Synthesis and Hydrogen Bonding Capabilities of Biphenyl-Based Amino Acids Designed To Nucleate β-Sheet Structure

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The syntheses of 3′-(aminoethyl)-2-biphenylpropionic acid (**1**) and 2-amino-3′-biphenylcarboxylic acid (**2**) are described. These residues were designed to nucleate β-sheet structure in aqueous solution when incorporated into small, amphiphilic peptides in place of the backbone of the $i + 1$ and $i + 2$ residues of the β-turn. *N*-Benzyl-3′-(2-(benzylamido)ethyl)-2-biphenylpropamide (**3**) and *N*-benzyl-(2-benzylamido)-3′-biphenylamide (**4**) were synthesized and studied as model compounds to investigate the hydrogen-bonding capabilities of residues **1** and **2**, respectively. The X-ray crystal structure of **3** indicates that a 13-membered intramolecular hydrogen-bonded ring is formed, while the remaining amide proton and carbonyl are involved in intermolecular hydrogen bonding. Infrared and variable-temperature NMR experiments indicate that, in solution (CH_2Cl_2), **3** exists as an equilibrium mixture of the 13- and the 15-membered intramolecularly hydrogen-bonded conformers with the 15-membered ring conformer being favored. Amide **4** was shown to exist in solution (CH_2Cl_2) as an equilibrium mixture of the 11-membered intramolecular hydrogen-bonded ring and a nonbonded conformation. No contribution from the 9-membered hydrogen-bonded ring conformation was observed. The X-ray crystal structure of **4** indicated the absence of intramolecular hydrogen bonding in the solid state.

Introduction

The mechanisms of β-sheet folding are under investigation in several laboratories using a variety of approaches.[1−13] While β-sheet structure is commonly observed in proteins, our understanding of this structural motif is poor relative to what is known about α-helical secondary structure. This is due, in part, to the difficulties inherent in creating a well-defined peptide model system for the study of β-sheet formation in aqueous solution.[14−17] Although studies on the conformational propensities of amino acid homopolymers and sequential copolymers have enhanced our understanding of β-sheet structure, the approach is limited because of competitive intra- and intermolecular folding which leads to heterogeneous aggregated β-sheet structures.[18−27] Small hydrophobic or amphiphilic peptides are also poor model systems as they too usually form self-associated β-sheet structures.[10,11,28−36] The ability to prepare a monomeric β-hairpin structure, where a β-turn reverses the polypeptide chain direction allowing two strands to interact with one another in an antiparallel orientation, would be advantageous. In principle, this could be accomplished using a consensus β-turn sequence combined with flanking strand sequences that have a high β-sheet propensity.

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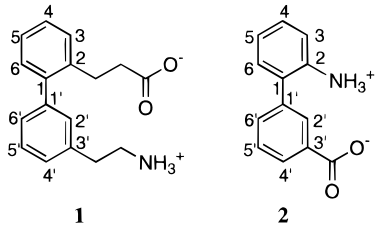

1 **2**

Figure 1. Structures of biphenyl-based amino acids 3′-(2-aminoethyl)-2-biphenylpropionic acid (**1**) and 2-amino-3′-biphenylcarboxylic acid (**2**).

However, the conformational propensities of known β-turn sequences do not appear to be sufficient to effect β-hairpin folding given what is currently known about the process.[2,37−40] In an effort to develop a reliable strategy to achieve β-sheet folding, we have developed unnatural amino acids which nucleate folding when incorporated into an appropriate α-amino acid sequence. The concept of utilizing a conformationally defined template to increase the stability of a given conformation in a predominantly α-amino acid sequence was pioneered by Hirschmann and his colleagues.[41−44] The utility of Cu(II) binding bipyridine-based amino acids and a dibenzofuran-based amino acid that employs a hydrogen-bonded hydrophobic cluster to facilitate β-hairpin folding in peptides in aqueous solution has been previously demonstrated by our group.[8,45−47]

Here, we present the syntheses of two 2,3′-substituted biphenyl-based amino acids, 3′-(aminoethyl)-2-biphenylpropionic acid (**1**) and 2-amino-3′-biphenylcarboxylic acid (**2**) (Figure 1), which are potential β-sheet nucleators. The biphenyl skeleton was chosen based on the 4.8 Å distance between C2 and C3′ which is very similar to the distance separating two strands of an antiparallel β-sheet (4.85 Å).[48,49] Amino acids **1** and **2** were designed to replace the backbone of the $i + 1$ and $i + 2$ residues of a β-turn. It should be noted that **1** and **2** do not actually mimic a specific β-turn type. Instead, these residues are meant to resemble a β-turn only in that they were designed to reverse the polypeptide chain direction by promoting intramolecular hydrogen bonding between the flanking α-amino acid residues. Simple diamide derivatives of **1** and **2** were prepared and studied by variable temperature ^{1}H NMR and FT-IR in an effort to evaluate the hydrogen-bonding capabilities of the 2,3′-substituted biphenyl-based amino acid residues. X-ray crystal structures of these amides (**3** and **4**) provided additional insight into the potential abilities of **1** and **2** to serve as templates for β-sheet nucleation.

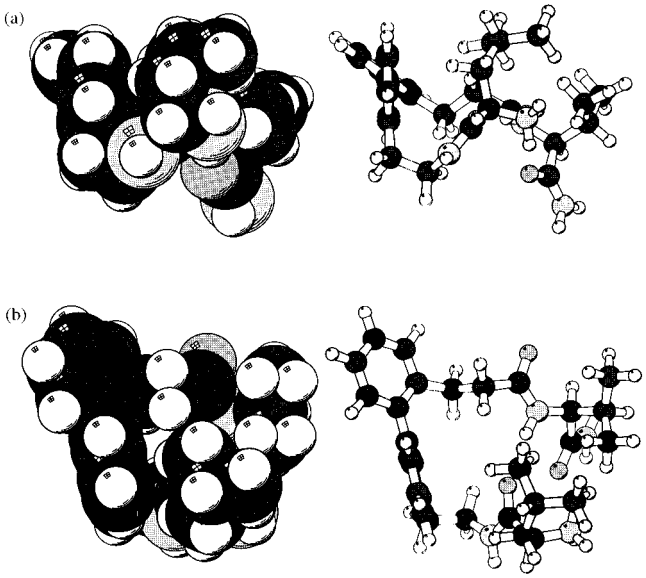

Figure 2. Molecular Graphics representation[70] of −Leu-**1**-Val− demonstrating the hydrophobic cluster conformation in which the ethyl side chains of **1** are perpendicular to the aromatic rings and hydrophobic interactions between one ring and the leucine side chain are present. The structure represents the lowest energy conformation predicted by molecular mechanics/molecular dynamics of the peptide H_3N-VOL-**1**-VOL-C(O)NH_2 in aqueous solution: (a) side view; (b) top view.

Molecular modeling suggests that both amino acids are expected to have a dihedral angle between the two phenyl rings of approximately 120° in order to avoid eclipsing of the *ortho* substituents. The 2,3′-substituted biphenyl-based residues **1** and **2** differ in that $-CH_2CH_2-$ fragments were incorporated into **1** to allow a potentially favorable hydrophobic interaction to occur between one or both of the biphenyl rings and the hydrophobic side chains of the flanking α-amino acid residues, which is not possible in residue **2**. Phenethyl compounds are known to adopt a low energy conformation in which the aliphatic carbon−carbon bond is oriented perpendicular to the plane of the aromatic ring.[50,51] In a peptide incorporating **1**, this conformation would orient one of the aromatic rings perpendicular to the plane of the resulting β-sheet, allowing the side chains of at least one of the flanking α-amino acids to pack against the aromatic skeleton to afford a hydrophobic cluster (Figure 2). This type of hydrophobic cluster has been shown to be critical for the nucleation of β-sheet structure in peptides incorporating the 4-(2-aminoethyl)-6-dibenzofuranpropionic acid residue.[8]

(37) Several small peptides are capable of populating a β-turn conformation; see: refs 2 and 38−43. However, concensus β-turns do not appear to be sufficient to nucleate folding within sequences which are known to fold when nucleated by unnatural amino acids such as the 4-(2-aminoethyl)-6-dibenzofuranpropionic acid. Unpublished results.

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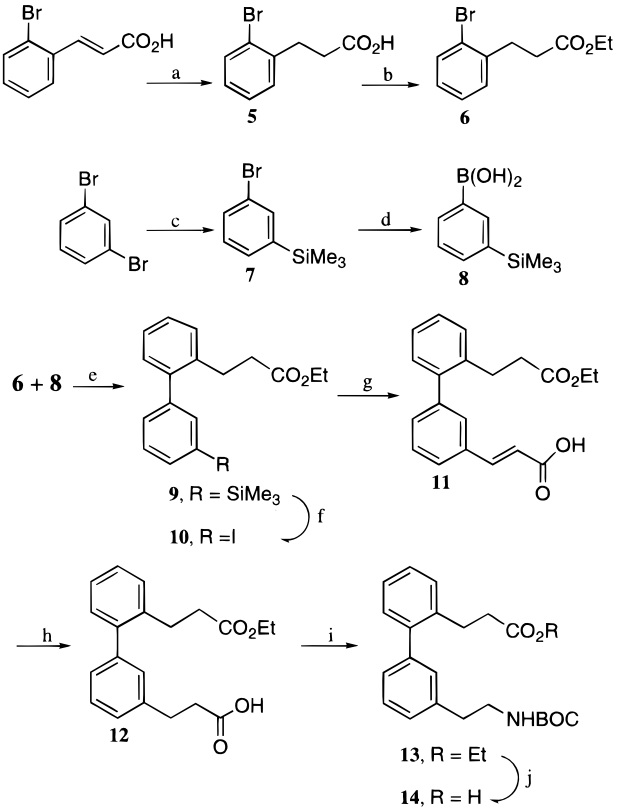

Figure 3. Outline of the synthesis of 3′-(*N*-(*tert*-butyloxycarbonyl)-2-aminoethyl)-2-biphenylpropionic acid (**14**). Reaction conditions: (a) 50 psi H_2, 5 mol % $Rh(PPh_3)_3Cl$, EtOH, room temperature, 40−50 h, 94%; (b) 1 mol % *p*-toluenesulfonic acid, EtOH, reflux, 22 h, 95%; (c) (i) 1.0 equiv of *n*-BuLi at −95 °C in THF, 5 min, (ii) 2.5 equiv of TMSCl, initially at −95 °C, warmed to −75 °C and stirred 2 h, and then warmed to room temperature overnight, 91%; (d) (i) 1.5 equiv of *n*-BuLi at −95 °C in THF, 5 min, (ii) 10.0 equiv of $B(OMe)_3$, initially at −95 °C, warmed to −78 °C and stirred 2 h, and then warmed to room temperature overnight, (iii) cooled to 0 °C and acidified to pH 6 with 10% HCl, 107% (crude); (e) 1.6 equiv of boronic acid, 5 mol % $Pd(PPh_3)_4$, 2.0 equiv of Na_2CO_3, DME, reflux, 22 h, 92%; (f) 2.4 equiv of ICl, 3.0 equiv of K_2CO_3, CCl_4, initially at 0 °C and then warmed to room temperature, 15 h, quantitative; (g) 2 mol % $Pd(OAc)_2$, 5 mol % PPh_3, 2.5 equiv of Et_3N, 1.5 equiv of acrylic acid, DMF, 130 °C, 5 h, 77%; (h) 1 atm of H_2, 7 mol % PtO_2, 1:1 EtOH:HOAc, room temperature, 6 h, 97%; (i) 1.1 equiv of diphenyl phosphorazidate, 1.2 equiv of Et_3N, *t*-BuOH, reflux, 24 h, 70%; (j) 10 equiv of 1.0 M aqueous LiOH, EtOH, room temperature, 2.5 h, quantitative.

Results and Discussion

Synthesis of *β*-Turn Mimics 1 and 2. The syntheses of **1** and **2** are based on the aryl−aryl cross-coupling strategies developed by Suzuki and modified by Snieckus.[52−54] The ethyl 2-bromodihydrocinnamate (**6**) required for the synthesis of the Boc-protected derivative of **1** (compound **14**) was obtained by hydrogenating 2-bromocinnamic acid in ethanol (50 psi) to afford 2-bromodihydrocinnamic acid (**5**) in 94% yield (Figure 3). Esterification using *p*-toluenesulfonic acid in ethanol provided the desired aryl bromide (**6**) in 95% yield. The required 3-(trimethylsilyl)phenylboronic acid (**8**) was obtained in two steps from 1,3-dibromobenzene. Treatment of 1,3-dibromobenzene with 1.0 equiv of *n*-butyllithium at −95 °C in THF provided the monolithiated species. The anion was quenched with trimethylsilyl chloride to afford 1-bromo-3-(trimethylsilyl)benzene (**7**) in 91% yield after vacuum distillation. Minor amounts of the *ortho*- and *para*-isomers were also observed in the crude product. A second metal−halogen exchange using 1.5 equiv of *n*-butyllithium at −95 °C in THF followed by addition of trimethyl borate and acidification afforded the crude boronic acid **8**. The biphenyl compound **9** was prepared in 92% yield by refluxing **6** and crude **8** in the presence of catalytic tetrakis(triphenylphosphine)palladium(II) and aqueous sodium carbonate in dimethylethyleneglycol. Iododesilylation of **9** was accomplished using iodine monochloride[55] in carbon tetrachloride to afford **10** in quantitative yield. Subjecting **10** to a palladium-catalyzed Heck cross-coupling reaction with acrylic acid[56,57] afforded ethyl 3′-(carboxyethenyl)-2-biphenylpropionate (**11**) in 77% yield. Hydrogenation using platinum oxide in 1:1 ethanol:acetic acid at 1 atm of H_2 afforded **12** in 97% yield. The acid functional group of **12** was transformed into a *tert*-butyl carbamate group via a Curtius rearrangement to afford **13** in 70% yield. Saponification of **13** with lithium hydroxide in ethanol provided the Boc-protected amino acid **14** in quantitative yield, which was used directly in solid phase peptide synthesis and in the preparation of the diamide derivative **3**. The overall yield of **14** from 2-bromocinnamic acid was 44%. The synthesis of the methyl ester-protected amino acid **2** (compound **23**) began with the conversion of 3-bromobenzoyl chloride (Figure 4) to 3-bromo-*N*-*tert*-butyl-*N*-methylbenzamide (**17**) in quantitative yield followed by a metal−halogen exchange employing 1.1 equiv of *sec*-butyllithium in THF at −95 °C to give the monolithiated species. Addition of trimethyl borate followed by acidification afforded the crude boronic acid **18** in 89% yield. Temperature control was important in this reaction; e.g., metalation at −80 °C resulted in a mixture of the *meta*- and *ortho*-isomers due to the ability of the amide group to act as an *ortho*-metalation director. Boronic acid **18** was coupled to methyl 2-bromobenzoate in the presence of catalytic tetrakis(triphenylphosphine)-palladium(II) and aqueous sodium carbonate in dimethylethylene glycol to afford methyl 3′-(*N*-*tert*-butyl-*N*-methylamidyl)-2-biphenylcarboxylate (**19**) in 69% yield. Saponification of the methyl ester functionality followed by a Curtius rearrangement afforded a mixture of the desired *tert*-butyl carbamate **21** as well as the urea **22**. Compounds **21** and **22** were hydrolyzed in concentrated HCl to afford the fully deprotected amino acid **2** in 46% yield from **20**. The methyl ester protected amino acid **23** was obtained in quantitative yield by refluxing amino acid **2** in methanol with excess thionyl chloride. The overall yield of **23** from 3-bromobenzoyl chloride was 27%.

Synthesis of the Diamide Derivatives of 1 and 2 for X-ray Crystallography, FT-IR, and VT-NMR Analysis. Diamides **3** and **4** (Figures 5 and 6, respectively) were prepared from the Boc-protected amino acid **14** and the amino ester **23**, respectively. These amide analogs were prepared to probe the intramolecular hydrogen-bonding preferences of residues **1** and **2** and

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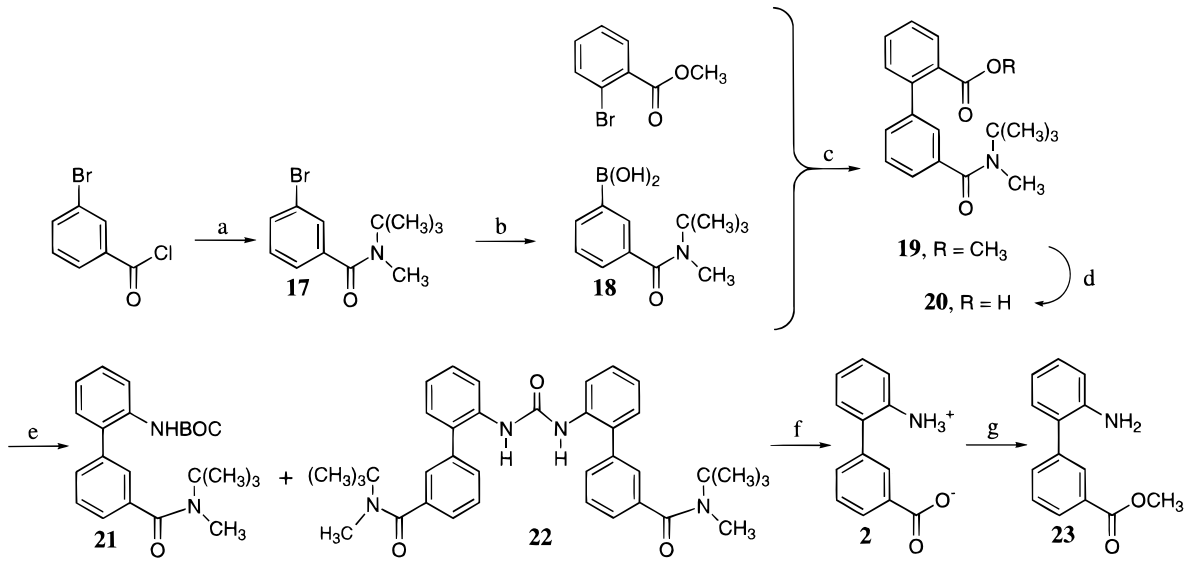
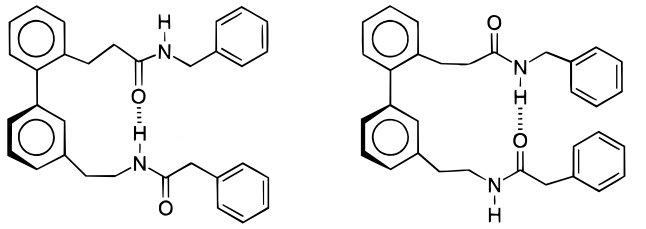


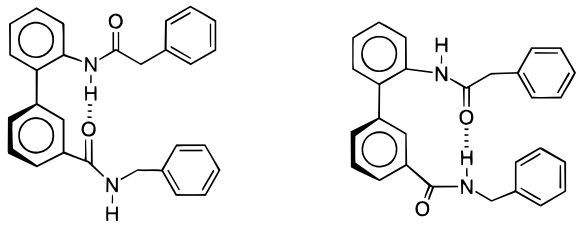
Figure 4. Outline of the synthesis of methyl 2-amino-3′-biphenylcarboxylate (**23**). Reaction conditions: (a) 1.0 equiv of *t*-BuMeNH, 1.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 2 h and then room temperature overnight, quantitative; (b) (i) 1.1 equiv of *s*-BuLi at −95 °C in THF, 10 min, (ii) 3.2 equiv of $B(OMe)_3$, initially at −95 °C, warmed to −80 °C and stirred for 2 h, and then warmed to −10 °C overnight, (iii) cooled to 0 °C and acidified to pH 6 with 10% HCl, 89%; (c) 2.2 equiv of boronic acid, 3 mol % $Pd(PPh_3)_4$, 2.0 equiv of Na_2CO_3, DME, reflux, 50 h, 69%; (d) 5.1 equiv of NaOH, MeOH, reflux, 6 h, 95%; (e) 1.2 equiv of diphenyl phosphorazidate, 1.2 equiv of Et_3N, *t*-BuOH, reflux, 22.5 h; (f) concd HCl, phenol, 110 °C, 45 h, 46%; (g) 19.8 equiv of $SOCl_2$, MeOH, initially at 0 °C and then refluxed, quantitative.



3a 13-membered H-bonded ring

3b 15-membered H-bonded ring

Figure 5. Representation of the two possible hydrogen-bonding conformations of diamide **3**.



4a 9-membered H-bonded ring

4b 11-membered H-bonded ring

Figure 6. Representation of the two possible hydrogen-bonding conformations of diamide **4**.

to identify the preferred dihedral angle about the carbon−carbon biphenyl bond in residues **1** and **2**. Diamide **3** was prepared by treatment of amino acid **14** with BOP reagent and benzylamine in DMF to obtain the Boc-protected amide, *N*-benzyl-3′-(*N*-(*tert*-butyloxycarbonyl)-2-aminoethyl)-2-biphenylpropamide (**15**), in 76% yield. Removal of the Boc group with TFA followed by reaction with the HOBt active ester of phenylacetic acid in CH_2Cl_2 afforded diamide **3** in 53% yield after purification by preparative C_{18} HPLC. The overall yield of **3** from **14** was 40%. Diamide **4** was prepared by acylating the amino group of **23** with an excess of the HOBt active ester of phenylacetic acid in CH_2Cl_2 to give the amide. The crude compound was then hydrolyzed to afford 2-(benzylamido)-3′-biphenylcarboxylic acid (**25**) in 81% yield (from **23**) after purification by preparative C_{18} HPLC. BOP activation of **25** followed by reaction with benzylamine in CH_2Cl_2 afforded diamide **4** in 96% yield after purification by flash chromatography. Thus, **4** was obtained from **23** in 78% overall yield.

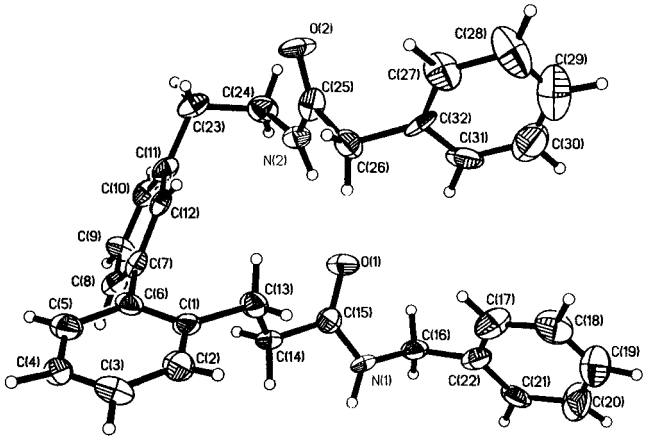


Figure 7. ORTEP depiction of *N*-benzyl-3′-(2-(benzylamido)-ethyl)-2-biphenylpropamide (**3**).

Single Crystal X-ray Analysis of Diamides 3 and 4. Orthorhombic crystals having a space group of Fdd2 were obtained for diamide **3** by dissolving the compound in hot chloroform and allowing the crystals to grow at room temperature over 48 h. The ORTEP depiction of the structure in Figure 7 exhibits an N(2) to O(1) bond distance of 2.98 Å, indicating that the formation of a 13-membered ring intramolecular hydrogen bond is preferred in the solid state (Figure 5, **3a**). An intermolecular hydrogen bond between N(1) and O(2) having a bond distance of 2.85 Å was also observed (Figure 8) which suggests that crystal packing forces may have influenced the preference for the 13-membered ring intramolecular

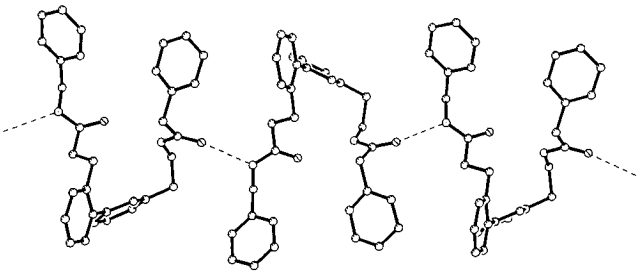


Figure 8. ORTEP depiction of *N*-benzyl-3′-(2-(benzylamido)-ethyl)-2-biphenylpropamide (**3**) showing the intermolecular hydrogen bond between N(1) and O(2).

hydrogen bond in the solid state. The structure demonstrates that the biphenyl system has the *R* configuration with a 120.8° dihedral angle between the two phenyl rings of the biphenyl unit. The aliphatic carbon−carbon bond of the 3′ side chain of residue **1** is perpendicular to the plane of phenyl ring 2, and the methylene groups of the side chain attached to the 2 position are perpendicular to the plane of ring 1. The average distance between the 2 and 3′ side chains was calculated to be 4.85 Å,[58] which is in excellent agreement with the distance between two strands of a naturally occurring antiparallel β-sheet. The bond lengths, angles, and coordinates and the isotropic and anisotropic displacement factors for the solid state structure of **3** are available from the Cambridge Crystallographic Data Center. Triclinic crystals having a space group of P1 were obtained for diamide **4** from a slowly cooled CCl_4 solution (Figure 9). Two closely related conformers were observed in the solid state structure. The first has an *S* configuration with a 120.0° angle between the two phenyl rings of the biphenyl ring while the second conformer has an *R* configuration with an angle of 121.3°. The crystal structure revealed an intermolecularly hydrogen-bonded system (Figure 10). The hydrogen bond is formed between O(1) and N(4) with a distance of 2.86 Å. The average distance between the 2 and 3′ side chains of the *S* conformer was calculated to be 5.53 Å while the average distance of the 2 and 3′ side chains of the *R* conformer was calculated to be 5.02 Å.[59] These distances are slightly larger than the distance separating two strands of a naturally occurring antiparallel β-sheet and than the distance calculated for diamide **3**.

Variable-Temperature ^{1}H NMR Results for Diamides 3 and 4. Variable temperature ^{1}H NMR spectroscopy has been employed to probe intramolecular hydrogen bonding and was used here to probe the preferred hydrogen bonds adopted by **3** and **4** in a noncompetitive solvent (CH_2Cl_2). Generally, hydrogen-bonded NHs have downfield chemical shifts (~7.0−9.0 ppm) relative to non-hydrogen-bonded NHs (~5.5−6.0 ppm) at 25 °C. In acyclic amides, hydrogen-bonded NHs typically exhibit a large temperature dependence of the chemical shift ($\Delta\delta/\Delta T \sim -10$ to -13 ppb/K) relative to

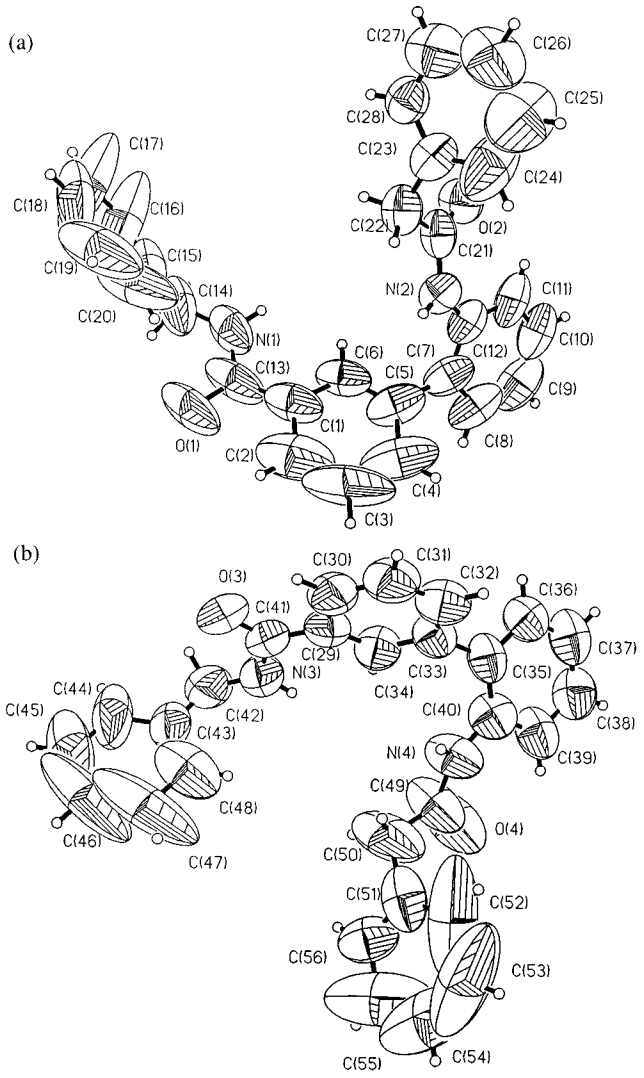


Figure 9. ORTEP depiction of *N*-benzyl-2-(benzylamido)-3′-biphenylamide (**4**) showing (a) the *S* conformer and (b) the *R* conformer.

free NHs ($\Delta\delta/\Delta T \sim -3$ ppb/K) in CD_2Cl_2.[60−64] Amides which are undergoing equilibration between the hydrogen-bonded and nonbonded states have been observed to exhibit intermediate temperature dependencies (−7 to −10 ppb/K) and room-temperature chemical shifts in the range of 5.5−6.5 ppm.[62] Since amino acid **1** has been designed to replace the backbone of the $i + 1$ and $i + 2$ residues of a β-turn, a 15-membered ring hydrogen bond was desired (Figure 5, **3b**) for nucleating β-sheet formation as this is the hydrogen bond which is formed between the NH and C═O of of the i and $i + 3$ residues in a β-hairpin. A proton NMR spectrum of **3** (4.2 mM solution in CD_2Cl_2 at room temperature) shows resonances for the amide protons at δ 6.3 and 6.1 ppm (298 K). The downfield signal shows a large temperature dependence ($\Delta\delta/\Delta T = -10$ ppb/K) consistent with an intramolecular hydrogen bond,

(58) The distances between N(2) and C(15), C(23) and C(13), C(24) and C(14), C(25) and C(15), and O(1) and O(2) were used to calculate the average strand distance in diamide **3**.

(59) The distances between N(4) and C(41), N(3) and C(49), N(3) and N(4), and C(42) and C(50) were used to calculate the average strand distance in the *R* conformer of diamide **4**, and the distances between N(2) and C(13), N(1) and N(2), N(1) and C(21), and C(14) and C(22) were used to calculate the average strand distance in the *S* conformer of diamide **4**.

(60) Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048−7050.

(61) Gellman, S. H.; Adams, B. R.; Dado, G. P. *J. Am. Chem. Soc.* **1990**, *112*, 460−461.

(62) Gellman, S. H.; Dado, G. P.; Liang, G.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164−1173.

(63) Liang, G.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994−3995.

(64) Liang, G.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4440−4442.

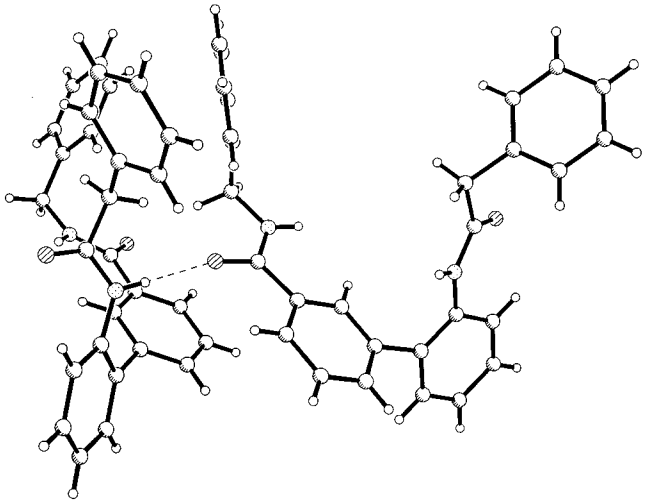


Figure 10. ORTEP depiction of *N*-benzyl-2-(benzylamido)-3′-biphenylamide (**4**) showing the intermolecular hydrogen bond between N(4) and O(1).

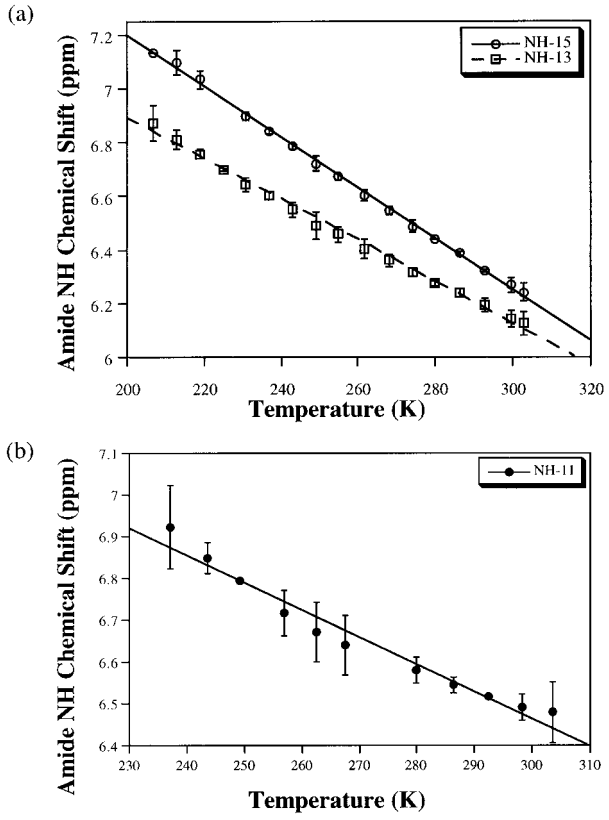


Figure 11. (a) Temperature dependence of chemical shifts of the amide protons of model compound **3** (4.2−6.3 mM CH_2Cl_2). ○: the amide proton corresponding to the 15-membered hydrogen-bonded ring conformation. □: represent the amide proton corresponding to the 13-membered ring conformation. (b) Temperature dependence of chemical shift of the amide proton corresponding to the 11-membered hydrogen-bonded ring conformation of model compound **4** (4.1−4.7 mM CH_2Cl_2, ●).

while the upfield signal shows a moderate temperature dependence ($\Delta\delta/\Delta T = -8$ ppb/K) (Figure 11a). These values suggest that both the 13- and 15-membered hydrogen-bonded rings (**3a** and **3b**) are in fast equilibrium on the NMR time scale. A DQ COSY experiment was used to unambiguously assign the amide proton signals. Crosspeaks between the NH signal at 6.1 ppm and the quartet at 3.46 ppm ($-CH_2CH_2NHCOCH_2Ph$) and between the NH signal at 6.3 ppm and the doublet at 4.28 ppm ($-CH_2CH_2CONHCH_2Ph$) were observed. Thus, the amide proton exhibiting the larger temperature coefficient is assigned to the amide proton capable of forming the 15-membered ring hydrogen bond (**3b**). The larger temperature coefficient suggests that the 15-membered ring (**3b**) is favored over the 13-membered ring (**3a**) in CH_2Cl_2 solution. These interpretations are consistent with the solution IR spectroscopy results discussed below but are opposite to the crystallography results, most likely owing to crystal packing forces in the solid state structure. While these data demonstrate the ability of **1** to hydrogen bond in a non-hydrogen-bonding solvent, intramolecular hydrogen bonding is less energetically favorable in aqueous solvents. However, slow amide proton deuterium exchange rates for the α-amino acids flanking **1** in small peptides indicate that the 15-membered ring hydrogen bond is preferentially formed in aqueous solution as well.[65] In a peptide incorporating **2**, the 11-membered hydrogen-bonded ring conformation (Figure 6, **4b**) is ideal for nucleating β-sheet formation as it is formed between the NH and C=O of the flanking α-amino acid residues. The ^{1}H NMR spectrum of **4** in CH_2Cl_2 at room temperature revealed one amide proton signal at 6.5 ppm. The remaining amide proton appears to be buried under the aromatic signals. A DQ COSY experiment exhibits a cross peak between the amide NH signal and the doublet at 4.3 ppm ($-C(O)NHCH_2Ph$), identifying the amide proton at 6.5 ppm (298 K) as that capable of forming the 11-membered ring hydrogen bond; Figure 4b. This proton exhibits an intermediate temperature dependence (−6.5 ppb/K) which is consistent with a proton in rapid equilibrium between the hydrogen-bonded and nonbonded states (Figure 11b). The remaining amide proton (that derived from residue **2**) has a small temperature dependence (≤−3 ppb/K)[66] which is consistent with a non-hydrogen-bonded amide proton.

FT-IR Study of the Amide Hydrogen Bonding of Diamides 3 and 4. Intramolecular amide−amide hydrogen bonding was also studied in CH_2Cl_2 by analyzing the amide NH infrared stretch region (3200−3500 cm^{-1}) where a sharp signal at 3400−3500 cm^{-1} generally corresponds to a free NH and a broader band at ∼3200−3400 cm^{-1} corresponds to a hydrogen-bonded NH.[60−64] Infrared studies on diamide **3** (1.7 mM in CH_2Cl_2) reveal that intramolecular hydrogen bonding does occur (Figure 12a). Two bands are observed in the amide stretch region: one having a maximum at 3429 cm^{-1} (nonbonded NH) and one having a maximum at 3337 cm^{-1} (hydrogen-bonded NH). These results have several possible interpretations. One possibility is that the diamide may exist entirely in the 15-membered ring hydrogen-bonded conformation which is possible; however, the moderate temperature coefficient for the amide NH capable of forming the 13-membered suggests that the 13-membered ring is also a minor conformer. Alternatively, because the time scale of IR measurements is fast compared to the equilibration rate of conformers **3a** and **3b**, it is possible to observe distinct NH stretch absorptions for each of the equilibrating states. Thus, the two bands observed are likely to result from a mixture of **3a**

(65) Nesloney, C. L.; Kelly, J. W. Unpublished results.
(66) Value calculated by dividing the width of the aromatic signals overlapping the amide proton resonance (0.3 ppm) by the temperature range of the experiment.

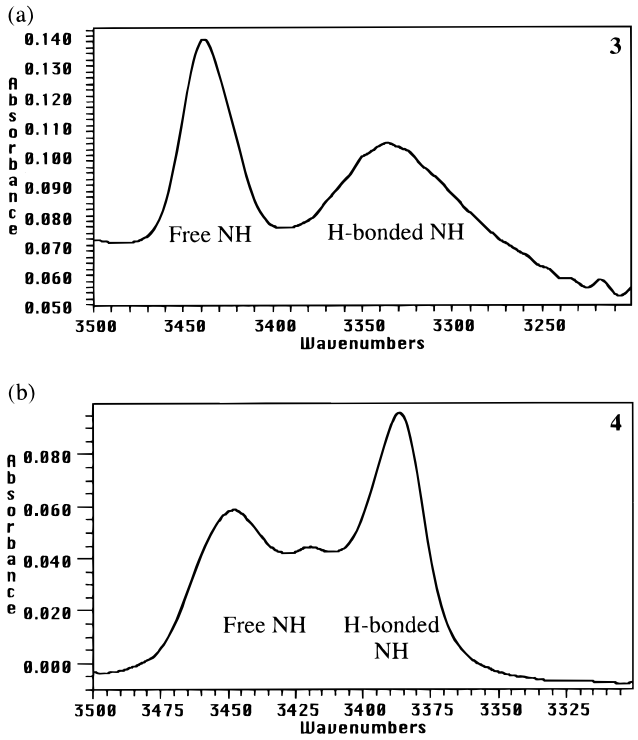


Figure 12. FT-IR spectral data of amide derivatives **3** and **4** from the NH stretch region in CH_2Cl_2. (a) 1.7 mM diamide **3** (maxima at 3337 and 3439 cm^{-1}) and (b) 3.0 mM diamide **4** (maxima at 3387, 3420, and 3449 cm^{-1}). Spectra were obtained at room temperature and have been corrected for CH_2Cl_2 contributions.

and **3b** such that the hydrogen-bonded NHs in **3a** and **3b** combine to give the observed broad band centered at 3337 cm^{-1} and the nonbonded NHs in **3a** and **3b** both contribute to the band at 3429 cm^{-1}. The most likely scenario is that **3b** is the major conformer with minor contributions from **3a** and perhaps even a small non-hydrogen-bonded component. This interpretation is consistent with all spectroscopic data including the recent data collected on peptides in aqueous solution.[65]

The FT-IR of **4** (3.0 mmol, CH_2Cl_2) reveals three bands in the amide stretch region having maxima at 3449, 3420, and 3387 cm^{-1} (Figure 12b). The first two bands correspond to nonbonded amide protons while the band at 3387 cm^{-1} corresponds to a hydrogen-bonded NH. These results are consistent with the ^1H NMR data which suggest that the amide proton capable of forming a 9-membered ring hydrogen-bonded conformation does not form an intramolecular hydrogen bond while the amide proton capable of forming an 11-membered ring hydrogen bond exists in an equilibrium between the hydrogen-bonded and non-hydrogen-bonded states. That the 11-membered ring hydrogen-bonded conformer is in equilibrium with a non-hydrogen-bonded state in the absence of a 9-membered ring hydrogen-bonded conformation suggests that the net energetic gain associated with intramolecular hydrogen bonding in **4** is small. In order to demonstrate that intramolecular hydrogen bonding rather than intermolecular hydrogen bonding was being probed, the concentration dependence of the hydrogen bonding of **3** and **4** was examined by FT-IR. A concentration dependent increase in hydrogen bonding was not observed in the IR spectra for samples ranging from 0.34 to 85 mM (**3**) and 0.18 to 44 mM (**4**), consistent with a lack of intermolecular hydrogen bonding. Although the samples for both the VT NMR and FT-IR studies were extensively dried (refer to the Experimental Section for details), the samples of **3** typically contained 5−10 mM H_2O. Studies by Gellman have shown that addition of up to 30 mM D_2O does not appear to significantly affect the data obtained in these types of studies.[62,67]

Conclusion

The biphenyl-based amino acids **1** and **2** have been synthesized, and simple amide derivatives have been prepared and studied by X-ray crystallography, FT-IR, and NMR. Biphenyl-based amino acid **2** can support a partially hydrogen-bonded conformation which should be consistent with β-sheet formation but is incapable of adopting a hydrophobic cluster conformation thought to be critical for β-sheet nucleation. FT-IR and NMR studies of the diamide derivative of residue **1** indicate that it is capable of adopting a 15-membered, intramolecularly hydrogen-bonded conformation which should support antiparallel β-sheet structure. In addition, computational modeling based on the solid state structure of **1** suggests that it should be capable of promoting hydrophobic cluster formation involving at least one of the phenyl rings of the biphenyl skeleton and one of the hydrophobic flanking α-amino acid side chains. Evaluations of peptides containing amino acids **1** and **2** support these predictions.[65]

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl under nitrogen (N_2). Dichloromethane (CH_2Cl_2), trimethylsilyl chloride (TMSCl), and trimethyl borate ($B(OMe)_3$) were distilled from calcium hydride under N_2. Triethylamine (TEA) and diisopropylethylamine (DIEA) were refluxed over ninhydrin, distilled, and then distilled from calcium hydride. Routine ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-200E spectrometer and are reported in parts per million (δ) relative to $CHCl_3$ (7.24 ppm). J values are given in Hz. Variable-temperature and 2D NMR studies of diamides **3** and **4** were obtained on a Varian XL-400 spectrometer. Data from the 400 MHz NMR were processed using Varian VNMR version 5.1 software. Analytical thin layer chromatography was performed on E. Merck silica gel 60 F_{254} plates. Column chromatography was performed as described by Still[68] using forced flow (flash) chromatography with the indicated solvents on Baxter SIP silica gel 60 Å (230−400 mesh). Melting points were obtained on a Bristoline apparatus and are uncorrected. Nominal resolution mass spectra were obtained on a Hewlett-Packard 5971 mass spectrometer, and high-resolution mass spectra were obtained on a VG-70S double-focusing high-resolution mass spectrometer. Preparative HPLC was carried out on a dual pump system equipped with Altex 110A pumps and a 420 gradient programmer or a Waters 600 preparative HPLC. Waters RCM Delta Pak C_{18} and C_4 (15 μm, 300 Å, 25 × 100 mm) columns and a Knauer 86 variable-wavelength detector were used. Solvent A was composed of 95% water, 5% acetonitrile, and 0.2% TFA. Solvent B was composed of 5% water, 95% acetonitrile, and 0.2% TFA.

Synthesis of 3′-(2-Aminoethyl)-2-biphenylpropionic Acid Derivatives. 2-Bromodihydrocinnamic Acid (5). To a solution of 2-bromocinnamic acid (1.08 g, 4.76 mmol) in EtOH (150 mL) was added tris(triphenylphosphine)rhodium(II) chloride (0.22 g, 0.24 mmol, 5.0 mol %) in a 500 mL hydrogenation

(67) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228−4245.
(68) Still, W. C.; Kahn, M.; Maitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

bottle. The resulting light yellow mixture contained some undissolved, dark red catalyst. The reaction mixture was hydrogenated at 50 psi (25 °C) for 40−50 h using a Parr hydrogenator. The bright yellow, homogeneous solution was concentrated in vacuo to give a light brown oil. The crude material was purified by flash chromatography (70:29:1 hexanes:ethyl acetate:acetic acid) to give 1.02 g (94%) of the fully saturated compound as a white solid: mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 11.98 (bs, 1 H), 7.56 (d, J = 7.7, 1 H), 7.31−7.06 (m, 3 H), 3.10 (t, J = 7.7 Hz, 2 H), 2.74 (t, J = 7.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 179.80, 139.87, 133.46, 130.93, 128.73, 128.15, 124.87, 34.42, 31.60; MS (+FAB, NBA/PEGH) m/z 228.9836 (^{79}Br) and 230.9837 (^{81}Br), $[M + H]^+$ calcd for $C_9H_9O_2Br$ 228.9864.

Ethyl 2-Bromodihydrocinnamate (6). An oven-dried, Ar-purged, 25 mL round-bottomed flask was charged with 2-bromodihydrocinnamic acid (0.73 g, 3.2 mmol) and absolute EtOH (15 mL). To the light yellow solution was added *p*-toluenesulfonic acid (6.0 mg, 0.03 mmol). The flask was fitted with a condenser, and the system was flushed with Ar. The solution was heated at reflux for 22 h. The EtOH was removed in vacuo, and the resulting light brown oil was taken up in ether (100 mL). The organic layer was washed with H_2O (3 × 75 mL), 5% $NaHCO_3$ (3 × 75 mL), and 5% $Na_2S_2O_5$ (2 × 75 mL) and then dried ($MgSO_4$). The pale yellow etheral solution was concentrated under reduced pressure. Further drying under high vacuum afforded 0.78 g (95%) of a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 8.2, 1 H), 7.27−7.17 (m, 2 H), 7.12−7.02 (m, 1 H), 4.13 (q, J = 7.2, 2 H), 3.06 (t, J = 7.8, 2 H), 2.63 (t, J = 7.8, 2 H), 1.23 (t, J = 7.2, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.63, 139.81, 132.87, 130.46, 128.04, 127.52, 124.36, 60.48, 34.12, 31.42, 14.19; MS (+FAB, NBA/PEGH) m/z 257.0176, $[M + H]^+$ calcd for $C_{11}H_{13}O_2Br$ 257.0177.

1-Bromo-3-(trimethylsilyl)benzene (7). A 50 mL round-bottomed flask was flame-dried under Ar and charged with 1,3-dibromobenzene (1.8 mL, 15 mmol) and freshly distilled THF (30 mL). The clear solution was cooled to −95 °C (methanol/liquid N_2 bath). Addition of *n*-BuLi (11.5 mL of a 1.3 M solution in hexanes, 15 mmol) over 15 min resulted in a pale yellow solution. The mixture was stirred at −95 °C for 5 min and then quenched with TMSCl (4.7 mL, 37 mmol). The pale yellow solution was stirred at −75 °C (methanol/dry ice) for an additional 2 h and then allowed to warm to 25 °C overnight. After 12−16 h, the reaction mixture was at room temperature, and the pale yellow solution contained a white solid. The mixture was concentrated in vacuo and then partitioned between ether and H_2O (75 mL each). The layers were separated, and the organic layer was washed with two additional 75 mL portions of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material (3.57 g, 105% of a light yellow oil) was purified by vacuum distillation. The fraction boiling at 79.0−79.5 °C (1.7 mmHg) (lit.[69] bp 50 °C (0.05 mmHg)) was collected as a clear oil (3.09 g, 91%): ^{1}H NMR ($CDCl_3$) δ 7.66−7.61 (m, 1 H, Ar H_2), 7.51−7.40 (m, 2 H), 7.22 (t, J = 7.7, 1 H) 0.27 (s, 8 H); ^{13}C NMR ($CDCl_3$) δ 144.25, 136.44, 132.22, 132.04, 129.96, 123.39, −0.86.

3-(Trimethylsilyl)phenylboronic Acid (8). A 500 mL round-bottomed flask was flame-dried under Ar and charged with 1-bromo-3-(trimethylsilyl)benzene (3.18 g, 13.9 mmol) and freshly distilled THF (75 mL). The clear solution was cooled to −95 °C (methanol/liquid N_2 bath). Addition of *n*-BuLi (16.0 mL of a 1.3 M solution, 21 mmol) over a 20 min period resulted in a yellow solution. After 5 min of stirring at −95 °C, the solution was quenched with $B(OMe)_3$ (15.8 mL, 139 mmol). The colorless solution was kept at −78 °C for 2 h and then allowed to warm to room temperature overnight (12−16 h). The mixture was then cooled to 0 °C and acidified to pH 6 with 10% HCl. A white precipitate formed. The mixture was stirred at 0 °C for 1 h and then concentrated in vacuo to yield a white slurry. The slurry was partitioned between ether and 10% HCl (150 mL each). The layers were separated, and the aqueous layer was washed with ether (2 × 100 mL). The organic layers were combined, washed with 10% HCl (2 × 125 mL), dried ($MgSO_4$), and concentrated in vacuo. Further drying under high vacuum afforded 2.88 g (107%) of a crude white solid. The crude compound was generally used in the following step without further purification. When required, pure material was obtained through crystallization from a CH_2Cl_2/hexanes mixture (28% recovery): mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (bd, J_p = 0.7, 1 H), 8.25 (dt, J_o = 7.4, J_m = 1.4, 1 H), 7.8 (dt, J_o = 7.3, J_m = 1.4, 1 H), 7.54 (td, J_o = 7.3, J_p = 0.7, 1 H), 0.39 (s, 8 H); ^{13}C NMR ($CDCl_3$) δ 140.86, 139.90, 137.77, 136.15, 129.44, 127.53, −0.98.

Ethyl 3′-(Trimethylsilyl)-2-biphenylpropionate (9). A three-necked, 100 mL round-bottomed flask was fitted with a reflux condenser, flame-dried under Ar, and charged with ethyl 2-bromodihydrocinnamate (2.26 g, 8.79 mmol), tetrakis(triphenylphosphine)palladium(II) (0.31 g, 0.27 mmol), and 60 mL of dimethylethylene glycol (DME). The bright yellow solution was stirred at room temperature in darkness for 20 min. Sequential addition of boronic acid **15** (2.88 g, 13.9 mmol) and Na_2CO_3 (8.8 mL of a 2.0 M aqueous solution, 18 mmol) resulted in a light brown solution and the formation of a white precipitate. The reaction mixture was heated at reflux for 22 h. The mixture was cooled, concentrated in vacuo, and taken up in CH_2Cl_2 (75 mL) and H_2O (150 mL). The layers were separated, and the aqueous layer was washed with three additional 75 mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Further drying under high vacuum afforded a dark yellow oil. The crude material was purified by flash chromatography (70:30 hexanes:$CHCl_3$) to give 2.65 g (92%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.55−7.20 (m, 8 H), 4.05 (q, J = 7.1, 2 H), 2.92 (m, 2 H), 2.44 (m, 2 H), 1.18 (t, J = 7.1, 3 H), 0.28 (s, 8 H); ^{13}C NMR ($CDCl_3$) δ 172.84, 142.26, 140.66, 140.39, 137.98, 133.91, 131.89, 130.25, 129.45, 129.06, 127.54, 127.48, 126.21, 60.29, 35.56, 28.39, 14.15, −1.13; EI MS m/z 326.1700, M^+ calcd for $C_{20}H_{26}O_2Si$ 326.1702.

Ethyl 3′-Iodo-2-biphenylpropionate (10). A 250 mL round-bottomed flask was flame-dried under Ar and charged with ethyl 3′-(trimethylsilyl)-2-biphenylpropionate (2.57 g, 7.87 mmol), K_2CO_3 (3.26 g, 23.6 mmol), and CCl_4 (50 mL, dried over $MgSO_4$). The solution was cooled to 0 °C. The ICl (1.0 mL, 19 mmol) was transferred via a Teflon cannula to a graduated cylinder which had been flame-dried under Ar and charged with CCl_4 (6.4 mL, 2.6 M solution). The solution was then transferred to the reaction flask via the Teflon cannula. The graduated cylinder and cannula were rinsed with three additional 4 mL portions of CCl_4. The cooling bath was removed after 30 min, and the red wine colored solution was stirred at room temperature, in darkness overnight (15 h). The reaction mixture was poured into 200 mL of a 10% $Na_2S_2O_3$ solution. This was diluted with 100 mL of CH_2Cl_2 and vigorously stirred. Additional solid $Na_2S_2O_3$ was added, and the mixture was stirred until light yellow. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with 10% $Na_2S_2O_3$ (3 × 120 mL), 10% $NaHCO_3$ (3 × 120 mL), 10% HCl (3 × 120 mL), and H_2O (2 × 100 mL). The colorless organic layer was then dried ($MgSO_4$), concentrated in vacuo, and further dried under high vacuum to afford 3.01 g (101%) of a yellow oil. An analytical sample was obtained by preparative C_4 HPLC as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.72−7.66 (m, 2 H), 7.31−7.10 (m, 6 H), 4.06 (q, J = 7.1, 2 H), 2.91 (m, 2 H), 2.42 (m, 2 H), 1.19 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.68, 143.65, 140.31, 137.94, 137.80, 136.02, 130.05, 129.85, 129.06, 128.39, 128.02, 126.32, 94.19, 60.40, 35.32, 28.18, 14.18; EI MS m/z 380.0266, M^+ calcd for $C_{17}H_{17}O_2I$ 380.0273.

Ethyl 3′-(Carboxyethenyl)-2-biphenylpropionate (11). The iodobiphenyl compound **10** (2.90 g, 7.63 mmol) was dried under high vacuum in an oven-dried, 50 mL round-bottomed flask. Palladium acetate (30.2 mg, 0.13 mmol) and triphenylphosphine (94.5 mg, 0.36 mmol) were added to the flask which was fitted with an oven-dried condenser. The system was alternately evacuated under high vacuum and purged with Ar (four cycles). The DMF (8 mL), triethylamine (2.7 mL,

(69) Klusener, P. A. A.; Hanskamp, J. C.; Brandsma, L.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1311−1321.

(70) This figure was prepared with MolScript; see: Kraulis, P. T. *J. Appl. Crystallogr.* **1991**, *24*, 946−950.

19 mmol), and acrylic acid (0.86 mL, 11 mmol) were added via syringe. The dark brown solution was immersed in a 55 °C oil bath. The temperature was increased to 150 °C over 70 min. The reaction mixture was kept at 150 °C for 5 min and then cooled to 130 °C. After 5 h at 130 °C, the reaction mixture was cooled and diluted with CH_2Cl_2 (100 mL) and H_2O (200 mL). The aqueous layer was washed with CH_2Cl_2 (5 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Further drying under high vacuum afforded 2.95 g (119%) of a dark brown oil. Purification by flash chromatography (75:24:1 hexanes:ethyl acetate:acetic acid) afforded 1.91 g (77%) of a light brown oil: ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 16.0, 1 H), 7.57−7.16 (m, 8 H), 6.48 (d, J = 16.0, 1 H), 4.05 (q, J = 7.1, 2 H), 2.93 (m, 2 H), 2.43 (m, 2 H), 1.17 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.79, 172.32, 146.91, 142.30, 140.95, 137.83, 134.05, 131.51, 130.10, 129.12, 129.03, 128.90, 127.98, 127.00, 126.40, 117.68, 60.44, 35.37, 28.24, 14.18; MS (+FAB, NBA/PEGH) m/z 325.1457, $[M + H]^+$ calcd for $C_{20}H_{20}O_4$ 325.1440.

Ethyl 3′-(Carboxyethenyl)-2-biphenylpropionate (12). The biphenyl compound **11** (0.38 g, 1.2 mmol) was dissolved in 50 mL of 1:1 ethanol:acetic acid in an oven-dried, 100 mL round-bottomed flask. To the clear solution was added PtO_2 (18.5 mg, 0.08 mmol). The system was alternately evacuated under reduced pressure and flushed with H_2. The reaction mixture was vigorously stirred under positive H_2 pressure (using a balloon) for 6 h. The PtO_2 was removed by filtration, and the pale yellow filtrate was concentrated under reduced pressure. The crude material was taken up in CH_2Cl_2 (30 mL) and washed with H_2O (3 × 40 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 0.37 g (97%) of the desired compound as an opaque oil: ^{1}H NMR ($CDCl_3$) δ 9.81 (bs, 1 H), 7.39−7.12 (m, 8 H), 4.08 (q, J = 7.1, 2 H), 3.02 (m, 2 H), 2.94 (m, 2 H), 2.72 (m, 2 H), 2.44 (m, 2 H), 1.20 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.28, 173.73, 141.84, 141.59, 139.98, 137.73, 130.16, 129.27, 128.94, 128.58, 127.55, 127.15, 127.00, 126.25, 60.68, 35.77, 35.38, 30.94, 28.36, 14.11; MS (+FAB, NBA/PEGH) m/z 327.1585, $[M + H]^+$ calcd for $C_{20}H_{22}O_4$ 327.1596.

Ethyl 3′-(*N*-(*tert*-Butyloxycarbonyl)-2-aminoethyl)-2-biphenylpropionate (13). Compound **12** (1.52 g, 4.66 mmol) was dissolved in *t*-BuOH (18.0 mL) in an oven-dried, Ar cooled, 50 mL cone-shaped flask. The flask was flushed with Ar, and diphenyl phosphorazidate (1.05 mL, 5.21 mmol) and Et_3N (0.75 mL, 5.4 mmol) were added. The flask was fitted with an oven-dried condenser, and the system was again flushed with Ar. The slightly yellow solution was heated at reflux for 24 h. The reaction mixture was concentrated under reduced pressure and dried under high vacuum to afford the crude material as an orange oil (3.71 g, 200%). The pure compound (1.30 g, 70%) was obtained after flash chromatography (80:20 hexanes:ethyl acetate) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.39−7.11 (m, 8 H), 4.75 (bs, 1 H), 4.08 (q, J = 7.1, 2 H), 3.39 (m, 2 H), 2.93 (m, 2 H), 2.83 (m, 2 H), 2.40 (m, 2 H), 1.42 (s, 8 H), 1.17 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.89, 155.89, 141.84, 141.66, 139.06, 137.88, 130.15, 129.63, 129.07, 128.43, 127.56, 127.50, 127.15, 126.26, 79.20, 60.35, 36.27, 36.19, 35.43, 28.50, 28.41, 14.15; MS (+FAB, NBA/PEGH) m/z 398.2334, $[M + H]^+$ calcd for $C_{24}H_{21}O_4N$ 398.2331.

3′-(*N*-(*tert*-Butyloxycarbonyl)-2-aminoethyl)-2-biphenylpropionic Acid (14). The ester carbamate **13** (162.0 mg, 0.41 mmol) was dissolved in absolute ethanol (6.2 mL) in an oven-dried, 10 mL round-bottomed flask. Addition of 1.0 M aqueous LiOH (4.0 mL, 4.0 mmol) to the clear solution resulted in the reaction mixture becoming turbid. The mixture was stirred under Ar at room temperature for 2.5 h. The mixture was diluted with 100 mL of 1 M citric acid and washed with ethyl acetate (3 × 75 mL). The combined organic layers were washed with ice-cold H_2O (3 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Further drying under high vacuum afforded the desired compound in quantitative yield as a clear oil: ^{1}H NMR ($CDCl_3$) δ 10.03 (bs, 1 H), 7.40−7.13 (m, 8 H), 4.83 (bs, 1 H), 3.39 (m, 2 H), 2.98 (m, 2 H), 2.83 (m, 2 H), 2.45 (m, 2 H), 1.45 (s, 8 H); ^{13}C NMR (acetone-d_6) δ 175.62, 172.03, 143.27, 142.94, 140.95, 139.51, 131.19, 130.86, 130.35, 129.47, 128.71, 128.06, 127.34, 78.97, 73.85, 43.60, 43.02, 37.18, 35.81; MS (+FAB, NBA/PEGH) m/z 370.2036, $[M + H]^+$ calcd for $C_{22}H_{27}O_4N$ 370.2018.

***N*-Benzyl-3′-(*N*-(*tert*-butyloxycarbonyl)-2-aminoethyl)-2-biphenylpropanamide (15).** Compound **14** (96.0 mg, 0.26 mmol), BOP reagent (0.19 g, 0.43 mmol), and DMF (8 mL) were cooled to 0 °C in an oven-dried, 50 mL cone-shaped flask. Freshly distilled benzylamine (0.60 mL, 5.5 mmol) was added, and the solution was warmed to ambient temperature. The reaction mixture became opaque. The mixture was stirred at room temperature under Ar for 40 h and then diluted with CH_2Cl_2 (40 mL). The organic solution was washed with 1 M citric acid (3 × 25 mL), 5% $NaHCO_3$ (3 × 25 mL), and H_2O (6 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. After the solution was dried under high vacuum, 182 mg (151%) of the crude material was obtained as an opaque yellow oil. Purification by flash chromatography (65:35 hexanes:ethyl acetate) afforded 0.09 g (76%) of the pure compound as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.35−7.05 (m, 13 H), 6.08 (bs, 1 H), 4.94 (bs, 1 H), 4.30 (d, J = 5.7, 2 H), 3.31 (m, 2 H), 2.98 (m, 2 H), 2.76 (m, 2 H), 2.29 (m, 2 H), 1.38 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.06, 156.02, 141.74, 139.15, 138.40, 138.17, 130.12, 129.64, 129.51, 128.54, 128.44, 127.64, 127.53, 127.25, 127.03, 126.25, 79.16, 43.33, 41.92, 37.66, 36.27, 29.37, 28.39; MS (+FAB, NBA/TROITON) m/z 459.2656, $[M + H]^+$ calcd for $C_{29}H_{37}O_3N_2$ 459.2648.

***N*-Benzyl-3′-(2-aminoethyl)-2-biphenylpropanamide (16).** Compound **15** (0.57 mmol) was dissolved in CH_2Cl_2 (21.0 mL) in an oven-dried, 100 mL round-bottomed flask. TFA (9.0 mL of a 30% solution in CH_2Cl_2) was added to the flask, and the clear solution was stirred at room temperature under Ar for 1.5 h. The resulting slightly yellow solution was concentrated to a yellow oil. The oil was dissolved in CH_2Cl_2 (60 mL), and the solution was washed with 10% $NaHCO_3$ (4 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated, and further dried under high vacuum to afford 0.212 g (104%) of the crude compound as an opaque yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.35−7.02 (m, 13 H), 5.93 (t, J = 5.7, 1 H), 4.30 (d, J = 5.7, 2 H), 2.94 (m, 4 H), 2.79 (m, 2 H), 2.25 (m, 2 H), 1.60 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.92, 141.83, 141.63, 139.73, 138.29, 138.11, 130.08, 129.65, 129.44, 128.60, 128.41, 127.66, 127.52, 127.35, 126.89, 126.29, 43.39, 43.18, 39.43, 37.74, 29.53; MS (+FAB, NBA/PEGH) m/z 359.2130, $[M + H]^+$ calcd for $C_{24}H_{26}ON_2$ 359.2123.

***N*-Benzyl-3′-(2-(benzylamido)ethyl)-2-biphenylpropanamide (3).** The crude compound **16** (0.57 mmol), phenyl acetic acid (216.0 mg, 1.59 mmol), and DIEA (362 μL, 2.08 mmol) were dissolved in CH_2Cl_2 (42 mL) in an oven-dried, Ar purged, 100 mL round-bottomed flask. The slightly cloudy solution was cooled to 0 °C, and BOP reagent (0.71 g, 1.6 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 21 h. The material was concentrated to a yellow oil, dissolved in DMSO, and purified by preparative C_{18} HPLC to afford 144.7 mg (53%) of the desired diamide as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.31−6.97 (m, 18 H), 6.56 (m, 1 H), 6.32 (m, 1 H), 4.28 (d, J = 5.7, 2 H), 3.51−3.39 (m, 4 H), 2.97 (m, 2 H), 2.73 (m, 2 H), 2.25 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.76, 171.90, 141.72, 141.66, 138.85, 137.97, 134.70, 130.12, 129.56, 129.40, 129.31, 128.84, 128.59, 128.39, 127.84, 127.73, 127.56, 127.45, 127.36, 127.23, 127.13, 126.41, 43.48, 43.22, 40.84, 37.57, 35.58, 29.56; MS (+FAB, NBA/PEGH) m/z 477.2548, $[M + H]^+$ calcd for $C_{32}H_{32}O_2N_2$ 477.2542.

Synthesis of 2-Amino-3′-biphenylcarboxylic Acid and Derivatives. 3-Bromo-*N*-*tert*-butyl-*N*-methylbenzamide (17). A solution of *tert*-butylmethylamine (10.0 mL, 83.4 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C under N_2 in a 250 mL round-bottomed flask. To the clear solution was added triethylamine (11.8 mL, 84.7 mmol) followed by slow addition of 3-bromobenzoyl chloride (11.0 mL, 83.3 mmol). After 2 h at 0 °C, the reaction mixture contained a white precipitate. The mixture was stirred at room temperature overnight. The reaction mixture was transferred to a separatory funnel and diluted with 100 mL each of CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O, 5% acetic acid, and 5%

aqueous NaOH (3 × 100 mL each). The clear, pale yellow organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 23.01 g (102%) of the crude product as a white solid: mp 41−44 °C; ^{1}H NMR ($CDCl_3$) δ 7.53−7.43 (m, 2 H), 7.34−7.17 (m, 2 H), 2.81 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.25, 141.00, 132.35, 130.18, 129.96, 125.72, 122.35, 56.69, 35.21, 27.63; MS (+FAB, NBA/PEGH) *m/z* 270.0506, $[M + H]^+$ calcd for $C_{12}H_{16}$-ONBr 270.0494.

3-(*N*-*tert*-Butyl-*N*-methylamidyl)phenylboronic Acid (18). A 500 mL round-bottomed flask was flame-dried under Ar and charged with **17** (6.80 g, 25.2 mmol) in 150 mL of THF. The clear solution was cooled to −95 °C. Addition of *s*-BuLi (20.2 mL, 27.7 mmol) resulted in a brown solution. After 10 min at −95 °C, the reaction mixture was treated with $B(OMe)_3$ (9.2 mL, 81 mmol). The resulting dark yellow solution was kept at −80 °C for 2 h and then warmed to −10 °C overnight. The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C, and acidified to pH 6 with 10% HCl. The resulting pale green mixture was stirred at 0 °C for 1.5 h. The THF was removed under reduced pressure, and the material was taken up in CH_2Cl_2 and H_2O (150 mL each). The aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 10% HCl (3 × 100 mL) and saturated NaCl (2 × 200 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 5.24 g (89%) of a yellow foam: ^{1}H NMR ($CDCl_3$) δ 8.11−8.07 (m, 1 H), 7.74−7.10 (m, 3 H), 2.86−2.85 (m, 3 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.76, 138.08, 136.00, 133.51, 129.39, 128.27, 127.11, 56.48, 35.41, 27.80.

Methyl 3′-(*N*-*tert*-Butyl-*N*-methylamidyl)-2-biphenylcarboxylate (19). An oven-dried, three-necked, 100 mL round-bottomed flask was charged with methyl 2-bromobenzoate (2.17 g, 10.1 mmol) and DME (20 mL). The flask was fitted with a condenser and purged with N_2. Tetrakis-(triphenylphosphine)palladium(II) (0.34 g, 0.29 mmol) was weighed out under N_2 and added to the flask. The resulting yellow solution was stirred at room temperature for 15 min. Sequential addition of the boronic acid **18** (5.17 g, 22.0 mmol in 10 mL of DME) and Na_2CO_3 (10.1 mL of a 2.0 M aqueous solution, 20 mmol) resulted in a biphasic reaction mixture. The mixture was heated at reflux for 50 h, and the solvents were removed in vacuo. The resulting residue was taken up in CH_2Cl_2 and H_2O (150 mL each). The aqueous layer was washed with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated NaCl (3 × 100 mL), dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum. The crude material was purified by flash chromatography (80:19:1 hexanes:ethyl acetate:acetic acid) to afford 2.25 g (69%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.86−7.81 and 7.52−7.29 (m, 8 H), 3.62 (s, 3 H), 2.88 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.86, 168.73, 141.94, 141.37, 138.91, 131.39, 130.76, 130.59, 129.94, 129.32, 128.06, 127.42, 127.18, 126.12, 56.50, 51.94, 35.33, 27.73; MS (+FAB, NBA/PEGH) *m/z* 326.1765, $[M + H]^+$ calcd for $C_{20}H_{23}O_3N$ 256.1756.

3′-(*N*-*tert*-Butyl-*N*-methylamidyl)-2-biphenylcarboxylic Acid (20). A 50 mL round-bottomed flask was charged with compound **19** (1.22 g, 3.75 mmol), NaOH (0.77 g, 19 mmol), and 20 mL of absolute MeOH. The mixture was heated at reflux under N_2 for 6 h. The reaction mixture was diluted with CH_2Cl_2 (35 mL) and 1 M citric acid (100 mL). The aqueous layer was washed with CH_2Cl_2 (5 × 35 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 1.1 g (95%) of a white solid: ^{1}H NMR ($CDCl_3$) δ 7.92 (dd, J_o = 7.8, J_m = 1.4, 1 H), 7.58−7.50 (m, 1 H), 7.45−7.28 (m, 6 H), 2.82 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.08, 172.12, 142.67, 141.15, 138.38, 137.29, 132.05, 131.10, 130.64, 129.78, 129.41, 128.17, 127.45, 126.17, 56.70, 35.30, 27.73; MS (+FAB, NBA/PEGH) *m/z* 312.1605, $[M + H]^+$ calcd for $C_{19}H_{21}O_3N$ 312.1600.

2-(*N*-(*tert*-Butyloxycarbonyl)amino)-3′-biphenylyl-*N*-methyl-*N*-*tert*-butylamide (21). The biphenyl acid amide **20** (1.83 g, 5.9 mmol) was dissolved in dry *t*-BuOH (25 mL) in an oven-dried, 50 mL round-bottomed flask. Triethylamine (0.85 mL, 6.1 mmol) and diphenyl phosphorazidate (1.55 mL, 7.2 mmol) were added at room temperature. The resulting dark orange solution was heated at reflux under N_2 for 22.5 h. The reaction mixture was concentrated under reduced pressure. The dark brown oil was taken up in Et_2O (150 mL) and washed with 1 M citric acid and 5% NaOH (3 × 100 mL each). The etheral layer was dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 2.02 g (100%) of a 1.6:1.0 mixture of the desired carbamate (**21**) and the corresponding urea compound (**22**) as a light brown foam. Analytical samples of both compounds were obtained by preparative C_{18} HPLC. The desired carbamate was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.92 (bd, J_o = 8.3, 1 H), 7.54−7.14 (m, 7 H), 6.65 (bs, 1 H), 2.94 (s, 3 H), 1.53 (s, 9 H), 1.43 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 174.06, 153.69, 138.82, 137.90, 134.83, 130.78, 130.13, 129.35, 128.69, 127.69, 126.13, 124.04, 120.12, 120.02, 80.93, 57.97, 35.70, 28.18, 27.73.

2-Amino-3′-biphenylcarboxylic Acid (2). The crude mixture of **21** and **22** (2.02 g, 5.9 mmol) was dissolved in concentrated HCl in a 250 mL round-bottomed flask. Phenol (5 drops) was added, and the solution was heated at 110 °C under Ar for 45 h. After being cooled to 0 °C, the material was filtered. The filtrate was diluted with H_2O and neutralized with NaOH (total volume of 800 mL). The aqueous solution was extracted with $CHCl_3$ (8 × 75 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and dried under high vacuum to afford 0.58 g (46%) of a beige solid. The material was purified by preparative C_{18} HPLC to obtain a white solid: ^{1}H NMR ($CDCl_3$) δ 8.11−8.10 (m, 1 H), 7.98 (dd, J_o = 7.6, J_m = 1.4, 1 H), 7.62−6.70 (m, 7 H), 6.61 (bs, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.67, 143.41, 139.64, 133.39, 131.41, 130.40, 128.77, 128.53, 126.55, 126.10, 118.64, 115.74, 114.85; MS (+FAB, NBA/PEGH) *m/z* 214.0852, $[M + H]^+$ calcd for $C_{13}H_{11}O_2N$ 214.0868.

Methyl 2-Amino-3′-biphenylcarboxylate (23). The amino acid **2** (0.12 g, 0.56 mmol) was suspended in anhydrous MeOH in an oven-dried, 5 mL round-bottomed flask. The slightly yellow suspension was cooled to 0 °C, and thionyl chloride (60 μL, 0.69 mmol) was added. The mixture immediately became clear and slightly darker. The reaction was heated at reflux for 10 h. Additional aliquots of $SOCl_2$ were added (a total of 0.90 mL, 10 mmol), and refluxing was continued over 90 h. The reaction mixture was partitioned between $CHCl_3$ and 5% $NaHCO_3$ (30 mL each). The aqueous layer was washed with $CHCl_3$ (2 × 30 mL) and Et_2O (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and further dried under high vacuum to afford 0.13 g (100%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.14 (t, J = 1.8, 1 H), 8.04−7.98 (m, 1 H), 7.69−7.64 (m, 1 H), 7.49 (t, J = 7.7, 1 H), 7.25−7.13 (m, 2 H), 6.94−6.84 (m, 2 H), 4.64 (bs, 2 H), 3.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.93, 141.86, 139.47, 133.69, 130.76, 130.51, 130.27, 128.95, 128.48, 127.45, 119.85, 116.69, 52.20; MS (+FAB, NBA/PEGH) *m/z* 227.0956, M^+ calcd for $C_{20}H_{23}O_3N$ 227.0946.

2-(Benzylamido)-3′-biphenylcarboxylic Acid (24). Phenylacetic acid (0.84 g, 6.2 mmol) and BOP reagent (2.77 g, 6.3 mmol) were dissolved in 30 mL of freshly distilled CH_2Cl_2 in an oven-dried, Ar-flushed, 100 mL round-bottomed flask. DIEA (1.6 mL, 9.2 mmol) was added, and the clear solution was cooled to 0 °C. Addition of **23** (0.14 g, 0.62 mmol in 30 mL of CH_2Cl_2) resulted in a very pale yellow solution. After 0.5 h at 0 °C, the solution was stirred at room temperature for 68 h. *N*,*N*′-Dimethylethylene (1.7 mL, 16 mmol) was added to the dark yellow solution to destroy the excess active ester. After 48 h at room temperature, the solution was transferred to a separatory funnel and partitioned between CH_2Cl_2 and 1 M citric acid (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with 1 M citric acid (4 × 75 mL), 5% $NaHCO_3$ (3 × 75 mL), and H_2O (2 × 75 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and further dried under high vacuum to afford 0.92 g of the crude product as an orange oil. The crude material was dissolved in MeOH (20 mL) in an oven-dried, Ar-flushed, 50 mL round-bottomed flask. To the orange solution was added aqueous LiOH (4.4 mL of a

1.0 N solution, 4.4 mmol). After 18.5 h at room temperature, the solution was concentrated to an orange oil and redissolved in $CHCl_3$ (75 mL) and 1 M citric acid (75 mL). The aqueous layer was washed with $CHCl_3$ (3 × 50 mL) and CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Further drying under high vacuum afforded 0.89 g of the crude product as an orange oil. Purification by preparative C_{18} HPLC afforded 0.17 g (81%) of the pure material as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.34 (d, $J_o = 8.2$, 1 H), 8.06 (dt, $J_o = 7.6$, $J_m = 1.6$, 1 H), 7.84 (s, 1 H), 7.43−7.00 (m, 10 H), 3.64 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.57, 169.21, 138.07, 134.54, 134.05, 133.48, 131.18, 130.57, 130.10, 129.96, 129.38, 129.17, 128.89, 128.70, 127.64, 126.74, 124.50, 121.18, 44.95; MS (+FAB, thiogly) *m/z* 332.1282, $[M + H]^+$ calcd for $C_{21}H_{17}O_3N$ 332.1287.

***N*-Benzyl-2-(benzylamido)-3′-biphenylamide (4).** An oven-dried, Ar-flushed, 50 mL round-bottomed flask was charged with **24** (0.07 g, 0.2 mmol) and BOP reagent (0.10 g, 0.23 mmol) in dry CH_2Cl_2 (10 mL). Freshly distilled benzylamine (0.50 mL, 4.6 mmol) was added, and the light yellow solution was stirred at room temperature for 12 h. The solution was concentrated under reduced pressure, and a crude yellow oil was obtained. Purification by flash chromatography (70:30 hexanes:ethyl acetate) afforded 0.085 g (96%) of a white solid: ^{1}H NMR ($CDCl_3$) δ 8.30 (d, $J_o = 8.2$, 1 H), 7.80 (dt, $J_o = 7.8$, 1 H), 7.48 (t, $J = 7.8$, 1 H), 7.39−6.96 (m, 16 H), 6.34 (bs, 1 H) 4.66 (d, $J = 5.7$, 2 H), 3.58 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.99, 166.45, 138.12, 137.99, 136.59, 134.93, 134.61, 133.61, 131.84, 131.33, 129.92, 129.30, 129.26, 129.15, 128.87, 128.84, 128.05, 127.80, 127.55, 127.24, 126.66, 124.39, 121.16, 44.98, 44.25; MS (+FAB, NBA) *m/z* 421.1905, $[M + H]^+$ calcd for $C_{28}H_{24}O_2N_2$ 421.1916.

^{1}H NMR and FT-IR Studies of Diamide 3. Diamide **3** was dried under high vacuum in the presence of P_2O_5 for 3−5 days prior to use. All samples were prepared under Ar or in a drybox under N_2. Despite the extensive dying and very careful sample preparation, up to 5−10 mmol of H_2O was still observed during the variable-temperature ^{1}H NMR studies. The CD_2Cl_2 used for the NMR studies was purchased from Aldrich. Variable-temperature ^{1}H NMR measurements and the DQCOSY were obtained on a Varian XL-400 spectrometer using residual CH_2Cl_2 (5.32 ppm) as the chemical shift reference. Concentrations of **3** for the VT experiment were 4.2−6.3 mM, and spectra were obtained at 6° increments over a temperature range of −72 to +30 °C. The DQCOSY was run on a 4.2 mM sample. The dichloromethane used for the IR study was freshly distilled from CaH_2. Diamide **3** was 0.34−85 mM in concentration. IR spectra were collected on a Galaxy 6021 spectrometer using CaF_2 solution cells with an optical pathlength of 3 mm or 0.02 mm (85 mM sample).

^{1}H NMR and FT-IR Studies of Diamide 4. Diamide **4** was dried under high vacuum in the presence of P_2O_5 for 3−5 days prior to use. All samples were prepared under Ar. The CD_2Cl_2 used for the ^{1}H NMR studies was purchased from Aldrich. Variable-temperature ^{1}H NMR measurements and the DQCOSY were obtained on a Varian XL-400 spectrometer using residual CH_2Cl_2 (5.32 ppm) as the chemical shift reference. Concentrations of **4** for the VT experiment were 4.1−4.7 mM, and spectra were obtained at 6° increments over a temperature range of −72 to +30 °C. The DQCOSY was run on a 4.7 mM sample. The dichloromethane used for the IR study was freshly distilled from CaH_2. Diamide **4** was 0.18−44 mM in concentration. IR spectra were collected on a Galaxy 6021 spectrometer using CaF_2 solution cells with an optical pathlength of 3 mm or 0.02 mm (44 mM sample).

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Supporting Information Available: The 200 MHz ^{1}H and ^{13}C spectra of new compounds lacking combustion data (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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