Supplementary Material

Protecting group assisted structural diversity: β-sheet to rhombus-shaped structure of a short aromatic γ-peptide

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Scheme 1. Reactions and conditions: (a) Dry DCM, DCC, HOBt, 0°C, 48h.

Scheme 2. Reactions and conditions: (b) Dioxarane, Pd/C, H₂, RT, 6 hours then Ditertiarybutylpyrocarbonate and triethylamine, RT, another 6 hours.

Experimental

General methods and materials:
3-nitrobenzoic acid, 2-amino isobutyric acid, DCC (dicyclohexylcarbodiimide) and HOBt (N-hydroxybenzotriazole) were purchased from Sigma-aldrich.

Synthesis:
The dipeptide 1 was synthesized by conventional solution phase methodology using a racemization free fragment condensation strategy. The coupling reaction was done by using DCC (dicyclohexylcarbodiimide) and HOBt (N-hydroxybenzotriazole). The final compounds were fully characterized by 400 and 500 MHz ¹H NMR spectroscopy, ¹³C NMR spectroscopy, FT-IR spectroscopy and mass spectrometry.

Synthesis of Mnba-Aib-OMe 1:  3-Nitrobenzoic acid (0.84 g, 5 mmol) was dissolved in 20 mL dry DCM in an ice-water bath. H-Aib- OMe was isolated from 1.17 g (10 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and ethyl acetate extract was concentrated to 10 mL. It was then added to the
reaction mixture, followed by immediate addition of 1.44 g (7 mmol) dicyclohexyl carbodiimide (DCC) and 0.95 g (7 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stirred for 48 hrs. After that, DCM was evaporated and the residue was dissolved in ethyl acetate (60 mL) and dicyclohexyl urea (DCU) was filtered off. The organic layer was washed with 2 (M) HCl (3 ×50 mL), brine (2 × 50 mL), 1(M) sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate. The solution was evaporated under vacuum to obtain dipeptide 1 as a white solid. The product was purified by silica gel (60-120 mesh) using n- hexane-ethyl acetate (3:1) as eluent.

\[ \text{H NMR (500 MHz, CDCl}_3, \delta \text{ in ppm):} \] 8.59 [1H, s, Maba(1) CH], 8.33- 8.31 [1H, d, J=8Hz, Maba(1) CH], 8.11 8.03 [1H, d, J=8 Hz, Maba(1) CH], 7.64-7.67 [1H, m, Maba(1) CH], 7.11 [1H, s, Aib(2) NH], 3.86 [3H, s, OCH3], 1.71 [6H, s, Aib Cβ H],

\[ \text{13C NMR (125 MHz, CDCl}_3, \delta \text{ in ppm):} \] 175.17, 166.32, 152.67, 138.79, 135.27, 129.27, 128.47, 123.36, 55.81, 54.69, 26.77.


\text{FT-IR Spectra (in cm}^{-1}): 713, 1352, 1523, 1734, 3233.

\text{One-pot N-terminus modification:} 0.27 g (1 mmol) of peptide 1 was dissolved in dioxane (10 mL) and was treated with 120 mg of Pd/C. Hydrogen gas was supplied into the solution through balloon. The reaction mixture was stirred under hydrogen atmosphere for about 6 hours. The completion of the reduction was monitored by TLC. After the completion of the reaction, hydrogen gas was removed. Then, Ditertiarybutylpyrocarbonate (0.22 g, 1 mmol) and triethylamine (2 mL) were added into it and the stirring was continued at room temperature for another 6 h. The mixture was diluted with dioxane (25 mL) and it was filtered through sintered funnel using celite bed and celite bed was washed with dioxane (3x25 mL). Then, the solution was concentrated under vacuum to about 15-20 mL, cooled in an ice-water bath, covered with a layer of ethyl acetate (about 30 mL), and acidified with a dilute solution of KHSO4 to pH 2-3 (Congo red). The aqueous phase was extracted with ethyl acetate, and this operation was done repeatedly. The ethyl acetate extracts were pooled, washed with water, dried over anhydrous Na2SO4, and evaporated under vacuum to obtain the dipeptide 2 as a white solid. Purification was done on a silica gel column (100-200 mesh) using ethyl acetate: hexane (3:1) as the eluent. Yield: 0.25 g (7.5 mmol, 75%). Mp: 175-176ºC. (237.10): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.77; H, 6.34; N, 5.95;

\[ \text{H NMR (500 MHz, CDCl}_3, \delta \text{ in ppm):} \] 7.71 [1H, s, Maba(1) CH], 7.57-7.59 [1H, d, J=8 Hz, Maba(1) CH], 7.40-7.42 [1H, d, J=8 Hz, Maba(1) CH], 7.30-7.33 [1H, m, Maba(1) CH], 6.83 [1H, s, Aib(2) NH], 6.76 [1H, s, Maba(1) NH], 3.76 [3H, s, OCH3], 1.65 [6H, s, Aib Cβ H], 1.50 [9H, s, Boc CH3].

\[ \text{13C NMR (125 MHz, CDCl}_3, \delta \text{ in ppm):} \] 175.17, 166.32, 152.67, 138.79, 135.27, 129.27, 121.47, 121.36, 116.97, 80.78, 56.81, 52.69, 28.28, 24.77.


Figure S1. ^1H NMR Spectra (CDCl₃, 500 MHz, δ in ppm, 298 K) of peptide 1.

Figure S2. ^13C NMR Spectra (CDCl₃, 125 MHz, δ ppm, 298 K) of peptide 1.
**Figure S3.** Mass spectra of peptide 1.

**Figure S4.** FT-IR spectra of peptide 1.
Figure S5. $^1$H NMR Spectra (CDCl$_3$, 500 MHz, $\delta$ in ppm, 298 K) of peptide 2.

Figure S6. $^{13}$C NMR Spectra (CDCl$_3$, 125 MHz, $\delta$ in ppm, 298 K) of peptide 2.
Figure S7. Mass spectra of peptide 2.

Figure S8. FT-IR spectra of peptide 2.