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FEATURE ARTICLE

β-Peptides: a surprise at every turn

Dieter Seebach* and Jennifer L. Matthews

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland

β-Peptides, *i.e.* oligomers of β-amino acids, containing as few as six residues may form surprisingly stable helices, with half-lives for the H/D exchange of the central NH protons of up to several days. Furthermore, these β-peptides (carrying the side chains of familiar α-amino acids such as Ala, Val, Leu, Phe, Lys in the 2- and/or 3-position of their 3-amino carboxylic moieties) have been shown to be stable to common peptidases for at least two days. In this article, a brief account of the results obtained since we started work in this area in early 1995 is given. The synthesis of enantiopure β-amino acids can be achieved by homologation of α-amino acids. The greater structural variability of β-amino acids leads to an even greater multitude of possible β-peptide primary and secondary structures. Circular dichroism, NMR and X-ray investigations have unveiled helical, pleated-sheet and tubular arrangements of linear and cyclic β-peptides composed of up to twelve β-amino acids. The prospects for the use of β-peptides as drugs, the construction of large, enzymatically-active β-proteins and their interaction with the natural, α-peptidic counterparts are discussed.

Polymers derived from β-amino acids (so-called Nylon-3 derivatives[1]) have been the subject of many investigations in the past few decades. In particular, those[2] derived from aspartic acid (the only proteinogenic β-amino acid) have attracted much attention. There has also been some—rather speculative—conjecture concerning the possibility that β-peptides might form secondary structures.[3] Even given this, three years ago, whenever we succeeded in eliciting an opinion from specialists, they were convinced that the extra carbon atom and hence, the additional 'freely-rotating' C–C σ-bond in the β-amino acid building blocks would result in β-peptides having a lower tendency to form highly ordered structures than the analogous natural α-peptides.

This question had been frequently asked because, at the start of 1995, we began to tackle a project that we had been contemplating for a long time—namely, replacing the oxygens in the chain of oligo-(*R*)-3-hydroxybutanoates[4] (oligo-HB) by NH groups in the hope that we would see whether the helical substructures found[5] in the crystalline oligolides of HB [Fig. 1(*a*)] would be stabilised by hydrogen bonds. Since then, it has turned out that the first of the β-hexapeptides we prepared[6] (from homologated valine, alanine and leucine) formed a helix when dissolved in MeOH [Fig. 1(*b*)]. Furthermore, it was found[6,7] to be stable against the peptidase pepsin. The results of the last two years have sparked off a flurry of activity and reports have now appeared with titles such as

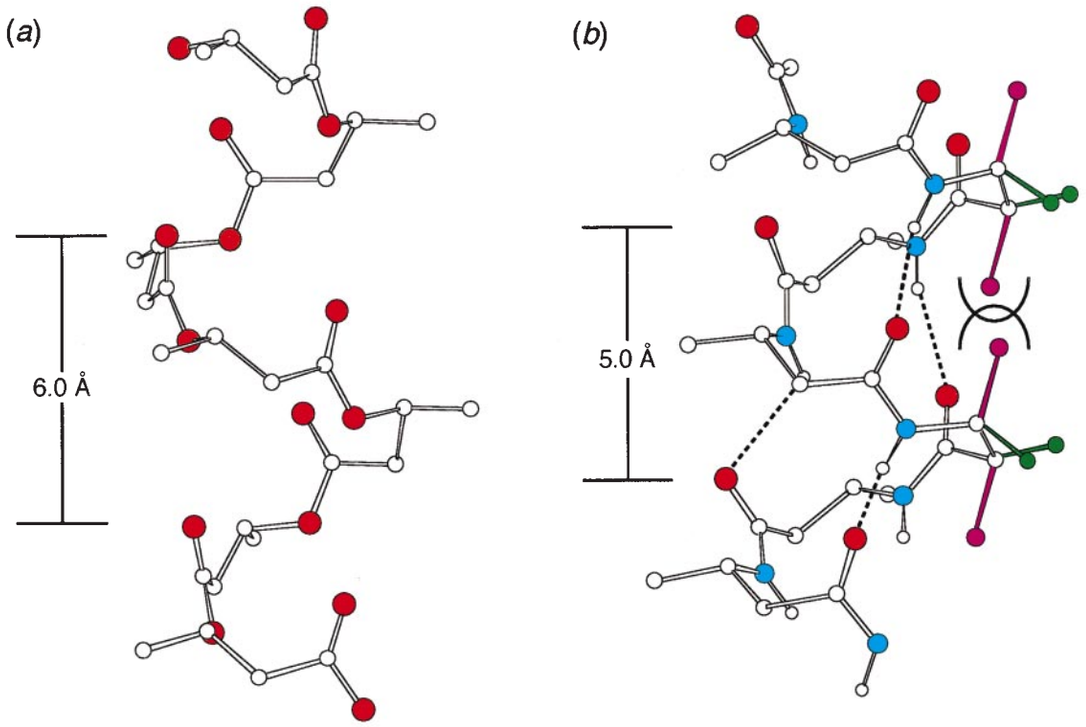


Fig. 1 (*a*) Left handed or (*M*) 3_1 helix of (*S*)-3-hydroxybutanoate (HB), modelled using X-ray structural parameters obtained from HB oligolides. The C=O bonds are approximately parallel to the helix axis and their oxygen atoms are close to the backbone oxygens. Top: O terminus, bottom: C terminus. (*b*) Idealised (*M*) 3_1 helix (crystallographic nomenclature) or 3_{14} helix (peptide nomenclature) of a β-peptide; top: N terminus, bottom: C terminus. Lateral substitution (substituents coloured green) does not break up the helix; axial substitution (purple substituents) prevents helix formation. (Taken with permission from ref. 6.)

'Betas are brought into the fold', 'β-Peptides: Novel secondary structures take shape', 'β-Peptides: nature improved?' and 'Molecules without life: the search for artificial proteins'.[8]

In the following sections, we will first discuss the preparation of the β-amino acids and the β-peptides constructed from them. The subsequent sections will compare and contrast the properties and structures of β-peptides investigated to date with those of α-peptides (peptides consisting of natural and unnatural α-amino acids).

β-Amino acid preparation

A glance through the eyes of a synthetic chemist at the formulae of an α- and β-amino acid immediately tells you that there is a much wider variety of possible strategies for the synthesis of the latter (Fig. 2). Furthermore, as you move from an α- to a β-amino acid (Fig. 3), the incorporation of an additional carbon atom between the carboxy and the amino groups results in an enormous increase in the number of possible constitutional and configurational isomers. A recently published book[9] reviews the methods available for the synthesis of β-amino acids and one of the chapters[10] deals with the method that we have made the most use of, namely, the Arndt–Eistert homologation [Scheme 1, route (*a*)]. Clearly, the big advantage of this reaction sequence is that the enantiomerically pure β-amino acid derivatives are readily prepared from the appropriate α-amino acid (for instance, with peptidic side chains[7]). Furthermore, reaction of the resulting β-amino acid derivatives leads[11] easily to the α,β-disubstituted compounds [Scheme 1, route (*b*)]. For the preparation of β-amino acids with the side chain in the α-carbonyl position [Scheme 1, route (*c*)], we turned to Evans' chiral auxiliary methodology.[12,13] Enantiomerically pure cyclic derivatives, such as *trans*-2-aminocyclopentanecarboxylic acid and *trans*-2-aminocyclohexanecarboxylic acid, have been prepared by other methods and also subsequently used in the construction of β-peptides.[14,15]

Before proceeding any further, we must first mention the nomenclature we have adopted for the description of β-amino acids and β-peptides. The derivatives with 'natural' side chains in the 2- or 3-position are described as H-β^2-Xxx-OH and H-β^3-Xxx-OH, respectively. β-Peptides built exclusively from one of these two types of β-amino acids are defined as β^2- or β^3-peptides, respectively [Fig. 4(*b*) and (*c*)].

β-Peptide preparation

In our own work we have, in the main, incorporated the sequence β-HVal-β-HAla-β-HLeu into the β-peptides. This is due to the fact that α-peptides with the analogous sequence Val-Ala-Leu have been the subject of numerous structural investigations (above all, those[16] of Karle *et al.*). We also hoped that this approach would facilitate the best possible comparison between the two types of peptides without reference to the distorted picture that would result from a restriction of conformational freedom.[14,15]

We have used[6,7,17–20] the well-established methods of peptide synthesis for the coupling of the β-amino acids, making use of Z-, Boc- or Fmoc-protected amino groups, methyl or benzyl esters for the acid terminus and, usually, carbodiimide methods for the coupling step. We have principally performed

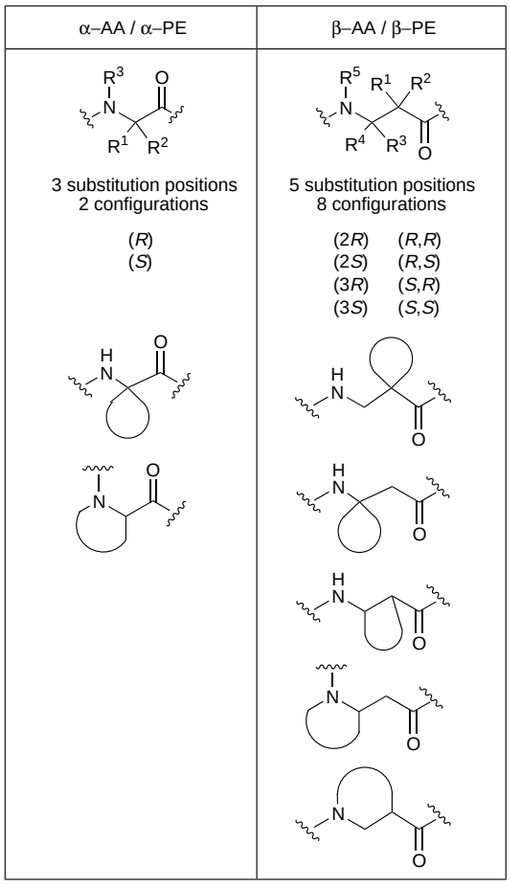
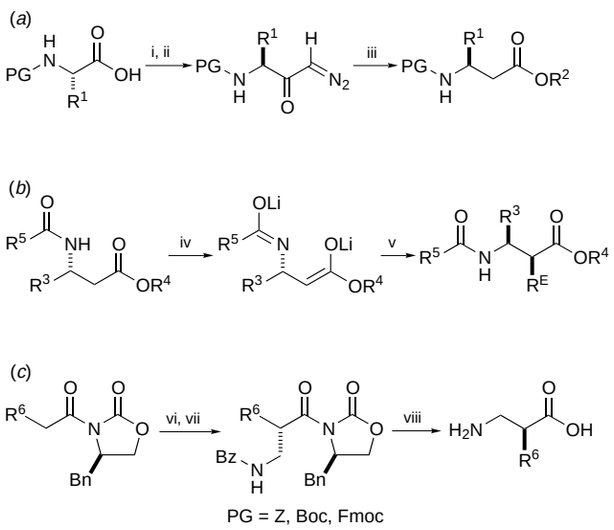


Fig. 3 Contrasting substitution patterns and configurations of α- and β-amino acid residues in peptides



Scheme 1 *Reagents and conditions*: i, $ClCO_2Et$, NEt_3, THF; ii, CH_2N_2, Et_2O; iii, Ag^+, NEt_3, R^2OH; iv, $LiNR_2$, LiCl; v, electrophile (R^EX); vi, $TiCl_4$, NEt_3; vii, $BzNHCH_2Cl$; viii, hydrolysis

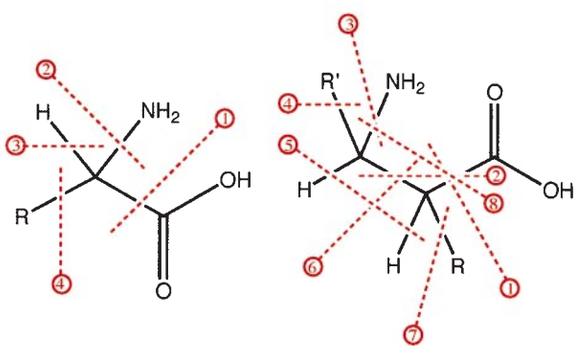


Fig. 2 Retrosynthetic analysis of an α- and a β-amino acid. The numbers ①–⑧ indicate the bond(s) made in the corresponding synthesis. For literature on α- and β-amino acid syntheses, see textbooks, monographs and a book (ref. 9), which has appeared recently.

these procedures in solution but have recently begun to investigate the use of solid phase techniques.[21] The yields of the coupling steps are excellent; racemisation or epimerisation is not possible for the β³-amino acids and we only occasionally observe a loss of configurational purity with the β²-amino acids. The products have been purified by preparative HPLC and their composition has been determined by both mass spectrometry and degradation of the component amino acids. To date, β-oligopeptides built from up to twelve amino acids have been prepared (the different types are shown in Fig. 4) including the β-peptides **1**–**14**, which are the objects of discussion in the following sections.

CD spectra of β-peptides

Circular dichroism is a powerful tool for the detection and determination of the secondary structures of α-peptides. Thus the most common, so-called α-helix of α-peptides[22] [a right handed or (*P*) 3.6_1 helix with a pitch of 5.6 Å containing 13-membered hydrogen bonded rings] gives rise to CD minima at *ca*. 208 and 222 nm. A chain of at least 15 amino acid residues is required for this helix to be observed in protic solvents such as water or MeOH. Most helical substructures of proteins and enzymes consist of 10–15 amino acids. In contrast, and to everybody's great surprise, β³- and β²-oligopeptides (*e.g.* **1** and **9**, respectively) built of only six or seven (*S*)-β-amino acids† show[6,13,17,21] an intense CD minimum at *ca*. 215 nm, followed by a maximum at *ca*. 200 nm in MeOH [Fig. 5(*a*)], a pattern which is independent of the presence or absence of terminal protecting groups and of the concentration (0.02 to 1 mM). Within this series, the most intense CD absorptions were observed[23] with the β²,³-hexapeptide **3** consisting of β-amino acids with methyl groups in the 2-position and the side chains Val, Ala and Leu in the 3-position‡ [(*S*,*S*)-β³-HXxx(2-Me)] [Fig. 5(*a*)]. Yet another surprise came when we measured[20,25] the CD spectra of mixed β-peptides **4**–**8** containing β²- and β³-amino acid moieties: depending upon the sequence of these isomeric building blocks in the chain and upon the presence or absence of terminal protecting groups, the corresponding peptides showed either the familiar 215/200 nm extrema or a

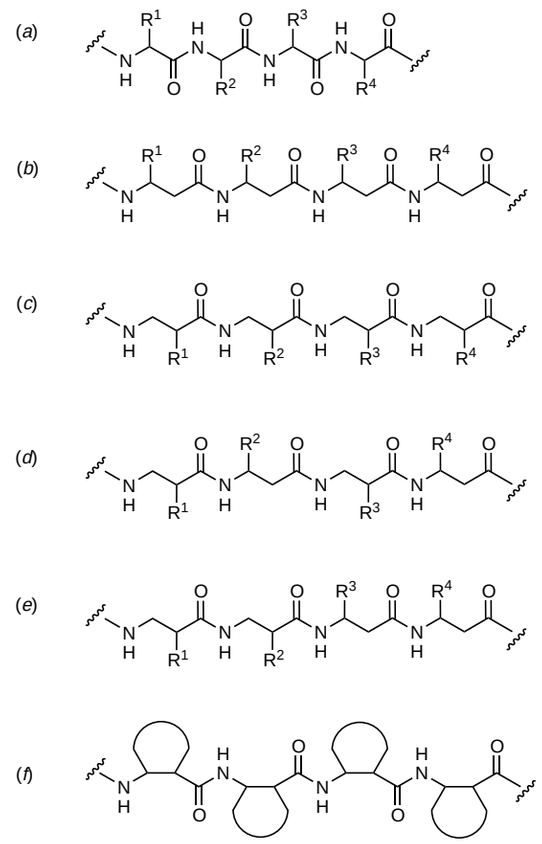
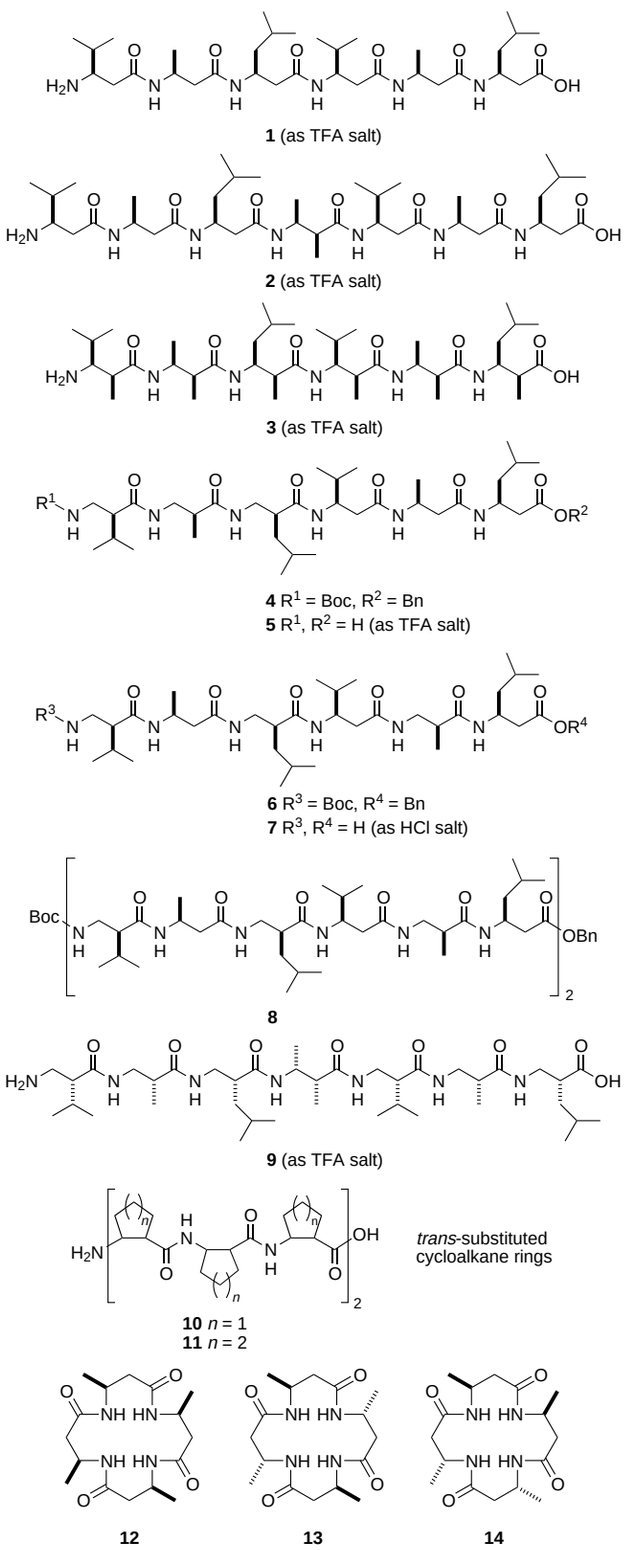


Fig. 4 (*a*) An α-peptide. (*b*) A β³-peptide: a β-peptide consisting of β-substituted β-amino acids. (*c*) A β²-peptide: a β-peptide consisting of α-substituted β-amino acids. (*d*) A β-peptide consisting of alternating β²- and β³-amino acids. (*e*) A β-peptide consisting of block-coupled β²- and β³-amino acids. (*f*) A β-peptide consisting of aminocycloalkanecarboxylic acids.



single intense maximum at *ca*. 205 nm [Fig. 5(*b*) and (*c*)], which is again essentially concentration independent. From NMR investigations, we can conclude that the former CD pattern is caused by a left-handed helix and the latter one by an as yet unknown, different secondary structure (see following section). The CD spectrum of an oligomer **10** built from (*R*,*R*)-2-aminocyclopentanecarboxylic acid shows a concentration independent minimum at *ca*. 221 nm and a maximum at 204 nm.[15]

Solution structures of β-peptides determined by NMR spectroscopy

Full NMR analyses (COSY, TOCSY, HSQC, HMBC, ROESY, NOE restrained modelling) have been performed[6,15,17,23,25] on the β^3-hexapeptides **1** and **2**, the β^{2,3}-hexapeptide **3**, the mixed β-hexapeptide **7**, the β^2-heptapeptide **9** and the derivative **10** containing cyclopentane rings. The result is that those β-peptides containing no ring and having identical configuration and substitution pattern of the amino acids adopt a 3_1-helical conformation in both [$^2H_5$]pyridine or CD_3OH solution [Fig. 6(*a*)]. These are left-handed or (*M*) helices for peptides containing amino acid residues with stereocentres of (*S*) configuration (*e.g.* **1**) and right-handed or (*P*) helices with amino acids of (*R*) configuration (*e.g.* **9**). The helix has a 5 Å pitch with the substituents in the 2- and 3-positions of the component amino acids and the hydrogens occupying lateral and axial positions, respectively [see Fig. 1(*b*)]. Lateral substituents at the *i* and (*i* + 3) position are directly aligned with a 5 Å distance between them and, if a substituent is forced into adopting an axial position, the 3_1 helix breaks up.[17]

Molecular dynamics calculations (GROMOS96 program package) on the β-heptapeptide **2** in MeOH produced[26] a remarkable result: after a sudden temperature increase from 298 to 350 K, the 3_1 helix unwinds. However, as the temperature is held at a constant 350 K, the helix is spontaneously restored within 400 ps and, even more amazingly, it is still stable after 2000 ps in this computational experiment which was performed without NOE restrictions. Such behaviour has never been observed with α-peptides.

In line with their different CD spectra, and most astonishingly for us, the mixed β-hexapeptides constructed from β^2- and β^3-amino acid building blocks (*e.g.* **6**–**8**, with β^2,β^3,β^2,β^3,β^2,β^3 sequences) form a different secondary structure. The NMR analysis shows strong NOEs between corresponding hydrogens of amino acids *i* and *i* + 2, rather than *i* and *i* + 3 as for the 3_1 helix. This finding[20,25] caught us by surprise because these molecules could have formed the 3_1 helix with all substituents in lateral positions. As Gellman has found,[15] the β-hexapeptide from *trans*-2-aminocyclopentanecarboxylic acid is present as a helix, but not a 3_1 helix, when dissolved in both MeOH and pyridine [Fig. 6(*b*)]. It may be that the secondary structures of our mixed β^2,β^3-peptides **6**–**8** are similar to the helix shown in Fig. 6(*b*); however, at the time of writing, the NMR analysis is not conclusive.

Thus, in contrast to the analogous α-peptides, the short-chain β-oligopeptides are able to form helical secondary structures and, indeed, it has now been experimentally proven that they are able to form at least two different helices which result from rather subtle changes in structure. Investigations and calculations on compounds of the general formula, H[NHCH(CO_2R)CH_2CO]$_n$OH (derived from aspartic acid) have revealed[2] that there might be additional stable β-peptide helices.

Solid state structures of β-peptides from X-ray scattering

While we have, so far, not succeeded in crystallising any of the helix-forming β-peptides bearing the side chains of natural amino acids, the β-oligopeptides derived from *l*-2-aminocyclopentane- and *l*-2-aminocyclohexane-carboxylic acid§ gave crystals of sufficient quality for X-ray analysis.[14,15] In both cases, the structures found in solution were confirmed to be also present in the solid state: the cyclohexane derivative folds to a 3_1 helix which is essentially superimposable with the NMR structures (the cyclohexane ring bonds occupy the two lateral positions). The 2.5_1 helix of the cyclopentane derivative has an average NH–C–C–CO dihedral angle of 86° (with a spread of 75° to 109°) which compares with 55° in the crystal of the cyclohexane analogue acid.[14]

A pleated-sheet arrangement of a β-peptide fragment was found in the crystal structure of Boc-β^3-HVal-β^3-HAla-β^3-HLeu-OMe (Fig. 7), with intermolecular hydrogen bonding in 14-membered rings.

Finally, the steroisomeric cyclo-β-tetrapeptides **12**, **13** and **14** [with (*S*,*S*,*S*,*S*), (*R*,*S*,*R*,*S*) and (*R*,*R*,*S*,*S*) configuration, respectively] were found[28] to form tube-like, hydrogen-bonded stacks in the solid state (Fig. 8).

Comparison of β-peptides with α-peptides—are they orthogonal to each other?

While the Gellman group approached the field of β-peptides from a supramolecular chemistry perspective[29] and hence made

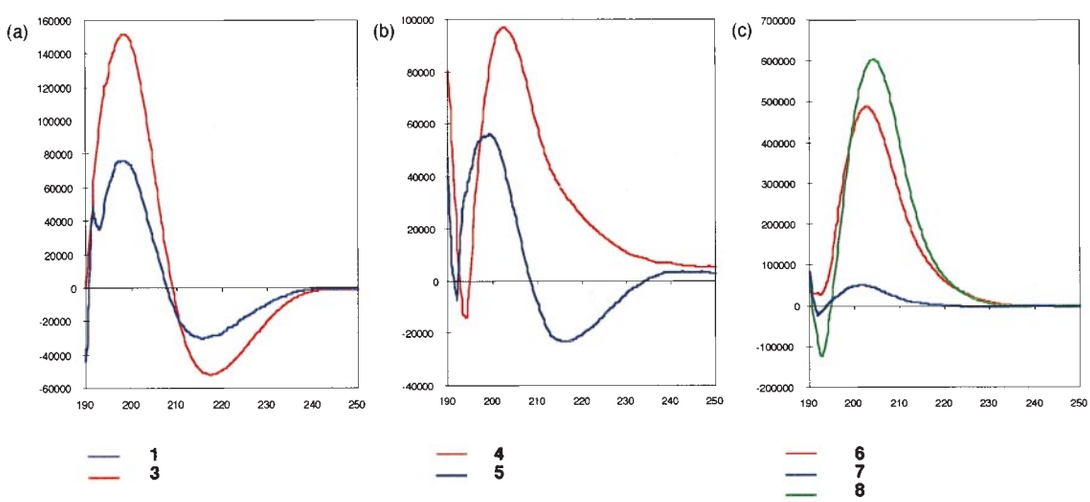


Fig. 5 Circular dichroism (CD) spectra of β-peptides **1**,**3**–**8** in MeOH (0.2 mM). The typical CD pattern assigned to a left-handed 3_1 helix [*cf*. Figs. 1(*b*) and 6(*a*)] is shown in (*a*) and the blue curve in (*b*). The characteristic CD pattern of a secondary structure which is, as yet, unassigned is shown in (*c*) and the red curve in (*b*). The most intensive Cotton effects were measured with disubstituted β-amino acid moieties [**3**, red in (*a*)], with a (β^2)$_3$(β^3)$_3$ (protected) sequence [**4**, red in (*b*)] and with the protected (β^2,β^3)$_6$ dodecapeptide [**8**, green in (*c*)].

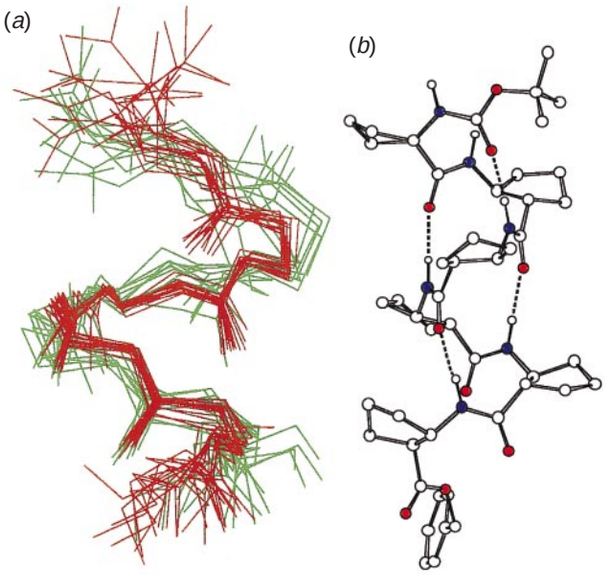


Fig. 6 NMR structural determination. (*a*) The 3_{14} (peptide nomenclature) helical conformations of **1** in MeOH (green) and in pyridine (red) (taken with permission from ref. 17); (*b*) MacMoMo presentation of the 2.5_{12} helical conformation of a hexa-β-peptide **10** derived from (*S*,*S*)-2-amino-cyclopentanecarboxylic acid. The NMR structure determination of **10** was carried out on the (*R*,*R*)-isomer; the coordinates were inverted for the presentation shown here to allow a better comparison with other known β-peptide structures.

cycloalkane derivatives (which, as far as the side chains are concerned, bear no resemblance to natural peptidic structures), our entry was triggered by research on the biopolymer[4] poly(hydroxybutanoate) (PHB) and on peptide backbone modifications[30–32] (*e.g.* in cyclosporine), so that we actually prepared β-peptides from α-amino acids. This now puts us in a

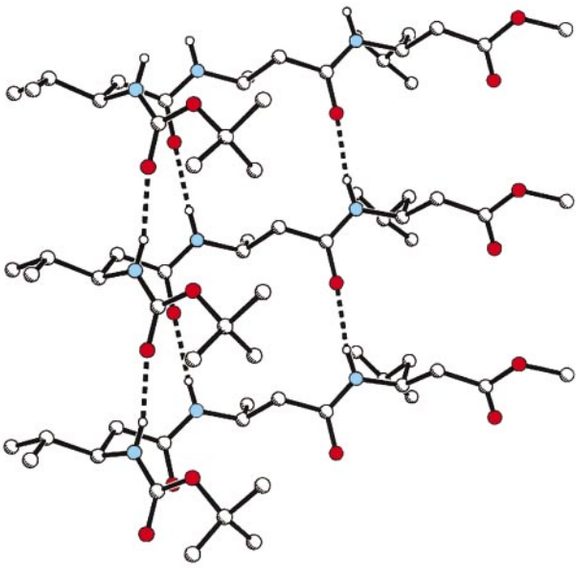


Fig. 7 Section of the crystal structure of Boc-β^3-HVal-β^3-HAla-β^3-HLeu-OMe with the pleated-sheet type arrangement of two parallel β-peptide fragments

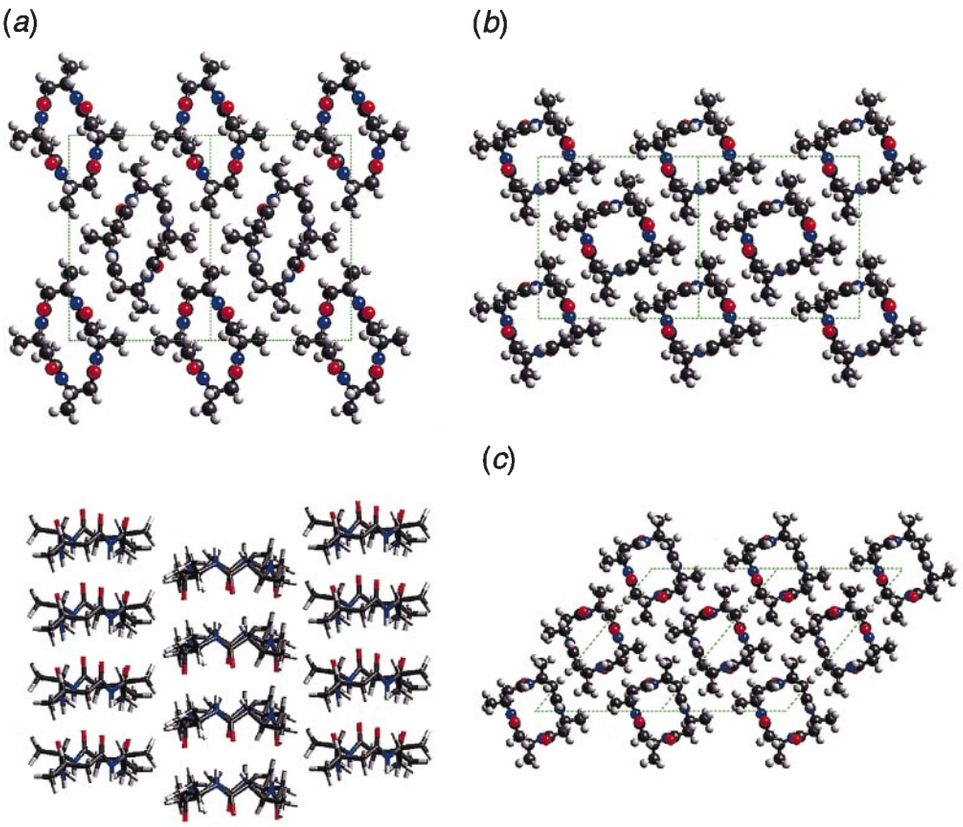


Fig. 8 Tubular stacking of cyclo-β-tetrapeptides in the solid state (from powder diffraction data). (*a*) **12** [(*S*,*S*,*S*,*S*); top view (above), side view (below)]; (*b*) **13** [(*R*,*S*,*R*,*S*)], top view; (*c*) **14** [(*R*,*R*,*S*,*S*)], top view. In **12**, the ring adopts a rhomboidal shape, in **13**, a square and in **14**, a rectangular shape. All four C=O and N–H bonds are unidirectional in (*a*), two C=O and two N–H bonds point up and down on opposite faces in (*b*) and on adjacent faces in (*c*). (Taken with permission from ref. 28.)

position where we can closely compare related α- and β-peptides and learn something about the hydrogen bonding along the backbones, side chain interactions and possible interactions between α- and β-peptidic structures.

The comparative structural analysis of an α-peptidic 3.6_1 helix with the 3_1 and 2.5_1 helices of β-peptides in Fig. 9 reveals the following points: (i) the helices have different polarities with respect to their C and N-termini; (ii) their shapes and sizes differ drastically; (iii) the 3_1 β-peptide helix can exist only when its residues are homochiral or have 2,3-*l* relative configuration,§ and not with geminal disubstitution (in contrast, the α-helix is stabilised[33] by incorporation of geminally disubstituted α-amino acids such as Aib or Iva); (iv) the helices are stabilised by hydrophobic interactions between side chains, a contribution which may be responsible for the difference between β^2- and β^3-peptides (3_1 helix) on the one hand and the mixed β^2/β^3-peptides on the other hand.

From the crystal structure shown in Fig. 7, we are able to make a comparison of pleated sheets of α- and β-peptides (Fig. 10) and they differ in the following features: (i) the amide planes in an extended conformation are separated by one and two tetrahedral carbons, respectively; (ii) these planes are thus arranged in a zig-zag and in a parallel-displaced fashion; (iii) the C=O and N–H bonds are pointing up and down (approximately perpendicular to the chain) in the α-peptidic sheet, with O,O and O,H distances of 6.5, 3.6 and 2.8 Å, while they are unidirectional (all C=O up, all N–H down) in the β-peptidic case (O,O and H,H distances 4.9 Å); (iv) the antiparallel and the less common parallel pleated sheet of an α-peptide carry the side chains pointing perpendicular, above and below, the average plane of the sheet, while the sheet of a β-peptide built from homochiral§ (*all*-β^2 or *all*-β^3) components is obscured on only one face by the side chains; (v) while α-peptides containing the twenty proteinogenic amino acids may show a certain *tendency* for forming either a helix or a β-sheet (the Chou–Fasman algorithm[34]), the chain of a β-peptide can be *prevented* from forming a 3_1 helix and *forced* to adopt an extended conformation, for instance, by constructing it from 2,3-disubstituted 3-amino acids of *u* configuration§¶ [R^1, $R^2 \neq$ H in Fig. 10(*b*)].

The additional versatility of β-peptides is further demonstrated by the cyclo-β-peptides: cyclic α-peptides are able to adopt a wide variety of conformations, but in order to exhibit regular tubular crystal packing each ring must be constructed from alternating (*R*)- and (*S*)-amino acid residues such that C=O and N–H bonds point alternately up and down and are parallel to the stacking direction[35] [Fig. 11(*d*)]. However, for cyclic β-peptides the extra CH_2 units remove these restrictions and more isomers are able to adopt a conformation suitable for the formation of tubular stacks [Fig. 11(*a*)–(*c*)].

Conformations other than extended chains, helices and circular stacks of β-peptides are yet to be found (*e.g.* turns or random coils); it will be interesting to see which conformation a β-peptide consisting of alternating (*R*)-β^2/(*S*)-β^2 or (*R*)-β^3/(*S*)-β^3 units[23] (sequences which should not be able to form either a 3_1 helix or a pleated sheet) adopts. In this context, a couple of unusual CD curves of β-heptapeptides and analogues wait to be interpreted on the basis of NMR analyses.

The structural differences between α- and β-peptides, as outlined in the previous sections, suggest that they cannot exhibit supramolecular back-bone interactions with each other—something that is a prerequisite, for instance, for peptides to be accepted by peptidases as substrates. Thus, we have subjected six different β-tetra-, β-hexa- and β-heptapeptides to the action of the same number of various peptidases (20 different combinations): There was no indication of cleavage after two days but the peptidases had maintained activity towards their standard substrates.[7] The α- and β-peptidic structures in this experiment do not appear to interact in a way which would lead to the cleavage of peptide bonds. Furthermore, preliminary results of animal experiments with a water-soluble β-heptapeptide indicate that, in contrast to a common α-peptide, the β-peptide has an unusually long half-life in the blood serum of a rodent.

Conclusion and outlook

At the outset of our work on β-peptides, the expectation of many a colleague and protein specialist was that insertion of a CH_2 group into each residue in a peptide backbone would lead to conformational chaos. Although we are convinced that we have by no means uncovered all secondary structures of β-peptides, we think that it is now justified to state that they have a much

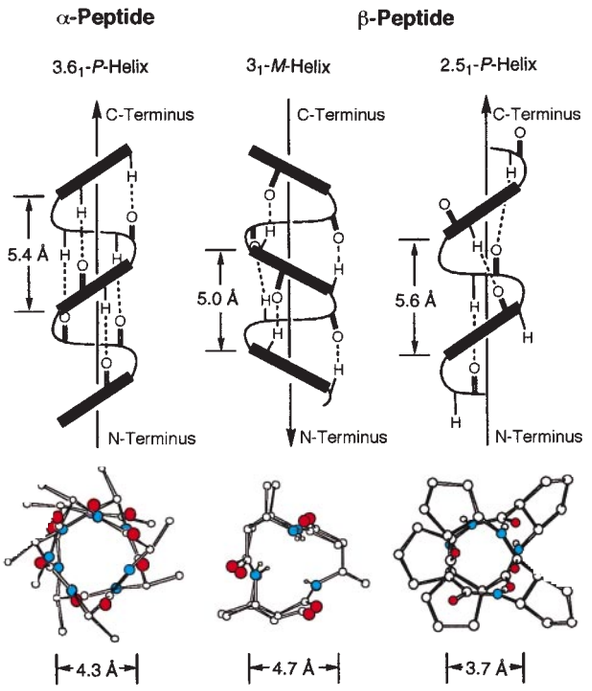


Fig. 9 Polarities, pitches, diameters and positioning of the side chain in α- and β-peptide helices. (*a*) Schematic presentation of the three helices from (*S*)-α-, (*S*)-β- and (*S*,*S*)-β-amino acids. (*b*) View along the helix axes of the 3.6_{13}, 3_{14} and 2.5_{12} helices (peptide nomenclature) as extracted from crystal or NMR structural data.

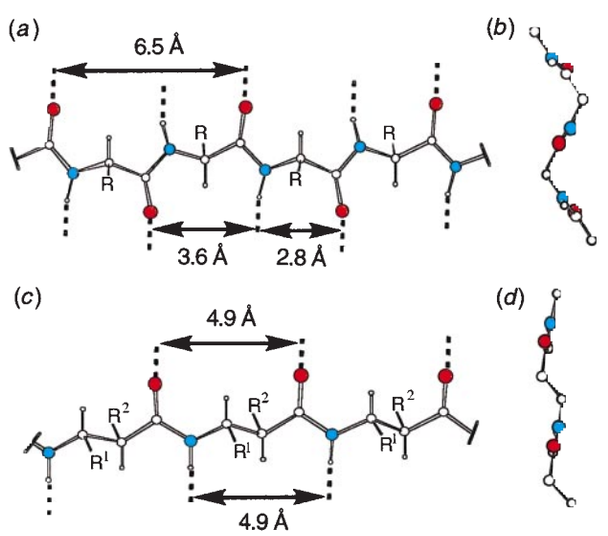


Fig. 10 Models of the extended conformation of (*a*) an α-peptide and (*b*) a β-peptide which would permit pleated sheet formation. Geminal disubstitution is helix-breaking in both cases. The two types of peptides cannot possibly form 'mixed' sheets. (Taken with permission from ref. 7.)

richer conformational energy surface, with more stable secondary structures, than their α-peptide counterparts. The biological stability of β-peptides suggests that compounds of this type, with recognition-specific side chains attached to the backbone in the right geometry, will be able to bind to an α-peptidic receptor. Combined with their stability towards cleavage by peptidases, this could mean that β-peptides are candidates for useful drugs. Large β-peptides will probably be immunogenic, and it will be exciting to see how an α-peptidic globular protein such as an antibody copes with the challenge of specifically binding (recognising!) a β-peptide. Finally, with various secondary and tertiary β-peptidic structural building blocks in our arsenal (there will be more possible combinations than with conventional amino acid residues) we hope to be able to construct large, complex, protein-like molecules from β-amino acids, with properly arranged functional groups, to create active sites and generate enzymatic properties. The results of research in this area will undoubtedly lead to insights about natural proteins and it will be amusing to discuss the question 'why did nature use α- and not β-amino acids for the construction of the molecules central to life on earth?'‖

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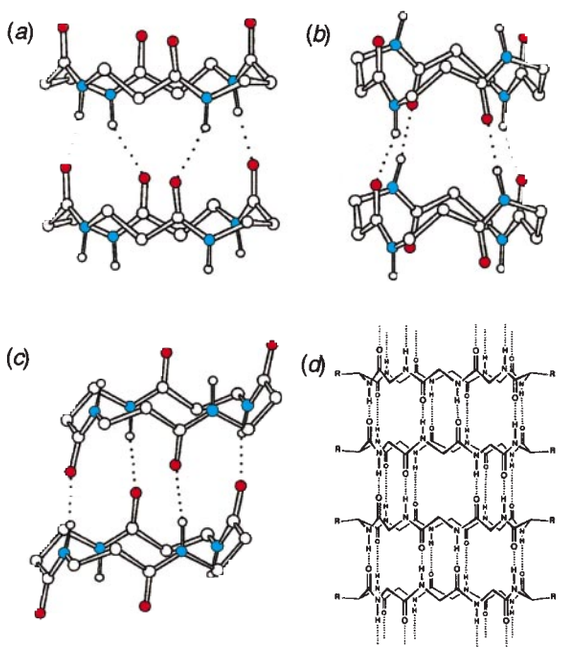

Fig. 11 Arrangement of the cyclo-β-tetrapeptides (*a*) **12**, (*b*) **13** and (*c*) **14** as found in the solid state (*cf.* Fig. 8). All hydrogen-bonded rings are 14-membered with (7 + 7) and (8 + 6) combinations of the participating fragments. Me substituents and hydrogen atoms bound to carbon are omitted for clarity. For comparison, the stacking of a cyclo-α-octapeptide with alternating configuration of the residues is shown in (*d*). [Taken with permission from refs. 28 and 35(*c*).]

Dieter Seebach was born in Karlsruhe, Germany, in 1937. He studied chemistry at the University of Karlsruhe and completed his PhD thesis on small rings and peroxides under the supervision of R. Criegee in 1964. After spending two years at Harvard University as postdoctoral co-worker (with E. J. Corey) and lecturer, he returned to Karlsruhe and, in 1969, completed his habilitation on the topic of S- and Se-stabilised carbanion and carbene derivatives. In 1971, he moved to the University of Giessen as a full professor and then in 1977 to the Eidgenössische Technische Hochschule in Zürich. He has received many prizes and titled lectureships, including the first Fluka Prize for Reagent of the Year (1987), the RSC Centenary Lectureship (1991) and the ACS Award for Creative Work in Organic Synthesis (1992), and he was the most recent Baker Lecturer at Cornell University (1997). His research has been directed towards the development of new synthetic methods and involves mechanistic studies and determination of structures. His attention is now focused on further developments of TADDOLs, on the short-chain oligomers of 3-hydroxybutanoic acid and the biopolymer PHB, on chiral dendrimers and on peptide modification.

Jennifer Matthews was born in Enfield, Middlesex in 1970. She studied chemistry at the University of Durham and after obtaining a BSc degree in 1991, remained there to complete a PhD on the preparation of asymmetric organosilicon compounds in 1994 under the supervision of Dr Patrick G. Steel. In January 1995, she joined Professor Seebach's group having obtained a Royal Society European Science Exchange Programme Fellowship. Throughout her stay in Zürich, her work has been in the β-peptide field. She has recently returned to the UK and is now a Royal Society Dorothy Hodgkin Research Fellow and Lecturer in Chemistry at the University of Glasgow.

Footnotes and References

* E-mail: seebach@org.chem.ethz.ch

† Due to a reversal of CIP priorities, H-β^3-HVal-OH has (*R*) configuration.

‡ β-Peptides built from identical 2,3-disubstituted β-amino acids (2-allyl-3-aminobutanoic acids of *like* configuration) have also been prepared *via* a stereocontrolled free radical allylation reaction by Hanessian and co-workers. Molecular modelling studies have suggested that a related β-hexapeptide might adopt a helical conformation (ref. 24).

§ For stereochemical definitions, see Helmchen's glossary (ref. 27).

¶ In fact, a β-tripeptide prepared from the amino acids (2*R*,3*S*)-Pr^i-CH(NH_2)-CH(Me)-CO_2H, (2*R*,3*S*)-Pr^i-CH_2-CH(NH_2)-CH(Me)-CO_2H and (2*R*,3*S*)-Me-CH(NH_2)-CH(Me)-CO_2H was so insoluble that we were unable to add a fourth such amino acid or to perform a fragment coupling to yield a hexamer (ref. 23).

‖ *Cf.* 'Why pentose and not hexose nucleic acids?' (ref. 36).

1 S. Muñoz-Guerra, F. López-Carrasquero, J. M. Fernández-Santin and J. A. Subirana, in *Polymeric Materials Encyclopedia*, ed. J. C. Salomone, CRC Press, Boca Raton, FL, 1996, vol. 6, pp. 4694–4700.

2 C. Alemán, J. J. Navas and S. Muñoz-Guerra, *Biopolymers*, 1997, **41**, 721; M. García-Alvarez, A. Martínez de Ilarduya, S. León, C. Alemán and S. Muñoz-Guerra, *J. Phys. Chem. A*, 1997, **101**, 4215 and references cited therein.

3 G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054.

4 D. Seebach, A. Brunner, B. M. Bachmann, T. Hoffmann, F. N. M. Kühnle and U. D. Lengweiler, *Biopolymers and oligomers of* (R)-*3-Hydroxyalkanoic Acids—Contributions of Synthetic Organic Chemists*, Ernst Schering Research Foundation, Berlin, 1995, vol. 28, pp. 1–105.

5 D. Seebach, T. Hoffmann, F. N. M. Kühnle and U. D. Lengweiler, *Helv. Chim. Acta*, 1994, **77**, 2007.

6 D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 913.

7 T. Hintermann and D. Seebach, *Chimia*, 1997, **51**, 244.
8 B. L. Iverson, *Nature* (*London*), 1997, **385**, 113; U. Koert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1836; S. Borman, *Chem. Eng. News*, June 16, 1997, 32; D. Bradley, *The Alchemist*, 1997, http://www.chemweb.com
9 *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi, Wiley-VCH, New York, 1997.
10 J. L. Matthews, C. Braun, C. Guibourdenche, M. Overhand and D. Seebach, *Preparation of Enantiopure β-Amino Acids from α-Amino Acids Using the Arndt–Eistert Homologation*, in *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi, Wiley-VCH, New York, 1997, pp. 105–126.
11 D. Seebach and H. Estermann, *Tetrahedron Lett.*, 1987, **28**, 3103; H. Estermann and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 1824.
12 D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215.
13 T. Hintermann and D. Seebach, *Synlett*, 1997, 437.
14 D. H. Apella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1996, **118**, 13 071.
15 D. H. Apella, L. A. Christianson, D. A. Klein, D. R. Powell, S. Huang, J. J. Barchi and S. H. Gellman, *Nature* (*London*), 1997, **387**, 381.
16 I. L. Karle, J. L. Flippen-Anderson, M. Sukumar, K. Uma and P. Balaram, *J. Am. Chem. Soc.*, 1991, **113**, 3952 and references cited therein.
17 D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 2043.
18 J. L. Matthews, M. Overhand, F. N. M. Kühnle, P. E. Ciceri and D. Seebach, *Liebigs Ann.*, 1997, 1371.
19 K. Gademann, Diplomarbeit (Master's Thesis), ETH Zürich, 1996.
20 J. V. Schreiber, Diplomarbeit (Master's Thesis), ETH Zürich, 1997.
21 G. Guichard and D. Seebach, *Chimia*, 1997, **51**, 315.
22 G. Quinkert, E. Egert and C. Griesinger, *Aspects of Organic Chemistry: Structure*, VCHA, Basel and VCH, Weinheim, 1996; *Peptides: Synthesis, Structures, and Applications*, ed. B. Gutte, Academic Press, San Diego, 1995.
23 S. Abele and D. Seebach, unpublished results. Part of the projected PhD Thesis of S. Abele, ETH Zürich.
24 S. Hanessian, H. Yang and R. Schaum, *J. Am. Chem. Soc.*, 1996, **118**, 2507; S. Hanessian, personal communication.
25 D. Seebach, K. Gademann, J. V. Schreiber, J. L. Matthews, T. Hintermann, B. Jaun, U. Hommel, L. Oberer and H. Widmer, *Helv. Chim. Acta*, 1997, **80**, November issue.
26 X. Daura, W. F. van Gunsteren, D. Rigo, B. Jaun and D. Seebach, *Chem. Eur. J.*, 1997, 1410.
27 G. Helmchen, in *Houben Weyl—Stereoselective Synthesis*, 4th edn., ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1996, vol. 1, pp. 1–74.
28 D. Seebach, J. L. Matthews, A. Meden, T. Wessels, C. Baerlocher and L. B. McCusker, *Helv. Chim. Acta*, 1997, **80**, 173.
29 G. P. Dado, J. M. Desper, S. K. Holmgren, C. J. Rito and S. H. Gellman, *J. Am. Chem. Soc.*, 1992, **114**, 4834.
30 D. Seebach, *How I became a Peptide Chemist*, Lonza Brochure, Lonza Ltd., Basel, 1990.
31 D. Seebach, *Aldrichimica Acta*, 1992, **25**, 59.
32 D. Seebach, A. K. Beck and A. Studer, *Some Effects of Lithium Salts, of Strong Bases, and of the Cosolvent DMPU in Peptide Chemistry, and Elsewhere*, in *Modern Synthetic Methods 1995*, ed. B. Ernst and C. Leumann, VCHA, Basel, and VCH, Weinheim, 1995, vol. 7, pp. 1–178.
33 I. L. Karle and P. Balaram, *Biochemistry*, 1990, **29**, 6747; B. Jaun, M. Tanaka, P. Seiler, F. N. M. Kühnle, C. Braun and D. Seebach, *Liebigs Ann.*, 1997, 1697 and references cited therein.
34 P. Prevelige and G. D. Fasman, in *Prediction of Protein Structure and the Principles of Protein Conformation*, ed. G. D. Fasman, Plenum Press, New York, 1989, pp. 391–416.
35 (*a*) X. Sun and G. P. Lorenzi, *Helv. Chim. Acta*, 1994, **77**, 1520; (*b*) J. D. Hartgerink, J. R. Granja, R. A. Milligan and M. R. Ghadiri, *J. Am. Chem. Soc.*, 1996, **118**, 43; (*c*) M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, N. Khazanovich, *Nature* (*London*), 1993, **366**, 324.
36 S. Pitsch, S. Wendeborn, B. Jaun and A. Eschenmoser, *Helv. Chim. Acta*, 1993, **76**, 2161; G. Otting, M. Billeter, K. Wüthrich, H.-J. Roth, C. Leumann and A. Eschenmoser, *Helv. Chim. Acta*, 1993, **76**, 2701.

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