232. A New Base-Labile Anchoring Group for Polymer-Supported Peptide Synthesis

by **Manfred Mutter*** and **Dieter Bellof**

Institute of Organic Chemistry, University of Basel, CH–4056 Basel

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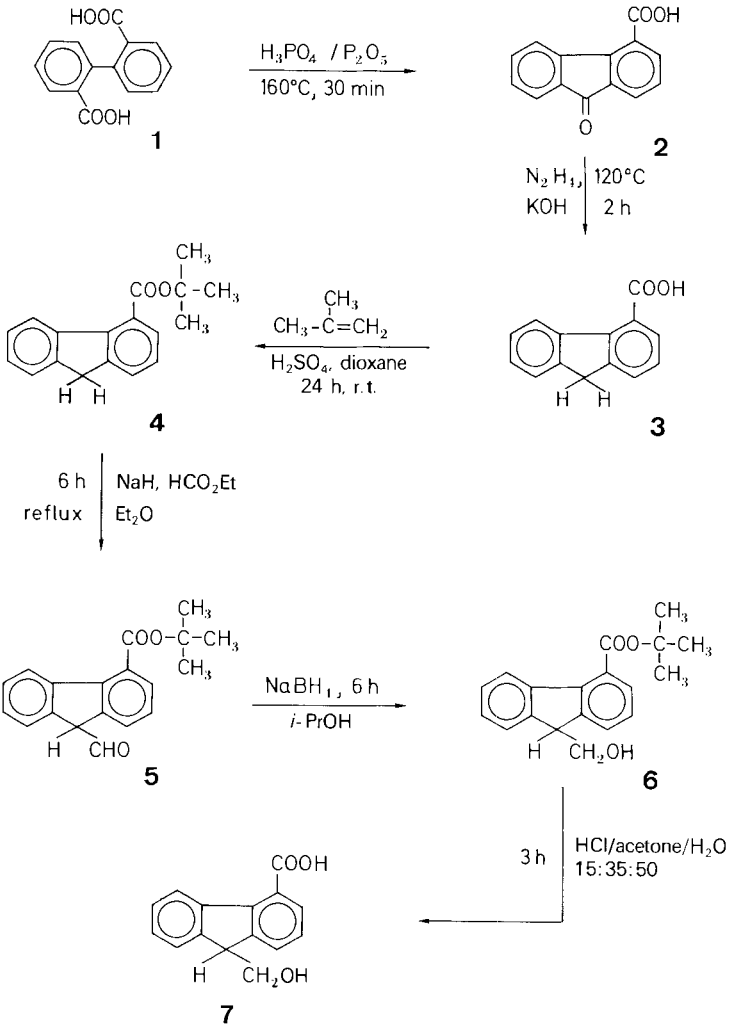
Summary

A new base-labile anchoring group, derived from 9-(hydroxymethyl)fluorene-4-carboxylic acid (HO_2CFmoH or $HOFmCO_2H$; **7**), for polymer-supported peptide synthesis is described. The synthesis of **7** starting from 2,2'-biphenyldicarboxylic acid (**1**) proceeds in an overall yield of 53%. The group HO_2CFmo exhibits properties similar to the well known Fmoc protecting group: It is stable to acidic conditions and cleavable by 15% piperidine in DMF. In combination with acid labile N^{α}-protecting groups (e.g. Boc, Ddz, Bpoc, Nps *etc.*), it renders more flexibility to the stepwise synthesis using polymer supports. The versatility of the new anchoring group in solid- and liquid-phase peptide synthesis is demonstrated for the synthesis of a model peptide.

Introduction. – One of the main problems in polymer-supported peptide synthesis is the reversible attachment of the growing peptide chain to the polymer support [1]. For cleaving off the peptide under mild conditions, so-called 'handles' or 'anchor groups' have been introduced. In order to make use of the full potential of peptide strategy in building up sequential peptides, the availability of a set of anchoring systems with variable chemical stability is substantial. Most notably, procedures for mild and quantitative cleavage of fully protected peptides for segment condensation are in need. The anchoring systems available so far are mostly of the benzyl type and are cleavable by strong acids [1]. Recently, moderately acid-labile systems were introduced in solid-phase peptide synthesis [2]; in combination with base-labile N^{α}-Fmoc[1]) protection, this strategy offers the advantage of orthogonal protection during stepwise synthesis and represents a considerable progress in the methodology of polymer-supported synthesis. However, this promising concept of orthogonal protection is limited to the small number of base-labile N^{α}-protecting groups. On the other hand, with the availability of a suitable base-labile anchoring group, the large spectra of acid-labile N^{α}-protecting groups become accessible, preserving the advantage of orthogonal protection. Furthermore, by mild base cleavage, fully protected peptides for segment condensation could be obtained. Recently, 9-fluorenyl-methyl (Fm) esters have been introduced as base-la-

[1]) Abbreviations according to [4b]; HO_2CFmoH or HOFmCOOH 9-(hydroxymethyl)fluorene-4-carboxylic acid; DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; $Et(i\text{-}Pr)_2N$, *N*-ethyl-*N*-isopropyl isopropylamine; DMF, dimethylformamide; HOBt, 1-hydroxy-1*H*-benzotriazole, M-PEG-NH_2, amino-poly(ethylene glycol monomethyl ether); Tcp, 2,4,5-trichlorophenyl; $(Me_2N)Py$, 4-(dimethylamino)pyridine; Et_3N, triethylamine.

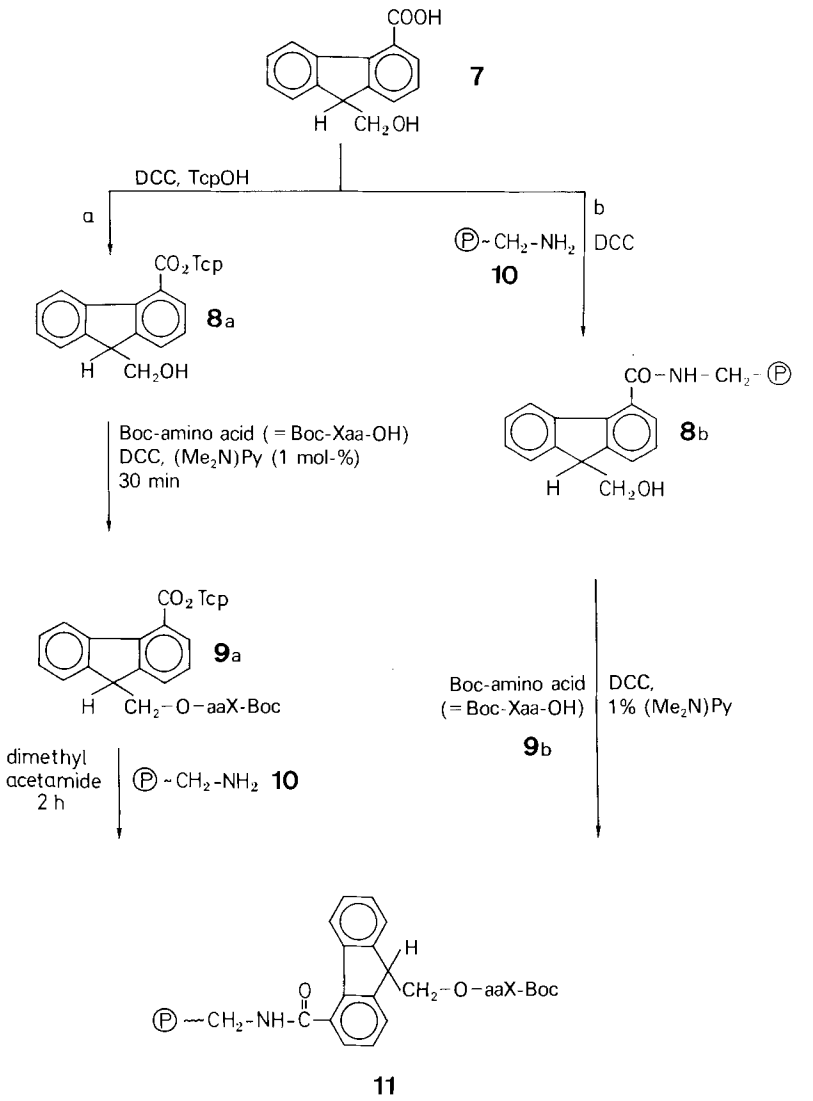
Scheme 1



bile C-terminal protecting group for conventional peptide synthesis [3]. For its use as linking group in polymer-supported peptide synthesis, we describe, in the present paper, the synthesis of 9-(hydroxymethyl)fluorene-4-carboxylic acid (HO_2CFmoH; **7**) and its use in solid- and liquid-phase peptide synthesis [4a][1]).

Results and Discussion. – 1. *Synthesis of* **7**. The carboxylic acid derivative of FmoH, 9-(hydroxymethyl)fluorene-4-carboxylic acid (HO_2CFmoH; **7**), was prepared from diacid **1** in a 6-step synthesis as depicted in *Scheme 1*. *Steps 1* to *3* (→**2**, **3**, **4**) proceeded in yields of about 90%. In contrast to fluorene [8], the formylation of the *tert*-butyl ester **4** resulted in a stable, crystalline compound **5**, which was reduced to **6**. The key compound **7** was obtained in crystalline form in an overall yield of 53%.

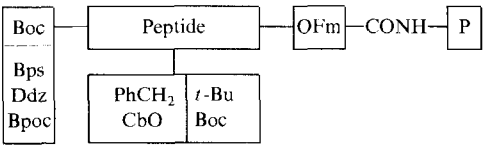
Scheme 2



2. *Attachment of the C-Terminal Amino Acid to HO_2CFmoH* (7). For the attachment of the C-terminal amino-acid derivative, two general procedures can be applied according to *Scheme 2*. In *pathway a,* the N^{α}-protected amino acid was reacted with the Tcp ester **8a** of **7** to yield **9a** almost quantitatively. The attachment of compound **9a** to amino group containing polymers **10** proceeded in quantitative yield to **11**. The preparation of the Tcp ester **8a** by DCC activation of the carboxylic acid suffered considerably from *N*-acyl rearrangement, which is responsible for the relatively low yield (49%) of **8a**. On the other hand, *pathway a* resulted in a well defined loaded polymer with no residual functional groups at the support.

In *pathway b (Scheme 2)*, the anchor **7** was first attached to the amino-methylated polymer **10** *via* DCC coupling to give **8b**. Under the conditions used here, no dimer formation of **7** could be observed. The esterification of the C-terminal amino-acid derivative **9b** to the polymer-anchor system **8b** proceeded in very high yield in the presence of $(Me_2N)Py$ without racemization.

3. *Properties of the Carbamoylfluorenemethanol/Amino Acid (or Peptide) Ester Linkage (RNHOCFmo-aaX or Xaa-OFmCONHR).* The Xaa-OFmoCONHR ester linkage is completely stable to acidic conditions as seen from the *Table*. Consequently, the standard tactics in stepwise synthesis on solid or soluble supports with acid-labile temporary N^{α}-protecting groups such as Boc, Ddz, Nps and Bpoc results in true orthogonal protection of the growing peptide chain.



Most notably, by using one of the highly acid-labile N^{ε}-protecting groups, the *tert*-butyl resp. Boc group can be used for side-chain protection of trifunctional amino acids. This tactics allows the synthesis of fully protected peptides or peptide segments for further condensation and is prone for a combination with conventional solution methods.

As seen from the *Table*, the new anchoring group OFmCONHR is cleavable under very mild alkaline conditions. Investigations of the kinetics of the cleavage show, that the peptide-OFmCONHR ester bond is split by 15% piperidine in DMF quantitatively within less than 5 min.

Careful studies on the stability of the OFmCO anchor under the conditions of peptide synthesis have been performed. Using $Et(i\text{-}Pr)_2N$ for neutralization of the N-terminal groups after acidic deprotection, no cleavage of the anchor could be observed.

Table. *Stability of the Xaa-OFmCONHR Bond in Boc-Val-OFm-CONH-CH_2-PS* (**11a**) *and in H-Ala-OFm-CONH-PEG-M (derived from* **11b**) *towards Acid and Base*

Conditions	Reaction time [min]	Cleavage [%] of Val resp. Ala from support	
1.2N HCl/HOAc	60	0	a)
CF_3COOH/CH_2Cl_2 1:1	60	0	
CF_3COOH	60	0	
30% HBr/HOAc	60	0	
15% Piperidine/DMF	30	100	b)
15% Et_2NH/DMF	30	97.8	
15% Morpholine/DMF	30	100	
15% Et_3N/DMF	60	97.3	
10% $Et(i\text{-}Pr)_2N$/DMF	180	8.7	

a) Value for Ala.
b) Value for Val.

Only in the case, where this base was allowed to react with the anchor system in large excess during several hours, some cleavage (*ca.* 10% within 3 h; *Table*) occurred. However, these conditions are not relevant for the reaction cycle of peptide synthesis. In order to avoid even traces of cleavage, the neutralization of the amino groups with $Et(i\text{-}Pr)_2N$ is performed with equimolar amounts of base or preferentially, *after* the addition of the activated coupling component. In this context it is noteworthy that the use of DMF as solvent may cause problems. Thus, when unpurified DMF was allowed to react with Boc-Val-OFm-CONH-polymer, 4% cleavage was observed within 12 h. To avoid any cleavage during synthesis, DMF has to be freshly destilled in all steps (similar to the Fmoc strategy in solid- or liquid-phase peptide synthesis) or, alternatively, other solvents such as *N,N*-dimethylacetamide, DMSO, or CH_2Cl_2 may be used.

4. *Synthesis of a Model Peptide Using the OFmCO Anchor.* The model tetrapeptide Leu-Ala-Gly-Val was synthesized using Boc-amino acids in combination with the OFmCO anchor attached to aminomethylated poly(styrene-co-2%-divinyl-benzene) resin *via* Gly as internal standard. The capacity of the resin was 1.38 mmol/g.

The coupling reaction was performed in CH_2Cl_2 using DCC/HOBt for activation according to standard conditions (see *Exper. Part*). The neutralization of the N-terminal amino groups after deprotection with 50% CF_3COOH/CH_2Cl_2 was achieved by treatment with 0.5M $Et(i\text{-}Pr)_2N$ in CH_2Cl_2 during 10 min. No cleavage of the peptide occurred during the 4 reaction cycles. The Boc-protected tetrapeptide could be quantitatively split off the resin by treatment with 15% piperidine in DMF during 30 min. The peptide proved to be homogeneous according to the usual analytical criteria.

Conclusions. – The new base-labile anchoring group OFmCO has proved very useful in stepwise synthesis on polymer supports. Specifically, it allows the synthesis of fully protected peptides in combination with moderately acid-labile N^{α}-protecting groups. In our experience, the quantitative cleavage of the peptide under very mild conditions renders more flexibility to polymer-supported syntheses and makes the combination of various strategies for building up longer peptides more attractive.

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Experimental Part

General. ^{1}H-NMR spectra were recorded on a *Bruker WP-60* spectrometer. Electron impact (EI) MS were taken on a *Varian MAT*, model *CH7A*, field desorption (FD) MS on a *Varian MAT*, model *711*. Elemental analysis were performed by Mr. *W. Dindorf* of tbe Microanalytical Laboratory, melting points were taken with a *Dr. Tottoli* capillary melting point apparatus and are uncorrected. The following solvents (*v/v*) were used for TLC (precoated silica gel *60* F_{254} (200 µm), *Merck*): A, AcOEt/cyclohexane 5:2; B, AcOEt/cyclohexane 1:1; C, AcOEt/cyclohexane 2:5; D, CH_2Cl_2/MeOH 7:1; E, BuOH/H_2O/AcOH 3:1:1. All solvents and bulk chemicals were reagent grade. The 2,2'-biphenyldicarboxylic acid (**1**) was obtained from *Aldrich*, all Boc-amino acids were synthesized according to [7]. Poly(styrene-co-2%-divinylbenzene) beads were purchased from *Fluka*, silica gel for dry-column chromatography from *Woelm Pharma GmbH*. The 9-oxofluorene-4-carboxylic acid (**2**) was prepared according to [5].

Fluorene-4-carboxylic acid (**3**). According to [5] with minor modifications: The mixture of 9-oxofluorene-4-carboxylic acid (**2**; 84 g, 0.375 mol; prepared according to [5]) *in 600 ml of diethylene glycol, 52 g of* NaOH, *and*

50 ml of 100% $NH_2NH_2 \cdot H_2O$ was slowly heated to 120°; the reaction suddenly started with vigorous N_2 evolution. During the next 20 min, the solution was stirred without further heating, decreasing the temp. to *ca.* 100°. Finally, the temp. was raised to 120° and the mixture stirred for another 2 h. The mixture was poured on ice and neutralized with conc. HCl. The crude product was filtered off, washed with cold H_2O and redissolved in dil. NaOH. After careful neutralization to pH 7, the solution was filtered again to remove a black oily residue and finally acidified to pH 3–4. The light tan compound was filtered off, washed with H_2O and recrystallized from EtOH/H_2O: 66 g (84%), m.p. 191°.

tert-*Butyl Fluorene-4-carboxylate* (**4**). A solution of **3** (21 g, 0.1 mol) in 220 ml of dioxane/conc. H_2SO_4 10:1 was transferred into a precooled autoclave. Then, 200 ml of 2-methyl-1-propene was added, and the solution was allowed to stand for 3 days with occasional shaking. After cooling to 5°, the mixture was poured into 500 ml of cold 1N NaOH, diluted with 500 ml of cold Et_2O and vigorously stirred for 2 min. The org. layer was separated and the aq. phase extracted 3 times with 100 ml of Et_2O. The combined org. phases were washed with H_2O (3 × 100 ml), dried with $MgSO_4$, and concentrated *in vacuo* at 40° to yield a yellow oil. The crude product crystallized from $CHCl_3$/petroleum ether: 23 g (87%), m.p. 55–56°; R_f (B) 0.9, R_f (C) 0.84. ^{1}H-NMR ($CDCl_3$): 1.65 (*s*, 9H, $(CH_3)_3C$); 3.8 (*s*, 2H, CH_2); 7.08–7.75 (*m*, 6 arom. H); 8.28–8.45 (*m*, 1H, H–C(3)). Anal. calc. for $C_{18}H_{18}O_2$ (226.14): C 81.16, H 6.77; found: C 81.15, H 6.65.

tert-*Butyl 9-Formylfluorene-4-carboxylate* (**5**). To a suspension of 10.1 g of NaH (80% in paraffine oil) in 200 ml of abs. Et_2O, **4** (18.8 g, 0.07 mol) in 150 ml of Et_2O was added dropwise under stirring, followed by 21 ml of HCOOEt. The mixture was heated and stirred at 75° (bath temp.) for 7 h, cooled to r.t. and poured into 200 ml of ice-cold H_2O. The aq. layer was separated, once extracted with 100 ml of Et_2O and 150 ml of petroleum ether, cooled to 5°, and acidified with 21 ml of AcOH. A brown oil precipitated, which was extracted with CH_2Cl_2 (3 × 100 ml). The combined solutions were washed with H_2O, 1M $NaHCO_3$ and H_2O again (2 × 100 ml each), dried with $MgSO_4$, and evaporated *in vacuo* at 40°C. The solid crude product was recrystallized from $CHCl_3$: 18 g (86%), m.p. 168°C, R_f (A) 0.8. ^{1}H-NMR ((D$_6$)acetone): 1.65 (*s*, 9H, $(CH_3)_3C$); 3.8 (*s*, 1H, H–C(9)); 7.07–7.9 (*m*, 6 arom. H); 8.1–8.5 (*m*, 1H, H–C(3)); 9.85 (*s*, 1H, C*H*O). MS (FD, 11 kV, 20 mA): 294 (100, M^+). Anal. calc. for $C_{19}H_{18}O_3$ (294.14): C 77.55, H 6.12; found C 77.52, H 6.28.

tert-*Butyl 9-(Hydroxymethyl)fluorene-4-carboxylate* (**6**). To a suspension of **5** (18 g, 0.06 mol) in 120 ml of i-PrOH, $NaBH_4$ (0.9 g, 0.024 mol) was added during 15 min. After 3 h stirring at r.t. once more 0.9 g of $NaBH_4$ was added to the mixture and stirring continued for 3 h. The solution was diluted with 500 ml of H_2O, cooled with ice, and acidified with AcOH to pH 5. The crude product was extracted with Et_2O (3 × 150 ml), the combined org. phases were washed with H_2O, 1M $NaHCO_3$, and H_2O (2 × 150 ml each), and dried over $MgSO_4$. Evaporation of the solvent left a brown oil, which could not be distilled without decomposing: 18 g; R_f (B) 0.75. ^{1}H-NMR ($CDCl_3$): 1.65 (*s*, 9H, $(CH_3)_3C$); 3.9–4.15 (*m*, 3H, H–C(9), CH_2OH); 7.1–7.9 (*m*, 6 arom. H); 8.1–8.5 (*m*, 1H, H–C(3)). MS (FD, 11 kV, 16 mA): 296 (100%, M^+).

9-(Hydroxymethyl)fluorene-4-carboxylic Acid (**7**). A solution of **6** (10 g, 0.034 mol) in 110 ml of acetone/conc. HCl/H_2O 9:1:1 was refluxed until no **6** could be detected by TLC (B) (3–4 h). The main part of acetone was evaporated *in vacuo* and the aq. residue extracted with $CHCl_3$ (3 × 50 ml). The org. layers were combined, washed with H_2O (3 × 50 ml), and carefully extracted with sat. $NaHCO_3$. The alkaline solutions were washed with $CHCl_3$ (2 × 50 ml), acidified with 6N HCl, and extracted with $CHCl_3$ (3 × 100 ml). After washing with H_2O (3 × 50 ml) and drying over $MgSO_4$, the combined org. phases were evaporated to obtain the crude acid as a tan coloured powder which was recrystallized from $CHCl_3$: 6 g (74%), m.p. 178°. ^{1}H-NMR ($CDCl_3$/(D$_6$)DMSO 1:1): 3.65–4.2 (*m*, 3H, H–C(9), CH_2OH); 7.15–8.0 (*m*, 6 arom. H); 8.25–8.6 (*m*, 1H, H–C(3)). MS: 240 (63, M^+, 210 (100, $M^+ - CH_2O$), 166 (52, $M^+ - CO_2 - CH_2O$). Anal. calc. for $C_{15}H_{12}O_3$ (240.1): C 75.0, H 5.0; found: C 75.3, H 4.91.

2,4,5-Trichlorophenyl 9-(Hydroxymethyl)fluorene-4-carboxylate (**8a**). To a solution of **7** (1.75 g, 7.3 mmol) and 2,4,5-trichlorophenol (1.6 g, 8 mmol) in 30 ml of DMF, cooled to 5°, were added dropwise 8 mmol of DCC (2M in CH_2Cl_2; 4 ml). The mixture was stirred at 2–5° for 1 h and 3 h at r.t., DCU was filtered off, and the resulting solution was diluted with AcOEt to 150 ml. After washing with sat. $NaHCO_3$ and H_2O (each 3 × 150 ml), drying over $MgSO_4$, and evaporation of the solvent, 2.9 g of an oily product was obtained. The crude material was purified by column chromatography using *dry* silica gel and AcOEt/cyclohexane 2:5. The product crystallized from $CHCl_3$/petroleum ether: 1.5 g (49%), m.p. 124–125°, R_f (B) 0.56. ^{1}H-NMR ($CDCl_3$): 3.25–3.5 (br. *s*, 1H, CH_2OH); 3.8–4.15 (*m*, 3H, H–C(9), CH_2OH); 7.2–8.6 (*m*, 9 arom. H). MS (FD, 11 kV, 16 mA): 418, 420, 422 (M^+, isotope pattern for Cl_3); 244 (100, $M^+ -$ Tcp). Anal. calc. for $C_{21}H_{13}Cl_3O_3$ (419.7): C 60.1, H 3.12, Cl 25.34; found: C 59.99, H 3.13, Cl 25.1.

N-(t-*Butoxycarbonyl*)-L-*valine [4'-(2,4,5-Trichlorophenyloxycarbonyl)fluoren-9'-yl]methyl Ester* (**9a**). To a solution of Boc-L-Val (912 mg, 4.2 mmol) and **8a** (1.68 g, 4 mmol) in 20 ml of CH_2Cl_2 at 5°, 4 mg of (Me_2N)Py

was added, followed by 2.1 ml of 2M DCC in CH_2Cl_2. After stirring for 30 min, precipitated DCU was removed by filtration, the filtrate was diluted with 100 ml of CH_2Cl_2 and washed with H_2O, 0.01M HCl, H_2O, 1M $NaHCO_3$, and H_2O (3 × 100 ml, each). The solution was dried over $MgSO_4$, and evaporated *in vacuo* at 40° to yield a colourless oil: 2.23 g (90%), R_f (C) 0.62. ^{1}H-NMR ($CDCl_3$): 0.925 (*d*, *J* = 6.75, 3H, CH_3–C(3)); 0.99 (*d*, *J* = 6.75, 3H, CH_3–C(3)); 1.45 (*s*, 9H, $(CH_3)_3C$); 2.05–2.4 (*m*, 1H, H–C(3)); 3.95–4.65 (*m*, 4H, H–C(2), H–C(9'), CH_2O); 7.25–8.6 (*m*, 9 arom. H). MS (FD, 11 kV, 15 mA): 617, 619, 621 (100, M^+).

{N-Glycyl-aminomethyl}-poly(styrene-co-2%-divinylbenzene) Resin (**10a**). Aminomethyl-poly(styrene-co-2%-divinylbenzene) beads [6] (3 g, 1.5 mmol NH_2/g) were suspended in 20 ml of CH_2Cl_2 for 30 min and then allowed to react with 18 mmol of symmetrical anhydride of Boc-Gly for 3 h. Coupling was quantitative as indicated by a *Kaiser* test [10] and the resin was filtered and washed with CH_2Cl_2, MeOH, and CH_2Cl_2. Deprotection was achieved by 50% CF_3COOH/CH_2Cl_2 for 30 min, neutralization by treatment with 10% Et_3N in CH_2Cl_2. The resin was washed with CH_2Cl_2, MeOH, H_2O, MeOH, and CH_2Cl_2 (3 × 25 ml) and dried *in vacuo*. Microtitration ($HClO_4$/HOAc) of an anal. sample gave a loading of 1.38 mmol NH_2/g.

{9-[N-(t-Butoxycarbonyl)-L-valyloxymethyl]fluorene-4-carbonyl}{N-glycyl-aminomethyl)-poly(styrene-co-2%-divinylbenzene) Resin (**11a**). Resin **10a** (2 g, 1.38 mmol NH_2/g) was suspended in 20 ml of DMF and allowed to stand for 30 min. Then, HOBt (0.48 g, 3.55 mmol) was added followed by **9a** (2.2 g, 3.55 mmol) in 10 ml of DMF. Coupling was quantitative after shaking for 24 h at r.t. The resin was filtered, washed with DMF, MeOH and CH_2Cl_2 (3 × 25 ml), and dried under high vacuum: 3.05 g, amino-acid analysis: Gly/Val 1.00:0.95.

L-Leucyl-L-alanylglycyl-L-valine. The following general procedure was used: 2.0 g of resin **11a** (0.905 mmol Val/g) was 1) washed with 40 ml of CH_2Cl_2 (3 × 1 min); 2) shaken with 20 ml of CF_3COOH/CH_2Cl_2 1:1 for 30 min; 3) washed with 40 ml of CH_2Cl_2 (6 × 1 min); 4) shaken with 40 ml of 0.5M Et(i-Pr)$_2$N in CH_2Cl_2 (2 × 5 min); 5) washed with 40 ml of CH_2Cl_2 (3 × 1 min); 6) treated with 4 equiv. of Boc-Gly-OBt in 40 ml of CH_2Cl_2/THF 2:1 (prepared separately) for 1 h; 7) washed with 40 ml of CH_2Cl_2/THF 1:1 and 40 ml of DMF. The cycle was repeated with Boc-L-Ala and Boc-L-Leu, the peptide-resin deprotected, neutralized, and washed as described. Cleavage from the resin was achieved by treatment with 20 ml of 15% piperidine/DMF (3 × 5 min). The combined piperidine/DMF solutions were evaporated *in vacuo* at 40°, the resulting oil solidified by treatment with AcOEt; yield: 467 mg (72%) of crude peptide, R_f (E) 0.33. The crude material was recrystallized from MeOH: 261 mg (40.2%) of tetrapeptide. Anal. calc. for $C_{10}H_{30}N_4O_5$ (358.6): C 53.78, H 8.12, N 15.69; found: C 54.1, H 8.38, N 15.35. Amino-acid analysis: Val, 1.00; Gly, 1.00; Ala, 1.00; Leu, 1.00.

Tests for the racemization showed no detectable amounts of *D*-amino acids[2]). A sample of the crude tetrapeptide was chromatographed on a μ-*Bondapak C-18* column with MeOH/H_2O 1:1. The peptide was shown to be 90% pure.

[9-(Hydroxymethyl)fluorene-4-carbonylamino]poly(ethylene glycol monomethyl ether) (**8b**). M-PEG-NH_2 [9] (5.5 g, 0.144 mmol/g, $\bar{M}$ = 5000) and **7** (0.38 g, 1.58 mmol) were dissolved in 50 ml of CH_2Cl_2 and cooled to 5°. Then, 2M DCC in CH_2Cl_2 (0.8 ml, 1.6 mmol) was added, and the solution was stirred at r.t. for 4 h. TLC control indicated that the reaction was quantitative. After the DCU had been filtered off, **8b** was precipitated by dropwise addition of 500 ml of Et_2O. Recrystallization from EtOH afforded 5.5 g, R_f (E) 0.0. IR (KBr): 3600–3140*w*, 2860*s*, 1645*w*, 1455*m*, 1342*m*, 1278*m*, 1240*m*, 1145–1060*s*, 962*m*, 945*m*, 842*m*.

{9-[N-(t-Butoxycarbonyl)-L-alanyloxymethyl]fluorene-4-carbonylamino}poly(ethylene glycol monomethyl ether) (**11b**). To **8b** (5.5 g, 0.14 mmol/g) in 50 ml of CH_2Cl_2. Boc-L-Ala (0.29 g, 1.54 mmol) was added, followed by 1 mg of (Me_2N)Py. After cooling to 5°, 2M DCC in CH_2Cl_2 (0.8 ml, 1.6 mmol) was added and the mixture stirred at r.t. for 10 h. DCU was filtered off, and the polymer compound was isolated as described above: 5.4 g, R_f (E) 0.0. IR (KBr): 3600–3160*w*, 2860*s*, 1735*w*, 1705*w*, 1650*w*, 1455*m*, 1341*m*, 1278*m*, 1240*m*, 1150–1060*s*, 963*m*, 945*m*, 842*m*.

Note added in proof. – Compounds **7** and **8b** are commercially available by *Novabiochem AG*, CH-4448 Läufelfingen.

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[2]) For the racemization tests, we are grateful to Prof. *W. König*, University of Hamburg.

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