A Microwave Enhanced Cross-Metathesis Approach to Peptidomimetics

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Supporting Information

**General information:** All reactions were carried out under an argon atmosphere, using oven-dried glassware. All chemicals were purchased from commercial sources and were used as received without further purification. Peptide coupling reactions were monitored in some cases using a Micromass Platform LC instrument. Acryloylations were monitored by thin-layer chromatography (app tLC) on pre-coated silica gel plates (254mm) and in some cases using a Micromass Platform LC instrument. All yields quoted are isolated yields unless otherwise stated. $^1$H NMR spectra were recorded at 300MHz and $^{13}$C at 75MHz on a Bruker AMX 300 at ambient temperature unless otherwise stated. The chemical shifts for $^1$H and $^{13}$C are quoted in ppm relative to residual protiated signals of the solvent. Mass spectra were obtained on a VG70-SE or a MAT 900 XP mass spectrometer. Infrared spectra were obtained on a Shimadzu FTIR 8700 Spectrophotometer. Optical rotations were measured using monochromatic light at 589 nm with a 1 dm cell and either a model AA-1000 polarimeter, at 294 K or a polAAR 2000 polarimeter at ambient temperatures. Melting points were measured, where appropriate, with a Gallenkamp apparatus and are uncorrected.

*A note on the assignment of $^1$H NMR –* Superscript a and b distinguish between diastereotopic protons on the same carbon and thus are not intended to uniquely define protons within the same molecule.

Protocol I
Protected amino acid [3.4 mmol] and HOBt [455 mg, 3.4 mmol] were dissolved in DCM [15 ml] and the mixture stirred vigorously. EDC [1.2 g, 6.8 mmol], DIPEA [1.18 ml, 6.8 mmol] and homoallyl amine [0.31 ml, 3.4 mmol] were added, in this
order, and the resultant mixture stirred for 4 h. The mixture was then diluted with DCM [15 ml], and washed with HCl [2x10 ml, 0.5 M], NaHCO₃ [2x10 ml, 0.5 M], water [2x10 ml] and saturated brine [10 ml], dried with anhydrous MgSO₄, and purified by column chromatography [petroleum ether and ethyl acetate].

Protocol II
An amino acid ester [1.7 mmol, as the HCl salt] and Et₃N [0.5 ml, 3.7 mmol] were stirred in DCM [10 ml] under anhydrous conditions. Acryloyl chloride [2 mmol, as a 1 M solution in DCM] was added over 1 H, and the resultant mixture stirred overnight. The DCM was removed under reduced pressure, and ethyl acetate added [80 ml]. The solid was filtered off and the filtrate was washed with HCl [10 ml, 0.5 M], NaHCO₃ [2x10 ml, 0.5 M], water [10 ml] and saturated brine [10 ml], dried with anhydrous MgSO₄, and purified by column chromatography [petroleum ether and ethyl acetate].

Protocol III – optimised microwave cross metathesis
An electron deficient olefin [0.1 mmol] and the more reactive cross metathesis partner olefin [1.3 equivalents] were stirred in DCM in a microwave vial. Grubb’s 2nd generation catalyst [18 mol%] was added, and the mixture stirred and subjected to microwave radiation [300 W, 100°C] for 30 mins. The reaction mixture was then degassed with argon for approximately 1 min, and the mixture stirred and subjected to microwave radiation [300 W, 100°C] for a further 30 mins. The mixture was then purified by column chromatography.

Compound 1a
BocPheOH [1.7g, 6.4 mmol] was reacted with homoallyl amine hydrochloride according to protocol I. purification yielded a waxy solid [1.3g, 64%, mp 64 – 66°C].

\[ \text{BocPheOH} \]

\[ 1a \]

\[ ^1H \text{NMR} (\text{CDCl}_3) – 7.17-7.29 \text{ (m, 5 H, Ar-H)}; 5.99 \text{ (br, 1 H, NH)}; 5.61 \text{ (ddt, } J = 17.1, \]
\[ \]
\[ J = 10.7, J = 6.7 \text{, 1 H, H}_2\text{CCH=CH}_2)\]; 5.20 \text{ (br, 1 H, NH)}; 4.91-4.98 \text{ (m, 2 H,} \]
H₂CCH=CH₂); 4.29 (app q, J = 7.0, 1 H, NHCH); 3.13 (m, 2 H, NHCH₂); 3.01 (m, 2 H, CHCH₂); 2.02-2.16 (m, 2 H, CH₂CHCH₂); 1.38 (s, 9 H, C(CH₃)₃).

¹³C NMR (CDCl₃) – 171.1 (C=O); 155.4 (C=O); 136.9 (C); 134.9 (CH); 129.3 (CH); 128.6 (CH); 126.9 (CH); 117.1 (CH₂); 80.0 (C); 56.0 (CH); 38.9 (CH₂); 38.4 (CH₂); 33.4 (CH₂); 28.3 (CH₃).

HRMS calc. for C₁₉H₂₈N₂O₄ - 319.20216 (M+H); found 319.20270.

IR, solution cell, DCM (cm⁻¹) – 3427; 2978; 2934; 1709; 1676.

[α]²⁵D +4.9 (c 0.50, CHCl₃)

Compound 1b
BocHis(Tos)OH [654 mg, 0.48 mmol] was reacted with homoallyl amine according to protocol I. Purification yielded a highly viscous clear liquid [537 mg, 73%].

¹H NMR (CDCl₃) – 8.00 (br s, 1 H, N=CΗ?); 7.92 (d, J = 8.2, 2 H, Ts-H); 7.35 (d, J = 8.0, 2 H, Ts-H); 7.09 (s, 1 H, NCH=C); 6.61 (br s, 1 H, NH); 5.86 (d, J = 7.3, 1 H, Ts-H); 5.63 (app ddt, 1 H, J = 17.3, J = 10.6, J = 6.8, H₂CCH=CH₂); 4.96-5.02 (m, 2 H, CH=CΗ₂); 4.40 (br s, 1 H, HNCΗ); 3.17 (app q, J = 5.9, 2 H, NHCH₂); 3.03 (dd, J = 5.6, J = 14.8, 1 H CHᵃHᵇIm); 2.90 (dd, J = 4.3, J = 14.6, 1 H CHᵃHᵇIm); 2.34 (s, 3 H, ArCH₃); 2.09 (app q, J = 6.7, 2 H, CH₂CH₂CHCH₂); 1.40 (s, 9 H, C(CH₃)₃).

¹³C NMR (MeOH d₄) – 173.7 (C=O); 157.5 (C=O); 148.0 (C); 141.7 (C); 138.1 (CH); 136.5 (CH); 136.2 (CH); 131.7 (CH); 128.7 (CH); 117.5 (CH₂); 116.4 (CH); 80.6 (C); 55.5 (CH); 39.8 (CH₂); 34.6 (CH₂); 31.7 (CH₂); 30.7 (CH₂); 28.7 (CH₂); 21.7 (CH₃).

IR, solution cell, DCM (cm⁻¹) – 3423; 2978; 2934; 1711; 1672; 1593.

HRMS calc. for C₂₂H₃₀N₄O₅S – 463.20097 (M+H); found 463.200480.

[α]¹⁴D +21.2 (c 0.62, CHCl₃)

Compound 1c
BocCys(4-MeBzl)OH [2.0 g, 6.2 mmol], HOBt [873 mg, 6.5 mmol], HBTU [2.3 g, 6.1 mmol] and DIPEA [1.1 ml, 6.2 mmol] were stirred in DCM [5 ml] and DMF [5 ml] for 20 min. Homoallyl amine hydrochloride [335 mg, 3.1 mmol] and DIPEA [0.6 ml, 3.4 mmol] in DCM [2 ml] were added, and the resultant mixture stirred for 3 h.
The majority of the solvent was removed under reduced pressure. DCM [20 ml] was then added, and the mixture washed with HCl [2x10 ml, 1 M], LiCl [2 x 10ml, 10%], NaHCO₃ [2x10 ml, 0.5 M], water [2x10 ml] and saturated brine [10 ml], dried with anhydrous MgSO₄, and purified by column chromatography [petroleum ether and ethyl acetate], yielding a waxy solid [989 mg, 84%].

1H NMR (CDCl₃) – 7.22 (d, J = 8.0, 2 H, Ph-H); 7.12 (d, J = 7.8, 2 H, Ph-H); 6.26 (br t, NHCH₂); 5.75 (app ddt, J = 17.1, J = 10.3, J = 6.8, 1 H, H₂CC=CH=CH₂); 5.26 (br, 1 H, NHCH₂); 5.06 – 5.13 (m, 2 H, H₂C=CH); 4.18 (br app q, J = 6.0, 1 H, NHC₃H); 3.71 (s, 2 H, SCH₂Ar); 3.29 – 3.36 (m, 2 H, NHCH₂); 2.86 (dd, J = 5.6, J = 13.9, 1 H, CHCH₃HS); 2.70 (dd, J = 9.6, J = 13.9, 1 H, CHCH₃HS); 2.32 (s, 3 H, ArCH₃); 2.22 – 2.29 (m, 2 H, NHCH₂CH₂); 1.45 (s, 9 H, C(CH₃)₃).

13C NMR (CDCl₃) – 170.5 (C=O); 155. 4 (C=O); 136.9 (C); 135.0 (CH); 134.9 (C); 129.3 (CH); 128.9 (CH); 117.4 (CH₂); 80.3 (C); 53.8 (CH); 38.6 (CH₂); 36.2 (CH₂); 33.8 (CH₂); 33.6 (CH₂); 28.3 (CH₃); 21.1 (CH₃).

IR, solution cell, DCM (cm⁻¹) – 3423; 2974; 2930; 2330; 1713; 1676; 1489.

HRMS calc. for C₂₀H₃₀N₂O₃S- 379.20553 (M+H); found 379.20468.

[α]¹⁹ D +3.9 (c 0.42, CHCl₃)

Compound 1d

BocTyr(Bzl)OH [594 mg, 1.6 mmol] was reacted with homoallyl amine according to protocol I. Purification yielded a waxy solid [417 mg, 61%].

1H NMR (DMSO d₆) – 7.86 (app t, J = 5.6, 1 H, NHCH₂); 7.30-7.43 (m, 5 H, CH₂Ar-H); 7.13 (d, J = 8.5, 2 H, H ortho to O); 6.89 (d, J = 8.5, 2 H, H meta to O); 6.82 (d, J = 8.5, 1 H, NHCH₂); 5.73 (app ddt, 1 H, J = 17.2, J = 10.3, J = 6.7, H₂CCH=CH₂); 5.04 (s, 2 H, OCH₂Ph); 4.96-5.02 (m, 2 H, CH=CH₂); 4.02 (app dt, J = 4.6, J = 9.1, 1
Compound 1e

BocSer(Bzl)OH [1.0 g, 3.4 mmol] was reacted with homoallyl amine according to protocol I. Purification yielded a clear liquid [541 mg, 46%].

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NH} & \quad \text{O} \\
\text{HN} & \quad \text{O} \\
\text{1e} & 
\end{align*}
\]

\( ^1 \text{H NMR (CDCl}_3) \) – 7.26-7.40 (m, 5 H, Ar-H); 6.49 (br t, \( J = 5.4 \), 1 H, NHCH\( _2 \)); 5.71 (ddt, \( J = 17.1, J = 10.2, J = 6.7 \), 1 H, H\( _2 \)CCH\( = \)CH\( _2 \)); 5.41 (br, 1 H, NH\( _2 \)); 4.92-5.00 (m, 2 H, H\( _2 \)CCH\( = \)CH\( _2 \)); 4.48 (d, \( J = 11.8 \), 1 H, OCH\( ^3 \)H\( ^3 \)Ph); 4.42 (d, \( J = 11.8 \), 1 H, OCH\( ^3 \)H\( ^3 \)Ph); 4.19 (br, 1 H, NHCH\( _2 \)); 3.81 (dd, \( J = 4.0, J = 9.1 \), 1 H, NHCH\( ^3 \)H\( ^3 \)Ph); 3.50 (dd, \( J = 9.4, J = 6.4 \), 1 H, NHCH\( ^3 \)H\( ^3 \)Ph); 3.17-3.34 (m, 2 H, NHCH\( _2 \)); 2.16 (app q, \( J = 6.4 \), 2 H, CH\( _2 \)CH\( _2 \)CHCH\( _2 \)); 1.39 (s, 9 H, C(CH\( _3 \))\( _3 \)).

\( ^{13} \text{C NMR (MeOH} d_4) \) – 172.8 (C=O); 157.6 (C=O); 139.2 (C); 136.6 (CH); 129.4 (CH); 128.9 (CH); 128.8 (CH); 117.1 (CH\( _2 \)); 80.9 (C); 74.1 (CH\( _2 \)); 71.1 (CH\( _2 \)); 56.2 (CH); 39.9 (CH\( _2 \)); 34.6 (CH\( _2 \)); 28.7 (CH\( _3 \)).

HRMS calc. for C\( _{22} \)H\( _{30} \)N\(_4 \)O\(_5 \)S – 371.19413 (M+Na); found 371.19302

IR, solution cell, DCM (cm\(^{-1}\)) – 3425; 2978; 2872; 1713; 1674.

\( [\alpha]^{19}_D +9.4 \) (c 0.64, CHCl\(_3 \)).

Compound 1f
BocArg(diZ)OH [869 mg, 1.6 mmol] was reacted with homoallyl amine according to protocol I. Purification yielded a waxy solid [520 mg, 54%].

\[ \text{1f} \]

\(^1\)H NMR (DMSO \(d_6\)) – 9.18 (br s, \((HN)_2C=N\)); 7.78 (app t, \(J = 5.5\), \(HNCH_2\)); 7.26-7.43 (m, 10 H, Ar-H); 6.77 (d, \(J = 8.1\), 1 H, \(NHCH\)); 5.71 (app ddt, \(J = 17.1\), \(J = 10.3\), \(J = 6.7\), 1 H, \(H_2CCH=CH_2\)); 5.23 (s, 2 H, \(CH_2Ph\)); 5.05 (s, 2 H, \(CH_2Ph\)); 4.99 (d, \(J = 17.1\), 1 H, \(CH=CH_{\text{trans}}\)); 4.95 (d, \(J = 9.5\), 1 H, \(CH=CH_{\text{cis}}\)); 3.85 (br d, 3 H, \(NHC\)); 2.95-3.20 (m, 2 H, \(CONHC\)); 2.10 (app q, \(J = 6.5\), 2 H, \(CH_2CHCH_2\)); 1.4-1.7 (m, 4 H, \(NHCHCH_2CH_2CH_2NH\)); 1.35 (s, 9 H, C(CH_3)_3).

\(^{13}\)C NMR (DMSO \(d_6\)) – 171.6 (C=O); 162.8 (C=O); 159.5 (app t, C=N); 155.1 (C=O); 154.9 (C=O); 137.0 (C); 135.8 (CH); 135.2 (CH); 128.4 (CH); 128.2 (CH); 128.19 (CH); 127.8 (CH); 127.78 (CH); 127.6 (CH); 116.1 (CH_2); 77.9 (C); 68.1 (CH_2); 66.0 (CH_2); 54.0 (CH); 44.3 (CH_2); 37.8 (CH_2); 33.3 (CH_2); 29.3 (CH_2); 28.1 (CH_3); 25.1 (CH_2).

IR, solution cell, DCM (cm\(^{-1}\)) – 3665; 3391; 3281; 3038; 2974; 2941; 1715; 1668; 1612; 1506.

HRMS calc. for C\(_{31}\)H\(_{41}\)N\(_5\)O\(_7\) – 596.30788 (M+H); found 596.308514.

[\(\alpha\)]\(^{25}\)D +15.1 (c 0.29, CHCl_3).

**Compound 1g**

BocLeuOH [1.0 g, 4.0 mmol], HATU [1.5 g, 3.9 mmol] and DIPEA [2 ml, 11.5 mmol] were stirred for 10 minutes in DMF [5 ml] and DCM [10 ml]. Homoallyl amine hydrochloride [395 mg, 3.66 mmol] and DIPEA [0.5 ml, 2.9 mmol] in DCM [2 ml] were added and the mixture monitored by LCMS. After 2 h the relative intensities of the peaks had stabilized. The solvent was removed under reduced pressure, DCM was added and worked up as described in Protocol I yielding a white waxy solid [940 mg, 89%].
\[1g\]

\(^1\)H NMR (MeOH \(d_4\), 400 MHz) – 5.81 (app ddt, \(J = 17.1, J = 10.3, J = 6.8\), 1 H, H\(_2\)CCH=CH\(_2\)); 5.10 (dd, \(J = 17.2, J = 1.6\), 1 H, H\(_2\)C=CH); 5.05 (d, \(J = 10.3\), 1 H, H\(_2\)C=CH); 4.05 (dd, \(J = 8.8, J = 6.1\), 1 H, NNCH); 3.15 – 3.33 (m, 2 H, NNCH\(_2\)); 2.26 (app q, \(J = 6.9\), 2 H, NNCH\(_2\)CH\(_2\)); 1.61 – 1.72 (m, 1 H, CH(CH\(_3\))\(_2\)); 1.52 (s, 9 H, C(CH\(_3\))\(_3\)); 0.93 – 0.97 (m, 6 H, CH(CH\(_3\))\(_2\)).

\(^{13}\)C NMR (MeOH \(d_4\), 100 MHz) – 176.1 (C=O); 137.0 (CH); 117.5 (CH\(_2\)); 81.0 (C); 55.1 (CH); 42.9 (CH\(_2\)); 40.2 (CH\(_2\)); 35.1 (CH\(_2\)); 29.1 (CH); 26.3 (CH); 23.8 (CH\(_3\)); 22.4 (CH\(_3\)).

IR, solution cell, DCM (cm\(^{-1}\)) – 3431; 3342; 3055; 2966; 2876; 1707; 1676; 1501.

HRMS calc. for C\(_{15}\)H\(_{28}\)N\(_2\)O\(_3\) – 285.21781 (M+H); found 285.21729.

\([\alpha]^{25}_D\) –39.2 (c 0.47, CHCl\(_3\)).

**Compound 2a**

PheOEt HCl [3.0 g, 13 mmol] was reacted with acryloyl chloride according to protocol II. In this case no column chromatography was required; two recrystallizations from ethyl acetate and petroleum ether proved sufficient, yielding white, needle-like crystals [78%].

\[2a\]

\(^1\)H NMR (MeOH \(d_4\)) – 7.17-7.29 (m, 5 H, Ar-\(H\)); 6.26 (dd, \(J = 9.5, J = 17.1\), 1 H, H\(_2\)CCH\(_2\)); 6.17 (dd, \(J = 2.5, J = 17.1\), 1 H, H\(_2\)CCH); 5.64 (dd, \(J = 2.5, J = 9.5\), 1 H, H\(_2\)CCH); 4.70 (dd, \(J = 6.1, J = 8.6\), 1 H, HNCH); 4.12 (app q, \(J = 7.3\), 2 H, OCH\(_2\)); 3.15 (dd, \(J = 6.1, J = 13.8\), 1 H, CH\(_2\)\(^9\)H\(_3\)Ph); 2.99 (dd, \(J = 8.6, J = 13.8\), 1 H, CH\(_2\)\(^9\)H\(_3\)Ph); 1.18 (app t, \(J = 7.1\), 3 H, CH\(_2\)CH\(_3\)).

\(^{13}\)C NMR (MeOH \(d_4\)) – 173.0 (C=O); 167.9 (C=O); 138.1 (C); 131.4 (CH); 130.2 (CH); 129.5 (CH); 127.9 (CH); 127.4 (CH\(_2\)); 62.4 (CH\(_2\)); 55.5 (CH); 38.5 (CH\(_2\)); 14.4 (CH\(_3\)).

IR, solution cell, DCM (cm\(^{-1}\)) – 3420; 2986; 2359; 1735; 1676; 1632; 1506.
HRMS calc. for C₁₄H₁₇NO₃ – 270.11061 (M+Na); found 270.11119.

\[\alpha\]^{25}_{D} +133.6 (c 0.24, CHCl₃).

**Compound 2b**

ValOEt HCl [1.7 g, 9.4 mmol] was reacted with acryloyl chloride according to protocol II. Purification yielded a yellow liquid [1.0 g, 54%].

![Structure of 2b]

\(^1\)H NMR (MeOH \(d_4\)) – 6.40 (dd, \(J = 10.1, J = 17.1, 1\) H, H₂CCH); 6.24 (dd, \(J = 2.0, J = 17.1, 1\) H, H₂CCH); 5.68 (dd, \(J = 2.0, J = 10.1, 1\) H, H₂CCH); 4.37 (d, \(J = 6.1, 1\) H, HNCH); 4.14-4.23 (m, 2 H, OCH₂); 2.16 (app oct, \(J = 6.7, 1\) H, CH(CH₃)₂); 1.26 (app t, \(J = 7.1, CH₂CH₃\)); 0.96 (d, \(J = 6.8, 6\) H, CH(CH₃)₂).

\(^{13}\)C NMR (MeOH \(d_4\)) – 173.0 (C=O); 168.2 (C=O); 131.5 (CH); 127.5 (CH₂); 62.2 (CH₂); 59.4 (CH); 31.8 (CH); 19.5 (CH₃); 18.5 (CH₃); 14.5 (CH₃).

IR, solution cell, DCM (cm\(^{-1}\)) – 3678; 3425; 2972; 1732; 1678; 1626; 1510.

HRMS calc. for C₁₀H₁₇NO₃ – 222.11061 (M+Na); found 222.11040.

\[\alpha\]^{16}_{D} +19.7 (c 1.24, CHCl₃).

**Compound 2c**

BocSer(Bzl)OH [1.8 g, 6.1 mmol] was stirred in methanol [10 ml] and toluene [10 ml]. 2 M TMS diazomethane in hexanes [3.1 ml, 6.2 mmol] was added. Acetic acid was then dripped in until the yellow colour disappeared. The solvent was removed under reduced pressure, and a further 20 ml of toluene added. This was removed under reduced pressure in order to azeotrope off impurities. TFA [5 ml] and DCM [12 ml] were then added and the mixture monitored by LCMS until the Boc protected material could no longer be seen. Toluene [10 ml] was added and the solvents removed under reduced pressure. This was repeated once. The resultant material was dissolved in DCM [40 ml] and triethylamine [0.12 ml, 0.76 mmol] added. Acryloyl chloride in DCM [0.17 mmol per ml] was slowly added until the starting free amine was no longer visible by LCMS. The solvent was removed under reduced pressure and the material worked up as described in protocol II, yielding a clear viscous liquid [1.24 g, 77%].
$^1$H NMR (CDCl$_3$, 400 MHz) – 7.25 – 7.36 (m, 5 H, Ph-H); 6.47 (d, J = 7.3, 1 H, NH); 6.34 (dd, J = 1.4, J = 17.0, 1 H, H$^a$H$^b$C=CH); 6.16 (dd, J = 10.2, J = 17.0, 1 H, H$_2$C=CH); 5.69 (dd, J = 1.4, J = 10.2, 1 H, H$^a$H$^b$C=CH); 4.84 (app dt, J = 3.1, J = 8.2, 1 H, NHCH); 4.51 (AB q, 2 H, CH$_2$OCH$_2$Ph); 3.93 (s, 3 H, OMe); 3.93 (dd, J = 3.1, J = 9.5, 1 H, CHCH$^a$H$^b$O).

$^{13}$C NMR (CDCl$_3$, 100 MHz) – 171.1 (C=O); 165.6 (C=O); 137.9 (C); 130.7 (CH); 128.9 (CH); 128.3 (CH); 128.0 (CH); 127.7 (CH$_2$); 73.7 (CH$_2$); 70.1 (CH$_2$); 53.1 (CH); 53.0 (CH$_3$).

IR, solution cell, DCM (cm$^{-1}$) – 3427; 3069; 3034; 2984; 2947; 2874; 1746; 1678; 1628; 1508.

HRMS calc. for C$_{14}$H$_{17}$NO$_4$ - 264.12358 (M+H); found 264.12226.

$[\alpha]^{25}_D$ +47.2 ($c$ 0.46 CHCl$_3$)

Compound 2d

BocThr(Bzl)OH [472 mg, 1.5 mmol] treated with a series of reagents, as described for Compound 2c. The product was obtained as a clear viscous liquid [414 mg, 99%].

$^1$H NMR (CDCl$_3$, 400 MHz) – 7.20 – 7.32 (m, 5 H, Ph-H); 6.30 (dd, J = 1.5, J = 17.0, 1 H, H$^a$H$^b$C=CH); 6.25 (br s, 1 H, NH); 6.16 (dd, J = 10.2, J = 17.0, 1 H, H$_2$C=CH); 5.66 (dd, J = 1.5, J = 10.2, 1 H, H$^a$H$^b$C=CH); 4.66 (dd, J = 2.3, J = 9.3, 1 H, NHCH); 4.54 (d, J = 11.8, 1 H, CH$^a$H$^b$Ph); 4.34 (d, J = 11.8, 1 H, CH$^a$H$^b$Ph); 4.13 (dq, J = 2.3, J = 6.3, 1 H, CH(CH$_3$)OCH$_2$); 3.63 (s, 3 H, OMe); 1.19 (d, J = 6.3, 3 H, CH$_3$CHOCH$_2$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) – 171.4 (C=O); 166.1 (C=O); 138.1 (C); 130.7 (CH); 128.8 (CH); 128.3 (CH); 128.2 (CH); 127.8 (CH$_2$); 74.8 (CH$_2$); 71.3 (CH$_2$); 57.0 (CH$_3$); 52.7 (CH$_3$); 16.7 (CH$_3$).

IR, solution cell, DCM (cm$^{-1}$) – 3427; 3069; 3034; 2984; 2947; 2874; 1746; 1678; 1628; 1508.

HRMS calc. for C$_{15}$H$_{19}$NO$_4$ - 278.13923 (M+H); found 278.13839.
Compound 2e
ProOMe HCl [415 mg, 2.5 mmol] was reacted with acryloyl chloride according to protocol II. Purification yielded a clear liquid [340 mg, 72%]. This consisted of a 3:1 mix of rotamers, clearly visible by NMR. Heating did not result in coalescence of peaks and thus the spectrum for each compound is reported separately.

Conformation 1 (75%)

$^1$H NMR (CDCl$_3$, 400 MHz) – 6.44 (dd, $J = 10.0$, $J = 16.8$, 1 H, CHCH$_2$); 6.35 (dd, $J = 2.2$, $J = 16.8$, 1 H, CHCH$_2$); 5.67 (dd, $J = 10.0$, $J = 2.2$, 1 H, CHCH$_2$); 4.51 (dd, $J = 4.0$, $J = 8.6$, 1 H, NCH); 3.69 (s, 3 H, OMe); 3.55-3.77 (m, 2 H, NCH$_2$); 1.91-2.27 (m, 4 H, NCH$_2$CH$_2$CH$_2$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) – 172.6 (C=O); 164.4 (C=O); 128.4 (CH$_2$); 128.0 (CH); 58.8 (CH$_3$); 52.1 (CH); 46.9 (CH$_2$); 29.1 (CH$_2$); 24.7 (CH$_2$).

Conformation 2 (25%)

$^1$H NMR (CDCl$_3$, 400 MHz) – 6.33 (dd, $J = 2.0$, $J = 16.9$, 1 H, CHCH$_2$); 6.20 (dd, $J = 10.3$, $J = 16.7$, 1 H, CHCH$_2$); 5.62 (dd, $J = 2.0$, $J = 10.2$, 1 H, CHCH$_2$); 4.48 (dd, $J = 2.8$, $J = 8.6$, 1 H, NCH); 3.70 (s, 3 H, OMe); 3.55-3.77 (m, 2 H, NCH$_2$); 1.91-2.27 (m, 4 H, NCH$_2$CH$_2$CH$_2$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) – 172.5 (C=O); 164.8 (C=O); 128.1 (CH$_2$); 128.0 (CH); 59.2 (CH$_3$); 52.5 (CH); 46.4 (CH$_2$); 31.3 (CH$_2$); 22.5 (CH$_2$).

IR, solution cell, DCM (cm$^{-1}$) – 3476; 2959; 2883; 1744; 1649; 1609.

HRMS calc. for C$_9$H$_{13}$NO$_3$ – 206.07931 (M+Na); found 206.07928.

$[\alpha]^{25}_D$ +13.0 (c 0.70, CHCl$_3$)

Compound 4a
1a [80 mg, 0.25 mmol], 2a [50 mg, 0.2 mmol] and Grubbs second generation catalyst [32 mg, 19 mol%] were subjected to microwave radiation [300 W, 80 °C] for 2 h. Purification by column chromatography yielded a brown waxy solid [92 mg, 86%].

\[ \text{O} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{O} \]

\[ \text{OEt} \]

**4a**

\[ 1 \text{H NMR (CDCl}_3, 400 MHz) – 7.14 – 7.28 (m, 5 H, Ph-H); 6.68 (br, 1 H, NH); 6.62 (app quintet, } J = 7.9, 1 H, \text{CH}_2\text{CH=CH}) \text{H}; 6.45 (br, 1 H, NH); 5.64 (d, } J = 15.4, 1 H, \text{CH}_2\text{CH=CH}) \text{H}; 5.53 (br, 1 H, NH); 4.90 (app dd, } J = 6.3, J = 14.0, 1 H, \text{NCHCOOEt}); 4.48 (br app q, } J = 6.6, 1 H, \text{BocNCH}) \text{H}; 4.16 (app q, } J = 7.1, 2 H, \text{OCH}_2\text{CH}_3) \text{H}; 3.17 – 3.25 \text{ (br m, 2 H, NHCH}_2\text{CH}_2) \text{H}; 3.06 – 3.17 (m, 2 H, EtO}_2\text{CHC}_2\text{H}_3) \text{H}; 2.99 (d, } J = 7.3, 2 H, \text{BocNHCHCH}_2\text{H}_2) \text{H}; 2.10 – 2.30 (br m, 2 H, NHCH}_2\text{CH}_2) \text{H}; 1.36 (s, 9 H, C(CH}_3)_3) \text{H}; 1.22 \text{ (app t, } J = 7.1, 2 H, \text{OCH}_2\text{CH}_3). \]

\[ 1^3 \text{C NMR (CDCl}_3) – 172.2 (C=O); 171.8 (C=O); 165.1 (C=O); 155.7 (C=O); 141.1 (CH); 137.0 (C); 136.1 (C); 129.5 (CH); 129.3 (CH); 128.5 (2CH); 127.0 (CH); 126.8 (CH); 124.9 (CH); 80.0 (C); 61.5 (CH}_2) \text{H}; 55.8 (CH); 53.9 (CH); 39.2 (CH}_2) \text{H}; 38.1 \text{ (CH}_2) \text{H}; 37.6 (CH}_2) \text{H}; 31.9 (CH}_2) \text{H}; 28.3 (CH}_3) \text{H}; 14.1 (CH}_3). \]

IR, solution cell, DCM (cm\(^{-1}\)) – 3425; 2980; 2936; 1726; 1501.

HRMS calc. for C\(_{30}\)H\(_{39}\)N\(_3\)O\(_6\) – 538.29170 (M+H); found 538.29181.

**Compound 4b**

1b, 2a and DMF (3 drops) were reacted according to protocol III, except without degassing and for two 15-minute periods. Purification yielded a red waxy solid [28 mg, 41%].

\[ \text{O} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{O} \]

\[ \text{OEt} \]

**4b**

\[ 1^1 \text{H NMR (DMSO } d_6, 353 K, 400 MHz) – 8.02 (d, } J = 7.5, 1 H, \text{N-H}) \text{H}; 7.75 (app t, } J = 5.8, 1 H, \text{N-H}) \text{H}; 7.27 (d, } J = 8.0, 2 H, \text{Ts-H}) \text{H}; 7.19-7.27 (m, 5 H, Phe-H); 7.09 (d, } J =
7.8, 5 H, Ts-H); 6.65 (br, 1 H, N-H); 6.57 (dt, J = 15.5, J = 7.0, 1 H, CH2CH=CH); 6.00 (d, J = 15.5, 1 H, CH2CH=CH); 4.57 (dt, J = 6.7, J = 8.0, 1 H, NHCH2CH2Ph); 4.24 (dt, J = 5.7, J = 8.4, 1 H, NHCH2CH2Im); 4.05 (app q, J = 7.0, 2 H, OCH2CH3); 3.10-3.22 (m, 2 H, CONCH2); 3.10 (dd, J = 15.1, J = 5.3, 1 H, CHaCHbAr); 3.05 (dd, J = 14.2, J = 6.2, 1 H, CHaCHbAr); 2.95 (dd, J = 13.9, J = 8.5, 1 H, CHaCHbAr); 2.29 (s, 3 H, ArCH3); 1.34 (s, 9 H, C(C3H3)3); 1.12 (app t, J = 7.1, 3 H, OCH2CH3).

13C NMR (CDCl3) – 171.9 (C=O); 171.2 (C=O); 165.1 (C=O); 155.6 (C=O); 141.4; 140.5; 136.4; 136.1; 134.7; 130.5 (CH); 129.3 (CH); 128.5 (CH); 127.5 (CH); 127.0 (CH); 125.2 (CH); 114.9; 80.2 (C); 61.5 (CH2); 54.1 (CH); 53.3 (CH); 38.0 (CH2); 37.9 (CH2); 32.1 (CH2); 30.3 (CH2); 28.3 (CH3); 21.7 (CH3); 14.1 (CH3).

IR, solution cell, DCM (cm−1) – 3422; 3296; 2932; 1762; 1674; 1501.

HRMS calc. for C34H43N5O8S – 682.29051 (M+H); found 682.291967.

Compound 4c

1c and 2a were reacted according to protocol III. Purification yielded a pale brown waxy solid [31 mg, 51%].

\[
\text{4c}
\]

1H NMR (CDCl3) – 7.09 – 7.30 (m, 9 H, Ar-H); 6.74 (dt, J = 15.2, J = 6.9, 1 H, CH2CH=CH); 6.55 (br t, 1 H, NHCH2); 6.34 (br d, J = 6.8, 1 H, NH(Ph)); 5.82 (d, J = 15.4, 1 H, CH2CH=CH); 5.45 (br, 1 H, NH(Cys)); 4.91 (dt, J = 7.6, J = 6.1, 1 H, NHCH(Ph)); 4.27 (br m, 1 H, NHCH(Cys)); 4.14 (app q, J = 7.1, 2 H, OCH2CH3); 3.30 – 3.40 (m, 2 H, CHCH2S); 3.10 – 3.14 (m, 2 H, CHCH2Ph); 2.80 (dd, J = 6.0, J = 13.9, 1 H, CHCH2HbS); 2.70 (dd, J = 6.8, J = 13.9, 1 H, CHCH2HbS); 2.36 (app q, J = 6.5, 2 H, NHCH2CH2); 2.35 (s, 3 H, PheMe); 1.44 (s, 9 H, C(CH3)3); 1.22 (app t, J = 7.1, OCH2CH3).

13C NMR (CDCl3) – 171.9 (C=O); 171.0 (C=O); 165.1 (C=O); 155.6 (C=O); 141.1 (CH); 136.9 (C); 136.0 (C); 134.9 (C); 129.33 (CH); 129.29 (CH); 128.9 (CH); 128.5 (CH); 127.1 (CH); 125.2 (CH); 80.3 (C); 61.6 (CH2); 53.8 (CH); 53.3 (CH); 38.0
Compound 4d

1d and 2a were reacted according to protocol III. Purification yielded a pale brown waxy solid [53 mg, 82%].

\[
\text{IR, solution cell, DCM (cm}^{-1}\text{) – 3422; 2980; 2932; 2332; 1726; 1678; 1504.}
\]

HRMS calc. for C_{32}H_{43}N_{3}O_{6}S – 598.29507 (M+H); found 598.29373.

Compound 4e

1e [39 mg, 0.11 mmol] and 2a [25 mg, 0.10 mmol] were reacted according to protocol III. Purification yielded a brown waxy solid [43 mg, 73%].
\[ \text{4e} \]

\[ ^1H \text{ NMR (MeOH} d_4, 400 \text{ MHz)} - 7.21 - 7.36 (m, 10 H, Ph-H); 6.72 (app dt, } J = 15.5, \ J = 6.9, 1 \ H, CH_2CH=CH); 6.01 (d, } J = 15.5, 1 \ H, CH_2CH=CH); 4.71 (dd, } J = 8.4, } J = 6.2, 1 \ H, NCHCOOEt); 4.47 - 4.57 (m, 2 H, CH_2OCH_2Ph); 4.26 (m, 1 \ H, BocNHCH_2); 4.13 (app q, } J = 7.1, 2 \ H, OCH_2CH_3); 3.63 - 3.72 (m, 2 H, CHCH_2O); 3.23 - 3.35 (m, 2 H, NHCH_2); 3.15 (dd, } J = 6.2, } J = 13.8, 1 \ H, CH^aH^bPh); 3.01 (dd, } J = 8.5, } J = 13.8, 1 \ H, CH^aH^bPh); 2.38 (app q, } J = 6.6, 2 \ H, NHCH_2CH_2); 1.45 (s, 9 H, C(CH_3)_3); 1.17 (app t, } J = 7.1, OCH_2CH_3).

\[ ^13C \text{ NMR (MeOH} d_4, 100 \text{ MHz)} - 173.5 (C=O); 173.4 (C=O); 168.5 (C=O); 158.1 (C=O); 143.3 (CH); 139.7 (C); 138.5 (C); 130.7 (CH); 129.8 (CH); 129.3 (CH); 129.2 (CH); 128.3 (CH); 126.3 (CH); 81.3 (C); 74.5 (CH_2); 71.5 (CH_2); 62.8 (CH_2); 56.5 (CH); 55.9 (CH); 39.7 (CH_2); 39.0 (CH_2); 31.1 (CH_2); 29.1 (CH_3); 14.8 (CH_3).

IR, solution cell, DCM (cm\(^{-1}\)) – 3423; 3059; 2980; 2936; 2870; 1722; 1678; 1499. HRMS calc. for C\(_{31}\)H\(_{41}\)N\(_3\)O\(_7\) – 568.30226 (M+H); found 568.30133.

Compound 4f

1f [134 mg, 0.23 mmol], 2a [52 mg, 0.21 mmol] and grubbs catalyst [21 mg, 12 mol\%] were refluxed in DCM for 96 h, by which time 3 was no longer visible. Purification yielded a brick red waxy solid [120 mg, 70%].

\[ \text{4f} \]

\[ ^1H \text{ NMR (400 MHz, 353 K) (DMSO} d_6) - 8.98 (s, 2 H, (HN)_2C=N); 7.93 (d, 1 H, NHCHCH_2Ph); 7.56 (br t, 1 H, NHCH_2); 7.19-7.40 (m, 15 H, Ar-H); 6.57 (app dt, 1
H, J = 15.5, J = 6.9, CH2CH=CH); 6.23 (br d, 1 H, NHCHCH2CH2); 5.98 (d, J = 15.5, 1 H, CH2CH=CH); 5.25 (app s, 2H, OCH2Ph); 5.07 (app s, 2H, OCH2Ph); 4.58 (ddd, J = 8.4, J = 7.8, J = 6.2, 1 H, NHCH2CH2Ph); 4.05 (app q, J = 7.1, 2 H, OCH2); 3.87 (m, 3 H, NHCHCH2CH2CH2N=C); 3.12 (m , 2 H, CONC); 3.05 (dd, J = 6.2, J = 12.9, 1 H, CHPh); 2.98 (dd, J = 8.4, J = 14.0, 1 H, CHPh); 2.23 (app q, 2 H, J = 6.8, H2CCH=C); 1.45-1.65 (m, 4 H, NHCHC); 1.36 (s, 9 H, C(CH3)3); 1.12 (app t, J = 7.1, 3 H, OCH2CH3).

13C NMR (CDCl3) – 172.0 (C=O); 171.7 (C=O); 165.1 (C=O); 163.4 (C=O); 160.9 (C=N); 155.8 (C=O); 155.5 (C=O); 141.3 (CH); 136.4 (C); 136.0 (C); 134.6 (C); 129.3 (CH); 128.8 (CH); 128.6 (CH); 128.5 (CH); 128.3 (CH); 128.2 (CH); 127.0 (CH); 124.9 (CH); 79.6 (C); 69.0 (CH2); 67.2 (CH2); 61.5 (CH2); 53.5 (CH); 53.2 (CH); 44.1 (CH2); 37.9 (CH2); 37.7 (CH2); 31.9 (CH2); 29.0 (CH2); 28.4 (CH3); 24.5 (CH2); 14.1 (CH3).

IR, solution cell, DCM (cm-1) – 3391; 2976; 2939; 1719; 1676; 1611; 1504.

HRMS calc. for C43H54N6O10 – 815.39742 (M+H); found 815.397854.

Compound 4g

1a [70 mg, 0.22 mmol] and 2b [40 mg, 0.20 mmol] were reacted according to protocol III. Purification yielded a brown waxy solid [33 mg, 34%].

\[
\text{4g}
\]

1H NMR (CDCl3, 400 MHz) – 7.22 – 7.32 (m, 5 H, Ph-H); 6.68 (dt, J = 15.2, J = 6.7, 1 H, CH2CH=CH); 6.52 (br d, 1 H, NH(Phe)); 6.29 (br t, 1 H, NH(Val)); 4.65 (dd, J = 4.9, J = 8.8, 1 H, NHCH(Val)); 4.42 (br m, 1 H, NHCH(Phe)); 4.18 – 4.42 (m, 2 H, OCH2CH3); 3.20 – 3.40 (m, 2 H, NHCH2); 3.04 (d, J = 7.1, CHCH2); 2.15 – 2.35 (m, 3 H, NHCH2CH2 and CH(CH3)2 superimposed); 1.40 (s, 9 H, C(CH3)3); 1.32 (app t, J = 7.1, OCH2CH3); 0.98 (app t, J = 7.2, CH(CH3)2).

13C NMR (MeOH d4, 100 MHz) – 174.8 (C=O); 173.5 (C=O); 168.8 (C=O); 158.0 (C=O); 143.26 (CH); 139.0 (C); 130.8 (CH); 129.8 (CH); 128.1 (CH); 126.4 (CH); 81.0 (C); 62.6 (CH2); 59.7 (CH); 58.0 (CH); 40.0 (CH2); 39.5 (CH2); 33.2 (CH2); 32.3 (CH2); 29.1 (CH3); 19.9 (CH3); 19.0 (CH3); 15.0 (CH3).
IR, solution cell, DCM (cm\(^{-1}\)) – 3427; 3329; 3057; 2974; 2936; 1726; 1678; 1504.

HRMS calc. for C\(_{26}H_{39}N_{3}O_{6}\) – 490.29170 (M+H); found 490.29253.

Compound 4h

1g [32 mg, 0.11 mmol] and 2c [26 mg, 0.10 mmol] were reacted according to protocol III. Purification yielded a pale brown waxy solid [39 mg, 75%].

\[
\text{4h}
\]

\(^1\)H NMR (CDCl\(_3\), 400 MHz) – 7.19 – 7.29 (m, 5 H, Ph-H); 6.70 (app dt, \(J = 15.3, J = 6.9\), 1 H, CH\(_2\)CH=CH); 6.70 (br s, 1 H, NH(Ser)); 6.59 (br s, 1 H, NHCH\(_2\)); 5.84 (d, \(J = 15.4\), 1 H, CH\(_2\)CH=CH\(_2\)); 5.14 (br d, \(J = 5.9\), 1 H, NH(Leu)); 4.77 (app dt, \(J = 4.8\), \(J = 3.4\), 1 H, NHCH(Ser)); 4.48 (d, \(J = 12.2\), 1 H, CH\(_2\)Ph); 4.41 (d, \(J = 12.2\), 1 H, CH\(_2\)Ph); 3.84 (dd, \(J = 9.6\), 1 H, CHCH\(_2\)); 3.67 (s, 3 H, OMe); 3.64 (dd, \(J = 9.6\), 1 H, CHCH\(_2\)); 3.24 – 3.37 (m, 2 H, NHC\(_2\)); 2.31 (app q, \(J = 6.5\), 2 H, NHCH\(_2\)CH\(_2\)); 1.51 – 1.60 (m, 2 H, CHCH\(_2\)CH\(_2\)); 1.35 – 1.45 (m, 1 H, CH(CH\(_3\))\(_2\)); 1.35 (s, 9 H, C(CH\(_3\))\(_3\)); 0.83 – 0.86 (m, 6 H, CH(CH\(_3\))\(_2\)).

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz) – 173.4 (C=O); 171.4 (C=O); 170.7\(^\dagger\) (C=O); 165.7 (C=O); 164.2\(^\dagger\) (C=O); 141.8 (CH); 137.9 (C); 137.8\(^\dagger\) (C); 133.5\(^\dagger\) (CH); 128.9\(^\dagger\) (CH); 128.8 (CH); 128.4\(^\dagger\) (CH); 128.3 (CH); 138.1\(^\dagger\) (CH); 128.0 (CH); 125.6 (CH); 80.4 (C); 73.74\(^\dagger\) (CH\(_2\)); 73.66 (CH\(_2\)); 70.1 (CH\(_2\)); 69.8\(^\dagger\) (CH\(_2\)); 53.3 (CH); 53.04 (CH); 52.96 (CH\(_3\)); 42.5\(^\dagger\) (CH\(_2\)); 41.8 (CH\(_2\)); 38.2 (CH\(_2\)); 32.5 (CH\(_2\)); 28.7 (CH\(_3\)); 25.2 (CH); 23.3 (CH\(_3\)); 22.4 (CH\(_3\)). \(^\dagger\)Minor peaks resulting from diastereoisomer.

IR, solution cell, DCM (cm\(^{-1}\)) – 3429; 2957; 2873; 1746; 1678; 1504.

HRMS calc. for C\(_{27}H_{41}N_{3}O_{7}\) - 520.30226 (M+H); found 520.30055.

Compound 4i

1g [32 mg, 0.11 mmol] and 2d [28 mg, 0.10 mmol] were reacted according to protocol III. Purification yielded a pale brown waxy solid [33 mg, 61%].


$^1$H NMR (CDCl$_3$, 400 MHz) – 7.16 – 7.29 (m, 5 H, Ph-H); 6.72 (app dt, $J = 15.1, J = 7.0, 1$ H, CH$_2$CH$=CH$); 6.45 (br s, 1 H, NH); 6.40 (br d, $J = 8.7, 1$ H, NH); 5.88 (d, $J = 15.4, 1$ H, CH$_2$CH=CH$)$; 5.05 (br s, 1 H, NH); 4.69 (dd, $J = 2.3, J = 9.3, 1$ H, NHCHCO$_2$Me); 4.51 (d, $J = 11.8, 1$ H, CH$_a^aH^b$Ph); 4.32 (d, $J = 11.8, 1$ H, CH$_a^aH^b$Ph); 4.09 (dq, $J = 2.3, J = 6.3, 1$ H, CH(CH$_3$)OCH$_2$); 4.06 (br s, 1 H, NHCHCH$_2$); 3.60 (s, 3 H, OMe); 3.23 – 3.38 (m, 2 H, NHCHCH$_2$); 2.32 (app q, $J = 6.7, 2$ H, NHCH$_2$CH$_2$); 1.51 – 1.60 (m, 2 H, CHCH$_2$CH$_2$); 1.37 - 1.44 (m, 1 H, CH(CH$_3$)$_2$); 1.16 (d, $J = 6.3, 3$ H, CH$_3$CHOCH$_2$); 0.83 – 0.86 (m, 6 H, CH(CH$_3$)$_2$).

$^{13}$C NMR (CDCl$_3$, 100 MHz) – 173.3 (C=O); 171.6 (C=O); 166.3 (C=O); 156.3 (C=O); 141.9 (CH); 138.2 (C); 128.8 (CH); 128.2 (CH); 125.6 (CH); 80.4 (C); 74.7 (CH); 71.2 (CH$_2$); 57.0 (CH$_3$); 53.4 (CH); 52.8 (CH); 41.7 (CH$_2$); 38.2 (CH$_2$); 32.6 (CH$_2$); 28.7 (CH$_3$); 25.2 (CH); 23.3 (CH$_3$); 22.4 (CH$_3$); 16.7 (CH$_3$).

IR, solution cell, DCM (cm$^{-1}$) – 3429; 2959; 2874; 1744; 1680; 1504.

HRMS calc. for C$_{28}$H$_{43}$N$_3$O$_7$ - 534.31791 (M+H); found 534.31871.

Compound 4j

1e and 2e were reacted according to protocol III. Purification yielded a pale brown waxy solid [25 mg, 50%].

$^1$H NMR (CDCl$_3$, 400 MHz) – 7.23-7.33 (m, 5 H, Ph-H); 6.81 (app quintet, $J = 7.1, 1$ H, CH$_2$CH=CH$)$; 6.51 (br, 1 H, NH$)$; 6.15 (d, $J = 15.2, 1$ H, CH$_2$CH=CH$)$; 5.29 (d, $J = 5.7, 1$ H, NHCH$)$; 4.51 (AB q, 2 H, OCH$_2$Ph$)$; 4.41 – 4.52 (br, 1 H, CHCO$_2$Me$)$; 4.20 (dt, $J = 4.4, J = 6.6, 1$ H, NHCH$)$; 3.84 (dd, $J = 9.4, J = 4.3, 1$ H, CHCH$^bH^b$O$)$; 3.68 (s, 3 H, OMe$)$; 3.64 (br t, 1 H, NHCH$^bH^b$CH$_2$CH$_2$); 3.56 (dd, $J = 6.5, J = 9.4, 1$ H, CHCH$^bH^b$O$)$; 3.51 – 3.57 (obs, 1 H, NCH$^bH^b$CH$_2$CH$_2$); 3.32-3.42 (m, 2 H, NHCH$_2$).
2.37 (app q, \( J = 6.1 \), 2 H, NHCH\(_2\)CH\(_2\)); 1.86-2.20 (m, 4 H, NCH\(_2\)CH\(_2\)CH\(_2\)); 1.41 (s, 9 H, C(CH\(_3\))\(_3\)).

\(^{13}\)C NMR (CDCl\(_3\)) – 172.7 (C=O); 170.3 (C=O); 164.4 (C=O); 155.5 (C=O); 142.6 (CH); 137.5 (C); 128.5 (CH); 127.9 (CH); 127.7 (CH); 123.0 (CH); 80.2 (C); 73.4 (CH\(_2\)); 69.9 (CH\(_2\)); 59.2\(^*\); 58.9 (CH\(_3\)); 52.6\(^*\); 54.0 (CH); 52.2 (CH); 46.8 (CH\(_2\)); 46.5\(^*\); 38.2 (CH\(_2\)); 32.3 (CH\(_2\)); 31.3\(^*\); 29.1 (CH\(_2\)); 28.3 (CH\(_3\)); 24.8 (CH\(_2\)); 22.5\(^*\).

\(^*\)Smaller peaks corresponding to a different conformation of the proline portion of the compound. Directly analogous to those seen in 2e.

IR, solution cell, DCM (cm\(^{-1}\)) – 3886; 3425; 2978; 2949; 2878; 1715; 1672; 1616.

HRMS calc. For C\(_{26}\)H\(_{36}\)N\(_3\)O\(_7\) – 504.27096 (M+H); found 504.27143.

**Compound 5a**

BocGlu(OcHex)OH [2.0 g, 6.2 mmol] was stirred in methanol [10 ml] and toluene [10 ml]. 2 M TMS diazomethane in hexanes [3.1 ml, 6.2 mmol] was added. Acetic acid was then dripped in until the yellow colour disappeared. The solvent was removed under reduced pressure, and a further 20 ml of toluene added. This was removed under reduced pressure in order to azeotrope off impurities. TFA [8 ml] and DCM [11 ml] were then added and the mixture monitored by LCMS until the Boc protected material could no longer be seen. Toluene [10 ml] was added and the solvents removed under reduced pressure. This was repeated once. The resultant material was dissolved in DMF [~5 ml] and added to a mixture of BocSer(Bzl)OH [502 mg, 1.7 mmol], HATU [646 mg, 1.7 mmol] and DIPEA [1 ml, 4 mmol] in DCM [4 ml] and DMF [8 ml]. This mixture had been left to preactivate for 10 minutes prior to this addition. The resultant mixture was monitored by LCMS, and the starting material (GluO\(^\text{t}\)HexOMe) was consumed after 0.5 h. The solvent was removed under reduced pressure, DCM was added and worked up as described in Protocol I yielding a viscous clear liquid [717 mg, 89%].
H NMR (CDCl₃, 400 MHz) – 7.29 – 7.38 (m, 5 H, Ph-H); 7.15 (br d, J = 5.4, 1 H, NH(Glu)); 5.42 (br s, 1 H, NH(Ser)); 4.75 (m, 1 H, OCH(CH₂)₂); 4.67 (dt, J = 5.1, J = 8.0, 1 H, NHCH(Glu)); 4.55 – 4.61 (m, 2 H, CH₂OCH₂Ph); 3.74 (br s, NHCH(Ser)); 3.93 (dd, J = 3.2, J = 9.3, 1 H, CHCH₂HPO); 3.74 (s, 3 H, OMe); 3.59 (dd, J = 6.3, J = 9.2, 1 H, CHCH₂HPO); 2.17 – 2.42 (m, 3 H, CH₃CH₂CO₂Hex); 1.80 – 1.87 (br m, 2 H, O₆Hex); 1.67 – 1.76 (br m, 2 H, O₆Hex); 1.50 – 1.59 (br m, 1 H, O₆Hex); 1.47 (s, 9 H, C(CH₃)₃); 1.38 (br m, 2 H, O₆Hex); 1.21 – 1.32 (br m, 1 H, O₆Hex).

¹³C NMR (CDCl₃, 100 MHz) – 172.4 (C=O); 172.3 (C=O); 170.7 (C=O); 155.8 (C=O); 137.8 (C); 128.9 (CH); 128.9 (CH); 128.3 (CH); 128.25 (CH); 80.7 (C); 72.9 (CH₂); 73.4 (CH); 70.2 (CH₂); 54.4 (CH); 52.9 (CH); 52.1 (CH₃); 32.0 (CH₂); 30.9 (CH₂); 28.7 (CH₃); 28.0 (CH₂); 25.7 (CH₂); 24.1 (CH₂).

IR, solution cell, DCM (cm⁻¹) – 3425; 2941; 2864; 1719; 1680; 1493.

HRMS calc. for C₂₇H₄₀N₂O₈ - 521.28628 (M+H); found 521.28751.

[α]²⁵ⁿᵈ +11.2 (c 0.59 CHCl₃)

**Compound 5b**

5a [808 mg, 1.6 mmol] was dissolved in DCM [7 ml] and TFA [5 ml]. The mixture monitored by LCMS until the Boc protected material could no longer be seen. Toluene [10 ml] was added and the solvents removed under reduced pressure. This was repeated once. The resultant material was dissolved in DCM [-20 ml] and a mixture of BocThr(Bzl)OH [525 mg, 1.7 mmol], HATU [646 mg, 1.7 mmol] and DIPEA [1 ml, 4 mmol] in DMF [2 ml] was added. This mixture had been left to preactivate for 10 minutes prior to this addition. The resultant mixture was monitored by LCMS, and the starting material (Ser(Bzl)GluO₆HexOMe) was consumed after 20
min. The solvent was removed under reduced pressure, DCM was added and worked up as described in Protocol I yielding a white waxy solid [644 mg, 58%].

![Chemical Structure](5b)

\[ \text{HN} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{NH} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{OMe} \]
\[ \text{O} \]
\[ \text{NH} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{O} \]

1H NMR (CDCl\textsubscript{3}, 400 MHz) – 7.24 – 7.37 (m, 10 H, Ph-H); 7.20 (d, J = 7.2, 1 H, NH); 7.18 (d, J = 7.8, 1 H, NH); 5.49 (d, J = 6.7, 1 H, NH); 4.71 – 4.79 (m, 1 H, OCH(CH\textsubscript{2})\textsubscript{2}); 4.64 (d, J = 11.4, 1 H, OCH\textsuperscript{a}H\textsuperscript{b}Ph); 4.16 (dt, J = 2.8, J = 7.6, 1 H, NHCH\textsubscript{3}); 4.58 – 4.66 (obs., 1 H, NHCH\textsubscript{3}); 4.55 (d, J = 11.8, 1 H, OCH\textsuperscript{a}H\textsuperscript{b}Ph); 4.51 (d, J = 11.4, 1 H, OCH\textsuperscript{a}H\textsuperscript{b}Ph); 4.45 (d, J = 11.8, 1 H, OCH\textsuperscript{a}H\textsuperscript{b}Ph); 4.30 (br d, 1 H, NHCH\textsuperscript{a}H\textsuperscript{b}Ph); 4.20 (br, 1 H, NHCH\textsubscript{3})(app thr)); 3.94 (dd, 1 H, J = 2.4, J = 8.9, CH\textsuperscript{a}H\textsuperscript{b}CH\textsubscript{2}CO\textsuperscript{2c}Hex); 1.67 – 1.89 (br m, 5 H, CH\textsuperscript{a}H\textsuperscript{b}CH\textsubscript{2}CO\textsuperscript{2c}Hex, O\textsuperscript{c}Hex superimposed); 1.50 – 1.60 (br m, 1 H, O\textsuperscript{d}Hex); 1.44 (s, 9 H, C(CH\textsubscript{3})\textsubscript{3}); 1.30 – 1.41 (m, 4 H, O\textsuperscript{d}Hex); 1.25 – 1.30 (obs., 1 H, O\textsuperscript{d}Hex); 1.25 (d, J = 6.4, 3 H, CH\textsubscript{3}CHOCH\textsubscript{2}).

\[ \text{13C NMR (CDCl\textsubscript{3}, 100 MHz) – 171.9 (C=O); 171.7 (C=O); 169.81 (C=O); 169.75 (C=O); 155.8 (C=O); 137.8 (C); 137.3 (C); 128.5 (CH); 128.4 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.6 (CH); 80.3 (C); 74.8 (CH); 73.5 (CH\textsubscript{2}); 72.9 (CH); 71.7 (CH\textsubscript{2}); 69.3 (CH\textsubscript{2}); 58.2 (CH); 52.9 (CH); 52.4 (CH); 51.7 (CH\textsubscript{2}); 31.6 (CH\textsubscript{2}); 30.5 (CH\textsubscript{2}); 28.3 (CH\textsubscript{3}); 27.3 (CH\textsubscript{2}); 25.3 (CH\textsubscript{2}); 23.7 (CH\textsubscript{2}); 15.6 (CH\textsubscript{3}). \]

IR, solution cell, DCM (cm\textsuperscript{-1}) – 3422; 3360; 2939; 2894; 1719; 1680; 1495.

HRMS calc. for C\textsubscript{38}H\textsubscript{53}N\textsubscript{3}O\textsubscript{10} - 712.38090 (M+H); found 712.38141.

\[ [\alpha]_{D}^{25} +11.3 (c 0.23 \text{ CHCl}\textsubscript{3}) \]

Compound 5
5b [490 mg, 0.69 mmol] was dissolved in DCM [8 ml] and TFA [6 ml]. The mixture monitored by LCMS until the Boc protected material could no longer be seen. Toluene [10 ml] was added and the solvents removed under reduced pressure. This was repeated once. The resultant material was dissolved in DCM [40 ml] and triethylamine [0.12 ml, 0.76 mmol] added. Acryloyl chloride in DCM [0.17 mmol per ml] was slowly added until the starting free amine was no longer visible by LCMS. The solvent was removed under reduced pressure and the material worked up as described in protocol II, yielding a white solid [359 mg, 78%].

![Chemical structure of 5b](image)

**1H NMR** (CDCl₃, 400 MHz) – 7.27 – 7.38 (m, 10 H, Ph-H); 7.20 (d, J = 7.5, 1 H, NH); 7.18 (d, J = 7.8, 1 H, NH); 6.64 (d, J = 6.5, 1 H, NH); 6.34 (dd, J = 1.2, J = 17.0, 1 H, H²H²C=CH); 6.19 (dd, J = 10.2, J = 17.0, 1 H, H₂C=CH); 5.71 (dd, J = 1.2, J = 10.2, 1 H, H²H²C=CH); 4.72 – 4.79 (m, 1 H, OCHO(CH₂)₂); 4.73 (d, J = 11.6, OCHOH²Ph); 4.69 (dd, J = 3.5, J = 6.6, 1 H, NHCHC(θ HCHC(θ)); 4.59 – 4.66 (obs., 1 H, NHCH); 4.63 (dt, J = 2.7, J = 7.6, 1 H, NHCH); 4.60 (d, J = 11.7, 1 H, OCHOH²Ph); 4.49 – 4.57 (m, 2 H, OCHO₂Ph); 4.23 (dq, J = 6.3, J = 3.7, 1 H, NHCHC(θ HCHC(θ)); 3.95 (dd, J = 3.3, J = 9.1, 1 H, CHCH²H²O); 3.23 (s, 3 H, OMe); 3.53 (dd, J = 5.7, J = 9.1, 1 H, CHCH²H²O); 2.08 – 2.35 (m, 3 H, CH²H²CH₂CO₂H; Hex); 1.65 – 1.90 (br m, 5 H, CH²H²CH₂CO₂H Hex, O²Hex superimposed); 1.50 -1.65 (br m, 1 H, O²Hex); 1.30 – 1.45 (br m, 4 H, O²Hex); 1.23 – 1.30 (obs., 1 H, O²Hex); 1.23 (d, J = 6.4, 3 H, CH₃CHOCH₂).

**13C NMR** (CDCl₃, 100 MHz) – 172.22 (C=O); 172.17 (C=O); 170.1 (C=O); 169.6 (C=O); 166.0 (C=O); 138.1 (C); 137.8 (C); 130.6 (CH); 128.83 (CH); 128.78 (CH); 128.23 (CH); 128.21 (CH); 128.11 (CH); 128.09 (CH); 127.8 (CH₂); 75.0 (CH); 73.8 (CH₂); 73.3 (CH); 72.1 (CH₂); 69.9 (CH₂); 56.9 (CH); 53.4 (CH); 52.7 (CH); 52.1 (CH₃); 32.0 (CH₂); 30.9 (CH₂); 27.6 (CH₂); 25.7 (CH₂); 24.1 (CH₂); 15.7 (CH₃).
Compound 6

1H [500 mg, 1.76 mmol] was dissolved in DCM [10 ml] and TFA [10 ml]. The mixture monitored by LCMS until the Boc protected material could no longer be seen. Toluene [20 ml] was added and the solvents removed under reduced pressure. This was repeated once. The resultant material was dissolved in DCM [5 ml] and DMF [10 ml] and a mixture of BocThr(Bzl)OH [525 mg, 1.7 mmol], HATU [646 mg, 1.7 mmol] and DIPEA [1 ml, 4 mmol] in DMF [5 ml] was added. This mixture had been left to preactivate for 10 minutes prior to this addition. The resultant mixture was monitored by LCMS, and the free amine was consumed after 35 min. The solvent was removed under reduced pressure, DCM was added and worked up as described in Protocol I yielding a cream waxy solid. The mixture was triturated in ether to remove tetramethyl urea, yielding a cream waxy solid [413 mg, 33%].

1H NMR (CDCl₃, 400 MHz) – 9.96 (br s, (HN)C=N); 9.31 (br s, (HN)C=N); 7.30 – 7.45 (m, 10 H, Ph-H); 6.60 (d, J = 8.2, NH(Leu)); 6.28 (br s, 1 H, NH); 5.73 (app ddt, J = 17.1, J = 10.3, J = 6.8, 1 H, H₂CCH=CH₂); 5.58 (br s, 1H, NH(Arg)); 5.27 (s, 2 H, (CH₂Ph)₂); 5.18 (AB q, 2 H, CH₃Ph); 5.04 – 5.09 (m, 2 H, H₂C=CH); 4.32 (app dt, J = 8.9, J = 7.1, 1 H, NHCH(Leu)); 4.15 (app q, J = 6.6, 1 H, NHCH(Arg)); 3.90 – 4.05 (m, 2 H, CH₂NCN₂); 3.16 – 3.37 (m, 2 H, NHCH₂CH₂), 2.22 (m, 2 H, NHCH₂CH₂); 1.60 – 1.70 (m, 4 H, CHCH₂CH₂CH₂); 1.45 (s, 9 H, C(CH₃)₃); 1.50 –
1.60 (m, 1 H, CH(CH$_3$)$_2$); 1.30 – 1.40 (m, 2 H, CHCH$_2$CH); 0.80 – 0.90 (m, 6 H, CH(CH$_3$)$_2$).

13C NMR (CDCl$_3$, 100 MHz) – 172.5 (C=O); 171.9 (C=O); 164.0 (C=O); 161.0 (C=O); 156.3 (C=N); 137.1 (C); 135.5 (CH); 135.0 (C); 129.32 (CH); 129.26 (CH); 128.9 (CH); 128.8 (CH); 128.4 (CH); 117.4 (CH$_2$); 80.6 (C); 69.4 (CH$_2$); 67.5 (CH$_2$); 55.0 (CH); 44.5 (CH$_2$); 40.8 (CH$_2$); 39.0 (CH$_2$); 34.0 (CH$_2$); 28.7 (CH$_3$); 28.4 (CH$_2$); 25.4 (CH$_2$); 25.1 (CH); 23.3 (CH$_3$); 22.2 (CH$_3$).

IR, solution cell, DCM (cm$^{-1}$) – 3391; 3281; 3072; 3036; 2961; 2875; 2330; 1717; 1672; 1612; 1508.

HRMS calc. for C$_{37}$H$_{52}$N$_6$O$_8$ - 425.24402 (M+H); found 425.24476.

$[\alpha]_{D}^{25}$ - 22.5 (c 0.18 CHCl$_3$)

Compound 7

6 [78 mg, 0.11 mmol] and 5 [67 mg, 0.10 mmol] were reacted according to protocol III. Purification yielded a pale brown waxy solid [51 mg, 38%]. Prior to this the HPLC yield was determined to be 67% by ELSD.
CH\textsuperscript{a}H\textsuperscript{b}NCN\textsubscript{2}); 3.69 (s, 3 H, OMe); 3.63 (dd, J = 5.2, J = 9.5, 1 H, CHCH\textsuperscript{a}H\textsuperscript{b}O); 3.45 – 3.52 (m, 1 H, NH\textsuperscript{a}H\textsuperscript{b}); 2.97 – 3.07 (m, 1 H, NH\textsuperscript{a}H\textsuperscript{b}); 2.40 – 2.50 (m, 1 H, CH\textsubscript{2}CH\textsuperscript{a}H\textsuperscript{b}CO\textsubscript{2}\textsuperscript{Hex} superimposed); 2.21 – 2.37 (m, 3 H, NHCH\textsubscript{2}CH\textsubscript{2}, CH\textsubscript{2}CH\textsuperscript{a}H\textsuperscript{b}CO\textsubscript{2}\textsuperscript{Hex} superimposed); 2.09 – 2.20 (m, 1 H, CH\textsuperscript{a}H\textsuperscript{b}CH\textsubscript{2}CO\textsubscript{2}\textsuperscript{Hex}); 1.80 – 1.91 (m, 1 H, CH\textsuperscript{a}H\textsuperscript{b}CH\textsubscript{2}CO\textsubscript{2}\textsuperscript{Hex}); 1.77 – 1.85 (br m, 2 H, O\textsuperscript{a}Hex); 1.68 – 1.72 (br m, 2 H, O\textsuperscript{a}Hex); 1.45 – 1.55 (br m, 5 H, CHCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2} (4 H), O\textsuperscript{a}Hex (1 H) superimposed); 1.42 (s, 9 H, C(CH\textsubscript{3})\textsubscript{3}); 1.2 – 1.4 (br m, 5 H, O\textsuperscript{a}Hex); 1.22 (d, J = 6.4, 3 H, CH\textsubscript{3}CHOCH\textsubscript{2}); 0.82 (d, J = 6.2, 3 H, CHC\textsuperscript{a}H\textsubscript{3}C\textsuperscript{b}H\textsubscript{3}); 0.76 (d, J = 6.2, 3 H, CHC\textsuperscript{a}H\textsubscript{3}C\textsuperscript{b}H\textsubscript{3}).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) – 172.7 (C=O); 172.3 (C=O); 171.84 (C=O); 171.77 (C=O); 170.3 (C=O); 170.0 (C=O); 166.9 (C=O); 163.6 (C=O); 160.9 (C=O); 156.1 (C=O); 155.7 (C=O); 140.6 (CH); 138.3 (C); 137.7 (C); 136.8 (C); 134.5 (C); 128.9 (CH); 128.8 (CH); 128.5 (CH); 128.4 (CH); 128.3 (CH); 128.2 (CH); 127.92 (CH); 127.87 (CH); 127.7 (CH); 127.6 (CH); 127.5 (CH); 127.3 (CH); 126.4 (CH); 80.3 (C); 74.5 (CH); 73.0 (CH); 72.8 (CH\textsubscript{2}); 71.7 (CH\textsubscript{2}); 69.2 (CH\textsubscript{2}); 69.0 (CH\textsubscript{2}); 67.0 (CH\textsubscript{2}); 58.4 (CH); 55.5 (CH); 52.8 (CH); 52.3 (CH\textsubscript{3}); 51.7 (CH); 51.4 (CH); 44.3 (CH\textsubscript{2}); 40.3 (CH\textsubscript{2}); 37.9 (CH\textsubscript{2}); 31.5 (CH\textsubscript{2}); 30.83 (CH\textsubscript{2}); 30.76 (CH\textsubscript{2}); 28.3 (CH\textsubscript{3}); 27.34 (CH\textsubscript{2}); 27.25 (CH\textsubscript{2}); 25.3 (CH\textsubscript{2}); 25.1 (CH\textsubscript{2}); 24.6 (CH); 23.7 (CH\textsubscript{2}); 22.8 (CH\textsubscript{3}); 21.5 (CH\textsubscript{3}); 16.1 (CH\textsubscript{3}).

IR, solution cell, DCM (cm\textsuperscript{-1}) – 3387; 3055; 2936; 2862; 2307; 1719; 1670; 1612; 1504.

HRMS calc. for C\textsubscript{71}H\textsubscript{95}N\textsubscript{9}O\textsubscript{17} - 1346.69238 (M+H); found 1346.69524.