The Sonogashira Cross-Coupling Reaction of Alkenyl Chlorides with Aliphatic Acetylenes

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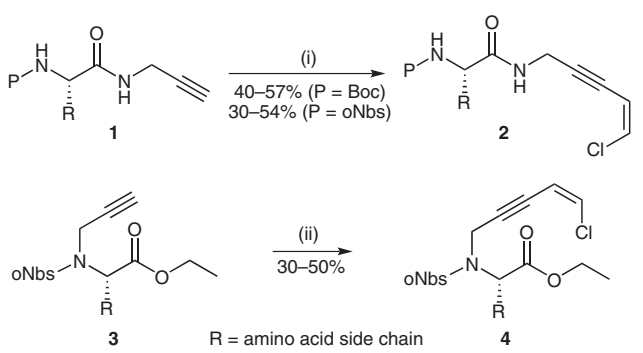
Abstract: The Sonogashira cross-coupling reaction between amino acid based alkenyl chlorides and aliphatic acetylenes is reported. The present approach can be used in natural product synthesis and as an alternative to usually more expensive and unstable vinyl-iodides.

Key words: acetylenes, alkenyl halides, Sonogashira cross-coupling , amino acids, enediynes

The Sonogashira reaction, first described in 1975, still represents one of the most valuable synthetic methods for the cross-coupling of sp^2-carbon halides and sp-carbon terminal acetylenes.[1] The majority of Sonogashira coupling reactions described in the literature involve one or both reactants to be aromatic compounds, which makes them relatively reactive partners in the cross-coupling reaction.[2] Nevertheless, different approaches have been examined, including variations in the catalyst system,[3] solvent,[4] and base,[5] indicating high interdependence of the Sonogashira reaction conditions and the nature of reactants involved.

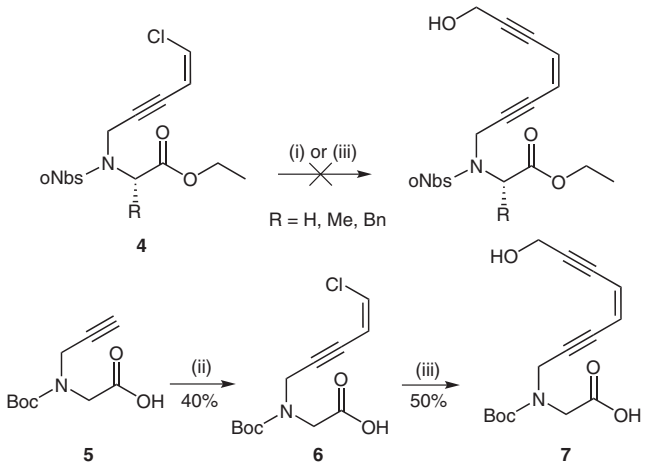
We have studied the Sonogashira reaction of amino acid derivatives as a crucial step in the synthesis of amino acid derived enediynes. Finding out optimal conditions for the coupling of aliphatic acetylenes with alkenyl chlorides, far less reactive than bromides and iodides,[6] was a challenging task. We have recently describe the synthesis and characterization of three types of the Sonogashira reaction products obtained from amino acid derived acetylenes (Scheme 1).[7]



Scheme 1 Our previous work. *Reagents and conditions*: (i) $(PhCN)_2PdCl_2$ (0.05 mmol), CuI (0.05 mmol), *cis*-ClCH=CHCl (1.00 mmol), $BuNH_2$ (1.00 mmol) in THF (1 mL), then **1** (0.5 mmol), $BuNH_2$ (1.00 mmol) in THF (2 mL); (ii) $(PhCN)_2PdCl_2$ (0.05 mmol), CuI (0.05 mmol), *cis*-ClCH=CHCl (1.00 mmol), $BuNH_2$ (1.00 mmol) in THF (1 mL), then **3** (0.5 mmol) in THF (2 mL).

In this context we decided to apply the described approach to even more demanding 'chemical cases' with the ultimate aim to decrease limitations of the Sonogashira reaction in respect of alkenyl chlorides and aliphatic reactants.

Our initial studies were undertaken on the cross-coupling reaction of chloroenyne-substituted amino acid derivatives **4** carrying the oNbs protecting group at the N-terminus with propargyl alcohol. Under the conditions applied to the synthesis of **4**, no traces of the desired enediyne compound were detected (Scheme 2). We then turned our attention back to Boc-protected N-substituted amino acid derivatives. The Sonogashira reaction of Boc-protected amino acids has been described; however, it involved coupling with different aryl and heteroaryl bromides[8,9] or 4-iodophenylalanine.[10] When coupled with *cis*-1,2-dichloroethene (*cis*-DCE), glycine derivative **5**[11] yielded 40% of the corresponding Sonogashira product **6**.[12] Contrary to our previous findings, optimization of reaction conditions required usage of piperidine instead of $BuNH_2$; 4 equivalents were mixed with Pd catalyst and CuI, while addition-



Scheme 2 *Reagents and conditions*: (i) $(PhCN)_2PdCl_2$ (0.05 mmol), CuI (0.05), $BuNH_2$ (1 mmol) and **4** (0.5 mmol) in THF (1 mL), then propargyl alcohol (1 mmol) in THF (1 mL); (ii) $(PhCN)_2PdCl_2$ (0.035 mmol), CuI (0.053 mmol), *cis*-ClCH=CHCl (0.70 mmol), piperidine (1.40 mmol) in THF (1 mL), then **5** (0.35 mmol) and piperidine (0.70 mmol) in THF (2 mL); (iii) $(PhCN)_2PdCl_2$ (0.011 mmol), CuI (0.041 mmol), **6** (0.164 mmol), piperidine (0.41 mmol) in THF (1 mL), then propargyl alcohol (0.328 mmol) in THF (1 mL).

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al 2 equivalents were added to the solution of acetylene component.

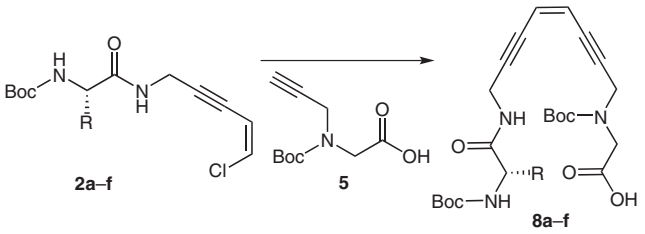
Further, chloroenyne derivative **6** was subjected to the cross-coupling reaction with propargyl alcohol and gave enediyne–amino acid conjugates **7** in 50% yield.[13] The Sonogashira coupling of **4** with propargyl alcohol, under the described reaction conditions again failed to give enediyne compound. It seems that the reactivity of N-propargylated amino acid derivatives is influenced by the nature of an additional group attached at the N-terminus (aromatic oNbs or aliphatic Boc). While oNbs-related N-propargylated derivatives gave the corresponding chloroenynes in fair yields with $BuNH_2$ as a base, Boc-related N-propargylated derivatives required piperidine as a stronger base. Also, oNbs-related chloroenynes turned out to be poorly reactive partners in the Sonogashira cross-coupling reaction with propargyl alcohol, while Boc-related chloroenyne derived from glycine gave the enediyne product in fair yield. Possible explanation can be sought in sterical factors and interaction between two electron-rich systems, aromatic (oNbs) and chloroenyne, which prevents efficient bounding to the catalyst and consequently coupling to another partner.

Encouraged by the obtained results, we decided to exploit the Sonogashira reaction for the synthesis of enediyne-bridged peptide motifs. In particular, we have published a general strategy comprising usage of amino acids carrying different protecting groups.[14] This approach is suitable when selective deprotection is required, however, its efficiency is highly dependent on the structure of amino acids. Alternatively, when single-step deprotection is an advantage, the presence of the Boc group can simplify the reaction procedure. Thus, we carried out a number of cross-coupling reactions between amino acid derived chloroenynes and N-propargylated amino acid (Table 1).

A cross-coupling reaction between chloroenynes derived from various amino acids (Tyr, Phe, Val, Gly, Ala, and Lys) and N-propargylated Boc-protected glycine derivative **5** was performed with $BuNH_2$ and piperidine as a base. As clearly seen from Table 1, considerably higher yields were obtained with piperidine. It was also found that 4 equivalents of piperidine added to acetylene component are essential for a successful coupling.[15]

Compounds **8a–f** were characterized by spectroscopic analysis, mass spectrometry, and HRMS. Optical purity was checked by acid hydrolysis (6 M HCl) at 105 °C for 24 hours and analysis on chiral plates for enantiomeric resolution by TLC. Purity was also checked by the RP HPLC under isocratic conditions (71.5% MeOH in 0.1% TFA, flow rate 0.5 mL/min). NMR spectra were recorded in CD_3OD and exhibit the presence of two conformers owing to the *cis–trans* isomerization of the tertiary peptide bond (Figure 1). Two sets of signals displayed both carbons and protons of the glycine residue and the enediyne moiety, with the approximate ratio 60:40 (Figure 1). Additionally, vinyl protons were found equivalent and present as a singlet at approximately δ = 5.88 ppm. MS/

Table 1 A Cross-Coupling Reaction between Chloroenynes **2a–f** and Glycine-Derived Acetylene **5**[a]



Compound	R	Yield (%)[b]	Yield (%)[c]
8a	$CH_2C_6H_4OBoc$	35	51
8b	Bn	30	58
8c	*i*-Pr	40	64
8d	H	15	37
8e	Me	30	77
8f	$(CH_2)_4NHBoc$	25	69

[a] *Reagents and conditions*: $(PhCN)_2PdCl_2$, (0.02 mmol), CuI (0.02 mmol), **2** (0.20 mmol), and base (0.40 mmol) in dry THF (1 mL), then solution of **5** (0.40 mmol) and base (0.80 mmol) in dry THF (2 mL).
[b] $BuNH_2$ was used as a base.
[c] Piperidine was used as a base.

MS spectra of compounds **8a–f** showed consecutive losses of 100 Da fragment originating from the cleavage of two or three Me_3COCO moieties. More interesting, all MS/MS spectra display relatively abundant ions arising from the combined loss of Me_3COCO and Me_3C moieties (156 Da).

Only a limited number of amino acid and peptide-related enediyne structures are reported in the literature,[16] though such conjugates show promising DNA cleavage abilities.[16c,d] In this respect, it is important to note that deprotected derivatives of enediyne-bridged dipeptide mimetics **8** showed a biologically relevant response in preliminary antimicrobial activity. Anticancer activity of these compounds is currently under investigation and will be published in due course.

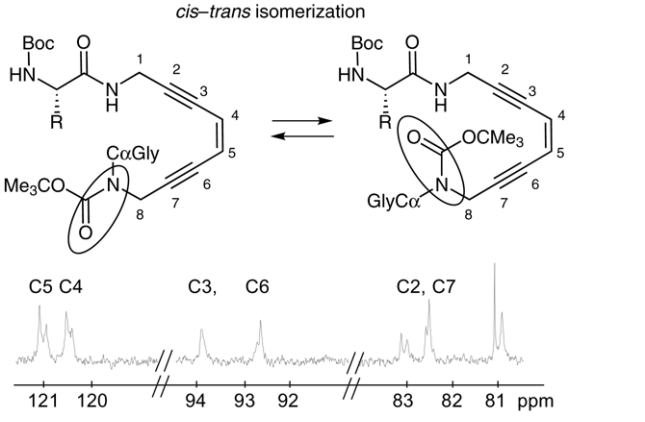


Figure 1 The *cis–trans* isomerization of **8b** (R = Bn) and enediyne part of the ^{13}C NMR spectrum

In summary, we have demonstrated that aliphatic amino acid derived acetylenes and chlorides can be successfully applied in the Sonogashira type of cross-coupling reactions. Although reactions must be performed under rigorous conditions and yields are lower than those obtained with aromatic substituents, the presented results encourage further utilization of the Sonogashira reaction. This is especially important for the synthesis of natural products, since many metabolites contain alkyne or enyne moieties.[17] Although aryl- and vinyl-chlorides have been rarely exploit so far, under defined reaction conditions they can be favorable alternatives to the usually more expansive and unstable aryl- and vinyl-iodides.

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(11) Boc-(prop-2-yne-1-yl)-Gly-OH (**5**) was prepared according to the procedure described in ref. 8. Yield 74%; yellow oil; R_f = 0.44 (toluene–EtOAc–AcOH, 10:2:0.5). ^{1}H NMR (300 MHz, $CDCl_3$, *trans* and *cis*): δ = 1.45, 1.49 (s, 9 H, CH_3 Boc), 2.28 (br t, 1 H, H3 propargyl), 4.17 (m, 4 H, H11′ propargyl, α Gly). ^{13}C NMR (75 MHz, $CDCl_3$, *trans* and *cis*): δ = 28.2 (CH_3 Boc), 36.6, 37.3 (C1 propargyl), 47.1 (α Gly), 72.7, 73.0 (C3 propargyl), 78.5 (C Boc), 81.4, 81.6 (C2 propargyl), 154.6, 154.8 (CO Boc), 175.3 (CO Gly). HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{10}H_{15}NNaO_4$: 236.0893; found: 236.0887.

(12) **Synthesis of Boc-[penta-5-chloro-4-(*Z*)-ene-2-yne-1-yl]-Gly-OH (6)**
A mixture of $Pd(Ph_3P)_4$ (12 mg, 0.035 mmol), CuI (12 mg, 0.053 mmol), *cis*-DCE (65 μL, 0.7 mmol), and piperidine (136 μL, 1.40 mmol) dissolved in dry THF (1 mL) was stirred for 30 min under argon. A solution of Boc-(prop-2-yne-1-yl)-Gly-OH (**5**, 75 mg, 0.35 mmol) and piperidine (68 μL, 0.70 mmol) in THF (2 mL) was added dropwise by the syringe, and the reaction was stirred at r.t. overnight. Solvent was evaporated, and the residue purified by flash chromatography. Yield 59% (56 mg); yellow oil; R_f = 0.54 (toluene–EtOAc–AcOH, 10:2:0.5). ^{1}H NMR (300 MHz, DMSO-d_6, *trans* and *cis*): δ = 1.36, 1.41 (s, 9 H, CH_3 Boc), 2.69 (s, 1 H, H3 chloroenyne), 3.91, 3.93 (br s, 2 H, α Gly), 4.26, 4.28 (H11′ chloroenyne), 6.19 (br td, 1 H, H4 chloroenyne), 6.79 (d, $^3J_{4,5}$ = 7.3 Hz, 1 H, H5 chloroenyne). ^{13}C NMR (75 MHz, DMSO-d_6, *trans* and *cis*): δ = 27.8, 27.9 (CH_3 Boc), 37.3, 38.03 (C1 chloroenyne), 47.4, 47.7 (α Gly), 77.6, 77.9 (C Boc), 79.9, 80.0 (C2 chloroenyne), 93.4, 93.5 (C3 chloroenyne), 112.0 (C4 chloroenyne), 129.1 (C5 chloroenyne), 154.6, 154.2 (CO Boc), 170.7 (CO Gly). HRMS (MALDI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}ClNNaO_4$: 296.0660; found: 296.0652.

(13) **Synthesis of Boc-[octa-8-hydroxy-2,6-diyne-4-(*Z*)-ene-1-yl]-Gly-OH (7)**
A mixture of $Pd(Ph_3P)_4$ (13 mg, 0.011mmol), CuI (10 mg, 0.041 mmol), Boc-[penta-5-chloro-4-(*Z*)-ene-2-yne-1-yl]-Gly-OH (**6**, 45 mg, 0.164 mmol), and piperidine (38 μL, 0.41 mmol) dissolved in dry THF (1 mL) was stirred for 30 min under argon. A solution of propargyl alcohol (20 μL, 0.328 mmol) in THF (1 mL) was added dropwise by the syringe, and the reaction was stirred at r.t. overnight. Solvent was evaporated and the residue purified by flash chromatography. Yield 67% (32 mg); yellow oil; R_f = 0.60 (EtOAc–toluene–AcOH, 10:5:0.5). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.37 (s, 9 H, CH_3 Boc), 3.94 (br s, 2 H, α Gly), 4.27 (br d, 4 H, H11′, H88′ enediyne), 6.00 (br td, 1 H, H4 enediyne), 6.04 (br td, 1 H, H5 enediyne). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.8 (CH_3 Boc), 37.2 (C1 enediyne), 47.4 (α Gly), 49.4 (C8 enediyne), 79.5 (C Boc), 79.8 (C2 enediyne), 81.3 (C7 enediyne), 92.4 (C3 enediyne), 97.5 (C6 enediyne), 119.0 (C4 enediyne), 120.1 (C5 enediyne), 154.2 (CO Boc), 170.8 (CO Gly). HRMS (MALDI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{19}NO_5$: 294.1336; found: 294.1322.

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(15) **General Procedure for the Synthesis of 8**

$(PhCN)_2PdCl_2$, (0.02 mmol), CuI (0.02 mmol), **2** (0.2 mmol), and piperidine (0.40 mmol) were dissolved in dry THF (1 mL), and the reaction was stirred for 30 min under argon. A solution of **5** (0.40 mmol) and piperidine (0.80 mmol) in 2 mL of dry THF was added dropwise by the syringe, and the reaction was stirred at r.t. until all acetylene was consumed. Solvent was evaporated and the residue purified by flash column chromatography.

Boc_2-Tyr-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl](Boc)-Gly-OH (8a)

Yield 51%; yellow oil; R_f = 0.64 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 11.54 min. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.37, 1.44, 1.48, 1.52 (s, 27 H, CH_3 Boc), 2.87, 3.08 (dd, $^3J_{\alpha,\beta}$ = 8.4 Hz, $^3J_{\alpha,\beta'}$ = 5.9 Hz, $^2J_{\beta,\beta'}$ = 13.5 Hz, 2 H, ββ′ Tyr), 4.12 (m, 5 H, α Tyr, α Gly, H88′ enediyne), 7.04 (d, $^3J_{\delta,\varepsilon}$ = 8.4 Hz, 2 H, ε Tyr), 4.35 (br d, 2 H, H11′ enediyne), 5.89 (s, 2 H, H4,5 enediyne), 7.26 (d, $^3J_{\delta,\varepsilon}$ = 8.4 Hz, 2 H, δ Tyr). ^{13}C NMR (75 MHz, CD_3OD, *trans* and *cis*): δ = 28.0, 28.6, 28.7, 28.8 (CH_3 NHBoc, OBoc), 30.5 (C1 enediyne), 38.6 (β Tyr), 38.9, 39.3 (C8 enediyne), 48.1 (α Gly), 57.4 (α Tyr), 80.9, 81.0, 84.4 (C Boc), 82.4, 82.5, 82.9, 83.00 (C2, C7 enediyne), 92.6, 92.7, 93.8, 93.9 (C3, C6 enediyne), 120.4, 120.5 (C4 enediyne), 120.9, 121.1 (C5 enediyne), 122.3 (ε Tyr), 131.6 (δ Tyr), 136.2 (γ Tyr), 151.6, 153.6 (CO Boc), 156.8, 157.7 (ζ Tyr), 173.2, 173.3 (CO Gly), 173.9 (CO Tyr). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{45}N_3NaO_{10}$: 678.2997; found: 678.2980.

Boc-Phe-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl](Boc)-Gly-OH (8b)

Yield 58%; yellow oil; R_f = 60 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 10.59 min. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.36, 1.44, 1.47 (s, 18 H, CH_3 Boc), 2.85, 3.08 (dd, $^3J_{\alpha,\beta}$ = 8.7 Hz, $^3J_{\alpha,\beta'}$ = 5.7 Hz, $^2J_{\beta,\beta'}$ = 13.5 Hz, 2 H, ββ Phe), 4.10 (m, 4 H, H88′ enediyne, α Gly), 4.27 (m, 1 H, α Phe), 4.35 (br d, 2 H, H11′ enediyne), 5.88 (s, 2 H, H4,5 enediyne), 7.22 (m, 5 H, arom. Phe). ^{13}C NMR (75 MHz, CD_3OD, *trans* and *cis*): δ = 28.6, 28.7, 28.8 (CH_3 Boc), 30.5 (C1 enediyne), 38.6, 39.2 (C8 enediyne), 39.5 (β Phe), 48.2 (α Gly), 57.4 (α Phe), 80.8, 81.0 (C Boc), 82.4, 82.5, 82.9, 83.0 (C2, C7 enediyne), 92.6, 92.7, 93.8, 93.9 (C3, C6 enediyne), 120.3, 120.4 (C4 enediyne), 120.9, 121.0 (C5 enediyne), 127.8 (ζ Phe), 129.5 (ε Phe), 130.6 (δ Phe), 138.5 (γ Phe), 156.8, 157.6 (CO Boc), 173.2 (CO Gly), 174.1 (CO Phe). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{37}N_3NaO_7$: 562.2523; found: 562.2509.

Boc-Val-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl](Boc)-Gly-OH (8c)

Yield 64%; yellow oil; R_f = 0.57 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 10.22 min. ^{1}H NMR (300 MHz, CD_3OD): δ = 0.94 (br t, 6H, γ Val), 1.44 (br s, 18 H, CH_3 Boc), 2.01 (s, 1 H, β Val), 3.85 (d, $^3J_{\alpha,\beta}$ = 6.9 Hz, 1 H, α Val), 4.14 (m, 4 H, H88′ enediyne, α Gly), 4.36 (br d, 2 H, H11′ enediyne), 5. 87 (s, 2 H, H4,5 enediyne). ^{13}C NMR (75 MHz, CD_3OD, *trans* and *cis*): δ = 18.7, 19.8 (γ Val), 28.6, 28.7, 28.8 (CH_3 Boc), 30.4 (C1 enediyne), 32.4 (β Val), 38.6, 39.2 (C8 enediyne), 48.1 (α Gly), 61.6 (α Val), 80.7, 80.9 (C, Boc), 82.4, 82.5, 82.8, 83.0, (C2, C6 enediyne), 92.5, 92.6, 93.9, 94.0 (C3, C7 enediyne), 120.3, 120.4 (C4 enediyne), 120.8, 120.9 (C5 enediyne), 156.8 (CO Boc), 173.3 (CO Gly), 174.4 (CO Val). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{37}N_3NaO_7$: 514.2524; found: 514.2537.

Boc-Gly-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl](Boc)-Gly-OH (8d)

Yield 37%; yellow oil; R_f = 0.27 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 9.14 min. ^{1}H NMR (600 MHz, CD_3OD): δ = 1.45 (s, 18 H, CH_3 Boc), 3.72 (br s, 2 H, α Gly^1), 4.09, 4.12 (br s, 2 H, H88′ enediyne), 4.20 (br s, 2 H, α Gly^2), 4.34, 4.36 (br s, 2 H, H11′ enediyne), 5.87 (s, 2 H, H4,5 enediyne). ^{13}C NMR (150 MHz, CD_3OD, *trans* and *cis*): δ = 28.6, 28.7, 28.8 (CH_3 Boc), 30.5 (C1 enediyne), 38.6, 39.3 (C8 enediyne), 44.7 (α Gly^1) 48.2 (α Gly^2), 80.9 (C Boc), 82.4, 82.5, 82.9 (C2, C7 enediyne), 92.6, 92.7, 94.0 (C3, C6 enediyne), 120.3, 120.4 (C4 enediyne), 120.8, 121.0 (C5 enediyne), 156.8, 157.7 (CO Boc), 172.4 (CO Gly^1), 173.4 (CO Gly^2). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{31}N_3NaO_7$: 472.2054; found: 472.2066.

Boc-Ala-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl](Boc)-Gly-OH (8e)

Yield 77%; yellow oil; R_f = 0.40 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 9.40 min. ^{1}H NMR (600 MHz, CD_3OD): δ = 1.30 (d, $^3J_{\alpha,\beta}$ = 7.2 Hz, 3 H, β Ala), 1.44 (s, 18 H, CH_3 Boc), 4.11 (m, 3 H, α Ala, α Gly), 4.18 (br d, 2 H, H88′ enediyne), 4.34 (br d, 2 H, H11′ enediyne), 5.88 (s, 2 H, H4,5 enediyne). ^{13}C NMR (150 MHz, CD_3OD, *trans* and *cis*): δ = 18.5 (δ Ala), 28.6, 28.7, 28.8 (CH_3 Boc), 30.6 (C1 enediyne), 38.6, 39.3 (C8 enediyne), 48.1 (α Gly), 51.7 (α Ala), 80.8, 80.9, 81.0 (C Boc), 82.4, 82.5, 83.0 (C2, C7 enediyne), 92.5, 94.0 (C3, C6 enediyne), 120.3, 120.4 (C4 enediyne), 120.9, 121.0 (C5 enediyne), 156.8, 157.7 (CO Boc), 173.3 (CO Gly), 175.7, 175.7 (CO, Ala). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_3N_3NaO_7$: 486.2211; found: 486.2233.

Boc-Lys(Boc)-*N*-[octa-2,6-diyne-4-(*Z*)-ene-1,8-diyl]-(Boc)-Gly-OH (8f)

Yield 69%; yellow oil; R_f = 0.24 (toluene–EtOAc–AcOH, 5:5:0.5); t_R = 10.07 min. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.43, 1.44 (br d, 31 H, CH_3 Boc, γγ′, δδ′ Lys), 1.75 (m, 2 H, ββ′ Lys), 3.03 (t, $^3J_{\delta,\varepsilon}$ = 6.6 Hz, 2 H, εε′ Lys), 3.99 (br d, 1 H, α Lys), 4.15 (m, 4 H, H88′ enediyne, α Gly), 4.35 (br d, 2 H, H11′ enediyne), 5.88 (s, 2 H, H4,5 enediyne). ^{13}C NMR (75 MHz, CD_3OD, *trans* and *cis*): δ = 24.3 (γ Lys), 28.6, 28.7, 28.9, 29.0 (CH_3 Boc), 30.6 (C1 enediyne), 30.7 (δ Lys), 33.2 (β Lys), 38.6, 39.3 (C8 enediyne), 41.2 (ε Lys), 48.1 (α Gly), 56.1 (α Lys), 80.0, 80.8, 81.0 (C Boc), 82.4, 82.5, 82.9, 83.0 (C2, C7 enediyne), 92.6, 92.7, 94.0 (C3, C6 enediyne), 120.4, 120.5 (C4 enediyne), 120.9, 121.0 (C5 enediyne), 156.7, 156.8, 158.0, 158.7 (CO Boc), 173.2, 173.3 (CO Gly), 175.1 (CO Lys). HRMS (MALDI): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{48}N_4NaO_9$: 643.3314; found: 643.3296.

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