Preparation and Structure of β-Peptides Consisting of Geminally Disubstituted $\beta^{2,2}$- and $\beta^{3,3}$-Amino Acids: A Turn Motif for β-Peptides

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We report on the synthesis of new and previously described β-peptides (**1**–**6**), consisting of up to twelve $\beta^{2,2}$- or $\beta^{3,3}$-geminally disubstituted β-amino acids which do not fit into any of the secondary structural patterns of β-peptides, hitherto disclosed. The required 2,2- and 3,3-dimethyl derivatives of 3-aminopropanoic acid are readily obtained from 3-methylbut-2-enoic acid and ammonia (*Scheme 1*) and from Boc-protected methyl 3-aminopropanoate by enolate methylation (*Scheme 2*). Protected (Boc for solution-, Fmoc for solid-phase syntheses) 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives (with cyclopropane, cyclobutane, cyclopentane, and cyclohexane rings) are obtained from 1-cyanocycloalkanecarboxylates and the corresponding dihaloalkanes (*Scheme 3*). Fully ^{13}C- and ^{15}N-labeled 3-amino-2,2-dimethylpropanoic-acid derivatives were prepared from the corresponding labeled precursors (see asterixed formula numbers and *Scheme 4*). Coupling of these amino acids was achieved by methods which we had previously employed for other β-peptide syntheses (intermediates **18**–**23**). Crystal structures of Boc-protected geminally disubstituted amino acids (**16a**–**d**) and of the corresponding tripeptide (**23a**), as well as NMR and IR spectra of an isotopically labeled β-hexapeptide (**2a***) are presented (*Figs. 1–4*) and discussed. The tripeptide structure contains a ten-membered H-bonded ring which is proposed to be a turn-forming motif for β-peptides (*Fig. 2*).

1. Introduction. – The discovery that short-chain β-peptides form much more stable secondary structures in solution than do their natural counterparts, the α-peptides, has brought about a spate of interest in the field of β-peptides [1] (reviews: [2]). Three types of β-peptide helices and two turn motifs [3–6], an antiparallel [7] and a parallel [3][8] sheet structure, and tubular arrangements of cyclic β-peptides [9][10] have been identified so far by CD and 2D-NMR spectroscopy, and by X-ray crystal-structure analysis. The high stability of the helical structure of β-heptapeptides has been further supported by molecular-dynamics calculations [11]. The greater structural variability of β-amino acids accounts for the multitude of possible β-peptide secondary structures. These findings allow the design of β-peptide secondary structures with well-defined folding propensities by choosing the 'correctly' substituted β-amino acids. The β-peptides are, therefore, valuable objects for the ultimate design of synthetic enzymes.

However, there do remain substitution patterns (Table 1 in [5]) of β-amino acids, particularly the $\beta^{2,2}$- and $\beta^{3,3}$-disubstituted ones, which do not fit in the secondary

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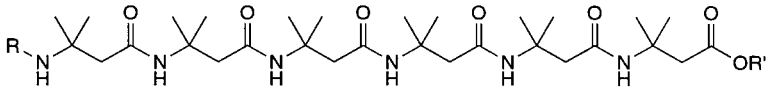
2) Postdoctoral research at ETH-Zürich as part of the *Swiss National Science Foundation Project* No. 20-50674.97/1.

3) Part of the Master Thesis (Diplomarbeit) of *M.H.*, ETH-Zürich, 1998.

4) Part of the Master Thesis (Diplomarbeit) of *S.G.*, Ecole Européenne de Chimie Polymères et Matériaux, Strasbourg, carried out at ETH-Zürich, 1998.

structures found to date (geminally disubstituted β-amino acids are helix- and pleated-sheet breaking residues in β-peptides; see the analysis presented in [5])[5]). Hence, we chose to synthesize the β-peptides **1**–**6** in order to study their structure[6]).

1



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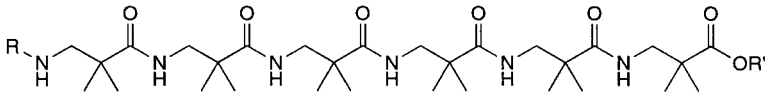
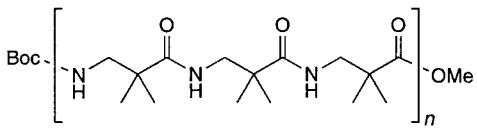


a, a* R = Boc, R' = Me
b R = Boc, R' = H
c R = H·CF_3COOH, R' = Me
d R = H·CF_3COOH, R' = H

an asterix indicates fully ^{15}N- and ^{13}C-labeled compounds (except protecting groups)

3a $n = 3$
3b $n = 4$



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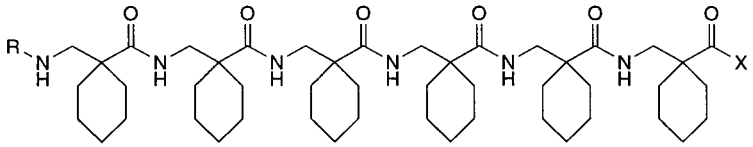
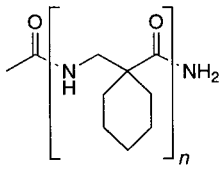


a R = Ac, X = NH_2
b R = Boc, X = OMe
c R = H·CF_3COOH, X = OH

5 $n = 3$
6 $n = 4$



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5) We have also prepared β-peptides consisting of alternating (*R*)- and (*S*)-β^3-amino acids [12b]. These β-peptides probably form a new type of secondary structure as indicated by their CD spectra [8].

6) By conformational analysis of these homopeptides, it should be possible to determine the minimum number of residues necessary for the formation of stable secondary structures.

Their design was encouraged by the high crystallinity of polypeptides from α-amino acids disubstituted at the C(α)-atom[7]) [13]. In addition, it was interesting to compare the β-analogues of Aib peptides with Aib peptides which are known adopt the 3_{10} helix (fully developed at the pentamer level); Aib is the strongest β-bend and helix promoter, when incorporated into peptides [15][16]. The 1-(aminomethyl)cyclohexanecarboxylic-acid moiety[8]) was supposed to increase the crystallization tendency by introducing restraints that could reduce the flexibility of the peptide backbone [17].

Many years ago, *Drey* and co-workers synthesized a tripeptide consisting of 3-amino-3-methylbutanoic acid (β-aminoisovaleric acid, β^3-HAib) [18] and a hexapeptide[9]) consisting of 3-amino-2,2-dimethylpropanoic acid (β-aminopivalic acid, β^2-HAib) [19]. Their primary goal was to test coupling of sterically demanding amino acids which could not be efficiently coupled by conventional methods[10]) [18b][20][21]. However, the structures of these compounds remained unknown.

In the present paper, we describe the synthesis and structural investigations of β-homopeptides **1**–**6** consisting of geminally dimethylated β-amino acids (**1**–**3**) or of 1-(aminomethyl)cyclohexanecarboxylic acid (**4**–**6**). For solid-state NMR experiments, the fully ^{13}C- and ^{15}N-labeled $\beta^{2,2}$-hexapeptide **2a*** was also synthesized. Furthermore, 1-(aminomethyl)cyclopropane-, -butane-, and -pentanecarboxylic-acid derivatives have been prepared, and their crystal structures determined.

2. Preparation of the $\beta^{2,2}$- and $\beta^{3,3}$-Amino-Acid Building Blocks. – Among several methods for the preparation of β-amino acids [22], only a few are suitable for the generation of a tertiary center at the β-position: The *Michael* addition of ammonia to 3-methylbut-2-enoic-acid derivatives [23], the cycloaddition of alkenes with chlorosulfonyl isocyanate, followed by protection of the β-lactam N-atom and saponification [18b][24], the hydrolysis of 6,6-disubstituted dihydrouracils [25], the three-component *Mannich* reaction of a ketone, ammonia, and a malonic-acid derivative [26], and the reaction of ethyl 3-hydroxy carboxylates with nitriles to give the corresponding *N*-acyl-β-amino acids [27].

In view of a straightforward multi-gram scale synthesis of the monomeric building blocks for peptide coupling, we chose the first-mentioned method for the preparation of 3-amino-3-methylbutanoic-acid derivatives (β^3-HAib residue; *Scheme 1*). Saponification of the amide **7**, obtained by reaction of ammonia with 3-methylbut-2-enoic acid[11]) and Boc-protection afforded the $\beta^{3,3}$-amino-acid derivative **8** [4][24b], the methyl ester **9** of which (required for peptide coupling) was prepared by methylation of the Cs salt.

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7) The number of solved structures of Aib homopeptides is rapidly increasing, much more so than for any other amino-acid derivatives [13]; see also the structures of oligo-lva-peptides consisting of enantiomerically pure 2-amino-2-methylbutanoic-acid residues [14].

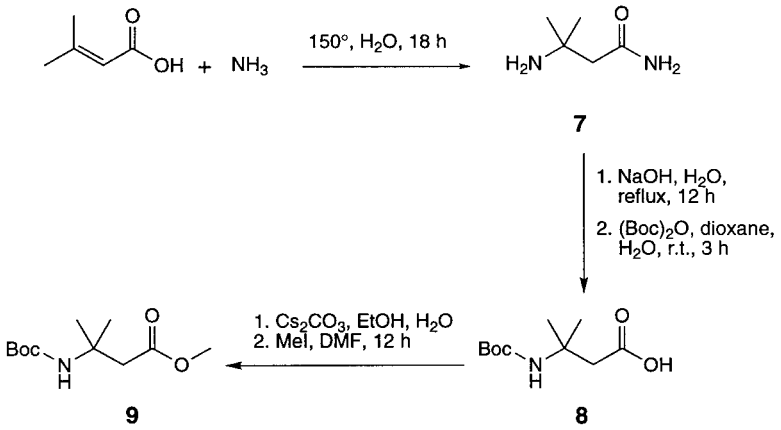
8) The X-ray structures of protected dimers, trimers, and tetramers of this α-amino acid have been reported (review: [13]).

9) *Cf.* compound **2d** in the present paper.

10) Eventually the synthesis of the trimer of β-aminoisovaleric acid (half the chain length of compound **1** described in the present paper) required the aminolysis of the corresponding dihydro-1,3-oxazinones [18b], whereas the synthesis of the hexamer of β-aminopivalic acid could be achieved with DCC and

11) In contrast to the results of our experiments, the corresponding carboxylic acid was reported [23a] as sole reaction product under the employed conditions.

Scheme 1. *Preparation of $\beta^{3,3}$-Amino-Acid Building Blocks*



For the preparation of α,α-disubstituted β-amino acids, several methods are known: the aminomethylation of silyl ketene acetals with *N,N*-bis[(trimethylsilyl)methoxy]-methylamine [28], a one-pot *Mannich*-type condensation of aldehydes, amines, and silyl ketene acetals in H_2O in the presence of $InCl_3$ [29], the *Reformatzky* reaction of an appropriate benzotriazol derivative with 2-bromoalkanoates [30], and the dimethylation of ethyl cyanoacetate with subsequent reduction of the CN to an aminomethyl group [31]. For the preparation of 3-amino-2,2-dimethylpropanoic-acid derivatives (β^2-HAib residue; *Scheme 2*), we chose to use a method developed by us [5][32]: methylation of the Boc-protected methyl 3-aminopropanoate **10** *via* doubly lithiated species. The monomethylated ester **11** underwent a second methylation to give the *N*-Boc-methyl ester **12** (80% from **10**), saponification of which with NaOH yielded the Boc-protected $\beta^{2,2}$-amino acid **13**.

The preparation of 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives **15**–**17** begins with the dialkylation of the corresponding methyl 1-cyanocycloalkanecarboxylates [33][34] by various dibromides[12]) (*Scheme 3*). The cyanoesters **14** [36] thus obtained were hydrogenated with *Raney*-Ni, and subsequent Boc-protection afforded the esters **15**[13]). The corresponding Boc-protected amino acids **16** were obtained by saponification of the amino esters **15** and subsequent Boc-protection[14]). Again, special conditions (*Scheme 3* and *Exper. Part*) had to be chosen for the preparation of cyclopropanecarboxylic acid **16a**. Cyano ester **14d** was also converted to the Fmoc derivative **17**, required for solid-phase β-oligopeptide syntheses.

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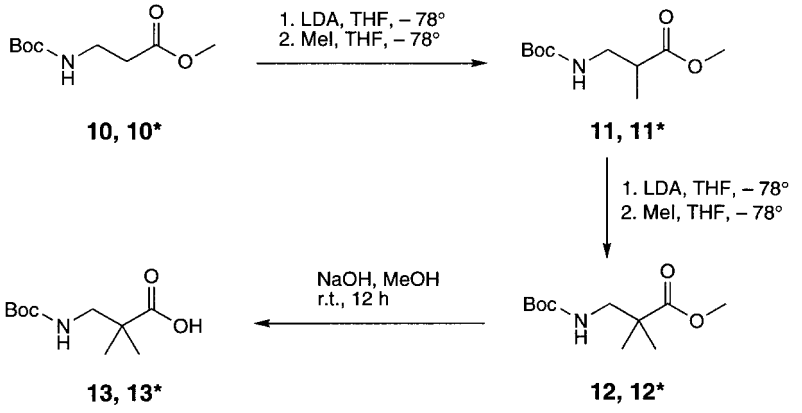
12) After the present work was completed, a similar dialkylation was reported with enantiomerically pure 2,2′-bis(bromomethyl)-1,1′-binaphthyl as alkylating reagent [35].

13) It is interesting to note the mild conditions for the *Raney*-Ni reduction of cyclopropane derivative **14a**. Higher pressure or temperature resulted in an increased amount of side products. The cobalt-boride method [35][37], checked also for this reduction, led to lower yields and side products.

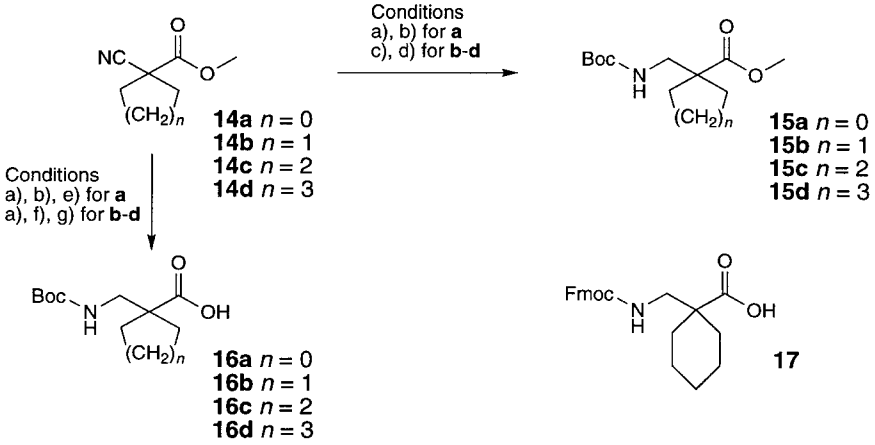
14) Acid **16d** was independently prepared by saponification of ester **15d**. Whereas saponification of the α,α-dimethylated ester **12** was accomplished at room temperature, deprotection of the cyclohexane derivative **15d** required heating at reflux.

Scheme 2. *Preparation of β²,²-Amino-Acid Building Blocks.* Asterix indicates fully ^{15}N- and ^{13}C-labeled compounds **10**–**13** (except protecting groups)[a]).



[a]) For specification of the asterixed compound numbers, see *Formula* **2** above.

Scheme 3. *Preparation of 1-(Aminomethyl)cycloalkanecarboxylic-Acid Derivatives*



a) H_2, *Raney*-Ni, MeOH, 1 bar, r.t., 4 h. *b*) Boc_2O, MeCN, Et_3N, 0°, 2 h. *c*) H_2, *Raney*-Ni, MeOH, 4 bar, 40°, 22 h. *d*) Boc_2O, dioxane, CH_2Cl_2, r.t., 16 h. *e*) LiOH, MeOH, r.t., 3 d. *f*) NaOH, MeOH, reflux, 5 h. *g*) Boc_2O, H_2O/dioxane.

3. Synthesis of the *β*-[2,2]- and *β*-[3,3]-Peptides. – The *β*-peptide derivatives **1**–**6** were synthesized by both, solution- and solid-phase synthetic procedures. The classical coupling in solution [3–5] was to supply *β*-peptides **1**, **2**, **3**, and **4b** in quantities, large enough for crystallization experiments, whereas the flexible solid-phase method, successfully developed in our laboratory for the synthesis of *β*-peptides [12][15]), was chosen for the synthesis of *β*-peptides **4a**, **4c**, **5**, and **6** with varying C- and N-terminal protecting groups.

[15]) *Cf.* also independent work [38].

3.1. *Synthesis in Solution*. The α,α- or β,β-disubstituted β-amino acids could be coupled by conventional methods (EDC/HOBt), without encountering the type of complications, known for sterically congested α,α-disubstituted α-amino acids [39]. Monomers **9**, **12**, and **15d** were Boc-deprotected with CF_3COOH and coupled with the Boc-protected amino acids **8**, **13**, or **16d** to yield the dipeptide esters **18a**–**20a**; *N*-deprotection of **18** and **19** with CF_3COOH and coupling with the Boc-protected acids **8** or **13** provided the tripeptides **21** and **22**, respectively. The CF_3COOH salt **20c** was obtained in the same way, and its free amino group was coupled with the acid **16d** to yield the tripeptide ester **23a**. The C-termini of the tripeptides were deprotected by saponification ($NaOH/H_2O/MeOH$) to yield the free acids **21b**–**23b** which were coupled with the corresponding *N*-deprotected tripeptide esters to give the fully protected hexapeptides **1a**, **2a**, and **4b**. It is interesting to note that the yields of the coupling steps involving $\beta^{2,2}$-peptides (*ca.* 80%) always[16]) exceeded those obtained with the corresponding $\beta^{3,3}$-peptides (*ca.* 60%). This behavior reminds of the difficulties encountered in acylations of α-aminoisobutyric acid (Aib) and other α,α-dialkylated glycine derivatives [40][17]). The CF_3COOH salts **1c** and **2c** and the free acids **1b** and **2b** were obtained by Boc deprotection and saponification of the fully protected hexapeptides. Boc Deprotection of the acids **1b** and **2b** finally led to the hexapeptide salts **1d** and **2d**. The *N*-deprotected hexapeptide derivative **2c** was coupled with $\beta^{2,2}$-tripeptide acid **22b** and $\beta^{2,2}$-hexapeptide acid **2b** to give the fully protected $\beta^{2,2}$-nonapeptide **3a** (colorless powder, 80%) and the $\beta^{2,2}$-dodecapeptide **3b** (colorless glass, 62%), respectively. Like all our geminally disubstituted, protected hexapeptides, the rather hydrophobic compound **3b** (M_r 1321.8) is surprisingly well soluble[18]) in protic and aprotic solvents (MeOH, $CHCl_3$, CH_2Cl_2). All fully protected peptides were white powders, but only the cyclohexylidene derivative **23a** could be obtained as crystalline material[19]) (see *Sect. 4*).

3.2. *Synthesis on Solid Support*. The target oligopeptides **4a**, **4c**, **5**, and **6** with three to six β-amino acids were synthesized on solid support. The hexapeptide **4c** was prepared according to the reported procedure on *ortho*-chlorotrityl-chloride resin [12a][41] by activation of the $\beta^{2,2}$-amino acids with BOP/HOBt/Etn)i-Pr)$_2$. Anchoring yield (55%) and HPLC purity (65–95%) of the crude peptide were comparable to the reported values [12a–b]; however, the cleavage yield (47%) was substantially lower for this sterically more demanding $\beta^{2,2}$-hexapeptide. The *Rink* amide resin [42] was chosen for the solid-phase synthesis of peptide amides **4a**, **5**, and **6**. Anchoring of the first $\beta^{2,2}$-amino acid to the *Rink* amide resin was achieved by deprotection of the Fmoc group on the resin and coupling with Fmoc-protected acid **17**, by the usual coupling procedure (BOP/HOBt/EtN(i-Pr)$_2$). Elongation of the peptide chain was achieved in the same way as decribed for our previous syntheses on *ortho*-chlorotrityl-chloride resin [12]. Acetylation of the N-terminus of these β-peptides was expected to increase their crystallinity; the free amino group of the peptide resin was thus acetylated with Ac_2O/

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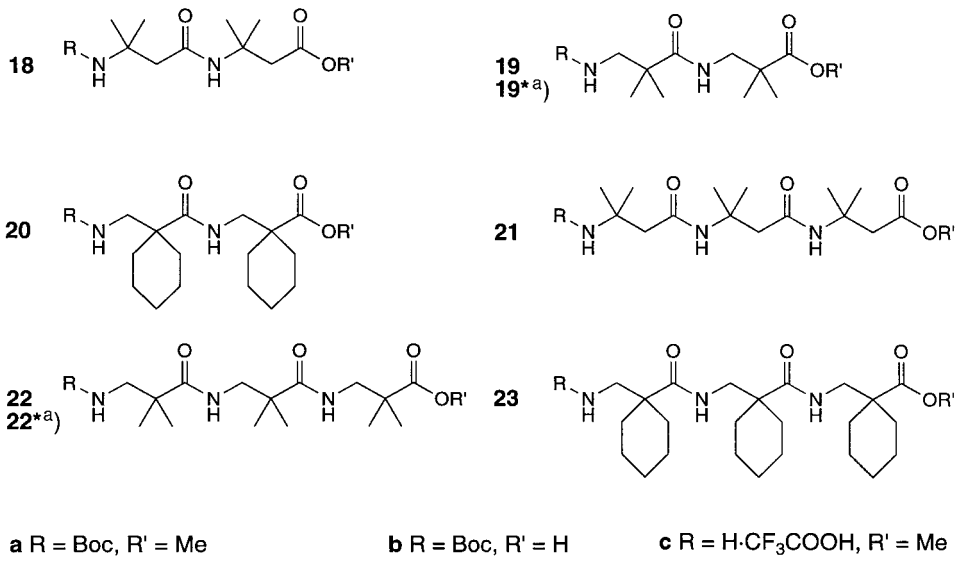
16) An exception was the fragment coupling to give the hexapeptide **4b** which gave only a 36% yield.

17) Coupling of α,α-diphenylglycine (Dph) with alanine by the EDC/HOBt method proceeded with high yields at the C-terminus but with very low yields at the N-terminus of Dph [40a].

18) Normally, β^2- and β^3-peptides with alkyl side chains become more and more insoluble in common organic solvents with growing chain lengths [3–5].

19) All attempts to crystallize the dimethylated peptides have so far led to amorphous powders.



a) For specification of the asterixed compound numbers, see *Formula* **2**, and **10**–**13** above.

$EtN(i\text{-}Pr)_2$ in 10 min. Cleavage from the resin gave satisfactory yields only if the flow method was applied (see *Exper. Part*). The crude peptide amides were recovered in good yields and with purities of 68–83%, as determined by reversed-phase (RP) HPLC. It is noteworthy that these α,α-disubstituted β-amino acids could be effectively coupled on both resin types under essentially the same conditions which had been used for less crowded β-amino acids, as indicated by both, the necessary coupling periods[20]) (15–60 min) and the purity of the crude products.

4. Structural Analyses. – 4.1. *X-Ray Crystal Structures.* Single crystals suitable for X-ray diffraction were obtained of Boc-protected $\beta^{2,2}$-amino acids **16a**–**d**, and of the fully protected $\beta^{2,2}$-tripeptide **23a**. Their high crystallinity parallels the behavior of the α-amino-acid analogues [13]. The conformation of these building blocks is of interest for studying the effect induced by the $\beta^{2,2}$-amino acids when incorporated into β-peptides. The crystal structures of the Boc-protected 1-(aminomethyl)cyclopropane-, -cyclobutane-, -cyclopentane-, and -cyclohexane-carboxylic acids, **16a**–**d**, respectively, are shown in *Fig. 1*; in the structures of **16c** and **16d** the carboxy groups occupy axial positions[21]) in the envelope and in the chair conformation, respectively.

The crystal structure of β-tripeptide **23a** (*Fig. 2,a*) is characterized by a ten-membered H-bonded ring between the N-terminal carboxy group and the amide NH of the second amino acid. This ring is quite similar to the central ten-membered H-bonded ring of the 12/10/12 helix of a β^2/β^3-hexapeptide [5], and it actually provides a turn (*Fig. 2,b*). In the crystal packing (*Fig. 2,c*), there are intermolecular H-bonds between

20) Coupling reactions were monitored using 2,4,6-trinitrobenzenesulfonic acid (TNBS) [43].

21) In almost all crystal structures containing the α-analogues of **16c** [44] and **16d** [45], the amino group occupies the axial position [46].

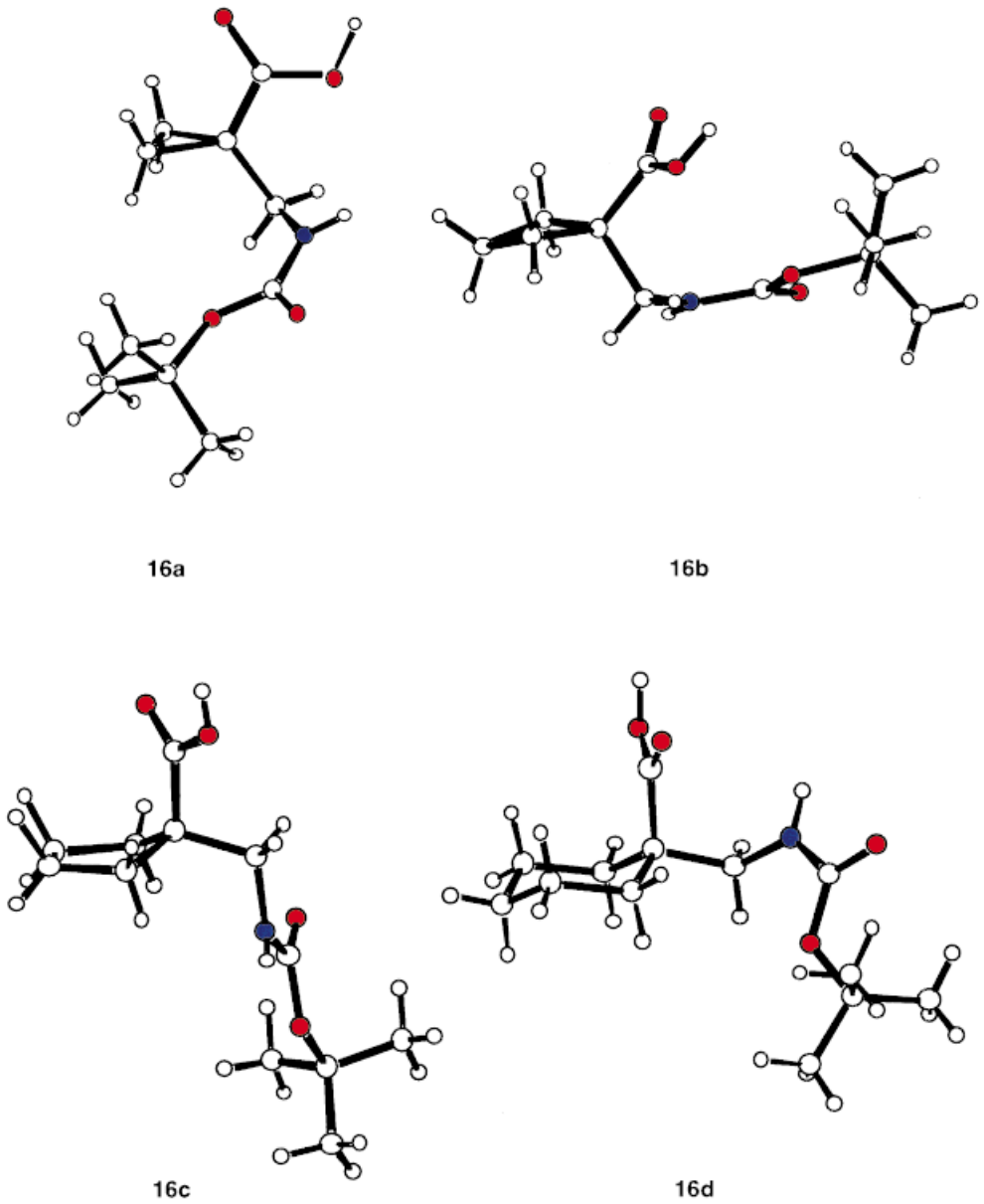


Fig. 1. *X-Ray crystal structures of 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives* **16a**–**d**. Interestingly, the conformation of the urethane C–N bond of compounds **16a**, **16b**, and **16d** is *cis* (angle O–CO–N–C(β) is *sp*). Compound **16c** adopts the *trans* conformation (angle O–CO–N–C(β) is *ap*). As expected for the three-membered ring in **16a**, the endocyclic angles have values close to 60°, but the CO–C(α)–C(β) angle (τ = 117.1°) is – expectedly so – greater than the standard tetrahedral angle. The angle τ is 106.5°, 107.0°, and 111.1° in the structures of compounds **16d**, **16c**, and **16b**, respectively. For structure determination of compound **16c** we thank Dr. *W. B. Schweizer*.

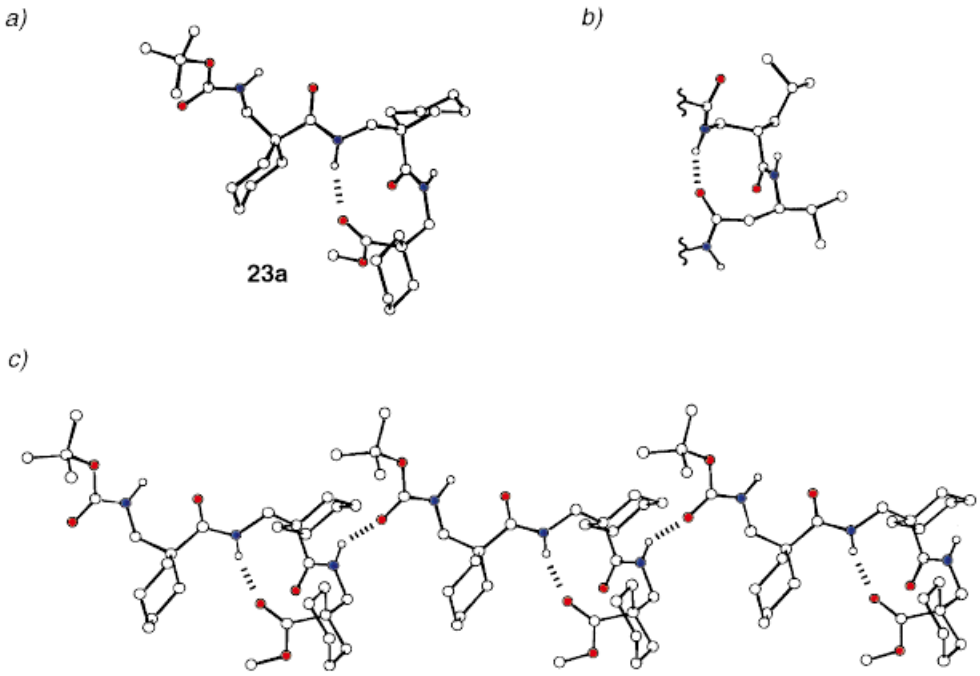


Fig. 2. *X-Ray structure of* **23a**. a) *Structure of the repeating unit of* **23a**. b) *Central ten-membered H-bonded ring of the 12/10/12 helix* [5]. c) *Crystal packing of* $\beta^{2,2}$*-tripeptide* **23a**, *showing intramolecular* (2.1 Å) *and intermolecular* (2.0 Å) *H-bonds.* Only the amide protons are drawn.

the carbonyl O-atom of the Boc group of one molecule and the amide NH of the C-terminal residue of the neighboring molecule.

4.2. *^{13}C,^{15}N-Labeled Peptide* **2a***. The restricted mobility of the peptide backbone of β-peptide **2a** in solution is demonstrated by the magnetic nonequivalence of the amide protons in the ^{1}H-NMR spectra (*Fig. 3,a*). From this nonequivalence, it may be concluded that at least one stable secondary structure is populated in $CDCl_3$ at room temperature. It is not possible to elucidate the 3D structure of this β-homopeptide with highly overlapping signals by standard 2D-NMR methods. Given the amorphous nature of the $\beta^{2,2}$-hexapeptides **1**–**3**, we decided to try to determine the secondary structure of the least strained α,α-dimethyl β-hexapeptide **2a** by combined liquid- and solid-state NMR studies of the corresponding ^{13}C,^{15}N-labeled hexapeptide **2a*** [47] (completely ^{13}C- and ^{15}N-labeled, except for the terminal protecting groups Boc and MeO; see labeled intermediates in *Scheme 2*, and compounds **19** and **22**).

The synthesis of **2a*** (*Scheme 4*) started with the commercially available labeled reagents β-alanine $^{15}NH_2$-$^{13}CH_2$-$^{13}CH_2$-$^{13}CO_2H$ (99% ^{13}C and 99% ^{15}N) and $^{13}CH_3I$ (99% ^{13}C), and was accomplished according to the procedures described for the corresponding unlabeled hexapeptide **2a**[22]). The ^{1}H-NMR spectra (*Fig. 3*) of the

[22]) For each alkylation, only 2 equiv. of $^{13}CH_3I$ were used, instead of 4 equiv. as for the synthesis of the unlabeled compounds. This modification did not alter the yields of the alkylation steps (97% for the first and 75% for the second alkylation step).

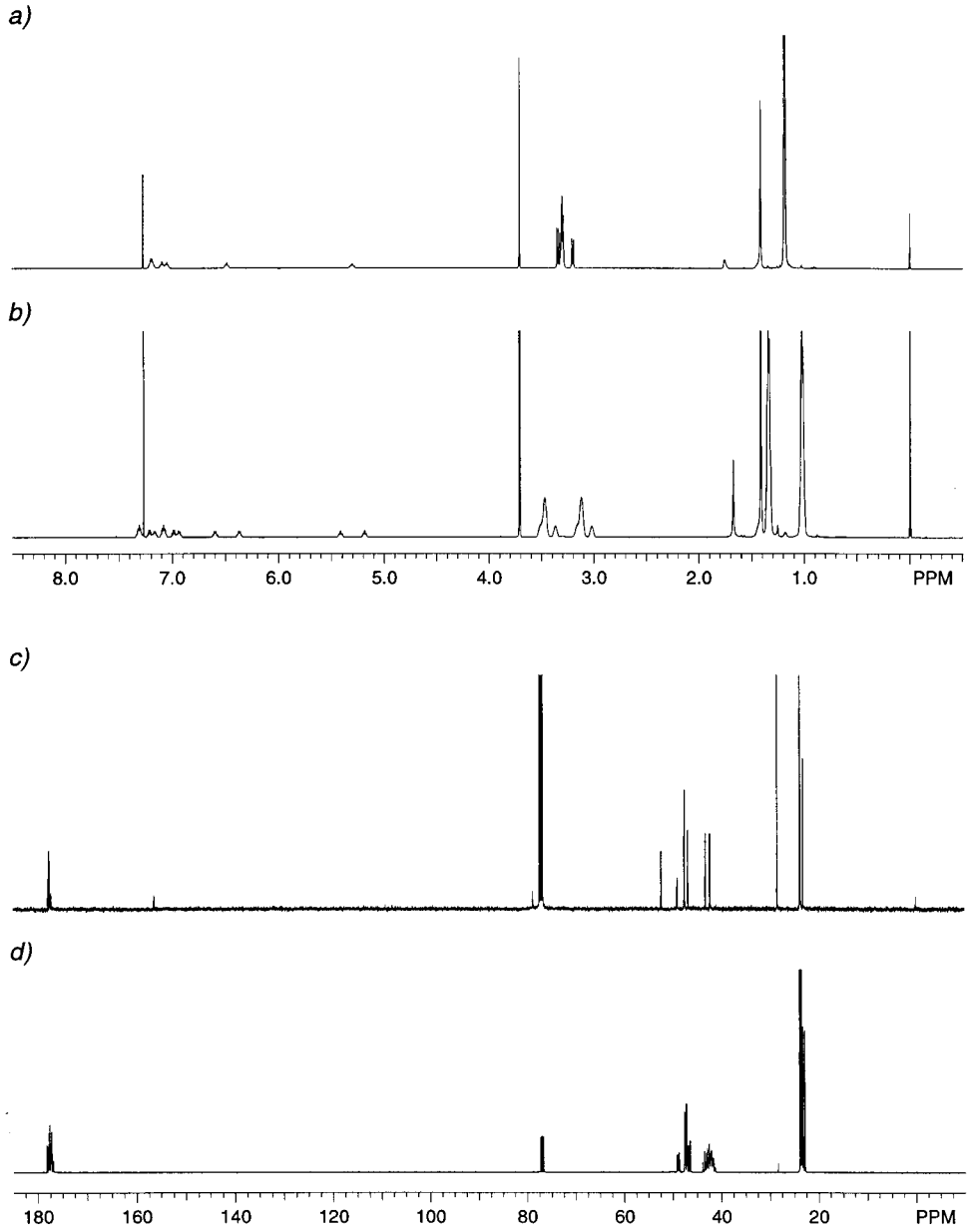


Fig. 3. *400-MHz ^{1}H-NMR Spectra of* a) *the unlabeled hexapeptide* **2a** *and* b) *the ^{13}C,^{15}N-labeled hexapeptide* **2a**. *100-MHz ^{13}C-NMR Spectra of* c) *the unlabeled hexapeptide* **2a**, *and* d) *the ^{13}C,^{15}N-labeled hexapeptide* **2a***. All spectra were measured in $CDCl_3$.

labeled compounds present *doublets* of *multiplets* for the α-Me groups, for the CH_2 protons, and for the NH protons (see, *e.g.*, the ^{1}H-NMR spectrum of the labeled hexapeptide **2a*** in *Fig. 3,b*). For all the labeled products the ^1J(H,C) coupling constants can easily be determined. They vary from 127 to 140 Hz, classical ^1J(H,C) values for sp^3-hybridized C-atoms. The ^1J(H,N) coupling constants are all very similar (between 90 and 92 Hz) for the various labeled products. The signal of the MeO group of the C-terminal protecting group is always a *doublet*, due to a ^3J(H,C) coupling of 4 Hz. The ^{13}C-NMR spectra of the labeled compounds are more complicated, due to the additional ^{13}C,^{13}C coupling (see, *e.g.*, the ^{13}C-NMR spectrum of the labeled hexapeptide **2a*** in *Fig. 3,d*).

Scheme 4[a])

$^{15}NH_2$-$^{13}CH_2$-$^{13}CH_2$-$^{13}CO_2H$ + $^{13}CH_3I$ ⟶ PG-(-^{15}NH-$^{13}CH_2$-$^{13}C(^{13}CH_3)_2$-^{13}CO-)$_n$-X

[a]) See asterixed compounds in previous *Schemes* and *Formulae*.

The IR spectrum of labeled **2a*** shows the expected differences[23]) as compared to the spectrum of unlabeled **2a** (*Fig. 4*). Below 1800 cm^{-1}, the vibrational frequencies of labeled peptide **2a*** are smaller than those of unlabeled **2a**; this ratio is inversed in the CH and NH stretching region.

5. Conclusion and Outlook. – We have reported the preparation of geminally dimethylated $\beta^{3,3}$-amino acid (*Scheme 1*) and $\beta^{2,2}$-amino-acid building blocks (*Scheme 2*), and of the 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives **16a**–**d** (*Scheme 3*). We have demonstrated that, in contrast to the α-analogues, geminally disubstituted β-amino acids can be coupled to give the corresponding β-hexa-, β-nona-, and β-dodecapeptides **1**–**6** in high yields by standard peptide-coupling procedures, both in solution and on solid phase.

The crystal structures of the 1-(aminomethyl)cycloalkanecarboxylic-acid derivatives **16a**–**d** (*Fig. 1*) and of the fully protected $\beta^{2,2}$-tripeptide **23a** (*Fig. 2*) underline the tendency of these geminally disubstituted derivatives to crystallize. $\beta^{2,2}$-Tripeptide **23a** (*Fig. 2*) adopts a ten-membered H-bonded turn, comparable to the central turn that we have already found in the 12/10/12 helix of a β^2/β^3-hexapeptide [5].

Ongoing solid-state NMR experiments with the labeled β-hexapeptide **2a*** will elucidate its structure and will eventually demonstrate the potential of a new technique for structural analysis in the solid state in the absence of single crystals [47].

The following questions and ideas are considered important for future β-peptide research projects: *i*) Is there yet another helix formed by $\beta^{2,2}$-homopeptides, besides the known 3_1 [3–5] and 2.5_1 [6b] helices? *ii*) Inspection of the structure of the turn-forming $\beta^{2,2}$-tripeptide **23a** (*Fig. 2*) suggests that $\beta^{2,2}$-amino acids can serve as bend promotors, if they are incorporated into β-peptides. *iii*) The structure of higher homologs of **23a** in this series still remains unknown (*e.g.*, **4b**); from models and classical conformational analysis, it is evident that a β-peptide consisting of $\beta^{2,2}$-amino acids does not fit into the known secondary structures of β-peptides (see Table 1 in [5]); the ten-membered H-

[23]) The maximum frequency difference is 3.22%, as compared to the maximum theoretical difference of 4.08%, due to the isotope effect.

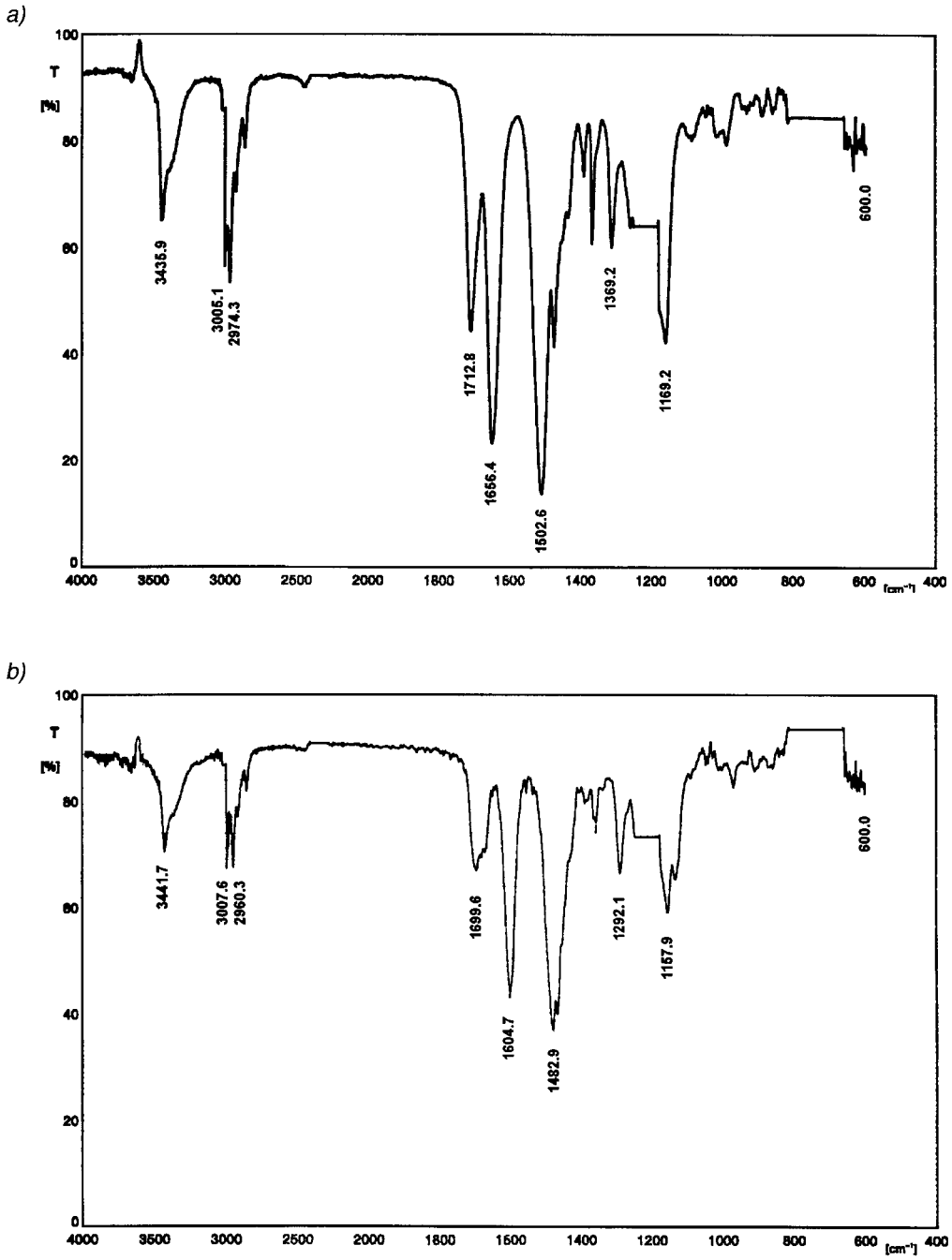


Fig. 4. *IR Spectra of* a) *the unlabeled hexapeptide* **2a** *and* b) *the* $^{13}C,^{15}N$*-labeled hexapeptide* **2a***. The spectra were measured in $CHCl_3$ (concentration: 10 mg in 1 ml $CHCl_3$).

bonded turn, formed by the $\beta^{2,2}$-tripeptide **23a**, might be the incipent moiety of a meander-like or string-of-pearls-type structure of a higher oligomer, stabilized by intramolecular H-bonds in the successive ten-membered H-bonded rings[24]). *iv*) It will be intriguing to determine the structure of $\beta^{2,2}$-homopeptides built from the cyclopropanecarboxylic-acid derivative **16a** which could impart a considerable restriction to the peptide backbone due to an exocyclic bond angle C(β)–C(α)–CO that is greater than the standard tetrahedral angle. The outcome of the corresponding structural investigations will be essential for the design and synthesis of more complex β-peptides, including synthetic β-enzymes and molecular scaffolds with predictable folding patterns.

Experimental Part

1. *General.* Abbreviations: Boc_2O: di(*tert*-butyl) dicarbonate, DCC: *N*,*N*′-dicyclohexylcarbodiimide, DMAP: 4-(dimethylamino)pyridine, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, FC: flash chromatography, Fmoc-OSu: *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyloxy]succinimide, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum, 0.01–0.1 Torr, β-HXxx: β-homoamino acid [3–5] [48], TBNS: 2,5,6-trinitrobenzenesulfonic acid. Flasks and stirring bars for the alkylations were dried for *ca.* 12 h at 120° and allowed to cool in a desiccator over silica gel (*Blaugel*). THF was freshly distilled over Na/benzophenone under Ar before use. $CHCl_3$ employed for the coupling reactions was filtered over Al_2O_3 (Alumina *Woelm N*, act. I) to remove EtOH. Et_3N was distilled from CaH_2 and stored under Ar. $(i\text{-}Pr)_2NH$ was freshly distilled over CaH_2. The BuLi employed was titrated according to the method of *Juaristi et al.* [49]. MeI was filtrated over Al_2O_3 (Alumina *Woelm N*, act. I) before use. *Raney*-Ni was activated according to [50]. Solvents for chromatography and workup were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). *ortho*-Chlorotrityl chloride and *Rink* amide resins were purchased from *Novabiochem.* The labeled reagents, β-alanine (99% ^{13}C, 99% ^{15}N) and $^{13}CH_3I$ (99% ^{13}C), were purchased from *Campro Scientific*. All other reagents were used as received from *Fluka*. TLC: *Merck* silica gel *60* F_{254} plates; detection with UV, I_2 (30 g of I_2, 20 g of Kl, 200 ml of EtOH, 200 ml of H_2O), anisaldehyde (9.2 ml of anisaldehyde, 3.75 ml of AcOH, 12.5 ml of conc. H_2SO_4, 350 ml of EtOH); or ninhydrine (0.6 g of ninhydrine, 2 ml of AcOH, 13 ml of H_2O, 285 ml of BuOH). FC: *Fluka* silica gel *60* (40–63 μm); at *ca.* 0.3 bar. Anal. HPLC: *a*) For peptide **4c**: *Knauer* HPLC system (pump type *64*, *EuroChrom 2000* integration package, degaser, UV detector (variable-wavelength monitor)); *b*) for compounds **4a**, **5**, and **6**: *Waters* HPLC system (pump type *515*, automated gradient controller type *680*, data module type *746*, tunable absorbance detector type *484*); *Macherey-Nagel* C_8 column (*Nucleosil 100-5* C_8 (250 × 4 mm)). Prep. HPLC: *Knauer* HPLC system (pump type *64*, programmer *50*, UV detector (variable-wavelength monitor)), *Macherey-Nagel* C_8 column (*Nucleosil 100-7* C_8 (250 × 21 mm)). All indicated temp. were monitored with an internal thermometer (*Ebro-TTX-690* digital thermometer). M.p.: *Büchi-510* apparatus; uncorrected. 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), *ARX 300* (^1H: 300 MHz), *Varian Gemini 300* (^1H: 300 MHz, ^{13}C: 75 MHz), or *Varian Gemini 200* (^1H: 200 MHz, ^{13}C: 50 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz; some compounds show the presence of rotamers which are indicated. MS: *VG Tribrid* (EI), *Hitachi Perkin-Elmer RHU-6M* (FAB, in a 3-nitrobenzyl-alcohol matrix), or *LDI-1700* (MALDI) spectrometer; in *m*/*z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Alkylation of β-Alanine Derivatives: General Procedure 1* (*GP 1*). BuLi (1 equiv.) was added to a soln. of $(i\text{-}Pr)_2NH$ in THF (0.5M) at −78°. After 20 min at −78°, a soln. of the β-alanine derivative in THF (0.8 mM) was added during 10 min and the mixture stirred for 20 min at −78°. MeI (4 equiv.) was then added slowly (temp. < −65°), and the mixture was stirred for 15 min at this temp., subsequently hydrolyzed with sat. NH_4Cl soln., diluted with Et_2O, and washed with sat $NaHCO_3$, NH_4Cl, and NaCl solns. The org. layer was dried ($MgSO_4$) and evaporated. FC yielded the pure product.

3. *Boc Deprotection: General Procedure 2* (*GP 2*). *GP 2a:* Similarly to the procedure reported in [3–5], the Boc-protected amino acid was dissolved in CH_2Cl_2 (0.5M) and cooled to 0°. An equal volume of CF_3COOH was

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[24]) The result will also help to understand the dependence of the secondary structure from the chain length in this series of β-homopeptides.

added, and the mixture was allowed to warm slowly to r.t. and stirred for further 1.5 h. Concentration under reduced pressure, co-evaporation with CH_2Cl_2, and drying of the residue under h.v. yielded the crude CF_3COOH salt, which was identified by NMR and used without further purification.

GP 2b: Similarly to the procedure reported in [3–5], the Boc-protected amino acid was dissolved in cold (4°) CF_3COOH (0.15M). After stirring at r.t. for 2 h, concentration under reduced pressure and drying of the residue under h.v. yielded the crude CF_3COOH salt, which was lyophilized from dioxane.

4. *Ester Hydrolysis: General Procedure 3* (*GP 3*). *GP 3a:* Similarly to the procedure reported in [51], a soln. of the fully protected amino acid or peptide in MeOH (1.2M) was treated with 1N NaOH (1.2 equiv.) at r.t. After stirring for 16 h, the mixture was diluted with H_2O (in the case of small-scale reactions) and extracted with pentane (2×). The soln. was adjusted to pH 2 with 1N HCl and extracted with AcOEt (3×). The org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. The acid was either recrystallized for anal. purpose or used in the next step without further purification.

GP 3b: As *GP 3a*, except that the reaction mixture (1.5 equiv. NaOH) was refluxed for 2–4 h.

5. *Esterification of Boc-Protected Amino Acids: General Procedure 4* (*GP 4*). Similarly to the procedure reported in [52], the Boc-protected amino acid was dissolved in EtOH/H_2O (0.25M). The pH was adjusted to 7 with aq. 10% Cs_2CO_3 soln. The mixture was evaporated and dried under h.v. The residue was dissolved in DMF (0.5M) and MeI (4 equiv.) was added under Ar at 0°. After stirring for 24 h at r.t., excess MeI was destroyed with a few ml 1N NaOH. Upon removal of the solvent, the residue was taken up in AcOEt, washed with sat. aq. $NaHCO_3$ and NaCl solns., and evaporated.

6. *Reduction of CN Derivatives* **14b–d** *and Subsequent Transformations: General Procedure 5* (*GP 5*). *GP 5a:* Freshly prepared *Raney*-Ni (*ca.* 100 g/mol) [50] was added to a soln. of **14** in MeOH (0.25M). This mixture was stirred for 24–36 h at 40° under H_2 (4 bar) in a glass autoclave. Excess H_2 was removed by bubbling Ar through the mixture. After filtration through *Celite* and evaporation (30°, 150 mbar), the crude methyl amino ester was obtained as yellowish oil in quant. yield. This crude product was identified by ^{1}H-NMR and immediately used for the Boc-protection step: To a stirred soln. of the free amine in CH_2Cl_2 (0.5M) a soln. of Boc_2O (1.1 equiv.) in dioxane (0.5M) was added at 0°. The mixture was alowed to warm to r.t., and stirring was continued for 2–12 h. After evaporation, the residue was dissolved in AcOEt. The org. phase was washed with sat. aq. NH_4Cl, $NaHCO_3$, and NaCl solns., dried ($MgSO_4$), and evaporated. FC yielded the pure product.

GP 5b: Compound **14** was reduced as described in *GP 5a*. The resulting amino ester was saponified by refluxing in MeOH (1M) with 1N NaOH (1.5 equiv.) for 5 h. After evaporation, the free amino acid was dissolved in H_2O (0.5M) and treated with a soln. of Boc_2O (1.1 equiv.) in dioxane (0.6M). The mixture was stirred for 24 h at r.t. and extracted with pentane. The aq. phase was adjusted to pH 2 with 1N HCl and extracted with AcOEt (3×). The org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. The acid was recrystallized after refluxing the AcOEt soln. with charcoal and filtration of the hot soln. through *Celite*.

7. *Peptide Coupling with EDC: General Procedure 6* (*GP 6*). According to [53], the appropriate CF_3COOH salt was dissolved in $CHCl_3$ (0.5M) and cooled to 0°. This soln. was treated successively with Et_3N (4 equiv.), HOBt (1.2 equiv.), a soln. of the Boc-protected fragment (1 equiv.) in $CHCl_3$ (0.25M), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t. and stirred for 15 h. Subsequent dilution with $CHCl_3$ was followed by thorough washing with 1N HCl and sat. aq. $NaHCO_3$ (3×) and NaCl solns. (1×). The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure. FC or recrystallization yielded the pure peptide.

8. *Anchoring of* N*-Fmoc-Protected β-Amino Acids on the Resin: General Procedure 7* (*GP 7*). *GP 7a:* Esterification of acid **17** with the *ortho*-chlorotrityl-chloride resin was performed according to [41]. The resin (initial loading: 1.00 mmol Cl/g) was dried under h.v. for 20 min and swelled in CH_2Cl_2 (20 ml/mmol) for 10 min. A soln. of acid **17** (0.8 equiv.) in CH_2Cl_2 (10 ml/mmol) and $(i\text{-Pr})_2EtN$ (2.8 equiv.) were then added successively, and the suspension was mixed by Ar bubbling for 4 h. Subsequently, the resin was filtered, washed (20 ml/mmol) with CH_2Cl_2/MeOH/$(i\text{-Pr})_2EtN$ 17:2:1 (3 × 3 min), $CHCl_3$ (3 × 3 min), DMF (2 × 3 min), CH_2Cl_2 (3 × 3 min), MeOH (2 × 3 min), and finally dried under h.v. for 12 h. The loading of the resin was then determined on a 5–9-mg sample (after treatment with 20% piperidine in DMF for 20 min) by measuring the absorbance of the dibenzofulvene-piperidine adduct (formed during deprotection) at 300, 289, and 266 nm ($\varepsilon = 7800$, 5800, and 17500, resp.), taking the average absorbance from the 3 measurements.

GP 7b: Rink amide resin [42] (loading 0.45 mmol/g) was swelled in DMF/CH_2Cl_2 1:1 (20 ml/mmol) for 30 min and Fmoc deprotected using 20% piperidine in DMF (30 ml/mmol; 2 × 15 min) under Ar bubbling. A soln. of acid **17** (3 equiv.), BOP (3 equiv.), and HOBt (3 equiv.) in DMF (2 ml) and $(i\text{-Pr})_2EtN$ (9 equiv.) were added successively to the resin, and the suspension was mixed for 12–60 min by Ar bubbling. Monitoring of the

coupling was performed with TNBS [43]. The resin was then filtered and washed (60 ml/mmol) with DMF/CH_2Cl_2 1:1 (3 × 3 min) prior to the following Fmoc-deprotection step.

9. *β-Peptide on Solid Support: General Procedure 8* (*GP 8*). *GP 8a:* The Fmoc group of the first amino acid attached to the *ortho*-chlorotrityl-chloride resin was removed using 20% piperidine in DMF (30 ml/mmol, 2 × 15 min) under Ar bubbling. The resin was then filtered and washed with DMF (30 ml/mmol, 6 × 3 min). For each coupling step, a soln. of the Fmoc-*β*-amino acid (3 equiv.), BOP (3 equiv.) and HOBt (3 equiv.) in DMF (2 ml), and $(i\text{-}Pr)_2EtN$ (9 equiv.) were added successively to the resin, and the suspension was mixed by Ar bubbling for 15–60 min. Monitoring of the coupling reaction was performed with TNBS [43]. In case of a positive TNBS test (indicating incomplete coupling), the suspension was allowed to react further for 15–60 min. The resin was then filtered and washed (30 ml/mmol) with DMF (3 × 3 min) prior to the following Fmoc-deprotection step. After the removal of the last Fmoc protecting group, the resin was washed (30 ml/mmol) with DMF (6 × 3 min), CH_2Cl_2 (3 × 3 min), Et_2O (5 × 1 min), and dried under h.v. for 12 h.

GP 8b: The Fmoc group of the first amino acid attached to the *Rink* amide resin was removed using 20% piperidine in DMF (30 ml/mmol, 2 × 15 min) under Ar bubbling. The resin was then filtered and washed with DMF/CH_2Cl_2 1:1 (50 ml/mmol, 6 × 3 min). For each coupling step, a soln. of the Fmoc-*β*-amino acid (3 equiv.), BOP (3 equiv.) and HOBt (3 equiv.) in DMF (2 ml), and $(i\text{-}Pr)_2EtN$ (9 equiv.) were added successively to the resin and the suspension was mixed by Ar bubbling for 15–60 min. Monitoring of the coupling reaction was performed with TNBS [43]. In case of a positive TNBS test (indicating incomplete coupling), the suspension was allowed to react further for 15–60 min with an additional equiv. of Fmoc-*β*-amino acid and coupling reagents. The resin was then filtered and washed (50 ml/mmol) with DMF/CH_2Cl_2 1:1 (3 × 3 min) prior to the following Fmoc deprotection step. After the removal of the last Fmoc protecting group, the resin was acetylated at the N-terminus according to *GP 9* prior to the cleaveage procedure.

10. *Acetylation of Peptides on Solid Support: General Procedure 9* (*GP 9*). The Fmoc-deprotected peptide-resin was washed (30 ml/mmol) with DMF/CH_2Cl_2 1:1 (5 × 3 min) and treated successively with $(i\text{-}Pr)_2EtN$ (20 equiv.), Ac_2O (10 equiv.) in DMF/CH_2Cl_2 1:1 (2 ml) under Ar bubbling for 10–15 min. Monitoring of the acetylation was performed with TNBS [43]. The resin was then washed (30 ml/mmol) with DMF (6 × 3 min), CH_2Cl_2 (3 × 3 min), Et_2O (5 × 1 min), and dried under h.v. for 12 h.

11. *Resin Cleavage and Final Deprotection: General Procedure 10* (*GP 10*). *GP 10a:* The dry Fmoc-deprotected *ortho*-chlorotrityl-chloride resin was treated with CF_3COOH (20 ml/mmol, 5 × 15 min) under Ar bubbling. The resin was removed by filtration washed with CF_3COOH, and the org. phases containing the peptide were evaporated and co-evaporated with CH_2Cl_2. The precipitate which formed upon addition of cold Et_2O to the oily residue was collected by filtration or centrifugation. The solid was then dissolved (at least partially) in H_2O (containing 5% AcOH in the case of insoluble material) and lyophilized to afford a crude product which was analyzed and purified by RP-HPLC.

GP 10b. The dry Fmoc-deprotected *Rink* amide peptide-resin was first treated with a mixture of CH_2Cl_2/CF_3COOH/$(i\text{-}Pr)_3SiH$ 90:9:1 (20 ml/mmol, 3 × 2 ml), then with a mixture of CH_2Cl_2/CF_3COOH/$(i\text{-}Pr)_3SiH$ 95:4:1 (20 ml/mmol, 3 × 2 ml), allowing the solvent to pass through the resin bed slowly. Excess CF_3COOH/CH_2Cl_2 was evaporated, and deprotection was completed by stirring the oily residue in 95% CF_3COOH in CH_2Cl_2 for 1 h. The solvent was evaporated, co-evaporated with CH_2Cl_2, dried under h.v., and the oily residue treated with Et_2O as described in *GP 10a*. Repeated treatment of the resin as described above yielded an additional fraction of the crude peptide.

12. *Reversed-Phase (RP) HPLC Analysis and Purification of β-Peptides: General Procedure 1* (*GP 11*). RP-HPLC Analysis was performed on a *Macherey-Nagel* C_8 column/*Nucleosil 100-5* C_8 (250 × 4 mm) or *Macherey-Nagel* C_{18} column/*Nucleosil 100-5* C_{18} (250 × 4 mm) by using a linear gradient of *A* (0.1% CF_3COOH in H_2O) and *B* (MeCN) at a flow rate of 1 ml/min with 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), gradient of *A* and *B* at a flow rate of 4 ml/min with UV detection at 220 nm) and then lyophilized.

13. *$\beta^{3,3}$-Hexapeptides* **1**. *3-Amino-3-methylbutanamide* (**7**). Similarly to [23a], 3,3-dimethylacrylic acid (50.0 g, 0.50 mol) in aq. NH_3 soln. (24%, 550 ml) was heated at 150° for 18 h in an autoclave. After cooling to r.t., the green soln. was refluxed for 3.5 h with $Ba(OH)_2$ (15.0 g, 97.2 mmol). The pH of the cooled suspension was adjusted to 3–4 with conc. H_2SO_4. This suspension was refluxed in the presence of charcoal for 15 min. The filtrate was concentrated to dryness and dried under h.v. The crude product was washed with cold EtOH to yield **7** (58.0 g, quant.). White powder. M.p. 230°. R_f 0.54 (EtOH/NH_3/H_2O 7:1:1). ^{1}H-NMR (200 MHz, D_2O): 1.45 (*s*, 2 Me); 2.75 (*s*, CH_2). ^{13}C-NMR (50 MHz, D_2O): 28.03 (Me); 45.84 (CH_2); 55.20, 177.36 (C).

*3-{[(*tert*-Butoxy)carbonyl]amino}-3-methylbutanoic Acid* (Boc-$\beta^{3,3}$-HAib-OH; **8**). Similarly to [50][51], **7** (17.86 g, 154.0 mmol) was refluxed in aq. NaOH (25%, 35 ml) for 24 h. The mixture was cooled to r.t. and diluted

with H_2O (235 ml) and dioxane (280 ml). At 0°, Boc_2O (33.6 g, 0.154 mol) was added. After stirring at r.t. for 12 h, dioxane was evaporated. The basic aq. soln. was extracted with pentane (1 ×) and adjusted to pH 2 with aq. HCl (10%). The aq. phase was extracted with AcOEt (3 ×). The AcOEt phases were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated. Recrystallization (AcOEt/pentane) yielded **8** (16.92 g, 51%). White powder. M.p. 98–99°. R_f 0.09 (Et_2O/pentane 1:2). ^{1}H-NMR: in agreement with [24b].

*Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-3-methylbutanoate* (Boc-$\beta^{3,3}$-HAib-OMe; **9**). The acid **8** (6.50 g, 29.9 mmol) was esterified according to *GP 4*. FC (Et_2O/pentane 1:4) yielded **9** (6.20 g, 90%). Colorless oil. R_f 0.27 (Et_2O/pentane 1:4). IR ($CHCl_3$): 3444*w*, 2978*m*, 1716*s*, 1502*s*, 1454*m*, 1438*m*, 1392*m*, 1368*s*, 1289*m*, 1166*s*, 1081*m*, 1013*w*, 864*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.38 (*s*, 2 Me); 1.43 (*s*, *t*-Bu); 2.70 (*s*, CH_2); 3.67 (*s*, MeO); 4.87 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.50, 28.42 (Me); 44.15 (CH_2); 51.11 (C); 51.43 (Me); 79.04, 154.63, 171.82 (C). EI-MS: 231 (0.1, M^+), 216 (16.3), 158 (34.5), 144 (24.9), 116 (62.0), 109 (13.1), 102 (51.3), 84 (85.9), 73 (27.7), 57 (100.0), 41 (25.2). Anal. calc. for $C_{11}H_{21}NO_4$ (231.29): C 57.12, H 9.15, N 6.06, O 27.67; found: C 57.05, H 9.06, N 6.05, O 27.70.

*Methyl 3-[(3-{[(*tert*-Butoxy)carbonyl]amino}-3-methylbutanoyl)amino]-3-methylbutanoate* (Boc-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OMe; **18a**). Compound **9** (4.50 g, 19.5 mmol) was saponified according to *GP 3a* and treated with **8** (4.23 g, 19.5 mmol) according to *GP 6*. FC (Et_2O/pentane 1:1 → Et_2O) yielded **18a** (3.87 g, 60%). White powder. M.p. 76–77°. R_f 0.14 (Et_2O/pentane 1:1). IR ($CHCl_3$): 3441*w*, 2978*m*, 1705*s*, 1666*s*, 1501*s*, 1454*m*, 1391*m*, 1368*m*, 1165*s*, 1081*m*, 1011*w*, 866*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.37 (*s*, 2 Me); 1.41 (*s*, 2 Me); 1.44 (*s*, *t*-Bu); 2.45 (*s*, CH_2); 2.79 (*s*, CH_2); 3.66 (*s*, MeO); 5.17 (*s*, OC(O)NH); 5.94 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.19, 27.74, 28.52 (Me); 43.45, 47.45 (CH_2); 51.45 (C); 51.76 (Me); 52.00, 79.02, 155.06, 170.57, 171.75 (C). EI-MS: 331 (1.6, $[M+1]^+$), 330 (5.8, M^+), 315 (6.5), 257 (23.9), 225 (19.6), 215 (36.2), 183 (25.4), 173 (33.9), 158 (51.8), 143 (45.4), 132 (21.1), 116 (100.0), 102 (50.2), 83 (21.5), 73 (19.0), 58 (33.0). Anal. calc. for $C_{16}H_{30}N_2O_5$ (330.42): C 58.16, H 9.15, N 8.48; found: C 58.03, H 9.22, N 8.45.

Boc-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OMe (**21a**). Ester **18a** (3.50 g, 10.6 mmol) was Boc-deprotected according to *GP 2a* and coupled with **8** (2.30 g, 10.6 mmol) according to *GP 6*. Recrystallization (AcOEt/pentane) and FC (AcOEt/pentane 1:1) yielded **21a** (2.69 g, 59%). White powder. M.p. 105–106°. R_f 0.15 (AcOEt/pentane 1:1). IR ($CHCl_3$): 3439*w*, 3005*m*, 2974*m*, 1707*s*, 1665*s*, 1501*s*, 1453*m*, 1390*m*, 1368*m*, 1165*s*, 1080*m*, 1047*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.38 (*s*, Me); 1.40 (*s*, Me); 1.41 (*s*, Me); 1.44 (*s*, *t*-Bu); 2.42 (*s*, CH_2); 2.47 (*s*, CH_2); 2.76 (*s*, CH_2); 3.66 (*s*, MeO); 5.38 (*s*, OC(O)NH); 6.03 (*s*, NH); 6.54 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.13, 27.21, 27.56, 28.52 (Me); 43.55, 47.42, 47.88 (CH_2); 51.48 (Me); 51.76, 52.09, 52.77, 78.95, 155.08, 170.54, 171.12, 171.75 (C). FAB-MS: 452 (1.2, $[M+Na]^+$), 430 (100.0, M^+), 330 (72.9), 299 (8.5), 272 (13.5), 257 (5.3), 231 (10.8), 182 (5.7), 142 (6.9), 132 (7.2), 115 (7.3), 102 (5.8). Anal. calc. for $C_{21}H_{39}N_3O_6$ (429.56): C 58.71, H 9.15, N 9.78; found: C 58.78, H 9.05, N 9.82.

Boc-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OH (**21b**). Ester **21a** (1.10 g, 2.6 mmol) was saponified according to *GP 3a* to yield **21b** (1.06 g, quant.). White powder. Acid **21b** was used in the next step without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.36 (*s*, Me); 1.40 (*s*, Me); 1.42 (*s*, Me); 1.45 (*s*, *t*-Bu); 2.50 (*s*, CH_2); 2.54 (*s*, CH_2); 2.81 (*s*, CH_2); 5.29 (br. *s*, OC(O)NH); 6.20 (*s*, NH); 6.42 (*s*, NH).

Boc-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OMe (**1a**). Tripeptide **21a** (1.10 g, 2.6 mmol) was Boc-deprotected according to *GP 2a* and coupled with **21b** (1.06 g, 2.6 mmol) according to *GP 6*. The cloudy viscous mass obtained after 15 h was dissolved in a few ml of $CHCl_3$. After addition of further HOBt (0.18 g, 1.3 mmol) and EDC (0.25 g, 1.3 mmol), the mixture was stirred for 24 h. FC (MeOH/CH_2Cl_2 1:18) yielded **1a** (2.69 g, 59%). White powder. M.p. 199–200°. R_f 0.11 (MeOH/CH_2Cl_2 1:18). IR ($CHCl_3$): 3439*w*, 3336*w*, 3006*m*, 2974*m*, 1706*m*, 1659*s*, 1506*s*, 1453*m*, 1390*w*, 1367*m*, 1261*m*, 1168*m*, 1080*w*, 1015*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.38 (*s*, 2 Me); 1.42–1.43 (*m*, 2 Me, *t*-Bu); 2.30 (*s*, CH_2); 2.31 (*s*, CH_2); 2.33 (*s*, CH_2); 2.34 (*s*, CH_2); 2.35 (*s*, CH_2); 2.73 (*s*, CH_2); 3.67 (*s*, MeO); 5.74 (*s*, OC(O)NH); 6.39 (*s*, NH); 7.13 (*s*, NH); 7.19 (*s*, NH); 7.32 (*s*, NH); 7.36 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.44, 26.58, 26.63, 27.02, 27.15, 28.53 (Me); 43.68, 47.96, 48.34, 48.42, 48.46 (CH_2); 51.51 (Me); 51.72, 52.41, 52.82, 53.93, 53.01, 53.03, 78.69, 155.07, 170.75, 170.84, 170.86, 170.91, 170.94, 171.84 (C). FAB-MS: 749 (6.4, $[M+Na]^+$), 727 (100.0, M^+), 627 (31.9), 429 (6.4), 330 (5.4), 297 (4.9), 231 (5.2), 198 (11.0), 182 (16.1), 154 (8.9), 142 (8.7), 136 (9.3), 115 (7.6). Anal. calc. for $C_{36}H_{66}N_6O_9$ (726.95): C 59.48, H 9.15, N 11.56; found: C 59.46, H 8.98, N 11.31.

Boc-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OH (**1b**). Compound **1a** (400 mg, 0.55 mmol) was dissolved in MeOH (5 ml), and 1N NaOH (0.66 ml) was added. After 30 min, a cloudy mass was formed that could be solubilized with MeOH (1 ml). The clear soln. was stirred for 14 h at r.t. The viscous mass was treated with MeOH (10 ml) and 1N NaOH (2.75 ml), and heated at 50° for 3 h. After evaporation of MeOH, the peptide acid was precipitated with 1N HCl, filtered, and washed with pentane and H_2O to yield **1b** (301 mg, 75%). White powder. M.p. 203–204°. R_f 0.06 (MeOH/CH_2Cl_2 1:18). IR ($CHCl_3$): 3437*w*, 3345*w*,

3004*m*, 2975*m*, 2027*w*, 1708*m*, 1655*s*, 1522*s*, 1453*m*, 1390*w*, 1367*m*, 1168*m*, 1082*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.38 (*s*, 2 Me); 1.37 (*s*, 2 Me); 1.40 (*s*, 4 Me); 1.42 (*s*, 4 Me); 1.43 (*s*, *t*-Bu); 2.31 (*s*, CH_2); 2.37 (*s*, CH_2); 2.38 (*s*, CH_2); 2.39 (*s*, CH_2); 2.47 (*s*, CH_2); 2.66 (*s*, CH_2); 5.57 (br. *s*, OC(O)NH); 6.45 (*s*, NH); 7.02 (br. *s*, NH); 7.07 (*s*, NH); 7.11 (*s*, NH); 7.24 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.43, 26.77, 26.82, 26.89, 27.71, 28.52 (Me); 44.20, 46.95, 48.07, 48.38, 48.49 (CH_2); 51.76, 52.39, 52.92, 52.93, 52.97, 53.02, 79.06, 155.40, 170.76, 170.82, 170.83, 171.17, 171.60, 173.59 (C). FAB-MS: 736 (12.1, $[M+Na]^+$), 714 (100.0, $[M+1]^+$), 614(29.3), 415(7.2), 316(5.9), 198(8.7), 182(14.4), 154(26.7), 142(9.5), 136(17.9), 107(5.7).

$CF_3CO_2H \cdot H_2N$-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OMe (**1c**). Compound **1a** (150 mg, 0.21 mmol) was Boc-deprotected according to *GP 2b* to yield **1c** (197 mg, quant.). Colorless oil. IR ($CHCl_3$): 3441*w*, 3006*m*, 2970*m*, 2955*w*, 2862*w*, 1778*w*, 1717*m*, 1647*s*, 1509*s*, 1474*m*, 1369*w*, 1312*w*, 1255*w*, 1177*s*, 1122*m*, 1048*w*, 874*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.35 (*s*, 2 Me); 1.37 (*s*, 2 Me); 1.42 (*s*,6 Me); 1.46 (*s*, 2 Me); 2.31–2.34 (*m*, 3 CH_2); 2.52 (*s*, CH_2); 2.62 (*s*, CH_2); 2.73 (*s*, CH_2); 3.67 (*s*, MeO); 6.28 (*s*, NH); 7.35 (*s*, NH); 7.39 (*s*, NH); 7.45 (*s*, NH); 7.98 (*s*, NH); 8.49 (br. *s*, NH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.25, 26.35, 26.48, 26.65, 26.99, 27.22 (Me); 43.66, 44.56, 46.65, 47.89, 48.02, 48.41 (CH_2); 51.64 (Me); 52.54, 52.90, 53.14, 53.17, 53.21, 53.67, 168.83, 170.96, 171.00, 171.20, 171.72, 171.90 (C). FAB-MS: 780(11.6), 650(15.5, $[M+Na]^+$), 628(100.0, $[M+1]^+$), 397(5.0), 298(5.7), 199(6.9), 170(16.6).

$CF_3CO_2H \cdot H_2N$-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-$\beta^{3,3}$-HAib-OH (**1d**). Compound **1b** (150 mg, 0.21 mmol) was Boc-deprotected according to *GP 2b* to yield **1d** (200 mg, quant.). White powder. RP-HPLC (5–65% *B* in 20 min): t_R 13.3 min, purity >99%. M.p. 50–62°. IR (KBr): 3334*m*, 3081*m*, 2978*m*, 1654*s*, 1540*s*, 1457*m*, 1368*m*, 1252*m*, 1202*s*, 1138*s*, 928*w*, 874*m*, 834*w*, 800*m*, 722*m*, 706*w*, 595*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.39–1.41 (*m*, 12 Me); 2.46 (*s*, CH_2); 2.49 (*s*, CH_2); 2.50 (*s*, 2 CH_2); 2.60 (*s*, CH_2); 2.79 (*s*, CH_2). ^{13}C-NMR (100 MHz, CD_3OD): 26.29, 27.29, 27.33, 27.37, 27.52, 27.60 (Me); 44.20, 45.24, 46.69, 47.45, 47.77, 47.79 (CH_2); 53.01, 53.87, 53.89, 53.91, 54.07, 54.10, 171.69, 172.80, 172.83, 172.85, 172.87, 174.65 (C). FAB-MS: 1416(1.9), 1286(1.3, $[2M+Na+K-2]^+$), 803(3.0), 6.52(36.8, $[M+K]^+$), 636(50.4, $[M+Na]^+$), 614(100, $[M+1]^+$), 182(5.8), 142(3.9).

14. *β-^{2,2}-Hexapeptides* **2** *and Dodecapeptide* **3**. *Labeled Methyl 3-{[(*tert-*Butoxy)carbonyl]amino}propanoate* (Boc-β-HGly-OMe; **10***). Similarly to [51], a soln. of labeled β-HAla-OH (2.11 g, 22.73 mmol) in a mixture of dioxane (45 ml), H_2O (22 ml), and 1N NaOH (23 ml) was stirred and cooled in an ice-water bath. At 0°, Boc_2O (5.70 g, 26.15 mmol) was added, and stirring was continued at r.t. for 1 h. The soln. was concentrated, cooled in an ice-water bath, covered with a layer of AcOEt (70 ml), and acidified with a 10% aq. soln. of $NaHSO_4$ (42 ml) to pH 2. The aq. phase was extracted with AcOEt (5 × 30 ml), then these AcOEt extracts were washed with H_2O (2 × 50 ml), dried ($MgSO_4$), evaporated, dried under h.v. to yield Boc-β-HAla-OH (4.03 g, 92%). White powder. Without further purification, Boc-β-HAla-OH (4.03 g, 20.86 mmol) was esterified according to *GP 4*. FC (Et_2O/pentane 1:2) yielded **10*** (4.00 g, 93%). Slightly yellowish oil. R_f 0.33 (Et_2O/pentane 1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*s*, *t*-Bu); 2.34–2.72 (*dm*, ^1J(H,C) = 127, CH_2); 3.16–3.61 (*dm*, ^1J(H,C) = 139, CH_2); 3.70 (*d*, ^3J(H,C) = 4, MeO); 4.88–5.18 (*dm*, ^1J(H,N) = 91, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.35 (Me); 33.90–37.22 (*m*, CH_2); 51.72 (Me); 79.34 (C); 172.93 (*d*, ^1J(C,C) = 57, C).

*Methyl 3-{[(*tert-*Butoxy)carbonyl]amino}-2-methylpropanoate* (Boc-β-HGly(α-Me)-OMe; **11**). Ester **10** [54] (12.00 g, 58.9 mmol) was alkylated according to *GP 1* to yield **11** (12.66 g, 98%) as a clear orange oil which was used in the following step without further purification. R_f 0.29 (Et_2O/pentane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.17 (*d*, *J* = 7.1, Me); 1.44 (*s*, *t*-Bu); 2.63–2.73 (*m*, CH); 3.20–3.38 (*m*, CH_2); 3.70 (*s*, MeO); 4.98 (br. *s*, NH).

*Labeled Methyl 3-{[(*tert-*Butoxy)carbonyl]amino}-2-methylpropanoate* (Boc-β-HGly(α-Me)-OMe; **11***). Ester **10*** (3.52 g, 16.99 mmol) was alkylated according to *GP 1* except that only 2 equiv. of labeled MeI (2.13 ml, 33.99 mmol) were used to yield **11*** (3.68 g, 97%) as an orange oil which was used in the following step without further purification. R_f 0.29 (Et_2O/pentane 1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98–1.36 (*dm*, ^1J(H,C) = 128, Me); 1.43 (*s*, *t*-Bu); 2.45–2.90 (*dm*, ^1J(H,C) = 131, CH); 3.01–3.56 (*m*, CH_2); 3.70 (*d*, ^3J(H,C) = 4, MeO); 4.79–5.09 (*dm*, ^1J(H,N) = 91, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.72 (*d*, ^1J(C,C) = 34, Me); 28.38 (Me); 39.32–43.19 (*m*, CH, CH_2); 51.85 (Me); 79.34 (C); 175.87 (*d*, ^1J(C,C) = 57, C).

*Methyl 3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-dimethylpropanoate* (Boc-$\beta^{2,2}$-HAib-OMe; **12**). Ester **11** (12.66 g, 58.1 mmol) was alkylated according to *GP 1*. FC (Et_2O/pentane 1:3) yielded **12** (10.84 g, 81%). Yellowish oil. R_f 0.31 (Et_2O/pentane 1:3). IR ($CHCl_3$): 3456*m*, 2981*m*, 1715*s*, 1509*s*, 1474*m*, 1453*m*, 1393*m*, 1368*m*, 1313*m*, 1155*s*, 1048*w*, 984*w*, 932*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.19 (*s*, 2 Me); 1.43 (*s*, *t*-Bu); 3.23 (*d*, *J* = 6.6, CH_2); 3.69 (*s*, MeO); 4.96 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.02, 28.38 (Me); 43.69 (C); 48.32 (CH_2); 52.00 (Me); 79.17, 156.18, 177.65 (C). EI-MS: 253 (3.3, $[M+Na]^+$), 231 (0.7, M^+), 199(6.5),

175(7.0), 158(19.4), 149(8.3), 144(33.3), 130(45.7), 126(12.1), 116(18.5), 102(100.0), 98(23.5), 57(56.5). Anal. calc. for $C_{11}H_{21}NO_4$ (231.29): C 57.12, H 9.15, N 6.06; found: C 57.02, H 9.15, N 6.08.

*Labeled Methyl 3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-dimethylpropanoate* (Boc-$\beta^{2,2}$-HAib-OMe; **12***). Ester **11*** (3.68 g, 16.57 mmol) was alkylated according to *GP 1* except that only 2 equiv. of labeled MeI (2.07 ml, 33.14 mmol) were used. FC (Et_2O/pentane 1:5) yielded **12*** (2.92 g, 75%). Yellowish oil. R_f 0.31 (Et_2O/pentane 1:3). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93–1.43 (*dm*, ^1J(H,C) = 127, 6 H, Me); 1.43 (*s*, *t*-Bu); 2.93–3.51 (*dm*, ^1J(H,C) = 138, CH_2); 3.68 (*d*, ^3J(H,C) = 32, MeO); 4.76–5.15 (*dm*, ^1J(H,N) = 91, NH).

*3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-methylpropanoic Acid* (Boc-$\beta^{2,2}$-HAib-OH; **13**). Ester **12** (2.00 g, 8.6 mmol) was saponified according to *GP 3a*. Recrystallization (AcOEt/pentane) yielded **13** (1.28 g, 69%). White powder. M.p. 114–115°. R_f 0.34 (Et_2O/pentane 1:2). IR ($CHCl_3$): 3456*w*, 2984*m*, 2933*w*, 1708*s*, 1508*s*, 1476*m*, 1456*w*, 1410*w*, 1395*w*, 1369*m*, 1308*w*, 1169*s*, 1041*w*, 933*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 1.23 (*s*, 2 Me); 1.44 (*s*, *t*-Bu); 3.22–3.27 (*m*, CH_2); 5.02, *6.37* (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.90, 28.37 (Me); 43.61 (C); 47.98 (CH_2); 79.40, 156.27, 183.12 (C). EI-MS: 161(9.1), 144(7.2), 130(4.6), 116(5.6), 98(11.4), 88(42.0), 70(24.3), 57(100.0), 41(30.7), 30(30.8). Anal. calc. for $C_{10}H_{19}NO_4$ (217.26): C 55.28, H 8.81, N 6.45; found: C 55.07, H 8.91, N 6.51.

*Labeled 3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-dimethylpropanoic Acid* (Boc-$\beta^{2,2}$-HAib-OH; **13***). Ester **12*** (1.97 g, 8.30 mmol) was saponified according to *GP 3a* to yield **13*** (1.81 g, 98%) as a white powder which was used in the following step without further purification. M.p. 117–119°. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.01–1.41 (*dm*, ^1J(H,C) = 129, 2 Me); 1.44 (*s*, *t*-Bu); 2.99–3.47 (*dm*, ^1J(H,C) = 139, CH_2); 4.89–5.18 (*dm*, ^1J(H,N) = 91, NH); 6.27–6.57 (*dm*, ^1J(H,N) = 92, NH, rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.85 (*d*, ^1J(C,C) = 35, Me); 22.96 (*d*, ^1J(C,C) = 35, Me); 28.34 (Me); 42.72–44.76 (*m*, C); 47.67–49-73 (*m*, CH_2); 79.38 (C); 156.10 (C); 181.30 (*d*, ^1J(C,C) = 55, C); 183.07 (*d*, ^1J(C,C) = 54, C).

*Methyl 3-[(3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-dimethylpropanoyl)amino]-2,2-dimethylpropanoate* (Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe; **19a**). Compound **12** (3.60 g, 15.5 mmol) was Boc-deprotected according to *GP 2a* and coupled with **13** (3.37 g, 15.5 mmol) according to *GP 6*. FC (Et_2O/pentane 3:2) yielded **19a** (3.98 g, 78%). White powder. M.p. 66–67°. R_f 0.33 (Et_2O/pentane 3:2). IR ($CHCl_3$): 3453*m*, 3006*m*, 2975*m*, 1710*s*, 1656*m*, 1506*s*, 1474*m*, 1392*w*, 1367*m*, 1312*m*, 1158*s*, 1046*w*, 930*w*, 863*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.18 (*s*, 2 Me); 1.19 (*s*, 2 Me); 1.42 (*s*, *t*-Bu); 3.21 (*d*, J = 6.5, CH_2); 3.35 (*d*, J = 6.3, CH_2); 3.71 (*s*, MeO); 5.20 (br., NH); 6.40 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.14, 23.65, 28.39 (Me); 43.25, 43.40 (C); 46.71, 48.92 (CH_2); 79.01, 156.42, 177.00, 177.88 (C). EI-MS: 330 (0.3, M^+), 257(7.8), 225(16.6), 201(61.9), 169(30.8), 155(52.7), 144(8.3), 126(34.3), 98(100.0), 87(4.1), 70(18.45), 59(20.8), 41(13.2), 30(5.0). Anal. calc. for $C_{16}H_{30}N_2O_5$ (330.42): C 58.16, H 9.15, N 8.48; found: C 58.06, H 9.27, N 8.45.

*Labeled Methyl 3-[(3-{[(*tert-*Butoxy)carbonyl]amino}-2,2-dimethylpropanoyl)amino]-2,2-dimethylpropanoate* (Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe; **19a***). Compound **12*** (957 mg, 4.03 mmol) was Boc-deprotected according to *GP 2a* and coupled with **13*** (901 mg, 4.03 mmol) according to *GP 6*. FC (Et_2O/pentane 3:2) yielded **19a*** (1.26 g, 91%). White powder. R_f 0.33 (Et_2O/pentane 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98–1.37 (*dm*, ^1J(H,C) = 127, 4 Me); 1.42 (*s*, *t*-Bu); 3.00–3.42 (*dm*, ^1J(H,C) = 139, CH_2); 3.13–3.55 (*dm*, ^1J(H,C) = 140, CH_2); 3.71 (*d*, ^3J(H,C) = 4, MeO); 5.05–5.35 (*dm*, ^1J(H,N) = 91, NH); 6.26–6.56 (*dm*, ^1J(H,N) = 91, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.95–23.81 (*m*, Me); 28.38 (Me); 42.38–44.14 (*m*, C); 46.44–49.12 (*m*, CH_2); 79.03 (C); 156.28 (C); 156.55 (C); 177.00 (*dd*, ^1J(C,C) = 49, ^1J(C,N) = 14, C); 177.90 (*d*, ^1J(C,C) = 56, C).

(Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe (**22a**). Dipeptide **19a** (3.40 g, 10.3 mmol) was Boc-deprotected according to *GP 2a* and coupled with **13** (2.24 g, 10.3 mmol) according to *GP 6*. FC (AcOEt/pentane 3:2) yielded **22a** (3.55 g, 80%). White powder. M.p. 107–108°. R_f 0.22 (AcOEt/pentane 3:2). IR ($CHCl_3$): 3451*m*, 3006*m*, 2972*m*, 1711*s*, 1652*s*, 1505*s*, 1474*m*, 1392*w*, 1368*m*, 1312*m*, 1158*s*, 932*w*, 860*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.17 (*s*, 2 Me); 1.18 (*s*, 2 Me); 1.19 (*s*, 2 Me); 1.42 (*s*, *t*-Bu); 3.21 (*d*, J = 6.4, CH_2); 3.32 (*d*, J = 5.9, CH_2); 3.35 (*d*, J = 6.3, CH_2); 3.71 (*s*, MeO); 5.26 (br., NH); 6.46 (br., NH); 6.88 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.11, 23.62, 23.80, 28.41 (Me); 42.55, 43.21 (C); 46.71, 47.36, 48.97 (CH_2); 52.21 (Me); 78.88, 156.42, 177.26, 177.46, 177.90 (C). FAB-MS: 452 (13.9, $[M+Na]^+$), 430 (100,0, M^+), 374(6.6), 330(75.9), 300(8.6), 243(5.9), 199(7.0), 170(6.6). Anal. calc. for $C_{21}H_{39}N_3O_6$ (429.56): C 58.72, H 9.15, N 9.78; found: C 58.52, H 9.05, N 9.76.

Labeled Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe (**22a***). Dipeptide **19a*** (625 mg, 1.82 mmol) was Boc-deprotected according to *GP 2a* and coupled with **13*** (408 mg, 1.82 mmol) according to *GP 6*. FC (AcOEt/pentane 3:2) yielded **22a*** (772 mg, 94%). White powder. R_f 0.22 (AcOEt/pentane 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98–1.38 (*dm*, ^1J(H,C) = 129, 6 Me); 1.42 (*s*, *t*-Bu); 3.00–3.41 (*dm*, ^1J(H,C) = 139, CH_2); 3.11–3.56 (*dm*, ^1J(H,C) = 140, 2 CH_2); 3.71 (*d*, ^3J(H,C) = 4, MeO); 5.11–5.41 (*dm*, ^1J(H,N) = 91, NH); 6.32–6.62 (*dm*, ^1J(H,N) = 91, NH); 6.75–7.04 (*dm*, ^1J(H,N) = 91, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.91–23.95

(*m*, Me); 28.39 (Me); 41.68–43.94 (*m*, C): 46.43–49.16 (*m*, CH_2); 78.89 (C); 176.95–177.77 (*m*, C); 177.92 (*d*, ^1J(C,C) = 56, C).

Boc-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OH (**22b**). Compound **22a** (1.61 g, 3.8 mmol) was saponified according to *GP 3a* to yield **22b** (1.53 g, 98%). White powder. **22b** was used in the next step without further purification. R_f 0.29 (MeOH/CH_2Cl_2 1:9). ^{1}H-NMR (200 MHz, CD_3OD): 1.15 (*s*, 2 Me); 1.17 (*s*, 4 Me); 1.43 (*s*, *t*-Bu); 3.18 (*s*, CH_2); 3.29–3.35 (*m*, 2 CH_2).

Labeled Boc-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OH (**22b***). Compound **22a*** (755 mg, 1.68 mmol) was saponified according to *GP 3a* to yield **22b*** (684 mg, 94%). White powder. **22b*** was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98–1.41 (*dm*, ^1J(H,C) = 127, 6 Me); 1.42 (*s*, *t*-Bu); 3.01–3.44 (*dm*, ^1J(H,C) = 140, CH_2); 3.11–3.59 (*dm*, ^1J(H,C) = 140, 2 CH_2); 5.10–5.39 (*dm*, ^1J(H,N) = 91, NH); 6.08–6.38 (*dm*, ^1J(H,N) = 90, NH); 6.38–6.68 (*dm*, ^1J(H,N) = 90, NH); 6.71–7.02 (*dm*, ^1J(H,N) = 91, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.97–23.89 (*m*, Me); 28.38 (Me); 42.08–44.03 (*m*, C); 46.53–50.62 (*m*, CH_2); 79.36 (C); 176.07–177.68 (*m*, C); 180.11 (*d*, ^1J(C,C) = 54, C).

Boc-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OMe (**2a**). Compound **22a** (1.61 g, 3.8 mmol) was Boc-deprotected according to *GP 2a* and coupled with **22b** (1.53 g, 3.7 mmol) according to *GP 6*. 2 × FC (MeOH/CH_2Cl_2 1:18) yielded **2a** (2.07 g, 79%). White powder. M.p. 168–170°. R_f 0.23 (MeOH/CH_2Cl_2 1:18). IR ($CHCl_3$): 3436*w*, 3323*w*, 3005*m*, 2975*m*, 2923*w*, 2872*w*, 1713*m*, 1656*s*, 1503*s*, 1451*m*, 1390*w*, 1369*m*, 1169*m*, 1077*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.17 (*s*, 2 Me); 1.18 (*s*, 4 Me); 1.19 (*s*, 6 Me); 1.41 (*s*, *t*-Bu); 3.20 (*d*, *J* = 6.4, CH_2); 3.29–3.32 (*m*, 4 CH_2); 3.34 (*d*, *J* = 6.2, CH_2); 3.71 (*s*, MeO); 5.30 (br., NH); 6.49 (br., NH); 7.05 (br., NH); 7.10 (br. *t*, *J* = 5.6, NH); 7.20 (br., 2 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.10, 23.64, 23.74, 23.78, 28.41 (Me); 42.16, 42.18, 42.27, 42.30, 43.15 (C); 46.74, 47.47, 49.00 (CH_2); 52.25 (Me); 78.80, 156.43, 177.22, 177.51, 177.62, 177.68, 177.93 (C). FAB-MS: 749 (28.8, $[M+Na]^+$), 727 (51.4, M^+), 627 (100.0), 199 (5.6), 170 (12.3), 154 (6.1), 140 (5.2). Anal. calc. for $C_{36}H_{66}N_6O_9$ (726.95): C 59.48, H 9.15, N 11.56; found: C 59.20, H 8.92, N 11.40.

Labeled Boc-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OMe (**2a***). Compound **22a*** (344 mg, 0.76 mmol) was Boc-deprotected according to *GP 2a* and coupled with **22b*** (333 mg, 0.76 mmol) according to *GP 6*. 2 × FC (MeOH/CH_2Cl_2 1:18) yielded **2a*** (492 mg, 84%). White powder. M.p. 167–169°. R_f 0.23 (MeOH/CH_2Cl_2 1:18). IR ($CHCl_3$): 3442*m*, 3008*m*, 2960*m*, 1700*m*, 1605*s*, 1483*s*, 1360*w*, 1292*m*, 1158*m*, 972*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98–1.38 (*dm*, ^1J(H,C) = 128, 12 Me); 1.41 (*s*, *t*-Bu); 2.99–3.40 (*dm*, ^1J(H,C) = 139, CH_2); 3.08–3.55 (*dm*, ^1J(H,C) = 140, 5, CH_2); 3.71 (*d*, ^3J(H,C) = 4, MeO); 5.16–5.45 (*dm*, ^1J(H,N) = 91, NH); 6.34–6.64 (*dm*, ^1J(H,N) = 91, NH); 6.91–7.19 (*dm*, ^1J(H,N) = 91, NH); 6.96–7.24 (*dm*, ^1J(H,N) = 91, NH); 7.04–7.35 (*dm*, ^1J(H,N) = 91, 2 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.88–23.87 (*m*, Me); 28.38 (Me); 41.26–43.86 (*m*, C); 46.44–49.16 (*m*, CH_2); 176.86–178.20 (*m*, C). FAB-MS: 785 (15.0, $[M+Na]^+$), 763 (96.7, M^+), 663 (100.0), 526 (8.7), 421 (11.7), 316 (11.1), 211 (18.2), 180 (17.1), 106 (13.4).

Boc-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OH (**2b**). Compound **2a** (520 mg, 0.72 mmol) was dissolved in MeOH (4 ml), treated with 1N NaOH (3.6 ml), and stirred for 15 h at r.t. The cloudy mixture was solubilized with MeOH (8 ml) and 1N NaOH (3.6 ml) which was further heated at 50° for 5 h. MeOH was evaporated, and the pH was adjusted to 1N HCl. The crude product was extracted with $CHCl_3$ (4 ×). The combined org. phases were washed with sat. aq. NaCl soln. (1 ×), dried ($MgSO_4$), and evaporated. **2b** (509 mg, quant.). Yellowish powder. M.p. 64–65°. R_f 0.06 (MeOH/CH_2Cl_2 1:9). IR ($CHCl_3$): 3447*w*, 3008*m*, 2972*m*, 2936*w*, 1706*m*, 1648*s*, 1509*s*, 1747*m*, 1394*w*, 1368*m*, 1310*w*, 1170*m*, 989*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.17 (*s*, 6 Me); 1.18 (*s*, 4 Me); 1.21 (*s*, 2 Me); 1.42 (*s*, *t*-Bu); 3.22 (*d*, *J* = 6.5, CH_2); 3.27–3.35 (*m*, 5 CH_2); 5.33 (br., NH); 6.55 (br., NH); 6.85 (br., NH); 7.05 (br., 2 NH); 7.15 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.22, 23.52, 23.67, 23.77, 28.42 (Me); 42.29, 42.53, 42.60, 42.81, 42.86, 43.34 (C); 46.77, 47.38, 47.44, 47.55, 47.65, 48.88 (CH_2); 79.00, 156.55, 177.31, 177.51, 177.73, 179.58 (C). FAB-MS: 736 (18.7, $[M+Na]^+$), 714 (83.8, $[M+1]^+$), 640 (6.0), 614 (100.0), 584 (5.6), 170 (8.3), 154 (9.4), 136 (8.3).

$CF_3COOH \cdot H_2N$-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-β^{2,2}-HAib-OMe (**2c**). Compound **2a** (320 mg, 0.44 mmol) was Boc-deprotected according to *GP 2b* to yield **2c** (335 mg, quant.). White solid. M.p. 42–50°. IR ($CHCl_3$): 3436*w*, 3323*w*, 3005*m*, 2977*m*, 1727*w*, 1663*s*, 1509*s*, 1453*m*, 1383*w*, 1367*m*, 1256*m*, 1177*s*, 1140*m*, 1085*w*, 1039*w*, 874*w*, 836*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.19 (*s*, 10 Me); 1.31 (*s*, 2 Me); 3.28–3.35 (*m*, 6 CH_2); 3.71 (*s*, MeO); 6.55 (br. *t*, *J* = 5.8, NH); 7.16 (br. *t*, *J* = 5.6, NH); 7.25 (br. *t*, NH); 7.27 (br. *t*, NH); 7.48 (br., NH); 8.42 (br., NH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.09, 23.54, 23.68, 23.84 (Me); 39.35, 42.07, 42.26, 42.34, 43.11 (C); 46.82, 47.52, 47.58, 47.63, 47.69, 48.08 (CH_2); 52.27 (Me); 177.62, 177.73, 177.85, 177.94 (C). FAB-MS: 650 (7.6, $[M+Na]^+$), 628 (100.0, $[M+1]^+$), 330 (3.6), 232 (3.3), 198 (4.0), 182 (6.4), 154 (4.1), 142 (4.8), 136 (3.8).

$CF_3COOH \cdot H_2N$-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OH (**2d**). Compound **2b** (200 mg, 0.28 mmol) was Boc-deprotected according to *GP 2b* to give **2d** (251 mg, quant.). Clear colorless oil. RP-HPLC (5–65% *A* in 20 min): t_R 12.6 min, purity 98.5%. IR (KBr): 3375*m*, 2973*m*, 2936*m*, 1654*s*, 1522*s*, 1475*m*, 1399*w*, 1368*w*, 1313*w*, 1202*s*, 1181*s*, 1139*s*, 1025*w*, 991*w*, 874*w*, 798*w*, 721*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.17 (*s*, 10 Me); 1.31 (*s*, 2 Me); 3.02 (*s*, CH_2); 3.30–3.34 (*m*, 5 CH_2). ^{13}C-NMR (100 MHz, CD_3OD): 23.72, 23.94, 23.98 (Me); 41.54, 44.26, 44.44, 44.48, 44.51, 44.53 (C); 48.03, 48.56, 48.67 (CH_2); 178.26, 179.29, 179.30, 179.35, 179.40, 180.42 (C). FAB-MS: 1416(1.5), 670(2.8), 652(55.6, $[M+K]^+$), 636 (12.1, $[M+Na]^+$), 614 (100.0, $[M+1]^+$), 298(5.1), 270(4.7), 170(7.7), 154(5.1), 136(4.3).

Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe (**3a**). Compound **2a** (235 mg, 0.32 mmol) was Boc-deprotected according to *GP 2a* and coupled with **22b** (135 mg, 0.32 mmol) according to *GP 6*. FC ($MeOH/CH_2Cl_2$ 1:14) yielded **3a** (265 mg, 80%). White powder. M.p. 173–175°. R_f 0.16 ($MeOH/CH_2Cl_2$ 1:14). IR ($CHCl_3$): 3447*m*, 3004*m*, 2970*m*, 2872*w*, 1711*m*, 1646*s*, 1506*s*, 1474*m*, 1392*w*, 1368*w*, 1312*w*, 1159*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16–1.21 (*m*, 18 Me); 1.41 (*s*, *t*-Bu); 3.20 (*d*, $J=6.3$, CH_2); 3.26–3.32 (*m*, 7 CH_2); 3.34 (*d*, $J=6.2$, CH_2); 3.71 (*s*, MeO); 5.30 (br., NH); 6.48 (br. *t*, $J=5.7$, NH); 7.05 (br. *t*, $J=5.7$, NH); 7.11 (br. *t*, $J=5.7$, NH); 7.16–7.28 (*m*, 5 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.10, 23.75, 23.79, 28.41 (Me); 46.74, 47.46, 47.48, 47.52, 48.98 (CH_2); 52.25 (Me); 78.80, 156.44, 177.23, 177.52, 177.64, 177.68, 177.94 (C). FAB-MS: 1047 (8.8, $[M+Na]^+$), 1025 (90.0, M^+), 925(100.0), 726(4.8), 307(4.7), 298(5.0), 200(11.7), 170(19.5), 154(27.8).

Boc-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-$\beta^{2,2}$-HAib-OMe (**3b**). A soln. of **2c** (126 mg, 0.17 mmol) in $CHCl_3$ (1 ml) was treated with Et_3N (100 µl, 0.73 mmol), HOBt (27 mg, 0.20 mmol), a soln. of **2b** (120 mg, 0.17 mmol) in DMF (2 ml), and EDC (38 mg, 0.20 mmol) under Ar at 0°. The mixture was stirred for 18 h at r.t. The solvent was evaporated and the residue dried under h.v. The oily residue was dissolved in $CHCl_3$ and washed with 1N HCl, sat. aq. $NaHCO_3$ (3×), and NaCl (1×) solns. The org. phase was dried ($MgSO_4$) and evaporated. FC ($MeOH/CH_2Cl_2$ 1:14) gave **3b** (135 mg, 62%). Glass. R_f 0.19 ($MeOH/CH_2Cl_2$ 1:14). IR ($CHCl_3$): 3440*w*, 3336*w*, 3007*m*, 2972*m*, 2931*w*, 2870*w*, 1711*w*, 1649*s*, 1506*s*, 1475*m*, 1452*m*, 1388*w*, 1367*m*, 1314*w*, 1260*m*, 1174*m*, 987*w*, 911*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16–1.19 (*m*, 12 Me); 1.40–1.43 (*m*, 12 Me, *t*-Bu); 2.23–2.31 (*m*, 6 CH_2); 3.20 (*d*, $J=6.4$, CH_2); 3.27–3.30 (*m*, 5 CH_2); 3.67 (*s*, MeO); 5.30 (br., NH); 6.16 (*s*, NH); 7.06 (*m*, 2 NH); 7.21 (br. *t*, $J=5.7$, NH); 7.25 (br., NH); 7.30 (br. *t*, $J=5.7$, NH); 7.36 (*s*, NH); 7.44 (*s*, NH); 7.61 (*s*, NH); 7.69 (*s*, NH); 7.78 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.95, 23.65, 23.72, 23.76, 23.79, 26.03, 26.12, 26.21, 26.38, 26.42, 27.01, 28.42 (Me); 42.08, 42.12, 42.25, 42.28, 43.09, 43.17 (C); 47.47, 47.50, 47.54, 47.73, 48.13, 48.17, 48.62, 48.71, 48.92, 48.99 (CH_2); 51.64 (Me); 52.50, 53.08, 53.10, 53.12, 78.78, 128.92, 134.68, 156.44, 170.80, 170.84, 170.91, 170.95, 171.85, 176.93, 177.22, 177.64, 177.69 (C). FAB-MS: 1322 (100.0, M^+), 1222(68.8), 695(6.9), 594(7.1), 567(7.2), 429(6.0), 397 (7.0), 369(6.2), 298(11.8), 225(20.0), 199(18.2), 182(32.2), 170(25.3).

15. *Cyclic $\beta^{2,2}$-Amino Acids and $\beta^{2,2}$-Peptides* **4**, **5**, *and* **6**. *Methyl 1-Cyanocyclohexane-1-carboxylate* (**14d**). Nitrile **14d** was prepared according to [33] in 52% yield. R_f 0.56 (Et_2O/pentane 1:1). $n_D=1.4580$ (in agreement with [36]). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24–1.31 (*m*, CH_2); 1.56–1.89 (*m*, 3 CH_2); 2.08–2.14 (*m*, CH_2); 3.82 (*m*, MeO). EI-MS: 167 (1.0, M^+), 152(0.7), 135(4.7), 122(62.0), 112(64.4), 108(91.3), 95(40.3), 81(85.1), 67(100.0), 59(28.9), 55(29.0), 42(37.1), 28(14.8).

*Methyl 1-({[(*tert*-Butoxy)carbonyl]amino}methyl)cyclopropane-1-carboxylate* (Boc-$\beta^{2,2}$-HAc_3c-OMe; **15a**). Freshly prepared *Raney*-Ni (2.0 g) was added to a soln. of **14a** (0.828 g, 6.62 mmol) [33], obtained from the corresponding cyano acid [34] by esterification (MeOH, DCC, DMAP), in MeOH (26.0 ml). This mixture was stirred for 4 h at r.t. under H_2 (balloon). Excess H_2 was removed by bubbling Ar through the mixture. Filtration through *Celite* and evaporation (30°, 100 mbar) gave the crude amine with varying amounts of side products. An aliquot of this crude primary amine intermediate (0.239 g, 1.89 mmol) was dissolved in MeCN (4.0 ml) at 0°. Et_3N (0.26 ml, 1.85 mmol) and Boc_2O (0.44 g, 2.0 mmol) were added, and the soln. was stirred for 2 h. After evaporation, the oil was dissolved in Et_2O. The Et_2O phase was washed with aq. sat. NH_4Cl soln., dried ($MgSO_4$), and evaporated. FC (Et_2O/pentane 1:2) yielded **15a** (0.34 g, 80%). Colorless oil. R_f 0.32 (Et_2O/pentane 1:2). IR ($CHCl_3$): 3450*w*, 3008*m*, 2980*w*, 1709*s*, 1507*m*, 1439*m*, 1392*w*, 1367*m*, 1160*s*, 939*w*, 854*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95–0.98 (*m*, 2 CH); 1.21–1.27 (*m*, 2 CH); 1.44 (*s*, *t*-Bu); 3.28 (*d*, $J=6.4$, CH_2N); 3.68 (*s*, MeO); 5.18 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.70 (CH_2); 24.96 (C); 28.38 (Me); 43.97 (CH_2); 51.98 (Me); 79.22, 156.17, 175.32 (C). FAB-MS: 459 (12.1, $[2M+1]^+$), 230 (69.4, $[M+1]^+$), 229 (3.1, M^+), 174(100), 130(56.9).

*Methyl 1-({[(*tert*-Butoxy)carbonyl]amino}methyl)cyclobutane-1-carboxylate* (Boc-$\beta^{2,2}$-HAc_4c-OMe; **15b**). Compound **14b** [33][36] (2.20 g, 15.8 mmol) was transformed according to *GP 5a*. FC (Et_2O/pentane 1:3) yielded **15b** (2.10 g, 55%). Colorless oil. R_f 0.33 (Et_2O/pentane 1:3). IR ($CHCl_3$): 3453*m*, 3026*m*, 3016*m*,

2981*m*, 2954*m*, 2874*w*, 1712*s*, 1507*s*, 1436*m*, 1393*m*, 1368*m*, 1333*m*, 1250*s*, 1236*m*, 1167*s*, 1128*s*, 1006*w*, 981*w*, 946*w*, 860*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*s*, *t*-Bu); 1.84–2.12 (*m*, 4 CH); 2.34–2.44 (*m*, 2 CH); 3.50 (*d*, J = 6.3, CH_2N); 3.73 (*s*, CO_2Me); 4.94 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.65, 27.64 (CH_2); 28.37 (Me); 45.36 (CH_2); 47.36 (C); 52.06 (Me); 79.26, 156.41, 176.58 (C). EI-MS: 244 (3.2, $[M+1]^+$), 188(43.8), 170(34.8), 156(38.1), 144(21.1), 142(12.8), 138(32.8), 127(14.2), 126(61.1), 115(10.1), 114(100), 110(13.7), 99(18.9), 83(17.3), 82(20.6), 67(34.7), 59(26.2), 57(95.8), 55(10.3), 41(17.5). Anal. calc. for $C_{12}H_{21}NO_4$ (243.30): C 59.24, H 8.70, N 5.76; found: C 59.33, H 8.62, N 5.70.

*Methyl 1-({[(*tert-*Butoxy)carbonyl]amino}methyl)cyclopentane-1-carboxylate* (Boc-$\beta^{2,2}$-HAc_5c-OMe; **15c**). Compound **14c** [33][36] (4.11 g, 26.8 mmol) was transformed according to *GP 5a*. FC (Et_2O/pentane 1:5) yielded **15c** (3.93 g, 57%). Colorless oil. R_f 0.33 (Et_2O/pentane 1:5). IR ($CHCl_3$): 3452*w*, 3146 (br.), 2982*m*, 2933*m*, 2862*w*, 1705*s*, 1507*s*, 1455*w*, 1393*w*, 1368*m*, 1326*w*, 1166*s*, 1128*m*, 1039*w*, 955*w*, 863*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.43 (*s*, *t*-Bu); 1.55–1.79 (*m*, 6 CH); 1.91–2.00 (*m*, 2 CH); 3.27 (*d*, J = 6.5, CH_2N); 3.70 (*s*, CO_2Me); 5.04 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 25.57 (CH_2); 28.40 (Me); 34.45, 46.13 (CH_2); 52.05 (Me); 54.37, 79.17, 156.34, 178.24 (C). EI-MS: 279 (< 1, $[M+Na]^+$), 257 (< 1, M^+), 170(11.0), 128(100), 57(37.3). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.79, H 9.08, N 5.38.

*Methyl 1-({[(*tert-*Butoxy)carbonyl]amino}methyl)cyclohexane-1-carboxylate* (Boc-$\beta^{2,2}$-HAc_6c-OMe; **15d**). Compound **14d** (14.7 g, 88.0 mmol) was transformed according to *GP 5a*. FC (Et_2O/pentane 1:7 → 2:7) yielded **15d** (13.59 g, 57%). Colorless oil. R_f 0.21 (AcOEt/pentane 1:12). IR ($CHCl_3$): 3451*w*, 2983*w*, 2936*m*, 2861*w*, 1711*s*, 1509*s*, 1454*m*, 1393*w*, 1368*m*, 1165*s*, 1137*m*, 1102*w*, 1022*w*, 967*w*, 859*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.27 (*t*, J = 7.1, Me); 1.42 (*s*, *t*-Bu); 1.25–1.64 (*m*, 4 CH_2); 1.96–2.01 (*m*, CH_2); 3.27 (*d*, J = 6.4, CH_2N); 4.16 (*q*, J = 7.1, CH_2O); 4.76 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.24 (Me); 22.51, 25.69 (CH_2); 28.37 (Me); 31.46, 47.37 (CH_2); 47.70 (C); 60.60 (CH_2); 79.18, 155.99, 175.99 (C). EI-MS: 286 (3.6, $[M+1]^+$), 230(31.7), 212 (11.7), 184(39.9), 156(100.0), 138(19.0), 128(29.4), 110(10.5), 95(26.1), 81(28.5), 74(8.9), 67(14.0), 57(80.4), 41(24.4), 30(16.1). Anal. calc. for $C_{15}H_{27}NO_4$ (285.38): C 63.13, H 9.54, N 4.91; found: C 63.34, H 9.52, N 5.07.

*1-({[(*tert-*Butoxy)carbonyl]amino}methyl)cyclopropane-1-carboxylic Acid* (Boc-$\beta^{2,2}$-HAc_3c-OH; **16a**). To a soln. of **15a** (132 mg, 0.57 mmol) in MeOH (0.6 ml) was added a soln. of LiOH (33 mg, 1.36 mmol) in H_2O (0.3 ml). This soln. was stirred for 3 d. MeOH was evaporated and the residue extracted with Et_2O. The aq. phase was acidified (pH 1–2) with 10% HCl and extracted with Et_2O (3×). The Et_2O phase was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude oil. FC (CH_2Cl_2/MeOH 15:1) and recrystallization (AcOEt/pentane) yielded **16a** (58 mg, 48%). Colorless needles. M.p. 121–122°. R_f 0.18 (CH_2Cl_2/MeOH 15:1). IR ($CHCl_3$): 3454*w*, 2974 (br.), 1705*s*, 1508*m*, 1451*w*, 1395*w*, 1367*w*, 1169*w*, 1046*w*, 939*w*, 850*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 0.88–1.02 (*m*, 2 CH); 1.24–1.30 (*m*, 2 CH); 1.44 (*s*, *t*-Bu); 3.28 (br. *d*, J = 5.6, CH_2N); 5.26, *6.11* (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.44 (CH_2); 24.99 (C); 28.40 (Me); 43.69 (CH_2); 79.43, 156.32, 181.34 (C). FAB-MS: 216 (42.7, $[M+1]^+$), 160(100), 116(35.6). Anal. calc. for $C_{10}H_{17}NO_4$ (215.25): C 55.80, H 7.96, N 6.51; found: C 55.32, H 7.52, N 6.27.

*1-({[(*tert-*Butoxy)carbonyl]amino}methyl)cyclobutane-1-carboxylic Acid* (Boc-$\beta^{2,2}$-HAc_4c-OH; **16b**). Compound **14b** [33][36] (4.29 g, 30.8 mmol) was transformed according to *GP 5b*. Recrystallization (AcOEt/pentane) yielded **16b** (2.57 g, 36%). Colorless crystals. M.p. 94.2–95.2°. R_f 0.67 (MeOH/CH_2Cl_2 1:9). IR ($CHCl_3$): 3453*w*, 2978*m*, 2922*m*, 1706*s*, 1506*s*, 1450*w*, 1394*w*, 1361*m*, 1322*w*, 1250*m*, 1167*m*, 1128*w*, 1039*w*, 1006*w*, 956*w*, 917*w*, 861*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 1.44, *1.49* (*s*, *t*-Bu); 1.96–2.18 (*m*, 4 CH); 2.41–2.47 (*m*, 2 CH); 3.53 (br. *d*, J = 6.3, CH_2N); 5.02, *6.22* (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$; signals of rotamers in italics): *14.13*, 15.66, *22.66*, 27.59 (CH_2); 28.36, *31.60* (Me); 45.03, *46.50* (CH_2); 47.25, *47.81*, 79.46, *80.88*, 156.53, *157.71*, *180.41*, 182.01 (C). FAB-MS: 459 (11.3, $[2M+1]^+$), 230 (49.6, $[M+1]^+$), 174(100). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found: C 57.73, H 8.33, N 6.18.

*1-({[(*tert-*Butoxy)carbonyl]amino}methyl)cyclopentane-1-carboxylic Acid* (Boc-$\beta^{2,2}$-HAc_5c-OH; **16c**). Compound **14c** [33][36] (13.79 g, 90.0 mmol) was transformed according to *GP 5b*. Recrystallization (AcOEt/hexane) yielded **16c** (7.03 g, 32%). Colorless crystals, suitable for X-ray analysis. M.p. 124.5–125.5°. R_f 0.45 (MeOH/CH_2Cl_2 (1:9). IR ($CHCl_3$): 3444*w*, 2967*m*, 2867*w*, 1700*s*, 1506*s*, 1450*w*, 1394*m*, 1367*m*, 1167*s*, 1039*w*, 906*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 1.44, *1.47* (*s*, *t*-Bu); 1.60–1.76 (*m*, 6 CH); 2.00–2.11 (*m*, 2 CH); 3.28 (*d*, J = 6.5, CH_2N); 5.11, *6.33* (br. *t*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$; signals of rotamers in italics): *25.33*, 25.70 (CH_2); 28.38 (Me); *34.15*, 34.62, 45.75, *46.88* (CH_2); 54.24, *54.70* (C); 79.36, *80.77*, 156.43, *157.74*, *181.86*, 183.97 (C). FAB-MS: 768 (8.7, $[3M+K]^+$), 525 (12.3, $[2M+K]^+$), 509 (10.8, $[2M+Na]^+$), 487 (16.3, $[2M+1]^+$), 266 (25.5, $[M+Na]^+$), 244 (11.6, $[M+1]^+$), 188(61.0), 170(100), 142(50.0). Anal. calc. for $C_{12}H_{21}NO_4$ (243.30): C 59.24, H 8.70, N 5.76; found: C 59.16, H 8.60, N 5.79.

*1-({[(*tert*-Butoxy)carbonyl]amino}methyl)cyclohexane-1-carboxylic Acid* (Boc-$\beta^{2,2}$-HAc$_6$c-OH; **16d**). Compound **15d** (2.92 g, 10.2 mmol) was saponified according to *GP 3b*. Recrystallization (CH_2Cl_2/AcOEt/hexane) yielded **16d** (2.35 g, 89%). Colorless crystals. M.p. 156–158°. R_f 0.29 (MeOH/CH_2Cl_2 1:20). IR (KBr): 3318*m*, 3260*m*, 3107*w*, 2982*m*, 2954*m*, 2867*m*, 2550*w*, 1894*w*, 1706*s*, 1656*s*, 1483*m*, 1449*s*, 1411*s*, 1367*s*, 1330*m*, 1319*m*, 1237*m*, 1204*m*, 1151*s*, 1140*s*, 1102*m*, 1082*w*, 1047*m*, 1027*m*, 980*m*, 950*w*, 934*w*, 921*w*, 881*w*, 849*w*, 822*w*, 784*w*, 767*w*, 749*w*, 687*w*, 659*w*, 590*w*, 554*w*, 536*w*, 446*w*, 410*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2NCDO$; signals of rotamers in italics): 1.19–1.39 (*m*, *t*-Bu, 5 CH); 1.51–1.59 (*m*, 3 CH); 1.91–1.99 (*m*, 2 CH); 3.21 (*d*, *J* = 6.5, CH_2N); *6.21*, 6.51 (br., NH). ^{13}C-NMR (100 MHz, $(CD_3)_2NCDO$, signals of rotamers in italics): 23.41, 26.19 (CH_2); 28.46 (Me); 32.00, 48.56, *48.76* (CH_2); 78.62, 157.04, 177.77 (C). FAB-MS: 537 (7.1, $[2M+Na]^+$), 515 (13.5, $[2M+1]^+$), 280 (21.4, $[M+Na]^+$), 258 (33.3, $[M+1]^+$), 202 (100), 184 (87.0), 156 (60.3). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.41, H 8.96, N 5.42.

*1-({[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}methyl)cyclohexane-1-carboxylic Acid* (Fmoc-$\beta^{2,2}$-HAc$_6$c-OH; **17**). Compound **14d** (3.0 g, 18.1 mmol) was reduced and saponified as described in *GP 3b*. The crude free amino acid was dissolved in H_2O (0.2M) and $NaHCO_3$ (*ca.* 2 equiv.) was added until a pH of 8–9 was reached. A soln. (0.2M) of Fmoc-OSu (1.1 equiv.) in acetone was added slowly. After 2 h, the mixture was evaporated, diluted with H_2O, and extracted with pentane. The pH was carefully adjusted to 1–2 with 1N HCl and the aq. phase extracted with AcOEt. The org. phase was washed with H_2O, dried ($MgSO_4$), evaporated, and dried under h.v. Recrystallization (CH_2Cl_2) gave **17** (5.00 g, 73%). Crystalline solid (needles). M.p. 175–185°. R_f 0.56 (CH_2Cl_2/MeOH 9:1). IR ($CHCl_3$): 3677*w*, 3448*w*, 3032*w*, 3012*m*, 2938*m*, 2860*w*, 1717*s*, 1517*s*, 1451*m*, 1228*s*, 1220*s*, 1204*s*, 1137*w*, 1106*w*, 1040*w*, 880*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88–2.17 (*m*, 10 CH); 3.13 (br. *s*, 0.2 H, CH_2N, rotamer); 3.36 (*d*, *J* = 6.6, 1.8 H, CH_2N, rotamer); 4.08–4.23 (*m*, 1 CH); 4.31 (*d*, *J* = 7.2, 1.8 H, CH_2O, rotamer); 4.47 (br. *s*, 0.2 H, CH_2O); 5.78 (br. *s*, 0.1 H, NH, rotamer); 6.41 (*s*, 0.9 H, NH, rotamer); 7.32 (*d*, *J* = 7.5, 2 arom. H); 7.39 (*d*, *J* = 7.5, 2 arom. H); 7.69 (*d*, *J* = 7.7, 2 arom. H); 7.85 (*d*, *J* = 7.6, 2 arom. H); 10.79 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.55, 26.46, 29.83, 32.23 (CH_2); 48.08 (CH); 48.74 (CH_2); 49.24 (C); 66.98 (CH_2); 120.77, 126.15, 127.90, 128.47 (CH); 142.08, 145.14, 157.43, 177.02 (C). FAB-MS: 759 (3.0, $[2M+1]^+$), 380 (50.6, $[M+1]^+$), 338 (7.4), 289 (43.4), 273 (11.9), 244 (6.0), 184 (10.4), 178 (30.4), 166 (8.9). Anal. calc. for $C_{23}H_{25}NO_4$ (379.45): C 72.80, H 6.64, N 3.69; found: C 72.64, H 6.69, N 3.66.

Boc-$\beta^{2,2}$-HAc$_6$c-$\beta^{2,2}$-HAc$_6$c-OMe (**20a**). Compound **15d** (1.31 g, 4.6 mmol) was Boc-deprotected according to *GP 2a* and coupled with **16d** (1.19 g, 4.6 mmol) according to *GP 6* except that **16d** was dissolved in DMF (0.25M) instead of $CHCl_3$. The crude product **20a** was purified by FC (AcOEt/pentane 1:2) yielding **20a** (1.169 g, 62%). Colorles oil. R_f 0.19 (Et_2O/pentane 1:1). IR ($CHCl_3$): 3457*w*, 3364*w*, 3007*m*, 2934*s*, 2859*m*, 1707*s*, 1660*m*, 1510*s*, 1454*m*, 1392*w*, 1367*m*, 1323*w*, 1246*m*, 1163*s*, 1140*m*, 1105*w*, 1045*w*, 964*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16–1.65 (*m*, *t*-Bu, 16 CH); 1.79–1.83 (*m*, 2 CH); 2.04–2.08 (*m*, 2 CH); 3.19 (*d*, *J* = 6.1, CH_2N); 3.40 (*d*, *J* = 6.2, CH_2N); 3.72 (*s*, CO_2Me); 5.30 (*s*, NH); 6.14 (*t*, *J* = 5.7, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.49, 25.65 (CH_2); 28.41 (Me); 31.83 (CH_2); 46.40 (CH_2); 47.60 (C); 48.00 (CH_2); 52.25 (Me); 77.04 (C); 156.38 (C); 175.00, 176.70 (C). FAB-MS: 843 (1.4, $[2M+Na]^+$), 821 (1.2, $2M^+$), 433 (11.9, $[M+Na]^+$), 411 (67.5, $[M+1]^+$), 355 (24.7), 311 (100), 281 (17.0). Anal. calc. for $C_{22}H_{38}N_2O_5$ (410.55): C 64.36, H 9.33, N 6.82; found: C 64.34, H 9.11, N 6.60.

$CF_3COOH \cdot$ H-$\beta^{2,2}$-HAc$_6$c-$\beta^{2,2}$-HAc$_6$c-OMe (**20c**). According to *GP 2a*, **20a** (1.145 g, 2.79 mmol) was Boc-deprotected yielding the crude CF_3COOH salt **20c** (1.844 g) which was used in the next step without further purification. Yellowish oil. R_f 0.09 (AcOEt/pentane 1:1). IR ($CHCl_3$): 3011*m*, 2941*s*, 2862*m*, 2568*w*, 1781*s*, 1529*m*, 1454*m*, 1174*s*, 1039*m*, 873*w*, 818*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20–2.39 (*m*, 20 CH); 3.12 (br. *s*, $CH_2NH_3^+$); 3.38 (*d*, *J* = 6.1, CH_2N); 3.71 (*s*, CO_2Me); 6.90 (*t*, *J* = 5.9, NH); 7.26 (br. *s*, NH_3^+); 10.65 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.52, 25.43, 28.63, 31.23, 41.46, 44.23, 47.26 (CH_2); 52.61 (CH_3); 111.09, 113.94, 116.81, 119.17, 161.26, 169.15, 175.40, 177.56 (C). FAB-MS: 931 (3.6, $[3M+1]^+$), 643 (5.5, $[2M+Na]^+$), 621 (79.8, $[2M+1]^+$), 333 (4.4, $[M+Na]^+$), 311 (100, $[M+1]^+$), 172 (9.6), 140 (6.3), 112 (14.0).

Boc-$\beta^{2,2}$-HAc$_6$c-$\beta^{2,2}$-HAc$_6$c-$\beta^{2,2}$-HAc$_6$c-OMe (**23a**). Compound **16d** (0.719 g, 2.79 mmol) was coupled with the CF_3COOH salt **20c** (1.145 g, 2.79 mmol) according to *GP 6*. Recrystallization (CH_2Cl_2/hexane) afforded **23a** (1.163 g, 76%). Crystalline solid. M.p. 98–101°. R_f 0.20 (AcOEt/pentane 1:2). IR ($CHCl_3$): 3453*m*, 3007*m*, 2935*s*, 2859*m*, 1707*s*, 1646*s*, 1511*s*, 1455*m*, 1392*w*, 1367*m*, 1248*m*, 1166*m*, 1140*w*, 1047*w*, 874*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26–1.64 (*m*, *t*-Bu, 24 CH); 1.78–1.86 (*m*, 4 CH); 2.2–2.05 (*m*, 2 CH); 3.24 (*d*, *J* = 6.1, CH_2N); 3.37 (*d*, *J* = 5.8, CH_2N); 3.40 (*d*, *J* = 6.1, CH_2N); 3.70 (*s*, CO_2Me); 5.20 (*s*, NH); 6.28 (*s*, NH); 6.68 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.35, 22.43, 22.54, 22.66, 25.60, 25.77, 25.81 (CH_2); 28.42 (Me); 31.71, 31.84, 31.92 (CH_2); 46.10, 46.18, 46.55, 47.00 (CH_2); 47.39 (C); 47.51 (CH_2); 52.22 (C); 53.43 (Me); 76.78, 77.03, 77.28 (C); 78.88 (C). FAB-MS: 1010 (7.9, $[2M+1]^+$), 550 (100, $[M+1]^+$), 450 (84.8), 420 (27.8), 323 (14.4),

281 (12.2), 250 (14.4), 184 (8.3), 172 (8.9). Anal. calc. for $C_{30}H_{51}N_3O_6$ (549.76): C 65.54, H 9.35, N 7.64; found: C 65.55, H 9.39, N 7.28.

Boc-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-OH (**23b**). Compound **23a** (1.10 g, 2 mmol) was saponified according to *GP 3b* to afford **23b** (1.056 g, 99%). White powder. M.p. 172–174°. R_f 0.18 (AcOEt/pentane 1:2). IR ($CHCl_3$): 3454*m*, 3383*m*, 3007*m*, 2932*s*, 2861*m*, 1706*s*, 1652*s*, 1515*s*, 1455*s*, 1404*m*, 13368*m*, 1318*w*, 1252*m*, 1165*s*, 1045*w*, 1024*w*, 959*w*, 908*m*, 849*w*, 652*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20–2.25 (*m*, *t*-Bu, 30 CH); 3.17 (*d*, *J* = 6.8, 1.4 H, CH_2N, rotamer); 3.21 (*d*, *J* = 6.1, 0.6 H, CH_2N, rotamer); 3.33–3.37 (*m*, CH_2N); 3.41–3.43 (*m*, CH_2N); 5.23 (br. *s*, 0.3 H, NH, rotamer); 6.01 (*t*, *J* = 6.4, 0.7 H, NH, rotamer); 6.34 (br. *s*, 0.3 H, NH, rotamer); 6.45 (*t*, *J* = 6.6, NH); 6.65 (br. *s*, 0.7 H, NH, rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.49, 22.64, 22.76, 22.97, 23.05, 25.79, 25.86, 26.08 (CH_2); 32.14 (Me); 31.58, 31.83, 31.97, 32.14, 46.46, 46.64, 47.04 (CH_2); 47.17 (C); 47.27, 47.36, 47.47, 47.85 (CH_2); 48.21 (C); 48.41, 49.84 (CH_2); 76.72, 77.04, 77.24, 77.35, 79.75, 81.38, 156.68, 158.31, 174.97, 175.40, 175.75, 177.95, 178.40 (C). FAB-MS: 1094 (1.1, $[2M+Na]^+$), 1072 (0.9, $[2M+1]^+$), 575 (1.1, $[M+K]^+$), 559 (8.0, $[M+Na]^+$), 537 (100.0, $[M+1]^+$), 437 (96.7), 407 (22.6), 323 (10.4), 267 (6.0), 250 (6.6), 112 (7.1).

CF$_3$COOH·H-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-OMe (**23c**). According to *GP 2a*, **23a** (1.150 g, 2.1 mmol) was Boc-deprotected to yield **23c** (1.162 g), which was used in the next step without further purification. Yellowish oil. R_f 0.08 (AcOEt/pentane 1:1). IR ($CHCl_3$): 3674*w*, 3446*w*, 3005*m*, 2936*s*, 2861*s*, 1780*m*, 1708*m*, 1643*s*, 1526*s*, 1454*m*, 1434*w*, 1362*w*, 1325*w*, 1296*w*, 1252*w*, 1173*s*, 1167*s*, 1041*m*, 986*w*, 874*m*, 836*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26–1.59 (*m*, 24 CH); 1.87–1.88 (*m*, 2 CH); 2.02–2.03 (*m*, 4 CH); 3.12 (br. *s*, CH_2N); 3.33–3.36 (*m*, 2 CH_2N); 3.71 (*s*, CO_2Me); 6.63 (*t*, *J* = 5.8, NH); 6.93 (br. *s*, NH_3^+); 7.39 (br. *s*, NH); 7.89 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.48, 25.47, 31.85, 44.37, 47.24, (CH_2); 52.35 (Me); 67.04 (CH_2); 77.03, 113.88, 160.41, 176.89 (C). FAB-MS: 922 (2.9, $[2M+Na]^+$), 900 (26.4, $[2M+1]^+$), 4.88 (0.4, $[M+K]^+$), 472 (4.1, $[M+Na]^+$), 451 (100.0, $[M+1]^+$), 250 (6.6), 140 (8.1), 112 (11.7).

Boc-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-OMe (**4b**). Compound **23c** (0.998 g, 1.87 mmol) was coupled with **23b** (1.00 g, 1.87 mmol) according to *GP 6*. FC (AcOEt/pentane 3:2), followed by recrystallization (Et_2O/pentane 5:95), yielded **4b** (0.651 g, 36%). White powder. M.p. 94–96°. R_f 0.29 (AcOEt/pentane 3:2). IR ($CHCl_3$): 3446*w*, 3378*w*, 3005*m*, 2933*s*, 2859*m*, 1708*m*, 1641*s*, 1509*s*, 1455*m*, 1252*w*, 1166*w*, 654*w*, 600*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16–1.54 (*m*, *t*-Bu, 48 CH); 1.84–1.94 (*m*, 10 CH); 2.03–2.13 (*m*, 2 CH); 3.22 (*d*, *J* = 6.2, CH_2N); 3.32–3.39 (*m*, 5 CH_2N); 5.46 (*t*, *J* = 5.8, NH); 6.44 (*t*, *J* = 6.0, NH); 6.84 (br. *s*, NH); 6.95 (*t*, *J* = 5.7, NH); 7.03 (br. *s*, NH); 7.08 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.34, 22.38, 22.45, 22.60, 23.73, 25.61, 25.70, 25.75, 25.83 (CH_2); 28.43 (Me); 30.65, 31.68, 31.89, 31.92, 31.98, 34.13, 45.89, 46.09 (CH_2); 46.15 (C); 46.20, 46.27, 46.50, 46.59, 46.68, 47.07, 47.39 (CH_2); 47.57 (C); 52.27 (Me); 78.78, 156.40, 175.76, 175.80, 176.09, 176.25, 176.31, 176.64 (C). FAB-MS: 990 (15.0, $[M+Na]^+$), 968 (72.3, $[M+1]^+$), 868 (100.0), 837 (9.2), 559 (5.9).

Ac-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-NH$_2$ (**5**). The *Rink* amide resin (691.6 mg, 0.45 mmol/g) was loaded with **17** (354 mg, 934 μmol) according to *GP 7b*. Synthesis according to *GP 8b* afforded the deprotected tripeptide on the resin. The resin was washed and filtered successively with DMF (5 × 3 min), CH_2Cl_2 (3 × 3 min), and Et_2O (3 × 3 min), and dried overnight under h.v., before being split in two equal parts. On the first aliquot, *N*-acetylation according to *GP 9* was accomplished. The rest was used to synthesize tetrapeptide **6**. Cleavage from the resin according to *GP 10b* afforded the crude tripeptide **5** (62.4 mg, 88%), purity 83% (RP-HPLC). Purification by RP-HPLC (20–80% *B* in 20 min) according to *GP 11* yielded **5** (25.6 mg, 36%). RP-HPLC (20–80% *B* in 20 min; C_8): t_R 11.97. White fluffy solid. M.p. 219° (dec., sintering at 200°). IR ($CHCl_3$): 3684*w*, 3453*w*, 3008*m*, 2936*s*, 2862*m*, 1658*s*, 1511*s*, 1454*m*, 1252*w*, 1167*w*, 939*w*, 816*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.19–2.12 (*m*, COMe, 30 CH); 3.26–3.32 (*m*, 2 CH_2N); 3.38 (*d*, *J* = 6.5, CH_2N); 7.28 (br. *s*, NH); 8.01 (*t*, *J* = 6.4, NH). ^{13}C-NMR (100 MHz, CD_3OD): 22.75 (Me); 23.89, 24.02, 26.31, 26.93, 26.94, 30.94, 32.74, 33.30, 34.83 (CH_2); 42.72 (C); 49.05 (CH_2); 124.03, 173.49, 177.26, 178.10, 178.17 (C). FAB-MS: 516 (1.8, $[M+K]^+$), 499 (24.6, $[M+Na]^+$), 477 (100.0, $[M+1]^+$), 460 (38.4), 443 (7.5), 338 (12.8), 329 (10.8).

Ac-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-NH$_2$ (**6**). According to *GP 8b*, one more coupling/deprotection sequence was performed on the *Rink* amide resin, loaded with the corresponding deprotected tripeptide (see synthesis of **5**). *N*-Acetylation according to *GP 9* and cleavage according to *GP 10b* yielded the crude tetrapeptide **6** (22.5 mg, 24%), purity 68% (RP-HPLC). Purification by RP-HPLC (20–80% *B* in 20 min) according to *GP 11* yielded **6** (7.3 mg, 10%). White fluffy solid. RP-HPLC (20–80% *B* in 20 min; C_8): t_R 11.84. M.p. 103–105° (sintering at 93°). IR ($CHCl_3$): 3685*w*, 3340*m*, 3008*m*, 2934*s*, 2859*m*, 1649*s*, 1520*s*, 1458*w*, 1167*w*, 932*w*, 650*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.16–1.98 (*m*, 40 CH); 2.02 (*s*, COMe); 3.28–3.32 (*m*, 3 CH_2N); 3.39 (*d*, *J* = 5.8, CH_2N); 5.91 (br. *s*, 0.3 H, NH_2); 6.49 (*s*, NH); 6.50 (br. *s*, 0.7 H, NH_2); 6.60 (*s*, NH); 6.81 (*s*, NH); 7.22 (*s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.48, 22.56 (CH_2); 22.99 (Me); 25.72, 25.74, 25.76, 29.71, 30.35,

31.73, 32.17, 32.25, 32.38, 46.40 (CH_2); 46.61, 46.76 (C); 46.90 (CH_2); 47.17 (C); 47.61 (CH_2); 76.77, 77.02, 77.28, 170.92, 175.57, 175.72, 175.95, 178.71 (C). FAB-MS: 639 (2.4, $[M+Na]^+$), 617 (100.0, $[M+1]^+$), 550(8.1), 443(6.1), 338(18.1).

Ac-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-NH$_2$ (**4a**). According to *GP 7b*, the *Rink* amide resin (195.6 mg, 0.45 mmol/g) was loaded with **17** (105 mg, 277 μmol). Synthesis according to *GP 8b*, acetylation according to *GP 9*, and cleavage from the resin according to *GP 10b* afforded the crude peptide **4a** (87.6 mg, 105%), purity 77% (RP-HPLC). The peptide was purified by RP-HPLC (35–80% *B* in 20 min) according to *GP 1*: **4a** (52 mg, 63%). White fluffy solid. RP-HPLC (75% *B* isocratic in 20 min; C_8): t_R 4.87. M.p. 99–102°. IR ($CHCl_3$): 3353*w*, 3008*m*, 2933*s*, 2859*m*, 1645*s*, 1516*s*, 1464*w*, 1448*s*, 1252*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26–1.60 (*m*, 48 CH); 1.80–1.85 (*m*, 2 CH); 1.92-2.10 (*m*, 10 CH); 2.11 (*s*, COMe); 3.26–3.41 (*m*, 6 CH_2N); 3.90 (br. *s*, NH_2); 6.57–6.60 (*m*, 2 NH); 6.91 (*s*, NH); 7.16 (*s*, NH); 7.29 (*s*, NH); 7.62 (*s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.33, 22.38 (CH_2); 22.49 (Me); 22.53, 25.67, 31.67, 31.90, 32.12, 32.36 (CH_2); 46.69 (C); 46.83, 46.88, 47.04, 47.15, 47.42, 47.72 (CH_2); 76.70, 77.22, 77.34, 172.70, 175.46, 176.03, 176.13, 180.34 (C). FAB-MS: 916 (2.34, $[M+Na]^+$), 894 (100.0, $[M+1]^+$), 766(7.8), 596(5.1).

CF$_3$COOH·H-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-β^{2,2}-HAc$_6$c-OH (**4c**). According to *GP 7a*, the *ortho*-chlorotrityl-choride resin (381 mg, 1 mmol/g) was esterified with **17** (116 mg, 305 μmol). Loading 0.35 mmol/g (55%), corresponding to 132 μmol of anchored **17**. Synthesis according to *GP 8a* and cleavage from the resin according to *GP 10a* afforded the crude peptide **4c** (55.6 mg, 47%), purity 65–95% (RP-HPLC), depending on the cleavage fraction (purity of first cleavage fraction: 65%; purity of the following cleavage fractions up to 95% (HPLC)). Prep. RP-HPLC (20–90% *B* in 45 min) according to *GP 11* yielded **4c** (30.7 mg, 26%). White powder. Colorless crystals were obtained from $CDCl_3$ by slow evaporation at r.t. RP-HPLC (30–90% *B* in 20 min; C_{18}): t_R 14.26. M.p. 140° (dec., sintering at 100°). R_f 0.03 (AcOEt). IR ($CHCl_3$): 3456*w*, 3364*w*, 3056*w*, 2935*s*, 2851*m*, 2236*w*, 1780*w*, 1643*s*, 1523*s*, 1251*w*, 1168*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20–1.38 (*m*, 48 CH); 1.51–1.92 (*m*, 8 CH); 2.07–2.23 (*m*, 4 CH); 3.05 (br. *s*, CH_2N); 3.28–3.40 (*m*, 5 CH_2N); 5.15 (br. *s*, NH_3^+); 6.44 (*s*, NH); 6.67 (*s*, NH); 6.90 (*s*, NH); 7.04 (*s*, NH); 7.52 (*s*, NH); 8.16 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.11, 22.47, 22.78, 25.30, 25.61, 29.71, 31.41, 32.03 (CH_2); 44.85 (C); 46.91, 47.26, 47.68 (CH_2); 77.02, 174.57, 175.96, 176.11, 176.43, 178.27 (C). FAB-MS: 892 (1.4, $[M+K]^+$), 876 (8.5, $[M+Na]^+$), 854 (100.0, $[M+1]^+$), 715(5.2), 329(9.7).

16. *X-Ray Crystal-Structure Analyses.* Compound **23b** ($C_{30}H_{51}N_3O_6$). Crystals were grown from a supersaturated CH_2Cl_2 soln. Crystal size 0.3 × 0.3 × 0.4 mm. Crystal data at 193 K for ($C_{30}H_{51}N_3O_6 \cdot CH_2Cl_2$, M_r 634.7): Triclinic, space group $P\bar{1}$ (No. 2), $\rho_{calc.} = 1.26$ g cm^{-3}, $Z = 2$, $a = 10.246(4)$ Å, $b = 10.959(2)$ Å, $c = 17.501(6)$ Å, $\alpha = 103.10(2)°$, $\beta = 95.12(3)°$, $\gamma = 116.47(2)°$, $V = 1672(1)$ Å^3. *Nonius CAD4* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å, 4918 unique reflections measured in the range $0 < \theta < 24.03°$, 4300 observed reflections with $I > 2\sigma(I)$. The structure was solved by direct methods (SIR92 [55]), and refined by full-matrix least-squares analysis (SHELXL93 [56]), using an isotropic extinction correction and $w = 1/[\sigma^2(F_o^2) + (0.0377P)^2 + 1.13P]$, where $P = (F_o^2 + 2F_c^2)/3$ (heavy atoms anisotropic, H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.037$, $wR(F^2) = 0.095$ for 428 variables and 4300 observations. Further details of the structure analysis are available on request from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB12 1EZ (UK), on quoting the full journal citation.

Compound **16a** ($C_{10}H_{17}NO_4$). Crystal data at 263 K. Monoclinic, space group $P2_1/a$ (No. 14), $\rho_{calc.} = 1.24$ g cm^{-3}, $Z = 4$, $a = 9.983(2)$ Å, $b = 10.312(3)$ Å, $c = 11.207(3)$ Å, $\beta = 93.49(2)°$, $V = 1151.6(5)$ Å^3. *Nonius CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å, 1820 unique reflections measured in the range $0 < \theta < 64.84$. Single crystals were obtained by slow evaporation of a CH_2Cl_2/hexane soln. The structure was solved by direct methods (SIR92 [55]), and refined by full-matrix least-squares analysis (SHELXL93 [56]), using $w = 1/[\sigma^2(F_o^2) + (0.069P)^2 + 0.335P]$, where $P = (F_o^2 + 2F_c^2)/3$ (heavy atoms anisotropic, H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.042$, $wR(F^2) = 0.108$ for 156 variables and 1404 observations with $I > 2\sigma(I)$.

Compound **16b** ($C_{11}H_{19}NO_4$). Crystal data at 263 K. Monoclinic, space group $P2_1/c$ (No. 14), $\rho_{calc.} = 1.21$ g cm^{-3}, $Z = 4$, $a = 11.242(1)$ Å, $b = 11.516(1)$ Å, $c = 11.228(1)$ Å, $\beta = 108.26(1)°$, $V = 1257.6(2)$ Å^3. *Nonius CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å, 2236 unique reflections measured in the range $0 < \theta < 66.98$. Single crystals were obtained by slow evaporation of a AcOEt/hexane soln. The structure was solved by direct methods (SIR92 [55]), and refined by full-matrix least-squares analysis (SHELXL93 [56]), using an isotropic extinction correction and $w = 1/[\sigma^2(F_o^2) + (0.056P)^2 + 0.493P]$, where $P = (F_o^2 + 2F_c^2)/3$ (heavy atoms anisotropic H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.037$, $wR(F^2) = 0.105$ for 168 variables and 1930 observations with $I > 2\sigma(I)$.

Compound **16c** ($C_{12}H_{21}NO_4$). Crystals were grown from AcOEt/hexane by slow evaporation at r.t. From a crystal of size $0.20 \times 0.15 \times 0.05$ mm, 2628 reflections were measured on an *Enraf Nonius CAD-4* diffractometer wtih CuK_α radiation (graphite monochromator, $\lambda = 1.54184$ Å). The structure was solved by direct method with SHELXS-96 [56]. The non-H-atoms were refined anisotropically with SHELXL-97. H-atoms were obtained from a difference *Fourier* map and refined with constrained isotropic displacement parameters.

Compound **16d** ($C_{13}H_{23}NO_4$). Crystals were grown from a AcOEt soln. by slow evaporation at r.t. Crystal size $0.20 \times 0.20 \times 0.20$ mm. Monoclinic, space group $P2_1/c$, $\rho_{calc.} = 1.223$ g cm^{-3}, $Z = 4$, $a = 11.026(2)$ Å, $b = 10.698(3)$ Å, $c = 12.127(4)$ Å, $\beta = 102.39(2)^\circ$, $V = 1397.1(7)$ Å^3. *Nonius CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å, 2367 unique reflections measured in the range $4.10 < \theta < 64.97^\circ$. The structure was solved by direct methods (SIR92 [55]), and refined by full-matrix least-squares analysis (SHELXL93 [56]), using an isotropic extinction correction and $w = 1/[\sigma^2(F_o^2) + (0.0434P)^2 + 0.5375P]$, where $P = (F_o^2 + 2F_c^2)/3$ (heavy atoms anisotropic, H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.0353$, $wR(F^2) = 0.0931$ for 190 variables and 2367 observations. Further details of the structure analysis are available on request from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB12 1EZ(UK), on quoting the full journal citation.

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