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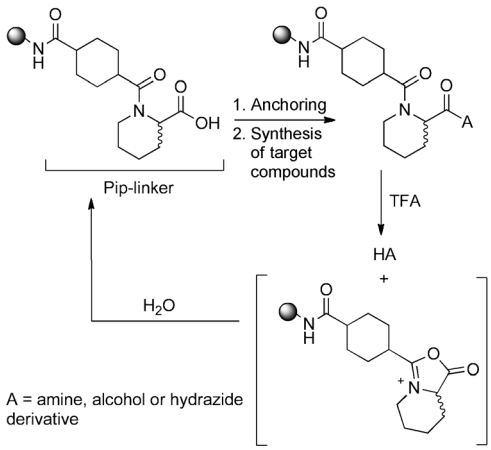
A New Highly Versatile Handle for Chemistry on a Solid Support: The Pipecolic Linker**

Nicolas Masurier,*[a] Paweł Zajdel,[b] Pascal Verdié,[a] Maciej Pawłowski,[b] Muriel Amblard,[a] Jean Martinez,[a] and Gilles Subra[a]

Peptides have drawn considerable attention as therapeutics[1] due to their roles as mediators of key biological functions associated with their low toxicity and high specificity. In 2010, about 60 peptide drugs were on the market (four of them have reached global sales over US$ 1 billion), and more than 500 peptides are in clinical development.[2] Despite their high potentials, peptides demonstrate some therapeutic limits: short half-life, rapid metabolism, poor oral bioavailability, and so forth.[3] Nevertheless, development of pseudopeptides by different chemical modifications can avoid these disadvantages. Various peptidomimetic approaches used for the design and synthesis of peptide-derived compounds with improved pharmacological and pharmacokinetic properties were proposed.[4]

In research, peptide synthesis is performed mostly by solid-phase procedures owing to the speed, ease of automation, and improvement of yields by use of excess of reactants and easy removal of reactants. In production, the majority of peptide synthesis is still performed in solution. However, the use of resins tends to gain popularity since the development of Fuzeon.[5] Solid-phase synthesis is normally performed from C to N terminus, requiring the anchoring of the carboxylic function of the first amino acid to the linker. However, for some modifications and pseudopeptide synthesis, nonconventional N-terminal anchoring is required to perform chemical modifications on the carboxylic function.[6] Several commercially available linkers are currently used to immobilize amino derivatives. Among them, the trityl-based linkers or carbamate/carbonate linkers are the most popular. However, these handles suffer from low yields of anchoring[7] and high sensitivity to acidic conditions, limiting the use of other orthogonal acid-labile protecting groups. Recently, we proposed the pipecolic linker (Pip-linker), a novel trifluoroacetic acid (TFA)-labile linker based on the pipecolic acid scaffold, which can be readily activated to anchor effectively and simply alcohol and amine groups.[8] Anchoring of hydrazine is also possible, which constitutes an efficient way for the preparation of C-terminal hydrazide peptides by conventional Fmoc solid-phase peptide synthesis (SPPS).[8] After anchoring and synthesis of target compound, the acidic treatment by TFA or acetic acid can easily release the target molecule from the Pip-linker (Scheme 1). The cleavage mechanism was assumed to involve an oxazolonium intermediate. This intermediate can then lead to the target molecule, in the presence of water, and the free carboxylic acid function of the pipecolic acid residue is recovered. This original mechanism of cleavage allows efficient and easy recycling of the Pip-linker.[9]



Scheme 1. Use of the pipecolic linker anchored on the aminomethyl polystyrene (PS) resin.

In this study, our aim was to enlarge the use of the Pip-linker to pseudopeptide and cyclic-peptide synthesis, as well as to the preparation of modified amino acids, on solid support. These different focuses are illustrated by the synthesis of a vinylogous γ-amino acid, urea-derived peptides, and peptide alcohols. The synthesis of an N^{α}-Lys anchoring

[a] Dr. N. Masurier, Dr. P. Verdié, Dr. M. Amblard, Prof. J. Martinez, Prof. G. Subra
Institut des Biomolécules Max Mousseron IBMM
UMR CNRS 5247, 15 avenue Charles Flahault
34000 Montpellier (France)
Fax: (+33) 467548654
E-mail: nicolas.masurier@univ-montp1.fr

[b] Dr. P. Zajdel, Prof. M. Pawłowski
Department of Medicinal Chemistry
Jagiellonian University Medical College
9 Medyczna Street, 30-688 Kraków (Poland)

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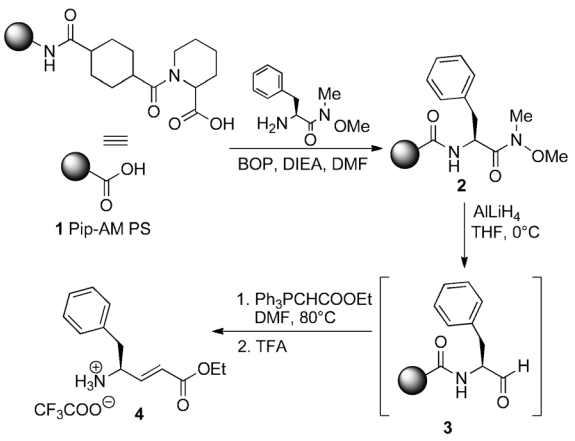
amino acid for the preparation of biotin-derived peptide and cyclic peptides was also undertaken.

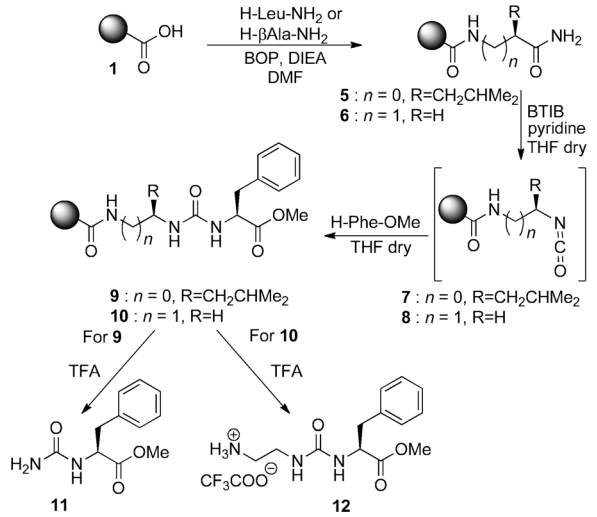
Vinylogous amino acid derivatives are found in certain natural cyclic peptides.[10] Moreover, incorporation of a vinylogous γ-amino acid derivative into a peptide sequence proved to be efficient to develop protease inhibitors[11] or to introduce conformational changes into a peptide backbone.[12] The use of the Pip-linker for the synthesis of modified amino acids was demonstrated by synthesizing a phenylalanine vinylogous γ-amino acid derivative (Scheme 2). For



Scheme 2. Synthesis of vinylogous γ-phenylalanine derivative **4**. AM-PS = aminomethyl polystyrene, BOP = benzotriazolyl-1-oxytris(dimethylamino)phosphonium hexafluorophosphate, DIEA = ethyldiisopropylamine.

the synthesis of such building blocks, the phenylalanine Weinreb amide derivative[13] was anchored on the support and was reduced in THF at 0 °C. Mixing with ten equivalents of hydride for 45 min were necessary to complete the reaction. To access the vinylogous derivative, a Wittig reaction was used, by using carboethoxymethylene triphenylphosphorane in DMF at 80 °C. After cleavage with TFA, compound **4** was obtained in 91 % overall yield and 95 % purity, which is better than the results obtained with the *p*-nitrophenylcarbonate derivatized Wang resin.[6b] The ^{1}H NMR spectrum of compound **4** reveals only the *trans* configuration for the double bound (coupling constant of 15.8 Hz).

Pseudopeptides containing urea moieties appeared to be useful to access various peptidomimetic foldamers.[14] Replacement of an amide bond by a urea was also used to develop enzyme inhibitors.[15] Generally, to synthesize urea derivatives, azido, carbamate, or protected isocyanate building blocks are needed.[16] To prepare such compounds, one or several steps performed in solution are required and toxic reactants are currently used. To avoid these disadvantages, we set up a solid-phase procedure based on the Hofmann rearrangement of C-terminal aminoamides to yield supported isocyanates that can readily be converted into ureas. To this end, H-Leu-NH_2 or H-β-Ala-NH_2 was coupled to the Pip-linker. Subsequent treatment with BTIB and pyridine in dry THF afforded the presumed isocyanate intermediate, followed by reaction with H-Phe-OMe as nucleophile. The β-alanine derivative TFA-mediated cleavage released the ureidodipeptide **12** in 92 % yield and 83 % purity (Scheme 3). When the leucine derivative was used, only the

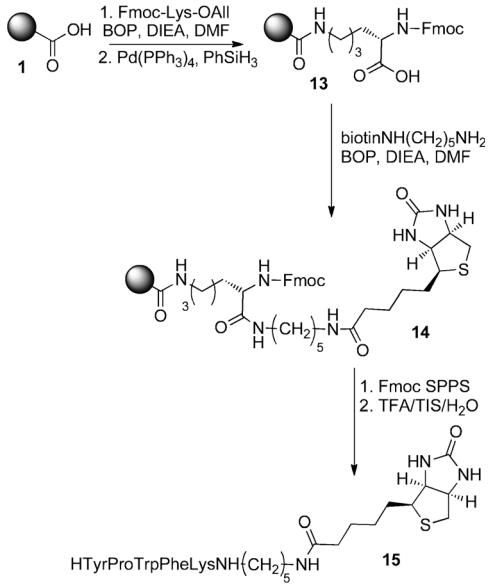


Scheme 3. Synthesis of ureidodipeptides. BTIB = (bistrifluoroacetoxy)-iodobenzene.

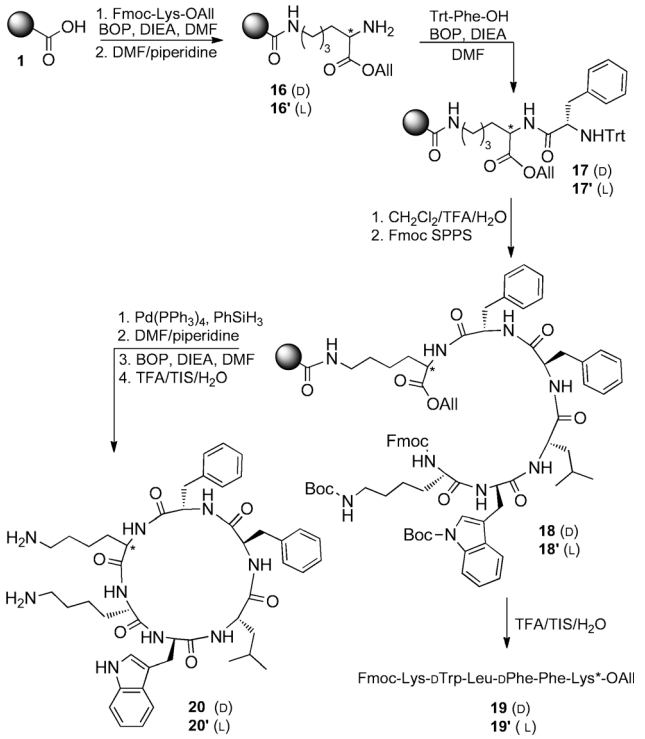
N-monosubstituted urea derivative **11** was obtained with 99 % yield and 91 % purity. The structure of compound **11** was ascertained by ^{1}H NMR and ESI-mass spectroscopy (m/z=223.1). The ureidodipeptide was not stable enough to be observed, contrary to the behavior of the corresponding monoacyl *gem*-diamino derivative.[8] This result can be explained by the well-known weak stability of pseudo *gem*-diamino compounds,[17] which lead to the N-monosubstituted urea derivative **11** after loss of isobutylamine. In compound **12**, the presence of a supplementary methylene increased the stability of the urea derivative and the ureidodipeptide could be isolated.

Anchoring of an amino acid through its side chain could represent a method of choice for the synthesis of N- to C-cyclic peptides, for the coupling of peptide fragments, or for generation of C-terminus-modified peptides. Anchoring of serine, threonine, or tyrosine by the side chains proved to be efficient with the Pip-linker.[8] We now explored the anchoring of the lysine side chain to access C-terminus-modified peptides and to synthesize cyclic peptides.

To access C-terminus-modified peptides, the lysine was anchored to the solid support through its N^{ε}-amino function. In this respect, the N^{α}-amino function constituted the starting point for the peptide elongation and the carboxylic acid function allowed C-terminal modification of the peptide without epimerization. In a first instance, we explored the introduction of a biotinylated probe onto the C-terminal position of a bioactive peptide by using the Pip-linker. For this purpose, Fmoc-Lys-OAll[18] was anchored on the Pip-linker and a biotin derivative[19] was introduced on compound **13** after deprotection of the allyl ester (Scheme 4). During acti-



Scheme 4. Synthesis of C-terminal-modified endomorphin-1 derivative. Fmoc = 9-fluorenylmethoxycarbonyl (coupling step: BOP, DIEA, Fmoc-Lys(Boc)-OH or Fmoc-Phe-OH or Fmoc-Trp(Boc)-OH or Fmoc-Pro-OH or Boc-Tyr(*t*Bu)-OH; deprotection step: DMF/piperidine 80:20 v/v), TIS = triisopropylsilane.

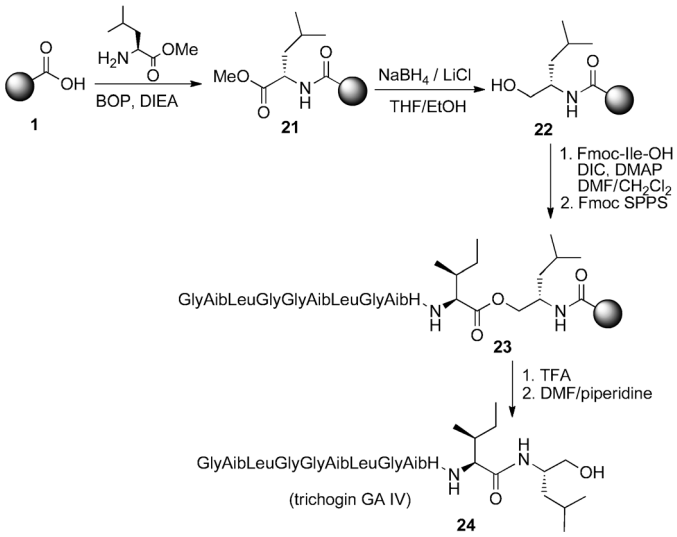


Scheme 5. Synthesis of cyclic peptides, Trt = trityl (triphenylmethyl) (coupling step: BOP, DIEA, Fmoc-DPhe-OH or Fmoc-Phe-OH or Fmoc-Leu-OH or Fmoc-DTrp(Boc)-OH or Fmoc-Lys(Boc)-OH; deprotection step: DMF/piperidine 80:20 v/v).

vation of the C-terminal carboxylic acid function, the lysine residue is *N*-urethane protected, avoiding epimerization via oxazolone formation. After *N*-Fmoc removal, the lysine N^{α}-amino group was used for the target peptide elongation. The endogenous opioid peptide endomorphin-1 (H-Tyr-Pro-Trp-Phe-NH_2) was chosen as the bioactive peptide model. TFA-mediated cleavage released biotinylated peptide **15** in 70% overall yield and 61% purity.

Immobilization of a lysine side chain could also constitute a simple way to access N- to C-cyclic peptides. As an example, the cyclic hexapeptide cyclo(Lys-D-Trp-Leu-D-Phe-Phe-D-Lys) (**20**), displaying high activity against multiresistant *Staphylococcus aureus* (MRSA) strains,[20] was synthesized by using the Pip-linker. In a first step, Fmoc-Lys-OAll[18] was anchored to the Pip resin, by BOP/DIEA activation (Scheme 5). The resin loading was evaluated based on Fmoc released, monitored by UV absorption at 290 nm (0.34 mmol g^{-1}, quantitative yield). To prevent diketopiperazine formation, Trt-Phe-OH was introduced as the second residue to give **17**. A first attempt to remove the trityl group was performed with the CH_2Cl_2/TFA/H_2O cocktail (98.8:0.2:1 v/v/v), as reported by Alsina et al.[21] However, trityl-group removal was not complete and a 97:2:1 (v/v/v) CH_2Cl_2/TFA/H_2O solution was required to achieve complete trityl removal. With these conditions, no premature peptide cleavage was observed from the Pip-linker; this would have happened on trityl-based linker. At this step, a cleavage of a resin aliquot confirmed the absence of diketopiperazine formation. The peptide sequence was then elongated by using a standard SPPS strategy to yield the supported linear peptide **18**. After removal of the Fmoc group and the allyl group by using $Pd(PPh_3)_4$ and phenylsilane, the peptide was cyclized by BOP/DIEA activation. After TFA/TIS/H_2O cleavage, the crude cyclic peptide **20** was obtained and purified by preparative HPLC. Peptide fragments lead to a certain extent of epimerization upon activation. Special attention was paid to evaluate this side reaction on the lysine residue. To this purpose, the diastereoisomer of compound **20**, cyclo(Lys-D-Trp-Leu-D-Phe-Phe-Lys) (**20′**), was synthesized. Epimerization was estimated to 2% by HPLC (see the Supporting Information).

Last but not least, we envisaged application of the Pip-linker for the synthesis of C-terminal peptide alcohols. Peptide alcohols constitute an important class of compounds and present a range of biological properties.[22] Recently, an efficient synthesis of peptide alcohols was reported, with a trityl chloride resin and a O–N acyl transfer reaction as the key step.[23] Based on this study, we propose a strategy in which the aminoalcohol is prepared directly on solid support from a supported aminoester. We applied this method to prepare the antibiotic trichogin GA IV (**24**, Scheme 6) on the Pip-linker. In a first step H-Leu-OMe was anchored, by BOP/DIEA coupling. The effectiveness of the coupling reaction was verified by using a malachite green colorimetric test. Reduction of the ester function by lithium borohydride led to the aminoalcohol derivative **22**. The free hydroxyl function was then acylated with Fmoc-Ile-OH in the presence of DIC/DMAP. As already mentioned, no epimerization was detected in the DIC/DMAP acylation.[23] Standard SPPS afforded the corresponding isopeptide as a TFA salt,



Scheme 6. Synthesis of trichogin IV using Pip support. DIC = diisopropylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

after TFA/TIS/H_2O cleavage. Peptide alcohol **24** was then obtained through an intramolecular O–N acyl transfer, after alkaline treatment (DMF/piperidine 80:20 v/v). The trichogin GA IV was isolated in 47% overall yield and 78% purity.

In conclusion, we have demonstrated that the Pip-linker could be regarded as a versatile handle for the synthesis of modified amino acids (a vinylogous γ-amino acid and an N-monosubstituted urea derivative), pseudopeptides (an ureidodipeptide and two functionalized C-terminal peptides). The Pip-linker was also efficient to access cyclic peptides, through side-chain anchoring of a lysine residue. Introduction of the first residue was easily accomplished by simple BOP/DIEA activation and the Pip-linker revealed to be robust enough to support various chemical modifications. Finally, the Pip-linker proved its usefulness for the synthesis of peptide alcohols through the O–N acyl transfer reaction.

Experimental Section

Synthesis of γ-vinylogous phenylalanine (4): The Weinreb amide of *N*-Boc phenylalanine was prepared in solution, as previously described.[13] This compound (72 mg, 0.23 mmol) was stirred at room temperature in a mixture of TFA/CH_2Cl_2 (2.5 mL, 4:1 v/v) for 1 h and then evaporated under reduced pressure, to offer the deprotected Weinreb amide of phenylalanine as a TFA salt. The Pip-AM-PS resin (**1**, 200 mg, 0.08 mmol, 0.40 mmol g^{-1}) was left in DMF for 15 min to swell. DMF (6 mL) containing BOP (106 mg, 0.24 mmol, 3 equiv), DIEA (93 mg, 125 μL, 0.72 mmol, 9 equiv) was added, along with the deprotected Weinreb amide of phenylalanine previously synthesized (0.23 mmol, 3 equiv). The resin was gently stirred for 3 h and then washed with DMF (3x), MeOH (2x), CH_2Cl_2 (3x), to give resin **2**. The Weinreb amide was reduced in dry THF at 0 °C with 30 mg of $AlLiH_4$ (0.79 mmol, 10 equiv) for 1 h. The reaction mixture was then hydrolyzed with a $KHSO_4$ solution (1 M). After filtration, the resin was washed successively with a saturated $NaHCO_3$ solution, water, MeOH, and CH_2Cl_2. A solution of carboethoxymethylene triphenylphosphine in dry DMF (5 mL) was then added. The suspension was stirred at 80 °C for 3 h. After cooling to room temperature and filtration, the resin was washed with DMF (3x), MeOH (2x), and CH_2Cl_2 (3x). After TFA-cleavage for 2 h under gentle stirring, the resin was filtered off and the TFA solution was concentrated to dryness to offer 24 mg of compound **4** (yield 91%, purity 95%). NMR data are in agreement with the literature.[24] R_t = 0.95 min; MS (ESI$^+$): *m*/*z*: 220.3 $[M+H]^+$.

Synthesis of ureidopeptides 11 and 12: After the Pip-PS resin (**1**, 100 mg, 0.045 mmol, 0.45 mmol g^{-1}) had been left to swell in DMF for 15 min, it was added to DMF (6 mL) containing BOP (60 mg, 0.14 mmol, 3 equiv), DIEA (52 mg, 70 μL, 0.40 mmol, 9 equiv) and H-Leu-NH_2 (18 mg, 0.14 mmol, 3 equiv) or H-β-AlaNH_2 (12 mg, 0.14 mmol, 3 equiv). The resin was gently stirred for 2 h and then washed with DMF (3x), MeOH (2x), CH_2Cl_2 (3x), and dried. The resin was then treated with a dry THF solution (5 mL) containing pyridine (40 μL, 39 mg, 0.49 mmol, 11 equiv) and BTIB (58 mg, 0.13 mmol, 3 equiv) and stirred for 1 h. Then the resin was filtered off and a mixture of H-Phe-OMe·HCl (29 mg, 0.13 mmol, 3 equiv), DIEA (17 mg, 24 μL, 0.13 mmol, 3 equiv) in dry THF (3 mL) was added. The resin was gently stirred for overnight and subsequently washed with DMF (3x), MeOH (2x), CH_2Cl_2 (3x). After TFA-cleavage for 2 h under gentle stirring, the resin was filtered off and the TFA solution was concentrated to dryness to offer compound **11** (6 mg, yield 99%, purity 91%) or compound **12** (15 mg, yield 92%, purity 83%). For NMR analysis, crude compounds **11** and **12** were purified by preparative HPLC to offer pure compounds as TFA salts.

*Compound **11***: ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.95 (m, 2H), 3.61 (s, 3H), 4.39 (d, J = 7.1 Hz, 1H), 6.30 (d, J = 7.1 Hz, 1H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 37.6, 51.6, 53.8, 126.5, 128.2, 129.1, 137.1, 157.9, 173.0 ppm; R_t = 1.09 min; MS (ESI$^+$): *m*/*z*: 223.1 $[M+H]^+$.

*Compound **12***: ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.79 (m, 2H), 2.94 (m, 2H), 3.17 (m, 2H), 3.59 (s, 3H), 4.39 (dd, J = 7.1, 8.1 Hz, 1H), 6.37 (br s, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.17–7.32 (m, 5H), 7.72 ppm (br s, 2H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 37.4, 37.5, 51.7, 54.3, 126.6, 128.2, 129.1, 137.0, 157.9, 172.9 ppm; R_t = 0.82 min; MS (ESI$^+$): *m*/*z*: 266.1 $[M+H]^+$.

Lysine side-chain anchoring on Pip-PS resin: After the Pip-PS resin (**1**, 200 mg, 0.09 mmol, 0.45 mmol g^{-1}) had been left to swell in DMF for 15 min, it was added to DMF (6 mL) containing BOP (120 mg, 0.27 mmol, 3 equiv), DIEA (105 mg, 141 μL, 0.81 mmol, 9 equiv), and Fmoc-Lys-OAll[18] (110 mg, 0.27 mmol, 3 equiv). The resin was gently stirred for 2 h and then washed with DMF (3x), MeOH (2x), CH_2Cl_2 (3x) and dried.

All other synthetic procedures, as well as characterization of the products (LC/MS, NMR spectroscopy analysis) are available in the Supporting Information.

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Keywords: C-terminal peptide alcohols · cyclic peptides · pipecolic linker · solid-phase synthesis · ureidopeptides

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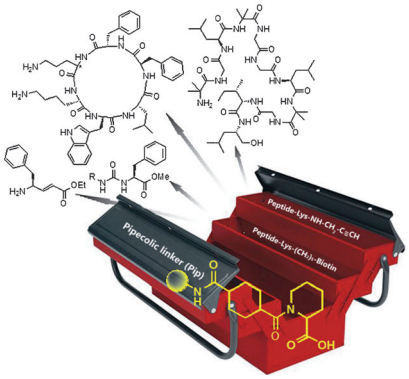
Solid-Phase Synthesis

N. Masurier, P. Zajdel, P. Verdié, M. Pawłowski, M. Amblard, J. Martinez, G. Subra* ..... ▮▮▮▮–▮▮▮▮

A New Highly Versatile Handle for Chemistry on a Solid Support: The Pipecolic Linker



The versatility of the pipecolic linker (Pip-linker) is illustrated by the synthesis of modified amino acids, C-terminal-modified pseudopeptides, and cyclic peptides, through side-chain anchoring of a lysine residue (see figure). Introduction of the first residue was easily accomplished and the Pip-linker revealed to be robust enough to support various chemical modifications.