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Solid-Phase Syntheses of Olefin-Containing Inhibitors for HTLV-1 Protease Using the Horner−Emmons Reaction

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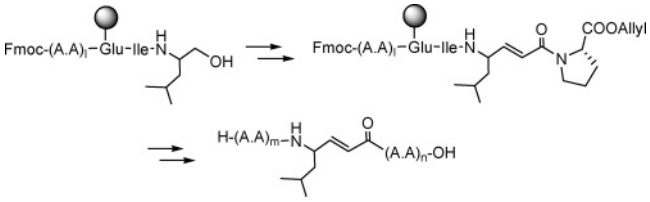

The solid-phase Horner−Emmons reaction was successfully applied for the convenient syntheses of olefin-containing protease inhibitors. The isomerization during the solid-phase Horner−Emmons reaction can be minimized simply by the use of an appropriate amount of the base. The synthesized olefin peptides, which have an olefin γ-amino acid at the scissile site, were found to act as effective inhibitors for the HTLV-1 protease for the first time.

The introduction of an olefin structure into a peptide backbone is a promising approach to induce conformational change, which permits a biologically active peptide to be more specific and potent.[1] The syntheses of (*E*)-alkene dipeptide isosteres, however, were all achieved in conventional solution phase,[2] and few applications of solid-phase syntheses of peptide mimetics containing the isostere have been reported.[3] In this paper, we report that the modification of an amino acid in a peptide sequence to the corresponding olefin γ-amino acid counterpart gives rise to enzyme inhibitors containing the olefin structure. For this modification, the solid-phase procedure using the oxidation of peptide alcohol with Dess−Martin periodinane and the following Horner−Emmons reactions on CLEAR support[4] was efficiently applied. As the peptide sequence, a substrate sequence (KGPPVILPI, in which LP is the scissile site) of human T-cell leukemia virus type 1 (HTLV-1) protease[5] was selected, since few effective inhibitors have been reported for this protease.[6] Leucine at the scissile site was replaced with the corresponding olefin γ-amino acid to evaluate the effect of olefin insertion in the substrate peptide. Prior to the solid-phase syntheses of the olefin-containing inhibitors, two small substrate peptide libraries containing substitutions at P_1−P_4 sites were constructed to search for the appropriate anchoring position to the CLEAR support.[7] As for the results, P_1 Leu and P_2 Ile residues were found to be essential in the substrate sequence, but Gln was a valid replacement for the P_3 Val residue.

Scheme 1 shows a typical synthetic route for an olefin peptide covering the P_6 to P_1' sites of the protease substrate, except for the P_3 Gln instead of the original Val. For the anchoring, Fmoc-Glu-O-allyl was reacted with the swollen CLEAR resin[8] in DMF using HBTU (1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium hexafluorophosphate 3-oxide)[9,10]/HOBt. The Fmoc group of the resulting resin, **1**, was removed with 20% piperidine/DMF, and Fmoc-Pro-OH was condensed by DCC/HOBt. The same deprotection/condensation procedure was repeated for the successive introduction of the corresponding Fmoc amino acids to afford the tetrapeptide resin, **2**. A part of each intermediate resin was separated for the parallel preparation of olefin peptides containing the shorter N-terminal sequences. The C-terminal allyl group of **2** was removed with $[(C_6H_5)_3P]_4$-Pd(0), and H-Ile-O-allyl was coupled to the resulting resin using DCC/HOBt. The same deprotection/condensation procedure was repeated for the introduction of H-leucinol to afford **3**. The resin was then treated with Dess−Martin periodinane followed by allyl diethylphosphonoacetate/$[(CH_3)_3Si]_2NLi$ (2 equiv) at 0 °C to afford **4**. After cleavage of the C-terminal allyl group, H-Pro-O-allyl was coupled using HATU(1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo [4,5-*b*]pyridinium hexafluorophosphate 3-oxide)/HOAt(7-aza-1-hydroxybenzotriazole)[10] to yield **5**. The C-terminal allyl and the N-terminal Fmoc groups of **5** were then removed, and the product resin was treated with TFA/H_2O (95:5). The product gave a single major peak accompanied with a small amount of a side peak on HPLC (Figure 4a in the Supporting Information). The

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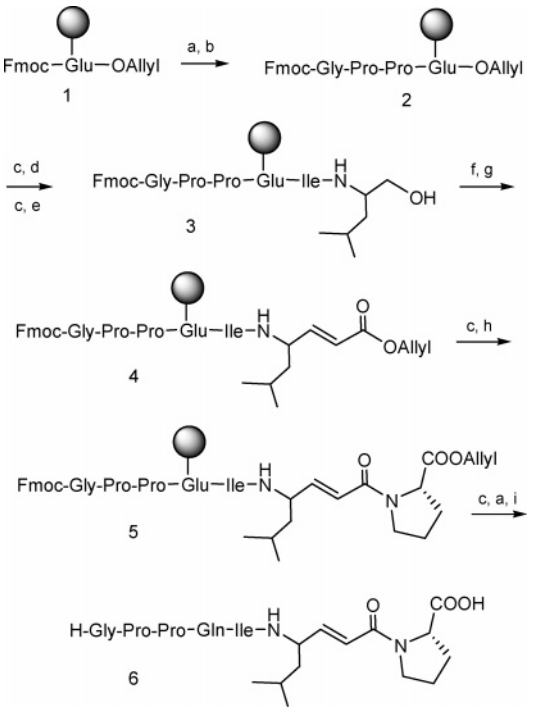
SCHEME 1. Synthetic Route to the Olefin Peptide 6[a]



[a] Key: (a) 20% piperidine/DMF; (b) Fmoc-based SPPS; (c) $[(C_6H_5)_3P]_4Pd(0)$; (d) H-Ile-O-allyl/DCC/HOBt; (e) H-leucinol/DCC/HOBt; (f) Dess−Martin periodinane; (g) $(EtO)_2P(O)CH_2COO$-allyl/$[(CH_3)_3Si]_2NLi$; (h) H-Pro-O-allyl/HATU/HOAt; (i) TFA/H_2O (95:5).

product of the major peak showed the desired molecular weight by MALDI TOF-MS analysis, which shows that the series of solid-phase reactions proceeded efficiently. In addition, the coupling constant of the vicinal protons at the olefin bond of the product was 15.3 Hz in ^{1}H NMR, indicating that only the (*E*)-isomer was produced in the Horner−Emmons reaction. The crude product was then purified by HPLC to afford a homogeneous olefin peptide, **6**. Other olefin−peptides containing different chain lengths (compounds **7** covering the P_6 to P_2' sites, compound **8** for the P_3 to P_1 sites, compound **9** for the P_4 to P_1 sites, compound **10** for the P_5 to P_1 sites, compound **11** for the P_6 to P_1 sites, and compound **12** for the P_7 to P_1 sites) were similarly synthesized on CLEAR support followed by treatment with TFA/H_2O (95:5) for the final cleavage.

A small amount of the byproduct that eluted just after the desired product on HPLC had the same molecular weight and coupling constant of (*E*) olefin protons as those of the desired product **6**. In addition, the amount of this byproduct increased in proportion to the reaction temperature (0−25 °C) and the equivalents of LHMDS (2−4 equiv) used in the Horner−Emmons reaction (Figure 4b in the Supporting Information).[11] These results strongly suggest that this byproduct is produced by isomerization, which is expected to occur at the aldehyde level.

(11) The reaction was incomplete when the amount of the base was less than 2 equiv, whereas fairly complex mixtures were obtained when the reaction was conducted at 25 °C. The results indicating the degree of epimerization at 0 and 25 °C are shown in the Supporting Information.

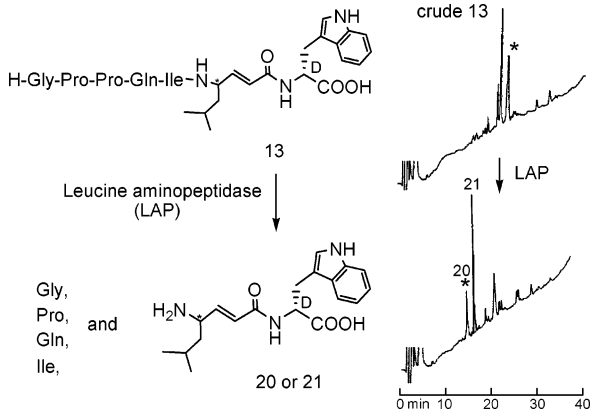
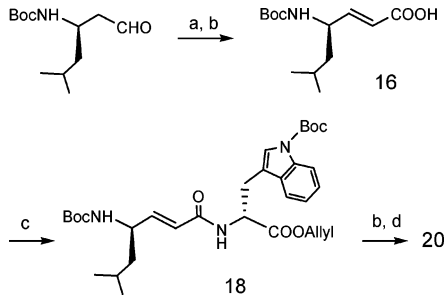


FIGURE 1. LAP digestion of the model peptide **13**. Asterisks in the chromatogram indicate the peaks derived from the isomer.

SCHEME 2. Synthetic Route for 20 (Diastereomer 21 was Similarly Synthesized Starting from Boc-L-leucinal)[a]



[a] Key: (a) $(EtO)_2P(O)CH_2COO$-allyl/$[(CH_3)_3Si]_2NLi$; (b) $[(C_6H_5)_3P]_4Pd(0)$; (c) H-Trp(Boc)-COO-allyl/HATU/HOAt; (d) 50% TFA/CH_2Cl_2.

To confirm that this side product derived from the isomerization, the model olefin peptide, **13**, was prepared using the same reaction conditions employed above. In this model peptide, C-terminal D-tryptophan was introduced instead of the Pro in compound **6**; this would make the detection and separation on reversed-phase HPLC easy due to the hydrophobicity of the indole moiety. The synthesized model compound **13** showed a major peak accompanied with a side peak on HPLC, as in the case of compound **6** (Figure 1). The products of these two peaks had the same expected molecular weight on MALDI TOF-MS analyses. Leucine aminopeptidase (LAP) digestion of the crude product, **13**, gave two major fragment peptides; those have the same retention time as the authentic compounds **20** and **21**, prepared by the conventional solution-phase procedure starting from Boc-(*R* or *S*)-leucinal (Scheme 2). In addition, each isolated product of the crude model peptide **13** gave only the expected diastereomer fragment (**20** or **21**) after LAP digestion, respectively. These results clearly show that the side product derived from the isomerization at the aldehyde residue during the solid-phase Horner−Emmons reaction, but the amount of this side product can be minimized by the use of an appropriate amount of the base.

The ability of the olefin-containing peptide as an inhibitor was then examined using a chemically synthesized mutant of HTLV-1 protease (C2A HTLV-1 PR),

TABLE 1. Inhibition of HTLV-1 Protease by the Olefin-Containing Peptides

	compounds	IC_{50} (μM)
6	H-Gly-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCO-Pro-OH	>180
7	H-Gly-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCO-Pro-Ile-OH	>180
8	H-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCOOH	>180
9	H-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCOOH	>180
10	H-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCOOH	32.7
11	H-Gly-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCOOH	11.5
12	H-Lys-Gly-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCOOH	9.7

since the kinetic properties of this autodigestion resistant mutant have already been evaluated.[12] The linear substrate[12,13] of the protease was incubated with C2A HTLV-1 PR in the presence of various concentrations of the olefin-containing peptides. The rate of cleavage was estimated from the amount of the corresponding cleavage fragment produced during the incubation. The inhibitory activity of each olefin-containing peptide was evaluated using the corresponding IC_{50} value obtained from the sigmoidal dose−response curve.[14] From the preliminary results (Table 1), olefin peptides, which have an olefin γ-amino acid at the scissile site without the C-terminal sequence, were found to act as inhibitors of HTLV-1 protease. The P_5 to P_2 sequence seems to be necessary for the inhibitory activity, although a detailed analysis will be the subject of future studies.

Thus, it has been shown for the first time that substrate peptides containing the olefin γ-amino acid at the scissile site are able to function as inhibitors for HTLV-1 protease. The key features of the present synthesis are the solid-phase Horner−Emmons reaction and the use of CLEAR support as a suitable resin for the multistep solid-phase synthesis. The isomerization during the solid-phase Horner−Emmons reaction can be minimized simply by the use of an appropriate amount of the base. The established solid-phase procedures are easily applicable for the preparation of olefin−peptide libraries without modifications: those would be a useful chemical tool for the examination of therapeutically important proteases.

Experimental Section

H-Gly-Pro-Pro-Gln-Ile-NHCH[$CH_2CH(CH_3)_2$]CH=CHCO-Pro-OH 6. To 1.0 g (0.35 mmol) of CLEAR were added Fmoc-Glu-O-allyl (0.29 g, 0.70 mmol), HBTU (0.26 g, 0.70 mmol), HOBt (0.11 g, 0.70 mmol), and DIEA (0.2 mL, 0.70 mmol) in DMF (5 mL). The mixture was stirred for 3 h at 25 °C. To the resulting resin, **1**, was added 20% piperidine in DMF, and the mixture was stirred for 20 min at 25 °C. Fmoc-Pro-OH, Fmoc-Pro-OH, and Fmoc-Gly-OH were successively condensed to this resin using DCC/HOBt. An aliquot of the resulting resin **2** was treated with TFA/H_2O (95:5) for 2 h. The crude product was analyzed with HPLC [t_R, 21.52 min (CH_3CN, 30−70%/30 min)] and MALDI-TOF MS [*m/z* 659.51 for $[M + H]^+$ (calcd 660.30 for $C_{35}H_{42}O_8N_5$)].

The resin, **2** (0.10 g, 29 μmol), was treated with $[PPh_3]_4Pd(0)$ (0.16 g, 0.14 mmol) in $CHCl_3$/AcOH/NEM (37:2:1) for 1.5 h under N_2. After the resin was washed with DCM, THF, and DMF, H-Ile-O-allyl (20 mg, 0.12 mmol), DCC (24 mg, 0.12 mmol), and HOBt (18 mg, 0.12 mmol) in DMF were added, and the mixture was stirred at 25 °C for 3 h. The solvent was removed, and the resin was dried. After the resin was swelled with $CHCl_3$, the same deprotection was repeated. H-Leucinol (14 mg, 0.12 mmol), DCC (24 mg, 0.12 mmol), and HOBt (18 mg, 0.12 mmol) in DMF were added to the resin, and the mixture was stirred at 25 °C for 1 h. An aliquot of **3** was similarly treated with TFA/H_2O (95:5) and analyzed: HPLC t_R, 20.52 min (CH_3CN, 30−70%/30 min); MALDI-TOF MS *m/z* 833.59 for $[M + H]^+$ (calcd 833.00 for $C_{44}H_{62}O_9N_7$).

To a suspension of **3** (0.10 g, 27 μmol) in DCM (10 mL) was added Dess−Martin periodinane (0.22 g, 0.52 mmol), and the mixture was stirred at 25 °C for 1 h. The resin was filtered, washed with DCM, MeOH, DCM, and ether, and then dried. An aliquot of the resin was treated with TFA/H_2O (95:5) and analyzed [HPLC, t_R, 21.20 min (CH_3CN, 30−70%/30 min), MALDI-TOF MS, *m/z* 830.96 for $[M + H]^+$ (calcd 830.98 for $C_{44}H_{60}O_9N_7$)]. Allyl diethylphosphonoacetate (61 μL, 0.29 mmol) in THF (10 mL) was treated with 55 μL of 1.0 M $[(CH_3)_3Si]_2NLi$ in THF, at 25 °C for 20 min under N_2. The obtained solution was added to the above dried resin, and the mixture was stirred for 3 h at 25 °C under N_2. The resin was washed with DMF, THF, and DCM and then dried to yield **4**. An aliquot of the resin was treated with TFA/H_2O (95:5) and analyzed: HPLC, t_R, 29.92 min (CH_3CN, 30−70%/30 min); MALDI-TOF MS, *m/z* 934.71 for $[M + Na]^+$ (calcd 934.02 for $C_{49}H_{65}O_{10}N_9Na$).

The above dried resin was swollen in $CHCl_3$ and treated with $[PPh_3]_4Pd(0)$ (0.16 g, 0.14 mmol) in $CHCl_3$/AcOH/NEM (37:2:1) for 1.5 h under N_2. The resin was washed with DCM, THF, and DMF. To this resin was added 3 mL of DMF solution containing HATU (41 mg, 0.11 mmol), HOAt (15 mg, 0.11 mmol), NEM (14 μL, 0.11 mmol), and H-Pro-O-allyl (84 mg, 0.54 mmol), and the mixture was stirred overnight at 25 °C. The mixture was filtered, and the resin was washed with DMF and ether and dried to yield **5**. The C-terminal allyl and N-terminal Fmoc groups were then removed as described above. The product resin (50 mg) was treated with TFA/H_2O (95:5, 1 mL) for 1 h at 25 °C. After evaporation of the TFA, ether was added, and the resulting precipitate was purified with semipreparative HPLC to yield a homogeneous product (yield 20%) showing a single peak on an analytical HPLC (data in the Supporting Information): HPLC t_R, 11.74 min (CH_3CN, 10−40%/30 min, Figure 4); MALDI-TOF MS *m/z* 747.79 for $[M + H]^+$ (calcd 747.89 for $C_{36}H_{59}N_8O_9$). Isomer: HPLC t_R, 12.91 min (CH_3CN, 10−40%/30 min, Figure 4); MALDI-TOF MS *m/z* 747.46 for $[M + H]^+$ (calcd 747.89 for $C_{36}H_{59}N_8O_9$). Compounds **7**−**12** were similarly prepared as above (analytical data are listed in the Supporting Information).

H-Gly-Pro-Pro-Gln-Ile-NH-CH[$CH_2CH(CH_3)_2$]CH=CHCO-D-Trp-OH, 13. Starting from **1**, the same procedure as described above was used. Major product: HPLC t_R 14.38 min [CH_3CN (10−40%/40 min)]; MALDI-TOF MS *m/z* 836.44 for $[M + H]^+$ (calcd 836.97 for $C_{42}H_{62}N_9O_9$). Minor product: HPLC t_R 15.20 min [CH_3CN (10−40%/40 min)]; MALDI-TOF MS *m/z* 836.78 for $[M + H]^+$ (calcd 836.97 for $C_{42}H_{62}N_9O_9$).

A 0.3 mg sample of the crude product was digested with 0.1 units of leucine amino peptidase (LAP, Sigma L-5006) in 47 mM sodium phosphate buffer (pH 7.2) at 37 °C overnight. The reaction mixture was analyzed by analytical HPLC [Cosmosil 5C18 AR-II (4.6 × 150 mm), 1.0 mL/min, CH_3CN (15%−35%/35 min)], and the elution times of the fragment peptides were compared with those of the authentic compounds synthesized below.

Prop-2-enyl (2*E*,4*R*)-4-[(*tert*-Butoxy)carbonylamino]-6-methylhept-2-enoate, 14. To a stirred solution of Boc-(*R*)-leucinal (0.14 g, 0.65 mmol) in THF (5 mL) were added allyl diethylphosphonoacetate (0.21 mL, 0.98 mmol) and lithium bis(trimethylsiyl)amide [0.98 mL of 1.0 M $(CH_3)_3Si]_2NLi$ in THF] in THF (5 mL), and the mixture was stirred at 0 °C for 2 h. The

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(14) A typical sigmoidal dose−response curve used for the estimation of IC_{50} values is shown in the Supporting Information.

solvent was removed in vacuo. The product was extracted with AcOEt (20 mL), and the organic layer was washed with H_2O, dried, and evaporated. The product was purified with siliga gel column chromatography using hexane/AcOEt = 6:1 to yield 0.14 g (79%) of **14** as an oil: $[\alpha]^{25}_D$ +17.39 (c = 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.35 Hz, 3H), 0.83 (d, J = 6.45 Hz, 3H), 1.36−1.44 (m, 1H), 1.44(s, 9H), 1.67−1.71 (m, 2H), 4.3−4.4 (br, 2 H), 4.63−4.64 (d, J = 5.5 Hz, 2H), 5.23−5.36 (m, 2H), 5.90−5.97 (m, 2H), 6.85 (dd, J = 15.64, 5.25 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 23.1, 25.1, 28.8, 44.2, 50.2, 65.5, 118.7, 120.5, 132.6, 149.8, 155.5. 166.4; HRFAB MS *m/z* 298.2024 for $[M + H]^+$ (calcd 298.2030 for $C_{16}H_{28}O_4N$).

(2*E*,4*R*)-4-[(*tert*-Butoxy)carbonylamino]-6-methylhept-2-enoic Acid, 16. A solution of compound **14** (0.13 g, 0.44 mmol) in THF (5 mL) was bubbled with argon for 5 min, and $[PPh_3]_4$-Pd(0) (0.17 g, 0.15 mmol) was added to the solution. After the mixture was stirred for 10 min, formic acid (40 μL, 1.0 mmol), and *n*-butylamine (50 μL, 0.50 mmol) were added, and the reaction mixture was stirred for 3 h at 25 °C. After removal of the solvent in vacuo, the residue was dissolved in $CHCl_3$ (15 mL) and washed with 1 N HCl (2 × 4 mL) and saturated NaCl (2 × 4 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified with siliga gel column chromatography using $CHCl_3$/MeOH = 7:1 to afford 75 mg (67%) of **16** as an oil: $[\alpha]^{25}_D$ +28.57 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.32 Hz, 3H), 0.84 (d, J = 6.45 Hz, 3H), 1.34−1.37 (m, 1 H), 1.44 (s, 9H), 1.67−1.72 (m, 2H), 4.37−4.45 (br, 2H), 5.92 (d J = 15.67 Hz, 1H), 6.84 (dd, J = 15.78, 5.73 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 23.1, 25.2, 28.7, 44.1, 50.3, 112.0, 151.9, 155.5, 170.9; HRFAB MS *m/z* 280.1517 for $[M + Na]^+$ (calcd 280.1508 for $C_{13}H_{23}O_4NNa$).

Prop-2-enyl 2-{(2*E*,4*R*)-4-[(*tert*-butoxy)carbonylamino]-6-methylhept-2-enoylamino}-(2*S*)-3-{1-[(*tert*-butyl)oxycarbonyl]indol-3-yl}propanoate, 18. To a solution of **16** (85 mg, 0.33 mmol) in DMF (5 mL) were added N^{in}-Boc-D-tryptophan allyl ester (0.14 g, 0.41 mmol), HATU (0.16 g, 0.42 mmol), HOAt (57 mg, 0.42 mmol), and NEM (53 μL, 0.42 mmol). The mixture was stirred at 25 °C for 24 h. The solvent was removed in vacuo, and the residue was dissolved in AcOEt (15 mL). The organic phase was washed with H_2O (2 × 10 mL) and saturated aq NaCl (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified with silica gel column chromatography using hexane/AcOEt = 2:1 to afford 0.14 g (73%) of **18** as an oil: $[\alpha]^{25}_D$ −36.17 (c =1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.35 Hz, 3H), 0.83 (d, J = 6.43 Hz, 3H), 1.34−1.37 (m, 1H), 1.43 (s, 9H), 1.60−1.65 (m, 2H), 1.67 (s, 9H), 3.28−3.30 (m, 2H), 4.31−4.54 (br, 2H), 4.58 (d, J = 5.11 Hz 2H), 5.02 (m, 1H), 5.23−5.31 (m, 2H), 5.83−5.86 (m, 2H), 6.01 (d, J = 7.42 Hz, 1H), 6.70 (dd, J = 15.28, 5.73 Hz, 1H), 7.21 (t, J = 7.42 Hz 1H), 7.30 (t, J = 7.33 Hz, 2H), 7.37 (s, 1H), 7.48 (d, J = 7.75 Hz, 1H), 7.9−8.1 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.1, 25.1, 28.0, 28.6, 28.8, 44.5, 50.2, 53.2, 66.7, 84.2, 115.3, 115.7, 119.4, 119.7, 122.7, 123.0, 124.6, 125.0, 131.0, 131.7, 146.0, 149.9, 155.4, 165.4, 171.6; HRFAB MS *m/z* 606.3155for $[M + Na]^+$ (calcd 606.3145 for $C_{32}H_{45}O_7N_3Na$).

2-[(2*E*,4*R*)-4-amino-6-methylhept-2-enoylamino]-(2*S*)-3-indol-3-ylpropanoic Acid, 20. A solution of compound **18** (26 mg, 45 μmol) in THF (5 mL) was bubbled with argon for 5 min, and $[PPh_3]_4Pd(0)$ (15 mg, 13 μmol) was added to the solution. After the solution was stirred for 10 min, formic acid (3.5 μL, 93 μmol), and *n*-butylamine (4.4 μL, 46 μmol) were added. The reaction mixture was stirred for 3 h at 25 °C, and the solvent was removed in vacuo. The residue was treated with 50% TFA/CH_2Cl_2 (1 mL) for 30 min. After evaporation of the solvent, cold ether (10 mL) was added. The resulting precipitate was washed with ether (10 mL) and then dissolved in 0.1% aqueous TFA. The solution was freeze-dried to yield 12 mg (80%) of **20** as a white powder: HPLC t_R 10.96 min [CH_3CN (10−40%/40 min)]; ^{1}H NMR (400 MHz, D_2O) δ 0.76 (d, J = 6.33 Hz, 3H), 0.83 (d, J = 6.44 Hz, 3H), 1.33−1.50 (m, 3H), 3.13−3.19 (m, 1H), 3.32−3.37 (m, 1H), 3.85−3.88 (m, 1H), 6.10 (d, J = 15.74 Hz, 1H), 6.36 (dd, J = 15.57, 8.68 Hz, 1H), 7.04 (t, J = 7.77 Hz 1H), 7.14 (t, J = 6.05 Hz, 2H), 7.38 (d, J = 8.06, 1H), 7.52 (d, J = 8.09 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 21.1, 22.4, 24.2, 27.2, 41.2, 50.8, 54.9, 109.8, 112.2, 118.8, 119.7, 122.2, 124.7, 127.0, 136.4, 138.8, 166.9, 176.2; HRFAB MS *m/z* 344.1979 for $[M + H]^+$ (calcd 344.1968 for $C_{19}H_{26}O_3N_3$).

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Supporting Information Available: General experimental procedures, preparation of olefin−peptide libraries, the degree of epimerization, syntheses and HPLC chromatograms of olefin peptides listed in Table 1, synthesis of compound **21**, ^{1}H NMR spectra of compounds **14**−**21**, and a typical sigmoidal dose−response curve. This material is available free of charge via the Internet at http://pubs.acs.org.

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