C-H olefination of tryptophan residues in peptides; control of residue selectivity and peptide–amino acid crosslinking

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Supporting Information

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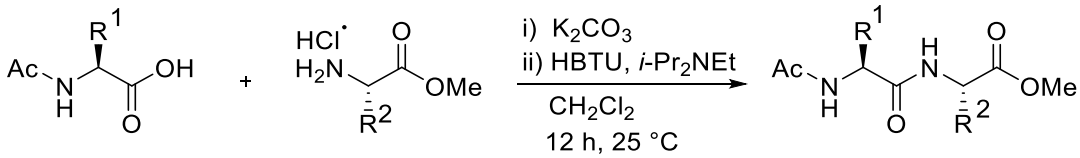
1. General experimental information

All manipulations were performed in oven-dried glassware in an atmosphere of air unless stated. All reagents and solvents were purchased from either Alfa Aesar, Fisher Scientific or Sigma Aldrich and used as supplied. Flash column chromatography was performed on silica gel (Fluorochem, silica gel 60 Å, particle size 40-63 μm). Thin layer chromatography was performed on glass-backed silica gel plates (2.5 x 7.5 cm; Merck, TLC silica gel 60 Å); compounds were visualised by exposure to UV light (254 nm) or using a permanganate stain. NMR spectra were recorded on a JEOL Eclipse 400 spectrometer at 298 K; chemical shifts are reported in parts per million and coupling constants are reported in Hz. For some compounds, assignments for ^{1}H and ^{13}C NMR peaks were aided by ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY and ^{1}H-^{13}C HMQC 2D NMR experiments. FTIR spectra were recorded in a diamond ATR cell using a Perkin-Elmer Spectrum 2 instrument or an Aligent Technologies Cary 630 instrument. Melting points were recorded on a Stuart SMP10 melting point apparatus and are uncorrected. High-resolution mass spectrometry was obtained from the EPSRC UK National Mass Spectrometry Facility at Swansea University on an LTQ Orbitrap XL 1, using positive electrospray ionisation (ESI+). HPLC was performed on a Waters Acquity UPLC instrument, in conjunction with a Waters Xevo-G2XS-QTOF for MS analysis, using a Restek Raptor C18 2.7 μm column with a gradient eluant from 0.1 % formic acid / 10% MeOH / H_2O to 0.1 % formic acid / MeOH over 10 minutes at a flow rate of 0.25 mL/min. Induction coupled plasma – mass spectroscopy (ICP-MS) analysis of Ag and Pd content was performed using a NexION® 1000 (PerkinElmer®, UK) operating in He KED mode to minimise polyatomic interferences. Peak hopping scans were used with 50 ms dwell time for Ag 106.905 and Pd 105.903 (corrected for Cd) AMU with 40 sweeps per reading and 3 replicate readings per sample. Calibration used external standards (10-1000 ppb) for Ag and Pd with the signal for In 114.904 AMU (20 ppb) as an internal standard. Concentration of samples and standards diluted in 1% low metal nitric acid (Sigma-Aldrich 225711) were determined from a calibration curve using a linear thru zero function.

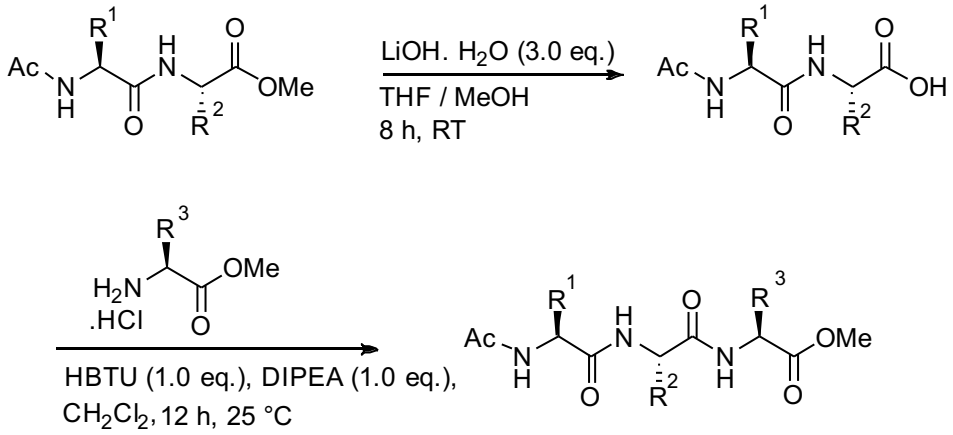
2. General experimental procedures

2.1. General procedure for the synthesis of dipeptides



The amino methyl ester hydrochloride (2.50 mmol) and K_2CO_3 (0.498 g, 3.60 mmol) were dissolved in distilled water (30 mL) and stirred for 10 min at room temperature. The free amino ester was then extracted with Et_2O (3 x 20 mL), unless the amino ester was L-tryptophan methyl ester, which was extracted with CH_2Cl_2 (3 x 20 mL). The solution of the amino ester was then dried ($MgSO_4$) and concentrated by rotary evaporation. The resulting oil was dissolved in CH_2Cl_2 (20 mL) and the appropriate *N*-acetyl amino acid (1.00 mmol), HBTU (0.379 g, 1.00 mmol) and *i*-Pr_2NEt (0.174 mL, 1.00 mmol) were then added to the reaction mixture, which was stirred for 12 h. The resulting suspension was filtered and washed with 1 M HCl (20 mL), sat. $NaHCO_3$ (3 x 20 mL) and H_2O (20 mL). The organic layers were then dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The resulting oil was recrystallized from CH_2Cl_2 / hexanes.

2.2. General procedure for the synthesis of tripeptides

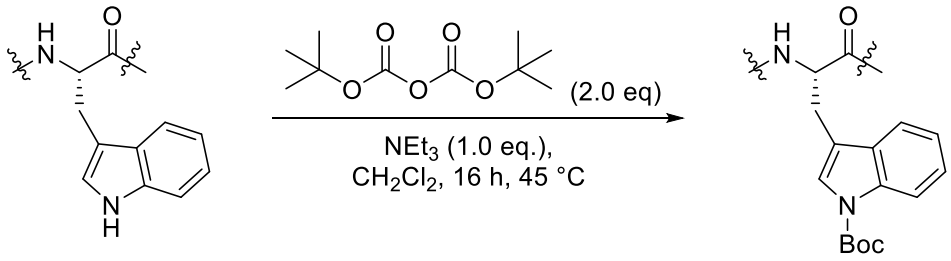


Lithium hydroxide monohydrate (0.101 g, 2.40 mmol) was dissolved in H_2O (2 mL) and added to a solution of the appropriate dipeptide ester (0.80 mmol) in a 3:1 mixture of THF / MeOH (8 mL). The solution was then stirred at room temperature for 8 h, followed by concentration to dryness *in vacuo*. The resulting residue was then acidified by the dropwise addition of 1 M HCl (~2 mL), before extracting with EtOAc (4 x 10 mL). The organic layers

were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give the dipeptide acid as an oil. The crude dipeptide acid was subsequently used without further purification.

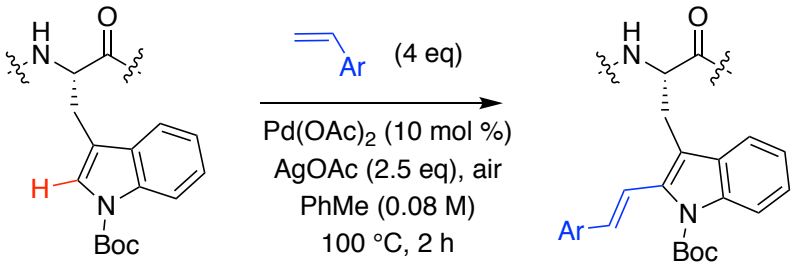
The appropriate amino acid methyl ester hydrochloride (2.00 mmol) and K_2CO_3 (0.398 g, 2.88 mmol) were dissolved in distilled water (30 mL) and stirred for 10 min at room temperature. The free amine was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$) and concentrated to dryness. The resulting residue was slurried in CH_2Cl_2 (20 mL), before the addition of the dipeptide acid (0.80 mmol), HBTU (0.303 g, 0.80 mmol) and *i*-Pr_2NEt (0.139 mL, 0.80 mmol). The resulting suspension was stirred for 16 h at room temperature. The suspension was then filtered and washed with 1M HCl (20 mL), sat. $NaHCO_3$ (3 x 20 mL) and water (20 mL). The organic layers were then dried ($MgSO_4$) and concentration to dryness *in vacuo*. The resulting solid was triturated in Et_2O (15 mL) and filtered to afford the tripeptide as a solid.

2.3. General procedure for the Boc protection of Trp residues



The tryptophan containing peptide (0.75 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with NEt_3 (0.105 mL, 0.75 mmol). A solution of Boc_2O (0.327 g, 1.50 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the peptide solution; the reaction mixture was then heated under reflux for 16 h. The solution was allowed to cool to room temperature, before concentration to dryness by rotary evaporation. The crude compound was purified by flash column chromatography and the resulting residue was recrystallised from CH_2Cl_2 / hexanes to afford the Boc-protected peptide.

2.4. General optimized procedure for the C-H olefination of Trp containing peptides

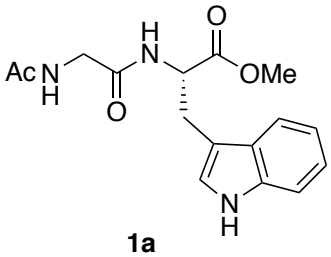


The appropriate tryptophan containing peptide (0.238 mmol), $Pd(OAc)_2$ (5 mg, 0.024 mmol, 10 mol%), AgOAc (0.100 g, 0.599 mmol) and styrene or styrene derivative (0.952 mmol) were stirred in toluene (3 mL) at 100 °C for 2 h. The reaction mixture was then allowed to cool to room temperature, filtered through a plug of Celite, and concentrated to dryness. The resulting crude residue was purified by flash column chromatography and recrystallized from CH_2Cl_2 / hexanes.

3. Detailed experimental procedures and analytical data

3.1. Synthesis of Ac-Gly-Trp-OMe (1a) and Ac-Gly-Trp(Boc)-OMe (1b)

Ac-Gly-Trp-OMe (1a)



1a

Peptide **1a** was synthesised from L-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetylglycine (0.117 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **1a** as an orange solid (0.279 g, 88%); m.p. 177-180 °C.

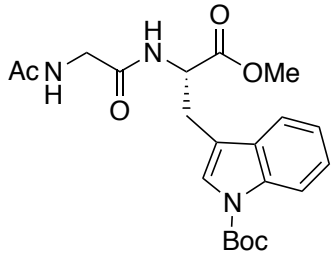
^{1}H NMR (400 MHz, CD_3OD) δ 1.93 (3H, s, acetyl-C*H*$_3$), 3.21 (1H, dd, *J* = 14.6, *J* = 7.4, Trp-CH*H*), 3.26-3.31 (1H, m, Trp-CH*H*), 3.65 (3H, s, ester-C*H*$_3$), 3.81 (2H, d, *J* = 4.1, Gly-C*H*$_2$), 4.74 (1H, app q, *J* = 7.4, Trp-α-C*H*), 6.99-7.03 (1H, m, Trp-Ar-*H*), 7.06-7.10 (2H, m, Trp-Ar-*H*), 7.30-7.33 (1H, m, Trp-Ar-*H*), 7.48-7.50 (1H, m, Trp-Ar-*H*).

$^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 22.4 (acetyl-CH_3), 28.4 (Trp-CH_2), 43.4 (Gly-CH_2), 52.7 (ester-CH_3), 54.8 (Trp-α-CH), 110.3 (Ar-C), 112.3 (Ar-CH), 119.1 (Ar-CH), 119.9 (Ar-CH), 122.5 (Ar-CH), 124.6 (Ar-CH), 128.7 (Ar-C), 138.0 (Ar-C), 171.4 (C=O), 173.7 (C=O), 173.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3235 m (N-H), 3060 w (C-H), 2951 w (C-H), 1749 s (ester C=O), 1642 m (amide C=O), 1436 m (C-H).

HRMS (ESI) [M+H^+] *m/z* calcd. for $C_{16}H_{20}N_3O_4$: 318.1448, found: 318.1451.

Ac-Gly-Trp(Boc)-OMe (1b)



Peptide **1b** was synthesised from Ac-Gly-Trp-OMe (**1a**) (0.238 g, 0.75 mmol) using the procedure in **section 2.3.** Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **1b** as an off-white solid (0.276 g, 88%); m.p. 92-95 °C, R_f 0.16 (EtOAc).

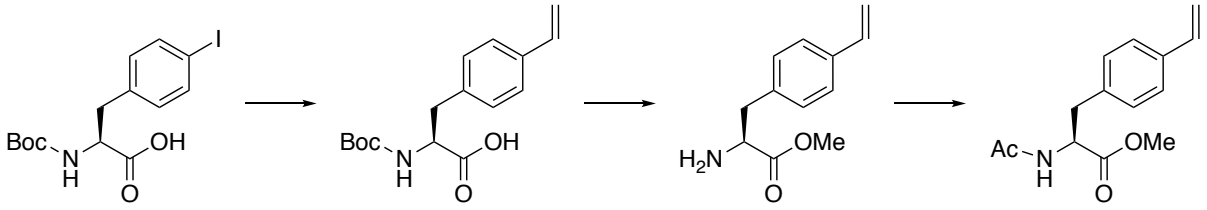
^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (9H, s, Boc-(CH_3)$_3$), 1.96 (3H, s, acetyl-CH_3), 3.19 (1H, dd, *J* = 14.6, *J* = 6.0, Trp-CH*H*), 3.27 (1H, dd, *J* = 14.6, *J* = 6.0, Trp-CH*H*), 3.69 (3H, s, ester-CH_3), 3.83-3.94 (2H, m, Gly-CH_2), 4.90 (1H, dd, *J* = 7.8, *J* = 6.0, Trp-α-C*H*), 6.48 (1H, br t, *J* = 5.0, Gly-N*H*), 6.94 (1H, br d, *J* = 7.8, Trp-N*H*), 7.22 (1H, t, *J* = 7.7, Trp-Ar-*H*), 7.30 (1H, t, *J* = 6.9, Trp-Ar-*H*), 7.41 (1H, s, Trp-Ar-*H*), 7.47 (1H, d, *J* = 7.7, Trp-Ar-*H*), 8.08 (1H, br d, *J* = 6.9, Trp-Ar-*H*).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 22.8 (acetyl-CH_3), 27.3 (Trp-CH_2), 28.1 (Boc-(CH_3)$_3$), 43.1 (Gly-CH_2), 52.5 (ester-CH_3), 52.6 (Trp-α-CH), 83.8 (Boc-C), 114.7 (Ar-C), 115.3 (Ar-C), 118.6 (Ar-C), 122.6 (Ar-C), 124.2 (Ar-C), 124.6 (Ar-C), 130.3 (Ar-C), 135.2 (Ar-C), 149.5 (C=O), 168.8 (C=O), 170.6 (C=O).

IR υ_{max} /cm^{-1} (solid) 3273 m (N-H), 3058 w (C-H), 2933 w (C-H), 1740 s (ester C=O), 1658 m (amide C=O), 1428 m (C-H), 1246 s (C-O).

HRMS (ESI) [M+H^+] *m/z* calcd. for $C_{21}H_{28}N_3O_6$: 418.1973, found: 418.1973.

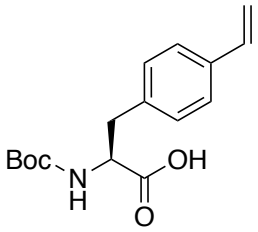
3.2. Synthesis of Ac-Phe(4-vinyl)-OMe (SI-3)



SI-1 **SI-2** **SI-3**

Boc-Phe(4-vinyl)-OH (SI-1)

Compound **SI-1** was prepared using a previously reported procedure.[S1]



SI-1

The unnatural amino acid *N*-Boc-4-iodophenylalanine (0.391 g, 1.00 mmol), potassium vinyl trifluoroborate (0.161 g, 1.20 mmol), K_2CO_3 (0.691 g, 5.00 mmol) and Pd(dppf)Cl_2 (0.008 g, 0.01 mmol) were dissolved in H_2O / *i*-PrOH (10 mL) and refluxed at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature before the organic solvent was removed *in vacuo*. The remaining aqueous solution was then acidified to pH 3 using 5N HCl (*ca.* 2.0 mL). The resulting aqueous solution was extracted using CH_2Cl_2 (4 x 25 mL) and the combined organics were dried ($MgSO_4$), before the solvent was removed *in vacuo*. Purification by flash column chromatography (CH_2Cl_2 / MeOH / AcOH, 97:1:2) yielded **SI-1** as a brown oil (0.256 g, 88%); R_f 0.30 (CH_2Cl_2 / MeOH / AcOH 97:1:2).

^{1}H NMR (400 MHz, D_6-DMSO) δ 1.31 (9H, s, Boc-C*H*$_3$), 2.81 (1H, dd, *J* = 13.7, 10.4, Phe-C*H*H), 2.99 (1H, dd, *J* = 13.7, 4.5, Phe-CH*H*), 4.02-4.11 (1H, m, Phe-α-C*H*), 5.21 (1H, d, *J* = 11.1, 0.6, alkene-CH*H*), 5.78 (1H, d, *J* = 17.7, 0.6, alkene-C*H*H), 6.69 (1H, dd, *J* = 17.7, 11.1, alkene-C*H*), 7.10 (1H, d, *J* = 8.5, N*H*), 7.22 (2H, d, *J* = 8.1, Ar-*H*), 7.38 (2H, d, *J* = 8.1, Ar-*H*).

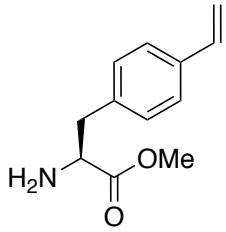
^{13}C NMR (100 MHz, D_6-DMSO) δ 28.2 (Boc-(CH_3)$_3$), 36.2 (Phe-CH_2), 55.2 (Phe-CH), 78.1 (Boc-C), 113.7 (alkene-CH_2), 126.0 (ArC), 129.4 (ArC), 135.3 (alkene-CH), 136.5 (4° ArC), 137.9 (4° ArC), 155.5 (C=O), 173.6 (C=O).

IR U_{max} /cm^{-1} (oil) 3442 m (N-H), 3027 w (C-H), 2958 w (C-H), 1729 s (C=O), 1534 s (C=C), 1217 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{16}H_{22}NO_4$: 292.1549, found: 292.1551.

The ^{1}H and ^{13}C NMR data match that previously reported.[S1]

H-Phe(4-vinyl)-OMe (SI-2)



SI-2

The unnatural amino acid Boc-Phe(4-vinyl)-OH (**SI-1**) (0.256 g, 0.88 mmol) was dissolved in ice cold MeOH (10 mL) and treated with the dropwise addition of thionyl chloride (0.290 mL, 4.00 mmol). The solution was allowed to warm to room temperature before refluxing for 4 h. The volatiles were removed *in vacuo*, and the residue was dissolved in toluene and concentrated to dryness three times. The resulting material was slurried in sat. aqueous $NaHCO_3$ solution and then extracted in CH_2Cl_2 (3 x 25 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to yield **SI-2** as a yellow oil. (0.165 g, 91%); R_f 0.25 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (2H, br s, N*H*$_2$), 2.85 (1H, dd, *J* = 13.5, 8.0, Phe-C*H*H), 3.07 (1H, dd, *J* = 13.5, 5.3, Phe-CH*H*), 3.69-3.74 (4H, m, ester-C*H*$_3$ / Phe-α-C*H*), 5.22 (1H, dd, *J* = 10.9, 0.9, alkene-C*H*H), 5.72 (1H, d, *J* = 17.6, 0.9, alkene-CH*H*), 6.68 (1H, dd, *J* = 17.6, 10.9, alkene-C*H*), 7.15 (2H, d, *J* = 8.2, Ar-*H*), 7.35 (2H, d, *J* = 8.2, Ar-*H*).

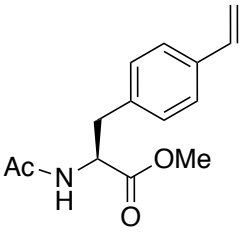
^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (Phe-CH_2), 51.9 (ester-CH_3), 55.6 (Phe-α-CH), 113.5 (alkene-CH_2), 126.3 (Ar C), 129.3 (Ar C), 131.2 (Ar C), 136.1 (4° Ar C), 136.3 (alkene-CH), 136.7 (4° Ar C), 175.3 (C=O).

IR U_{max} /cm^{-1} (oil) 3377 m (N-H), 3030 w (C-H), 2793 w (C-H), 1735 s (C=O), 1511 s (C=C), 1172 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{12}H_{16}NO_2$: 206.1181, found: 206.1182

The ^{1}H NMR data match that previously reported.[S2]

Ac-Phe(4-vinyl)-OMe (SI-3)



SI-3

The unnatural amino ester H-Phe(4-vinyl)-OMe (**SI-2**) (0.410 g, 2.00 mmol), acetic anhydride (0.945 mL, 10.00 mmol) and pyridine (0.805 mL, 10.00 mmol) were dissolved in CH_2Cl_2 (20 mL) and stirred at room temperature for 12 h. The volatiles were removed *in vacuo* before the resulting residue was re-dissolved in CH_2Cl_2 and washed with 1 M HCl (20 mL), distilled H_2O (20 mL), sat. aqueous $NaHCO_3$ (20 mL) and distilled H_2O (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated to dryness. Purification of the crude residue by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes yielded **SI-3** as a white solid (0.232 g, 47%); m.p. 123-126 °C, R_f 0.45 (EtOAc).

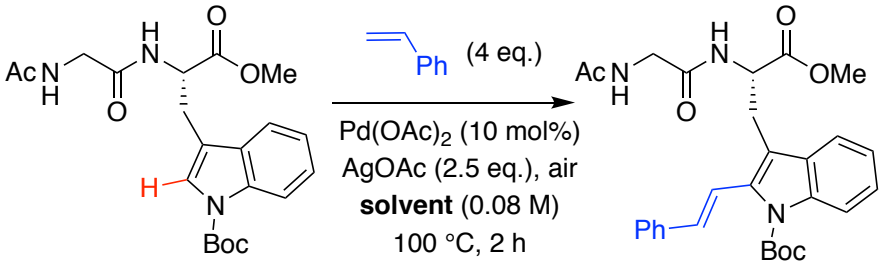
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (3H, s, acetyl-C*H*$_3$), 3.05 (1H, dd, *J* = 13.9, 6.0, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.9, 5.8, Phe-CH*H*), 3.72 (3H, s, ester-C*H*$_3$), 4.84-4.90 (1H, m, Phe-α-C*H*), 5.23 (1H, dd, *J* = 10.9, 0.8, alkene-C*H*H), 5.72 (1H, dd, *J* = 17.6, 0.8, alkene-CH*H*), 6.23 (1H, d, *J* = 7.8, Phe-N*H*), 6.67 (1H, dd, *J* = 17.6, 10.9, alkene-C*H*), 7.06 (2H, d, *J* = 8.0, Ar-*H*), 7.33 (2H, d, *J* = 8.0, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 37.4 (Phe-CH_2), 52.2 (ester-CH_3), 53.0 (Phe-α-CH), 113.7 (alkene-CH_2), 126.2 (Ar-C), 129.3 (Ar-C), 135.4 (4° Ar-C), 136.2 (alkene-CH) 136.3 (4° Ar-C), 169.6 (acetyl C=O), 172.0 (ester C=O).

IR U_{max} /cm^{-1} (solid) 3327 m (N-H), 3027 w (C-H), 2958 w (C-H), 1743 s (ester C=O), 1649 s (amide C=O), 1534 s (C=C), 1217 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{14}H_{18}NO_3$: 248.1287, found: 248.1286.

3.3. Effect of solvent on the C-H olefination of Ac-Gly-Trp(Boc)-OMe (1b)



1b **2b**, 82%

Peptide **1b** (0.100 g, 0.238 mmol), $Pd(OAc)_2$ (5 mg, 0.024 mmol, 10 mol%), AgOAc (0.100 g, 0.599 mmol) and styrene (0.109 mL, 0.952 mmol) were stirred in solvent (3 mL) at the temperature and for the time indicated. The reaction mixture was then allowed to cool to room temperature, filtered through a plug of Celite, and the filtrate was concentrated to dryness. The resulting crude residue was purified by flash column chromatography (EtOAc) and recrystallized from CH_2Cl_2 / hexanes.

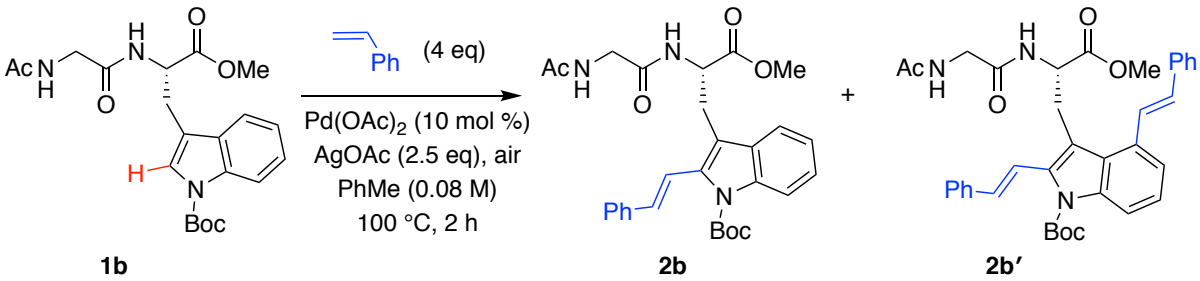
Table S1. Optimisation of reaction solvent on the C-H olefination of 1b.

entry	solvent	*T* / °C	time / h	yield [a] / %
1	*t*-amylOH	100	48	60
2	*t*-amylOH	100	96	61
3	1,2-DCE	100	48	60
4	MeCN	100	48	42
5	1,4-dioxane	100	48	40
6	THF	100	48	36
7	HFIP	100	48	0
8	PhMe	100	48	85
9	**PhMe**	**100**	**2**	**82** [b]
10	PhMe	100	2	74 [c]

[a] Isolated yields of di-olefinated peptide **2b**;
[b] The di-olefinated peptide **2b'** was also isolated in 1% yield
[c] Reaction conducted on a 1.14 mmol scale

3.4. Synthesis of modified peptides 2b and 3a-f

3.4.1. Synthesis of modified peptide 2b



1b **2b** **2b′**

Following the general procedure in **section 2.4**, the reaction of Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol), $Pd(OAc)_2$ (5 mg, 0.024 mmol, 10 mol%), AgOAc (0.100 g, 0.599 mmol) and styrene (0.109 mL, 0.952 mmol) gave a crude product that was a mixture of the mono-olefinated peptide **2b** and the di-olefinated peptide **2b′** in a ratio of 20:1, as judged by ^{1}H NMR spectroscopy. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **2b** as an off-white solid (0.101 g, 82); m.p. 116-118 °C, R_f 0.26 (EtOAc) and **2b′** as an off-white solid (0.002 g, 1%); m.p. 98-99 °C, R_f 0.42 (EtOAc).

Data for 2b:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s, Boc-(CH_3)$_3$), 1.92 (3H, s, acetyl-CH_3), 3.38 (1H, dd, *J* = 14.5, *J* = 6.6, Trp-C*H*H), 3.47 (1H, dd, *J* = 14.5, *J* = 6.6, Trp-C*H*H), 3.55 (3H, s, ester-CH_3), 3.74 (1H, dd, *J* = 16.7, *J* = 5.0, Gly-C*H*H), 3.84 (1H, dd, *J* = 16.7, *J* = 5.0, Gly-CH_2), 4.89 (1H, dt, *J* = 7.6, *J* = 6.6, Trp-α-C*H*), 5.89 (1H, br t, *J* = 5.0, Gly-N*H*), 6.41 (1H, br d, *J* = 7.6, Trp-N*H*), 6.78 (1H, d, *J* = 16.6, alkene-C*H*), 7.27-7.34 (4H, m, alkene-C*H* / Ar-*H*), 7.39 (2H, t, *J* = 7.6, Ar-*H*), 7.51-7.56 (3H, m, Ar-*H*), 8.13 (1H, d, *J* = 8.1, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.3 (Trp-CH_2), 28.3 (Boc-(CH_3)$_3$), 42.9 (Gly-CH_2), 52.6 (ester-CH_3), 52.6 (Trp-α-CH), 84.2 (Boc-C), 114.3 (Ar-C), 115.6 (Ar-C), 118.5 (Ar-C), 119.9 (alkene-CH), 122.9 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 128.1 (Ar-C), 128.8 (Ar-C), 129.9 (Ar-C), 132.5 (alkene-CH), 135.8 (Ar-C), 136.2 (Ar-C), 136.7 (Ar-C), 150.4 (C=O), 168.3 (C=O), 170.3 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3281 m (N-H), 2955 w (C-H), 1726 s (ester C=O), 1647 m (amide C=O), 1523 m (C=C), 1455 m (C-H), 1205 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{29}H_{34}N_3O_6$: 520.2442, found: 520.2436.

ICP analysis of modified peptide **2b** indicated more than 99.9% removal of Pd and Ag from the purified compound (Pd 6 ppm; Ag 50 ppm).

Data for 2b′:

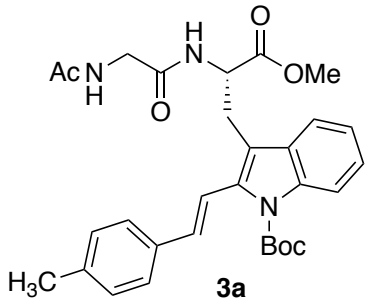
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s, Boc-(C*H*$_3$)$_3$), 1.84 (3H, s, acetyl-C*H*$_3$), 3.43-3.46 (1H, m, Trp-C*H*H), 3.50 (3H, s, ester-C*H*$_3$), 3.63-3.68 (3H, m, Gly-C*H*$_2$ / Trp-C*H*H), 4.78-4.84 (1H, m, Trp-α-C*H*), 5.92 (1H, br t, *J* = 4.6, Gly-N*H*), 6.26 (1H, br d, *J* = 7.7, Trp-N*H*), 6.67 (1H, d, *J* = 16.6, alkene-C*H*), 7.04 (1H, d, *J* = 16.6, alkene-C*H*), 7.21-7.34 (5H, m, alkene-C*H* / Ar-*H*), 7.35-7.44 (5H, m, Ar-*H*), 7.53 (2H, d, *J* = 7.4, Ar-*H*), 7.57 (2H, d, *J* = 7.4, Ar-*H*), 7.84 (1H, d, J = 16.2, alkene-C*H*), 8.15 (1H, d, *J* = 8.1, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.7 (acetyl-CH_3), 28.3 (Boc-$(CH_3)_3$), 28.5 (Trp-CH_2), 42.7 (Gly-CH_2), 52.4 (ester-CH_3), 53.1 (Trp-α-CH), 84.2 (Boc-C), 114.7 (Ar-C),114.9 (Ar-C), 119.6 (Ar-C), 121.8 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 126.6 (Ar-C), 126.8 (Ar-C), 127.8 (Ar-C), 128.2 (Ar-C), 128.6 (Ar-C), 128.8 (Ar-C), 131.4 (Ar-C), 132.3 (Ar-C), 133.7 (Ar-C), 136.4 (Ar-C), 136.9 (Ar-C), 137.1 (Ar-C), 137.2 (Ar-C), 150.1 (C=O), 168.4 (C=O), 170.1 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3226 m (N-H), 2978 w (C-H), 1720 s (ester C=O), 1638 m (amide C=O), 1424 m (C-H), 1250 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{37}H_{40}N_3O_6$: 622.2912, found: 622.2910.

3.4.2. Synthesis of modified peptide 3a



3a

Modified peptide **3a** was prepared from Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol) and 4-methylstyrene (0.125 mL, 0.952 mmol), using the general procedure in **section 2.4**. As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **3a** and a di-olefinated peptide in a ratio of 24:1. Purification by flash column chromatography (EtOAc) gave **3a** as a yellow oil (0.099 g, 78%); R_f 0.25 (EtOAc).

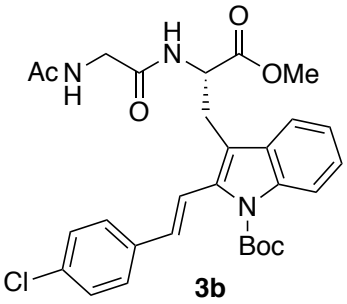
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.91 (3H, s, acetyl-C*H*$_3$), 2.37 (3H, s, Ar-C*H*$_3$), 3.37 (1H, dd, *J* = 14.4, *J* = 6.4, Trp-C*H*H), 3.46 (1H, dd, *J* = 14.4, *J* = 6.4, Trp-C*H*H), 3.55 (ester-C*H*$_3$), 3.72 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 3.83 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 4.88 (1H, dt, *J* = 7.6, *J* = 6.4, Trp-α-C*H*), 5.86 (1H, m, Gly-N*H*), 6.38 (1H, br d, *J* = 7.6, Trp-N*H*), 6.73 (1H, d, *J* = 16.7, alkene-C*H*), 7.18-7.24 (2H, m, alkene-C*H* / Ar-*H*), 7.27-7.32 (2H, m, Ar-*H*), 7.38 (1H, d, *J* = 4.6, Ar-*H*), 7.44 (2H, d, *J* = 8.0, Ar-*H*), 7.51 (1H, br d, *J* = 7.0, Ar-*H*), 8.13 (1H, d, *J* = 8.0, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3 (Ar-CH_3), 22.8 (acetyl-CH_3), 27.2 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 42.9 (Gly-CH_2), 52.5 (ester-CH_3), 52.6 (Trp-α-CH), 84.0 (Boc-C), 114.2 (Ar-C), 115.5 (Ar-C), 118.4 (Ar-C), 118.8 (alkene-C), 122.8 (Ar-C), 124.7 (Ar-C), 126.4 (Ar-C), 127.0 (Ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 129.9 (Ar-C), 132.4 (alkene-C), 133.9 (Ar-C), 135.8 (Ar-C), 136.3 (Ar-C), 138.0 (Ar-C), 150.4 (C=O), 168.4 (C=O), 170.3 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (oil) 3286 m (N-H), 3053 w (C-H), 2978 w (C-H), 1728 s (ester C=O), 1648 m (amide C=O), 1235 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{36}N_3O_6$: 534.2599, found: 534.2602.

3.4.3. Synthesis of modified peptide 3b



3b

Modified peptide **3b** was prepared from Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol) and 4-chlorostyrene (0.114 mL, 0.952 mmol), using the general procedure in **section 2.4**. As judged by ^{1}H NMR spectroscopy, the crude residue contained only the mono-olefinated peptide **3b**. Purification by flash column chromatography (EtOAc) gave **3b** as a yellow oil (0.113 g, 87%); R_f 0.27 (EtOAc).

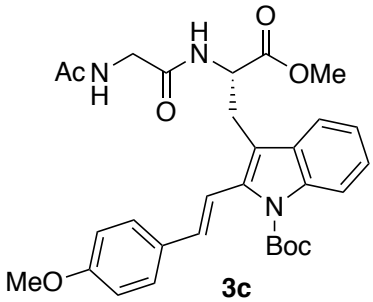
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.92 (3H, s, acetyl-C*H*$_3$), 3.33 (1H, dd, *J* = 14.4, *J* = 6.6, Trp-C*H*H), 3.41 (1H, dd, *J* = 14.4, *J* = 6.6, Trp-C*H*H), 3.53 (3H, s, ester-C*H*$_3$), 3.72 (1H, dd, *J* = 16.7, *J* = 5.0, Gly-C*H*H), 3.83 (1H, dd, *J* = 16.7, *J* = 5.0, Gly-C*H*H), 4.87 (1H, dt, *J* = 7.4, *J* = 6.6, Trp-α-C*H*), 6.01 (1H, br t, *J* = 5.0, Gly-N*H*), 6.73 (1H, d, *J* = 16.9, alkene-C*H*), 7.22-7.24 (6H, m, alkene-C*H* / Ar-*H*), 7.46-7.52 (3H, m, Ar-*H*), 8.10 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (acetyl-CH_3), 27.4 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 43.0 (Gly-CH_2), 52.6 (ester-CH_3), 52.6 (Trp-α-CH), 84.2 (Boc-C), 114.6 (Ar-C), 115.6 (Ar-C), 118.5 (Ar-C), 122.9 (Ar-C), 124.9 (Ar-C), 127.0 (Ar-C), 127.7 (Ar-C), 128.5 (Ar-C), 128.9 (Ar-C), 129.9 (Ar-C), 130.9 (Ar-C), 133.6 (Ar-C), 135.3 (Ar-C), 135.8 (Ar-C), 150.3 (C=O), 168.4 (C=O), 170.4 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (oil) 3281 m (N-H), 2950 w (C-H), 1728 s (ester C=O), 1648 m (amide C=O), 1455 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{29}H_{33}N_3O_6Cl$: 554.2052, found: 554.2056.

3.4.4. Synthesis of modified peptide 3c



3c

Modified peptide **3c** was prepared from Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol) and 4-methoxystyrene (0.127 mL, 0.952 mmol), using the general procedure in **section 2.4**. As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **3c** and a di-olefinated peptide in a ratio of 14:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3c** as yellow solid (0.077 g, 59%); m.p. 150-152 °C, R_f 0.18 (EtOAc).

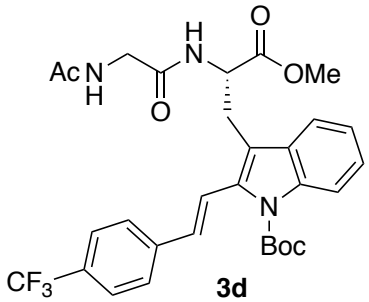
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(C*H*$_3$)$_3$), 1.90 (3H, s, acetyl-C*H*$_3$), 3.35 (1H, dd, *J* = 14.2, *J* = 6.6, Trp-C*H*H), 3.44 (1H, dd, *J* = 14.2, *J* = 6.6, Trp-C*H*H), 3.54 (3H, s, ester-C*H*$_3$), 3.71 (1H, dd, *J* = 16.9, *J* = 5.0, Gly-C*H*H), 3.80-3.85 (4H, m, Ph-OC*H*$_3$ / Gly-C*H*H), 4.87 (1H, dt, *J* = 7.4, *J* = 6.6, Trp-α-C*H*), 5.92 (1H, br t, *J* = 5.0, Gly-N*H*), 6.44 (1H, d, *J* = 7.4, Trp-N*H*), 6.70 (1H, d, *J* = 16.4, alkene-C*H*), 6.91 (2H, d, *J* = 8.9, Ar-*H*), 7.15 (1H, d, *J* = 16.4, alkene-C*H*), 7.21-7.24 (1H, m, Trp-Ar-*H*), 7.26-7.30 (1H, m, Trp-Ar-*H*), 7.36 (1H, d, *J* = 4.6, Ar-*H*), 7.46-7.50 (3H, m, Ar-*H*), 8.11 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (acety-CH_3), 27.2 (Trp-CH_2), 28.3 (Boc-(CH_3)$_3$), 42.9 (Gly-CH_2), 52.6 (ester-CH_3), 55.3 (Trp-α-CH), 84.0 (Boc-C), 113.8 (OMe), 114.2 (Ar-C), 115.6 (Ar-C), 117.7 (Ar-C), 118.4 (Ar-C), 122.8 (Ar-C), 124.6 (Ar-C), 127.0 (Ar-C), 127.8 (Ar-C), 128.5 (Ar-C), 129.5 (Ar-C), 130.0 (Ar-C), 132.1 (Ar-C), 135.8 (Ar-C), 136.5 (Ar-C), 150.4 (C=O), 168.3 (C=O), 170.3 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3296 m (N-H), 3051 w (C-H), 2963 w (C-H), 1727 s (ester C=O), 1658 m (amide C=O), 1510 m (C=C), 1260 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{36}N_3O_7$: 550.2548, found: 550.2549.

3.4.5. Synthesis of modified peptide 3d



3d

Modified peptide **3d** was prepared from Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol) and 4-(trifluoromethyl)styrene (0.141 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **3d** and a di-olefinated peptide in a ratio of 13:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3d** as an off-white solid (0.099 g, 71%); m.p. 169-172 °C, R_f 0.36 (EtOAc).

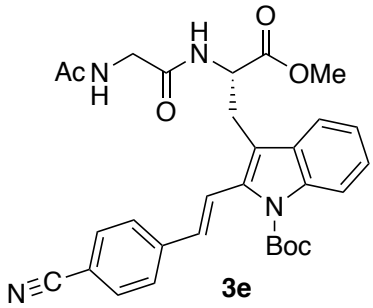
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.91 (3H, s, acetyl-C*H*$_3$), 3.33 (1H, dd, *J* = 14.6, *J* = 6.4, Trp-C*H*H), 3.41 (1H, dd, *J* = 14.6, *J* = 6.4, Trp-C*H*H), 3.53 (3H, s, ester-C*H*$_3$), 3.74 (1H, dd, *J* = 16.9, *J* = 5.0, Gly-C*H*H), 3.85 (1H, dd, *J* = 16.9, *J* = 5.0, Gly-C*H*H), 4.89 (1H, dt, *J* = 7.8, *J* = 6.6, Trp-α-C*H*), 6.10 (1H, br t, *J* = 5.0, Gly-N*H*), 6.72 (1H, d, *J* = 7.8, Trp-N*H*), 6.81 (1H, d, *J* = 16.6, alkene-C*H*), 7.22-7.26 (1H, m, Ar-*H*), 7.29-7.35 (2H, m, Ar-*H*), 7.45 (1H, d, *J* = 16.6, alkene-C*H*), 7.52 (1H, d, *J* = 7.3, Ar-*H*), 7.63 (4H, dt, *J* = 8.2, *J* = 7.3, Ar-*H*), 8.11 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (acetyl-CH_3), 27.6 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 43.0 (Gly-CH_2), 52.6 (ester-CH_3), 52.6 (Trp-α-CH), 84.3 (Boc-C), 115.1 (Ar-C), 155.6 (Ar-C), 118.6 (Ar-C), 122.5 (Ar-C), 123.0 (Ar-C), 125.1 (Ar-C), 125.6 (Ar-C), 126.6 (Ar-C), 127.6 (Ar-C), 128.5 (Ar-C), 129.8 (Ar-C), 130.5 (Ar-C), 135.4 (Ar-C), 135.8 (Ar-C), 140.3 (Ar-C), 150.3 (C=O), 168.4 (C=O), 170.5 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3282 m (N-H), 3070 w (C-H), 2980 w (C-H), 1728 s (ester C=O), 1647 m (amide C=O), 1541 m (C=C), 1237 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{33}N_3O_6F_3$: 588.2316, found: 588.2312.

3.4.6. Synthesis of modified peptide 3e



3e

Modified peptide **3e** was prepared from Ac-Gly-Trp(Boc)-OMe (**1b**) (0.100 g, 0.238 mmol) and 4-cyanostyrene (0.123 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained only the mono-olefinated peptide **3e**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3e** as a yellow solid (0.105 g, 81%); m.p. 144-147 °C, R_f 0.18 (EtOAc).

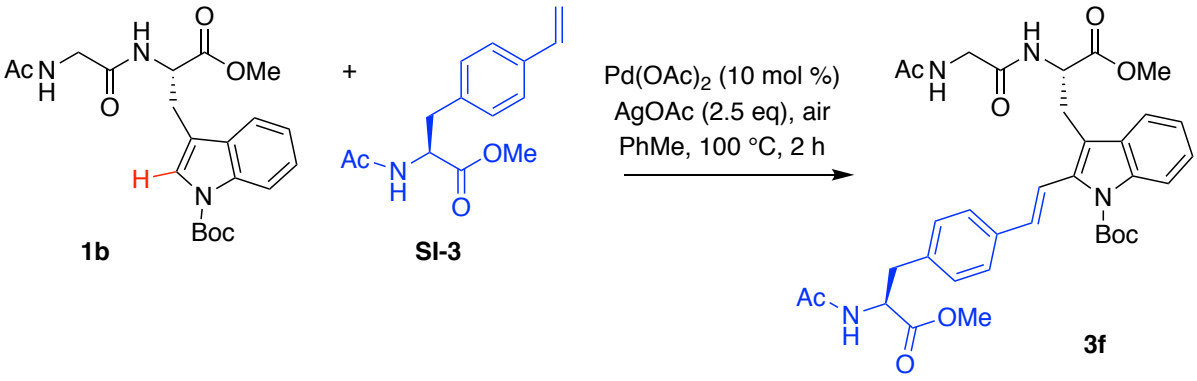
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s, Boc-(C*H*$_3$)$_3$), 1.95 (3H, s, acetyl-C*H*$_3$), 3.31-3.41 (2H, m, Trp-C*H*$_2$), 3.52 (3H, s, ester-C*H*$_3$), 3.76 (1H, dd, *J* = 16.6, *J* = 5.0, Gly-N*H*), 3.86 (1H, dd, *J* = 16.6, *J* = 5.0, Gly-C*H*H), 4.88 (1H, app q, *J* = 8.2, Trp-α-C*H*), 6.04 (1H, br t, *J* = 5.0, Gly-N*H*), 6.65 (1H, d, *J* = 8.2, Trp-N*H*), 6.83 (1H, d, *J* = 16.4, alkene-C*H*), 7.23-7.27 (1H, m, Ar-*H*), 7.30-7.36 (2H, m, Ar-*H*), 7.49-7.53 (2H, m, alkene-C*H* / Ar-*H*), 7.65 (4H, s, Ar-*H*), 8.09 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.8 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 43.1 (Gly-CH_2), 52.6 (ester-CH_3), 52.6 (Trp-α-CH), 84.5 (Boc-C), 110.9 (Ar-C), 115.5 (Ar-C), 115.7 (Ar-C), 118.7 (Ar-C), 119.0 (Ar-C), 123.1 (Ar-C), 123.7 (Ar-C), 125.33 (Ar-C), 127.0 (Ar-C), 129.8 (Ar-C), 130.0 (Ar-C), 132.5 (Ar-C), 135.8 (Ar-C), 141.4 (Ar-C), 150.3 (C=O), 168.4 (C=O), 170.5 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3283 m (N-H), 3050 w (C-H), 2979 w (C-H), 2225 s (C≡N), 1728 s (ester C=O), 1649 m (amide C=O), 1239 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{30}H_{33}N_4O_6$: 545.2395, found: 545.2398.

3.4.7. Synthesis of modified peptide 3f



The peptide Ac-Gly-Trp(Boc)-OMe (**1b**) (0.030 g, 0.071 mmol), $Pd(OAc)_2$ (1 mg, 0.003 mmol, 10 mol%), AgOAc (0.030 g, 0.180 mmol) and Ac-Phe(4-vinyl)-OMe (**SI-3**) (0.071 g, 0.287 mmol) were stirred in toluene (3 mL) at 100 °C for 2 h. The reaction mixture was then allowed to cool to room temperature, filtered through a plug of Celite, and concentrated to dryness. As judged by ^{1}H NMR spectroscopy, the crude residue contained only the mono-olefinated peptide **3f**. Purification by flash column chromatography (EtOAc), followed by recrystallisation from CH_2Cl_2 / hexanes, gave **3f** as a yellow solid (0.032 g, 64%); m.p. 239-242 °C, R_f 0.10 (EtOAc).

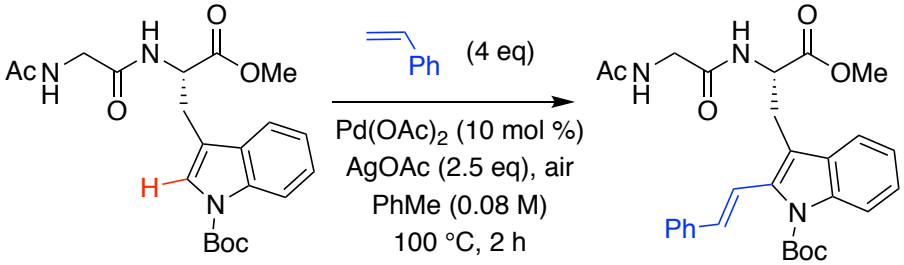
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s, Boc-C*H*$_3$), 1.92 (3H, s, acetyl-C*H*$_3$), 2.02 (3H, s, acetyl-C*H*$_3$), 3.10 (1H, dd, *J* = 14.0, 5.6, Phe-C*H*H), 3.17 (1H, dd, *J* = 14.0, 5.5, Phe-CH*H*), 3.35 (1H, dd, *J* = 14.5, 6.5, Trp-C*H*H), 3.42 (1H, dd, *J* = 14.5, 6.6, Trp-CH*H*), 3.54 (3H, s, ester-C*H*$_3$), 3.67-3.79 (5H, m, ester-C*H*$_3$ / Gly-C*H*$_2$), 4.87-4.97 (2H, m, Phe-α-C*H* / Trp-α-C*H*), 6.23 (1H, t, *J* = 4.9, Gly-N*H*), 6.30 (1H, d, *J* = 8.0, Phe-N*H*), 6.68-6.75 (2H, m, alkene-C*H* / Trp-N*H*), 7.09 (2H, d, *J* = 8.1, Ar-*H*), 7.22-7.35 (3H, m, Ar-*H* / alkene-C*H*), 7.45 (2H, d, *J* = 8.1, Ar-*H*), 7.53 (1H, d, *J* = 7.7, Ar-*H*), 8.10 (1H, d, *J* = 8.0, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (acetyl-CH_3), 23.1 (acetyl-CH_3), 27.4 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 37.6 (Phe-CH_2), 42.9 (Gly-CH_2), 52.4 (ester-CH_3), 52.5 (ester-CH_3), 52.5 (Trp-α-CH), 53.0 (Phe-α-CH), 84.2 (Boc-C), 114.4 (Ar-C), 115.6 (Ar-C), 118.5 (Ar-C), 119.9 (alkene-C), 122.9 (Ar-C), 124.8 (Ar-C), 126.7 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C), 131.9 (alkene-C), 135.6 (Ar-C), 135.7 (Ar-C), 135.8 (Ar-C), 136.1 (Ar-C) 150.4 (Boc C=O), 160.5 (C=O), 169.9 (C=O), 170.5 (C=O), 172.0 (C=O), 172.0 (C=O).

IR U_{max} /cm^{-1} (solid) 3291 w (N-H), 3055 w (C-H), 2952 w (C-H), 1728 s (ester C=O), 1653 s (amide C=O), 1523 s (C=C), 1210 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{35}H_{43}N_4O_9$: 663.3030, found: 663.3068.

3.5. Detailed synthetic method at >1 mmol scale



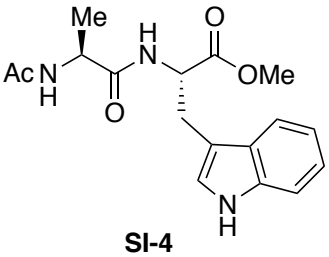
1b **2b**

The peptide Ac-Gly-Trp(Boc)-OMe (**1b**) (1.14 mmol), $Pd(OAc)_2$ (24 mg, 0.114 mmol, 10 mol%), AgOAc (0.479 g, 2.85 mmol) and styrene (0.52 mL, 4.56 mmol) were stirred in toluene (14 mL) at 100 °C for 2 h. The reaction mixture was then allowed to cool to room temperature, filtered through a plug of Celite, and concentrated to dryness. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **2b** as an off-white solid (0.438 g, 74%). The data for **2b** agreed with that reported above.

3.6. Synthesis of Trp containing peptides 4a-j

3.6.1. Synthesis of Ac-Ala-Trp(Boc)-OMe (4a)

Ac-Ala-Trp-OMe (SI-4)



SI-4

The peptide Ac-Ala-Trp-OMe (**SI-4**) was synthesised from L-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetyl-L-alanine (0.131 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-4** as an off-white solid (0.315 g, 95%); m.p. 77-79 °C.

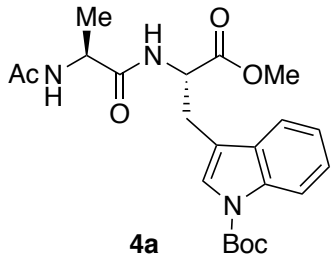
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, d, *J* = 6.9, Ala-C*H*$_3$), 1.86 (3H, s, acetyl-C*H*$_3$), 3.27-3.36 (2H, m, Trp-C*H*$_2$), 4.48 (1H, dq, *J* = 7.3, *J* = 6.9, Ala-α-C*H*), 4.88 (1H, dt, *J* = 7.8, *J* = 5.5, Trp-α-C*H*), 5.57 (1H, br d, *J* = 7.3, Ala-N*H*), 6.49 (1H, br d, *J* = 7.8, Trp-N*H*), 7.03 (1H, d, Trp-Ar-*H*), 7.09-7.19 (1H, m, Trp-Ar-*H*), 7.16-7.20 (1H, m, Trp-Ar-*H*), 7.33-7.36 (1H, m, Trp-Ar-*H*), 7.50-7.51 (1H, m, Trp-Ar-*H*), 8.18 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.3 (Ala-CH_3), 23.0 (acetyl-CH_3), 27.3 (Trp-CH_2), 48.7 (Ala-α-CH), 52.5 (ester-CH_3), 52.9 (Trp-α-CH), 109.6 (Ar-C), 111.3 (Ar-C), 118.5 (Ar-C), 119.7 (Ar-C), 122.3 (Ar-C), 123.1 (Ar-C), 127.5 (Ar-C), 136.0 (Ar-C), 169.8 (C=O), 171.8 (C=O), 172.0 (C=O).

IR U_{max} /cm^{-1} (solid) 3276 m (N-H), 3060 w (C-H), 2976 w (C-H), 1723 s (ester C=O), 1631 m (amide C=O), 1550 m (C=C), 1405 m (C-H), 1256 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{22}N_3O_4$: 332.1605, found: 332.1605.

Ac-Ala-Trp(Boc)-OMe (4a)



4a

Peptide **4a** was synthesised from Ac-Ala-Trp-OMe (**SI-4**) (0.249 g, 0.75 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4a** as an off-white solid (0.291 g, 90%); m.p. 83-84 °C, R_f 0.19 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, d, *J* = 6.9, Ala-C*H*$_3$), 1.66 (9H, s, Boc-(C*H*$_3$)$_3$), 1.90 (3H, s, acetyl-C*H*$_3$), 3.20 (1H, dd, *J* = 14.6, *J* = 5.5, Trp-C*H*H), 3.30 (1H, dd, *J* = 14.6, *J* = 5.5, Trp-C*H*H), 3.71 (3H, s, ester-C*H*$_3$), 4.39-4.47 (1H, m, Ala-α-C*H*), 4.85-4.90 (1H, m, Trp-α-C*H*), 5.91 (1H, br d, *J* = 7.3, Ala-N*H*), 6.59 (1H, br d, *J* = 7.3, Trp-N*H*), 7.22 (1H, t, *J* = 7.3, Trp-Ar-*H*), 7.30 (1H, t, *J* = 7.3, Trp-Ar-*H*), 7.39 (1H, s, Trp-Ar-*H*), 7.47 (1H, d, *J* = 7.3, Trp-Ar-*H*), 8.08-8.10 (1H, m, Trp-Ar-*H*),

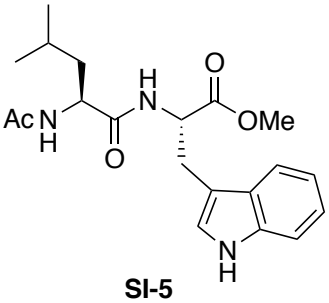
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.1 (Ala-CH_3), 22.8 (acetyl-CH_3), 27.2 (Trp-CH_2), 28.1 (Boc(CH_3)$_3$), 48.6 (Ala-α-CH), 52.4 (ester-CH_3), 52.6 (Trp-α-CH), 83.7 (Boc-C), 114.8 (Ar-C), 115.2 (Ar-C), 118.7 (Ar-C),122.5 (Ar-C), 124.1 (Ar-C), 124.4 (Ar-C), 130.3 (Ar-C), 135.1 (Ar-C), 149.5 (C=O), 170.0 (C=O), 171.7 (C=O), 172.3 (C=O).

IR U_{max} /cm^{-1} (solid) 3286 m (N-H), 2933 w (C-H), 1728 s (ester C=O), 1648 m (amide C=O), 1452 m (C-H), 1213 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{22}H_{30}N_3O_6$: 432.2129, found: 432.2130.

3.6.2. Synthesis of Ac-Leu-Trp(Boc)-OMe (4b)

Ac-Leu-Trp-OMe (SI-5)



SI-5

The peptide Ac-Leu-Trp-OMe (**SI-5**) was synthesised from L-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetyl-L-leucine (0.173 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-5** as a white solid (0.261 g, 78%); m.p. 79-81 °C.

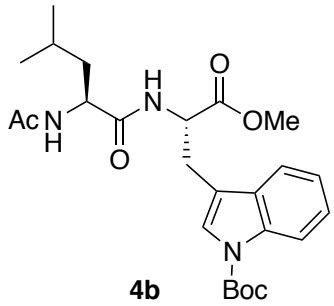
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-0.86 (6H, m, Leu-C*H*$_3$ (x2)), 1.48-1.64 (3H, m, (Leu-C*H*/Leu-C*H*$_2$), 1.80 (3H, s, acetyl-C*H*$_3$), 3.25-3.37 (2H, m, Trp-C*H*$_2$), 3.64 (3H, s, ester-C*H*$_3$), 4.56 (1H, dt, *J* = 8.0, *J* = 5.6, Leu-α-C*H*), 4.86 (1H, dt, *J* = 7.7, *J* = 5.4, Trp-α-C*H*), 6.65 (1H, br d, *J* = 8.0, Leu-N*H*), 6.99 (1H, d, *J* = 2.1, Trp-Ar-*H*), 7.03-7.14 (2H, m, Trp-Ar-*H* / Trp-N*H*), 7.10-7.16 (1H, br d, *J* = 7.7, Trp-Ar-*H*), 7.26-7.28 (1H, m, Trp-Ar-*H*), 7.49 (1H, d, *J* = 7.7, Trp-Ar-*H*), 8.73 (1H, s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.2 (Leu-CH_3 x2), 22.9 (Leu-CH_2), 23.1 (acetyl-CH_3), 24.8 (Leu-C*H*$(CH_3)_2$), 27.5 (Trp-CH_2), 41.3 (Leu-CH_2), 51.7 (Leu-α-CH), 52.6 (ester-CH_3), 52.9 (Trp-α-CH), 109.5 (Ar-C), 111.4 (Ar-C), 118.6 (Ar-C), 119.7 (Ar-C), 122.2 (Ar-C), 123.5 (Ar-C), 127.6 (Ar-C), 136.1 (Ar-C), 170.2 (C=O), 172.0 (C=O), 172.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3226 m (N-H), 3058 w (C-H), 2954 w (C-H), 1733 s (ester C=O), 1638 m (amide C=O), 1541 m (C=C), 1452 m (C-H), 1254 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{20}H_{28}N_3O_4$: 374.2074, found: 374.2069.

Ac-Leu-Trp(Boc)-OMe (4b)



4b

Peptide **4b** was synthesised from Ac-Leu-Trp-OMe (**SI-5**) (0.280 g, 0.75 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4b** as a white solid (0.337 g, 95%); m.p. 84-86 °C, R_f 0.20 (75% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-0.91 (6H, m, Leu-C*H*$_3$ (x2)), 1.46-1.50 (1H, m, Leu-C*H*), 1.59-1.63 (2H, m, Leu-C*H*$_2$), 1.66 (9H, s, Boc-(C*H*$_3$)$_3$), 1.91 (3H, s, acetyl-C*H*$_3$), 3.19 (1H, dd, *J* = 14.7, *J* = 5.8, Trp-C*H*H), 3.26 (1H, dd, *J* = 14.7, *J* = 5.8, Trp-C*H*H), 3.68 (3H, s, ester-C*H*$_3$), 4.49 (1H, dt, *J* = 8.4, *J* = 5.4, Leu-α-C*H*), 4.83-4.88 (1H, m, Trp-α-C*H*), 6.24 (1H, br d, *J* = 8.4, Leu-N*H*), 6.93 (1H, br d, *J* = 7.3, Trp-N*H*), 7.20-7.24 (1H, m, Trp-Ar-*H*), 7.28-7.32 (1H, m, Trp-Ar-*H*), 7.46 (1H, s, Trp-Ar-*H*), 7.49 (1H, d, *J* = 7.7, Trp-Ar-*H*), 8.06-8.10 (1H, m, Trp-Ar-*H*).

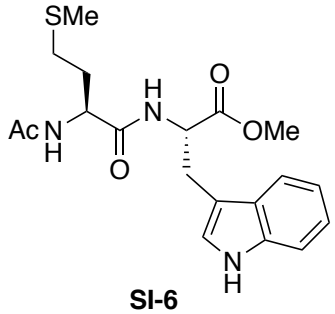
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.0 (Leu-CH_3), 22.9 (Leu-CH_3), 23.0 (acetyl-CH_3), 24.7 (Leu-CH), 27.3 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 41.0 (Leu-CH_2), 51.6 (Leu-α-CH), 52.5 (ester-CH_3), 52.6 (Trp-α-CH), 83.8 (Boc-C), 114.8 (Ar-C), 115.3 (Ar-C), 118.8 (Ar-C), 122.6 (Ar-C), 124.3 (Ar-C), 124.5 (Ar-C), 130.4 (Ar-C), 135.2 (Ar-C), 149.6 (C=O), 170.2 (C=O), 171.8 (C=O), 172.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3284 m (N-H), 2932 w (C-H), 1731 s (ester C=O), 1647 m (amide C=O), 1526 m (C=C), 1452 m (C-H), 1254 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{25}H_{36}N_3O_6$: 474.2599, found: 474.2595.

3.6.3. Synthesis of Ac-Met-Trp(Boc)-OMe (4c)

Ac-Met-Trp-OMe (SI-6)



SI-6

The peptide Ac-Met-Trp-OMe (**SI-6**) was synthesised from L-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetyl-L-methionine (0.191 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-6** as a white solid (0.376 g, 96%); m.p. 70-72 °C.

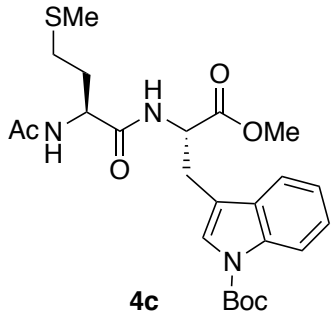
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82-1.90 (4H, m, acetyl-C*H*$_3$ / Met-C*H*H), 1.96-2.02 (4H, m, Met-C*H*$_3$ / Met-C*H*H), 2.48 (2H, br t, *J* = 7.4, Met-C*H*$_2$), 3.26 (2H, br d, *J* = 5.6, Trp-C*H*$_2$), 3.65 (3H, s, ester-C*H*$_3$), 4.65-4.71 (1H, m, Met-α-C*H*), 4.82-4.87 (1H, m, Trp-α-C*H*), 6.94 (1H, s, Trp-Ar-*H*), 7.01-7.08 (2H, m, Trp-Ar-*H* / Met-N*H*), 7.12 (1H, t, *J* = 7.6, Trp-Ar-*H*), 7.26 (1H, br d, *J* = 7.6, Trp-Ar-*H*), 7.32 (1H, br d, *J* = 7.6, Trp-N*H*), 7.49 (1H, br d, *J* = 7.6, Trp-Ar-*H*), 8.82 (1H, m, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.9 (Met-CH_3), 23.1 (acetyl-CH_3), 27.3 (Trp-CH_2), 29.9 (Met-CH_2), 31.5 (Met-CH_2), 51.9 (Met-α-CH), 52.5 (ester-CH_3), 52.8 (Trp-α-CH), 109.5 (Ar-C), 111.4 (Ar-C), 118.4 (Ar-C), 119.7 (Ar-C), 122.3 (Ar-C), 123.1 (Ar-C), 127.4 (Ar-C), 136.1 (Ar-C), 169.9 (C=O), 170.8 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3275 m (N-H), 3058 w (C-H), 2976 w (C-H), 1731 s (ester C=O), 1640 m (amide C=O), 1451 m (C-H), 1254 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{19}H_{26}N_3O_4S$: 392.1639, found: 392.1640.

Ac-Met-Trp(Boc)-OMe (4c)



4c

Peptide **4c** was synthesised from Ac-Met-Trp-OMe (**SI-6**) (0.294 g, 0.75 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4c** as a white solid (0.262 g, 71%); m.p. 80-81 °C, R_f 0.17 (75% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (9H, s, Boc-(C*H*$_3$)$_3$), 1.84-1.88 (4H, m, acetyl-C*H*$_3$ / Met-C*H*H), 1.94-1.97 (4H, m, Met-C*H*H / Met-C*H*$_3$), 2.42-2.52 (2H, m, Met-C*H*$_2$), 3.13 (1H, dd, *J* = 14.8, *J* = 6.2, Trp-C*H*H), 3.18 (1H, dd, *J* = 14.8, *J* = 6.2, Trp-C*H*H), 3.62 (3H, s, ester-C*H*$_3$), 4.54 (1H, app q, *J* = 7.1, Met-α-C*H*), 4.78-4.82 (1H, m, Trp-α-C*H*), 6.42 (1H, br d, *J* = 7.1, Met-N*H*), 6.98 (1H, br d, *J* = 7.7, Trp-N*H*), 7.12-7.16 (1H, m, Trp-Ar-*H*), 7.20-7.24 (1H, m, Trp-Ar-*H*), 7.36 (1H, br s, Trp-Ar-*H*), 7.40 (1H, d, *J* = 7.9, Trp-Ar-*H*), 8.01 (1H, m, Trp-Ar-*H*).

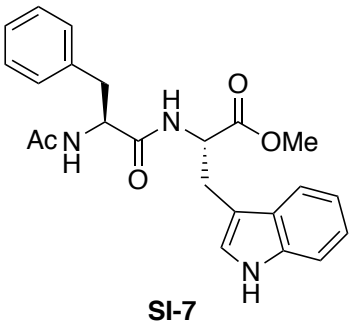
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.9 (Met-CH_3), 22.9 (acetyl-CH_3), 27.2 (Trp-CH_2), 28.1 (Boc-$(CH_3)_3$), 29.8 (Met-CH_2), 31.4 (Met-CH_2), 51.8 (Met-α-CH), 52.4 (ester-CH_3), 52.5 (Trp-α-CH), 83.7 (Boc-C), 114.6 (Ar-C), 115.2 (Ar-C), 118.6 (Ar-C),122.5 (Ar-C),124.1 (Ar-C), 124.5 (Ar-C), 130.1 (Ar-C), 135.2 (Ar-C), 148.4 (C=O), 170.0 (C=O), 171.1 (C=O), 171.5 (C=O)

IR U_{max} /cm^{-1} (solid) 3287 m (N-H), 3050 w (C-H), 2978 w (C-H), 1739 s (ester C=O), 1636 m (amide C=O), 1445 m (C-H), 1220 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{24}H_{34}N_3O_6S$: 492.2163, found: 492.2156.

3.6.4. Synthesis of Ac-Phe-Trp(Boc)-OMe (4d)

Ac-Phe-Trp-OMe (SI-7)



SI-7

The peptide Ac-Phe-Trp-OMe (**SI-7**) was synthesised from L-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetyl-L-phenylalanine (0.207 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-7** as an off-white solid (0.363 g, 89%); m.p. 75-76 °C.

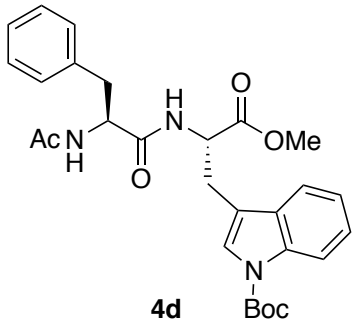
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (3H, s, acetyl-C*H*$_3$), 2.95 (1H, dd, *J* = 14.0, *J* = 6.7, Phe-C*H*H), 3.03 (1H, dd, *J* = 14.0, *J* = 6.7, Phe-C*H*H), 3.22 (2H, d, *J* = 5.5, Trp-C*H*$_2$), 3.62 (3H, s, ester-C*H*$_3$), 4.76 (1H, app q, *J* = 7.6, Phe-α-C*H*), 4.81-4.86 (1H, m, Trp-α-C*H*), 6.41 (1H, d, *J* = 7.6, Phe-N*H*), 6.83 (1H, d, *J* = 7.8, Trp-N*H*), 6.86 (1H, d, *J* = 1.8, Ar-*H*), 7.02 (1H, t, *J* = 7.8, Ar-*H*), 7.09-7.14 (3H, m, Ar-*H*), 7.19-7.26 (4H, m, Ar-*H*), 7.37 (1H, d, *J* = 7.8, Ar-*H*), 8.54 (1H, m, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0 (acetyl-CH_3), 27.4 (Trp-CH_2), 38.1 (Phe-CH_2), 52.4 (ester-CH_3), 52.9 (Trp-α-CH), 54.1 (Phe-α-CH), 109.5 (Ar-C), 111.4 (Ar-C), 118.4 (Ar-C), 119.7 (Ar-C), 122.3 (Ar-C), 123.1 (Ar-C), 127.0 (Ar-C), 127.4 (Ar-C), 128.6 (Ar-C), 129.4 (Ar-C), 136.0 (Ar-C), 136.4 (Ar-C), 169.9 (C=O), 170.3 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3275 m (N-H), 3024 w (C-H), 2989 w (C-H), 1727 s (ester C=O), 1646 m (amide C=O), 1550 m (C=C), 1401 m (C-H), 1220 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{23}H_{26}N_3O_4$: 408.1918, found: 408.1914.

Ac-Phe-Trp(Boc)-OMe (4d)



4d

Peptide **4d** was synthesised from Ac-Phe-Trp-OMe (**SI-7**) (0.306 g, 0.75 mmol) using the procedure in **section 2.3.** Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4d** as a white solid (0.305 g, 80%); m.p. 79-81 °C, R_f 0.28 (75% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (9H, s, Boc-(C*H*$_3$)$_3$), 1.79 (3H, s, acetyl-C*H*$_3$), 2.93 (1H, dd, *J* = 13.8, *J* = 7.4, Phe-C*H*H), 2.97-3.18 (2H, m, Phe-C*H*H / Trp-C*H*H), 3.13 (1H, dd, *J* = 14.8, *J* = 5.8, Trp-C*H*H), 3.59 (3H, s, ester-C*H*$_3$), 4.57 (1H, app q, *J* = 7.3, Phe-α-C*H*), 4.75 (1H, dt, *J* = 7.6, *J* = 5.8, Trp-α-C*H*), 6.03 (1H, br d, *J* = 7.6, Trp-N*H*), 6.31 (1H, br d, *J* = 7.4, Phe-N*H*), 7.07-7.12 (3H, m, Ar-*H*), 7.13-7.22 (4H, m, Ar-*H*), 7.24-7.28 (2H, m, Ar-*H*), 8.01 (1H, m Ar-*H*).

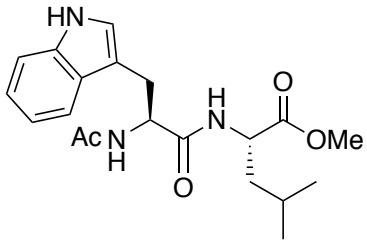
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.3 (Trp-CH_2), 28.1 (Boc-$(CH_3)_3$), 38.0 (Phe-CH_2), 52.4 (ester-CH_3), 52.6 (Trp-α-CH), 54.2 (Phe-α-CH), 83.7 (Boc-C), 114.5 (Ar-C), 115.3 (Ar-C), 118.6 (Ar-C), 122.5 (Ar-C), 124.2 (Ar-C), 124.5 (Ar-C), 126.9 (Ar-C), 128.5 (Ar-C), 129.2 (Ar-C), 130.2 (Ar-C), 135.2 (Ar-C), 136.3 (Ar-C), 149.5 (C=O), 169.9 (C=O), 170.6 (C=O), 171.3 (C=O).

IR U_{max} /cm^{-1} (solid) 3278 m (N-H), 3033 w (C-H), 2934 w (C-H), 1736 s (ester C=O), 1642 m (amide C=O), 1441 m (C-H), 1235 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{28}H_{34}N_3O_6$: 508.2442, found: 508.2436.

3.6.5. Synthesis of Ac-Trp(Boc)-Leu-OMe (4e)

Ac-Trp-Leu-OMe (SI-8)



SI-8

The peptide Ac-Trp-Leu-OMe (**SI-8**) was synthesised from L-leucine methyl ester hydrochloride (0.454 g, 2.50 mmol) and *N*-acetyl-L-tryptophan (0.246 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-8** as a yellow solid (0.295 g, 79%); m.p. 74-76 °C.

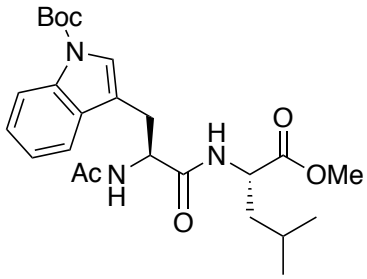
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83-0.89 (6H, m, Leu-C*H*$_3$ (x2)), 1.09-1.17 (1H, m, Leu-C*H*), 1.46-1.53 (2H, m, Leu-C*H*$_2$), 2.00 (3H, s, acetyl-C*H*$_3$), 3.14 (1H, dd, *J* = 14.5, *J* = 8.3, Trp-C*H*H), 3.29-3.35 (1H, m, Trp-C*H*H), 3.66 (3H, s, ester-C*H*$_3$), 4.48 (1H, dt, *J* = 8.3, *J* = 5.2, Trp-α-C*H*), 4.73-4.78 (1H, m, Leu-N*H*), 6.04-6.06 (1H, m, Trp-N*H*), 6.34-6.35 (1H, m, Leu-N*H*), 7.12-7.16 (2H, m, Trp-Ar-*H*), 7.21 (1H, t, *J* = 7.6, Trp-Ar-*H*), 7.37 (1H, d, *J* = 7.6, Trp-Ar-*H*), 7.75 (1H, d, *J* = 7.6, Trp-Ar-*H*), 8.17 (1H, m, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 22.6 (Leu-CH_3), 23.3 (acetyl-CH_3), 24.6 (Leu-CH), 28.5 (Trp-CH_2), 41.4 (Leu-CH_2), 50.9 (Leu-α-CH), 52.2 (ester-CH_3), 53.7 (Trp-α-CH), 110.6 (Ar-C), 111.1 (Ar-C), 118.9 (Ar-C), 119.8 (Ar-C), 122.2 (Ar-C), 123.4 (Ar-C), 127.4 (Ar-C), 136.1 (Ar-C), 169.9 (C=O), 171.0 (C=O), 172.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3274 m (N-H), 3058 w (C-H), 2918 w (C-H), 1735 s (ester C=O), 1640 m (amide C=O), 1433 m (C-H), 1340 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{20}H_{28}N_3O_4$: 374.2074, found: 374.2077.

Ac-Trp(Boc)-Leu-OMe (4e)



4e

Peptide **4e** was synthesised from Ac-Trp-Leu-OMe (**SI-8**) (0.280 g, 0.75 mmol) using the procedure in **section 2.3.** Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4e** as a white solid (0.464 g, 98%); m.p. 80-81 °C, R_f 0.21 (75% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.88 (6H, m, Leu-C*H*$_3$ (x2)), 1.49-1.55 (3H, m, Leu-C*H*$_2$ / Leu-C*H*), 1.65 (9H, s, Boc-(C*H*$_3$)$_3$), 1.99 (3H, s, acetyl-C*H*$_3$), 3.11 (1H, dd, *J* = 14.5, *J* = 7.9, Trp-C*H*H), 3.20 (1H, dd, *J* = 14.5, *J* = 5.6, Trp-C*H*H), 3.66 (3H, s, ester-C*H*$_3$), 4.46-4.51 (1H, m, Trp-α-C*H*), 4.79 (1H, dt, *J* = 7.6, *J* = 5.7, Leu-α-C*H*), 6.36 (1H, d, *J* = 7.9, Trp-N*H*), 6.53 (1H, d, *J* = 7.6, Leu-N*H*), 7.23 (1H, t, *J* = 7.1, Trp-Ar-*H*), 7.31 (1H, t, *J* = 7.1, Trp-Ar-*H*), 7.50 (1H, br s, Trp-Ar-*H*), 7.67 (1H, d, *J* = 7.8, Trp-Ar-*H*), 8.12 (1H, m, Trp-Ar-*H*).

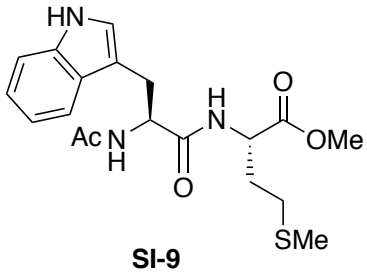
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Leu-CH_3), 22.7 (Leu-CH_3), 23.2 (acetyl-CH_3), 24.7 (Leu-CH), 28.2 (Boc-$(CH_3)_3$), 28.2 (Trp-CH_2), 41.4 (Leu-CH_2), 50.9 (Leu-α-CH), 52.3 (ester-CH_3), 53.2 (Trp-α-CH), 83.6 (Boc-C), 115.2 (Ar-C), 115.3 (Ar-C), 119.1 (Ar-C), 122.7 (Ar-C), 124.5 (Ar-C), 124.6 (Ar-C), 130.3 (Ar-C), 135.4 (Ar-C), 149.6 (C=O), 170.0 (C=O), 170.7 (C=O), 172.5 (C=O).

IR υ_{max} /cm^{-1} (solid) 3263 m (N-H), 3060 w (C-H), 2955 w (C-H), 1741 s (ester C=O), 1622 m (amide C=O), 1541 m (C=C), 1430 m (C-H), 1252 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{25}H_{36}N_3O_6$: 474.2599, found: 474.2595.

3.6.6. Synthesis of Ac-Trp(Boc)-Met-OMe (4f)

Ac-Trp-Met-OMe



SI-9

The peptide Ac-Trp-Met-OMe (**SI-9**) was synthesised from L-methionine methyl ester hydrochloride (0.499 g, 2.50 mmol) and *N*-acetyl-L-tryptophan (0.246 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **SI-9** as a yellow solid (0.348 g, 89%); m.p. 126-127 °C.

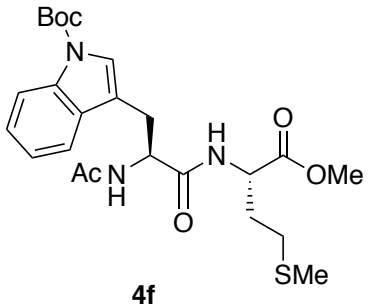
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.81 (1H, m, Met-C*H*H), 1.87 (3H, s, Met-CH_3), 1.92-1.98 (4H, m, acetyl-CH_3 / Met-C*H*H), 2.27 (2H, d, *J* = 7.7, Met-CH_2), 3.10 (1H, dd, *J* = 14.6, *J* = 7.6, Trp-C*H*H), 3.20 (1H, dd, *J* = 14.6, *J* = 5.4, Trp-C*H*H), 3.56 (3H, s, ester-CH_3), 4.48 (1H, dt, *J* = 7.6, *J* = 5.4, Met-α-C*H*), 4.73 (1H, dt, *J* = 7.4, *J* = 5.4, Trp-α-C*H*), 6.50 (1H, d, *J* = 7.7, Met-N*H*), 6.71 (1H, d, *J* = 7.4, Trp-N*H*), 7.00-7.03 (2H, m, Trp-Ar-*H*), 7.09 (1H, t, *J* = 7.5, Trp-Ar-*H*), 7.26 (1H, d, *J* = 7.5, Trp-Ar-*H*), 7.56 (1H, d, *J* = 7.5, Trp-Ar-*H*), 8.47 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.2 (Met-CH_3), 23.1 (acetyl-CH_3), 28.3 (Met-CH_2), 29.6 (Met-CH_2), 31.2 (Trp-CH_2), 51.5 (Trp-α-CH), 52.4 (ester-CH_3), 53.9 (Met-α-CH), 110.1 (Ar-C), 111.2 (Ar-C), 118.5 (Ar-C), 119.5 (Ar-C), 122.0 (Ar-C), 123.4 (Ar-C), 124.4 (Ar-C), 136.1 (Ar-C), 170.2 (C=O), 171.4 (C=O), 171.7 (C=O).

IR U_{max} /cm^{-1} (solid) 3291 m (N-H), 3054 w (C-H), 2914 w (C-H), 1743 s (ester C=O), 1631 m (amide C=O), 1431 m (C-H), 1224 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{19}H_{26}N_3O_4S$: 392.1639, found: 392.1637.

Ac-Trp(Boc)-Met-OMe (4f)



4f

Peptide **4f** was synthesised from Ac-Trp-Met-OMe (**SI-9**) (0.294 g, 0.75 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4f** as a white solid (0.398 g, 81%); m.p. 154-155 °C, R_f 0.19 (75% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (9H, s, Boc-(C*H*$_3$)$_3$), 1.87-1.94 (1H, m, Met-C*H*H), 2.00-2.09 (7H, m, Met-C*H*H / Met-C*H*$_3$ / acetyl-C*H*$_3$), 2.38 (1H, br t, *J* = 7.3, Met-C*H*$_2$), 3.10 (1H, dd, *J* = 14.4, *J* = 8.0, Trp-C*H*H), 3.22 (1H, dd, *J* = 14.4, *J* = 5.5, Trp-C*H*H), 3.66 (3H, s, ester-C*H*$_3$), 4.55 (1H, dt, *J* = 7.3, *J* = 5.0, Met-α-C*H*), 4.77 (1H, dt, *J* = 8.0, *J* = 5.5, Trp-α-C*H*), 6.49 (1H, d, *J* = 7.3, Met-N*H*), 6.57 (1H, d, *J* = 8.0, Trp-N*H*), 7.23 (1H, t, *J* = 7.5, Trp-Ar-*H*), 7.31 (1H, t, *J* = 7.5, Trp-Ar-*H*), 7.49 (1H, s, Trp-Ar-*H*), 7.65 (1H, d, *J* = 7.5, Trp-Ar-*H*), 8.10 (1H, m, Trp-Ar-*H*),

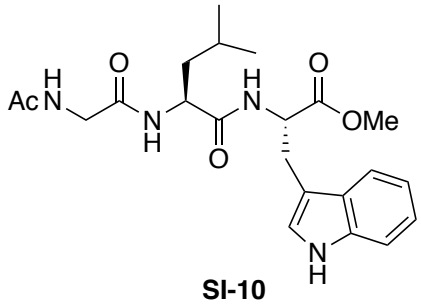
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.3 (Met-CH_3), 23.2 (acetyl-CH_3), 28.1 (Boc-(CH_3)$_3$), 28.2 (Trp-CH_2), 29.7 (Met-CH_2), 31.3 (Met-CH_2), 51.6 (Trp-α-CH), 52.5 (ester-CH_3), 53.3 (Met-α-CH), 83.6 (Boc-C), 115.1 (Ar-C), 115.2 (Ar-C), 119.0 (Ar-C), 122.7 (Ar-C), 124.5 (Ar-C), 124.6 (Ar-C), 130.1 (Ar-C), 135.4 (Ar-C), 149.5 (C=O), 170.0 (C=O), 170.7 (C=O), 171.4 (C=O).

IR U_{max} /cm^{-1} (solid) 3291 m (N-H), 3055 w (C-H), 2915 w (C-H), 1743 s (ester C=O), 1631 m (amide C=O), 1431 m (C-H), 1224 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{24}H_{34}N_3O_6S$: 492.2163, found: 492.2160.

3.6.7. Synthesis of Ac-Gly-Leu-Trp(Boc)-OMe (4g)

Ac-Gly-Leu-Trp-OMe (SI-10)



SI-10

The peptide Ac-Gly-Leu-Trp-OMe (**SI-10**) was synthesised from Ac-Gly-Leu-OMe (0.241 g, 0.80 mmol) and L-tryptophan methyl ester hydrochloride (0.509 g, 2.00 mmol), using the procedure in **section 2.2**. Purification by trituration (Et_2O) afforded **SI-10** as a white solid (0.255 g, 74%); m.p. 144-146 °C.

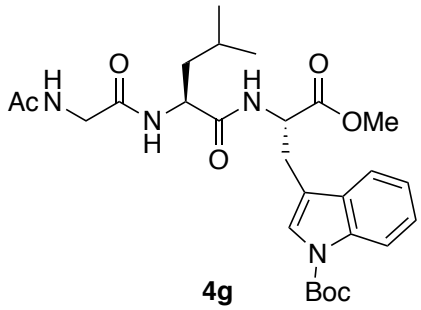
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 9.5, Leu-C*H*$_3$), 0.88 (3H, d, *J* = 9.5, Leu-C*H*$_3$), 1.48-1.50 (1H, m, Leu-C*H*H), 1.57-1.63 (1H, m, Leu-C*H*H), 1.70-1.76 (1H, m, Leu-C*H*$(CH_3)_2$), 1.91 (3H, s, acetyl-C*H*$_3$), 3.24 (1H, dd, *J* = 14.9, *J* = 6.3, Trp-C*H*H), 3.31 (1H, dd, *J* = 14.9, *J* = 5.0, Trp-C*H*H), 3.66-3.72 (1H, m, Gly-C*H*H), 3.70 (3H, s, ester-C*H*$_3$), 3.80 (1H, dd, *J* = 16.8, *J* = 5.6, Gly-C*H*H), 4.58-4.60 (1H, m, Leu-α-C*H*), 4.88-4.93 (1H, m, Trp-α-C*H*), 6.28 (1H, br t, *J* = 5.3, Gly-N*H*), 6.70 (1H, br d, *J* = 8.6, Leu-N*H*), 6.98 (1H, m, Trp-Ar-*H*), 7.05-7.10 (2H, m, Trp-Ar-*H* / Trp-N*H*), 7.16 (1H, t, *J* = 7.4, Trp-Ar-*H*), 7.32 (1H, d, *J* = 7.4, Trp-Ar-*H*), 7.50 (1H, d, *J* = 7.4, Trp-Ar-*H*), 8.66 (1H, s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Leu-CH_3 (x2)), 22.8 (acetyl-CH_3), 24.7 (Leu-CH), 27.5 (Trp-CH_2), 41.0 (Leu-CH_2), 42.8 (Gly-CH_2), 51.6 (Leu-α-CH), 52.5 (ester-CH_3), 52.7 (Trp-α-CH), 109.3 (Ar-C), 111.4 (Ar-C), 118.3 (Ar-C), 119.4 (Ar-C), 122.1 (Ar-C), 123.4 (Ar-C), 127.4 (Ar-C), 136.0 (Ar-C),169.0 (C=O), 171.0 (C=O), 171.9 (C=O), 172.2 (C=O).

IR U_{max} /cm^{-1} (solid) 3282 m (N-H), 3055 w (C-H), 2928 w (C-H), 1739 s (ester C=O), 1631 m (amide C=O), 1431 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{22}H_{31}N_4O_5$: 431.2289, found: 431.2286.

Ac-Gly-Leu-Trp(Boc)-OMe (4g)



4g

Peptide **4g** was synthesised from Ac-Gly-Leu-Trp-OMe (**SI-10**) (0.237 g, 0.55 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4g** as a white solid. (0.181 g, 62%); m.p. 116-118 °C, R_f 0.10 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 10.0, Leu-C*H*$_3$), 0.91 (3H, d, *J* = 10.0, Leu-C*H*$_3$), 1.46-1.52 (1H, m, Leu-C*H*), 1.55-1.64 (2H, m, Leu-C*H*$_2$), 1.68 (9H, s, Boc-(C*H*$_3$)$_3$), 2.01 (3H, s, acetyl-C*H*$_3$), 3.19 (1H, dd, *J* = 14.8, *J* = 6.3, Trp-C*H*H), 3.27 (1H, dd, *J* = 14.8, *J* = 6.3, Trp-C*H*H), 3.68 (3H, s, ester-C*H*$_3$), 3.80-3.92 (2H, m, Gly-C*H*$_2$), 4.42-4.48 (1H, m, Leu-α-C*H*), 4.88 (1H, dt, *J* = 7.4, *J* = 6.3, Trp-α-C*H*), 6.86-6.71 (2H, m, Gly-N*H* / Leu-N*H*), 6.94 (1H, d, *J* = 7.4, Trp-N*H*), 7.22 (1H, t, *J* = 7.4, Trp-Ar-*H*), 7.30 (1H, t, *J* = 7.4, Trp-Ar-*H*), 7.42 (1H, s, Trp-Ar-*H*), 7.48 (1H, d, *J* = 7.4, Trp-Ar-*H*), 8.05 (1H, br d, Trp-Ar-*H*).

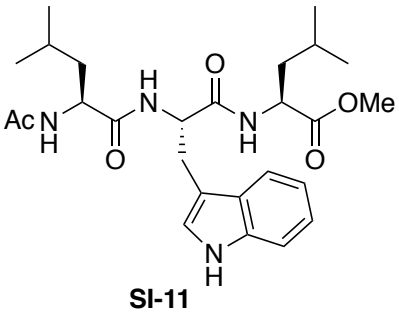
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Leu-CH_3), 22.8 (acetyl-CH_3), 24.6 (Leu-CH), 27.2 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 40.4 (Leu-CH_2), 43.2 (Gly-CH_2), 51.7 (Leu-α-CH), 52.4 (ester-CH_3), 52.5 (Trp-α-CH), 84.0 (Boc-C), 114.9 (Ar-C), 115.3 (Ar-C), 118.8 (Ar-C), 122.6 (Ar-C), 124.3 (Ar-C), 124.5 (Ar-C), 130.4 (Ar-C), 135.1 (Ar-C), 149.9 (C=O), 169.2 (C=O), 170.9 (C=O), 171.5 (C=O), 172.7 (C=O).

IR U_{max} /cm^{-1} (solid) 3278 m (N-H), 3060 w (C-H), 2954 w (C-H), 1731 s (ester C=O), 1631 m (amide C=O), 1451 m (C-H), 1226 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{27}H_{39}N_4O_7$: 531.2813, found: 531.2808.

3.6.8. Synthesis of Ac-Leu-Trp(Boc)-Leu-OMe (4h)

Ac-Leu-Trp-Leu-OMe (SI-11)



SI-11

The peptide Ac-Leu-Trp-Leu-OMe (**SI-11**) was synthesised from Ac-Leu-Trp-OMe (0.299 g, 0.80 mmol) and L-leucine methyl ester hydrochloride (0.363 g, 2.00 mmol), using the procedure in **section 2.2**. Purification by trituration (Et_2O) afforded **SI-11** as a white solid (0.343 g, 88%); m.p. 212-215 °C.

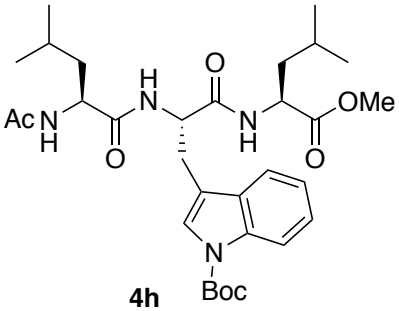
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83-0.85 (6H, m, Leu-C*H*$_3$ (x2)), 0.91 (6H, m, Leu-C*H*$_3$ (x2)), 1.37-1.69 (6H, m, Leu-C*H* (x2) / Leu-C*H*$_2$ (x2)), 1.79 (3H, s, acetyl-C*H*$_3$), 3.17 (1H, dd, *J* = 14.6, *J* = 7.6, Trp-C*H*H), 3.36 (1H, dd, *J* = 14.6, *J* = 5.4, Trp-C*H*H), 3.67 (3H, s, ester-C*H*$_3$), 4.36-4.42 (1H, m, Leu-α-C*H*), 4.47 (1H, dt, *J* = 8.4, *J* = 5.0, Leu-α-C*H*), 4.73 (1H, dt, *J* = 7.6, *J* = 5.4, Trp-α-C*H*), 5.69 (1H, d, *J* = 7.8, Leu-N*H*), 6.22 (1H, d, *J* = 8.4, Leu-N*H*), 6.70 (1H, d, *J* = 7.6, Trp-N*H*), 7.13-7.16 (2H, m, Trp-Ar-*H*), 7.21 (1H, *J* = 8.0, Trp-Ar-*H*), 7.38 (1H, d, *J* = 8.0, Trp-Ar-*H*), 7.72 (1H, d, *J* = 8.0, Trp-Ar-*H*), 8.14 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.8 (Leu-CH_3), 21.9 (Leu-CH_3), 22.3 (acetyl-CH_3), 23.3 (Leu-CH_3), 23.3 (Leu-CH_3), 25.7 (Leu-CH), 25.8 (Leu-CH), 28.4 (Trp-CH_2), 41.4 (Leu-CH_2), 41.5 (Leu-CH_2), 52.1 (Leu-α-CH), 52.6 (ester-CH_3), 53.4 (Trp-α-CH), 55.2 (Leu-α-CH), 110.6 (Ar-C), 112.2 (Ar-C), 119.3 (Ar-C), 119.8 (Ar-C), 122.3 (Ar-C), 124.7 (Ar-C), 128.9 (Ar-C), 138.0 (Ar-C), 173.5 (Ar-C), 173.8 (Ar-C), 174.3 (Ar-C), 147.5 (Ar-C).

IR U_{max} /cm^{-1} (solid) 3290 m (N-H), 3068 w (C-H), 2956 w (C-H), 1741 s (ester C=O), 1629 m (amide C=O), 1430 m (C-H), 1220 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{39}N_4O_5$: 487.2915, found: 487.2915.

Ac-Leu-Trp(Boc)-Leu-OMe (4h)



4h

Peptide **4h** was synthesised from Ac-Leu-Trp-Leu-OMe (**SI-11**) (0.268 g, 0.55 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4h** as a white solid. (0.287 g, 89%); m.p. 180-184 °C, R_f 0.14 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-0.91 (12H, m, Leu-C*H*$_3$ (x4)), 1.42-1.61 (6H, m, Leu-C*H* (x2) / Leu-C*H*$_2$ (x2)), 1.66 (9H, s, Boc-(C*H*$_3$)$_3$), 1.90 (3H, s, acetyl-C*H*$_3$), 3.11-3.24 (2H, m, Trp-C*H*$_2$), 3.65 (3H, s, ester-C*H*$_3$), 4.43-4.52 (2H, m, Leu-α-C*H* (x2)), 4.73-4.79 (1H, m, Trp-α-C*H*), 5.95 (1H, br d, *J* = 7.3, Leu-N*H*), 6.43 (1H, br d, *J* = 8.7, Trp-N*H*), 6.90 (1H, br d, *J* = 7.8, Leu-N*H*), 7.24-7.34 (2H, m, Trp-Ar-*H*), 7.49 (1H, s, Trp-Ar-*H*), 7.64 (1H, d, *J* = 7.8, Trp-Ar-*H*), 8.11 (1H, m, Trp-Ar-*H*).

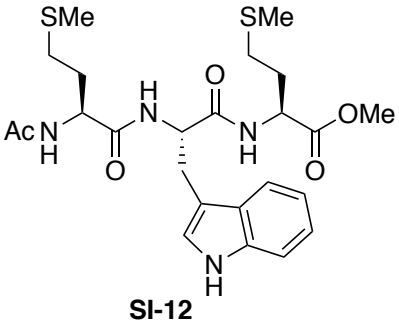
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 22.1 (Leu-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 22.9 (acetyl-CH_3), 24.7 (Leu-CH), 24.7 (Leu-CH), 27.7 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 41.1 (Leu-CH_2), 41.2 (Leu-CH_2), 50.8 (Leu-α-CH), 51.8 (Trp-α-CH), 52.2 (ester-CH_3), 53.0 (Leu-α-CH), 83.7 (Boc-C), 115.2 (Ar-C), 115.3 (Ar-C), 119.1 (Ar-C), 122.7 (Ar-C), 124.5 (Ar-C), 124.6 (Ar-C), 130.1 (Ar-C), 135.4 (Ar-C), 149.6 (C=O), 170.2 (C=O), 170.3 (C=O), 172.0 (C=O), 172.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3254 m (N-H), 3073 w (C-H), 2957 w (C-H), 1720 s (ester C=O), 1631 m (amide C=O), 1545 m (C=C), 1439 m (C-H), 1291 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{31}H_{47}N_4O_7$: 587.3439, found: 587.3441.

3.6.9. Synthesis of Ac-Met-Trp(Boc)-Met-OMe (4i)

Ac-Met-Trp-Met-OMe (SI-12)



SI-12

The peptide Ac-Met-Trp-Met-OMe (**SI-12**) was synthesised from Ac-Met-Trp-OMe (**SI-6**) (0.313 g, 0.80 mmol) and L-methionine methyl ester hydrochloride (0.399 g, 0.80 mmol), using the procedure in **section 2.2**. Purification by trituration (Et_2O) afforded **SI-12** as a white solid (0.335 g, 80%); m.p. 191-193 °C.

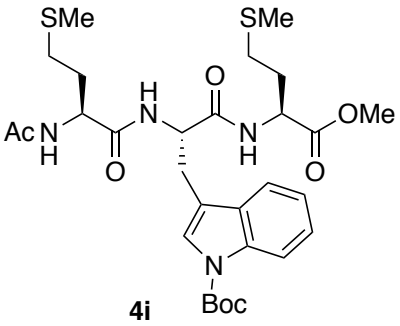
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (3H, s, Met-C*H*$_3$), 1.89-1.97 (2H, m, Met-C*H*$_2$), 2.00 (3H, s, acetyl-C*H*$_3$), 2.03-2.06 (2H, m, Met-C*H*$_2$), 2.09 (3H, s, Met-C*H*$_3$), 2.23-2.29 (2H, m, Met-C*H*$_2$), 2.49-2.61 (2H, m, Met-C*H*$_2$), 3.17 (1H, dd, *J* = 14.5, *J* = 7.0, Trp-C*H*H), 3.39 (1H, dd, *J* = 14.5, *J* = 5.5, Trp-C*H*H), 3.68 (3H, s, ester-C*H*$_3$), 4.51-4.60 (2H, m, Met-α-C*H* (x2)), 4.73-4.78 (1H, m, Trp-α-C*H*), 6.40 (1H, d, *J* = 7.3, Met-N*H*), 6.68 (1H, d, *J* = 7.8, Met-N*H*), 6.92 (1H, d, *J* = 7.7, Trp-N*H*), 7.10 (1H, d, *J* = 2.3, Trp-Ar-*H*), 7.12-7.16 (1H, m, Trp-Ar-*H*), 7.18-7.22 (1H, m, Trp-Ar-*H*), 7.37 (1H, d, *J* = 7.6, Trp-Ar-*H*), 7.64 (1H, d, *J* = 7.6, Trp-Ar-*H*), 8.27 (1H, br s, Trp-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.2 (Met-CH_3), 15.3 (Met-CH_3), 22.8 (acetyl-CH_3), 27.7 (Trp-CH_2), 29.6 (Met-CH_2), 30.2 (Met-CH_2), 30.8 (Met-CH_2), 31.0 (Met-CH_2), 51.5 (Met-α-CH), 52.5 (ester-CH_3), 52.9 (Met-α-CH), 54.0 (Trp-α-CH), 109.8 (Ar-C), 111.4 (Ar-C), 118.6 (Ar-C), 119.8 (Ar-C), 122.3 (Ar-C), 123.8 (Ar-C), 127.4 (Ar-C), 136.2 (Ar-C), 170.5 (C=O), 170.8 (C=O), 171.8 (C=O), 172.3 (C=O).

IR υ_{max} /cm^{-1} (solid) 3254 m (N-H), 3070 w (C-H), 2915 w (C-H), 17437 s (ester C=O), 1627 m (amide C=O), 1436 m (C-H), 1224 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{24}H_{35}N_4O_5S_2$: 523.2043, found: 523.2037.

Ac-Met-Trp(Boc)-Met-OMe (4i)



4i

Peptide **4i** was synthesised from Ac-Met-Trp-Met-OMe (**SI-12**) (0.268 g, 0.55 mmol) using the procedure in **section 2.3.** Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4i** as a white solid. (0.287 g, 87%); m.p. 180-184 °C, R_f 0.35 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.88 (1H, dd, *J* = 14.6, *J* = 7.3 Met-C*H*H), 1.92-1.94 (4H, m, Met-C*H*$_3$ / Met-C*H*H), 1.96-1.99 (4H, m, Met-C*H*$_3$ / Met-C*H*H), 2.01-2.04 (4H, m, acetyl-C*H*$_3$ / Met-C*H*H), 2.33 (2H, t, *J* = 7.3, Met-C*H*$_2$), 2.46-2.51 (2H, m, Met-C*H*$_2$), 3.09-3.20 (2H, m, Trp-C*H*$_2$), 3.64 (3H, s, ester-C*H*$_3$), 4.54 (1H, dt, *J* = 7.3, *J* = 5.0, Met-α-C*H*), 4.66 (1H, dt, *J* = 7.3, *J* = 6.8, Met-α-C*H*), 4.82 (1H, dt, *J* = 7.5, *J* = 6.8, Trp-α-C*H*), 6.68 (1H, d, *J* = 7.8, Met-N*H*), 6.99 (1H, d, *J* = 7.8, Met-N*H*), 7.18 (1H, t, *J* = 7.8, Trp-Ar-*H*), 7.25-7.30 (2H, m, Trp-Ar-*H* / Trp-N*H*), 7.48 (1H, s, trp-Ar-*H*), 7.53 (1H, d, *J* = 7.8, Trp-Ar-*H*), 8.06 (1H, m, Trp-Ar-*H*).

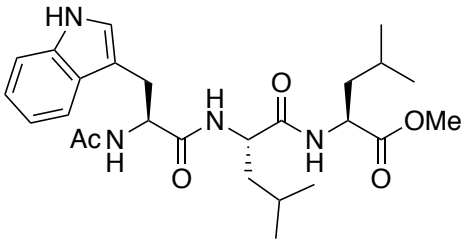
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.2 (Met-CH_3), 15.3 (Met-CH_3), 23.0 (acetyl-CH_3), 28.0 (Trp-CH_2), 28.1 (Boc-$(CH_3)_3$), 29.7 (Met-CH_2), 30.0 (Met-CH_2), 31.2 (Met-CH_2), 31.5 (Met-CH_2), 51.5 (Met-α-CH), 52.3 (ester-CH_3), 52.4 (Met-α-CH), 53.3 (Trp-α-CH), 83.6 (Boc-C), 115.0 (Ar-C), 115.2 (Ar-C), 118.9 (Ar-C), 122.6 (Ar-C), 124.5 (Ar-C), 124.6 (Ar-C), 130.1 (Ar-C), 135.4 (Ar-C), 149.5 (C=O), 170.3 (C=O), 170.5 (C=O), 171.1 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3260 m (N-H), 3069 w (C-H), 2919 w (C-H), 1728 s (ester C=O), 1631 m (amide C=O), 1453 m (C-H), 1224 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{29}H_{43}N_4O_7S_2$: 623.2568, found: 623.2571.

3.6.10. Synthesis of Ac-Trp-Leu-Leu-OMe (4j)

Ac-Trp-Leu-Leu-OMe (SI-13)



SI-13

The peptide Ac-Trp-Leu-Leu-OMe (**SI-13**) was synthesised from Ac-Trp-Leu-OMe (**SI-8**) (0.299 g, 0.80 mmol) and L-leucine methyl ester hydrochloride (0.363 g, 2.00 mmol), using the procedure in **section 2.2.** Purification by trituration (Et_2O) afforded **SI-13** as a white solid (0.370 g, 95%); m.p.187-188 °C,

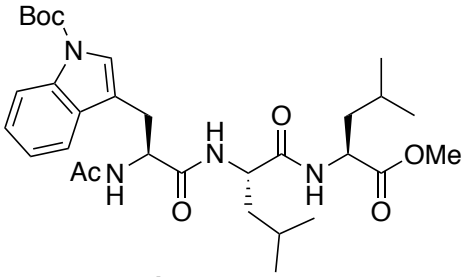
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83-0.86 (6H, m, Leu-(C*H*$_3$)$_2$), 0.92-0.94 (6H, m, Leu-(C*H*$_3$)$_2$), 1.36-1.43 (1H, m, Leu-C*H*H), 1.48-1.55 (2H, m, Leu-C*H*H / Leu-C*H*$(CH_3)_2$), 1.58-1.65 (3H, m, Leu-C*H*$_2$ / Leu-C*H*$(CH_3)_2$), 1.97 (3H, s, acetyl-C*H*$_3$), 3.15 (1H, dd, *J* = 14.6, *J* = 7.4, Trp-C*H*H), 3.28 (1H, dd, *J* = 14.6, *J* = 6.0, Trp-C*H*H), 3.73 (3H, s, ester-C*H*$_3$), 4.40 (1H, m, Leu-α-C*H*), 4.56 (1H, dt, *J* = 8.4, *J* = 5.0, Leu-α-C*H*), 4.78 (1H, app q, *J* = 6.0, Trp-α-C*H*), 6.35-6.41 (2H, m, Leu-N*H* / Trp-N*H*), 6.54 (1H, d, *J* = 8.4, Leu-N*H*), 7.08 (1H, m, Trp-Ar-*H*), 7.14 (1H, t, *J* = 7.9, Trp-Ar-*H*), 7.21 (1H, t, *J* = 7.9, Trp-Ar-*H*), 7.36 (1H, d, *J* = 7.9, Trp-Ar-*H*), 7.72 (1H, d, *J* = 7.9, Ar-*H*), 8.23 (1H, br s, Trp-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Leu-CH_3), 22.0 (Leu-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 23.2 (acetyl-CH_3), 24.6 (Leu-CH_2), 24.8 (Leu-CH_2), 28.1 (Trp-CH_2), 40.8 (Leu-CH), 41.2 (Leu-CH), 50.7 (Leu-α-CH), 52.0 (Trp-α-CH), 52.3 (ester-CH_3), 53.8 (Leu-α-CH), 110.4 (Ar-C), 111.3 (Ar-C), 118.8 (Ar-C), 119.8 (Ar-C), 122.4 (Ar-C), 123.3 (Ar-C), 127.4 (Ar-C), 136.2 (Ar-C), 170.2 (C=O), 171.4 (C=O), 171.4 (C=O), 173.2 (C-O).

IR U_{max} /cm^{-1} (solid) 382 m (N-H), 3029 w (C-H), 2988 w (C-H), 1739 s (ester C=O), 1632 m (amide C=O), 1221 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{39}N_4O_5$: 487.2915, found: 487.2914.

Ac-Trp(Boc)-Leu-Leu-OMe (4j)



4j

Peptide **4j** was synthesised from Ac-Trp-Leu-Leu-OMe (**SI-13**) (0.268 g, 0.55 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **4j** as a white solid. (0.284 g, 88%); m.p. 198-199 °C, R_f 0.16 (EtOAc).

^{1}H NMR (400 MHz, CD_3OD) δ 0.88-0.95 (12H, m, Leu-C*H*$_3$ (x4)), 1.52-1.63 (6H, m, Leu-C*H* (x2) / Leu-C*H*$_2$ (x2)), 1.67 (9H, s, Boc-(C*H*$_3$)$_3$), 1.91 (3H, s, acetyl-C*H*$_3$), 3.00 (1H, dd, *J* = 15.0, *J* = 8.2, Trp-C*H*H), 3.22 (1H, dd, *J* = 15.0, *J* = 5.1, Trp-C*H*H), 3.69 (3H, s, ester-C*H*$_3$), 4.39-4.45 (2H, m, Leu-α-C*H* (x2)), 4.71-4.75 (1H, m, Trp-α-C*H*), 7.21-7.24 (1H, m, Trp-Ar-*H*), 7.26-7.30 (1H, m, Trp-Ar-*H*), 7.51 (1H, s, Trp-Ar-*H*), 7.65 (1H, d, *J* = 8.0, Trp-Ar-*H*), 8.07 (1H, br d, *J* = 8.0, Trp-Ar-*H*).

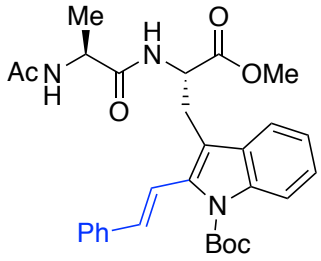
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Leu-CH_3), 22.1 (Leu-CH_3), 22.6 (Leu-CH_3), 22.7 (Leu-CH_3), 23.0 (acetyl-CH_3), 24.5 (Leu-CH), 24.9 (Leu-CH), 27.6 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 41.0 (Leu-CH_2), 41.1 (Leu-CH_2), 50.8 (Leu-α-CH), 51.9 (Trp-α-CH), 52.2 (ester-CH_3), 53.1 (Leu-α-CH), 83.8 (Boc-C), 115.2 (Ar-C), 115.3 (Ar-C), 118.9 (Ar-C), 122.7 (Ar-C), 124.3 (Ar-C), 124.5 (Ar-C), 130.3 (Ar-C), 135.3 (Ar-C), 149.7 (C=O), 170.4 (C=O), 171.3 (C=O), 171.5 (C=O), 173.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3297 m (N-H), 2960 w (C-H), 1750 s (ester C=O), 1628 m (amide C=O), 1246 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{31}H_{47}N_4O_7$: 587.3439, found: 587.3441.

3.7. Synthesis of modified peptides 5a-j

Synthesis of modified peptide 5a



5a

Modified peptide **5a** was prepared from Ac-Ala-Trp(Boc)-OMe (**4a**) (0.103 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5a** and a di-olefinated peptide in a ratio of 14:1. Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5a** as an off-white solid (0.086 g, 68%); m.p. 93-95 °C, R_f 0.26 (75% EtOAc/pet. ether).

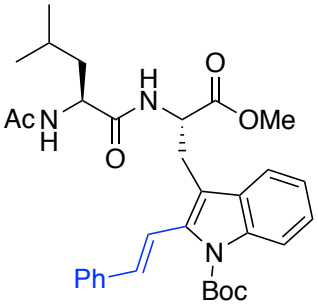
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, *J* = 7.0, Ala-C*H*$_3$), 1.56 (9H, s, Boc-(C*H*$_3$)$_3$), 1.79 (3H, s, acetyl-C*H*$_3$), 3.25-3.36 (2H, m, Trp-C*H*$_2$), 3.48 (3H, s, ester-C*H*$_3$), 4.33 (1H, dq, *J* = 7.4, *J* = 7.0, Ala-α-C*H*), 4.81 (1H, dt, *J* = 7.8, *J* = 7.3, Trp-α-C*H*), 5.82 (1H, br d, *J* = 7.4, Ala-N*H*), 6.51 (1H, br d, *J* = 7.8, Trp-N*H*), 6.69 (1H, d, *J* = 16.7, alkene-C*H*), 7.15-7.27 (4H, m, Ar-*H*/alkene-C*H*), 7.31 (2H, t, *J* = 7.4, Ar-*H*), 7.48 (3H, d, *J* = 7.4, Ar-*H*), 8.06 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.3 (Ala-CH_3), 23.1 (acetyl-CH_3), 27.5 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 48.5 (Ala-α-CH), 52.5 (ester-CH_3), 52.6 (Trp-α-CH), 84.1 (Boc-C), 114.4 (Ar-C), 115.6 (Ar-C), 118.7 (Ar-C), 119.3 (alkene-CH), 122.8 (Ar-C), 124.7 (Ar-C), 126.5 (Ar-C), 128.0 (Ar-C), 128.7 (Ar-C), 129.9 (Ar-C), 132.4 (alkene-CH), 135.8 (Ar-C), 136.2 (Ar-C), 136.7 (Ar-C), 150.3 (C=O), 169.7 (C=O), 171.8 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3281 m (N-H), 3036 w (C-H), 2928 w (C-H), 1725 s (ester C=O), 1631 m (amide C=O), 1541 m (C=C), 1448 m (C-H), 1221 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{30}H_{36}N_3O_6$: 534.2599, found: 534.2600.

Synthesis of modified peptide 5b



5b

Modified peptide **5b** was prepared from Ac-Leu-Trp(Boc)-OMe (**4b**) (0.113 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5b** and a di-olefinated peptide in a ratio of 19:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5b** as an off-white solid (0.085 g, 62%); m.p. 97-98°C, R_f 0.22 (50% EtOAc/pet. ether).

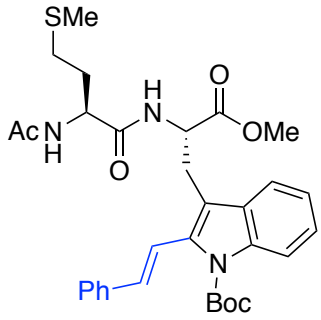
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-0.88 (6H, m, Leu-C*H*$_3$ (x2)), 1.37-1.41 (1H, m, Leu-C*H*), 1.54-1.59 (2H, m, Leu-C*H*$_2$), 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.87 (3H, s, acetyl-C*H*$_3$), 3.31-3.43 (2H, m, Trp-C*H*$_2$), 3.57 (3H, s, ester-C*H*$_3$), 4.41 (1H, dt, *J* = 8.6, *J* = 5.4, Leu-α-C*H*), 4.87 (1H, app q, *J* = 7.2, Trp-α-C*H*), 5.66 (1H, br d, *J* = 8.6, Leu-N*H*), 6.51 (1H, br d, *J* = 7.7, Trp-N*H*), 6.75 (1H, d, *J* = 16.6, alkene-C*H*), 7.24-7.33 (5H, m, Ar-*H* / alkene-C*H*), 7.39 (2H, t, *J* = 7.4, Ar-*H*), 7.56-7.58 (2H, m, Ar-*H*), 8.13 (1H, d, *J* = 8.3, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.0 (Leu-CH_3), 22.8 (Leu-CH_3), 23.1 (acetyl-CH_3), 24.6 (Leu-CH), 27.7 (Trp-CH_2), 28.3 (Boc-$(CH_3)_3$), 41.2 (Leu-CH_2), 51.3 (Leu-α-CH), 52.5 (ester-CH_3), 52.5 (Trp-α-CH), 84.0 (Boc-C), 114.5 (Ar-C), 115.6 (Ar-C), 118.7 (Ar-C), 120.0 (alkene), 122.9 (Ar-C), 124.7 (Ar-C), 126.6 (Ar-C), 128.0 (Ar-C), 128.7 (Ar-C), 129.9 (Ar-C), 132.4 (alkene), 135.8 (Ar-C), 136.2 (Ar-C), 136.8 (Ar-C), 150.4 (C=O), 169.8 (C=O), 171.7 (C=O), 172.0 (C=O).

IR υ_{max} /cm^{-1} (solid) 3268 m (N-H), 2927 w (C-H), 1728 s (ester C=O), 1647 m (amide C=O), 1451 m (C-H), 1255 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{33}H_{42}N_3O_6$ 576.3068, found: 576.3062.

Synthesis of modified peptide 5c



5c

Modified peptide **5c** was prepared from Ac-Met-Trp(Boc)-OMe (**4c**) (0.117 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5c** and a di-olefinated peptide in a ratio of 8.1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5c** as an off-white solid (0.105 g, 74%); m.p. 94-96°C, R_f 0.15 (50% EtOAc/pet. ether).

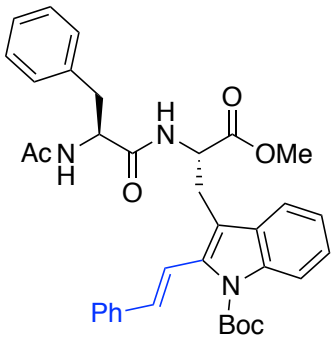
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (9H, s, Boc-(C*H*$_3$)$_3$), 1.86-1.90 (4H, m, Met-C*H*H / acetyl-C*H*$_3$), 1.93-1.97 (1H, m, Met-C*H*), 2.00 (3H, s, Met-C*H*$_3$), 2.47-2.53 (2H, m, Met-C*H*$_2$), 3.35 (1H, dd, *J* = 14.5, *J* = 6.9, Trp-C*H*H), 3.41 (1H, dd, *J* = 14.5, *J* = 6.9, Trp-C*H*H), 3.59 (3H, s, ester-C*H*$_3$), 4.54 (1H, dt, *J* = 7.3, *J* = 7.0, Met-α-C*H*), 4.87 (1H, dt, *J* = 7.3, *J* = 6.9, Trp-α-C*H*), 6.11 (1H, d, *J* = 7.3, Met-N*H*), 6.73-6.78 (2H, m, alkene-C*H* / Ar-*H*), 7.25-7.32 (3H, m, alkene-C*H* / Ar-*H*), 7.36-7.40 (2H, m, Ar-*H*), 7.54-7.57 (3H, m, Ar-*H*), 8.14 (1H, d, *J* = 8.4, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.8 (Met-CH_3), 23.1 (acetyl-CH_3), 27.4 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 29.8 (Met-CH_2), 31.4 (Met-CH_2), 51.6 (Met-α-CH), 52.5 (ester-CH_3), 52.6 (Trp-α-CH), 84.1 (Boc-C), 114.2 (Ar-C), 115.6 (Ar-C), 118.6 (Ar-C), 120.0 (alkene-CH), 122.9 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 128.1 (Ar-C), 128.7 (Ar-C), 129.7 (Ar-C), 132.6 (alkene-CH), 135.8 (Ar-C), 136.2 (Ar-C), 136.7 (Ar-C), 150.3 (C=O), 169.7 (C=O), 170.7 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3282 m (N-H), 3060 w (C-H), 2927 w (C-H), 1743 s (ester C=O), 1646 m (amide C=O), 1459 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{32}H_{40}N_3O_6S$: 594.2632 found: 594.2631.

Synthesis of modified peptide 5d



5d

Modified peptide **5d** was prepared from Ac-Phe-Trp(Boc)-OMe (**4d**) (0.121 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5d** and a di-olefinated tryptophan residue in a ratio of 12:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5d** as an off-white solid (0.075 g, 52%); m.p. 150-151 °C, R_f 0.31 (50% EtOAc/pet. ether).

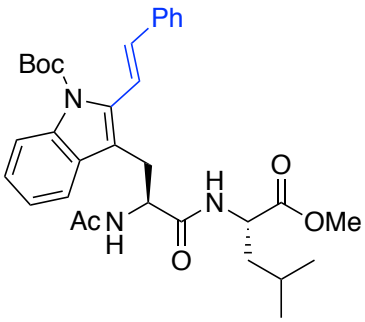
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(C*H*$_3$)$_3$), 1.82 (3H, s, acetyl-C*H*$_3$), 2.92 (1H, dd, *J* = 13.7, *J* = 7.8, Phe-C*H*H), 3.00 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.23-3.33 (2H, m, Trp-C*H*$_2$), 3.50 (3H, s, ester-C*H*$_3$), 4.53-4.59 (1H, m, Phe-α-C*H*), 4.80 (1H, app q, *J* = 7.3, Trp-α-C*H*), 5.59-5.62 (1H, m, Phe-N*H*), 6.19-6.22 (1H, m, Trp-N*H*), 6.71 (1H, d, *J* = 16.5, alkene-C*H*), 7.13-7.25 (6H, m, Ar-*H*), 7.26-7.30 (3H, m, Ar-*H* / alkene-C*H*), 7.35-7.42 (3H, m, Ar-*H*), 7.53 (2H, d, *J* = 7.3, Ar-*H*), 8.11 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.2 (acetyl-CH_3), 27.7 (Trp-CH_2), 28.4 (Boc-(CH_3)$_3$), 38.4 (Phe-CH_2), 52.6 (ester-CH_3), 52.7 (Trp-α-CH), 54.4 (Phe-α-CH), 84.2 (Boc-C), 114.4 (Ar-C), 115.7 (Ar-C), 118.7 (Ar-C), 120.0 (alkene-CH), 123.0 (Ar-C), 124.9 (Ar-C), 126.7 (Ar-C), 127.1 (Ar-C), 128.1 (Ar-C), 128.7 (Ar-C), 128.9 (Ar-C), 129.4 (Ar-C), 130.0 (Ar-C), 132.5 (alkene-CH), 135.9 (Ar-C), 136.2 (Ar-C), 136.5 (Ar-C), 136.9 (Ar-C), 150.5 (C=O), 169.9 (C=O), 170.5 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3238 m (N-H), 3058 w (C-H), 2950 w (C-H), 1749 s (ester C=O), 1638 m (amide C=O), 1523 m (C=C), 1213 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{36}H_{40}N_3O_6$: 610.2912, found: 610.2912.

Synthesis of modified peptide 5e



5e

Modified peptide **5e** was prepared from Ac-Trp(Boc)-Leu-OMe (**4e**) (0.113 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5e** and a di-olefinated peptide in a ratio of 14:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5e** as an off-white solid (0.064 g, 47%); m.p. 94-97 °C, R_f 0.38 (50% EtOAc/pet. ether).

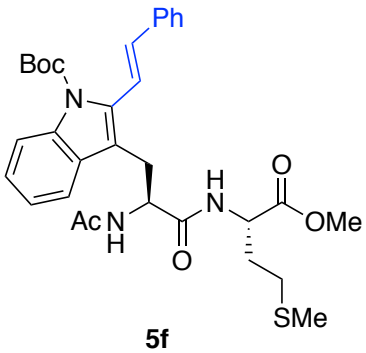
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.86 (6H, m, Leu-C*H*$_3$ (x2)), 1.31-1.41 (1H, m, Leu-C*H*), 1.43-1.47 (2H, m, Leu-C*H*$_2$), 1.65 (9H, s, Boc-(C*H*$_3$)$_3$), 2.00 (3H, s, acetyl-C*H*$_3$), 3.20 (1H, dd, *J* = 14.0, *J* = 9.7, Trp-C*H*H), 3.33 (1H, dd, *J* = 14.0, *J* = 5.6, Trp-C*H*H), 3.50 (3H, s, ester-C*H*$_3$), 4.42 (1H, dt, *J* = 8.3, *J* = 5.6, Trp-α-C*H*), 4.77-4.83 (1H, m, Leu-α-C*H*), 5.78 (1H, d, *J* = 8.3, Trp-N*H*), 6.55 (1H, d, *J* = 7.6, Leu-N*H*), 6.79 (1H, d, *J*= 16.6, alkene-C*H*), 7.25-7.34 (4H, m, alkene-C*H* / Ar-*H*), 7.35-7.39 (2H, m, Ar-*H*), 7.58 (2H, d, *J* = 7.1, Ar-*H*), 7.74 (1H, d, *J* = 7.1, Ar-*H*), 8.13 (1H, d, *J* = 7.7, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.0 (Leu-CH_3), 22.5 (Leu-CH_3), 23.2 (acetyl-CH_3), 24.5 (Leu-CH), 28.2 (Boc-$(CH_3)_3$), 28.8 (Trp-CH_2), 42.0 (Leu-CH_2), 50.8 (Leu-α-CH), 52.1 (ester-CH_3), 53.4 (Trp-α-CH), 83.8 (Boc-C), 114.8 (Ar-C), 115.5 (Ar-C), 118.9 (Ar-C), 119.8 (alkene-CH), 123.1 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 129.6 (Ar-C), 132.0 (alkene-CH), 135.9 (Ar-C), 136.2 (Ar-C), 136.9 (Ar-C), 150.4 (C=O), 169.7 (C=O), 170.3 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3282 m (N-H), 3058 w (C-H), 2955 w (C-H), 1728 s (ester C=O), 1637 m (amide C=O), 1325 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{33}H_{42}N_3O_6$: 576.3068, found: 576.3062.

Synthesis of modified peptide 5f



5f

Modified peptide **5f** was prepared from Ac-Trp(Boc)-Met-OMe (**4f**) (0.117 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5f** and a di-olefinated peptide in a ratio of 10:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5f** as an off-white solid (0.064 g, 45%); m.p. 100-103 °C, R_f 0.18 (50% EtOAc/pet. ether).

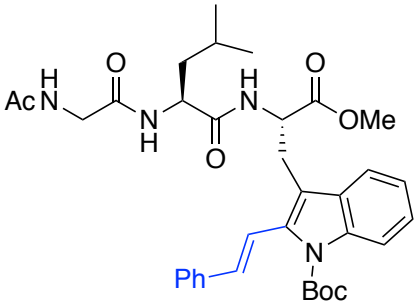
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (9H, s, Boc-(C*H*$_3$)$_3$), 1.78-1.85 (1H, m, Met-C*H*H), 1.94-2.01 (7H, m, Met-C*H*H / Met-C*H*$_3$ / acetyl-C*H*$_3$), 2.28-2.35 (2H, m, Met-C*H*$_2$), 3.19 (1H, dd, *J* = 13.8, *J* = 9.8, Trp-C*H*H), 3.38 (1H, dd, *J* = 13.8, *J* = 5.5, Trp-C*H*H), 3.52 (3H, s, ester-C*H*$_3$), 4.40 (1H, m, Trp-α-C*H*), 4.79 (1H, m, Met-α-C*H*), 6.00 (1H, br d, *J* = 7.4, Trp-N*H*), 6.47 (1H, *J* = 7.4, Met-N*H*), 6.84 (1H, dd, *J* = 16.7, alkene-C*H*), 7.28-7.32 (3H, m, alkene-C*H* / Ar-*H*), 7.35-7.40 (3H, m, Ar-*H*), 7.58-7.60 (2H, m, Ar-*H*), 7.69 (1H, d, J = 7.6, Ar-*H*), 8.12 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.3 (Met-CH_3), 23.2 (acetyl-CH_3), 28.3 (Boc-(CH_3)$_3$), 28.8 (Trp-CH_2), 29.5 (Met-CH_2), 31.9 (Met-CH_2), 51.6 (Met-α-CH), 52.4 (ester-CH_3), 53.5 (Trp-α-CH), 83.9 (Boc-C), 114.8 (Ar-C), 115.6 (Ar-C), 118.8 (Ar-C), 119.7 (alkene-CH), 123.1 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 129.6 (Ar-C), 132.0 (alkene-CH), 136.0 (Ar-C), 136.1 (Ar-C), 136.9 (Ar-C), 150.4 (C=O), 169.7 (C=O), 170.6 (C=O), 170.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3282 m (N-H), 3053 w (C-H), 2965 w (C-H), 1726 s (ester C=O), 1642 m (amide C=O), 1455 m (C-H), 1260 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{32}H_{40}N_3O_6S$: 594.2632, found: 594.2635.

Synthesis of modified peptide 5g



5g

Modified peptide **5g** was prepared from Ac-Gly-Leu-Trp(Boc)-OMe (**4g**) (0.126 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5g** and a di-olefinated peptide in a ratio of 20:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5g** as an off-white solid (0.102 g, 68%); m.p. 165-167 °C, R_f 0.20 (EtOAc).

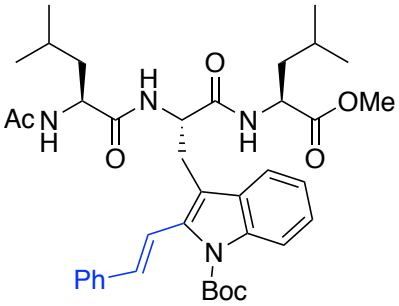
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 9.0, Leu-C*H*$_3$), 0.86 (3H, d, *J* = 9.0, Leu-C*H*$_3$), 1.49-1.57 (3H, m, Leu-C*H* / Leu-C*H*$_2$), 1.64 (9H, s, Boc-(C*H*$_3$)$_3$), 1.97 (3H, s, acetyl-C*H*$_3$), 3.32 (1H, dd, *J* = 14.4, *J* = 7.3, Trp-C*H*H), 3.39 (1H, dd, *J* = 14.4, *J* = 7.3, Trp-C*H*H), 3.59 (3H, s, ester-C*H*$_3$), 3.69-3.83 (2H, m, Gly-C*H*$_2$), 4.34-4.39 (1H, m, Leu-α-C*H*), 4.88-4.93 (1H, m, Trp-α-C*H*), 6.31 (2H, br m, N*H* (x2)), 6.77 (1H, d, *J* = 16.6, alkene-C*H*), 7.15-7.23 (1H, m, Ar-*H*), 7.25-7.40 (6H, m, Ar-*H* / alkene-C*H* / N*H*), 7.56 (2H, d, *J* = 8.0, Ar-*H*), 8.11 (1H, d, *J* = 8.0, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 22.8 (Leu-CH_3), 22.8 (acetyl-C*H*$_3$), 24.6 (Leu-CH), 27.6 (Trp-CH_2), 28.3 (Boc-(C*H*$_3$)$_3$), 40.6 (Leu-CH_2), 43.1 (Gly-CH_2), 51.5 (Leu-α-CH), 52.4 (ester-CH_3), 52.5 (Trp-α-CH), 84.2 (Boc-C), 114.6 (Ar-C), 115.4 (Ar-C), 118.8 (Ar-C), 119.9 (alkene-C), 122.9 (Ar-C), 124.7 (Ar-C), 126.6 (Ar-C), 128.1 (Ar-C), 128.8 (Ar-C), 129.9 (Ar-C), 132.4 (alkene-C), 135.8 (Ar-C), 136.2 (Ar-C), 136.7 (Ar-C), 150.5 (C=O), 168.9 (C=O), 170.9 (C=O), 171.4 (C=O), 172.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3273 m (N-H), 3060 w (C-H), 2958 w (C-H), 1730 s (ester C=O), 1631 m (amide C=O), 1541 m (C=C), 1224 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{35}H_{45}N_4O_7$: 633.3283, found: 633.3286.

Synthesis of modified peptide 5h



5h

Modified peptide **5h** was prepared from Ac-Leu-Trp(Boc)-Leu-OMe (**4h**) (0.140 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5h** and a di-olefinated peptide in a ratio of 12:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5h** as an off-white solid (0.113 g, 69%); m.p. 100-104 °C, R_f 0.24 (50% EtOAc/pet. ether).

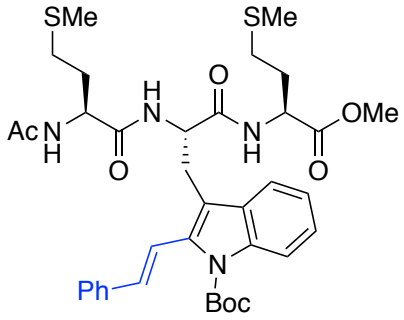
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, *J* = 6.2, Leu-C*H*$_3$), 0.83 (3H, t, *J* = 6.2, Leu-C*H*$_3$), 0.87 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 0.88 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 1.36-1.47 (4H, m, Leu-C*H*H (x2) / Leu-CH (x2)), 1.51-1.59 (2H, m, Leu-C*H*H (x2)), 1.64 (9H, s, Boc-(C*H*$_3$)$_3$), 1.91 (3H, s, acetyl-C*H*$_3$), 3.27-3.37 (2H, m, Trp-C*H*$_2$), 3.55 (3H, s, ester-C*H*$_3$), 4.39-4.48 (2H, m, Leu-α-C*H* / Trp-α-C*H*), 4.77 (1H, app q, *J* = 7.7, Leu-α-C*H*), 5.75 (1H, br d, *J* = 8.0, Leu-N*H*), 5.99 (1H, br d, *J* = 8.0, Trp-N*H*), 6.73-6.77 (2H, m, alkene-C*H* / Leu-N*H*), 7.25-7.32 (3H, m, alkene-C*H* / Ar-*H*), 7.36 (1H, d, *J* = 7.4, Ar-*H*), 7.38-7.40 (2H, m, Ar-*H*), 7.58 (2H, d, *J* = 7.4, Ar-*H*), 7.71 (1H, br d, *J* = 7.4, Ar-*H*), 8.13 (1H, d, *J* = 7.8, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.0 (Leu-CH_3), 22.0 (Leu-CH_3), 22.6 (Leu-CH_3), 22.8 (Leu-CH_3), 23.1 (acetyl-CH_3), 24.6 (Leu-CH), 24.7 (Leu-CH), 28.0 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 41.3 (Leu-CH_2), 41.6 (Leu-CH_2), 50.8 (Leu-α-CH), 51.7 (Trp-α-CH), 52.2 (ester-CH_3), 53.3 (Leu-α-CH), 83.9 (Boc-C), 114.8 (Ar-C), 115.6 (Ar-C), 119.0 (alkene-C), 120.0 (Ar-C), 123.1 (Ar-C), 124.8 (Ar-C), 126.7 (Ar-C), 128.0 (Ar-C),128.7 (Ar-C), 129.5 (Ar-C), 132.2 (alkene-C), 135.9 (Ar-C), 136.3 (Ar-C), 136.8 (Ar-C), 150.4 (C=O), 169.9 (C=O), 170.0 (C=O), 171.8 (C=O), 172.2 (C=O).

IR U_{max} /cm^{-1} (solid) 3273 m (N-H), 3056 w (C-H), 2957 w (C-H), 1730 s (ester C=O), 1627 m (amide C=O), 1541 m (C=C).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{39}H_{53}N_4O_7$: 689.3909, found: 689.3908.

Synthesis of modified peptide 5i



5i

Modified peptide **5i** was prepared from Ac-Met-Trp(Boc)-Met-OMe (**4i**) (0.148 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5i** and the di-olefinated peptide in a ratio of 19:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5i** as an off-white solid (0.095 g, 55%); m.p. 144-146 °C, R_f 0.39 (50% EtOAc/pet. ether).

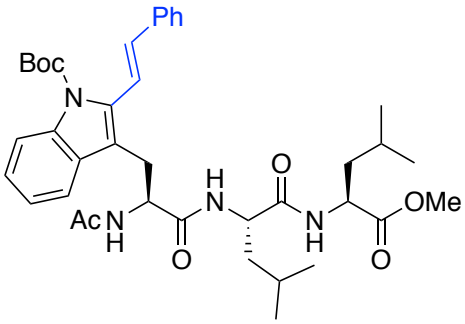
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (9H, s, Boc-(C*H*$_3$)$_3$), 1.76-1.84 (2H, Met-C*H*$_2$), 1.86 (3H, s, Met-C*H*$_3$), 1.92 (3H, s, Met-C*H*$_3$), 1.95-1.97 (4H, s, acetyl-C*H*$_3$ / Met-C*H*H), 2.00-2.08 (1H, m, Met-C*H*H), 2.19-2.28 (2H, m, Met-C*H*$_2$), 2.35-2.45 (2H, m, Met-C*H*$_2$), 3.22 (1H, dd, *J* = 14.3, *J* = 8.6, Trp-C*H*H), 3.29 (1H, dd, *J* = 14.3, *J* = 6.8, Trp-C*H*H), 3.50 (3H, s, ester-C*H*$_3$), 4.40 (1H, dt, *J* = 7.3, *J* = 5.7, Met-α-C*H*), 4.50 (1H, app q, *J* = 7.8, Trp-α-C*H*), 4.69 (1H, app q, *J* = 7.4, Met-α-C*H*), 6.18 (1H, d, *J* = 7.0, Met-N*H*), 6.20 (1H, d, *J* = 7.0, Met-N*H*), 6.71 (1H, d, *J* = 16.8, alkene-C*H*), 6.91 (1H, br d, *J* = 7.8, Trp-N*H*), 7.16-7.33 (7H, m, alkene-C*H* / Ar-*H*), 7.51 (2H, d, *J* = 7.4, Ar-*H*), 7.59 (1H, d, *J* = 7.4, Ar-*H*), 8.06 (1H, d, *J* = 7.4, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.1 (Met-CH_3), 15.3 (Met-CH_3), 23.1 (acetyl-CH_3), 28.1 (Trp-CH_2), 28.2 (Boc-(CH_3)$_3$), 29.6 (Met-CH_2), 30.0 (Met-CH_2), 31.4 (Met-CH_2), 31.6 (Met-CH_2), 51.7 (Met-α-CH), 52.3 (ester-CH_3), 52.4 (Trp-α-CH), 53.6 (Met-α-CH), 84.0 (Boc-C), 114.6 (Ar-C), 115.6 (Ar-C), 118.8 (Ar-C), 119.9 (alkene-C), 123.0 (Ar-C), 124.8 (Ar-C), 126.7 (Ar-C), 128.0 (Ar-C), 128.7 (Ar-C), 129.5 (Ar-C), 132.3 (alkene-C), 136.0 (Ar-C), 136.3 (Ar-C), 136.8 (Ar-C), 150.4 (C=O), 170.0 (C=O), 170.2 (C=O), 170.8 (C=O), 171.2 (C=O).

IR U_{max} /cm^{-1} (solid) 3275 m (N-H), 3060w (C-H), 2920 w (C-H), 1728 s (ester C=O), 1634 m (amide C=O), 1453 m (C-H), 1258 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{37}H_{49}N_4O_7S_2$: 725.3037, found: 725.3040.

Synthesis of modified peptide 5j



5j

Modified peptide **5j** was prepared from Ac-Trp(Boc)-Leu-Leu-OMe (**4j**) (0.140 g, 0.238 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **5j** and a di-olefinated peptide in a ratio of 11:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5j** as an off-white solid (0.097 g, 59%); m.p. 165-167 °C, R_f 0.26 (50% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74-0.80 (12H, Leu-C*H*$_3$ (x4)), 1.24-1.50 (6H, m, Leu-C*H*$_2$ (x2) / Leu-C*H* (x2)), 1.58 (Boc-(C*H*$_3$)$_3$), 1.85 (acetyl-C*H*$_3$), 3.21 (1H, dd, *J* = 14.3, *J* = 7.1, Trp-C*H*H), 3.28 (1H, dd, *J* = 14.3, *J* = 7.1, Trp-C*H*H), 3.60 (3H, s, ester-C*H*$_3$), 4.24 (1H, dt, *J* = 8.1, *J* = 5.7, Leu-α-C*H*), 4.33-4.39 (1H, m, Leu-α-C*H*), 4.72 (1H, app q, *J* = 7.3, Trp-α-C*H*), 6.12 (1H, br d, *J* = 8.1, Leu-N*H*), 6.20 (1H, br d, *J* = 7.9, Leu-N*H*), 6.25 (1H, br d, *J* = 7.3, Trp-N*H*), 6.69 (1H, d, *J* = 16.6, alkene-C*H*), 7.16-7.25 (4H, m, Ar-*H*), 7.28-7.35 (3H, m, alkene-C*H* / Ar-*H*), 7.49 (2H, d, *J* = 7.5, Ar-*H*), 7.64 (1H, br d, *J* = 7.5, Ar-*H*), 8.04 (1H, br d, *J* = 8.4, Ar-*H*).

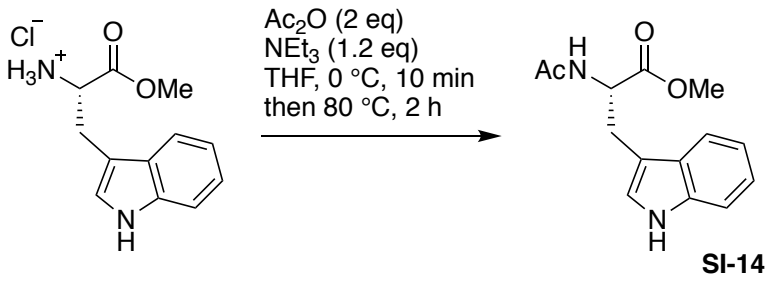
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.0 (Leu-CH_3), 21.0 (Leu-CH_3), 21.6 (Leu-CH_3), 21.7 (Leu-CH_3), 22.1 (acetyl-CH_3), 23.5 (Leu-CH), 23.8 (Leu-CH), 27.3 (Boc-$(CH_3)_3$), 28.7 (Trp-CH_2), 40.0 (Leu-CH_2), 40.3 (Leu-CH_2), 49.8 (Trp-α-CH), 50.8 (Leu-α-CH), 51.2 (Leu-α-CH), 52.6 (ester-CH_3), 83.0 (Boc-C), 113.8 (Ar-C), 114.7 (Ar-C), 117.9 (Ar-C), 119.1 (alkene-C), 122.0 (Ar-C), 123.9 (Ar-C), 125.6 (Ar-C), 127.0 (Ar-C), 127.8 (Ar-C), 128.6 (Ar-C), 131.3 (alkene-C), 134.8 (Ar-C), 135.2 (Ar-C),135.8 (Ar-C), 149.4 (C=O), 169.2 (C=O), 169.7 (C=O), 169.9 (C=O), 172.1 (C=O).

IR υ_{max} /cm^{-1} (solid) 3276 m (N-H), 2961 w (C-H), 1728 s (ester C=O), 1631 m (amide C=O), 1541 m (C=C), 1455 m (C-H), 1258 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{39}H_{52}N_4O_7$: 689.3909, found: 689.3908.

3.8. C-H olefination of Ac-Trp(Boc)-OMe (6); synthesis of modified amino acid 7

Ac-Trp-OMe (SI-14)



SI-14

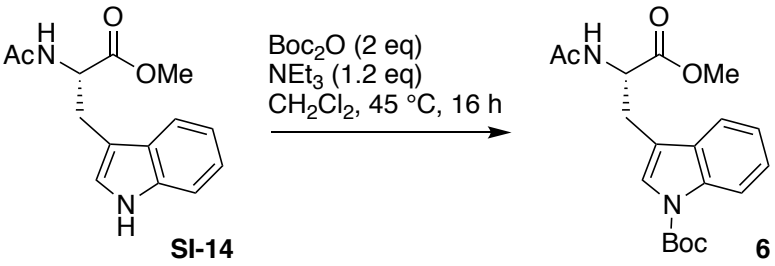
The salt L-tryptophan methyl ester hydrochloride (0.300 g, 1.178 mmol) was slurried in THF (15 mL) and cooled to 0 °C in an ice bath, before the addition of NEt_3 (0.197 mL, 1.414 mmol). Acetic anhydride (0.223 mL, 2.356 mmol) was then added, and the reaction mixture was stirred at 0 °C for 10 minutes before it was heated at 80 °C for 2 h. The resulting solution was allowed to cool to room temperature, before it was added to water (25 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined and washed with 1M HCl (20 mL), sat. $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), and reduced to a brown solid by rotary evaporation. The solid was then triturated (Et_2O) and filtered to give **SI-14** as a sandy brown solid (0.240 g, 78%), m.p. 154-155 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, s, acetyl-C*H*$_3$), 3.27-3.37 (2H, m, Trp-C*H*$_2$), 3.70 (3H, s, ester-CH_3), 4.95 (1H, dt, *J* = 7.8, *J* = 5.0, Trp-α-C*H*), 5.98 (1H, br d, *J* = 7.8, Trp-N*H*), 6.97 (1H, d, *J* = 2.3, Trp-Ar-*H*), 7.10-7.13 (1H, m, Trp-Ar-*H*), 7.17-7.21 (1H, m, Ar-*H*), 7.36 (1H, d, *J* = 7.5, Trp-Ar-*H*), 7.52 (1H, d, *J* = 7.5, Trp-Ar-*H*) 8.14 (1H, m, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.3 (acetyl-CH_3), 27.6 (Trp-CH_2), 52.4 (ester-CH_3), 53.0 (Trp-α-CH), 110.1(Ar-C), 113.3 (Ar-C), 118.5 (Ar-C), 119.7 (Ar-C), 122.3 (Ar-C), 122.6 (Ar-C), 127.7 (Ar-C), 136.0 (Ar-C), 169.7 (C=O), 172.4 (C=O).

The data match that previously reported.[S3]

Ac-Trp(Boc)-OMe (6)



Ac-Trp-OMe (**SI-14**) (0.200 g, 0.768 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with NEt_3 (0.129 mL, 0.922 mmol). A solution of Boc_2O (0.335 g, 1.537 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the solution, which was then heated under reflux for 16 h. The solution was then allowed to cool to room temperature, and concentrated by rotary evaporation. The crude compound was purified by flash column chromatography (50% EtOAc/pet. ether) to afforded **6** as a yellow solid (0.271 g, 98%); m.p. 57-59 °C, R_f 0.19 (50% EtOAc/pet. ether).

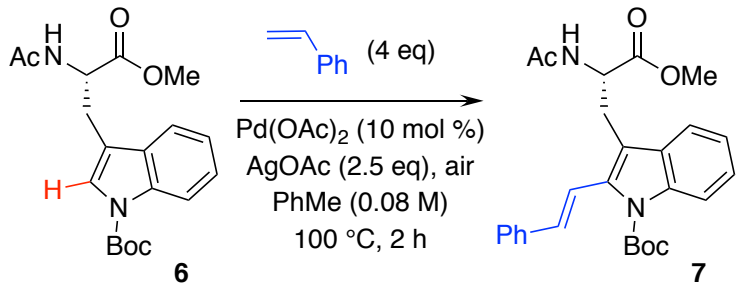
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (Boc-(C*H*$_3$)$_3$), 1.88 (3H, s, acetyl-C*H*$_3$), 3.10 (1H, dd, *J* = 14.8, *J* = 5.5, Trp-C*H*H), 3.18 (1H, dd, *J* = 14.8, *J* = 5.5, Trp-C*H*H), 3.60 (3H, s, ester-C*H*$_3$), 4.84 (1H, dt, *J* = 7.7, *J* = 5.5, Trp-α-C*H*), 6.27 (1H, br d, *J* = 7.7, Trp-N*H*), 7.13 (1H, t, *J* = 7.7, Trp-Ar-*H*), 7.21 (1H, t, *J* = 7.7, Trp-Ar-*H*), 7.29 (1H, br s, Trp-Ar-*H*), 7.38 (1H, d, *J* = 7.7, Trp-Ar-*H*), 8.01 (1H, br d, *J* = 6.3, Trp-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.1 (Trp-CH_2), 28.0 (Boc-$(CH_3)_3$), 52.3 (ester-CH_3), 52.5 (Trp-α-CH), 83.6 (Boc-C), 114.8 (Ar-C), 115.1 (Ar-C), 118.6 (Ar-C), 122.4 (Ar-C), 123.8 (Ar-C), 124.4 (Ar-C), 130.4 (Ar-C), 135.1 (Ar-C), 149.4 (C=O), 169.7 (C=O), 172.0 (C=O).

IR U_{max} /cm^{-1} (solid) 3286 m (N-H), 2978 w (C-H), 1727 s (ester C=O), 1654 m (amide C=O), 1452 m (C-H), 1227 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{19}H_{25}N_2O_5$: 361.1758, found: 361.1755.

Synthesis of modified amino acid 7



Modified amino acid **7** was prepared from Ac-Trp(Boc)-OMe (**6**) (0.058 g, 0.161 mmol) and styrene (0.074 mL, 0.644 mmol), using the general procedure in **section 2.4.** As judged by ^{1}H NMR spectroscopy, the crude residue contained a mixture of the mono-olefinated peptide **7** and the starting material **6** only; there was no evidence of a di-olefinated product. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **7** as an off-white solid (0.029 g, 39%); m.p. 55-56 °C, R_f 0.37 (50% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s, Boc-(C*H*$_3$)$_3$), 1.88 (3H, s, acetyl-C*H*$_3$), 3.38 (2H, d, *J* = 6.4, Trp-C*H*$_2$), 3.51 (3H, s, ester-CH$_3$), 4.93 (1H, dt, *J* = 7.6, *J* = 6.4, Trp-α-C*H*), 6.02 (1H, br d, *J* = 7.6, Trp-N*H*), 6.79 (1H, d, *J* = 16.6, alkene-C*H*), 7.23-7.33 (4H, m, Ar-*H* /alkene-C*H*), 7.38 (2H, m, Ar-*H*), 7.55 (3H, m, Ar-*H*), 8.12 (1H, d, *J* = 8.4, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1 (acetyl-CH$_3$), 27.6 (Trp-CH$_2$), 28.3 (Boc-(CH$_3$)$_3$), 52.4 (ester-CH$_3$), 52.5 (Trp-α-CH), 84.0 (Boc-C), 114.6 (Ar-C), 115.5 (Ar-C), 118.7 (Ar-C), 119.8 (alkene-CH), 122.8 (Ar-C), 124.7 (Ar-C), 126.5 (Ar-C), 128.0 (Ar-C), 128.8 (Ar-C), 130.1 (Ar-C), 132.4 (alkene-CH), 135.8 (Ar-C), 136.0 (Ar-C), 136.8 (Ar-C), 150.4 (C=O), 169.6 (C=O), 172.4 (C=O).

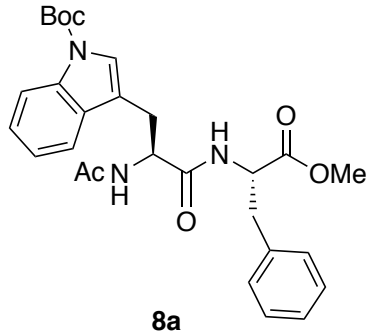
IR U_{max} /cm^{-1} (solid) 378 m (N-H), 2976 w (C-H), 1726 s (ester C=O), 1655 m (amide C=O), 1359 m (C-H), 1206 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{27}H_{31}N_2O_5$: 463.2227, found: 463.2225.

3.9. Control of residue selectivity in the C-H olefination of Trp / Phe peptides; synthesis of modified peptides 9-13

3.9.1. Synthesis of peptides 8a, 8b, 8c

Ac-Trp(Boc)-Phe-OMe (8a)



8a

Peptide **8a** was synthesised from Ac-Trp-Phe-OMe (**8b**) (0.306 g, 0.75 mmol) using the general procedure described in **section 2.3.** Purification by flash column chromatography (75% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **8a** as a white solid (0.381 g, 94%); m.p. 89-93 °C, R_f 0.25 (75% EtOAc/pet. ether).

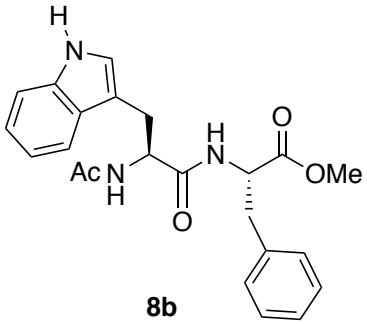
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (9H, s, Boc-(C*H*$_3$)$_3$), 1.98 (3H, s, acetyl-C*H*$_3$), 2.94 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.01-3.08 (2H, m, Phe-CH*H*/Trp-CH*H*), 3.20 (1H, dd, *J* = 14.6, *J* = 5.5, Trp-C*H*H), 3.63 (3H, s, ester-C*H*$_3$), 4.66-4.71 (2H, m, Ph-α-C*H*/Trp-α-C*H*), 6.09 (1H, br d, *J* = 7.3, Trp-N*H*), 6.21 (1H, br d, *J* = 7.3, Phe-N*H*), 6.90-6.92 (2H, m, Phe-Ar-*H*), 7.15-7.18 (3H, m, Phe-Ar-*H*), 7.22-7.26 (1H, m, Trp-Ar-*H*), 7.32 (1H, t, *J* = 8.2, Trp-Ar-*H*), 7.45 (1H, s, Trp-Ar-*H*), 7.64 (1H, d, *J* = 7.8¸ Trp-Ar-*H*), 8.11-8.13 (1H, m, Trp-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.2 (acetyl-CH_3), 28.1 (Trp-CH_2), 28.2 (Boc-(CH_3)$_3$), 37.8 (Phe-CH_2), 52.3 (ester-CH_3), 53.3 (Trp-α-CH), 53.4 (Phe-α-CH), 83.6 (Boc-C), 115.2 (Ar-C), 115.3 (Ar-C), 119.0 (Ar-C), 122.7 (Ar-C), 124.5 (Ar-C), 124.6 (Ar-C), 127.1 (Ar-C), 128.5 (Ar-C), 129.1 (Ar-C), 130.1 (Ar-C), 135.3 (Ar-C), 135.4 (Ar-C), 149.5 (C=O), 169.9 (C=O), 170.3 (C=O), 171.0 (C=O).

IR U_{max} /cm^{-1} (solid) 3276 m (N-H), 3056 w (C-H), 2986 w (C-H), 1735 s (ester C=O), 1639 m (amide C=O), 1457 m (C-H), 1341 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{28}H_{34}N_3O_6$: 508.2442, found: 508.2446.

Ac-Trp-Phe-OMe (8b)



8b

The peptide Ac-Trp-Phe-OMe (**8b**) was synthesised from *N*-acetyl-L-tryptophan (0.246 g, 1.00 mmol) and L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) using the general procedure described in **section 2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **8b** as a cream solid (0.371 g, 91%); m.p. 73-76 °C.

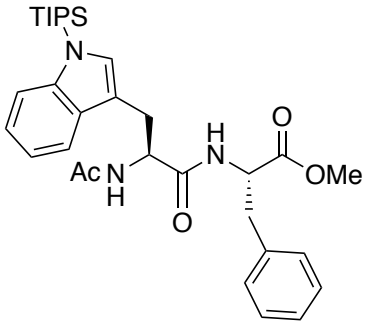
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (acetyl-C*H*$_3$), 2.93 (1H, dd, *J* = 13.8, *J* = 7.8, Phe-C*H*H), 2.97 (1H, dd, *J* = 13.8, *J* = 7.8, Phe-C*H*H), 3.10 (1H, dd, *J* = 14.1, *J* = 7.3, Trp-C*H*H), 3.27 (1H, dd, *J* = 14.1, *J* = 5.0, Trp-C*H*H), 3.64 (3H, s, ester-C*H*$_3$), 4.66-4.73 (2H, m, Trp-α-C*H*, Phe-α-C*H*), 6.08 (1H, br d, *J* = 7.3, Trp-N*H*), 6.26 (1H, br d, *J* = 7.8, Phe-N*H*), 6.85-6.87 (2H, m, Phe-Ar-*H*), 7.05 (1H, d, *J* = 2.3, Trp-Ar-*H*), 7.13-7.16 (5H, m, Phe-Ar-*H* / Trp-Ar-*H*), 7.35 (1H, d, *J* = 7.6, Trp-Ar-*H*), 7.71 (1H, d, *J* = 8.4, Trp-Ar-N*H*), 8.11 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.2 (acetyl-CH_3), 28.2 (Trp-CH_2), 37.7 (Phe-CH_2), 52.2 (ester-CH_3), 53.3 (Phe-α-CH), 53.7 (Trp-α-CH), 110.3 (Ar-C), 111.2 (Ar-C), 118.7 (Ar-C), 119.7 (Ar-C), 122.1 (Ar-C), 123.4 (Ar-C), 127.0 (Ar-C), 127.4 (Ar-C), 128.5 (Ar-C), 129.1 (Ar-C), 135.5 (Ar-C), 136.1 (Ar-C), 170.0 (C=O), 170.9 (C=O), 171.3 (C=O).

IR U_{max} /cm^{-1} (solid) 3291 m (O-H), 3064 w (C-H), 2969 w (C-H), 1737 s (ester C=O), 1637 m (amide C=O), 1541 m (C=C), 1445 m (C-H), 1216 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{23}H_{26}N_3O_4$: 408.1918, found: 408.1923.

Ac-Trp(TIPS)-Phe-OMe (8c)



Peptide Ac-Trp-Phe-OMe (**8b**) (0.200 g, 0.394 mmol) was dissolved in dry THF (10 mL) and cooled in a dry ice/acetone bath. NaHMDS (1M in THF, 0.394 mL, 0.394 mmol) was added dropwise at -78 °C and the reaction mixture was stirred for 1 h. Tri-*iso*-propylsilyl chloride (0.084 mL, 0.394 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature overnight. The resulting solution was added to water (30 mL), extracted with EtOAc (4 x 30 mL), dried ($MgSO_4$) and concentrated to a brown oil in *vacuo.* Following purification by flash column chromatography (50% EtOAc/pet. ether), peptide **8c** was isolated as a yellow oil (0.162 g, 73%), R_f 0.31 (50% EtOAc/pet. ether).

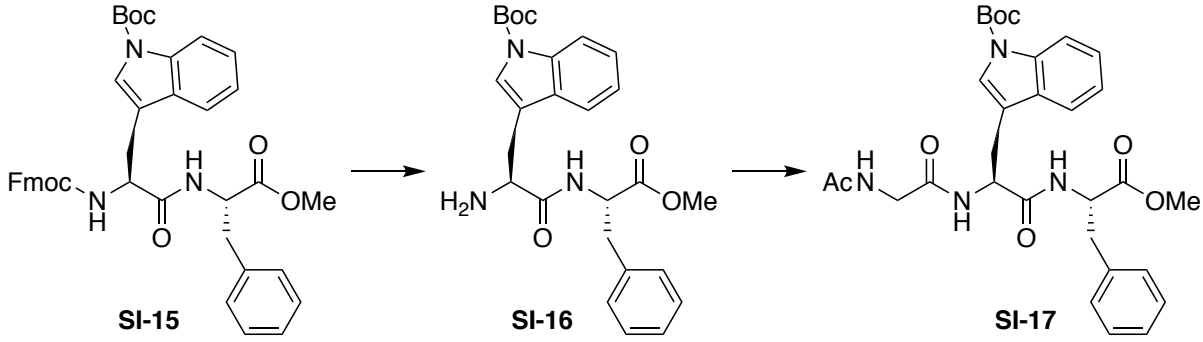
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (18H, d, *J* = 7.3, TIPS-(CH_3)$_2$ (x3)), 1.86 (3H, septet, *J* = 7.5, TIPS-C*H* (x3)), 1.89 (3H, s, acetyl-CH_3), 2.95 (1H, dd, *J* = 13.7, *J* = 5.9, Phe-C*H*H), 3.05 (1H, dd, *J* = 13.7, *J* = 5.9, Phe-C*H*H), 3.20 (2H, d, *J* = 6.9, Trp-CH_2), 3.62 (3H, s, ester-CH_3), 4.67-4.78 (2H, m, Phe-α-C*H* / Trp-α-C*H*), 6.26 (1H, d, *J* = 7.3, Phe-N*H*), 6.47 (1H, d, *J* = 7.8, Trp-N*H*), 6.94-6.97 (2H, m, Phe-Ar-*H*), 7.08-7.13 (3H, m, Ar-*H*), 7.18-7.20 (3H, m, Ar-*H*), 7.46 (1H, d, *J* = 8.2, Trp-Ar-*H*), 7.58 (1H, d, *J* = 8.2, Trp-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 12.8 (TIPS-CH), 18.2 (TIPS-CH_3), 23.2 (acetyl-CH_3), 28.0 (Trp-CH_2), 37.9 (Phe-CH_2), 52.3 (ester-CH_3), 53.5 (α-CH), 53.6 (α-CH), 112.4 (Ar-C), 114.1 (Ar-C), 118.7 (Ar-C), 119.9 (Ar-C), 121.7 (Ar-C), 127.2 (Ar-C), 128.6 (Ar-C), 129.3 (Ar-C), 130.1 (Ar-C), 131.1 (Ar-C), 135.8 (Ar-C), 141.3 (Ar-C), 170.2 (C=O), 171.1 (C=O), 171.4 (C=O).

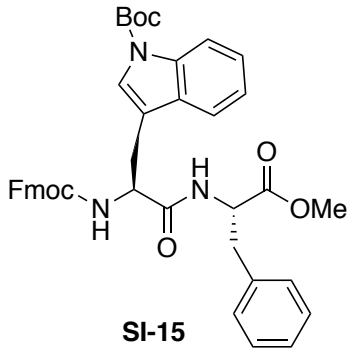
IR U_{max} /cm^{-1} (oil) 3280 m (N-H), 3062 w (C-H), 2946 w (C-H), 2866 w (C-H), 1746 s (ester C=O), 1638 m (amide C=O), 1541 m (C=C), 1452 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{32}H_{46}N_3O_4Si$: 564.3252, found: 564.3250.

3.9.2. Synthesis of peptide Ac-Gly-Trp(Boc)-Phe-OMe (SI-17)



Fmoc-Trp(Boc)-Phe-OMe (SI-15)



The dipeptide Fmoc-Trp(Boc)-Phe-OMe (**SI-15**) was synthesised from L-phenylalanine methyl ester hydrochloride (0.543 g, 2.50 mmol) and Fmoc-Trp(Boc)-OH (0.527 g, 1.00 mmol), using the procedure in **section 2.1**. The crude compound was purified by flash column chromatography (25% EtOAc / pet ether) then recrystallised from CH_2Cl_2 / hexanes to afford **SI-15** as a white solid (0.421 g, 61%); m.p. 100-103 °C, R_f 0.19 (25% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(CH_3)$_3$), 2.90-3.15 (3H, m, Trp-C*H*H/Phe-CH_2), 3.26 (1H, dd, *J* = 14.5, 4.1, Trp-CH*H*), 3.61 (3H, s, ester-CH_3), 4.21 (1H, t, *J* = 6.8, Fmoc-C*H*), 4.31-4.44 (2H, m, Fmoc-CH_2), 4.45-4.54 (1H, m, Trp-α-C*H*), 4.68-4.75 (1H, m, Phe-α-C*H*), 5.49 (1H, br d, *J* = 7.0, Trp-N*H*), 6.10 (1H, d, *J* = 7.4, Phe-N*H*), 6.86 (2H, br d, *J* = 7.0, Ar-*H*), 7.07-7.17 (3H, m, Ar-*H*), 7.23-7.35 (4H, m, Ar-*H*), 7.37-7.44 (2H, m, Ar-*H*), 7.47 (1H, s, Ar-*H*), 7.51-7.56 (2H, m, Ar-*H*), 7.63 (1H, d, *J* = 7.3, Ar-*H*), 7.77 (2H, d, *J* = 7.6, Ar-*H*), 8.14 (1H, br d, *J* = 7.1, Ar-*H*).

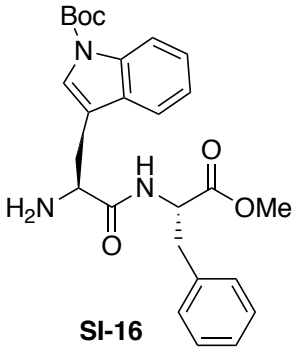
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.1 (Boc-(CH_3)$_3$), 28.3 (Trp-CH_2), 37.8 (Phe-CH_2), 47.0 (Fmoc-CH), 52.3 (ester-CH_3), 53.3 (Phe-α-CH), 54.9 (Trp-α-CH), 67.3 (Fmoc-CH_2), 83.7 (Boc-C), 115.1 (Ar-C), 115.3 (Ar-C), 119.0 (Ar-C), 120.0 (Ar-C), 122.8 (Ar-C), 124.6 (Ar-C), 124.7 (Ar-C), 125.1 (Ar-C), 127.1 (Ar-C), 127.1 (Ar-C), 127.7 (Ar-C), 128.5 (Ar-C), 129.0 (Ar-

C), 130.1 (Ar-C), 135.3 (Ar-C), 135.5 (Ar-C), 141.3 (Ar-C), 143.7 (Ar-C), 149.4 (C=O), 155.8 (C=O), 170.2 (C=O), 171.0 (C=O);

IR U_{max} /cm^{-1} (solid) 3302 w (N-H), 3063 w (C-H), 2930 (C-H), 1727 m (ester C=O), 1675 s (Fmoc C=O), 1654 s (amide C=O), 1533 m (C=C), 1366 s (C-O), 1248 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{41}H_{42}N_3O_7$: 688.3023, found: 688.3006.

H-Trp(Boc)-Phe-OMe (SI-16)



SI-16

Fmoc-Trp(Boc)-Phe-OMe (**SI-15**) (0.421 g, 0.612 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with tris(2-aminoethyl)amine (0.914 mL, 6.120 mmol). The reaction mixture was stirred for 2 h before being quenched with H_2O (20 mL). The organic layer was then washed with 1 M HCl (20 mL), sat. $NaHCO_3$ (20 mL) and H_2O (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an off-white solid. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes yielded **SI-16** as a white solid (0.223 g, 78%); m.p. 81-83 °C, R_f 0.22 (EtOAc).

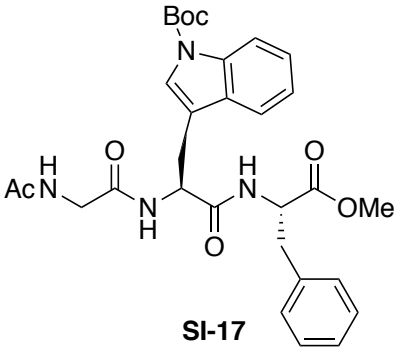
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (2H, br s, N*H*$_2$), 1.65 (9H, s, Boc-(C*H*$_3$)$_3$), 2.76 (1H, dd, *J* = 14.4, 8.9, Trp-C*H*H), 3.04 (2H, d, *J* = 6.1, Phe-C*H*$_2$), 3.22 (1H, dd, *J* = 14.4, 3.7, Trp-CH*H*), 3.66-3.73 (4H, m, ester-C*H*$_3$/Trp-α-C*H*), 4.88 (1H, dt, *J* = 8.4, 6.1, Phe-α-C*H*), 6.94-6.99 (2H, m, Ar-*H*), 7.17-7.28 (4H, m Ar-*H*), 7.33 (1H, t, *J* = Ar-*H*), 7.46 (1H, s, Ar-*H*), 7.61 (1H, d, *J* = 7.7, Ar-*H*), 7.77 (1H, d, *J* = 8.2, Phe-N*H*), 8.13 (1H, br d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.1 (Boc-(CH_3), 30.3 (Trp-CH_2), 37.9 (Phe-CH_2), 52.2 (Phe-α-CH), 52.6 (Trp-α-CH), 54.6 (ester-CH_3), 83.6 (Boc-C), 115.2 (Ar-C), 116.4 (Ar-C), 119.2 (Ar-C), 122.6 (Ar-C), 124.1 (Ar-C), 124.6 (Ar-C), 126.9 (Ar-C), 128.3 (Ar-C), 129.1 (Ar-C), 130.2 (Ar-C), 135.5 (Ar-C), 135.8 (Ar-C), 149.5 (C=O), 171.8 (C=O), 173.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3353 w (N-H), 3029 w (C-H), 2930 w (C-H), 1728 s (ester C=O), 1664 s (amide C=O), 1496 (C=C), 1252 (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{32}N_3O_5$: 466.2342, found: 466.2341.

Ac-Gly-Trp(Boc)-Phe-OMe (SI-17)



SI-17

The dipeptide H-Trp(Boc)-Phe-OMe (**SI-16**) (0.365 g, 0.784 mmol) was dissolved in CH_2Cl_2 (30 mL), treated with *N*-acetyl-glycine (0.037 g, 0.314 mmol), DIPEA (0.055 mL, 0.314 mmol), HBTU (0.119 g, 0.314 mmol) and stirred for 16 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1M HCl (20 mL), sat. $NaHCO_3$ solution (3 x 20 mL) and water (20 mL). The solution was dried ($MgSO_4$) and then concentrated *in vacuo*. The crude compound was purified by flash column chromatography (EtOAc) and then recrystallised from CH_2Cl_2 / hexanes to afford peptide **SI-17** as a white solid (0.134 g, 76%); m.p. 186-188 °C, R_f 0.19 (EtOAc).

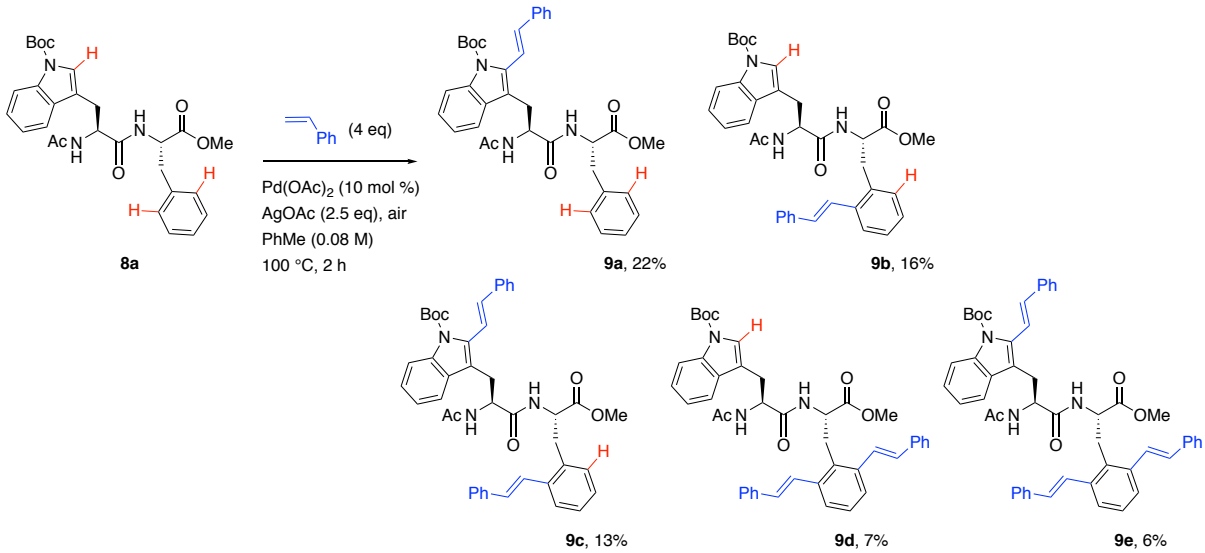
^{1}H NMR (400 MHz, CD_3CN) δ 1.64 (9H, s, Boc-(CH_3)$_3$), 1.86 (3H, s, acetyl-CH_3), 2.90-3.01 (2H, m, Phe-C*H*H / Trp-C*H*H), 3.05 (1H, dd, *J* = 13.8, 5.8, Trp-CH*H*), 3.14 (1H, dd, *J* = 14.9, 5.5, Phe-CH*H*), 3.61 (3H, s, ester-CH_3), 3.65 (2H, dd, *J* = 5.6, 3.5, Gly-CH_2), 4.54-4.65 (2H, m, Phe-α-C*H* / Trp-α-C*H*), 6.70 (1H, br t, *J* = 5.3, Gly-N*H*), 6.87 (1H, d, *J* = 8.0, Phe-N*H*), 7.03 (1H, d, *J* = 7.6, Trp-N*H*), 7.10-7.17 (2H, m, Ar-*H*), 7.20-7.35 (5H, m, Ar-*H*), 7.47 (1H, s, Ar-*H*), 7.59 (1H, d, *J* = 7.6, Ar-*H*), 8.09 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, D_6-DMSO) δ 22.4 (acetyl-CH_3), 27.4 (Phe-CH_2), 27.7 (Boc-(CH_3)$_3$), 36.6 (Trp-CH_2), 41.9 (Gly-CH_2), 51.8 (ester-CH_3), 52.1 (Phe-α-CH), 53.7 (Trp-α-CH), 83.5 (Boc-C), 114.6 (Ar-C), 116.2 (Ar-C), 119.4 (Ar-C), 122.4 (Ar-C), 124.1 (Ar-C), 124.3 (Ar-C), 126.6 (Ar-C), 128.3 (Ar-C), 129.1 (Ar-C), 130.3 (Ar-C), 134.6 (Ar-C), 137.0 (Ar-C), 149.1 (C=O), 168.8 (C=O), 169.5 (C=O), 171.1 (C=O), 171.7 (C=O).

IR U_{max} /cm^{-1} (solid) 3302 m (N-H), 3066 w (C-H), 2982 w (C-H), 1731 s (ester C=O), 1634 s (amide C=O), 1519 s (C=C), 1209 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{30}H_{37}N_4O_7$: 565.2662, found: 565.2673.

3.9.3. C-H olefination of Ac-Trp(Boc)-Phe-OMe (8a); synthesis of modified peptides 9a-e



C-H olefination of Ac-Trp(Boc)-Phe-OMe (**8a**) (0.100 g, 0.197 mmol) with styrene (0.087 mL, 0.788 mmol) was carried out as described by the general procedure in **section 2.4.** The crude residue was purified by column chromatography followed by recrystallization from CH_2Cl_2 / hexanes to afford the following modified peptides, all as off-white solids:

9a (0.048 g, 22%); m.p. 152-153 °C, R_f 0.29 (50% EtOAc/pet. ether)

9b (0.035 g, 16%); m.p. 117-118 °C, R_f 0.22 (50% EtOAc/pet. ether)

9c (0.033 g, 13%); m.p. 100-102 °C, R_f 0.45 (50% EtOAc/pet. ether)

9d (0.018 g, 7%); m.p. 120-122 °C, R_f 0.39 (50% EtOAc/pet. ether)

9e (0.018 g, 6%); m.p.106-108 °C, R_f 0.61 (50% EtOAc/pet. ether).

Data for 9a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (9H, s, Boc-(CH_3)$_3$), 1.90 (3H, s, acetyl-CH_3), 2.79 (1H, dd, *J* = 13.8, *J* = 6.0, Phe-C*H*H), 2.90 (1H, dd, *J* = 13.8, *J* = 6.0, Phe-C*H*H), 3.12 (1H, dd, *J* = 14.1, *J* = 9.7, Trp-C*H*H), 3.25 (1H, dd, *J* = 14.0, *J* = 5.6, Trp-C*H*H), 3.37 (3H, s, ester-CH_3), 4.45-4.50 (1H, m, Trp-α-C*H*), 4.63-4.68 (1H, m, Phe-α-C*H*), 5.87 (1H, br d, *J* = 7.8, Trp-N*H*), 6.42 (1H, br d, *J* = 7.4, Phe-N*H*), 6.75 (1H, d, *J* = 16.7, alkene-C*H*), 6.83-6.85 (2H, m, Ar-*H*), 7.08-7.10 (2H, m, Ar-*H*), 7.16-7.22 (4H, m, Ar-*H*), 7.28-7.31 (3H, m, Ar-*H*), 7.48-7.58 (3H, m, Ar-*H*), 8.02 (1H, br d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1 (acetyl-CH_3), 28.2 (Boc-(CH_3)$_3$), 28.6 (Trp-CH_2), 38.1 (Phe-CH_2), 52.1 (ester-CH_3), 53.5 (α-CH), 53.5 (α-CH), 83.9 (Boc-C), 114.9 (Ar-C), 115.4 (Ar-C), 118.8 (Ar-C), 119.7 (alkene-C), 123.0 (Ar-C), 124.7 (Ar-C), 126.6 (alkene-C), 127.0 (Ar-C), 127.9 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 129.1 (Ar-C), 129.7 (Ar-C), 132.1 (alkene-

C), 135.4 (Ar-C), 135.9 (Ar-C), 136.0 (Ar-C), 136.9 (Ar-C), 150.4 (C=O), 169.7 (C=O), 170.4 (C=O), 170.4 (C=O).

IR υ_{max} /cm^{-1} (solid) 3282 m (N-H), 3060 w (C-H), 2963 w (C-H), 1726 s (ester C=O), 1642 m (amide C=O), 1522 m (C=C), 1258 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{36}H_{40}N_3O_6$: 610.2912, found: 610.2912.

Data for 9b:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (9H, s, Boc-(C*H*$_3$)$_3$), 1.74 (3H, s, acetyl-C*H*$_3$), 2.94 (1H, dd, *J* = 14.4, *J* = 8.2, Phe-C*H*H), 2.98-3.09 (2H, m, Phe-C*H*H / Trp-C*H*H), 3.20 (1H, dd, *J* = 14.0, *J* = 6.4, Trp-C*H*H), 3.47 (3H, s, ester-C*H*$_3$), 4.52-4.60 (2H, m, Phe-α-C*H* / Trp-α-C*H*), 6.14-6.20 (2H, m, Phe-N*H* / Trp-N*H*), 6.79 (1H, d, *J* = 7.6, Ar-*H*), 6.87 (1H, d, *J* = 16.1, alkene-C*H*), 7.00 (1H, t, *J* = 7.3, Ar-*H*), 7.13 (2H, app q, *J* = 7.6, Ar-*H*), 7.19-7.23 (3H, m, Ar-*H* / alkene-C*H*), 7.26-7.32 (3H, m, Ar-*H*), 7.45-7.52 (4H, m, Ar-*H*), 8.02 (1H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 28.1 (Trp-CH_2), 28.1 (Boc-$(CH_3)_3$), 35.0 (Phe-CH_2), 52.3 (ester-CH_3), 53.2 (α-CH), 53.3 (α-CH), 83.5 (Boc-C), 115.1 (Ar-C), 115.2 (Ar-C), 119.0 (Ar-C), 122.6 (Ar-C), 124.4 (Ar-C), 124.5 (Ar-C), 125.1 (Ar-C), 125.7 (alkene-C), 126.5 (Ar-C), 126.6 (Ar-C), 127.5 (Ar-C), 127.6 (Ar-C), 127.8 (Ar-C), 128.7 (Ar-C), 130.1 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 133.3 (alkene-C), 136.5 (Ar-C), 137.2 (Ar-C), 149.4 (C=O), 169.9 (C=O), 170.4 (C=O), 171.1 (C=O).

IR υ_{max} /cm^{-1} (solid) 3280 m (N-H), 2963 w (C-H), 1731 s (ester C=O), 1638 m (amide C=O), 1452 m (C-H), 1258 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{36}H_{40}N_3O_6$: 610.2912, found: 610.2912.

Data for 9c:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(C*H*$_3$)$_3$), 1.77 (3H, s, acetyl-C*H*$_3$), 3.04 (1H, dd, *J* = 14.2, *J* = 5.2, Phe-C*H*H), 3.11 (1H, dd, *J* = 14.0, *J* = 10.0, Trp-C*H*H), 3.23 (1H, dd, *J* = 14.2, *J* = 7.2, Phe-C*H*H), 3.32-3.41 (1H, m, Trp-C*H*H), 3.38 (3H, s, ester-C*H*$_3$), 4.48-4.52 (1H, m, Trp-α-C*H*), 4.61-4.67 (1H, m, Phe-α-C*H*), 5.82 (1H, br d, *J* = 7.2, Trp-N*H*), 6.33 (1H, br d, *J* = 7.2, Phe-N*H*), 6.61-6.85 (2H, m, alkene-C*H* / Ar-*H*), 6.98 (1H, d, *J* = 16.0, alkene-C*H*), 7.17-7.40 (13H, m, Ar-*H* / alkene-C*H*), 7.55-7.63 (5H, m, Ar-*H*), 8.08 (1H, d, *J* = 8.4, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 28.2 (Boc-$(CH_3)_3$), 28.8 (Trp-CH_2), 35.2 (Phe-CH_2), 52.2 (ester-CH_3), 53.5 (α-CH), 53.5 (α-CH), 83.8 (Boc-C), 115.0 (Ar-C), 115.4 (Ar-C), 118.8 (Ar-C), 119.6 (alkene-C), 123.0 (Ar-C), 124.7 (Ar-C), 125.2 (Ar-C), 125.6 (Ar-C), 126.6 (Ar-C), 126.7 (Ar-C), 127.4 (Ar-C), 127.5 (Ar-C), 127.7 (Ar-C), 127.8 (Ar-C), 128.7

(Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 131.9 (Ar-C), 133.3 (alkene-C), 135.9 (Ar-C), 135.9 (Ar-C), 136.6 (Ar-C), 136.9 (Ar-C), 137.4 (Ar-C), 150.4 (C=O), 169.6 (C=O), 170.3 (C=O), 170.5 (C=O).

IR υ_{max} /cm^{-1} (solid) 3282 m (N-H), 2976 w (C-H), 1726 s (ester C=O), 1645 m (amide C=O), 1541 m (C=C), 1233 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{44}H_{46}N_3O_6$: 712.3381, found: 712.3382.

Data for 9d:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(C*H*$_3$)$_3$), 1.80 (3H, s, acetyl-C*H*$_3$), 2.96 (1H, dd, *J* = 14.5, *J* = 8.2, Trp-C*H*H), 3.12 (1H, dd, *J* = 14.5, *J* = 8.2, Trp-C*H*H), 3.34-3.37 (2H, m, Phe-C*H*$_2$), 3.41 (3H, s, ester-C*H*$_3$), 4.57-4.68 (2H, m, Trp-α-C*H* / Phe-α-C*H*), 6.12 (1H, br d, *J* = 7.3, Trp-N*H*), 6.17 (1H, br d, *J* = 7.7, Phe-N*H*), 6.96 (2H, d, *J* = 16.0, alkene-C*H*), 7.12 (1H, t, *J* = 7.4, Ar-*H*), 7.23-7.31 (4H, m, Ar-*H* / alkene-C*H*), 7.33-7.42 (6H, m, Ar-*H* /alkene-C*H*), 7.50-7.57 (8H, m, Ar-*H*), 8.08 (1H, d, *J* = 8.1, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1 (acetyl-CH_3), 28.3 (Boc-$(CH_3)_3$), 28.4 (Trp-CH_2), 31.6 (Phe-CH_2), 52.7 (Phe-α-CH), 53.1 (ester-CH_3), 53.5 (Trp-α-CH), 83.7 (Boc-C), 115.3 (Ar-C), 119.1 (Ar-C), 119.7 (Ar-C), 122.8 (Ar-C), 123.1 (Ar-C), 124.6 (Ar-C), 125.7 (Ar-C), 126.1 (alkene-C), 126.9 (Ar-C), 127.7 (Ar-C), 128.0 (Ar-C), 128.9 (Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 131.7 (alkene-C), 132.1 (Ar-C), 137.3 (Ar-C), 137.9 (Ar-C), 149.6 (C=O), 169.9 (C=O), 170.4 (C=O), 171.3 (C=O).

IR υ_{max} /cm^{-1} (solid) 3282 m (N-H), 3055 w (C-H), 2965 w (C-H), 1728 s (ester C=O), 1638 m (amide C=O), 1451 m (C-H), 1258 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{44}H_{46}N_3O_6$: 712.3381, found: 712.3375.

Data for 9e:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s, Boc-(C*H*$_3$)$_3$), 1.82 (3H, s, acetyl-C*H*$_3$), 3.10 (1H, dd, *J* = 13.8, *J* = 10.0, Trp-C*H*H), 3.21 (3H, s, ester-C*H*$_3$), 3.26-3.44 (3H, m, Trp-C*H*H / Phe-C*H*$_2$), 4.55 (1H, dt, *J* = 7.8, *J* = 6.4, Trp-α-C*H*), 4.65-4.71 (1H, m, Phe-α-C*H*), 5.90 (1H, br d, *J* = 7.8, Trp-N*H*), 6.36 (1H, br d, *J* = 7.3, Phe-N*H*), 6.81 (1H, d, *J* = 16.7, Trp-alkene-C*H*), 6.95 (2H, d, *J* = 16.0, Phe-alkene-C*H*), 7.10 (2H, t, *J* = 7.8, Ar-*H*), 7.20-7.31 (7H, m, Ar-*H* / alkene-C*H*), 7.36-7.41 (7H, m, Ar-*H* / alkene-C*H*), 7.50-7.61 (8H, m, Ar-*H*), 8.05 (1H, d, *J* = 7.8, Ar-*H*).

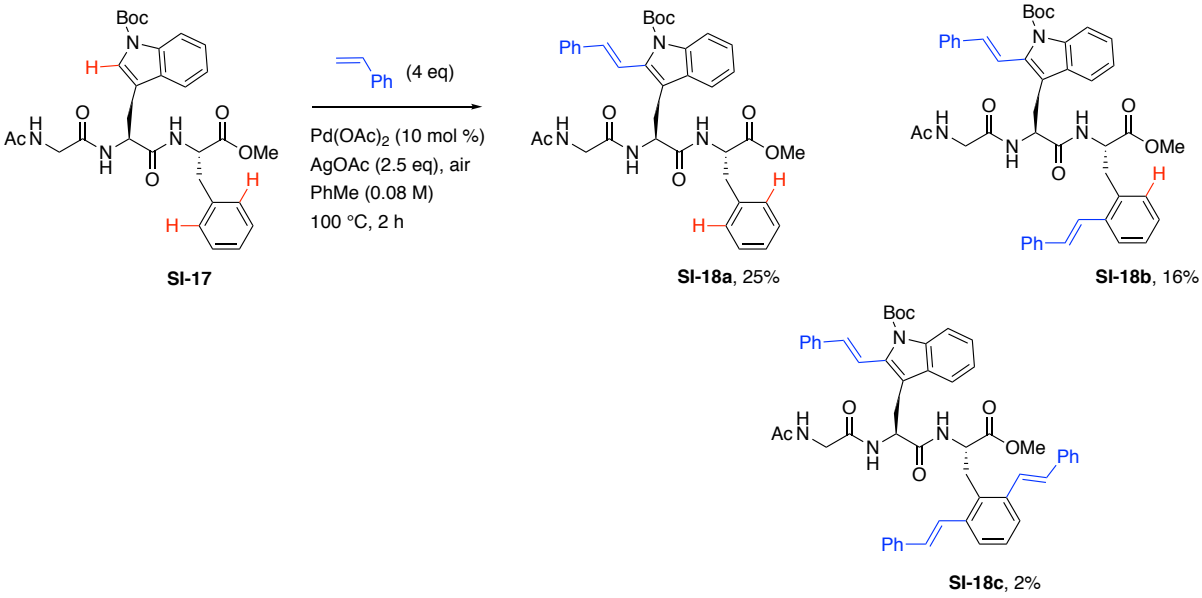
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1 (acetyl-CH_3), 28.4 (Boc-$(CH_3)_3$), 29.8 (Trp-CH_2), 31.9 (Phe-CH_2), 52.6 (ester-CH_3), 53.1 (α-CH), 53.8 (α-CH), 84.0 (Boc-C), 115.1 (Ar-C), 115.4 (Ar-C), 118.9 (alkene-C), 119.7 (Ar-C), 123.1 (Ar-C), 123.2 (Ar-C), 124.8 (Ar-C), 125.6 (Ar-

C), 126.1 (alkene-C), 126.8 (Ar-C), 126.9 (Ar-C), 127.5 (Ar-C), 127.9 (Ar-C), 128.8 (Ar-C), 128.9 (Ar-C), 128.9 (Ar-C), 129.6 (Ar-C), 131.4 (alkene-C), 131.8 (alkene-C), 136.0 (Ar-C), 137.5 (Ar-C), 137.9 (Ar-C), 150.4 (C=O), 169.7 (C=O), 170.3 (C=O), 170.6 (C=O). There are two Ar-C signals missing; presumably these overlap with other signals in the spectrum.

IR U_{max} /cm^{-1} (solid) 3308 m (N-H), 3026 w (C-H), 2963 w (C-H), 1726 s (ester C=O), 1655 m (amide C=O), 1508 m (C=C), 1450 m (C-H), 1237 s (C-O).

HRMS (ESI) [M+H^+] *m/z* calcd. for $C_{52}H_{52}N_3O_6$: 814.3851, found: 814.3852.

3.9.4. C-H olefination of Ac-Gly-Trp(Boc)-Phe-OMe (SI-17); synthesis of modified peptides SI-18a, SI-18b and SI-18c



SI-17

SI-18a, 25%

SI-18b, 16%

SI-18c, 2%

C-H olefination of Ac-Gly-Trp(Boc)-Phe-OMe (**SI-17**) (0.134 g, 0.237 mmol) with styrene (0.109 mL, 0.952 mmol) was carried out as described in the general procedure in **section 2.4.** The crude residue was purified by flash column chromatography (EtOAc) followed by recrystallization from CH_2Cl_2 / hexanes to afford the following modified peptides, all as yellow solids.

SI-18a (0.040 g, 25%); m.p. 104-106 °C, R_f 0.25 (EtOAc).

SI-18b (0.029 g, 16%); m.p. 119-122 °C, R_f 0.30 (EtOAc).

SI-18c (0.005 g, 2%); m.p. 159-161 °C, R_f 0.43 (EtOAc).

Data for SI-18a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (9H, s, Boc-(CH_3)$_3$), 1.97 (3H, s, acetyl-CH_3), 2.89 (1H, dd, *J* = 13.7, 5.9, Trp-C*H*H), 2.98 (1H, dd, *J* = 13.7, 6.0, Trp-CH*H*), 3.25 (1H, dd, *J* = 14.1, 8.9, Phe-C*H*H), 3.33 (1H, dd, *J* = 14.1, 6.3, Phe-CH*H*), 3.50 (3H, s, ester-CH_3), 3.84-3.88 (2H, m, Gly-CH_2), 4.55-4.62 (1H, m, Trp-α-C*H*), 4.71-4.78 (1H, m, Phe-α-C*H*), 6.06-6.16 (2H, m, Trp-N*H* / Gly-N*H*), 6.74 (1H, d, *J* = 7.6, Phe-N*H*), 6.78 (1H, d, *J* = 16.7, alkene-C*H*), 6.89-6.93 (1H, m, Ar-*H*), 7.13-7.17 (2H, m, Ar-*H*), 7.19-7.32 (5H, m, Ar-*H* / alkene-C*H*), 7.33-7.40 (3H, m, Ar-*H*), 7.51-7.58 (2H, m, Ar-*H*), 7.62 (1H, d, *J* = 7.6, Ar-*H*), 8.10 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 28.2 (Boc-(CH_3)$_3$), 28.8 (Phe-CH_2), 38.0 (Trp-CH_2), 43.0 (Gly-CH_2), 52.2 (ester-CH_3), 53.4 (Phe-α-CH), 53.5 (Trp-α-CH), 84.0 (Boc-

C), 114.6 (Ar-C), 115.6 (Ar-C), 118.7 (Ar-C), 119.8 (alkene-C), 123.0 (Ar-C), 124.8 (Ar-C), 126.6 (Ar-C), 127.0 (Ar-C), 128.0 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 129.1 (Ar-C), 129.6 (Ar-C), 132.2 (alkene-C), 135.4 (Ar-C), 135.9 (Ar-C), 136.2 (Ar-C), 136.8 (Ar-C), 150.4 (C=O), 168.4 (C=O), 169.8 (C=O), 170.4 (C=O), 170.7 (C=O).

IR U_{max} /cm^{-1} (solid) 3278 m (N-H), 3060 w (C-H), 2968 w (C-H), 1725 s (ester C=O), 1636 s (amide C=O), 1522 s (C=C), 1210 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{38}H_{43}N_4O_7$: 667.3132, found: 667.3127.

Data for SI-18b:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (9H, s, Boc-(C*H*$_3$)$_3$), 1.96 (3H, s, acetyl-C*H*$_3$), 3.05 (1H, dd, *J* = 14.2, 5.3 Trp-C*H*H), 3.16 (1H, dd, *J* = 14.1, 9.4, Phe-C*H*H), 3.24 (1H, dd, *J* = 14.2, 7.0, Trp-CH*H*), 3.31 (1H, dd, *J* = 14.1, 5.8, Phe-CH*H*), 3.43 (3H, s, ester-C*H*$_3$), 3.60 (1H, dd, *J* = 16.8, 5.0, Gly-C*H*H), 3.69 (1H, dd, *J* = 16.8, 5.0, Gly-CH*H*), 4.50-4.58 (1H, m, Trp-α-C*H*), 4.62 (1H, m, Phe-α-C*H*), 5.90-5.99 (2H, m, Gly-N*H* / Trp-N*H*), 6.60 (1H, d, *J* = 7.3, Phe-N*H*), 6.76 (1H, d, *J* = 16.6, Trp-alkene-C*H*), 6.83 (1H, d, *J* = 7.4, Ar-*H*), 6.94 (1H, d, *J* = 16.0, Phe-alkene-C*H*), 7.06 (1H, t, *J* = 7.3, Ar-*H*), 7.10-7.22 (2H, m, Ar-*H*), 7.23-7.30 (3H, m, Ar-*H*), 7.31-7.41 (6H, m, Ar-*H* / Phe-alkene-C*H* / Trp-alkene-C*H*), 7.50-7.60 (6H, m, Ar-*H*), 8.09 (1H, d, *J* = 8.0, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 28.2 (Boc-$(CH_3)_3$), 28.5 (Phe-CH_2), 35.1 (Trp-CH_2), 42.7 (Gly-CH_2), 52.3 (ester-CH_3), 53.4 (Phe-α-CH), 53.5 (Trp-α-CH), 83.9 (Boc-C), 114.6 (Ar-C), 115.5 (Ar-C), 118.7 (Ar-C), 119.7 (Trp-alkene-C), 123.0 (Ar-C), 124.8 (Ar-C), 125.3 (Ar-C), 125.7 (Ar-C), 126.6 (Ar-C) 126.7 (Ar-C), 127.5 (Ar-C), 127.5 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 128.8 (Phe-alkene-C), 129.6 (Ar-C), 130.2 (Phe-alkene-C), 130.4 (Ar-C), 132.1 (Trp-alkene-C), 133.4 (Ar-C), 135.9 (Ar-C), 136.1 (Ar-C), 136.6 (Ar-C), 136.8 (Ar-C), 137.4 (Ar-C), 150.4 (C=O), 168.1 (C=O), 169.8 (C=O), 170.2 (C=O), 170.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3273 w (N-H), 3056 w (C-H), 2976 w (C-H), 1728 s (ester C=O), 1634 s (amide C=O), 1523 s (C=C), 1216 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{46}H_{49}N_4O_7$: 769.3601, found: 769.3625.

Data for SI-18c:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s, Boc-(C*H*$_3$)$_3$), 1.98, (3H, s, acetyl-C*H*$_3$), 3.14 (1H, dd, *J* = 13.8, 9.8, Phe-C*H*H), 3.25 (3H, s, ester-CH_3), 3.26-3.40 (3H, m, Phe-CH*H* / Trp-C*H*$_2$), 3.64 (1H, dd, *J* = 16.7, 5.0, Gly-C*H*H), 3.71 (1H, dd, *J* = 16.7, 5.0, Gly-CH*H*), 4.54-4.62 (1H, m, Trp-α-C*H*), 4.63-4.70 (1H, m, Phe-α-C*H*), 5.90 (1H, t, *J* = 5.9, Gly-N*H*), 5.96 (1H, d, *J* =

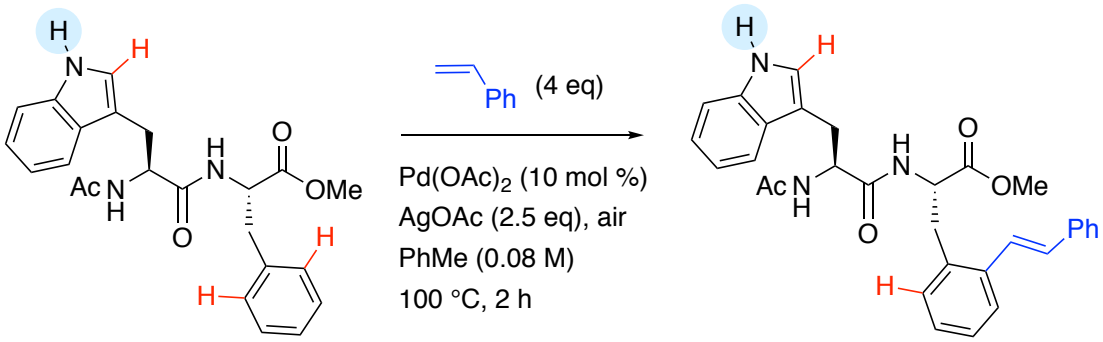
7.4, Trp-N*H*), 6.54 (1H, d, *J* = 6.6, Phe-N*H*), 6.74 (1H, d, *J* = 16.7, Trp-alkene-C*H*), 6.93 (2H, d, *J* = 16.0, Phe-alkene-C*H*), 7.07-715 (1H, m, Ar-*H*), 7.20-7.33 (9H, m, Ar-*H* / Trp-alkene-C*H*), 7.34-7.42 (6H, m, Ar-*H* / Phe-alkene-C*H*), 7.47-7.60 (8H, m, Ar-*H*), 8.07 (1H, d, *J* = 8.1, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0 (acetyl-CH_3), 28.2 (Boc-$(CH_3)_3$), 29.7 (Phe-CH_2), 31.7 (Trp-CH_2), 42.8 (Gly-CH_2), 52.5 (ester-CH_3), 53.0 (Phe-α-CH), 53.5 (Trp-α-CH), 83.9 (Boc-C), 114.6 (Ar-C), 115.5 (Ar-C), 118.7 (Ar-C), 119.6 (Trp-alkene-C), 123.1 (Ar-C), 124.8 (Ar-C), 125.5 (Ar-C), 126.1 (Ar-C), 126.6 (Ar-C), 126.8 (Ar-C), 127.5 (Ar-C), 127.9 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 128.8 (Phe-alkene-C), 129.6 (Ar-C), 131.3 (Phe-alkene-C), 131.4 (Ar-C), 132.0 (Trp-alkene-C), 135.9 (Ar-C), 136.2 (Ar-C), 136.8 (Ar-C), 137.3 (Ar-C), 137.7 (Ar-C), 150.4 (C=O), 168.0 (C=O), 169.6 (C=O), 170.2 (C=O), 170.7 (C=O);

IR U_{max} /cm^{-1} (solid) 3304 m (N-H), 3058 w (C-H), 2980 w (C-H), 1731 s (ester C=O), 1634 s (amide C=O), 1519 s (C=C), 1215 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{54}H_{55}N_4O_7$: 871.4071, found: 871.4060.

3.9.5. C-H olefination of Ac-Trp-Phe-OMe (8b); synthesis of modified peptide 10



8b **10**, 21%, only isolated product

Modified peptide **11** was prepared from Ac-Trp-Phe-OMe (**8b**) (0.146 g, 0.359 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol, 10 mol%), AgOAc (0.150 g, 0.898 mmol) and styrene (0.165 mL, 1.436 mmol) were stirred together in toluene (4 mL) at 130 °C for 12 h. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **10** as a brown solid (0.039 g, 21%); m.p. 171-173 °C, R_f 0.25 (EtOAc).

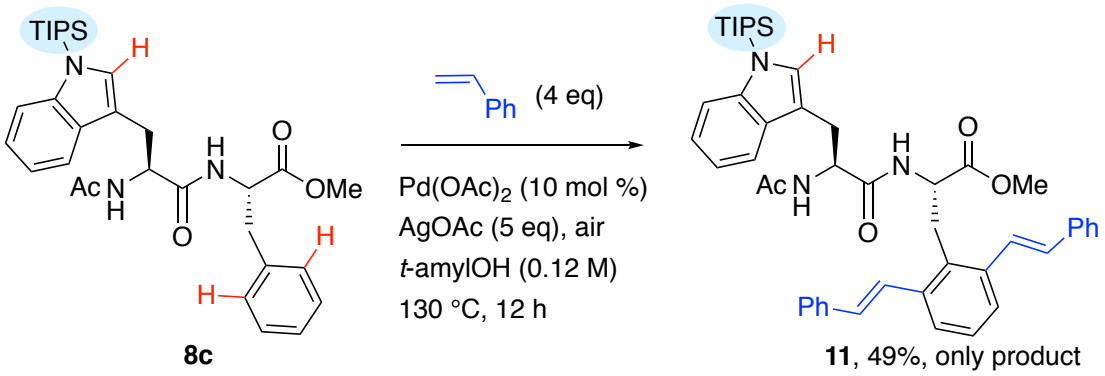
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (3H, s, Acetyl-CH_3), 2.82 (1H, dd, *J* = 13.5, 5.5, Trp-C*H*H), 2.92 (1H, dd, *J* = 14.0, 5.7, Trp-CH*H*), 3.17 (1H, dd, *J* = 14.2, 9.5, Phe-C*H*H), 3.45-3.55 (4H, m, Phe-CH*H* / Ester-CH_3), 4.51-4.58 (1H, m, Trp-α-C*H*), 4.62-4.69 (1H, m, Phe-α-C*H*), 6.01 (1H, d, *J* = 6.9, Trp-N*H*), 6.43 (1H, d, *J* = 7.3, Phe-N*H*), 6.75-6.80 (2H, m, Ar-*H*), 6.84 (1H, d, *J* = 16.5, Alkene-C*H*), 7.02-7.38 (10H, m, Alkene-C*H* / Ar-*H*), 7.54 (2H, d, *J* = 7.6, Ar-*H*), 7.61 (1H, d, *J* = 7.8, Ar-*H*), 8.52 (1H, s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.3 (Acetyl-CH_3), 27.6 (Phe-CH_2), 37.9 (Trp-CH_2), 52.1 (Ester-CH_3), 53.6 (Trp-α-CH), 54.5 (Phe-α-CH), 110.6 (Ar-C), 110.9 (Ar-C), 116.5 (Alkene-CH), 118.8 (Ar-C), 120.1 (Ar-C), 123.3 (Ar-C), 126.4 (Ar-C), 126.9 (Ar-C), 127.1 (Alkene-CH), 127.8 (Ar-C), 128.3 (Ar-C), 128.6 (Ar-C), 128.8 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-C), 134.0 (Ar-C), 135.4 (Ar-C), 136.5 (Ar-C), 136.7 (Ar-C), 169.9 (C=O), 170.5 (C=O), 170.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3424 w (N-H), 3282 m (N-H), 3030 w (C-H), 2924 w (C-H), 1730 s (Ester C=O), 1636 (Amide C=O), 1541 s (C=C), 1218 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{31}H_{32}N_3O_4$: 510.2393, found: 510.2392.

3.9.6. C-H olefination of Ac-Trp(TIPS)-Phe-OMe (8c); synthesis of modified peptide 11



8c **11**, 49%, only product

Ac-Trp(TIPS)-Phe-OMe (**8c**) (0.065 g, 0.115 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol, 10 mol%), AgOAc (0.096 g, 0.576 mmol) and styrene (0.063 mL, 0.461 mmol) were stirred together in *t*-amyl-OH (1 mL) at 130 °C for 12 h. The reaction was then allowed to cool to room temperature and filtered through a plug of Celite; the filtrate was then concentrated to dryness *in vacuo*. Examination of the ^{1}H NMR spectrum for the crude product indicated that **11** was the only modified peptide in the residue. Purification by flash column chromatography (30% EtOAc/pet. ether) gave modified peptide **11** as a yellow oil (0.043 g, 49%); R_f 0.35 (30% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04-1.06 (18H, d, *J* = 7.6, TIPS-(CH_3)$_2$ (x3)), 1.55-1.63 (3H, m, TIPS-C*H* (x3)), 1.83 (3H, s, acetyl-CH_3), 3.16 (2H, br d, *J* = 6.0, Phe-CH_2), 3.28 (1H, dd, *J* = 14.2, *J* = 8.1, Trp-C*H*H), 3.39 (3H, s, ester-CH_3), 3.46 (1H, dd, *J* = 14.2, *J* = 6.3, Trp-C*H*H), 4.61-4.72 (2H, m, Phe-α-C*H* / Trp-α-C*H*), 6.05 (1H, br d, *J* = 8.1, Trp-N*H*), 6.44 (1H, br d, *J* = 7.2, Phe-N*H*), 6.99-7.10 (5H, m, alkene-C*H* / Ar-*H*), 7.26-7.32 (2H, m, Ar-*H*), 7.36-7.42 (5H, m, Ar-*H*), 7.46-7.54 (4H, m, alkene-C*H* / Ar-*H*), 7.56-7.62 (6H, m, Ar-*H*).

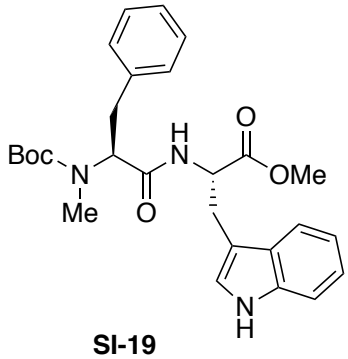
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 12.6 (TIPS-CH), 18.0 (TIPS-CH_3), 23.1 (acetyl-CH_3), 27.9 (Trp-CH_2), 31.7 (Phe-CH_2), 52.5 (ester-CH_3), 53.1 (Trp-α-CH), 53.8 (Phe-α-CH), 112.3 (Ar-C), 113.9 (Ar-C), 118.4 (Ar-C), 119.7 (Ar-C), 121.5 (Ar-C), 125.5 (Ar-C), 126.0 (alkene-C), 126.8 (Ar-C), 127.5 (Ar-C), 127.8 (Ar-C), 128.7 (Ar-C), 129.8 (Ar-C), 131.0 (Ar-C), 131.6 (Ar-C), 131.8 (alkene-C), 137.2 (Ar-C), 137.8 (Ar-C), 141.1 (Ar-C), 169.9 (C=O), 170.8 (C=O), 171.4 (C=O).

IR U_{max} /cm^{-1} (oil) 3249 m (N-H), 3058 w (C-H), 2948 w (C-H), 2866 w (C-H), 1743 s (ester C=O), 1629 m (amide C=O), 1508 m (C=C), 1211 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{48}H_{58}N_3O_4Si$: 768.4191, found: 768.4190.

3.9.7. Synthesis of Ac-Gly-(*N*-Me)Phe-Trp-OMe (12)

Boc-(*N*-Me)-Phe-Trp-OMe (SI-19)



SI-19

Tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and K_2CO_3 (0.498 g, 3.60 mmol) were dissolved in distilled water (30 mL) and stirred for 10 min at room temperature. The free amine was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting yellow oil was dissolved in CH_2Cl_2 (30 mL) and treated with Boc-(*N*-Me)-phenylalanine (0.279 g, 1.00 mmol), *i*-Pr_2NEt (0.174 mL, 1.00 mmol) and HATU (0.380 g, 1.00 mmol). The reaction mixture was stirred for 12 h, and then diluted with CH_2Cl_2 (30 mL) The organic phase was washed with 1 M HCl (20 mL), sat. $NaHCO_3$ (3 x 20 mL) and H_2O (20 mL), and then dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (80% EtOAc/pet ether), followed by recrystallisation from CH_2Cl_2 / hexanes gave **SI-19** as a cream solid (0.353 g, 74%); m.p. 71-73 °C, R_f 0.24 (80% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) The spectrum contained a mixture of rotamers in the ratio 11:9.

major rotamer: δ 1.20 (9H, s, Boc-(C*H*$_3$)$_3$), 2.41 (3H, s, N-C*H*$_3$), 2.75-2.85 (1H, m, Phe-C*H*H), 3.19-3.40 (3H, m, Phe-CH*H* / Trp-C*H*$_2$), 3.68 (3H, s, ester-C*H*$_3$), 4.69 (1H, br d, *J* = 7.8, Phe-α-C*H*), 4.80-4.90 (1H, m, Trp-α-C*H*), 6.40 (1H, d, *J* = 6.5, Trp-N*H*), 6.88 (1H, s, Ar-*H*), 7.03-7.34 (8H, m, Ar-*H*), 7.52 (1H, d, *J* = 7.8, Ar-*H*), 8.81 (1H, br s, Trp-Ar-N*H*);

minor rotamer δ 1.30 (9H, s, Boc-(C*H*$_3$)$_3$), 2.43 (3H, s, N-C*H*$_3$), 2.86-2.97 (1H, m, Phe-C*H*H), 3.19-3.40 (3H, m, Phe-CH*H* / Trp-C*H*$_2$), 3.60 (3H, s, ester-C*H*$_3$), 4.80-4.90 (2H, m, Trp-α-C*H* / Phe-α-C*H*), 6.65 (1H, d, *J* = 6.2, Trp-N*H*), 6.92 (1H, s, Ar-*H*), 7.03-7.34 (8H, m, Ar-*H*), 7.52 (1H, d, *J* = 7.8, Ar-*H*), 8.77 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)

minor rotamer: δ 27.3 (Trp-CH_2), 27.8 (Boc-$(CH_3)_3$), 30.8 (N-CH_3), 33.6 (Phe-CH_2), 52.3 (ester-CH_3), 52.6 (Trp-α-CH), 61.2 (Phe-α-CH), 80.7 (Boc-C), 109.0 (Ar-C), 111.3 (Ar-C),

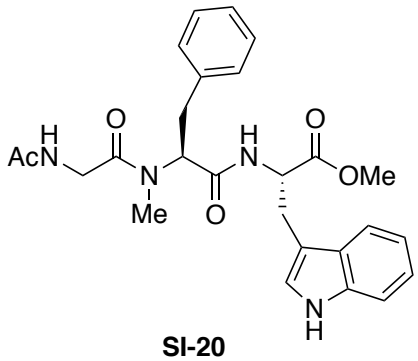
118.0 (Ar-C), 119.5 (Ar-C), 122.0 (Ar-C), 122.7 (Ar-C), 126.3 (Ar-C), 127.0 (Ar-C), 128.3 (Ar-C), 128.7 (Ar-C), 136.1 (Ar-C), 137.6 (Ar-C), 154.9 (C=O), 170.0 (C=O), 172.1 (C=O);

minor rotamer: δ 27.3 (Trp-CH_2), 27.9 (Boc-$(CH_3)_3$), 30.2 (N-CH_3), 33.8 (Phe-CH_2), 52.2 (ester-CH_3), 53.0 (Trp-α-CH), 59.6 (Phe-α-CH), 80.2 (Boc-C), 109.3 (Ar-C), 111.2 (Ar-C), 118.1 (Ar-C), 119.3 (Ar-C), 121.9 (Ar-C), 122.7 (Ar-C), 126.2 (Ar-C), 127.3 (Ar-C), 128.2 (Ar-C), 128.7 (Ar-C), 136.0 (Ar-C), 137.2 (Ar-C), 156.1 (C=O), 170.5 (C=O), 172.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3316 w (N-H), 3028 w (C-H), 2954 w (C-H), 1739 m (ester C=O), 1664 s (amide C=O), 1507 m (C=C), 1211 m (C-O).

HRMS (ESI) [M+H^+] *m/z* calcd. For $C_{27}H_{34}N_3O_5$: 480.2498, found: 480.2490.

Ac-Gly-(*N*-Me)-Phe-Trp-OMe (SI-20)



SI-20

Boc-(*N*-Me)-Phe-Trp-OMe (**SI-19**) (0.320 g, 0.667 mmol) was stirred in a solution of 20% trifluoroacetic acid in CH_2Cl_2 (7.5 mL). Subsequently, the volatiles were removed *in vacuo* and the resulting residue was dissolved in EtOAc (50 mL). This solution was then washed with sat. $NaHCO_3$ (25 mL), dried ($MgSO_4$) and concentrated to dryness. The resulting amine was dissolved in DMF (5 mL), and treated with *N*-acetyl glycine (0.078 g, 0.667 mmol), NEt_3 (0.186 mL, 1.334 mmol) and HATU (0.304 g 0.800 mmol). The reaction mixture was stirred at room temperature for 18 h, before being quenched with sat. $NaHCO_3$ (5 mL) and stirred for a further 30 min. The reaction mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude, yellow oil was purified by flash column chromatography (EtOAc) and recrystallised from CH_2Cl_2 / hexanes to give **SI-20** as an off-white solid. (0.198 g, 62%), 92-96 °C, R_f 0.20 (EtOAc).

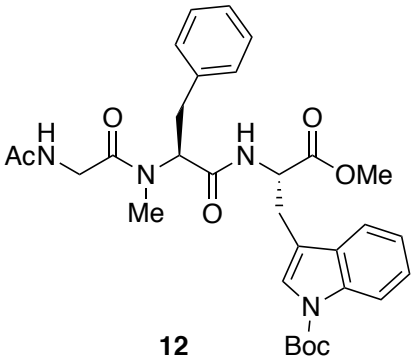
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s, acetyl-C*H*$_3$), 2.33 (3H, s, N-C*H*$_3$), 2.82-2.87 (1H, m Phe-C*H*H), 3.11 (1H, dd, *J* = 14.6, 8.5, Trp-C*H*H), 3.20 (1H, dd, *J* = 14.6, 6.2, Phe-CH*H*), 3.37 (1H, dd, *J* = 14.6, 5.0, Trp-CH*H*), 3.44 (1H, dd, *J* = 17.6, 3.7, Gly-C*H*H), 3.71 (3H, s, ester-C*H*$_3$), 3.78 (1H, dd, *J* = 17.6, 5.5, Gly-CH*H*), 4.84-4.92 (1H, m, Trp-α-C*H*), 5.29-5.37 (1H, m, Phe-α-C*H*), 6.45 (1H, t, *J* = 4.6, Gly-N*H*), 6.57 (1H, d, *J* = 7.8, Trp-N*H*), 6.87 (1H, d, *J* = 2.3, Ar-*H*), 7.02-7.10 (3H, m, Ar-*H*), 7.12-7.22 (4H, m, Ar-*H*), 7.34 (1H, d, *J* = 8.2, Ar-*H*), 7.51 (1H, d, *J* = 7.8, Ar-*H*), 9.03 (1H, s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (acetyl-CH_3), 27.2 (Trp-CH_2), 29.5 (N-CH_3), 33.4 (Phe-CH_2), 40.9 (Gly-CH_2), 52.1 (Trp-α-CH), 52.4 (ester-CH_3), 57.2 (Phe-α-CH), 109.3 (Ar-C), 111.3 (Ar-C), 118.2 (Ar-C), 119.4 (Ar-C), 122.1 (Ar-C), 123.1 (Ar-C), 126.6 (Ar-C), 127.0 (Ar-C), 128.4 (Ar-C), 128.5 (Ar-C), 136.0 (Ar-C), 136.5 (Ar-C), 169.2 (C=O), 169.2 (C=O), 170.5 (C=O), 172.2 (C=O).

IR υ_{max} /cm^{-1} (solid) 3299 m (N-H), 3058 w (C-H), 2954 w (C-H), 1735 m (ester C=O), 1636 s (amide C=O), 1522 m (C=C), 1210 m (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{26}H_{31}N_4O_5$: 479.2294, found: 479.2300.

Ac-Gly-(*N*-Me)-Phe-Trp(Boc)-OMe (12)



12

Peptide **12** was synthesised from Ac-Gly-(*N*-Me)-Phe-Trp-OMe (0.198 g, 0.414 mmol) using the procedure in **section 2.3.** Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **12** as a white solid (0.129 g, 54%); m.p. 63-66 °C, R_f = 0.2 (EtOAc).

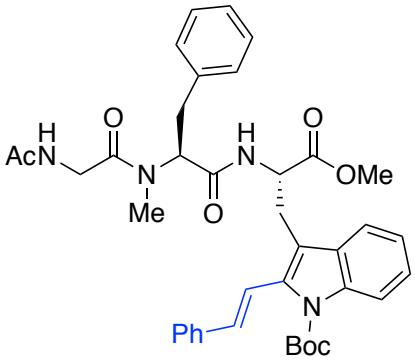
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (9H, s, Boc-(C*H*$_3$)$_3$), 2.03 (3H, s, acetyl-C*H*$_3$), 2.68 (3H, s, N-C*H*$_3$), 2.93 (1H, dd, *J* = 14.6, 9.2, Phe-C*H*H), 3.17 (1H, dd, *J* = 15.1, 6.9, Trp-C*H*H), 3.22-3.31 (2H, m, Phe-CH*H* / Trp-CH*H*), 3.58-3.70 (4H, m, ester-C*H*$_3$ / Gly-C*H*H), 3.83 (1H, dd, *J* = 18.5, 4.4, Gly-CH*H*), 4.84-4.91 (1H, m, Trp-α-C*H*), 5.24 (1H, dd, *J* = 9.2, 6.9, Phe-α-C*H*), 6.50 (1H, br s, Gly-N*H*), 6.58 (1H, d, *J* = 7.8, Trp-N*H*), 7.08-7.27 (6H, m, Ar-*H*), 7.31 (1H, t, *J* = 7.3, Ar-*H*), 7.40 (1H, s, Ar-*H*), 7.45 (1H, d, *J* = 7.8, Ar-*H*), 8.04 (1H, br d, *J* = 7.8, Ar-*H*).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.0 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 30.2 (N-CH_3), 33.5 (Phe-CH_2), 41.4 (Gly-CH_2), 52.1 (Trp-α-CH), 52.5 (ester-CH_3), 57.9 (Phe-α-CH), 84.1 (Boc-C), 114.6 (Ar-C), 115.3 (Ar-C), 118.6 (Ar-C), 122.5 (Ar-C), 124.3 (Ar-C), 124.6 (Ar-C), 126.8 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C) 128.9 (Ar-C), 130.4 (Ar-C), 136.4 (Ar-C), 149.7 (C=O), 169.2 (C=O), 169.4 (C=O), 170.0 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3319 w (N-H), 3060 w (C-H), 2953 m (C-H), 1730 s (ester C=O), 1638 s (amide C=O), 1522 s (C=C), 1254 (C-O).

HRMS (ESI) [$M+H^+$] *m/z* calcd. For $C_{31}H_{39}N_4O_7$: 579.2819, found: 579.2816.

3.9.8. C-H olefination of Ac-Gly-(*N*-Me)-Phe-Trp(Boc)-OMe (12); synthesis of modified peptide 13



13

Modified peptide **13** was prepared from Ac-Gly-(*N*-Me)-Phe-Trp(Boc)-OMe (**8c**) (0.129 g, 0.223 mmol) and styrene (0.103 mL, 0.892 mmol), using the general procedure in **section 2.4.** Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **13** as a yellow solid (0.084 g, 55%); m.p. 94-98 °C, R_f 0.28 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s, Boc(C*H*$_3$)$_3$), 1.97 (3H, s, acetyl-C*H*$_3$), 2.41 (3H, s, N-C*H*$_3$), 2.85 (1H, dd, *J* = 14.6, 9.8, Phe-C*H*H), 3.16 (1H, dd, *J* = 14.7, 6.3, Phe-CH*H*), 3.24 (1H, dd, *J* = 14.4, 8.6, Trp-C*H*H), 3.40 (1H, dd, *J* = 14.4, 6.4, Trp-CH*H*), 3.52 (1H, dd, *J* = 17.7, 3.4, Gly-C*H*H), 3.62 (3H, s, ester-C*H*$_3$), 3.67 (1H, dd, *J* = 17.9, 4.5, Gly-CH*H*), 4.93-5.01 (1H, m, Trp-α-C*H*), 5.23 (1H, dd, *J* = 9.6, 6.4, Phe-α-C*H*), 6.29 (1H, br s, Gly-N*H*), 6.45 (1H, d, *J* = 8.0, Trp-N*H*), 6.77 (1H, d, *J* = 16.7, alkene-C*H*), 7.00-7.10 (2H, m, Ar-*H*), 7.12-7.24 (4H, m, Ar-*H*), 7.27-7.41 (5H, m, Ar-*H* / alkene-C*H*), 7.51 (1H, d, *J* = 7.8, Ar-*H*), 7.56 (2H, d, *J* = 7.9, Ar-*H*), 8.11 (1H, d, *J* = 8.8, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (acetyl-CH_3), 27.5 (Trp-CH_2), 28.3 (Boc-$(CH_3)_3$), 29.7 (N-CH_3), 33.5 (Phe-CH_2), 41.4 (Gly-CH_2), 52.0 (Trp-CH), 52.6 (ester-CH_3), 57.6 (Phe-CH), 84.3 (Boc-C), 114.5 (Ar-C). 115.6 (Ar-C), 118.5 (Ar-C), 120.0 (alkene-C), 122.9 (Ar-C), 124.9 (Ar-C), 126.6 (Ar-C), 126.8 (Ar-C), 128.1 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-C), 128.8 (Ar-C), 130.0 (Ar-C), 132.2 (alkene-C), 135.7 (Ar-C), 136.2 (Ar-C), 136.4 (Ar-C), 136.7 (Ar-C), 150.4 (C=O), 169.2 (C=O), 169.2 (C=O), 169.8 (C=O), 172.0 (C=O);

IR U_{max} /cm^{-1} (solid) 3275 w (N-H), 3058 w (C-H), 2976 w (C-H), 1728 s (ester C=O), 1634 s (amide C=O), 1541 m (C=C), 1237 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{39}H_{45}N_4O_7$: 681.3288, found: 681.3308.

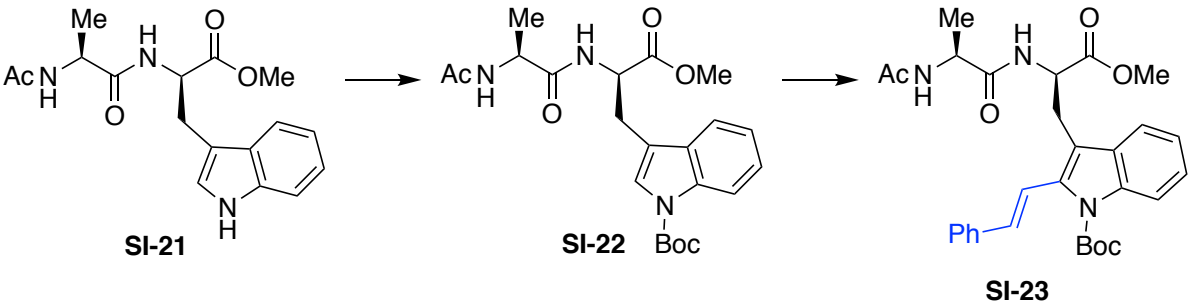
3.10. Investigation of potential racemization in the C-H olefination reaction

For the synthesis of modified peptides that contained more than one stereogenic centre, there was no evidence for the formation of diastereomeric products, as judged by NMR spectroscopy.

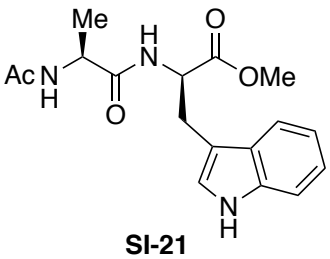
In addition, a detailed stereochemical investigation was carried out for the reaction of peptide Ac-Ala-Trp(Boc)-OMe (**4a**) to give modified peptide **5a**. Specifically, the diastereomeric peptide Ac-Ala-D-Trp(Boc)-OMe (**SI-22**), prepared from D-tryptophan methyl ester and acetyl-L-alanine, followed by Boc protection of the D-Trp residue, was modified to give the diastereomeric modified peptide **SI-23**.

Comparison of the HPLC chromatograms revealed that the modified peptide **5a** contained *ca*. 0.1% of the diastereomeric peptide **SI-23**.

The relevant synthetic procedures, characterisation data, and comparison of HPLC chromatograms are presented below.



Ac-Ala-D-Trp-OMe (SI-21)



Ac-Ala-D-Trp-OMe (SI-21) was synthesised from D-tryptophan methyl ester hydrochloride (0.637 g, 2.50 mmol) and *N*-acetylalanine (0.131 g, 1.00 mmol), using the procedure in section 2.1. The crude compound was washed with CH_2Cl_2 to afford SI-21 as a white solid (0.205 g, 62%); m.p. 192-195 °C.

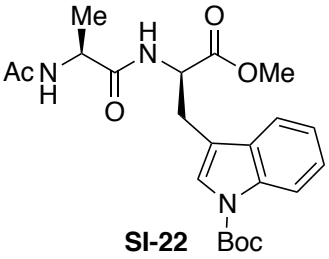
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 7.1, Ala-C*H*$_3$), 1.84 (3H, s, acetyl-C*H*$_3$), 3.30 (2H, d, *J* = 6.0, Trp-C*H*$_2$), 3.67 (3H, s, ester-C*H*$_3$), 4.38-4.47 (1H, m, Ala-α-C*H*), 4.83 (1H, dt, *J* = 6.0, 6.0, Trp-α-C*H*), 6.36 (1H, d, *J* = 7.3, Ala-N*H*), 6.95-7.02 (2H, m, Trp-N*H*, Ar-*H*), 7.09 (1H, t, *J* = 7.5, Ar-*H*), 7.16 (1H, t, *J* = 7.6, Ar-*H*), 7.32 (1H, d, *J* = 8.0, Ar-*H*), 7.52 (1H, d, *J* = 7.8, Ar-*H*), 8.60 (1H, br s, Trp-Ar-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.3 (Ala-CH_3), 23.0 (acetyl-CH_3), 27.3 (Trp-CH_2), 48.7 (Ala-α-CH), 52.4 (ester-CH_3), 52.9 (Trp-α-CH), 109.5 (Ar-C), 111.4 (Ar-C), 118.3 (Ar-C), 119.5 (Ar-C), 122.1 (Ar-C), 123.1 (Ar-C), 127.4 (Ar-C), 136.1 (Ar-C), 170.1 (C=O), 172.2 (C=O), 172.3 (C=O).

IR U_{max} /cm^{-1} (solid) 3239 m (N-H), 3060 s (C-H), 2976 m (C-H), 1742 s (ester C=O), 1641 s (amide C=O), 1541 s (C=C), 1217 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{22}N_3O_4$: 332.1610, found: 332.1609.

Ac-Ala-D-Trp(Boc)-OMe (SI-22)



SI-22

Diastereomeric peptide **SI-22** was synthesised from Ac-Ala-D-Trp-OMe (0.205 g, 0.62 mmol) using the procedure in **section 2.3**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **SI-22** as a white solid (0.105 g, 88%); m.p. 181-183 °C, R_f 0.2 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, d, *J* = 7.1, Ala-C*H*$_3$), 1.66 (9H, s, Boc-(C*H*$_3$)$_3$), 1.96 (3H, s, acetyl-C*H*$_3$), 3.20 (1H, dd, *J* = 14.9, 6.1, Trp-C*H*H), 3.28 (1H, dd, *J* = 14.9, 5.6, Trp-C*H*H), 3.69 (1H, s, ester-C*H*$_3$), 4.45-4.53 (1H, m, Ala-α-C*H*), 4.89 (1H, dt, *J* = 6.1, 5.6, Trp-α-C*H*), 6.19 (1H, d, *J* = 7.6, Ala-N*H*), 6.79 (1H, d, *J* = 7.6, Trp-N*H*), 7.23 (1H, t, *J* = 7.6, Ar-*H*), 7.31 (1H, t, *J* = 7.3, Ar-*H*), 7.39 (1H, s, Ar-*H*), 7.48 (1H, d, *J* = 7.8, Ar-*H*), 8.11 (1H, br. d, *J* = 7.3, Ar-*H*).

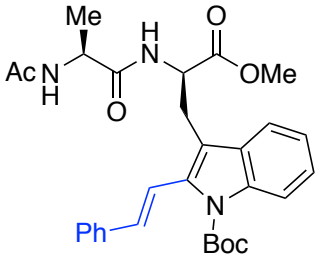
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.5 (Ala-CH_3), 23.1 (acetyl-CH_3), 27.2 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 48.7 (Ala-α-CH), 52.4 (ester-CH_3), 52.5 (Trp-α-CH), 83.7 (Boc-C), 114.7 (Ar-

C), 115.3 (Ar-C) 118.7 (Ar-C), 122.6 (Ar-C), 124.2 (Ar-C), 124.6 (Ar-C), 130.3 (Ar-C), 135.3 (Ar-C), 149.5 (C=O), 169.9 (C=O), 171.7 (C=O), 172.0 (C=O).

IR U_{max} /cm^{-1} (solid) 3278 w (N-H), 3071 w (C-H), 2978 w (C-H), 1730 s (ester C=O), 1640 s (amide C=O), 1530 (C=C), 1254 (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{22}H_{30}N_3O_6$: 432.2135, found: 432.2132.

Synthesis of modified peptide SI-23



SI-23

Diastereomeric, modified peptide **SI-23** was prepared from Ac-Ala-D-Trp(Boc)-OMe (**SI-22**) (0.100 g, 0.232 mmol) and styrene (0.109 mL, 0.952 mmol), using the general procedure in **section 2.4.** Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **SI-23** as a brown solid (0.078 g, 61%); m.p. 171-174 °C, R_f 0.26 (EtOAc).

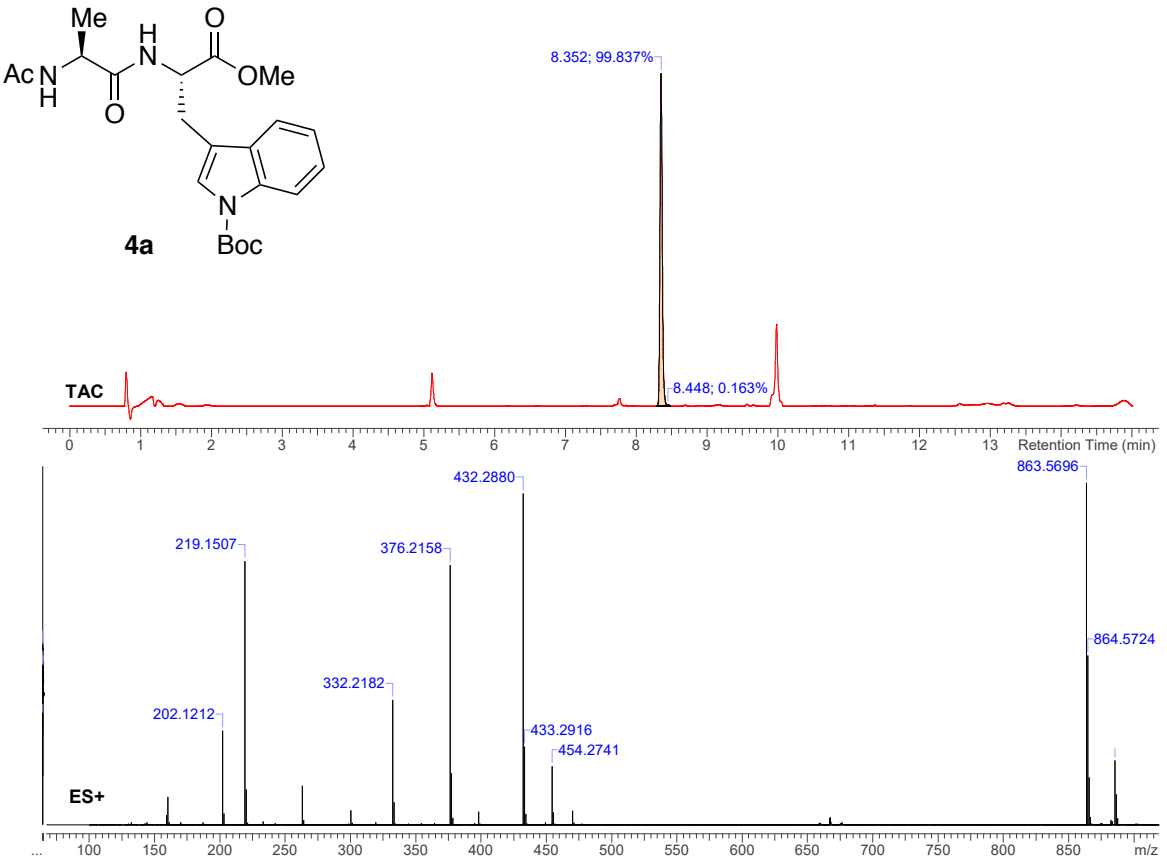
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, *J* = 7.1, Ala-C*H*$_3$), 1.62 (9H, s, Boc-C*H*$_3$), 1.90 (3H, s, acetyl-C*H*$_3$), 3.30 (1H, dd, *J* = 14.4, 7.3, Trp-C*H*H), 3.39 (1H, dd, *J* = 14.4, 6.7, Trp-CH*H*), 3.56 (3H, s, ester-C*H*$_3$), 4.40-4.50 (1H, m, Ala-α-C*H*), 4.89 (1H, app q, *J* = 7.4, Trp-α-C*H*), 6.27 (1H, d, *J* = 7.6, Trp-N*H*), 6.79 (1H, d, *J* = 16.5, alkene-C*H*), 7.06 (1H, d, *J* = 8.2, Ala-N*H*), 7.20-7.33 (4H, m, Ar-*H*), 7.35-7.40 (2H, m, alkene-C*H*/Ar-*H*), 7.55 (2H, d, *J* = 7.3, Ar-*H*), 7.60 (1H, d, *J* = 7.3, Ar-*H*), 8.12 (1H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.0 (Ala-CH_3), 23.0 (acetyl-CH_3), 27.7 (Trp-CH_2), 28.2 (Boc-$(CH_3)_3$), 48.5 (Ala-α-CH), 52.4 (ester-CH_3), 52.6 (Trp-α-CH), 84.0 (Boc-C), 114.8 (Ar-C), 115.5 (Ar-C), 118.7 (Ar-C), 120.0 (alkene-CH),122.8 (Ar-C),124.7 (Ar-C), 126.5 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 130.0 (Ar-C), 132.3 (alkene-CH), 135.8 (Ar-C), 136.0 (Ar-C), 136.8 (Ar-C), 150.3 (C=O), 169.9 (C=O), 172.0 (C=O), 172.1 (C=O).

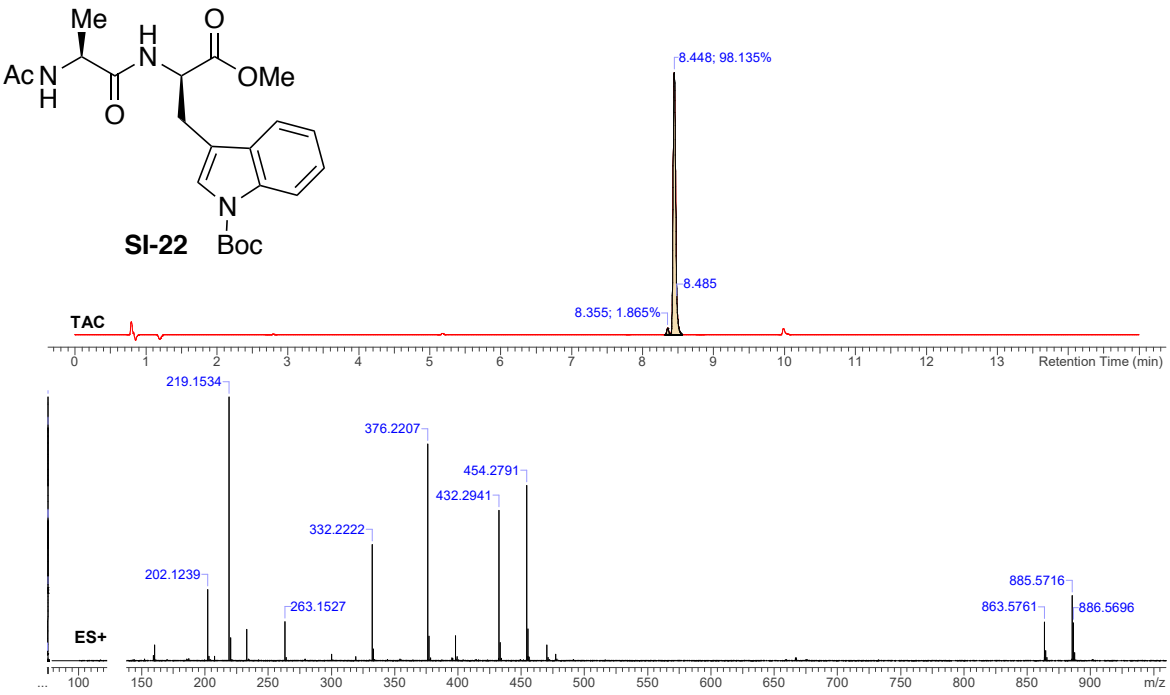
IR U_{max} /cm^{-1} (solid) 3058 w (C-H), 2978 w (C-H), 1728 s (ester C=O), 1634 s (amide C=O), 1541 m (C=C), 1272 m (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. For $C_{30}H_{36}N_3O_6$: 534.2604, found: 534.2613.

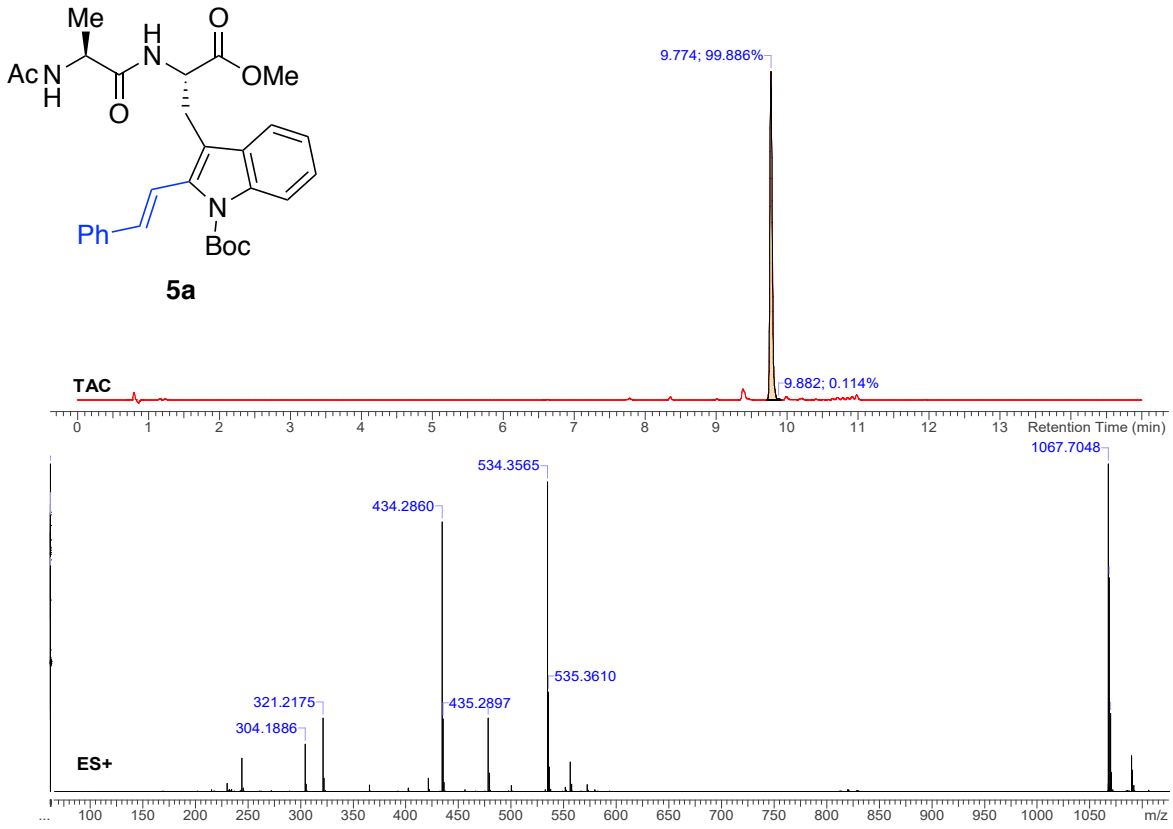
HPLC- chromatogram and ES-MS for peptide **4a**.



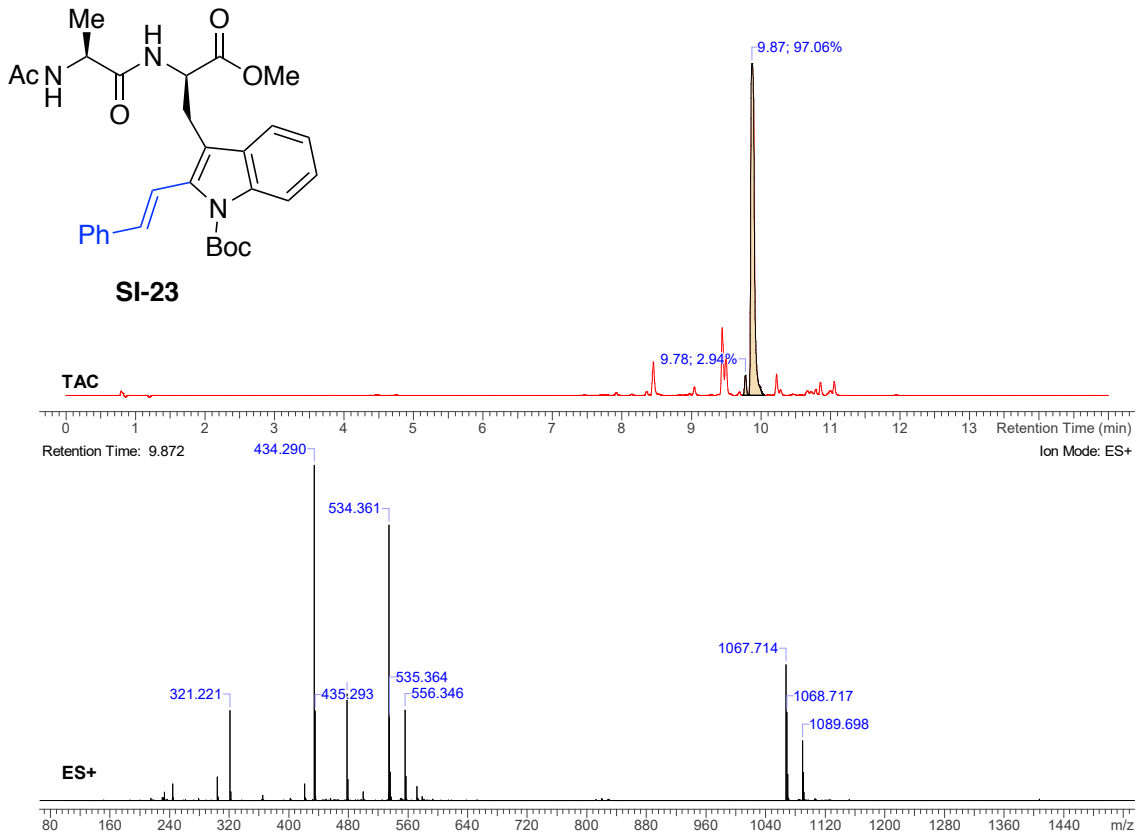
HPLC-chromatogram and ES-MS for diastereomeric peptide **SI-22**.



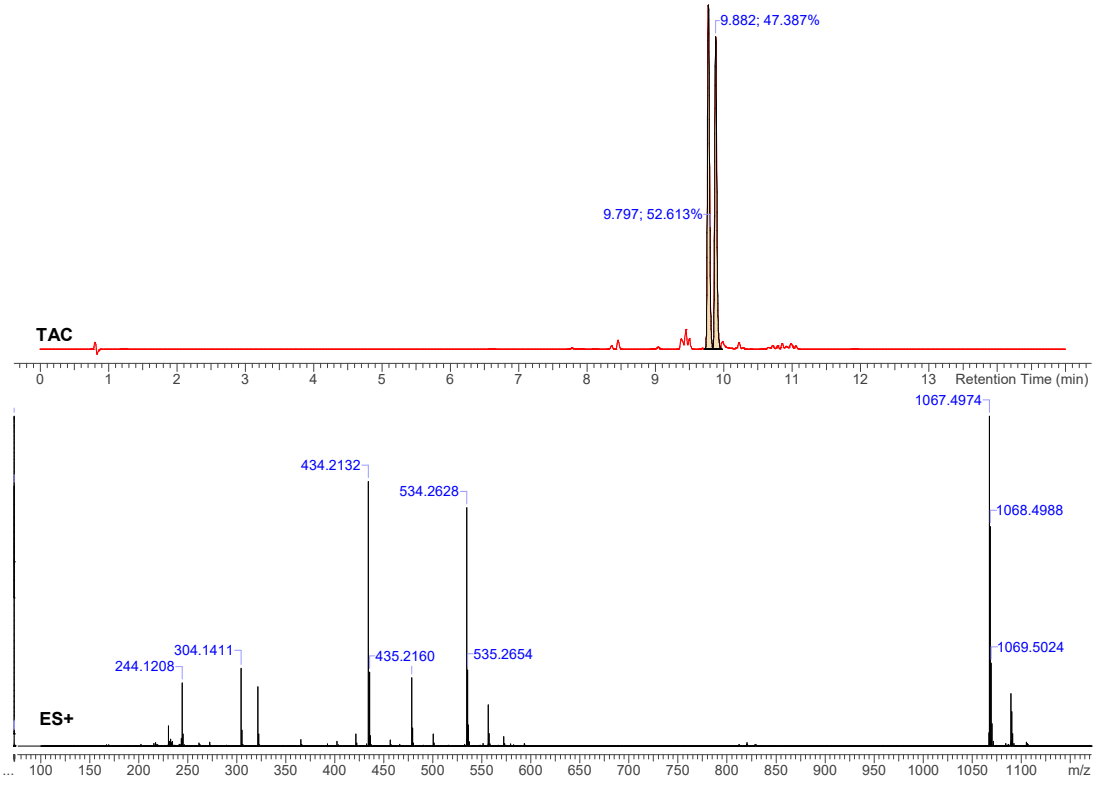
HPLC-chromatogram and ES-MS for modified peptide **5a**.



HPLC-chromatogram and ES-MS for diastereomeric modified peptide **SI-23**.



HPLC-chromatogram and ES-MS for **5a** spiked with *ca*. 50% **SI-23**.



4. References

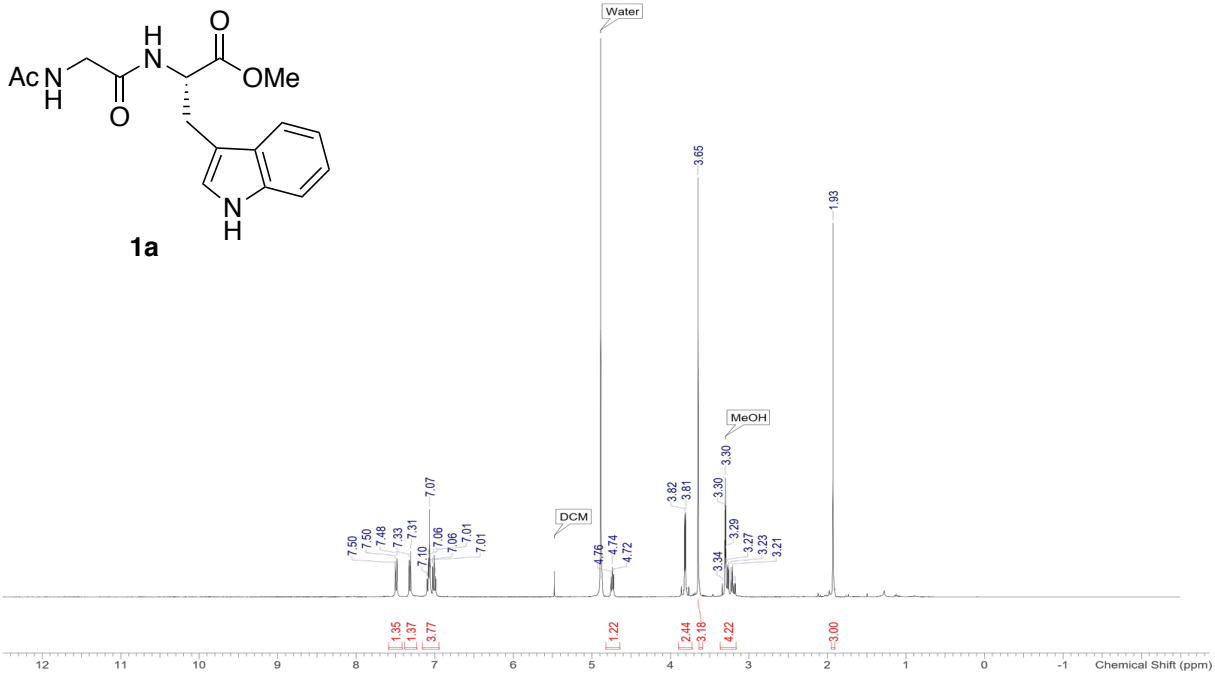
(S1) Willemse, T.; Van Imp, K.; Goss, R. J. M.; Van Vlijmen, H. W. T.; Schepens, W.; Maes, B. U. W.; Ballet, S. Suzuki–Miyaura Diversification of Amino Acids and Dipeptides in Aqueous Media *ChemCatChem* **2015**, *7* (14), 2055–2070.

(S2) Rudolf, J. D.; Poulter, C. D. (2013). Tyrosine *O*-Prenyltransferase SirD Catalyzes *S*-, *C*-, and *N*-Prenylations on Tyrosine and Tryptophan Derivatives *ACS Chem. Biol.* **2013**, *8* (12), 2707–2714.

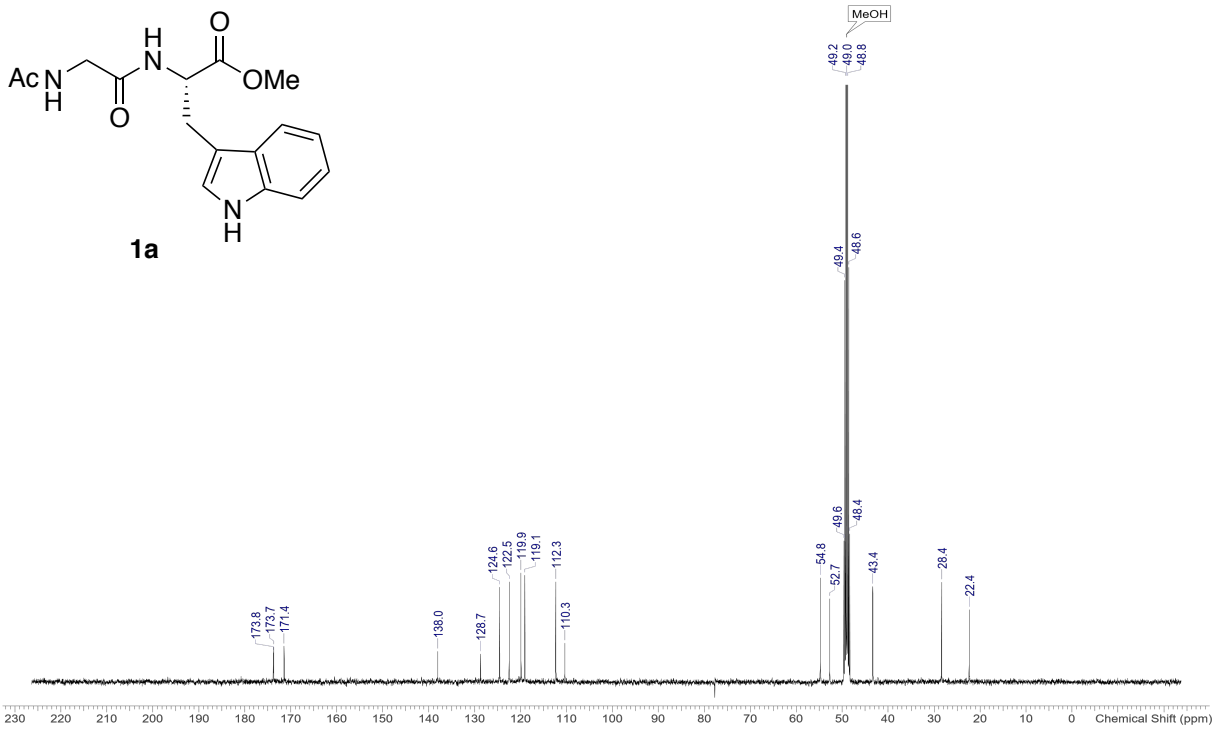
(S3) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. A Mild and Selective Pd-Mediated Methodology for the Synthesis of Highly Fluorescent 2-Arylated Tryptophans and Tryptophan-Containing Peptides: a Catalytic Role for Pd^0 Nanoparticles? *Chem. Commun.* **2014**, *50* (23), 3052–3054.

5. ^{1}H and ^{13}C NMR spectra of compounds 1-13

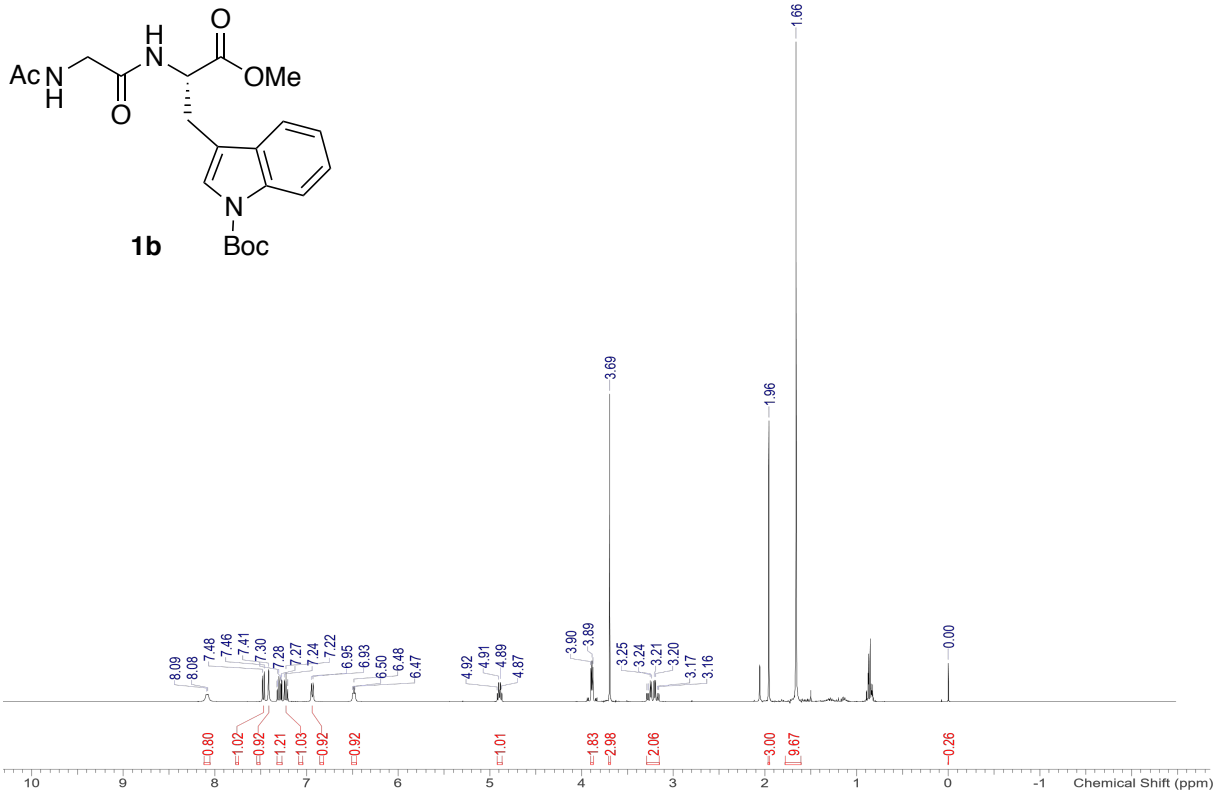
^{1}H NMR spectrum (400 MHz, CD_3OD) of **1a**



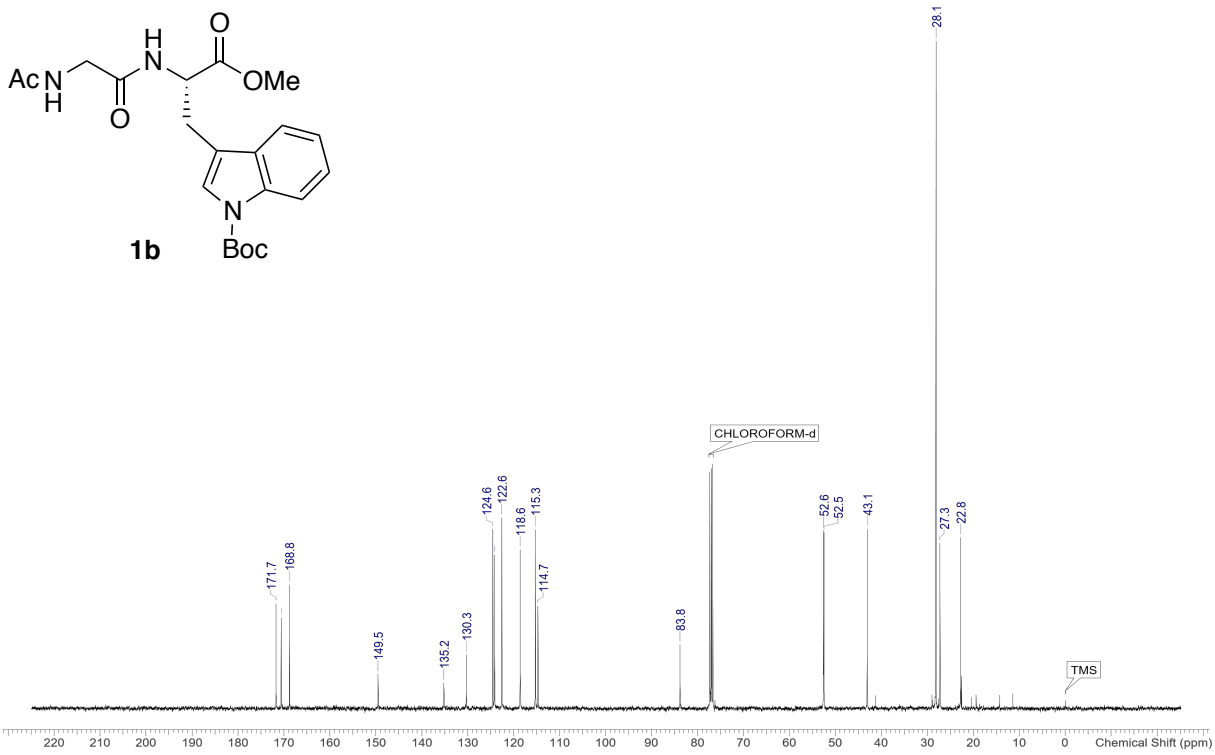
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **1a**



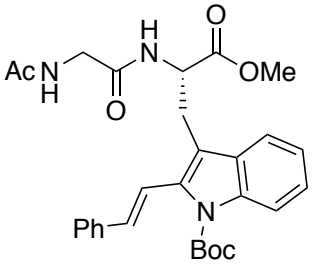
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1b**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1b**

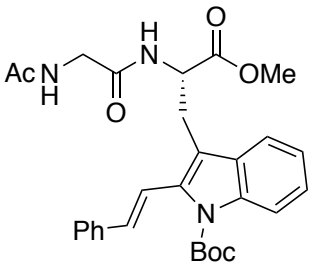


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2b**



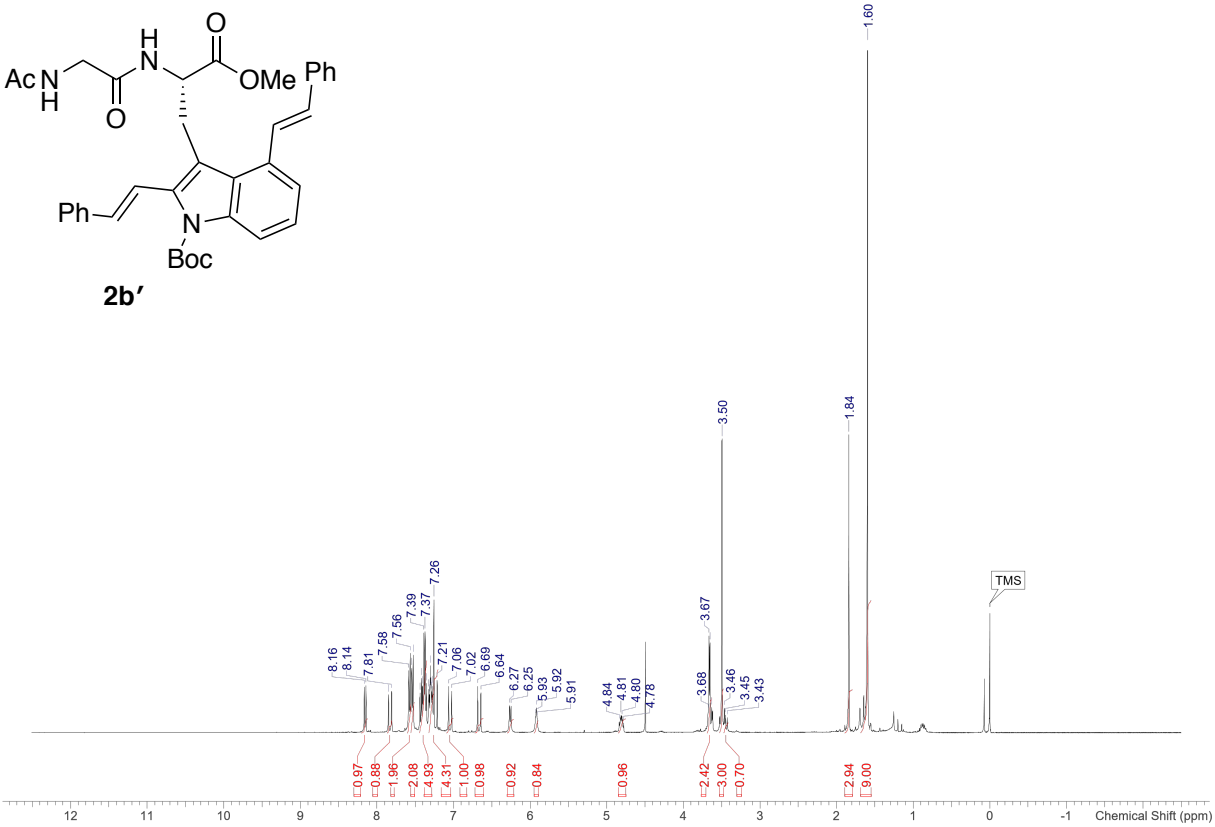
2b

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2b**



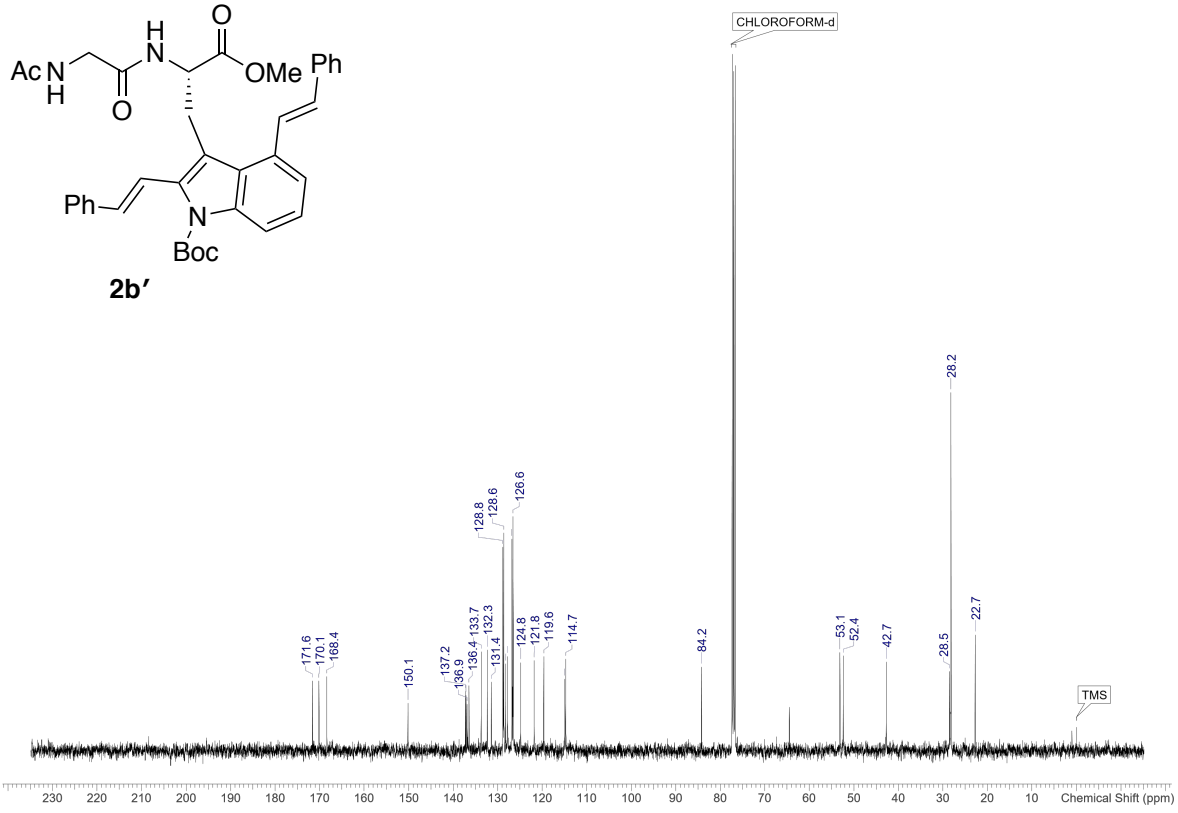
2b

^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2b'**



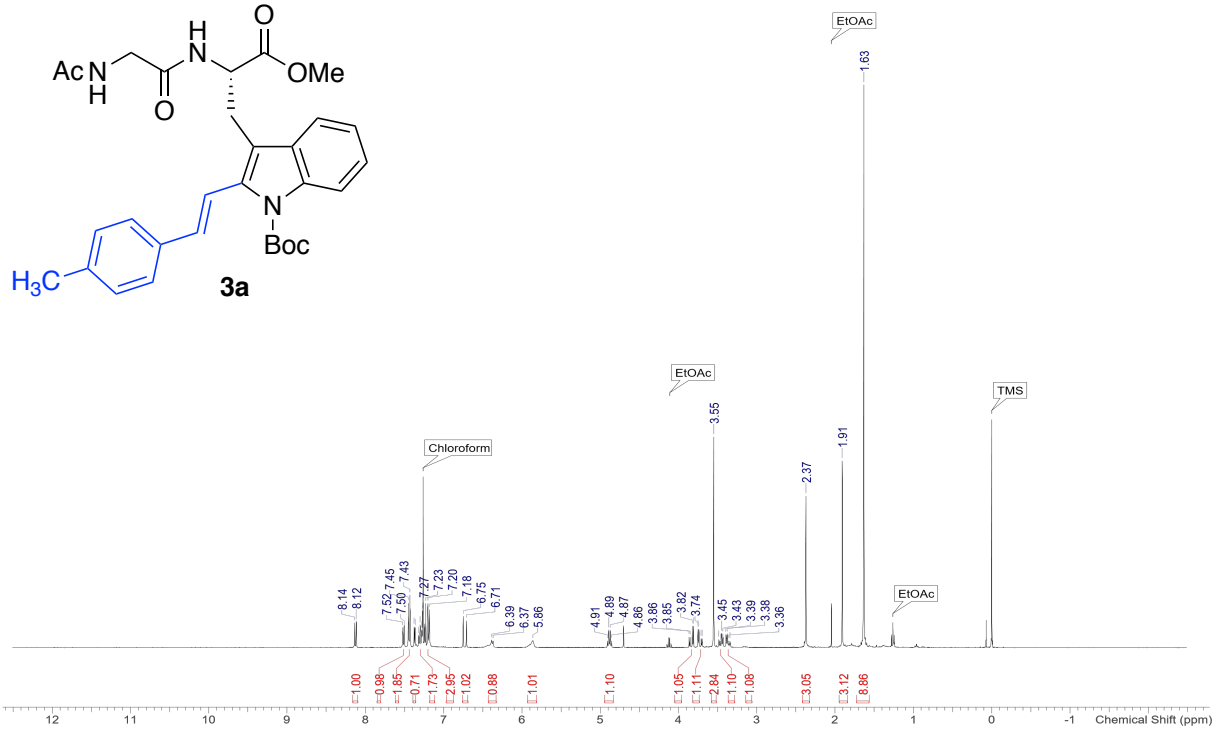
2b'

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2b'**

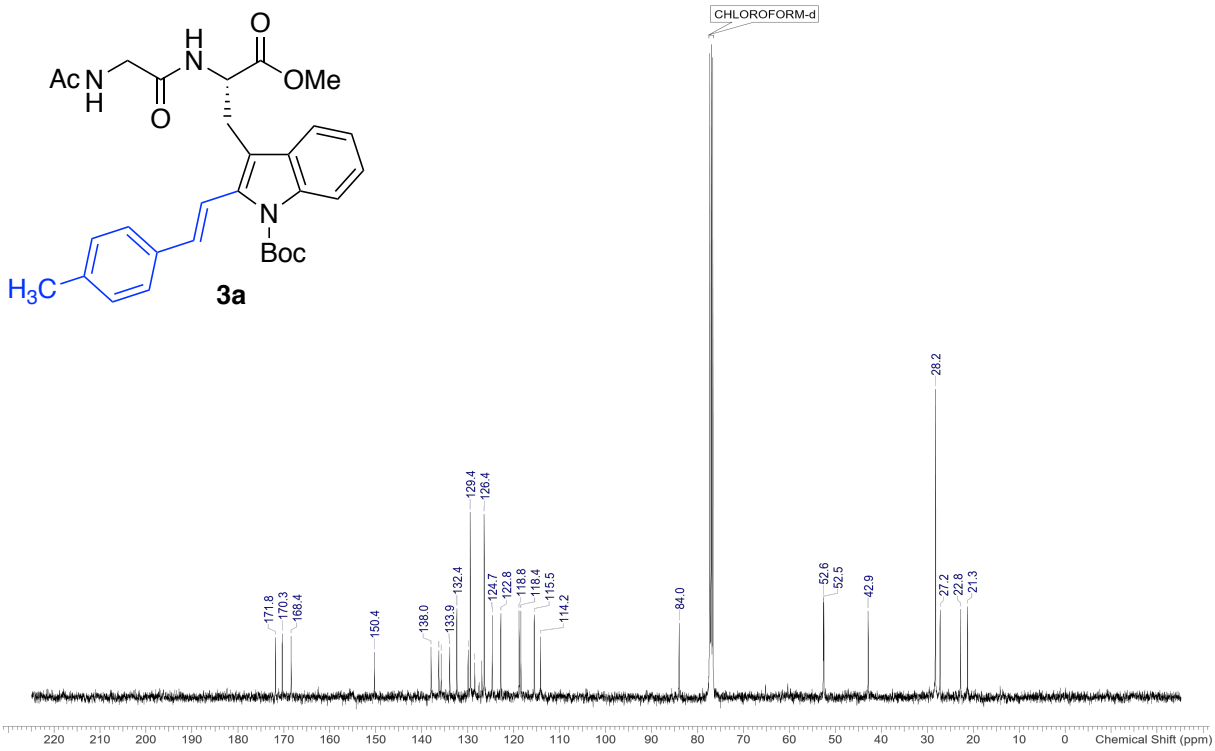


2b'

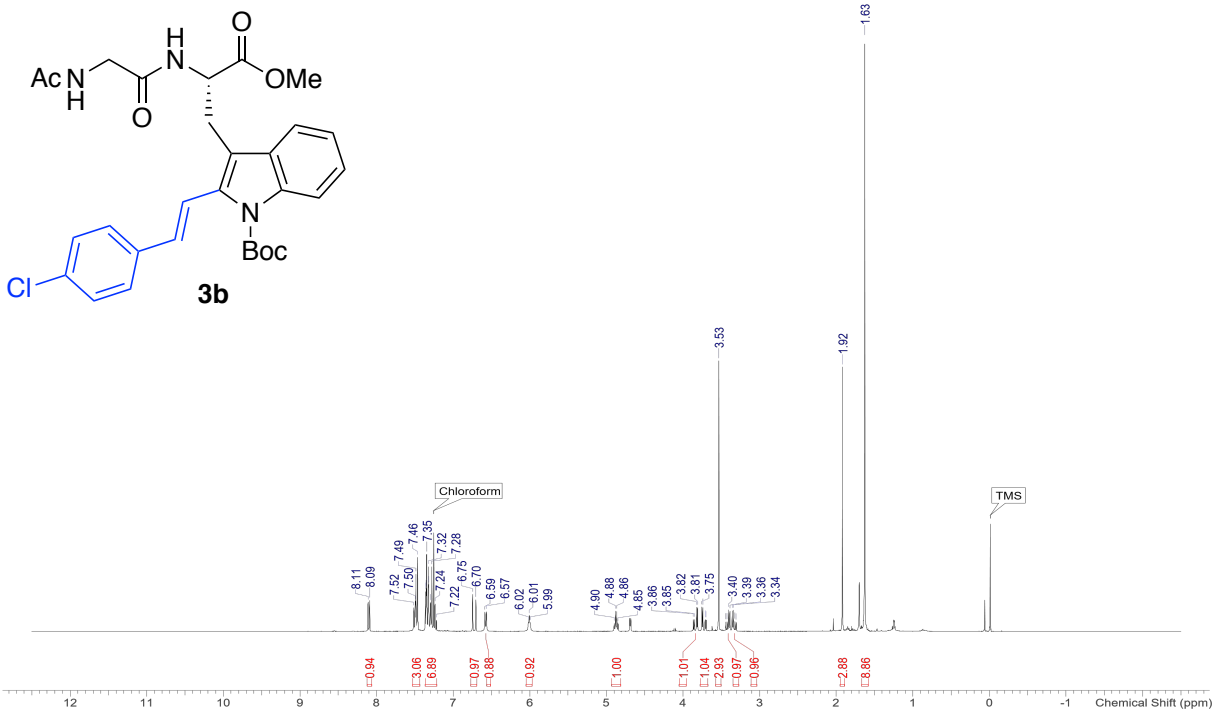
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3a**



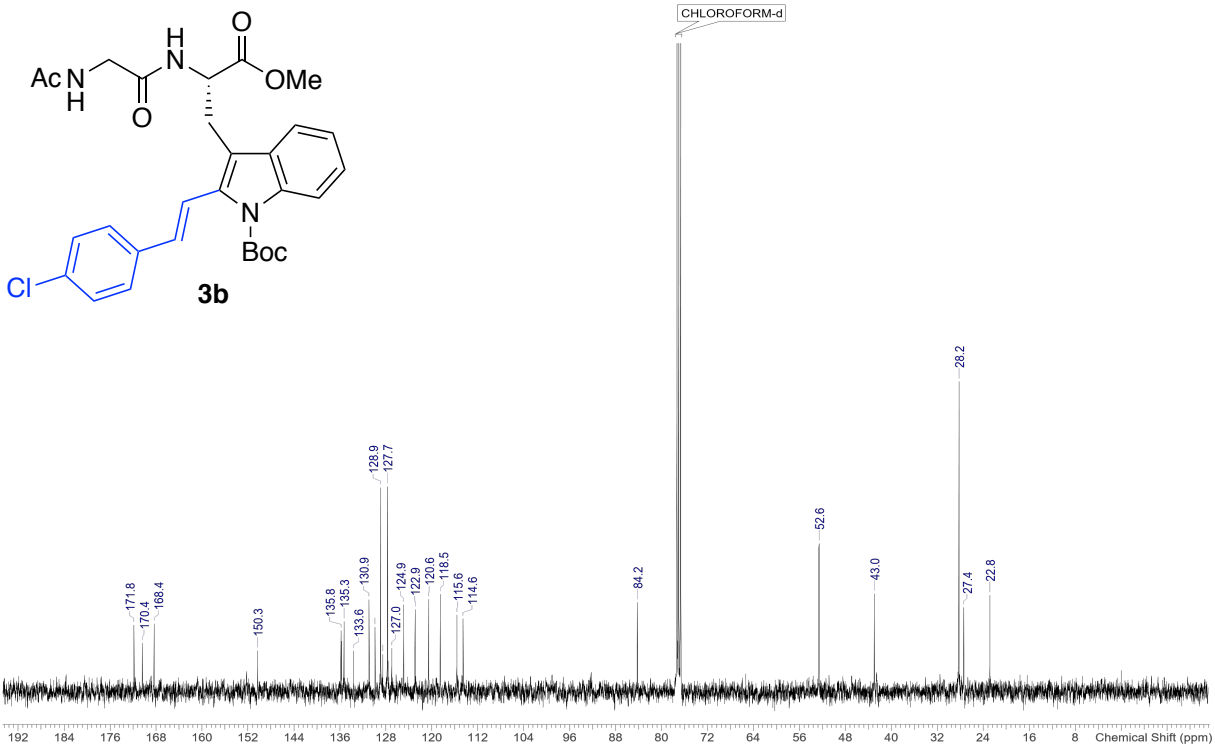
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3a**



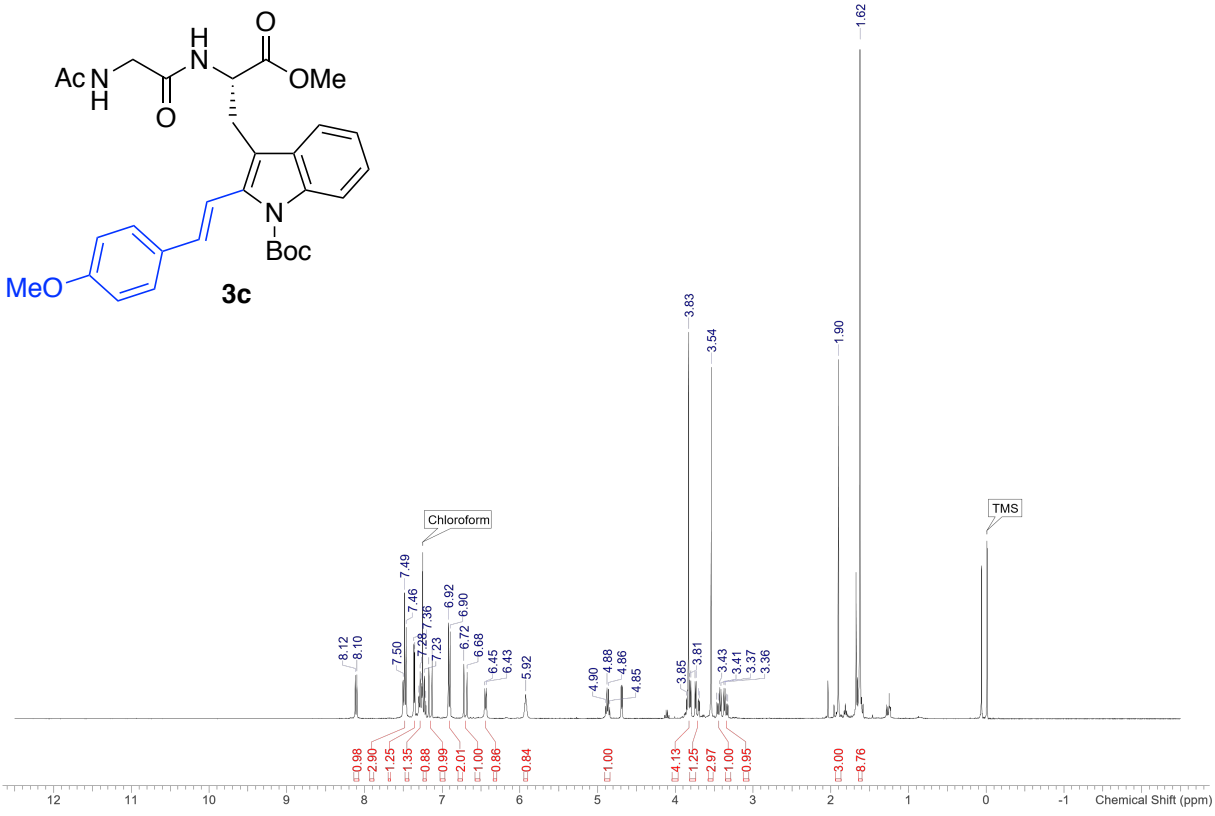
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3b**



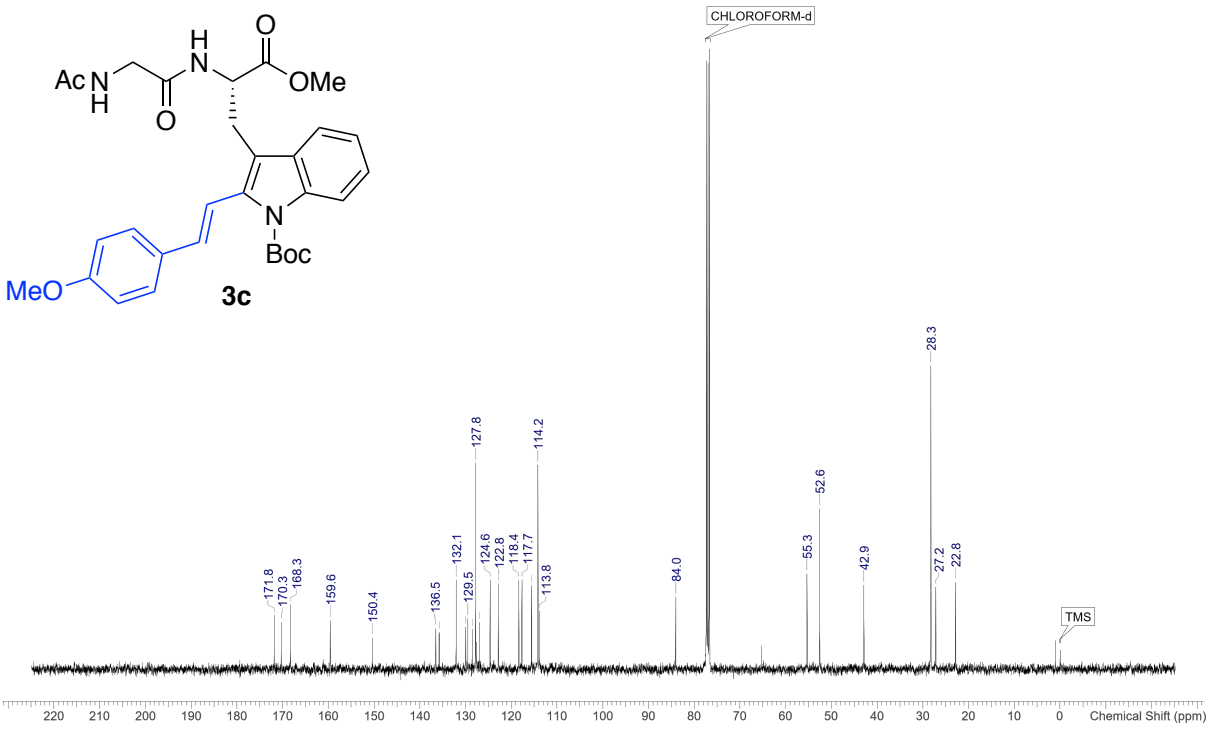
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3b**



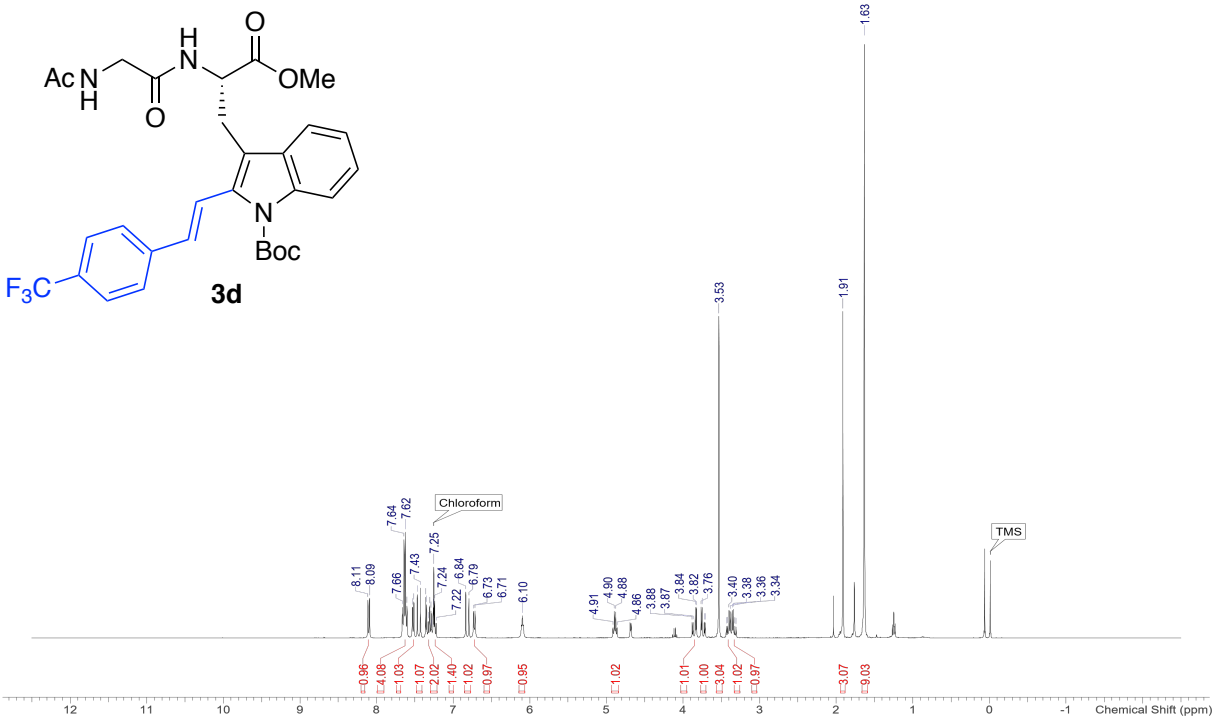
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3c**



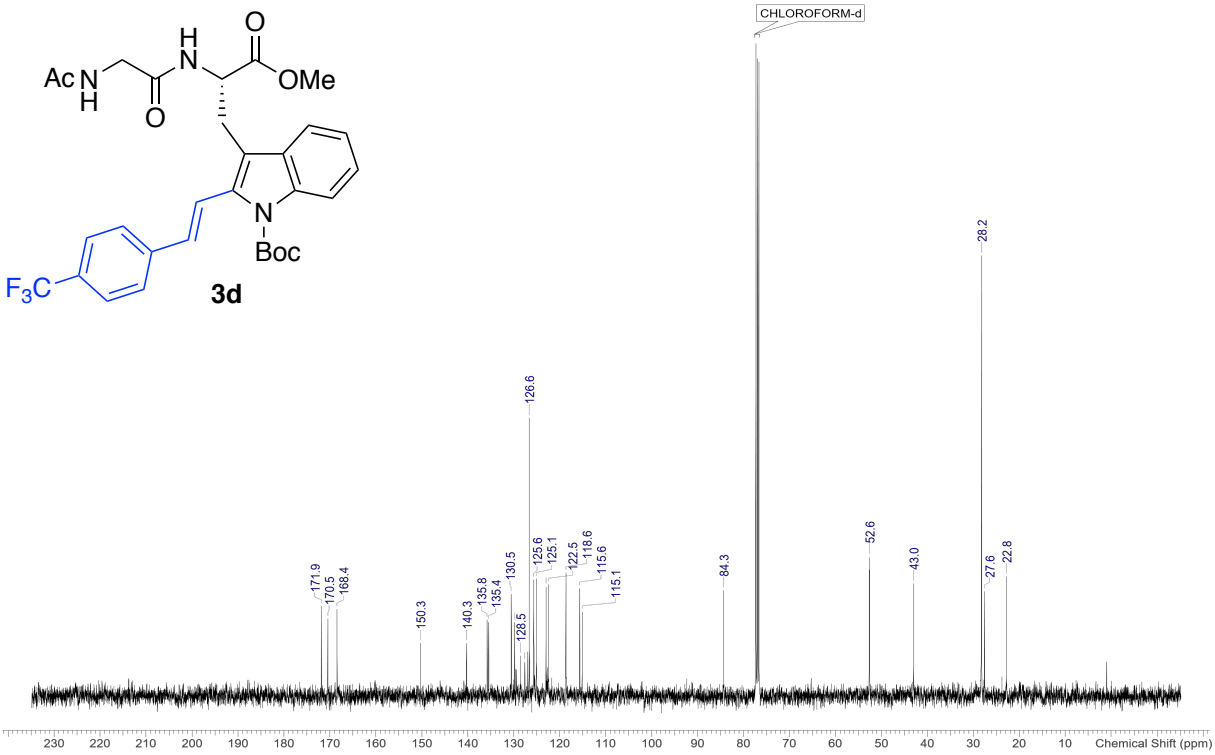
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3c**



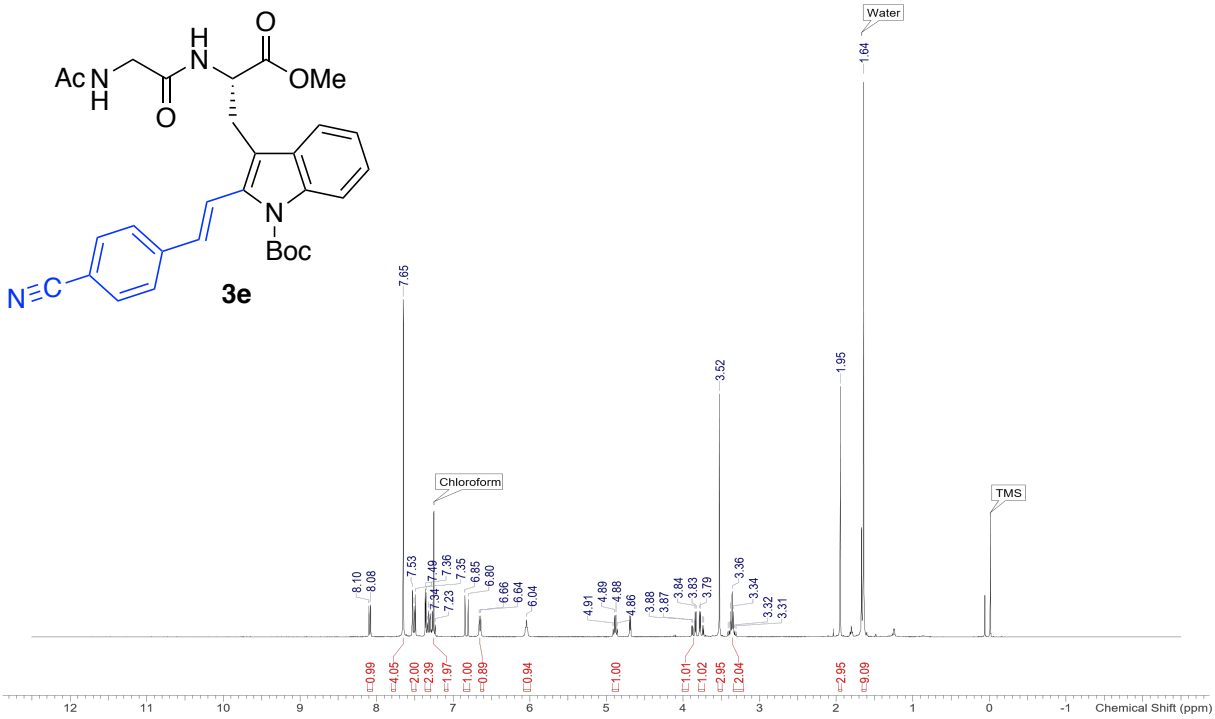
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3d**



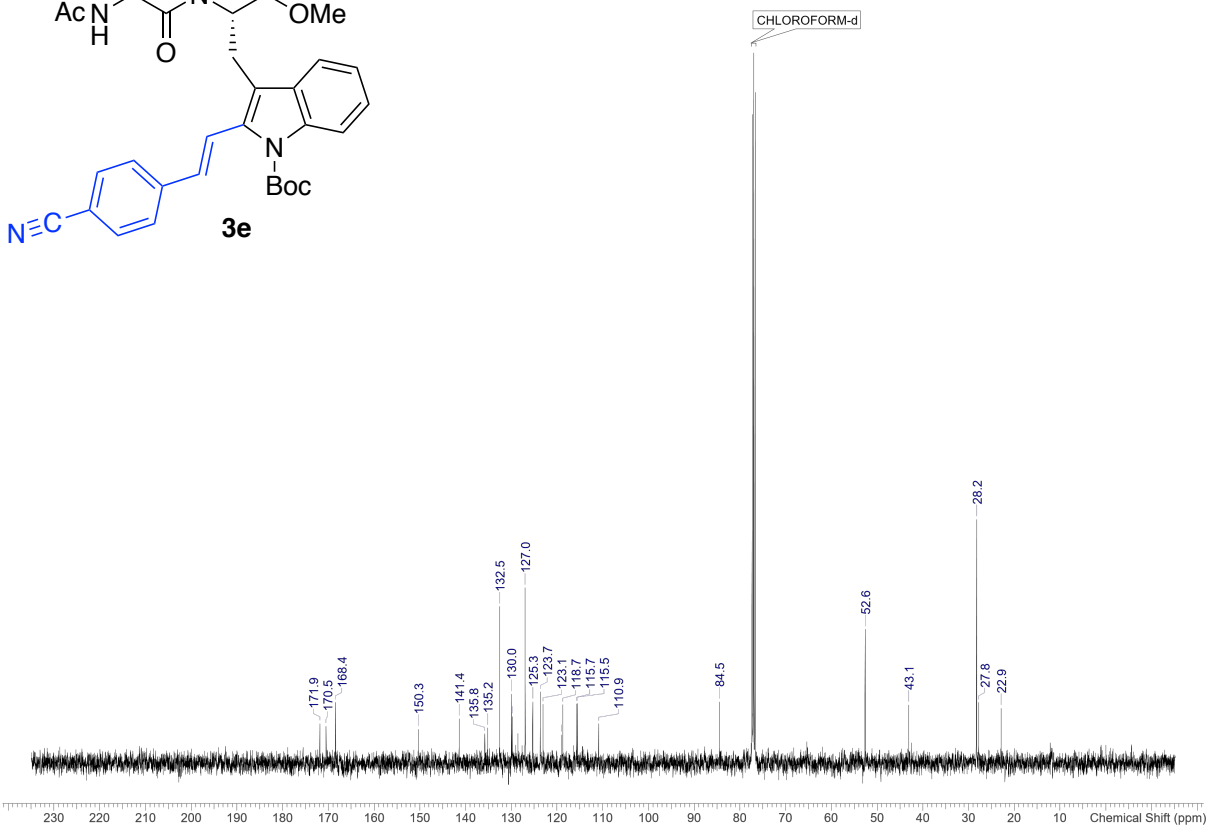
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3d**



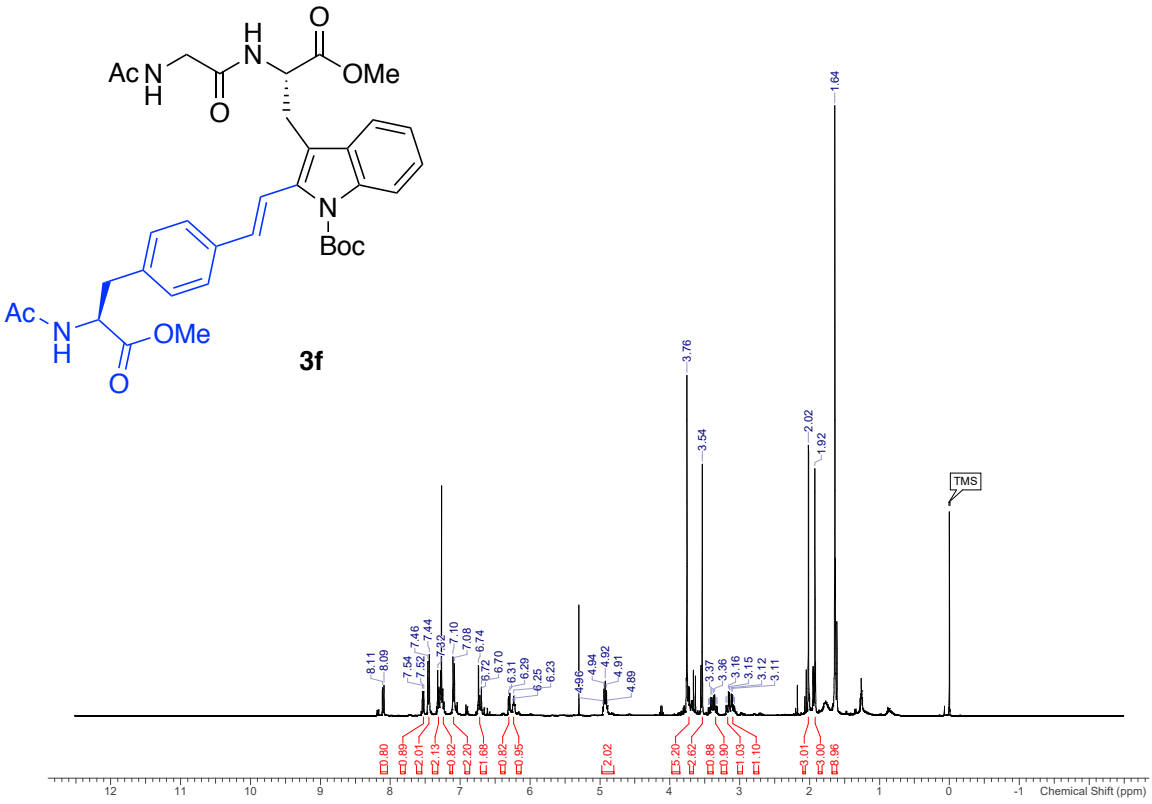
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3e**



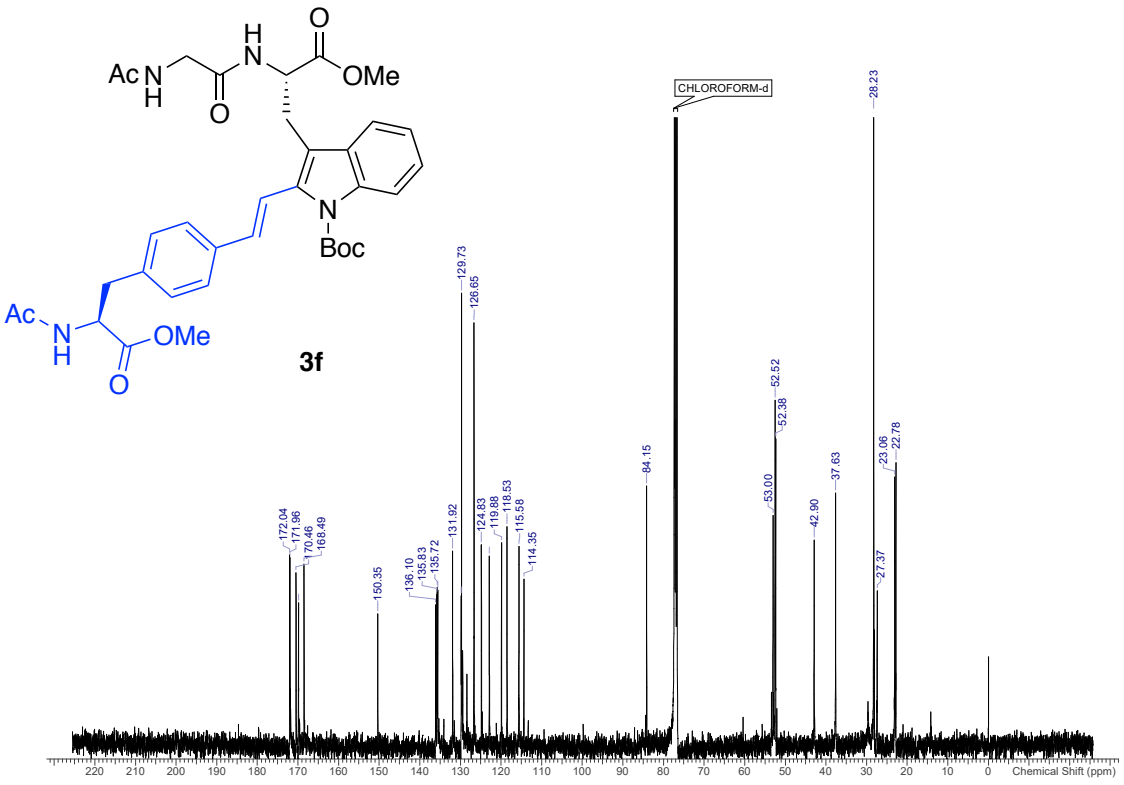
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3e**



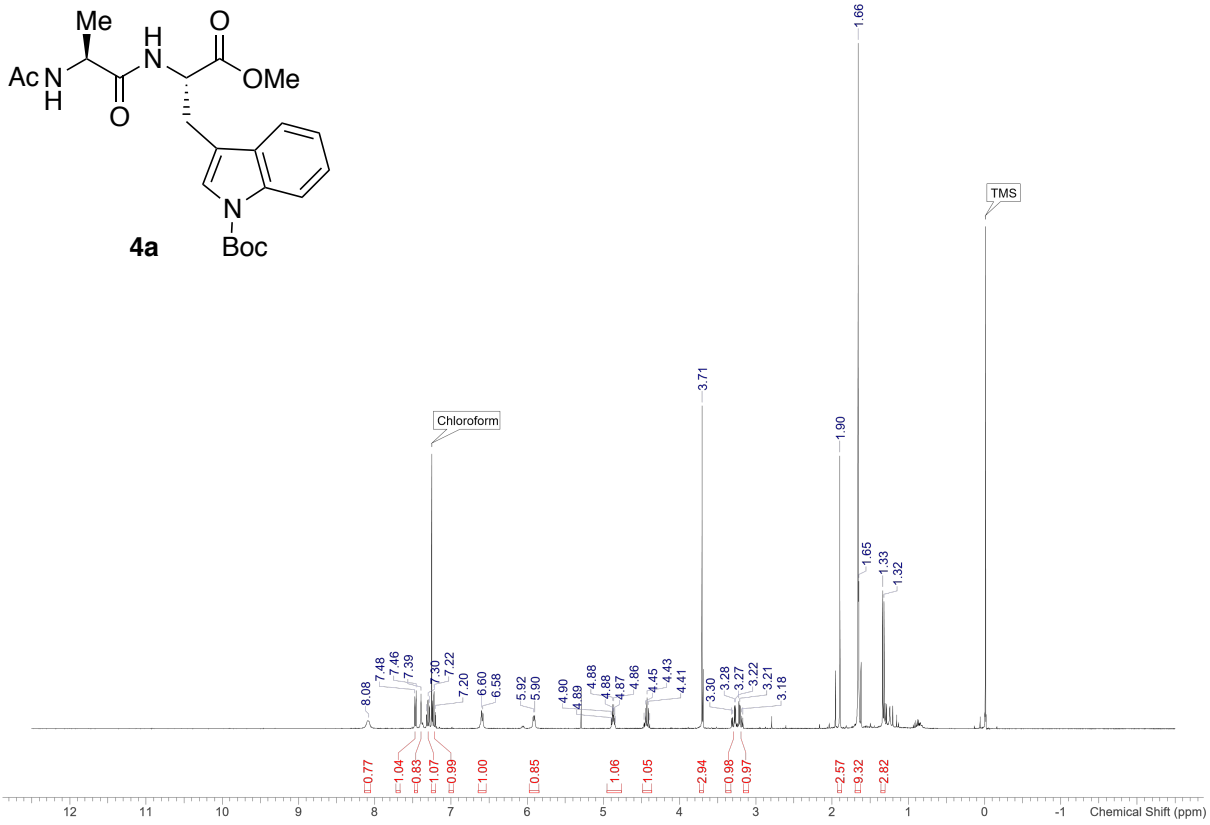
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3f**



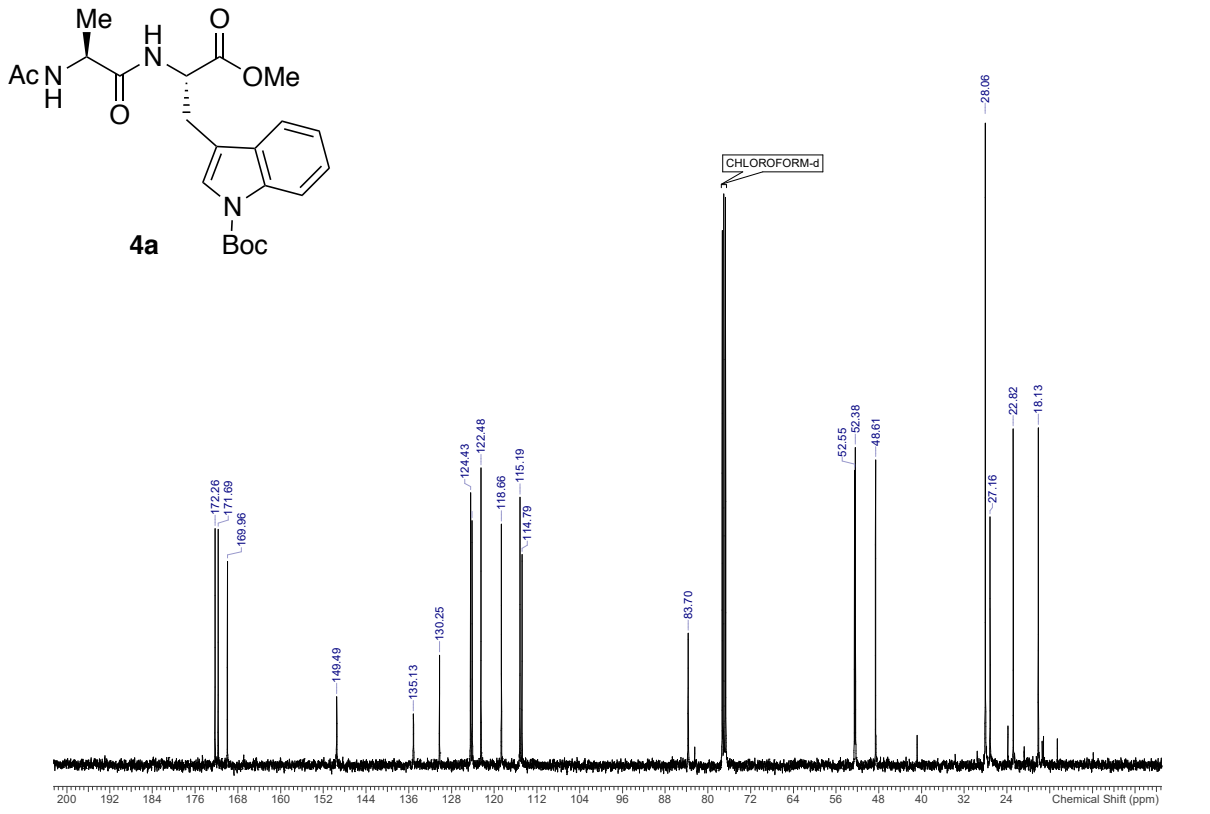
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3f**



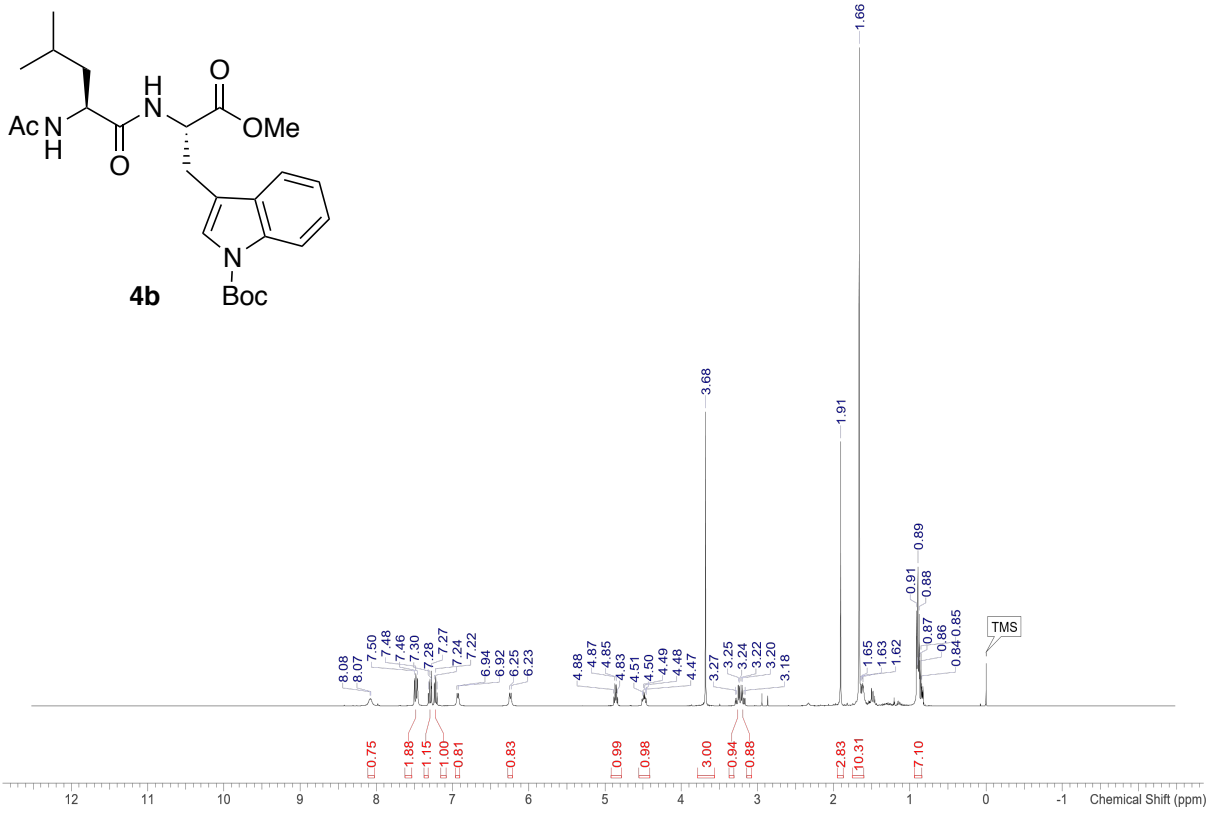
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4a**



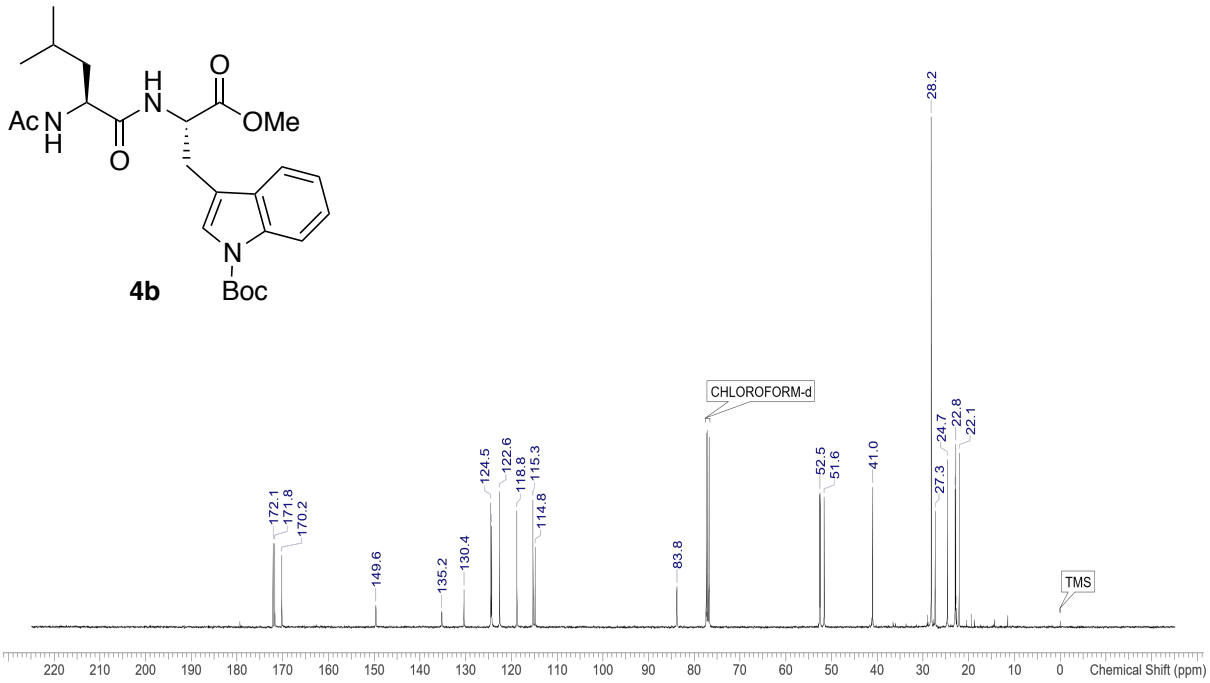
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4a**



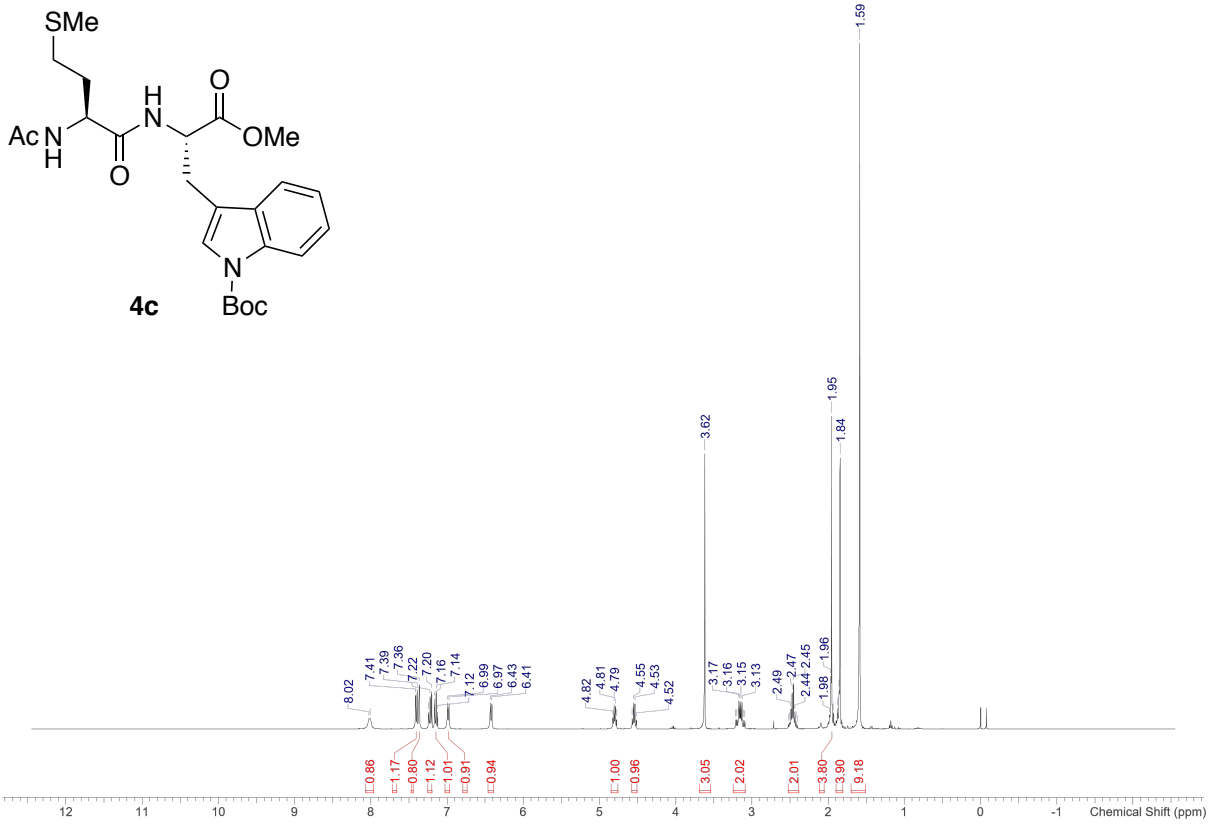
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4b**



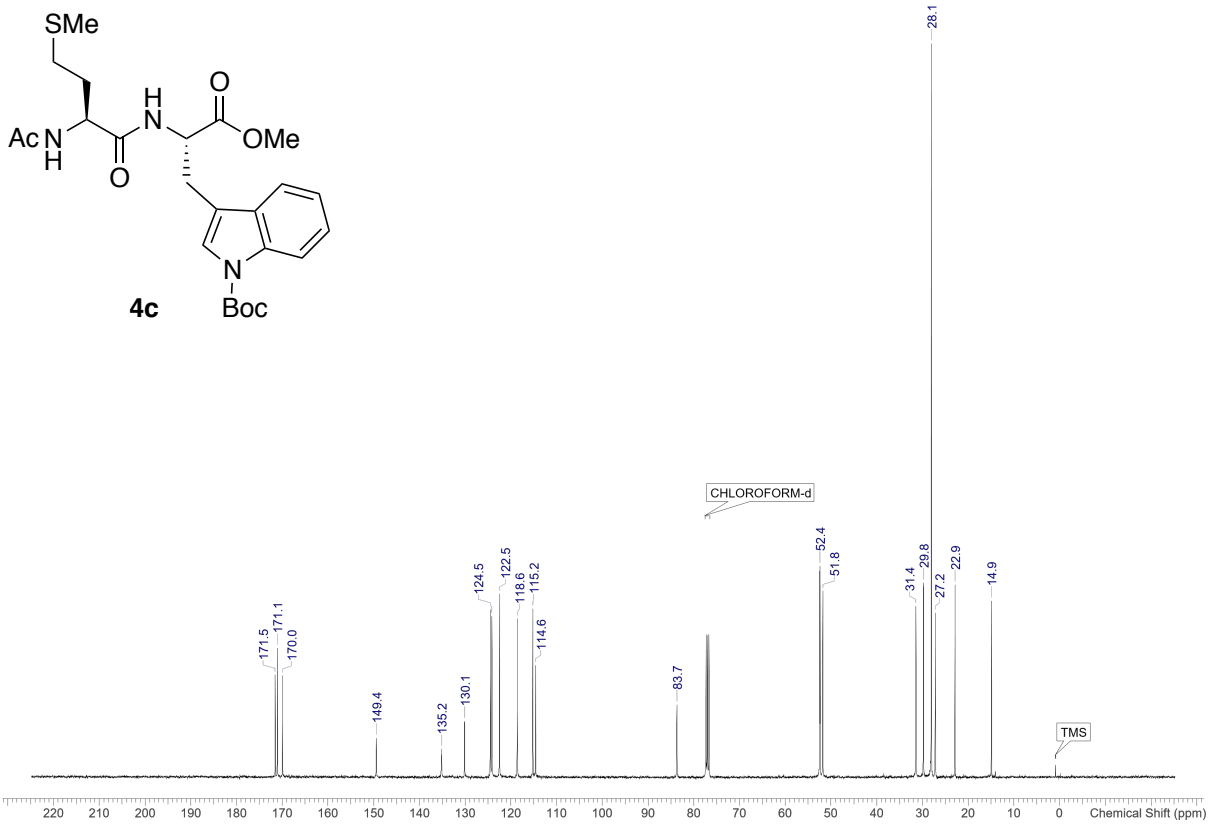
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4b**



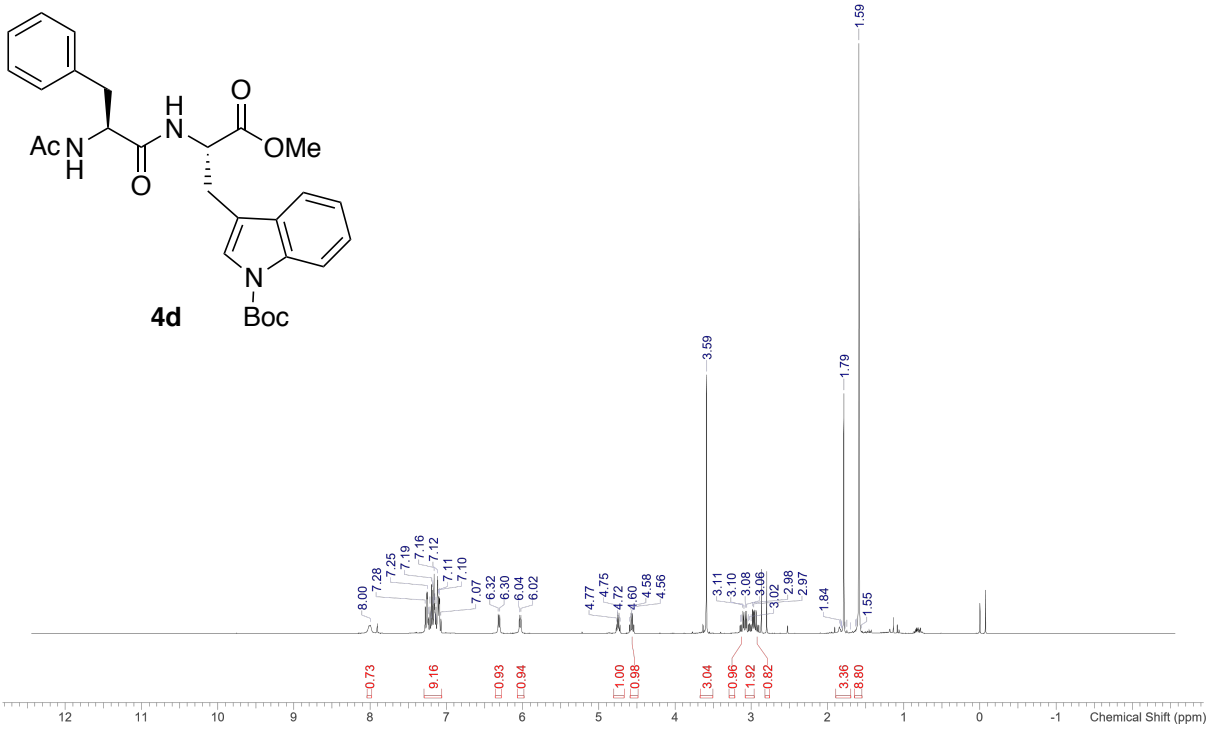
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4c**



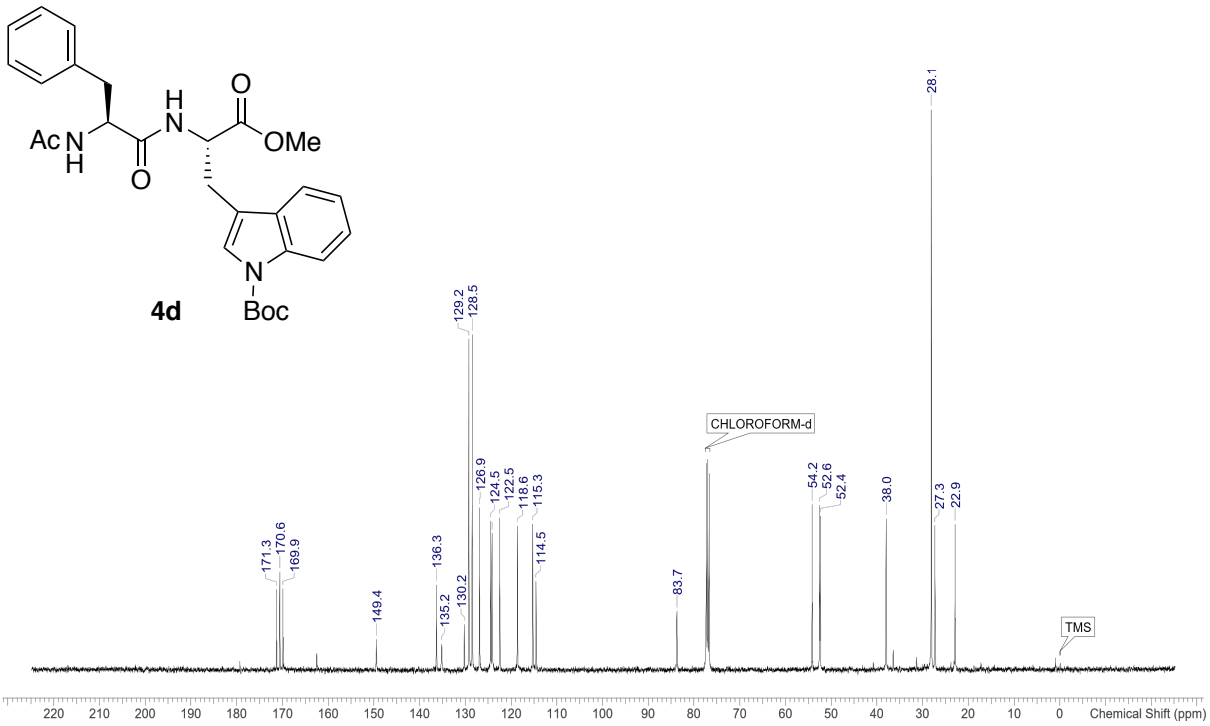
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4c**



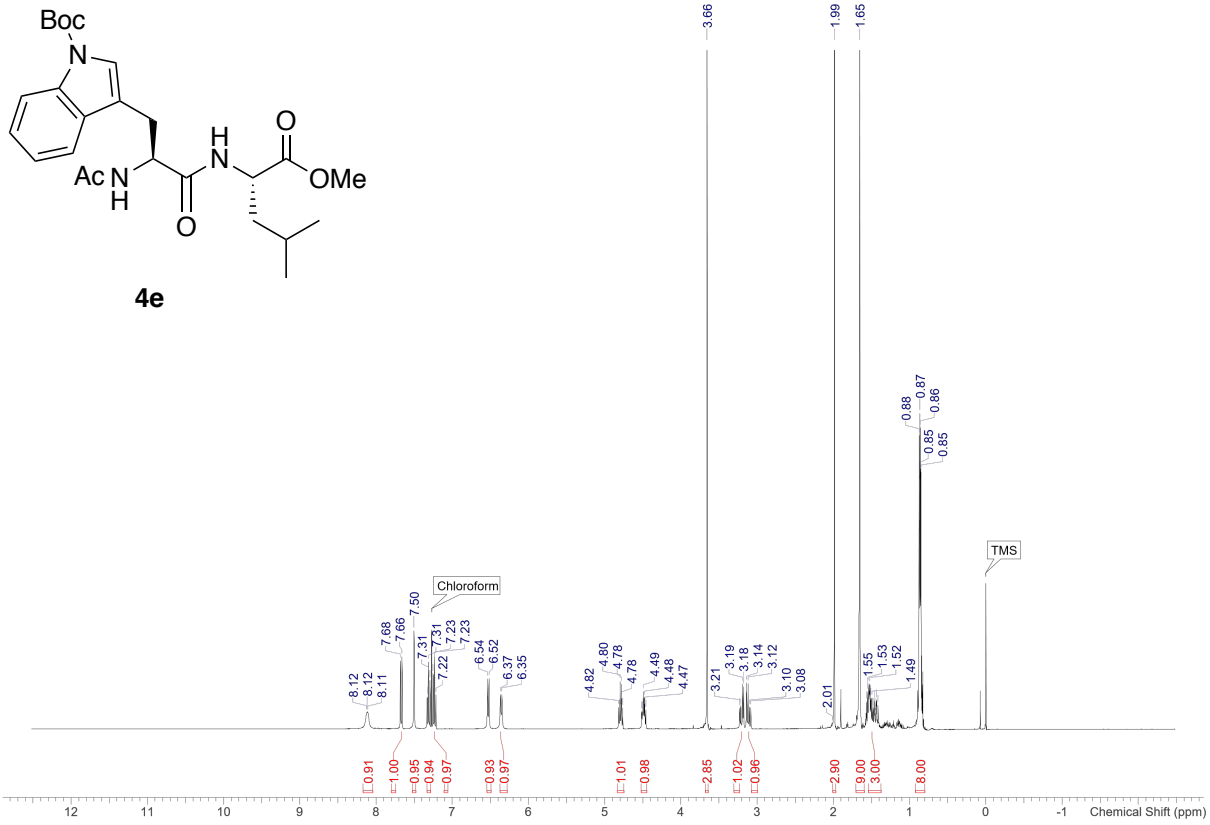
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4d**



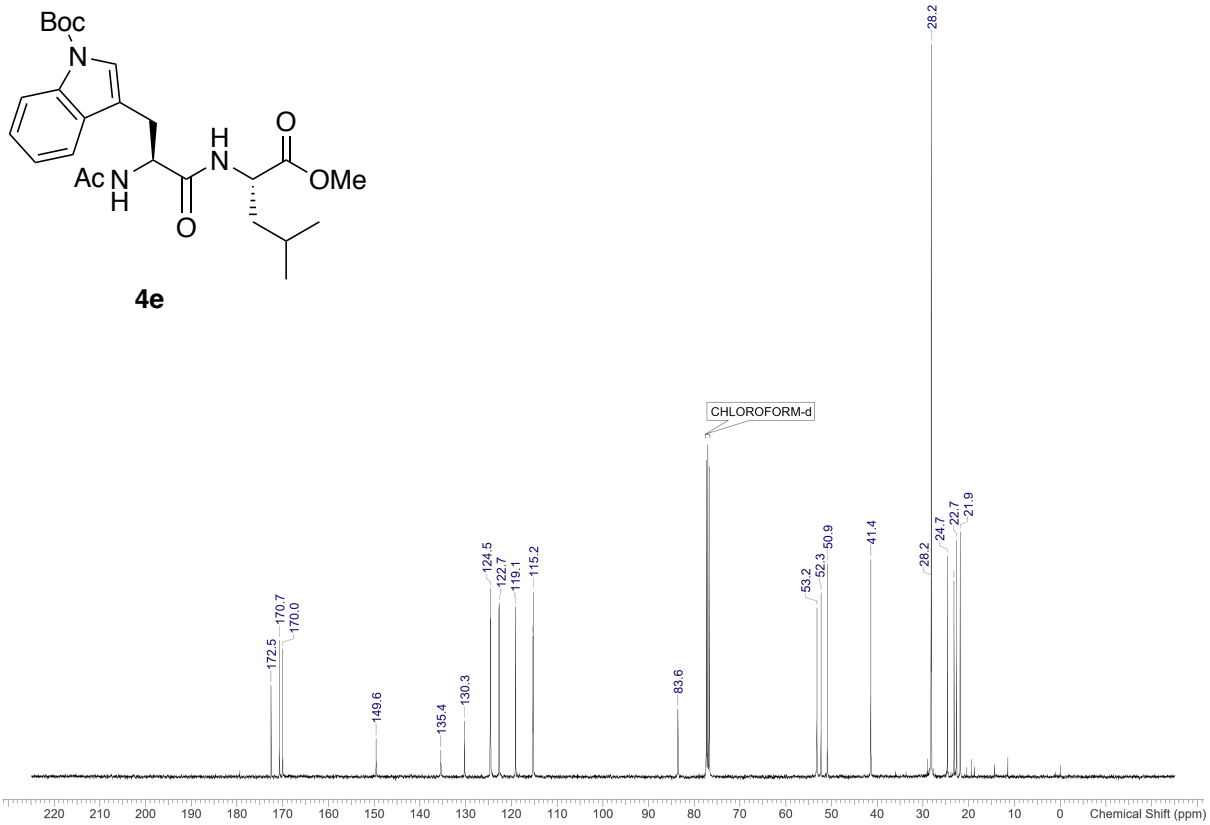
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4d**



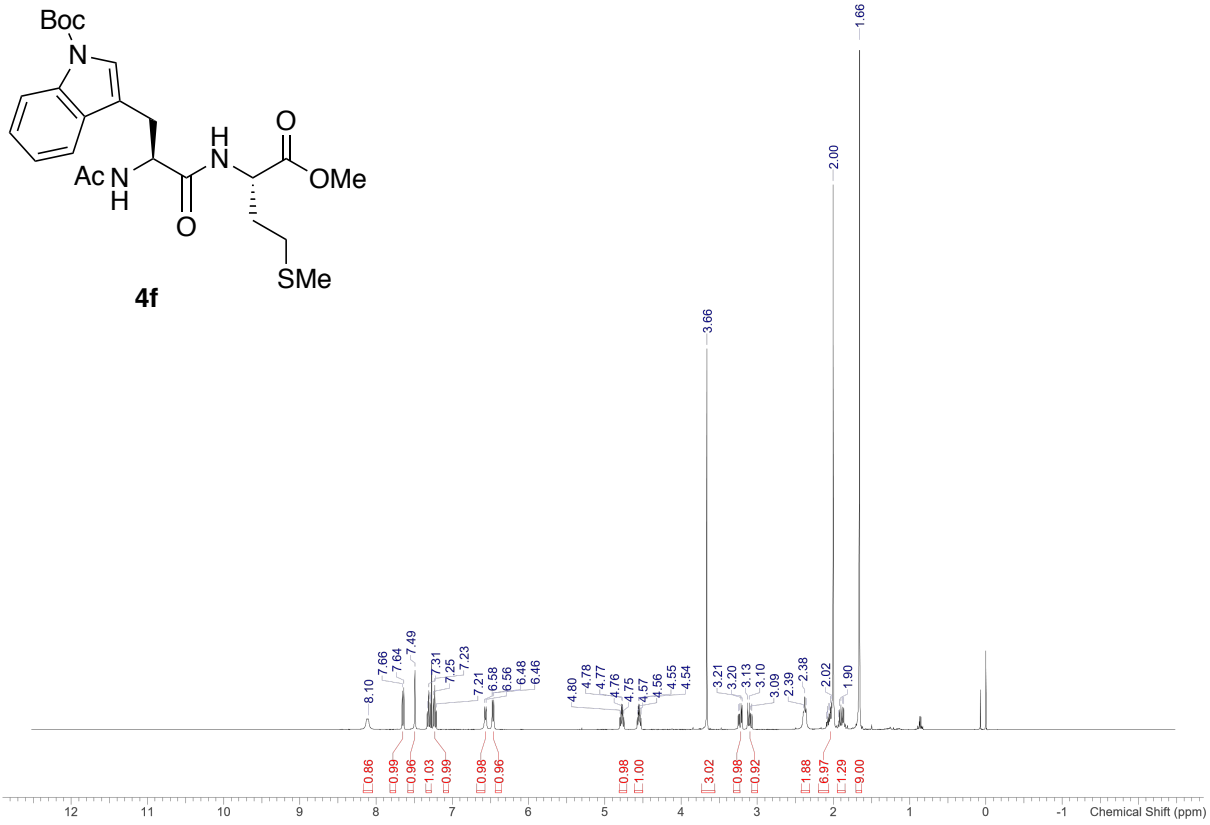
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4e**



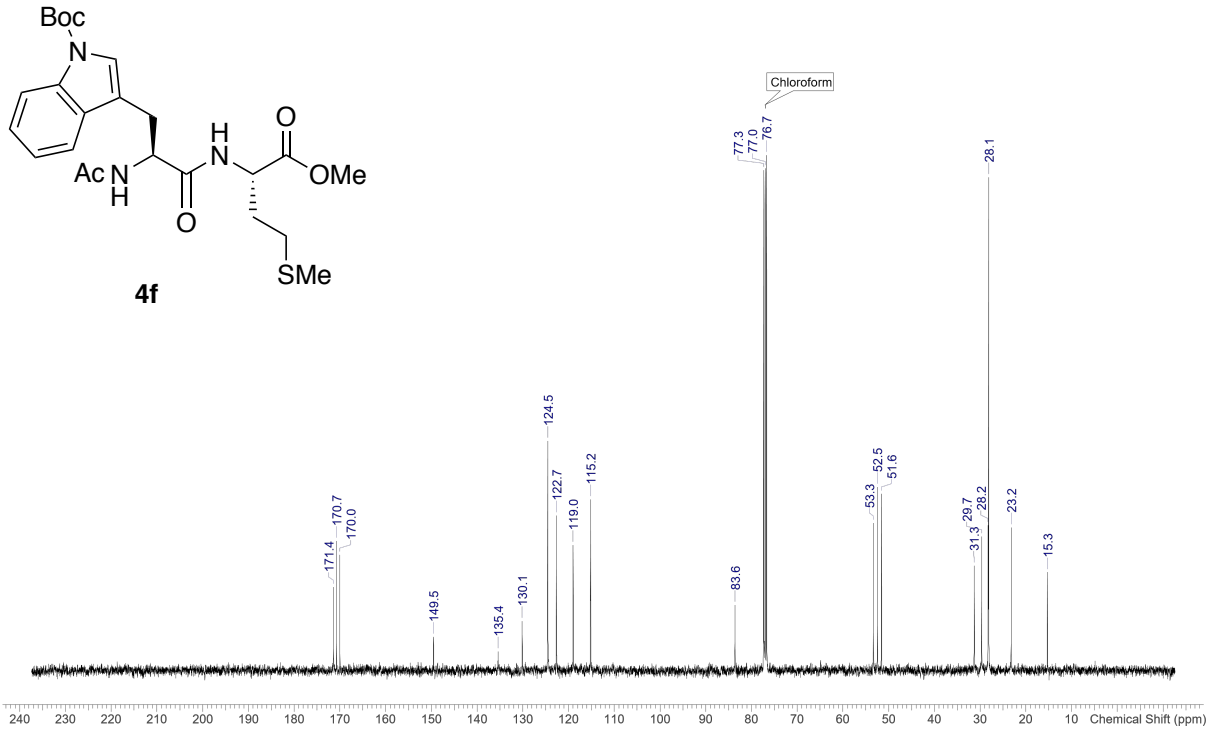
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4e**



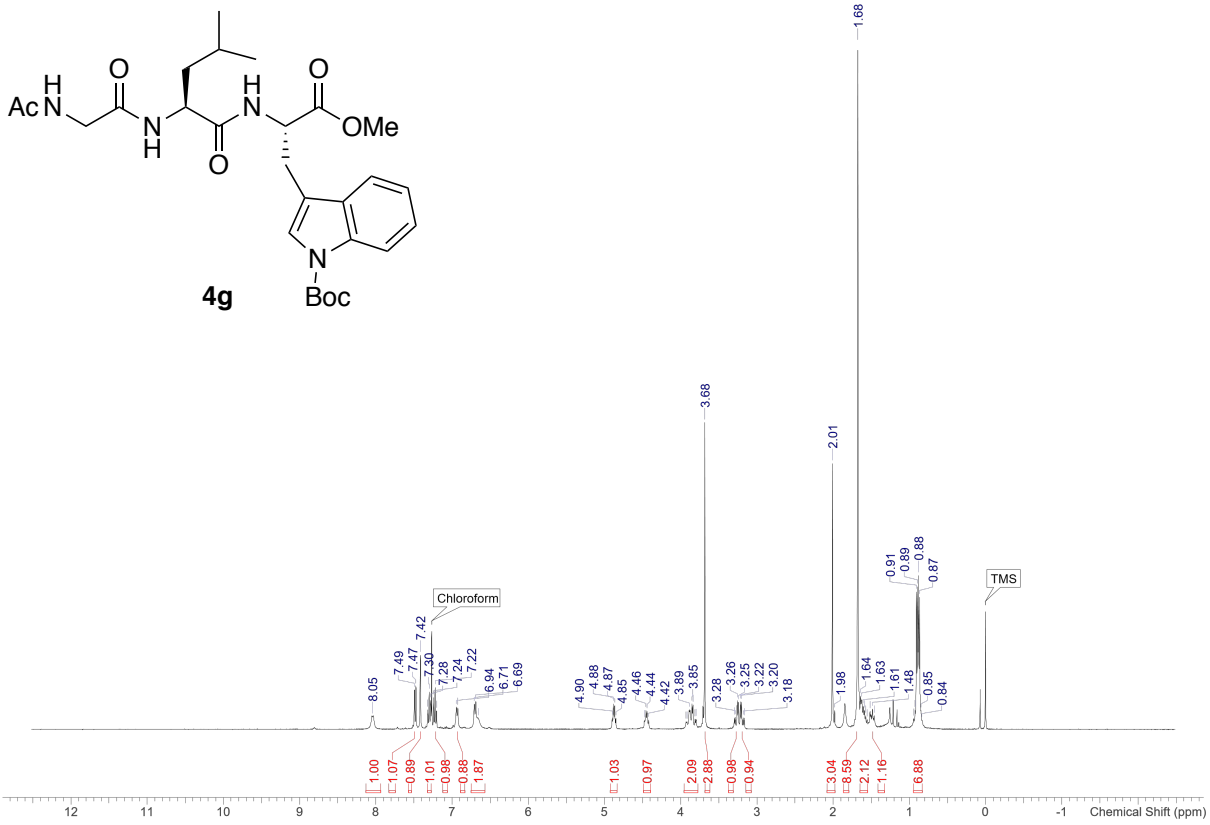
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4f**



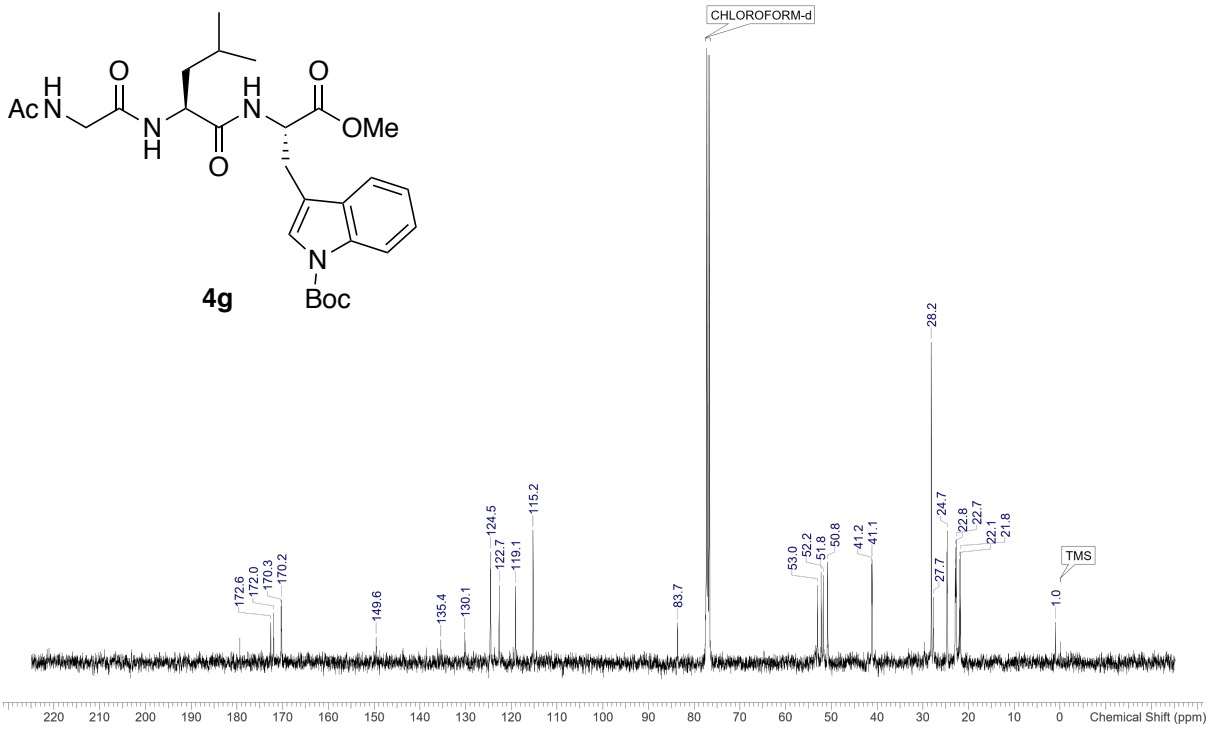
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4f**



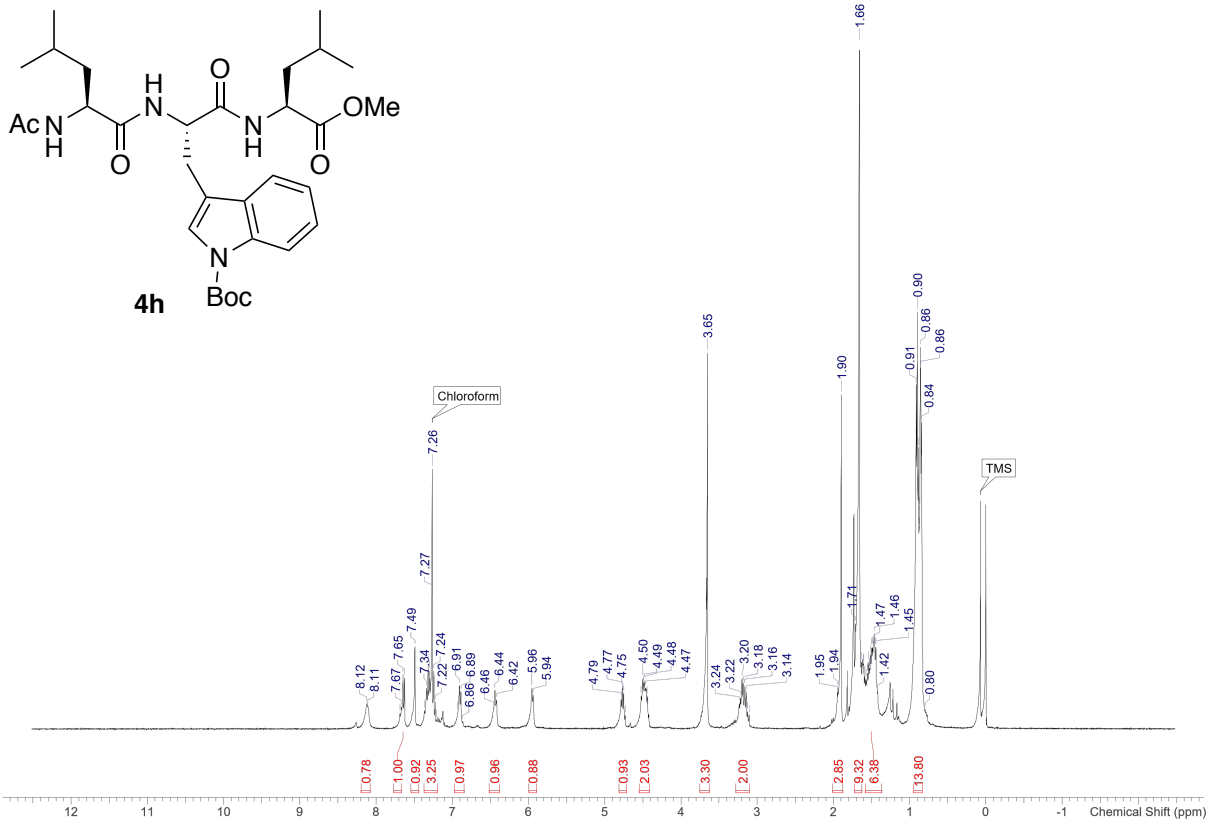
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4g**



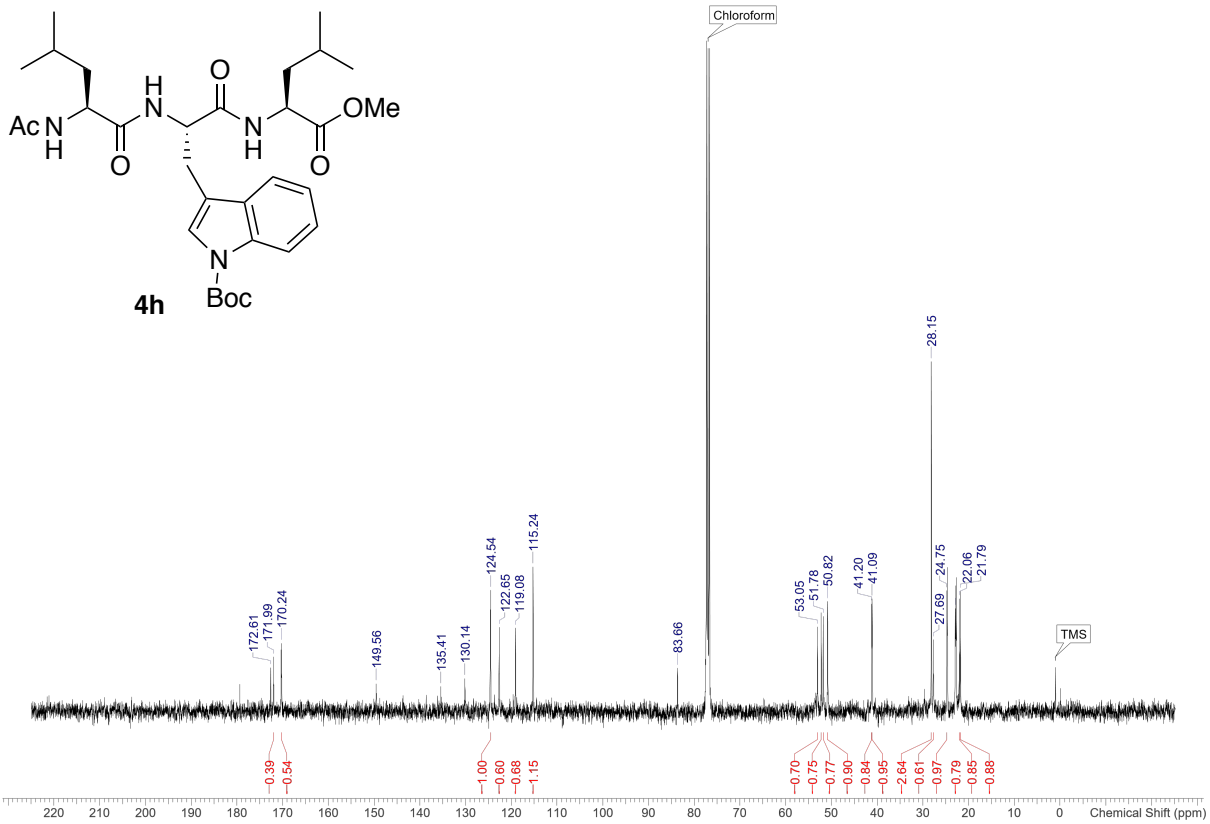
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4g**



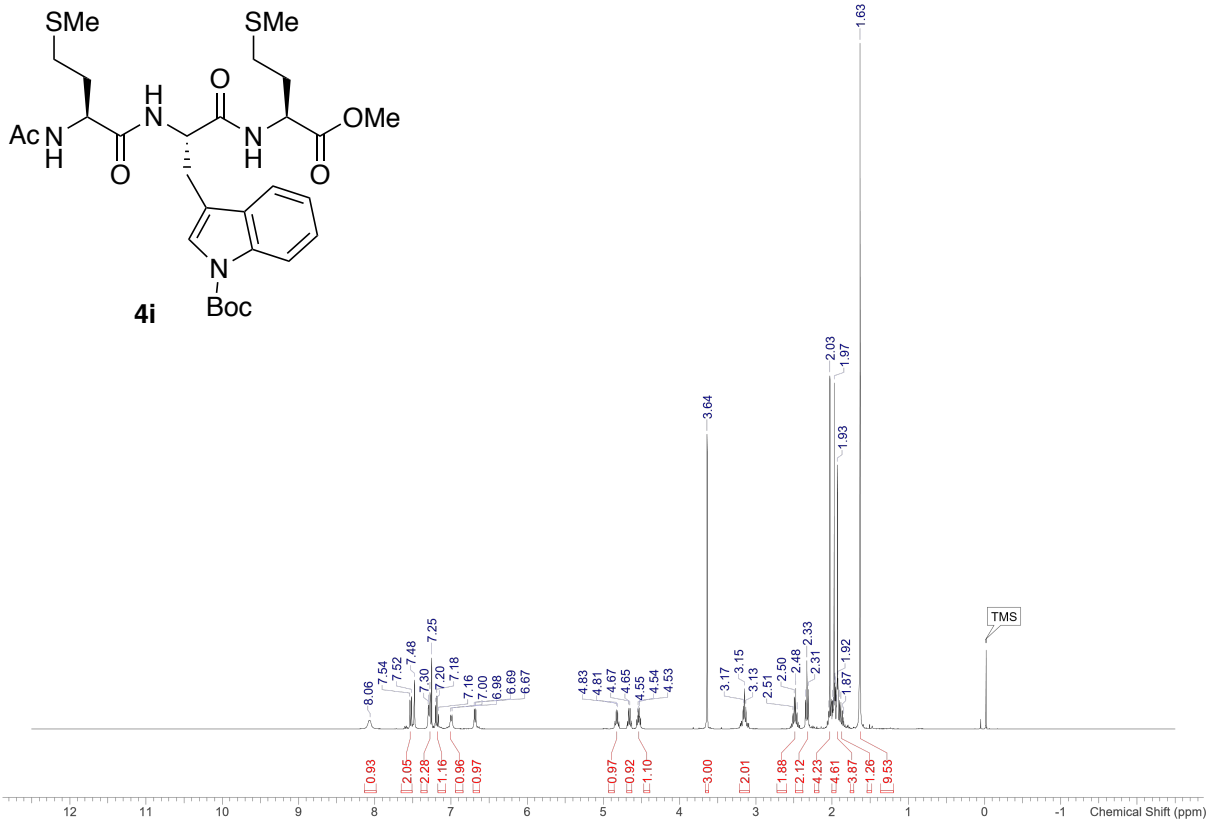
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4h**



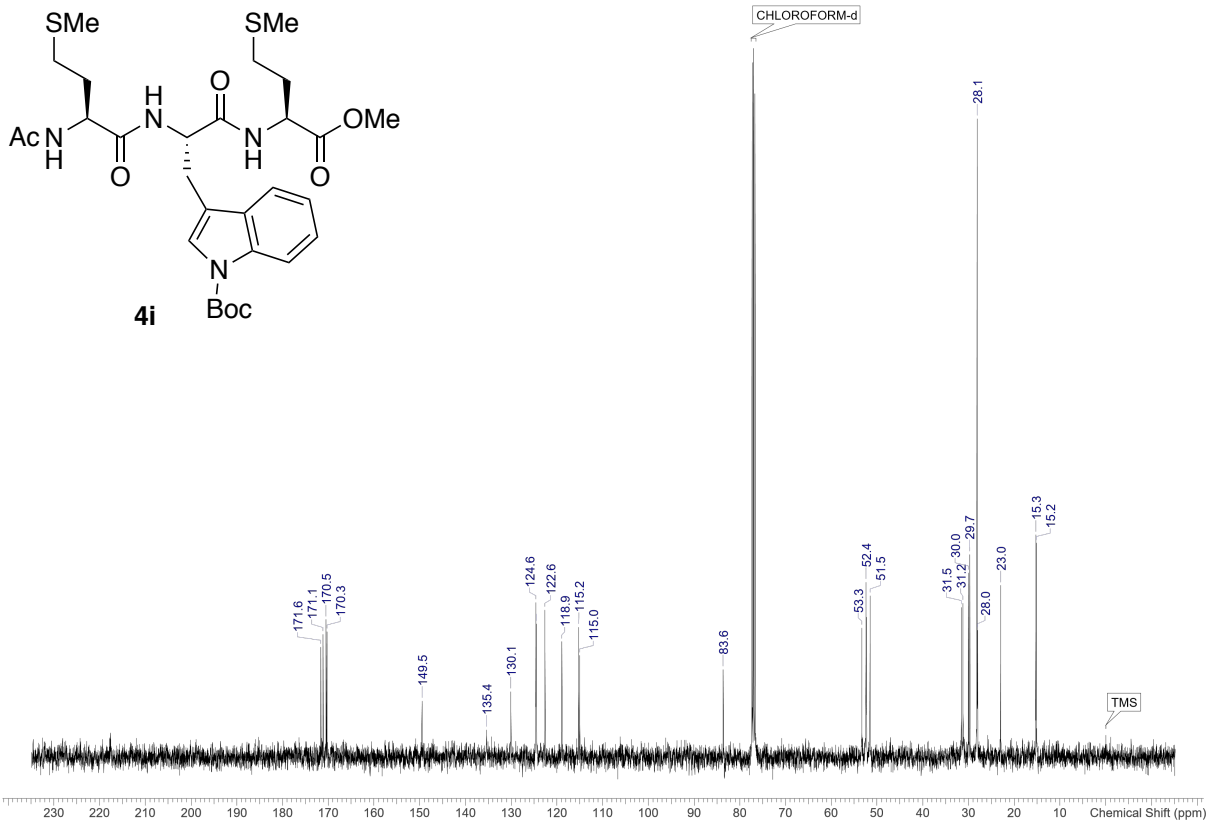
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4h**



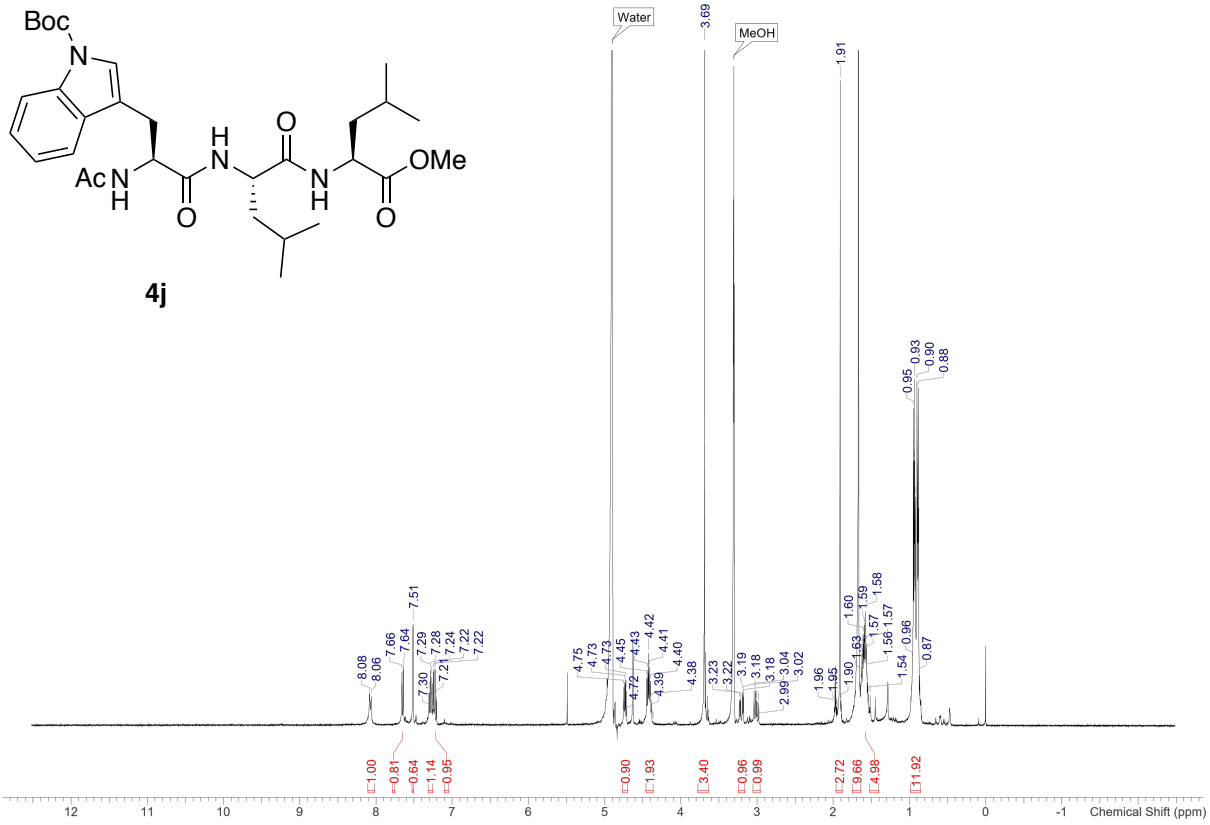
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4i**



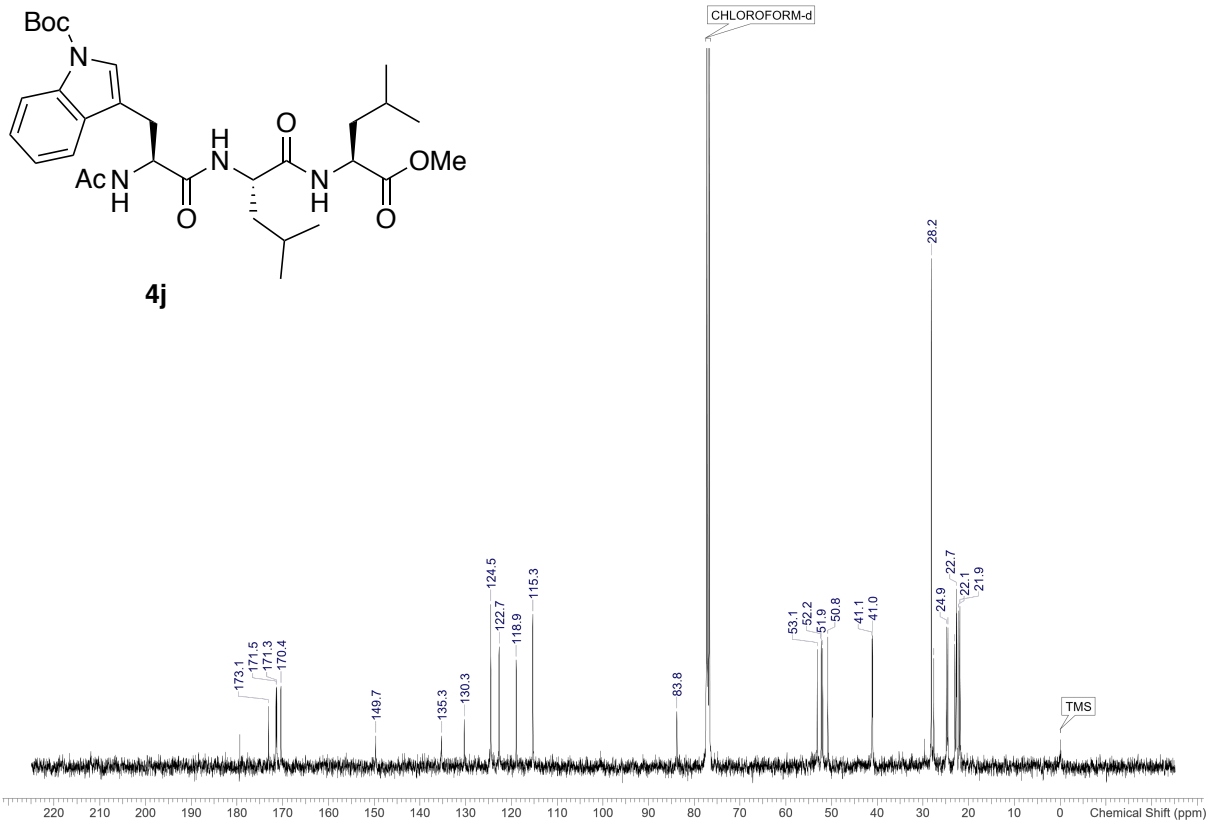
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4i**



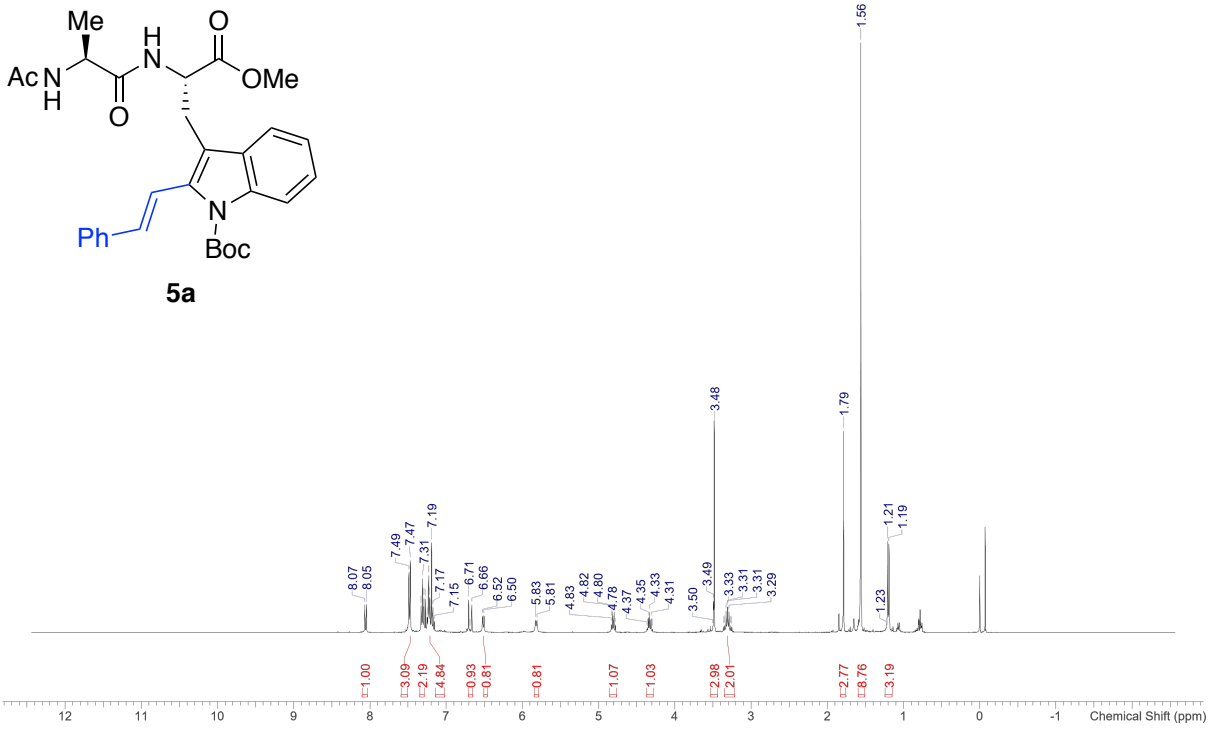
^{1}H NMR spectrum (400 MHz, CD_3OD) of **4j**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4j**

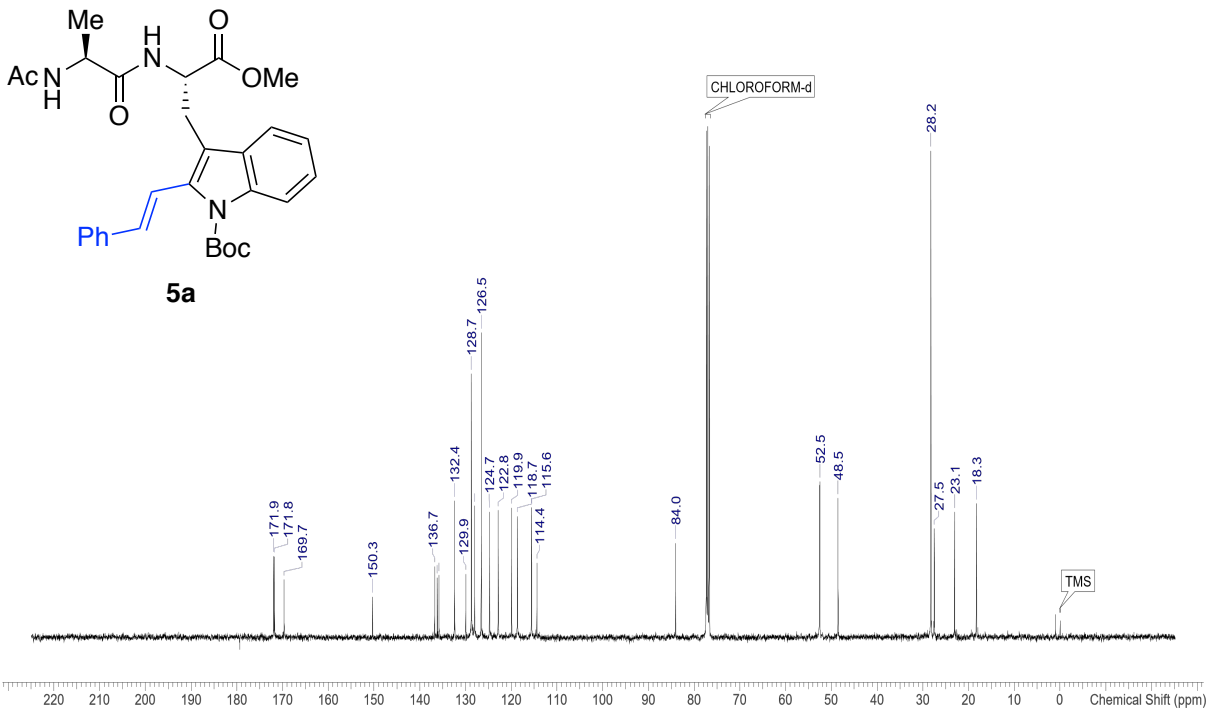


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5a**



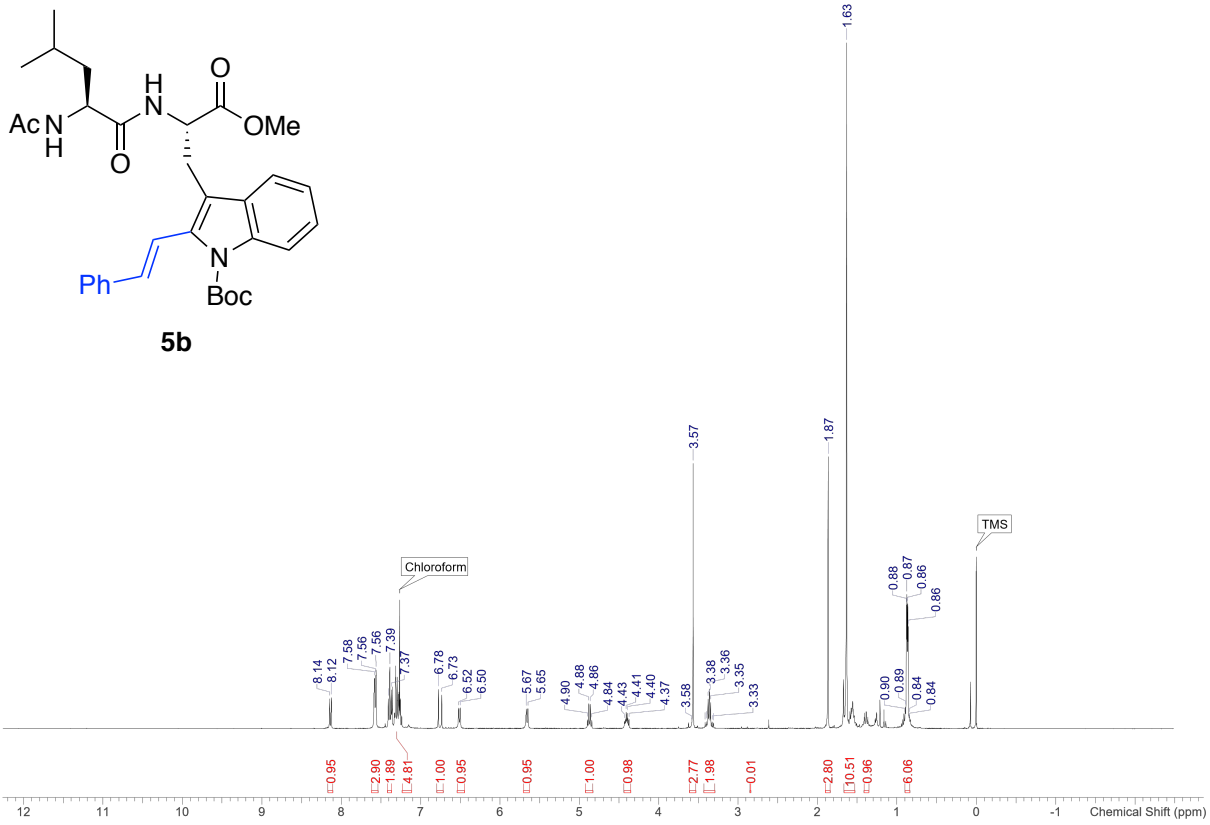
5a

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5a**

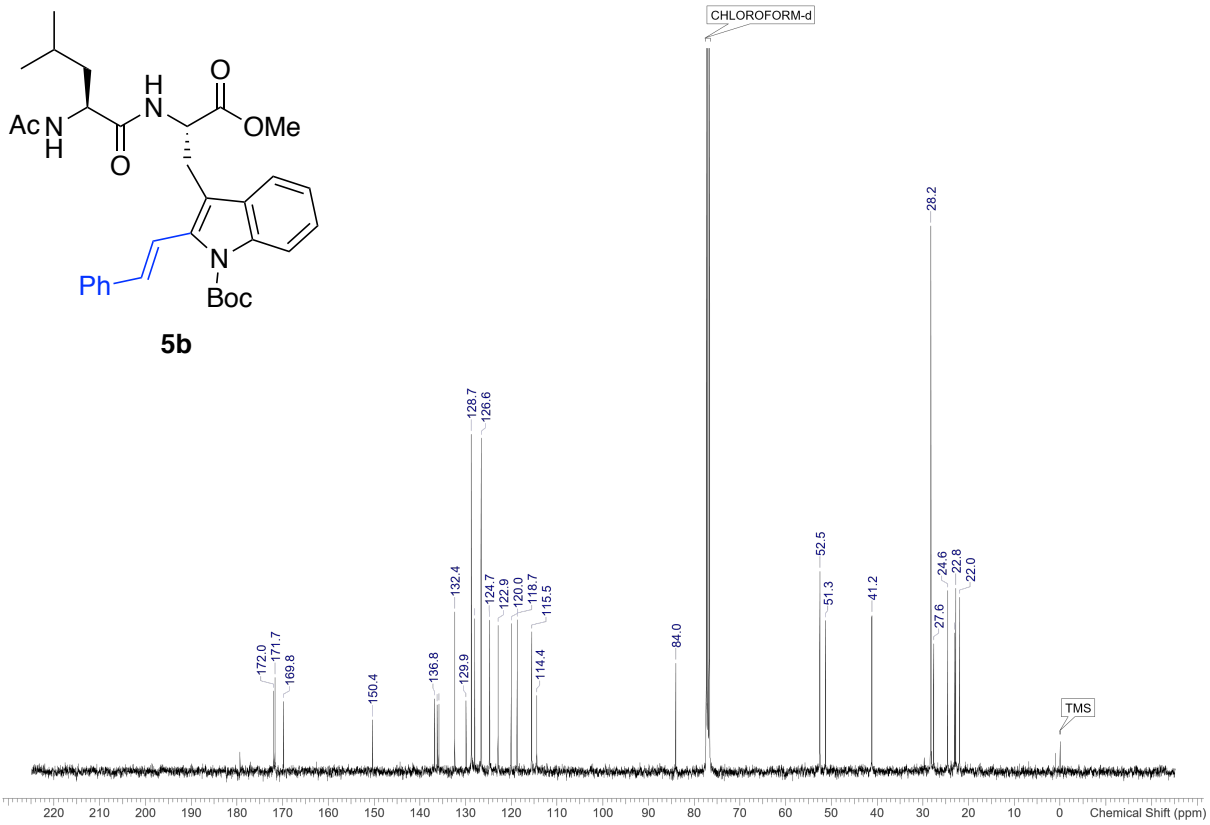


5a

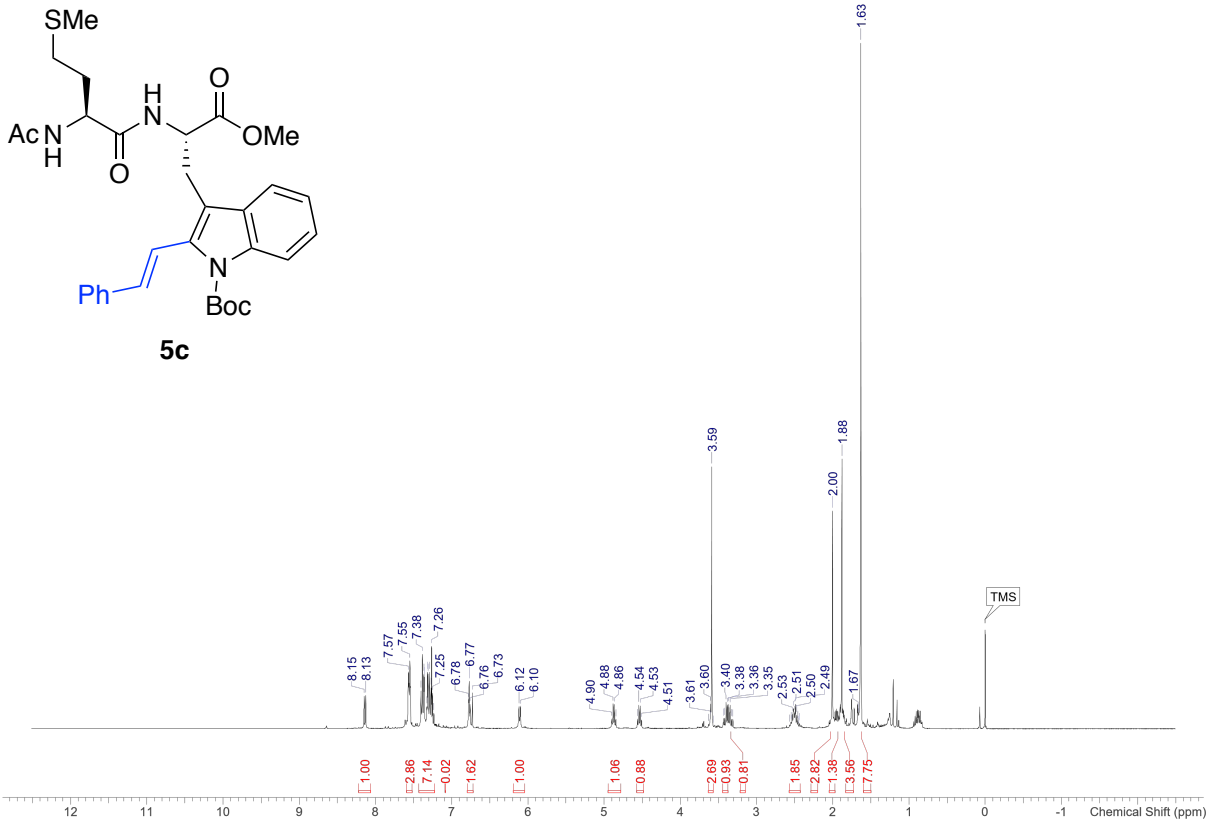
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5b**



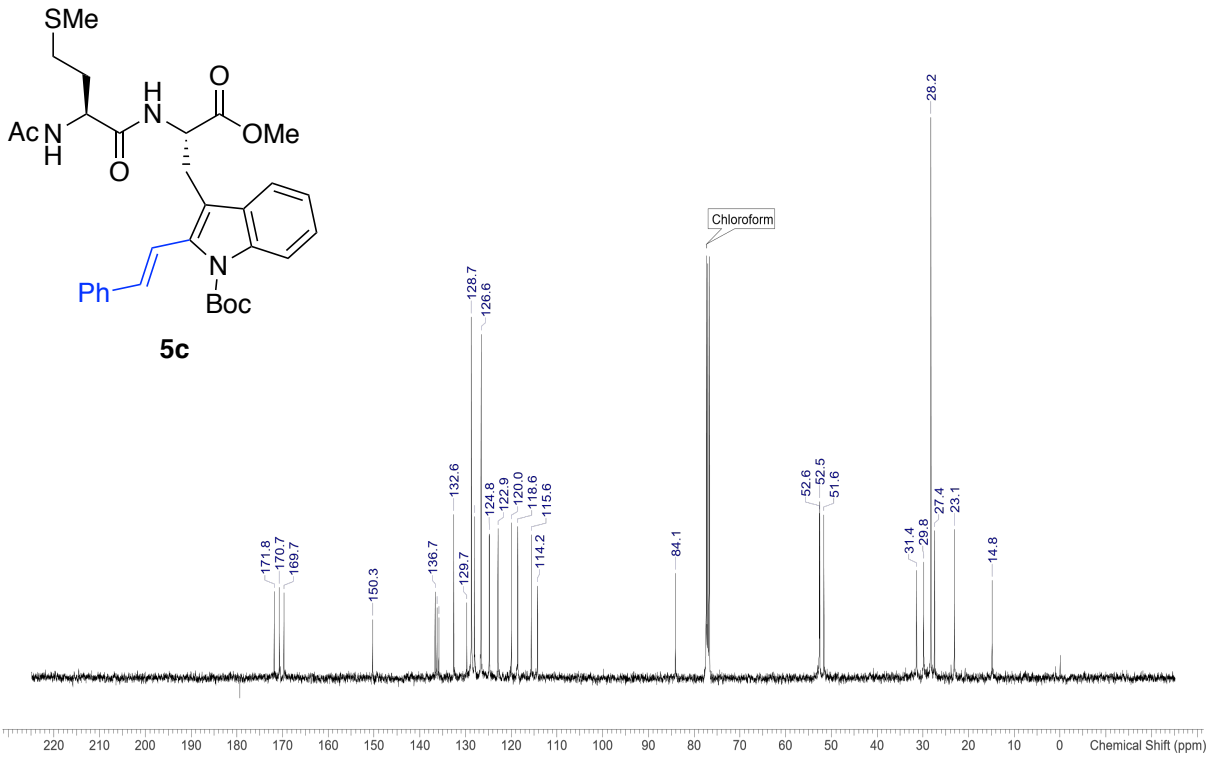
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5b**



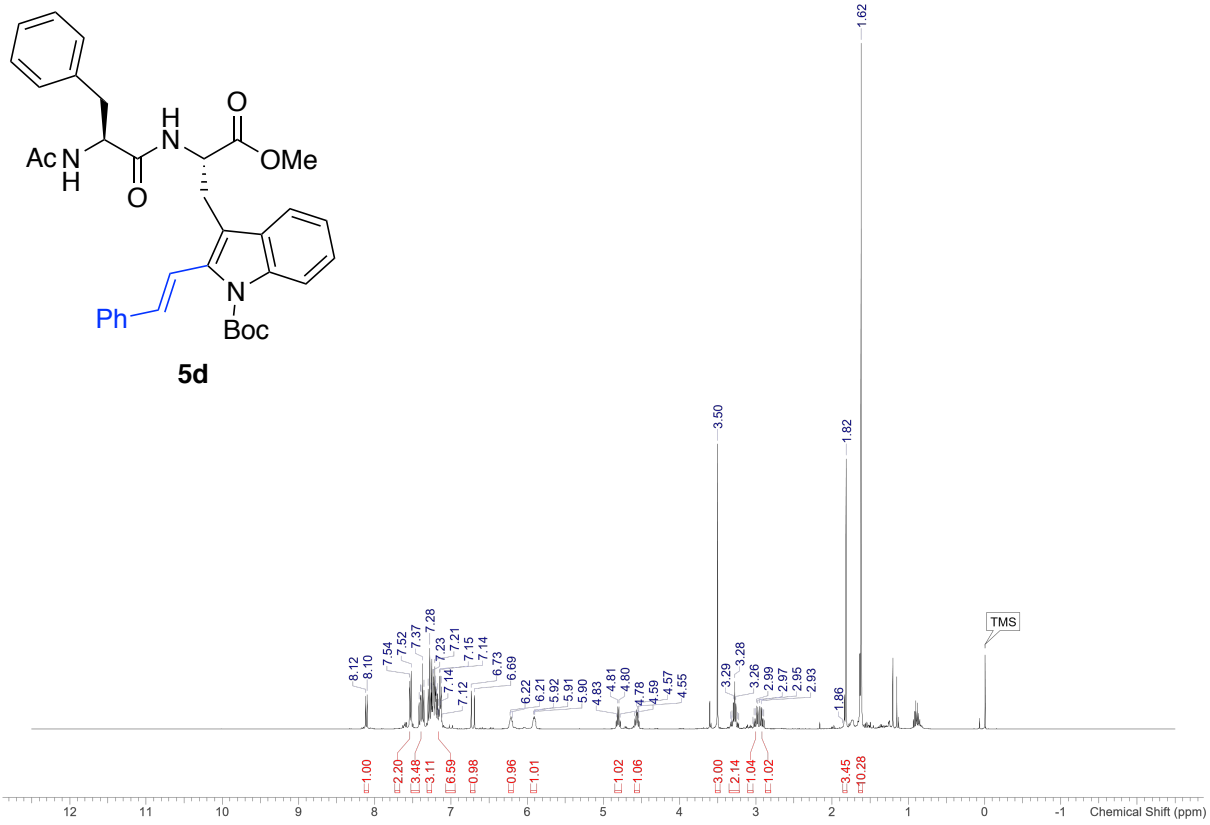
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5c**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5c**

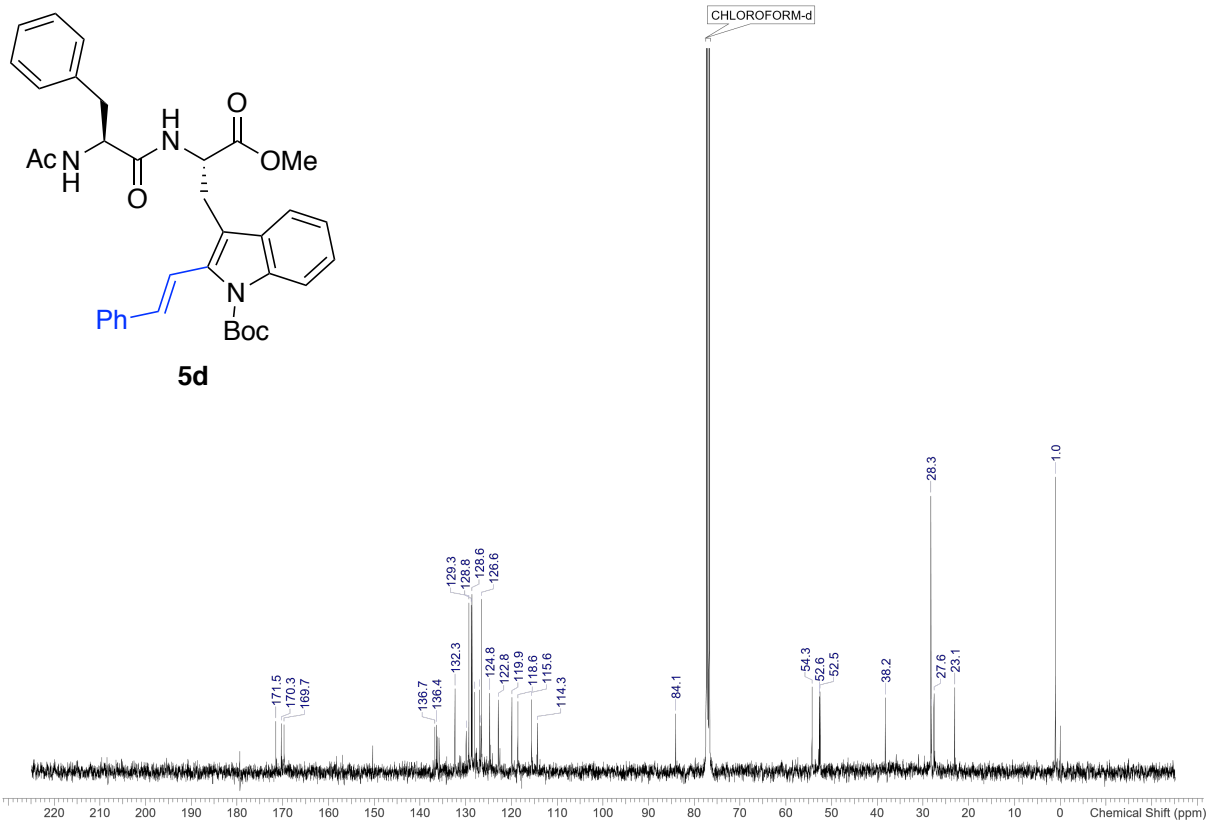


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5d**



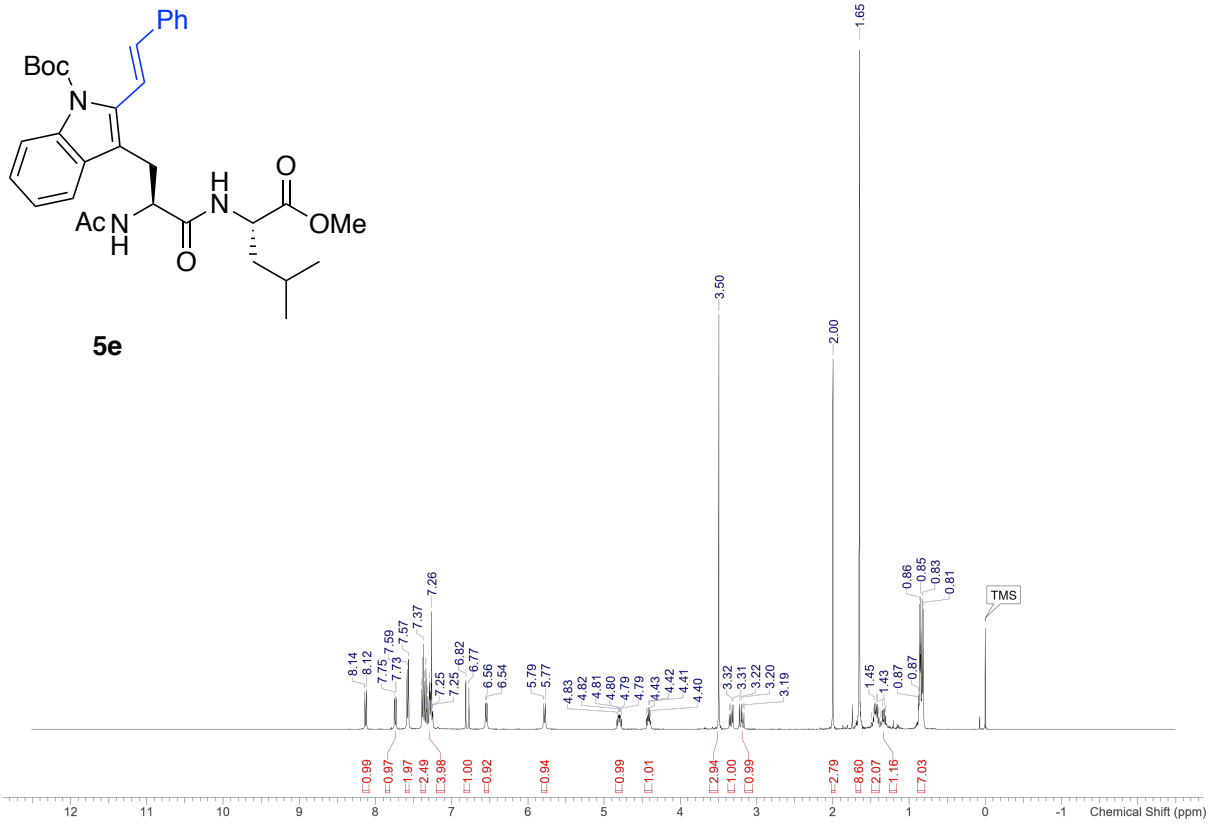
5d

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5d**

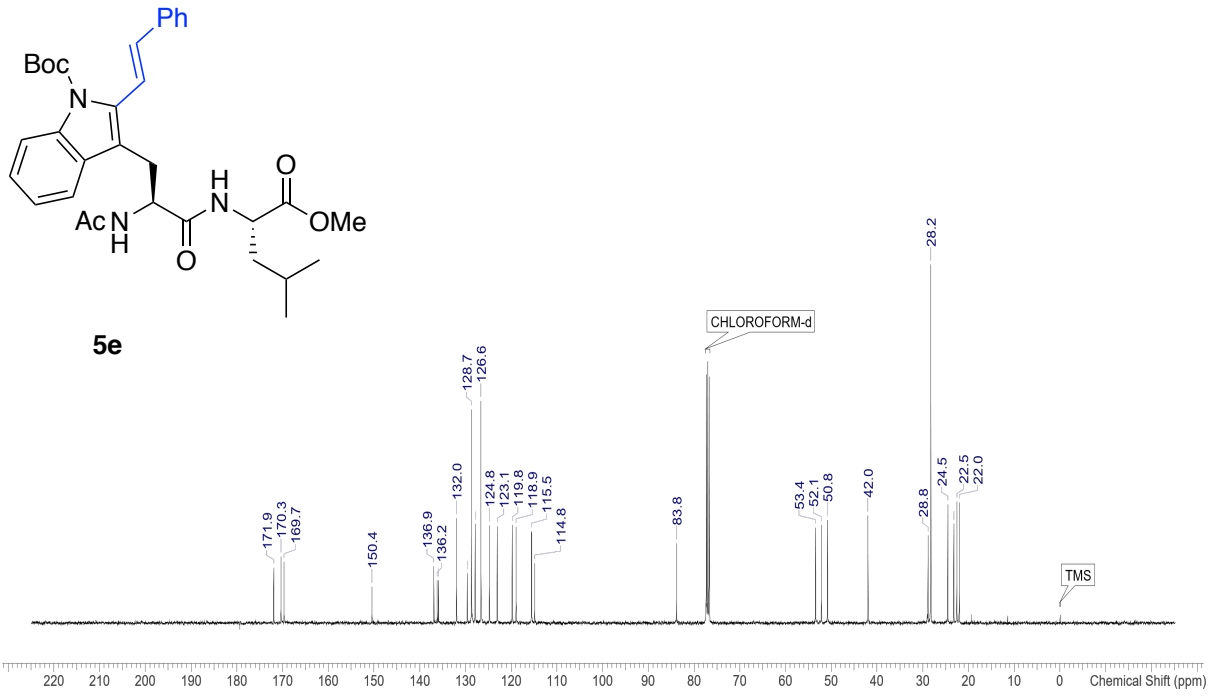


5d

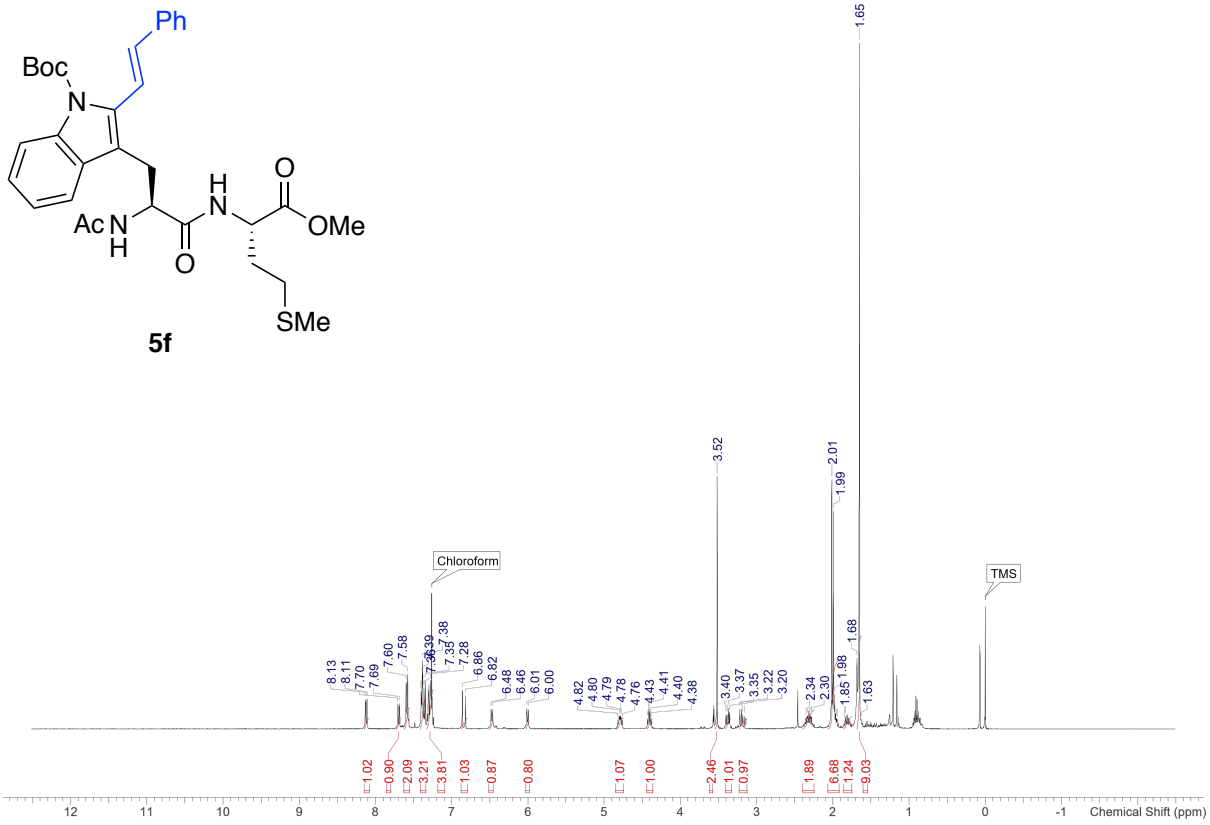
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5e**



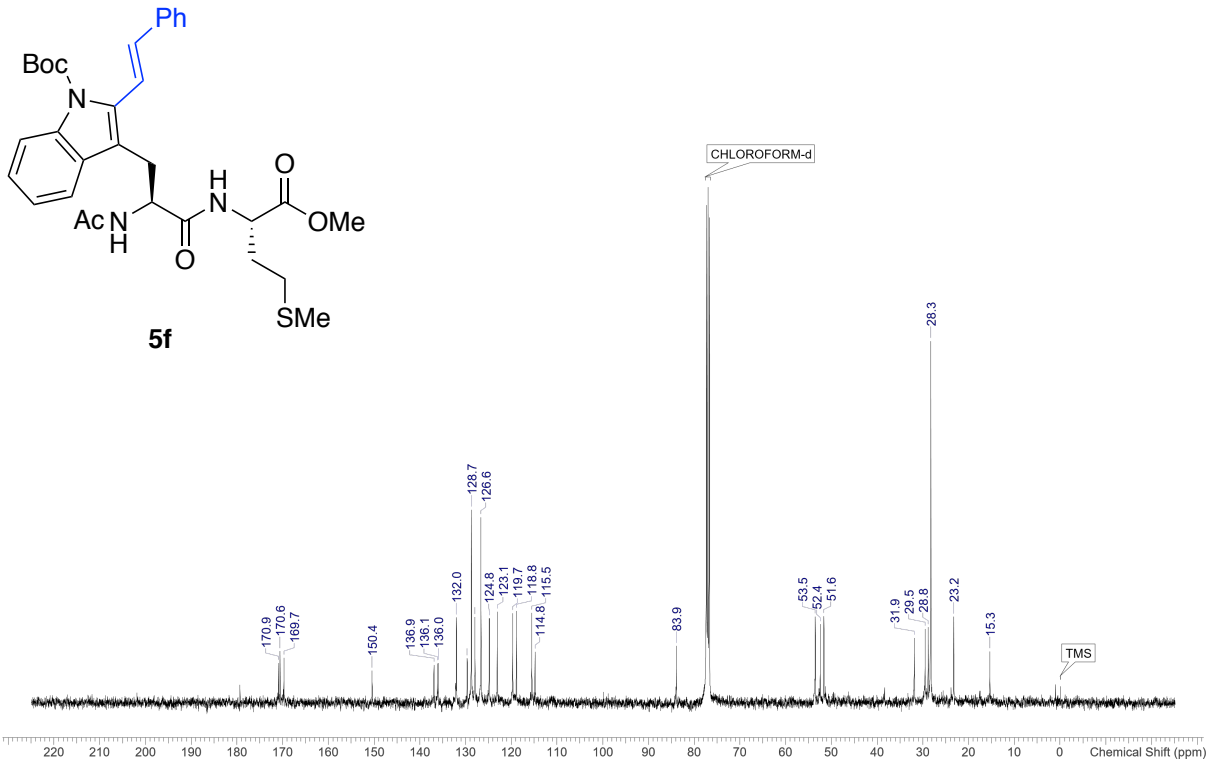
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5e**



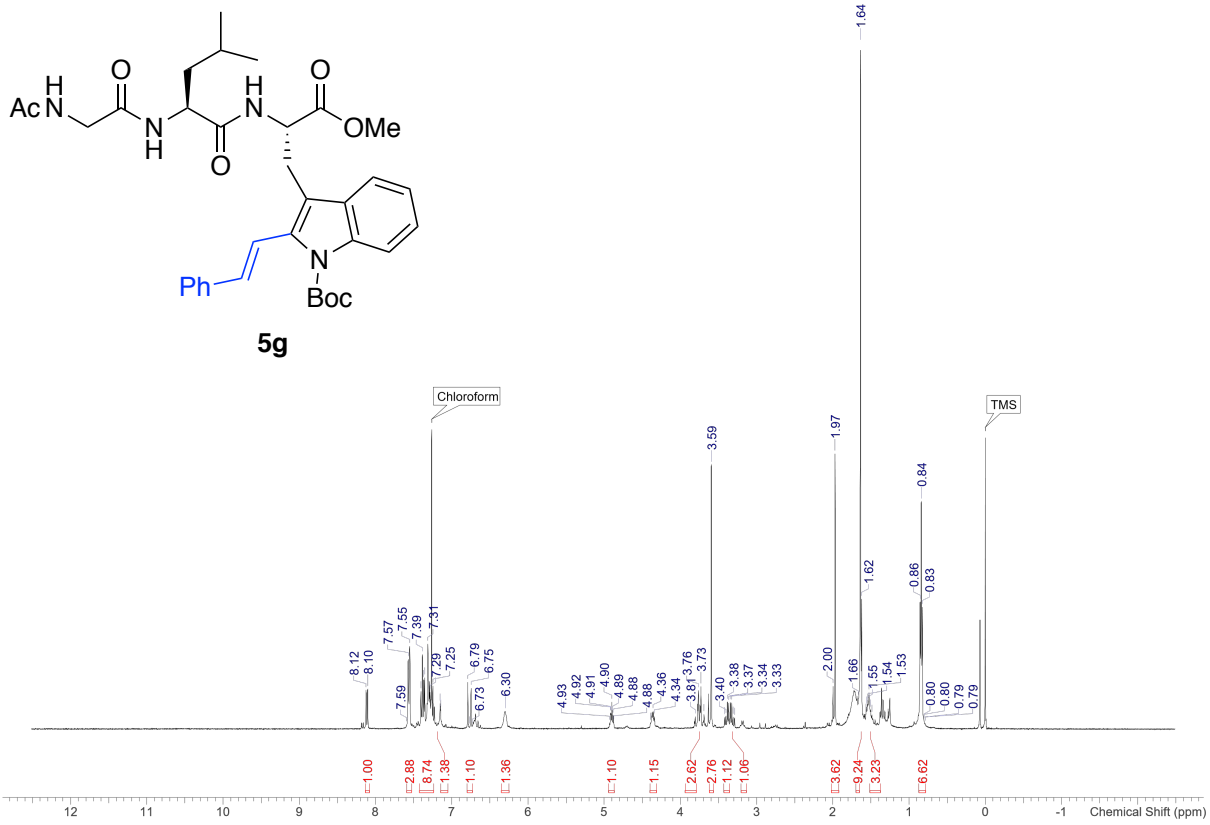
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5f**



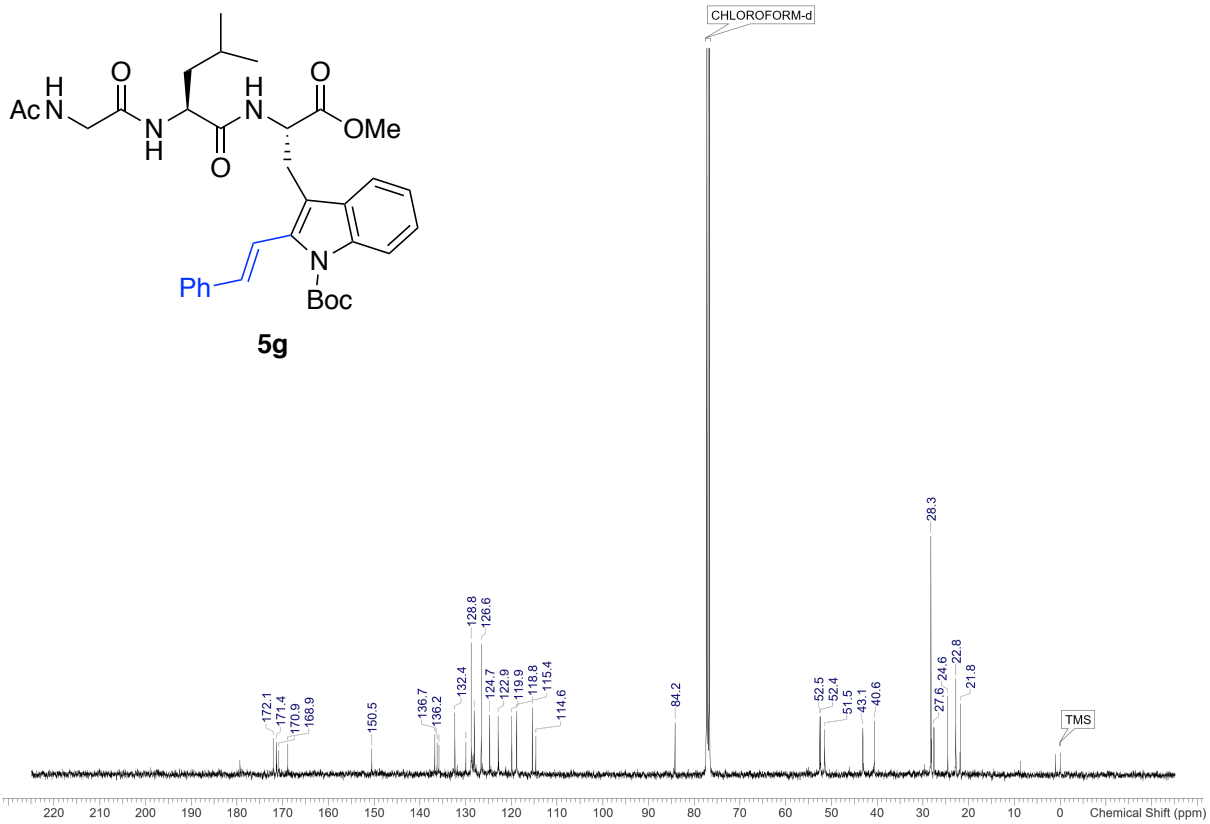
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5f**



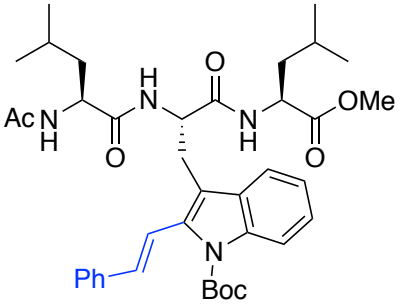
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5g**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5g**

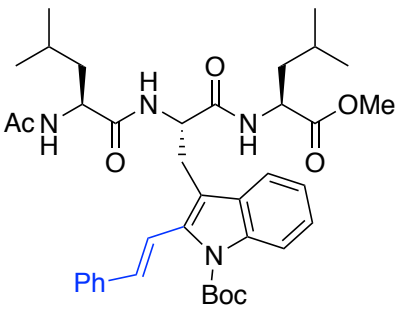


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5h**



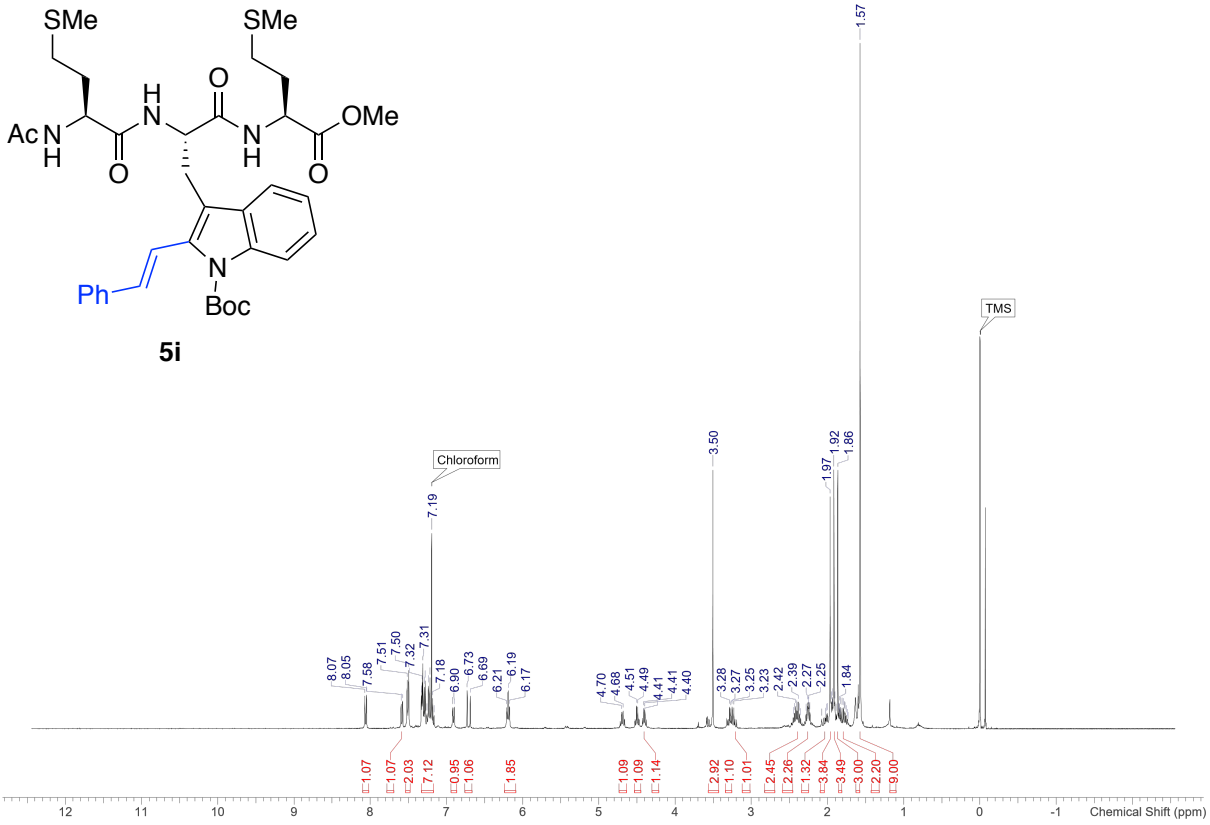
5h

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5h**



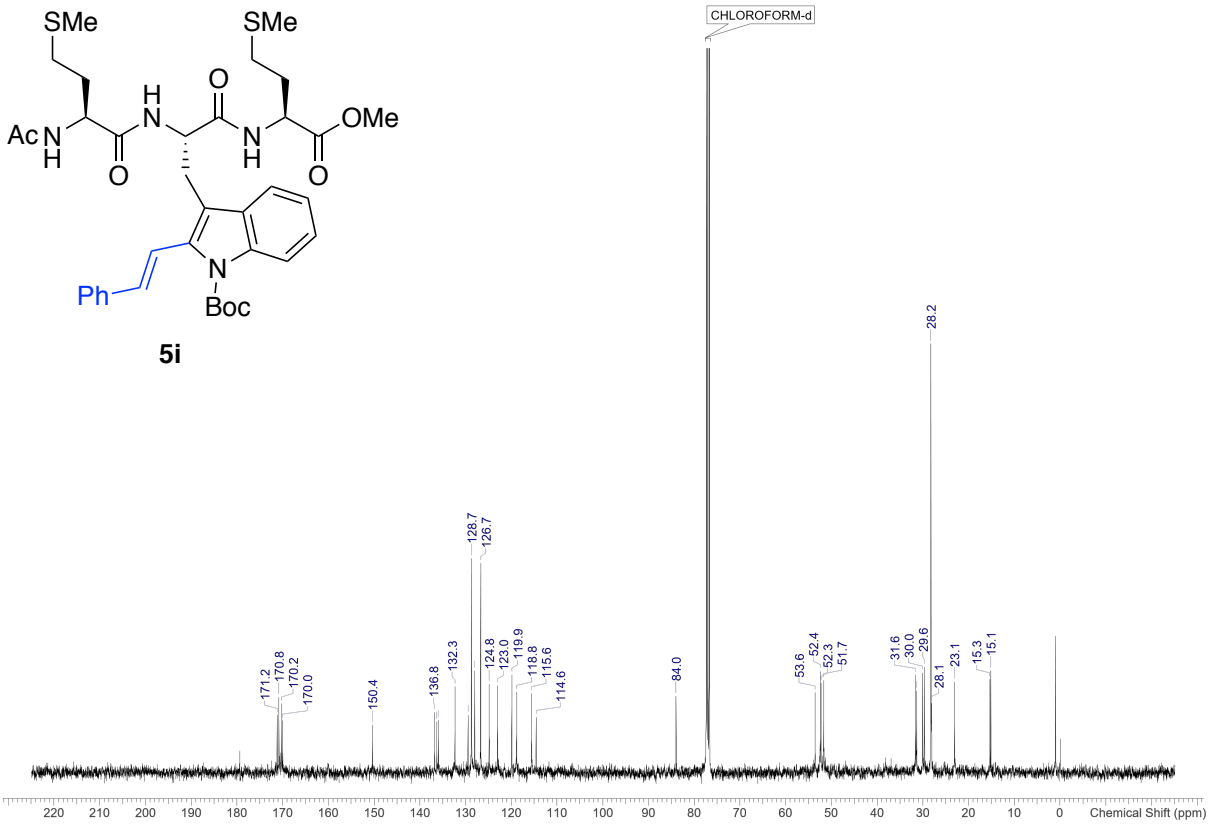
5h

^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5i**

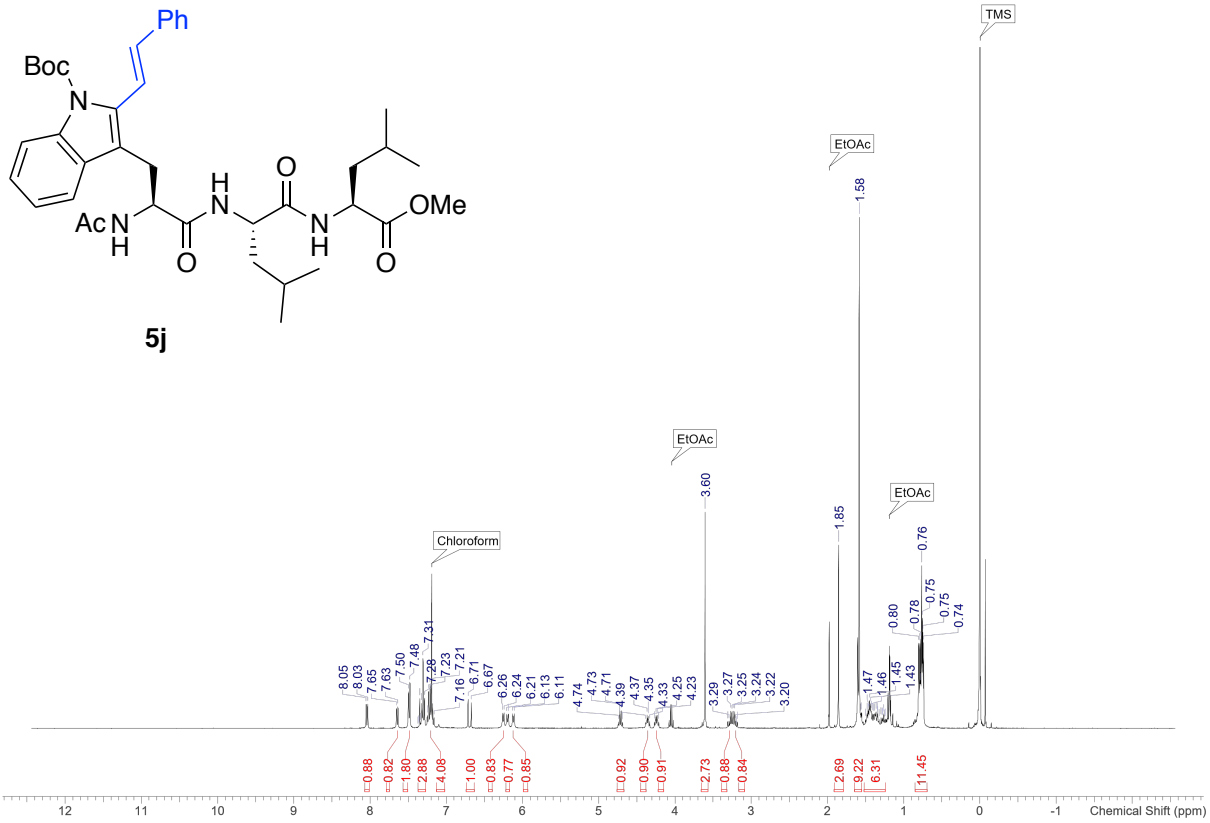


5i

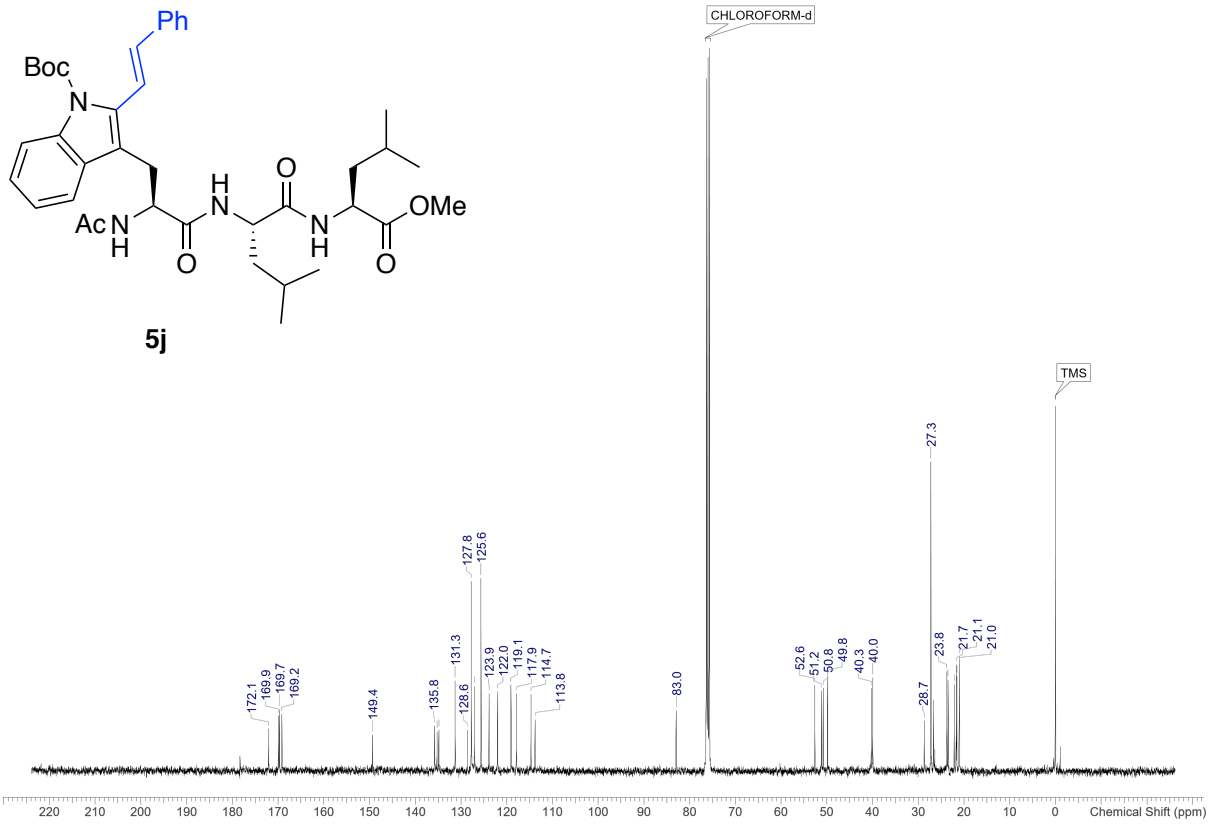
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5i**



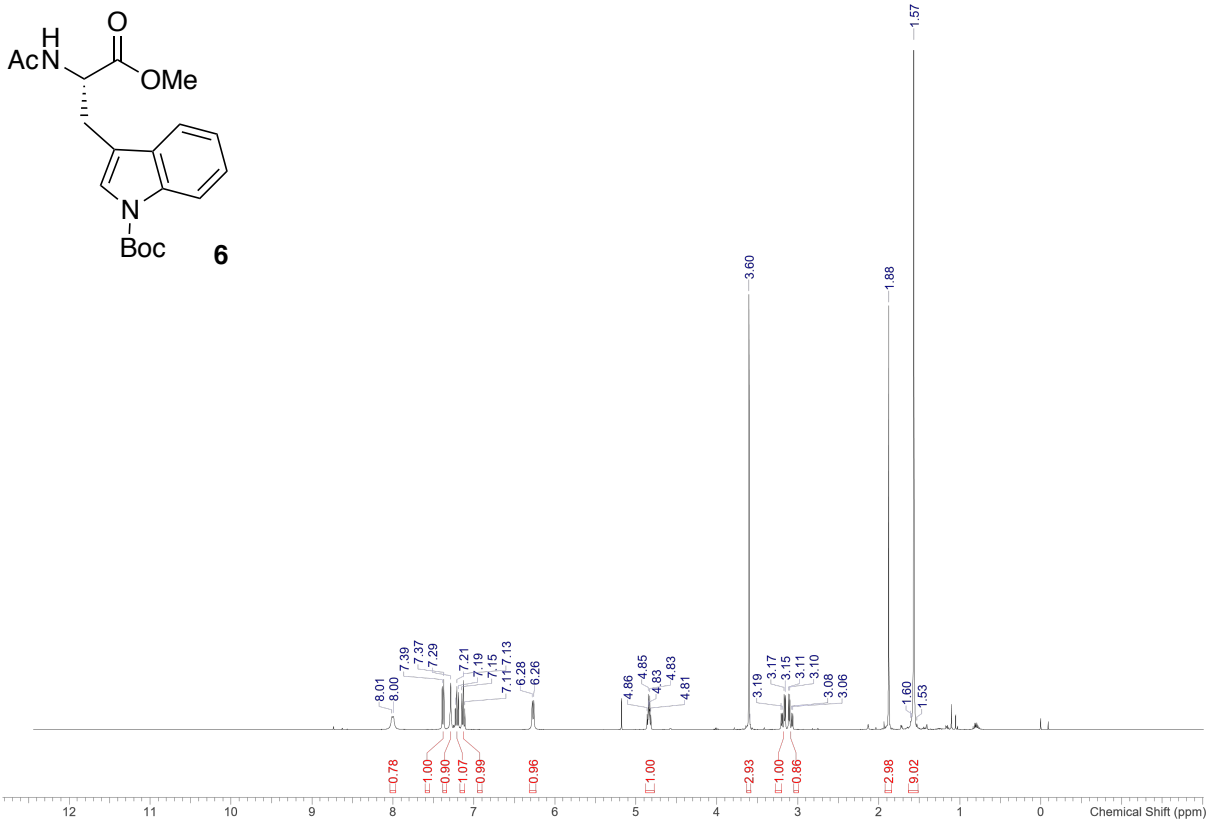
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5j**



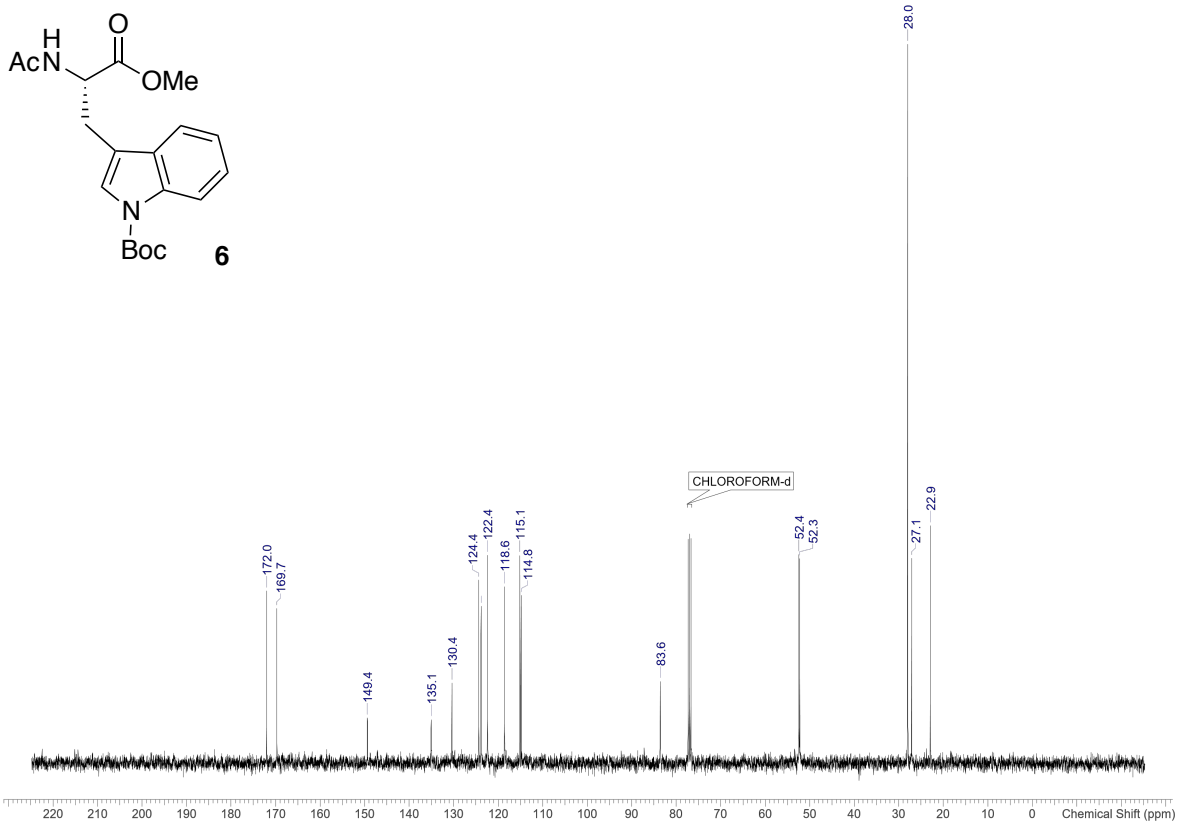
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5j**



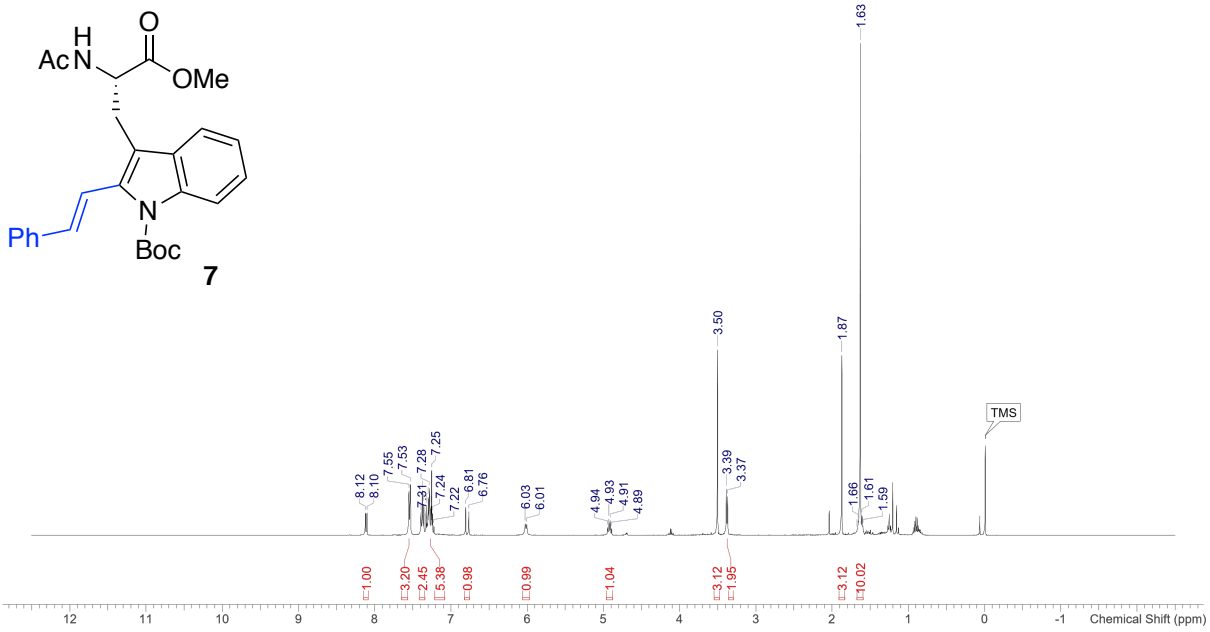
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6**



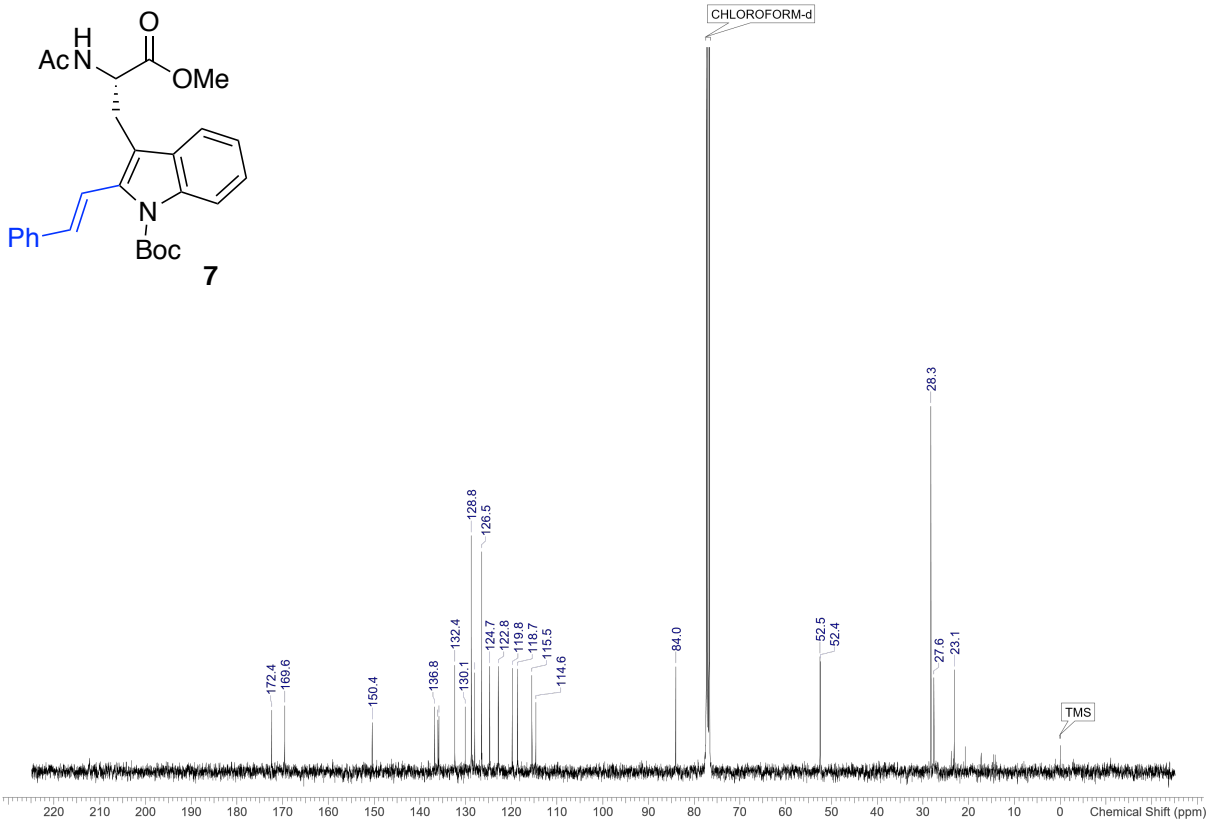
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **6**



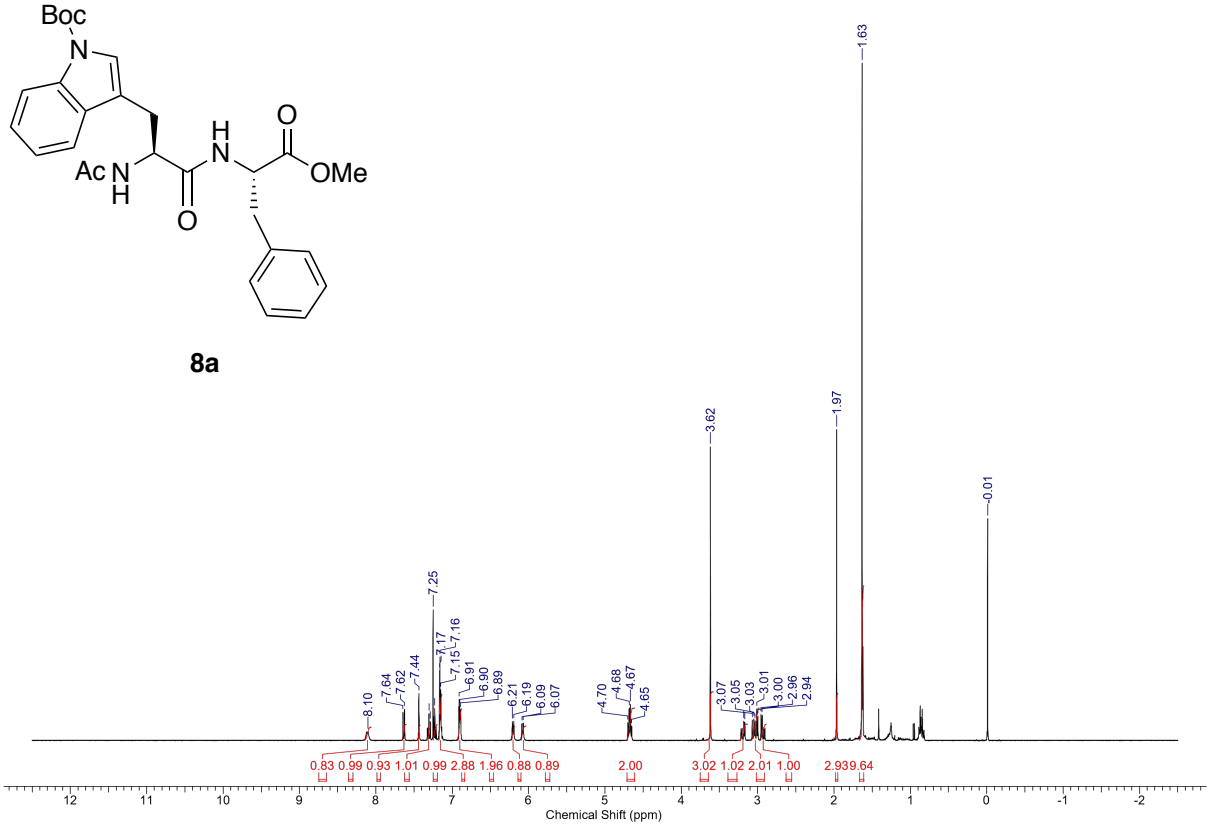
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7**



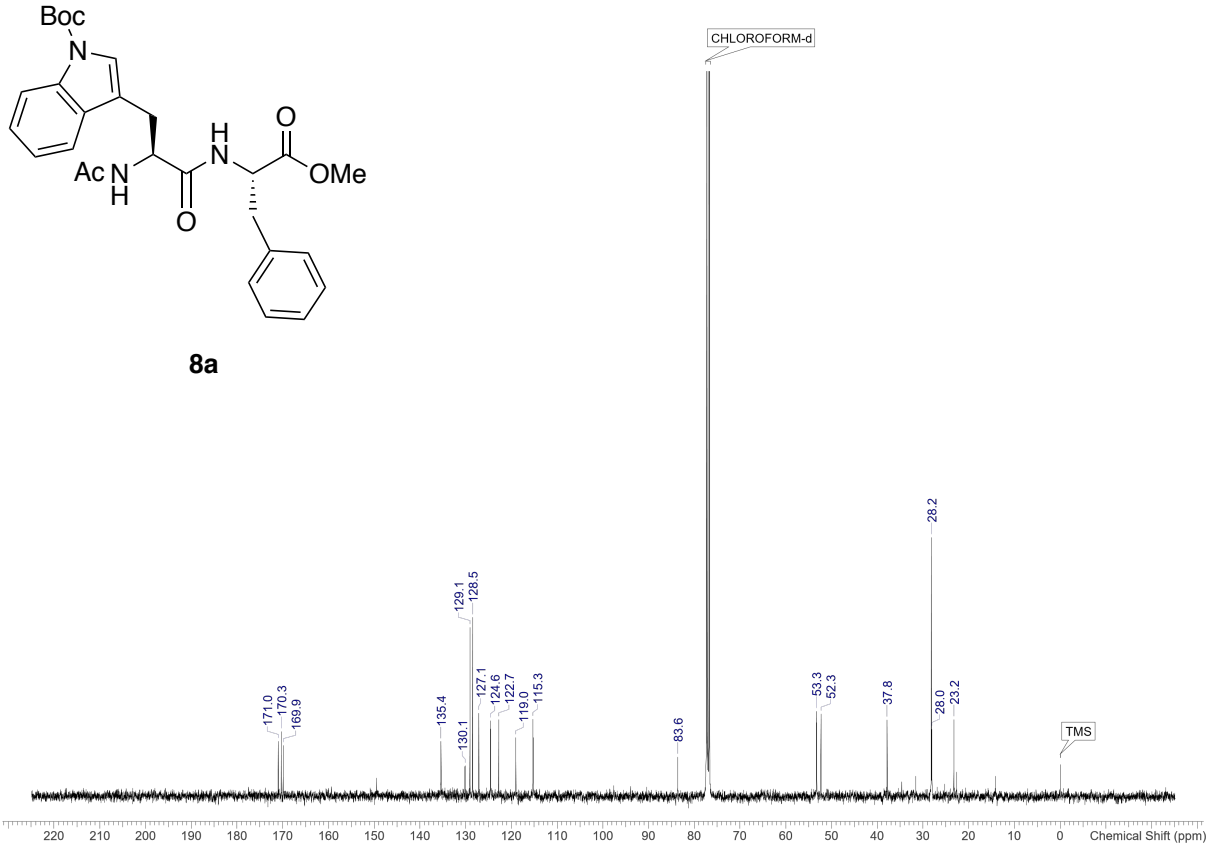
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **7**



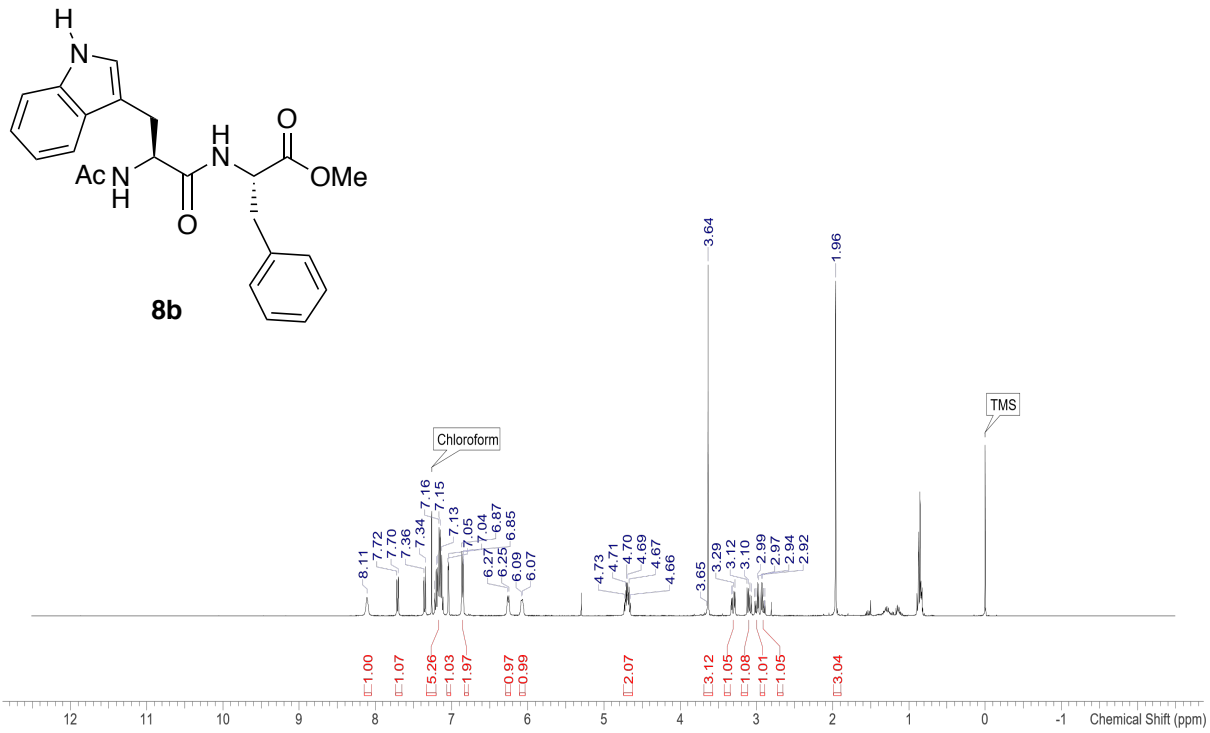
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8a**



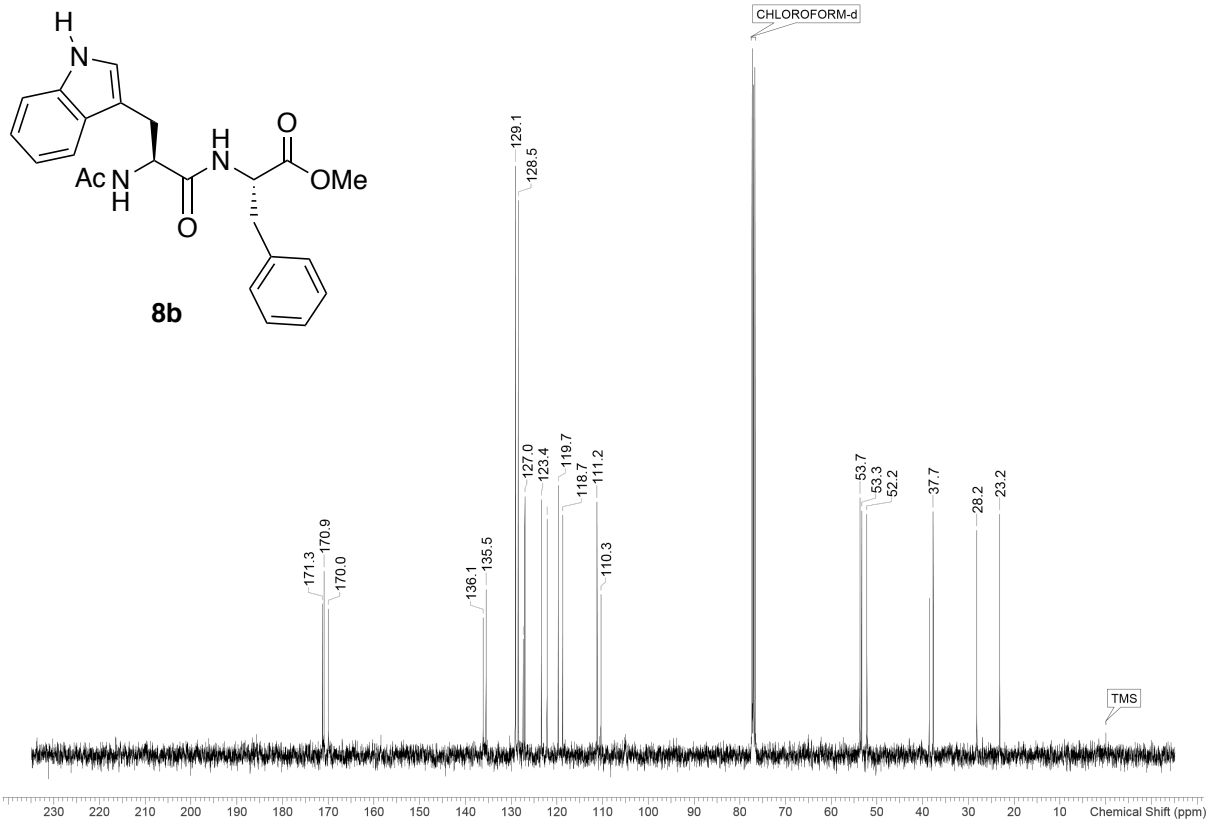
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **8a**



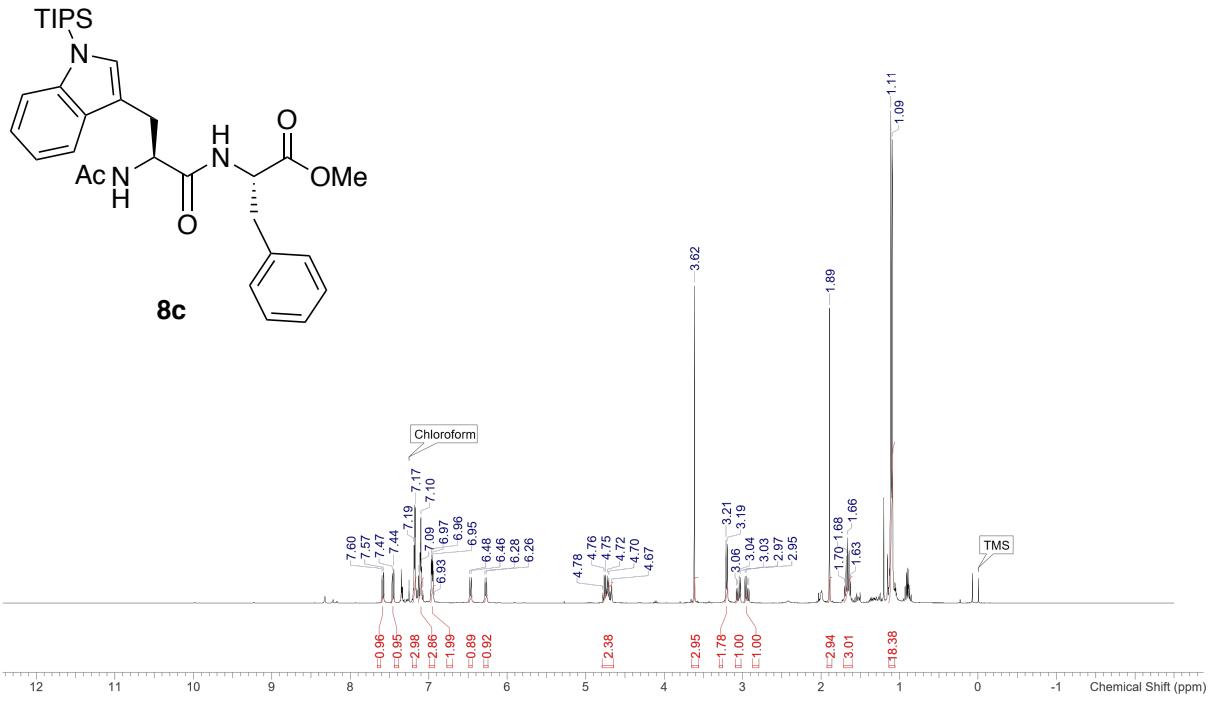
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8b**



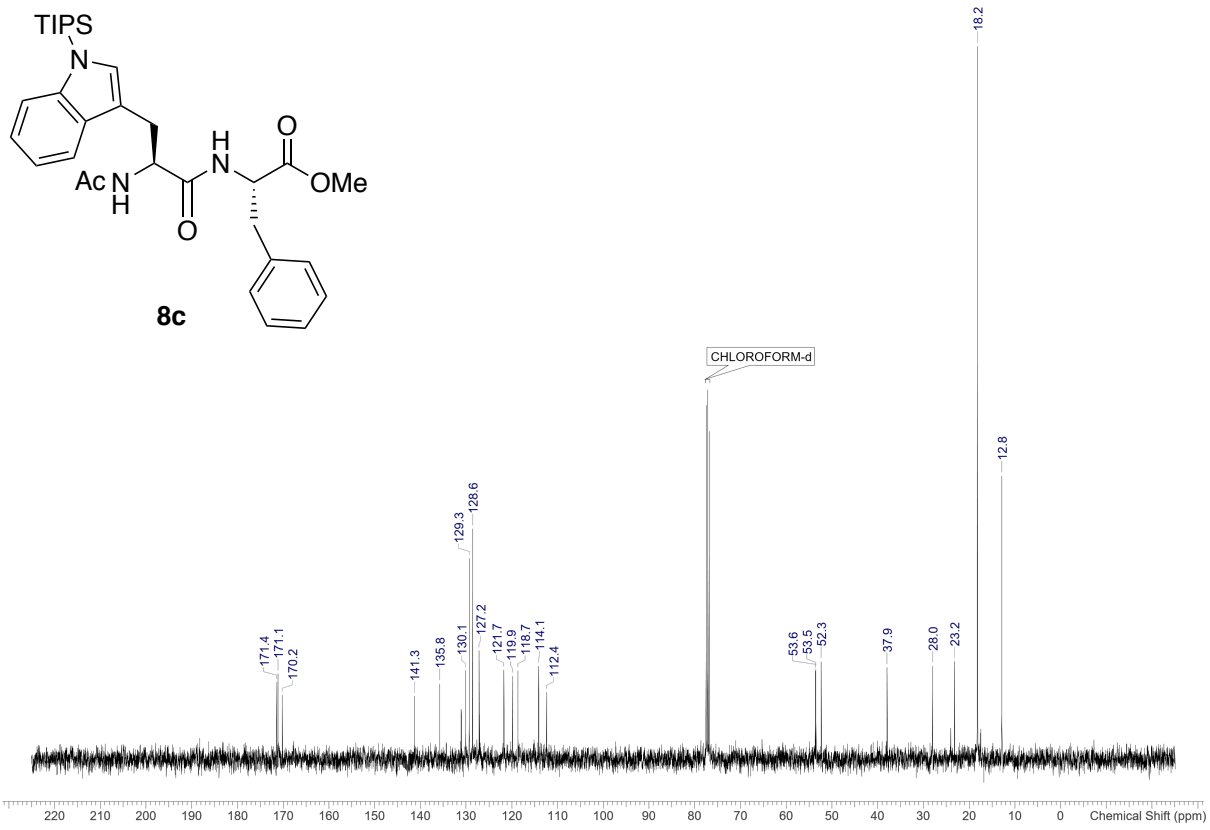
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **8b**



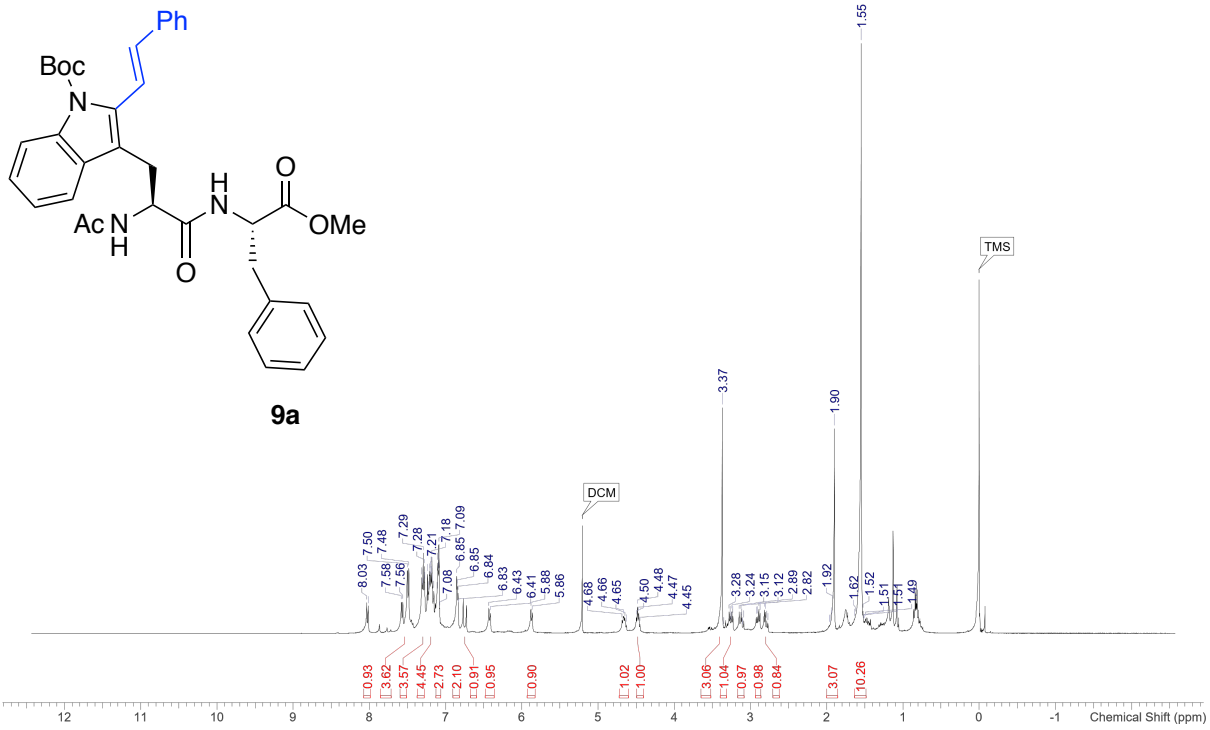
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8c**



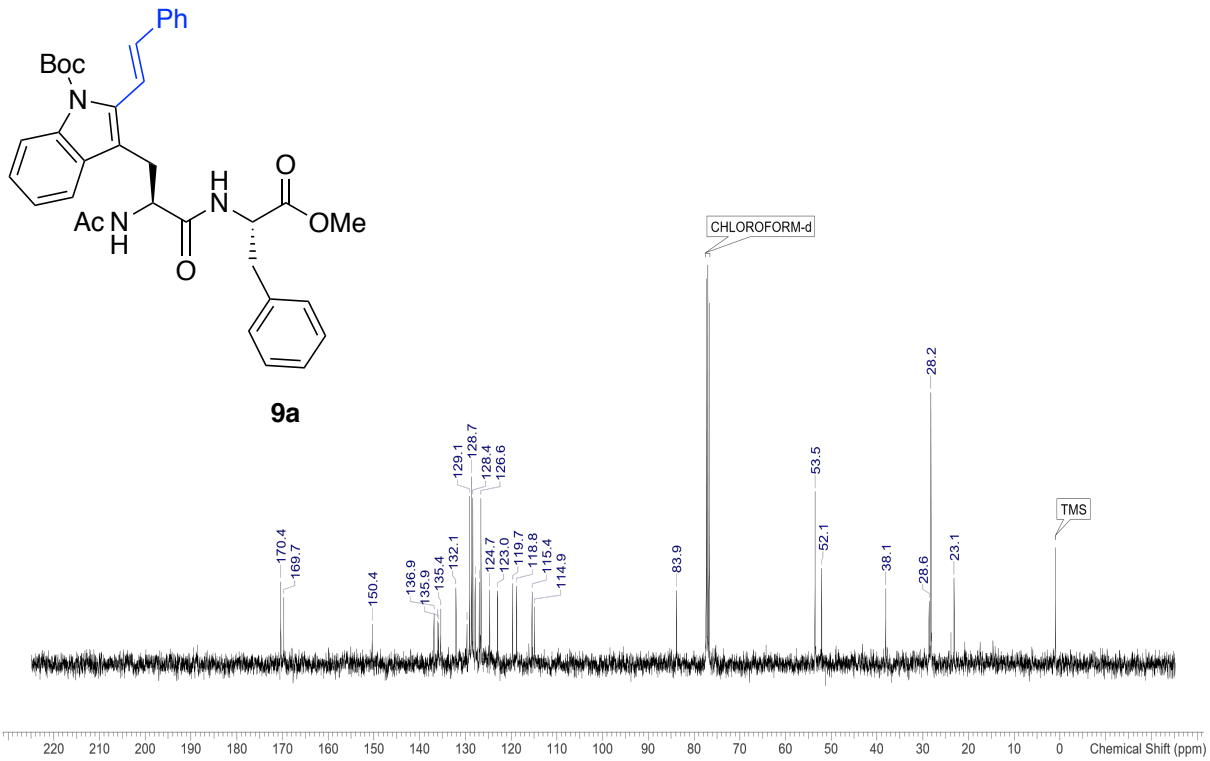
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **8c**



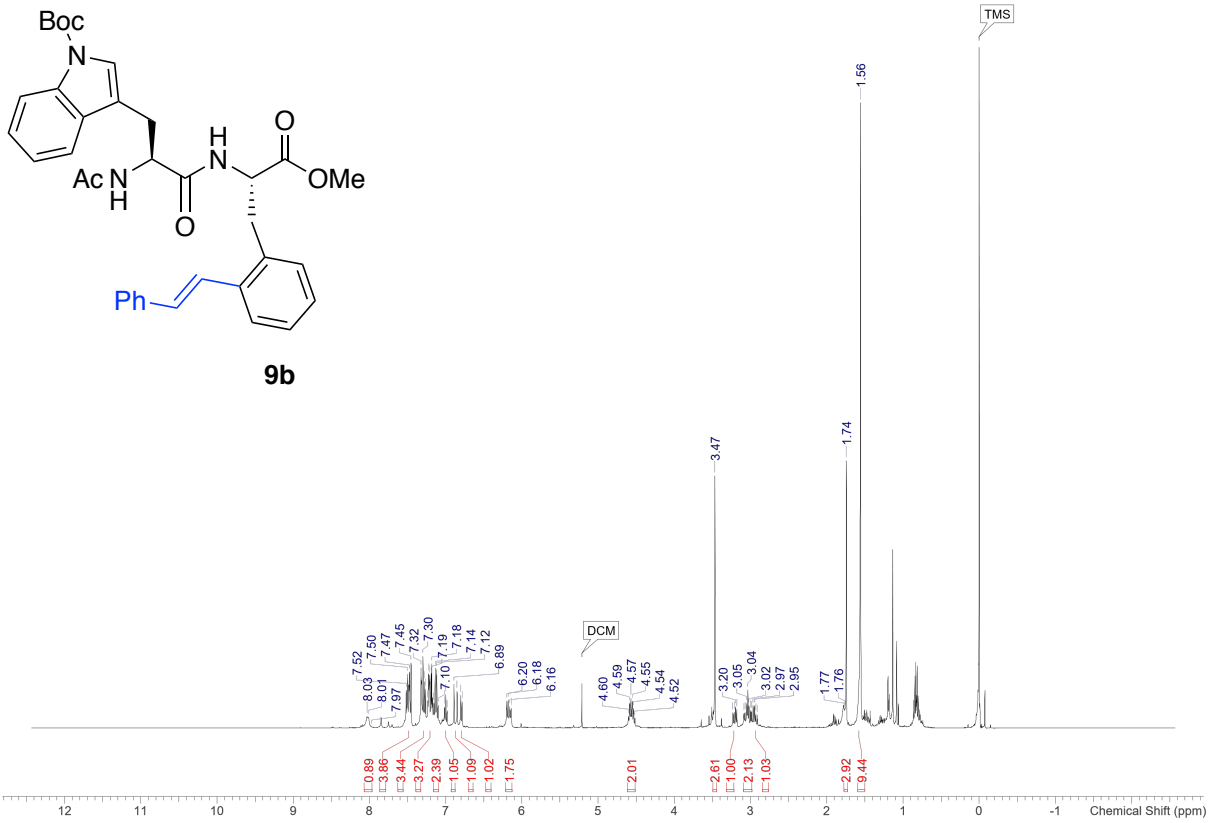
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9a**



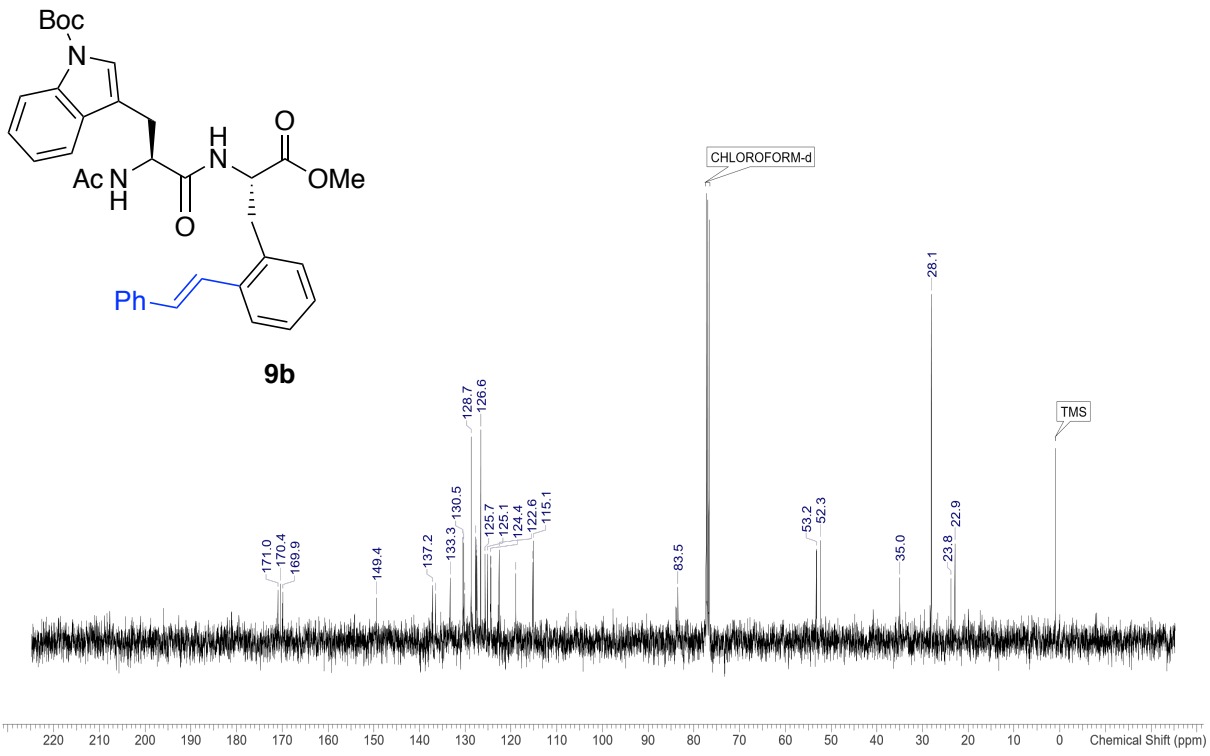
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **9a**



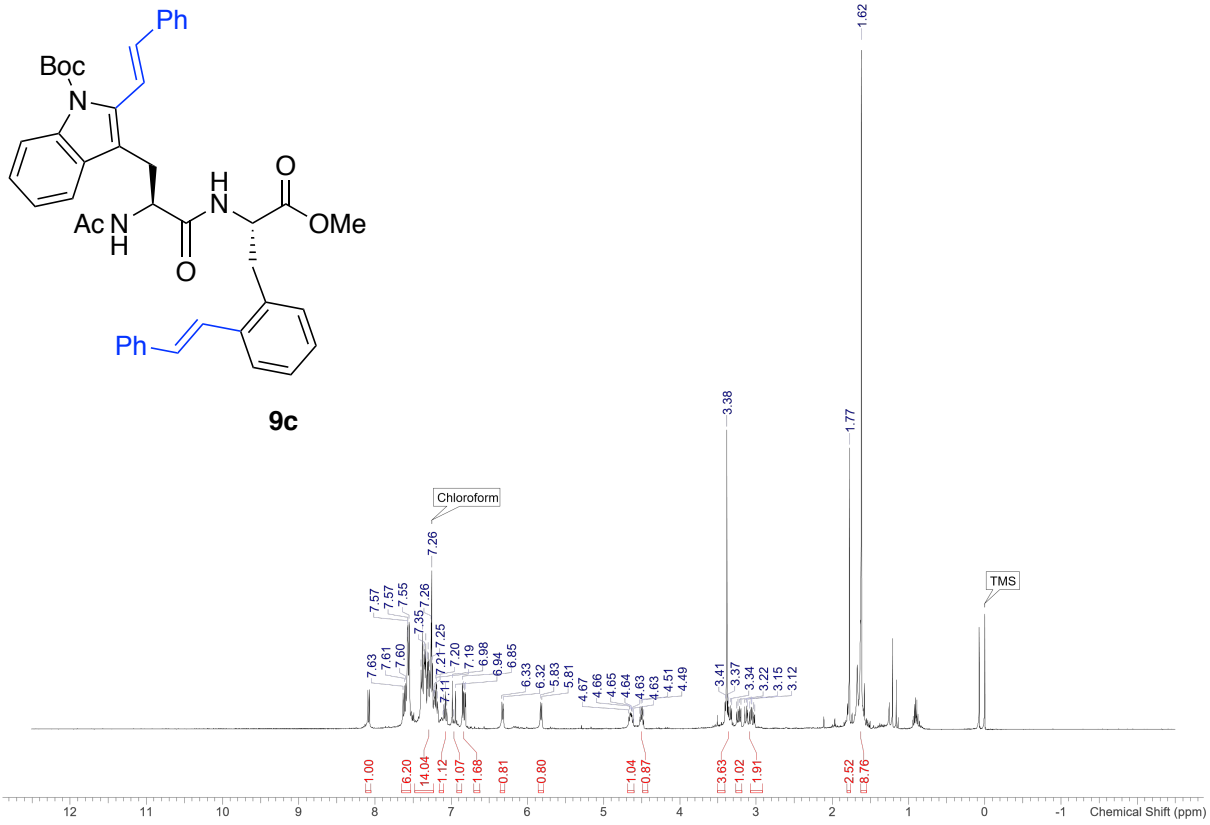
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9b**



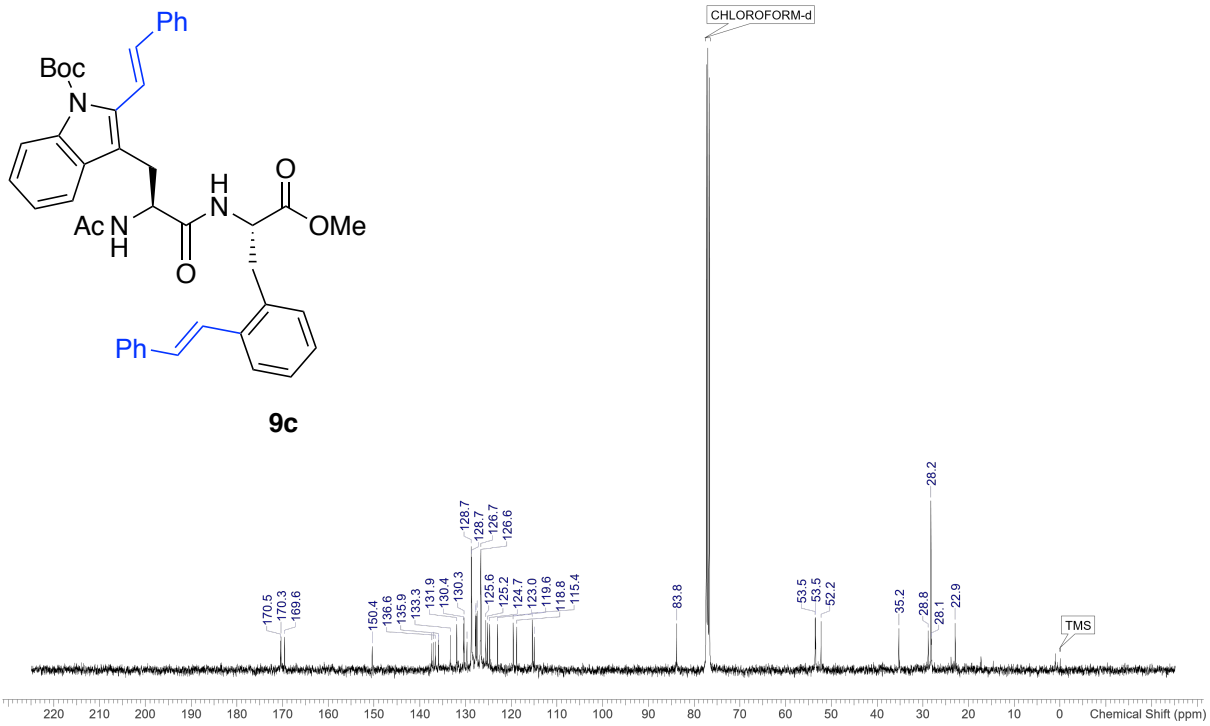
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **9b**



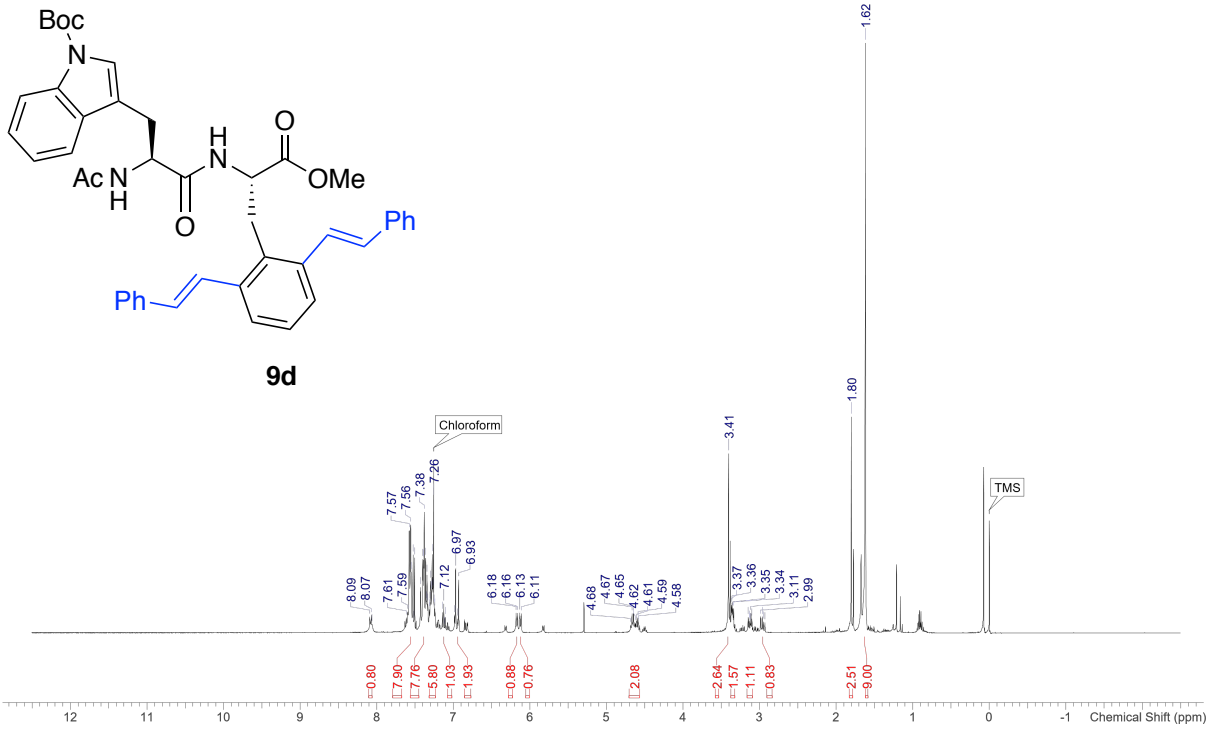
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9c**



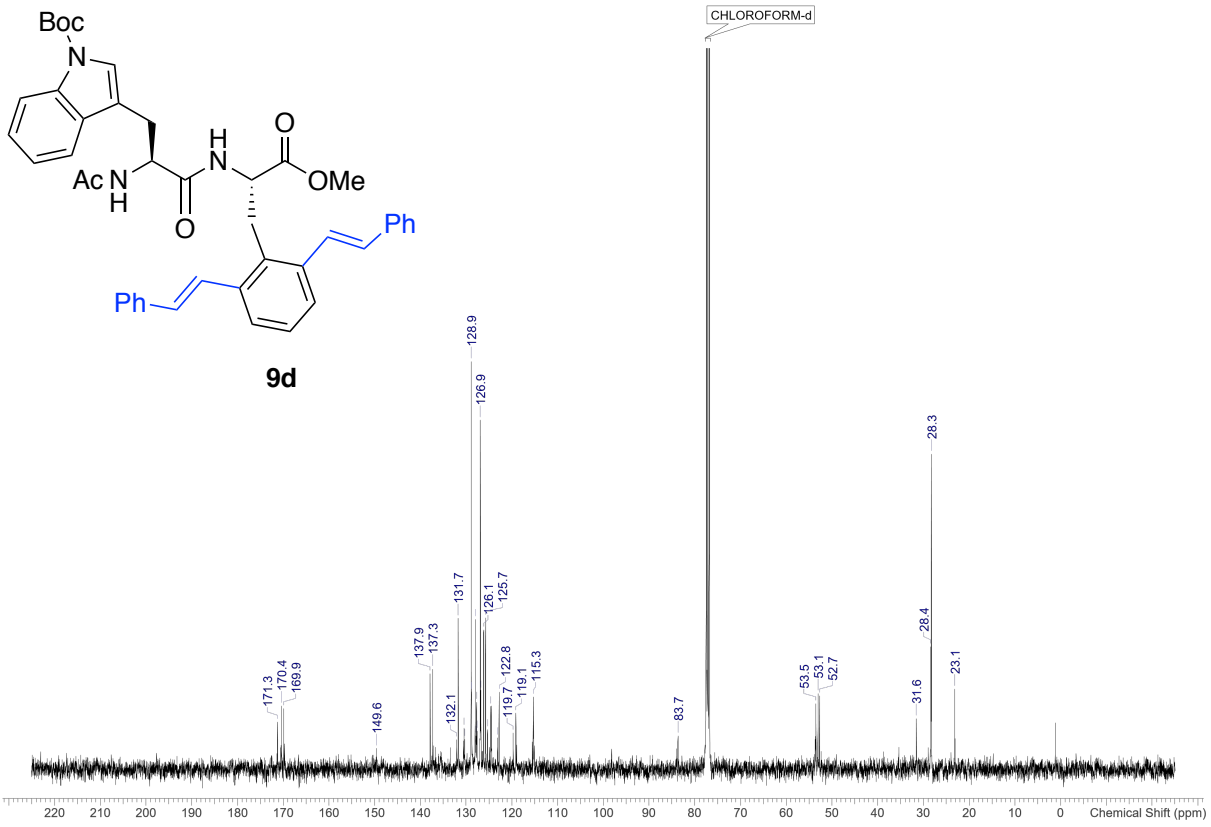
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **9c**



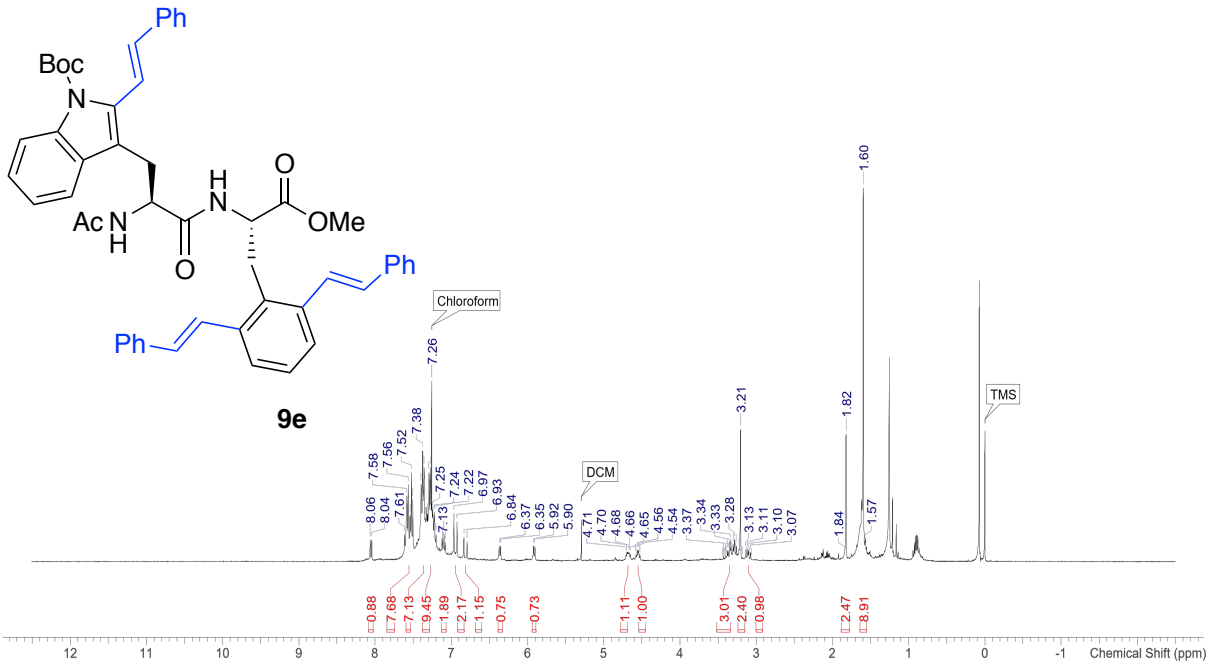
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9d**



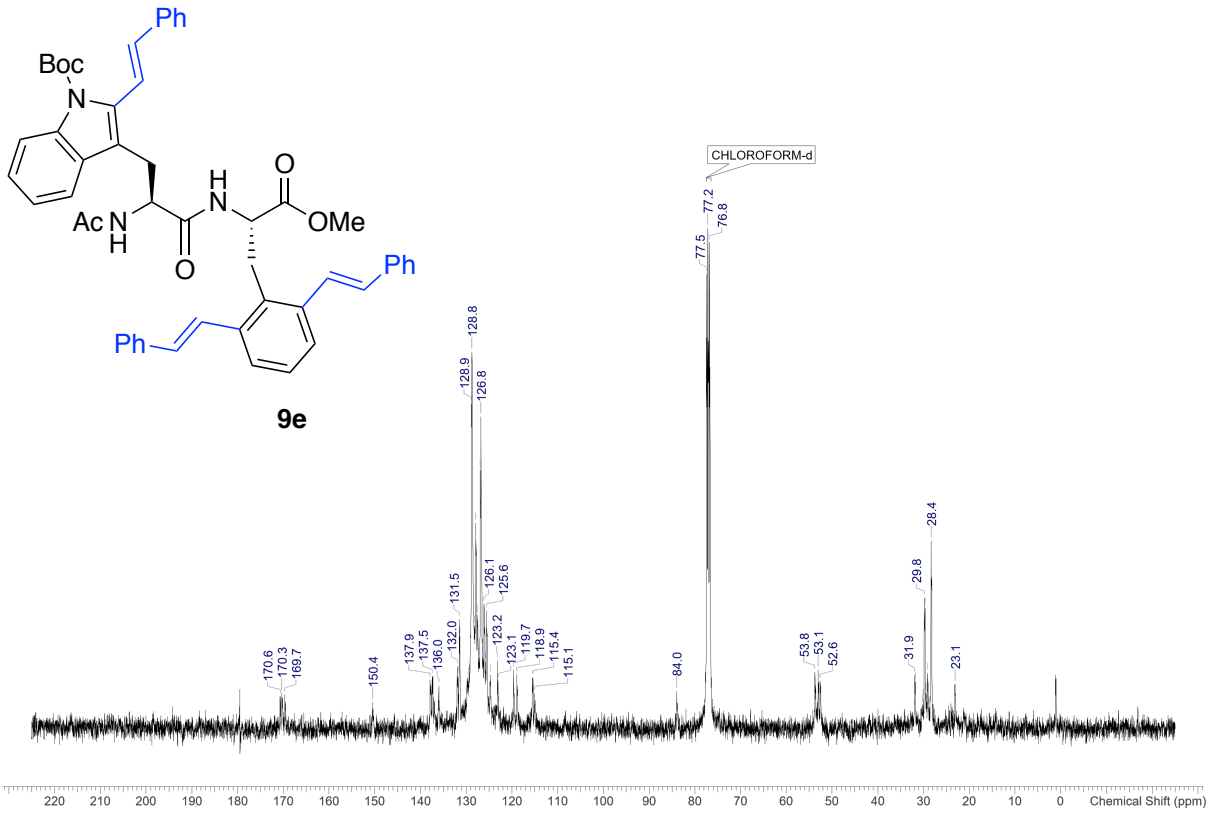
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **9d**



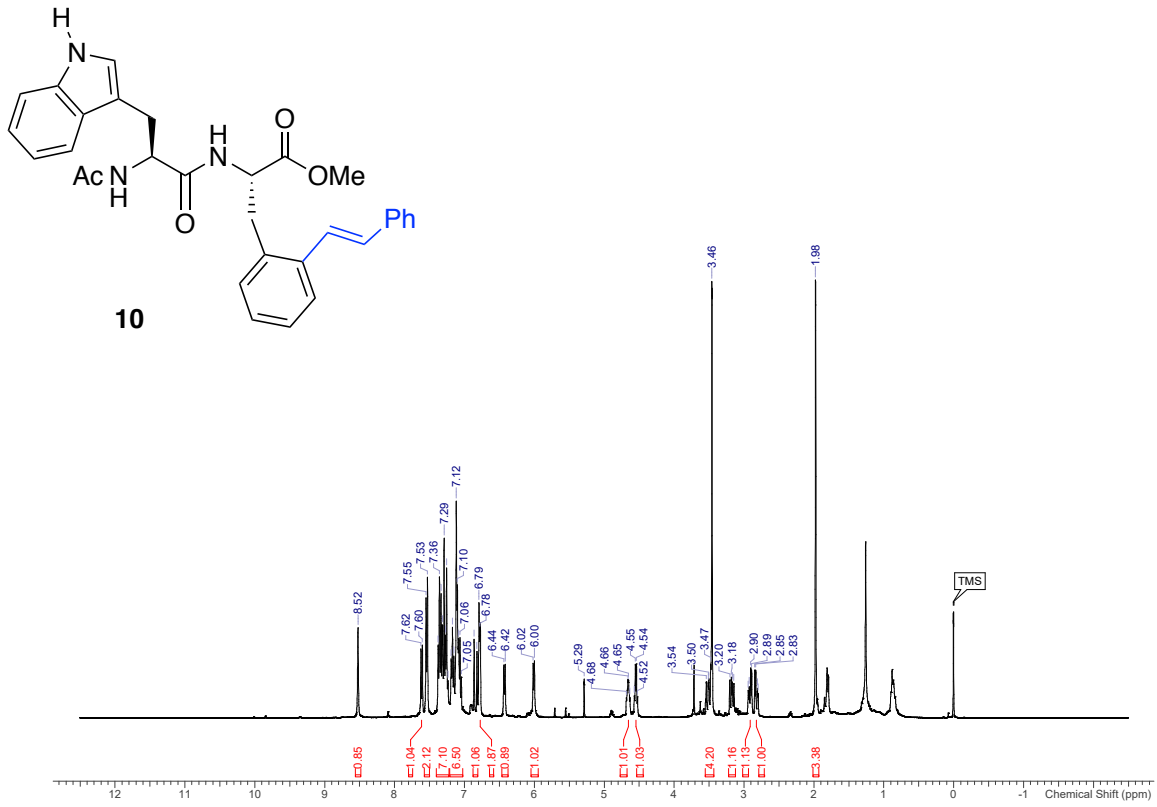
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9e**



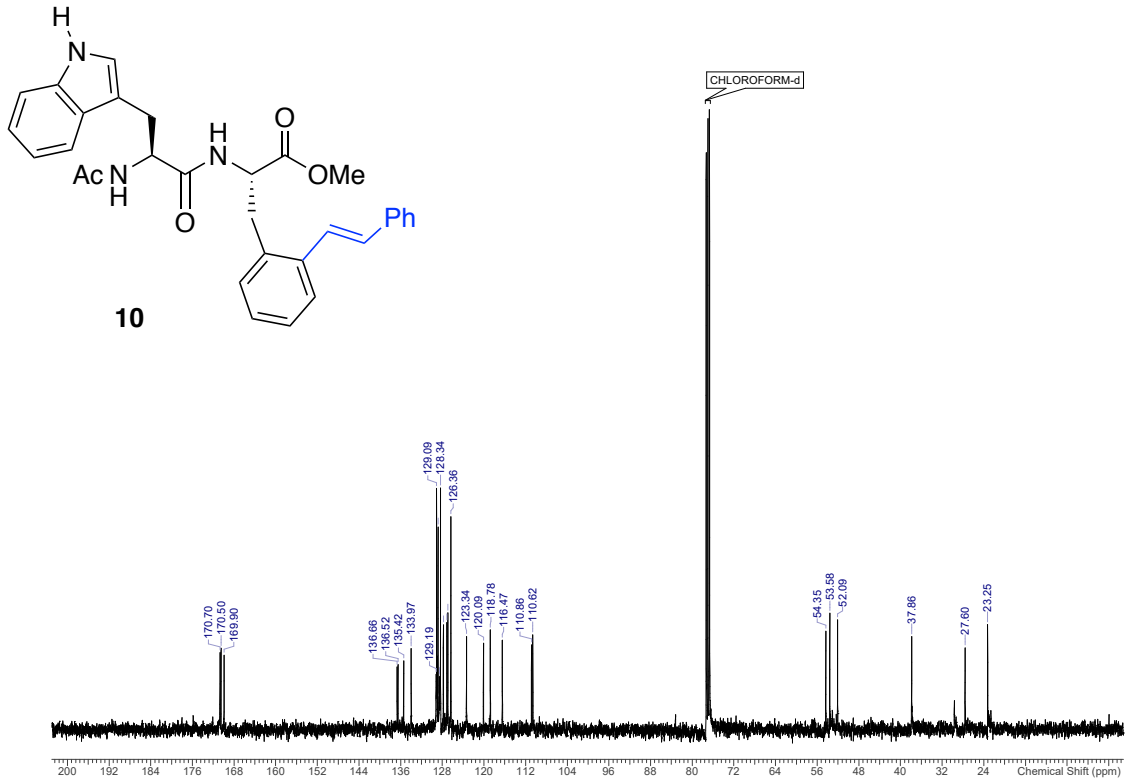
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **9e**



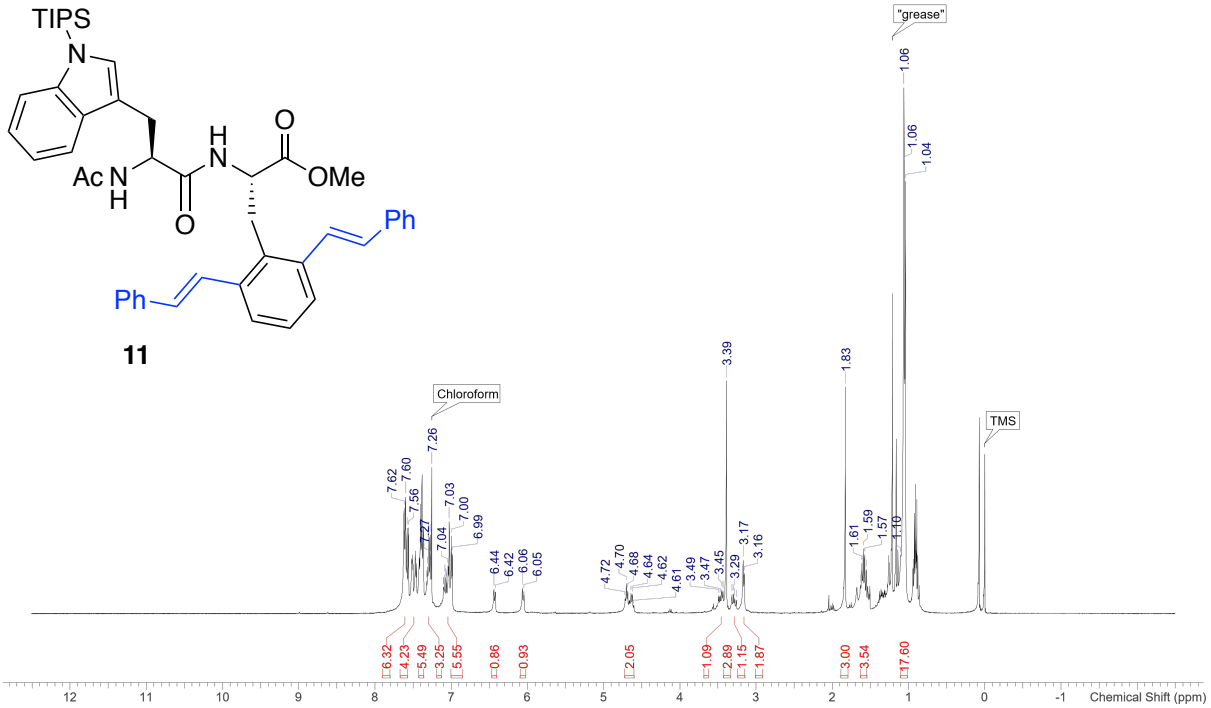
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **10**



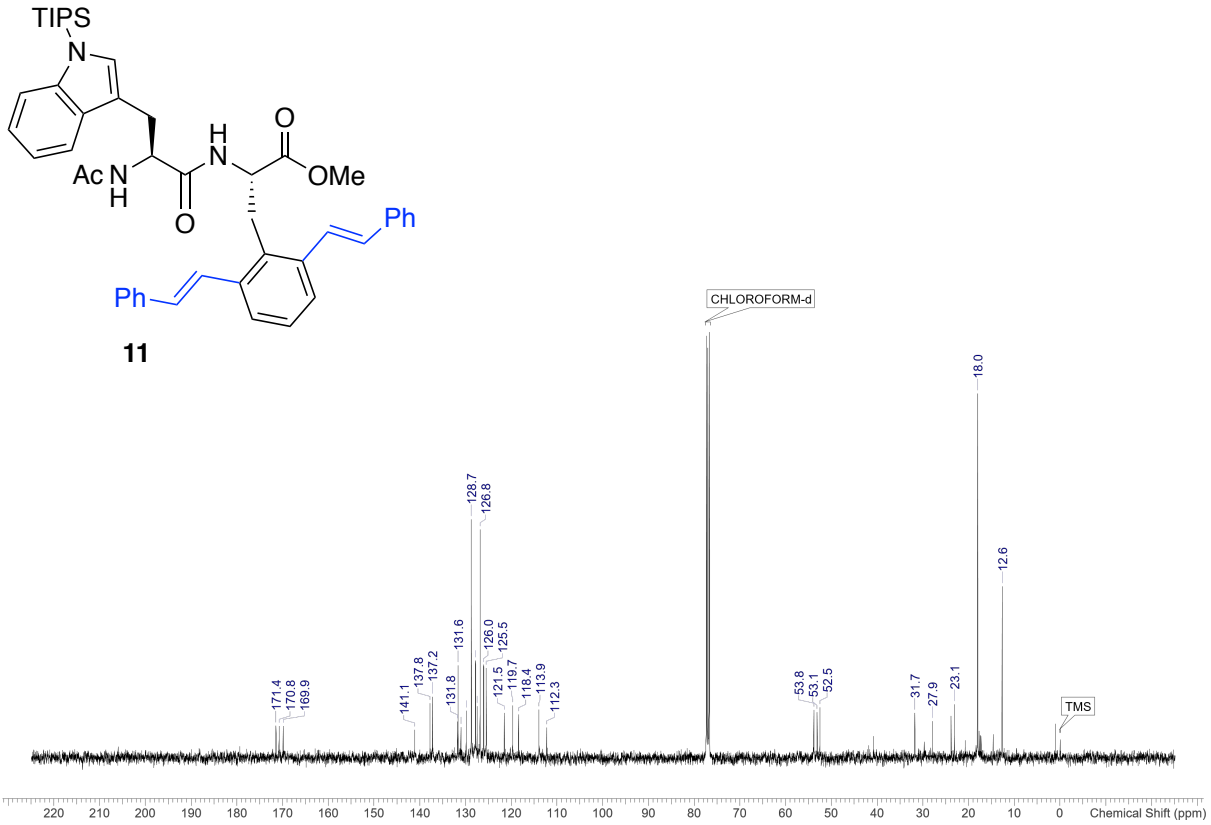
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **10**



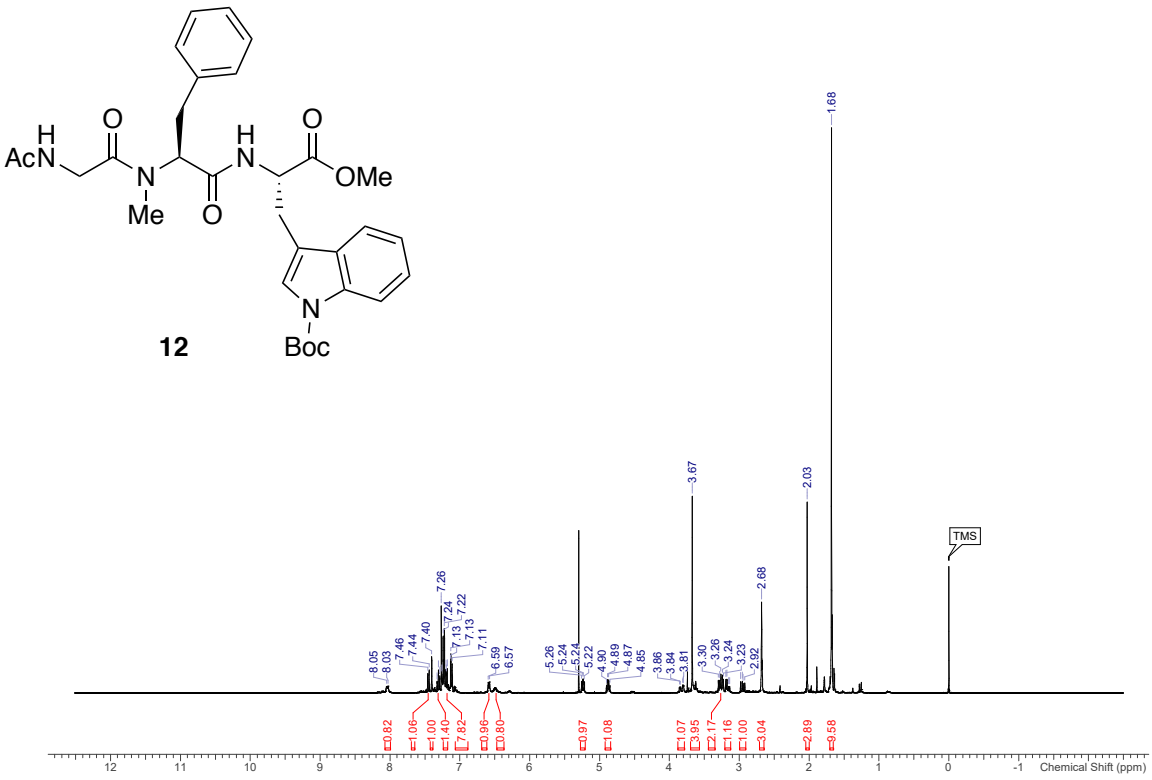
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **11**



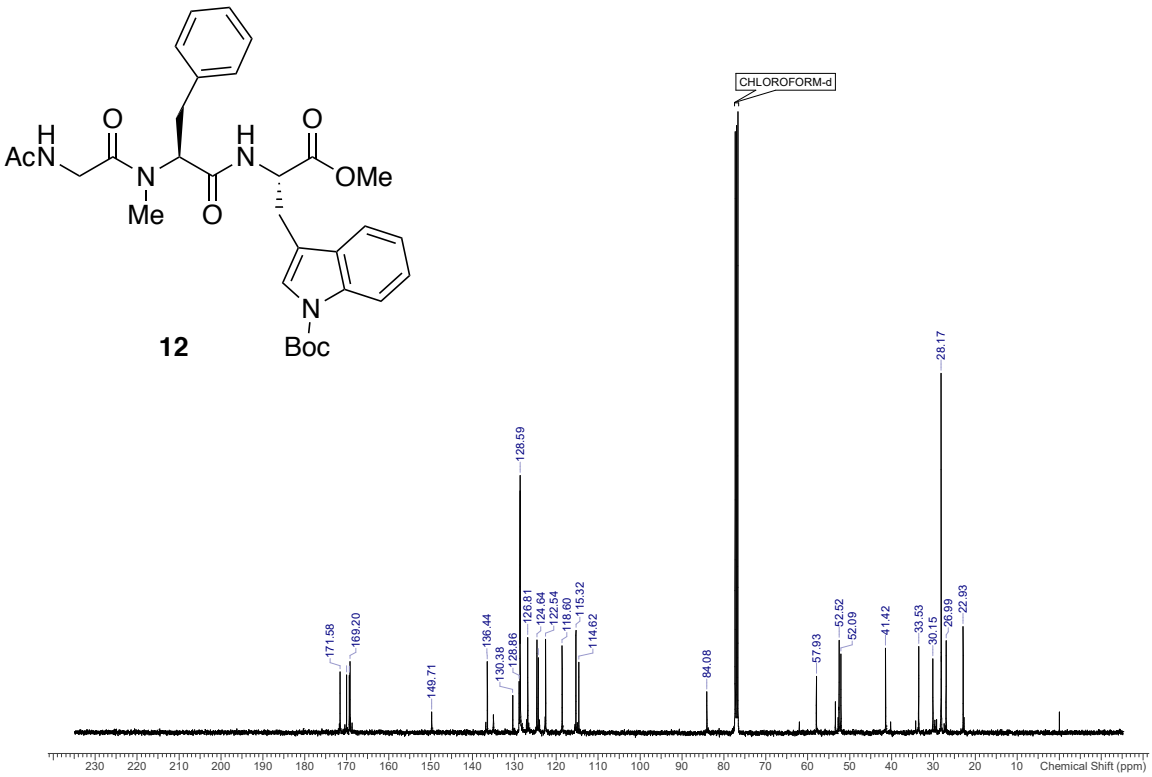
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **11**



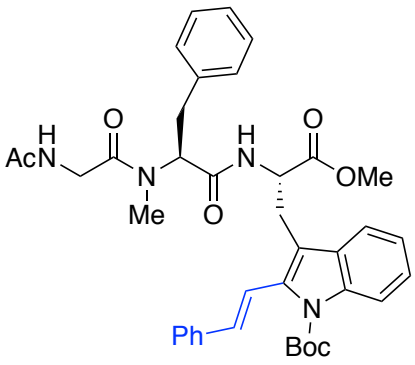
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **12**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **12**

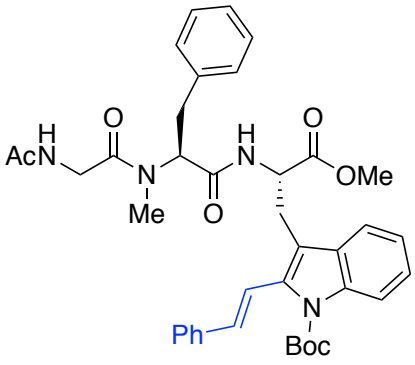


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **13**



13

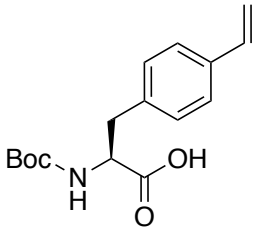
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **13**



13

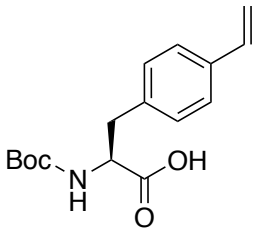
6. ^{1}H and ^{13}C NMR spectra of compounds SI-1 to SI-23

^{1}H NMR spectrum (400 MHz, D_6-DMSO) of **SI-1**



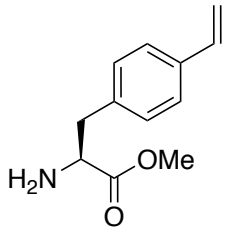
SI-1

^{13}C NMR spectrum (100 MHz, D_6-DMSO) of **SI-1**



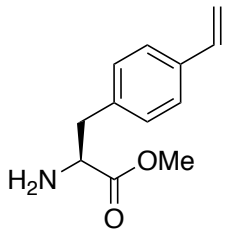
SI-1

^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-2**

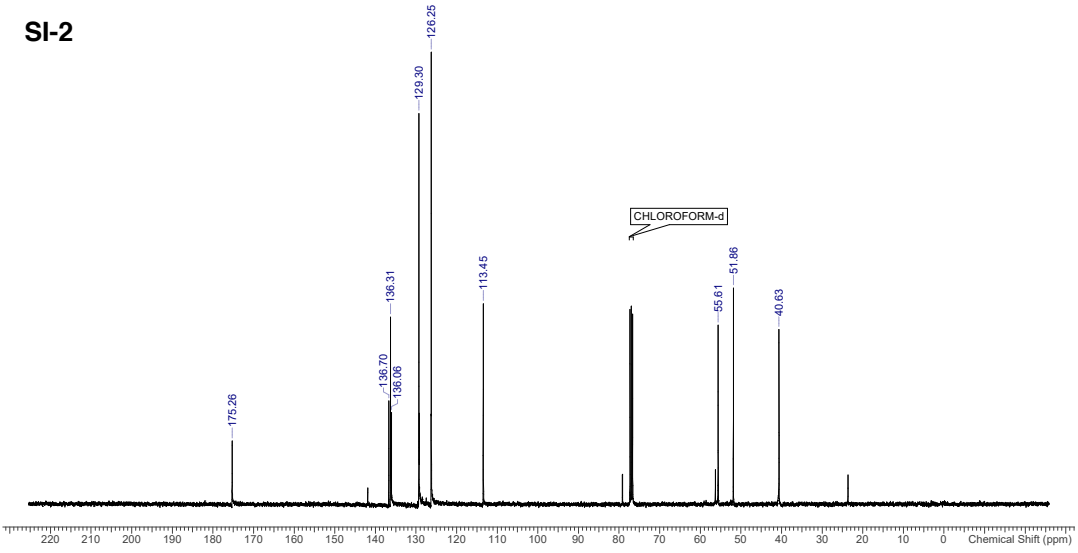


SI-2

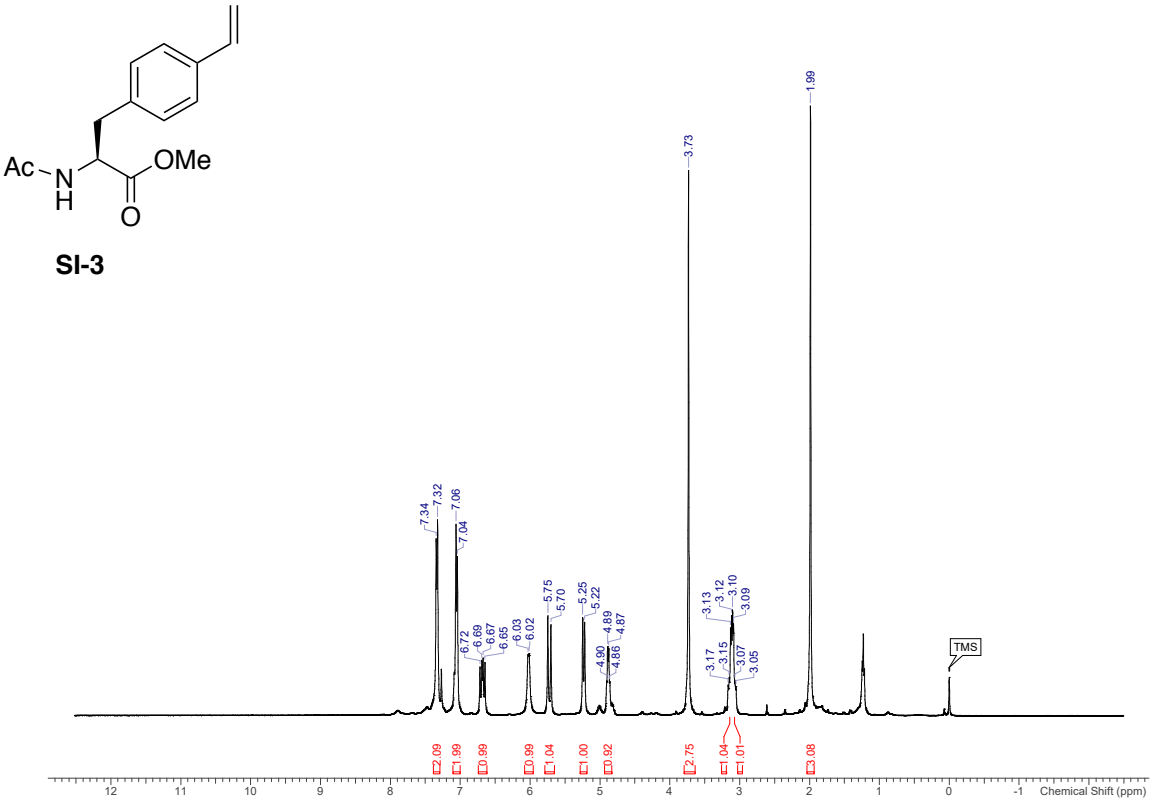
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **SI-2**



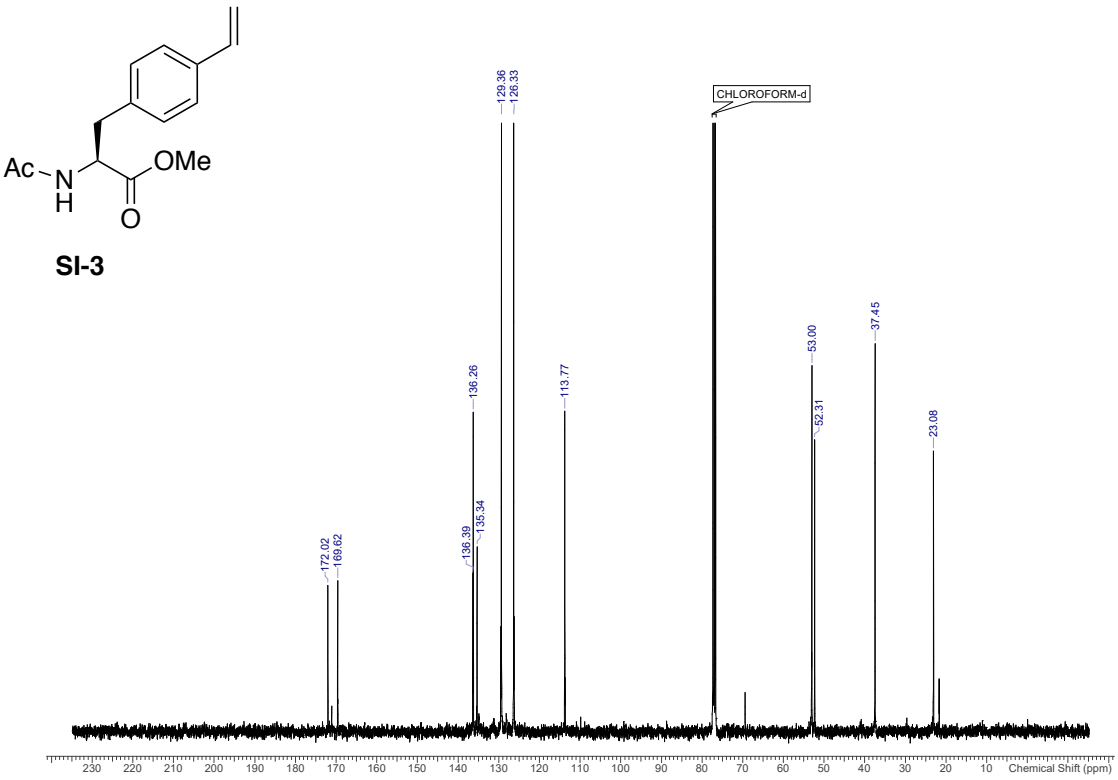
SI-2



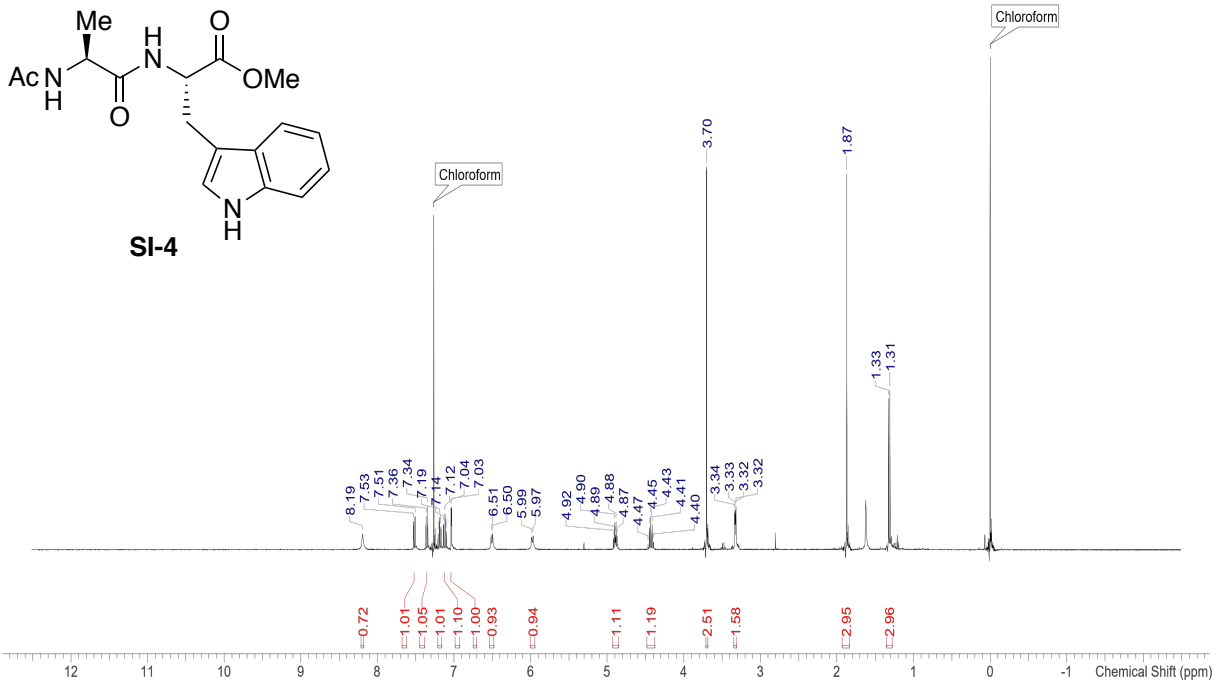
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-3**



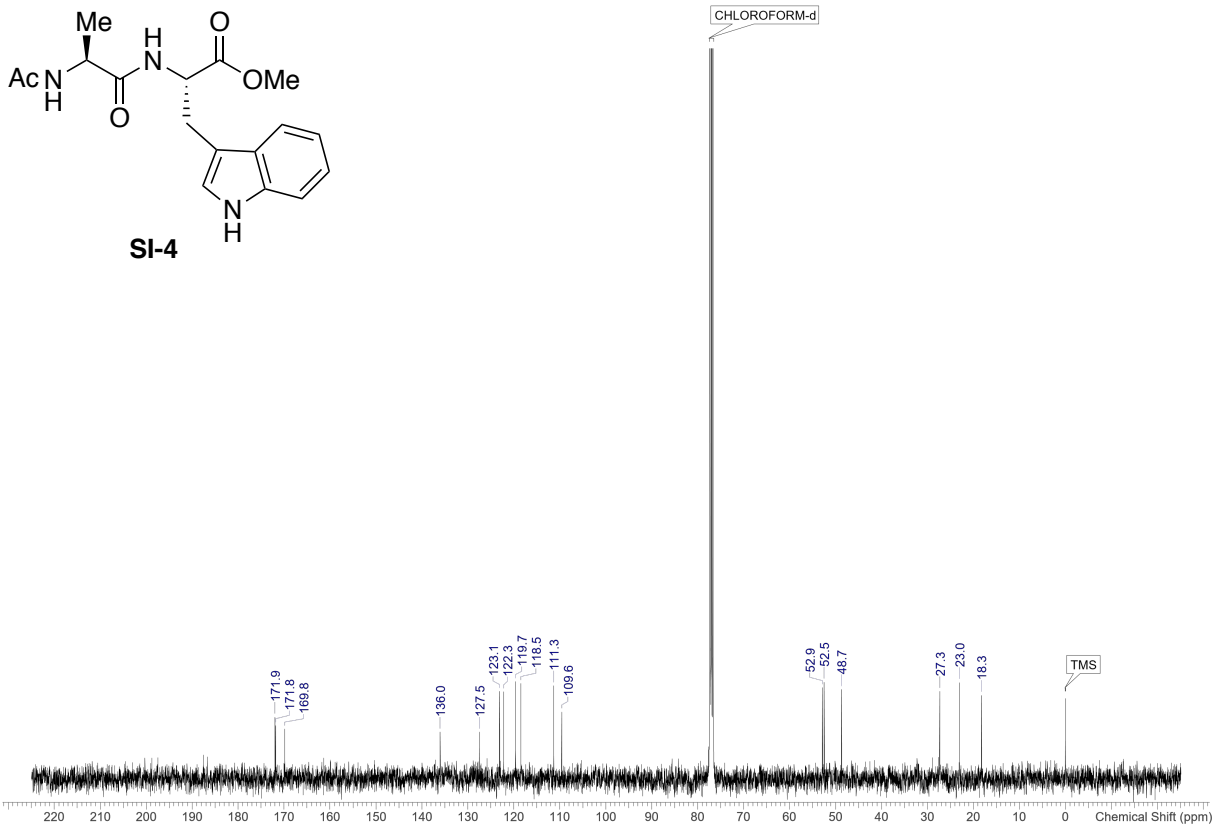
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-3**



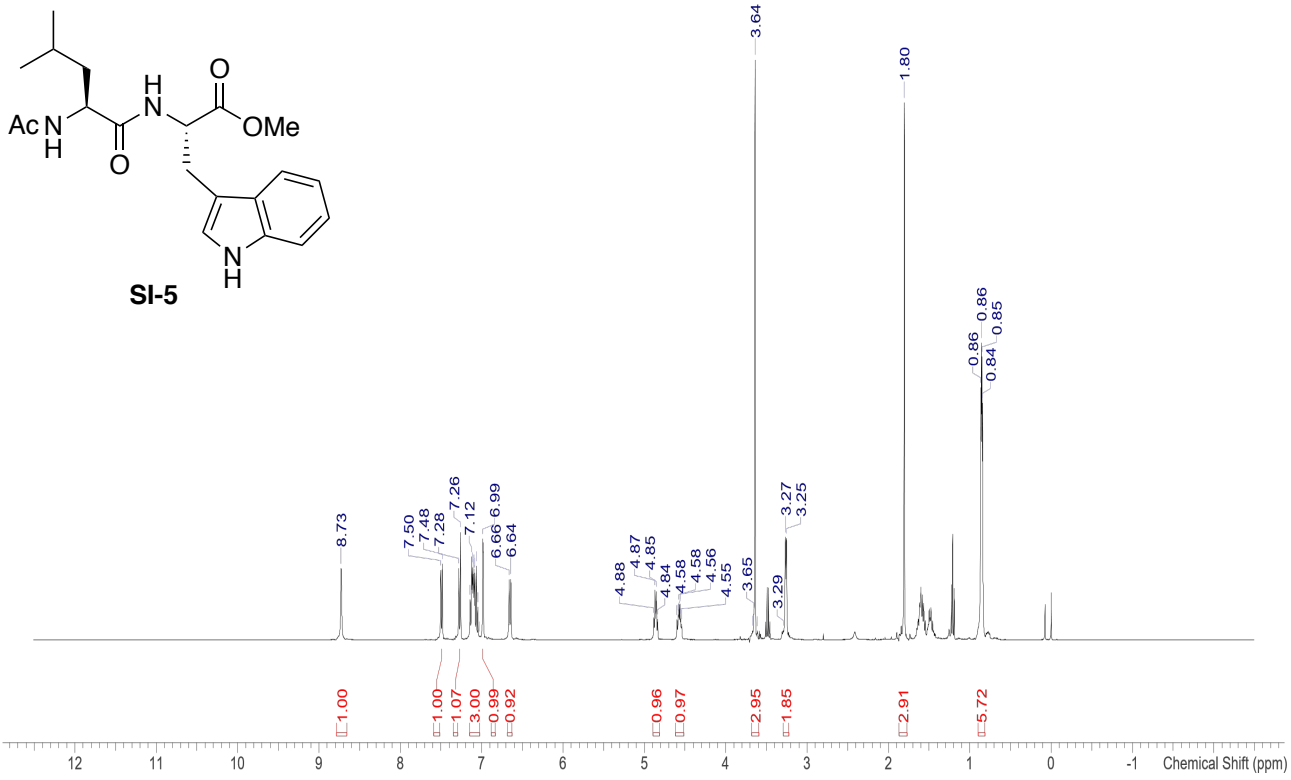
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-4**



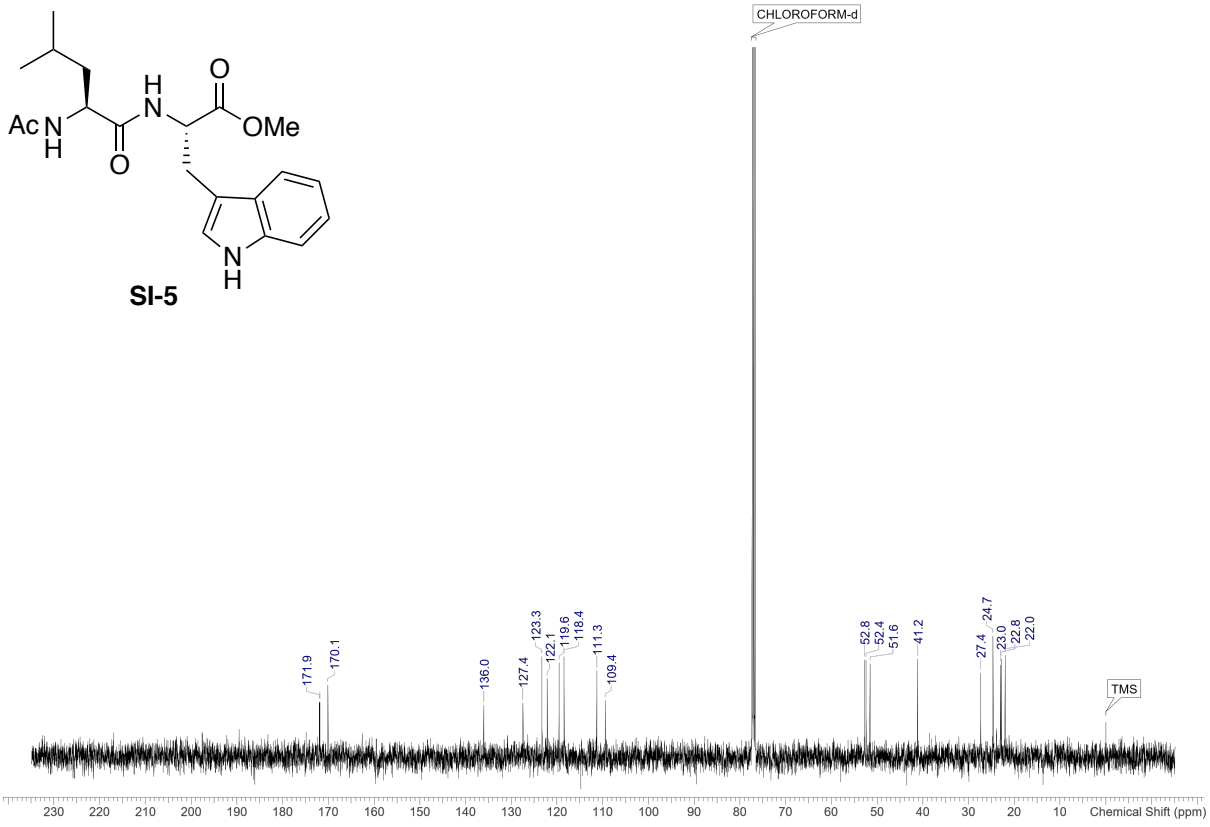
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-4**



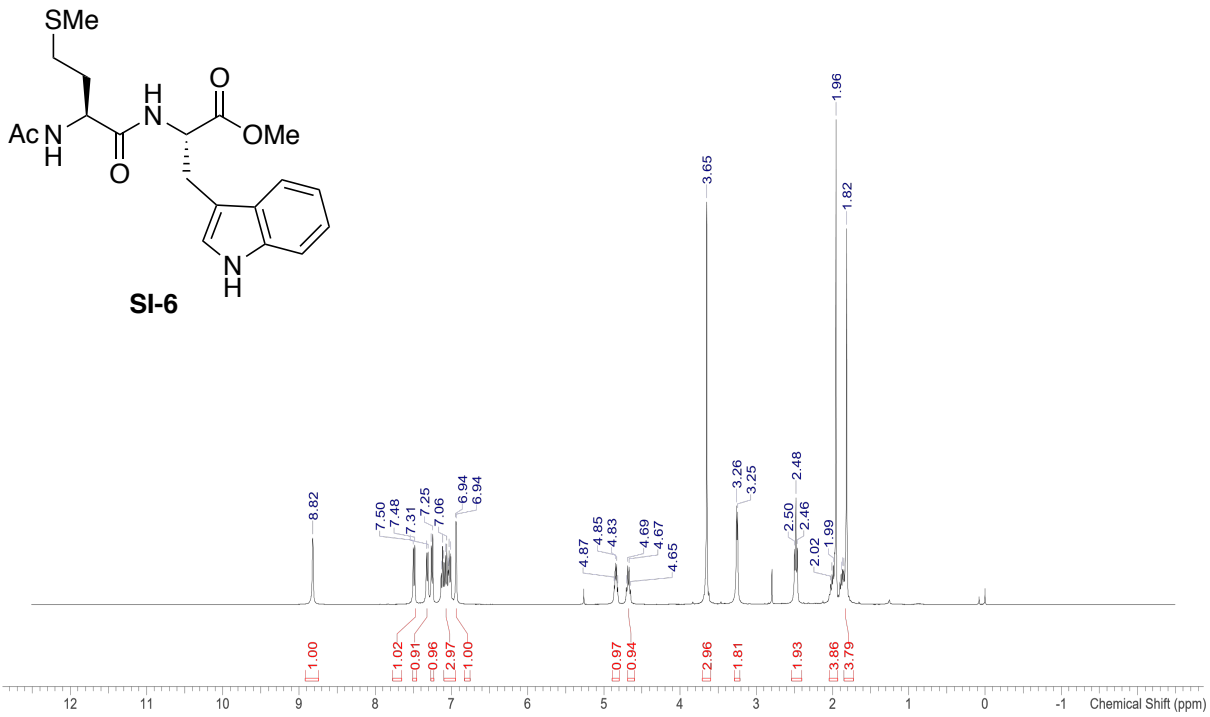
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-5**



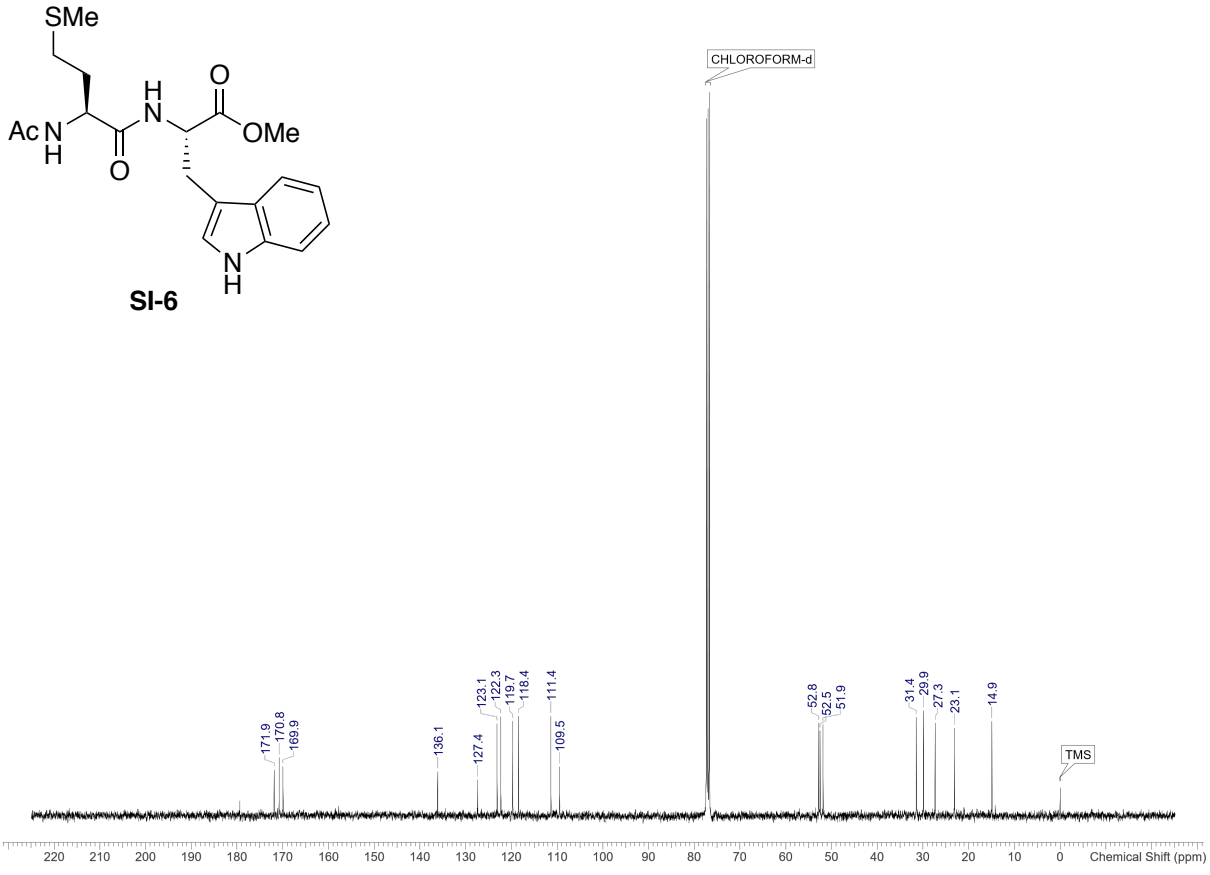
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-5**



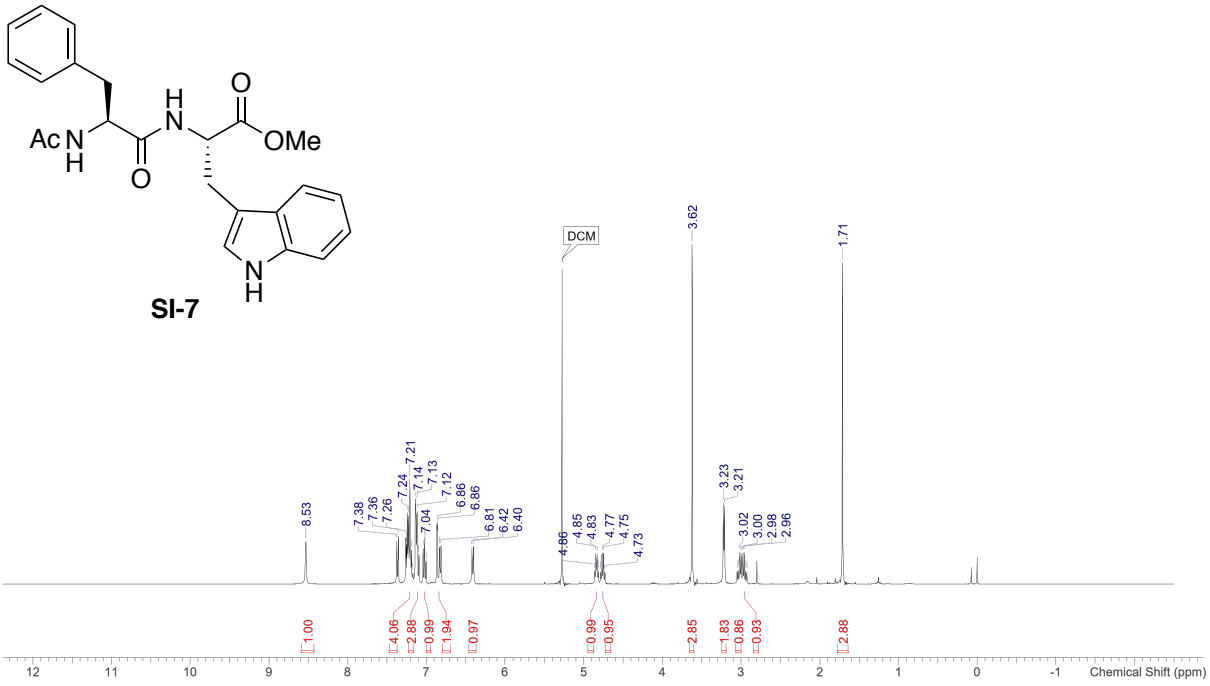
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-6**



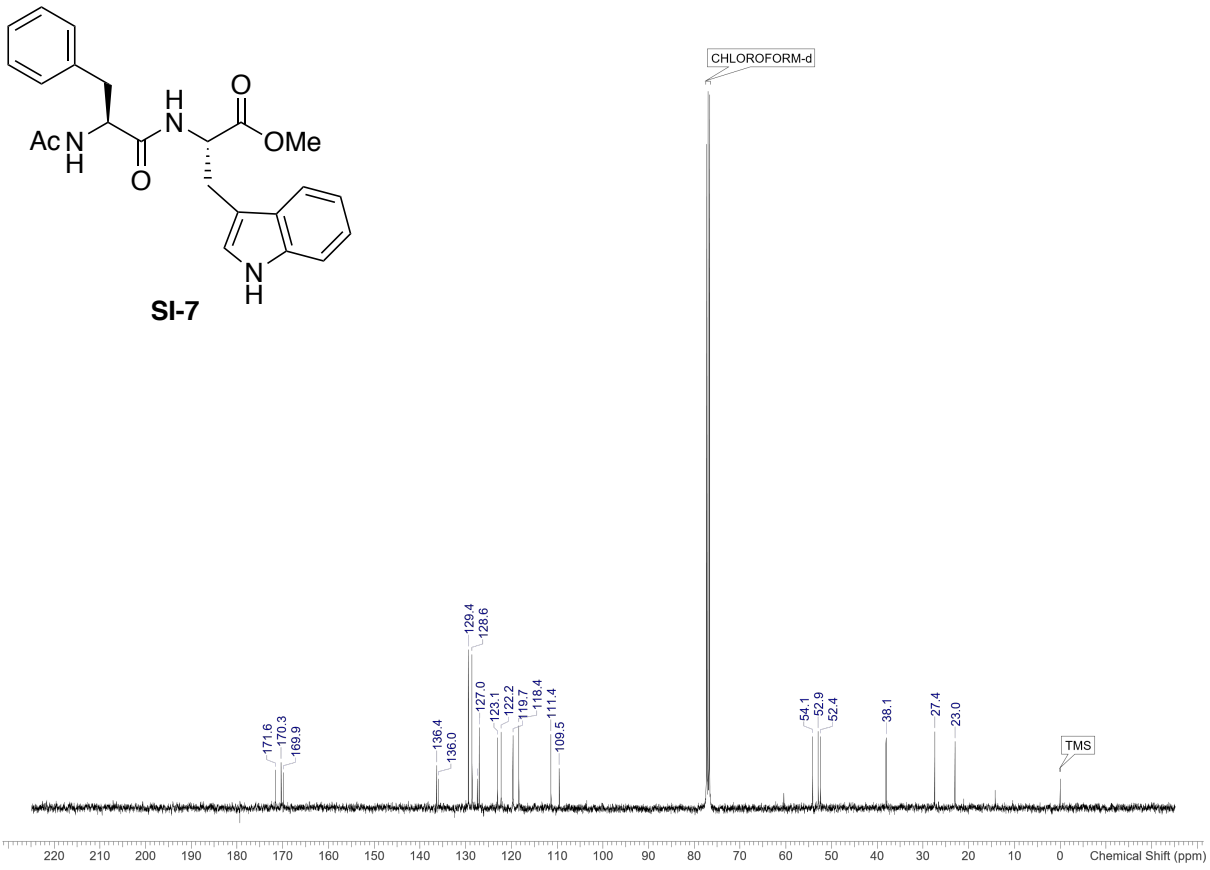
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-6**



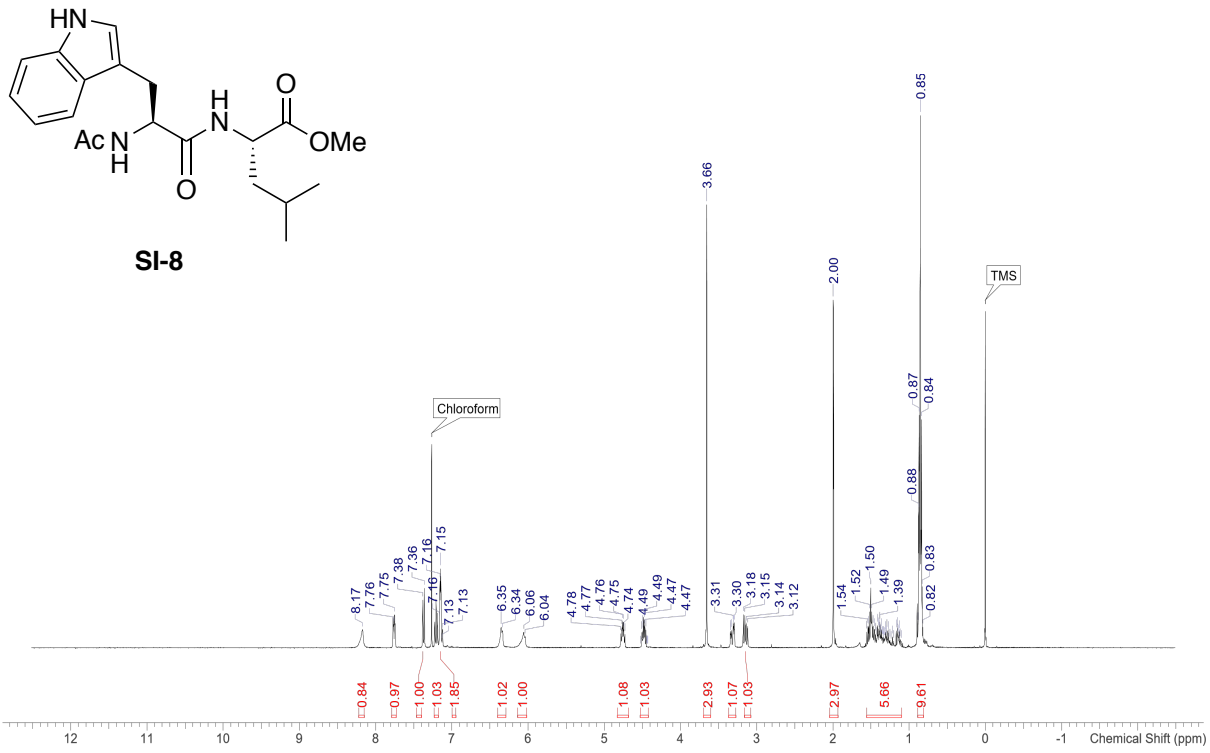
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-7**



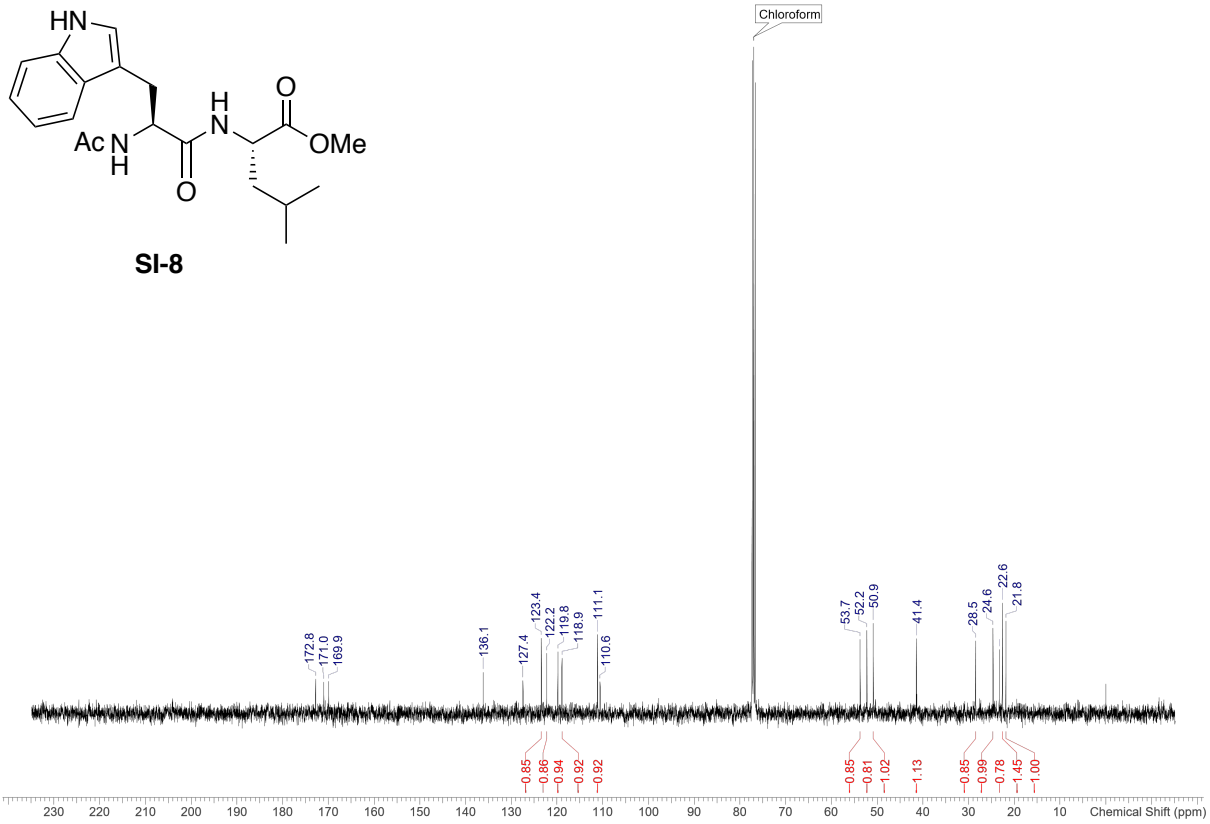
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-7**



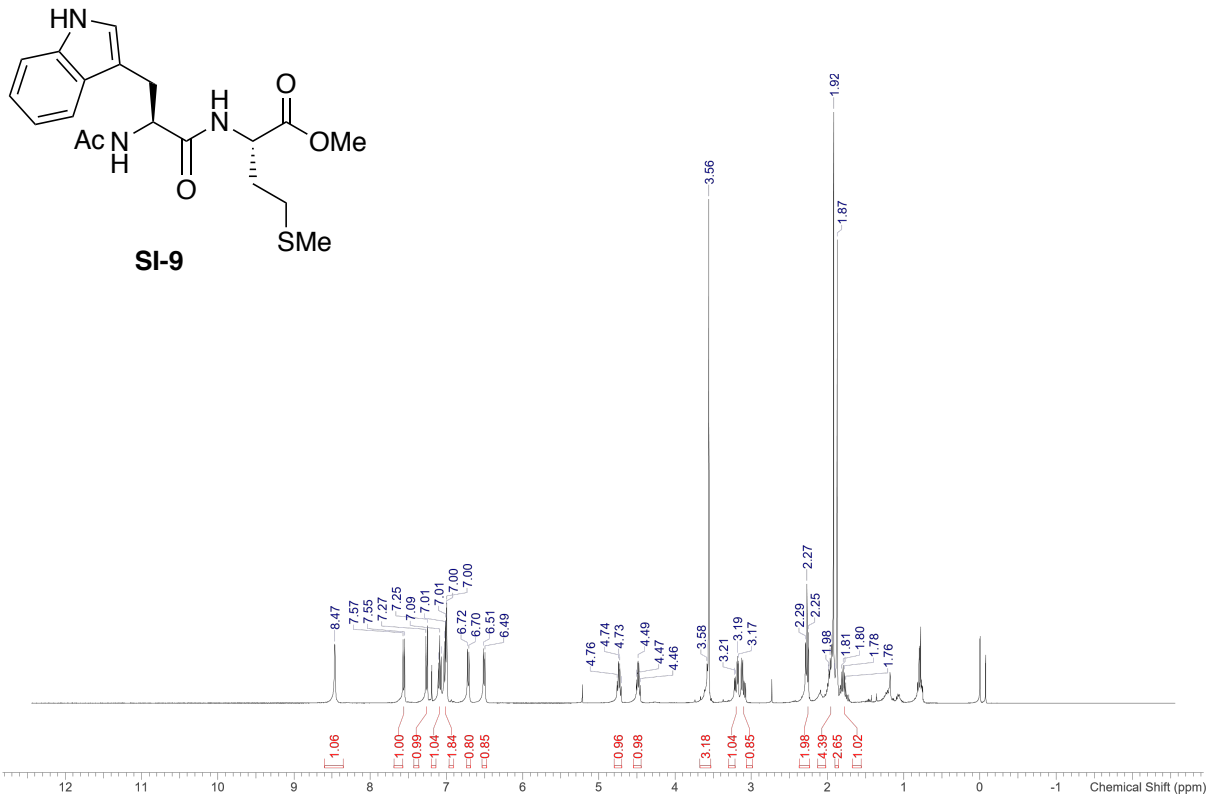
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-8**



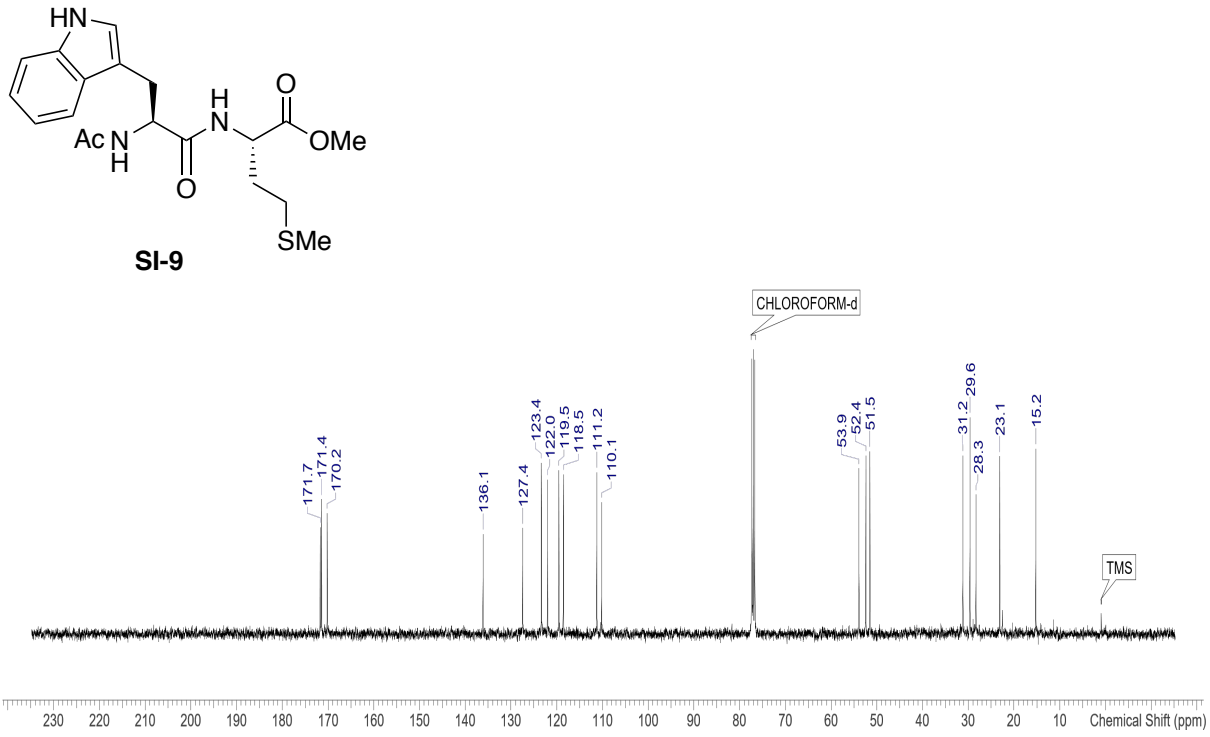
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-8**



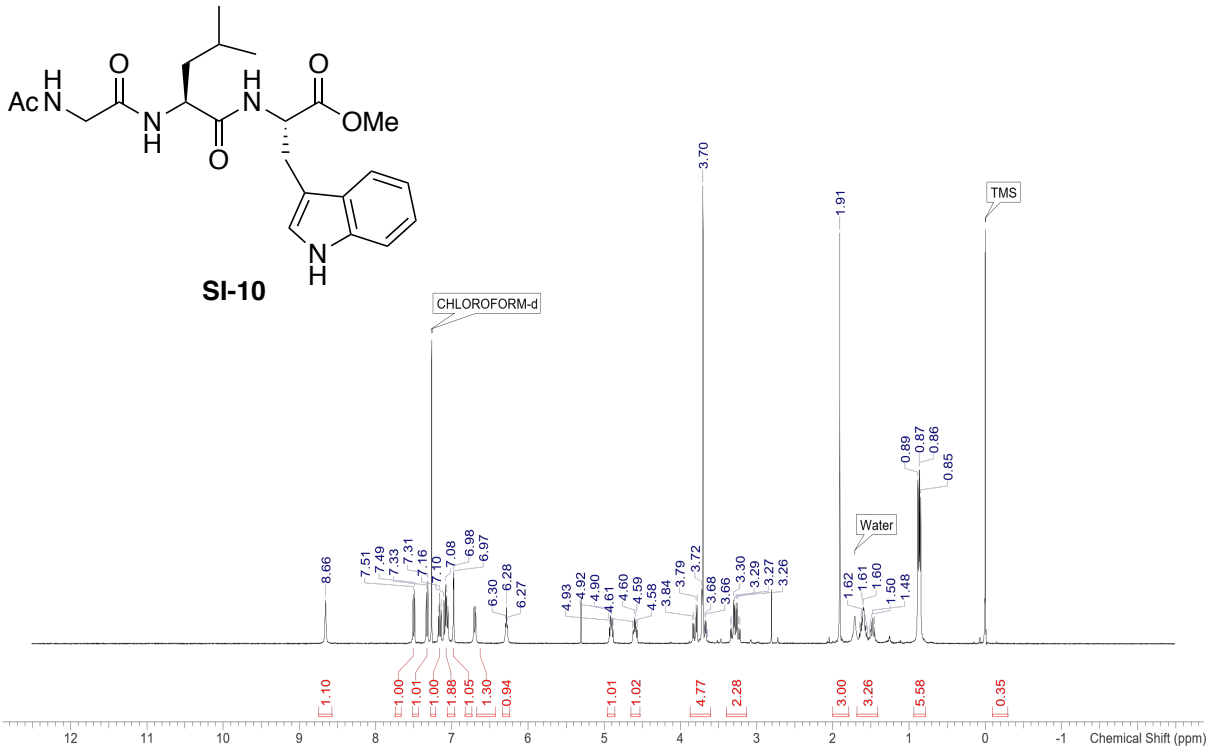
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-9**



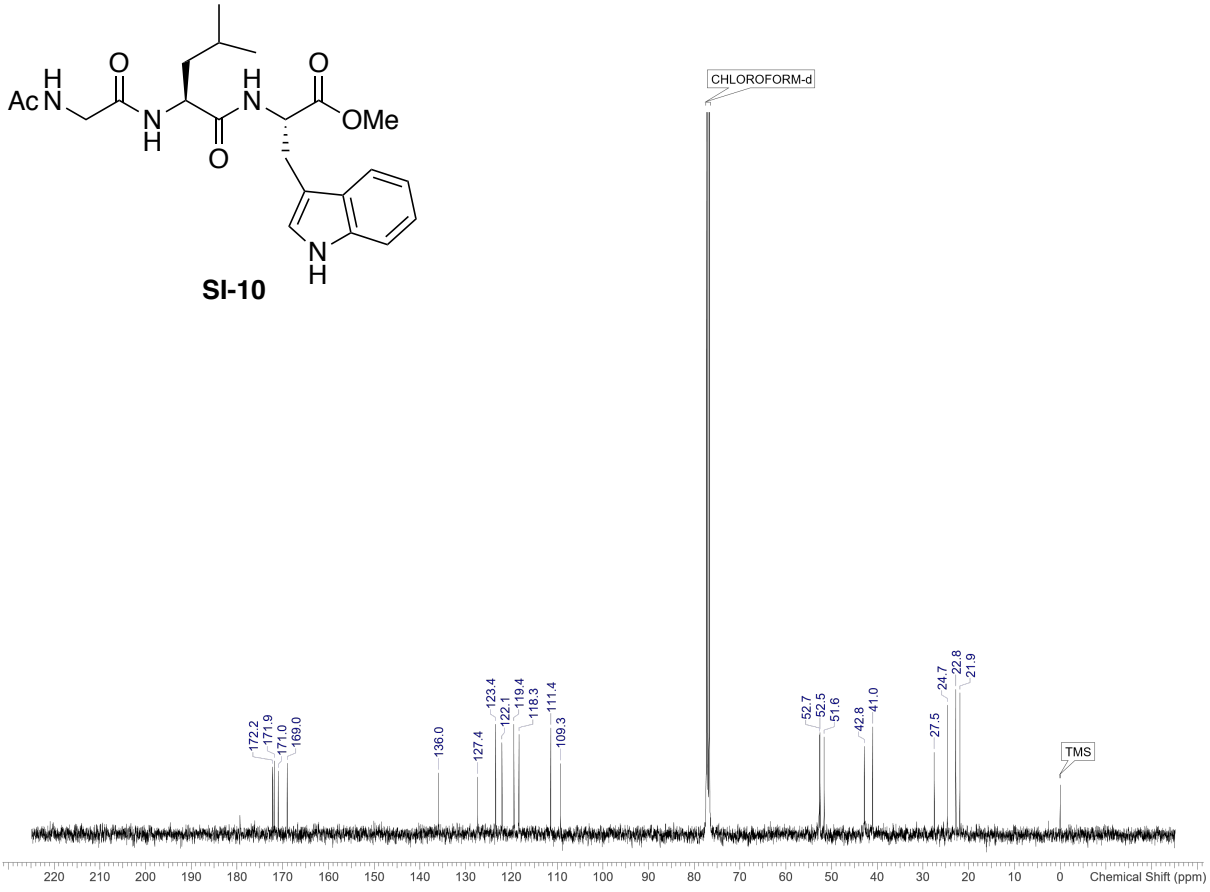
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-9**



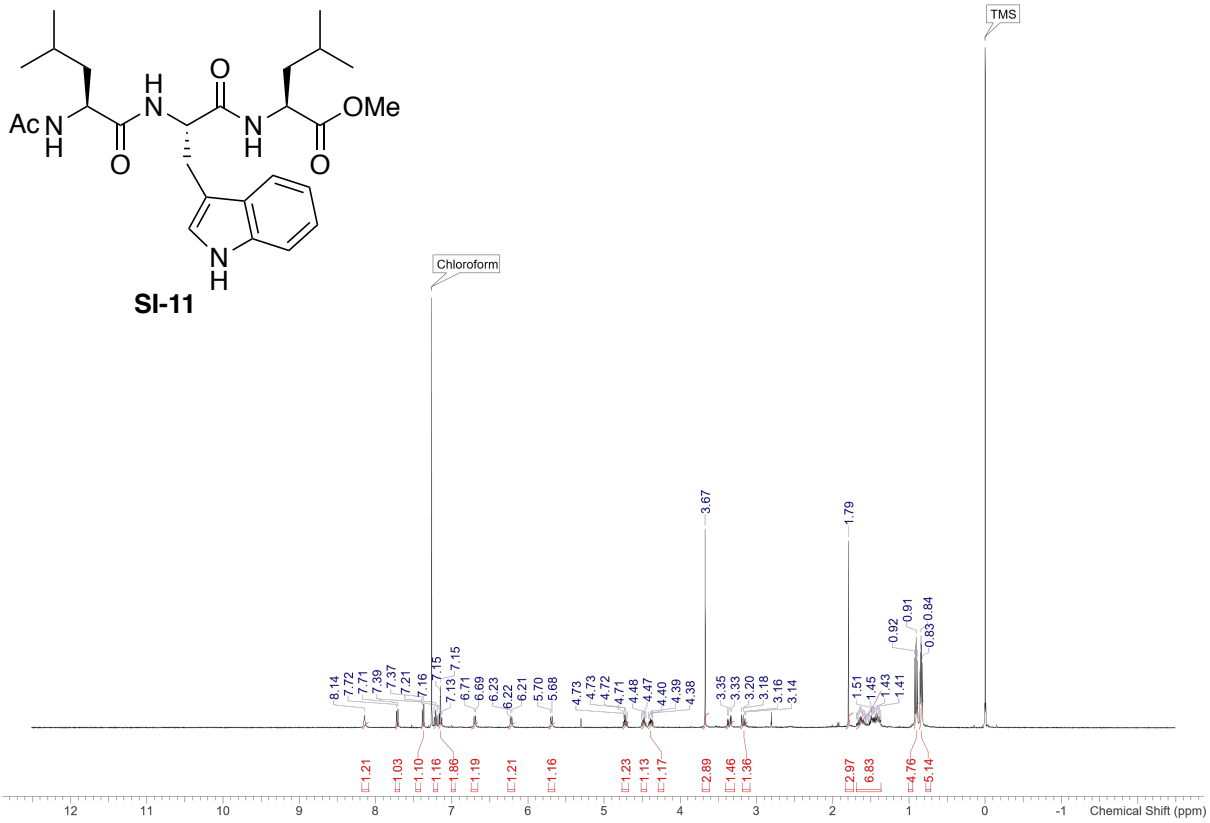
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-10**



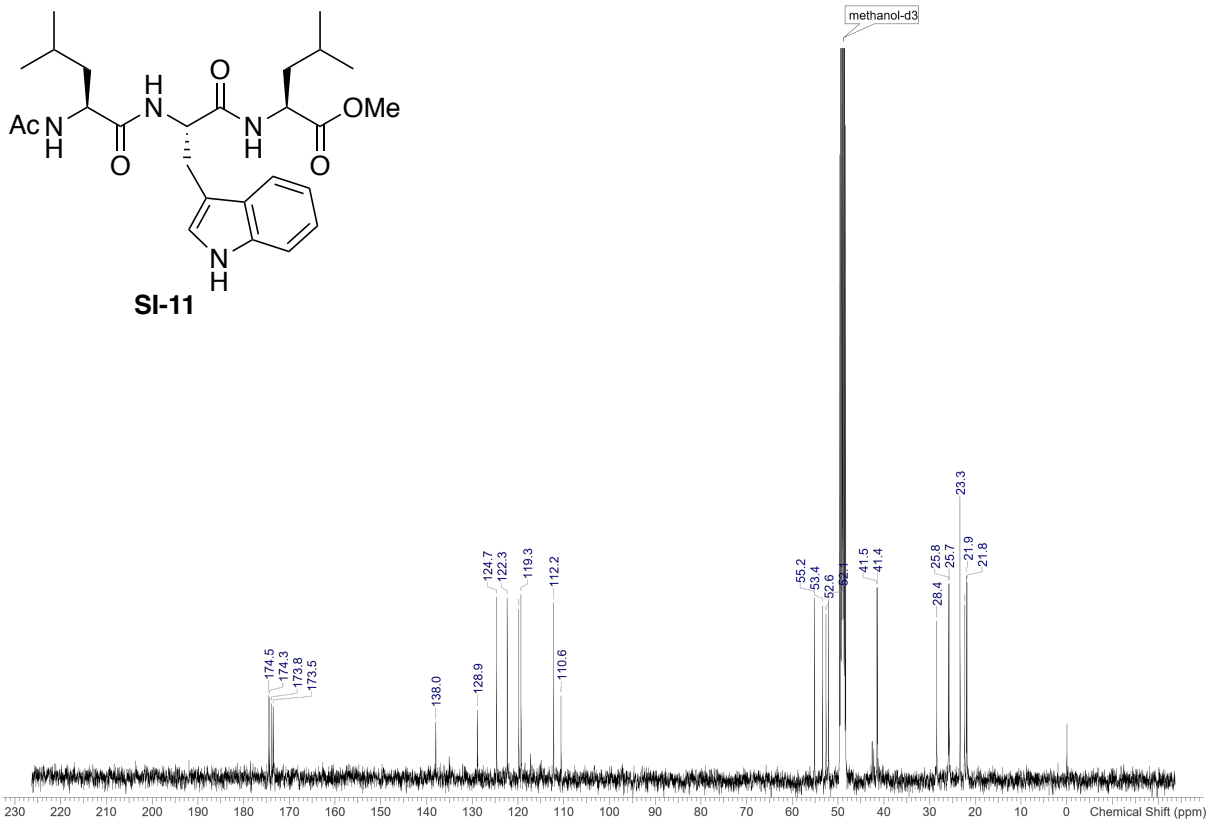
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-10**



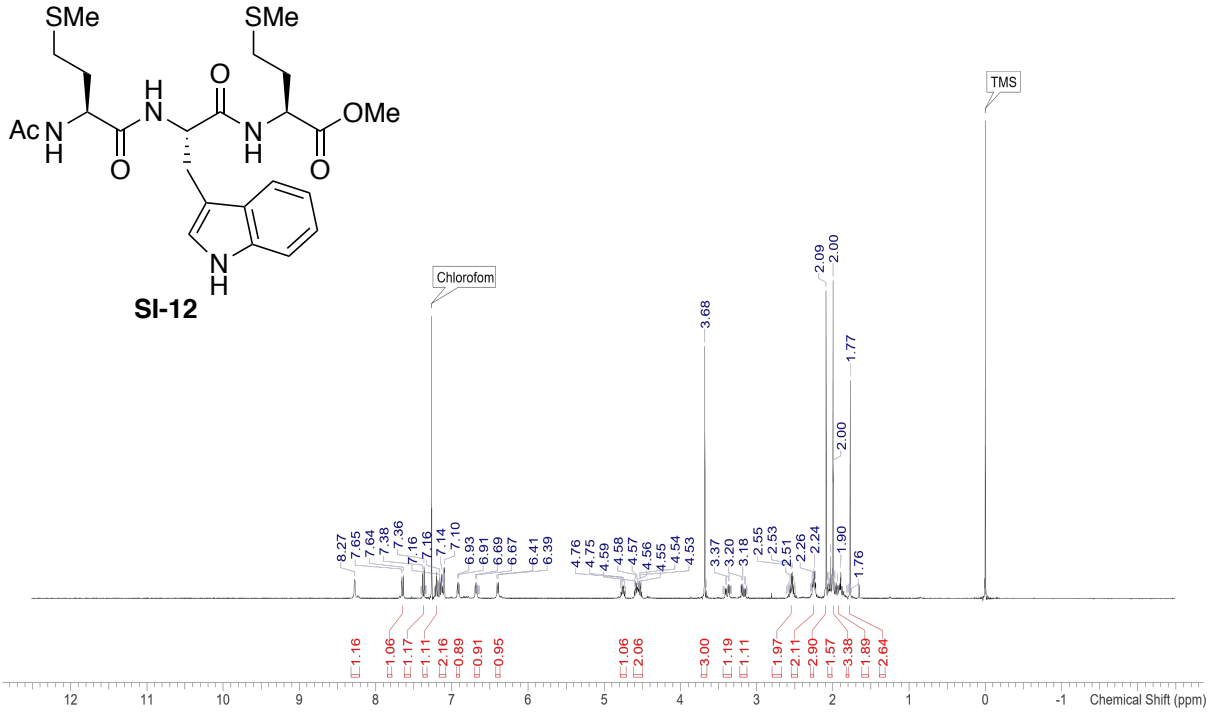
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-11**



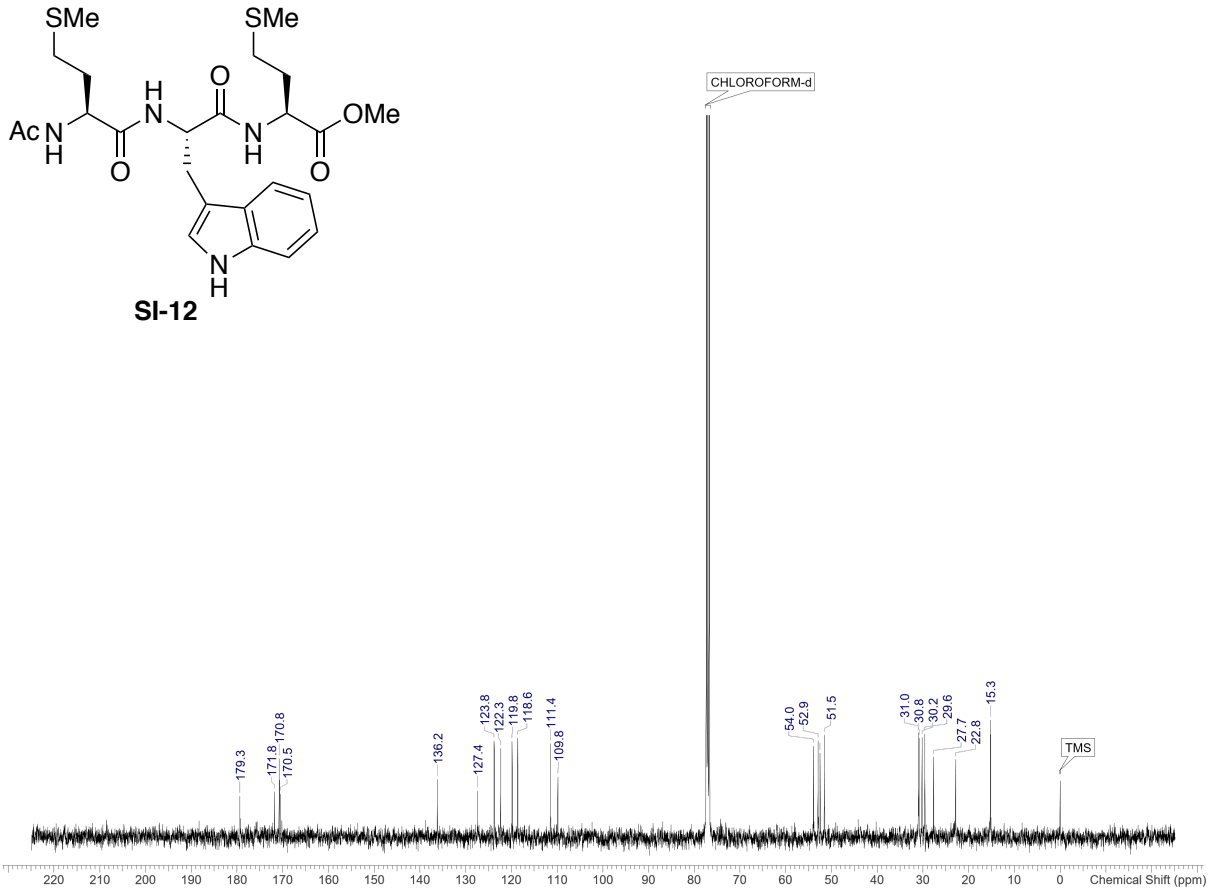
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **SI-11**



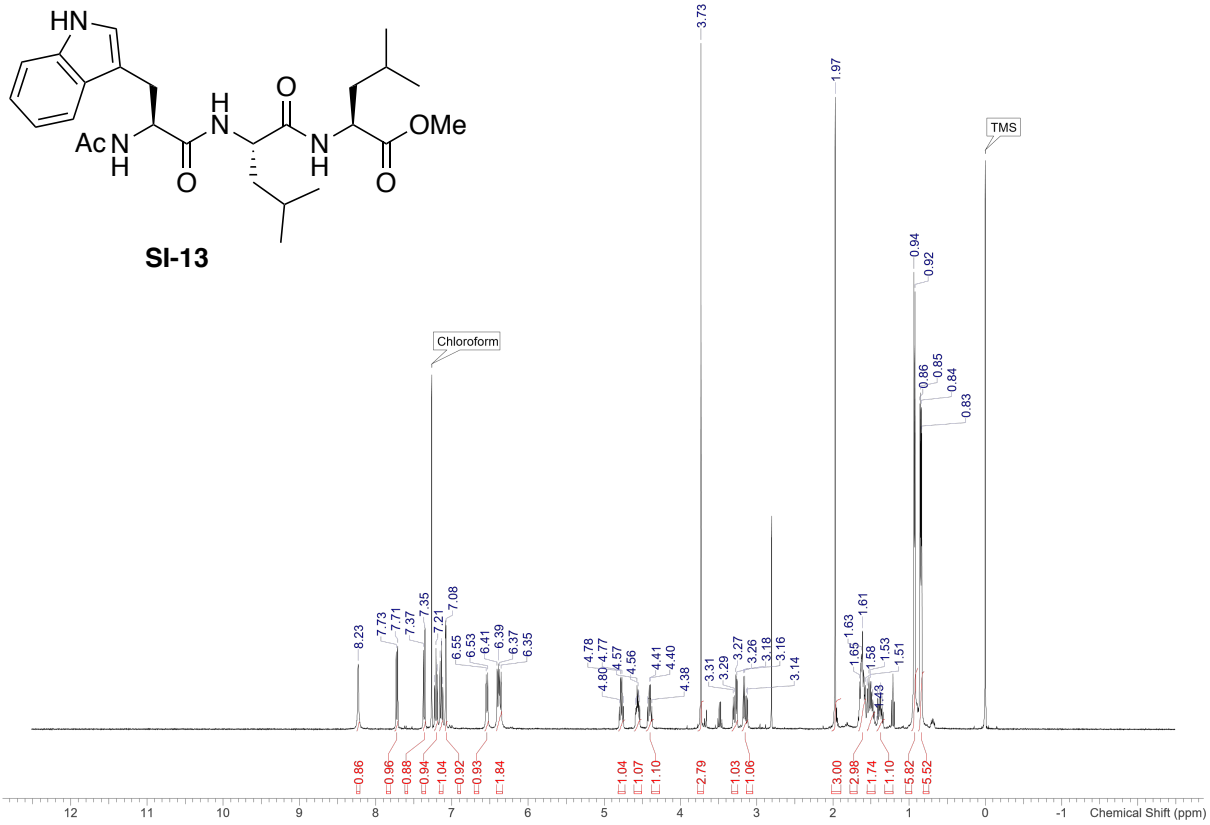
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-12**



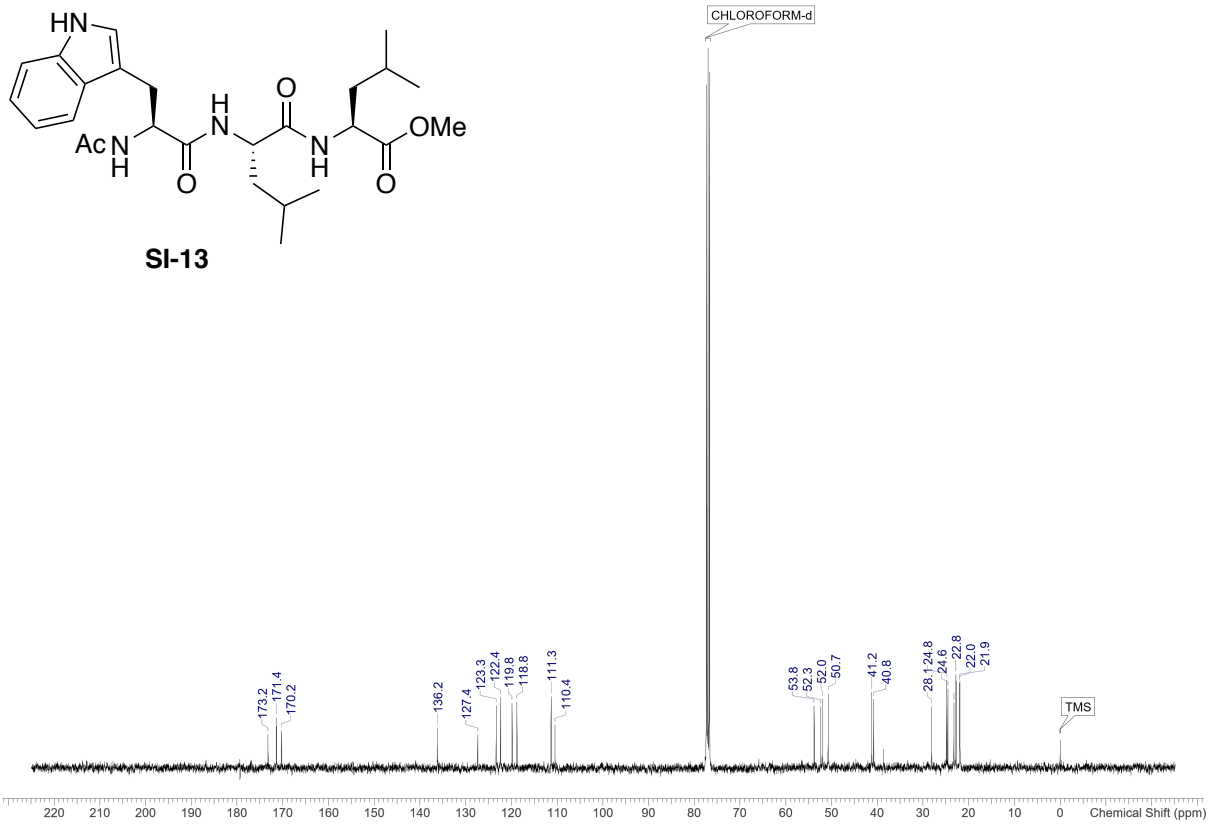
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-12**



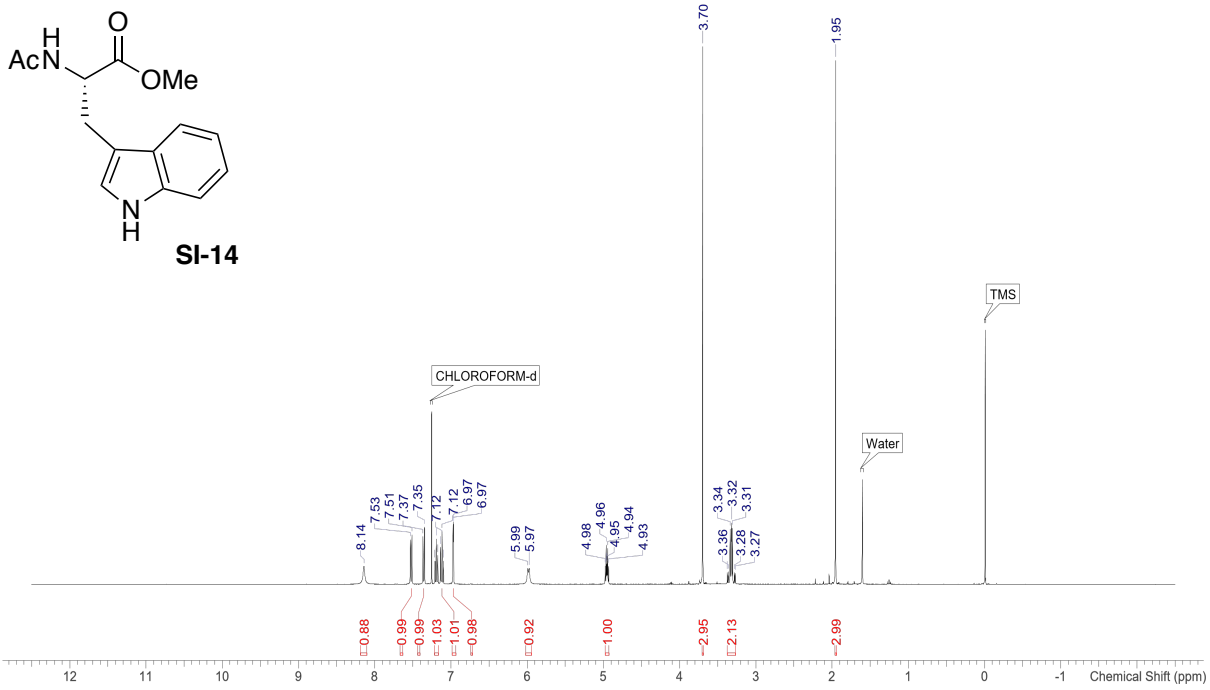
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-13**



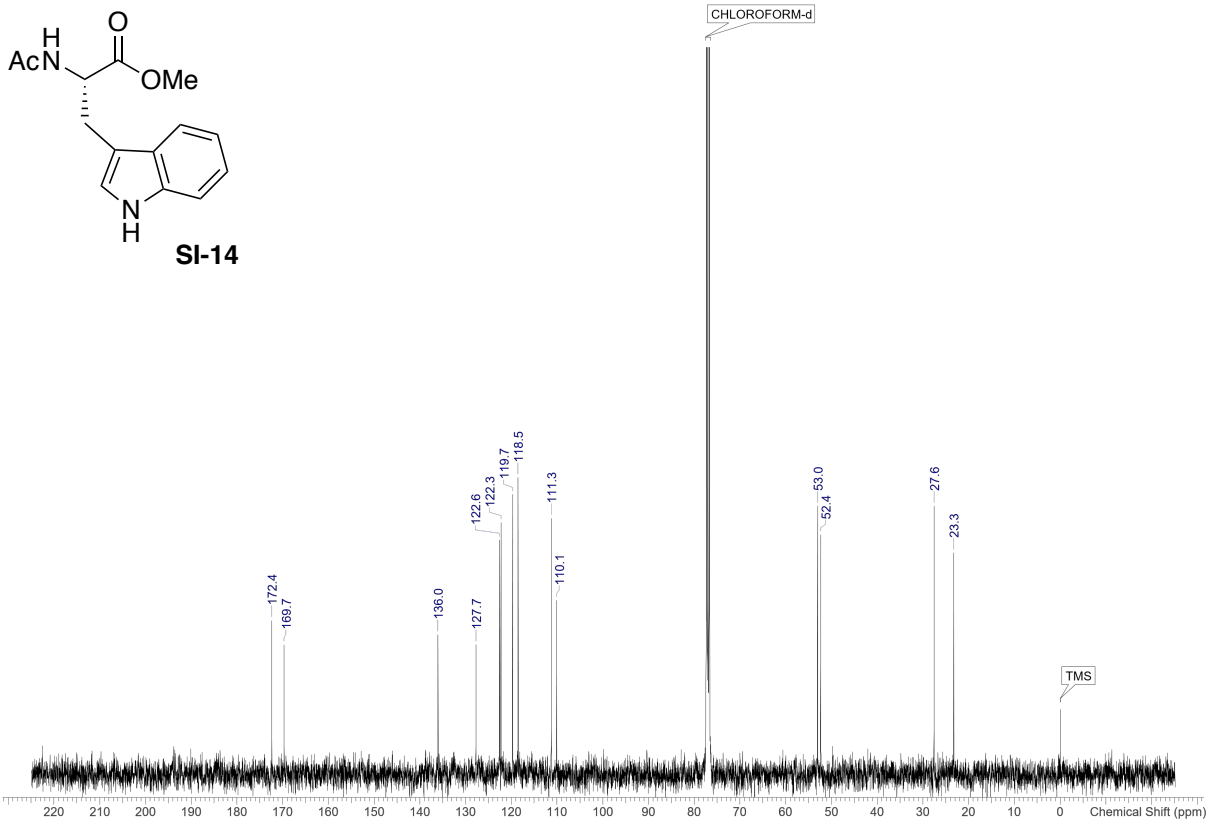
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-13**



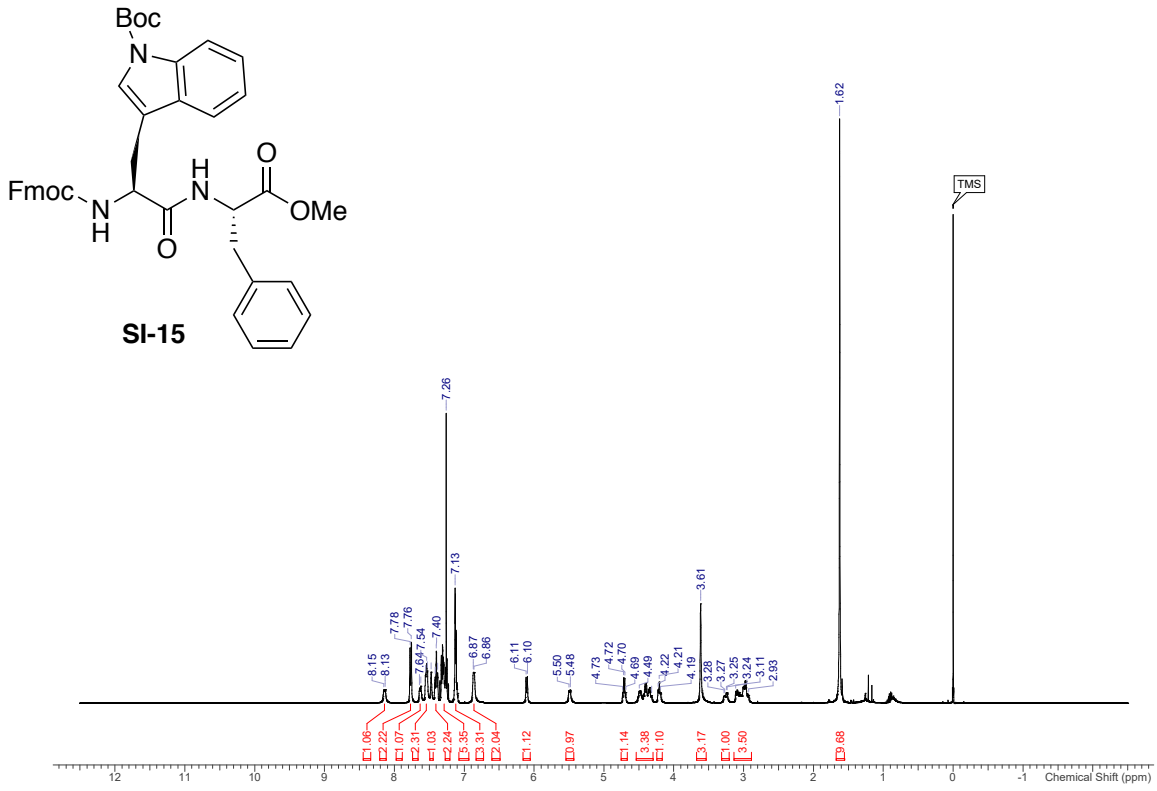
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-14**



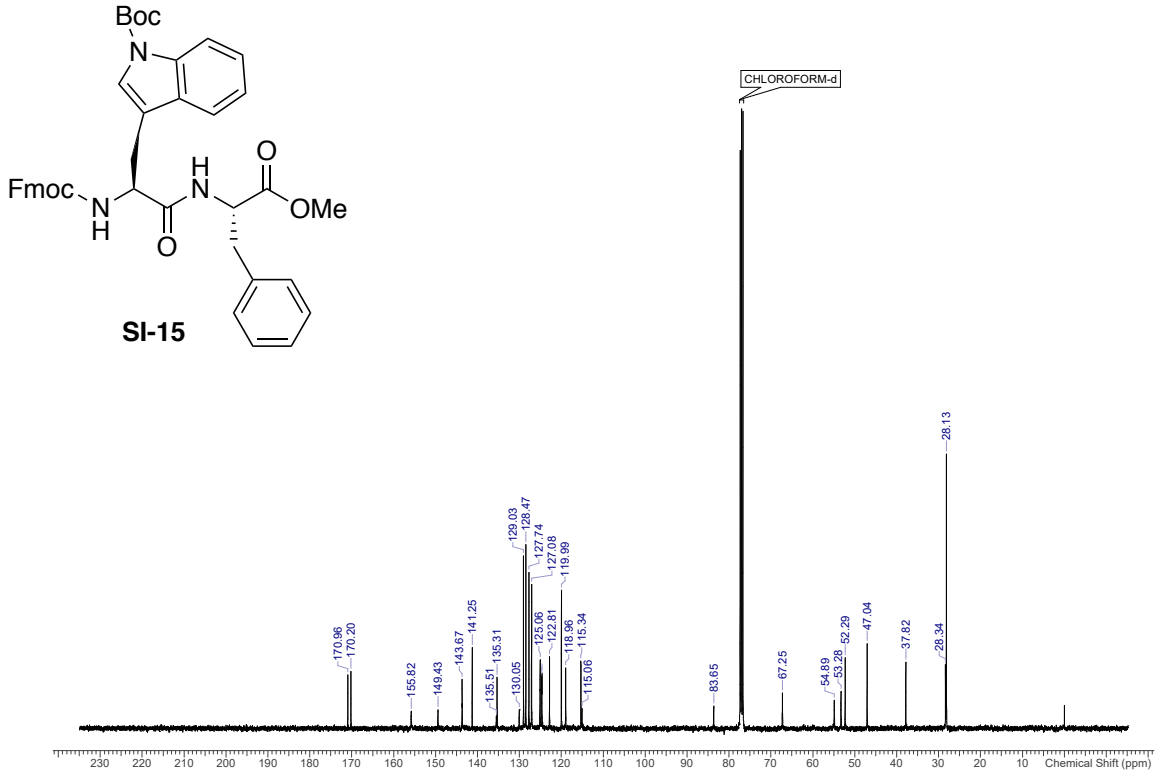
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-14**



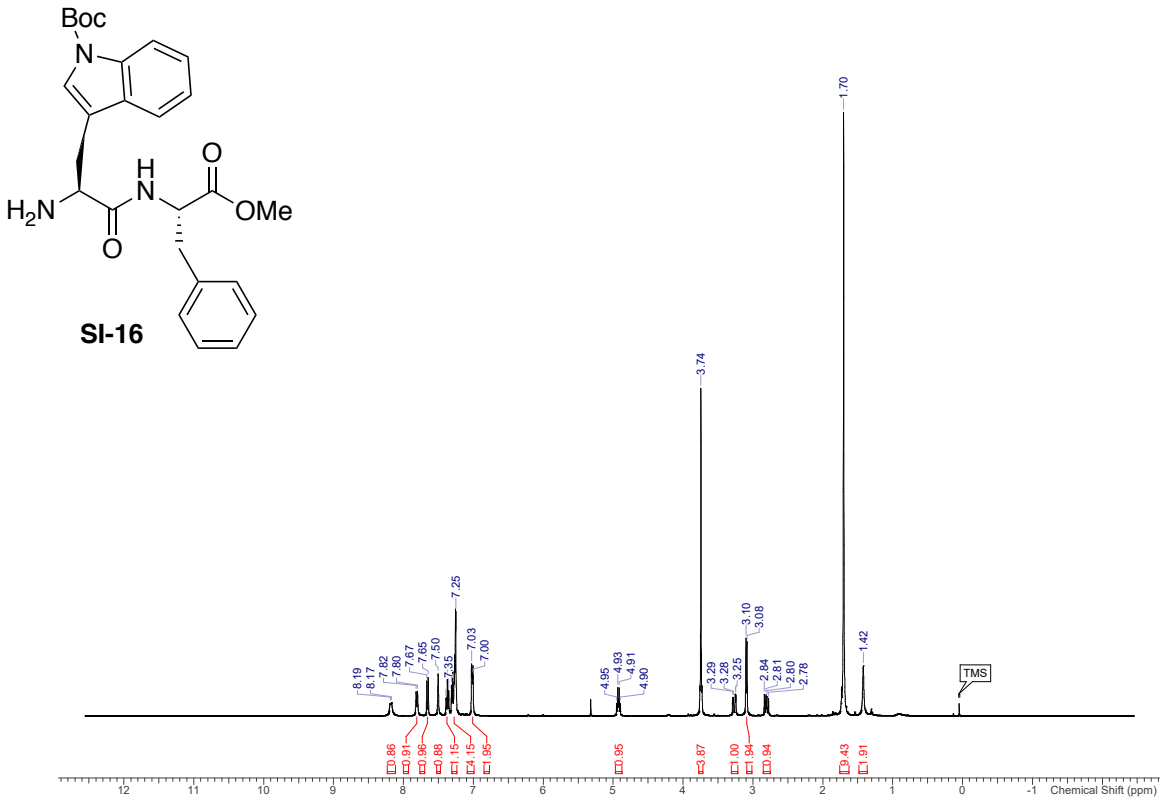
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-15**



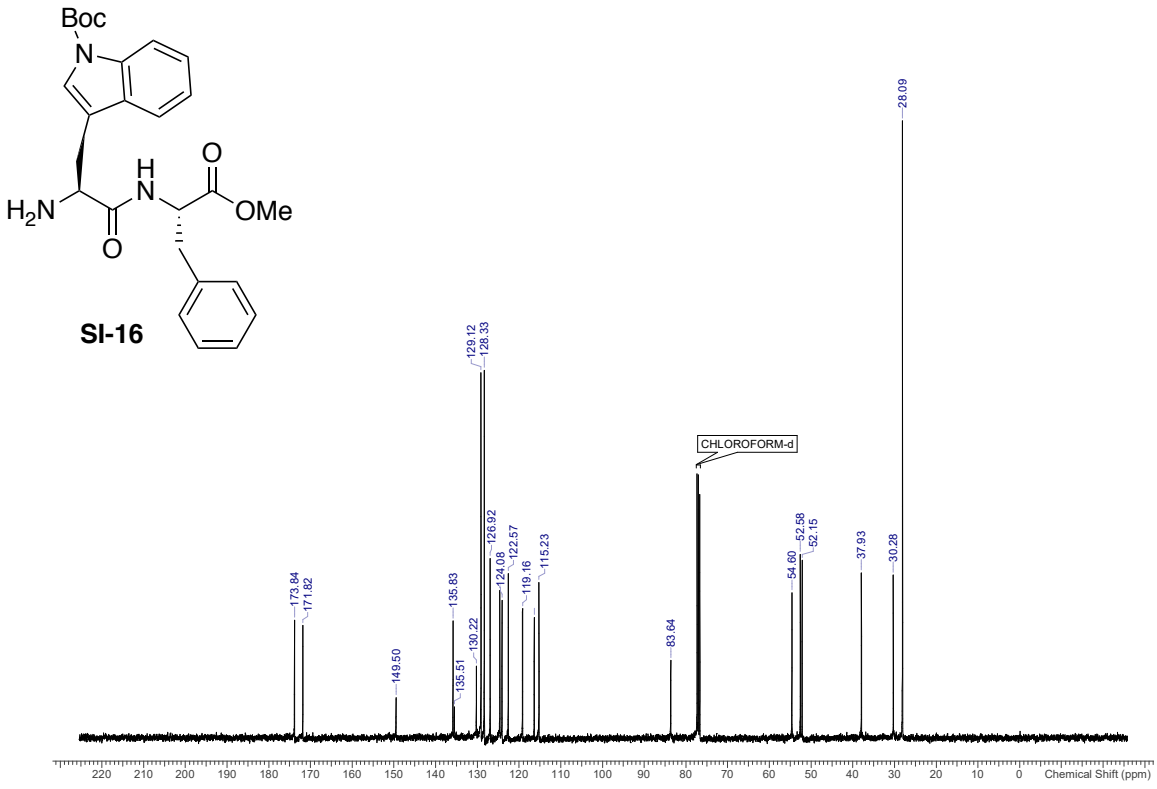
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-15**



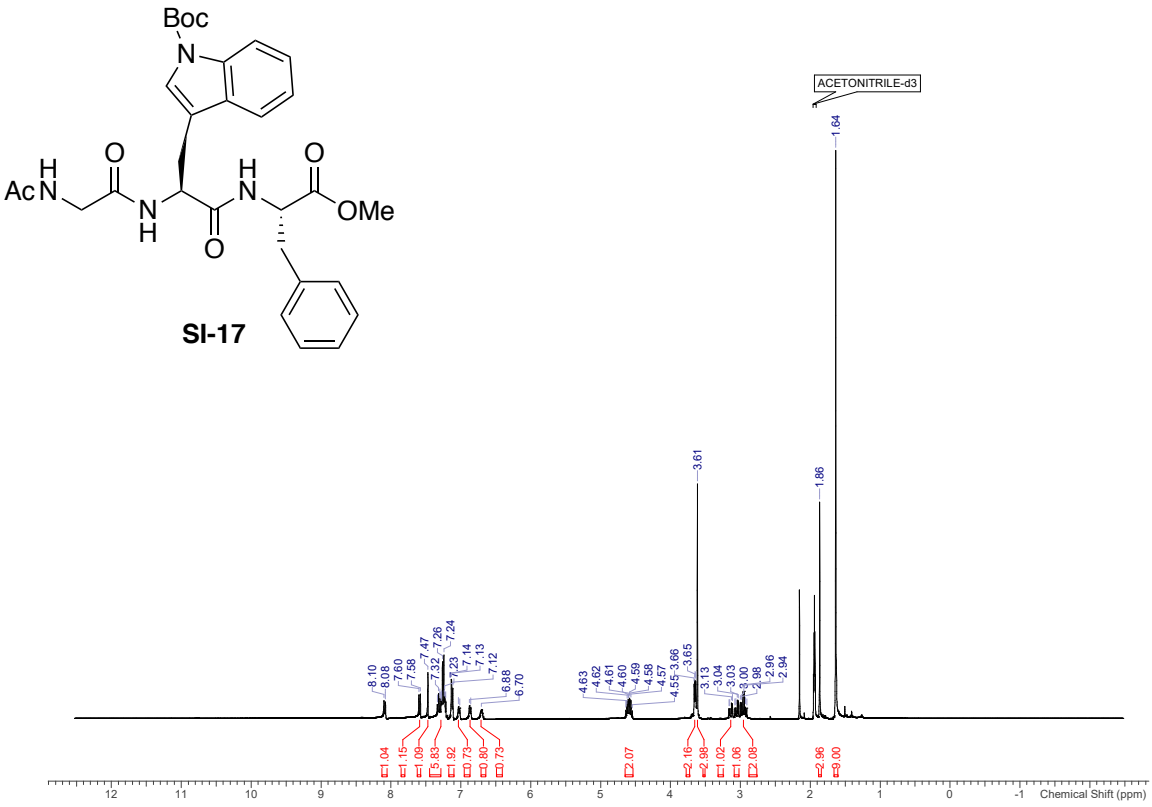
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-16**



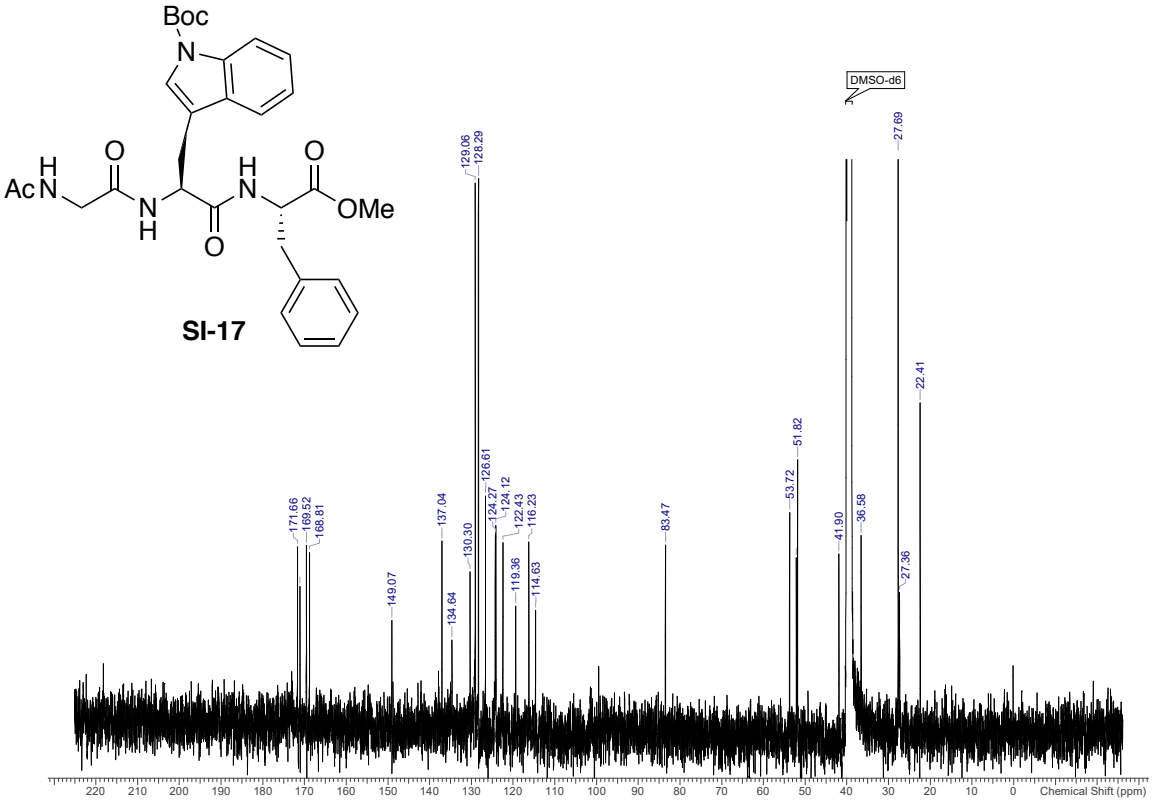
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-16**



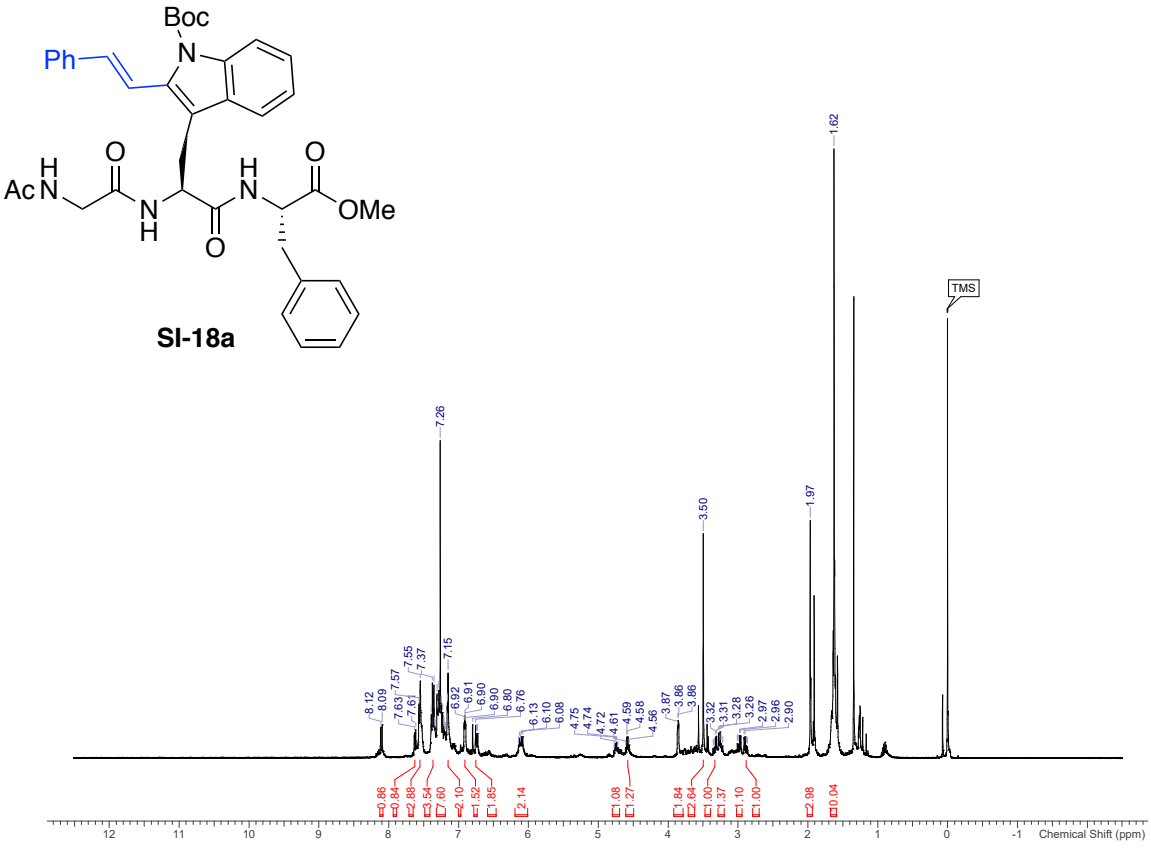
^{1}H NMR spectrum (400 MHz, CD_3CN) of **SI-17**



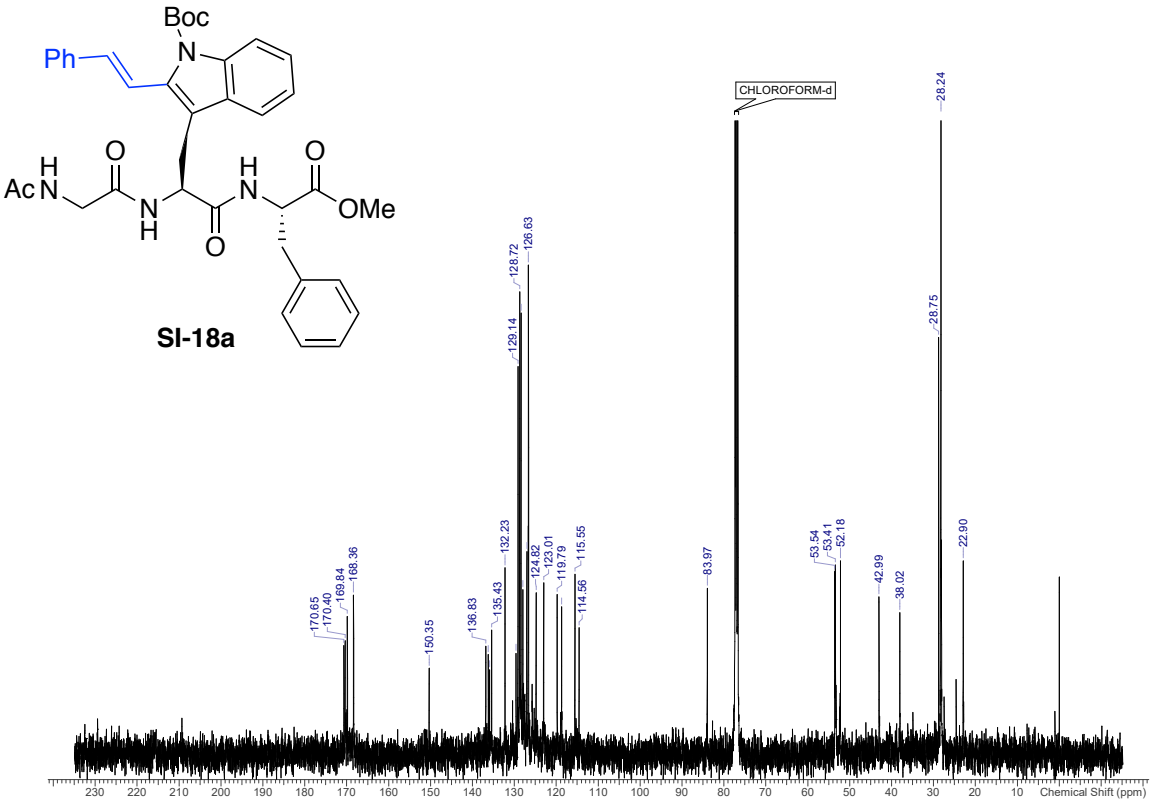
^{13}C{^{1}H} NMR spectrum (100 MHz, D6-DMSO) of **SI-17**



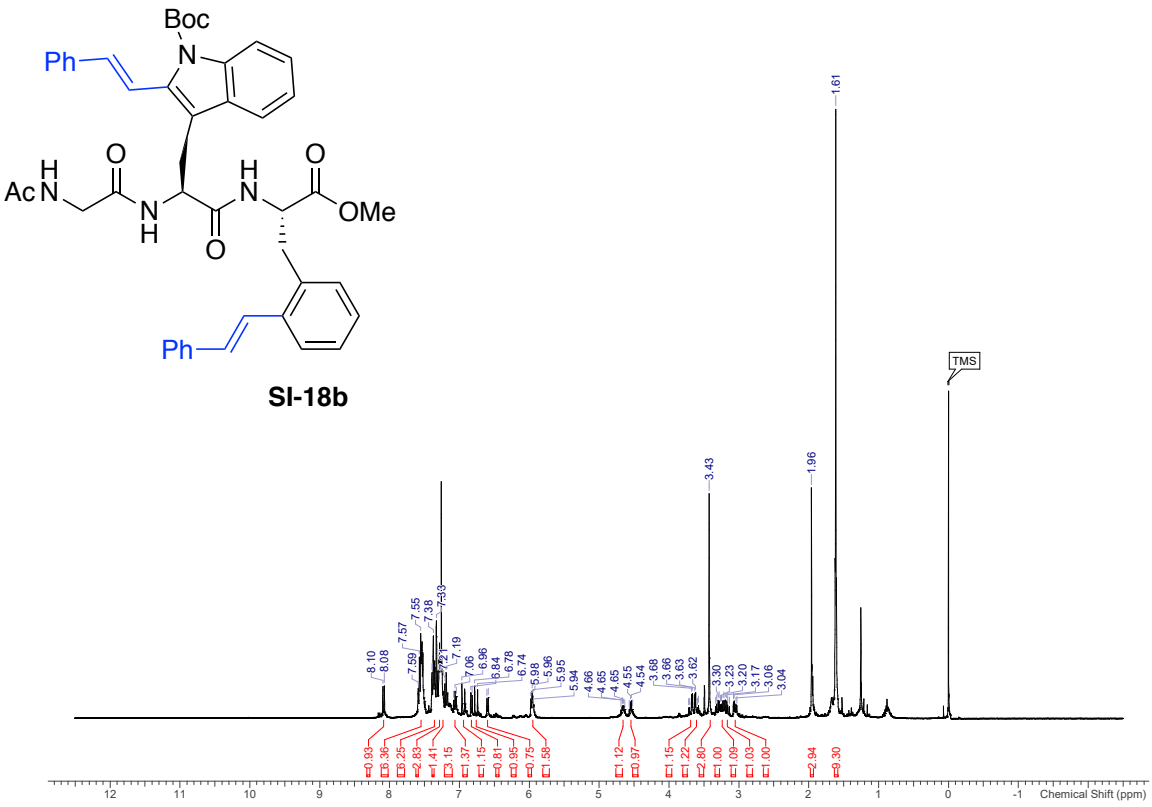
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-18a**



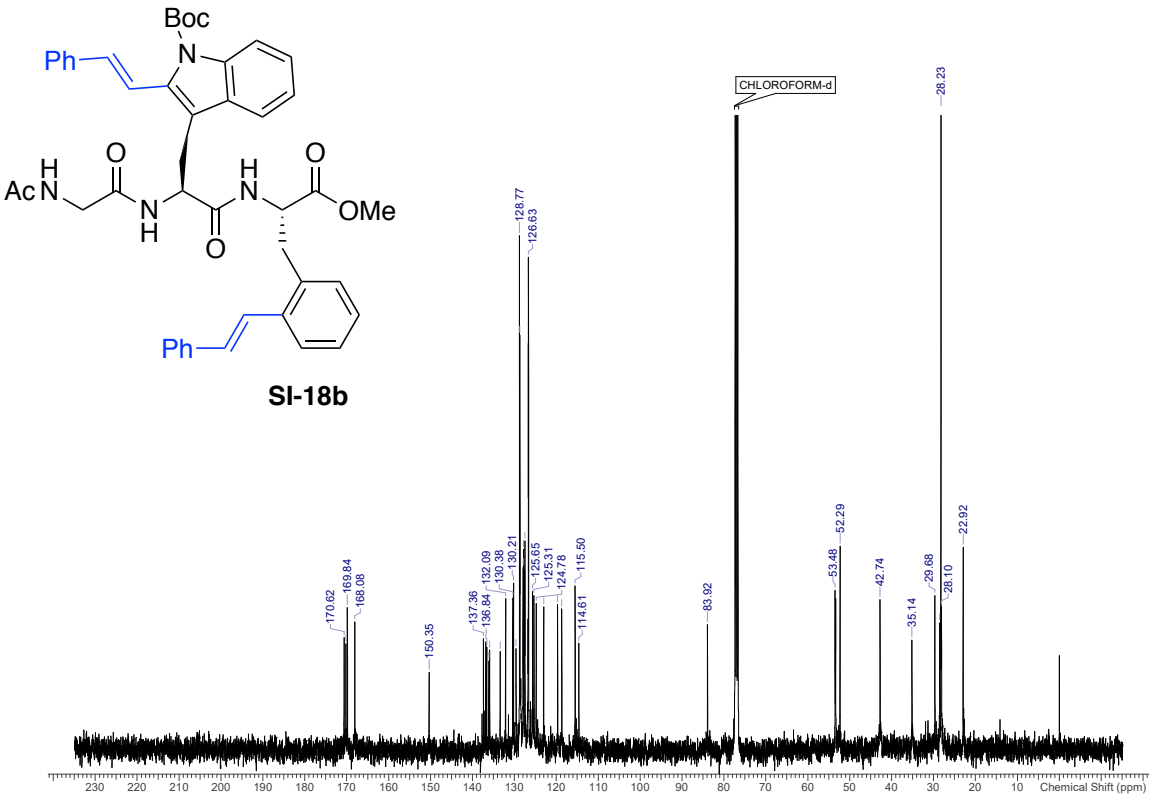
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-18a**



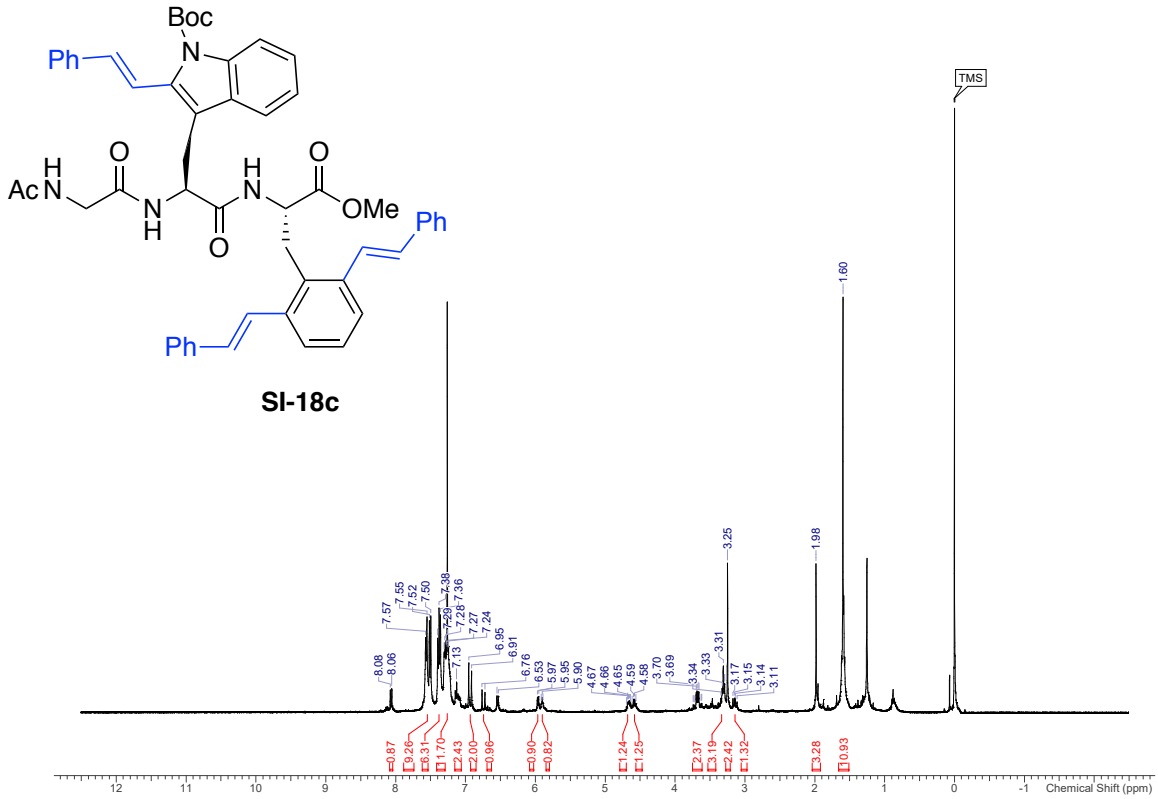
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-18b**



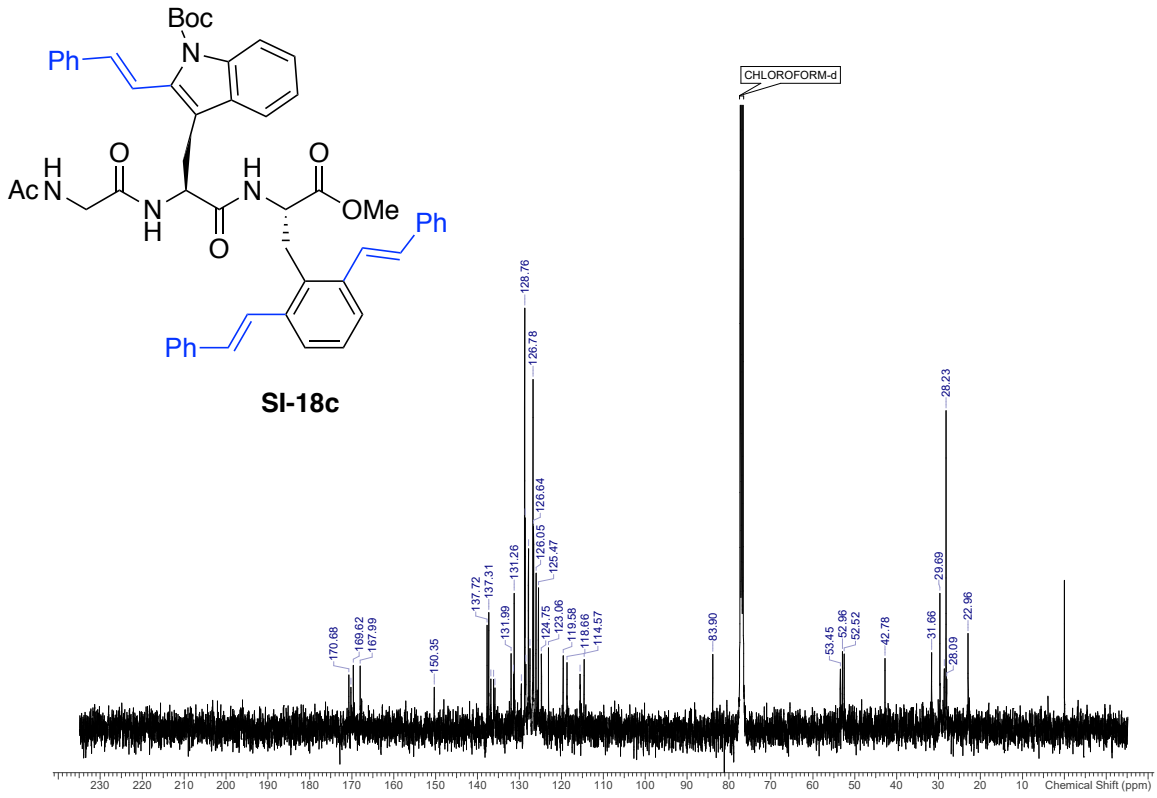
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-18b**



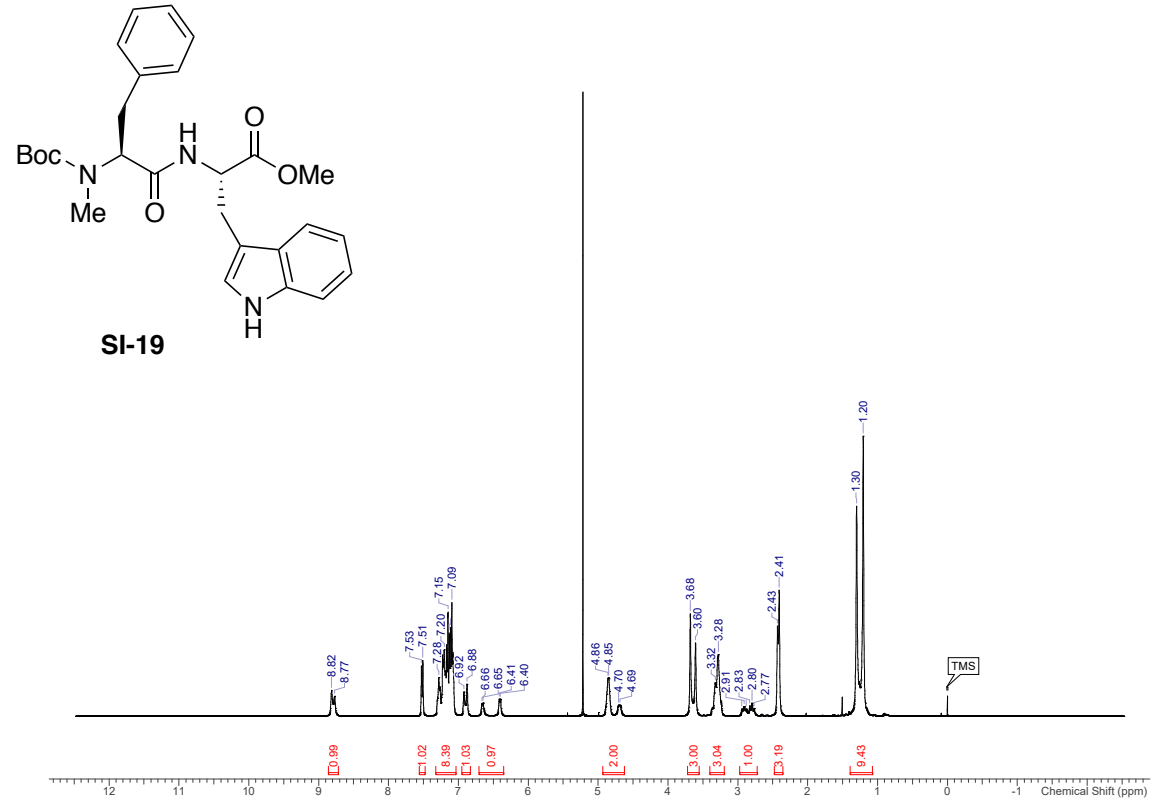
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-18c**



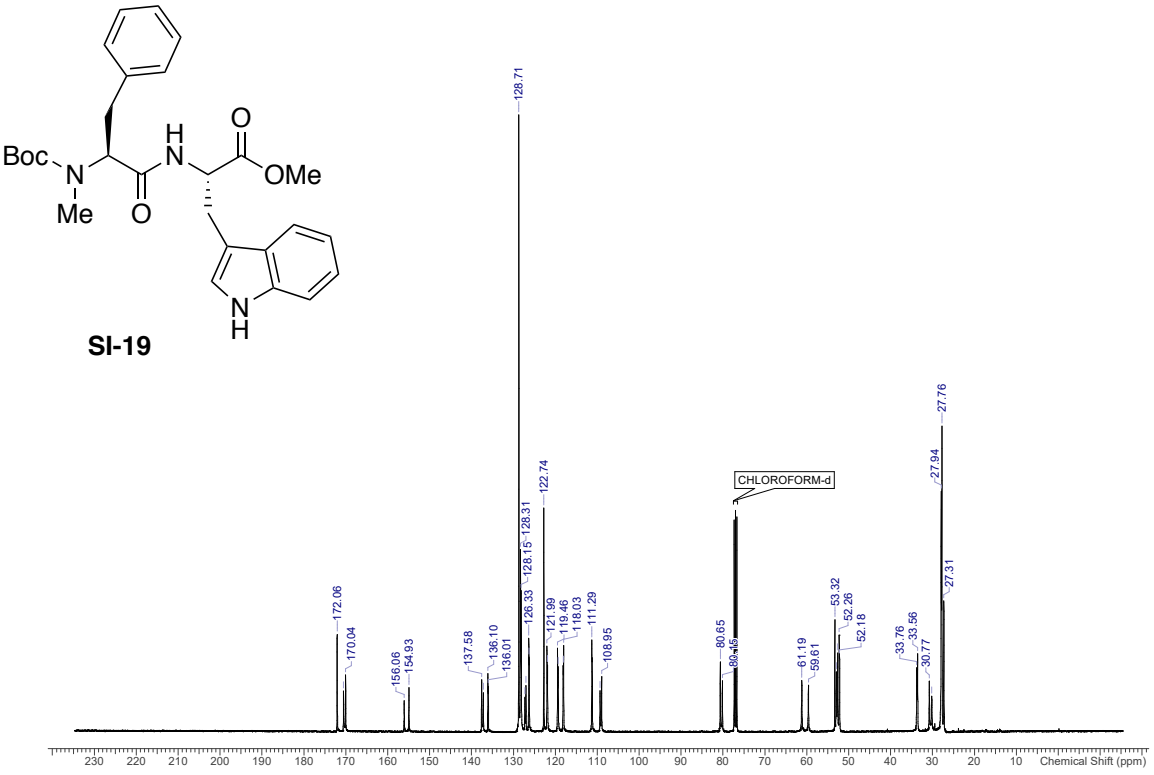
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-18c**



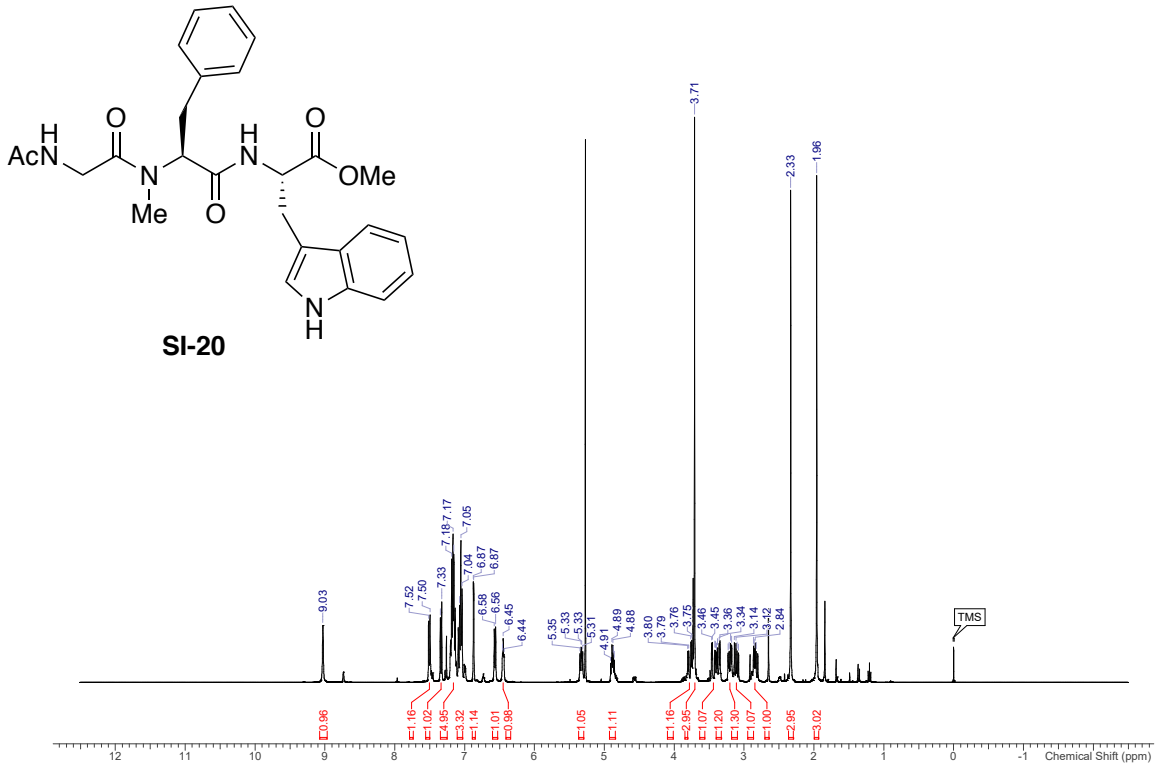
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-19**



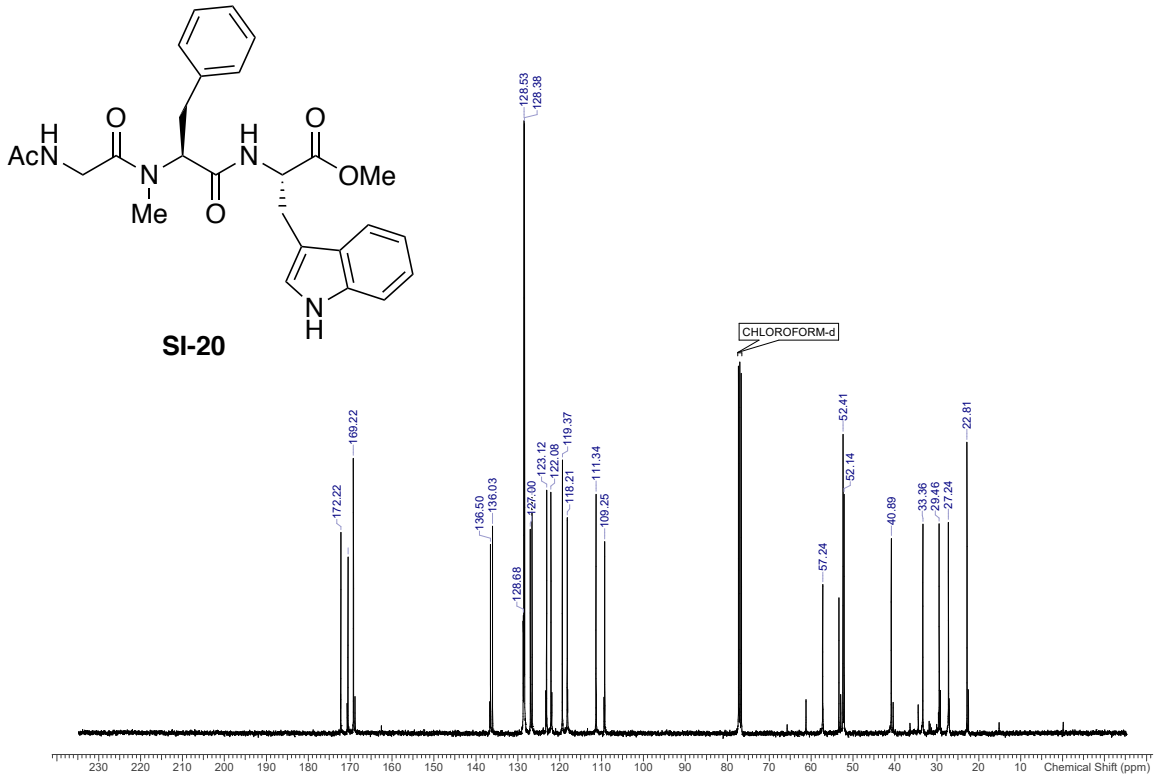
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-19**



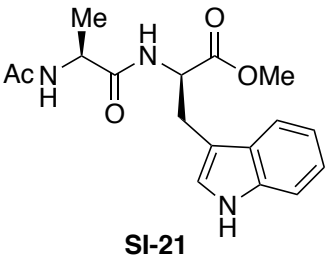
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-20**



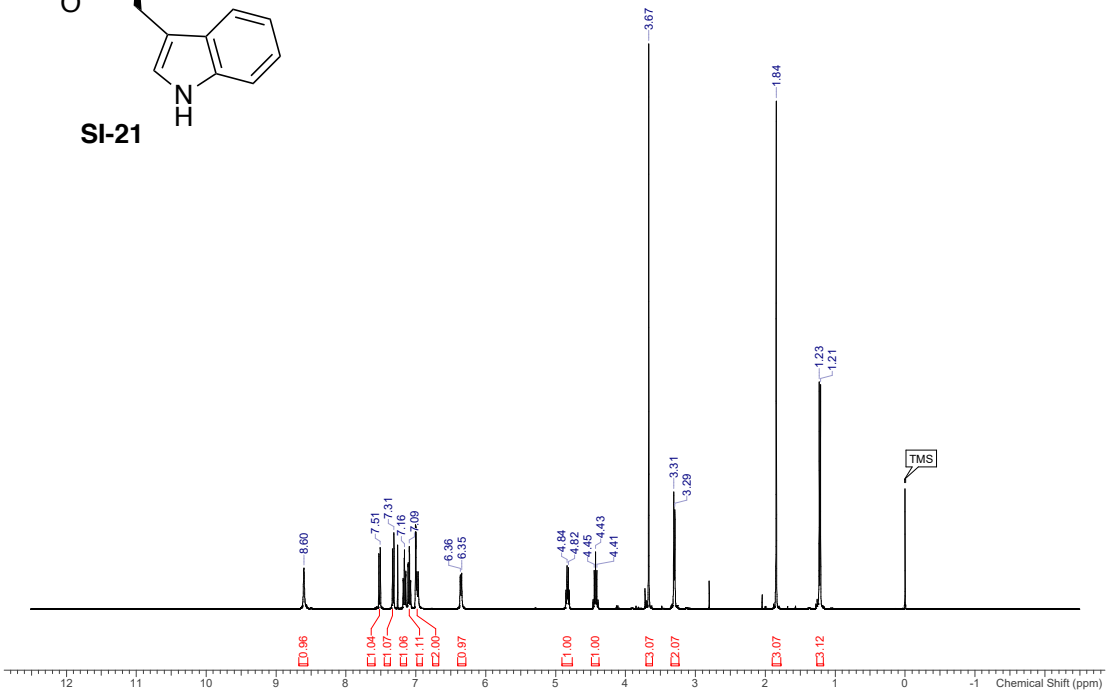
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-20**



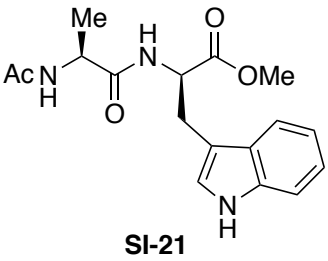
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-21**



SI-21

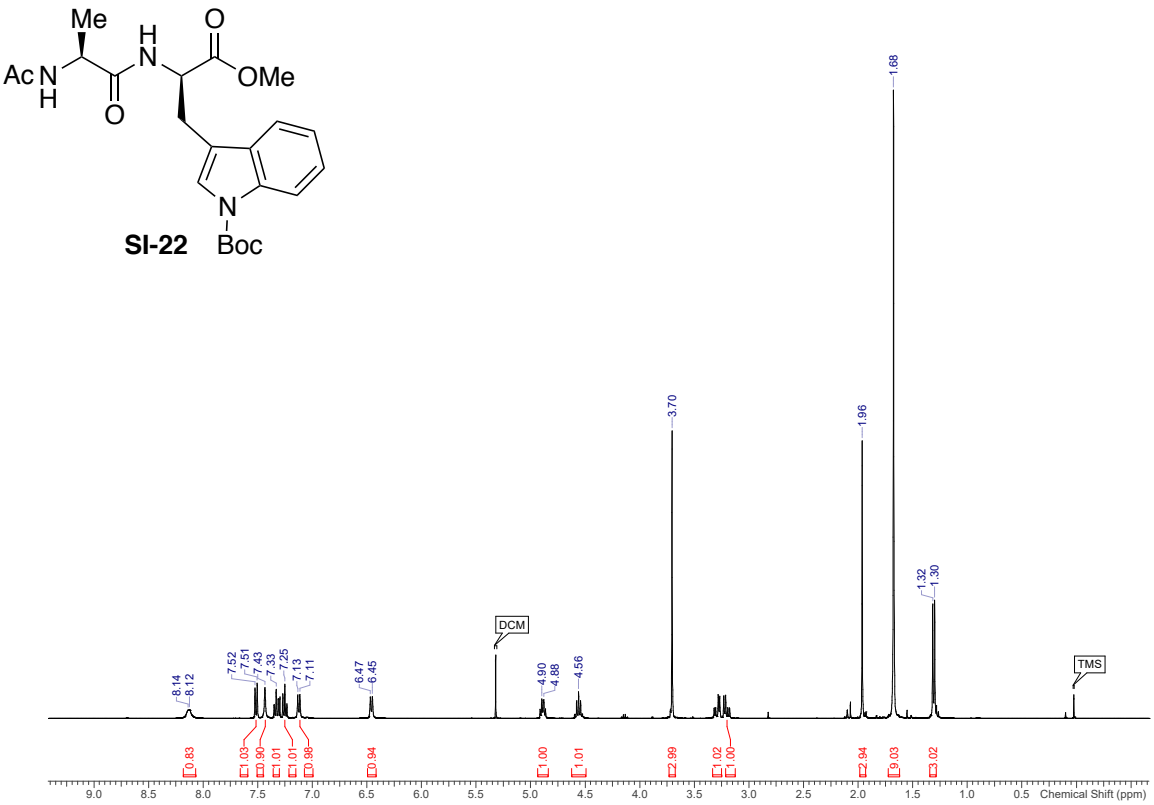


^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-21**

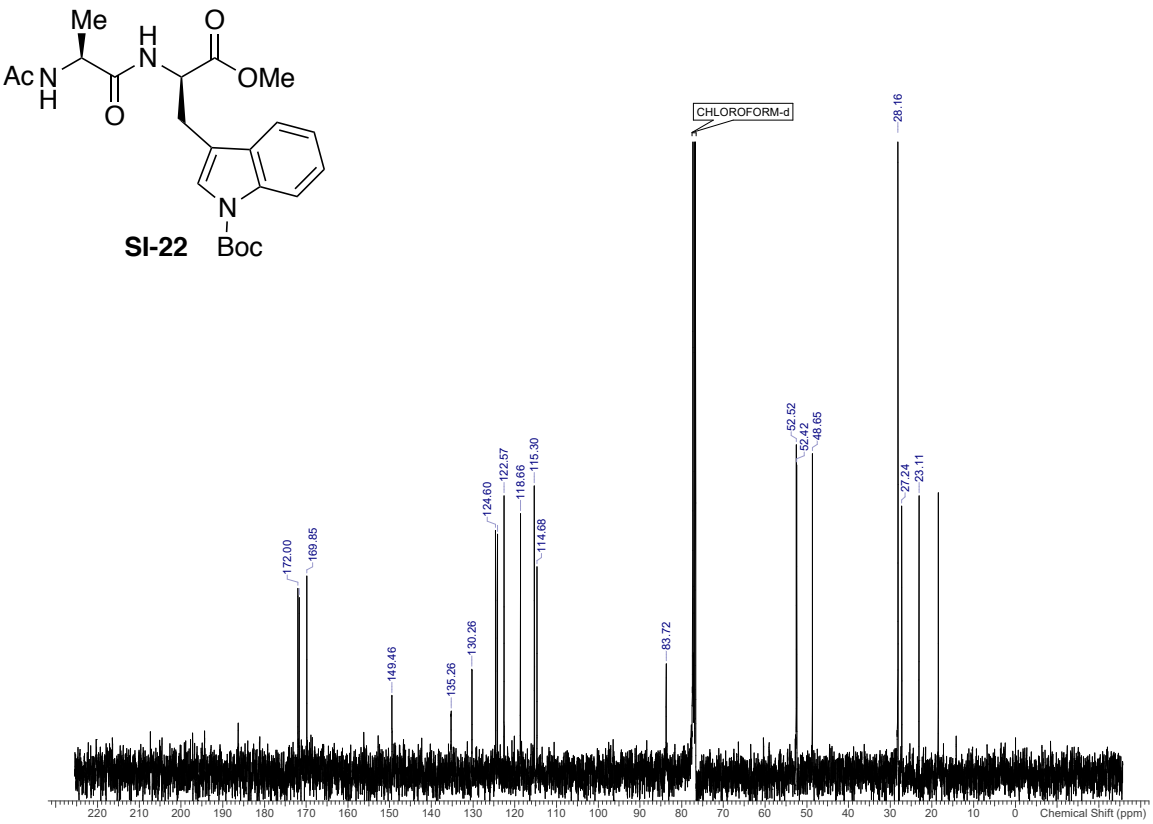


SI-21

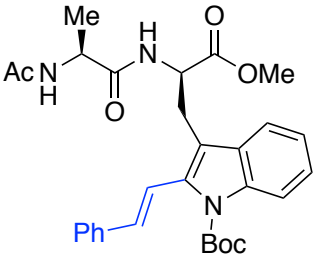
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-22**



^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-22**

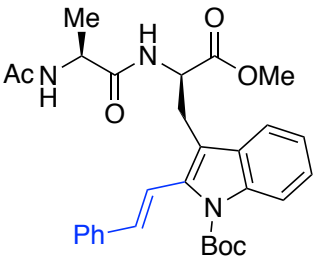


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **SI-23**



SI-23

^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **SI-23**



SI-23