Synthesis of the Prototypical Cyclopropyl Dipeptide Mimic and Evaluation of Its Turn-Inducing Capability

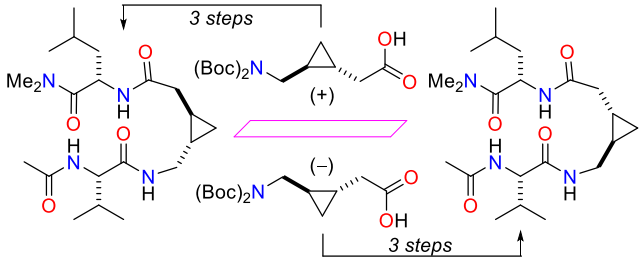
Albane Neckebroeck,† Sharon M. Kelly, Brian O. Smith, and J. Stephen Clark*

J. Stephen Clark – *School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom*

Albane Neckebroeck – *School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom*

Sharon M. Kelly – *Institute of Molecular, Cell and Systems Biology, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom*

Brian O. Smith – *Institute of Molecular, Cell and Systems Biology, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom*



ABSTRACT: The (+) and (–) enantiomers of a new turn-inducing cyclopropyl dipeptide mimic have been synthesized and evaluated. The mimic derives its turn-inducing capabilities solely from the cyclopropyl group and without the conformational biasing that would be provided by side-chain substituents. The mimic and peptide-mimic hybrids prepared from it have been studied using a combination of spectroscopic techniques (NMR, IR and CD). The dipeptide mimic itself displays intramolecular hydrogen bonding in organic solvents which differs from that observed in natural peptide turns. In contrast, more elaborate mimic-peptide hybrids exhibit hydrogen bonding characteristics that vary with solvent but are consistent with structures found in the tetrapeptide portion ($i \rightarrow i + 3$) of a native β-turn.

INTRODUCTION

β-Turns are ubiquitous and important elements of peptide and protein secondary structure.[1] A β-turn involves four amino acid residues (labelled $i \rightarrow i + 4$ from the *N*- to *C*-terminus) and is usually stabilized by the presence of a hydrogen bond between the carbonyl oxygen of residue *i* and the amide proton of residue $i + 4$ (Figure 1). There are four main types of β-turn – type I and type II and their main-chain mirror image forms type I' and type II' – and they are defined by the torsion angles (ϕ and ψ) of the backbone in the $i + 1$ and $i + 2$ residues of each turn (Figure 1).

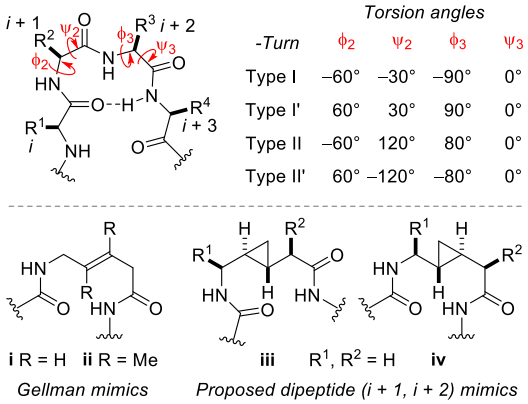


Figure 1. Type I, I', II and II' peptide β-turns, Gellman's mimics (**i** and **ii**) and the novel cyclopropane-containing mimics (**iii** and **iv**) used in this study.

β-Turns cause a reversal in the direction of the main peptide chain and their occurrence is strongly associated with other elements of protein secondary structure such as

β-sheets and helices. They often occur between regions of ordered secondary structure and so are frequently located at the surfaces of proteins; in these cases, β-turns are usually composed of polar residues or non-polar residues with low hydrophobicity. Surface-exposed β-turns can engage in ligand-binding and molecular recognition events that result in modulation of protein function.[2] β-Turns bearing polar residues can also serve as sites for post-translational modifications such as phosphorylation and glycosylation.[3] In addition, β-turns have been implicated in the folding processes that produce well-defined protein tertiary structures.[4] It has been proposed that β-turns perform an active role in protein folding by serving as nucleation sites through local interactions or that they simply enable folding to occur as a result of long-range hydrophobic interactions due to their flexibility; there is evidence to support both of these propositions in different proteins.[5,6]

The prevalence and importance of β-turns in proteins has resulted in a longstanding and widespread interest in the design and synthesis of non-peptidic replacements for β-turns that enforce turn-like conformations when attached to peptide chains.[7] Many candidate structures have emerged from this work, but very few of them satisfy all the requirements necessary to make them good mimics such as ease of synthesis, minimal steric requirements, appropriate hydrogen bonding characteristics and the ability to replicate the conformation of native peptides accurately when incorporated into peptides.[8]

The simplest of the mimics, and those that cause minimal structural perturbation, generally involve replacement of the amide bond between residues i + 1 and i + 2 with an isosteric group. The least complex example of such an isostere is an *E*-alkene, which is achiral and provides geometrical and conformational constraints that resemble closely those of an amide. Gellman and co-workers replaced an amide group in simple peptides with a simple disubstituted or tetrasubstituted *E*-alkene, as summarized in Figure 1 (**i** and **ii**), and obtained spectroscopic evidence to suggest that turn formation with intramolecular hydrogen bonding was achieved in organic solvents.[9] In contemporaneous studies, Wipf and co-workers studied the incorporation of trisubstituted *E*-alkenes as amide bond isosteres in peptides and obtained evidence for β-turn formation in the solid state.[10]

The aim of the work described herein was to discover whether a cyclopropane could be used as an isostere to replace the amide bond between the i + 1 and i + 2 residues of a peptide β-turn with preservation of the natural conformation. At the outset we proposed to synthesize the cyclopropane-containing dipeptide mimics necessary to construct hybrid systems such as **iii** and **iv** (R^1, R^2 = H) shown in Figure 1. The mimics would therefore act as surrogates for a Gly-Gly dipeptide in a β-turn sequence. The Gly-Gly sequence has low prevalence in natural β-turns even though single glycine residues are common.[11] However, in preliminary studies we wanted to establish whether the cyclopropane would induce a turn on its own and without the additional conformational constraints that would be provided by side chains**.**

Shuto and coworkers have used a cyclopropane to replace three atoms – carbonyl carbon, amide nitrogen and α-carbon – that span two amino acid residues in a natural peptide (e.g. **1**, Figure 2).[12] However, the use of a trans-disubstituted cyclopropane as a direct amide bond replacement has received scant attention and there appear to be only two pertinent examples in the literature.[13,14] In the first example,[13] the carboxylic acid **2** was prepared and incorporated into a cyclic cell-penetrating peptide by Shuto and co-workers and in the latter case, Wipf and co-workers prepared the carboxylic acid **3**, which contains an additional methyl substituent on the cyclopropane (Figure 2).[14] Neither of the mimics **2** or **3** has been incorporated into peptide chains in order to investigate their turn-inducing capabilities.

The primary objective of our work was the evaluation of the turn-inducing capabilities of both enantiomers of the dipeptide surrogate **4** when deprotected and incorporated into peptide-mimic hybrids analogous to the tetrapeptide sequences found in β-turns. It should be noted that the structure of our mimic and the methods used to evaluate it differ considerably those described by Wipf and co-workers (e.g. **3**, Fig. 2). Wipf's dipeptide mimics possess a trisubstituted cyclopropane and alkyl substituents adjacent to the cyclopropane on the amino acid chain,[14] whereas our mimic lacks branching substituents on this chain. Thus, tetrapeptide analogues derived from our dipeptide surrogate **4** rely solely on the stereochemistry of trans-1,2-disubstituted cyclopropane to enforce a turn-like structure because conformational locking by substituents adjacent to the cyclopropane is absent. In our studies, various spectroscopic techniques have been used to probe the solution conformations of peptide-mimic hybrids that serve as tetrapeptide analogues. The only evidence reported by Wipf and co-workers to support turn formation has been obtained by X-ray analysis of simple protected dipeptide mimics in the solid state and the conformations of these compounds in solution has not been studied.[14]

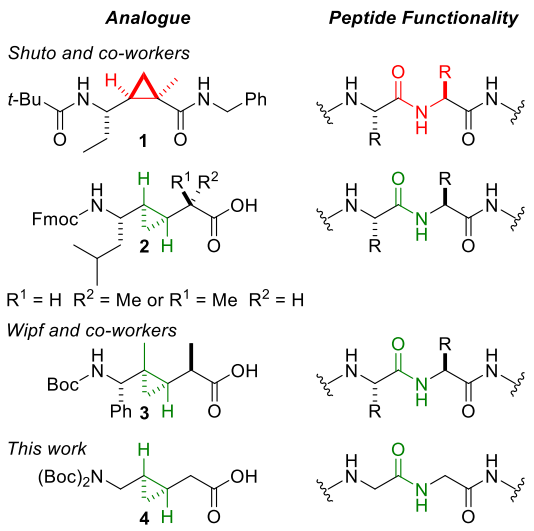


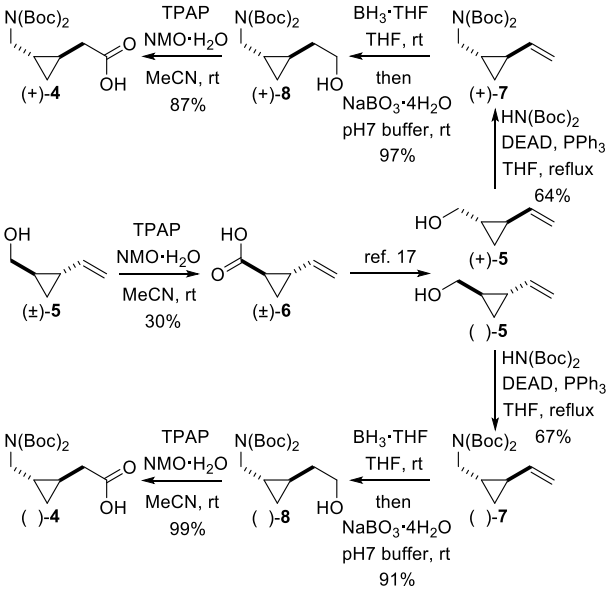
Figure 2. Cyclopropane-containing dipeptide mimics.

RESULTS AND DISCUSSION

Both enantiomers of the dipeptide mimic **4** were synthesized from the vinyl cyclopropane (±)-**5** (Scheme 1). The racemic starting material was prepared from commercially

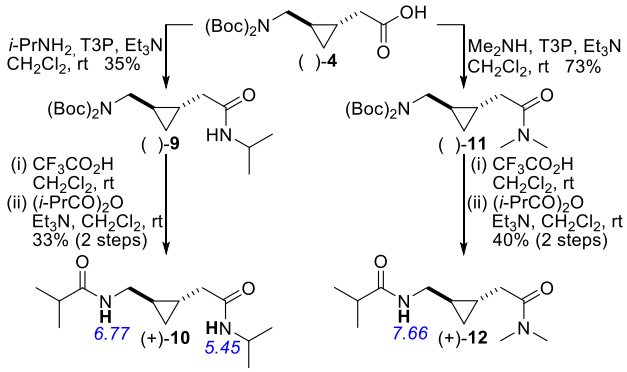
available (±)-1,2-epoxy-5-hexene, according to the procedure of Mordini and co-workers.[15] Direct oxidation of the alcohol (±)-**5** to give the carboxylic acid (±)-**6** was performed with TPAP along with hydrated NMO as the stoichiometric reoxidant.[16] The resulting carboxylic acid (±)-**6** was resolved by reaction with (*R*)-phenylglycinol to give diastereomeric amides according to the procedure of Jaenicke and co-workers.[17] The amides were separated and then converted into the individual enantiomers of the alcohol **5**. The requisite amine was installed in protected form by reaction of the alcohols (+)-**5** and (–)-**5** with di-*t*-butyliminodicarboxylate under Mitsunobu conditions and the resulting bis-protected amines (+)-**7** and (–)-**7** were then subjected to sequential hydroboration and oxidation to give the alcohols (+)-**8** and (–)-**8**. Subsequent oxidation of the alcohols with TPAP delivered both enantiomers of the carboxylic acid **4**.[16]

Scheme 1. Synthesis of Both Enantiomers of the *N*-Protected Dipeptide Mimic



The mimic **4** was capped with an amide group at both termini so that the degree of intramolecular hydrogen bonding in solution could be assessed in the absence of additional amino acid residues (Scheme 2). The amide groups were chosen to be the same as those used by Gellman and co-workers to explore the hydrogen bonding capabilities of mimics containing an alkene as a peptide bond isostere (i and ii, Figure 1).[9] Conversion of the carboxylic acid (–)-**4** into the amide (–)-**9** was accomplished by propylphosphonic anhydride (T3P) mediated coupling to isopropylamine.[18] Removal of the Boc groups followed by *N*-acylation with isobutyric anhydride afforded the bis-amide (+)-**10**. In a similar manner, the acid (–)-**4** was converted into the amide (–)-**11** by T3P-mediated coupling to dimethylamine. Subsequent Boc removal and *N*-acylation with isobutyric anhydride produced the bis-amide (+)-**12**.

Scheme 2. Synthesis of Amide Functionalized Dipeptide Mimics with the ^{1}H NMR Chemical Shifts (δ) of NH Indicated



The extent of hydrogen bonding in bis-amides (+)-**10** and (+)-**12** was probed by ^{1}H NMR and IR spectroscopy.[19] An intramolecularly hydrogen bonded amide proton in a peptide or protein undergoes a significant downfield shift in the ^{1}H NMR spectrum.[20] Consequently, it was anticipated that the presence of a hydrogen bond would manifest itself as a significant chemical shift difference between the signal corresponding to NH of the mimic and that of a simple amide. It was observed that the chemical shift of the NH (■) of mimic (+)-**10** was shifted downfield (δ 6.77 ppm) and was essentially invariant at concentrations below 20 mM (Figure 3). The chemical shift for *i*-PrNH (●) of the bis-amide (+)-**10** (δ 5.45 ppm) was typical of a standard amide, an observation that suggests there was little hydrogen bonding and the proton was exposed to solvent. The chemical shift of this proton (●) was consistent at concentrations below 1 mM, which rules out significant intermolecular hydrogen bonding, but it varied more at higher concentrations (>5 mM). The conclusions from the ^{1}H NMR data were supported by solution IR data. The IR spectrum of mimic (+)-**10** displays a strong band at 3323 cm^{-1}, which arises from intramolecular hydrogen bonding of NH, and a band at 3431 cm^{-1} that is due to NH exposed to solvent.[21]

To estimate the degree of hydrogen bonding that occurs in (+)-**10**, the ^{1}H NMR and IR data were compared to those of the bis-amide (+)-**12**, in which only one intramolecular hydrogen bond can be formed. The ^{1}H NMR chemical shift for the NH of (+)-**12** was further downfield (δ 7.66 ppm) than the signal for the corresponding NH in (+)-**10** and exhibited little variation at concentrations of up to 20 mM. A strong band at 3310 cm^{-1} was observed in the IR spectrum of (+)-**12** and there was a very much weaker band at 3441 cm^{-1}, which indicates that there is significant intramolecular hydrogen bonding in (+)-**12**. The corresponding ester (±)-**13** was prepared and then analyzed by IR spectroscopy. In this case, a narrow NH band was observed at 3433 cm^{-1} and there was no band 3300–3350 cm^{-1}, which suggests that intramolecular hydrogen bonding between the NH and ester carbonyl group does not occur.

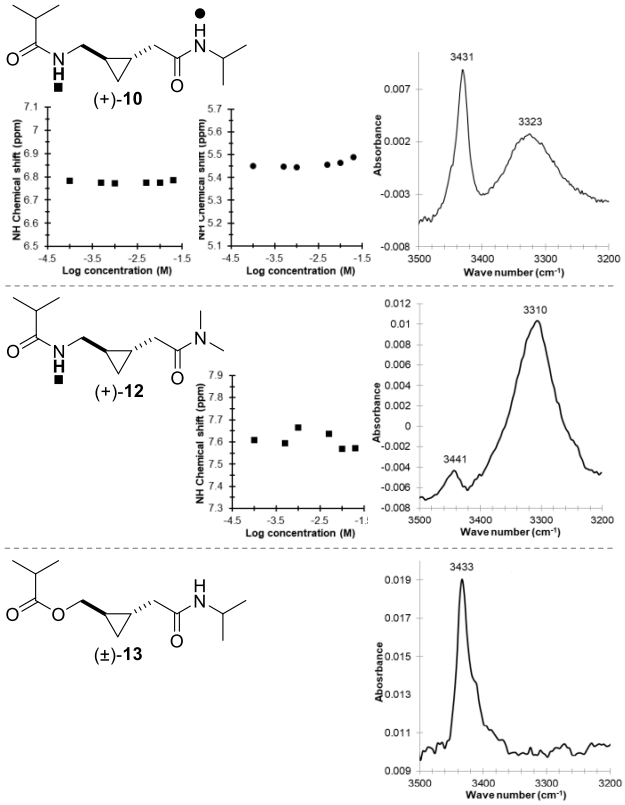


Figure 3. Concentration-dependency of the ^{1}H NMR (CD_2Cl_2) chemical shifts of amide protons in *bis*-amides (+)-**10** and (+)-**12**, and the IR spectra (10 mM, CH_2Cl_2) showing NH stretches for compounds (+)-**10**, (+)-**12** and (±)-**13**.

The data shown in Figure 3 provide consistent evidence that even in the very small parent mimic (+)-**10** there is significant intramolecular hydrogen bonding between the mimic NH (■) and the carbonyl oxygen. The predominant mode of hydrogen bonding in (+)-**10** is that in which an eight-membered ring is formed and there appears to be very little hydrogen bonding to form a 10-membered ring analogous to that found in a Type I or Type II β-turn (Figure 4). The type of hydrogen bonding arrangement observed in (+)-**10** is intermediate between that found in a β-turn and the smaller (seven-membered) γ-turn, but it cannot be accommodated in a natural peptide due to amide bond planarity.

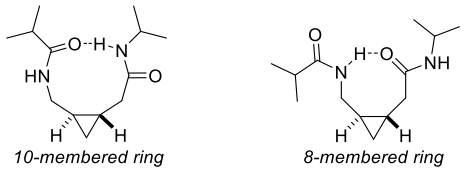
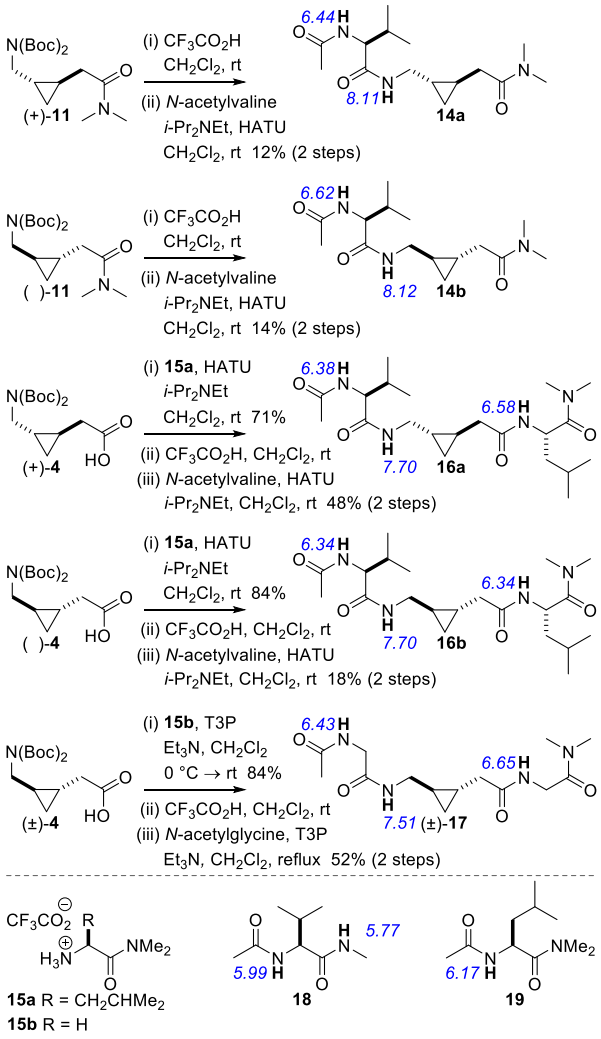


Figure 4. Intramolecular hydrogen-bonding possibilities for the bis-amide (+)-**10**.

Peptide-mimic hybrids that were synthesized to explore the effect of attachment of natural amino acids on both the mode and degree of hydrogen bonding (Scheme 3). The *N*-protected mimics (+)-**11** and (−)-**11** were subjected to acid-mediated deprotection and the resulting amines were then coupled to *N*-acetyl-L-valine to give the diastereomeric coupled products **14a** and **14b** in low yield, but in sufficient quantities to permit full spectroscopic evaluation. The more complex peptide-mimic hybrids **16a** and **16b** (analogues of the tetrapeptide in a β-turn) were prepared from the carboxylic acids (+)-**4** and (−)-**4** by sequential HATU-mediated coupling with the free amine derived from the salt **15a**, removal of both Boc groups and amide bond formation with *N*-acetyl-L-valine.[22] The final analogue (±)-**17** was prepared by T3P coupling of the acid (±)-**4** with the TFA salt of 2-amino-*N*,*N*-dimethylacetamide (**15b**), followed by acid-mediated cleavage of the Boc groups and final acylation of the free amino group with *N*-acetylglycine.

Scheme 3. Synthesis of Peptide-Mimic Hybrids 14a, 14b, 16a, 16b and 17 with ^{1}H NMR Chemical Shifts (δ) of NH Indicated



The peptide-mimic hybrids **14a** and **14b**, in which a valine residue is attached to the *N*-terminus of the mimic, were analyzed first (Figure 5). In the ^{1}H NMR (CD_2Cl_2) spectra of both diastereomers, the mimic amide protons (■ and □) had similar chemical shifts and there was significant deshielding (δ 8.11, 8.12) compared to published chemical shift data for the benchmark amides **18** and **19**.[9b] The chemical shift of the valine NH (▲ and △) varied slightly over the concentration range of 0.05–20 mM, while that of the mimic NH (■ and □) varied little for both peptide-mimic hybrids **14a** and **14b**. These results suggest that

both amide protons are involved in intramolecular hydrogen bonding. Furthermore, when the NH-stretching bands in the IR spectra are considered, the bands at 3418 and 3410 cm^{-1} suggest that intermolecular interactions are occurring in solution to a lesser extent than intramolecular interactions indicated by the NH-stretching bands at 3302 and 3310 cm^{-1}. Furthermore, the ^1H NMR chemical shift data show that the signal for the mimic NH (■ and □) is downfield (>8 ppm) in each case, which suggests that hydrogen bonding occurs to produce an eight-membered ring rather than the alternative 11-membered ring.

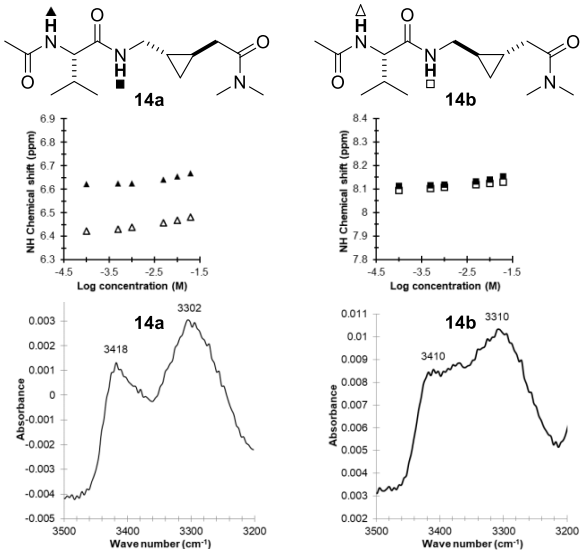


Figure 5. Concentration dependency of the ^1H NMR (CD_2Cl_2) chemical shifts of the amide protons and IR (10 mM in CH_2Cl_2) spectra showing NH stretches for peptide-mimic hybrids **14a** and **14b.**

In the final set of experiments, the peptide-mimic hybrids **16a**, **16b** and **17** were analyzed by NMR, IR and CD spectroscopy. These compounds were designed to serve as analogues of tetrapeptide sequences that are found in complete peptide β-turns. ^1H NMR (CD_2Cl_2) analysis of the analogues showed that the NH (■, □ and ■) of the mimic was the most deshielded in all three peptide-mimic hybrids, with chemical shifts in the range δ 7.51–7.70 ppm; the chemical shifts for the other amide protons were in the range δ 6.34–6.65 in each case. The chemical shift for the NH (■, □ and ■) of the mimic also remained constant across a wide range of concentrations in each peptide-mimic hybrid whereas there were significant changes in the chemical shifts of the other amide protons, particularly at higher concentrations. These results suggest that the mimic NH (■, □ and ■) forms a strong intramolecular bond whereas the other amide protons undergo increasing intermolecular hydrogen bonding as the concentration rises. In the case of the peptide-mimic hybrid **17**, in which amino acid side chains are absent, the chemical shifts of two of the NH (■ and •) lie approximately 0.2 ppm upfield compared to the chemical shifts of the corresponding amide protons in **16a** and **16b**. This observation suggests that intramolecular hydrogen bonding is weaker in the more conformationally flexible hybrid **17**.

The bands at 3418 and 3310 cm^{-1} in the NH-stretching region of the IR spectrum of **16a** show that there is an intramolecular hydrogen bonding network in this peptide with some flexibility of both the external residues constituting the strands (band at 3418 cm^{-1}). For the IR spectrum of the peptide-mimic hybrid **16b**, bands at 3422 and 3310 cm^{-1}, which arise from solvent exposed / intermolecularly hydrogen bonded NHs and intramolecularly hydrogen bond NHs, were evident. In the IR spectrum of the less conformationally constrained peptide-mimic hybrid **17**, bands are found at 3404 and 3316 cm^{-1}. The peak at higher wavenumber arises from an NH that is either solvent exposed or intermolecularly hydrogen bonded and the other peak arises from intramolecularly hydrogen bonded NHs.

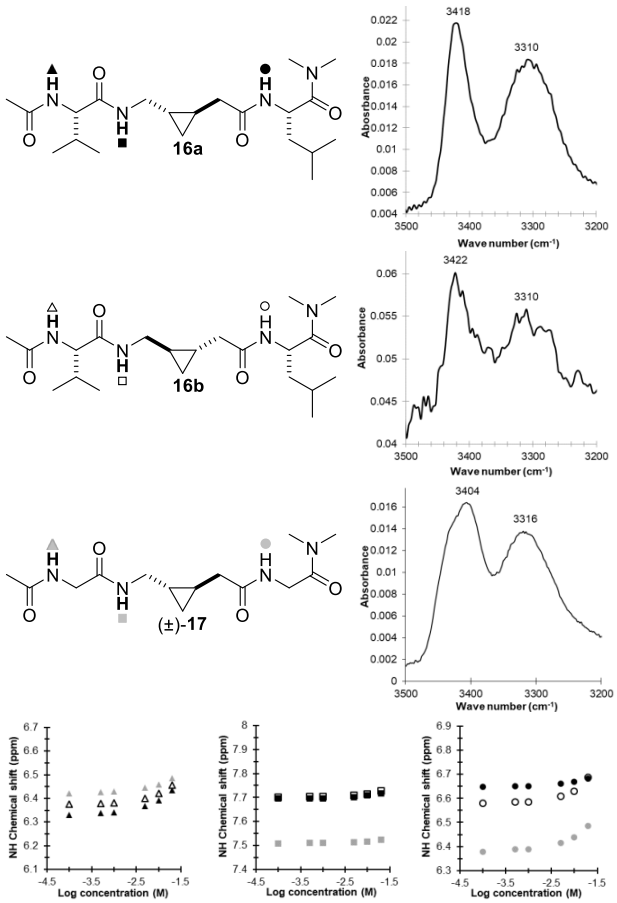


Figure 6. Concentration dependency of the ^1H NMR (CD_2Cl_2) chemical shifts of the amide protons and IR spectra (10 mM in CH_2Cl_2) showing NH stretches for the peptide-mimic hybrids **16a**, **16b** and **(±)-17**.

Overall, the data demonstrate that the mimic NH (■, □ and ■) is strongly intramolecularly hydrogen bonded in each of the tetrapeptide analogues studied. In principle, it is possible for the mimic NH to form a hydrogen bond with either the carbonyl oxygen of the mimic to form an eight-membered ring, or the carbonyl oxygen of the leucine residue to produce an 11-membered ring.

Additional ^1H NMR NOESY experiments were performed to provide information about the conformational preferences of the peptide-mimic hybrids **16a** and **16b**. The cross peaks observed for both **16a** and **16b** suggest that the configurations of the stereocenters in the trans-cyclopropane relative to those in the amino acid units have little influence on the folded arrangement of the peptide, a

finding that is consistent with the IR and NMR data. In the case of **16b**, two interesting cross peaks were observed between the mimic NH and the valine NH and between the mimic NH and the leucine NH (Figure 7). These peaks do not correspond to features expected in natural peptides, but the latter interaction establishes that the mimic NH and leucyl NH are in proximity and thereby provides evidence that the peptide-mimic hybrid adopts a folded conformation. Formation of a folded conformation instead of an extended conformation in CD_2Cl_2 is also supported by the observation of an NOE between the NH of leucine and both the proximal methine proton of the cyclopropane and the NH of the mimic. An NOE was also observed between the mimic NH and the α-CH of the valine residue when the compound **16b** was analyzed in either water or CD_2Cl_2.

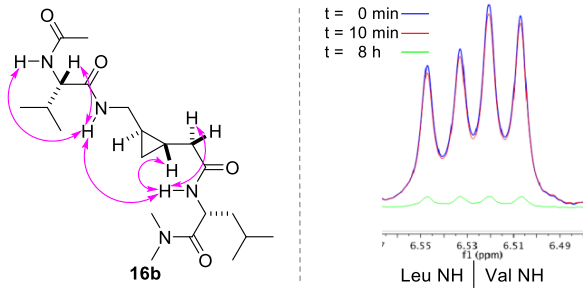


Figure 7. NOEs observed in ^{1}H NMR NOESY spectrum **16b** (10 mM in CD_2Cl_2; 278 K); the region δ 6.49–6.57 of the ^{1}H NMR spectrum of **16b** (10 mM in TFE-d3; 278 K) showing H/D exchange of leucine and valine NH.

The NOE interactions of the peptide **16b** in deuterated trifluoroethanol (TFE-d3), a solvent that is known to promote intramolecular interactions,[23] were also studied. The NH of both the leucine and valine residues underwent slow exchange (hours) with the deuterium of TFE-d3 (Figure 7), whereas the NH of the mimic (□) exchanges immediately.[24] This can be explained if the NH of the leucine and valine residues are protected from exchange with the solvent by intramolecular hydrogen bond formation, while the NH of the Gly-Gly mimic is relatively exposed to solvent. This result suggests that intramolecular hydrogen bonding occurs to produce a 10-membered ring, a finding that contrasts with the results of NMR concentration experiments performed in CD_2Cl_2 described above. This finding suggests that intramolecular interactions and hydrogen bonding arrangements in our analogues are highly solvent-dependent.[25]

To discover whether the folded conformations adopted by peptide-mimic hybrids **16a** and **16b** resemble those of natural turns and the degree to which they are solvent dependent, CD spectra were recorded in acetonitrile, TFE and water (Figure 8).[26,27] Acetonitrile was selected as a solvent because chlorinated solvents are incompatible with CD spectroscopy and the peptides exhibited similar NMR characteristics in CD_2Cl_2 and CD_3CN. TFE was selected as a solvent because it enhances intramolecular interactions and promotes the formation of secondary structure, even in small peptides.[23]

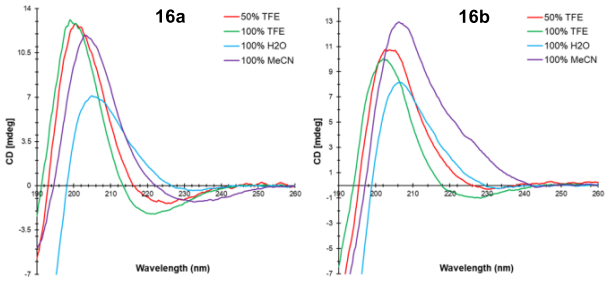


Figure 8. Far-UV CD spectra of **16a** and **16b** in TFE-water (1:1), TFE, water and acetonitrile (concentration 1 mg/mL).

The peptide was expected to adopt an extended conformation in water due to extensive solvation. However, the CD spectrum for peptide-mimic hybrid **16a** in water (Figure 8) was found to have a large positive band at 205 nm, as would be expected of a type II turn. The peptide seems to adopt a turn structure in water, which is an unexpected observation for such a small system in a polar solvent. The CD spectrum of **16a** in acetonitrile has positive and negative peaks at 205 and 235 nm respectively, which indicates that the peptide-mimic hybrid contains structural features analogous to those of a type II β-turn or a β-sheet. The compound **16a** appears to be more structured when trifluoroethanol is used as the solvent (1:1 TFE/water or 100% TFE) with an ellipticity that is almost two times higher than that in water at 200 nm. Thus, the CD spectra of peptide-mimic hybrid **16a** suggest that a type II β-turn is formed in all four solvents. Similar results were obtained when the peptide-mimic hybrid **16b** was analyzed (Figure 8). The CD data suggest that the peptide has a better-defined structured in TFE than in the other solvents and that it has features that are characteristic of a type II β-turn or β-sheet.

CONCLUSIONS

A combination of NMR, IR and CD spectroscopic techniques has been used to show that the novel enantiomeric cyclopropyl dipeptide mimics (–)-**4** and (+)-**4** promote formation of hydrogen-bonded turn structures when incorporated into small peptide systems. In the absence of additional amino acid residues, the mimics adopt a hydrogen bonding arrangement that is intermediate between that found in a β-turn and that in a γ-turn and is unprecedented in natural peptides. In contrast, diastereomeric peptide-mimic hybrids created by attachment of natural amino acids to the mimics (–)-**4** and (+)-**4**, display more complex hydrogen-bonded arrangements that are solvent-dependent. Conformational analysis of the tetrapeptide analogues **16a** and **16b** by ^{1}H NMR spectroscopy revealed that they adopt folded conformations in both CH_2Cl_2 and TFE, but with different hydrogen bond networks. In both compounds, the mimic NH was found to exchange with TFE-d3 solvent immediately and so this proton is not protected by intramolecular hydrogen bonding in the manner observed in CH_2Cl_2. This observation suggests that an eight-membered ring is not generated by hydrogen bonding in TFE.

Overall, results suggest that cyclopropyl-containing dipeptide mimic **4** is a sterically minimal unit that is capable of constraining small peptides to adopt a turn confor-

mation, stabilized by intramolecular hydrogen bonding, in solution. In the case of the small peptide-mimic hybrids evaluated in this study, the NMR, IR and CD spectroscopy data for compounds **16a** and **16b** are similar, which suggests that the stereochemical relationship between the trans-disubstituted cyclopropyl unit and the amino acid residues has little influence on the formation of a turn or the type of hydrogen bonding that stabilizes it.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from commercial suppliers and were used without further purification, unless otherwise stated. Air- and moisture-sensitive reactions were performed under an atmosphere of argon in flame-dried apparatus. THF, toluene, acetonitrile, dichloromethane and diethyl ether were purified using a Pure-SolvTM 500 Solvent Purification System. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F_{254}. TLC plates were visualized under UV light and stained using potassium permanganate solution, acidic ethanolic anisaldehyde solution or ninhydrin solution. Flash column chromatography was performed on silica gel (Merck 60, 40–63 μm) as the solid support. Petroleum ether used for column chromatography was the 40–60 °C fraction. IR spectra were recorded as thin films or in solution and selected frequencies ($\nu_{max.}$) are reported. NMR spectra were obtained from a dilute solution of each compound in either $CDCl_3$ or CD_2Cl_2 at ambient temperature using the deuterated solvent as the internal deuterium lock. ^{1}H Chemical shift data are given in units of δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (CD_2Cl_2) = 5.32. ^{1}H signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), broad (br) or a combination of these along with the coupling constant J (Hz). ^{13}C NMR spectra were recorded at 101 MHz, 126 MHz or 151 MHz with broadband proton decoupling and chemical shift data are given in units of δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (CD_2Cl_2) = 53.5. Details of the equipment used to obtain spectroscopic data and other characterization data are provided in Supporting Information

(1*R,2*S**)-2-Ethenylcyclopropane-1-methanol [(±)-5].**[28] To THF (110 mL) cooled to −78 °C under argon was added carefully, *n*-BuLi (40.0 mL of an 11 M solution in hexane, 440 mmol). Diisopropylamine (62.0 mL, 439 mmol) was added dropwise followed by potassium *tert*-butoxide (49.0 g, 437 mmol) and the reaction mixture was stirred at −78 °C for 45 min. (±)-1,2-Epoxy-5-hexene (5.60 mL, 49.6 mmol) was added dropwise at −78 °C and the reaction mixture was stirred at −50 °C for 15 h. The reaction was quenched at −50 °C by the addition of water (30 mL) and the mixture was allowed to warm to rt. The solution was extracted with ether (3 × 15 mL) and the combined organic layers were dried (magnesium sulfate). Most of the solvent was removed by distillation at atmospheric pressure to afford (±)-**5** (35.1 g, 68 wt %, quant.) as a solution in THF. $\nu_{max.}$ ($CHCl_3$) 3329, 2924, 1636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, ddd, J = 17.1, 10.3, 8.5 Hz), 5.06 (1H, dd, *J* = 17.1, 1.6 Hz), 4.88 (1H, dd, *J* = 10.3, 1.6 Hz), 3.54–3.47 (2H, m), 1.51 (1H, brs), 1.35 (1H, m), 1.21–1.13 (1H, m), 0.70–0.64 (2H, m); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.7, 112.5, 66.4, 23.1, 20.7, 11.7.

(1*R,2*S**)-2-Ethenylcyclopropane-1-carboxylic acid [(±)-6].**[17] The alcohol (±)-**5** (1.00 g, 10.2 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (11.9 g, 88.0 mmol) were dissolved in acetonitrile (41 mL). Tetra-*n*-propylammonium perruthenate (358 mg, 1.02 mmol, 10 mol %) was added portionwise (20 mg / 20min) at rt. The mixture was stirred at rt overnight and the reaction was then quenched by the addition of an excess of isopropanol. Water (30 mL) was added to the mixture and it was adjusted carefully to pH 1 by the addition of 2 M aq. hydrochloric acid. The aqueous phase was extracted with ether (3 × 50 mL) and the combined organic extracts were then washed with brine (20 mL), dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by silica gel column chromatography (pet. ether-ethyl acetate, 1:1) to afford the carboxylic acid (±)-**6** (371 mg, 30%) as a brown oil. $\nu_{max.}$ 2957, 1692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (1H, br s), 5.39 (1H, ddd, *J* = 17.0, 10.2, 8.3 Hz), 5.18 (1H, ddd, *J* = 17.0, 1.4, 0.6 Hz), 5.02 (1H, ddd, *J* = 10.2, 1.4, 0.4 Hz), 2.13–2.06 (1H, m), 1.64 (1H, ddd, *J* = 8.3, 5.0, 4.2 Hz), 1.43 (1H, ddd, *J* = 8.6, 5.0, 4.4 Hz), 1.06 (1H, ddd, *J* = 8.6, 6.4, 4.2 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.9, 137.6, 115.4, 26.6, 21.7, 16.3; *m/z* (CI, isobutene) $[M+H]^+$ 113 (72%).

(1*R*,2*S*)-2-Ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl] cyclopropane-1-carboxamide and (1*S*,2*R*)-2-ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]cyclopropane-1-carboxamide.[17] To a well-stirred solution of the carboxylic acid (±)-**6** (4.0 g, 36 mmol) in THF (160 mL) were added dropwise, at −20 °C, *N*-methylmorpholine (3.9 mL, 35 mmol) and isobutylchloroformate (4.6 mL, 35 mmol). The mixture was stirred at this temperature for 15 min and (*R*)-phenylglycinol (4.9 g, 36 mmol) was added portionwise over a period of 30 min. The reaction mixture was stirred at −20 °C for 1 h and then allowed to warm to rt. The solvent was removed under vacuum and the residue was then dissolved in ethyl acetate (70 mL). The solution was washed successively with water (3 × 20 mL), sat. aq. sodium bicarbonate (3 × 20 mL), 2 M aq. hydrochloric acid (3 × 20 mL) and brine (20 mL). The organic phase was dried (magnesium sulfate) and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (pet. ether-ethyl acetate, gradient elution) to give the diastereomeric amides (1*R*,2*S*)-2-ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl] cyclopropane-1-carboxamide (1.53 g, 19%) and (1*S*,2*R*)-2-ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]cyclopropane-1-carboxamide (1.63 g, 20%) as solids. Each product was then recrystallized from ethyl acetate to produce colorless crystals. (1*R*,2*S*)-2-Ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]cyclopropane-1-carboxamide: $[\alpha]_D^{20}$ −17.5 (*c* = 1.05, in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3310, 2961, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (2H, m), 7.34–7.30 (3H, m), 6.25 (1H, d, *J* = 5.4 Hz), 5.42 (1H, ddd, *J* = 17.0, 10.2, 8.5 Hz), 5.18 (1H, dd, *J* = 17.0, 1.5 Hz), 5.07 (1H, td, *J* = 6.2, 3.8 Hz), 5.00 (1H, dd, *J* = 10.2, 1.5 Hz), 3.97–3.87 (2H, m), 2.73 (1H, dd, *J* = 7.3, 5.4 Hz), 2.09–2.02 (1H, m), 1.47–1.37 (2H, m), 0.91 (1H, ddd, *J* = 8.0, 6.2, 4.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.8, 139.0, 138.6, 129.1, 128.2, 126.9, 114.7, 67.2, 56.7, 25.0, 24.1, 15.0; HRMS (ESI) for

$C_{14}H_{16}NO_2$ $[M-H]^+$ calcd 230.1186 found 230.1187. (1*S*,2*R*)-2-ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl] cyclopropane-1-carboxamide $[\alpha]_D^{20}$ +9.89 (*c* = 1.05, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3298, 2959, 1634 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.37 (2H, m), 7.34–7.30 (3H, m), 6.23 (1H, d, *J* = 5.4 Hz), 5.40 (1H, ddd, *J* = 17.1, 10.2, 8.5 Hz), 5.14 (1H, dd, *J* = 17.1, 1.5 Hz), 5.07 (1H, td, *J* = 6.4, 4.0 Hz), 4.97 (1H, dd, *J* = 10.2, 1.5 Hz), 3.96–3.86 (2H, m), 2.77 (1H, dd, *J* = 7.2, 5.4 Hz), 2.05–2.01 (1H, m), 1.47–1.40 (2H, m), 0.97–0.93 (1H, m); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.6, 139.4, 138.8, 128.8, 127.8, 126.9, 114.4, 66.7, 56.4, 24.6, 23.9, 14.9; HRMS (ESI) for $C_{14}H_{16}NO_2$ $[M-H]^+$ calcd. 230.1186, found 230.1187.

(1*R*,2*S*)-2-Ethenylcyclopropane-1-carboxylic acid [(−)-6]. (1*R*,2*S*)-2-Ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]cyclopropane-1-carboxamide (2.43 g, 10.5 mmol) was dissolved in a mixture of 10 % potassium hydroxide in methanol (100 mL) and water (35 mL). The solution was heated (oil bath) to reflux and stirred overnight. Methanol was then removed under vacuum and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate) and concentrated under vacuum to recover (*R*)-phenyglycinol. The aqueous phase was acidified to pH 1 using conc. aq. hydrochloric acid and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (20 mL) and dried (magnesium sulfate). The solvent was removed under reduced pressure to give the carboxylic acid (−)-**6** (964 mg, 82%) as an oil. $[\alpha]_D^{20}$ −100 (*c* = 1.00, $CHCl_3$) [Lit.[29] $[\alpha]_D^{26}$ −160 (*c* = 1.0, EtOH)]; $\nu_{max.}$ 3219, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (1H, ddd, *J* = 16.9, 10.2, 8.3 Hz), 5.18 (1H, dt, *J* = 16.9, 1.1 Hz), 5.02 (1H, dd, *J* = 10.2, 1.1 Hz), 2.17–2.03 (1H, m), 1.64 (1H, ddd, *J* = 8.5, 5.1, 4.1 Hz), 1.44 (1H, ddd, *J* = 8.8, 5.1, 5.1 Hz), 1.06 (1H, ddd, *J* = 8.8, 6.4, 4.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 180.0, 137.7, 115.5, 26.6, 21.8, 16.3; *m/z* (EI) $[M+H]^+$ 113 (99%).

(1*S*,2*R*)-2-Ethenylcyclopropane-1-carboxylic acid [(+)-6]. (1*S*,2*R*)-2-Ethenyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]cyclopropane-1-carboxamide (1.86 g, 8.08 mmol) was dissolved in a mixture of 10% potassium hydroxide in methanol (60 mL) and water (30 mL). The solution was heated (oil bath) to reflux and stirred overnight. Methanol was then removed under vacuum and the aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried (magnesium sulfate) and concentrated under vacuum to recover (*R*)-phenyglycinol. The aqueous phase was acidified to pH 1 using conc. aq. hydrochloric acid and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried (magnesium sulfate). The solvent was removed under pressure gave the carboxylic acid (+)-**6** (863 mg, 95%) as an oil. $[\alpha]_D^{26}$ +115 (*c* = 1.00, $CHCl_3$) [Lit. $[\alpha]_D^{26}$ +178 (c = 1.1, EtOH)][3]; $\nu_{max.}$ 3219, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.27 (1H, br s), 5.40 (1H, ddd, *J* = 17.0, 10.2, 8.3 Hz), 5.18 (1H, dd, *J* = 17.0, 1.6 Hz), 5.01 (1H, dd, *J* = 10.2, 1.6 Hz), 2.14–2.02 (1H, m), 1.64 (1H, ddd, *J* = 8.3, 5.1, 4.2 Hz), 1.43 (1H, ddd, *J* = 8.6, 5.1, 4.4 Hz), 1.05 (1H, ddd, *J* = 8.6, 6.4, 4.2 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 179.6, 137.7, 115.4, 26.6, 21.8, 16.3; *m/z* (CI, isobutene) $[M+H]^+$ 113 (80%).

(1*R*,2*S*)-2-Ethenylcyclopropane-1-methanol [(−)-5]. A solution of acid (−)-**6** (1.40 g, 12.5 mmol) in THF (18 mL) was added dropwise to a slurry of lithium aluminium hydride (941 mg, 24.8 mmol) in THF (19 mL) at 0 °C. The mixture was heated to reflux (oil bath) for 5 h. The reaction was then quenched by the sequential addition of water (1 mL), 1 M aq. sodium hydroxide (1 mL) and water (3 mL) at 0 °C. The resulting mixture was stirred for 15 min and an excess of magnesium sulfate was added. The suspension was stirred for extra further 15 min and filtered. Most of the solvent was removed by distillation at atmospheric pressure to give the volatile alcohol (−)-**5** (1.51 g, 49 wt %, 62%) as a solution in THF. $[\alpha]_D^{26}$ −61 (*c* = 1.0, $CHCl_3$) [Lit.[17] $[\alpha]_D$ −64.3 (*c* = 8.54, CH_2Cl_2)]; $\nu_{max.}$ 3337, 2924, 1636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (1H, ddd, *J* = 17.1, 10.2, 8.7 Hz), 5.02 (1H, dd, *J* = 17.1, 1.6 Hz), 4.83 (1H, dd, *J* = 10.2, 1.6 Hz,), 3.47 (1H, dd, *J* = 11.2, 6.8 Hz), 3.44 (1H, dd, *J* = 11.2, 6.8 Hz), 1.31 (1H, dddd, *J* = 8.7, 8.7, 4.6, 4.6 Hz), 1.16–1.06 (1H, m), 0.67–0.57 (2H, m); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.8, 112.2, 66.1, 23.0, 20.6, 11.6.

(1*S*,2*R*)-2-Ethenylcyclopropane-1-methanol [(+)-5]. A solution of acid (+)-**6** (1.50 g, 13.4 mmol) in THF (19 mL) was added dropwise to a slurry of lithium aluminium hydride (1.10 g, 29.0 mmol) in THF (19 mL) at 0 °C. The mixture was heated (oil bath) to reflux for 5 h. The reaction was then quenched by the sequential addition of water (1 mL), 1 M aq. sodium hydroxide (1 mL) and water (3 mL) at 0 °C. The resulting mixture was stirred for 15 min and an excess of magnesium sulfate was added. The suspension was stirred for extra further 15 min and filtered. Most of the solvent was removed by distillation at atmospheric pressure to give the volatile alcohol (+)-**5** (1.18 g, 41 wt %, 59%) as a solution in THF. $[\alpha]_D^{26}$ +51 (*c* = 1.0, $CHCl_3$) [Lit.[29] $[\alpha]_D$ +65.4 (*c* = 8.06, CH_2Cl_2)]; $\nu_{max.}$ 3333, 2924, 1636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (1H, ddd, *J* = 17.1, 10.2, 8.5 Hz), 5.03 (1H, dd, *J* = 17.1, 1.6 Hz), 4.84 (1H, dd, *J* = 10.2, 1.6 Hz), 3.55–3.40 (2H, m), 1.34–1.29 (1H, m), 1.18–1.08 (1H, m), 0.70–0.56 (2H, m); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.8, 112.3, 66.2, 23.0, 20.6, 11.7.

***tert*-Butyl-*N*-(*tert*-butoxycarbonyl-*N*-[(1*R**,2*S**)-2-ethenylcyclopropyl]methylcarbamate [(±)-7].** The alcohol (±)-**5** (3.00 g, 30.6 mmol), di-t-butyl-iminodicarboxylate (16.6 g, 76.4 mmol) and triphenylphosphine (20 g, 76 mmol) were dissolved in THF (310 mL) and the mixture was cooled to 0 °C. Diethyl azodicarboxylate (12.1 mL, 77.1 mmol) was added dropwise at 0 °C. The mixture was warmed to rt and stirred for 12 h. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (pet. ether then pet. ether-ethyl acetate, 99:1 → 90:10) to afford (±)-**7** (6.05 g, 67%) as an oil. $\nu_{max.}$ ($CHCl_3$) 3080, 2980, 2934, 1732, 1694, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (1H, ddd, *J* = 17.1, 10.2, 8.6 Hz), 5.01 (1H, dd, *J* = 17.1, 1.6 Hz), 4.83 (1H, dd, *J* = 10.2, 1.6 Hz), 3.53 (2H, d, *J* = 7.5 Hz), 1.51 (18H, s), 1.47–1.40 (1H, m), 1.21 (1H, ddddd, *J* = 7.5, 5.0, 4.0, 1.1, 1.1 Hz), 0.73 (1H, ddd, *J* = 8.5, 5.2, 5.2 Hz), 0.58 (1H, ddd, *J* = 8.5, 5.0, 4.9 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.9, 141.0, 133.9, 128.7, 112.2, 82.3, 49.5, 28.2, 21.5, 20.4, 12.3; HRMS (ESI) for $C_{16}H_{27}NO_4Na$ $[M+Na]^+$ calcd. 320.1832, found 320.1819.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-[(1*R*,2*S*)-2-ethenylcyclopropyl]methylcarbamate [(−)-7].** The alcohol (−)-**5** (743 mg, 7.57 mmol), di-*t*-butyliminodicarboxylate (4.00 g, 18.4 mmol) and triphenylphosphine (4.96 g, 18.9 mmol) were dissolved in THF (76 mL) and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (3.70 mL, 18.8 mmol) was added dropwise at 0 °C. The mixture was heated (oil bath) to reflux and stirred overnight. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 99:1 → 90:10) to afford (−)-**7** (1.50 g, 67%) as an oil. $[\alpha]_D^{26}$ −6.3 (*c* = 1.0, $CHCl_3$); $\nu_{max.}$ 2978, 1748, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (1H, ddd, *J* = 17.1, 10.2, 8.5 Hz), 5.01 (1H, ddd, *J* = 17.1, 1.7, 0.6 Hz), 4.83 (1H, dd, *J* = 10.2, 1.7 Hz), 3.53 (2H, d, *J* = 6.9 Hz), 1.50 (18 H, s), 1.46–1.39 (1H, dddd, *J* = 8.6, 8.5, 5.1, 4.9 Hz), 1.19 (1H, ddddd, *J* = 8.6, 6.9, 6.9, 5.1, 4.9 Hz), 0.73 (1H, ddd, *J* = 8.5, 5.1, 5.1 Hz), 0.57 (1H, ddd, *J* = 8.5, 4.9, 4.9 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.9, 141.0, 132.3, 128.6, 112.2, 82.3, 49.5, 28.2, 21.5, 20.5, 12.3; HRMS (ESI) for $C_{16}H_{27}NO_4Na$ $[M+Na]^+$ calcd. 320.1832, found 320.1828.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-[(1*S*,2*R*)-2-ethenylcyclopropyl]methylcarbamate [(+)-7].** The alcohol (+)-**5** (213 mg, 2.17 mmol), di-*t*-butyliminodicarboxylate (1.18 g, 5.43 mmol) and triphenylphosphine (1.42 g, 5.41 mmol) were dissolved in THF (20 mL) and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (1.10 mL, 5.60 mmol) was added dropwise at 0 °C. The mixture was heated (oil bath) to reflux and stirred for overnight. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 99:1 → 85:15) to afford (+)-**7** (412 mg, 64%) as an oil. $[\alpha]_D^{26}$ +6.6 (*c* = 1.0, $CHCl_3$); $\nu_{max.}$ 2978, 17.39, 1694, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, ddd, *J* = 17.1, 10.2, 8.5 Hz), 5.01 (1H, dd, *J* = 17.1, 1.7 Hz), 4.83 (1H, dd, *J* = 10.2, 1.7 Hz), 3.53 (2H, d, *J* = 6.9 Hz), 1.50 (18H, s), 1.46–1.40 (1H, m), 1.19 (1H, ddddd, *J* = 8.6, 6.9, 6.9, 5.5, 4.5 Hz), 0.73 (1H, ddd, *J* = 8.6, 5.5, 4.8 Hz), 0.58 (1H, ddd, *J* = 8.6, 4.9, 4.5 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.9, 141.0, 132.2, 128.6, 112.2, 82.3, 49.5, 28.2, 21.5, 14.9, 20.4, 12.3; HRMS (ESI) for $C_{16}H_{27}NO_4Na$ $[M+Na]^+$ calcd. 320.1832, found 320.1827.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-[(1*R**,2*S**)-2-(2-hydroxyethyl)cyclopropyl]methylcarbamate [(±)-8].** A flask with an argon inlet was charged with borane-THF complex (65.4 mL of a 1 M solution in THF, 65.4 mmol). A solution of the alkene (±)-**7** (12.9 g, 43.4 mmol) in THF (55 mL) was added dropwise at rt and the reaction mixture was stirred overnight. Water (55 mL) was added carefully followed by pH 7 phosphate buffer solution (50 mL). Sodium perborate tetrahydrate (13.4 g, 87.1 mmol) was added and the reaction mixture was stirred for a further 2 h. The excess of sodium perborate was removed by filtration and the filtrate was concentrated under vacuum. The aqueous residue was extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (magnesium sulfate) and concentrated under vacuum to give the alcohol (±)-**8** (13.3 g, 97%) as a colorless liquid. The product was used in the subsequent oxidation reaction without purification. $\nu_{max.}$ ($CHCl_3$) 3464, 2980, 2934, 2674, 1732, 1692cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66–3.64 (3H, m), 3.62–3.60 (1H, m), 3.34 (1H, dd, *J* = 14.3, 7.5 Hz), 1.63 (1H, dq, *J* = 13.6, 6.7 Hz), 1.50 (18H, s), 1.30–1.24 (1H, m), 0.90–0.87 (1H, m), 0.82–0.75 (1H, m), 0.47 (1H, ddd, *J* = 8.5, 4.8, 4.8 Hz), 0.31 (1H, ddd, *J* = 8.5, 5.0, 5.0 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.3, 82.4, 63.0, 50.1, 36.8, 28.2, 17.9, 14.9, 10.2; HRMS (ESI) for $C_{16}H_{29}NO_5Na$ $[M+Na]^+$ calcd. 338.1943, found 338.1917.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-[(1*R*,2*S*)-2-(2-hydroxyethyl)cyclopropyl]methylcarbamate [(−)-8].** A flask with an argon inlet was charged with borane-THF complex (9.0 mL of a 1 M solution in THF, 9.0 mmol). A solution of the alkene (−)-**7** (1.32 g, 4.44 mmol) in THF (7 mL) was added dropwise at 0 °C. The mixture was allowed to warm to rt and was stirred for 2 h. Water (9 mL) was added carefully followed by pH 7 phosphate buffer solution (9 mL). Sodium perborate tetrahydrate (2.00 g, 13.0 mmol) was added and the mixture was stirred at rt overnight. The excess of sodium perborate was removed by filtration and the filtrate was concentrated under vacuum. The aqueous residue was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (magnesium sulfate) and concentrated under vacuum to give the alcohol (−)-**8** (1.27 g, 91%) as a colorless liquid. The product was used in the subsequent oxidation reaction without purification. $[\alpha]_D^{27}$ −0.10 (*c* = 1.0, $CHCl_3$); $\nu_{max.}$ 3522, 2978, 2932, 1732, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69–3.61 (3H, m), 3.34 (1H, dd, *J* = 14.3, 7.5 Hz), 1.67–1.60 (1H, m), 1.50 (18H, s), 1.32–1.23 (1H, m), 0.94–0.85 (1H, m), 0.82–0.76 (1H, m), 0.47 (1H, ddd, *J* = 8.6, 4.8, 4.8 Hz), 0.31 (1H, ddd, *J* = 8.6, 5.0, 5.0 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.3, 82.4, 63.0, 50.1, 36.8, 28.2, 17.9, 14.9, 10.2; HRMS (ESI) for $C_{16}H_{29}NO_5Na$ $[M+Na]^+$ calcd. 338.1938, found 338.1937.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-[(1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl]methylcarbamate [(+)-8].** A flask with an argon inlet was charged with borane-THF complex (7.0 mL of a 1 M solution in THF, 7.0 mmol). A solution of the alkene (+)-**7** (1.01 g, 3.40 mmol) in THF (6 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm up to rt and was stirred for 2 h. Water (7 mL) was added carefully followed by pH 7 phosphate buffer solution (7 mL). Sodium perborate tetrahydrate (1.60 g, 10.4 mmol) was added and the mixture was stirred at rt overnight. The excess of sodium perborate was removed by filtration and the filtrate was concentrated under vacuum. The aqueous residue was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (magnesium sulfate) and concentrated under vacuum to give the alcohol (+)-**8** (970 mg, 91%) as a colorless liquid. The product was used in the subsequent oxidation reaction without purification. $[\alpha]_D^{27}$ +0.5 (*c* = 1, $CHCl_3$); $\nu_{max.}$ 3522, 2978, 2931, 1732, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69–3.59 (3H, m), 3.61 (1H, dd, *J* = 8.5, 5.6 Hz), 3.34 (1H, dd, *J* = 14.3, 7.5 Hz), 1.66–1.60 (1H, m), 1.50 (18H, s), 1.31–1.21 (1H, m), 0.91–0.85 (1H, m), 0.81–0.73 (1H, m), 0.47 (1H, ddd, *J* = 8.5, 4.8, 4.8 Hz), 0.31 (1H, ddd, *J* = 8.5, 5.0, 5.0 Hz); $^{13}C\{^1H\}$ (126 MHz, $CDCl_3$) δ 153.3, 82.4, 63.0, 50.1, 36.8, 28.2, 17.9, 14.9, 10.2; HRMS (ESI) for $C_{16}H_{29}NO_5Na$ $[M+Na]^+$ calcd. 338.1938, found 338.1932.

(1*S,2*R**)-2-{[Bis(*tert*-butoxycarbonyl)amino]-methyl}cyclopropylacetic acid [(±)-4].** The alcohol (±)-**8** (1.46 g, 4.63 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (6.26 g, 46.3 mmol) were dissolved in acetonitrile (19 mL). Tetra-*n*-propylammonium perruthenate (162 mg, 0.46 mmol, 10 mol %) was added portionwise (20 mg / 20 min) at rt and the mixture was stirred at rt overnight. The reaction was quenched by the addition of excess of isopropanol. Water (50 mL) was added and the pH was carefully adjusted to 1 using 2 M aq. hydrochloric acid. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated under vacuum to give the carboxylic acid (±)-**4** as a dark oil, which was used in the subsequent reaction without purification. $\nu_{max.}$ ($CHCl_3$) 2980, 2936, 1709, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (2H, dd, *J* = 6.9, 1.2 Hz), 2.28 (1H, dd, *J* = 16.2, 7.0 Hz), 2.21 (1H, dd, *J* = 16.2, 7.2 Hz), 1.50 (18H, s), 1.10–1.02 (2H, m), 0.61 (1H, ddd, *J* = 8.5, 5.1, 5.1 Hz), 0.40 (1H, ddd, *J* = 8.5, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 178.3, 153.0, 82.4, 49.6, 38.5, 28.2, 18.3, 13.1, 10.7; HRMS (ESI) for $C_{16}H_{27}NO_6Na$ $[M+Na]^+$ calcd. 352.1736, found 352.1680.

(1*R*,2*S*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropylacetic acid [(+)-4]. The alcohol (+)-**8** (646 mg, 2.05 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (2.40 g, 20.5 17.8 mmol) were dissolved in acetonitrile (8 mL). Tetra-*n*-propylammonium perruthenate (72 mg, 0.20 mmol, 10 mol %) was added portionwise (20 mg / 20 min) at rt and the mixture was stirred at rt overnight. The reaction was quenched by the addition of excess of isopropanol. Water (20 mL) was added and the pH was carefully adjusted to 1 using conc. aq. hydrochloric acid. The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were dried (magnesium sulfate) and concentrated under vacuum to give the carboxylic acid (+)-**4** (588 mg, 87%) as a dark oil, which was used in the subsequent reaction without purification. $[\alpha]_D^{20}$ +0.72 (*c* = 1, $CHCl_3$); $\nu_{max.}$ 2978, 2935, 1778, 1709, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.52 (2H, dd, *J* = 6.9, 5.6 Hz), 2.30 (1H, dd, *J* = 16.2, 6.7 Hz), 2.19 (1H, dd, *J* = 16.2, 7.3 Hz), 1.50 (18H, s), 1.11–1.02 (2H, m), 0.61 (1H, ddd, *J* = 8.4, 5.2, 5.2 Hz), 0.40 (1H, ddd, *J* = 8.4, 5.2, 5.2 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.9, 152.9, 82.4, 49.7, 38.4, 28.2, 18.3, 13.1, 10.7; HRMS (ESI) for $C_{16}H_{27}NO_6Na$ $[M+Na]^+$ calcd. 352.1731, found 352.1716.

(1*S*,2*R*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropylacetic acid [(−)-4]. The alcohol (−)-**8** (970 mg, 3.08 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (3.61 g, 30.8 26.7 mmol) were dissolved in acetonitrile (12 mL). Tetra-*n*-propylammonium perruthenate (109 mg, 0.310 mmol, 10 mol %) was added portionwise (20 mg / 20 min) at rt and the mixture was stirred at rt overnight. The reaction was quenched by the addition of excess of isopropanol. Water (30 mL) was added and the pH was carefully adjusted to 1 using conc. aq. hydrochloric acid. The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were dried (magnesium sulfate) and concentrated under vacuum to give the carboxylic acid (−)-**4** (1.04 g, quant.) as a dark oil, which was used in the subsequent reaction without purification. $[\alpha]_D^{27}$ −0.34 (*c* = 1.0, $CHCl_3$); $\nu_{max.}$ 3233, 2978, 2936, 1778, 1709, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.52 (2H, dd, *J* = 6.9, 1.6 Hz), 2.29 (1H, dd, *J* = 16.2, 6.9 Hz), 2.21 (1H, dd, *J* = 16.2, 7.1 Hz), 1.50 (18H, s), 1.13–1.01 (2H, m), 0.61 (1H, ddd, *J* = 8.4, 5.2, 5.2 Hz), 0.40 (1H, ddd, *J* = 8.4, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 178.4, 153.0, 82.4, 49.6, 38.5, 28.2, 18.3, 13.1, 10.7; HRMS (ESI) for $C_{16}H_{27}NO_6Na$ $[M+Na]^+$ calcd. 352.1731, found 352.1719.

(1*S*,2*R*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropyl-*N*-isopropylacetamide [(−)-9]. The carboxylic acid (−)-**4** (92 mg, 0.28 mmol), isopropylamine (50 μL, 0.61 mmol) and triethylamine (136 μL, 0.98 mmol) were dissolved in dichloromethane (1.5 mL). The solution was stirred at rt for 15 min and T3P (250 μL of a 50% solution in ethyl acetate, 0.39 mmol) was added dropwise. The reaction mixture was stirred at rt for 8 h. Water (2 mL) was added and the phases were separated. The organic phase was dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 1:1) to give the amide (−)-**9** (36 mg, 35%) as an oil. $[\alpha]_D^{17}$ −8.63 (*c* = 1.80, $CHCl_3$); $\nu_{max.}$ 3294, 2971, 2929, 1732, 1693, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (1H, d, *J* = 8.1 Hz), 4.17–4.04 (1H, m), 3.60 (1H, dd, *J* = 14.4, 6.0 Hz), 3.50 (1H, dd, *J* = 14.4, 6.2 Hz), 2.16 (1H, dd, *J* = 16.5, 6.7 Hz), 2.04 (1H, dd, *J* = 16.5, 7.2 Hz), 1.48 (18H, s), 0.92 (3H, d, *J* = 6.5 Hz), 0.92 (3H, d, *J* = 6.5 Hz), 0.99–0.81 (2H, m), 0.55 (1H, ddd, *J* = 8.4, 5.0, 5.0 Hz), 0.35 (1H, ddd, *J* = 8.4, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 153.2, 82.6, 49.1, 41.3, 41.0, 28.2, 22.8, 18.4, 13.1, 10.4; HRMS (ESI) for $C_{19}H_{34}N_2O_5Na$ $[M+Na]^+$ calcd. 393.2360, found 393.2359.

(1*S*,2*R*)-2-{[(2-Methyl-1-oxopropyl)amino]methyl}-cyclopropyl-*N*-isopropylacetamide [(+)-10]. To a solution of the bis-carbamate (−)-**9** (70 mg, 0.19 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (115 μL, 1.5 mmol) dropwise at rt. The mixture was stirred at rt for 2 h and solvent was removed under vacuum. The resulting trifluoroacetate salt was dissolved in dichloromethane (300 μL) and triethylamine (42 μL, 0.30 mmol) was added. Isobutyric anhydride (50 μL, 0.30 mmol) was added dropwise at rt and the reaction mixture was stirred for 8 h. Water (15 mL) was added and phases were separated. The organic phase was washed with sat. aq. sodium bicarbonate (5 mL) and 1 M aq. hydrochloric acid (5 mL). The organic phase was dried (magnesium sulfate) and concentrated under vacuum. The resulting colorless solid was triturated with cold ether to give the bis amide (+)-**10** (15 mg, 33% over 2 steps) as a colorless solid. $[\alpha]_D^{21}$ +48 (*c* = 0.30, $CHCl_3$); m.p. 134–135 °C; $\nu_{max.}$ (10 mm, CH_2Cl_2) 3429, 3325, 2974, 2932, 1663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (1H, br s), 5.40 (1H, br s), 4.10 (1H, dq, *J* = 7.6, 6.5 Hz), 3.73 (1H, ddd, *J* = 13.5, 6.0, 4.7 Hz), 2.60–2.48 (2H, m), 2.43 (1H, h, *J* = 6.9 Hz), 1.70 (1H, dd, *J* = 16.2, 9.4 Hz), 1.18 (3H, d, *J* = 6.9 Hz), 1.18 (3H, d, *J* = 6.9 Hz), 1.17 (3H, d, *J* = 6.5 Hz), 1.16 (3H, d, *J* = 6.5 Hz), 0.83–0.71 (2H, m), 0.53 (1H, ddd, *J* = 8.1, 5.3, 5.3 Hz), 0.42 (1H, ddd, *J* = 8.1, 5.3, 5.3 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.5, 171.7, 43.9, 41.6, 39.9, 35.7, 22.9, 19.8, 18.0, 13.5, 10.2; HRMS (ESI) for $C_{13}H_{24}N_2O_2Na$ $[M+Na]^+$ calcd. 263.1730, found 263.1726.

(1*S*,2*R*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropyl-*N*,*N*-dimethylacetamide [(−)-11]. The carboxylic acid (−)-**4** (110 mg, 0.334 mmol), dimethylamine

(330 μL of a 2 M solution in THF, 0.66 mmol) and triethylamine (162 μL, 1.16 mmol) were dissolved in dichloromethane (2 mL). The solution was stirred at rt for 15 min and T3P (320 μL of a 50% solution in ethyl acetate, 0.50 mmol) was added dropwise. The mixture was stirred at rt for 8 h. Water (3 mL) was added and phases were separated. The organic phase was washed with sat. aq. sodium bicarbonate dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 1:1) to give the amide (−)-**11** (87 mg, 73%) as an oil. $[\alpha]_D^{23}$ −16 (*c* = 0.50, $CHCl_3$); $\nu_{max.}$ 2981, 2943, 1736, 1692, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.58 (1H, dd, *J* = 14.4, 7.1 Hz), 3.46 (1H, dd, *J* = 14.4, 7.1 Hz), 2.97 (3H, s), 2.93 (3H, s), 2.44 (1H, dd, *J* = 15.3, 5.0 Hz), 2.11 (1H, dd, *J* = 15.3, 7.6 Hz), 1.50 (18H, s), 1.09 (1H, ddddd, *J* = 7.6, 7.1, 5.0, 5.0, 5.0 Hz), 1.01 (1H, ddddd, *J* = 7.1, 7.1, 7.1, 5.0, 5.0 Hz), 0.62 (1H, ddd, *J* = 8.5, 5.0, 5.0 Hz), 0.39 (1H, ddd, *J* = 8.5, 5.0, 5.0 Hz); $^{13}C\{^1H\}$ (126 MHz, $CDCl_3$) δ 172.3, 153.0, 82.3, 49.9, 37.9, 37.5, 35.4, 28.2, 18.3, 13.9, 10.9; HRMS (ESI) for $C_{18}H_{32}N_2O_5Na$ $[M+Na]^+$ calcd. 379.2203, found 379.2200.

(1*R*,2*S*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropyl-*N*,*N*-dimethylacetamide [(+)-11]. The carboxylic acid (+)-**4** (139 mg, 0.42 mmol), dimethylamine (400 μL of a 2 M solution in THF, 0.80 mmol) and triethylamine (200 μL, 1.43 mmol) were dissolved in dichloromethane (2.5 mL). The solution was stirred at rt for 15 min and T3P (400 μL of a 50% solution in ethyl acetate, 0.63 mmol) was added dropwise. The mixture was stirred at rt for 8 h. Water (3 mL) was added and phases were separated. The organic phase was washed with sat. aq. sodium bicarbonate, dried (magnesium sulfate) and concentrated under vacuum. The organic phase was dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 1:1) to give the amide (+)-**11** (67 mg, 45%) as an oil. $[\alpha]_D^{22}$ +9.8 (*c* = 0.50, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 2977, 1744, 1693, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (1H, dd, *J* = 14.4, 6.6 Hz), 3.44 (1H, dd, *J* = 14.4, 7.2 Hz), 2.95 (3H, s), 2.91 (3H, s), 2.41 (1H, dd, *J* = 15.3, 5.8 Hz), 2.09 (1H, dd, *J* = 15.3, 7.5 Hz), 1.48 (18H, d, *J* = 1.7 Hz), 1.10–1.03 (1H, m), 1.01–0.96 (1H, m), 0.60 (1H, ddd, *J* = 8.4, 5.0, 5.0 Hz), 0.36 (1H, ddd, *J* = 8.4, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.2, 152.9, 82.2, 49.9, 37.8, 37.4, 35.4, 28.2, 18.2, 13.8, 10.8; HRMS (ESI) for $C_{18}H_{32}N_2O_5Na$ $[M+Na]^+$ calcd. 379.2203, found 379.2201.

(1*S*,2*R*)-2-{[(2-Methyl-1-oxopropyl)amino]methyl}-cyclopropyl-*N*,*N*-dimethylacetamide [(+)-12]. The amide (−)-**11** (122 mg, 0.342 mmol) was dissolved in dichloromethane (3.4 mL) and trifluoroacetic acid (250 μL, 3.3 mmol) was added. The mixture was stirred at rt for 2 h and solvent was removed under vacuum. The resulting trifluoroacetate salt and triethylamine (71 μL, 0.51 mmol) were dissolved in dichloromethane (0.5 mL). Isobutyric anhydride (85 μL, 0.51 mmol) was added dropwise to the solution at rt and the mixture was stirred for 18 h. Water (5 mL) was added and the phases were separated. The organic phase was washed with sat. aq. sodium bicarbonate solution (5 mL) and 1 M aq. hydrochloric acid (5 mL), then dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (dichloromethane then dichloromethane-methanol, 99:1 → 97:3) to afford the bis amide (+)-**12** (31 mg, 40% over 2 steps) as a colorless semi-solid. $[\alpha]_D^{28}$ +68 (*c* = 0.50, $CHCl_3$); $\nu_{max.}$ (10 mm, CH_2Cl_2) 3287, 2967, 2928, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (1H, br s), 3.92 (1H, ddd, *J* = 13.5, 6.4, 4.9 Hz), 2.97 (3H, s), 2.95 (3H, s), 2.89 (1H, dd, *J* = 17.0, 3.8 Hz), 2.47 (1H, h, *J* = 7.0 Hz), 2.32 (1H, ddd, *J* = 13.5, 10.0, 2.0 Hz), 1.65 (1H, dd, *J* = 17.0, 10.5 Hz), 1.18 (3H, d, *J* = 7.0 Hz), 1.18 (3H, d, *J* = 7.0 Hz), 0.83–0.75 (1H, m), 0.63 (1H, ddddd, *J* = 10.0, 8.2, 4.9, 4.9, 4.9 Hz), 0.55 (1H, ddd, *J* = 8.3, 4.9, 4.9 Hz), 0.45 (1H, ddd, *J* = 8.3, 4.9, 4.9 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.6, 173.0, 44.5, 37.3, 36.9, 35.7, 35.5, 19.8, 17.7, 13.5, 10.5; HRMS (ESI) for $C_{12}H_{22}N_2O_2Na$ $[M+Na]^+$ calcd. 249.1573, found 249.1566.

(1*R*,2*S*)-2-({[(2*S*)-2-(*N*-Acetylamino)-3-methyl-1-oxobutyl]amino}methyl)cyclopropyl-*N*,*N*-dimethylacetamide [14a]. The amide (+)-**11** (161 mg, 0.452 mmol) was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (400 μL, 5.2 mmol) was added to the solution. The mixture was stirred at rt for 2h and the solvent was removed was removed under vacuum. The resulting trifluoroacetate salt was dissolved in CH_2Cl_2 (2 mL) and diisopropylethylamine (235 μL, 1.35 mmol) was added dropwise. *N*-Acetyl-(*S*)-valine (72 mg, 0.45 mmol) was added, followed by HATU (171 mg, 0.45 mmol) and the mixture was stirred at rt overnight. The solution was washed with water (3 × 10 mL) and the organic phase was dried (magnesium sulfate). The solvent was removed and cold ether (5 mL) was added to the residue, which produced a precipitate. Ether was decanted and the procedure was repeated to give the coupled product **14a** (16 mg, 12%) as a colorless solid. $[\alpha]_D^{21}$ −39 (*c* = 0.55, $CHCl_3$); m.p. 130–131 °C; $\nu_{max.}$ (*c* = 10 mm, CH_2Cl_2) 3418, 3294, 2963, 2932, 1678, 1659, 1632 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.18 (1H, br s), 6.51 (1H, d, *J* = 9.3 Hz), 4.33 (1H, dd, *J* = 9.3, 5.3 Hz), 3.80 (1H, dd, *J* = 13.1, 5.2, 5.2 Hz), 2.96 (3H, s), 2.98–2.95 (1H, m), 2.93 (3H, s), 2.32 (1H, ddd, *J* = 13.1, 10.6, 2.1 Hz), 2.17–2.09 (1H, m), 2.02 (3H, s), 1.63 (1H, dd, *J* = 17.3, 11.2 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.88 (3H, d, *J* = 6.9 Hz), 0.74–0.68 (1H, m), 0.68–0.63 (1H, m), 0.58 (1H, ddd, *J* = 8.3, 5.1, 5.1 Hz), 0.50 (1H, ddd, *J* = 8.3, 5.2, 5.2 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 173.5, 171.6, 170.4, 58.9, 45.0, 37.5, 37.3, 35.9, 31.9, 23.7, 19.6, 17.9, 17.6, 13.8, 11.1; HRMS (ESI) for $C_{15}H_{27}N_3O_3Na$ $[M+Na]^+$ calcd. 320.1945, found 320.1933.

(1*S*,2*R*)-2-({[(2*S*)-2-(*N*-acetylamino)-3-methyl-1-oxobutyl]amino}methyl)cyclopropyl-*N*,*N*-dimethylacetamide [14b]. The (−)-**11** (87 mg, 0.24 mmol) was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (185 μL, 2.40 mmol) was added to the solution. The reaction mixture was stirred at rt for 8 h and the solvent was then removed under vacuum. The resulting trifluoroacetate salt was dissolved in dichloromethane (1 mL) and diisopropylethylamine (125 μL, 0.72 mmol) was added dropwise. *N*-Acetyl-(*S*)-valine (38 mg, 0.24 mmol) was added, followed by HATU (91 mg, 0.24 mmol) and the mixture was stirred at rt overnight. The solution was washed with water (3 × 5 mL) and the organic phase was dried (magnesium sulfate). The solvent was removed under vacuum and the resulting brown oil was purified by column chromatography on silica gel (dichloromethane-methanol, 99:1 → 96:4) to afford the coupled product **14b** (10 mg, 14%) as a white powder. $[\alpha]_D^{21}$ +41 (*c* = 0.13, CH_2Cl_2); m.p.

123–125 °C; $\nu_{max.}$ (c = 10 mM, CH_2Cl_2) 3410, 3306, 2963, 2932, 1678, 1659, 1632 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.16 (1H, s), 6.70 (1H, d, J = 9.2 Hz), 4.34 (1H, dd, J = 9.2, 5.0 Hz), 3.98 (1H, ddd, J = 13.4, 7.0, 4.4 Hz), 2.97 (3H, s), 2.93 (3H, s), 2.97–2.92 (1H, m), 2.24–2.15 (2H, m), 2.03 (3H, s), 1.63 (1H, dd, J = 17.5, 10.5 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.86 (3H, d, J = 6.9 Hz), 0.77–0.71 (1H, m), 0.62–0.56 (2H, m), 0.52–0.47 (1H, m); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 173.6, 171.5, 170.6, 59.0, 44.6, 37.5, 37.3, 35.9, 31.5, 23.6, 19.7, 18.5, 17.8, 13.6, 10.8; HRMS (ESI) for $C_{15}H_{27}N_3O_3Na$ $[M+Na]^+$ calcd. 320.1945, found 320.1934.

(1*R*,2*S*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide. *N*-Boc-(*S*)-leucine dimethylamide (1.12 g, 4.34 mmol) was dissolved in dichloromethane (44 mL) and trifluoroacetic acid (1.7 mL, 22 mmol) was added and mixture was stirred at rt for 8 h. The solvent was removed under vacuum to give the trifluoroacetate salt **15**, which was used in the subsequent reaction without purification.

A portion of the salt **15** (106 mg, 0.39 mmol) was dissolved in dichloromethane (1.3 mL), diisopropylethylamine (200 µL, 1.15 mmol) was added followed by the carboxylic acid (+)-**4** (130 mg, 0.395 mmol). The mixture was stirred for 15 min and HATU (148 mg, 0.39 mmol) was added. The mixture was stirred at rt overnight and water (10 mL) was added. The phases were separated, and the organic phase was washed with sat. aq. sodium bicarbonate (10 mL) and brine (10 mL), then dried (magnesium sulfate). The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 1:1) to afford the title amide (131 mg, 71%) as an oil. $[\alpha]_D^{22}$ +15 (c = 0.25, $CHCl_3$); $\nu_{max.}$ 3287, 2926, 1711, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.52 (1H, d, J = 8.6 Hz), 5.01 (1H, ddd, J = 12.8, 8.6, 4.0 Hz), 3.66 (1H, dd, J = 14.4, 5.7 Hz), 3.47 (1H, dd, J = 14.4, 6.9 Hz), 3.09 (3H, s), 2.94 (3H, s), 2.34 (1H, dd, J = 15.9, 5.7 Hz), 1.98 (1H, dd, J = 15.9, 7.7 Hz), 1.70–1.60 (1H, m), 1.49 (18H, s), 1.45–1.36 (2H, m), 1.02–0.95 (2H, m), 0.99 (3H, d, J = 6.5 Hz), 0.91 (3H, d, J = 6.8 Hz), 0.65 (1H, ddd, J = 7.8, 5.1, 5.1 Hz), 0.40 (1H, ddd, J = 7.8, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.6, 171.6, 152.9, 82.3, 49.2, 47.3, 42.2, 40.6, 37.0, 35.7, 28.1, 24.7, 23.4, 21.8, 18.3, 13.4, 10.5; HRMS (ESI) for $C_{24}H_{43}N_3O_6Na$ $[M+Na]^+$ calcd. 492.3044, found 492.3028.

(1*R*,2*S*)-2-({[(2*S*)-2-(*N*-Acetylamino)-3-methyl-1-oxobutyl]amino}methyl)cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide [16a]. (1*R*,2*S*)-2-{[Bis(*tert*-butoxycarbonyl)amino]-methyl}cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide (310 mg, 0.66 mmol) was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (505 µL, 6.60 mmol) was added to the solution. The mixture was stirred at rt for 8 h and the solvent was removed in vacuum. The resulting trifluoroacetate salt was dissolved in dichloromethane (3 mL) diisopropylethylamine (345 µL, 1.98 mmol) was added dropwise. *N*-Acetyl-(*S*)-valine (105 mg, 0.66 mmol) was added followed by HATU (251 mg, 0.66 mmol) and the mixture was stirred at rt overnight. The solution was washed with water (3 × 10 mL) and the organic phase was dried (magnesium sulfate) and the solvent were removed under vacuum. The resulting brown oil was purified by chromatography on silica gel (dichloromethane-methanol, 99:1 → 90:10) to give the turn mimic **16a** (130 mg, 48% over two steps) as a colorless solid. $[\alpha]_D^{21}$ −17 (c = 0.55, $CHCl_3$); m.p. 155–156 °C; $\nu_{max.}$ (c = 10 mm, CH_2Cl_2) 3422, 3306, 2963, 2874, 1659, 1639 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.74 (1H, br s), 6.63 (1H, d, J = 8.6 Hz), 6.43 (1H, d, J = 8.8 Hz), 5.01 (1H, ddd, J = 10.6, 8.6, 3.7 Hz), 4.31 (1H, dd, J = 8.8, 6.4 Hz), 3.65 (1H, ddd, J = 13.8, 4.2, 4.2 Hz), 3.11 (3H, s), 2.96 (3H, s), 2.74 (1H, dd, J = 17.0, 3.8 Hz), 2.57 (1H, ddd, J = 13.8, 10.2, 4.2 Hz), 2.12–2.00 (1H, m), 1.97 (3H, s), 1.70–1.60 (2H, m), 1.54 (1H, ddd, J = 14.1, 10.6, 4.3 Hz), 1.41 (1H, ddd, J = 14.1, 9.5, 3.7 Hz), 0.99 (3H, d, J = 6.5 Hz), 0.93 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.2 Hz), 0.89 (3H, d, J = 6.9 Hz), 0.82–0.73 (2H, m), 0.54 (1H, ddd, J = 10.2, 5.4, 5.4 Hz), 0.46 (1H, ddd, J = 10.2, 5.4, 5.4 Hz); $^{13}C\{^1H\}$ (151 MHz, CD_2Cl_2) δ 174.1, 173.3, 172.5, 171.9, 58.7, 48.0, 44.4, 42.3, 40.2, 37.5, 36.2, 32.0, 25.3, 23.7, 23.6, 22.0, 19.6, 18.5, 18.4, 14.0, 11.2; HRMS (ESI) for $C_{21}H_{38}N_4O_4Na$ $[M+Na]^+$ calcd. 433.2785, found 433.2782.

(1*S*,2*R*)-2-{[Bis(*tert*-butoxycarbonyl)amino]methyl}-cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide. *N*-Boc-(*S*)-leucine dimethylamide (1.12g, 4.34 mmol) was dissolved in dichloromethane (44 mL) and trifluoroacetic acid (1.7 mL, 21.7 mmol) was added. The mixture was stirred at rt for 8 h and the solvent was removed under vacuum to give the trifluoroacetate salt **15**, which was used in the subsequent reaction without purification.

The carboxylic acid (−)-**4** (110 mg, 0.333 mmol) was dissolved in dichloromethane (1 mL). Diisopropylethylamine (200 µL, 1.15 mmol) was added followed by a portion of the salt **15** (90 mg, 0.33 mmol). The mixture was stirred for 15 min, HATU (125 mg, 0.329 mmol) was added and the mixture was stirred at rt overnight. Water (10 mL) was added and the phases were separated. The organic phase was washed with sat. aq. sodium bicarbonate (10 mL) and brine (10 mL), then dried (magnesium sulfate). The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (pet. ether-ethyl acetate, 1:1) to afford the title amide (131 mg, 84%) as an oil. $[\alpha]_D^{23}$ −13 (c = 0.50, $CHCl_3$); $\nu_{max.}$ 3304, 2930, 1711, 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (1H, d, J = 8.6 Hz), 5.02 (1H, ddd, J = 9.5, 8.6, 3.9 Hz), 3.65 (1H, dd, J = 14.3, 5.8 Hz), 3.45 (1H, dd, J = 14.3, 7.1 Hz), 3.09 (3H, s), 2.95 (3H, s), 2.41 (1H, dd, J = 16.0, 5.3 Hz), 1.92 (1H, dd, J = 16.0, 8.0 Hz), 1.71–1.61 (1H, m), 1.51 (18H, s), 1.46–1.40 (2H, m), 1.04–0.98 (2H, m), 1.00 (3H, d, J = 6.5 Hz), 0.92 (3H, d, J = 6.6 Hz), 0.70 (1H, ddd, J = 8.0, 5.1, 5.1 Hz), 0.43 (1H, ddd, J = 8.0, 5.2, 5.2 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.7, 171.7, 153.0, 82.4, 49.5, 47.3, 42.8, 40.8, 37.2, 35.9, 28.2, 24.9, 23.6, 22.1, 18.4, 13.7, 10.8; HRMS (ESI) for $C_{24}H_{43}N_3O_6Na$ $[M+Na]^+$ calcd. 492.3044, found 492.3026.

(1*S*,2*R*)-2-({[(2*S*)-2-(*N*-Acetylamino)-3-methyl-1-oxobutyl]amino}methyl)cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide [16b]. (1*S*,2*R*)-2-{[Bis(*tert*-butoxycarbonyl)amino]-methyl}cyclopropyl-*N*-{(1*S*)-2-(dimethyl-amino)-1-[(2-methyl)propyl]-2-oxoethyl}acetamide (130 mg, 0.277 mmol) was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (215 µL, 2.8 mmol) was added to the solu-

tion. The mixture was stirred at rt for 8 h and the solvent was removed in vacuum. The resulting trifluoroacetate salt was dissolved in dichloromethane (1 mL) and diisopropylethylamine (150 μL, 0.86 mmol) was added dropwise. N-Acetyl-(S)-valine (45 mg, 0.28 mmol) was added followed by HATU (106 mg, 0.279 mmol) and the mixture was stirred at rt overnight. The solution was washed with water (3 × 10 mL) and the organic phase was dried (magnesium sulfate). The solvent was removed under vacuum and the resulting brown oil was purified by chromatography on silica gel (dichloromethane-methanol, 99:1 → 90:10) to give the turn mimic **16b** (20 mg, 18% over two steps) as a colorless solid. $[\alpha]_D^{21}$ +47 (*c* = 0.90, CH_2Cl_2); m.p. 95–97 °C; $\nu_{max.}$ (c = 10 mm, CH_2Cl_2) 3418, 3302, 3051, 2963, 1659, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 6.7 Hz), 6.44 (1H, d, *J* = 8.6 Hz), 6.37 (1H, d, *J* = 8.7 Hz), 5.03 (1H, ddd, *J* = 10.5, 8.6, 3.6 Hz), 4.42 (1H, dd, *J* = 8.7, 6.0 Hz), 3.97 (1H, ddd, *J* = 13.8, 6.7, 4.3 Hz), 3.13 (3H, s), 2.98 (3H, s), 2.69 (1H, dd, *J* = 16.3, 3.6 Hz), 2.35 (1H, ddd, *J* = 13.8, 9.8, 2.7 Hz), 2.14–2.02 (1H, m), 2.01 (3H, s), 1.75–1.69 (2H, m), 1.53–1.42 (2H, m), 1.02 (3H, d, *J* = 6.6 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.85–0.74 (2H, m), 0.54 (1H, ddd, *J* = 8.3, 5.2, 5.2 Hz), 0.46 (1H, ddd, *J* = 8.3, 5.4, 5.4 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 172.9, 172.4, 171.4, 169.8, 58.1, 47.6, 44.0, 42.4, 39.7, 37.2, 36.0, 32.0, 24.9, 23.6, 23.6, 21.8, 19.3, 18.5, 18.3, 14.2, 10.2; HRMS (ESI) for $C_{21}H_{38}N_4O_4Na$ $[M+Na]^+$ calcd. 433.2785, found 433.2768.

(1*S,2*R**)-2-{2-[Bis(*tert*-butoxycarbonyl)amino]-methyl}cyclopropyl-*N*-[2-(dimethylamino)-1-oxoethyl] acetamide.** *N*-Boc-glycine dimethylamide (2.96 g, 14.6 mmol) was dissolved in dichloromethane (150 mL) and trifluoroacetic acid (11.0 mL, 144 mmol) was added dropwise at rt. The reaction mixture was stirred at rt overnight and then the solvent was removed under vacuum to give glycine dimethylamide trifluoroacetate salt (**15b**). The carboxylic acid (±)-**4** (2.87 g, 8.72 mmol), the salt **15b** (2.91 g) and triethylamine (4.30 mL, 30.9 mmol) were dissolved in dichloromethane (43 mL). The solution was stirred at rt for 15 min and T3P (50% in ethyl acetate, 7.80 mL, 12.3 mmol) was added 0 °C. The mixture was stirred at rt for 16 h and then washed with water (3 × 10 mL), sat. aq. sodium bicarbonate (3 × 10 mL) and brine (10 mL). The phases were separated, and the organic phase was dried (magnesium sulfate) and concentrated under vacuum. The residue was purified by silica gel column chromatography (pet. ether-ethyl acetate, 1:1) to give the title amide (2.26 g, 63%) as an oil. $\nu_{max.}$ ($CHCl_3$) 3312, 2978, 2933, 1690, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, t, *J* = 4.0 Hz), 4.03 (2H, d, *J* = 4.0 Hz), 3.62 (1H, dd, *J* = 14.4, 6.0 Hz), 3.45 (1H, dd, *J* = 14.4, 6.9 Hz), 2.98 (3H, s), 2.97 (3H, s), 2.37 (1H, dd, *J* = 16.0, 5.7 Hz), 2.01 (1H, dd, *J* = 16.0, 7.8 Hz), 1.48 (18H, s), 1.07–0.97 (2H, m), 0.68 (1H, ddd, *J* = 8.0, 5.1, 5.1 Hz), 0.42 (1H, ddd, *J* = 8.0, 5.1, 5.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.2, 168.1, 152.9, 82.3, 49.5, 41.4, 40.6, 36.0, 35.7, 28.2, 18.4, 13.8, 10.8; HRMS (ESI) for $C_{20}H_{35}N_3O_6Na$ $[M+Na]^+$ calcd. 436.2418, found 436.2402.

(1*S,2*R**)-2-[(*N*-Acetylamino)acetyl]amino}methyl)-cyclopropyl-*N*-[2-(dimethylamino)-2-oxoethyl]-acetamide [(±)-17].** (1*S**,2*R**)-2-{2-[Bis(*tert*-butoxycarbonyl)amino]methyl}cyclopropyl-*N*-[2-(dimethylamino)-1-oxoethyl]acetamide (2.26 g, 5.47 mmol) was dissolved in dichloromethane (55 mL) and trifluoroacetic acid (4.20 mL, 54.9 mmol) was added dropwise at rt. The mixture was stirred at rt overnight and the solvent was then removed under vacuum and the trifluoroacetate salt was used in the subsequent reaction without purification.

A portion of the trifluoroacetate salt (200 mg), triethylamine (300 μL, 2.1 mmol) and *N*-acetylglycine (143 mg, 1.22 mmol) were dissolved in dichloromethane (3.0 mL). The solution was stirred at rt for 15 min and T3P (550 μL of a 50% solution in ethyl acetate, 0.86 mmol) was added dropwise. The mixture was heated to reflux and stirred overnight. The reaction mixture was cooled and washed with water (3 × 5 mL). The organic phase was dried (magnesium sulfate) and concentrated under vacuum. The residue was triturated with cold pet. ether in ethyl acetate to afford the mimic **(±)-17** (100 mg, 52%) as a white solid. m.p. 138–140 °C; $\nu_{max.}$ (20 mM in $CHCl_3$) 3408, 3319, 3053, 2984, 1659, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (1H, s), 6.75 (1H, s), 6.56 (1H, s), 4.10 (1H, dd, *J* = 17.4, 4.3 Hz), 4.04 (1H, dd, *J* = 17.4, 4.4 Hz), 3.95 (2H, d, *J* = 4.8 Hz), 3.93–3.86 (1H, m), 3.03 (6H, s), 2.79 (1H, dd, *J* = 16.6, 3.4 Hz), 2.45 (1H, ddd, *J* = 13.7, 10.0, 3.2 Hz), 2.03 (3H, s), 1.68 (1H, dd, *J* = 16.6, 10.4 Hz), 0.86–0.78 (2H, m), 0.56 (1H, ddd, *J* = 8.2, 5.3, 5.3 Hz), 0.47 (1H, ddd, *J* = 8.2, 5.4, 5.4 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.6, 170.4, 168.9, 168.4, 44.2, 42.9, 41.3, 39.7, 36.2, 35.9, 23.2, 18.1, 14.0, 10.4; HRMS (ESI) for $C_{14}H_{24}N_4O_4Na$ $[M+Na]^+$ calcd. 335.1690, found 335.1688.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the preparation of the amide (±)-**13** along with copies of ^1H and ^{13}C NMR data for new compounds and enlarged copies of the concentration-dependent NMR, IR and CD data shown in Figures 3, 5, 6 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* **J. Stephen Clark** – *School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom*; orcid.org/0000-0003-3935-0377; E-mail: stephen.clark@glasgow.ac.uk

Present Addresses

† UMR 7021, Faculty of Pharmacy, University of Strasbourg, 74 route du Rhin – CS60024, 67401 Illkirch-Graffenstaden cedex, France

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors acknowledge the award of a studentship to A.N. by the Loudon Endowment Fund of the University of Glasgow.

REFERENCES

1 (a) Chou, P. Y.; Fasman, G. D. β-Turns in Proteins. *J. Mol. Biol.* **1977**, *115*, 135–175. (b) Chou, K.-C. Prediction of Tight Turns and Their Types in Proteins. *Anal. Biochem.* **2000**, *286*, 1–16.

2 Tyndall, J. D. A.; Pfeiffer, B.; Abbenante G.; Fairlie, D. P. Over One Hundred Peptide-Activated G Protein-Coupled Receptors Recognize Ligands with Turn Structure. *Chem. Rev.* **2005**, *105*, 793–826.

3 Rose, G. D.; Gierasch L. M.; Smith, J. A. Turns in Peptides and Proteins. *Adv. Protein Chem.* **1985**, *37*, 1–109.

4 Marcelino, A. M. C.; Gierasch, L. M. Role of β-Turns in Protein Folding: From Peptide Models to Protein Folding. *Biopolymers* **2008**, *89*, 380–391.

5 (a) Dyson, H. J.; Wright, P. E. Peptide Conformation and Protein Folding. *Curr. Opin. Struct. Biol.* **1993**, *3*, 60–65. (b) Baldwin, R. L.; Rose, G. D. Is Protein Folding Hierarchic? I. Local Structure and Peptide Folding. *Trends Biochem. Sci.* **1999**, *24*, 26–33. (c) Baldwin, R. L.; Rose, G. D. Is Protein Folding Hierarchic? II. Folding Intermediates and Transition States. Trends *Biochem. Sci.* **1999**, *24*, 77–83.

6 (a) Brunet, A. P.; Huang, E. S.; Huffine, M. E.; Loeb, J. E.; Weltman, R. J.; Hecht, M. H. The Role of Turns in the Structure of an α-Helical Protein. *Nature* **1993**, *364*, 355–358. (b) Dinner, A. R.; Lazaridis, T.; Karplus, M. Understanding β-Hairpin Formation. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 9068–9073.

7 (a) Ball J. B.; Alewood, P. F. Conformational Constraints: Nonpeptide β-Turn Mimics. *J. Mol. Recognit.* **1990**, *3*, 55–64. (b) Giannis A.; Kolter, T. Peptidomimetics for Receptor Ligands–Discovery, Development and Medical Perspectives. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244–1267. (c) Kahn, M. Peptide Secondary Structure Mimetics: Recent Advances and Future Challenges. *Synlett* **1993**, 821–826. (d) Burgess, K. Solid-Phase Syntheses of β-Turn Analogues to Mimic or Disrupt Protein-Protein Interactions. *Acc. Chem Res.* **2001**, *34*, 826–835. (e) Eguchi, M.; Kahn, M. Design, Synthesis, and Application of peptide Secondary Structure Mimetics. *Mini Rev. Med. Chem.* **2002**, *2*, 447–462.

8 (a) Gillespie, P.; Cicariello J.; Olsen, G. L. Conformational Analysis of Dipeptide Mimetics. *Biopolymers* **1997**, *43*, 191–217. (b) Kee, S.; Jois, S. D. S. Design of β-Turn Based Therapeutic Agents. *Curr. Pharm Des.* **2003**, *9*, 1209–1224. (c) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. Universal Peptidomimetics. *J. Am. Chem. Soc.* **2011**, *133*, 462–477.

9 (a) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. An Achiral Dipeptide Mimetic That Promotes β-Hairpin Formation. *J. Am. Chem. Soc.* **1995**, *117*, 3280–3281. (b) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. β-Turn and β-Hairpin Mimicry with Tetrasubstituted Alkenes. *J. Am. Chem. Soc.* **1999,** *121*, 1806–1816.

10 (a) Wipf, P.; Henninger, T. C. Solid-Phase Synthesis of Peptide Mimetics with (*E*)-Alkene Amide Bond Replacements Derived from Alkenylaziridines. *J. Org. Chem.* **1997**, *62*, 1586–1857. (b) Wipf, P.; Henninger, T. C.; Geib, S. J. Methyl- and (Trifluoromethyl)alkene Peptide Isosteres: Synthesis and Evaluation of Their Potential as β-Turn Promoters and Peptide Mimetics. *J. Org. Chem.* **1998**, *63*, 6088–6089.

11 (a) Hollośi, M.; Kawai, M.; Fasman, G. D. Studies on Proline-Containing Tetrapeptide Models of β-Turns. *Biopolymers* **1985**, *24*, 211–242. (b) Hutchinson, E. G.; Thornton, J. M. A Revised Set of Potentials for β-Turn Formation in Proteins. *Protein Sci.* **1994**, *3*, 2207–2216.

12 (a) Mizuno, A.; Kameda, T.; Kuwahara, T.; Endoh, H.; Ito, Y.; Yamada, S.; Hasegawa, K.; Yamano, A.; Watanabe, M.; Arisawa, M.; Shuto, S. Cyclopropane-Based Peptidomimetics Mimicking Wide-Ranging Secondary Structures of Peptides: Conformational Analysis and Their Use in Rational Ligand Optimization. *Chem. Eur. J.* **2017**, *23*, 3159–3168. (b) Mizuno, A.; Matsui, K.; Shuto, S. From Peptides to Peptidomimetics: A Strategy Based on the Structural Features of Cyclopropane. *Chem. Eur. J.* **2017**, *23*, 14394–14409.

13 Matsui, K.; Kido, Y.; Watari, R.; Kashima, Y.; Yoshida, Y.; Shuto, S. Highly Conformationally Restricted Cyclopropane Tethers with Three-Dimensional Structural Diversity Drastically Enhance the Cell Permeability of Cyclic Peptides. *Chem. Eur. J.* **2017**, *23*, 3034–3041.

14 (a) Wipf, P.; Xiao, J. Convergent Approach to (*E*)-Alkene and Cyclopropane Peptide Isosteres. Org. Lett. 2005, 7, 103. (b) Wipf, P.; Xiao, J.; Geib, S. J. Imine Additions of Internal Alkynes for the Synthesis of Trisubstituted (*E*)-Alkene and Cyclopropane Peptide Isosteres. *Adv. Synth. Catal.* **2005**, *347*, 1605–1613.

15 Mordini, A.; Peruzzi, D.; Russo, F.; Valacchi, M.; Reginato, G.; Brandi, A. Superbase-Promoted Rearrangement of Oxiranes to Cyclopropanes. *Tetrahedron* **2005**, *61*, 3349–3360.

16 Schmidt, A.-K. C.; Stark, C. B. W. TPAP-Catalyzed Direct Oxidation of Primary Alcohols to Carboxylic Acids through Stabilized Aldehyde Hydrates. *Org. Lett.* **2011**, *13*, 4164–4167.

17 Schotten, T.; Boland W.; Jaenicke, L. Synthesis of Enantiomerically Pure Pheromones of South-Pacific Brown Algae: Hormosirene and Dictyopterene A. *Helv. Chim. Acta* **1985**, *68*, 1186–1192.

18 Wissmann, H.; Kleiner, H.-J. New Peptide Synthesis. *Angew. Chem. Ind. Ed. Engl.* **1980**, *19*, 133–134.

19 Gellman, S. H.; Dado, G. P.; Liang, G.-B., Adams, B. R. Conformation-Directing Effects of a Single Intramolecular Amide-Amide Hydrogen Bond: Variable-Temperature NMR and IR Studies on a Homologous Diamide Series. *J. Am. Chem. Soc.* **1991**, *113*, 1164–1173.

20 (a) Wishart, D. S.; Sykes, B. D.; Richards, F. M. Relationship Between Nuclear Magnetic Resonance Chemical Shift and Protein Secondary Structure. *J. Mol. Biol.* **1991**, *222*, 311–333. (b) Scheiner, S. Assessment of the Presence and Strength of H-Bonds by Means of Corrected NMR. *Molecules* **2016**, *21*, 1426–1432.

21 Liang, G.-B.; Dado, G. P.; Gellman, S. H. Anatomy of a Stable Intramolecularly Hydrogen Bonded Folding Pattern. *J. Am. Chem. Soc.* **1991**, *113*, 3994–3995.

22 The ^{1}H and ^{13}C NMR spectra of **14a**, **14b**, **16a** and **16b** indicated the presence of a small amounts (<15%) of another rotamer. In contrast, the NMR spectra for compound **17**, which lacks amino acid side chains, indicated that rotamers were not present in this case.

23 (a) Goodman, M.; Naider, F.; Toniolo, C. Circular Dichroism Studies of Isoleucine Oligopeptides in Solution. *Biopolymers* **1971**, *10*, 1719–1730. (b) Mammi, S.; Mammi, N. J.; Peggion, E. Conformational Studies of Human Des-Trp^{1},Nle^{12}-minigastrin in Water-Trifluoroethanol Mixtures by ^{1}H NMR and Circular Dichroism. B*iochemistry* **1988**, *27*, 1374–1379. (c) Sönnichsen, F. D.; Van Eyk, J. E.; Hodges, R. S.; Sykes, B. D. Effect of Trifluoroethanol on Protein Secondary Structure: An NMR and CD Study Using a Synthetic Actin Peptide. *Biochemistry* **1992**, *31*, 8790–8798.

24 Englander, S. W.; Sosnick, T. R.; Englander, J. J.; Mayne, L. Mechanisms and Uses of Hydrogen Exchange. *Curr. Opin. Struct. Biol.* **1996**, *6*, 18–23.

25 For solvent-dependent stabilization of β-turns in small peptides, see: Awasthi, S. K.; Raghothama, S. R.; Balaram, P. Conformational variability in short acyclic peptides. Stabilization of multiple β-turn structures in organic solvent. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2701–2706.

26 For examples of the use of CD spectroscopy in conjunction with NMR spectroscopy to detect the formation of β-turns in small peptides, see: Perczel, A.; Hollośi, M.; Sándor, P.; Fasman, G. D. The Evaluation of Type I and Type II β-Turn Mixtures. Circular Dichroism, NMR and Molecular Dynamics Studies. *Int. J. Peptide Protein Res.* **1993**, *41*, 223–236.

27 Brahms, S.; Brahms, J. Determination of Protein Secondary Structure in Solution by Vacuum Ultraviolet Circular Dichroism. *J. Mol. Biol.* **1980**, *138*, 149–178.
28 Apparu, M.; Barrelle, M. Reactivity of Epoxides 3. Methods for the Synthesis of 1-Hydroxyalkyl-2-vinylcyclopropanes – Reactions of γ,δ-Ethylenic Epoxides with Lithium Amides in HMPT. *Tetrahedron* **1978**, *34*, 1691–1697.
29 Kajiwara, T.; Nakatomi, T.; Sasaki, Y.; Hatanaka, A. Stereoselective Synthesis of Optically Active Dictyopterenes A and B and Their Geometrical Isomers *Agric. Biol. Chem.* **1980**, *44*, 2099–2104.