Cyclopropane Amino Acids That Mimic Two χ^1-Conformations of Phenylalanine

Destardi Moye-Sherman, Song Jin, Shiming Li, Michael B. Welch, Joe Reibenspies, and Kevin Burgess*[a]

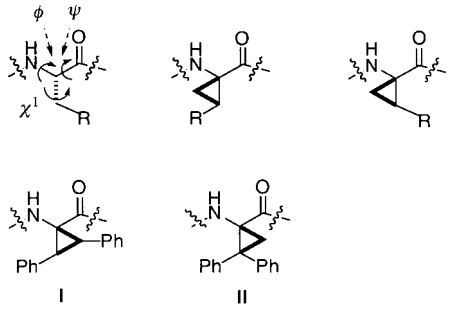
Abstract: A highly constrained analogue of phenylalanine was prepared in optically pure form. This disubstituted cyclopropane amino acid, DiFi, realises two χ^1 values of the phenylalanine side chain. Unlike monosubstituted analogues, amino acids of this type impart very specific perturbations at the N and C termini simultaneously. Model studies were performed to elucidate the intrinsic conformational biases of this amino acid and its isomeric analogue FiFi. These derivatives were incorporated into a simple model to determine the propensity of these compounds for γ-turn (or inverse γ-turn) conformations. Three other phenylalanine derivatives (**1--3**) were also prepared for comparison purposes. Structural biases were assessed by CD, IR, and NMR spectrsocopy, X-ray crystal structure analysis, and molecular simulations. CD and IR spectra indicated that the two disubstituted derivatives DiFi and FiFi contain secondary structural elements that appear to be absent in the other analogues. Molecular simulation protocols that involved grid-search routines were used to explore the conformational space accessible to derivatives **1**–**5**. These indicated that the FiFi derivative **5** was the most rigid of the analogues and that both the inverse γ-turn and the left-handed α-helix appear to be accessible conformations.

Keywords: amino acids · cyclopropane · molecular dynamics · peptidomimetics

Introduction

Constrained amino acids may be incorporated into peptide mimics to impart highly localized biases that may be used to explore bioactive conformations.[1–5] Our group,[6–14] and others,[3, 15–21] have investigated the fundamental aspects of these effects for 2,3-methanoamino acids and compared them with some other analogues, notably α-methylamino acids.[9] Predictably, the substituents on the "side-chain" cyclopropane ring have more conformational effects on the parts of the peptidomimetic that are *cis* to them than on those which are on the opposite face of the three-membered ring. 2,3-Methanoamino acids with one "R substituent", as indicated below, therefore cannot have similar conformational effects on the C and N termini simultaneously.

The work reported here features 2,3-methanoamino acids that can impart appreciable and similar conformational effects on the C and N termini simultaneously, namely,



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derivatives of the type **I** and **II**. Compounds **1**–**3** were prepared as a basis for comparative studies; these compounds contain phenylalanine, *N*-methylphenylalanine, and *cis*-2,3-methanophenylalanine, respectively. Similar derivatives of two new disubstituted 2,3-methanoamino acids, compounds **4** and **5**, were also prepared. There are two amide bonds in compounds **1**–**5**, hence they mimic tripeptides, and this resemblance is reinforced by the presence of the isopropyl group at the N terminus. The 4-bromobenzoic acid moiety was included for several reasons. This group gives the derivatives crystallinity and the presence of the heavy atom (Br) facilitates X-ray structural analyses. Further, Toniolo and co-workers have been able to deduce conformational information by using this group as a chromophore in CD studies.[22–24] We were hoping to use this probe to identify

[a] Prof. K. Burgess, D. Moye-Sherman, S. Jin, S. Li, Dr. M. B. Welch, Dr. J. Reibenspies
Texas A & M University, Chemistry Department
P.O. Box 30012 College Station, Texas 77842. (USA)
Fax: (+1) 409 845-8839
E-mail: burgess@mail.chemvx.tamu.edu

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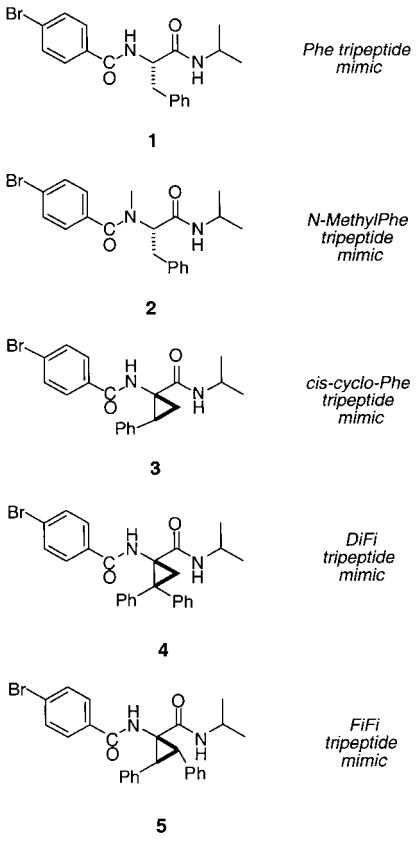


similar trends in the data if they existed, though the compounds in this work are significantly smaller than those studied previously. Finally, several techniques were then used to compare the conformations of compounds **1** to **5**, including CD, IR, and NMR spectroscopy, X-ray analyses, and molecular simulations.

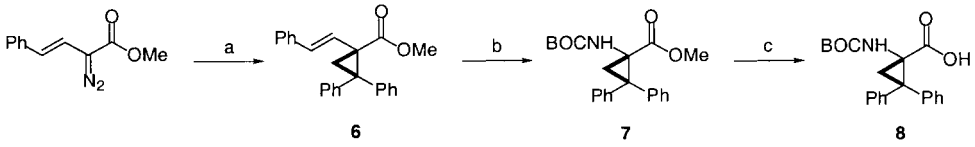
Results and Discussion

Syntheses of diphenyl cyclopropane amino acids and derivatives 1–5: An asymmetric synthesis of the Boc-protected amino acid Boc-FiFi has already been reported.[25] In that synthesis, chirality was introduced by means of an asymmetric bishydroxylation[26, 27] of *trans*-1,2-diphenylethene; the optically active diol produced was converted to a cyclopropane and then to the desired cyclopropane amino acid. The same approach would not be applicable to Boc-DiFi because bishydroxylation of 1,1-diphenylethene does not generate chirality. Consequently, a modification of the Davies approach to phenyl-substituted cyclopropane amino acids[28, 29] was developed (Scheme 1). Selection of a catalyst for the key cyclopropanation, and subsequent steps in the synthesis have been outlined previously,[13] full experimental details are given here.

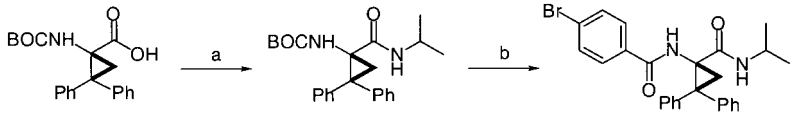
The absolute configuration of the Boc-DiFi **8** produced in this synthesis was assigned by reference to Davies' model for cyclopropanations, which incolves $[Rh_2(S\text{-TBSP})_4]$ and vinyl diazocompounds.[29] Asymmetric cyclopropanations of 1,1-disubstituted alkenes were reported to give the same sense of induction as proposed here.

Scheme 2 illustrates the two-step procedure that was used to convert Boc-DiFi **8** into derivative **4**. A similar sequence was used to prepare the analogous compounds **1**–**3** and **5** (see Experimental Section).

CD studies of the tripeptide mimics: Aromatic chromophores dominate the CD spectra in the region considered in Figure 1. Consequently, conclusions about the conformations of these analogues based on CD shape and/or intensity are difficult to formulate with a high degree of certainty. The most notable aspect of the data shown is that the FiFi derivative **5** displays an opposite Cotton effect to the other members of this series; this observation is consistent with the molecular simulation data reported below. Repetition of the CD measurements at 0 °C (data not shown) demonstrated little variation; this is indicative of temperature-independent conformational biases in this temperature range.



Scheme 1. a) 1,1-Diphenylethene, 1 mol% $[Rh_2(S\text{-TBSP})_4]$, THF, −42 to 25 °C, 17.5 h, 86%, >99% ee; b) cat. $RuCl_3$, $NaIO_4$, $MeCN/H_2O$, CCl_4, 25 °C, 5 h, then $(PhO)_2P(O)N_3$, NEt_3, *t*BuOH, reflux, 17 h, 90%; c) LiOH, MeOH(aq), reflux, 4 h, 86%.



Scheme 2. a) *i*$PrNH_2$, $[Me_2NCFNMe_2][PF_6]$, diisopropylethylamine, CH_2Cl_2, 0 °C, 4 h, 92%; b) 50% TFA/CH_2Cl_2, 0 to 25 °C, 45 min, then: $[Me_2NCFNMe_2][PF_6]$, 4-$BrC_6H_4CO_2H$, *i*Pr_2NEt, CH_2Cl_2, 0 °C, 30 min, 74%.

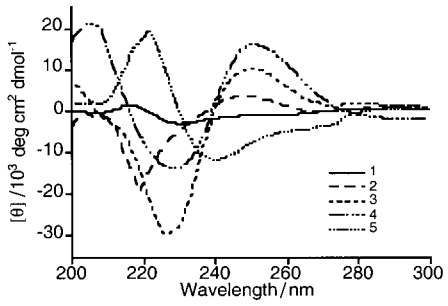


Figure 1. CD spectra of **1**–**5** in MeOH/H_2O (65:35) at 25 °C.

IR studies: Data from IR spectra of compounds **1**–**5** in dichloromethane at 1 mM concentration are shown in Figure 2. Spectra were also recorded at 10 mM and 5 mM concentrations to verify that intermolecular associations did not influence the results. Non-hydrogen-bonded N–H stretches are predicted to appear as relatively sharp bands at around 3450–3460 cm^{-1}, whereas hydrogen-bonded N–H stretches tend to appear as broader peaks centered at 3300–3350 cm^{-1}.[30–34] The IR spectra of the Phe derivative (Figure 2a) displays little or no evidence for hydrogen bonding. Figure 2b, which corresponds to the *N*-methyl derivative **2**, shows a broad shoulder on the sharper 3420 cm^{-1} peak that is possibly indicative of intramolecular hydrogen bonding; however, this observation is ambiguous because of the unusually high wavenumber for the shoulder. Comparison of the spectra for compounds **3**–**5** reveals increasing hydrogen-bonding character from the cyclo-Phe derivative **3** through to the FiFi compound **5**. This seems to suggest greater rigidity along this series, an inference that is supported by the molecular simulation data described below.

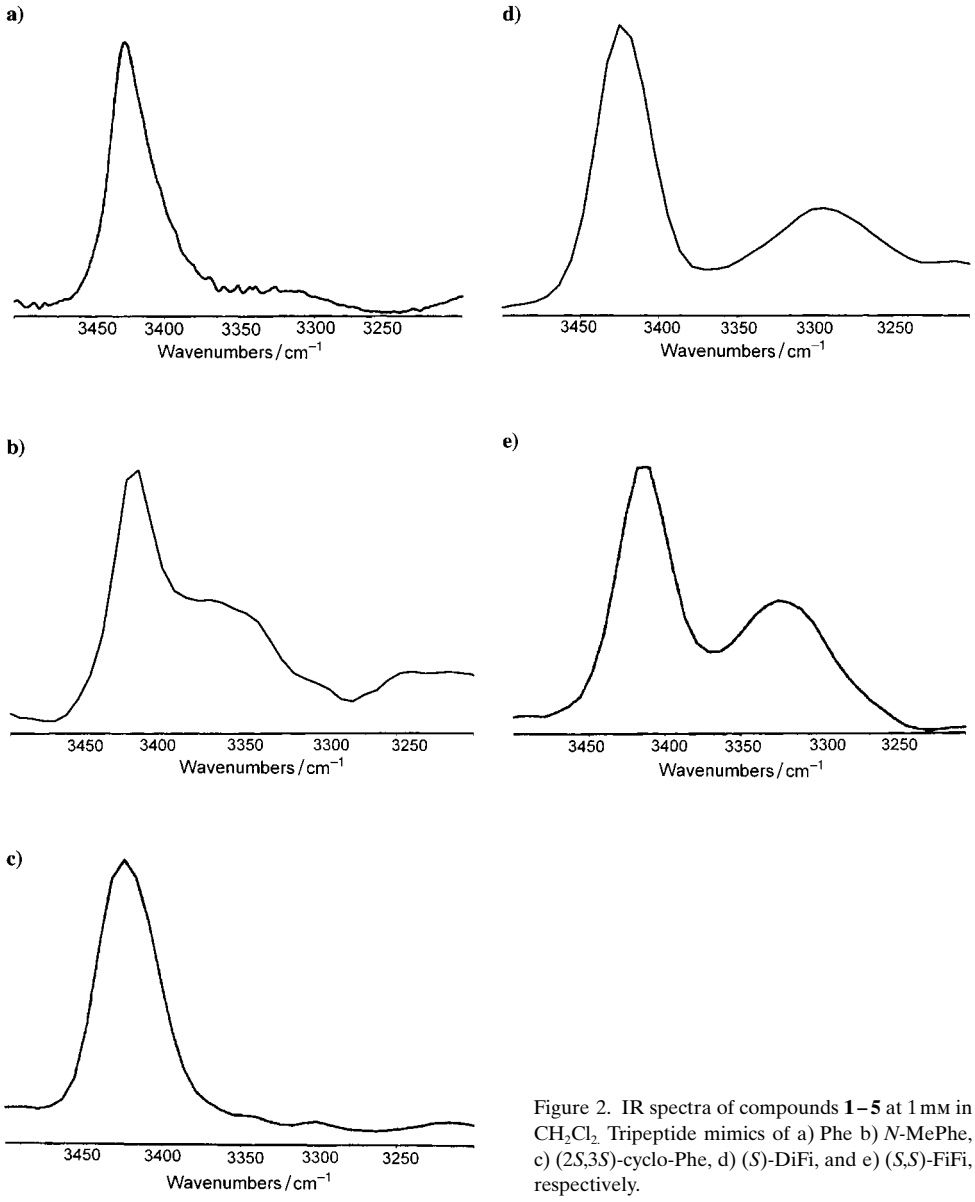


Figure 2. IR spectra of compounds **1**–**5** at 1 mM in CH_2Cl_2. Tripeptide mimics of a) Phe b) *N*-MePhe, c) (2*S*,3*S*)-cyclo-Phe, d) (*S*)-DiFi, and e) (*S*,*S*)-FiFi, respectively.

Solid-state conformational analyses: Single crystals of derivatives **4** and **5** were formed and subjected to X-ray structural analyses; the structure of **4** has been reported as part of a communication.[13] Representations of the solid-state structures are shown in Figure 3 and some essential bond parameters are shown in Table 1. Comparison of the structures reveals two fundamental differences. First, the orientation of the HN–C_αCO torsional angle, corresponding to ϕ, is similar in both molecules, but that of the CO–C_αNH torsional angle is opposite. Thus for the DiFi derivative **4**, the CO vector is oriented above the phenyl ring on the same side of the cyclopropane, whereas the same vector for the FiFi derivative **5** is oriented away. This is reflected in the opposite signs for the ψ angles. It is impossible to deduce whether this particular difference is an artifact of the crystallization procedure, a consequence of crystal-packing factors (that is, compound **4** is a dimer in the crystal lattice whereas **5** is a trimer), or a manifestation of intrinsic differences in the molecules that may be reflected in their conformations in solution.

The second difference observed between the two structures shown in Figure 3 is in the HN–C_α–CO bond angle. For the DiFi derivative **4** this angle is 110°, whereas in the FiFi analogue **5** it is 118°. We have previously noted that 2,3-methanomethionine has a larger HN–C_α–CO bond angle than the corresponding α-methylamino acid, α-methylmethionine.[9] Consequently, in the current work, it is the DiFi derivative **4** that has an unusually small HN–C_α–CO bond angle for a 2,3-methanoamino acid, whereas the bond angle for the FiFi analogue **5** is standard for this type of compound.[10] This difference is potentially important because large HN–C_α–CO bond angles facilitate formation of tighter turns, for example, C7 turns, whereas smaller bond angles favor formation of more open-turn structures like β-turns.

Molecular modeling: Two grid-search routines were used to explore the conformational space accessible to derivatives **1**–**5**. Throughout, a dielectric continuum of 45 was used to simulate DMSO (or 65:35 MeOH/H_2O). In the first protocol, six (or five in the case of **3**) rotatable bonds were al-

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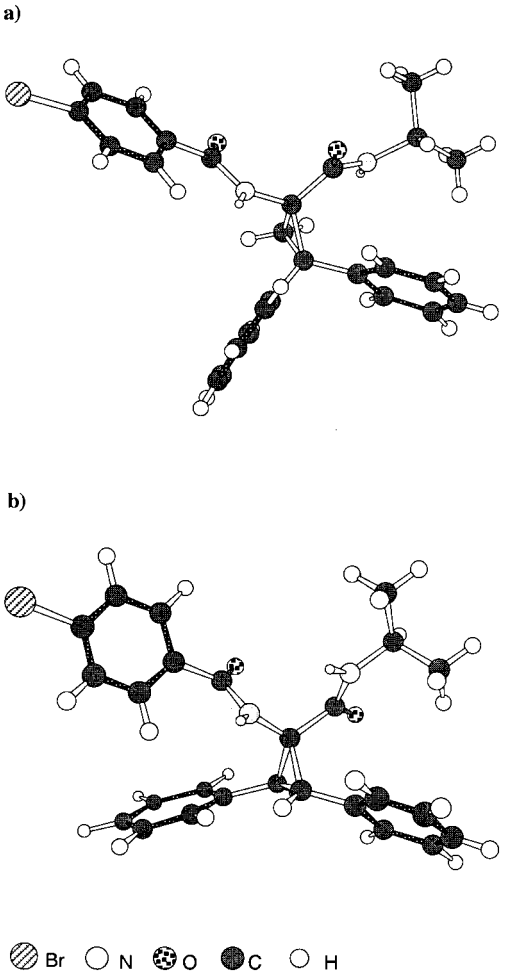

Figure 3. Chem 3D diagrams of a) *p*-BrBz-DiFi-NH*i*Pr **4** and b) *p*-BrBz-FiFi-NH*i*Pr **5** from X-ray crystal structure analyses.

Table 1. Important bond parameters for the single crystal X-ray structural analyses of compounds **4** and **5**.

	HN–C_α–CO [°]	ϕ [°]	ψ [°]	χ_1 [°]	χ'_1 [°]
4	109.9	−87.7	−152.0	+0.5	−143.0
5	117.5	+64.6	+44.4	+3.0	−139.9

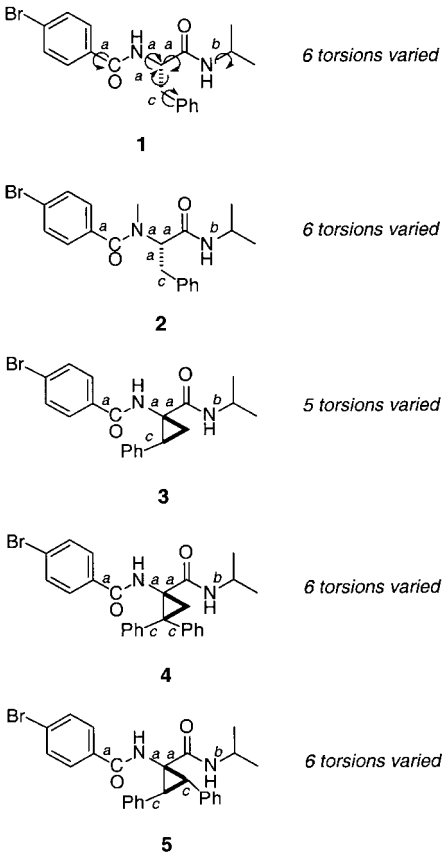

Figure 4. Torsion angles examined in the grid search that involved energy minimizations. Torsions: a) 0 to 360° in increments of 60°, b) 0 to 360° in increments of 120°, c) 0 to 180° in increments of 60°.

lowed to vary in increments of either 60° or 120° as indicated in Figure 4. The resulting conformers were then minimized by means of molecular mechanics without any constraints on the torsion angles, giving a total of 5832 structures (3888 in the case of **3**). An energy threshold of 3–4 kcal mol^{-1} above the lowest energy conformer identified in each case was established. Conformers below this threshold were selected and used to generate the scatter plots shown in Figure 5 (see p. 2734). This procedure revealed low-energy conformations that corresponded to limited values of some of the bond vectors, consequently a second search was designed to more fully explore conformations in the low-energy regions located in the first search. In this second procedure, only ϕ and ψ values were varied, but in increments of 15° over all possible values. For each structure the ϕ and ψ values were fixed and the rest of the molecule was allowed to relax by means of molecular mechanics routines. Unlike the first procedure, this gives a set of energy contours, and these are displayed in Figure 6 (see p. 2735). Overall, the two procedures are complementary. The first reveals true low-energy regions of conformational space. The second protocol gives energy contours over all conformational space; however, the structures used to generate these plots are not truly minimized since their ϕ and ψ values were fixed.

Results from the first grid search on the Phe derivative **1** are shown in Figure 5a. It is evident from this plot that several regions of conformational space are accessible, but negative ϕ values around −120° and ψ values between −50° and +170° are favored. These correspond to extended conformations. Inclusion of an *N*-methyl substituent, as in derivative **2**, alters the distribution of low-energy conformers to include positive ϕ values (Figure 5b). The difference between the Phe and *N*-methyl-Phe derivatives is easily rationalized by considering Newman projections.[8] Overall the scatter plots in Figure 5a and 5b indicate that an *N*-methyl substituent changes the conformational bias, but does not significantly lower the number of accessible conformations. Conversely, the scatter plots in Figures 5c–e demonstrate significantly fewer regions of conformational space are accessible to derivatives **3**–**5**. It is clear from these plots that the FiFi derivative **5** is the most constrained of the amino acids in this series.

The second grid-search protocol facilitates elaboration of the points that emerged from the first study. Contours in Figure 6a show the deepest valley in the plot corresponds to

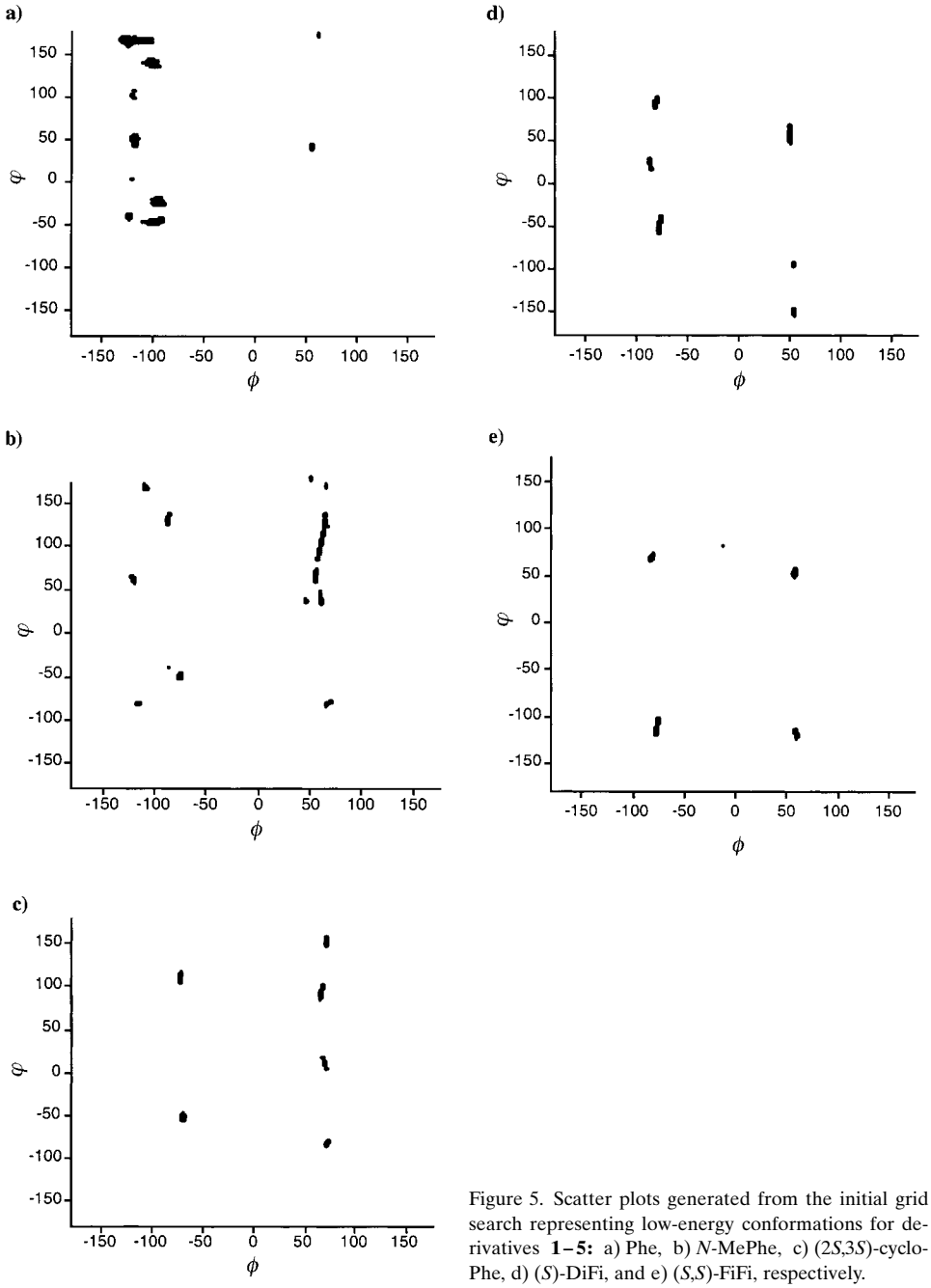

Figure 5. Scatter plots generated from the initial grid search representing low-energy conformations for derivatives **1–5:** a) Phe, b) *N*-MePhe, c) (2*S*,3*S*)-cyclo-Phe, d) (*S*)-DiFi, and e) (*S*,*S*)-FiFi, respectively.

negative ϕ values, and the hill to be climbed between positive and negative ψ values in the negative ϕ region is relatively low. Newman projections are illustrated that correspond to this contour plot (and the others; see p. 2736). The preference for a negative ϕ orientation is easily understood in terms of relieving steric interactions between the N terminus and the phenyl substituent. Figure 6b shows that in the corresponding contour map for the DiFi derivative **4**, the lowest valleys are more isolated than in the Phe case. They correspond to negative ϕ regions. Incidentally, the single-crystal X-ray analysis of compound **4** gave a structure with negative ϕ and ψ values, that is, in the valley featured in the lower left quadrant (right-handed helical region). The ϕ,ψ values in the crystal structure (-88°, -152°) of compound **4** do not correspond exactly with those of the minimum energy conformer shown in Figure 7 (see p. 2736) (-69°, -52°), but they have similar orientations. Preference for the negative ϕ region is again consistent with minimization of phenyl-to-N-terminus interactions. A preference for the negative ψ region can be explained on the basis of greater steric demands associated with the carbonyl than the NH group (see the Newman projections and Figure 6). However, electronic repulsions between the carbonyl-oxygen lone pairs and the phenyl π-clouds may also play a role. Finally, the contour plot for the FiFi derivative **5** (Figure 6c) shows isolated valleys with the lowest energy corresponding to positive ψ values. Surprisingly, the preference for negative ϕ values that would be anticipated for this derivative is not as prevalent as would be expected in the contour plot shown in Figure 6c; both the inverse γ-turn and the left-handed helical regions (negative/positive and positive/positive, ϕ,ψ, respectively) appear to be accessible. The lowest energy conformations overall for each of the derivatives are shown in Figure 7. These are consistent with the arguments presented above.

Conclusions

The disubstituted-cyclopropane amino acids FiFi and DiFi are accessible in an enantiomerically pure form from relatively short syntheses. These materials provide substituents oriented in such a way that the C and N termini of a peptidomimetic can be perturbed simultaneously. These perturbations are logical, relating directly to the stereochemistry of the cyclopropane substituents.

The tripeptide analogues **1–5** are too small to be studied by NMR or similar techniques that operate on a relatively slow time-scale; many experiments of this type were attempted, as described in the supporting material. Useful information can be obtained from IR/CD spectroscopy and from solid-state X-ray crystallography, but the results must be interpreted with caution. For example, the IR data and solid-state X-ray structure analysis of the FiFi derivative **5** are consistent with the calculated low-energy conformer for this molecule (Fig-

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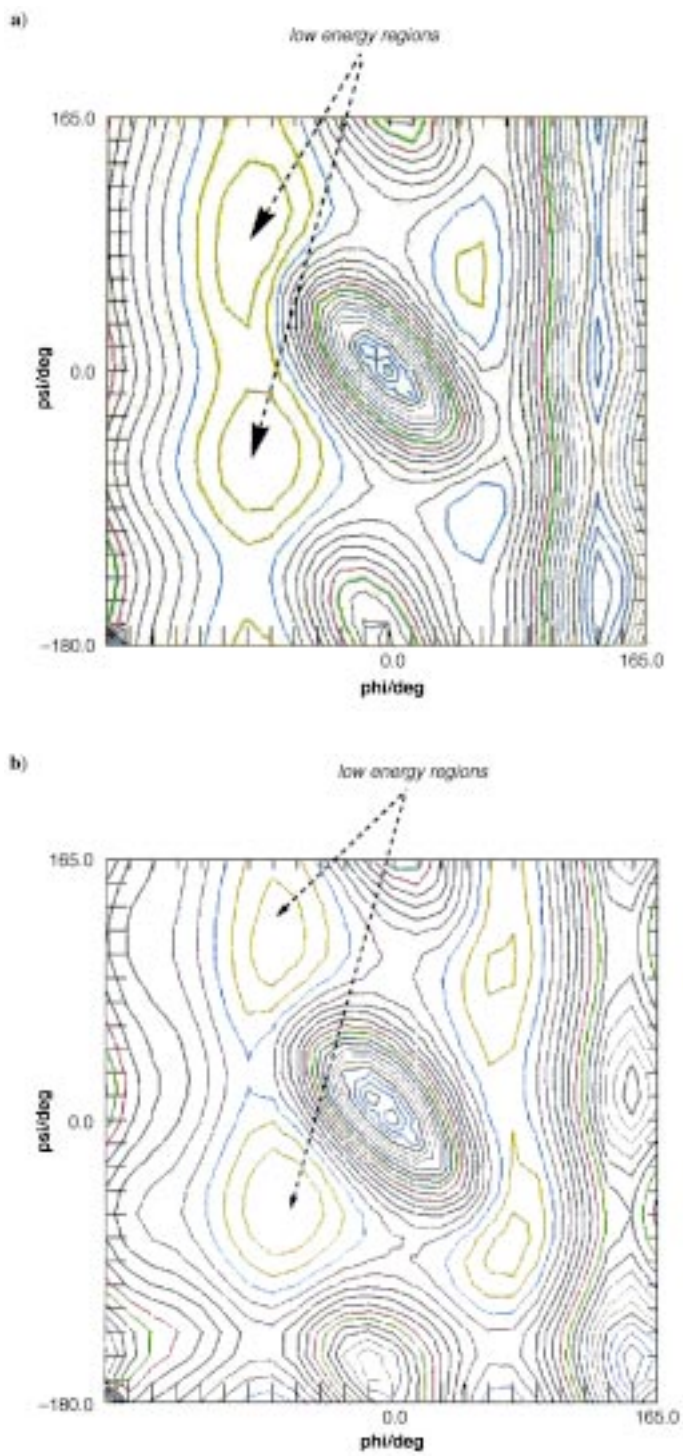
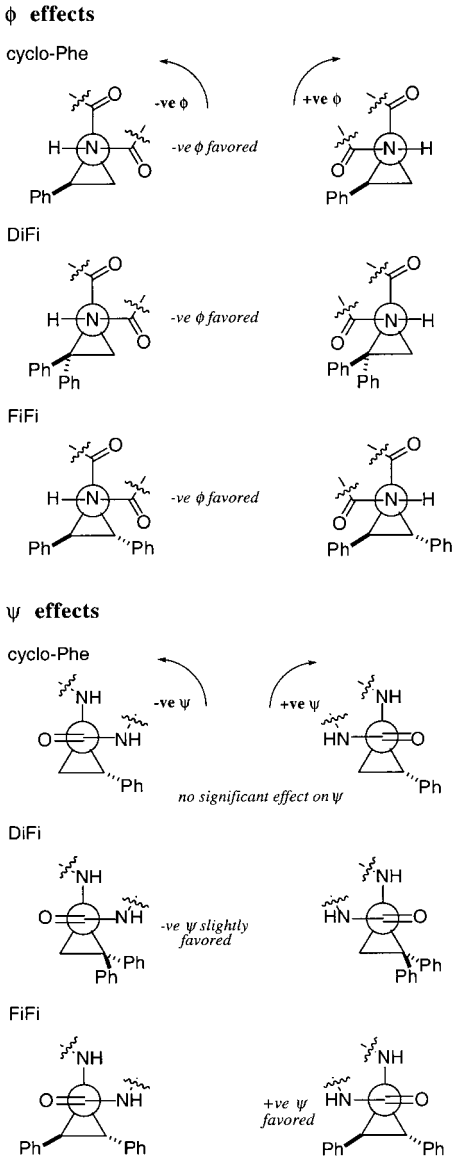


Figure 6. Contour plots generated from the second grid search for compounds **3**–**5**: a) cyclo-Phe, b) DiFi, c) FiFi, respectively. The contour levels shown are spaced by 0.8 kcal mol^{-1}.

ure 7a). However, in the case of the DiFi derivative **4**, the correlations are not as satisfying. Thus, the low-energy conformer of **4** predicted from calculations (Figure 7b) does not allow an intramolecular hydrogen bond, but there is evidence for this in the IR spectrum. One must consider the other easily accessible low-energy conformation of **4** (Figure 6b) for the accommodation of such hydrogen bonding, and/or suggest that the hydrogen bonding is favored in the less polar medium used in the IR spectroscopic studies.

Some results from this study are totally unambiguous and point to significant differences that can be rationalized in terms of the compound substitution patterns. For instance, the X-ray crystallographic studies show that the HN−C_α−CO vector of the DiFi derivative **4** is more acute than the corresponding vectors in the FiFi derivative **5** and other 2,3-methanoamino acids. This is interesting because, as noted by us previously,[9] wider bond angles favor tighter turns (for example, C7 over β-turns). Consequently, the conformational preferences of DiFi and FiFi residues in peptides may be significantly different. Conformational differences between DiFi and FiFi are also evident from the grid-search routines performed in the molecular modeling part of this work. These



indicate that FiFi is the more hindered analogue and that the local conformations accessible to peptidomimetics prepared from these building blocks can be constrained to relatively narrow regions of conformational space.

Experimental Section

General procedures: Melting points were uncorrected. High-field NMR spectra were recorded on a Varian Unity + 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz), or a Varian Unity + 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). ^{1}H chemical shifts are reported in δ relative to C*H*Cl$_3$ ($\delta = 7.24$) as internal standard, and ^{13}C chemical shifts are reported in ppm relative to C*D*Cl$_3$ ($\delta = 77.0$) unless otherwise specified. Multiplicities in ^{1}H NMR are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet. Optical rotations were taken on a JASCO DIP-360 Digital Polarimeter equipped with a sodium lamp. Enantiomeric excess was measured by chiral HPLC (Whelk-O1 SS chiral column, Regis Technologies, 3% isopropyl alcohol/97% hexanes, 0.9 mL min^{-1}). Thin layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography was performed on SP silica gel 60 (230–600 mesh ASTM). Dichloromethane and *tert*-butyl alcohol were distilled from CaH_2. Other chemicals were purchased from commercial suppliers and used as received.

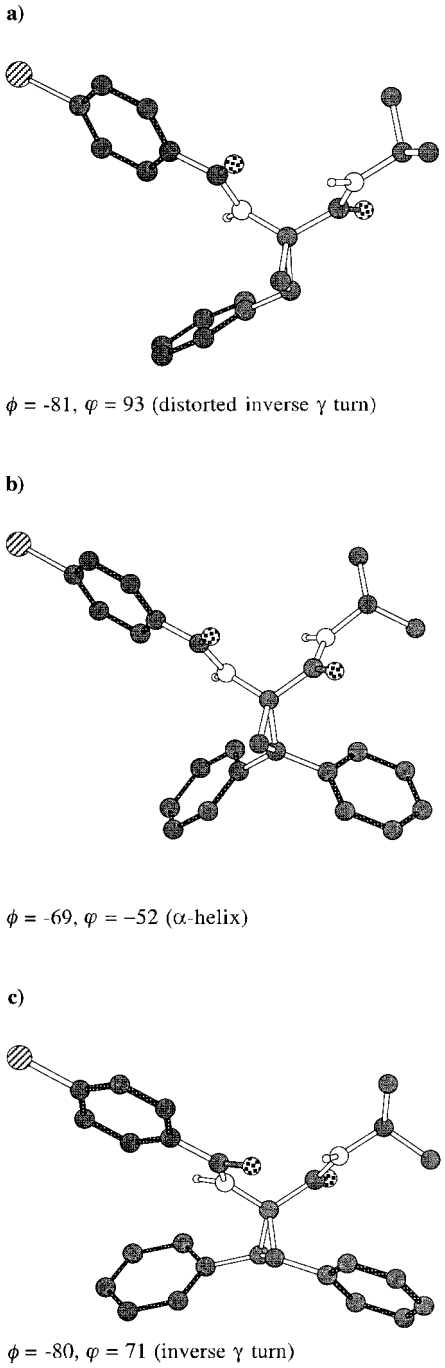


Figure 7. Low-energy conformations for compounds **3**–**5**: a) cyclo-Phe, b) DiFi, and c) FiFi derivatives, respectively.

(1*S*)-Methyl-1-[2-(*E*)-phenylethenyl]-2,2-diphenylcyclopropane-1-carboxylate (6): 1,1-Diphenylethylene (3.6 g, 19.9 mmol), [Rh$_2$(*S*-TBSP)$_4$] (96 mg, 0.06 mmol, 1 mol%), and THF (33 mL) was added to a flame-dried 100 mL round-bottomed flask. The reaction mixture was then cooled to −67 °C (dry ice/acetone) under a nitrogen atmosphere. A solution of 2-diazo-4-phenylbut-3-enoate[28] (1.3 g, 6.6 mmol) in THF (10 mL) was added through a syringe pump at 0.2 mL min^{-1} to the above solution. After 5 h at −67 °C, the reaction mixture was warmed to 25 °C, and stirring was continued for a total of 17.5 h. The reaction mixture was then concentrated to a thick liquid. The crude product was purified by flash chromatography with a gradient of 0.5–3% EtOAc/hexanes as eluent yielding **6** (1.47 g, 64% yield, 94.9% ee) as a yellow solid. Recrystallization from hexanes provided long colorless crystals (>99% ee). $R_f = 0.38$ (10% EtOAc/hexanes); m.p. 119–120 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 7.49$–7.41 (m, 5H), 7.28–7.10 (m, 10H), 6.48 (d, $J = 15.9$ Hz, 1H), 6.20 (d, $J = 15.9$ Hz,

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1H), 3.41 (s, 3H), 2.64 (d, $J = 5.4$ Hz, 1H), 2.07 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.1, 142.1, 140.7, 137.2, 130.8, 129.9, 128.7, 128.3, 128.3, 128.2, 127.1, 126.8, 126.7, 126.6, 126.07, 51.8, 47.1, 38.8, 22.5$; IR (neat): $\nu = 3065, 3034, 2951, 2368, 1739, 1494$ cm^{-1}; $[\alpha]_D^{25} = -137$ ($c = 8.85$ in $CHCl_3$); HRFAB: calcd $[M+H]^+$ 354.1620, found 354.1632; $C_{25}H_{22}O_2$ (354.45): C 84.7, H 6.26; found: C 84.6, H 6.33.

(1*S*)-Methyl-1-{*N*-[(1,1-dimethylethyl)oxycarbonyl]amino}-2,2-diphenylcyclopropane-1-carboxylate (7): $RuCl_3 \cdot H_2O$ (7 mg, 0.0036 mmol, 2 mol %) was added to a rapidly stirred solution of **6** (591 mg, 1.7 mmol, 1 equiv), sodium periodate (2.9 g, 13.6 mmol, 8 equiv), MeCN, CCl_4 (3.4 mL, 2 mL mol^{-1}), and H_2O (5.1 mL, 3 mL mol^{-1}). This solution was stirred at 25 °C for 2 h. The crude reaction mixture was filtered through a plug of silica gel on Celite, washed with EtOAc (500 mL), concentrated to a dark viscous oil, and azeotroped with benzene (3 × 4 mL) to remove water. The crude acids were dissolved in freshly distilled *t*BuOH (30 mL), diphenylphosphoryl azide (1.0 g, 0.4 mmol, 2.2 equiv), and triethylamine (413 mg, 4.1 mmol, 2.4 equiv), and then heated to reflux for 33 h. The reaction mixture was then concentrated to a thick oil. The crude product was purified by flash chromatography using 1:1 CH_2Cl_2/10 % (EtOAc/hexanes) as the eluent yielding **7** (624 mg, 90 % yield) as a yellow oil. $R_f = 0.38$ (10 % EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.38-7.10$ (m, 10H), 4.91 (br s, 1H), 3.46–3.32 (m, 3H), 2.62–2.54 (m, 1H), 2.06–2.01 (m, 1H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.9, 155.8, 141.2, 129.0, 128.8, 128.6, 128.5, 127.3, 127.0, 80.3, 52.0. 28.2, 25.9$; HRFAB: calcd $[M+H]^+$ 368.1862, found 368.1891.

(1*S*)-1-{*N*-[(1,1-Dimethylethyl)oxycarbonyl]amino}-2,2-diphenylcyclopropane-1-carboxylic acid (8): Compound **7** (428 mg, 1.16 mmol, 1 equiv), MeOH (10 mL), H_2O (5 mL), and LiOH (487 mg, 11.6 mmol) were heated to reflux for 4 h. The reaction mixture was concentrated and taken up in EtOAc. The organic layer was extracted with NaOH (1 M, 3 × 5 mL). The aqueous layer was then acidified with Hcl (1 M), extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated yielding a yellow solid (356 mg, 86 % yield). Recrystallization from EtOAc/$CHCl_3$ and hexanes produced long white needles. $R_f = 0.13$ (6 % MeOH/CH_2Cl_2), 0.41 (11 % MeOH/CH_2Cl_2); m.p. 189–190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 10.65–10.01 (br s, 1H), 7.43–7.14 (m, 10H), 5.63 (br s, 1H), 2.56 (d, $J =$ 4.8 Hz, 1H), 1.96 (d, $J = 5.1$ Hz, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.6, 156.5, 140.6, 139.2, 128.8, 128.6, 128.5, 127.3, 127.2, 80.2, 46.6, 44.5, 28.1, 26.0$; IR (neat): $\nu = 3021, 2979, 1723, 1537$ cm^{-1}; HRFAB: calcd $[M+H]^+$ 368.1862, found 368.1891; $[\alpha]_D^{25} = +121$ ($c = 8.15$ in $CHCl_3$); $C_{12}H_{23}NO_4$ (245.32): C 71.4, H 6.56, N 3.96; found: C 71.3, H 6.58, N 3.87.

(1*S*)-1-{*N*-[(1,1-Dimethylethyl)oxycarbonyl]amino}-2,2-diphenylcyclopropane-1-*N*′-(methylethyl)carboxamide (9): Compound **8** (150 mg, 0.42 mmol), tetramethylfluoroformamidium hexafluorophosphate (TFFH; 168.1 mg, 0.64 mmol, 1.5 equiv), CH_2Cl_2 (2.1 mL), and diisopropylethylamine (NE*t*iPr_2; 82.3 mg, 0.64 mmol, 1.5 equiv, 111 μL) were stirred at 25 °C for 40 min. This solution was transferred through a cannula to a 0 °C solution of isopropylamine (501 mg, 8.48 mmol, 722 μL) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to warm to 25 °C for 30 min after the addition, and stirred for an additional 4 h. The reaction mixture was then concentrated, taken up in EtOAc, and extracted with Hcl (0.5 M, 3 × 40 mL). The organic layer was dried, filtered, and concentrated yielding an off-white viscous liquid. The crude product was purified by flash chromatography with 30–40 % EtOAc/hexanes as eluent yielding **9** (144 mg, 92 % yield) as an off-white viscous liquid. $R_f = 0.44$ (EtOAc/hexanes); m.p. 206–207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.50-7.10$ (m, 10H), 5.30 (br s, 1H), 3.87 (d, $J = 6.3$ Hz, 1H), 2.59 (d, $J = 5.7$ Hz, 1H), 1.78 (d, $J = 5.7$ Hz 1H,), 1.28 (s, 9H), 1.09–1.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 168.0, 156.7, 140.7, 139.5, 129.4, 128.9, 128.$ 1, 126.9, 80.3, 46.1, 45.2, 41.4, 27.9, 23.6, 22.4; IR (neat): $\nu = 3439, 3316, 2976, 1694, 1652, 1175$ cm^{-1}; HRFAB: calcd $[M+H]^+$ 395.2335, found 395.2346; $[\alpha]_D^{25} = +171$ ($c = 0.52$ in $CHCl_3$); $C_{24}H_{30}N_2O_3$ (394.51): C 73.1, H 7.66, N 7.10; found: C 73.0, H 7.57, N 7.13.

(1*S*)-1-[*N*-(4-Bromobenzoyl)amino]-2,2-diphenylcyclopropane-1-*N*′-(methylethyl)carboxamide (4): Compound **9** (62 mg, 0.17 mmol) and CH_2Cl_2 (2.0 mL, 0.09 M) were cooled to 0 °C. A solution of 50 % TFA/CH_2Cl_2 (2.0 mL) was added to this mixture, and it was stirred for 10 min. The reaction mixture was allowed to warm to 25 °C and stirring was continued for an additional 1.5 h. The reaction mixture was concentrated and co-evaporated with CH_2Cl_2 (2 × 2 mL) then placed in a high vacuum for 0.5 h. Aside, a flame-dried flask was charged with 4-bromobenzoic acid (51 mg, 0.26 mmol), TFFH (90 mg, 0.34 mmol), CH_2Cl_2 (1.0 mL), and then NE*t*iPr_2 (110 mg, 0.85 mmol, 148 μL). This was stirred at 25 °C for 34 min. This acid fluoride was added to a solution of the free amine, CH_2Cl_2 (2.0 mL) and NE*t*iPr_2 (300 μL) at 25 °C. The reaction mixture was concentrated after 30 min yielding a thick oil. The crude product was purified by flash chromatography with a gradient of 25–30 % EtOAc/hexanes as the eluting solvent and **4** was yielded (60.2 mg, 74 % yield) as a white powder. $R_f = 0.40$ (40 % EtOAc/hexanes); m.p. 231–232 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.60-7.43$ (m, 6H), 7.35–7.16 (m, 8H), 6.91 (br, 1H), 3.85 (d, $J = 6.9$ Hz, 1H), 2.66 (d, $J = 6.0$ Hz, 1H), 2.04 (d, $J = 6.3$ Hz, 1H), 1.11 (d, $J = 6.3$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 168.6, 167.6, 140.1, 139.4, 132.5, 131.7, 129.5, 128.9, 128.5, 128.4, 128.4, 127.2, 127.2, 126.5, 46.3, 45.4, 41.8, 23.8, 22.4, 22.4$; IR (neat): $\nu = 2933$, 2409, 1665 cm^{-1}; HRFAB: calcd $[M+H]^+$ 499.0997, found 499.1006; $[\alpha]_D^{25} = +79.3$ ($c = 0.56$ in $CHCl_3$); $C_{26}H_{25}N_2O_2Br$ (477.40): C 65.41, H 5.28, N 5.87; found: C 65.77, H 5.72, N 5.69.

(*S*)-*N*-(4-Bromobenzoyl)phenylalanine-*N*′-(methylethyl)carboxamide (1): Compund Boc-Phe-NH*i*Pr was prepared by means of a procedure similar to **9** except that Boc-Phe-OH (Advanced ChemTech) (150 mg, 0.565 mmol, 1 equiv) was used as substrate and the reaction time was reduced to 30 min to give 125 mg (75 %) of the intermediate Boc-Phe-NH*i*Pr as a white solid. $R_f = 0.29$ (20 % EtOAc/hexanes); m.p. 102–104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.31-7.23$ (m, 5H), 5.60 (d, $J = 6.6$ Hz, 1H), 5.25 (s, 1H), 4.25 (q, $J = 8.4$ Hz, 1H), 3.95 (m, 1H), 3.12–2.95 (m, 2H), 1.43 (s, 9H), 1.05 (d, $J = 6.6$ Hz, 4H), 0.95 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.0, 153.8, 136.9, 129.3, 128.5, 126.8, 95.0, 41.3, 39.0, 28.3, 22.5, 22.4$; IR (KBr): $\nu = 3303, 2979, 1679, 1646, 1165$ cm^{-1}; HRFAB: $[M+Na]^+$ calcd 329.1841, found 329.1852; $[\alpha]_D^{25} = +9.7$ ($c = 0.75$ in $CHCl_3$).

Product **1** was prepared by means of the procedure outlined above for the synthesis of **4**, but with compound Boc-Phe-NH*i*Pr as prepared above (166 mg, 0.57 mmol, 1 equiv) as substrate to give 200 mg (91 %) of **1** as a white solid. $R_f = 0.68$ (40 % EtOAc/hexanes); m.p. 217–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (q, $J = 33.5, 8.5$ Hz, 4H), 7.33–7.26 (br m, 5H), 7.21 (d, $J = 8.0$ Hz, 1H), 5.54 (d, $J = 7.5$ Hz, 1H), 4.74 (m, 1H), 3.95 (m, 1H), 3.26 (dd, $J = 7.5$, 6.0 Hz, 1H), 3.03 (m, 1H), 0.96 (dd, $J = 36.0$, 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.6, 165.9, 136.7, 132.7, 131.9, 129.4, 128.7, 128.65, 127.1, 126.5, 55.3, 41.6, 39.2, 22.5, 22.3$; IR (KBr): $\nu = 3421, 1717, 1656, 1287, 1073$ cm^{-1}; HRFAB: calcd $[M+Na]^+$ 411.0684, found 411.0694; $[\alpha]_D^{25} = +5.04$ ($c = 0.67$ in $CHCl_3$).

(2*S*)-*N*-(4-Bromobenzoyl)-*N*-(methyl)phenylalanine-*N*′-(methylethyl)carboxamide (2): Boc-*N*-MePhe-NH*i*Pr was prepared by means of the method outlined above for Boc-Phe-NH*i*Pr, but with Boc-*N*-MePhe-OH (Advanced ChemTech; 250 mg, 0.895 mmol) as substrate to give 211 mg (74 %) of Boc-*N*-MePhe-NH*i*Pr as a colorless oil: R_f 0.36 (20 % ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.29-7.20$ (br m, 5H), 5.82 (s, 1H), 4.72 (d, $J = 5.7$ Hz, 1H), 4.03–4.08 (m, 1H), 3.30 (br m, 1H), 2.90–2.98 (m, 1H), 2.76 (s, 3H), 1.38 (s, 6H), 1.29 (s, 3H), 1.10–1.18 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.4, 156.5, 138.1, 137.6, 128.9, 128.2, 126.3, 80.2, 62.0, 59.47, 41.4, 41.1, 34.0, 30.9, 30.5, 28.1, 22.6, 22.5$; IR (NaCl): $\nu = 3418$, 1689, 1219 cm^{-1}; HRFAB: calcd $[M+H]^+$ 321.2178, found 321.2181; $[\alpha]_D^{25} = -84.5$ ($c = 1.01$ in $CHCl_3$).

Compound **2** was prepared by means of the procedure described for **1** above with Boc-*N*-MePhe-NH*i*Pr (120 mg, 0.375 mmol) as substrate to give 111 mg (74 %) of **2** as a white foam: $R_f = 0.33$ (40 % EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.43$ (d, $J = 8.4$ Hz, 2H), 7.29–7.26 (br m, 5H), 6.93 (d, $J = 8.1$ Hz, 2H), 6.32 (d, $J = 6.9$ Hz), 5.28 (q, $J = 6.8$, 3 Hz, 1H), 4.00 (m, 1H), 3.26–3.31 (m, 1H), 3.09–3.14 (m, 1H), 2.81 (s, 3H), 1.10 (d, $J = 6.3$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.0, 168.7, 137.0, 134.22, 131.6, 128.8, 128.6, 126.7, 124.5, 57.6, 41.34, 33.7, 33.5, 22.7, 22.5$; IR ($CH_2Cl_2$): $\nu = 3418, 1676, 1622, 1281, 1074$ cm^{-1}; HRFAB: calcd $[M+Na]^+$ 425.0841, found 425.0859; $[\alpha]_D^{25} = -105$ ($c = 0.53$ in $CHCl_3$).

(2*S*,3*S*)-1-[*N*-(4-Bromobenzoyl)amino]-2-phenylcyclopropyl-1-*N*′-(methylethyl)carboxamide (3): Boc-cyclo-Phe-NH*i*Pr was prepared as described above for Boc-Phe-NH*i*Pr, but with (2*S*,3*S*)-Boc-cyclo-Phe-OH[29] (300 mg, 1.08 mmol) as the substrate and increasing the reaction time to 8 h to give 263 mg (64 %) of Boc-cyclo-Phe-NH*i*Pr as a white powder. $R_f = 0.48$ (40 % ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.36-7.16$ (m, 5H), 6.28 (d, $J = 7.8$ Hz, 1H), 4.11–4.18 (m, 1H), 3.06 (br m, 1H), 2.10 (br m, 1H), 1.33 (br s, 9H), 1.17 (dd, $J = 5.1$, 1.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.25, 155.53, 128.34, 126.95, 80.65, 41.71, 31.84,$

27.93, 22.82; IR (NaCl): $\nu = 3431, 1704, 1650, 1264\ cm^{-1}$; HRFAB: $[M+H]^+$ calcd 319.2021, found 319.2010; $[\alpha]_D^{25} = -80.2$ ($c = 0.51$ in $CHCl_3$).

Product **3** was prepared by means of the procedure described for compound **1** above, except that Boc-cyclo-Phe-NH*i*Pr was used as a substrate (100 mg, 0.265 mmol) and the reaction time was increased to 12 h, to give 92 mg (87%) of **3** as pale yellow foam. $R_f = 0.68$ (75% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.48-7.22$ (m, 10H), 6.32 (d, $J = 7.8$ Hz, 1H), 6.20 (s, 1H), 4.04 (m, 1H), 3.16 (t, $J = 9.0$ Hz, 1H), 2.14 (q, $J = 6.0$, 3.3 Hz, 1H), 1.64 (q, $J = 6.0$, 1.8 Hz, 1H), 1.14 (q, $J = 4.8$, 1.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.5$, 167.6, 134.8, 131.9, 131.8, 128.7, 128.6, 128.5, 127.4, 126.9, 42.0, 40.5, 31.5, 22.6, 22.6, 20.3; IR (CH_2Cl_2): $\nu =$ 3427, 2967, 1686, 1665, 1515, 1469 cm^{-1}; HRFAB: $[M\mathrm{Na}]^+$ calcd 423.0684, found 423.0689; $[\alpha]_D^{25} = -15.6$ ($c = 0.55$ in CH_2Cl_2)

(2*S*,3*S*)-1-[*N*-(4-Bromobenzoyl)amino]-2,3-diphenylcyclopropane-1-*N*′-(methylethyl)carboxamide (5): Boc-FiFi-NH*i*Pr was prepared as an intermediate by the following procedure. Tetramethylfluoroamidinium hexafluorophosphate (TFFH; 0.280 g, 1.5 equiv) was added to a well stirred solution of (2S,3S)-2-(*tert*-butyloxycarbonyl)amino-2-(2,3-diphenyl)cyclopropane-1-carboxylate (0.708 mmol, 0.250 g) and pyridine (0.708 mmol, 0.06 mL) in dry CH_2Cl_2 (9 mL). The mixture was stirred at room temperature for 3 h. The reaction was then quenched with crushed ice (10 mL). The organic layer was extracted with ice-cold water (2×10 mL), and dried over $MgSO_4$. The solvent was removed at room temperature on a rotary evaporator, and the residue dried at high vacuum for 4 h. Freshly distilled isopropylamine (0.42 g, 7.08 mmol, 10 equiv) and CH_2Cl_2 (10 mL) was added to the crude acid fluoride (0.250 g, 0.708 mmol). The mixture was stirred at 25 °C overnight. The organic layer was washed with H_2O ($2 \times$ 10 mL) and dried over $MgSO_4$. The crude product was recrystallized (CH_2Cl_2/hexanes) to give Boc-FiFi-NH*i*Pr as tiny white crystals (180 mg, 65%): R_f 0.75 (40% EtOAc/hexanes); m.p. 163–164 °C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40-7.19$ (m, 10H), 6.70 (br, 1H), 4.69 (s, 1H), 3.79–3.84 (m, 1H), 3.07 (d, $J = 8.4$ Hz, 1H), 1.40 (s, 9H), 0.99 (d, $J = 6.3$ Hz, 3H), 0.72 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$, 135.2, 134.7, 128.8, 128.67, 128.0, 127.1, 126.9, 121.95, 80.8, 47.6, 41.4, 37.7, 31.7, 28.1, 22.4; IR ($CHCl_3$): $\nu = 3418$, 3336, 2978, 2250, 1706, 1663, 1508, 1159 cm^{-1}; HRFAB: calcd $[M+H]^+$ 395.2335, found 395.2340; $[\alpha]_D^{25} = -69.7$ ($c = 1.01$ in $CHCl_3$); $C_{24}H_{30}N_2O_3$ (394.51): C 73.1, H 7.67, N 7.1; found: C 72.5, H 7.61, N 7.0.

Product **5** was prepared by means of the procedure described for **1**, except that Boc-FiFi-NH*i*Pr (200 mg, 0.507 mmol) was used as the substrate, and the reaction was run for 16 h, to give 200 mg (83%) of **5** as white solid: R_f 0.57 (40% ethyl acetate/hexanes); m.p. 182–184 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.20$ (m, 14H), 6.96 (d, $J = 8.5$ Hz, 1H), 6.08 (s, 1H), 3.91 (d, $J = 8.5$ Hz, 1H), 3.69–3.76 (m, 1H), 3.14 (d, $J = 8.0$ Hz, 1H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.68 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 168.75, 166.38, 134.65, 134.5, 132.0, 129.0, 128.9, 128.8, 128.5, 128.1, 127.6, 127.1, 47.3, 41.5, 37.4, 31.3, 22.4, 22.1; IR (CH_2Cl_2): $\nu = 3412$, 3315, 3078, 1672, 1274, 1247, 1075 cm^{-1}; HRFAB: calcd $[M+Na]^+$ 499.0997, found 499.1002; $[\alpha]_D^{25} = -119$ ($c = 0.53$ in $CHCl_3$).

CD spectroscopy: CD measurements were obtained on an Aviv (Model 62DS) spectrometer. Solutions of the peptidomimetics were prepared by dissolving the amides in spectral grade MeOH and H_2O that had been degassed immediately prior to use. A mixture of 65:35 MeOH/H_2O was used (this mixture has the same dielectric constant as DMSO, which is unsuitable for CD investigations). The concentration of the peptidomimetics studied was in the range of $5.5-6 \times 10^{-2}$ mM. The data presented represents an average of 4 scans per sample with a time constant of 2 s, bandwidth of 1 nm, and sampling every 0.5 nm from 320 to 198 nm. For temperature-dependence studies, the samples were equilibrated for at least 10 min before data acquisition. A quartz cell of pathlength 2 cm was used in all cases.

IR spectroscopy: IR spectra were measured on a Nicolet Impact 410 FTIR spectrometer. A cell equipped with CaF_2 windows and a path length of 1.00 mm was used. The spectra presented represent the average of 128 scans. Solvent subtraction was carried out using reference spectra obtained under identical conditions as the sample spectra. The amides used were vacuum-dessicated at ambient temperature overnight before sample preparation. The samples were prepared in a dry box by dissolving several milligrams of the amide in CH_2Cl_2 (degassed) and diluted to a final concentration of 1 mM.

NMR spectroscopy: NMR spectra of the samples in [D_6]DMSO were recorded on a Varian Unity + 500 spectrometer (500 MHz). Solutions of the peptidomimetics at a concentration of approximately 10 mM were used unless otherwise indicated. The samples were prepared in a dry box by dissolving the sample in the appropriate solvent. One-dimensional (1D) ^1H NMR spectra were recorded with a spectral width of 8000 Hz, 30272 data points, a 5 s acquisition time, and 32 transients. Chemical shifts of the amide protons were monitored over a concentration range; near constant chemical shift values were obtained ($\Delta\delta \leq 0.04$ ppm) indicating no significant aggregation had occurred in the 10 mM [D_6]DMSO solutions. Temperature coefficients of the amide protons in DMSO were measured by several 1D experiments between 25–60 °C in 5 °C increments. The samples were each equilibrated for at least 10 min before data acquisition. Solvent titration experiments were performed by monitoring the changes in the chemical shifts of the amide protons upon titration of the tripeptide derivatives in $CDCl_3$ with increasing amounts of [D_6]DMSO (1–15%). The concentration of these solutions was in the order of 10 mM. T_1 experiments were performed with the inversion recovery pulse sequence. Each ^{13}C NMR spectrum was recorded in $CDCl_3$ with a delay (d_1) of at least 6 T_1, while d_2 was an array of 9 data points (0.01, 0.1, 0.5, 1, 3, 5, 10, 15, 25 s). The concentration of the samples for the T_1 experiments was in the order of 0.1–0.2 M.

Molecular modeling: A Silicon Graphics IRIX-O_2 workstation was used for the conformational search performed in this work. All calculations were performed with QUANTA97/CHARMm version 23.2 software (Molecular Simulations Incorporated) with extended representations of the nonpolar hydrogen atoms. Since CHARMm does not have parameters for the cyclopropane amino acids, additional atom types were assigned and a parameter set was built based on crystallographic data and CHARMm default parameters, then appended to the CHARMm standard parameter file. The residue topology files (RTFs) of cyclo-Phe, 3-Ph-cyclo-Phe, and FiFi amino acids were built according to the standard geometry of these unnatural amino acids, then appended to the CHARMm standard RTF. The combined CHARMm parameters and RTFs were imported to QUANTA/CHARMm for the following calculations.

A systematic grid search was used to explore the conformational space available to the derivatives studied. The search was performed and these results were all repeated at least once with slight modifications. In the first run, six torsion angles were defined for each compound, except for compound **3** for which only five torsion angles were defined. A grid-scan search was then used to generate conformations systematically by varying specified torsion angles of either 60 or 120°. For each compound, the conformers generated were further minimized with CHARMm (an unconstrained Cartesian minimization process) to obtain the low-energy regions of conformational space. From these, only structures with the energy less than 3–4 kcal mol^{-1} from the lowest energy conformer were selected for further analysis. Moreover, during the minimization the grid torsion was constrained to the grid point with a penalty energy function. A contour plot was generated from this search by computing a contour of potential energy varying over the set of grid points.

Supporting information available: CD spectra of compound **1**-**5** at 0 °C, solvent titration data, NH chemical shift data, temperature coefficient data, T_1 relaxation times and CHARMm parameterization files for compound **1**--**5**, X-ray data for compound **5**. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 117417. Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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