

# Supporting Information

## Efficient Solution-Phase Dipeptide Synthesis Using Titanium Tetrachloride and Microwave Heating

Palmira Alessia Cavallaro, Marzia De Santo, Rocco Marinaro, Emilia Lucia Belsito, Angelo Liguori and Antonella Leggio\*

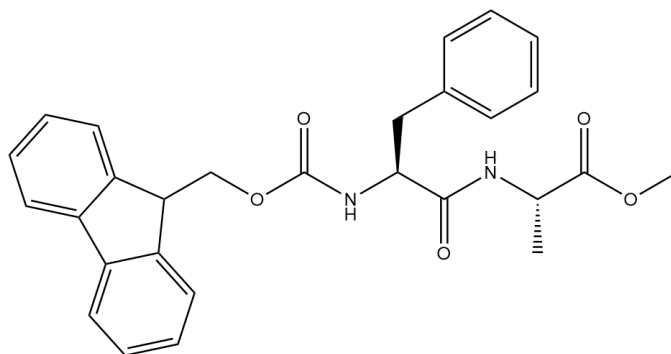
Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Via P. Bucci, 87036 Arcavacata di Rende, Italy; ; alessia.cavallaro@unical.it (P.A.C.); marzia.desanto@unical.it (M.D.S.); rocco.marinaro@unical.it (R.M.); emili-alucia.belsito@unical.it (E.L.B.); angelo.liguori@unical.it (A.L.)

Correspondence: antonella.leggio@unical.it

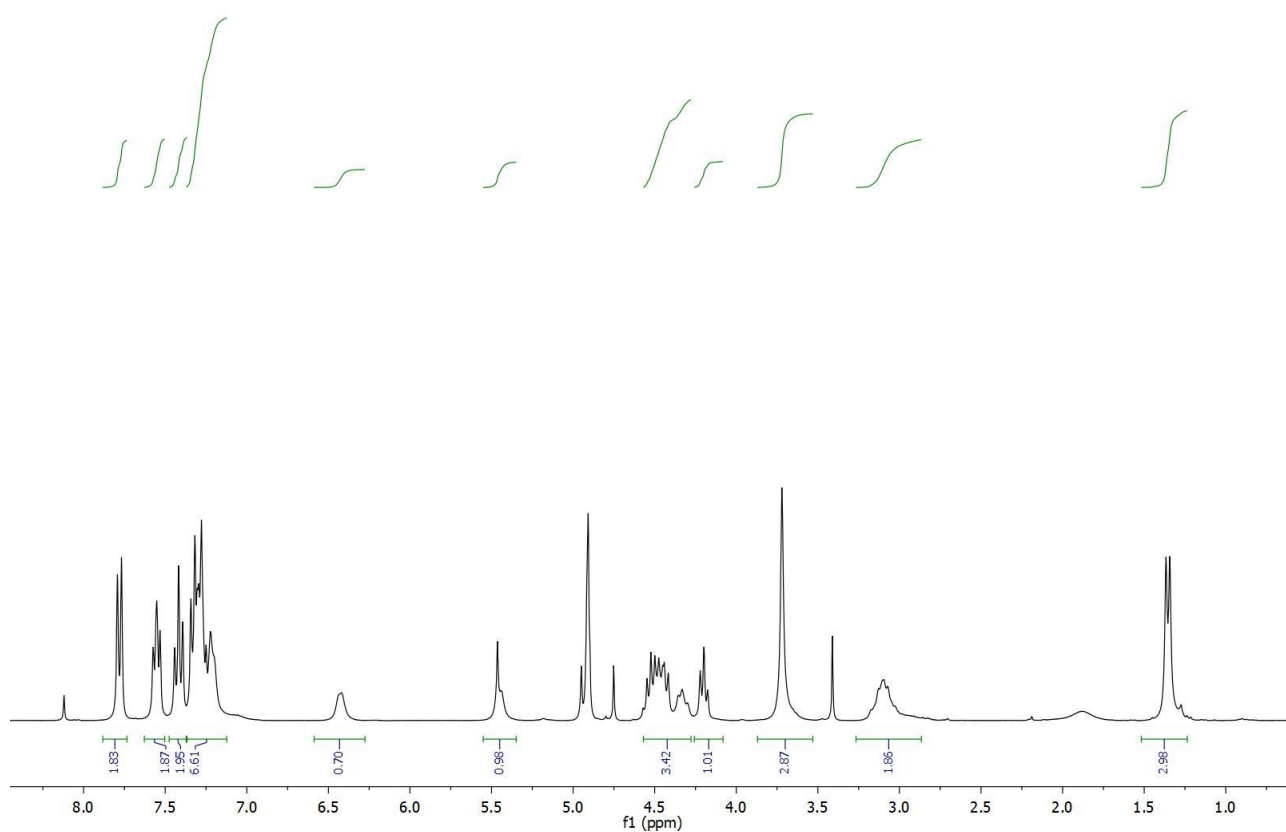
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## ***N*-Fmoc-L-Phe-L-Ala-OMe (1a)**

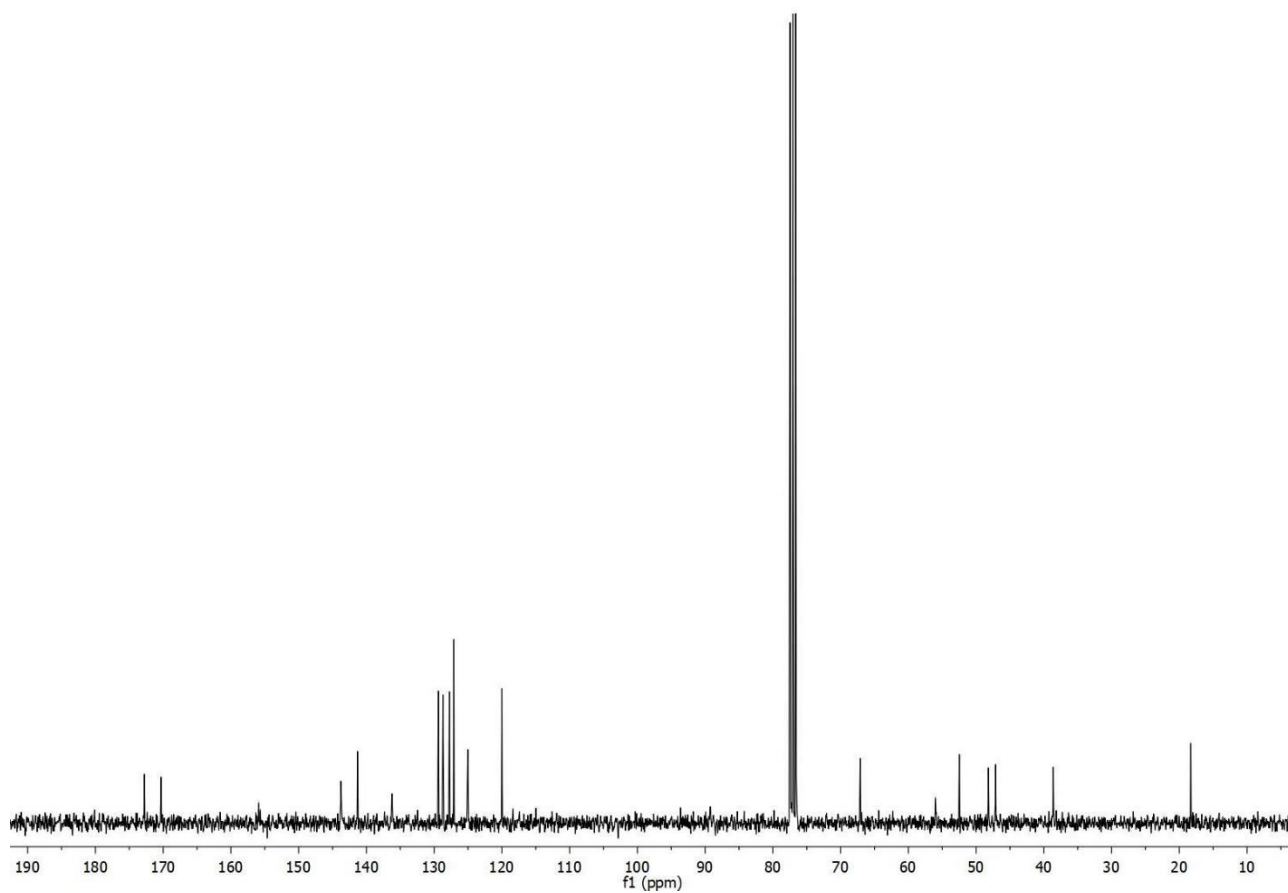


### **<sup>1</sup>H NMR**

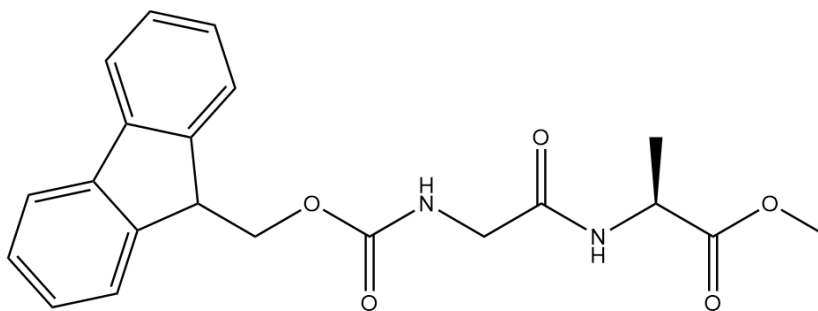


**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 (d,  $J$  = 7.5 Hz, 2H, ArH), 7.55 (t,  $J$  = 6.4 Hz, 2H, ArH), 7.42 (t,  $J$  = 7.4 Hz, 2H, ArH), 7.37 – 7.09 (m, 5H, ArH), 6.43 (s<sub>broad</sub>, 1H, CONH), 5.45 (s<sub>broad</sub>, 1H, OCONH), 4.66 – 4.41 (m, 3H, CH<sub>2</sub>Fmoc, CHCOOMe), 4.33 (m, 1H, CHCONH), 4.20 (t,  $J$  = 6.9 Hz, 1H, CHFmoc), 3.72 (s, 3H, OCH<sub>3</sub>), 3.20-3.96 (m, 2H, CH<sub>2</sub>Ph), 1.35 (d,  $J$  = 7.1 Hz, 3H, CH<sub>3</sub>).

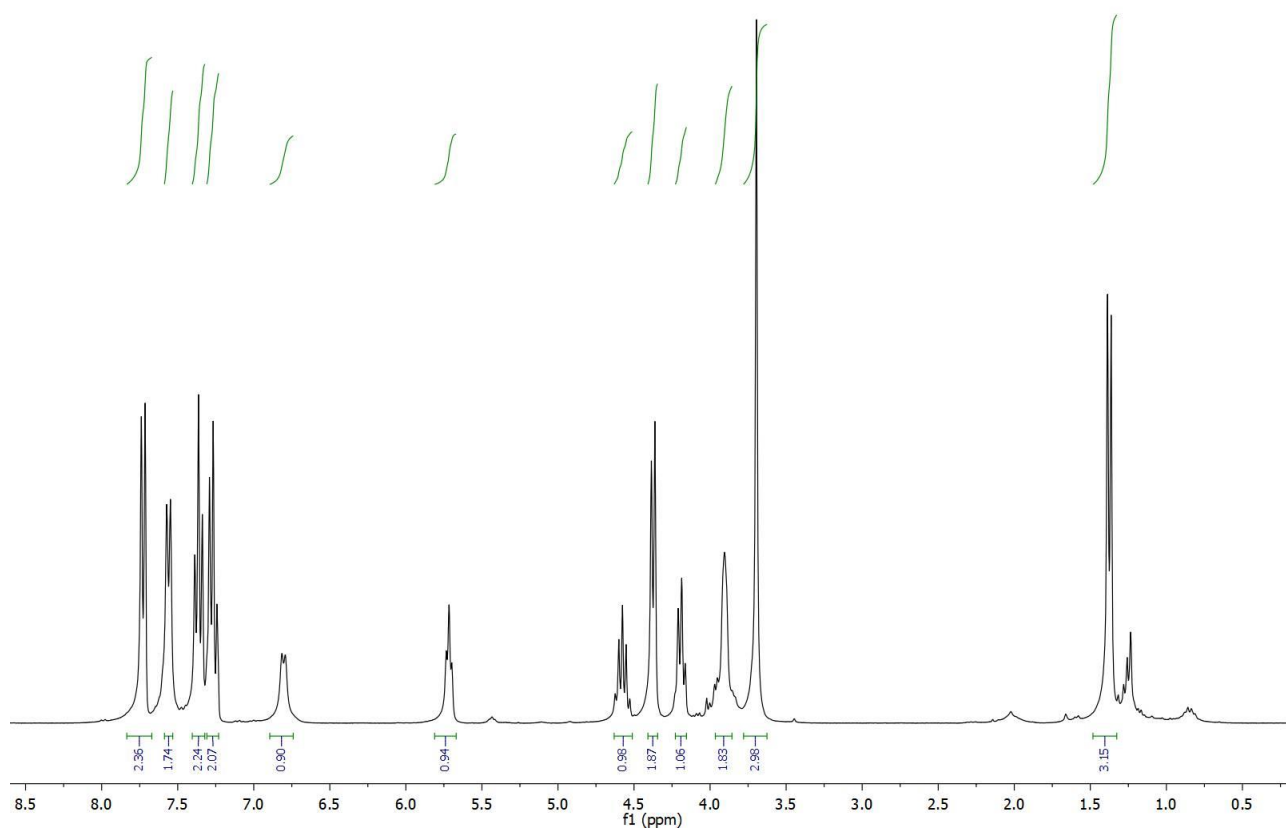
$^{13}\text{C}$  NMR



## N-Fmoc-Gly-L-Ala-OMe (2a)

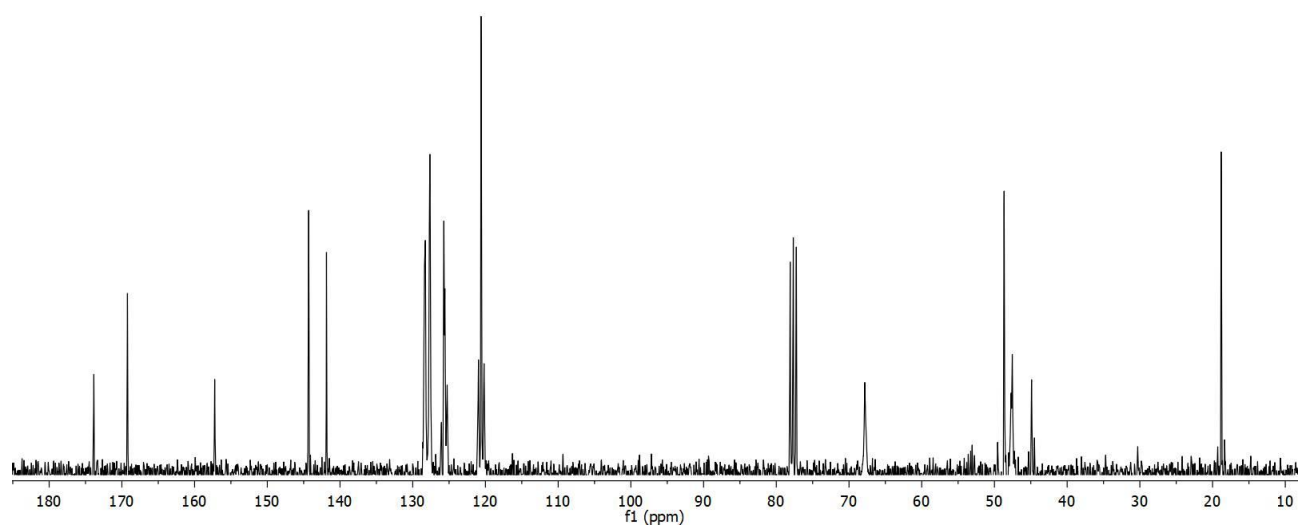


### $^1\text{H}$ NMR

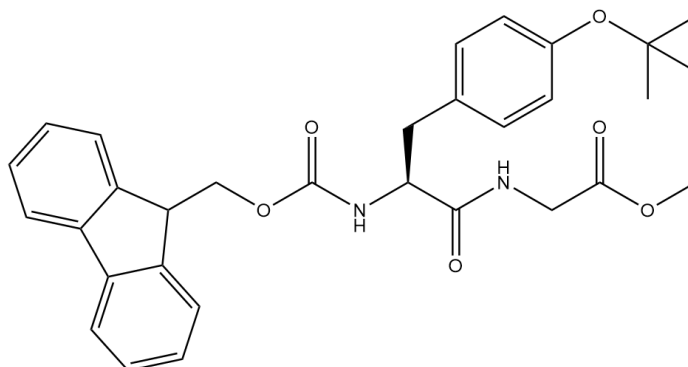


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J$  = 7.5 Hz, 2H, ArH), 7.56 (d,  $J$  = 7.3 Hz, 2H, ArH), 7.47 - 7.19 (m, 4H, ArH), 6.80 (d<sub>broad</sub>,  $J$  = 6.4 Hz, 1H, CONH), 5.72 (t<sub>broad</sub>,  $J$  = 5.4 Hz, 1H, OCONH), 4.78 - 4.48 (m, 1H,  $\text{CHCOOCH}_3$ ), 4.37 (d,  $J$  = 7.0 Hz, 2H,  $\text{CH}_2\text{Fmoc}$ ), 4.19 (t,  $J$  = 7.0 Hz, 1H,  $\text{CHFmoc}$ ), 4.05 - 3.81 (m, 2H,  $\text{CH}_2\text{CONH}$ ), 3.69 (s, 3H,  $\text{OCH}_3$ ), 1.37 (d,  $J$  = 7.1 Hz, 3H,  $\text{CH}_3\text{CH}$ ).

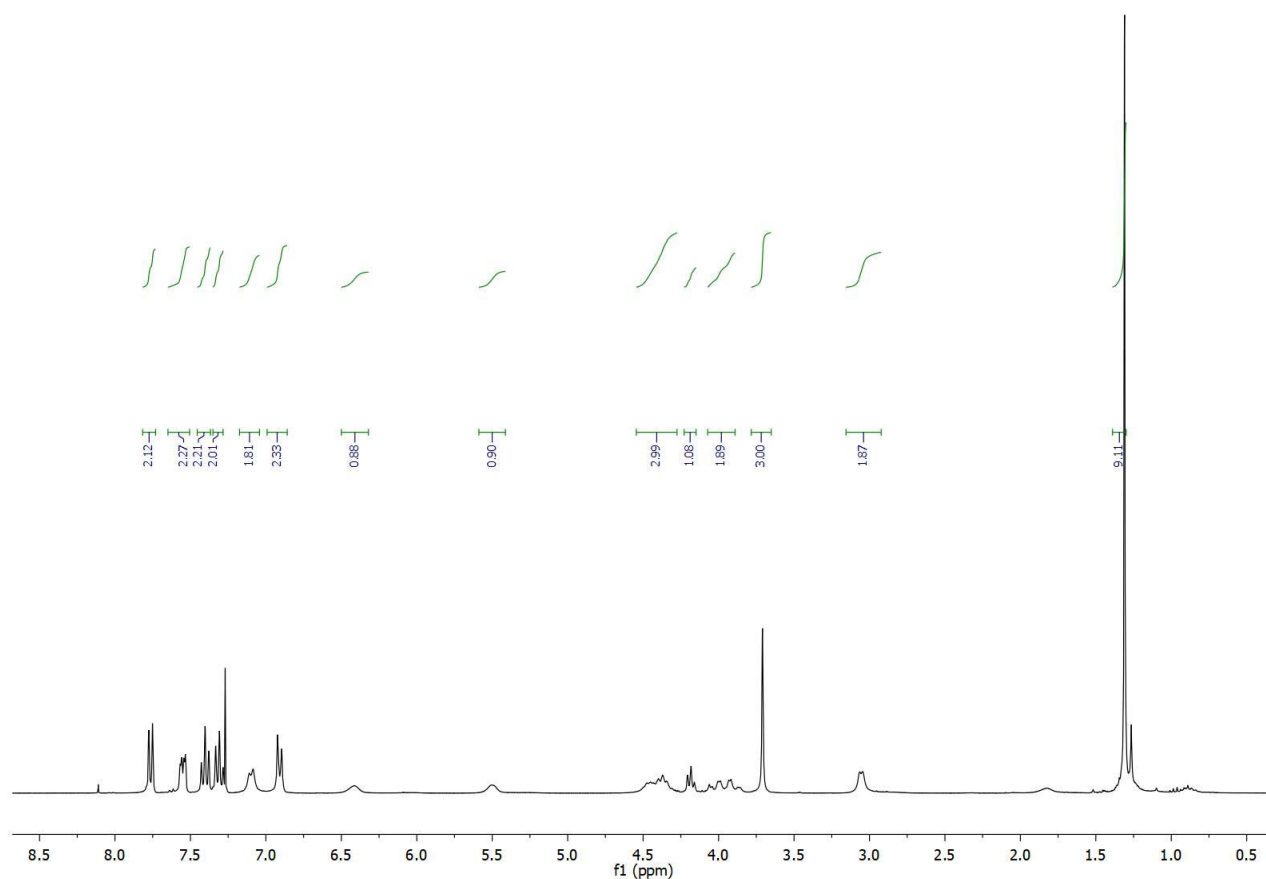
$^{13}\text{C}$  NMR



### N-Fmoc-L-Tyr(tBu)-Gly-OMe (3a)

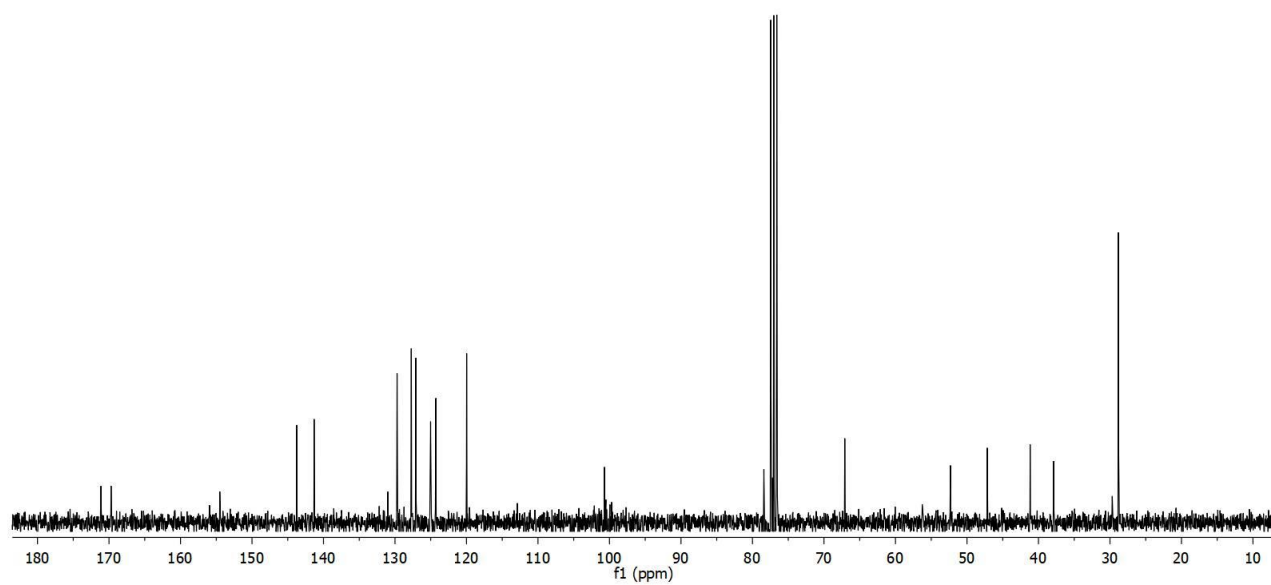


### $^1\text{H}$ NMR

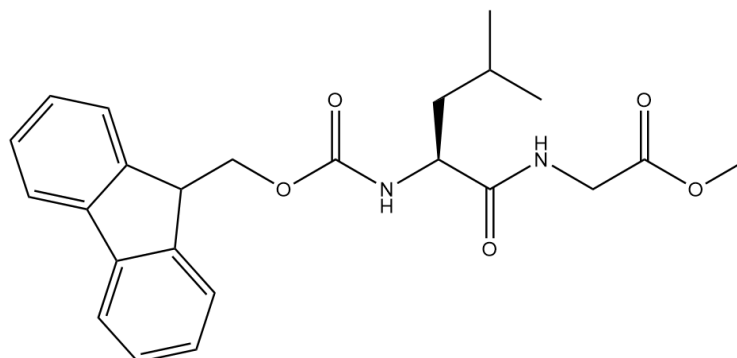


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 7.76 (d,  $J = 7.4$  Hz, 2H, ArH), 7.59-7.49 (m, 2H, ArH), 7.40 (t,  $J = 7.2$  Hz, 2H, ArH), 7.32 (d,  $J = 7.2$  Hz, 2H, ArH), 7.17-7.03 (m, 2H, ArH), 6.91 (d,  $J = 7.4$  Hz, 2H, ArH), 6.41 (s<sub>broad</sub>, 1H, OCONH), 5.50 (s<sub>broad</sub>, 1H, CONH), 4.55 – 4.28 (m, 3H,  $\text{CH}_2\text{Fmoc}$ ,  $\text{CHCONH}$ ), 4.18 (t,  $J = 6.8$  Hz, 1H,  $\text{CHFmoc}$ ), 4.07 – 3.89 (m, 2H,  $\text{CH}_2\text{COOMe}$ ), 3.71 (s, 3H,  $\text{OCH}_3$ ), 3.11-2.99 (m 2H,  $\text{CH}_2\text{-Tyr}$ ), 1.31 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ).

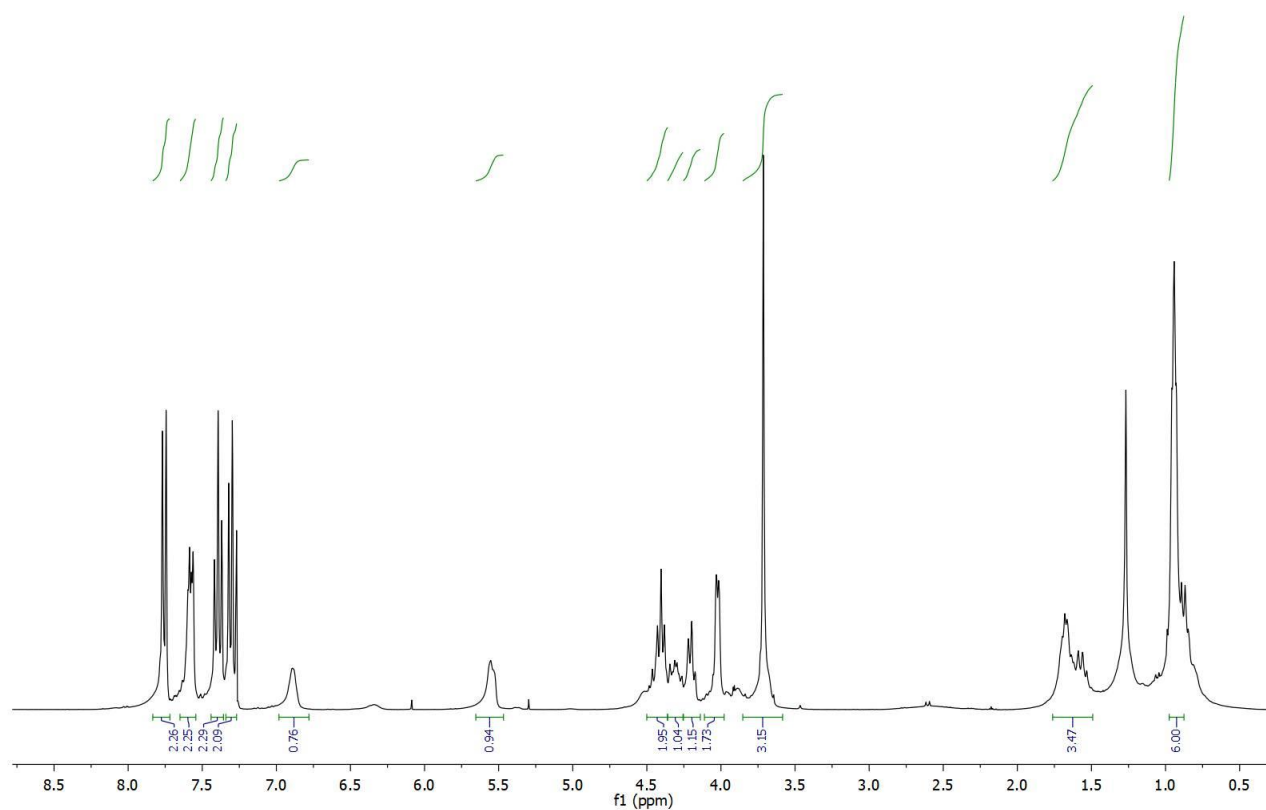
$^{13}\text{C}$  NMR



# **N-Fmoc-L-Leu-Gly-OMe (4a)**



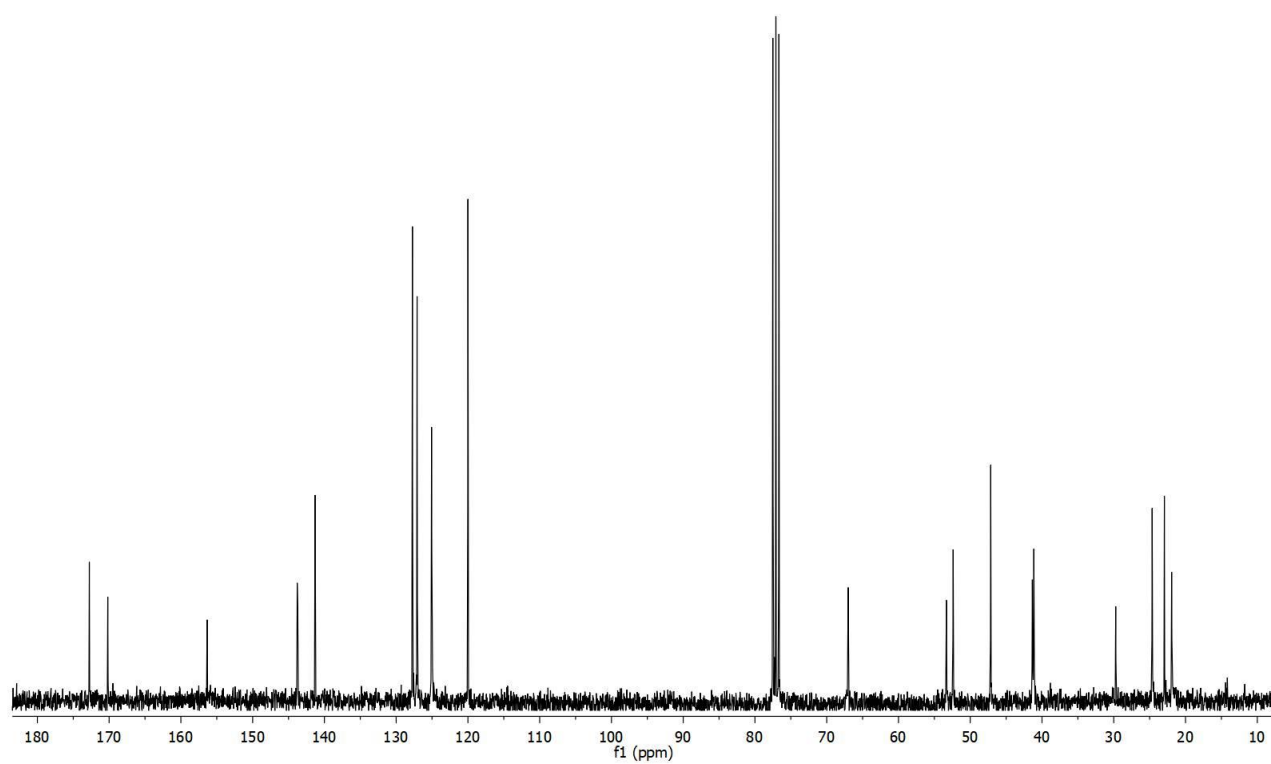
## **<sup>1</sup>H NMR**



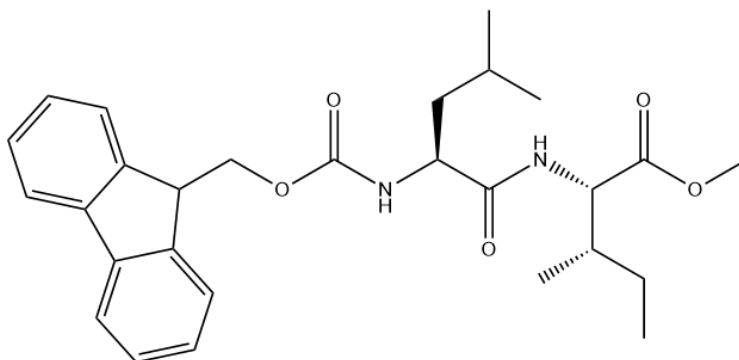
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 7.5 Hz, 2H, ArH), 7.65-7.53 (m, 2H, ArH), 7.38 (d, *J* = 7.4 Hz, 2H, ArH), 7.35 – 7.27 (m, 2H, ArH), 6.89 (s<sub>broad</sub>, 1H, CONH), 5.55 (s<sub>broad</sub>, 1H, OCONH), 4.50-4.37 (m, 2H, CH<sub>2</sub>Fmoc), 4.34-4.26 (m, 1H, CHCONH), 4.20 (t, *J* = 6.9 Hz, 1H, CHFmoc) 4.02 (m, 2H, CH<sub>2</sub>COOCH<sub>3</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 1.80 – 1.46 (m, 3H, CH<sub>2</sub>CH), 1.04 – 0.88 (m, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).



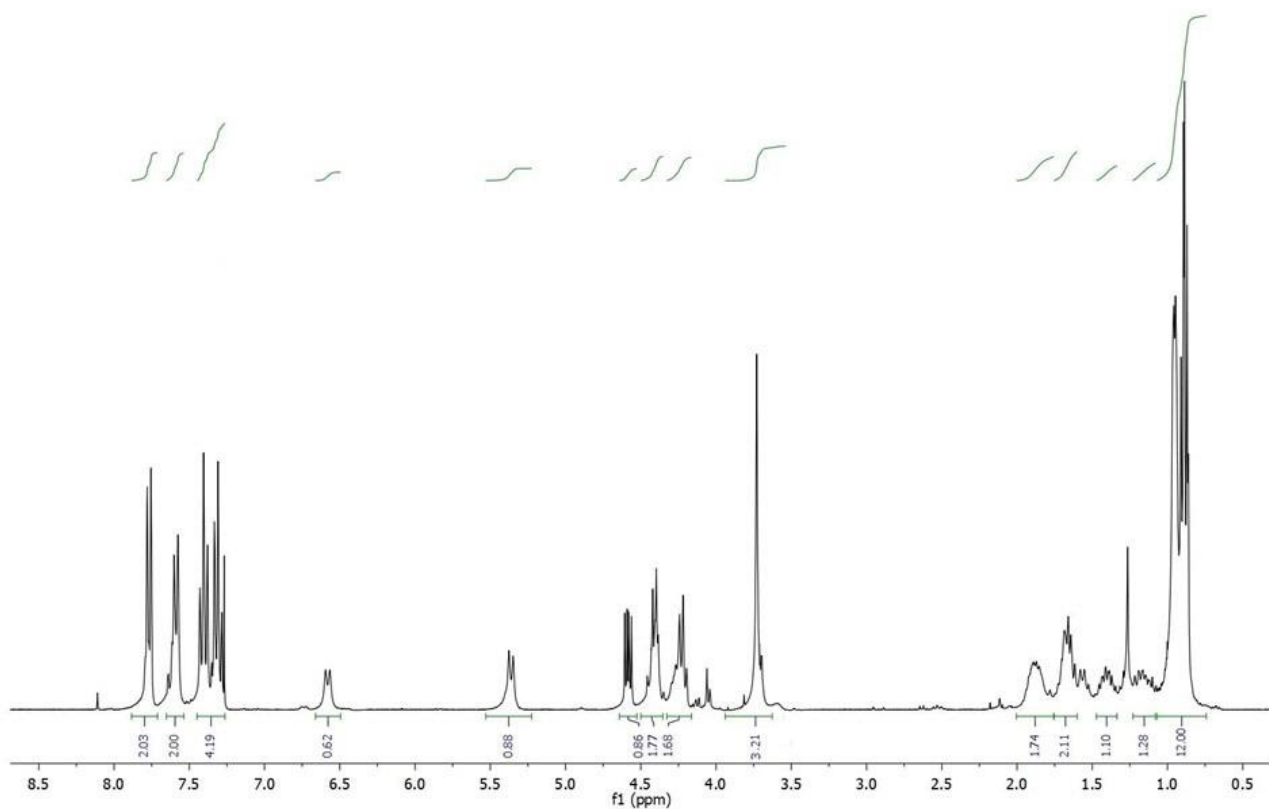
$^{13}\text{C}$  NMR



**N-Fmoc-L-Leu-L-Ile-OMe (5a)**



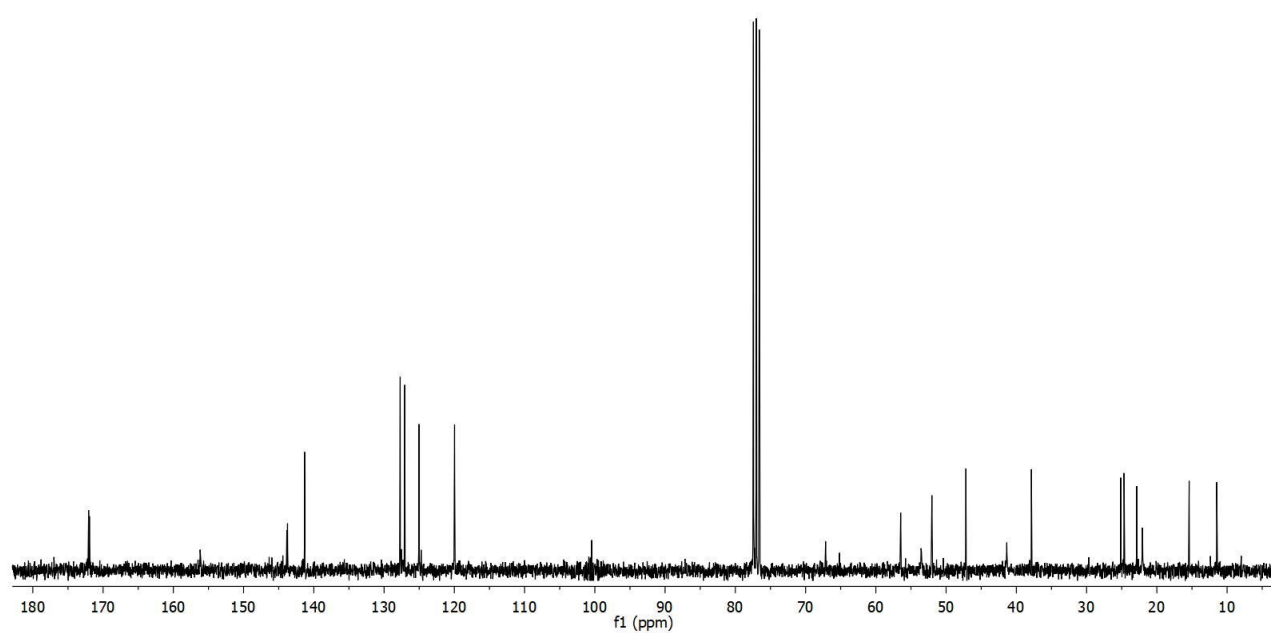
**$^1\text{H}$  NMR**



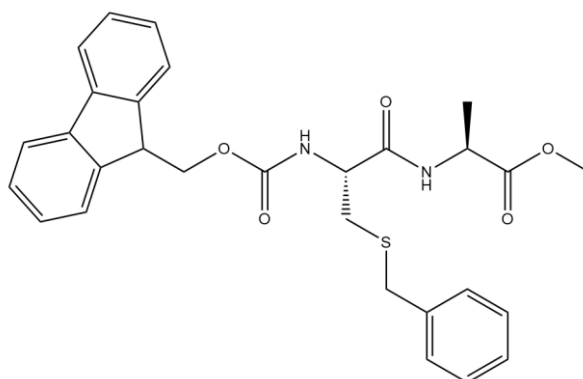
**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J$  = 7.5 Hz, 2H, ArH), 7.59 (d,  $J$  = 7.5 Hz, 2H, ArH), 7.49 – 7.20 (m, 4H, ArH), 6.58 (d,  $J$  = 8.4 Hz, 1H, CONH), 5.36 (d,  $J$  = 8.4 Hz, 1H, OCONH), 4.58 (dd,  $J$  = 8.4, 5.1 Hz, 1H,  $\text{CHCOOMe}$ ), 4.50-4.35 (m, 2H,  $\text{CH}_2\text{-Fmoc}$ ), 4.33-4.16 (m, 2H,  $\text{CH-Fmoc}$ ,  $\text{CHCONH}$ ), 3.73 (s, 3H,  $\text{OCH}_3$ ), 1.98-1.75 (m, 2H,  $\text{CHCH}_3$ ,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.74-1.59

(m, 2H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.47 -1.33 (m, 1H,  $\text{CH}_2\text{CH}_3$ ), 1.23 – 1.08 (m, 1H,  $\text{CH}_2\text{CH}_3$ ), 1.07 – 0.74 (m, 12H,  $\text{CHCH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ).

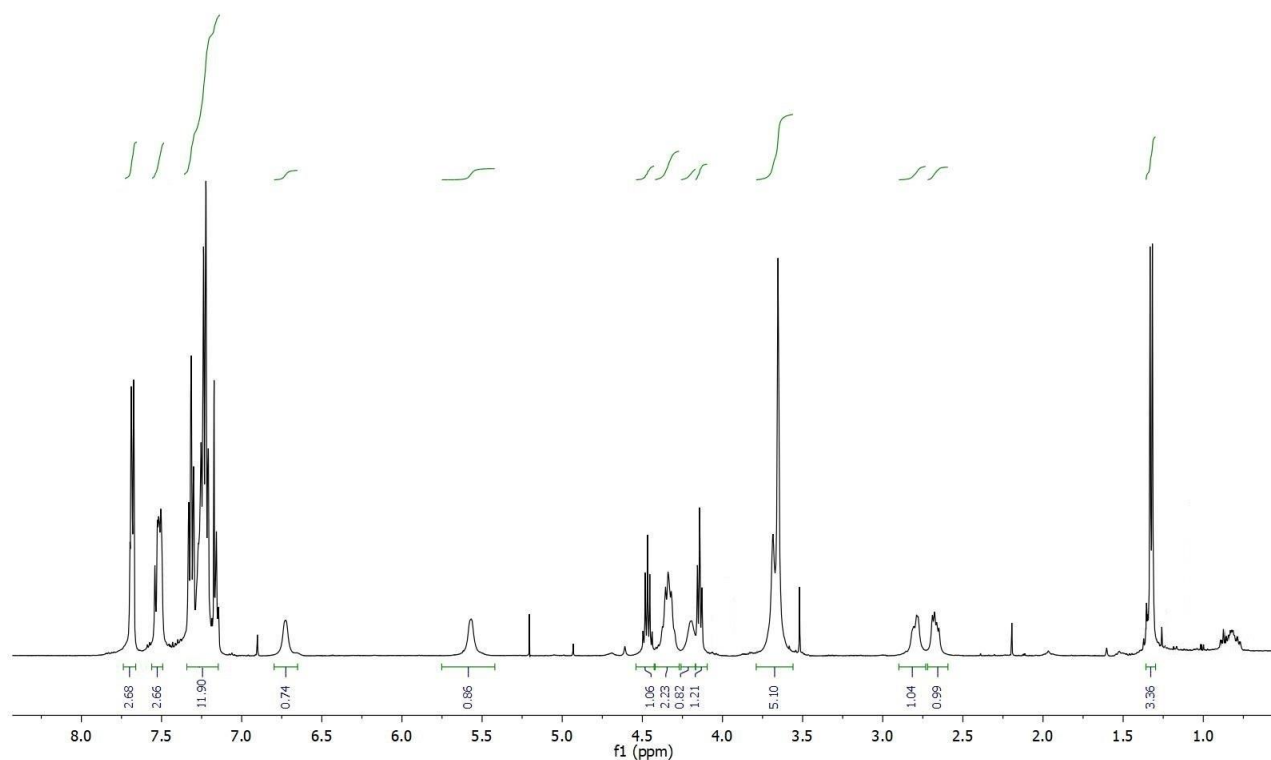
### $^{13}\text{C}$ NMR



# **N-Fmoc-L-Cys(Bzl)-L-Ala-OMe (6a)**

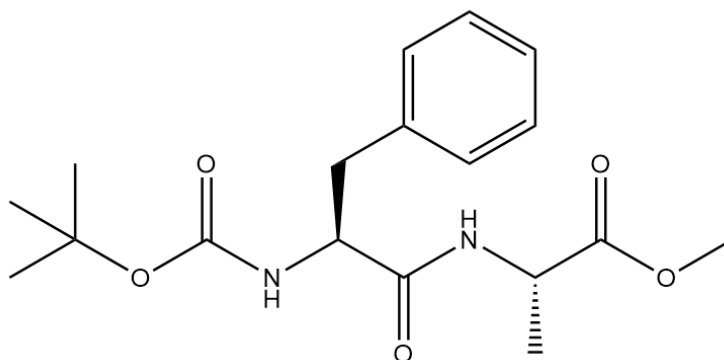


## **<sup>1</sup>H NMR**

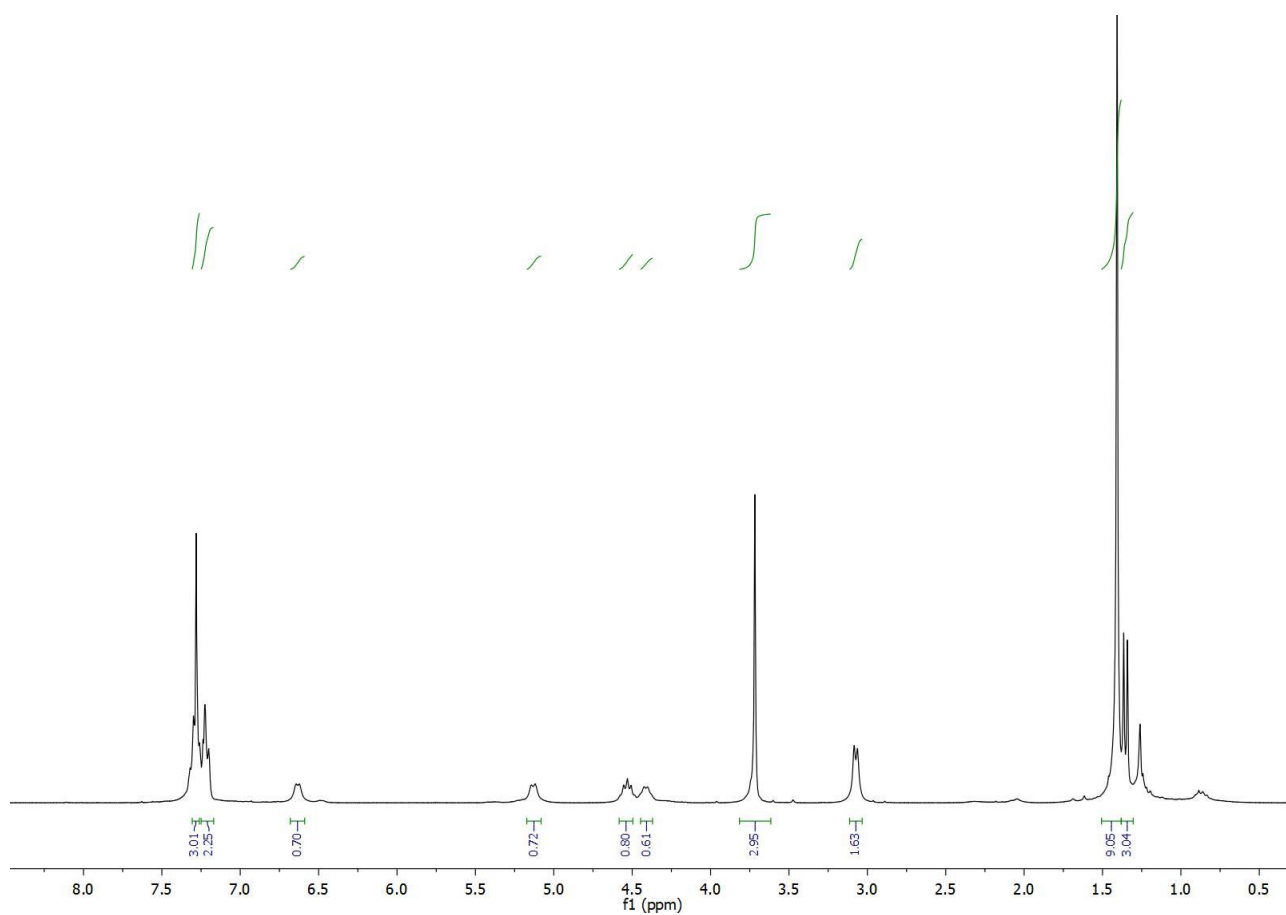


**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.68 (d, 2H, J = 7.5 Hz, ArH), 7.58-7.46 (m, 2H, ArH), 7.42-7.09 (m, 9H, ArH), 6.72 (s<sub>broad</sub>, 1H, CONH), 5.57 (s<sub>broad</sub>, 1H, OCONH), 4.47 (m, 1H, CHCOOCH<sub>3</sub>), 4.41-4.26 (m, 2H, CH<sub>2</sub>-Fmoc), 4.25-4.15 (m, 1H, CHCONH), 4.14-4.10 (m, 1H, CH-Fmoc), 3.75-3.56 (m, 5H, SCH<sub>2</sub>Ph, OCH<sub>3</sub>), 2.80 (m, 1H, CHCH<sub>2</sub>S), 2.67 (m, 1H, CHCH<sub>2</sub>S), 1.32 (d, 3H, J = 7.2 Hz, CH<sub>3</sub>).

# **N-Boc-L-Phe-L-Ala-OMe (1b)**

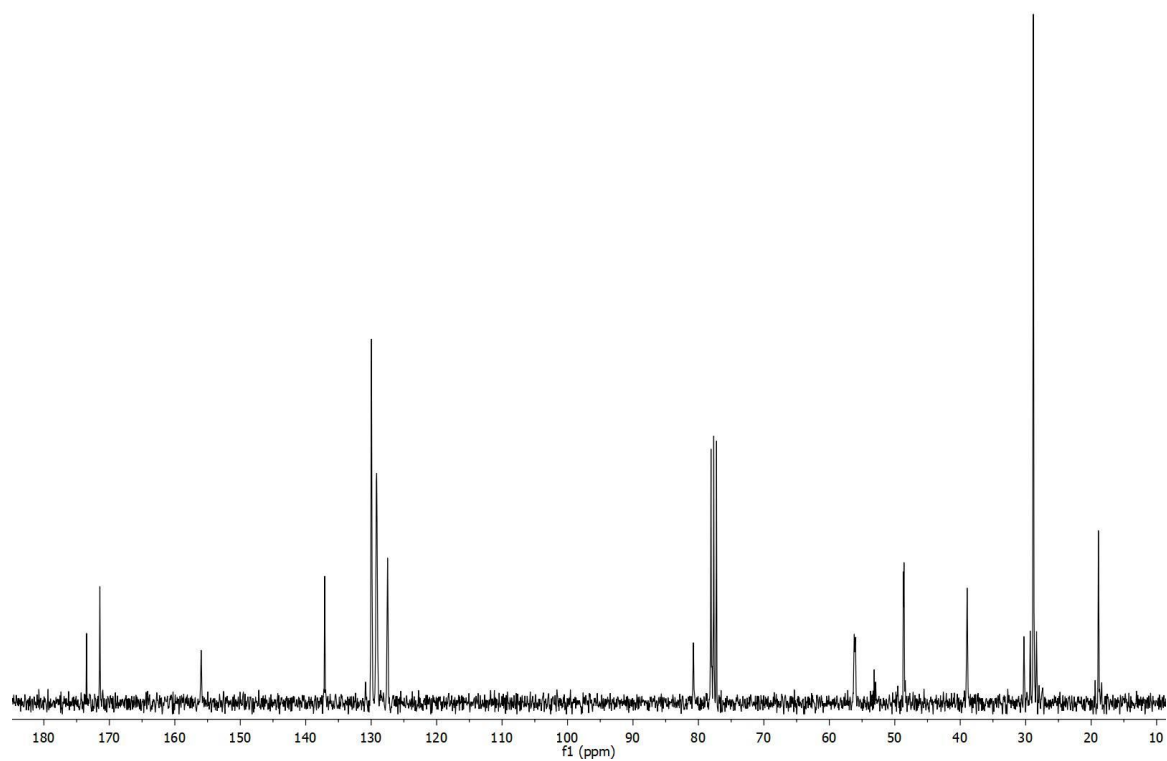


## **$^1\text{H}$ NMR**

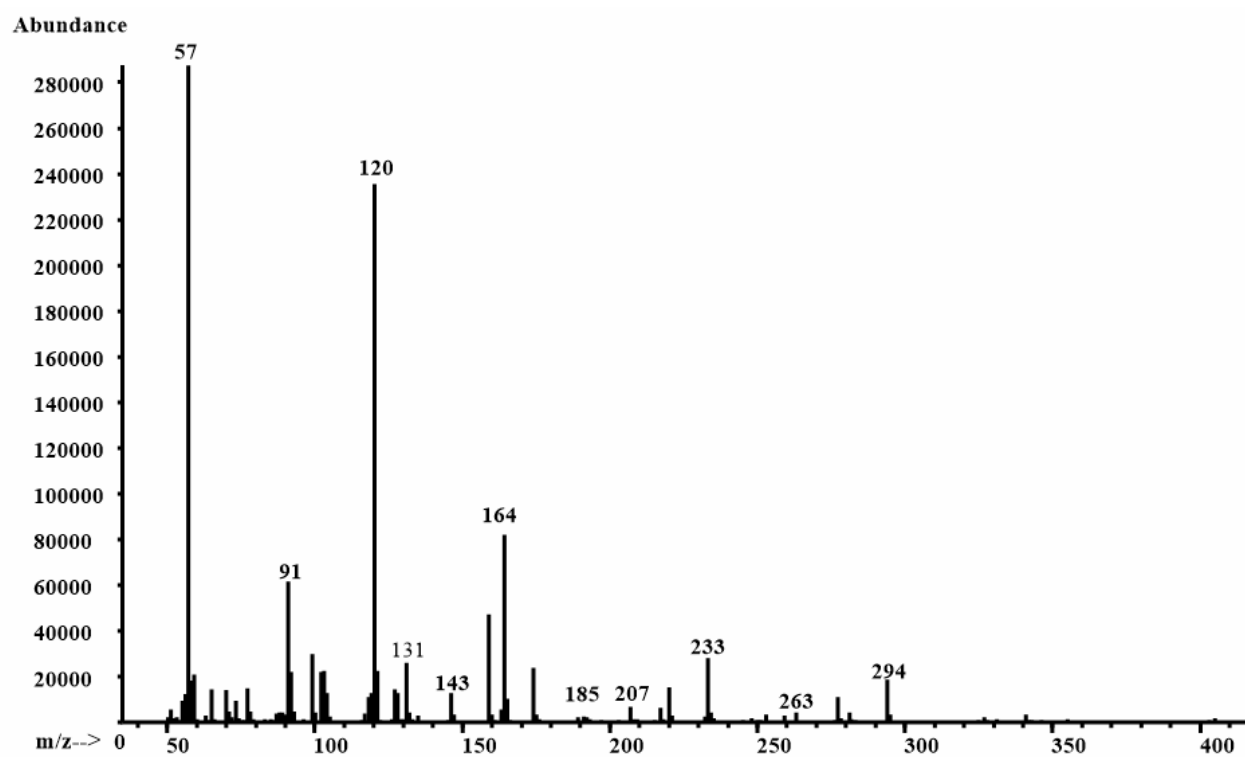


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.11 (m, 5H, ArH), 6.63 (sbroad, 1H, CONH), 5.14 (sbroad, 1H, OCONH), 4.54 (m, 1H,  $\text{CHCOOMe}$ ), 4.40 (m, 1H,  $\text{CHCH}_2\text{Ph}$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.07 (d,  $J$  = 6.2 Hz, 2H,  $\text{CH}_2\text{Ph}$ ), 1.41 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.35 (d,  $J$  = 7.2 Hz, 3H,  $\text{CHCH}_3$ ).

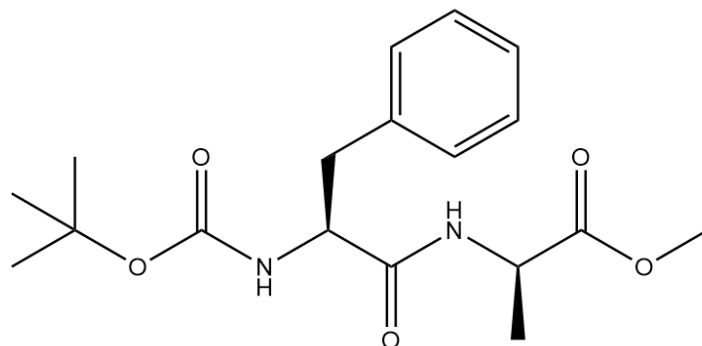
# <sup>13</sup>C NMR



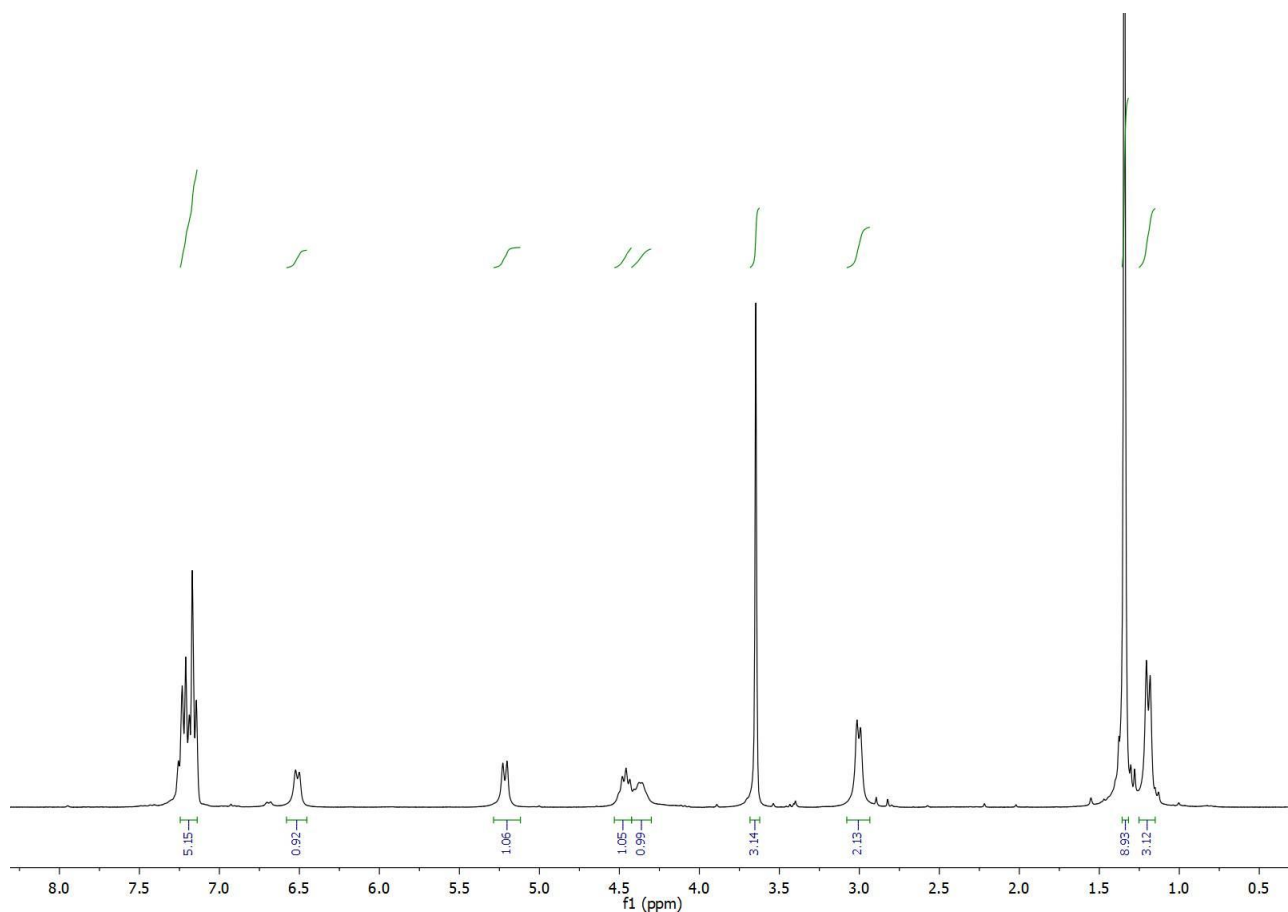
# MS (EI)



**N-Boc-L-Phe-D-Ala-OMe (2b)**

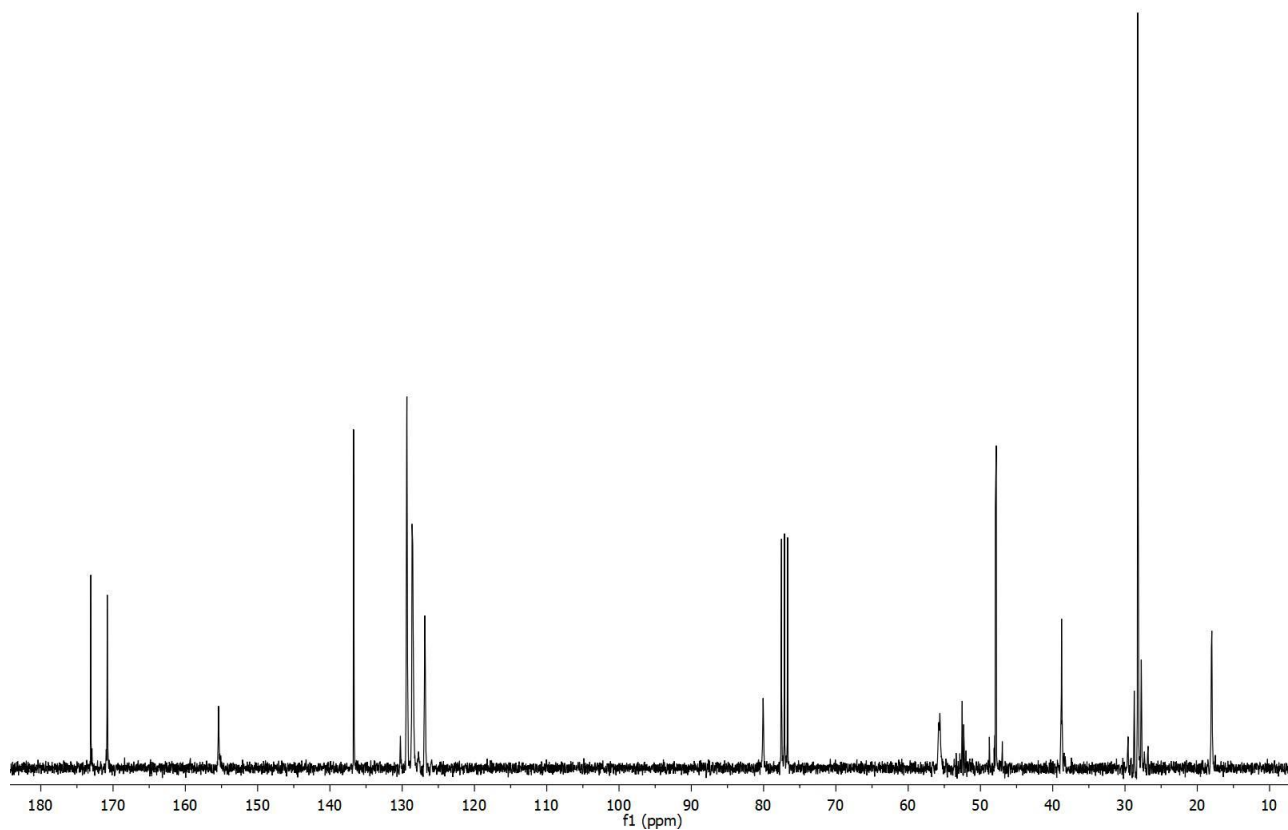


**$^1\text{H}$  NMR**

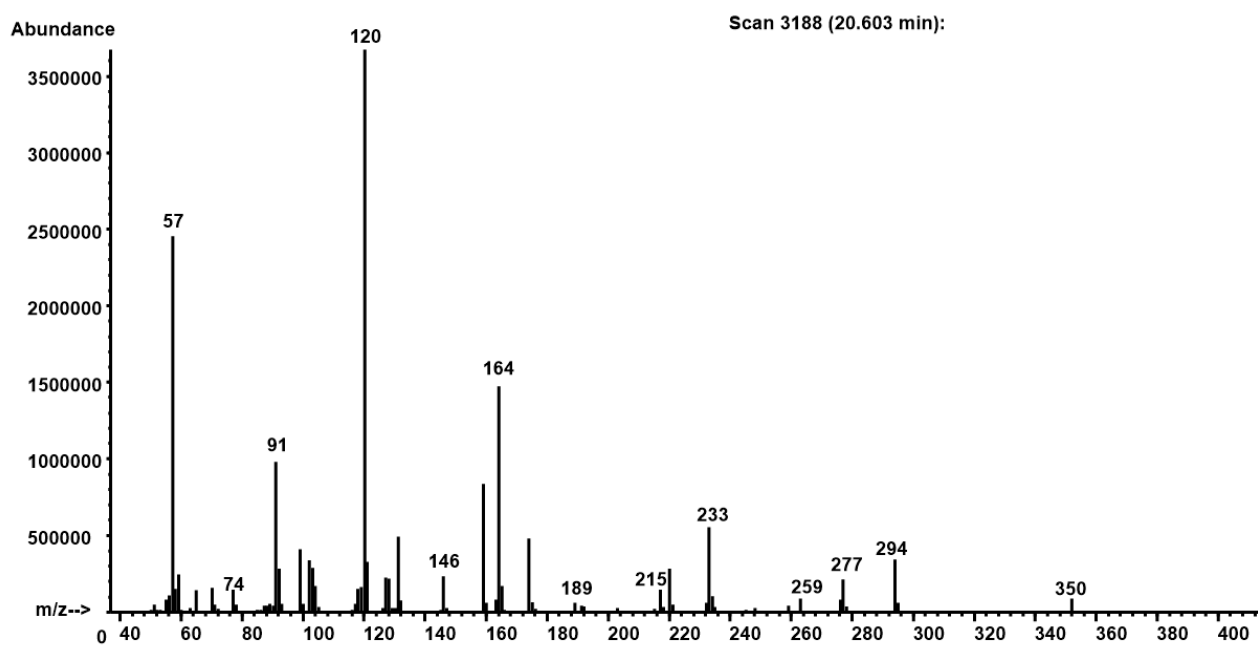


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 – 7.14 (m, 5H, ArH), 6.51 (d,  $J$  = 7.0 Hz, 1H, CONH), 5.22 (d,  $J$  = 8.0 Hz, 1H, OCONH), 4.45 (m, 1H,  $\text{CHCOOMe}$ ), 4.35 (m, 1H,  $\text{CHCH}_2\text{Ph}$ ), 3.65 (s, 3H,  $\text{OCH}_3$ ), 3.01 (d,  $J$  = 6.5 Hz, 2H,  $\text{CH}_2\text{Ph}$ ), 1.34 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.19 (d,  $J$  = 6.9 Hz, 3H,  $\text{CHCH}_3$ ).

<sup>13</sup>C NMR

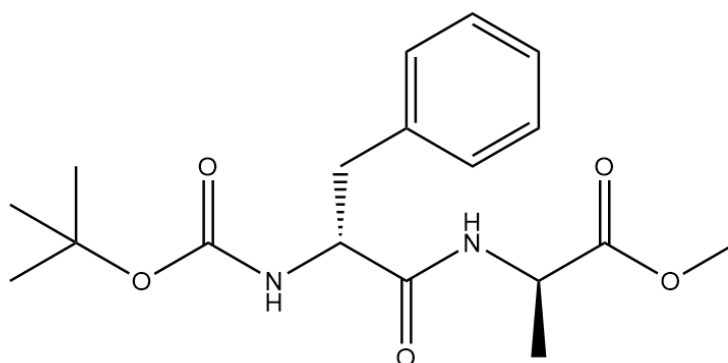


MS (EI)

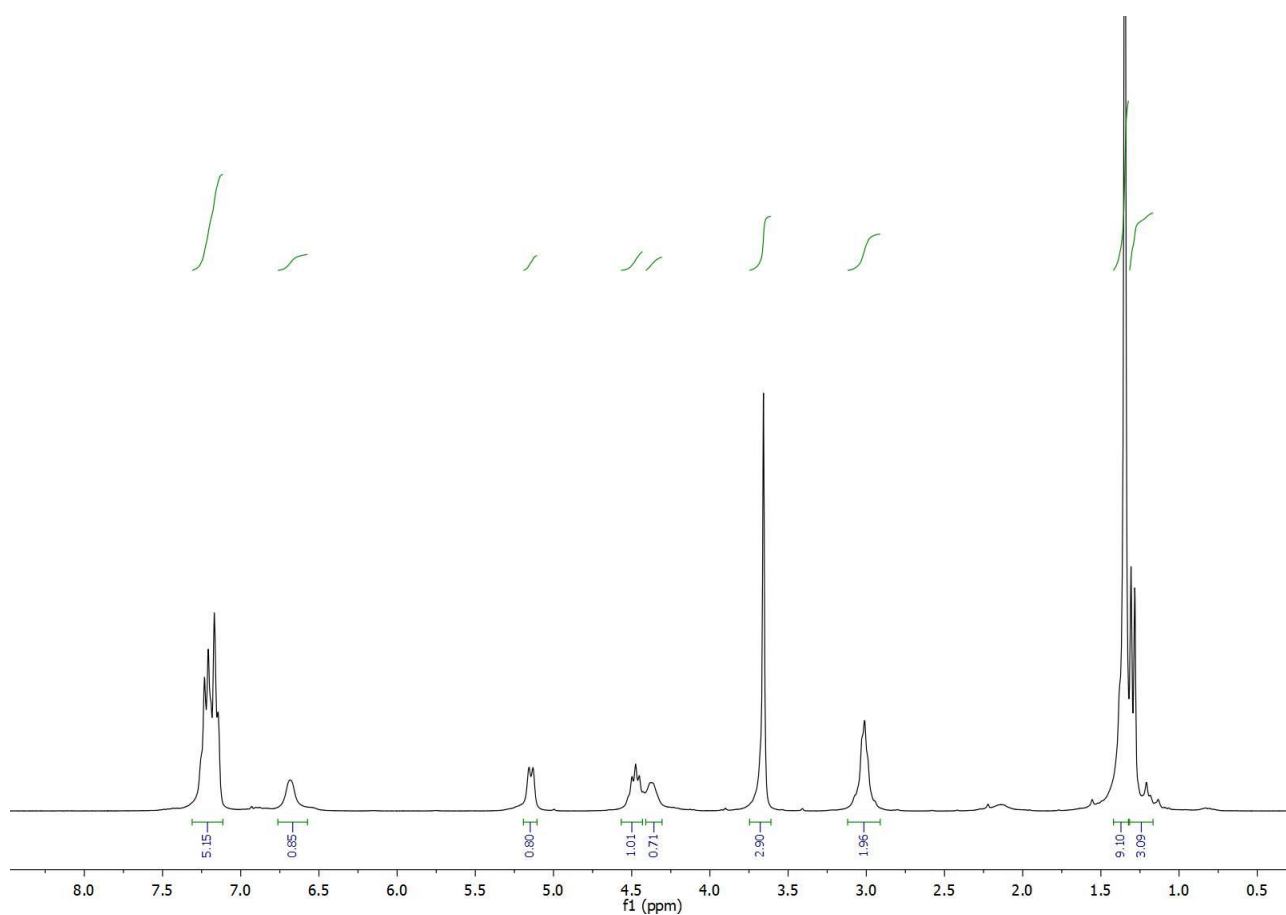




**N-Boc-D-Phe-D-Ala-OMe (3b)**

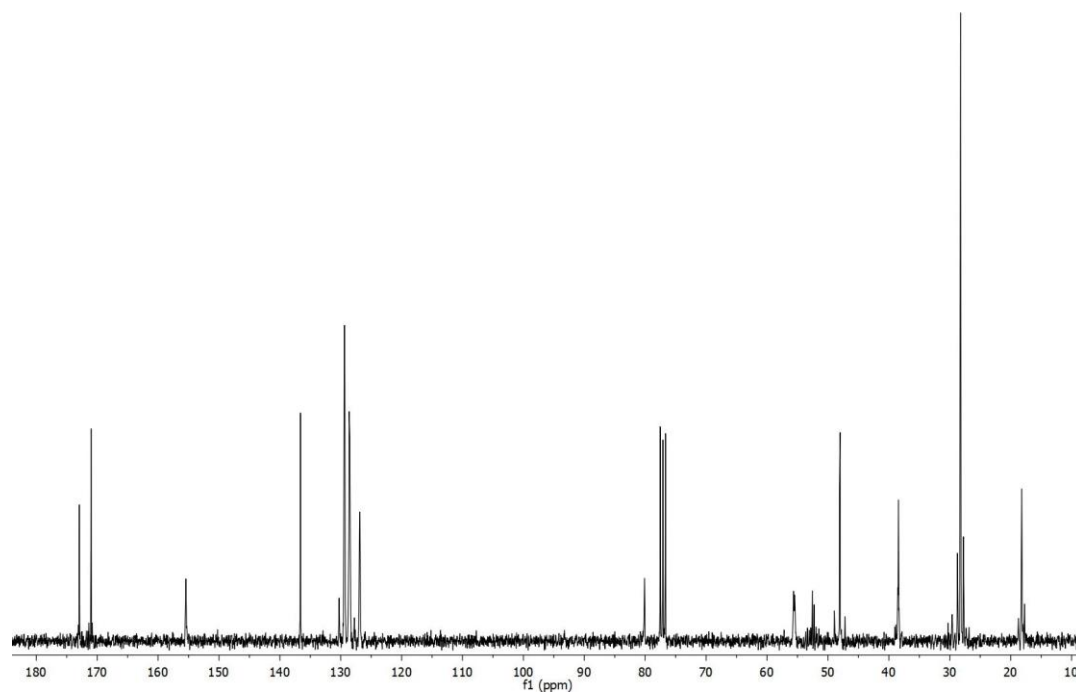


**$^1\text{H}$  NMR**

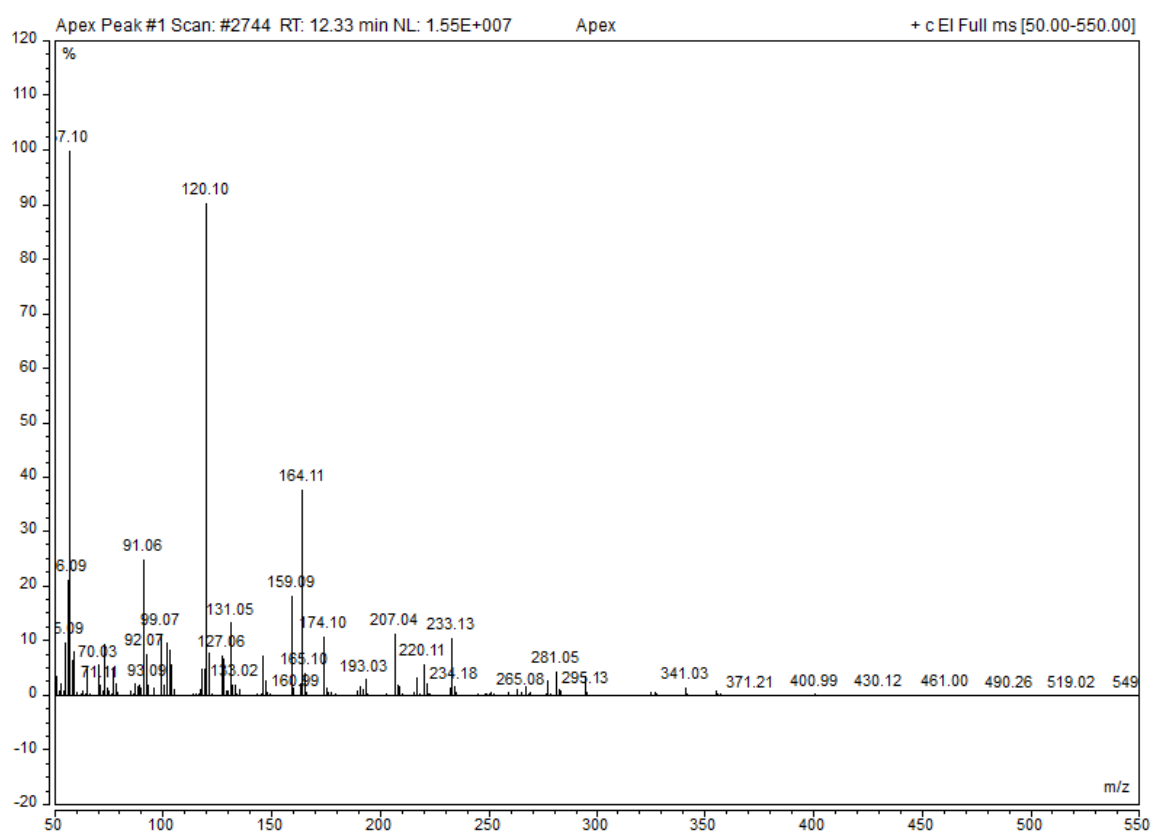


**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (t,  $J = 9.4$  Hz, 5H, ArH), 6.69 (s, 1H, CONH), 5.14 (d,  $J = 7.6$  Hz, 1H, OCONH), 4.48 (t,  $J = 6.8$  Hz, 1H,  $\text{CHCOOMe}$ ), 4.36 (m, 1H,  $\text{CHCH}_2\text{Ph}$ ), 3.66 (s, 3H,  $\text{OCH}_3$ ), 3.01 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 1.35 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.30 (d,  $J = 7.2$  Hz, 3H,  $\text{CHCH}_3$ ).

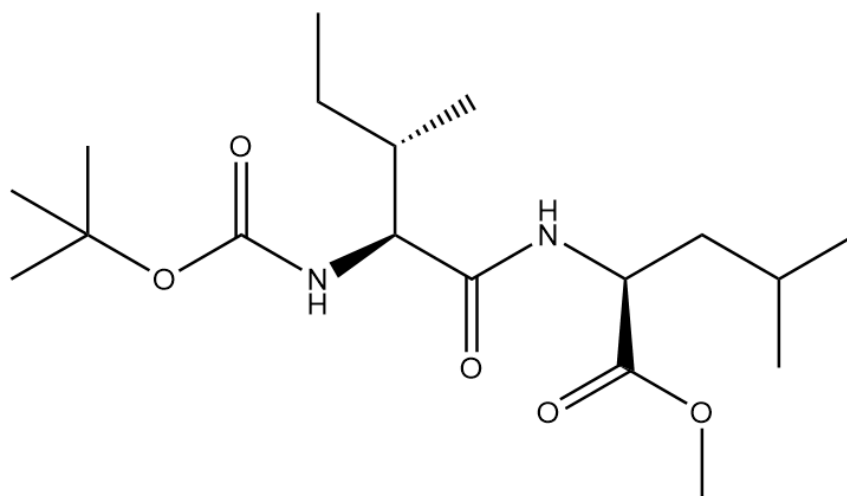
# <sup>13</sup>C NMR



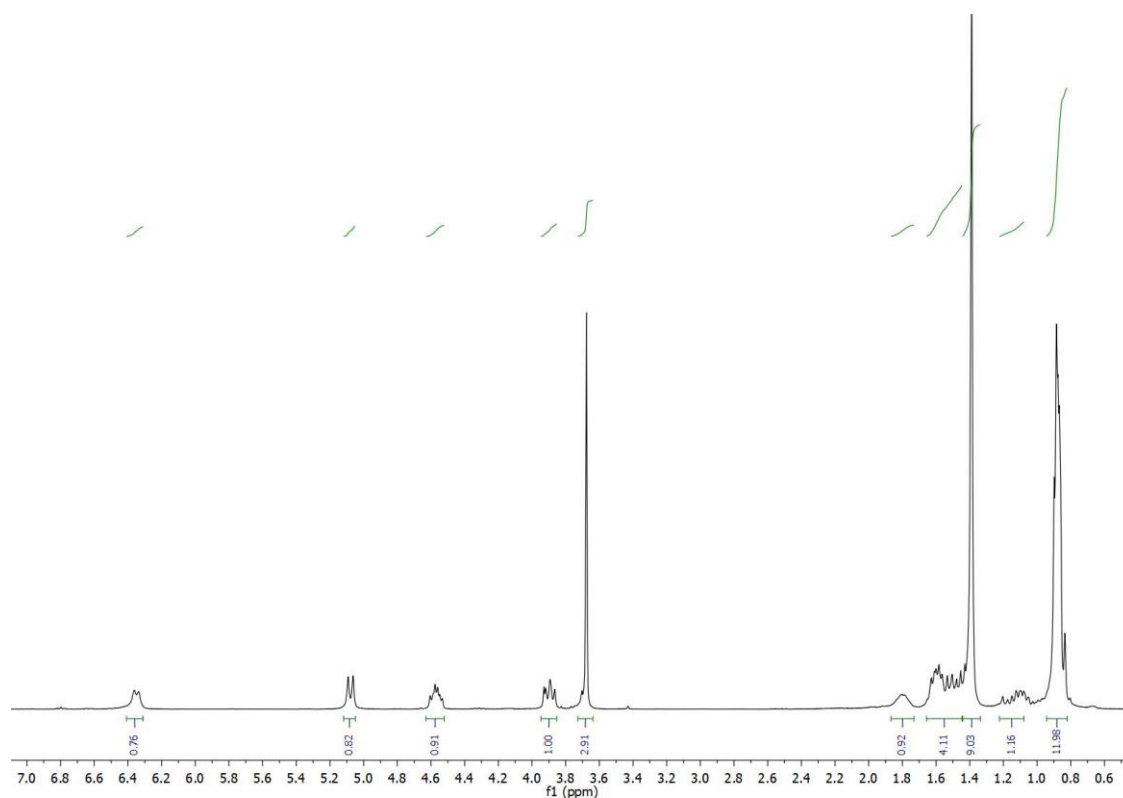
# MS (EI)



**N-Boc-L-Ile-L-Leu-OMe (4b)**

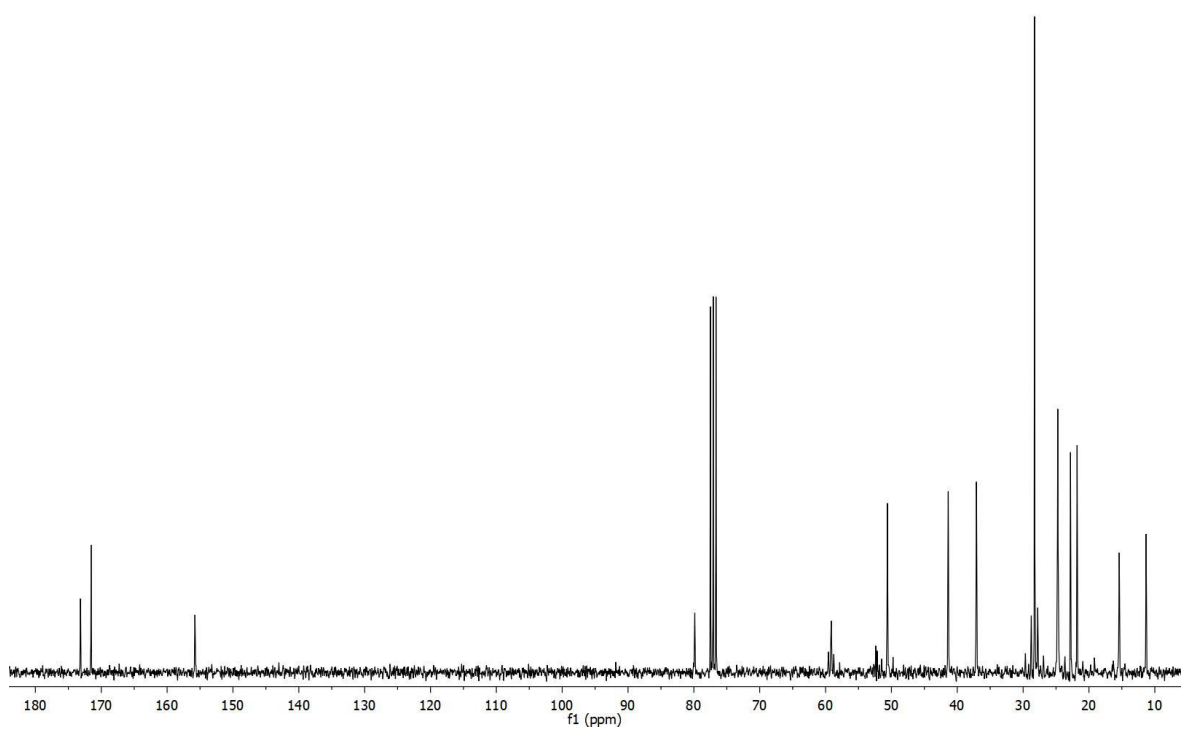


**$^1\text{H}$  NMR**

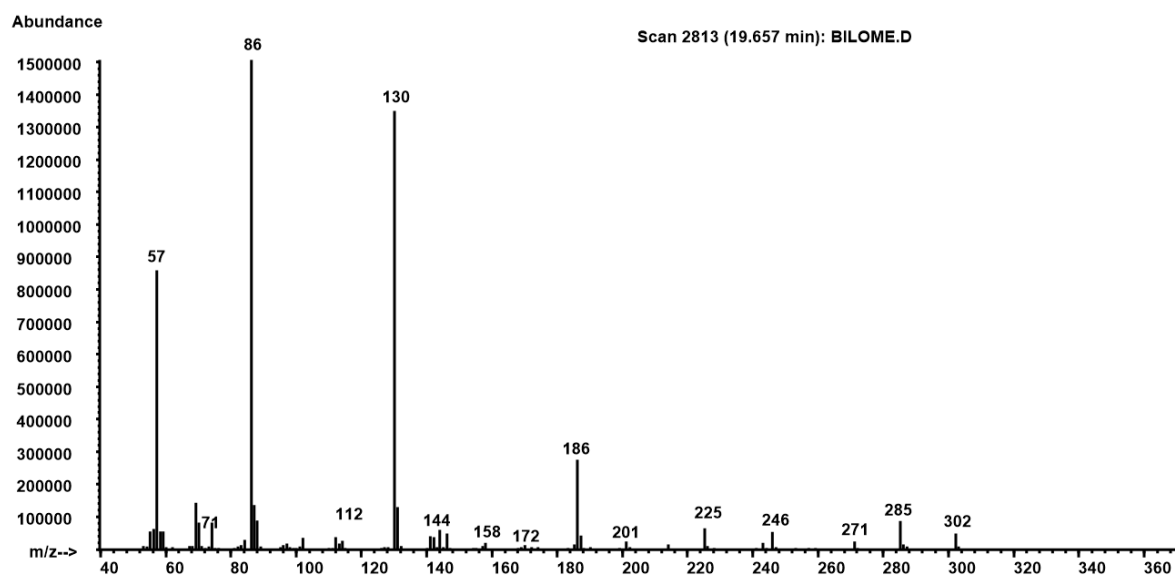


**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.35 (d,  $J$  = 7.6 Hz, 1H, CONH), 5.08 (d,  $J$  = 8.9 Hz, 1H, OCONH), 4.57 (m, 1H,  $\text{CHCOOMe}$ ), 3.89 (m, 1H,  $\text{CHCONH}$ ), 3.68 (s, 3H,  $\text{OCH}_3$ ), 1.81 ( $\text{s}_{\text{broad}}$ , 1H,  $\text{CHCH}_3$ ), 1.66 – 1.45 (m, 4H,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}$ ), 1.38 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.22 – 1.08 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 0.99-0.89 (m, 12H,  $\text{CH}(\text{CH}_3)_2$ ,  $\text{CH}_2(\text{CH}_3)_2$ ).

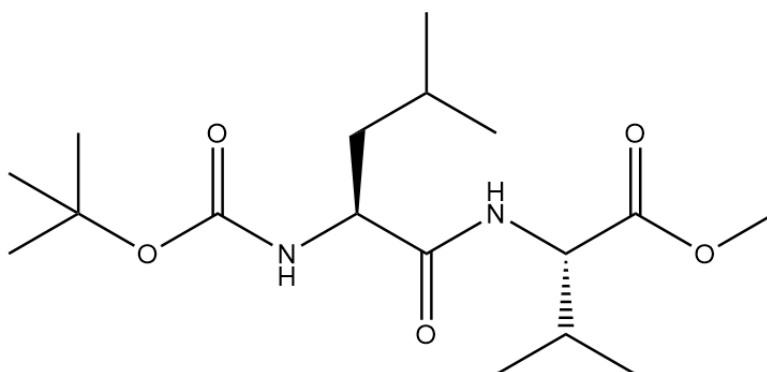
# <sup>13</sup>C NMR



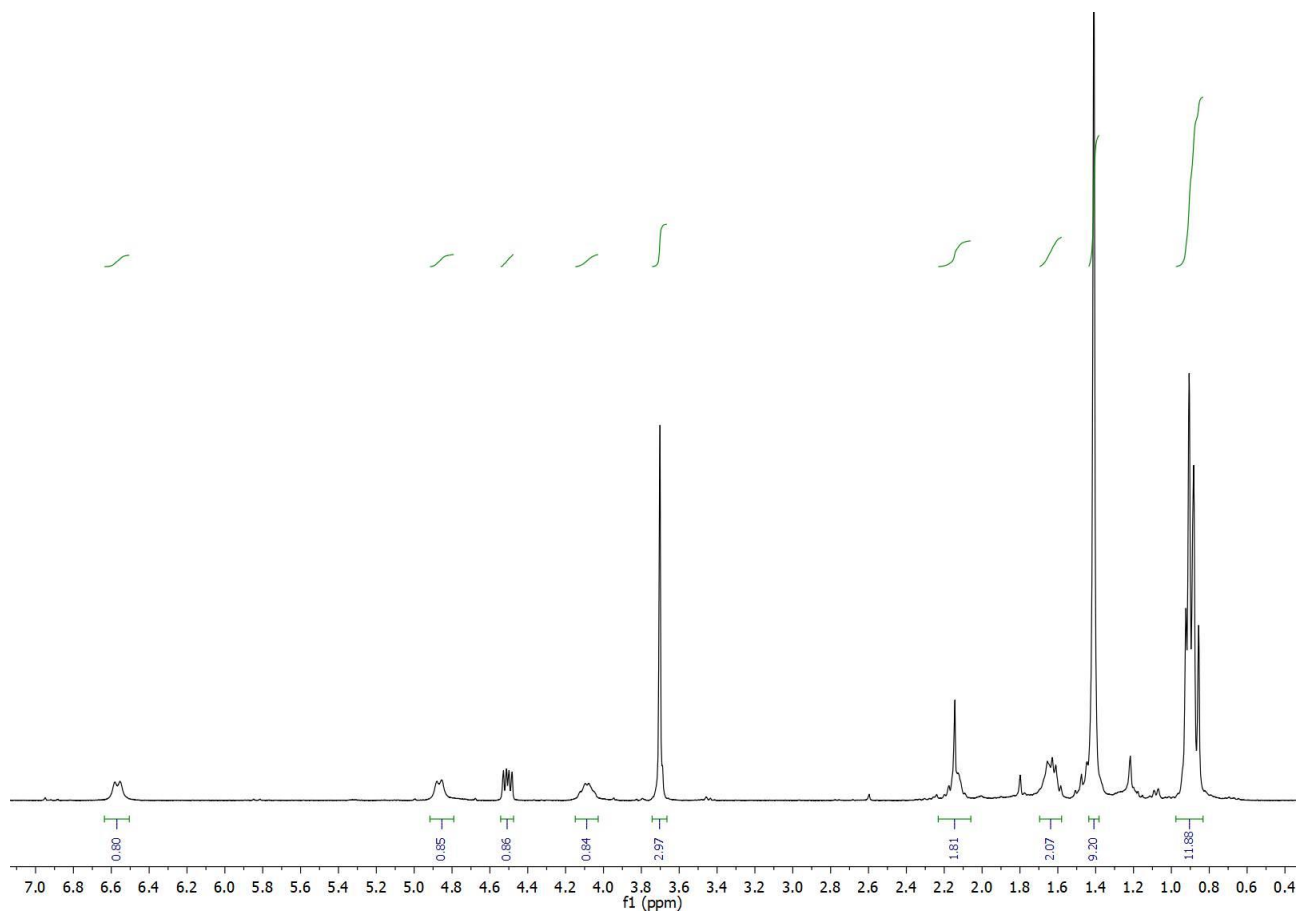
# MS (EI)



**N-Boc-L-Leu-L-Val-OMe (5b)**

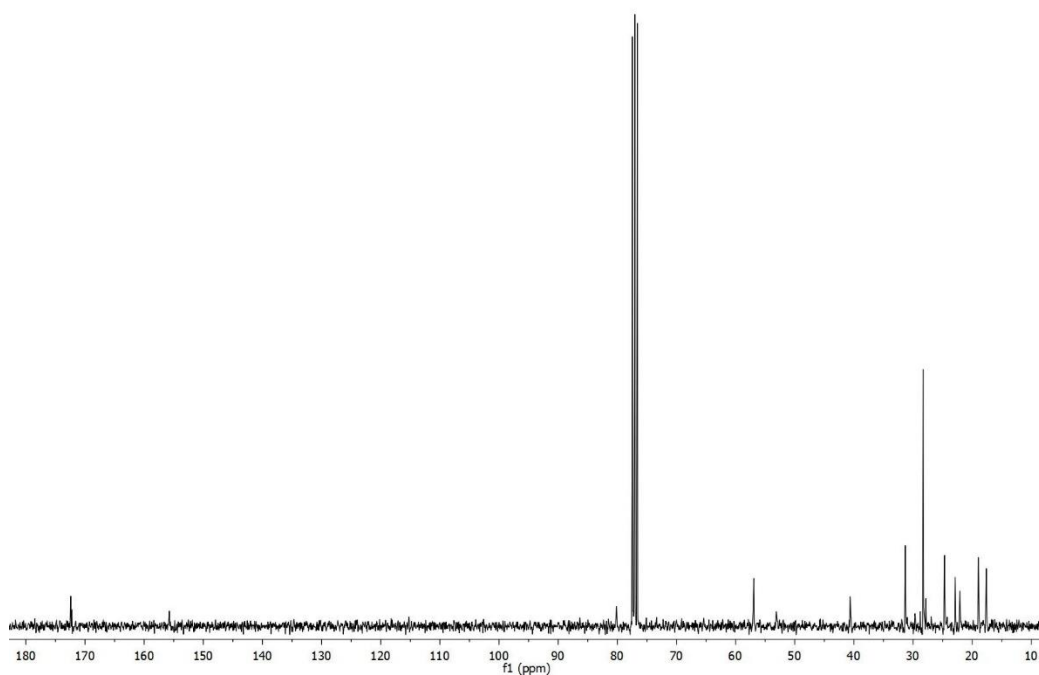


**$^1\text{H}$  NMR**

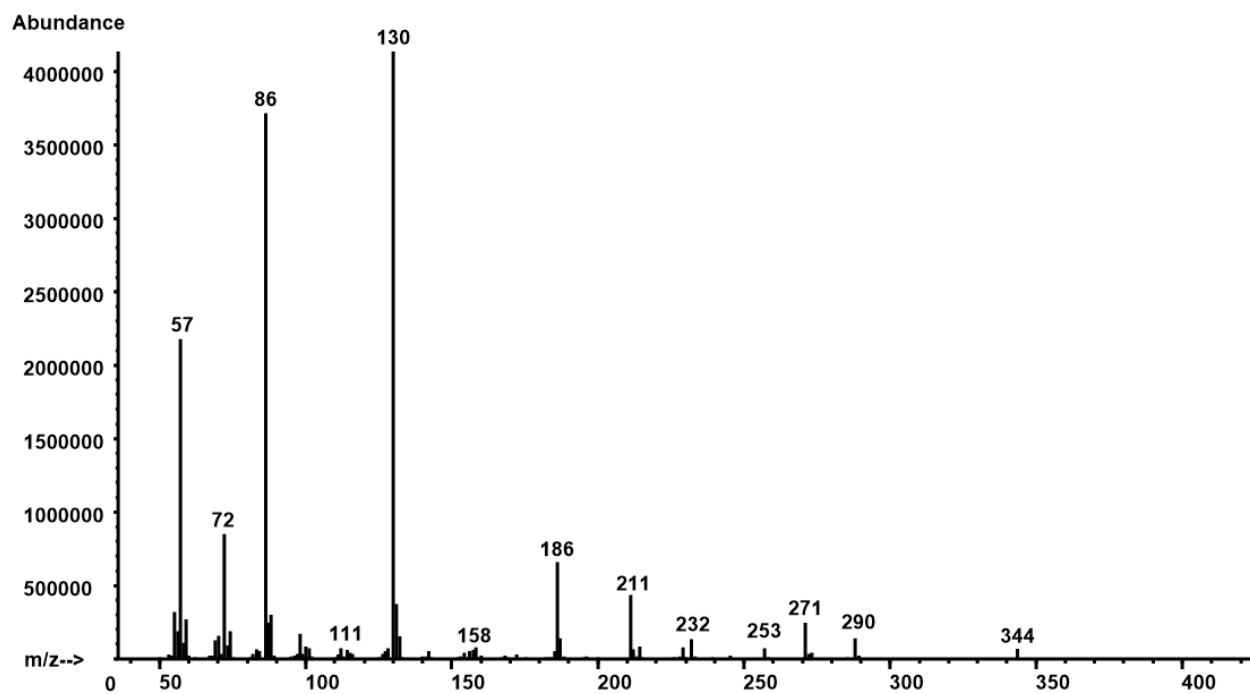


**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.57 ( $\text{d}_{\text{broad}}$ ,  $J = 8.0$  Hz, 1H, CONH), 4.87 (d,  $J = 8.2$  Hz, 1H, OCONH), 4.51 (dd,  $J = 8.0, 4.9$  Hz, 1H,  $\text{CHCOOMe}$ ), 4.09 (m, 1H,  $\text{CHCONH}$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 2.21-2.07 (d,  $J = 4.6$  Hz, 2H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ,  $\text{CH}(\text{CH}_3)_2$ ), 1.73-1.58 (m, 2H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.41 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.97-0.83 (m 12H,  $\text{CH}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ).

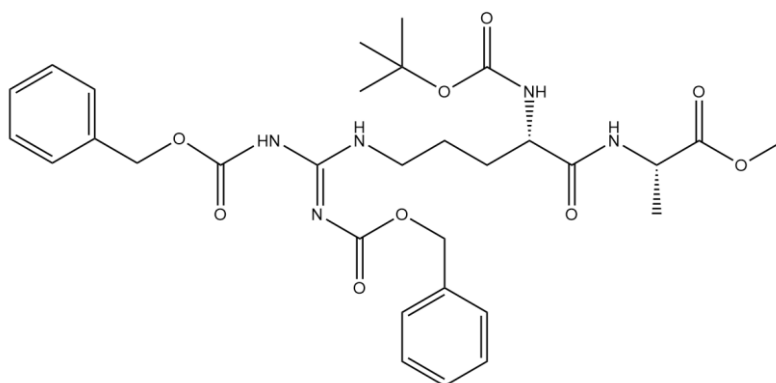
$^{13}\text{C}$  NMR



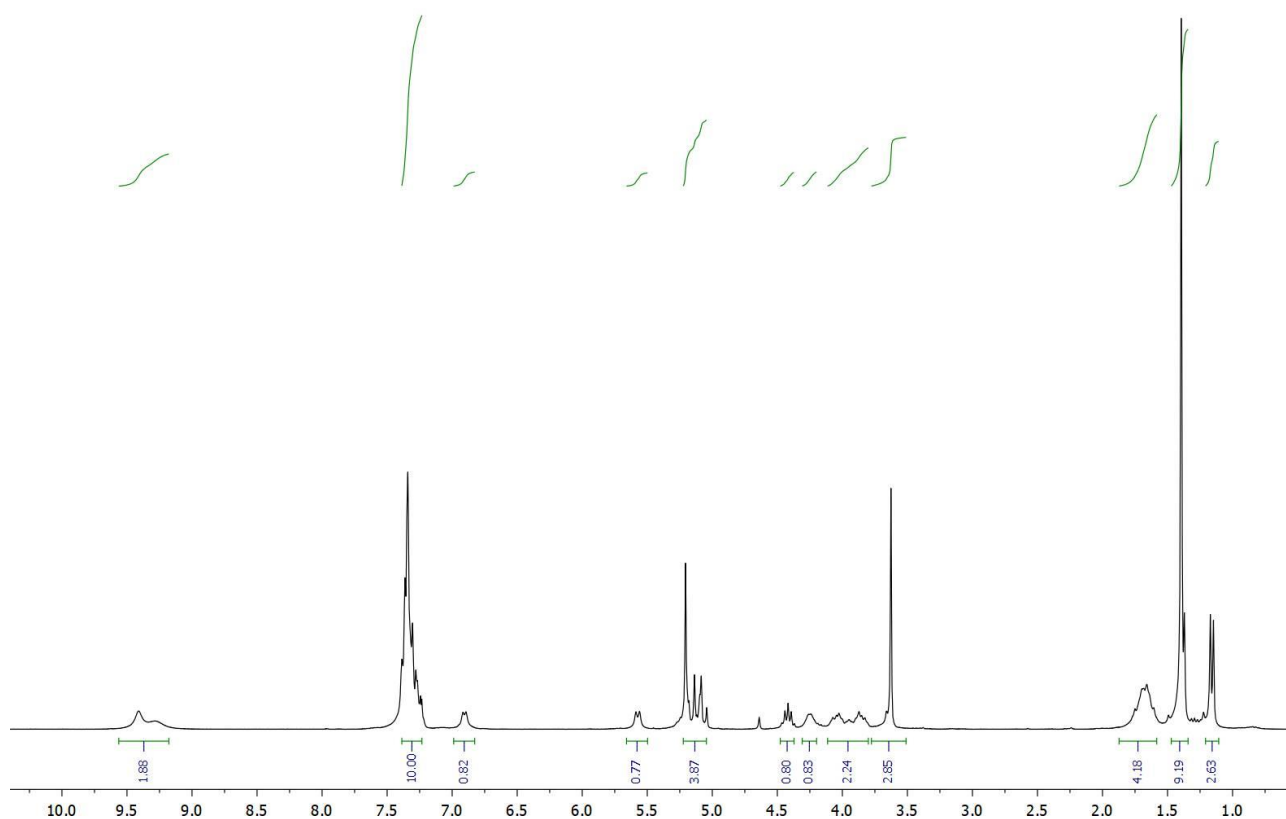
MS (EI)



**N-Boc-L-Arg(Z)<sub>2</sub>-L-Ala-OMe (6b)**

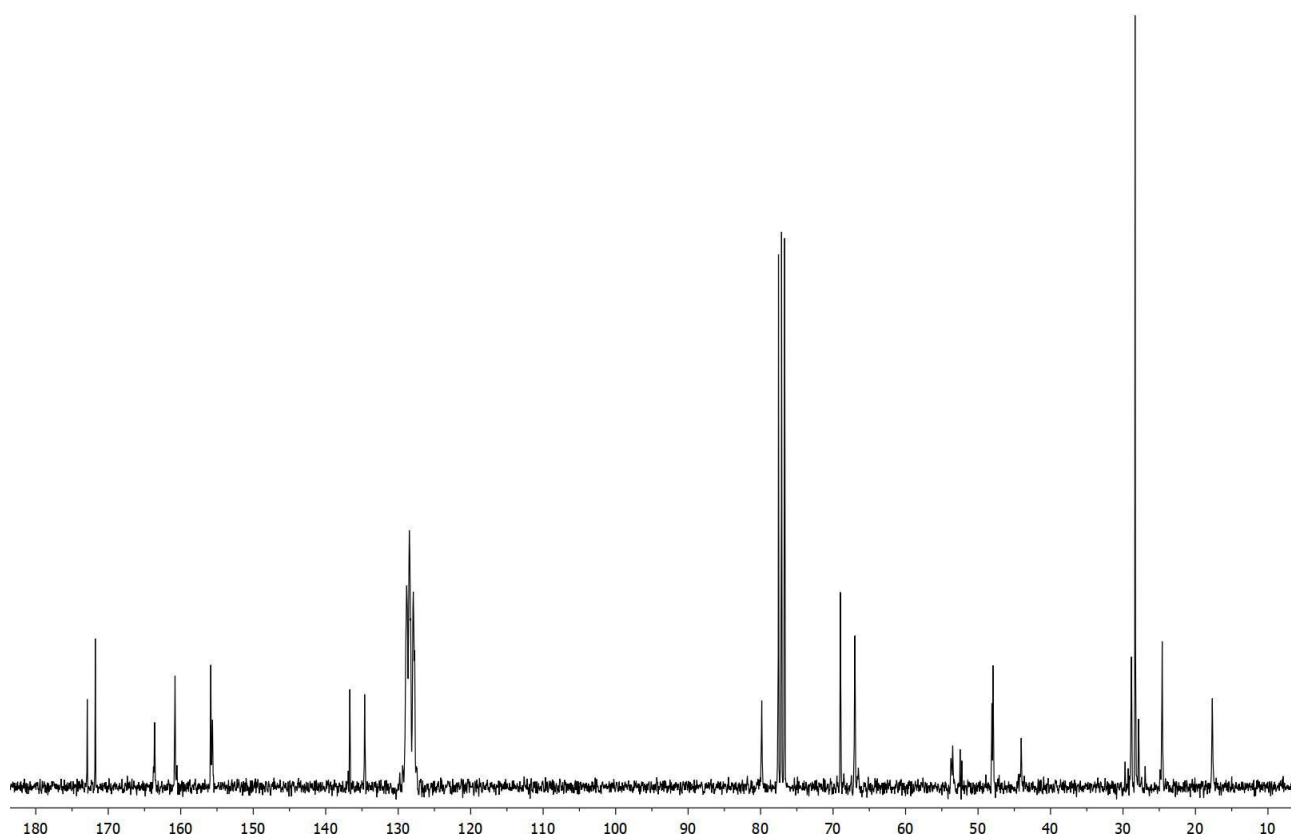


**<sup>1</sup>H NMR**



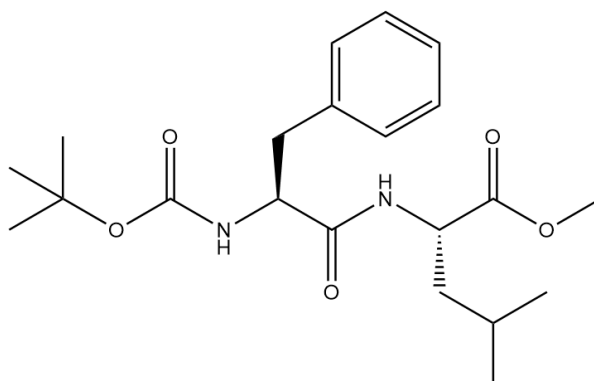
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  9.56 – 9.18 (m, 2H, NHZ, NH), 7.39 – 7.23 (m, 10H, ArH), 6.91 (d,  $J$  = 7.0 Hz, 1H, CONH), 5.57 (d,  $J$  = 8.4 Hz, 1H, OCONH), 5.22 – 5.05 (m, 4H, CH<sub>2</sub>Ph), 4.43 (m, 1H, CHCOOMe), 4.25 (m, 1H, CHCONH), 4.12 – 3.75 (m, 2H, CH<sub>2</sub>NH), 3.63 (s, 3H, OCH<sub>3</sub>), 1.82-1.55 (m, 4H, CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH), 1.39 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.16 (d,  $J$  = 7.2 Hz, 3H, CHCH<sub>3</sub>).

$^{13}\text{C}$  NMR

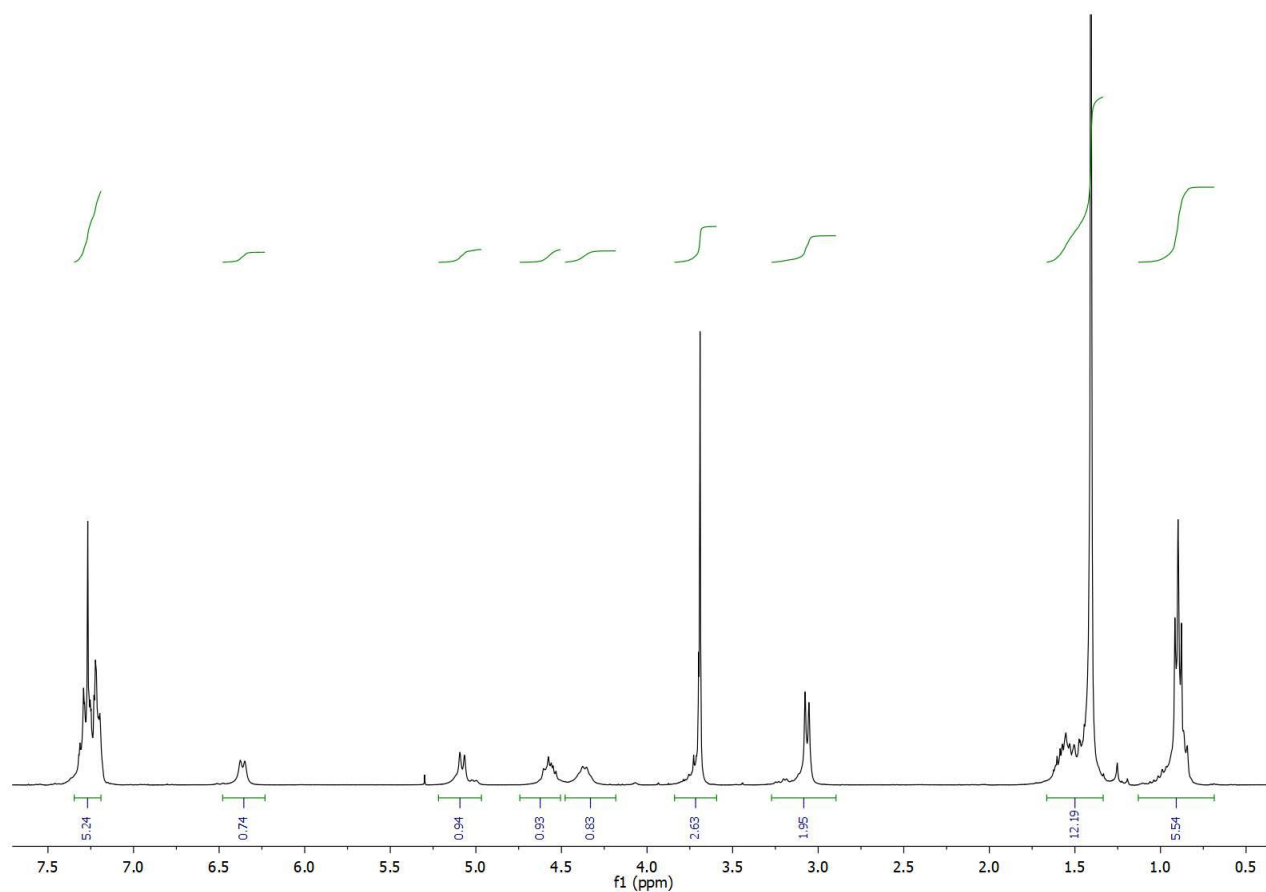




**N-Boc-L-Phe-L-Leu-OMe (7b)**

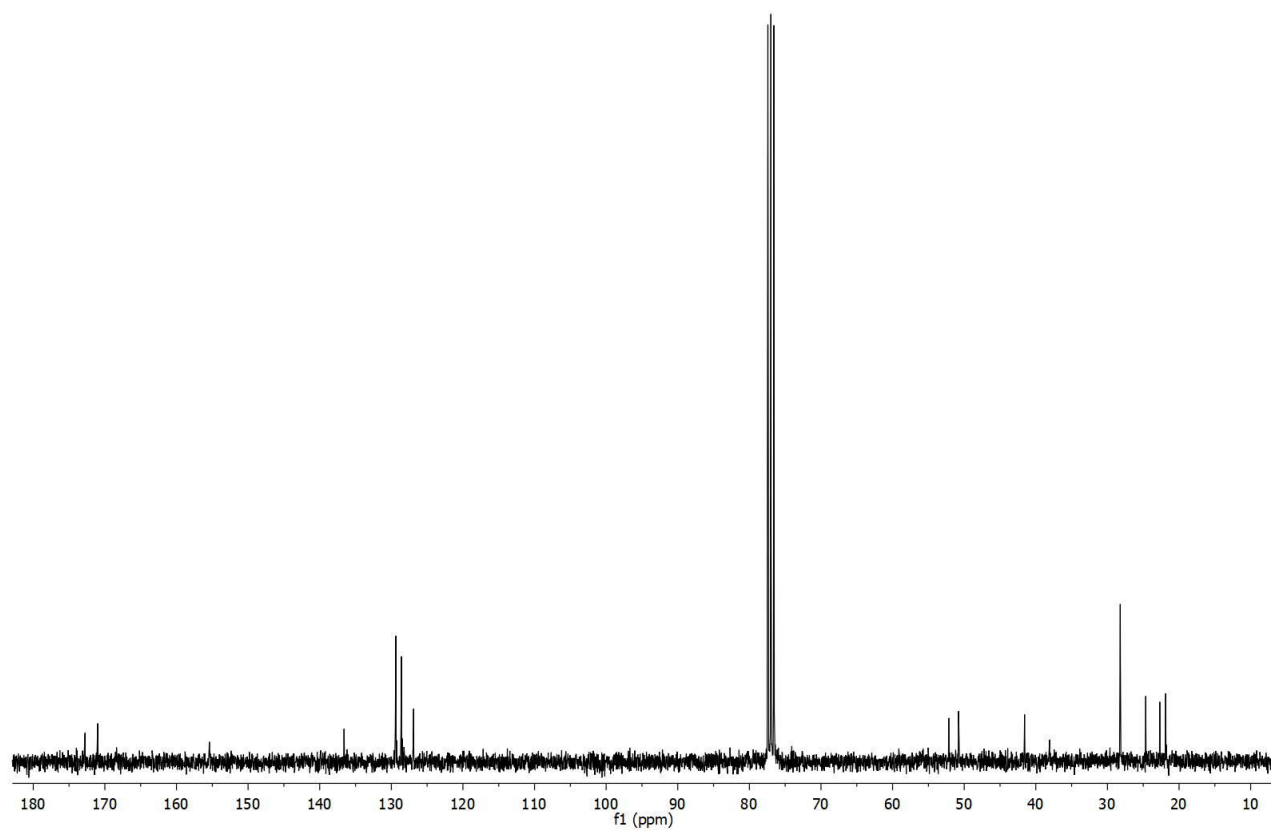


**$^1\text{H}$  NMR**

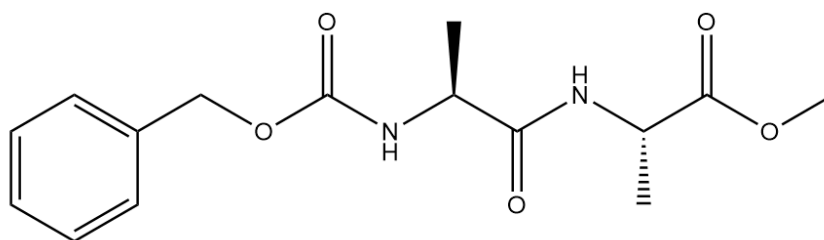


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.09 (m, 5H, ArH), 6.36 (d,  $J$  = 7.9 Hz, 1H, CONH), 5.08 (d,  $J$  = 8.0 Hz, 1H, OCONH), 4.57 (m, 1H,  $\text{CHCOOMe}$ ), 4.36 (m, 1H,  $\text{CHCONH}$ ), 3.69 (s, 3H,  $\text{OCH}_3$ ), 3.07 (d,  $J$  = 6.7 Hz, 2H,  $\text{CHCH}_2\text{Ph}$ ), 1.66 – 1.33 (m, 12H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ,  $\text{C}(\text{CH}_3)_3$ ), 1.03–0.75 (m, 6H,  $\text{CH}(\text{CH}_3)_2$ ).

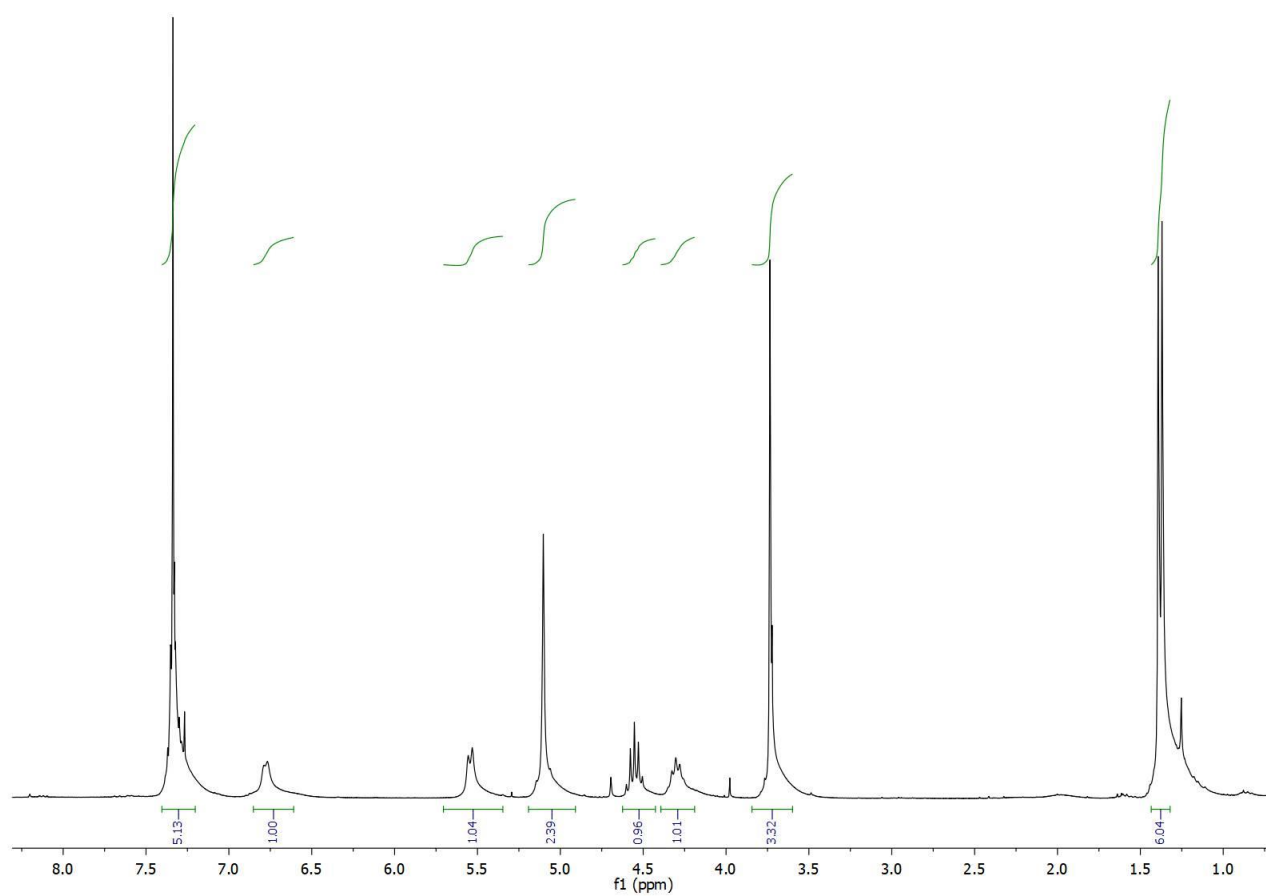
$^{13}\text{C}$  NMR



***N*-Z-L-Ala-L-Ala-OMe (1c)**

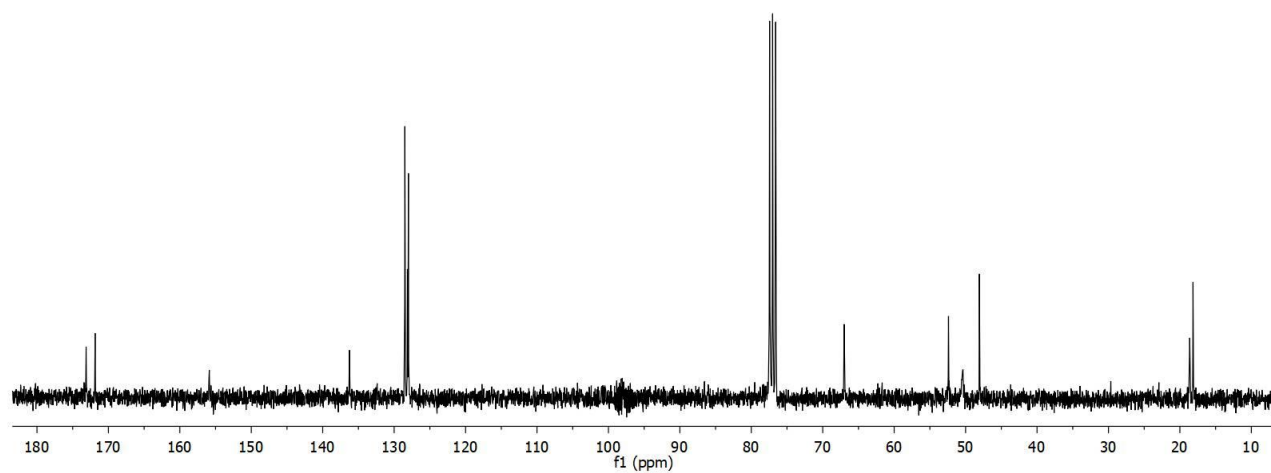


**$^1\text{H}$  NMR**

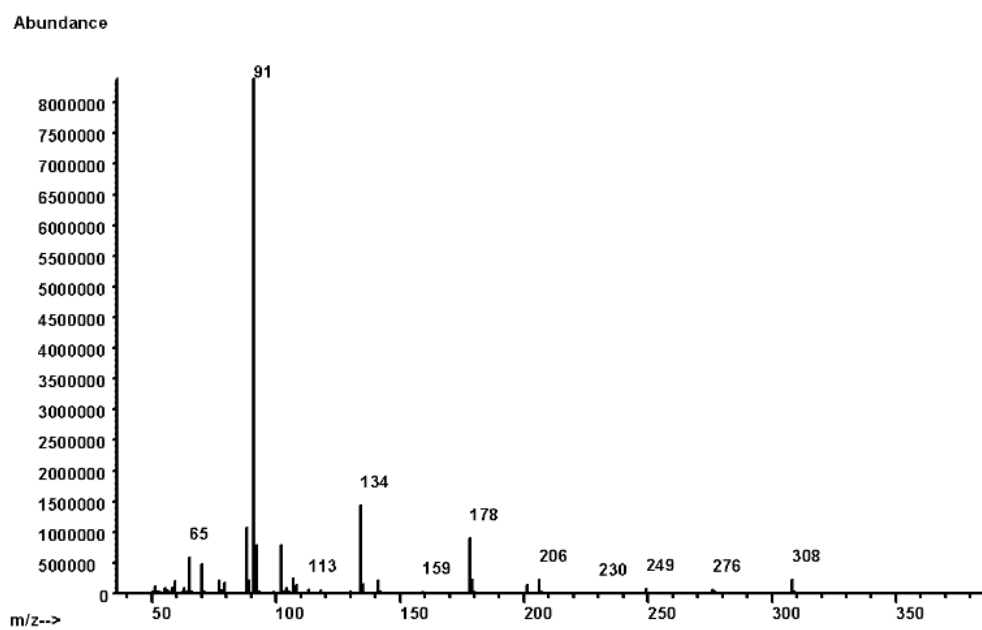


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.20 (m, 5H, ArH), 6.78 (d,  $J$  = 6.2 Hz, 1H, CONH), 5.54 (d,  $J$  = 7.5 Hz, 1H, OCONH), 5.10 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 4.55 (m, 1H,  $\text{CHCOOMe}$ ), 4.30 (m, 1H,  $\text{CHCH}_3$ ), 3.73 (s, 3H,  $\text{OCH}_3$ ), 1.38 (d,  $J$  = 7.0 Hz, 6H,  $\text{CH}_3$ ).

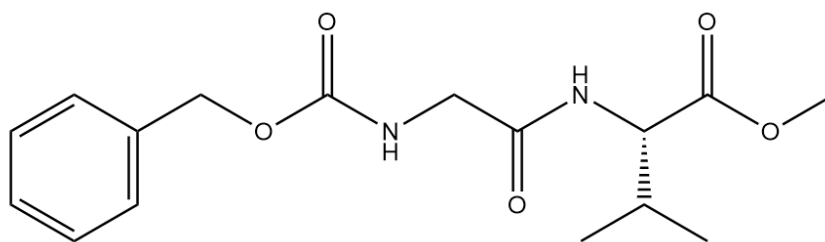
# <sup>13</sup>C NMR



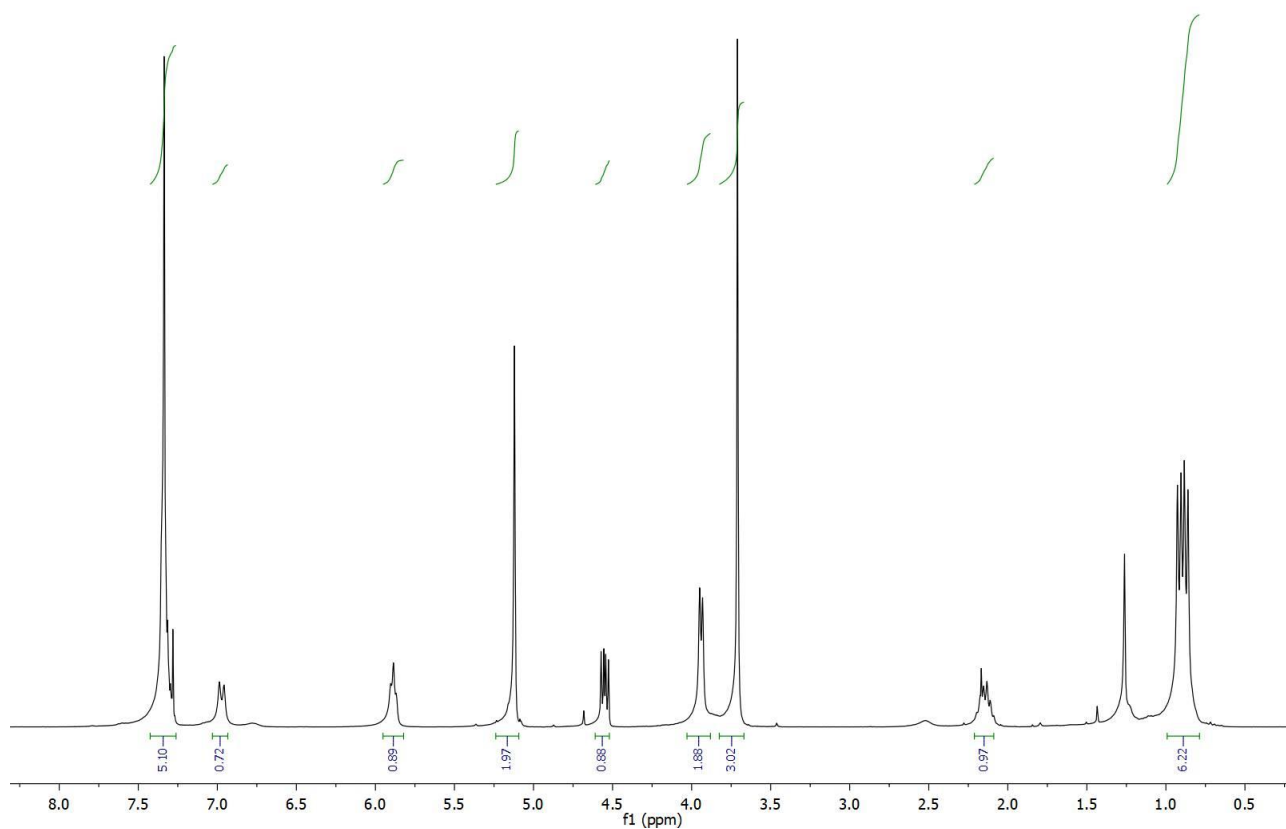
# MS (EI)



**N-Z-Gly-L-Val-OMe (2c)**

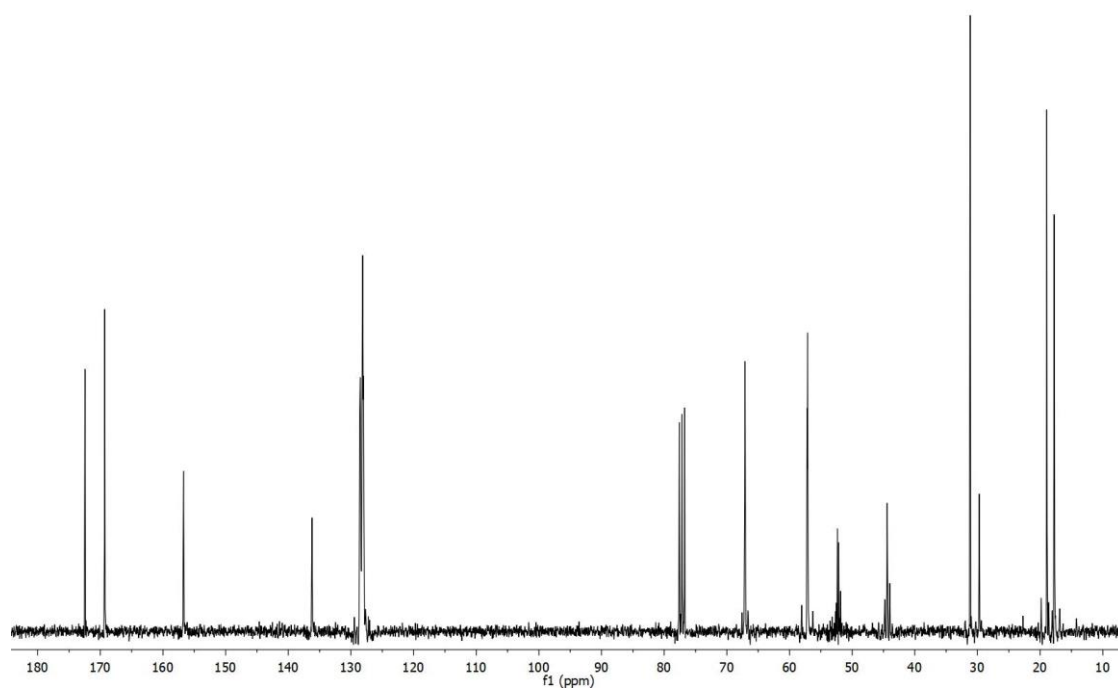


**$^1\text{H}$  NMR**

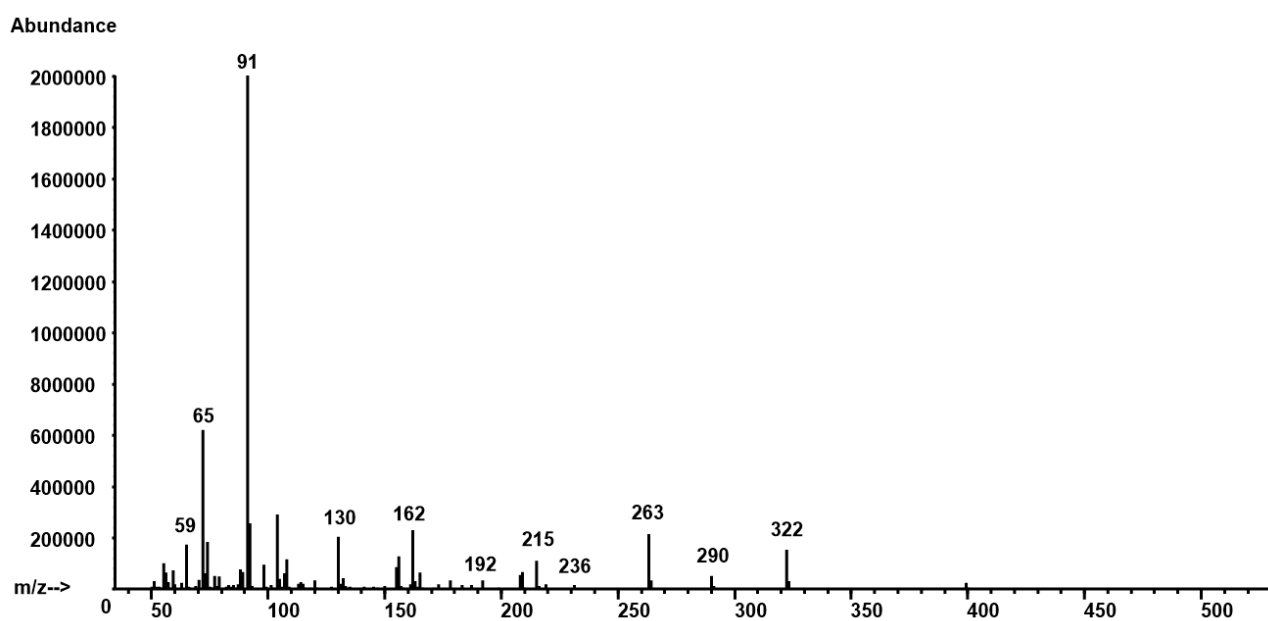


**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.26 (m, 5H, ArH), 6.97 (d,  $J$  = 8.8 Hz, 1H, CONH), 5.89 (m, 1H, OCONH), 5.12 (s, 2H,  $\text{CH}_2\text{Z}$ ), 4.55 (dd,  $J$  = 8.8, 5.2 Hz, 1H,  $\text{CHCOOMe}$ ), 3.94 (d,  $J$  = 5.5 Hz, 2H,  $\text{CH}_2\text{CONH}$ ), 3.71 (s, 3H,  $\text{OCH}_3$ ), 2.21-2.09 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 1.03-0.77 (m, 6H,  $\text{CH}(\text{CH}_3)_2$ ).

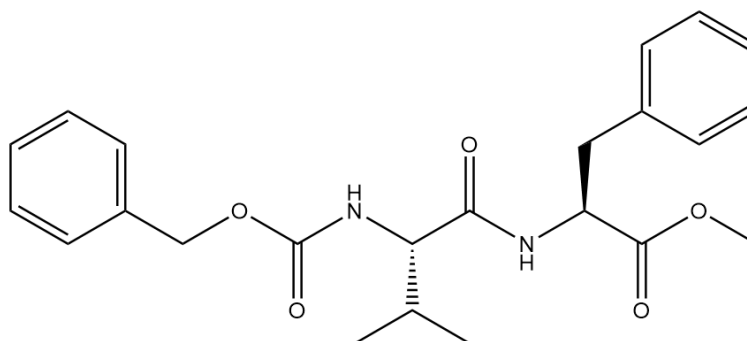
<sup>13</sup>C NMR



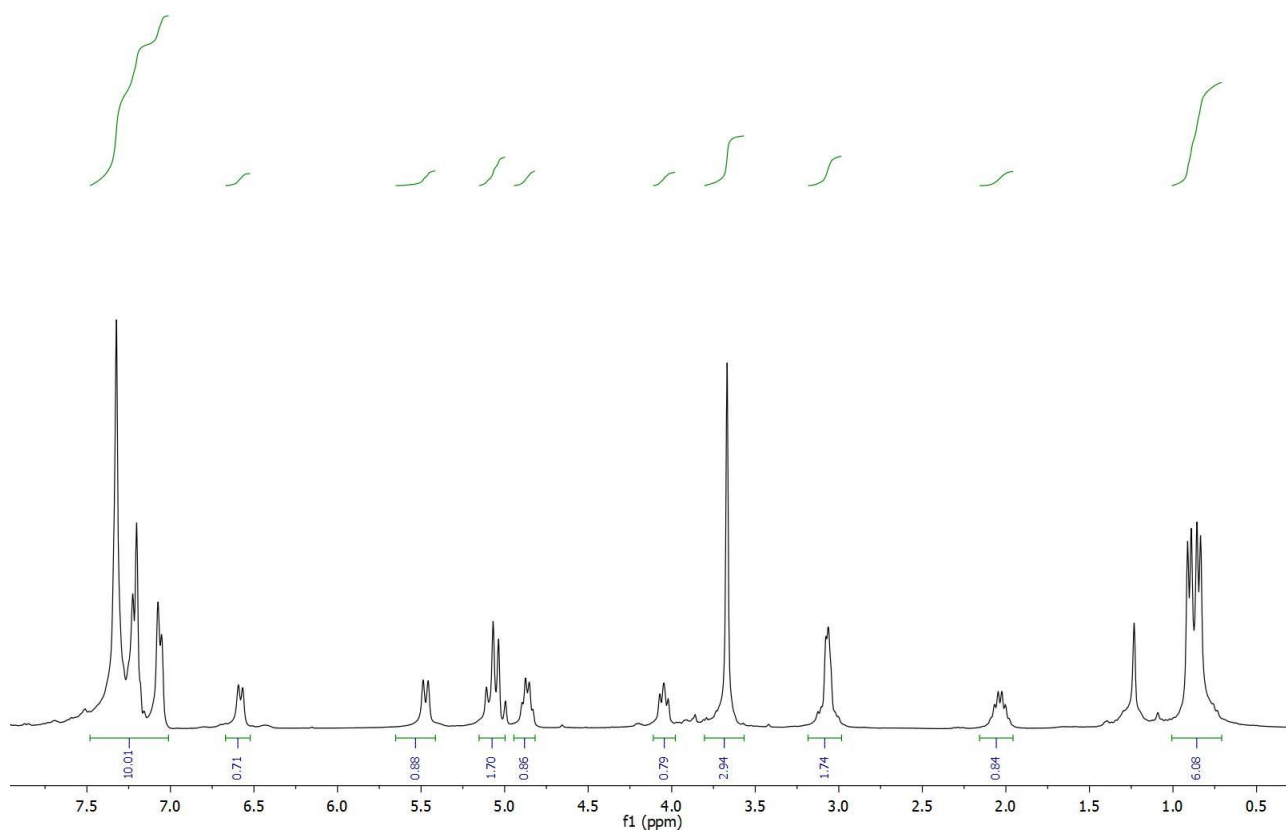
MS (EI)



***N*-Z-L-Val-L-Phe-OMe (3c)**



**<sup>1</sup>H NMR**



**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.51-7.00 (m, 10H, ArH), 6.58 (d, *J* = 7.6 Hz, 1H, CONH), 5.47 (d, *J* = 8.8 Hz, 1H, OCONH), 5.16-4.96 (m, 2H, CH<sub>2</sub>Z), 4.94-4.82 (m, 1H, CHCOOMe), 4.11-3.98 (m, 1H, CHCH(CH<sub>3</sub>)<sub>2</sub>), 3.67 (s, 3H, OCH<sub>3</sub>), 3.15-2.99 (m, 2H, CH<sub>2</sub>Ph), 2.02 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.97-0.73 (m, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

# MS (EI)

