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CAPT LOW TAMMY K
DANIEL COOPER, ERIC ENHOLM, ION GHIVIRIGA

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# Synthesis of Diketopiperizine Peptide Derivatives by Cross-Metathesis

Tammy Low, Daniel Cooper, Ion Ghiviriga, and Eric Enholm *

*Department of Chemistry, University of Florida, Gainesville, Florida 32611*

enholm@chem.ufl.edu

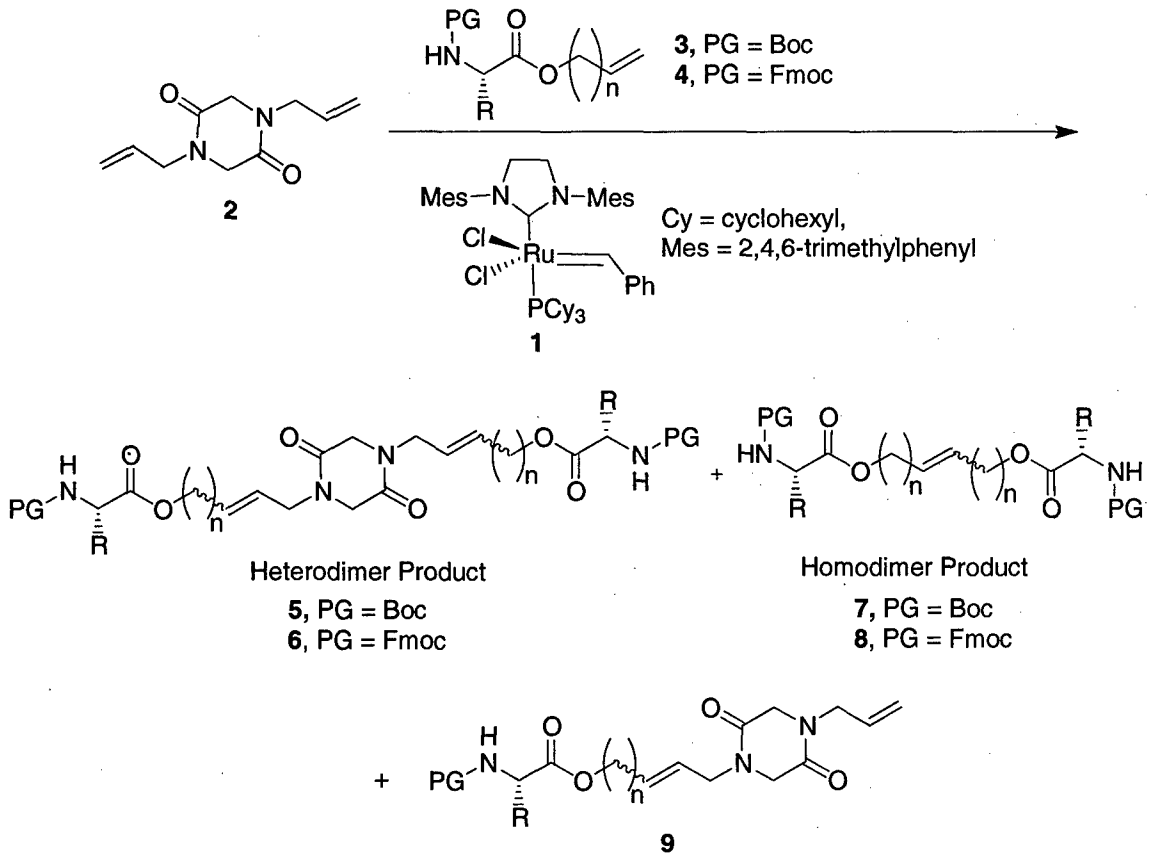
**Abstract**

The olefin CM reactivity and selectivity of amino acid derivatives with a cyclic scaffold to generate diketopiperizine peptide derivatives were investigated. Product yields were dependent on the amino acid R groups, and whether the amino acid possessed an allyl or homoallyl moiety at the caroxylate side. The stereoselectivity of the dipeptide derivatives was found to be predominantly *trans*.

**Introduction**

Peptidomimetic research is an important tool in 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 are covalently achored.[1-4] As part of our ongoing study directed toward the attachment of amino acid derivatives to a cyclic scaffold by olefin cross-metathesis (CM),[5] we are utlizing diketopiperazines as scaffolds to generate cyclic dipeptide derivatives. There is a great interest in cyclic dipeptides because of their important biological and medicinal properties. In comparison to linear peptides,diketopiperazines are conformationally constrained and more stable against hydrolysis, which is critical in drug design.[6-8] Cyclic dipeptides can exhibit antimicrobial, antiviral, and many other medicinal properties.[9-12] In addition, the diketopiperize peptide derivatives could also be used as building blocks for the synthesis of larger or more complexed cyclic peptides.

We report on the synthesis of cyclic dipeptide derivatives using Grubbs' second generation ruthenium catalyst[13] [$(H_2IMes)(PCy_3)(Cl)_2Ru$=CHPh] (**1**) to couple amino acids to the diketopiperazine scaffold by CM (Scheme 1). Miller and coworkers recently demonstrated the importance of remote functionality of olefin CM using Grubbs' first generation catalyst [$(PCy_3)_2(Cl)_2Ru$=CHPh] where they employed allyl and homoallylamides.[14] Here we report the product yields and distributions of CM reactions of allyl and homoallylester amino acid derivatives with a rigid cyclic scaffold using Grubbs'second generation catalyst **1**.



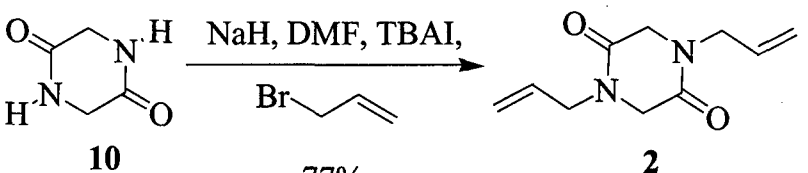

Scheme 1

We envisioned allyl groups attached to the nitrogen of the diketopiperazine, which can couple with amino acids possessing either an allyl or homoallyl moiety at the

caroxylate side. Fmoc and Boc protected amino acids were investigated to determine the influence of the protecting groups, if any, on the CM reaction. The CM of dimer scaffold **2** with the amino acid derivatives can result in three products: heterodimers **5** and **6**, homodimers **6** and **7**, and the mono-coupled compound **9**.

**Results and Discussion**

To obtain the N-allyl dimer scaffold **2**, NaH was added to a solution of commercially available glycine anhydride (**10**) and DMF (Scheme 2). Excess allyl bromide was added and the reaction stirred at 70 °C to give the desired product in 4 h. However, workup of the reaction was more cumbersome. Due to the polarity, some of dimer **2** would remain in DMF during the aqueous workup even after numerous extractions with organic solvents. The best method we found 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 off. Concentration *in vacuo* and purification by chromatography gave the desired product as a white solid in good yields.

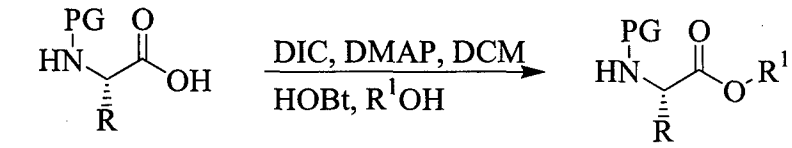



**10** **2**

Scheme 2

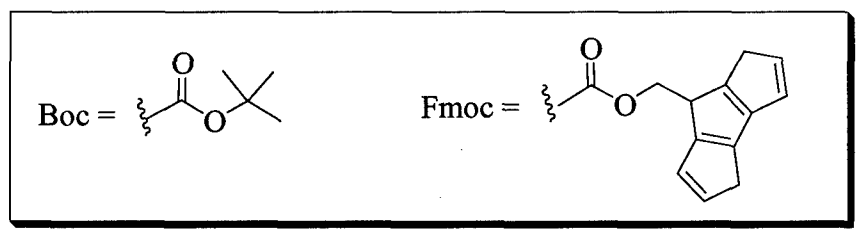
Various amino acid derivatives were synthesized to determine the effects of protecting groups, side chains, and alkene moieties in olefin CM. A series of amino acid derivatives were made by coupling *t*-Boc or Fmoc protected amino acids with allyl alcohol or 3-buten-1-ol using 1,3-diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), and hydroxybenzotriazole (HOBt) (Scheme 3). HOBt

was required to prevent racemization.[15] The starting material was typically consumed within 20 minutes as indicated on thin layer chromatography (TLC). The urea byproduct was filtered off and purification by column chromatography gave the amino acid products in good yield (Scheme 3, Table 1).




**11**, PG = Boc
**12**, PG = Fmoc

**3**, PG = Boc
**4**, PG = Fmoc




Scheme 3

Table 1

| Entry | *N*-PG-AA | $R^1$ | Product | 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 | Butenyl | **3e** | 90 |
| 6 | Boc-Ala | Butenyl | **3f** | 98 |
| 7 | Boc-Pro | Butenyl | **3g** | 89 |
| 8 | Boc-Met | Butenyl | **3h** | 88 |
| 9 | Boc-Leu | Butenyl | **3i** | 86 |
| 10 | Fmoc-Phe | Butenyl | **4a** | >95 |
| 11 | Fmoc-Pro | Butenyl | **4b** | 92 |

| | | | | |
|---|---|---|---|---|
| 12 | Fmoc-Gly | Butenyl | **4c** | 85 |

The CM reactivity of dimer scaffold **2** with amino acid derivatives possessing different protecting groups and olefin moiety was examined. Dimer scaffold **2** was allowed to react with an amino acid derivative (5 eq.) using 10 mol% Grubbs' second generation catalyst **1** (Scheme 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 gave the desired products in moderate yields (Table 2).

Table 2

| Entry | Starting Material | *N*-PG-AA | $R^1$, n | Hetero-dimer Product | Yield (%) | Homo-dimer Product | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | Boc-Phe | Allyl, n=1 | **5a** | 37 | **7a** | 38 |
| 2 | **3b** | Boc-Ala | Allyl, n=1 | **5b** | 40 | **7b** | 42 |
| 3 | **3c** | Boc-Pro | Allyl, n=1 | **5c** | 42 | **7c** | 31 |
| 4 | **3d** | Boc-Met | Allyl, n=1 | **5d** | 0 | **7d** | 0 |
| 5 | **3e** | Boc-Phe | Butenyl, n=2 | **5e** | 44 | **7e** | 50 |
| 6 | **3f** | Boc-Ala | Butenyl, n=2 | **5f** | 39 | **7f** | 66 |
| 7 | **3g** | Boc-Pro | Butenyl, n=2 | **5g** | 45 | **7g** | 55 |
| 8 | **3h** | Boc-Met | Butenyl, n=2 | **5h** | 0 | **7h** | 14 |
| 9 | **3i** | Boc-Leu | Butenyl, n=2 | **5i** | 30 | **7i** | 59 |
| 10 | **4a** | Fmoc-Phe | Butenyl, n=2 | **6a** | 42 | **8a** | 48 |
| 11 | **4b** | Fmoc-Pro | Butenyl, n=2 | **6b** | 46 | **8b** | 52 |
| 12 | **4c** | Fmoc-Gly | Butenyl, n=2 | **6c** | 30 | **8c** | 44 |

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

We attempted to isolate mono-coupled compound **9**, the CM product of one amino acid derivative with dimer scaffold **2** by column chromatography. Separation and

purification of low yielding **9** from other byproducts were unsuccessful. The low yield of **9** was expected due to excess amount of amino acid derivatives which would favor the homodimer or heterodimer products. In addition, these CM reactions were conducted in small scale. We were able to isolate heterodimer products **5** and **6** by column chromatography. Based on TLC, these compounds have $R_f$ values similar to dimer **2**, as well as possible compound **9.** Therefore, a gradient of solvents were required for the column chromatography. For all of the CM reactions, amino acid starting material was not fully consumed. We were able to obtain pure samples of homodimers **7** and **8** by column chromatography. Homodimer products **7a**, **7b**, **7e**, **8a**, and **8c** were isolated as solids.

The yields for the heterodimer products **5** and **6** 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 **7 e-h** and **8 a-b,** which possess the homoallyl olefin chain, in comparison to homodimerized products **7 a-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 longer chain terminal olefin.[16] Again we saw little differences between the Fmoc **8 a-b** and Boc protected **7 e and 7g**. In all cases, CM of methionine derivatives resulted in zero or low yields. Analysis by TLC showed that mostly starting material **3h** and dimer **2** were present even after 2 days of reflux. In comparison to Miller's work,[14] our yields were overall higher by using Grubbs' second generation catalyst **1** and having the olefin moiety attached to the carboxylate side and the amide protected with Boc or Fmoc. Only

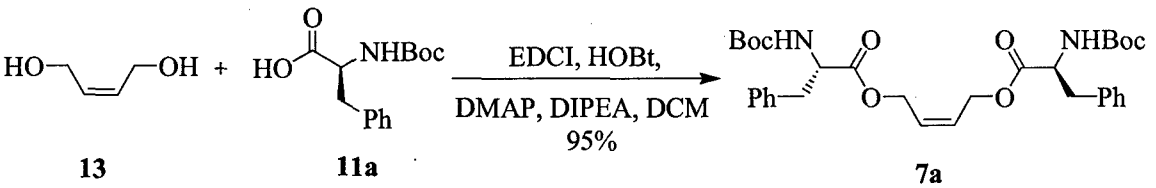
the *trans* isomers for products heterodimer products **5** and **6** were isolated and elucidated by NMR.

We examined the $^{1}H$ and $^{13}C$ NMR of the crude reaction mixture to determine the *cis/trans* ratio of homodimerized products **7** and **8**. The chemical shifts of the *cis* isomers were expected to be further downfield than the *trans* isomers. However, the large number of library constituents in the crude reaction mixture made the NMR data complex. Therefore, we isolated the homodimerized products by column chromatography. Based on the NMR spectra, most of the isolated compounds appeared to a pure isomer, 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 McNaugton *et al.* showed a 3:1 ratio of *cis/trans* but with the utilization of Grubbs first generation catalyst.[14]

To ensure we properly assigned the *trans/cis* ratio of homodimer 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.[17] The satellites were located 80 Hz to the right and left side of the of the stronger proton signal. 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).[18]

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 (*Z*)-2-butene-1,4-diol (**13**) with 3 equivalents of *N*-(tert-butoxycarbonyl)-phenylalanine (**11a**), DMAP, HOBt, DIPEA, and EDCI in 95% yield (Scheme 4-6). Homodimer **7a** was also synthesized

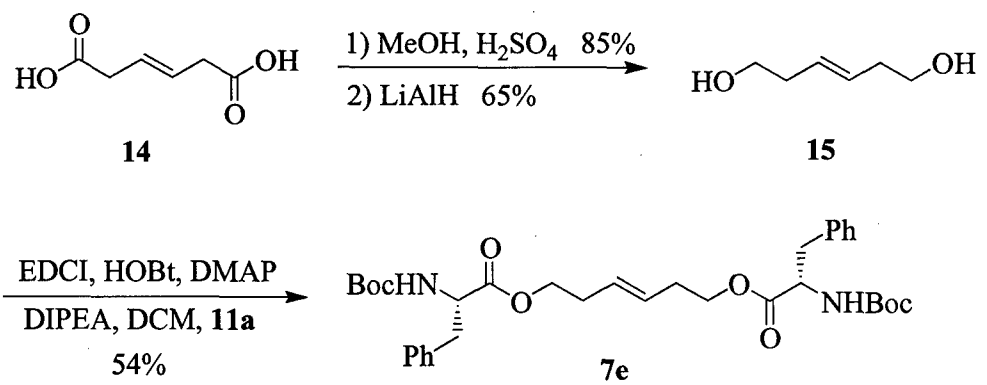
using DIC as the coupling agent. However, removal of the urea byproduct was cumbersome, and the yield was 88%. NMR analysis of the weak satellites of the *cis* alkene protons indicated a pattern of a doublet of a triplet with $J = 11$ and 6 Hz.




**13** **11a** **7a**

Scheme 4-6

We also independently synthesized the *trans* homoallyl dimer product by employing the same method as above, but starting from the less expensive *trans*-3-hexenedioic acid **14** rather than diol **15** (Scheme 4-7). The acid was easily reduced to the diol by LiAlH,[14] followed by amino acid coupling with Boc-protected L-phenylalanine **11a** to obtain the *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.




**14** **15** **7e**

Scheme 4-7

NMR analysis of our homodimer samples from the CM reactions indicated the presence of predominantly *trans* isomers, as determined by the *J* coupling of the weak satellites. We observed a doublet of a triplet pattern with $J = 16$ and 7 Hz.

**Conclusions**

We report the olefin CM reactivity and selectivity of amino acid derivatives with a cyclic scaffold to generate diketopiperizine peptide derivatives. Having the olefin moiety further from the amino acid functional groups increased the yields of the homodimer products, but there were little differences in yields for the heterodimer products. The heterodimer and homodimer products were isolated in moderate yields, except when methionine derivatives were employed. Altering protecting groups on the amino acids from Boc to Fmoc resulted in little changes to the yields as well. The stereochemistry of the heterodimers and homodimers was found to be predominantly *trans*.

**Acknowledgement**

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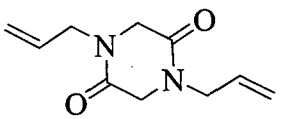
**General Experimentals.**

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 ($^1$H 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 ppm downfield relative to tetramethylsilane (TMS) as an internal standard. Infrared spectra were reported in wavenumbers ($cm^{-1}$).

**Supporting Information**

**N-allyl dimer scaffold 2**



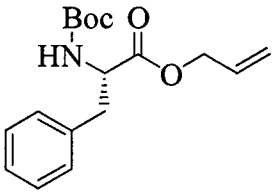
NaH (60% mass, 4.0 g, 100 mmol) was added in portions to a stirred solution of glycine anhydride (**10**) (3.14 g, 27.5 mmol) and anhydrous DMF (55 mL). After stirring for an additional 15 minutes, TBAI (1.60 g, 4.33 mmol) and allyl bromide (12 mL, 140 mmol) were added. The reaction mixture was heated 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, m.p. 97.5-99.0 ˚C.

**2:** $R_f$ = 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 163.36, 130.94, 119.80, 49.27, 48.32; 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%.

**General amino acid coupling procedures**

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 derivative.

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

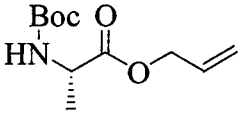



Following amino acid coupling procedures, t-Boc-L-phenylalanine **11a** (2.04 g, 7.69 mmol), $CH_2Cl_2$ (13 mL), DIC (2.4 mL, 15 mmol), DMAP (0.186 g, 1.52 mmol), HOBt (1.08 g, 7.99 mmol), and allyl alcohol (0.85 mL, 12 mmol) gave **3a** (2.2 g, 92%) as a white solid, m.p. 71-72 °C.

**3a**: $R_f$ = 0.35 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = -8.05° (c = 1.1 , MeOH); 1H 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 171.63, 155.14, 136.07, 131.59, 129.42, 128.58, 127.06, 118.94, 79.91, 65.97, 54.57, 38.39, 28.39; 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%. Spectral data are in agreement with literature. Lit[20] $[\alpha]^{29}_D$ = -10.2. (c = 1.10 , MeOH).

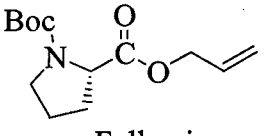
**t-Boc-allylester alanine 3b**



Following amino acid coupling procedures, t-Boc-L-alanine **11b** (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.

**3b:** $R_f$= 0.42 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$= -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 173.19, 155.23, 131.78, 118.72, 79.95, 65.94, 49.39, 28.47, 18.81; 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.

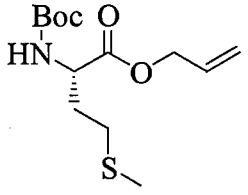
**t-Boc-allylester proline 3c**



Following amino acid coupling procedures, t-Boc-L-proline **11c** (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) yield **3c** (4.7 g, 95%) as a clear oil.

**3c**: $R_f$ = 0.25 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = -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 172.99, 153.89, 131.96, 118.73-118.24 (2 lines), 80.00-79.86 (2 lines), 65.58, 59.28-58.98 (s lines), 46.68-46.46 (2 lines) 31.05-30.08 (2 lines), 28.57-28.45 (2 lines), 24.46-23.77 (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.

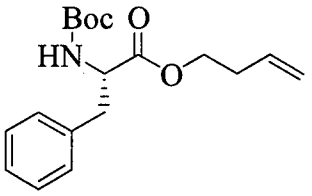
**t-Boc-allylester methionine 3d**




Following amino acid coupling procedures, t-Boc-L-methionine **11d** (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.

**3d:** $R_f$ = 0.28 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ = -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 172.11, 155.44, 131.67, 119.01, 80.07, 66.09, 52.95, 32.26, 30.08, 28.41, 15.56; 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.

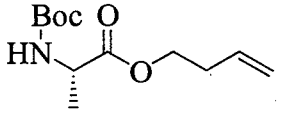
**t-Boc-homoallyl phenylalanine 3e**



Following amino acid coupling procedures, t-Boc-L-phenylalanine **11e** (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 precipitate, m.p. = 79-80.5 °C.

**3e:** $R_f$ = 0.40 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = -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 172.06, 155.24, 136.21, 133.78, 129.50, 128.68, 127.15, 117.68, 80.01, 64.50, 54.58, 38.54, 33.01, 28.45; 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%.

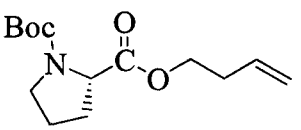
**t-Boc-homoallyl alanine 3f**



Following amino acid coupling procedures, t-Boc-L-alanine **11f** (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.

**3f**: $R_f$ = 0.35 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = -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 173.46, 155.21, 133.76, 117.61, 79.88, 64.32, 49.35, 33.15, 28.47, 18.87; 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.

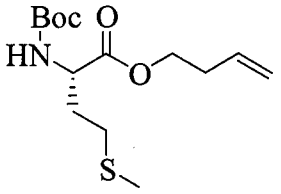
**t-Boc-homoallyl proline 3g**




Following amino acid coupling procedures, t-Boc-L-proline **11g** (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) yield **3g** (4.5 g, 89%) as a clear oil.

**3g**: $R_f$ = 0.41 (hexane/EtOAc, 7:3); $[\alpha]^{25}_D$ = -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.

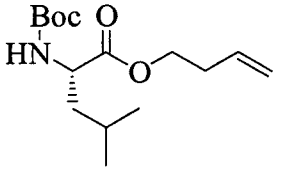
**t-Boc-homoallyl methionine 3h**



Following amino acid coupling procedures, t-Boc-L-methionine **11h** (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) yield **3h** (6.0 g, 88 %) as a clear oil.

**3h**: $R_f$ = 0.26 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ = -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.

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

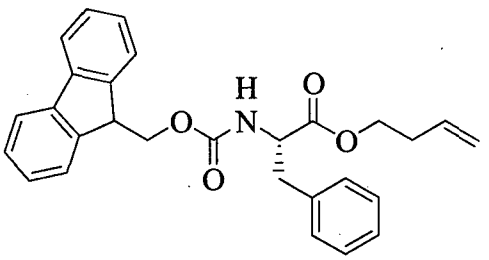


Following amino acid coupling procedures, t-Boc-L-leucine **11i** (2.08 g, 8.99 mmol), DIC (2.0 mL, 13 mmol), DMAP (0.179 g, 1.47 mmol), HOBt (1.44 g, 10.6 mmol), 3-buten-1-ol (1.0 mL, 12 mmol), and $CH_2Cl_2$ (50 mL) yield **3i** (2.1 g, 83%) as a clear oil.

**3i**: $R_f$ = 0.33 (hexane/EtOAc, 9:1); $[\alpha]^{25}_D$ = -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, 3 H); $^{13}$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%.

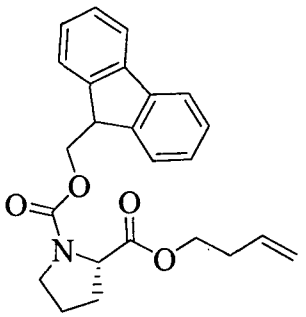
**Fmoc homoallyl phenylalanine 4a**



Following amino acid coupling procedures, Fmoc-L-phenylalanine **12a** (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) yield **4a** (1.1 g, 99 %) as a white solid, m.p. = 52-54 °C .

**4a**: $R_f$ = 0.44 (hexane/EtOAc, 7:3); $[\alpha]^{25}_D$ = -20.0° (c = 1.06, MeOH); $^1$H NMR ($CDCl_3$) δ 7.85-7.16 (m, 13 H), 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%.

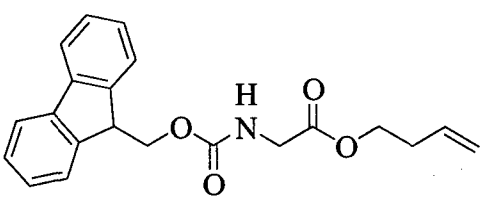
**Fmoc homoallyl proline 4b**



Following amino acid coupling procedures, Fmoc-L-proline **12b** (1.04 g, 3.07mmol), 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) yield **4b** (1.1 g, 92%) as a colorless oil.

**4b**: $R_f = 0.35$ (hexane/EtOAc, 7:3); $[\alpha]^{25}_D = -49.4^\circ$ (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%.

**Fmoc homoallyl glycine 4c**



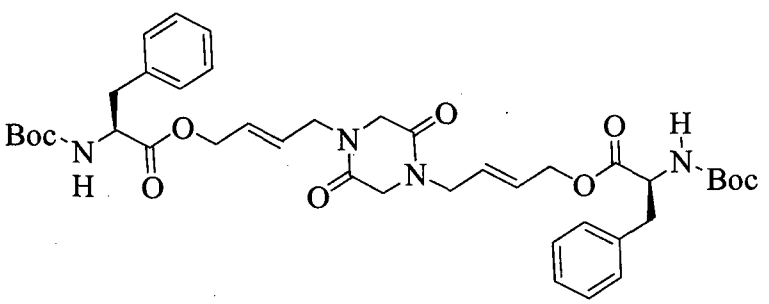
Following amino acid coupling procedures, Fmoc-glycine **12c** (1.90 g, 6.39 mmol), DIC (1.5 mL, 9.7 mmol), DMAP (0.318 g, 2.60 mmol), HOBt (1.38 g, 10.2 mmol), 3-

buten-1-ol (0.85 mL, 9.9 mmol), and THF (15 mL) yield **4c** (2.2 g, 85 %) as a white solid, m.p. = 78.5-80 °C .

**4c**: $R_f$ = 0.40 (hexane/EtOAc, 7:3); $^1$H NMR ($CDCl_3$) δ 7.81-7.30 (m, 8 H), 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%.

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

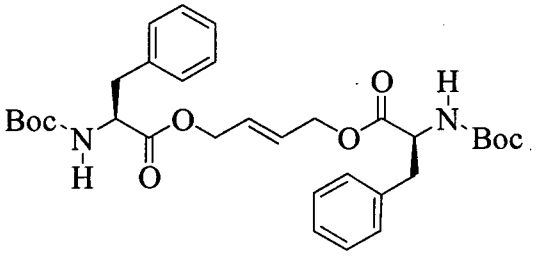
**Cross-metathesis product t-Boc-allylester phenylalanine-dimer 5a**




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.

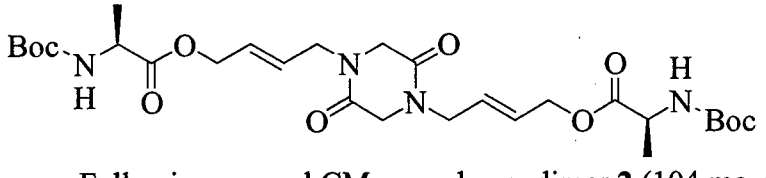
**5a**: $R_f$ = 0.33 (EtOAc); $^1$H NMR ($CDCl_3$) δ 7.35-7.09 (m, 10H), 5.78-5.57 (m, 4H), 5.03 (d, J = 7.9 Hz, 2H), 4.66-4.51 (m, 6H), 4.07-3.90 (m, 8H), 3.16-2.98 (m, 4H), 1.41 (s, 18H); $^{13}$C NMR ($CDCl_3$) δ 171.70, 163.08, 155.14, 135.99, 129.39, 128.80, 128.65, 127.40, 127.13, 80.07, 64.56, 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.

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



**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%.

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

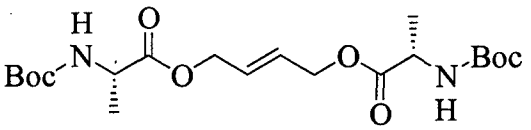


Following general CM procedures, dimer **2** (104 mg, 0.533 mmol), amino acid **3b** (600 mg, 2.62 mmol), Grubbs' catalyst **1** (46 mg, 0.054 mmol), and $CHCl_3$ (0.5 mL) gave

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, m.p. = 96-97 °C.

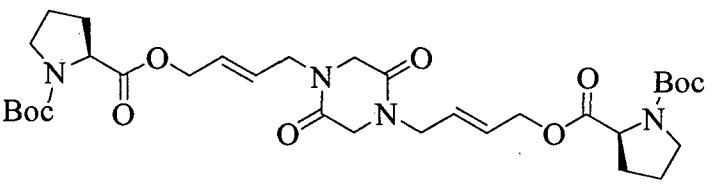
**5b**: $R_f$ = 0.21 (EtOAc); $^1$H NMR ($CDCl_3$) δ 5.85-5.60 (m, 4H), 5.10 (d, J =7.2 Hz, 2H), 4.65-4.55 (m, 4H), 4.35-3.89 (m, 10H), 1.40 (s, 18H), 1.35 (d, J = 7.3 Hz, 6H); $^{13}$C NMR ($CDCl_3$) δ 173.13, 163.14, 155.17, 128.93, 127.24, 79.95, 64.49, 51.52, 49.30, 47.03, 28.41, 18.61; IR (KBr) 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.

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



**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.

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

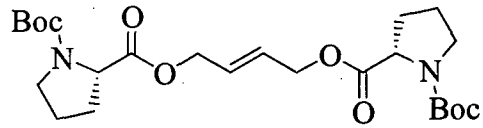


Following general CM procedures, dimer **2** (95.5 mg, 0.492 mmol), amino acid **3c** (726 mg, 2.51 mmol), Grubbs' catalyst **1** (42.0 mg, 0.0495 mmol), and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by column chromatography on silica gel with

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.

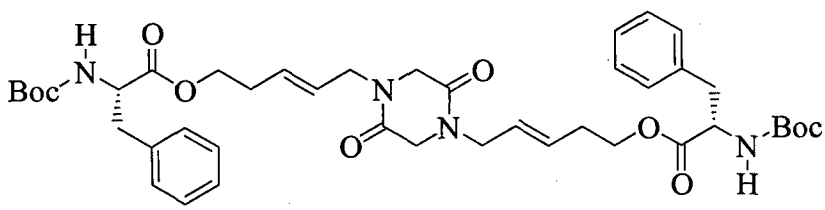
**5c**: $R_f$ = 0.28 (EtOAc); $^1$H NMR ($CDCl_3$) δ 5.88-5.65 (m, 4H), 4.66-4.58 (m, 4H), 4.36-4.20 (m, 2H), 4.07-3.92 (m, 8H), 3.60-3.35 (m, 4H), 2.30-2.13 (m, 2H), 2.02-1.82 (m, 6H), 1.46 and 1.41 (s, 18H).

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




**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%

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

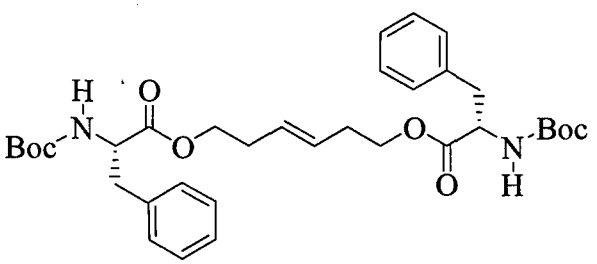



Following general CM procedures, dimer **2** (103 mg, 0.530 mmol), amino acid **3e** (908 mg, 2.84 mmol), catalyst **1** (45.9 mg, 0.0541 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (100:0

– 0:100) gave **5e** (180 mg, 44%) as a silver foam and homodimer **7e** (440 mg, 50%) as a gray solid, m.p. = 142-144 °C.

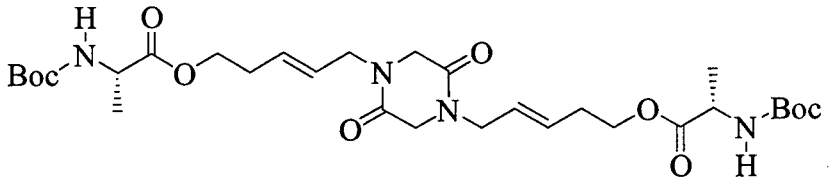
**5e:** $R_f$ = 0.27 (EtOAc); $^1$H NMR ($CDCl_3$) δ 7.38-7.08 (m, 10H), 5.58 (dt, J = 15.2, 6.3 Hz, 2H), 5.42 (dt, J = 15.3, 6.3 Hz, 2H), 5.10 (d, J = 8.0 Hz, 2H), 4.63-4.47 (m, 2H), 4.18-3.83 (m, 12H), 3.15-2.96 (m, 4H), 2.39-2.25 (m, 4H), 1.41 (s, 18H); $^{13}$C NMR ($CDCl_3$) δ 172.01, 163.28, 155.21, 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.

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




**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.

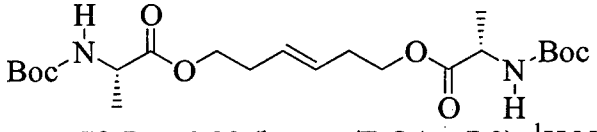
**Cross-metathesis product t-Boc-homoallylester alanine-dimer 5f**



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.

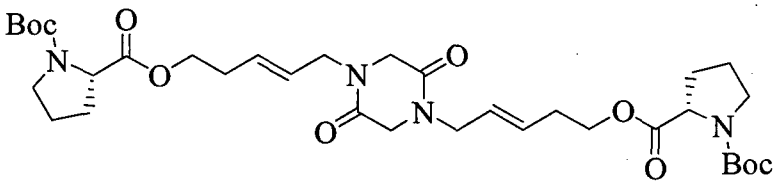
**5f:** $R_f$= 0.31 (EtOAc); $^1$H NMR ($CDCl_3$) δ 5.65 (dt, J = 15.4, 6.8 Hz, 2H), 5.46 (dt, J = 15.3, 6.4 Hz, 2H), 5.16 (s, 2H), 4.28-4.07 (m, 6H), 4.01-3.90 (m, 8H), 2.44-2.37 (m, 4H), 1.43 (s, 18H), 1.36 (d, J = 7.7, 6H); $^{13}$C NMR (CDCl3) δ 173.20, 163.22, 155.10, 131.37, 125.49, 79.45, 63.73, 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.

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



**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 (CDCl3) 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.

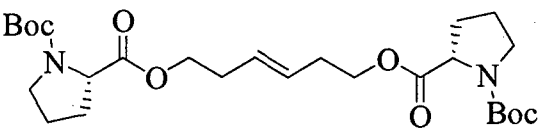
**Cross-metathesis product t-Boc-homoallylester proline-dimer 5g**



Following general CM procedures, dimer **2** ( mg, mmol), amino acid **3g** ( mg, mmol), Grubbs' catalyst **1** (mg, mmol) and $CHCl_3$ (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.

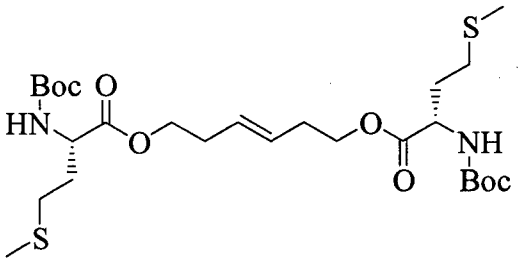
**5g:** $R_f$= 0.28 (EtOAc); $^1$H NMR ($CDCl_3$) δ 5.68-5.31 (m, 4H), 4.24-3.75 (m, 14H), 3.52-3.24 (m, 4H), 2.44-1.73 (m, 12H), 1.39 and 1.34 (s, 18H); $^{13}$C NMR (CDCl3) δ 173.13, 172.92, 163.24, 163.14, 154.36, 153.75, 131.75, 131.41, 125.60, 125.38, 79.83, 79.69, 63.62, 59.14, 58.81, 49.05, 47.35, 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.

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



**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 (CDCl3) 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.

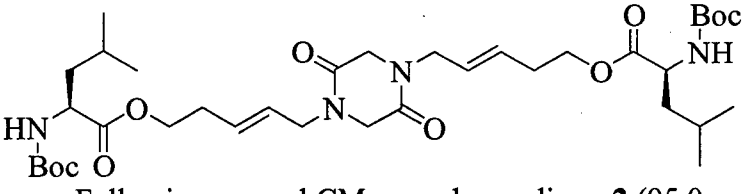
**Homodimer t-Boc-homoallylester methionine 7f**



Following general CM procedures, dimer **2** (86.0 mg, 0.443 mmol), amino acid **3f** (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 **7f** (94 mg, 14%) as an oil.

**7f:** $R_f$ = 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 172.39, 155.48, 128.42-126.62 (3 lines), 80.09, 65.63-64.19 (4 lines), 52.98, 32.38-31.69 (4 lines), 30.14-29.80 (2 lines), 28.45, 27.19-26.95 (2 lines), 15.59; 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.

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

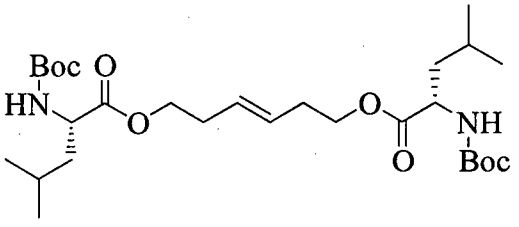


Following general CM procedures, dimer **2** (95.0 mg, 0.489 mol), amino acid **3i** (682 mg, 2.39 mmol), Grubbs' catalyst **1** (43.5 mg, 0.0512 mmol) and $CHCl_3$ (1.0 mL) gave a brown residue. Purification by chromatography on silica gel with hexane/EtOAc (9:1 – 1:9) gave **5i** (103 mg, 30%) and homodimer **7i** (381 mg, 59%) as an oil.

**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 =

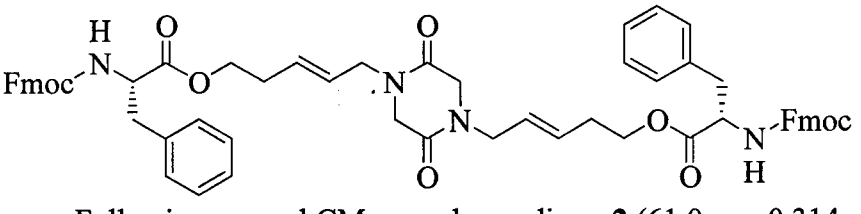
6.72, 12H); $^{13}$C NMR (CDCl3) δ 173.58, 163.41, 155.60, 131.74, 125.74, 79.90, 64.01, 52.35, 49.21, 47.53, 41.85, 31.84, 28.54, 25.00, 23.04, 22.09; IR 3325, 2960, 1713, 1665, 1522, 1475, 1390, 1366, 1334, 1253, 1166, 1048, 1020 cm$^{-1}$. HRMS (CI pos) for $C_{36}H_{60}N_4O_{10}$ $[M+H]^+$: calcd 709.4388, found 709.4390.

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



**4-26i**: $R_f$ =0.29 (hexane/EtOAc, 8:2); 1H 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 173.49, 155.49, 128.33, 127.42 (*cis*) 79.77, 64.38, 52.25, 41.95, 32.05, 28.45, 26.95-24.89 (2 lines), 22.94-22.05 (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 %

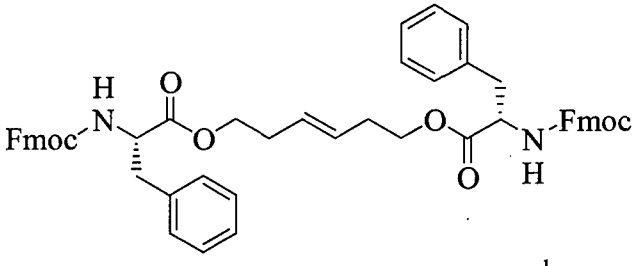
**Cross-metathesis Fmoc-homoallylester phenylalanine-dimer 6a**



Following general CM procedures, dimer **2** (61.0 mg, 0.314mol), 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, m.p. = 54-56 °C.

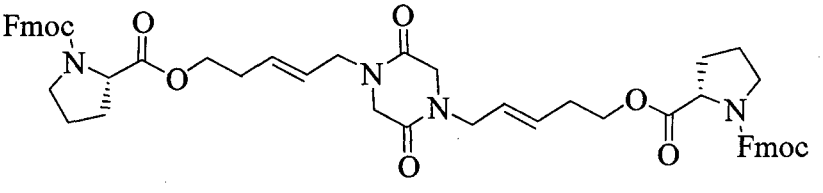
**6a**: $R_f$ = 0.35 (EtOAc/hexane, 8:2); $^1$H NMR ($CDCl_3$) δ 7.70-7.01 (m, 26H), 5.53-5.26 (m, 6H), 4.59-3.74 (m, 18H), 3.09-2.92 (m, 4H), 2.34-2.17 (m, 4H) ; $^{13}$C NMR (CDCl3) δ 171.65, 163.35, 155.75, 143.87, 141.39, 136.02, 131.46, 129.42, 128.70, 127.82, 127.17, 125.73, 125.19, 120.09, 67.01, 64.28, 55.06, 49.10, 48.32, 47.30, 38.31, 31.63; IR 3304, 2956, 1721, 1662, 1478, 1451, 1334, 1260 cm$^{-1}$. HRMS (ESI-FTICR) for $[M+Na]^+$: calcd 1043.4202, found 1043.4214.

**Homodimer Fmoc-homoallylester phenylalanine 8a**



**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 171.64, 155.73, 144.01-143.90 (2 lines), 141.46, 135.96, 129.49, 128.74, 128.38, 127.87, 127.29-127.21 (2 lines), 125.29-125.21 ( 2 lines), 120.15, 67.10, 64-87-64.77 (2 lines), 54.99, 47.30, 38.44, 31.93; 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 %

**Cross-metathesis product Fmoc-homoallylester proline-dimer 6b**

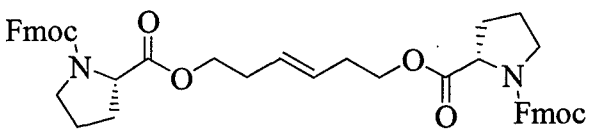


Following general CM procedures, dimer **2** (63.0 mg, 0.324mol), amino acid **4b** (558 mg, 1.42 mmol), Grubbs' catalyst **1** (30.0 mg, 0.0353 mmol) and $CHCl_3$ (1.5 mL)

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.

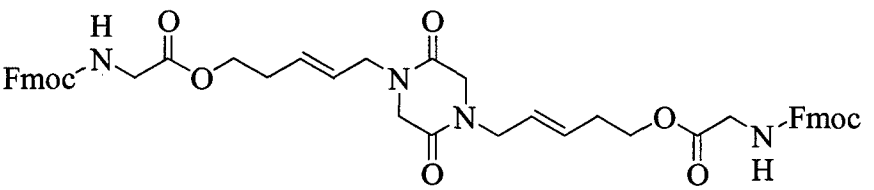
**6b**: $R_f = 0.32$ (EtOAc); $^1H$ NMR ($CDCl_3$) δ 7.67-7.18 (m, 16H), 5.58-5.27 (m, 4H), 4.41-3.38 (m, 24H), 2.31-1.80 (m, 12H); $^{13}C$ NMR ($CDCl_3$) δ 172.56, 163.27-163.15 (2 lines), 154.84-154.40 (2 lines), 144.18-143.77 (3 lines), 141.32, 131.53-131.28 (2 lines), 127.73, 127.12, 125.58-125.02 (4 lines), 120.02, 67.49, 63.84, 59.27-58.88 (2 lines), 49.06, 47.34-46.54 (4 lines), 31.64-31.59 (2 lines), 31.15, 30.00, 24.42, 23.42; HRMS (ESI-FTIR-MS) for $[M+Na]^+$: calcd 943.3899, found 943.3900 .

**Homodimer Fmoc-homoallylester proline 8b**




**8b:** $R_f = 0.37$ (hexane/EtOAc, 1:1); $^1H$ 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 172.57, 154.91-154.49 (2 lines), 144.24-143.86 (2 lines), 141.37, 128.44-128.11 (3 lines), 127.77, 127.13, 125.28-125.07 (3 lines), 120.06, 67.57, 64.39, 59.38-58.97 (2 lines), 47.43-46.58 (4 lines) 32.05, 31.22, 30.06, 24.46, 23.45; HRMS (ESI-FTIR) for $[M+Na]^+$ calcd 777.3148, found 777.3129.

**Cross-metathesis product Fmoc-homoallylester glycine-dimer 6c**

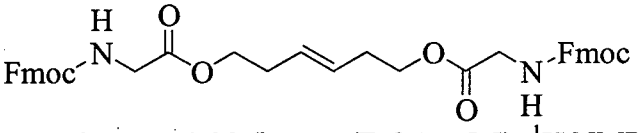



Following general CM procedures, dimer **2** (94.0 mg, 0.484 mol), amino acid **4c** (854 mg, 2.43 mmol), Grubbs' catalyst 5 (67.5 mg, 0.0795 mmol) and $CHCl_3$ (2.0 mL)

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, m.p. = 52-54 °C, and homodimer **8c** (357 mg, 44%) as a white solid, m.p. = 121-123 °C.

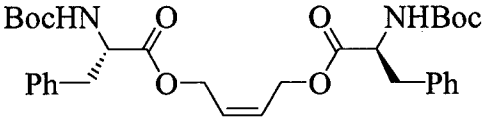
**6c**: $R_f$ = 0.42 (EtOAc); $^1$H NMR ($CDCl_3$) δ 7.67-7.15 (m, 16H), 5.86-5.20 (m, 6H), 4.32-3.72 (m, 22H), 2.37-2.18 (m, 4H); $^{13}$C NMR (CDCl3) δ 170.24, 163.54, 156.62, 143.93, 141.33, 131.84, 127.78, 127.13, 125.59, 125.23, 120.04, 67.12, 63.94, 48.89, 47.18, 42.77, 31.80; IR 3319, 3065, 2957, 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.

**Homodimer Fmoc-homoallylester glycine 8c**



**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 170.24, 156.52, 143.99, 141.48, 128.48, 127.91, 127.26, 125.27, 120.18, 67.38, 67.38, 64.80, 47.28, 42.93, 32.03; 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%

**Independent synthesis of *cis* 7a**

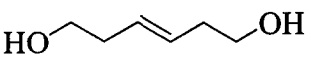


A flame dried flask under argon was charged with acid **11a** (2.07 g, 7.8 mmol), and $CH_2Cl_2$ (10 mL). The solution was cooled to 0 °C, followed by the addition of EDCI

(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 (**13**) 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 **7a** (1.7 g, 97%) as a white solid.

**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 171.81, 136.09, 129.54, 128.76, 128.09, 127.27, 80.16, 60.74, 54.64, 38.57, 28.48

**Hex-3-ene, 1,6-diol (15)**




Following literature procedures[14], a solution of *trans*-β-hydromuconic acid **14** (1.00g, 6.94 mmol), concentrated sulfuric acid (0.34 mL), and absolute methanol (50 mL) were 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, $NaHCO_3$, $H_20$ 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 **15** (0.44 g, 65%).

**15**: $^{1}$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 ($CDCl_3$); 129.424, 61.648, 35.979

**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 (0.130g, 1.06 mmol), and DIPEA (4.0 mL, 23 mmol). After stirring for 20 min, diol **15** 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 **7e** (1.2 g, 54%) as a white solid. Analytical data are identical to data from CM product **7e**.

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