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Structural Analysis of β-Turn Mimics Containing a Substituted 6-Aminocaproic Acid Linker

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Abstract: A series of β-turn models have been prepared consisting of the dipeptide Ala-Gly cyclized with all stereoisomers of 6-amino-3,5-dimethylcaproic acid and 6-amino-3-methylcaproic acid, as were related peptides based on Gly-Gly and Ala-Ala. The requisite linkers were made using routes featuring stereoselective ring-expansion reactions and the syntheses completed using standard methodology. A preliminary examination of these compounds has been carried out using NMR spectroscopy, circular dichroism, and, in several cases, X-ray crystallography. These studies indicate that, depending on linker stereochemistry, different proportions of type II and type I turns were observed in solution. Both type I and type II turns were observed in the solid state.

The β-turn is an important feature of peptide and protein secondary structure, involving as many as one-third of the residues of a given protein.[1] Efforts to elucidate the spectroscopic and chiroptical properties of β-turns have utilized simple peptide derivatives, such as Boc-Pro-Ser-$NHCH_3$, and, with the careful choice of residues and some bioisosteric replacements, have more recently been extended to include small-peptide models of β-hairpin moieties.[2] A complementary approach has been to synthesize cyclic peptides, most notably hexapeptides, which feature one or two β-turns at either end of the macrocyclic ring (Figure 1).[3] Besides backbone cyclizations,[4] macrocyclizations induced by disulfide linkage formation[5] and nonpeptidic spacers, such as δ-aminovaleric acid (δ-Ava),[6] have proved particularly useful in this context.

Dipeptides cyclized with 6-aminocaproic acid (Aca) are among the most important small-molecule models of β-turns.[7]

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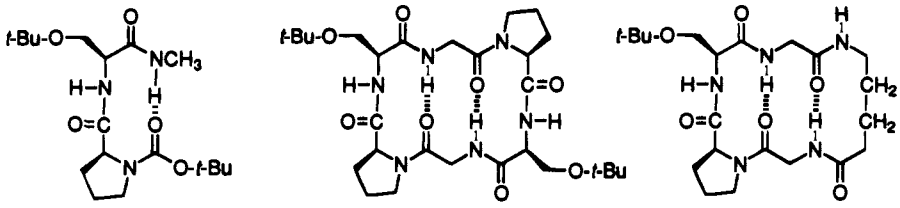

Figure 1. Some β-turn-containing model peptides.

Using spectroscopy and conformational energy calculations, Scheraga and co-workers have convincingly argued that *cyclo*(L-Ala-Gly-Aca) **1** exists in solution in an 85:15 mixture of type II and type I β-turns, whereas *cyclo*(L-Ala-L-Ala-Aca) and *cyclo*(L-Ala-D-Ala-Aca) predominantly exist as type I or type II β-turns, respectively (Figure 2). The seven-atom Aca linker is used to place the ends of the central dipeptide, corresponding to positions $i + 1$ and $i + 2$ of the β-turn, at an appropriate distance allowing turn formation. Although this system was extensively studied by nuclear magnetic resonance (NMR) and circular dichroism (CD) techniques, no solid-state structural information has been obtained for this class of β-turn models.

The β-turn has also attracted the attention of medicinal chemists because of its importance in such events as hormone-receptor and peptide-enzyme recognition. Because of the well-known difficulties in using bona fide peptides as orally active drugs, a number of imaginative ways of preparing β-turn peptidomimetics have been developed.[8] Often, residues involved in a turn are replaced by modified amino acids[9] or a totally non-peptidic unit,[10] or a covalent linkage is inserted in place of the $i \rightarrow i + 3$ hydrogen bond.[11] An attractive alternative is to modify a portion of the targeted peptide by introducing a linker or scaffold that encourages adoption of the desired turn type.[12] Particularly interesting is the installation of β-turn mimics into bioactive cyclic peptides, where they may function as either scaffolds or as the molecular recognition site itself.[13]

We felt that cyclized dipeptides of the type **1** should be useful mimics of bioactive β-turns. Despite longstanding interest in this kind of β-turn model, the Aca linker has not been employed specifically in the design of potentially bioactive peptidomimetics, to our knowledge. Since most common β-turn mimics contain synthetic replacements for the $i + 1$ and $i + 2$ residues, the survey of a number of dipeptides in these positions generally requires the preparation of a new bioisostere for each analogue. In contrast, the use of an off-the-shelf dipeptide in combination with a modular linker would ameliorate this situation. We were especially intrigued by the possibility that Aca substituent

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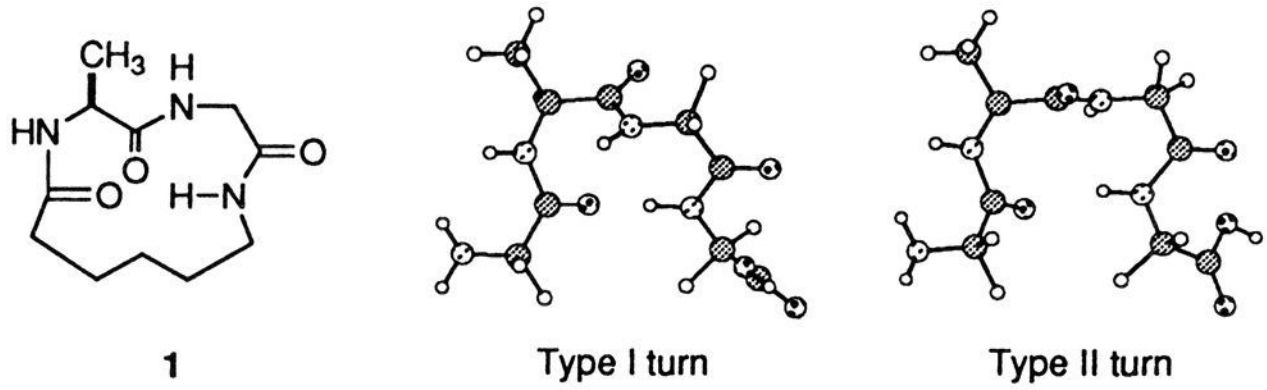
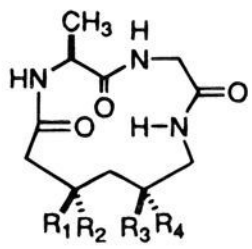


Figure 2. cyclo[L-Ala-Gly-Aca] **1** and ball-and-stick depictions of idealized type I and type II β-turns.

stereochemistry could affect the conformational preferences of the macrocyclic ring and perhaps allow access to more than one subtype of β-turn for each dipeptide. In addition, it might be possible to employ the linker as a site of installing other useful functional groups, such as those able to impart desirable solubility properties or containing additional macromolecular recognition sites.

We have begun to investigate the conformational properties of substituted Aca analogs in the synthesis of β-turn-containing peptidomimetics. Simple 1,3-dialkyl substitution was initially chosen due to the effectiveness of this pattern in controlling local conformational behavior in acyclic and cyclic systems.[14] Accordingly, this paper describes the synthesis of L-Ala-Gly dipeptides constrained with all possible isomers of 3,5-dimethyl-Aca **2**–**5** (and some appropriate control compounds). These studies have provided spectroscopic evidence that linker stereochemistry has a substantial effect on the solution conformations of the cyclic peptides. And finally, the first X-ray crystallographic data for this series of important β-turn models has been obtained and shows that the conformational trend observed in solution extends to the solid state.

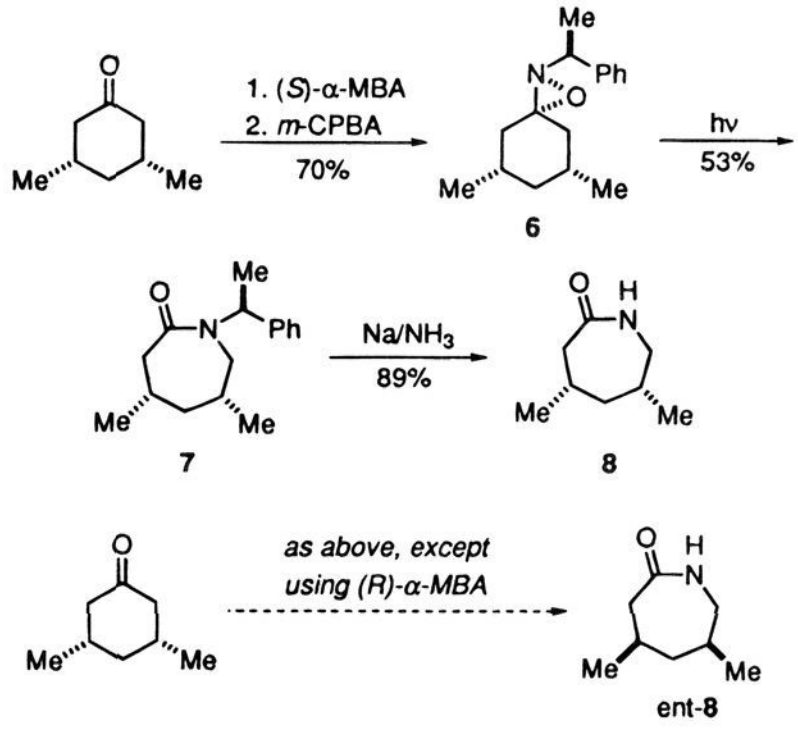


	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	Me	H	Me
3	Me	H	Me	H
4	Me	H	H	Me
5	H	Me	Me	H

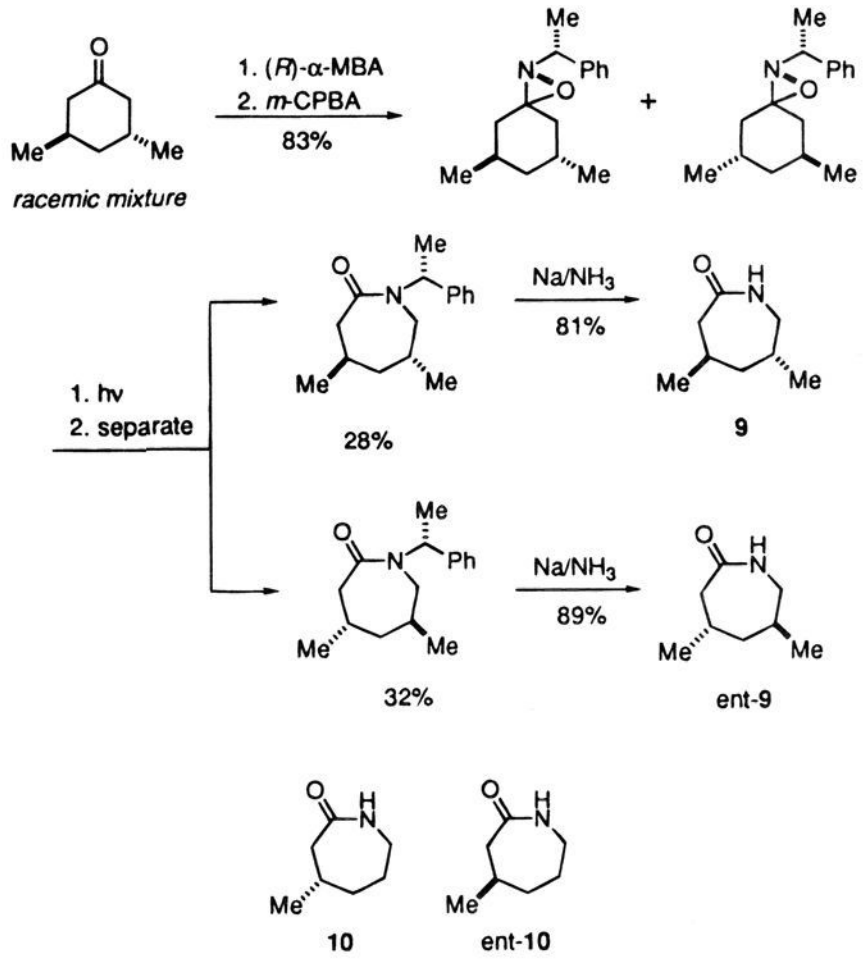
Results and Discussion

Synthesis of Cyclic Peptides. We required easy access to a variety of structurally related cyclic peptides. The ready availability of masked dipeptides is a given. All four stereoisomeric linkers were prepared in multigram quantities using an oxaziridine-mediated nitrogen ring-expansion process previously studied in this laboratory.[15] Thus, both enantiomers of *cis*-4,6-dimethylcaprolactam (**8** and ent-**8**) were synthesized by carrying out the stereospecific ring-expansion reaction of 3,5-dimethylcyclohexanone with α-methylbenzylamine (α-MBA, Scheme 1). Imine formation followed by oxidation with *m*-CPBA gave oxaziridine **6** as the predominant product, along with small amounts (<20%) of other oxaziridine isomers.

Scheme 1



Scheme 2



Photolysis of the mixture followed by chromatographic separation afforded stereochemically homogenous **7** in 54% yield. Removal of the nitrogen substituent under Birch conditions produced the linker precursor **8**. The analogous ring expansion of *cis*-3,5-dimethylcyclohexanone with (*S*)-α-MBA proceeded similarly to afford ent-**8** in 33% overall yield.

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Scheme 3

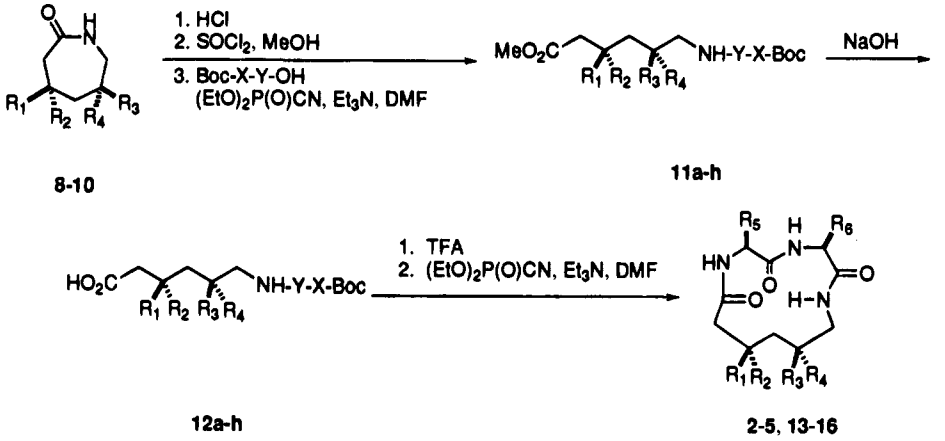


Table 1. Yields for the Synthesis of Cyclic Peptides

entry	lactam	X-Y[a]	R_1	R_2	R_3	R_4	yield of **11** (%)[b]	yield of **12** (%)	cyclic peptide[c]	yield of cyclic peptide (%)
a	**8**	Ala-Gly	H	Me	H	Me	96	67	**2**	51
b	ent-**8**	Ala-Gly	Me	H	Me	H	75	60	**3**	63
c	**9**	Ala-Gly	Me	H	H	Me	80	61	**4**	71
d	ent-**9**	Ala-Gly	H	Me	Me	H	81	43	**5**	58
e	**10**	Ala-Gly	H	Me	H	H	74	83	**13**	42
f	ent-**10**	Ala-Gly	Me	H	H	H	85	77	**14**	51
g	ent-**10**	Gly-Gly	Me	H	H	H	65	80	**15** ($R_5 = R_6 = H$)	35
h	**9**	Ala-Ala	Me	H	H	Me	71	89	**16** ($R_5 = R_6 = Me$)	59

[a] Only L-Ala residues were used. [b] Purified yield from the corresponding lactam (three steps). [c] Except where noted, R_5 = Me and R_6 = H.

The trans isomers needed for macrocycles **4** and **5** could be obtained via the simultaneous ring expansion and resolution[16] of *trans*-3,5-dimethylcyclohexanone (Scheme 2). Accordingly, the racemic ketone was converted to an equimolar mixture of two oxaziridine stereoisomers by treatment with (*R*)-α-MBA and then oxidation. Photolysis and separation afforded diastereomerically pure lactams **9** and ent-**9** as above. Monomethyl-substituted analogues **10**/ent-**10** were obtained using similar chemistry as previously reported.[16]

The conversions of these lactams to the target macrocyclic peptides featured the expected series of hydrolysis and condensation reactions (Scheme 3).[7] After methanolysis of the variously substituted lactams, coupling with Boc-Ala-Gly-OH afforded the acyclic intermediates **11** in protected form. Sequential removal of the methyl ester and the N-Boc group afforded a seco amide that was cyclized using diethylcyanophosphonate under moderately dilute conditions. In this way, compounds **2**−**5** were readily obtained on a 50−100 mg scale. The ease of the macrocyclization reactions is a noteworthy aspect of these syntheses. Several "control" compounds were also synthesized using analogous chemistry; the data for compounds **13**−**16** are thus included in Table 1 and the Experimental Section. In addition, compound **1** was synthesized according to the original route for direct comparison to the substituted compounds.[7]

General Spectroscopic Observations. As the target macrocylic peptides became available, their spectroscopic properties were examined using NMR and CD. The water solubility of these compounds is undesirably low for 2-D NMR studies, so **3** was initially evaluated in neat DMSO-d_6 and a DMSO-d_6/water mixture. There were no significant changes in any chemical shifts or coupling constants with the addition of water, so the other compounds were examined in DMSO-d_6 only. Stereospecific assignments of all protons were made on the basis of COSY and ROESY (t_{mix} = 300 ms) spectra. Given the small size of the molecules, high quality NOESY spectra with all negative crosspeaks (i.e., positive NOEs) were obtained at longer (900 ms) mixing times.

Table 2. Selected NMR Data for Compounds **1**−**5**

compd	chemical shifts (δ, ppm)[a] C-4[b]	Ala_{NH}	Gly_{NH}	(di-Me)Aca_{NH}	TCs (−ppb/K)[c]
1	1.01,* 1.30	8.47	8.48	6.99	4.0
2	0.80, 1.61*	8.41	8.16	6.61	2.4
3	0.67, 1.05*	8.67	8.72	6.83	2.0
4	0.92, 1.22*	8.72	8.79	7.45	4.1
5	1.06, 1.23*	8.53	8.50	7.06	3.0

[a] Measured at 500 MHz in DMSO-d_6. [b] Linker numbering. The proton marked with an asterisk has a strong NOE interaction with the (di-Me)Aca_{NH} proton. [c] Temperature coefficient of the (di-Me)Aca_{NH} proton, measured at 500 MHz in DMSO-d_6 (*c* 1 mg/mL).

Some features were common to each of **2**-**5**. In each case, the diastereotopic protons on the "central" C-4 methylene group of the linker were dispersed with $\Delta\nu$ = 0.17−0.81 ppm (Table 2). NOE measurements additionally indicated that the downfield proton in **2**−**5** is close to the Aca amide proton and is possibly experiencing deshielding effects from the Aca carbonyl group. Interestingly, in compound **1**, lacking linker substitution, the upfield proton selectively experiences the analogous NOE.

Amide temperature coefficients (TCs) were also measured for **1**−**5** (Table 2). The linker amide NH TC is of particular interest for evaluating the degree of $i \rightarrow i + 3$ hydrogen bonding characteristic of canonical type I or II β-turns. These were found to show substantial concentration dependence above 1 mg/mL (0.004 M), which is lower than the concentration used in the earlier studies of **1**.[7c] The TCs at higher concentrations have lower absolute values (a value of 0 ppb/K was observed for **3** at 20 mg/mL), which would lead to significant overestimation of the amount of intramolecular hydrogen bonding. The TCs observed at *c* = 1 mg/mL range from −2.0 to −4.1 ppb/K (cf. −3.3 ppb/K reported for **1** at 0.069 M[7c]). Although all of the linker NH TCs are evidently "depressed", only the smallest

(16) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499−508. Correction: Aubé, J.; Hammond, M.; Gherardini, E.; Takasagawa, F. *J. Org. Chem.* **1991**, *56*, 4086.

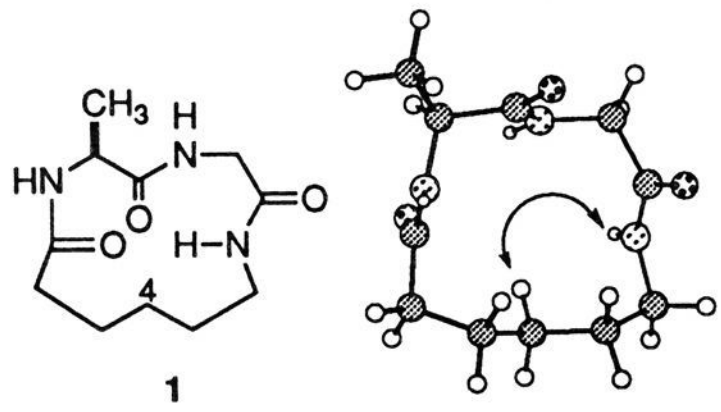


Figure 3. Ball-and-stick depiction of the major conformation of compound **1**, as proposed in ref 7b, showing the NOE observed between one of the Aca C-4 methylene protons and the Aca NH.

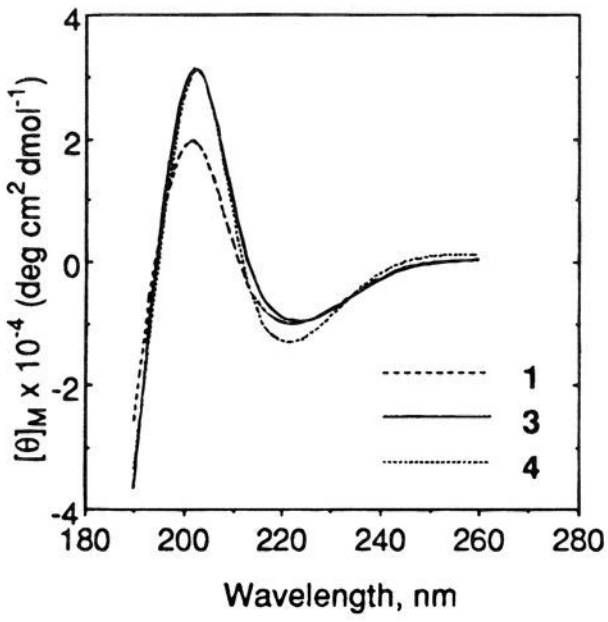


Figure 4. CD spectra of compounds **1**, **3**, and **4** in methanol.

approach the −2.5 ppb/K value suggested for robust hydrogen bonds in cyclic peptides.[1] It should be pointed out, however, that since the β-turn is ultimately defined by the backbone dihedral angles of the central dipeptide unit, the presence of this hydrogen bond is unnecessary for the successful utilization of compounds like **2**−**5** as β-turn peptidomimetics.

Overall, these data are consistent with the overall shape of **1** as originally suggested by Scheraga based on NMR and conformational energy calculations (Figure 3).[7] The dispersion of the C-4 methylene chemical shifts makes sense in the context of this carbon being oriented toward the center of the macrocycle, where one, but not both, of these protons can experience the indicated NOE. Aside from the adjacent C-6 methylene protons, none of the other linker protons are subject to a comparable effect. The chemical shift of the "inward" proton should depend on its orientation relative to the Aca-Ala amide plane; the difference observed in **1** vs compounds **2**−**5** may reflect some differences in this feature. Although one must always be concerned about the over-interpretation of NMR spectra of conformationally averaged species, it seemed reasonable to use this conformation as a starting point for our examination of the central dipeptide portion of this series.

Conformational Analysis in Solution. The CD measurements of all compounds were carried out in methanol solution (c = 1 mg/mL, 0.02 cm path length). Compounds bearing 3*R*-methyl substitution bore the most chiroptical resemblance to the parent compound **1** (Figure 4). Each of these spectra indicated a high population of type II β-turn, with the 3*R*-methyl-containing compounds **3** and **4**, nearly identical, having a somewhat higher θ_{max} at ca. 203 nm than the parent **1**.[1,7,17] Both **3** and **4** exhibited a strong Gly_{NH}-(di-Me)Aca_{NH} NOE, which

(17) Woody, R. W. *The Peptides*; Hruby, V. J., Ed.; Academic: New York, 1985; Vol. 7, pp 15−114.

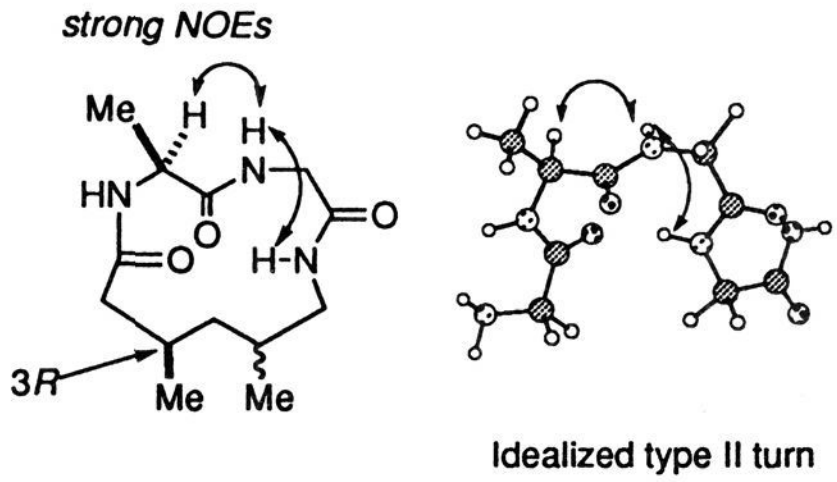


Figure 5. Strong NOEs observed for compounds **3** (C-5 Aca Me group β) and **4** (C-5 Aca Me group α). The Ala_{α}-Gly_{NH} crosspeak expected in the NMR of a type II β-turn, and the Gly_{NH}-Aca_{NH} crosspeak expected in either type I or II β-turn are shown in the idealized structure at the right.

is characteristic in spectra of both type I and type II β-turns. In addition, an $Ala_{\alpha H}$-Gly_{NH} crosspeak was evident in the ROESY spectrum, as expected for type II geometry (Figures 5 and 6a). Unfortunately, the Ala_{NH} and Gly_{NH} signals were insufficiently resolved in **3** ($\Delta\nu$ < 20 Hz at 500 MHz) to ascertain unambiguously whether the Ala_{NH}-Gly_{NH} crosspeak expected to arise from a minor amount of type I turn was present. However, it appears this crosspeak is absent in the spectrum of the somewhat better resolved **4**, as expected (Figure 6a).

The modest minimum at ca. 220 nm was lost from the CD spectra of 3*S*-methyl-configured compounds **5** and **6** (Figure 7). Although the significance of this is unclear at present, compounds **13** and **14**, derived from Ala-Gly and bearing linkers with 3*S*- and 3*R*-monomethyl substitution, were prepared and shown to duplicate the effect. Thus, compound **13** lacked the 220 nm minimum, whereas the CD of the 3*R*-methyl isomer **14** resembled **3** and **4**. It is possible that 3*S* stereochemistry introduces a steric interaction unfavorable toward type II turn formation and that small amounts of other turn types or "random" conformations begin to intrude. To probe this further, *cyclo*(Gly-Gly-(3*R*)-Me-Aca) **15** was prepared and examined by NMR and CD spectroscopy. For this compound, a widely dispersed NMR spectrum, with clearly resolved $Gly_{\alpha H}$ and Gly_{NH} protons, was obtained. A very strong crosspeak between the α-proton of the "N-terminal" Gly and the "C-terminal" Gly_{NH} was observed (consistent with type II conformation), and no Gly_{NH}-Gly_{NH} crosspeak (expected for a type I conformation) was evident; indeed the CD for this material was also a type II signature spectrum (Figure 8). Apparently, the single methyl group on the linker is able to bias the entire macrocycle into one predominant conformation bearing type II character about the dipeptide portion.

In sharp contrast, **2**, with 3*S*, 5*R*-linker stereochemistry, plainly exists as a mixture with substantial type I β-turn character. In this case, the Ala_{NH}-Gly_{NH} NOESY crosspeak expected for a population of type I turn is faintly observed (Figure 6b). It is approximately an order of magnitude weaker than the Gly amide-Aca amide crosspeak expected for either type I or II turns (Figure 9). Additionally, the CD spectrum of **2** is similar to that previously calculated for a predominately type I β-turn, with some type II and "open" character calculated in (Figure 9).[2m] It is illustrative to compare this CD spectrum with that of *cyclo*(L-Ala-L-Ala-(3*R*,5*R*)-(di-Me)Aca) **16**, expected[7e,f] to predominantly exist in a type I turn due to the replacement of the Gly in the formal $i + 3$ position with an L amino acid. In the NOESY spectrum of **16**, which is primarily type I, the $(Ala\text{-}1)_{NH}$-$(Ala\text{-}2)_{NH}$ crosspeak is seen to be about twice as intense as the $(Ala\text{-}2)_{NH}$-(di-Me)Aca_{NH} crosspeak

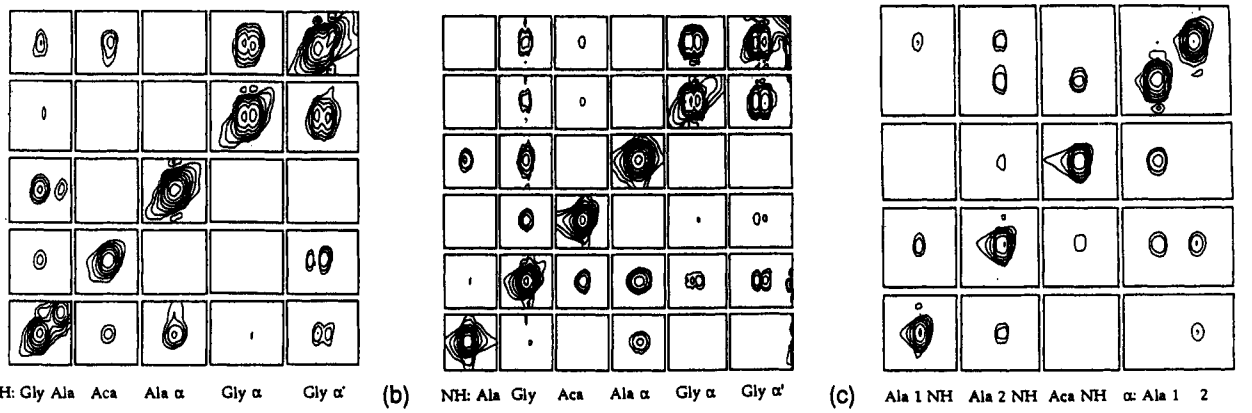


Figure 6. Tile plots for amide-α NOE connectivities for (a) **4**, 300 msec ROESY; (b) **2**, 900 ms NOESY; and (c) **16**, 900 ms NOESY. All diagonal peaks are positive, and all crosspeaks are negative in the phase sensitive 2D data.

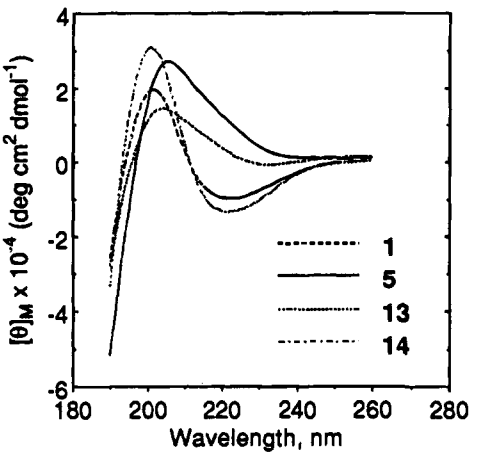


Figure 7. CD spectra of compounds **1**, **5**, **13**, and **14** in methanol.

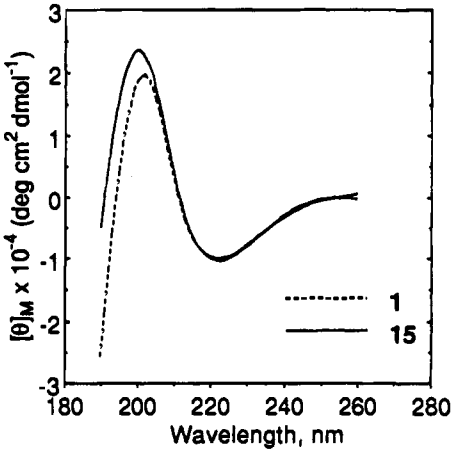


Figure 8. CD spectra of compounds **1** and **15** in methanol.

(Figure 6c). The varying proportions of type II vs type I populations over a series of cyclic compounds prepared from a single dipeptide should prove useful in peptidomimetic design.

X-ray Crystallographic Studies. X-ray crystallographic structures could be obtained of compounds **2**, **4**, and **5** after recrystallization from methanol/CH_2Cl_2 (Figure 11, Table 3, and supplementary material; compounds **1** and **3** have thus far eluded crystallization). As seen in Table 3, the central dipeptide unit in compound **2** takes up a quite reasonable type I structure, whereas the other two cyclized compounds closely resemble type II turns. This parallels the solution state conformations as suggested by the CD/NMR analysis above; in every case, the crystallographically observed dihedral angles for the dipeptide lie within 21° of the idealized values.[18] Although the linker N−H and C=O bonds are substantially bent in each case, intramolecular hydrogen bonds were explicitly observed for the *trans*-dimethyl compounds (intramolecular H· · ·O distances: **2**, 2.65 Å; **4**, 1.94 Å; **5**, 2.10 Å).

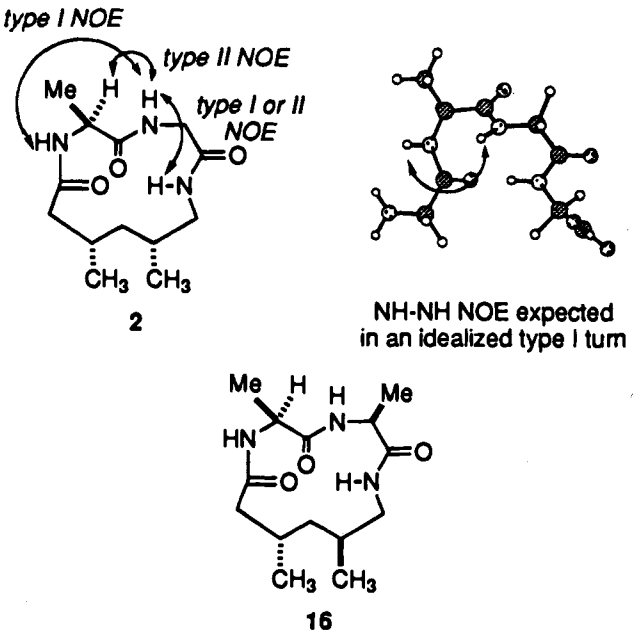


Figure 9. NOEs observed in compounds **2** and **16**. The Ala_{NH}-Gly_{NH} crosspeak expected in the NMR of a type I β-turn-containing dipeptide is shown in the idealized structure to the right.

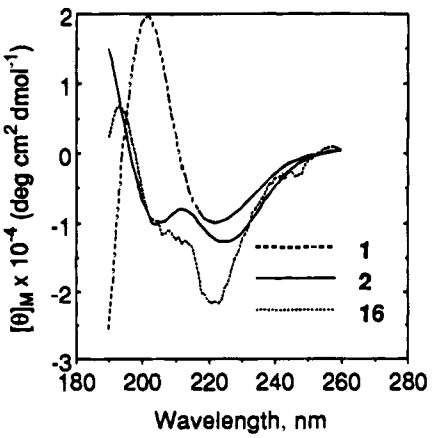
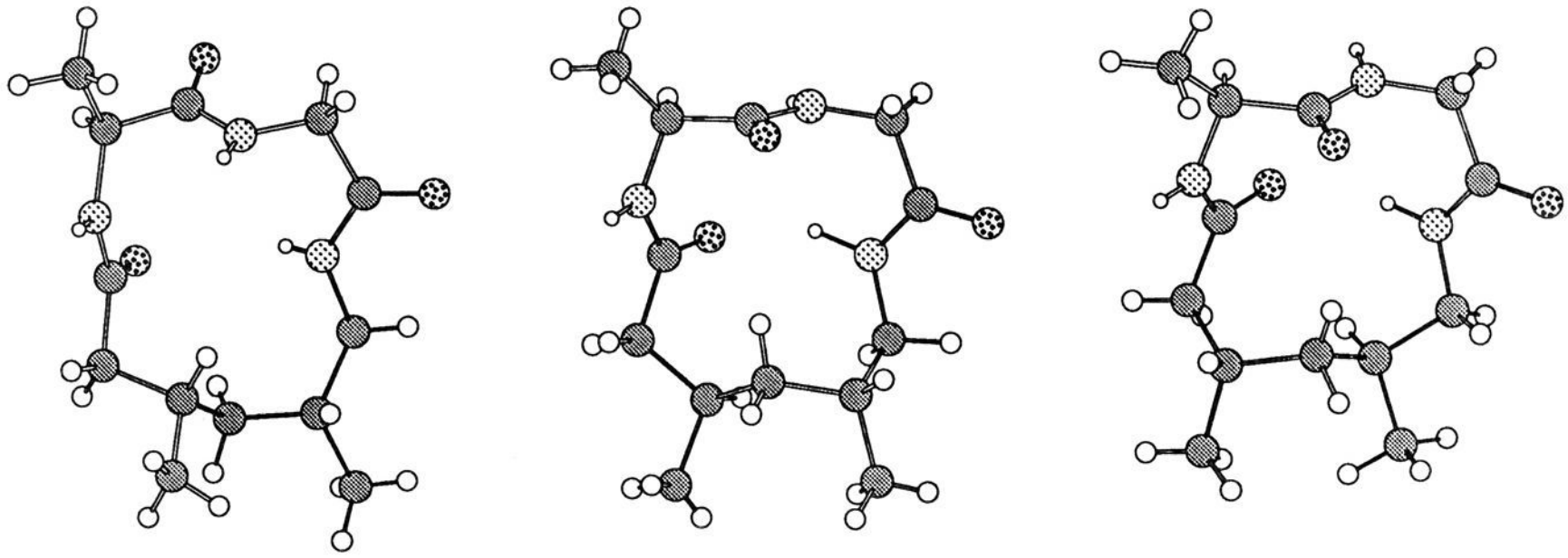


Figure 10. CD spectra of compounds **1**, **2**, and **16** in methanol.

(18) Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425−1436.



2 **4** **5**

Figure 11. Ball and stick representations of X-ray crystallographic data for compounds **2**, **4**, and **5**.

Table 3. Selected Dihedral Angles for **2**, **4** and **5** (deg)

	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}
type I[a]	−60	−30	−90	0
type II[a]	−60	120	80	0
2	−60.5	−42.8	−108.7	18.4
4	−73.3	108.6	84.7	8.3
5	−67.1	106.6	72.1	20.7

[a] Idealized values (ref 18).

Interestingly, the linker conformation proposed above was essentially corroborated by the structures of compounds **4** and **5**, with the C-4 (central) methylene of the substituted Aca moiety pointing into the macrocycle. In compound **2**, however, it is the C-3 methylene group that buckles inward while the C-4 group projects outward. Future work will hopefully elucidate whether this effect is directly related to the type I conformation observed in the crystal state for compound **2**.

Summary. The constraint of a dipeptide into various β-turn conformations by cyclizing it with a synthetic linker is a simple and potentially general approach to the problem of peptide mimicry. In addition, the ability of substituted linkers to affect the type of turn obtained in a single *i* + *2*/*i* + *3* dipeptide is novel and may be useful in fine-tuning a series of biologically active peptidomimetics. Finally, the observation of both type II and type I β-turns in the solid state is further validation of these compounds as β-turn models. We are currently investigating the synthesis and analysis of potentially bioactive β-turn mimics containing other dipeptides and linker units.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 Aspect 3000 (500 and 125.5 MHz, respectively), QE 300, or a Varian XL 300 (300 and 75.6 MHz, respectively) instrument. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual solvent as an internal reference. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. *Two-dimensional NMR:* All spectra were acquired at ambient temperature on a Bruker AM-500 operating at 500.14 MHz for protons. Peak assignments were made via phase-sensitive double quantum filtered COSY and either TPPI phase sensitive ROESY (t_{mix} 300 ms, nominal 4000 Hz spinlock field) or NOESY (t_{mix} 900 ms). Typical conditions for NOESY and ROESY were as follows: 5000 Hz sweep width, 300 t_1 increments with 48 scans and four dummy scans per increment, carrier frequency set at the position of the adventitious water signal with phase-coherent presaturation applied during a 2-s preacquisition delay. The data were transferred to a Silicon Graphics Indigo workstation and processed using Felix version 2.3.

X-ray crystallographic measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation and a 12KW rotating anode generator. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Low resolution mass spectra (EI, electron impact or CI, chemical ionization) were obtained using Ribermag R10−10 quadrupole instrument, and high resolution mass spectra (HRMS) were obtained using VG Analytical ZAB double focusing spectrometer. CD measurements were made on an Aviv 60DS spectrometer at ambient temperature. Optical rotations were taken on a Perkin-Elmer 241 polarimeter at ambient temperature; the concentrations are reported in g/dL. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out in-house.

Materials. Compound **1**[7] and lactams ent-**8**[15] and ent-**10**[16] were prepared as published previously. The sequence **6** → **7** → **8** was carried out using the published procedure (but substituting (*S*)-α-MBA for (*R*)-α-MBA) and produced **8**, which was spectroscopically identical to ent-**8** and had $[\alpha]_D$ +16.3 (c = 0.35, MeOH). THF was distilled from sodium benzophenone ketyl; other solvents were dried over molecular sieves before use. All other starting materials were purchased from Aldrich or Sigma and used as received.

(1′*R*,4*S*,6*S*)- and (1′*R*,4*R*,6*R*)-Hexahydro-4,6-dimethyl-1-(1′-phenylethyl)-2*H*-azepin-2-one. A solution of racemic *trans*-3,5-dimethyl cyclohexanone (5.05 g, 40 mmol) and (*R*)-α-MBA (5 g, 41.2 mmol) in toluene was refluxed for 5 h with azeotropic removal of water. The crude solution of imine was then cooled to room temperature and added through an addition funnel dropwise under nitrogen to a round-bottomed flask that contained a suspension of *m*-CPBA in toluene at −78 °C. After stirring for 1 h at −78 → −20 °C, the reaction mixture was quenched with $Na_2S_2O_3$. The reaction mixture was then poured into a separatory funnel and partitioned between saturated $Na_2S_2O_3$ and Et_2O. The ether layer was washed with saturated $NaHCO_3$ and H_2O and dried with $MgSO_4$. The crude product was purified by evaporation followed by flash column chromatography (hexane/EtOAc = 40:1 → 25:1) to afford 8.1 g of oxaziridine (83%). The oxaziridine (8.4 g, 34.3 mmol) was then dissolved in CH_2Cl_2 (680 mL) in a quartz tube. The solution was degassed with nitrogen for 1.5 h and then photolyzed in a RPR-100 chamber reactor (room temperature, 2537 Å) for 22 h. The solution was concentrated and the products were purified by flash column chromatography (hexane/EtOAc = 7:1 → 1:1) to give 2.72 g (32%) of (1′*R*,4*S*,6*S*)-hexahydro-4,6-dimethyl-1-(1′-phenylethyl)-2*H*-azepin-2-one (less polar) and 2.31 g (28%) of (1′*R*,4*R*,6*R*)-hexahydro-4,6-dimethyl-1-(1′-phenylethyl)-2*H*-azepin-2-one (more polar) as yellow oils. **(1′*R*,4*S*,6*S*)-isomer**: $[\alpha]_D$ +128.3 (c 0.23, CH_2Cl_2); IR (neat) 2940, 2900, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.36 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 1.68 (m, 1H), 1.80 (m, 1H), 2.12 (m, 1H), 2.53 (dd, J = 6.9, 13.5 Hz, 1H), 2.73−2.83 (m, 3H), 6.09 (q, J = 7.2 Hz, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 16.9, 18.5, 20.5, 27.0, 30.3, 43.4, 45.4, 50.7, 51.0, 127.5, 127.7, 128.8, 141.5, 173.9; MS (EI) *m/e* 246 (M^+ + 1), 245 (M^+), 230, 188, 154, 120, 105; HRMS calcd

for $C_{16}H_{23}NO$ 245.1776, found 245.1779. **(1′*R*,4*R*,6*R*)-isomer:** $[\alpha]_D$ +141.8 (*c* 0.17, CH_2Cl_2); IR (neat) 2940, 2905, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.54 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 1.08 (m, 1H), 1.29 (m, 1H), 1.44 (d, J = 7.1 Hz, 3H), 1.48 (m, 1H), 2.05 (m, 1H), 2.49 (dd, J = 6.9, 13.7 Hz, 1H), 2.71 (dd, J = 2.1, 13.7 Hz, 1H), 2.85−2.92 (m, 2H), 6.07 (q, J = 7.1 Hz, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.7, 18.5, 19.8, 26.6, 28.8, 43.5, 44.8, 49.5, 50.7, 127.4, 127.7, 128.2, 140.8, 173.4; MS (EI) *m/e* 246 (M^+ + 1), 245 (M^+), 230, 188, 154, 120, 105; HRMS calcd for $C_{16}H_{23}NO$ 245.1776; found 245.1779.

(4*S*,6*S*)-Hexahydro-4,6-dimethyl-2H-azepin-2-one (ent-9). Ammonia was condensed into a three-necked flask that was equipped with a dry ice condenser and contained (1′*R*,4*S*,6*S*)-hexahydro-4,6-dimethyl-1-(1′-phenylethyl)-2*H*-azepin-2-one (2.7 g, 11.0 mmol) dissolved in a minimum amount of Et_2O at −78 °C. After removal of the cold bath, small pieces of sodium metal were added to the reaction mixture until a deep blue color persisted for 30 min, at which time the reaction mixture was quenched with solid NH_4Cl, added in small portions. After removal of ammonia by heating to 40 °C, the reaction mixture was extracted with CH_2Cl_2 and dried with $MgSO_4$. The product was purified by flash column chromatography (EtOAc) to give 1.38 g (89%) of ent-**9** as white crystals: mp 85−86 °C; $[\alpha]_D$ +14.0 (*c* 0.2, CH_2Cl_2); IR (KBr) 3210, 2940, 2890, 1655, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.51−1.68 (m, 2H), 1.86−2.18 (m, 2H), 2.35 (dd, J = 11.7, 13.5 Hz, 1H), 2.47 (br d, J = 13.5 Hz, 1H), 2.98 (m, 1H), 3.21 (dd, J = 6.0, 14.4 Hz, 1H), 6.45 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.4, 21.2, 25.8, 30.5, 43.7, 45.8, 48.6, 177.9; MS (EI) *m/e* 142 (M^+ + 1), 141(M^+), 126, 112, 97, 70, 69, 42. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.80; H, 11.10; N, 10.21.

(4*R*,6*R*)-Hexahydro-4,6-dimethyl-2H-azepine-2-one (9). According to the procedure for ent-**9**, (1′*R*,4*R*,6*R*)-hexahydro-4,6-dimethyl-1-(1′-phenylethyl)-2*H*-azepin-2-one (2.3 g, 9.4 mmol) was reacted to obtain 1.08 g (81%) of **9** as white crystals: mp 86−87 °C; $[\alpha]_D$ −13.0 (*c* 0.2, CH_2Cl_2).

(*S*)-Hexahydro-4-methyl-2*H*-azepin-2-one (10). A toluene solution of racemic 3-methylcyclohexanone (4.5 g, 40.2 mmol) and (*S*)-α-MBA (5.1 g, 42.2 mmol) was refluxed with azeotropic removal of water for 4 h. The crude solution of imine was added dropwise to a toluene solution of *m*-CPBA (6.9 g, 44.2 mmol) at −78 °C. After stirring for 1 h at −78 °C → 0 °C, saturated $Na_2S_2O_4$ was added. The mixture solution was extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and H_2O and dried with $MgSO_4$. After evaporation of solvent, the crude product was purified by flash column chromatography (hexane/EtOAc = 80:1), affording (3*S*)-Me oxaziridine (less polar, 2.45 g, 26%) and a mixture (1:1, 3.27 g, 35%) of (3*S*)-Me and (3*R*)-Me oxaziridines (more polar). The (3*S*)-Me oxaziridine from above (2.5 g, 10.8 mmol) was dissolved in CH_2Cl_2 (250 mL) and placed in a quartz tube. The solution was degassed by bubbling nitrogen through it for 1.5 h and then photolyzed in a Rayonet RPR-100 chamber reactor (room temperature, 2537 Å) for 17 h. The solvent was evaporated, and the product was purified by flash column chromatography (hexane/EtOAc = 7:1) to afford 1.3 g of lactam (52%). Ammonia was condensed in a three-necked flask that was equipped with a dry ice condenser and contained the lactam (1.3 g, 5.6 mmol) dissolved in a minimum amount of THF at −78 °C. After removal of the cold bath, small pieces of sodium metal were added to the reaction mixture until a deep blue color persisted for 30 min, whereupon it was quenched with solid NH_4Cl, added in small portions. After removal of NH_3, the reaction mixture was extracted with CH_2Cl_2 and dried with $MgSO_4$. The product was purified by flash column chromatography (EtOAc/MeOH = 200:1 to afford 0.62 g of **10** (87%), which was spectroscopically equivalent to ent-**10**[16] and had $[\alpha]_D$ = +33.1 (*c* 0.26, H_2O).

(3*R*,5*S*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic Acid Methyl Ester (11b). A solution of ent-**8** (200 mg, 1.42 mmol) in concentrated HCl (2 mL) and H_2O (6 mL) was maintained at gentle reflux for 5 h. The solvent was removed under reduced pressure to afford crude carboxylic acid (not characterized). Thionyl chloride (1 mL) was added to MeOH (4 mL) at 0 °C and stirred for 20 min. To this solution at 0 °C was added carboxylic acid (crude from above) in MeOH (4 mL), and the mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure to afford (3*R*,5*S*)-3,5-dimethyl-6-aminohexanoic acid methyl ester hydrochloride: ^1H NMR (300 MHz, CD_3OD) δ 0.94 (d, J = 5.7 Hz, 3H), 0.99 (d, J = 5.7 Hz, 3H), 1.13 (m, 1H), 1.34 (m, 1H), 1.82−2.18 (m, 3H), 2.34 (m, 1H), 2.68 (m, 1H), 2.91 (m, 1H), 3.63 (s, 3H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 17.0, 19.8, 27.7, 29.4, 40.7, 41.4, 45.5, 51.3, 174.2.

The crude methyl ester from above, Boc-Ala-Gly-OH (420 mg, 1.7 mmol), and diethyl cyanophosphonate (0.23 mL, 1.56 mmol) were dissolved in 5 mL of DMF. To this solution was added triethylamine (0.45 mL, 3.12 mmol), and then the reaction mixture was stirred for 5 h. EtOAc (200 mL) was added, and the solution was washed with 25 mL of saturated $NaHCO_3$, 25 mL of 10% aqueous citric acid, and 25 mL of H_2O. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc) to give 444 mg (75%) of **11b** as white crystals: mp 104 °C; $[\alpha]_D$ +12.8 (*c* 0.125, CH_2Cl_2); IR (KBr) 3325, 3270, 2965, 2915, 1725, 1680, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.02 (m, 1H), 1.34 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.75 (m, 1H), 2.01 (m, 1H), 2.15 (dd, J = 6.9, 15.3 Hz, 1H), 2.27 (dd, J = 6.9, 15.3 Hz, 1H), 3.15 (m, 2H), 3.68 (s, 3H), 3.90 (dd, J = 5.4, 16.5 Hz, 1H), 4.03 (dd, J = 6.0, 16.5 Hz, 1H), 4.14 (dq, J = 6.9, 6.9 Hz, 1H), 5.14 (d, J = 6.3 Hz, 1H), 6.80 (br s, 1H), 6.96 (t, J = 6.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.5, 18.8, 20.7, 28.2, 28.7, 31.0, 41.5, 41.9, 43.6, 45.3, 51.1, 51.9, 80.5, 156.1, 169.5, 173.9, 174.3; MS (EI) *m/e* 402 (M^+ + 1), 401 (M^+), 346, 345, 328, 327, 296, 59. Anal. Calcd for $C_{19}H_{35}N_3O_6$: C, 56.84; H, 8.79; N, 10.47. Found: C, 56.82; H, 9.09; N, 10.10.

(3*R*,5*S*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic Acid (12b). NaOH (0.5 N, 3 mL) was added to the dioxane solution (3 mL) of **11b** (429 mg, 1.07 mmol) at room temperature. After stirring 3 h at room temperature, the reaction mixture was acidified carefully with 2 N HCl to pH 2 at 0 °C. The solution was extracted with EtOAc and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 20:1) to give 251 mg (60%) of **12b** as white crystals. ^1H NMR (300 MHz, CD_3OD) δ 0.89 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.0 Hz, 3H), 1.04 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H), 1.25−1.4 (m, 1H), 1.78 (m, 1H), 1.95−2.10 (m, 2H), 2.29 (m, 1H), 2.95−3.15 (m, 2H), 3.83 (AB q, J = 16.8 Hz, $\Delta\nu$ = 17.6 Hz, 2H), 3.98 (q, J = 7.2 Hz, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 16.9, 17.8, 20.0, 28.0, 28.0, 31.0, 41.3, 42.0, 42.7, 45.4, 51.3, 80.0, 157.1, 170.6, 175.5, 176.1.

(2*S*,9*S*,11*R*)-2,9,11-Trimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (3). **12b** (240 mg, 0.62 mmol) was dissolved in CH_2Cl_2 (3 mL) and trifluoroacetic acid (3 mL), and the solution was stirred for 2 h at room temperature. The solution was then evaporated in vacuo. The crude product from above was dissolved in DMF (140 mL), and $NaHCO_3$ (254 mg, 3.1 mmol) was added. To the reaction mixture was added diethyl cyanophosphonate (0.48 mL, 3.1 mmol). After stirring overnight, DMF was evaporated carefully in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 25:1 to give 105 mg (63%) of **3** as white crystals: mp 303 °C dec; $[\alpha]_D$ +29.6 (*c* 0.23, MeOH); IR (KBr) 3280, 3040, 2940, 2920, 1630−1655 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.67 (m, 1H), 0.71 (d, J = 6.8 Hz, 3H), 1.06 (dd, J = 11.7, 13.7 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H), 1.61 (m, 1H), 1.90−2.10 (m, 3H), 2.78 (m, 1H), 3.29 (dd, J = 5.2, 16.7 Hz, 1H), 3.38 (m, 1H), 3.79 (dd, J = 7.0, 16.7 Hz, 1H), 4.25 (dq, J = 6.7, 7.0 Hz, 1H), 6.83 (br d, J = 5.7 Hz, 1H), 8.67 (d, J = 6.7 Hz, 1H), 8.72 (dd, J = 5.2, 7.0 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.1, 20.5, 21.2, 28.8, 31.7, 38.5, 40.5, 42.9, 43.1, 49.2, 168.5, 172.6, 175.0; MS (CI) *m/e* 270 (M^+ + 1), 269 (M^+), 241, 239, 211, 140, 73, 69, 44; HRMS calcd for $C_{13}H_{24}N_3O_3$ 270.1818; found 270.1810.

The syntheses of the other cyclic peptides followed the same experimental procedures reported for the series above, except where noted. See Table 1 for starting materials and yields. Spectral data are given below.

(3*S*,5*R*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid methyl ester (11a): mp 99 °C; $[\alpha]_D$ −5.8 (*c* 0.172, CH_2Cl_2); IR (KBr) 3320, 2955, 2920, 1717, 1670, 1653, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 0.95 (d, J =

6.6 Hz, 3H), 1.02 (m, 1H), 1.30 (m, 1H), 1.37 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.74 (m, 1H), 2.03 (m, 1H), 2.12 (dd, J = 7.2, 14.7 Hz, 1H), 2.28 (dd, J = 6.0, 14.7 Hz, 1H), 2.97 (m, 1H), 3.30 (m, 1H), 3.67 (s, 3H), 3.96 (AB of ABX pattern, 2H), 4.16 (m, 1H), 5.51 (d, J = 6.9 Hz, 1H), 7.06 (t, J = 5.4 Hz, 1H), 7.36 (t, J = 5.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.5, 18.8, 20.8, 28.2, 28.7, 31.1, 41.5, 41.8, 43.6, 45.3, 51.1, 51.9, 80.6, 156.1, 169.5, 173.9, 174.3; MS (EI) *m/e* 402 (M^+ + 1), 401 (M^+), 346, 345, 328, 327, 296, 59. Anal. Calcd for $C_{19}H_{35}N_3O_6$: C, 56.84; H, 8.79; N, 10.47. Found: C, 56.50; H, 9.10; N, 10.20.

(3*S*,5*R*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid (12a): ^{1}H NMR (300 MHz, CD_3OD) δ 0.65 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.3 Hz, 3H), 0.78 (m, 1H), 1.06 (d, J = 7.2 Hz, 3H), 1.01−1.11 (m, 1H), 1.19 (s, 9H), 1.53 (m, 1H), 1.70−1.85 (m, 2H), 2.07 (dd, J = 9.6, 18.6 Hz, 1H), 2.64 (dd, J = 7.5, 12.6 Hz, 1H), 3.00 (dd, J = 5.5, 12.6 Hz, 1H), 3.55 (d, J = 16.8 Hz, 1H), 3.57 (AB q, J = 16.8 Hz, Δν = 15.9 Hz, 1H), 3.73 (q, J = 7.2 Hz, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 16.7, 17.6, 19.9, 27.8, 27.9, 30.9, 41.2, 41.9, 42.6, 45.4, 51.3, 79.8, 157.2, 170.7, 175.6, 176.1.

(2*S*,9*R*,11*S*)-2,9,11-Trimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (2). This peptide was purified by washing with water followed by CH_2Cl_2: mp 305 °C dec; $[\alpha]_D$ −83.8 (*c* 0.105, MeOH); IR (KBr) 3280, 3060, 2940, 2920, 1640−1660 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75 (m, 1H), 0.81 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 5.3 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.52−1.78 (m, 4H), 2.23 (m, 1H), 2.88 (m, 1H), 3.02 (m, 1H), 3.40-3.50 (obscured, 1H), 3.75 (dd, J = 6.9, 15.8 Hz, 1H), 4.20 (m, 1H), 6.55 (br s, 1H), 8.16 (m, 1H), 8.41 (m, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.7, 20.1, 21.5, 30.3, 31.0, 38.7, 42.6, 43.0, 43.1, 48.6, 169.0, 172.1, 172.8; MS (CI) *m/e* 270 (M^+ + 1), 269 (M^+), 241, 239, 140, 69, 44. Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61; N, 15.60. Found: C, 57.59; H, 9.00; N, 15.25.

(3*R*,5*R*)-3,5-Dimethyl-6-aminohexanoic acid methyl ester hydrochloride: ^{1}H NMR (300 MHz, CD_3OD) δ 0.91 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H), 1.13−1.30 (m, 2H), 1.95 (m, 1H), 2.03 (m, 1H), 2.24 (AB of ABX pattern, 2H), 2.73 (m, 1H), 2.86 (m, 1H), 3.63 (s, 3H).

(3*R*,5*R*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid methyl ester (11c): mp 85−87 °C; $[\alpha]_D$ +14.8 (*c* 0.21, CH_2Cl_2); IR (KBr) 3320, 3270, 2960, 2920, 1733, 1670, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H), 1.04−1.27 (m, 2H), 1.37 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.76 (m, 1H), 2.06 (m, 1H), 2.13 (m, 1H), 2.31 (m, 1H), 2.97 (m, 1H), 3.22 (m, 1H), 3.67 (s, 3H), 3.97 (AB of ABX pattern, 2H), 4.13 (m, 1H), 5.48 (br d, 1H), 7.07 (br t, J = 5.1 Hz, 1H), 7.40 (br t, J = 5.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.8, 18.5, 19.8, 28.1, 28.7, 31.1, 42.0, 42.5, 43.8, 46.4, 51.2, 51.5, 80.6, 156.0, 169.3, 173.7, 173.8; MS (FAB) *m/e* 402 (M^+ + 1), 401(M^+), 386, 346, 310, 302, 231, 174, 142. Anal. Calcd for $C_{19}H_{35}N_3O_3$: C, 56.84; H, 8.79; N, 10.47. Found: C, 56.45; H, 9.18; N, 10.68.

(3*R*,5*R*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid (12c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.14−1.26 (m, 2H), 1.37 (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.79 (m, 1H), 2.07 (m, 1H), 2.20 (dd, J = 6.6, 15.0 Hz, 1H), 2.28 (dd, J = 7.2, 15.0 Hz, 1H), 3.04 (m, 1H), 3.22 (m, 1H), 3.96 (AB of ABX pattern, 2H), 4.16 (m, 1H), 5.35 (br d, 1H), 7.07 (br t, 1H), 7.33 (br t, 1H).

(2*S*,9*R*,11*R*)-2,9,11-Trimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (4): mp 263 °C dec; $[\alpha]_D$ +18.6 (*c* 0.21, MeOH); IR (KBr) 3275, 3030, 2920, 1663, 1635 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (d, J = 7.1 Hz, 3H), 0.85−0.95 (m, 1H), 0.93 (d, J = 6 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.27 (dd, J = 3.5, 14.5 Hz, 1H), 1.68 (m, 1H), 1.96−2.07 (m, 3H), 2.44 (m, 1H), 3.30−3.39 (m, 2H), 3.73 (dd, J = 7.2, 16.5 Hz, 1H), 4.24 (m, 1H), 7.36 (dd, J = 3.5, 8.3 Hz, 1H), 8.72 (d, J = 7.0 Hz, 1H), 8.79 (t, J = 6.4 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.3, 17.9, 23.9, 25.3, 31.9, 35.2, 42.1, 43.3, 43.9, 49.7, 168.7, 173.6, 175.4; MS (EI) *m/e* 270 (M^+ + 1), 269 (M^+), 241, 239, 211, 168, 140, 69. Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61; N, 15.60. Found: C, 57.57; H, 9.00; N, 15.80.

(3*S*,5*S*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid methyl ester (11d): mp 101 °C; $[\alpha]_D$ −15.0 (*c* 0.22, CH_2Cl_2); IR (KBr) 3325, 3290, 2965, 2920, 1730, 1685, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H), 1.06−1.25 (m, 2H), 1.38 (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.75 (m, 1H), 1.98−2/32 (m, 3H), 3.00−3.20 (m, 2H), 3.66 (s, 3H), 3.94 (AB of ABX pattern, 2H), 4.14 (m, 1H), 5.38 (br d, 1H), 6.95 (br t, 1H), 7.28 (br t, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.8, 18.5, 19.8, 28.1, 28.7, 31.1, 42.0, 42.5, 43.8, 46.4, 51.2, 51.6, 80.6, 156.1, 169.3, 173.9; MS (FAB) *m/e* 402 (M^+ + 1), 401 (M^+), 386, 346, 302, 231, 174, 142. Anal. Calcd for $C_{19}H_{35}N_3O_6$: C, 56.84; H, 8.79; N, 10.47. Found: C, 56.42; H, 8.99; N, 10.63

(3*S*,5*S*)-3,5-Dimethyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]-aminohexanoic acid (12d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H), 1.10−1.19 (m, 2H), 1.32 (d, J = 7.2 Hz, 3H), 1.39 (s, 9H), 1.73 (m, 1H), 2.02 (m, 1H), 2.12 (dd, J = 6.9, 15.0 Hz, 1H), 2.23 (dd, J = 6.6, 15.0 Hz, 1H), 3.00 (m, 1H), 3.11 (m, 1H), 3.93 (AB of ABX pattern, 2H), 4.13 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.0, 18.5, 20.2, 27.8, 28.7, 31.0, 41.6, 42.4, 43.6, 46.3, 51.2, 80.9, 156.3, 169.6, 174.3, 176.8.

(2*S*,9*S*,11*S*)-2,9,11-Trimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (5): mp 257 °C dec; $[\alpha]_D$ −36 (*c* 0.2, MeOH); IR (KBr) 3345, 3280, 2940, 1660, 1633 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.07 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 1.24 (m, 1H), 1.84 (dd, J = 11.5, 12.6 Hz, 1H), 1.95 (m, 1H), 2.09 (m, 1H), 2.27 (dd, J = 4.6, 12.6 Hz, 1H), 2.72 (m, 1H), 2.90 (br d, J = 12.6 Hz, 1H), 3.32 (obscured, 1H), 3.78 (dd, J = 7.3, 16.0 Hz, 1H), 4.05 (m, 1H), 6.99 (br s, 1H), 8.50 (br t, J = 5.8 Hz, 1H), 8.53 (br d, J = 5.8 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.2, 19.4, 22.6, 27.6, 28.1, 35.8, 42.9, 43.4, 44.7, 49.2, 168.9, 172.2, 173.8; MS (EI) *m/e* 270 (M^+ + 1), 269 (M^+), 241, 239, 211, 168, 140, 69, 44; HRMS calcd for $C_{13}H_{23}N_3O_3$: 269.1748; found 269.1739.

(3*S*)-3-Methyl-6-aminohexanoic acid methyl ester hydrochloride: ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (d, J = 6.3 Hz, 2H), 1.28 (m, 1H), 1.39 (m, 1H), 1.58−1.68 (m, 2H), 1.93 (m, 1H), 2.15 (dd, J = 7.5, 15.0 Hz, 1H), 2.33 (dd, J = 5.7, 15.0 Hz, 1H), 2.90 (br t, 2H), 3.63 (s, 3H).

(3*S*)-3-Methyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]aminohexanoic acid methyl ester (11e): mp 70−72 °C; $[\alpha]_D$ −10.6 (*c* 0.18, CH_2Cl_2); IR (KBr) 3280, 2960, 2915, 1727, 1680, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 1.12−1.68 (m, 4H), 1.39 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.96 (m, 1H), 2.15 (dd, J = 7.5, 15 Hz, 1H), 2.28 (dd, J = 6.6, 15 Hz, 1H), 3.15 (m, 1H), 3.32 (m, 1H), 3.67 (s, 3H), 3.94 (AB of ABX pattern, 2H), 4.10 (m, 1H), 5.15 (d, J = 6.0 Hz, 1H), 6.77 (br s, 1H), 6.92 (br t, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.4, 19.9, 27.1, 28.7, 30.3, 34.0, 39.9, 41.7, 43.6, 51.2, 51.6, 80.5, 156.1, 169.2, 173.8 (2C); MS (EI) *m/e* 388 (M^+ + 1), 387 (M^+), 332, 331, 314, 286, 128, 44. Anal. Calcd for $C_{18}H_{33}N_3O_6$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.80; H, 8.91; N, 10.59.

(3*S*)-3-Methyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]aminohexanoic acid (12e): ^{1}H NMR (300 MHz, $CDCl_3$ + 3 drops of DMSO-d_6) δ 0.95 (d, J = 6.6 Hz, 3H), 1.12−1.16 (m, 4H), 1.36 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.89−2.30 (m, 3H), 3.12 (m, 1H), 3.30 (m, 1H), 3.91 (AB of ABX pattern, 2H), 4.13 (m, 1H), 5.61 (br d, 1H), 7.09 (br s, 1H), 7.42 (br t, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 15.2, 17.6, 25.3, 26.3, 28.7, 32.4, 38.1, 40.0, 41.2, 49.9, 78.4, 155.7, 169.0, 174.0, 174.3.

(2*S*,11*S*)-2,11-Dimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (13): mp 316 °C dec; $[\alpha]_D$ −24.0 (*c* 0.1, MeOH); IR (KBr) 3405, 3280, 2925, 1640, 1630 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (d, J = 6.7 Hz, 3H), 1.05 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.27−1.33 (m, 2H), 1.58 (m, 1H), 1.72 (dd, J = 11.0, 12.6 Hz, 1H), 1.89 (m, 1H), 2.32 (dd, J = 4.8, 12.6 Hz, 1H), 2.97−3.08 (m, 2H), 3.35 (dd, J = 5.4, 15.6 Hz, 1H), 3.76 (dd, J = 7.1, 15.6 Hz, 1H), 4.21 (m, 1H), 6.77 (br t, J = 4.8 Hz, 1H), 8.36 (d, J = 7.1 Hz, 1H), 8.40 (br t, J = 6.1 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.5, 20.5, 22.8, 28.9, 30.0, 37.4, 42.6, 43.6, 48.7, 169.3, 172.4, 173.2; MS (EI) *m/e* 256 (M^+ + 1), 255 (M^+), 227, 198, 197, 154, 140, 69, 44.

(3*R*)-3-Methyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]aminohexanoic Acid Methyl Ester (11f). To mixture of Boc-Ala-Gly-OH (747 mg, 3.03 mmol), (3*R*)-3-methyl-6-aminohexanoic acid methyl ester hydrochloride, and triethylamine (0.46 mL, 3.31 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC·HCl, 580 mg, 3.03 mol). The reaction mixture was stirred at room temperature overnight. The solvent was concentrated in vacuo,

and the residue was partitioned between EtOAc and water. The organic layer was washed with 40 mL of 10% aqueous citric acid, 40 mL of saturated $NaHCO_3$, and 40 mL of water. The organic layer was dried with $MgSO_4$ and evaporated. The product was purified by flash column chromatography (EtOAc) to give 910 mg (85%) of **11f** as white crystals: mp 94 °C; $[\alpha]_D$ +8.5 (*c* 0.46, CH_2Cl_2); IR (KBr) 3335, 2970, 2940, 1738, 1678, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 1.14−1.62 (m, 4H), 1.39 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.95 (m, 1H), 2.15 (dd, J = 7.5, 14.7 Hz, 1H), 2.28 (dd, J = 6.6, 14.7 Hz, 1H), 3.13−3.36 (m, 2H), 3.68 (s, 3H), 3.94 (AB of ABX pattern, 2H), 4.09 (m, 1H), 5.02 (d, J = 6.3 Hz, 1H), 6.63 (br s, 1H), 6.77 (br t, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.4, 20.0, 27.0, 28.7, 30.3, 34.0, 39.9, 41.7, 43.5, 51.2, 51.8, 80.6, 156.2, 169.3, 173.9, 174.0; MS (EI) *m/e* 388 (M^+ + 1), 387 (M^+), 332, 331, 314, 128, 44. Anal. Calcd for $C_{18}H_{33}N_3O_6$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.40; H, 8.80; N, 10.60.

(3*R*)-3-Methyl-6-[*N*-(*tert*-butoxycarbonyl)-L-alanyl-glycyl]aminohexanoic acid (12f): ^1H NMR (300 MHz, $CDCl_3$ + 6 drops of DMSO-d_6) δ 0.95 (d, J = 6.6 Hz, 3H), 1.12−1.63 (m, 4H), 1.34 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.95 (m, 1H), 2.09 (dd, J = 7.5, 14.7 Hz, 1H), 2.25 (dd, J = 6.3, 14.7 Hz, 1H), 3.05−3.30 (m, 2H), 3.80 (dd, J = 5.4, 16.8 Hz, 1H), 3.95 (dd, J = 6.3, 16.8 Hz, 1H), 4.09 (m, 1H), 5.93 (d, J = 6.9 Hz, 1H), 7.24 (br t, 1H), 7.63 (br t, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 16.6, 19.1, 26.8, 27.8, 30.2, 33.9, 39.6, 41.5, 42.6, 51.4, 79.9, 157.2, 170.5, 175.6, 175.9.

(2*S*,11*R*)-2,11-Dimethyl-1,4,7-triazacyclotridecan-3,6,9-trione (14): mp >310 °C; $[\alpha]_D$ +39.5 (*c* 0.105, MeOH); IR (KBr) 3280, 3080, 2940, 2920, 2860, 1660, 1635 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.85 (m, 1H), 0.88 (d, J = 5.3 Hz, 3H), 1.13−1.27 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 1.41 (m, 1H), 1.94−2.08 (m, 3H), 2.74 (m, 1H), 3.32 (dd, J = 5.4, 16.0 Hz, 1H), 3.45 (m, 1H), 3.77 (dd, J = 7.3, 16.0 Hz, 1H), 4.30 (m, 1H), 7.05 (dd, J = 4.4, 7.9 Hz, 1H), 8.63 (d, J = 7.0 Hz, 1H), 8.71 (dd, J = 5.4, 7.3 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.2, 20.3, 24.5, 28.2, 29.2, 35.4, 42.6, 43.3, 48.9, 168.5, 172.9, 174.8; MS (EI) *m/e* 256 (M^+ + 1), 255 (M^+), 227, 198, 197, 154, 140, 69, 44.

(3*R*)-3-Methyl-6-[*N*-(*tert*-butoxycarbonyl)-glycyl-glycyl]aminohexanoic acid methyl ester (11g): mp 78 °C; $[\alpha]_D$ +7 (*c* 0.5, CH_2Cl_2); IR (neat) 3300, 3100, 2910, 1738, 1676, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 1.14−1.16 (m, 3H), 1.45 (s, 9H), 1.46−1.60 (m, 1H), 1.93 (m, 1H), 2.15 (dd, J = 7.5, 14.7 Hz, 1H), 2.28 (dd, J = 6.6, 15 Hz, 1H), 3.20 (m, 2H), 3.66 (s, 3H), 3.82 (br d, J = 5.4 Hz, 2H), 3.94 (br d, J = 5.4 Hz, 2H), 5.38 (br s, 1H), 6.6 (br s, 1H), 7.0 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.7, 28.7, 30.4, 32.0, 35.7, 41.6, 43.4, 45.1, 46.4, 53.5, 80.6, 158.2, 171.1, 172.6, 175.8; MS (EI) *m/e* 374 (M^+ + 1). Anal. Calcd for $C_{17}H_{31}N_3O_6$: C, 54.67; H, 8.36; N, 11.25. Found: C, 54.40; H, 8.66; N, 10.96.

(3*R*)-3-Methyl-6-[*N*-*tert*-butoxycarbonyl)-glycyl-glycyl]aminohexanoic acid (12g): mp 145 °C; ^1H NMR (300 MHz, CD_3OD) δ 0.93 (d, J = 6.3 Hz, 3H), 1.10−1.40 (m, 3H), 1.43 (s, 9H), 1.48 (m, 1H), 1.90 (m, 1H), 2.06 (dd, J = 7.8, 14.7 Hz, 1H), 2.25 (dd, J = 5.7, 14.7 Hz, 1H), 3.16 (t, J = 6.9 Hz, 2H) 3.67 (m, 2H), 3.75 (m, 2H); ^{13}C NMR (75.4 MHz, CDCl3) δ 19.1, 26.8, 27.8, 30.1, 33.8, 39.6, 39.7, 41.5, 42.5, 53.9, 80.0, 158.1, 171.1, 172.1, 176.0.

(11*R*)-11-Methyl-1,4,7-triazacyclotridecan-3,6,9-trione (15): 260 °C dec; $[\alpha]_D$ +34 (*c* 0.1); IR (KBr) 3300, 3060, 2940, 1640, 1630, 1540 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.88 (obscured, 1H), 0.89 (d, J = 6.7 Hz, 3H), 1.22−1.26 (m, 2H), 1.45 (m, 1H), 1.88−1.90 (m, 2H), 2.10 (dd, J = 3.1, 12.3 Hz, 1H), 2.80 (m, 1H), 3.30 (m, 2H), 3.45 (dd, J = 5.8, 15.9 Hz, 1H), 3.65 (dd, J = 9.3, 15.9 Hz, 1H), 3.86 (dd, J = 6.6, 13,4 Hz, 1H), 7.02 (br t, J = 6.8 = 7.1 Hz, 3H), 8.61 (t, 6.1 Hz, 1H), 8.87 (t, 6.0 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 20.2, 24.2, 28.7, 29.08, 35.8, 42.5, 43.4, 43.8, 168.5, 169.9, 174.9; MS (EI) *m/e* 241 (M^+ + 1). Anal. Calcd for $C_{11}H_{19}N_3O_3$): C, 54.75; H, 7.93: N, 17.41. Found: C, 54.46; H, 8.01; N, 17.18.

(3*R*,5*R*)-3,5-Dimethyl-6-[*N*-*tert*-butoxycarbonyl)-L-alanyl-L-alanyl]aminohexanoic acid methyl ester (11h): mp 154 °C; $[\alpha]_D$ −20 (*c* 0.35, CH_2Cl_2); IR (KBr) 3300, 3200, 2930, 1670, 1630 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 1.07−1.18 (m, 2H), 1.36 (d, J = 7.2 Hz, 3H), 1.38 (d, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.72 (m, 1H), 2.12 (m, 1H), 2.14, (dd, J = 7.7, 14.9 Hz, 1H), 2.25 (dd, J = 6.3, 14.8 Hz), 2.29 (m, J = 6.1 Hz, 1H), 3.17 (m, J = 6.1 Hz, 1H), 3.65 (s, 3H), 4.12 (dd, J = 7.0, 14.1 Hz, 1H), 4.44 (m, J = 7.1 Hz, 1H), 4.99 (m, 1H), 6.55 (m, 1H), 6.68 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 17.1, 18.0, 19.2, 27.5, 28.2, 30.0, 30.6, 41.3, 42.2, 45.9, 48.9, 50.6, 51.3, 80.5, 155.7, 171.8, 172.4, 173.5; MS (EI) *m/e* 415 (M^+).

(3*R*,5*R*)-3,5-Dimethyl-6-[*N*-*tert*-butoxycarbonyl)-L-alanyl-L-alanyl]aminohexanoic acid (12h): ^1H NMR (500 MHz, CD_3OD) δ 0.89 (d, J = 6.2 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.11−1.21 (m, 2H), 1.31 (d, J = 7.1 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.45 (s, 9H), 1.77 (m, 1H), 2.01 (m, 1H), 2.11 (dd, J = 7.7, 14.7, 1H), 2.24 (dd, J = 6.2, 14.8, 1H), 3.12 (dd, J = 6.1, 13.1 Hz, 1H), 4.11 (dd, J = 7.1, 14.3 Hz, 1H), 4.35 (m, 1H), 6.89 (m, 1H), 7.87 (m, 1H), 8.02 (m, 1H); ^{13}C NMR (125.7 MHz, CD_3OD) δ 17.7, 18.1, 18.3, 19.7, 28.8, 28.9, 32.0, 42.6, 43.4, 47.0, 80.9, 58.1, 175.0, 175.8, 176.9.

(2*S*,5*S*,9*R*,11*R*)-2,5,9,11-Tetramethyl-1,4,7-triazacyclotridecan-3,6,9-trione (16): mp 300 °C dec; $[\alpha]_D$ −71 (*c* 0.1, MeOH); IR (KBr); 3280, 3040, 2940, 2920, 1630, 1655 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.80 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 8.7 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.32 (dd, J = 6.8, 14.1 Hz, 1H), 1.74 (m 1H), 1.90−2.10 (m, 3H), 2.49 (m, 2H), 3.52 (m, 1H), 4.11 (m, 1H), 4.37 (m, 1H), 7.36 (m, 1H), 7.87, d, J = 8.4 Hz, 1H), 8.29 (d, J = 6.2 Hz, 1H), ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 16.1, 17.2, 22.0, 25.8, 30.5, 35.7, 43.1, 43.9, 48.1, 50.9, 171.1, 172.5, 173.4; MS (EI) *m/e* 283 (M^+).

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Supplementary Material Available: ORTEP diagrams and tables of crystal parameters, positional and thermal parameters, intramolecular distances, bond angles, and torsional angles for compounds **2**, **4**, and **5** (39 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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