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Using Cross-Metathesis to Couple L-Phenylalanine to a Macrocyclic Lactam

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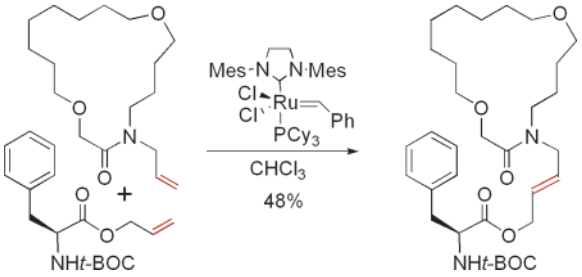

Grubbs' second generation ruthenium catalyst was used to couple the amino acid L-phenylalanine to a 17-membered lactam, using cross-metathesis with an *E*-alkene favored in the process. The best coupling conditions gave the product in 48% yield. The reversibility of the process was also confirmed. Ring-closing metathesis was a key reaction used to form the macrocyclic lactam.

Introduction

Peptidomimetic research is a vital tool for the field of medicinal chemistry. One approach toward the synthesis of peptidomimetics is to use a molecular template or scaffold to which important pharmacophoric groups such as amino acid side chains are covalently anchored.[1−4] These molecules have an excellent potential for chiral discrimination and display stabilization of functional groups. Macrocyclic lactams have also been used as scaffolds for biomolecules.[5]

During the course of our studies to link amino acids to macrocyclic scaffolds using cross-metathesis (CM), we needed to construct **1**, shown in Figure 1. The compound is ideally suited to a cross-metathesis reaction[6] because it has a dumb-bell shape with two halves connected together by an *E*-alkene

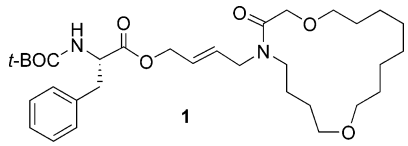

FIGURE 1. Phenylalanine on a Macrocylic Lactam.

tether. We believed that Grubbs' well-defined second generation catalyst would be an ideal choice to mediate this reaction.[7]

The left side of the molecule has a modified L-phenylalanine, bearing a t-BOC protecting group. It is attached to the *E*-alkene on the carboxylate side. The 17-membered macrocyclic lactam, on the right side of the molecule, was to be assembled by using ring-closing metathesis (RCM), using Grubbs' second generation catalyst. In addition, the reversibility of the CM reaction was confirmed in these studies.[8]

In examining the viability of our approach to the synthesis of **1**, we decided that anchoring the amino acid to the nitrogen atom of a large-ring lactam would function well, as shown in Scheme 1. As just discussed, **1** could be prepared from protected

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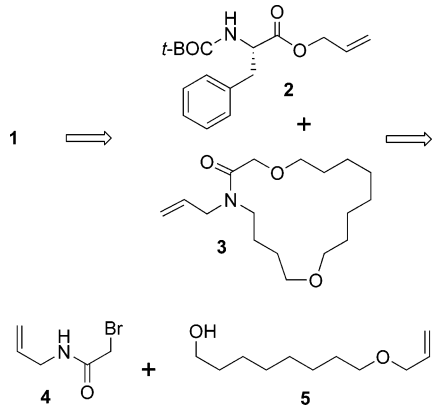
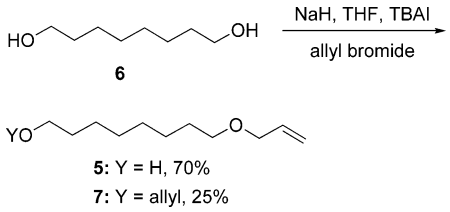
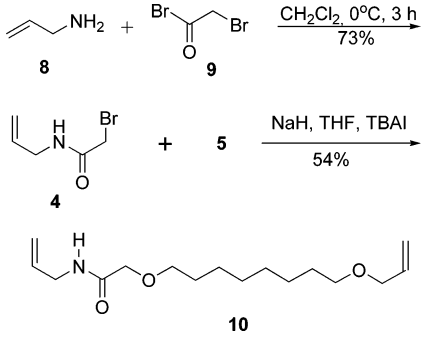
SCHEME 1



SCHEME 2



SCHEME 3



phenylalanine **2** bearing an allyl ester and allyl lactam **3**. Each of these halves of the molecule contains a terminal alkene to be used in the CM reaction. The 17-membered lactam contained the allyl moiety attached at the nitrogen atom. Precursor **3** was to be prepared by RCM and the alkene would later be removed by hydrogenolysis. Eventually we envisioned **3** as emanating from the S_N2 coupling of bromo-amide **4** and alcohol **5**.

Results and Discussion

We began our synthesis with a Williamson etherification using commercially available 1,8-octanediol (**6**) and allyl bromide, as shown in Scheme 2. The desired allyl ether **5** was obtained in 70% yield, while the minor product, double Williamson ether **7**, was isolated in 25% yield. The use of tetrabutylammonium iodide (TBAI) was essential in obtaining good yields.[9]

N-Allyl-2-bromoacetamide (**4**) was next readily synthesized in 73% yield from allylamine (**8**) and dibromide **9** followed by recrystallization in hexane/ether, as shown in Scheme 3. Deprotonation of **5** with NaH, addition of TBAI, and nucleophilic substitution of allyl-bromoacetamide **4** gave a 54% yield

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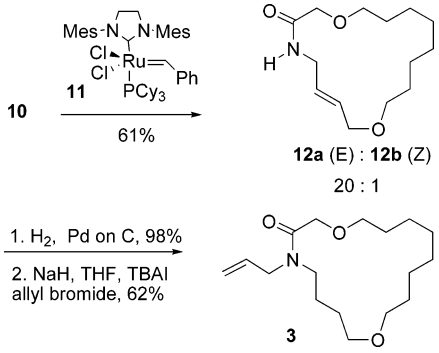
TABLE 1. RCM To Obtain 12a and 12b

entry	concn (M)[a]	mol % of **11**	time (h)	yield (%)	E:Z **12a**:**12b**
1	0.001	10	25	59	97:3
2	0.0014	10	21	45	98:2
3	0.0016	10	24	46	92:8
4	0.0016	10	16	61	96:4
5	0.0018	8	19	60	93:7
6	0.003	14	3.5	48	NA[b]
7	0.007	8	2	35	NA[b]
8	0.013	5	20	18	NA[b]

[a] All reactions were run in dichloromethane. [b] Cis-isomer not isolated due to small scale reaction.

SCHEME 4



of the terminal diene **10**. Diene **10** was reacted with Grubbs' 2nd generation catalyst **11** under various conditions (Table 1 and Scheme 4) to give two 17-membered RCM lactams, **12a** and **12b**, as geometric isomers.[10] Prior to the addition of catalyst **11**, a few crystals of butylated hydroxyl toluene (BHT) were added to prevent atom transfer radical polymerization (ATRP).[11] All reactions were refluxed in CH_2Cl_2 and monitored by TLC. In every entry, **10** was never fully consumed. Moreover, data showed that refluxing for longer periods of time did not improve the yield of RCM products **12a** and **12b**. *E*-Isomer **12a** was the major product and was separated from *Z*-isomer **12b** by chromatography over silica gel.

After ring-closing metathesis, **12a** and **12b** were hydrogenated with Pd on activated C (10% Pd) to give the corresponding saturated lactam in good yields. NMR spectra and TLC showed that it was pure enough for the next step without chromatography. Addition of TBAI, and nucleophilic substitution of allyl bromide, gave **3** in 62% yield. Two different conformations of **3**, in roughly equal amounts, were present at ambient temperature and readily detected by ^{1}H NMR and ^{13}C NMR by the doubling of peaks.

The next step involved the cross-metathesis of the *N*-allyl lactam **3** with **2**, the allyl ester of t-BOC-phenylalanine (Scheme 5). Commercially available t-BOC-L-phenylalanine was reacted with 1,3-diisopropylcarbodiimide (DIC), hydroxybenzotriazole (HOBt), and allyl alcohol to afford amino acid derivative **2** in 95% yield. The starting material was completely consumed within 20 min as indicated on TLC.[12] Upon recrystallization in hexane/Et_2O, we obtained **2** as colorless needles with mp 70−71 °C. We were pleased that the cross-metathesis of phenyl-

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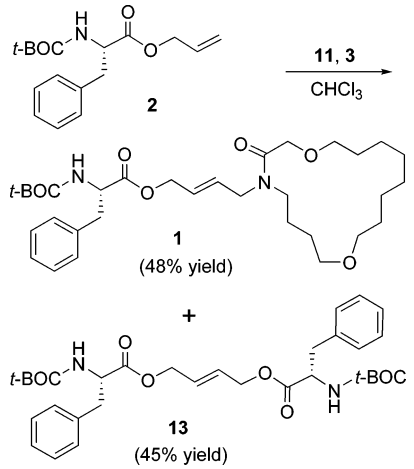
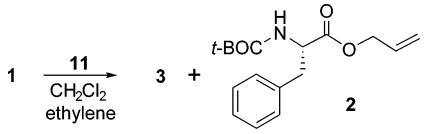
SCHEME 5



SCHEME 6



alanine derivative **2** (2 equiv) and *N*-allyl lactam **3** was observed with 5 mol % of catalyst **11** (Scheme 5). The reaction was heated at reflux in $CHCl_3$ for 21 h while continuously flushing out ethylene with argon to drive the reaction forward. Additional $CHCl_3$ was added as needed, to keep the concentration to ca. 1 M. After the reaction was quenched with ethyl vinyl ether, purification gave the desired product **1** in 48% yield with an *E*:*Z* ratio of 1.2:1 and the amino acid dimer **13** in 45%. Similar to the ^{13}C NMR of *N*-allyl lactam **3**, we also observed the doubling of peaks for **1**. Interestingly, the dimer of *N*-allyl lactam **3** was not observed.

It is known that CM is reversible and this could be tested in our system.[8,13] We were able to confirm that **1** can be converted back to allyl lactam **3** and amino acid derivative **2**, as shown in Scheme 6. Ethylene gas, used without purification, was admitted via a balloon to a stirred solution of compound **1**, catalyst **11** (2 mol %), in CH_2Cl_2. The solution was first maintained at room temperature overnight. TLC showed the formation of *N*-allyl lactam **3** and allyl ester **2**. In an attempt to drive the reaction further, the solution was refluxed in CH_2Cl_2 for 2.5 h under an atmosphere of ethylene gas, then quenched with ethyl vinyl ether upon cooling. Purification by chromatography gave 36% of *N*-allyl lactam **3** and 37% of allyl ester **2**. Both the amino acid dimer **13** (4%) and unreacted starting material **1** (27%) were recovered as well.

Conclusion

In summary, Grubbs' second generation ruthenium catalyst was used to couple the amino acid phenylalanine to a 17-membered lactam by using cross-metathesis in 48% yield. Ring-closing metathesis was a key reaction used to form the macrocyclic lactam. The reversibility of the process was confirmed.[15]

Experimental Section

General Experimental Procedures. See the Supporting Information.

***N*-Allyl-2-bromoacetamide (4).** Preparation is modified from a published procedure.[14] A flame-dried 250-mL round-bottom flask was charged with bromoacetyl bromide (8.0 mL, 61 mmol) and freshly distilled CH_2Cl_2 (80 mL) and cooled in an ice bath to 0 °C. To the stirred solution was added a solution of allylamine (12 mL, 160 mmol) and CH_2Cl_2 (40 mL) dropwise and the mixture was stirred at 0 °C for 4 h. Distilled H_2O was added and the organic layer was extracted and washed with 1 N HCl, followed by H_2O. After drying (anhydrous Na_2SO_4), concentration gave a crude yellow-orange oil. Recrystallization from hexane and ethyl ether (9:1) at 0 °C overnight gave **4** (8.0 g, 73%) as analytically pure white crystals, mp 27 °C: R_f 0.39 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 6.62 (s, 1H), 5.85 (ddt, J = 17.2, 10.2, 5.3 Hz, 1H), 5.23 (dq, J = 17.1, 1.5 Hz, 1H), 5.19 (dq, J = 10.0, 1.5 Hz, 1H), 3.96−3.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 165.9, 133.3, 116.8, 42.5, 29.1; IR (neat) 3285, 3082, 1654, 1552, 1430, 1309, 1211, 1132, 990, 925 cm^{-1}. HRMS (CI pos) for C_5H_9BrNO $[M + H]^+$: calcd 177.9868, found 177.9862.

8-Allyloxyoctan-1-ol (5). A flame-dried flask flushed with argon was charged with sodium hydride (60% in oil) (1.1 g, 28 mmol). The gray powder was washed three times with pentane to remove the protective oil. To the NaH was added 1,8-octanediol (**6**) (3.55 g, 24.3 mmol) dissolved in THF (25 mL). Tetrabutylammonium iodide (TBAI) (25 mg, 0.068 mmol) was added and the mixture was stirred for 40 min. A solution of allyl bromide (1.9 mL, 22 mmol) and THF (25 mL) was added dropwise to the reaction flask and heated at reflux for 12 h. The reaction mixture was cooled to room temperature, neutralized with saturated ammonium chloride, and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried with sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH (100:0 to 98:2) to give colorless oil **5** (2.9 g, 70%) and double Williamson etherification product **7** (0.62 g, 25%).

Allyl ether **5** (0.62 g, 25%): R_f 0.23 (CH_2Cl_2/MeOH, 96:4); ^1H NMR ($CDCl_3$) δ 5.91 (ddt, J = 17.1, 10.2, 5.6 Hz, 1H), 5.26 (dq, J = 17.2, 1.6 Hz, 1H), 5.16 (dq, J = 10.7, 1.4 Hz, 1H), 3.95 (dt, J = 5.6, 1.3 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 3.41 (t, J = 6.7 Hz, 2H), 1.66 (s, 1H), 1.60−1.49 (m, 4H), 1.31 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 135.2, 116.9, 72.0, 70.6, 63.1, 32.9, 29.9, 29.6, 29.5, 26.3, 25.8; IR (neat) 3385 (broad), 2931, 2856, 1647, 1463, 1348, 1101 cm^{-1}. HRMS (CI pos) for $C_{11}H_{23}O_2$ $[M + H]^+$: calcd 187.1698, found 187.1697.

Diether **7**: R_f 0.74 (CH_2Cl_2/MeOH, 96:4); ^1H NMR ($CDCl_3$); 5.90 (ddt, J = 17.2, 10.3, 5.65 Hz, 1H), 5.89 (ddt, J = 17.2, 10.3, 5.65 Hz, 1H), 5.25 (dq, J = 17.1, 1.7 Hz, 1H), 5.24 (dq, J = 17.1, 1.8 Hz, 1H), 5.15 (dq, J = 10.4, 1.5 Hz, 1H), 5.14 (dq, J = 10.4, 1.5 Hz, 1H), 3.94 (dt, J = 5.6, 1.5 Hz, 2H), 3.93 (dt, J = 5.4, 1.5 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H), 3.39 (t, J = 6.7 Hz, 2H), 1.61−1.50 (m, 4H), 1.30 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 135.2, 116.8, 71.9, 70.6, 29.9, 29.6, 26.3; IR (neat) 3080, 2932, 2856, 1647, 1457, 1420, 1400, 1347, 1264, 1106 cm^{-1}. HRMS (CI pos) for $C_{14}H_{27}O_2$ $[M + H]^+$: calcd 227.2011, found 227.2015.

***N*-Allyl-2-(8-allyloxyoctyloxy)acetamide (10).** A flame-dried 25-mL round-bottom flask under argon was charged with alcohol **5** (2.97 g, 16.0 mmol) and THF (9.5 mL). NaH (60% in oil, 0.64 g, 16 mmol) was added portion wise slowly into the stirred solution and the mixture continued to be stirred for 20 min. TBAI (26 mg, 0.070 mmol) and *N*-allyl-2-bromoacetamide (**4**) (2.20 g, 12.3 mmol) were added and the mixture was heated at reflux for 4 h. The mixture was diluted with CH_2Cl_2 and washed with brine. The

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(15) The views in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on silica gel with hexane/EtOAc (100:0 to 80:20) to give **10** (1.9 g, 54%) as a colorless oil: R_f 0.53 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 1H), 5.87 (ddt, J = 17.2, 10.7, 5.4 Hz, 1H), 5.82 (ddt, J = 17.0, 10.6, 5.3 Hz, 1H), 5.23 (dq, J = 17.2, 1.6 Hz, 2H), 5.12 (dq, J = 10.5, 1.6 Hz, 2H), 3.94−3.86 (m, 6H), 3.46 (t, J = 6.6 Hz, 2H), 3.38 (t, J = 6.7 Hz, 2H), 1.61−1.49 (m, 4H), 1.28 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 169.9, 135.2, 134.1, 116.8, 116.5, 72.0, 71.9, 70.5, 70.3, 41.2, 29.8, 29.6, 29.5, 29.4, 26.2, 26.1; IR (neat) 3426, 3335, 3081, 2932, 2856, 1738, 1676, 1526, 1432, 1342, 1277, 1111, 997, 921 cm^{-1}. HRMS (CI pos) for $C_{16}H_{30}O_3N$ [M + H]$^+$: calcd 284.2226, found 284.2225.

***E*-Cycloheptadecene (12a) and *Z*-Cycloheptadecene (12b).** To a stirred solution of diene **10** (377 mg, 1.33 mmol) and CH_2Cl_2 (750 mL) was added a few crystals of butylated hydroxytoluene (BHT). A solution of Grubbs' 2nd generation catalyst **11** (108 mg, 0.127 mmol) and CH_2Cl_2 (100 mL) was added then the solution was heated at reflux for 16 h. The reaction was cooled to room temperature, quenched with ethyl vinyl ether (ca. 3 mL), and maintained for 1 h. The solution was concentrated under reduced pressure and the residue was chromatographed on silica gel with hexane/EtOAc (9:1 to 7:3) to give the *E*-isomer **12a** (200 mg, 58%) and *Z*-isomer **12b** (8.2 mg, 3%) as a brown oil.

E-isomer **12a**: R_f 0.35 (EtOAc/hexane, 4:1); ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 1H), 5.80 (dd, J = 14.8, 4.4 Hz, 1H), 5.72 (dd, J = 14.8, 4.3 Hz, 1H), 3.99−3.89 (m, 6H), 3.53 (t, J = 5.7 Hz, 2H), 3.46 (t, J = 5.7 Hz, 2H), 1.65−1.29 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 170.0, 130.1, 127.9, 71.9, 70.2, 69.9, 69.3, 40.0, 29.2, 28.9, 28.4, 28.1, 26.1, 25.3; IR (neat) 3419, 2929, 2856, 1683, 1525, 1460, 1340, 1263, 1111 cm^{-1}. HRMS (CI pos) for $C_{14}H_{26}NO_3$ [M + H]$^+$: calcd 256.1913, found 256.1911.

Z-isomer **12b**: R_f 0.43 (EtOAc/hexane, 4:1); ^{1}H NMR ($CDCl_3$) δ 6.65 (s, 1H), 5.89 (dd, J = 10.6, 6.3 Hz, 1H), 5.81 (dd, J = 10.3, 7.2 Hz, 1H), 4.03−3.90 (m, 6H), 3.55−3.45 (m, 4H), 1.70−1.23 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 170.0, 130.3, 130.0, 71.2, 70.7, 70.4, 65.6, 35.4, 29.2, 28.4, 27.3, 27.2, 24.9, 24.6; HRMS (ESI-FTICR) for [2M + Na]$^+$: calcd 533.3561, found 533.3580.

Allyl Lactam 3. Palladium on activated carbon (10% Pd) (58 mg, 0.055 mmol) was added to a solution of **12** (507 mg, 1.99 mmol) and EtOAc (9 mL). Hydrogen was admitted via a balloon and the reaction mixture was stirred for 45 min and the catalyst removed by filtering through a small pipet column of Celite. The column was rinsed with EtOAc (3 × 5 mL) and the combined fractions were concentrated under reduced pressure leaving the crude saturated lactam (500 mg, 98%) as a yellow-brown oil. The hydrogenated saturated lactam product was used in the next step without further purification.

To a stirred solution of the saturated lactam (570 mg, 2.22 mmol) in THF (2.2 mL) under argon was added NaH (60% in oil, 270 mg, 6.7 mmol) slowly in portions. The mixture was stirred for 30 min. TBAI (8.18 mg, 0.022 mmol) and allyl bromide (0.97 mL, 11 mmol) were added and the reaction was heated at reflux for 9 h. The reaction mixture was cooled to room temperature, neutralized with saturated ammonium chloride, and extracted with EtOAc. The organic layer was washed with saturated NaCl, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography on silica gel with hexane/EtOAc (4:1) gave **3** (410 mg, 62%) as a slightly yellow oil.

Saturated lactam: R_f 0.32 (EtOAc/hexane, 4:1); ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 1H), 3.83 (s, 2H), 3.43−3.21 (m, 8H), 1.66−1.21 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 170.0, 71.6, 70.2, 70.1, 38.0, 29.0, 28.8, 27.5, 27.4, 26.7, 26.6, 25.1, 24.7; IR (neat) 3420, 2932, 2857, 1681, 1530, 1446, 1340, 1261, 1120 cm^{-1}. HRMS (CI pos) for $C_{14}H_{28}NO_3$ [M + H]$^+$: calcd 258.2069, found 258.2073.

Allyl lactam **3**: R_f 0.37 (hexane/EtOAc, 1:1) ^{1}H NMR ($CDCl_3$) δ 5.84−5.68 (m, 1H), 5.18−5.07 (m, 2H), 4.17−3.93 (m, 4H), 3.57−3.22 (m, 8H), 1.79−1.21 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.3, 133.5, 133.4, 117.2, 116.3, 71.7, 71.45, 71.41, 70.8, 70.21, 70.15, 70.03, 70.00, 49.0, 48.0, 47.3, 45.0, 29.5, 28.71, 28.67, 28.5, 28.0, 27.5, 27.4, 27.1, 26.7, 26.6, 25.9, 25.7, 25.1, 24.3, 24.2; IR (neat) 2931, 2858, 1651, 1459, 1352, 1282, 1232, 1118, 1038, 995, 922 cm^{-1}. HRMS (CI pos) for $C_{17}H_{32}NO_3$ [M + H]$^+$: calcd 298.2382, found 298.2391. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.31; H, 10.73; N, 4.94.

BOC-Allyl Ester of Phenylalanine 2. To a cooled (0 °C) solution of BOC-L-phenylalanine (2.04 g, 7.69 mmol) and CH_2Cl_2 (13 mL) was added 1,3-diisopropylcarbodiimide (DIC) (2.4 mL, 15 mmol), 4-(dimethylamino)pyridine (DMAP) (0.186 g, 1.52 mmol), and hydroxybenzotriazole (HOBt) (1.08 g, 7.99 mmol). After the mixture was stirred for 5 min, allyl alcohol (0.85 mL, 12 mmol) was slowly added. The mixture was allowed to warm to room temperature with stirring for a total of 3 h. All solids were filtered and the filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel with hexane/EtOAc (10:1) gave **2** (2.2 g, 92%) as a white solid, mp 71−72 °C: R_f 0.35 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ −8.05 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.08−7.32 (m, 5H), 5.84 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.28 (dq, J = 17.1, 1.4 Hz, 1H), 5.22 (dq, J = 10.3, 1.3 Hz, 1H), 4.98 (d, J = 7.9 Hz, 1H), 4.63−4.54 (m, 3H), 3.11 (dd, J = 13.8, 6.3 Hz, 1H), 3.04 (dd, J = 13.8, 6.5 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.1, 136.1, 131.6, 129.4, 128.6, 127.1, 118.9, 79.9, 66.0, 54.6, 38.4, 28.4; IR (neat) 3362, 3088, 2971, 1705, 1509, 1455, 1368, 1169, 1053 cm^{-1}. HRMS (CI pos) for $C_{17}H_{24}NO_4$ [M + H]$^+$: calcd 306.1705, found 306.1703. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.65, H, 7.78; N, 4.52. Spectral data are in agreement with literature.[12] Lit.[12] $[\alpha]^{29}_D$ −10.2 (*c* 1.1, MeOH).

Cross-Metathesis of BOC-Allyl Ester Phenylalanine 2 and Lactam 3. To a stirred solution of **3** (140 mg, 0.469 mmol), **2** (290 mg, 0.950 mmol), and $CHCl_3$ (0.50 mL) was added a solution of catalyst **11** (19.9 mg, 23 mmol) in $CHCl_3$ (0.40 mL). The solution was heated at reflux for 21 h while flushing the headspace with argon to remove evolved ethylene. The reaction was allowed to cool to room temperature and quenched with ethyl vinyl ether (EVE, ca. 0.75 mL). The solution was stirred for 30 min and concentrated under reduced pressure. Purification by chromatography with hexane/EtOAc (90:10−65:35) gave cross-metathesis product **1** (130 mg, 48%) as a colorless oil and homodimer **13** (120 mg, 45%) as a white solid, mp 148−150 °C. Starting materials **2** (40 mg, 29%) and **3** (71 mg, 25%) were recovered as well.

Cross-metathesis product **1**: R_f 0.26 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.09−7.32 (m, 5H), 5.79−5.53 (m, 2H), 4.99 (d, J = 8.5 Hz, 1H), 4.62−4.53 (m, 3H), 4.19−3.94 (m, 4H), 3.59−3.22 (m, 8H), 3.11 (dd, J = 13.4, 6.3 Hz, 1H), 3.03 (dd, J = 13.4, 6.5 Hz, 1H), 1.81−1.14 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 171.8, 169.8, 169.4, 155.2, 136.1, 130.7, 130.5, 129.5, 129.4, 128.7, 127.2, 126.2, 125.4, 80.0, 71.8−70.0 (7 lines), 65.2−64.8 (2 lines), 54.6, 47.7−45.0 (4 lines), 38.5, 29.5−24.3 (13 lines); IR (neat) 3439, 2933, 2860, 2247, 1712, 1640, 1497, 1456, 1367, 1254, 1168, 1114, 910, 733 cm^{-1}. HRMS (CI pos) for $C_{32}H_{51}N_2O_7$ [M + H]$^+$: calcd 575.3696, found 575.3680. Anal. Calcd for $C_{32}H_{50}N_2O_7$: C, 66.87; H, 8.77; N, 4.87. Found: C, 66.56; H, 9.00; N, 4.70.

Homodimer BOC-allyl ester phenylalanine **13**: R_f 0.67 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.34−7.09 (m, 10H), 5.76−5.64 (m, 2H), 4.99 (d, J = 7.9 Hz, 2H), 4.65−4.54 (m, 6H), 3.10 (dd, J = 13.6, 5.8 Hz, 2H), 3.03 (dd, J = 13.6, 5.8 Hz, 2H), 1.41 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 171.7, 155.2, 136.0, 129.5, 128.7, 128.0, 127.2, 80.2, 64.7, 54.6, 38.5, 28.5; IR (neat) 3354, 2971, 1736, 1519, 1455, 1367, 1187, 1086, 1053 cm^{-1}. HRMS (ESI-FTICR) for [M + Na]$^+$: calcd 605.2833, found 605.2859. Anal. Calcd for $C_{32}H_{42}N_2O_8$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.16, H, 7.53; N, 4.77.

General Procedure for the Reverse Metathesis of 1. A flame-dried 5-mL round-bottom flask equipped with a reflux condenser capped with a three-way stopcock was charged with **1** (110 mg, 0.191 mmol) and CH_2Cl_2 (95 μL). To the stirred solution was added a solution of catalyst **11** (3.5 mg, 0.0041 mmol) in CH_2Cl_2 (95

μL). The headspace was evacuated with use of a water aspirator attached to the stopcock. Ethylene gas, used without purification, was admitted via a balloon also attached to the stopcock. The solution was heated at reflux for 2.5 h, cooled to room temperature, and quenched with EVE (ca. 0.5 mL). Concentration by reduced pressure and purification of the residue by chromatography on silica gel with hexane/EtOAc (10:0−8:2) gave **3** (20 mg, 36%) and **2** (22 mg, 37%) as a colorless oil. Starting material **1** (30 mg, 27%) and amino acid dimer **13** (2.2 mg, 4%) were isolated as well. All spectral and TLC data were identical with data for **2**, **3**, **13**, and **1** as previously isolated.

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Supporting Information Available: General procedures, ^{1}H NMR, and ^{13}C NMR for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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