Comparison of Backbone Modification in Protein β-Sheets by α→γ Residue Replacement and α-Residue Methylation

George A. Lengyel, Zachary E. Reinert, Bryan D. Griffith, and W. Seth Horne*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

SUPPORTING INFORMATION

Contents

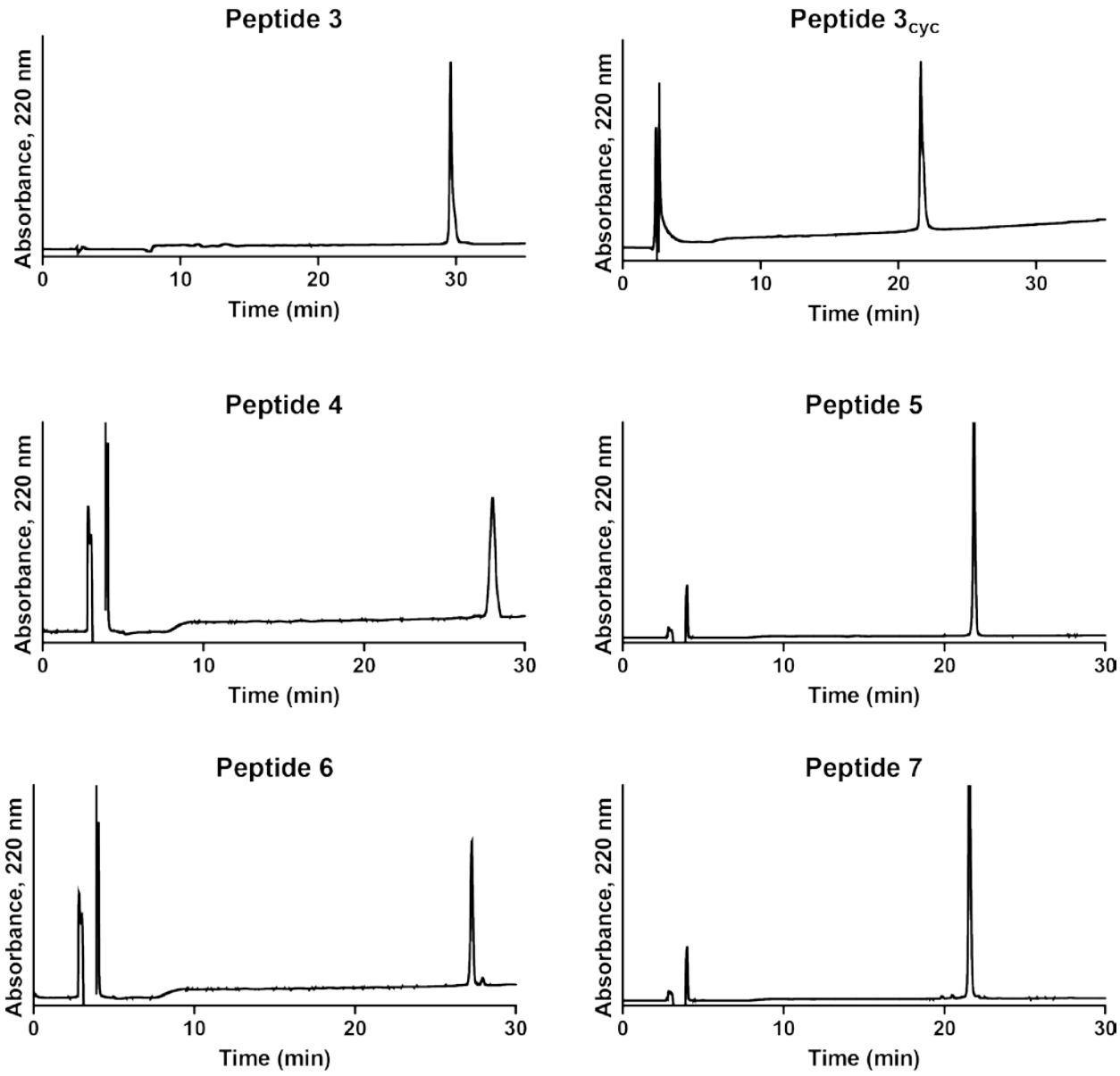


Figure S1. Analytical HPLC traces of peptides **3**-**7**.

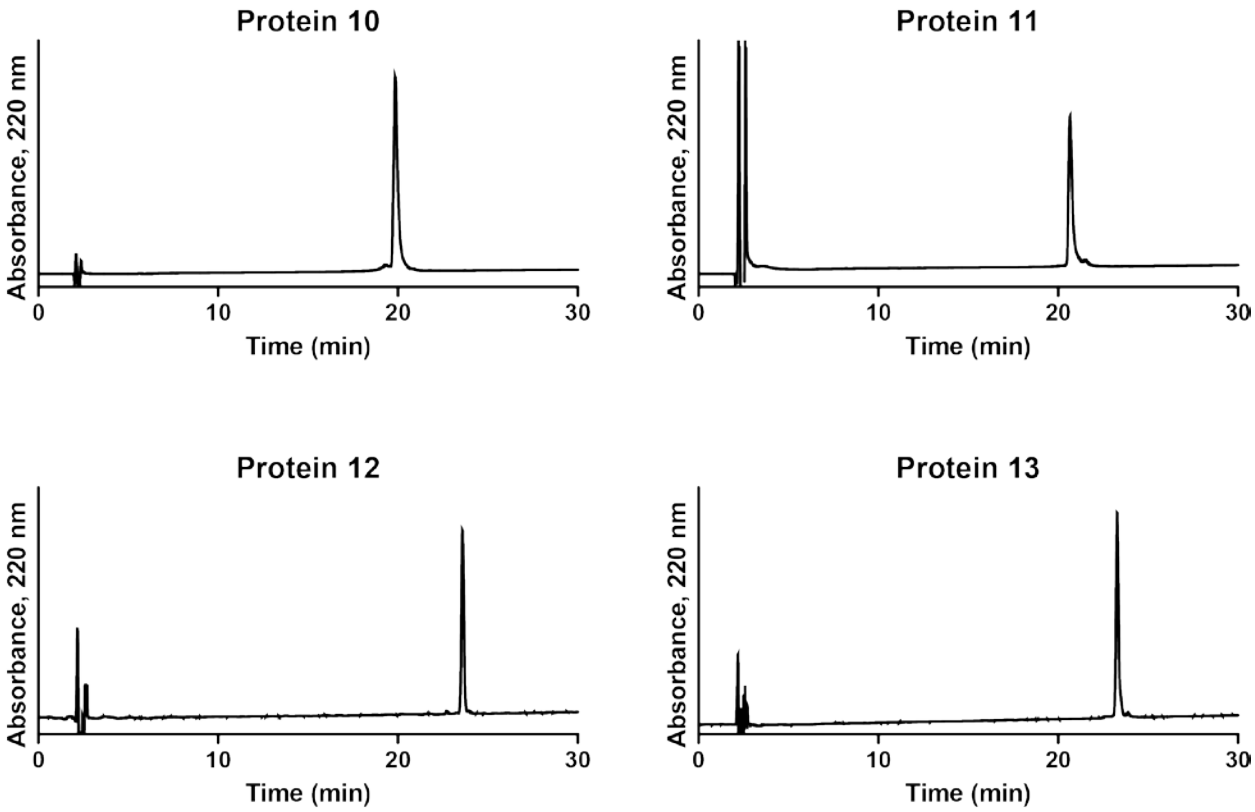


Figure S2. Analytical HPLC traces of proteins **10**-**13**.

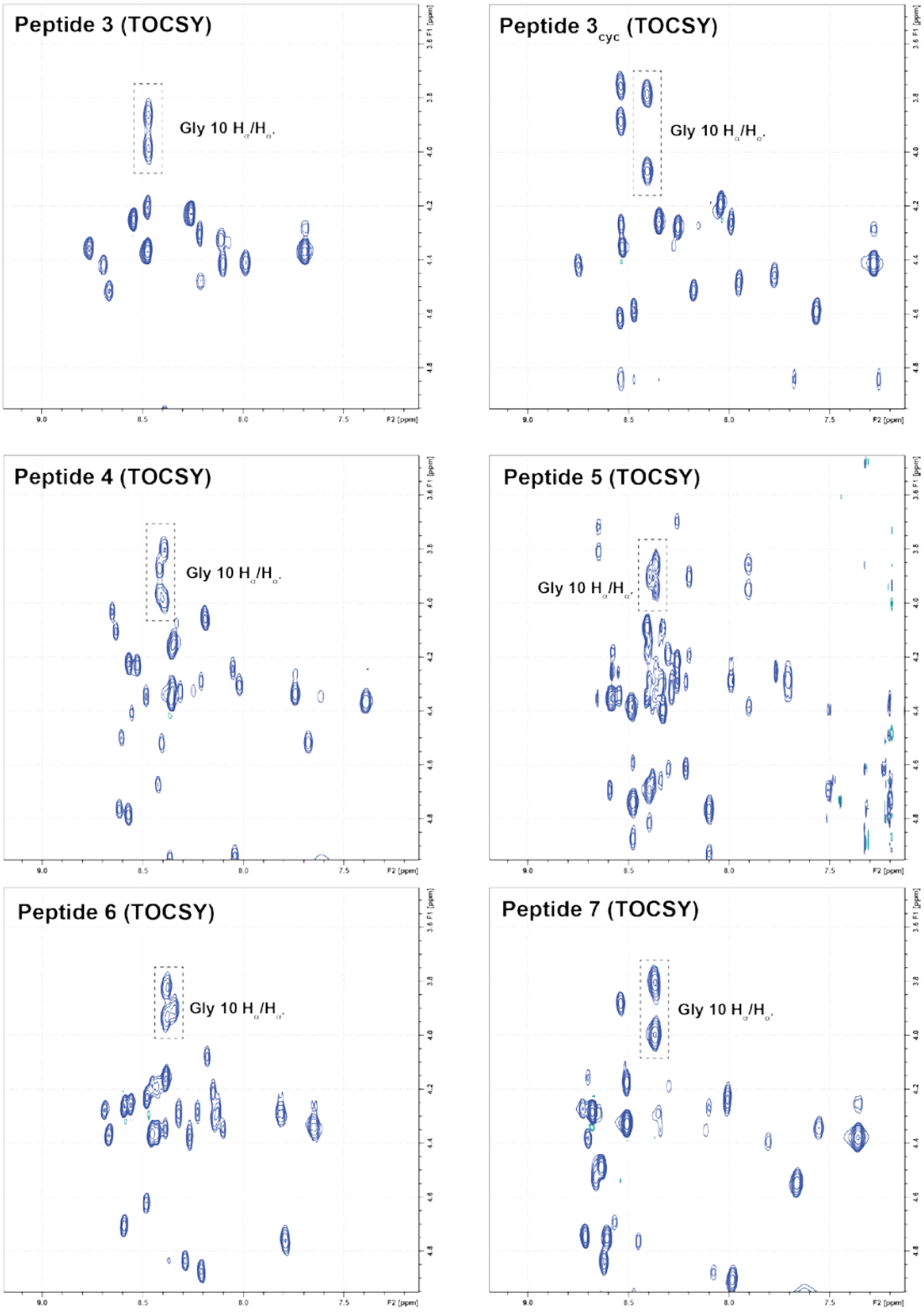
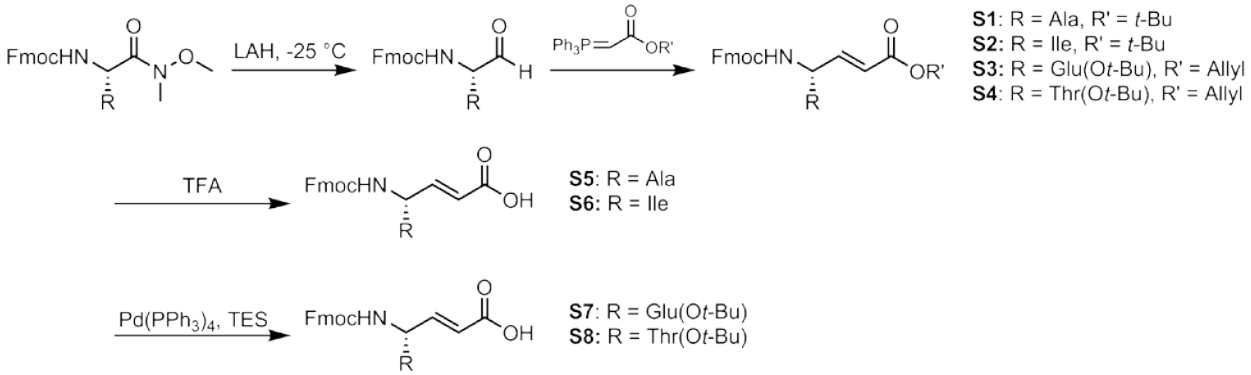


Figure S3. N_H-H_α regions of the TOCSY spectra of peptides **3-7**.

Experimental Methods

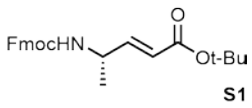
General Information. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature. NMR spectra of synthetic small molecules were recorded on a Bruker Avance-400 spectrometer. 2-(6-chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU), NovaPEG Rink Amide Resin, 9-fluorenylmethyl *N*-succinimidyl carbonate (Fmoc-OSu), and Fmoc-protected α-amino acids were purchased from Novabiochem. Solvents and all other reagents were purchased from Aldrich, Baker, Fisher, or TCI and used as received without further purification. Flash chromatography was performed using SorbTech silica gel (60 Å, 40-63 μm). The Weinreb amides of Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Glu(tBu)-OH, and Fmoc-Thr(tBu)-OH were synthesized using a published protocol.[S1]



Standard Procedure A: To a stirred solution of Fmoc-Weinreb amide (1 equiv) in tetrahydrofuran (0.1 M) at −25 °C was added lithium aluminum hydride (1.1 equiv). The reaction was allowed to stir for 30 minutes and then quenched with 1 M hydrochloric acid, diluted with water, and extracted three times with ethyl acetate. The combined organics were washed with brine, dried with magnesium sulfate, and concentrated to afford the desired Fmoc-aldehyde which was used directly without purification.

Standard Procedure B:[S2] To a stirred solution of aldehyde (1 equiv) in tetrahydrofuran (0.2 M) was added the appropriate triphenylphosphorane (1 equiv). The reaction was stirred overnight, concentrated, and purified using column chromatography.

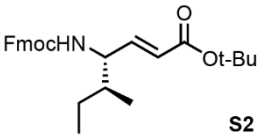
Standard Procedure C:[S3] To a stirred solution of aldehyde (1 equiv) in toluene (0.1 M) at 80 °C was added (allyloxycarbonylmethyl)triphenylphosphonium iodide (1.6 equiv) and DIEA (1.4 equiv). The reaction was stirred 3 h. After this time, the reaction was washed with 0.1 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and brine. The organics were dried with magnesium sulfate, concentrated, and purified using column chromatography.



S1

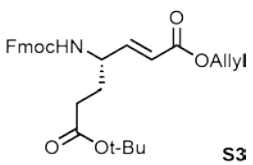
Fmoc-γ[4]-Ala-OtBu (S1). Standard Procedure A was followed using 673 mg Fmoc-Ala Weinreb amide (1.90 mmol), 15 mL tetrahydrofuran, and 79 mg lithium aluminum hydride (2.1 mmol). The resulting aldehyde was subjected to Standard Procedure B using 10 mL tetrahydrofuran and 717 mg (*tert*-butoxycarbonylmethylene) triphenylphosphorane (1.90 mmol). The crude mixture was purified using column chromatography (20% ethyl acetate in hexanes) to afford the product as a white foam (426 mg, 1.08 mmol, 57% yield over 2 steps). $[\alpha]_D = -13.2$ (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2 H), 7.59 (d, J = 7.3 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 2 H), 6.77 (dd, J = 4.6, 15.7, 1 H), 5.83 (d, J = 15.6 Hz, 1 H), 4.78 (d, J = 6.8 Hz, 1 H), 4.44 (m, 3 H), 4.22 (t, J = 6.7 Hz, 1 H), 1.50 (s, 9 H), 1.30 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 155.4, 147.4, 143.8,

141.3, 127.7, 127.0, 125.0, 122.3, 120.0, 80.6, 66.7, 47.2, 28.1, 20.3. HRMS *m*/*z* calculated for $C_{24}H_{28}NO_4$ $[M+H]^+$ 394.2018; found 394.2014.



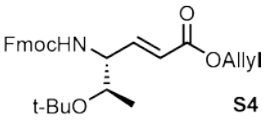
S2

Fmoc-γ^4-Ile-OtBu (S2) Standard Procedure A was followed using 1.149 g Fmoc-Ile Weinreb amide (2.89 mmol), 23 mL tetrahydrofuran, and 124 mg lithium aluminum hydride (3.27 mmol). The resulting aldehyde was subjected to Standard Procedure B using 15 mL tetrahydrofuran and 1.092 g (*tert*-butoxycarbonylmethylene) triphenylphosphorane (2.90 mmol). The crude mixture was purified using column chromatography (20% ethyl acetate in hexanes) to afford the product as a white solid (815 mg, 1.87 mmol, 64% yield over 2 steps). $[\alpha]_D = -3.4$ (*c* = 1.00, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. Existence of two conformers is precedented for similar Fmoc-protected compounds.[S4,5] ^{1}H NMR, Main Conformer (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2 H), 7.60 (d, *J* = 7.3 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 2 H), 7.32 (*J* = 7.3 Hz, 2 H), 6.76 (dd, *J* = 5.5, 15.6 Hz, 1 H), 5.84 (d, *J* = 15.6 Hz, 1 H), 4.82 (d, *J* = 9.0 Hz, 1 H), 4.45 (m, 2 H), 4.30 (m, 1 H), 4.23 (t, *J* = 6.5 Hz, 1 H), 1.63 (m, 1 H), 1.50 (s, 9 H), 1.46 (m, 1 H), 1.13 (m, 1 H), 0.91 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 155.4, 144.8, 143.5, 141.0, 127.4, 126.7, 124.6, 123.3, 119.6, 80.2, 66.3, 55.9, 47.0, 38.6, 27.8, 24.9, 14.9, 11.2. HRMS *m*/*z* calculated for $C_{27}H_{34}NO_4$ $[M+H]^+$ 436.2488; found 436.2488.



S3

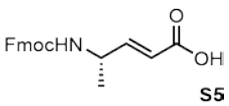
Fmoc-γ^4-Glu(tBu)-OAllyl (S3). Standard Procedure A was followed using 1.835 g Fmoc-Glu(tBu) Weinreb amide (3.92 mmol), 30 mL tetrahydrofuran, and 162 mg lithium aluminum hydride (4.27 mmol). Standard Procedure C was followed using 3.06 g phosphonium (6.27 mmol), 960 μL DIEA (5.51 mmol), and 39 mL toluene. The crude mixture was purified using column chromatography (20% ethyl acetate in hexanes) to afford the product as a white solid (1.272 g, 2.59 mmol, 66% yield over 2 steps). $[\alpha]_D = -6.7$ (*c* = 1.00, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. ^{1}H NMR, Major Conformer (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 2 H), 6.86 (dd, *J* = 5.3, 15.6 Hz, 1 H), 5.94 (m, 2 H), 5.34 (dd, *J* = 1.4, 17.2 Hz, 1 H), 5.26 (dd, *J* = 1.1, 10.4 Hz, 1 H), 5.12 (d, *J* = 8.3 Hz, 1 H), 4.64 (d, *J* = 5.7 Hz, 2 H), 4.43 (m, 2 H), 4.36 (m, 1 H), 4.20 (t, *J* = 6.7 Hz, 1 H), 2.32 (m, 2 H), 1.93 (m, 1 H), 1.83 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 165.7, 155.7, 147.5, 143.8, 141.3, 132.0, 127.7, 127.1, 125.0, 121.1, 120.0, 118.4, 81.0, 66.7, 65.2, 51.8, 47.2, 31.7, 28.9, 28.0. HRMS *m*/*z* calculated for $C_{27}H_{34}NO_6$ $[M+H]^+$ 492.2386; found 492.2362.



S4

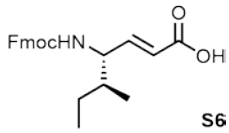
Fmoc-γ^4-Thr(tBu)-OAllyl (S4). Standard Procedure A was followed using 2.385 g Fmoc-Glu(tBu) Weinreb amide (5.41 mmol), 43 mL tetrahydrofuran, and 228 mg lithium aluminum hydride (6.00 mmol). Standard Procedure C was followed using 4.22 g phosphonium (8.64 mmol), 1.35 mL DIEA (7.75 mmol), and 54 mL toluene. The crude mixture was purified using column chromatography (20% ethyl acetate in hexanes) to afford the product as a colorless oil (1.652 g, 3.56 mmol, 66% yield over 2 steps). $[\alpha]_D = +9.4$ (*c* = 1.00, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. ^{1}H NMR, Major Conformer (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 2 H), 7.62 (d, *J* = 7.2 Hz, 2 H), 7.41 (t, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 6.8 Hz, 2 H), 6.98 (dd, *J* = 4.9, 15.7 Hz, 1 H), 5.96 (m, 2 H), 5.34 (dd, *J* = 1.3, 17.2 Hz, 1 H), 5.24 (m, 2 H), 4.66 (d, *J* = 5.7 Hz, 2 H), 4.45 (m, 2 H), 4.26 (m, 2 H), 3.82 (m, 1 H), 1.17 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 156.1, 147.7, 143.8, 141.3, 132.1, 127.7, 127.0, 125.0, 121.1, 119.9, 118.1, 74.11, 68.0, 66.8, 65.0, 57.4, 47.3, 28.5, 20.3. HRMS *m*/*z* calculated for $C_{28}H_{33}NO_5Na$ $[M+Na]^+$ 486.2256; found 486.2242.

Standard Procedure D: To a stirred solution of ester in 5 mL dichloromethane was added 5 mL trifluoroacetic acid. The reaction was stirred 4 h, concentrated, solvent-exchanged with chloroform three times, and purified using column chromatography.



S5

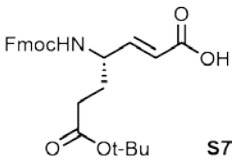
Fmoc-γ⁴-Ala-OH (S5). Standard procedure D was followed using 351 mg **S1** (0.892 mmol). Column chromatography (50% ethyl acetate in hexanes) afforded the product as a white solid (240 mg, 0.711 mmol, 80% yield). $[\alpha]_D = -13$ (*c* = 0.50, DMSO-d_6). Spectral data matched previously reported results.[S5] HRMS *m*/*z* calculated for $C_{20}H_{20}NO_4$ $[M+H]^+$ 338.1392; found 338.1382.



S6

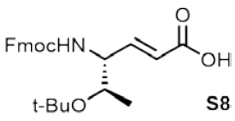
Fmoc-γ⁴-Ile-OH (S6). Standard procedure D was followed using 815 mg **S2** (1.87 mmol). Column chromatography (50% ethyl acetate in hexanes) afforded the product as a white solid (659 mg, 1.74 mmol, 93% yield). $[\alpha]_D = -7.6$ (*c* = 1.0, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. ^{1}H NMR, Major Conformer (400 MHz, $CDCl_3$) δ 10.04 (s, 1 H), 7.77 (d, *J* = 7.3 Hz, 2 H), 7.60 (d, *J* = 7.3 Hz, 2 H), 7.41 (t, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 6.7 Hz, 2 H), 6.96 (dd, *J* = 15.6, 5.2 Hz, 1 H), 5.91 (d, *J* = 15.6 Hz, 1 H), 4.88 (d, *J* = 9.0 Hz, 1 H), 4.48 (d, *J* = 6.4 Hz, 2 H), 4.35 (m, 1 H), 4.22 (t, *J* = 6.3 Hz, 1 H), 1.28-1.71 (m, 2 H), 1.13 (m, 1 H), 0.91 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.9, 149.0, 143.7, 141.3, 127.7, 127.1, 124.9, 121.2, 120.0, 66.6, 56.3, 47.3, 38.8, 25.2, 15.3, 11.5. HRMS *m*/*z* calculated for $C_{23}H_{26}NO_4$ $[M+H]^+$ 380.1862; found 380.1864.

Standard Procedure E: To a stirred solution of allyl ester (1 equiv) in dichloromethane (0.1 M) was added tetrakis(triphenylphosphine)palladium (0.1 equiv) and triethylsilane (5 equiv). The reaction was stirred 3 h, then diluted with ethyl acetate and washed once with 1 M HCl and twice with brine. The organics were dried with magnesium sulfate, concentrated, and purified using column chromatography.



S7

Fmoc-γ⁴-Glu(tBu)-OH (S7). Standard Procedure E was followed using 71 mg **S3** (0.14 mmol), 18 mg tetrakis (0.016 mmol), 115 μL triethylsilane (0.72 mmol), and 1.4 mL dichloromethane. Column chromatography (50% ethyl acetate in hexanes) afforded the product as a pale yellow solid (15 mg, 0.033 mmol, 23% yield). $[\alpha]_D = -9.1$ (*c* = 1.0, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. ^{1}H NMR, Major Conformer (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 2 H), 7.59 (d, *J* = 7.0 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 6.93 (dd, *J* = 15.7, 5.0 Hz, 1 H), 5.92 (d, *J* = 15.6 Hz, 1 H), 5.24 (d, *J* = 8.2 Hz, 1 H), 4.43 (m, 3 H), 4.20 (t, *J* = 6.3 Hz, 1 H), 2.31 (m, 2 H), 1.92 (m, 1 H), 1.83 (m, 1 H), 1.44 (s, 9 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.5, 155.8, 149.4, 143.7, 141.3, 127.7, 127.0, 124.9, 120.8, 119.9, 81.1, 66.7, 51.8, 47.2, 31.7, 28.9, 28.0. HRMS *m*/*z* calculated for $C_{26}H_{30}NO_6$ $[M+H]^+$ 452.2073; found 452.2070.



S8

Fmoc-γ⁴-Thr(tBu)-OH (S8). Standard Procedure E was followed using 1.517 g **S4** (3.27 mmol), 378 mg tetrakis (0.327 mmol), 2.6 mL triethylsilane (16 mmol), and 32 mL dichloromethane. Following a silica plug eluting with ethyl acetate, column chromatography (20% → 50% ethyl acetate in hexanes) afforded the product as a pale yellow solid (905 mg, 2.14 mmol, 65% yield). $[\alpha]_D = +3.8$ (*c* = 1.0, $CHCl_3$). This compound exists as a mixture of conformers on the NMR time scale. ^{1}H NMR, Major Conformer (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 2 H), 7.62 (d, *J* = 7.0 Hz, 2 H), 7.41 (t, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.06 (dd, *J* = 15.7, 4.6 Hz, 1 H), 5.92 (d, *J* = 15.7 Hz, 1 H), 5.25 (d, *J* = 9.0 Hz, 1 H), 4.47 (d, *J* = 6.8 Hz, 2 H), 4.31 (m, 1 H), 4.25 (t, *J* = 6.7 Hz, 1 H), 3.83 (m, 1 H), 1.17 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 156.2, 149.9, 143.8, 141.3, 127.7, 127.1, 125.0, 120.8, 120.0, 74.2, 68.0, 66.9, 57.4, 47.3, 28.5, 20.3. HRMS *m*/*z* calculated for $C_{25}H_{28}NO_5$ $[M+H]^+$ 422.1962; found 422.1976.

Table S1. MALDI-TOF Data for Peptides **3-7** and proteins **10-13**.

#	$[M+H]^+$ *m/z*	
	Calculated	**Observed**
1	1739.8	1739.2
2	1849.1	1849.1
3	1791.9	1791.4
$\mathbf{3_{cyc}}$	2037.9	2037.5
4	1753.9	1753.8
5	1753.9	1753.8
6	1753.9	1753.7
7	1753.9	1752.8
8	6179.7	6178.6
9	6207.7	6207.5
10	6280.9	6281.8
11	6232.1	6231.3
12	6114.1	6114.7
13	6204.1	6203.7

Table S2. Peptide **3** backbone chemical shifts.

Residue	Atom	δ (ppm)
G1	$H_{\alpha1}$	3.798
G1	$H_{\alpha2}$	3.857
E2	H	8.767
E2	H_{α}	4.363
W3	H	8.669
W3	H_{α}	4.521
X4	H	8.114
X4	H_{α}	5.3
X4	H_{β}	6.137
X4	H_{γ}	4.333
Y5	H	8.216
Y5	H_{α}	4.487
N6	H	8.395
N6	H_{α}	4.99
P7	H_{α}	4.264
A8	H	8.221
A8	H_{α}	4.308
T9	H	7.697
T9	H_{α}	4.378
G10	H	8.474
G10	$H_{\alpha1}$	3.869
G10	$H_{\alpha2}$	3.991
K11	H	7.993
K11	H_{α}	4.419
F12	H	8.698
F12	H_{α}	4.424
X13	H	8.104
X13	H_{α}	5.763
X13	H_{β}	6.302
X13	H_{γ}	4.421
V14	H	8.263
V14	H_{α}	4.238
T15	H	8.477
T15	H_{α}	4.378
E16	H	8.548
E16	H_{α}	4.251

Table S3. Peptide $\mathbf{3_{cyc}}$ backbone chemical shifts.

Residue	Atom	δ (ppm)
C1	H	8.478
C1	H_{α}	4.59
G2	H	8.544
G2	$H_{\alpha1}$	3.756
G2	$H_{\alpha2}$	3.889
E3	H	8.257
E3	H_{α}	4.277
W4	H	8.184
W4	H_{α}	4.514
$\gamma^4$5	H	7.78
$\gamma^4$5	H_{α}	5.819
$\gamma^4$5	H_{β}	6.404
$\gamma^4$5	H_{γ}	4.46
Y6	H	8.542
Y6	H_{α}	4.271
N7	H	8.037
N7	H_{α}	5.009
P8	H_{α}	4.149
A9	H	7.993
A9	H_{α}	4.266
T10	H	7.284
T10	H_{α}	4.416
G11	H	8.41
G11	$H_{\alpha1}$	3.784
G11	$H_{\alpha2}$	4.073
K12	H	7.568
K12	H_{α}	4.597
F13	H	8.755
F13	H_{α}	4.425
$\gamma^4$14	H	7.955
$\gamma^4$14	H_{α}	5.834
$\gamma^4$14	H_{β}	6.357
$\gamma^4$14	H_{γ}	4.489
V15	H	8.049
V15	H_{α}	4.192
T16	H	8.356
T16	H_{α}	4.26
E17	H	8.54
E17	H_{α}	4.349
C18	H	8.546
C18	H_{α}	4.62

Table S4. Peptide **4** backbone chemical shifts.

Residue	Atom	δ (ppm)	
		$\mathbf{4}_{trans}$	$\mathbf{4}_{cis}$
G1	$H_{\alpha 1}$	3.599	*
G1	$H_{\alpha 2}$	3.794	*
E2	H	8.572	8.557
E2	H_{α}	4.791	4.807
W3	H_{α}	5.330	5.230
W3	H_{Me}	3.118	2.902
A4	H	8.403	8.561
A4	H_{α}	4.524	4.407
Y5	H	8.637	8.612
Y5	H_{α}	4.117	4.508
N6	H	8.061	8.375
N6	H_{α}	4.948	4.961
P7	H_{α}	4.126	4.250
A8	H	8.061	8.219
A8	H_{α}	4.254	4.301
T9	H	7.409	7.752
T9	H_{α}	4.373	4.349
G10	H	8.400	8.426
G10	$H_{\alpha 1}$	3.813	3.887
G10	$H_{\alpha 2}$	4.001	3.973
K11	H	7.697	8.028
K11	H_{α}	4.522	4.317
F12	H	8.618	8.427
F12	H_{α}	4.766	4.682
A13	H	8.480	8.319
A13	H_{α}	4.355	4.333
V14	H	8.204	8.353
V14	H_{α}	4.077	4.152
T15	H	8.362	8.350
T15	H_{α}	4.367	4.321
E16	H	8.572	8.534
E16	H_{α}	4.231	4.237

*Indicates an ambiguous or overlapping assignment.

Table S5. Peptide **5** backbone chemical shifts.

Residue	Atom	δ (ppm)	
		$\mathbf{5}_{rans}$	$\mathbf{5}_{cis}$
G1	$H_{\alpha 1}$	3.724	3.707
G1	$H_{\alpha 2}$	3.814	3.804
E2	H	8.648	8.7
E2	H_{α}	4.356	4.334
W3	H	8.59	8.34
W3	H_{α}	4.696	4.656
A4	H	8.397	*
A4	H_{α}	4.809	*
Y5	H	4.769	4.879
Y5	H_{Me}	2.989	2.93
N6	H	8.099	8.478
N6	H_{α}	4.923	4.594
P7	H_{α}	4.222	4.343
A8	H	8.258	8.287
A8	H_{α}	4.289	4.288
T9	H	7.707	7.992
T9	H_{α}	4.345	4.293
G10	H	8.366	8.394
G10	$H_{\alpha 1}$	3.864	3.909
G10	$H_{\alpha 2}$	3.956	---
K11	H	7.905	8.197
K11	H_{α}	4.388	4.194
F12	H	8.487	8.3
F12	H_{α}	4.738	4.614
A13	H	8.476	8.218
A13	H_{α}	4.403	4.291
V14	H	8.329	8.335
V14	H_{α}	4.099	4.145
T15	H	8.404	*
T15	H_{α}	4.356	*
E16	H	8.576	8.546
E16	H_{α}	4.258	4.26

*Indicates an ambiguous or overlapping assignment.

Table S6. Peptide **6** backbone chemical shifts.

	Atom	δ (ppm)	
		$\mathbf{7}_{trans}$	$\mathbf{7}_{cis}$
G1	$H_{\alpha 1}$	3.708	3.703
G1	$H_{\alpha 2}$	3.817	3.806
E2	H	8.666	8.69
E2	H_{α}	4.371	4.275
W3	H	8.594	8.482
W3	H_{α}	4.709	4.625
A4	H	8.331	8.153
A4	H_{α}	4.292	4.212
Y5	H	8.182	8.099
Y5	H_{α}	4.072	4.346
N6	H	8.204	8.286
N6	H_{α}	4.878	4.831
P7	H_{α}	4.167	4.239
A8	H	8.125	8.227
A8	H_{α}	4.271	4.278
T9	H	7.645	7.815
T9	H_{α}	4.339	4.288
G10	H	8.387	8.352
G10	$H_{\alpha 1}$	3.823	3.905
G10	$H_{\alpha 2}$	3.94	---
K11	H	7.786	8.138
K11	H_{α}	4.765	4.307
F12	H_{α}	5.204	5.05
F12	H_{Me}	3.083	2.902
A13	H	8.27	8.386
A13	H_{α}	4.382	4.345
V14	H	8.386	8.474
V14	H_{α}	4.162	4.23
T15	H	8.453	8.431
T15	H_{α}	4.36	4.366
E16	H	8.589	8.557
E16	H_{α}	4.261	4.257

Table S7. Peptide **7** backbone chemical shifts.

Residue	Atom	δ (ppm)	
		$\mathbf{8}_{trans}$	$\mathbf{8}_{cis}$
G1	$H_{\alpha 1}$	3.683	*
G1	$H_{\alpha 2}$	3.831	*
E2	H	8.637	8.729
E2	H_{α}	4.492	4.282
W3	H	8.717	8.453
W3	H_{α}	4.754	4.771
A4	H	8.662	8.342
A4	H_{α}	4.541	4.354
Y5	H	8.543	8.302
Y5	H_{α}	3.888	4.196
N6	H	7.986	8.08
N6	H_{α}	4.912	4.885
P7	H_{α}	4.082	4.149
A8	H	8.01	8.101
A8	H_{α}	4.244	4.275
T9	H	7.364	7.556
T9	H_{α}	4.383	4.35
G10	H	8.37	8.357
G10	$H_{\alpha 1}$	3.811	3.857
G10	$H_{\alpha 2}$	4.006	3.974
K11	H	7.663	7.808
K11	H_{α}	4.55	4.402
F12	H	8.61	8.573
F12	H_{α}	4.757	4.699
A13	H	8.625	8.477
A13	H_{α}	4.844	4.97
V14	H_{α}	4.668	4.675
V14	H_{Me}	3.029	2.891
T15	H	8.513	*
T15	H_{α}	4.334	*
E16	H	8.682	*
E16	H_{α}	4.287	*

*Indicates an ambiguous or overlapping assignment.

Table S8. NOE-Derived Distance Restraints for Peptide $\mathbf{3}_{cyc}$.

Residue		Proton	Residue		Proton	Distance
1	C	HA	2	G	H	2.70
3	E	HA	4	W	H	2.70
3	E	HB1	3	E	H	2.70
4	W	H	3	E	HA	2.70
5	γ^4	HA	6	Y	H	2.70
6	Y	H	5	γ^4	HA	2.70
6	Y	HA	7	N	H	2.70
7	N	H	6	Y	HA	2.70
7	N	HA	8	P	QD	2.70
10	T	H	11	G	H	2.70
11	G	H	10	T	H	2.70
14	γ^4	HA	15	V	H	2.70
15	V	H	14	γ^4	HA	2.70
15	V	HA	15	T	H	2.70
16	T	H	15	V	HA	2.70
16	T	HA	17	E	H	2.70
17	E	H	16	T	HA	2.70
2	G	H	3	E	H	3.50
2	G	HA1	3	E	H	3.50
2	G	HA2	3	E	H	3.50
3	E	H	2	G	H	3.50
3	E	H	2	G	HA1	3.50
3	E	H	2	G	HA2	3.50
3	E	HB2	4	W	H	3.50
4	W	H	5	γ^4	H	3.50
4	W	HA	5	γ^4	H	3.50
4	W	HA	15	V	HA	3.50
5	γ^4	H	4	W	H	3.50
5	γ^4	H	4	W	HA	3.50
5	γ^4	HA	13	F	QD	3.50
5	γ^4	HB	14	γ^4	H	3.50
6	Y	HA	13	F	QD	3.50
6	Y	HA	14	γ^4	H	3.50
6	Y	HB2	7	N	H	3.50
6	Y	QE	7	P	HA	3.50
7	P	HA	6	Y	QE	3.50
7	P	HA	9	A	H	3.50
7	P	QB	6	Y	QE	3.50
7	P	QD	9	A	H	3.50
7	P	QG	9	A	H	3.50
9	A	H	8	P	HA	3.50
9	A	H	8	P	QD	3.50
9	A	H	10	T	H	3.50
9	A	HA	9	A	H	3.50
9	A	HA	10	T	H	3.50
10	T	H	9	A	H	3.50
10	T	H	9	A	HA	3.50
10	T	H	9	A	QXB	3.50
10	T	HA	6	Y	QD	3.50
10	T	QXGT	10	T	HA	3.50
10	T	QXGT	10	T	HB	3.50
11	G	H	12	K	H	3.50
11	G	HA1	12	K	H	3.50
11	G	HA2	12	K	H	3.50
12	K	H	11	G	H	3.50
12	K	QB	13	F	H	3.50
13	F	H	12	K	QB	3.50

Residue		Proton	Residue		Proton	Distance
13	F	HA	7	N	H	3.50
13	F	HA	14	γ^4	H	3.50
14	γ^4	H	5	γ^4	HB	3.50
14	γ^4	H	13	F	HA	3.50
14	γ^4	H	13	F	QB	3.50
15	V	H	14	γ^4	HB	3.50
15	V	HB	16	T	H	3.50
16	T	H	15	V	H	3.50
16	T	H	15	V	QXG2	3.50
16	T	H	17	E	H	3.50
17	E	H	16	T	H	3.50
17	E	H	17	E	HA	3.50
18	C	H	17	E	HA	3.50
3	E	HB1	4	W	H	4.50
4	W	HH2	16	T	QXGT	4.50
4	W	HZ3	5	γ^4	H	4.50
4	W	QB	5	γ^4	H	4.50
5	γ^4	H	15	V	HA	4.50
5	γ^4	HA	13	F	QE	4.50
6	Y	HB1	7	N	H	4.50
6	Y	HB2	13	F	QD	4.50
6	Y	HB2	13	F	QE	4.50
6	Y	QD	7	N	H	4.50
6	Y	QD	8	P	QD	4.50
6	Y	QD	13	F	QD	4.50
7	N	H	6	Y	H	4.50
7	N	H	6	Y	QD	4.50
7	N	H	6	Y	QE	4.50
7	N	H	12	K	H	4.50
7	N	HA	9	A	H	4.50
8	P	HA	6	Y	QD	4.50
8	P	QB	6	Y	QD	4.50
8	P	QG	6	Y	QE	4.50
9	A	H	11	G	H	4.50
9	A	QXB	10	T	H	4.50
10	T	H	12	K	H	4.50
10	T	HA	11	G	H	4.50
10	T	HB	12	K	H	4.50
10	T	QXGT	9	A	HA	4.50
11	G	H	10	T	HA	4.50
11	G	HA1	6	Y	QD	4.50
11	G	HA1	6	Y	QE	4.50
12	K	H	7	N	H	4.50
12	K	H	10	T	H	4.50
12	K	HA	6	Y	QD	4.50
12	K	HA	6	Y	QE	4.50
12	K	HA	13	F	H	4.50
13	F	H	12	K	HA	4.50
13	F	H	12	K	QD	4.50
13	F	QD	6	Y	QD	4.50
13	F	QD	14	γ^4	H	4.50
14	γ^4	QXD	5	γ^4	HB	4.50
15	V	H	14	γ^4	QXD	4.50
15	V	HA	5	γ^4	H	4.50
15	V	QXG1	4	W	HZ3	4.50
15	V	QXG2	2	G	HA1	4.50
15	V	QXG2	2	G	HA2	4.50
15	V	QXG2	16	T	H	4.50

Residue		Proton	Residue		Proton	Distance
16	T	H	3	E	H	4.50
16	T	H	15	V	QXG1	4.50
16	T	QXGT	15	V	H	4.50
16	T	QXGT	17	E	H	4.50
5	γ^4	QXD	6	Y	H	5.50
8	P	QD	6	Y	QD	5.50
14	γ^4	HB	5	γ^4	H	5.50
15	V	QXG1	16	T	H	5.50

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