Supporting Information

Microwave-Assisted Synthesis of Difficult Sequence Containing Peptide Using Isopeptide Method.

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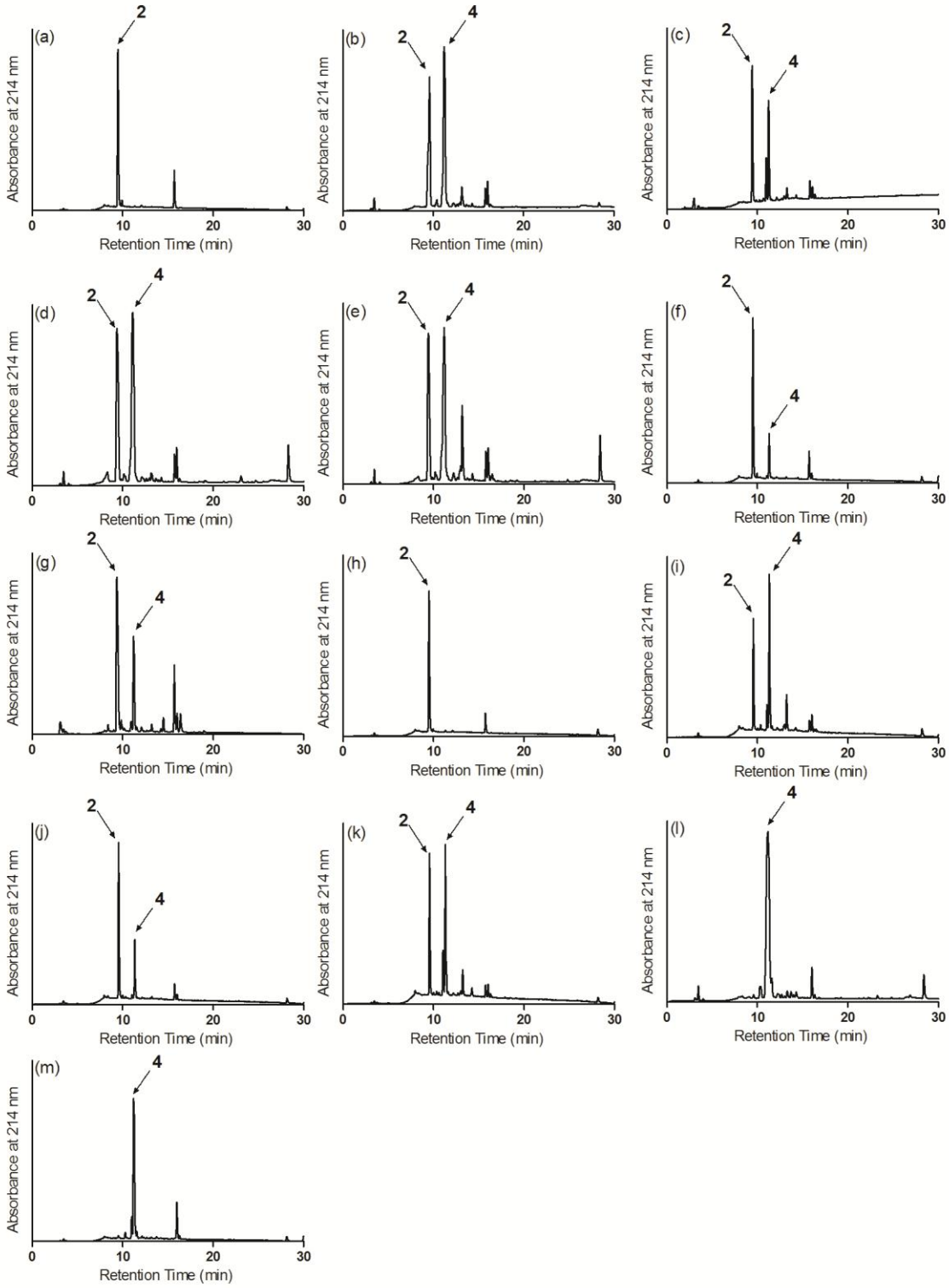

Figure S1. HPLC traces of crude product **4** obtained after coupling the isodipeptide unit (**1**) to peptide **2** on the resin under different coupling conditions. (a) The first 6 amino acids (**2**) synthesized by the microwave. HPLC signal of **2** was used as a reference to calculate the efficiency of the isodipeptide unit coupling. Coupling conditions of isodipeptide unit: (b) HATU/DIPEA at 50 °C (2 x 15 min); (c) HATU/DIPEA at RT (3 min) and at 50 °C (2 x 15 min); (d) HATU/DIPEA at 70 °C (2 x 10 min); (e) HATU/DIPEA at 70 °C (2 x 20 min); (f)

DIC/HOBT at 50 °C (2 x 15 min); (g) DIC/HOBT at 70 °C (2 x 10 min); (h) EEDQ at 70 °C (2 x 10 min); (i) PyBOP/DIPEA at 70 °C (2 x 10 min); (j) EDC/HOBT at 70 °C (2 x 10 min); (k) HBTU/HOBT/ DIPEA at 70 °C (2 x 10 min); (l) HATU/DIPEA at RT (2 x 2 h); (m) HATU/DIPEA at RT (1 x 30 min).

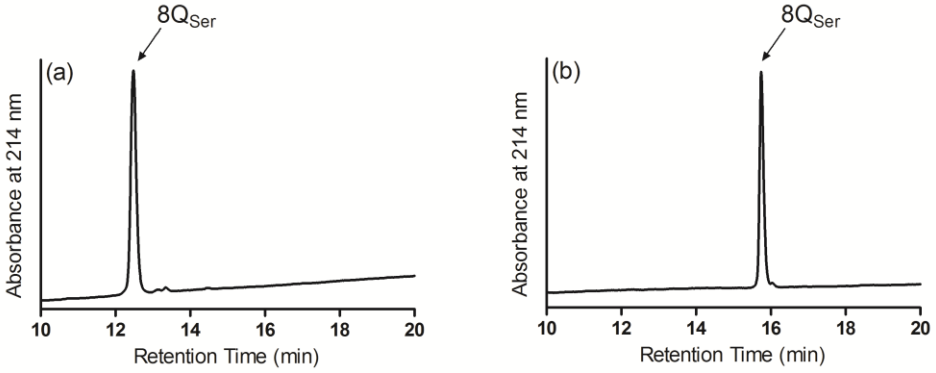

Figure S2. HPLC analysis of purified 8Q$_{Ser}$ carried out on (a) C4 column, purity > 98% and (b) C18 column, purity > 98%.

Table S1. Effect of 20% piperidine at 70 °C on the ester bond of the isodipeptide unit.

number of cycles[a]	HPLC Yield[b] of isopeptide **4** (%)
1	72
5	62
10	57
20	51

[a] One cycle is (1 x 2.5 min and 1 x 5 min) at 70 °C.
[b] HPLC Yield calculated based on the integration of the analytical HPLC signals.

Table S2. Comparison of the purity of the crude iso-8Q_{Ser} synthesized by using different methods.

method	conditions for the synthesis of iso-8Q_{Ser}	HPLC Yield[a] (%)
B	isopeptide method at RT	70
C	isopeptide method under microwave irradiation and 20% piperidine (1 x 2.5 min and 1 x 5 min at 70 °C) for removal of Fmoc	46
D	isopeptide method under microwave irradiation and 20% piperidine (1 x 1 min and 2 x 5 min at RT) for removal of Fmoc	71

[a] Yield calculated based on the integration of the analytical HPLC signals

Table S3. Comparison of the purity of the crude 8Q_{Ser} synthesized by using different methods.

method	conditions for the synthesis of 8Q_{Ser}	HPLC Yield[a] (%)
A	standard SPPS at RT	43
B	isopeptide method at RT	73
C	isopeptide method under microwave irradiation and 20% piperidine (1 x 2.5 min and 1 x 5 min at 70 °C) for removal of Fmoc	53
D	isopeptide method under microwave irradiation and 20% piperidine (1 x 1 min and 2 x 5 min at RT) for removal of Fmoc	73

[a] Yield calculated based on the integration of the analytical HPLC signals