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Brief Communication

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Silyl-Based Alkyne-Modifying Linker for the Preparation of C-Terminal Acetylene-Derivatized Protected Peptides

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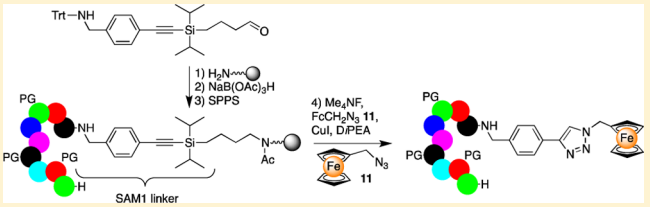
Supporting Information

ABSTRACT: A novel linker for the synthesis of C-terminal acetylene-functionalized protected peptides is described. This SAM1 linker is applied in the manual Fmoc-based solid-phase peptide synthesis of Leu-enkephalin and in microwave-assisted automated synthesis of Maculatin 2.1, an antibacterial peptide that contains 18 amino acid residues. For the cleavage, treatment with tetramethylammonium fluoride results in protected acetylene-derivatized peptides. Alternatively, a one-pot cleavage-click procedure affords the protected 1,2,3-triazole conjugate in high yields after purification.



Since the dawn of solid-phase peptide synthesis (SPPS), this preferred method for preparing peptides significantly contributed to the identification of the role of peptides in numerous diseases.[1] Of these, a prominent class that is gaining momentum is the antibacterial and anticancer peptides,[2,3] which often need a free N-terminal amino group for their activity.[4] Together with the increasing number of bioactive peptides known, sophisticated techniques for conjugated peptides have become available.[5] Just over a decade ago, Meldal et al. reported a DiPEA-assisted Cu(I)-catalyzed version of Huisgen's alkyne–azide cycloaddition reaction that was compatible with standard SPPS procedures and selectively provided the 1,4-regioisomer of the 1,2,3-triazole.[6] Together with a solution-phase version discovered by Sharpless et al.,[7] this became known as the copper-catalyzed alkyne–azide cycloaddition (abbreviated as CuAAC) reaction[8] and is now applied across the chemical landscape.[9] Importantly, click reactions compatible with biological systems[10] and a ruthenium-based method that affords the 1,5-regioisomer of the 1,2,3-triazole have become available.[11]

At this moment, many methods are available for the introduction of specific reactive functionalities for bioconjugation strategies.[12] Within the spectrum of available strategies, the alkyne is among the most popular functionalities due to its inertness under many conditions. Among the methods that are currently available to introduce the alkyne and azide moieties—for which incorporation of artificial amino acid residues[13] or N-terminal acylation of peptides with azido- or acetylene-containing moieties are the most straightforward methods—a diazo transfer reaction on the N-terminal amino group of a resin-bound peptide[14] and modified BAL linkers are applicable.[15] Concerning the latter, formation of side products during the on-resin reductive amination and acylation of the resulting secondary amine have been reported.[16] Whereas silyl protection has proven to be very useful in acetylene chemistry, a linker based on this principle and that is compatible with peptide chemistry has not been described.[17] Therefore, we designed a silyl-protected acetylene-based linker that is compatible with standard and microwave-assisted SPPS procedures, which upon cleavage with fluoride anions affords an acetylene moiety on the C-terminal amide of protected peptides. In addition, it is also compatible with a one-pot cleavage-click procedure, affording the 1,2,3-triazole conjugate in high yields.

For the synthesis of the linker, we used commercially available (3-cyanopropyl)diisopropylchlorosilane **1** and 4-iodobenzylamine hydrochloride **2**. The bulky isopropyl groups on the silicon atom were chosen in order to ensure stability of the linker during SPPS procedures. For the preparation of the silyl-protected acetylene moiety, chlorosilane **1** was reacted with ethynylmagnesium bromide **3** to give 4-(ethynyldiisopropylsilyl)butanenitrile **4** in high yields (Scheme 1).[18] The other part of the linker was prepared using 4-iodobenzylamine **2**, which was protected with the trityl (Tr) group, providing Tr-protected 4-iodobenzylamine **5**. After this, benzylamine **5** and silyl-protected acetylene **4** were coupled using the Sonogashira cross-coupling reaction,[19] which gave Tr-protected cyano-functionalized silyl alkyne **6**. Reduction of the nitrile group with DiBAL-H gave the target aldehyde **7** in good yields with an overall yield from chlorosilane **1** to SAM linker **7** of 44%. This first generation of the silyl-based alkyne-modifying linkers is called the SAM1 linker.

Compatibility of SAM1 linker **7** with SPPS was initially assessed by preparing Leu-enkephalin **10** using standard SPPS procedures under ambient conditions. For this, TentaGel HL NH_2 resin (loading: 0.55 mmol/g) was loaded using 1 equiv of the SAM1 linker in the reductive amination reaction. After Tr removal of SAM1-loaded resin **8** and coupling of the first amino

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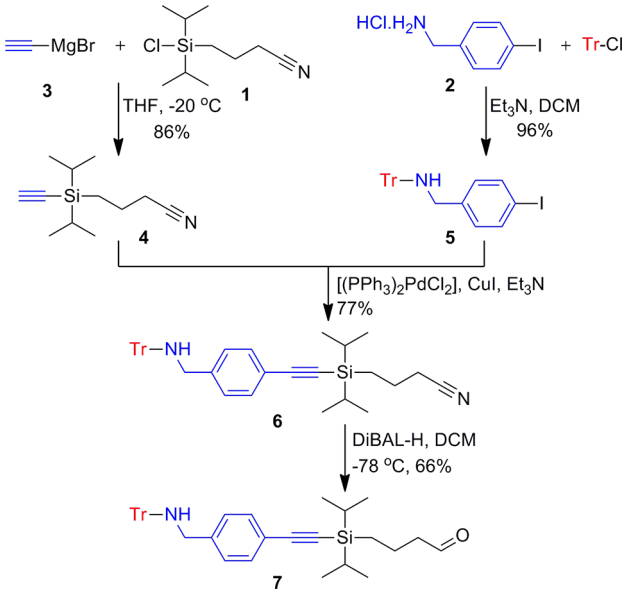
Scheme 1. Synthesis of SAM1 Linker 7

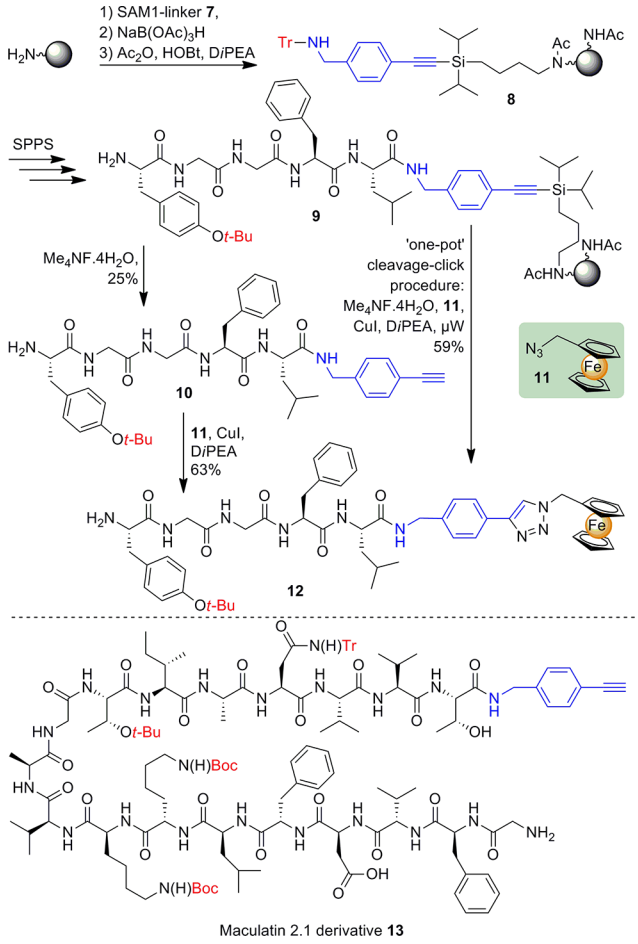


acid (Fmoc-Leu-OH) to the H_2N-SAM1-TentaGel resin, Fmoc determination revealed that a loading of 0.36 mmol/g was achieved. Although five steps preceded this Fmoc loading determination—the imine forming immobilization of the linker, imine reduction using $NaB(OAc)_3H$, acetylation of reactive amino functionalities, trityl removal, and coupling of Fmoc-Leu-OH—a yield of 67% for loading of the resin with the SAM1 linker can be assumed since the last three steps usually proceed quantitatively. Fmoc loading determination during the synthesis indicated that the SAM1 linker was stable during the Fmoc-based SPPS procedures (see Supporting Information). After completion of the synthesis, Leu-enkephalin **10** was cleaved from 100 mg of resin using tetramethylammonium fluoride (Me_4NF), resulting in 18.1 mg (87%) of crude material. Cleavage with TFA results in hydration of the arylacetylene moiety.[20] According to HPLC analysis, the crude peptide was 72% pure, and subsequent purification by HPLC gave pure peptide **10** in 25% yield. Importantly, no Me_4N ions were shown by ^1H NMR analysis of this sample (see Supporting Information).

Applicability of the generated arylacetylene-derivatized peptide in the CuAAC reaction was assessed by conjugation of peptide **10** to azidomethylferrocene **11** (Scheme 2).[21] Using 2.3 equiv of azide **11** and conditions that were described by Meldal et al.,[6] complete consumption of the peptide was obtained under formation of a species for which the HRMS *m*/*z* value and isotope pattern correspond to the expected 1,2,3-triazole-linked conjugate **12** (see Supporting Information). Purification afforded a yield of 63%, which results in a yield of only 16% over two reaction steps. However, a one-pot cleavage-click procedure using Me_4NF, azide **11**, CuI, and D*i*PEA in MeOH under 20 min of microwave-assisted heating to 60 °C provided a yield of 59% of the desired click product (**12**) after purification.[22]

Lastly, we assessed the applicability of the SAM1 linker in automated microwave-assisted SPPS by preparing a peptide of intermediate length (i.e., 18 amino acid residues). For this, we prepared derivative **13** (Scheme 2 for the structure) of the antibacterial Maculatin 2.1 peptide,[23] a C-terminally amidated peptide with the sequence H-GFVDFLKKVAGTIANVVT-

Scheme 2. Solid-Phase Peptide Synthesis of Leu-Enkephalin 9 Using SAM1 Linker 7 and Its CuAAC Conjugation to Azidomethylferrocene 11 (Structure of the Maculatin Derivative 13 Is Also Shown)



NH_2. This peptide allowed us to assess if the integrity of the protecting groups in this peptide is maintained during the course of the synthesis. Using Fmoc-Thr-SAM1-TentaGel, automated synthesis of the protected peptide was performed. The Fmoc loading of the resin before and after the automated synthesis dropped marginally, that is, from 0.14 to 0.13 mmol/g, indicating that the SAM1 linker is applicable in microwave-assisted SPPS of long peptides. Cleavage of the peptide was affected using an excess of Me_4NF dissolved in 9:1 DMF/MeOH (v/v) under heating of the sample to 60 °C in a microwave (20 min). HPLC analysis revealed that the crude peptide was ~80% pure, and HRMS analysis confirmed formation of the 18-meric peptide (see Supporting Information). Interestingly, the *m*/*z* value of the obtained product corresponds to the mass of the desired peptide lacking one *t*Bu group. We assume that ester hydrolysis of the aspartic acid side-chain *tert*-butyl ester takes place under the alkaline conditions of the cleavage reaction.

In conclusion, we have developed a new linker that is compatible with standard and microwave-assisted Fmoc/*t*-Bu-based solid-phase peptide synthesis. When treated with Me_4NF, peptides are released, having a C-terminal amide that is alkylated with an arylacetylene moiety. Alternatively, a one-pot cleavage-click procedure can be applied in which the 1,2,3-triazole-linked conjugate of the protected peptide is obtained in

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high yields. The linker can be used for the synthesis of peptides of intermediate length, as was shown by the synthesis of 18-meric Maculatin 2.1 derivative **13**. We anticipate that silyl-based alkyne-modifying (SAM) linkers will find widespread applications in the preparation of C-terminally labeled peptides and peptide conjugates.

EXPERIMENTAL SECTION

General Experimental Details. All reagents were obtained from commercial sources and used without purification. Solvents were dried according to standard protocols, distilled, and stored over molecular sieves (4 Å). For the Sonogashira reaction, *trans*-dichlorobis(triphenylphosphine)palladium(II), Premion (Alfa Aesar) was used. TLC analysis was performed on silica gel 60 F_{254} aluminum sheets, and spots were visualized by UV light. Kaiser tests[24] on the resin-bound material were carried out with a mixture of ninhydrin (1 g) in *t*-BuOH/H_2O/AcOH (95:4.5:0.5, % v/v/v, V_{tot} = 500 mL). Elemental analysis was performed in CHN mode. FT-IR spectroscopy was carried out on a spectrophotometer equipped with an attenuated total reflection (ATR) unit at 4 cm^{-1} resolution; abbreviations are s (strong), m (medium), and w (weak). ^1H NMR spectroscopy was performed in deuterated solvents at 30 °C. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, and the solvent residual signal is used as a reference. Abbreviations for peak multiplicities are s (singlet), d (doublet), t (triplet), dt (doublet of triplets), m (multiplet), and br (broad). Mass spectra were measured using an electrospray ionization (ESI) or electron impact (EI) mass spectrometer. Details for the spectrometers and methods that were used for HRMS analysis are given in the Supporting Information. Analytical HPLC was performed on an automated HPLC system using a C_{18}-AQ RP column (250 × 4.6 mm) at a flow-rate of 1 mL/min. A linear gradient of 5% buffer B per min starting at 5 min of buffer A (A: H_2O/MeCN/TFA, 95:5:0.1, v/v/v; B: MeCN/H_2O/TFA, 95:5:0.1, v/v/v) was used. Purification of the peptides was performed on an HPLC machine equipped with PDA detector that was coupled to an RP-18e reversed phase column (250 × 25 mm), using a similar gradient as for the analytical HPLC but with a flow rate of 20 mL/min.

4-(Ethynyldiisopropylsilyl)butanenitrile 4. This compound was prepared according to a literature procedure.[19] The obtained material was analyzed using TLC, ^1H NMR, ^{13}C NMR, IR, and EI-MS.

***N*-(Triphenylmethyl)-4-iodobenzylamine 5.** A mixture of 4-iodobenzylamine hydrochloride **2** (1 g, 3.7 mmol) and Et_3N (1.28 mL, 9.25 mmol) in DCM (15 mL) was prepared and to this triphenylmethylchloride (1.14 g, 4.08 mmol) was added in portions. The mixture was allowed to stir at rt overnight. Subsequently, water (20 mL) was added to the reaction mixture, the organic layer was separated, and remaining organic material present in the water phase was extracted using DCM (2 × 25 mL). The organic phases were combined and washed with brine (15 mL), dried over $MgSO_4$, and after filtration, the solvent was removed by rotary evaporation under reduced pressure. Column chromatography over silica with 9:1 hexanes/ethyl acetate (v/v) as eluent yielded product **5** as a white solid (1.695 g, 96%): R_f = 0.47 (silica; eluent, 9:1 hexanes/ethyl acetate (v/v)); mp 159.6−160.7 °C; IR (ATR) 3299 (s), 3057 (s), 2849 (s), 1596 (s) cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 7.74−7.43 (m, 8H), 7.41−7.08 (m, 11H), 3.28 (d, J = 7.3 Hz, 2H), 1.91 (t, J = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, CD_2Cl_2) δ 146.6, 141.5, 137.9, 130.5, 129.2, 128.5, 127.0, 92.3, 71.6, 47.9; MS (EI^+) m/z = 476.2 (calcd 476.1 for $[M + H]^+$). Anal. Calcd for $C_{26}H_{22}IN$: C, 65.69; H, 4.66; N, 2.95. Found: C, 65.90; H, 4.63; N, 2.78.

***N*-(Trityl)-4-(2-(3-cyanopropyl)diisopropylsilylethynyl)-benzylamine 6.** A solution of 4-(ethynyldiisopropylsilyl)butanenitrile **4** (655.4 mg, 3.16 mmol) and *N*-(triphenylmethyl)-4-iodobenzylamine **5** (1 g, 2.1 mmol) in THF/NEt_3 (3:1, v/v, V_{tot} = 32 mL) was prepared and degassed thoroughly. Then, copper(I) iodide (40 mg, 0.21 mmol) and bis(triphenylphosphine)palladium(II) chloride (36.8 mg, 0.05 mmol) were added, and the yellowish solution was again thoroughly degassed. The reaction mixture was allowed to stir at room temperature for 2 h, after which it was diluted with Et_2O (30 mL). This solution was washed with water (25 mL) and brine (15 mL), dried over $MgSO_4$, and after filtration, the solvent was removed by rotary evaporation. Column chromatography over silica using an eluent of 95:5 hexanes/ethyl acetate (v/v) yielded product **6** as colorless oil which solidified slowly (896.3 mg, 77%): R_f = 0.43 (silica; eluent, 4:1 hexanes/ethyl acetate (v/v)); mp 92.3−93.2 °C; IR (ATR) 3316 (m), 3058 (m), 2942 (s), 2863 (s), 2243 (m), 2151 (s), 1596 (s) cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 7.73−7.03 (m, 19H), 3.36 (s, br, 2H), 2.44 (t, J = 3.5 Hz, 2H), 2.03−1.77 (m, 3H), 1.24−1.01 (m, 14H), 0.94−0.79 (m, 2H); ^{13}C NMR (50 MHz, CD_2Cl_2) δ 146.6, 142.6, 132.5, 129.2, 128.5, 128.4, 127.0, 122.0, 120.4, 108.5, 89.7, 71.7, 48.3, 22.0, 21.2, 18.6, 18.4, 12.4, 10.2; MS (EI^+) m/z = 577.4 (calcd 577.3 for $[M + Na]^+$). Anal. Calcd for $C_{38}H_{42}N_2Si$: C, 82.26; H, 7.63; N, 5.05. Found: C, 82.54; H, 7.65; N, 5.10.

***N*-(Trityl)-4-(2-(3-formylpropyl)diisopropylsilylethynyl)-benzylamine 7.** Nitrile **6** (720.6 mg, 1.3 mmol) was dissolved in dry DCM (20 mL) and cooled to −78 °C, after which 2.1 equiv of DiBAL-H (2.73 mL, 2.73 mmol, 1 M in *n*-hexane) was added dropwise. The solution was maintained at −78 °C for 2 h followed by cautious addition of 2-propanol (1 mL). Upon warming, an aqueous solution saturated with citric acid (8 mL) was added, and the mixture was allowed to reach rt within 1 h. The crude organic material was extracted with DCM (2 × 20 mL), after which the combined organic phases were washed with brine (15 mL) and dried over $MgSO_4$. Then, the drying agent was removed by filtration, and the filtrate was concentrated by rotary evaporation under reduced pressure. Column chromatography (silica) using an eluent of 15:1 petroleum ether (40−60)/ethyl acetate (v/v) yielded product **7** as colorless oil (476.0 mg, 66%): R_f = 0.26 (silica; eluent, 7:1 hexanes/ethyl acetate (v/v)); IR (ATR) 3329 (w), 3057, 3029 (m), 2940, 2863 (s), 2152 (s), 1725 (s), 1595, 1505 (m) cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 9.75 (t, J = 1.9 Hz, 1H), 7.62−7.12 (m, 19H), 3.33 (s, br, 2H), 2.51 (dt, J = 7.1 Hz, 1.8 Hz, 2H), 1.93−1.73 (m, 3H), 1.22−0.95 (m, 14H), 0.80−0.65 (m, 2H); ^{13}C NMR (50 MHz, CD_2Cl_2) δ 203.2, 146.6, 142.4, 132.5, 129.2, 128.5, 128.4, 127.0, 122.2, 108.0, 90.3, 71.7, 48.3, 48.0, 18.6, 18.4, 12.4, 10.5; HRMS (ESI^+) m/z = 558.3184 (calcd 558.3187 for $[M + H]^+$, M = $C_{38}H_{43}NOSi$).

Loading of the Resin with SAM1 Linker 7 To Provide SAM1-Loaded Resin 8. For the attachment of the SAM1 linker to the resin, 1 equiv of aldehyde **7** (307 mg, 0.55 mmol) was dissolved in dry THF (5 mL) and the solution was added to the TentaGel HL NH_2 resin (1 g, 0.55 mmol, loading = 0.55 mmol/g). The mixture was agitated at rt for 2 h, after which 1.2 equiv of $NaB(OAc)_3H$ (140 mg, 0.66 mmol) was added (overnight, rt). After this, the reagents were removed and the resin was washed with THF (5 × 6 mL × 2 min), DMF (5 × 6 mL × 2 min), and DCM (5 × 6 mL × 2 min). Immediately after this, all reactive amino groups were capped using a solution of Ac_2O (0.5 M), D*i*PEA (0.125 M), and HOBt (0.015 M) in NMP (rt, 2 × 6 mL × 10 min). Lastly, the resin was washed with NMP (5 × 6 mL × 2 min) and DCM (5 × 6 mL × 2 min). Infrared analysis showed the presence of a weak band at 2154 cm^{-1}, which can be assigned to the alkyne functionality (see Supporting Information).

SPPS of Leu-Enkephalin 10 Using the SAM1 Linker 7. Removal of the Tr group was affected using a solution of DCM/TFA/TIS (94:4:2, v/v/v) that was added to the resin followed by agitation at rt (2 × 6 mL × 10 min). The reagents were removed by filtration, and the resin was washed with DCM (5 × 6 mL × 2 min), 10% D*i*PEA in DCM (v/v, 1 × 6 mL × 2 min), and DCM (5 × 6 mL × 2 min). For coupling of the amino acid residues, a solution of the Fmoc-protected amino acid (4 equiv), HOBt (4 equiv), and HBTU (3.8 equiv) in DMF (6 mL) was prepared and preactivated with D*i*PEA (10 equiv) shortly before the solution was added to the resin. Coupling was performed under agitation (rt, 2 h). The chemicals were removed by filtration, and the resin was washed with DMF (3 × 6 mL × 2 min) and DCM (2 × 6 mL × 2 min). Removal of the Fmoc group was affected using a solution of 20% piperidine in NMP (2 × 6 mL × 10 min). The resin was gently agitated (rt, 10 min), after which the chemicals were removed by filtration and the resin was washed with DMF (3 × 6 mL × 2 min) and DCM (2 × 6 mL × 2 min). Lastly, peptide-bound resin (100 mg, 28.7 μmol) was treated once with a

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solution containing excess Me_4NF (9.1 mg, 55 μmol) in DMF/MeOH (9:1, 1 mL, v/v) for 30 min. The solution was separated from the resin by filtration, and the latter was washed with DMF (3 × 0.5 mL × 2 min). After combining the organic phases, the solvents were removed in vacuo (T < 40 °C) and the solid material was lyophilized from H_2O/MeCN (1:1, v/v) to give acetylene-functionalized peptide **10** with a crude yield of 18.1 mg with 72% purity according to HPLC. Preparative HPLC yielded 6.1 mg (7.3 μmol, 25%) of pure peptide **10**: HPLC (C_{18}) t_R = 21.4 min; MS (ESI$^+$) m/z = 725.4 (calcd 725.4 for $[M + H]^+$); HRMS (ESI$^+$) m/z 725.4031 (calcd 725.4021 for $[M + H]^+$, M = $C_{41}H_{52}N_6O_6$). ^{1}H NMR, COSY, and TOCSY spectra of peptide **10** are available in the Supporting Information.

Azidomethylferrocene 11. This compound was prepared according to a literature procedure.[25] The obtained material was analyzed using TLC, HPLC, ^{1}H NMR, IR, and ESI-MS.

Solution-Phase Labeling of Leu-Enkephalin 12. A solution of Leu-enkephalin derivative **10** (0.99 mg, 1.18 μmol), D*i*PEA (0.48 μL, 2.76 μmol), and azidomethylferrocene **11** (0.67 mg, 2.76 μmol) in MeCN (1 mL) was prepared and degassed. Then, copper(I) iodide (0.13 mg, 0.69 μmol) was added, and the yellow solution was stirred at rt overnight. The crude reaction mixture was directly subjected to semipreparative HPLC, affording the desired product with a yield of 0.8 mg (0.74 μmol, 63%): UPLC-HRMS (ESI$^+$) t_R = 18.8−18.9 min; m/z = 966.4312 (calcd 966.4323 for $[M + H]^+$, M = $C_{52}H_{63}FeN_9O_6$).

Cleavage-Click Labeling of Leu-Enkephalin 9. In a reaction vessel, peptide-loaded resin **9** (75.2 mg, 21.5 μmol), TMAF·4H_2O (11.9 mg, 72 μmol), azidomethylferrocene **11** (8.7 mg, 36 μmol), D*i*PEA (1.5 μL, 9.6 μmol), and MeOH (0.7 mL) were mixed, and the suspension was degassed. Then, copper(I) iodide (0.91 mg, 4.8 μmol) was added, the vessel sealed, and the mixture heated to T_{max} = 60 °C (external surface sensor) under microwave irradiation for 20 min (in a CEM Discover microwave reactor). The resin was filtered, washed with MeCN (3 × 1 mL), and the solvents were removed in vacuo. Preparative HPLC yielded peptide **12** as yellowish solid (13.7 mg, 12.7 μmol, 59%): HPLC (C_{18}) t_R = 22.3 min; ESI-MS (ESI$^+$) m/z = 966.3 (calcd 966.4 for $[M + H]^+$). ^{1}H NMR, COSY, and TOCSY spectra of conjugate **12** are available in the Supporting Information.

Microwave-Assisted SPPS of Maculatin 2.1 Derivative 13. First, Fmoc-Thr-OH was coupled to the Tr-deprotected SAM1-TentaGel resin using the manual procedure described above (for the loading of Fmoc-Leu-OH). This resin was then subjected to microwave-assisted SPPS in which Fmoc deprotection is affected by two treatments of the resin with 20% piperidine in NMP and exposure of the reaction mixture to microwave irradiation with a power of 50 W for 180 s with a T_{max} of 75 °C. Coupling of Fmoc-protected amino acid residues is performed using a single treatment with 4 equiv of Fmoc-amino acid, 4 equiv of HOBt, 3.8 equiv of HBTU, and 10 equiv of D*i*PEA in DMF/NMP; the reaction mixture was exposed to microwave irradiation with a power of 24 W for 300 s with a T_{max} of 75 °C. All manipulations were performed using a sealed reaction vessel with internal temperature sensor in a CEM Discover microwave reactor. After completion of the automated synthesis program (approximately 14 h), the peptide-containing resin (13.2 mg, 1.1 μmol, contains approximately 3 mg peptide) and $Me_4NF·4H_2O$ (5.9 mg, 36 μmol) were mixed in DMF/MeOH (9:1, v/v, 1 mL) and the mixture was heated in a sealed reaction vessel under microwave irradiation (with T_{max} = 60 °C, as measured with an external surface sensor) for 20 min (in a CEM Discover microwave reactor). The resin was filtered and washed with DMF (3 times 0.5 mL), after which the solvents of the combined organic phases were removed in vacuo (T < 40 °C). The obtained material was lyophilized from MeCN:H_2O (1:1, v/v, 15 mL) and yielded the crude product as white solid (6.4 mg). During the weighing process, the hygroscopic solid slowly increased in weight, and the given yield corresponds to the first value obtained. Since this material contains approximately 3.33 mg of ammonium salt that originates from the excess of Me_4NF used in the cleavage, it contains approximately 3.1 mg of peptide. Therefore, quantitative cleavage of the peptide from the resin can be assumed: HPLC (C_{18}) t_R = 22.5 min; HRMS (ESI$^+$) m/z = 1245.7078 (calcd 1245.7085 for $[M - t\text{Bu} + 2H]^{2+}$, M = $C_{130}H_{188}N_{22}O_{27}$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed procedures, NMR spectra of all new compounds, IR spectrum of the resin-bound SAM1 linker **8**, 2D NMR spectra of peptides **10** and **12**, UPLC-HR-MS analysis of ferrocene conjugate **12**, and the crude HPLC trace and HRMS analysis of peptide **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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