

Amino Acid Derived Enamides: Synthesis and Aminopeptidase Activity

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General experimental

¹H NMR spectra were recorded on a Bruker Avance (600 MHz and 300 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance resulting from incomplete deuteration as the internal standard (CDCl₃: δ 7.25 ppm, DMSO-*d*₆: δ 2.54 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants. ¹³C NMR spectra were recorded on a Bruker Avance (150 MHz or 75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl₃: δ 77.0 ppm, DMSO-*d*₆: δ 39.5 ppm). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associates Chirasil-Val column (25 m x 0.25 mm)) through comparison with the authentic racemic amino acids.¹ Low-resolution mass spectrometry was performed on an Agilent Technologies 1100 Series LC/MS ESI-MS (positive mode). High-resolution mass spectrometry was performed on an Ionspec Ultima FTMS or an Agilent Technologies 1100 Series LC/MS-TOF; ESI-MS (positive mode).

Unless otherwise stated, all reactions were conducted in oven- (150 °C) and flame-dried glassware under an inert atmosphere of dry nitrogen. Indicated temperatures refer to those of the reaction bath, while ambient laboratory temperature is noted as 22 °C. Anhydrous solvents were obtained from Aldrich. Amino acid derivatives were obtained from Advanced Chemtech, Novabiochem, or Bachem Bioscience. All amino amides were utilized as their respective free bases; most were prepared obtained through purchase of the corresponding Cbz-protected derivatives and subsequent hydrogenolysis.² Within each experimental are additional footnotes concerning the preparation of specific reagents and starting materials.

The following is a description of reagents which required special handling prior to use; listed in order of appearance.³ *N,N'*-Dimethylethylenediamine (DMED) was distilled from and stored over KOH. Cuprous iodide was recrystallized from a saturated aqueous solution of sodium iodide. Chlorotrimethylsilane (TMSCl) was distilled from CaH₂ immediately prior to use. Butyllithium (Aldrich; solution in hexanes) was titrated using *N*-pivaloyl-*o*-toluidine according to the method of Suffert.⁴ PPh₃ was recrystallized from hexanes. All other reagents were used as obtained from Aldrich, Alfa-Aesar, Fluka, Lancaster, or Strem Chemicals.

Synthesis of enamides

General Procedure I: Cu-catalyzed coupling in THF

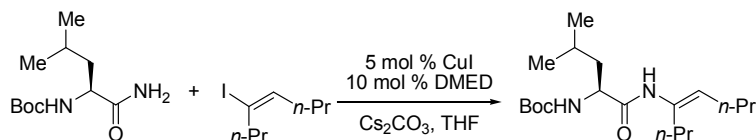
A solution of the vinyl iodide and DMED in THF (1.00 mL) was prepared in a flame-dried 5 mL conical flask then set aside. Separately, an oven-dried 10 mL Schlenk tube fitted with a septum was charged with the amide, CuI and Cs₂CO₃ then evacuated and back-filled with dry nitrogen three times. The vinyl iodide solution was then transferred to the Schlenk tube, the septum rapidly exchanged for a glass stopper and the vessel sealed with Teflon tape. The resulting suspension was then immersed in a preheated oil bath and maintained at 70 °C for 16 h. After cooling to 22 °C the reaction mixture was diluted with EtOAc (2 mL) and placed directly atop a previously prepared silica gel column for purification.

General Procedure II: Cu-catalyzed coupling in DMF

A solution of the vinyl iodide and DMED in DMF (1.00 mL) was prepared in a flame-dried 5 mL conical flask then set aside. Separately, an oven-dried 10 mL Schlenk tube fitted with a septum was charged with the amide, CuI and Cs₂CO₃ then evacuated and back-filled with

dry nitrogen three times. The vinyl iodide solution was then transferred to the Schlenk tube, the septum rapidly exchanged for a glass stopper and the vessel sealed with Teflon tape. The resulting suspension was then immersed in a preheated oil bath and maintained at 50 °C for 1 h. After cooling to 22 °C, all volatiles were removed in vacuo and the residue directly purified by preparative HPLC. Alternatively, the crude reaction mixture was diluted with EtOAc (50 mL) then exhaustively washed with a saturated solution of NaCl. After drying over Na₂SO₄, filtration and concentration in vacuo, the crude residue was purified by silica gel chromatography.

Preparation of *N*-((1*E*)-1-propylpent-1-enyl)(2*S*)-2-[(*tert*-butoxy)carbonylamino]-4-methylpentanamide (1)



Following General Procedure I, Boc-Leu-NH₂ (0.230 g, 1.00 mmol), *E*-4-iodooct-4-ene (119 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (4:1 hexanes/EtOAc) to afford a white powder (158 mg, 0.463 mmol; 92.6%).

¹H NMR: (300 MHz, CDCl₃)

7.23 (1H, brs), 5.82 (1H, brt, *J* = 7.2 Hz), 4.94 (1H, brd, *J* = 7.2 Hz), 4.05 (1H, brs), 2.17 (2H, brt, *J* = 7.5 Hz), 2.00 (2H, dt, *J* = 7.5, 7.5 Hz), 1.70-1.63 (2H, m), 1.49-1.30 (5H, m), 1.42 (9H, s), 0.92 (3H, d, *J* = 6.3 Hz), 0.91 (3H, d, *J* = 6.1 Hz), 0.89 (3H, d, *J* = 7.4 Hz), 0.88 (3H, d, *J* = 7.3 Hz).

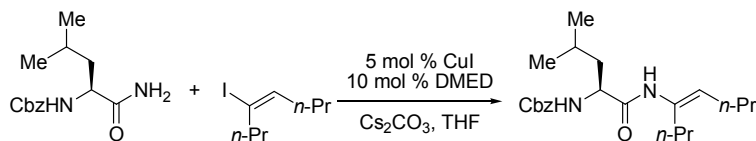
¹³C NMR: (151 MHz, CDCl₃)

170.7, 156.0, 133.7, 118.4, 80.1, 53.6, 40.7, 31.6, 29.2, 28.3, 24.8, 23.1, 22.7, 22.1, 21.0, 13.8, 13.6

HRMS: calcd for C₁₉H₃₆N₂O₃ (M+Na): 363.2618; found: 363.2617

TLC: *R_f* 0.6 (silica gel, 4:1 hexanes/EtOAc, ninhydrin)

Preparation of *N*-((1*E*)-1-propylpent-1-enyl)(2*S*)-4-methyl-2-[(phenylmethoxy)carbonylamino]pentanamide (2)



Following General Procedure I, Cbz-Leu-NH₂ (0.264 g, 1.00 mmol), *E*-4-iodooct-4-ene (119 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (step gradient from 4:1 to 3:2 hexanes/EtOAc) to afford the expected product as a white powder (104 mg, 0.278 mmol; 55.6%) and the hydantoin also as a white solid (47.5, 0.178 mmol; 31.0%).

^1H NMR: (600 MHz, CDCl_3)

7.36-7.30 (5H, m), 7.01 (1H, brs), 5.82 (1H, brs), 5.20 (1H, brd, $J = 7.4$ Hz), 5.11 (2H, s), 4.14 (1H, s), 2.19 (2H, ABqt, $J_{\text{AB}} = 14.2$ Hz, $J_{\text{t}} = 7.5$ Hz), 2.02 (2H, q, $J = 7.5$ Hz), 1.72-1.65 (2H, m), 1.54-1.48 (1H, m), 1.43-1.36 (4H, m), 0.94-0.88 (12H, m)

^{13}C NMR: (151 MHz, CDCl_3)

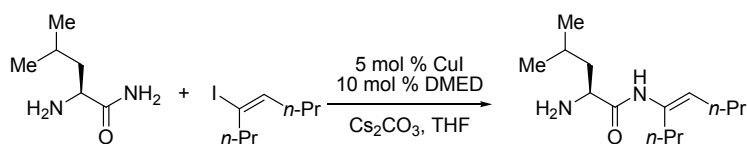
170.3, 156.3, 136.1, 133.6, 128.5, 128.2, 128.0, 118.9, 67.1, 54.2, 41.1, 31.6, 29.2, 24.7, 23.1, 22.9, 22.1, 21.0, 13.9, 13.6

HRMS: calcd for $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_3$ (M+H): 375.2642; found: 375.2646

TLC: R_f 0.4 (silica gel, 4:1 hexanes/EtOAc, CAM)

R_f 0.2 (silica gel, 4:1 hexanes/EtOAc, CAM)

Preparation of *N*-((1*E*)-1-propylpent-1-enyl)(2*S*)-2-amino-4-methylpentanamide (3)



Following General Procedure I, H-Leu-NH₂ (0.130 g, 1.00 mmol), *E*-4-iodooct-4-ene (119 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (49.5 mg, 0.206 mmol; 41.2%).

^1H NMR: (600 MHz, CDCl_3)

8.46 (1H, brs), 5.94 (1H, t, $J = 7.6$ Hz), 3.35 (1H, dd, $J = 9.8, 3.6$ Hz), 2.21 (2H, dd, $J = 7.7, 7.3$ Hz), 2.02 (2H, dt, $J = 7.5, 7.3$ Hz), 1.75-1.68 (2H, m), 1.48-1.31 (7H, m), 0.95 (3H, d, $J = 6.4$ Hz), 0.92-0.86 (9H, m)

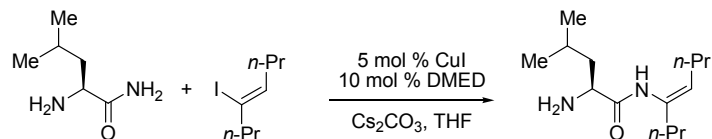
^{13}C NMR: (151 MHz, CDCl_3)

173.5, 133.6, 116.6, 54.0, 44.1, 31.7, 29.2, 25.0, 23.4, 23.3, 21.3, 21.2, 13.9, 13.7

HRMS: calcd for $\text{C}_{14}\text{H}_{28}\text{N}_2\text{O}$ (M+H): 241.2274; found: 241.2274

TLC: R_f 0.4 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Preparation of (2*S*)-*N*-((1*Z*)-1-propylpent-1-enyl)-2-amino-4-methylpentanamide (4)



Following General Procedure I, H-Leu-NH₂ (0.130 g, 1.00 mmol), *Z*-4-iodooct-4-ene (119 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled

to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (6.4 mg, 27 μmol; 5.3%).

¹H NMR: (600 MHz, CDCl₃)

8.57 (1H, brs), 4.91 (1H, t, *J* = 7.0 Hz), 3.42 (1H, dd, *J* = 9.8, 3.6 Hz), 2.41-2.32 (2H, m), 1.95 (2H, q, *J* = 7.3 Hz), 1.78-1.71 (2H, m), 1.45-1.35 (5H, m), 0.98 (3H, d, *J* = 6.3 Hz), 0.94 (3H, d, *J* = 6.2 Hz), 0.90 (3H, t, *J* = 7.4 Hz), 0.89 (3H, t, *J* = 7.4 Hz)

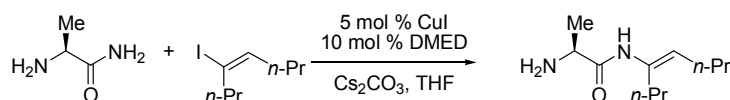
¹³C NMR: (151 MHz, CDCl₃)

173.2, 134.8, 118.7, 54.0, 44.2, 36.5, 28.8, 25.0, 23.4, 22.5, 21.3, 20.9, 13.8, 13.5

HRMS: calcd for C₁₄H₂₈N₂O (M+H): 241.2274; found: 241.2273

TLC: *R_f* 0.3 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Preparation of *N*-((*1E*)-1-propylpent-1-enyl)(*2S*)-2-aminopropanamide (5)



Following General Procedure I, H-Ala-NH₂ (88.1 mg, 1.00 mmol), *E*-4-iodooct-4-ene (119 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (36.9 mg, 0.186 mmol; 37.2%).

¹H NMR: (600 MHz, CDCl₃)

8.44 (1H, brs), 5.98 (1H, t, *J* = 7.5 Hz), 3.49 (1H, q, *J* = 6.9 Hz), 2.23 (2H, dd, *J* = 7.7, 7.4 Hz), 2.04 (2H, q, *J* = 7.5 Hz), 1.50-1.45 (2H, m), 1.44-1.37 (2H, m), 1.36 (3H, d, *J* = 7.0 Hz), 0.93 (3H, t, *J* = 7.4 Hz), 0.92 (3H, t, *J* = 7.4 Hz)

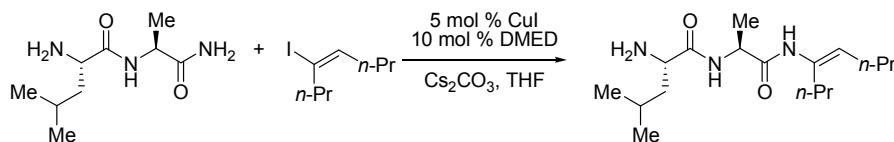
¹³C NMR: (151 MHz, CDCl₃)

173.6, 133.6, 116.8, 51.3, 31.7, 29.2, 23.3, 21.7, 21.2, 13.9, 13.7

HRMS: calcd for C₁₂H₂₂N₂O (M+H): 199.1805; found: 199.1803

TLC: *R_f* 0.3 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Preparation of *N*-{1-[*N*-((*1E*)-1-propylpent-1-enyl)carbamoyl](*1S*)ethyl}(*2S*)-2-amino-4-methylpentanamide (7)



Following General Procedure I, H-Leu-Ala-NH₂ (0.101 g, 0.500 mmol), *E*-4-iodooct-4-ene (59.5 mg, 0.250 mmol), CuI (2.40 mg, 12.5 μmol; 5 mol %), DMED (2.7 μL, 25 μmol) and Cs₂CO₃ (122 mg, 0.375 mmol) were combined. After 16 h at 70 °C, the suspension was cooled

to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (40.5 mg, 0.130 mmol; 52.0%).

¹H NMR: (300 MHz, CDCl₃)

7.73 (1H, brd, *J* = 7.7 Hz), 7.49 (1H, brs), 5.88 (1H, t, *J* = 7.5 Hz), 4.42 (1H, dq, *J* = 7.2 Hz), 3.40 (1H, dd, *J* = 9.9, 3.4 Hz), 2.19 (2H, Abqt, *J*_{AB} = 14.1 Hz, *J*_d = 7.3 Hz), 2.02 (2H, q, *J* = 7.2 Hz), 1.79-1.65 (2H, m), 1.48-1.33 (5H, m), 1.38 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 6.1 Hz), 0.91 (3H, t, *J* = 7.5 Hz), 0.91 (3H, t, *J* = 7.4 Hz)

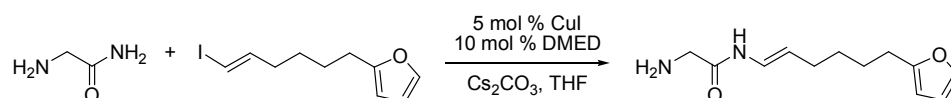
¹³C NMR: (151 MHz, CDCl₃)

176.1, 170.4, 133.9, 118.1, 53.3, 49.1, 43.9, 31.7, 29.2, 24.8, 23.4, 23.2, 21.3, 21.1, 17.3, 13.9, 13.6

HRMS: calcd for C₁₇H₃₃N₃O₂ (M+H): 312.2646; found: 312.2645

TLC: *R*_f 0.4 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)-2-aminoacetamide (**12**)



Following General Procedure I, H-Gly-NH₂ (53.7 mg, 0.724 mmol), **8** (0.100 mg, 0.362 mmol), CuI (3.4 mg, 18 μmol; 5 mol %), DMED (4.0 μL, 36 μmol) and Cs₂CO₃ (177 mg, 0.543 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (step gradient from 9:1 to 4:1 CH₂Cl₂/MeOH) to afford a white solid (22.6 mg, 0.102 mmol; 28.1%).

¹H NMR: (600 MHz, CDCl₃)

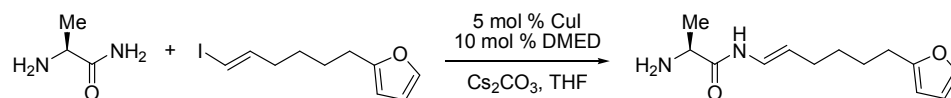
8.81 (1H, brd, *J* = 8.1 Hz), 7.2 (1H, s), 6.74 (1H, brt, *J* = 12.5 Hz), 6.26 (1H, dd, *J* = 2.8, 1.8 Hz), 5.96 (1H, d, *J* = 2.5 Hz), 5.23 (1H, dt, *J* = 14.2, 7.0 Hz), 3.40 (2H, s), 2.61 (2H, t, *J* = 7.5 Hz), 2.06 (2H, dt, *J* = 6.9, 6.9 Hz), 1.64 (2H, tt, *J* = 7.6, 7.4 Hz), 1.42 (2H, tt, *J* = 7.6, 7.4 Hz)

¹³C NMR: (151 MHz, CDCl₃)

169.6, 156.3, 140.7, 122.0, 113.5, 110.0, 104.7, 44.4, 29.5, 29.4, 27.8, 27.5

HRMS: calcd for C₁₂H₁₈N₂O₂ (M+H): 223.1441; found: 223.1444

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*)-2-aminopropanamide (**13**)



Following General Procedure I, H-Ala-NH₂ (95.7 mg, 1.09 mmol), **8** (0.150 mg, 0.543 mmol), CuI (5.2 mg, 27 μmol; 5 mol %), DMED (6.0 μL, 54 μmol) and Cs₂CO₃ (265 mg, 0.815 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted

with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a white solid (103 mg, 0.435 mmol; 80.0%).

¹H NMR: (600 MHz, CDCl₃)

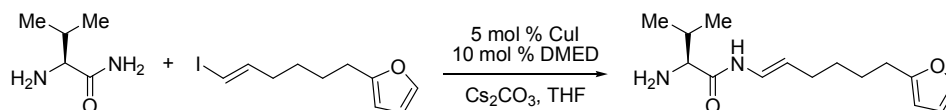
8.86 (1H, brd, *J* = 10.3 Hz), 7.28 (1H, dd, *J* = 1.6, 0.7 Hz), 6.69 (1H, ddt, *J* = 14.2, 11.0, 1.3 Hz), 6.26 (1H, dd, *J* = 3.2, 1.8 Hz), 3.52 (1H, q, *J* = 7.1 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 2.05 (2H, dtd, *J* = 7.3, 7.3, 1.3 Hz), 1.64 (2H, tt, *J* = 7.8, 7.6 Hz), 1.41 (2H, tt, *J* = 7.6, 7.6 Hz), 1.35 (3H, d, *J* = 7.1 Hz)

¹³C NMR: (151 MHz, CDCl₃)

172.5, 156.2, 140.7, 122.3, 113.5, 110.0, 104.7, 50.4, 29.5, 29.3, 27.8, 27.4, 21.5

HRMS: calcd for C₁₃H₂₀N₂O₂ (M+H): 237.1598; found: 237.1594

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*)-2-amino-3-methylbutanamide (14)



Following General Procedure I, H-Val-NH₂ (126 mg, 1.09 mmol), **8** (0.150 mg, 0.543 mmol), CuI (5.2 mg, 27 μmol; 5 mol %), DMED (6.0 μL, 54 μmol) and Cs₂CO₃ (265 mg, 0.815 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (84.0 mg, 0.318 mmol; 58.5%).

¹H NMR: (300 MHz, CDCl₃)

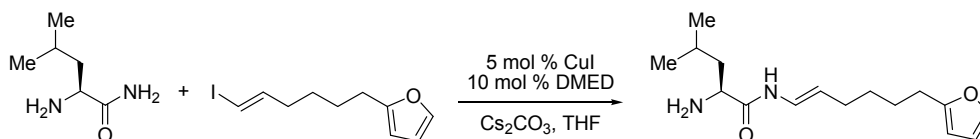
8.89 (1H, brd, *J* = 10.4 Hz), 7.27 (1H, dd, *J* = 1.9, 0.8 Hz), 6.72 (1H, ddt, *J* = 14.2, 11.0, 1.4 Hz), 6.25 (1H, dd, *J* = 3.1, 1.9 Hz), 5.95 (1H, dq, *J* = 3.1, 0.8 Hz), 5.19 (1H, dt, *J* = 14.3, 7.1 Hz), 3.25 (1H, d, *J* = 3.7 Hz), 2.60 (2H, brt, *J* = 7.5 Hz), 2.34 (1H, qqd, *J* = 7.9, 6.9, 3.7 Hz), 2.04 (2H, dtd, *J* = 7.4, 7.2, 1.3 Hz), 1.68-1.58 (2H, m), 1.46-1.36 (2H, m), 0.98 (3H, d, *J* = 7.0 Hz), 0.80 (3H, d, *J* = 6.9 Hz)

¹³C NMR: (75 MHz, CDCl₃)

171.5, 156.2, 140.7, 122.2, 113.2, 110.0, 104.7, 59.8, 30.7, 29.5, 29.4, 27.8, 27.5, 19.7, 15.9

HRMS: calcd for C₁₅H₂₄N₂O₂ (M+H): 265.1911; found: 265.1912

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*)-2-amino-4-methylpentanamide (15)



Following General Procedure I, H-Leu-NH₂ (141 mg, 1.09 mmol), **8** (0.150 mg, 0.543 mmol), CuI (5.2 mg, 27 μmol; 5 mol %), DMED (6.0 μL, 54 μmol) and Cs₂CO₃ (265 mg, 0.815 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted

with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (139 mg, 0.498 mmol; 91.7%).

¹H NMR: (300 MHz, CDCl₃)

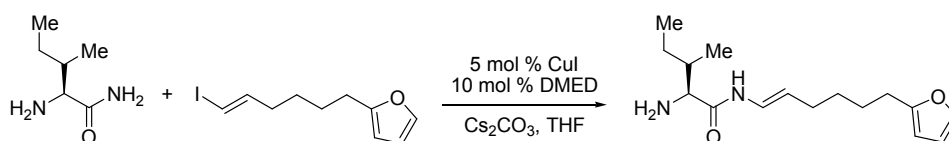
8.89 (1H, brd, *J* = 9.7 Hz), 7.28 (1H, dd, *J* = 1.9, 0.8 Hz), 6.71 (1H, ddt, *J* = 14.0, 11.0, 1.4 Hz), 6.26 (1H, dd, *J* = 3.1, 1.9 Hz), 5.96 (1H, ddq, *J* = 3.1, 1.7, 0.9 Hz), 5.20 (1H, dt, *J* = 14.3, 7.2 Hz), 3.41 (1H, dd, *J* = 9.9, 3.6 Hz), 2.61 (2H, t, *J* = 7.4 Hz), 2.06 (2H, qd, *J* = 7.3, 1.4 Hz), 1.78-1.59 (4H, m), 1.47-1.28 (5H, m), 0.96 (3H, d, *J* = 6.4 Hz), 0.93 (3H, d, *J* = 6.2 Hz)

¹³C NMR: (151 MHz, CDCl₃)

172.6, 156.3, 140.7, 122.4, 113.2, 110.0, 104.7, 53.2, 43.9, 29.5, 29.4, 27.8, 27.5, 24.9, 23.4, 21.3

HRMS: calcd for C₁₆H₂₆N₂O₂ (M+H): 279.2067; found: 279.2065

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*,3*S*)-2-amino-3-methylpentanamide (16)



Following General Procedure I, H-Ile-NH₂ (141 mg, 1.09 mmol), **8** (0.150 mg, 0.543 mmol), CuI (5.2 mg, 27 μmol; 5 mol %), DMED (6.0 μL, 54 μmol) and Cs₂CO₃ (265 mg, 0.815 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (139 mg, 0.344 mmol; 63.4%).

¹H NMR: (300 MHz, CDCl₃)

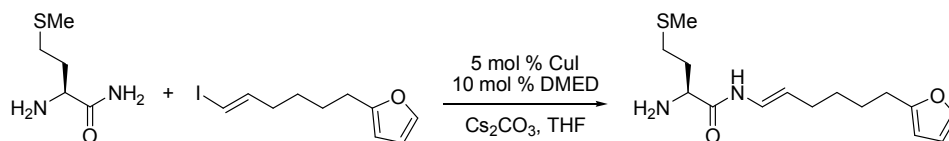
8.92 (1H, brd, *J* = 10.8 Hz), 7.29 (1H, dd, *J* = 1.9, 0.9 Hz), 6.71 (1H, ddt, *J* = 14.3, 11.0, 1.4 Hz), 6.25 (1H, dd, *J* = 3.1, 1.9 Hz), 5.95 (1H, dq, *J* = 3.1, 0.9 Hz), 5.18 (1H, dt, *J* = 14.3, 7.2 Hz), 3.29 (1H, d, *J* = 3.6 Hz), 2.60 (2H, brt, *J* = 7.5 Hz), 2.08-1.98 (3H, m), 1.68-1.58 (2H, m), 1.46-1.27 (5H, m), 1.12-1.00 (1H, m), 0.96 (3H, d, *J* = 7.0 Hz), 0.88 (3H, dd, *J* = 7.4, 7.2 Hz)

¹³C NMR: (75 MHz, CDCl₃)

171.5, 156.2, 140.7, 122.2, 113.1, 110.0, 104.6, 59.6, 37.8, 29.5, 29.4, 27.8, 27.4, 23.6, 16.2, 11.9

HRMS: calcd for C₁₆H₂₆N₂O₂ (M+H): 279.2067; found: 279.2068

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*)-2-amino-4-methylthiobutanamide (17)



Following General Procedure I, H-Met-NH₂ (107 mg, 0.724 mmol), **8** (0.100 mg, 0.362 mmol), CuI (3.4 mg, 18 μmol; 5 mol %), DMED (4.0 μL, 36 μmol) and Cs₂CO₃ (177 mg, 0.543

mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a white solid (78.9 mg, 0.266 mmol; 73.5%).

¹H NMR: (600 MHz, CDCl₃)

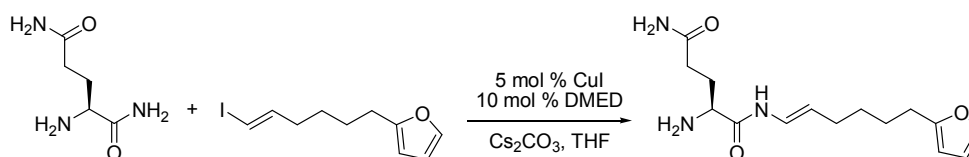
8.84 (1H, brd, *J* = 10.5 Hz), 7.28 (1H, dd, *J* = 1.7, 0.8 Hz), 6.70 (1H, ddt, *J* = 14.2, 11.0, 1.3 Hz), 6.26 (1H, dd, *J* = 3.0, 1.9 Hz), 5.95 (1H, dd, *J* = 3.2, 0.9 Hz), 5.21 (1H, dt, *J* = 14.2, 7.1 Hz), 3.52 (1H, dd, *J* = 8.4, 4.4 Hz), 2.64-2.57 (4H, m), 2.21 (1H, dtd, *J* = 14.0, 8.1, 4.6 Hz), 2.10 (3H, s), 2.06 (2H, dtd, *J* = 7.2, 7.2, 1.2 Hz), 1.79-1.73 (1H, m), 1.64 (2H, tt, *J* = 7.7, 7.5 Hz), 1.42 (2H, tt, *J* = 7.7, 7.5 Hz)

¹³C NMR: (75 MHz, CDCl₃)

171.5, 156.2, 140.7, 122.0, 113.6, 110.0, 104.7, 54.0, 33.9, 30.7, 29.5, 29.3, 27.8, 27.5, 15.3

HRMS: calcd for C₁₅H₂₄N₂O₂S (M+H): 297.1631; found: 297.1634

Preparation of *N*-((*E*)-6-(2-furyl)hex-1-enyl)(*2S*)-2-amino-4-carbamoylbutanamide (**18**)



Following General Procedure II, H-Gln-NH₂ (145 mg, 1.00 mmol), **8** (138 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 1 h at 50 °C, the suspension was cooled to 22 °C, all volatiles removed in vacuo and the residue redissolved in 1:1 MeCN/H₂O (~10 mL). After lyophilization, the crude product mixture was purified by HPLC on a Phenomenex Luca C18 column (21.2 x 250 mm) using a 1%/min gradient from 5-90% MeCN containing 10% H₂O and 0.1 % HCO₂H at 20 mL/min. The expected product eluting at 18 min was collected and lyophilized to a white solid (55.3 mg, 0.162 mmol; 32.6%). The derived lactam, eluting at 40 min, was also collected and lyophilized to a white solid (7.9 mg, 0.029 mmol; 5.7%).

¹H NMR: (600 MHz, DMSO-*d*₆)

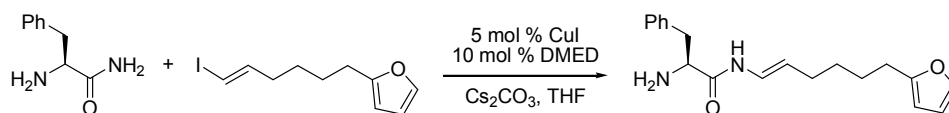
9.90 (1H, brs), 8.33 (1H, brs), 7.47 (1H, dd, *J* = 1.8, 0.7 Hz), 7.33 (1H, s), 6.76 (1H, s), 6.58 (1H, d, *J* = 14.3 Hz), 6.32 (1H, dd, *J* = 3.1, 1.9 Hz), 6.06 (1H, dd, *J* = 3.1, 0.7 Hz), 5.36 (3H, brs), 5.26 (1H, dt, *J* = 14.3, 7.2 Hz), 3.38 (1H, brs), 2.59 (2H, t, *J* = 7.5 Hz), 2.11 (2H, t, *J* = 7.8 Hz), 2.00 (2H, q, *J* = 7.0 Hz), 1.86-1.81 (1H, m), 1.74-1.68 (1H, m), 1.57 (2H, tt, *J* = 7.6, 7.5 Hz), 1.37-1.32 (2H, m)

¹³C NMR: (151 MHz, DMSO-*d*₆)

173.7, 170.0, 164.8, 155.6, 141.1, 122.8, 112.6, 110.2, 104.9, 53.5, 31.1, 29.2, 28.9, 28.9, 27.0

HRMS: calcd for C₁₅H₂₃N₃O₃ (M+H): 294.1812; found: 294.1811

Preparation of *N*-((*E*)-6-(2-furyl)hex-1-enyl)(*2S*)-2-amino-3-phenylpropanamide (**19**)



Following General Procedure I, H-Phe-NH₂ (178 mg, 1.09 mmol), **8** (0.150 mg, 0.543 mmol), CuI (5.2 mg, 27 μmol; 5 mol %), DMED (6.0 μL, 54 μmol) and Cs₂CO₃ (265 mg, 0.815 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (153 mg, 0.488 mmol; 89.9%).

¹H NMR: (600 MHz, CDCl₃)

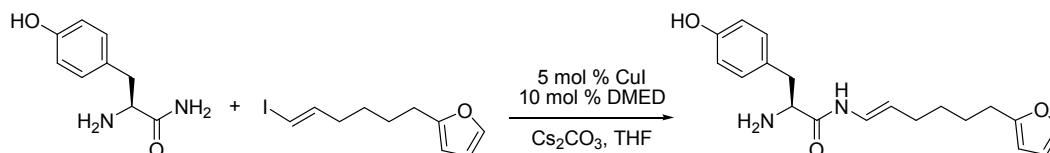
8.84 (1H, brd, *J* = 10.6 Hz), 7.31 (2H, dd, *J* = 7.4, 7.2 Hz), 7.28 (1H, dd, *J* = 1.8, 0.9 Hz), 7.26-7.23 (1H, m), 7.21 (2H, brd, *J* = 7.0 Hz), 6.73 (1H, ddt, *J* = 14.3, 10.9, 1.4 Hz), 6.26 (1H, dd, *J* = 3.0, 1.9 Hz), 5.96 (1H, dd, *J* = 3.2, 0.9 Hz), 5.18 (1H, dt, *J* = 14.4, 7.2 Hz), 3.62 (1H, dd, *J* = 9.7, 3.8 Hz), 3.30 (1H, ABX, *J*_{AB} = 14.0 Hz, *J*_{AX} = 3.8 Hz), 2.67 (1H, ABX, *J*_{AB} = 14.0 Hz, *J*_{BX} = 9.7 Hz), 2.61 (2H, t, *J* = 7.5 Hz), 2.06 (2H, dtd, *J* = 7.2, 7.2, 1.1 Hz), 1.64 (2H, tt, *J* = 7.7, 7.7 Hz), 1.42 (2H, tt, *J* = 7.7, 7.4 Hz)

¹³C NMR: (151 MHz, CDCl₃)

171.3, 156.2, 140.7, 137.7, 129.2, 128.7, 126.9, 122.2, 113.7, 110.0, 104.7, 56.1, 40.8, 29.4, 29.3, 27.8, 27.4

HRMS: calcd for C₁₉H₂₄N₂O₂ (M+H): 313.1911; found: 313.1910

Preparation of *N*-((*1E*)-6-(2-furyl)hex-1-enyl)(*2S*)-2-amino-3-(4-hydroxyphenyl)propanamide (**20**)



Following General Procedure II, H-Tyr-NH₂ (0.180 g, 1.00 mmol), **8** (138 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 1 h at 50 °C, the suspension was cooled to 22 °C then diluted with EtOAc (50 mL), washed with saturated aqueous NaCl (5 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by chromatography on silica (step gradient from 1:1 hexanes/EtOAc to 19:1 CH₂Cl₂/MeOH to 9:1 CH₂Cl₂/MeOH) afforded the expected product (52.1 mg, 0.159 mmol; 31.7%) and the individual imidazolidinone diastereomers resulting from condensation with the liberated aldehyde (4.6 mg, 9.7 μmol; 3.9%) and (8.6 mg, 18 μmol; 7.2%) respectively, all as colorless oils.

¹H NMR: (300 MHz, CDCl₃)

8.84 (1H, brs, *J* = 11.0 Hz), 7.29 (1H, dd, *J* = 1.9, 0.9 Hz), 7.04 (2H, AA'BB', *J*_{AB} = 8.5 Hz, *J*_{AA'} = 2.4 Hz), 6.79 (2H, AA'BB', *J*_{AB} = 8.6 Hz, *J*_{BB'} = 2.5 Hz), 6.72 (1H, ddt, *J* = 13.8, 10.9, 1.3 Hz), 6.27 (1H, dd, *J* = 3.1, 1.9 Hz), 5.97 (1H, dq, *J* = 3.1, 0.8 Hz), 5.20 (1H, dt, *J* = 14.3, 7.2 Hz), 3.59 (1H, ABX, *J*_{AX} = 4.1 Hz, *J*_{BX} =

9.3 Hz), 3.17 (1H, ABX, $J_{AB} = 13.9$ Hz, $J_{AX} = 4.0$ Hz), 2.67-2.49 (3H, m), 2.07 (2H, dq, $J = 7.3, 1.3$ Hz), 1.69-1.59 (2H, m), 1.47-1.37 (2H, m)

^{13}C NMR: (75 MHz, CDCl_3)

171.8, 156.2, 155.1, 140.7, 130.4, 129.0, 122.0, 115.7, 114.3, 110.0, 104.7, 56.2, 39.9, 29.4, 29.3, 27.8, 27.4

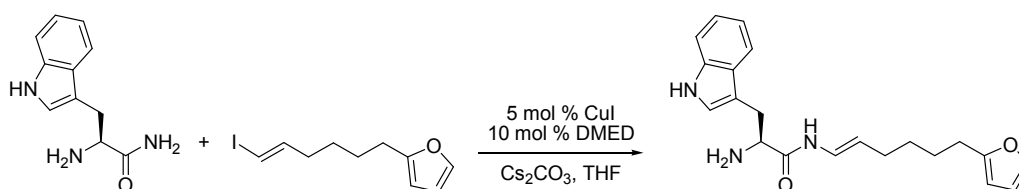
HRMS: calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_3$ (M+H): 329.1860; found: 329.1865

TLC: R_f 0.3 (silica gel, 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$, ninhydrin)

R_f 0.5 (silica gel, 1:1 hexanes/EtOAc, ninhydrin)

R_f 0.4 (silica gel, 1:1 hexanes/EtOAc, ninhydrin)

Preparation of *N*-((1*E*)-6-(2-furyl)hex-1-enyl)(2*S*)-2-amino-3-indol-3-ylpropanamide (**21**)



Following General Procedure I, H-Trp-NH₂ (147 mg, 0.724 mmol), **8** (0.100 mg, 0.362 mmol), CuI (3.4 mg, 18 μmol ; 5 mol %), DMED (4.0 μL , 36 μmol) and Cs₂CO₃ (177 mg, 0.543 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the expected product as a colorless oil (72.3 mg, 0.206 mmol; 56.8%) and the dimeric product as a pale yellow oil (20.0 mg, 0.040 mmol; 22.1%).

^1H NMR: (600 MHz, CDCl_3)

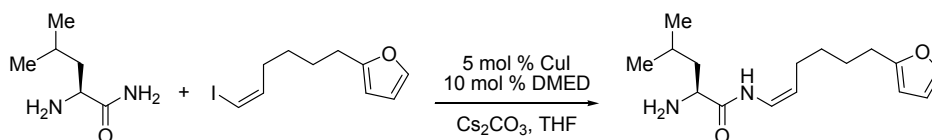
8.86 (1H, brd, $J = 10.5$ Hz), 8.09 (1H, brs), 7.67 (1H, d, $J = 7.8$ Hz), 7.37 (1H, d, $J = 8.3$ Hz), 7.29 (1H, dd, $J = 1.8, 0.9$ Hz), 7.22-7.19 (1H, m), 7.14-7.12 (1H, m), 7.06 (1H, brd, $J = 2.0$ Hz), 6.74 (1H, ddt, $J = 14.3, 11.0, 1.2$ Hz), 6.27 (1H, dd, $J = 3.1, 2.0$ Hz), 5.97 (1H, dd, $J = 3.1, 0.9$ Hz), 5.16 (1H, dt, $J = 14.2, 7.2$ Hz), 3.74 (1H, dd, $J = 9.2, 4.0$ Hz), 3.41 (1H, ABX, $J_{AB} = 14.7$ Hz, $J_{AX} = 4.0$ Hz), 2.92 (1H, ABX, $J_{AB} = 14.6$ Hz, $J_{BX} = 9.0$ Hz), 2.61 (2H, t, $J = 7.5$ Hz), 2.06 (2H, qd, $J = 7.2, 1.2$ Hz), 1.64 (2H, tt, $J = 7.8, 7.4$ Hz), 1.42 (2H, tt, $J = 7.8, 7.4$ Hz)

^{13}C NMR: (151 MHz, CDCl_3)

171.8, 156.3, 140.7, 136.4, 127.5, 123.0, 122.4, 122.3, 119.7, 118.9, 113.5, 111.7, 111.2, 111.0, 104.7, 55.4, 30.5, 29.5, 29.4, 27.8, 27.4

HRMS: calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2$ (M+H): 352.2020; found: 352.2015

Preparation of (2*S*)-*N*-((1*Z*)-6-(2-furyl)hex-1-enyl)-2-amino-4-methylpentanamide (**22**)



Following General Procedure I, H-Leu-NH₂ (0.130 g, 1.00 mmol), **9** (138 mg, 0.500 mmol), CuI (4.8 mg, 25 μmol; 5 mol %), DMED (5.4 μL, 0.05 mmol) and Cs₂CO₃ (244 mg, 0.750 mmol) were combined. After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (70.4 mg, 0.253 mmol; 50.6%).

¹H NMR: (300 MHz, CDCl₃)

9.18 (1H, brd, *J* = 11.1 Hz), 7.27 (1H, dd, *J* = 1.9, 0.9 Hz), 6.65 (1H, ddt, *J* = 11.4, 8.9, 1.6 Hz), 6.25 (1H, dd, *J* = 3.1, 1.8 Hz), 5.95 (1H, dq, *J* = 3.1, 0.9 Hz), 4.74 (1H, dt, *J* = 9.0, 7.3 Hz), 3.42 (1H, dd, *J* = 10.0, 3.5 Hz), 2.62 (2H, brt, *J* = 7.5 Hz), 2.05 (2H, dtd, *J* = 7.3, 7.3, 1.6 Hz), 1.78-1.61 (4H, m), 1.50-1.30 (5H, m), 0.95 (3H, d, *J* = 6.3 Hz), 0.92 (3H, d, *J* = 6.2 Hz)

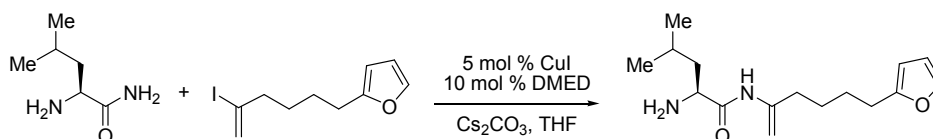
¹³C NMR: (75 MHz, CDCl₃)

172.7, 156.1, 140.7, 120.8, 111.2, 110.0, 104.7, 53.3, 43.8, 28.7, 27.7, 27.5, 25.4, 24.9, 23.4, 21.2

HRMS: calcd for C₁₆H₂₆N₂O₂ (M+H): 279.2067; found: 279.2067

TLC: *R*_f 0.6 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Preparation of (2*S*)-2-amino-*N*-[1-(4-(2-furyl)butyl)vinyl]-4-methylpentanamide (**23**)



Following General Procedure I, H-Leu-NH₂ (76.4 mg, 0.587 mmol), **10** (81.0 mg, 0.293 mmol), CuI (2.8 mg, 15 μmol; 5 mol %), DMED (3.2 μL, 0.03 mmol) and Cs₂CO₃ (143 mg, 0.440 mmol) were combined in THF (587 μL). After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (EtOAc) to afford the expected product (19.5 mg, 0.070 mmol; 19.5%) and the individual imidazolidinone diastereomers (10.9 mg, 0.039 mmol; 13.3%) and (12.0 mg, 0.043 mmol; 14.7%) respectively, all as colorless oils.

¹H NMR: (600 MHz, CDCl₃)

8.73 (1H, brs), 7.29 (1H, dd, *J* = 1.8, 0.8 Hz), 6.27 (1H, dd, *J* = 3.1, 1.9 Hz), 5.98 (1H, dd, *J* = 3.1, 0.8 Hz), 5.59 (1H, s), 4.49 (1H, s), 3.39 (1H, dd, *J* = 9.9, 3.6 Hz), 2.65 (2H, t, *J* = 7.4 Hz), 2.20 (2H, dd, *J* = 7.6, 7.5 Hz), 1.78-1.72 (2H, m), 1.71-1.66 (2H, m), 1.57-1.52 (2H, m), 1.39-1.32 (1H, m), 0.98 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 6.2 Hz)

¹³C NMR: (151 MHz, CDCl₃)

174.0, 156.0, 140.7, 140.6, 110.1, 105.7, 98.1, 54.0, 43.9, 35.5, 27.7, 27.3, 27.0, 25.0, 23.4, 21.3

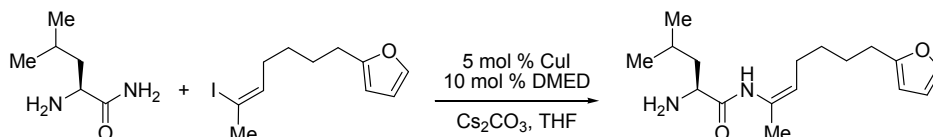
HRMS: calcd for C₁₆H₂₆N₂O₂ (M+H): 279.2067; found: 279.2067

TLC: *R*_f 0.4 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

R_f 0.4 (silica gel, EtOAc, ninhydrin)

R_f 0.2 (silica gel, EtOAc, ninhydrin)

Preparation of (2*S*)-*N*-((1*Z*)-6-(2-furyl)-1-methylhex-1-enyl)-2-amino-4-methylpentanamide (24)



Following General Procedure I, H-Leu-NH₂ (0.100 g, 0.772 mmol), **11** (112 mg, 0.386 mmol), CuI (3.7 mg, 19 μmol; 5 mol %), DMED (4.2 μL, 0.04 mmol) and Cs₂CO₃ (189 mg, 0.579 mmol) were combined in THF (770 μL). After 16 h at 70 °C, the suspension was cooled to 22 °C then diluted with EtOAc (2 mL) and purified directly by chromatography on silica (9:1 CH₂Cl₂/MeOH) to afford a colorless oil (47.7 mg, 0.163 mmol; 42.3%).

¹H NMR: (300 MHz, CDCl₃)

8.79 (1H, brs), 7.27 (1H, dd, $J = 1.9, 0.9$ Hz), 6.25 (1H, dd, $J = 3.1, 1.9$ Hz), 5.95 (1H, dq, $J = 3.1, 0.9$ Hz), 4.76 (1H, brs, $J = 7.1$ Hz), 3.38 (1H, dd, $J = 9.8, 3.6$ Hz), 2.60 (2H, brt, $J = 7.3$ Hz), 2.05 (3H, q, $J = 1.3$ Hz), 1.98 (2H, brq, $J = 7.4$ Hz), 1.75-1.58 (4H, m), 1.46-1.32 (4H, m), 0.96 (3H, d, $J = 6.4$ Hz), 0.93 (3H, d, $J = 6.2$ Hz)

¹³C NMR: (75 MHz, CDCl₃)

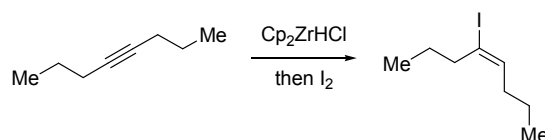
173.3, 156.2, 140.6, 131.5, 116.8, 110.0, 104.6, 54.0, 44.1, 28.7, 27.7, 27.6, 26.2, 25.0, 23.4, 21.3, 21.0

HRMS: calcd for C₁₇H₂₈N₂O₂ (M+H): 293.2224; found: 293.2223

TLC: R_f 0.5 (silica gel, 9:1 CH₂Cl₂/MeOH, ninhydrin)

Synthesis of vinyl iodides

Preparation of *E*-4-iodooct-4-ene⁵



A suspension of Cp₂ZrHCl (15.5 g, 60.0 mmol) in CH₂Cl₂ (250 mL) was treated with 4-octyne (7.34 mL, 50.0 mmol) dropwise over 5 min at 22 °C. During the next several hours, the suspension became homogeneous and red-orange in color. After 13.5 h, the now pale yellow solution was cooled to 0 °C and treated with I₂ (14.0 g, 55.0 mmol) in one portion. Upon complete dissolution, the ice bath was removed and the solution warmed to 22 °C. After 1 h, the solution was poured into 1 M HCl (200 mL) containing ~50 g ice and the resulting biphase vigorously stirred 0.5 h. The layers were then separated and the aqueous layer washed with CH₂Cl₂ (3 x 75 mL). The combined CH₂Cl₂ layers were washed with saturated aqueous Na₂S₂O₃ and NaCl (200 mL each), then dried over MgSO₄, filtered and concentrated in vacuo. The crude

product was purified by chromatography on silica (hexanes) to obtain a pale yellow oil (6.57 g, 27.6 mmol; 55.2%).

$^1\text{H NMR}$: (600 MHz, CDCl_3)

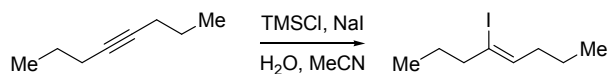
6.20 (1H, t, $J = 7.5$ Hz), 2.35 (2H, t, $J = 7.2$ Hz), 2.03 (2H, q, $J = 7.4$ Hz), 1.56-1.49 (2H, m), 1.42-1.36 (2H, m), 0.91 (3H, t, $J = 7.4$ Hz), 0.91 (3H, t, $J = 7.4$ Hz)

$^{13}\text{C NMR}$: (151 MHz, CDCl_3)

141.5, 103.4, 40.3, 32.9, 22.4, 22.3, 13.6, 12.8

TLC: R_f 0.8 (silica gel, pentane, uv)

Preparation of **Z-4-iodooct-4-ene**⁶



TMSI was prepared in situ through the addition of TMSCl (3.04 mL, 24.0 mmol) to a solution of NaI (3.60 g, 24.0 mmol) in MeCN (40.0 mL) at 22 °C. The resulting suspension was then treated with H_2O (216 μL , 12.0 mmol) and, after 10 min, 4-octyne (2.93 mL, 20.0 mmol) at a rate of 0.5 mL/min. The reaction mixture became homogeneous and dark yellow in color during the addition. After 1 h, the solution was diluted with H_2O (20 mL), and the resulting red-orange biphase washed with Et_2O (3 x 60 mL). The combined Et_2O layers were washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (3 x 30 mL), then dried over MgSO_4 , filtered and concentrated in vacuo. Purification by chromatography on silica (hexanes) afforded a colorless oil (2.50 g, 10.5 mmol; 52.5%).

$^1\text{H NMR}$: (300 MHz, CDCl_3)

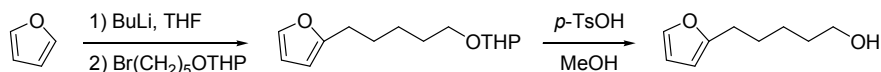
5.47 (1H, tt, $J = 6.7, 1.2$ Hz), 2.46-2.41 (2H, m), 2.13-2.06 (2H, m), 1.60-1.49 (2H, m), 1.47-1.37 (2H, m), 0.93 (3H, t, $J = 7.4$ Hz), 0.88 (3H, t, $J = 7.4$ Hz)

$^{13}\text{C NMR}$: (75 MHz, CDCl_3)

134.8, 109.6, 47.1, 38.4, 22.5, 21.7, 13.7, 12.6

TLC: R_f 0.8 (silica gel, pentane, uv)

Preparation of **5-(2-furyl)pentan-1-ol**

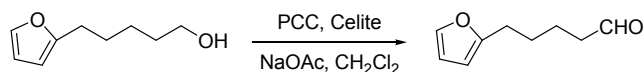


BuLi (302 mmol; 121 mL of a 2.50 M solution in hexanes) was added dropwise over 0.5 h to a solution of furan (27.0 mL, 371 mmol) in THF (530 mL) at 0 °C. After 1 h, the pale yellow solution was treated with 2-(5-bromopentyloxy)tetrahydro-2H-pyran⁷ (25.3 g, 101 mmol) at a rate of 1 mL/min and the resulting mixture warmed slowly to 22 °C as the ice bath melted overnight. After 16 h the solution was treated with saturated aqueous NH_4Cl (300 mL) with transfer to a separatory funnel and the layers separated. The aqueous layer was then washed with Et_2O (3 x 250 mL) and the combined THF and Et_2O layers dried over MgSO_4 , filtered and concentrated in vacuo. Purification by chromatography on silica using a gradient from 19:1 to

4:1 pentane/Et₂O (*R_f* = 0.5 in 9:1 pentane/Et₂O) afforded a colorless oil (21.6 g, 90.6 mmol; 90.0%) that was used directly in the subsequent deprotection step.

A solution of the THP ether (20.0 g, 83.9 mmol) in wet MeOH (168 mL) was treated with *p*-TsOH (1.60 g, 8.39 mmol; 10 mol %) in one portion at 22 °C. After 5 h, all volatiles were removed in vacuo and the residue loaded directly onto a silica gel column previously prepared in 4:1 pentane/Et₂O. A 4:1 to 1:4 pentane/Et₂O step gradient was then utilized to elute the product as a colorless oil (10.2 g, 66.1 mmol; 78.8%). Spectroscopic data were consistent with a published report.⁸

Preparation of 5-(2-furyl)pentanal



A suspension of PCC (25.9 g, 0.120 mol), NaOAc (984 mg, 12.0 mmol) and Celite (5 g) in CH₂Cl₂ (280.0 mL) at 22 °C was treated with 5-(2-furyl)pentan-1-ol (60.0 mmol; 15.0 mL of a 4.00 M solution in CH₂Cl₂) at a rate of 1 mL/min. Additional CH₂Cl₂ (5 x 1 mL) was used to quantitate the transfer and the resulting brown slurry stirred 1.5 h. The suspension was diluted with Et₂O (300 mL), vigorously stirred 0.5 h then filtered through Florisil. The filter cake was exhaustively washed with Et₂O and the combined filtrates concentrated in vacuo. Purification by chromatography on silica (9:1 to 4:1 pentane/Et₂O gradient) afforded a foul-smelling, colorless oil (6.07 g, 39.9 mmol; 66.5%).

¹H NMR: (600 MHz, CDCl₃)

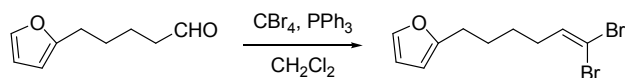
9.74 (1H, t, *J* = 1.8 Hz), 7.28 (1H, dd, *J* = 1.8, 0.8 Hz), 6.26 (1H, dd, *J* = 3.1, 1.8 Hz), 5.97 (1H, dd, *J* = 3.1, 0.8 Hz), 2.65-2.63 (2H, m), 2.45-2.42 (2H, m), 1.68-1.66 (4 H, m)

¹³C NMR: (151 MHz, CDCl₃)

202.2, 155.5, 140.8, 110.1, 104.9, 43.5, 27.6, 27.5, 21.5

TLC: *R_f* 0.4 (silica gel, 4:1 pentane/Et₂O, KMnO₄)

Preparation of 2-(6,6-dibromohex-5-enyl)furan



A solution of PPh₃ (34.5 g, 131 mmol) in CH₂Cl₂ (200.0 mL) was cooled to 0 °C and treated with CBr₄ (21.8 g, 65.7 mmol) in one portion. Using a cannula, a solution of 5-(2-furyl)pentanal (5.00 g, 32.9 mmol) in CH₂Cl₂ (100.0 mL) was then added over 0.75 h with additional CH₂Cl₂ (3 x 10 mL) used to quantitate the transfer. Complete conversion was noted within 5 min. The red-orange solution was then poured into pentane (300 mL) with vigorous stirring and the resulting suspension filtered through Celite. The filter cake was washed with pentane (3 x 150 mL) and the combined filtrates concentrated in vacuo. Purification by chromatography on silica (pentane) afforded a colorless oil (9.24 g, 30.0 mmol; 91.3%).

¹H NMR: (300 MHz, CDCl₃)

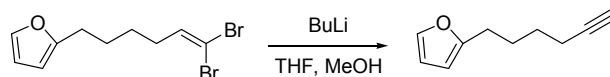
7.29 (1H, dd, $J = 1.9, 0.9$ Hz), 6.37 (1H, t, $J = 7.3$ Hz), 6.27 (1H, ddt, $J = 3.2, 1.9, 0.3$ Hz), 5.98 (1H, dq, $J = 3.2, 0.9$ Hz), 2.63 (2H, brt, $J = 7.3$ Hz), 2.12 (2H, dt, $J = 7.3, 7.3$ Hz), 1.72-1.62 (2H, m), 1.52-1.42 (2H, m)

^{13}C NMR: (75 MHz, CDCl_3)

155.8, 140.8, 138.4, 110.1, 104.9, 88.9, 32.7, 27.6, 27.4, 27.2

TLC: R_f 0.8 (silica gel, 4:1 pentane/ Et_2O , KMnO_4)

Preparation of 2-hex-5-ynylfuran



2-(6,6-dibromohex-5-enyl)furan (6.88 g, 22.3 mmol) was dissolved in THF (112 mL), cooled to -78 °C and treated with BuLi (46.9 mmol; 22.3 mL of a 2.10 M solution in hexanes) at a rate of 1 mL/min. Upon completion of the addition, the solution was warmed to -20 °C, maintained 0.75 h, then cooled back to -78 °C and treated with MeOH (1.81 mL, 44.7 mmol). The resulting solution was warmed immediately back to 22 °C, stirred 0.75 h, then poured into saturated aqueous NH_4Cl (300 mL). The layers were separated and the aqueous layers washed with Et_2O (4 x 150 mL). The combined THF and Et_2O layers were dried over MgSO_4 , filtered and concentrated to a pale yellow oil. *NOTE: compound is volatile and care should be taken during solvent removal operations.* Subsequent purification by chromatography on silica (pentane) afforded a colorless oil (3.30 g, 22.3 mmol; >98%).

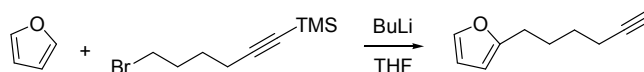
^1H NMR: (600 MHz, CDCl_3)

7.29 (1H, dd, $J = 1.8, 0.8$ Hz), 6.27 (1H, dd, $J = 3.1, 1.8$ Hz), 5.98 (1H, dd, $J = 3.1, 0.8$ Hz), 2.64 (2H, t, $J = 7.6$ Hz), 2.21 (2H, td, $J = 7.0, 2.6$ Hz), 1.94 (1H, t, $J = 2.7$ Hz), 1.79-1.73 (2H, m), 1.60-1.55 (2H, m)

^{13}C NMR: (151 MHz, CDCl_3)

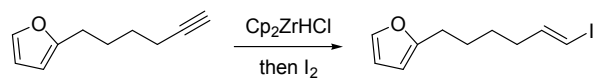
155.9, 140.8, 110.0, 104.8, 84.2, 68.4, 27.9, 27.4, 27.1, 18.2

Alternative preparation of 2-hex-5-ynylfuran



BuLi (75.0 mmol; 31.2 mL of a 2.40 M solution in hexanes) was added dropwise at 1 mL/min to a solution of furan (6.36 mL, 87.5 mmol) in THF (125 mL) at 0 °C. After 1 h, the pale yellow solution was treated with 8-bromo-2,2-dimethyl-2-sila-oct-3-yne⁹ (5.83 g, 25.0 mmol) at a rate of 0.5 mL/min and the resulting mixture warmed slowly to 22 °C as the ice bath melted overnight. After 18 h the yellow-orange solution was treated with saturated aqueous NH_4Cl (100 mL) with transfer to a separatory funnel and the layers separated. The aqueous layer was then washed with Et_2O (3 x 100 mL) and the combined THF and Et_2O layers washed with saturated aqueous NaCl (100 mL), then dried over MgSO_4 , filtered and concentrated in vacuo. Purification by chromatography on silica (pentane) afforded a colorless oil (2.57 g, 17.3 mmol; 69.4%).

Preparation of 2-((5E)-6-iodohex-5-enyl)furan (8)



2-Hex-5-ynylfuran (1.96 g, 13.2 mmol) was dissolved in CH₂Cl₂ (53.0 mL), cooled to 0 °C, then treated with Cp₂ZrHCl (5.12 g, 19.8 mmol) in one portion. The resulting suspension was warmed to 22 °C, maintained 0.75 h, then cooled back to 0 °C and treated with I₂ (19.8 mmol; 5.00 M solution in THF) at a rate of 1 mL/min. The red-orange reaction mixture was stirred 0.25 h then treated with 5% aqueous NaHCO₃ until gas evolution was complete (~10 mL). The CH₂Cl₂ solution was then transferred to a separatory funnel and washed with saturated aqueous NaHCO₃ (3 x 10 mL); any solids which form can be removed by filtration through Celite. The combined aqueous layers were further washed with pentane (3 x 10 mL) then discarded. The CH₂Cl₂ and pentane solutions were combined, dried over MgSO₄, filtered and concentrated in vacuo to an orange oil. Purification by chromatography on silica (pentane) afforded a pale pink oil that was decolorized by passage through a short pad of Florisil to yield a colorless oil (2.23 g, 8.08 mmol; 61.1%).

¹H NMR: (600 MHz, CDCl₃)

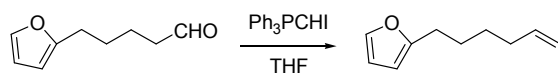
7.29 (1H, dd, *J* = 1.8, 0.8 Hz), 6.50 (1H, dt, *J* = 14.3, 7.3 Hz), 6.27 (1H, dd, *J* = 3.1, 1.9 Hz), 5.99 (1H, dt, *J* = 14.3, 1.4 Hz), 5.96 (1H, dd, *J* = 3.1, 0.7 Hz), 2.61 (2H, t, *J* = 7.4 Hz), 2.08 (2H, dtd, *J* = 7.4, 7.3, 1.3 Hz), 1.64 (2H, tt, *J* = 7.6, 7.6 Hz), 1.44 (2H, tt, *J* = 7.6, 7.4 Hz)

¹³C NMR: (151 MHz, CDCl₃)

155.9, 146.3, 140.8, 110.0, 104.8, 74.6, 35.7, 27.8, 27.7, 27.3

TLC: *R*_f 0.4 (silica gel, pentane, KMnO₄)

Preparation of 2-((5Z)-6-iodohex-5-enyl)furan (9)¹⁰



A suspension of [Ph₃PCH₂I]¹¹ (1.99 g, 3.75 mmol) in THF (15.0 mL) was treated with NaHMDS (3.50 mmol; 3.50 mL of a 1.00 M solution in THF) at 22 °C. After nearly complete dissolution, the orange reaction mixture was cooled to -78 °C and treated with DMPU (2.26 mL, 18.7 mmol). After 10 min, a solution of 5-(2-furyl)pentanal (381 mg, 2.50 mmol) in THF (7.00 mL) was added over 0.25 h using a cannula. Additional THF (3 x 1.00 mL) was used to quantitate the transfer and the resulting suspension maintained at -78 °C for 0.5 h. The cooling bath was then removed and the reaction mixture warmed to 22 °C during the next 0.5 h. The suspension was poured into hexanes (150 mL), stirred vigorously for 5 min then filtered through Celite. The filter cake was washed with hexanes (3 x 25 mL), and the combined filtrates transferred to a separatory funnel and washed with saturated aqueous NH₄Cl (2 x 25 mL) followed by saturated aqueous NaCl (25 mL), then dried over MgSO₄, filtered and concentrated in vacuo. Purification by chromatography on silica (pentane) afforded a colorless oil (466 mg, 1.69 mmol 67.5%). The *Z*:*E* ratio was determined by ¹H NMR to be 13:1.

¹H NMR: (600 MHz, CDCl₃)

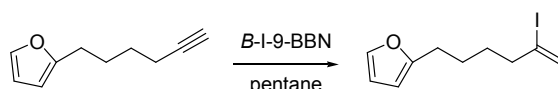
7.29 (1H, brs), 6.27 (1H, dd, $J = 3.1, 1.8$ Hz), 6.20 (1H, dt, $J = 7.2, 1.0$ Hz), 6.16 (1H, td, $J = 6.9, 6.7$ Hz), 5.98 (1H, dd, $J = 3.1, 0.8$ Hz), 2.64 (2H, t, $J = 7.6$ Hz), 2.17 (2H, dtd, $J = 7.4, 7.4, 1.0$ Hz), 1.68 (2H, tt, $J = 7.7, 7.7$ Hz), 1.48 (2H, tt, $J = 7.7, 7.4$ Hz)

^{13}C NMR: (151 MHz, CDCl_3)

156.1, 141.0, 140.7, 110.0, 104.8, 82.5, 34.4, 27.8, 27.5, 27.4

TLC: R_f 0.9 (silica gel, 4:1 pentane/ Et_2O , CAM)

Preparation of 2-(5-iodohex-5-enyl)furan (10)¹²



B-I-9-BBN (10.8 mmol; 10.8 mL of a 1.0 M solution in hexanes) was diluted with pentane (60.0 mL), cooled to 0 °C then treated with 2-hex-5-ynylfuran (1.33 g, 9.00 mmol) dropwise over 5 min. The purple solution became red-brown in color during the addition. After 1 h, the mixture was treated with glacial AcOH (6.00 mL), maintained at 0 °C for 0.5 h, then treated with H_2O (84 mL). The resulting biphasic mixture was warmed to 22 °C, stirred vigorously for 0.5 h then separated. The aqueous layer was then washed with hexanes (3 x 50 mL). The combined hexanes washes were further washed with H_2O , saturated aqueous NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ and finally H_2O (50 mL each), then dried over MgSO_4 , filtered and concentrated in vacuo. Purification by chromatography on silica (hexanes) afforded a colorless oil (764 mg, 2.77 mmol; 30.7%).

^1H NMR: (600 MHz, CDCl_3)

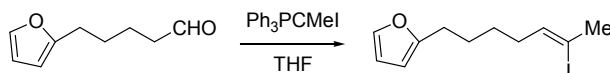
7.30 (1H, dd, $J = 1.8, 0.8$ Hz), 6.28 (1H, dd, $J = 3.1, 1.9$ Hz), 6.02 (1H, q, $J = 1.4$ Hz), 5.99 (1H, dq, $J = 3.1, 0.9$ Hz), 5.69 (1H, dt, $J = 1.4, 0.6$ Hz), 2.65 (2H, t, $J = 7.4$ Hz), 2.41 (2H, td, $J = 7.4, 1.2$ Hz), 1.68-1.62 (2H, m), 1.60-1.54 (2H, m)

^{13}C NMR: (151 MHz, CDCl_3)

156.0, 140.8, 125.5, 112.1, 110.1, 104.8, 45.0, 28.5, 27.7, 26.6

TLC: R_f 0.3 (silica gel, hexanes, KMnO_4)

Preparation of 2-((5Z)-6-iodohept-5-enyl)furan (11)¹³



A solution of I_2 (673 mg, 2.65 mmol) in THF (22.0 mL) was cooled to -78 °C then set aside. A suspension of $[\text{Ph}_3\text{PEt}]\text{I}$ (1.25 g, 3.00 mmol) in THF (15.0 mL) was treated with BuLi (3.00 mmol; 2.12 mL of a 1.42 M solution in THF) at 22 °C. Following complete dissolution, the red-orange reaction mixture was then transferred to the iodine solution over 25 min using a cannula. The now light yellow solution was stirred 5 min, then warmed to -20 °C and treated with NaHMDS (2.55 mmol; 2.55 mL of a 1.00 M solution in THF). The now homogeneous red-orange solution was then treated with 5-(2-furyl)pentanal (381 mg, 2.50 mmol) dropwise over 5 min; the solution became heterogeneous during the addition with formation of a yellow-brown

precipitate. After 10 min, the suspension was poured into pentane (150 mL), stirred vigorously for 5 min then filtered through Celite. The filter cake was washed with hexanes (5 x 10 mL), and the combined filtrates transferred to a separatory funnel and washed with saturated aqueous NH_4Cl and NaCl (25 mL each), then dried over MgSO_4 , filtered and concentrated in vacuo. Purification by chromatography on silica (pentane) afforded a colorless oil (256 mg, 0.882 mmol 35.3%). The *Z:E* ratio was determined by ^1H NMR to be >25:1.

^1H NMR: (600 MHz, CDCl_3)

7.29 (1H, dd, $J = 1.9, 0.9$ Hz), 6.27 (1H, dd, $J = 3.3, 2.1$ Hz), 5.98 (1H, dq, $J = 3.1, 0.8$ Hz), 5.39 (1H, tq, $J = 6.8, 1.5$ Hz), 2.63 (2H, brt, $J = 7.6$ Hz), 2.48 (3H, q, $J = 1.4$ Hz), 2.13-2.09 (2H, m), 1.67 (2H, tt, $J = 7.4, 7.4$ Hz), 1.44 (2H, tt, $J = 7.4, 7.4$ Hz)

^{13}C NMR: (151 MHz, CDCl_3)

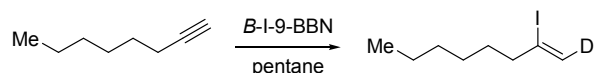
156.2, 140.7, 135.1, 110.0, 104.7, 101.1, 36.3, 33.5, 27.8, 27.8, 27.5

TLC: R_f 0.8 (silica gel, 9:1 pentane/ Et_2O , CAM)

Determination of HI addition stereochemistry

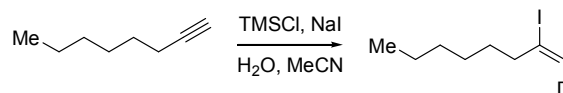
In order to establish the stereochemistry of HI addition to acetylenes in the method of Kamiya, we performed a series of labeling experiments with 1-octyne. Our benchmark reaction was the haloboration method of Suzuki,¹¹ who reported similar labeling studies to establish the addition stereochemistry. For purposes of comparison, each labeling experiment was run alongside the protio variant such that a direct overlay of spectroscopic data could be performed; see stacked spectra at the end of the supporting information. The levels of incorporation we obtained were consistent with related studies reported in the literature.¹⁴ It should also be noted that ^1H NMR analysis of the crude material was consistent with the purified products shown; spectroscopic data was also consistent with published reports.¹⁵ Based on these results, we reason the discrepancy in stereochemical assignment derives from the fact that in terminal vinyl iodides, the proton *cis* to the iodine atom resides upfield of the corresponding *trans* proton; a phenomenon opposite to that observed for internal derivatives.

Preparation of *Z*-1-deuterio-2-iodooct-1-ene¹¹



B-I-9-BBN (1.80 mmol; 1.80 mL of a 1.0 M solution in hexanes) was diluted with pentane (10.0 mL), cooled to 0 °C then treated with 1-octyne (222 μL , 1.50 mmol) dropwise over 5 min. The purple solution became yellow-orange and cloudy during the addition; within 20 min, the solution cleared. After 1 h, the mixture was treated with glacial $\text{CD}_3\text{CO}_2\text{D}$ (1.00 mL), maintained at 0 °C for 0.5 h, then treated 3M NaOH (12 mL) and 30% H_2O_2 (2 mL). The resulting biphasic mixture was warmed to 22 °C, stirred vigorously for 0.5 h then separated. The aqueous layer was then washed with hexanes (3 x 30 mL). The combined hexanes washes were further washed with H_2O , saturated aqueous NaHCO_3 and H_2O (30 mL each), then dried over MgSO_4 , filtered and concentrated in vacuo. Purification by distillation under reduced pressure and chromatography on silica (R_f 0.8 in hexanes) afforded a colorless oil (0.190 g, 0.793 mmol; 52.9%).

Preparation of *E*-1-deuterio-2-iodooct-1-ene⁵



TMSI was prepared in situ through the addition of TMSCl (759 μL , 6.00 mmol) to a solution of NaI (899 mg, 6.00 mmol) in MeCN- d_3 (10.0 mL) at 22 $^\circ\text{C}$. The resulting opaque solution was then treated with D₂O (54 μL , 3.00 mmol) and, after 10 min, 1-octyne (739 μL , 5.00 mmol) at a rate of 0.5 mL/min. The reaction mixture became homogeneous and dark yellow in color during the addition. After 1 h, the solution was diluted with H₂O (5 mL), and the resulting red-orange biphasic mixture was washed with pentane (3 x 15 mL). The combined pentane layers were washed with saturated aqueous Na₂S₂O₃ and NaCl (15 mL each), then dried over MgSO₄, filtered and concentrated in vacuo. Purification by chromatography on silica (hexanes) afforded a colorless oil (442 mg, 1.85 mmol; 37.0%).

Determination of aminopeptidase activity

Test substrates (0.0376 μmol ; 8.0 mM solution in DMSO) were diluted into 0.5 mL micro-centrifuge tubes containing buffer (50 mM HEPES/pH 7.5, 10 mM CaCl₂, 1% Brij), then treated with APM (0.2 U/mL buffer; Roche Applied Science) to a final reaction volume of 75 μL . The solution was mixed, and immediately 30 μL transferred to an HPLC vial containing 15 μL of MeCN for $t = 0$ measurement. The remaining reaction solution was incubated at 37 $^\circ\text{C}$ for 25 min; 30 μL was again transferred to an HPLC vial containing 15 μL of MeCN for $t = 25$ measurement. This process was repeated for 0, 6.5×10^{-4} and 1.5×10^{-3} U enzyme respectively; each run was performed in duplicate. The test substrates and products were analyzed by reverse phase HPLC on a Phenomenex Luna C18 column (4.6 x 150 mm, 5 μm) using 0.1% HCO₂H/MeCN gradient with UV detection at 220 nm. The change in substrate peak area was used to determine rate constant k from the following equation:

$$k = \{(\% \text{ hydrolyzed}/100) \cdot [S]\} / [E] \cdot [\text{time}]$$

Where: S = test substrate concentration in μmol

E = APN concentration in U/mL

k = μmol substrate hydrolyzed/minute/U

References

1. Substrates (and standards) were prepared for chiral analysis using a three-step digestion (DCI/D₂O, 110 °C, 16-18 h), esterification (DCI/MeOH, 90 °C, 0.5 h) and protection ((CF₃CO)₂O/CF₃CO₂Et, 130 °C, 10 min) sequence.
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