Synthesis, Crystal Structures, and Modelling of β-Oligopeptides Consisting of 1-(Aminomethyl)cyclopropanecarboxylic Acid: Ribbon-Type Arrangement of Eight-Membered H-Bonded Rings

by **Stefan Abele**[1], **Paul Seiler**, and **Dieter Seebach***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

Partially and fully protected, and unprotected β-oligopeptides (**3**–**9**) were prepared from 1-(aminomethyl)cyclopropanecarboxylic acid, which, in turn, is readily available from cyanoacetate and dibromoethane. *N*-Boc and *C*-OMe protection were applied for the fragment-coupling (1-hydroxy-1*H*-benzotriazole (HOBt)/1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC)) solution synthesis. X-Ray crystal structures of the dimer (**3**), trimer (**5**), and tetramer (**6**) are described, and compared with those of the Boc-protected building blocks (**2**) and of the corresponding trimer (**10**) consisting of 1-(aminomethyl)cyclohexanecarbonyl residues (*cf. Figs. 1* and *2*). While the cyclohexane derivative forms ten-membered hydrogen-bonded rings, the characteristic secondary-structural motif in the cyclopropane derivatives is an eight-membered ring with H-bonding between next neighbors (*Fig. 1*). All cyclopropanecarbonyl moieties in the reported structures have the – generally more stable – s-*cis* ('bisected') conformation of the C=O groups on the three-membered rings (not preferred with the cyclohexane analog, the exocyclic CO group of which may be in an s-*trans*, a perpendicular, an axial, or an equatorial position). The bisecting effect and the large exocyclic bond angle (120°) in the cyclopropane units are proposed to provide the 'ordering' elements – on top of the staggering effect of the C(2)–C(3) ethane bond in all β-peptides – which lead to the observed substituent-induced turn formation. A high degree of intramolecular H-bonding is evident also from IR spectroscopy (*Fig. 3*), and concentration- and temperature-dependent NMR measurements (*Fig. 4*) of $CHCl_3$ and CD_2Cl_2 solutions, indicating that the boat-type arrangement of the eight-membered rings with their unusual H-bonding geometry (*Fig. 1, f*) is also present in solution. A possible structure of a poly[1-(aminomethyl)cyclopropane-carboxylic acid] consisting of a *flight of stairs* formed by folded H-bonded eight-membered rings is modelled, using the oligomer X-ray data (*Fig. 5*). The type of secondary structure found in the solid state of the $\beta^{2,2}$-peptides reported here is unprecedented in the realm of α-peptides and proteins.

1. Introduction. – In the course of our investigations on β-amino acids with substitution patterns that do not fit into the β-peptide secondary structures identified to date (helices [1–3], the pleated sheet [1][4], hairpins [4], and tubes [5])[2]), we have recently turned our attention to geminally disubstituted β-amino acids (disubstituted at C(α)-, $\beta^{2,2}$, or at C(β), $\beta^{3,3}$) [11], and we have already discovered a turn-forming motif adopted by a $\beta^{2,2}$-tripeptide consisting of 1-(aminomethyl)cyclohexanecarboxylic-acid residues [12][3]). Yet, we thought that additional (residue-controlled) conformations might be within reach with the corresponding cyclopropane derivatives; their β-peptide backbone experiences a further rotational constraint by hyperconjugation (*Walsh* orbitals → π*(C=O)) and by a change of geometry in that the exocyclic angle

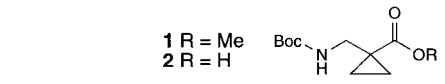
[1]) Part of the Ph. D. thesis of *S.A.*, Dissertation ETH-Zürich, No. 13203, 1999.

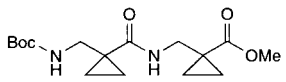
[2]) For helix and hairpin structures of β-peptides realized by incorporation of cyclic β- (and α)-amino acids (imposing backbone rotational restrictions), see the work by *Gellman* and co-workers [6–10].

[3]) β-Peptides consisting of β-homoproline residues have also been prepared and are, according to their distinct, intense CD spectra, candidates for a β-peptide secondary structure lacking H-bonds [13]!

$\tau(C(\beta)-C(\alpha)-CO)$ is larger than tetrahedral by more than 10°. In the present paper, we describe the synthesis and the structural investigation of β-peptides composed of 1-(aminomethyl)cyclopropanecarboxylic acid, the question being: is there yet another helical supramolecular structure formed by this class of β-peptides, or do they form a novel type of secondary structure?

2. Preparation of β-Peptides. – The β-peptides consisting of 1-(aminomethyl)cyclopropanecarbonyl moieties were synthesized by the same methodology as the non-cyclic $\beta^{2,2}$- and $\beta^{3,3}$-geminally dimethylated analogs [12]. The hydrogen trifluoroacetate salt of the methyl ester derived from **1**[4]) by Boc deprotection, was used for coupling with the corresponding Boc-protected $\beta^{2,2}$-amino acid **2**. The $\beta^{2,2}$-dipeptide derivative **3**, obtained in 70% yield on a six-gram scale, was Boc-deprotected and coupled once more with **2** to yield the $\beta^{2,2}$-tripeptide derivative **4** which was saponified to the tripeptide acid **5**. The *N*-deprotected β-tripeptide from **4** was then used for coupling with monomer **2** and with tripeptide acid **5**, to provide fully protected $\beta^{2,2}$-tetra- and $\beta^{2,2}$-hexapeptides **6** and **7**[5])[6]). Saponification of **7** required heating with NaOH at reflux in





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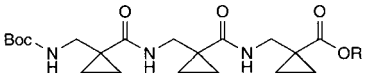
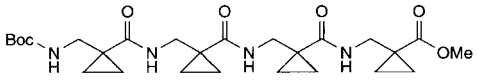


4 R = Me
5 R = H



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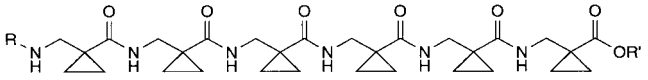
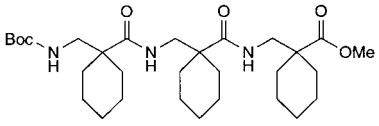


7 R = Boc, R' = Me
8 R = Boc, R' = H
9 R = TFA · H, R' = H



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[4]) The methyl ester **1** was prepared from methyl 1-cyanocyclopropane-1-carboxylate [14] according to a procedure previously described by us [12].

[5]) All coupling steps led to high yields (see *Exper. Part*).

[6]) The idea was to overcome the inability to produce suitable single crystals, which we have experienced with β-hexapeptides (exceptions are *Gellman*'s conformationally restricted compounds [6][7]), by preparing smaller oligomers (*cf.* the crystal structures of β-peptides in [1][4]).

CF_3CH_2OH to give $\beta^{2,2}$-hexapeptide acid **8**, the N-terminus of which was deprotected by TFA to yield $\beta^{2,2}$-hexapeptide **9**.

3. Structural Analysis. – 3.1 *X-Ray Crystal Structures.* Suitable samples for X-ray crystal-structure analysis could be obtained of the Boc-protected $\beta^{2,2}$-amino-acid derivatives **3**, **5**, and **6**, and the resulting structures are shown in *Fig. 1*, together with that of the *N*-Boc-acid building block **2**. All structures of the oligomers are characterized by eight-membered H-bonded rings between the amide NH of residue *i* and the carbonyl O-atom of residue $(i-2)$[7]), in a ribbon-like arrangement. The same H-bonding pattern is restored in **6**; however, the ribbon-like structure is not flat – as in the di- and tripeptide derivatives **3** and **5** – but forms a bend (*Fig. 1, d* and *e*); the first two eight-membered H-bonded rings in **5** and **6** are almost superimposable, but the third one in the structure of **6** is not in a position to continue the regular pleated-ribbon arrangement of the first two; rather, it folds back to form kind of a bowl, see *Fig. 1, e*.

The distances and angles of the intramolecular H-bonds in the crystals of **3**, **5**, and **6** are listed in *Table 1*; typically, the H-bond-donor and -acceptor atoms are *ca*. 2.9 Å apart [17]. The torsion angles in the crystal structures of the three oligomers are collected in *Table 2*. Interestingly, most angles in the di- and tetrapeptide derivatives **3** and **6** are similar to those found in the tripeptide acid **5**, but of opposite sign!

The secondary structures shown in *Fig. 1, b–e*, are not only without precedent in the α-peptide world, but they occur as a surprise also in the realm of β-peptides. On the one hand, the preference of the cyclopropane derivatives for eight-membered H-bonded ring formation contrasts with the folding propensities of unsubstituted β-amino-acid analogues (3-aminopropanoic acid): *Dado* and *Gellman* [18], and *Gung et al.* [19][20] have studied β-alanine (β-HGly) derivatives by FT-IR spectroscopy and have found that formation of intramolecular H-bonds between neighboring amide groups are unfavorable[8]). Thus, a distinct substituent and ring-size effect on intramolecular H-bonding in β-peptides has now been established.

On the other hand, the – likewise geminally disubstituted – $\beta^{2,2}$-tripeptide **10** constructed of 1-(aminomethyl)cyclohexanecarbonyl residues has been found to adopt a *ten*-membered H-bonded ring [12] see (*Fig. 2, d.*)

In any attempt to rationalize the effect of the cyclopropane ring on the β-peptide backbone structure and H-bonding pattern, we have to remember that cyclopropanecarbonyl derivatives (like cyclopropyl carbenium ions [21]) are subject to a hyperconjugative effect, favoring the so-called bisecting conformation (see *Fig. 2, a*). Both, the s-*cis*- and the s-*trans*-form are stabilized by interaction of the HOMO, π-type *Walsh* orbitals [22][23] of the cyclopropane ring with the LUMO, antibonding π^* orbital of

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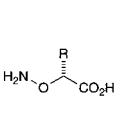
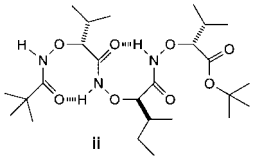
7) Comparable eight-membered rings were suggested by X-ray and NMR studies of oligomers composed of chiral α-aminooxy acids of type **i**, see **ii** [15][16]:



i



ii

8) Only β-alanine derivatives with a tertiary amide group were found to fold into the eight-membered ring [18].

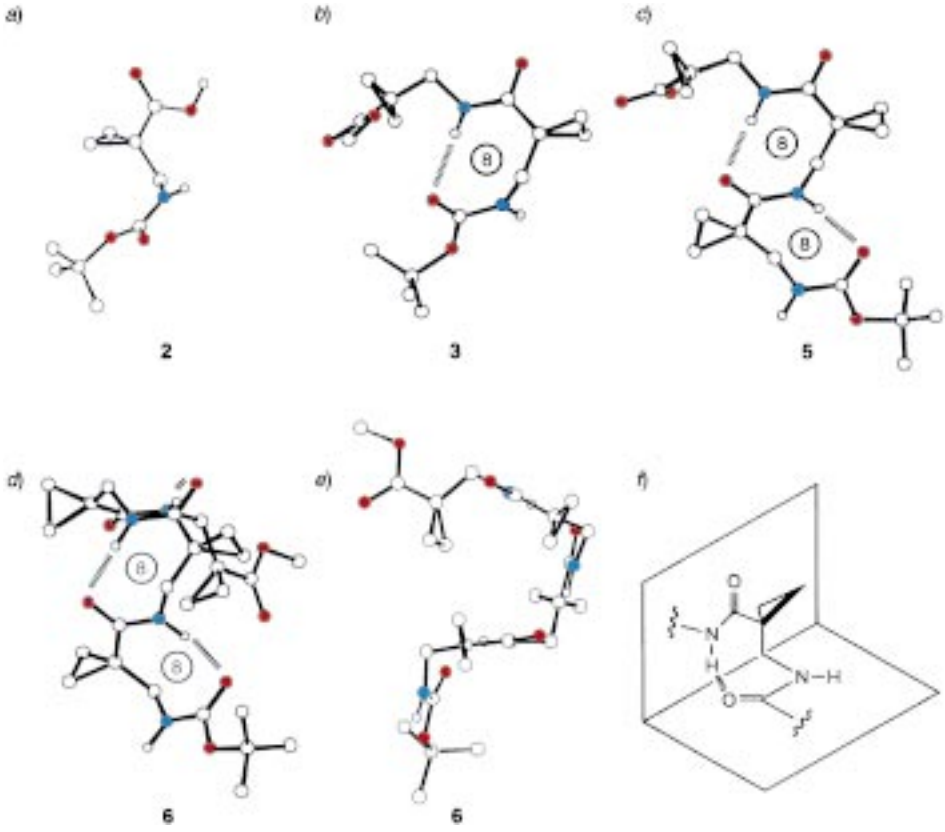


Fig. 1. *X-Ray crystal structures of the β-amino-acid derivative* **2** *and of the* $\beta^{2,2}$*-di-,* $\beta^{2,2}$*-tri-, and* $\beta^{2,2}$*-tetrapeptides* **3**, **5**, *and* **6**. *a*) 1-({[(*tert*-Butoxy)carbonyl]amino}methyl)cyclopropane-1-carboxylate (**2**). *b*), *c*), *d*) Structures of the di-, tri-, and tetrapeptide derivatives with a view on the N-terminal (**3**) and the two N-terminal (**5**, **6**) eight-membered H-bonded rings. *e*) Side view of the X-ray crystal structure of $\beta^{2,2}$-tetrapeptide derivative **6**. *f*) Boat-like eight-membered H-bonded ring. The structure of **2** is taken from [12].

Table 1. *Intramolecular H-Bond Parameters for the* $\beta^{2,2}$*-Homopeptides* **3**, **5**, *and* **6** *with an assumed N–H bond Length of 1.00 Å*

β-Peptide	Atoms[a])	Distance N···O [Å]	Angle NH···O [°]
3	H–N(2)···O(Boc)	3.02	+164.1
5	H–N(2)···O(Boc)	2.90	+156.6
	H–N(3)···O(1)	2.99	+166.9
6	H–N(2)···O(Boc)	2.80	+149.4
	H–N(3)···O(1)	2.89	+163.7
	H–N(4)···O(2)	3.14	+178.5

[a]) Donor group (H–N) and acceptor group (carbonyl O-atom) of the corresponding residues or of the Boc group. Residues are numbered starting from the N-terminus.

Table 2. *Torsion Angles Φ, Θ, and Ψ in the 1-(Aminomethyl)cyclopropanecarboxylic-Acid Units of the Crystal Structures of* **3**, **5**, *and* **6**. Angles Φ, Θ, and Ψ ([°]) on residues (1), (2), (3), and (4) are defined in *Fig. 5*.

Torsion angles [a])	**3**	**5**	**6**
$\Phi(1)$	−116.5	+110.5	−105.5
$\Theta(1)$	+70.0	−65.4	+71.3
$\Psi(1)$	+2.6	−8.8	+1.7
$\Phi(2)$	+147.5	+111.7	−110.8
$\Theta(2)$	+72.7	−73.4	+72.6
$\Psi(2)$	+2.6	−2.0	+1.8
$\Phi(3)$	–	−151.4	+118.0
$\Theta(3)$	–	−71.6	−69.5
$\Psi(3)$	–	–	+4.6
$\Phi(4)$	–	–	−92.9
$\Theta(4)$	–	–	+177.5
$\Psi(4)$	–	–	+3.3

[a]) The residues are numbered starting from the N-terminus of the peptide.

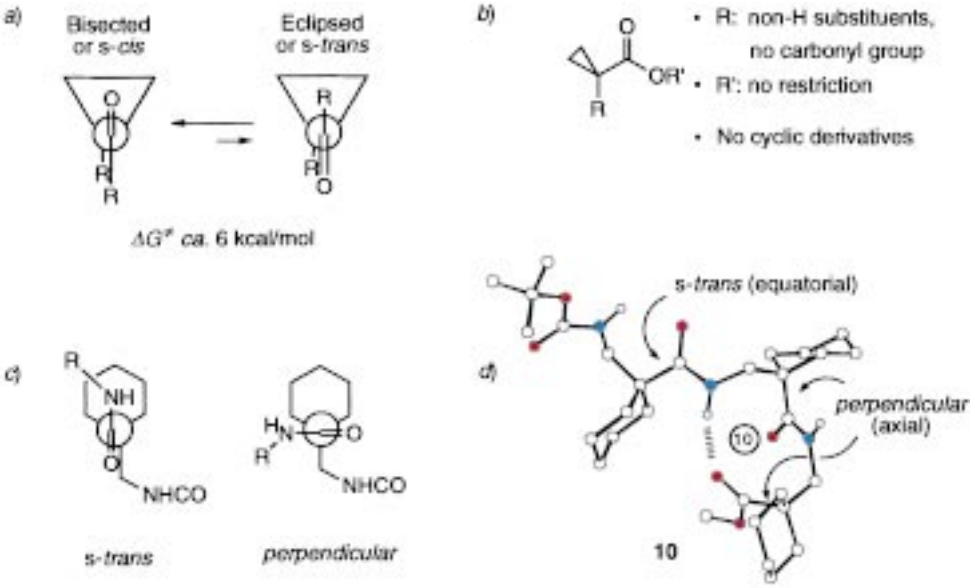


Fig. 2. *Conformations around the exocyclic C–CO bond in cyclopropyl ketones and cyclopropanecarboxylates, and a comparison with the cyclohexane analogs. a*) s-*cis* ('bisecting') and s-*trans* ('eclipsed') conformations of cyclopropyl methyl ketones, the energy difference ΔG^0 is reported to be 1.6–3 kcal/mol [28][29]. *b*) Starting structures for *CCDC* search with excluded substituents. 1,1-Dicarbonylcyclopropane derivatives and cyclic (spiro) compounds were excluded from the search. *c*) The two conformations around the C(α)–CO bond of the residues encountered in the crystal structure of $\beta^{2,2}$-tripeptide **10** consisting of 1-(aminomethyl)cyclohexanecarbonyl residues. *d*) X-Ray crystal structure of β-peptide **10** with a ten-membered H-bonded ring [12].

the C=O bond [24–26]. In the cyclopropanecarboxylic-acid derivatives **3**, **5**, and **6**, there is an s-*cis* conformation around the C(α)–CO bond in all residues. A search in the *Cambridge File* (*CCDC*) for structures as defined in *Fig. 2, b*, provided eleven X-ray crystal structures. Among these, seven have the s-*cis*- and three the s-*trans*-

conformation[9]), demonstrating the general preference for the former [27]. This is also indicated by theoretical [28], NMR [29][30], electron-diffraction [31], and CD [29][32] studies; the rotational barrier for the interconversion of the s-*cis*- and s-*trans*-conformers of cyclopropyl methyl ketones was calculated to be *ca.* 6 kcal/mol [28][29][10])[11])[12]). When going from the cyclopropane (**5**) to the cyclohexane (**10**) derivatives (*cf.* the structures in *Fig. 1, c* and *Fig. 2, d*), there is no more preference for a bisected conformation. Actually, the 'perpendicular' geometry of the transition state of rotation around the cyclopropyl–CO bond corresponds to an energy minimum for the cyclohexyl–CO bond (*Fig. 2, c* and *d*); there is no clear-cut preference for one conformation in the cyclohexane derivative. Thus, besides the ethane-staggering effect on the backbone of β-peptides (dihedral angle Θ, *see Fig. 5*) [37], the bisecting effect in the (aminomethyl)cyclopropanecarbonyl residues (dihedral angle Ψ) is an additional conformational lock, fixing the five atoms **H**–**N**–**C**(O)–**C**(CH_2)$_2$–**C**(H_2) in a common plane to form a boat-like eight-membered H-bonded ring with the next three atoms **N**(H)–**C**=**O** in the chain (see *Fig. 1, f*).

The enlarged exocyclic bond angle τ on the cyclopropane ring (*ca.* 120° in all structures **3**, **5**, **6**), compared to the angle of *ca.* 107° in the cyclohexane analog **10**, is presumably another structural feature contributing to the stability of the eight-membered H-bonded ring. The geometry of the N–H···O=C H-bonds is remarkable (see *Fig. 1, f*): the amide H-atom lies above the C=O plane. Normally, there is a distinct preference for N–H···O=C H-bonds to form approximately along the sp^2 lone-pair direction in the plane of the carbonyl group, according to statistical comparison of X-ray structures [38–40].

3.2. *NMR and IR Spectroscopy of the $\beta^{2,2}$-Peptides* **3**, **4**, **6**, *and* **7**. To gain information about the solution structure of these β-peptides, we have undertaken some IR and NMR measurements. The good solubility of the fully protected derivatives in aprotic solvents allowed for FT-IR measurements in $CHCl_3$. In dilute solution, inter- and intramolecular H-bonding is directly detectable by analysis of the N–H stretch region in the IR spectra [18][41–43]. It was to be expected that an increasing number of NH groups is intramolecularly H-bonded with increasing chain length (*cf. Fig. 1*). The IR spectra of the fully protected $\beta^{2,2}$-di-, -tri-, -tetra-, and -hexapeptides[13]) indeed display the expected tendency (*Fig. 3*). Assignment of the corresponding bands was facilitated by comparison with IR data of β-alanine derivatives [18–20][44–46]. The dipeptide derivative **3** shows little H-bonded N–H stretching at 3344 cm^{-1}; a much higher population of amide-amide H-bonding is indicated by the relative intensity of the two bands found for hexapeptide **7** (see the intense broad peak at 3285 cm^{-1} in *Fig. 3*). This

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[9]) Only one structure displayed an angle O=C–C(α)–R (– 129°), which did not fit into any of the two categories.

[10]) A value which is higher than that for the rotational barrier around a corresponding C=C–C or a O=C–C single bond ($\leq$ 2 kcal/mol for propene and acetaldehyde).

[11]) For a scholarly discussion of conformational effects in organic chemistry, see the textbook by *G. Quinkert*, *E. Egert*, *C. Griesinger* 'Aspect of Organic Chemistry – Structure', Verlag Helvetica Chimica Acta, Basel, and VCH, Weinheim, 1996.

[12]) Recently, the diastereoselective hydroboration of isopropenylcyclopropanes was rationalized as occurring *via* the more reactive s-*cis*-conformation [33]. For diastereoselective nucleophilic attack on cyclopropyl-substituted carbonyl compounds, see [34–36].

[13]) The peptide acids **5** and **8** are insoluble in $CHCl_3$ and could, therefore, not be included in this comparative study.

correlates with the proportions of the H-bonded to the non-H-bonded amide H-atoms in the crystal structures of **3**, **5**, and **6**, where this ratio increases gradually with chain length. When studying *intra*molecular H-bonding by this method, the existence of *inter*molecular aggregates should be excluded. As a representative example, β-tetrapeptide **6** was used for variable-concentration ^{1}H-NMR experiments which showed that no intermolecular aggregation occurred in the concentration range of 2–20 mM[14]). Thus, the observed IR bands at lower frequency (measured at 5 mM in $CHCl_3$) arise mainly from the intramolecularly bonded amide H-atoms.

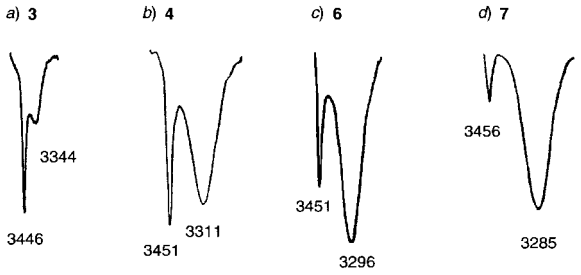

Fig. 3. *N–H Stretch region of the IR spectra of oligomers* **3**, **4**, **6**, *and* **7** *consisting of 1-(aminomethyl)cyclopropanecarbonyl moieties at 25°*. Concentration *ca.* 5 mM in $CHCl_3$, wavenumber in [cm^{-1}]. The sharp band at 3446–3456 cm^{-1} corresponds to the free N–H stretch and the broad band at 3285–3344 cm^{-1} to intramolecularly bonded amide N–H groups (concentration-dependent ^{1}H-NMR measurements show that there is little or no aggregation in a 5 mM $CHCl_3$ solution).

Alternatively, the degree of intramolecularity of H-bonding in peptides and proteins can be evaluated by temperature-dependent NMR measurements [37][47][48]. The ^{1}H-NMR spectra of the $\beta^{2,2}$-peptides **3**–**7** display well separated amide NH signals; in many instances, the NH signals are *triplets* with coupling constants of 5–7 Hz. The temperature coefficients ($\Delta\delta/\Delta T$) determined over the range of 75 K for the amide NH of β-peptide **6**[15]) are between -3.2 and -4.0 ppb/K, corresponding to the values observed for the NH signals in proteins (*Fig. 4*). In general, values from 0 to -4 ppb/K are correlated with solvent-inaccessible or H-bonded amide protons in protic solvents; if $\Delta\delta/\Delta T$ is between -6 and -10 ppb/K, the H-bonding interactions occur mainly between solute and solvent [47]. Thus, this analysis indicates that, at the concentration chosen, the NH protons in β-peptide **6** are strongly intramolecularly H-bonded.

3.3. *Model of a Possible Secondary Structure for H-($\beta^{2,2}$-HAc$_3$c)$_n$-OH.* The repetitive eight-membered turn motif stimulated the design of a model structure of a β-peptide consisting of 1-(aminomethyl)cyclopropanecarbonyl building blocks (*Fig. 5*). 'Ideal' values were assigned to the torsion angles; the resulting structure is a pleated ribbon, or a flight of stairs, the steps of which consist of the folded eight-membered H-bonded rings.

Continuing financial support from *Novartis Pharma* and *Agro*, Basel, is gratefully acknowledged. *T. Styner* has carried out some experiments described herein, as part of the advanced laboratory course in organic chemistry at the ETH-Zürich.

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14) The largest $\Delta\delta$ value (0.06 ppm) was measured for the NH(1), the Boc-NH proton, which is not involved in intramolecular H-bonding in the crystal structure. The $\Delta\delta$ values of the other three NH protons were in the range of 0.01–0.02 ppm. This suggests that **6** adopts the ribbon-type structure also in solution.

15) The *triplet* is retained for all NH protons at $-25°$; at $-50°$ the NH signals are broad singulets.

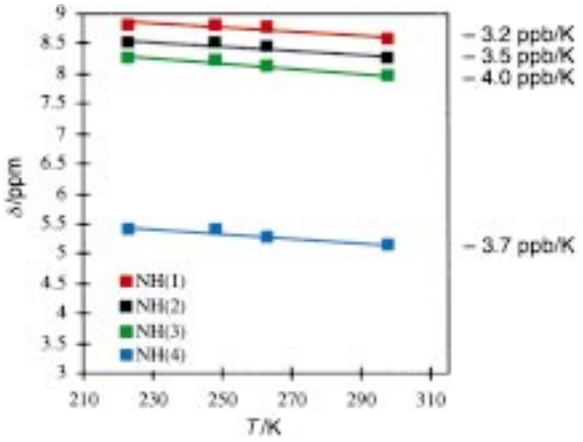

Fig. 4. *Temperature coefficients for the NH proton chemical shifts of the $\beta^{2,2}$-tetrapeptide derivative* **6** *measured over a range of 75 K* (at 25, −10, −25, and −50°) and calculated by linear regression. The NH protons are numbered according to their decreasing chemical shifts. 300-MHz ^{1}H-NMR Spectra were recorded at 25 mM in CD_2Cl_2.

Experimental Part

1. *General.* Abbreviations: Boc_2O: di(*tert*-butyl) dicarbonate, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, FC: flash chromatography, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum (0.01–0.1 Torr), β-HXaa (β-homoamino acid) [1][3], TFE: 2,2,2-trifluoroethanol, TFA: trifluoroacetic acid. $CHCl_3$ employed for the coupling reactions was filtered over Al_2O_3 (Alumina *Woelm N*, act. I) to remove EtOH. Et_3N was distilled from CaH_2 and stored under Ar. Solvents for chromatography and workup were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). Reagents were used as received from *Fluka* and *Quantum Biotechnologies*, Montreuil (EDC). TLC: *Merck* silica gel *60* F_{254} plates; detection with anisaldehyde (9.2 ml of anisaldehyde, 3.75 ml of AcOH, 12.5 ml of conc. H_2SO_4, 350 ml of EtOH) or ninhydrine (0.6 g of ninhydrine, 2 ml of AcOH, 13 ml of H_2O, 285 ml of BuOH). FC: *Fluka* silica gel *60* (40–63 μm); at *ca.* 0.3 bar. M.p.: *Büchi-510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-782* spectrophotometer. NMR Spectra: *Bruker AMX 400* (^{1}H: 400 MHz, ^{13}C: 100 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz. MS: *Hitachi Perkin-Elmer RHU-6M* (FAB, in a 3-nitrobenzyl-alcohol matrix) in *m/z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Boc Deprotection: General Procedures 1* (*GP 1*). Similarly to the reported procedure [1][3], the Boc-protected β-amino acid was dissolved in CH_2Cl_2 (0.5M) and cooled to 0°. An equal volume of TFA was added, and the mixture was allowed to warm slowly to r.t. and stirred for further 1.5 h. Concentration under reduced pressure, co-evaporation with CH_2Cl_2, and drying of the residue under h.v. yielded the crude TFA salt, which was identified by NMR and FAB-MS, and used without further purification.

3. *Peptide Coupling with EDC: General Procedure 2* (*GP 2*). The appropriate TFA salt was dissolved in $CHCl_3$ (0.5M) and cooled to 0°. This soln. was treated successively with Et_3N (4 equiv.), HOBt (1.2 equiv.), a soln. of the Boc-protected fragment (1 equiv.) in $CHCl_3$ (0.25M), and EDC (1.2 equiv). The mixture was allowed to warm to r.t. After TLC displayed complete reaction (12 h–3 d), the mixture was diluted with $CHCl_3$, followed by thorough washing with 1N HCl, sat. aq. $NaHCO_3$ (3×), and NaCl soln. (1×). The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure. FC or recrystallization yielded the pure peptide.

4. *β-Peptides. Methyl 1-({[(*tert*-Butoxy)carbonyl]amino}methyl)cyclopropane-1-carboxylate* (Boc-$\beta^{2,2}$-HAc_3c-OMe; **1**)[16]. Methyl 1-cyanocyclopropane-1-carboxylate [14] (12.40 g, 97.6 mmol) was transformed as described in [12]. FC (Et_2O/pentane 1:2) yielded **1** (15.88 g, 71%). Colorless oil. A second batch yielded **1**

[16]) The nomenclature of the 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives is proposed in analogy to the corresponding 1-aminocycloalkanecarboxylic-acid derivatives [49].

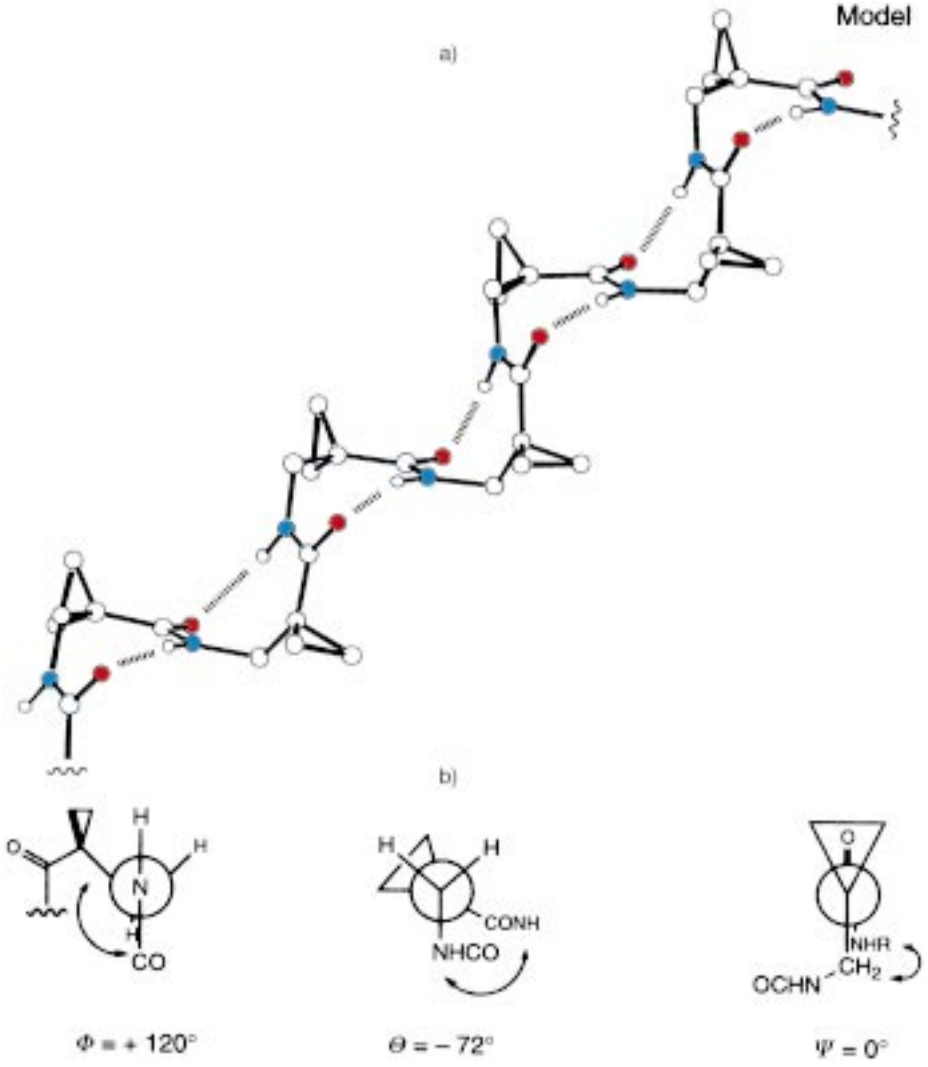

Fig. 5. a) *Model for a possible pleated-ribbon or stair-like structure of β-peptides consisting of 1-(aminomethyl)cyclopropanecarbonyl residues.* b) *For the torsion angles Φ, Θ, and Ψ used for the construction of the model*, cf. *the crystal structure of* **5**. The model was generated with MacMoMo (program by Prof. Dr. *M. Dobler*, ETH-Zürich).

(10.45 g, 69%). B.p. 77°/0.3 Torr. R_f (Et_2O/pentane 1:2) 0.32. IR, ^{1}H-NMR, ^{13}C-NMR, and FAB-mass spectra: corresponding to [12]. Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found: C 57.61, H 8.08, N 6.05.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OMe (**3**)**.** Compound **1** (6.00 g, 26.2 mmol) was Boc-deprotected according to *GP 1*. The resulting TFA salt was coupled with Boc-β^{2,2}-HAc$_3$c-OH (**2**; 5.63 g, 26.2 mmol) according to *GP 2* for 62 h. Recrystallization (Et_2O/pentane) yielded **3** (5.98 g, 70%). Colorless crystals, suitable for X-ray analysis. M.p. 121.5–122.5°. R_f (AcEt/pentane 2:1) 0.54. IR ($CHCl_3$): 3446*m*, 3344*m*, 3007*s*, 2473*w*, 1709*s*, 1648*s*, 1515*s*, 1439*s*, 1392*m*, 1367*s*, 1058*w*, 1034*m*, 979*m*, 863*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.69–0.72 (*m*, 2 CH); 0.93–0.96 (*m*, 2 CH); 1.17–1.23 (*m*, 4 CH); 1.45 (*s*, *t*-Bu); 3.30 (*d*, $J = 6.3$, CH_2N); 3.43 (*d*, $J = 5.9$, CH_2N); 3.73 (*s*, MeO); 4.97 (br., NH); 7.27 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.02, 14.82 (CH_2); 24.28, 25.20 (C); 28.35 (Me);

42.71, 44.87 (CH_2); 52.01 (Me); 79.90 (C); 156.48, 172.91, 175.10 (C). EI-MS: 326 (< 1, M^+), 224 (82.7), 193 (100), 124 (82.2). Anal. calc. for $C_{16}H_{26}N_2O_5$ (326.39): C 58.88, H 8.03, N 8.58; found: C 58.90, H 7.92, N 8.45.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OMe (**4**). Compound **3** (5.95 g, 18.3 mmol) was Boc-deprotected according to *GP 1*. The resulting TFA salt was coupled overnight with **2** (3.93 g, 18.3 mmol) according to *GP 2*. Recrystallization (Et_2O/AcOEt/pentane 5:1:10) yielded **4** (6.27 g, 80%). White powder. M.p. 131–133°. R_f (AcOEt/pentane 2:1) 0.37. IR ($CHCl_3$): 3451*w*, 3311*w*, 3087*w*, 3005*m*, 2451*w*, 1696*s*, 1642*s*, 1561*m*, 1516*s*, 1439*m*, 1367*m*, 1162*s*, 1034*w*, 980*w*, 940*w*, 860*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.66–0.69 (*m*, 2 CH); 0.72–0.75 (*m*, 2 CH); 0.88–0.91 (*m*, 2 CH); 1.18–1.28 (*m*, 6 CH); 1.44 (*s*, *t*-Bu); 3.32 (*d*, $J = 6.8$, CH_2N); 3.42 (*d*, $J = 6.2$, CH_2N); 3.45 (*d*, $J = 5.6$, CH_2N); 3.71 (*s*, MeO); 5.04 (br. *t*, $J = 6.8$, NH), 7.84 (br., NH); 7.92 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.56, 14.60, 14.64 (CH_2); 23.94, 25.07, 25.44 (C); 28.36 (Me); 42.55, 43.82, 44.76 (CH_2); 51.97 (Me); 80.55, 157.11, 172.78, 173.65, 174.96 (C). FAB-MS: 848 (< 1, $[2M+1]^+$), 847 (1.8, $[2M]^+$), 425 (27.3, $[M+1]^+$), 424 (100, M^+). Anal. calc. for $C_{21}H_{33}N_3O_6$ (423.51): C 59.56, H 7.85, N 9.92; found: C 59.54, H 7.79, N 9.89.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OH (**5**). A soln. of **4** (3.19 g, 7.53 mmol) in MeOH (37 ml, 0.2M) was treated with a soln. of LiOH (0.45 g, 18.8 mmol) in H_2O (18 ml) at r.t. After stirring at r.t. for 1–3 d, the mixture was extracted with Et_2O (2×). The soln. was adjusted to pH 2 at 0° with 10% HCl and extracted with Et_2O (3×). The org. phase was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization (CH_2Cl_2) and drying under h.v. over P_2O_5 yielded **5** (2.44 g, 79%). M.p. 184–185.5°. R_f (MeOH/CH_2Cl_2 1:9) 0.48. IR ($CHCl_3$): 3450*w*, 3303*w*, 3008*m*, 1695*s*, 1638*m*, 1569*m*, 1517*m*, 1369*m*, 1041*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.77–0.84 (*m*, 4 CH); 0.88–0.96 (*m*, 2 CH); 1.12–1.21 (*m*, 6 CH); 1.44 (*s*, *t*-Bu); 3.28 (*s*, CH_2N); 3.40–3.44 (*m*, 2 CH_2N); 8.09 (br., NH); 8.40 (br., NH). ^{13}C-NMR (100 MHz, CD_3OD, rotamers!): 14.72, 14.90, 14.96 (CH_2); 24.23, 26.06, 26.75, 26.78 (C); 28.83 (Me); 44.00, 44.14, 44.48, 44.60, 45.16 (CH_2); 80.71, 159.27, 175.31, 176.51, 176.59, 177.89 (C). FAB-MS: 857 (< 1, $[2M+K]^+$), 841 (9.2, $[2M+Na]^+$), 819 (5.4, $[2M]^+$), 432 (31.9, $[M+Na]^+$), 411 (28.8, $[M+1]^+$), 410 (100, M^+). Anal. calc. for $C_{20}H_{31}N_3O_6$ (409.48): C 58.66, H 7.63, N 10.26; found: C 58.59, H 7.70, N 10.24.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OMe (**6**). Compound **4** (150 mg, 0.35 mmol) was Boc-deprotected according to *GP 1*. The resulting TFA salt was coupled with **2** (75 mg, 0.35 mmol) according to *GP 2* for 20 h. Recrystallization (AcOEt) yielded **6** (170 mg, 93%). Colorless crystals, suitable for X-ray analysis. M.p. 145°. R_f (CH_2Cl_2/MeOH 15:1) 0.33. IR ($CHCl_3$): 3451*w*, 3296*m*, 3092*w*, 3007*m*, 1692*s*, 1634*s*, 1573*s*, 1517*s*, 1439*m*, 1368*s*, 1163*s*, 1051*w*, 1035*w*, 980*w*, 943*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.63–0.74 (*m*, 4 CH); 0.76 (*dd*, $J =$ 6.8, 3.9, 2 CH); 0.86–0.93 (*m*, 2 CH); 1.18–1.24 (*m*, 4 CH); 1.26–1.29 (*m*, 4 CH); 1.45 (*s*, *t*-Bu); 3.32 (*d*, $J = 7.0$, CH_2N); 3.38 (*d*, $J = 6.3$, CH_2N); 3.40 (*d*, $J = 6.6$, CH_2N); 3.46 (*d*, $J = 5.6$, CH_2N); 3.71 (*s*, MeO); 5.06 (*t*, $J = 7.0$, NH); 8.07 (*t*, $J = 5.4$, NH); 8.31 (br., NH); 8.62 (br. *t*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.47, 14.77, 14.97, 15.03 (CH_2); 23.82, 25.25, 25.46, 25.52 (C); 28.35 (Me); 42.30, 43.69, 43.90, 44.74 (CH_2); 51.97 (Me); 80.79, 157.40, 173.03, 173.69, 174.34, 174.90 (C). FAB-MS: 543 (2.7, $[M+Na]^+$), 521 (100, M^+). Anal. calc. for $C_{26}H_{40}N_4O_7$ (520.62): C 59.98, H 7.74, N 10.76; found: C 59.99, H 7.68, N 10.68.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OMe (**7**). Compound **4** (2.413 g, 5.7 mmol) was Boc-deprotected according to *GP 1*. The resulting TFA salt was coupled overnight with **5** (2.34 g, 5.7 mmol) according to *GP 2*, except that **5** was dissolved in DMF (10 ml) instead of $CHCl_3$ prior to addition. Recrystallization (CH_2Cl_2/pentane) yielded **7** (3.56 g, 87%). White powder. M.p. 190° (sintering at 118–120°). R_f (MeOH/CH_2Cl_2 1:10) 0.55. IR ($CHCl_3$): 3456*w*, 3285*m*, 3086*w*, 3004*m*, 1689*m*, 1630*s*, 1582*m*, 1516*m*, 1439*m*, 1367*m*, 1163*m*, 1036*w*, 980*w*, 945*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.68–0.82 (*m*, 10 CH); 0.86–0.90 (*m*, 2 CH); 1.18–1.29 (*m*, 12 CH); 1.45 (*s*, *t*-Bu); 3.32–3.46 (*m*, 6 CH_2N); 3.70 (*s*, MeO); 5.15 (br. *t*, $J = 6.9$, NH); 8.10 (br. *t*, $J = 5.4$, NH); 8.41 (*br.*, NH); 8.80 (br. *t*, $J = 6.2$, NH); 8.96–9.01 (*m*, 2 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.49, 14.76, 15.09, 15.37, 15.43 (CH_2); 23.81, 25.30, 25.52, 25.64, 25.66, 25.72 (C); 28.36 (Me); 42.28, 43.60, 43.78, 43.89, 43.94, 44.73 (CH_2); 51.96 (Me); 80.84, 157.51, 173.10, 174.05, 174.61, 174.64, 174.93 (C). FAB-MS: 737 (5.6, $[M+Na]^+$), 715 (100, $[M+1]^+$). Anal. calc. for $C_{36}H_{54}N_6O_9$ (714.86): C 60.49, H 7.61, N 11.76; found: C 60.41, H 7.62, N 11.73.

Boc-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-OH (**8**). A soln. of **7** (0.125 g, 0.175 mmol) in TFE (0.9 ml) was heated under reflux with a soln. of LiOH (0.20 g, 8.75 mmol) in H_2O (0.4 ml) for 6 h. The product was precipitated by adding 1N HCl to the soln. at 0°. After evaporation of TFE under reduced pressure, crude **8** was filtered and washed intensively with H_2O. Recrystallization (CH_2Cl_2/pentane, −20°) yielded **8** (100 mg, 82%). White powder. M.p. 198°. R_f (MeOH/CH_2Cl_2 1:9) 0.31. IR ($CHCl_3$): 3686*w*, 3448*m*, 3281*m*, 3082*m*, 3008*m*, 2933*m*, 1691*m*, 1628*s*, 1518*m*, 1440*m*, 1369*m*, 1164*m*, 1037*w*, 946*m*. ^{1}H-NMR (400 MHz, CD_3OD): 0.78–0.90 (*m*, 12 CH); 1.10–1.20 (*m*, 12 CH); 1.44 (*s*, *t*-Bu); 3.27 (*s*, CH_2N); 3.40–3.42 (*m*, 5 CH_2N); 8.55–8.58 (br. *t*, $J = 6.0$, NH). ^{13}C-NMR (100 MHz, CD_3OD): 14.74, 14.91, 15.17 (CH); 24.21,

26.06, 26.40, 26.43, 26.47, 26.77 (C); 28.83 (Me); 43.93, 44.43, 44.55, 45.08 (CH_2); 80.76 (C); 159.30, 175.33, 176.12, 176.23, 176.29, 176.74, 177.86 (C). FAB-MS: 739 (1.4, $[M+K]^+$), 723 (16.1, $[M+Na]^+$), 702 (36.2, $[M+1]^+$), 701 (100, M^+).

H-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-β^{2,2}-HAc$_3$c-COH (**9**). Compound **8** (98 mg, 0.136 mmol) was Boc-deprotected according to *GP 1* (in pure TFA). The crude product was precipitated with $CHCl_3$/pentane to yield the TFA salt of **9** (22 mg, 27%). White solid. M.p. 203°. IR (KBr): 3274*s*, 3080*s*, 3000*s*, 2934*s*, 1718*s*, 1636*s*, 1439*s*, 1362*s*, 1272*s*, 1204*s*, 1036*s*, 947*s*, 703*m*. ^{1}H-NMR (400 MHz, CD_3OD): 0.80–0.90 (*m*, 10 CH); 1.09–1.21 (*m*, 12 CH); 1.28–1.32 (*m*, 2 CH); 3.10 (*s*, CH_2N); 3.40 (*m*, 10 CHN); 8.06–8.08 (*m*, NH); 8.48 (*t*, *J* = 5.8, NH); 8.59 (*t*, *J* = 5.8, NH). ^{13}C-NMR (100 MHz, CD_3OD): 14.54, 14.88, 15.00 (CH_2); 23.42, 24.24, 26.15, 26.41, 26.47, 26.54 (C); 43.91, 44.11, 44.43, 44.48, 45.82 (CH_2); 175.37, 176.08, 176.25, 176.31, 176.44, 177.90 (C). FAB-MS: 602 (28.3, $[M+1]^+$), 601 (75.1, M^+).

6. *X-Ray Crystal-Structure Determination of* **3**, **5**, *and* **6** (see *Fig. 1*, and *Tables 1* and *2*). The intensities were collected on a *Nonius CAD-4* diffractometer (graphite monochromized CuK_α radiation, $\lambda = 1.5418$ Å). The structures were solved by direct methods with SIR-92 [50] and refined by full-matrix least-squares analysis with SHELXL-93 [51] (for **3**) and SHELXL-97 [52] (for **5** and **6**) (heavy atoms anisotropic, H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-129239 (**3**), CCDC-129240 (**5**), and CCDC-129241 (**6**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. *Crystallographic Data for the β^{2,2}-Peptides* **3**, **5**, *and* **6**

	3	**5**	**6**
Crystallized from	AcOEt	MeOH	AcOEt
Empirical formula	$C_{16}H_{26}N_2O_5$	$C_{20}H_{31}N_3O_6$	$C_{26}H_{40}N_4O_7$
Crystal temp. [K]	295	258	273
Crystal dimensions [nm]	0.3 × 0.2 × 0.2	0.25 × 0.25 × 0.2	0.25 × 0.25 × 0.25
Crystal system	monoclinic	triclinic	triclinic
Space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
Lattice parameters			
2θ range [°]	$3.19 < 2\theta < 64.95$	$2.91 < 2\theta < 59.95$	$3.37 < 2\theta < 64.93$
a [Å]	5.963(1)	9.538(2)	10.133(2)
b [Å]	27.741(2)	15.165(2)	11.769(2)
c [Å]	11.003(1)	15.342(2)	13.975(2)
α [°]	90	83.23(1)	73.10(1)
β [°]	102.59(1)	83.64(2)	73.03(1)
γ [°]	90	82.94(2)	65.97(1)
V [Å^3]	1776.3(4)	2176.5(6)	1427.4(4)
Z	4	4	2
ρ_{calc} [g cm^{-3}]	1.220	1.250	1.211
μ [mm^{-1}]	0.748	0.765	0.726
Total reflections measured	3251	6904	5146
Independent reflections	2985	6443	4842
Reflections observed	2466	4991	4052
Criterion	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Variables	235	589	380
Final $R(F)$	0.0402	0.0440	0.0494
$wR(F^2)$	0.1043	0.0938	0.1295
Goodness of fit	3.680	3.144	1.051
$\Delta\rho$ (max, min) [eÅ^{-3}]	0.193, −0.172	0.264, −0.236	0.409, −0.308

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Received July 7, 1999