Preparation of *N*-Fmoc-Protected β^2- and β^3-Amino Acids and Their Use as Building Blocks for the Solid-Phase Synthesis of β-Peptides[1])

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Dedicated to Professor *A. I. Meyers*, University of Colorado, Fort Collins, on the occasion of his 65th birthday

N-Fmoc-Protected (Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl) β-amino acids are required for an efficient synthesis of β-oligopeptides on solid support. Enantiomerically pure Fmoc-β^3-amino acids (β^3: side chain and NH_2 at C(3)(= C(β))) were prepared from Fmoc-protected (*S*)- and (*R*)-α-amino acids with aliphatic, aromatic, and functionalized side chains, using the standard or an optimized *Arndt-Eistert* reaction sequence. Fmoc-β^2-Amino acids (β^2 side chain at C(2), NH_2 at C(3)(= C(β))) configuration bearing the side chain of Ala, Val, Leu, and Phe were synthesized *via* the *Evans*' chiral auxiliary methodology. The target β^3-heptapeptides **5**–**8**, a β^3- pentadecapeptide **9** and a β^2-heptapeptide **10** were synthesized on a manual solid-phase synthesis apparatus using conventional solid-phase peptide synthesis procedures (*Scheme 3*). In the case of β^3-peptides, two methods were used to anchor the first β-amino acid: esterification of the *ortho*-chlorotrityl chloride resin with the first Fmoc-β-amino acid **2** (*Method I*, *Scheme 2*) or acylation of the 4-(benzyloxy)benzyl alcohol resin (*Wang* resin) with the ketene intermediates from the *Wolff* rearrangement of amino-acid-derived diazo ketone **1** (*Method II*, *Scheme 2*). The former technique provided better results, as exemplified by the synthesis of the heptapeptides **5** and **6** (*Table 2*). The intermediate from the *Wolff* rearrangement of diazo ketones **1** was also used for sequential peptide-bond formation on solid support (synthesis of the tetrapeptides **11** and **12**). The CD spectra of the β^2- and β^3-peptides **5**, **9**, and **10** show the typical pattern previously assigned to an (*M*) 3_1 helical secondary structure (*Fig.*). The most intense CD absorption was observed with the pentadecapeptide **9** (strong broad negative *Cotton* effect at *ca.* 213 nm); compared to the analogous heptapeptide **5**, this corresponds to a 2.5 fold increase in the molar ellipticity per residue!

1. Introduction. – In the past few years, there has been intense interest in the design and synthesis of nonnatural oligomers that are able to form well-defined novel three-dimensional structures [2]. In this area, peptides, consisting exclusively of β-amino acids have recently emerged as a promising new class of compounds being able to form stable, helical or pleated-sheet secondary structures (for review and highlight articles, see [3–6]). Three different helical secondary structures have been identified so far. We have established that β-peptides containing either β^2- or β^3-amino acids of (*S*)-configuration exist as left-handed 3_1-helices in MeOH solution, as determined by NMR spectroscopy and/or CD measurements (the helix handedness being opposite for peptides built from amino acids of (*R*) configuration) [7–9]. Conversely, NMR analysis of a 'mixed' β-hexapeptide

[1]) Partially published in a preliminary communication [1]; β^2 means that the NH_2 group ist at C(3)(= C(β)) and the side chain at C(2) of the amino acid, and β^3 indicates that both the NH_2 group and the side chain are at C(3)(= C(β)). Fmoc = (9*H*-Fluoren-9-ylmethoxy)carbonyl.

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[3]) Part of the projected Ph. D. Thesis of *S.A.*, ETH-Zürich.

containing both β^2- and β^3-amino acids revealed a novel, irregular, helical secondary structure [10][11] differing from both previously reported 3_1- and 2.5_1- [12] helices[4]). These striking structural features along with the remarkably high resistance of β^2- and β^3-peptides to proteolytic digestion [13] suggest the use of such compounds as candidates for new drugs and as tools to gain further insight into protein folding [14] and molecular recognition processes.

In our previous work, β-peptides have been synthesized in solution, either by conventional methods using *Z*- or Boc-protected (*Z* = (benzyloxy)carbonyl, Boc = (*tert*-butoxy)carbonyl) amino acids and carbodiimide activation, or by sequential *Arndt-Eistert* homologation with concomitant amide-bond formation (in the case of β^3-peptides). However, solid-phase techniques, by providing a rapid access to a larger and more diverse set of β-peptides, are particularly suited for new lead discovery and further exploration of the structural versatility of β-peptides. In an earlier paper, we reported an efficient solid-phase synthesis of oligonucleo-peptides *via* the *Wolff* rearrangement of diazo ketones from amino acids in the presence of amino-functionalized oligonucleotides [15]. Most recently, we have started to investigate the synthesis of β-peptides on a solid support [1].

Here, we report in detail the preparation of *N*-Fmoc-protected β^2- and β^3-amino acids and their use in conventional solid-phase peptide synthesis. In addition, procedures involving the use of diazo ketones derived from *N*-Fmoc-protected α-amino acids for esterification of the 4-(benzyloxy)benzyl alcohol resin (*Wang* resin) and for β-peptide-bond formation *via Arndt-Eistert* homologation on the solid phase are also described[5]).

2. Results and Discussion. – 2.1. *Synthesis of* N-*Fmoc-Protected* β^3*-Amino Acids.* So far, the preparation of enantiomerically pure β-amino acids using the *Arndt-Eistert* homologation has been successfully achieved starting either from phthaloyl- or urethane-protected α-amino acids (Z or Boc) (for review articles, see [18][19]). In an earlier study, we investigated the use of Fmoc-protected α,α-disubstituted α-amino acids unter *Arndt-Eistert* conditions in the preparation of the corresponding β,β-disubstituted β-amino acids [19]. We have now applied the *Arndt-Eistert* methodology to the preparation of *N*-Fmoc-protected β-amino acids **2a**–**g** starting from the corresponding commercially available α-amino-acid derivatives. Using previously reported procedures [7][20], *N*-Fmoc-protected L-alanine, L-valine, L-leucine, L-phenylalanine, L-lysine, L-serine, and L-glutamic-acid derivatives were converted to the corresponding diazo ketones by reaction of the mixed anhydrides (formed with i-BuOCOCl/*N*-methyl morpholine (NMM)) with CH_2N_2. Although it has recently been suggested [16a][21] that this procedure was not ideally suited to amino acids bearing an Fmoc protecting group, we encountered no

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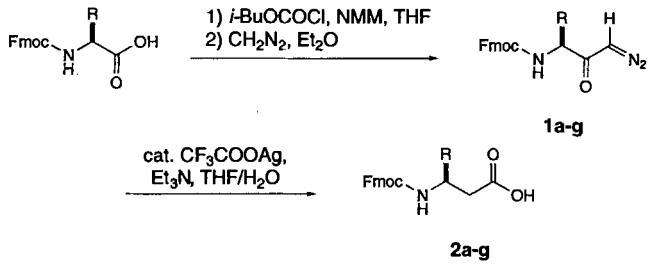
[4]) It is worth mentioning that the β-amino acids used for our studies contain 'natural' (proteinaceous) side chains and, thereby, are rotationally unrestricted. This is in contrast to the *trans*-2-aminocyclopentane- and -cyclohexanecarboxylic acids reported in *Gellman*'s work [12].

[5]) Independent of our own work on solid-phase peptide synthesis of β-peptides, there have been a couple of reports on the preparation of *N*-Fmoc-protected β^3-amino acids [16] and on a solid-phase β-peptide synthesis [17].

problems in obtaining diazo ketones **1a–g** in good-to-excellent yields after FC and/or crystallization (*Scheme 1*). As reported in previous investigations [20][22], the methyl ester formed by partial hydrolysis of the mixed anhydride (moisture in the ethereal CH_2N_2 solution!) was found to be the major side product of this reaction (up to 15%)[6]). In a study published while our work was in progress, *Leggio et al.* reported to have overcome this problem by using a dry solution of CH_2N_2 in CH_2Cl_2 [16a].

Scheme 1. *Direct Homologation of* N-*Fmoc-Protected Amino Acids* via *the* Arndt-Eistert *Reaction*. NMM = *N*-Methylmorpholine.



	R	Yield [%]			R	Yield [%]	
		1	**2**			**1**	**2**
a	Me	68	72	**e**	$(CH_2)_4NHBoc$	88	38
b	i-Pr	75	75	**f**	$(CH_2)_2CO_2(t\text{-Bu})$	88	47
c	i-$PrCH_2$	87	66	**g**	$CH_2O(t\text{-Bu})$	93	63
d	Bn	74	65				

The diazo ketones **1a–g** were decomposed in THF containing 10% H_2O with catalytic amounts of CF_3COOAg [7] added as a homogeneous solution in Et_3N (*Scheme 1*) [20][23]. *N*-Fmoc-Protected β^3-amino acids **2a–g** were obtained in pure form after FC and/or recrystallization from $CHCl_3$/hexane, although in somewhat lower yield than the corresponding Boc or Z derivatives [20]: as may have been expected, a significant loss of the Fmoc protecting group was observed under these conditions. However, for a given reaction time, we found that the extent of Fmoc loss was dependent upon the nature of the amino-acid side chain. While Ala and Val gave yields in the order of 70–75%, Fmoc-β^3-HLys(Boc)-OH (**2e**) and Fmoc-β^3-HGlu(*t*-Bu)-OH (**2f**) could not be isolated in yields above 40–50%, due to extensive Fmoc cleavage. Therefore, we tested milder conditions to perform the Ag-catalyzed *Wolff* rearrangement (see *Table 1*)[7]). The use of a weaker base such as NMM led to a significant improvement: diazo ketone **1e** was cleanly converted to **2e** in 81% yield (after recrystallization, *Entry 4*), and the acids **2f** (*Entry 6*) and **2g** (*Entry 8*) were formed in better yields as well, even after prolonged

[6]) The formation of surprisingly large amounts of methyl ester has been reported in [16a] (up to 38% starting from Fmoc-Ala-OH).

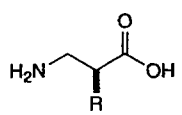
[7]) Alternatively, the photochemically initiated *Wolff* rearrangement was used by us to decompose diazo ketones derived from *N*-Fmoc α,α-disubstituted α-amino acids [19].

reaction times. In the absence of a base, rearrangement of the diazo ketone was also found to proceed smoothly, but in this case, 12 h were required for the reaction to reach completion (*Entry 3*). Following a recent literature procedure [16a], according to which diazo ketones derived from *N*-Fmoc-protected α-amino acids are decomposed by heating in the presence of silver ions, we observed rapid conversion of **1e** to **2e**, but the yield was poorer (69%, *Entry 2*) than under our optimized conditions (81%, *Entry 4*, of *Table 1*).

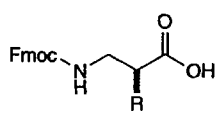
Table 1. Wolff *Rearrangement of the Diazo Ketones* **1e–g** *to the Homologated Carboxylic Acids* **2e–g** *under Various Conditions*

Entry	Diazo ketone	Base	Solvent	Temp. [°]	Reaction time [h]	Yield [%]
1	**1e**	Et_3N	THF/H_2O	−25 → r.t.	4	38
2	**1e**	–	dioxane/H_2O [16a]	60	1	69
3	**1e**	–	THF/H_2O	0 → r.t.	12	78
4	**1e**	NMM	THF/H_2O	0 → r.t.	3	81
5	**1f**	Et_3N	THF/H_2O	0 → r.t.	4.5	47
6	**1f**	NMM	THF/H_2O	0 → r.t.	8	71
7	**1g**	Et_3N	THF/H_2O	0 → r.t.	4.5	63
8	**1g**	NMM	THF/H_2O	0 → r.t.	8	70

2.2. *Synthesis of* N-*Fmoc-Protected* β^2*-Amino Acids.* (*S*)-2-(Aminomethyl)alkanoic acids **3a–d** with side chains corresponding to Ala, Val, Leu, and Phe were prepared *via* asymmetric aminomethylation of (*R*)-*N*-acyl-4-(phenylmethyl)oxazolidin-2-ones (*Evans*' methodology [24]), followed by removal of the auxiliary and hydrolysis of the benzamide group as previously reported [9][11]. Treatment of **3a–d** with *N*-{[(9*H*-fluoren-9-yl-methoxy)carbonyl]oxy}succinimide (Fmoc-OSu) in H_2O/acetone in the presence of Na_2CO_3 (2 equiv.) afforded *N*-Fmoc-protected derivatives **4a–d** in satisfactory yields after FC and recrystallization from $CHCl_3$/hexane.



3a R = Me
b R = i-Pr
c R = i-PrCH$_2$
d R = Bn

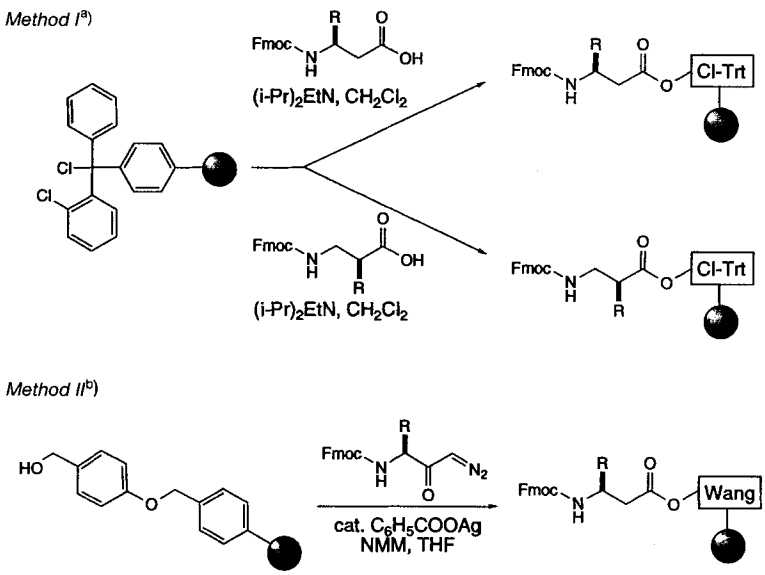


4a R = Me
b R = i-Pr
c R = i-PrCH$_2$
d R = Bn

2.3. *Attachment of the First* β*-Amino Acid to the Resin.* The two methods used to anchor the first β-amino acid to resins are outlined in *Scheme 2*. In *Method I*, the *ortho*-chlorotrityl-chloride resin (initial loading: 1.05 or 1.3 mmol Cl/g) [25] was esterified for 4 h with an *N*-Fmoc-protected β^2- or β^3-amino acid (0.7–0.9 equiv.) in the presence of $(i\text{-}Pr)_2EtN$ (4 equiv. with respect to the amino acid), as previously decribed for α-amino acids [25]. Unreacted chloride was neutralized by addition of MeOH, and the resin loading was determined, after treatment with 20% piperidine in DMF, by measuring the absorbance of the dibenzofulvene-piperidine adduct at 300, 289, and

266 nm. Satisfactory esterification yields were thus monitored for the Fmoc-β-amino acids **2c** (up to 73%), **2d** (86%), **2e** (up to 59%), and **4c** (85%). Attempts to determine possible racemization upon anchoring of β^2-amino acids **4** to the *ortho*-chlorotrityl-chloride resin, either by GC [26] or by reversed-phase HPLC (*vide infra*), after Fmoc deprotection, cleavage from the resin, and derivatization were unsuccessful. However, the esterification of **4** to the *ortho*-chlorotrityl-chloride resin avoids electrophilic activation of the carboxy group and is likely to proceed without racemization, as previously reported for α-amino acids [25].

Scheme 2. *Methods Used to Anchor the First β-Amino Acid to the Resin*



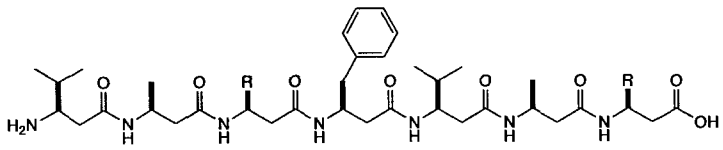
[a]) *Method I* = standard esterification of *ortho*-chlorotrityl-chloride resin with *N*-Fmoc-protected β-amino acids **2** or **4**. [b]) *Method II* = *Wolff* rearrangement of *N*-Fmoc-protected diazo ketones **1** in the presence of 4-(benzyloxy)benzyl alcohol resin (*Wang* resin).

In *Method II*, the β^3-amino acids were anchored to the resin by esterification of the 4-(benzyloxy)benzyl-alcohol resin (*Wang* resin [27]) *via Wolff* rearrangement of a diazo ketone **1** (*Scheme 2*). This procedure was chosen as an alternative to classical 4-(dimethylamino)pyridine (DMAP)-catalyzed esterification of hydroxy-functionalized resins with symmetrical anhydrides. Thus, decomposition of the diazo ketones **1c** and **1e** (1.5–2.5 equiv. with respect to the resin) in a suspension of *Wang* resin (0.83 mmol/g) in dry THF at 0°, in the presence of a catalytic amount of silver benzoate (added as solution in NMM), followed by treatment of the resin with benzoyl chloride (in order to block the remaining free OH groups) gave the desired *N*-Fmoc-protected β^3-amino-acid resin. Typically, the loading of the resin (determined as mentioned above) was in the range 0.26–0.29 mmol/g which corresponds to esterification yields of 40–50%[8]). The config-

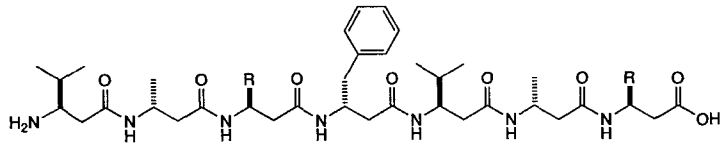
[8]) For a higher loading, longer reaction times, higher temperature, and/or larger excess of diazo ketone should be used. In a recent communication [17], a good esterification yield of *Wang* resin (80%) was reported using **1d** (2 equiv.) under conditions similar to those used by us.

urational purity of the β^3-amino acids attached to the *Wang* resin was determined by reversed-phase HPLC after Fmoc deprotection, cleavage from the resin, and derivatization with *N*-(2,4-dinitro-5-fluorophenyl)-L-valinamide [28] (*cf. Marfey*'s reagent [29][30]). The result of this analysis is that the entire sequence of reactions leading to the *Wang*-resin-bound Fmoc-β-amino acids from the α-amino acids L-leucine and L-lysine takes place without racemization and with complete retention of configuration.

2.4. *Solid Phase β-Peptide Synthesis.* With the Fmoc-protected β^2- and β^3-amino acids at hand and with their successful attachment to the *ortho*-chlorotrityl-chloride or to the *Wang* resin, we were ready to prepare various β-peptides on solid phase. We chose the target oligopeptides **5**–**12** containing four to 15 β-amino acids. All of them contain



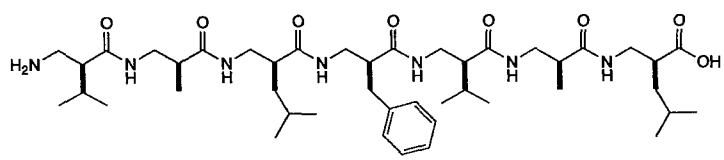
5 R = CH_2CHMe_2
6 R = $(CH_2)_4NH_2$



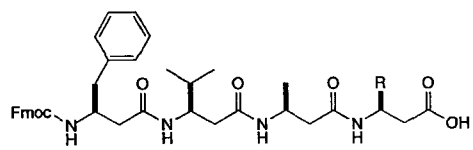
7 R = CH_2CHMe_2
8 R = $(CH_2)_4NH_2$

H-β^3-HLeu-β^3-HAla-β^3-HVal-β^3-HPhe-β^3-HVal-β^3-HAla-β^3-HLeu-β^3-HPhe-
-β^3-HLeu-β^3-HAla-β^3-HVal-β^3-HPhe-β^3-HVal-β^3-HAla-β^3-HLeu-OH

9



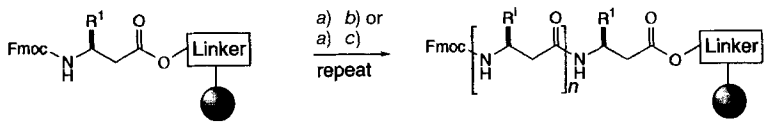
10



11 R = CH_2CHMe_2
12 R = $(CH_2)_4NH_2$

the side chains of proteinaceous amino acids; we incorporated (for the first time)[9] β-HPhe, an aromatic β-amino acid, and β-HLys, a β-amino acid with a positively charged hydrophilic side chain; the β-heptapeptides **5** and **6** and the β-pentadecapeptide **9** as well as the tetrapeptides **11** and **12** are built of homochiral β^3-amino acids exclusively ((*R*)-β^3-HVal arises from (*S*)-Val), while the β-heptapeptide **10** (a constitutional isomer of **5**) is constructed entirely from (*S*)-β^2-amino acids; the β-heptapeptides **7** and **8** contain an alternating sequence of heterochiral β^3-amino-acid residues ((*R*)-β^3-HVal arises from (*S*)-Val), an array which (according to our analysis [3][7][8]) can form neither a 3_1 helix nor a sheet-like secondary structure; the β-peptides **5**–**10** were prepared by standard solid-phase peptide synthesis techniques, while **11** and **12** were synthesized by using the ketene intermediates from the *Wolff* rearrangement of diazo ketones **1** for the solid-phase β-peptide coupling steps[10]). The general reaction sequence for the solid-phase synthesis of β-peptides is outlined in *Scheme 3*.

Scheme 3. *General Procedure for the Solid-Phase Synthesis of β-Peptides as Shown for the β^3-Derivatives Using either* N-*Fmoc-Protected β-Amino Acids* **2** *and Standard Coupling Procedures or* Arndt-Eistert *Homologation of Diazo Ketones* **1**. BOP = (1*H*-Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole.



a) Piperidine/DMF 2:8. *b*) **2**, BOP, HOBt, $(i\text{-Pr})_2$EtN. *c*) **1**, cat. PhCOOAg, NMM, THF, 0°.

β^3-Heptapeptides **5**–**8**, β^3-pentadecapeptide **9** and β^2-heptapeptide **10** were synthesized on *ortho*-chlorotrityl-chloride or *Wang* resins (*vide supra*) using conventional solid-phase peptide synthesis procedures (*Scheme 3*). Fmoc-β-Amino acids **2** or **4** (2.5–3 equiv. with respect to the resin) were activated using BOP/HOBt/$(i\text{-Pr})_2$EtN, and coupling reactions were performed in DMF at room temperature for 15–60 min. It is important to mention that the *Kaiser* ninhydrin test [33] of Fmoc-deprotected β^3-peptide-resins failed. Hence, coupling reactions were monitored using 2,4,6-trinitrobenzenesulfonic acid (TNBS) [34]. After removal of the last Fmoc protecting group, peptide-resins were treated with CH_2Cl_2/CF_3COOH 98:2 or $CF_3COOH/(i\text{-Pr})_3SiH/H_2O$ 95:2.5:2.5 to give the crude unprotected β-peptides **5**–**9** in good overall yields. Yields and purities of crude peptides are given in *Table 2*. HPLC Purification on a *C8* column afforded the pure β-peptides which were identified by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry (see *Table 2*). The best results were obtained on *ortho*-chlorotrityl-chloride resin for peptides **5** (*Entry 1*), **6** (*Entry 3*), and **7** (*Entry 5*), which were obtained by cleavage from the resin in high yields and in purities of the crude products of 94, 86, and 80%, respectively, as determined by reversed-phase HPLC. Under the same conditions, synthe-

[9]) In our previous work, we have described, in full detail, only β-peptides containing β-HAla, β-HVal, and β-HLeu residues [7] [8] [31].

[10]) We have previously demonstrated that such ketenes can be used for homologative peptide coupling in solution [7] [32].

sis on *Wang* resins esterified *via Wolff* rearrangement of diazo ketone **1c** or **1e** yielded crude products **5** (*Entry 2*) and **6** (*Entry 4*) of somewhat lower purity (71% and 41%, resp.). In the latter case as well as for β-peptide **8** with alternating configurations (*Entry 6*), the identification of the two main impurities revealed incomplete Fmoc deprotection occurring in the last two steps of the synthesis. Incomplete Fmoc removal has previously been noticed in the solid-phase peptide synthesis of long peptides [35]. In our case, the use of higher concentrations of piperidine in DMF or longer deprotection times did not give any improvement; however, switching to a stronger base such as 1,8-diazabicyclo[5.4.0]undec-7-ene [36] gave more satisfactory results with suppression of the impurity resulting from incomplete Fmoc removal in the last stage of the synthesis.

Table 2. *Isolation and Characterization by HPLC and MS of β-Peptides* **5–8** *and* **10–12**

Entry	Product	Anchoring by *Method*	Yield [%][a]	Purity [%][b]	t_R [min][c]	MS
1	**5**	*I*	89	94	15.33[d]	830.7
2	**5**	*II*	49	71	14.88[d]	830.7
3	**6**	*I*	74	86	13.24[e]	860.6
4	**6**	*II*	67	41	13.29[e]	860.9
5	**7**	*I*	99	80	9.52[d]	830.5
6	**8**	*I*	99	50	11.43[e]	860.1
7	**10**	*I*	79	40	11.31[d]	830.5
8	**11**	*II*	65	77	15.17[d]	727.4
9	**12**	*II*	55	86	9.86[d]	743.5

[a]) % Mass recovered based on polymer loading. [b]) HPLC Purity of the crude product. [c]) Retention time in the HPLC (*RP-C8* column, linear gradient of *A* (0.1% CF_3COOH in H_2O) and *B* (MeCN); see *GP 7* in *Exper. Part*). [d]) 30–90% *B* in 20 min. [e]) 5–65% *B* in 20 min.

Crude β^3-pentadecapeptide **9** was successfully synthesized on *ortho*-chlorotrityl-chloride resin in 87% overall yield. During the synthesis, after the incorporation of the first seven amino acids, a portion of the resin was cleaved, and the purity of the intermediate heptapeptide was found to be 86% (by HPLC). The crude product **9** was purified by reversed-phase HPLC (*C8* column); however, due to its poor solubility and hydrophobicity, neither the purity nor the retention time of **9** could be determined accurately by anal. HPLC. The peptide was considered to be pure on the basis of the MALDI-TOF and ^{1}H-NMR analyses. No traces of incomplete Fmoc removal were detected.

Synthesis of the β^2-heptapeptide **10**, using *ortho*-chlorotrityl-chloride resin, was more problematic (the purity of crude **10** being only 40%, *Entry 7*). The HPLC profile of the crude product (30–90% MeCN within 20 min, conditions given in the *Exper. Part*) revealed three main peaks close to each other (9.51, 9.79, and 10.48 min, resp.) eluting before the major peak (11.31 min; *cf.* Fig. 2 in our preliminary communication [1]). These faster eluted compounds could have arisen from incomplete coupling (missing β^2-amino-acid residues!) or from epimerization (diastereoisomeric β^2-heptapeptides!). As shown by the TNBS test during the synthesis, the coupling efficiency of β^2-amino acids **4** using the BOP/HOBt/(i-Pr)$_2$EtN procedure was comparable to that observed with β^3-amino acids. However, electron spray ionization (ESI) MS analysis of the major impurities isolated by prep. HPLC revealed that they consisted of epimers of the desired

β^2-peptide. Under the basic conditions used for coupling, racemization is possible *via* enolization of the activated species or of the corresponding dihydro-oxazinone [32][11]).

In earlier work, we have demonstrated that the reactive intermediate which arises from the *Wolff* rearrangement of a diazo ketone could be trapped by the amino group of an amino-acid derivative [32]. β^3-Peptides could thus be synthesized by applying this procedure sequentially [7]. Here we investigated acylation of the growing peptide chain by ketene intermediates as an alternative method to produce β^3-peptides on solid support. According to the route described in *Scheme 3*, Fmoc-protected β^3-tetrapeptides **11** (*Entry 8*) and **12** (*Entry 9*) were obtained in good purities (77 and 86%, resp., according to reversed-phase HPLC), although in moderate yields. However, attempts to synthesize heptapeptide **5** by this procedure were not successful (23% purity of **5** by HPLC).

2.5. *Structural Investigation by CD.* As shown in our previous studies [7–9], circular dichroism (CD) is a reliable tool to detect the presence of 3_1-helical secondary structures in β-peptides. The left-handed (*M*) 3_1 helix found in β-oligopeptides built of (*S*)-β^3-amino acids presents a CD signature which includes a trough at *ca.* 215 nm, a zero crossover at *ca.* 208 nm, and a maximum at *ca.* 200 nm [7][8]. An overlay of the CD spectra in MeOH of β^3-heptapeptides **5** and **6**, β^2-heptapeptide **10** (0.2 mM concentration) and β^3-pentadecapeptide **9** (0.02 mM concentration) is shown in the *Figure*, *a.*

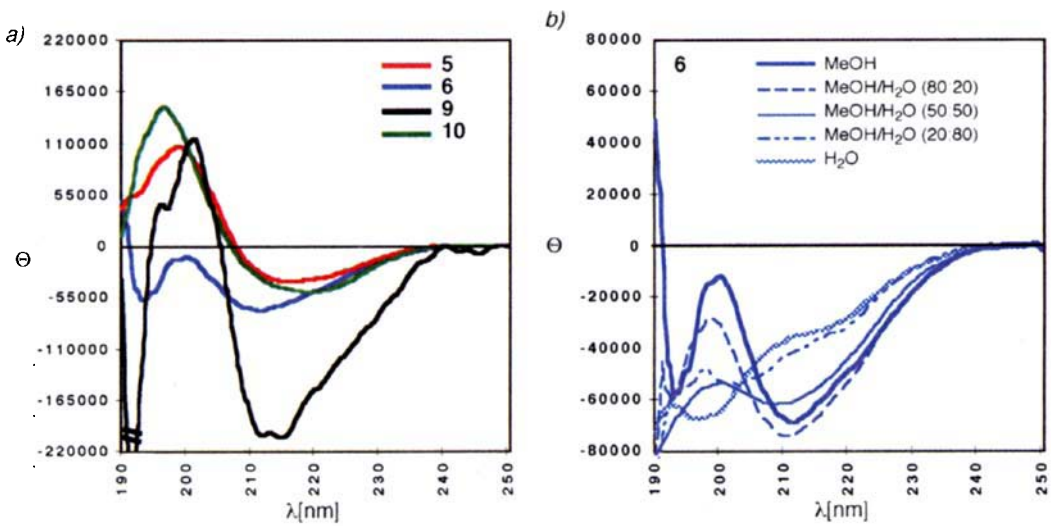


Figure. *CD Spectra of the β^3-peptides* **5**, **6**, *and* **9** *and of the β^2-peptide* **10**: a) *overlay of the CD spectra of peptides* **5**, **6**, **9**, *and* **10** (as trifluoroacetate salts) *in MeOH*; b) *overlay of the CD spectra of the β-heptapeptide* **6** (as trifluoroacetate salt) *in different solvents.* Molar ellipticity [Θ] in 10 deg · cm^2 · mol^{-1}.

[11]) It is interesting to note that β-peptides consisting of β^2-amino acids contained epimers when prepared by solid-phase synthesis. In contrast to the enol form of the oxazolone which has been shown to be responsible for racemization of the 'activated α-amino acid' [37], the enol form of dihydro-oxazinone (activated β-amino acid [32]) is not expected to be 'aromatically stabilized'. A careful analysis of the source of epimer formation is being carried out and will be published separately (collaboration with the group of *P. Fischer*, Universität Stuttgart).

While β-peptide **5** exhibits the typical pattern which we assign to the 3_1-helical conformation, it can be seen from the spectrum of **6** that the introduction of two positively charged residues at the third and the C-terminal positions in the peptide sequence results in a perturbation of the secondary structure. The short-wavelength positive *Cotton* effect and the zero crossover are replaced by a maximum at 200 nm ($\Theta = -1.21 \cdot 10^4$) and the trough is shifted to 212 nm. Further alteration in the CD spectrum of **6** occurs when water is added in increasing amounts (*Fig., b*); in pure water, the CD spectrum shows a negative *Cotton* effect at 197 and a shoulder at *ca.* 214 nm.

The most intensive CD absorption was observed with the pentadecapeptide **9** (*Fig., a*): It shows a CD curve typical of (*M*) 3_1-helices, with a very strong broad negative *Cotton* effect at *ca.* 213 nm ($\Theta = -2.02 \cdot 10^5$). Compared to **5**, this corresponds to a 2.5-fold increase in the molar ellipticity per residue[12][13])!

The β^2-heptapeptide **10** exhibits a CD pattern similar to that of the isomeric β^3-heptapeptide **5** (*Fig., a*) with a negative *Cotton* effect at 220 nm ($\Theta = -4.95 \cdot 10^4$ *vs.* $-3.81 \cdot 10^4$ (216 nm)) followed by a maximum at 197 nm ($\Theta = +1.49 \cdot 10^5$ *vs.* $+1.05 \cdot 10^5$ (199 nm)). This pattern is in agreement with NMR and CD analyses [9][11] showing that a β-hexapeptide built exclusively from (*R*)-β^2-amino acids is present as a right-handed (*P*) 3_1 helix in MeOH.

The CD and NMR investigations of β-peptides **7** and **8**, which contain heterochiral β^3-residues, are underway, and the results of their interpretation will be published in due course.

3. Conclusion. – We have described the preparation of the Fmoc-protected β^3- and β^2-amino acids **2** and **4**, respectively, and their use in solid-phase synthesis of β-oligopeptides. The *Arndt-Eistert* homologation of the commercially available Fmoc-protected Ala, Val, Leu, Phe, Lys, Glu, and Ser derivatives afforded the corresponding β-amino acids **2a–g** in good yields and in enantiomerically pure form. Optimized conditions involve the use of NMM in place of Et_3N in the *Wolff* rearrangement of diazo ketones **1**.

We have also demonstrated that β^3-peptides built from up to 15 amino acids can be readily prepared on solid support under standard solid-phase peptide synthesis conditions. The synthesis of β^2-peptides under the BOP/HOBt/(i-Pr)$_2$EtN coupling conditions proved to be more difficult since epimers of the desired peptide **10** could be detected in the crude product. The sequential acylation of the growing peptide chain by ketene intermediates from the *Wolff* rearrangement of diazo ketones **1** was also used to produce β^3-peptides on solid support, but this approach (under the conditions we used) is likely to be limited to the synthesis of short β-peptides.

As suggested by the CD spectrum of the β^3-pentadecapeptide **9** in MeOH, additional stabilization of helical secondary structures can be achieved with long-chain β^3-peptides. An exciting prospect is the possibility of using such large β-peptides to raise antibodies and learn about the molecular mechanisms of specific β-peptide/antibody recognition.

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[12]) Peptide **9** is poorly soluble in MeOH, and, therefore, the spectrum of **9** had to be measured with a less concentrated solution than that of **5**. On the other hand, we know from previous investigations [7] that the CD pattern of most β^3-peptides shows little dependence from the concentration.

[13]) The NH/ND exchange rate in CD_3OD also demonstrates the conformational stability of the pentadecapeptide **9** [11].

Furthermore, by providing a quick access to a whole new range of β-oligopeptides carrying the side chains of natural (or unnatural) amino acids and by allowing for the construction of β-peptide libraries, this solid-phase methology should facilitate our search for new types of secondary structures (β-sheets, turns, *etc.*) and for bioactive β-peptides.

Experimental Part

1. *General.* Abbreviations: BOP (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), FC (flash chromatography), GP (general procedure), HOBt (1-hydroxy-1*H*-benzotriazole), h.v. (high vacuum, 0.01–0.1 Torr), NMM (*N*-methyl morpholine), TNBS (2,4,6-trinitrobenzenesulfonic acid), β-HXaa (β-homoamino acid). THF was freshly distilled over K under Ar before use. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). Et_3N was distilled from CaH_2 and stored over KOH. i-BuOCOCl was distilled and stored at + 4° under Ar. All indicated temp. were monitored with an internal thermometer (*Ebro-TTX-690* digital thermometer). Amino-acid derivatives were purchased from *Bachem*, *Senn*, or *Degussa*. *Ortho*-chlorotrityl-chloride and *Wang* resins were purchased from *Novabiochem*. All other reagents were used as received from *Fluka*. **Caution:** The generation and the handling of diazomethane requires special precautions [38]. TLC: *Merck* silica gel *60* F_{254} plates; detection with UV and I_2. FC: *Fluka* silica gel *60* (40–63 mm); at *ca.* 0.2 bar. Anal. HPLC: *Knauer* HPLC system (pump type *64*, *EuroChrom 2000* integration package, degaser, UV detector (variable-wavelength monitor)). Prep. HPLC: *Knauer* HPLC system (pump type *64*, programmer *50*, UV detector (variable-wavelength monitor)). M.p.: *Büchi-510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer-241* polarimeter (10-cm, 1-ml cell); at r.t. Circular dichroism (CD) spectra: *Jasco J-710*; recording from 190 to 250 nm at r.t.; 1-mm rectangular cell; average of five scans, corrected for the baseline; peptide concentration 0.2 mM or 0.02 mM in MeOH; molar ellipticity Θ in deg · cm^2 · dmol^{-1} (λ in nm); smoothing by *Jasco* software. IR Spectra: *Perkin-Elmer-782* spectrophotometer. NMR Spectra: *Bruker AMX-II 500* (^{1}H 500 MHz, ^{13}C 125 MHz), *AMX 400* (^{1}H 400 MHz, ^{13}C 100 MHz), *ARX 300* (^{1}H 300 MHz), *Varian Gemini 300* (^{1}H 300 MHz, ^{13}C 75 MHz), or *Gemini 200* (^{1}H 200 MHz, ^{13}C 50 MHz); chemical shifts δ in ppm downfield from internal $SiMe_4$ (= 0 ppm); *J* values in Hz; some compounds show the presence of rotamers which are indicated. Mass Spectra: *VG-Tribrid* (EI), *Hitachi-Perkin-Elmer-RHU-6M* (FAB), *LDI-1700* (MALDI), or *Finnigan-MAT-TSQ-7000* (ESI) spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. N-*Fmoc-Protected Diazo Ketones* **1**: *General Procedure 1* (*GP 1*). Similarly to the reported procedure [20], the *N*-Fmoc-protected amino acid was dissolved in THF (0.35M) under Ar and cooled to −20°. After addition of i-BuOCOCl (1.05 equiv.) and NMM (1.05 equiv.), the mixture was stirred at −20° for 20 min. The resulting white suspension was allowed to warm up to −5°, and a soln. of CH_2N_2 in Et_2O was added until the rich yellow color persisted. Stirring was continued for 4 h as the mixture was allowed to warm to r.t. Excess CH_2N_2 was destroyed by vigorous stirring or by the addition of a few drops of AcOH. The mixture was then diluted with Et_2O and washed with sat. $NaHCO_3$ soln., 1N HCl, and sat. NaCl soln. The org. phase was dried ($MgSO_4$) and evaporated. FC and/or recrystallization afforded the pure diazo ketone.

3. *Homologated Carboxylic Acids* **2**: *General Procedures 2* (*GP 2*). *GP 2a*: Similarly to the reported procedures [7][20], the diazo ketone **1** was dissolved in THF (0.25M) containing 10% H_2O and then cooled to −25° under Ar with the exclusion of light. A soln. of CF_3COOAg (0.11 equiv.) in Et_3N (2.8 equiv.) was added, and the resulting mixture was allowed to warm to r.t. in 4–5 h in the dark. After evaporation of the bulk of THF, the mixture was diluted with sat. aq. $NaHCO_3$ soln. and extracted with Et_2O. The aq. phase was then carefully adjusted to pH 2–3 at 0° with 1N HCl and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and evaporated. FC and/or recrystallization afforded the pure *N*-Fmoc-protected β^3-amino acids.

GP 2b: Diazo ketone **1** was dissolved in THF (0.25M) containing 10% H_2O and then cooled to 0° under Ar with the exclusion of light. A soln. of CF_3COOAg (0.11 equiv.) in NMM (2.5 equiv.) was added, and the resulting mixture was allowed to warm to r.t. in 4–8 h in the dark. Workup as in *GP 2a*. FC and/or recrystallization afforded the pure *N*-Fmoc-protected β^3-amino acids.

4. N-*Fmoc-Protected Derivatives* **4**: *General Procedure 3* (*GP 3*). A stirred soln. of the free β^2-amino acid **3** in 0.15M aq. Na_2CO_3 soln. (2 equiv.) was treated with a soln. of Fmoc-OSu (1.2 equiv.) in acetone (0.1M). After 2 h, the mixture was concentrated *in vacuo*, diluted with H_2O, and extracted with Et_2O. The aq. phase was

carefully adjusted to pH 2–3 at 0° with 1N HCl and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and evaporated. FC and/or recrystallization afforded the pure *N*-Fmoc-protected β^2-amino acids.

5. *Anchoring of* N-*Fmoc-Protected β-Amino Acids on the Resin: General Procedures 4* (*GP 4*). *GP 4a* (*cf. Scheme 2, Method I*): Esterification of **2** and **4** with the *ortho*-chlorotrityl-chloride resin was performed according to [25]. The resin (initial loading: 1.05 or 1.3 mmol Cl/g) was swelled in CH_2Cl_2 (10 ml/mmol) for 10 min. A soln. of **2** or **4** (0.7–0.9 equiv.) in CH_2Cl_2 (10 ml/mmol) and $(i\text{-Pr})_2EtN$ (2.8–3.6 equiv.) were then added successively, and the suspension was mixed under Ar for 4 h. Subsequently, the resin was filtered, washed (10 ml/mmol) with CH_2Cl_2/MeOH/$(i\text{-Pr})_2EtN$ 17:2:1 (3 × 3 min), CH_2Cl_2 (3 × 3 min), DMF (2 × 3 min), CH_2Cl_2 (3 × 3 min), MeOH (2 × 3 min), and finally dried (KOH) under h.v. for 12 h. The loading of the resin was then determined on a 3- to 5-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 (ε = 7800, 5800, and 17500), taking the average absorbance from the 3 measurements.

GP 4b (*cf. Scheme 2, Method II*). A stirred mixture of the *Wang* resin (0.83 mmol/g) and diazo ketone **1** (1.5–2.5 equiv.) in dry THF (24 ml/mmol) was cooled to 0° under Ar with the exclusion of light. A soln. of PhCOOAg (0.11 equiv. with respect to **1**) in NMM (2.5 equiv. with respect to **1**) was added, and the resulting mixture was stirred for 6 h in the dark. The suspension was then transferred to a manual solid-phase apparatus, and excess of reagents was removed by filtration. The resin was washed (12 ml/mmol) with THF (2 × 2 min), DMF (2 × 2 min), 5% diethyldithiocarbamic acid sodium salt in DMF (3 × 4 min), DMF (3 × 3 min), CH_2Cl_2 (3 × 2 min), Et_2O (5 × 1 min), and finally dried for 12 h under h.v. The loading of the resin was then determined as in *GP 4a*.

6. *β-Peptide on Solid Support: General Procedures 5* (*GP 5*). *GP 5a* (*cf. Scheme 3*): The Fmoc group of the first amino acid attached to the resin was removed using 20% piperidine in DMF (30 ml/mmol, 2 × 20 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 **2** or **4** (2.5–3 equiv.), BOP (2.5–3 equiv.), and HOBt (2.5–3 equiv.) in DMF (1–2 ml) and $(i\text{-Pr})_2EtN$ (9 equiv.) were added successively to the resin, and the suspension was mixed for 15–60 min under Ar. Monitoring of the coupling was performed with TNBS [34]. 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 (12 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 (12 ml/mmol) with DMF (6 × 3 min), CH_2Cl_2 (3 × 3 min) and Et_2O (5 × 1 min) and dried under h.v. over KOH for 4 h.

GP 5b: As in *GP 5a*, except that the Fmoc group was removed using 30 ml/mmol DBU/piperidine/DMF (1:1:48, 1 × 3 min and 1 × 8 min) under Ar bubbling.

GP 5c (*cf. Scheme 3*): The Fmoc group of the first amino acid attached to the *Wang* resin (esterified according to *GP 4b*) was removed using 20% piperidine in DMF (30 ml/mmol, 2 × 20 min) under Ar bubbling. The resin was then filtered, washed with DMF (30 ml/mmol, 6 × 3 min) and suspended in dry THF (50 ml/mmol) with the exclusion of light. Diazo ketone **1** (3 equiv.) was added, and the mixture was cooled to 0°. A soln. of PhCOOAg (0.11 equiv. with respect to **1**) in NMM (2.5 equiv. with respect to **1**) was added, and the resulting mixture was stirred for 6 h in the dark. Monitoring of the coupling reaction was performed with TNBS. The suspension was then transferred to a manual solid-phase apparatus, and excess of reagents was removed by filtration. The resin was washed (12 ml/mmol) with THF (2 × 2 min), DMF (2 × 2 min), 5% diethyldithiocarbamic acid sodium salt in DMF (3 × 4 min), and DMF (3 × 3 min), prior to the following Fmoc deprotection. After the removal of the last Fmoc protecting group, the resin was washed (12 ml/mmol) with DMF (6 × 3 min), CH_2Cl_2 (3 × 3 min), and Et_2O (5 × 1 min) and dried under h.v. over KOH for 4 h.

7. *Resin Cleavage and Final Deprotection: General Procedures 6* (*GP 6*). *GP 6a*: The dry Fmoc-deprotected peptide-resin was treated with 2% CF_3COOH in CH_2Cl_2 (2 ml, 5 × 15 min) under Ar bubbling. The resin was removed by filtration and the combined org. phase containing the peptide evaporated. 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) or in 1,4-dioxane and lyophilized to afford a crude product which was analyzed and purified by RP-HPLC.

GP 6b: The dry Fmoc-deprotected peptide-resin was treated for 2 h with 10 ml of $CF_3COOH/H_2O/(i\text{-Pr})_3SiH$ 95:2.5:2.5. The resin was removed hy filtration and washed with CF_3COOH, and the org. phase containing the peptide was evaporated. The oily residue was then treated as in *GP 6a* to give the crude β-peptide which was analyzed and purified by HPLC.

8. *Reversed-Phase* (RP) *HPLC Analysis and Purification of β-Peptides: General Procedure 7* (*GP 7*). RP-HPLC Analysis was performed on a *Macherey-Nagel C8* column/*Nucleosil 100-5 C8* (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 C8* column/*Nucleosil 100-7* C_8 (250 × 21 mm), gradient of *A* and *B* at a flow rate of 4 ml/min, UV detection at 214 nm) and the lyophilized.

9. *Diazo Ketones* **1**. *(S)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butan-2-one* (Fmoc-(*S*)-Ala-CHN_2; **1a**). Fmoc-Ala-OH (10.88 g, 35 mmol) was transformed according to *GP 1*. FC (Et_2O/hexane 7:3) yielded **1a** (8.11 g, 69%). Light-yellow solid. M.p. 118–119°. R_f 0.51 (AcOEt/hexane 1:1). $[\alpha]_D^{r.t.} = -38.2$ ($c = 1.02$, $CHCl_3$). IR ($CHCl_3$): 3433*m*, 3008*m*, 2114*s*, 1718*s*, 1644*s*, 1504*s*, 1450*m*, 1386*m*, 1362*s*, 1328*w*, 1147*m*, 1103*m*, 1079*m*, 1030*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.36 (*d*, $J = 7.1$, Me); 4.24 (*t*, $J = 6.6$, $CHCH_2O$); 4.43 (*m*, CHCO); 4.46 (*d*, $J = 7.1$, $CHCH_2O$); 5.31 (*s*, CHN_2); 5.42 (br. *d*, NH); 7.27–7.45 (*m*, 4 arom. H); 7.61 (*d*, $J = 6.6$, 2 arom. H); 7.78 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.5 (Me); 47.4, 53.7 (CH); 66.9 (CH_2); 120.2, 125.2, 125.4, 127.3, 128.0 (CH); 141.6, 144.0 (C); 156.0, 194.1 (C). FAB-MS: 671 (7.1, $[2M + 1]^+$), 358 (12.9, $[M + Na]^+$), 336 (67.1, $[M + 1]^+$), 335 (25.4, M^+), 179 (79.5). Anal. calc. for $C_{19}H_{17}N_3O_3$ (335.36): C 68.05, H 5.11, N 12.53; found: C 67.92, H 4.93, N 12.29.

(R)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butan-2-one (Fmoc-(*R*)-Ala-CHN_2; *ent*-**1a**). Fmoc-D-Ala-OH · H_2O (13.17 g, 40 mmol) was transformed according to *GP 1*. FC (CH_2Cl_2/Et_2O 20:1) yielded *ent*-**1a** (9.5 g, 71%). Light-yellow solid. M.p. 116–117°. R_f 0.38 (CH_2Cl_2/Et_2O). $[\alpha]_D^{r.t.} = +42.1$ ($c = 1.0$, $CHCl_3$). Other spectroscopic data: corresponding to **1a**.

(S)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-methylpentan-2-one (Fmoc-(*S*)-Val-CHN_2; **1b**). Fmoc-Val-OH (11.86 g, 35 mmol) was transformed according to *GP 1*. FC (AcOEt/hexane 3:7) and recrystallization from AcOEt/hexane yielded **1b** (9.62 g, 76%). Light-yellow crystals. M.p. 125–127°. R_f 0.69 (AcOEt/hexane 1:1). $[\alpha]_D^{r.t.} = -43.3$ ($c = 1.05$, $CHCl_3$). IR ($CHCl_3$): 3430*m*, 3118*w*, 3067*w*, 3008*m*, 2966*m*, 2111*s*, 1719*s*, 1639*s*, 1506*s*, 1465*w*, 1450*m*, 1364*s*, 1262*m*, 1146*w*, 1105*m*, 1024*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*d*, $J = 6.6$, Me); 0.99 (*d*, $J = 6.6$, Me); 2.06–2.16 (*m*, Me_2CH); 4.13 (*m*, CHCO); 4.23 (*t*, $J = 6.6$, $CHCH_2O$); 4.45 (*d*, $J = 5.8$, $CHCH_2O$); 5.32 (*s*, CHN_2); 5.39 (br. *d*, $J = 7.1$, NH); 7.29–7.45 (*m*, 4 arom. H); 7.61 (*d*, $J = 7.1$, 2 arom. H); 7.78 (*d*, $J = 7.1$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.9, 16.9 (CH_2); 28.6 (CH); 44.9, 52.3, 60.4 (CH); 64.4 (CH_2); 117.7, 122.7, 122.8, 124.8, 125.4, 126.0 (CH); 139.1, 141.5 (C); 154.0, 191.0 (C). FAB-MS: 727 (3.1, $[2M + 1]^+$), 386 (1.2, $[M + Na]^+$), 364 (14.6, $[M + 1]^+$), 363 (6.5, M^+), 336 (9.8), 179 (100). Anal. calc. for $C_{21}H_{21}N_3O_3$ (363.42): C 69.41, H 5.82, N 11.56; found: C 69.25, H 5.81, N 11.37.

(S)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-methylhexan-2-one (Fmoc-(*S*)-Leu-CHN_2; **1c**). Fmoc-Leu-OH (12.37 g, 35 mmol) was transformed according to *GP 1*. FC (AcOEt/hexane 3:7) and recrystallization from AcOEt/hexane yielded **1c** (11.8 g, 89%). Yellow solid. M.p. 90–91°. R_f 0.70 (AcOEt/hexane 1:1). $[\alpha]_D^{r.t.} = -48.4$ ($c = 1.18$, $CHCl_3$). IR ($CHCl_3$): 3432*m*, 3118*w*, 3067*w*, 3008*m*, 2961*m*, 2872*w*, 2111*s*, 1719*s*, 1643*s*, 1507*s*, 1467*w*, 1450*m*, 1364*s*, 1248*m*, 1147*w*, 1122*w*, 1102*m*, 1040*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.2$, 2 Me); 1.43–1.68 (*m*, Me_2CH, Me_2CHCH_2); 4.21 (*t*, $J = 6.5$, $CHCH_2O$); 4.40–4.50 (*m*, $CHCH_2O$, CHCO); 5.30 (br. *d*, NH); 7.30–7.43 (*m*, 4 arom. H); 7.59 (*d*, $J = 6.5$, 2 arom. H); 7.77 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.3, 20.6 (Me); 22.2 (CH); 38.9 (CH_2); 44.9, 51.4, 53.9 (CH); 64.3 (CH_2); 117.7, 122.6, 122.8, 124.8, 125.4 (CH); 139.1, 141.5 (C); 153.8, 191.9 (C). Anal. calc. for $C_{22}H_{23}N_3O_3$ (377.44): C 70.01, H 6.14, N 11.13; found: C 70.04, H 5.97, N 10.94.

(S)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylbutan-2-one (Fmoc-(*S*)-Phe-CHN_2; **1d**). Fmoc-Phe-OH (13.56 g, 35 mmol) was transformed according to *GP 1*. FC (AcOEt/hexane 3:7) and recrystallization from AcOEt/hexane yielded **1d** (10.7 g, 74%). Light-yellow crystals. M.p. 133–135°. R_f 0.64 (AcOEt/hexane 1:1). $[\alpha]_D^{r.t.} = -15.3$ ($c = 1.28$, $CHCl_3$). IR ($CHCl_3$): 3426*m*, 3117*w*, 3067*w*, 3008*w*, 2956*w*, 2112*s*, 1718*s*, 1638*s*, 1504*s*, 1450*m*, 1366*m*, 1333*m*, 1287*w*, 1144*m*, 1107*m*, 1085*m*, 1032*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.05 (*d*, $J = 6.2$, $PhCH_2$); 4.19 (*t*, $J = 6.6$, $CHCH_2O$); 4.43 (*d*, $J = 6.6$, $CHCH_2O$); 4.45 (*m*, CHCO); 5.13 (*s*, 1 CHN_2); 5.35 (br. *d*, NH); 7.16–7.45 (*m*, 9 arom. H); 7.53–7.59 (*m*, 2 arom. H); 7.78 (*d*, $J = 7.1$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 36.0 (CH_2); 44.9, 52.2, 56.4 (CH); 64.4 (CH_2); 117.7, 121.5, 122.7, 124.8, 125.4, 126.0, 126.4, 127.0, 133.7 (CH); 139.1, 141.4 (C); 153.4, 190.4 (C). FAB-MS: 823 (3.2, $[2M + 1]^+$), 434 (5.2, $[M + Na]^+$), 412 (29.4, $[M + 1]^+$), 411 (8.8, M^+), 179 (100). Anal. calc. for $C_{25}H_{21}N_3O_3$ (411.46): C 72.98, H 5.14, N 10.21; found: C 73.20, H 5.22, N 10.16.

(R)-1-Diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylbutan-2-one (Fmoc-(*R*)-Phe-CHN_2; *ent*-**1d**). Fmoc-D-Phe-OH (15.5 g, 40 mmol) was transformed according to *GP 1*. Recrystallization from CH_2Cl_2/pentane yielded *ent*-**1d** (13.72 g, 83%). Light-yellow crystals. M.p. 133–134°. R_f 0.33 (AcOEt/pentane). $[\alpha]_D^{r.t.} = +16.5$ ($c = 1.0$, $CHCl_3$). Other spectroscopic data: corresponding to **1d**.

(S)-7-{[(tert-Butoxy)carbonyl]amino}-1-diazo-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}heptan-2-one (Fmoc-(*S*)-Lys(Boc)-CHN_2; **1e**). Fmoc-Lys(Boc)-OH (16.4 g, 35 mmol) was transformed according to *GP 1*. FC (AcOEt/hexane 2:8 → 3:7) and recrystallization from AcOEt/hexane yielded **1e** (15.2 g, 88%). Light-yellow

solid. m.p. 117–118°. R_f 0.41 (AcOEt/hexane 1:2). $[\alpha]_D^{r.t.} = -21.0$ ($c = 1.26$, $CHCl_3$). IR ($CHCl_3$): 3453*m*, 3008*m*, 2940*m*, 2118*s*, 1711*s*, 1641*s*, 1600*w*, 1509*s*, 1450*m*, 1392*m*, 1367*s*, 1328*w*, 1165*m*, 1104*m*, 1037*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33–1.56 (*m*, $CHCH_2(CH_2)_2$); 1.43 (*s*, *t*-Bu); 1.61–1.64 (*m*, 1 H, $CHCH_2CH_2$); 1.80–1.85 (*m*, 1 H, $CHCH_2CH_2$); 3.09–3.11 (*m*, CH_2N); 4.19–4.23 (*m*, CHCO); 4.21 (*t*, $J = 6.5$, $CHCH_2O$); 4.37–4.56 (*m*, $CHCH_2O$, CH_2NH); 5.33 (*s*, CHN_2); 5.48 (br. *d*, NH); 7.26–7.43 (*m*, 4 arom. H); 7.60 (*d*, $J = 7.2$, 2 arom. H); 7.77 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.8 (CH_2); 26.0 (Me); 27.3, 29.4, 37.4 (CH_2); 44.5, 51.5, 55.3 (CH); 64.3 (CH_2); 76.8 (C); 117.7, 122.7, 122.8, 124.8, 125.4 (CH); 139.1, 141.5 (C); 153.8, 153.9, 191.4 (C). FAB-MS: 515 (2.5, $[M + Na]^+$), 493 (2.9, $[M + 1]^+$), 393 (1.6), 179 (100). Anal. calc. for $C_{27}H_{32}N_4O_5$ (492.57): C 65.84, H 6.55, N 11.37; found: C 65.93, H 6.60, N 11.16.

*(S)-5-[(*tert*-Butoxy)carbonyl]-1-diazo-3-{[(*9H*-fluoren-9-ylmethoxy)carbonyl]amino}pentan-2-one* (= tert-*Butyl (S)-6-Diazo-4-{[(*9H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxohexanoate* Fmoc-(*S*)-Glu(*t*-Bu)-CHN_2; **1f**). Fmoc-Glu(*t*-Bu)-OH · H_2O (17.74 g, 40 mmol) was transformed according to *GP 1*. FC (AcOEt/pentane 1:3) and recrystallization from $CHCl_3$/hexane yielded **1f** (15.75 g, 88%). Light-yellow solid. M.p. 138.5–139.5°. R_f 0.29 (AcOEt/pentane 1:3). $[\alpha]_D^{r.t.} = -25.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3425*w*, 3004*w*, 2978*w*, 2112*s*, 1720*s*, 1643*m*, 1506*m*, 1450*m*, 1368*s*, 1248*m*, 1153*s*, 1081*w*, 1041*m*, 844*w*, 650*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*s*, *t*-Bu); 1.79–1.88 (*m*, 1 H, CH_2); 2.08–2.15 (*m*, 1 H, CH_2); 2.24–2.41 (*m*, CH_2CO); 4.20 (*t*, $J = 6.7$, $CHCH_2O$); 4.26 (br. *s*, CHCO); 4.37–4.49 (*m*, 1 H, $CHCH_2O$); 4.45–4.49 (*m*, 1 H, $CHCH_2O$); 5.40 (*s*, CHN_2); 5.61 (*d*, $J = 7.8$, NH); 7.29–7.33 (*m*, 2 arom. H); 7.38–7.42 (*m*, 2 arom. H); 7.52 (*m*, 2 arom. H); 7.76 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.6 (CH_2); 28.1 (Me); 31.3 (CH_2); 47.3, 54.1, 57.4 (CH); 66.9 (CH_2); 81.0 (C); 120.0, 125.0, 125.1, 127.1, 127.7, 127.8 (CH); 141.4, 143.8 (C); 156.1, 172.3, 193.0 (C). FAB-MS: 450 (26.5, $[M + 1]^+$), 422 (47.1), 366 (15.4), 324 (49.0), 307 (34.6), 289 (23.7), 188 (62.6), 179 (100). Anal. calc. for $C_{25}H_{27}N_3O_5$ (449.51): C 66.80, H 6.05, N 9.35; found: C 66.86, H 5.79, N 9.35.

*(S)-4-(*tert*-Butoxy)-1-diazo-3-{[(*9H*-fluoren-9-ylmethoxy)carbonyl]amino}butan-2-one* (Fmoc-(*S*)-Ser(*t*-Bu)-CHN_2; **1g**). Fmoc-Ser(*t*-Bu)-OH (15.0 g, 39 mmol) was transformed according to *GP 1*. FC (AcOEt/pentane 1:3) yielded **1g** (14.85 g, 93%). Viscous yellow oil. R_f 0.29 (AcOEt/pentane 1:3). $[\alpha]_D^{r.t.} = -12.8$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3432*w*, 3008*w*, 2976*m*, 2877*w*, 2112*s*, 1719*s*, 1638*m*, 1500*s*, 1450*m*, 1365*s*, 1260*m*, 1150*m*, 1059*m*, 1010*m*, 876*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.16 (*s*, *t*-Bu); 3.45 (*dd*, $J = 5.8$, 2.7, 1 H, CH_2O); 3.76–3.77 (*m*, 1 H, CH_2O); 4.22 (*t*, $J = 6.6$, $CHCH_2O$); 4.28 (br. *s*, CHCO); 4.41–4.56 (*m*, $CHCH_2O$); 5.39 (*s*, CHN_2); 5.62 (br. *d*, $J = 7.3$, NH); 7.30–7.34 (*m*, 2 arom. H); 7.38–7.43 (*m*, 2 arom. H); 7.51–7.62 (*m*, 2 arom. H); 7.77 (*d*, $J = 7.6$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.3 (Me); 47.3, 54.2, 58.4 (CH); 61.7, 66.8 (CH_2); 73.8 (C); 120.0, 125.0, 125.2, 127.1, 127.7, 127.8 (CH); 141.4, 143.7, 143.8 (C); 156.0, 192.8 (C). FAB-MS: 408 (12.3, $[M + 1]^+$), 380 (18.0), 179 (100), 146 (33.8).

10. *Fmoc-Protected β³-Amino Acids* **2**. *(S)-3-{[(*9H*-Fluoren-9-ylmethoxy)carbonyl]amino}butanoic Acid* (Fmoc-(*S*)-β³-HAla-OH; **2a**). Diazo ketone **1a** (3 g, 8.9 mmol) was transformed according to *GP 2a*. FC (AcOEt/hexane/AcOH 3:7:0.3) and recrystallization from $CHCl_3$/hexane yielded **2a** (2.1, 72%). White solid. M.p. 163°. R_f 0.69 (AcOEt/hexane/AcOH 5:5:0.5). $[\alpha]_D^{r.t.} = +3.0$ ($c = 0.79$, MeOH). IR ($CHCl_3$): 3438*m*, 3032*m*, 2959*w*, 1717*s*, 1603*w*, 1510*s*, 1450*m*, 1408*w*, 1336*w*, 1261*m*, 1102*m*, 1076*m*, 1008*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): 1.29 (br. *d*, Me); *2.38*, 2.59 (*m*, CH_2CO); 4.11 (*m*, CHN); 4.22 (*t*, $J = 6.8$, $CHCH_2O$); 4.40 (*m*, $CHCH_2O$); 5.20, *5.82* (br. *d*, NH); 7.28–7.42 (*m*, 4 arom. H); 7.59 (*d*, $J = 7.5$, 2 arom. H); 7.76 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.3 (Me); 39.8 (CH_2); 43.5, 46.8 (CH); 66.3 (CH_2); 119.6, 124.6, 126.7, 127.3 (CH); 140.9, 143.5 (C); 157.8, 176.0 (C). FAB-MS: 976 (7.9, $[3M + 1]^+$), 651 (74.0, $[2M + 1]^+$), 348 (7.3, $[M + Na]^+$), 326 (100, $[M + 1]^+$), 325 (11.6, M^+), 178 (60.9). Anal. calc. for $C_{19}H_{19}NO_4$ (325.36): C 70.14, H 5.89, N 4.30; found: C 70.18, H 5.87, N 4.27.

*(R)-3-{[(*9H*-Fluoren-9-ylmethoxy)carbonyl]amino}butanoic Acid* (Fmoc-(*R*)-β³-HAla-OH; *ent*-**2a**). Diazo ketone *ent*-**1a** (9.34 g, 27.8 mmol) was transformed according to *GP 2a*. FC (CH_2Cl_2/MeOH 10:1) and recrystallization from CH_2Cl_2/hexane yielded *ent*-**2a** (6.44 g, 73%). White solid. M.p. 165–166.5° (sintering at 125°). R_f 0.30 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{r.t.} = -7.4$ ($c = 1.0$, MeOH). Other spectroscopic data: corresponding to **2a**.

*(R)-3-{[(*9H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-methylpentanoic Acid* (Fmoc-(*R*)-β³-HVal-OH; **2b**). Diazo ketone **1b** (7.06 g, 19.4 mmol) was transformed according to *GP 2a*. FC (AcOEt/hexane/AcOH 3:7:0.3) and recrystallization from $CHCl_3$/hexane yielded **2b** (5.07 g, 75%). White solid. M.p. 158°. R_f 0.45 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -20.2$ ($c = 1.03$, $CHCl_3$). IR ($CHCl_3$): 3436*m*, 3032*m*, 2963*w*, 1716*s*, 1602*w*, 1511*s*, 1465*w*, 1450*m*, 1411*w*, 1333*w*, 1261*m*, 1108*m*, 1036*w*, 1008*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): 0.95 (*d*, $J = 6.2$, 2 Me); 1.81–1.94 (*m*, Me_2CH); *2.39*, 2.59 (*m*, CH_2CO); 3.64–3.87 (*m*, CHN); 4.23 (*t*, $J = 6.6$, $CHCH_2O$); 4.43 (*d*, $J = 6.6$, $CHCH_2O$); 5.15, *5.82* (*d*, $J = 9.1$, NH); 7.32–7.45 (*m*, 4 arom. H); 7.61 (*d*, $J = 7.1$, 2 arom. H); 7.77 (*d*, $J = 7.1$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.6, 19.4 (Me); 31.7 (CH); 36.8 (CH_2); 47.4, 53.6 (CH); 66.8 (CH_2); 120.2, 125.3, 127.3, 127.9, (CH); 141.6, 144.2 (C); 156.5, 177.0 (C).

FAB-MS: 1060 (7.0, $[3M]^+$), 708 (46.0, $[2M + 1]^+$), 707 (46.0, $[2M]^+$), 354 (100, $[M + 1]^+$), 353 (11.5, M^+), 178 (98.1). Anal. calc. for $C_{21}H_{23}NO_4$ (353.42): C 71.37, H 6.56, N 3.96; found: C 71.33, H 6.36, N 3.95.

(S)-3-{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}-5-methylhexanoic Acid (Fmoc-(*S*)-β^3-HLeu-OH; **2c**). Diazo ketone **1c** (4.6 g, 12.2 mmol) was transformed according to *GP 2a*. FC (AcOEt/hexane/AcOH 4:6:0.3) and recrystallization from $CHCl_3$/hexane yielded **2c** (2.95 g, 66%). White solid. M.p. 106–107°. R_f 0.50 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -22.2$ ($c = 1.12$, $CHCl_3$). IR ($CHCl_3$): 3433*m*, 3038*w*, 2959*m*, 2872*w*, 1716*s*, 1603*w*, 1511*s*, 1467*w*, 1450*m*, 1410*w*, 1330*w*, 1261*m*, 1113*m*, 1035*w*, 1005*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): 0.93 (*d*, $J = 5.8$, 2 Me); 1.33–1.37 (*m*, Me_2CH); 1.49–1.60 (*m*, Me_2CHCH_2); *2.33*, 2.59–2.67 (*m*, CH_2CO); *3.78*, 4.06 (*m*, CHN); 4.22 (*t*, $J = 6.2$, $CHCH_2O$); 4.42 (*d*, $J = 6.6$, $CHCH_2O$); 5.12, 5.66 (*d*, $J = 9.1$, NH); 7.31–7.44 (*m*, 4 arom. H); 7.59 (*d*, $J = 7.5$, 2 arom. H); 7.76 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.0, 23.0 (Me); 25.0 (CH); 39.6, 45.5 (CH_2); 46.3, 47.4 (CH); 66.8 (CH_2); 120.2, 125.3, 127.3, 127.9 (CH); 141.6, 144.1 (C); 156.3, 177.1 (C). FAB-MS: 757 (6.0, $[2M + Na]^+$), 735 (8.7, $[2M + 1]^+$), 390 (68.0, $[M + Na]^+$), 368 (66.3, $[M + 1]^+$), 367 (6.5, M^+), 179 (100). Anal. calc. for $C_{22}H_{25}NO_4$ (367.44): C 71.91, H 6.86, N 3.81; found: C 71.74, H 6.95, N 3.86.

(S)-3-{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylbutanoic Acid (Fmoc-(*S*)-β^3-HPhe-OH; **2d**). Diazo ketone **1d** (2.1 g, 5.1 mmol) was transformed according to *GP 2a*. FC (AcOEt/hexane/AcOH 4:6:0.3) and recrystallization from $CHCl_3$/hexane yielded **2d** (1.33 g, 65%). White solid. M.p. 157–158° (sintering at 125°). R_f 0.31 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -19.3$ ($c = 1.23$, $CHCl_3$). IR ($CHCl_3$): 3435*m*, 3032*m*, 2956*w*, 1718*s*, 1602*m*, 1509*s*, 1451*m*, 1405*w*, 1333*w*, 1287*w*, 1261*m*, 1128*w*, 1103*w*, 1082*w*, 1041*w*, 1010*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): *2.36*, 2.58 (*m*, CH_2CO); *2.70*, 2.92 (*m*, $PhCH_2$); *3.96*, 4.18 (*t*, $J = 6.5$, $CHCH_2O$); 4.25–4.38 (*m*, CHN, $CHCH_2O$); 5.24, *5.90* (*d*, $J = 7.8$, NH); 7.20–7.47 (*m*, 9 arom. H); 7.54 (*dd*, $J = 7.5$, 2.2, 2 arom. H); 7.76 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.0, 37.8 (CH_2); 44.8, 46.7 (CH); 64.4 (CH_2); 117.7, 122.7, 124.5, 124.7, 125.4, 126.3, 127.0, 135.0 (CH); 139.0, 141.6 (C); 153.5, 173.7 (C). FAB-MS: 825 (16.4, $[2M + Na]^+$), 803 (41.4, $[2M + 1]^+$), 424 (65.3, $[M + Na]^+$), 402 (100, $[M + 1]^+$), 401 (57.8, M^+), 178 (100). Anal. calc. for $C_{25}H_{23}NO_4$ (401.46): C 74.80, H 5.77, N 3.49; found: C 74.59, H 5.98, N 3.36.

(R)-3-{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylbutanoic Acid (Fmoc-(*R*)-β^3-HPhe-OH; *ent*-**2d**). Diazo ketone *ent*-**1d** (13.6 g, 33 mmol) was transformed according to *GP 2a*. Recrystallization from CH_2Cl_2/hexane yielded *ent*-**2d** (5.19 g, 39%). White solid. M.p. 186–190°. R_f 0.36 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{r.t.} = +23.9$ ($c = 1.0$, $CHCl_3$). Other spectroscopic data: corresponding to **2d**.

(S)-7-{[(tert-Butoxy)carbonyl]amino}-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}heptanoic Acid (Fmoc-(*R*)-β^3-HLys(Boc)-OH; **2e**). *Method A*: Diazo ketone **1e** (3 g, 6.1 mmol) was transformed according to *GP 2a*. FC (AcOEt/hexane/AcOH 5:5:0.5) and recrystallization from $CHCl_3$/hexane yielded **2e** (1.11 g, 38%). White solid.

Method B: Similarly to the reported procedure [16a], **1e** (984 mg, 2 mmol) was dissolved in 1,4-dioxane (0.13M) containing 25% H_2O under Ar with the exclusion of light. CF_3COOAg (48 mg, 0.22 mmol) was added and the resulting mixture stirred at 60° for 1 h. The mixture was then concentrated *in vacuo*, diluted with sat. aq. $NaHCO_3$ soln., and extracted with Et_2O. The aq. phase was then carefully adjusted to pH 2–3 at 0° with 1N HCl and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and evaporated. FC (AcOEt/hexane/AcOH 5:5:0.5) and recrystallization from $CHCl_3$/hexane yielded **2e** (662 mg, 69%). White solid.

Method C: Diazo ketone **1e** (200 mg, 0.40 mmol) was dissolved in THF (0.15M) containing 10% H_2O and then cooled to 0° under Ar with the exclusion of light. CF_3COOAg (9.9 mg, 0.045 mmol) was added and the resulting mixture allowed to warm to r.t. overnight in the dark. Workup as in *GP 2a*. FC (AcOEt/hexane/AcOH 5:5:0.5) and recrystallization from $CHCl_3$/hexane yielded **2e** (152 mg, 78%). White solid.

Method D: Diazo ketone **1e** (500 mg, 1.01 mmol) was transformed according to *GP 2b*. FC (AcOEt/hexane/AcOH 5:5:0.5) and recrystallization from $CHCl_3$/hexane yielded **2e** (397 mg, 81%). White solid. M.p. 97° (dec.). R_f 0.40 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -8.3$ ($c = 0.92$, $CHCl_3$). IR ($CHCl_3$): 3448*m*, 2981*w*, 2940*w*, 1710*s*, 1510*s*, 1472*w*, 1451*m*, 1405*w*, 1368*m*, 1248*m*, 1168*m*, 1105*w*, 1087*w*, 1041*w*, 1020*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): 1.16–1.72 (*m*, Me_2); 1.43 (*s*, *t*-Bu); *2.32*, 2.56 (br. *d*, $J = 5.0$, CH_2CO); *2.70*, 2.92 (*m*, $PhCH_2$); 3.10 (*m*, CH_2N); *3.65*, 3.95 (*m*, CHN); 4.20 (*t*, $J = 6.9$, $CHCH_2O$); 4.38–4.63 (*m*, $CHCH_2O$, CH_2NH); 5.36, *5.51*, *5.89*, *6.0* (br. *d*, NH); 7.27–7.41 (*m*, 4 arom. H); 7.58 (*d*, $J = 7.5$, 2 arom. H); 7.75 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.6 (CH_2); 25.9 (Me); 27.1, 31.3, 36.5, 37.7 (CH_2); 44.9, 45.5 (CH); 64.2 (CH_2); 76.9 (C); 117.6, 122.7, 124.7, 125.4 (CH); 139.0, 141.6 (C); 153.8, 173.2 (C). FAB-MS: 987 (3.0, $[2M + Na]^+$), 965 (4.1, $[2M + 1]^+$), 505 (43.5, $[M + Na]^+$), 483 (22.1, $[M + 1]^+$), 482 (1.7, M^+), 427 (10.2), 383 (100), 178 (58.9). Anal. calc. for $C_{27}H_{34}N_2O_6$ (482.58): C 67.20, H 7.10, N 5.80; found: C 67.00, H 6.86, N 5.79.

*6-(*tert*-Butyl) Hydrogen (S)-3-{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}hexanedioate* (Fmoc-(*S*)-β^3-HGlu(*t*-Bu)-OH; **2f**). *Method A*: Diazo ketone **1f** (2.0 g, 4.45 mmol) was transformed according to *GP 2a*. FC (CH_2Cl_2/MeOH) yielded **2f** (0.91 g, 47%).

Method B: Diazo ketone **1f** (7.0 g, 15.6 mmol) was transformed according to *GP 2b*. FC (CH_2Cl_2/MeOH 10:1) and recrystallization from CH_2Cl_2/pentane yielded **2f** (4.7 g, 71%). White solid. M.p. 58–60°. R_f 0.33 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{r.t.} = -11.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3430*w*, 3008*w*, 2982*w*, 1720*s*, 1510*m*, 1450*w*, 1369*w*, 1248*m*, 1154*m*, 1046*w*, 658*w*, 630*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 1.44 (*s*, *t*-Bu); 1.74–1.88 (*m*, CH_2); 2.16–2.31 (*m*, CH_2CO); 2.62 (*d*, $J = 5.1$, CH_2CO); *3.76*, 3.79 (*m*, NCH); 4.20 (*t*, $J = 6.8$, $CHCH_2O$); 4.34–4.43 (*m*, $CHCH_2O$); 5.35, *5.58* (*d*, $J = 9.0$, NH); 7.28–7.32 (*m*, 2 arom. H); 7.36–7.40 (*m*, 2 arom. H); 7.57 (*d*, $J = 7.5$, 2 arom. H); 7.75 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.1 (Me); 29.1, 32.3, 38.9 (CH_2); 47.3, 47.8 (CH); 66.7 (CH_2); 80.9 (C); 120.0, 125.1, 127.1, 127.7 (CH); 141.3, 143.8, 143.9 (C); 156.0, 172.8, 175.6 (C). FAB-MS: 917 (3.3, $[2M + K]^+$), 902 (0.7, $[2M + Na]^+$), 880 (3.6, $[2M + 1]^+$), 879 (6.5, $[2M]^+$), 478 (1.4, $[M + K]^+$), 462 (7.0, $[M + Na]^+$), 441 (10.1, $[M + 1]^+$), 440 (33.9, M^+), 384 (100), 178 (32.7). Anal. calc. for $C_{25}H_{29}NO_6$ (439.51): C 68.32, H 6.65, N 3.19; found: C 68.28, H 6.73, N 3.15.

*(S)-4-(*tert*-Butoxy)-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butanoic Acid* (Fmoc-(*S*)-β^3-HSer(*t*-Bu)-OH; **2g**). *Method A*: Diazo ketone **1g** (2.0 g, 4.91 mmol) was transformed accordig to *GP 2a*. Recrystallization from CH_2Cl_2/pentane yielded **2g** (1.23 g, 63%).

Method B: Diazo ketone **1g** (4.26 g, 10.4 mmol) was transformed according to *GP 2b*. FC (AcOEt/pentane/AcOH 5:5:0.1) and recrystallization from CH_2Cl_2/pentane yielded **2g** (2.89 g, 70%). White solid. M.p. 96–98°. R_f 0.23 (AcOEt/pentane/AcOH 5:5:0.1). $[\alpha]_D^{r.t.} = +15.7$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3425*w*, 2978*m*, 1717*s*, 1509*s*, 1450*m*, 1365*m*, 1082*m*, 872*w*, 620*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3): 1.17 (*s*, *t*-Bu); 2.55 (*dd*, $J = 15.9$, 7.2, 1 H, CH_2CO); 2.68 (*dd*, $J = 16.0$, 6.1, 1 H, CH_2CO); 3.38–3.41 (*m*, 1 H, CH_2O); 3.48–3.52 (*m*, 1 H, CH_2O); 4.06–4.14 (*m*, CHN); 4.21–4.24 (*m*, $CHCH_2O$); 4.32–4.33 (*m*, $CHCH_2O$); 6.35 (br. *d*, $J = 8.4$, NH); 7.30–7.34 (*m*, 2 arom. H); 7.39–7.43 (*m*, 2 arom. H); 7.69 (*d*, $J = 7.3$, 2 arom. H); 7.84 (*d*, $J = 7.3$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3COCD_3): 27.7 (Me); 36.5 (CH_2); 48.1 (CH); 49.6 (CH); 63.7 (CH_2); 66.9 (CH_2); 73.4 (C); 120.8, 126.1, 127.9, 128.5 (CH); 142.1, 145.1, 145.2 (C); 156.5 (C); 172.9 (C). FAB-MS: 795 (14.8, $[2M]^+$), 420 (20.9, $[M + Na]^+$), 398 (100, M^+), 342 (45.7), 178 (62.1). Anal. calc. for $C_{23}H_{27}NO_5$ (397.47): C 69.50, H 6.85, N 3.52; found: C 69.54, H 7.03, N 3.50.

11. *Fmoc-Protected β^2-Amino Acids* **4**. *(S)-3-{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}-2-methylpropanoic Acid* (Fmoc-(*S*)-β^2-HAla-OH; **4a**). (*S*)-3-Amino-2-methylpropanoic acid (**3a**; 580 mg, 5.63 mmol) was transformed according to *GP 3*. Recrystallization from $CHCl_3$/hexane yielded **4a** (1.17 g, 65%). White solid. M.p. 162–163°. R_f 0.69 (AcOEt/hexane/AcOH 5:5:0.5). $[\alpha]_D^{r.t.} = +9.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3452*m*, 3032*m*, 2954*w*, 1718*s*, 1600*w*, 1515*s*, 1467*m*, 1451*m*, 1410*w*, 1333*w*, 1261*m*, 1149*w*, 1092*w*, 1041*w*, 1007*w*. ^{1}H-NMR (200 MHz, CD_3OD): 1.12 (*d*, $J = 7.1$, Me); 2.54–2.71 (*m*, CHCO); 3.16 (*dd*, $J = 6.6$, 7.1, 1 H, CH_2N); 3.34 (*dd*, $J = 6.6$, 7.5, 1 H, CH_2N); 4.18 (*t*, $J = 6.2$, $CHCH_2O$); 4.41 (*d*, $J = 6.7$, $CHCH_2O$); 7.25–7.41 (*m*, 4 arom. H); 7.62 (*d*, $J = 7.5$, 2 arom. H); 7.77 (*d*, $J = 6.6$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.6 (Me); 39.9 (CH); 43.2 (CH_2); 47.3 (CH); 67.0 (CH_2); 120.2, 125.3, 127.3, 128.0 (CH); 141.6, 144.1 (C); 156.9, 180.8 (C). FAB-MS: 673, (18.7, $[2M + Na]^+$), 651, (63.5, $[2M + 1]^+$), 348 (62.5, $[M + Na]^+$), 326 (100, $[M + 1]^+$), 325 (11.1, M^+), 178 (100). Anal. calc. for $C_{19}H_{19}NO_4$ (325.36): C 70.14, H 5.89, N 4.30; found: C 69.97, H 5.76, N 4.29.

(S)-2-{{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}methyl}-3-methylbutanoic Acid (Fmoc-(*S*)-β^2-HVal-OH; **4b**). (*R*)-2-(Aminomethyl)-3-methylbutanoic acid (**3b**; 400 mg, 3.05 mmol) was transformed according to *GP 3*. Recrystallization from $CHCl_3$/hexane yielded **4b** (793 mg, 74%). Colorless crystals. M.p. 112°. R_f 0.74 (AcOEt/hexane/AcOH 5:5:0.5). $[\alpha]_D^{r.t.} = +11.5$ ($c = 0.97$, $CHCl_3$). IR ($CHCl_3$): 3451*m*, 3036*m*, 2966*w*, 1716*s*, 1602*w*, 1515*s*, 1477*w*, 1450*m*, 1415*w*, 1336*w*, 1262*m*, 1138*w*, 1102*w*, 1078*w*, 1036*w*, 1009*w*. ^{1}H-NMR (200 MHz, CD_3OD): 0.96 (*d*, $J = 7.1$, Me); 0.99 (*d*, $J = 6.6$, Me); 1.81–1.98 (*m*, Me_2CH); 2.36–2.47 (*m*, CHCO); 3.33 (*m*, CH_2N); 4.18 (*t*, $J = 6.2$, $CHCH_2O$); 4.30 (*d*, $J = 5.8$, $CHCH_2O$); 7.25–7.41 (*m*, 4 arom. H); 7.62 (*d*, $J = 7.1$, 2 arom. H); 7.78 (*d*, $J = 6.6$, 2 arom. H). ^{13}C-NMR (75 MHz, CD_3OD): 20.4, 20.8 (Me); 29.9 (CH); 41.9 (CH_2); 53.7 (CH); 68.0 (CH_2); 121.2, 126.5, 128.5, 129.1 (CH); 142.9, 145.6 (C); 159.1, 179.1 (C). FAB-MS: 729 (6.3, $[2M + Na]^+$), 707 (28.8, $[2M + 1]^+$), 392 (6.3, $[M + K]^+$), 376 (46.5, $[M + Na]^+$), 354 (100, $[M + 1]^+$), 353 (9.4, M^+), 178 (96.5). Anal. calc. for $C_{21}H_{23}NO_4$ (353.42): C 71.37, H 6.56, N 3.96; found: C 71.22, H 6.44, N 3.98.

(S)-2-{{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}methyl}-4-methylpentanoic Acid (Fmoc-(*S*)-β^2-HLeu-OH, **4c**). (*S*)-2-(Aminomethyl)-4-methylpentanoic acid (**3c**; 370 mg, 2.55 mmol) was transformed according to *GP 3*. Recrystallization from $CHCl_3$/hexane yielded **4c** (682 mg, 73%). White solid. M.p. 134°. R_f 0.76 (AcOEt/hexane/AcOH 5:5:0.5). $[\alpha]_D^{r.t.} = +10.8$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3455*m*, 2960*m*, 1717*s*, 1602*w*, 1516*m*,

1467*w*, 1450*m*, 1415*w*, 1369*w*, 1333*w*, 1261*m*, 1149*w*, 1091*w*, 1012*w*. ^{1}H-NMR (200 MHz, $CDCl_3$; signals of rotamers in italics): 0.95 (*d*, *J* = 6.2, 2 Me); 1.21–1.41 (*m*, Me_2CH); 1.48–1.79 (*m*, Me_2CHCH_2); 2.52–2.81 (*m*, CHCO); 3.13–3.52 (*m*, CH_2N); 4.18–4.32 (*m*, $CHCH_2O$); 4.37–4.51 (*m*, $CHCH_2O$); 5.27, *6.71* (br. *d*, NH); 7.31–7.44 (*m*, 4 arom. H); 7.59 (*d*, *J* = 7.1, 2 arom. H); 7.77 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.4 (Me); 25.9 (CH); 38.6, 42.3 (CH_2); 43.7, 47.3 (CH); 67.0 (CH_2); 120.2, 125.3, 127.3, 128.0 (CH); 141.6, 144.1 (C); 156.8, 180.8 (C). FAB-MS: 757 (4.9, $[2M + Na]^+$), 735 (36.8, $[2M + 1]^+$), 390 (25.6, $[M + Na]^+$), 368 (100, $[M + 1]^+$), 367 (10.3, M^+), 178 (47.5). Anal. calc. for $C_{22}H_{25}NO_4$ (367.44): C 71.91, H 6.86, N 3.81; found: C 71.89, H 7.14, N 3.83.

(S)-2-{{[(9H-Fluoren-9-ylmethoxy)carbonyl]amino}methyl}-3-phenylpropanoic Acid (Fmoc-(*S*)-β^2-HPhe-OH; **4d**). (*S*)-2-(Aminomethyl)-3-phenylpropanoic acid (**3d**; 380 mg, 2.12 mmol) was transformed according to *GP 3*. FC (AcOEt/hexane/AcOH 4:6:0.4) and recrystallization from $CHCl_3$/hexane yielded **2d** (668 mg, 78%). White solid. M.p. 148–150°. R_f 0.71 (AcOEt/hexane/AcOH 5:5:0.5). $[\alpha]_D^{r.t.} = +8.2$ (*c* = 0.91, $CHCl_3$). IR ($CHCl_3$): 3448*m*, 3068*m*, 3015*m*, 2954*m*, 1717*s*, 1604*w*, 1515*s*, 1476*w*, 1450*m*, 1415*w*, 1333*w*, 1260*m*, 1143*w*, 1088*w*, 1035*w*, 1005*w*. ^{1}H-NMR (200 MHz, CD_3OD): 2.61–2.76 (*m*, PhC*H*, CHCO); 2.92–2.98 (*m*, PhC*H*); 3.11–3.19 (*m*, 1 H, CH_2N); 3.38–3.46 (*m*, 1 H, CH_2N); 4.13 (*t*, *J* = 6.6, $CHCH_2O$); 4.37–4.51 (*d*, *J* = 6.2, $CHCH_2O$); 7.13–7.38 (*m*, 9 arom. H); 7.59 (*d*, *J* = 7.5, 2 arom. H); 7.74 (*d*, *J* = 7.1, 2 arom. H). ^{13}C-NMR (75 MHz, CD_3OD): 35.7, 41.8 (CH_2); 47.1 (CH); 67.0 (CH_2); 120.2, 125.3, 127.1, 127.3, 128.0, 128.9, 129.1, 138.1 (CH); 141.6, 144.1 (C); 156.8, 179.5 (C). FAB-MS: 803 (38.0, $[2M + 1]^+$), 424 (11.2, $[M + Na]^+$), 402 (100, $[M + 1]^+$), 401 (8.6, M^+), 178 (66.2). Anal. calc. for $C_{25}H_{23}NO_4$ (401.46): C 74.80, H 5.77, N 3.49; found: C 74.56, H 5.52, N 3.57.

12. *Peptides. (R)-β³-Homovalyl-(S)-β³-homoalanyl-(S)-β³-homoleucyl-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homoleucine* (H-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OH; **5**). *Method A*: According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (150 mg, 1.05 mmol Cl/g) was esterified with **2c** (41 mg, 112 μmol). Loading 0.43 mmol/g (75%), corresponding to 80 μmol of anchored **2c**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6a* afforded crude **5** as trifluoroacetate (68 mg, 89%). Purity of the crude product: 94% (RP-HPLC).

Method B: According to *GP 4b*, the *Wang* resin (1 g, 0.83 mmol/g) was esterified with **1c** (625 mg, 1.66 mmol). Loading 0.26 mmol/g (41%). Synthesis (52 μmol) according to *GP 6b* afforded crude **5** as trifluoroacetate (27 mg, 49%), purity 71% (RP-HPLC). The peptide was purified by RP-HPLC (40–50% *B* in 10 min and 50–99% *B* in 5 min) according to *GP 7*: trifluoroacetate salt of **5**. White fluffy solid. HPLC (30–90% *B*, 20 min): t_R 15.33. M.p. 285° (dec., sintering at 220°). CD (0.2 mM in MeOH); $+1.05 \cdot 10^5$ (199), $-3.81 \cdot 10^4$ (216). IR (KBr): 3283*s*, 3087*w*, 2964*m*, 2922*w*, 1653*s*, 1560*s*, 1458*w*, 1438*w*, 1374*m*, 1317*w*, 1203*m*, 1143*m*, 1050*w*, 989*w*, 835*w*, 800*w*, 722*w*, 699*w*. ^{1}H-NMR (500 MHz, CD_3OD): 0.89 (*d*, *J* = 6.7, Me); 0.90 (*d*, *J* = 6.8, Me); 0.92 (*d*, *J* = 6.8, Me); 0.94 (*d*, *J* = 6.8, 2 Me); 0.96 (*d*, *J* = 6.5, Me); 1.04 (*d*, *J* = 6.8, Me); 1.06 (*d*, *J* = 6.5, Me); 1.16 (*d*, *J* = 6.5, Me); 1.22 (*d*, *J* = 6.5, Me); 1.24–1.29 (*m*, 1 H, Me_2CHCH_2); 1.31–1.39 (*m*, 2 H, Me_2CHCH_2); 1.43–1.49 (*m*, 1 H, Me_2CHCH_2); 1.54–1.59 (*m*, 1 H, Me_2CHCH_2); 1.63–1.74 (*m*, 2 H, Me_2CHCH_2, Me_2CH); 1.91–1.99 (*m*, Me_2CH); 2.15–2.93 (*m*, 16 H, CH_2CO, $PhCH_2$); 3.31–3.42 (*m*, $CHNH_2$); 4.22–4.24 (*m*, 1 CHN); 4.33 (*m*, 1 CHN); 4.47–4.58 (*m*, 4 CHN); 7.16–7.26 (*m*, 5 arom. H); 7.32 (*d*, *J* = 9.0, NH); 7.66 (*d*, *J* = 7.8, NH); 7.77 (*d*, NH); 8.34 (*d*, *J* = 9.7, NH); 8.43 (*d*, *J* = 9.3, NH). ^{13}C-NMR (125 MHz, CD_3OD): 18.9, 19.4, 19.5, 19.8, 21.0, 21.3, 22.9, 23.0, 23.6, 23.7 (Me); 26.0, 26.1, 32.0, 34.2 (CH); 37.0, 39.3, 41.0, 41.1, 42.4, 42.9, 43.0, 43.1 (CH_2); 43.5, 45.5, 45.6 (CH); 45.7, 46.9 (CH_2); 53.1, 56.8 (CH); 127.6, 129.4, 130.5 (CH); 139.6 (C); 171.5, 171.6, 171.8, 171.9, 172.0, 173.5, 175.1. ESI-MS: 853 (8, $[M + Na]^+$), 833 (16, $[M + 2]^+$), 832 (52, $[M + 1]^+$), 831 (100, M^+).

(R)-β³-Homovalyl-(S)-β³-homoalanyl-(S)-β³-homolysyl-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homolysine (H-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLys-OH; **6**). *Method A*: According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (300 mg, 1.3 mmol Cl/g) was esterified with **2e** (160 mg, 331 μmol). Loading 0.44 mmol/g (59%), corresponding to 70 μmol of anchored **2e**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6b* afforded crude **6** as tris(trifluoroacetate) (62 mg, 74%), purity 86% (RP-HPLC).

Method B: According to *GP 4b*, the *Wang* resin (600 mg, 0.83 mmol/g) was esterified with **1e** (367 mg, 747 μmol). Loading 0.29 mmol/g (50%). Synthesis (55 μmol) according to *GP 5b* and cleavage from the resin according to *GP 6b* afforded crude **6** as tris(trifluoroacetate) (44 mg, 67%), purity 41% (RP-HPLC). The peptide was purified by RP-HPLC (5–40% *B* in 15 min and 40–99% *B* in 3 min) according to *GP 7*: tris(trifluoroacetate) salt of **6**. White hygroscopic solid. HPLC (5–65% *B*, 20 min) t_R 13.24. $[\alpha]_D^{r.t.} = +8.1$ (*c* = 1.0, MeOH). CD (0.2 mM in MeOH): $-1.21 \cdot 10^4$ (200), $-6.88 \cdot 10^4$ (212). IR (KBr): 3288*m*, 3089*m*, 2968*m*, 1654*s*, 1560*s*, 1438*w*, 1376*w*, 1300*w*, 1261*w*, 1203*s*, 1135*s*, 836*w*, 800*w*, 722*m*, 694*w*. ^{1}H-NMR (300 MHz, CD_3OD): 0.90

(*d*, *J* = 6.5, Me); 0.92 (*d*, *J* = 5.9, Me); 1.02 (*d*, *J* = 7.2, Me); 1.04 (*d*, *J* = 6.9, Me); 1.14 (*d*, *J* = 6.5, Me); 1.22 (*d*, *J* = 6.5, Me); 1.30–1.79 (*m*, 13 H, Me_2CH, $CHCH_2CH_2CH_2$); 1.91–1.98 (*m*, Me_2CH); 2.19–2.96 (*m*, 20 H, CH_2CO, $PhCH_2$, CH_2N); 3.39 (*m*, $CHNH_2$); 4.10–4.24 (*m*, 3 CHN); 4.40–4.56 (*m*, 3 CHN); 7.16–7.29 (*m*, 5 arom. H); 7.74 (br. *d*, *J* = 9.3, NH); 7.71 (br. *d*, *J* = 9.3, NH); 7.78 (br. *d*, *J* = 8.4, NH); 7.95 (br. *d*, *J* = 8.7, NH); 8.32 (br. *d*, *J* = 9.3, NH); 8.42 (br. *d*, *J* = 9.0, NH). ^{13}C-NMR (100 MHz, D_2O): 19.8, 20.0, 21.1, 22.0 (Me); 24.5, 24.7, 24.9, 28.9, 29.1 (CH_2); 32.7, 34.4 (CH); 35.2, 35.7, 37.2, 41.3, 41.5, 42.0, 42.2, 42.3, 42.6, 42.7, 43.5, 43.7, 44.7 (CH_2); 46.0, 46.2, 46.3, 49.1, 51.2, 51.4, 55.2, 55.3, 56.9 (CH); 129.5, 131.2, 131.3, 132.0, 132.1 (CH); 140.5 (C); 173.9, 174.6, 175.0, 175.3, 175.4, 178.5, 178.6. ESI-MS: 899 (1.8, $[M + K]^+$), 884 (2.0, $[M + Na]^+$), 832 (2.0, $[M + 2]^+$), 831 (3.6, $[M + 1]^+$), 450 (6, $[M + K + 1]^{2+}$), 442 (5, $[M + Na + 1]^{2+}$), 288 (70, $[M + 3]^{3+}$).

(R)-β³-Homovalyl-(R)-β³-homoalanyl-(S)-β³-homoleucyl-(R)-β³-homophenylalanyl-(R)-β³-homovalyl-(R)-β³-homoalanyl-(S)-β³-homoleucine (H-(*R*)-β³-HVal-(*R*)-β³-HAla-(*S*)-β³-HLeu-(*R*)-β³-HPhe-(*R*)-β³-HVal-(*R*)-β³-HAla-(*S*)-β³-HLeu-OH; **7**). According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (140 mg, 1.3 mmol Cl/g) was esterified with **2c** (47 mg, 128 μmol). Loading 0.38 mmol/g (54%), corresponding to 53 μmol of anchored **2c**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6a* afforded crude **7** as trifluoroacetate (49.5 mg, 99%), purity 80% (RP-HPLC). The peptide was purified by RP-HPLC (20–80% *B* in 40 min) *GP 7*: trifluoroacetate salt of **7** (26.2 mg, 53%). White solid. HPLC (30–90% *B*, 20 min) t_R 9.52. M.p. 320° (dec.). CD (0.2 mM in MeOH): $+1.02 \cdot 10^4$ (224), $-1.02 \cdot 10^5$ (202). IR (KBr): 3430*w*, 3278*w*, 3088*w*, 2966*w*, 1718*s*, 1654*m*, 1577*w*, 1560*w*, 1541*w*, 1506*w*, 1458*w*, 1410*m*, 1374*w*, 1341*s*, 1246*s*, 1124*s*, 1098*s*, 1017*s*, 971*w*, 872*m*, 789*w*, 725*s*. ^{1}H-NMR (200 MHz, CD_3CO_2D): 0.84–0.94 (*m*, 6 Me); 1.01 (*d*, *J* = 7.2, Me); 1.04 (*d*, *J* = 6.9, Me); 1.15 (*d*, *J* = 6.9, Me); 1.20 (*d*, *J* = 6.5, Me); 1.23–1.41 (*m*, 3 CH); 1.43–1.64 (*m*, 4 CH); 1.79–1.81 (*m*, 1 CH); 2.24–2.91 (*m*, 16 H, 7 CH_2CO, $PhCH_2$); 3.42–3.51 (*m*, 1 CHN); 4.12–4.20 (*m*, 1 CHN); 4.21–4.41 (*m*, 4 CHN); 4.42–4.59 (*m*, 1 CHN); 7.20–7.30 (*m*, 5 arom. H); 7.45–8.15 (*m*, 7 NH). FAB-MS: 968 (9.0, $[M + Na]^+$), 830 (100, M^+), 717 (8.5), 600 (13.8), 460 (18.1), 307 (30.0).

(R)-β³-Homovalyl-(R)-β³-homoalanyl-(S)-β³-homolysyl-(R)-β³-homophenylalanyl-(R)-β³-homovalyl(R)-β³-homoalanyl-(S)-β³-homolysine (H-(*R*)-β³-HVal-(*R*)-β³-HAla-(*S*)-β³-HLys-(*R*)-β³-HPhe-(*R*)-β³-HVal-(*R*)-β³-HAla-(*S*)-β³-HLys-OH; **8**). According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (162 mg, 1.3 mmol Cl/g) was esterified with **2e** (92 mg, 190 μmol). Loading 0.35 mmol/g (45%), corresponding to 56 μmol of anchored **2e**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6b* afforded crude **8** as trifluoroacetate (67 mg, 99%), purity 50% (RP-HPLC). The peptide was purified by RP-HPLC (5–30% *B* in 60 min) according to *GP 7*: trifluoroacetate salt of **8** (39.2 mg, 56%). White solid. HPLC (5–65% *B* in 20 min) t_R 11.43. M.p. 200° (dec.). $[\alpha]_D^{r.t.} = +11.4$ (*c* = 0.465, MeOH). CD (0.2 mM in CF_3CH_2OH): $-2.54 \cdot 10^4$ (202), +257 (218). IR (KBr): 3288*m*, 3087*m*, 2970*m*, 2933*m*, 2872*m*, 1654*s*, 1560*s*, 1542*s*, 1508*m*, 1438*w*, 1376*w*, 1204*s*, 1182*s*, 1135*s*, 836*w*, 800*w*, 722*m*, 700*w*, 598*w*, 518*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.93 (*d*, *J* = 6.8, Me); 0.95 (*d*, *J* = 6.8, Me); 1.01 (*d*, *J* = 6.9, Me); 1.03 (*d*, *J* = 6.9, Me); 1.13 (*d*, *J* = 6.7, Me); 1.19 (*d*, *J* = 6.7, Me); 1.31–1.70 (*m*, 12 H, CH_2); 1.72–1.81 (*m*, Me_2CH); 1.92–2.00 (*m*, Me_2CH); 2.19–2.54 (*m*, 13 H, CH_2); 2.63 (*dd*, *J* = 16.2, 3.9, 1 CH); 2.76 (*dd*, *J* = 13.7, 8.6, 1 CH); 2.82–2.95 (*m*, 5 H, CH_2); 3.34–3.39 (*m*, 1 CHN); 4.06–4.13 (*m*, 2 CHN); 4.18–4.32 (*m*, 3 CHN); 4.45–4.50 (*m*, 1 CHN); 7.17–7.29 (*m*, 5 arom. H); 7.89 (*d*, *J* = 8.1, NH); 7.95 (*d*, *J* = 9.3, NH); 8.01 (*d*, *J* = 8.5, NH); 7.64 (*d*, *J* = 8.9, NH). ^{13}C-NMR (100 MHz, CD_3OD): 18.2, 18.7, 18.8, 20.0, 20.3, 20.6 (Me); 24.0, 24.1, 28.2 (CH_2); 31.8, 33.3 (CH); 34.5, 35.0, 35.3, 40.2, 40.4, 40.6, 41.4, 41.6, 42.3, 43.7, 43.8 (CH_2); 44.3, 44.6, 47.4, 48.1, 50.0, 53.8, 55.8 (CH); 127.6, 127.8, 128.7, 129.5, 130.1, 130.4 (CH); 139.8 (C); 171.6, 172.4, 172.7, 172.8, 174.9 (C). MALDI-MS: 899 ($[M + K]^+$), 883 ($[M + Na]^+$), 860 (M^+). FAB-MS: 1720 (2.1, $[2M]^+$), 882 (21.7, $[M + Na]^+$), 860 (100, M^+).

(S)-β³-Homoleucyl-(S)-β³-homoalanyl-(R)-β³-homovalyl-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homoleucyl-(S)-β³-homophenylalanyl-(S)-β³-homoleucyl-(S)-β³-homoalanyl-(R)-β³-homovalyl-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homoleucine (H-(*S*)-β³-HLeu-(*S*)-β³-HAla-(*R*)-β³-HVal-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-(*S*)-β³-HPhe-(*S*)-β³-HLeu-(*S*)-β³-HAla-(*R*)-β³-HVal-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OH; **9**). According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (150 mg, 1.7 mmol Cl/g) was esterified with **4c** (60 mg, 165 μmol). Loading 0.54 mmol/g (69%), corresponding to 108 μmol of anchored **4c**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6a* afforded crude **9** as trifluoroacetate (180 mg, 87%). The peptide was purified by RP-HPLC (60–100% *B* in 6 min and 100% *B* for 10 min) according to *GP 7*: trifluoroacetate salt of **9**. White fluffy solid. M.p. 305° (dec.). CD (0.02 mM in MeOH): $+1.14 \cdot 10^5$ (201), $-2.02 \cdot 10^5$ (213). IR (KBr): 3292*s*, 3087*m*, 2962*s*, 2873*m*, 2467*w*, 2421*w*, 1649*s*, 1543*s*, 1458*m*, 1374*m*, 1311*w*, 1260*w*, 1203*s*, 1138*s*, 1027*w*, 977*w*, 836*w*, 800*w*, 722*m*, 699*m*, 595*w*. ^{1}H-NMR (300 MHz, CD_3OD): 0.92–1.10 (*m*, 15 Me); 1.11–1.16 (*m*, 2 Me); 1.22–1.28 (*m*, 3 Me); 1.35–1.93 (*m*, 16 H, Me_2CHCH_2, Me_2CH); 2.21–3.10 (*m*, 36 H, CH_2CO,

PhCH_2); 3.66–3.70 (*m*, 1 CHN); 7.14–7.29 (*m*, 15 arom. H); 7.79 (br. *d*, *J* = 9.3, NH); 8.02 (br. *d*, *J* = 8.7, NH); 8.16 (br. *d*, *J* = 9.3, NH); 8.22 (br. *d*, *J* = 9.3, NH); 8.26–8.42 (*m*, NH); 8.44–8.76 (*m*, NH). MALDI-MS: 1841 ([*M* + K]$^+$), 1825 ([*M* + Na]$^+$), 1803 (*M*$^+$).

(S)-β²-Homovalyl-(S)-β²-homoalanyl-(S)-β²-homoleucyl-(S)-β²-homophenylalanyl-(S)-β²-homovalyl-(S)-β²-homoalanyl-(S)-β²-homoleucine (H-(*S*)-β²-HVal-(*S*)-β²-HAla-(*S*)-β²-HLeu-(*S*)-β²-HPhe-(*S*)-β²-HVal-(*S*)-β²-HAla-(*S*)-β²-HLeu-OH; **10**). According to *GP 4a*, the *ortho*-chlorotrityl-chloride resin (150 mg, 1.05 mmol Cl/g) was esterified with **4c** (41 mg, 112 μmol). Loading 0.43 mmol/g (75%), corresponding to 80 μmol of anchored **4c**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6a* afforded crude **10** as trifluoroacetate (60 mg, 79%), purity 40% (RP-HPLC). The peptide was purified by RP-HPLC (40–50% *B* in 10 min and 50–99% *B* in 5 min) according to *GP 7*: trifluoroacetate salt of **10**. White fluffy solid. HPLC (30–90% *B*, 20 min) t_R 11.31: M.p. 166° (dec., sintering at 115°). $[\alpha]_D^{r.t.} = -6.1$ (*c* = 0.72, MeOH). CD (0.2 mM in MeOH): $+1.49 \cdot 10^5$ (197), $-4.95 \cdot 10^4$ (220). IR (KBr): 3294*s*, 3089*m*, 2962*s*, 2878*m*, 1654*s*, 1560*s*, 1458*m*, 1388*m*, 1370*m*, 1255*m*, 1203*s*, 1137*s*, 1072*w*, 917*w*, 836*w*, 800*w*, 722*m*, 702*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.87 (*d*, *J* = 6.5, Me); 0.89 (*d*, *J* = 6.3, 2 Me); 0.91 (*d*, *J* = 6.4, Me); 0.92 (*d*, *J* = 7.4, Me); 0.96 (*d*, *J* = 6.8, Me); 1.05 (*d*, *J* = 6.7, Me); 1.06 (*d*, *J* = 6.8, Me); 1.08 (*d*, *J* = 6.8, Me); 1.09 (*d*, *J* = 7.1, Me); 1.11–1.23 (*m*, 2 H, Me_2CHCH_2); 1.41–1.64 (*m*, 4 H, Me_2CHCH_2); 1.70–1.78 (*m*, Me_2CH); 1.87–1.95 (*m*, Me_2CH); 2.19–2.24 (*m*, CHCO); 2.56–2.76 (*m*, 4 CHCO); 2.80–3.10 (*m*, 9 H, CHCO, CH_2N); 3.15–3.25 (*m*, 4 H, CH_2N); 3.38 (*dd*, *J* = 13.1, 10.5, 1 H, CH_2N); 3.56 (*dd*, *J* = 13.2, 11.4, 1 H, CH_2); 3.70–3.77 (*m*, 2 H, CH_2N); 3.80–3.88 (*m*, 2 H, CH_2N); 7.19–7.29 (*m*, 5 arom. H); 7.60 (br. *d*, *J* = 6.0, NH); 7.66 (br. *d*, *J* = 6.1, NH); 8.32 (br. *d*, *J* = 7.3, NH); 8.41 (br. *d*, *J* = 7.0, NH). ^{13}C-NMR (100 MHz, CD_3OD): 16.2, 16.8, 20.6, 20.7, 20.9, 21.2, 22.6, 23.0, 23.4, 23.7 (Me); 27.2, 27.4, 30.6, 31.1 (CH); 38.9, 40.2, 41.0, 41.6 (CH_2); 41.6 (CH); 41.8, 42.4, 42.9, 43.0, 43.2 (CH_2); 45.3, 45.5, 52.2, 53.9 (CH); 127.9, 129.7, 130.1 (CH); 140.0 (C); 174.0, 174.9, 175.0, 176.5, 176.6, 176.7, 179.3 (C). ESI-MS: 853 (8, [*M* + Na]$^+$), 833 (20, [*M* + 2]$^+$), 832 (56, [*M* + 1]$^+$), 831 (100, *M*$^+$).

N-[(9H-Fluoren-9-ylmethoxy)carbonyl]-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homoleucine (Fmoc-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLeu-OH; **11**). According to *GP 4b*, the *Wang* resin (300 mg, 0.83 mmol/g) was esterified with **1c** (189 mg, 500 μmol). Loading 0.29 mmol/g (45%). Synthesis (30 μmol) according to *GP 5c* and cleavage from the resin according to *GP 6b* afforded crude **11** (14 mg, 65%), purity 77% (RP-HPLC). The peptide was purified by RP-HPLC (40–50% *B* in 10 min and 50–99% *B* in 5 min) according to *GP 7*: **11**. White solid. HPLC (30–90% *B*, 20 min) t_R 15.17. M.p. 220° (dec.). IR (KBr): 3670(br.), 2928*m*, 1683*s*, 1636*s*, 1543*m*, 1452*m*, 1429*m*, 1373*w*, 1344*w*, 1203*m*, 1155*s*, 1080*s*, 1030*s*, 946*w*, 840*w*, 800*w*, 740*w*, 701*w*. ^{1}H-NMR (200 MHz, CD_3OD): 0.88 (*d*, *J* = 6.6, 2 Me); 1.10 (*d*, *J* = 6.6, 2 Me); 1.28–1.75 (*m*, Me_2CHCH_2); 1.90–1.93 (*m*, Me_2CH); 2.14–2.41 (*m*, 8 H, CH_2CO); 2.80–2.89 (*m*, 2 H, CH_2); 4.06–4.29 (*m*, 7 H, CHN, $CHCH_2O$); 7.21–7.41 (*m*, 13 arom. H); 7.58 (*d*, *J* = 6.6, 2 H arom. H); 7.78 (*d*, *J* = 6.6, 2 arom. H). MALDI-MS: 766 ([*M* + K]$^+$), 751 ([*M* + Na]$^+$), 727 (*M*$^+$).

N-[(9H-Fluoren-9-ylmethoxy)carbonyl]-(S)-β³-homophenylalanyl-(R)-β³-homovalyl-(S)-β³-homoalanyl-(S)-β³-homolysine (Fmoc-(*S*)-β³-HPhe-(*R*)-β³-HVal-(*S*)-β³-HAla-(*S*)-β³-HLys-OH; **12**). According to *GP 4b*, the *Wang* resin (600 mg, 0.83 mmol/g) was esterified with **1e** (367 mg, 747 μmol). Loading 0.30 mmol/g (50%). Synthesis (60 μmol) according to *GP 5c* and cleavage from the resin according to *GP 6b* afforded crude **12** (24 mg, 55%). Purity of the crude product: 86% (RP-HPLC). The peptide was purified by RP-HPLC (5–60% *B* in 10 min and 60–99% *B* in 5 min) *GP 7*: **12**. White fluffy solid. HPLC (30–90% *B*, 20 min) t_R 9.86. M.p. 170° (dec.). $[\alpha]_D^{r.t.} = -10.8$ (*c* = 0.18, DMF). IR (KBr): 3299*m*, 3065*m*, 2926*m*, 1689*s*, 1646*s*, 1540*s*, 1450*m*, 1374*w*, 1328*w*, 1270*m*, 1203*m*, 1137*m*, 1083*m*, 1040*m*, 837*w*, 799*w*, 741*m*, 722*m*, 699*m*. ^{1}H-NMR (400 MHz, CD_3OD): 0.88 (*d*, *J* = 6.8, Me); 0.89 (*d*, *J* = 6.8, Me); 1.13 (*d*, *J* = 6.7, Me); 1.31–1.64 (*m*, $CHCH_2CH_2CH_2$); 1.71–1.79 (*m*, Me_2CH); 2.14–2.30 (*m*, 3 H, CH_2CO); 2.35–2.51 (*m*, 5 H, CH_2CO); 2.70–2.76 (*m*, 1 H, PhCH_2); 2.83–2.91 (*m*, 3 H, PhCH_2, CH_2N); 4.06–4.29 (*m*, 6 H, CHN, $CHCH_2O$); 4.31–4.35 (*m*, 1 CHN); 7.14–7.41 (*m*, 9 arom. H); 7.58 (*d*, *J* = 7.4, 2 arom. H); 7.78 (*d*, *J* = 7.6, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 18.4, 19.6, 21.1 (Me); 23.9, 28.1 (CH_2); 33.2 (CH); 34.9, 40.0, 40.6, 40.8, 41.9, 42.4, 44.3 (CH_2); 44.9, 47.1, 48.5, 51.6, 53.2 (CH); 67.7 (CH_2); 121.0, 126.2, 126.3, 127.5, 128.2, 128.8, 129.4, 130.6 (CH); 139.6, 142.6, 145.3, 145.4 (C); 158.1, 172.6, 173.0, 174.8 (C). MALDI-MS: 781 ([*M* + K]$^+$), 766 ([*M* + Na]$^+$), 744 (*M*$^+$).

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