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RAPID COMMUNICATION

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Novel amino-Li resin for water-based solid-phase peptide synthesis

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We report the first application of a novel amino-Li resin to water-based solid-phase peptide synthesis (SPPS) applying the Smoc-protecting group approach. We demonstrated that it is a suitable support for the sustainable water-based alternative to a classical SPPS approach. The resin possesses good swelling properties in aqueous milieu, provides significant coupling sites, and may be applicable to the synthesis of difficult sequences and aggregation-prone peptides.

KEYWORDS
ASPPS, Smoc strategy, solid support, sustainable peptide synthesis, water-based peptide synthesis

1 | APPLICATION

In recent years, there has been a growing interest in synthetic peptides. Indeed, they can be endowed with a plethora of different functionalities and, therefore, are broadly applied in many fields—as pharma–and cosmeceuticals, food additives, health and life-style products, just to name a few. Considering only the pharmaceutical industry, as of 2020, about 100 peptide drugs are already on the market, about 170 are in clinical trials, and more than 200 in preclinical development.[1,2] Despite their tremendous commercial success, current peptide production faces the problem of sustainability[3–5]; as to date, peptide synthesis is still associated with the usage of large amounts of highly hazardous reagents[3] and solvents,[6] and only little focus lays on green chemistry and engineering.[7] Indeed, current peptide chemistry is one of the most consumptive chemical processes, far from being environmentally friendly, and a number of approaches has been to date reported to improve this situation.[8–10]

Though the first synthetic peptides have been successfully produced in solution, classical solution peptide synthesis (CSPS)[11,12] requires very careful manipulation of protecting groups and sophisticated, often multistep workup and isolation procedures.[13] Therefore, CSPS is currently mostly considered for the synthesis of rather short peptides.[14]

The field of solid-phase peptide synthesis (SPPS) was pioneered by R.B. Merrifield; his technology allowed to significantly simplify the assembly of peptide sequences as a growing peptide chain was covalently linked to a special polymeric support and as a consequence all nonreacted entities, for example, reagents and solvents, were easily removed from the reaction upon washing.[15,16] To date, a vast number of challenging peptides has been synthesized using SPPS approach. However, even today, more than 60 years after Merrifield's seminal papers, peptide production still faces certain problems, with sustainability issues being the most challenging ones. Indeed, the most common reagents in SPPS are *N*,*N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP) and—in lower amounts—dichloromethane, diethyl ether and tert-butyl methyl ether. They represent the biggest portion of wastes generated by chemical synthesis of peptides; therefore, the use of "green" solvents is definitely an asset. To overcome these environmental issues, many researchers proposed alternative ways, among them liquid-phase peptide synthesis (LPPS)

Dedicated to the memory of Michael Przybylski.

that combines the advantages of SPPS and CSPS,[17] as well as solution-phase and SPPS in water, albeit with little success regarding yields and product puritiy.[18,19] In our earlier paper, we have described a sulfonated version of an Fmoc protecting group, 2,7-disulfo-9-fluorenylmethoxycarbonyl (Smoc), that allowed SPPS under aqueous conditions as well as efficient postsynthetic purification of the peptides.[20] Thus, we have established a concept for efficient aqueous solid-phase peptide synthesis (ASPPS) and optimized it in view of coupling efficiency and *N*-terminal deprotection conditions. However, the majority of current solid supports and linker systems are not suitable for SPPS under aqueous conditions. It can be expected that effectiveness of peptide assembly in water is strongly affected by the solid support that anchors the growing peptide chain, as in the case of peptide synthesis in organic solvents.[21] Briefly, the research field, dealing with the issue of making polymeric supports "greener", is still rather small. Thus, it is focused on resin recycling—mostly of a 2-chlorotrityl-based support[22,23] and on the development of polymeric supports based on renewable sources, as for example, the poly-ε-lysine-based SpheriTide resin.[24] However, according to the literature, this resin has only limited compatibility with green solvents[25] and the focus is still on the "classic" polyethylene glycol-based resins.

To be applied to SPPS in general, but in particular also for water-based peptide synthesis, the resin must match certain requirements. Thus, a linker must be permanently bound to the polymeric support, which has to assure anchoring of a growing peptide chain through the whole process of peptide assembly, and all addressable groups must be located outside the resin beads.[26] Moreover, solid supports for ASPPS must be compatible with water and efficiently swell in aqueous media. Therefore, the commonly used divinylbenzene–polystyrene polymers with their poor swelling capacity in water are not suitable for this synthetic approach. Good loading capacity, in an ideal case, more than 0.5 mmol/g, is also desirable. In addition, it must possess only minor interchain interactions and be mechanically stable. To date, from the set of available supports,[26–31] the PEG-based coreless ChemMatrix resin[32,33] was found to be the most suitable for aqueous SPPS.[20] However, this support shares the common drawbacks of its class, namely, low loading capacity, unpredictable swelling, and acid lability. Recently, as an alternative, a second generation of amino-polyacrylamide resin (amino-Li-resin,[33,34] Figure 1) was developed that has proven applicability for SPPS[33] in view of its excellent swelling in most polar organic solvents, including the green solvents most commonly used in SPPS, water, and even in aqueous buffers.

Prepared by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED)-initiated polymerization of *N*,*N*-dimethylacrylamide with *N*,*N*′-bis(acryloyl)piperazine as cross-linker, this polymer has an addressable primary amine at its functionalizing 1-[1-(*N*-acrylyl)piperidin-4-yl] methanamine moiety (shown in red at Figure 1). Obviously, this aliphatic amine is more reactive compared with benzylamine or

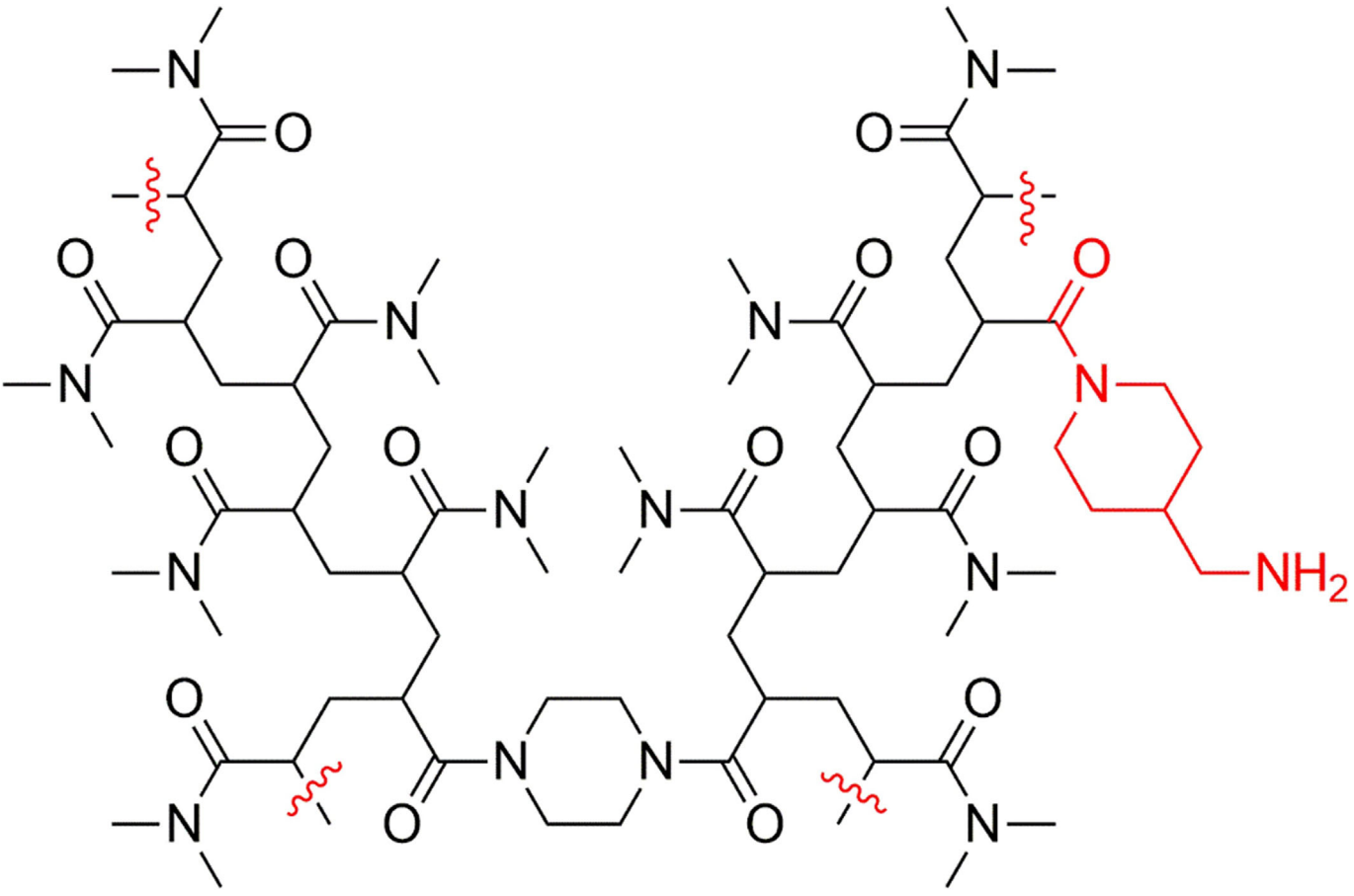


FIGURE 1 Structure of Li resin. Addressable site is shown in red.

benzhydrylamine usually applied in PS-based resins, which is of particular importance in view of further incorporation of RAM linker by amidation. In addition, the formed amide possesses enhanced acid stability, compared with the PS-based counterparts, which is also important during chain assembly and global cleavage.[33]

This resin was reported to display a high loading capacity (0.5 mmol/g) and good chemical stability towards acidic and basic reagents. Using this support, a set of peptides was successfully assembled according to Fmoc-SPPS and applying classic DMF-based solvent system, among them enkephalin- and RGD-derived pentapeptides, a decapeptide *H*-VGAAIDYING-NH_2, and a decaalanine-based tridecapeptide bearing several lysines for solubility.[33] These findings prompted us to investigate the usability of amino-Li-resin as a solid support for the Smoc-based aqueous SPPS (Smoc-ASPPS) approach. Herein, we report synthesis of selected reference peptides using Smoc-ASPPS on amino-Li resin and show that it is a suitable support for water-based green variant of solid-phase peptide production.

Applicability of amino-Li resin to aqueous peptide synthesis was examined on four reference oligopeptide sequences: *H*-YGGFL-NH_2 (**1**), *H*-YIIFL-NH_2 (**2**), *H*-QRNA-NH_2 (**3**), and *H*-RGD-NH_2 (**4**) (Scheme 1). The choice of these peptides was based on the fact that they are often used as test sequences to evaluate the applicability of synthesis approaches and to water-based synthesis in particular.[35] Peptides **1** and **2** are variants of a Leu-Enkephalin, an endogenous opioid peptide neurotransmitter, found naturally in the brain of many animals, including humans. Peptides **3** and **4** are two arginine-bearing peptides, an arginylglycylaspartic acid **4** (RGD)—the most common peptide motif responsible for cell adhesion to the extracellular matrix, found in species ranging from *Drosophila* to humans,[36,37] and a glutaminylarginylasparaginylalanine **3** was chosen as a model peptide to demonstrate the ASPPS without side-chain protecting groups—an additional step to greener peptide synthesis in view of atom economy.

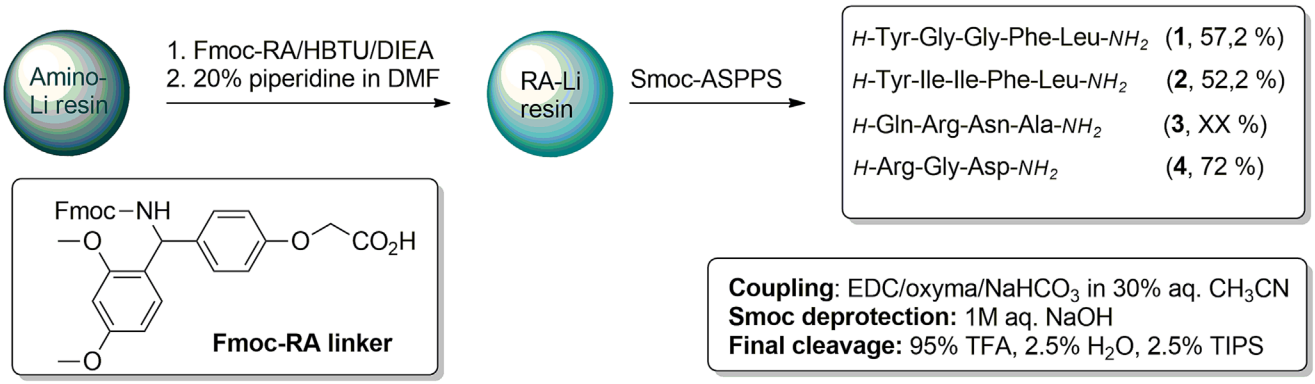
The synthesis started with modification of Li-resin with Fmoc-Rink amide linker (Figure 2) to make the support applicable to peptide synthesis. Done in DMF under HBTU/DIEA activation followed by Fmoc cleavage with 20% piperidine in DMF, it is one of two nongreen steps upon assembly of peptides. The second one is TFA cleavage of the fully assembled peptide from the support. Notably, dried Rink-Amide Li (RA-Li) resin demonstrated good swelling behavior in water (Figure 2).

Then, the Smoc-ASPPS was conducted as described in Section 2. Briefly, N_α-Smoc protected amino acids were coupled under EDC/oxyma activation in the presence of aqueous sodium bicarbonate at ambient temperature. The C-terminal amino acids as well as the second Ile in the sequence of Leu-Enkephalin peptide were attached by double coupling to increase coupling efficacy, while all other amino acids were introduced by single coupling. It is important to mention that N_α-Smoc building blocks D, N, Q, R, Y possessed unprotected side chains.[20]

High–performance liquid chromatography (HPLC) traces of crude peptides, shown at Figure 3, clearly demonstrate that all constructs were assembled in sufficient purity and good yield (see also Section 2). Electrospray ionization mass spectrometry (ESI-MS) analysis revealed that the observed *mz* signals corresponded to the calculated ones.

For demonstration of the feasibility of ASPPS on Li-resin, YIIFL was used as model peptide, as it has been shown to be synthesizable on the Li-resin in organic media by Albericio *et al* and contains the difficult sequence Ile-Ile. To circumvent loss in yield and purity, ASPPS of the second Ile was performed as double coupling step. However, as the synthesis protocols were not optimized, there is still improvement with respect to yield and purity possible. Moreover, we have successfully demonstrated the use of several amino acids (Asn, Gln, Tyr, Trp) without side-chain protecting groups (see synthesis of QRNA) improving the atom economy of peptide synthesis.

To summarize, we demonstrated that the novel amino-Li resin is a suitable support for the sustainable water-based alternative to a classical SPPS approach. It possesses good swelling properties in aqueous milieu, provides significant coupling sites and may be applicable to the synthesis of difficult sequences and aggregation-prone peptides. We have extensive experience with Smoc-based SPPS using ChemMatrix resin. Being a polymer based on polyethene cross-linked with PEG supports and therefore polyacrylamide or polystyrene backbones, this amphiphilic resin is an excellent support for ASPPS since it swells extensively in a wide range of solvents, among them water, tetrahydrofuran (THF), methanol, dichloromethane (DCM) and DMF.



SCHEME 1 General scheme for the aqueous Smoc-based solid-phase peptide synthesis (SPPS) (Smoc-ASPPS) on amino-Li resin. Yields are given as well as the structure of Fmoc-rink amide linker and reaction conditions. TFA: trifluoracetic acid. TIPS: triisopropyl silane.

FIGURE 2 Swelling of RA-Li resin in water. Left: dry resin. Right: resin swollen in water for 30 min.

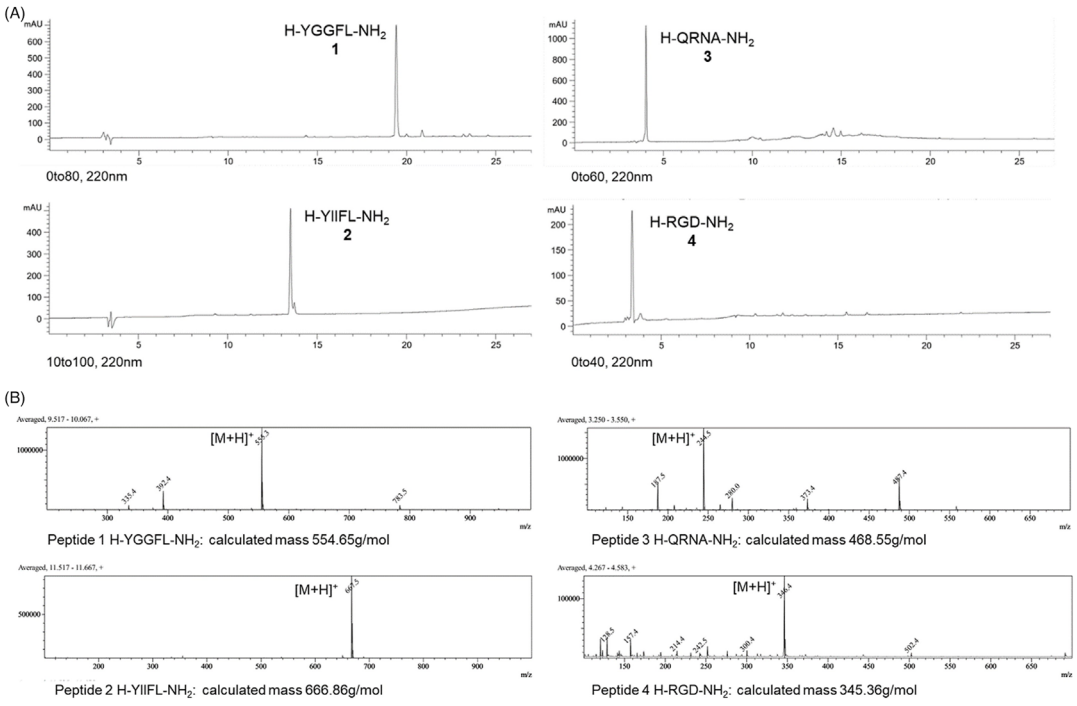


FIGURE 3 (A) HPLC traces of crude peptides **1–4** at 220 nm. Peptide **1**: gradient 0% to 60% CH_3CN, purity 91%. Peptide **2:** gradient 10% to 100% CH_3CN, purity 86%. Peptide **3** at 220 nm, gradient 0% to 60% CH_3CN, purity 48%. Peptide **4**: gradient 0% to 40% CH_3CN, purity 83%. (B) ESI-MS spectra of peptides **1–4**.

However, in our hands, its major drawback was PEG leakage upon TFA cleavage. In addition, ChemMatrix resin has an extremely large swelling volume, which becomes a problem upon industrial application. In this respect, Amino-Li resin displays significantly better performance. The next step would be application of this resin to the synthesis of long peptides, especially those endowed with so called "difficult sequences", requiring on-resin cyclization or postsynthetic oxidative folding.

2 | EXPERIMENTAL

2.1 | Modification of the amino-Li resin for peptide synthesis

To use the amino-Li-resin (loading 0.5 mmol/g) for water-based peptide synthesis, it was modified with an Fmoc-Rink amide linker. To that end, the resin was swollen in DMF for 1 h. Coupling of the Fmoc-Rink amide linker was performed using 3 eq. linker, 2.9 eq. HBTU, and 6 eq. DIEA in DMF for 1 h at ambient temperature. After washing three times with DMF, the Fmoc group was removed using 20% piperidine in DMF for 5 and 10 min. The resin was washed with DMF and water and was dried in vacuum.

2.2 | General procedure for aqueous peptides synthesis

The resin was swollen in water or water/acetonitrile mixture for 1 h at ambient temperature in a syringe equipped with a frit. Loading of the first Smoc building block was performed as double coupling for 2 × 25 min in 30% aq. CH_3CN applying 4 eq. Smoc-amino acid, 4.5 eq. oxyma, 5.5 equation EDC, and 3.5 eq. $NaHCO_3$. Reaction mixture was kept on a shaker with little agitation without stirring; therefore, no significant fragility of the resin was observed; however, it cannot be completely excluded. After washing three times with water, capping with acetic acid was done. The Smoc-group was removed with 1 M NaOH for 1 × 5 min, 1 × 10 min and washed three times with water. If not otherwise mentioned, coupling of the following amino acids was performed as single coupling for 45 min. After completion of the synthesis, the resin was washed with aq. NaCl to remove ionically bound Smoc derivatives. After washing with water, the peptide was cleaved using 95% TFA, 2.5% water, and 2.5% TIPS for 1 h. If not otherwise mentioned, the cleavage mixture was poured into ice-cold diethyl ether to precipitate the peptide. The precipitated peptide was dissolved in water/acetonitrile, freeze-dried, and analyzed.

2.3 | Synthesis of *H*-YGGFL-NH_2 (1)

The RA-Li resin (loading 0.5 mmol/g) was swollen in water for 1 h at ambient temperature. The first amino acid was loaded as double coupling using 3 eq. Smoc-aa, 3.5 eq. oxyma, 4 equation EDC, and 3 eq. NaHCO3 for 2 × 25 min in water. Coupling was performed as single coupling using 3 eq. Smoc-aa, 3.5 eq. oxyma, 4 equation EDC, and 3 eq. $NaHCO_3$ for 45 min in water.

Removal of the Smoc-group was performed using 1 M NaOH for 1 × 5 min and 1 × 10 min. All Smoc-aa were used without side-chain protecting groups.

Washing steps were done with water, and cleavage was performed as described above to yield 15.85 mg of Leu-Enkephalin **1** as white powder (yield 57.2%).

ESI-MS: calculated mass for $C_{28}H_{38}N_6O_6$: 554.65 g/mol; measured *m/z* 555.3 $[M+H]^+$.

2.4 | Synthesis of *H*-YIIFL-NH_2 (2)

The Rink-amide modified Li-resin (RA-Li resin, loading 0.5 mmol/g) was swollen in water for 1 h at ambient temperature. The first amino acid was loaded as double coupling using 4 eq. Smoc-aa, 4.5 eq. oxyma, 5.5 equation EDC, and 3.5 eq. $NaHCO_3$ for 2 × 25 min in 30% aq. CH_3CN. Capping was performed with 4 eq. acetic acid, 4.5 eq. oxyma, 5.5 equation EDC, and 7.5 eq. $NaHCO_3$ for 30 min.

Coupling was done as single coupling except for the second Ile, for which a double coupling was used. Single coupling was performed using 4 eq. Smoc-aa, 4.5 eq. oxyma, 5.5 equation EDC, and 3.5 eq. $NaHCO_3$ for 45 min in 30% aq. CH_3CN.

Removal of the Smoc-group was performed using 1 M NaOH for 1 × 5 min and 1 × 10 min.

Washing steps were done with water, and cleavage was performed as described above.

As the peptide sequence is too hydrophobic and does not precipitate in ether, the cleavage cocktail was poured in water and lyophilized to yield 22.4 mg of peptide **2** as white powder (yield 70%).

ESI-MS: calculated molecular mass for $C_{36}H_{54}N_6O_6$: 666.86 g/mol; measured *m/z* 667.5 $[M+H]^+$.

2.5 | Synthesis *H*-QRNA-NH_2 (3)

The RA-Li resin (loading 0.5 mmol/g) was swollen in water for 1 h at ambient temperature. The first amino acid was loaded as double coupling using 4 eq. Smoc-aa, 4.5 eq. oxyma, 5.5 equation EDC, and 3.5 eq. $NaHCO_3$ for 2 × 25 min in 30% aq. CH_3CN. Coupling was performed with the same equivalents as single coupling for 45 min.

Removal of the Smoc-group was performed using 1 M NaOH for 1 × 5 min and 1 × 10 min. All Smoc-aa were used without side-chain protecting groups.

Washing steps were done with water, and cleavage was performed as described above to yield 5 mg of **3** as white powder (yield 51.4%).

ESI-MS: calculated molecular mass for $C_{18}H_{34}N_{10}O_6$: 486.5 g/mol; measured *m/z* 244.5 $[M+2H]^{2+}$, 487.4 $[M+H]^+$.

2.6 | Synthesis of *H*-RGD-NH_2 (4)

The RA-Li resin (loading 0.5 mmol/g) was swollen in water for 1 h at ambient temperature. The first amino acid was loaded as double coupling using 3 eq. Smoc-aa, 3.5 eq. oxyma, 4 equation EDC, and 3 eq. $NaHCO_3$ for 2 × 25 min in water. Coupling was performed as single coupling using 3 eq. Smoc-aa, 3.5 eq. oxyma, 4 equation EDC, and 3 eq. $NaHCO_3$ for 45 min in water.

Removal of the Smoc-group was performed using 1 M NaOH for 1 × 5 min and 1 × 10 min. All Smoc-aa were used without side-chain protecting groups.

Washing steps were done with water, and cleavage was performed as described above to yield 12.9 mg of **4** as white powder (yield 72%).

ESI-MS: calculated molecular mass for $C_{12}H_{23}N_7O_5$: 345.36 g/mol; measured *m/z* 346.4 $[M+H]^+$.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

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