Z-selective olefin metathesis on peptides: Investigation of side chain influence, preorganization, and guidelines in substrate selection

Shane L. Mangold,† Daniel J. O'Leary,*,§ and Robert H. Grubbs*,†

† Arnold and Mabel Beckman Laboratories for Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States and

§ Department of Chemistry, Pomona College, Claremont, California 91711, United States

Supporting Information
### Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Information</td>
<td>S3–S4</td>
</tr>
<tr>
<td>General procedure for homoallyl modification of amino acids</td>
<td>S4</td>
</tr>
<tr>
<td>Characterization data of homoallyl-modified amino acids</td>
<td>S5–S13</td>
</tr>
<tr>
<td>General procedure for homodimerization of amino acids</td>
<td>S13</td>
</tr>
<tr>
<td>Characterization data for homodimerized amino acids</td>
<td>S13–S20</td>
</tr>
<tr>
<td>General procedure for cross metathesis of amino acids</td>
<td>S20</td>
</tr>
<tr>
<td>Characterization data for cross metathesis products</td>
<td>S20–S21</td>
</tr>
<tr>
<td>Procedures for synthesis of allyl-modified amino acids</td>
<td>S21</td>
</tr>
<tr>
<td>Characterization data for allyl-modified amino acids</td>
<td>S21–S23</td>
</tr>
<tr>
<td>Procedure for homodimerization of allyl-modified amino acids</td>
<td>S24</td>
</tr>
<tr>
<td>Characterization data for homodimerized allyl-modified amino acids</td>
<td>S24–S25</td>
</tr>
<tr>
<td>General procedure for cross metathesis of allyl-modified amino acids</td>
<td>S25</td>
</tr>
<tr>
<td>Characterization data for allyl-modified amino acid cross products</td>
<td>S25–S27</td>
</tr>
<tr>
<td>General procedure for the synthesis of homoallyl-modified peptides</td>
<td>S27</td>
</tr>
<tr>
<td>Characterization data for homoallyl-modified peptides</td>
<td>S27–S28</td>
</tr>
<tr>
<td>General procedure for cross metathesis of homoallyl-modified peptides</td>
<td>S28</td>
</tr>
</tbody>
</table>

Supporting Information  S2
HPLC of cross metathesis on homoallyl-modified peptides  S29
Solid-phase synthesis of olefinic peptides  S30
General procedure for Z-selective RCM on peptides  S31
LC/MS TOF to monitor conversion of RCM on peptides  S32
Conversion of peptide 16 to product 17  S33–35
Conversion of peptide 18 to product 19  S36–38
HPLC of purified stapled peptides  
  Macrocyclic peptide 17  S35
  Macrocyclic peptide 19  S39
MALDI-TOF characterization data of stapled peptides  S36
  Macrocyclic peptide 17  S36
  Macrocyclic peptide 19  S39
General procedure for RCM on Aib-containing peptides bearing i, i+3 crosslinks  S40
Characterization data for RCM on Aib-rich peptides  S40
HPLC of Aib-rich macrocyclic peptides  S41
  Conversion of peptide 20 to product 21  S41-43
  Conversion of peptide 24 to product 25  S44-46
NMR spectra  S47-S150

General Information

All reactions were carried out in dry glassware under an atmosphere of argon using standard Schlenk line techniques. Cyclometalated ruthenium catalysts 1 and 2 were obtained from Materia, Inc. and used as received. All solvents were purified by passage through solvent purification columns and further degassed by bubbling argon. Commercially available reagents were used as received unless otherwise noted. Solid substrates were used after purification by column chromatography (SiO2; (230-400 mesh)). Thin-layer chromatography utilized EMD Sciences silica gel 60 F254 pre-cast glass plates (Cat. No. 1.05714.0001). Microwave-assisted chemistry utilized a Biotage Initiator 2.5 reactor. Wang resin, MBHA resin, and TentaGel MB RAM resin were purchased from Novabiochem or RAPP Polymere. All Boc-protected or Fmoc-protected amino acids were purchased from ChemImpex or Peptides International. Fmoc-(S)-2-(4-pentenyl)alanine or Fmoc-(R)-2-(7-...
octenyl)alanine were synthesized as previously described\(^1\) and confirmed by spectroscopic analysis (NMR). HBTU (N,N,N\(^{\prime}\),N\(^{\prime}\)-tetramethyl-O-\((1H\text{-}benzotriazol-1-y)uranium hexafluorophosphate), HATU (1-[Bis(dimethylamino)methylene]-\(1H\)-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), and HOBt (1-hydroxybenzotriazol) were purchased from NovaBioChem. Piperidine, trifluoroacetic acid (TFA), triisopropylsilane (TIPS), and N,N\(^{\prime}\)-dimethylformamide (DMF) were purchased from Sigma-Aldrich. Triethylamine (TEA) or N,N-diisopropylethylamine (DIEA) were purchased from Sigma-Aldrich and distilled prior to use.

Standard NMR spectroscopy experiments were conducted on a Varian INOVA 500 (\(1H\): 500 MHz, \(13C\): 125 MHz) or Varian INOVA 300 (\(1H\): 300 MHz, \(13C\): 75 MHz) spectrometer. NMR spectra are reported as \(\delta\) values in ppm relative to the reported solvent (CDCl\(_3\) referenced to 7.27, CD\(_3\)OD referenced to 3.31). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (b), apparent (app), and combinations thereof. Spectra were analyzed and processed using MestReNova.

High-resolution mass spectra (HRMS) data was obtained on a JEOL JMS-600H high resolution mass spectrometer operating in FAB\(^{+}\) or positive-ion ESI mode. MALDI-TOF spectra were recorded on a Voyager DE-PRO MALDI TOF-MS spectrometer (Applied Biosystems) operating in reflector ion mode using \(\alpha\)-cyano-4-hydroxycinnamic acid as the matrix.

Analytical HPLC was performed on an Agilent 1200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), or mixed (MM) ionization mode equipped with an Eclipse Plus C\(_8\) column (1.8 \(\mu\)m, 2.1 x 50 mm). Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C\(_{18}\) column (5 \(\mu\)m, 9.4 x 250 mm) or an Agilent Zorbax RX-SIL column (5 \(\mu\)m, 9.4 x 250 mm) using a gradient of double distilled water and HPLC grade acetonitrile containing 0.1% TFA or 0.1% acetic acid (AcOH). LCMS was performed on an Agilent 1200 Series LCMS equipped with a Quadrupole 6120 MS detector and an Eclipse XDB-C\(_{18}\) reverse-phase column (5, 4.6 \(\mu\)m x 150 mm).

**General Procedure for Homoallyl Modification of Peptides**

**tert-butyl (S)-(1-(but-3-en-1-ylamino)-1-oxopropan-2-yl)carbamate (3)**

\[\text{BocHNN} \quad \text{3: C}\(_{12}\)H\(_{22}\)N\(_2\)O\(_3\) \quad \text{Exact mass: 242.1630} \]

A round-bottom flask was charged with Boc-Ala-OH (1.0 g, 5.3 mmol), HOBt (0.72 g, 5.3 mmol, 1.0 eq) and HBTU (3.0 g, 7.9 mmol, 1.5 eq) under Ar(g). To this was added anhydrous DMF (5 mL) and N,N-diisopropylethylamine (DIEA, 2.7 mL, 15.8 mmol, 3 eq.). The reaction mixture

---

was allowed to stir at room temperature for 15 min upon which the solution turned to a pale yellow. A solution of 3-butenylamineHCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction mixture heated to 50°C and allowed to stir for 1 h. The solution was cooled to room temperature and H2O (20 mL) was added, followed by CH2Cl2 (50 mL). The organic layer was removed and the aqueous layer was extracted with CH2Cl2 (5 x 50 mL). The combined organic layers were washed with brine (5 x 50 mL), and dried over Na2SO4. The solvent was removed in vacuo and the crude residue was purified by flash chromatography (SiO2, 0% to 50% EtOAc in hexanes) to provide 1.16 g (91%) of 3 as a white solid: 1H NMR (300 MHz, CDCl3) δ 6.51 (bs, 1H), 5.72 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.22 (d, J = 7.7 Hz, 1H), 5.12–4.96 (m, 2H), 4.12 (q, J = 7.6 Hz, 1H), 3.38–3.18 (m, 2H), 2.22 (qt, J = 6.9, 1.3 Hz, 2H), 1.40 (s, 9H), 1.31 (d, J = 7.0 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 172.71, 155.48, 135.04, 117.09, 79.83, 50.02, 38.41, 33.67, 28.30 (3C), 18.64. HRMS (ESI) m/z calcd for C12H22N2O3 [M+H]+: 243.1630, found 243.1626

tert-butyl (S)-(1-(but-3-en-1-ylamino)-3-methyl-1-oxobutan-2-yl)carbamate (5a)

Following the general procedure for the synthesis of 3, 5a was synthesized from Boc-Val-OH (1.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), and DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, 0% to 33% EtOAc in hexanes) to provide 1.17 g (82%) of 5a as a white solid. 1H NMR (300 MHz, CDCl3) δ 6.72–6.53 (m, 1H), 5.69 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H), 5.32 (d, J = 9.3 Hz, 1H), 5.08–4.93 (m, 2H), 3.86 (dd, J = 9.1, 6.8 Hz, 1H), 3.36–3.15 (m, 2H), 2.19 (qt, J = 6.9, 1.3 Hz, 2H), 2.06–1.95 (m, 1H), 1.37 (s, 9H), 0.87 (dd, J = 8.2, 6.7 Hz, 6H); 13C NMR (126 MHz, CDCl3) δ 171.84, 155.94, 135.10, 117.19, 79.34, 59.95, 38.50, 33.71, 30.99, 28.26 (3C), 19.19, 18.10. HRMS (ESI) m/z calcd for C14H26N2O3 [M+H]+: 271.1943, found 271.1940

tert-butyl ((2S,3R)-1-(but-3-en-1-ylamino)-3-methyl-1-oxopentan-2-yl)carbamate (5b)

Following the general procedure for the synthesis of 3, 5b was synthesized from Boc-Ile-OH (1.2 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, 0% to 33% EtOAc in hexanes) to provide 1.27 g (85%) of 5b as a white solid. 1H NMR (300 MHz, CDCl3) δ 6.26 (d, J = 6.1 Hz, 1H), 5.73 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.15 (d, J = 8.9
Hz, 1H), 5.11–4.98 (m, 2H), 3.88 (dd, J = 8.9, 6.7 Hz, 1H), 3.39-3.21 (m, 2H), 2.23 (qt, J = 6.8, 1.3 Hz, 2H), 1.90–1.70 (m, 1H), 1.52-1.44 (m, 1H), 1.41 (s, 9H), 1.18–0.98 (m, 1H), 0.95–0.78 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.83, 155.87, 135.13, 116.87, 79.43, 59.20, 38.48, 37.15, 33.70, 28.27 (3C), 24.76, 15.43, 11.20. HRMS (ESI) m/z calcd for C$_{15}$H$_{28}$N$_2$O$_3$ [M+H]$^+$: 285.2100, found 284.5101

**tert-butyl (S)-(1-(but-3-en-1-ylamino)-4-methyl-1-oxopentan-2-yl)carbamate (5c)**

Following the general procedure for the synthesis of 3, 5c was synthesized from Boc-Leu-OH (1.3 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) and 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF at 40°C. The crude product was purified by flash chromatography (SiO$_2$, 0% to 33% EtOAc in hexanes) to provide 1.18 g (79%) of 5c as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.34 (bs, 1H), 5.74 (dtt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.12–5.02 (m, 2H), 5.00 (d, J = 8.5 Hz, 1H), 4.06 (q, J = 7.6 Hz, 1H), 3.38–3.20 (m, 2H), 2.24 (qt, J = 6.8, 1.4 Hz, 2H), 1.66–1.60 (m, 2H), 1.45-1.40 (m, 1H), 1.42 (s, 9H), 0.96–0.86 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.83, 155.78, 135.10, 116.81, 79.55, 53.02, 41.51, 38.45, 33.66, 28.27 (3C), 24.65, 22.82, 22.00. HRMS (ESI) m/z calcd for C$_{15}$H$_{28}$N$_2$O$_3$ [M+H]$^+$: 285.2100, found 285.2102

**tert-butyl (S)-(1-(but-3-en-1-ylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (5d)**

Following the general procedure for the synthesis of 3, 5d was synthesized from Boc-Phe-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO$_2$, 0% to 33% EtOAc in hexanes) to provide 1.53 g (91%) of 5d as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.26–7.16 (m, 5H), 6.30 (bs, 1H), 5.63-5.57 (m, 1H), 5.38 (d, J = 7.9 Hz, 1H), 5.00–4.90 (m, 2H), 4.41–4.26 (m, 1H), 3.26-3.22 (m, 1H), 3.20-3.13 (m, 1H), 3.04–2.95 (m, 2H), 2.13–2.04 (m, 2H), 1.37 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.54, 155.57, 137.05, 135.00 (2C), 129.32 (2C), 128.38, 126.64, 116.85, 79.67, 55.91, 39.02, 38.49, 33.48, 28.28 (3C). HRMS (ESI) m/z calcd for C$_{18}$H$_{28}$N$_2$O$_3$ [M+H]$^+$: 319.1943, found 319.1940

Supporting Information
**tert-butyl (2-(but-3-en-1-ylamino)-2-oxoethyl)carbamate (5e)**

Following the general procedure for the synthesis of 3, 5e was synthesized from Boc-Gly-OH (0.92 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 3:1 EtOAc:hexane) to provide 0.84 g (70%) of 5e as a white solid. 

1H NMR (300 MHz, CDCl₃) δ 6.19 (bs, 1H), 5.75 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.13–5.02 (m, 2H), 3.77 (s, 2H), 3.35 (q, J = 6.5 Hz, 2H), 2.27 (qt, J = 6.8, 1.4 Hz, 2H), 1.45 (s, 9H); 13C NMR (126 MHz, CDCl₃) δ 169.85, 156.20, 134.92, 117.10, 80.00, 44.22, 38.45, 33.52, 28.25 (3C). HRMS (ESI) m/z calcd for C₁₁H₂₀N₂O₃ [M+H]+ : 228.1474, found 229.1474

**tert-butyl (S)-2-(but-3-en-1-ylcarbamoyl)pyrrolidine-1-carboxylate (5f)**

Following the general procedure for the synthesis of 3, 5f was synthesized from Boc-Pro-OH (1.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 3:1 EtOAc:hexane) to provide 1.02 g (72%) of 5f as a white solid (mixture of cis and trans proline isomers). 

1H NMR (500 MHz, CDCl₃) δ 6.84 (bs, 1H), 6.14 (bs, 1H), 5.68-5.61 (m, 1H), 4.99-4.94 (m, 2H), 4.23-3.99 (m, 1H), 3.34–3.19 (m, 4H), 2.14–1.89 (m, 4H), 1.89–1.67 (m, 2H), 1.35 (s, 9H); 13C NMR (126 MHz, CDCl₃) δ 172.42, 171.87, 155.57, 154.57, 135.10, 116.88, 80.15, 61.18, 59.90, 46.94, 38.22, 33.66, 31.01, 28.28 (3C), 24.41, 23.56. HRMS (ESI) m/z calcd for C₁₄H₂₄N₂O₃ [M+H]+ : 269.1782, found 269.1782

**tert-butyl (S)-(1-(but-3-en-1-ylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (5g)**

Following the general procedure for the synthesis of 3, 5g was synthesized from Boc-Trp-OH (1.6 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 0% to 50% EtOAc in hexanes) to provide 1.40 g (74%) of 5g as a
white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.24 (bs, 1H), 7.66 (d, $J$ = 7.9 Hz, 1H), 7.37 (dt, $J$ = 8.2, 0.9 Hz, 1H), 7.20 (ddt, $J$ = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, $J$ = 8.1, 7.1, 1.1 Hz, 1H), 7.05 (d, $J$ = 2.4 Hz, 1H), 5.67 (bs, 1H), 5.58–5.41 (m, 1H), 5.19 (bs, 1H), 4.95–4.75 (m, 2H), 4.39 (q, $J$ = 7.2 Hz, 1H), 3.38–3.25 (m, 1H), 3.20–3.11 (m, 3H), 2.05–1.94 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.61, 155.48, 136.28, 134.81, 127.41, 123.17, 122.20, 119.65, 118.87, 117.08, 111.26, 110.63, 80.03, 55.34, 38.35, 33.25, 28.65, 28.32 (3C). HRMS (ESI) m/z calcd for C$_{20}$H$_{27}$N$_3$O$_3$ [M+H]$^+$: 358.2052, found 358.2058

tert-butyl (S)-(1-(but-3-en-1-ylamino)-1-oxo-3-(1-tosyl-1H-imidazol-4-yl)propan-2-yl)carbamate (5h)

Following the general procedure for the synthesis of 3, 5h was synthesized from Boc-His(Tos)-OH (2.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO$_2$, 3:1 EtOAc:hexanes) to provide 1.73 g (71%) of 5h as a white solid. $^1$H NMR (500 MHz, CD$_3$OD) δ 8.16 (bs, 1H), 7.94–7.86 (m, 2H), 7.46–7.38 (m, 2H), 7.30 (bs, 1H), 5.70 (ddt, $J$ = 17.0, 10.2, 6.8 Hz, 1H), 5.02–4.97 (m, 2H), 4.79 (bs, 1H), 4.28 (dd, $J$ = 8.9, 5.3 Hz, 1H), 3.20–3.06 (m, 2H), 2.95 (m, 1H), 2.78 (m, 1H), 2.40 (s, 3H), 2.12 (q, $J$ = 6.9 Hz, 2H), 1.34 (s, 9H); $^{13}$C NMR (126 MHz, CD$_3$OD) δ 172.32, 156.06, 146.73, 140.21, 136.73, 135.07, 134.64, 130.33 (2C), 127.29 (2C), 115.80, 115.09, 79.41, 54.14, 38.34, 33.14, 30.23, 27.24 (3C), 20.34. HRMS (ESI) m/z calcd for C$_{22}$H$_{30}$N$_4$O$_5$S [M+H]$^+$: 462.1937, found 462.1937

tert-butyl (S)-(1-(but-3-en-1-ylamino)-3-(tert-butoxy)-1-oxopropan-2-yl)carbamate (5i)

Following the general procedure for the synthesis of 3, 5i was synthesized from Boc-Ser(OtBu)-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO$_2$, 0% to 33% EtOAc in hexanes) to provide 1.46 g (88%) of 5i as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.61 (s, 1H), 5.76–5.65 (m, 1H), 5.39 (bs, 1H), 5.07–4.99 (m, 2H), 4.1–3.99 (m, 1H), 3.74–3.66 (m, 1H), 3.36–3.24 (m, 3H), 2.24–2.15 (m, 2H), 1.39 (m, 9H), 1.12 (m, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.47, 155.42, 135.06, 117.08,
79.74, 73.77, 61.82, 54.24, 38.42, 33.58, 28.25 (3C), 27.37 (3C). HRMS (ESI) m/z calcd for C_{16}H_{30}N_{2}O_{4} [M+H]^+ : 315.2206, found 315.2212

**tert-butyl ((2S,3R)-1-(but-3-en-1-ylamino)-3-(tert-butoxy)-1-oxobutan-2-yl)carbamate (5j)**

Following the general procedure for the synthesis of 3, 5j was synthesized from Boc-Thr(OtBu)-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) A solution of 3-butenylamineHCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 0% to 25% EtOAc in hexanes) to provide 1.48 g (85%) of 5j as a white solid. 

\[ \delta_{1H} = 6.57 (t, J = 3.5 Hz, 1H), 6.38 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.53 (d, J = 5.6 Hz, 1H), 5.05–4.92 (m, 2H), 3.99 (qd, J = 6.4, 3.5 Hz, 1H), 3.93 (m, 1H), 3.29–3.19 (m, 2H), 2.15 (qt, J = 6.9, 1.2 Hz, 2H), 1.33 (s, 9H), 1.13 (s, 9H), 0.91 (d, J = 6.4 Hz, 3H); \]

\[ \delta_{13C} = 169.46, 155.42, 135.02, 117.10, 79.23, 74.92, 66.80, 58.29, 38.35, 33.54, 28.24 (3C), 28.18 (3C), 17.27. \]

HRMS (ESI) m/z calcd for C_{17}H_{32}N_{2}O_{4} [M+H]^+ : 328.2362, found 328.2362

**tert-butyl ((5)-(1-(but-3-en-1-ylamino)-3-(4-(tert-butoxy)phenyl)-1-oxopropan-2-yl)carbamate (5k)**

Following the general procedure for the synthesis of 3, 5k was synthesized from Boc-Tyr(OtBu)-OH (1.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamineHCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 0% to 33% EtOAc in hexanes) to provide 1.73 g (84%) of 5k as a white solid. 

\[ \delta_{1H} = 7.06 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.4, 2H), 5.81 (bs, 1H), 5.63 (ddt, J = 17.1, 10.4, 6.9 Hz, 1H), 5.10 (bs, 1H), 5.04–4.89 (m, 2H), 4.23 (q, J = 7.5 Hz, 1H), 3.22 (q, J = 6.5 Hz, 2H), 3.03–2.93 (m, 2H), 2.15–2.09 (m, 2H), 1.40 (s, 9H), 1.32 (s, 9H); \]

\[ \delta_{13C} = 171.31, 155.43, 154.15, 134.87, 131.68, 129.69 (2C), 124.15 (2C), 117.06, 79.83, 78.26, 56.00, 38.40, 38.16, 33.47, 28.77 (3C), 28.26 (3C). \]

HRMS (ESI) m/z calcd for C_{22}H_{34}N_{2}O_{4} [M+H]^+ : 391.2519, found 391.2516
**tert-butyl (S)-(1-(but-3-en-1-ylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (5l)**

Following the general procedure for the synthesis of 3, 5l was synthesized from Boc-Met-OH (1.3 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butylamine HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 0% to 33% EtOAc in hexanes) to provide 1.10 g (69%) of 5l as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 6.60 (bs, 1H), 5.71 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.52–5.35 (m, 1H), 5.11–4.95 (m, 2H), 4.29–4.11 (m, 1H), 3.40–3.13 (m, 2H), 2.59–2.38 (m, 2H), 2.21 (qt, J = 6.8, 1.3 Hz, 2H), 2.05 (s, 3H), 2.02–1.98 (m, 1H), 1.96–1.77 (m, 1H), 1.39 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 171.72, 155.70, 134.98, 117.01, 79.75, 53.46, 38.51, 33.63, 32.05, 30.10, 28.28 (3C), 15.17. HRMS (ESI) m/z calcd for C₁₁H₂₆N₂O₅S [M+H]^+ : 303.1664, found 303.1668

**tert-butyl (R)-(1-(but-3-en-1-ylamino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate (5m)**

Following the general procedure for the synthesis of 3, 5m was synthesized from Boc-Cys(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butylamine HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO₂, 0% to 35% EtOAc in hexanes) to provide 2.04 g (75%) of 5m as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.44–7.40 (m, 6H), 7.32–7.27 (m, 6H), 7.25–7.20 (m, 3H), 6.05 (bs, 1H), 5.71 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.10–4.99 (m, 2H), 4.82 (bs, 1H), 3.87–3.84 (m, 1H), 3.32–3.19 (m, 2H), 2.75–2.71 (m, 1H), 2.54–2.50 (m, 1H), 2.21 (qt, J = 6.8, 1.3 Hz, 2H), 1.42 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 170.37, 155.35, 144.47 (3C), 135.01, 129.58 (6C), 128.03 (6C), 126.85 (3C), 117.23, 80.06, 67.13, 53.57, 38.51, 34.05, 33.58, 28.33 (3C). HRMS (ESI) m/z calcd for C₃₁H₃₆N₂O₅S [M+H]^+ : 517.2447, found 517.2450

**tert-butyl (S)-4-(but-3-en-1-ylamino)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate (5n)**

Following the general procedure for the synthesis of 3, 5n was synthesized from Boc-Asp(OtBu)-OH (1.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g,
5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, 0% to 50% EtOAc in hexanes) to provide 1.55 g (86%) of 5n as a white solid. 1H NMR (500 MHz, CDCl3) δ 6.58 (t, J = 5.7 Hz, 1H), 5.74–5.67 (m, 2H), 5.11–4.96 (m, 2H), 4.46–4.30 (m, 1H), 3.32–3.23 (m, 2H), 2.80 (dd, J = 16.8, 4.9 Hz, 1H), 2.56 (dd, J = 16.8, 6.6 Hz, 1H), 2.21 (qt, J = 6.7, 1.3 Hz, 2H), 1.41 (s, 9H), 1.40 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 171.17, 170.71, 155.45, 134.96, 117.15, 81.49, 80.11, 50.69, 38.50, 37.36, 33.55, 28.27 (3C), 27.99 (3C). HRMS (ESI) m/z calcld for C17H30N2O5 [M+H]+: 343.2155, found 343.2151

tert-butyl (S)-5-(but-3-en-1-ylamino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate (5o)

Following the general procedure for the synthesis of 3, 5o was synthesized from Boc-Glu(OrBu)-OH (1.6 g, 5.3 mmol) in the presence of a stock solution of HOBT (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), and DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, 0% to 40% EtOAc in hexanes) to provide 1.53 g (82%) of 5o as a white solid. 1H NMR (500 MHz, CDCl3) δ 6.93–6.81 (m, 1H), 5.69–5.57 (m, 2H), 4.99–4.87 (m, 2H), 4.07–4.03 (m, 1H), 3.26–3.21 (m, 1H), 3.14–3.10 (m, 1H), 2.29–2.07 (m, 4H), 1.99–1.87 (m, 1H), 1.84–1.71 (m, 1H), 1.31 (s, 18H). 13C NMR (126 MHz, CDCl3) δ 172.32, 171.69, 155.62, 134.98, 116.79, 80.32, 79.48, 53.85, 38.47, 33.57, 31.66, 28.21 (3C), 27.93 (3C), 27.90. HRMS (ESI) m/z calcld for C17H30N2O5 [M+H]+: 357.2311, found 357.2314

tert-butyl (S)-(1-(but-3-en-1-ylamino)-1,4-dioxo-4-(tritylamino)butan-2-yl)carbamate (5p)

Following the general procedure for the synthesis of 3, 5p was synthesized from Boc-Asn(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBT (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, 0% to 50% EtOAc in hexanes) to provide 2.17 g (78%) of 5p as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.31–7.17 (m, 16H), 6.74 (bs, 1H), 6.29 (bs, 1H), 5.72 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.12–4.99 (m, 2H), 4.43 (dd, J = 8.5, 4.6 Hz, 1H), 3.34–3.14 (m, 2H), 3.14–2.99 (m, 1H), 2.54 (dd, J = 15.0, 5.8 Hz, 1H), 2.21–
2.17 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.43, 170.49, 155.68, 144.44 (3C), 134.98, 128.73 (6C), 127.88 (6C), 126.93 (3C), 117.20, 79.94, 70.63, 51.76, 38.54, 38.18, 33.45, 28.40 (3C). HRMS (ESI) m/z calcld for C$_{32}$H$_{37}$N$_3$O$_4$ [M+H]$^+$: 528.2784, found 528.2782

**tert-butyl (S)-(1-(but-3-en-1-ylamino)-1,5-dioxo-5-(tritylamino)pentan-2-yl)carbamate (5q)**

Following the general procedure for the synthesis of 3, 5q was synthesized from Boc-Gln(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO$_2$, 0% to 50% EtOAc in hexanes) to provide 2.37 g (83%) of 5q as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37–7.12 (m, 17H), 6.41 (bs, 1H), 5.79–5.56 (m, 2H), 5.12–4.91 (m, 2H), 3.00–3.93 (m, 1H), 3.34–3.04 (m, 2H), 2.56–2.24 (m, 2H), 2.25–2.08 (m, 2H), 2.07–1.76 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.86, 171.47, 155.88, 144.59 (3C), 135.05, 128.69 (6C), 127.92 (6C), 126.95 (3C), 117.09, 79.74, 70.57, 53.62, 38.54, 33.73, 33.62, 29.87, 28.36 (3C). HRMS (ESI) m/z calcld for C$_{33}$H$_{39}$N$_3$O$_4$ [M+H]$^+$: 542.2941, found 542.2942

**di-tert-butyl (6-(but-3-en-1-ylamino)-6-oxohexane-1,5-diyl)(S)-dicarbamate (5r)**

Following the general procedure for the synthesis of 3, 5r was synthesized from Boc-Lys(Boc)-OH (1.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO$_2$, 0% to 50% EtOAc in hexanes) to provide 1.90 g (90%) of 5r as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.60 (bs, 1H), 5.69 (ddt, $J = 17.1, 10.2, 6.8$ Hz, 1H), 5.43–5.29 (m, 1H), 5.07–4.96 (m, 2H), 4.83–4.70 (m, 1H), 4.02 (m, 1H), 3.35–3.25 (m, 1H), 3.21 (m, 1H), 3.11–2.98 (m, 2H), 2.20 (qt, $J = 6.8, 1.3$ Hz, 2H), 1.79–1.69 (m, 1H), 1.62–1.51 (m, 1H), 1.49–1.41 (m, 2H), 1.41–1.34 (bs, 18H), 1.35–1.26 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.14, 156.13, 155.76, 135.05, 117.03, 79.75, 78.96, 54.36, 39.92, 38.44, 33.63, 32.15, 29.59, 28.39 (3C), 28.30 (3C), 22.60. HRMS (ESI) m/z calcld for C$_{20}$H$_{37}$N$_3$O$_5$ [M+H]$^+$: 400.2733, found 400.2730
**tert-butyl (S)-(1-(but-3-en-1-ylamino)-1-oxo-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentan-2-yl)carbamate (5s)**

Following the general procedure for the synthesis of 3, 5s was synthesized from Boc-Arg(Pbf)-OH (2.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine-HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO2, EtOAc) to provide 2.14 g (70%) of 5s as a white solid.

**1H NMR (500 MHz, CDCl3) δ 7.03 (bs, 1H), 6.36 (bs, 2H), 5.79–5.60 (m, 2H), 5.09–4.96 (m, 2H), 4.13 (m, 1H), 3.36–3.17 (m, 4H), 2.96 (s, 2H), 2.58 (s, 3H), 2.51 (s, 3H), 2.23 (q, J = 6.9 Hz, 2H), 2.10 (s, 3H), 1.80–1.78 (m, 1H), 1.69–1.53 (m, 4H), 1.47 (s, 6H), 1.40 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 172.36, 158.82, 156.44, 156.00, 138.31, 135.13, 132.71, 132.24, 124.65, 117.55, 116.85, 86.40, 79.92, 64.33, 53.99, 43.25, 40.55, 38.71, 33.56, 30.43, 28.57 (2C), 28.33 (3C), 25.56, 19.26, 17.92, 12.43. HRMS (ESI) m/z calcd for C28H45N5O6S [M+H]+ : 580.3091, found 580.3096

**General Procedure for Homodimerization of Amino Acids**

**di-tert-butyl ((2S,2’S)-(hex-3-ene-1,6-diylbis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate (4)**

The homoallyl-modified alanine 3 (0.20 g, 0.83 mmol) was dissolved in THF (1.4 mL) under a gentle stream of argon. A solution of catalyst 1 or 2 (619 µL of a 0.10 M solution in THF) was added and the reaction heated to 40°C and stirred for 4 h. The solution was allowed to cool to room temperature upon which an excess of ethyl vinyl ether (1.0 mL, 10.4 mmol, 12 eq.) was added to quench the reaction. The solvent was removed in vacuo and the residue purified by column chromatography (SiO2; 0% to 25% EtOAc in hexane) to afford 0.28 g (74%) of product 4 as a white solid. **1H NMR (500 MHz, CDCl3) δ 7.16 (bs, 2H), 5.49–5.34 (m, 2H), 5.24 (d, J = 8.4 Hz, 2H), 4.31–4.14 (m, 2H), 3.73–3.60 (m, 2H), 3.03–2.86 (m, 2H), 2.26–2.16 (m, 4H), 1.43 (s, 18H), 1.39–1.27 (m, 6H); 13C NMR (126 MHz, CDCl3) δ 173.34 (2C), 155.73 (2C), 129.23 (2C), 79.91 (2C), 50.08 (2C), 38.65 (2C), 28.35 (3C), 28.32 (3C), 27.97 (2C), 18.53 (2C). HRMS (ESI) m/z calcd for C32H46N4O6 [M+H]+ : 457.2948, found 457.2945
di-tert-butyl ((2S,2’S)-(hex-3-ene-1,6-diylibis(azanediyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (6a)

Following the procedure for 4, the homodimerization product 6a was obtained when homoallyl-modified valine 5a (0.22 g, 0.81 mmol) was reacted with catalyst 1 or 2 (610 µl of a 0.10 M solution in THF) in THF (1.4 mL) under argon for 4 h and quenched with excess ethyl vinyl ether. The residue was purified by column chromatography (SiO2; 0% to 50% EtOAc in hexane) to afford 0.30 g (71%) of the product 6a as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.43–7.36 (m, 2H), 5.42–5.34 (m, 2H), 5.17 (d, J = 9.6 Hz, 2H), 3.95 (dd, J = 9.7, 7.7 Hz, 2H), 3.93–3.83 (m, 2H), 2.80–2.76 (m, 2H), 2.25–2.21 (m, 2H), 2.18–2.12 (m, 2H), 1.94–1.90 (m, 2H), 1.67 (bs, 2H), 1.43 (s, 18H), 0.96 (d, J = 6.7 Hz, 6H), 0.95 (d, J = 6.6 Hz, 6H); 13C NMR (126 MHz, CDCl3) δ 172.31 (2C), 156.28 (2C), 129.56 (2C), 79.70 (2C), 60.43 (2C), 38.07 (2C), 30.92 (2C), 28.32 (6C), 19.21 (2C), 18.59 (2C). HRMS (ESI) m/z calcd for C26H48N4O6 [M+H]+: 512.3574, found 513.3570

di-tert-butyl ((2S,2’S,3R,3’R)-(hex-3-ene-1,6-diylibis(azanediyl))bis(3-methyl-1-oxopentan-1,2-diyl))dicarbamate (6b)

Following the procedure for 4, the homodimerization product 6b was obtained when homoallyl-modified isoleucine 5b (0.21 g, 0.74 mmol) was reacted with catalyst 1 or 2 (553 µl of a 0.10 M solution in THF) in THF (1.3 mL) under argon. The residue was purified by column chromatography (SiO2; 0% to 50% EtOAc in hexane) to afford 0.27 g (68%) of the product 6b as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.52–7.45 (m, 2H), 5.42–5.33 (m, 2H), 5.14 (d, J = 9.7 Hz, 2H), 4.02–3.93 (m, 4H), 2.81–2.70 (m, 2H), 2.27–2.18 (m, 2H), 2.18–2.08 (m, 2H), 1.76–1.63 (m, 2H), 1.58 (m, 2H), 1.42 (s, 18H), 1.21–1.09 (m, 2H), 0.94–0.82 (m, 12H); 13C NMR (126 MHz, CDCl3) δ 172.46 (2C), 156.14 (2C), 129.59 (2C), 79.64 (2C), 59.02 (2C), 37.95 (2C), 36.86 (2C), 29.69 (2C), 28.33 (6C), 24.90 (2C), 15.31 (2C), 10.60 (2C). HRMS (ESI) m/z calcd for C26H52N4O6 [M+H]+: 541.3887, found 541.3880

di-tert-butyl ((2S,2’S)-(hex-3-ene-1,6-diylibis(azanediyl))bis(4-methyl-1-oxopentane-1,2-diyl))dicarbamate (6c)

Following the procedure for 4, the homodimerization product 6c was obtained when homoallyl-modified leucine 5c (0.18 g, 0.63 mmol) was reacted with catalyst 1 or 2 (475 µl of a 0.10 M solution in THF) in THF (1.1 mL) under argon. The residue was purified
by column chromatography (SiO₂; 0% to 50% EtOAc in hexane) to afford 0.24 g (70%) of the product 6c as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.64–7.55 (m, 2H), 5.40–5.38 (m, 2H), 5.06 (d, J = 9.1 Hz, 2H), 4.28–4.23 (m, 2H), 3.92–3.90 (m, 2H), 2.77–2.73 (m, 2H), 2.23 (m, 2H), 2.20–2.11 (m, 2H), 1.70–1.64 (m, 4H), 1.56–1.47 (m, 4H), 1.42 (s, 18H), 0.92 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 173.36 (2C), 155.95 (2C), 129.57 (2C), 79.75 (2C), 53.17 (2C), 41.68 (2C), 38.30 (2C), 28.33 (6C), 24.67 (4C), 23.04 (2C), 21.82 (2C). HRMS (ESI) m/z calcd for C₂₈H₅₂N₄O₆ [M+H]+: 541.3887, found 541.3879

di-tert-butyl ((2S,2’S)-(hex-3-ene-1,6-diylbis(azonediyl))bis(1-oxo-3-phenylpropane-1,2-diyldiyl))dicarbamate (6d)

Following the procedure for 4, the homodimerization product 6d was obtained when homoallyl-modified phenylalanine 5d (0.23 g, 0.72 mmol) was reacted with catalyst 1 or 2 (542 µl of a 0.10 M solution in THF) in THF (1.2 mL) under argon. The residue was purified by column chromatography (SiO₂; 0% to 50% EtOAc in hexane) to afford 0.32 g (73%) of the product 6d as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.09 (m, 10H), 7.10–6.91 (m, 2H), 5.36–5.33 (m, 4H), 5.29 (bs, 2H), 4.50–4.30 (m, 2H), 3.62 (m, 2H), 3.12–2.72 (m, 4H), 2.15–2.04 (m, 4H), 1.35 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 171.98 (2C), 155.80 (2C), 137.01 (2C), 129.21 (4C), 128.46 (4C), 126.63 (2C), 79.94 (2C), 56.03 (2C), 38.92 (2C), 38.61 (2C), 28.28 (6C), 27.91 (2C). HRMS (ESI) m/z calcd for C₃₄H₄₈N₄O₆ [M+H]+: 608.3574, found 609.3578

di-tert-butyl ((2S,2’S)-(hex-3-ene-1,6-diylbis(azonediyl))bis(3-(1H-indol-3-yl)-1-oxopropane-1,2-diyldiyl))dicarbamate (6g)

Following the procedure for 4, the homodimerization product 6g was obtained when homoallyl-modified tryptophan 5g (0.21 g, 0.59 mmol) was reacted with catalyst 1 or 2 (440 µl of a 0.10 M solution in THF) in THF (1.0 mL) under argon. The residue was purified by column chromatography (SiO₂; 3:1 EtOAc:hexanes) to afford 0.26 g (66%) of the product 6g as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.74 (bs, 2H), 7.59 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.16 (ddd, J = 8.1, 6.9, 1.1 Hz, 2H), 7.06 (t, J = 7.5 Hz, 2H), 6.94 (bs, 2H), 6.37 (bs, 2H), 5.38 (d, J = 8.1 Hz, 2H), 5.14–5.12 (m, 2H), 4.56–4.35 (m, 2H), 3.30–3.11 (m, 6H), 2.98–2.96 (m, 2H), 1.91–1.71 (m, 4H), 1.42 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 172.14 (2C), 155.71 (2C), 136.28 (2C), 128.53 (2C), 127.43 (2C), 123.38 (2C), 121.97 (2C), 119.47 (2C), 118.74 (2C), 111.34 (2C), 110.39 (2C), 80.08
di-tert-butyl ((5S,16S)-2,2,19,19-tetramethyl-6,15-dioxo-3,18-dioxa-7,14-diazaicos-10-ene-5,16-diyl)dicarbamate (6i)

Following the procedure for 4, the homodimerization product 6i was obtained when homoallyl-modified serine 5i (0.20 g, 0.63 mmol) was reacted with catalyst 1 or 2 (477 μl of a 0.10 M solution in THF) in THF (1.1 mL) under argon. The residue was purified by column chromatography (SiO2; 0% to 50% EtOAc in hexane) to afford 0.27 g (72%) of the product 6i as a white solid. 1H NMR (500 MHz, CDCl3) δ 6.70 (s, 2H), 5.48–5.43 (m, 4H), 5.38 (s, 18H), 1.17 (s, 18H); 13C NMR (126 MHz, CDCl3) δ 170.66 (2C), 155.56 (2C), 128.55 (2C), 79.90 (2C), 73.86 (2C), 61.88 (2C), 54.34 (2C), 39.09 (2C), 28.32 (6C), 27.48 (2C), 27.44 (6C). HRMS (ESI) m/z calcd for C30H56N4O8 [M+H]+: 601.4098, found 601.4100


Following the procedure for 4, the homodimerization product 6j was obtained when homoallyl-modified threonine 5j (0.19 g, 0.58 mmol) was reacted with catalyst 1 or 2 (433 μl of a 0.10 M solution in THF) in THF (1.0 mL) under argon. The residue was purified by column chromatography (SiO2; 0% to 40% EtOAc in hexane) to afford 0.26 g (73%) of the product 6j as a white solid. 1H NMR (500 MHz, CDCl3) δ 5.90 (t, J = 5.4 Hz, 2H), 5.65 (d, J = 5.8 Hz, 2H), 5.50 (td, J = 4.4, 2.1 Hz, 2H), 4.11 (qd, J = 6.3, 3.3 Hz, 2H), 4.08–4.00 (m, 2H), 3.40–3.23 (m, 4H), 2.31–2.25 (m, 4H), 1.45 (s, 18H), 1.25 (s, 18H), 1.03 (d, J = 6.3 Hz, 6H); 13C NMR (126 MHz, CDCl3) δ 169.73 (2C), 155.61 (2C), 128.63 (2C), 79.53 (2C), 75.13 (2C), 66.92 (2C), 58.39 (2C), 39.05 (2C), 28.37 (6C), 28.31 (6C), 27.55 (2C), 17.41 (2C). HRMS (ESI) m/z calcd for C32H60N4O8 [M+H]+: 629.4411, found 629.4413

di-tert-butyl ((2S,2'S)-(hex-3-ene-1,6-diylbis(azanediyl))bis(3-(4-(tert-butoxy)phenyl)-1-oxopropane-1,2-diyl))dicarbamate (6k)

Following the procedure for 4, the homodimerization product 6k was obtained when homoallyl-modified tyrosine 5k (0.17 g, 0.44 mmol) was reacted with
catalyst 1 or 2 (326 µl of a 0.10 M solution in THF) in THF (0.76 mL) under argon. The residue was purified by column chromatography (SiO2; 0% to 50% EtOAc in hexane) to afford 0.21 g (64%) of the product 6k as a white solid. 1H NMR (300 MHz, CDCl3) δ 7.11–7.03 (m, 4H), 6.91–6.85 (m, 4H), 5.34 (dt, J = 6.4, 4.8 Hz, 2H), 5.23 (d, J = 8.8 Hz, 2H), 4.42–4.35 (m, 2H), 3.59–3.51 (m, 2H), 2.97–2.83 (m, 6H), 2.17–2.05 (m, 6H), 1.36 (s, 18H), 1.31 (s, 18H); 13C NMR (126 MHz, CDCl3) δ 171.84 (2C), 155.70 (2C), 154.04 (2C), 131.82 (2C), 129.67 (4C), 129.02 (2C), 124.23 (4C), 79.90 (2C), 78.32 (2C), 55.98 (2C), 38.61 (2C), 38.21 (2C), 28.82 (6C), 28.28 (6C), 27.80 (2C). HRMS (ESI) m/z calcld for C42H64N4O8 [M+H]+ : 753.4724, found 753.4719

di-tert-butyl ((4R,15R)-5,14-dioxo-1,1,1,18,18,18-hexaphenyl-2,17-dithia-6,13-diazaoctadec-9-ene-4,15-diyl)dicarbamate (6m)

Following the procedure for 4, the homodimerization product 6m was obtained when homoallyl-modified cysteine 5m (0.23 g, 0.44 mmol) was reacted with catalyst 1 or 2 (334 µl of a 0.10 M solution in THF) in THF (0.78 mL) under Ar(g). The residue was purified by column chromatography (SiO2; 0% to 40% EtOAc in hexane) to afford 0.25 g (55%) of the product 6m as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.41 (m, 12H), 7.31–7.24 (m, 12H), 7.23–7.17 (m, 6H), 6.72 (bs, 1H), 6.11 (bs, 1H), 5.38–5.34 (m, 2H), 5.00–4.86 (m, 2H), 4.06–4.02 (m, 1H), 3.86 (bs, 1H), 3.51–3.48 (m, 1H), 3.19–3.16 (m, 1H), 2.98–2.92 (m, 1H), 2.67 (bs, 1H), 2.53 (m, 4H), 2.23–2.10 (m, 4H), 1.42–1.37 (m, 18H); 13C NMR (126 MHz, CDCl3) δ 170.67 (2C), 155.52 (2C), 146.86 (2C), 144.46 (3C), 144.43 (3C), 129.57 (2C), 129.56 (6C), 128.92 (2C), 128.02 (2C), 128.00 (6C), 127.95 (2C), 127.91 (2C), 127.23 (2C), 126.84 (2C), 126.77 (2C), 80.14 (2C), 66.95 (2C), 53.58 (2C), 38.82 (2C), 33.98 (2C), 29.69 (2C), 28.32 (3C), 28.29 (3C), 27.66 (2C). HRMS (ESI) m/z calcld for C60H68N4O8S2 [M+H]+ : 1006.35, found 1006.44


Following the procedure for 4, the homodimerization product 6n was obtained when homoallyl-modified aspartate 5n (0.19 g, 0.55 mmol) was reacted with catalyst 1 or 2 (416 µl of a 0.10 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO2; 0% to 50% EtOAc in hexane) to afford 0.22 g (61%) of the product 6n as a white solid. 1H NMR (500 MHz, CDCl3) δ 6.74 (bs, 2H), 5.76 (bs, 2H), 5.48–5.38 (m, 2H), 4.47–4.42 (m, 2H), 3.41–3.35 (m, 2H), 3.31–3.29 (m, 2H), 3.23–3.18 (m, 2H), 2.84–2.80 (m, 2H), 2.76–2.72 (m, 2H), 2.37–2.33 (m, 2H), 2.18–2.14 (m, 2H), 1.74–1.70 (m, 2H), 1.42–1.38 (m, 2H), 1.32–1.28 (m, 2H), 1.06–1.02 (m, 2H), 0.94–0.90 (m, 2H), 0.88–0.84 (m, 2H), 0.82–0.78 (m, 2H), 0.74–0.70 (m, 2H), 0.69–0.65 (m, 2H), 0.64–0.60 (m, 2H), 0.60–0.56 (m, 2H), 0.56–0.52 (m, 2H), 0.52–0.48 (m, 2H), 0.47–0.43 (m, 2H), 0.43–0.39 (m, 2H), 0.39–0.35 (m, 2H), 0.35–0.31 (m, 2H), 0.31–0.27 (m, 2H), 0.27–0.23 (m, 2H), 0.23–0.19 (m, 2H), 0.19–0.15 (m, 2H), 0.15–0.11 (m, 2H), 0.11–0.07 (m, 2H), 0.07–0.03 (m, 2H), 0.03–0.00 (m, 2H).
2.67–2.57 (m, 2H), 2.26–2.24 (m, 4H), 1.45 (s, 18H), 1.44 (s, 18H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.96 (2C), 155.54 (2C), 128.59 (2C), 81.51 (2C), 80.17 (2C), 50.82 (2C), 39.12 (2C), 37.48 (2C), 29.69 (2C), 28.33 (6C), 28.03 (6C), 27.41 (2C). HRMS (ESI) m/z calcd for \(C_{27}H_{56}N_{4}O_{10}\) [M+H]\(^+\) : 657.8180, found 657.8177

**tert-butyl (6S,17S)-6-((3-(tert-butoxy)-3-oxopropyl)-17-((tert-butoxycarbonyl)amino)-2,2-dimethyl-4,7,16-trioxo-3-oxa-5,8,15-triazaicos-11-en-20-oate (60)**

Following the procedure for 4, the homodimerization product 60 was obtained when homoallyl-modified glutamate 50 (0.17 g, 0.48 mmol) was reacted with catalyst 1 or 2 (357 µl of a 0.10 M solution in THF) in THF (0.83 mL) under Ar(g). The residue was purified by column chromatography (SiO\(_2\) 0% to 50% EtOAc in hexane) to afford 0.24 g (74%) of the product 60 as a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.19 (bs, 2H), 5.46 (d, \(J = 8.3\) Hz, 2H), 5.42-5.36 (m, 2H), 4.18-4.14 (m, 2H), 3.70–3.64 (m, 2H), 2.91–2.90 (m, 2H), 2.32–2.29 (m, 4H), 2.25–2.13 (m, 4H), 2.01–1.96 (m, 2H), 1.93–1.83 (m, 2H), 1.41 (s, 36H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.31 (2C), 172.01 (2C), 155.91 (2C), 129.04 (2C), 80.47 (2C), 79.85 (2C), 54.15 (2C), 38.70 (2C), 31.94 (2C), 28.31 (6C), 28.04 (6C), 27.98 (2C), 27.84 (2C). HRMS (ESI) m/z calcd for \(C_{27}H_{56}N_{4}O_{10}\) [M+H]\(^+\) : 685.4309, found 685.4312

**di-tert-butyl ((5S,16S)-3,6,15,18-tetraoxo-1,1,20,20-hexaphenyl-2,7,14,19-tetraazaicos-10-ene-5,16-diyl)dicarbamate (6p)**

Following the procedure for 4, the homodimerization product 6p was obtained when homoallyl-modified asparagine 5p (0.18 g, 0.34 mmol) was reacted with catalyst 1 or 2 (255 µl of a 0.10 M solution in THF) in THF (0.60 mL) under Ar(g). The residue was purified by column chromatography (SiO\(_2\) 0% to 66% EtOAc in hexane) to afford 0.24 g (70%) of the product 6p as a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.30–7.22 (m, 18H), 7.20–7.15 (m, 12H), 7.09 (bs, 2H), 6.84–6.71 (m, 2H), 6.19 (d, \(J = 7.7\) Hz, 2H), 5.45–5.31 (m, 2H), 4.40–4.37 (m, 2H), 3.26–3.18 (m, 4H), 2.97–2.94 (m, 2H), 2.57–2.43 (m, 2H), 2.24–2.09 (m, 4H), 1.41 (s, 18H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 171.20 (2C), 170.37 (2C), 144.31 (6C), 128.64 (12C), 128.61 (2C), 128.43 (2C), 127.99 (2C), 127.93 (12C), 127.90 (2C), 127.04 (6C), 70.68 (2C), 39.21 (2C), 29.70 (2C), 28.32 (6C), 27.29 (2C). HRMS (ESI) m/z calcd for \(C_{62}H_{70}N_{6}O_{8}\) [M+H]\(^+\) : 1027.5255, found 1027.5251
di-tert-butyl ((6S,17S)-3,7,16,20-tetraoxo-1,1,12,22,22-hexaphenyl-2,8,15,21-tetraazadocos-11-ene-6,17-diyl)dicarbamate (6q)

Following the procedure for 4, the homodimerization product 6q was obtained when homoallyl-modified glutamine 5q (0.14 g, 0.26 mmol) was reacted with catalyst 1 or 2 (194 µl of a 0.10 M solution in THF) in THF (0.45 mL) under Ar(g). The residue was purified by column chromatography (SiO2; 3:1 EtOAc:hexanes) to afford 0.20 g (74%) of the product 6q as a white solid. ¹H NMR (500 MHz, CDCl3) δ 7.34–7.26 (m, 12H), 7.25–7.20 (m, 18H), 7.15 (bs, 2H), 6.75–6.64 (m, 2H), 5.62 (d, J = 7.7 Hz, 2H), 5.36–5.30 (m, 2H), 4.01–3.97 (m, 2H), 3.25–3.20 (m, 2H), 3.15–3.12 (m, 2H), 2.40–2.27 (m, 4H), 2.18–2.10 (m, 4H), 2.01–1.91 (m, 2H), 1.87–1.82 (m, 3H), 1.42 (s, 18H); ¹³C NMR (126 MHz, CDCl3) δ 171.77 (2C), 155.91 (2C), 144.57 (6C), 128.83 (2C), 128.69 (12C), 127.95 (2C), 127.90 (12C), 126.94 (6C), 79.76 (2C), 70.53 (2C), 53.60 (2C), 38.78 (2C), 33.65 (2C), 29.75 (2C), 28.35 (6C), 27.60 (2C). HRMS (ESI) m/z calcd for C₆₄H₇₄N₈O₈ [M+H]⁺: 1055.5568, found 1055.5549

tetra-tert-butyl ((5S,5’S)-(hex-3-ene-1,6-diylbis(azanediyl))bis(6-oxohexane-6,1,5-triyl))tetracarbamate (6r)

Following the procedure for 4, the homodimerization product 6r was obtained when homoallyl-modified lysine 5r (0.21 g, 0.53 mmol) was reacted with catalyst 1 or 2 (394 µl of a 0.10 M solution in THF) in THF (0.92 mL) under Ar(g). The residue was purified by column chromatography (SiO2; 3:1 EtOAc:hexanes) to afford 0.32 mg (78%) of the product 6r as a white solid. ¹H NMR (500 MHz, CDCl3) δ 7.24 (bs, 1H), 5.43–5.39 (m, 2H), 5.26 (d, J = 8.7 Hz, 2H), 4.68 (bs, 2H), 4.17–4.13 (m, 2H), 3.78–3.74 (m, 2H), 3.11–3.07 (m, 4H), 2.89–2.85 (m, 2H), 2.32–2.11 (m, 4H), 1.70 (m, 4H), 1.65–1.54 (m, 4H), 1.48–1.46 (m, 4H) 1.44 (s, 18H), 1.43 (s, 18H), 1.33–1.21 (m, 4H); ¹³C NMR (126 MHz, CDCl3) δ 172.67 (2C), 156.04 (4C), 129.32 (2C), 79.89 (4C), 54.47 (2C), 40.15 (2C), 38.47 (2C), 32.34 (2C), 29.69 (2C), 29.63 (2C), 28.44 (6C), 28.34 (6C), 22.86 (2C). HRMS (ESI) m/z calcd for C₃₈H₇₀N₆O₁₀ [M+H]⁺: 771.5153, found 771.5138

di-tert-butyl ((6S,17S)-1,22-diimino-7,16-dioxo-1,22-bis((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran)-5-sulfonamido)-2,8,15,21-tetraazadocos-11-ene-6,17-diyl)dicarbamate (6s)

6s: C₅₆H₇₈N₁₉O₁₂S₂
Exact mass: 1130.5868
Supporting Information
Following the procedure for 4, the homodimerization product 6s was obtained when homoallyl-modified arginine 5s (0.14 g, 0.24 mmol) was reacted with catalyst 1 or 2 (181 µl of a 0.10 M solution in THF) in THF (0.42 mL) under Ar(g). The residue was purified by column chromatography (SiO2 : 0% to 2% MeOH in EtOAc) to afford 93 mg (34%) of the product 6s as a white solid. \(^1^H\) NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.95–7.93 (m, 1H), 7.87–7.85 (m, 1H), 5.44–5.42 (m, 2H), 4.09–3.95 (m, 2H), 3.28–3.07 (m, 8H), 2.99 (s, 4H), 2.57 (s, 6H), 2.51 (s, 6H), 2.30–2.25 (m, 2H), 2.18–2.16 (m, 2H), 2.07 (s, 6H), 1.73–1.69 (m, 2H), 1.63–1.49 (m, 6H), 1.44 (s, 12H) 1.42 (s, 18H); \(^1^C\) NMR (126 MHz, CD\(_3\)OD) \(\delta\) 176.57 (2C), 173.66 (2C), 158.45 (2C), 156.69 (2C), 156.33 (2C), 137.98 (2C), 132.91 (2C), 132.09 (2C), 124.59 (2C), 117.02 (2C), 86.25 (2C), 79.19 (2C), 54.37 (2C), 42.57 (2C), 39.93 (2C), 38.69 (2C), 32.21 (2C), 29.42 (2C), 27.36 (4C), 27.33 (6C), 25.74 (2C), 18.22 (2C), 17.04 (2C), 11.14 (2C). HRMS (ESI) m/z calcld for C\(_{54}\)H\(_{86}\)N\(_{10}\)O\(_{12}\)S [M+H]\(^+\) : 1131.5868, found 1131.5877

**General Procedure for Cross Metathesis of Amino Acids**

tert-butyl (\(5\)\(_S\),17S)\(-\)6-isopropyl\(-\)2,2\(-\)dimethyl\(-\)4,7\(-\)16\(-\)trioxo\(-\)3\(-\)oxa\(-\)5,8,15\(-\)triaza\(-\)octadec\(-\)11\(-\)en\(-\)17\(-\)yl)carbamate (7)

A round bottom flask was charged with Boc-protected homoallyl alanine 3 (50 mg, 0.20 mmol) and the cross partner homoallyl valine 5a (223 mg, 0.80 mmol, 4 equiv) under a gentle stream of Ar(g). To this was added anhydrous THF (0.40 mL). A solution of catalyst 1 or 2 (155 µl of a 0.10 M solution in THF) was added and the reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether (0.50 mL, 5.2 mmol). The solvent was removed in vacuo and the residue purified by column chromatography (SiO2 : 0% to 66% EtOAc in hexane) to afford 61 mg (60%) of product 7 as a white solid. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.24 (bs, 1H), 5.46–5.36 (m, 2H), 5.29–5.24 (m, 2H), 4.34–4.25 (m, 1H), 3.90 (dd, \(J = 9.4, 7.4\) Hz, 1H), 3.78–3.73 (m, 2H), 2.94–2.82 (m, 2H), 2.31–2.12 (m, 4H), 1.98–1.89 (m, 2H), 1.43 (s, 18H), 1.33 (d, \(J = 7.0\) Hz, 3H), 0.94 (dd, \(J = 6.8, 4.5\) Hz, 6H); \(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.49, 172.14, 157.21, 155.76, 129.25 (2C), 79.85, 79.72, 60.33, 50.09, 38.63, 38.41, 30.94, 29.67, 28.33 (6C), 28.03, 19.24, 18.51 (2C). HRMS (ESI) m/z calcld for C\(_{24}\)H\(_{44}\)N\(_4\)O\(_6\) [M+H]\(^+\) : 485.3261, found 485.3258

tert-butyl (\(5\)\(_S\),17S,\(_Z\))\(-\)2,2\(-\)dimethyl\(-\)4,7\(-\)16\(-\)trioxo\(-\)6\(-\)-(3\(-\)\((2,2,4,6,7\)\)-pentamethyl\(-\)2,3\(-\)dihydrobenzofuran\(-\)5\(-\)yl)sulfonyl\)guanidino)methyl\(-\)3\(-\)oxa\(-\)5,8,15\(-\)triaza\(-\)octadec\(-\)11\(-\)en\(-\)17\(-\)yl)carbamate (8)

Following the procedure for 7, the cross product 8 was obtained when homoallyl-modified arginine 5s (50 mg, 0.086 mmol) was reacted with alanine 3 (84
mg, 0.35 mmol, 4 eq.) in THF (0.17 mL) in the presence of catalyst 1 or 2 (65 µl of a 0.10 M solution in THF) under Ar(g). The residue was purified by column chromatography (SiO2; 0% to 2% MeOH in EtOAc) to afford 28 mg (41%) of the product 6s as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.13 (bs, 1H), 6.93 (bs, 1H), 6.35 (bs, 2H), 5.74 (bs, 1H), 5.65 (bs, 1H), 5.45–5.36 (m, 2H), 4.34–4.13 (m, 2H), 3.40–3.16 (m, 6H), 2.95 (s, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.24–2.17 (m, 4H), 2.09 (s, 3H), 1.77 (bs, 1H), 1.61–1.53 (m, 3H), 1.46 (s, 6H), 1.41 (s, 18H), 1.33 (d, J = 7.0 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 173.70, 172.70, 158.68, 156.45, 155.77 (2C), 138.29, 133.17, 132.25, 129.77 (2C), 129.26, 124.51, 117.40, 86.27, 79.98 (2C), 53.83, 50.38, 43.29, 40.28, 38.91, 38.60, 32.61, 30.29, 28.54 (2C), 28.36 (3C) 28.35 (3C), 25.51, 19.20, 18.47, 17.86, 12.37. HRMS (ESI) m/z calcd for C24H44N4O6 [M+H]+ : 794.4408, found 794.4411

Synthesis of Allyl-Modified Amino Acids

Methyl (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoate (9a)

The Boc-protected allyl glycine 9a was synthesized using a two-step procedure starting from allyl glycine. Briefly, to a stirring suspension of (S)-allyl glycine S1 (2.0 g, 17.3 mmol) in CH2Cl2 (25 mL) was added triethylamine (TEA, 1.9 mL, 26.0 mmol, 1.5 eq.) under Ar(g). The solution was cooled to 0°C by immersion in an ice bath. Di-tert-butyl dicarbonate (5.6 g, 26.0 mmol, 1.5 eq.) was dissolved in CH2Cl2 (10 mL) and added dropwise to the stirring solution. The reaction was removed from the ice bath and allowed to stir at room temperature for 12 h. The crude mixture was diluted with H2O (10 mL) and extracted with 1 M HCl (3 x 10 mL), brine (3 x 10 mL), and dried over Na2SO4. The solvent was removed in vacuo to afford a light yellow oil which was carried on to the next step without further purification.

To the oil was added acetone (20 mL) and solid K2CO3 (4.8 g, 34.6 mmol, 2 eq.) at room temperature. The reaction was stirred for 10 min, followed by the addition of iodomethane (2.2 mL, 34.6 mmol, 2 eq.) and the mixture stirred for 12 h. The solvent was evaporated and the residue taken up in EtOAc (25 mL) and washed with saturated Na2SO3 (2 x 20 mL), brine (2 x 20 mL), and dried over Na2SO4. The solvent was removed in vacuo and the crude residue was purified by flash chromatography (3:1 Hex:EtOAc) to afford 3.1 g (78%) of 9a as a colorless oil. 1H NMR (500 MHz, CDCl3) δ 5.64 (ddt, J = 16.5, 10.7, 7.2 Hz, 1H), 5.15–4.99 (m, 3H), 4.39–4.25 (m, 1H), 3.68 (s, 3H), 2.56–2.35 (m, 2H), 1.39 (s, 9H); 13C NMR (126 MHz,
Supporting Information

Synthesis of homoallyl-modified amino acids

Boc-homoallyl glycine 9b was synthesized using a three-step protocol from commercially available Boc-Ser-OMe (S2). In a typical procedure, a flask was charged with Boc-Ser-OMe (2.0 g, 9.1 mmol) and triphenylphosphine (3.6 g, 13.7 mmol, 1.5 eq.) under Ar(g). To this was added THF (20 mL) and the solution cooled to 0°C by immersion in an ice bath. Pyridine (1.5 mL, 18.2 mmol, 2 eq.) was added dropwise, followed by solid iodine (3.5 g, 13.7 mmol, 1.5 eq.) in three portions at 0°C. The ice bath was removed and stirring was continued for 4 h at room temperature. The mixture was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with 1M HCl (3 x 20 mL), 1M Na₂S₂O₃ (2 x 20 mL), brine (2 x 20 mL) and dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was of sufficient purity to be used in the next step without further purification.

The iodopropanoate S3 was dissolved in DMF (5 mL) and added dropwise to a flask containing activated zinc (2.4 g, 36.4 mmol, 4 eq.) at 0°C under Ar(g). The reaction mixture was removed from the ice bath and allowed to stir at room temperature for 3 h, upon which TLC (4:1 petroleum ether: EtOAc) indicated loss of starting material and formation of a lower Rf spot. At this point, the reaction mixture was stopped to let the solid settle to the bottom. The supernatant was then carefully transferred by syringe to a suspension of copper(I) bromide (0.26 g, 1.8 mmol) in DMF (mL) at -15°C that also contained allyl chloride (1.3 mL, 15.5 mmol, 1.7 eq.). After complete addition, the cooling bath was removed and stirring was continued overnight. At this point, EtOAc (20 mL) was added to the reaction mixture and stirring was continued for 15 min. To the mixture was added H₂O (20 mL), the organic layer was removed and successively washed with 1M Na₂S₂O₃ (2 x 20 mL), H₂O (2 x 20 mL), brine (2 x 20 mL), and dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO₂, 8:1 petroleum ether:EtOAc) to afford 2.0 g (90%) of 9b as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.72 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.18–5.07 (m, 1H), 5.01–4.90 (m, 2H), 4.26-4.23 (m, 1H), 3.67 (s, 3H), 2.08–2.01 (m, 2H), 1.88–1.79 (m, 1H), 1.70–1.61

Methyl (S)-2-((tert-butoxycarbonyl)amino)hex-5-enoate (9b)

9b: C₁₂H₂₁NO₄
Exact mass: 243.1471
(m, 1H), 1.37 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.11, 155.23, 136.87, 115.50, 79.64, 52.09, 51.99, 31.85, 29.39, 28.21 (3C). HRMS (ESI) m/z calcd for C$_{12}$H$_{21}$NO$_4$ [M+H]$^+$: 244.1471, found 244.1474

**Methyl O-allyl-N-(tert-butoxycarbonyl)-L-serine (9c)**

A solution of Boc-Ser-OMe S2 (2.0 g, 9.1 mmol) in anhydrous THF (40 mL) was degassed and treated with allylmethyl carbonate (1.4 mL, 12.7 mmol, 1.4 eq). Tetrakis(triphenylphosphine)palladium (0.21 g, 0.18 mmol, 0.02 eq.) was added and the reaction mixture heated to 60°C for 4 h upon which TLC (2:1 EtOAc:hexanes) indicated loss of starting material. The solvent was removed under reduced pressure and the residue was diluted with EtOAc (30 mL) and washed with NaHCO$_3$ (2 x 30 mL) and brine (30 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO$_2$; 0% to 66% EtOAc in hexane) to afford 1.6 g (68%) of the product 9c as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.79 (ddt, $J = 17.3, 10.4, 5.6$ Hz, 1H), 5.41–5.31 (m, 1H), 5.25–5.10 (m, 2H), 4.40–4.37 (m, 1H), 3.95–3.92 (m, 2H), 3.80 (dd, $J = 9.5, 3.3$ Hz, 1H), 3.71 (s, 3H), 3.61 (dd, $J = 9.5, 3.4$ Hz, 1H), 1.41 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.11, 155.42, 134.01, 117.29, 79.85, 72.14, 69.86, 53.92, 52.37, 28.25 (3C). HRMS (ESI) m/z calcd for C$_{12}$H$_{21}$N$_5$O$_5$ [M+H]$^+$: 260.1420, found 260.1428

**Methyl S-allyl-N-(tert-butoxycarbonyl)-L-cysteine (9d)**

Following the procedure for 9c, the allyl-protected cysteine 9d was obtained when Boc-Cys-OMe 1.8 g, 7.6 mmol) was treated with allylmethyl carbonate (1.2 mL, 10.7 mmol, 1.4 eq.) and tetrakis(triphenylphosphine)palladium (0.17 g, 0.15 mmol, 0.02 eq.) in THF (30 mL). The residue was purified by column chromatography (SiO$_2$; 0% to 25% EtOAc in hexane) to afford 1.4 g (69%) of the product 9d as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.70 (ddt, $J = 16.9, 9.6, 7.2$ Hz, 1H), 5.38–5.29 (m, 1H), 5.12–5.04 (m, 2H), 4.48–4.46 (m, 1H), 3.72 (s, 3H), 3.13–3.03 (m, 2H), 2.88 (dd, $J = 13.9, 5.0$ Hz, 1H), 2.80 (dd, $J = 13.9, 5.7$ Hz, 1H), 1.41 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.55, 155.06, 133.62, 117.78, 80.00, 53.10, 52.45, 35.07, 32.76, 28.25 (3C). HRMS (ESI) m/z calcd for C$_{12}$H$_{21}$NO$_4$S [M+H]$^+$: 276.1191, found 276.1188
Procedure for homodimerization of allyl-modified amino acids

dimethyl (2S,7S,Z)-2,7-bis((t-tert-butoxycarbonyl)amino)oct-4-enedioate (10a)

Acetyl BocHN

MeO2C

NHBoc

CO2Me

10a: C_{20}H_{34}N_{2}O_{8}

Exact mass: 430.2315

Allyl-modified glycine 9a (0.18 g, 0.79 mmol) was dissolved in THF (1.5 mL) under a gentle stream of Ar(g). A solution of catalyst 1 or 2 in THF (588 µl of a 0.10 M solution in THF) was added and the reaction heated to 40°C and stirred for 4 h. The solution was allowed to cool to room temperature upon which an excess of ethyl vinyl ether (0.5 mL, 5.2 mmol) was added to quench the reaction. The solvent was removed in vacuo and the residue purified by column chromatography (SiO_{2}; 0% to 25% EtOAc in hexane) to afford 0.15 g (45%) of product 10a as a clear oil. \(^{1}H\) NMR (500 MHz, CDCl_{3}) \(\delta 5.50-5.46\) (m, 2H), 5.17 (d, J = 8.3 Hz, 2H), 4.44-4.40 (m, 2H), 3.75 (s, 6H), 2.62-2.54 (m, 2H), 2.47-2.42 (m, 2H), 1.45 (s, 18H); \(^{13}C\) NMR (126 MHz, CDCl_{3}) \(\delta 172.36\) (2C), 155.09 (2C), 123.72 (2C), 109.99 (2C), 80.11 (2C), 52.87 (2C), 52.36 (2C), 30.40 (3C), 28.27 (3C). HRMS (ESI) m/z calcd for C_{20}H_{34}N_{2}O_{8} [M+H]^+: 431.2315, found 431.2318

dimethyl (2S,9S,Z)-2,9-bis((t-tert-butoxycarbonyl)amino)dec-5-enedioate (10b)

Acetyl BocHN

CO2Me

MeO2C

NHBoc

10b: C_{22}H_{38}N_{2}O_{8}

Exact mass: 458.2628

Following the procedure for 10a, the homodimerization product 10b was obtained when homoallyl-modified glycine 9b (0.13 g, 0.53 mmol) was reacted with catalyst 1 or 2 (395 µl of a 0.10 M solution in THF) in THF (1.1 mL) under Ar(g). The residue was purified by column chromatography (SiO_{2}; 3:1 EtOAc:hexanes) to afford 0.14 g (58%) of the product 10b as a clear oil. \(^{1}H\) NMR (300 MHz, CDCl_{3}) \(\delta 5.43-5.37\) (m, 2H), 5.07 (d, J = 8.4 Hz, 2H), 4.32-4.25 (m, 2H), 3.74 (s, 6H), 2.12-2.04 (m, 4H), 1.94-1.76 (m, 2H), 1.74-1.64 (m, 2H), 1.48 (s, 18H); \(^{13}C\) NMR (126 MHz, CDCl_{3}) \(\delta 173.15\) (2C), 155.34 (2C), 129.31 (2C), 79.89 (2C), 63.96 (2C), 52.13 (2C), 32.48 (2C), 28.30 (6C), 23.18 (2C). HRMS (ESI) m/z calcd for C_{22}H_{38}N_{2}O_{8} [M+H]^+: 459.2628, found 459.2631

methyl (6S,15S,Z)-15-((t-tert-butoxycarbonyl)amino)-6-(methoxy carbonyl)-2,2-dimethyl-4-oxo-3,8,13-trioxa-5-azahexadec-10-en-16-oate (10c)

Acetyl BocHN

MeO2C

O

O

NHBoc

CO2Me

10c: C_{22}H_{38}N_{2}O_{10}

Exact mass: 490.2526

Following the procedure for 10a, the homodimerization product 10c was obtained when allyl-modified serine 9c (0.14 g, 0.54 mmol) was reacted with catalyst 1 or 2 (400 µl of a 0.10 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO_{2}; 0% to 33% EtOAc in hexanes) to afford 0.17 g (67%) of the
product **10c** as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.67–5.62 (m, 2H), 5.37 (d, $J$ = 8.8 Hz, 2H), 4.46–4.39 (m, 2H), 4.05–3.99 (m, 4H), 3.85–3.81 (m, 2H), 3.76 (s, 6H), 3.66–3.60 (m, 2H), 1.45 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.08 (2C), 155.44 (2C), 129.06 (2C), 80.02 (2C), 70.15 (2C), 66.97 (2C), 53.92 (2C), 52.49 (2C), 28.31 (6C). HRMS (ESI) m/z calcd for C$_{22}$H$_{38}$N$_2$O$_{10}$ [M+H]$^+$: 491.2526, found 491.2533.

**methyl (6R,15R,Z)-15-((tert-butoxycarbonyl)amino)-6-(methoxycarbonyl)-2,2-dimethyl-4-oxo-3-oxa-8,13-dithia-5-azahexadec-10-en-16-oate (10d)**

Following the procedure for **10a**, the homodimerization product **10d** was obtained when allyl-modified cysteine **9d** (0.15 g, 0.54 mmol) was reacted with catalyst **1** or **2** (400 µl of a 0.1 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO$_2$: 0% to 33% EtOAc in hexanes) to afford 0.20 g (71%) of the product **10d** as a clear oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.60 (td, $J$ = 5.1, 2.5 Hz, 2H), 5.40 (d, $J$ = 8.1 Hz, 2H), 4.60–4.45 (m, 2H), 3.76 (s, 6H), 3.29–3.15 (m, 4H), 2.90 (m, 4H), 1.45 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.54 (2C), 155.17 (2C), 128.31 (2C), 80.17 (2C), 53.31 (2C), 52.57 (2C), 33.95 (2C), 28.76 (2C), 28.31 (6C). HRMS (ESI) m/z calcd for C$_{22}$H$_{38}$N$_2$O$_{9}$S$_2$ [M+H]$^+$: 523.3070, found 523.3081.

**Procedure for cross metathesis of allyl modified amino acids and allyl acetate**

**methyl (S,Z)-6-acetoxy-2-((tert-butoxycarbonyl)amino)hex-4-enoate (12a)**

Boc-protected allyl glycine **9a** (0.15 g, 0.65 mmol) was dissolved in THF (1.1 mL) under a gentle stream of Ar(g). To this was added allyl acetate (0.35 mL, 3.3 mmol, 5 eq.), followed by a solution of catalyst **1** or **2** (490 µl of a 0.10 M solution in THF). The reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether (0.5 mL, 5.2 mmol). The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO$_2$: 0% to 25% EtOAc in hexane) to afford 83 mg (42%) of product **12a** as a clear, colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.71–5.68 (m, 1H), 5.59–5.53 (m, 1H), 5.20 (d, $J$ = 8.4 Hz, 1H), 4.63–4.52 (m, 2H), 4.42–4.32 (m, 1H), 3.73 (s, 3H), 2.69–2.49 (m, 2H), 2.05 (s, 3H), 1.42 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.21, 170.69, 155.17, 128.61, 127.40, 79.90, 59.77, 52.88, 52.26, 30.42, 28.25 (3C), 20.82. HRMS (ESI) m/z calcd for C$_{14}$H$_{23}$NO$_6$ [M+H]$^+$: 302.1525, found 302.1588.
methyl (SZ)-7-acetoxy-2-((tert-butoxycarbonyl)amino)hept-5-enoate (12b)

Following the procedure for 12a, the cross product 12b was obtained when homoalyl-modified glycine 9b (0.14 g, 0.57 mmol) in THF (1.0 mL) was reacted with catalyst 1 or 2 (431 µl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.31 mL, 2.9 mmol, 5 eq.). The residue was purified by column chromatography (SiO2; 0% to 20% EtOAc in hexane) to afford 0.10 g (56%) of the product 12b as a clear oil. 1H NMR (300 MHz, CDCl3) δ 5.65–5.48 (m, 2H), 5.08 (d, J = 8.5 Hz, 1H), 4.66–4.51 (m, 2H), 4.32–4.26 (m, 1H), 3.72 (s, 3H), 2.23–2.09 (m, 2H), 2.04 (s, 3H), 1.97–1.80 (m, 1H), 1.78–1.61 (m, 1H), 1.43 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 172.96, 170.70, 155.28, 133.10, 124.85, 79.90, 60.04, 52.96, 52.16, 32.34, 28.26 (3C), 23.47, 20.82. HRMS (ESI) m/z calcd for C15H25NO6 [M+H]+: 316.1682, found 316.1690

methyl (Z)-O-(4-acetoxybut-2-en-1-yl)-N-(tert-butoxycarbonyl)-L-serine (12c)

Following the procedure for 12a, the cross product 12c was obtained when homoalyl-modified serine 9c (0.13 g, 0.50 mmol) in THF (0.88 mL) was reacted with catalyst 1 or 2 (375 µl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.27 mL, 2.5 mmol, 5 eq.). The residue was purified by column chromatography (SiO2; 0% to 33% EtOAc in hexane) to afford 0.11 g (63%) of the product 12c as a clear oil. 1H NMR (500 MHz, CDCl3) δ 5.74–5.65 (m, 2H), 5.43–5.35 (m, 1H), 4.63–4.58 (m, 2H), 4.46–4.41 (m, 1H), 4.13–4.04 (m, 2H), 3.90–3.85 (m, 1H), 3.77 (s, 3H), 3.68–3.62 (m, 1H), 2.07 (s, 3H), 1.46 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 173.14, 172.71, 155.24, 136.90, 115.56, 79.77, 53.00, 52.13, 31.97, 29.41, 28.26 (3C), 28.23, 18.56. HRMS (ESI) m/z calcd for C15H25NO7 [M+H]+: 332.1631, found 332.1638

methyl (Z)-S-(4-acetoxybut-2-en-1-yl)-N-(tert-butoxycarbonyl)-L-cysteine (12d)

Following the procedure for 12a, the cross product 12d was obtained when homoalyl-modified cysteine 9d (0.14 g, 0.51 mmol) in THF (0.87 mL) was reacted with catalyst 1 or 2 (377 µl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.27 mL, 2.5 mmol, 5 eq.). The residue was purified by column chromatography (SiO2; 0% to 33% EtOAc in hexane) to afford 0.11 g (62%) of the product 12d as a clear oil. 1H NMR (500 MHz, CDCl3) δ 5.73–5.63 (m, 2H), 5.38–5.30 (m, 1H), 4.68–4.58 (m, 2H), 4.57–4.51 (m, 1H), 3.77 (s, 3H), 3.28–3.21 (m, 2H), 2.95 (dd, J = 13.8, 4.9 Hz, 1H), 2.87 (dd, J = 13.8, 5.9 Hz, 1H), 2.06 (s, 3H), 1.45 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 171.41, 170.60, 155.09,
Supporting Information

130.09, 126.61, 80.14, 59.55, 53.36, 52.44, 33.97, 29.08, 28.27 (3C), 20.81. HRMS (ESI) m/z calcd for C_{15}H_{25}NO_6S [M+H]^+: 348.1403, found 348.1419

**General procedure for the synthesis of homoallyl-modified peptides**

**Boc-Ser(OtBu)-Asp(OtBu)-Phe-Ile-Gln(Trt)-Val** homoallyl peptide 13

![Chemical structure of peptide 13]

Peptide 13 was synthesized by solution phase methods using iterative coupling of Fmoc-protected amino acids. Briefly, Boc-protected homoallyl-modified valine 5a (1.0 g, 3.7 mmol) was dissolved in a mixture of 1:1 TFA:DCM (4 mL) and allowed to stir for 4 h at room temperature upon which TLC (1:1 EtOAc:hexanes) indicated loss of starting material. The solution was diluted with CH_2Cl_2 (30 mL) and the solvent was removed *in vacuo*. The crude residue was dissolved in a mixture of DMF (10 mL) and N,N-disisopropylethylamine (DIEA, 5.3 mL, 30.0 mmol, 8 eq.) and allowed to stir at room temperature for 20 min. At this point, a solution of Fmoc-Gln(Trt)-OH (4.5 g, 7.4 mmol, 2 eq.), HOBt (1.0 g, 7.4 mmol, 2 eq.), HBTU (2.8 g, 7.4 mmol, 2 eq.), and DIEA (2.6 mL, 14.8 mmol, 4 eq.) in DMF (8 mL) was added to the stirring solution. The reaction mixture was heated to 50°C and allowed to stir for 1 h. The solution was cooled to room temperature and quenched with H_2O (20 mL), and to this was added EtOAc (50 mL). The organic layer was removed and washed with H_2O (5 x 20 mL), brine (5 x 20 mL) and dried over MgSO_4. The solvent was removed *in vacuo* to afford the Fmoc-protected dipeptide as a white solid which was found to be of sufficient purity to be used in subsequent reactions.

The Fmoc-protected dipeptide (2.1 g, 2.7 mmol) was dissolved in a mixture of piperidine (3.0 mL, 30 mmol) in DMF (9.0 mL) and allowed to stir at room temperature for 1 h, upon which a white precipitate had formed. The precipitate was filtered off, and the filtrate concentrated under reduced pressure. The crude filtrate was dissolved in EtOAc (50 mL) and extracted with H_2O (5 x 30 mL), brine (5 x 30 mL) and dried over MgSO_4. The solvent was removed *in vacuo* to afford a clear oil (1.3 g) which was used in the next step without further purification.

This iterative procedure was used for subsequent amino acid couplings, at each step monitoring the conversion by LC/MS. The termination of the sequence was carried out using the requisite Boc-protected amino acid. After the final coupling, the crude peptide was dissolved in EtOAc (50 mL) and washed with H_2O (5 x 30 mL), brine (5 x 30 mL), and dried over MgSO_4. The solvent was removed *in vacuo* and the product purified by column chromatography (SiO_2; 1:1 DCM:EtOAc + 1 to 5% MeOH) to afford a white solid (R_f = 0.45 in 1:1 DCM:EtOAc + 2% MeOH).

\[^1\text{H} NMR (500 MHz, CDCl}_3 + CD_3OD\) \delta 7.79 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.44–7.32 (m, 3H), 7.25–7.09 (m, 17H), 5.75–5.65 (m, 1H), 5.48 (d, J = Hz, 1H), 5.04–4.91 (m, 2H), 4.37–4.35 (m, 1H), 4.33–4.24 (m, 2H), 4.19–4.14 (m, 2H), 4.02–3.97 (m,

Supporting Information
2H), 3.79–3.77 (m, 2H), 3.56–3.54 (m, 4H), 3.21–3.19 (m, 4H), 2.57–2.25 (m, 4H), 2.22–2.14 (m, 4H), 2.07–1.92 (m, 3H), 1.85–1.80 (m, 2H), 1.43–1.42 (m, 2H), 1.41 (s, 18H) 1.38–1.35 (m, 6H), 1.13–1.11 (m, 14H), 0.89–0.79 (m, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$ + CD$_3$OD) δ 172.87, 171.95, 171.93, 171.84, 171.63, 171.18, 170.52, 155.83, 144.50 (3C), 135.36, 129.03, 128.90, 128.70 (3C), 128.67 (3C), 128.57, 128.55, 127.71 (3C), 127.68, 126.77 (3C), 126.74, 126.60, 125.43, 117.87, 116.39, 110.47, 82.01, 80.70, 73.90, 73.53, 61.91, 59.06, 59.03, 58.96, 58.92, 54.02, 38.73, 35.76, 33.36, 33.33, 29.63, 28.22 (3C), 28.13, 27.88 (3C), 27.25, 27.23, 27.22, 27.17 (3C), 25.21, 19.21, 17.59, 17.55, 15.37, 11.03. HRMS (ESI) m/z calcd for C$_{68}$H$_{94}$N$_{9}$O$_{12}$ [M+H]$^+$: 1215.7016, found 1215.7082

**Boc-Lys(Boc)-Val-Leu-Tyr(OtBu)-Arg(Pbf)-Arg(Pbf) homoallylic peptide 14**

![Peptide Structure](image)

Peptide 14 was synthesized by iterative amino acid coupling in a manner analogous to that of peptide 13. Purification of the final peptide was achieved by column chromatography (SiO$_2$; 1:1 DCM:EtOAc + 1 to 5% MeOH) to afford a clear gel. (R$_f$ = 0.55 in 1:1 DCM:EtOAc + 10% MeOH). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, J = 6.7 Hz, 1H), 7.54–7.35 (m, 5H), 7.17 (bs, 1H), 7.10–7.07 (m, 2H), 6.79–6.77 (m, 2H), 6.61 (bs, 1H), 6.28 (bs, 4H), 5.72–5.63 (m, 1H), 5.42 (m, 1H), 4.98–4.89 (m, 2H), 4.29–4.15 (m, 3H), 3.19–3.06 (m, 8H), 2.99–2.95 (m, 2H), 2.88–2.84 (m, 8H), 2.78–2.77 (m, 3H), 2.47–2.45 (m, 6H), 2.40–2.39 (m, 6H), 2.20–2.10 (m, 3H), 1.98–1.96 (m, 6H), 1.81–1.50 (m, 12H), 1.38 (s, 9H), 1.36 (s, 9H), 1.34 (s, 9H), 1.20 (m, 12H), 0.93–0.86 (m, 6H), 0.77–0.74 (m, 4H), 0.68–0.66 (m, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$ + CD$_3$OD) δ 175.42, 174.51, 173.21, 172.91 (2C), 172.32, 162.89 (2C), 158.53, 157.30 (2C), 157.09, 156.43 (2C), 156.36, 153.99, 138.11 (2C), 135.18 (2C), 133.02, 132.06 (2C), 129.26 (2C), 124.45 (2C), 123.94 (2C), 117.32, 116.33, 86.29 (2C), 80.65, 79.30, 78.36, 61.40, 57.09, 56.46, 54.52, 54.31, 53.28, 43.12 (2C), 40.38 (2C), 39.49 (2C), 38.95 (2C), 36.44, 35.82, 33.24, 31.34, 28.65 (3C), 28.35 (3C), 28.29 (3C), 28.12 (2C), 25.31, 24.52, 22.55 (2C), 20.87 (2C), 18.98 (2C), 18.26 (2C), 17.69 (2C), 12.18 (2C). HRMS (ESI) m/z calcd for C$_{62}$H$_{130}$N$_{14}$O$_{17}$S$_{2}$ [M+H]$^+$: 1648.9180, found 1648.9332

**Procedure for the synthesis of peptide 15 by cross metathesis**

A 1 mL vial was charged with peptides 13 (23 mg, 0.020 mmol) and 14 (33 mg, 0.020 mmol) under a gentle stream of Ar(g). To this was added THF (150 µL), followed by the addition of a solution of catalyst 2 (30 µL of a 0.10 M solution in THF). The reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether.
(0.5 mL, 5.2 mmol). The solvent was removed in vacuo and the crude mixture analyzed by LC/MS to measure the extent of conversion. (Rf of cross product = 0.32 in 1:1 DCM:EtOAc + 10% MeOH). HRMS (ESI) m/z calcd for C\textsubscript{148}H\textsubscript{220}N\textsubscript{22}O\textsubscript{29}S\textsubscript{2} [M + 2H]\textsuperscript{2+}: 1418.7929, found 1418.7948.

**HPLC of cross metathesis on homoallyl–modified peptides**

**Figure S1:** Analytical HPLC to assess conversion for cross metathesis between peptides 13 and 14. The percentage conversion was calculated by the ratio of cross product 15 (peak 8) to starting material (peaks 3 corresponding to 13 and peak 5 corresponding to 14). The homodimers of 13 (peak 4) and 14 (peak 6) are also evident. HPLC conditions: 40-95% acetonitrile:H\textsubscript{2}O + 0.1% AcOH.
Solid phase synthesis of peptides

Peptides were produced on a Titan 357 (AAPPTec, Louisville, KY) automated peptide synthesizer using Rink Amide MBHA resin (NovaBioChem, 0.4 mmol/g resin), Wang resin (NovaBioChem, 0.5 mmol/g resin), or TentaGel MB RAM resin (RappPolymere, 0.4 mmol/g resin) at 40 µmol scale. The resin was swelled with N-Methyl 2-pyrrolidinone (NMP, 10 mL) for 30 min before use. To load the first amino acid onto the resin, the resin-bound Fmoc-protecting group was removed by treatment with 25% (vol/vol) piperidine in NMP (2 x 10 min). Standard amino acids were coupled for 1 h using HATU as the activating agent (4 eq. based on loading capacity), Fmoc-protected amino acid (5 eq.), and N,N-diisopropylethylamine (DIEA, 10 eq.) in NMP. After each coupling or deprotection reaction, the resin was washed successively with DCM (1 x 1 min), NMP (1 x 1 min), DCM (1 x 1 min) and NMP (1 x 1 min). For the coupling of olefin amino acids, a reaction time of 2 h was used with Fmoc-(S)-2-(4-pentenyl)alanine (3 eq.) or Fmoc-(R)-2-(7-octenyl)alanine (3 eq.), HATU (3 eq.) and DIEA (6 eq.) in NMP. After the final amino acid coupling, the resin was washed with DCM (2 x 1 min) and dried in vacuo overnight.
Sequence of peptides used in Z-selective RCM

Peptide 16: Ac-Glu-Asp-Ile-Ile-Arg-Ile-S5*-Arg-Leu-Leu-S5*-Glu-Val-Gly-Asp

*S5 denotes position of (S)-2-(4-pentenyl)alanine

*R8 denotes position of (R)-2-(7-octenyl)alanine

Peptide 18: Ac-Leu-Ser-Gln-Glu-Tyr-Phe-R8*-Asn-Leu-Trp-Lys-Leu-Leu-S5*-Gln-Asp

General procedure for Z-selective RCM on resin-bound olefinic peptides

The N-terminal modified peptide on resin (25 mg, 0.01 mmol) was dissolved in degassed dichloroethane (DCE, 2.0 mL). To this was added a stock solution of cyclometalated ruthenium catalyst 2 in degassed DCE (20 µL of a 0.05 M solution in DCE). The reaction was stirred under a gentle stream of Ar(g) for 2 h, the catalyst was filtered off, and the resin washed first with DCE (5 x 2 min) and then with DMF (2 x 2 min). Exposure of the resin bound peptide to an additional round of catalyst stock solution (20 µL) for 2 h ensured nearly quantitative conversion. Upon completion of RCM, the resin bound peptide was washed with DCE (2 x 2 min), DMF (2 x 2 min), and DCM (2 x 2 min) and dried under vacuum.

For N-terminal acetylation of the peptide, the resin was swelled with NMP (1 mL) for 20 min and then washed with NMP (2 x 1 min). The resin was treated with 25% (vol/vol) piperidine in NMP (2 mL), gently agitated for 20 min, and then drained. The resin was washed with DCM (5 x 2 min) and allowed to dry under a gentle stream of argon to afford the amine-terminated peptide. To this was added
NMP (1 mL), the resin was agitated for 10 min, and the solvent was drained. Acetic anhydride (30 µL, 0.3 mmol, 30 eq.) in NMP (1.0 mL) was added, followed by N,N-dimethylpropylamine (DIEA, 104 µL, 60 eq.) and the resin was agitated for 45 min at room temperature. The resin was washed with DCM (1 x 1 min), NMP (1 x 1 min), and DCM (1 x 1 min) and dried in vacuo overnight.

Cleavage of the peptide from the resin and global deprotection were achieved by reacting the resin with 95% TFA, 2.5% triisopropylsilane, 2.5% H₂O (vol/vol/vol) for 2 h. The TFA and other volatiles were removed by evaporation under a stream of argon. The peptides were precipitated with cold diethyl ether (4 mL), vortexed, and collected by centrifugation. The pellet was dried under a gentle stream of argon and subsequently dissolved in a mixture of 50% acetonitrile, 50% H₂O (vol/vol) and the resin was removed by filtration. The cleaved peptides were purified by reverse-phase HPLC using a Zorbax C₈ or C₁₈ column (Agilent, 5 µm, 9.4 x 250 mm) and characterized by LC/MS TOF using a Zorbax C₈ column (Agilent, 3.5 µm, 2.1 x 150 mm) or matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF).

**Representative Z-selective RCM across one turn of a helix**

![Diagram](image1)

**Representative Z-selective RCM across two helical turns**

![Diagram](image2)

**Monitoring the conversion of RCM on resin-bound olefinic peptides**

To measure the percentage conversion of RCM on peptides 16 and 18, aliquots of the resin suspension (25 µL) were taken from the reaction mixture at the indicated time points, quenched with ethyl vinyl ether (50 µL), filtered, and washed with DCE (300 µL). The resin was dried under a stream of argon and suspended in 100 µL of the cleavage cocktail TFA/TIS/H₂O (95:2.5:2.5) and allowed to stir at room temperature for 1 h. The TFA and other volatiles were removed by evaporation and
the crude residue dissolved in diethyl ether (200 µL), vortexed, and centrifuged. The ether was carefully decanted and the pellet was dried under a stream of argon. The pellet was dissolved in 100 µL of 50% (vol/vol) aqueous acetonitrile and filtered to afford the crude peptide. For LC/MS TOF analysis, 5 µL of dissolved peptide was injected onto an analytical column (Eclipse Plus C8 column (1.8 µm, 2.1 x 50 mm)) operating in positive electrospray ionization (ESI) mode.

*Monitoring ring-closing metathesis on peptide 16*

**Figure S2:** Evaluation of RCM on peptide 16 as a function of time (t = 0 min). The indicated mass corresponding to starting material (987.5823) is observed as the [M+2H]^2+ ion in ESI and was used to monitor the extent of conversion during the course of the reaction.

**Figure S3:** Evaluation of RCM on peptide 16 as a function of time (t = 30 min). Indicated masses correspond to starting material 16 (987.5814) and product 17 (973.5669) as the [M+2H]^2+ ion as measured by LC/MS TOF.
Figure S4: Evaluation of RCM on peptide 16 as a function of time \((t = 60\ \text{min})\). Indicated masses correspond to starting material 16 (987.5808) and product 17 (973.5672) as the \([\text{M+2H}]^{2+}\) ion as measured by LC/MS TOF.

Figure S5: Evaluation of RCM on peptide 16 as a function of time \((t = 120\ \text{min})\). Indicated masses correspond to starting material 16 (987.5812) and product 17 (973.5674) as the \([\text{M+2H}]^{2+}\) ion as measured by LC/MS TOF.
**Figure S6:** Evaluation of RCM on peptide 16 as a function of time (t = 240 min). Indicated masses correspond to starting material 16 (987.5805) and product 17 (973.5672) as the [M+2H]^2+ ion as measured by LC/MS TOF.

**HPLC chromatogram of RCM product 17**

**Figure S7.** HPLC chromatogram (UV absorbance at 210 nm) of purified peptide 17 (Rt of Z-olefin macrocycle is 348 sec). Column conditions: 5–95% ACN:H₂O + 0.1% AcOH.
**MALDI-TOF spectrum of purified peptide 17.**

![MALDI-TOF spectrum](image)

**Figure S8:** MALDI-TOF of purified peptide 17. Indicated masses correspond to 1945.7777 [M+H]+ and 1966.7576 [M+Na]+ for the product of Z-selective RCM.

**Monitoring RCM on peptide 18**

![ESI Scan](image)

**Figure S9:** Evaluation of RCM on peptide 18 as a function of time (t = 0 min). The indicated mass corresponding to starting material (1070.5990) is observed as the [M+2H]2+ + Na+ ion in ESI and was used to monitor the extent of conversion during the course of the reaction.
**Figure S10:** Evaluation of RCM on peptide 18 as a function of time (t = 30 min). Indicated masses correspond to starting material 18 (1070.5992) and product 19 (1056.5834) as the [M+2H]^{2+} ion as measured by LC/MS TOF.

**Figure S11:** Evaluation of RCM on peptide 18 as a function of time (t = 60 min). Indicated masses correspond to starting material 18 (1070.5977) and product 19 (1056.5829) as the [M+2H]^{2+} ion as measured by LC/MS TOF.
Figure S12: Evaluation of RCM on peptide 18 as a function of time (t = 120 min). Indicated masses correspond to starting material 18 (1070.5977) and product 19 (1056.5833) as the [M+2H]^{2+} ion as measured by LC/MS TOF.

Figure S13: Evaluation of RCM on peptide 18 as a function of time (t = 240 min). Indicated masses correspond to starting material 18 (1070.5976) and product 19 (1056.5830) as the [M+2H]^{2+} ion as measured by LC/MS TOF.
**HPLC chromatogram of RCM product 19**

![HPLC Chromatogram](image)

**Figure S14:** HPLC chromatogram (UV absorbance at 254 nm) of purified peptide 20 (R of Z-olefin macrocycle is 302 sec). Column conditions: 5–95% ACN:H₂O + 0.1% AcOH.

**MALDI-TOF spectrum of purified peptide 19.**

![MALDI-TOF Spectrum](image)

**Figure S15:** MALDI-TOF of purified peptide 19. Indicated masses correspond to 2068.3980 [M+H]⁺ and 2089.2790 [M+Na]⁺ for the product of Z-selective RCM.
General procedure for RCM on Aib-containing peptides bearing i, i+3
crosslinks

Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe 20\(^2\) (20.0 mg, 0.033 mmol) was
dissolved in dichloroethane (6.5 mL) in a nitrogen-flushed flask. Second-
generation Grubbs catalyst 22 (2.77 mg, 0.0033 mmol), Grubbs-Hoveyda
catalyst 23 (2.04 mg, 0.0033 mmol), or cyclometalated ruthenium catalyst 1
(6.11 mg, 0.099 mmol) was added in a single portion and then heated at 40 °C for 4 h.
At this point, a 60 µL aliquot was removed and quenched by the addition of H\(_2\)O
(3 mL) and 30% hydrogen peroxide (3 mL) and the biphasic mixture was vigorously
stirred for 8 h. The organic layer was passed through a plug of Na\(_2\)SO\(_4\) and an
aliquot was removed for LCMS analysis. \(^1\)HNMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 7.48 (1H, d, \(J = 7.4\) Hz), 7.47 (1H, s), 6.96 (1H, s), 6.78 (1H, s), 5.74 (2H, m), 5.22 (1H, d, \(J = 7.8\) Hz), 4.56
(1H, dt, \(J = 2.3, 8.7\) Hz), 4.24 (1H, m), 4.16 (2H, m), 3.90 (1H, dd, \(J = 2.9, 9.3\) Hz),
3.822 (2H, m), 3.76 (1H, t, \(J = 9.0\) Hz), 3.65 (3H, s), 3.48 (1H, dd, \(J = 4.3, 8.7\) Hz), 1.55
(3H, s), 1.50 (3H, s), 1.46 (3H, s), 1.44 (15H, s), 1.42 (3H, s). \(^{13}\)C NMR (100 MHz,
CD\(_2\)Cl\(_2\)): \(\delta\) 175.26, 174.51, 174.46, 171.98, 169.44, 156.31, 132.33, 126.45, 81.17,
70.97, 70.23, 69.29, 66.70, 57.71, 57.45, 56.29, 55.18, 54.73, 52.42, 28.33, 27.78,
26.91, 25.23, 25.08, 23.55, 23.40. HRMS (ESI) m/z calcd for C\(_{28}\)H\(_{47}\)N\(_5\)O\(_{10}\) [M+H]\(^+\): 613.3521, found 614.3533

Following the procedure for RCM on peptide 21, Boc-Val-L-Ser(Al)-Leu-Aib-L-Ser(Al)-Val-Leu-OMe 24\(^2\) (9.1 mg, mmol)
was dissolved in DCM (1.9 mL) under a stream of nitrogen. To this was added catalysts 22, 23,
or 1 (10 mol%) and the reaction heated at 40 °C for 4 h. The reaction was diluted with DCM
(4 mL) and quenched by addition of water (2 mL) and 30% hydrogen peroxide (2 mL). The biphasic mixture
was vigorously stirred for 4 h. An aliquot of the organic layer (60 µL) was removed
for LCMS analysis. HRMS (FAB) m/z calcd for C\(_{42}\)H\(_{72}\)N\(_7\)O\(_{12}\) [M+Na]\(^+\): 890.5209, found 890.5180

---

\(^2\) For full characterization of this compound and its ring-closed form, see: Boal, A.K.
**LCMS chromatogram of RCM product 21 in the presence of catalyst 1**

**Figure S16:** Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe 20 using catalyst 1. Indicated masses correspond to starting material (663.2 M + Na) (Rt of starting material is 6.91 min) and product 21 (635 M + Na) (Rt of macrocycle is 5.86 min). Column conditions: 25–100% ACN:H2O + 0.1% TFA.
Figure S17: Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe 20 using catalyst 22. Indicated masses correspond to starting material (663.2 M + Na) (R_t of starting material is 6.92 min) and product 21 (635 M + Na) (R_t of macrocycle is 5.86 min). Column conditions: 25–100% ACN:H_2O + 0.1% TFA.
**LCMS chromatogram of RCM product 21 in the presence of catalyst 23**

**Figure S18:** Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe 20 using catalyst 23. Indicated masses correspond to starting material (663.2 M + Na) (Rt of starting material is 6.92 min) and product 21 (635 M + Na) (Rt of macrocycle is 5.85 min). Column conditions: 25–100% ACN:H₂O + 0.1% TFA.
**LCMS chromatogram of RCM product 25 in the presence of catalyst 1**

**Figure S19:** Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe 24 using catalyst 1. Indicated masses correspond to starting material (916.8 M + Na) (R\textsubscript{t} of starting material is 19.24 min). Column conditions: 25–100% ACN:H\textsubscript{2}O + 0.1% TFA.
**LCMS chromatogram of RCM product 25 in the presence of catalyst 22**

**Figure S20:** Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe 24 using catalyst 22. Indicated masses correspond to starting material (916.8 M + Na) (Rt of starting material is 19.24 min) and product 25 (889.1 M + Na) (Rt of Z-olefin macrocycle is 14.96 min and E-macrocycle 15.21 min). Column conditions: 25–100% ACN:H₂O + 0.1% TFA.
**LCMS chromatogram of RCM product 25 in the presence of catalyst 23**

**Figure S21:** Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe 24 using catalyst 23. Indicated masses correspond to starting material (917.0 M + Na) (R_t of starting material is 19.24 min) and product 25 (889.0 M + Na) (R_t of Z-olefin macrocycle is 14.95 min and E-macrocycle 15.19 min). Column conditions: 25–100% ACN:H2O + 0.1% TFA.
NMR Spectra: $^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 3
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 3

![Diagram of the compound structure]

- 172.71
- 155.48
- 135.04
- 117.09
- 79.83
- 77.31
- 76.95
- 50.02
- 38.41
- 33.67
- 28.50
- 18.64
- 18.64

f1 (ppm)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5a
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5a
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5b
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5b
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5c
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5c
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5d
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5d
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5e
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5e

BocHN

O

H

N
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5f
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5f
\(^1\)H NMR (500 MHz, CDCl\(_3\)) spectrum of compound 5g
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5g
$^1$H NMR (500 MHz, CD$_3$OD) spectrum of compound 5h
$^{13}$C NMR (126 MHz, CD$_3$OD) spectrum of compound 5h
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5i
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5i

![NMR Spectrum](image-url)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5j

![NMR Spectrum Image]

Supporting Information
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5j
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5k
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5k
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound **5l**
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 51
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5m
\(^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}\) spectrum of compound \textbf{5m}
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5n
\[^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\text{)} \text{ spectrum of compound 5n}\]
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5o
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5o
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5p

![NMR Spectrum](image-url)
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5p
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5q
\[13^C\text{ NMR (126 MHz, CDCl}_3\text{) spectrum of compound 5q}\]
¹H NMR (500 MHz, CDCl₃) spectrum of compound 5r
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5r
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 5s
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 5s
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 4
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 4

![Spectrum Image]
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6a

![NMR spectrum of compound 6a]
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6a
$^1\text{H}$ NMR (500 MHz, CDCl$_3$) spectrum of compound 6b
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6b
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6c
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6c
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6d
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) spectrum of compound 6d
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6g
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6g
1H NMR (500 MHz, CDCl$_3$) spectrum of compound 6i
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6i
$\text{H NMR (500 MHz, CDCl$_3$) spectrum of compound 6j}$
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6j
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6k
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6k
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6m
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6m
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6n
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6n
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 60

![NMR spectrum of compound 60](image-url)
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 60
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6p
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6p
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6q
$^{13}$C NMR (126 MHz, CDCl₃) spectrum of compound 6q
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 6r
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 6r
\[^1\text{H} \text{NMR} \ (500 \text{ MHz, } \text{CD}_3\text{OD}) \text{ spectrum of compound 6s}\]
$^{13}$C NMR (126 MHz, CD$_3$OD) spectrum of compound 6s
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 7
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 7
$^1$H NMR (500 MHz, CDC$_3$) spectrum of compound 8
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 8
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 9a
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 9a
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 9b
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 9b
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 9c
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 9c
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 9d
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 9d
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 10a
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 10a
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 10b
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) spectrum of compound 10b
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 10c
$^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}$ spectrum of compound 10c
\(^1\)H NMR (500 MHz, CDCl\(_3\)) spectrum of compound 10d
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 10d
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 12a
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 12a
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 12b
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 12b
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 12c
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 12c
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 12d
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 12d
$^1$H NMR (500 MHz, CDCl$_3$ + CD$_3$OD) spectrum of compound 13
$^{13}$C NMR (126 MHz, CDCl$_3$ + CD$_3$OD) spectrum of compound 13
$^1$H NMR (500 MHz, CDCl$_3$ + CD$_3$OD) spectrum of compound 14
$^{13}$C NMR (126 MHz, CDCl$_3$ + CD$_3$OD) spectrum of compound 14