JOC Article

Structural Investigation of "cis" and "trans" Vinylogous Peptides: *cis*-Vinylog Turn in Folded *cis*-Vinylogous Peptides, an Excellent Mimic of the Natural *β*-Turn

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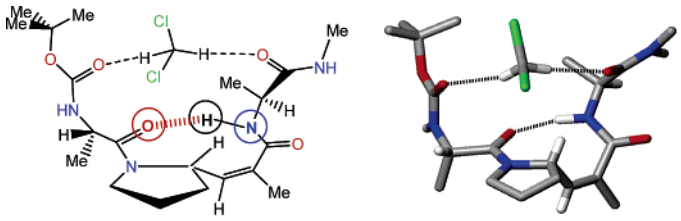

Various sequences of modified peptides including those containing a *cis*- or *trans*-vinylogous residue have been studied using X-ray diffraction in the solid state and ^{1}H NMR and IR spectroscopy in solution. A *cis*-vinylogous residue promotes an NH to CO intramolecular H-bond, closing a nine-membered pseudocycle that stabilizes a folded moiety that we proposed to name the *cis*-vinylogous turn. A *trans*-vinylogous residue involves an extended conformation. Two consecutive vinylogous residues retain their own structural propensity: "Xaa^{tr}"-"Xaa^{cis}" or "Xaa^{cis}"-"Xaa^{tr}" sequence is singly folded, whereas "Xaa^{cis}"-"Xaa^{cis}" sequence is doubly folded. Oligo vinylogs with all-trans or all-cis or alternating cis−trans motifs could constitute new classes of foldamers.

Introduction

The determination of the conformational features of peptides is a crucial precondition for the rational design of new bioactive peptides. Different investigations have shown that peptides that adopt specific compact conformations were particularly suited for peptide synthesis targeted toward increasing receptor selectivity, metabolic stability, and the development of potent agonists, antagonists, or enzymatic inhibitors.[1] The most straightforward approach to induce structural restrictions is the incorporation of unnatural amino acids that adopt well-defined conformations.[2] Among numerous and interesting examples are various homologous amino acids such *β*-amino acids,[3] *γ*-amino acids,[3d,4] and *δ*-amino acids.[5] *β*-Amino acid analogues such as hydrazinoacids,[6] aminoxyamino acids,[7] or sulfonamides[8] have been also examined. In this respect, *β*-peptides have been extensively investigated over the past few years. They can adopt helix, sheet, or reverse turn conformations; these structures are stable, and they are adapted with short chain lengths.

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γ-Peptides have also been studied, and various secondary structures have been identified depending on degrees of substitution and configurations of γ-amino acid units. Different studies have revealed that γ^{2-4}-peptides can also adopt helical conformations in solution.[4c] The conformational preferences of the $\gamma^{2,4}$-peptides have been also determined. The 2*S*,4*S*-γ-dipeptide moiety induces a β-like folded structure by an intramolecular hydrogen bond, whereas the 2*S*,4*R*-diastereomer assumes an open structure.[4e] Oligomers consisting of α,β-unsaturated γ-amino acids, so-called vinylogous peptides, have been little explored. The first example of a *trans*-ethylenic bond was proposed by Schreiber and co-workers as a rigid extension of a peptide residue.[9] We have reported in a short communication that the insertion of a *cis*-propenyl CH=CMe group between the α-carbon and the carboxyl group of proline can be used to induce the formation of a very stable intramolecular hydrogen bond closing a nine-membered pseudocycle that involved an excellent mimic of the natural β-turn.[10] Recently, computational studies have shown that the introduction of a trans double bond into the backbone of the γ-amino acid constituents, which leads to vinylogous glycine, supports the folding into helices with larger H-bonded pseudocycles in the resulting peptides.[11] Synthesis and conformational studies of peptides with *cis*-amide bonds in *trans*-vinylogous proline-containing peptides have revealed the formation of 12-membered intramolecularly hydrogen-bonded structures very similar to type β-turn.[12] Therefore, vinylogous peptides are particularly attractive structures for the construction of new peptide materials and can be used to control the structure of a peptide. A recent publication by Baldauf, Gunther, and Hofmann in this journal[13] prompted us to publish our structural investigations concerning *cis*- and *trans*-vinylogous peptides.

In this work, we propose a detailed study of the structural features of various vinylogous peptides. The influence of the side chain, the configuration of the double bond, the position of the vinylogous amino acid in the peptide backbone, the number of vinylogous amino acid residues, and the influence of solvation are described.

TABLE 1. Synthesized Vinylogous Peptides with Their Abbreviated Codes Where "Xaa" Represents the Vinylogous Residue of the Xaa Aminoacid

"Xaa" residue	"Ala"	"Pro"	"Val"	"Gly"	"β-Ala"
Vinylogous Aminoamides					
Boc-"Xaa^{tr}"-NH-*i*-Pr	1a	1c	1e	1g	1i
Boc-"Xaa^{cis}"-NH-*i*-Pr	1b	1d	1f	1h	1j
Piv-"Xaa^{tr}"-NH-*i*-Pr	2a	2c			
Piv-"Xaa^{cis}"-NH-*i*-Pr	2b	2d			
Monovinylogous Dipeptides					
Boc-Pro-"Xaa^{tr}"-NH-*i*-Pr	3a				
Boc-Pro-"Xaa^{cis}"-NH-*i*-Pr	3b				
Piv-Pro-"Xaa^{tr}"-NH-*i*-Pr	4a				
Boc-"Xaa^{tr}"-Ala-NH-*i*-Pr		5c			
Boc-"Xaa^{cis}"-Ala-NH-*i*-Pr		5d			
Boc-"Xaa^{tr}"-Ala-NH-Me		6c			
Boc-"Xaa^{cis}"-Ala-NH-Me		6d			
Monovinylogous Tripeptides					
Boc-Ala-"Xaa^{tr}"-Ala-NH-*i*-Pr		7c			
Boc-Ala-"Xaa^{cis}"-Ala-NH-*i*-Pr		7d			
Boc-Ala-"Xaa^{tr}"-Ala-NH-Me		8c			
Boc-Ala-"Xaa^{cis}"-Ala-NH-Me		8d			
Divinylogous Dipeptides					
Boc-"Xaa^{tr}"-"Ala^{tr}"-NH-*i*-Pr		9c			
Boc-"Xaa^{tr}"-"Ala^{cis}"-NH-*i*-Pr		9d			
Boc-"Xaa^{cis}"-"Ala^{tr}"-NH-*i*-Pr		9e			
Boc-"Xaa^{cis}"-"Ala^{cis}"-NH-*i*-Pr	9f	9g			
Piv-"Xaa^{tr}"-"Ala^{tr}"-NH-*i*-Pr		10c			
Piv-"Xaa^{cis}"-"Ala^{tr}"-NH-*i*-Pr		10e			

In this article, for clarity of the nomenclature, we propose to note "Xaa^{cis}" and "Xaa^{tr}" the *cis*-(*Z*)- and *trans*-(*E*)-vinylogous analogues of the α-amino acid Xaa, with insertion of the *cis*- or *trans*-propenyl CH=CMe group between the α-carbon and the carbonyl.

Results

Synthesis. Different vinylogous aminoamides and vinylogous peptides (*cis*-monovinylogs and *trans*-monovinylogs), β-alanine vinylogs, and divinylog dipeptides have been synthesized. They are shown in Table 1, which shows the various synthesized vinylogous peptides together with their codes.

Recently, we demonstrated the utility of Horner reagents as starting materials for the stereoselective synthesis of *trans*- and *cis*-vinylogous amino acids.[14] In the present work, we present new developments of this methodology, especially the extension to *trans*- and *cis*-vinylogous peptides and divinylogous dipeptides. The strategy is based on stereoselective Horner reactions applied to α-aminoaldehydes with the stereochemical control of the olefination determined by the choice of the Horner reagent (Scheme 1).

trans-Vinylogous amino acids were obtained by reaction between the lithiated dianion derived from 2-diethylphosphonopropanoic acid and an aminoaldehyde Boc-X_{aa}-H. The preparation of *cis*-vinylogous amino acids needed another stereoselective synthesis, based on the use of two systems, either KH/ethyl 2-bis(trifluoroethyl)-phosphonopropanoate or BuLi/ethyl 2-diethylphosphonopropanoate. On the basis of our previous works, a high cis stereoselectivity was obtained with the second system when aminoaldehydes were slightly hindered (Boc-Ala-

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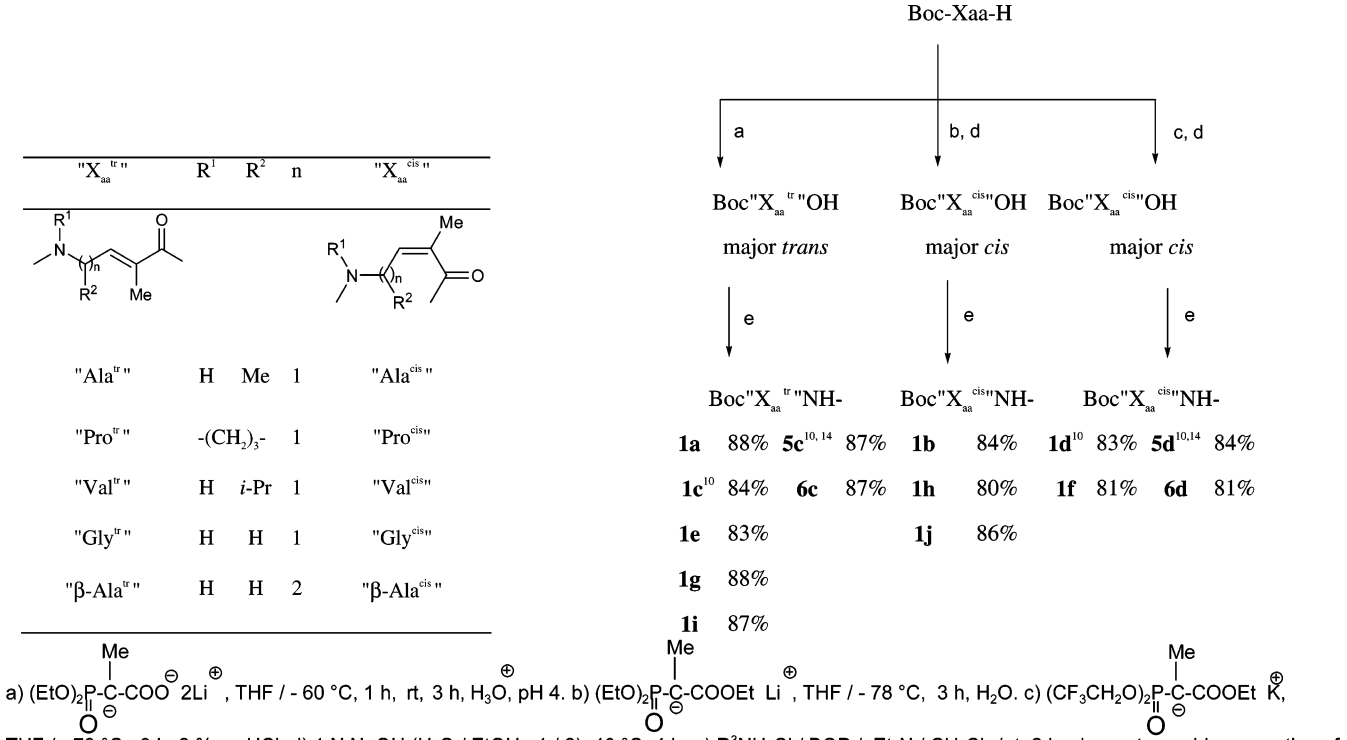
SCHEME 1. Representative Syntheses for Vinylogous Aminoamides and Vinylogous Peptides



H, Boc-Gly-H, Boc-*β*-Ala-H), while bulkier aminoaldehydes (Boc-Pro-H, Boc-Val-H) needed Still reagent.[14,15] The basic hydrolysis of pure *cis*-vinylogous aminoesters was effected with 1 N solution of NaOH (2.5 equiv) in H_2O/EtOH (1/2) for 2 h at 20 °C. Due to the steric hindrance of the pyrrolidine cycle, the time (4 h) and the heating (40 °C) required for completion of the reaction with Boc-"Pro"-OEt were significantly higher than those under the standard conditions.

The mixture of *cis*- and *trans*-vinylogous amino acids was coupled with the amino partners in the presence of BOP as coupling reagent and led to good yields of the desired peptides **1a**−**1j** and **5c**−**6d**. The reaction occurred at room temperature with 2 equiv of triethylamine in dichloromethane and was complete after being stirred for 2 h. These conditions could be applied to each amino partner (isopropylamine, H-Ala-NH-*i*-Pr, H-Ala-NH-Me). The pure trans and cis isomers could be easily obtained after a chromatographic separation.

The Boc group was removed by treatment with anhydrous HCl in Et_2O, and the amino group of the unsaturated aminoamides was acylated with pivaloyl chloride to give **2a**−**2d** or coupled with a carboxylic partner to give **3a**,**3b**. The best activation method was attained with BOP as coupling reagent in CH_2Cl_2.

The vinylogous tripeptides **7c**−**8d** may be obtained using the same sequence: removal of the *N*-Boc group of **5c**−**6d** with HCl/coupling with a carboxylic partner using BOP as coupling reagent. The unsaturated tripeptides were easily purified on a silica gel chromatography column.

The divinylogous dipeptides **9c**−**10e** were accessible starting from the corresponding vinylogous amino acids. The presence of the double bonds did not need modification of coupling conditions (BOP/CH_2Cl_2/Et_3N/20 °C/2h). The divinylog compounds **9c**−**9g** were purified on silica gel without decomposition and were obtained in good yields. This purification was easy if the stereomer ratio of the ethylenic precursors was higher. The replacement of the Boc group by the pivaloyl moiety was achieved with the system HCl/Et_2O/*t*-BuCOCl/DIPEA and gave **10c** and **10e**. All the yields were high, and the reactions were relatively insensitive to the presence of the vinylogous amino acid residue. In all cases, the configuration integrity of the double bond and chiral carbons was maintained.

X-ray Diffraction. Single crystals of Piv-"Ala^{cis}"-NH-*i*-Pr **2b** and Boc-Ala-"Pro^{cis}"-Ala-NH-Me **8d** were grown by slow evaporation of ethyl acetate/dichloromethane solution. The X-ray diffraction data set of the former was collected at room temperature on a diffractometer using Cu Kα radiation from a rotating anode generator. A crystal of compound **8d** was measured at room temperature on a system equipped with a Mo sealed tube (λ = 0.7107 Å). The X-ray data were processed with WinGx[16] and with HKL 2000 suite[17] for the former and the latter, respectively. The crystal structures were solved by direct methods using SIR92,[18] and the models were refined by full-matrix least-squares procedures on

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F^2 using SHELXL97.[19] The positions of H atoms attached to N atoms were located from difference maps, and the N−H bond distance was restrained to 1.03(1) Å.[20] The CH hydrogen atoms were placed at a calculated position and refined using a riding model. The N-terminal *tert*-butyl group of Piv-"Ala^{cis}"-NH-*i*-Pr **2b** was found to be disordered. It was modeled over two sites A and B with occupancy factors 0.769(8) and 0.231(8), respectively. In site A the three carbon atoms were refined anisotropically; in site B they were refined isotropically. In both sites the C−C bond distances were restrained to 1.51(1) Å. The crystal structure determination of **8d** revealed an asymmetric unit containing one Boc-Ala-"Pro^{cis}"-Ala-NH-Me molecule, one dichloromethane molecule, and one disordered water molecule. This disordered water molecule was refined isotropically with a fixed occupancy factor of 0.3, and no hydrogen atoms were modeled. The main crystallographic data are as following: **2b**, $C_{14}H_{26}N_2O_2$, $M = 254.37$, orthorhombic, $P2_12_12$, $a = 14.747(2)$ Å, $b = 18.745(2)$ Å, $c = 5.702(1)$ Å, $Z = 4$, $D_{calcd} = 1.072$ Mg·m^{-3}, 1569 unique reflections, 1533 with $I > 2\sigma(I)$, $R_1 = 0.0443$ [$I > 2\sigma(I)$] and $wR_2 = 0.1228$ [$I > 2\sigma(I)$], 181 parameters; **8d**, $C_{20}H_{34}N_4O_5$, CH_2Cl_2, $O_{0.3}$, $M = 500.24$, triclinic, $P1$, $a = 8.6350(4)$ Å, $b = 8.7930(3)$ Å, $c = 10.3560(6)$ Å, $\alpha = 82.257(3)°$, $\beta = 73.341(2)°$, $\gamma = 66.915(3)°$, $Z = 1$, $D_{calcd} = 1.199$ Mg·m^{-3}, 2569 unique reflections, 2369 with $I > 2\sigma(I)$, $R_1 = 0.0445$ [$I > 2\sigma(I)$] and $wR_2 = 0.1137$ [$I > 2\sigma(I)$], 302 parameters. All crystal data, fractional coordinates for the hydrogen and non-hydrogen atoms, equivalent thermal parameters and anisotropic temperature parameters for the non-hydrogen atoms, interatomic bond lengths and bond angles, and torsional angles have been deposited as Supporting Information.

IR Spectroscopy. IR spectra were scanned on an apparatus using a cell path length of 0.5 mm to investigate the amide N−H stretching (3200−3500 cm^{-1}), C=O stretching (amide I frequency at 1580−1720 cm^{-1}) and in-plane N−H bending (amide II frequency at 1480−1550 cm^{-1}). All the vinylog peptides also presented a weak to medium C=C stretching absorption at around 1640 cm^{-1}, but it turned out that it was not informative on the extended or folded conformational properties of the molecules. The peptide concentration was 0.005 M in DCM and in DMSO, and further dilution confirmed the absence of molecular aggregation. The N−H and C=O stretching frequencies were assigned on the basis of previous studies on related peptides and pseudopeptides and particularly on the influence of the adjacent groups.[21]

For this purpose, a Boc or Piv N-terminal group, and a Me or *i*-Pr C-terminal group attached to the same molecular backbone in some cases. For example, the NH frequency decreases by around 15 cm^{-1} when changing NH-Me into NH-*i*-Pr as a C-terminal group. On the other hand, changing Piv into Boc as an N-terminal group decreases the CO stretching frequency by around 50 cm^{-1} and increases the NH stretching frequency by around 20 cm^{-1}. In DCM, a free amide NH gives a sharp absorption in the 3400−3450 cm^{-1} region and a free Piv-CO a strong absorption at 1610−1625 cm^{-1}. The occurrence of an N−H to C=O hydrogen bond results in a shift to low stretching frequencies for both NH and CO and to higher frequencies for the in-plane NH bending.

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were run at 250 or 400 MHz with Me_4Si as internal reference, and the spin systems were solved by COSY and TOCSY experiments. The solvent accessibility, and therefore the extent of free or hydrogen-bonded character for the N*H* protons, was investigated in the pseudodipeptides by considering the shift of the N*H* proton resonance from $CDCl_3$ to DMSO-d_6, which proved to give more reliable results than the temperature coefficient for small model peptides.[21−23] The signal of a hydrogen-bonded, solvent-shielded N*H* is only slightly sensitive to the solvent, whereas the signal of a free, solvent-exposed N*H* is shifted downfield by DMSO-d_6. In the case of a rapid equilibrium between an extended (solvent-exposed N*H*) and a folded (solvent-protected N*H*) conformer, the average solvent sensitivity of the N*H* resonance translates the relative percentages of both conformers.

Molecular Structures by X-ray Crystallography. The atomic structures of four *cis*-vinylog peptides and two *trans*-vinylog peptides have been solved by X-ray diffraction experiments. The crystal structures of Boc-"Pro^{cis}"-NH-*i*-Pr **1d**, Boc-"Pro^{tr}"-NH-*i*-Pr **1c**, Boc-"Pro^{tr}"-Ala-NH-*i*-Pr **5c**, and Boc-"Ala^{cis}"-NH-*i*-Pr **1b** have been published elsewhere.[10] The main torsional angles for the six vinylog derivatives are indicated in Table 2. The average dimensions of the vinylog fragment do not depend on the cis or trans disposition of the ethylenic bond (Figure 1). The geometry of the amide group is similar to that of the standard peptide group.[24] The ethylenic bond length is that of an isolated double bond,[25] and both =C−C bonds have practically the same dimensions, suggesting that there is no electronic conjugation between the amide and the ethylenic bonds which are far from coplanarity (see angle ψ_2 in Table 2). As expected, the cis (*Z*) and trans (*E*) derivatives accommodate completely different conformations of the main chain. Both trans-derivatives **1c** and **5c** have an open structure with a cis-planar Boc-Pro amide bond and no intramolecular interaction. On the contrary, all four *cis*-vinylogs **1b**, **1d**, **2b**, and **8d** assume a folded conformation with an intramolecular NH to CO hydrogen bond closing a nine-membered pseudocycle that we propose to name the *cis*-vinylog turn.

All the amide groups are trans-planar. Figure 2 presents two examples of such open or folded crystallographic molecular structures, respectively **5c** and **8d**. A similar nine-membered folded conformation has been reported for the acylurea peptide *Z*-Val-Ni-Pr-CO-NH-*i*-Pr in the solid state, where the cis−trans urea fragment plays a role similar to the *cis*-ethylenic group.[26]

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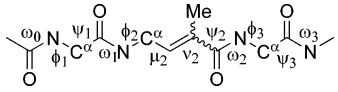
TABLE 2. Main Torsional Angles (deg) for the Six Crystallized Vinylog Peptides[a]



compound		ω_0	ϕ_1	ψ_1	ω_1	ϕ_2	μ_2	ν_2	ψ_2	ω_2	ϕ_3	ψ_3	ω_3
cis-Vinylog Peptides													
Boc-"Pro^{cis}"-NH-*i*-Pr	**1d**[b]				−174	−75	125	−3	−54	−177			
Boc-"Ala^{cis}"-NH-*i*-Pr	**1b**[c]				172	−76	123	0	−57	−176			
Piv-"Ala^{cis}"-NH-*i*-Pr	**2b**[d]				177	−82	122	2	−49	176			
Boc-Ala-"Pro^{cis}"-Ala-NH-Me	**8d**[d]	173	−69	161	177	−72	125	−3	−53	−177	−65	139	173
standard *cis*-vinylog turn					180	−75	125	0	−55	180			
trans-Vinylog Peptides													
Boc-"Pro^{tr}"-NH-*i*-Pr	**1c**[b]				−6	−78	129	−177	−33	−179			
Boc-"Pro^{tr}"-Ala-NH-*i*-Pr	**5c**[b]				1	−82	128	−179	−22	177	−85	141	177

[a] The torsional angles are defined according to IUPAC-IUB Commission on Nomenclature. [b] See ref 10. [c] See ref 4e. [d] This work.

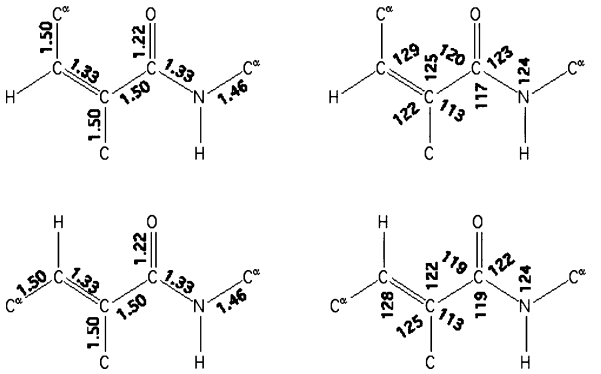


FIGURE 1. Average dimensions (Å, deg) for the *cis*- (up) and *trans*-vinylog (down) peptide unit in the crystal state.

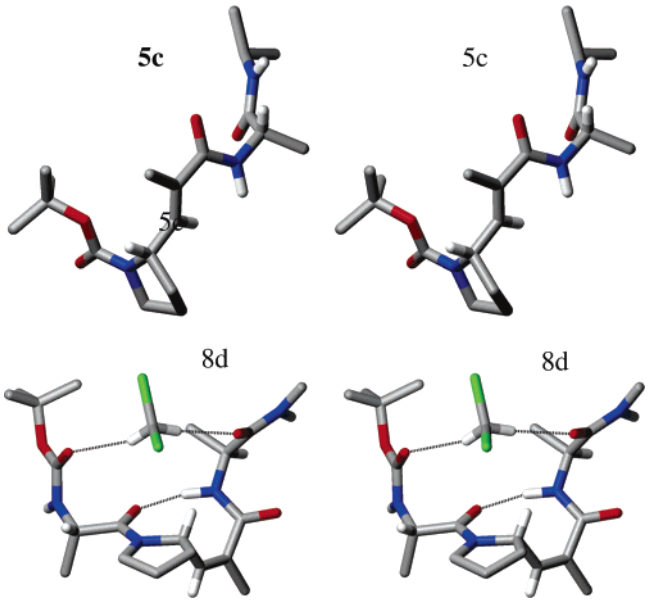


FIGURE 2. Stereoscopic view of the crystal molecular structures of the *trans*-vinylog dipeptide Boc-"Pro^{tr}"-Ala-NH-*i*-Pr **5c** and the *cis*-vinylog tripeptide Boc-Ala-"Pro^{cis}"-Ala-NH-Me **8d** with a dichloromethane molecule joining the N- and C-terminals.

Classically, the NH protons that are not involved in any intramolecular interaction are proton donors to a carbonyl of a neighboring molecule (Table 3). The *cis*-vinylog tripeptide Boc-Ala-"Pro^{cis}"-Ala-NH-*i*-Pr **8d** molecule is also solvated by a water molecule, and the distance between the water oxygen and two amide oxygens is compatible with two O−H···O=C H-bonds. The dichloromethane molecule that crystallizes with **8d** connects both N- and C-terminal carbonyls of the vinylog tripeptide skeleton, with two C to O distances that are a little shorter than a van der Waals contact (Figure 2).

Conformational Analysis in Solution. *cis*-Monovinylogs. In dichloromethane, all the *cis*-vinylog derivatives exhibit two components in the NH stretching absorption domain (Table 4). The high-frequency absorption at 3430−3455 cm^{-1} classically corresponds to free NHs, while the low frequency domain at 3260−3290 cm^{-1} is typical of H-bonded NHs. The invariant IR spectra with dilution suggesting the absence of molecular aggregation indicates that the *cis*-vinylog peptides are all folded by an intramolecular NH to CO H-bond that can be characterized by considering NH stretching frequency of Boc-"Pro^{cis}"-NH-*i*-Pr **1d**.

In **1d**, only the *i*-Pr-NH to Boc-CO H-bond is to be considered and forms what we name the *cis*-vinylog turn containing a nine-membered pseudocycle.

The low solvent sensitivity for derivatives **1b**,**d**,**f**,**h**,**j** and **2b**,**d** (−0.37 to 0.12 ppm) of the *i*-Pr-NH proton signal when changing from chloroform to DMSO supports the IR observation. In ^{1}H NMR spectroscopy, this observation still holds true for the other *cis*-vinylog derivatives where the acrylic NH resonance is systematically less solvent-sensitive than the other NH signals (Tables 5 and 6).

Another peculiarity of an H-bond is to shift the amide II IR absorption to high frequencies, and we effectively observe an absorption at around 1550 cm^{-1} for the acrylamide, approximately 50 cm^{-1} above the value for the N-terminal secondary amide (Table 4).

Insertion of an Ala residue at the C-terminus of the *cis*-vinylog **1d** affords monovinylog dipeptides Boc-"Pro^{cis}"-Ala-NH-R′ **5d** (R′ = *i*-Pr) or **6d** (R′ = Me) which give rise to an additional NH stretching absorption at around 3340−3360 cm^{-1}, with medium intensity, which is attributed to the C-terminal NH on the basis of its variation with the adjacent Me or *i*-Pr group (Table 7). This observation is consistent with the rather low solvent effect (0.87 ppm) on the *i*-Pr-NH resonance of Boc-"Pro^{tr}"-Ala-NH-*i*-Pr **5c** in ^{1}H NMR spectroscopy (Table 6).

The broad amide I profile prevents the assigning of the proton accepting carbonyl but, due to the very low occurrence of the γ-turn in dichloromethane for non Pro-

TABLE 3. Short X···O Distances (Å) in the X−H···O H-Bonds for the Six Crystallized Vinylog Peptides

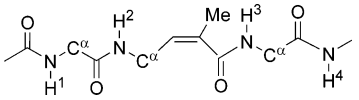
compound[a]		H-bond	X···O distance intramolecular	X···O distance intermolecular
Boc-"Pro^{cis}"-NH-*i*-Pr	**1d**[a]	*i*-Pr-NH to Boc-CO	2.86	
Boc-"Ala^{cis}"-NH-*i*-Pr	**1b**[b]	*i*-Pr-NH to Boc-CO	2.86	
		"Ala^{cis}"-NH to "Ala^{cis}"-CO		2.92
Piv-"Ala^{cis}"-NH-*i*-Pr	**2b**[c]	*i*-Pr-NH to Piv-CO	2.86	
		"Ala^{cis}"-NH to "Ala^{cis}"-CO		3.00
Boc-Ala^1-"Pro^{cis}"-Ala^2-NH-Me	**8d**[c]	Ala^2-NH to Ala^1-CO	2.84	
		Me-NH to Boc-CO		2.92
		Ala^1-NH to Ala^2-CO		2.94
		WH to "Pro^{cis}"-CO		3.18
		WH′ to Ala^1-CO		3.30
		Cl_2CH_A to Boc-CO		3.31
		Cl_2CH_B to Ala^2-CO		3.22
Boc-"Pro^{tr}"-NH-*i*-Pr	**1c**[a]	*i*-Pr-NH to Boc-CO		3.02
Boc-"Pro^{tr}"-Ala-NH-*i*-Pr	**5c**[a]	*i*-Pr-NH to "Pro^{tr}"-CO		2.84
		Ala-NH to Boc-CO		3.04

[a] See ref 10. [b] See ref 4e. [c] This work.

TABLE 4. IR Data for the Monovinylogs RCO-"Xaa"-NH*i*-Pr in Dichloromethane[a]

compound		free NH "Xaa"-NH	free NH *i*-PrNH	H-bonded NH *i*-PrNH	amide I Boc-"Xaa"	amide I "Xaa"-CONH	amide II Boc"Xaa"	amide II "Xaa"-CONH
				cis-Derivatives				
Boc-"Gly^{cis}"-NH-*i*-Pr	**1h**	3454		3284^s	1703	1667	1506	1548
Boc-"Ala^{cis}"-NH-*i*-Pr	**1b**	3439		3283^s	1700	1666	1498	1549
Piv-"Ala^{cis}"-NH-*i*-Pr	**2b**	3455		3252^s	1650	1663	1507	1552
Boc-"Val^{cis}"-NH-*i*-Pr	**1f**	3440		3284^s	1697	1664	1496	1546
Boc-"Pro^{cis}"-NH-*i*-Pr	**1d**		3443^w	3260^s	1674	1665		1552
Piv-"Pro^{cis}"-NH-*i*-Pr	**2d**		3443^w	3242^s	1604	1664		1554
Boc-"β-Ala^{cis}"-NH-*i*-Pr	**1j**	3445	3434	3305^w	1706	1665	1508	
				trans-Derivatives				
Boc-"Gly^{tr}"-NH-*i*-Pr	**1g**	3447			1711	1667	1505	
Boc-"Ala^{tr}"-NH-*i*-Pr	**1a**	3440			1709	1670	1502	
Boc-"Val^{tr}"-NH -*i*-Pr	**1e**	3441			1709	1669	1505	
Boc-"Pro^{tr}"-NH-*i*-Pr	**1c**		3445		1685	1674		1508
Piv-"Pro^{tr}"-NH-*i*-Pr	**2c**		3450		1615	1668		1508
Boc-"β-Ala^{tr}"-NH-*i*-Pr	**1i**	3450		3377^{vw}	1709	1666	1508	

TABLE 5. Chemical Shift δ and Solvent Sensitivity $\Delta\delta$ (ppm) in Chloroform/DMSO of the NH Proton Resonances for the *cis*-Monovinylog Peptides

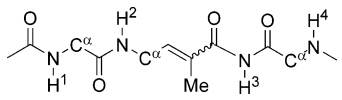


compound		NH^1 δ	NH^1 $\Delta\delta$	NH^2 δ	NH^2 $\Delta\delta$	NH^3 δ	NH^3 $\Delta\delta$	NH^4 δ	NH^4 $\Delta\delta$
Boc-"Xaa^{cis}"-NH-*i*-Pr									
"Gly^{cis}"	**1h**			5.01/7.00	2.00	7.74/7.86	0.12		
"Ala^{cis}"	**1b**			4.58/7.04	2.46	8.47/8.15	−0.32		
"Val^{cis}"	**1f**			4.59/7.05	2.46	8.29/8.11	−0.18		
"Pro^{cis}"	**1d**					9.02/8.65	−0.37		
"β-Ala^{cis}"	**1j**			5.03/6.84	1.81	5.59/7.59	2.00		
Boc-Pro-"Ala^{cis}"-NH-*i*-Pr	**3b**								
trans-Boc-Pro				7.14/8.08	0.94	8.59/8.50	−0.09		
cis-Boc-Pro				5.92/7.96	2.04	8.59/8.40	−0.19		
Boc-"Pro^{cis}"-Ala-NH-*i*-Pr	**5d**					9.45/9.05	−0.40	6.73/7.67	0.94
Boc-Ala-"Pro^{cis}"-Ala-NH-*i*-Pr	**7d**	5.34/6.96	1.62			9.23/9.34	0.11	6.57/7.66	1.09

containing related model peptides,[21] an $i + 2\varnothing i$ H-bond involving the acrylic carbonyl is a highly improbable. Therefore, an $i + 3\varnothing i$ H-bond with the Boc carbonyl and closing a 12-membered pseudocycle is the only possibility that is actually compatible with the *cis*-vinylog turn (Figure 3a).

Insertion of a Pro residue at the N-terminus of the *cis*-vinylog Boc-"Ala^{cis}"-NH-*i*-Pr **1b**, leading to the monovinylog dipeptide Boc-Pro-"Ala^{cis}"-NH-*i*-Pr **3b**, induces less conformational perturbation. We only observe a very weak and broad absorption around 3330 cm^{-1}, which is attributed to the middle NH (Table 7) on the basis of the rather low solvent effect (0.94 ppm) on the NH proton resonance for the major trans form of the Boc-Pro amide bond (Table 5). This may denote a small percentage of γ-folded Pro residue, which is known to promote the

TABLE 6. Chemical Shift δ and Solvent Sensitivity Δδ (ppm) in Chloroform/DMSO of the NH Proton Resonances for the Trans Monovinylog Peptides



compound		NH[1] δ	NH[1] Δδ	NH[2] δ	NH[2] Δδ	NH[3] δ	NH[3] Δδ	NH[4] δ	NH[4] Δδ
Boc-"Xaa[tr]"-NH-*i*-Pr									
"Gly[tr]"	**1g**			4.78/7.06	2.28	5.60/7.56	1.96		
"Ala[tr]"	**1a**			4.70/6.99	2.30	5.64/7.51	1.87		
"Val[tr]"	**1e**			4.54/6.88	2.34	5.52/7.50	1.98		
"Pro[tr]"	**1c**					5.54/7.55	2.00		
"β-Ala[tr]"	**1i**			4.67/6.86	2.19	5.63/7.43	1.80		
Boc-Pro-"Ala[tr]"-NH-*i*-Pr	**3a**								
trans-Boc-Pro				7.12/7.97	0.85	5.50/7.49	1.89		
cis-Boc-Pro				6.05/7.91	1.86	5.60/7.49	1.89		
Boc-"Pro[tr]"-Ala-NH-*i*-Pr	**5c**					6.25/7.62	1.37	6.75/7.62	0.87
Boc-Ala-"Pro[tr]"-Ala-NH-*i*-Pr	**7c**								
trans-Ala-"Pro[tr]"-		5.19/6.89	1.70			7.58/7.61	0.03	6.30/7.74	1.44
cis-Ala-"Pro[tr]"-		5.38/6.99	1.61			6.41/7.52	1/11	5.91/7.66	1.75

TABLE 7. IR Data for the *cis*- and *trans*-Monovinylog Dipeptides Boc-"Pro"-Ala-NH-R′ and R-Pro-"Ala"-NH-R′ in Dichloromethane[a]

compound	free NH$_s$		H-bonded NHs		amide I			amide II	
cis Derivatives									
Boc-"Pro[cis]"-AlaNH-*i*-Pr, **5d**	3423[b,c]		3230[b,s]	3340[c,m]		1672[d,e,f]		1546[e]	1524[f]
Boc-"Pro[cis]"-AlaNH-Me, **6d**	3450[c]		3229[b,w]	3362[c,m]		1675[d,e,f]		1550[e,f]	
Boc-Pro-"Ala[cis]"NH-*i*-Pr , **3b**	3410[b,m]	3425[c,w]	3330[b,w]	3255[c,s]	1695[d]	1662[e]	1672[f]	1512[e]	1551[f]
trans Derivatives									
Boc-"Pro[tr]"-Ala-NH-*i*-Pr, **5c**	3424[b,c,s]		3325[c,s]			1682[d,e,f]		1500[e]	1524[f,w]
Boc-"Pro[tr]"-Ala-NH-Me, **6c**	3429[b,w]	3449[c,s]	3337[c,w]			1684[d,e,f]		1500[e]	1543[f,w]
Boc-Pro-"Ala[tr]"-NH-*i*-Pr, **3a**	3449[b]	3418[c]	3305[b,w]		1693[d]	1672[e,f]		1505[e,f]	
Piv-Pro-"Ala[tr]"-NH-*i*-Pr, **4a**	3445[b]	3425[c]	3293[b,w]		1626[d]	1670[e,f]		1508[e,f]	

[a] w, weak; m, medium; and s, strong absorption peak. [b] Ala-NH or "Ala"-NH. [c] R′NH. [d] RCO-Pro or RCO-"Pro". [e] Pro-CONH or "Pro"-CONH. [f] Ala-CONH or "Ala"-CONH.

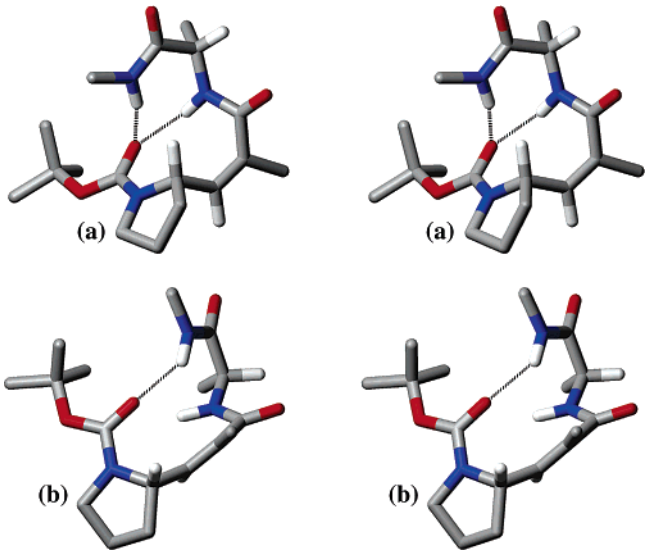


FIGURE 3. Stereoscopic view showing the $i + 3\varnothing i$ H-bond between NH-Me and Boc carbonyl closing a 12-membered pseudocycle in (a) Boc-"Pro[cis]"-Ala-NH-Me **6d** and in (b) Boc-"Pro[tr]"-Ala-NH-Me **6c**.

γ-turn in Pro-containing model peptides,[20] and this motif is compatible with an adjacent *cis*-vinylog turn. As a supporting argument, the middle NH resonance is very sensitive to solvent (2.04 ppm) for the minor cis form of the Boc-Pro amide bond (Table 5), a conformation that is not compatible with the γ-turn.

When the *cis*-vinylog is in the middle position of a tripeptide, as for *cis*-Boc-Ala[1]-"Pro[cis]"-Ala[2]-NH-*i*-Pr **7d** (Table 8), the NH stretching frequencies are quite similar to that for the monovinylog dipeptide Boc-"Pro[cis]"-Ala-NH-*i*-Pr **5d** (Table 7), with a more intense component at high frequencies due to free NHs. The NH protons also exhibit quite similar solvent accessiblity (Table 5). We therefore conclude that the molecules share the same conformational properties. The great majority of the molecules **7d** accommodate the nine-membered *cis*-vinylog turn, and on the basis of the medium solvent sensitivity of the NH-*i*-Pr proton resonance (Table 5), a significant part of these molecules also contain an *i*-PrNH to Ala[1]-CO H-bond closing a 12-membered pseudocycle (Figure 3a).

***trans*-Monovinylogs.** The *trans*-monovinylogs RCO-"Xaa[tr]"-NH-R′ **1a**,**c**,**e**,**g**,**i** and **2a**,**c** only exhibit an NH absorption profile restricted to the high frequency domain in dichloromethane, while the Boc-"Xaa[tr]" amide I absorption is around 10 cm^{-1} higher than that for the cis-analogues, and the amide II absorption is observed at a lower frequency (Table 4). Moreover, the acrylamide NH proton resonance is more sensitive to solvation than for the *cis*-vinylog derivatives (Table 5). All these data

TABLE 8. IR Data for the *cis*- and *trans*-Monovinylog Tripeptides Boc-Ala[1]-"Pro"-Ala[2]-NH-R′ in Dichloromethane[a]

	R′	free NHs	H-bonded NHs		amide I				amide II		
					cis-						
7d	*i*-Pr	3429	3229[b,s]	3339[c,m]	1709[d]	1631[e]	1672[f,g]		1502[d,s]	1547[f,m]	1525[g,w]
8d	Me	3444/3432	3230[b,s]	3366[c,m]	1706[d]	1633[e]	1674[f]	1683[g]	1501[d,s]	1549[f,m]	1530[g,w]
					trans-						
7c	*i*-Pr	3426	3340[b,s]		1700[d]	1644[e]	1672[f,g]		1505[d,s]	1521[f,m]	1505[g,s]
8c	Me	3434/3434	3341[b,s]		1697[d]	1640[e]	1671[f]	1684[g]	1508[d,s]	1525[f,m]	1508[g,s]

[a] w, weak; m, medium; and s, strong absorption band. [b] Ala[2]-NH. [c] R′NH. [d] *t*-BuO-CONH. [e] CO-"Pro". [f] "Pro"-CONH. [g] CONHR′.

TABLE 9. IR Data for the Divinylog Dipeptides Boc-"Pro"-"Ala"-NH-*i*-Pr with Various Stereochemistry in Dichloromethane[a]

compound		free NHs	H-bonded NHs	amide I		amide II	
trans−trans derivative	**9c**	3447[b,c,s]		1684[d]	1671[e,f]	1505[e,f,s]	
cis−cis derivative	**9g**	3445[b,c,s,vw]	3234[b,c,vs]	1668[d,e,f]		1557[e,f,s]	
trans−cis derivative	**9d**	3446[b,m]	3256[c,s]	1685[d]	1668[e,f]	1504[e]	1549[f]
cis−trans derivative	**9e**	3445[c,m]	3244[b,s]	1668[d,e,f]		1547[e]	1508[f]

[a] vw, very weak; m, medium;s, strong; and vs, very strong absorption band. [b] "Ala"-NH. [c] *i*-PrNH. [d] CO-"Pro". [e] "Pro"-CONH. [f] "-"Ala"-CONH.

indicate that the *trans*-vinylogs actually adopt extended conformations.

Addition of a Pro residue on the N-terminus in Boc-Pro-"Ala[tr]"-NH-*i*-Pr **3a** results in a weak and broad absorption band around 3305 cm^{-1} attributed to Ala-NH in the present case (Table 7). The solvent sensitivity of the Ala-NH proton resonance depends on the cis or trans conformation of the Boc-Pro amide, and it is highly probable that *trans*-Pro is γ-folded by an $i + 2 \varnothing i$ H-bond while the *trans*-vinylog residue retains an extended conformation.

Similarly, the addition of an Ala residue at the C-terminus in Boc-"Pro[tr]"-Ala-NH−R′ **5c** and **6c** also results in a weak and broad absorption to appear around 3330 cm^{-1}, and its position depends on the Me or *i*-Pr C-terminal group. This is therefore assigned to a small percentage of H-bonded C-terminal NH which also shows a rather small solvent sensitivity (0.87 ppm, Table 6). Similarly, the broad amide I profile prevents the assigning of the carbonyl partner, but the very low occurrence of the γ-turn in dichloromethane for non Pro-containing related model peptides is to be noted,[4,21] and an H-bond involving the acrylic carbonyl in a γ-turn is not probable. Therefore, an H-bond with the Boc carbonyl closing a 12-membered pseudocycle is the only possibility (Figure 3b).

The two-component NH absorption profile for the *trans*-vinylog tripeptide Boc-Ala[1]-"Pro[tr]"-Ala[2]-NH-*i*-Pr **7c** is qualitatively similar to that for the *trans*-vinylog dipeptides Boc-"Pro[tr]"-Ala-NH-*i*-Pr **5c** and Boc-Pro-"Ala[tr]"-NH-*i*-Pr **3a**, but the low-frequency contribution is much more intense, indicating a higher percentage of intramolecular H-bonding. ^{1}H NMR reveals a cis−trans equilibrium of the Ala[1]-Pro amide bond, and the major trans and the minor cis conformers have been characterized by the NOESY correlations between Ala[1]-H$^\alpha$ and Pro-H$^\delta$ or Pro-H$^\alpha$, respectively. In the major trans conformer, Ala[2] NH is highly protected from DMSO solvation with a low solvent variation of 0.03 ppm (Table 6) and is responsible for the absorption around 3340 cm^{-1}, which is actually not sensitive to the *i*-Pr ∅ Me change (Table 8). The CO low stretching frequency of Boc-CO (which is around 10 cm^{-1} smaller than that for the *cis*-vinylog tripeptide **7c**) denotes an H-bonding participation, and the major trans conformer is therefore folded by an *i*-PrNH to Boc-CO interaction closing a 12-membered pseudocycle (Figure 3b). We may then conclude that the Ala-"Pro[tr]" sequence in *trans*-Boc-Ala-"Pro[tr]"-Ala-NH-*i*-Pr **7c** is more favorable to the above folded conformation than the Pro-"Ala[tr]" sequence in *trans*-Boc-Pro-"Ala[tr]"-NH-*i*-Pr **3a**. This observation is corroborated by the ^{1}H NMR structural analysis of various vinylogous hexapeptides containing the Val-"Pro[tr]" sequence which is actually folded by an NH to CO H-bond closing a 12-membered pseudocycle.[12]

In the minor cis conformer of Boc-Ala[1]-"Pro[tr]"-Ala[2]-NH-*i*-Pr, **7c**, Ala[2]-NH shows a rather low solvent sensitivity (Table 6) and is still engaged in an interaction with Boc-CO, also closing a 12-membered pseudocycle that is then flexible enough to accommodate a *cis*- or *trans*-ethylenic bond (Figure 3).

***β*-Alanine Vinylogs.** Whatever the cis or trans disposition of the ethylenic bond, one additional carbon in the main chain of Boc-"β-Ala[cis]"-NH-*i*-Pr **1j** or Boc-β-"Ala[tr]"-NH-*i*-Pr **1i** results in a high solvent sensitivity for the *i*-Pr-NH resonance (Tables 5 and 6). However, the weak to very weak broad absorption at 3305/3377 cm^{-1} in both cases (Table 4) indicates a small amount of folded molecules presenting a 10-membered pseudocycle. It is probably more flexible than the nine-membered pseudocycle in the *cis*-vinylog turn and is capable of accommodating a rigid *trans*-ethylenic bond to some extent although it affects only a small number of the molecules.

Divinylog Dipeptides. The spectroscopic observations on monovinylogs integrally hold true for molecules containing two consecutive vinylog residues. The high NH stretching frequencies, the low amide II frequencies (Table 9), and the high solvent accessibility (Table 10) for the *trans*−*trans*-divinylog dipeptide Boc-"Pro[tr]"-"Ala[tr]"-NH-*i*-Pr **9c** coincide with the data for the *trans*-monovinylogs and denote an extended conformation devoid of any short-range intramolecular interaction. On the contrary, the low NH stretching frequencies, the high amide

TABLE 10. Chemical Shift δ and Solvent Sensitivity Δδ (ppm) in Chloroform/DMSO of the NH Proton Resonances for the Divinylog Dipeptides Boc-"Pro"-"Ala"-NH-*i*-Pr with Various Stereochemistry

		"Ala"-NH		*i*-Pr-NH	
compound		δ	Δδ	δ	Δδ
trans−*trans*-divinylog	**9c**	5.71/7.83	2.12	5.05/7.50	2.45
cis−*cis*-divinylog	**9g**	9.40/9.07	−0.33	9.13/8.62	−0.51
trans−*cis*-divinylog	**9d**	5.70/7.80	2.10	8.72/8.52	−0.20
cis−*trans*-divinylog	**9e**	9.38/8.92	−0.46	5.56/7.31	1.75

II frequencies (Table 9), and the low solvent accessibility (Table 10) for the *cis*−*cis*-divinylog dipeptide Boc-"Pro^{cis}"-"Ala^{cis}"-NH-*i*-Pr **9g** coincide with the data for the *cis*-monovinylogs and denote two consecutive *cis*-vinylog turns (Figure 4). Both series of the above data are present for the *cis*−*trans*- and *trans*−*cis*-divinylog dipeptides Boc-"Pro^{cis}"-"Ala^{tr}"-NH-*i*-Pr **9e** and Boc-"Pro^{tr}"-"Ala^{cis}"-NH-*i*-Pr **9d**, so that each vinylog residue retains its own conformational properties in these molecules. Hence, we conclude that two consecutive vinylog residues are not capable of inducing a new structure containing a medium-range H-bond differing from that already present in monovinylogs. We may therefore infer that an oligo *cis*-vinylog should adopt a helical structure with consecutive *cis*-vinylog turns.

Structural Influence of DMSO Solvation. All the above observations have been carried out in dichloromethane or chloroform, and we wonder whether the folded vinylog structures are stable in a strong solvating system such as DMSO. This solvent strongly solvates the amide NHs. It is also capable of breaking intramolecular H-bonding and therefore destabilizing folded structures.

The most informative IR region around the amide NH to amide CO intramolecular interactions in DMSO is the CO stretching absorption region (see Supporting Information), but because of the high dielectric constant, a small shift to lower frequencies by 2−5 cm^{-1} with reference to dichloromethane must be taken into account. In ^{1}H NMR, the temperature coefficient for the NH proton resonances is commonly used for the structural analysis of peptides in DMSO. However, it has been reported that it can lead to erroneous conclusions for small model peptides.[22] In this case, comparing the chemical shifts of analogous protons in related molecules seems to be of more valuable use. In the present case, the resonance of a free amide NH proton for the *trans*-monovinylogs in DMSO is observed at 7.5−7.7 ppm (Table 6) and of a free urethane NH proton at 6.8−7.0 ppm. If an NH resonance is found at a higher chemical shift, it can be considered as protected from DMSO solvation by H-bonding.

The *trans*-monovinylogs Boc-"Xaa^{tr}"-NH-*i*-Pr in DMSO exhibit a single Boc-CO stretching frequency around 1710 cm^{-1} ("Xaa" = "Gly" **1g**, "Ala" **1a**, "Val" **1e**) or 1685 cm^{-1} ("Xaa" = "Pro" **1c**), a high frequency typical of an open conformer with a free Boc-CO. On the contrary, the Boc-CO stretching absorption for the *cis*-monovinylogs Boc-"Xaa^{cis}"-NH-*i*-Pr in DMSO exhibits two components denoting a conformational equilibrium. The high-frequency contribution (around 1705 cm^{-1}) corresponds to a free Boc-CO, and therefore to an open conformer, and the low-frequency contribution (around 1685 cm^{-1} for "Xaa" = "Gly" **1h**, "Ala" **1b**, "Val" **1f**, and 1665 cm^{-1} for

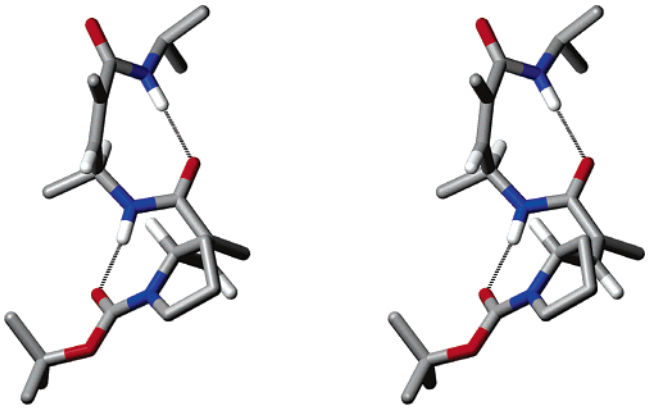


FIGURE 4. Stereoscopic view of the molecular structure associating two vinylog turns for the di-*cis*-vinylog dipeptide Boc-"Pro^{cis}"-"Ala^{cis}"-NH-*i*-Pr **9g** in solution.

"Xaa" = "Pro" **1d**) corresponds to an H-bonded Boc-CO, and therefore to a *cis*-vinylog folded conformer. The relative intensities of the two components are related to the populations of each conformer. Taking the intensity of the free component as a reference, "Pro^{cis}" is the most favorable to folding in DMSO, with no evidence of open conformer, followed by "Val^{cis}", "Ala^{cis}", and then "Gly^{cis}" with a *cis*-vinylog folding percentage of around 60, 50, and 30%, respectively. We also note that the *i*-PrNH proton resonance is lower in DMSO than in chloroform (Table 6). This observation still holds true for the *cis*-monovinylog dipeptides Boc-"Pro^{cis}"-Ala-NH-*i*-Pr **5d** and Boc-Pro-"Ala^{cis}"-NH-*i*-Pr **3b** (Table 5) and for the divinylog dipeptides containing one or two *cis*-residues (Table 10). We therefore conclude that the *cis*-vinylog turn has an intrinsic stability and is retained to a large extent in a strong NH-solvating medium.

We have pointed out that the folded structure presenting a 12-membered pseudocycle (Figure 3b) essentially concerns the trans-conformer of Boc-Ala-"Pro^{tr}"-Ala-NH-*i*-Pr **7c**, and its retention in DMSO is questionable. In comparison with Boc-Ala-"Pro^{cis}"-Ala-NH-*i*-Pr **7d** where Boc-CO is free, the only support in favor of its partial retention in Boc-Ala-"Pro^{tr}"-Ala-NH-*i*-Pr **7c** is the higher half width (28 versus 22 cm^{-1}) and the smaller CO stretching frequency (1703 versus 1706 cm^{-1}) of the Boc-CO amide I absorption. This suggests a two-component profile, the one at a higher frequency corresponding to the free Boc-CO, the other at a lower frequency denoting some amount of H-bonded Boc-CO. Hence, we conclude that the 12-membered pseudocycle is more sensitive to DMSO solvation than the nine-membered pseudocycle.

Conclusion

Insertion of an ethylenic group between the α-carbon and the carbonyl of a peptide residue results in a vinylogous peptide analogue also called vinylog. Starting from an α-amino aldehyde, it is rather easy to achieve either a *cis*- or *trans*-ethylenic bond and obtain the Boc-"Xaa^{cis}"-OH and Boc-"Xaa^{tr}"-OH synthons which can be classically introduced in a peptide chain or coupled with another vinylogous fragment. It is then possible to change one or several residues of a peptide into one or several vinylogous fragments. Moreover, the ethylenic bond may bear various substituting groups, allowing a chemical

modification on a second center beside the side chain in the starting α-amino aldehyde.

The structural consequences of inserting a vinylogous fragment in a peptide chain have been investigated for various sequences using X-ray diffraction in the solid state and ^{1}H NMR and IR spectroscopy in solution. The structural consequences greatly depend on the stereochemistry of this vinylogous fragment. A *cis*-vinylogous residue essentially promotes an NH to CO H-bond closing a nine-membered pseudocycle which stabilizes a folded motif that we propose to name the *cis*-vinylog turn. This *cis*-vinylog turn is particularly favored by the "Pro^{cis}" residue, and it is stable enough to be retained in a strong solvating medium (DMSO). On the contrary, a *trans*-vinylogous residue essentially adopts an extended conformation.

A H-bond closing a larger pseudocycle containing 12 atoms is also observed in solution, but under our experimental conditions, it is only present in a small percentage of the molecules and particularly present in the Ala-"Pro^{tr}" sequence but its retention in DMSO is questionable.

Two consecutive vinylogous residues retain their own structural preference, so that a "Xaa^{tr}"-"Xaa^{cis}" or "Xaa^{cis}"-"Xaa^{tr}" sequence is singly folded, and a "Xaa^{cis}"-"Xaa^{cis}" sequence is doubly folded. It seems to indicate that oligo vinylogs with all-cis, or all-trans, or alternating cis−trans stereochemistry could constitute new classes of foldamers presenting two centers for chemical modulation in each vinylogous residue. They could give access to additional tools for the rational design of potent peptide analogues.

Experimental Section

Vinylogous Aminoamides. General Procedure for the Preparation of the *trans*-Monovinylogous Aminoamides 1a, 1c, 1e, 1g, and 1i. To a solution of *n*-BuLi (1.56 M in hexane, 9.22 mL, 14 mmol) in THF (20 mL) was added dropwise at −60 °C a solution of 2-diethylphosphonopropanoic acid[27] (1.43 g, 6.8 mmol) in THF (10 mL). After being stirred for 30 min at −60 °C, the aminoaldehyde[28] (6.8 mmol) in THF (5 mL) was added dropwise and the stirring was continued for 1 h at this temperature. The mixture was allowed to warm to room temperature during 30 min. After being stirred for an additional 3 h, it was hydrolyzed with water (20 mL). The organic layer was separated and washed with 10% aqueous $NaHCO_3$ (2 × 15 mL). The aqueous phases were combined and acidified to pH = 3.5 with 12 N HCl and extracted with Et_2O (2 × 30 mL). After drying over $MgSO_4$, the solvent was removed under vacuum to leave the crude carboxylic acid (60/40 < trans/cis < 98/2), which was purified by column chromatography.[14] To the so-obtained pure *trans*-carboxylic acid (0.70 mmol) dissolved in dichloromethane (10 mL) at room temperature were successively added triethylamine (0.071 g), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (0.310 g, 0.70 mmol), followed after a few minutes by isopropylamine hydrochloride (0.070 g, 0.70 mmol) and triethylamine until basic pH was reached (around 0.100 g, 1.0 mmol). The resulting mixture was stirred at room temperature until TLC analysis indicated the total achievement (after around 2 h, depending to the substrate). The mixture was then diluted with dichloromethane (25 mL) and washed successively with 3 N HCl (3 × 5 mL), brine (5 mL), aqueous saturated solution of $NaHCO_3$ (3 × 5 mL), and brine (3 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The resulting crude syrup monovinylogous aminoamide was purified by column chromatography on silica gel leading to pure trans isomer.

(4*S*)-(2*E*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-2-pentenoic Acid Isopropylamide (1a): 47.5 mg (88% isolated); white solid; mp 134 °C; R_f 0.32 (ethyl acetate/hexane 1/1); IR (4.51 mM/DCM, CaF_2) ν_{max} 3440, 1709, 1630, 1670 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_{ppm} 1.15 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.19 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.41 (s, 9 H), 1.88 (d, $^4J_{H-H}$ = 1.0 Hz, 3 H), 4.08 (m, $^3J_{H-H}$ = 6.5 Hz, 1 H), 4.44 (m, 1 H), 4.70 (d, $^3J_{H-H}$ = 7.0 Hz, 1 H), 5.64 (d, $^3J_{H-H}$ = 7.0 Hz, 1 H), 6.10 (d, $^3J_{H-H}$ = 8.5 Hz, 1 H). ^{1}H NMR(250 MHz, C_6D_6) δ_{ppm} 1.10 (d, $^3J_{H-H}$ = 6.6 Hz, 3 H), 1.12 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.67 (s, 9 H), 1.98 (d, $^4J_{H-H}$ = 0.8 Hz, 3 H), 4.40 (m, 1 H), 4.51 (d, $^3J_{H-H}$ = 6.8 Hz, 1 H), 4.76 (m, 1 H), 5.33 (m, 1 H), 6.40 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H). ^{1}H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.09 (d, $^3J_{H-H}$ = 6.6 Hz, 6 H), 1.10 (d, $^3J_{H-H}$ = 6.3 Hz, 3 H), 1.38 (s, 9 H), 1.78 (d, $^4J_{H-H}$ = 1.1 Hz, 3 H), 3.94 (m, 1 H), 4.31 (m, 1 H), 6.04 (dd, $^3J_{H-H}$ = 8.8 Hz, $^4J_{H-H}$ = 1.1 Hz, 1 H), 6.99 (d, $^3J_{H-H}$ = 7.1 Hz, 1 H), 7.51 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H); ^{13}C NMR (62.896 MHz, $CDCl_3$) δ_{ppm} 12.9, 21.0, 22.7, 28.4, 41.5, 44.6, 79.5, 131.4, 136.8, 155.0, 168.0; $[\alpha]_D$ −20.5° (*c* 0.4, $HCCl_3$); MS (EI$^+$) calcd for $C_{14}H_{26}N_2O_3$ $[M]^+$ 270.2, found 271.2 $[M + 1]^+$. Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 61.89; H, 9.52; N, 10.65.

General Procedure for the Preparation of the *cis*-Monovinylogous Aminoamides 1b, 1h, and 1j. *n*-BuLi (1.54 M in hexane, 1.54 mL, 2.37 mmol) was added dropwise to ethyl 2-diethylphosphonopropanoate (0,55 g, 2.37 mmol) in THF (10 mL) with being stirred at room temperature. After 20 min, the mixture was cooled to − 78 °C and the aminoaldehyde (Boc-Ala-H, Boc-Gly-H, or Boc-*β*-Ala-H, 2.26 mmol) in THF (10 mL) was added dropwise. After being stirred for 3 h, the reaction was quenched with an aqueous saturated ammonium chloride solution (12 mL) at −78 °C. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic phases were washed with water (2 × 5 mL). Then, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude mixture of monovinylogous ester (60/40 < cis/trans < 90/10), which was purified by column chromatography on silica gel. To the so-obtained pure *cis*-vinylogous aminoester (1.20 mmol) in ethanol (6 mL) was added dropwise NaOH (1 N, 3 mL). The mixture was stirred at room temperature until TLC analysis indicated that all aminoester was reacted (2−3 h). Then HCl (1 N, 1.2 mL) was added, and the mixture was evaporated to remove ethanol. HCl (1 N, 1.6 mL) was added again, keeping the temperature below 25 °C, before the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined and dried ($MgSO_4$). The solvent was removed under vacuum to afford the crude *cis*-monovinylogous amino acid. The coupling of this last compound with isopropylamine hydrochloride was similar to that described above to synthesize the *trans*-aminoamides **1a**, **1c**, **1e**, **1g**, and **1i**. The crude product was purified on a silica gel chromatographic column leading to pure *cis*-aminoamide **1b**, **1h**, or **1j**.

(4*S*)-(2*Z*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-2-pentenoic Acid Isopropylamide (1b): 34.5 mg (84% isolated); crystals; mp 118 °C; R_f 0.43 (ethyl acetate/hexane 1/1); IR (4.86 mM/DCM, CaF_2) ν_{max} 3439, 3283, 1700, 1666, 1636, 1549, 1498 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_{ppm} 1.15 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.22 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.43 (s, 9 H), 1.90 (d, $^4J_{H-H}$ = 1.0 Hz, 3 H), 4.12 (m, 1 H), 4.34 (m, 1 H), 4.58 (d, $^3J_{H-H}$ = 5.0 Hz, 1 H), 5.13 (dd, $^3J_{H-H}$ = 10.5 Hz, $^4J_{H-H}$ = 1.0 Hz, 1 H), 8.47 (m, 1 H); ^{1}H NMR (250 MHz, C_6D_6) δ_{ppm} 0.85 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H), 1.47 (d, $^3J_{H-H}$ = 6.5

(27) Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* **1978**, 133−134.

(28) Boc-L-alanilal, Boc-L-*β*-alanilal, and Boc-L-valinal were prepared from corresponding Boc-L-amino acids according to Fehrentz and Castro. See: Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676−678. Boc-L-prolinal was synthesized similarly. See: Le Coz, S.; Mann, A.; Thareau, F.; Taddei, M. *Heterocycles* **1993**, *36*, 2073−2080. Some modifications were described by us to obtain the Boc-glycinal. See ref 14.

Hz, 3 H), 1.52 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.58 (s, 9 H), 2.18 (d, $^4J_{H-H}$ = 1.4 Hz, 3 H), 4.32 (d, $^3J_{H-H}$ = 6.0 Hz, 1 H), 4.68 (m, 1 H), 4.72 (m, 1 H), 5.06 (dd, $^3J_{H-H}$ = 10.3 Hz, $^4J_{H-H}$ = 1.4 Hz, 1 H), 8.77 (m, 1 H); ^{1}H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.07 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H), 1.10 (d, $^3J_{H-H}$ = 6.6 Hz, 3 H), 1.12 (d, $^3J_{H-H}$ = 6.6 Hz, 3 H), 1.39 (s, 9 H), 1.77 (d, $^4J_{H-H}$ = 1.1 Hz, 3 H), 3.91 (m, 1 H), 4.30 (m, 1 H), 5.06 (dd, $^3J_{H-H}$ = 9.5 Hz, $^4J_{H-H}$ = 1.1 Hz, 1 H), 7.04 (d, $^3J_{H-H}$ = 6.7 Hz, 1 H), 8.15 (d, $^3J_{H-H}$ = 7.8 Hz, 1 H). ^{13}C NMR (62.896 MHz, $CDCl_3$) δ_{ppm} 21.1, 21.2, 22.4, 28.3, 41.1, 45.6, 79.9, 131.1, 134.3, 155.8, 168.3; $[\alpha]_D$ +114.3° (*c* 0.6, $HCCl_3$); MS (FAB$^+$) calcd for C_{14} $H_{26}N_2O_3$ $[M]^+$ 270.2, found 271.3 $[M + 1]^+$, 51%, 215.2, $[M + 1 - t\text{-Bu}]^+$, 100%, 541.4, $[2M + 1]^+$, 55%. Anal. Calcd for C_{14} $H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 62.30; H, 9.45; N, 10.23.

General Procedure for the Preparation of the *cis*-Monovinylogous Aminoamides 1d and 1f. The ethyl bis-(trifluoroethyl)phosphonopropanoate[29] (1.08 g, 3.12 mmol) was added to a slurry of oil-free potassium hydride (0.125 g, 3.12 mmol) in THF (10 mL) at 0 °C. The solution was stirred for 15 min at this temperature followed by cooling to −78 °C. Boc-Pro-H or Boc-Val-H (2.6 mmol) in THF (5 mL) was added over 15 min. The reaction mixture was stirred at −78 °C for 3 h and then quenched with 2% aqueous HCl (15 mL). The aqueous phase was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and dried ($MgSO_4$). After filtration, the solvent was removed under vacuum to afford the crude monovinylogous aminoester (cis/trans = 90/10) which was purified by column chromatography on silicagel. The so-obtained pure *cis*-monovinylogous aminoester was successively hydrolyzed into the corresponding *cis*-monovinylogous amino acid and coupled with isopropylamine hydrochloride as described above to give the crude corresponding monovinylogous aminoamide. The resulting syrup was purified on a silica gel chromatographic column leading to pure *cis*-monovinylogous aminoamide **1d** or **1f**.

(2*S*)-2-[(1*Z*)-2-Methyl-3-[(1-methylethyl)amino]-3-oxo-1-propenyl]-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (1d):[10] 34.0 mg (83% isolated); crystals; mp 150 °C; R_f 0.55 (ethyl acetate/hexane 1/1); IR (5.48 mM/DCM, CaF_2) ν_{max} 3260, 1674, 1665, 1635, 1552 cm^{-1}, (6.36 mM/DMSO, CaF_2) ν_{max} 1673, 1665, 1635, 1548 cm^{-1}; ^{1}H NMR(250 MHz, $CDCl_3$);[10] ^{1}H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.17 (d, $^3J_{H-H}$ = 7.2 Hz, 6 H), 1.50 (s, 9 H), 1.51−2.27 (m, 4 H), 1.85 (s, 3 H), 3.31−3.48 (m, 2 H), 3.97 (m, 1 H), 4.57 (m, 1 H), 5.32 (d, $^3J_{H-H}$ = 9.9 Hz, 1 H), 8.65 (d, $^3J_{H-H}$ = 6.3 Hz, 1 H); ^{13}C NMR(62.896 MHz, $CDCl_3$) δ_{ppm} 21.0, 22.4, 23.8, 28.4, 32.7, 41.0, 46.9, 51.4, 79.7, 129.0, 134.6, 155.0, 168.6; $[\alpha]_D$ +101.7° (*c* 0.6, $HCCl_3$); MS (EI$^+$) calcd for C_{16} $_{H28}N_2O_3$ $[M]^+$ 296.4, found 297.1 $[M + 1]^+$. Anal. Calcd for C_{16} $H_{28}N_2O_3$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.59; H, 9.69; N, 9.10.

General Procedure for the Preparation of the Monovinylogous Aminoamides 2a−d. A solution of pure *cis*- or *trans*-*N*-Boc-monovinylogous aminoamide **1a**−**j** (3 mmol) in anhydrous Et_2O (20 mL) was submitted to a hydrochloride acid gaseous barbotage. A precipitate of monovinylogous aminoamide hydrochloride occurred before it dissolved in the reaction medium. When TLC analysis indicated the complete removal of Boc (around 2.5 h) and the complete formation of the corresponding monovinylogous aminoamide hydrochloride, the mixture was evaporated to give a paste. The so-obtained paste was washed with ether (5 × 20 mL) before it was evaporated under vacuum to dryness. To this monovinylogous aminoamide hydrochloride (0.13 mmol) dissolved in $CHCl_3$ (4 mL) were added 2,2-dimethylpropanoyl chloride (0.024 g, 0.20 mmol) and diisopropylethylamine (DIPEA) (0.034 g, 0.26 mmol) at 0 °C. After being stirred for 1 h, the mixture was concentrated. The resulting crude *cis*- or *trans*-*N*-Piv-monovinylogous aminoamides **2a**−**d** were purified on a silica gel chromatographic column.

(29) Patois, C.; Savignac, P.; About-Jaudet, N.; Collignon, N. *Synth. Commun.* **1991**, *21*, 2391−2396.

(4*S*)-(2*E*)-4-(2,2-Dimethylpropionyl amino)-2-methylpent-2-enoic Acid Isopropylamide (2a): 64.0 mg (78% isolated); oil; R_f 0.28 (ethyl acetate/hexane 1/1); IR (4.25 mM/DCM, CaF_2) ν_{max} 3460, 3250, 1670, 1550 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_{ppm} 1.15−1.29 (m, 18 H), 1.95 (d, $^3J_{H-H}$ = 1.2 Hz, 3 H), 4.00 (h, 1 H), 4.63 (m, 1 H), 5.48 (dd, 1 H, $^3J_{H-H}$ = 10.2 Hz, $^4J_{H-H}$ = 1.2 Hz, 1 H), 5.82 (m, 1 H), 8.85 (m, 1 H); ^{13}C NMR (62.896 MHz, $CDCl_3$) δ_{ppm} 20.9, 22.4, 22.6, 27.5, 38.2, 41.0, 45.2, 130.0, 134.4, 168.1, 178.2; $[\alpha]_D$ −51° (*c* 0.3, $HCCl_3$); MS (FAB$^+$) calcd for C_{14} $H_{26}N_2O_2$ $[M]^+$ 254.2, found 255.3 $[M + 1]^+$, 100%. Anal. Calcd for C_{14} $H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.34; H, 10.65; N, 11.30.

Monovinylogous Dipeptides. General Procedure for the Preparation of the Monovinylogous Dipeptides 3a,b, 4a. The Boc protection of Boc-"Ala^{tr}"-NH-*i*-Pr **1a** or Boc-"Ala^{cis}"-NH-*i*-Pr **1b** was removed by treatment with anhydrous HCl in Et_2O exactly as described above in the preparation of the monovinylogous aminoamides **2a**−**d**. The procedure for the coupling of the so-obtained HCl, H-"Ala^{tr}"-NH-*i*-Pr with Boc-Pro-OH or Piv-Pro-OH, leading to **3a** or **4a**, respectively, was the same as that employed above to prepare the vinylogous aminoamides **1a**−**j**. This procedure was also used for the coupling between HCl, H-"Ala^{cis}"-NH-*i*-Pr, and Boc-Pro-OH that provided **3b**.

(2*S*)-(*E*)-2-(3-Isopropylcarbamoyl-1-methylbut-2-enylcarbamoyl)-pyrrolidine-1-carboxylic Acid 1,1-Dimethyl Ethyl Ester (3a): 36.0 mg (87% isolated); white powder; mp 155 °C; R_f 0.49 (acetone/dichloromethane 3/7); IR (6.73 mM/DCM, CaF_2) ν_{max} 3449, 3418, 3305, 1693, 1672, 1505 cm^{-1}; (5.63 mM/DMSO, CaF_2) ν_{max} 1693, 1678, 1667, 1626, 1532 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_{ppm} 1.18 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.24 (d, $^3J_{H-H}$ = 6.8 Hz, 3 H), 1.47 (s, 9 H), 1.94 (d, $^4J_{H-H}$ = 0.7 Hz, 3 H), 1.81−2.50 (m, 4 H), 3.28−3.59 (m, 2 H), 4.07 (m, 1 H), 4.17 (m, 1 H), 4.71 (m, 1 H), 5.60 (m, 1 H), 6.06 (d, $^3J_{H-H}$ = 7.5 Hz, 1 H), 6.05 (m, 1 H), 7.12 (m, 1 H); ^{1}H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.09 (d, $^3J_{H-H}$ = 6.6 Hz, 6 H), 1.16 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.34 (s, 9 H), (major), 1.40 (s, 9 H) (minor), 1.78 (m, 3 H), 1.65−2.28 (m, 4 H), 3.17−3.60 (m, 2 H), 3.81−4.19 (m, 2 H), 4.61 (m, 1 H), 6.13 (d, $^3J_{H-H}$ = 8.6 Hz, 1 H) (minor), 6.15 (d, $^3J_{H-H}$ = 8.6 Hz, 1 H) (major), 7.49 (d, $^3J_{H-H}$ = 7.4 Hz, 1 H), 7.92 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H) (minor), 7.97 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H) (major); ^{1}H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.09 (d, $^3J_{H-H}$ = 6.6 Hz, 6 H), 1.16 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.34 (s, 9 H) (major), 1.40 (s, 9 H) (minor), 1.78 (m, 3 H), 1.65−2.28 (m, 4 H), 3.17−3.60 (m, 2 H), 3.81−4.19 (m, 2 H), 4.61 (m, 1 H), 6.13 (d, $^3J_{H-H}$ = 8.6 Hz, 1 H) (minor), 6.15 (d, $^3J_{H-H}$ = 8.6 Hz, 1 H) (major), 7.49 (d, $^3J_{H-H}$ = 7.4 Hz, 1 H), 7.92 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H) (minor), 7.97 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H) (major); ^{13}C NMR (62.896 MHz, $CDCl_3$) δ_{ppm} 13.0, 20.6, 22.6, 23.8, 24.4, 28.3, 27.5, 30.9, 41.5, 43.2, 47.0, 59.9, 61.1, 80.5, 132.4, 135.7, 155.8, 155.9, 168.1, 168.2, 171.3; $[\alpha]_D$ −52° (*c* 0.3, $HCCl_3$); MS (EI$^+$) calcd for C_{19} $H_{33}N_3O_4$ $[M]^+$ 367.5, found 368.2 $[M + 1]^+$. Anal. Calcd for C_{19} $H_{33}N_3O_4$: C, 62.10; H, 9.05; N, 11.43. Found: C, 62.15; H, 9.27; N, 11.25.

General Procedure for the Preparation of the Monovinylogous Dipeptides 5c,d and 6c,d. Monovinylogous dipeptide **5c** or **6c** was prepared by coupling Boc-"Pro"-OH (trans/cis = 80/20), obtained as described above in the synthesis of **1c** and HCl, H-Ala-NH-*i*-Pr or HCl, H-Ala-NH-Me, respectively, using BOP as coupling reagent according to the procedure described above for the preparation of aminoamides **1a**−**j**. Pure trans stereomer **5c** or **6c** was obtained after purification of the crude product (trans/cis = 80/20) on a silica gel chromatographic column. The same procedure was used to prepare **5d** or **6d** from Boc-"Pro"-OH (cis/trans = 90/10) obtained as described above in the synthesis of **1d** and HCl, H-Ala-NH-*i*-Pr or HCl, H-Ala-NH-Me, respectively. Pure cis stereomer **5d** or **6d** was obtained after purification of the crude product (cis/trans = 90/10) on a silica gel chromatographic column.

(*S*)-(*E*)-(*S*)-2-{2-Methyl-3-[[1-methyl-2-[(1-methylethyl)-amino]-2-oxoethoxy] amino]-3-oxo-1-propenyl}-1-pyrro-

lidine Carboxylic Acid 1,1-Dimethylethylester (5c):[14] 45.0 mg (84% isolated); white solid; mp 114 °C; R_f 0.42 (ethyl acetate); IR (5.52 mM/DCM, CaF_2) ν_{max} 3424, 3325, 1682, 1637, 1524, 1500 cm^{-1}; (5.64 mM/DMSO, CaF_2) ν_{max} 1682, 1628, 1565 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$),[13] ^1H NMR(250 MHz, DMSO-d_6), δ_{ppm} 1.03 (m, 6 H), 1.12 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.31 (s, 9 H), 1.80 (s, 3 H), 1.55−2.77 (m, 4 H), 3.17−3.45 (m, 2 H), 3.79 (m, 1 H), 4.28 (m, 1 H), 4.43 (m, 1 H), 6.15 (d, $^3J_{H-H}$ = 8.0 Hz, 1 H), 7.62 (m, 2 H).

General Procedure for the Preparation of the Monovinylogous Tripeptides 7c−8d. Removal of Boc of monovinylogous dipeptides Boc-"Pro^{tr}"-Ala-NH-*i*-Pr **5c**, Boc-"Pro^{cis}"-Ala-NH-*i*-Pr **5d**, Boc-"Pro^{tr}"-Ala-NH-Me **6c**, or Boc-"Pro^{cis}"-Ala-NH-Me **6d** was effected with the procedure previously described using anhydrous gaseous HCl in Et_2O to afford HCl, H-"Pro^{tr}"-Ala-NH-*i*-Pr; HCl, H-"Pro^{cis}"-Ala-NH-*i*-Pr; HCl, H-"Pro^{tr}"-Ala-NH-Me; or HCl, H-"Pro^{tr}"-Ala-NH-Me; respectively. Then, these last compounds were coupled with Boc-Ala-OH using BOP as coupling reagent according to the procedure described above for the preparation of aminoamides **1a**−**j**.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-alanyl-[(2*E*)-3-(pyrrolidin-2-yl)-2-methyl-2-propenoyl]-L-alanine Isopropylamide (7c):** 40.0 mg (74% isolated); powder; mp 194−195 °C; R_f 0.42 (acetone/ethyl acetate/hexane 1/1/1); IR (6.36 mM/DCM, CaF_2) ν_{max} 3426, 3340, 1700, 1672, 1644, 1521, 1505 cm^{-1}; (5.47 mM/DMSO, CaF_2) ν_{max} 1704, 1664, 1655, 1636, 1533 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_{ppm} major trans conformer (Ala^1-Pro bond) 55% 1.11 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H), 1.15 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H), 1.28 (d, $^3J_{H-H}$ = 7.7 Hz, 3 H), 1.43 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.43 (s, 9 H), 1.81−1.93 (m, 2 H), 1.95 (s, 3 H), 2.24−2.37 (m, 2 H), 3.48−3.76 (m, 2 H), 4.00 (m, 1 H), 4.37−4.53 (m, 3 H), 5.20 (d, $^3J_{H-H}$ = 9.6 Hz, 1 H), 6.11 (d, $^3J_{H-H}$ = 8.2 Hz, 1 H), 6.30 (d, $^3J_{H-H}$ = 6.4 Hz, 1 H), 7.58 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H); minor cis conformer (Ala^1-Pro bond) 45%: 1.14 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H); 1.15 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H), 1.30 (d, $^3J_{H-H}$ = 7.4 Hz, 3 H), 1.38 (d, $^3J_{H-H}$ = 6.9 Hz, 3 H), 1.43 (s, 9 H), 1.68−1.75 (m, 2 H), 1.95−2.18 (m, 2 H), 2.02 (d, $^4J_{H-H}$ = 0.9 Hz, 3 H), 3.55−3.66 (m, 2 H), 4.02 (m, 1 H), 4.37−4.53 (m, 2 H), 4.80 (m, 1 H), 5.38 (d, $^3J_{H-H}$ = 7.8 Hz, 1 H), 5.91 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H), 6.11 (d, $^3J_{H-H}$ = 8.2 Hz, 1 H), 6.22 (d, $^3J_{H-H}$ = 9.7 Hz, 1 H); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} major trans conformer (Ala^1-Pro bond) 65% 1.04 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.06 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.17 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.22 (d, $^3J_{H-H}$ = 7.2 Hz, 3 H), 1.38 (s, 9 H), 1.61 (m, 1 H), 1.86 (s, 3 H), 1.71−1.95 (m, 2 H), 2.03 (m, 1 H), 3.55−3.63 (m, 2 H), 3.81 (m, 1 H), 4.19−4.34 (m, 2 H), 4.66 (m, 1 H), 6.10 (d, $^3J_{H-H}$ = 8.7 Hz, 1 H), 6.89 (d, $^3J_{H-H}$ = 7.2 Hz, 1 H), 7.61 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H); 7.74 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H); minor cis conformer (Ala^1-Pro bond) 35%: 1.01 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.08 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.20 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.27 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.36 (s, 9 H), 1.61 (m, 1 H), 1.84 (s, 3 H), 1.71−1.95 (m, 2 H), 2.03 (m, 1 H), 3.55−3.63 (m, 2 H), 3.81 (m, 1 H), 4.13 (m, 1 H), 4.34 (m, 1 H), 4.66 (m, 1H), 6.19 (d, $^3J_{H-H}$ = 8.7 Hz, 1 H), 6.99 (d, $^3J_{H-H}$ = 7.2 Hz, 1 H), 7.52 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H; 7.66 (d, $^3J_{H-H}$ = 7.4 Hz, 1 H); ^{13}C RMN (62.896 MHz, $CDCl_3$) δ_{ppm} major trans conformer (Ala^1-Pro bond) 55%: 12.8, 16.6, 18.3, 22.6, 22.7, 24.9, 28.4, 33.4, 41.3, 46.9, 47.3, 49.4, 55.2, 80.0, 130.6, 135.4, 154.4, 168.0, 171.2, 171.7; minor cis conformer (Ala^1-Pro bond)-45%: 13.4, 18.6, 18.9, 22.6, 24.9, 28.4, 30.9, 41.6, 46.8, 47.8, 49.0, 55.2, 79.5, 133.2, 136.3, 155.2, 169.0, 172.1, 172.4; $[\alpha]_D$ −90° (*c* 0.5, $HCCl_3$); MS (CI$^-$) calcd for $C_{22}H_{38}N_4O_5$: 438.6 [M − 1]$^-$, found 438.3, (49%), 364.4 [M − *t*BuO]$^-$, 100%. Anal. Calcd for $C_{22}H_{38}N_4O_5$: C, 60.25; H, 8.73; N, 12.77. Found: C, 60.42; H, 8.48; N, 12.63.

General Procedure for the Preparation of the Divinylogous Dipeptides 9c−g and 10c−e. The divinylogous dipeptides **9c**−**g** and **10c**−**e** were obtained by coupling Boc- or Piv-"Xaa^{tr}"-OH or Boc- or Piv-"Xaa^{cis}"-OH with the corresponding HCl, H-"Ala^{tr}"-NH-*i*-Pr or HCl, H-"Ala^{cis}"-NH-*i*-Pr. The coupling procedure was the same as that described for the preparation of aminoamides **1a**−**j**.

(*S*)-(*S*)-2-{2-Methyl-3-[[2(*Z*)-1,3-dimethyl-4-[(1-methylethyl)amino]-4-oxo-2-butenyl]amino]-(1*E*)-3-oxo-1-propenyl}-1-pyrrolidine Carboxylic Acid 1,1-Dimethylethyl Ester (9e): 52.0 mg (73% isolated); powder; mp 130 °C; R_f 0.32 (ethyl acetate); IR (4.29 mM/DCM, CaF_2) ν_{max} 3445, 3244, 1685, 1668, 1547, 1508 cm^{-1}; (4.29 mM/DMSO, CaF_2) ν_{max} 1680, 1666, 1630, 1530 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_{ppm} 1.22 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.26 (d, $^3J_{H-H}$ = 7.0 Hz, 3 H), 1.45 (s, 9 H), 1.90 (s, 3 H), 1.94 (s, 3 H), 1.52−2.13 (m, 4 H), 3.34 (m, $^3J_{H-H}$ = 7.0 Hz, 2 H), 4.09 (m, 1 H), 4.51 (m, 1 H), 4.76 (m, 1 H), 5.25 (d, $^3J_{H-H}$ = 10 Hz, 1 H), 5.56 (d, $^3J_{H-H}$ = 7.5 Hz, 1 H), 6.24 (dd, $^3J_{H-H}$ = 9.0 Hz, $^4J_{H-H}$ = 1.0 Hz, 1 H), 9.38 (d, $^3J_{H-H}$ = 6.5 Hz, 1 H); ^1H NMR (250 MHz, DMSO-d_6) δ_{ppm} 1.13 (d, $^3J_{H-H}$ = 6.5 Hz, 6 H), 1.20 (d, $^3J_{H-H}$ = 6.5 Hz, 3 H), 1.43 (s, 9 H), 1.82 (s, 3H), 1.82 (s, 3H), 1.50−2.18 (m 4 H), 3.21−3.49 (m, 2 H), 3.91 (m, 1 H), 4.47 (m, 1 H), 4.64 (m, 1 H), 5.41 (d, $^3J_{H-H}$ = 10.75 Hz, 1 H), 6.12 (d, $^3J_{H-H}$ = 9.0 Hz, 1 H), 7.51 (d, $^3J_{H-H}$ = 7.0 Hz, 1 H), 8.92 (d, $^3J_{H-H}$ = 6.5 Hz, 1 H); ^{13}C NMR (62.896 MHz, $CDCl_3$) δ_{ppm} 13.0, 19.9, 21.0, 22.6, 23.7, 28.4, 32.6, 41.5, 43.8, 46.9, 55.3, 80.1, 130.3, 131.1, 133.5, 136.5, 155.2, 168.3, 168.8; $[\alpha]_D$ 57° (*c* 0.9, $HCCl_3$); MS (EI$^+$) calcd for $C_{22}H_{37}N_3O_4$ [M + 1]$^+$: 407.27, found 407.0 (2%), 169.0 [M − CH=C(CH$_3$)−CO−NH−CH(CH$_3$)−CH=C(CH$_3$)−CO−NH−*i*Pr]$^+$, 22%, 154.0 [M − *t*Bu−CO−NH−CH(CH$_3$)−CH=C(CH$_3$)−CO−NH−*i*Pr]$^+$, 56%, 138.0 [M − *t*BuO−CO−NH−CH(CH$_3$)−CH=C(CH$_3$)−CO−NH−*i*Pr]$^+$, 59%, 110 [M − *t*BuOCO−CO−NH−CH(CH$_3$)−CH=C(CH$_3$)−CO−NH−*i*Pr]$^+$, 100%. Anal. Calcd for $C_{22}H_{37}N_3O_4$: C, 64.84; H, 9.15; N, 10.31. Found: C, 64.72; H, 9.40; N, 10.68.

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Supporting Information Available: General methods and description of the data for compounds **1c**,**e**−**j**, **2b**−**d**, **3b**, **4a**, **5d**, **6c**,**d**, **7d**, **8c**,**d**, **9c**,**d**,**f**,**g**, and **10c**,**e**. ^1H NMR ($CDCl_3$) of compounds **1a**,**b**,**e**−**j**, **2b**−**d**, **3a**,**b**, **4a**, **5c**,**d**, **6c**,**d**, **7d**, **8c**,**d**, **9c**−**g**, and **10c**−**e**. ^1H NMR (DMSO-d_6) of compounds **6c**,**d** and **8d**. ^{13}C NMR of compounds **5c**,**d**, **6c**,**d**, **7d**, **8c**,**d**, **9c**−**g**, and **10c**−**e**. ^1H−^1H NMR ($CDCl_3$) of compound **7d**. NOESY and TOCSY of compound **7c**. Crystallographic information files (CIF format) for compounds **2b** and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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