Synthesis of β-Hexa- and β-Heptapeptides Containing Novel $\beta^{2,3}$-Amino Acids with Two Serine or Two Cysteine Side Chains – CD- and NMR-Spectroscopic Evidence for 3_{14}-Helical Secondary Structures in Water

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Dedicated to *Albert Eschenmoser* with admiration and best wishes on the occasion of his 75th birthday

Two representatives of a new type of β-amino acids, carrying *two* functionalized side chains, one in the 2- and one in the 3-position, have been prepared stereoselectively: a β-Ser derivative with an additional CH_2OH group in the 2-position (for β-peptides with better water solubility; *Scheme 2*) and a β-HCys derivative with an additional CH_2SBn group in the 2-position (for disulfide formation and metal complexation with the derived β-peptides; *Scheme 3*). Also, a simple method for the preparation of α-methylidene-β-amino acids is presented (see Boc-2-methylidene-β-HLeu-OH, **8** in *Scheme 3*). The two amino acids with two serine or two cysteine side chains are incorporated into a β-hexa- and two β-heptapeptides (**18** and **23/24**, resp.), which carry up to four CH_2OH groups. Disulfide formation with the β-peptides carrying two CH_2SH groups generates very stable 1,2-dithiane rings in the centre of the β-heptapeptides, and a cyclohexane analog was also prepared (*cf.* **27** in *Scheme 6*). The CD spectra in H_2O clearly indicate the presence of 3_{14}-helical structures of those β-peptides (**18**, **23**, **24**, **27b**) having the '*right*' configurations at all stereogenic centers (*Fig. 2*). NMR Measurements (*Tables 1* and *2*, and *Fig. 4*) in aqueous solution of one of the new β-peptides (**24**) are interpreted on the assumption that the predominant secondary structure is the 3_{14}-helix, a conformation that has been found to be typical for β-peptides in MeOH or pyridine solution, according to our previous NMR investigations.

1. Introduction. – β-Peptides have been shown to differ fundamentally from α-peptides and, yet, they have made their entry as a promising class of peptidomimetics. They fold into a variety of stable and well-ordered secondary structures like helices [1], turns, and sheets [2]. Their large structural diversity, together with the finding that β-peptides are not subject to degradation by mammalian peptidases [3], makes them interesting for pharmaceutical applications. Several examples of biologically active β-peptides have been reported in the past year [4].

In the course of our most recent structural investigations, we focused on water-solubility of β-peptides as this property is a prerequisite for *in vivo* function, and hence applicability in biological systems. While water-soluble β-peptides with various degrees of 3_{14}-helical conformation in aqueous solution were reported [5], to date the only

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[1]) Postdoctoral Fellow at ETH 1998–2000, partially financed by the *Deutsche Forschungsgemeinschaft* (*DFG*).

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[4]) Part of the Master's Thesis of *M.E.* ETH-Zürich 1998.

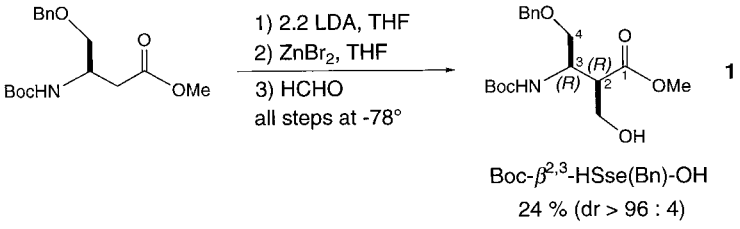
high-resolution structural data have been obtained on a β-hexapeptide with conformational constraints on its backbone caused by 'unnatural' cyclohexane moieties [5c]. This approach limits the structural variability needed for the design of β-peptides that could account for selective binding to proteins.

On the other hand, our β-peptides with proteinogenic side chains, while being structurally more diverse, showed only low helix-forming propensities in aqueous solution [5a,b][5]). Based on our experience concerning the helix-stabilizing ability of a particular β-amino-acid substitution pattern, we decided to prepare novel 2,3-disubstituted β-amino acids that should increase the helical content [1d] of β-peptides upon their introduction into peptide sequences[6]). The β-peptides presented in this paper were rendered water-soluble using an appropriate combination of residues with lipophilic and functionalized side chains; ionic side chains were excluded here, as they had been found to destabilize the 3_{14}-helical structure [5a].

2. Preparation of the β^3- and of Two Novel $\beta^{2,3}$-Amino-Acid Derivatives for Incorporation into β-Peptides. – The β^3-amino-acid building blocks used in the construction of water-soluble β-peptides were prepared starting from commercially available *N*-Boc-protected α-amino acids by the *Arndt-Eistert* homologation procedure [1a,b]. Additional Ser and Cys side chains were introduced into the 2-position of β^3-amino acids *via* alkylation of doubly lithiated derivatives to obtain the $\beta^{2,3}$-amino acids [8].

We first set out to prepare the *l*-$\beta^{2,3}$-disubstitued β-amino acid with two Ser side chains. While the employment of $PhCH_2OCH_2Cl$ in the alkylation of Boc-(*R*)-β^3-HSer(Bn)-OMe produced the desired derivative of the hydroxy ester **1** (*Scheme 1*) in only 11% yield, the use of formaldehyde as the electrophile gave better results: a series of experiments revealed this reaction to be highly diastereoselective when gaseous formaldehyde in the presence of 2 equiv. of $ZnBr_2$ was used (albeit in moderate yields). To assign the stereochemical course of this alkylation reaction, a 1.2 : 1 mixture of **1** and the epimer **2** obtained *via Claisen* condensation of Boc-(*R*)-β^3-HSer(Bn)-OMe with HCO_2Me and subsequent borohydride reduction (*Scheme 2*) was debenzylated, leading to the lactones **3** and **4** in a 1 : 2 ratio, together with uncyclized dihydroxy ester **5**. Separation of these compounds by flash chromatography (FC) was easily achieved,

Scheme 1. *Preparation of Boc-$\beta^{2,3}$-HSse(Bn)-OH* (**1**) *from Boc-(*R*)-β^3-HSer(Bn)-OMe*



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5) We were nevertheless able to prepare a macrocyclic helical β^3-peptide, which partially retains its secondary structure as deduced from its CD spectra (compound **1** in [6]). Due to its poor solubility in H_2O, a high-resolution structure of this β-peptide could be obtained only in MeOH solution [7].

6) Additionally, the novel $\beta^{2,3}$-amino acids were deviced to, possibly, act as metal-binding residues by forming seven-membered-ring metal chelates (see below).

Scheme 2. *Preparation of* (R,R)- *and* (R,S)-$\beta^{2,3}$-*Amino-Acid Derivatives* **1** *and* **2** *and Preparation of the Corresponding Lactones* **3** *and* **4**

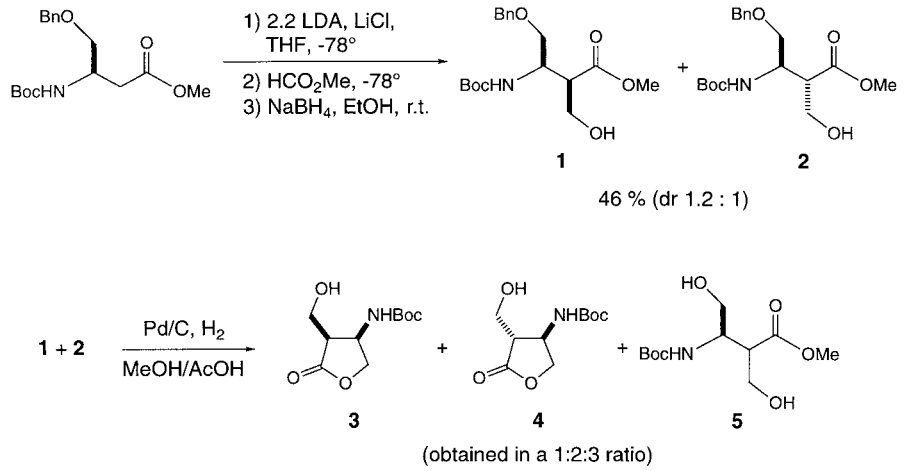


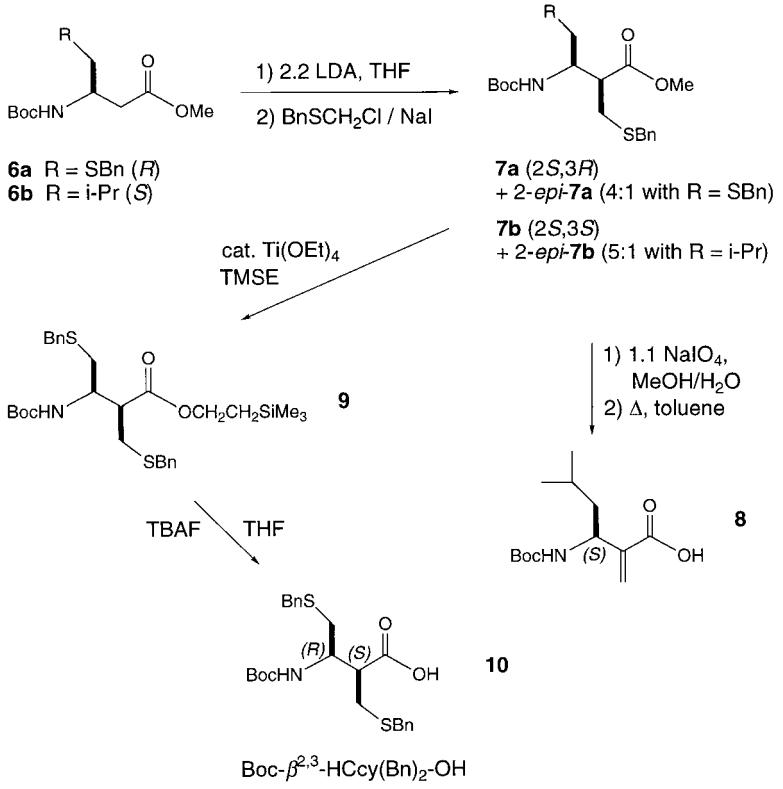
Fig. 1. *Stereoscopic view* (ORTEP plots [9]) *of the X-ray structure of* **3**. The structure was determined by Dr. *B. Schweizer.*

and the relative configuration of both lactones **3** and **4** was established by one-dimensional NOE spectroscopy. Strong NOEs from the C(α)–H to the C(β)–H in **3** are compatible with a *cis*-relationship of these two protons; for the *trans*-lactone **4**, only weak NOEs were observed. Also the diastereoisomerically pure amino acid ester **2** was converted to a lactone, the structure of which turned out to be **4**, thus establishing the relative configuration of **1** and **2**. A final proof of the configuration was provided by an X-ray crystal-structure analysis of the *cis*-lactone **3** (*Fig. 1*).

We then prepared the homochiral sulfur analogs, *i.e.*, $\beta^{2,3}$-amino-acid derivatives of *l*- or *ul*-configuration (reversal of *CIP* priority!) with one or two Cys side chains.

Enantiomerically pure Boc-(*R*)-β^3-HCys(Bn)-OMe (**6a**) was obtained in 78% overall yield from Boc-(*R*)-Cys(Bn)-OH on a multigram scale by the standard *Arndt-Eistert* sequence. While the α-alkylation of β^3-amino-acid derivatives with $BnOCH_2Cl$ was not successful (see above), the use of $BnSCH_2Cl$/NaI as the electrophile gave a 4:1 mixture of **7a** and 2-*epi*-**7a** in 34% yield from **6a** (*Scheme 3*). The diastereoisomers could be separated by FC, and the major product **7a** was isolated in 25% yield. Saponification of the methyl-ester group in **7a** required rather harsh conditions, which led to partial epimerization in the product (as detected by ^{1}H-NMR spectroscopy). As the method with $LiOH/H_2O_2$ (see below) could not be applied because of possible oxidation of the thioether group(s), we decided to use the titanate-mediated transesterification method [10] with $Me_3SiCH_2CH_2OH$ (TMSE) and fluoride-ion-induced cleavage of the TMSE ester [11]. The transesterification of methyl to silylethyl ester (**7a** → **9**) was carried out during 20 h at 95°, and the product was obtained in diastereoisomerically pure form (*Scheme 3*), and the cleavage with Bu_4NF (TBAF) in THF was fast and clean to produce the acid **10** without any ^{1}H-NMR-detectable isomerization. Starting from the β-H-Leucine derivative **6b**, compound **7b** was

Scheme 3. *Preparation of Boc-$\beta^{2,3}$-HCcy(Bn)$_2$-OH* (**10**) *and of the Substituted Acrylic-Acid Derivative* **8**



prepared analogously. The selectivity of the alkylation step was comparable, and the major diastereoisomer **7b** was obtained in 23% yield after repeated FC.

Compound **7b**, carrying a thioether functionality in the 2-position, was used to prepare an acrylic-acid derivative (*Scheme 3*): oxidation with 1.1 equiv. $NaIO_4$ gave the corresponding diastereoisomeric sulfoxides (1:1 mixture, as deduced from the ^{1}H-NMR spectrum), and thermolysis [12] by refluxing in toluene led to essentially quantitative formation of the methylidene derivative **8**, which was purified by FC. This method is very mild and should be applicable to β-peptides containing β-thioester side chains, allowing for the introduction of a novel type of β-amino-acid residue in a late step of the synthesis[7])[8]).

3. Synthesis of the β-Peptides 18, 23, 24 (Containing the New $\beta^{2,3}$-Amino Acids) and of the Cyclohexane Derivative 27. – A maximum protection strategy with *N-terminal* Boc and *C-terminal* MeO groups together with Bn groups for OH and SH side chains was chosen in order to build the new β-peptides by solution synthesis[9]) and fragment coupling through the di-, tri-, and tetrapeptide derivatives **11**–**16**, **19**, and **20**.

Since Bn protection of the free OH group in amino-acid derivative **1** turned out to be problematic, we decided to leave this group unprotected for the construction of β-peptide **18**. Thus, the methyl-ester group in **1** was cleaved by $LiOH/H_2O_2/H_2O$ in quantitative yield – yet some epimerization occurred. Coupling with H-β-HLeu-OMe [1a] was carried out (with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC)/1-hydroxy-1*H*-benzotriazole (HOBt) and *N*-methylmorpholine)[10]), with the mixture of the epimeric acids, and the mixture of diastereoisomeric dipeptides formed was separated by repeated recrystallization to give the pure β-dipeptide ester **11** in 10% yield. Boc Deprotection in **11** and – sluggish – coupling with Boc-(*R*)-β^3-HVal-OH [1a] gave the β-tripeptide-ester **12a** in only 26% yield[11]).

Methyl-ester hydrolysis in **12a**, and Boc deprotection in **12a**, followed by fragment coupling of the resulting tripeptide derivatives **12b** and **12c**, gave the protected β-hexapeptide **17** in 35% yield, which was sequentially deprotected at the C-terminus, at the N-terminus, and at the side chains (for conditions, see *Exper. Part*), to provide the target β-peptide **18** (*Scheme 4*). Compound **18** was purified by preparative reversed-phase (RP) HPL chromatography to a homogeneity of > 98% and characterized by FAB mass spectrometry (FAB-MS) and by one- and two-dimensional NMR spectroscopy.

The preparation of the β-heptapeptides **23** and **24** containing a 1,2-dithiane ring in the central residue (formed upon deprotection of the Cys side chains) was quite

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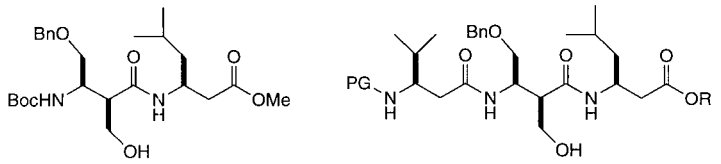
[7]) Another possible use of **8** might be the reaction with *Michael* donors in order to obtain $\beta^{2,3}$-amino acids, which might not be accessible through enolate alkylation.

[8]) The synthesis of β-peptides with an α-methylidene group in each and every residue is underway in our laboratory.

[9]) This strategy had already been successfully employed in the synthesis of macrocyclic disulfide-bridged β-peptides [6].

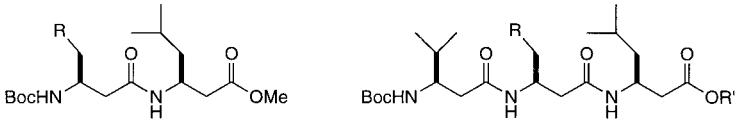
[10]) Although Et_3N was replaced by the weaker base NMM, 5–10% epimerization occurred during the coupling.

[11]) As several side-products were observed in the ^{1}H-NMR spectrum of crude **12a**, the low yield is possibly due to competing formation of the corresponding ester by reaction with the free OH group in the amino-hydroxy ester from Boc-deprotected **11**.



11 (52 %)

12a R = Me, PG = Boc
12b R = H, PG = Boc
12c R = Me, PG = H



13 R = H
14 R = BnO

15a R = H, R' = Me
15b R = H, R' = H

16a R = BnO, R' = Me
16b R = BnO, R' = H

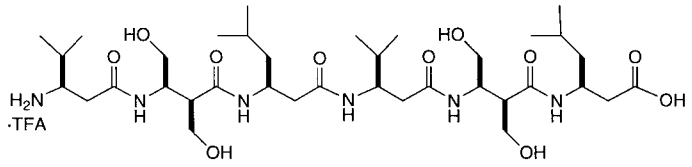
Scheme 4. *Preparation of the β-Hexapeptide Derivative* **17** *by Fragment Coupling of* **12a** *and* **12b** *and Deprotection to β-Peptide* **18**

12a

1) CF_3CO_2H
2) **12b**, NEt_3, EDC, HOBt

Boc-β^3-HVal-$\beta^{2,3}$-HSse(Bn)-β^3-HLeu-β^3-HVal-$\beta^{2,3}$-HSse(Bn)-β^3-HLeu-OMe **17**

1) NaOH, 5N
2) CF_3CO_2H
3) Pd/C, H_2, THF



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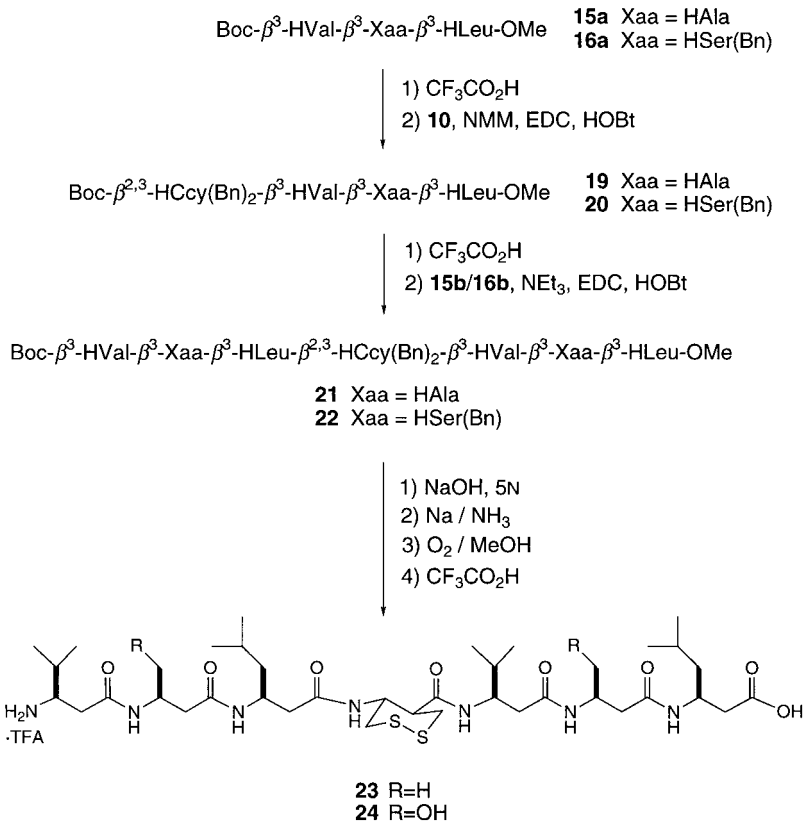
straightforward (*Scheme 5*): the *N*-Boc- and *S*-Bn-protected β-amino acid **10** was coupled with the tripeptides **15a** [1a] and **16a**, respectively, with EDC/HOBt and NMM. β-Tetrapeptides **19** and **20** were thus obtained without any epimerization detectable by ^{1}H-NMR analysis. Subsequent fragment-coupling reactions gave the fully protected β-heptapeptide derivatives **21** (from **19** and **15b**) and **22** (from **20** and **16b**).

The deprotection of **21** and **22**, and cyclization by disulfide formation was achieved by a protocol that was employed before in the construction of macrocyclic disulfide-bridged β-peptides [6]: methyl-ester saponification as the first step was quantitative in both cases. Subsequent Na/NH_3 reduction led to cleavage of the benzyl-ether and thioether moieties in these peptides. Air oxidation of the debenzylated products under

Scheme 5. *Preparation of β-Heptapeptides* **23** *and* **24** *Containing a 1,2-Dithiane Ring in the Central Residue* (5-Amino-1,2-dithiane-4-carboxylic acid residue is abbreviated as ADTC in the text and *Exper. Part*)



high-dilution conditions (0.08 mM in MeOH) produced the corresponding disulfide-bridged compounds, which were Boc-deprotected in a final step. Purification by preparative RP-HPLC gave β-heptapeptides **23** and **24** in *ca.* 35% overall yield. While the uniformity of **23** and **24** was established by analytical RP-HLPC (homogeneity > 98%), electrospray mass spectroscopy (ESI-MS) was used to further corroborate the presence of the disulfide moiety in these compounds[12]). Interestingly, **23** and **24** were not susceptible to reductive cleavage by excess dithiothreitol[13]). β-Peptide **23** was sufficiently soluble (*ca.* 0.2 mM) for us to be able to obtain CD spectra in aqueous solution, but NMR-spectroscopic characterization in H_2O was not possible. Replacement of the two β^3-H-Ala residues in the amino-acid sequence of **23** by two β^3-H-Ser (in **24**) resulted in an at least fiftyfold increase of the solubility in H_2O (> 10 mM).

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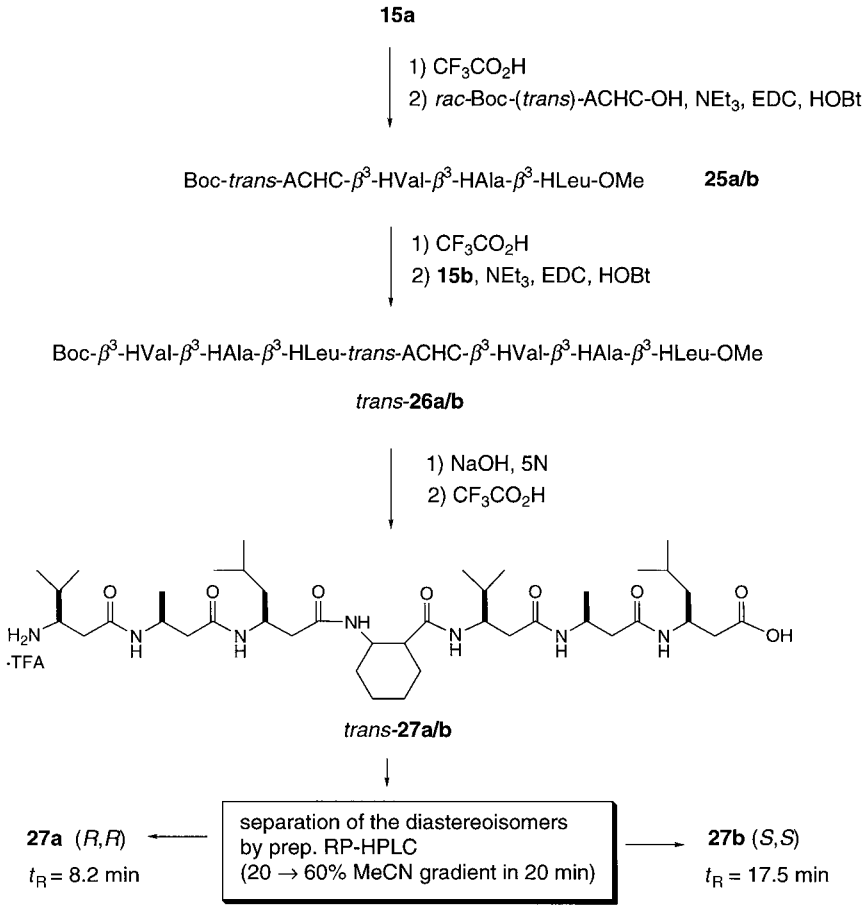
12) *Ellman*'s tests, which were performed on samples of **23** and **24** after preparative RP-HPLC purification, showed that no free SH groups were present.

13) See *Exper. Part*. In contrast, various macrocyclic disulfide bridges in β-peptides could easily be cleaved under these conditions [6].

To study the CD contribution of the disulfide chromophore in **23** and **24**, the carbocyclic analogue **27b** was also prepared (*Scheme 6*). Since the preparation of enantiomerically pure Boc-protected *trans*-2-aminocyclohexanecarboxylic acid (Boc-*trans*-ACHC-OH) by resolution was described as being rather capricious and not readily reproducible [13], and since the enantioselective access to this compound involves a multistep procedure [14], we decided to incorporate *rac*-Boc-*trans*-ACHC-OH[14]) and to separate the resulting isomers in a later stage of the synthesis. We had good reason to expect that this separation would be readily achieved, because the diastereoisomeric β-peptides have totally different secondary structures and thereby different properties: (1*R*,2*R*)-*trans*-ACHC does not fit into an (*M*)-3_{14}-helical

Scheme 6. *Preparation of Diastereoisomeric β-Heptapeptides* **27a** *and* **27b**, *and Separation by Preparative RP-HPLC*



[14]) Starting from 2-aminobenzoic acid, the racemic Boc-protected *trans*-ACHC [13] was prepared by dissolving-metal reduction [15] and subsequent Boc protection in 9% overall yield.

conformation which should be formed by the target β-heptapeptide containing the 'correct' (1*S*,2*S*)-*trans*-ACHC unit [1b][1d].

Thus, *rac*-Boc-*trans*-ACHC-OH [13][15] was coupled to the β-tripeptide ester resulting from Boc deprotection of **15a** (EDC/HOBt and NEt_3). The 1:1 mixture of β-tetrapeptides **25a**/**b** obtained could be separated neither by FC nor crystallization, and was used as such in the next coupling step with the β-tripeptide acid **15b**.

The fully protected diastereoisomeric β-heptapeptides **26a** and **26b** have indeed drastically different solubilities: while **26a** is sufficiently soluble in MeOH/$CHCl_3$ mixtures to allow for measurement of ^{1}H-NMR spectra, **26a** cannot be dissolved in common organic solvents at all[15]). Nevertheless, we were able to saponify the 1:1 mixture of **26a**/**b** in high yield, and, after a final Boc deprotection, the mixture **27a**/**27b** was analyzed by RP-HPLC, which showed that the two isomers were still present in a 1:1 ratio. Separation of **27a** and **27b** by preparative RP-HPLC was indeed an easy task, as their respective retention times on a C_8 column differed by almost 10 min. The diastereoisomers **27a** and **27b** were thus obtained in 31 and 26% yield, respectively, and with over 98% purity (*Scheme 6*).

The ^{1}H-NMR spectra, together with NH/ND-exchange rates in CD_3OD, gave a first hint for the assignment of the isomers: while the half-life values $\tau_{1/2}$ of all NH protons were smaller than 10 min for the more polar compound **27a** (t_R 8.2 min), three NH protons in compound **27b** (t_R 17.5 min) showed half-life values $\tau_{1/2}$ larger than 20 h. The reduced solvent accessibility of the amide protons is typical of stable (*e.g.*, helical) secondary and of tertiary structures [1d][16]. The large dispersion of the ^{1}H-NMR signals from the NH protons and also of the C(α) as well as the C(β) protons of **27b**, as compared to **27a**, further corroborates the assignment[16]) of **27a** as the (*R*,*R*)- and of **27b** as the (*S*,*S*)-isomer.

4. Structural Characterization. – 4.1. *CD Spectroscopy.* Solutions of the β-peptides **17**, **18**, **22**, **23**, **24**, and **27** in MeOH and H_2O were investigated by CD spectroscopy. In MeOH solution, a pattern of a trough at *ca*. 216 and a peak at *ca*. 198 nm is indicative of a (*M*)-3_{14}-helix[17]). In aqueous solutions, similar CD spectra have been observed [5a], but no independent proof of the structure of β-peptides without conformational backbone restriction exists, so far. The situation with **23** and **24** is somewhat more complicated, as these peptides contain disulfide chromophores that are conformationally constrained in six-membered rings[18]). The CD spectra of the β-peptides **23**, **24** (each containing 1,2-dithiane ring), and of **27** (with a cyclohexane instead the 1,2-dithiane ring) were thus recorded in an extended range from 190 to 350 nm.

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15) The configuration of the central $\beta^{2,3}$-amino-acid residue in stereoisomer-enriched samples of **26** was deduced from a comparison with their fully deprotected analogues **27** of which the absolute configuration of the central $\beta^{2,3}$-amino acid has been assigned (see below).

16) β^3-Peptides forming a stable helical secondary structure usually exhibit an increased ^{1}H-NMR signal dispersion in these ranges of the spectrum.

17) This was derived from numerous CD measurements and corresponding NMR structural investigations of β-peptides lacking additional chromophoric groups in the side chains [1][5a][17].

18) Several long- and short-wavelength CD bands have been identified for 1,2-dithiane model compounds having an unequal distribution of (*M*)- and (*P*)-chiral C–S–S–C groups, that is caused by stereogenic centers in their six-membered rings [18].

The protected β-peptides **17** and **22** show a pattern compatible with a 3_{14}-helical structure in MeOH solution (*Fig. 2*,*a*). Compound **17** presents the first example of a terminally protected β-hexapeptide with proteinogenic side chains that is judged to be

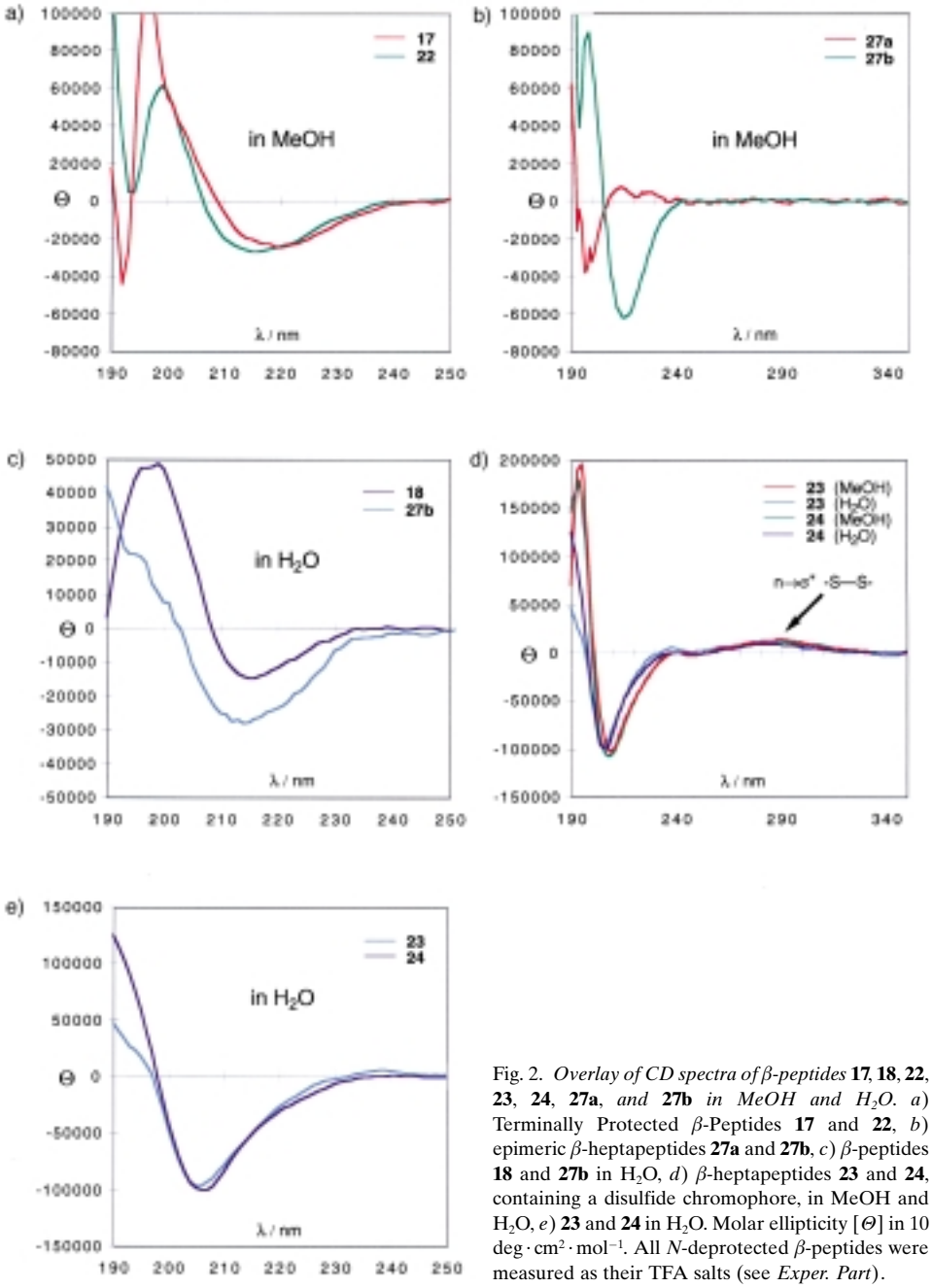

Fig. 2. *Overlay of CD spectra of* β*-peptides* **17**, **18**, **22**, **23**, **24**, **27a**, *and* **27b** *in MeOH and* H_2O. *a*) Terminally Protected β-Peptides **17** and **22**, *b*) epimeric β-heptapeptides **27a** and **27b**, *c*) β-peptides **18** and **27b** in H_2O, *d*) β-heptapeptides **23** and **24**, containing a disulfide chromophore, in MeOH and H_2O, *e*) **23** and **24** in H_2O. Molar ellipticity $[\Theta]$ in 10 deg · cm^2 · mol^{-1}. All *N*-deprotected β-peptides were measured as their TFA salts (see *Exper. Part*).

helical on the basis of its CD spectrum; until now, a β-heptapeptide was the shortest terminally protected β-peptide in which the helical conformation was detectable[19]).

While first hints concerning the secondary structures of β-peptides **27a** and **27b** came from one-dimensional ^{1}H-NMR spectra (see above), the configuration of the central cyclic amino acid in the two diastereoisomers can now be assigned by comparison of their CD spectra: whereas **27a** shows no pronounced *Cotton* effects even at wavelengths below 200 nm, **27b** displays the typical pattern assigned previously to the 3_{14}-helical structure with a maximum at 198 nm and a minimum at 216 nm (*Fig. 2*,*b*)[20]). On the basis of this analytical evidence, the configuration of the central amino acid residue in **27a** must be (*R*,*R*) and that of the isomer **27b** (*S*,*S*).

The β-hexapeptide **18** shows a weaker *Cotton* effect at 216 nm in H_2O (*Fig. 2*,*c*). This is in aggreement with the absence of the typical 'helical' NOE crosspeaks in 2D-NMR-spectroscopic measurements, indicating a small helical content of **18** in H_2O (see below). β-Heptapeptide **27b**, on the other hand, seems to retain a 'considerable amount of helicity' in H_2O (*Fig. 2*,*c*).

In MeOH as well as in aqueous solution the β-heptapeptides **23** and **24** show even more intense *Cotton* effects than **27b** (*Fig. 2*,*d*). The fact that the disulfide chromophore in **23** and **24** contributes to the CD spectrum is quite obvious, as a new band appears at *ca.* 285 nm (*cf. Fig. 2*, *b* and *d*), which can be assigned to an $n \rightarrow \sigma^*$ transition of the disulfide bond [19]. Assuming that the six-membered ring is present in a chair conformation[21]), and further assuming that the cyclic conformer with the substituents in equatorial positions is predominant (otherwise a helical structure could not be formed), a (*P*)-chirality axis of the C–S–S–C unit should be present in **23** and **24**[22]). The positive sign of the band at *ca.* 285 nm is consistent with the empirical 'quadrant rule' of *Carmack* and *Neubert* [21][23]), and also with experimental data in the literature [21–24].

A very weak second band is found around 240 nm (*Fig. 2*, *d*). This band is described in the literature as being of opposite sign compared to the longer-wavelength band and to be very sensitive to minor perturbations and thus not very informative [25].

Concerning the CD spectra of **23** and **24** in the short-wavelength region, it must be pointed out that the disulfide optical activity, in terms of specific structural parameters in this region, is still not very well-understood. On the other hand, an accurate experimental characterization below 200 nm is usually hampered by the interference of other chromophores (*e.g.*, amide transitions) [25].

In conclusion, it is not entirely clear to what extent the increased intensity and the blue shift of the minimum at 208 nm in the CD spectra of **23** and **24** (compared to the

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[19]) The effect of protecting groups and chain length on the stability of helical β-peptides is discussed in [17].

[20]) CD Spectra obtained with β-heptapeptides with a central β^3-alanine of 'wrong' and 'right' configuration (*cf.* Fig. 5, a in[1b]) suggest that a helical secondary structure should not be possible for a β-heptapeptide (built from L-β^3-amino acids) with a cyclohexanecarboxylic acid of the 'wrong' (2*R*,3*R*)-configuration in the central position.

[21]) It had been shown on the basis of dipole-moment data, that 1,2-dithiane prefers a chair conformation [20].

[22]) NOE Cross-peaks as well as the respective vicinal coupling constants observed in aqueous solution support a chair conformation of the 1,2-dithiane ring in **24** (see below).

[23]) The dependence of this lowest-energy transition on the disulfide torsion angle has also been deduced on the basis of the *Bergson* model [19][22] as shown by *Linderberg* and *Michl* [23].

carbocyclic analogue **27b**) is caused by a contribution of the disulfide chromophore. Upon switching from MeOH to H_2O, the intensity of this *Cotton* effect decreased by only 10% (in comparison to a 50% decrease found for **27b**), and a small blue shift is observed. As the conformation of the 1,2-dithiane moiety should not be too dependent on the solvent employed [20], this finding could point towards a comparatively large disulfide contribution within this band.

It is noteworthy that the spectra of **23** and **24** are identical within experimental error, which indicates that replacing lipophilic Ala by polar Ser residues has neither a disrupting nor a stabilizing effect on the helix.

4.2. *NMR Spectroscopy of the β-Peptide* **24**. – CD Measurements of peptide **24** in aqueous solution (*Fig. 2*) displayed the typical 3_{14}-helical pattern. Hence, it was of interest to determine the secondary structure of the β-peptide **24** in H_2O/D_2O in order to ascertain whether a 3_{14}-helical conformation as shown in *Fig. 3* is really present. Therefore, this β-heptapeptide, H-(*R*)-β^3-HVal-(*R*)-β^3-HSer-(*S*)-β^3-HLeu-(2*S*,3*S*)-ADTC-(*R*)-β^3-HVal-(*R*)-β^3-HSer-(*S*)-β^3-HLeu–OH · CF_3CO_2H, in H_2O/D_2O was investigated by NMR spectroscopy. The assignment of all resonances in the ^{1}H-NMR spectrum, as well the determination of the sequence, was achieved by DQF-COSY, TOCSY, HSQC, and HMBC experiments, and the chemical shifts are listed in *Table 1*.

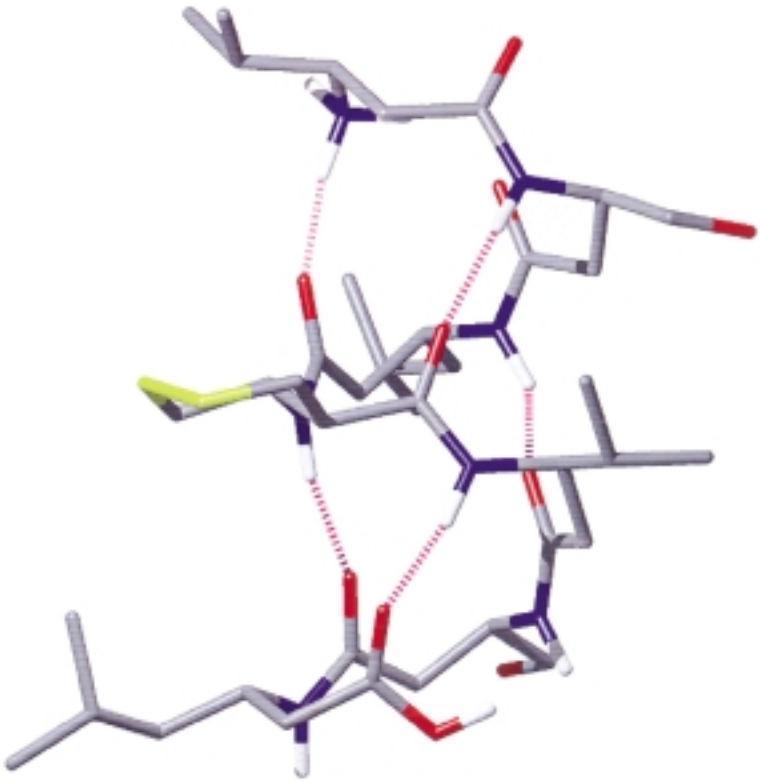

Fig. 3. *Model of the typical* 3_{14}*-helical structure of hexapeptide* **24**

Table 1. *^{1}H-NMR Chemical Shifts of the Heptapeptide* **24** *in H_2O*

β-Amino acid	NH	H–C(β)	H–C(α) (α_{la})/(α_{ax})	H–C(γ) (γ1)/(γ2)	H–C(γ')	H–C(δ)	H–Me
Val[1]	7.65	3.43	2.72/2.62	1.96			0.95/0.95
Ser[2]	8.10 (J(NH,β) = 8.9)	4.28	2.46/2.46	3.54/3.49			
Leu[3]	7.90 (J(NH,β) = 9.4)	4.19	2.44/2.21	1.31/1.21		1.45	0.80/0.80
Cys[4]	8.21 (J(NH,β) = 9.0)	4.10	2.76	2.86/2.81	3.07/3.07		
Val[5]	7.81 (J(NH,β) = 9.7)	4.00	2.49/2.25	1.68			0.78
Ser[6]	7.85 (J(NH,β) = 9.5)	4.23	2.50/2.36	3.47/3.47			
Leu[7]	7.83 (J(NH,β) = 9.9)	4.29	2.53/2.40	1.36/1.30		1.50	0.97/0.97

The NH protons of residues 2–7 show coupling constants J(NH,H–C(β)) in the range of 9–10 Hz, which corresponds to an *antiperiplanar* arrangement of the NH and H–C(β). The assignments of the diastereotopic $CH_2(\alpha)$ protons were made on the assumption that the axial protons, H_{ax}–C(α) exhibit a large and the lateral protons, H_{la}–C(α) a small coupling with H–C(β) as evident from ^{1}H-NMR and DQF-COSY spectra. This is in agreement with the observation that the H–C(β) show stronger NOE to the H_{la}–C(α), the proton with the smaller vicinal coupling constant, than to H_{ax}–C(α). To gather more information about the three-dimensional structure, ROESY spectra at different mixing times were acquired, and NOEs were extracted from the ROESY spectra with a mixing time of 150 ms. A total of 96 NOEs were extracted and classified according to their cross-peak volume into three distance categories: strong, medium, and weak (*Table 2*).

Table 2. *Weak* (w, 4.5 Å), *Medium* (m, 3.5 Å), *and Strong* (s, 3.0 Å) *NOEs Observed in the ROESY NMR Spectrum of Compound* **24** *in H_2O*

Residue	H-Atom(s)	Residue	H-Atom(s)	NOE
1	NH	1	Me	m
1	NH	1	γ	w
1	NH	1	β	m
1	NH	1	α_{ax}	w
1	β	1	γ	m
1	α_{1a}	1	Me	m
1	α_{1a}	1	γ	w
1	α_{ax}	1	Me	m
1	α_{ax}	1	γ	m
2	NH	2	β	w
2	NH	4	β	w
2	NH	5	β	w
2	NH	2	γ1	m
2	NH	2	γ2	w
2	NH	1	α_{1a}	m
2	NH	1	α_{ax}	s
2	NH	2	α	m
2	NH	1	Me	w
2	NH	3	Me	w
2	β	2	α_{1a}	w
2	β	3	γ1	w

Table 2 (cont.)

Residue	H-Atom(s)	Residue	H-Atom(s)	NOE
2	β	3	Me	m
2	$\gamma 1$	2	α	m
2	$\gamma 2$	2	α	m
3	NH	3	β	w
3	NH	5	β	w
3	NH	6	γ	w
3	NH	2	α	s
3	NH	3	α_{ax}	s
3	NH	3	δ	m
3	NH	3	$\gamma 1$	m
3	NH	3	$\gamma 2$	w
3	NH	3	Me	w
3	β	3	α_{ax}	w
3	β	3	α_{ax}	m
3	β	3	$\gamma 1$	w
3	β	3	$\gamma 2$	w
3	β	3	Me	w
3	α_{1a}	3	$\gamma 2$	w
3	α_{1a}	3	$\gamma 1$	w
3	α_{1a}	3	δ	w
3	α_{1a}	3	Me	w
3	α_{ax}	3	$\gamma 2$	w
3	α_{ax}	3	$\gamma 1$	w
4	NH	3	β	m
4	NH	4	$\gamma 1$	w
4	NH	4	$\gamma 2$	m
4	NH	4	α	s
4	NH	3	α_{1a}	m
4	NH	3	α_{ax}	s
4	β	4	$\gamma\alpha$	m
4	β	1	Me	w
4	γ'	1	Me	w
4	β	1	α_{1a}	w
4	γ'	4	Me	m
4	$\gamma 1$	3	Me	w
4	$\gamma 2$	3	Me	w
4	α	3	Me	w
5	NH	4	β	w
5	NH	5	β	w
5	NH	4	γ'	m
5	NH	4	α	s
5	NH	5	α_{1a}	w
5	NH	5	α_{ax}	m
5	NH	5	γ	m
5	NH	5	Me	m
5	β	2	α_{1a}	w
5	β	5	α_{1a}	m
5	β	5	α_{ax}	w
5	β	5	γ	m
5	β	5	Me	m
5	α_{1a}	5	γ	w
5	α_{ax}	5	Me	m

Table 2 (cont.)

Residue	H-Atom(s)	Residue	H-Atom(s)	NOE
5	α_{ax}	5	γ	w
6	NH	5	β	w
6	NH	6	γ	m
6	NH	5	α_{ax}	m
6	NH	5	α_{1a}	w
6	NH	6	α_{ax}	w
6	β	6	γ	w
6	β	6	α_{1a}	w
6	γ	6	α_{1a}	m
6	γ	6	α_{ax}	w
6	γ	5	Me	w
6	α_{1a}	5	Me	w
7	NH	6	β	w
7	NH	6	α_{1a}	s
7	NH	6	α_{ax}	s
7	NH	5	α_{1a}	w
7	NH	5	α_{ax}	m
7	NH	7	δ	m
7	β	6	α_{ax}	w
7	β	4	α	m
7	β	7	α_{1a}	w
7	α_{1a}	7	δ	w
7	α_{1a}	7	$\gamma 1$	w

Qualitative inspection reveals that NOEs typical for the 3_{14}-helix (*Fig. 3*) are indeed found in the ROESY spectra of **24** in H_2O/D_2O 9:1, but some of these NOEs are considerably weaker than those observed for 3_{14}-helical β-peptidic structures in organic solvents [1].

Inside the 3_{14}-helix, each NH_i typically exhibits two strong sequential NOEs to the $H_{ax}-C(\alpha)$ protons of residues $i-1$ and i. Structurally more significant, however, are the NOEs of medium strength of NH_i to $H-C(\beta)_{i+2}$ (and $H-C(\beta)_{i+3}$ and between $H_{ax}-C(\alpha)_i$ and $H-C(\beta)_{i+2}$ which connect non sequential residues (*Fig. 4*).

Compared to heptapeptide H-β-HVal-β-HAla-β-HLeu-β-HAla(αMe)-β-HVal-β-HAla-β-HLeu-OH in CD_3OH [1d,e], which forms the most stable 3_{14}-helix, we have observed so far, the ratio between nonsequential and sequential NOEs is much smaller for heptapeptide **24** in H_2O. This result would be consistent with either a major conformation with a more extended helix or, more plausibly, with the population of both 3_{14}-helical and nonhelical or at least partially unwound conformations [1e][17].

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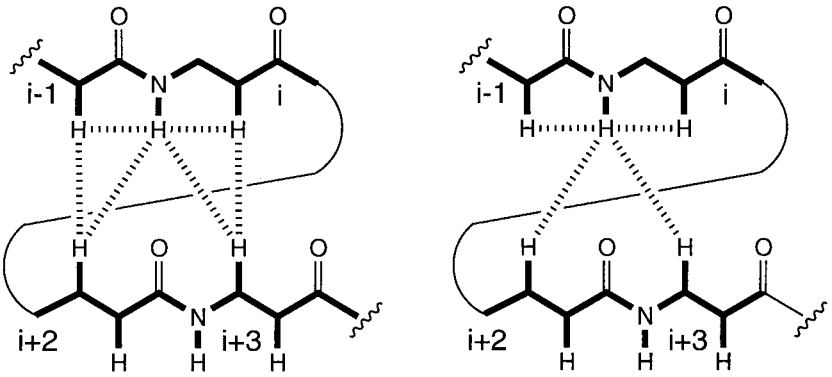

Fig. 4. *Schematic NOE pattern observed for 3_{14}-helical conformations in MeOH* (left). NH_i shows strong NOEs to protons $H_{ax}-C(\alpha)_{i-1,i}$ and NOEs of medium strength to $H-C(\beta)_{i+2}$ and $H-C(\beta)_{i+3}$, and between $H_{ax}-C(\alpha)_i$ and $H-C(\beta)_{i+2}$, compared to NOEs observed in H_2O for heptapeptide **24** (*right*), where NOEs between NH and $H-C(\beta)$ are weaker and NOEs from $H_{ax}-C(\alpha)_i$ to $H-C(\beta)_{i+2}$ are partially not observed.

Experimental Part

1. *General*. Abbreviations: Boc_2O: di(*tert*-butyl) dicarbonate, DME: 1,2-dimethoxyethane, DTT: dithiothreitol, 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), LDA: lithium diisopropylamide, NMM: *N*-methylmorpholine. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). Et_3N and NMM were distilled from CaH_2 and stored over KOH. $ClCO_2Et$ was distilled and stored at $+4°$ (refrigerator) under Ar. DME was distilled over Na. NaI was dried under h.v. at 150° for 16 h. BuLi was used as a 1.5M soln. in hexane. All indicated temp. were monitored with an internal thermometer (*Ebro-TTX-690* digital thermometer). Amino-acid derivatives were purchased from *Bachem*, *Degussa*, or *Senn*. All other reagents were used as received from *Fluka*. The β-amino-acid derivatives Boc-(*R*)-β^3-HVal-OH [1a], Boc-(*R*)-β^3-HSer(Bn)-OH [6], and Boc-(*S*)-β^3-HLeu-OMe [1a], and the peptide derivatives Boc-(*R*)-β^3-HVal-(*R*)-β^3-HAla-(*S*)-β^3-HLeu-OMe (**15a**) [1a] and Boc-(*R*)-β^3-HVal-(*R*)-β^3-HAla-(*S*)-β^3-HLeu-OH (**15b**) [1a], and *trans*-Boc-ACHC-OH [13][15] were prepared according to literature procedures. $BnSCH_2Cl$ was prepared according to literature procedure [26]. Reactions carried out with the exclusion of light were performed in flasks completely wrapped in aluminium foil. TLC: *Merck* silica gel *60* F_{254} plates; detection with UV and anisaldehyde or I_2. FC: *Fluka* silica gel *60* (40–63 μm); at *ca.* 0.2 bar. Anal. HPLC: *Knauer* HPLC system *K 1000*, *EuroChrom 2000 Integration Package*, degasser, UV detector *K 2000* (variable-wavelength monitor), *Macherey-Nagel* C_{18} column: *Nucleosil 100-5* C_{18} (250 × 4 mm). Prep. HPLC: *Knauer* HPLC system: pump type *64*, programmer *50*, UV detector (variable-wavelength monitor); *Macherey-Nagel* C_{18} column: *Nucleosil 100-7* C_{18} (250 × 21 mm). M.p. *Büchi-510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1 ml cell) at r.t. Circular dichroism (CD) spectra: *Jasco J-710*, recording from 190 to 250 nm at r.t.; 1 mm rectangular cell; average of five scans, corrected for the baseline; peptide concentration 0.2 mM in MeOH or H_2O; molar ellipticity Θ in $deg \cdot cm^2 \cdot dmol^{-1}$ (λ in nm); smoothing by *Jasco* software. IR Spectra: *Perkin-Elmer-782* spectrophotometer. NMR Spectra: *Bruker AMX 500* (^1H: 500 MHz, ^{13}C: 125 MHz), *AMX 400* (^1H: 400 MHz, ^{13}C: 100 MHz), *Varian Gemini 300* (^1H: 300 MHz, ^{13}C: 75 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz. Mass Spectra: *VG Tribrid* (EI), *VG ZAB2-SEQ* (FAB, in a 3-nitrobenzyl-alcohol (3-NOBA) matrix), and *Finnigan TSQ 7000* (ESI, sprayed from a 10^{-5}M MeOH/soln.; volumetric flow 20 μl/min) spectrometer; 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 Procedure 1* (*GP 1*). Similarly to the reported procedure [1], the Boc-protected amino acid was dissolved in CH_2Cl_2 (0.5M) and cooled to 0°. An equal volume of CF_3CO_2H was added, and the mixture was allowed to slowly warm to r.t. and then stirred for further 1.5 h. Concentration under reduced pressure and drying of the residue under h.v. (12 h) yielded the crude CF_3CO_2H salt, which was identified by NMR and used without further purification.

3. *Methyl-Ester Hydrolysis: General Procedures 2* (*GP 2*). *a*) The fully protected oligopeptide was dissolved in MeOH (0.1M) and treated with 1N NaOH (1.2 equiv.). After 24 h, the mixture was diluted with H_2O, and the pH was adjusted to 2–3 with 1N HCl. The soln. was extracted with AcOEt, and the combined org. phases were washed successively with sat. aq. NaCl soln. and H_2O. The org. phase was evaporated and dried under h.v.

b) The fully protected oligopeptide was dissolved in CF_3CH_2OH (0.1M) and treated with 5N NaOH (100 equiv.) and stirred at 45°. After completion of the reaction (TLC), the mixture was diluted with H_2O, and the pH was adjusted to 2–3 with 5N HCl (0°). The soln. was extracted with AcOEt, and the combined org. phases were washed successively with sat. NaCl soln. and H_2O. The org. phase was evaporated and dried under h.v.

4. *Peptide Coupling with EDC: General Procedures 3* (*GP 3*). *a*) The appropriate CF_3CO_2H salt was dissolved in $CHCl_3$ (0.5M) and cooled to 0°. This was treated successively with Et_3N (5 equiv.), HOBt (1.2 equiv.), a soln. of the Boc-protected fragment (1 equiv.) in $CHCl_3$ (0.5M), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t. and then stirred for 18 h. Subsequent dilution with $CHCl_3$ was followed by thorough washing with 1N HCl, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln. The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure. FC yielded the pure peptide.

b) The appropriate CF_3CO_2H salt was dissolved in $CHCl_3$ (0.5M) and cooled to 0°. This was treated successively with Et_3N (5 equiv.), HOBt (1.2 equiv.), a soln. of the Boc-protected fragment (1 equiv.) in DMF (0.1M), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t. and then stirred for 18 h. The solvents were removed under reduced pressure, and the residue was dispersed in $CHCl_3$ (0.02M). The resulting suspension was washed with 1M HCl, sat. aq. $NaHCO_3$ soln., sat. aq. NaCl soln., and H_2O. The org. phase was concentrated under reduced pressure. FC or recrystallization yielded the pure peptide.

5. *Cleavage of* S-*Benzyl Groups/*O-*Benzyl Groups and Cyclization to the Disulfide: General Procedure 4* (*GP 4*). According to [3], the Boc-protected oligopeptide derivative was dissolved in NH_3 (2 mM) at −33°. An amount of 5 equiv. of Na per Bn group was added. The dark blue soln. was stirred for 2 h (TLC) and subsequently quenched by addition of MeOH. The resulting MeOH soln. of NH_3 was immediately diluted to a peptide concentration of 0.08 mM. Air was bubbled through the soln. for 12 h with slow stirring. MeOH was removed under reduced pressure, and the resulting crude cyclic peptide was Boc-deprotected according to *GP 1*.

6. *Reversed-Phase (RP) HPLC Analysis and Purification of β-Peptides: General Procedure 5* (*GP 5*). RP-HPLC Analysis was performed on a *Macherey-Nagel* C_{18} column/*Nucleosil 100-5* C_{18} (250 × 4 mm) with a linear gradient of *A* (0.1% CF_3CO_2H in H_2O) and *B* (MeCN) at a flow rate of 1 ml/min (UV detection at 220 nm); t_R in min. Crude products were purified by prep. RP-HPLC (*Macherey-Nagel* C_{18} column/*Nucleosil 100-7* C_{18} (250 × 21 mm) with a gradient of *A* and *B* at a flow rate of 20 ml/min (UV detection at 220 nm) and then lyophilized.

7. *Attempted Ring Opening of* **23** *and* **24**. A 0.2 mM MeOH soln. of the respective peptide was purged with Ar and treated with 50 equiv. KOH and 25 equiv. DTT under Ar. The reaction was monitored by RP-HPLC. No hint for the formation of ring opened species in the respective reaction solns. of **23** and **24** was obtained during 2 d.

8. *NMR Spectroscopy of the Heptaptide* **24**. Sample: 8 mg dissolved in 0.6 ml H_2O/D_2O. 1D-NMR (AMX500): ^{1}H-NMR (500 MHz): suppression of the D_2O signal by presaturation; 90-K data points, 256 scans, 5.6-s acquisition time. {^{1}H}-BB-Decoupled-^{1}H-NMR (125 MHz): 80-K data points, 25-K scans, 1.3-s acquisition time, 1-s relax. delay 45° excitation pulse. Processed with 1.8-Hz exponential line broadening. 2D-NMR. All with solvent suppression by presat. DQF.COSY (500 MHz, D_2O) with pulsed field gradients (PFG) for coherence pathway selection [27]: *Acquisition:* 2K(t_2) × 512 (t_1) data points. 8 scans per t_1 increment, 0.22-s acquisition time in t_2; relaxation delay 2.0 s. TPPI Quadrature detection in ω_1. *Processing:* Zero filling and FT to 1K × 1K real/real data points after multiplication with sin^2 filter shifted by $\pi/3$ in ω_2 and $\pi/2$ in ω_1. HSQC with PFG [28] (500, 125 MHz, D_2O): *Acquisition:* 2K(t_2) × 512 (t_1) data points, 48 scans per t_1 increment. ^{13}C-GARP Decoupling during t_2, 0.22-s acquisition time in t_2. *Processing:* Zero filling and FT to 1K × 1K real/real data points after multiplication with sin^2 filter shifted by $\pi/2$ in ω_2 and sin filter shifted by $\pi/2$ in ω_1. HMBC with PFG [29] (500, 125 MHz, D_2O): *Acquisition:* Delay for evolution of long-range antiphase magn. 50 ms. No ^{13}C-decoupling, otherwise identical to parameters for HSQC. *Processing:* Zero filling and FT to 1K × 1K after multiplication with cos^2 filter in ω_2 and gaussian filter in ω_1; power spectrum in both dimensions. ROESY [30] (500 MHz, D_2O; see *Table 2*). *Acquisition:* 2 ROESY Spectra with mixing times of 80 and 150 ms were acquired. CW-spin lock (3.8 kHz) between trim pulses, 2K(t_2) × 480 (t_1) data points, 64 scans per t_1 increment. 0.22-s acquisition time in t_2, other parameters identical to DQF.COSY. *Processing:* Zero filling and FT to 1K × 512K real/real data points after multiplication by cos^2 filter in ω_2 and ω_1. Baseline correction with 3rd degree polynomial in both dimensions.

*Methyl (2*R,*3*R*)-4-(Benzyloxy)-3-[[(*tert*-butoxy)carbonyl]amino]-2-(hydroxymethyl)butanoate* (**1**). (i-Pr)$_2$NH (2.2 ml) was dissolved in 40 ml of THF and cooled to −25° under Ar. BuLi (10.5 ml, 1.78M in

hexane, freshly titrated) was added under stirring, and the resulting soln. was cooled after 30 min to −78°. Boc-β^3-HSer(OBn)-OMe (2.3 g, 7.1 mmol) were dissolved in a separate flask in 12 ml of THF and cooled to −78°. This soln. was added *via* syringe to the LDA soln. at −78°, and the resulting suspension was stirred for 30 min. In another flask, a suspension of $ZnBr_2$ (3.2 g, 14.2 mmol) in 8 ml of THF was cooled to −78°, stirred for 10 min, and added to the enolate. The resulting soln. was stirred for additional 30 min. Paraformaldehyde was heated to *ca.* 180° (heatgun) in a different flask, and the resulting HCHO was transported in an Ar stream over the reaction soln. at −78° for 15 min. After stirring the mixture for additional 40 min, the reaction was stopped by the addition of sat. NH_4Cl soln., Et_2O was added, and the org. phase was washed with Na_2SO_4 soln. and sat. NaCl soln. The org. phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. FC (Et_2O/pentane) gave 0.6 g (1.7 mmol, 24%) of diastereoisomerically pure **1**. Colorless oil. R_f 0.32 (Et_2O/pentane 1.5 :1). $[\alpha]_D = +5.0$ ($c = 1.04$, $CHCl_3$).IR ($CHCl_3$): 3684*w*, 3618*w*, 3438*w*, 3008*s*, 2976*m*, 2434*w*, 1723*m*, 1505*s*, 1436*m*, 1393*m*, 1368*m*, 1248*s*, 1165*s*, 1046*s*, 929*m*, 877*w*, 850*w*, 636*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 2.90–2.97 (*m*, CHC(O)O); 3.56–3.84 (*m*, MeO, CH_2O); 4.20–4.26 (*m*, CHN); 4.50 (*s*, $PhCH_2$); 5.35 (*d*, $J = 9.7$, BocNH); 7.28–7.38 (*m*, 5 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 28.30; 48.01; 49.28; 51.69; 60.69; 70.95; 73.31; 80.25; 127.65; 127.79; 128.41; 137.64; 159.81; 172.88. FAB-MS: 729.3 (43.8, $[2M + Na]^+$), 376.1 (31.1, $[M + Na]^+$), 354.15 (45.4, $[M + H]^+$). Anal. calc. for $C_{18}H_{27}NO_6$ (353.41): C 61.17, H 7.70, N 3.96; found: C 61.00, H 7.60, N 3.98.

*Methyl (2*S*,3*R*)-4-(Benzyloxy)-3-{[(*tert*-butoxy)carbonyl]amino}-2-(hydroxymethyl)butanoate* (**2**). $(i\text{-}Pr)_2NH$ (0.61 ml) was dissolved in 11 ml of THF and cooled to −25° under Ar. BuLi (2.95 ml, 1.78M in hexane, freshly titrated) was added under stirring, and the resulting soln. was cooled after 30 min to −78°. Boc-β^3-HSer(OBn)-OMe (650 mg, 2 mmol) was dissolved in a separate flask in 3.4 ml of THF and cooled to −78°. This soln. was added *via* syringe to the LDA soln. at −78°, and the resulting suspension was stirred for 30 min. HCO_2Me (0.25 ml) was added to the enolate, and the mixture was stirred for 1 h at −70°. After stirring the mixture for additional 40 min, the reaction was stopped by the addition of sat. NH_4Cl soln., Et_2O was added, and the org. phase was washed with Na_2SO_4 and sat. NaCl soln. The combined org. layers were dried ($MgSO_4$) and evaporated. The resulting β-amino β-oxo acid ester was dissolved in 2 ml of EtOH, and $NaBH_4$ (31 mg, 0.8 mmol) was added. The mixture was stirred for 1 h, and the solvent was evaporated. The residue was taken up in Et_2O, and washed with Na_2SO_4 and sat. NaCl solns. The combined org. layers were dried ($MgSO_4$) and evaporated to give a mixture of the diastereoisomers **1** and **2** (dr 1.2 :1; 326 mg; 46%). This mixture was separated by prep. HPLC on *ChiraSpher* (hexane/i-PrOH 95 :5) to give **1** (154 mg; 22%) and **2** (129 mg; 28%). Colorless oil. R_f 0.32 (Et_2O/pentane 1.5 :1). $[\alpha]_D = +8.0$ ($c = 1.03$, $CHCl_3$). IR ($CHCl_3$): 3438*m*, 3008*m*, 2980*m*, 1729*s*, 1503*s*, 1455*m*, 1437*m*, 1393*w*, 1368*m*, 1329*m*, 1169*s*, 1129*w*, 1082*m*, 862*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 2.76 (*dt*, $J = 3.1, 9.4$, CHC(O)O); 3.58–3.68 (*m*, MeO, CH_2O); 3.78–3.96 (*m*, CH_2O); 4.21–4.30 (*m*, CHN); $\nu_A = 4.46$, $\nu_B = 4.52$ (*AB*, $J_{AB} = 11.8$, $PhCH_2O$); 5.25 (*d*, $J = 9.0$, BocNH); 7.26–7.38 (*m*, 5 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 28.30, 48.46; 48.57; 51.84; 60.98; 70.40; 73.32; 80.26, 127.76; 127.89; 128.45; 137.59; 157.50; 173.05. FAB-MS: 730.0 (3.9, $[2M + Na]^+$), 376.5 (16.5, $[M + Na]^+$), 354.5 (21.5, $[M + H]^+$). Anal. calc. for $C_{18}H_{27}NO_6$ (353.41): C 61.17, H 7.70, N 3.96; found: C 61.14, H 7.57, N 3.98.

tert-*Butyl* N-*[(3*R*,4*R*)-2,3,4,5-Tetrahydro-4-(hydroxymethyl)-5-oxofuran-3-yl]carbamate* (**3**) *and* tert-*Butyl* N-*[(3*R*,4*S*)-2,3,4,5-Tetrahydro-4-(hydroxymethyl)-5-oxofuran-3-yl]carbamate* (**4**). A mixture of **1** and **2** (1.02 g, 2.8 mmol) was treated with 300 mg of Pd/C (10%) in 7 ml of MeOH and 0.5 ml of AcOH for 48 h under an H_2 atmosphere. Filtration over *Celite* and FC (1. Et_2O/Pentane 3 :1 to Et_2O and 2. CH_2Cl_2/MeOH 15 :1) gave **3** (50 mg, 8%) and **4** (106 mg, 14%).

Data for **3**: Colorless crystals. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 2.88–2.93 (*m*, CHC=O)); 3.94–4.07 (*m*, CH_2OH); 4.24 (*dd*, $J = 2.5, 10.0$, 1 H, CH_2O); 4.44 (*dd*, $J = 6.3, 10.0$, 1 H, CH_2O); 4.62–4.66 (*m*, CHN); 5.61 (br., BocNH). ^{13}C-NMR (300 MHz, $CDCl_3$): 28.27; 45.75; 50.29; 58.25; 72.87; 80.81;156.25; 175.59. NOE: Irrad. at 4.64 ppm, strong pos. NOE at 2.90 ppm. X-Ray crystal structure of **3**: from a crystal of size 0.35 × 0.3 × 0.2 mm 1251 reflections were measured on an *Enraf Nonius CAD-4* Diffractometer with CuK_α radiation (graphite monochromator, $\lambda = 1.54184$ Å). The structure was solved by direct method with SHELXS-96 [31]. The non-H-atoms were refined anisotropically with SHELXL-97 [32]. H-Atoms were obtained from a difference *Fourier* map and refined isotropically. Drawings of the molecule were done with PLUTO, ORTEP [33]. For final *R* values and experimental data, see *Table 3*.

Data for **4**: Colorless crystals. R_f 0.17 (Et_2O/pentane 3 :1). M.p. 114–115°. $[\alpha]_D = +13.2$ ($c = 0.50$, $CHCl_3$). IR ($CHCl_3$): 3437*w*, 2980*w*, 1776*s*, 1709*s*, 1503*m*, 1393*w*, 1369*m*, 1162*s*, 1035*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 2.65–2.71 (*m*, CHC=O)); 3.95–4.08 (*m*, 1 H, CH_2O); 4.36–4.47 (*m*, CHN); 4.59 (*dd*, $J = 7.8, 8.7$, 1 H, CH_2O); 4.81 (br., BocNH). ^{13}C-NMR (300 MHz, $CDCl_3$): 28.27; 48.89; 50.25; 60.09; 70.04; 81.09; 156.51; 175.00. NOE: Irrad. at 4.40 ppm, weak NOE at 4.00 ppm. EI-MS: 232.1 (0.4, $[M + H]^+$), 158.1 (79.6, $[M - t$-

Table 3. *Crystallographic Data and Structure Refinement for Compound* **3**

Crystallized from	Et_2O/pentane
Empirical formula	$C_{10}H_{17}NO_5$
Formula weight	231.25
Temp.	293(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit-cell dimensions	$a = 10.411(3)$ Å $\alpha = 90°$
	$b = 12.055(2)$ Å $\beta = 90°$
	$c = 9.534(6)$ Å $\gamma = 90°$
V	1196.6(9) A^3
Z	4
Density (calc.)	1.284 Mg/m^3
Absorption coefficient	0.870 mm^{-1}
$F(000)$	496
Crystal size	$0.35 \times 0.3 \times 0.2$ mm
θ Range for data collection	5.61 to 66.91°
Index ranges	$0 \leq h \leq 12$, $0 \leq k \leq 14$, $0 \leq l \leq 11$
Reflections collected	1251
Independent reflections	1245 (R(int) = 0.0000)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1216/0/213
Goodness-of-fit on F^2	1.523
Final R indices [$I > 3\sigma(I)$]	$R_1 = 0.0418$, $wR_2 = 0.1426$
R Indices (all data)	$R_1 = 0.0423$, $wR_2 = 0.1441$
Absolute structure parameter	0.7(3)
Extinction coefficient	0.021(4)
Largest diff. peak and hole	0.204 and −0.301 eA^{-3}

Bu + H]$^+$), 131.1 (26.7, [M − Boc + H]$^+$), 57.0 (100, [*t*-Bu]$^+$). Anal. calc. for $C_{10}H_{17}NO_5$ (231.25): C 51.94, H 7.41, N 6.06; found: C 51.93, H 7.39, N 6.06.

*Methyl (3*R*)-4-(Benzylsulfanyl)-3-{[(*tert*-butoxy)carbonyl]amino}butanoate* (Boc-(*R*)-β^3-HCys(Bn)-OMe; **6a**). Treatment of a soln. of Boc-(*S*)-Cys(Bn)-CHN_2 (8.0 g, 23.9 mmol) according to [1] followed by workup gave **6a** as a yellow oil. FC (cyclohexane/AcOEt 4:1) yielded pure **6a** (7.56 g, 94%) in the form of colorless crystals. M.p. 61–62°. R_f 0.55 (cyclohexane/AcOEt 4:1). $[\alpha]_D^{r.t.} = +5.9$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3349*s*, 2965*m*, 1734*s*, 1681*s*, 1534*s*, 1433*m*, 1389*w*, 1370*m*, 1352*m*, 1303*m*, 1275*m*, 1207*m*, 1159*s*, 1053*m*, 1028*m*, 987*w*, 706*s*, 652*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 2.56–2.72 (*m*, CH_2O, CH_2S); 3.66 (*s*, MeO); 3.73 (*s*, PhCH_2S); 4.06–4.14 (*m*, CHN); 5.11 (br., NH); 7.22–7.34 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.4 (Me); 35.2, 36.3, 37.3 (CH_2); 46.8 (CH); 51.8 (Me); 79.6 (C); 127.1, 127.5, 128.5, 129.0 (arom. C); 138.0, 155.1, 171.8 (C). FAB-MS: 679 (25, [2M + 1]$^+$), 362 (11, [M + Na]$^+$), 340 (94, [M + 1]$^+$), 284 (100, [M − C_4H_8 + 1]$^+$), 240 (91, [M − Boc + 1]$^+$). Anal. calc. for $C_{17}H_{25}NO_4S_2$ (339.45): C 60.15, H 7.42, N 4.13, S 9.45; found: C 60.30, H 7.42, N 4.19, S 9.51.

*Methyl (2*S*,3*R*)-4-(Benzylsulfanyl)-2-[(benzylsulfanyl)methyl]-3-{[(*tert*-butoxy)carbonyl]amino}butanoate* (Boc-(2*S*,3*R*)-HCy(Bn)$_2$-OMe; **7a**). NaI (1.5 g, 10 mmol) was dissolved in 6 ml of DME. $BnSCH_2Cl$ (1.72 g, 10 mmol) was added, and the soln. was stirred for 30 min at r.t. In a second flask, (i-Pr)$_2$NH (1.22 g, 12 mmol) was dissolved in 7 ml of THF and cooled to −78°. BuLi (7.5 ml, 12 mmol) was added during 10 min. Compound **6a** (1.7 g, 5 mmol) was dissolved in 12 ml of THF and added over 20 min to the (i-Pr)$_2$NH soln. After 30 min, the cooled (−78°) soln. of $BnSCH_2Cl$ was added *via* a *Teflon* cannula during 10 min, and the mixture was allowed to reach 0° over 14 h. The mixture was quenched with sat. NH_4Cl soln., diluted with Et_2O, and extracted with $NaHCO_3$, NH_4Cl, and NaCl solns. The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure to yield a crude epimeric mixture (803 mg; 34%; **7a**/*epi*-**7a** 4:1). FC (cyclohexane/AcOEt 6:1) yielded pure **7a** (583 mg, 25%). White solid. M.p. 79–80°. R_f 0.65 (cyclohexane/AcOEt 6:1). $[\alpha]_D^{r.t.} = -7.0$ ($c = 1.0$,

$CHCl_3$). IR (KBr): 3382*m*, 2962*m*, 1735*s*, 1677*s*, 1509*s*, 1262*m*, 1165*m*, 1090*s*, 1024*s*, 858*w*, 801*s*, 699*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 2.36–2.40, 2.51–2.56, 2.72–2.77 (3*m*, 2 CH_2S); 3.04–3.08 (*m*, CHCO); 3.67 (*s*, MeO); 3.72, 3.75 (2*s*, 2 C*H*$_2$); 4.06–4.14 (*m*, CHN); 5.32 (br., NH); 7.22–7.35 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 28.4 (Me); 30.8, 34.7, 36.0, 36.4 (CH_2); 46.6, 50.1 (CH); 52.0 (Me); 79.6 (C); 127.1; 127.2, 128.5, 128.6, 129.0, 129.1 (arom. C); 137.8, 137.9, 155.5, 173.6 (C). FAB-MS: 476 (15, $[M+1]^+$), 420 (24), 385 (46, $[M-Bn+1]^+$), 376 (100, $[M-Boc+1]^+$), 328 (66), 296 (29). Anal. calc. for $C_{25}H_{33}NO_4S_2$ (475.67): C 63.13, H 6.99, N 2.94, S 13.48; found: C 63.17, H 6.82, N 2.84, S 13.42.

*Methyl (2*S*,3*S*)-2-[(Benzylsulfanyl)methyl]-3-{[(*tert*-butoxy)carbonyl]amino}-5-methylhexanoate* (**7b**). NaI (1.5 g, 10 mmol) was dissolved in 6 ml of DME. $BnSCH_2Cl$ (1.72 g, 10 mmol) was added, and the soln. was stirred for 30 min at r.t. In a second flask, $(i\text{-}Pr)_2NH$ (1.22 g, 12 mmol) was dissolved in 7 ml of THF and cooled to −78°. BuLi (7.5 ml, 12 mmol) was added during 10 min. Boc-(*S*)-β^3-HLeu-OMe (777 mg, 3 mmol) was dissolved in 12 ml of THF and added over 20 min to the $(i\text{-}Pr)_2NH$ soln. After 30 min, the cooled (−78°) soln. of $BnSCH_2Cl$ was added *via* a *Teflon* cannula during 10 min, and the mixture was allowed to reach 0° over 14 h. The mixture was quenched with sat. NH_4Cl soln., diluted with Et_2O, and extracted with $NaHCO_3$, NH_4Cl, and NaCl solns. The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure yielding a crude epimeric mixture (681 mg, 57%; **7b**/*epi*-**7b** 5:1). FC (cyclohexane/AcOEt 6:1) yielded pure **7b** (268 mg, 23%). White solid. M.p. 43–44°. R_f 0.6 (cyclohexane/AcOEt 6:1). $[\alpha]_D^{r.t.} = -6.9$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3392*m*, 2956*m*, 1719*s*, 1503*s*, 1454*m*, 1437*m*, 1366*m*, 1246*m*, 1206*m*, 1164*s*, 1111*w*, 1022*w*, 805*w*, 702*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*d*, $J = 6.5$, Me); 0.89 (*d*, $J = 6.0$, Me); 1.11–1.30 (*m*, 2 H, 2 CH_2); 1.42 (*s*, *t*-Bu); 1.58–1.63 (*m*, CH); 2.56–2.77 (*m*, CH_2S, CHCO); 3.71 (br., MeO, $PhCH_2S$); 3.90–3.97 (*m*, CHN); 5.01 (br., NH); 7.22–7.33 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.2, 22.8 (Me); 24.5 (CH); 28.4 (Me); 30.7, 36.3, 43.3 (CH_2); 49.2, 49.3 (CH); 51.8 (Me); 79.2 (C); 127.1; 128.6, 128.9 (arom. C); 138.0, 155.6, 174.0 (C). FAB-MS: 396 (16, $[M+1]^+$), 340 (100, $[M-C_4H_8+1]^+$), 296 (88, $[M-Boc+1]^+$). Anal. calc. for $C_{21}H_{33}NO_4S_2$ (395.56): C 63.77, H 8.41, N 3.54, S 8.11; found: C 63.81, H 8.33, N 3.59, S 8.21.

*Methyl (1*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propenoate* (**8**). Compound **7b** (25 mg, 0.06 mmol) was dissolved in 3 ml of MeOH. $NaIO_4$ (14 mg, 0.06 mmol) was dissolved in 0.5 ml of H_2O and added dropwise to the first soln. at 0°. The mixture was allowed to warm to r.t. within 1 h and stirred for an additional 2 h. Solvents were removed, and the residue was extracted two times with CH_2Cl_2. The org. phase was washed with sat. $NaHCO_3$, NH_4Cl, and NaCl solns., and dried ($MgSO_4$). Concentration under reduced pressure yielded a 1:1 mixture of the diastereoisomeric sulfoxides (NMR), which was subjected to thermal pyrolysis by refluxing in 5 ml of toluene for 4 h (TLC). After removing toluene, FC (cyclohexane/AcOEt 6:1) yielded pure **8** (11 mg, 63%). Colorless solid. R_f 0.46 (cyclohexane/AcOEt 6:1). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*d*, $J = 6.5$, Me); 0.93 (*d*, $J = 6.0$, Me); 1.42 (*s*, *t*-Bu); 1.47–1.60 (*m*, CH_2, CH); 3.77 (*s*, MeO); 4.45–4.51 (*m*, CHN); 5.11 (br., NH); 5.11 (br., 1 H, C=CH_2); 6.17 (*d*, $J = 1.1$, 1 H, C=CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.3, 22.6 (Me); 25.1 (CH); 28.4 (Me); 43.9 (CH_2); 51.8 (Me); 79.3 (C); 126.0 (CH_2); 140.8, 155.1, 166.5 (C). FAB-MS: 307 (70, $[M+Na]^+$), 272 (70, $[M+1]^+$), 216 (100, $[M-C_4H_8+1]^+$), 172 (38, $[M-Boc+1]^+$).

*2-(Trimethylsilyl)ethyl (2*S*,3*R*)-4-(Benzylsulfanyl)-2-[(benzylsulfanyl)methyl]-3-{[(*tert*-butoxy)carbonyl]-amino}butanoate* (Boc-(2*S*,3*R*)-HCcy(Bn)$_2$-OTMSE; **9**). Compound **7a** (461 mg. 0.97 mmol) was dissolved in 10 ml of $Me_3SiCH_2CH_2OH$; 460 mg (2 mmol) $Ti(OC_2H_5)_4$ was added, and the soln. was stirred at 95° for 20 h. After filtration over *Celite*, 40 ml of AcOEt was added, and the mixture was extracted with $NaHCO_3$, NH_4Cl, and NaCl solns. The org. phase was dried ($MgSO_4$) and concentrated under reduced pressure. Residual $Me_3SiCH_2CH_2OH$ was removed by bulb-to-bulb distillation (130°/0.1 Torr). FC (cyclohexane/AcOEt 6:1) yielded **9** (420 mg, 77%). White solid. M.p. 53–54°. R_f 0.7 (cyclohexane/AcOEt 7:1). $[\alpha]_D^{r.t.} = -4.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3402*m*, 2972*m*, 1725*s*, 1692*s*, 1507*s*, 1264*m*, 1247*m*, 1165*s*, 1040*m*, 947*s*, 862*m*, 836*m*, 696*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.04 (*s*, Me_3Si); 0.95–1.00 (*m*, CH_2Si); 1.44 (*s*, *t*-Bu); 2.36–2.42, 2.50–2.56, 2.72–2.78 (3*m*, 2 CH_2S); 3.00–3.05 (*m*, CHCO); 3.73, 3.76 (2*s*, 2 PhC*H*$_2$S); 4.07–4.18 (*m*, CHN, CH_2O); 5.39 (br., NH); 7.23–7.36 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): −1.5 (Me); 17.5 (CH_2); 28.4 (Me); 30.8, 34.8, 36.0, 36.3 (CH_2); 46.5, 50.1 (CH); 63.5 (CH_2); 79.5 (C); 127.0, 127.1, 128.5, 128.6, 129.0, 129.1 (arom. C); 137.9, 138.0, 155.5, 173.3 (C). FAB-MS: 562 (22, $[M+1]^+$), 506 (37), 470 (72, $[M-Bn]^+$), 462 (32, $[M-Boc+1]^+$), 434 (100), 414 (43), 386 (23). Anal. calc. for $C_{29}H_{43}NO_4S_2Si$ (561.87): C 61.99, H 7.71, N 2.49, S 11.41; found: C 61.89, H 7.59, N 2.51, S 11.41.

*Boc-(2*R*,3*R*)-(α-CH$_2$OH)-$\beta^{2,3}$-HSer(OBn)-β^3-HLeu-OMe* (**11**). Compound **1** (0.93 g; 2.6 mmol) was reacted with 1.0 ml of H_2O_2 (30%) and 175 mg of $LiOH \cdot H_2O$ (1.6 equiv.) in 12.5 ml of THF/H_2O 4:1 for 24 h at r.t. The mixture was treated with 1.26 g of Na_2SO_3 in 5 ml of H_2O and 1M HCl, and extracted with AcOEt/CH_2Cl_2. The resulting compound was dissolved in 7 ml of H_2O and 10 ml of MeOH, and treated with 190 mg of $LiOH \cdot H_2O$ (1.74 equiv.) for another 24 h. Acidification with 1M HCl soln. and extraction with CH_2Cl_2 gave

0.92 g of the free Boc-β-amino acid. Boc-β^3-HLeu-OMe (1.07 g, 3.9 mmol) was deprotected according to *GP 1* and coupled according to *GP 3a*. Repeated recrystallization gave **11** (648 mg, 75%). Colorless solid. M.p. 118–119°. R_f 0.52 (Et_2O). $[\alpha]_D = -18.5$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3426*w*, 3007*m*, 2957*m*, 1732*m*, 1702*m*, 1657*m*, 1499*s*, 1454*w*, 1368*m*, 1171*s*, 1089*w*, 1046*w*, 644*w*, 627*w*, 615*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.5$, Me_2CH); 1.19–1.28 (*m*, CH); 1.32–1.45 (*m*, *t*-Bu, CH_2); 1.48–1.64 (*m*, CH); $\nu_A = 2.36$, $\nu_B = 2.44$ (*ABM*, $J_{AB} = 15.6$, $J_{AM} = 5.6$, $J_{BM} = 5.3$, $CH_2C(O)$); 2.70–2.76 (*m*, CHC(O)); 3.44–3.49 (*m*, CH_2O); 3.62–3.67 (*m*, MeO, 1 H of CH_2O); 3.72–3.84 (*m*, 1 H of CH_2O); 4.11–4.19 (*m*, CHN); 4.23–4.31 (*m*, CHN); 4.51 (*s*, PhCH_2); 5.54 (*d*, $J = 9.7$, BocNH); 6.41 (*d*, $J = 6.4$, BocNH); 7.27–7.38 (*m*, 5 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 22.01; 22.85; 24.95; 28.31; 39.09; 43.09; 44.30; 48.52; 49.24; 51.78; 61.53; 70.69; 73.19; 76.94; 127.76; 127.89; 128.50; 137.72; 156.59; 171.68; 172.17. FAB-MS: 983.4 (9.9, $[2M + Na]^+$), 503.2 (57.7, $[M + Na]^+$), 481.3 (76.5, $[M + H]^+$), 381.2 (100.0, $[M - t\text{-Bu} + 2H]^+$).

*Boc-β^3-HVal-(2*R*,3*R*)-(α-CH_2OH)-$\beta^{2,3}$-HSer(OBn)-β^3-HLeu-OMe* (**12a**). Compound **11** (520 mg, 1.38 mmol) was deprotected according to *GP 1* and coupled to Boc-β^3-HVal-OH (240 mg, 1.05 mmol) according to *GP 6*. FC (CH_2Cl_2/MeOH 90:8) gave **12a** (178 mg, 26%). Colorless solid. $[\alpha]_D = -25.7$ ($c = 0.66$, $CHCl_3$). IR ($CHCl_3$): 3420*m*, 3003*m*, 2962*s*, 1704*s*, 1657*s*, 1499*s*, 1454*w*, 1391*m*, 1367*m*, 1173*s*, 1096*w*, 1044*w*, 1014*w*, 913*w*, 861*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 50°): 0.75–0.83 (*m*, 12 H); 1.10–1.19 (*m*, 1 H); 1.34 (*s*, 10 H); 1.61–1.68 (*m*, 2 H); 2.17–2.19 (*m*, 2 H); 2.34–2.36 (*m*, 2 H); 2.57–2.61 (*m*, 1 H); 3.27–3.39 (*m*, 2 H); 3.45–3.62 (*m*, 3 H); 3.53 (*s*, 3 H); 3.87–3.89 (*m*, 2 H); 4.14–4.36 (*m*, 2 H); 4.37–4.47 (*m*, 3 H); 7.26–7.33 (*m*, 5 H).

*Boc-(*R*)-β^3-HSer(Bn)-(*S*)-β^3-HLeu-OMe* (**14**). Boc-(*S*)-β^3-HLeu-OMe (560 mg, 2.16 mmol) was deprotected according to *GP 1*, dissolved in 4 ml of $CHCl_3$, and treated with Et_3N (1.09 g, 10.8 mmol), HOBt (350 mg, 2.6 mmol), Boc-(*R*)-β^3-HSer(Bn)-OH (668 mg, 2.16 mmol) in 4 ml of $CHCl_3$, and EDC (480 mg, 2.6 mmol) according to *GP 3a*. FC (CH_2Cl_2/MeOH 20:1) yielded **14** (878 mg, 90%). White solid. M.p. 102–103°. R_f 0.6 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{rt} = -11.0$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3269*s*, 3068*m*, 2961*s*, 2870*m*, 1738*s*, 1696*s*, 1653*s*, 1547*s*, 1451*m*, 1364*m*, 1294*m*, 1252*m*, 1179*m*, 1085*m*, 1066*m*, 862*w*, 746*m*, 698*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89 (*d*, $J = 6.6$, Me); 0.90 (*d*, $J = 6.5$, Me); 1.23–1.30 (*m*, 1 H, CH_2); 1.40–1.46 (*m*, *t*-Bu, 1 H of CH_2); 1.52–1.62 (*m*, CH); 2.41–2.54 (*m*, 2 CH_2CO); 3.48 (*dd*, $J = 9.4$, 6.2, 1 H, CH_2O); 3.60 (br., 1 H, CH_2O); 3.66 (*s*, MeO); 4.04–4.12 (*m*, CHN); 4.27–4.36 (*m*, CHN); 4.51 (*s*, PhCH_2O); 5.45 (br., NH); 6.20 (br., NH); 7.27–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.1, 22.9 (Me); 25.0 (CH); 28.4 (Me); 38.1, 38.9, 43.1 (CH_2); 44.2 (CH); 51.7 (Me); 71.2, 73.2 (CH_2); 79.4 (C); 127.7; 127.8, 128.5 (arom. C); 138.0, 155.5, 170.1, 172.2 (C). FAB-MS: 473 (14, $[M + Na]^+$), 451 (48, $[M + 1]^+$), 351 (100, $[M - Boc + 1]^+$). Anal. calc. for $C_{24}H_{38}N_2O_6$ (450.57): C 63.98, H 8.50, N 6.22; found: C 64.01, H 8.43, N 6.25.

*Boc-(*R*)-β^3-HVal-(*R*)-β^3-HSer(Bn)-(*S*)-β^3-HLeu-OMe* (**16a**). Compound **14** (849 mg, 1.88 mmol) was deprotected according to *GP 1*, dissolved in $CHCl_3$ (3.5 ml), and treated with Et_3N (960 mg, 9.5 mmol), HOBt (311 mg, 2.3 mmol), Boc-(*R*)-β^3-HVal-OH (436 mg, 1.88 mmol) in $CHCl_3$ (3.5 ml), and EDC (440 m, 2.3 mmol) according to *GP 3a*. FC (CH_2Cl_2/MeOH 20:1) yielded **16a** (987 mg, 92%). White solid. M.p. 142–143°. R_f 0.65 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{rt} = -12.7$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3308*s*, 2960*s*, 2871*m*, 1741*m*, 1687*s*, 1647*s*, 1541*s*, 1438*w*, 1367*m*, 1310*w*, 1248*w*, 1174*m*, 1044*w*, 1022*w*, 867*w*, 735*m*, 697*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89–0.92 (*m*, 4 Me); 1.22–1.29 (*m*, 1 H, CH_2); 1.39–1.49 (*m*, *t*-Bu, 1 H of CH_2); 1.51–1.62 (*m*, CH); 1.76–1.84 (*m*, CH); 2.26–2.54 (*m*, 3 CH_2CO); 3.48 (*dd*, $J = 9.5$, 6.4, 1 H, CH_2O); 3.62–3.72 (*m*, MeO, 1 H of CH_2O, CHN); 4.25–4.37 (*m*, 2 CHN); 4.51 (*s*, PhCH_2O); 5.16 (br., NH); 6.50 (br., NH); 6.80 (br., NH); 7.27–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.5, 19.5, 22.1, 22.2 (Me); 25.0 (CH); 28.4 (Me); 32.2 (CH); 37.9; 39.2, 43.2 (CH_2); 44.4, 46.9 (CH); 51.7 (Me); 53.7 (CH); 70.8,73.3 (CH_2); 79.1 (C), 127.8, 127.9, 128.5 (arom. C); 138.0, 156.0, 170.3, 171.0, 172.3 (C). FAB-MS: 586 (100, $[M + Na]^+$), 564 (72, $[M + 1]^+$), 464 (79, $[M - Boc + 1]^+$). Anal. calc. for $C_{30}H_{49}N_3O_7$ (563.73): C 63.92, H 8.76, N 7.45; found: C 63.91, H 8.55, N 7.44.

*Boc-(*R*)-β^3-HVal-(*R*)-β^3-HSer(Bn)-(*S*)-β^3-HLeu-OH* (**16b**). Compound **16a** (395 mg, 0.7 mmol) was dissolved in 3 ml of MeOH/CF_3CH_2OH 1:1 and treated with 2 ml of 5N NaOH according to *GP 2b* (reaction time 14 h) to yield **16b** (378 mg, 98%). White solid. M.p. 188–189°. R_f 0.45 (CH_2Cl_2/MeOH 15:1). $[\alpha]_D^{rt} = +1.7$ ($c = 0.5$, MeOH). IR (KBr): 3332*w*, 2960*s*, 2871*m*, 2475*m*, 1721*s*, 1679*s*, 1630*s*, 1590*m*, 1528*w*, 1456*s*, 1367*m*, 1310*w*, 1250*w*, 1175*m*, 1122*m*, 1020*w*, 968*w*, 865*w*, 776*w*, 738*m*, 697*m*. ^{1}H-NMR (400 MHz, CD_3OD): 0.86–0.93 (*m*, 4 Me); 1.26–1.33 (*m*, 1 H, CH_2); 1.41–1.49 (*m*, *t*-Bu, 1 H of CH_2); 1.55–1.65 (*m*, CH); 1.69–1.77 (*m*, CH); 2.20–2.50 (*m*, 3 CH_2CO); 3.46–3.56 (*m*, CH_2O); 3.71–3.76 (*m*, CHN); 4.25–4.32 (*m*, CHN); 4.33–4.39 (*m*, CHN); 4.51 (*s*, PhCH_2O); 7.23–7.34 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 18.3, 19.7, 22.2, 23.7 (Me); 26.1 (CH); 28.9 (Me); 33.6 (CH); 39.1, 40.2, 41.0, 44.5 (CH_2); 45.9, 48.4 (CH); 54.9 (CH); 72.0, 74.3 (CH_2); 80.0 (C), 128.7, 128.9, 129.4 (arom. C); 139.6, 158.0, 172.3, 173.5, 174.9 (C). FAB-MS: 572 (100, $[M + Na]^+$), 550 (21, $[M + 1]^+$), 450 (33, $[M - Boc + 1]^+$).

*Boc-(β^3-HVal-(2*R*,3*R*)-(α-CH_2OH)-$\beta^{2,3}$-HSer(OBn)-β^3-HLeu)$_2$-OMe* (**17**). Compound **12a** (177 mg, 0.298 mmol) was dissolved in 5.5 ml of MeOH, 0.6 ml of 1M NaOH was added, and the resulting mixture was stirred at r.t. for 2 d. The pH of the resulting soln. was adjusted to 2 using 1M HCl soln., and the precipitate was collected by filtration resulting in **12b** (92 mg, 52%). The other fragment was obtained by deprotecting **12a** according to *GP 1*. Both fragments were coupled according to *GP 3a*. FC (CH_2Cl_2/MeOH 10:1) gave **17** (108.6 mg, 66%). Colorless solid. CD: 220 (−25000), 200 (125000). ^{1}H-NMR (300 MHz, CD_3OD): 0.88–0.94 (*m*, 8 Me); 1.21–1.50 (*m*, 4 H); 1.43 (*s*, *t*-Bu); 1.60–1.82 (*m*, 4 H); 2.26–2.53 (*m*, 8 H−C(α)); 2.70–2.76 (*m*, 1 H); 2.90–2.94 (*m*, 1 H); 3.43–3.51 (*m*, 2 CH_2O); 3.62–3.70 (*m*, 2 CH_2O, MeO); 3.79–3.86 (*m*, H−C(β)); 4.35–4.51 (*m*, 2 PhCH_2, 4 H−C(β)). FAB-MS: 1208.4 (10, $[M+\{3\text{-NOBA}\}]^+$), 1077.5 (100, $[M+Na]^+$), 955.5 (8, $[M-Boc]^+$).

*H_2N-(β^3-HVal-(2*R*,3*R*)-(α-CH_2OH)-$\beta^{2,3}$-HSer(OBn)-β^3-HLeu)$_2$-OH* (**18**). β-Peptide **17** (55.5 mg, 0.525 mmol) was dissolved in 2 ml of TFE. NaOH (210 mg, 100 equiv.) dissolved in 1 ml of H_2O was added, and the resulting suspension was stirred overnight at r.t. The resulting clear soln. was acidified with 6M HCl to pH 2 and extracted with AcOEt. The org. phase was dried ($MgSO_4$) and evaporated. The resulting 54.5 mg (0.523 mmol) Boc-β-peptide acid were deprotected according to *GP 1*. The resulting colorless oil was dissolved in 5 ml of THF, 0.5 ml of AcOH, and 10 mg of Pd/C (10%) were added, and the apparatus was evacuated and flushed with H_2 three times. The mixture was stirred for 40 h at r.t. The resulting suspension was filtered over *Celite* and evaporated. Purification by prep. RP-HPLC gave **18** (9.2 mg; 23%) after lyophilization. Colorless fluffy solid. Anal. RP-HPLC: t_R 15.3 min (C_{18}; gradient 20 min 25–50% *B*; 10 min 50–99% *B*). ^{1}H-NMR (500 MHz, CD_3OH): chemical shifts of non-Me protons of **18** were assigned by 2D-NMR (DQF-COSY, TOCSY). Xaa = (2*R*,3*R*)-(α-CH_2OH)-$\beta^{2,3}$-HSer(OBn).

	Val1	Xaa2	Leu3	Val4	Xaa5	Leu6
NH	n/d	7.95	7.98	7.91	7.71	7.89
H−C(β)	3.39	4.11	4.15	3.99	4.08	4.21
H−C(γ)	1.91	3.57	1.34	1.69	3.51	1.37
H′−C(γ)	–	3.48	1.18	–	3.44	1.24
H−C(α)	2.68	2.71	2.38	2.49	2.64	2.47
H′−C(α)	2.53	–	2.31	2.26	–	2.36
H−C(β')	–	3.65	–	–	3.61	–
H′−C(β')	–	3.65	–	–	3.61	–

FAB-MS: 799.6 (67, $[M+K]^+$), 783.6 (100, $[M+Na]^+$), 761.6 (67, $[M+H]^+$).

*Boc-(2*S*,3*R*)-HCcy(Bn)$_2$-(*R*)-β^3-HVal-(*S*)-β^3-HAla-(*S*)-β^3-HLeu-OMe* (**19**). Compound **9** (200 mg, 0.36 mmol) was dissolved in 4 ml of THF and cooled to 0°. TBAF (220 mg, 0.7 mmol) was added, and the soln. was stirred at r.t. for 1 h. H_2O (5 ml) and Et_2O (5 ml) were added, and the mixture was stirred for 10 min. The phases were divided, and the aq. phase was extracted with AcOEt. The org. phases were dried ($MgSO_4$) and then concentrated under reduced pressure: **10** was obtained as a colorless oil and used without further purification. In a second flask, **15a** (165 mg, 0.36 mmol) was deprotected according to *GP 1*, dissolved in 1 ml of $CHCl_3$, and treated with NMM (145 mg, 1.44 mmol), HOBt (65 mg, 0.48 mmol), **10** (see above) in 1 ml of $CHCl_3$, and EDC (92 mg, 0.48 mmol) according to *GP 3a*, FC (CH_2Cl_2/MeOH 12:1) yielded **19** (180 mg, 63%). White solid. M.p. 169–170°. R_f 0.5 (CH_2Cl_2/MeOH 15:1). $[\alpha]_D^{r.t.} = -7.3$ ($c = 1.0$, $CHCl_3$): IR (KBr): 3301*m*, 2963*m*, 1735*m*, 1718*m*, 1686*s*, 1654*s*, 1560*s*, 1542*s*, 1262*m*, 1247*m*, 1170*m*, 802*m*, 696*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.90–0.92 (*m*, 4 Me); 1.18 (*d*, *J* = 6.7, Me); 1.25–1.32 (*m*, 1 H, CH_2); 1.42 (*s*, *t*-Bu); 1.43–1.50 (*m*, 1 H, CH_2); 1.54–1.62 (*m*, CH); 1.79–1.86 (*m*, CH); 2.18–2.82 (*m*, 3 CH_2CO, CHCO, 2 CH_2S); 3.67 (*s*, MeO); 3.72, 3.75 (2*s*, 2 PhCH_2); 3.91–3.97 (*m*, CHN); 4.00–4.06 (*m*, CHN); 4.10–4.18 (*m*, CHN); 4.27–4.36 (*m*, CHN); 6.08 (br., NH); 6.27 (br., NH); 6.53 (br., NH); 6.94 (br., NH); 7.21–7.35 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.9, 19.5, 19.6, 22.2, 22.8 (Me); 25.1 (CH); 28.4 (Me); 31.6 (CH); 34.8, 36.0, 36.9, 38.4, 40.0, 41.3 (CH_2); 43.2, 44.4, 46.7, 50.9 (CH); 51.8 (Me); 52.2 (CH); 79.1 (C); 127.0, 127.2, 128.5, 128.6, 128.9, 129.1 (arom. C); 138.2, 138.3, 155.7, 170.0, 170.7, 172.0, 172.3 (C). FAB-MS: 823 (5, $[M+Na]^+$), 801 (25, $[M+1]^+$), 701 (100, $[M-Boc+1]^+$). Anal. calc. for $C_{42}H_{64}N_4O_7S_2$ (801.11): C 62.97, H 8.05, N 6.99; found: C 62.63, H 7.73, N 6.92.

*Boc-(2*S*,3*R*)-HCcy(Bn)$_2$-(*R*)-β^3-HVal-(*R*)-β^3-HSer(Bn)-(*S*)-β^3-HLeu-OMe* (**20**). Compound **9** (216 mg, 0.385 mmol) was dissolved in 4 ml of THF and cooled to 0°. TBAF (240 mg, 0.76 mmol) was added, and the soln. was stirred at r.t. for 1 h. H_2O (5 ml) and Et_2O (5 ml) were added, and the mixture was stirred for 10 min. The

phases were divided, and the aq. phase was extracted with AcOEt. The org. phases were dried ($MgSO_4$) and then concentrated under reduced pressure: **10** was obtained as a colorless oil and used without further purification. In a second flask, **16a** (217 mg, 0.385 mmol) was deprotected according to *GP 1*, dissolved in 1 ml of $CHCl_3$, and treated with NMM (155 mg, 1.54 mmol), HOBt (68 mg, 0.5 mmol). **10** (see above) in 1 ml of $CHCl_3$, and EDC (96 mg, 0.5 mmol) according to *GP 3a*. FC (CH_2Cl_2/MeOH 20:1) yielded **20** (110 mg, 34%). White solid. M.p. 146–147°. R_f 0.55 (CH_2Cl_2/MeOH 15:1). $[\alpha]_D^{r.t.} = -2.3$ ($c = 0.5$, $CHCl_3$). IR (KBr): 3297*s*, 3063*w*, 3030*w*, 2958*m*, 1740*m*, 1690*s*, 1647*s*, 1541*s*, 1496*m*, 1452*m*, 1437*m*, 1367*m*, 1290*w*, 1248*w*, 1170*m*, 1028*w*, 699*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88–0.95 (*m*, 4 Me); 1.20–1.27 (*m*, 1 H, CH_2); 1.35–1.48 (*m*, *t*-Bu, 1 H of CH_2); 1.51–1.61 (*m*, CH); 1.79–1.85 (*m*, CH); 2.25–2.82 (*m*, 3 CH_2CO, CHCO, 2 CH_2S); 3.65 (*s*, MeO); 3.71, 3.74 (2*s*, 2 PhCH_2S); 3.90–4.05 (*m*, 2 CHN); 4.23–4.36 (*m*, 2 CHN); 4.47 (*s*, PhCH_2O); 6.13 (br., NH); 6.39 (br., NH); 6.53 (br., NH); 6.90 (br., NH); 7.19–7.36 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.9, 19.5, 22.1, 22.8 (Me); 25.0 (CH); 28.4 (Me); 31.4 (CH); 31.8, 34.8, 35.9, 36.9, 37.2, 38.2, 38.9, 43.2 (CH_2); 44.4, 46.6, 50.8 (CH); 51.7 (Me); 52.1 (CH); 79.1 (C); 127.0, 127.2, 127.8, 127.9, 128.5, 128.6, 128.9, 129.1 (arom. C); 137.8, 138.2, 138.3, 155.7, 170.4, 172.0, 172.3 (C). FAB-MS: 929 (100, $[M+Na]^+$), 907 (39, $[M+1]^+$), 807 (95, $[M-Boc+1]^+$).

Boc(R)-*β*^{3}-*HVal*-(S)-*β*^{3}-*HAla*-(S)-*β*^{3}-*HLeu*-(2*S*,3R)-*HCcy*(*Bn*)$_2$-(R)-*β*^{3}-*HVal*-(S)-*β*^{3}-*HAla*-(S)-*β*^{3}-*HLeu*-*OMe* (**21**). Compound **19** (140 mg, 0.175 mmol) was deprotected according to *GP 1*, dissolved in 0.5 ml of $CHCl_3$, and treated with NMM (71 mg, 0.7 mmol), HOBt (54 mg, 0.4 mmol), **15b** (78 mg, 0.175 mmol) in 0.6 ml of DMF, and EDC (76 mg, 0.4 mmol) according to *GP 3b*. Recrystallization from MeOH yielded **21** (156 mg, 79%). White solid. M.p. 243–244°. R_f 0.33 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{r.t.} = -7.3$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3304*s*, 2960*m*, 1741*m*, 1684*s*, 1636*s*, 1541*s*, 1457*s*, 1261*m*, 1175*m*, 1142*m*, 1018*m*, 804*w*, 698*m*. ^{1}H-NMR (500 MHz, $CDCl_3$/CD_3OD 3:1): 0.88–0.96 (*m*, 6 Me); 1.13, 1.16 (2*d*, $J = 6.7$, 2 Me); 1.27–1.35 (*m*, 3 CH); 1.43 (*s*, *t*-Bu); 1.43–1.48 (*m*, 1 H, CH_2); 1.57–1.64 (*m*, 2 H, 2 CH_2); 1.74–1.85 (*m*, 2 CH); 2.21–2.78 (*m*, 7 CH_2CO, 2 CH_2S); 3.67–3.73 (*m*, CHN); 3.68 (*s*, MeO); 3.71, 3.74 (2*s*, 2 PhCH_2S); 4.10–4.17 (*m*, 2 CHN); 4.22–4.32 (*m*, 3 CHN); 4.33–4.37 (*m*, CHN); 5.87 (br., NH); 7.21–7.33 (*m*, 10 arom. H); 7.41 (br., NH); 7.53 (br., NH). ^{13}C-NMR (125 MHz, $CDCl_3$/CD_3OD 3:1): 18.1, 18.5, 18.9, 19.0, 19.7, 21.6, 21.7, 22.5, 22.5, 24.6 (Me); 24.6 (CH); 27.9 (Me); 31.3 (CH_2); 31.6, 32.0 (CH); 33.9, 35.5, 36.0, 37.3, 38.3, 39.3, 39.7, 41.0, 41.3, 41.9 (CH_2); 42.7 (CH); 42.7, 43.2 (CH_2); 44.2, 44.6, 46.5, 49.0, 51.4 (CH); 51.7 (Me); 53.2 (CH); 78.8 (C); 126.7, 126.9, 128.2, 128.3, 128.5, 128.7, 130.0 (arom. C); 137.6, 137.9, 156.2, 170.3, 170.5, 170.8, 171.3, 172.0, 172.0 (C). FAB-MS: 1149 (100, $[M+Na]^+$), 1126 (5, $[M+1]^+$), 1026 (15, $[M-Boc+1]^+$).

Boc-(R)-*β*^{3}-*HVal*-(R)-*β*^{3}-*HSer*(*Bn*)-(S)-*β*^{3}-*HLeu*-(2*S*,3R)-*HCcy*(*Bn*)$_2$-(R)-*β*^{3}-*HVal*-(R)-*β*^{3}-*HSer*(*Bn*)-(S)-*β*^{3}-*HLeu*-*OMe* (**22**). Compound **20** (98 mg, 0.11 mmol) was deprotected according to *GP 1*, dissolved in 0.5 ml of $CHCl_3$ and treated with Et_3N (61 mg, 0.6 mmol), HOBt (27 mg, 0.2 mmol), **16b** (61 mg, 0.11 mmol) in 0.3 ml of DMF, and EDC (38 mg, 0.2 mmol) according to *GP 3b*. FC (CH_2Cl_2/MeOH 20:1) yielded **22** (117 mg, 80%). White solid. CD (0.2 mM in MeOH): $+6.2 \cdot 10^4$ (199 nm); $-2.7 \cdot 10^4$ (215 nm). IR (KBr): 3297*s*, 3065*w*, 2958*m*, 2870*m*, 1734*m*, 1685*s*, 1653*s*, 1541*s*, 1452*w*, 1366*m*, 1311*w*, 1248*m*, 1175*m*, 1122*w*, 1028*w*, 735*w*, 698*w*. ^{1}H-NMR (400 MHz, $CDCl_3$/CD_3OD 3:1): 0.77–0.87 (*m*, 8 Me); 1.13–1.35 (*m*, 4 H of 4 CH_2, *t*-Bu); 1.50–1.58 (*m*, 2 CH); 1.60–1.69 (*m*, 2 CH); 2.13–2.62 (*m*, 6 CH_2CO, CHCO, 2 CH_2S); 3.31–3.69 (*m*, MeO, 2 PhCH_2S, 3 CHN); 3.96–4.35 (*m*, 3 CHN); 4.41 (*s*, PhCH_2O); 4.51 (*s*, PhCH_2O); 6.03 (br., NH); 7.15–7.26 (*m*, 20 arom. H). FAB-MS: 1377 (14, $[M+K]^+$), 1361 (100, $[M+Na]^+$), 1339 (6, $[M+1]^+$), 1239 (79, $[M-Boc+1]^+$).

H-(R)-*β*^{3}-*HVal*-(S)-*β*^{3}-*HAla*-(S)-*β*^{3}-*HLeu*-(2*S*,3R)-*ADTC*-(R)-*β*^{3}-*HVal*-(S)-*β*^{3}-*HAla*-(S)-*β*^{3}-*HLeu*-*OH*·CF_3CO_2H (**23**). Compound **21** (83 mg, 0.074 mmol) was dissolved in 2 ml of CF_3CH_2OH and treated with 2 ml of 5N NaOH at 45° over 40 h. The mixture was diluted with H_2O, and the pH was adjusted to 2–3 with 5N HCl (0°). The soln. was extracted with AcOEt, and the combined org. phases washed successively with sat. NaCl soln. and H_2O. The org. phase was evaporated and dried under h.v. The resulting white solid (80 mg) was deprotected and cyclized according to *GP 4*. The crude peptide was purified by prep. RP-HPLC (30 → 70% *B* in 35 min) according to *GP 5* to yield **23** (22 mg, 36%). White solid. RP-HPLC (45 → 60% *B* in 20 min): t_R 24.1 min, purity > 98%. M.p. 149–151° (dec.). CD (0.2 mM in MeOH): $-1.03 \cdot 10^5$ (209 nm); $+1.4 \cdot 10^4$ (289 nm). CD (0.2 mM in H_2O): $-9.7 \cdot 10^4$ (205 nm); $1.1 \cdot 10^4$ (281 nm). IR (KBr): 3292*s*, 3082*m*, 2964*m*, 1734*m*, 1654*s*, 1542*s*, 1458*m*, 1374*m*, 1261*m*, 1202*m*, 1137*m*, 800*w*, 699*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.84–0.93 (*m*, 6 Me); 1.05–1.10 (*m*, 3 Me); 1.18 (*d*, $J = 6.7$, Me); 1.21–1.39 (*m*, 4 CH); 1.50–1.61 (*m*, CH_2); 1.62–1.72 (*m*, 1 H, CH_2); 2.01–3.12 (*m*, 1 H of CH_2, 6 CH_2CO, CHCO, 2 CH_2S); 3.50–3.54 (*m*, CHN); 4.10–4.18 (*m*, CHN); 4.23–4.29 (*m*, CHN); 4.35–4.43 (*m*, CHN); 4.44–4.48 (*m*, CHN); 4.49–4.56 (*m*, 2 CHN); 7.41 (br., NH); 8.39 (br., NH); 8.57 (br., NH). ^{13}C-NMR (125 MHz, CD_3OD): 18.3, 19.2, 19.5, 19.9, 21.0, 21.5, 23.0, 23.1, 23.4, 23.5 (Me); 25.9, 26.1, 32.0, 34.3 (CH); 35.9, 37.9, 39.4, 40.2, 40.4, 42.3, 42.9, 43.3 (CH_2); 43.5, 45.3, 45.6 (CH); 46.0, 46.9 (CH_2); 50.3, 51.8, 53.2, 56.0 (CH); 171.2, 171.4, 171.6, 172.0, 173.1, 173.2, 175.2 (C). FAB-MS: 1660 (4, $[2M+1]^+$), 852

(4, $[M+Na]^+$), 830 (100, $[M+1]^+$). ESI-MS (pos.): 869 (6, $[M+K]^+$), 853 (36, $[M+Na]^+$), 831 (100, $[M+1]^+$). ESI-MS (neg.): 828 (100, $[M-1]^-$).

*H-(*R*)-β³-HVal-(*R*)-β³-HSer-(*S*)-β³-HLeu-(2*S*,3*R*)-ADTC-(*R*)-β³-HVal-(*R*)-β³-HSer-(*S*)-β³-HLeu–OH · CF_3CO_2H* (**24**). Compound **22** (108 mg, 0.08 mmol) was dissolved in 2 ml of CF_3CH_2OH and treated with 2 ml of 5N NaOH at 45° over 17 h. The mixture was diluted with H_2O, and the pH was adjusted to 2–3 with 5N HCl (0°). The soln. was extracted with AcOEt, and the combined org. phases were washed successively with sat. NaCl soln. and H_2O. The org. phase was evaporated and dried under h.v. The resulting white solid (106 mg) was deprotected and cyclized according to *GP 4*. The crude peptide was purified by prep. RP-HPLC (20 → 50% *B* in 45 min) according to *GP 5* to yield **24** (23 mg, 36%). White solid. RP-HPLC (30 → 45%, *B* in 30 min): t_R 26.1 min, purity >98%. M.p. 145–146° (dec.). CD (0.2 mM in MeOH): $-1.08\cdot10^5$ (208 nm); $+1.2\cdot10^4$ (285 nm). CD (0.2 mM in H_2O): $-1.00\cdot10^5$ (206 nm); $+0.9\cdot10^4$ (286 nm). IR (KBr): 3293*s*, 3092*w*, 2963*m*, 1654*m*, 1550*s*, 1466*w*, 1430*w*, 1388*w*, 1203*s*, 1137*s*, 1057*w*, 1028*w*, 801*w*, 723*m*. ^{1}H-NMR (500 MHz, CD_3OD): 0.90–0.99 (*m*, 6 Me); 1.10–1.13 (*m*, 2 Me); 1.24–1.73 (*m*, 3 CH, 2 CH_2); 2.06–3.17 (*m*, 1 H of CH_2, 6 CH_2CO, CHCO, 2 CH_2S); 3.44–3.62 (*m*, 2 CH_2O, CHN), 4.21–4.26 (*m*, CHN); 4.30–4.36 (*m*, CHN); 4.38–4.50 (*m*, 2 CHN); 4.51–4.60 (*m*, 2 CHN); 7.41 (br., NH); 7.68 (br., NH); 7.84 (br., NH); 8.28 (br., NH); 8.43 (br., NH); 8.62 (br., NH). ^{1}H-NMR (500 MHz, H_2O/D_2O 9:1): 0.83–0.90 (*m*, 6 Me); 0.99–1.03 (*m*, 2 Me); 1.23–1.76 (*m*, 3 CH, 2 CH_2); 1.96–2.94 (*m*, 1 H of CH_2, 6 CH_2CO, CHCO, CH_2S); 3.10–3.14 (*m*, CH_2S); 3.51–3.63 (*m*, 2 CH_2O, CHN); 4.04–4.08 (*m*, CHN); 4.06–4.10 (*m*, CHN); 4.17–4.21 (*m*, CHN); 4.18–4.23 (*m*, CHN); 4.23–4.28 (*m*, CHN); 4.25–4.30 (*m*, CHN); 7.87 (br., NH); 7.89 (br., NH); 7.91 (br., NH); 7.96 (br., NH); 8.17 (br., NH); 8.27 (br., NH). ^{13}C-NMR (125 MHz, H_2O/D_2O 9:1): 19.9, 20.2, 20.3, 21.0, 24.2, 24.2, 25.0, 25.0 (Me); 27.1, 27.2, 32.9, 34.8 (CH); 37.0, 39.0, 39.4, 39.5, 39.8, 39.9, 40.4, 40.5, 40.7, 43.0, 44.2, 46.0, 46.8 (CH_2); 47.9, 48.1, 51.2, 51.3, 51.8, 52.9 (CH); 53.5 (CH_2); 54.7, 57.0, 57.1 (CH); 65.7, 66.1 (CH_2); 174.3, 174.6, 174.7, 174.9, 175.0, 175.3, 179.0 (C). FAB-MS: 884 (51, $[M+Na]^+$), 862 (100, $[M+1]^+$).

Boc-trans-*ACHC-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OMe* (**25a**/**b**). Compound **15a** (458 mg, 1 mmol) was deprotected according to *GP 1*, dissolved in 1.8 ml of $CHCl_3$, and treated with Et_3N (505 mg, 5 mmol), HOBt (165 mg, 1.2 mmol), Boc-*trans*-ACHC–OH (243 mg, 1 mmol) in 1.8 ml of $CHCl_3$, and EDC (230 mg, 1.2 mmol) according to *GP 3a*. Recrystallization from MeOH yielded **25a**/**25b** (411 mg, 72%). White solid. M.p. 169–170°. R_f 0.4 (CH_2Cl_2/MeOH 15:1). IR (KBr): 3304*s*, 3297*s*, 3080*w*, 2959*m*, 2931*m*, 2871*w*, 1744*m*, 1684*s*, 1646*s*, 1541*s*, 1458*w*, 1438*w*, 1368*m*, 1320*w*, 1270*w*, 1174*m*, 1141*w*, 1051*w*, 1001*w*. ^{1}H-NMR (300 MHz, $CDCl_3$/CD_3OD 3:1; 2 epimers): 0.81–0.85 (*m*, 3 Me); 1.06, *1.08* (2*d*, *J* = 6.2, Me); 1.32 (*s*, *t*-Bu); 1.17–2.43 (*m*, 2 CH, 5 CH_2, 3 CH_2CO, CHCO); 3.42–3.46 (*m*, CHN); 3.59 (*s*, MeO); 3.85–3.93 (*m*, CHN); 3.95–4.6 (*m*, CHN); 4.10–4.18 (*m*, CHN). FAB-MS: 605 (42, $[M+Na]^+$), 583 (45, $[M+1]^+$), 483 (17, $[M-Boc+1]^+$).

*Boc-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu*-trans-*ACHC-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OMe* (**26a**/**26b**). The epimer mixture **25a**/**25b** (291 mg, 0.5 mmol) was deprotected according to *GP 1*, dissolved in 3 ml of DMF/$CHCl_3$ 1:1 and treated with Et_3N (253 mg, 2.5 mmol), HOBt (81 mg, 0.6 mmol), **15b** (243 mg, 1 mmol) in 2 ml of DMF, and EDC (115 mg, 0.6 mmol) according to *GP 3b*. The resulting crude **26a**/**26b** (444 mg) could not be purified due to low solubility in all common org. solvents. White solid. M.p. 201–202°. R_f 0.4 (CH_2Cl_2/MeOH 10:1): IR (KBr): 3296*s*, 3081*w*, 2959*m*, 2933*m*, 2872*w*, 1740*m*, 1689*s*, 1649*s*, 1543*s*, 1438*m*, 1367*m*, 1311*m*, 1249*m*, 1175*m*, 1144*w*, 1052*w*, 1020*w*. ^{1}H-NMR (500 MHz, $CDCl_3$/CD_3OD 3:1; 2 epimers): 0.81–0.87 (*m*, 8 Me); 1.02–1.30 (*m*, 2 Me, 3 CH_2); 1.35, *1.38* (2*s*, *t*-Bu); 1.47–2.21 (*m*, 3 CH_2, 4 CH); 2.25–3.15 (*m*, 6 CH_2CO, CHCO); 3.60, *3.65* (2*s*, MeO); 3.62–4.36 (*m*, 7 CHN). FAB-MS: 1149 (100, $[M+Na]^+$), 1126 (5, $[M+1]^+$), 1026 (15, $[M-Boc+1]^+$).

*H-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-(2*R*,3*R*)-ACHC-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OH · CF_3CO_2H* (**27a**) *and H-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-(2*S*,3*S*)-ACHC-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OH · CF_3CO_2H* (**27b**). The epimer mixture **26a**/**26b** (59 mg, 0.052 mmol) was deprotected according to *GP 1* and *GP 2b*. The crude peptide was purified by prep. RP-HPLC (10 → 40% *B* in 35 min) according to *GP 5* to yield **27a** (13 mg, 31%) and prep. RP-HPLC (20 → 60% *B* in 45 min) to yield **27b** (11 mg, 26%).

Data for **27a**: White solid. RP-HPLC (0 → 40% *B* in 45 min): t_R 32.9 min, purity >99%. M.p. 280° (dec.). CD (0.2 mM in MeOH): $-3.2\cdot10^4$ (200 nm); $+0.8\cdot10^4$ (214 nm); $+0.5\cdot10^4$ (228 nm). IR (KBr): 3293*s*, 3081*w*, 2960*m*, 2935*m*, 1654*s*, 1543*s*, 1458*w*, 1388*w*, 1312*w*, 1202*m*, 1140*m*, 800*w*, 722*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.89–0.93 (*m*, 6 Me); 1.06 (*dd*, *J* = 6.9, 3.9, 2 Me); 1.13 (*d*, *J* = 6.7, Me); 1.19 (*d*, *J* = 6.3, Me); 1.22–2.04 (*m*, 4 CH, 6 CH_2); 2.21–2.62 (*m*, 6 CH_2CO, CHCO); 3.40–3.45 (*m*, CHN); 3.90–3.97 (*m*, CHN); 4.03–4.08 (*m*, CHN); 4.11–4.23 (*m*, 2 CHN); 4.25–4.34 (*m*, 2 CHN). ^{13}C-NMR (125 MHz, CD_3OD): 18.3, 18.7, 18.8, 19.9, 20.2, 20.9, 22.3, 22.5, 23.5, 23.7 (Me); 26.0 (CH); 26.0 (CH_2); 26.1 (CH); 26.3, 31.3 (CH_2); 31.9, 33.4 (CH); 33.8, 35.7, 39.8, 41.0, 41.7, 43.4, 44.4 (CH_2); 44.5, 44.6 (CH); 44.8 (CH_2); 45.9, 46.3, 50.7, 52.2, 53.0, 55.9 (CH);

171.7, 172.2, 172.5, 172.6, 172.7, 174.9, 175.9 (C). FAB-MS: 832 (10, $[M+K]^+$), 816 (100, $[M+Na]^+$), 794 (81, $[M+1]^+$).

Data for **27b**: White solid. RP-HPLC ($20 \rightarrow 55\%$ *B* in 20 min): t_R 19.0 min, purity >98%. M.p. 148–149° (dec.). CD (0.2 mM in MeOH): $+8.9 \cdot 10^4$ (198 nm); $-6.2 \cdot 10^4$ (216 nm). CD (0.2 mM in H_2O): $+2.2 \cdot 10^4$ (195 nm); $-2.8 \cdot 10^4$ (214 nm). IR (KBr): 3290*s*, 3085*w*, 2963*m*, 2940*m*, 1654*s*, 1560*s*, 1458*w*, 1388*w*, 1312*w*, 1202*m*, 1140*m*, 799*w*, 722*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.90–0.96 (*m*, 6 Me); 1.09–1.14 (*m*, 3 Me); 1.23–2.10 (*m*, 4 CH, 6 CH_2, Me); 2.18–2.97 (*m*, 6 CH_2CO, CHCO); 3.54–3.60 (*m*, CHN); 3.95–4.03 (*m*, CHN); 4.18–4.26 (*m*, CHN); 4.37–4.45 (*m*, CHN); 4.45–4.53 (*m*, 2 CHN); 4.54–4.63 (*m*, CHN); 7.51 (br., NH); 7.81 (br., NH); 7.90 (br., NH); 7.93 (br., NH). ^{13}C-NMR (125 MHz, CD_3OD): 17.9, 19.2, 19.5, 20.0, 21.1, 21.4, 22.9, 23.1, 23.5, 23.6 (Me); 26.0, 26.1 (CH); 26.2, 26.3 (CH_2); 32.0 (CH); 32.2, 33.2 (CH_2); 34.4 (CH); 36.0, 39.4, 40.6, 42.3, 42.8, 43.1 (CH_2); 43.3, 43.5, 45.4, 45.6 (CH); 45.9, 47.1 (CH_2); 51.1, 52.8, 52.9, 56.0 (CH); 171.2, 171.4, 171.7, 171.8, 173.4, 175.0, 175.7 (C). FAB-MS: 832 (93, $[M+K]^+$), 816 (31, $[M+Na]^+$),794 (100, $[M+1]^+$).

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