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Synthesis of dipeptide isosteres by cross-metathesis

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ABSTRACT

This work describes the attachment of two amino acid derivatives by olefin cross-metathesis using Grubbs' second generation catalyst. They were connected at the carboxyl termini. In addition, a cyclic dilactam scaffold was used, which reacted with only a fraction of the amino acid derivatives. The remaining fraction coupled directly coupled with no scaffold. This highly trans-selective double attachment resulted in the cross-metathesis of a variety of amino acids in a single reaction.

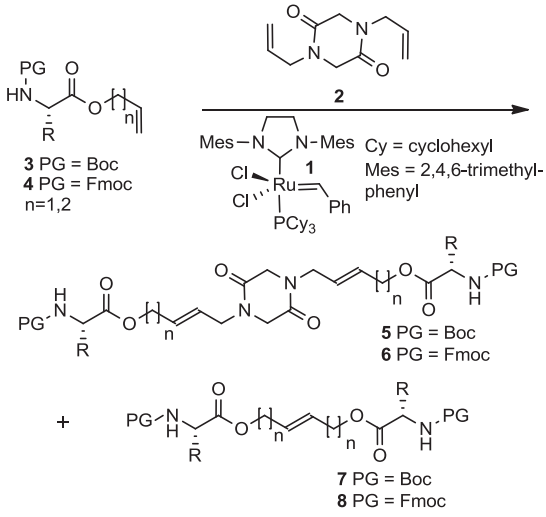
1. Introduction

Dipeptidomimetics and dipeptides linked by various non-peptides are isosteres of diamino acids.[1] These have been constructed by classic methods over the years.[2] Each can avoid the problems associated with poor stability, crossing the blood–brain barrier and polarity of the peptide bond.[3] Moreover, the standard dipeptide amide bond is easily broken by peptidase enzymes making another mode of connectivity worthy of synthetic investigation. Previous investigators have focused on an amine-linked alkene side chain of amino acids,[4,5] but a carboxyl-linked alkene chain on the amino acid has been little studied.[6] Efforts in this area are expected to useful, especially those coupling methods that use new metathetical methods.[7]

This effort describes the attachment of two amino acid derivatives by olefin cross-metathesis (CM), at the carboxyl termini. In addition, a cyclic dilactam scaffold was used, which reacted with only a fraction of the amino acid derivatives.[8–11] The remaining fraction coupled directly coupled by CM with no scaffold. This highly trans-selective type of double attachment with a variety of amino acids in a single reaction has not been examined prior to this work to the best of our knowledge.

2. Results and discussion

We report on the synthesis of cyclic dipeptide derivatives using Grubbs' second generation ruthenium catalyst benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (**1**). In this reaction modified amino acid **3** (protecting group=Boc) and **4** (protecting group=Fmoc), were coupled with diketopiperazine scaffold **2** by cross-metathesis, as shown in Scheme 1. This produced coupled products **5** and **6** with **7** and **8**, which underwent cross-metathesis without the scaffold. It should be noted that both sets of products we obtained



Scheme 1.

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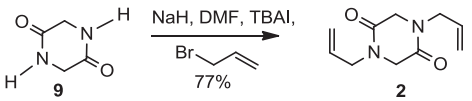
are synthetically important to report because of the rare amino acid carboxyl end coupling by metathesis.[6,12] In the cross-metathesis bonds, *trans* alkenes were observed as a single product. This was confirmed by ^{1}H NMR and independent synthesis of two products.

Different lengths for the alkenes (n=1, 2) lead to an allyl or homoallyl chain at the carboxylate site on the amino acid. It was believed that different tether lengths might give a variation in yields based on that minimal distance and negative neighboring group participation. Fmoc and Boc protected amino acids were investigated to determine the influence of the protecting groups, if any, on the cross-metathesis reaction. The ease of construction of these protected amino acids was also a consideration.

2.1. Synthesis of the scaffold

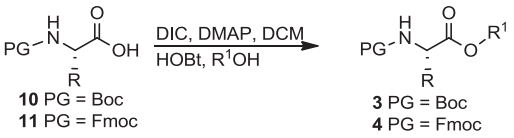
To obtain the *N*-diallyl scaffold **2**, NaH was added to a solution of commercially available dilactam **9**[13–15] in DMF as shown in Scheme 2. Excess allyl bromide was added and the reaction heated to 70 °C gave the desired product over 4 h. However, workup of the reaction was more cumbersome. Due to the polarity, some **2** would remain in DMF during the aqueous workup even after numerous extractions with organic solvents. The best method to obtain good yields was to quench the reaction with H_2O, then remove the DMF and water in vacuo with heat. The residue was redissolved in EtOAc, leaving behind the sodium salts, which were filtered. Concentration and purification by flash chromatography gave the desired product as a white solid in 77% yield.



Scheme 2.

2.2. Synthesis of the protected amino acids with alkene chains

Various amino acid derivatives **3a**–**i** and **4a**–**c** were synthesized by coupling **10** (protecting group=Boc) or **11** (protecting group=Fmoc) amino acid derivatives with allyl alcohol or 3-buten-1-ol, as shown in Scheme 3. DIC (1,3-diisopropylcarbodiimide) was used and HOBt was required to prevent racemization.[16] The starting material was typically consumed within 20 min as indicated on TLC. The urea byproduct was filtered and purification by column chromatography affording the amino acid products **3a**–**i** and **4a**–**c** in very good yields as shown in Table 1.



Scheme 3.

The CM reactivity of dimer scaffold **2** with amino acid derivatives **3a**–**i** and **4a**–**c** was examined next. Thus, scaffold **2** was reacted with amino acid derivatives using a catalytic amount (10 mol %) of Grubbs' second generation catalyst **1**. The reaction was stirred at reflux in $CHCl_3$ for 10 h while flushing the headspace with argon to remove evolved ethylene. The reaction was quenched with EVE and purification by column chromatography and gave the desired products, as shown in Table 2.

Table 1
Preparation and yields of the protected amino acids with olefin side chains

Entry	Amino acid	R^1	**3** and **4**	Yield
1	Boc-Phe	Allyl	**3a**	95
2	Boc-Ala	Allyl	**3b**	95
3	Boc-Pro	Allyl	**3c**	95
4	Boc-Met	Allyl	**3d**	95
5	Boc-Phe	Homoallyl	**3e**	90
6	Boc-Ala	Homoallyl	**3f**	98
7	Boc-Pro	Homoallyl	**3g**	89
8	Boc-Met	Homoallyl	**3h**	88
9	Boc-Leu	Homoallyl	**3i**	86
10	Fmoc-Phe	Homoallyl	**4a**	95
11	Fmoc-Pro	Homoallyl	**4b**	92
12	Fmoc-Gly	Homoallyl	**4c**	85

Table 2
Preparation and yields of the CM reaction products

Entry	Precursor	**5** and **6**	Yield	**7** and **8**	Yield[a]
1	**3a**	**5a**	37	**7a**	38
2	**3b**	**5b**	40	**7b**	42
3	**3c**	**5c**	42	**7c**	31
4	**3d**	**5d**	0	**7d**	0
5	**3e**	**5e**	44	**7e**	50
6	**3f**	**5f**	39	**7f**	66
7	**3g**	**5g**	35	**7g**	55
8	**3h**	**5h**	0	**7h**	14
9	**3i**	**5i**	30	**7i**	59
10	**4a**	**6a**	42	**8a**	48
11	**4b**	**6b**	46	**8b**	52
12	**4c**	**6c**	30	**8c**	44

[a] Isolated yields except **8b**, which is based on NMR.

Two sets of compounds that included the scaffold, **5a**–**i** and **6a**–**c**, and those that were coupled directly by metathesis, **7a**–**i** and **8a**–**c**, were obtained. We were able to isolate compounds by flash column chromatography. Based on thin layer studies, several CM products were difficult to isolate and a gradient of solvents was required for the column chromatography. We were also able to obtain pure samples by flash column chromatography. Some products, **7a**, **7b**, **7e**, **8a**, and **8c** were isolated as crystalline solids.

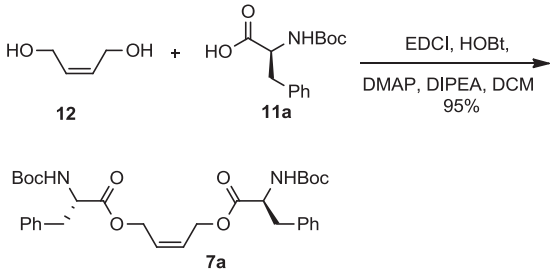
The yields of products **5a**–**i** and **6a**–**c** were comparable to each other, whether an allyl or homoallyl moiety was attached to the amino acid. There was also little difference between the yields of Fmoc protected **6a** and Boc protected **5a** and **5e**. However, the yields improved for the homodimerized products **7e**–**h** and **8a**–**b**, which possess the homoallyl olefin chain, one methylene longer, in comparison to homodimerized products **7a**–**d** with the allyl chain. A possible reason for the higher yield is that the ruthenium catalyst is less sterically hindered by the amino acid moiety and has better access to the slightly longer chain terminal olefin.[17] Again, we saw little differences between the Fmoc **8a**–**b** and Boc protected **7e** and **7g**. Interestingly, CM of sulfur-containing methionine derivatives resulted in zero or low yields. Analysis by TLC showed that mostly starting material **3h** and unreacted **2** were present, even after 2 d at reflux. Only the trans isomers for products **7** and **8** were isolated and this was elucidated by NMR.

We examined the ^{1}H and ^{13}C NMR of the crude reaction mixture to determine the *cis*/*trans* ratio of products **7** and **8**. The chemical shifts of the cis isomers were expected to be further downfield than the trans isomers. Further confirmation was made by independent

synthesis of *cis*-**7a** and *trans*-**7e**. Careful examination of the crude NMR and the isolated homodimerized products by column chromatography indicated the compounds were single pure trans isomers (over 99%), rather than a mixture of cis and trans isomers. We expected them to be mostly trans based on Grubb's studies. However, experiments conducted by Miller group showed a mostly *cis*/*trans* 3:1 ratio of but differed with the utilization of Grubbs' first generation catalyst[4] and N-linked amino acids.

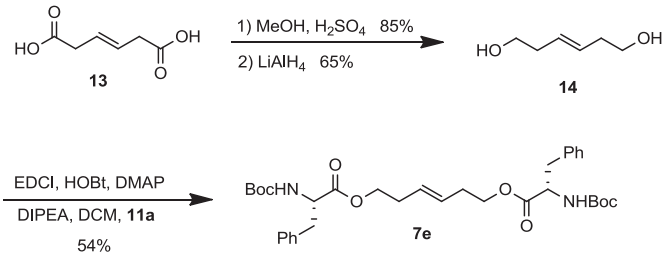
To ensure we properly assigned the *cis*/*trans* ratio of products, we examined the satellites of the alkene protons using a 500 MHz spectrometer with deuterated acetone as the solvent. These weak satellites were formed from protons attached directly to the ^{13}C (1% natural abundance), rather than protons attached to the more abundant ^{12}C isotope.[18] We expected the alkene protons of the trans isomers to have a larger coupling constant (J=15–17 Hz) than the cis isomers (J=9–11 Hz).[19]

We independently synthesized two authentic homodimers, where the stereochemistry was known, to confirm the predicted J coupling values of the weak satellites. We first synthesized the *cis* allyl homodimer **7a** by coupling (*Z*)-2-butene-1,4-diol (**12**) with 3 equiv of *N*-(*t*-BOC)-phenylalanine (**11a**), DMAP, HOBt, DIPEA, and EDCI in 95% yield as shown in Scheme 4. Homodimer *cis*-**7a** was prepared as shown and the yield was 88%. NMR analysis of the satellites of the *cis* alkene protons indicated a pattern of a doublet of a triplet with J=11 and 6 Hz.



Scheme 4.

We also independently synthesized the *trans* homoallyl dimer product by employing the same method as above, but starting from *trans*-3-hexenedioic acid **14** as in Scheme 5. The acid was converted to the diester, which was then reduced to the diol by $LiAlH_4$. Amino acid coupling with Boc protected L-phenylalanine **11a** afforded *trans* homodimer product **7e**. NMR analysis of *trans*-**7e** and the weak satellites of the alkene protons indicated a doublet of a triplet pattern with J=16 and 7 Hz.



Scheme 5.

We conducted an NMR analysis of our homodimer samples from Table 2 clearly indicated trans isomers. This was determined by the J coupling of the weak satellites since we observed a doublet of a triplet pattern with J=16 and 7 Hz.

3. Conclusion

This work shows the attachment of two amino acid derivatives by olefin cross-metathesis (CM), at the carboxyl termini. The carboxyl-linked alkene chain on the amino acid we used has been little studied, however, more light is shed on this mode of synthesis. A cyclic dilactam scaffold was used, which reacted with only a fraction of the amino acid derivatives. The remaining fraction coupled directly with no scaffold. This type of attachment with a variety of amino acids in a single reaction has not been examined prior to this work to the best of our knowledge. The stereochemistry of the newly formed products was found to be *trans*.[20]

4. Experimental section

4.1. General

All moisture and air-sensitive reactions were run under argon with flame dried glassware. Solvents were distilled under N_2 from appropriate drying agents according to established procedures. Analytical Thin Layer Chromatography (TLC) was performed using 0.25 mm silica gel plates. UV light, phosphomolybdic acid in ethanol, anisaldehyde in ethanol, permanganate, and vanillin were used as indicators. Yields reported refer to the isolated materials. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on 300 MHz and 500 MHz spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts were reported in parts per million downfield relative to tetramethylsilane (TMS) as an internal standard. Infrared spectra were reported in wavenumbers (cm^{-1}).

4.2. *N*-Allyl dimer scaffold 2

NaH (60% mass, 4.0 g, 100 mmol) was added in portions to a stirred solution of glycine anhydride (**10**) (3.14 g, 27.5 mmol) and anhydrous DMF (55 mL). After stirring for an additional 15 min, TBAI (1.60 g, 4.33 mmol) and allyl bromide (12 mL, 140 mmol) were added. The reaction mixture was maintained at room temperature for 3.5 h, then quenched with H_2O. DMF and H_2O were removed in vacuo, leaving behind an orange semi-solid. EtOAc was added to the residue and the sodium salts filtered. The filtrate was concentrated in vacuo. Column chromatography on silica gel with EtOAc/hexane (7:3) afforded **2** (4.1 g, 77%) as a white solid, mp 98–99 °C; R_f=0.24 (EtOAc); ^1H NMR ($CDCl_3$) δ 5.82–5.63 (ddt, J=17.1, 10.2, 6.3 Hz, 2H), 5.29–5.17 (m, 4H), 4.02–3.97 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 163.4, 130.9, 119.8, 49.3, 48.3; IR (KBr) 3079, 2914, 1656, 1487, 1441, 1415, 1336, 1294, 1193, 1142, 1074, 1011 cm^{-1}; HRMS (EI pos) for $C_{10}H_{14}N_2O_2$ $[M]^+$: calcd 194.1055, found 194.1047. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.75; H, 7.42; N, 14.29%.

4.3. General amino acid esterification procedure for 3a–4c

To a cooled (0 °C) solution of amino acid (7.7 mmol) and CH_2Cl_2 (13 mL) was added 1,3-diisopropylcarbodiimide (DIC) (15 mmol), 4-(dimethylamino)pyridine (DMAP) (1.5 mmol), and hydroxybenzotriazole (HOBt) (8.0 mmol). After stirring the mixture for 5 min, the alcohol (12 mmol) was slowly added. The mixture was allowed to warm to room temperature while stirring for a total of 3 h. All solids were filtered and the filtrate was concentrated under reduced pressure. The crude product was purified on a silica gel column,

eluting with hexane/EtOAc to provide the amino acid derivatives **3a**–**4c** in Table 1.

4.4. *t*-Boc-allylester phenylalanine 3a

The protected amino acid *t*-Boc-L-phenylalanine (2.04 g, 7.69 mmol), CH_2Cl_2 (13 mL), DIC (2.4 mL, 15 mmol), DMAP (0.186 g, 1.52 mmol), HOBt (1.08 g, 7.99 mmol), and allyl alcohol (0.85 mL, 12 mmol) gave **3a** (2.2 g, 92%) as a white solid, mp 71–72 °C; R_f=0.35 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ −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; 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%; $[\alpha]_D^{29}$ −10.2 (*c* 1.10, MeOH).[12]

4.5. *t*-Boc-allylester alanine 3b

The protected amino acid *t*-Boc-L-alanine (1.73 g, 9.14 mmol), DIC (2.8 mL, 18 mmol), DMAP (0.230 g, 1.89 mmol), HOBt (1.27 g, 9.40 mmol), allyl alcohol (1.0 mL, 15 mmol), and CH_2Cl_2 (15 mL) yielded **3b** (2.0 g, 95%) as a colorless oil; R_f=0.42 (hexane/EtOAc, 8:2); $[\alpha]_D^{25}$ −35.0 (*c* 1.04, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.89 (ddt, *J*=17.0, 10.2, 5.6 Hz, 1H), 5.37–5.19 (m, 2H), 5.11 (br s, 1H), 4.69–4.54 (m, 2H), 4.39–4.26 (m, 1H), 1.43 (s, 9H), 1.38 (d, *J*=7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 155.2, 131.8, 118.7, 80.0, 65.9, 49.4, 28.5, 18.8; IR (neat) 3368, 2980, 2937, 1716, 1650, 1518, 1455, 1367, 1251, 1167, 1069; HRMS (ESI-FTICR) for $[M+Na]^+$, calcd 252.1206, found 252.1227. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.88; H, 8.77; N, 6.47.

4.6. *t*-Boc-allylester proline 3c

The protected amino acid *t*-Boc-L-proline (4.15 g, 19.3 mmol), DIC (6.0 mL, 39 mmol), DMAP (0.707 g, 5.79 mmol), HOBt (2.74 g, 20.3 mmol), allyl alcohol (2.24 g, 38.6 mmol), and CH_2Cl_2 (32 mL) yielded **3c** (4.7 g, 95%) as a clear oil; R_f=0.25 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ −70.9 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.89 (ddt, *J*=16.7, 10.5, 5.7 Hz, 1H), 5.37–5.15 (m, 2H), 4.68–4.51 (m, 2H), 4.36–4.18 (m, 1H), 3.58–3.30 (m, 2H), 2.28–2.09 (m, 1H) 2.02–1.71 (m, 3H), 1.43 and 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 153.9, 131.9, 118.7–118.2 (2 lines), 80.00–79.9 (2 lines), 65.6, 59.3–59.0 (s lines), 46.7–46.6 (2 lines) 31.1–30.1 (2 lines), 28.6–28.5 (2 lines), 24.5–23.8 (2 lines); IR (KBr) 2978, 2882, 1749, 1702, 1397, 1258, 1162, 1122, 1089; HRMS (CI pos) for $C_{13}H_{21}NO_4$ $[M+H]^+$, calcd 256.1549, found 256.1541.

4.7. *t*-Boc-allylester methionine 3d

The protected amino acid *t*-Boc-L-methionine (2.23 g, 8.94 mmol), DIC (2.8 mL, 18 mmol), DMAP (0.300 g, 2.46 mmol), HOBt (1.26 g, 9.33 mmol), allyl alcohol (0.90 mL, 13 mmol), and CH_2Cl_2 (15 mL) yielded **3d** (2.5 g, 97%) as a colorless oil; R_f=0.28 (hexane/EtOAc, 8:2); $[\alpha]_D^{25}$ −32.4 (*c* 1.04, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.88 (ddt, *J*=17.1, 10.4, 5.7 Hz, 1H), 5.35–5.16 (m, 3H), 4.67–4.55 (m, 2H), 4.44–4.34 (m, 1H), 2.51 (t, *J*=7.5 Hz, 2H), 2.18–1.83 (m, 5H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.1, 155.4, 131.7, 119.0, 80.1, 66.1, 52.9, 32.3, 30.1, 28.4, 15.6; IR (neat) 3362, 2977, 2920, 1716, 1650, 1511, 1447, 1367, 1251, 1167, 1050; HRMS (CI pos) for $C_{13}H_{24}NO_4S$ $[M+H]^+$, calcd 290.1426, found 290.1421.

4.8. *t*-Boc-homoallyl phenylalanine 3e

The protected amino acid *t*-Boc-L-phenylalanine (5.35 g, 20.2 mmol), DIC (5.2 mL, 33.6 mmol), DMAP (0.48 g, 3.93 mmol), HOBt (2.96 g, 21.9), 3-buten-1-ol (2.7 mL, 31.4 mmol), and CH_2Cl_2 (40 mL) yielded **3e** (5.8 g, 90%) as a white solid; mp=79–80.5 °C; R_f=0.40 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ −9.01 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.33–7.10 (m, 5H), 5.72 (ddt, *J*=17.1, 10.6, 6.6 Hz, 1H), 5.14–5.03 (m, 2H), 4.99 (d, *J*=8.2 Hz, 1H), 4.57 (dt, *J*=8.2, 6.4 Hz, 1H), 4.14 (t, *J*=6.8 Hz, 2H), 3.11 (dd, *J*=13.6, 6.5 Hz, 1H), 3.03 (dd, *J*=13.7, 6.6 Hz, 1H), 2.40–2.29 (m, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.1, 155.3, 136.21, 133.78, 129.50, 128.68, 127.15, 117.68, 80.01, 64.50, 54.6, 38.5, 33.0, 28.5; IR (KBr) 3355, 3077, 3030, 3006, 2973, 2930, 1735, 1708, 1645, 1516, 1455, 1391, 1365, 1288, 1220, 1187, 1086, 1054, 1020; Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.83; H, 8.07; N, 4.36%.

4.9. *t*-Boc-homoallyl alanine 3f

The protected amino acid *t*-Boc-L-alanine (1.86 g, 9.83 mmol), DIC (2.5 mL, 16 mmol), DMAP (0.240 g, 1.96 mmol), HOBt (1.45 g, 10.7 mmol), 3-buten-1-ol (1.3 mL, 16 mmol), and CH_2Cl_2 (20 mL) yielded **3f** (2.4 g, 98%) as a colorless oil; R_f=0.35 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ −45.7 (*c* 1.11, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.75 (ddt, *J*=17.1, 10.5, 6.8, 1H), 5.16–5.00 (m, 3H), 4.34–4.08 (m, 3H), 2.43–2.34 (m, 2H), 1.42 (s, 9H), 1.35 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 155.2, 133.8, 117.6, 79.9, 64.3, 49.4, 33.2, 28.5, 18.9; IR (KBr) 3368, 2980, 1718, 1644, 1517, 1168, 1069; HRMS (CI pos) for $C_{12}H_{22}NO_4$ $[M+H]^+$: calcd 244.1549, found 244.1549.

4.10. *t*-Boc-homoallyl proline 3g

The protected amino acid *t*-Boc-L-proline (4.06 g, 18.9 mmol), DIC (5.0 mL, 32 mmol), DMAP (0.730 g, 5.98 mmol), HOBt (2.82 g, 20.9 mmol), 3-buten-1-ol (2.7 mL, 32 mmol), and CH_2Cl_2 (31 mL) yielded **3g** (4.5 g, 89%) as a clear oil; R_f=0.41 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ −72.3 (*c* 1.24, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.71 (ddt, *J*=17.0, 10.2, 6.8 Hz, 1H), 5.11–4.96 (m, 2H), 4.27–4.01 (m, 3H), 3.54–3.26 (m, 2H), 2.38–2.27 (m, 2H), 2.21–1.73 (m, 4H), 1.39 and 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.21–172.95 (2 lines), 153.87, 134.05–133.83 (2 lines), 117.46–117.23 (2 lines), 79.89–79.76 (2 lines), 63.93, 59.28–58.98 (2 lines), 46.63–46.41 (2 lines), 33.20, 31.03–30.08 (2 lines), 28.54–28.45 (2 lines), 24.37–23.67 (2 lines); IR (KBr) 3482, 3080, 2977, 1699, 1395, 1160; HRMS (CI pos) for $C_{14}H_{23}NO_4$ $[M+H]^+$: calcd 270.1705, found 270.1701.

4.11. *t*-Boc-homoallyl methionine 3h

The protected amino acid *t*-Boc-L-methionine (5.59 g, 22.4 mmol), DIC (5.2 mL, 34 mmol), DMAP (0.577 g, 4.72 mmol), HOBt (3.35 g, 24.8 mmol), 3-buten-1-ol (2.9 mL, 34 mmol), and CH_2Cl_2 (40 mL) yielded **3h** (6.0 g, 88%) as a clear oil; R_f=0.26 (hexane/EtOAc, 8:2); $[\alpha]_D^{25}$ −23.8 (*c* 1.10, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.76 (ddt, *J*=17.5, 10.3, 6.7 Hz, 1H), 5.16–5.05 (m, 3H), 4.44–4.33 (m, 1H), 4.26–4.13 (m, 2H), 2.52 (t, *J*=7.6 Hz, 2H), 2.40 (qt, *J*=6.7, 1.2, 2H), 2.18–1.86 (m, 5H); 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) 172.40, 155.46, 133.75, 117.74, 80.13, 64.59, 53.02, 33.16, 32.49, 30.15, 28.50, 15.64; IR (KBr) 3362, 3079, 2978, 2919, 1716, 1643, 1509, 1446, 1391, 1367, 1251; HRMS (CI pos) for $C_{14}H_{26}NO_4S$ $[M+H]^+$, calcd 304.1582, found 304.1570.

4.12. *t*-Boc-homoallyl leucine 3i

The protected amino acid *t*-Boc-L-leucine (2.08 g, 8.99 mmol), DIC (2.0 mL, 13 mmol), DMAP (0.179 g, 1.47 mmol), HOBt (1.44 g, 10.6 mmol), 3-buten-1-ol (1.0 mL, 12 mmol), and CH_2Cl_2 (50 mL) yield **3i** (2.1 g, 83%) as a clear oil; R_f=0.33 (hexane/EtOAc, 9:1); $[\alpha]_D^{25}$

−39.2 (*c* 1.42, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.72 (ddt, J=17.3, 10.1, 6.7 Hz, 1H), 5.10–4.92 (m, 3H), 4.28–4.05 (m, 3H), 2.35 (qt, J=6.7, 1.1 Hz, 2H), 1.71–1.39 (m, 12H), 0.90 (d, J=1.2, 3H), 0.88 (d, J=1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) 173.50, 155.48, 133.79, 117.48, 79.72, 64.17, 52.24, 41.97, 33.10, 28.40, 24.86, 22.87, 22.03; IR (neat) 3368, 3081, 2960, 2872, 1718, 1644, 1509, 1455, 1367, 1165, 1122, 1048, 1023; Anal. Calcd for $C_{15}H_{27}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.83; H, 8.07; N, 4.36%.

4.13. Fmoc homoallyl phenylalanine 4a

The protected amino acid Fmoc-L-phenylalanine (1.00 g, 2.58 mmol), DIC (0.60 mL, 3.87 mmol), DMAP (60.0 mg, 0.491 mmol), HOBt (422 mg, 3.12 mmol), 3-buten-1-ol (0.33 mL, 3.86 mmol), and THF (5.0 mL) yielded **4a** (1.1 g, 99%) as a white solid; mp=52–54 °C; R_f=0.44 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ −20.0 (*c* 1.06, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.85–7.16 (m, 13H), 5.86–5.72 (m, 1H), 5.46–5.09 (m, 3H), 4.80–4.20 (m, 6H), 3.25–3.15 (m, 2H), 2.48–2.32 (m, 2H); ^{13}C NMR ($CDCl_3$) 171.61, 155.67, 143.98–143.88 (2 lines), 141.42, 135.93, 133.67, 129.47, 128.69, 127.83, 127.23–127.17 (2 lines), 125.25–125.18 (2 lines), 120.11, 117.70, 67.05, 64.60, 54.94, 47.26, 38.38, 32.94; IR (KBr) 3327, 3064, 2962, 1696, 1605, 1536, 1450, 1388, 1263, 1104, 1086, 1045; HRMS (CI pos) for $C_{28}H_{28}NO_4$ $[M+H]^+$: calcd 442.2018, found 442.2025; Anal. Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 75.81; H, 6.22; N, 3.16%.

4.14. Fmoc homoallyl proline 4b

The protected amino acid Fmoc-L-proline (1.04 g, 3.07 mmol), DIC (0.71 mL, 4.6 mmol), DMAP (0.0749 g, 0.613 mmol), HOBt (0.502 g, 3.71 mmol), 3-buten-1-ol (0.40 mL, 4.7 mmol), and THF (7.0 mL) yielded **4b** (1.1 g, 92%) as a colorless oil; R_f=0.35 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ −49.4 (*c* 1.25, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.62–7.12 (m, 8H), 5.69–5.50 (m, 1H), 5.00–4.84 (m, 2H) 4.33–3.89 (m, 6H), 3.55–3.29 (m, 2H), 2.27–1.66 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.43–172.36 (2 lines), 154.67–154.27 (2 lines), 144.10–143.68 (4 lines), 141.18–141.13 (2 lines), 133.79–133.60 (2 lines)127.58, 126.94, 125.09–124.86 (3 lines), 119.86, 117.31–117.17 (2 lines), 67.31, 63.85, 59.20–58.75 (2 lines), 47.20–46.34 (4 lines), 32.96–32.91 (2 lines) 30.96–29.80 (2 lines) 24.19, 23.17; IR (KBr) 3068, 2957, 2884, 1745, 1705, 1451, 1417, 1349, 1194, 1120, 1089; HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 414.1676, found 414.1669; Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.28; H, 6.61; N, 3.54%.

4.15. Fmoc homoallyl glycine 4c

The protected amino acid Fmoc-glycine (1.90 g, 6.39 mmol), DIC (1.5 mL, 9.7 mmol), DMAP (0.318 g, 2.60 mmol), HOBt (1.38 g, 10.2 mmol), 3-buten-1-ol (0.85 mL, 9.9 mmol), and THF (15 mL) yielded **4c** (2.2 g, 85%) as a white solid; mp=78.5–80 °C; R_f=0.40 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 7.81–7.30 (m, 8H), 5.79 (ddt, J=17.2, 10.2, 6.7 Hz, 1H), 5.49–5.41 (m, 1H), 5.18–5.08 (m, 2H), 4.43 (d, J=7.0 Hz), 4.28–4.20 (m, 3H), 4.00 (d, J=5.6 Hz, 2H), 2.42 (qt, J=6.8, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) 170.15, 156.43, 143.93, 141.40, 133.63, 127.83, 127.19, 125.20, 120.10, 117.71, 67.28, 64.54, 47.21, 42.85, 33.02; IR (KBr) 3335, 3065, 3017, 2947, 1767, 1685, 1541, 1451, 1414, 1389, 1361, 1288, 1192, 1104, 1081, 1055; HRMS (CI pos) for $C_{21}H_{22}NO_4$ $[M+H]^+$: calcd 352.1549, found 352.1556; Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.62; H, 6.06; N, 3.98%.

4.16. General procedure for cross-metathesis of dimer 2 with an amino acid derivative

As shown in Scheme 1, a solution of catalyst **1** (0.05 mmol) and $CHCl_3$ (0.50 mL) was added to a stirred solution of dimer **2** (0.541 mmol), amino acid **3**/**4** (2.70 mmol), and $CHCl_3$ (0.50 mL). The reaction was heated at reflux for 10 h while flushing the headspace with argon to remove evolved ethylene. The reaction was allowed to cool to room temperature and quenched with EVE (ca. 0.5 mL). The solution was stirred for 30 min and concentrated under reduced pressure. Purification by column chromatography on silica gel with hexane/EtOAc yielded **5**/**6** and **7**/**8**.

4.17. Cross-metathesis product *t*-Boc-allylester phenylalanine-dimer 5a

A solution of catalyst **1** (46 mg, 0.054 mmol) and $CHCl_3$ (0.50 mL) was added to a stirred solution of dimer **2** (105 mg, 0.541 mmol), amino acid **3a** (825 mg, 2.70 mmol), and $CHCl_3$ (0.50 mL). The reaction was heated at reflux for 10 h while flushing the headspace with argon to remove evolved ethylene. The reaction was allowed to cool to room temperature and quenched with EVE (ca. 0.5 mL). The solution was stirred for 30 min and concentrated under reduced pressure. Purification by column chromatography on silica gel with hexane/EtOAc (9:1–4:6) yielded **5a** as an oil (150 mg, 37%) and homodimer **7a** (301 mg, 38%) as a white solid.

Compound **5a**: R_f=0.33 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.35–7.09 (m, 10H), 5.78–5.57 (m, 4H), 5.03 (d, J=7.9 Hz, 2H), 4.66–4.51 (m, 6H), 4.07–3.90 (m, 8H), 3.16–2.98 (m, 4H), 1.41 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 171.70, 163.08, 155.14, 135.99, 129.39, 128.80, 128.65, 127.40, 127.13, 80.07, 64.56, 54.57, 49.34, 47.03, 38.41, 28.40; IR (KBr) 3324, 2978, 1666, 1498, 1366, 1169, 1022 cm^{-1}; HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 771.3576, found 771.3544.

4.18. Homodimer *t*-Boc-allylester phenylalanine 7a

Compound **7a**: 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 171.76, 155.25, 136.07, 129.53, 128.76, 128.06, 127.26, 80.18, 64.70, 54.64, 38.54, 28.47; IR (neat) 3367, 2977, 1715, 1498, 1455, 1367, 1252, 1166, 1054, 1022 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%.

4.19. Cross-metathesis product *t*-Boc-allylester alanine-dimer 5b

Following general CM procedures, dimer **2** (104 mg, 0.533 mmol), amino acid **3b** (600 mg, 2.62 mmol), Grubbs' catalyst **1** (46 mg, 0.054 mmol), and $CHCl_3$ (0.5 mL) gave a brown residue. Purification by column chromatography on silica gel with hexane/EtOAc (9:1 to 6:4, 2:8 to 0:10) yielded **5b** (130 mg, 40%) as an oil and homodimer **7b** (180 mg, 42%) as a white solid, mp=96–97 °C.

Compound **5b**: R_f=0.21 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.85–5.60 (m, 4H), 5.10 (d, J=7.2 Hz, 2H), 4.65–4.55 (m, 4H), 4.35–3.89 (m, 10H), 1.40 (s, 18H), 1.35 (d, J=7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.13, 163.14, 155.17, 128.93, 127.24, 79.95, 64.49, 51.52, 49.30, 47.03, 28.41, 18.61; IR (KBr) 3330, 2980, 2935, 2361, 2250, 1666, 1520, 1478, 1366, 1252, 1165, 1070, 1023 cm^{-1}; HRMS (EI pos) for $C_{28}H_{44}N_4O_4$ $[M]^+$: calcd 619.2950, found 619.2946.

4.20. Homodimer *t*-Boc-allylester alanine 7b

Compound **7b**: R_f=0.34 (hexane/EtOAc, 6:4); ^{1}H NMR ($CDCl_3$) δ 5.87–5.78 (m, 2H) 5.11 (d, J=7.2 Hz, 2H), 4.64–4.57 (m, 4H), 4.35–4.22 (m, 2H), 1.40 (s, 18H), 1.36 (d, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.12, 155.19, 127.91, 79.95, 64.60, 49.32, 28.43, 18.67; IR (KBr) 3370, 2983, 2938, 1737, 1685, 1522, 1456, 1369, 1274, 1163, 1085, 1024 cm^{-1}; HRMS (CI pos) for $C_{20}H_{35}N_2O_8$ $[M+H]^+$: calcd 431.2393, found 431.2379.

4.21. Cross-metathesis product *t*-Boc-allylester proline-dimer 5c

Following general CM procedures, dimer **2** (95.5 mg, 0.492 mmol), amino acid **3c** (726 mg, 2.51 mmol), Grubbs' catalyst **1** (42.0 mg, 0.0495 mmol), and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by column chromatography on silica gel with hexane/EtOAc (9:1 to 7:3, 2:8 to 0:10) yielded **5c** (135 mg, 42% NMR yield) as an oil and homodimer **7c** (188 mg, 31%) as an oil.

Compound **5c**: R_f=0.28 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.88–5.65 (m, 4H), 4.66–4.58 (m, 4H), 4.36–4.20 (m, 2H), 4.07–3.92 (m, 8H), 3.60–3.35 (m, 4H), 2.30–2.13 (m, 2H), 2.02–1.82 (m, 6H), 1.46 and 1.41 (s, 18H).

4.22. Homodimer *t*-Boc-allylester proline 7c

Compound **7c**: R_f=0.37 (hexane/EtOAc, 5:5); ^{1}H NMR ($CDCl_3$) δ 5.94–5.60 (m, 2H), 4.76–4.52 (m, 4H), 4.36–4.18 (m, 2H), 3.58–3.32 (m, 4H), 2.29–2.10 (m, 2H), 2.02–1.77 (m, 6H), 1.44 and 1.38 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 172.92, 172.67, 154.48, 153.83, 128.46–127.61 (3 lines), 80.00, 64.41, 64.27, 59.22, 58.92, 46.68, 46.46, 31.04, 30.06, 28.55, 28.45, 24.47, 23.78 cm^{-1}; IR (neat) 3482, 2974, 1950, 1747, 1698, 1399, 1259, 1170 cm^{-1}. HRMS (CI pos) for $C_{24}H_{39}N_2O_8$ $[M+H]^+$: calcd 483.2706, found 483.2724. Anal. Calcd for $C_{24}H_{38}N_2O_8$: C, 59.73; H, 7.94; N, 5.81. Found: C, 60.05; H, 8.20; N, 5.70%

4.23. Cross-metathesis product *t*-Boc-homoallylester phenylalanine-dimer 5e

Following general CM procedures, dimer **2** (103 mg, 0.530 mmol), amino acid **3e** (908 mg, 2.84 mmol), catalyst **1** (45.9 mg, 0.0541 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (100:0–0:100) gave **5e** (180 mg, 44%) as a silver foam and homodimer **7e** (440 mg, 50%) as a gray solid, mp=142–144 °C.

Compound **5e**: R_f=0.27 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.38–7.08 (m, 10H), 5.58 (dt, J=15.2, 6.3 Hz, 2H), 5.42 (dt, J=15.3, 6.3 Hz, 2H), 5.10 (d, J=8.0 Hz, 2H), 4.63–4.47 (m, 2H), 4.18–3.83 (m, 12H), 3.15–2.96 (m, 4H), 2.39–2.25 (m, 4H), 1.41 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 172.01, 163.28, 155.21, 136.22, 131.46, 129.39, 128.63, 127.09, 125.68, 79.92, 64.11, 54.62, 49.11, 47.40, 38.41, 31.56, 28.40; IR (KBr) 3328, 2976, 2249, 1713, 1664, 1498, 1366, 1170, 1052 cm^{-1}; HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 799.3889; found 799.3879.

4.24. Homodimer *t*-Boc-homoallylester phenylalanine 7e

Compound **7e**: R_f=0.30 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 7.35–7.10 (m, 10H); 5.47–5.35 (m, 2H), 5.09 (d, J=7.2 Hz, 2H), 4.56 (dt, J=7.6, 7.0 Hz, 2H) 4.08 (t, J=6.8 Hz, 4H), 3.09 (dd, J=13.6, 6.5 Hz, 2H), 3.02 (dd, J=13.6, 6.2 Hz, 2H), 2.37–2.20 (m, 4H), 1.40 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 171.90, 155.13, 136.17, 129.34, 128.53, 128.24, 126.99, 79.80, 64.55, 54.52, 38.39, 31.81, 28.33; IR (KBr) 3365, 3003, 2971, 2931, 1709, 1517, 1456, 1391, 1365, 1222, 1184, 1087, 1053, 1019 cm^{-1}; HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 633.3146, found 633.3156.

4.25. Cross-metathesis product *t*-Boc-homoallylester alanine-dimer 5f

Following general CM procedures, dimer **2** (200 mg, 1.03 mmol), amino acid **3f** (1200 mg, 4.94 mmol), Grubbs' catalyst **1** (84.0 mg, 0.099 mmol) and $CHCl_3$ (3.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (100:0–0:100) gave **5f** (250 mg, 39%) as a silver foam and homodimer **7f** (750 mg, 66%) as an oil.

Compound **5f**: R_f=0.31 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.65 (dt, J=15.4, 6.8 Hz, 2H), 5.46 (dt, J=15.3, 6.4 Hz, 2H), 5.16 (s, 2H), 4.28–4.07 (m, 6H), 4.01–3.90 (m, 8H), 2.44–2.37 (m, 4H), 1.43 (s, 18H), 1.36 (d, J=7.7, 6H); ^{13}C NMR ($CDCl_3$) δ 173.20, 163.22, 155.10, 131.37, 125.49, 79.45, 63.73, 49.13, 48.87 47.15, 31.51, 28.24, 22.81, 18.20; IR (neat) 3327, 2979, 2934, 1666, 1521, 1478, 1391, 1367, 1335, 1250, 1166, 1115, 1068, 1023 cm^{-1}; HRMS (CI pos) for $C_{30}H_{49}N_4O_{10}$ $[M+H]^+$: calcd 625.3449, found 625.3450.

4.26. Homodimer *t*-Boc-homoallylester alanine 7f

Compound **7f**: R_f=0.39 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 5.47–5.39 (m, 2H), 5.15 (s, 2H), 4.28–4.02 (m, 6H), 2.38–2.24 (m, 4H), 1.37 (s, 18H), 1.30 (d, J=7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.41, 155.19, 131.70, 128.29, 127.39 (*cis*), 79.81, 64.47, 49.31, 32.01, 28.43, 18.73; IR 3366, 2979, 1715, 1518, 1455, 1392, 1367, 1251, 1166, 1069, 1025 cm^{-1}; HRMS (CI pos) for $C_{22}H_{39}N_2O_8$ $[M+H]^+$: calcd 459.2706, found 459.2705.

4.27. Cross-metathesis product *t*-Boc-homoallylester proline-dimer 5g

Following general CM procedures, dimer **2** (90.0 mg, 0.463 mmol), amino acid **3g** (624 mg, 2.32 mmol), Grubbs' catalyst **1** (41.2 mg, 0.048 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (100:0–0:100) gave **5g** (140 mg, 45%) and homodimer **7g** (325 mg, 55%) as an oil.

Compound **5g**: R_f=0.28 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.68–5.31 (m, 4H), 4.24–3.75 (m, 14H), 3.52–3.24 (m, 4H), 2.44–1.73 (m, 12H), 1.39 and 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 173.13, 172.92, 163.24, 163.14, 154.36, 153.75, 131.75, 131.41, 125.60, 125.38, 79.83, 79.69, 63.62, 59.14, 58.81, 49.05, 47.35, 46.58, 46.34, 31.66, 30.93, 29.99, 28.46, 28.36, 24.32, 23.64; IR (neat) 3494, 2975, 1745, 1670, 1477, 1399, 1279, 1162 cm^{-1}; HRMS (CI pos) for $C_{34}H_{53}N_4O_{10}$ $[M+H]^+$: calcd 677.3762, found 677.3751.

4.28. Homodimer *t*-Boc-homoallylester proline 7g

Compound **7g**: R_f=0.33 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 5.50–5.32 (m, 2H), 4.26–3.92 (m, 6H), 3.54–3.20 (m, 4H), 2.36–1.74 (m, 12H), 1.39 and 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 173.10, 172.82, 154.32, 153.73, 128.43, 128.22, 127.98, 79.71, 79.61, 64.07, 59.11, 58.81, 46.51, 46.28, 31.97, 30.89, 29.94, 28.40, 28.30, 26.86, 24.25, 23.55 IR (neat) 3522, 2976, 2882, 1747, 1700, 1478, 1455, 1397, 1258, 1162, 1122 cm^{-1}; HRMS (CI pos) for $C_{26}H_{43}N_2O_8$ $[M+H]^+$: calcd 511.3019, found 511.3017.

4.29. Homodimer *t*-Boc-homoallylester methionine 7h

Following general CM procedures, dimer **2** (86.0 mg, 0.443 mmol), amino acid **3h** (690 mg, 2.27 mmol), Grubbs' catalyst **1** (39.9 mg, 0.0470 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (9:1) gave homodimer **7h** (94 mg, 14%) as an oil and **5h** was not observed.

Compound **7h**: R_f=0.31 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 5.78–5.39 (m, 2H), 5.19 (s, 2H), 4.44–4.30 (m, 2H), 4.22–4.07 (m, 4H), 2.56–2.29 (m, 8H), 2.17–1.83 (m, 10H), 1.42 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 172.4, 155.5, 128.4–126.6 (3 lines), 80.1, 65.6–64.2 (4 lines), 53.0, 32.4–31.7 (4 lines), 30.1–29.8 (2 lines), 28.5, 27.2–27.0 (2 lines), 15.9; IR (neat) 3357, 2976, 1715, 1515, 1366, 1252, 1166, 1051 cm^{-1}; HRMS (CI pos) for $C_{26}H_{47}N_2O_8S_2$ $[M+H]^+$: calcd 579.2774, found 579.2768.

4.30. Cross-metathesis product *t*-Boc-homoallylester leucine-dimer 5i

Following general CM procedures, dimer **2** (95.0 mg, 0.489 mol), amino acid **3i** (682 mg, 2.39 mmol), Grubbs' catalyst **1** (43.5 mg, 0.0512 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification

by chromatography on silica gel with hexane/EtOAc (9:1–1:9) gave **5i** (103 mg, 30%) and homodimer **7i** (381 mg, 59%) as an oil.

Compound **5i**: R_f=0.42 (EtOAc/hexane, 8:2); ^{1}H NMR ($CDCl_3$) δ 5.72–5.41 (m, 4H), 5.03 (d, J=7.6 Hz, 2H), 4.31–3.90 (m, 14H), 2.53–2.35 (m, 4H), 1.86–1.38 (m, 24H), 0.94 (d, J=6.72, 12H); ^{13}C NMR ($CDCl_3$) δ 173.6, 163.4, 155.6, 131.7, 125.7, 79.9, 64.0, 52.4, 49.2, 47.5, 41.9, 31.8, 28.5, 25.0, 23.0, 22.1; IR 3325, 2960, 1713, 1665, 1522, 1475, 1390, 1366, 1334, 1253, 1166, 1048, 1020 cm^{-1}; HRMS (CI pos) for $C_{36}H_{60}N_4O_{10}$ $[M+H]^+$: calcd 709.4388, found 709.4390.

4.31. Homodimer *t*-Boc-homoallylester leucine 7i

Compound **7i**: R_f=0.29 (hexane/EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) δ 5.53–5.36 (m, 2H), 4.97 (d, J=6.4 Hz, 2H), 4.30–4.00 (m, 6H), 2.41–2.26 (m, 4H), 1.73–1.37 (m, 24H), 0.90 (d, J=6.3 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 173.5, 155.5, 128.3, 127.4 (*cis*) 79.8, 64.4, 52.3, 42.0, 32.1, 28.5, 27.0–24.9 (2 lines), 22.9–22.1 (2 lines); IR 3379, 2960, 1716, 1510, 1391, 1367, 1253, 1165, 1048 cm^{-1}. HRMS (CI pos) for $C_{28}H_{50}N_2O_8$ $[M+H]^+$ calcd 543.3645, found 543.3630; Anal. Calcd for $C_{28}H_{50}N_2O_8$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.13; H, 9.62; N, 5.04%

4.32. Cross-metathesis Fmoc-homoallylester phenylalanine-dimer 6a

Following general CM procedures, dimer **2** (61.0 mg, 0.314 mol), amino acid **4a** (614 mg, 1.39 mmol), Grubbs' catalyst **1** (30.0 mg, 0.035 mmol) and $CHCl_3$ (1.5 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (9:1–2:8) gave **6a** (136 mg, 42%) as brown foam, and homodimer **8a** (285 mg, 48%) as a white solid, mp=54–56 °C.

Compound **6a**: R_f=0.35 (EtOAc/hexane, 8:2); ^{1}H NMR ($CDCl_3$) δ 7.70–7.01 (m, 26H), 5.53–5.26 (m, 6H), 4.59–3.74 (m, 18H), 3.09–2.92 (m, 4H), 2.34–2.17 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.7, 163.4, 155.8, 143.9, 141.7, 136.0, 131.5, 129.4, 128.7, 127.8, 127.2, 125.7, 125.2, 120.1, 67.0, 64.3, 55.1, 49.1, 48.3, 47.3, 38.3, 31.6; IR 3304, 2956, 1721, 1662, 1478, 1451, 1334, 1260 cm^{-1}; HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 1043.4202, found 1043.4214.

4.33. Homodimer Fmoc-homoallylester phenylalanine 8a

Compound **8a**: R_f=0.30 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 7.72–6.98 (m, 26H), 5.55–5.20 (m, 4H), 4.64–3.92 (m, 12H), 3.10–2.75 (m, 4H), 2.29–2.12 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.7, 144.0–143.9 (2 lines), 141.5, 136.0, 129.5, 128.7, 128.4, 127.9, 127.3–127.2 (2 lines), 125.3–125.2 (2 lines), 120.2, 67.1, 64.9–64.8 (2 lines), 55.0, 47.3, 38.4, 31.9; IR 3343, 2953, 1728, 1521, 1450, 1211, 1051 cm^{-1}; HRMS (ESI-FTICR) for $[M+Na]^+$ calcd 877.3459, found 877.3485. Anal. Calcd for $C_{54}H_{50}N_2O_8$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.46; H, 5.99; N, 3.26%

4.34. Cross-metathesis product Fmoc-homoallylester proline-dimer 6b

Following general CM procedures, dimer **2** (63.0 mg, 0.324 mol), amino acid **4b** (558 mg, 1.42 mmol), Grubbs' catalyst **1** (30.0 mg, 0.0353 mmol) and $CHCl_3$ (1.5 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (9:1–2:8) gave **6b** (140 mg, 46% NMR yield) and homodimer **8b** (280 mg, 52% NMR yield) as a brown semi-solid.

Compound **6b**: R_f=0.32 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.67–7.18 (m, 16H), 5.58–5.27 (m, 4H), 4.41–3.38 (m, 24H), 2.31–1.80 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 172.6, 163.3–163.2 (2 lines), 154.8–154.4 (2 lines), 144.2–143.8 (3 lines), 141.3, 131.5–131.8 (2 lines), 127.7, 127.1, 125.6–125.0 (4 lines), 120.0, 67.5, 63.8, 59.3–58.9 (2 lines), 49.1, 47.3–46.5 (4 lines), 31.6–31.6 (2 lines), 31.2, 30.0, 24.4, 23.4; HRMS (ESI-FTIR-MS) for $[M+Na]^+$: calcd 943.3899, found 943.3900.

4.35. Homodimer Fmoc-homoallylester proline 8b

Compound **8b**: R_f=0.37 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.73–7.15 (m, 16H), 5.43–5.27 (m, 2H), 4.40–3.88 (m, 12H), 3.62–3.37 (m, 4H), 2.32–1.73 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 172.6, 154.9–154.5 (2 lines), 144.2–143.9 (2 lines), 141.4, 128.4–128.1 (3 lines), 127.8, 127.1, 125.3–125.1 (3 lines), 120.1, 67.6, 64.4, 59.4–59.0 (2 lines), 47.4–46.6 (4 lines) 32.1, 31.2, 30.1, 24.5, 23.5; HRMS (ESI-FTIR) for $[M+Na]^+$ calcd 777.3148, found 777.3129.

4.36. Cross-metathesis product Fmoc-homoallylester glycine-dimer 6c

Following general CM procedures, dimer **2** (94.0 mg, 0.484 mol), amino acid **4c** (854 mg, 2.43 mmol), Grubbs' catalyst 5 (67.5 mg, 0.0795 mmol) and $CHCl_3$ (2.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (9:1–1:9) gave **6c** (120 mg, 30%) as a silver solid, mp=52–54 °C, and homodimer **8c** (357 mg, 44%) as a white solid, mp=121–123 °C.

Compound **6c**: R_f=0.42 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.67–7.15 (m, 16H), 5.86–5.20 (m, 6H), 4.32–3.72 (m, 22H), 2.37–2.18 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.2, 163.5, 156.6, 143.9, 141.3, 131.8, 127.8, 127.13, 125.6, 125.2, 120.1, 67.1, 63.9, 48.9, 47.2, 42.8, 31.8; IR 3319, 3065, 2957, 1724, 1662, 1534, 1478, 1450, 1333, 1263, 1193, 1104, 1051, 1008 cm^{-1}; HRMS (ESI-FTICR) for $[M+H]^+$: calcd 841.3443, found 841.3432.

4.37. Homodimer Fmoc-homoallylester glycine 8c

Compound **8c**: R_f=0.39 (hexane/EtOAc, 5:5); ^{1}H NMR ($CDCl_3$) δ 7.78–7.27 (m, 16H), 5.50–5.36 (m, 4H), 4.40 (d, J=7.3 Hz, 4H), 4.26–4.14 (m, 6H), 3.98 (d, J=5.7 Hz, 4H), 2.43–2.31 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.2, 156.5, 144.0, 141.5, 128.5, 127.9, 127.3, 125.3, 120.2, 67.4, 67.4, 64.8, 47.3, 42.9, 32.0; IR 3319, 2950, 1758, 1691, 1541, 1450, 1411, 1361, 1287, 1191, 1105, 1082, 1053 cm^{-1}. HRMS (ESI-FTICR) for $[M+Na]^+$ calcd 697.2520, found 697.2528. Anal. Calcd for $C_{40}H_{38}N_2O_8$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.83; H, 5.74; N, 4.12%

4.38. Independent synthesis of *cis*-7a

A flame dried flask under argon was charged with acid **11a** (2.07 g, 7.8 mmol), and CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, followed by the addition of EDCI (1.47 g, 7.67 mmol), HOBt (1.05 g, 7.77 mmol), DMAP (0.095 g, 0.78 mmol), and DIPEA (1.8 mL, 10 mmol). After stirring for 20 min, (*Z*)-2-butene-1,4-diol (**12**) was added drop-wise to the solution and maintained for 6 h. The solvent was removed in vacuo, and the residue redissolved in EtOAc. The organic layer was washed with 1 N $KHSO_4$, 1 N $NaHCO_3$, water, and brine. The organic layer was then dried with Na_2SO_4 and concentrated in vacuo to give *cis*-**7a** (1.7 g, 97%) as a white solid.

Compound **7a**: ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 7.32–7.09 (m, 10H), 5.72–5.60 (m, 2H), 4.98 (d, J=8.1 Hz, 2H), 4.72–4.54 (m, 6H), 3.15–2.96 (m, 4H), 1.39 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 171.8, 136.1, 129.5, 128.8, 128.1, 127.3, 80.2, 60.7, 54.6, 38.6, 28.5.

4.39. Hex-3-ene-1,6-diol (15)

Following literature procedures,[14] a solution of *trans*-β-hydromuconic acid **13** (1.00 g, 6.94 mmol), concentrated sulfuric acid (0.34 mL), and absolute methanol (50 mL) refluxed overnight under an atmosphere of argon. The solution was cooled to room temperature and the MeOH was removed by reduced pressure. Extraction with ether, $NaHCO_3$, H_2O, and brine, and drying with $MgSO_4$ gave the diester (1.0 g, 85%). A solution of the diester (1.0 g, 5.8 mmol) and THF (30 mL) was added to a reaction vessel containing $LiAlH_4$ (925 mg, 24.4 mmol) and THF (12 mL) by an addition funnel, and the reaction mixture stirred under argon at room temperature for 6 h. The

reaction was quenched with EtOAc. The white precipitate that was formed was filtered off and washed with cold ether. The combined organic layers was passed through a pad of Celite and concentrated under reduced pressure to give diol **14** (0.44 g, 65%).

Compound **14**: ^{1}H NMR ($CDCl_3$) δ 5.48–5.36 (m, 2H), 3.78 (s, 2H) 3.53 (t, J=7.0 Hz, 4H); ^{13}C NMR ($CDCl_3$); 129.4, 61.7, 36.0.

4.40. Independent synthesis of *trans*-7e

A flame dried flask under argon was charged with acid **11e** (3.45 g, 13.0 mmol), and CH_2Cl_2 (40 mL). The solution was cooled to 0 °C, followed by the addition of EDCI (2.90 g, 15.1 mmol), HOBt (2.21 g, 16.4 mmol), DMAP (0.130 g, 1.06 mmol), and DIPEA (4.0 mL, 23 mmol). After stirring for 20 min, diol **14** was added drop-wise to the solution and maintained for 16 h. The solvent was removed in vacuo, and the residue redissolved in EtOAc. The organic layer was washed with 1 N $KHSO_4$, 1 N $NaHCO_3$, water, and brine. The organic layer was then dried with Na_2SO_4 and concentrated in vacuo to give *trans*-**7e** (1.2 g, 54%) as a white solid. Analytical data are identical to data from CM product **7e**.

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