Post-synthetic modification of phenylalanine containing peptides by C-H functionalization.

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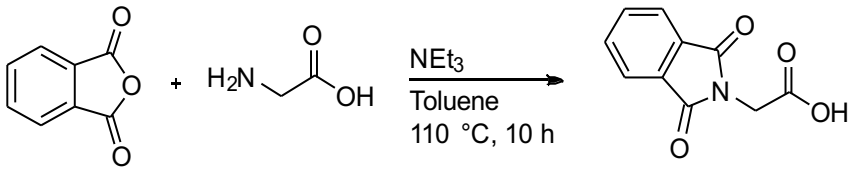
1. General Experimental Information

All manipulations were performed in oven-dried glassware in an atmosphere of air unless stated. Ag_2CO_3 and AgOPiv were prepared according to literature procedures.[S1,S2] All other 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 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.

2. Detailed experimental procedures and analytical data

2.1. Synthesis of protected amino acids

N-Phthaloyl glycine (Phth-Gly-OH)



Phth-Gly-OH

Phthalic anhydride (2.000 g, 13.50 mmol) and glycine (0.780 g, 10.39 mmol) were slurried in toluene before the addition of triethylamine (1.88 mL, 13.50 mmol). The resulting suspension was refluxed under Dean-Stark conditions for 10 h. After allowing the mixture to cool to room temperature, the toluene was removed by rotary evaporation to give a crude oil. The oil was suspended in water and acidified using conc. HCl(aq.) (3 mL) to give a white solid that was isolated by filtration and dried on the filter pad to afford off-white needles of Phth-Gly-OH (2.005 g, 94%), m.p. 190-192 °C.

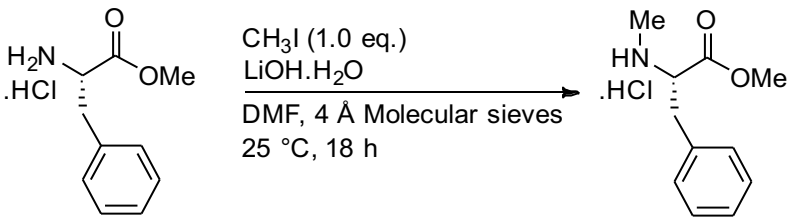
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (2H, s, Gly-C*H*$_3$), 7.76 (2H, dd, *J* = 5.5, *J* = 3.1, Ar-*H*), 7.90 (2H, dd, *J* = 5.5, *J* = 3.1, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 38.5 (Gly-CH_2), 123.7 (Phth-CH), 131.9 (Phth-C), 134.3 (Phth-CH), 167.4 (C=O), 171.6 (C=O).

IR υ_{max}/cm^{-1} (solid) 3559 m (O-H), 3051 w (C-H), 2988 w (C-H), 2937 w (C-H), 1773 s (Phth C=O), 1710 s (carboxylic acid C=O), 1610 m (C=C).

HRMS (ESI) [M+H$^+$][-HCl] *m/z* calcd. for $C_{10}H_8NO_2$: 206.0448, found: 206.0448.

***N*-methyl-L-phenylalanine methyl ester hydrochloride (Me-Phe-OMe.HCl)**



Me-Phe-OMe.HCl

Under an atmosphere of dry nitrogen, $LiOH.H_2O$ (0.418 g, 9.967 mmol) and 4 Å molecular sieves were stirred in anhydrous DMF (15 mL) for 20 min. L-phenylalanine methyl ester hydrochloride (1.000 g, 4.636 mmol) was added to the solution and stirred for a further 45 min before the addition of iodomethane (0.317 mL, 5.100 mmol). The resulting suspension was left to stir at room temperature for 18 h. The brown suspension was then filtered and the filter cake washed with EtOAc (50 mL). The filtrate was then washed with water (3 x 30 mL), dried ($MgSO_4$) and concentrated to dryness *in vacuo*. to give a yellow oil. The oil was purified by flash column chromatography using EtOAc as eluent to give Me-Phe-OMe.HCl as a pale-yellow oil (0.682 g, 64%), R_f 0.33 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s, C*H*$_3$), 2.90 (2H, d, *J* = 6.7, Phe-C*H*$_2$) 3.39 (1H, t, *J* = 6.7, Phe-α-C*H*), 3.60 (3H, s, Ester-C*H*$_3$), 7.11-7.13 (2H, m, Ar-*H*), 7.16-7.19 (1H, m, Ar-*H*), 7.21-7.25 (2H, m, Ar-*H*).

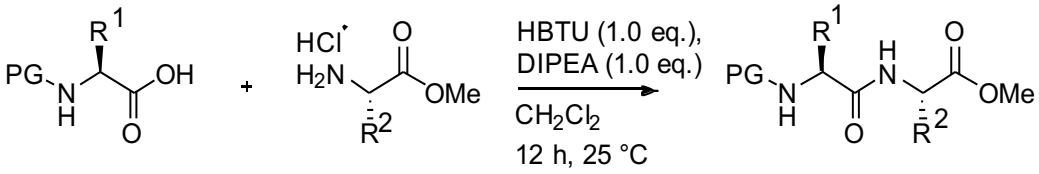
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 34.4 (NCH_3), 39.2 (Phe-CH_2), 51.3 (ster-CH_3), 64.4 (Phe-α-CH), 126.4 (Ar-C), 128.2 (Ar-C), 128.8 (Ar-C), 136.9 (Ar-C), 174.5 (C=O).

IR U_{max}/cm^{-1} (oil) 3028 w (C-H), 2949 w (C-H), 1732 s (Ester C=O), 1454 m (C-H).

HRMS (ESI) [M+H$^+$][-HCl] *m/z* calcd. for $C_{11}H_{16}NO_2$: 194.1176 found: 194.1174.

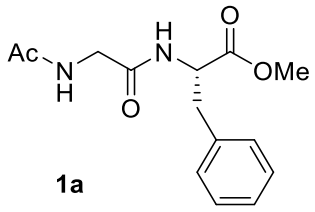
2.2. Synthesis of Gly-Phe dipeptides 1a-1e

2.2.1. General procedure for the preparation of dipeptides



The L-(amino acid) 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 amine was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$) and concentrated by rotary evaporation. The resulting colourless oil was dissolved in CH_2Cl_2 (20 mL); the *N*-protected amino acid (1.00 mmol), HBTU (0.379 g, 1.00 mmol) and DIPEA (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 recrystallised from CH_2Cl_2 / hexanes.

Ac-Gly-Phe-OMe (1a)



1a

Peptide **1a** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetylglycine (0.117 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **1a** as a white solid (0.218 g, 78%); m.p. 95-97 °C.

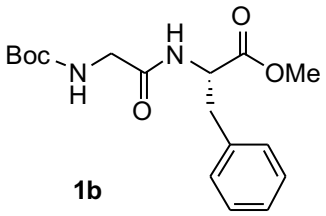
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s, Acetyl-C*H*$_3$), 3.07 (1H, dd, *J* = 13.9, *J* = 6.0, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.9, *J* = 6.0, Phe-C*H*H), 3.72 (3H, s, Ester-C*H*$_3$), 3.88 (2H, app dd, *J* = 16.5, *J* = 5.0, Gly-C*H*$_2$), 4.84 (1H, dt, *J* = 7.6, *J* = 6.0, Phe-α-C*H*), 6.33 (1H, m, Gly-N*H*), 6.57 (1H, br d, *J* = 7.6, Phe-N*H*), 7.08 (2H, d, *J* = 6.4, Ar-*H*) 7.23-7.30 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0 (Acetyl-CH_3), 37.9 (Phe-CH_2), 43.2 (Gly-CH_2), 52.6 (Ester-CH_3), 53.3 (Phe-α-CH), 127.3 (Ar-C), 128.7 (Ar-C), 129.3 (Ar-C), 135.7 (Ar-C), 168.6 (C=O), 170.7 (C=O), 171.8 (C=O).

IR U_{max}/cm^{-1} (solid) 3263 m (N-H), 3072 w (C-H), 2958 w (C-H), 1751 s (Ester C=O), 1709 s (Amide C=O), 1657 m (C=C), 1445 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{14}H_{19}N_2O_4$: 279.1339, found: 279.1339.

Boc-Gly-Phe-OMe (1b)



1b

Peptide **1b** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and Boc-glycine (0.175 g, 1.00 mmol), using the procedure in **section 2.2.1**, to afford **1b** as a colourless oil (0.205 g, 61%).

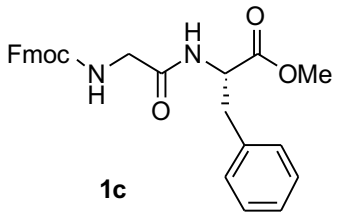
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s, Boc-(C*H*$_3$)$_3$), 3.08 (1H, dd, *J* = 13.8, *J* = 6.0, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.8, *J* = 6.0, Phe-C*H*H), 3.70-3.84 (5H, m, Ester-C*H*$_3$ / Gly-C*H*$_2$), 4.87 (1H, dt, *J* = 7.5, *J* = 6.0, Phe-α-C*H*), 5.29 (1H, m, Gly-N*H*), 6.74 (1H, br d, *J* = 7.5, Phe-N*H*), 7.09-7.11 (2H, m, Ar-*H*) 7.22-7.30 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.2 (Boc-$(CH_3)_3$), 37.8 (Phe-CH_2), 44.0 (Gly-CH_2), 52.3 (Ester-CH_3), 53.0 (Phe-α-CH), 80.0 (Boc-C), 127.0 (Ar-C), 128.5 (Ar-C), 129.1 (Ar-C), 135.6 (Ar-C), 155.9 (C=O), 169.2 (C=O), 171.7 (C=O).

IR U_{max} /cm^{-1} (oil) 3251 m (N-H), 3071 w (C-H), 2979 w (C-H), 1753 s (Ester C=O), 1741 s (Carbamate C=O), 1536 s (C=C), 1497 m (C=C), 1436 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{24}N_2O_5$: 337.1758, found: 337.1756.

Fmoc-Gly-Phe-OMe (1c)



1c

Peptide **1c** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and Fmoc-glycine (0.297 g, 1.00 mmol), using the procedure in **section 2.2.1.** The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **1c** as a white solid (0.307 g, 67%); m.p. 127-128 °C.

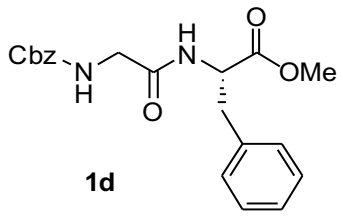
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08-3.18 (2H, m, Phe-C*H*$_2$), 3.74 (3H, s, Ester-C*H*$_3$), 3.82-3.94 (2H, m, Gly-C*H*$_2$), 4.22 (1H, br dd, *J* = 7.2, *J* = 7.0, Fmoc-C*H*), 4.41 (2H, br d, *J* = 7.2, Fmoc-C*H*$_3$), 4.90 (1H, dt, *J* = 7.6, *J* = 6.0, Phe-α-C*H*), 5.34-5.36 (1H, m, Gly-N*H*), 6.31 (1H, br d, *J* = 7.6, Phe-N*H*), 7.07 (2H, br d, *J* = 6.4, Ar-*H*), 7.21-7.28 (3H, m, Ar-*H*), 7.32 (2H, t, *J* = 7.3, Fmoc-Ar-*H*), 7.41 (2H, t, *J* = 7.3, Fmoc-Ar-*H*), 7.59 (2H, br d, *J* = 7.3, Fmoc-Ar-*H*), 7.78 (2H, d, *J* = 7.3, Fmoc-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 37.8 (Phe-CH_2), 44.3 (Gly-CH_2), 47.0 (Fmoc-CH), 52.4 (Ester-CH_3), 53.1 (Phe-α-CH), 67.3 (Fmoc-CH_2), 120.0 (Ar-C), 125.0 (Ar-C), 127.1 (Ar-C), 127.2 (Ar-C), 127.7 (Ar-C), 128.6 (Ar-C), 129.2 (Ar-C), 135.5 (Ar-C), 141.2 (Ar-C), 143.7 (Ar-C), 156.4 (C=O), 168.5 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3302 m (N-H), 3029 w (C-H), 2950 w (C-H), 1724 s (Ester C=O), 1665 s (Amide C=O), 1515 m (C=C), 1479 m (C=C).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{27}H_{27}N_2O_5$: 459.1914, found: 459.1908.

Cbz-Gly-Phe-OMe (1d)



1d

Peptide **1d** was synthesised from L-Phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and Cbz-glycine (0.209 g, 1.00 mmol), using the procedure in **section 2.2.1,** to afford **1b** as a colourless oil (0.193 g, 52%).

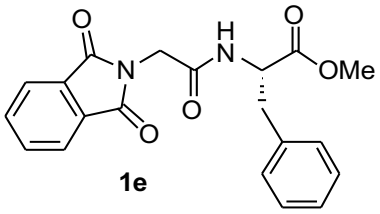
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.10 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.67 (3H, s, Ester-CH_3), 3.75-3.87 (2H, m, Gly-CH_2), 4.86 (1H, dt, *J* = 7.8, *J* = 6.0, Phe-α-C*H*), 5.08 (2H, s, Cbz-CH_2) 5.71 (1H, m, Gly-N*H*), 6.82 (1H, m, Phe-N*H*), 7.07 (2H, br d, *J* = 6.4, Ar-*H*) 7.18-7.26 (3H, m, Ar-*H*), 7.29- 7.33 (5H, m, Cbz-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 37.7 (Phe-CH_2), 44.2 (Gly-CH_2), 52.3 (Ester-CH_3), 53.0 (Phe-α-CH), 67.0 (Z-CH_2), 127.0 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 128.4 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 135.5 (Ar-C), 136.0 (Ar-C), 156.5 (C=O), 168.8 (C=O), 171.7 (C=O).

IR U_{max} /cm^{-1} (oil) 3317 m (N-H), 3030 w (C-H), 2952 w (C-H), 1723 s (Carbamate C=O), 1656 s (Amide C=O), 1604 m (C=C), 1518 m (C=C), 1215 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{20}H_{23}N_2O_5$: 371.1601, found: 371.1602.

Phth-Gly-Phe-OMe (1e)



1e

Peptide **1e** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and Phth-glycine (0.205 g, 1.00 mmol), using the procedure in **section 2.2.1.** The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **1e** as a white solid (0.231 g, 63%); m.p. 172-173 °C.

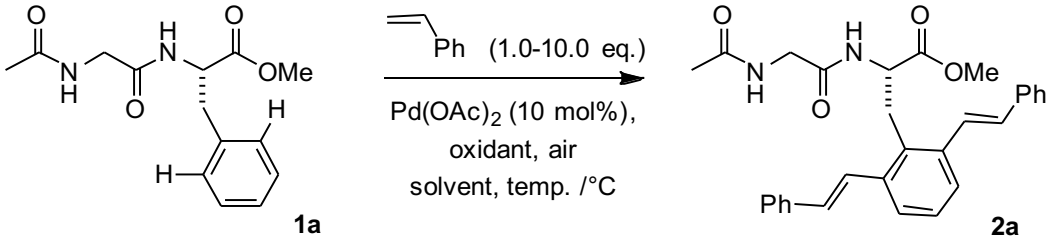
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (1H, dd, *J* = 13.7, *J* = 5.5, Phe-C*H*H), 3.16 (1H, dd, *J* = 13.7, *J* = 5.5, Phe-C*H*H), 3.73 (3H, s, Ester-CH_3) 4.35 (2H, dt, *J* = 17.4, *J* = 16.5, Gly-CH_2), 4.87 (1H, dt, *J* = 7.3, *J* = 5.5, Phe-α-C*H*), 6.36 (1H, m, Phe-N*H*), 7.07-7.09 (2H, m, Ar-*H*), 7.17-7.27 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 37.5 (Phe-CH_2), 40.5 (Gly-CH_2), 52.5 (Ester-CH_3), 53.3 (Phe-α-CH), 123.6 (Ar-C), 127.1 (Ar-C), 128.5 (Ar-C), 129.3 (Ar-C), 131.9 (Ar-C), 134.2 (Ar-C), 135.4 (Ar-C), 165.6 (C=O), 167.6 (C=O), 171.5 (C=O).

IR U_{max} /cm^{-1} (solid) 3308 m (N-H), 3032 w (C-H), 2950 w (C-H), 1776 s (Ester C=O), 1714 s (C=O), 1659 s (Amide C=O), 1543 m (C=C), 1417 m (C=C), 1206 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{20}H_{19}N_2O_5$: 367.1288, found: 367.1289.

2.3. Optimisation of the C-H olefination



1a **2a**

Peptide **1a** (0.100 g, 0.359 mmol), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol, 10 mol%), oxidant (2.5-5.0 eq.) and styrene (1.0-10.0 eq.) were stirred together in solvent (3 mL) at 130 °C for 12 h. The reaction was then allowed to cool to room temperature, filtered through a plug of Celite, and the filtrate was concentrated to dryness. The resulting residue was purified by flash column chromatography (EtOAc) and recrystallised from CH_2Cl_2 / hexanes.

Table 1: Optimisation of the olefination of (**1a**)

entry	oxidant	solvent	equiv. styrene	equiv. oxidant	temp / °C	time / h	yield[a] / %
1	AgOAc	DCE/DMF[b]	1.0	2.5	130	48	19
2	AgOAc	DCE/DMF[b]	2.0	2.5	130	48	31
3	AgOAc	DCE/DMF[b]	4.0	2.5	130	48	35
4	AgOAc	DCE/DMF[b]	10.0	2.5	130	48	39
5	AgOAc	DCE/DMF[b]	4.0	2.5	100	48	20
6	AgOAc	DCE/DMF[b]	4.0	2.5	80	48	8
7	AgOAc	DCE/DMF[b]	4.0	2.5	80	96	12
8	AgOAc	DCE/DMF[b]	4.0	2.5	25	48	Trace
9	AgOAc	DCE/DMF[b]	4.0	2.5	130	96	38
10	AgOAc	DCE/DMF[b]	4.0	2.5	130	24	8
11	AgOAc	Toluene	4.0	2.5	130	48	26
12	AgOAc	DMF	4.0	2.5	130	48	26
13	AgOAc	HFIP	4.0	2.5	130	48	Trace
14	AgOAc	MeCN	4.0	2.5	130	48	23
15	AgOAc	*t*-amyl-OH	4.0	2.5	130	48	67
16	AgOAc	*t*-amyl-OH/DMF[c]	4.0	2.5	130	48	48
17	Benzoquinone[d]	*t*-amyl-OH	4.0	2.5	130	48	24
18	$Cu(OAc)_2$	*t*-amyl-OH	4.0	2.5	130	48	34
19	$Ag(OPiv)_2$	*t*-amyl-OH	4.0	2.5	130	48	16
20	$AgCO_3$	*t*-amyl-OH	4.0	2.5	130	48	11
21	AgOAc	*t*-amyl-OH	4.0	5.0	130	24	83
22	**AgOAc**	***t*-amyl-OH**	**4.0**	**5.0**	**130**	**12**	**81**[e]
23	AgOAc	*t*-amyl-OH	4.0	5.0	130	6	70
24	AgOAc	*t*-amyl-OH	4.0	5.0	100	12	76
25	AgOAc	*t*-amyl-OH	4.0	5.0	80	12	68
26	AgOAc	*t*-amyl-OH	4.0	5.0	130	36	70 [f]

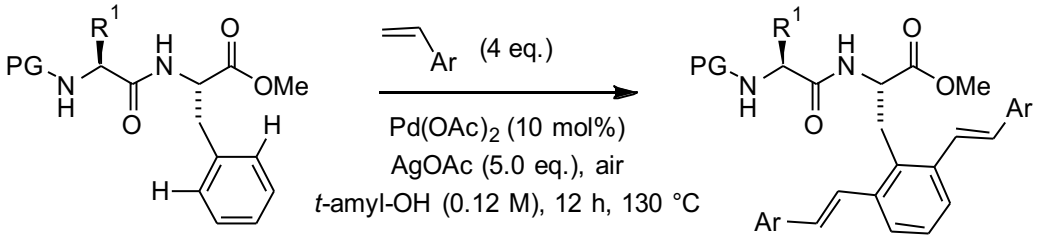
[a] Isolated yields of di-olefinated peptide **2a**; [b] DCE/DMF = 15:1; [c] *t*-amyl-OH/DMF = 15:1

[d] 5 eq. of NaOAc were also included in the reaction mixture

[e] The mono-olefinated peptide **2a′** was also isolated in 8% yield

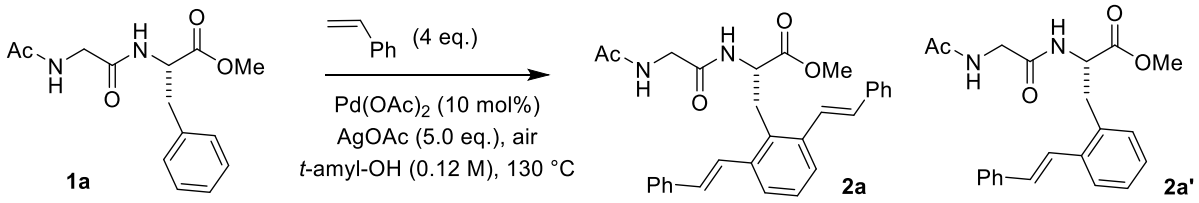
[f] Reaction conducted on a 1 mmol scale

2.3.1. General procedure for the olefination of phenylalanine containing peptides



The peptide (0.359 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol, 10 mol%), AgOAc (0.300 g, 1.780 mmol) and styrene (0.166 mL, 1.440 mmol) were stirred in *t*-amyl-OH (3 mL) at 130 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and filtered through a plug of Celite. The filtrate was then concentrated to dryness. The resulting residue was purified by flash column chromatography and recrystallised from CH_2Cl_2 / hexanes.

C-H olefination of model dipeptide 1a; synthesis of modified peptides 2a and 2a'



Following the general procedure in **section 2.3.1**, the reaction of Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol), styrene (0.166 mL, 1.440 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol, 10 mol%) and AgOAc gave a crude product that was a mixture of the di-olefinated peptide **2a** and the mono-olefinated peptide **2a′** in a ratio of 8:1, as judged by ^{1}H NMR spectroscopy. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **2a** as an off-white solid (0.140 g, 81%); m.p. 198-199 °C, R_f 0.33 (EtOAc), and **2a'** as an off-white solid (0.011 g, 8%); m.p. 129-132 °C, R_f 0.15 (EtOAc).

Data for 2a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (3H, s, Acetyl-C*H*$_3$), 3.49 (2H, d, *J* = 7.0, Phe-C*H*$_2$), 3.55 (3H, s, Ester-C*H*$_3$), 3.70 (1H, dd, *J* = 16.9, *J* = 5.0, Gly-C*H*H), 3.79 (1H, dd, *J* = 16.9, *J* = 5.0, Gly-C*H*H), 4.78 (1H, dt, *J* = 7.4, *J* = 6.9, Phe-α-C*H*), 5.82 (1H, m, Gly-N*H*), 6.40 (1H, br d, *J* = 7.7, Phe-N*H*), 7.01 (2H, d, *J* = 16.0, Alkene-C*H*), 7.27-7.33 (3H, m, Ar-*H*), 7.39 (4H, t, *J* = 7.8, Ar-*H*), 7.47 (2H, d, *J* = 16.0, Alkene-C*H*), 7.58 (6H, d, *J* = 7.8, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (Acetyl-CH_3), 31.0 (Phe-CH_2), 42.8 (Gly-CH_2), 52.7 (Ester-CH_3), 53.0 (Phe-α-CH), 125.8 (Ar-C), 126.2 (Alkene-C=C), 126.7 (Ar-C), 127.7 (Ar-C), 128.0 (Ar-C), 128.8 (Ar-C), 131.6 (Ar-C), 131.8 (Alkene-C=C), 137.1 (Ar-C), 137.8 (Ar-C), 168.2 (C=O), 170.2 (C=O), 171.6 (C=O).

IR υ_{max} /cm^{-1} (solid) 3300 m (N-H), 3057 w (C-H), 2954 w (C-H), 1727 s (Ester C=O), 1632 s (Amide C=O), 1535 m (C=C), 1436 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{30}H_{31}N_2O_4$: 483.2278 found: 483.2275.

Data for 2a′:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (3H, s, Acetyl-C*H*$_3$), 3.18 (1H, dd, *J* = 14.2, *J* = 6.2, Phe-C*H*H), 3.41 (1H, dd, *J* = 14.2, *J* = 6.2, Phe-C*H*H), 3.65 (3H, s, Ester-C*H*$_3$), 3.68 (1H, m, Gly-C*H*H), 3.85 (1H, dd, *J* = 16.9, *J* = 5.3, Gly-C*H*H), 4.81 (1H, dt, *J* = 7.3, *J* = 6.2, Phe-α-C*H*), 6.34 (1H, t, *J* = 5.3, Gly-N*H*), 6.94 (1H, d, *J* = 7.3, Phe-N*H*), 7.01 (1H, d, *J* = 16.0, Alkene-C*H*), 7.07-7.11 (1H, m, Ar-*H*), 7.18 (1H, t, *J* = 7.3, Ar-*H*), 7.24-7.29 (2H, m, Ar-H), 7.35-7.40 (3H, m, Ar-*H* / Alkene-C*H*), 7.54 (2H, d, *J* = 7.3, Ar-*H*), 7.63 (1H, d, *J* = 7.3, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.7 (Acetyl-CH_3), 34.8 (Phe-CH_2), 42.9 (Gly-CH_2), 52.4 (Ester-CH_3), 53.3 (Phe-α-CH), 125.4 (Ar-C),125.8 (Ar-C), 126.6 (Alkene-C=C), 127.1 (Ar-C), 127.6 (Ar-C), 127.8 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 130.5 (Ar-C), 133.7 (Alkene-C=C), 136.7 (Ar-C), 137.1 (Ar-C), 168.2 (C=O), 170.2 (C=O), 171.6 (C=O).

IR υ_{max} /cm^{-1} (solid) 3302 m (N-H), 3027 w (C-H), 2950 w (C-H), 1733 s (Ester C=O), 1636 s (Amide C=O), 1511 m (C=C), 1215 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{22}H_{25}N_2O_4$: 381.1814, found: 381.1810.

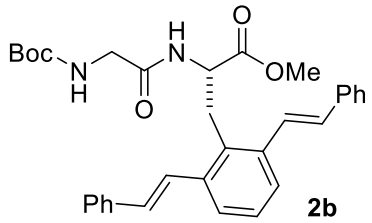
2.4. Detailed synthetic method at 1 mmol scale

The peptide Ac-Gly-Phe-OMe (**1a**) (0.278 g, 1.0 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 10 mol%), AgOAc (0.835 g, 5.0 mmol) and styrene (0.46 mL, 4.0 mmol) were stirred in *t*-amyl-OH (8.5 mL), in a microwave vial, at 130 °C for 36 h. The reaction mixture was then allowed to cool to room temperature and filtered through a plug of Celite. The filtrate was then concentrated to dryness. The resulting residue was purified by flash column chromatography (EtOAc) and recrystallised from CH_2Cl_2 / hexanes to give **2a** as an off-white solid (0.338 g, 70%). The data for **2a** was in agreement with that reported above.

2.5. Modification of Gly-Phe dipeptides

2.5.1. Scope of the *N*-protecting group

Synthesis of modified peptide 2b



2b

Modified peptide **2b** was prepared from Boc-Gly-Phe-OMe (0.121 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1.** The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **2b** and the mono-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 **2b** as an off-white solid (0.138 g, 71%); m.p. 164-166 °C, R_f 0.45 (EtOAc).

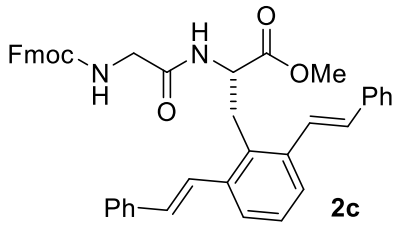
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s, Boc-(C*H*$_3$)$_3$), 3.39 (1H, dd, *J* = 14.4, *J* = 7.1, Phe-C*H*H), 3.48 (1H, d, *J* = 14.4, *J* = 7.1, Phe-C*H*H), 3.51 (3H, s, Ester-C*H*$_3$), 3.62-3.70 (2H, m, Gly-C*H*$_2$), 4.80 (1H, app q, *J* = 7.1, Phe-α-C*H*), 4.88-4.93 (1H, m, Gly-N*H*), 6.68 (1H, br d, *J* = 7.1, Phe-N*H*), 7.01 (2H, d, *J* = 16.0, Alkene-C*H*), 7.26-7.31 (3H, m, Ar-*H*), 7.38 (4H, t, *J* = 7.4, Ar-*H*), 7.49 (2H, d, *J* = 16.0, Alkene-C*H*), 7.56-7.59 (6H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.2 (Boc-(CH_3)$_3$), 31.5 (Phe-CH_2), 44.0 (Gly-CH_2), 52.6 (Ester-CH_3), 53.0 (Phe-α-CH), 80.1 (Boc-C), 125.7 (Ar-C), 126.1 (Ar-C), 126.7 (Alkene-C=C), 127.6 (Ar-C), 127.9 (Ar-C), 128.8 (Ar-C), 131.6 (Alkene-C=C), 131.8 (Ar-C), 137.2 (Ar-C), 137.2 (Ar-C), 137.7 (Ar-C), 155.8 (C=O), 169.8(C=O), 171.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3324 m (N-H), 2977 w (C-H), 1725 s (Ester C=O), 1647 s (Amide C=O), 1598 m (C=C), 1449 m (C-H).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{33}H_{37}N_2O_5$: 541.2697, found: 541.2692.

Synthesis of modified peptide 2c



2c

Modified peptide **2c** was prepared from Fmoc-Gly-Phe-OMe (0.165 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1.** The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **2c** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **2c** as an off-white solid (0.124 g, 52%); m.p. 145-148 °C, R_f 0.34 (25% EtOAc/pet. ether).

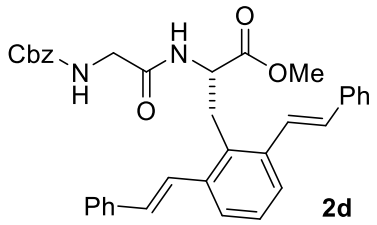
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (2H, br d, *J* = 6.9, Phe-C*H*$_2$), 3.53 (3H, s, Ester-C*H*$_3$), 3.70-3.74 (2H, m, Gly-C*H*$_2$), 4.16-4.19 (1H, m, Fmoc-C*H*), 4.31-4.33 (2H, m, Fmoc-C*H*$_2$), 4.81 (1H, dt, *J* = 7.3, *J* = 6.9, Phe-α-C*H*), 5.10 (1H, m, Gly-N*H*), 6.51 (1H, br d, *J* = 7.3 Phe-N*H*), 7.00 (2H, d, *J* = 15.8, Alkene-C*H*), 7.26-7.32 (6H, m, Ar-*H*), 7.35-7.42 (6H, m, Ar-*H*), 7.48 (2H, d, *J* = 15.8, Alkene-C*H*), 7.55-7.58 (7H, m, Ar-*H*), 7.75-7.77 (2H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.4 (Phe-CH_2), 44.3 (Gly-CH_2), 47.1 (Fmoc-CH), 52.8 Ester-CH_3), 53.2 (Phe-α-CH), 67.2 (Fmoc-CH_2), 120.1 (Ar-C), 124.8 (Ar-C), 125.2 (Ar-C), 125.9 (Ar-C), 126.3 (Alkene-C=C), 126.8 (Ar-C), 127.2 (Ar-C), 127.8 (Ar-C), 128.1 (Ar-C), 128.9 (Ar-C), 131.8 (Alkene-C=C), 131.9 (Ar-C), 137.3 (Ar-C), 137.9 (Ar-C), 141.4 (Ar-C), 143.9 (Ar-C), 156.4 (C=O), 168.4 (C=O), 171.9 (C=O).

IR υ_{max} /cm^{-1} (solid) 3300 m (N-H), 3057 w (C-H), 2949 w (C-H), 1725 s (Ester C=O), 1691 s (C=O), 1645 s (Amide C=O), 1530 m (C=C), 1448 m (C-H).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{43}H_{39}N_2O_5$: 663.2853 found: 663.2851.

Synthesis of modified peptide 2d



2d

Modified peptide **2d** was prepared from Cbz-Gly-Phe-OMe (**1d**) (0.133 g, 0.359 mmol) styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1.** The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **2d** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **2d** as an off-white solid (0.144 g, 70%); m.p. 177-179 °C, R_f 0.55 (25% EtOAc/pet. ether).

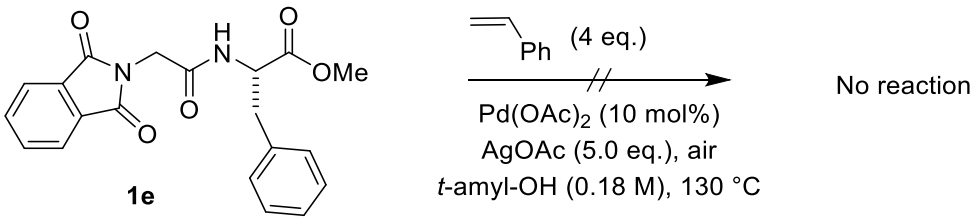
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41-3.45 (2H, m, Phe-C*H*$_2$), 3.51 (3H, s, Ester-C*H*$_3$), 3.65-3.76 (2H, m, Gly-C*H*$_2$), 4.80 (1H, app q, *J* = 7.3, Phe-α-C*H*), 5.03 (2H, s, Cbz-C*H*$_2$), 5.71 (1H, m, Gly-N*H*), 6.60 (1H, br d, *J* = 7.3, Phe-N*H*), 6.99 (2H, d, *J* = 16.0, Alkene-C*H*), 7.24-7.31 (7H, m, Ar-*H*), 7.36 (5H, t, *J* = 7.6, Ar-*H*), 7.47 (2H, d, *J* = 16.0, Alkene-C*H*), 7.54-7.57 (6H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.3 (Phe-CH_2), 44.2 (Gly-CH_2), 52.7 (Ester-CH_3), 53.0 (Phe-α-CH), 67.1 (Cbz-CH_2), 125.7 (Ar-C), 126.1 (Ar-C), 126.7 (Alkene-C=C), 127.7 (Ar-C), 128.0 (Ar-C), 128.0 (Ar-C), 128.2 (Ar-C), 125.5 (Ar-C), 128.8 (Ar-C), 131.7 (Alkene-C=C), 131.7 (Ar-C), 136.1 (Ar-C), 137.1 (Ar-C), 137.8 (Ar-C), 156.2 (C=O), 168.3 (C=O), 171.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3317 m (N-H), 3029 w (C-H), 2954 w (C-H), 1726 s (Ester C=O), 1688 s (Amide C=O), 1644 m (C=C), 1533 m (C=C), 1441 m (C-H).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{36}H_{35}N_2O_5$: 575.2540 found: 575.2534.

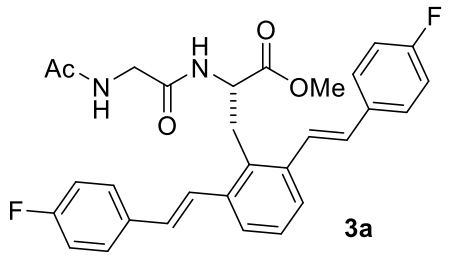
Attempted olefination of Phth-Gly-Phe-OMe (1e)



Peptide **1e** was subjected to the general procedure described in **section 2.3.1**. After 12 h, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a mixture of unreacted peptide **1e** and styrene only. There was no evidence for modification of the peptide.

2.5.2. Scope of the alkene

Synthesis of modified peptide 3a



3a

Modified peptide **3a** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-fluorostyrene (0.172 mL, 1.440 mmol), using the general procedure in **section 2.3.1.** The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3a** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3a** as an off-white solid (0.128 g, 69%); m.p. 190-193 °C, R_f 0.25 (50% EtOAc/pet. ether).

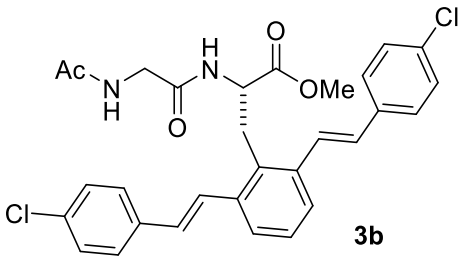
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s, Acetyl-C*H*$_3$), 3.42 (1H, dd, *J* = 14.5, *J* = 7.3, Phe-C*H*H), 3.45 (1H, dd, *J* = 14.5, *J* = 6.4, Phe-C*H*H), 3.53 (3H, s, Ester-C*H*$_3$), 3.72-3.76 (1H, m, Gly-C*H*H), 3.82 (1H, dd, *J* = 16.5, *J* = 5.0, Gly-C*H*H), 4.77 (1H, dt, *J* = 7.5, *J* = 7.3, Phe-α-C*H*), 6.03 (1H, br t, *J* = 5.0, Gly-N*H*), 6.59 (1H, br d, *J* = 7.5, Phe-N*H*), 6.96 (2H, d, *J* = 16.0, Alkene-C*H*$_3$), 7.07 (4H, t, *J* = 8.7, Ar-*H*), 7.30 (1H, t, *J* = 7.8, Ar-*H*), 7.38 (2H, d, *J* = 16.0, Alkene-C*H*$_3$), 7.54-7.57 (6H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (Acetyl-CH_3), 31.3 (Phe-CH_2), 42.9 (Gly-CH_2), 52.7 (Ester-CH_3), 53.1 (Phe-α-C), 115.6 (Ar-C), 115.8 (Ar-C), 125.7 (Ar-C), 125.8 (Alkene-C=C), 127.7 (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 130.5 (Alkene-C=C), 131.6 (Ar-C), 133.4 (Ar-C), 137.7 (Ar-C), 161.2 (Ar-C-F), 163.7 (Ar-C-F), 168.3 (C=O), 170.4 (C=O), 171.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3298 m (N-H), 3066 w (C-H), 2930 w (C-H), 1726 s (Ester C=O), 1630 m (Amide C=O), 1507 m (C=C).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{29}F_2N_2O_4$: 519.2090 found: 519.2086.

Synthesis of modified peptide 3b



3b

Modified peptide **3b** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-chlorostyrene (0.173 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3b** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3b** as a yellow solid (0.121 g, 61%); m.p. 234-238 °C, R_f 0.53 (EtOAc).

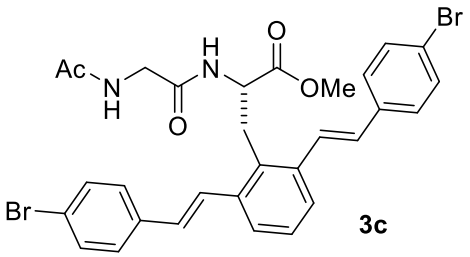
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s, Acetyl-C*H*$_3$), 3.41-3.51 (2H, m, Phe-C*H*$_2$), 3.52 (3H, s, Ester-C*H*$_3$), 3.74 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 3.82 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 4.76 (1H, dt, *J* = 7.4, *J* = 7.1, Phe-α-C*H*), 5.87 (1H, m, Gly-N*H*), 6.39 (1H, br d, *J* = 7.4, Phe-N*H*), 6.96 (2H, d, *J* = 16.0, Alkene-C*H*), 7.31 (1H, t, *J* = 8.2, Ar-*H*), 7.36 (4H, d, *J* = 8.5, Ar-*H*), 7.45 (2H, d, *J* = 16.0, Alkene-C*H*), 7.52 (4H, d, *J* = 8.2, Ar-*H*), 7.57 (2H, d, *J* = 8.2, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 22.4 (Acetyl-CH_3), 30.6 (Phe-CH_2), 41.6 (Gly-CH_2), 52.1 (Ester-CH_3), 53.1 (Phe-α-CH), 125.6 (Ar-C), 126.8 (Alkene-C=C), 127.3 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 129.8 (Ar-C), 132.1 (Alkene-C=C), 133.2 (Ar-C), 136.2 (Ar-C), 137.0 (Ar-C), 169.2 (C=O), 169.5 (C=O), 171.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3344 m (N-H), 3063 w (C-H), 2949 w (C-H), 1725 s (Ester C=O), 1659 s (C=C), 1630 s (Amide C=O), 1514 m (C=C), 1437 m (C-H).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{29}Cl_2N_2O_4$: 551.1499, found: 551.1492.

Synthesis of modified peptide 3c



3c

Modified peptide **3c** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-bromostyrene (0.188 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3c** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (65% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3c** as a yellow solid (0.113 g, 49%); m.p. 177-180 °C, R_f 0.31 (65% EtOAc/pet. ether).

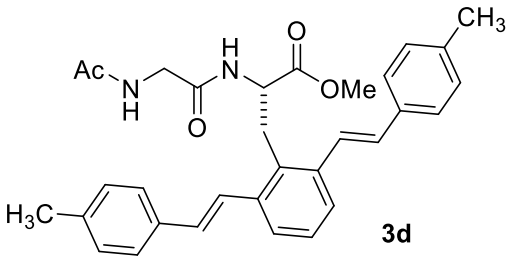
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (3H, s, Acetyl-C*H*$_3$), 3.24-3.26 (1H, m, Phe-C*H*H), 3.36-3.42 (1H, m, Phe-C*H*H), 3.45 (3H, s, Ester-C*H*$_3$), 3.54-3.59 (1H, m, Gly-C*H*H), 3.64-3.70 (1H, m, Gly-C*H*H), 4.41-4.47 (1H, m, Phe-α-C*H*), 7.07 (2H, d, *J* = 16.0, Alkene-C*H*$_3$), 7.25-7.29 (2H, m, Ar-*H*), 7.53-7.62 (11H, m, Alkene-C*H* / Ar-*H*), 7.94-7.96 (1H, m, Gly-N*H*), 8.55-8.57 (1H, m, Phe-N*H*).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 22.4 (Acetyl-C*H*$_3$), 30.6 (Phe-CH_2), 41.6 (Gly-CH_2), 52.1 (Ester-CH_3), 53.1 (Phe-α-CH), 120.7 (Ar-C), 125.6 (Ar-C), 126.9 (Alkene-C=C), 127.3 (Ar-C), 128.8 (Ar-C), 129.9 (Ar-C), 131.6 (Alkene-C=C), 133.2 (Ar-C), 136.5 (Ar-C), 137.0 (Ar-C), 169.2 (C=O), 169.5 (C=O), 171.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3309 m (N-H), 2924 w (C-H), 1725 s (Ester C=O), 1639 m (C=C), 1488 m (C-H).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{29}Br_2N_2O_4$: 641.0471, found: 641.0465.

Synthesis of modified peptide 3d



3d

Modified peptide **3d** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-methylstyrene (0.190 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3d** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3d** as an off-white solid (0.141 g, 77%); m.p. 239-242 °C, R_f 0.39 (EtOAc).

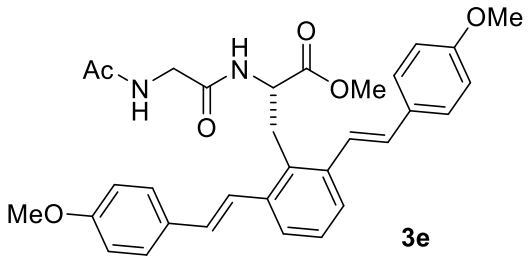
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (3H, s, Acetyl-C*H*$_3$), 2.37 (6H, s, Ar-C*H*$_3$), 3.45-3.53 (2H, m, Phe-C*H*$_2$), 3.55 (3H, s, Ester-C*H*$_3$), 3.68 (1H, dd, *J* = 16.9, *J* = 5.1, Gly-C*H*H), 3.77 (1H, dd, *J* = 16.9, *J* = 5.1, Gly-C*H*H), 4.75 (1H, dt, *J* = 7.5, *J* = 6.9, Phe-α-C*H*), 5.71 (1H, m, Gly-N*H*), 6.24 (1H, br d, *J* = 7.5, Phe-N*H*), 6.98 (2H, d, *J* = 15.9, Alkene-C*H*), 7.20 (4H, d, *J* = 7.9, Ar-*H*), 7.30 (1H, t, *J* = 7.9, Ar-*H*), 7.40 (2H, d, *J* = 15.9, Alkene-C*H*), 7.47 (4H, d, *J* = 7.9, Ar-*H*), 7.55 (2H, d, *J* = 7.9, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3 (Ar-CH_3), 22.7 (Acetyl-CH_3), 30.8 (Phe-CH_2), 42.8 (Gly-CH_2), 52.7 (Ester-CH_3), 53.1 (Phe-α-CH), 125.2 (Ar-C), 125.3 (Ar-C), 126.6 (Alkene C=C), 127.6 (Ar-C), 129.5 (Ar-C), 131.4 (Ar-C), 131.6 (Alkene C=C), 134.4 (Ar-C), 137.9 (Ar-C), 137.9 (Ar-C), 168.3 (C=O), 170.3 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3264 m (N-H), 3056 w (C-H), 2917 w (C-H), 1740 s (Ester C=O), 1696 s (Amide C=O), 1652 m (C=C), 1510 m (C=C).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{32}H_{35}N_2O_4$: 511.2591, found: 511.2582.

Synthesis of modified peptide 3e



3e

Modified peptide **3e** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-methoxystyrene (0.194 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3e** and the mono-olefinated peptide in a ratio of 3:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3e** as an off-white solid (0.097 g, 50%); m.p. 260-262 °C, R_f 0.34 (EtOAc).

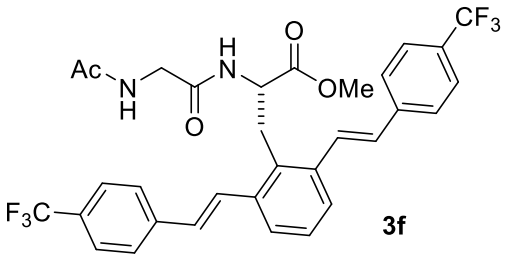
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (3H, s, Acetyl-C*H*$_3$), 3.48 (2H, br d, *J* = 7.1, Phe-C*H*$_2$), 3.54 (3H, s, Ester-C*H*$_3$), 3.69 (1H, dd, *J* = 16.9, *J* = 4.9, Gly-C*H*H), 3.76 (1H, dd, *J* = 16.9, *J* = 4.9, Gly-C*H*H), 3.83 (6H, s, OC*H*$_3$), 4.77 (1H, dt, *J* = 7.4, *J* = 7.0, Phe-α-C*H*), 5.76 (1H, m, Gly-N*H*), 6.25 (1H, br d, *J* = 7.4, Phe-N*H*), 6.92-6.98 (6H, m, Alkene-C*H* / Ar-*H*), 7.28-7.33 (4H, m, Alkene-C*H* / Ar-*H*), 7.50-7.54 (5H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (Acetyl-CH_3), 30.9 (Phe-CH_2), 42.8 (Gly-CH_2), 52.7 (Ester-CH_3), 53.1 (Phe-α-CH), 55.3 (OCH_3), 114.2 (Ar-C), 124.1 (Ar-C), 125.3 (Alkene-C=C), 127.6 (Ar-C), 128.0 (Ar-C), 130.0 (Ar-C), 131.0 (Ar-C), 131.3 (Alkene-C=C), 138.1 (Ar-C), 159.5 (Ar-C), 168.3 (C=O), 170.2 (C=O), 171.7(C=O).

IR υ_{max} /cm^{-1} (solid) 3265 m (N-H), 3062 w (C-H), 2943 w (C-H), 1738 s (Ester C=O), 1694 s (Amide C=O), 1651 m (C=C), 1538 m (C=C).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{32}H_{35}N_2O_6$: 543.2490, found: 543.2486.

Synthesis of modified peptide 3f



3f

Modified peptide **3f** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-trifluoromethylstyrene (0.213 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3f** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3f** as a white solid (0.162 g, 73%); m.p. 218-220 °C, R_f 0.40 (50% EtOAc/pet. ether).

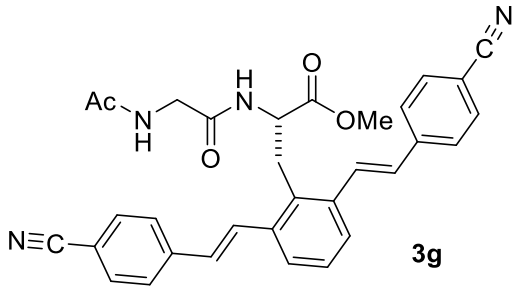
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (3H, s, Acetyl-C*H*$_3$), 3.43 (1H, dd, *J* = 14.2, *J* = 7.8, Phe-C*H*H), 3.50-3.56 (4H, m, Phe-C*H*H / Ester-C*H*$_3$), 3.78 (1H, dd, *J* = 16.5, *J* = 5.0, Gly-C*H*H), 3.87 (1H, dd, *J* = 16.5, *J* = 5.0, Gly-C*H*H), 4.78 (1H, dt, *J* = 7.3, *J* = 6.9, Phe-α-C*H*), 5.92-5.95 (1H, m, Gly-N*H*), 6.51 (1H, br d, *J* = 7.3, Phe-N*H*), 7.05 (2H, *J* = 16.0, Alkene-C*H*), 7.35 (1H, t, *J* = 7.8, Ar-*H*), 7.58-7.71 (12H, m, Ar-*H* / Alkene-CH).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (Acetyl-CH_3), 31.6 (Phe-CH_2), 43.0 (Gly-CH_2), 52.8 (Ester-CH_3), 53.1 (Phe-α-CH), 125.7 (Ar-C), 126.3 (Ar-C), 126.9 (Ar-C), 127.8 (Ar-C), 128.4 (Ar-C), 129.4 (Ar-C), 129.7 (Alkene-C=C), 130.2 (Alkene-C=C), 132.2 (Ar-C), 137.3 (Ar-C), 140.5 (Ar-C), 168.3 (C=O), 170.4 (C=O), 171.6 (C=O).

IR υ_{max} /cm^{-1} (solid) 3318 m (N-H), 3055 w (C-H), 2956 w (C-H), 1720 s (Ester C=O), 1612 m (C=C), 1507 m (C=C), 1321 s (C-F), 1109 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{32}H_{30}F_6N_2O_4$: 619.2026, found 619.2028.

Synthesis of modified peptide 3g



3g

Modified peptide **3g** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 4-cyanostyrene (0.173 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3g** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3g** as a yellow solid (0.145 g, 76%); m.p. 209-211 °C, R_f 0.40 (EtOAc).

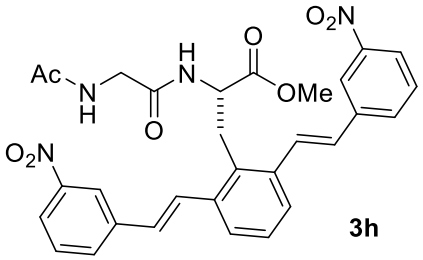
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s, Acetyl-C*H*$_3$), 3.36 (1H, dd, *J* = 14.4, *J* = 8.3, Phe-C*H*H), 3.48-3.54 (4H, m, Phe-C*H*H / Ester-C*H*$_3$), 3.82 (1H, dd, *J* = 16.6, *J* = 5.3, Gly-C*H*H), 3.90 (1H, dd, *J* = 16.6, *J* = 5.3, Gly-C*H*H), 4.75 (1H, dt, *J* = 8.0, *J* = 6.5, Phe-α-C*H*), 6.08 (1H, br t, *J* = 5.3, Gly-N*H*), 6.75 (1H, d, *J* = 8.0, Phe-N*H*), 7.02 (2H, d, *J* = 15.9, Alkene-C*H*), 7.35 (1H, t, *J* = 7.8, Ar-*H*), 7.62-7.64 (3H, m, Ar-*H*), 7.66-7.71 (9H, m, Ar-*H* / Alkene-C*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (Acetyl-CH_3), 31.9 (Phe-CH_2), 43.2 (Gly-CH_2), 52.8 (Ester-CH_3), 53.2 (Phe-α-CH), 110.9 (Ar-C), 119.0 (Ar-C), 126.5 (Ar-C), 127.2 (Ar-C), 127.9 (Ar-C), 129.4 (Alkene-C=C), 130.0 (Alkene-C=C), 132.5 (Ar-C), 132.6 (Ar-C), 137.0 (Ar-C), 141.5 (Ar-C), 168.5 (C=O), 170.6 (C=O), 171.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3301 m (N-H), 3090 w (C-H), 2958 w (C-H), 1728 s (Ester C=O), 1653 m (C=C), 1518 m (C=C), 1262 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{32}H_{29}N_4O_4$: 533.2183, found 533.2181.

Synthesis of modified peptide 3h



3h

Modified peptide **3h** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 3-nitrostyrene (0.201 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3h** and the mono-olefinated peptide in a ratio of 8:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3h** as a white solid (0.123 g, 60%); m.p. 172-174 °C, R_f 0.31 (EtOAc).

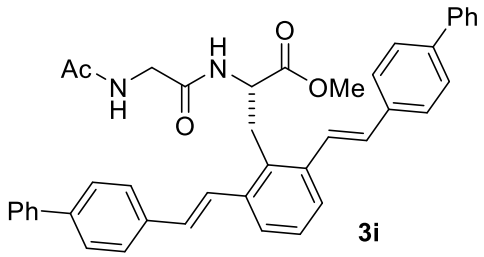
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s, Acetyl-C*H*$_3$), 3.36 (1H, dd, *J* = 14.2, *J* = 9.2, Phe-C*H*H), 3.50-3.55 (4H, m, Ester-C*H*$_3$ / Phe-C*H*H), 3.91-4.02 (2H, m, Gly-C*H*$_2$), 4.75 (1H, m, Phe-α-C*H*), 6.63 (1H, m, Gly-N*H*), 7.05 (2H, d, *J* = 16.0, Alkene-C*H*), 7.14 (1H, d, *J* = 7.3, Phe-N*H*), 7.33 (1H, t, *J* = 7.8, Ar-*H*), 7.53 (2H, t, *J* = 8.2, Ar-*H*), 7.62 (2H, d, *J* = 7.8, Ar-*H*), 7.74 (2H, d, *J* = 16.0, Alkene-C*H*), 7.82 (2H, d, *J* = 7.8, Ar-*H*), 8.09 (2H, d, *J* = 8.2, Ar-*H*) 8.61 (2H, s, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (Acetyl-CH_3), 32.4 (Phe-CH_2), 43.1 (Gly-CH_2), 52.9 (Ester-CH_3), 53.8 (Phe-α-CH), 121.2 (Ar-C), 122.4 (Ar-C), 126.3 (Ar-C), 127.9 (Ar-C), 128.9 (Ar-C), 129.4 (Alkene-C=C), 129.8 (Alkene-C=C), 132.7 (Ar-C), 133.1 (Ar-C), 137.0 (Ar-C), 139.1 (Ar-C), 149.0 (Ar-C), 168.7 9 (C=O), 171.0 (C=O), 171.9 (C=O).

IR U_{max} /cm^{-1} (solid) 3301 m (N-H), 3070 w (C-H), 2957 w (C-H), 2222 m (C≡N), 1727 s (Ester C=O), 1653 m (C=C), 1519 m (C=C), 1349 s (N=O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{30}H_{30}N_4O_8$: 573.1980, found 573.1984.

Synthesis of modified peptide 3i



3i

Modified peptide **3i** was prepared from Ac-Gly-Phe-OMe (0.100 g, 0.359 mmol) and 4-vinylbiphenyl (0.260 g, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3i** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3i** as an off-white solid (0.075 g, 33%); m.p. 246-249 °C, R_f 0.52 (EtOAc).

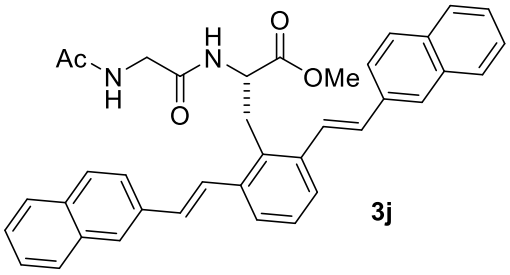
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (3H, s, Acetyl-C*H*$_3$), 3.55 (2H, d, *J* = 6.9, Phe-C*H*$_2$), 3.57 (3H, s, Ester-C*H*$_3$), 3.75 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 3.82 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 4.82 (1H, dt, *J* = 7.5, *J* = 6.9, Phe-α-C*H*), 5.81 (1H, br t, *J* = 5.0, Gly-N*H*), 6.34 (1H, br d, *J* = 7.5, Phe-N*H*), 7.07 (2H, d, *J* = 15.9, Alkene-C*H*), 7.32-7.39 (4H, m, Ar-*H*), 7.45-7.48 (4H, m, Ar-*H*), 7.52 (2H, d, *J* = 15.9, Alkene-C*H*), 7.60-7.68 (13H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 22.4 (Acetyl-CH_3), 30.7 (Phe-CH_2), 41.7 (Gly-CH_2), 52.1 (Ester-CH_3), 53.2 (Phe-α-CH), 126.0 (Ar-C), 126.5 (Ar-C), 126.6 (Ar-C), 126.9 (Alkene-C=C), 127.0 (Ar-C), 127.4 (Ar-C), 127.5 (Ar-C), 129.0 (Ar-C), 129.1 (Ar-C), 130.0 (Ar-C), 130.6 (Ar-C), 132.9 (Alkene-C=C), 136.5 (Ar-C), 139.3 (Ar-C), 139.7 (Ar-C), 169.2 (C=O), 169.5 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3266 m (N-H), 3029 w (C-H), 2924 w (C-H), 1725 s (Ester C=O), 1633 s (Amide C=O), 1601 m (C=C), 1518 m (C=C).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{42}H_{39}N_2O_4$: 635.2904 found: 635.2895.

Synthesis of modified peptide 3j



3j

Modified peptide **3j** was prepared from Ac-Gly-Phe-OMe (**1a**) (0.100 g, 0.359 mmol) and 2-vinylnapthalene (0.222 g, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **3j** and the mono-olefinated peptide in a ratio of 3:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **3j** as an off-white solid (0.079 g, 38%); m.p. 224-227 °C, R_f 0.54 (50% EtOAc/pet. ether).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (3H, s, Acetyl-C*H*$_3$), 3.48-3.52 (5H, m, Ester-C*H*$_3$ / Phe-C*H*$_2$), 3.61 (1H, dd, *J* = 16.5, *J* = 5.7, Gly-C*H*H), 3.65 (1H, dd, *J* = 16.5, *J* = 5.7, Gly-C*H*H), 4.57 (1H, dt, *J* = 7.9, *J* = 6.5, Phe-α-C*H*), 7.28 (2H, d, *J* = 16.0, Alkene-C*H*$_2$), 7.33 (1H, t, *J* = 7.8, Ar-*H*), 7.45-7.52 (4H, m, Ar-*H*), 7.69 (2H, d, *J* = 7.8, Ar-*H*), 7.72 (2H, d, *J* = 16.0, Alkene-C*H*), 7.88-7.90 (4H, m, Ar-*H*), 7.92-7.96 (4H, m, Ar-*H*), 7.99 (1H, br t, *J* = 6.5, Phe-N*H*), 8.05 (2H, s, Ar-*H*), 8.64 (1H, br d, *J* = 8.2, Ar-*H*).

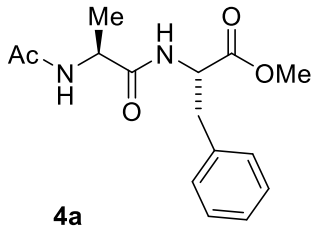
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 22.9 (Acetyl-CH_3), 31.4 (Phe-CH_2), 42.4 (Gly-CH_2), 52.7 (Ester-CH_3), 53.7 (Phe-α-CH), 124.0 (Ar-C), 125.5 (Ar-C), 126.1 (Ar-C), 126.5 (Ar-C), 126.7 (Alkene-C=C), 127.4 (Ar-C), 127.6 (Ar-C), 128.0 (Ar-C), 128.2 (Ar-C), 131.2 (Alkene-C=C), 132.7 (Ar-C), 133.0 (Ar-C), 133.3 (Ar-C), 134.9 (Ar-C), 137.4 (Ar-C), 169.2 (C=O), 169.5 (C=O), 171.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3289 m (N-H), 2958 w (C-H), 1726 s (Ester C=O), 1636 m (C=C), 1508 m (C=C).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{38}H_{35}N_2O_4$: 583.2591 found 583.2579.

2.6. Synthesis of dipeptides 4a-j

Ac-Ala-Phe-OMe (4a)



4a

Peptide **4a** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-alanine (0.131 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4a** as a white solid (0.261 g, 89%); m.p. 125-126 °C.

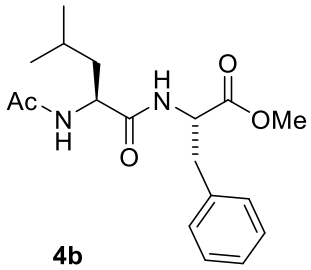
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, d, *J* = 7.0, Ala-C*H*$_3$), 1.93 (3H, s, Acetyl-C*H*$_3$), 3.03 (1H, dd, *J* = 13.7, *J* = 6.4, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.7, *J* = 6.4, Phe-C*H*H), 3.70 (3H, s, Ester-C*H*$_3$), 4.48 (1H, dq, *J* = 7.4, *J* = 6.9, Ala-α-C*H*), 4.80-4.85 (1H, m, Phe-α-C*H*), 6.33 (1H, br d, *J* = 7.4, Ala-N*H*), 6.81 (1H, br d, *J* = 7.9, Phe-N*H*), 7.08-7.10 (2H, m, Ar-*H*), 7.18-7.27 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.5 (Ala-CH_3), 23.1 (Acetyl-CH_3), 38.3 (Phe-CH_2), 48.1 (Ala-α-CH), 52.7 (Ester-CH_3), 53.8 (Phe-α-CH), 127.1 (Ar-C), 128.5 (Ar-C), 129.2 (Ar-C), 135.7 (Ar-C), 169.9 (C=O), 171.1 (C=O), 172.1 (C=O).

IR U_{max} /cm^{-1} (solid) 3252 m (N-H), 3075 w (C-H), 2988 w (C-H), 2938 w (C-H), 1753 s (Ester C=O), 1637 s (Amide C=O), 1537 m (C=C), 1436 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{15}H_{21}N_2O_4$: 293.1496, found: 293.1492.

Ac-Ala-Phe-OMe (4b)



4b

Peptide **4b** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-leucine (0.173 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4b** as a white solid (0.261 g, 78%); m.p. 110-111 °C.

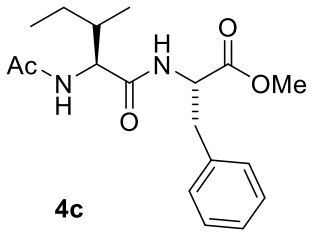
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, d, *J* = 5.5, Leu-(C*H*$_3$)$_2$), 1.43-1.50 (1H, m, Leu-CH$_2$C*H*(CH$_3$)$_2$), 1.55-1.64 (2H, m, Leu-C*H*$_2$), 1.91 (3H, s, Acetyl-C*H*$_3$), 3.03 (1H, dd, *J* = 13.9, *J* = 6.4, Phe-C*H*H), 3.10 (1H, dd, *J* = 13.9, *J* = 6.4, Phe-C*H*H), 3.68 (3H, s, Ester-C*H*$_3$), 4.45-4.50 (1H, m, Leu-α-C*H*), 4.79 (1H, dt, *J* = 7.8, *J* = 6.4, Phe-α-C*H*), 6.34 (1H, br d, *J* = 8.2, Leu-N*H*), 6.83 (1H, br d, *J* = 7.8, Phe-N*H*), 7.09-7.11 (2H, m, Ar-*H*) 7.18-7.27 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.3 (Leu-CH_3), 22.9 (Leu-CH_3), 23.1 (Acetyl-CH_3), 24.8 (Leu-CH), 38.0 (Phe-CH_2), 41.2 (Leu-CH_2), 51.6 (Leu-α-CH), 52.4 (Ester-CH_3), 53.4 (Phe-α-CH), 127.0 (Ar-C), 128.5 (Ar-C), 129.2 (Ar-C), 135.9 (Ar-C), 170.3 (C=O), 171.9 (C=O), 172.3 (C=O).

IR υ_{max} /cm^{-1} (solid) 3265 m (N-H), 3055 w (C-H), 2896 w (C-H), 1753 s (Ester C=O), 1687 s (Amide C=O), 1601 m (C=C), 1566 m (C=C).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{18}H_{27}N_2O_4$: 335.1965, found: 335.1963.

Ac-Ile-Phe-OMe (4c)



4c

Peptide **4c** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-isoleucine (0.173 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4c** as a white solid (0.234 g, 70%); m.p. 194-195 °C.

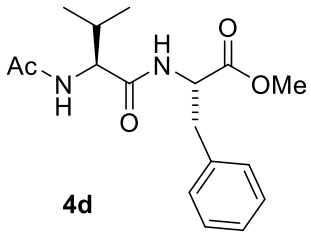
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.88 (6H, m, Ile-(C*H*$_3$)$_2$), 1.04-1.14 (1H, m, Ile-C*H*HCH$_3$), 1.41-1.51 (1H, m, Ile-C*H*HCH$_3$), 1.72-1.82 (1H, m, Ile-CH$_2$C*H*CH$_3$), 1.98 (3H, s, Acetyl-C*H*$_3$), 3.07 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H) 3.12 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.71 (3H, s, Ester-C*H*$_3$), 4.26 (1H, dd, *J* = 8.7, *J* = 6.5, Ile-α-C*H*), 4.85 (1H, dt, *J* = 7.8, *J* = 6.0, Phe-α-C*H*), 6.07 (1H, br d, *J* = 6.5, Ile-N*H*), 6.29 (1H, br d, *J* = 7.8, Phe-N*H*), 7.08-7.10 (2H, m, Ar-*H*), 7.21-7.30 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.3 (Ile-CH$_2$*C*H$_3$), 15.2 (Ile-CH*C*H$_3$), 23.3 (Acetyl-CH$_3$), 24.9 (Ile-CH), 37.4 (Ile-CH$_2$), 37.8 (Phe-CH$_2$), 52.4 (Ester-CH$_3$), 53.1 (Phe-α-CH), 57.5 (Ile-α-CH), 127.2 (Ar-C), 128.7 (Ar-C), 129.2 (Ar-C), 135.5 (Ar-C), 169.8 (C=O), 170.8 (Ar-C), 171.5 (C=O).

IR U_{max} /cm^{-1} (solid) 3296 m (N-H), 2971 w (C-H), 1741 w (Ester C=O), 1663 s (Amide C=O), 1647 m (C=C), 1541 m (C=C), 1384 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{18}H_{27}N_2O_4$: 335.1965, found: 335.1965.

Ac-Val-Phe-OMe (4d)



4d

Peptide **4d** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-valine (0.159 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4d** as a white solid (0.224 g, 70%); m.p 176-177 °C.

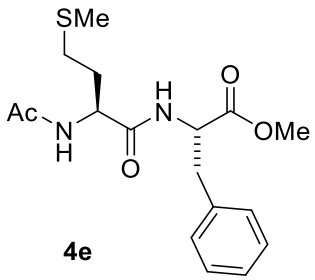
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, app t, *J* = 6.4, Val-C*H*$_3$), 2.00-2.07 (4H, m, Acetyl-C*H*$_3$ / Val-CH$_3$C*H*CH$_3$) 3.07 (1H, dd, *J* = 14.0, *J* = 6.2, Phe-C*H*H), 3.12 (1H, dd, *J* = 14.0, *J* = 6.2, Phe-C*H*H), 3.72 (3H, s, Ester-C*H*$_3$), 4.28 (1H, dd, *J* = 9.2, *J* = 6.9, Val-α-C*H*), 4.85 (1H, dd, *J* = 7.8, *J* = 6.2, Phe-α-C*H*), 6.19 (1H, br d, *J* = 9.2, Val-N*H*), 6.49 (1H, br d, *J* = 7.8, Phe-N*H*), 7.10-7.12 (2H, m, Ar-*H*), 7.22-7.30 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.1 (Val-CH_3), 19.0 (Val-CH_3), 23.2 (Acetyl-CH_3), 31.2 (Val-CH), 37.8 (Phe-CH_2), 52.3 (Ester-CH_3), 53.1 (Phe-α-CH), 58.2 (Val-α-CH), 127.2 (Ar-C), 128.6 (Ar-C), 129.2 (Ar-C), 135.5 (Ar-C), 170.0 (C=O), 170.9 (C=O), 171.6 (C=O).

IR U_{max} /cm^{-1} (solid) 3288 m (N-H), 3030 w (C-H), 2954 w (C-H), 1743 s (Ester C=O), 1643 s (Amide C=O), 1538 m (C=C), 1383 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{25}N_2O_4$: 321.1809, found: 321.1810.

Ac-Met-Phe-OMe (4e)



4e

Peptide **4e** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-methionine (0.191 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4e** as a white solid (0.268 g, 76%); m.p. 110-111 °C.

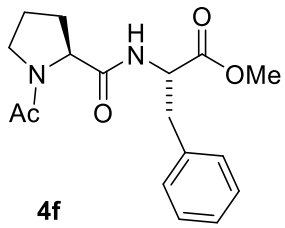
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89-2.03 (5H, m, Met-SC*H*$_3$ / Met-CH_2C*H*$_2$S), 2.04 (3H, s, Acetyl-C*H*$_3$), 2.47-2.60 (2H, m, Met-CHC*H*$_2$$CH_2$), 3.06 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.72 (3H, s, Ester-C*H*$_3$), 4.58 (1H, dt, *J* = 7.8, *J* = 6.9, Met-α-C*H*), 4.80-4.85 (1H, m, Phe-α-C*H*), 6.26 (1H, br d, *J* = 7.8, Met-N*H*), 6.68 (1H, br d, *J* = 8.2, Phe-N*H*), 7.10-7.12 (2H, m, Ar-*H*), 7.22-7.31 (3H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.9 (Met-CH_3), 23.2 (Acetyl-CH_3), 29.9 (Met-SCH_2), 31.3 (Met-CH_2), 37.7 (Phe-CH_2), 51.8 (Met-α-CH), 52.4 (Ester-CH_3), 53.2 (Phe-α-CH), 127.2 (Ar-C), 128.7 (Ar-C), 129.2 (Ar-C), 135.5 (Ar-C), 169.9 (C=O), 170.8 (C=O), 171.5 (C=O).

IR U_{max} /cm^{-1} (solid) 3287 m (N-H), 3061 w (C-H), 2952 w (C-H), 2914 w (C-H), 1750 s (Ester C=O), 1641 s (Amide C=O). 1537 m (C=C), 1367 m (C=C), 1158 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{25}N_2O_4S$: 353.1530, found: 353.1529.

Ac-Pro-Phe-OMe (**4f**)



4f

Peptide **4f** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-proline (0.157 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude compound was recrystallised from CH_2Cl_2 / hexanes to afford **4f** as a white solid (0.213 g, 67%); m.p. 106-108 °C.

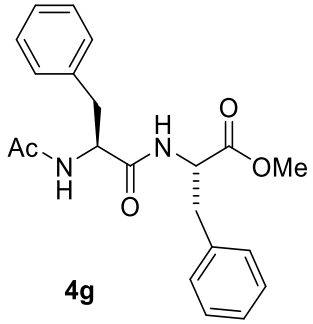
^{1}H NMR (400 MHz, CD_3OD) δ 1.72-1.80 (1H, m, Pro-CHC*H*HCH$_2$), 1.88-1.95 (2H, m, Pro-CH$_2$C*H*$_2$CH$_2$), 2.01 (3H, s, Acetyl-C*H*$_3$), 2.34-2.40 (1H, m, Pro-CHC*H*HCH$_2$), 2.98 (1H, dd, *J* = 14.0, *J* = 7.8, Phe-C*H*H), 3.21 (1H, dd, *J* = 14.0, *J* = 5.5, Phe-C*H*H), 3.33 (2H, t, *J* = 7.0, Pro-NHC*H*$_2$CH$_2$), 3.73 (3H, s, Ester-C*H*$_3$), 4.56 (1H, dd, *J* = 8.0, *J* = 7.0, Pro-α-C*H*), 4.83 (1H, dt, *J* = 7.8, *J* = 5.5, Phe-α-C*H*), 7.10-7.15 (2H, m, Ar-*H*), 7.20-7.30 (3H, m, Ar-*H*), 7.54 (1H, br d, *J* = 5.5, Phe-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.4 (Acetyl-CH_3), 24.8 (Pro-CH_2), 26.9 (Pro-CH_2), 37.9 (Phe-CH_2), 48.0 (Pro-CH_2), 52.3 (Ester-CH_3), 53.1 (Phe-α-CH), 59.3 (Pro-α-CH_3), 126.8 (Ar-C), 128.2 (Ar-C), 129.3 (Ar-C), 136.3 (Ar-C), 170.8 (C=O), 170.8 (C=O), 171.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3524 m (N-H), 3065 w (C-H), 2900 w (C-H), 1732 s (Ester C=O), 1644 s (Amide C=O), 1497 m (C=C), 1292 s (C-O).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{17}H_{23}N_2O_4$: 319.1652, found: 319.1652.

Ac-Phe-Phe-OMe (4g)



4g

Peptide **4g** was synthesised from L-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-phenylalanine (0.207 g, 1.00 mmol), using the procedure in **section 2.2.1**, and isolated as a white solid (0.195 g, 53%); m.p. 170-171 °C.

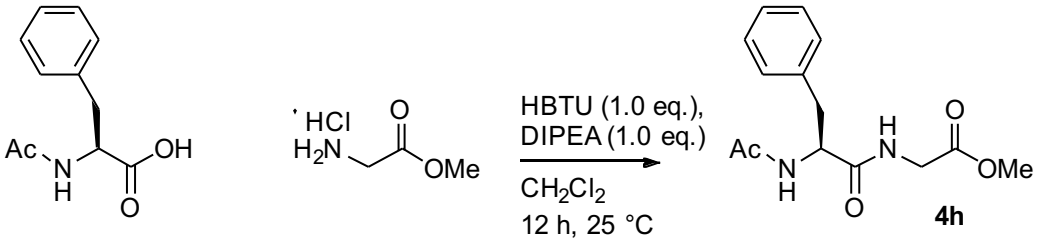
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s, Acetyl-C*H*$_3$), 2.94-3.12 (4H, m, Phe-C*H*$_2$), 3.65 (3H, s, Ester-C*H*$_3$), 4.74 (2H, m, Phe-α-C*H* (x2)), 6.57 (1H, br d, *J* = 8.2, Phe-N*H*), 6.72 (1H, d, *J* = 7.8, Phe-N*H*), 7.02-7.04 (2H, m, Ar-*H*) 7.15-7.26 (8H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9 (Acetyl-CH_3), 37.8 (Phe-CH_2), 38.1 (Phe-CH_2), 52.2 (Ester-CH_3), 53.4 (Phe-α-CH), 54.2 (Phe-α-CH), 126.8 (Ar-C), 127.0 (Ar-C), 128.4 (Ar-C), 129.1 (Ar-C), 129.2 (Ar-C), 135.6 (Ar-C), 136.3 (Ar-C), 170.1 (C=O), 170.8 (C=O), 171.2 (C=O).

IR U_{max} /cm^{-1} (solid) 3308 m (N-H), 3066 w (C-H), 2973 w (C-H), 1733 s (Ester C=O), 1646 s (Amide C=O), 1538 m (C=C), 1435 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{21}H_{25}N_2O_4$: 369.1809, found: 369.1813.

Ac-Phe-Gly-OMe (4h)



4h

Glycine methyl ester hydrochloride (0.314 g, 2.50 mmol) was dissolved in H_2O (20 mL) before the addition of Amberlyst A21 ion exchange resin (3.140 g, 10.0 w/w). The suspension was stirred for 20 min at room temperature before filtration and concentration to dryness *in vacuo*. The resulting residue was slurried in CH_2Cl_2 (30 mL), along with *N*-acetyl-L-phenylalanine (0.207 g, 1.00 mmol), HBTU (0.379 g, 1.00 mmol) and DIPEA (0.174 mL, 1.00 mmol) and stirred for 12 h. The resulting suspension was filtered and washed with 1M HCl (20 mL), sat. $NaHCO_3$ (3 x 20 mL) and H_2O (20 mL). The organic layers were then dried ($MgSO_4$) and concentration to dryness *in vacuo*. The resulting oil was recrystallised from CH_2Cl_2 / hexanes to afford **4h** as a white solid (0.078 g, 28%); m.p. 129-130 °C.

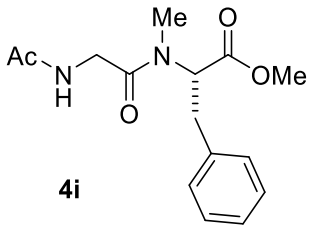
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s Acetyl-C*H*$_3$), 3.03-3.13 (2H, m, Phe-C*H*$_2$), 3.72 (3H, s, Ester-C*H*$_3$), 3.91 (1H, dd, *J* = 18.0, *J* = 5.3, Gly-C*H*H), 4.00 (1H, dd, *J* = 18.0, *J* = 5.3 Gly-C*H*H), 4.77 (1H, dt, *J* = 8.0, *J* = 7.3, Phe-α-C*H*), 6.49 (1H, br d, *J* = 8.0, Phe-N*H*), 6.80 (1H, br t, *J* = 5.3, Gly-N*H*), 7.20-7.31 (5H, m, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0 (Acetyl-CH_3), 38.1 (Phe-CH_2), 41.1 (Gly-CH_2), 52.3 (Ester-CH_3), 54.2 (Phe-α-CH), 126.9 (Ar-C), 128.6 (Ar-C), 129.2 (Ar-C), 136.4 (Ar-C), 169.8 (C=O), 170.3 (C=O), 171.4 (C=O).

IR U_{max} /cm^{-1} (solid) 3278 m (N-H), 3070 w (C-C), 2976 w (C-C), 2923 s (C-C), 1748 s (Ester C=O), 1657 s (Amide C=O), 1548 m (C=C), 1498 m (C=C), 1433 m (C-H).

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{14}H_{19}N_2O_4$: 279.1339 found: 279.1334.

Ac-Gly-(*N*-Me)Phe-OMe (4i)



4i

Peptide **4i** was synthesised from *N*-methyl-L-phenylalanine methyl ester hydrochloride (0.574 g, 2.50 mmol) and *N*-acetylglycine (0.173 g, 1.00 mmol), using the procedure in **section 2.2.1**. Purification by flash column chromatography (EtOAc) afforded peptide **4i** as a yellow oil (0.164 g, 56%), R_f 0.18 (EtOAc).

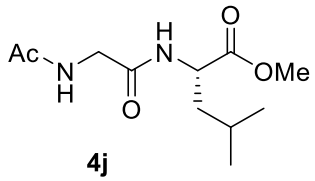
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s, Acetyl-C*H*$_3$), 2.80 (3H, s, NC*H*$_3$), 3.04 (1H, dd, *J* = 14.4, *J* = 11.0, Phe-C*H*H), 3.35 (1H, dd, *J* = 14.4, *J* = 5.3, Phe-C*H*H), 3.75 (3H, s, Ester-C*H*$_3$), 3.86 (1H, dd, *J* = 17.7, *J* = 4.0, Gly-C*H*H), 4.02 (1H, dd, *J* = 17.7, *J* = 4.0, Gly-C*H*H), 5.22 (1H, dd, *J* = 11.0, *J* = 5.3, Phe-α-C*H*), 6.55 (1H, m, Gly-N*H*), 7.16 (2H, br d, *J* = 7.3, Ar-*H*), 7.20-7.32 (3H, m, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8 (Acetyl-CH_3), 31.9 (NCH_3), 34.4 (Phe-CH_2), 41.4 (Gly-CH_2), 52.4 (Ester-CH_3), 58.9 (Phe-α-CH), 126.9 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 136.5 (Ar-C), 168.8 (C=O), 170.0 (C=O), 170.6 (C=O);

IR υ_{max} /cm^{-1} (oil) 3327 m (N-H), 2952 w (C-H), 1737 s (Ester C=O), 1636 s (Amide C=O), 1496 m (C=C), 1260 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{15}H_{21}N_2O_4$: 293.1496 found: 293.1496.

Ac-Gly-Leu-OMe (4j)



4j

Peptide **4j** was synthesised from L-leucine methyl ester hydrochloride (0.454 g, 2.50 mmol) and *N*-acetylglycine (0.117 g, 1.00 mmol), using the procedure in **section 2.2.1**, to afford **4j** as a yellow oil (0.171 g, 70%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (6H, app t, *J* = 6.2, Leu-(C*H*$_3$)$_3$), 1.47-1.63 (3H, m, Leu-C*H*C*H*$_2$), 1.95 (3H, s, Acetyl-C*H*$_3$), 3.64 (3H, s, Ester-C*H*$_3$), 3.89-3.99 (2H, m, Gly-C*H*$_2$), 4.44-4.49 (1H, m, Leu-α-C*H*), 7.36 (1H, br t, *J* = 5.3, Gly-N*H*), 7.67 (1H, d, *J* = 7.8, Leu-N*H*);

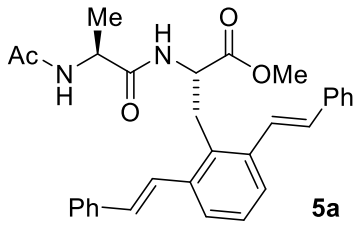
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.4 (Leu-$(CH_3)_3$), 22.5 (Ester-CH_3), 24.5 (Leu-CH), 40.5 (Leu-CH_2), 42.7 (Gly-CH_2), 50.7 (Leu-α-CH), 52.1 (Ester-CH_3), 169.4 (C=O), 171.1 (C=O), 173.2 (C=O);

IR U_{max} /cm^{-1} (oil) 3283 m (N-H), 3073 w (C-H), 2957 w (C-H), 2871 w (C-H), 1739 s (Ester C=O), 1646 s (Amide C=O), 1533 m (C=C), 1438 m (C-H), 1206 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{11}H_{21}N_2O_4$: 245.1496, found: 245.1496.

2.7. Modification of Phe dipeptides 4a-g

Synthesis of modified peptide 5a



5a

Modified peptide **5a** was prepared from Ac-Ala-Phe-OMe (**4a**) (0.105 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5a** and the mono-olefinated peptide in a ratio of 8:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5a** as an off-white solid (0.135 g, 76%); m.p. 193-194 °C, R_f 0.48 (EtOAc).

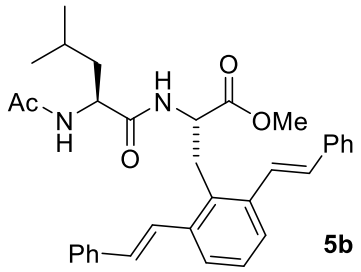
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 7.3, Ala-C*H*$_3$), 1.83 (3H, s, Acetyl-C*H*$_3$), 3.44 (2H, d, *J* = 7.3, Phe-C*H*$_2$), 3.56 (3H, s, CO_2C*H*$_3$), 4.38 (1H, dq, *J* = 7.3, *J* = 6.8, Ala-α-C*H*), 4.76 (1H, dq, *J* = 7.8, *J* = 7.3, Phe-α-C*H*), 6.07 (1H, br d, *J* = 7.3, Ala-N*H*), 6.65 (1H, br d, *J* = 7.8, Phe-N*H*), 7.01 (2H, d, *J* = 15.8, Alkene-C*H*), 7.26 - 7.31 (3H, m, Ar- *H*), 7.38 (4H, dt, *J* = 7.8, *J* = 7.3, Ar-*H*), 7.47 (2H, d, *J* = 15.8, Alkene-C*H*), 7.56 (2H, d, *J* = 7.8, Ar-*H*), 7.58 (4H, br d, *J* = 7.3, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.4 (Ala-CH_3), 22.9 (Acetyl-CH_3), 31.3 (Phe-CH_2), 48.6 (Ala-α-CH), 52.6 (Ester-CH_3), 53.1 (Phe-α-CH), 125.8 (Ar-C), 126.1 (Alkene-C=C), 126.7 (Ar-C), 127.6 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 131.8 (Ar-C), 131.9 (Alkene-C=C), 137.1 (Ar-C), 137.8 (Ar-C), 169.7 (C=O), 171.8 (C=O), 171.8 (C=O);

IR υ_{max} /cm^{-1} (solid) 3290 m (N-H), 3057 w (C-H), 2979 w (C-H), 1732 s (Ester C=O), 1632 m (C=C), 1532 m (C=C), 1260 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{31}H_{33}N_2O_4$: 497.2435 found: 497.2428.

Synthesis of modified peptide 5b



5b

Modified peptide **5b** was prepared from Ac-Leu-Phe-OMe (**4b**) (0.120 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5b** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5b** as an off-white solid (0.128 g, 66%); m.p. 198-202 °C, R_f = 0.30 (50% EtOAc/pet. ether).

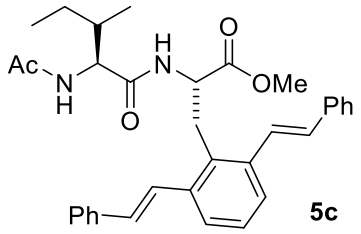
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (6H, dd, *J* = 6.1, *J* = 5.7, Leu-(C*H*$_3$)$_2$), 1.36-1.43 (1H, m, Leu-CH$_2$C*H*(CH$_3$)$_2$), 1.46-1.52 (2H, m, Leu-C*H*$_2$CH), 1.87 (3H, s, Acetyl-C*H*$_3$), 3.41 (1H, dd, *J* = 14.4, *J* = 7.6, Phe-C*H*H), 3.46 (1H, dd, *J* = 14.4, *J* = 7.6, Phe-C*H*H), 3.60 (3H, s, Ester-C*H*$_3$), 4.36 (1H, dt, *J* = 8.2, *J* = 5.4, Leu-α-C*H*), 4.76 (1H, dt, *J* = 7.7, *J* = 7.5, Phe-α-C*H*), 6.30 (1H, br d, *J* = 8.2, Leu-N*H*), 6.57 (1H, br d, *J* = 7.6, Phe-N*H*), 7.03 (2H, d, *J* = 16.0, Alkene-C*H*), 7.27-7.32 (3H, m, Ar-*H*), 7.39 (4H, t, *J* = 7.8, *J* = 7.3, Ar-*H*), 7.48 (2H, d, *J* = 16.0, Alkene-C*H*), 7.56 (2H, d, *J* = 7.8, Ar-*H*), 7.59 (4H, d, *J* = 7.3, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Acetyl-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 24.5 (Leu-CH), 31.4 (Phe-CH_2), 41.4 (Leu-CH_2), 51.6 (Leu-α-CH_3), 52.7 (Ester-CH_3), 53.3 (Phe-α-CH), 125.9 (Ar-C), 126.0 (Ar-C), 126.8 (Alkene-C=C), 127.7 (Ar-C), 128.0 (Ar-C), 128.8 (Ar-C), 131.7 (Alkene-C=C), 132.2 (Ar-C), 137.1 (Ar-C), 137.8 (Ar-C), 170.7 (C=O), 171.7 (C=O), 171.8 (C=O);

IR υ_{max} /cm^{-1} (solid) 3260 m (N-H), 3021 w (C-H), 2964 w (C-H), 1728 s (Ester C=O), 1671 s (Amide C=O), 1650 m (C=C), 1555 m (C=C), 1207 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{34}H_{39}N_2O_4$: 539.2904, found: 539.2897.

Synthesis of modified peptide 5c



5c

Modified peptide **5c** was prepared from Ac-Ile-Phe-OMe (**4c**) (0.120 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5c** and the mono-olefinated peptide in a ratio of 10:3. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5c** as an off-white solid (0.116 g, 60%); m.p. 198-200 °C, R_f = 0.34 (25% EtOAc/pet. ether).

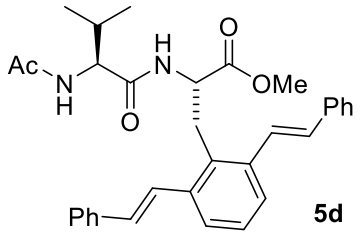
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73-0.77 (6H, m, Ile-(C*H*$_3$)$_2$), 0.96-1.04 (1H, m, Ile-C*H*HCH$_3$), 1.27-1.35 (1H, m, Ile-C*H*HCH$_3$), 1.63-1.70 (1H, m, Ile-CH$_2$C*H*CH$_3$), 1.87 (3H, s, Acetyl-C*H*$_3$), 3.37 (1H, dd, *J* = 14.5, *J* = 8.6, Phe-C*H*H), 3.45 (1H, dd, *J* = 14.5, *J* = 6.8, Phe-C*H*H), 3.63 (3H, s, Ester-C*H*$_3$), 4.16 (1H, dd, *J* = 8.6 Ile-α-C*H*), 4.70-4.75 (1H, m, Phe-α-C*H*), 5.95 (1H, br d, *J* = 8.6, Ile-N*H*), 6.28 (1H, br d, *J* = 6.8, Phe-N*H*), 7.05 (2H, d, *J* = 16.0, Alkene-C*H*), 7.28-7.33 (3H, m, Ar-*H*), 7.38-7.41 (4H, m, Ar-*H*), 7.49 (2H, d, *J* = 16.0, Alkene-C*H*), 7.56 (2H, d, *J* = 7.7, Ar-*H*), 7.61 (4H, br d, *J* = 7.7, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.4 (Ile-CH_3), 14.8 (Ile-CHCH_3), 23.2 (Acetyl-CH_3), 24.9 (Ile-CH_2), 31.3 (Phe-CH_2), 37.9 (Ile-CH), 52.6 (Ester-CH_3), 53.4 (Phe-α-CH), 57.4 (Ile-α-CH), 126.0 (Ar-C), 126.1 (Alkene-C=C), 126.8 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 128.8 (Ar-C), 131.7 (Alkene-C=C), 132.5 (Ar-H), 137.1 (Ar-C), 137.8 (Ar-C), 169.6 (C=O), 170.7 (C=O), 171.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3278 m (N-H), 3061 w (C-H), 2923 w (C-H), 1736 s (Ester C=O), 1632 m (C=C), 1538 m (C=C), 1256 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{34}H_{39}N_2O_4$: 539.2904, found: 539.2900.

Synthesis of modified peptide 5d



5d

Modified peptide **5d** was prepared from Ac-Val-Phe-OMe (**4d**) (0.115 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5d** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5d** as an off-white solid (0.121 g, 64%); m.p. 210-213 °C; R_f 0.36 (25% EtOAc/pet. ether).

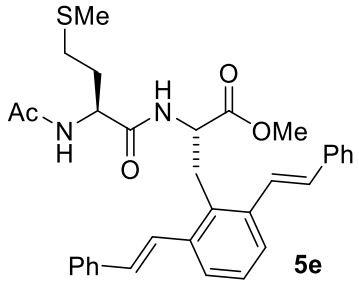
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (6H, dd, *J* = 6.8, *J* = 6.3, Val-(C*H*$_3$)$_2$), 1.88-1.96 (4H, m, Acetyl-C*H*$_3$ / Val-CH$_3$C*H*CH$_3$), 3.37 (1H, dd, *J* = 14.3, *J* = 8.5, Phe-C*H*H), 3.45 (1H, dd, *J* = 14.3, *J* = 6.5, Phe-C*H*H), 3.63 (3H, s, Ester-C*H*$_3$), 4.15 (1H, dd, *J* = 8.5, *J* = 6.5, Val-α-C*H*), 4.72 (1H, dt, *J* = 8.5, *J* = 6.5, Phe-α-C*H*), 5.99 (1H, br d, *J* = 6.5, Val-N*H*), 6.34 (1H, br d, *J* = 6.5, Phe-N*H*), 7.04 (2H, d, *J* = 15.9, Alkene-C*H*), 7.28-7.33 (3H, m, Ar-*H*), 7.39 (4H, t, *J* = 7.8, Ar-*H*), 7.49 (2H, d, *J* = 15.9, Alkene-C*H*), 7.55 (2H, d, *J* = 7.8, Ar-*H*), 7.61 (4H, d, *J* = 7.8, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.2 (Val-CH_3), 19.0 (Val-CH_3), 23.2 (Acetyl-CH_3), 31.4 (Val-CH), 35.4 (Phe-CH_2), 52.6 (Ester-CH_3), 53.3 (Phe-α-CH), 58.2 (Val-α-CH), 125.4 (Ar-C), 126.2 (Alkene-C=C), 126.6 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 128.9 (Ar-C), 130.6 (Ar-C), 131.3 (Alkene-C=C), 133.7 (Ar-C), 136.8 (Ar-C), 137.4 (Ar-C), 170.0 (C=O), 171.1 (C=O), 171.9 (C=O);

IR U_{max} /cm^{-1} (solid) 3268 m (N-H), 3060 w (C-H), 2926 w (C-H), 1736 s (Ester C=O), 1629 m (C=C), 1538 m (C=C), 1256 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{33}H_{37}N_2O_4$: 525.2743, found: 525.2743.

Synthesis of modified peptide 5e



5e

Modified peptide **5e** was prepared from Ac-Met-Phe-OMe (**4e**) (0.127 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5e** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5e** as an off-white solid (0.120 g, 60%); m.p. 186-190 °C; R_f 0.38 (50% EtOAc/pet. ether).

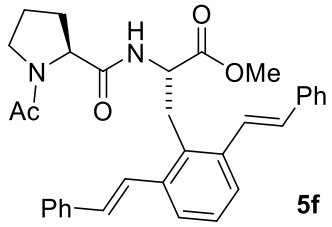
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81-1.90 (5H, m, Met-SC*H*$_3$ / Met-CH_2C*H*$_2$S), 1.93 (3H, s, Acetyl-C*H*$_3$), 2.38-2.48 (2H, m, Met-CHC*H*$_2$CH$_2$), 3.39 (1H, dd, *J* = 14.4, *J* = 8.2, Phe-C*H*H), 3.47 (1H, dd, *J* = 14.4, *J* = 6.6, Phe-C*H*H), 3.61 (3H, s, Ester-C*H*$_3$), 4.47 (1H, dt, *J* = 7.7, *J* = 6.9, Met-α-C*H*), 4.77 (1H, dt, *J* = 7.8, *J* = 6.6, Phe-α-C*H*), 6.13 (1H, br d, *J* = 7.7, Met-N*H*), 6.73 (1H, br d, *J* = 7.8, Phe-N*H*), 7.03 (2H, d, *J* = 16.0, Alkene-C*H*), 7.27-7.32 (3H, m, Ar-*H*), 7.39 (4H, app t, *J* = 7.8, *J* = 7.4, Ar-*H*), 7.48 (2H, d, *J* = 16.0, Alkene-C*H*), 7.56 (2H, d, *J* = 7.8, Ar-*H*), 7.60 (4H, br d, *J* = 7.4, Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.7 (Met-SCH_3), 23.0 (Acetyl-CH_3), 29.6 (Met-CH_2S), 31.3 (Met-CH_2), 31.5 (Phe-CH_2), 51.7 (Met-α-CH), 52.7 (Ester-CH_3), 53.2 (Phe-α-CH), 126.0 (Ar-C), 126.0 (Alkene-C=C), 126.8 (Ar-C), 127.7 (Ar-C), 128.8 (Ar-C), 131.7 (Ar-C), 132.2 (Alkene-C=C), 137.1 (Ar-C), 137.8 (Ar-C), 169.9 (C=O), 170.6 (C=O), 171.7 (C=O).

IR υ_{max} /cm^{-1} (solid) 3286 s (N-H), 3027 w (C-H), 2924 w (C-H), 1738 s (Ester C=O), 1679 s (Amide C=O), 1649 m (C=C), 1511 m (C=C), 1200 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{33}H_{37}N_2O_4S$: 557.2469, found: 557.2464.

Synthesis of modified peptide 5f



5f

Modified peptide **5f** was prepared from Ac-Pro-Phe-OMe (**4f**) (0.114 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5f** and the mono-olefinated peptide in a ratio of 5:4. Purification by flash column chromatography (25% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5f** as an off-white solid (0.045 g, 24%); m.p. 194-197 °C, R_f 0.21 (50% EtOAc/pet. ether).

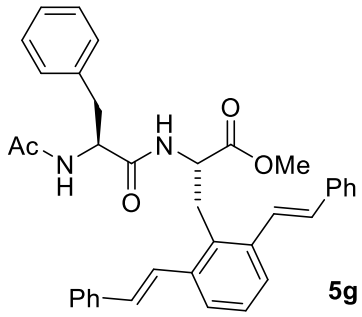
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.68 (1H, m, Pro-CHC*H*HCH$_2$), 1.81-1.86 (2H, m, Pro-CH$_2$C*H*$_2$CH$_2$), 1.95 (3H, s, Acetyl-C*H*$_3$), 2.29-2.32 (1H, m, Pro-CHC*H*HCH$_2$), 3.24-3.36 (2H, m, Pro-NHC*H*$_2$CH$_2$), 3.42 (2H, d, *J* = 7.5, Phe-C*H*$_2$), 3.59 (3H, s, Ester-C*H*$_3$), 4.49-4.51 (1H, m, Pro-α-C*H*), 4.77 (1H, app q, *J* = 7.8, Phe-α-C*H*), 6.98 (2H, d, *J* = 15.8, Alkene-C*H*), 7.27-7.29 (3H, m, Ar-*H*), 7.35-7.39 (4H, m, Ar-*H*), 7.50 (2H, d, *J* = 15.8, Alkene-C*H*); 7.54-7.66 (6H, m, Ar-*H*), 7.71 (1H,d, *J* = 7.8, Phe-N*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.4 (Acetyl-CH_3), 24.9 (Pro-CH_2), 27.2 (Pro-CH_2), 31.7 (Phe-CH_2), 48.3 (Pro-CH_2), 52.7 (Ester-CH_3), 53.2 (Phe-α-CH), 59.6 (Pro-α-CH_3), 125.6 (Ar-C), 126.4 (Ar-C), 127.0 (Alkene-C=C), 127.5 (Ar-C), 127.9 (Ar-C), 128.8 (Ar-C), 131.8 (Ar-C), 132.4 (Ar-C), 137.5 (Alkene-C=C), 138.0 (Ar-C), 171.1 (C=O), 171.2 (C=O), 172.1 (C=O).

IR υ_{max} /cm^{-1} (solid) 3275 m (N-H), 2921 w (C-H), 1735 s (Ester C=O), 1630 m (C=C), 1536 m (C=C), 1255 s (C-O).

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{33}H_{35}N_2O_4$: 523.2591, found: 523.2589.

Synthesis of modified peptide 5g



5g

Modified peptide **5g** was prepared from Ac-Phe-Phe-OMe (**4g**) (0.132 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **5g** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (50% EtOAc/pet. ether) followed by recrystallisation from CH_2Cl_2 / hexanes gave **5g** as an off-white solid (0.107 g, 52%); m.p. 202-204 °C; R_f 0.52 (50% EtOAc/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$) (* denotes the modified phenylalanine residue) δ 1.78 (3H, s, Acetyl-C*H*$_3$), 2.89 (1H, dd, *J* = 13.7, *J* = 7.3, Phe-C*H*H), 2.97 (1H, dd, *J* = 13.7, *J* = 6.0, Phe-C*H*H), 3.38* (2H, d, *J* = 7.3, Phe-C*H*$_2$), 3.52 (3H, s, Ester-C*H*$_3$), 4.54 (1H, dt, *J* = 7.7, *J* = 7.3, Phe-α-C*H*), 4.71* (1H, dt, *J* = 7.8, *J* = 7.3, Phe-α-C*H*), 5.88 (1H, br d, *J* = 7.7, Phe-N*H*), 6.18* (1H, br d, *J* = 7.8, Phe-N*H*), 6.99 (2H, d, *J* = 16.0, Alkene-C*H*), 7.03-7.05 (2H, m, Phe-Ar-*H*), 7.15-7.20 (3H, m, Phe-Ar-*H*), 7.27-7.32* (3H, m, Ar-*H*), 7.40* (4H, t, *J* = 7.8, Ar-*H*), 7.46 (2H, d, *J* = 16.0, Alkene-C*H*), 7.55* (2H, d, *J* = 7.8, Ar-*H*), 7.59* (4H, d, *J* = 7.8, Ar-*H*);

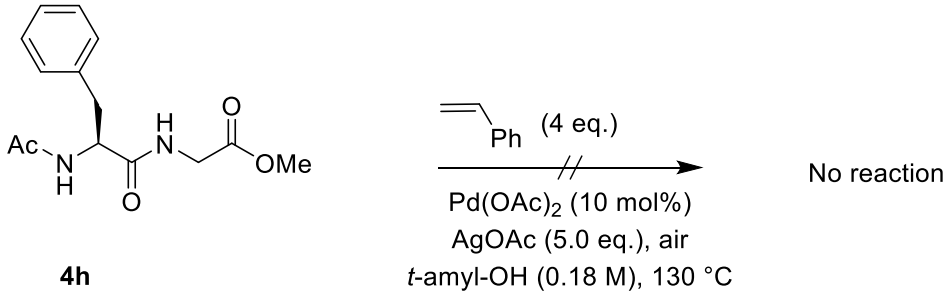
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0 (Acteyl-CH_3), 31.5 (Phe-CH_2), 38.3 (Phe-CH_2), 52.6 (Ester-CH_3), 53.1 (Phe-α-CH), 54.2 (Phe-α-CH), 125.8 (Ar-C), 126.1 (Alkene-C=C), 126.8 (Ar-C), 126.9 (Ar), 127.6 (Ar-C), 127.9 (Ar-C), 128.6 (Ar-C), 128.8 (Ar-C), 129.2 (Ar-C), 131.7 (Ar-C), 131.9 (Alkene-C=C), 136.6 (Ar-C), 137.2 (Ar-C), 137.8 (Ar-C), 169.7 (C=O), 170.3 (C=O), 171.4 (C=O);

IR U_{max} /cm^{-1} (solid) 3221 m (N-H), 3058 w (C-H), 2927 w (C-H), 1736 s (Ester C=O), 1636 m (C=C), 1537 m (C=C), 1214 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{37}H_{37}N_2O_4$: 573.2748, found: 573.2744.

2.8. Attempted modification of Phe dipeptides 4h and 4i

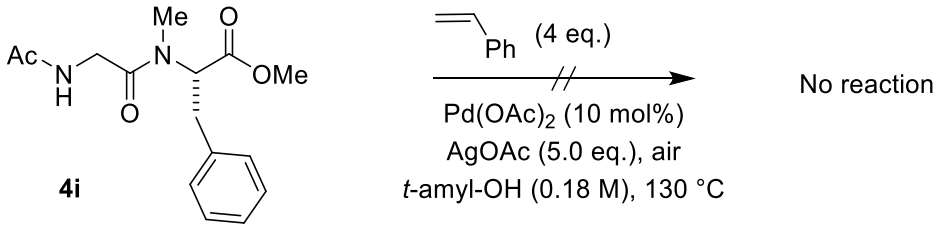
Attempted olefination of Ac-Phe-Gly-OMe (4h)



4h

Peptide **4h** was subjected to the general procedure described in **section 2.3.1**. After 12 h, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a mixture of unreacted peptide **4h** and styrene only. There was no evidence for modification of the peptide.

Attempted olefination of Ac-Gly-(N-Me)Phe-OMe (4i)

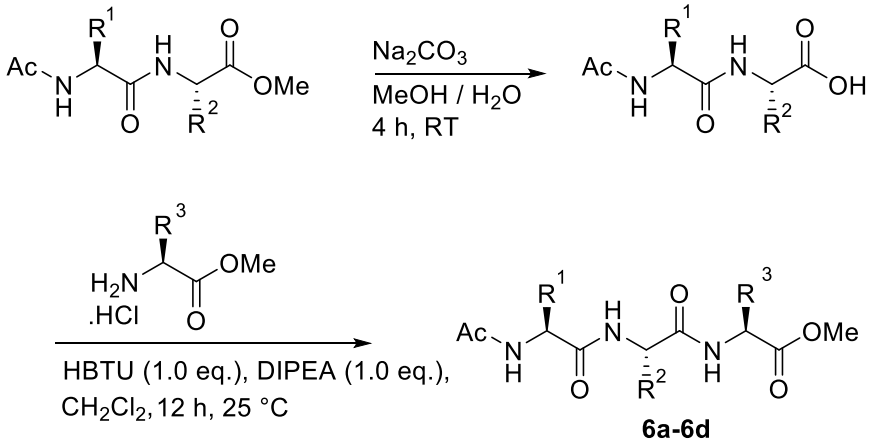


4i

Peptide **4i** was subjected to the general procedure described in **section 2.3.1**. After 12 h, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a mixture of unreacted peptide **4i** and styrene only. There was no evidence for modification of the peptide.

2.9. Synthesis of tri- and tetra-peptides

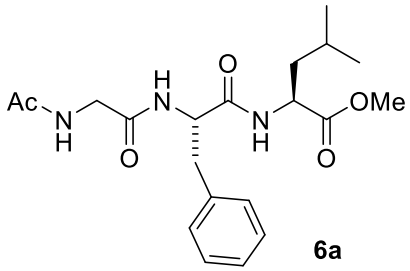
2.9.1. General procedure for the synthesis of tripeptides



6a-6d

Sodium carbonate (0.206 g, 1.940 mmol) was dissolved in H_2O (15 mL) and added to a solution of the appropriate dipeptide ester (0.970 mmol) in MeOH (15 mL). The resulting suspension was stirred at room temperature for 4 h before acidification by the dropwise addition of 1 M HCl (~3 mL). The aqueous solvent was then removed and the resulting solid washed with ethanol (3 x 10 mL), before the filtrate was evaporated to dryness. The crude dipeptide acid was then used without further purification. L-(amino acid) methyl ester hydrochloride (2.280 mmol) and K_2CO_3 (0.454 g, 3.283 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 N-protected dipeptide (0.912 mmol), HBTU (0.346 g, 0.912 mmol) and DIPEA (0.158 mL, 0.912 mmol) were added. The suspension was then 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 residue was purified by column chromatography using EtOAc as eluent, before being recrystallised using CH_2Cl_2 / hexanes.

Ac-Gly-Phe-Leu-OMe (6a)



6a

Peptide **6a** was synthesised from Ac-Gly-Phe-OMe (**1a**) (0.270 g, 0.970 mmol) and L-leucine methyl ester hydrochloride (0.414 g, 2.280 mmol), using the procedure in **section 2.9.1**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **6a** as a white solid (0.186 g, 52% over 2 steps); m.p. 180-181 °C**,** R_f 0.11 (EtOAc).

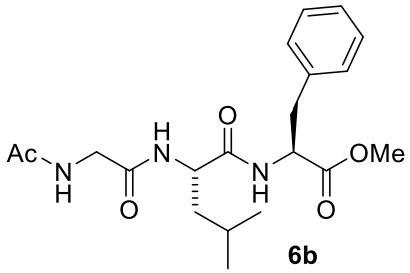
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.90 (6H, m, Leu-(C*H*$_3$)$_2$), 1.49-1.56 (3H, m, Leu-CH$_2$C*H*CH$_3$)$_2$), 2.01 (3H, s, Acetyl-C*H*$_3$), 3.03-3.14 (2H, m, Phe-C*H*$_2$), 3.71 (3H, s, Ester-C*H*$_3$), 3.89 (2H, d, *J* = 5.5, Gly-C*H*$_2$), 4.49-4.55 (1H, m, Phe-α-C*H*), 4.68-4.74 (1H, dt, *J* = 7.8, *J* = 6.9, Leu-α-C*H*), 6.30 (1H, m, Gly-N*H*), 6.37 (1H, br d, *J* = 7.8, Phe-N*H*), 6.70 (1H, br d, *J* = 7.8, Leu-N*H*), 7.20-7.22 (2H, m, Ar-*H*), 7.24-7.31 (3H, m, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.8 (Leu-CH_3), 22.4 (Leu-CH_3), 23.3 (Acetyl-CH_3), 25.8 (Leu-CH), 38.8 (Phe-CH_2), 41.4 (Leu-CH_2), 43.5 (Gly-CH_2), 52.2 (Ester-CH_3), 52.7 (Phe-α-CH), 55.6 (Leu-α-CH), 127.8 (Ar-C), 129.4 (Ar-C), 130.4 (Ar-C), 138.2 (Ar-C), 171.4 (C=O), 173.5 (C=O), 173.8 (C=O), 174.3 (C=O);

IR U_{max} /cm^{-1} (solid) 3278 m (N-H), 2975 w (C-H), 1748 s (Ester C=O), 1694 s (Amide C=O), 1530 m (C=C), 1435 m (C-H), 1224 s (C-O);

HRMS (ESI) [M+H$^+$] m/z calcd. for $C_{20}H_{30}N_3O_5$: 392.2180, found: 392.2178.

Ac-Gly-Leu-Phe-OMe (6b)



6b

Peptide **6b** was synthesised from Ac-Gly-Leu-OMe (**4j**) (0.237 g, 0.970 mmol) and L-phenylalanine methyl ester hydrochloride (0.499 g, 2.280 mmol), using the procedure in **section 2.9.1**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **6b** as a white solid (0.164 g, 46% over 2 steps); m.p. 125-128 °C, R_f 0.11 (EtOAc).

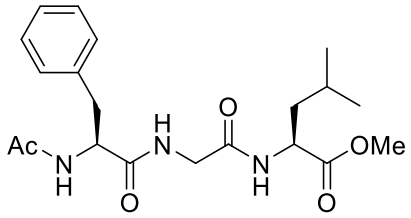
^{1}H NMR (400 MHz, CD_3OD) δ 0.89 (3H, d, *J* = 6.4, Leu-C*H*$_3$), 0.93 (3H, d, *J* = 6.4, Leu-C*H*$_3$), 1.47-1.51 (2H, m, Leu-C*H*$_2$), 1.59-1.63 (1H, m, Leu-CH$_2$C*H*(CH$_3$)$_2$), 2.00 (3H, s, Acetyl-C*H*$_3$), 2.97-3.03 (1H, m, Phe-C*H*H), 3.14 (1H, dd, *J* = 14.2, *J* = 6.0, Phe-C*H*H), 3.67 (3H, s, Ester-C*H*$_3$), 3.82 (2H, s, Gly-C*H*$_2$), 4.42 (1H, dd, *J* = 8.7, *J* = 6.4, Leu-α-C*H*), 4.62 (1H, dd, *J* = 8.7, *J* = 6.0, Phe-α-C*H*), 7.18-7.21 (2H,m, Ar-*H*), 7.25-7.29 (3H, m, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 22.0 (Leu-CH_3), 22.4 (Leu-CH_3), 23.4 (Acetyl-CH_3), 25.8 (Leu-CH), 38.2 (Phe-CH_2), 41.9 (Leu-CH_2), 43.5 (Gly-CH_2), 52.7 (Phe-α-CH), 52.9 (Ester-CH_3), 55.2 (Leu-α-CH), 127.9 (Ar-C), 129.5 (Ar-C), 130.3 (Ar-C), 138.1 (Ar-C), 171.5 (C=O), 173.2 (C=O), 173.9 (C=O), 174.6 (C=O);

IR U_{max} /cm^{-1} (solid) 3285 m (N-H), 2956 w (C-H), 1745 s (Ester C=O), 1694 s (Amide C=O), 1659 s (Amide C=O), 1531 m (C=C), 1435 m (C-H), 1210 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{20}H_{30}N_3O_5$: 392.2180, found: 392.2181.

Ac-Phe-Gly-Leu-OMe (6c)



6c

Peptide **6c** was synthesised from Ac-Phe-Gly-OMe (**4h**) (0.270 g, 0.970 mmol) and L-leucine methyl ester hydrochloride (0.414 g, 2.280 mmol), using the procedure in **section 2.9.1**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **6c** as a white solid (0.157 g, 44% over 2 steps); m.p. 144-145 °C, R_f 0.14 (EtOAc).

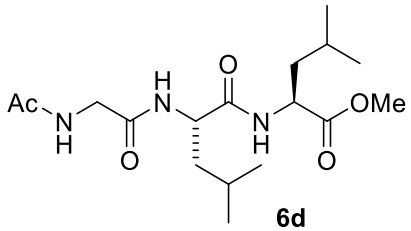
^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 0.94 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 1.56-1.67 (3H, m, Leu-C*H*$_2$C*H*$(CH_3)_2$), 1.91 (3H, s, Ester-C*H*$_3$), 2.92 (1H, dd, *J* = 13.7, *J* = 8.9, Phe-C*H*H), 3.13 (1H, dd, *J* = 13.7, *J* = 6.2, Phe-C*H*H), 3.65-3.70 (4H, m, Ester-C*H*$_3$ / Gly C*H*H), 3.93 (1H, d, *J* = 16.9, Gly-C*H*H), 4.44-4.50 (1H, m, Phe-α-C*H*), 7.19-7.30 (5H, m, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.6 (Acetyl-CH_3), 22.4 (Leu-CH_3), 23.4 (Leu-CH_3), 25.8 (Leu-CH), 38.2 (Phe-CH_2), 41.2 (Gly-CH_2), 43.3 (Leu-CH_2), 52.1 (Ester-CH_3), 52.7 (Leu-α-CH), 57.0 (Phe-α-CH), 127.8 (Ar-C), 129.5 (Ar-C), 130.2 (Ar-C), 138.4 (Ar-C), 171.6 (C=O), 173.6 (C=O), 174.4 (C=O), 174.6 (C=O);

IR U_{max} /cm^{-1} (solid) 3285 m (N-H), 2959 w (C-H), 1750 s (Ester C=O), 1692 s (Amide C=O), 1631 s (Amide C=O), 1436 m (C-H), 1228 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{20}H_{29}N_3O_5$: 392.2180, found: 392.2181.

Ac-Gly-Leu-Leu-OMe (6d)



6d

Peptide **6d** was synthesised from Ac-Gly-Leu-OMe (**4j**) (0.237 g, 0.970 mmol) and L-leucine methyl ester hydrochloride (0.414 g, 2.280 mmol), using the procedure in **section 2.9.1**. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **6d** as a white solid (0.235 g, 72% over 2 steps); m.p. 125-128 °C; Rf 0.19 (EtOAc).

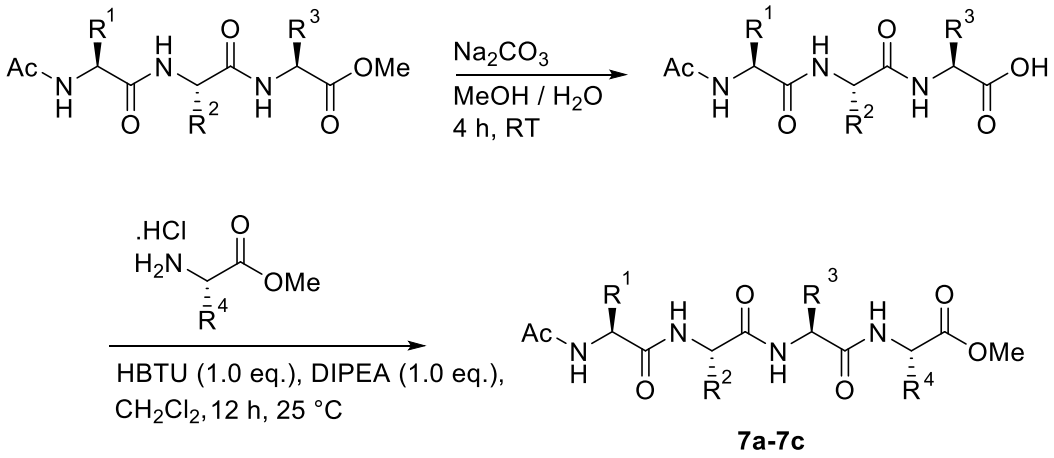
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91-0.95 (12H, m, (Leu-(C*H*$_3$)$_2$) x2), 1.52-1.69 (6H, m, (Leu-C*H*$_2$C*H*(CH$_3$)$_2$) x2), 2.04 (3H, s, Acetyl-C*H*$_3$), 3.73 (3H, s, Ester-C*H*$_3$), 3.93-4.03 (2H, m, Gly-C*H*$_2$), 4.52-4.58 (2H, m, (Leu-α-C*H*) x2), 6.62 (1H, br t, *J* = 5.0, Gly-N*H*), 6.72 (1H, br d, *J* = 8.2, Leu-N*H*), 6.86 (1H, br d, *J* = 8.7, Leu-N*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9 (Acetly-CH_3), 22.2 (Leu-CH_3), 22.7 (Leu-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 22.8 (Leu-CH_3), 24.6 (Leu-CH, 24.8 (Leu-CH), 40.9 (Leu-CH_2), 41.7 (Leu-CH_2), 43.2 (Gly-CH_2), 50.9 (Leu-α-CH), 51.7 (Leu-α-CH), 52.2 (Ester-CH_3), 169.0 (C=O), 170.9 (C=O), 172.1 (C=O), 173.2 (C=O);

IR υ_{max} /cm^{-1} (solid) 3275 m (N-H), 3075 w (C-H), 2957 w (C-H), 1750 s (Ester C=O), 1691 s (Amide C=O), 1630 s (Amide C=O), 1532 m (C=C), 1438 m (C-H), 1202 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{41}N_4O_6$: 505.3021 found: 505.3020.

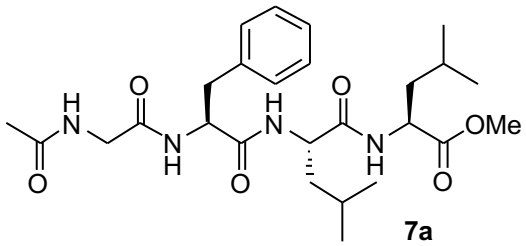
2.9.2. General procedure for the synthesis of tetrapeptides



7a-7c

Sodium carbonate (0.068 g, 0.646 mmol) was dissolved in H_2O (10 mL) and added to a solution of the appropriate tripeptide ester (0.323 mmol) in MeOH (10 mL). The resulting suspension was stirred at room temperature for 4 h before acidification by the dropwise addition of 1 M HCl (~3 mL). The aqueous solvent was then removed and the resulting solid washed with ethanol (3 x 10 mL), before the filtrate was evaporated to dryness. The crude tripeptide acid was carried through without further purification. The appropriate L-(amino acid) methyl ester hydrochloride (0.808 mmol) and K_2CO_3 (0.161 g, 1.162 mmol) were dissolved in distilled water (30 mL) and stirred for 10 mins 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 N-protected dipeptide (0.323 mmol), HBTU (0.122 g, 0.323 mmol) and DIPEA (0.056 mL, 0.323 mmol) were added. The suspension was then 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 concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography using EtOAc as eluent, before being recrystallised using CH_2Cl_2 / hexanes.

Ac-Gly-Phe-Leu-Leu-OMe (7a)



7a

Peptide **7a** was synthesised from Ac-Gly-Phe-Leu-OMe (**6a**) (0.126 g, 0.323 mmol) and L-leucine methyl ester hydrochloride (0.147 g, 0.808 mmol), using the general procedure in **section 2.9.2**. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **7a** as a white solid (0.104 g, 64%); m.p. 179-181 °C, R_f 0.13 (10% MeOH/CH_2Cl_2).

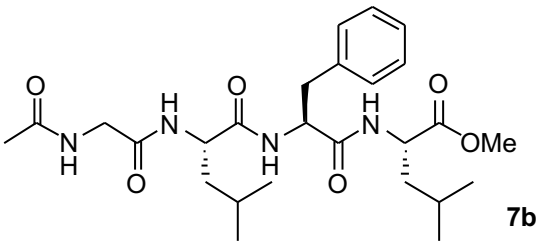
^{1}H NMR (400 MHz, CD_3CN) δ 0.80-0.87 (12H, m, Leu-(C*H*$_3$)$_2$ (x2)), 1.42-1.61 (6H, m, Leu-C*H*$_2$ / Leu-CH$_2$C*H*(CH$_3$)$_2$ (x2)), 1.81 (3H, s, Acetly-C*H*$_3$), 2.96 (1H, dd, *J* = 14.2, *J* = 8.2, Phe-C*H*H), 3.10 (1H, dd, *J* = 14.2, *J* = 5.0, Phe-C*H*H), 3.56 (1H, dd, *J* = 5.3, *J* = 2.6, Gly-C*H*H), 3.59 (4H, m, Ester-C*H*$_3$ / Gly-C*H*H), 4.19-4.29 (1H, m, Phe-α-C*H* / Leu-α-C*H*), 4.38-4.43 (1H, m, Leu-α-C*H*), 6.78 (1H, br d, *J* = 6.0, N*H*), 6.88 (2H, m, N*H*), 7.02 (1H, d, *J* = 8.7, N*H*), 7.16-7.28 (5H, m, Phe-Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.8 (Leu-CH_3), 22.0 (Leu-CH_3), 22.4 (Acetyl-CH_3), 23.4 (Leu-CH_3), 23.5 (Leu-CH_3), 25.7 (Leu-CH), 25.8 (Leu-CH), 38.3 (Phe-CH_2), 41.4 (Leu-CH_2), 41.8 (Leu-CH_2), 43.6 (Gly-CH_2), 52.6 (Ester-CH_3), 53.0 (Leu-α-CH), 53.2 (Leu-α-CH), 55.2 (Phe-α-CH), 127.9 (Ar-C), 129.5 (Ar-C), 130.3 (Ar-C), 138.0 (Ar-C), 171.9 (C=O), 173.2 (C=O), 173.9 (C=O), 174.6 (C=O), 174.8 (C=O).

IR υ_{max} /cm^{-1} (solid) 3279 m (N-H), 3067 w (C-H), 2956 w (C-H), 1748 s (Ester C=O), 1692 s (Amide C=O), 1630 m (C=C), 1526 m (C=C), 1439 m (C-H), 1203 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{41}N_4O_6$: 505.3021 found: 505.3013.

Ac-Gly-Leu-Phe-Leu-OMe (7b)



7b

Peptide **7b** was synthesised from Ac-Gly-Leu-Phe-OMe (**6b**) (0.126 g, 0.323 mmol) and L-leucine methyl ester hydrochloride (0.147 g, 0.808 mmol), using the general procedure in **section 2.9.2**. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **7b** as a white solid (0.112 g, 69%); m.p. 190-193 °C, R_f 0.10 (10% MeOH/CH_2Cl_2).

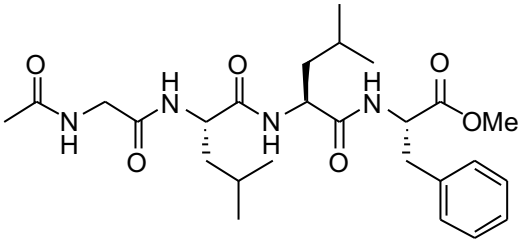
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-0.98 (12H, m, Leu-(C*H*$_3$)$_2$ (x2)), 1.54-1.65 (6H, m, Leu-C*H*$_2$ / Leu-CH$_2$C*H*(CH$_3$)$_2$ (x2)), 1.99 (3H, s, Acetly-C*H*$_3$), 3.02-3.11 (2H, m, Phe-C*H*$_2$), 3.71 (3H, s, Ester-C*H*$_3$), 3.89-3.94 (1H, m, Gly-C*H*H), 4.06-4.13 (1H, m, Gly-C*H*H), 4.47-4.54 (1H, α-C*H*), 4.77-4.78 (1H, m, α-C*H*), 4.96-5.01 (1H, m, α-C*H*), 7.16-7.28 (7H, m, Phe-Ar-*H* / N*H* / N*H*), 7.54-7.59 (2H, m, N*H* (x2)).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.8 (Leu-CH_3), 21.9 (Leu-CH_3), 22.5 (Acetyl-CH_3), 23.1 (Leu-CH_3), 23.4 (Leu-CH_3), 25.5 (Leu-CH), 25.8 (Leu-CH), 38.4 (Phe-CH_2), 41.4 (Leu-CH_2), 41.7 (Leu-CH_2), 43.7 (Gly-CH_2), 52.2 (α-CH), 52.7 (Ester-CH_3), 53.3 (α-CH), 55.8 (α-CH), 127.7 (Ar-C), 129.4 (Ar-C), 130.4 (Ar-C), 138.5 (Ar-C), 171.9 (C=O), 173.4 (C=O), 174.2 (C=O), 174.4 (C=O), 174.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3277 m (N-H), 3073 w (C-H), 2956 w (C-H), 1745 s (Ester C=O), 1694 s (Amide C=O), 1630 m (C=C), 1526 m (C=C), 1438 m (C-H), 1205 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{41}N_4O_6$: 505.3021 found: 505.3017.

Ac-Gly-Leu-Leu-Phe-OMe (7c)



7c

Peptide **7c** was synthesised from Ac-Gly-Leu-Leu-OMe (**6d**) (0.155 g, 0.323 mmol) and L-phenylalanine methyl ester hydrochloride (0.174 g, 0.808 mmol), using the procedure in **section 2.9.2**. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **7c** as a white solid (0.072 g, 44%); m.p. 181-184 °C, R_f 0.09 (10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, CD_3OD) δ 0.88-0.97 (12H, m, Leu-C*H*$_3$ (x2)), 1.46-1.65 (6H, m, Leu-C*H*$_2$ / Leu-CH_2C*H*$(CH_3)_2$ (x2)), 1.98 (3H, s, Acetyl-C*H*$_3$), 2.98-3.03 (1H, m, Phe-C*H*H), 3.11-3.19 (1H, m, Phe-C*H*H), 3.66 (3H, s, Ester-C*H*$_3$), 3.83-3.86 (2H, m, Gly-C*H*$_2$), 4.29-4.40 (3H, m, Leu-α-C*H* / Leu-α-C*H*), 4.60-4.65 (1H, m, Phe-α-C*H*) 7.18-7.28 (5H, m, Phe-Ar-*H*).

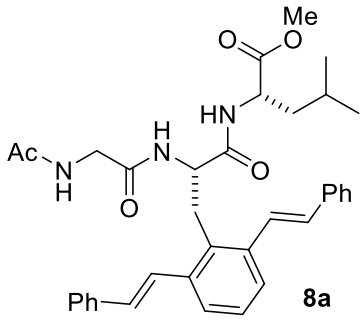
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 21.8 (Leu-CH_3), 22.0 (Leu-CH_3), 22.4 (Acetyl-CH_3), 23.4 (Leu-CH_3), 23.5 (Leu-CH_3), 25.8 (Leu-CH), 25.8 (Leu-CH), 38.3 (Phe-CH_2), 41.4 (Leu-CH_2), 41.7 (Leu-CH_2), 43.7 (Gly-CH_2), 52.6 (Ester-CH_3), 53.2 (α-CH), 53.8 (α-CH), 55.2 (α-CH), 127.9 (Ar-C), 129.5 (Ar-C), 130.3 (Ar-C), 138.0 (Ar-C), 171.9 (C=O), 173.2 (C=O), 173.9 (C=O), 174.5 (C=O), 174.8 (C=O).

IR U_{max} /cm^{-1} (solid) 3270 m (N-H), 3070 w (C-H), 2955 w (C-H), 1744 s (Ester C=O), 1692 s (Amide C=O), 1630 m (C=C), 1532 m (C=C), 1436 m (C-H), 1210 s (C-O);

HRMS (ESI) [M+H$^+$] *m/z* calcd. for $C_{26}H_{41}N_4O_6$: 505.3021 found: 505.3015.

2.10. Modification of tri- and tetra-peptides

Synthesis of modified peptide 8a



8a

Modified peptide **8a** was prepared from Ac-Gly-Phe-Leu-OMe (**6a**) (0.100 g, 0.255 mmol) and styrene (0.118 mL, 1.022 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **8a** and the mono-olefinated peptide in a ratio of 4:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **8a** as an off-white solid (0.090 g, 59%); m.p. 206-207 °C, R_f 0.24 (EtOAc).

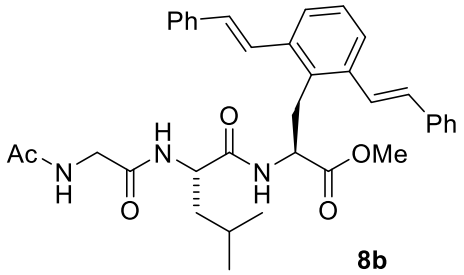
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 0.83 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 1.32-1.37 (1H, m, Leu-CH$_2$C*H*(CH$_3$)$_3$), 1.42-1.48 (2H, m, Leu-C*H*$_2$), 1.91 (3H, s, Acetyl-C*H*$_3$), 3.34-3.46 (2H, m, Phe-C*H*$_2$), 3.76 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 3.85 (1H, dd, *J* = 16.8, *J* = 5.0, Gly-C*H*H), 4.43 (1H, dt, *J* = 7.4, *J* = 5.5, Leu-α-C*H*), 4.60 (1H, dt, *J* = 7.9, *J* = 7.4, Phe-α-C*H*), 6.05 (1H, br d, *J* = 7.9, Phe-N*H*), 6.13 (1H, br t, *J* = 5.0, Gly-N*H*), 6.79 (1H, br d, *J* = 7.4, Leu-N*H*), 6.98 (2H, d, *J* = 16.0, Alkene-C*H*), 7.26-7.32 (3H, m, Ar-*H*), 7.37-7.41 (4H, m, Ar-*H*), 7.54-7.59 (4H, m, Alkene-C*H* / Ar-*H*), 7.61 (4H, d, *J* = 7.4, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.0 (Leu-CH_3), 22.4 (Leu-CH_2), 22.8 (Acetyl-CH_3), 24.6 (Leu-CH), 32.1 (Phe-CH_2), 41.5 (Gly-CH_2), 42.9 (Leu-CH_2), 51.1 (Phe-α-CH), 52.2 (Ester-CH_3), 54.4 (Leu-α-CH) 125.9 (Ar-C), 126.3 (Alkene-C=C), 126.8 (Ar-C), 127.6 (Ar-C), 128.0 (Ar-C), 128.8 (Ar-C), 131.9 (Alkene-C=C), 132.1 (Ar-C), 137.1 (Ar-C), 137.9 (Ar-C), 168.2 (C=O), 170.0 (C=O), 170.4 (C=O), 127.3 (C=O);

IR υ_{max} /cm^{-1} (solid) 3276 m (N-H), 3062 w (C-H), 2928 w (C-H), 1741 s (Ester C=O), 1632 m (C=C), 1533 m (C=C), 1448 m (C-H), 1150 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{36}H_{42}N_3O_5$: 596.3119 found: 596.3113.

Synthesis of modified peptide 8b



8b

Modified peptide **8b** was prepared from Ac-Gly-Leu-Phe-OMe (**6b**) (0.100 g, 0.255 mmol) and styrene (0.118 mL, 1.022 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **8b** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave **8b** as an off-white solid (0.096 g, 63%); m.p. 204-207 °C, R_f 0.22 (EtOAc)

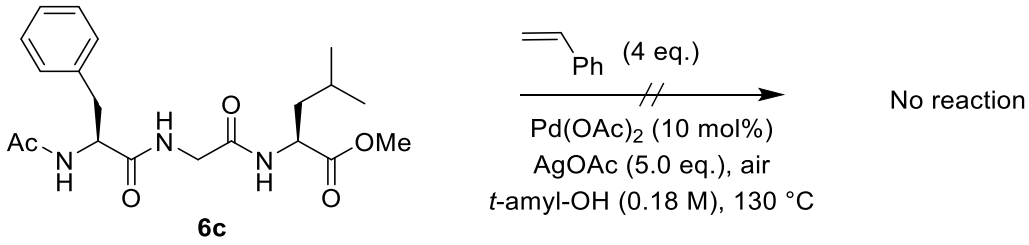
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 0.80 (3H, d, *J* = 6.2, Leu-C*H*$_3$), 1.34-1.40 (1H, m, Leu-CH$_2$C*H*(CH$_3$)$_3$), 1.44-1.56 (2H, m, Leu-C*H*$_2$), 1.91 (3H, s, Acetyl-C*H*$_3$), 3.42 (2H, d, *J* = 7.7, Phe-C*H*$_2$), 3.57 (3H, s, Ester-C*H*$_3$), 3.63 (1H, dd, *J* = 16.5, *J* = 5.0, Gly-C*H*H), 3.71 (1H, dd, *J* = 16.5, *J* = 5.0, Gly-C*H*H), 4.39 (1H, dt, *J* = 5.5, *J* = 4.6, Leu-α-C*H*), 4.76 (1H, app q, *J* = 7.7, Phe-α-C*H*), 6.43 (1H, br d, *J* = 8.3, Leu-N*H*), 6.48 (1H, m, Gly-N*H*), 6.92 (1H, br d, *J* = 7.7, Phe-N*H*), 6.99 (2H, d, *J* = 16.0, Alkene-C*H*), 7.25-7.29 (3H, m, Ar-*H*), 7.35-7.39 (4H, m, Ar-*H*), 7.48-7.55 (4H, m, Alkene-C*H* / Ar-*H*), 7.58 (4H, d, *J* = 7.7, Ar-*H*);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.7 (Acetyl-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 24.6 (Leu-CH), 31.4 (Phe-CH_2), 41.0 (Gly-CH_2), 43.2 (Leu-CH_2), 51.7 (Leu-α-CH), 52.6 (Ester-CH_3), 53.1 (Phe-α-CH), 125.8 (Ar-C), 126.3 (Alkene-C=C), 126.8 (Ar-C), 127.6 (Ar-C), 127.9 (Ar-C), 128.8 (Ar-C), 131.8 (Alkene-C=C), 132.1 (Ar-C), 137.2 (Ar-C), 137.7 (Ar-C), 168.8 (C=O), 170.8 (C=O), 171.4 (C=O), 171.9 (C=O);

IR U_{max} /cm^{-1} (solid) 3275 s (N-H), 3062 w (C-H), 2954 w (C-H), 1743 s (Ester C=O), 1634 m (C=C), 1527 m (C=C), 1207 s (C-O);

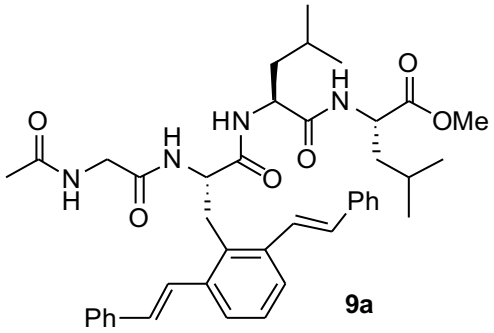
HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{36}H_{42}N_3O_5$: 596.3119 found: 596.3114.

Attempted olefination of Ac-Phe-Gly-Leu-OMe (6c)



Peptide **6c** was subjected to the general procedure described in **section 2.3.1**. After 12 h, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a mixture of unreacted peptide **6c** and styrene only. There was no evidence for modification of the peptide.

Synthesis of modified peptide 9a



9a

Modified peptide **9a** was prepared from Ac-Gly-Phe-Leu-Leu-OMe (**7a**) (0.060 g, 0.119 mmol) and styrene (0.055 mL, 0.476 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **9a** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **9a** as an off-white solid (0.025 g, 30%); m.p. 206-209 °C, R_f 0.15 (10% MeOH/CH_2Cl_2)

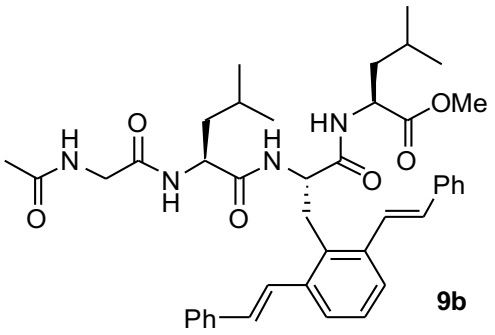
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76-0.83 (12H, m, Leu-(C*H*$_3$)$_2$ (x2)), 1.42-1.52 (6H, m, Leu-C*H*$_2$ / Leu-CH$_2$C*H*(CH$_3$)$_2$ (x2)), 1.91 (3H, s, Acetly-C*H*$_3$), 3.35-3.40 (1H, m, Phe-C*H*H), 3.45-3.56 (2H, m, Phe-C*H*H / Gly-C*H*H), 3.59 (3H, s, Ester-C*H*$_3$), 3.66 (1H, d, *J* = 15.6, Gly-C*H*H), 4.37-4.46 (2H, m, α-C*H* (x2)), 4.73 (1H, m, α-C*H*), 6.94 (2H, d, *J* = 15.6, Alkene-C*H*), 7.22-7.25 (2H, m, Ar-*H*), 7.35 (5H, m, Ar-*H*), 7.50 (2H, d, *J* = 7.3, Ar-*H*), 7.58-7.63 (6H, m, Alkene-C*H* / Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 22.0 (Leu-CH_3), 22.6 (Acetyl-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 24.7 (Leu-CH), 24.7 (Leu-CH), 31.9 (Phe-CH_2), 41.1 (Leu-CH_2), 41.6 (Leu-CH_2), 43.3 (Gly-CH_2), 51.1 (Ester-CH_3), 52.0 (Leu-α-CH), 52.1 (Leu-α-CH), 54.5 (Phe-α-CH), 125.9 (Ar-C), 126.8 (Ar-C), 126.9 (Ar-C), 127.5 (Ar-C),127.9 (Ar-C), 128.8 (Ar-C), 131.8 (Ar-C), 132.7 (Ar-C), 137.2 (Ar-C), 138.0 (Ar-C), 168.8 (C=O), 170.6 (C=O), 170.6 (C=O), 171.4 (C=O), 172.4 (C=O).

IR U_{max} /cm^{-1} (solid) 3272 m (N-H), 3068 w (C-H), 2957 w (C-H), 1747 s (Ester C=O), 1693 s (Amide C=O), 1626 m (amide C=O), 1521 m (C=C), 1438 m (C-H), 1203 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{42}H_{53}N_4O_6Na$: 731.3779 found: 731.3782

Synthesis of modified peptide 9b



9b

Modified peptide **9b** was prepared from Ac-Gly-Leu-Phe-Leu-OMe (**7b**) (0.060 g, 0.119 mmol) and styrene (0.055 mL, 0.476 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **9b** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **9b** as an off-white solid (0.036 g, 43%); m.p. 208-211 °C, R_f 0.15 (10% MeOH/CH_2Cl_2)

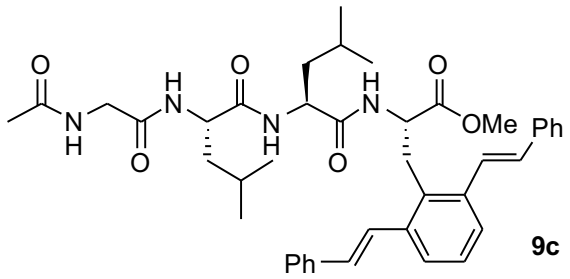
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77-0.85 (12H, m, Leu-(C*H*$_3$)$_2$ (x2)), 1.45-1.52 (6H, m, Leu-C*H*$_2$ / Leu-CH$_2$C*H*(CH$_3$)$_2$ (x2)), 1.92 (3H, s, Acetly-C*H*$_3$), 3.36-3.42 (1H, m, Phe-C*H*H), 3.46-3.56 (2H, m, Phe-C*H*H / Gly-C*H*H), 3.60 (3H, s, Ester-C*H*$_3$), 3.74-3.79 (1H, m, Gly-C*H*H), 4.37 (1H, m, α-C*H*), 4.43-4.47 (1H, m, α-C*H*) 4.74 (1H, m, α-C*H*), 6.95 (2H, d, *J* = 15.9, Alkene-C*H*), 7.23-7.25 (2H, m, Ar-*H*), 7.35 (5H, t, *J* = 7.4, Ar-*H*), 7.51 (2H, d, *J* = 7.8, Ar-*H*), 7.59-7.65 (6H, m, Alkene-C*H* / Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 22.0 (Leu-CH_3), 22.6 (Acetyl-CH_3), 22.7 (Leu-CH_3), 22.8 (Leu-CH_3), 24.6 (Leu-CH), 24.7 (Leu-CH), 31.9 (Phe-CH_2), 41.1 (Leu-CH_2), 41.5 (Leu-CH_2), 43.3 (Gly-CH_2), 51.1 (Ester-CH_3), 52.0 (Leu-α-CH), 52.1 (Leu-α-CH), 54.5 (Phe-α-CH), 125.9 (Ar-C), 126.7 (Ar-C), 126.9 (Ar-C), 127.5 (Ar-C),127.9 (Ar-C), 128.8 (Ar-C), 131.8 (Ar-C), 132.7 (Ar-C), 137.2 (Ar-C), 137.9 (Ar-C), 168.9 (C=O), 170.6 (C=O), 170.8 (C=O), 171.5 (C=O), 172.4 (C=O).

IR U_{max} /cm^{-1} (solid) 3275 m (N-H), 3062 w (C-H), 2957 w (C-H), 2923 w (C-H), 1742 s (Ester C=O), 1628 m (amide C=O), 1532 m (C=C), 1449 m (C-H), 1259 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{42}H_{53}N_4O_6$: 709.3965 found: 709.3964.

Synthesis of modified peptide 9c



9c

Modified peptide **9c** was prepared from Ac-Gly-Leu-Leu-Phe-OMe (**7c**) (0.060 g, 0.119 mmol) and styrene (0.055 mL, 0.476 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide **9c** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) followed by recrystallisation from CH_2Cl_2 / hexanes gave **9c** as an off-white solid (0.034 g, 40%); m.p. 205-209 °C, R_f 0.19 (10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75-0.87 (12H, m, Leu-(C*H*$_3$)$_2$ (x2)), 1.42-1.54 (6H, m, Leu-C*H*$_2$ / Leu-CH$_2$C*H*(CH$_3$)$_2$ (x2)), 1.93 (3H, s, Acetly-C*H*$_3$), 3.34-3.41 (1H, m, Phe-C*H*H), 3.43-3.49 (1H, m, Phe-C*H*H), 3.59 (3H, s, Ester-C*H*$_3$), 3.64-3.68 (2H, m, Gly-C*H*$_2$), 4.36 (1H, m, α-C*H*), 4.43-4.44 (1H, m, α-C*H*), 4.69-4.71 (1H, m, α-C*H*), 6.94 (2H, d, *J* = 16.0, Alkene-C*H*), 7.09-7.06 (2H, m, Ar-*H*), 7.21-7.23 (2H, m, Ar-*H*), 7.34 (5H, t, *J* = 7.4, Ar-*H*), 7515 (2H, d, *J* = 7.8, Ar-*H*), 7.58-7.63 (6H, m, Alkene-C*H* / Ar-*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8 (Leu-CH_3), 21.9 (Leu-CH_3), 22.6 (Acetyl-CH_3), 22.8 (Leu-CH_3), 23.0 (Leu-CH_3), 24.5 (Leu-CH), 24.6 (Leu-CH), 31.7 (Phe-CH_2), 40.7 (Leu-CH_2), 41.3 (Leu-CH_2), 43.3 (Gly-CH_2), 50.9 (Ester-CH_3), 51.8 (Leu-α-CH), 52.3 (Leu-α-CH), 53.9 (Phe-α-CH), 125.7 (Ar-C), 126.4 (Ar-C), 126.9 (Ar-C), 127.4 (Ar-C),127.9 (Ar-C), 128.7 (Ar-C), 131.9 (Ar-C), 132.3 (Ar-C), 137.2 (Ar-C), 137.9 (Ar-C), 169.2 (C=O), 170.6 (C=O), 170.8 (C=O), 171.6 (C=O), 173.3 (C=O).

IR U_{max} /cm^{-1} (solid) 3274 m (N-H), 3062 w (C-H), 2956 w (C-H), 2920 w (C-H), 1742 s (Ester C=O), 1630 m (amide C=O), 1533 m (C=C), 1450 m (C-H), 1203 s (C-O);

HRMS (ESI) [M+H^{+}] *m/z* calcd. for $C_{42}H_{53}N_4O_6$: 709.3965 found: 709.3958.

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

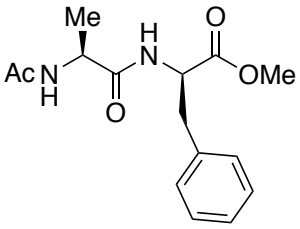
For the synthesis of modified peptides that contained more than one stereogenic centre, there was no evidence for the formation of diastereomeric products, as judged by NMR spectroscopy.

In addition, a detailed stereochemical investigation was carried out for the reaction of peptide Ac-Ala-Phe-OMe (**4a**) to give modified peptide **5a**. Specifically, the diastereomeric peptide Ac-Ala-D-Phe-OMe, (L,D)-**4a**, prepared from D-phenylalanine methyl ester and acetyl-L-alanine, was modified to give the diastereomeric modified peptide (L,D)-**5a**.

Comparison of the ^{1}H NMR spectra revealed no signals for (L,D)-**5a** in the spectrum for **5a**. Comparison of the HPLC chromatograms revealed that **5a** contained at very most, less than 2.5% (L,D)-**5a**. The small amount of the L,L contaminant **5a** in the reference sample (L,D)-**5a** arises from the enantiomeric impurity in the starting D-phenylalanine.

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

Ac-Ala-D-Phe-OMe, (L,D)-**4a**



(L,D)**4a**

Peptide (L,D)-**4a** was synthesised from D-phenylalanine methyl ester hydrochloride (0.539 g, 2.50 mmol) and *N*-acetyl-L-alanine (0.131 g, 1.00 mmol), using the procedure in **section 2.2.1**. The crude product was recrystallised from CH_2Cl_2 / hexanes to afford (L,D)-**4a** as a white solid (0.251 g, 86%); m.p. 125-128 °C.

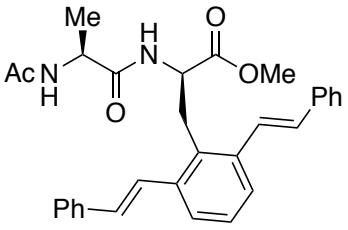
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, d, *J* = 7.0, Ala-C*H*$_3$), 1.98 (3H, s, Acetyl-C*H*$_3$), 3.06 (1H, dd, *J* = 13.8, *J* = 6.4, Phe-C*H*H), 3.17 (1H, dd, *J* = 13.8, *J* = 6.4, Phe-C*H*H), 3.73 (3H, s, Ester-C*H*$_3$), 4.47 (1H, dq, *J* = 7.0, *J* = 6.4, Ala-α-C*H*), 4.81-4.86 (1H, m, Phe-α-C*H*), 6.21 (1H, br d, *J* = 7.0, Ala-N*H*), 6.81 (1H, br d, *J* = 7.6, Phe-N*H*), 7.10-7.13 (2H, m, Ar-*H*), 7.24-7.31 (3H, m, Ar-*H*).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 18.4 (Ala-CH_3), 23.1 (Acetyl-CH_3), 38.6 (Phe-CH_2), 48.7 (Ala-α-CH), 52.4 (Ester-CH_3), 53.1 (Phe-α-CH), 127.2 (Ar-C), 128.6 (Ar-C), 129.2 (Ar-C), 135.7 (Ar-C), 169.9 (C=O), 171.7 (C=O), 171.9 (C=O).

IR υ_{max} /cm^{-1} (solid) 3298 m, 3265 m (N-H), 3075 s (C-H), 3088 w, 3029 w, 2959 w, 2932 w (C-H), 1735 s (Ester C=O), 1636 s (Amide C=O), 1539 m (C=C), 1437 m (C-H).

HRMS (ESI) $[M+H^+]$ *m/z* calcd. for $C_{15}H_{21}N_2O_4$: 293.1496, found: 293.1495.

Synthesis of modified peptide (L,D)-**5a**



(L,D)**5a**

Modified peptide (L,D)-**5a** was prepared from Ac-Ala-D-Phe-OMe, (L,D)-**4a**, (0.105 g, 0.359 mmol) and styrene (0.166 mL, 1.440 mmol), using the general procedure in **section 2.3.1**. The ^{1}H NMR spectrum for the crude product contained a mixture of the di-olefinated peptide (L,D)-**5a** and the mono-olefinated peptide in a ratio of 5:1. Purification by flash column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 / hexanes gave (L,D)-**5a** as an off-white solid (0.124 g, 70%); m.p. 166-169 °C, R_f 0.46 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, *J* = 7.0, Ala-C*H*$_3$), 1.88 (3H, s, Acetyl-C*H*$_3$), 3.40-3.48 (2H, m, Phe-C*H*$_2$), 3.59 (3H, s, CO_2CH_3), 4.42 (1H, dq, *J* = 7.4, *J* = 7.0, Ala-α-C*H*), 4.76 (1H, app q, *J* = 7.6, Phe-α-C*H*), 6.08 (1H, br d, *J* = 7.4, Ala-N*H*), 6.90 (1H, br d, *J* = 7.9, Phe-N*H*), 7.01 (2H, d, *J* = 15.9, Alkene-C*H*), 7.26-7.31 (3H, m, Ar- *H*), 7.36-7.40 (4H, m, Ar-*H*), 7.50 (2H, d, *J* = 15.8, Alkene-C*H*), 7.56-7.59 (6H, m Ar-*H*);

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 18.1 (Ala-CH_3), 23.0 (Acetyl-CH_3), 31.3 (Phe-CH_2), 48.5 (Ala-α-CH), 52.6 (Ester-CH_3), 53.0 (Phe-α-CH), 125.7 (Ar-C), 126.1 (Alkene-C=C), 126.8 (Ar-C), 127.6 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 131.8 (Ar-C), 132.0 (Alkene-C=C), 137.2 (Ar-C), 137.7 (Ar-C), 169.8 (C=O), 171.8 (C=O), 172.0 (C=O);

IR υ_{max} /cm^{-1} (solid) 3284 m (N-H), 3050 w (C-H), 2950 w (C-H), 2927 w (C-H), 1731 s (Ester C=O), 1631 m (amide C=O), 1528 m (C=C).

HRMS (ESI) $[M+H^+]$ *m/z* calcd. for $C_{31}H_{33}N_2O_4$: 497.2435 found: 497.2430.

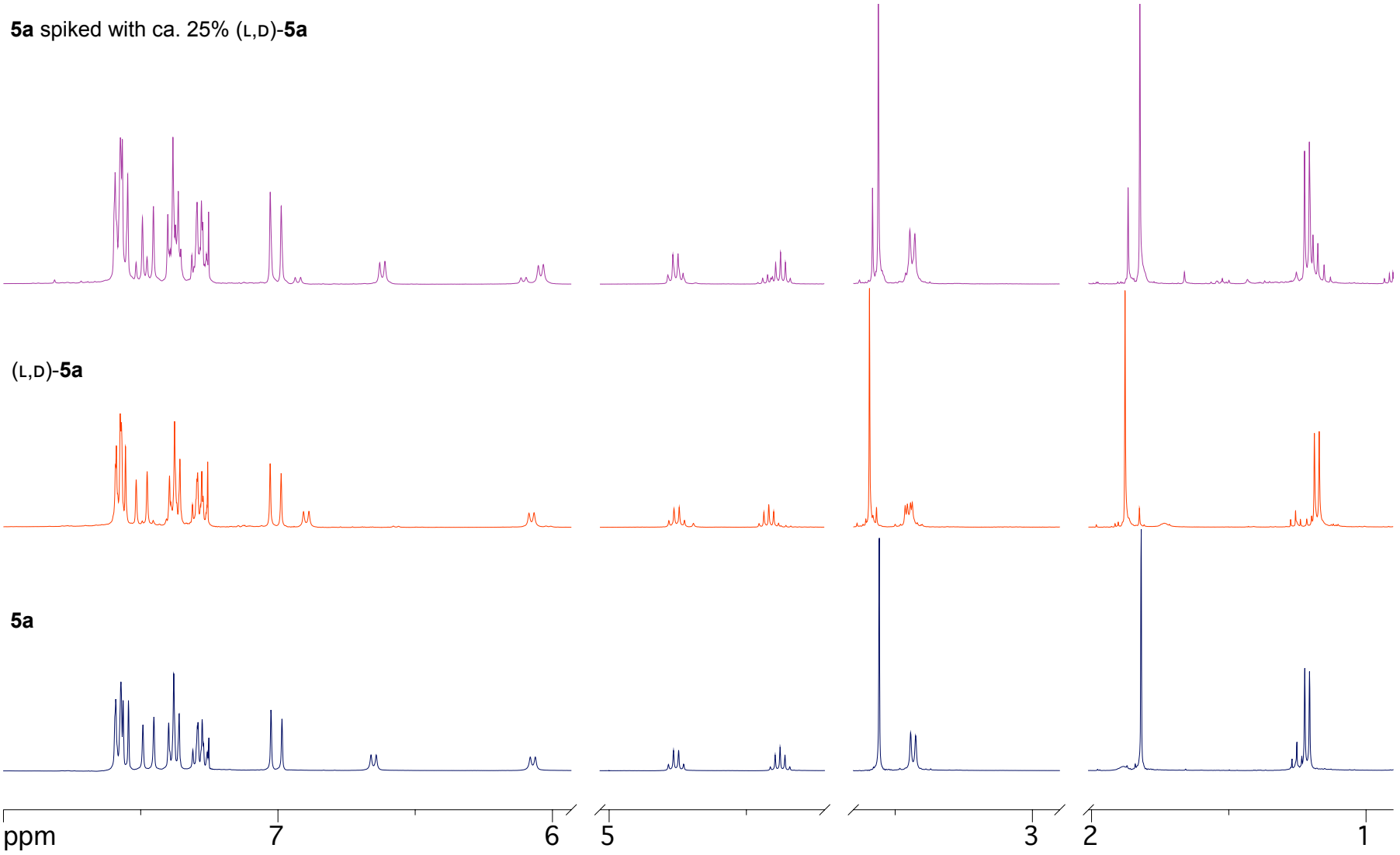
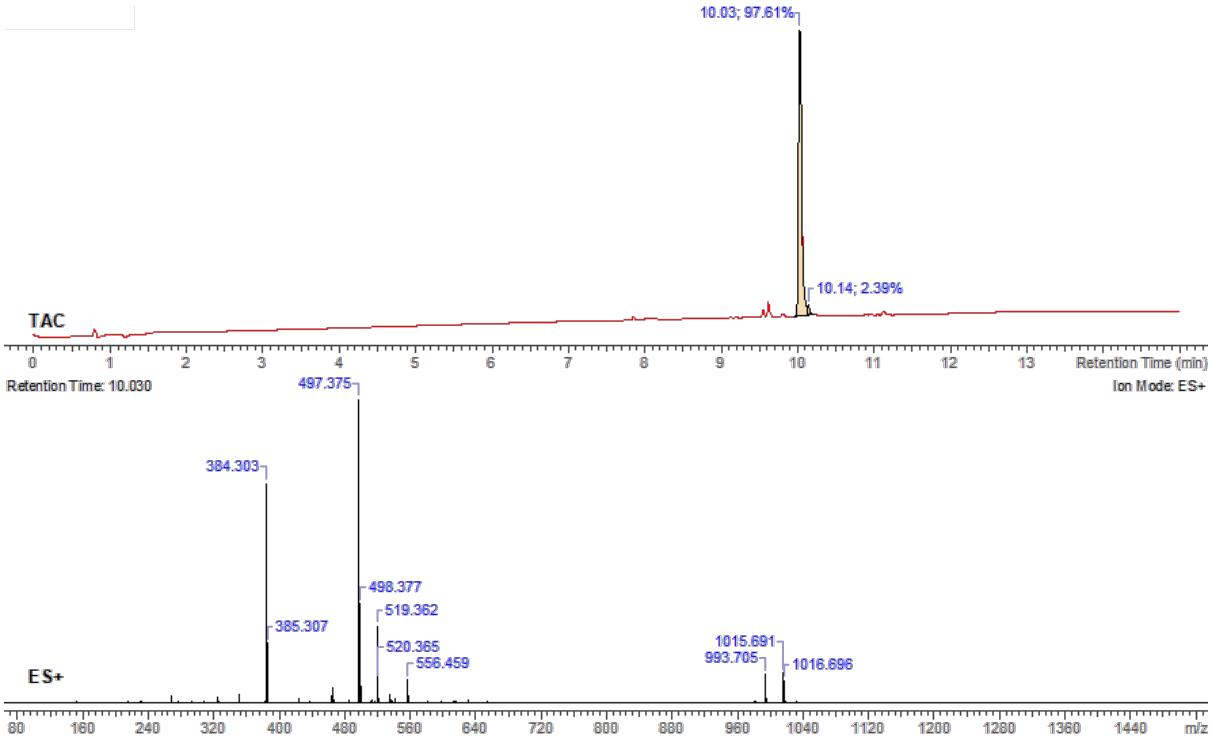
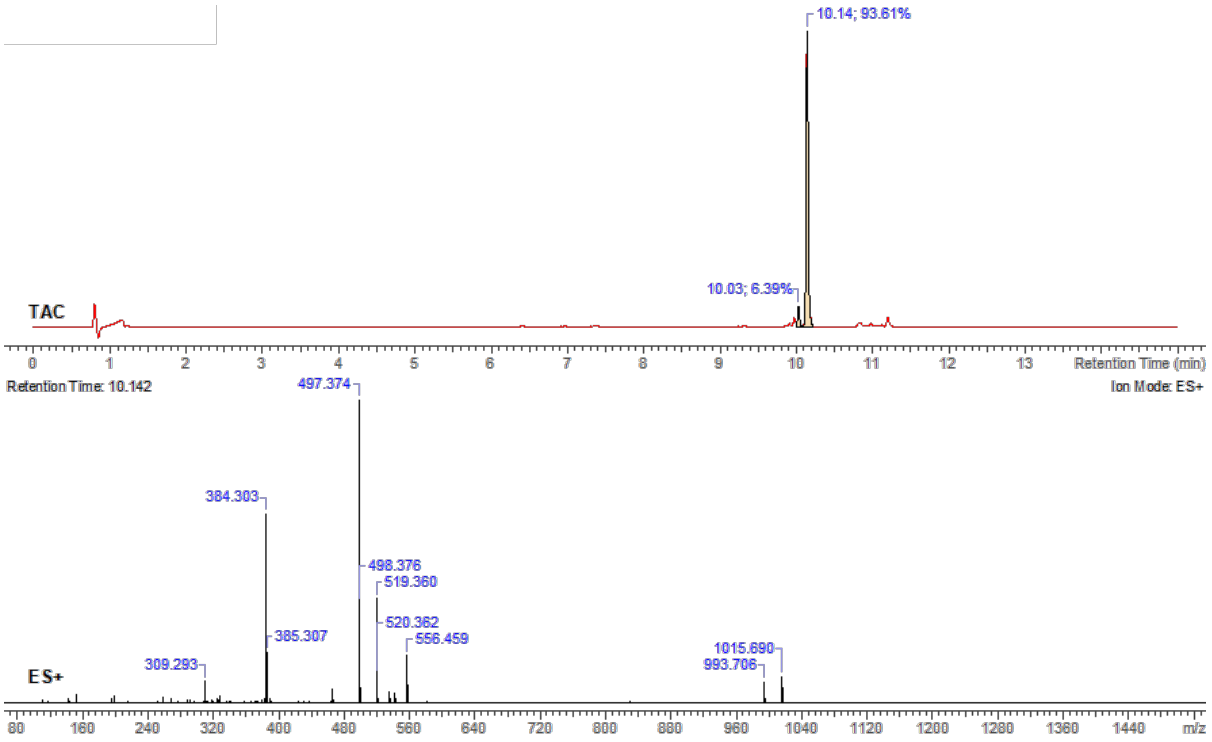


Figure S1. Comparison of ^{1}H NMR spectra for the modified peptides **5a** and (L,D)-**5a**. Complete spectra are presented in **section 3**.

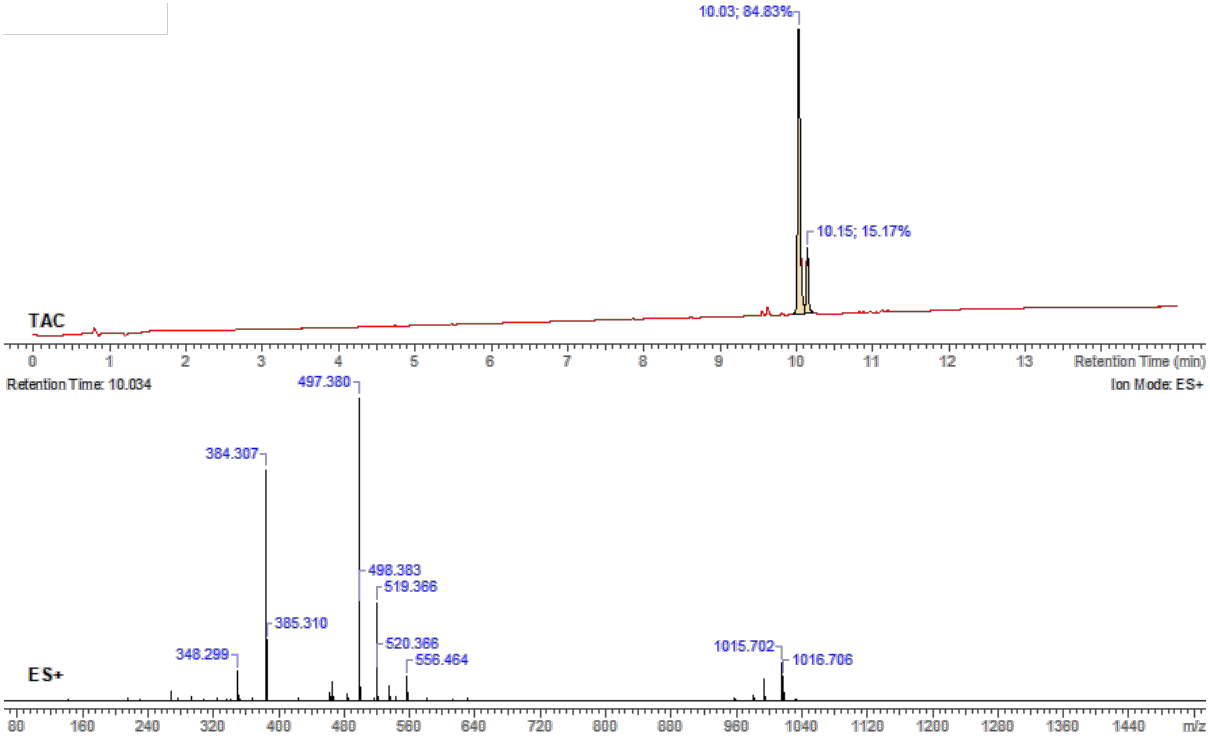
HPLC-chromatogram and ES-MS for modified peptide **5a**.



HPLC-chromatogram and ES-MS for diastereomeric modified peptide (L,D)-**5a**.

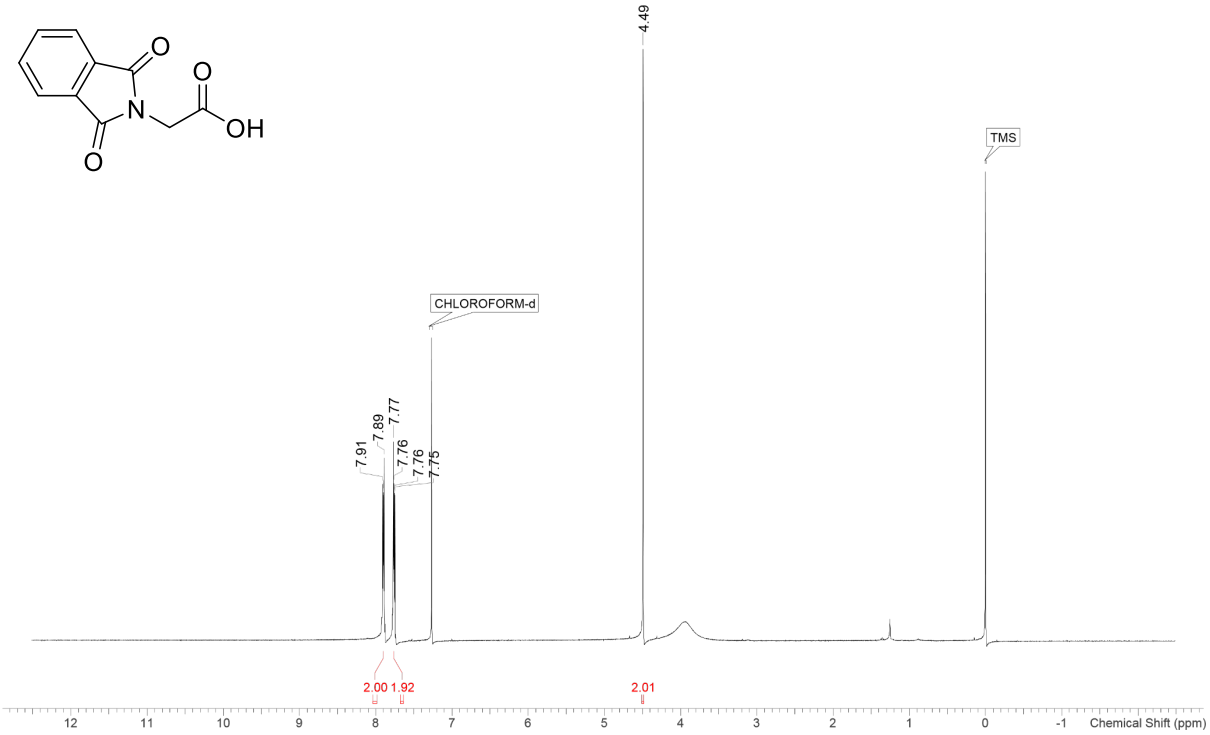


HPLC-chromatogram and ES-MS for **5a** spiked with *ca*. 15% (L,D)-**5a**.

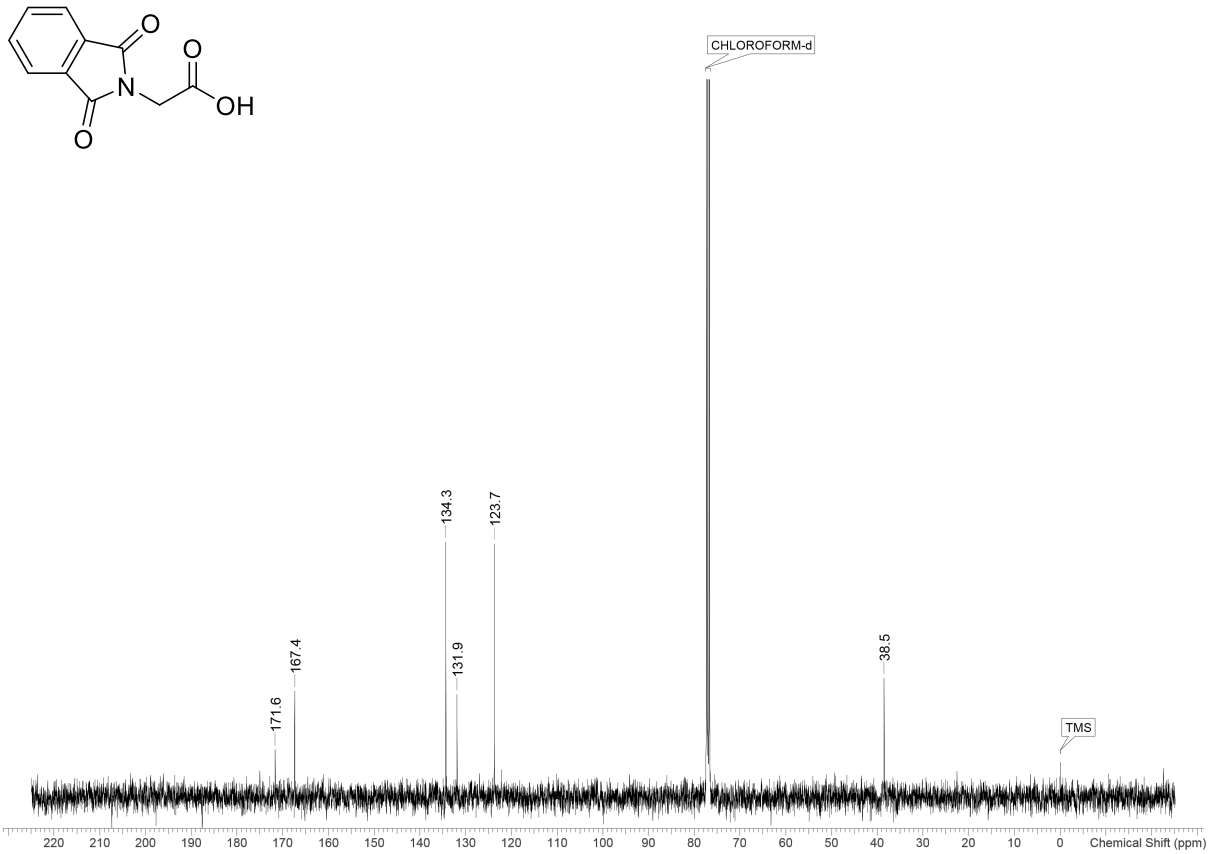


3. ^{1}H and ^{13}C NMR spectra

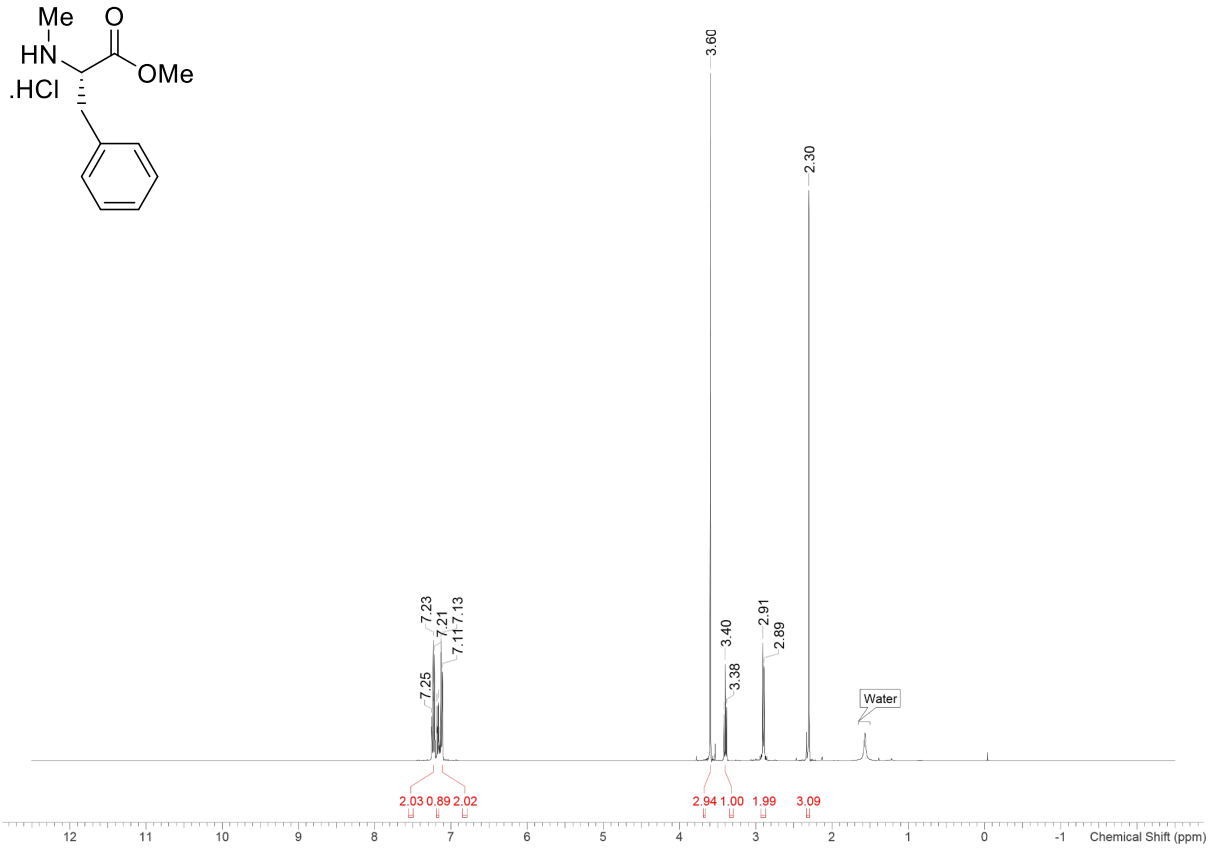
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of Phth-Gly-OH



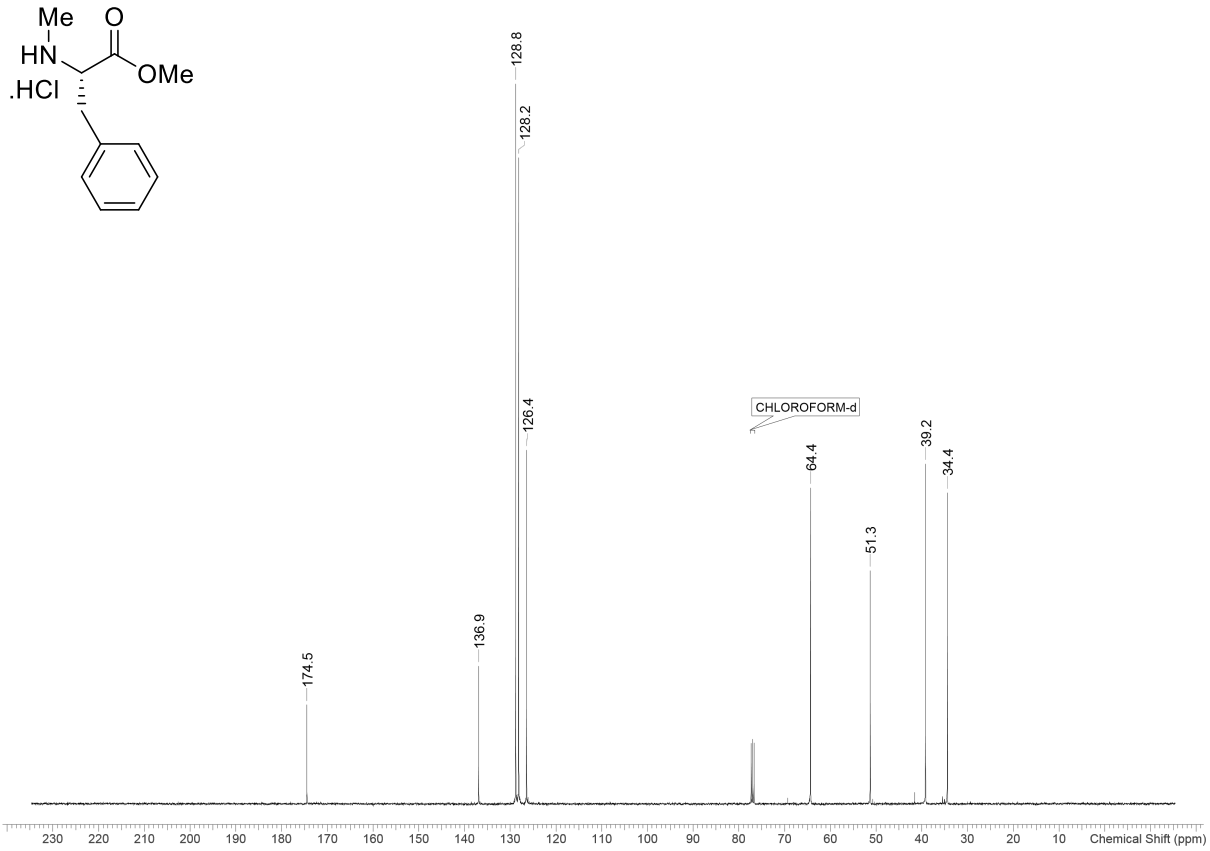
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of Phth-Gly-OH



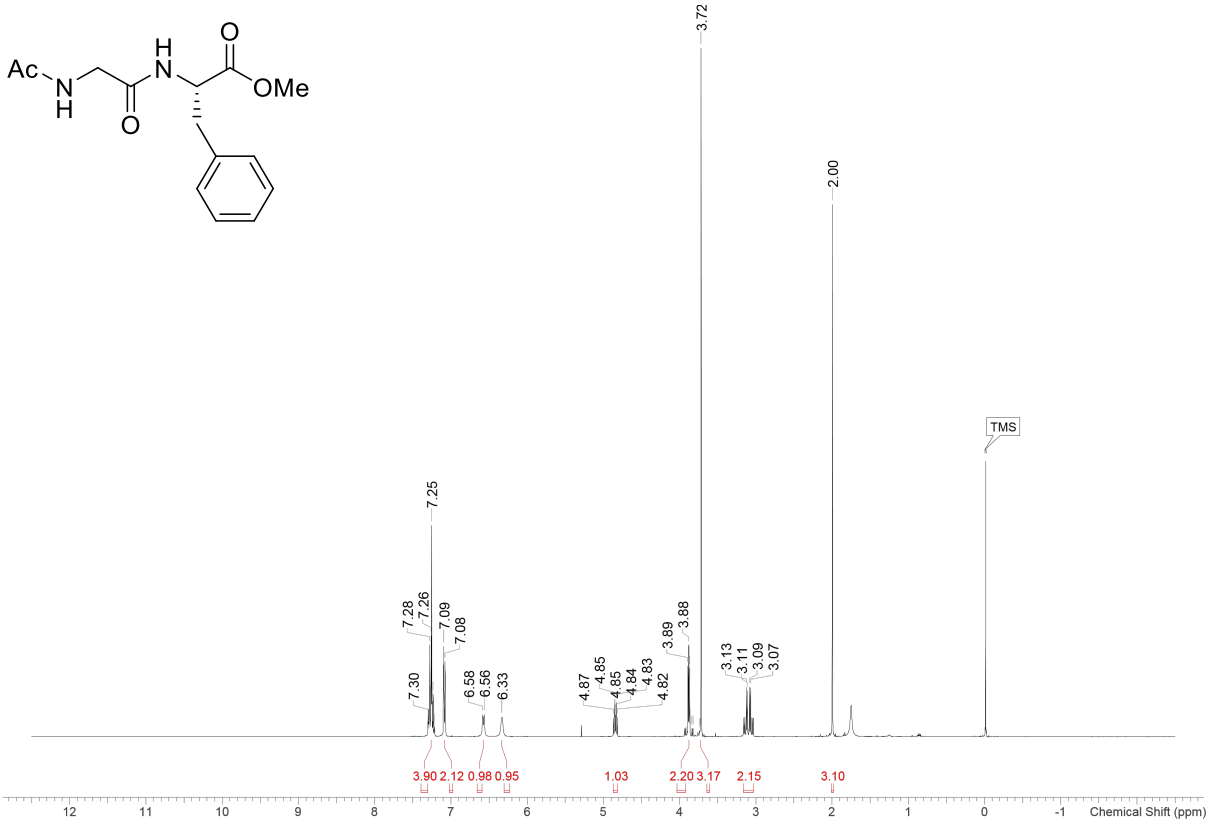
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of Me-Phe-OH.HCl



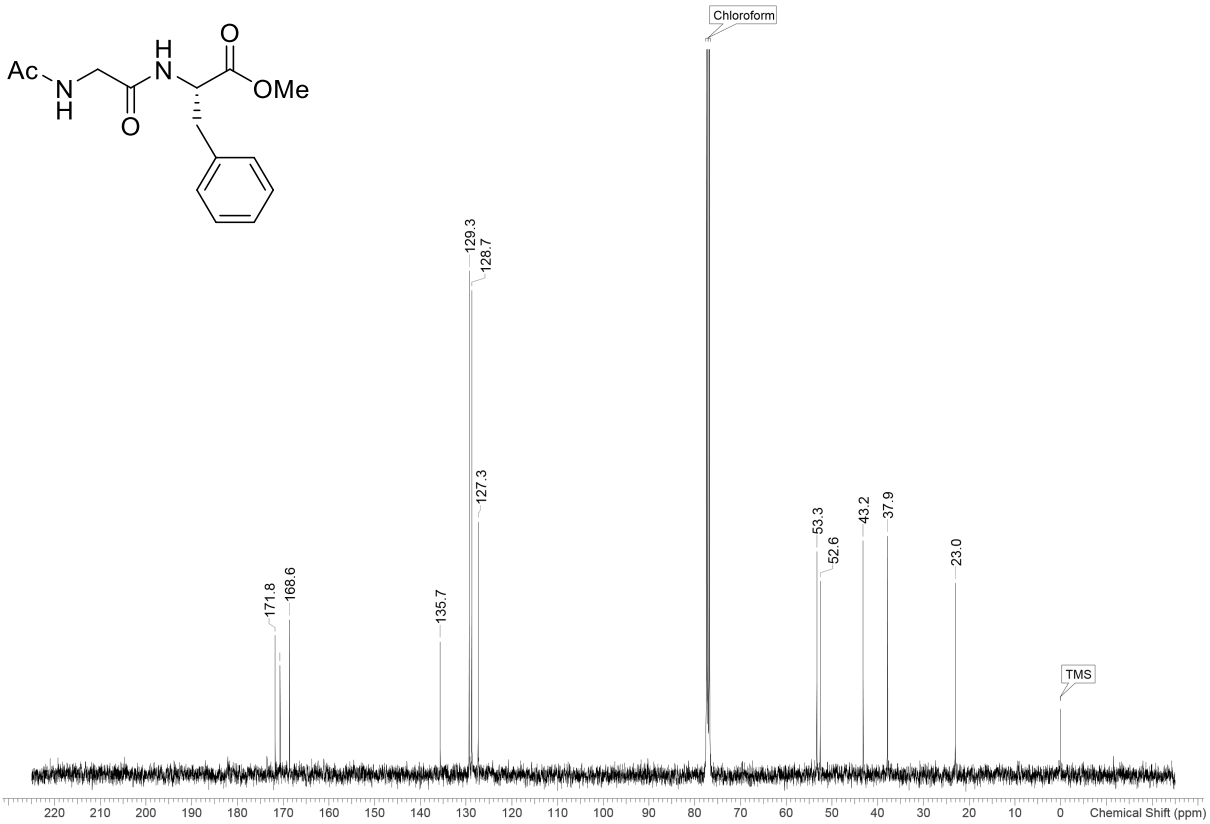
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of Me-Phe-OH.HCl



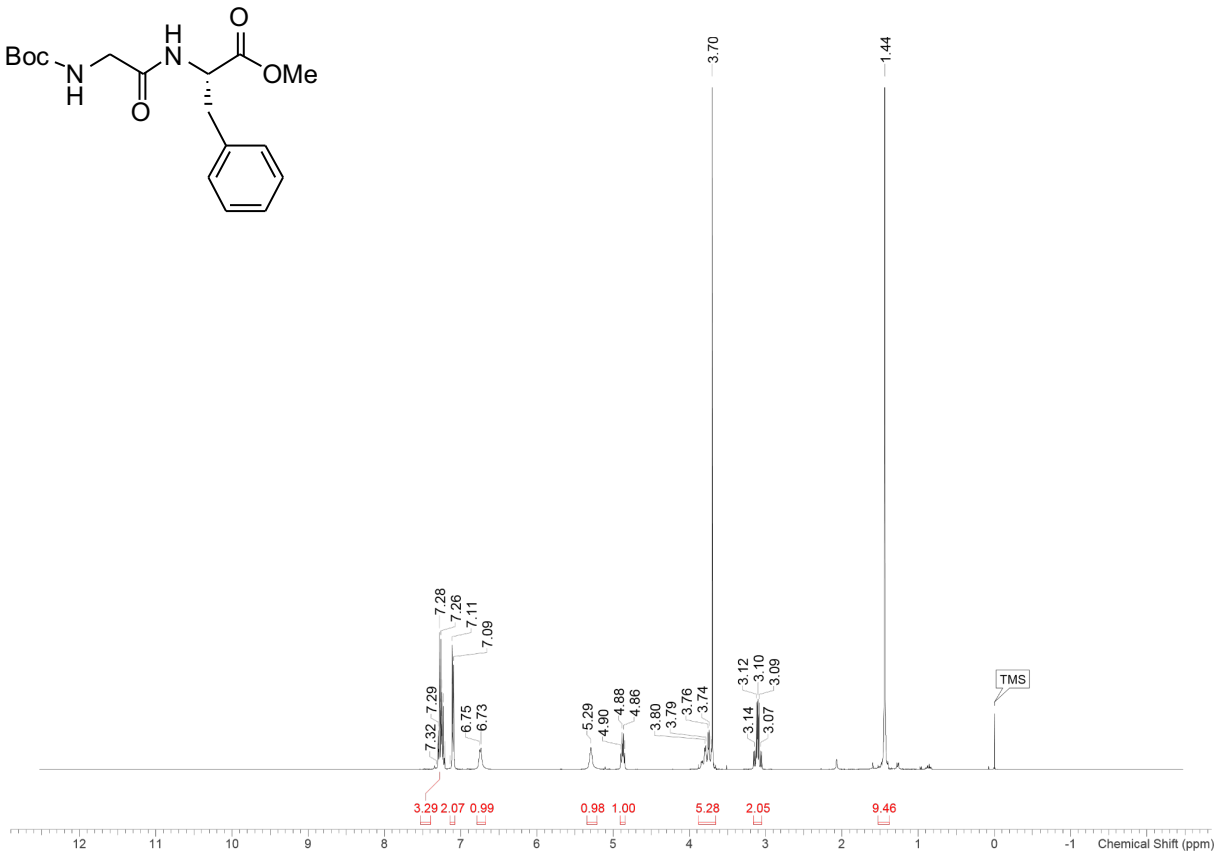
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1a**



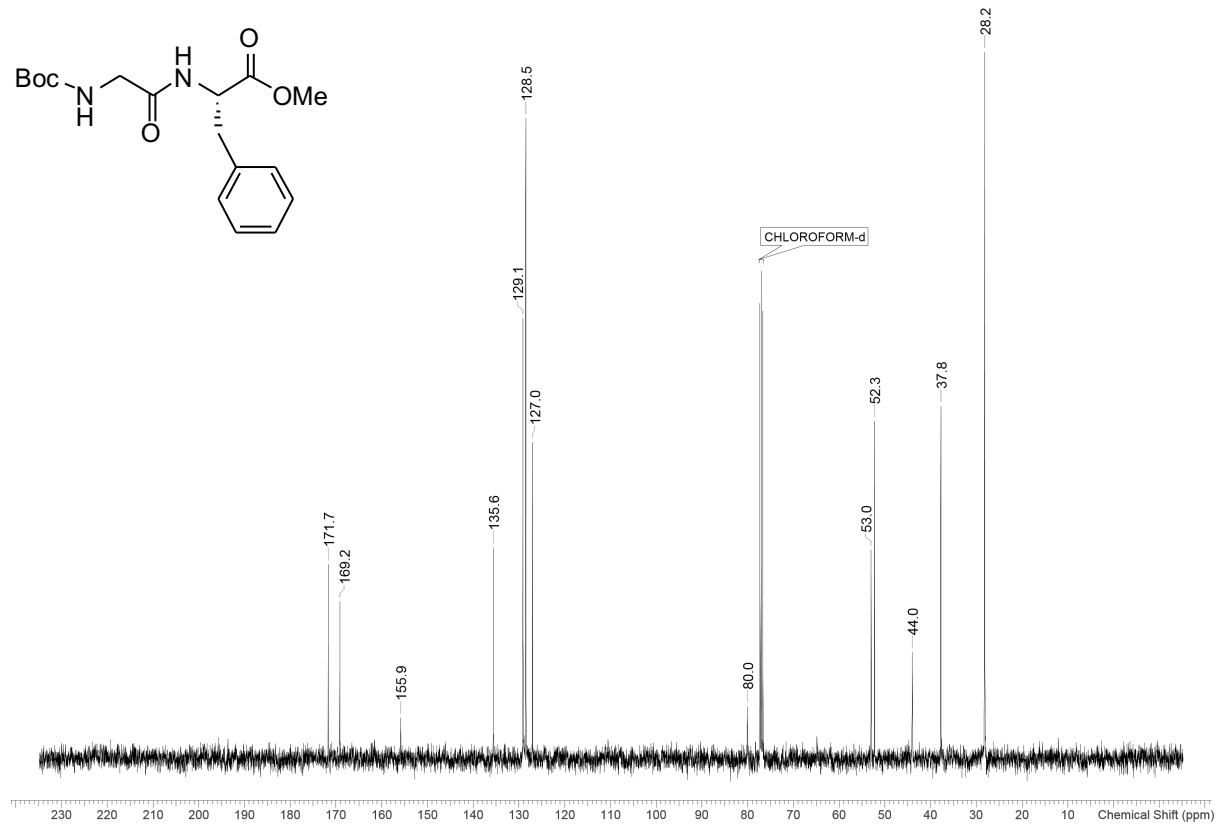
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1a**



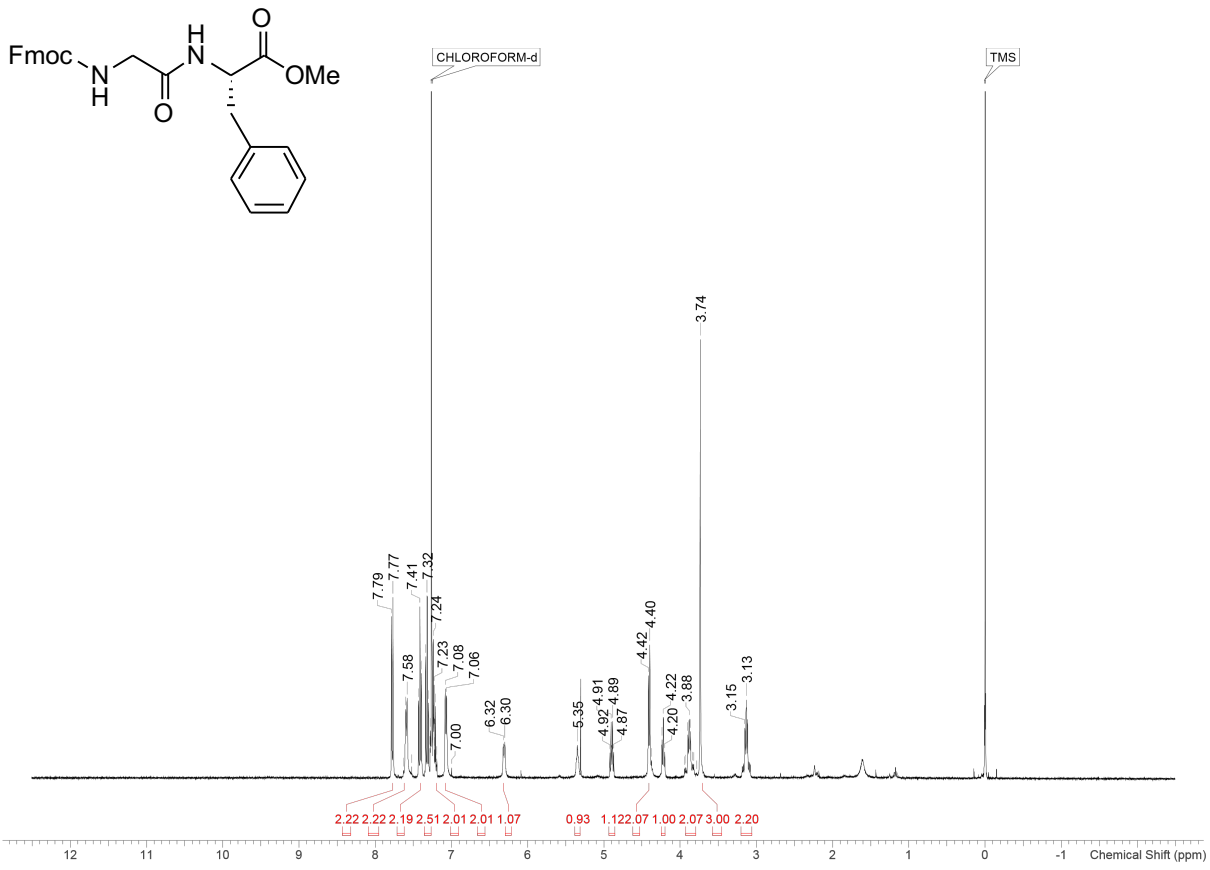
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1b**



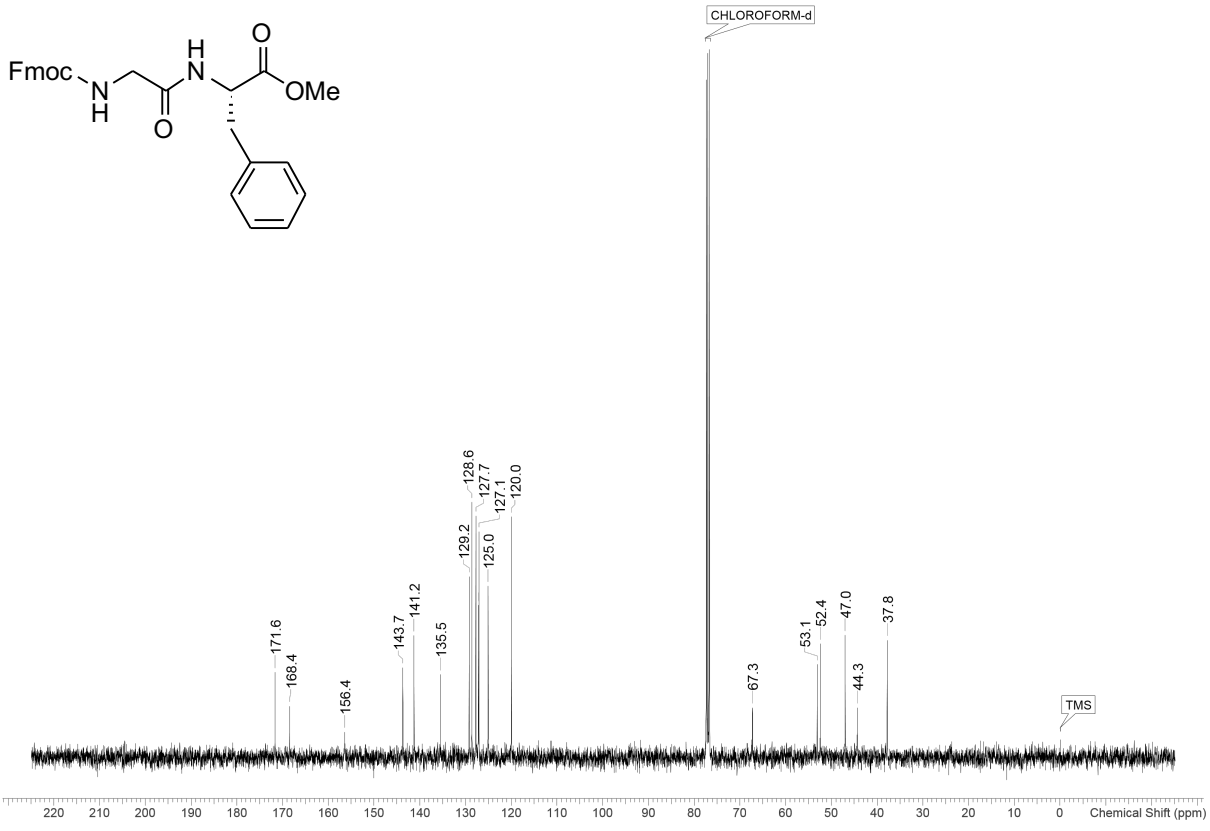
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1b**



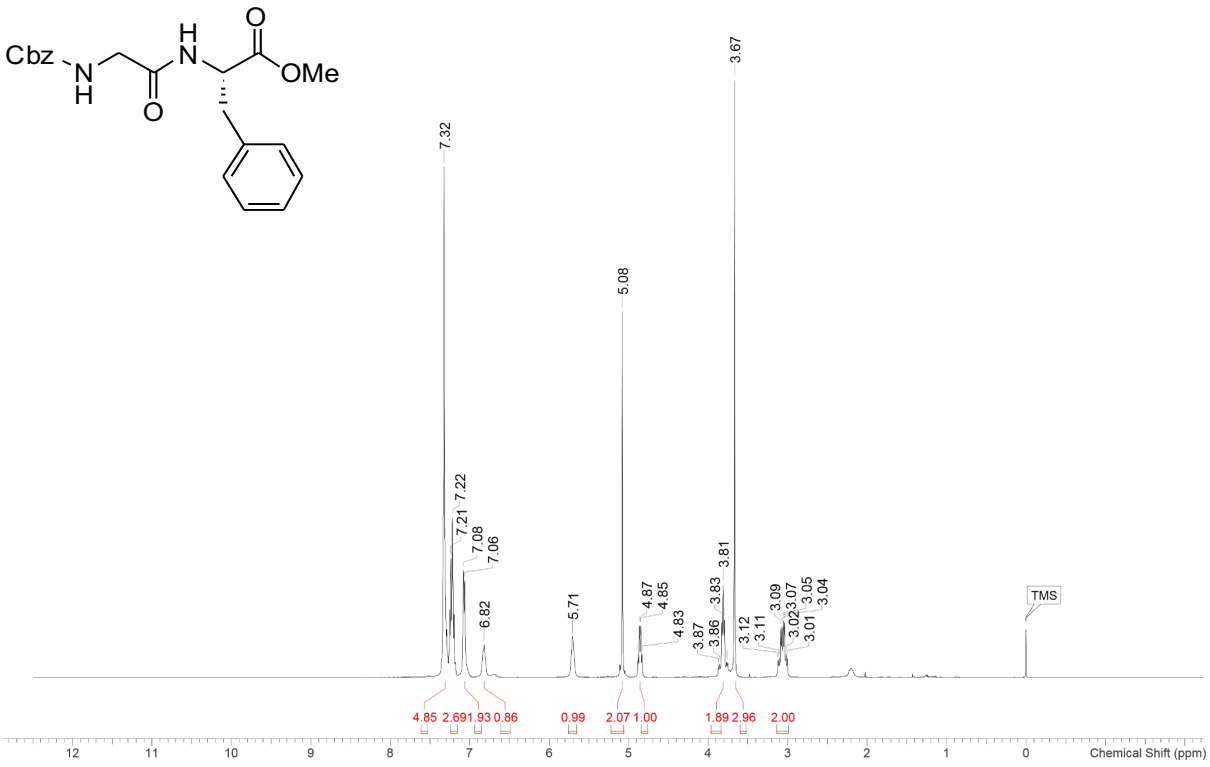
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1c**



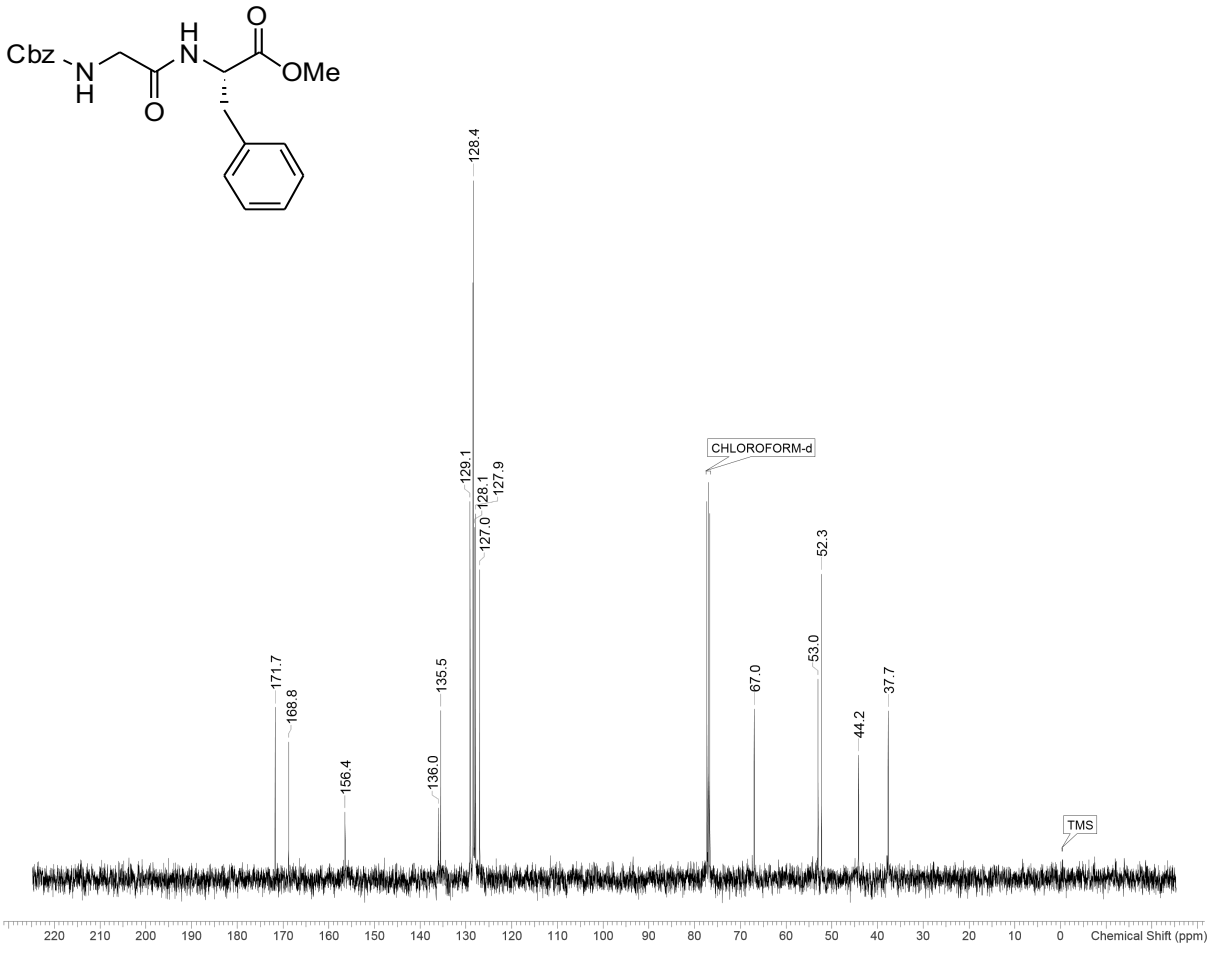
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1c**



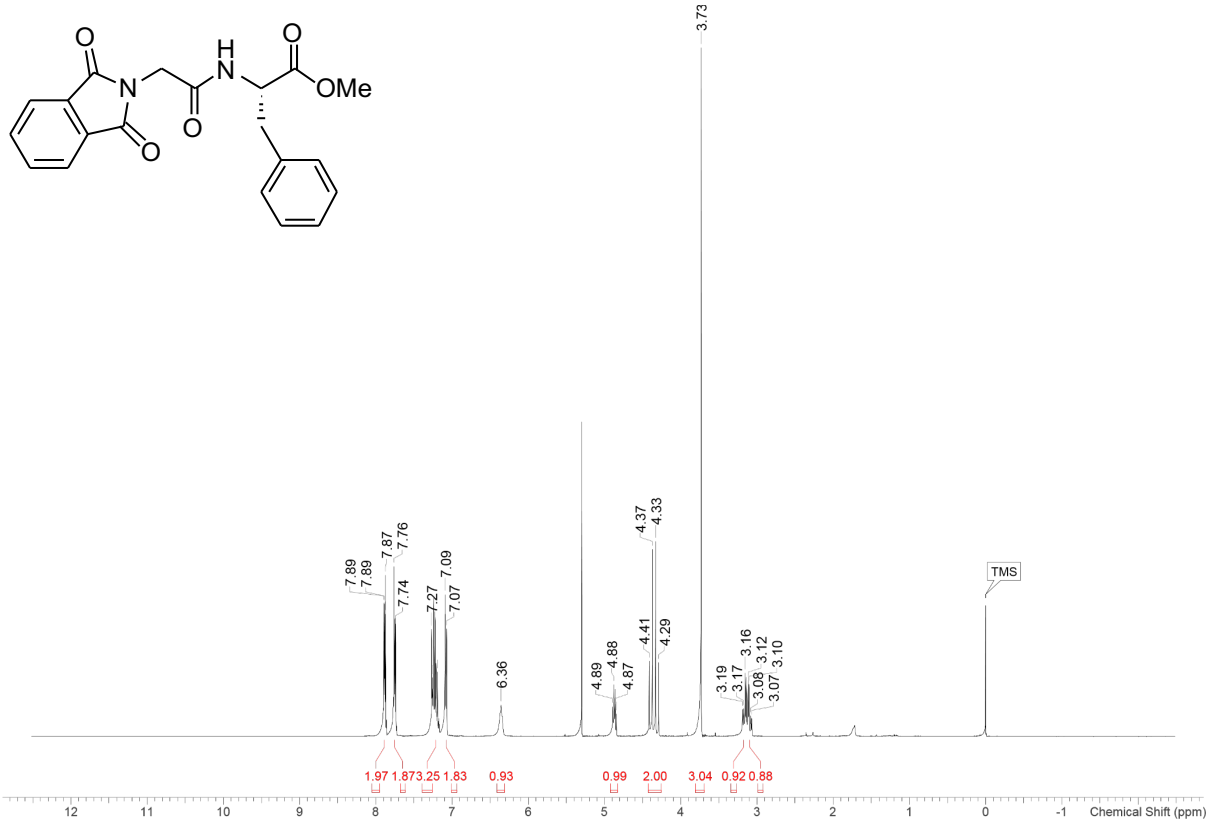
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1d**



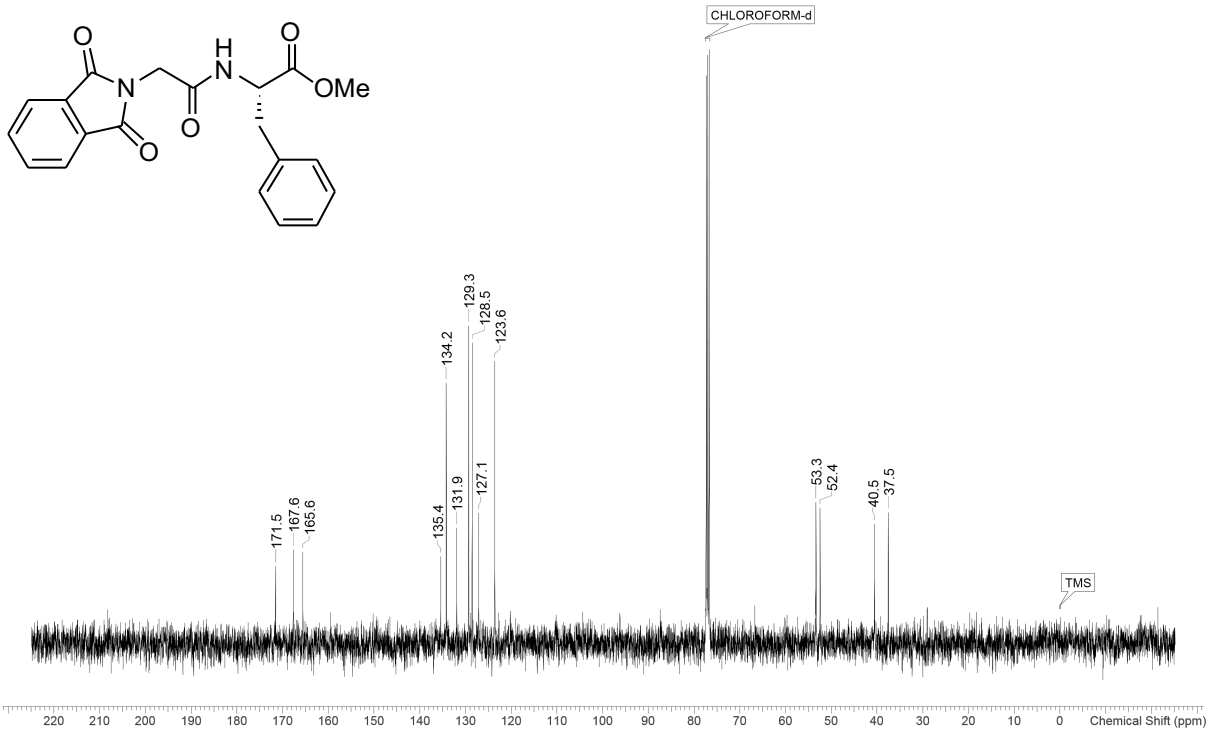
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1d**



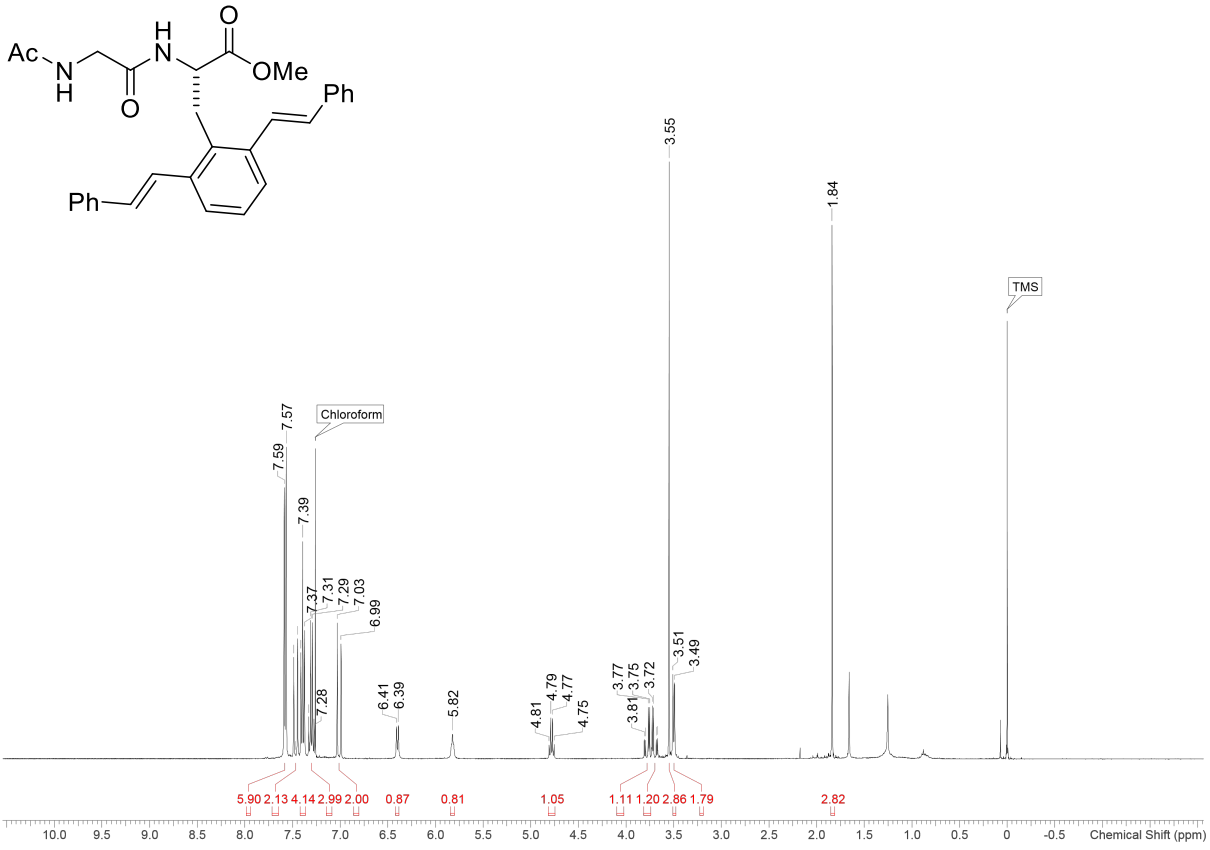
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1e**



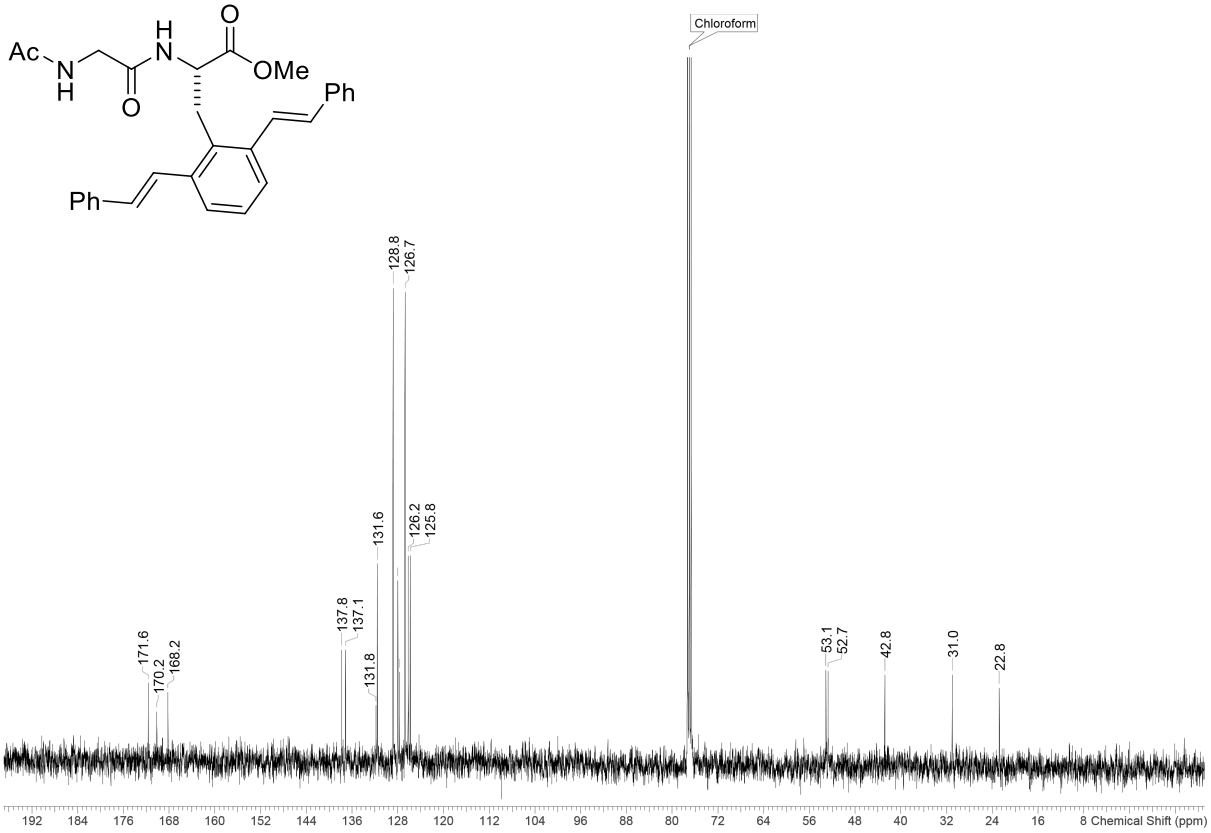
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **1e**



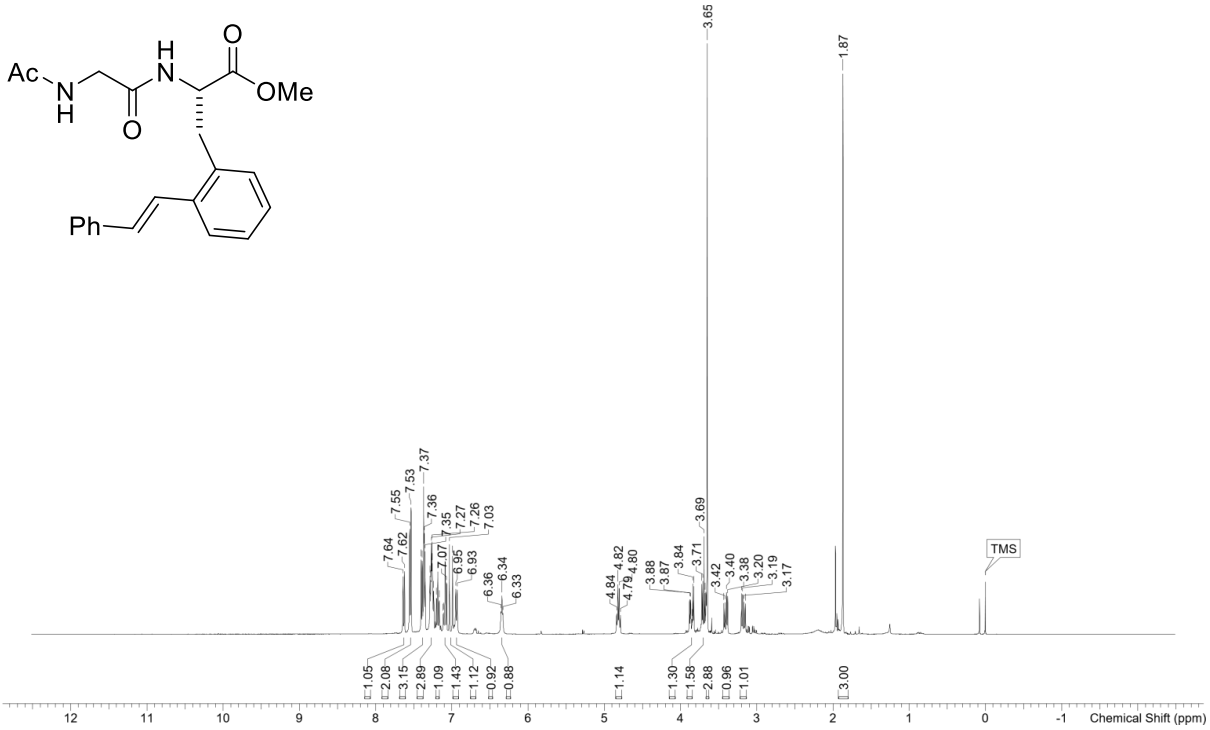
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2a**



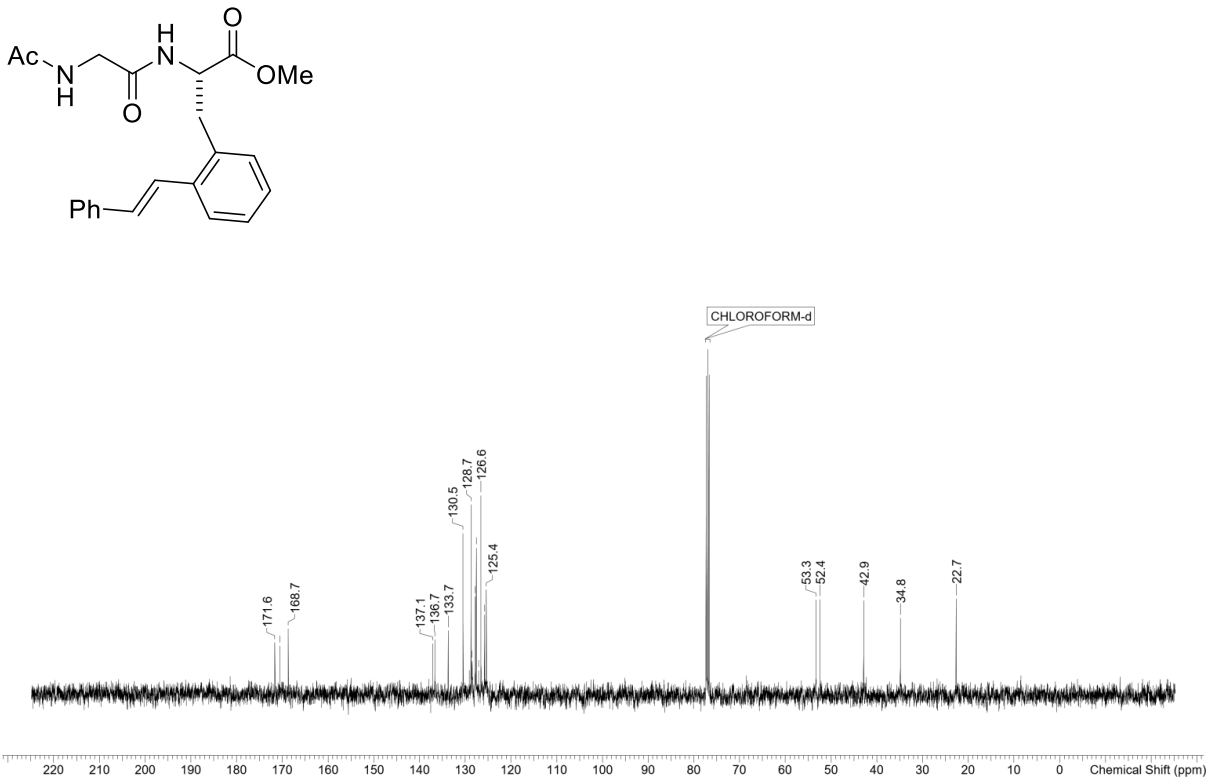
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2a**



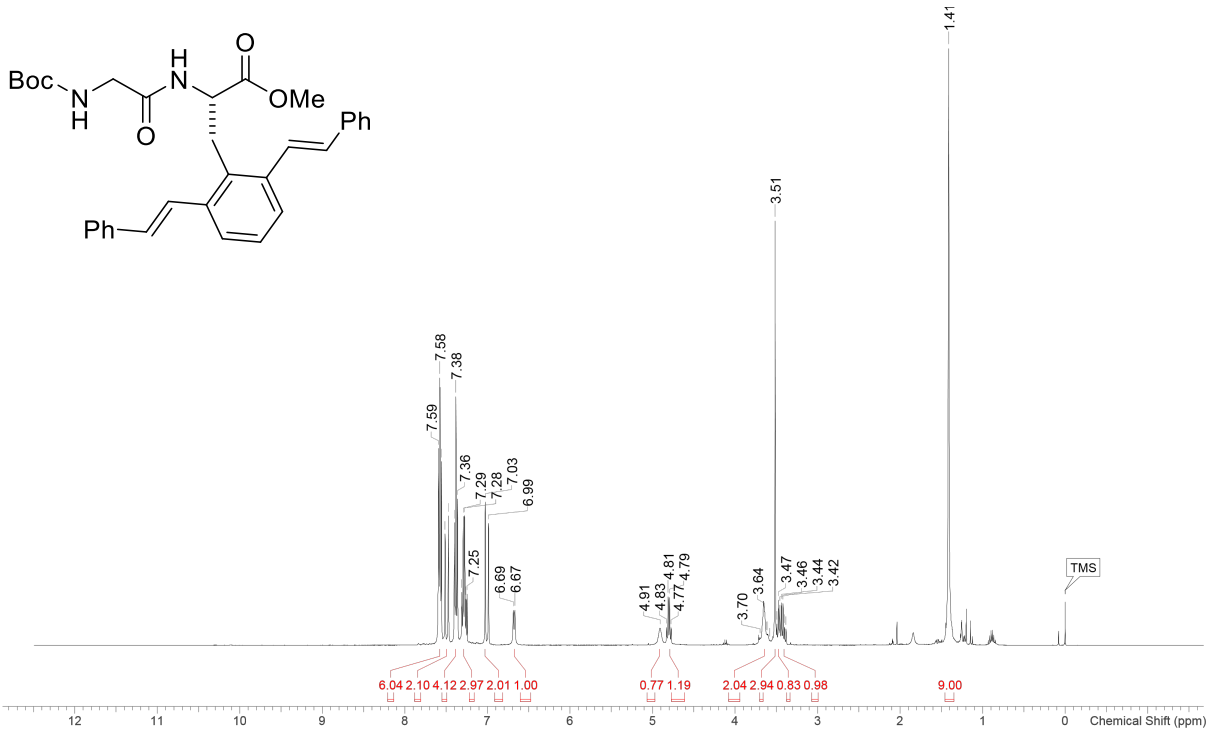
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2a'**



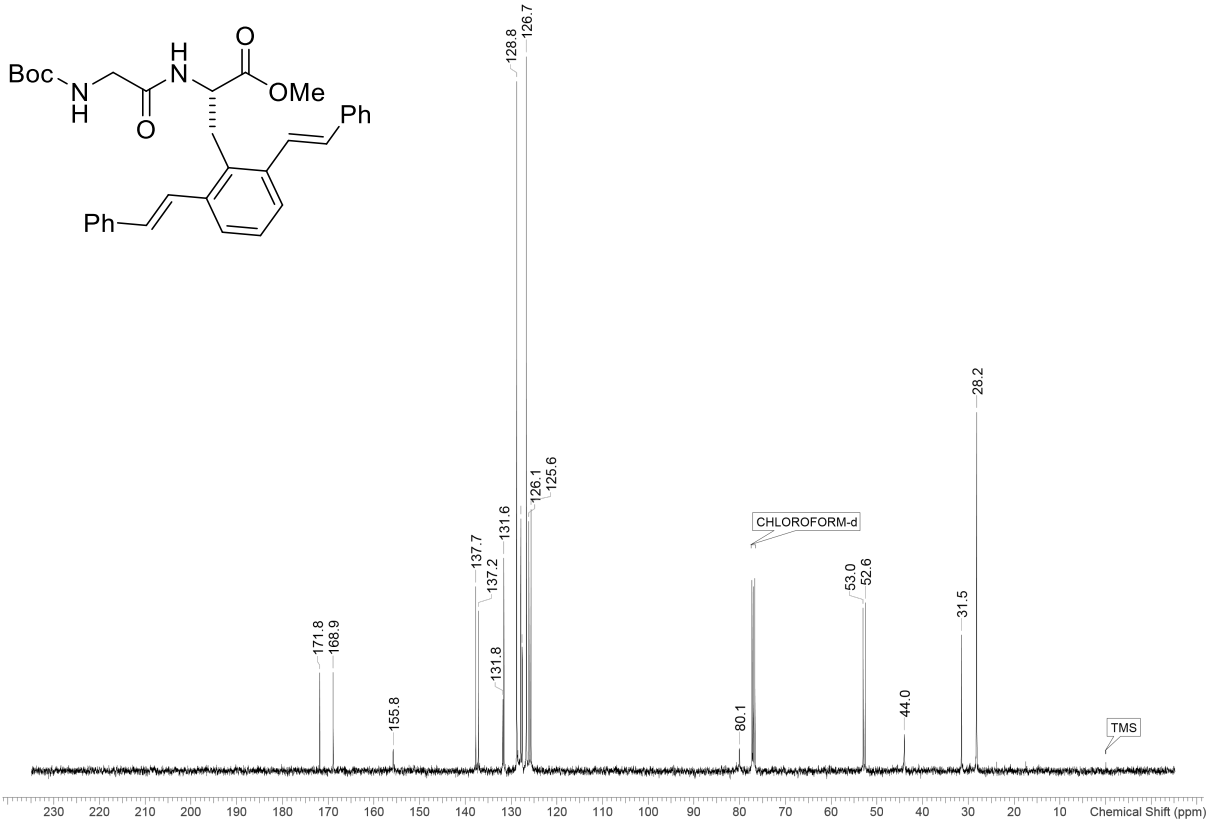
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2a'**



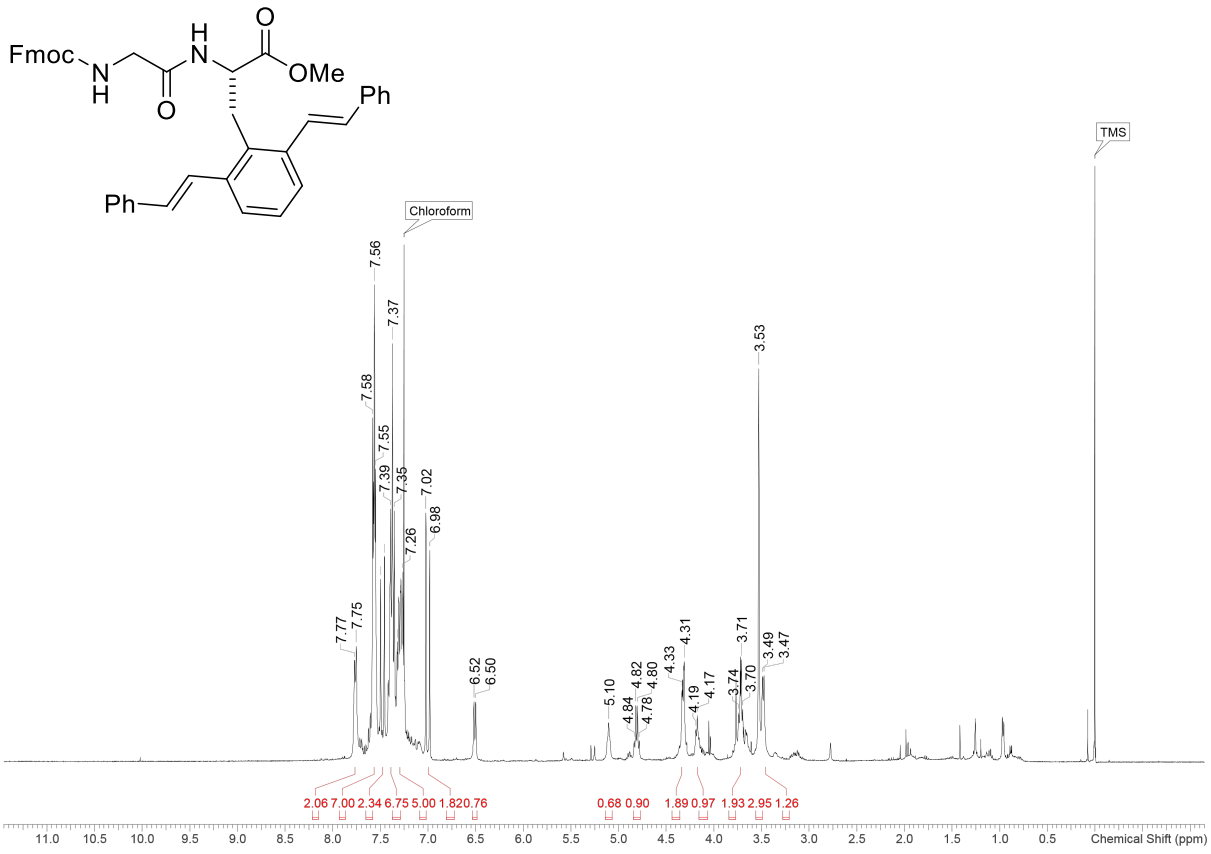
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2b**



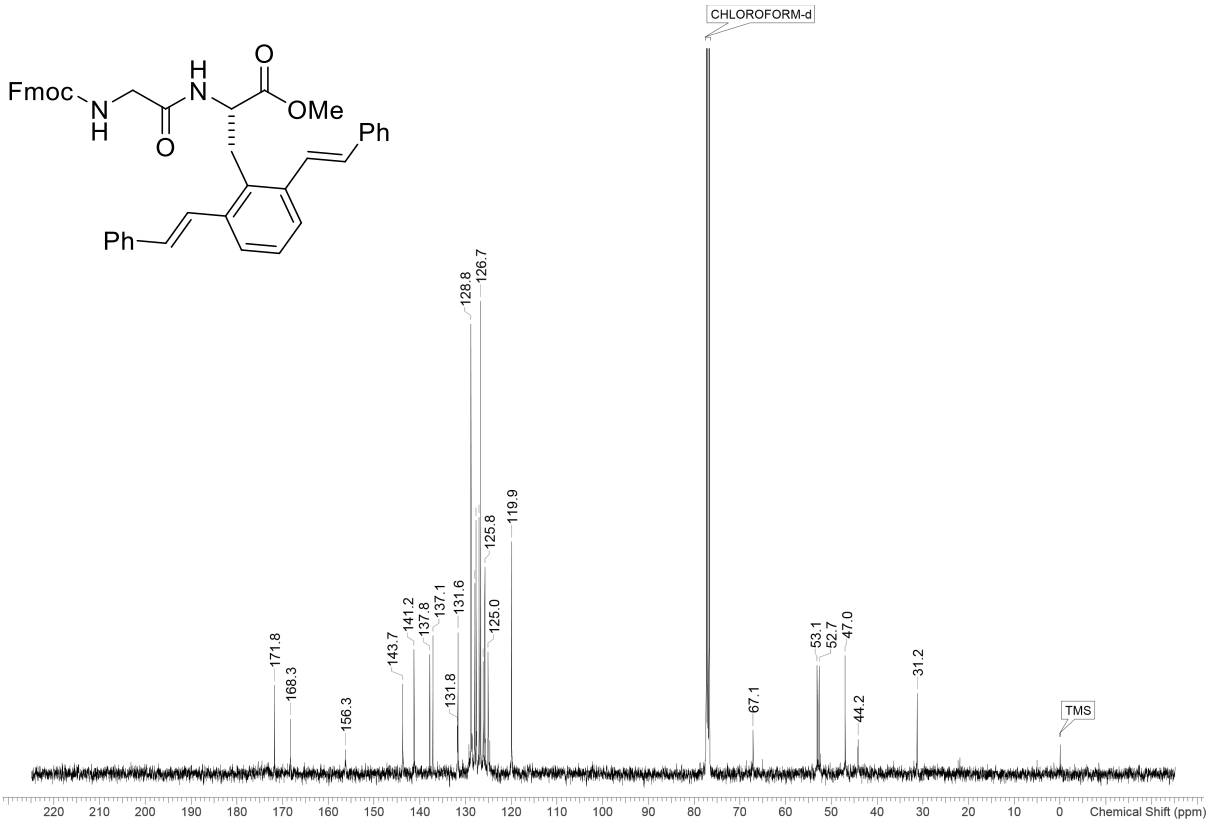
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2b**



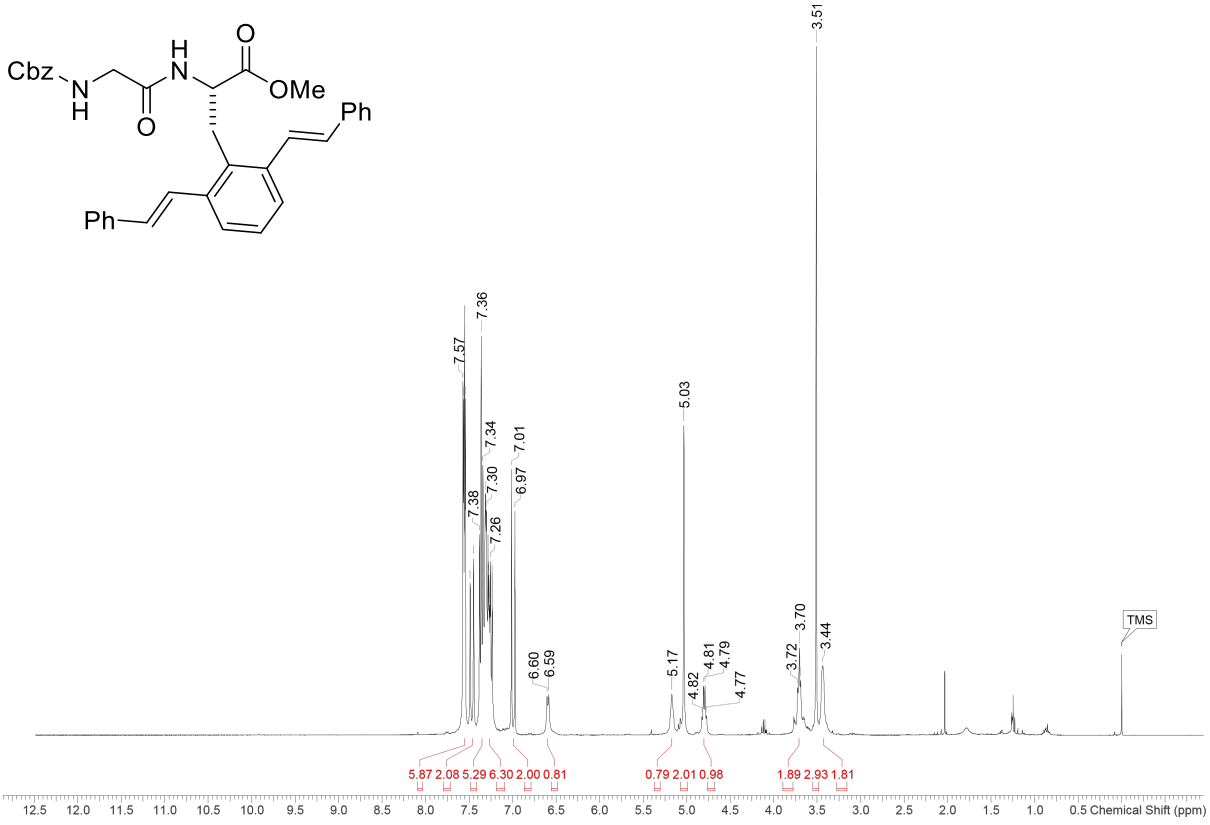
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2c**



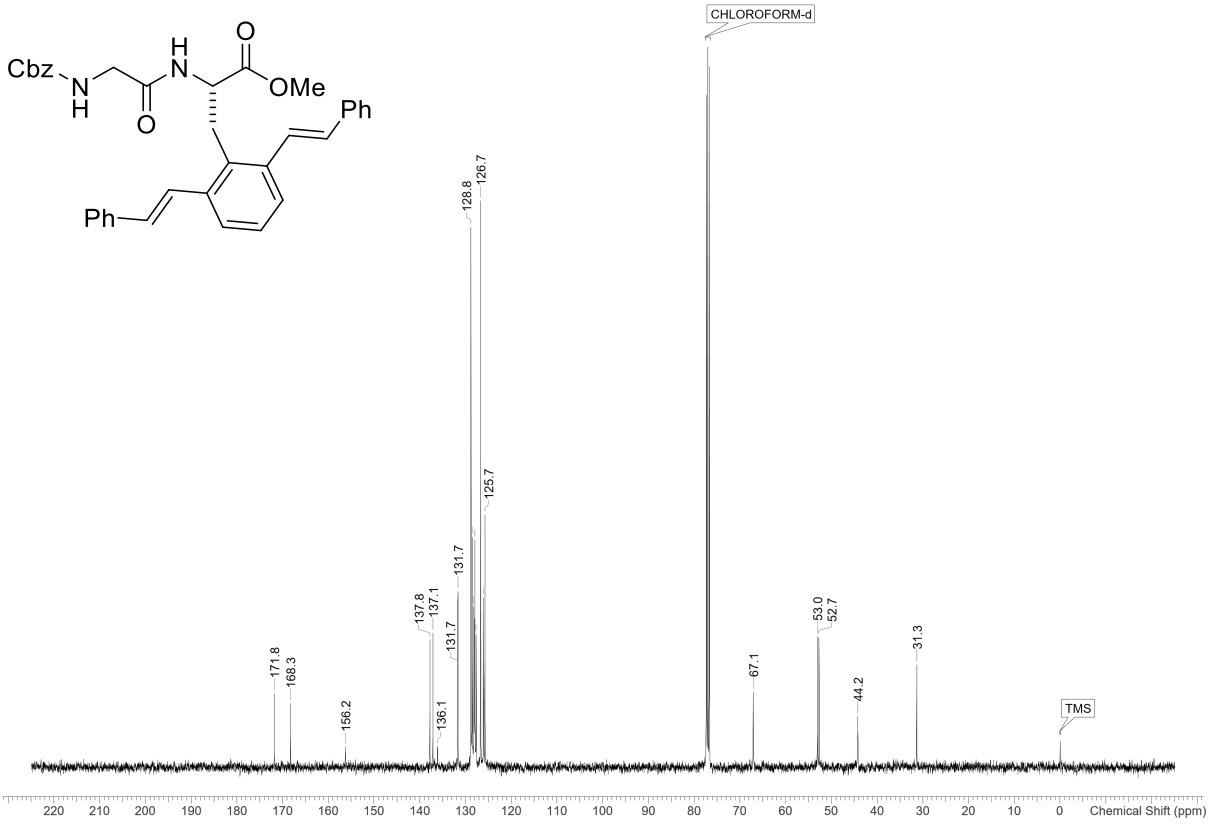
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2c**



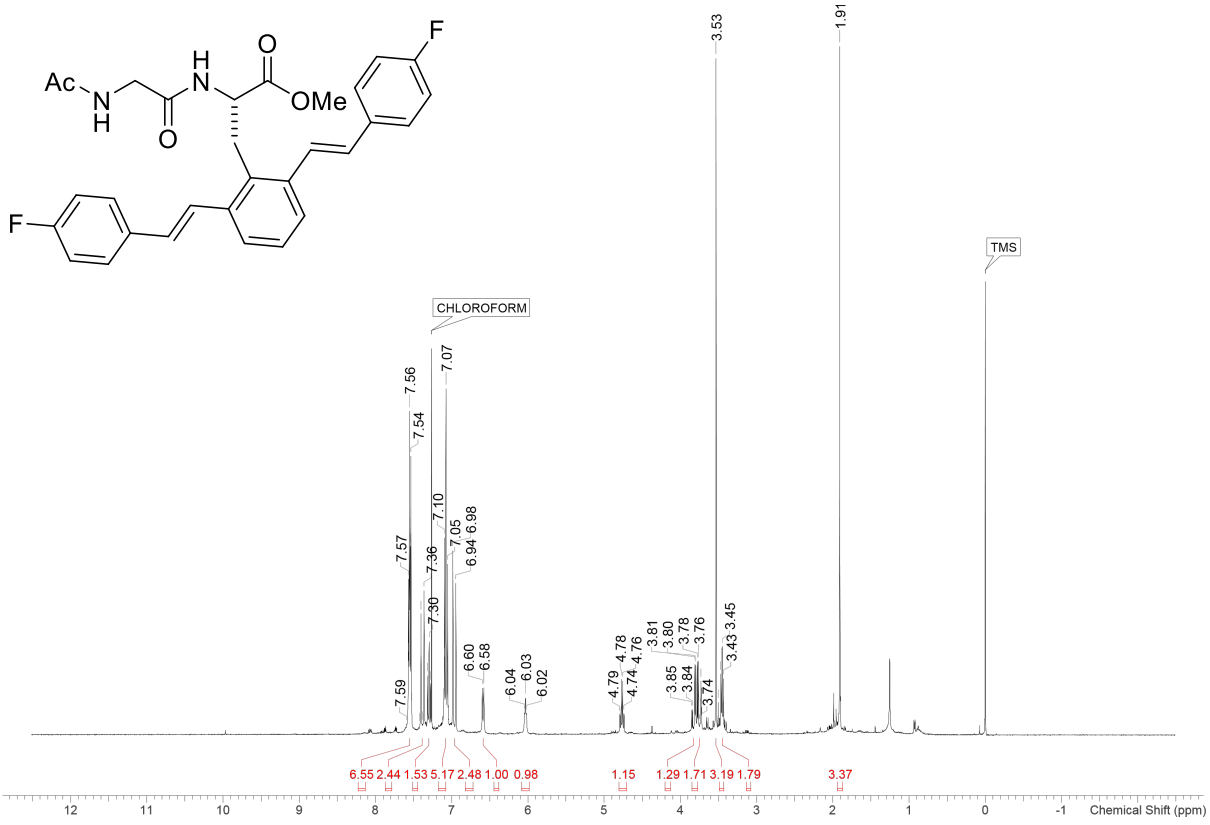
^{1}H NMR spectrum (100 MHz, $CDCl_3$) of **2d**



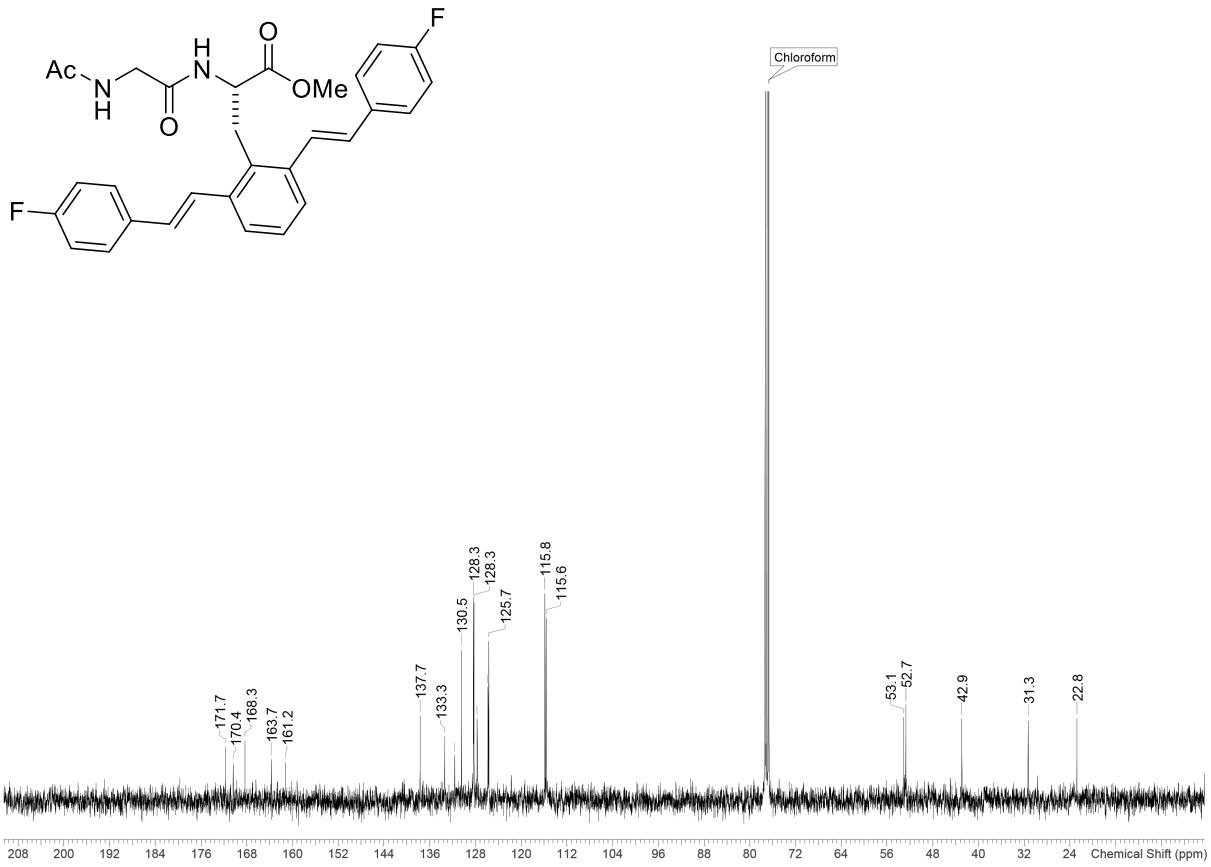
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **2d**



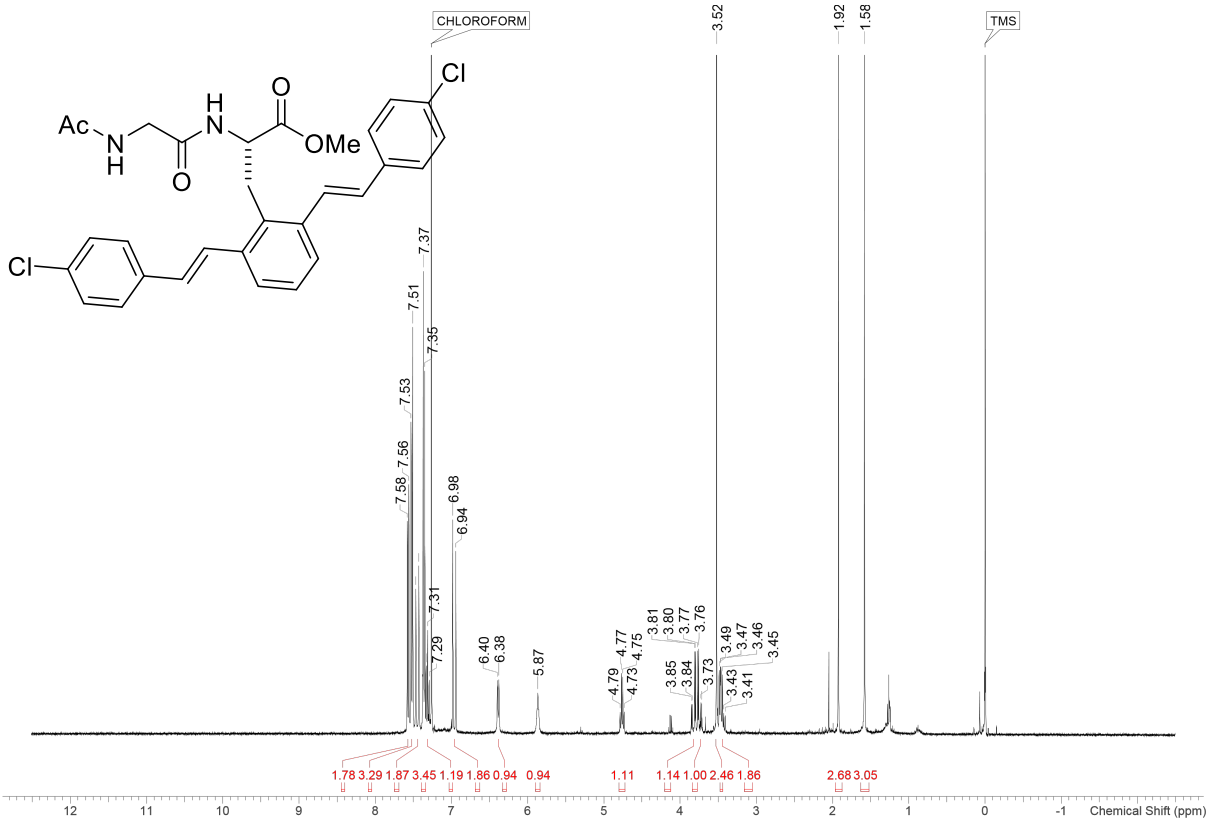
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3a**



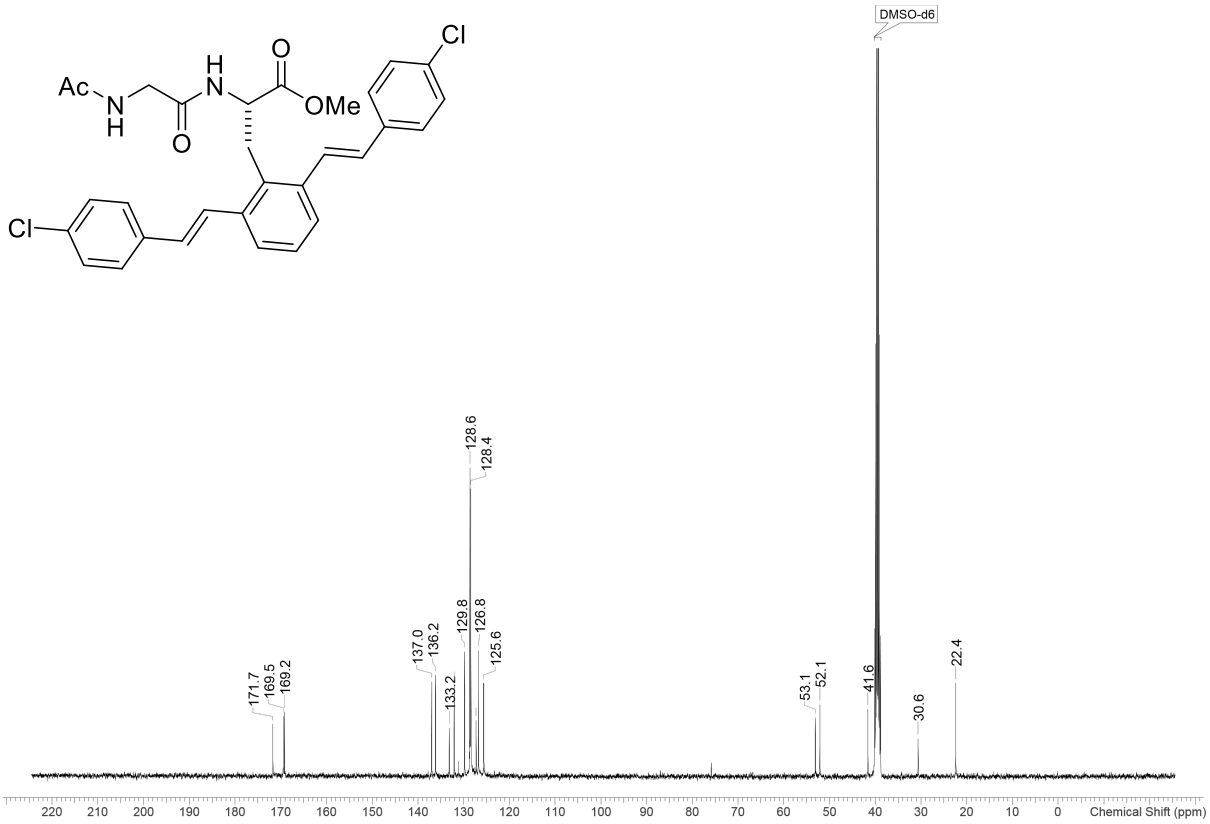
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3a**



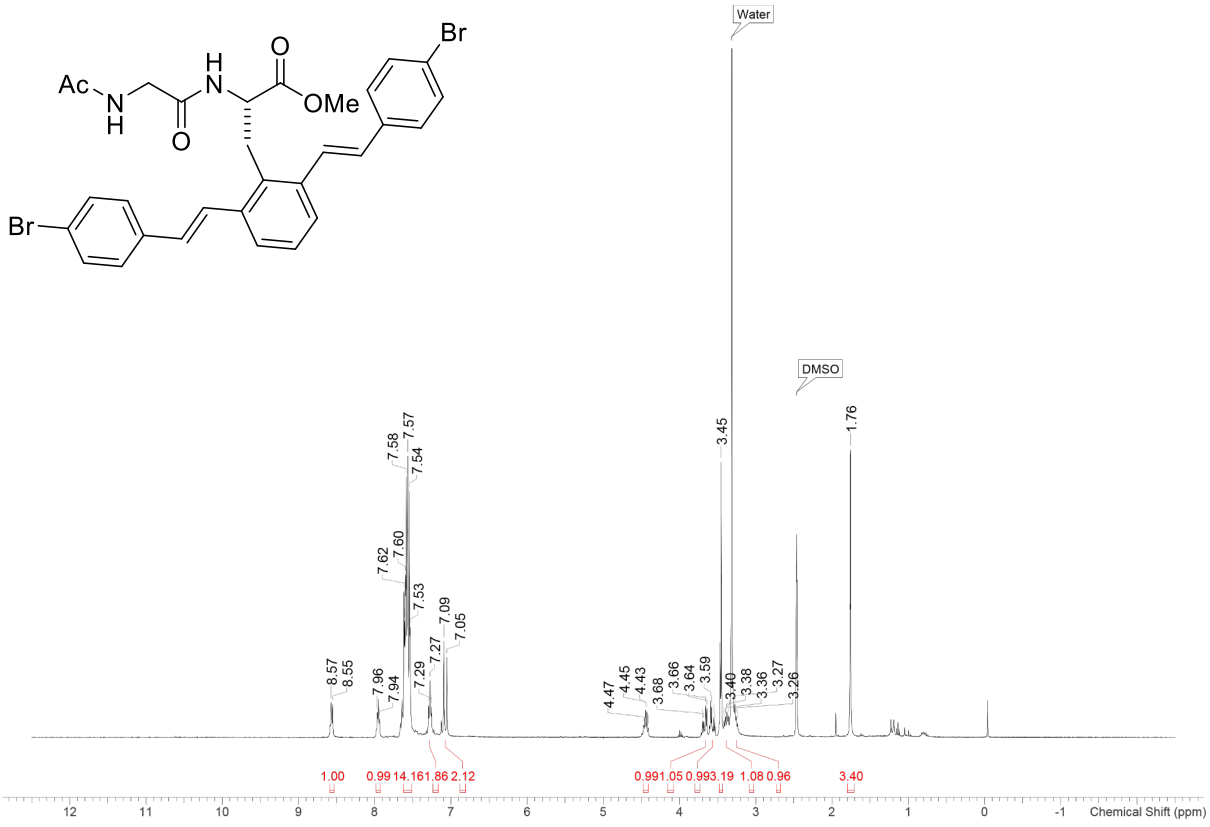
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3b**



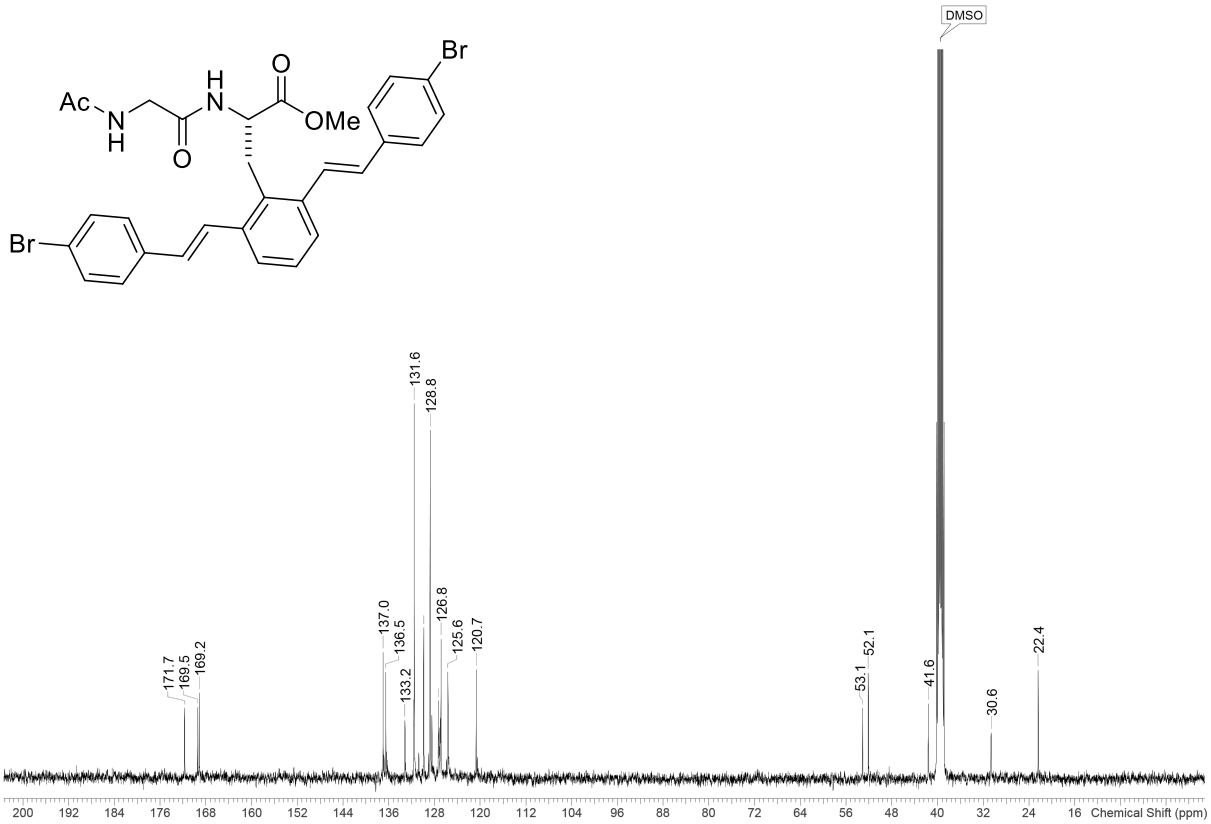
^{13}C{^{1}H} NMR spectrum (100 MHz, DMSO-d_6) of **3b**



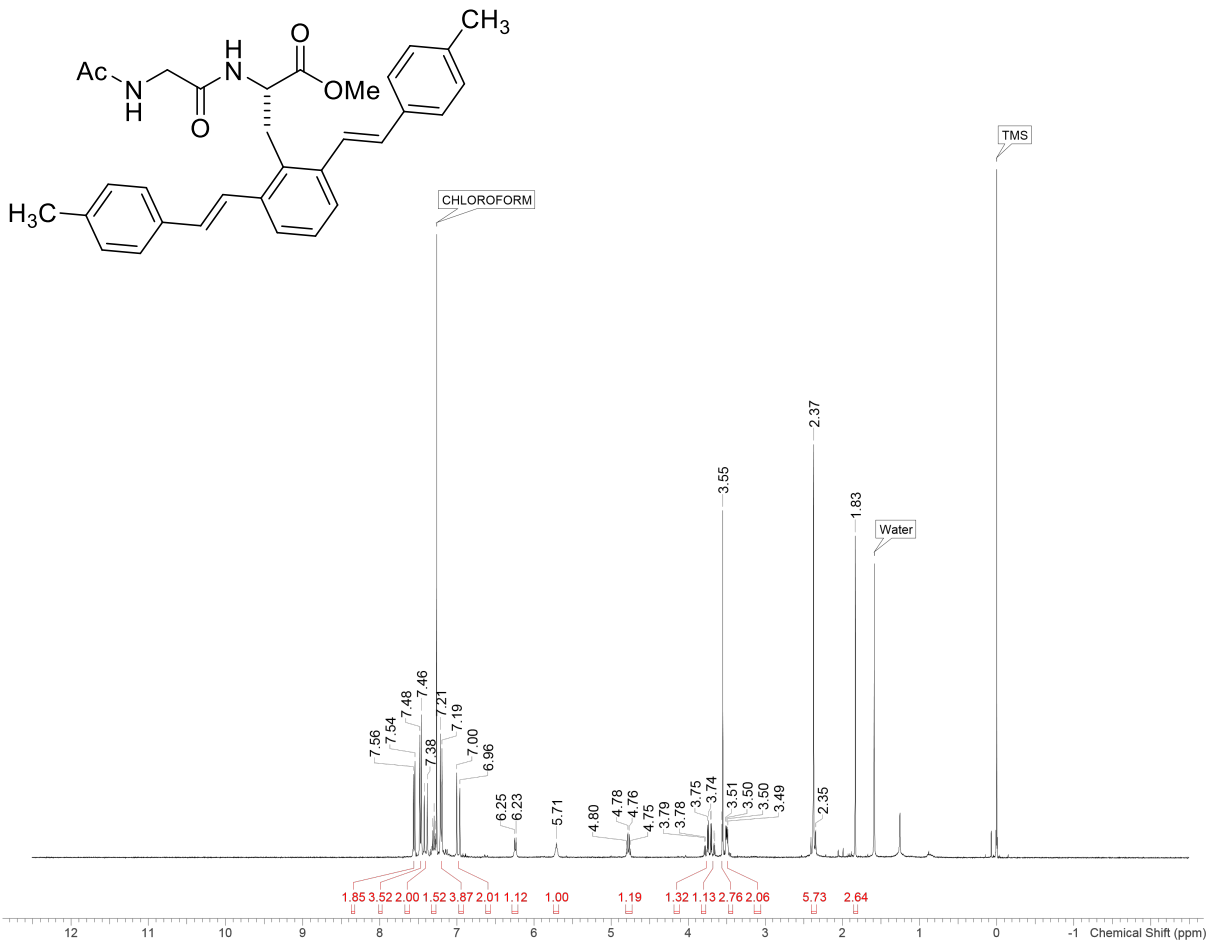
^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **3c**



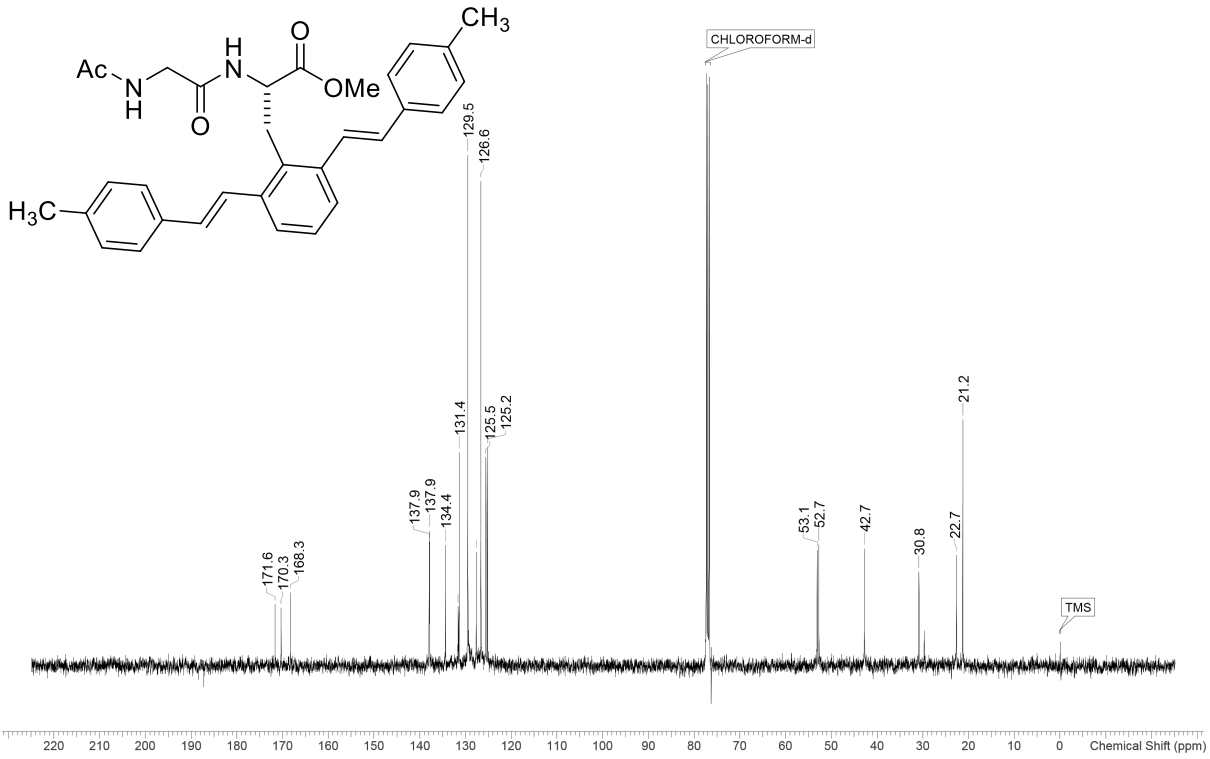
^{13}C{^{1}H} NMR spectrum (100 MHz, DMSO-d_6) of **3c**



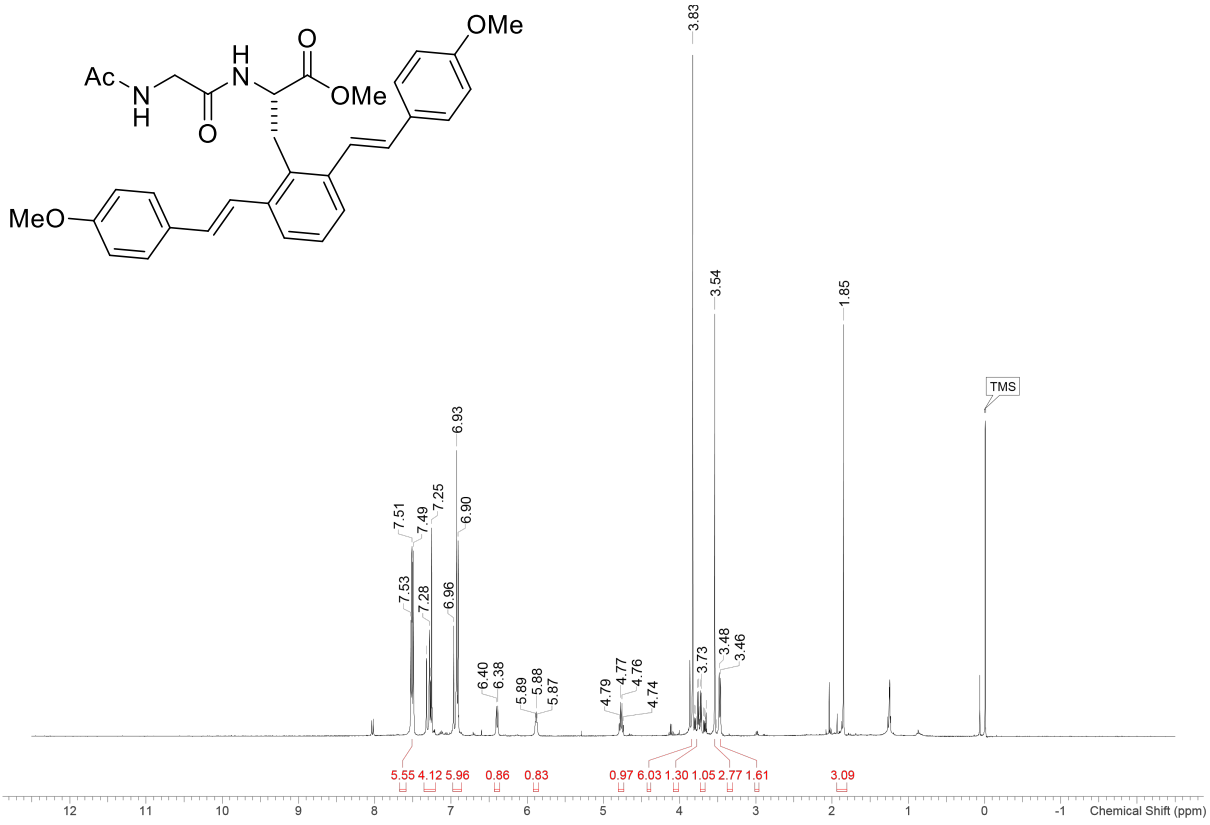
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3d**



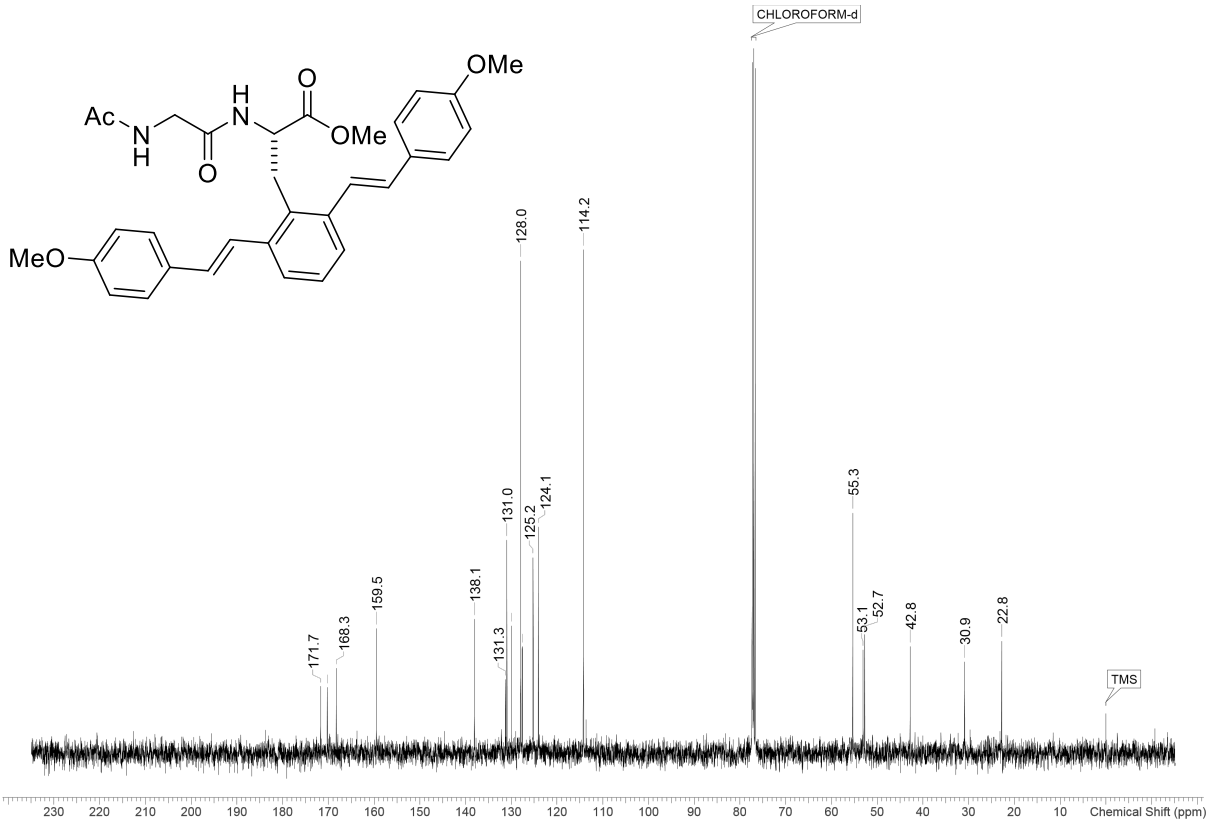
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3d**



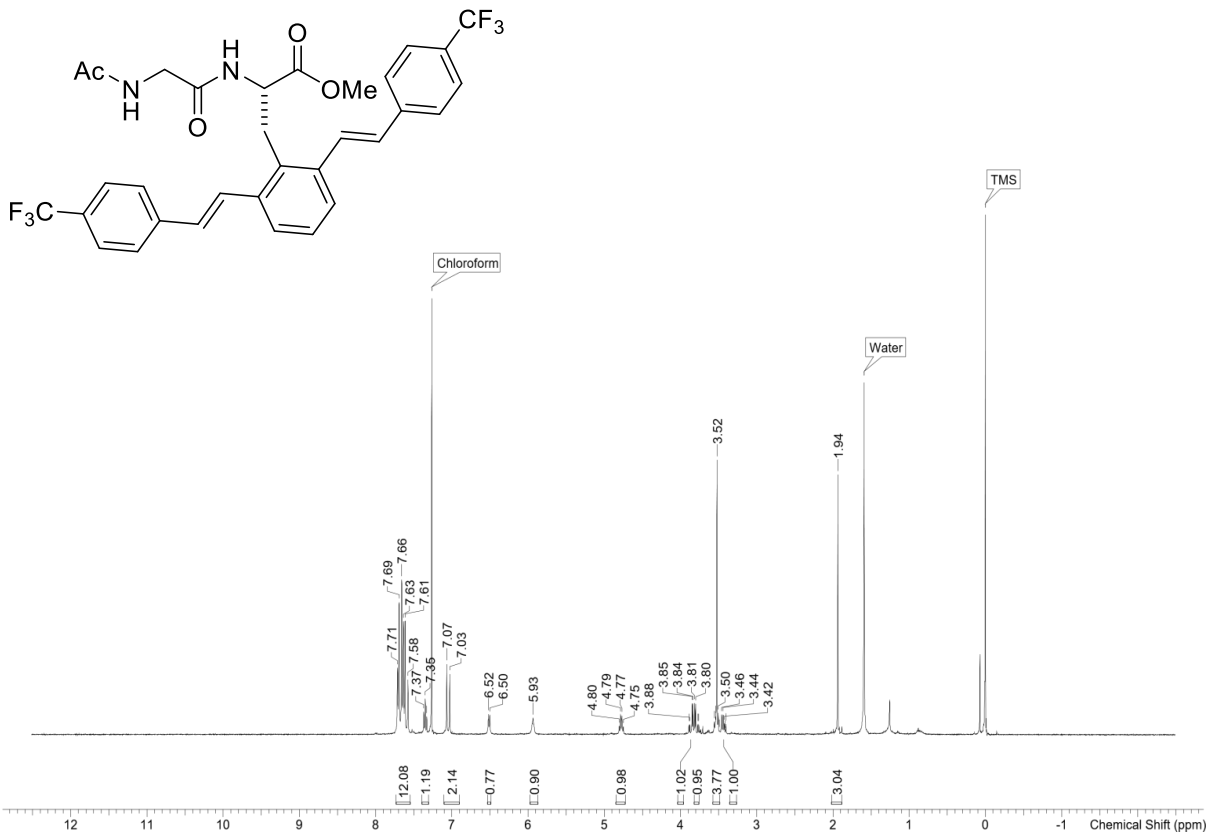
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3e**



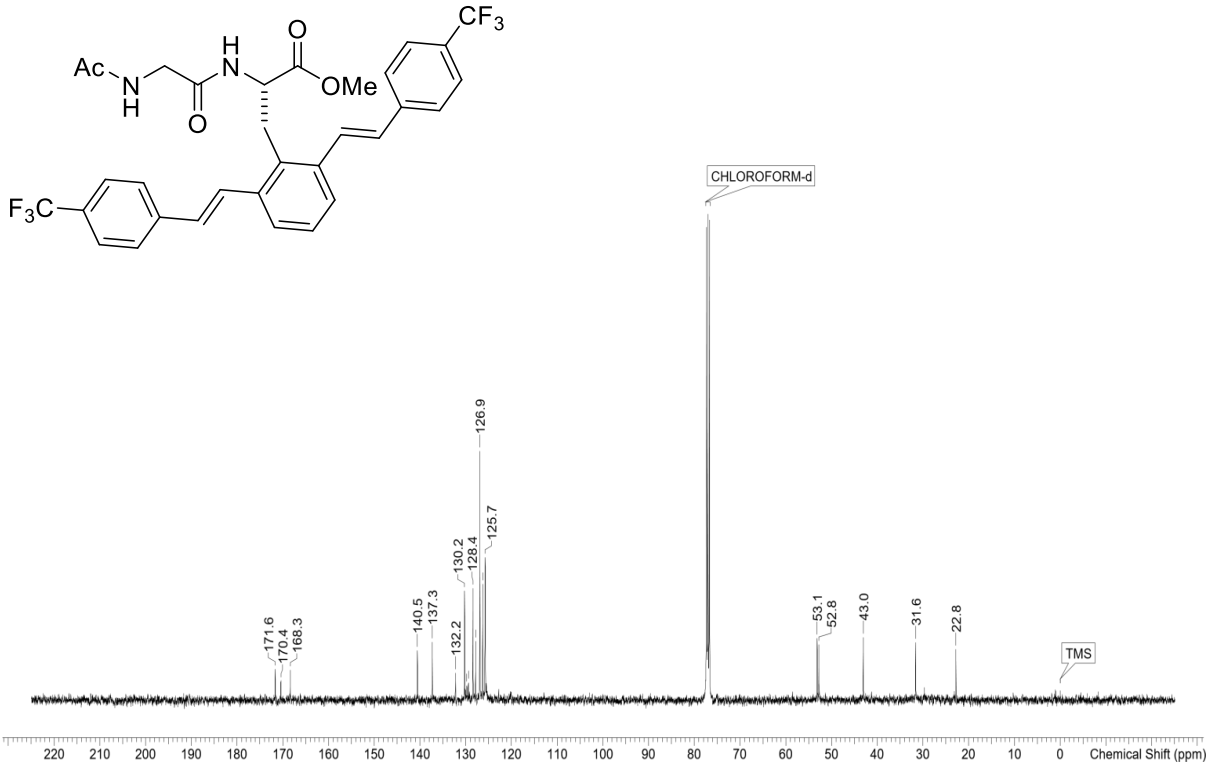
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3e**



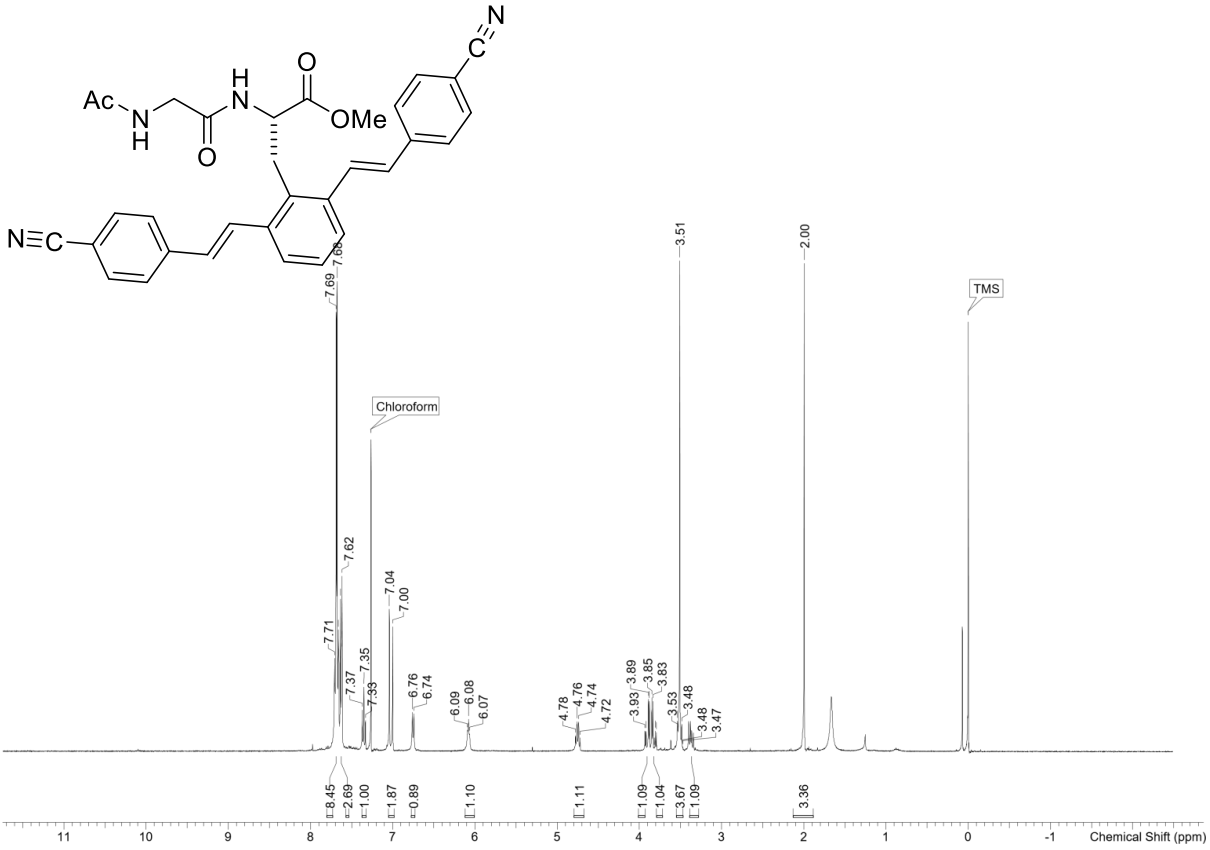
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3f**



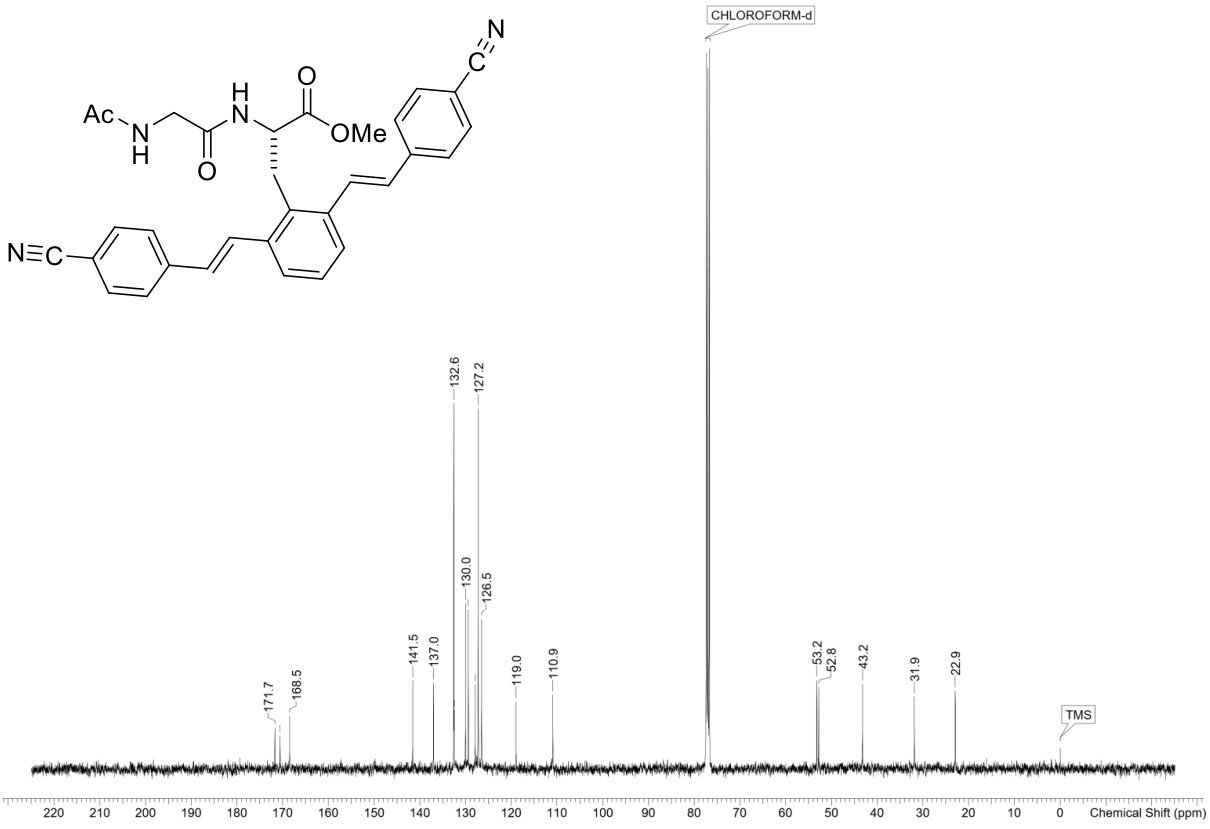
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3f**



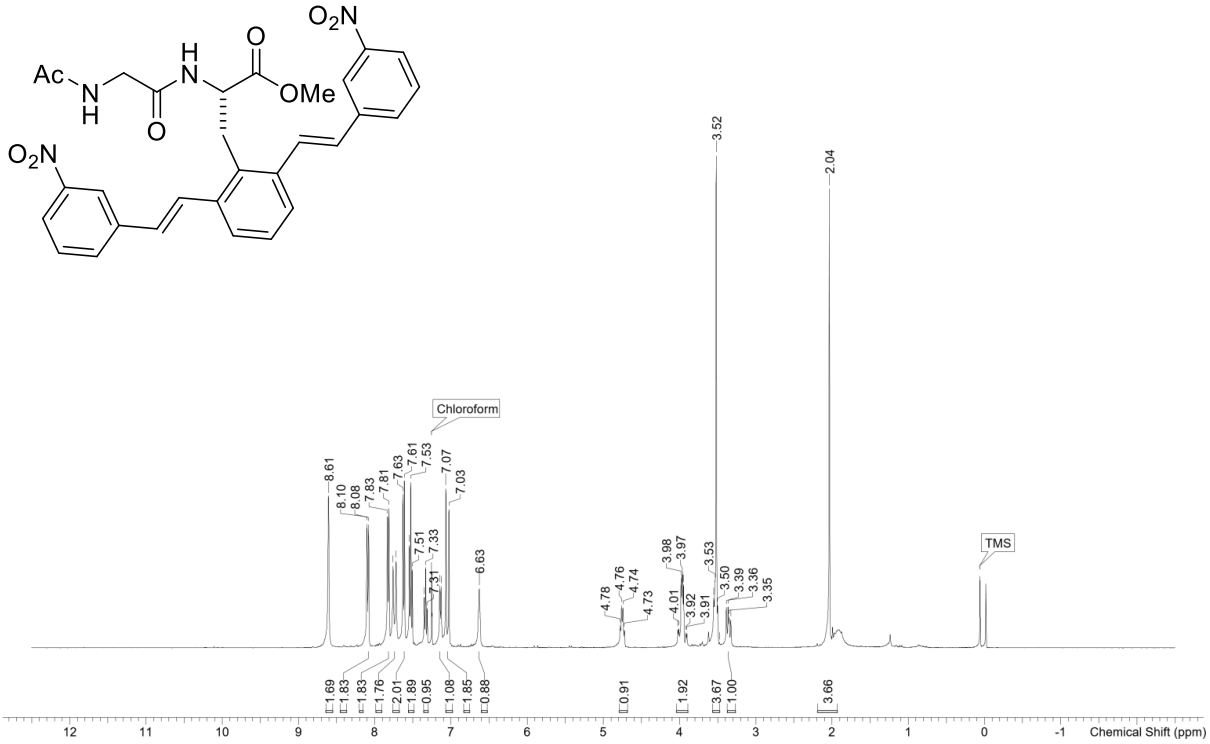
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3g**



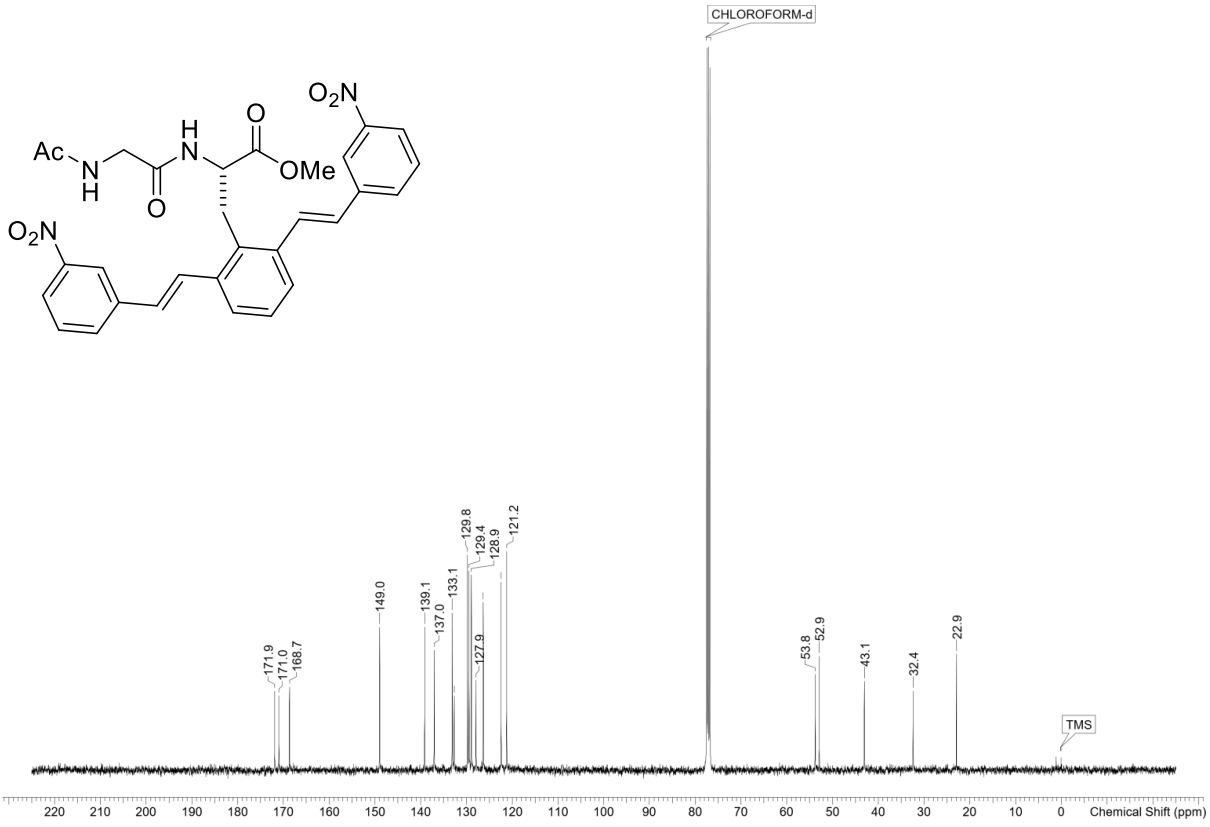
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **3g**



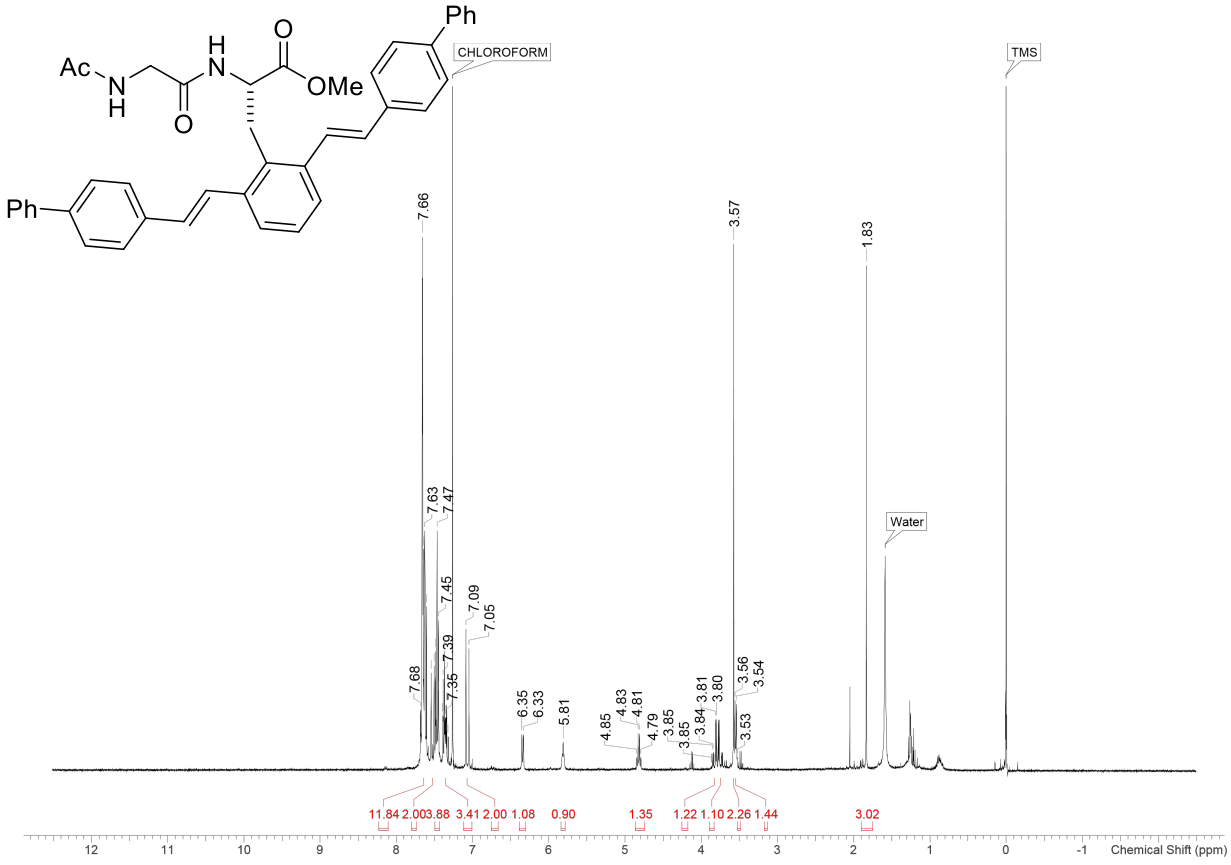
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3h**



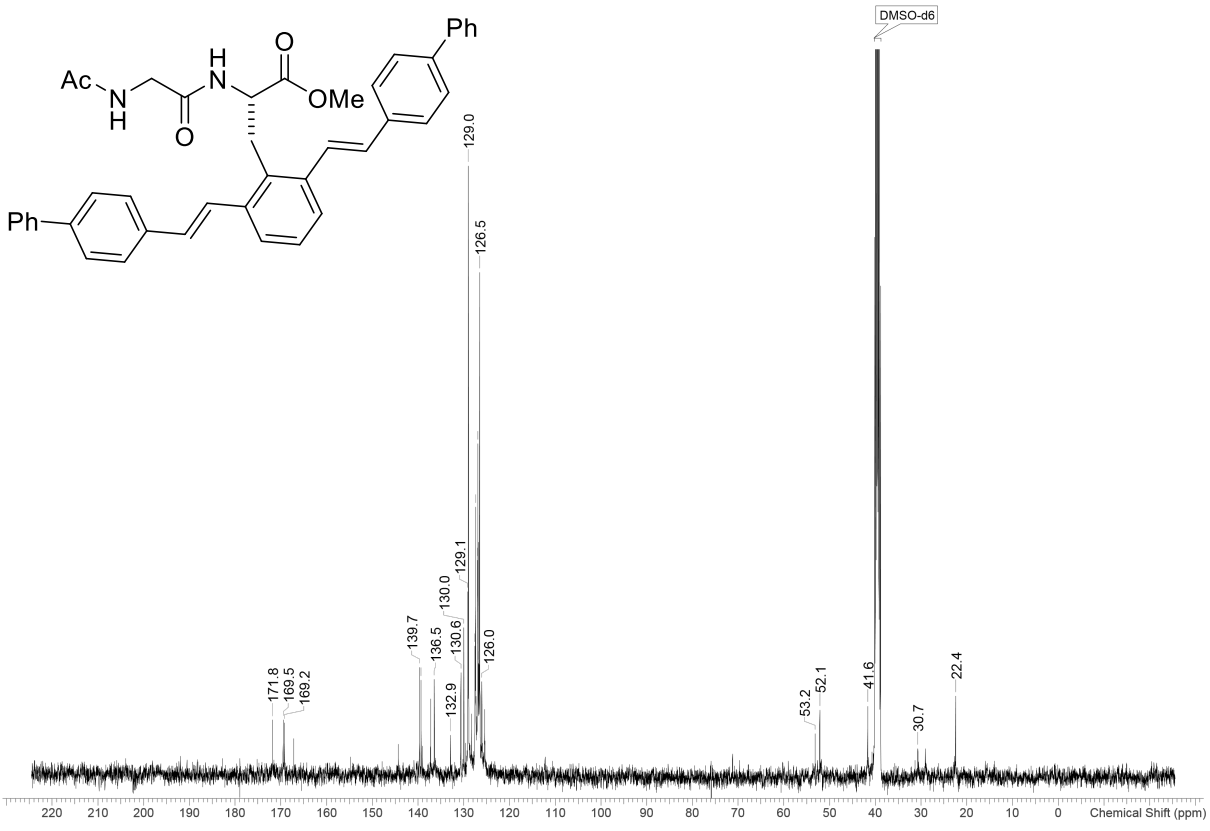
$^{13}C\{^{1}H\}$ NMR spectrum (100 MHz, $CDCl_3$) of **3h**



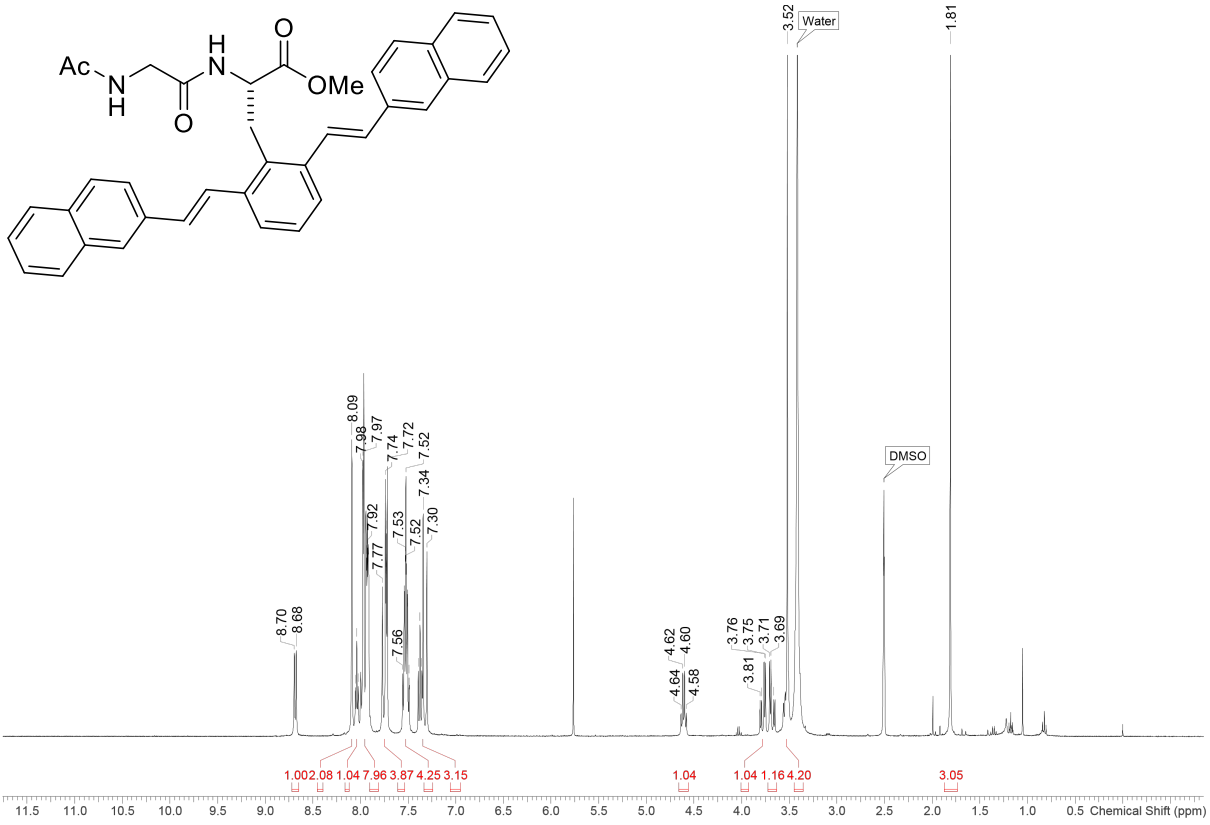
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3i**



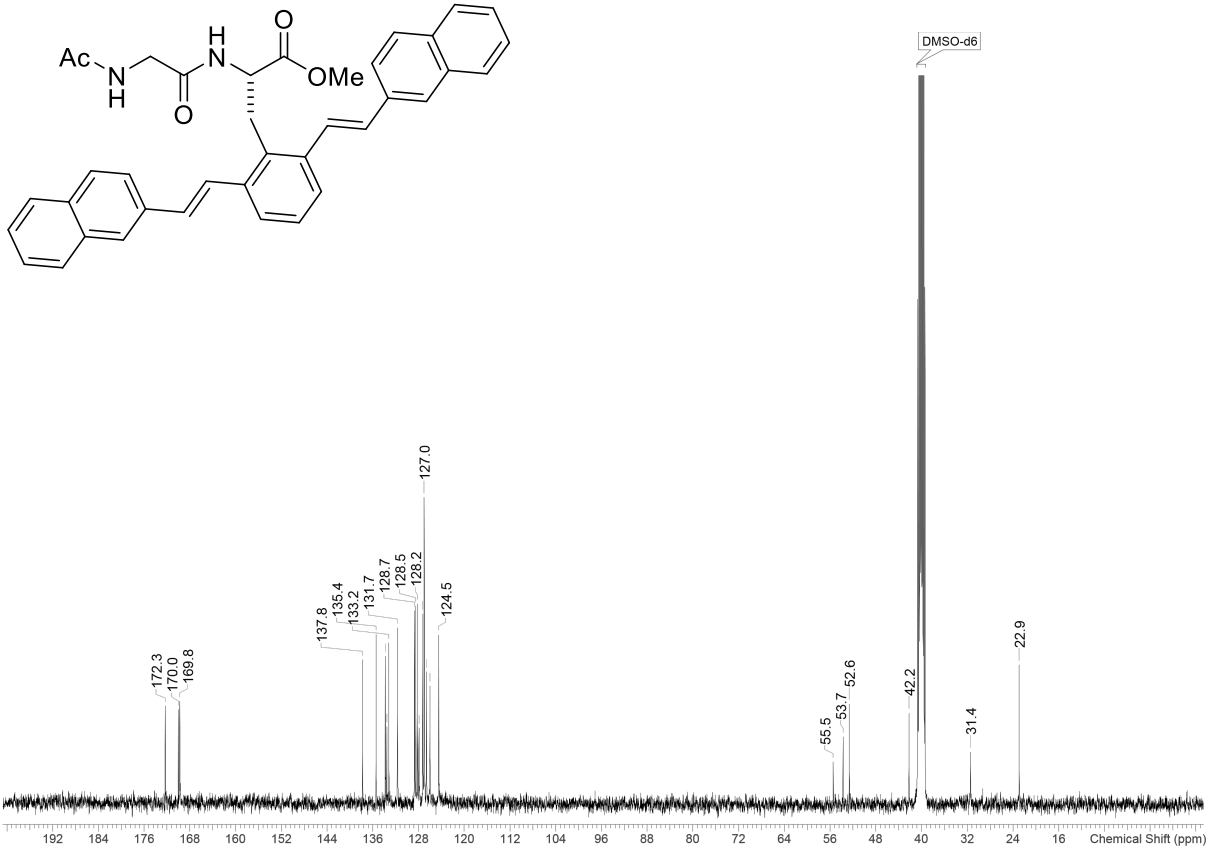
^{13}C{^{1}H} NMR spectrum (100 MHz, DMSO-d_6) of **3i**



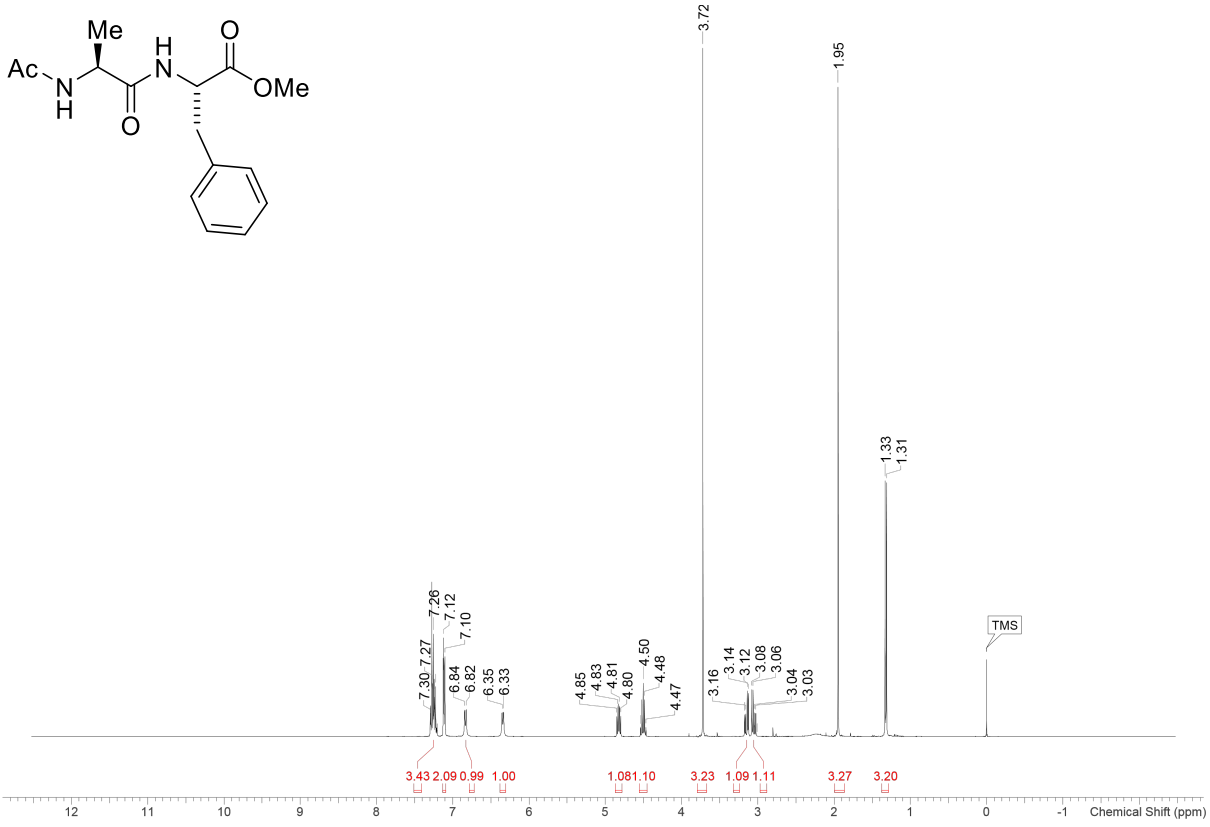
^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **3j**



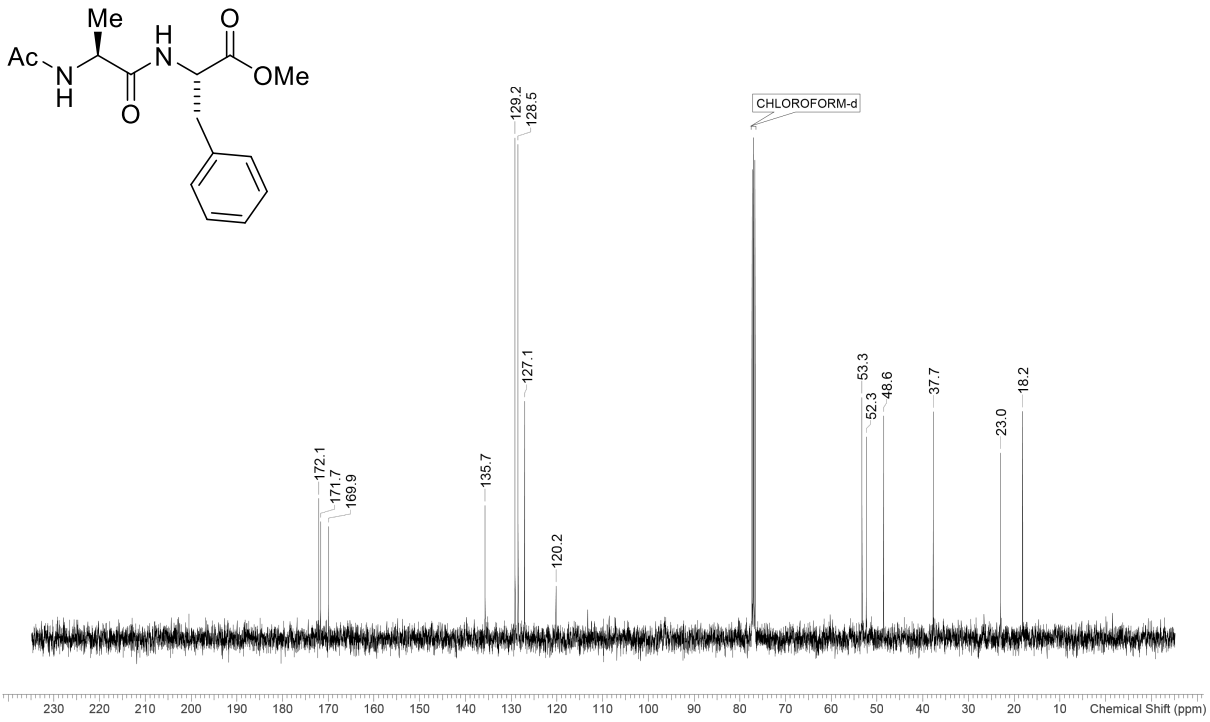
^{13}C {^{1}H} NMR spectrum (100 MHz, DMSO-d_6) of **3j**



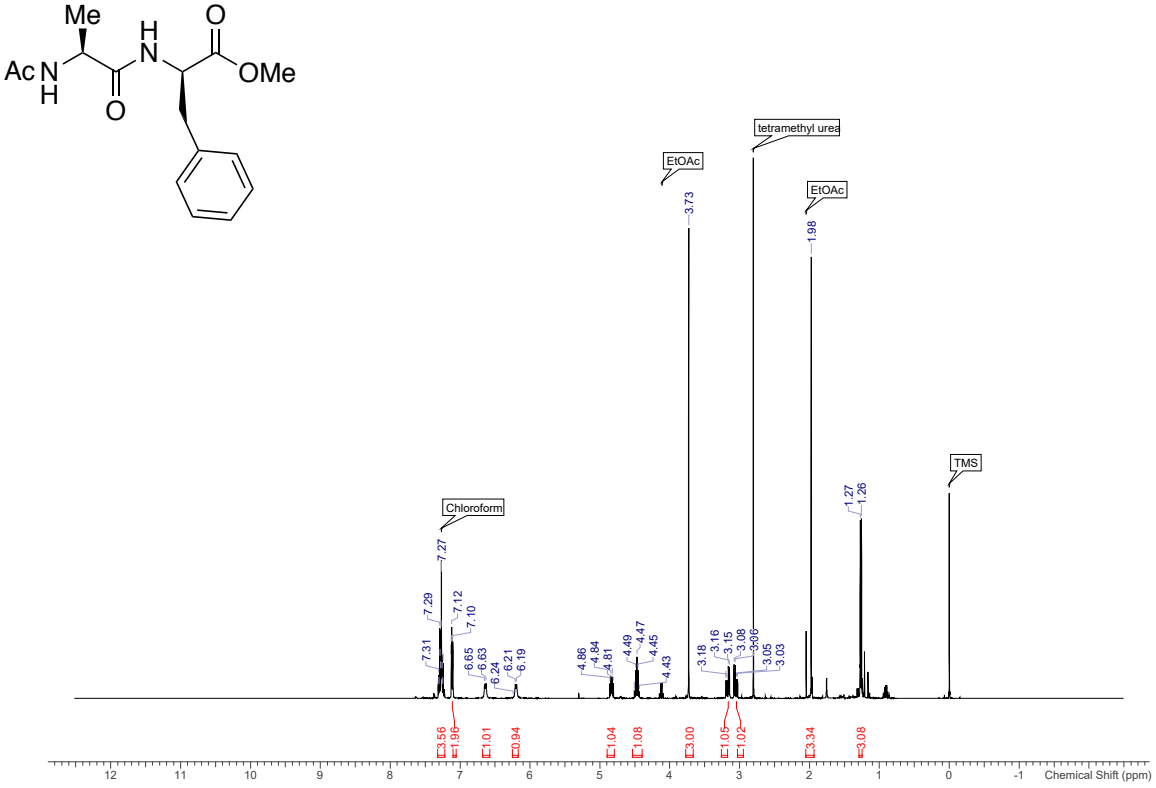
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4a**



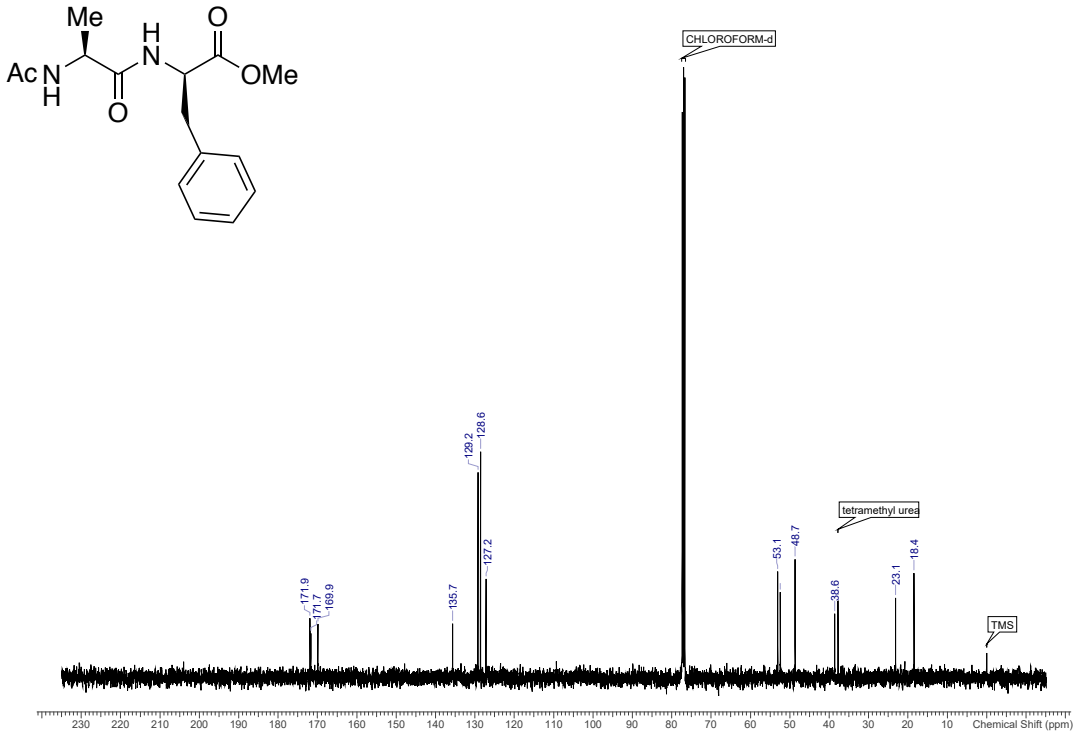
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4a**



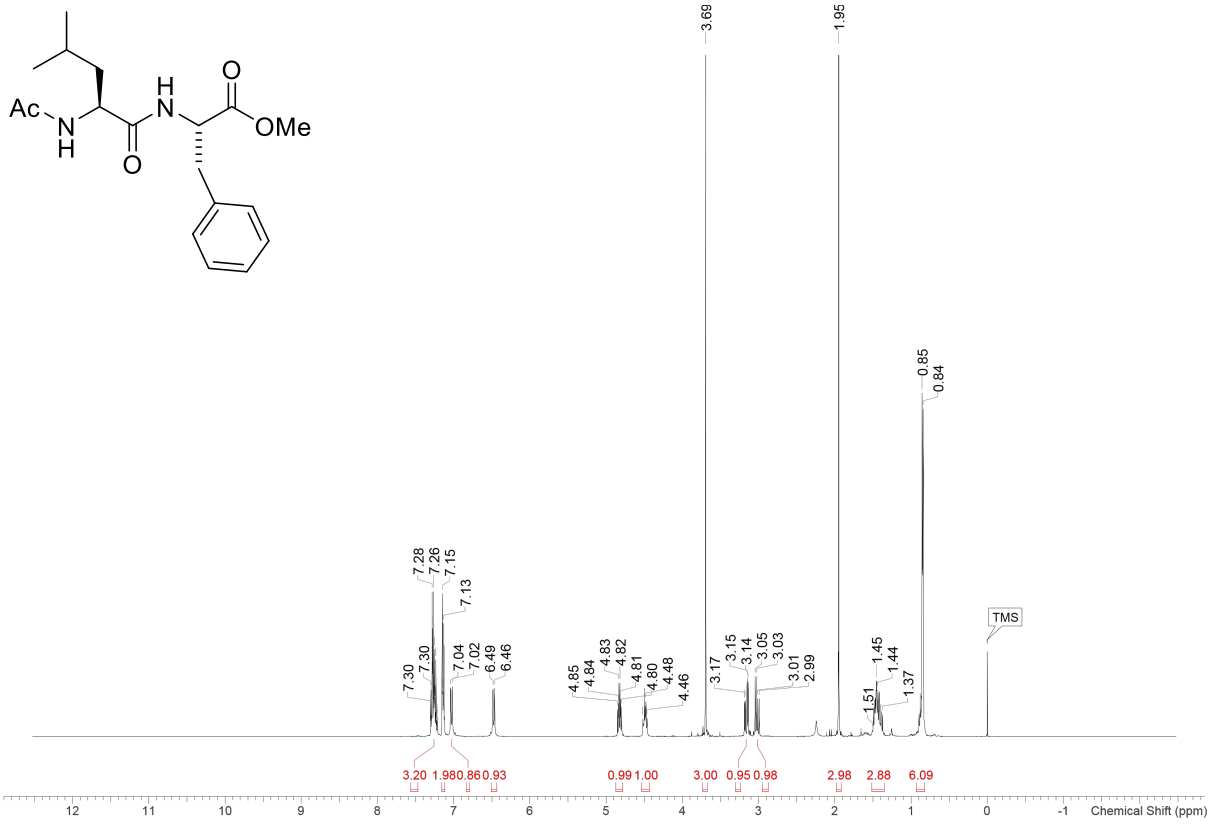
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (L,D)-**4a**



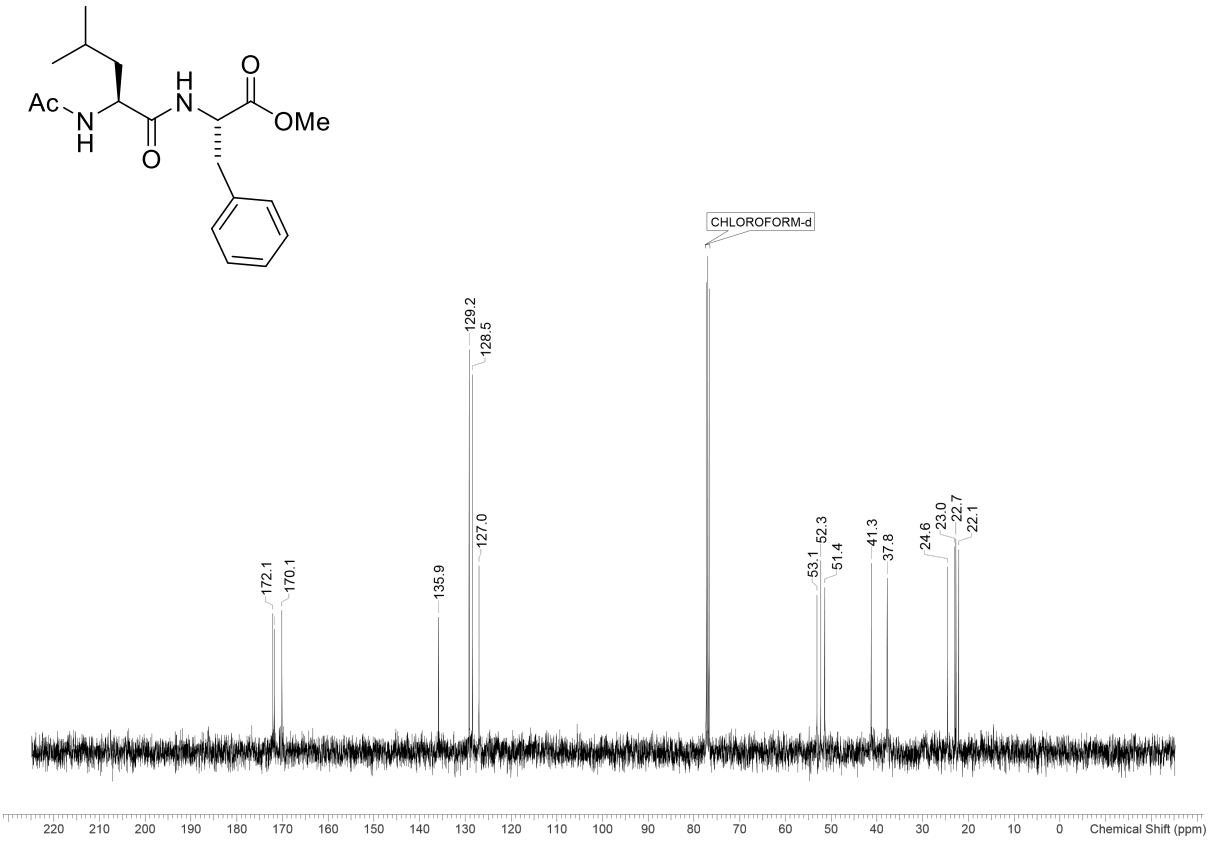
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (L,D)-**4a**



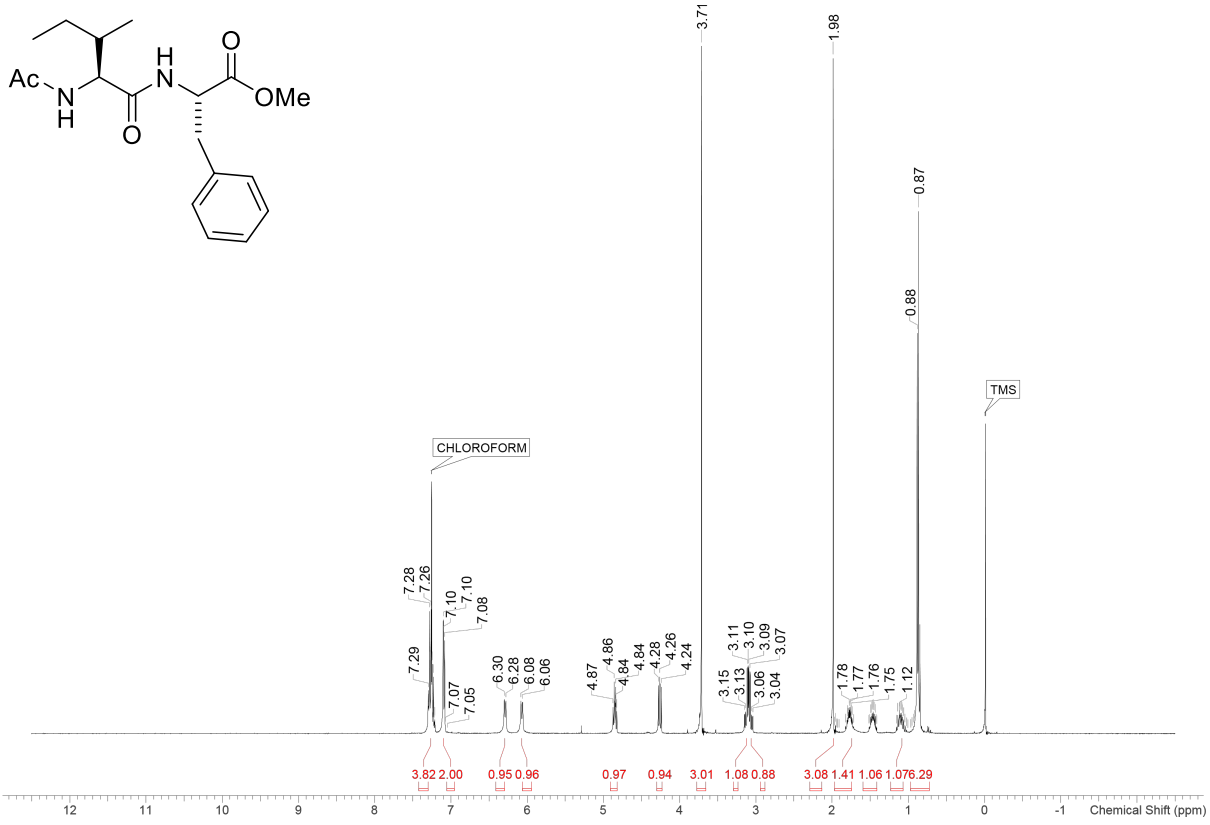
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4b**



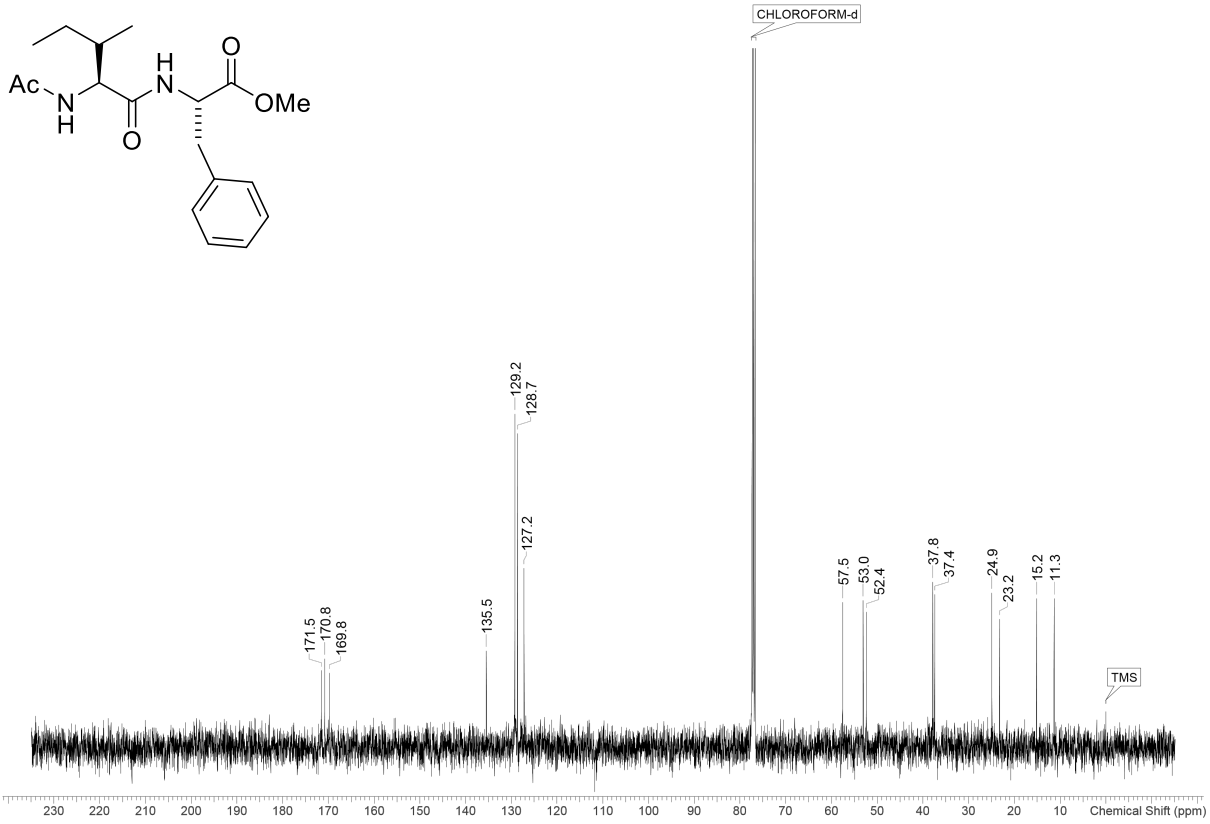
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4b**



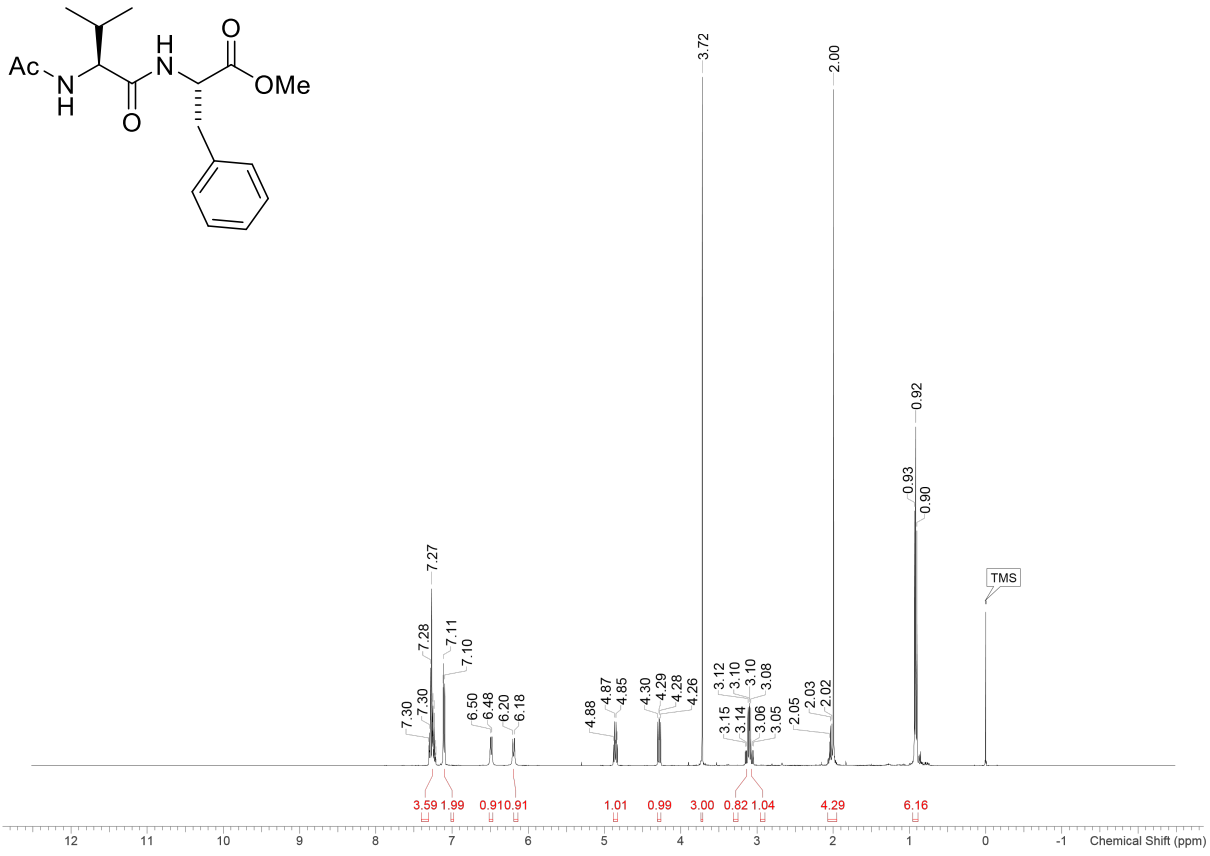
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4c**



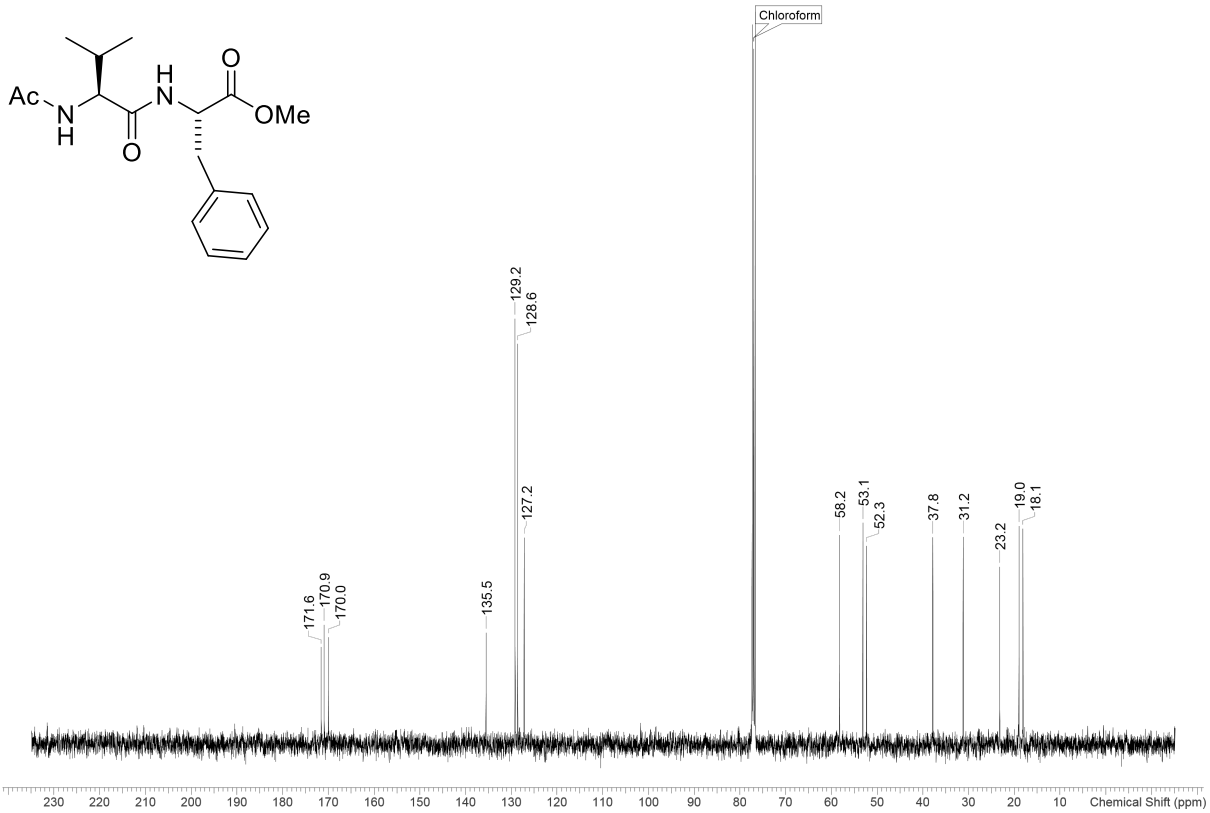
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4c**



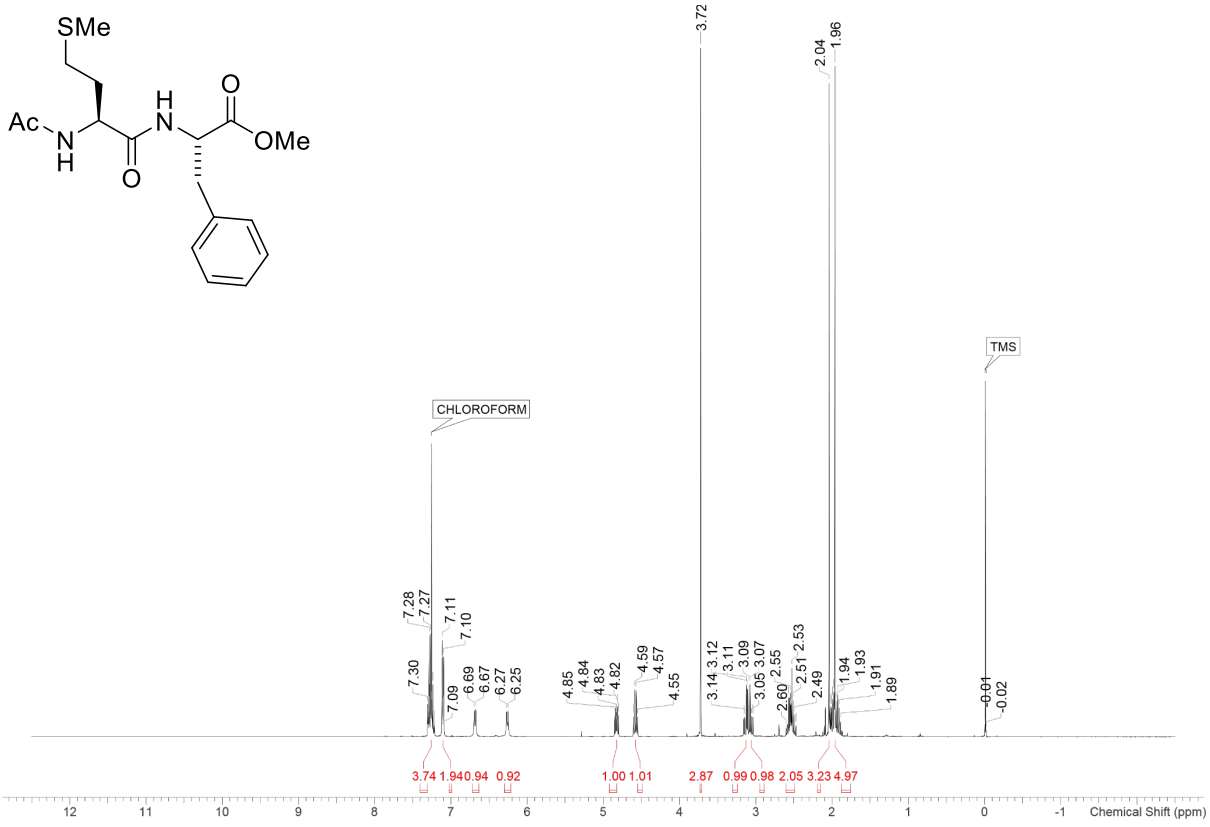
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4d**



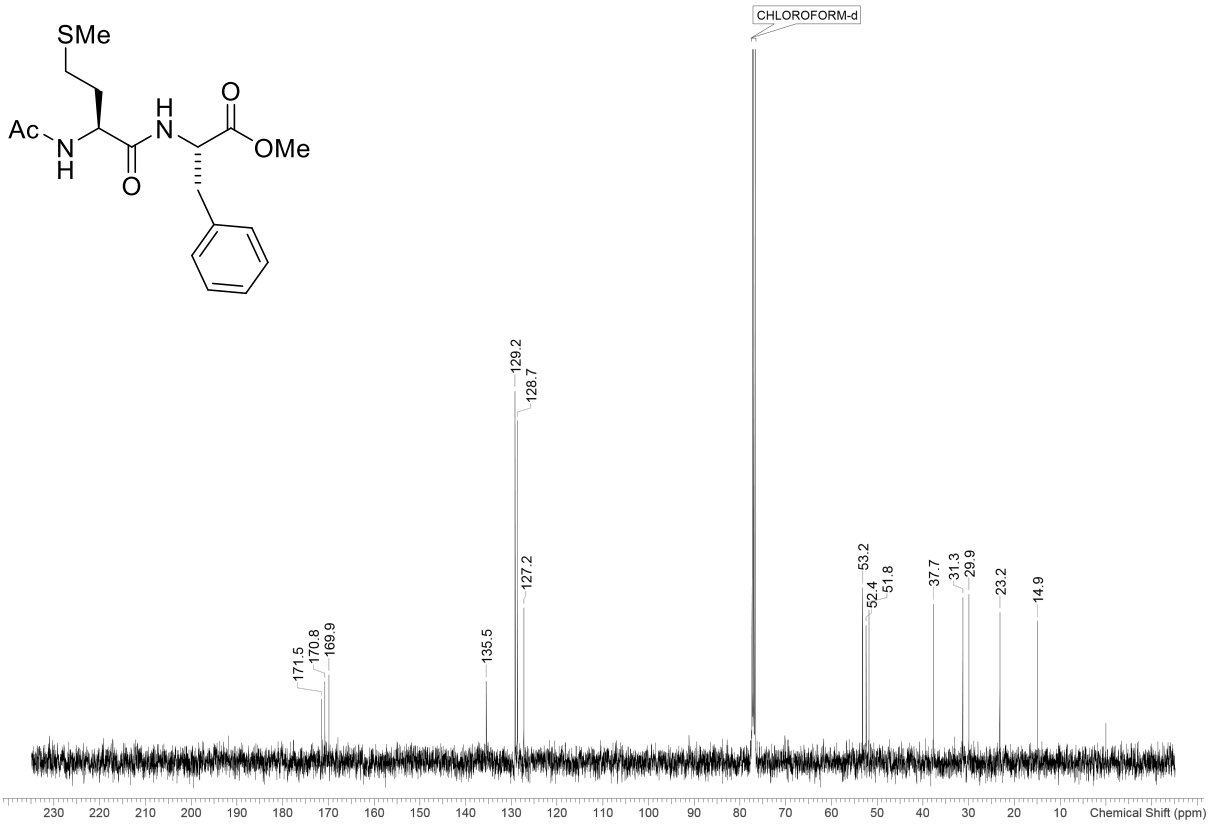
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4d**



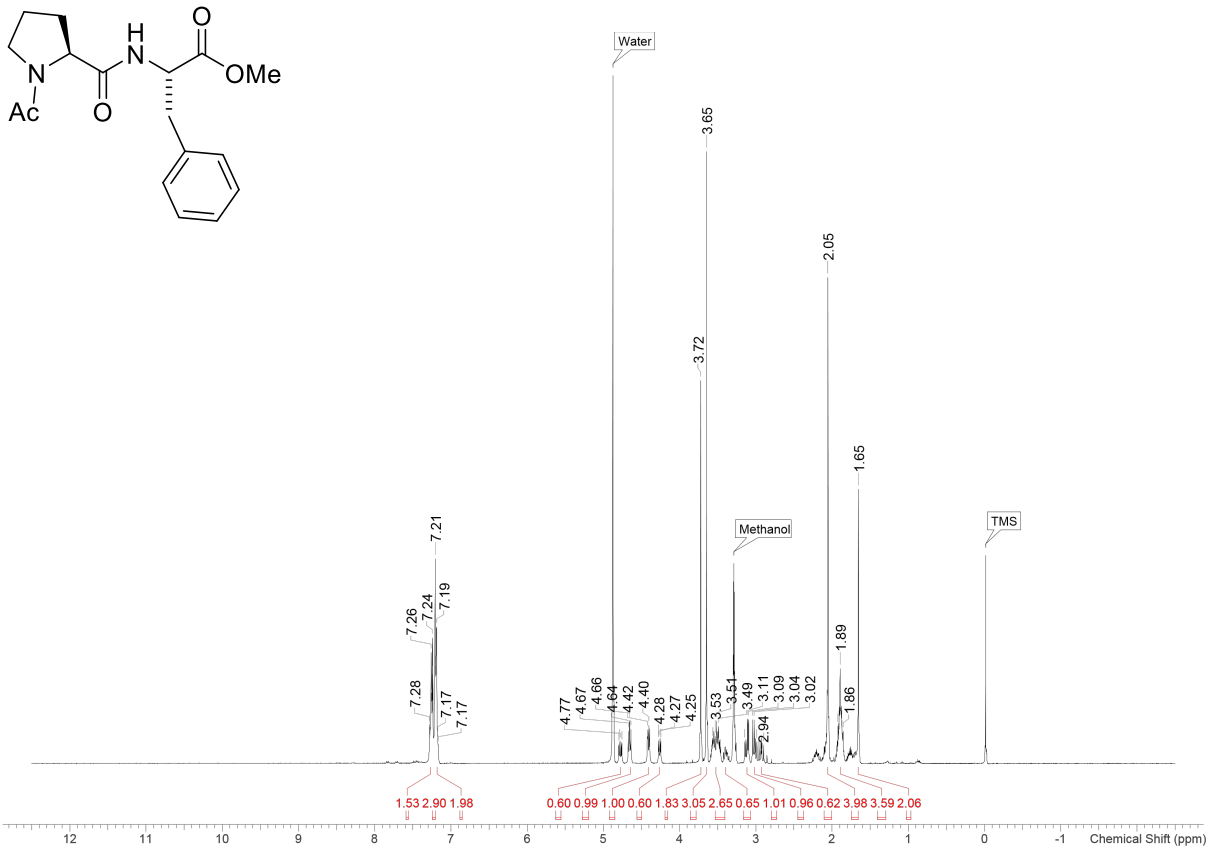
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4e**



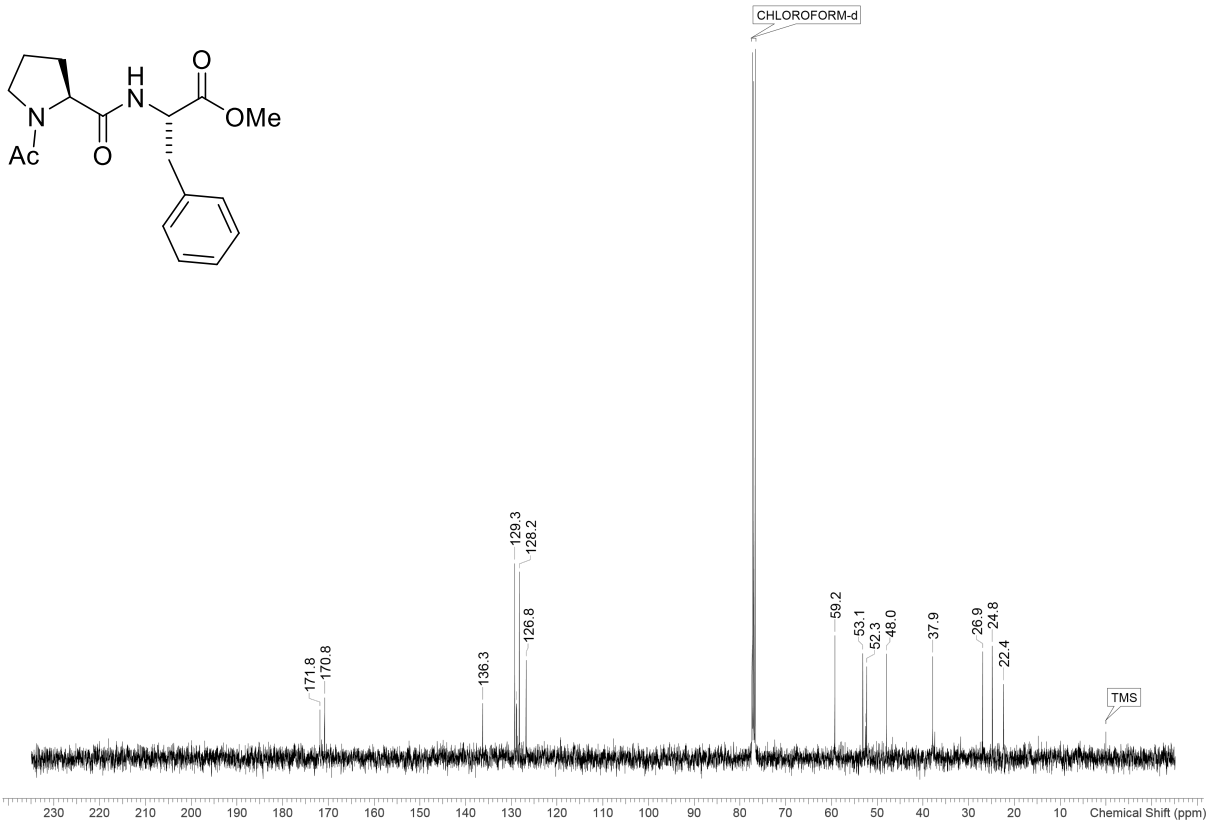
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4e**



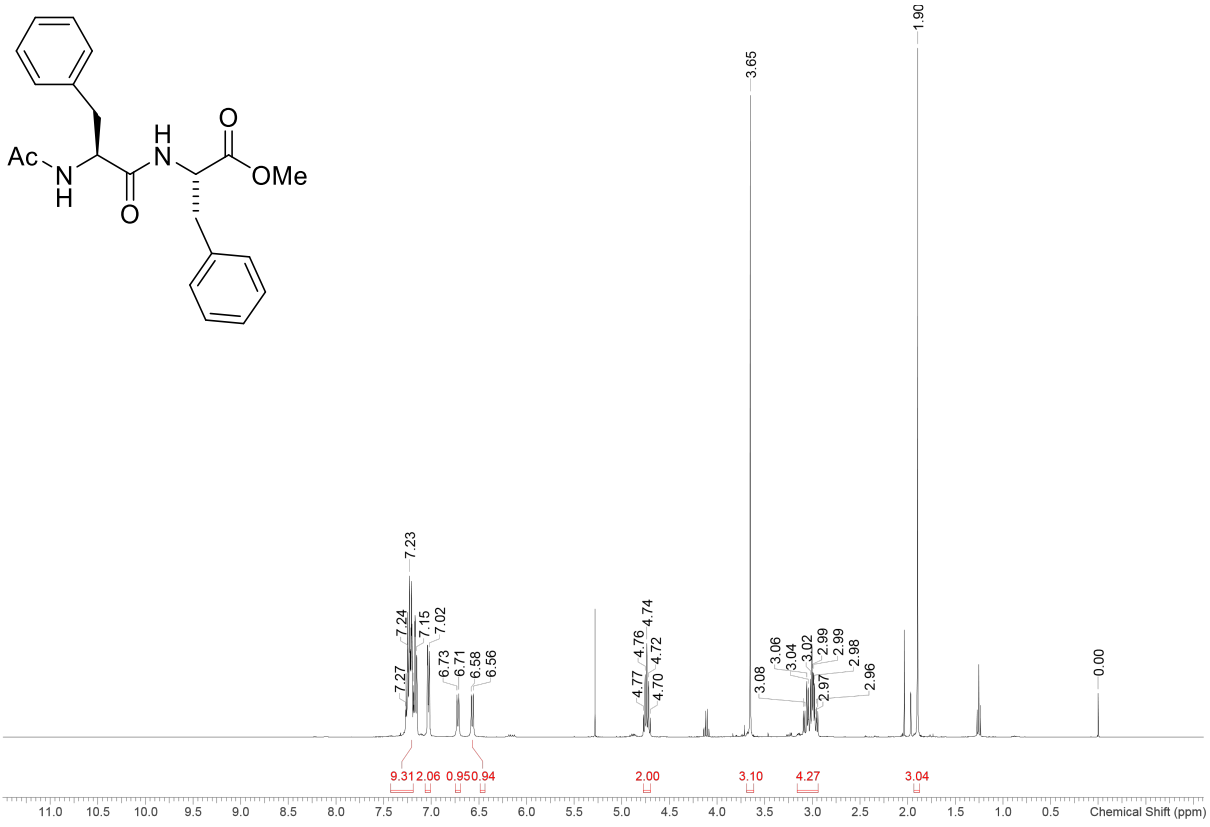
^{1}H NMR spectrum (400 MHz, CD_3OD) of **4f**



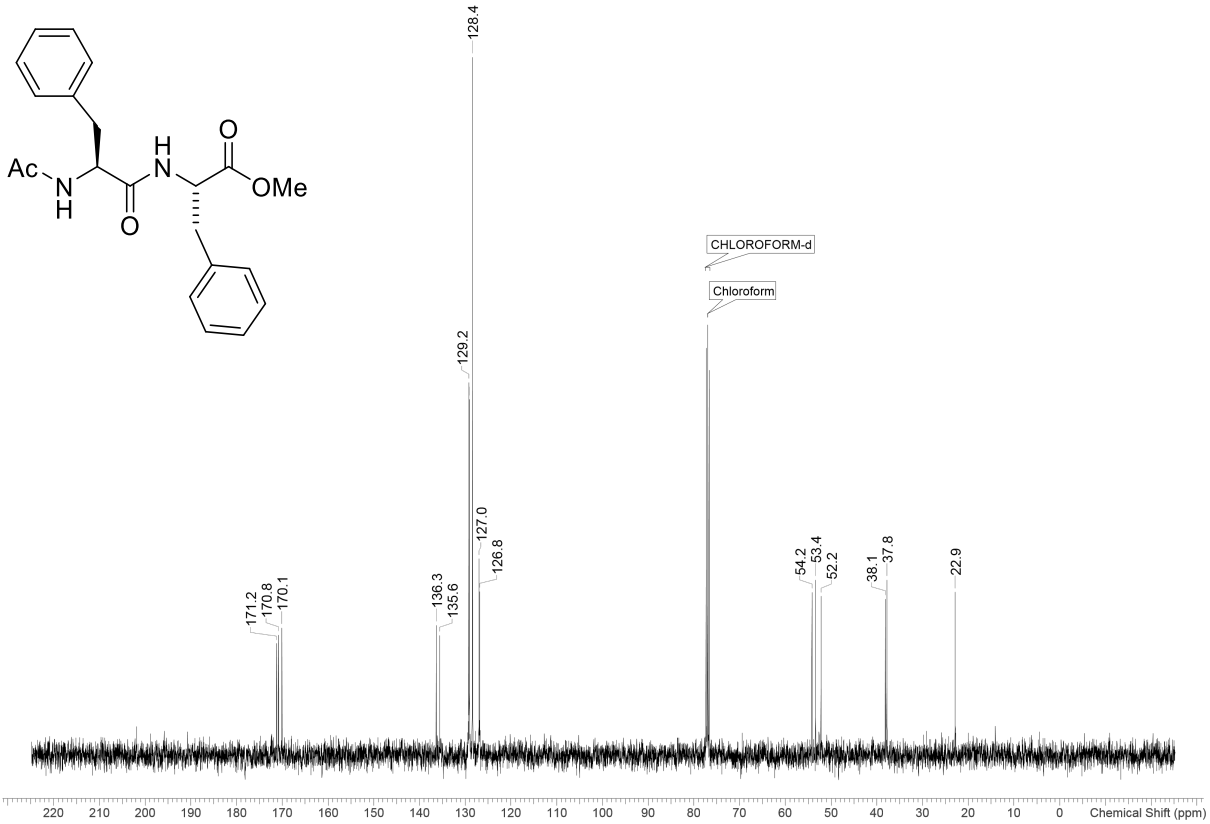
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4f**



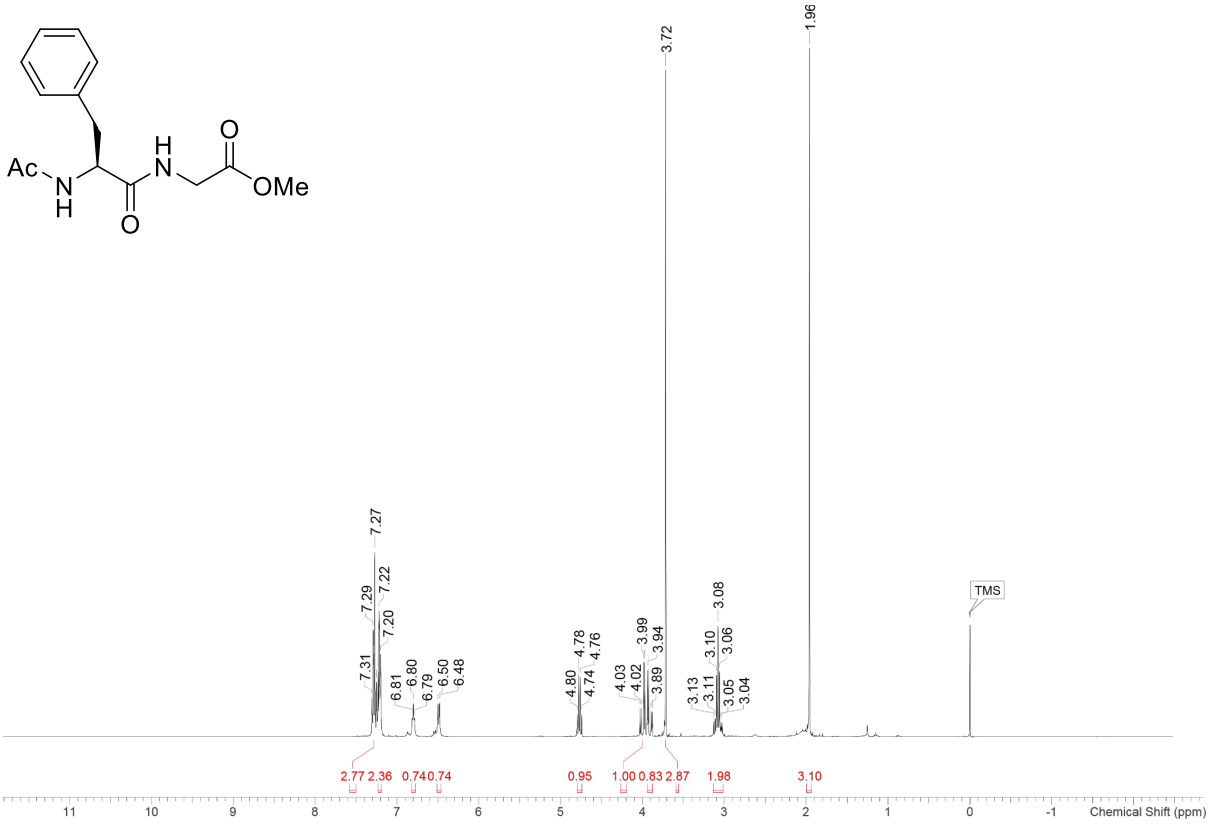
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4g**



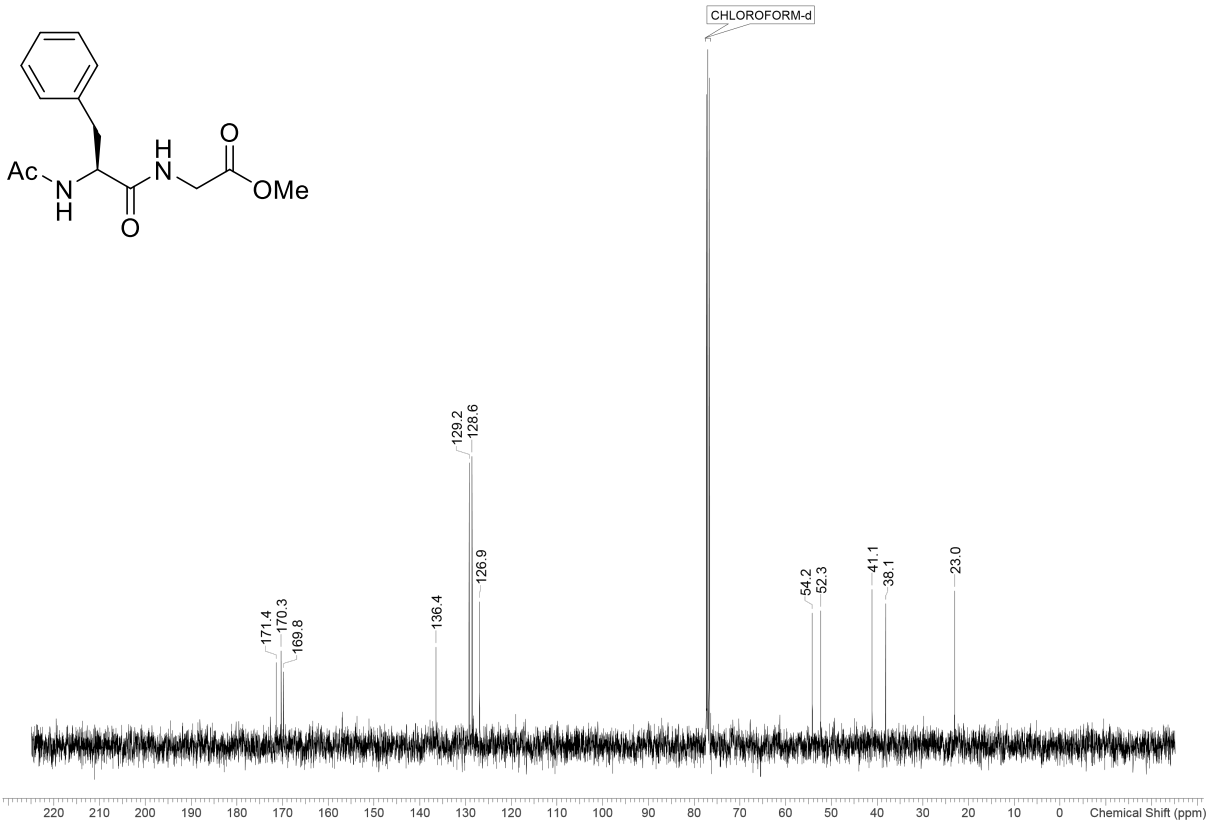
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4g**



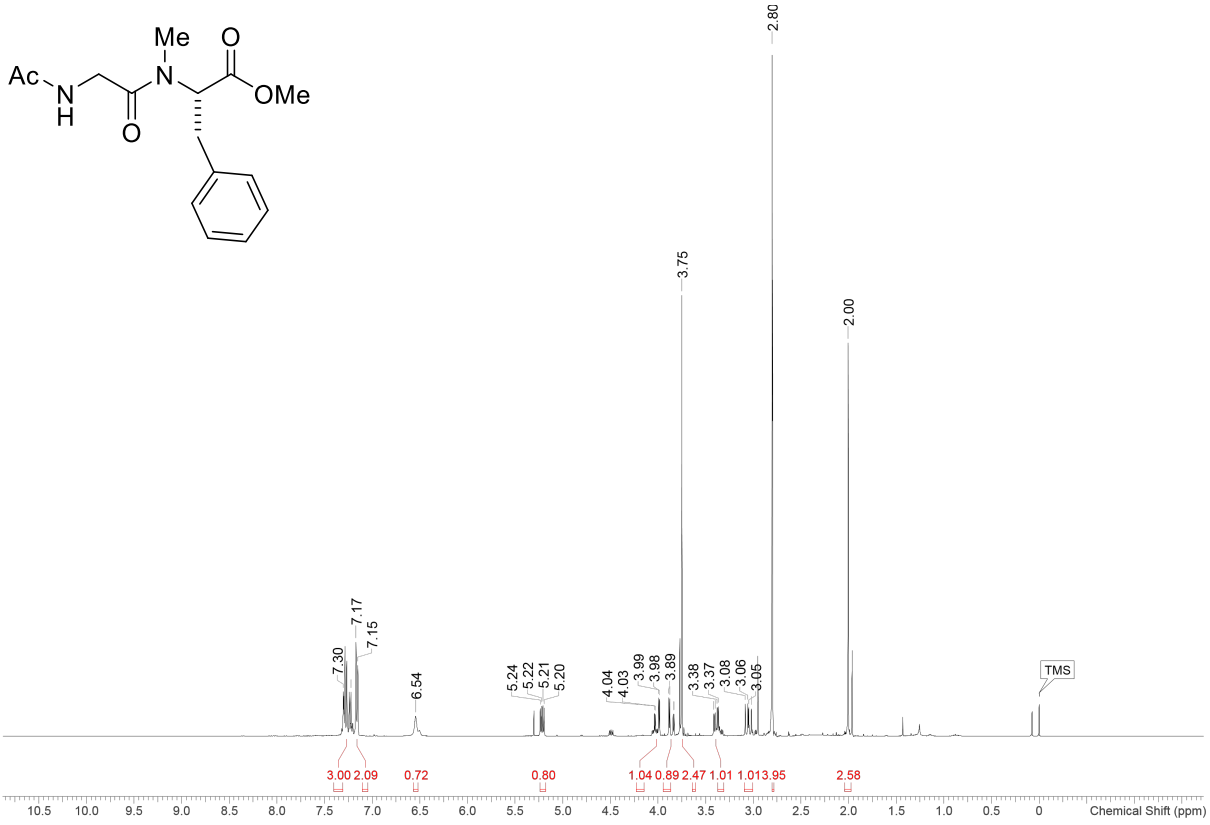
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4h**



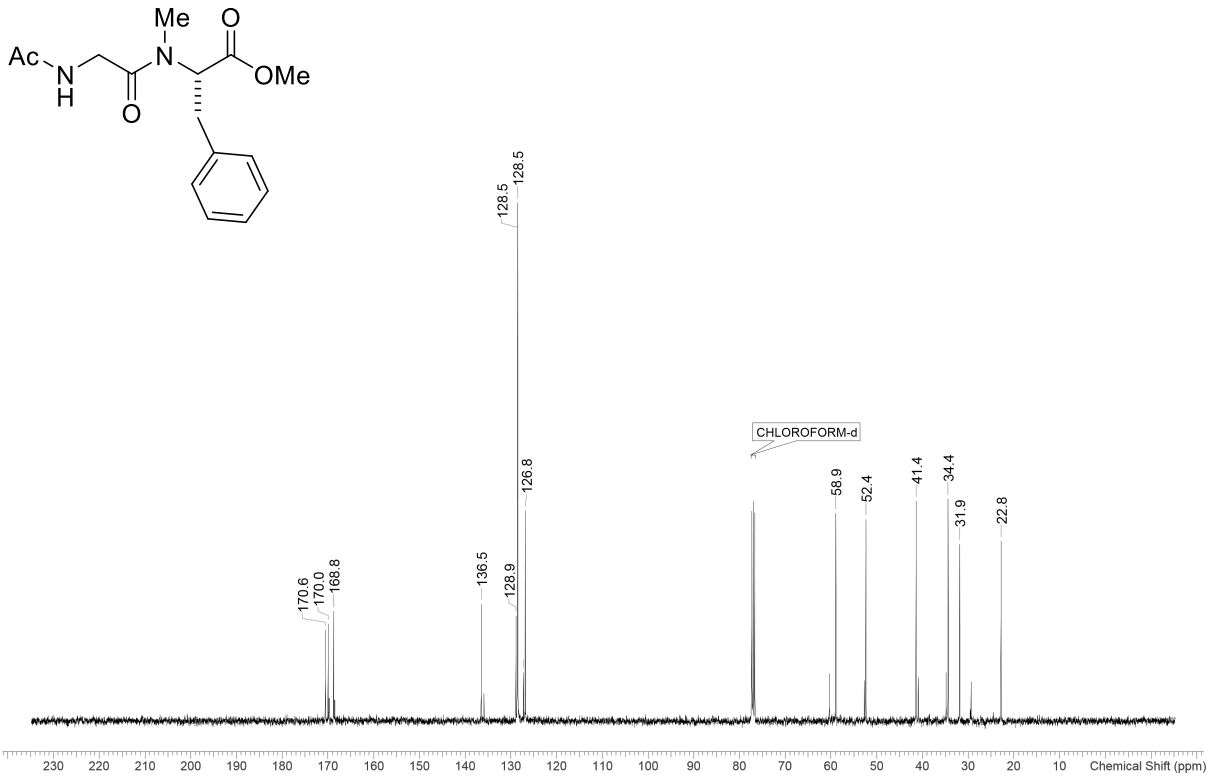
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4h**



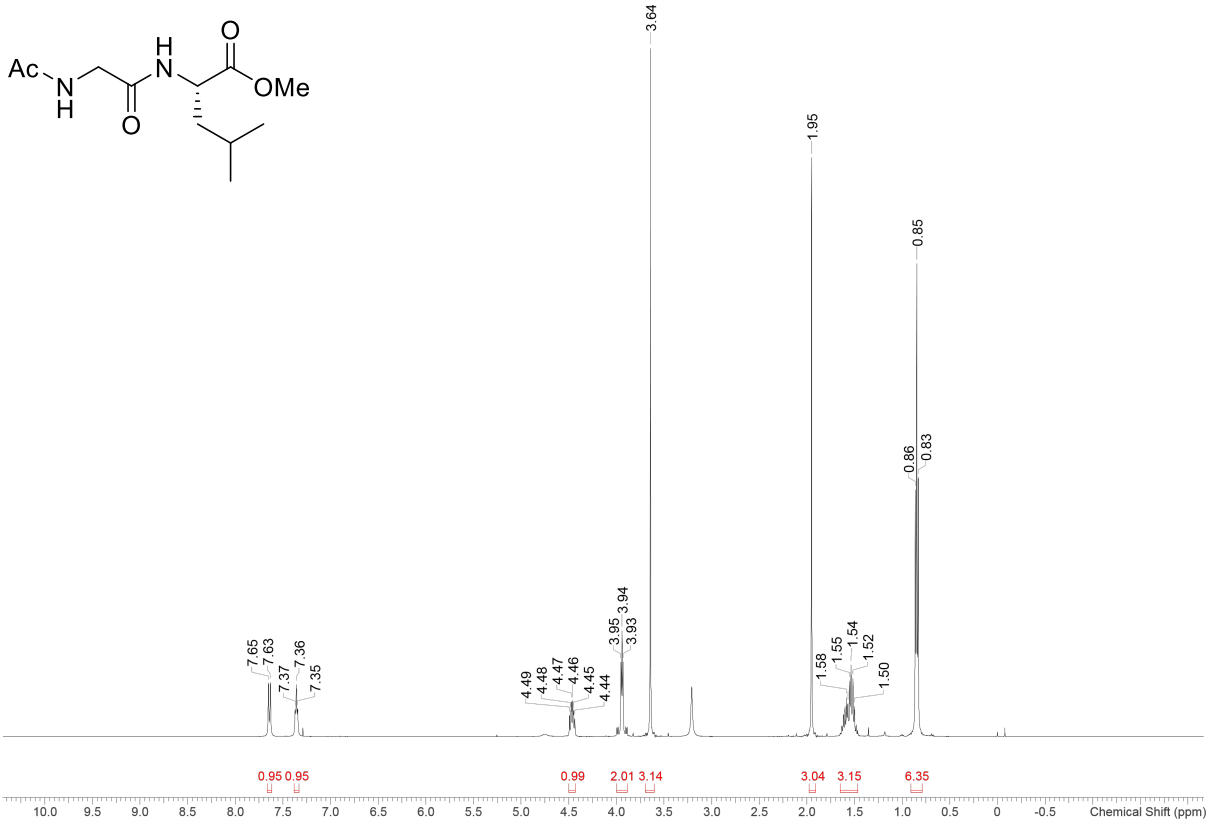
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4i**



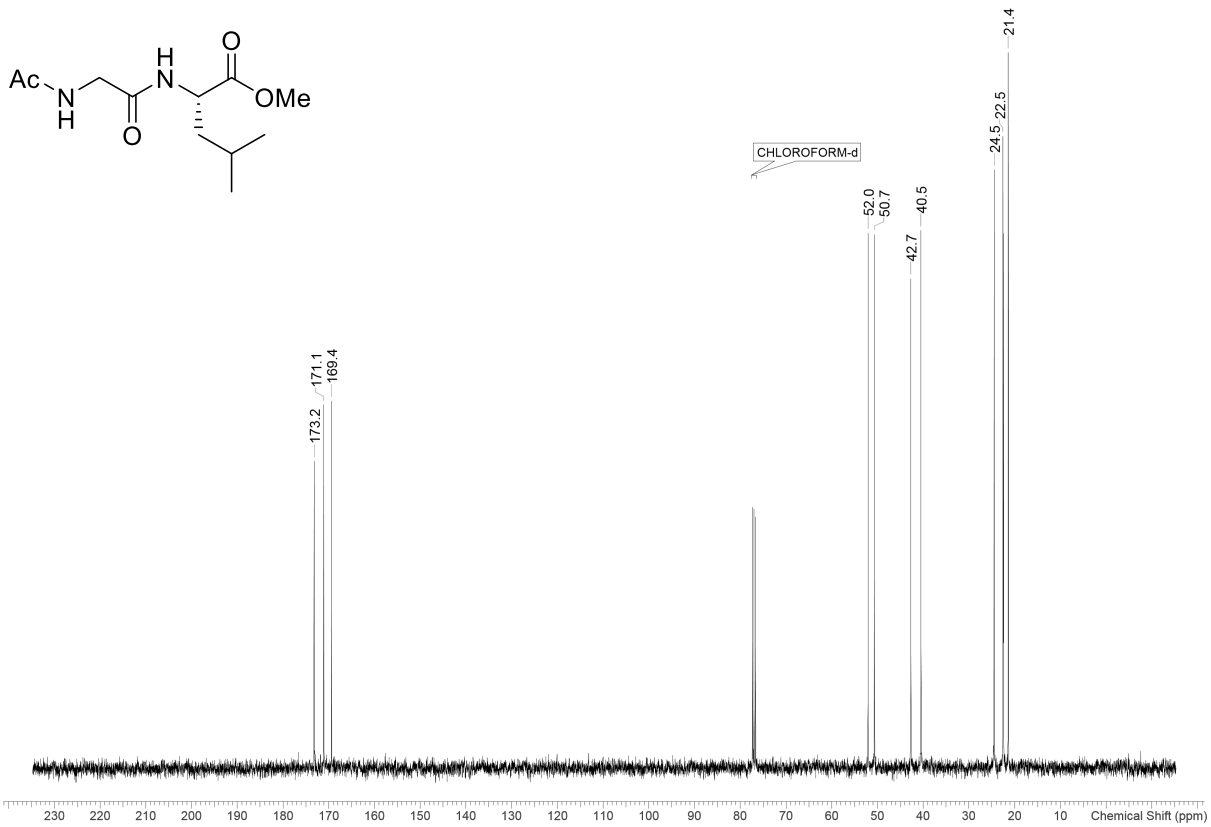
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4i**



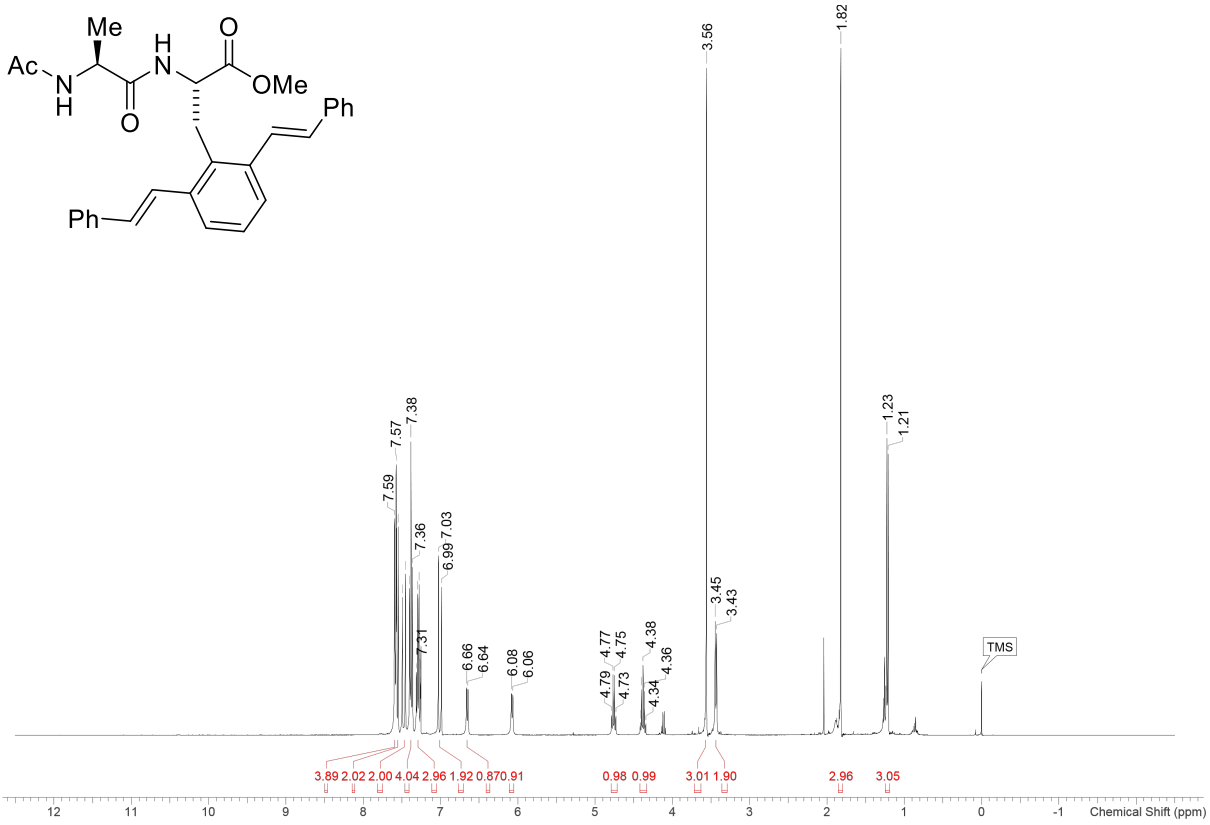
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4j**



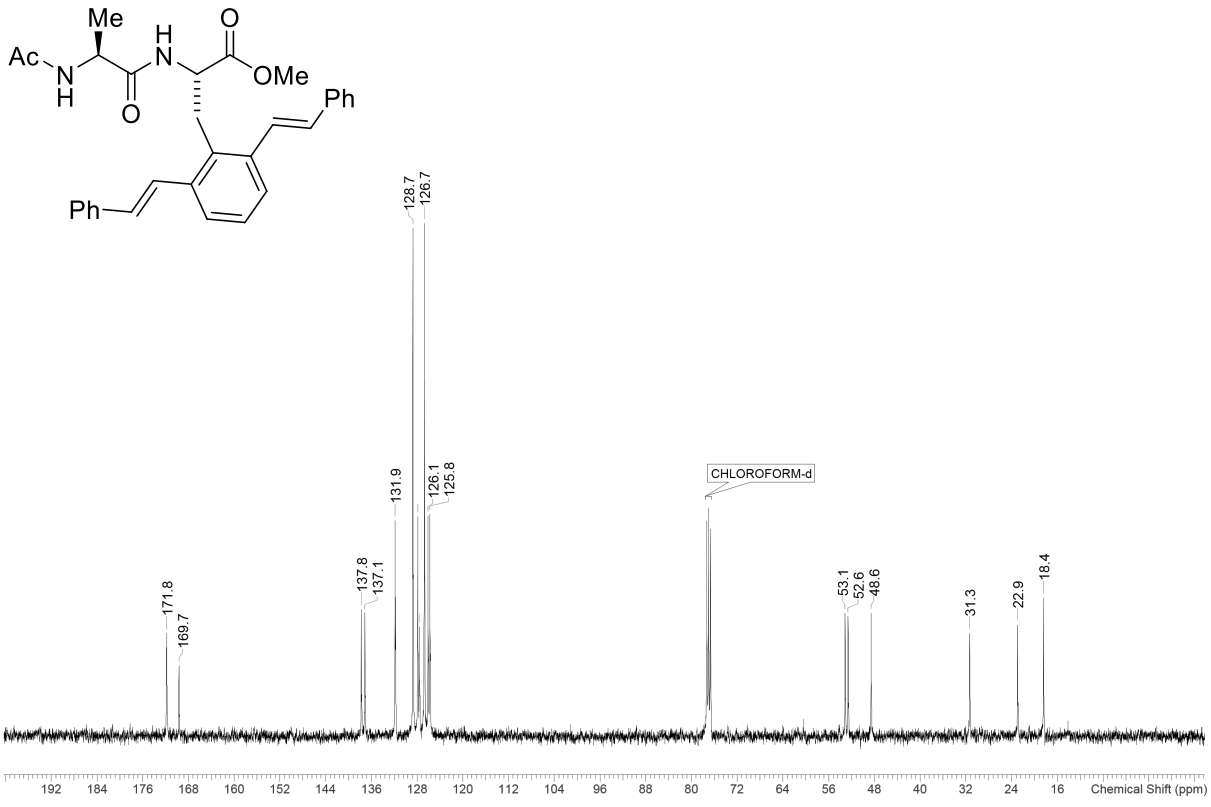
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **4j**



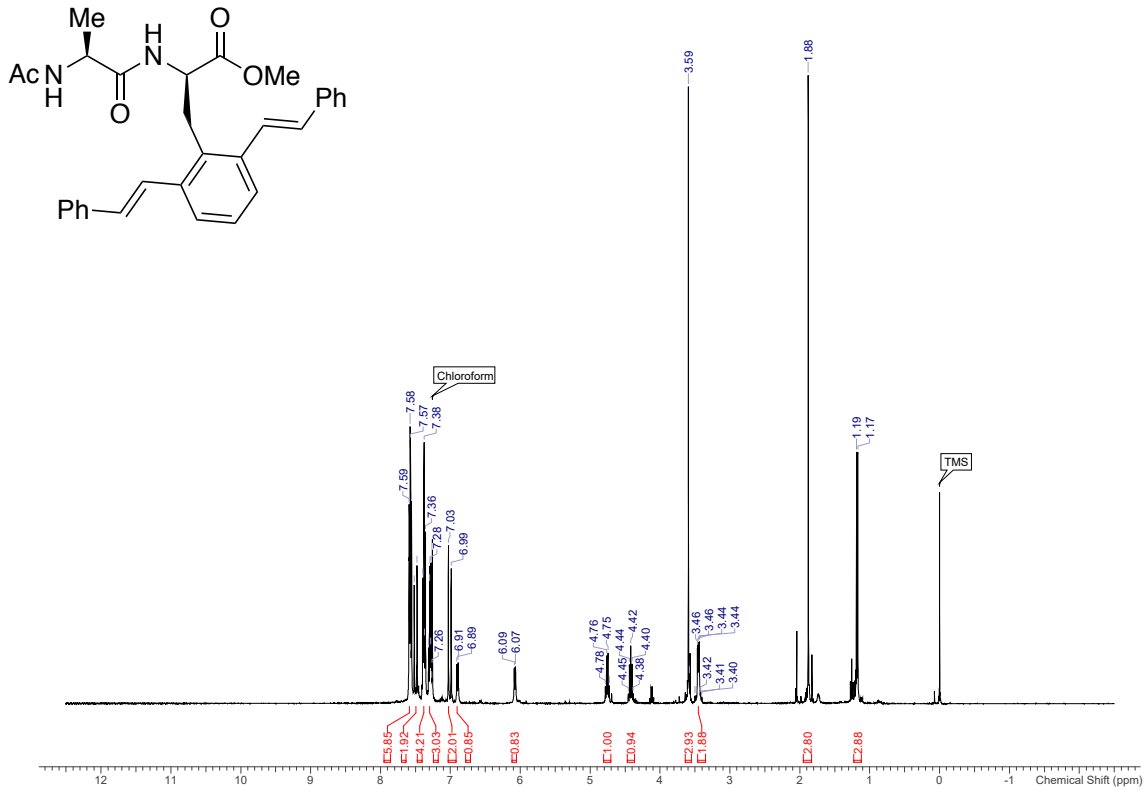
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5a**



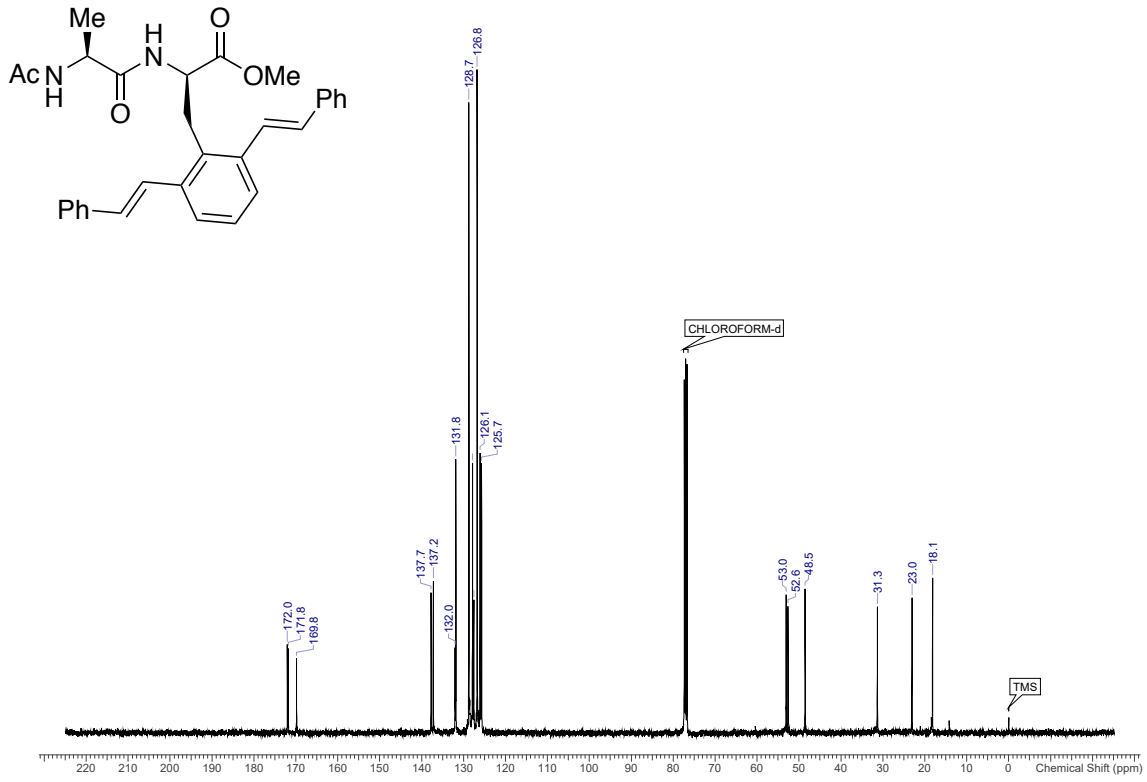
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5a**



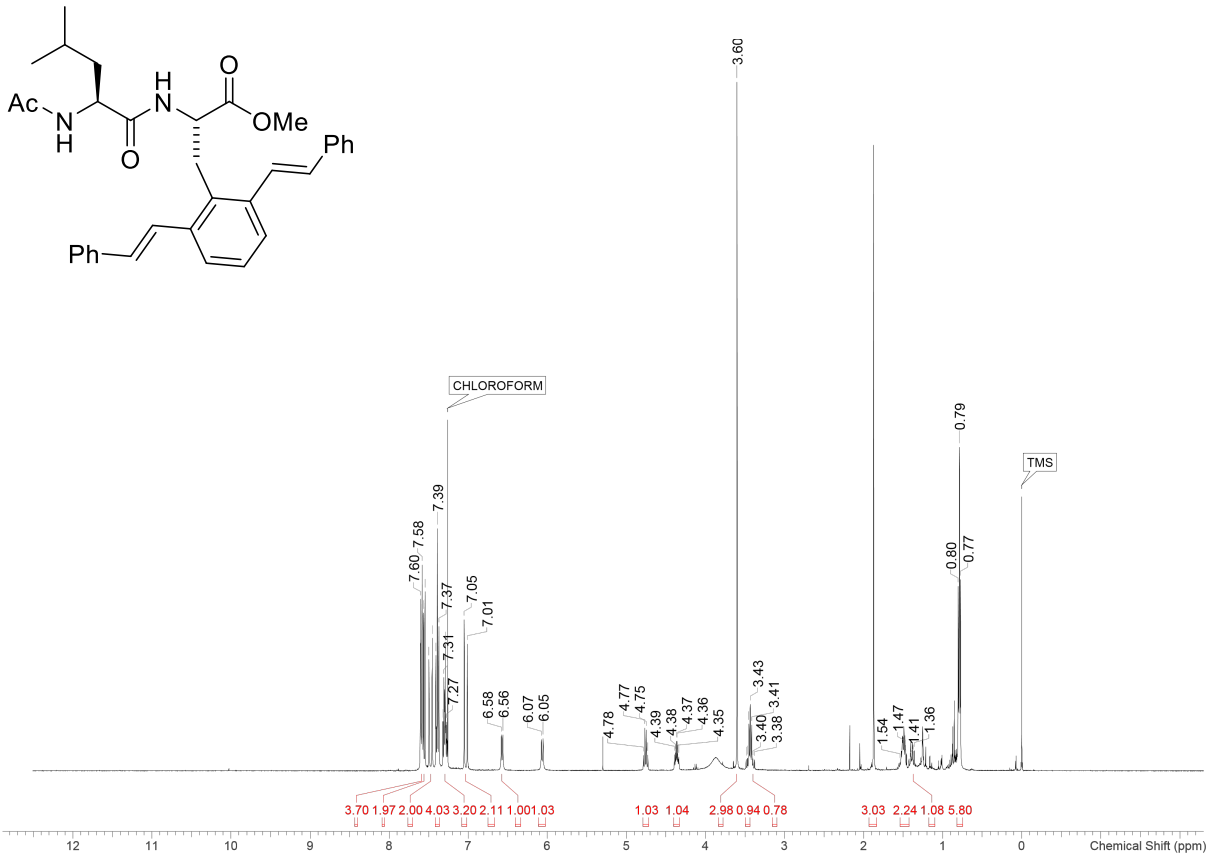
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (L,D)-**5a**



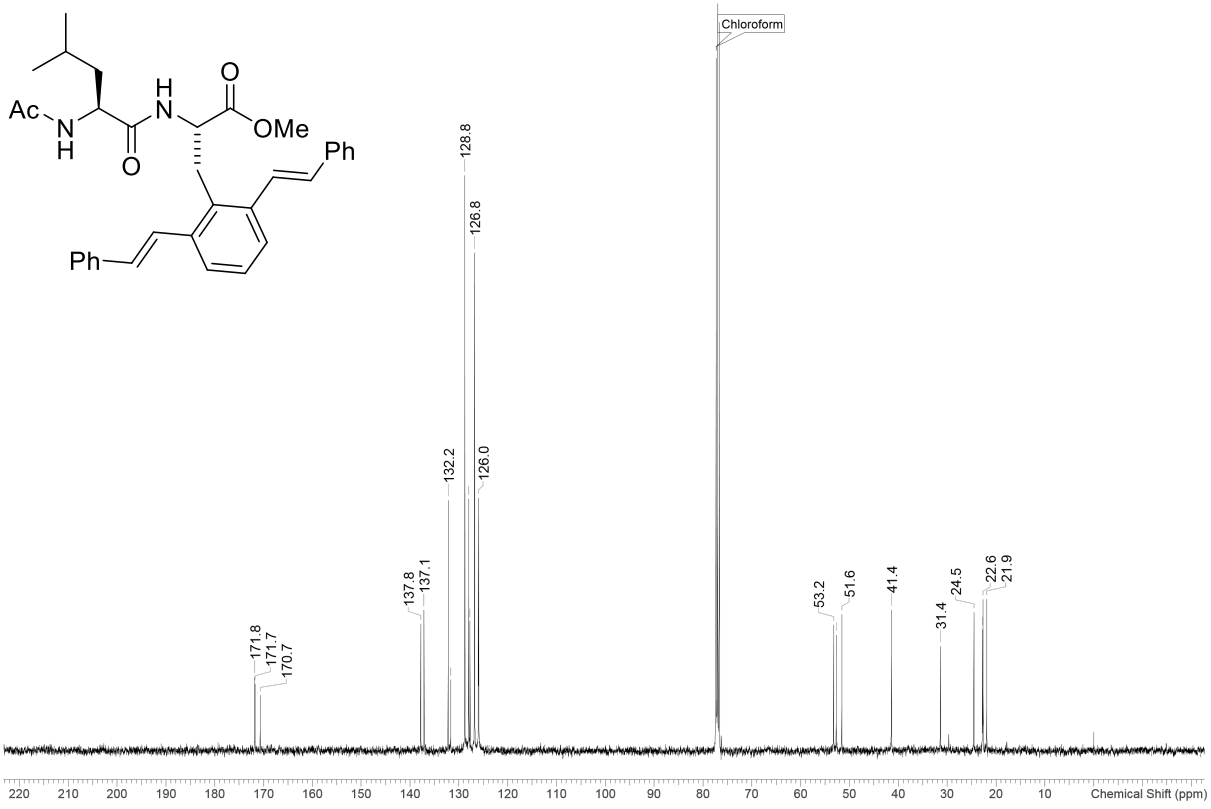
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (L,D)-**5a**



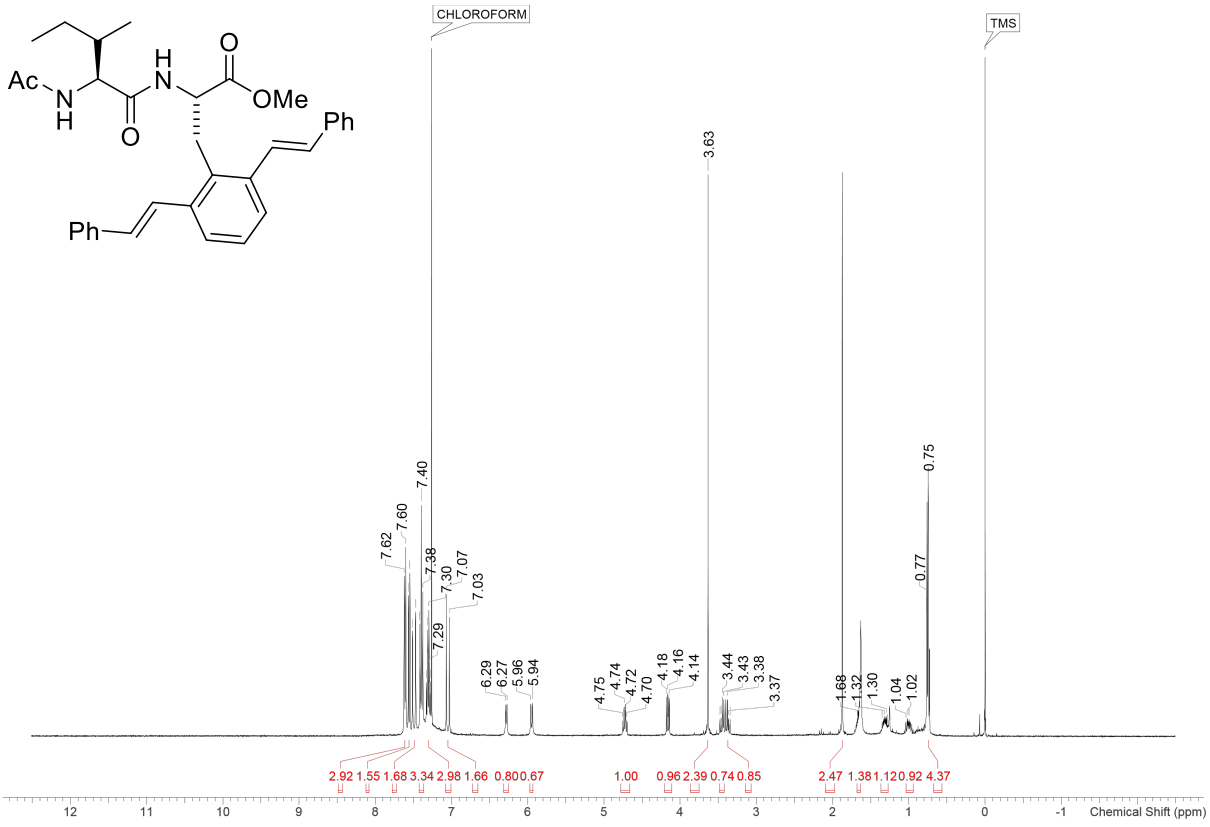
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5b**



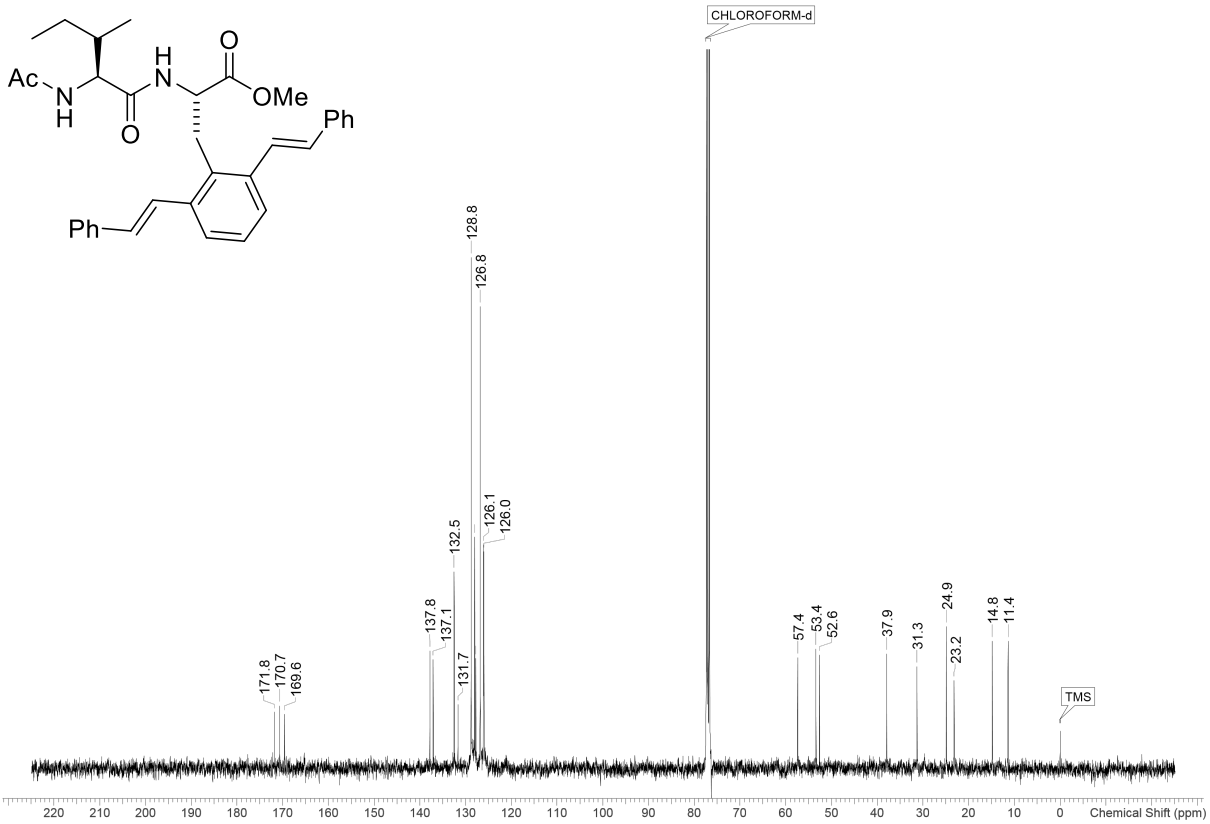
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5b**



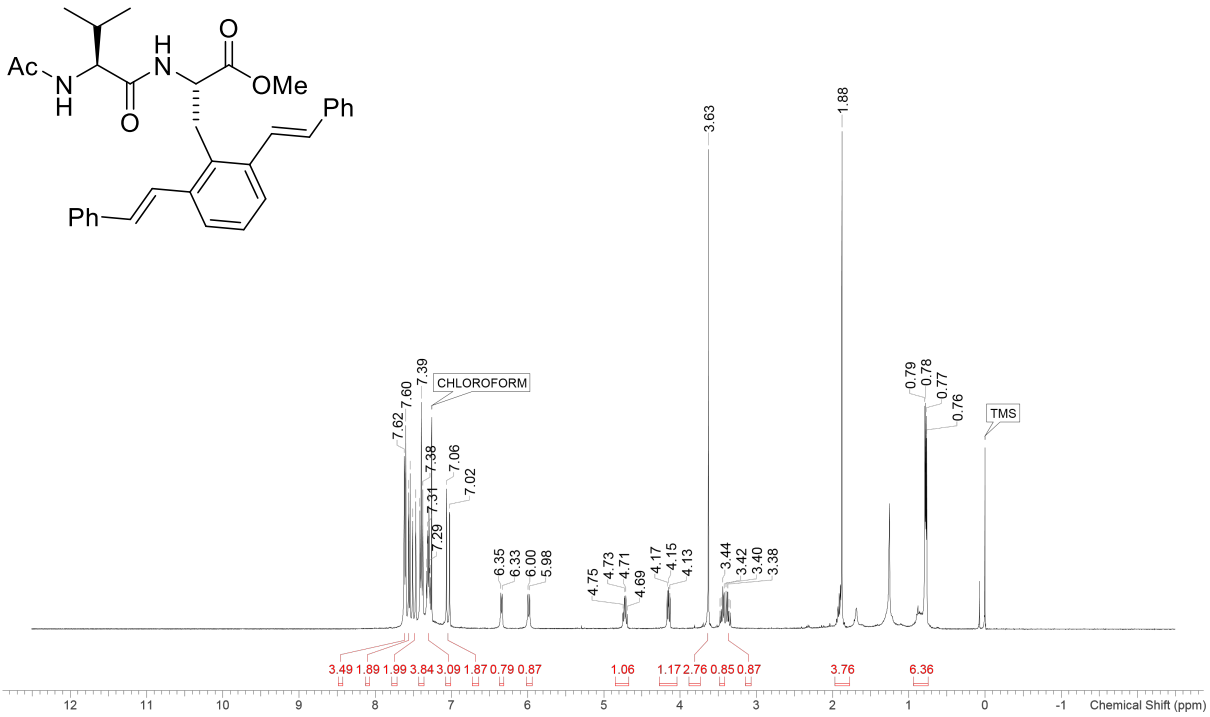
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5c**



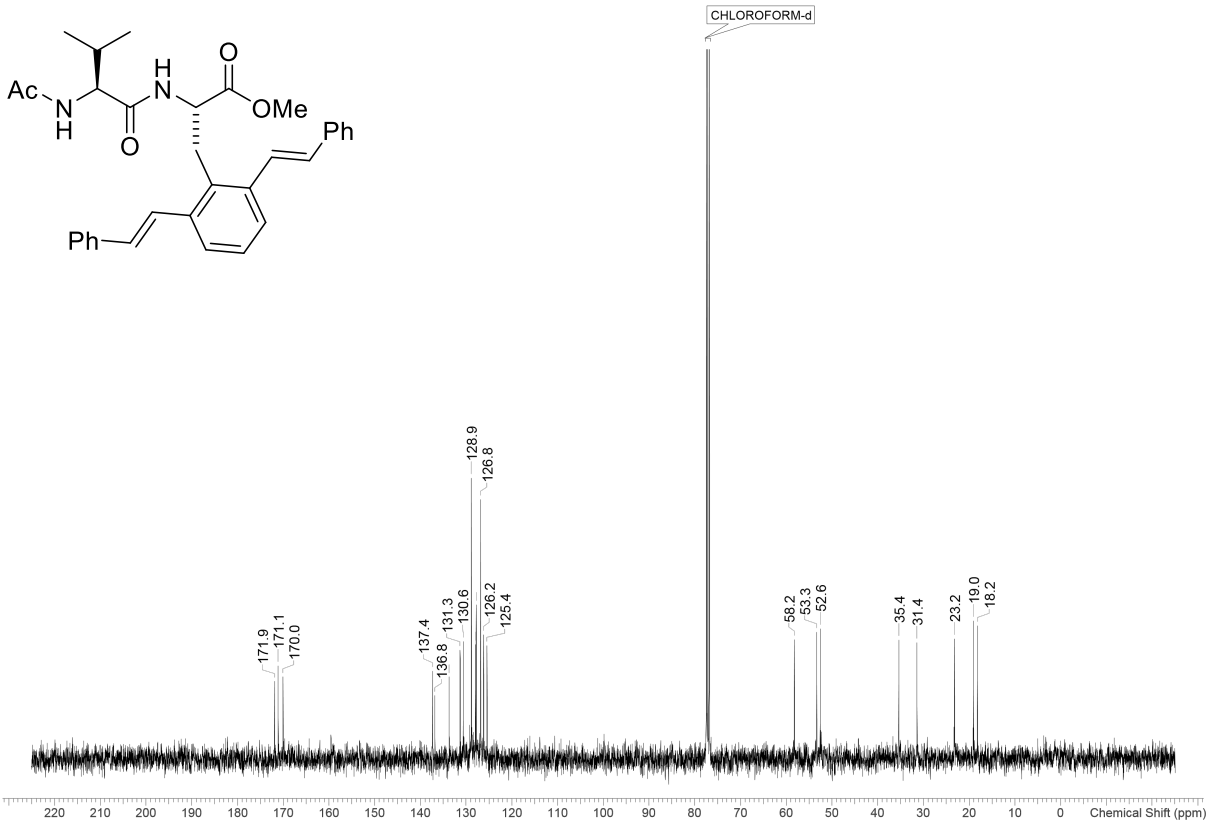
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5c**



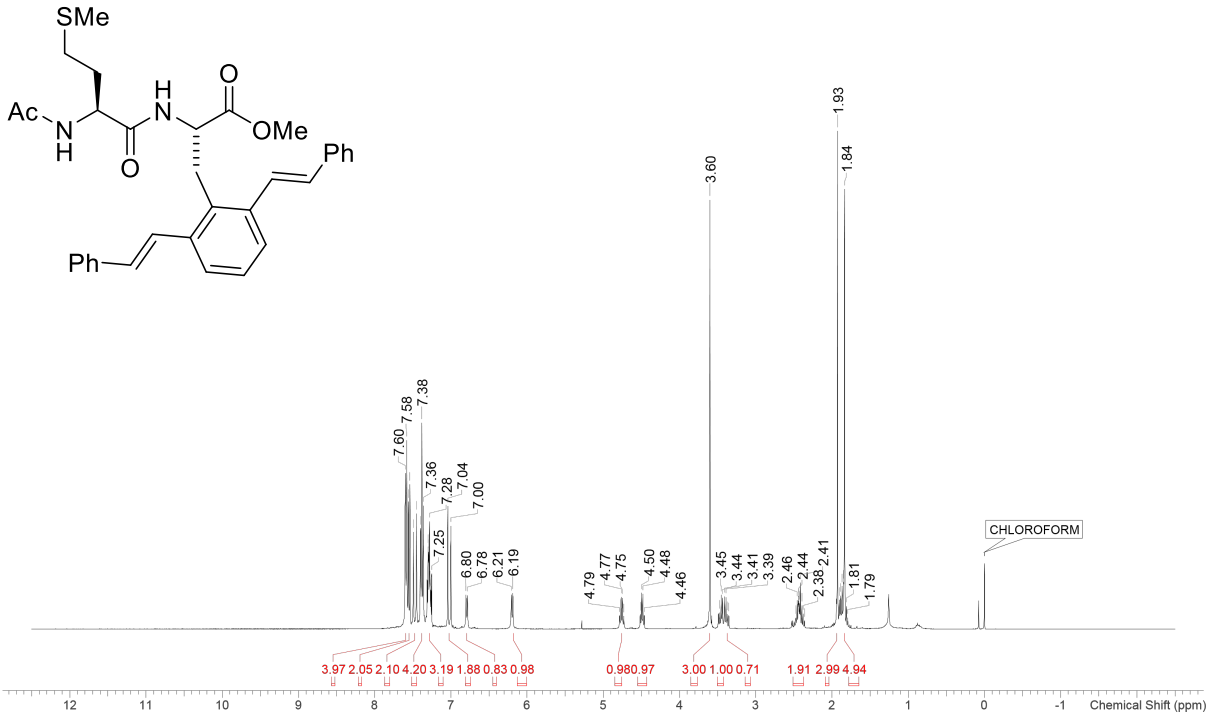
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5d**



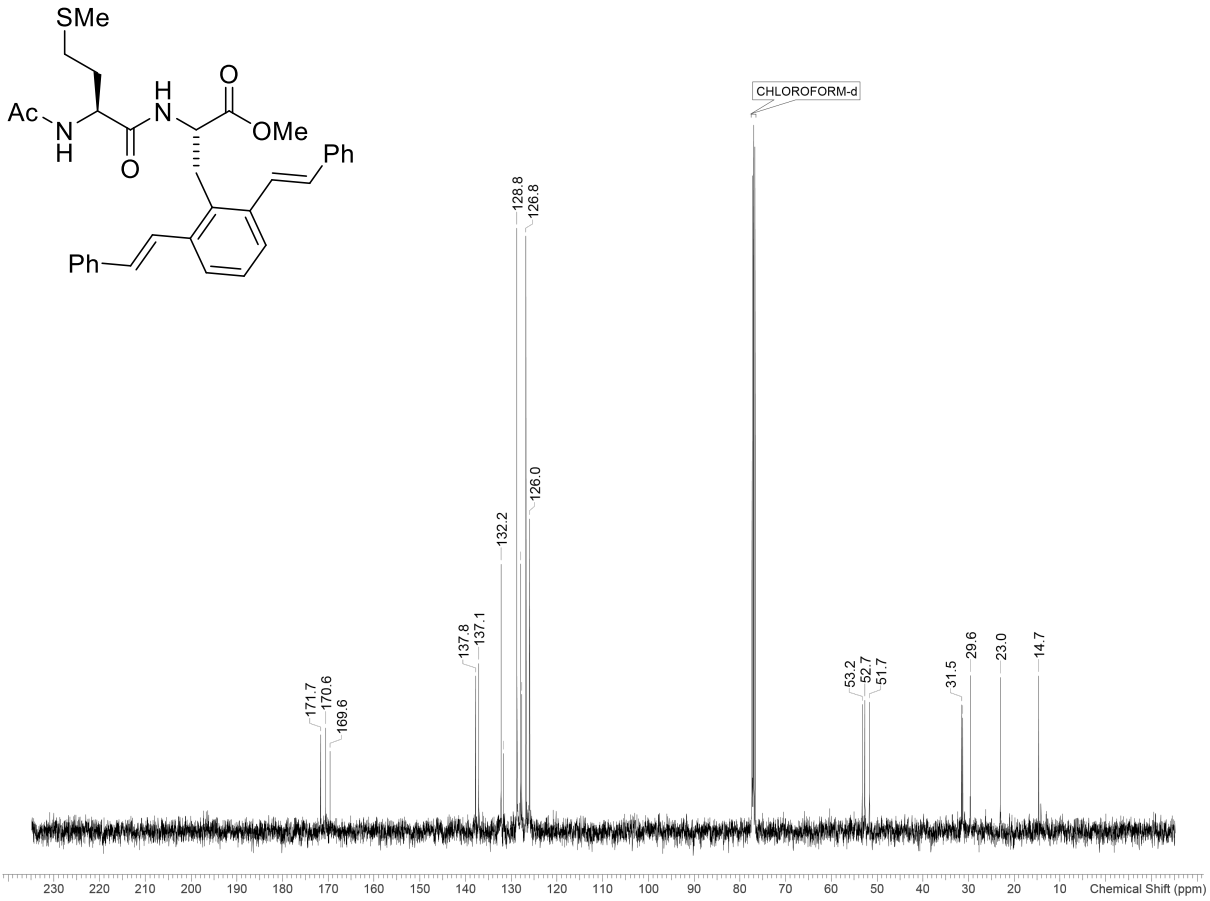
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5d**



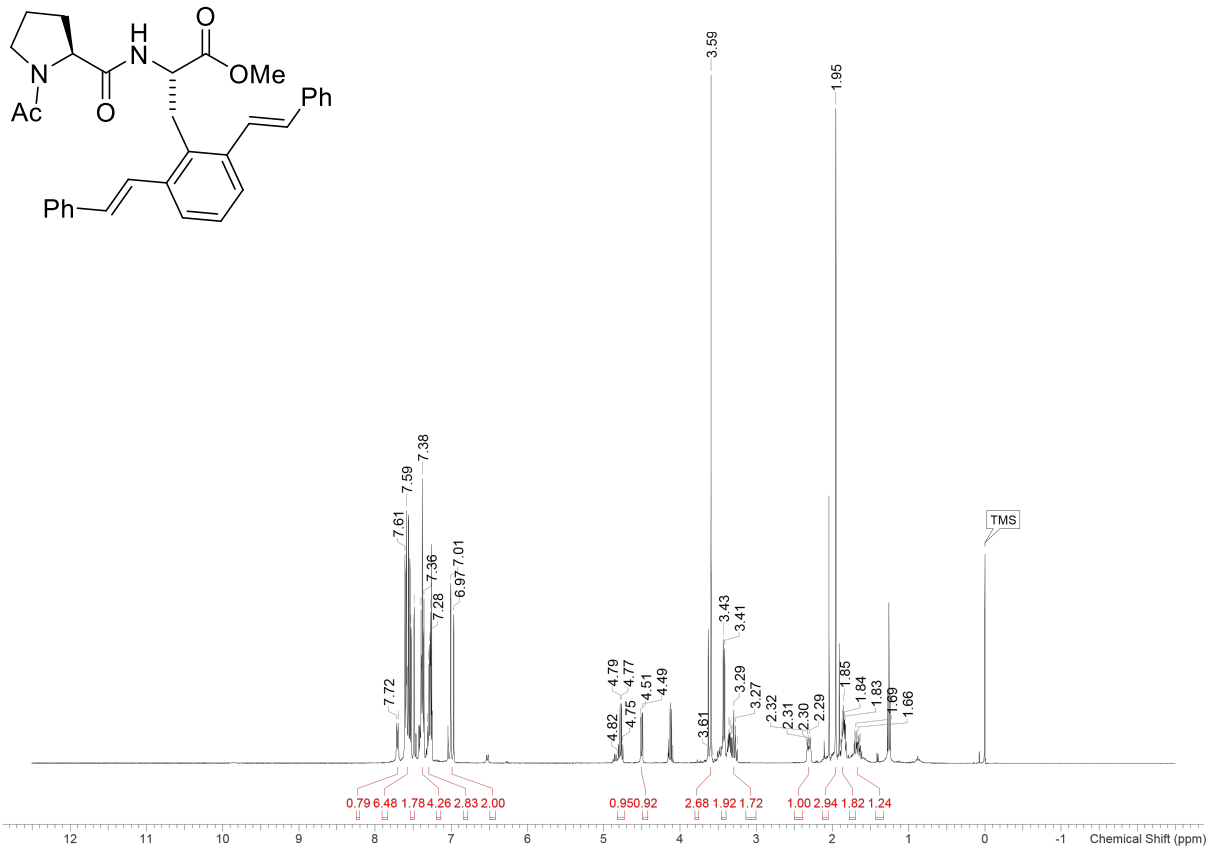
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5e**



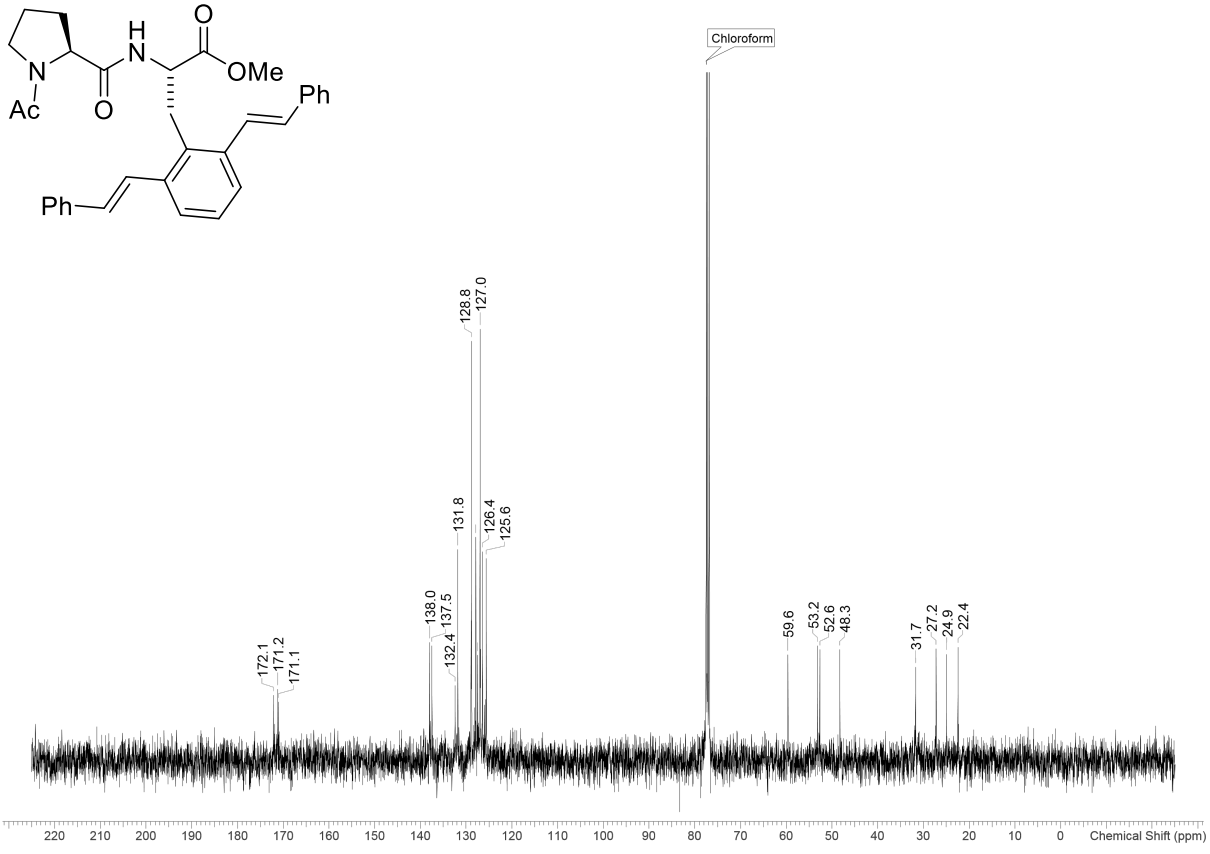
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5e**



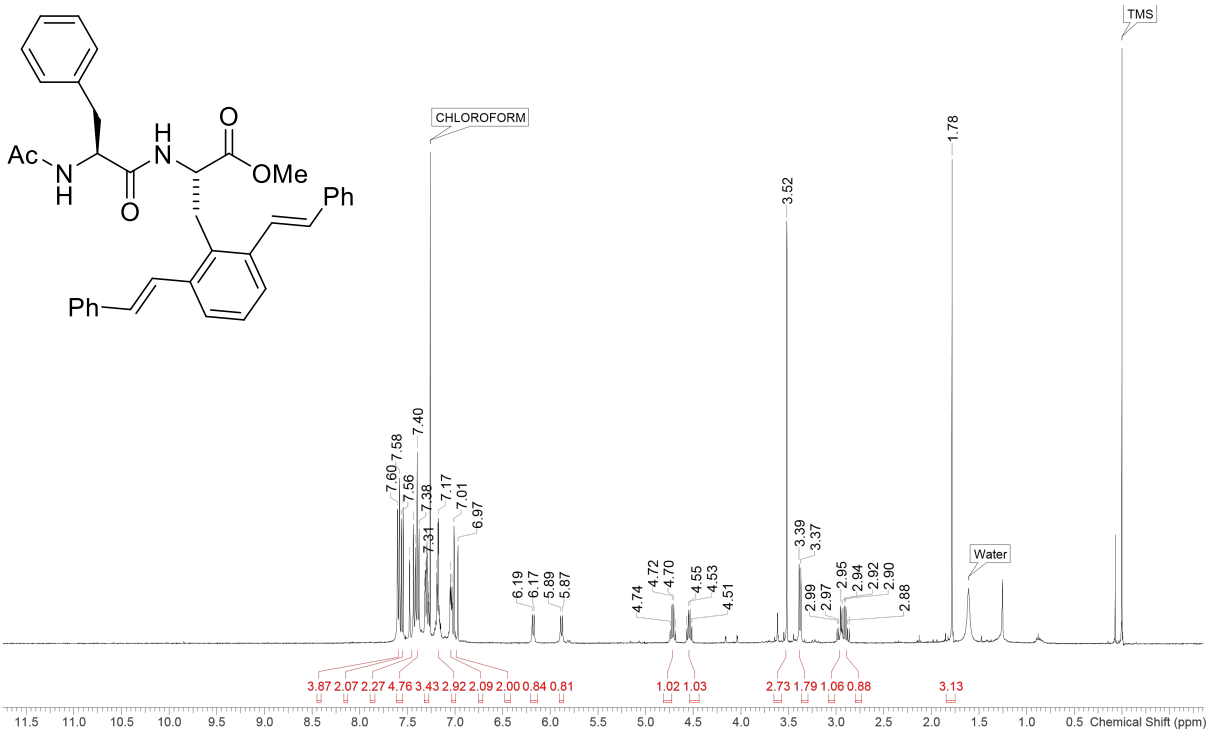
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5f**



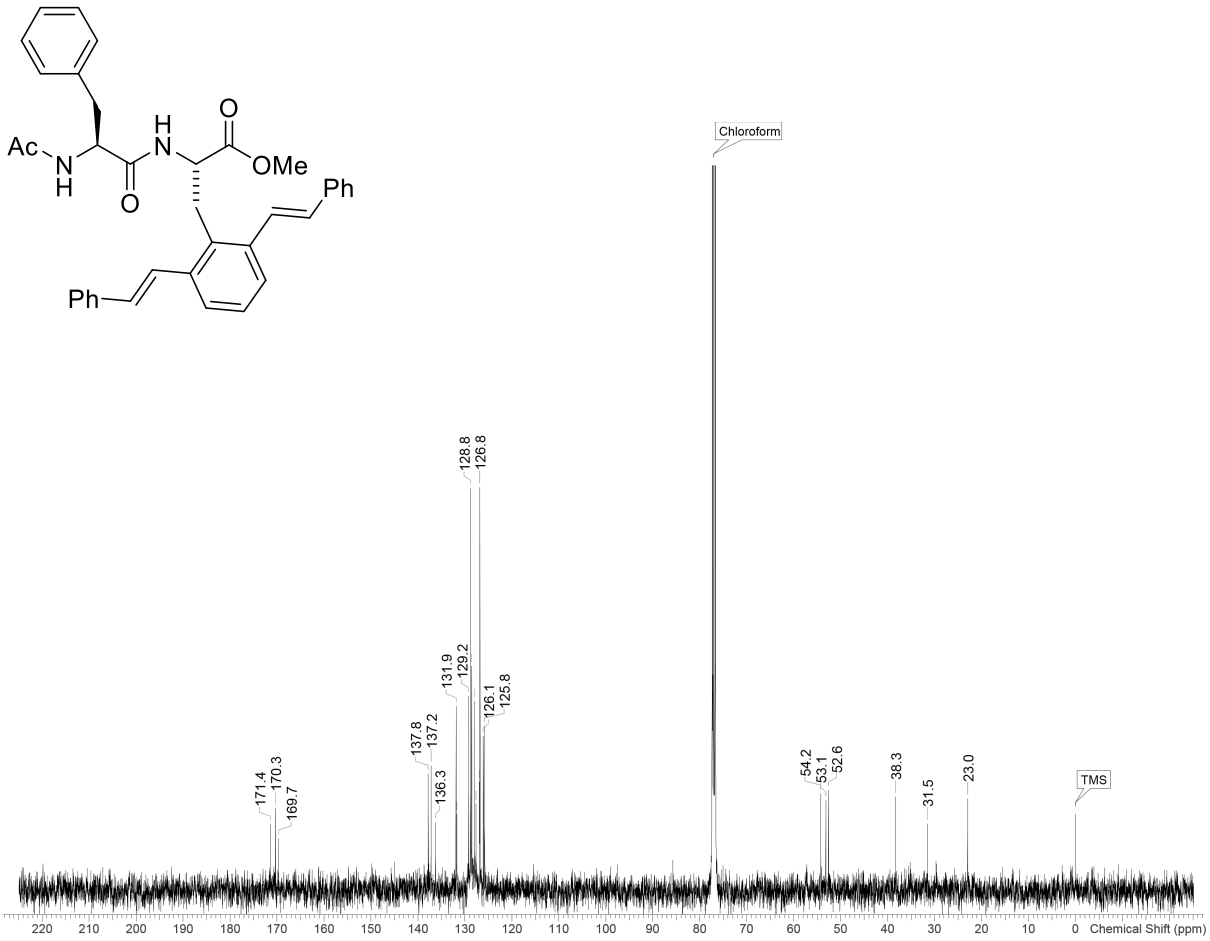
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5f**



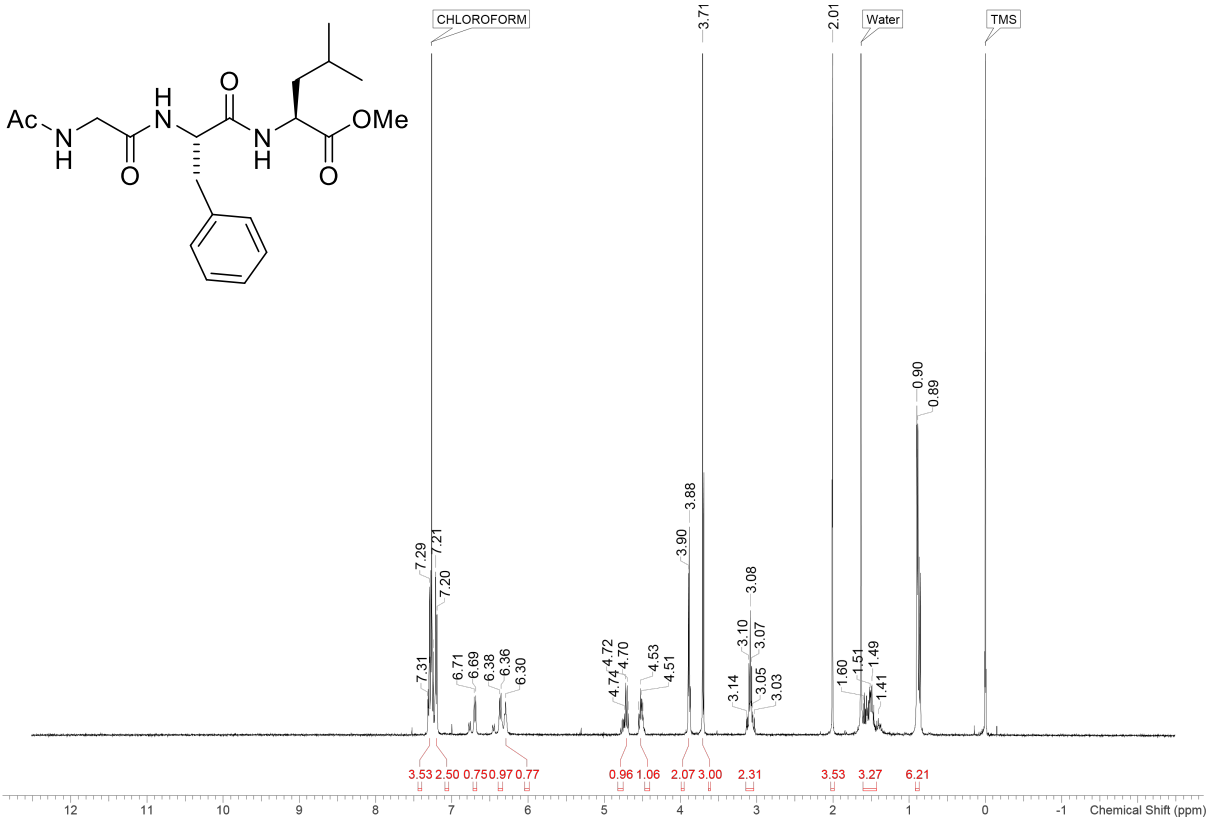
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5g**



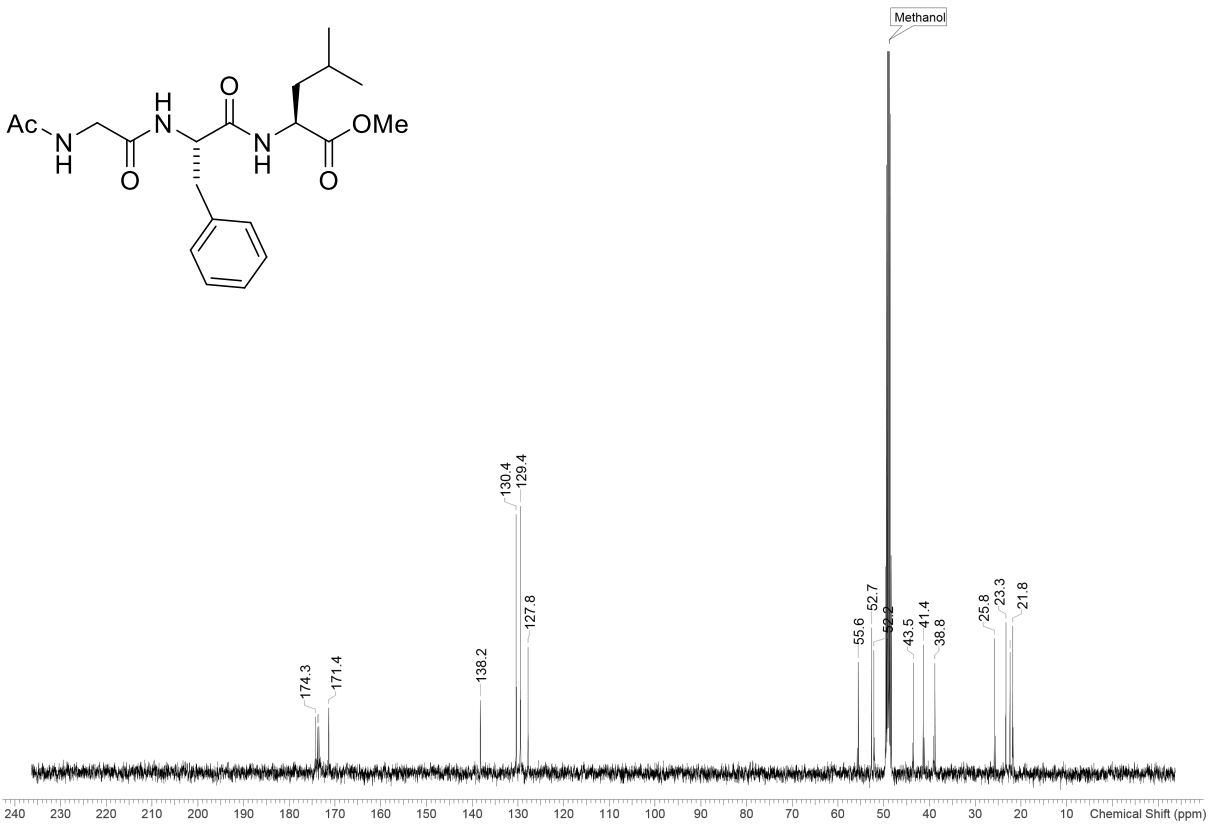
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **5g**



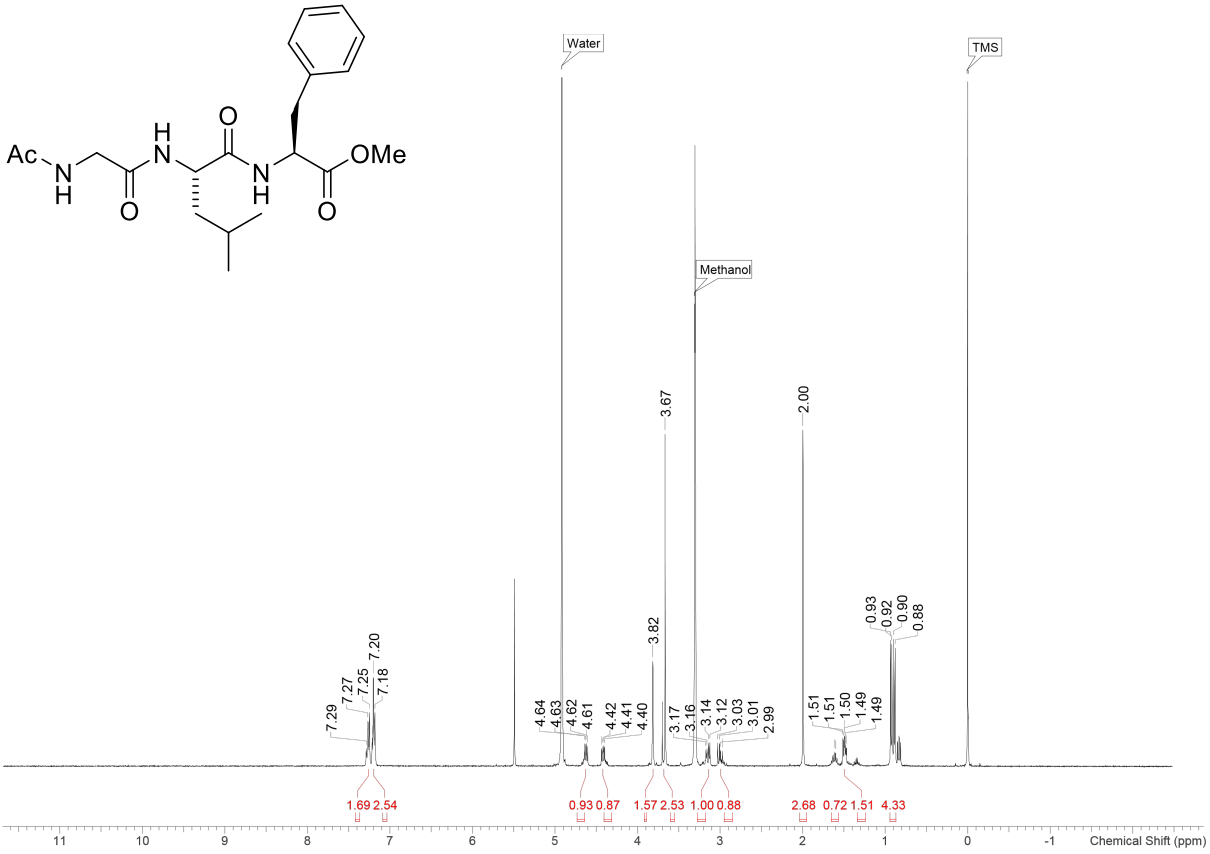
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6a**



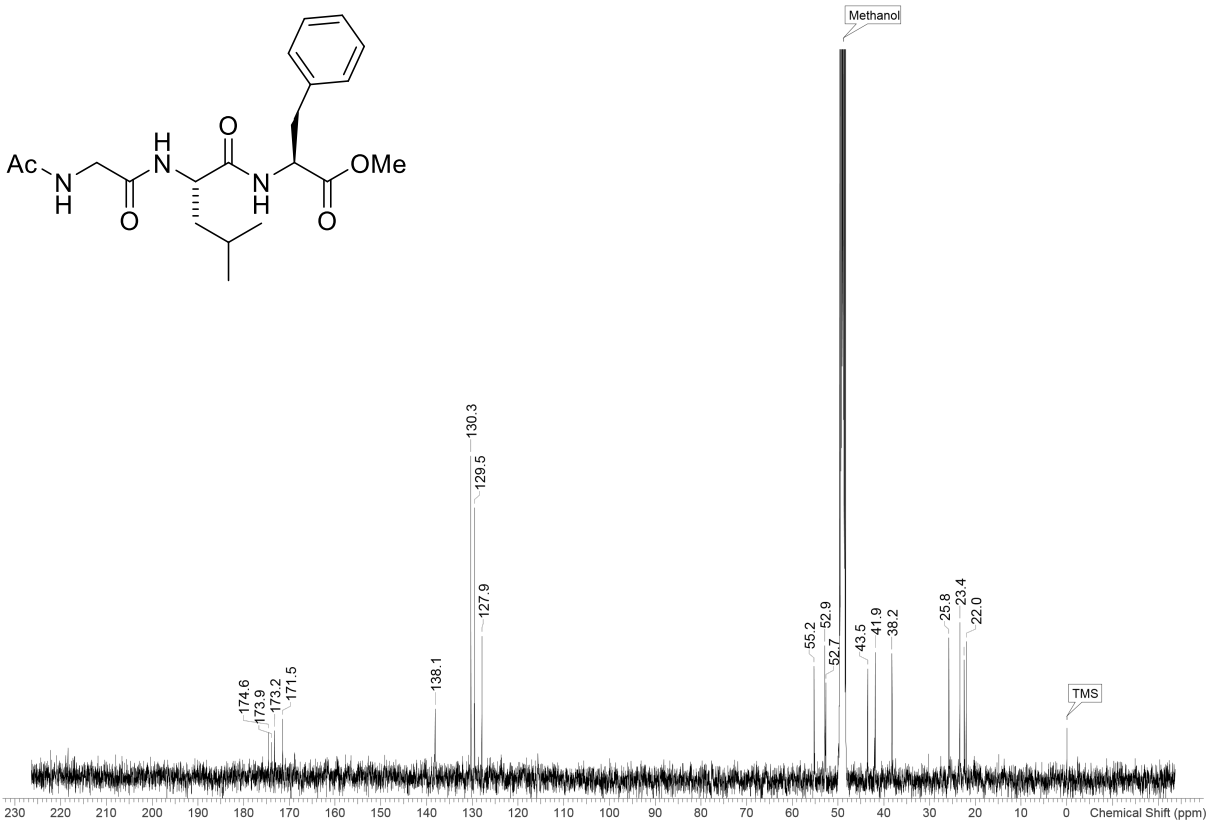
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **6a**



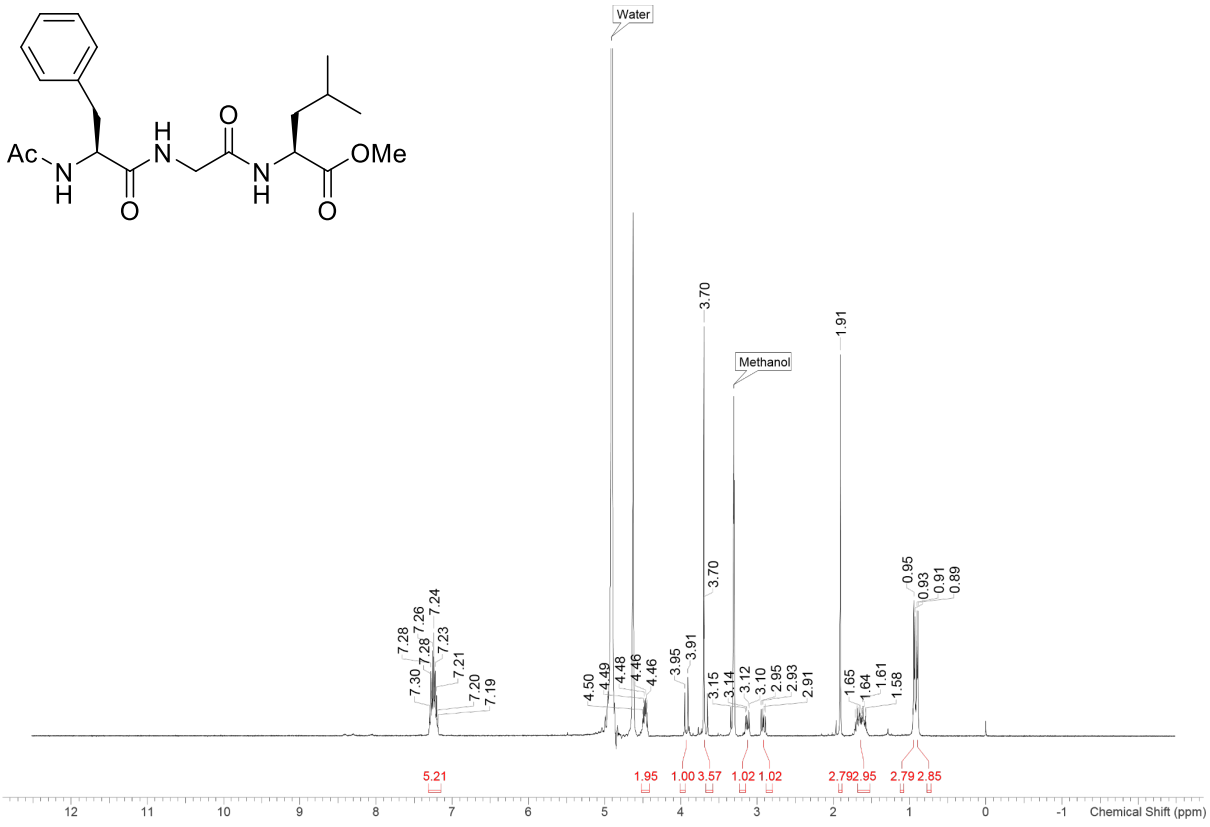
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6b**



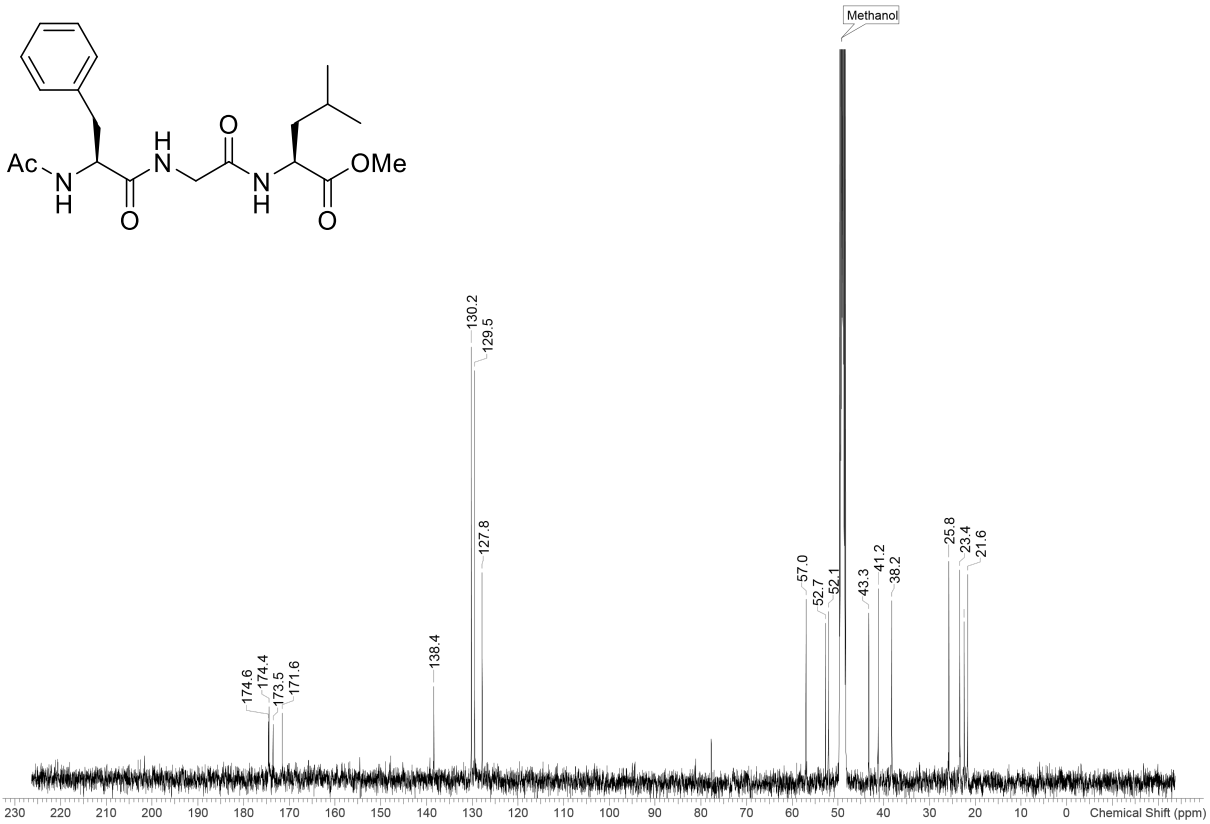
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **6b**



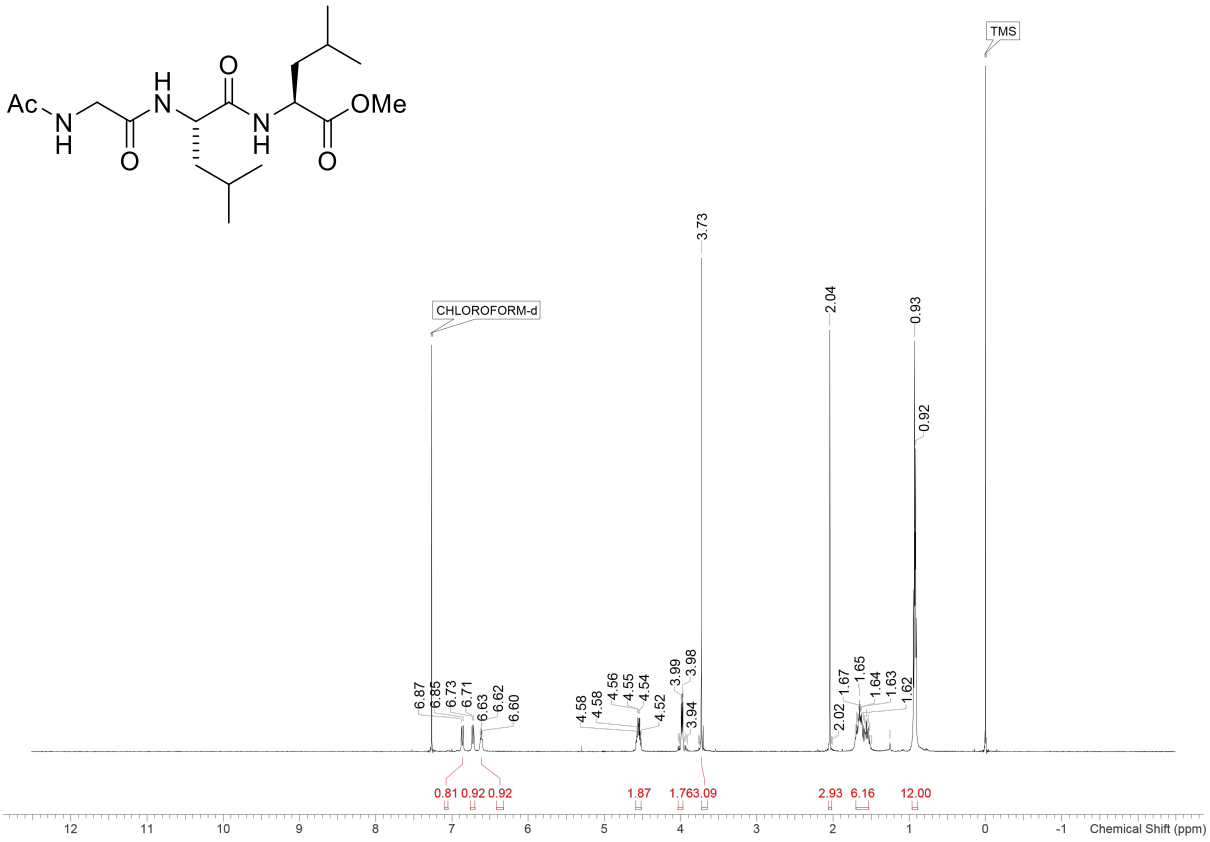
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6c**



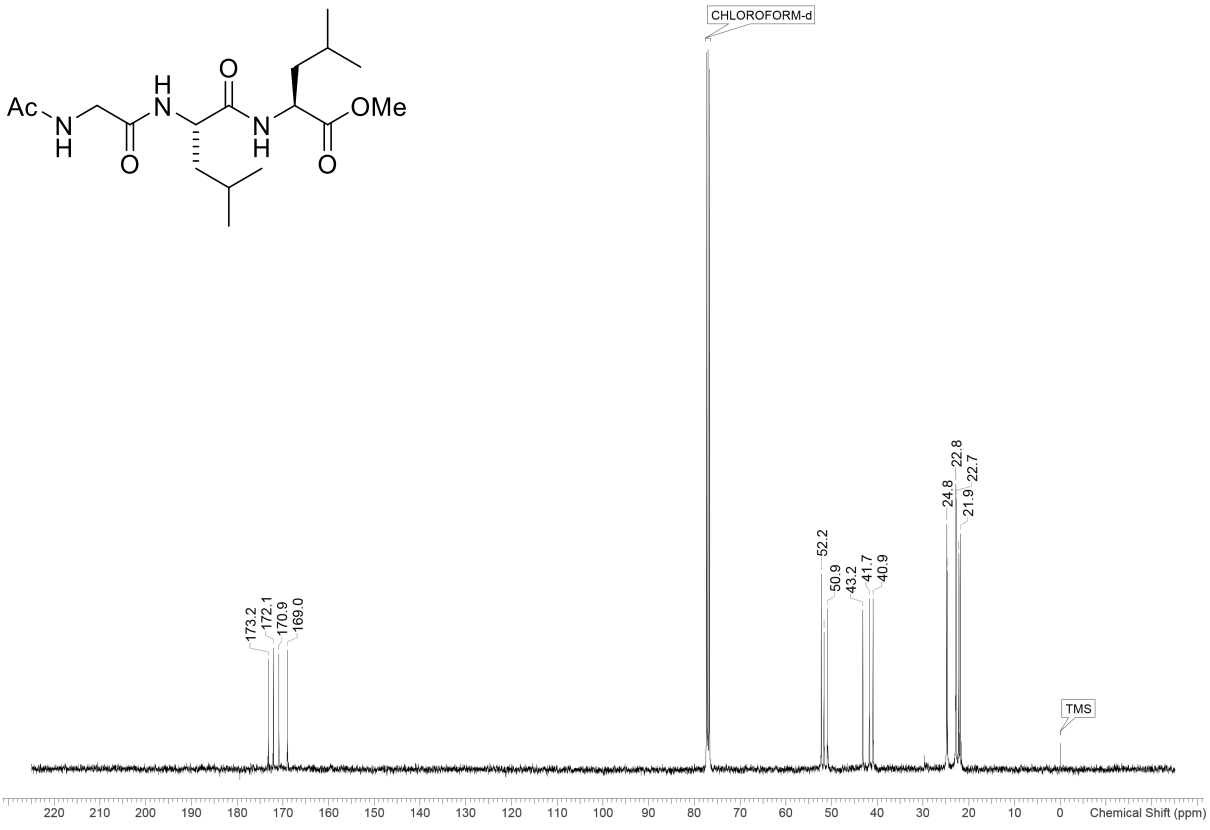
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **6c**



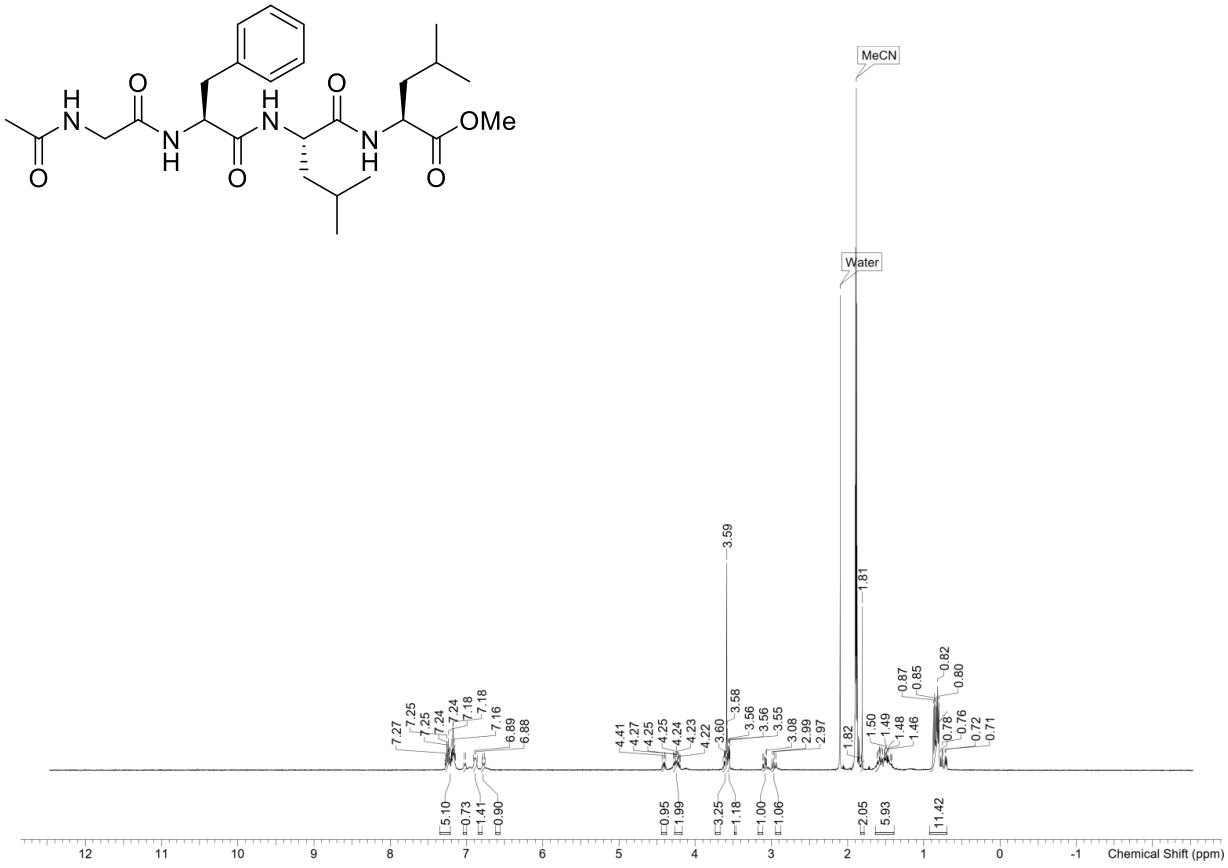
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6d**



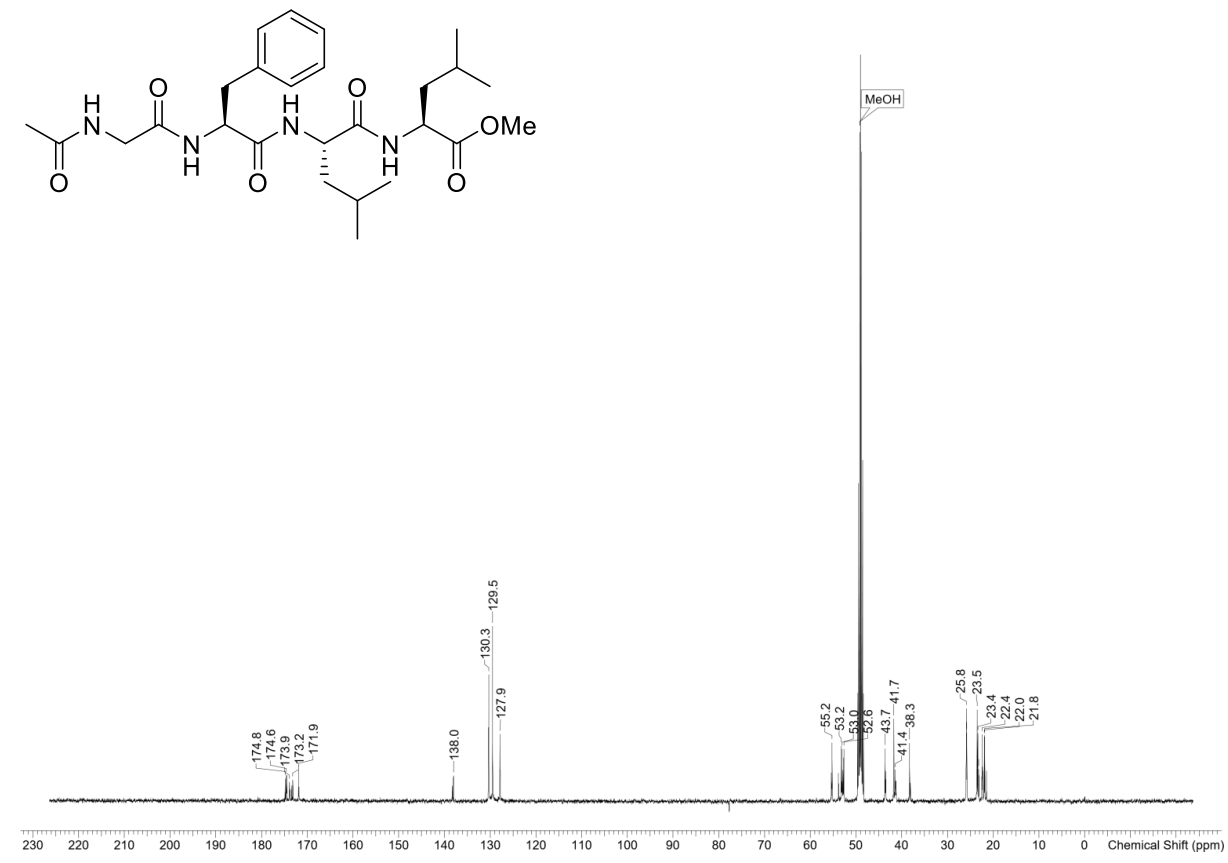
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **6d**



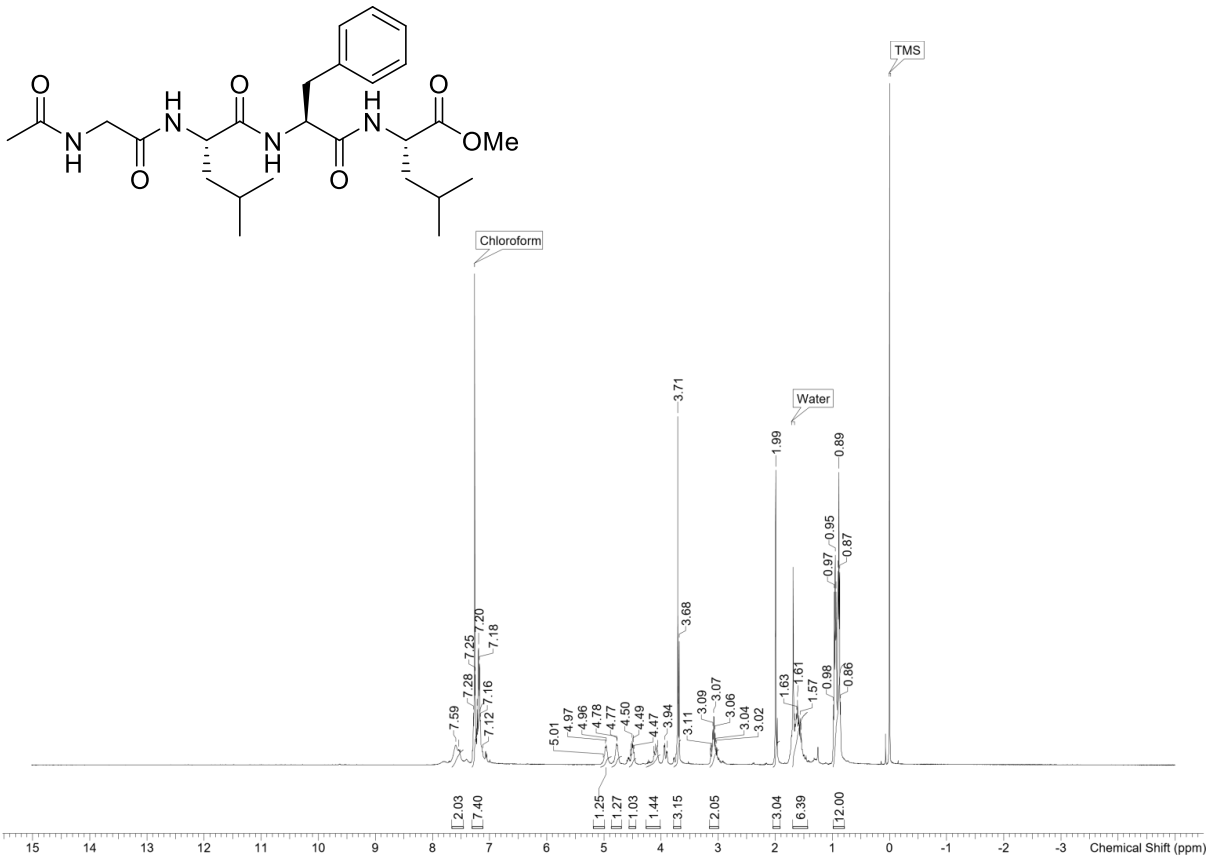
^{1}H NMR (400 MHz, CD_3CN) of **7a**



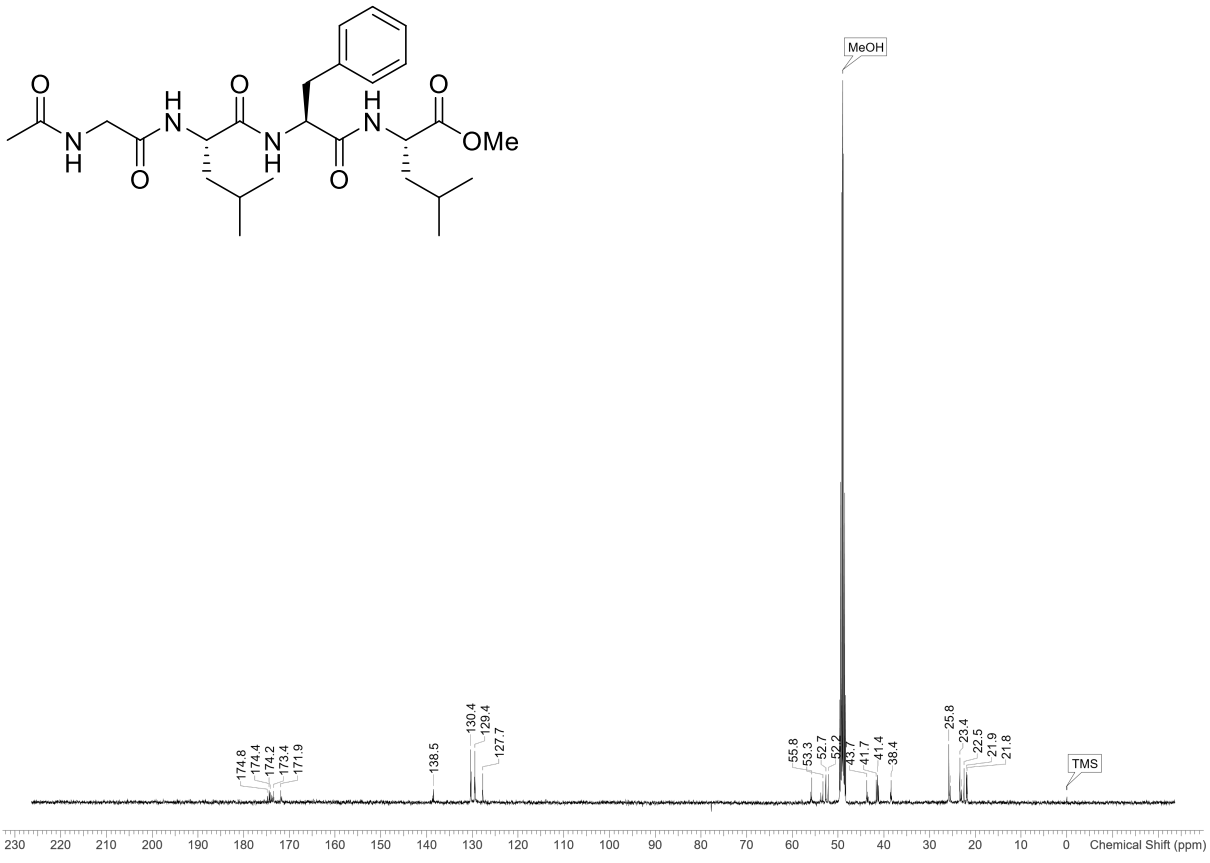
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **7a**



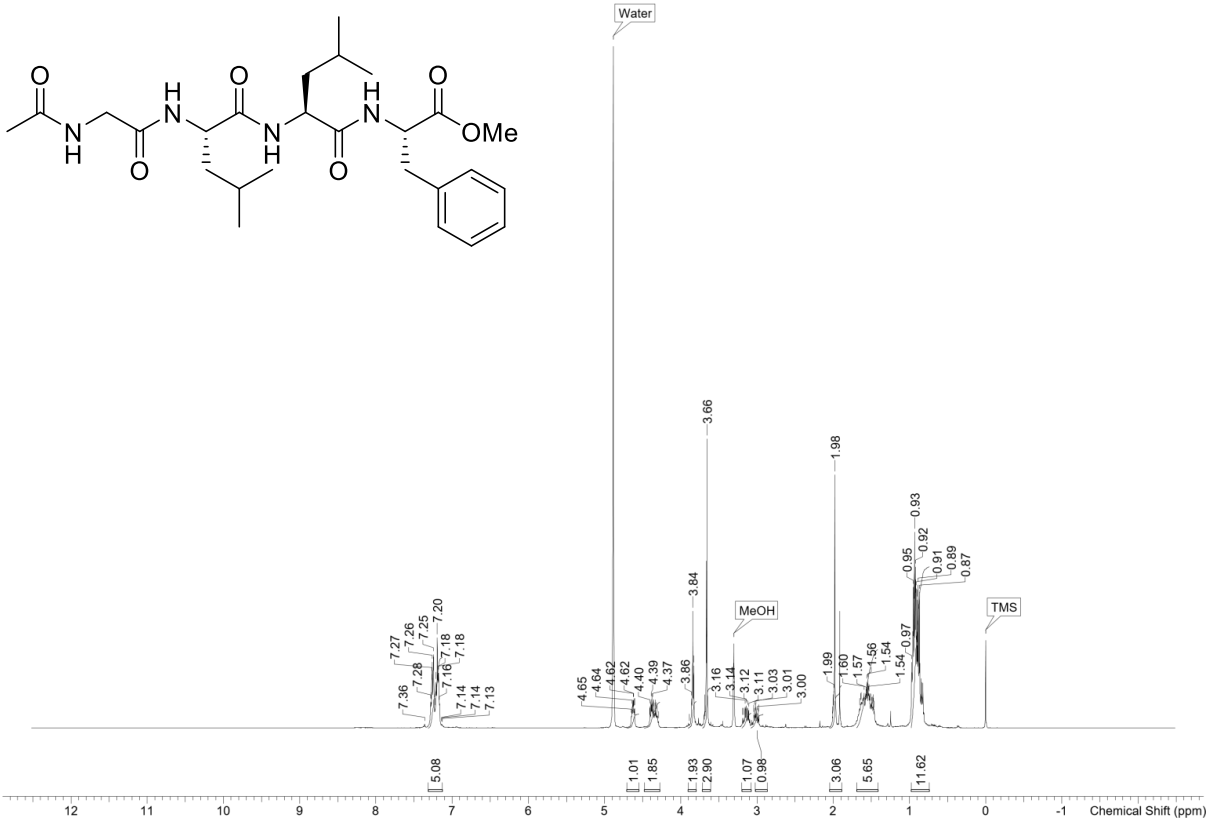
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7b**



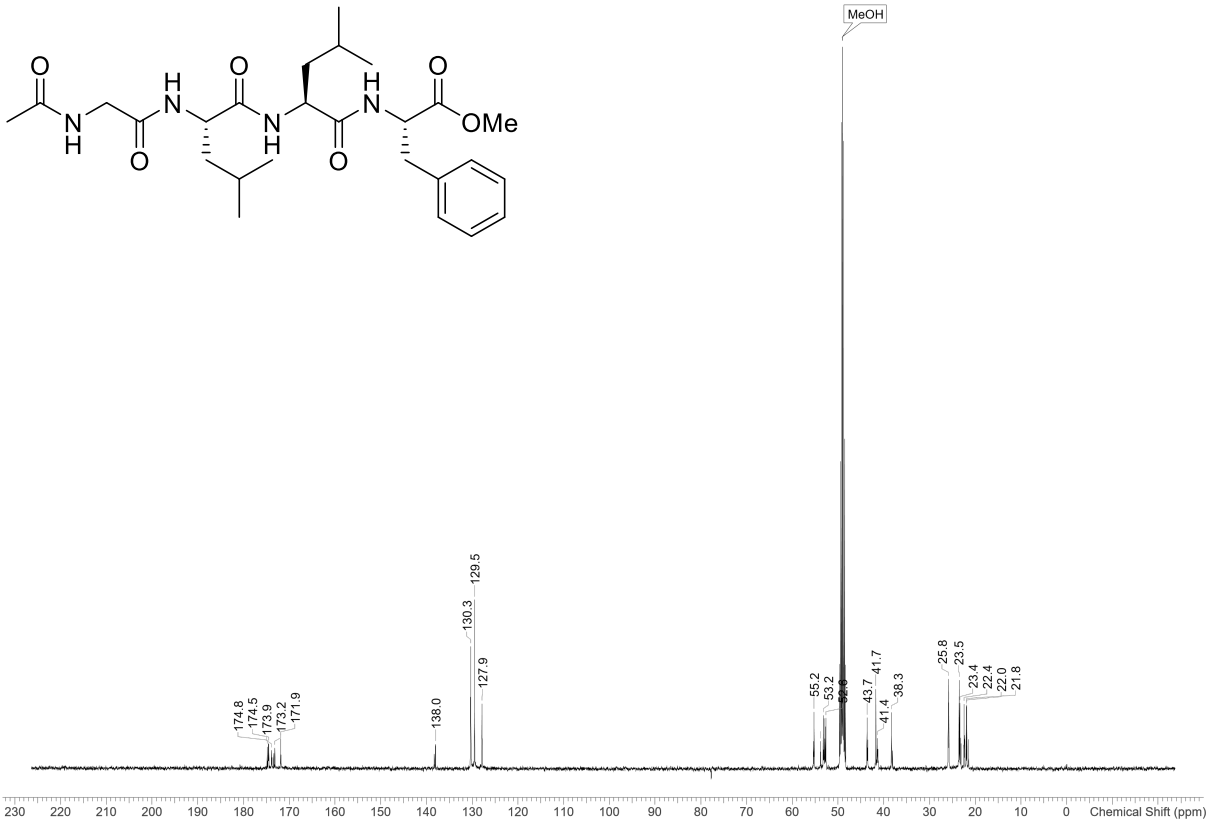
^{13}C{^{1}H} NMR spectrum (100 MHz, CD_3OD) of **7b**



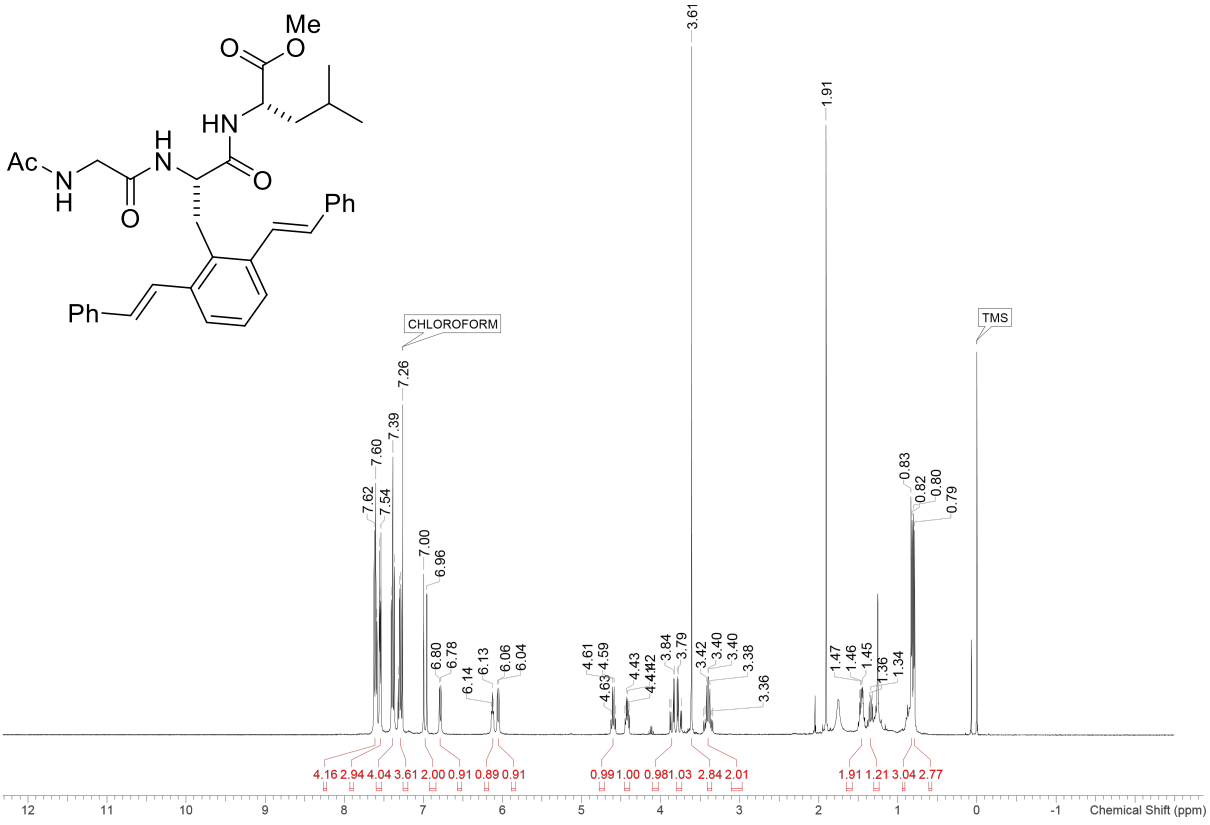
^{1}H NMR (400 MHz, CD_3OD) of **7c**



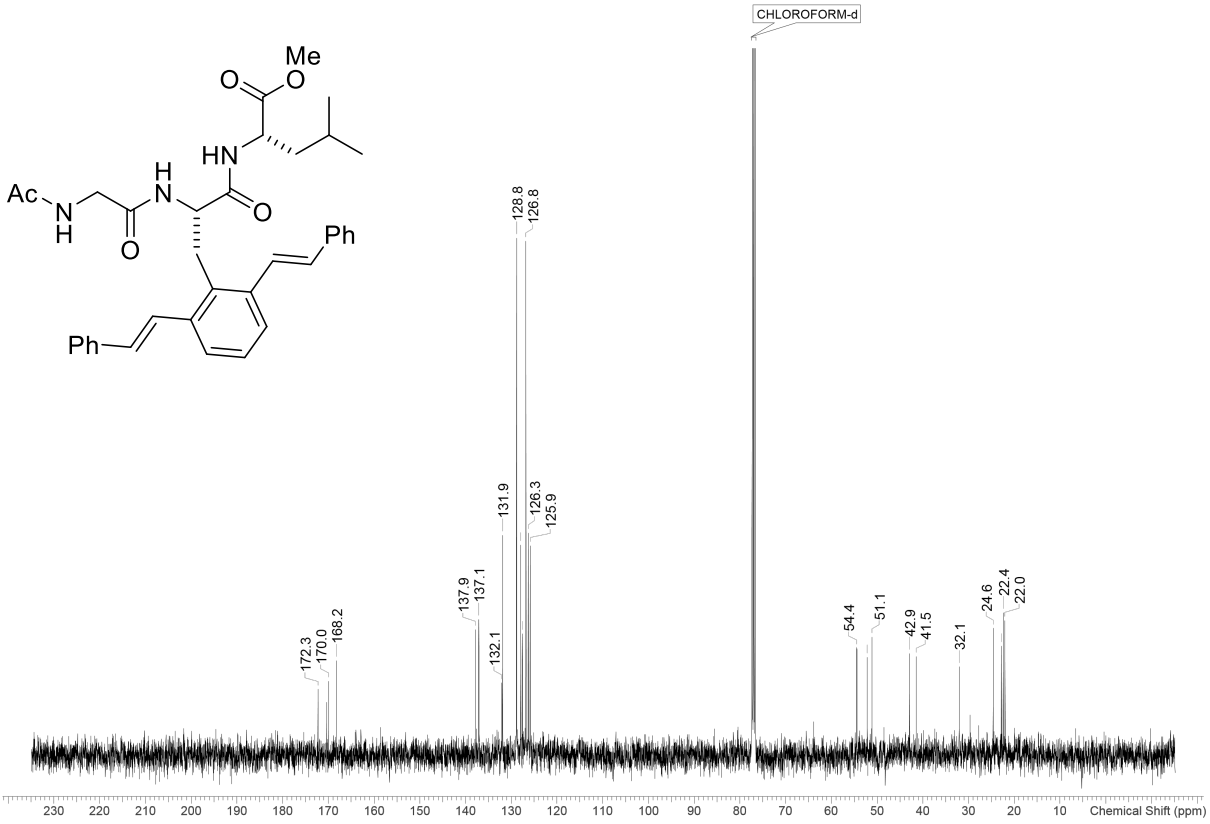
$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) of **7c**



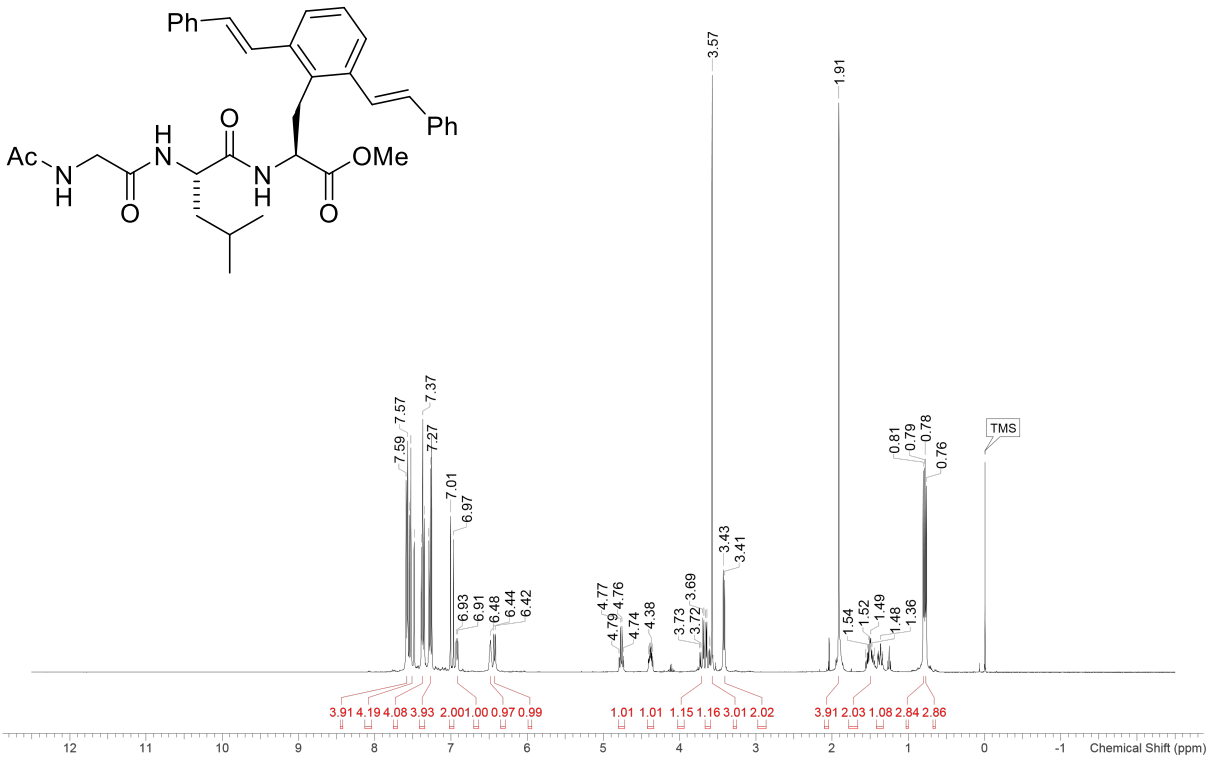
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8a**



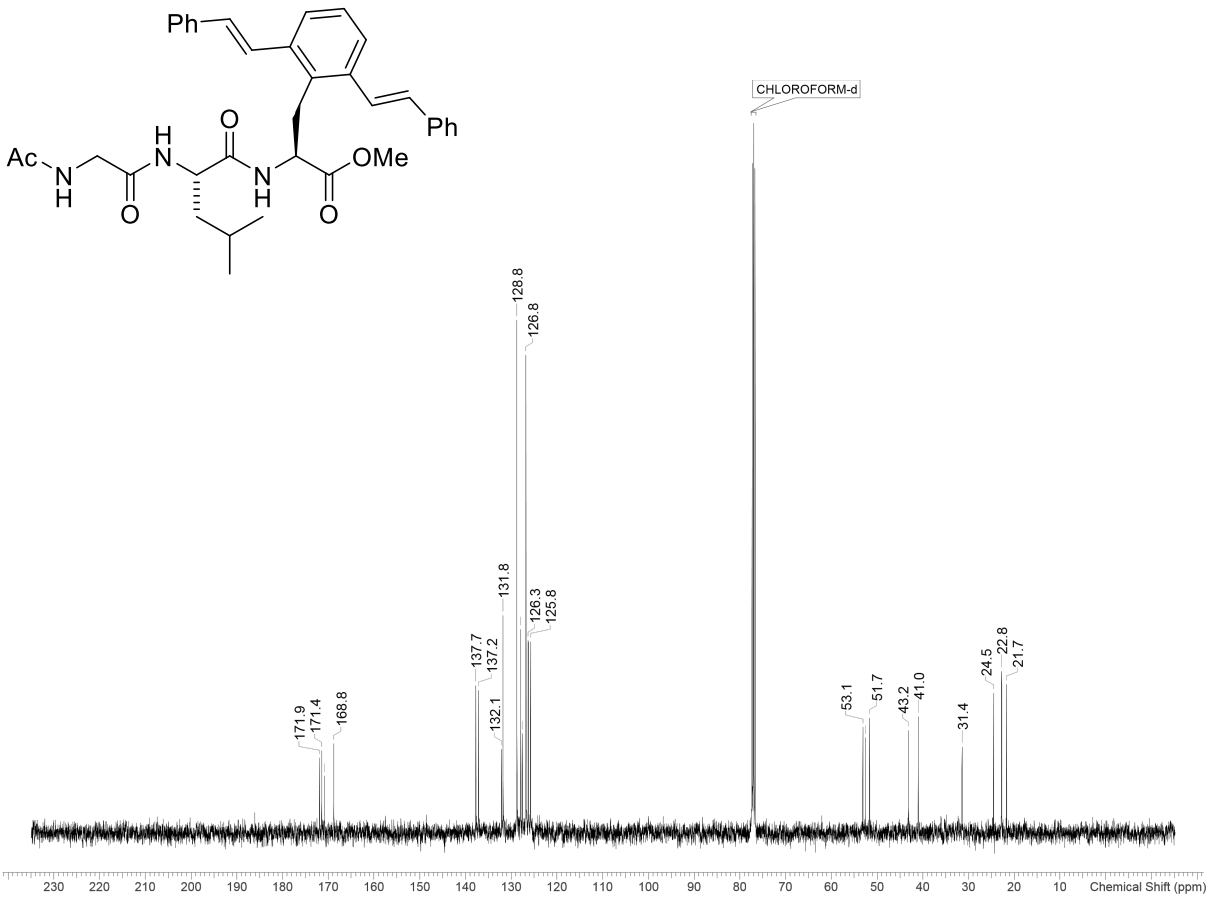
^{13}C{^{1}H} NMR spectrum (400 MHz, $CDCl_3$) of **8a**



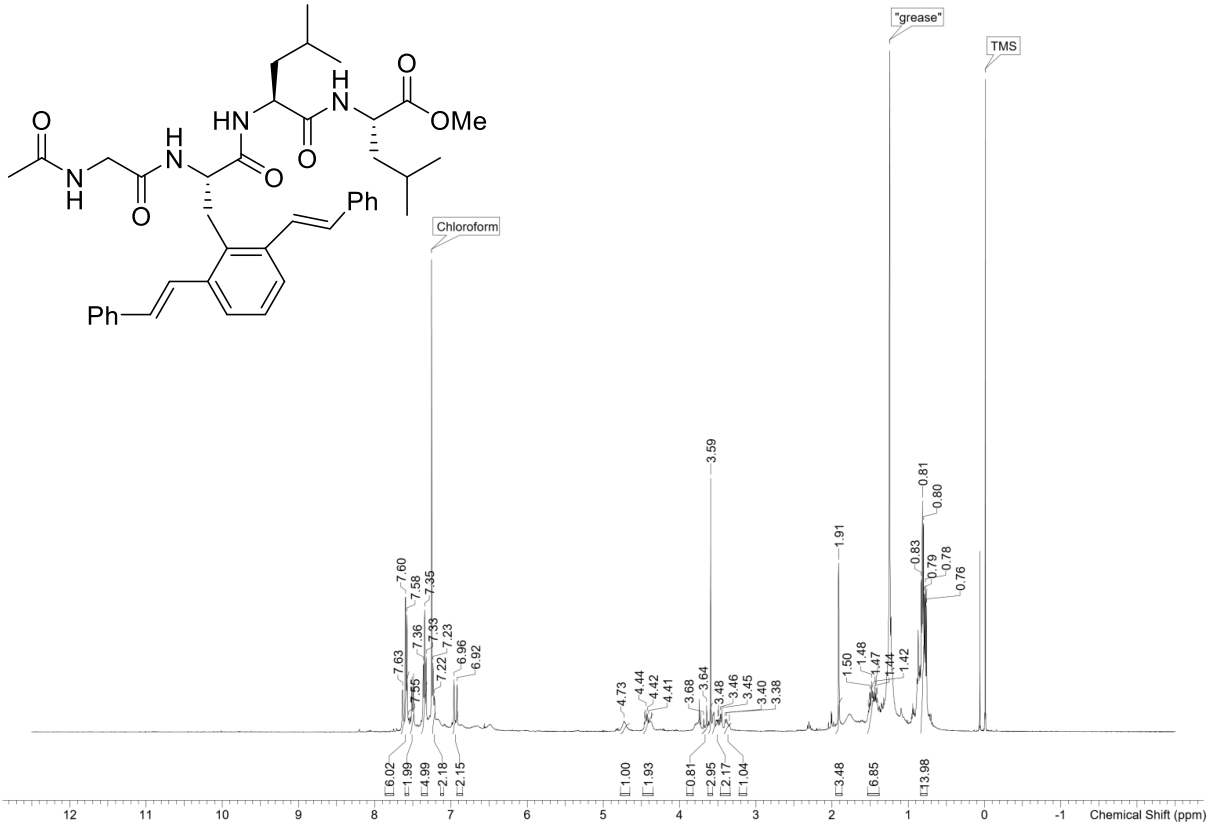
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8b**



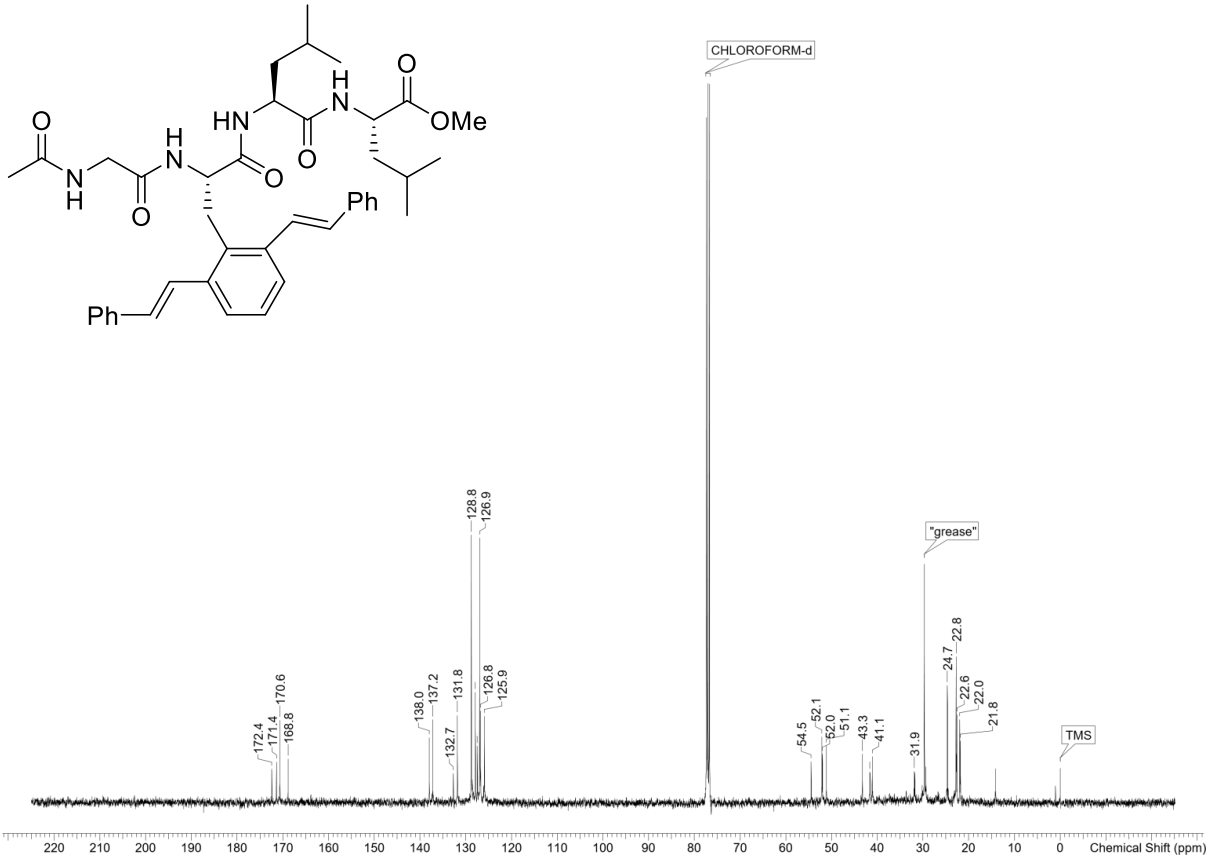
^{13}C{^{1}H} NMR spectrum (100 MHz, $CDCl_3$) of **8b**



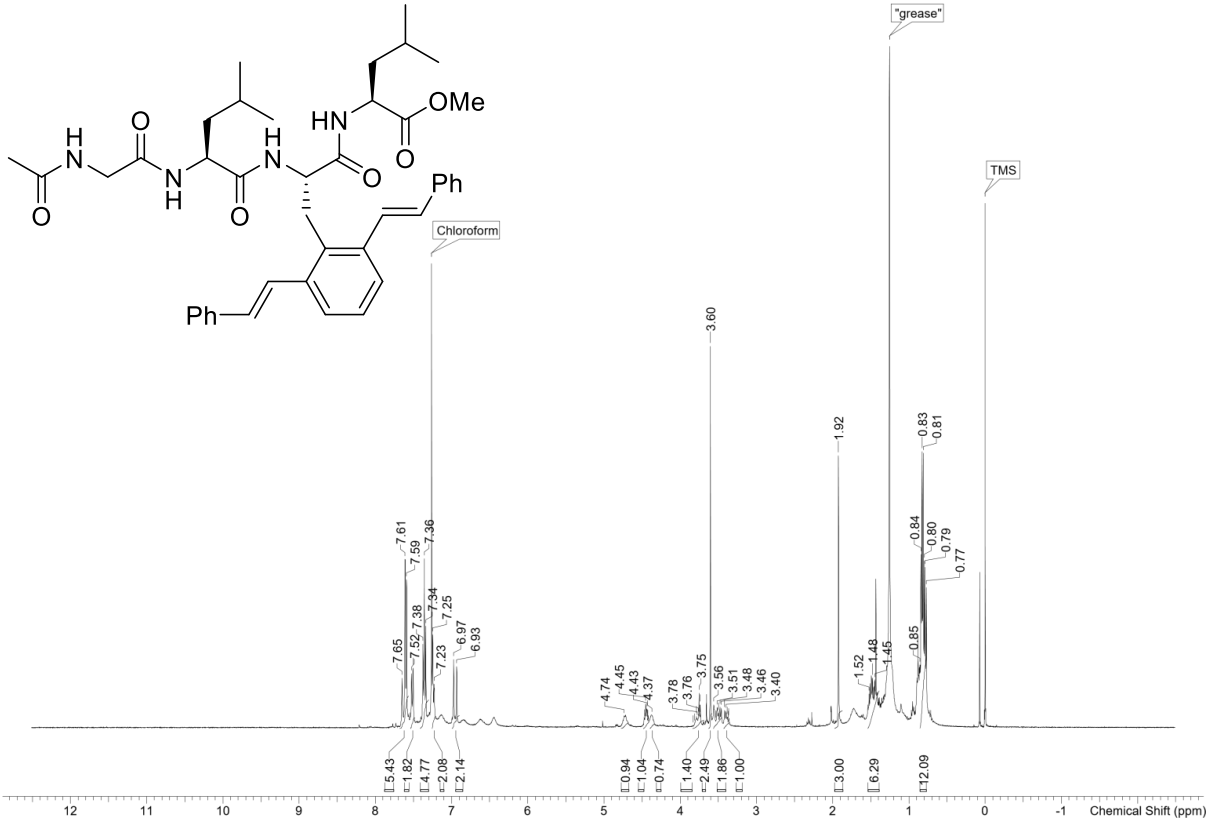
^{1}H NMR (400 MHz, $CDCl_3$) of **9a**



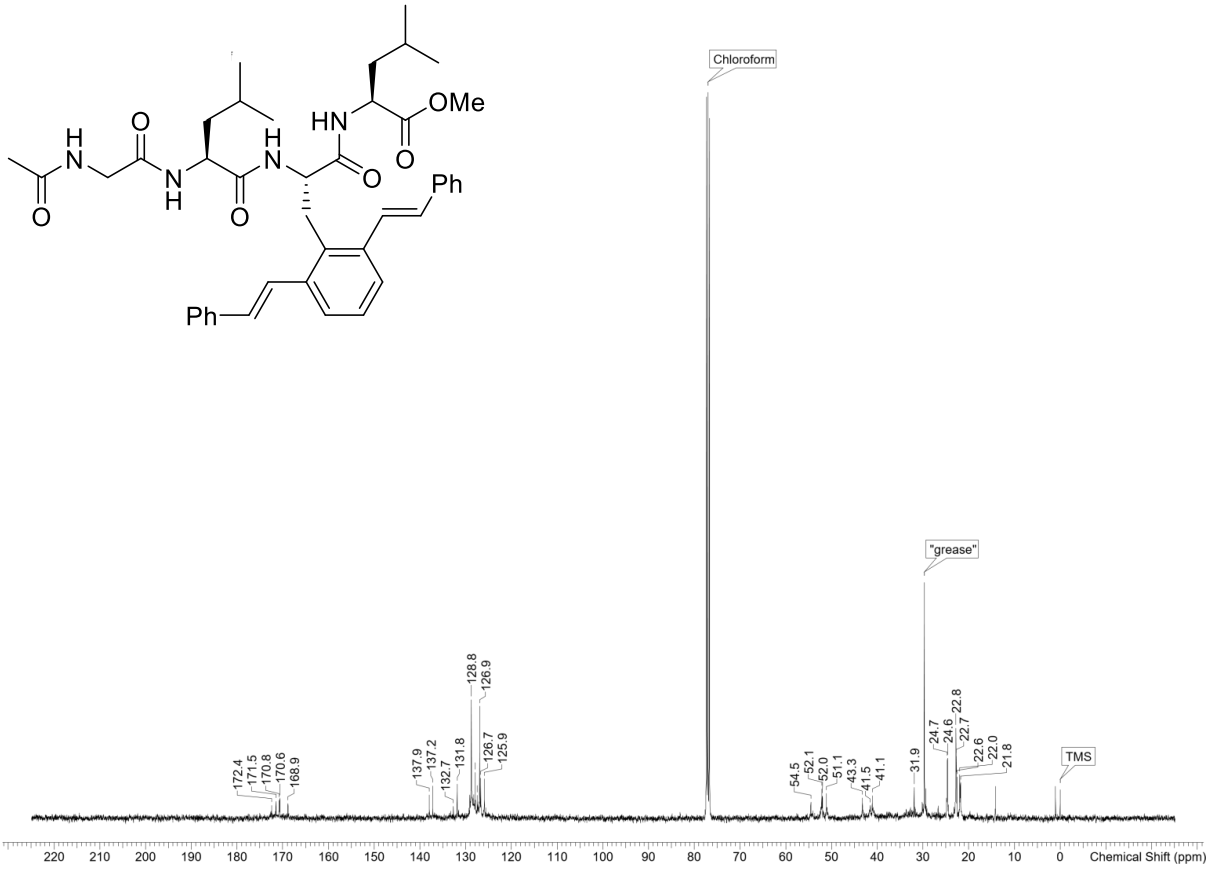
$^{13}C\{^{1}H\}$ NMR spectrum (100 MHz, $CDCl_3$) of **9a**



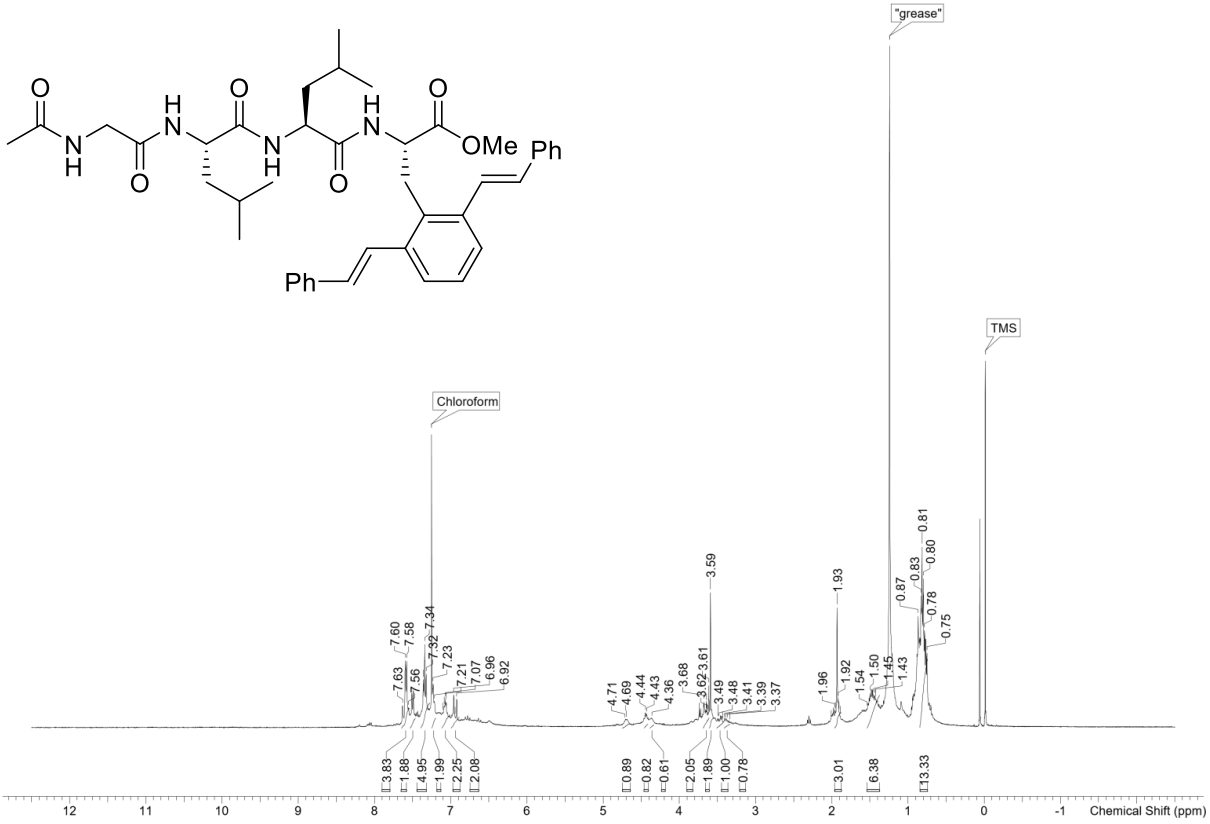
^{1}H NMR (400 MHz, $CDCl_3$) of **9b**



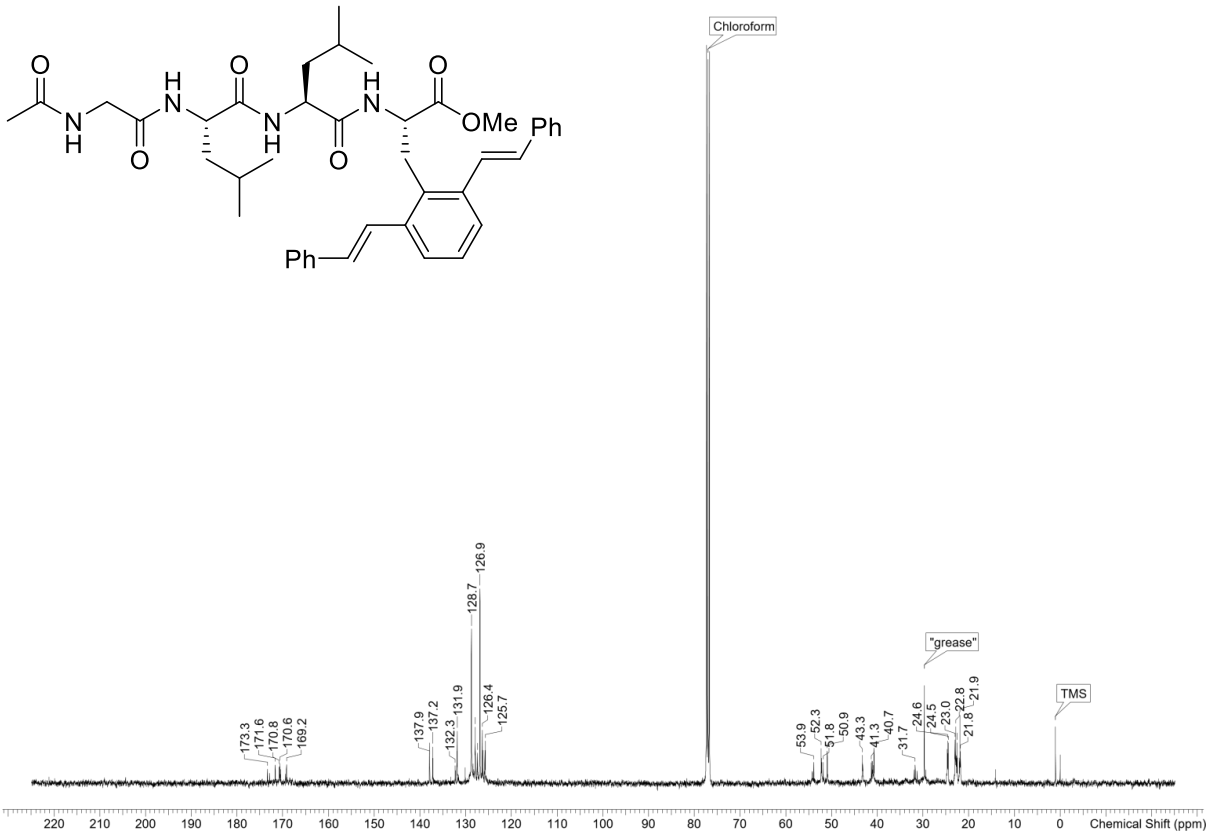
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **9b**



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



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



4. References

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(S2) Stromnova, T. A.; Paschenko, D. V.; Boganova, L. I.; Daineko, M. V.; Katser, S. B.; Churakov, A. V.; Kuz'mina, L. G.; Howard, J. A. K. *Inorg. Chim. Acta* **2003**, *350*, 283.