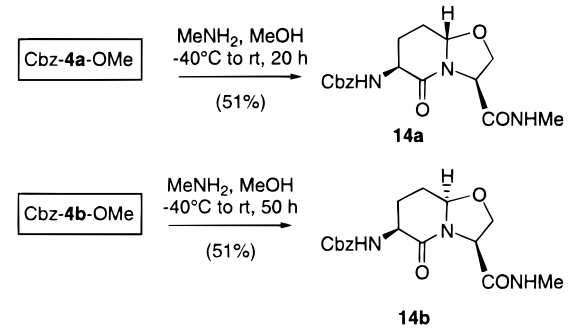

Figure 6.

Results and Discussion

Synthesis and Structural Assignment. Oxazolopiperidones Cbz-**4**-OMe were prepared by condensation of aldehyde **5** and Ser-OMe in a "one pot" process. Aldehyde **5** was obtained from Cbz-(*S*)-glutamic acid in three steps, following Fukuyama's procedure.[13,14] The condensation reaction of aldehyde **5** with Ser-OMe was assayed in a number of experimental conditions, summarized in Table 1. We observed that the yields and the number of stereoisomers varied according to the reaction conditions. When the reaction was carried out at room temperature in pyridine, followed by evaporation of the base and subsequent treatment with K_2CO_3 in MeOH (entry 7), the reaction yielded oxazolopiperidone Cbz-**4a**-OMe as the sole product. In the other conditions assayed we obtained mixtures of the three Cbz/OMe stereoisomers **4a**, **4b**, and **4c**.

Compounds Cbz-**4**-OMe were identified from their analytical data. Thus, the most characteristic signals of

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(14) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

Table 1. Condensation Conditions Assayed to Obtain Oxazolopiperidones Cbz-4-OMe

entry	ref	reagents	solvent	conditions	Cbz-**4**-OMe (**a**:**b**:**c**)	yield (%)
1	15	Et_3N, Na_2SO_4	Et_2O	0 °C − rt, 24 h		
2	8a	(1) $NaHCO_3$	EtOH, H_2O	rt, 16 h	10:5.5:1	8
		(2) DMF	DMF	42 °C, 24 h		
3	16	TFA	1,2-dichloroethane	reflux, 48 h	10:5.7:1	45
5		Et_3N	toluene	reflux, Dean−Stark, 48 h	10:5.7:1	58
6	17	pyridine	pyridine	reflux, 18 h	10:5:1	40
7	6	(1) pyridine	pyridine	rt, 6 d	1:0:0	54
		(2) K_2CO_3	MeOH	rt, 4 h		

the oxazolopiperidone backbone in the ^{1}H NMR spectra are as follows: an AMX system consisting of two double doublets (J = 9, 7 Hz) and a triplet (J = 9 Hz), that correspond to the C8- and C9-protons, and the signals of the protons H-3 and H-6, at δ ~4.1 and ~4.9. In the ^{13}C NMR spectra, the bicyclic system typically shows the methine signals at δ ~87 and δ ~51, corresponding to C6 and C3, respectively. In isomer Cbz-**4a**-OMe, H-6 resonated at δ 4.91 as a double doublet (J = 9 and 4 Hz), and H-3 appeared as a double triplet (J = 11 and 5 Hz) at δ 4.16. These multiplicities indicated that both H-3 and H-6 adopt a pseudoaxial disposition (Figure 3). In compound Cbz-**4b**-OMe, H-3 also appears as a double triplet (J = 11, 5 Hz, δ 4.10), and is therefore in an axial disposition; however, H-6 appeared here as a broad signal at δ 4.83, proving that Cbz-**4b**-OMe is the C6-epimer of Cbz-**4a**-OMe. In contrast, the third isomer Cbz-**4c**-OMe was identified as the C3-epimer of compound Cbz-**4a**-OMe: the H-3 proton resonated as a triplet (J = 5 Hz) at δ 4.02, whereas H-6 was a double doublet (J = 8, 6 Hz) at 4.90 ppm. The fact that Cbz-**4c**-OMe was detected when the condensation was performed at temperatures above 40 °C (Table 1) meant that once Cbz-**4a**-OMe was formed, it underwent a limited degree of epimerization on C3 in these conditions.[18]

The absolute configuration of oxazolopiperidones **4a** and **4b** was determined from the NOESY experiments (Figure 3). Thus, in oxazolopiperidone Cbz-**4a**-OMe, H-6 was correlated with H-4 and H-8, whereas H-3 was correlated with H-5. Since the *S* configuration of C3 was fixed, Cbz-**4a**-OMe could be identified as the (3*S*,6*S*,9*S*) isomer. In compound Cbz-**4b**-OMe, protons H-6, H-3, and H-5 were correlated, and this isomer was thus identified as (3*S*,6*R*,9*S*).

When we tried to rationalize the synthetic outcome of the condensation reaction, we observed that the only relevant difference in the experimental conditions used was the temperature (Table 1). When the reaction was carried out at 0 °C no reaction was observed, at room temperature only Cbz-**4a**-OMe was obtained, and when we heated to temperatures over 40 °C, the epimeric mixtures were formed. These results can be explained if we consider that there are two mechanisms that can lead to the formation of the oxazolopiperidone bicyclic system (Figure 4). Thus, if Ser-OMe reacts first with the aldehyde function of compound **5** to form imine **6**, the alcohol group can then attack either side of the intermediate imine, resulting in an epimeric mixture of oxazolidines **7** (pathway A). Subsequent lactamization would yield the epimeric mixture of oxazolopiperidones **4a** and **4b**. This mechanism explains why the **a**:**b** ratios obtained were always similar (about 10:6). However, it does not explain how a single isomer can be obtained at room temperature. Alternatively, if the closure of the oxazolidine ring took place on the acyliminium salt **8**,[20] the approach of the alcohol group on C6 could be stereocontrolled (pathway B).[21]

Treatment of pure Cbz-**4a**-OMe with TFA in dry 1,2-dichloroethane for 2.5 days at room temperature yielded a C6 epimeric mixture of isomers **a**:**b** of Cbz-**4**-OMe in a 9:1 proportion (NMR), which increased up to 2:1 when the mixture was refluxed for 3 days (Table 1, entry 3).[22] This indicates that in the acid medium, an equilibrium with the intermediate acyliminium salt **8** is established by protonation on the O7 oxigen atom, and that the ring closure is not fully stereoselective in the acid medium.

Several derivatives of oxazolopiperidone **4a** were prepared for further application in peptide synthesis (Figure 5). Selective hydrogenolysis of the *N*-Cbz protecting group in the presence of Boc_2O yielded the *N*-Boc/OMe derivative **9**. When the hydrogenolysis was done in the absence of Boc_2O, pseudodipeptide **10** was obtained quantitatively, and compound **10** was transformed to the *N*-Fmoc/OMe **11**. Selective cleavage of the ester was performed on Cbz-**4a**-OMe and on **11** to yield **12** (Cbz/OH) and **13** (Fmoc/OH). The stability of the bicyclic system in acid/base conditions that are common in peptide synthesis was also checked. Thus, compound **12** was recovered unaltered after treatment with a 20% solution of piperidine in CH_2Cl_2 at room temperature; and compound **13** was unaltered in a 30% solution of TFA in DMF. Most importantly, no epimerization was observed during these experiments.

Finally, we prepared the Cbz/NHMe compounds **14a** and **14b** that we needed for the conformational analysis by NMR experiments by treatment of Cbz-**4a**-OMe and Cbz-**4b**-OMe with $MeNH_2$ (Figure 6).

Conformational Studies. To determine whether the oxazolopiperidone system can promote a β-turn formation, we performed conformational studies by NMR and

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(16) Siddiqui, M. A.; Préville, P.; Tarazi, M.; Warder, S. E.; Eby, P.; Gorseth, E.; Puumala, K.; DiMaio, J. *Tetrahedron Lett*. **1997**, *38*, 8807−8810.

(17) Baldwin, J. E.; Lee, E. *Tetrahedron* **1986**, *42*, 6551−6554.

(18) Compound **4c** was always isolated together with **4a**. The C3 epimerization in the basic medium probably occurs through the formation of a 4*H*-oxazolo-5-one, rather than through a keto−enol tautomeric equilibrium.[19] This would explain why the epimerization is not observed in the reaction at room temperature, in which the protecting *N*-hydroxymethyl chain is lost only during the K_2CO_3 treatment.

(19) Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Chemical Approaches to the Synthesis of Peptides and Proteins*; CRC Press: Boca Raton, FL, 1997; pp 116−119.

(20) The acyliminium salt **8** could be formed either from imine **6** through an imine-enamine tautomeric equilibrium in the basic medium, or by reaction of **5** on the oxazolidone carbonyl group, via an amide intermediate.

(21) The stereocontrolled cyclization of chiral oxazolopiperidones is well documented. See, for instance: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569, and references therein. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev*. **1999**, *6*, 383−394. (c) See also ref 15.

(22) No epimerization was observed when treating pure Cbz-**4a**-OMe with TFA in CH_2Cl_2 at room temperature for 30 min.

Table 2. Standard Torsion Angles in the Major β-Turn Types[12]

turn	ϕ_2[a]	ψ_2[a]	ϕ_3[a]	ψ_3[a]
βI	−60	−30	−90	0
βI′	60	30	90	0
βII	−60	120	80	0
βII′	60	−120	−80	0
βIII	−60	−30	−60	−30
βIII′	60	30	60	30

[a] All angles are given in degrees.

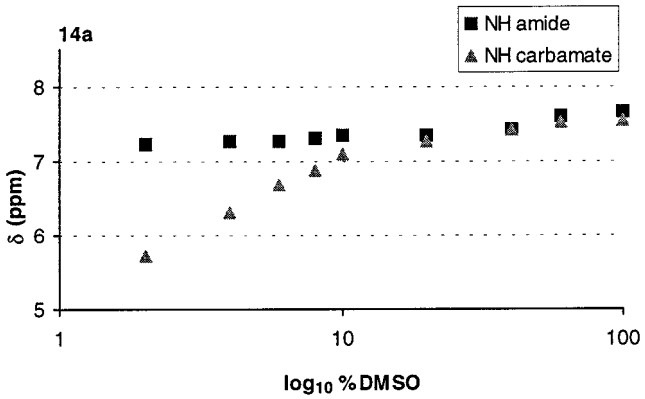

Figure 7. ^{1}H NMR chemical shift of the NH protons of pseudopeptide **14a** at different proportions of DMSO-d_6 in $CDCl_3$ (25 °C).

by molecular modeling. β-Turns are nonperiodic tetrapeptide segments which reverse the orientation of the peptide chain.[12] The most general β turn features are the distance R (R ≤ 7 Å) between the Cα atoms of the first and the fourth amino acids, and the dihedral angle τ(−90° ≤ τ ≤ +90°) formed by the four Cα atoms. Many conformers fulfill these requirements.[12a] The major types[12e] show a characteristic hydrogen bond between the carbonyl function of the first amino acid and the amide group of the fourth. The major β turns (Table 2, Figure 8a) are classified according to the torsion angles of the second amino acid (ϕ_2, ψ_2) and of the third (ϕ_3, ψ_3). We shall maintain this classification for the β turn mimetics of the oxazolopiperidone type **14a** and **14b**.

Compounds **14a** and **14b** were used as the models because they possess the minimum structural elements required to form a β turn. NMR experiments allowed us to search for the characteristic intramolecular hydrogen bond that would prove that oxazolopiperidones **14** form β turns. The molecular mechanics/dynamics (MM/MD) calculations were performed to provide further insight into the static and dynamic conformational properties of the two derivatives.

NMR Studies. 1. Chemical Shift and Addition of a Competitive Solvent. In solvents such as $CDCl_3$, NH amide protons that are involved in hydrogen bonding resonate around δ 7−8. In the ^{1}H NMR spectrum of compound **14a** in $CDCl_3$, the carbamate NH (NH_i) resonates at δ 5.72, and the amide NH (NH_{i+3}) at δ 7.23. This suggests that in $CDCl_3$ the NH_i proton is free, while the NH_{i+3} proton is involved in a hydrogen bond. However, in DMSO both the NH_i and the NH_{i+3} protons undergo a downfield shift ($\Delta\delta$ = +1.99 ppm and $\Delta\delta$ = +0.45, respectively), which proves that in DMSO both are accessible to the solvent, i.e., that NH_{i+3} is no longer hydrogen-bonded in the presence of a competitive solvent.

To prove that NH_{i+3} establishes an *intramolecular* hydrogen bond rather than an intermolecular one, and to evaluate the strength of this hydrogen bond, we carried out a second experiment which consisted of running the ^{1}H NMR spectrum in a gradient of DMSO in $CDCl_3$.[23] Thus, at low concentrations of DMSO, protons that are non-hydrogen-bonded or intermolecularly hydrogen-bonded will immediately establish a bond with the DMSO, and will therefore quickly shift downfield. However, intramolecularly bonded protons are less accessible to DMSO, and will not shift until the intramolecular hydrogen bond is broken. Figure 7 summarizes the spectral evidence that NH_i shifted immediately, but that the NH_{i+3} proton needed a 20% solution of DMSO in $CDCl_3$ to start shifting. This result demonstrated that in compound **14a** the NH_{i+3} is intramolecularly hydrogen-bonded, and that this hydrogen bond is stable until the concentration of the competitive solvent reaches 20%.

NMR Studies. 2. Temperature Coefficient. The temperature dependence of the ^{1}H NMR chemical shift of peptide NH protons also reflects their hydrogen-bonding state. In this regard, several interpretations of the temperature coefficient ($\Delta\delta/\Delta T$) values have been suggested.[24] The most meaningful results are usually obtained in DMSO: coefficients above −4 ppb/K (in absolute value) indicate an external orientation of the NH amide proton, whereas coefficients below −3 ppb/K (in absolute value) indicate shielding from the solvent. However, in our case the intramolecular hydrogen bond that NH_{i+3} establishes was cleaved in DMSO, and a high-temperature coefficient value would be expected in DMSO. In accordance with this expectation, we observed $\Delta\delta/\Delta T$ (NH_{i+3}) = −5.4 ppb/K.

Scolastico and co-workers have recently described the hydrogen-bonding states of amide protons in $CDCl_3$, taking into account all their ^{1}H NMR parameters.[24a] They distinguish three different states: (a) *strongly bonded amide protons*: low-temperature coefficient, high chemical shift value (δ = 7.0), and small $\Delta\delta$ upon addition of competitive solvent ($\Delta\delta$ ≤ 0.2 ppm); (b) *non-hydrogen-bonded amide protons*: low-temperature coefficient ($\Delta\delta/\Delta T$ = −2.6 ppb/K), low chemical shift (δ = 7), and high $\Delta\delta$ upon addition of competitive solvent ($\Delta\delta$ ≥ 0.2 ppm); and (c) *amide protons in equilibrium between hydrogen-bonded and non-hydrogen-bonded states*: large temperature coefficient ($\Delta\delta/\Delta T$ > −2.6 ppb/K).

According to this classification, our results indicate that the amide NH proton is weakly hydrogen bonded, in equilibrium with a non-hydrogen-bonded state ($\Delta\delta/\Delta T$(NH_{i+3}) = −3.4 ppb/K), whereas the carbamate proton is non-hydrogen-bonded ($\Delta\delta/\Delta T$ (NH_i) = −4.6 ppb/K).

Similar results were obtained for isomer **14b** by NMR experiments. The chemical shifts in $CDCl_3$ and addition of competitive solvent experiments showed that the NH_i carbamate proton is non-hydrogen-bonded and that the NH_{i+3} amide proton is intramolecularly hydrogen-bonded, although weakly, i.e., the hydrogen bond breaks at a 20% concentration of DMSO in $CDCl_3$, and the temperature coefficient in $CDCl_3$ is $\Delta\delta/\Delta T$ (NH_{i+3}) = −3.3 ppb/K ($CDCl_3$) (see Supporting Information).

Molecular Modeling Calculations. According to the simulated annealing calculations (see the Experimental

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(24) (a) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 389−400 and references therein. (b) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−523 and references therein.

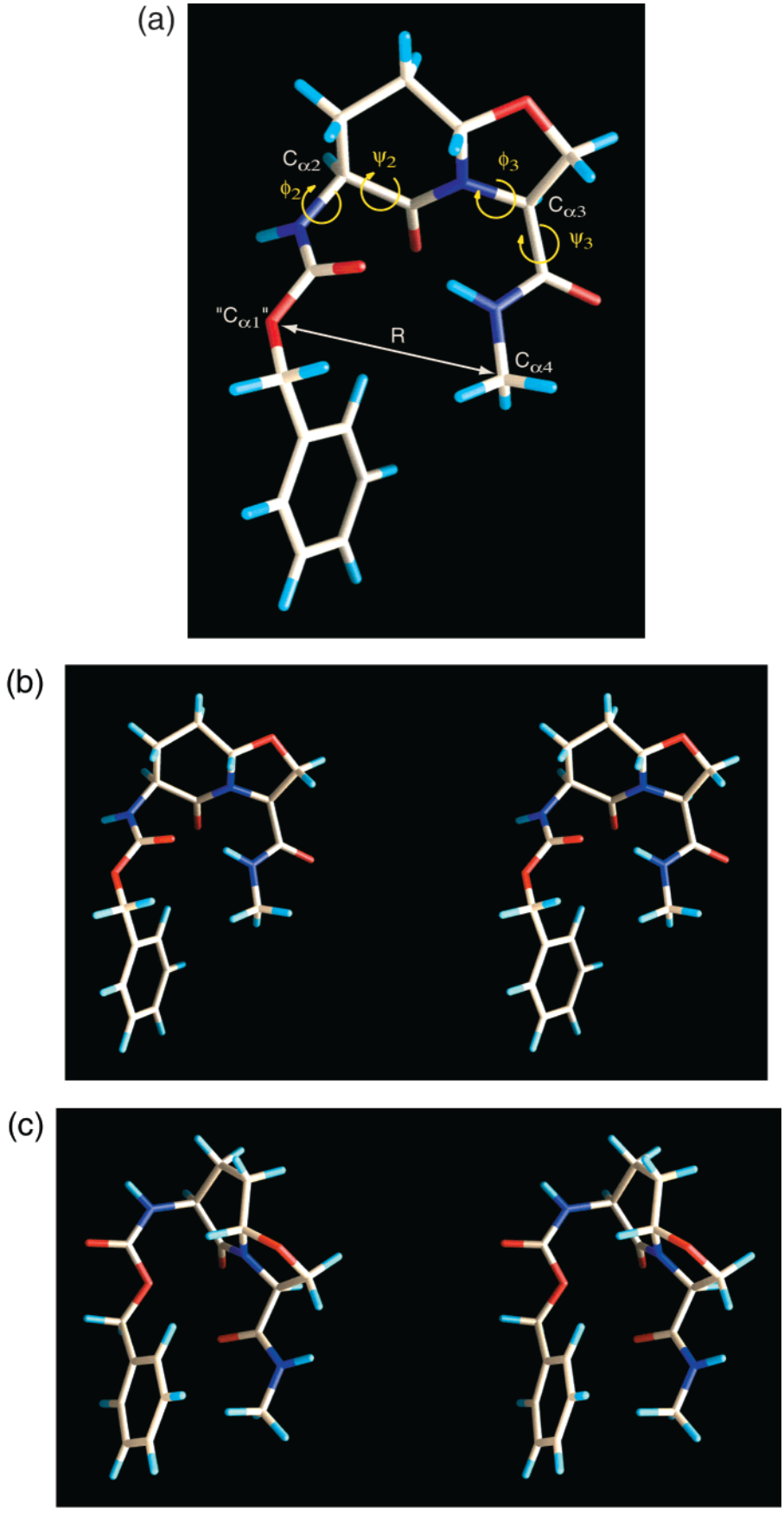

Figure 8. (a) Minimum energy conformation of compound **14a** resulting from simulated annealing calculations (Table 3), in continuum. Used β turn descriptors are also indicated. (b) Stereoview of (a). (c) Snapshot of compound **14a** after 500 ps simulation time in DMSO.

Table 3. Population of Secondary Structures of Compounds 14, As Obtained by Simulated Annealing

compd	ϕ_2	ψ_2	ϕ_3	ψ_3	E[a]	conformer
14a	52.1	−123.4	−68.4	−6.0	−61.9	βII′
	−169.0	−141.7	−64.3	114.9	−56.5	L-shaped
14b	58.8	−130.2	−63.1	−8.7	−60.8	βII′
	−167.3	−166.3	−38.5	115.9	−56.6	L-shaped

[a] Energies in kcal/mol.

Table 4. β-Turn Propensities of Compounds 14 As Derived from MD Calculations in Different Media

compd	medium	β_T[a,b]	βI[a]	βI′[a]	βII[a]	βII′[a]	βIII[a]	βIII′[a]
	continuum	98.1	0.1	0.0	0.0	93.3	0.0	0.0
14a	DMSO	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	H_2O	99.1	0.1	0.0	0.0	83.8	0.1	0.0
	continuum	67.7	0.0	0.0	0.0	42.9	0.0	0.0
14b	DMSO	89.5	0.0	0.0	0.0	0.0	0.0	0.0
	H_2O	18.7	0.0	0.0	0.0	3.0	0.0	0.0

[a] In percent. [b] Based on the general β-turn criteria *R* and τ.

Section), epimers **14a** and **14b** present two distinct conformers (Table 3). In both cases, the most stable conformer corresponds to a type II′ β-turn (Figure 8), and the second conformer adopts an L-shaped structure[25] due to the more extended conformation of the $i + 1$ residue in the pseudodipeptide moiety. The βII′ turns are about 4−5 kcal/mol more stable than the corresponding L-shaped conformations, and the βII′ turn of compound **14a** is about 1 kcal/mol more stable than that of compound **14b**. The distance of the O−H hydrogen bond ($d = 1.92$ Å) of the βII′ turns is the same in both isomers, but the hydrogen bond angle ∠OHN is 162.0° for **14a** and 149.8° for **14b**. This leads to a weaker hydrogen bond in **14b**, which might account for its slightly lower stabilization.

In a next step, the βII′ conformers of both compounds were taken as the starting points for MD calculations in order to get some insight into their dynamic behavior in different media. The results are summarized in Table 4. The βII′ turn conformation of compound **14a** shows no major dihedral angle fluctuations, and remains very stable in the continuum during 10 ns. In water, the preferred conformation is also a βII′ turn. In DMSO, despite the fact that **14a** shows a tendency to adopt β-turn conformations and not L-shaped ones, these turns do not correspond to any of the major β-turn types. In DMSO the intramolecular hydrogen bond is broken, allowing the amide proton to point outward and form a hydrogen bond with the solvent. This behavior is consistent with the experimental NMR data.

In contrast, pseudopeptide **14b** flips to the L-shaped form after 2 ns and flips back to the βII′ turn conformation after 5.5 ns. In DMSO, the competitive solvent again breaks the intramolecular hydrogen bond, as observed by NMR. More interestingly, the proportion of β-conformations in water is extremely low (less than 20%), and the analysis of the trajectory shows that isomer **14b** adopts the L-shaped form after about 50 ps and maintains it to the end of the evolution time.

These conformational studies indicate that pseudopeptide **14a** (6H-β) is a good βII′ turn mimetic in water. In contrast, **14b** (6H-α) exhibits a pronounced ψ_2 flexibility in the bicyclic framework, which leads to a preference for an L-shaped conformation in water.

(25) For an example of an L-shaped conformation of the Ala-Pro moiety in a cyclic peptide, see: Brown, J. N.; Teller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7565−7569.

Conclusion

We have established a straightforward synthesis of the epimeric oxazolopiperidin-2-one systems (3*S*,6*S*,9*S*)-Cbz-**4a**-OMe and (3*S*,6*R*,9*S*)-Cbz-**4b**-OMe. Experimental and theoretical conformation studies by NMR and by MM/MD have been performed on the *N*-methyl derivatives **14a** and **14b**. These demonstrate that **14a** is an excellent βII′ turn mimetic, whereas **14b** is more flexible and adopts either unusual β-turns or L-shaped conformations. The bicyclic system (3*S*,6*S*,9*S*)-**4a** is therefore a new dipeptide scaffold for the synthesis of βII′ turn mimetics, which might have its application in bioactive peptide-based rational drug design.

Experimental Section[26]

Methyl (3*S*,6*RS*,9*S*)-3-Benzyloxycarbonylamino-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-carboxylates (Cbz-4a-OMe and Cbz-4b-OMe). Method A (Table 1, Entry 7). A solution of aldehyde **5**[27] (12.8 g, 46.2 mmol) and the hydrochloride of *(S)*-Ser-OMe (7.93 g, 50.9 mmol) in dry pyridine (462 mL) was stirred at room temperature for 10 d. The reaction mixture was filtered and the solvent evaporated. The residue was dissolved in dry CH_3OH (380 mL), and solid K_2CO_3 (4.4 g, 32.3 mmol) was added until the starting substrate disappeared (TLC control, 3−5 h). The reaction mixture was filtered, the solvent was evaporated, and the resulting oil was chromatographed (hexane/AcOEt, 7:3) to yield oxazolopiperidone (3*S*,6*S*,9*S*)-Cbz-**4a**-OMe (8.7 g, 54%) as a single isomer: $[\alpha]^{22}_D = -100.1$ (*c* 1, $CHCl_3$); IR (NaCl) 3390, 1721, 1667 cm^{-1}; ^1H NMR 1.61−1.87 (m, 2H), 2.32−2.38 (m, 1H), 2.52 (br s, 1H), 3.77 (s, 3H), 3.84 (dd, $J = 9$, 7 Hz, 1H), 4.16 (dt, $J = 11$, 5 Hz, 1H), 4.44 (d, $J = 9$ Hz, 1H), 4.68 (dd, $J = 9$, 7 Hz, 1H), 4.91 (dd, $J = 9$, 4 Hz, 1H), 5.12 (s, 2H), 5.61 (d, $J = 5$ Hz, 1H), 7.34 (s, 5H); ^{13}C NMR 24.9, 26.6, 52.0, 52.6, 55.8, 66.8, 68.4, 87.9, 127.9, 128.4, 136.2, 156.4, 166.7, 170.1.

Method B (Table 1, Entry 5). To a solution of the hydrochloride of *(S)*-Ser-OMe (1.3 g, 8.4 mmol) and Et_3N (1.17 mL, 8.4 mmol) in dry toluene (10 mL), cooled at 0 °C and under N_2 atmosphere, was added via cannula a solution of aldehyde **5** (2.54 g, 8.4 mmol) in dry toluene (32 mL). The reaction mixture was refluxed for 24 h in a Dean−Stark trap. More Et_3N (1.17 mL, 8.4 mmol) was added, and after 24 h at reflux, the reaction mixture was filtered and the solvent was evaporated to give an oil which was chromatographed (hexane/AcOEt, 3:7) to yield oxazolopiperidone (3*S*,6*R*,9*S*)-Cbz-**4b**-OMe (555 mg, 19%) as an orange oil, and a yellow foam identified as a 10:1 diastereomeric mixture of compound (3*S*,6*S*,9*S*)-Cbz-**4a**-OMe and a third isomer (3*R*,6*S*,9*S*)-Cbz-**4c**-OMe (1.14 g, 39%). **Oxazolopiperidone** (3*S*,6*R*,9*S*)-Cbz-**4b**-OMe (higher R_f): $[\alpha]^{22}_D = +98.5$ (*c* 1, $CHCl_3$); IR (NaCl) 3380, 1742, 1721, and 1667 cm^{-1}; ^1H NMR 1.61 (dtd, $J = 13$, 11 and 5.5 Hz, 1H), 1.99 (ddd, $J = 14.5$, 8.5, 5 Hz, 1H), 2.13−2.20 (m, 1H), 2.24−2.28 (m, 1H), 3.69 (s, 3H), 3.74 (dd, $J = 9$, 7 Hz, 1H), 4.10 (dt, $J = 11$, 5 Hz, 1H), 4.24 (t, $J = 9$ Hz, 1H), 4.83 (br s, 1H), 4.85 (dd, $J = 9$, 7 Hz, 1H), 5.04 (s, 2H), 5.72 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR 23.9, 24.5, 51.2, 52.7, 56.1, 66.8, 67.0, 86.8, 128.0, 128.1, 128.4, 136.2, 155.9, 168.7, 170.1. EIMS *m/z* 348 (M^+, 5), 257 (5), 241 (9), 197 (12), 130 (13), 91 (100). Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.58; H, 5.99; N, 7.77. **Oxazolopiperidone** Cbz-**4c**-OMe (from a 10:1 mixture of **4a** and **4c**, lower R_f): ^1H NMR 1.69−1.77 (m, 2H), 1.82−1.89 (m, 1H), 2.18−2.32 (m, 2H), 3.69 (s, 6H), 3.74 (dd, $J = 9$, 7 Hz, 2H), 4.02 (t, $J = 5$ Hz, 1H), 4.19 (d, $J = 10$ Hz, 1H), 4.42 (d, $J = 7$ Hz, 1H), 4.90 (dd, $J = 8$, 6 Hz, 1H), 5.04 (s, 4H), 5.74 (d, $J = 5$ Hz, 1H), 7.27 (s, 10H); ^{13}C NMR 24.1, 24.4, 49.3, 52.5, 56.1, 66.7, 69.9, 86.2, 127.8, 128.3, 136.2, 156.3, 166.7, 170.0.

(26) Estiarte, M. A.; de Souza, M. V. N.; Del Río, X.; Dodd, R. H.; Rubiralta, M.; Diez, A. *Tetrahedron* **1999**, *55*, 10173−10186.

(27) Aldehyde **5**: $[\alpha]^{22}_D = +92$ (*c* = 1, CH_3CN) [lit.[14] $[\alpha]^{22}_D = +89$ (*c* = 1.4, MeCN)].

Methyl (3*S*,6*S*,9*S*)-3-*tert*-Butoxycarbonylamino-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-carboxylate (9). A solution of oxazolopiperidone Cbz-**4a**-OMe (200 mg, 0.28 mmol), $(Boc)_2O$ (163 mg, 0.74 mmol), and 10% Pd/C in CH_3OH (5 mL) was hydrogenated at P_{atm} for 2 h at room temperature. An AcOH/NaOAc buffer solution (pH = 3, 2 mL) was added, and the mixture was stirred for 3 h at room temperature. The reaction mixture was filtered through Celite, and the resulting oil was chromatographed (hexane/AcOEt, 2:8) to yield the Boc-oxazolopiperidone **9** (112 mg, 72%) as a white foam: $[\alpha]^{22}_D = -102.3$ (*c* 1, $CHCl_3$); IR (NaCl) 3320, 1749, 1714, 1671 cm^{-1}; ^1H NMR 1.45 (s, 9H), 1.61−1.82 (m, 2H), 2.31−2.38 (m, 1H), 2.48 (br s, 1H), 3.77 (s, 3H), 3.84 (dd, *J* = 9, 7 Hz, 1H), 4.17 (br s, 1H), 4.44 (t, *J* = 9 Hz, 1H), 4.68 (dd, *J* = 9, 7 Hz, 1H), 4.92 (dd, *J* = 9, 4 Hz, 1H), 5.23 (br d, *J* = 6 Hz, 1H); ^{13}C NMR 25.0, 26.6, 28.1, 51.6, 52.5, 55.8, 68.3, 79.7, 87.9, 155.8, 167.1, 170.1; EIMS *m*/*z* 258 ($M^+ - C(CH_3)_3$, 2), 197 (10), 130 (18), 57 (100). Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.32; H, 7.38; N, 8.72.

Methyl (3*S*,6*S*,9*S*)-3-Amino-2-oxo-7,1-oxazabicyclo[4.3.0]-nonane-9-carboxylate (10). To a solution of oxazolopiperidone Cbz-**4a**-OMe (2 g, 5.74 mmol) in CH_3OH (57.4 mL) was added 10% Pd/C (10 mg), and the mixture was hydrogenated at P_{atm} for 2 h, at room temperature. The reaction mixture was filtered through Celite, and the solvent was evaporated to yield amine **10** (1.22 g, 99%) as pale yellow oil: $[\alpha]^{22}_D = -157.3$ (*c* 1, $CHCl_3$); IR (NaCl) 3410, 1741, 1658 cm^{-1}; ^1H NMR 1.54−1.74 (m, 2H), 1.96 (br s, 2H), 2.24−2.38 (m, 2H), 3.34 (dd, *J* = 11, 5 Hz, 1H), 3.78 (s, 3H), 3.85 (dd, *J* = 9, 7 Hz, 1H), 4.44 (t, *J* = 9 Hz, 1H), 4.70 (t, *J* = 9 Hz, 1H), 4.92 (dd, *J* = 9, 4 Hz, 1H); ^{13}C NMR 26.1, 26.8, 51.8, 52.5, 55.5, 68.2, 88.1, 170.1, 170.5. EIMS *m*/*z* 214 (M^+, 2), 197 (36), 149 (50), 130 (88), 57 (100). Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.72; H, 6.47; N, 13.27.

Methyl (3*S*,6*S*,9*S*)-3-[9-(Fluorenyl)methoxycarbonyl-amino]-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-carboxylate (11). To a solution of amine **10** (500 mg, 2.34 mmol) in a mixture of CH_3CN-H_2O (15 mL, 1:1) was added Fmoc-OSu (800 mg, 2.34 mmol). Et_3N was added until pH = 8 (10 drops), and the solution was stirred at room temperature for 5 h. The CH_3CN was evaporated, and the remains were partitioned in CH_2Cl_2 and H_2O. The mixture was acidified by careful addition of 1 N aqueous HCl. The layers were separated, and the aqueous phase was washed with CH_2Cl_2. The organic extracts, dried and evaporated, gave a white solid, which was chromatographed (hexane/AcOEt, 1:9) to yield the Fmoc-oxazolopiperidone **11** (836 mg, 82%): mp 160−161 °C (AcOEt); $[\alpha]^{22}_D = -74.1$ (*c* 0.5, $CHCl_3$); IR (NaCl) 3417, 1736, 1720, 1669 cm^{-1}; ^1H NMR 1.68−1.85 (m, 2H), 2.35 (br s, 1H), 2.59 (br s, 1H), 3.78 (s, 3H), 3.84 (t, *J* = 9 Hz, 1H), 4.19 (br s, 1H), 4.22 (t, *J* = 7 Hz, 1H), 4.39 (br d, *J* = 6.5 Hz, 2H), 4.45 (t, *J* = 9 Hz, 1H), 4.69 (dd, *J* = 9, 7 Hz, 1H), 4.92 (br s, 1H), 5.49 (br s, 1H), 7.31 (td, *J* = 7.5, 1 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7, 3 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR 24.8, 26.5, 47.0, 52.0, 52.6, 55.7, 66.8, 68.3, 87.9, 119.8, 125.0, 126.9, 127.5, 141.1, 143.8, 156.3, 166.6, 170.0. EIMS *m*/*z* 259 (M^+ − Fmoc, 0.1), 196 (22), 178 (100), 165 (97), 130 (16), 57 (40). Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.05; H, 5.54; N, 6.42. Found: C, 66.73; H, 5.34; N, 6.42.

(3*S*,6*S*,9*S*)-3-Benzyloxycarbonylamino-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-carboxylic Acid (12). To a solution of oxazolopiperidone Cbz-**4a**-OMe (820 mg, 2.35 mmol) in CH_3OH (5.5 mL) cooled at 0 °C was added aqueous 1 N NaOH (5,18 mL, 5,18 mmol), and the mixture was stirred for 1 h. The reaction was quenched by addition of 1 N HCl at 0 °C, until pH = 1. The CH_3OH was evaporated, the residue was partitioned with AcOEt−H_2O, and the organic layer was washed with brine. The organic phase, dried and evaporated, yielded acid **12** (744 mg, 95%) as a white foam: IR (NaCl) 3380, 3200, 1720, 1666 cm^{-1}; ^1H NMR 1.63−1.95 (m, 2H), 2.46 (br s, 2H), 4.04 (t, *J* = 8 Hz, 1H), 4.13−4.19 (m, 1H), 4.42 (t, *J* = 9 Hz, 1H), 4.64 (t, *J* = 8 Hz, 1H), 4.84 (br d, *J* = 5 Hz, 1H), 5.11 (s, 2H), 5.72 (br s, 1H), 5.98 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR 24.7, 26.6, 51.7, 56.2, 67.0, 68.0, 87.9, 128.0, 128.4, 136.1, 156.6, 168.7, 170.9; EIMS *m*/*z* 334 (M^+, 7), 290 (1), 227 (12), 178 (48), 108 (47), 91 (100). Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 55.64; H, 5.61; N, 8.11. Found: C, 55.64; H, 5.38; N, 8.22.

(3*S*,6*S*,9*S*)-3-[9-(Fluorenyl)methoxycarbonylamino]-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-carboxylic Acid (13). To a solution of oxazolopiperidone **11** (60 mg, 0.13 mmol) in THF (2 mL), cooled at 0 °C, was added aqueous 1 N NaOH (0.3 mL, 0.3 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of 1 N HCl, until pH = 1, at 0 °C. The CH_3OH was evaporated, and the remains were partitioned in AcOEt−H_2O. The organic layer was washed with brine, dried, and evaporated to yield acid **13** (45 mg, 77%) as a white solid: mp 200−202 °C (AcOEt); $[\alpha]^{22}_D = -114.7$ (*c* 0.5, $CHCl_3$); IR (NaCl) 3417, 3010, 1726, 1694 cm^{-1}; ^1H NMR 1.68−1.85 (m, 2H), 2.35 (br s, 1H), 2.59 (br s, 1H), 3.84 (t, *J* = 9 Hz, 1H), 4.19 (br s, 1H), 4.22 (t, *J* = 7 Hz, 1H), 4.39 (br d, *J* = 6.5 Hz, 2H), 4.45 (t, *J* = 9 Hz, 1H), 4.69 (dd, *J* = 9, 7 Hz, 1H), 4.92 (br s, 1H), 5.49 (br s, 1H), 7.31 (td, *J* = 7.5, 1 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7, 3 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3/CD_3OD$) 24.8, 25.5, 47.0, 51.6, 56.0, 66.9, 68.2, 87.9, 119.8, 125.0, 127.0, 127.6, 141.1, 143.5 and 143.8, 156.6, 167.7, 171.1; EIMS *m*/*z* 244 (M^+ − Fmoc, 0.1), 196 (13), 178 (100), 165 (48), 57 (15). Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.39; H, 5.45; N, 6.37.

(3*S*,6*S*,9*S*)-3-Benzyloxycarbonylamino-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-methylcarboxamide (14a). To a saturated solution of CH_3NH_2 in CH_3OH (28 mL), cooled at −40 °C, was added oxazolopiperidone Cbz-**4a**-OMe (200 mg, 0.57 mmol), and the tube was sealed. The reaction mixture was stirred at room temperature for 12 h. More CH_3NH_2 was bubbled into the mixture, and the reaction was continued for 48 h. The mixture was filtered, and the solvent was evaporated to give an oil that was chromatographed (AcOEt/CH_3OH, 98:2) to yield amide **14a** (97 mg, 50%): $[\alpha]^{22}_D = -87.4$ (*c* 1, $CHCl_3$); IR (NaCl) 3350, 1702, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) 1.54 (ddd, *J* = 13, 10, 3 Hz, 1H), 1.98−2.06 (m, 1H), 2.13−2.23 (m, 1H), 2.33 (ddd, *J* = 13, 7, 3 Hz, 1H), 2.68 (d, *J* = 5 Hz, 3H), 3.70 (dt, *J* = 11, 6 Hz, 1H), 4.03 (t, *J* = 8 Hz, 1H), 4.34 (t, *J* = 9 Hz, 1H), 4.65 (t, *J* = 8 Hz, 1H), 4.77 (dd, *J* = 9, 4 Hz, 1H), 5.02 (s, 2H), 5.67 (br s, 1H), 7.22 (br s, 1H), 7.29−7.35 (m, 5H); ^1H NMR (C_6D_6) 0.74−0.81 (m, 1H), 1.20−1.25 (m, 1H), 1.30−1.36 (m, 2H), 2.39 (d, *J* = 4 Hz, 3H), 3.16 (br s, 1H), 3.85 (t, *J* = 8.5 Hz, 2H), 4.14 (dd, *J* = 9.5, 4 Hz, 1H), 4.35 (ta, *J* = 7 Hz, 1H), 4.66 and 4.74 (2d, *J* = 12.5 Hz, 1H each), 6.73 (d, *J* = 7 Hz, 1H), 6.75−6.85 (m, 5H), 7.05 (s, 1H); ^1H NMR (DMSO-d_6) 1.52−1.60 (m, 1H), 1.75−1.82 (m, 1H), 1.94−1.98 (m, 1H), 2.18−2.23 (m, 1H), 2.57 (d, *J* = 4, 5 Hz, 3H), 3.67 (t, *J* = 8 Hz, 1H), 3.94 (dt, *J* = 10, 7 Hz, 1H), 4.33 (t, *J* = 9 Hz, 1H), 4.43 (t, *J* = 8 Hz, 1H), 4.81 (dd, *J* = 9, 4 Hz, 1H), 5.03 (s, 2H), 7.29−7.35 (m, 5H), 7.68 (d, *J* = 4 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 24.1, 26.1, 26.7, 52.1, 56.9, 67.1, 68.3, 87.4, 127.7, 128.2 and 128.5, 135.9, 156.5, 167.7, 169.4; EIMS *m*/*z* 347 (M^+, 1), 289 (3), 181 (11), 153 (15), 108 (43), 91 (100). Anal. Calcd for $C_{23}H_{22}N_2O_6 \cdot {}^2/_3H_2O$: C, 56.97; H, 6.25; N, 11.72. Found: C, 56.97; H, 6.03; N, 11.47.

(3*S*,6*R*,9*S*)-3-Benzyloxycarbonylamino-2-oxo-7,1-oxazabicyclo[4.3.0]nonane-9-methylcarboxamide (14b). Operating as above, from oxazolopiperidone Cbz-**4b**-OMe (200 mg, 0.57 mmol) and a saturated solution of CH_3NH_2 in CH_3OH (28 mL), amide **14b** (99 mg, 51%) was obtained: $[\alpha]^{22}_D = +79.7$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.49 (tdd, *J* = 13, 9.5 and 3 Hz, 1H), 1.98 (q, *J* = 13 Hz, 1H), 2.14 (dddd, *J* = 13, 7, 4 and 3 Hz, 1H), 2.28 (ddd, *J* = 13, 7 and 4 Hz, 1H), 2.67 (d, *J* = 5 Hz, 3H), 3.70 (t, *J* = 4 Hz, 1H), 4.03 (t, *J* = 8 Hz, 1H), 4.34 (t, *J* = 9 Hz, 1H), 4.65 (t, *J* = 8 Hz, 1H), 4.77 (dd, *J* = 9, 4 Hz, 1H), 5.03 (s, 2H), 5.67 (br s, 1H), 7.22 (br s, 1H), 7.29−7.35 (m, 5H); ^1H NMR (DMSO-d_6) 1.56 (tdd, *J* = 13, 9.5, 3 Hz, 1H), 1.79 (q, *J* = 13 Hz, 1H), 1.94−1.99 (m, 1H), 2.19−2.22 (m, 1H), 2.58 (d, *J* = 4.5 Hz, 3H), 3.68 (dd, *J* = 8, 7 Hz, 1H), 3.93 (dt, *J* = 10, 7 Hz, 1H), 4.32 (t, *J* = 9 Hz, 1H), 4.43 (t, *J* = 8 Hz, 1H), 4.81 (dd, *J* = 9, 4 Hz, 1H), 5.04 (s, 2H), 7.29−7.35 (m, 5H), 7.68 (d, *J* = 4 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 24.2, 26.2, 26.8, 52.2, 56.9, 67.2, 68.2, 87.3, 127.8, 128.3 and 128.6, 135.8, 156.5, 167.7, 169.3.

Molecular Modeling Studies. Theoretical conformational analyses of compounds **14a** and **14b** were performed using the CHARMM24b2 program package[28] and the CHARMm 23.1 force field.[29] To get insight on the possible conformations of these compounds, a simulated annealing approach was used to sample their conformational space. One hundred structures were obtained by subsequent cycles of heating (20 ps from 0 to 1000 K), cooling (20 ps from 1000 to 0 K), and energy minimization (100 steps steepest descend and 10000 steps adopted basis Newton−Raphson) and were clustered by conformation and energy. The resulting lowest energy conformations were the starting points for molecular dynamics studies using an implicit solvent description ($\epsilon = 80$) and two different explicit solvent models for H_2O and DMSO. NVT calculations at 300 K were performed using cubic boxes of 30 Å side length and 1000 TIP3P water molecules,[30] and of 31 Å side length and 216 DMSO molecules,[31] respectively. Periodic boundary conditions were applied. After adequate heating and equilibration of the system, evolution times were of 10 ns for the implicit water model and of 1 ns for both explicit models. 6000 structures were saved periodically from each trajectory for further analyses.

Trajectories were analyzed for conformational preferences measuring the dihedral angles ψ_2,ϕ_2, ψ_3, ϕ_3, and the β-turn descriptors R and τ (Figure 8). A conformation was accepted as a general β-turn if $R < 7$ Å and $-90° < \tau < 90°$, and classified as one of the main β-turn types if none of the four dihedral angles differed by more than 30° from the standard torsion angle values as given in Table 2.

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Supporting Information Available: Graphic representation of the ^{1}H NMR chemical shift of the NH protons of pseudodipeptide **14b** at different proportions of DMSO-d_6 in $CDCl_3$, ^{1}H NMR spectra of compounds **14a** and **14b** at different proportions of DMSO-d_6 in $CDCl_3$, calculated trajectories of compounds **14a** and **14b** in continuum, in water, and in DMSO, and snapshots of compound **14b** in water (L-shaped) and in DMSO (unusual β-turn). This material is available free of charge via the Internet at http://pubs.acs.org.

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