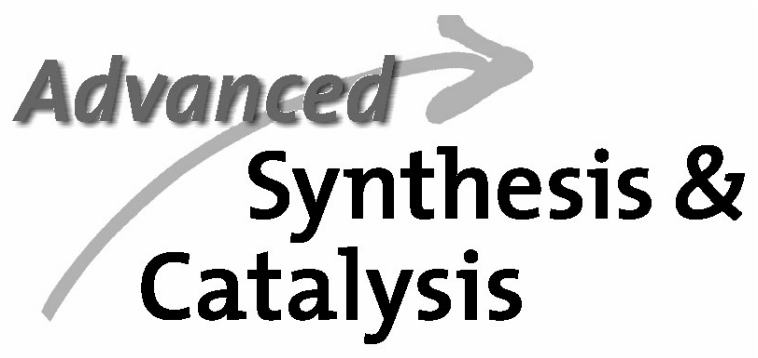

Supporting Information

A Cross-Metathesis Route to Functionalized Unsaturated α-Methyl-α-Substituted Amino Acids

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Supporting Information

General information. All reactions were carried out under an atmosphere of dry argon, unless stated otherwise. Infrared (IR) spectra were obtained using an ATI Mattson Genesis Series FTIR spectrometer and wavelengths are reported in cm^{-1}. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$, unless indicated otherwise, using a Bruker DMX300 (300 MHz) spectrometer. HRMS measurements were carried out using a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. Flash chromatography was performed with Acros Organics silica gel (0.035-0.070 nm) using the indicated solvent (mixture). TLC was performed on silica gel-coated glass plates (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Toluene was distilled from sodium and deoxygenated prior to use. Heptane, EtOAc and CH_2Cl_2 were distilled from CaH_2. Et_3N was distilled from and stored over KOH. If necessary, other solvents were distilled from the appropriate drying agents prior to use. Unless stated otherwise, all commercially available reagents were used as received.

Representative procedure for the amino acid amide formation:

*2-Amino-2-methyl-6-heptenoic amide (**9**).* To a solution of NaCN (6.7 g, 134 mmol) and 5-hexen-2-one (**6**, 15 g, 134 mmol) in 25% aqueous NH_4OH (360 mL), AcOH (8 mL, 134 mmol) was added dropwise. MeOH (13 mL) was added and the mixture was stirred for 24 h at room temperature. The aminonitrile was extracted with CH_2Cl_2 (3 × 400 mL), the combined organic layers were dried ($MgSO_4$) and evaporated. The crude aminonitrile was then dissolved in EtOH (100 mL) and 32% aqueous NaOH (10 mL) and PhCHO (1 equiv) were added. The mixture was stirred for 4 h at room temperature and concentrated. The residue was dissolved in 4 N HCl, stirred for 4 h at room temperature, washed with CH_2Cl_2 (3 × 200 mL) and brought to pH 8.9 with 10 N NaOH. Then, **9** was extracted from the water layer with EtOAc (3 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give **9** (13 g, 62%) as a white solid. This solid was without any further purification subjected to the enzymatic resolution experiments. **9**: IR: ? = 3286, 2980, 2928, 1662, 1381, 910 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (bs, 1H), 6.37 (bs, 1H), 5.75-5.66 (m, 1H), 4.95-4.86 (m, 2H), 2.05-1.90 (m, 2H), 1.79-1.53 (m, 2H), 1.50-1.44 (m, 1H), 1.42-1.19 (m, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 137.7, 114.3, 57.2, 40.5, 33.6, 27.7, 23.1.

Representative examples of precursor synthesis:

*2-(tert-Butoxycarbonylamino)-2-methyl-4-pentenoic acid methyl ester (**14**).* A solution of racemic **7** (83.8 mmol) in MeOH (200 mL) was treated with $SOCl_2$ (2 equiv) and refluxed for 17 h. The mixture was cooled, concentrated and the residue was dissolved in CH_2Cl_2 (300 mL). It was cooled

to 0 °C, Boc_2O (20.0 g, 91.8 mmol) was added and the mixture was stirred for 20 h at room temperature. After evaporation, the residue was purified by column chromatography (EtOAc/heptane 1:1) to give **14** (12.4 g, 61%) as a colorless oil. **14**: IR: ? = 3369, 2976, 1709, 1234, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.70-5.64 (m, 1H), 5.26 (b s, 1H), 5.14-5.08 (m, 2H), 3.73 (s, 3H), 2.72-2.67 (m, 1H) 2.61-2.54 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.52 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 154.2, 132.2, 119.2, 79.3, 58.9, 52.2, 41.3, 28.1, 23.0; HRMS (CI) calcd for $C_{12}H_{22}NO_4$ (MH^+) 244.1549, found 244.1545.

*2-Formamido-2-methyl-4-pentenoic acid methyl ester (**17**).* A solution of racemic **7** (27.8 mmol) in MeOH (70 mL) was treated with $SOCl_2$ (2 equiv) and refluxed for 17 h. The mixture was cooled, concentrated, dissolved in formic acid (100 mL) and treated with Ac_2O (15.8 mL, 167 mmol) at 0 °C. The mixture was stirred for 1 h at 0° C, Et_3N (7.7 mL, 55.5 mmol) was added dropwise, after which the mixture was stirred for 20 h at room temperature. It was evaporated, azeotroped with 100 mL toluene/water (9:1) and purified with column chromatography (EtOAc/heptane 1:1) to give **17** (3.10 g, 65%) as a colorless oil. **17**: IR: ? = 3308, 3028, 2950, 1740, 1662, 1230, 1122, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 6.34 (bs, 1H), 5.68-5.54 (m, 1H), 5.29-5.08 (m, 2H), 3.76 (s, 3H), 3.00 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.56 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 160.4, 131.8, 119.4, 59.6, 52.6, 40.7, 22.7; HRMS (EI) calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0896.

*(S)-2-(Benzyloxycarbonylamino)-2-methyl-4-pentenoic acid methyl ester (**33**).* A solution of (*S*)-**11** (2.00 g, 15.5 mmol) in MeOH (15 mL) was treated dropwise at 0 °C with $SOCl_2$ (3.2 mL). The mixture was allowed to reach room temperature, refluxed for 17 h, concentrated and dissolved in CH_2Cl_2 (250 mL). CbzOSu (4.24 g) and Et_3N (4.5 mL) were added and the reaction mixture was stirred for 17 h at room temperature. It was concentrated and purified with column chromatography (EtOAc/heptane 1:4) to provide **33** (3.59 g, 84%) as a colorless oil. **33**: $[a]_D$ = +14.8 (c 1.0, CH_2Cl_2); IR: ? = 3352, 2950, 1718, 1498, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 5H), 5.71-5.57 (m, 1H), 5.50 (bs, 1H), 5.11-5.04 (m, 4H), 3.74 (s, 3H), 2.80-2.72 (m, 1H), 2.61-2.54 (dd, *J* = 7.2, 13.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 154.7, 136.5, 132.1, 128.3, 127.9, 127.9, 119.3, 66.3, 59.3, 52.4, 41.1, 22.9; HRMS (EI) calcd for $C_{15}H_{19}NO_4$ 277.1314, found 277.1317.

Selected cross-metathesis examples:

General procedure: To a 0.1 M solution of the olefinic amino acid in freshly distilled oxygen free toluene were added the cross-metathesis reagent (4 equiv) and catalyst **13** (5 mol %) under an argon atmosphere. The mixture was stirred for 24 h at room temperature, concentrated and purified with column chromatography to provide the pure cross-metathesis product.

*(E)-2-(tert-Butoxycarbonylamino)-2-methyl-6-(trimethylsilyl)-4-hexenoic acid methyl ester (**21**).* Following the general cross-metathesis procedure, **14** (0.25 mmol) was reacted with the metathesis catalyst **13** (10.6 mg, 5 mol%) and allyltrimethylsilane (159 µl, 1.00 mmol) in toluene (1.5 mL). After 17 h, concentration and column chromatography (EtOAc/heptane 2:1) yielded **21** (58.0 mg, 70%) as a colorless oil (5:1 mixture of *E*/*Z*-isomers). **21**: IR: ? = 3429, 2980, 2949, 1718, 1493, 1247, 1156, 1061, 849 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.54-5.44 (m, 1H), 5.12-5.02 (m, 2H), 3.70 (s, 3H), 2.51-2.42 (m, 2H), 1.50-1.40 (m, 15H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 154.4, 132.1, 121.4, 79.3, 59.0, 52.2, 41.1, 28.2, 23.0, 18.6, –2.1; HRMS (CI) calcd for $C_{16}H_{32}NO_4Si$ (MH^+) 330.2101, found 330.2099.

*(E)-2-(tert-Butoxycarbonylamino)-2-methyl-6-phenyl-4-hexenoic acid methyl ester (**23**).* Following the general cross-metathesis procedure, **14** (0.25 mmol) was reacted with the metathesis catalyst **13** (10.6 mg, 5 mol%) and styrene (115 µl, 1.00 mmol) in toluene (1.5 mL). After 17 h, concentration and column chromatography (EtOAc/heptane 1:4) yielded **23** (51.1 mg, 64%) as a colorless oil (7:1 mixture of *E*/*Z*-isomers). **23**: IR: ? = 3425, 3369, 2984, 1744, 1714, 1493, 1256, 1169 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35-7.19 (m, 5H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.10-6.00 (m, 1H), 5.19 (bs, 1H), 3.75 (s, 3H), 2.96-2.80 (m, 1H), 2.74 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.57 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 154.3, 137.0, 134.2, 128.4, 127.4, 126.2, 123.7, 79.6, 59.4, 52.5, 40.5, 28.2, 23.3; HRMS (CI) calcd for $C_{18}H_{26}NO_4$ (MH^+) 320.1862, found 320.1863.

*(E)-1,1-diethyl 6-methyl 6-(tert-butoxycarbonylamino)hept-3-ene-1,1,6-tricarboxylate (**24**).* Following the general cross-metathesis procedure, **14** (0.25 mmol) was reacted with the metathesis catalyst **13** (10.6 mg, 5 mol%) and diethyl allylmalonate (197 µl, 1.00 mmol) in toluene (1.5 mL). After 17 h, concentration and column chromatography (EtOAc/heptane 2:1) yielded **24** (57.0 mg, 55%) as a colorless oil (5:1 mixture of *E*/*Z*-isomers). **24**: IR: ? = 2980, 1731, 1713, 1368, 1161, 1057, cm^{-1}; ^{1}H-NMR (300 MHz, $CDCL_3$): δ = 5.51-5.32 (m, 1H), 5.09 (bs, 2H), 4.20-4.13 (m, 4H), 3.70 (s, 3H), 3.32 (m, 1H), 2.62-2.43 (m, 4H), 1.51 (s, 3H), 1.40 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 168.8, 154.3, 130.5, 128.8, 79.4, 61.3, 59.1, 52.3, 51.7, 40.0, 31.6, 28.2, 23.0, 14.0; HRMS (CI) calcd for $C_{20}H_{34}NO_8$ (MH^+) 416.2284, found 416.8892.

*(E)-2-Formamido-2-methyl-4-undecenoic acid methyl ester (**29**).* Following the general cross-metathesis procedure, **17** (0.25 mmol) was reacted with the metathesis catalyst **13** (10.6 mg, 5 mol %) and 1-octene (157 µl, 1.00 mmol) in toluene (1.5 mL). After 17 h, concentration and column chromatography (EtOAc/heptane 1:1) yielded **29** (35.0 mg, 55%) as a colorless oil (ca. 3:1 mixture of *E*/*Z*-isomers). **29**: IR: ? = 2924, 2859, 1739, 1666, 1221, 1113 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 6.28 (bs, 1H), 5.55-5.50 (m, 1H), 5.48-5.15 (m, 1H), 3.77 (s, 3H), 2.89 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.48 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.97 (q, *J* = 6.3 Hz, 2H), 1.67 (s, 3H), 1.26 (m, 8H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 159.4, 135.6, 122.4, 60.0, 52.4, 39.6, 32.3, 31.5, 29.1, 28.5, 22.7, 22.4, 13.9; HRMS (CI) calcd for $C_{14}H_{26}NO_3$ (MH^+) 256.1913, found 256.1908.

*(E)-1-Ethyl 6-methyl 5-formamido-5-methylhex-2-enedioate (**30**).* Following the general cross-metathesis procedure, **17** (0.25 mmol) was reacted with the metathesis catalyst **13** (10.6 mg, 5 mol %) and ethyl acrylate (90 µl, 1.00 mmol) in toluene (1.5 mL). After 17 h, concentration and column chromatography (EtOAc/heptane 2:1) yielded **30** (42.0 mg, 70%) as a colorless oil (>20:1 mixture of *E*/*Z*-isomers). **30**: IR: ? = 2984, 1722, 1658, 1269, 1187 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 6.73-6.63 (m, 1H), 6.48 (bs, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 3.77 (s, 3H), 3.26-3.18 (m, 1H), 2.84-2.76 (m, 1H), 1.64 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 165.2, 159.6, 141.2, 124.8, 60.1, 59.4, 52.8, 38.0, 22.8, 14.0; HRMS (CI) calcd for $C_{11}H_{18}NO_5$ (MH^+) 244.1185, found 244.1184.