Effect of Progressive Benzyl Substitution on the Conformations of Aminocaproic Acid-Cyclized Dipeptides

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Received August 30, 2000

The constraint of dipeptides into a β-turn conformation can be accomplished by linking the two ends of a standard dipeptide with a linker derived from aminocaproic acid (Aca). To elucidate the possibility of using substituted Aca linkers in peptidomimetic design, a series of five macrocycles composed of a monobenzylated Aca linker (containing the benzyl group on each of the five methylene groups of the parent linker) and Gly-Gly were synthesized. The requisite linkers were made by regiochemically controlled ring expansion techniques (for substitution on Aca positions C-3, C-4, or C-5), an Evans alkylation route (for C-2), or by chain extension of L-phenylalanal (for C-6). The solution-phase conformations of the macrocycles were examined by NMR and CD techniques; in addition, crystal structures of the C-4- and C-6-benzyl-substituted linkers were obtained. Four out of the five macrocycles were found to exist with the dipeptide portion taking up either a type II or II′ β-turn conformation, but the Gly-Gly unit in the compound derived from 4-benzyl-Aca did not correspond to one of the standard β-turn types.

Introduction

Understanding the bound conformations of bioactive peptides is an important goal of rational drug design. Because peptides, per se, can be difficult to develop as drugs, the use of peptidomimetics has greatly expanded in recent years. Besides ameliorating the problems of poor oral bioavailability and proteolytic degradation, such molecules are often designed to bias the structure toward the active conformation, thus increasing its affinity to the target. Peptidomimetics based on β-turns[1] are important because numerous peptides require such a conformation to produce a biological response.[2−6] Many turn replacements consist of rigid heterocyclic units that are incorporated into a polypeptide chain in place of the central dipeptide of the reported turn.[7] An alternative method of mimicry constrains the dipeptide in question with a tether, often incorporating heteroatoms[8,9] or aromatic groups[10,11] into the carbon chain. Some tethers are attached to resins to allow for solid-phase syntheses which permit the development of β-turn-inspired peptidomimetic libraries.[12−16]

Woody, Scheraga, and co-workers first described the use of 6-aminocaproic acid (Aca) as a linker to constrain L-alanylglycine into a β-turn (e.g., see compound **1a** for an example).[17−20] Conformational analysis of these compounds were carried out using molecular mechanics, nuclear magnetic resonance (NMR), circular dichroism (CD), and infrared (IR) spectroscopies. In this work, they found that the amino acid stereochemistry had a profound influence on the subtype of β-turn adopted by these macrocycles. In general, macrocycles derived from L,L-dipeptides preferred a type I turn conformation, whereas L,D-dipeptides took up a type II solution structure.

Earlier work in this laboratory has focused on the effect of substitution within the Aca tether on the conforma-

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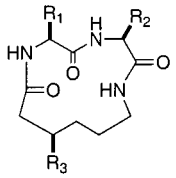
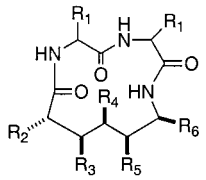
Published on Web 03/29/2001



1a: R_1=CH_3, R_2=R_3=H
1b: R_1=R_2=H, R_3=CH_3

cyclo(L-Ala-Gly-Aca) (**1a**) and
cyclo(Gly-Gly-(3*R*)-methyl-Aca) (**1b**)



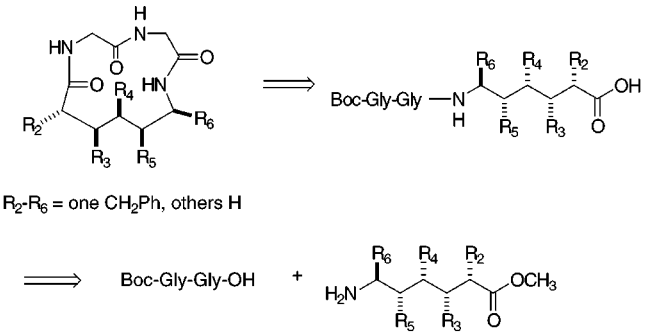
2: R_2 = CH_2Ph
3: R_3 = CH_2Ph
4: R_4 = CH_2Ph
5: R_5 = CH_2Ph
6: R_6 = CH_2Ph

R groups not designated as an alkyl group are H.

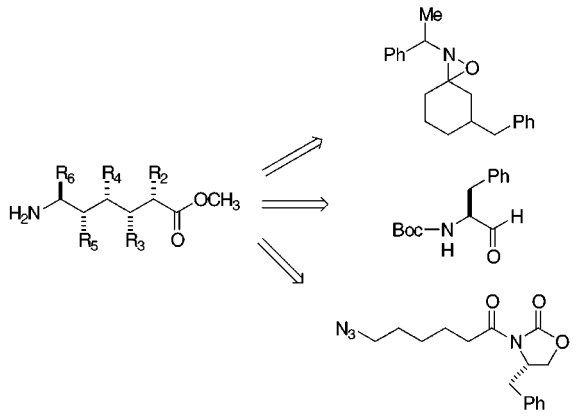
tional preference of similar macrocycles.[21] Compounds consisting of L-alanylglycine cyclized with various diastereomers of 3,5-dimethyl-Aca were synthesized. In addition to exhibiting the general dependence of conformation on dipeptide stereochemistry expected from the Woody/Scheraga results, the methyl group configurations also influenced the type of β-turn adopted. While cyclo-(L-Ala-Gly-Aca) had been previously shown to prefer the type II orientation,[18,19] some stereoisomers containing a disubstituted linker existed largely in the type I conformation. Interestingly, cyclo(Gly-Gly-(3*R*)-methyl-Aca) (**1b**), which contains only a single stereocenter, had a CD spectrum that bore a great resemblance to more highly substituted compounds. Thus, it appeared that the presence of a single methyl group on the Aca linker could persuade the dipeptide to reside predominantly in one orientation.

In this paper, we report the synthesis and conformational analysis of a series of Gly-Gly-derived macrocycles containing an Aca tether that possesses a single benzyl substituent at each position of the tether. One purpose of this study was to examine how a substituent at each position of the Aca linker might influence the overall macrocyclic conformation. Besides a role in influencing conformation, such linkers may (1) serve as a surrogate for a third amino acid (e.g., as needed for the mimicry of the RGD sequence, which is a common target of β-turn peptidomimetics[22−24]), (2) provide a site for attachment to a solid support, or (3) play a role in solubilizing the molecule. The broad application of these concepts in medicinal chemistry will require straightforward routes to an array of substituted linkers that can be plugged into standard peptide synthesis protocols. Accordingly, enantioselective syntheses of linkers containing a benzyl group in positions 2−6 were carried out to help establish the general synthetic routes required for future work. In addition, preliminary conformational analyses of the

Scheme 1



Scheme 2



derived macrocycles using NMR, CD, and X-ray techniques are described herein.[25]

Results and Discussion

The general retrosynthetic analysis of the macrocycles, shown in Scheme 1, followed precedent set by previous groups working in this field.[17−20] This modular approach allows for the combination of a standard-issue dipeptide with an appropriately substituted linker capped by one of the commonly used amino acid protecting groups. The linker syntheses will be described in the following section, which will also include a brief discussion of cyclization conditions. The paper will be concluded by presentation and discussion of the conformational analysis of the macrocycles.

Linker Synthesis. The routes devised to make each linker in enantiomerically enriched form varied according to the position of the substitution (Scheme 2). Aca derivatives bearing C-3, C-4, and C-5 substitution (**14a**, **10**, and **14b**, respectively) were synthesized from the corresponding lactam, which was prepared using a stereospecific ring expansion sequence.[26] The linker containing the benzyl group in the C-6 position was derived from L-phenylalanal,[27] whereas linker bearing the C-2 benzyl group utilized an Evans chiral alkylation[28] to establish the stereocenter on Aca.

Enantiomerically pure **10**, containing a 4-benzyl substituent, was synthesized according to the oxaziridine ring-expansion protocol reported earlier by this group

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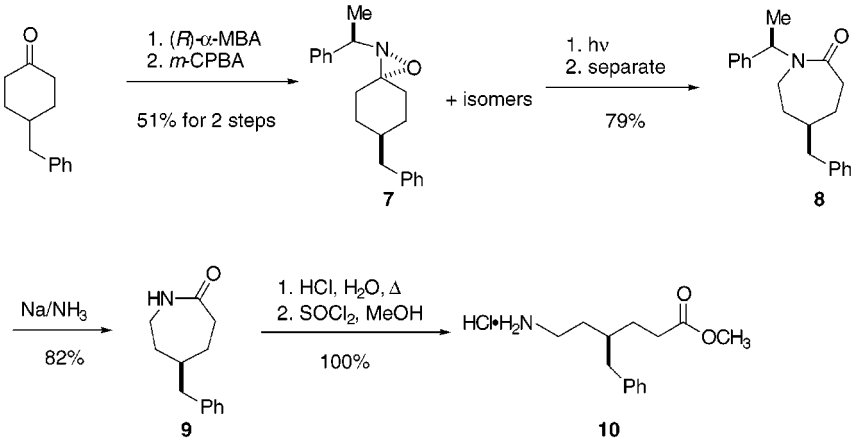
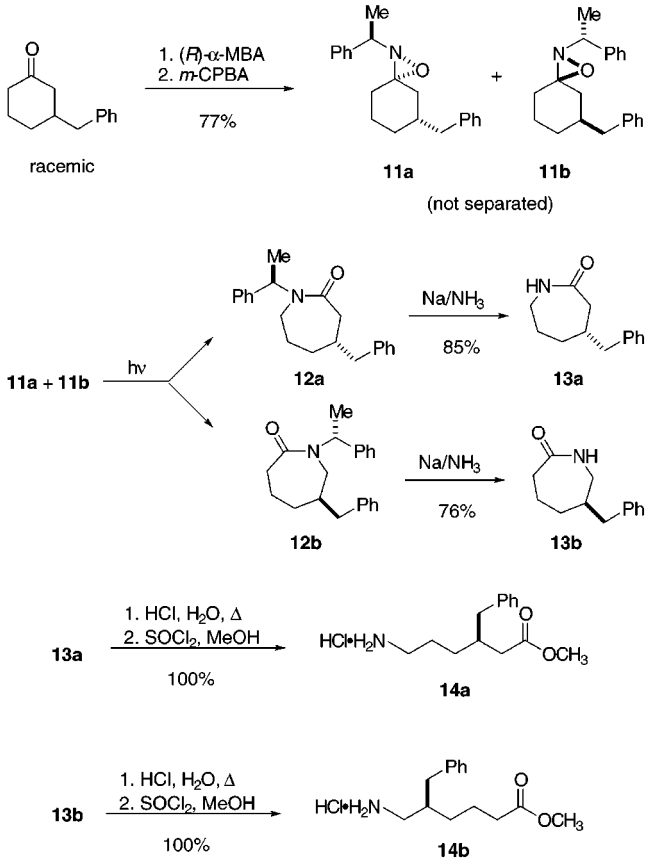
Scheme 3



(Scheme 3).[29] Thus, 4-benzylcyclohexanone[30] was condensed with (*R*)-α-methylbenzylamine ((*R*)-α-MBA), forming an imine that was immediately oxidized with *m*-CPBA at −78 °C to give a mixture of oxaziridines. The stereochemistry of the major diastereomeric oxaziridine **7** was assigned as previously described.[31] The oxaziridine mixture was photolyzed (benzene or cyclohexane, 254 nm, room temperature) to produce a mixture of lactams that were separated by column chromatography to produce the major isomer **8** in good overall yield. Reductive removal of the phenethyl group upon treatment of **8** with Na/NH_3 provided **9**. The enantiomeric purity of **9** was examined by chiral HPLC (Chirobiotic T column, 35% EtOH/hexane) and determined to be 98% ee. Subsequent acid hydrolysis and esterification furnished the HCl salt of 4-benzyl-Aca methyl ester (**10**).

Compounds **14a** and **14b** were simultaneously prepared from (±)-3-benzylcyclohexanone, also using oxaziridine chemistry (Scheme 4). In this case, synthesis of the oxaziridines yielded two major diastereomers (**11a** and **11b**), with some minor diastereomeric impurities evident in the ^1H NMR. The combination of a racemic, unsymmetrical ketone with enantiomerically pure α-MBA permits the conversion of each enantiomer of ketone to its own particular oxaziridine, each resulting from equatorial addition of the oxidant and formation of the *unlike* relationship between the stereogenic nitrogen and benzylic stereocenters.[31,32] Each of these major oxaziridines has been established to lead to different regioisomeric lactams, thus allowing for the simultaneous synthesis of enantiomerically pure lactams. In practice, the oxaziridines were subjected to photolysis as a mixture, following which the two predominant lactams (**12a** and **12b**) were isolated by column chromatography and purified further by crystallization from Et_2O/hexane. X-ray analysis of **12a** and **12b** verified the stereochemical assignments (Supporting Information), and removal of the phenethyl groups from each yielded lactams **13a** and **13b**, respectively. Acid hydrolysis and esterification of each precursor yielded the HCl salts of the substituted linkers **14a** and **14b**.

Scheme 4



Synthesis of the linker with the benzyl group adjacent to the amine (C-6) used a chiral pool approach (Scheme 5). Wittig reaction of Boc-L-phenylalanal[27] with [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide[33] provided the olefin **15**. The stereochemistry of the double bond was not relevant but was assigned the cis config-

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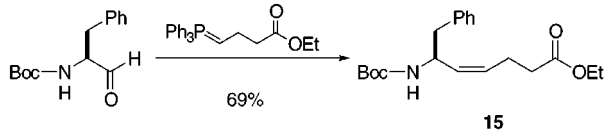
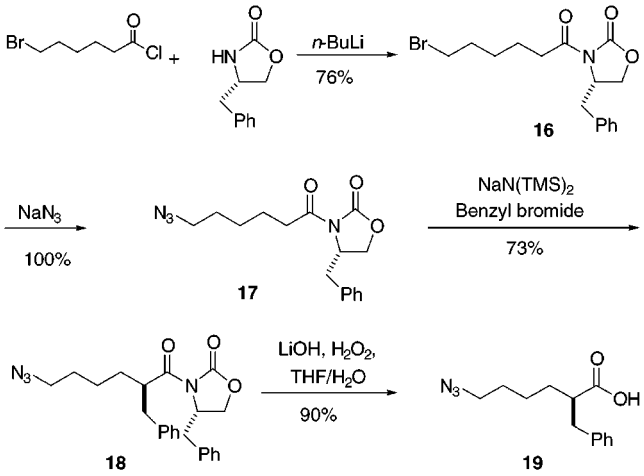
Scheme 5



Scheme 6



uration. Although the double bond of **15** could be reduced or alternatively modified at this stage, this material was directly used in the ensuing macrocycle synthesis to optimize synthetic efficiency (see Scheme 9 below).

The key step in the synthesis of the 2-benzylated linker was an asymmetric alkylation reaction (Scheme 6). Thus, 6-bromohexanoyl chloride was coupled to (*S*)-(−)-4-benzyl-2-oxazolidinone to form **16**. After displacement of the bromide with sodium azide, **17** was alkylated with benzyl bromide to form **18**. The azido acid **19** was isolated after removal of the auxiliary using standard conditions and brought to the next phase of the synthesis.[34]

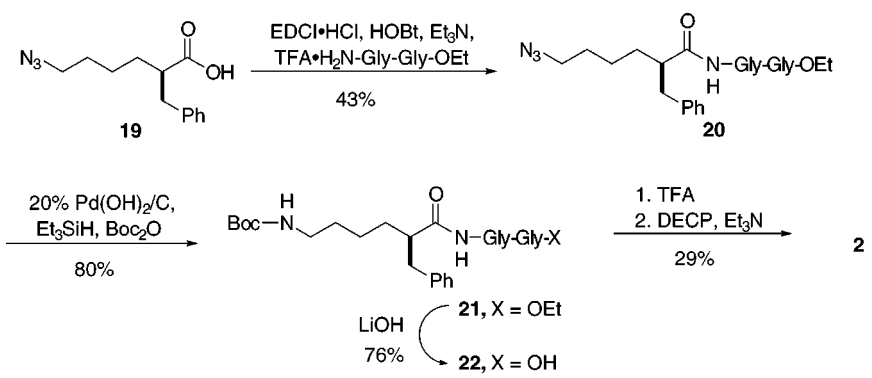
Peptide Coupling and Cyclization. The Aca linkers were attached to the *N*- or *C*-terminally protected glycylglycine peptide units under standard conditions.[35] Cyclizations were carried out using diethyl cyanophosphonate (DECP)[36] and triethylamine (Et_3N) in a DMF/toluene (1:1) mixture at a peptide concentration of approximately 0.005 M. Scheme 7 illustrates how the azido acid **19** was coupled to glycylglycine ethyl ester, affording the tripeptide **20**. Subsequent reduction of the azide to the Boc-protected amine[37] afforded **21**. The short-lived Boc-protection aided in the handling of the intermediates leading to the final target. Compound **2** was isolated after hydrolysis of the ester, Boc deprotection, and peptide cyclization.

The synthesis of macrocycles **3**−**5** is summarized in Scheme 8. Boc-protected glycylglycine was coupled to 3-, 4-, and 5-benzyl-Aca methyl ester (**14a**, **10**, and **14b**, respectively). Hydrolysis of the ester, Boc deprotection, and cyclization yielded the final compounds. The synthesis of **6** proceeded via a different order of attachment of glycine residues in an effort to increase cyclization yields (Scheme 9). Linker **15** was first deprotected and coupled to Boc-glycine. Ester hydrolysis and the attachment of the second glycine residue to the *C*-terminus furnished the protected, olefinic tripeptide **27**. Hydrogenation of the olefin produced the tripeptide **28**. After hydrolysis of the ethyl ester, **29** was treated with TFA for Boc removal and then cyclized using the conditions mentioned above to afford compound **6**. Hydrogenation of **25** formed **30**, which was examined by chiral HPLC (Chiralcel OD-H, 4% EtOH/hexane). The compound was obtained in ca. 93% ee, indicating that some epimerization probably occurred during the basic olefination step resulting in **15**.

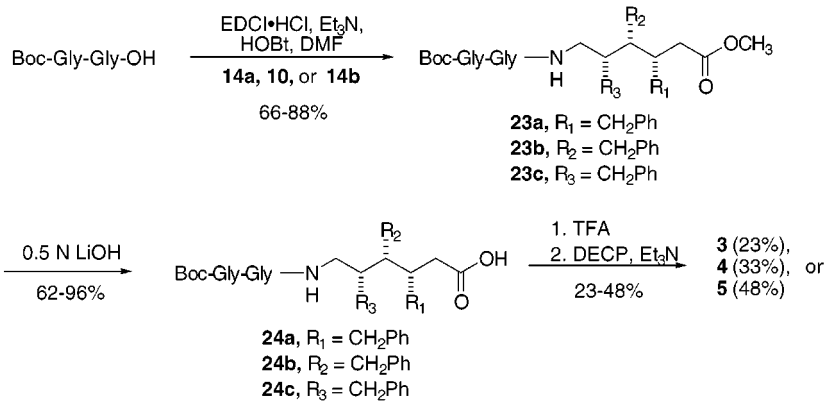
Due to the difficulties encountered during the ring closure step, various cyclization conditions to form **6** were surveyed (Table 1). First, after little success in closing the macrocycle by forming the Gly-Aca bond as was done for compounds **3**−**5**, we decided to investigate cyclization forming the less sterically encumbered Gly-Gly linkage. After several low-yielding attempts using DECP/$NaHCO_3$ in various solvents (entries 1−4), additional coupling agents such as bis(oxazolidinyl)phosphinyl chloride (BOP-Cl),[38] diphenylphosphoryl azide (DPPA),[39] and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt (EDCI·HCl)[35] were tried (entries 5−7). While BOP-Cl and DPPA did not produce favorable results, EDCI·HCl gave promising but variable yields. Et_3N was added as base (entry 8), and eventually toluene was added to the solvent system in the hope that greater solvent hydrophobicity would aid cyclization (entries 9 and 10). To date, the combination of DECP (EDCI·HCl is not soluble in toluene) and Et_3N in the mixture of DMF/toluene (1:1) has consistently provided the final macrocycles in the best yield. It is worth noting that none of the cyclizations carried out with the monosubstituted linkers discussed herein have proved as efficient as cyclizations with either dimethyl-substituted Aca linkers or more highly substituted dipeptide units.

Conformational Analysis. Conformational analysis of macrocycles **2**−**6** in solution were performed using NMR and CD spectroscopy. As previously shown prudent,[21] NMR COSY and ROESY spectra were obtained using samples dissolved in DMSO-d_6 at approximately 1 mg/mL to minimize aggregation. In general, the NMR

Scheme 7



Scheme 8



Scheme 9

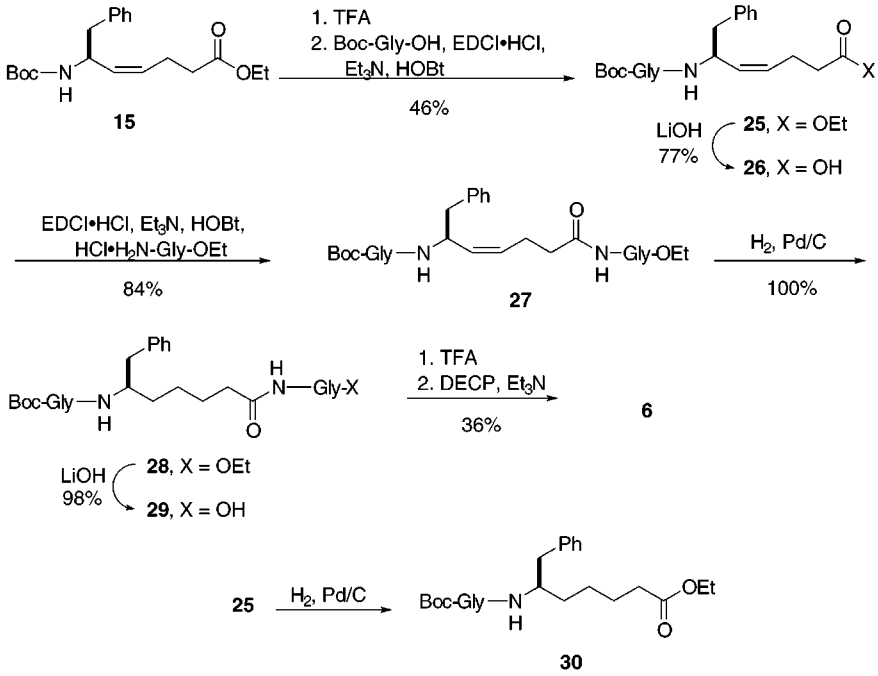
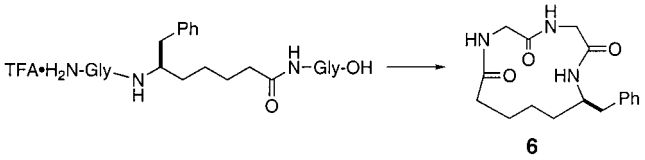


Table 1. Conditions for Cyclization Reactions



entry	conditions	yield (%)
1	DECP, $NaHCO_3$, DMF	-
2	DECP, $NaHCO_3$, DMF/CH_2Cl_2	-
3	DECP, $NaHCO_3$, CH_3CN	-
4	DECP, $NaHCO_3$, CH_2Cl_2	-
5	EDCI·HCl, $NaHCO_3$, DMF	5−30
6	DPPA, $NaHCO_3$, DMF	15
7	BOP-Cl, $NaHCO_3$, DMF/CH_2Cl_2	-
8	EDCI·HCl, Et_3N, DMF	13
9	EDCI·HCl, Et_3N, DMF/toluene	-
10	DECP, Et_3N, DMF/toluene	23−26

data were consistent with either a type II or II′ β-turn conformation. This conclusion was primarily based on the presence of ROE cross-peaks between Gly_2NH and one of the prochiral Gly_1H_α protons (specific for type II β-turns) and between the Gly_2NH and AcaNH hydrogen atoms (observed in both type I and II β-turns). A significant concentration of the type I or type I′ turns seemed unlikely due to a lack of NOE interactions between Gly_1NH and Gly_2NH, which are indicative of such conformations. On the basis of these results, each of the macrocycles was believed to largely reside in some form of a type II β-turn (although other conformations are presumably kinetically accessible by these flexible compounds). However, because the Gly-Gly dipeptide does not contain a stereogenic center, these data do not indicate which enantiomorphic backbone is most prevalent (βII or βII′).

There was some hope that the conformation of the Aca tether could be determined from NMR studies to see if a correlation between tether and turn existed. In the research preceding this project, it was noted that one of the C4 protons of Aca had an interaction with the AcaNH in each of the macrocycles incorporating the disubstituted constraint.[21] The central methylene protons were well separated in the ^1H NMR spectra with ranges of $\Delta\nu$ = 0.17−0.81 ppm. In each of the examples mentioned here, the C-4 protons were not well-resolved, the greatest difference being $\Delta\nu$ = 0.14 ppm. There were no obvious ROEs observed between either of the C4 protons and AcaNH. In general, there was significant averaging of

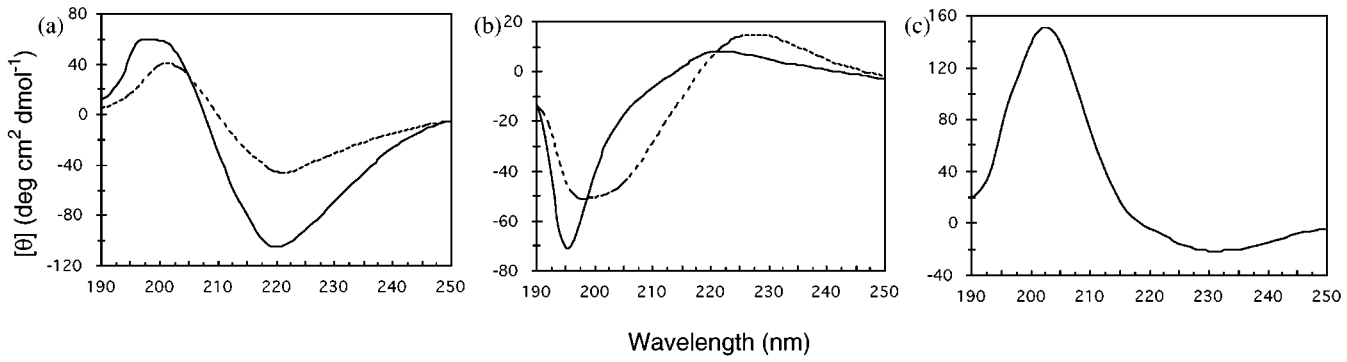


Figure 1. CD spectra of macrocycles (a) **2** (solid line) and **3** (dotted line), (b) **5** (solid line) and **6** (dotted line), and (c) **4**.

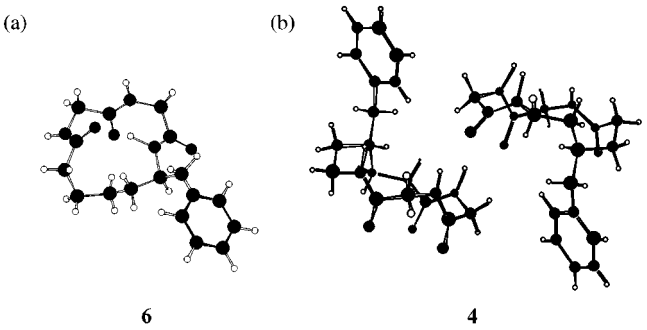


Figure 2. Ball-and-stick representations of the X-ray crystallographic structures of compounds (a) **6** and (b) **4**.

the chemical shifts for the protons on the tether, which indicated flexibility within that region of the macrocycle.

Circular dichroism was used to obtain additional solution-phase conformational information and, in particular, to differentiate between type II and II′ turns for each compound. All measurements were performed in methanol (c = 1 mg/mL, 0.02 cm path length). The CD spectra for compounds **5** and **6** (Figure 1b) resemble the standard curve a type II′ β-turn.[40,41] Each curve has a minimum ellipticity between 195 and 200 nm and a maximum in the region of 220−230 nm. Conversely, the CD spectra for compounds **2** and **3** (Figure 1a) indicate a preferred conformation of a type II β-turn in that they both contain maxima near 200 nm and minima at 220 nm. Compound **4** was the outlier in this series (Figure 1c). The maximum at 200 nm is much more intense than any of its isomers, and a modest minimum is noted near 230 nm. This CD data is somewhat reminiscent of that expected for a type II turn; indeed, the NMR data would seem to suggest that at least some of this material exists as a type II turn in solution. However, the amplitude of this curve, when combined with the lack of a well-defined minimum at 220 nm, suggested that the βII turn makes up only a small component of the solution structure.

In addition, X-ray structures were obtained for compounds **4** and **6** following crystallization from methanol/$CHCl_3$ and methanol/CH_2Cl_2, respectively (Figure 2; stereoviews of these structures can be found in the Supporting Information). Interestingly, the racemate of **6** crystallized from the 93% ee mixture obtained as described above, as evidenced by the space group $P2_1/a$. The crystal structure of **6** clearly demonstrates a type II′ β-turn in agreement with the CD and NMR data. The observed dihedral angles obtained from the X-ray data are all within 26° of the idealized type II′ values shown in Table 2.[1] The X-ray structure also revealed the presence of a hydrogen bond between the Aca(C═O) and Gly_1NH (O−H distance 1.892 Å). The position of the benzyl substituent on Aca appears to occupy an equatorial-like position of the macrocycle.

Table 2. Selected Dihedral Angles for 6 and 4 (deg)

β-turn	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}
type I[a]	−60	−30	−90	0
type II	−60	120	80	0
type II′	60	−120	−80	0
6	71	−115	−67	−26
4 (conformer 1)	−54	53	−80	94
4 (conformer 2)	104	−77	68	38

[a] Idealized values (ref 1).

Crystallographic analysis of **4** showed the presence of two distinct conformers, neither of which resemble a β-turn conformation. For example, the Aca(C═O)/AcaNH distance in this compound is 5.03−5.55 Å (with the carbonyl groups and the N−H bond pointing in opposite directions) compared to 1.89 Å for **6**. In both conformations of **4**, all of the amide bonds approximately describe a ring, or crown, structure about the plane of the macrocycle, with each of the carbonyl oxygens pointing in the same direction. In addition, the Aca linker has been significantly skewed from conformations seen in other examples. In this case, the 4-benzyl group appears to be placed into a pseudoaxial position, with the adjacent methine proton pointing into the macrocycle cavity. It is likely that at least some of these observations result from crystal-packing considerations. Overall, considering the proton NMR data (which indicate some βII or -II′ character), the CD (which shows significant deviations from a "pure" type II β-turn spectrum), and these X-ray results, it would appear that this single substitution type among all of those examined herein is least likely to adopt one of the classically recognized β-turn subtypes.

Summary

Cyclization of a dipeptide with Aca constrains the dipeptide into a β-turn with the amino acid residues occupying the $i + 1$ and $i + 2$ positions. The use of a monosubstituted Aca tether to constrain glycylglycine has been shown to vary the β-turn conformation from type II to type II′. However, placement of the substituent in the central C-4 position of the tether does not lead to a macrocycle corresponding to a known turn type. We are

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(41) Venkatachalam, C. M.; Ramachandran, G. M. *Annu. Rev. Biochem.* **1969**, *38*, 45−82.

currently applying this methodology toward the synthesis of biologically relevant β-turn mimics.

Experimental Section

General methods have been previously published.[21]

General Procedure for Macrocyclization. The Boc-protected tripeptide was dissolved in a mixture of TFA/CH_2Cl_2 (1:2) and stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was redissolved in a 1:1 mixture of DMF/toluene (0.005 M). DECP (5 equiv) and enough Et_3N to make the solution slightly basic were added to the solution, which was stirred at room temperature for 19 h. After removal of the solvent in vacuo, the residue was redissolved in CH_2Cl_2 and washed with 10% citric acid and brine. The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (MeOH/CH_2Cl_2 = 1:50, 1:25) to obtain the cyclized peptide.

(9*R*)-9-Benzyl-1,4,7-triazacyclotridecane-2,5,8-trione (2). White solid; mp 249 °C dec; $[\alpha]_D$ −45 (*c* 0.06, MeOH); IR (film) 3262, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03 (m, 1H), 1.16 (m, 2H), 1.32 (m, 1H), 1.50 (m, 2H), 2.55 (m, 2H), 2.76 (m, 1H), 2.88 (m, 1H), 3.19 (dd, J = 4.9, 13.3 Hz, 1H), 3.29 (obscured by solvent, 1H), 3.45 (dd, J = 5.8, 15.7 Hz, 1H), 3.65 (dd, J = 6.5, 15.7 Hz, 1H), 3.91 (dd, J = 7.2, 13.3 Hz, 1H), 6.94 (t, J = 5.8 Hz, 1H), 7.15 (m, 3H), 7.25 (m, 2H), 8.57 (t, J = 5.9 Hz, 1H), 8.73 (t, J = 5.9 Hz, 1H); ^{13}C NMR (125.6 MHz, DMSO-d_6) δ 20.9, 26.7, 30.0, 36.0, 38.8, 43.9, 47.5, 126.4, 128.6, 129.1, 140.1, 168.9, 170.1, 177.2; MS (CI) *m*/*e* 318 (M^+ + 1), 317 (M^+), 147, 74; HRMS calcd for $C_{17}H_{24}N_3O_3$ (M^+ + 1): 318.1818; found 318.1823.

(10*S*)-10-Benzyl-1,4,7-triazacyclotridecane-2,5,8-trione (3). White solid; mp 238 °C dec; $[\alpha]_D$ +26 (*c* 0.05, MeOH); IR (film) 3325, 3068, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.07 (m, 1H), 1.21 (m, 2H), 1.43 (m, 1H), 1.92 (m, 1H), 2.06 (dd, J = 3.7, 13.2 Hz, 1H), 2.19 (m, 1H), 2.39 (dd, J = 8.6, 13.2 Hz, 1H), 2.69 (dd, J = 5.5, 13.2 Hz, 1H), 2.85 (m, 1H), 3.31 (partially obscured by solvent, 2H), 3.47 (dd, J = 5.9, 16.1 Hz, 1H), 3.65 (dd, J = 6.6, 13.5 Hz, 1H), 3.85 (dd, J = 6.6, 13.5 Hz, 1H), 7.04 (m, 1H), 7.2 (m, 3H), 7.29 (m, 2H), 8.69 (t, J = 6.1 Hz, 1H), 8.94 (t, J = 6.0 Hz, 1H); ^{13}C NMR (125.6 MHz, DMSO-d_6) δ 25.1, 27.8, 36.6, 36.7, 41.3, 44.3, 44.7, 126.8, 129.1, 130.0, 141.3, 169.4, 170.9, 175.9, (one carbon signal obscured by solvent); MS (CI) *m*/*e* 318 (M^+ + 1), 204, 128, 91, 60; HRMS calcd for $C_{17}H_{24}N_3O_3$ (M^+ + 1): 318.1817; found 318.1793.

(11*R*)-11-Benzyl-1,4,7-triazacyclotridecane-2,5,8-trione (4). White solid; mp 193−194 °C; $[\alpha]_D$ +98 (*c* 0.07, MeOH); IR (film) 3291, 1654, 1635 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.08 (m, 1H), 1.27 (m, 2H), 1.49 (m, 1H), 1.78 (m, 1H), 2.13 (m, 1H), 2.22 (m, 1H), 2.37 (dd, J = 8.0, 13.6 Hz, 1H), 2.63 (dd, J = 5.4, 13.7 Hz, 1H), 2.80 (m, 1H), 3.16 (m, 1H), 3.42 (m, 2H), 3.72 (dd, J = 6.9, 16.3 Hz, 1H), 3.86 (dd, J = 6.0, 13.3 Hz, 1H), 7.04 (dd, J = 3.4, 7.6 Hz, 1H), 7.14 (m, 1H), 7.21 (m, 4H), 8.69 (t, J = 6.0 Hz, 1H), 8.91 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 28.5, 32.1, 33.0, 33.4, 35.8, 41.5, 43.9, 44.7, 126.5, 128.8, 130.2, 140.8, 169.2, 170.7, 176.6; MS (CI) *m*/*e* 318 (M^+ + 1), 91; HRMS calcd for $C_{17}H_{24}N_3O_3$ (M^+ + 1): 318.1817; found 318.1814.

(12*R*)-12-Benzyl-1,4,7-triazacyclotridecane-2,5,8-trione (5). White solid; mp 189−190 °C; $[\alpha]_D$ +26 (*c* 0.05, MeOH); IR (film) 3325, 3068, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.05 (m, 2H), 1.49 (m, 1H), 1.65 (m, 1H), 1.81 (m, 1H), 2.10 (m, 2H), 2.41 (d, J = 7.3 Hz, 1H), 2.89 (m, 1H), 3.15 (m, 1H), 3.52 (dd, J = 5.6, 13.4 Hz, 1H), 3.58 (d, J = 6.1 Hz, 2H), 3.70 (dd, J = 6.3, 13.4 Hz, 1H), 7.01 (t, J = 5.9 Hz, 1H), 7.19 (m, 3H), 7.28 (m, 2H), 8.63 (t, J = 6.1, 1H), 8.94 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100.6 MHz, MeOH-d_4) δ 18.7, 24.9, 33.0, 36.8, 38.1, 39.3, 41.9, 43.0, 124.5, 126.8, 127.3, 139.1, 169.0, 169.9, 176.5; MS (CI) *m*/*e* 318 (M^+ + 1), 204, 128, 91, 60, 44; HRMS calcd for $C_{17}H_{24}N_3O_3$ (M^+ + 1): 318.1817; found 318.1793.

(13*R*)-13-Benzyl-1,4,7-triazacyclotridecane-2,5,8-trione (6). White solid; mp 287 °C dec; $[\alpha]_D$ +9.3 (*c* 0.11, MeOH); IR (film) 3281, 3087, 2951, 1658, 1635 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11 (m, 2H), 1.37 (m, 3H), 1.65 (m, 1H), 2.13 (m, 2H), 2.54 (dd, J = 7.7, 13.3 Hz, 1H), 2.80 (dd, J = 6.0, 13.3 Hz, 1H), 3.54 (m, 1H), 3.59 (m, 1H), 3.64 (m, 3H), 7.03 (d, J = 8.0 Hz, 1H), 7.18 (m, 3H), 7.28 (m, 2H), 8.24 (t, J = 5.9 Hz, 1H), 8.55 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 23.1, 25.0, 32.2, 34.8, 42.2, 44.4, 44.7, 51.3, 126.9, 129.0, 129.9, 139.7, 169.7, 170.4, 174.4; MS (CI) *m*/*e* 318 (M^+ + 1), 226, 128, 91; HRMS calcd for $C_{17}H_{24}N_3O_3$ (M^+ + 1): 318.1817; found 318.1815.

Acknowledgment. This work was supported by the American Heart Association—Heartland and the National Institutes of Health (GM-49093). M.M. would like to acknowledge receipt of an NIH Predoctoral Training Grant (GM-07775). We thank Martha Morton and Lawrence Seib for expert assistance with NMR and X-ray work, respectively.

Supporting Information Available: Experimental procedures for compounds **7**−**29**, spectral data for compounds **2**−**29**, X-ray crystal reports for compounds **4**, **6**, **12a**, and **12b**, and pertinent ROE data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001308B