# Supporting Information

# Precision Synthesis of Peptide Chimeras through Site-Specific Azomethine Ylide–Dehydroalanine Cycloaddition

Masaki Iwata,[1] Yuzuki Takami,[1] Sena Miura,[1] Hibiki Ohno,[1] Eunsang Kwon,[2,3] Naohiko Yoshikai,[1] and Kazuya Kanemoto*[1,4]

[1]*Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, 980-8578 (Japan)*
[2]*Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai, 980-8578 (Japan)*
[3]*Endowed Research Laboratory of Dimensional Integrated Nanomaterials, Graduate School of Science, Tohoku University, Sendai, 980-8578 (Japan)*
[4]*Chemical Bioscience Team, Laboratory for Biomaterials and Bioengineering, Institute of Integrated Research, Institute of Science Tokyo, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062 (Japan). Email: kanemoto.k.136d@m.isct.ac.jp*

## Contents



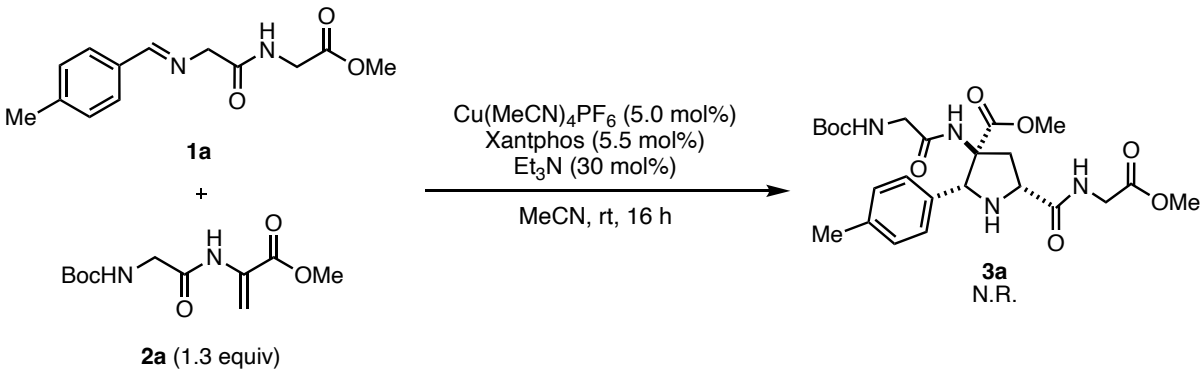
## General Remarks

All reactions were performed with dry glassware under atmosphere of nitrogen unless otherwise noted. The $^{1}$H NMR spectra were obtained with a Varian Mercury 400 NMR spectrometer at 400 MHz or a JEOL JNM-ECA-600 at 600 MHz. The $^{13}$C NMR spectra were obtained with a Varian Mercury 400 NMR spectrometer at 101 MHz or a JEOL JNM-ECA-600 at 150 MHz, respectively. All NMR measurements were carried out at 25 ºC unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ (δ 0.00 for $^{1}$H NMR in $CDCl_3$) or the solvent peak (δ 3.31 for $^{1}$H NMR in $CD_3OD$, δ 77.16 for $^{13}$C NMR in $CDCl_3$, or δ 49.00 for $^{13}$C NMR in $CD_3OD$). The abbreviations s, d, t, q, m, and br signify singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Melting points were determined with an MPA100 OptiMelt apparatus. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX- 303, a JEOL JMS-700, or a JEOL JMS-T100GC spectrometer with magnetic sector time-of-flight mass analyzer. Column chromatography was performed with silica gel (Kanto Chemical Co., Inc., 60 (spherical, neutral), 37563-84) or florisil (Kanto Chemical Co., Inc., 16231-08).

Methyl (2-((4-methylbenzylidene)amino)acetyl)glycinate (**1a**),[1] methyl (*S*)-(2-((4-methylbenzylidene)amino)propanoyl)glycinate (**1b**),[1] (2-((4-chlorobenzylidene)amino)acetyl)glycinate (**1c**),[1] Boc-Gly-Dha-OMe (**2a**),[2] Boc-L-Phe-Dha-OMe (**2b**),[3] Boc-L-Tyr-Dha-OMe (**2c**),[3] Boc-L-Val-Dha-OMe (**2d**),[3] Boc-L-Trp-Dha-OMe (**2e**),[3] Boc-Gly-Dhb-OMe (**2h**),[2] H-Gly-Gly-OMe (**4a**),[1] H-Gly-L-Phe-OMe·TFA (**4c**·TFA),[4]

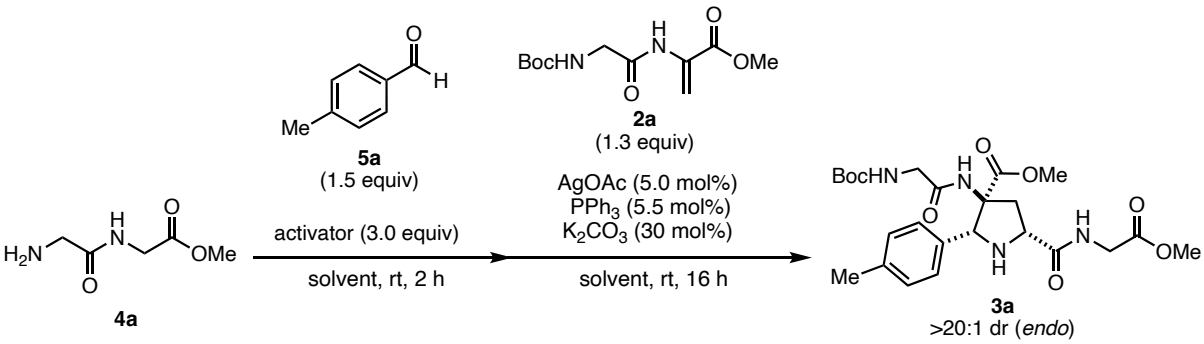
H-Gly-L-Pro-OMe·TFA (**4f**·TFA),[5] H-Gly-Gly-Gly-OMe (**4i**),[1] H-Gly-Gly-NHBn (**4j**),[1] 4-formylphenyl (*tert*-butoxycarbonyl)-*L*-valinate (**5k**), [6] and (1*S*,2*R*,3*R*,4*R*,6*R*)-4-(acetoxymethyl)-6-(4-formylphenoxy)cyclohexane-1,2,3-triyl triacetate (**5l**), [7] Boc-L-Leu-Dha-OMe (**7a**),[8] were prepared according to the reported methods. All other chemical reagents used were commercial grade and used as received.

## Conditions Study




Scheme S1. Copper-catalyzed [3+2] cycloaddition

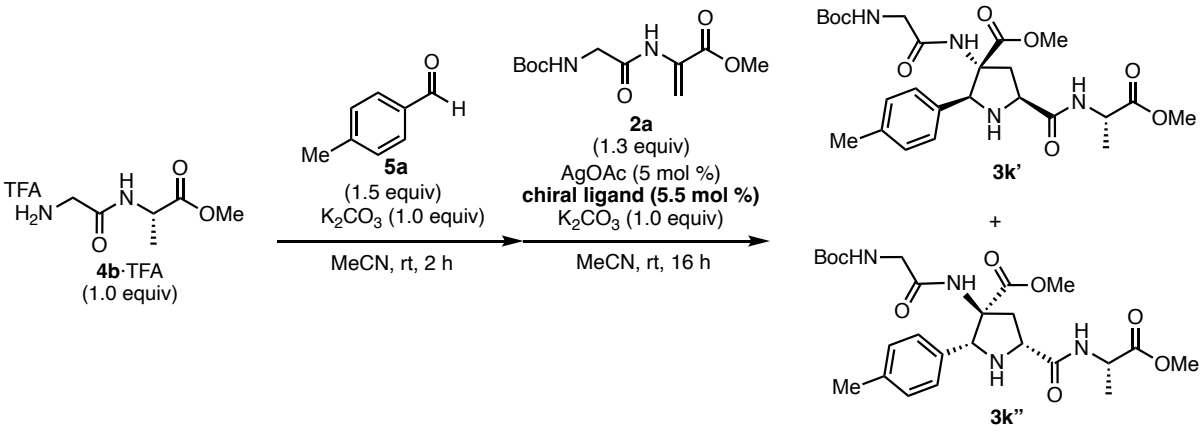
Table S1. Optimization of reaction conditions for one-pot reaction




| entry | activator | solvent | yield (%)[a] |
|---|---|---|---|
| 1 | - | MeCN | quant |
| 2 | $MgSO_4$ | MeCN | quant |
| 3[b] | - | MeCN | 26 |
| 4 | - | DMF | 96 |
| 5 | - | THF | 61 |
| 6 | - | acetone | 71 |
| 7 | $MgSO_4$ | acetone | 86 |

[a]Yields were determined by NMR analysis, unless otherwise noted. [b]Three components were added at the same time.

Table S2. Optimization of chiral ligands

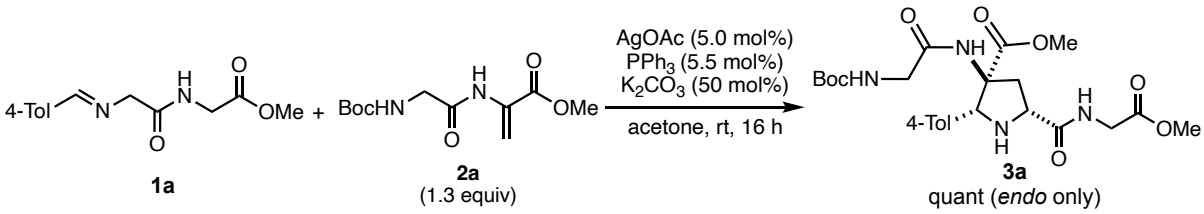



| entry | chiral ligand | yield (%)[a] | dr (3k':3k") |
|---|---|---|---|
| 1 | (*S*)-SEGPHOS | 72 | 91:9 |
| 2 | (*S*)-SEGPHOS | 62[b] | 87:13 |
| 3 | (*S*, $S_p$)-FcPHOX | 57 | 85:15 |
| 4 | (*R*)-Fesulphos | 77 | 90:10 |
| 5 | (*S*)-DTBM-SEGPHOS | 60[c] | >20:1 |
| 6 | (*R*)-SEGPHOS | 57 | 28:72 |
| 7 | (*R*)-DTBM-SEGPHOS | 40 | <1:20 |
| 8[c] | (*R*)-DTBM-SEGPHOS | 57[d] | <1:20 |

[a]Determined by $^1$H NMR. [b]Reaction was conducted at 0 °C. [c]Isolated yield. [d]10 mol% of silver catalyst and ligand were used.

**Experimental Procedures**

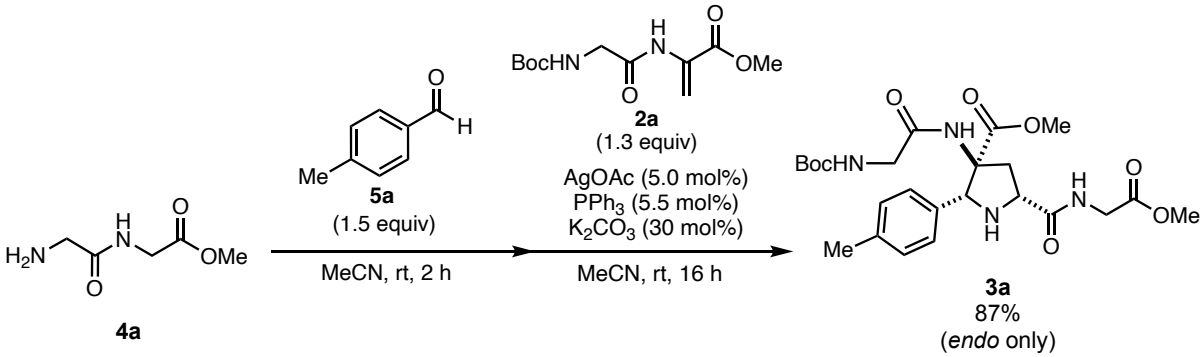
*A typical procedure for the [3+2] cycloaddition of iminopeptides **1** with dehydroalanines **2***




**1a** | **2a** (1.3 equiv) | **3a** quant (*endo* only)

A mixture of AgOAc (1.9 mg, 11 μmol) and $PPh_3$ (3.1 mg, 12 μmol) was dissolved in dry acetone (1.0 mL) at room temperature, and stirred for 30 minutes to prepare stock solution. Iminopeptide **1a** (12.4 mg, 49.9 μmol, 1.00 equiv), $K_2CO_3$ (3.6 mg, 26 μmol, 52 mol%), and dehydroalanine **2a** (16.8 mg, 65.0 μmol, 1.30 equiv) were dissolved in the 0.25 mL of the stock solution at room temperature. After stirring for 16 h at the same temperature, the mixture was diluted with 20 mL EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatograpy (florisil, 5 g, $CHCl_3$/MeOH = 100:1 to 10:1) to give methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3a**) (26.2 mg, 51.7 μmol, quant, >20:1 dr) as colorless oil.

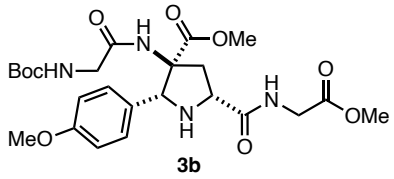
*A typical procedure for the one-pot [3+2] cycloaddition of free-base peptide **4** with aldehyde **5** and dehydroalanine **2***




**4a** | **5a** | **2a** | **3a** 87% (*endo* only)

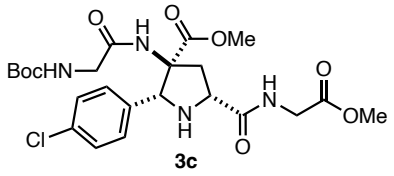
To a mixture of H-Gly-Gly-OMe (**4a**) (14.8 mg, 0.101 mmol, 1.00 equiv) dissolved in MeCN (0.5 mL) was added *p*-tolualdehyde (**5a**) (18.3 mg, 0.152 mmol, 1.50 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (5.3 mg, 32 μmol) and $PPh_3$ (8.7 mg, 33 μmol) was dissolved in dry MeCN (3.0 mL) at room temperature and stirred for 30 minutes to prepare stock solution. To crude imine were added dehydroalanine **2a** (33.8 mg, 0.131 mmol, 1.29 equiv), 0.5 mL of the stock solution, and $K_2CO_3$ (4.5 mg, 33 μmol, 32 mol%) at room temperature. After stirring for 16 h at the same temperature, the mixture was diluted with 20 mL EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (florisil, 2 g, $CHCl_3$/MeOH = 100:1 to 10:1) to give methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3a**) (44.3 mg, 87.6 μmol, 86.5%, >20:1 dr) as a colorless oil.

According to the procedure for preparing methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3a**), **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j, 3q**, **3s**, **3t**, **3u**, **3v**, **3w**, **3x**, **3y**, **3z**, **3aa**, **8a**, and **8b** were prepared from the corresponding peptides **4**, aldehydes **5**, and dehydroalanines **2**.



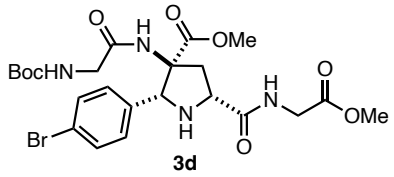
**3b**

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate (**3b**) (44.7 mg, 85.1%, >20:1 dr).



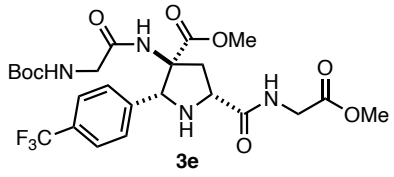
**3c**

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(4-chlorophenyl)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3c**) (48.9 mg, 92.3%, >20:1 dr).



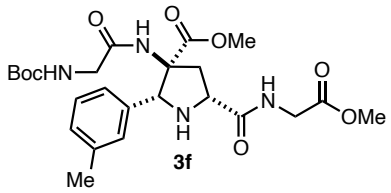
**3d**

Methyl (2*R**,3*S**,5*R**)-2-(4-bromophenyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3d**) (52.3 mg, 91.0%, >20:1 dr).

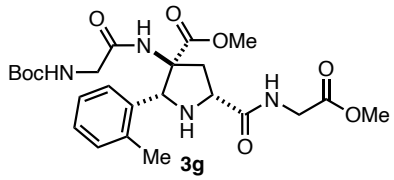


**3e**

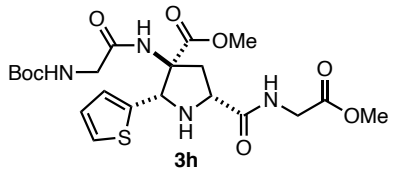
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylate (**3e**) (48.8 mg, 87.2%, >20:1 dr).



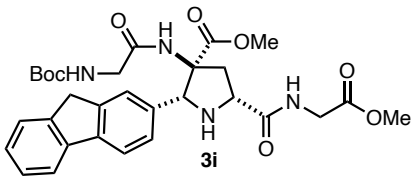

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*m*-tolyl)pyrrolidine-3-carboxylate (**3f**) (46.1 mg, 89.9%, >20:1 dr).



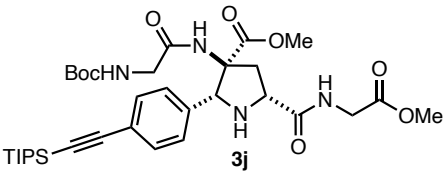

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*o*-tolyl)pyrrolidine-3-carboxylate (**3g**) (35.7 mg, 69.6%, >20:1 dr).



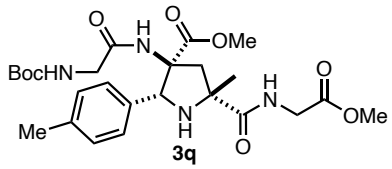

Methyl (2*S**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(thiophen-2-yl)pyrrolidine-3-carboxylate (**3h**) (31.2 mg, 62.2%, >20:1 dr).



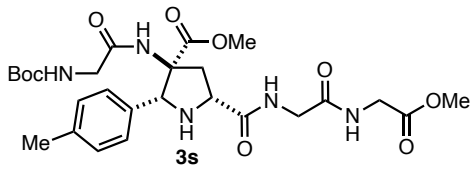

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(9*H*-fluoren-2-yl)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3i**) (42.0 mg, 71.4%).



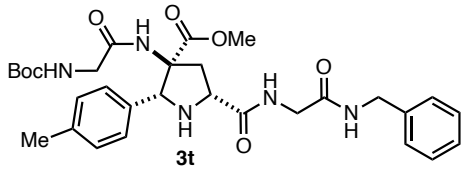

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-((triisopropylsilyl)ethynyl)phenyl)pyrrolidine-3-carboxylate **(3j)** (64.3 mg, 93.0%, >20:1 dr)



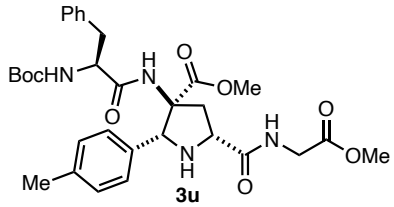
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-5-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3q**) (26.6 mg, 51.4%, >20:1 dr, preformed iminopeptide (1.0 equiv), AgOAc (20 mol%), $PPh_3$ (22 mol%), $K_2CO_3$ (1.0 equiv) were used. Reaction was conducted at 50 °C.).



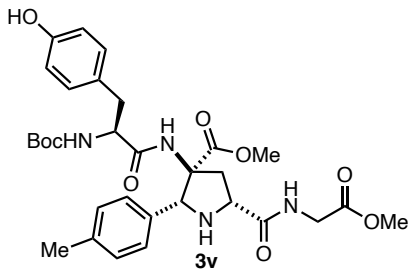
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3s**) (37.1 mg, 64.6%, 75:25 dr)



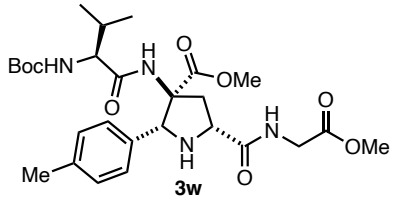
Methyl (2*R**,3*S**,5*R**)-5-((2-(benzylamino)-2-oxoethyl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3t**) (45.9 mg, 78.3%, >20:1 dr).



Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3u**) (43.6 mg, 71.7%, 54:46 dr).

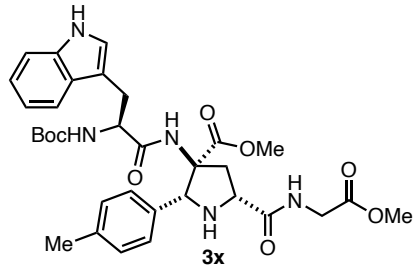


Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3v**) (48.6 mg, 79.4%, 52:48 dr).



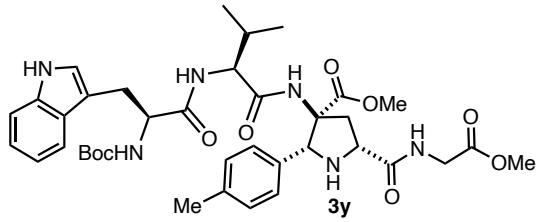
**3w**

Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w**) (53.5 mg, 97.6%, 54:46 dr),



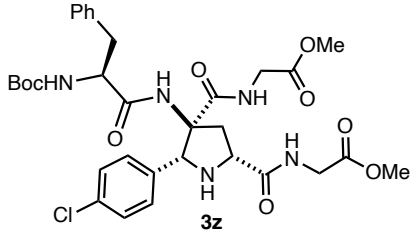
**3x**

Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3x**) (64.3 mg, quant, 55:45 dr)



**3y**

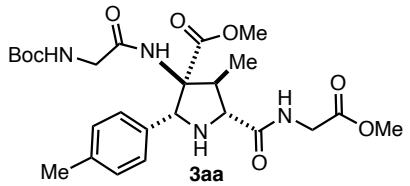
Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3y**) (26.7 mg, 69.9%, 51:49 dr),



**3z**

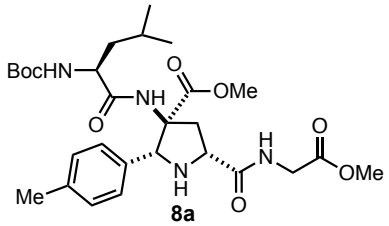
Dimethyl 2,2'-(((2*R**,4*S**,5*R**)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-(4-chlorophenyl)pyrrolidine-2,4-dicarbonyl)bis(azanediyl))diacetate (**3z**) (23.1 mg, NMR yield: quant, isolated yield: 66.7%, 52:48 dr, preformed iminopeptide (1.0

equiv), AgOAc (20 mol%), $PPh_3$ (22 mol%), and $K_2CO_3$ (1.0 equiv) were used. Reaction was conducted at 37 °C.).



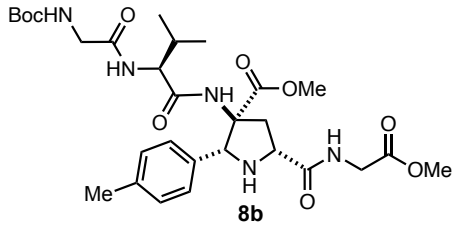

**3aa**

Methyl (2*R**,3*S**,4*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-4-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3aa**) (11.2 mg, 41.9%, >20:1 dr, $K_2CO_3$ (1.0 equiv) was used in [3+2] cycloaddition).




**8a**

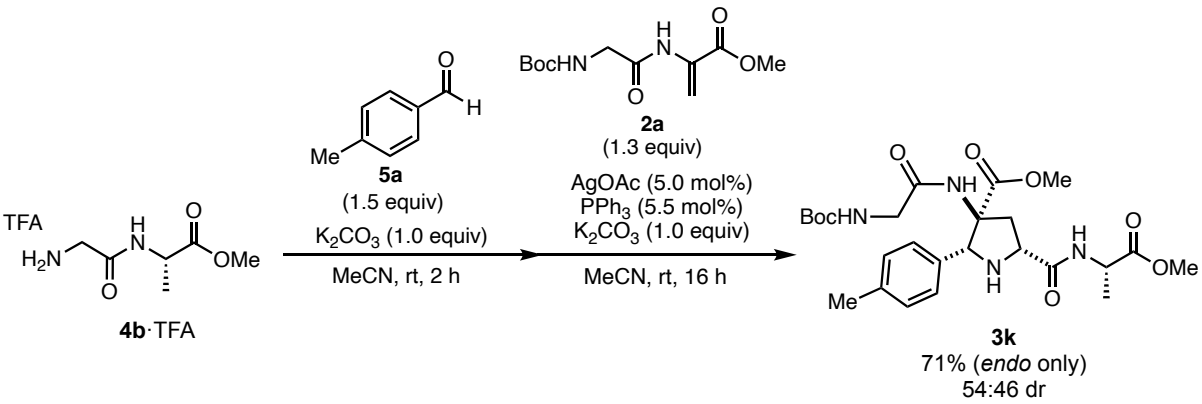
Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8a**) (53.4 mg, 94.3%, 56:44 dr, preformed imine was used.).




**8b**

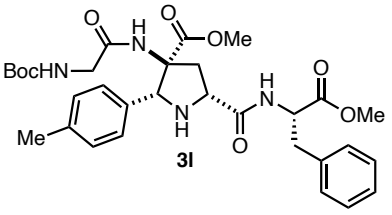
Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8b**) (47.1 mg, 77.8%, 50:50 dr, preformed imine was used.).

*A typical procedure for the one-pot [3+2] cycloaddition of peptide salt **4**·TFA with aldehyde **5** and dehydroalanine **2***

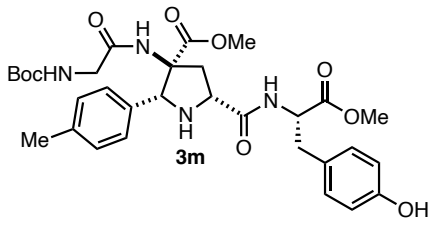



To a mixture of H-Gly-L-Ala-OMe·TFA (**4b**·TFA) (27.5 mg, 0.100 mmol, 1.00 equiv) dissolved in MeCN (0.5 mL) were added *p*-tolualdehyde (**5a**) (18.3 mg, 0.152 mmol, 1.52 equiv) and $K_2CO_3$ (14.2 mg, 0.103 mmol, 1.02 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (5.4 mg, 32 μmol) and $PPh_3$ (8.8 mg, 34 μmol) was dissolved in dry MeCN (3.0 mL) at room temperature and stirred for 30 minutes to prepare stock solution. To crude imine were added dehydroalanine **2a** (33.7 mg, 0.130 mmol, 1.30 equiv), 0.5 mL of the stock solution, and $K_2CO_3$ (13.8 mg, 99.8 μmol, 1.00 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was diluted with 20 mL EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (florisil, 2 g, $CHCl_3$/MeOH = 100:1 to 10:1) to give methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k**) (36.8 mg, 70.6 μmol, 70.7%, 54:46 dr) as a colorless oil.

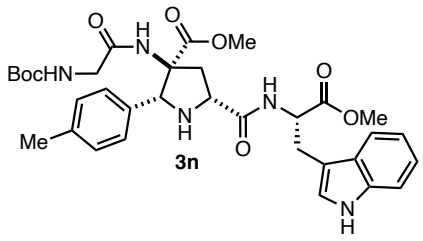
According to the procedure for preparing methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k**), **3l**, **3m**, **3n**, **3o**, and **3r** were prepared from the corresponding peptides **4**·TFA, aldehydes **5**, and dehydroalanines **2**.



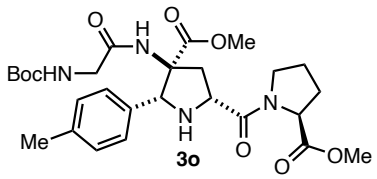

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3l**) (56.1 mg, 94.1%, 54:46 dr)



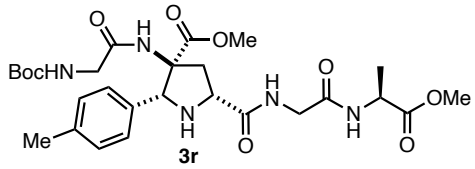

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3m**) (39.8 mg, 78.6%, 54:46 dr)




Methyl (2*R**,3*S**,5*R**)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n**) (56.7 mg, 89.0%, 51:49 dr)

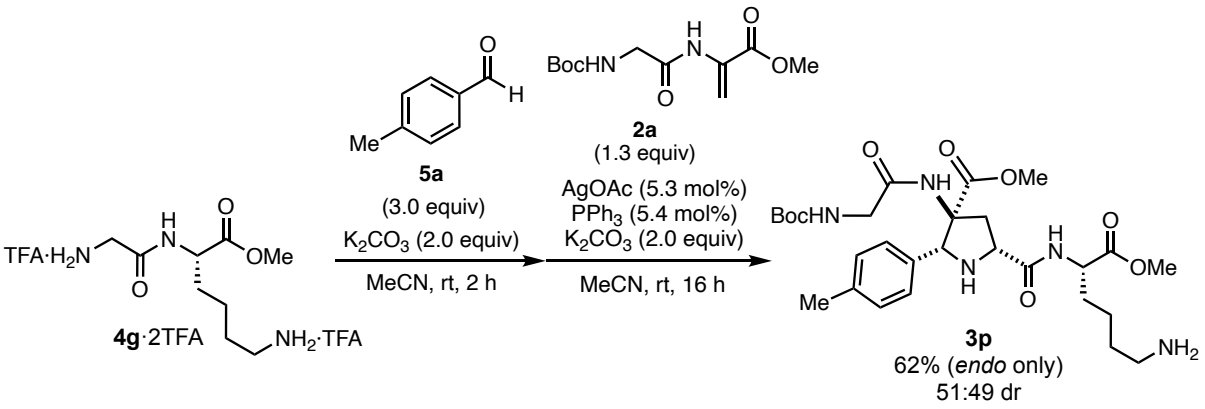



Methyl ((2*R**,4*S**,5*R**)-4-(2-((*tert*-butoxycarbonyl)amino)acetamido)-4-(methoxycarbonyl)-5-(*p*-tolyl)pyrrolidine-2-carbonyl)-*L*-prolinate (**3o**) (51.4 mg, 94.1%, 61:39 dr)



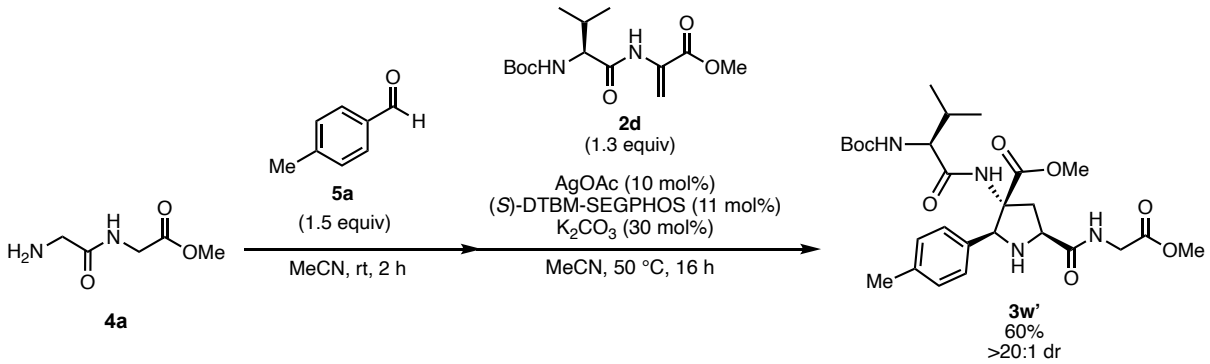

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3r**) (45.4 mg, 78.7%, 54:46 dr)

*Procedure for the one-pot [3+2] cycloaddition of H-Gly-L-Lys-OMe·2TFA (**4g**·2TFA) with aldehyde **5a** and dehydroalanine **2a***



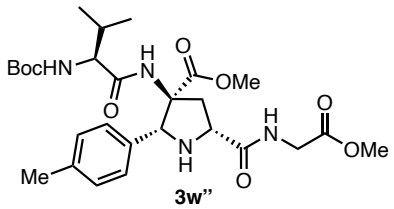

To a mixture of H-Gly-L-Lys-OMe·2TFA (**4g**·2FTA) (22.7 mg, 51.0 μmol, 1.00 equiv) dissolved in MeCN (0.25 mL) were added *p*-tolualdehyde (**5a**) (18.5 mg, 0.154 mmol, 3.02 equiv) and $K_2CO_3$ (13.6 mg, 98.4 μmol, 1.93 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (3.6 mg, 22 μmol) and $PPh_3$ (5.8 mg, 22 μmol) was dissolved in dry MeCN (2.0 mL) at room temperature and stirred for 30 minutes to prepare stock solution. To crude imine were added dehydroalanine **2a** (17.1 mg, 66.2 μmol, 1.30 equiv), 0.25 mL of the stock solution, and $K_2CO_3$ (13.8 mg, 0.998 mmol, 1.96 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was diluted with 20 mL EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in MeOH (0.25 mL), and added $MeONH_2$·HCl (126 mg, 1.51 mmol) at room temperature. After stirring for 3 h at the same temperature, to the mixture was added $Et_3N$ (0.150 mL, 1.08 mmol), and concentrated under reduced pressure. The residue was purified by column chromatography (amino silica gel (NH-DM2035), 2 g, $CHCl_3$/MeOH = 100:1 to 10:1) to give methyl (2*R**,3*S**,5*R**)-5-(((*S*)-6-amino-1-methoxy-1-oxohexan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3p**) (18.3 mg, 31.7 μmol, 62.1%, 51:49 dr) as a colorless oil.

*Diastereoselective [3+2] cycloaddition using (S)-and (R)-DTBM-SEGPHOS*

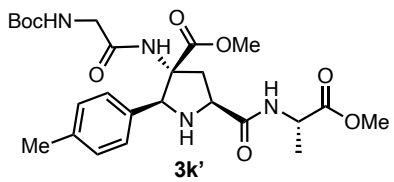



To a mixture of H-Gly-Gly-OMe (**4a**) (7.6 mg, 52 μmol, 1.0 equiv) dissolved in MeCN (0.25 mL) was added *p*-tolualdehyde (**5a**) (9.5 mg, 79 μmol, 1.5 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (4.3 mg, 26 μmol) and (*S*)-DTBM-SEGPHOS (32.3 mg, 27.4 μmol) was dissolved in MeCN (1.25 mL) at room temperature and stirred for 30 minutes to prepare stock solution. To crude imine were added dehydroalanine **2d** (19.7 mg, 65.6 μmol, 1.26 equiv), 0.25 mL of the stock solution, and $K_2CO_3$ (2.7 mg, 20 μmol, 0.38 equiv) at room temperature. After stirring for 16 h at 50 °C, the mixture was diluted with 20 mL EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (florisil, 2 g, $CHCl_3$/MeOH = 100:1 to 10:1) to give methyl (2*S*,3*R*,5*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w'**) (17.1 mg, 31.2 μmol, 59.9%, >20:1 dr) as a colorless solid.

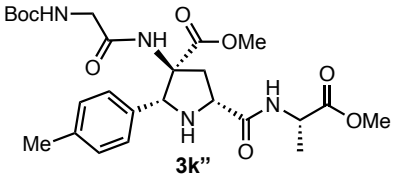
According to the procedure for preparing methyl (2*S*,3*R*,5*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w'**), **3w"**, **3k'**, **3k"**, **3n'**, and **3n"** were prepared from the corresponding peptides **4**, aldehydes **5**, and dehydroalanines **2** using corresponding chiral ligand.



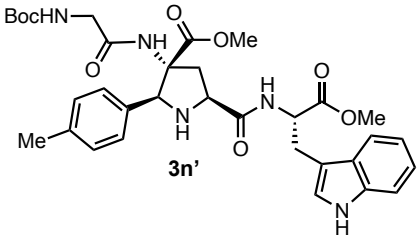

Methyl (2*R*,3*S*,5*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w"**) (22.9 mg, 41.7 μmol, 81.3%, <1:20 dr, ligand: (*R*)-DTBM-SEGPHOS)



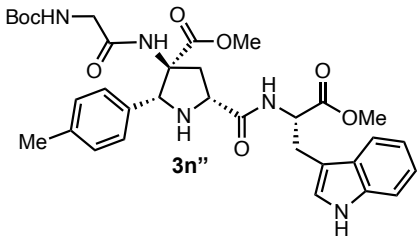
Methyl (2*S*,3*R*,5*S*)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k'**) (18.9 mg, 36.3 μmol, 70.6%, >20:1 dr, ligand: (*S*)-DTBM-SEGPHOS, The TFA salt of the peptide was used, and 1.0 equiv of $K_2CO_3$ was added for both imine formation and the subsequent cycloaddition.).




Methyl (2*R*,3*S*,5*R*)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k"**) (18.9 mg, 36.3 μmol, 72.1%, <1:20 dr, ligand: (*R*)-DTBM-SEGPHOS, The TFA salt of the peptide was used, and 1.0 equiv of $K_2CO_3$ was added for both imine formation and the subsequent cycloaddition.).

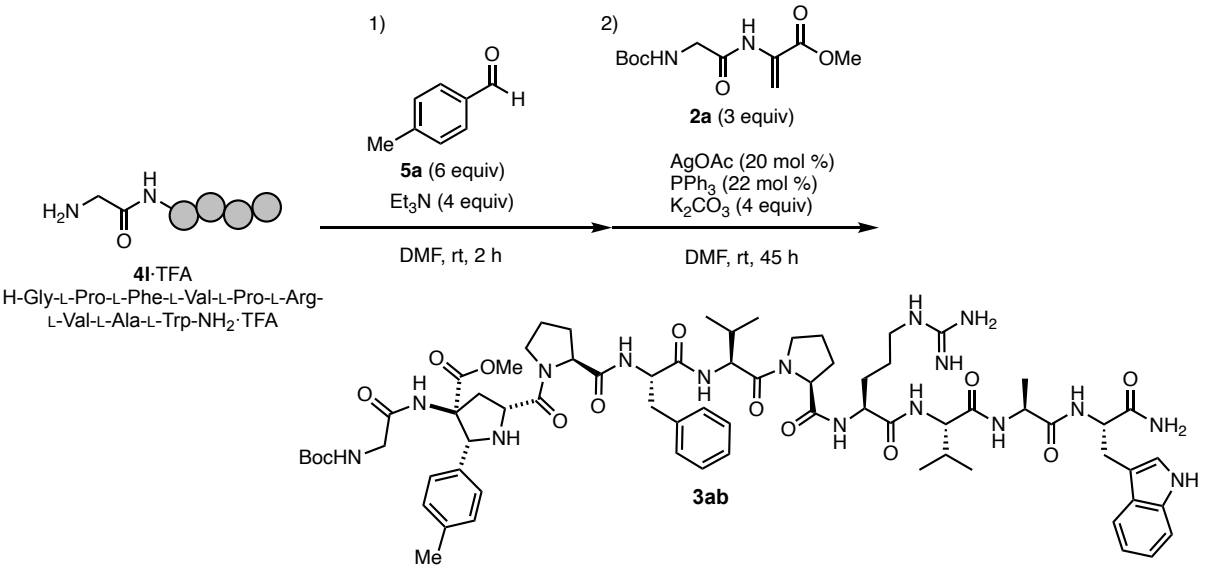



Methyl (2*S*,3*R*,5*S*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n'**) (16.5 mg, 26.0 μmol, 51.5%, >20:1 dr, ligand: (*S*)-DTBM-SEGPHOS, The TFA salt of the peptide was used, and 1.0 equiv of $K_2CO_3$ was added for both imine formation and the subsequent cycloaddition.).



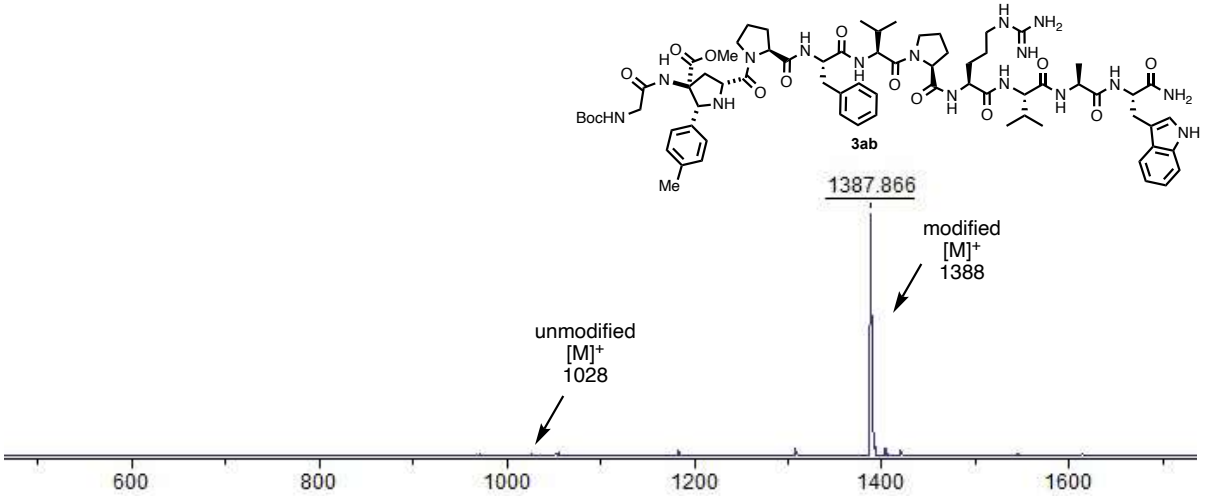

Methyl (2*R*,3*S*,5*R*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n"**) (21.0 mg, 33.3 μmol, 64.9%, <1:20 dr, ligand: (*R*)-DTBM-SEGPHOS, The TFA salt of the peptide was used, and 1.0 equiv of $K_2CO_3$ was added for both imine formation and the subsequent cycloaddition.).

*One-pot [3+2]cycloaddition of H-Gly-L-Pro-L-Phe-L-Val-L-Pro-L-Arg-L-Val-L-Ala-L-Trp-$NH_2$·TFA (**4l**·TFA) with p-tolualdehyde (**5a**) and dehydroalanine (**2a**)*

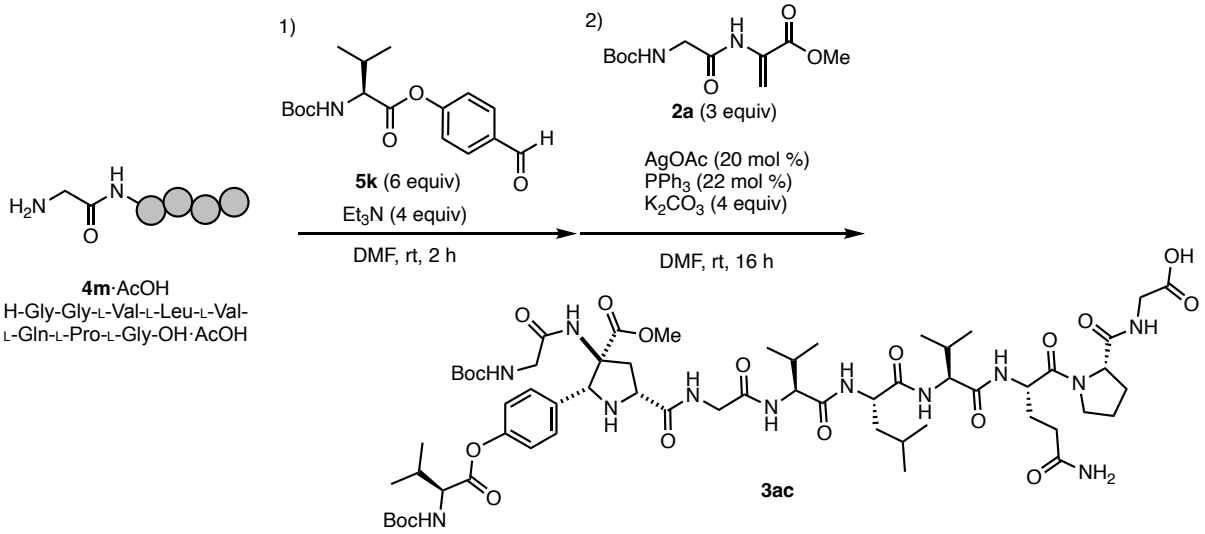



To a solution of *p*-tolualdehyde (**5a**) (21.3 mg, 0.177 mmol) dissolved in dry DMF (0.15 mL) was added $Et_3N$ (16.2 μL, 116 μmol) at room temperature to prepare stock solution A. To the 15 μL of the stock solution A was added H-Gly-L-Pro-L-Phe-L-Val-L-Pro-L-Arg-L-Val-L-Ala-L-Trp-$NH_2$·TFA (**4l**·TFA) (3.4 mg, 3.0 μmmol, 1.0 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (1.1 mg, 6.6 μmol) and $PPh_3$ (2.1 mg, 8.0 μmol) was dissolved in dry DMF (0.15 mL) at room temperature and stirred for 30 minutes to prepare stock solution B. To crude imine were added dehydroalanine **2a** (2.7 mg, 10 μmol, 3.5 equiv), 15 μL of the stock solution B, and $K_2CO_3$ (1.9 mg, 14 μmol, 4.6 equiv) at room temperature. After stirring for 45 h at the same temperature, the mixture was diluted with MeCN and water, and the progress of the reaction was confirmed by MALDI-MS and FAB-MS analysis.
HRMS ($FAB^+$) *m/z* ($[M+H]^+$, calcd for $C_{70}H_{99}N_{16}O_{14}^+$, 1387.7521; found, 1387.7471).

MALDI-MS spectrum of reaction mixture (Bruker Autoflex maX ($MALDI^+$), Matrix: 2,5-dihydroxybenzoic acid).

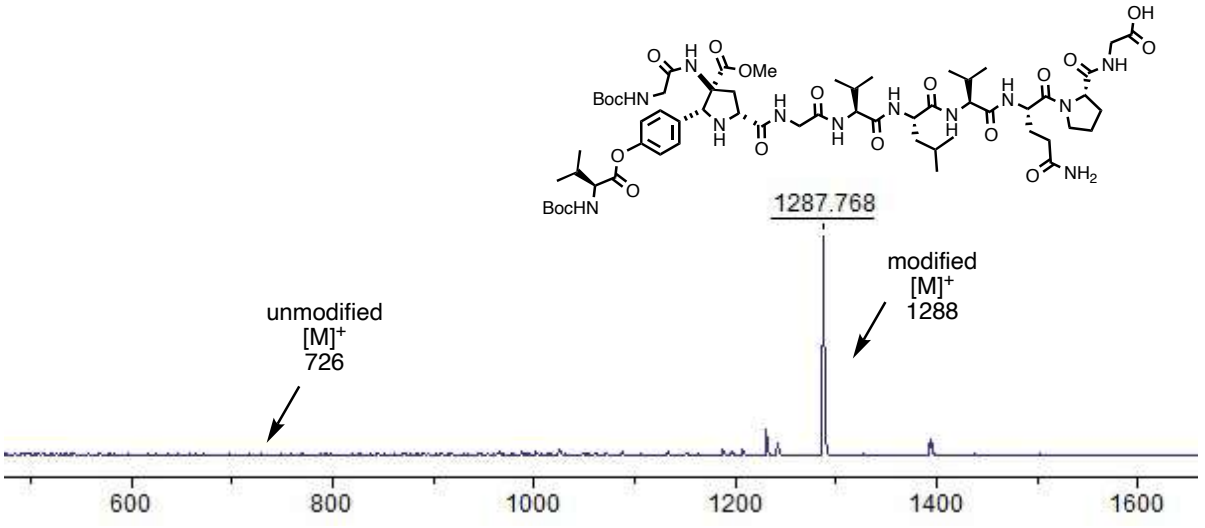


*One-pot [3+2]cycloaddition of H-Gly-Gly-L-Val-L-Leu-L-Val-L-Gln-L-Pro-Gly-OH·AcOH (**4m**·AcOH) with 4-formylphenyl(tert-butoxycarbonyl)-L-valinate (**5k**) and dehydroalanine **2a***

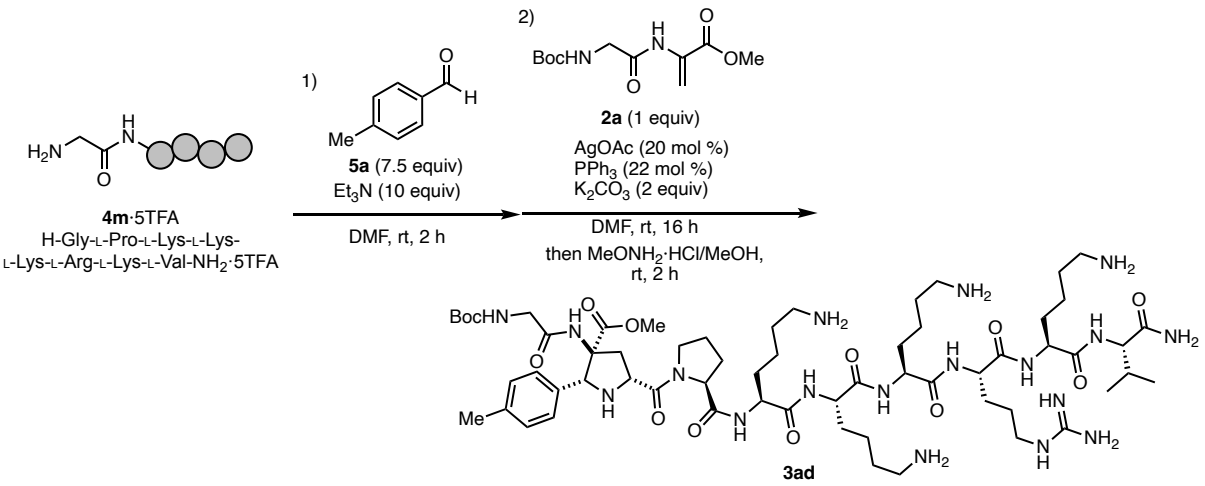



To a mixture of H-Gly-Gly-L-Val-L-Leu-L-Val-L-Gln-L-Pro-Gly-OH·AcOH (**4m**·AcOH) (2.4 mg, 3.1 μmmol, 1.0 equiv) dissolved in dry DMF (15.0 μL) were added 4-formylphenyl(*tert*-butoxycarbonyl)-*L*-valinate (**5k**) (5.8 mg, 18 μmol, 5.9 equiv) and $Et_3N$ (1.5 μL, 11 μmol, 3.5 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (2.4 mg, 14 μmol) and $PPh_3$ (3.6 mg, 14 μmol) was dissolved in dry DMF (0.3 mL) at room temperature and stirred for 30 minutes to prepare stock solution. To crude imine were added dehydroalanine **2a** (2.3 mg, 8.9 μmol, 2.9 equiv), 15 μL of the stock solution, and $K_2CO_3$ (1.7 mg, 12 μmol, 4.0 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was diluted with MeCN and water, and the progress of the reaction was confirmed by MALDI-MS and FAB-MS analysis. HRMS ($FAB^+$) *m/z* ($[M+H]^+$, calcd for $C_{60}H_{95}N_{12}O_{19}^+$, 1287.6831; found, 1287.6847).

MALDI-MS spectrum of reaction mixture (Bruker Autoflex maX ($MALDI^+$), Matrix: 2,5-dihydroxybenzoic acid).

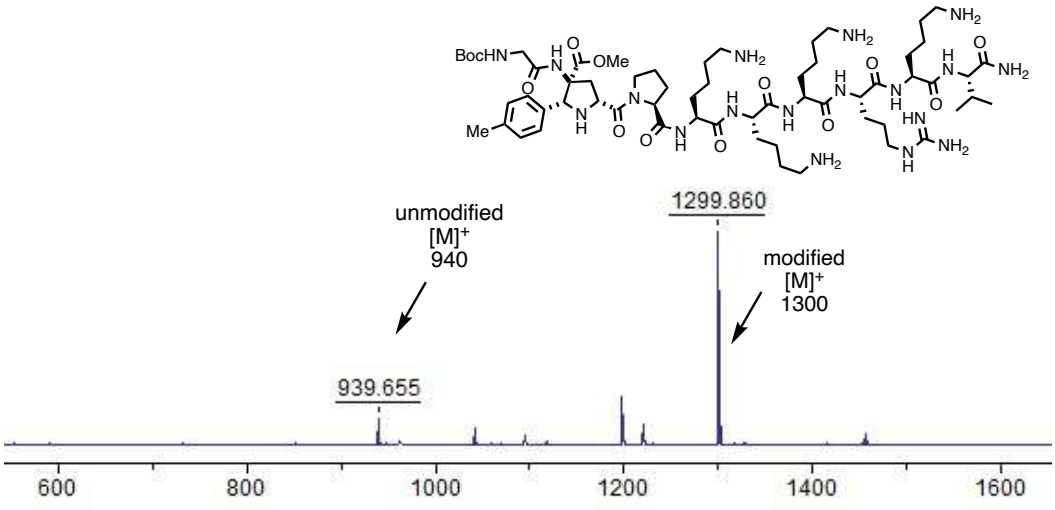


*One-pot [3+2]cycloaddition of H-Gly-L-Pro-L-Lys-L-Lys-L-Lys-L-Arg-L-Lys-L-Val-$NH_2$·5TFA (**4m**·5TFA) with p-tolualdehyde (**5a**) and dehydroalanine **2a***

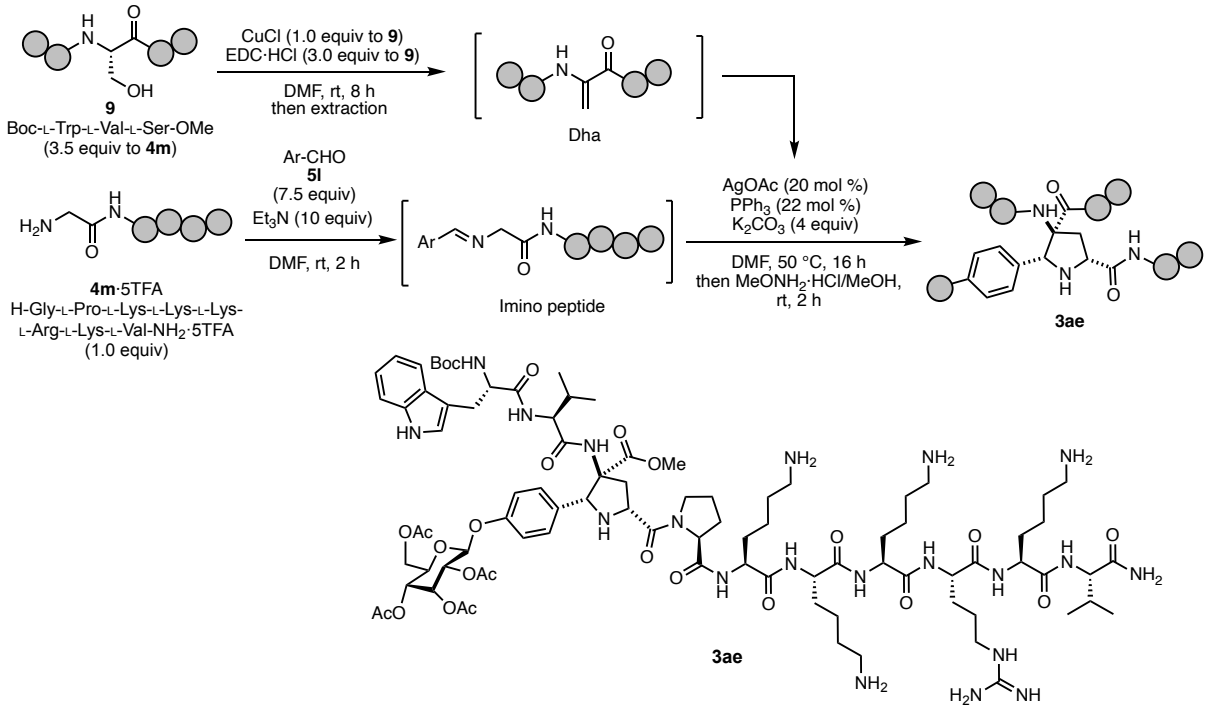



To a solution of *p*-tolualdehyde (**5a**) (45.0 mg, 0.375 mmol) dissolved in dry DMF (0.25 mL) was added $Et_3N$ (69.0 μL, 0.495 mmol) at room temperature to prepare stock solution A. To the 25 μL of the stock solution A was added H-Gly-L-Pro-L-Lys-L-Lys-L-Lys-L-Arg-L-Lys-L-Val-$NH_2$·5TFA (**4m**·5TFA) (7.7 mg, 5.1 μmmol, 1.0 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine. A mixture of AgOAc (3.4 mg, 20 μmol) and $PPh_3$ (6.0 mg, 23 μmol) was dissolved in dry DMF (0.50 mL) at room temperature and stirred for 30 minutes to prepare stock solution B. To crude imine were added dehydroalanine **2a** (1.3 mg, 5.0 μmol, 0.97 equiv), 25 μL of the stock solution B, and $K_2CO_3$ (1.7 mg, 12 μmol, 2.4 equiv) at room temperature. After stirring for 16 h at the same temperature, the solvent was removed under reduced pressure. The residue was dissolved in MeOH (25 μL), and added $MeONH_2$·HCl (12.9 mg, 0.154 mmol) at room temperature. After stirring for 2 h at the same temperature, the solvent was removed under reduced pressure. The residue was diluted with MeCN and water, and the progress of the reaction was confirmed by MALDI-MS and FAB-MS analysis. HRMS ($FAB^+$) *m/z* ($[M+H]^+$, calcd for $C_{61}H_{107}N_{18}O_{13}^+$, 1299.8260; found, 1299.8269).

MALDI-MS spectrum of reaction mixture (Bruker autoflex maX ($MALDI^+$), Matrix: 2,5-dihydroxybenzoic acid).



*Three-component integration of complex peptides from H-Gly-L-Pro-L-Lys-L-Lys-L-Lys-L-Arg-L-Lys-L-Val-$NH_2$·5TFA (**4m**·5TFA) with sugar-tagged aldehyde (**5l**) and Boc-L-Trp-L-Val-L-Ser-OMe (**9**) via in situ generation of iminopeptides and dehydroalanines*




To a mixture of H-Gly-L-Pro-L-Lys-L-Lys-L-Lys-L-Arg-L-Lys-L-Val-$NH_2$·5TFA (**4m**·5TFA) (3.02 mg, 2.00 μmol, 1.00 equiv) dissolved in dry DMF (10 μL) were added sugar-tagged aldehyde (**5l**) (6.76 mg, 14.9 μmol, 7.47 equiv) and $Et_3N$ (2.9 μL, 21 μmol, 10 equiv) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated under reduced pressure to give the crude imine.

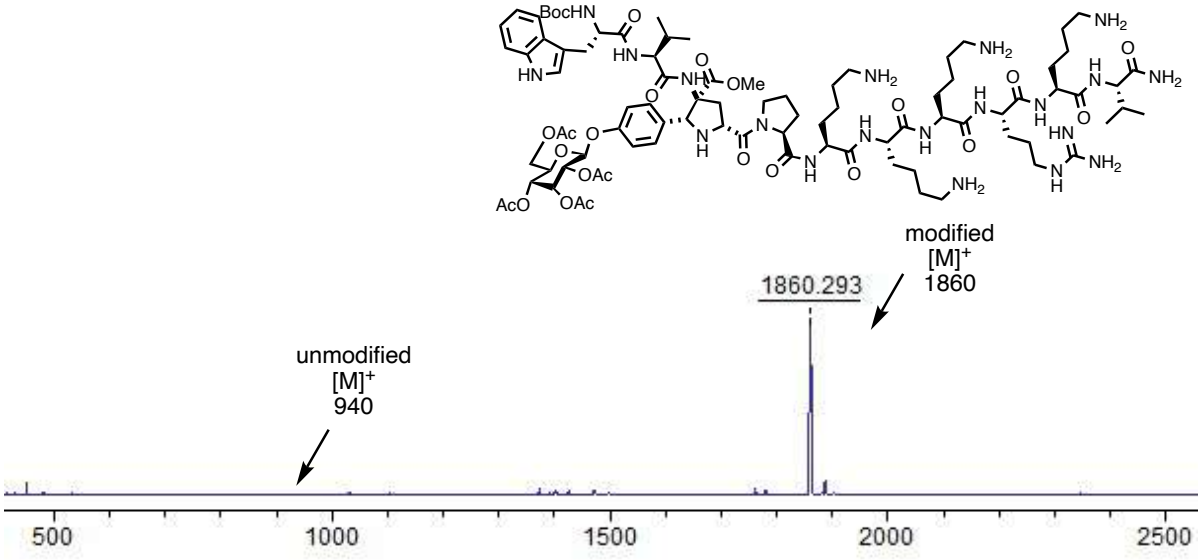
To a mixture of Boc-L-Trp-L-Val-L-Ser-OMe (**9**) (50.4 mg, 99.9 μmol) dissolved in DMF (1.0 mL) were added CuCl (10.1 mg, 0.102 mmol, 1.02 equiv to **9**) and EDC·HCl (57.4 mg, 0.299 mmol, 3.00 equiv to **9**) at room temperature. After stirring for 8 h at the same temperature, the mixture was added water. The mixture was extracted with EtOAc (5 mL×3), and washed with 1 M HCl aq. (5 mL×1) and saturated $NaHCO_3$ aq. (5 mL×1). The organic extract was washed with brine (5 mL×1) and dried over with $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in dry DMF (71 μL) to prepare stock solution A.

A mixture of AgOAc (2.80 mg, 16.8 μmol) and $PPh_3$ (4.60 mg, 17.5 μmol) was dissolved in dry DMF (0.20 mL) at room temperature and stirred for 30 minutes to prepare stock solution B.

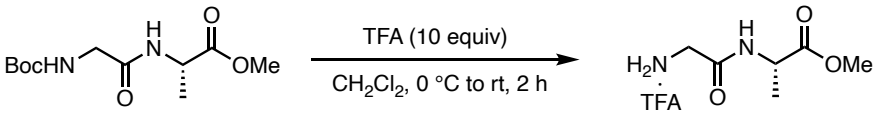
To crude imine were added 5 μL of the stock solution A and B, and $K_2CO_3$ (1.20 mg, 8.68 μmol, 4.34 equiv to **4m**) at 50 °C. After stirring for 16 h at the same temperature, the solvent was removed under reduced pressure. The residue was dissolved in MeOH (10 μL), and added $MeONH_2$·HCl (5.2 mg, 62 μmol) at room temperature. After stirring for 2 h at the same temperature, the solvent was removed under reduced pressure. The residue was diluted with MeCN and water, and the progress of the reaction was confirmed by MALDI-MS and FAB-

MS analysis. HRMS (FAB$^+$) *m/z* ([M+H]$^+$, calcd for $C_{88}H_{139}N_{20}O_{24}^+$, 1860.0266; found, 1860.0362).

MALDI-MS spectrum of reaction mixture (Bruker Autoflex maX (MALDI$^+$), Matrix: 2,5-dihydroxybenzoic acid).




*A typical procedure for the synthesis of peptide trifluoroacetate salts* ***4***

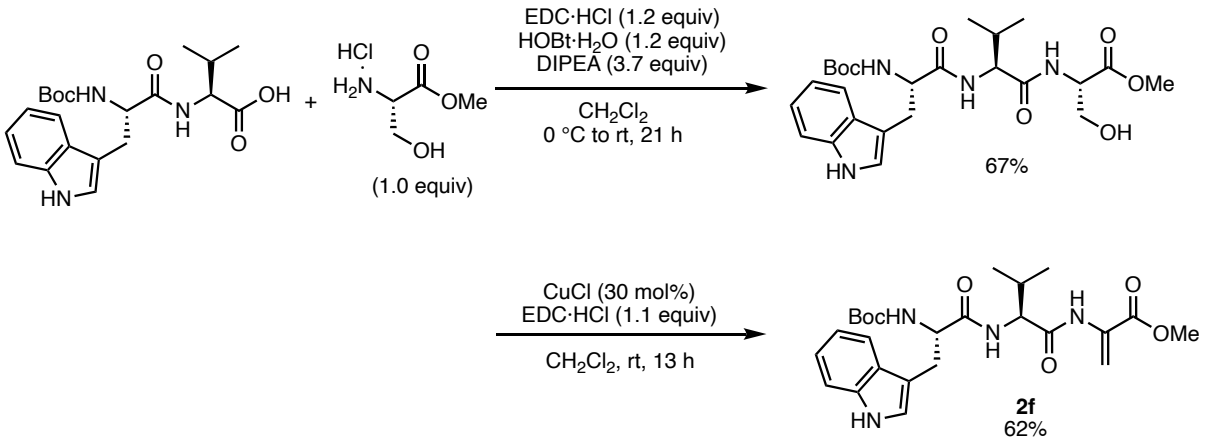



**4b** 98%

To a mixture of Boc-Gly-Ala-OMe (1.41 g, 5.42 mmol, 1.00 equiv) dissolved in $CH_2Cl_2$ (10.8 mL) was slowly added trifluoroacetic acid (4.70 mL, 61.4 mmol, 11.3 equiv) at 0 °C. After stirring for 30 minutes at 0 °C, the mixture was warmed to room temperature. The reaction mixture was concentrated with toluene under reduced pressure and washed with $Et_2O$ to afford H-Gly-L-Ala-OMe·TFA (**4b**·TFA) (1.45g, 5.29 mmol, 97.6%) as a colorless solid.

According to the procedure for preparing H-Gly-L-Ala-OMe·TFA (**4b**·TFA), H-Gly-L-Tyr-OMe·TFA (**4d**·TFA) (1.20 g, 97.9%), H-Gly-L-Trp-OMe·TFA (**4e**·TFA) (377 mg, 96.7%), H-Gly-L-Lys-OMe·2TFA (**4g**·2TFA) (248 mg, quant), and H-Gly-Gly-L-Ala-OMe·TFA (**4h**·TFA) (542 mg, quant) were prepared from the corresponding Boc-protected peptides.

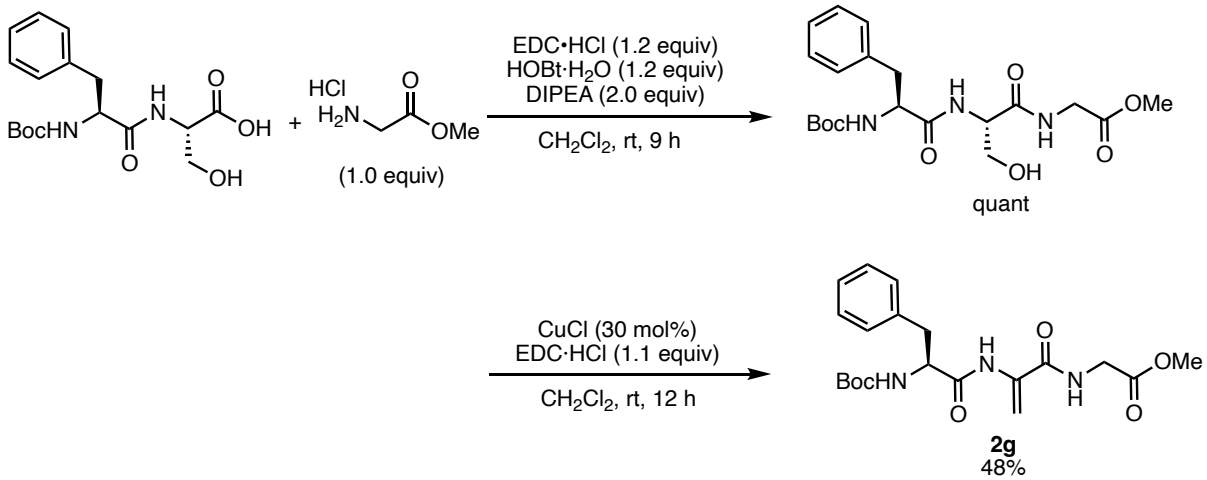
*A procedure for the synthesis of dehydroalanine **2f***




A mixture of Boc-L-Trp-L-Val-OH (310 mg, 0.768 mmol, 1.00 equiv), H-L-Ser-OMe·HCl (120 mg, 0.771 mmol, 1.00 equiv), HOBt·$H_2O$ (142 mg, 0.927 mmol, 1.21 equiv), DIPEA (0.480 mL, 2.82 mmol, 3.67 equiv) was dissolved in $CH_2Cl_2$ (3.0 mL) at 0 °C. After stirring for 20 min at the 0 °C, to the mixture was added EDC·HCl (177 mg, 0.923 mmol, 1.20 equiv) at the same temperature and the mixture was warmed to room temperature. After stirring at room temperature for 21 h, the mixture was diluted with $CH_2Cl_2$ (10 mL) and saturated $NH_4Cl$ aq. (10 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL×3), washed with 1M HCl aq. (20 mL), saturated $NaHCO_3$ aq. (20 mL) and brine (20 mL), and dried with $MgSO_4$. After filtration, the residue was concentrated under reduced pressure. The residue was purified with column chromatography (silica gel, 22 g, hexane/EtOAc = 3:1 to EtOAc) to give the Boc-L-Trp-L-Val-L-Ser-OMe (260 mg, 0.515 mmol, 67.0%) as colorless solid.

A mixture of Boc-L-Trp-L-Val- L-Ser-OMe (252 mg, 0.500 mmol, 1.00 equiv), CuCl (15.2 mg, 0.154 mmol, 0.307 equiv), and EDC·HCl (105 mg, 0.548 mmol, 1.10 equiv) was dissolved in $CH_2Cl_2$ (6.3 mL) at 0 °C. After stirring at room temperature for 13 h, the mixture was diluted with $CH_2Cl_2$ (10 mL) and saturated $NH_4Cl$ aq. (10 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL×3), washed with 1M HCl aq. (20 mL), saturated $NaHCO_3$ aq. (20 mL), and brine (20 mL), and dried with $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified with column chromatography (silica gel, 25 g, hexane/EtOAc = 5:1 to 1:1) to give the Boc-L-Trp-L-Val-Dha-OMe (**2f**, 150 mg, 0.308 mmol, 61.5%) as a yellow oil.

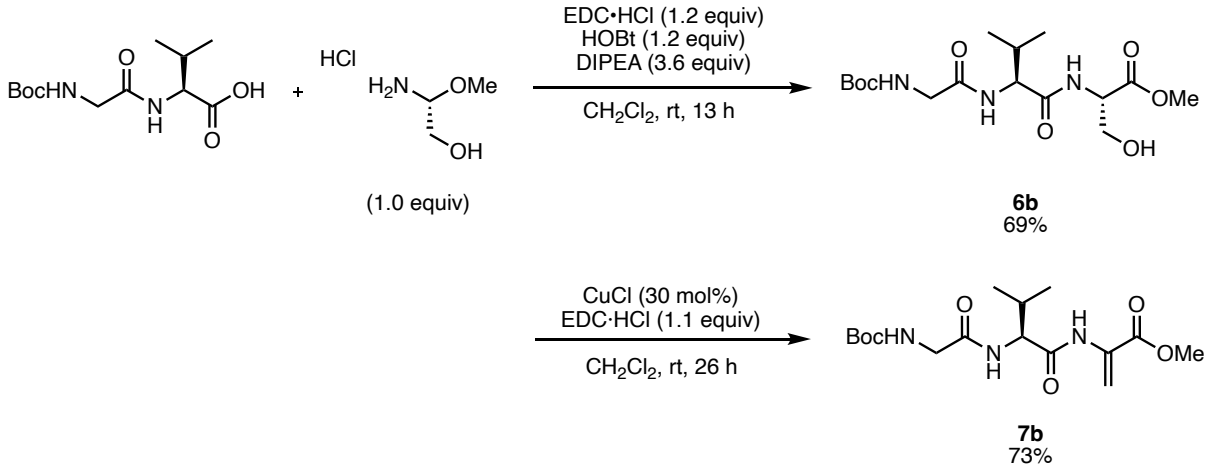
*A procedure for the synthesis of tripeptide dehydroalanine* ***2g***




A mixture of Boc-L-Phe-L-Ser-OH (1.05 g, 2.98 mmol, 1.00 equiv), H-Gly-OMe·HCl (376 mg, 2.99 mmol, 1.01 equiv), HOBt·$H_2O$ (552 mg, 3.60 mmol, 1.21 equiv), DIPEA (1.00 mL, 5.88 mmol, 1.97 equiv) was dissolved in $CH_2Cl_2$ (6.0 mL) at 0 °C. After stirring for 10 min at the 0 °C, to the mixture was added EDC·HCl (690 mg, 3.60 mmol, 1.21 equiv) at the same temperature and the mixture was warmed to room temperature. After stirring at room temperature for 9 h, the mixture was diluted with $CH_2Cl_2$ (50 mL) and saturated $NH_4Cl$ aq. (50 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL×3), washed with 1M HCl aq. (50 mL), saturated $NaHCO_3$ aq. (50 mL) and brine (50 mL), and dried with $MgSO_4$. After filtration, the residue was concentrated under reduced pressure to give the Boc-L-Phe-L-Ser-L-Gly-OMe (1.33 g, 3.13 mmol, quant) as colorless solid.

A mixture of Boc-L-Phe-L-Ser- L-Gly-OMe (1.26 g, 2.97 mmol, 1.00 equiv), CuCl (88.2 mg, 0.891 mmol, 0.299 equiv), and EDC·HCl (628 mg, 3.28 mmol, 1.10 equiv) was dissolved in $CH_2Cl_2$ (6.3 mL) at 0 °C. After stirring at room temperature for 12 h, the mixture was diluted with $CH_2Cl_2$ (50 mL) and saturated $NH_4Cl$ aq. (50 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL×3), washed with 1M HCl aq. (50 mL), saturated $NaHCO_3$ aq. (50 mL) and brine (50 mL), and dried with $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified with column chromatography (silica gel, 25 g, hexane/EtOAc = 5:1 to 1:1) to give the Boc-L-Phe-Dha-Gly-OMe (**2g**, 577 mg, 1.42 mmol, 47.8%) as a colorless solid.

*A typical procedure for the synthesis of tripeptide dehydroalanine* ***7b***




A mixture of Boc-Gly-L-Val-OH (275 mg, 1.00 mmol, 1.00 equiv), H-L-Ser-OMe·HCl (155 mg, 0.996 mmol, 0.994 equiv), HOBt·$H_2O$ (184 mg, 1.20 mmol, 1.20 equiv), DIPEA (0.610 mL, 3.59 mmol, 3.58 equiv) was dissolved in $CH_2Cl_2$ (1.35 mL) at 0 °C. After stirring for 10 min at the 0 °C, to the mixture was added EDC·HCl (230 mg, 1.20 mmol, 1.20 equiv) at the same temperature and the mixture was warmed to room temperature. After stirring at room temperature for 13 h, the mixture was diluted with $CH_2Cl_2$ (20 mL) and saturated $NH_4Cl$ aq. (20 mL). The mixture was extracted with $CH_2Cl_2$ (10 mL×3), washed with 1M HCl aq. (20 mL), saturated $NaHCO_3$ aq. (20 mL) and brine (20 mL), and dried with $MgSO_4$. After filtration, the residue was concentrated under reduced pressure to give the Boc-Gly-L-Val-L-Ser-OMe (**6b**, 259 mg, 0.690 mmol, 68.8%) as colorless solid.

A mixture of Boc-Gly-L-Val-L-Ser-OMe (132 mg, 0.352 mmol, 1.00 equiv), CuCl (10.7 mg, 0.108 mmol, 0.307 equiv) and EDC·HCl (74.8 mg, 0.390 mmol, 1.11 equiv) was dissolved in $CH_2Cl_2$ (4.4 mL) at 0 °C. After stirring at room temperature for 26 h, the mixture was diluted with $CH_2Cl_2$ (20 mL) and saturated $NH_4Cl$ aq. (20 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL×3), washed with 1M HCl aq. (20 mL), saturated $NaHCO_3$ aq. (20 mL) and brine (20 mL), and dried with $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified with column chromatography (silica gel, 25 g, hexane/EtOAc = 5:1 to 1:1) to give the Boc-Gly-L-Val-Dha-OMe (**7b**, 91.4 mg, 0.256 mmol, 72.7%) as colorless solid.

## X-Ray Crystallographic Analysis

### X-ray crystal structure analysis of 3w'

Single crystals suitable for X-ray crystallography were obtained by recrystallization from MeCN, $CH_2Cl_2$/hexane. Diffraction data were collected on a Rigaku XtaLAB Synergy R diffractometer utilizing a HyPix Hybrid Pixel Array Detector. The system was equipped with a copper rotating-anode X-ray source and a multilayered confocal mirror for monochromatic radiation. Measurements were conducted at 100 K using ω scans. Using Olex2,[9] the structure was solved with the olex2.solve[10] structure solution program using Charge Flipping and refined with the SHELXL[11] refinement package using Least Squares minimization.

**Table S3.** Crystal data and structure refinements for methyl (2*S*,3*R*,5*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w'**).

| | |
|---|---|
| CCDC number | 2452634 |
| Empirical formula | $C_{27}H_{40}N_4O_8$ |
| Formula weight | 548.63 |
| Space system | orthorhombic |
| Space group | $P2_12_12$ |
| a/Å | 8.9233(2) |
| b/Å | 27.6931(5) |
| c/Å | 11.4689(2) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/Å$^3$ | 2834.12(10) |
| Z | 4 |
| Temperature/K | 99.90(14) |
| 2Θ range for data collection/° | 6.384 to 152.566 |
| $\rho_{calcd}$ g/cm$^3$ | 1.286 |
| μ/mm$^{-1}$ | 0.787 |
| F(000) | 1176.0 |
| Crystal_size/mm$^3$ | 0.07 x 0.01 x 0.01 |
| Radiation | Cu Kα (l = 1.54184) |
| Reflections collected | 104985 |
| Independent | 5861 |
| Index ranges | $-11 \leqq h \leqq 11$, $-31 \leqq k \leqq 34$, $-14 \leqq l \leqq 14$ |
| Data/restraints/parameters | 5861/0/413 |
| Final R indexes R [I>2σ (I)] | $R_1 = 0.0400$, $wR_2 = 0.1078$ |
| Final R indexes R [all data] | $R_1 = 0.0434$, $wR_2 = 0.1102$ |
| Goodness-of-fit on F$^2$ | 1.070 |
| Largest peak/deepest hole eÅ$^{-3}$ | 0.21/–0.19 |
| Flack parameter | 0.01(9) |

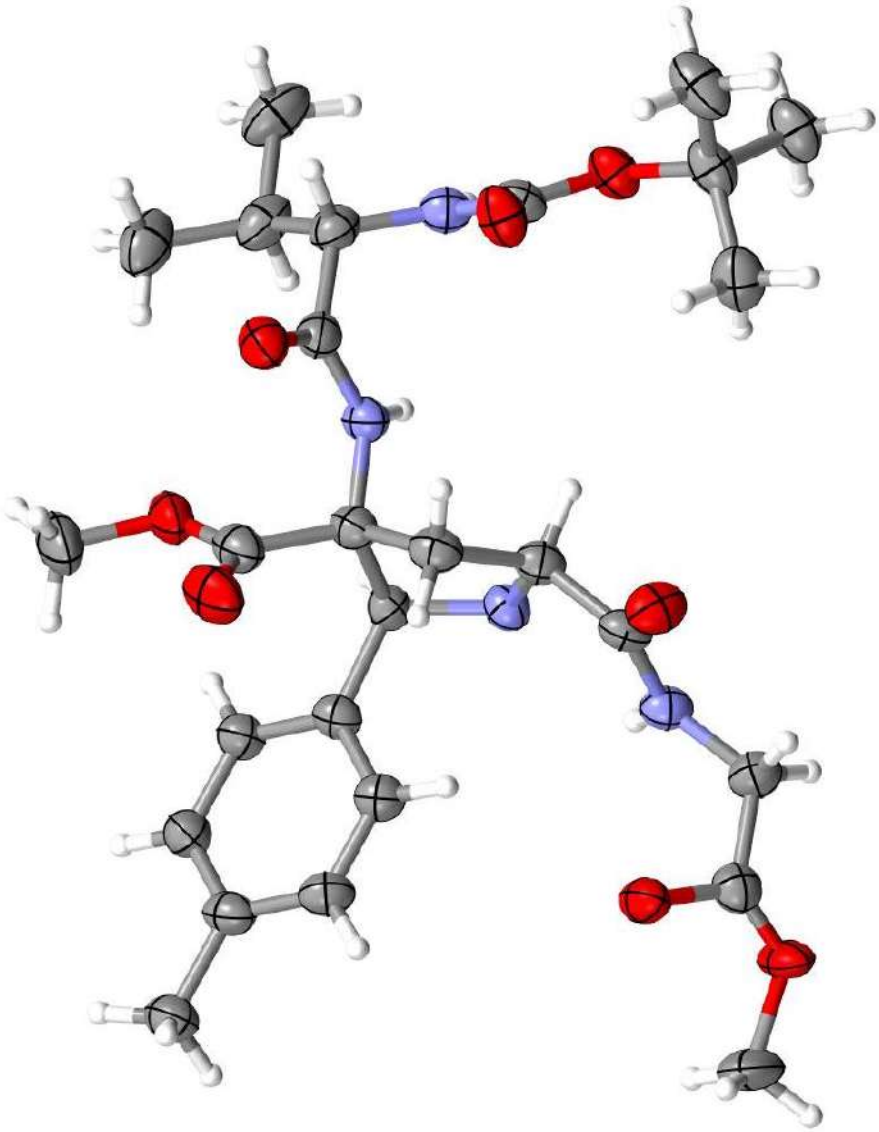
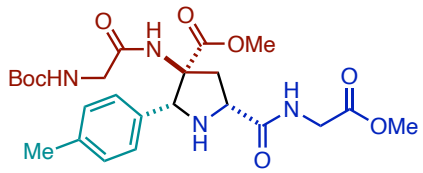
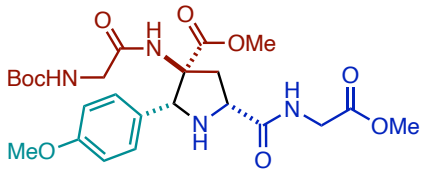


**Figure S1.** Thermal ellipsoid (50 % probability) plot of **3w'**, Color code of atoms: hydrogen, white; carbon, gray; nitrogen, purple; oxygen, red

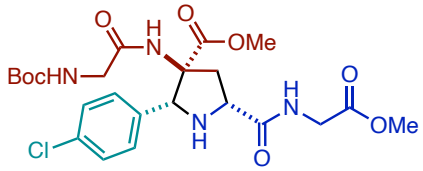
**Characterization Data of New Compounds**



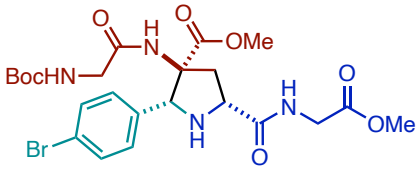
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3a**)**:** Colorless oil; $R_f$ 0.18 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 5.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.15 (br s, 1H), 4.91 (s, 1H), 4.29 (dd, *J* = 9.4, 7.6 Hz, 1H), 4.21 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.11 (dd, *J* = 18.4, 5.3 Hz, 1H), 3.89-3.70 (m, 5H), 3.39 (s, 3H), 3.01 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.64 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.32 (s, 3H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 171.4, 170.4, 169.3, 156.2, 137.9, 134.3, 128.9, 126.6, 80.3, 69.1, 67.9, 58.9, 52.4, 52.3, 44.9, 40.9, 38.3, 28.3, 21.1; **HRMS** ($FAB^+$) Calcd for $C_{24}H_{35}N_4O_8^+$ $[M+H]^+$ 507.2449, found 507.2469.



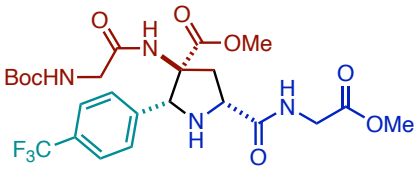
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate (**3b**)**:** Colorless oil; $R_f$ 0.20 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 5.7 Hz, 1H), 7.30-7.27 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.16 (br s, 1H), 4.89 (s, 1H), 4.28 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.20 (dd, *J* = 18.4, 5.6 Hz, 1H), 4.11 (dd, *J* = 18.4, 5.2 Hz, 1H), 3.91-3.70 (m, 8H), 3.41 (s, 3H), 3.01 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.63 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 171.4, 170.4, 169.2, 159.5, 156.2, 129.2, 127.9, 113.6, 80.3, 69.0, 67.5, 58.7, 55.2, 52.5, 52.3, 44.8, 40.9, 38.1, 28.2; **HRMS** ($FAB^+$) Calcd for $C_{24}H_{35}N_4O_9^+$ $[M+H]^+$ 523.2399, found 523.2423.



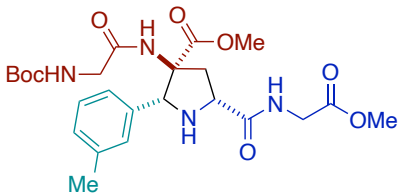
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(4-chlorophenyl)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3c**)**:** Colorless solid; m.p. 75-76 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 5.4 Hz, 1H), 7.40-7.28 (m, 4H), 5.21 (br s, 1H), 4.98 (s, 1H), 4.32 (dd, *J* = 9.3, 7.5 Hz, 1H), 4.21 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.09 (dd, *J* = 18.5, 5.0 Hz, 1H), 3.91-3.70 (m, 5H), 3.40 (s, 3H), 3.08-2.99 (m, 1H), 2.60 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.46 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.7, 171.2, 170.4, 169.3, 156.2, 136.1, 133.9, 128.4, 128.1, 80.5, 69.0, 66.9, 58.9, 52.6, 52.3, 44.9, 40.9, 38.1, 28.2; **HRMS** ($FAB^+$) Calcd for $C_{23}H_{32}{}^{35}ClN_4O_8^+$ $[M+H]^+$ 527.1903 found 527.1884.



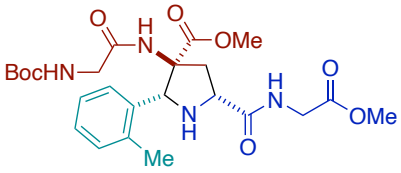
Methyl (2*R**,3*S**,5*R**)-2-(4-bromophenyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3d**)**:** Colorless solid; m.p. 75-76 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 5.5 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 5.16 (br s, 1H), 4.99 (s, 1H), 4.33 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.22 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.09 (dd, *J* = 18.5, 5.0 Hz, 1H), 3.90-3.71 (m, 5H), 3.41 (s, 3H), 3.05 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.59 (dd, *J* = 13.8, 7.3 Hz, 1H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.7, 171.2, 170.4, 169.4, 156.2, 136.6, 131.3, 128.4, 122.1, 80.5, 69.0, 67.0, 58.9, 52.6, 52.3, 44.9, 40.9, 38.1, 28.2; **HRMS** ($FAB^+$) Calcd for $C_{23}H_{32}{}^{79}BrN_4O_8^+$ $[M+H]^+$ 571.1398, found 571.1416.



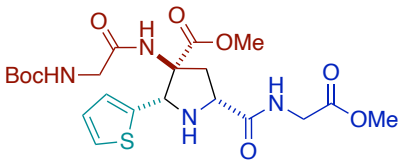
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylate (**3e**)**:** Colorless oil; $R_f$ 0.15 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.65-7.56 (m, 2H), 7.43 (app. t, *J* = 7.7 Hz, 1H), 7.00 (br s, 1H), 5.06-4.96 (m, 2H), 4.20 (app. t, *J* = 8.5 Hz, 1H), 4.16 (d, *J* = 5.5 Hz, 2H), 3.84-3.74 (m, 5H), 3.33 (s, 3H), 3.07 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.82 (dd, *J* = 14.0, 9.1 Hz, 1H), 1.45 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.4, 170.5, 170.4, 169.7, 155.9, 136.8, 131.7, 129.9, 128.5, 128.4 (q, $J_{C\text{-}F}$ = 29.1 Hz), 125.8 (q, $J_{C\text{-}F}$ = 5.7 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272.5 Hz), 80.2, 69.4, 64.5, 59.1, 52.33, 52.29, 44.4, 40.9, 39.8, 28.2; **HRMS** ($FAB^+$) Calcd for $C_{24}H_{32}F_3N_4O_8^+$ $[M+H]^+$ 561.2167, found 561.2199.



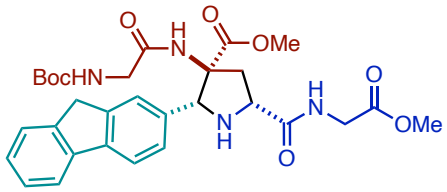
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*m*-tolyl)pyrrolidine-3-carboxylate (**3f**)**:** Colorless oil; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 5.6 Hz, 1H), 7.22-7.07 (m, 4H), 5.16 (br s, 1H), 4.90 (s, 1H), 4.30 (dd, *J* = 9.8, 7.2 Hz, 1H), 4.21 (dd, *J* = 18.6, 5.6 Hz, 1H), 4.11 (dd, *J* = 18.5, 5.2 Hz, 1H), 3.85-3.72 (m, 5H), 3.38 (s, 3H), 3.01 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.65 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.35 (s, 3H), 1.46 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 171.3, 170.3, 169.3, 156.2, 137.8, 137.3, 129.0, 128.1, 127.4, 123.8, 80.3, 69.2, 68.0, 58.9, 52.35, 52.27, 44.8, 40.9, 38.3, 28.2, 21.3; **HRMS** ($FAB^+$) Calcd for $C_{24}H_{35}N_4O_8^+$ $[M+H]^+$ 507.2449, found 507.2456.



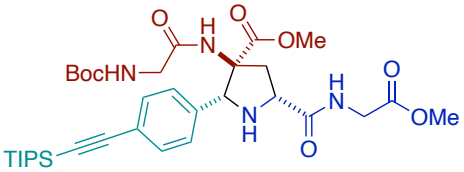
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*o*-tolyl)pyrrolidine-3-carboxylate (**3g**)**:** Colorless oil; $R_f$ 0.38 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 5.4 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.24-7.08 (m, 3H), 5.25 (s, 1H), 5.13 (br s, 1H), 4.32 (app. t, *J* = 8.6 Hz, 1H), 4.21 (dd, *J* = 18.4, 5.6 Hz, 1H), 4.11 (dd, *J* = 18.4, 5.3 Hz, 1H), 3.83-3.67 (m, 5H), 3.37 (s, 3H), 2.96 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.73 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.33 (s, 3H), 1.45 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 171.0, 170.4, 169.4, 156.3, 136.4, 136.2, 130.6, 128.0, 127.2, 125.9, 80.5, 70.2, 64.4, 64.3, 59.4, 52.5, 52.4, 41.0, 38.8, 28.3, 19.9; **HRMS** (FAB$^+$) Calcd for $C_{24}H_{35}N_4O_8^+$ $[M+H]^+$ 507.2449, found 507.2431.



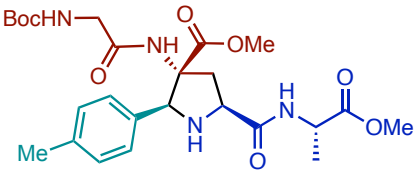
Methyl (2*S**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(thiophen-2-yl)pyrrolidine-3-carboxylate (**3h**)**:** Yellow oil; $R_f$ 0.18 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 5.4 Hz, 1H), 7.21 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.03-6.98 (m, 1H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.33 (d, *J* = 4.0 Hz, 1H), 5.11 (br s, 1H), 4.32-4.24 (m, 1H), 4.19 (dd, *J* = 18.6, 5.4 Hz, 1H), 4.11 (dd, *J* = 18.6, 5.5 Hz, 1H), 3.86-3.73 (m, 5H), 3.52 (s, 3H), 3.17 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.82 (br s, 1H), 2.62 (dd, *J* = 13.8, 6.6 Hz, 1H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.6, 171.1, 170.3, 169.3, 156.2, 141.6, 127.0, 125.0, 124.7, 80.4, 69.0, 63.9, 58.7, 52.8, 52.3, 44.9, 41.0, 37.1, 28.3; **HRMS** (FAB$^+$) Calcd for $C_{21}H_{31}N_4O_8S^+$ $[M+H]^+$ 499.1857, found 499.1855.



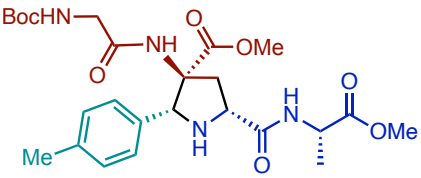
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(9*H*-fluoren-2-yl)-5-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-3-carboxylate (**3i**)**:** Yellow oil; $R_f$ 0.20 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.75 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.58-7.52 (m, 2H), 7.40-7.27 (m, 3H), 5.13 (br s, 1H), 5.05 (s, 1H), 4.35 (dd, *J* = 9.6, 7.3 Hz, 1H), 4.24 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.14 (dd, *J* = 18.5, 5.1 Hz, 1H), 3.94-3.72 (m, 7H), 3.37 (s, 3H), 3.05 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.68 (dd, *J* = 13.6, 7.3 Hz, 1H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.8, 171.5, 170.4, 169.1, 156.2, 143.4, 143.3, 141.9, 141.3, 135.8, 126.9, 126.8, 125.4, 125.1, 123.3, 119.9, 119.6, 80.4, 69.1, 68.0, 58.9, 52.6, 52.3, 41.0, 38.3, 36.9, 29.7, 28.3; **HRMS** (FAB$^+$) Calcd for $C_{30}H_{37}N_4O_8^+$ $[M+H]^+$ 581.2606, found 581.2618.



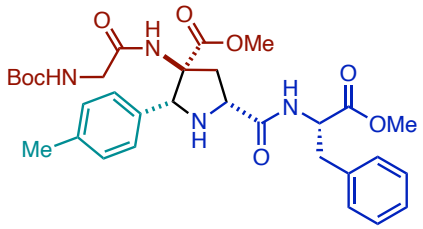
Methyl (3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(4-((triisopropylsilyl)ethynyl)phenyl)pyrrolidine-3-carboxylate (**3j**)**:** Colorless solid; m.p. 86-88 °C; $R_f$ 0.25 ($CHCl_3$/MeOH = 10/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.14 (br s, 1H), 5.01 (s, 1H), 4.33 (app t, *J* = 8.7 Hz, 1H), 4.22 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.10 (dd, *J* = 18.5, 5.1 Hz, 1H), 3.91-3.70 (m, 5H), 3.42 (s, 3H), 3.06 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.60 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.46 (s, 9H), 1.13 (s, 21H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.8, 171.2, 170.3, 169.3, 156.2, 137.7, 131.9, 126.5, 123.4, 106.7, 91.0, 80.4, 69.1, 67.4, 58.9, 52.6, 52.3, 44.9, 40.9, 38.1, 28.2, 18.6, 11.2; **HRMS** ($FAB^+$) Calcd for $C_{34}H_{53}N_4O_8Si^+$ $[M+H]^+$ 673.3627, found 673.3639.



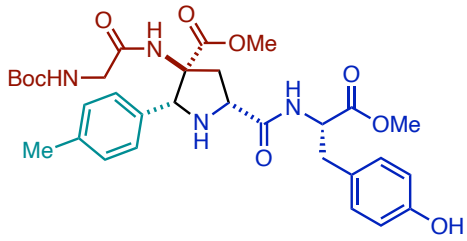
Methyl (2*S*,3*R*,5*S*)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k'**)**:** Colorless oil; $R_f$ 0.15 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.12 (br s, 1H), 4.85 (s, 1H), 4.72-4.62 (m, 1H), 4.24 (dd, *J* = 9.6, 7.5 Hz, 1H), 3.84-3.71 (m, 5H), 3.38 (s, 3H), 2.97 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.60 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.32 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.47 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.5, 173.0, 171.4, 169.1, 156.1, 138.0, 134.1, 129.0, 126.5, 80.4, 69.0, 67.9, 58.9, 52.42, 52.39, 47.7, 44.9, 38.6, 28.3, 21.1, 18.4; **HRMS** ($ESI^+$) Calcd for $C_{25}H_{36}N_4NaO_8^+$ $[M+Na]^+$ 543.2425, found 543.2411; $[\alpha]^{29}_D$ = −24.6 (*c* = 0.076 in $CHCl_3$).



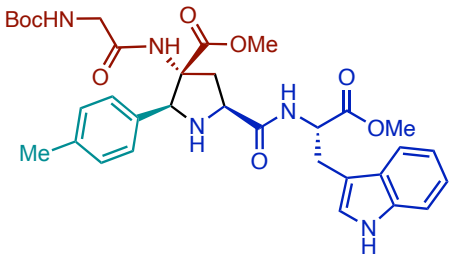
Methyl (2*R*,3*S*,5*R*)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3k''**)**:** Colorless oil; $R_f$ 0.15 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.18 (br s, 1H), 4.93 (s, 1H), 4.72-4.64 (m, 1H), 4.27 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.85-3.69 (m, 5H), 3.41 (s, 3H), 3.02 (dd, *J* = 13.7, 9.5 Hz, 1H), 2.59 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.32 (s, 3H), 1.51-1.46 (m, 3H+9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.4, 173.0, 171.4, 169.1, 156.1, 137.9, 134.2, 129.0, 126.6, 80.4, 69.2, 67.5, 58.9, 52.5, 52.4, 47.7, 44.9, 37.8, 28.3, 21.1, 18.6; **HRMS** ($ESI^+$) Calcd for $C_{25}H_{36}N_4NaO_8^+$ $[M+Na]^+$ 543.2425, found 543.2412; $[\alpha]^{29}_D$ = +86.0 (*c* = 0.076 in $CHCl_3$).



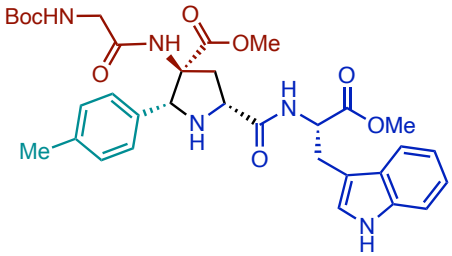

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3l**)**:** Colorless oil; $R_f$ 0.18 ($CHCl_3$/MeOH = 50/1); Isolated as 1.2:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H, minor), 7.60 (d, *J* = 7.6 Hz, 1H, major), 7.43-7.28 (m, 4H+4H), 7.25-7.15 (m, 2H+2H), 7.15-7.06 (m, 3H+3H), 5.15 (br s, 1H+1H), 5.01-4.87 (m, 1H+2H), 4.80 (s, 1H), 4.30-4.20 (m, 1H+1H), 3.85-3.68 (m, 5H+5H), 3.28 (dd, *J* = 14.0, 5.6 Hz, 2H), 3.23 (s, 3H), 3.22-3.14 (m, 3H+2H), 2.99 (dd, *J* = 13.8 Hz, 9.8 Hz, 1H), 2.90 (dd, *J* = 13.8 Hz, 9.3 Hz, 1H), 2.56 (dd, *J* = 13.9 Hz, 7.9 Hz, 1H), 2.50 (dd, *J* = 13.9 Hz, 7.4 Hz, 1H), 2.32 (s, 3H, major), 2.32 (s, 3H, minor), 1.47 (s, 9H), 1.46 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.3, 173.2, 172.0, 171.8, 171.5, 171.2, 169.1, 169.0, 156.14, 156.08, 137.8, 136.0, 134.2, 133.9, 133.8, 132.1, 132.0, 129.34, 129.33, 128.84, 128.81, 128.59, 128.55, 127.10, 127.06, 126.55, 126.52, 80.3, 69.0, 68.8, 67.9, 67.0, 59.1, 58.7, 52.9, 52.34, 52.30, 52.25, 52.17, 44.8, 38.4, 37.85, 37.8, 37.6, 28.2, 21.1; **HRMS** (FAB$^+$) Calcd for $C_{31}H_{41}N_4O_8^+$ $[M+H]^+$ 597.2919, found 597.2936.



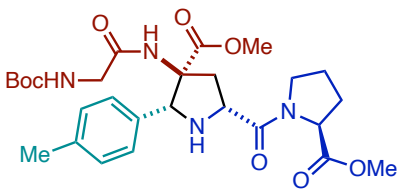

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3m**)**:** Colorless oil; $R_f$ 0.25 ($CHCl_3$/MeOH = 20/1); Isolated as 1.2:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H, minor), 7.63 (d, *J* = 7.2 Hz, 1H, major), 7.18-7.07 (m, 4H+4H), 7.10-7.00 (m, 2H+2H), 6.78 (d, *J* = 8.4 Hz, 2H, minor), 6.73 (d, *J* = 8.2 Hz, 2H, major), 5.28 (br s, 1H, minor), 5.20 (br s, 1H, major), 4.95-4.85 (m, 1H+1H), 4.82 (s, 1H, minor), 4.68 (s, 1H, major), 4.20-4.10 (m, 1H+1H), 3.88-3.62 (m, 5H+5H), 3.27 (s, 3H, minor), 3.22 (s, 3H, major), 3.17-3.03 (m, 2H+2H), 2.93 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.75 (dd, *J* = 13.9, 8.6 Hz, 1H), 2.57-2.37 (m, 1H+1H), 2.31 (s, 3H+3H), 1.46 (s, 9H+9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.7, 173.4, 172.2, 171.9, 171.3, 171.1, 169.7, 169.3, 156.4, 156.2, 155.8, 138.0, 137.9, 133.9, 133.8, 130.41, 130.38, 129.1, 129.0, 128.90, 128.89, 127.0, 126.8, 126.64, 126.59, 115.63, 115.59, 80.4, 69.1, 68.4, 67.5, 58.9, 58.7, 53.1, 52.7, 52.39, 52.36, 52.35, 52.28, 44.6, 38.9, 37.6, 37.1, 36.9, 28.3, 21.08, 21.06; **HRMS** (FAB$^+$) Calcd for $C_{31}H_{41}N_4O_9^+$ $[M+H]^+$ 613.2868, found 613.2881.




Methyl (2*S*,3*R*,5*S*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n'**)**:** Colorless solid; m.p. 107-109 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.23-7.11 (m, 4H), 7.10-7.00 (m, 4H), 5.13 (br s, 1H), 4.95 (q, *J* = 6.4 Hz, 1H), 4.77 (s, 1H), 4.21 (app t, *J* = 8.6 Hz, 1H), 3.83-3.72 (m, 5H), 3.46 (dd, *J* = 14.9, 5.5 Hz, 1H), 3.38 (dd, *J* = 14.9, 6.3 Hz, 1H), 3.03 (s, 3H), 2.89 (dd, *J* = 14.1, 8.8 Hz, 1H), 2.54 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.29 (s, 3H), 1.46 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.2, 172.6, 171.2, 169.2, 156.2, 137.8, 136.2, 134.2, 128.8, 127.5, 126.5, 123.1, 122.2, 119.6, 118.5, 111.3, 109.9, 80.4, 69.2, 68.0, 59.2, 52.39, 52.37, 52.1, 44.8, 38.4, 28.3, 27.7, 21.1; **HRMS** ($FAB^+$) Calcd for $C_{33}H_{42}N_5O_8^+$ $[M+H]^+$ 636.3028, found 636.3036; $[\alpha]^{29}_D$ = −42.5 (*c* = 0.354 in $CHCl_3$).

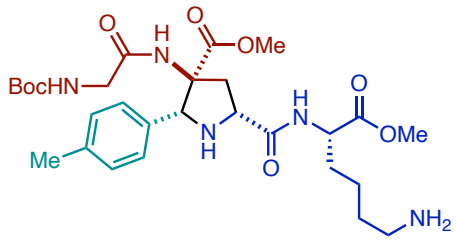



Methyl (2*R*,3*S*,5*R*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n''**)**:** Colorless solid; m.p. 113-115 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.20-6.96 (m, 7H), 5.13 (br s, 1H), 5.05-4.99 (m, 1H), 4.84 (s, 1H), 4.19 (app t, *J* = 8.8 Hz, 1H), 3.81-3.63 (m, 5H), 3.40 (d, *J* = 5.3 Hz, 2H), 3.19 (s, 3H), 3.01-2.94 (m, 1H), 2.49 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.30 (s, 3H), 1.45 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.3, 172.3, 171.4, 169.0, 156.1, 137.7, 136.1, 129.8, 129.7, 128.8, 127.6, 126.5, 123.0, 122.2, 119.5, 118.5, 111.3, 80.3, 69.0, 67.2, 58.8, 52.4, 52.3, 52.2, 44.8, 37.4, 28.3, 27.6, 21.1; **HRMS** ($FAB^+$) Calcd for $C_{33}H_{42}N_5O_8^+$ $[M+H]^+$ 636.3028, found 636.3027; $[\alpha]^{29}_D$ = −97.0 (*c* = 0.146 in $CHCl_3$).

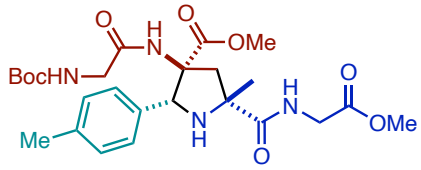



Methyl ((2*R**,4*S**,5*R**)-4-(2-((*tert*-butoxycarbonyl)amino)acetamido)-4-(methoxycarbonyl)-5-(*p*-tolyl)pyrrolidine-2-carbonyl)-*L*-prolinate (**3o**)**:** Isolated as 1.6:1 mixture of diastereomers; Colorless oil; $R_f$ 0.18 ($CHCl_3$/MeOH = 50/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.47 (s, 1H, major), 7.43 (s, 1H minor), 7.16-7.05 (m, 4H+4H), 5.20 (br s, 1H+1H), 4.78 (s, 1H, major), 4.73 (s, 1H, minor), 4.65-4.50 (m, 2H+2H), 3.95-3.62 (m, 7H+7H), 3.34 (s, 3H, major), 3.33

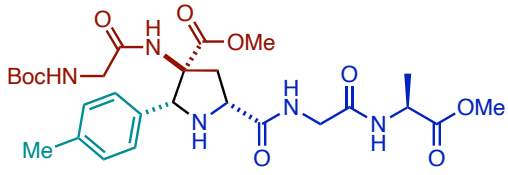
(s, 3H, minor), 2.94-2.79 (m, 1H+1H), 2.56-2.41 (m, 1H+1H), 2.38-2.19 (m, 4H+4H), 2.13-1.91 (m, 3H+3H), 1.48 (s, 9H+9H); **$^{13}$C{$^{1}$H} NMR** (150 MHz, $CDCl_3$) δ 172.4, 172.3, 172.2, 172.0, 170.7, 170.5, 168.9, 168.8, 156.0, 137.4, 137.3, 133.3, 133.2, 132.1, 132.0, 128.80, 128.79, 128.5, 128.4, 125.9, 125.8, 80.3, 71.24, 71.19, 69.2, 69.0, 59.01, 58.96, 58.9, 58.7, 52.5, 52.3, 52.2, 46.7, 46.5, 44.9, 40.0, 39.8, 29.1, 28.9, 28.2, 24.7, 24.6, 21.0; **HRMS** ($FAB^+$) Calcd for $C_{27}H_{39}N_4O_8^+$ $[M+H]^+$ 547.2762, found 547.2778.



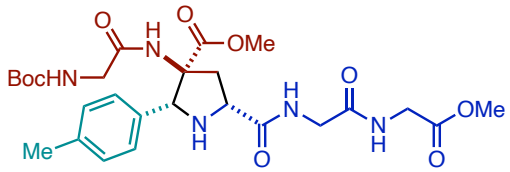

Methyl (2*R**,3*S**,5*R**)-5-(((*S*)-6-amino-1-methoxy-1-oxohexan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3p**)**:** Colorless oil; $R_f$ 0.00 ($CHCl_3$/MeOH = 10/1); Isolated as 1:1 mixture of diastereomers.; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 8.00 (br s, 1H+1H), 7.22-7.15 (m, 2H+2H), 7.10-7.04 (m, 2H+2H), 5.68 (br s, 1H), 5.62 (br s, 1H), 4.76-4.55 (m, 2H+2H), 4.31 (app. t, *J* = 8.5 Hz, 1H), 4.25 (app. t, *J* = 8.7 Hz, 1H), 3.89-3.80 (m, 2H+2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 3.01-2.88 (m, 2H+2H), 2.85-2.71 (m, 1H+1H), 2.70-2.53 (m, 1H+1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.98-1.49 (m, 6H+6H), 1.44 (s, 9H), 1.42 (s, 9H); **$^{13}$C{$^{1}$H} NMR** (150 MHz, $CDCl_3$) δ 174.5, 173.4, 172.5, 171.1, 170.6, 170.1, 169.5, 156.4, 137.8, 137.4, 135.7, 134.3, 128.9, 128.7, 127.2, 126.7, 80.13, 80.06, 70.4, 70.2, 68.5, 68.3, 59.3, 59.1, 52.5, 52.4, 52.3, 52.1, 51.9, 51.5, 44.5, 44.2, 39.6, 39.4, 37.3, 31.4, 31.0, 28.3, 27.1, 27.0, 22.34, 22.28, 21.1; **HRMS** ($FAB^+$) Calcd for $C_{28}H_{44}N_5O_8^+$ $[M+H]^+$ 578.3184, found 578.3205.



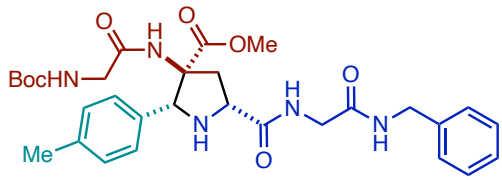

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-5-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3q**)**:** Colorless oil; $R_f$ 0.30 ($CHCl_3$/MeOH = 20/1); **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.27 (t, *J* = 5.4 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.08 (br s, 1H), 5.24 (s, 1H), 5.11 (br s, 1H), 4.20 (dd, *J* = 18.6, 5.4 Hz, 1H), 4.10 (dd, *J* = 18.6, 5.2 Hz, 1H), 3.88-3.75 (m, 5H), 3.43 (s, 3H), 2.87 (d, *J* = 14.2 Hz, 1H), 2.80 (d, *J* = 14.2 Hz, 1H), 2.32 (s, 3H), 1.75 (s, 3H), 1.45 (s, 9H); **$^{13}$C{$^{1}$H} NMR** (150 MHz, $CDCl_3$) δ 177.1, 171.5, 170.6, 169.0, 156.1, 138.0, 134.1, 133.9, 133.8, 129.1, 126.5, 80.3, 69.2, 65.2, 63.3, 52.5, 52.2, 45.0, 43.7, 41.3, 28.2, 27.2, 21.1; **HRMS** ($FAB^+$) Calcd for $C_{25}H_{37}N_4O_8^+$ $[M+H]^+$ 521.2606, found 521.2626.



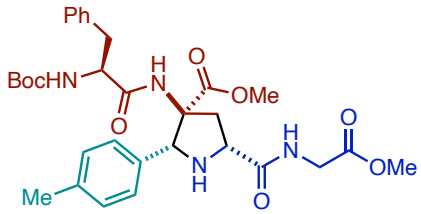
Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3r**)**:** Light yellow oil; $R_f$ 0.28 ($CHCl_3$/MeOH = 20/1); Isolated as 1.2:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H+1H), 7.45-7.32 (m, 2H+2H), 7.25-7.20 (m, 2H+2H), 7.18-7.09 (m, 2H+2H), 5.21 (br s, 1H+1H), 4.79 (s, 1H, minor), 4.76 (s, 1H, major), 4.68-4.59 (m, 1H+1H), 4.40-4.18 (m, 2H+2H), 3.97-3.68 (m, 6H+6H), 3.32 (s, 3H, major), 3.30 (s, 3H, minor), 3.00-2.77 (m, 2H+2H), 2.35-2.32 (m, 3H+3H), 1.46 (s, 9H, major), 1.45 (s, 9H, minor), 1.45-1.41 (m, 3H+3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.40, 174.35, 173.3, 173.0, 171.5, 171.4, 169.7, 169.6, 169.0, 168.8, 156.3, 138.3, 138.2, 133.9, 133.8, 129.12, 129.06, 129.00, 128.9, 128.8, 126.7, 126.6, 80.3, 68.5, 68.1, 58.2, 58.0, 52.42, 52.40, 52.39, 52.27, 48.00, 47.97, 42.8, 39.1, 38.8, 28.2, 21.09, 21.08, 17.9, 17.6; **HRMS** (FAB$^+$) Calcd for $C_{27}H_{40}N_5O_9^+$ $[M+H]^+$ 578.2821, found 578.2840.



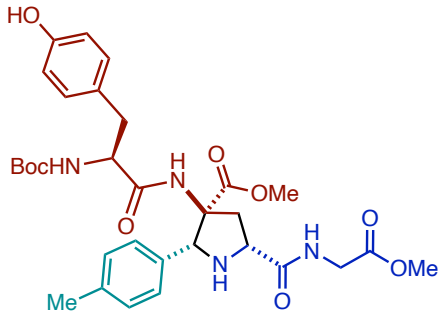

Methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3s**)**:** Light yellow oil; $R_f$ 0.28 ($CHCl_3$/MeOH = 10/1); Isolated as 3:1 mixture of diastereomers (*endo*/*exo*).; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.05-7.94 (m, 1H+1H), 7.52-7.31 (m, 2H+2H), 7.26-7.20 (m, 2H+2H), 7.17-7.08 (m, 2H+2H), 5.35-5.30 (m, 1H+1H), 4.80-4.73 (m, 1H+1H), 4.37-3.84 (m, 5H+5H), 3.82-3.68 (m, 5H+5H), 3.32-3.28 (m, 3H+3H), 2.93-2.78 (m, 2H+2H), 2.33 (s, 3H+3H), 1.46 (s, 9H, minor), 1.45 (s, 9H, major); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.5, 171.5, 170.2, 169.9, 169.7, 156.3, 138.2, 133.9, 133.8, 129.1, 126.7, 126.2, 80.3, 79.8, 68.5, 68.4, 58.2, 52.3, 52.2, 42.8, 41.0, 38.9, 28.2, 21.1, 21.0; **HRMS** (FAB$^+$) Calcd for $C_{26}H_{38}N_5O_9^+$ $[M+H]^+$ 564.2664, found 564.2689.



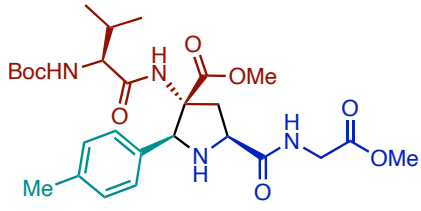

Methyl (2*R**,3*S**,5*R**)-5-((2-(benzylamino)-2-oxoethyl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3t**)**:** Colorless oil; $R_f$ 0.15 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.32-7.28 (m, 3H), 7.25-7.20 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.13 (br s, 1H), 4.77 (s, 1H), 4.60 (dd, *J* = 15.0, 6.4 Hz, 1H), 4.43-4.34 (m, 2H), 4.23-4.15 (m, 1H), 3.84 (dd, *J* = 16.9, 4.5 Hz, 1H), 3.76 (d, *J* = 6.0 Hz, 2H), 3.11 (s, 3H), 2.92-2.79 (m, 2H), 2.33 (s, 3H), 1.45 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.4, 171.4, 169.7, 169.2, 165.7, 156.3, 138.32, 138.27, 133.7, 129.2, 129.1, 128.6, 128.5, 128.3, 127.6, 127.2, 126.6, 126.1, 80.4, 68.4, 68.2, 58.0, 52.3, 44.7, 43.3, 43.1, 38.9, 28.2, 21.1; **HRMS** (FAB$^+$) Calcd for $C_{30}H_{40}N_5O_7^+$ $[M+H]^+$ 582.2922, found 582.2910.



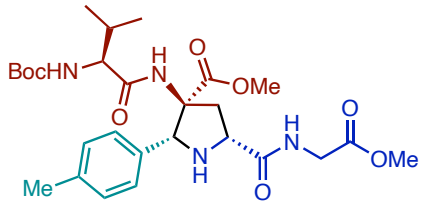

Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3u**)**:** Colorless oil; $R_f$ 0.40 ($CHCl_3$/MeOH = 20/1); Isolated as 1.1:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.71 (m, 1H+1H), 7.41-6.97 (m, 9H+9H), 6.93 (br s, 1H+1H), 5.13 (br s, 1H, minor), 5.00 (br s, 1H, major), 4.83 (s, 1H, minor), 4.67 (s, 1H, major), 4.45-4.32 (m, 1H+1H), 4.28-4.07 (m, 2H+2H), 3.81-3.62 (s, 4H+4H), 3.325 (s, 3H), 3.318 (s, 3H), 3.17-2.98 (m, 2H+2H), 2.96-2.83 (m, 1H+1H), 2.63 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.51 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.44 (s, 9H, minor), 1.41 (s, 9H, major); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 171.4, 171.3, 170.9, 170.8, 170.5, 155.6, 155.5, 138.0, 136.6, 134.3, 134.1, 132.2, 132.1, 129.5, 129.4, 129.0, 128.9, 128.8, 128.64, 128.56, 127.2, 127.1, 126.7, 126.6, 80.4, 69.2, 69.0, 68.0, 67.5, 58.94, 58.91, 56.1, 52.50, 52.48, 52.4, 41.04, 41.03, 38.4, 37.9, 28.4, 28.33, 28.29, 21.2; **HRMS** (FAB$^+$) Calcd for $C_{31}H_{41}N_4O_8^+$ $[M+H]^+$ 597.2919, found 597.2944.



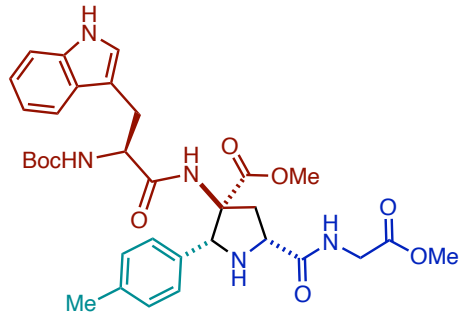

Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3v**)**:** Colorless solid; m.p. 90-92 °C; $R_f$ 0.25 ($CHCl_3$/MeOH = 20/1); Isolated as 1.1:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H, minor), 7.70 (br s, 1H, major), 7.16-7.02 (m, 6H+6H), 6.92 (br s, 1H+1H), 6.83-6.73 (m, 2H+2H), 5.21 (br s, 1H, minor), 5.12 (br s, 1H, major), 4.71 (s, 1H, major), 4.48 (s, 1H, minor), 4.36-4.26 (m, 1H+1H), 4.22-4.06 (m, 2H+2H), 3.96-3.86 (m, 1H, major), 3.81-3.64 (m, 3H+3H+1H, minor), 3.30 (s, 3H, minor), 3.26 (s, 3H, major), 3.14-3.02 (m, 2H), 2.96-2.78 (m, 2H), 2.73-2.48 (m, 2H+2H), 2.29 (s, 3H, minor), 2.28 (s, 3H, major), 1.45 (s, 9H, minor), 1.42 (s, 9H, major); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.3, 174.2, 171.14, 171.12, 170.84, 170.78, 170.4, 170.3, 155.7, 155.6, 137.9, 137.8, 134.3, 134.2, 133.9, 133.8, 130.5, 128.8, 127.6, 126.7, 126.6, 115.9, 115.7, 80.3, 69.2, 68.5, 58.8, 58.7, 56.2, 52.4, 52.3, 52.2, 40.98, 40.96, 38.3, 37.9, 37.3, 28.2, 21.05, 21.03; **HRMS** (FAB$^+$) Calcd for $C_{31}H_{41}N_4O_9^+$ $[M+H]^+$ 613.2868, found 613.2871.



Methyl (2*S*,3*R*,5*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w'**)**:** Colorless solid; m.p. 82-84 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 5.5 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.19 (br s, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.92 (br s, 1H), 4.89 (s, 1H), 4.31 (dd, *J* = 9.4, 7.6 Hz, 1H), 4.20 (dd, *J* = 18.5, 5.6 Hz, 1H), 4.11 (dd, *J* = 18.5, 5.3 Hz, 1H), 3.80 (s, 3H), 3.73-3.60 (m, 1H), 3.37 (s, 3H), 2.95 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.65 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.31 (s, 3H), 2.29-2.24 (m, 1H), 1.45 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.8, 171.7, 171.3, 170.5, 156.0, 138.0, 134.2, 129.0, 126.7, 80.3, 69.1, 67.8, 60.4, 59.0, 52.5, 52.4, 41.0, 38.5, 30.2, 28.4, 21.2, 19.6, 17.5; **HRMS** (FAB$^+$) Calcd for $C_{27}H_{41}N_4O_8^+$ $[M+H]^+$ 549.2919, found 549.2932; $[\alpha]^{27}_D$ = −69.1 (*c* = 0.108 in $CHCl_3$).

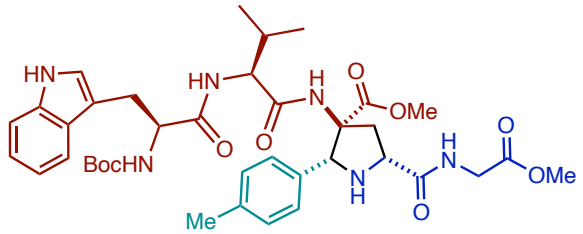



Methyl (2*R*,3*S*,5*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w''**)**:** Colorless solid; m.p. 82-84 °C; $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 6.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.02 (br s, 1H), 5.06 (br s, 1H), 4.89 (s, 1H), 4.29 (app. t, *J* = 8.3 Hz, 1H), 4.20 (dd, *J* = 18.4, 5.7 Hz, 1H), 4.11 (dd, *J* = 18.4, 5.2 Hz, 1H), 3.90 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.80 (s, 3H), 3.38 (s, 3H), 2.96 (dd, *J* = 13.1, 9.3 Hz, 1H), 2.64 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.32 (s, 3H), 2.15-2.06 (m, 1H), 1.46 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 6H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.7, 171.3, 170.4, 156.0, 138.0, 134.1, 129.0, 126.6, 80.0, 69.1, 67.7, 60.3, 58.9, 52.4, 52.3, 40.9, 38.1, 30.6, 28.3, 21.1, 19.2, 18.0; **HRMS** (FAB$^+$) Calcd for $C_{27}H_{41}N_4O_8^+$ $[M+H]^+$ 549.2919, found 549.2931; $[\alpha]^{29}_D$ = +58.6 (*c* = 0.136 in $CHCl_3$).

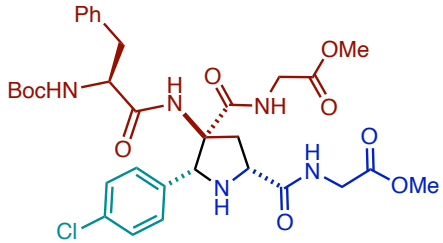



Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3x**)**:** Colorless solid; m.p. 100-102 °C; $R_f$ 0.28 ($CHCl_3$/MeOH = 20/1); Isolated as ca. 1.2:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.52 (br s, 1H, major), 8.36 (br s, 1H, minor), 7.77-7.68 (m, 2H+2H), 7.42-7.32 (m, 1H+1H), 7.25-7.05 (m, 3H+3H), 7.02-6.90 (m, 3H+3H), 5.20 (br s, 1H+1H), 4.69 (br s, 1H, minor), 4.52-4.46 (m, 1H+1H), 4.25 (s, 1H, major), 4.22-3.94 (m, 3H+3H), 3.87-3.60 (m, 4H+4H), 3.44-3.28 (m, 1H+1H), 3.25 (s, 3H, minor), 3.24 (s, 3H, major), 3.22-3.10 (m, 1H+1H), 2.83 (dd, *J* = 13.6, 9.1 Hz, 1H), 2.69-2.56 (m, 1H+1H), 2.55-2.42 (m, 1H), 2.28 (s, 3H, minor), 2.27 (s, 3H, major), 1.46 (s, 9H, minor), 1.43 (s, 9H, major); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.1, 174.0, 171.4, 171.3, 170.8,

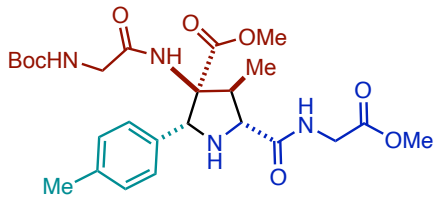
170.3, 155.6, 155.5, 137.8, 137.7, 136.4, 136.2, 134.5, 134.1, 133.8, 133.7, 128.95, 128.89, 128.79, 128.75, 127.5, 127.2, 126.6, 123.8, 123.6, 122.13, 122.05, 119.7, 119.6, 118.7, 118.6, 111.6, 111.4, 110.3, 110.1, 80.2, 80.0, 69.3, 68.8, 68.6, 58.8, 58.6, 55.5, 54.9, 52.3, 52.2, 52.1, 40.89, 40.88, 38.4, 37.9, 31.2, 29.6, 28.3, 21.0; **HRMS** (FAB$^+$) Calcd for $C_{33}H_{42}N_5O_8^+$ [M+H]$^+$ 636.3028, found 636.3036.



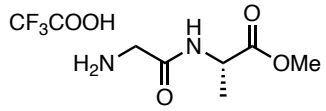

Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3y**)**:** Colorless solid; m.p. 116-118 °C; $R_f$ 0.30 ($CHCl_3$/MeOH = 20/1); Isolated as 1.1:1 mixture of diastereomers.; **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.96 (br s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.43-6.99 (m, 8H+9H), 6.95 (br s, 1H), 6.57 (br s, 1H), 6.40 (br s, 1H), 5.46 (br s, 1H), 5.27 (br s, 1H), 4.58 (s, 1H), 4.55-4.48 (m, 1H), 4.45 (dd, *J* = 12.3, 6.2 Hz, 1H), 4.38-4.32 (m, 1H), 4.27-4.04 (m, 4H+4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.29-3.21 (m, 2H+2H), 3.19 (s, 3H), 3.15 (s, 3H), 2.76-2.60 (m, 2H+2H), 2.290 (s, 3H), 2.285 (s, 3H), 2.20-2.11 (m, 1H), 2.00-1.91 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 0.90-0.80 (m, 6H+6H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 174.6, 174.1, 172.0, 171.9, 170.7, 170.5, 170.4, 170.2, 169.6, 156.2, 155.4, 137.7, 136.5, 136.4, 128.8, 128.7, 127.3, 127.1, 123.6, 123.0, 122.2, 121.9, 119.7, 119.3, 118.6, 111.6, 111.5, 109.5, 80.7, 80.0, 70.3, 69.2, 68.6, 59.5, 59.3, 59.2, 59.1, 58.3, 55.6, 55.4, 52.4, 52.3, 51.9, 40.83, 40.81, 38.1, 37.4, 31.2, 29.7, 28.3, 21.1, 19.2, 18.8; **HRMS** (EI$^+$) Calcd for $C_{38}H_{50}N_6O_9^+$ [M]$^+$ 734.3634, found 734.3641.



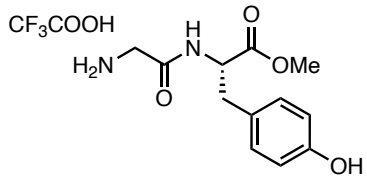

Dimethyl 2,2'-(((2*R**,4*S**,5*R**)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-(4-chlorophenyl)pyrrolidine-2,4-dicarbonyl)bis(azanediyl))diacetate (**3z**)**:** Colorless oil; $R_f$ 0.38 ($CHCl_3$/MeOH = 20/1); Isolated as 1.1:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H, major), 7.68-7.61 (m, 1H, minor), 7.50-7.28 (m, 5H+5H), 7.25-7.10 (m, 4H+4H), 5.18 (s, 1H), 5.15 (s, 1H), 5.12-5.07 (m, 1H), 4.95-4.88 (m, 1H), 4.45-4.30 (m, 1H+1H), 4.24-4.13 (m, 1H+1H), 4.05 (dd, *J* = 18.1, 5.4 Hz, 1H+1H), 3.97-3.43 (m, 9H+9H), 3.35-2.97 (dd, 3H+3H), 2.38 (dd, *J* = 14.2, 7.5 Hz, 1H, major), 2.29 (dd, *J* = 14.2, 7.5 Hz, 1H, minor), 1.43 (s, 9H, minor), 1.39 (s, 9H, major); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.4, 173.3, 171.0, 170.8, 170.5, 170.44, 170.41, 170.38, 155.53, 155.47, 136.31, 136.28, 135.15, 135.07, 134.1, 133.9, 133.7, 133.6, 129.41, 129.36, 129.2, 129.1, 129.0, 128.9, 128.4, 128.3, 127.83, 127.78, 127.3, 127.2, 80.6, 80.4, 66.6, 66.4, 63.39, 63.36, 57.5, 57.4, 56.5, 52.5, 41.59, 41.56, 40.9, 38.3, 38.2, 37.9, 37.7, 28.4, 28.3; **HRMS** (FAB$^+$) Calcd for $C_{32}H_{41}{}^{35}ClN_5O_9^+$ [M+H]$^+$ 674.2587, found 674.2596.



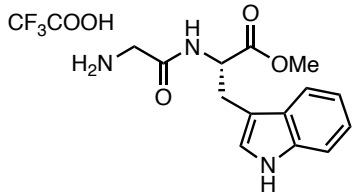
Methyl (2*R**,3*S**,4*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-4-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3aa**)**:** Colorless oil; $R_f$ 0.25 ($CHCl_3$/MeOH = 20/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.15 (br s, 1H), 4.76 (s, 1H), 4.21 (dd, *J* = 18.3, 5.7 Hz, 1H), 4.11 (dd, *J* = 18.3, 5.3 Hz, 1H), 3.84-3.73 (m, 5H), 3.26 (s, 3H), 3.13-3.07 (m, 1H), 2.33 (s, 3H), 1.48 (s, 9H), 1.15 (d, *J* = 7.1 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.3, 171.3, 170.4, 169.6, 159.4, 137.9, 134.6, 128.9, 126.7, 80.5, 71.8, 67.7, 66.8, 52.29, 52.26, 45.4, 40.9, 29.7, 28.3, 21.1, 14.3; **HRMS** (FAB$^+$) Calcd for $C_{25}H_{37}N_4O_8^+$ $[M+H]^+$ 521.2606, found 521.2622.



Methyl glycyl-*L*-alaninate trifluoroacetate salt (**4b**)**:** Colorless solid; m.p. 85-87 °C; **$^1$H NMR** (400 MHz, $CD_3OD$) δ 4.46 (q, *J* = 14.6, 7.3 Hz 1H), 3.70 (s, 3H), 3.68 (s, 2H), 1.38 (d, *J* = 7.3 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $D_2O$) δ 175.0, 166.9, 163.0 (q, $J_{C\text{-}F}$ = 35.2 Hz), 116.4 (q, $J_{C\text{-}F}$ = 288.7 Hz), 53.1, 48.8, 40.4, 16.1; **HRMS** (EI$^+$) Calcd for $C_6H_{12}N_2O_3^+$ $[M]^+$ 160.0842, found 160.0853.

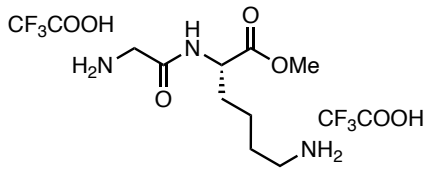


Methyl glycyl-*L*-tyrosinate trifluoroacetate salt (**4d**)**:** Colorless oil; **$^1$H NMR** (400 MHz, $D_2O$) δ 7.11-7.03 (m, 2H), 6.83-6.77 (m, 2H), 3.80-3.66 (m, 6H), 3.13-3.03 (m, 1H), 2.96-2.86 (m, 1H); **$^{13}$C{$^1$H} NMR** (150 MHz, $D_2O$) δ 173.4, 166.8, 162.9 (q, $J_{C\text{-}F}$ = 34.8 Hz), 154.6, 130.6, 128.1, 116.4 (q, $J_{C\text{-}F}$ = 290.1 Hz), 115.5, 54.5, 53.0, 40.3, 35.9; **HRMS** (FAB$^+$) Calcd for $C_{12}H_{17}N_2O_4^+$ $[M+H]^+$ 253.1183, found 253.1188.

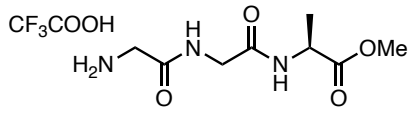


Methyl glycyl-*L*-tryptophanate trifluoroacetate salt (**4e**)**:** Orange solid; m.p. 31-33 °C; **$^1$H NMR** (400 MHz, $CD_3OD$) δ 7.49 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.09-7.04 (m, 2H), 7.03-6.97 (m, 1H), 4.83-4.78 (m, 1H), 3.68-3.52 (m, 6H), 3.34-3.30 (m, 1H), 3.19-3.16 (dd, *J* = 14.7, 7.9 Hz, 1H); **$^{13}$C{$^1$H} NMR** (150 MHz, $D_2O$) δ 173.7, 166.7, 163.0 (q, $J_{C\text{-}F}$ = 35.2 Hz), 136.2, 126.9, 124.5, 122.0, 119.4, 118.3, 116.4 (q, $J_{C\text{-}F}$ = 289.0 Hz), 112.0, 108.9,

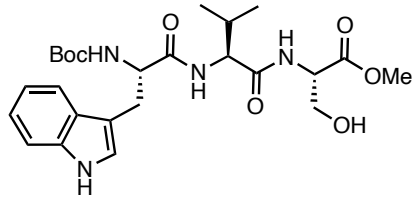
53.9, 53.0, 40.3, 26.8; **HRMS** (FAB$^+$) Calcd for $C_{14}H_{18}N_3O_3^+$ [M+H]$^+$ 276.1343, found 276.1341.



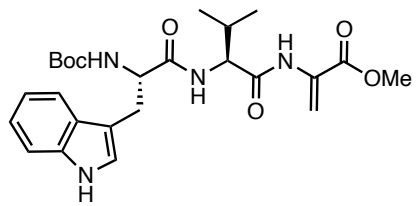

Methyl glycyl-*L*-lysinate bis(trifluoroacetate) salt (**4g**)**:** Colorless oil; **$^1$H NMR** (400 MHz, $CD_3OD$) δ 4.49 (q, *J* = 8.6, 5.4 Hz, 1H), 3.75-3.72 (m, 5H), 2.92 (t, *J* = 7.7 Hz, 2H), 1.95-1.86 (m, 1H), 1.80-1.71 (m, 1H), 1.71-1.64 (m, 2H), 1.51-1.42 (m, 2H); **$^{13}$C{$^1$H} NMR** (150 MHz, $D_2O$) δ 174.1, 167.2, 163.0 (q, $J_{C\text{-}F}$ = 35.3 Hz), 116.4 (q, $J_{C\text{-}F}$ = 290.1 Hz), 53.1, 52.8, 40.3, 39.2, 30.0, 26.3, 22.0; **HRMS** (FAB$^+$) Calcd for $C_9H_{20}N_3O_3^+$ [M+H]$^+$ 218.1499, found 218.1512.



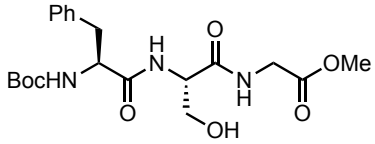

Methyl glycylglycyl-*L*-alaninate trifluoroacetate salt (**4h**)**:** Colorless oil; **$^1$H NMR** (400 MHz, $CD_3OD$) δ 4.48-4.39 (m, 1H), 3.98 (d, *J* = 4.4 Hz, 2H), 3.74 (s, 2H), 3.72 (s, 3H), 1.39 (d, *J* = 7.3 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $D_2O$) δ 175.1, 170.9, 167.7, 162.9 (q, $J_{C\text{-}F}$ = 35.6 Hz), 116.4 (q, $J_{C\text{-}F}$ = 289.8 Hz), 53.0, 48.7, 42.1, 40.4, 16.0; **HRMS** (FAB$^+$) Calcd for $C_8H_{16}N_3O_4^+$ [M+H]$^+$ 218.1135, found 218.1144.



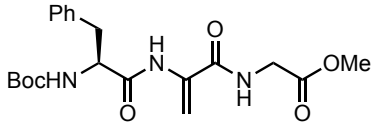

Methyl (*tert*-butoxycarbonyl)-*L*-tryptophyl-*L*-valyl-*L*-serinate**:** Colorless solid (**9**); m.p. 85-87 °C; $R_f$ 0.18 (hexane/EtOAc = 1/2); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.70-7.62 (m, 1H), 7.40-7.34 (m, 1H), 7.26-7.08 (m, 3H), 7.00 (br s, 1H), 6.42 (br s, 1H), 5.19 (br s, 1H), 4.53 (br s, 1H), 4.48-4.36 (m, 1H), 4.28-4.18 (m, 1H), 3.96-3.90 (m, 1H), 3.77 (s, 3H), 3.75 (s, 2H), 3.26 (d, *J* = 6.3 Hz, 2H), 1.88-1.83 (m, 1H), 1.43 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CD_3OD$) δ 172.7, 171.3, 170.0, 155.7, 136.0, 126.8, 122.5, 120.3, 117.7, 117.4, 110.2, 109.0, 78.7, 77.4, 60.8, 57.7, 54.9, 54.2, 50.7, 30.4, 26.6, 17.5, 16.5; **HRMS** (FAB$^+$) Calcd for $C_{25}H_{37}N_4O_7^+$ [M+H]$^+$ 505.2657, found 505.2642.



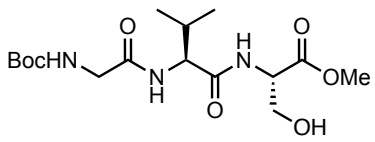
Methyl (6*S*,9*S*)-6-((1*H*-indol-3-yl)methyl)-9-isopropyl-2,2-dimethyl-12-methylene-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (**2f**)**:** Light yellow oil; $R_f$ 0.55 (hexane/EtOAc = 1/1); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 8.02 (br s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20-7.05 (m, 3H), 6.52 (s, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 5.19 (br s, 1H), 4.49 (br s, 1H), 4.18 (t, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 3.36-3.16 (m, 2H), 2.09-2.03 (m, 1H), 1.60 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 172.0, 169.4, 164.2, 155.5, 136.2, 130.7, 123.1, 122.34, 122.28, 119.83, 119.77, 118.8, 111.2, 109.5, 80.2, 59.3, 55.1, 53.0, 30.5, 28.2, 19.0, 17.7; **HRMS** (FAB$^+$) Calcd for $C_{25}H_{35}N_4O_6^+$ $[M+H]^+$ 487.2551, found 487.2558.



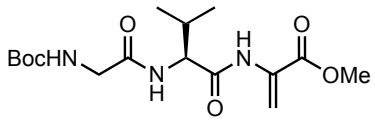

Methyl (*tert*-butoxycarbonyl)-*L*-phenylalanyl-*L*-serylglycinate**:** Colorless oil; $R_f$ 0.35 (EtOAc only); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 3H), 7.24-7.18 (m, 2H), 6.90 (br s, 1H), 4.95 (br s, 1H), 4.46-4.41 (m, 1H), 4.35-4.29 (m, 1H), 4.20-4.12 (m, 2H), 3.85-3.76 (m, 1H), 3.74 (s, 3H), 3.59 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.17-3.12 (m, 1H), 3.07-3.02 (m, 2H), 1.39 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 172.1, 170.8, 170.2, 155.7, 136.4, 129.2, 128.4, 126.7, 80.1, 62.5, 55.8, 54.6, 52.2, 41.1, 38.2, 28.0; **HRMS** (FAB$^+$) Calcd for $C_{20}H_{30}N_3O_7^+$ $[M+H]^+$ 424.2078, found 424.2067.



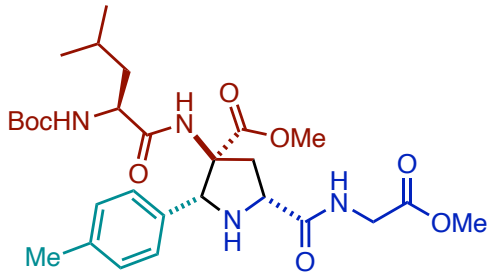

Methyl (*S*)-(2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)acryloyl)glycinate (**2g**)**:** Colorless solid; $R_f$ 0.40 (hexane/EtOAc = 1:1); m.p. 129-131 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.17 (m, 3H), 6.66 (br s, 1H), 6.50 (s, 1H), 5.37 (s, 1H), 4.97 (br s, 1H), 4.46 (br s, 1H), 4.09 (dd, *J* = 5.2, 2.5 Hz, 2H), 3.79 (s, 3H), 3.16 (dd, *J* = 14.0, 6.2 Hz, 1H), 3.06 (br s, 1H), 1.39 (s, 9H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 170.4, 169.9, 163.6, 155.4, 136.2, 133.4, 129.2, 128.7, 127.1, 103.2, 80.5, 56.5, 52.6, 41.6, 38.2, 28.2; **HRMS** (FAB$^+$) Calcd for $C_{20}H_{28}N_3O_6$ $[M+H]^+$ 406.1973, found 406.1970.



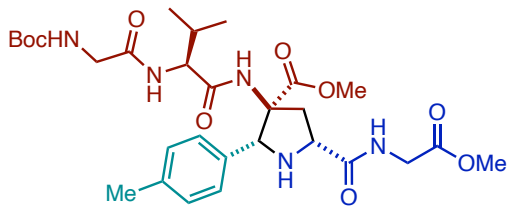

Methyl (*tert*-butoxycarbonyl)glycyl-*L*-valyl-*L*-serinate (**6b**)**:** Colorless solid; $R_f$ 0.43 (EtOAc only); m.p. 32-34 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.28 (br s, 1H), 4.67-4.62 (m, 1H), 4.29 (t, *J* = 7.6, 1H), 4.00-3.90 (m, 2H), 3.88-3.77 (m, 2H), 3.79 (s, 3H), 3.42 (br s, 1H), 2.18-2.14 (m, 1H), 1.45 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CD_3OD$) δ 171.5, 170.4, 170.0, 156.4, 78.7, 60.7, 57.5, 54.2, 50.7, 42.6, 30.4, 26.7, 17.6, 16.4; **HRMS** (FAB$^+$) Calcd for $C_{16}H_{30}N_3O_7^+$ $[M+H]^+$ 376.2078, found 376.2066.



Methyl (*S*)-9-isopropyl-2,2-dimethyl-12-methylene-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (**7b**)**:** Colorless solid; $R_f$ 0.30 (hexane/EtOAc = 1:1); m.p. 110-111 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 6.75 (br s, 1H), 6.59 (s, 1H), 5.93 (d, *J* = 1.3 Hz, 1H), 5.13 (br s, 1H), 4.36 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.94-3.76 (m, 2H), 3.86 (s, 3H), 2.23-2.17 (m, 1H), 1.46 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 169.89, 169.86, 164.2, 156.2, 130.6, 109.6, 80.5, 59.0, 53.0, 44.4, 30.9, 28.2, 19.2, 17.7; **HRMS** (FAB$^+$) Calcd for $C_{16}H_{28}N_3O_6^+$ $[M+H]^+$ 358.1973, found 358.1991.



Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8a**)**:** Colorless solid; m.p. 51-53 °C; (53.4 mg, 94%); $R_f$ 0.45 ($CHCl_3$/MeOH = 20/1); Isolated as ca. 1.2:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.77-7.68 (m, 1H+1H), 7.26-7.21 (m, 2H+2H), 7.17 (br s, 1H+1H), 7.14-7.08 (m, 2H+2H), 4.92-4.85 (m, 1H+2H), 4.78 (br s, 1H, minor), 4.32-4.25 (m, 1H+1H), 4.24-4.07 (m, 2H+2H), 3.82-3.68 (s, 4H+4H), 3.39 (s, 3H, minor), 3.37 (s, 3H, major), 3.02-2.87 (m, 1H+1H), 2.70-2.58 (m, 1H+1H), 2.32 (s, 3H, minor), 2.31 (s, 3H, major), 1.77-1.65 (m, 2H+2H), 1.55-1.47 (m, 1H+1H), 1.46 (s, 9H, minor), 1.44 (s, 9H, major), 1.01-0.89 (m, 6H+6H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.8, 172.2, 172.1, 171.5, 171.4, 170.37, 170.35, 155.8, 137.82, 137.79, 134.3, 128.88, 128.86, 126.7, 126.5, 80.2, 80.1, 69.04, 68.98, 67.8, 67.6, 58.9, 58.8, 52.37, 52.35, 52.2, 40.9, 40.7, 40.5, 38.5, 38.1, 28.2, 24.8, 24.7, 22.9, 22.8, 22.0, 21.9, 21.07, 21.06; **HRMS** (FAB$^+$) Calcd for $C_{28}H_{43}N_4O_8^+$ $[M+H]^+$ 563.3075, found 563.3080.



Methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8b**)**:** Colorless solid; m.p. 116-118 °C; (47.1 mg, 78%); $R_f$ 0.23 ($CHCl_3$/MeOH = 20/1); Isolated as 1:1 mixture of diastereomers.; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H+1H), 7.25-7.20 (m, 2H+2H), 7.15-7.08 (m, 2H+2H), 6.82 (br s, 1H), 6.72 (br s, 1H), 5.38 (br s, 1H), 5.27 (br s, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 4.36-4.28 (m, 1H+1H), 4.27-4.05 (m, 3H+3H), 3.95-3.70 (m, 5H+5H), 3.36-3.29 (m, 3H+3H), 2.93-2.75 (m, 1H+1H), 2.74-2.61 (m, 1H+1H), 2.32 (s, 3H+3H), 2.21-2.06 (m, 1H+1H), 1.47 (s, 9H), 1.45 (s, 9H), 1.05-0.92 (m, 6H+6H); **$^{13}$C{$^1$H} NMR** (150 MHz, $CDCl_3$) δ 173.9, 173.8, 170.9, 170.8, 170.4, 170.3, 170.2, 156.5, 156.2, 137.8, 137.7, 135.1, 128.8, 127.0, 126.9, 80.5, 80.2, 70.1, 70.0, 69.0, 68.5, 59.2,

59.1, 58.6, 58.1, 52.3, 52.2, 52.1, 52.0, 44.5, 44.4, 40.9, 40.8, 38.6, 38.0, 31.2, 30.3, 28.24, 28.21, 21.1, 21.0, 19.4, 19.0, 17.9, 17.5; **HRMS** ($FAB^+$) Calcd for $C_{29}H_{44}N_5O_9^+$ $[M+H]^+$ 606.3134, found 606.3150.

**References for Supporting Information**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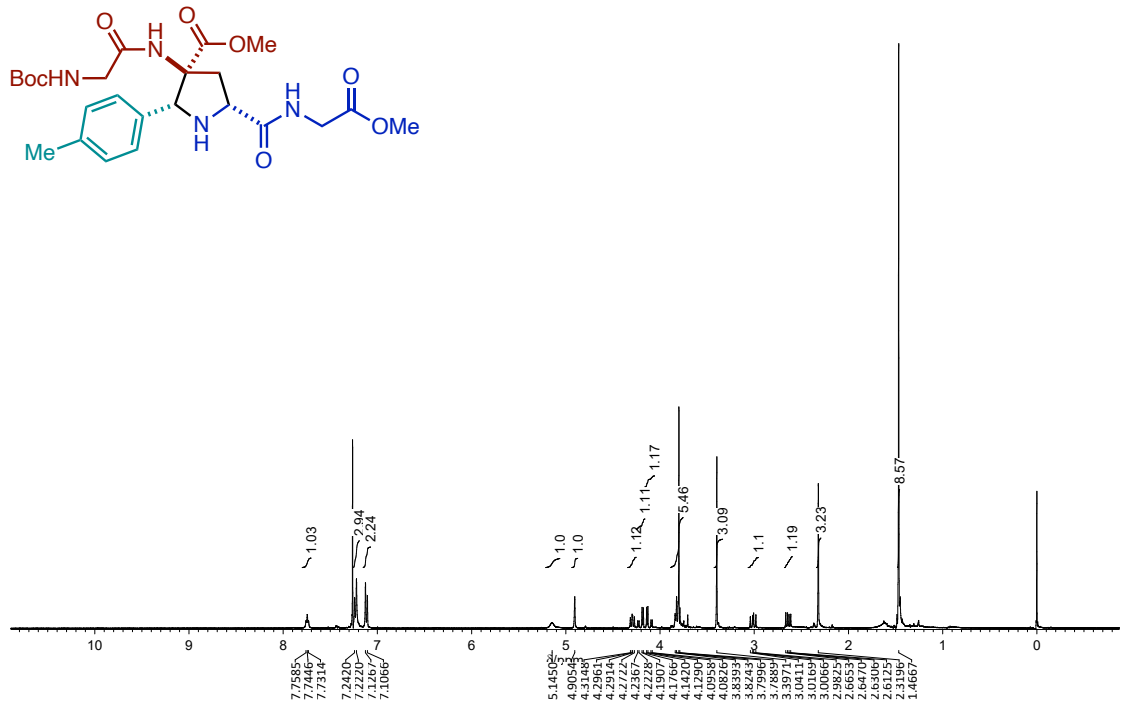
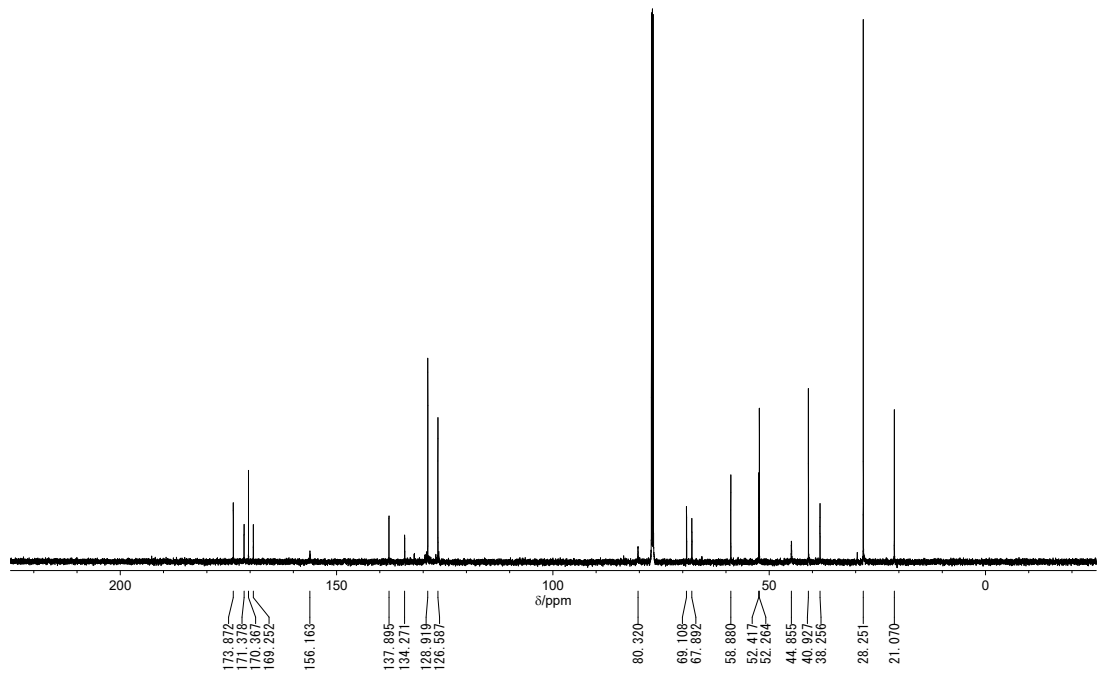
## $^{1}$H and $^{13}$C NMR Spectra of Compounds

$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3a**) ($CDCl_3$)



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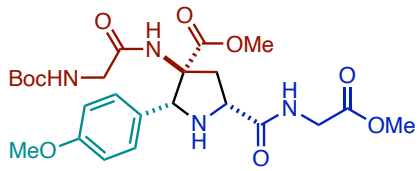





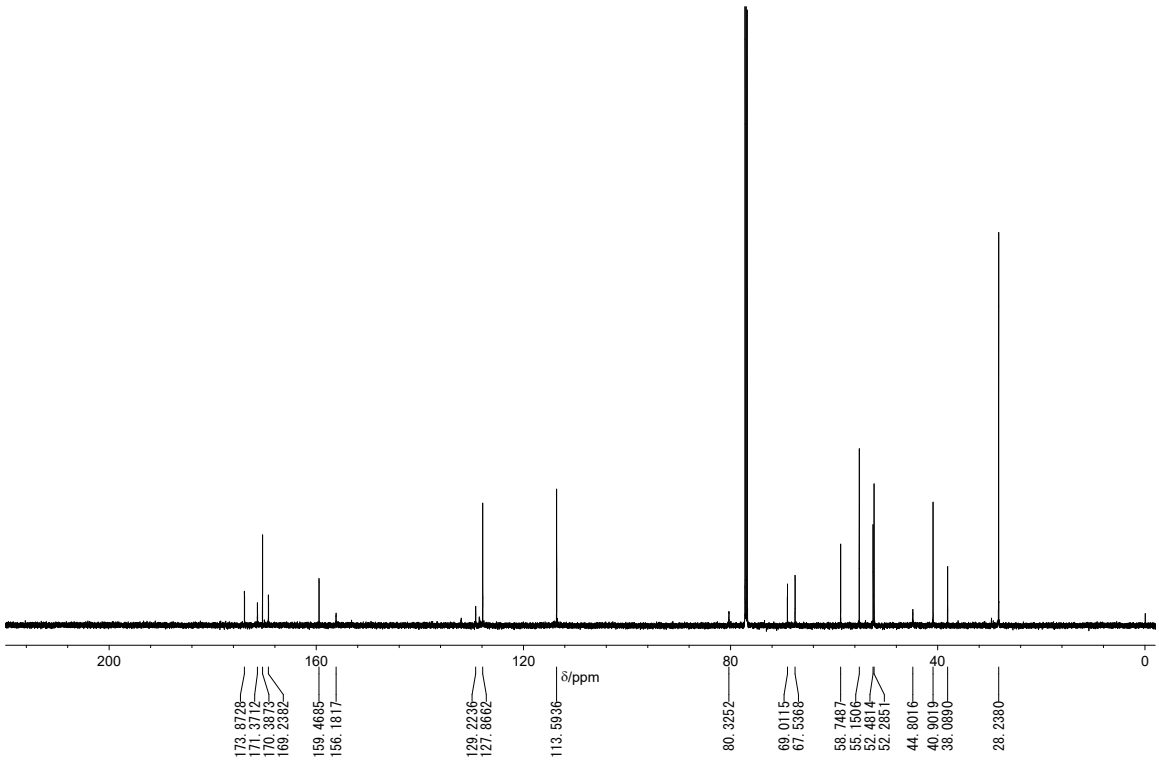

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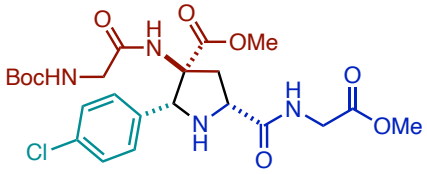





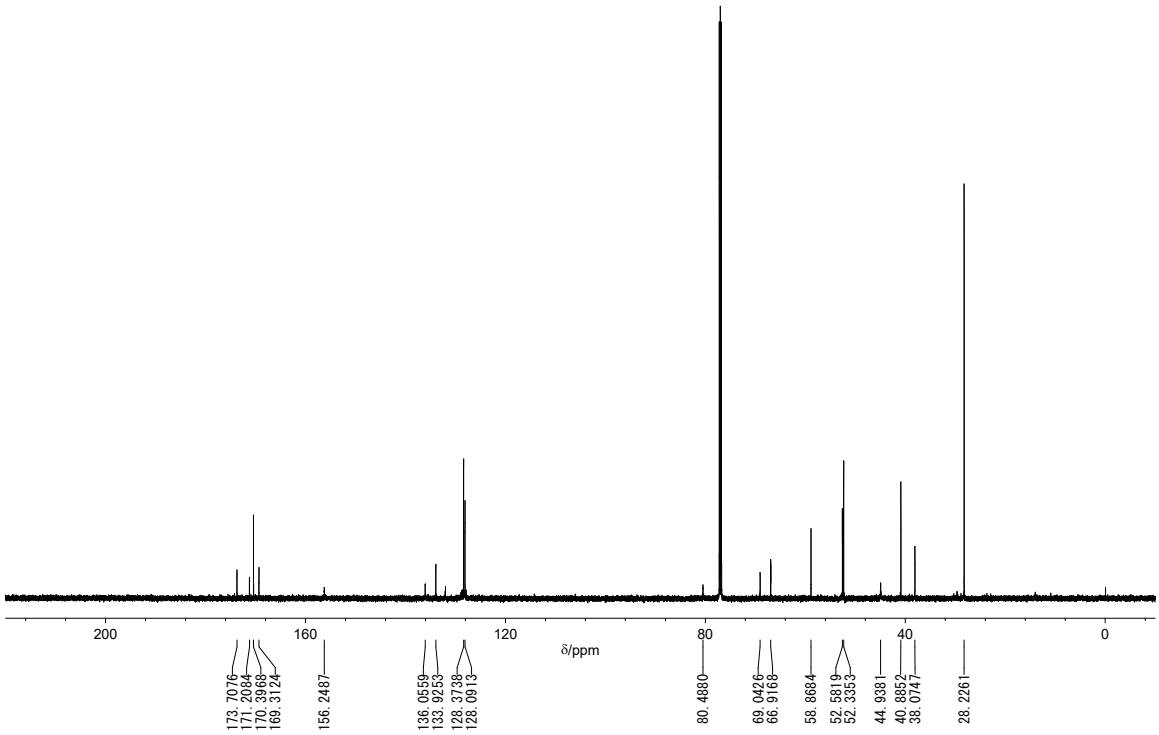

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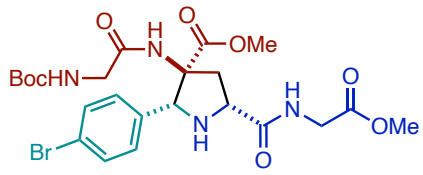





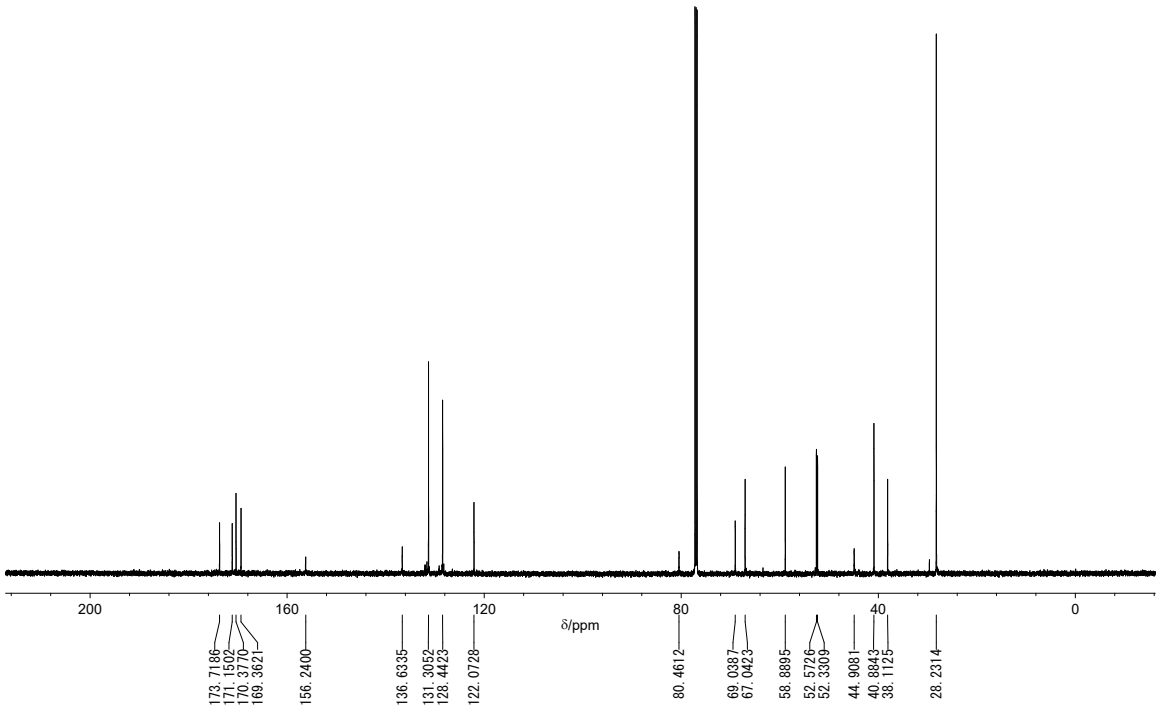

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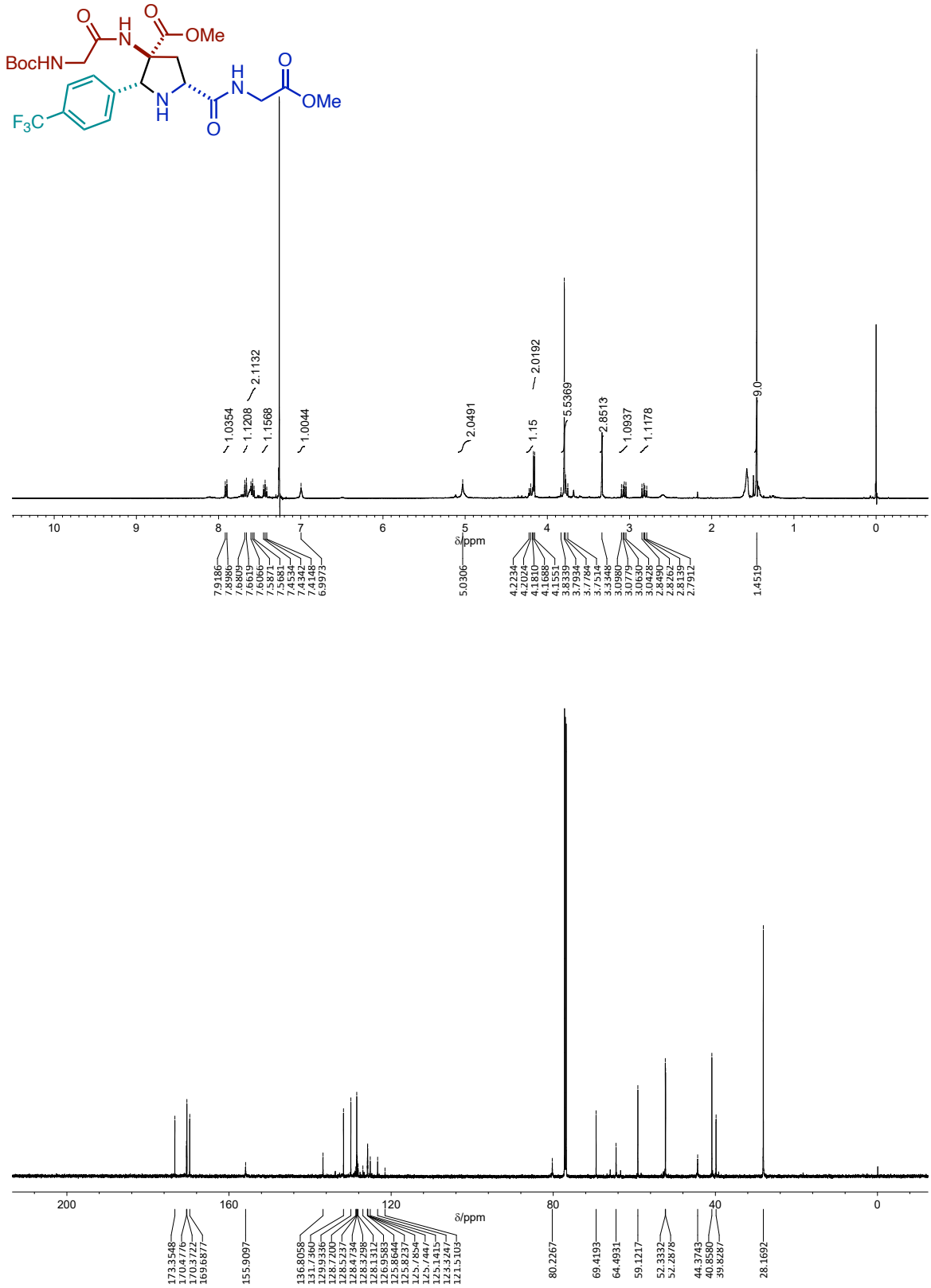

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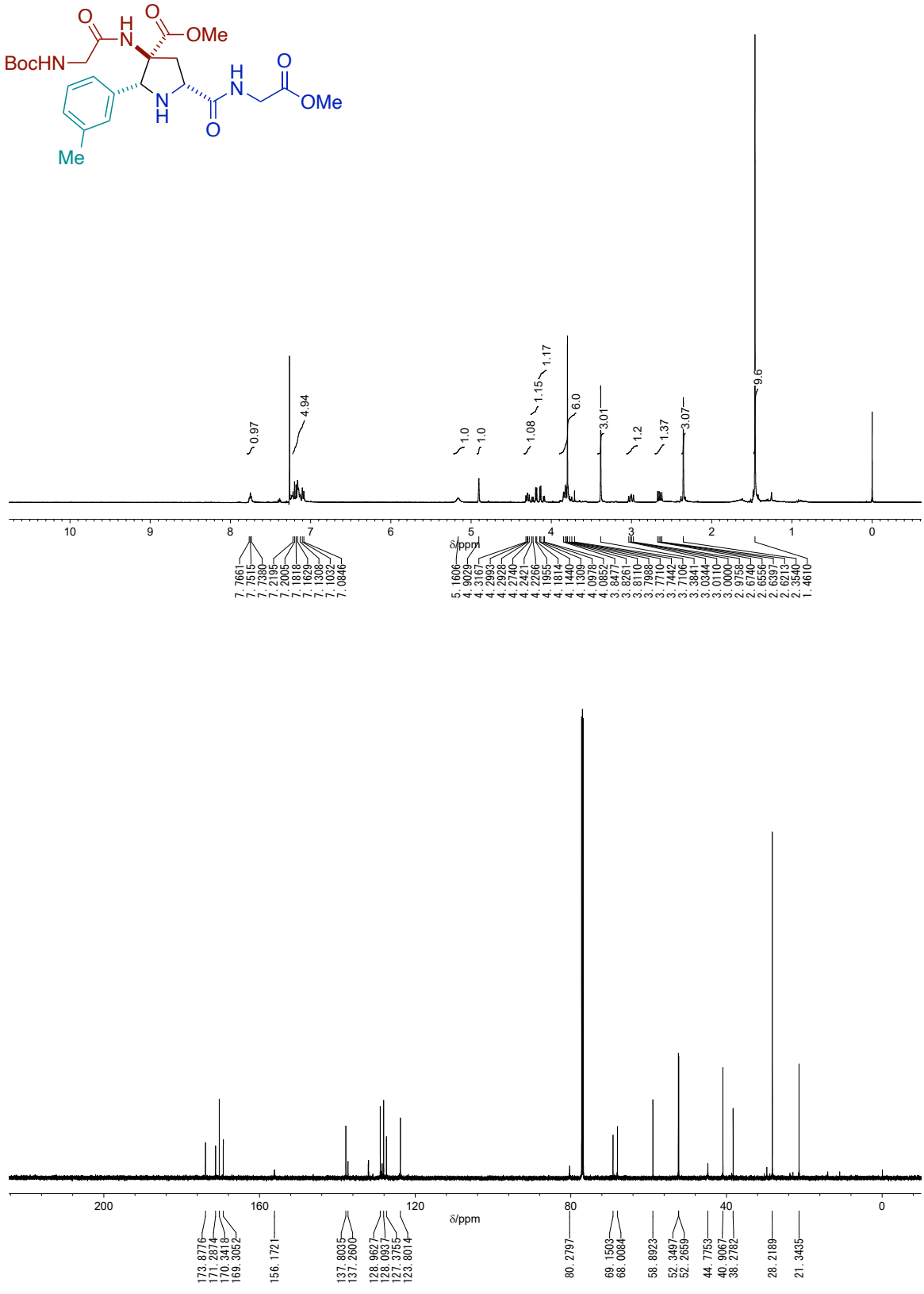

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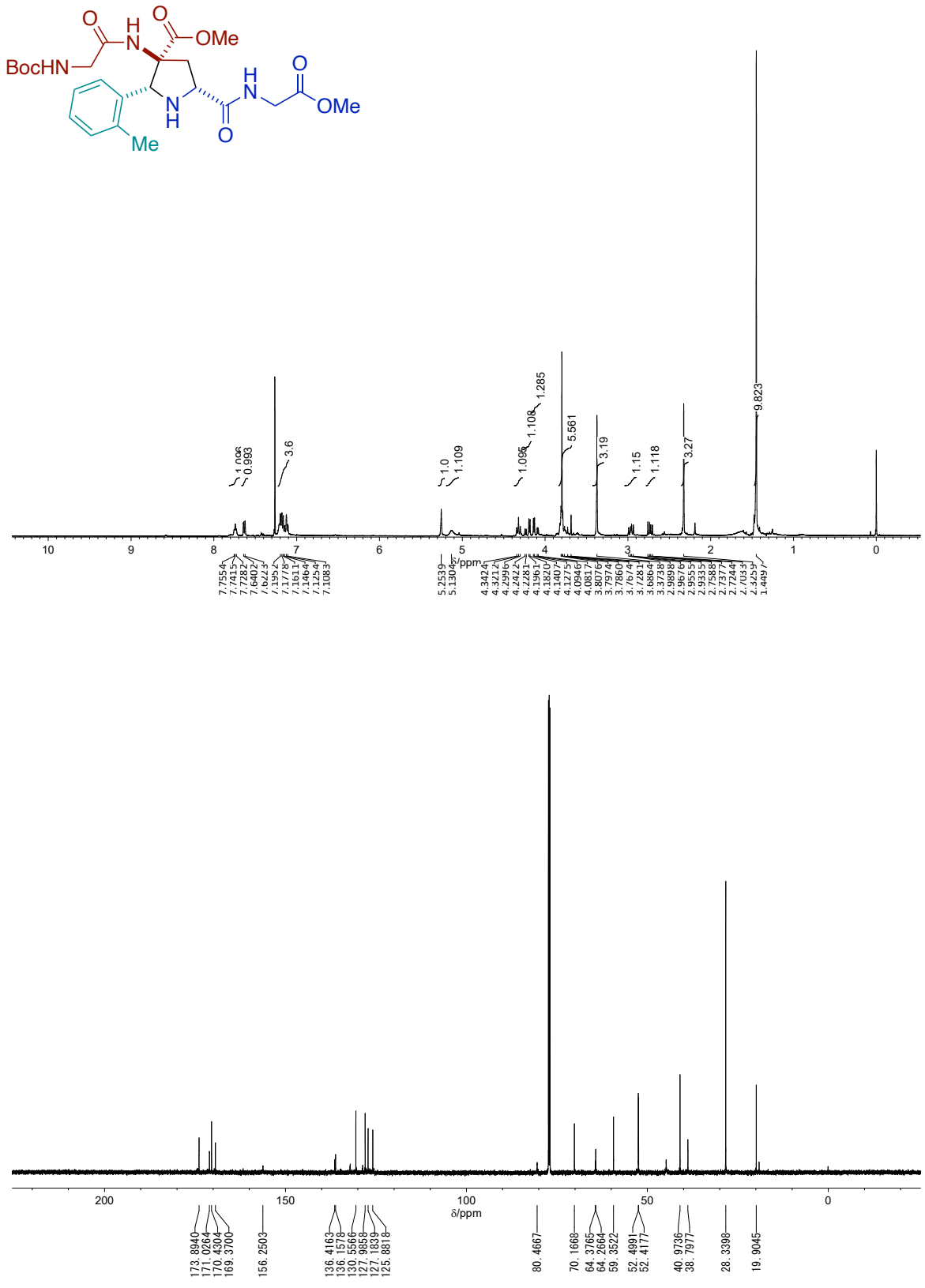

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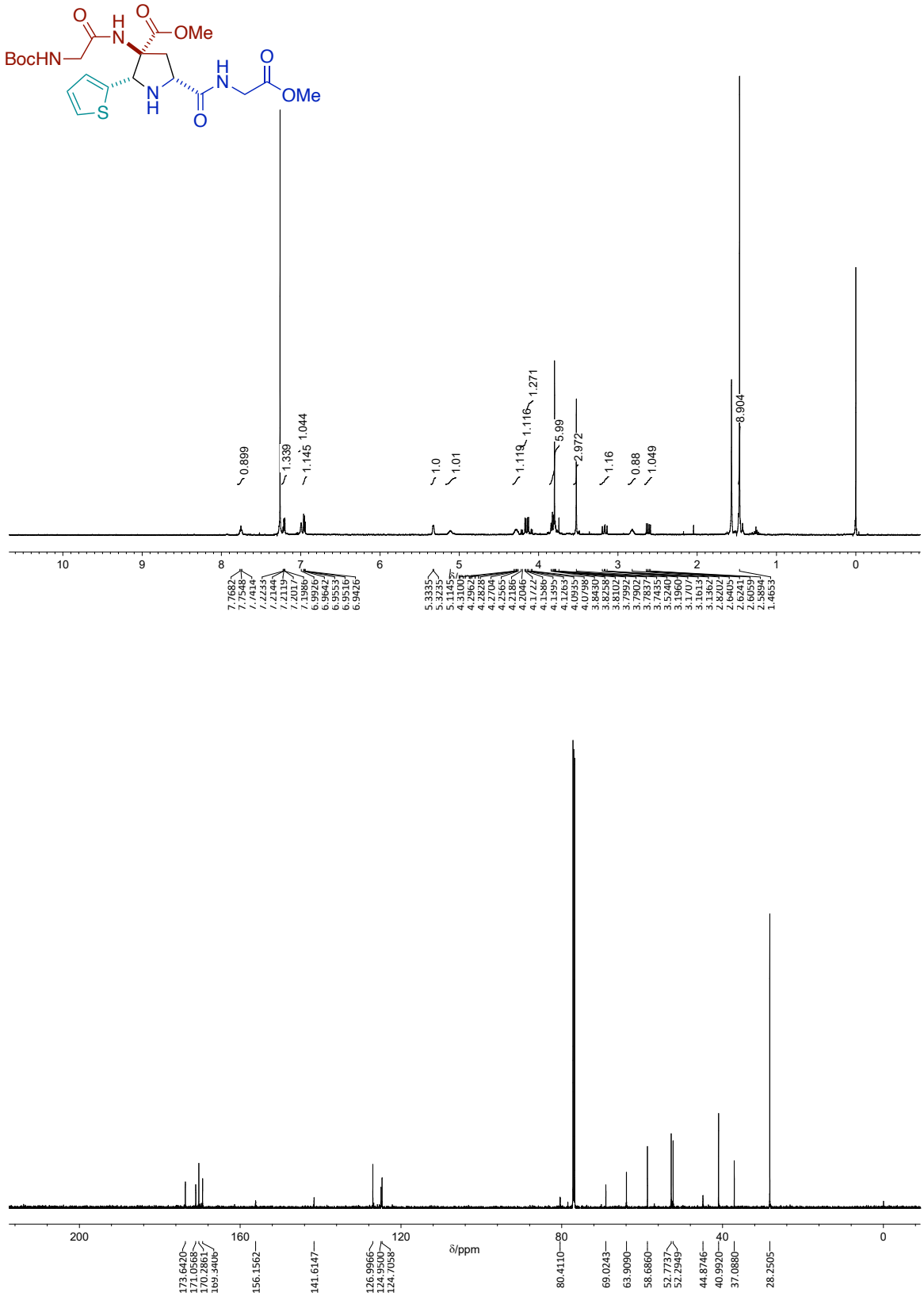

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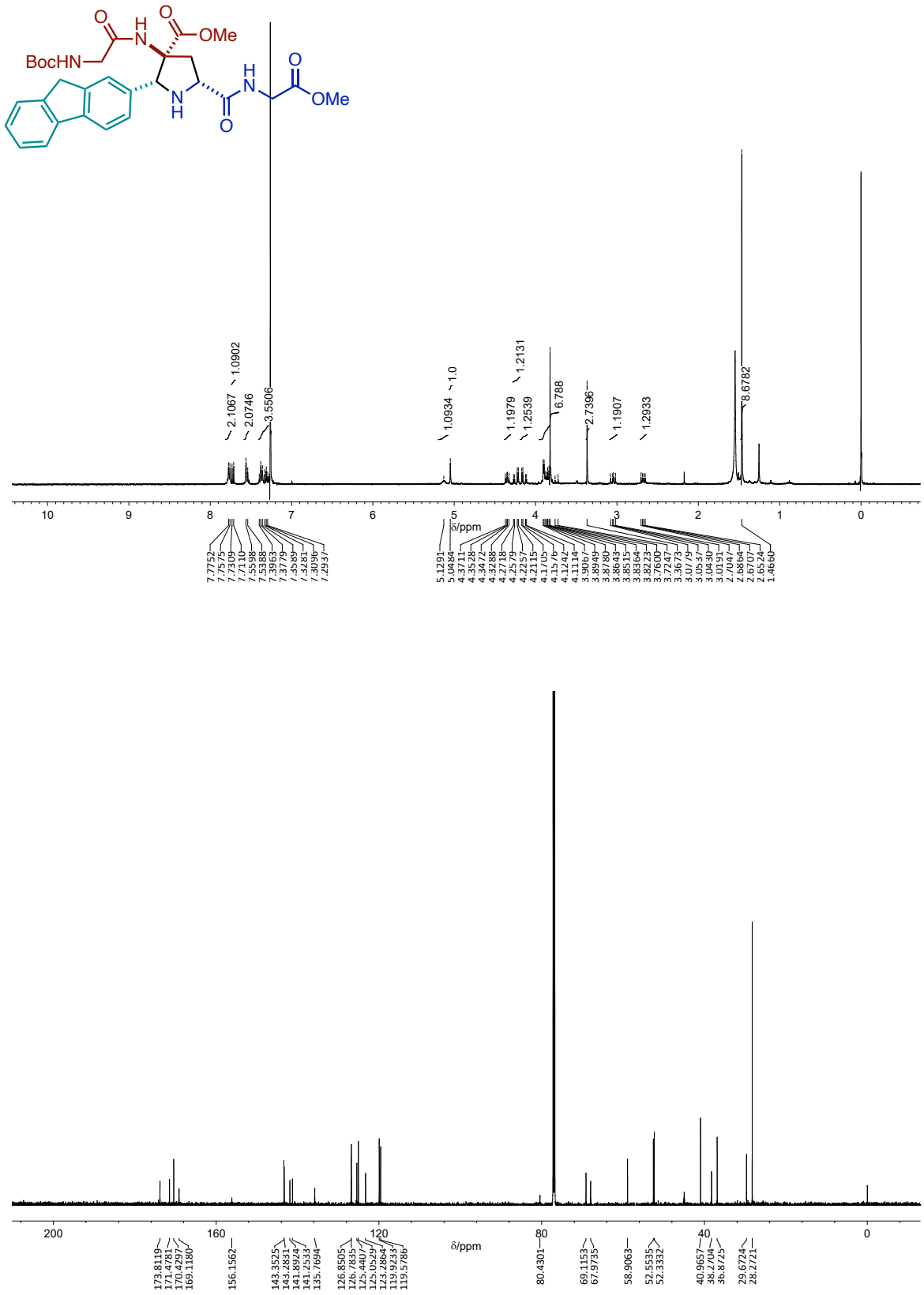

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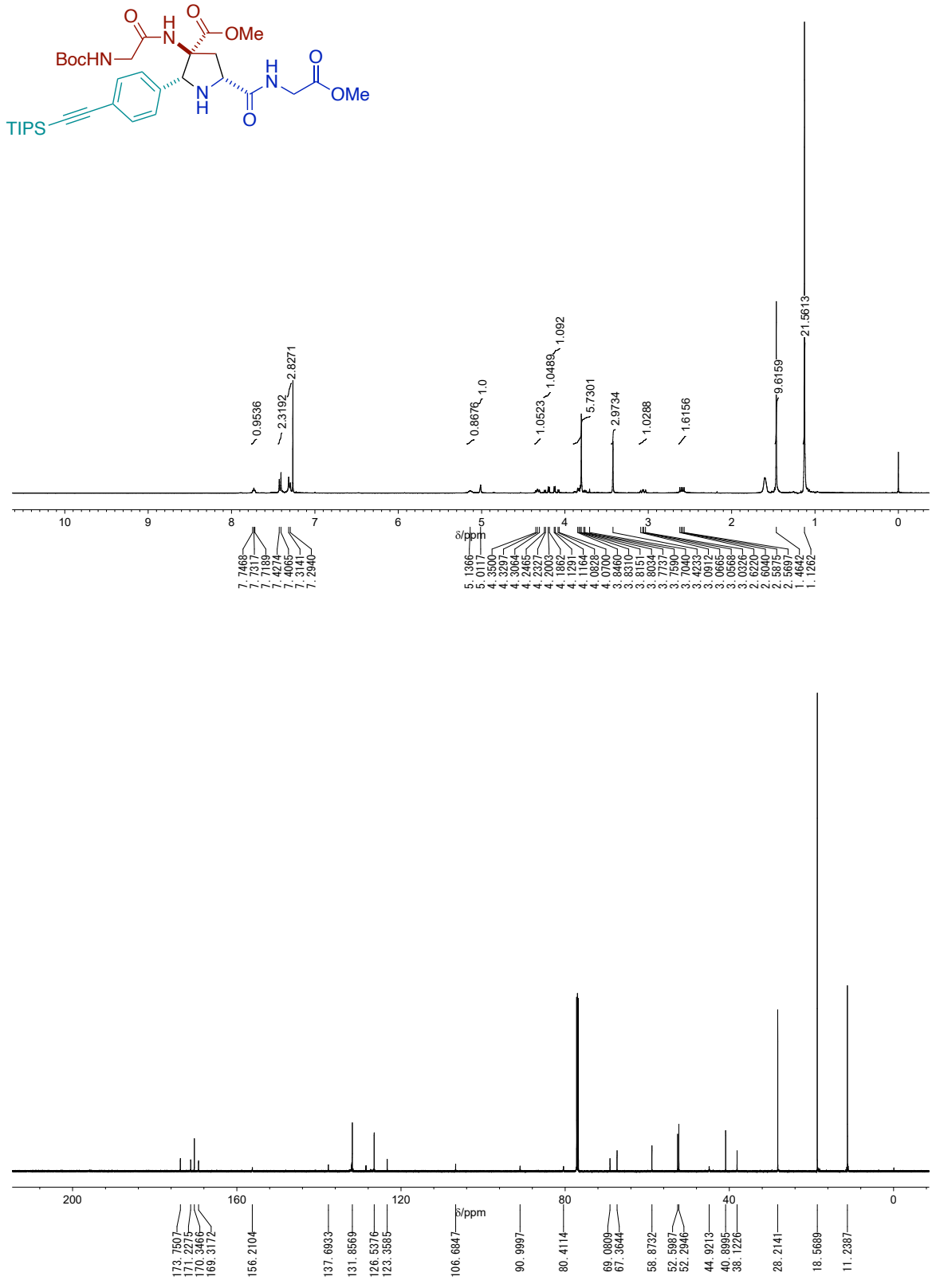

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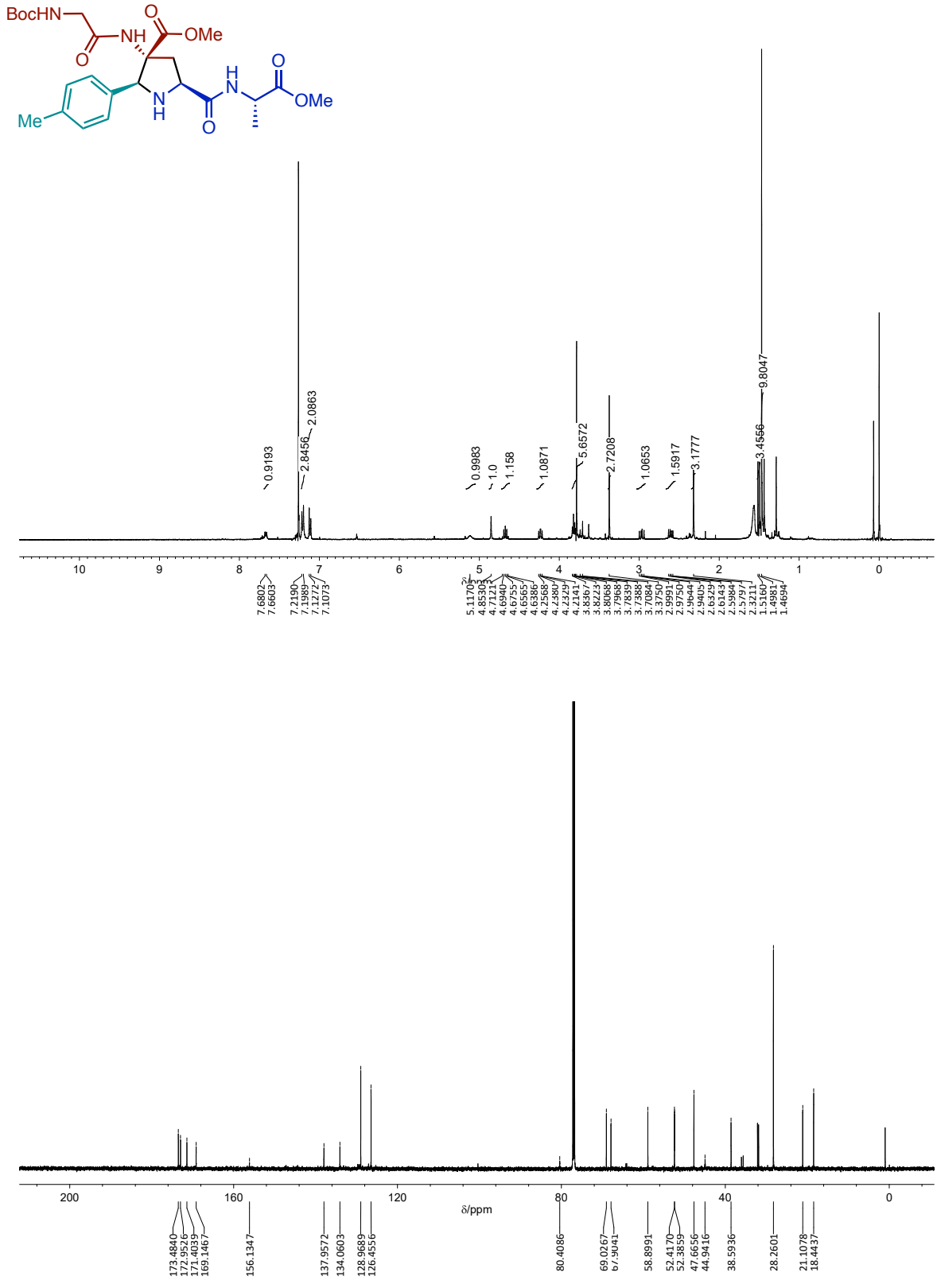

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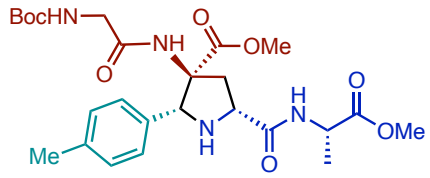
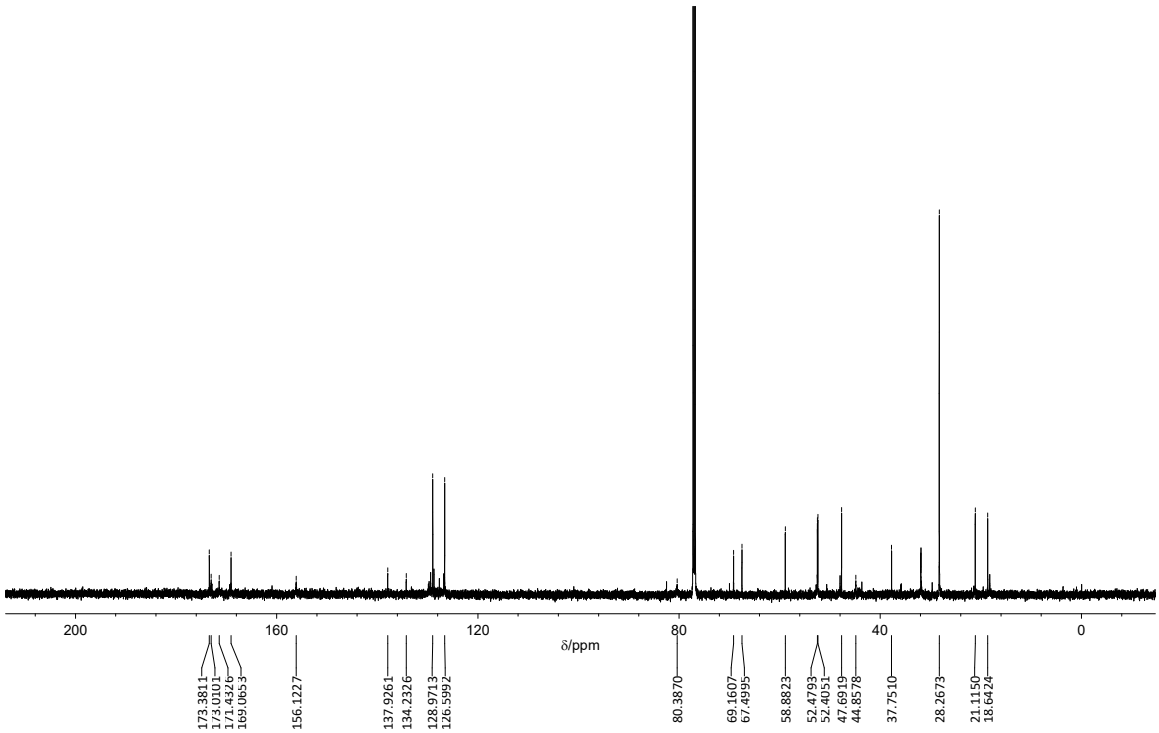
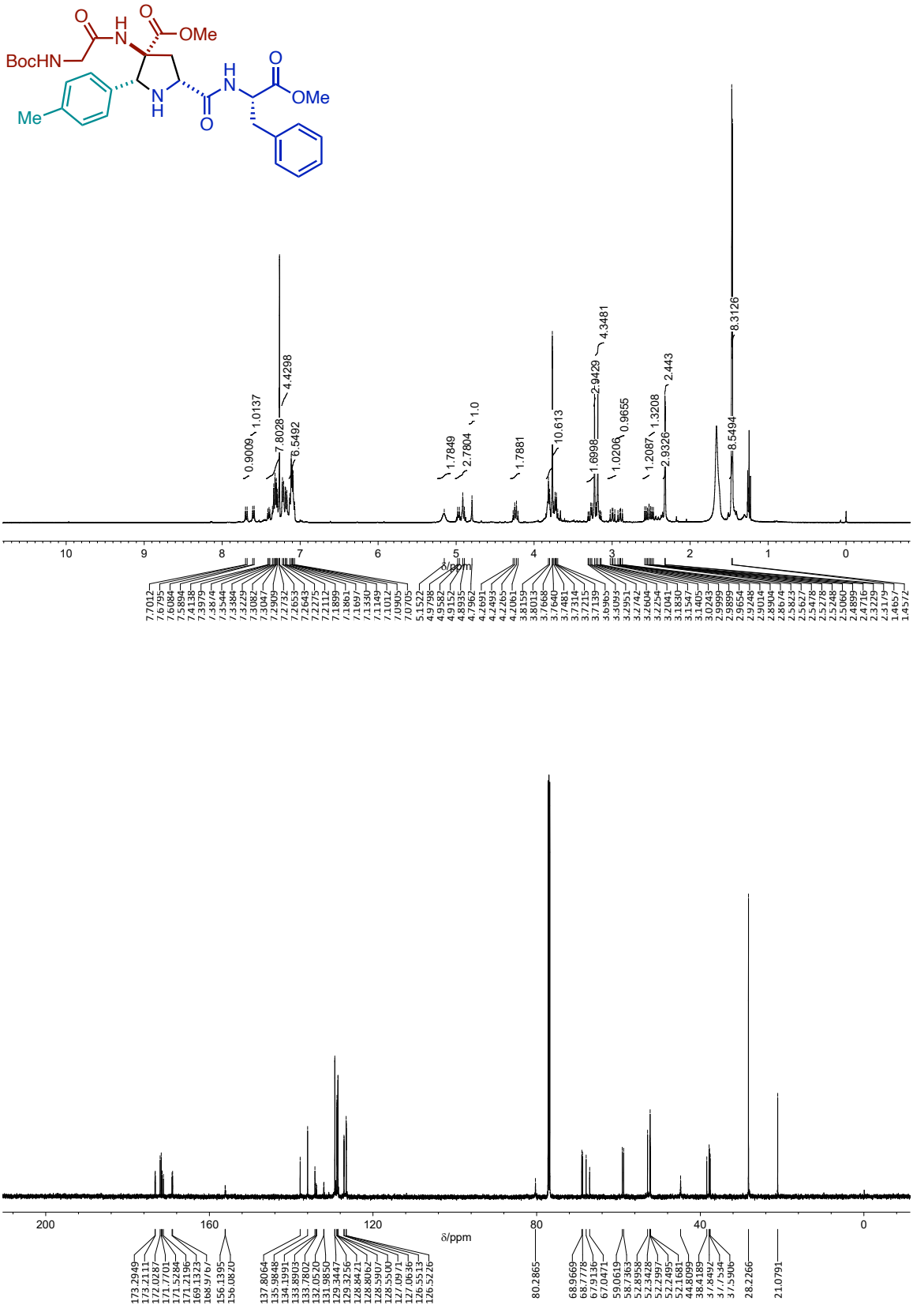








$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3l**) ($CDCl_3$)



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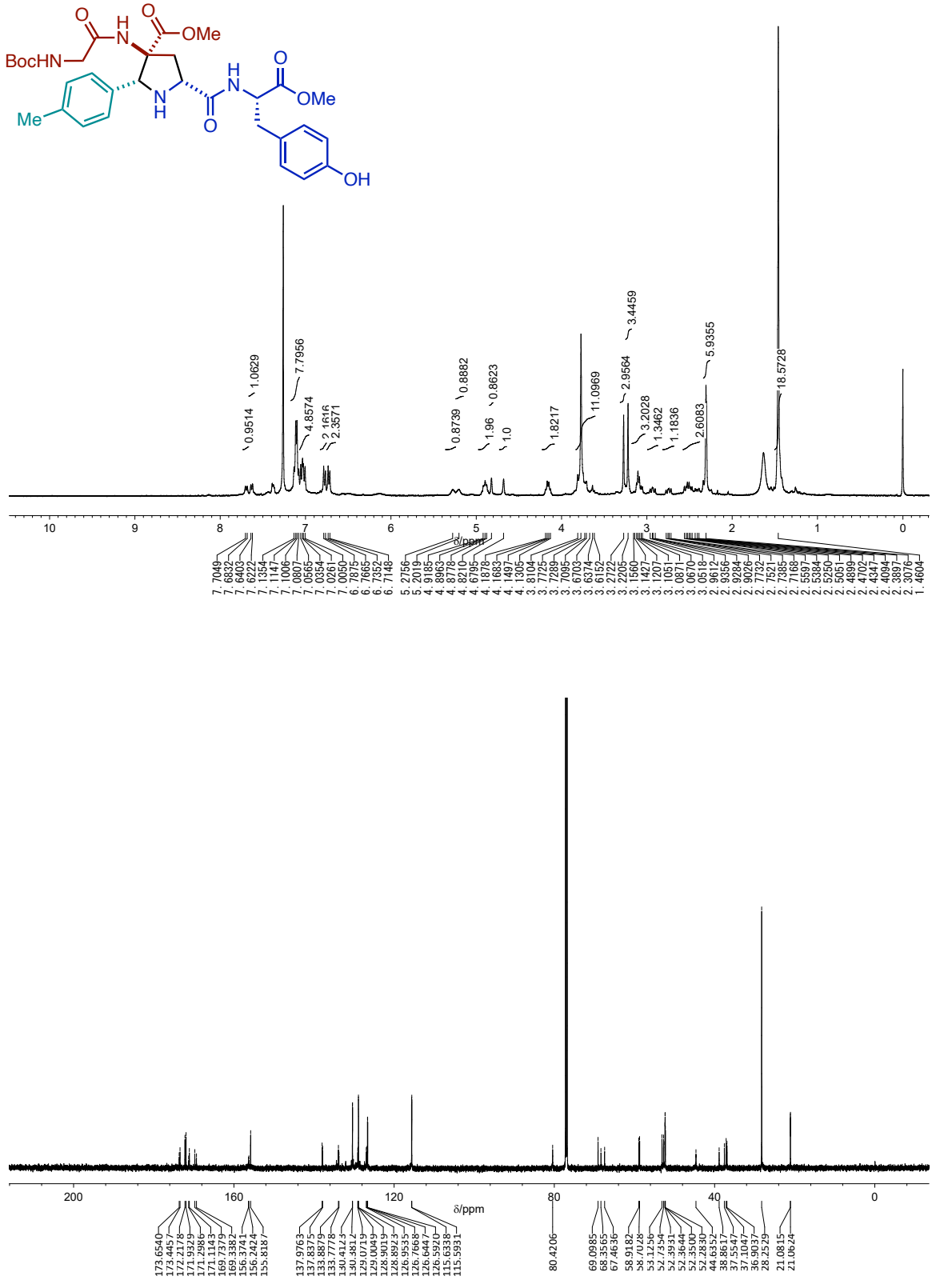
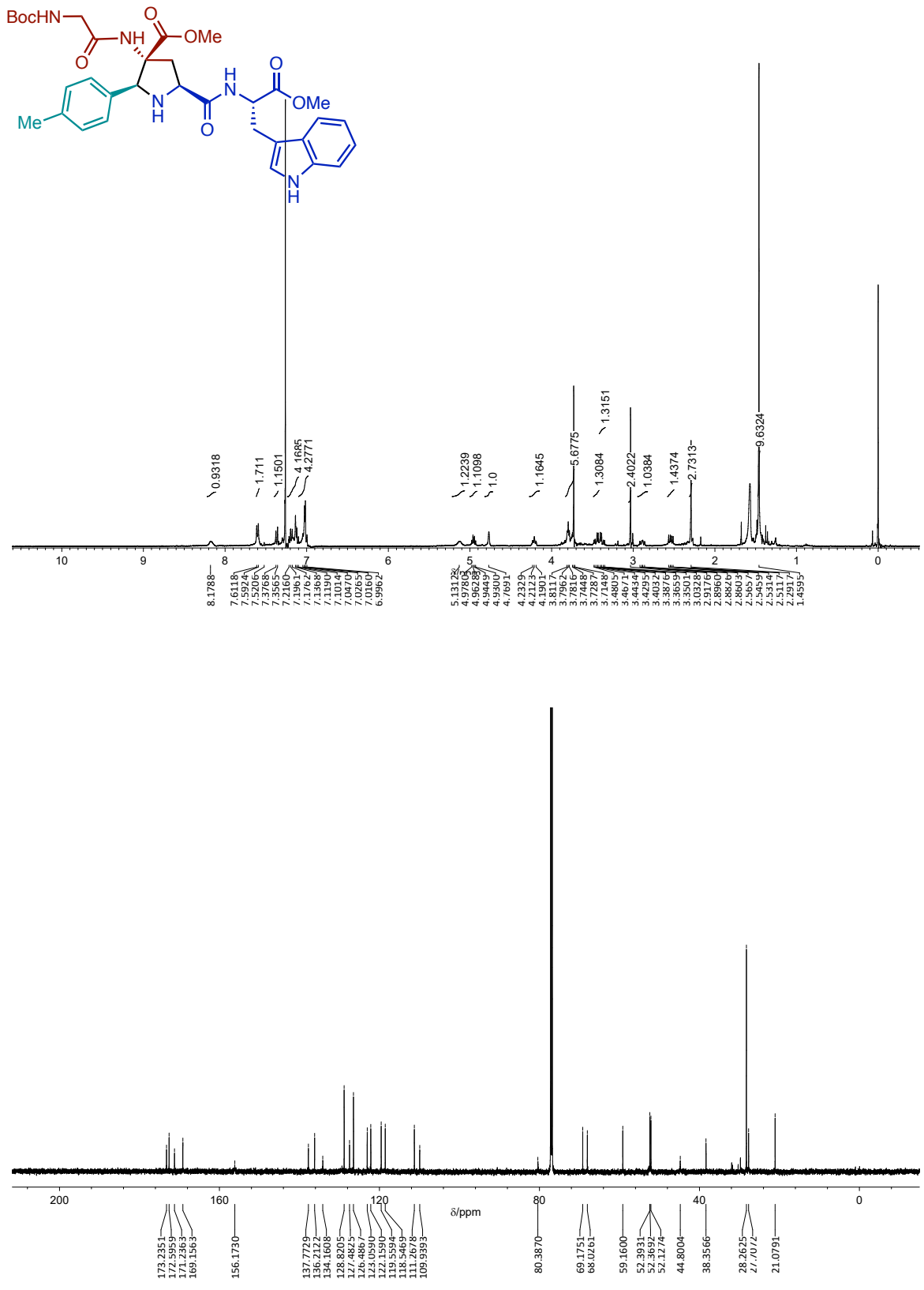


$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*S*,3*R*,5*S*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3n'**) ($CDCl_3$)



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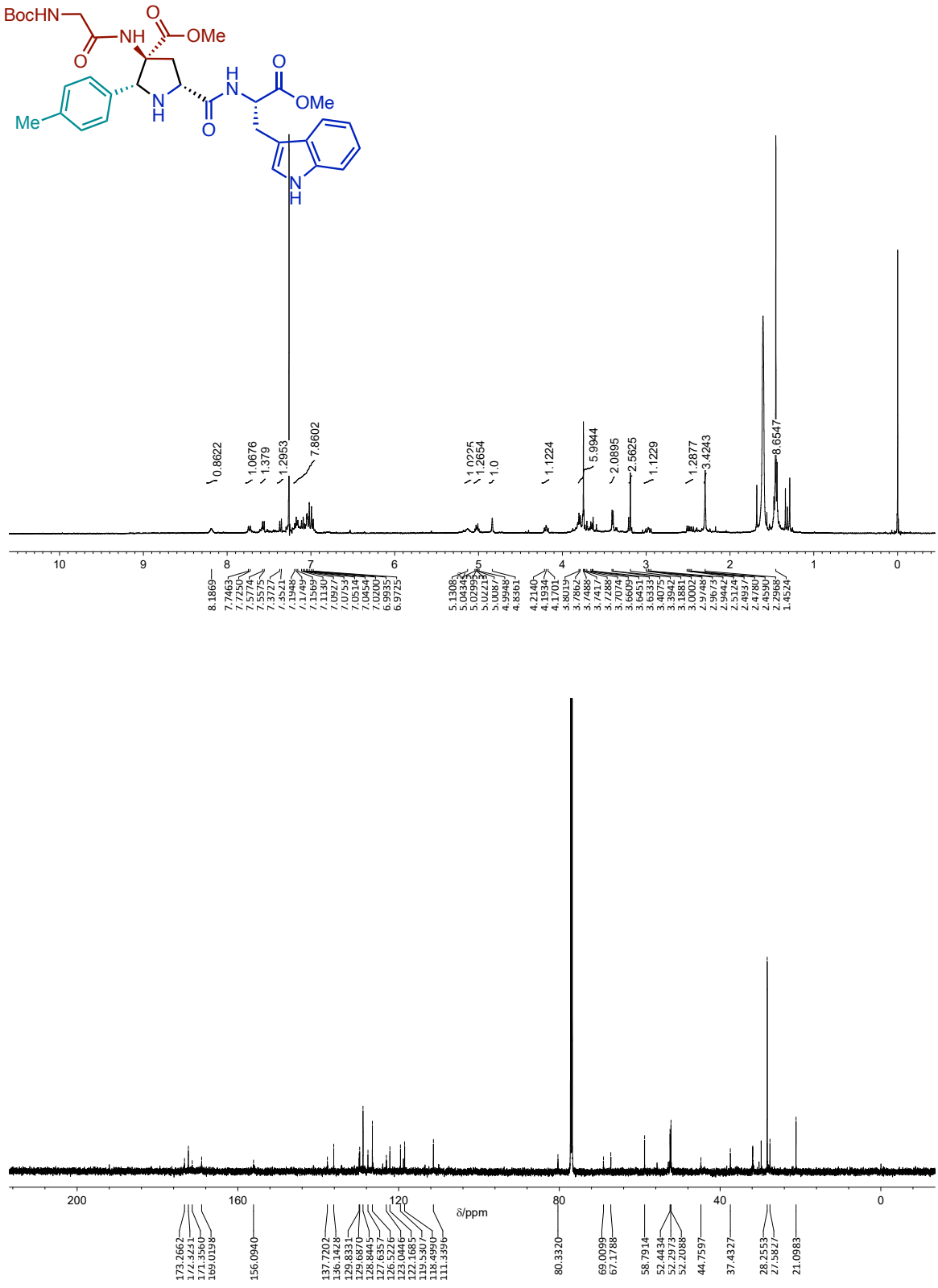
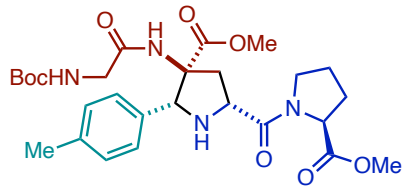
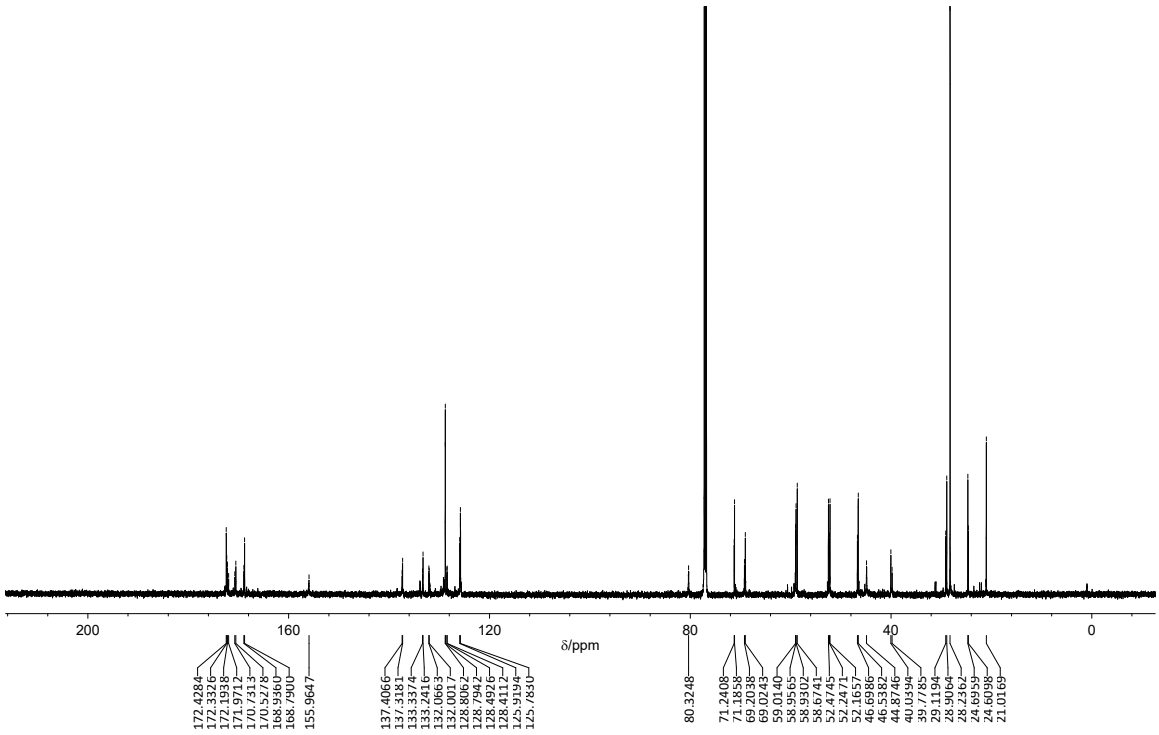


$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl ((2*R**,4*S**,5*R**)-4-(2-((*tert*-butoxycarbonyl)amino)acetamido)-4-(methoxycarbonyl)-5-(*p*-tolyl)pyrrolidine-2-carbonyl)-*L*-prolinate (**3o**) ($CDCl_3$)

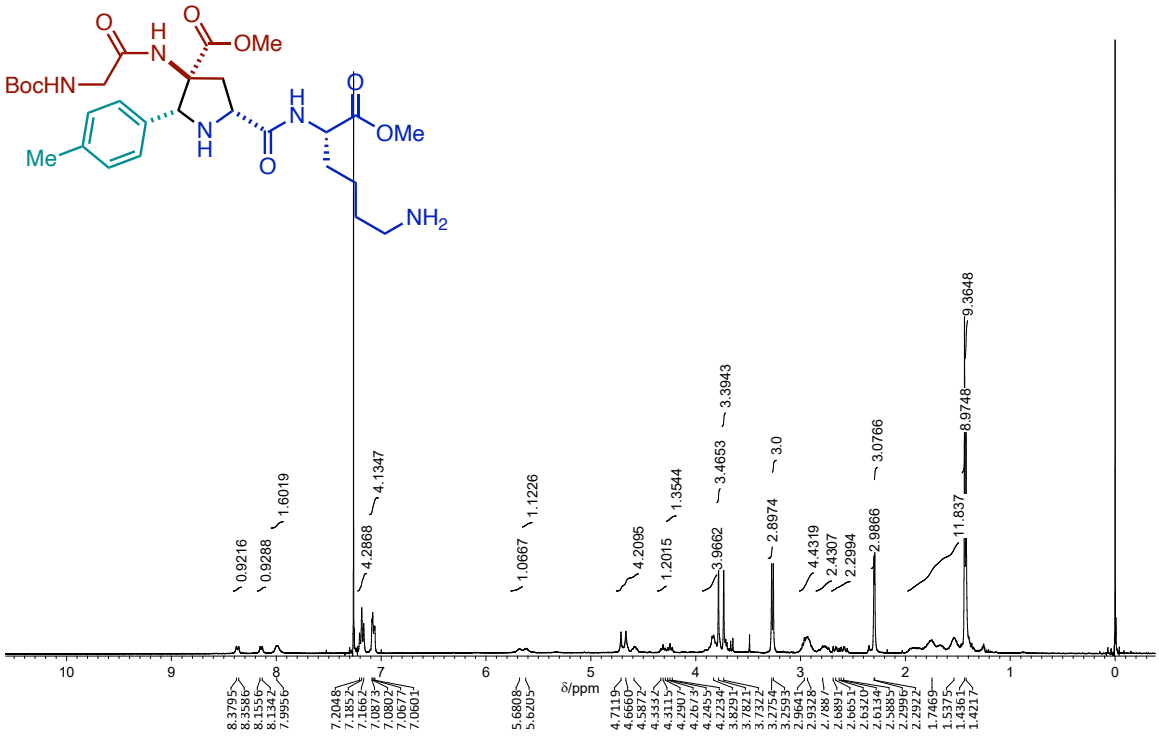


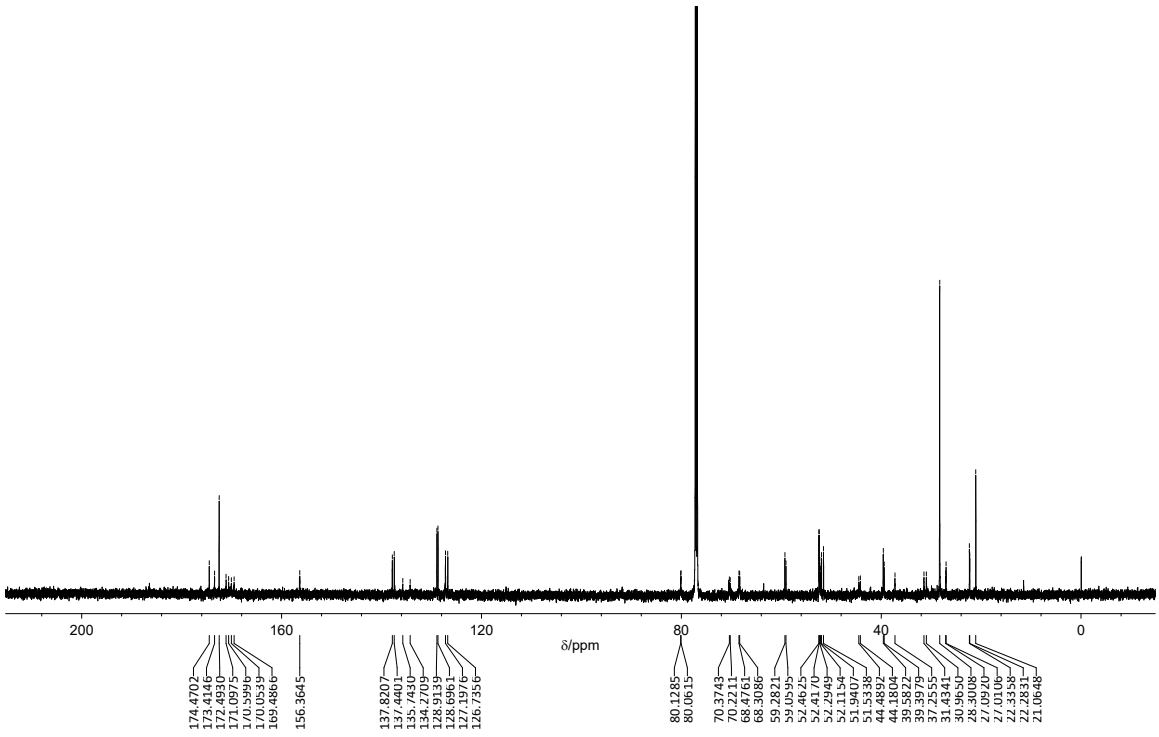




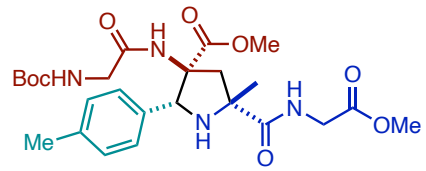


$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-5-(((*S*)-6-amino-1-methoxy-1-oxohexan-2-yl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3p**) ($CDCl_3$)



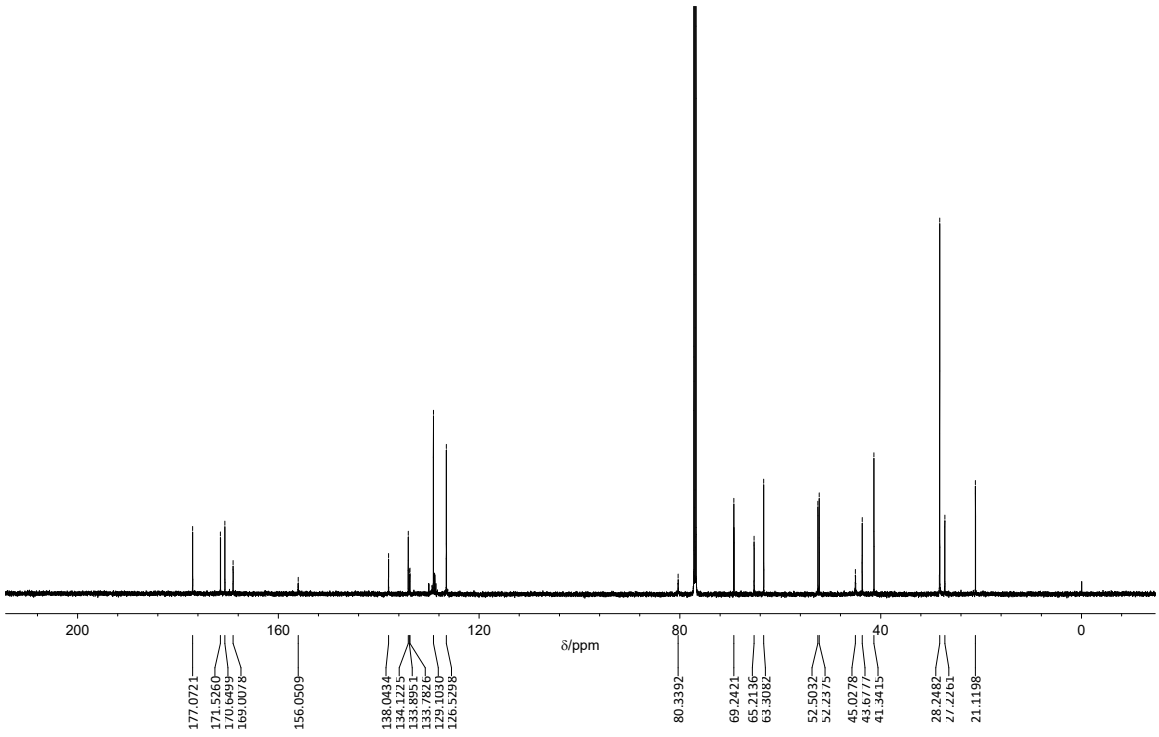



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-5-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3q**) ($CDCl_3$)

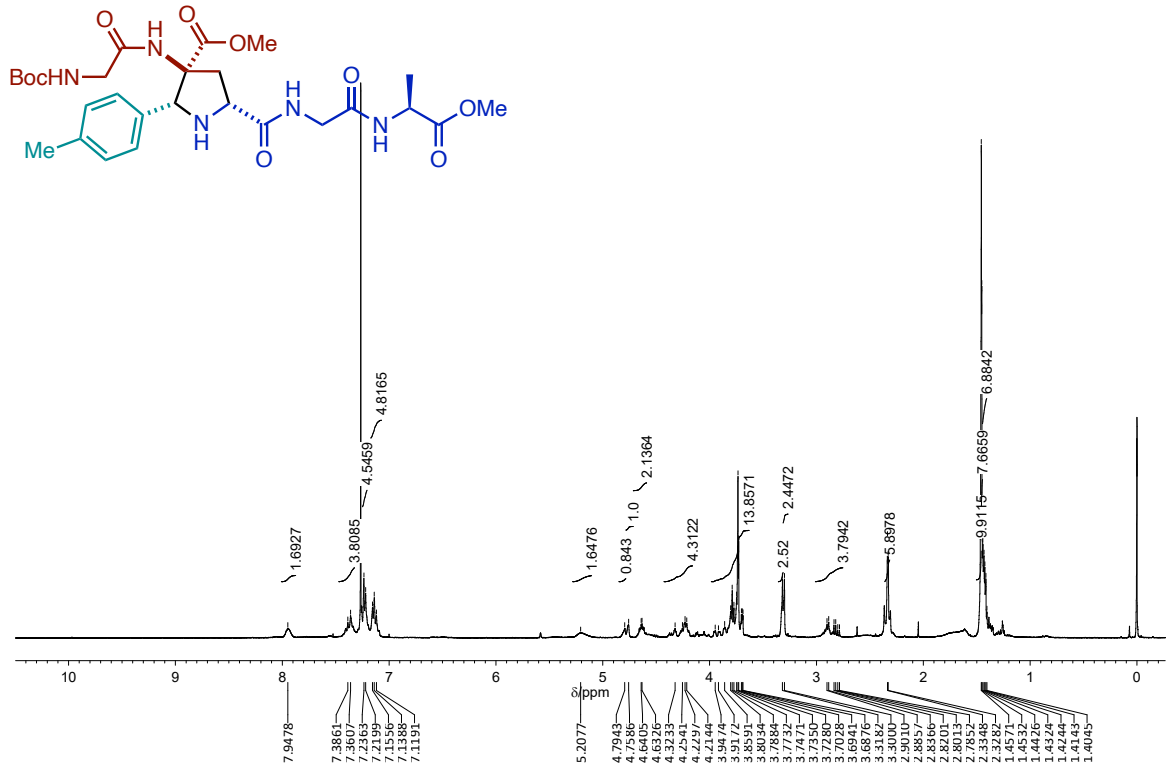


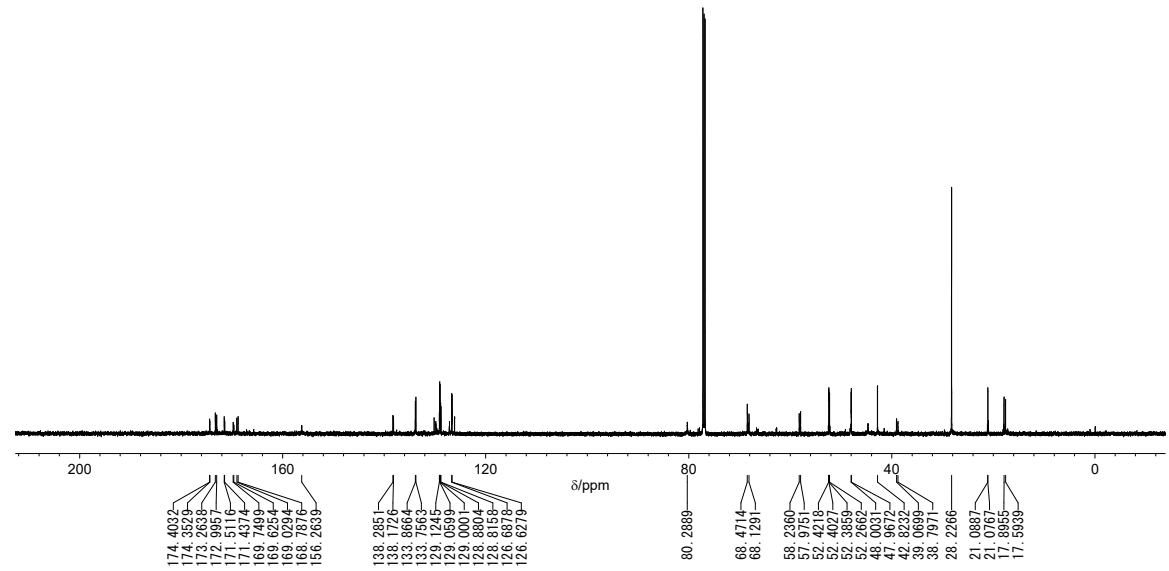




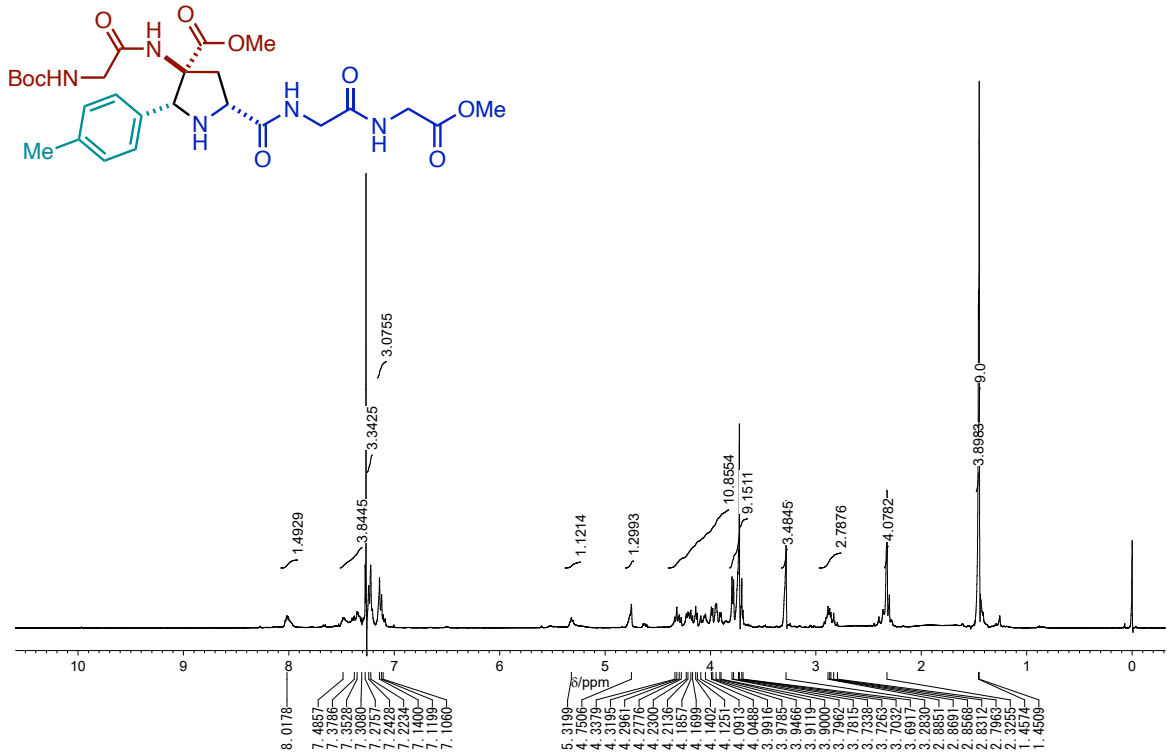


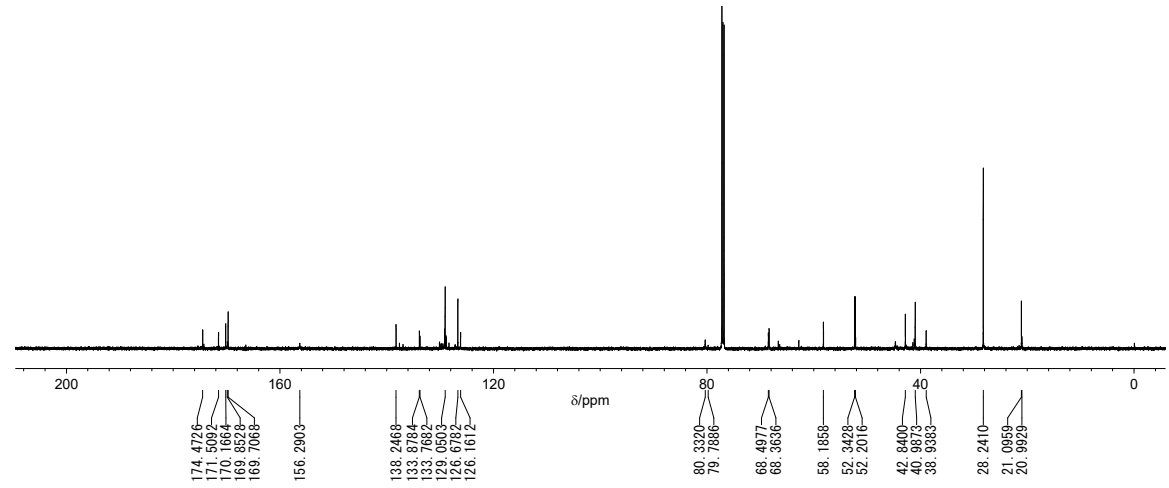
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3r**) ($CDCl_3$)



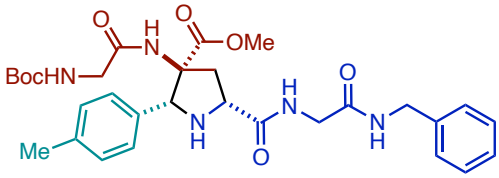



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3s**) ($CDCl_3$)



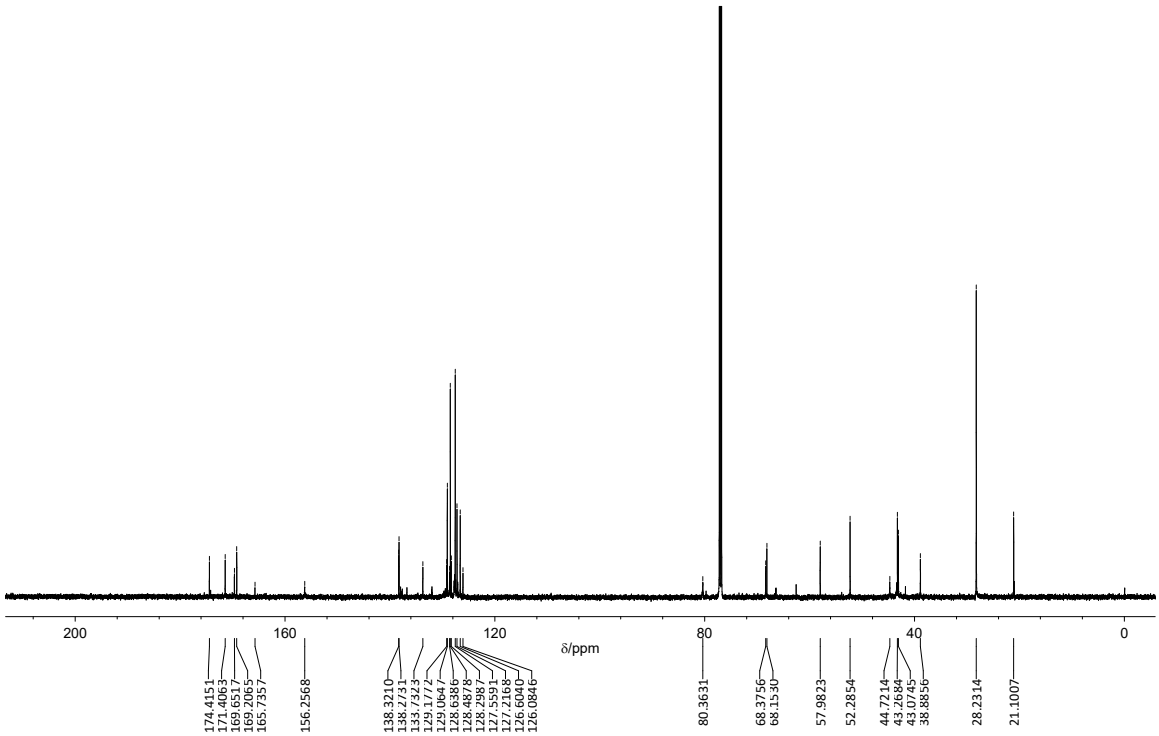



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-5-((2-(benzylamino)-2-oxoethyl)carbamoyl)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3t**) ($CDCl_3$)

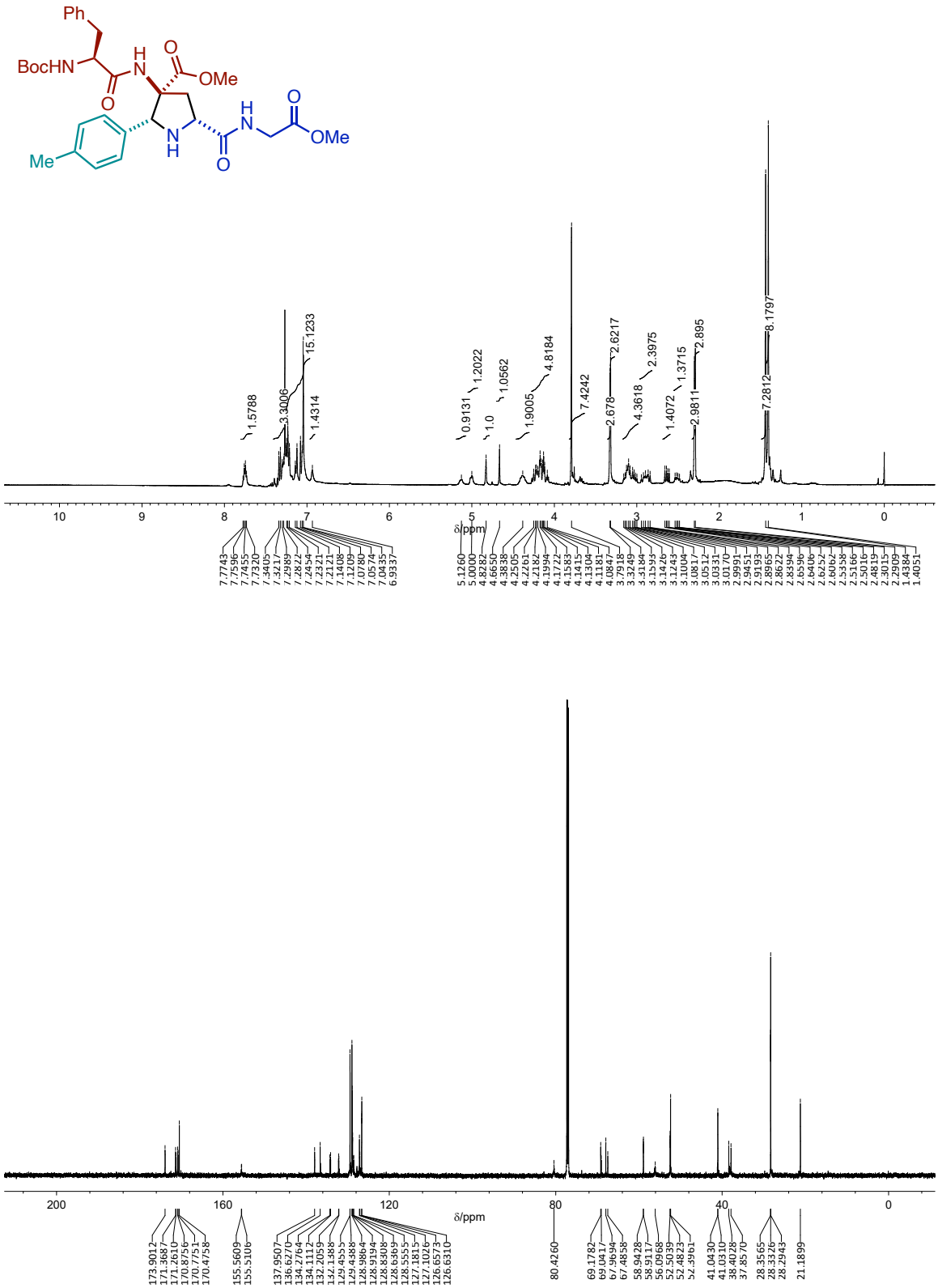




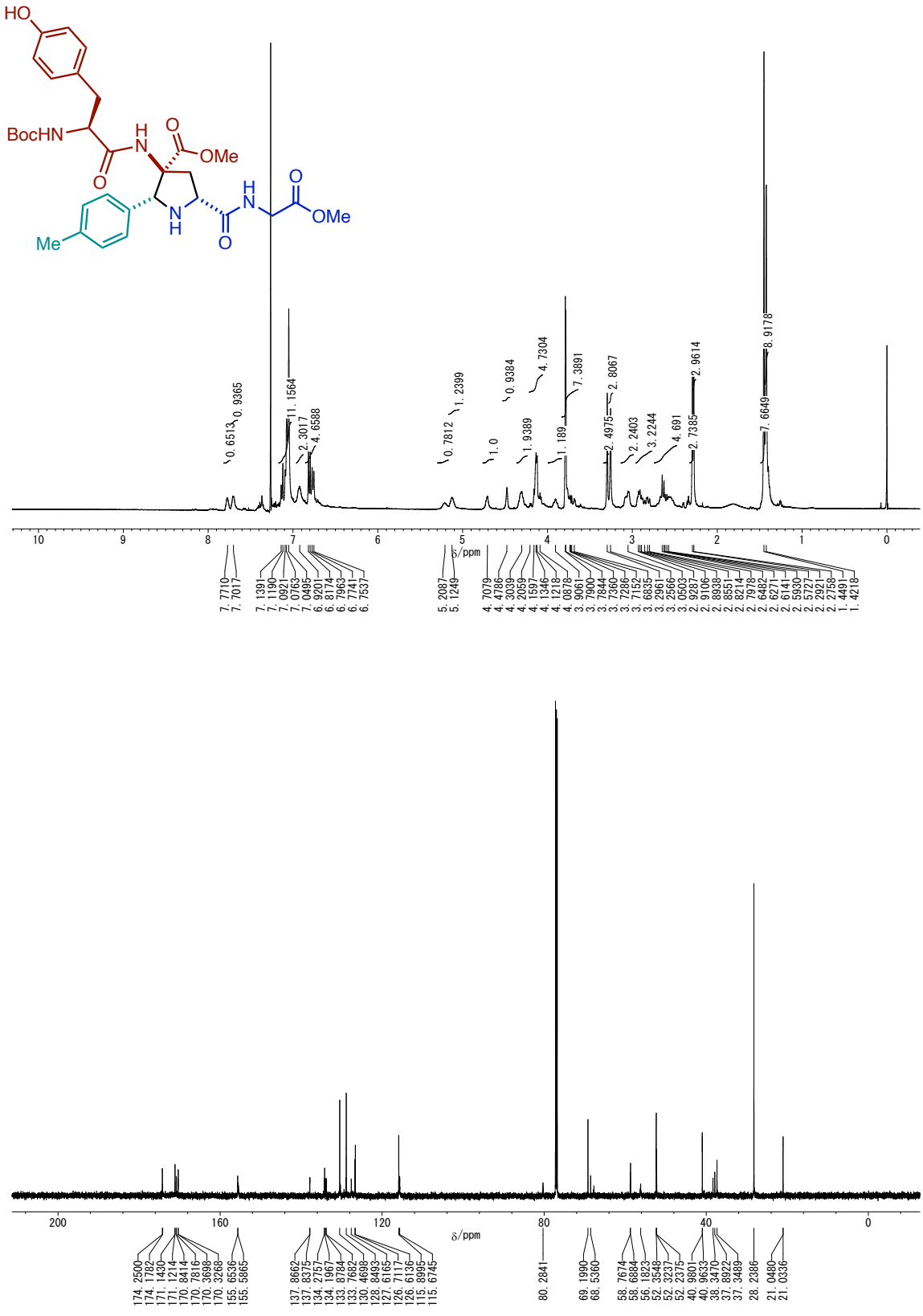




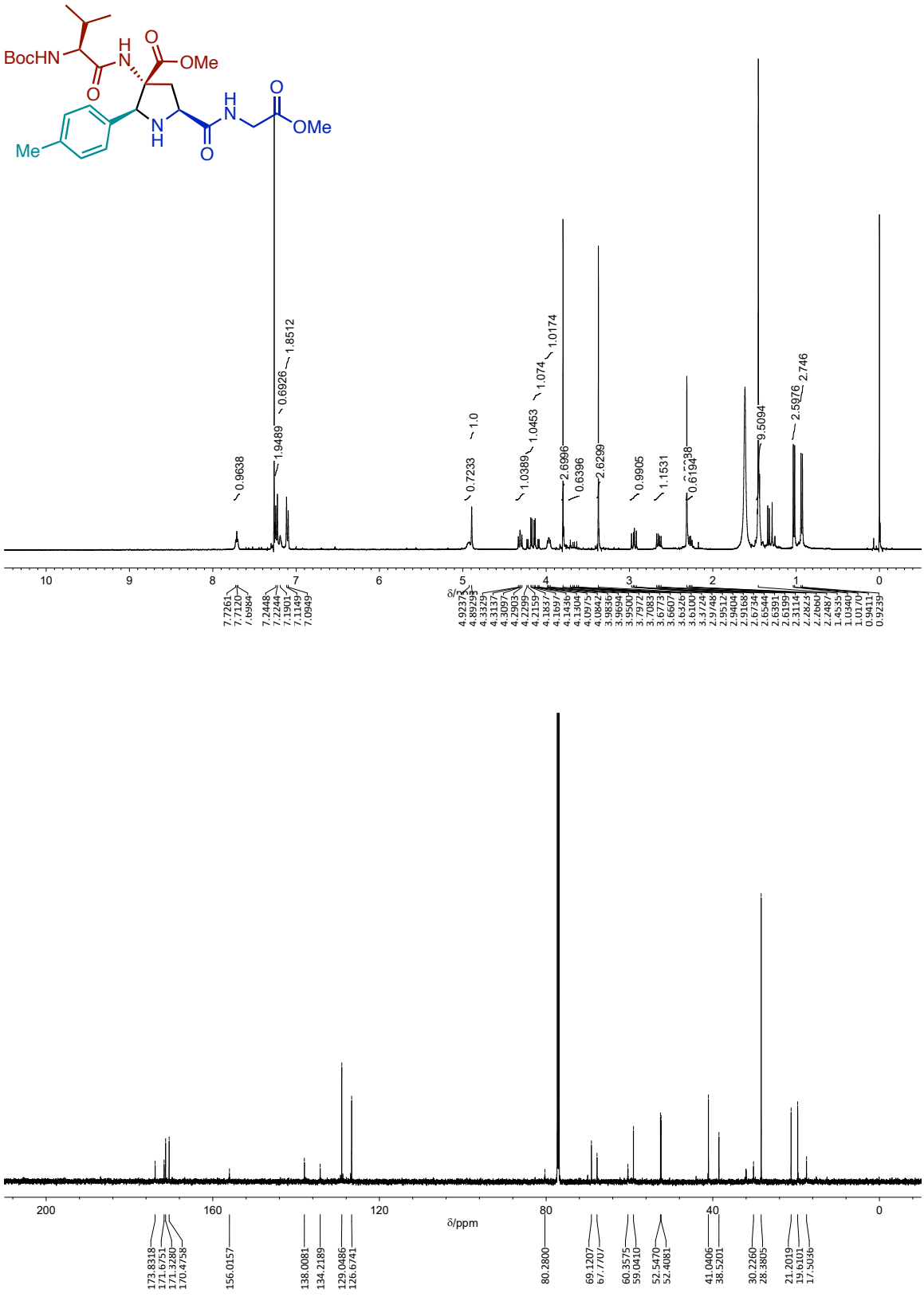
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3u**) ($CDCl_3$)



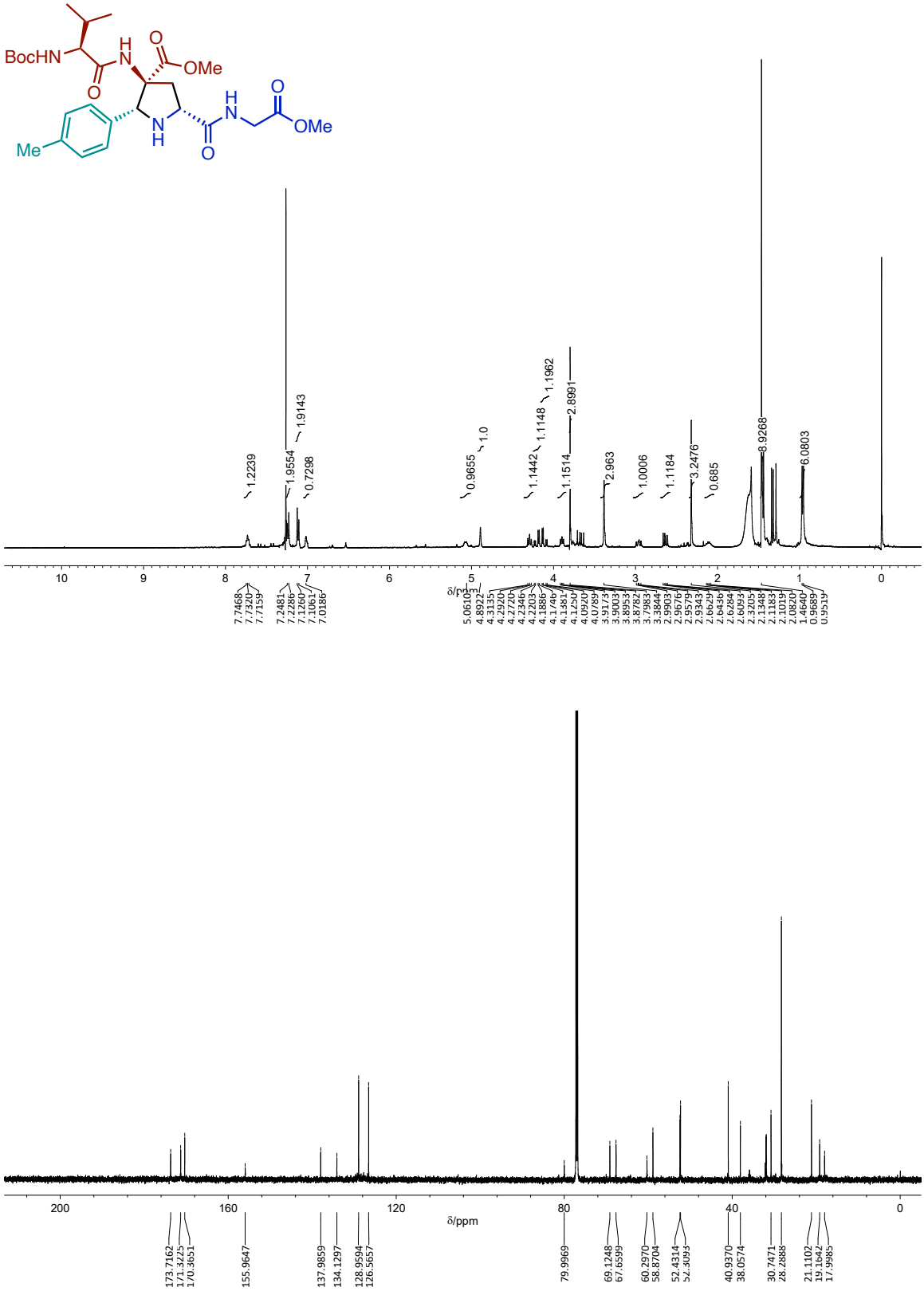
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3v**) ($CDCl_3$)



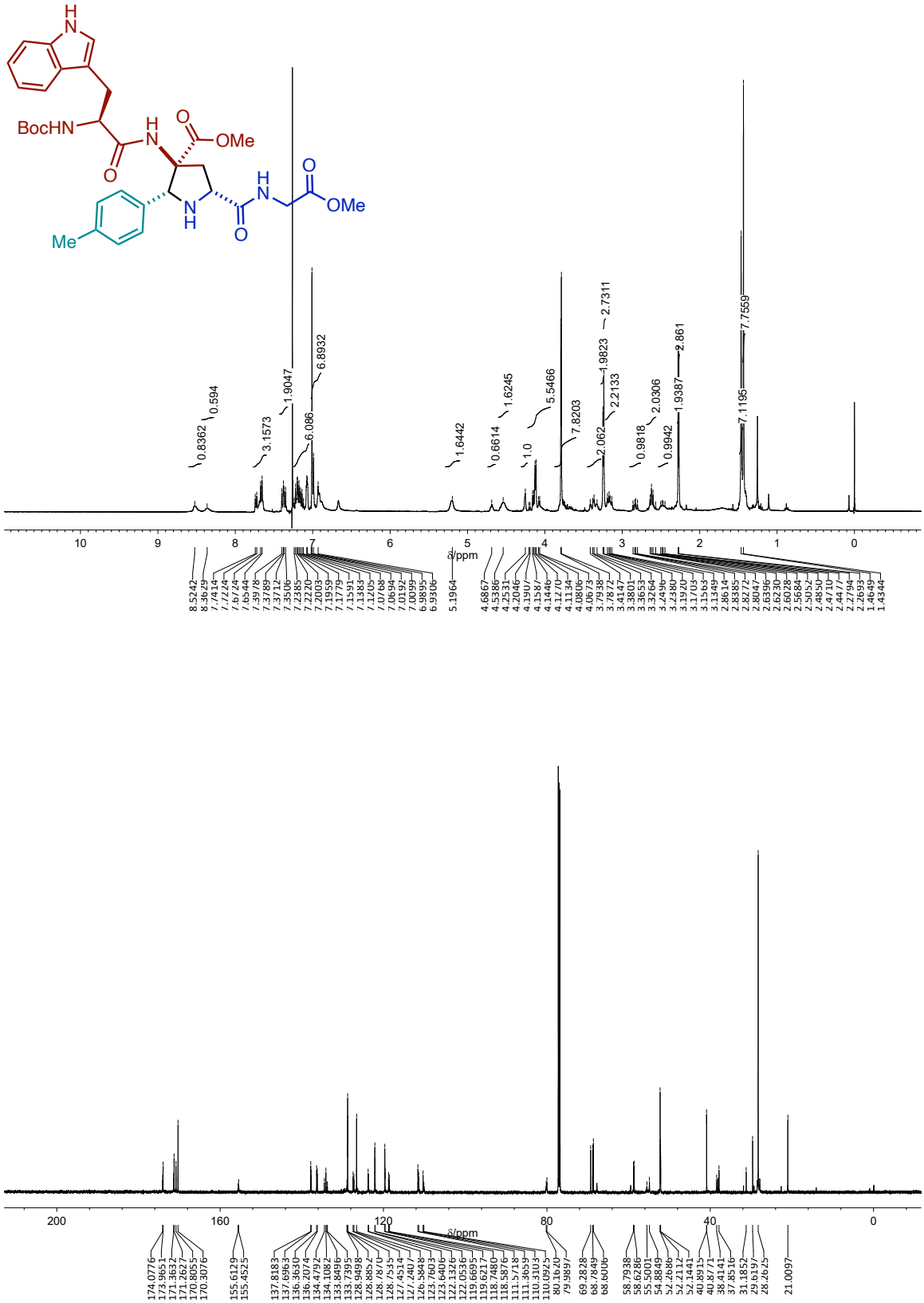
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*S*,3*R*,5*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w'**) ($CDCl_3$)



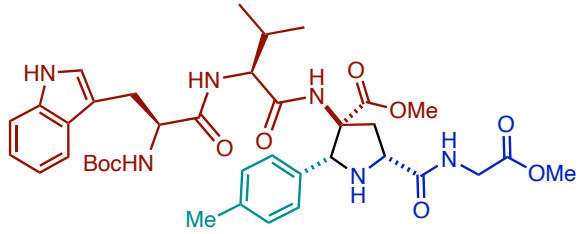
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R*,3*S*,5*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3w''**) ($CDCl_3$)

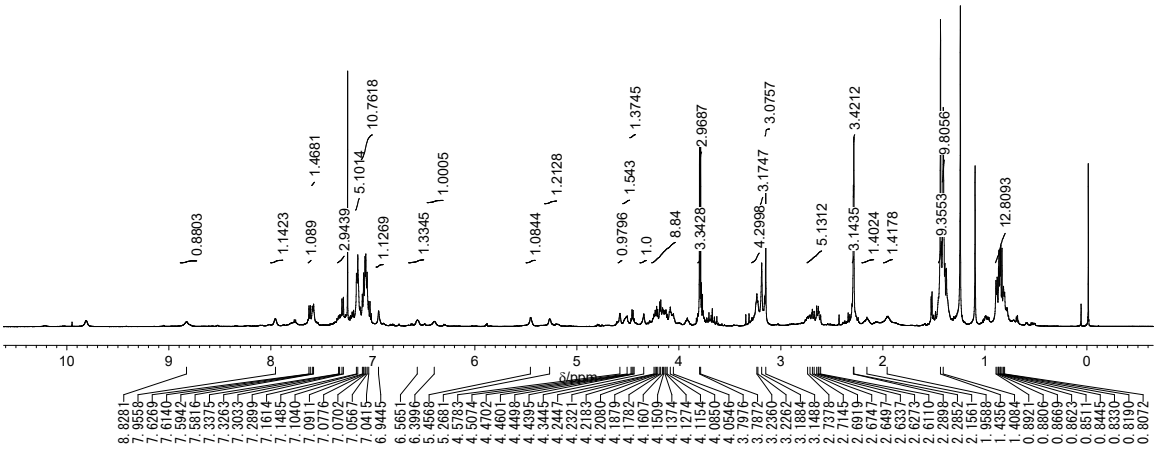


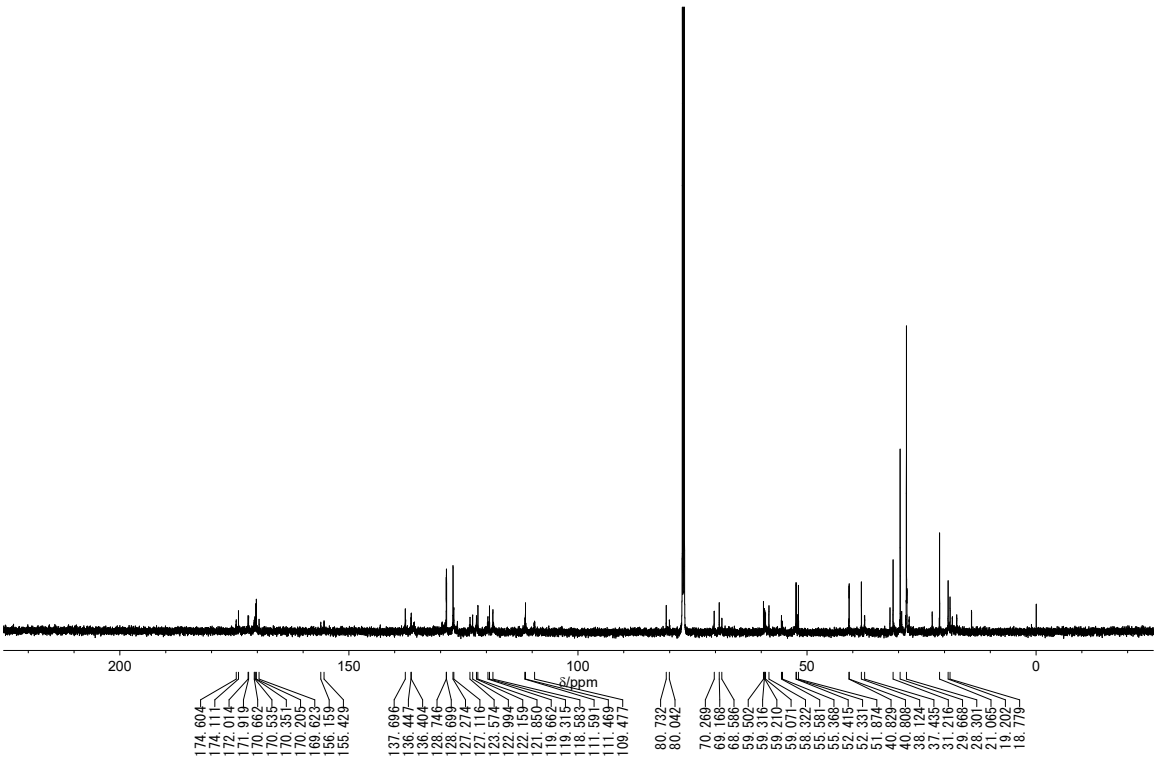
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3x**) ($CDCl_3$)



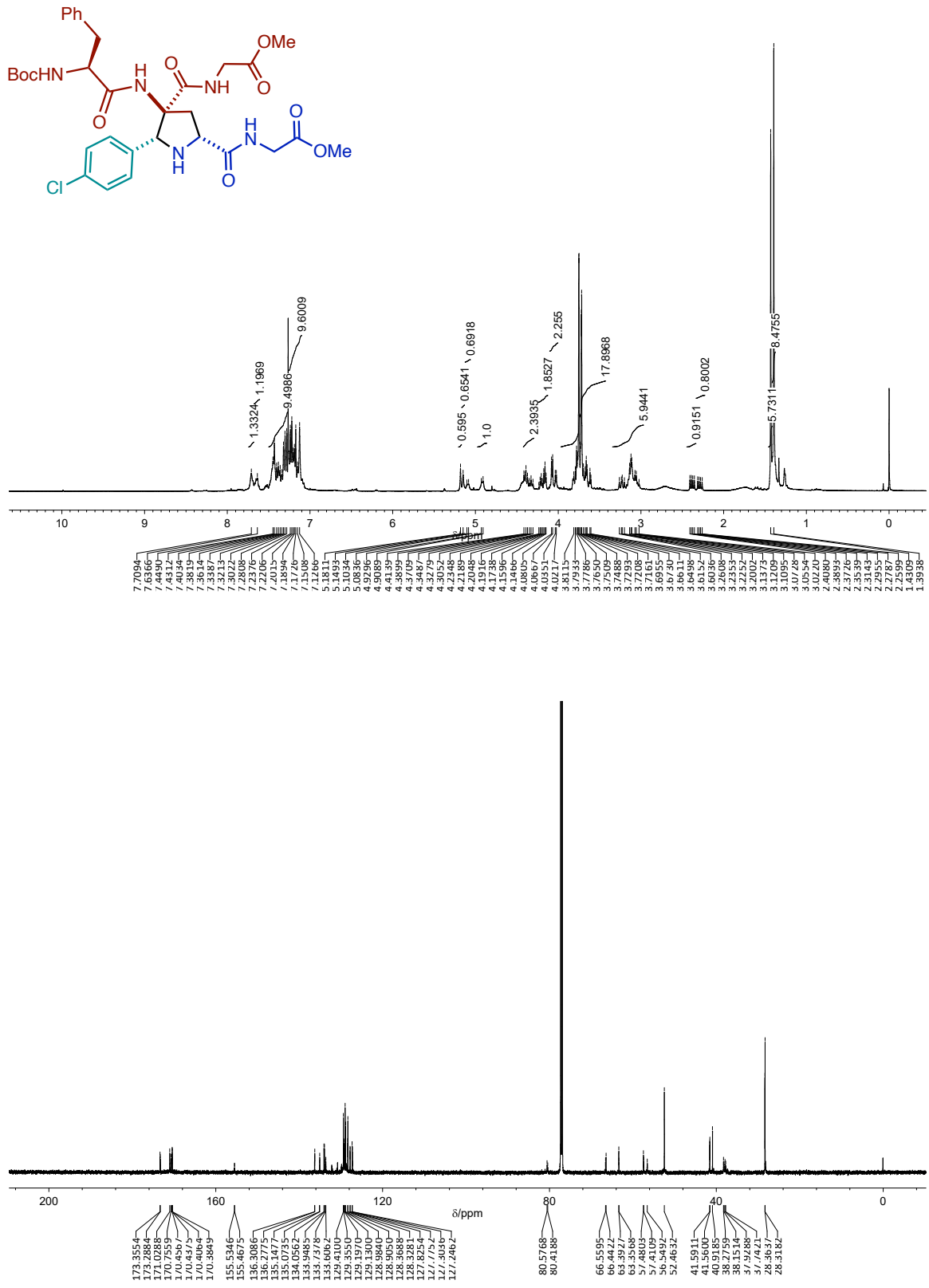
$^{1}$H NMR (600 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3y**) ($CDCl_3$)



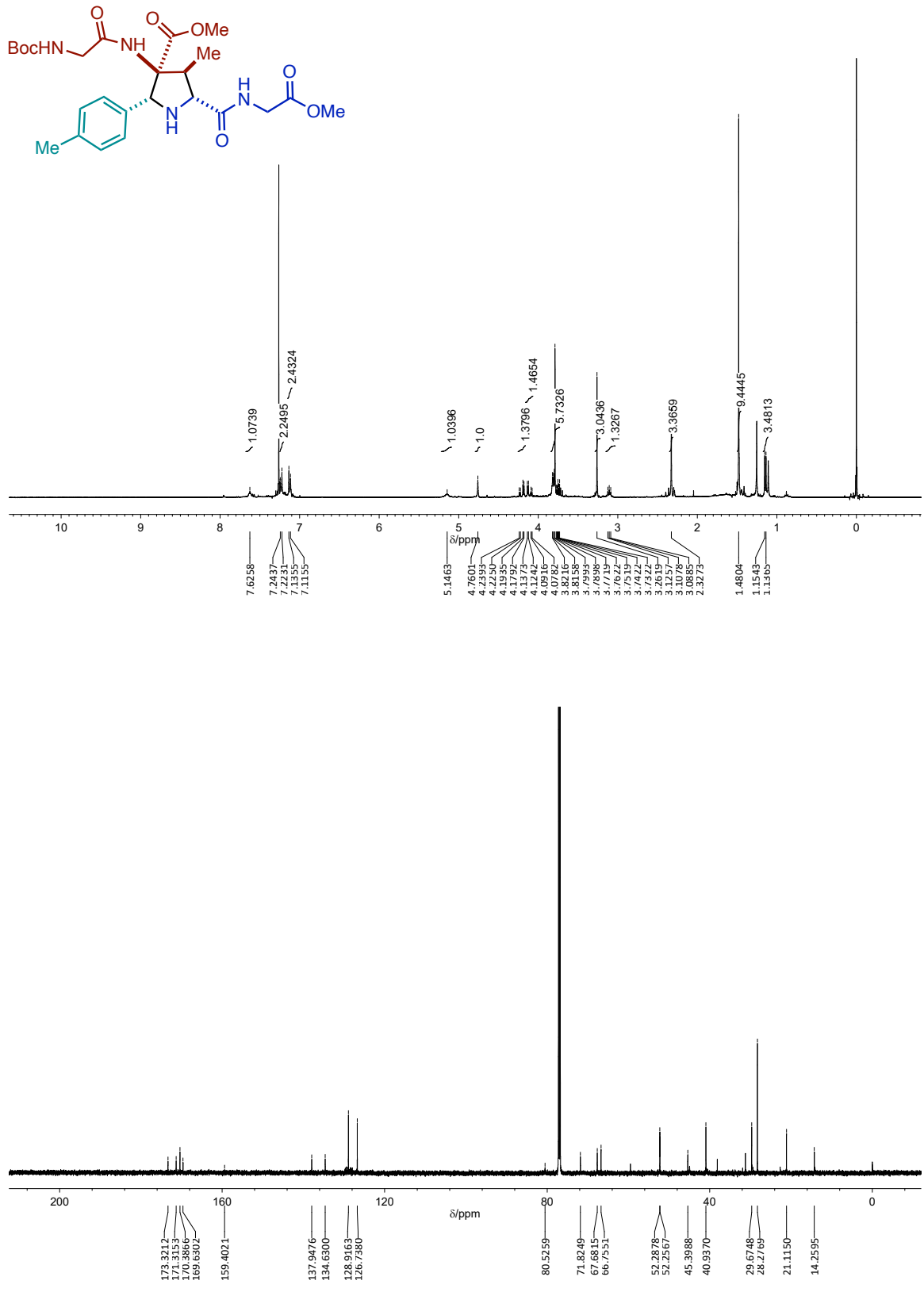



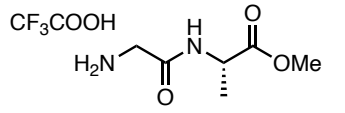
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of dimethyl 2,2'-(((2*R**,4*S**,5*R**)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-5-(4-chlorophenyl)pyrrolidine-2,4-dicarbonyl)bis(azanediyl))diacetate (**3z**) ($CDCl_3$)



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,4*S**,5*R**)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-4-methyl-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**3aa**) ($CDCl_3$)

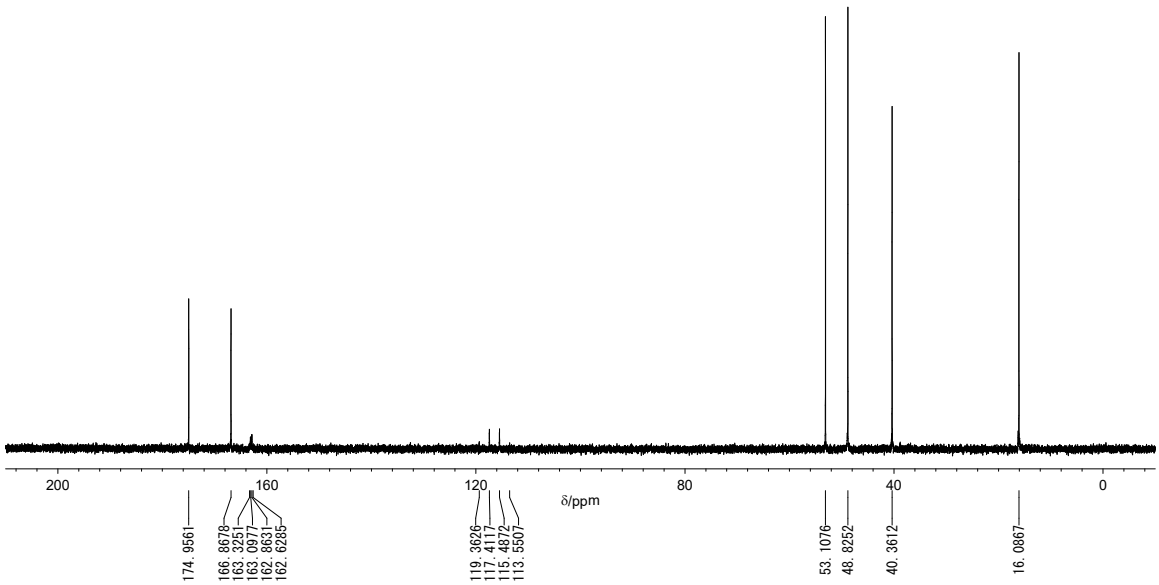


$^{1}$H NMR (400 MHz, $CD_3OD$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $D_2O$) spectra of methyl glycyl-*L*-alaninate trifluoroacetate salt (**4b**)

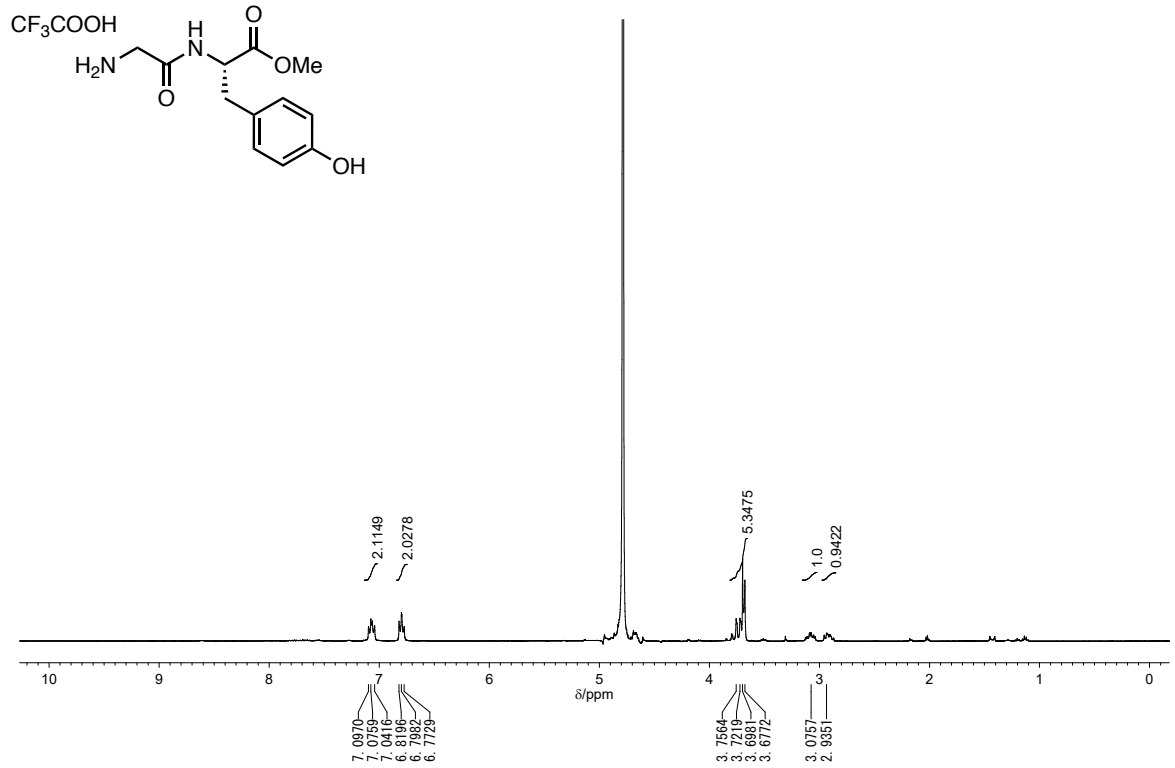


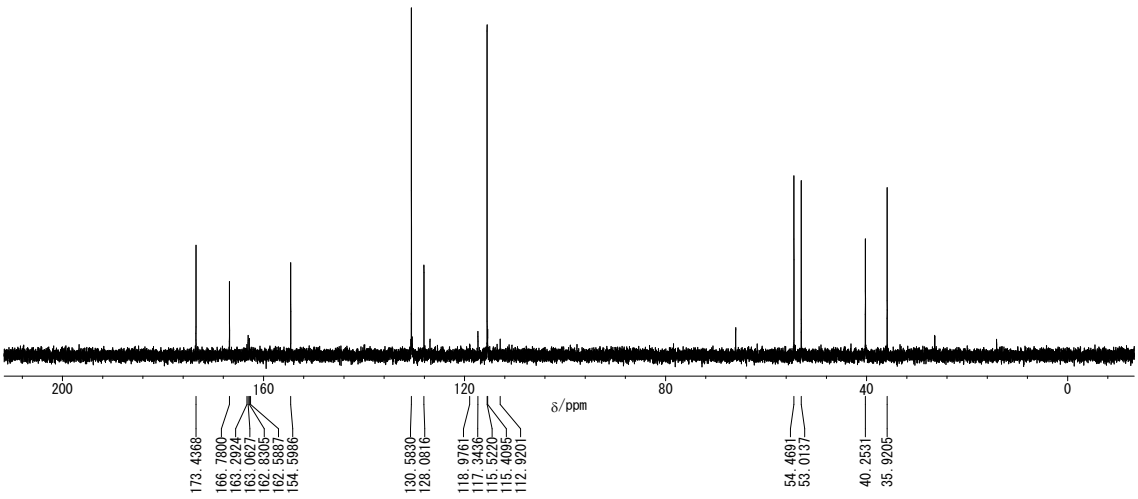




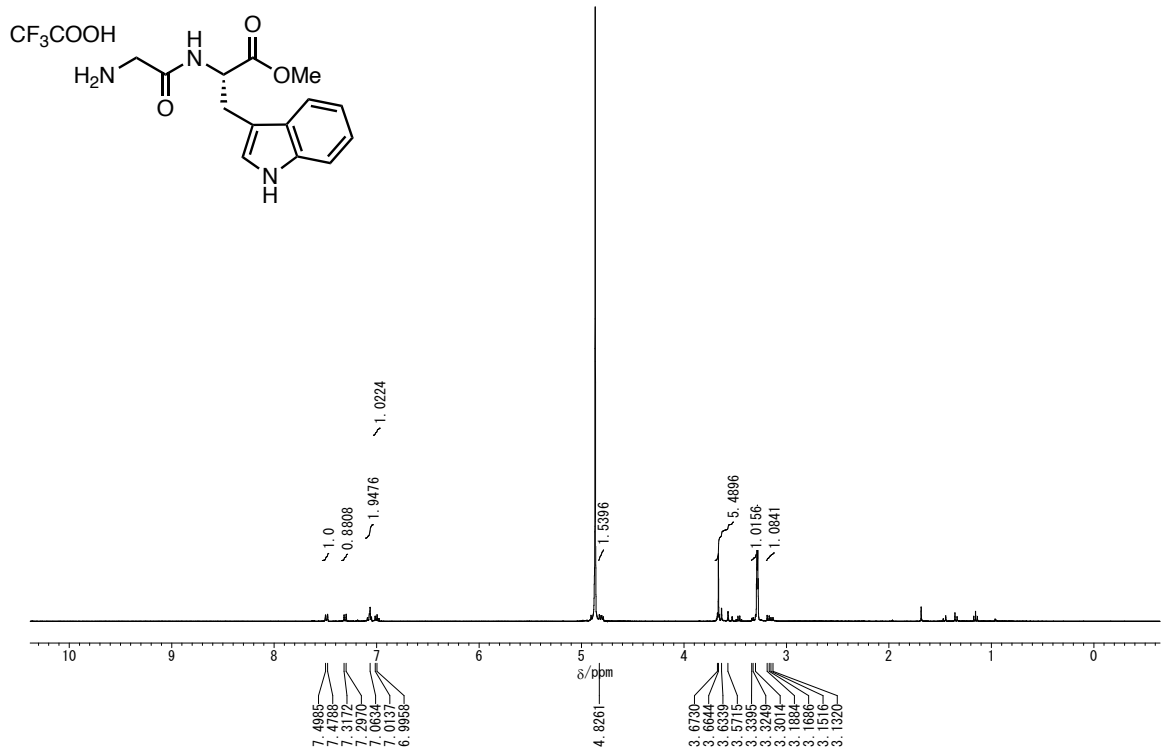


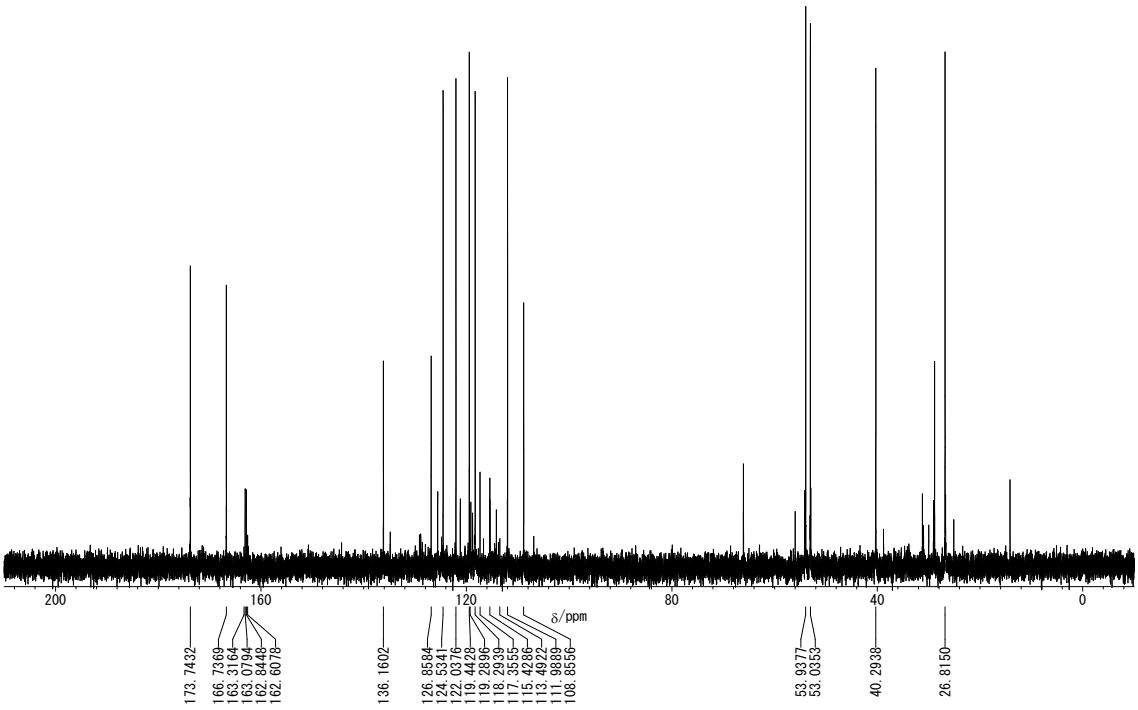
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl glycyl-*L*-tyrosinate trifluoroacetate salt (**4d**) ($D_2O$)



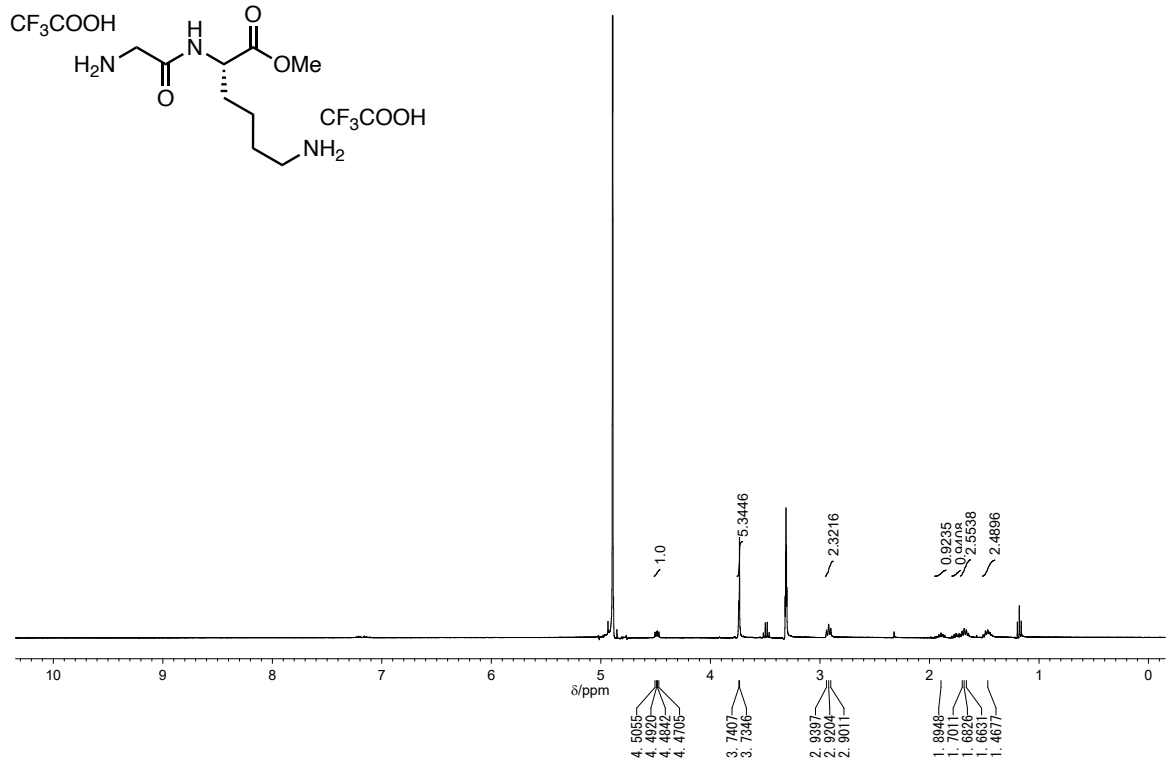



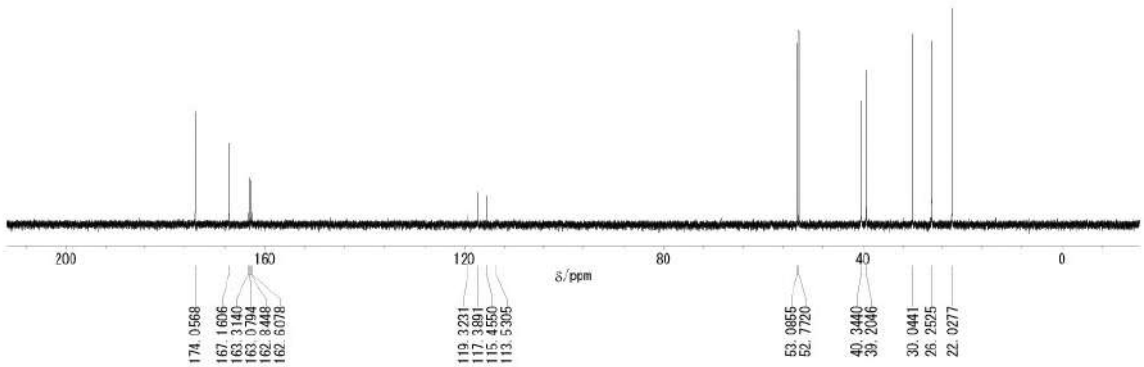
$^{1}$H NMR (400 MHz, $CD_3OD$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $D_2O$) spectra of methyl glycyl-*L*-tryptophanate trifluoroacetate salt (**4e**)



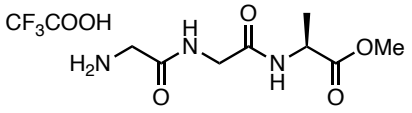



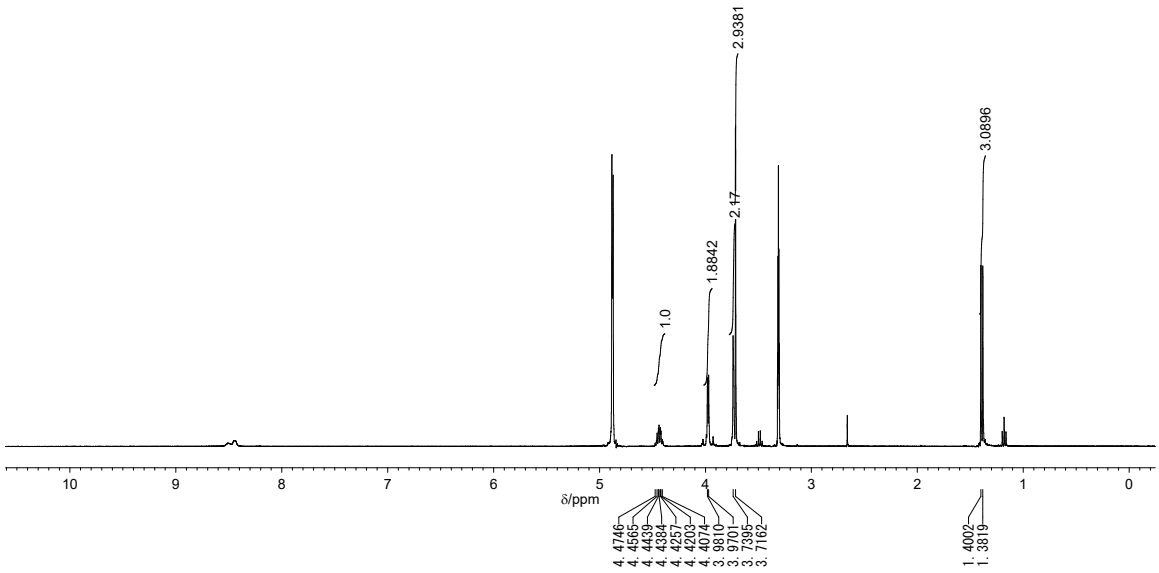
$^{1}$H NMR (400 MHz, $CD_3OD$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $D_2O$) spectra of methyl glycyl-*L*-lysinate bis(trifluoroacetate) salt (**4g**)

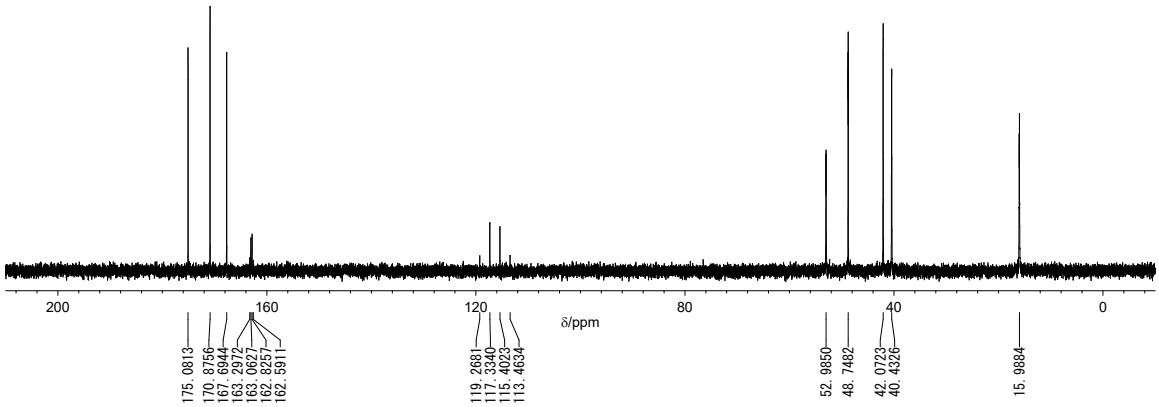


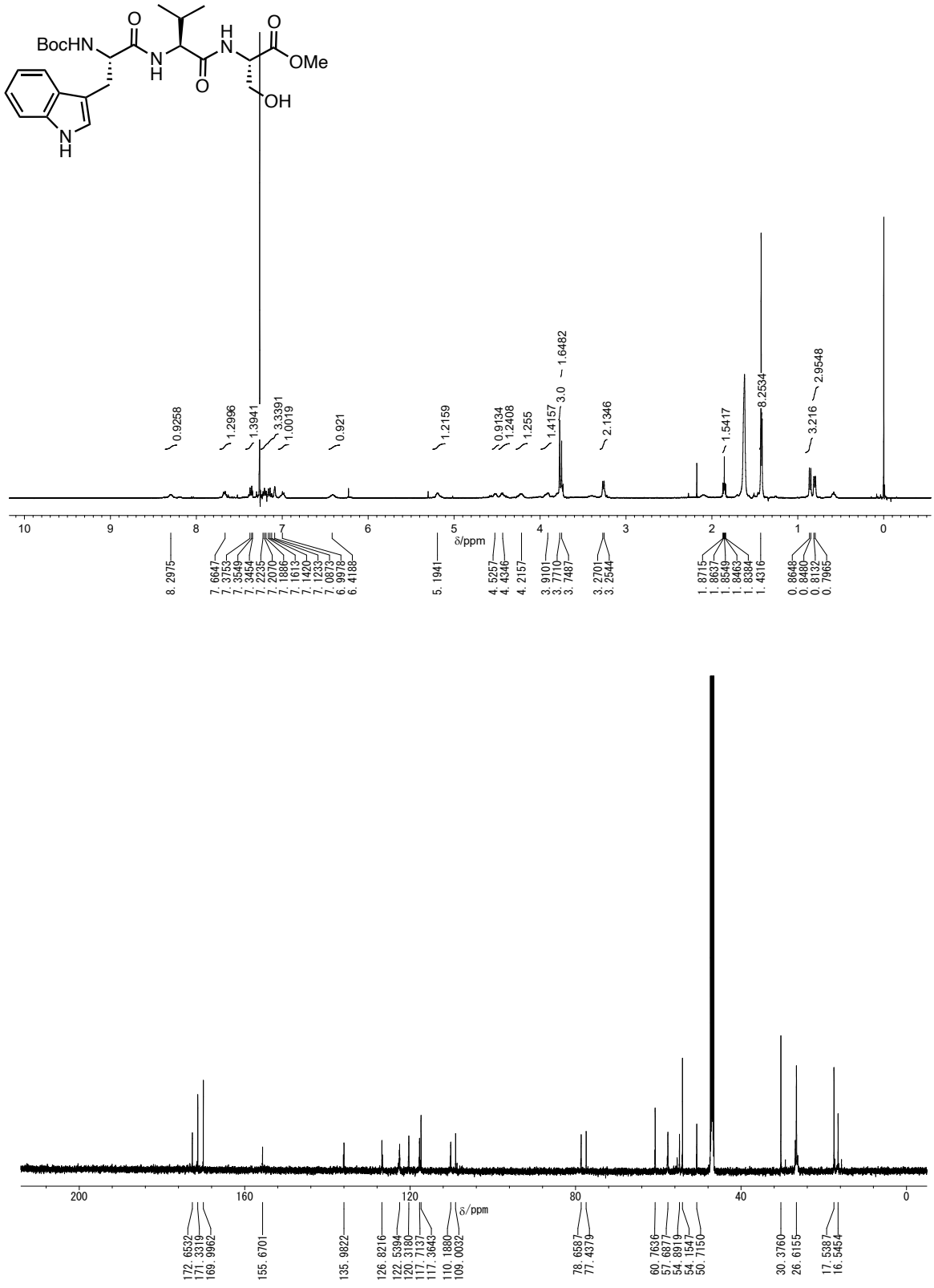
$^{1}$H NMR (400 MHz, $CD_3OD$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $D_2O$) spectra of methyl glycylglycyl-*L*-alaninate trifluoroacetate salt (**4h**)



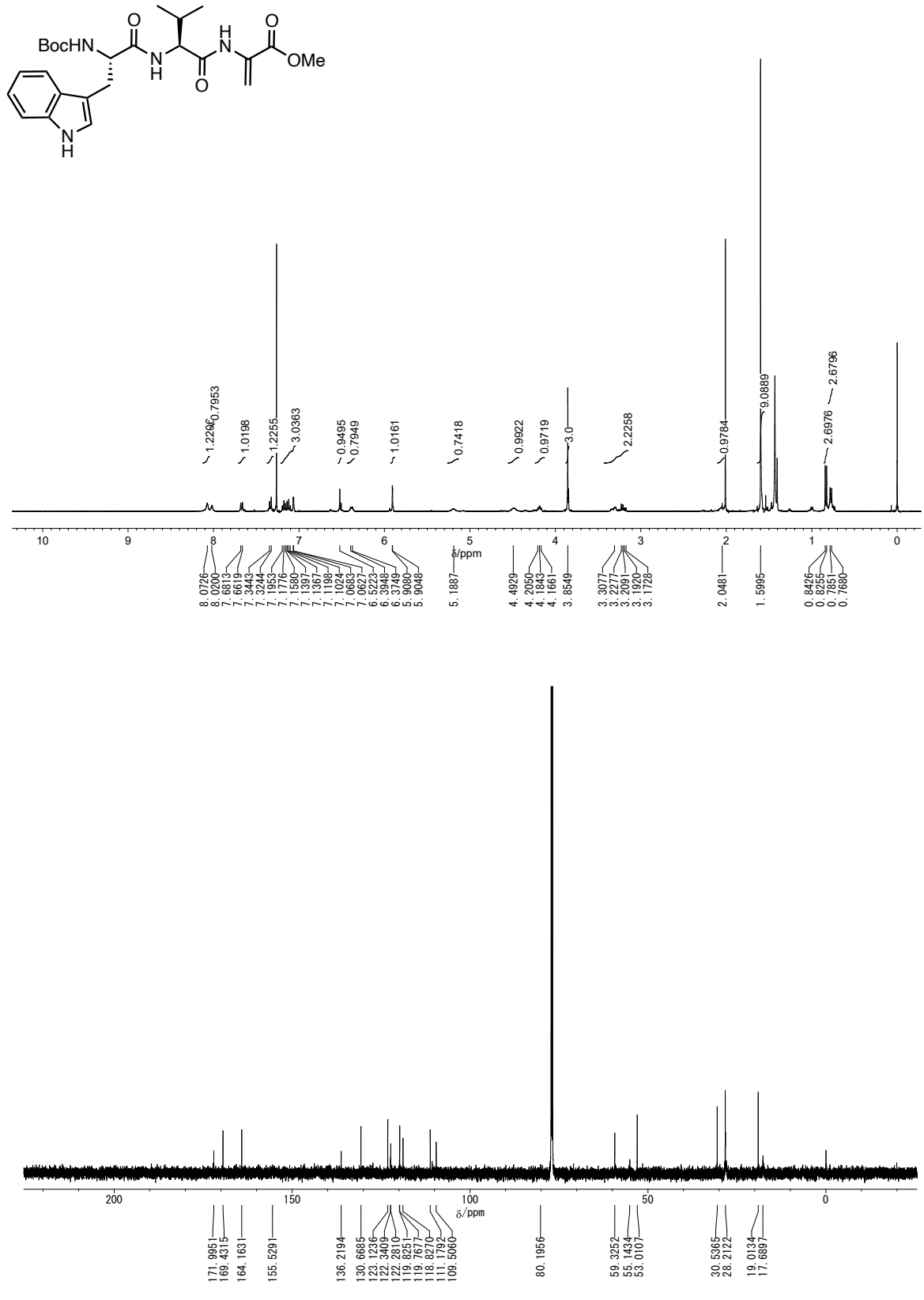



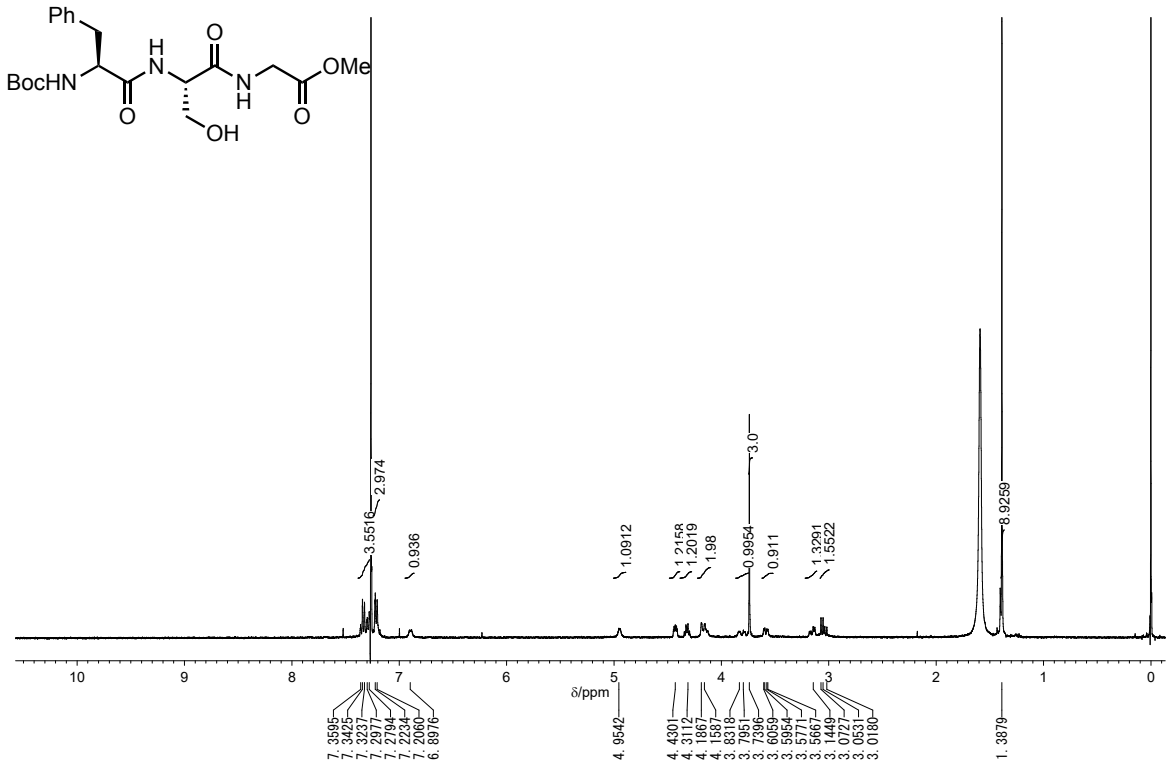
$^{1}$H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $CD_3OD$) spectra of methyl (*tert*-butoxycarbonyl)-*L*-tryptophyl-*L*-valyl-*L*-serinate (**9**)

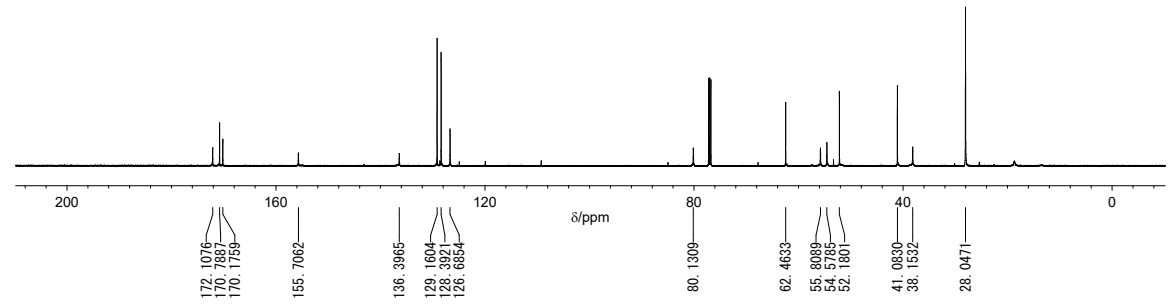


$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (6*S*,9*S*)-6-((1*H*-indol-3-yl)methyl)-9-isopropyl-2,2-dimethyl-12-methylene-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (**2f**) ($CDCl_3$)

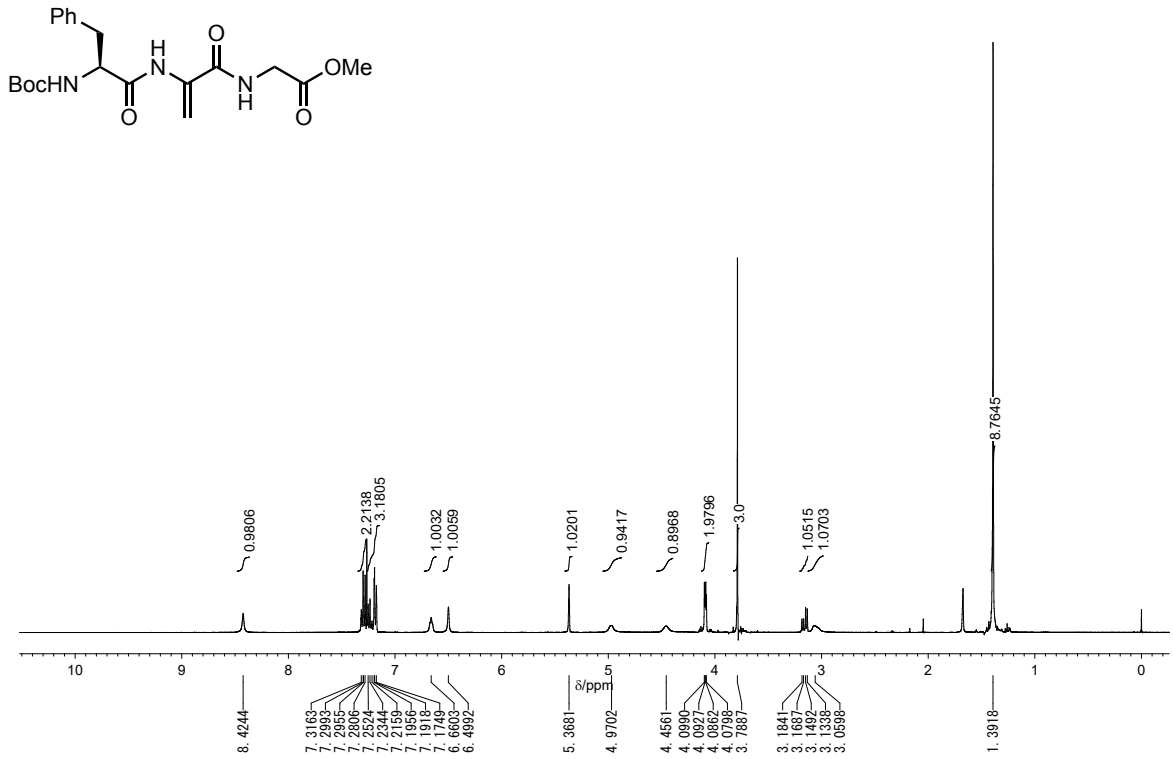


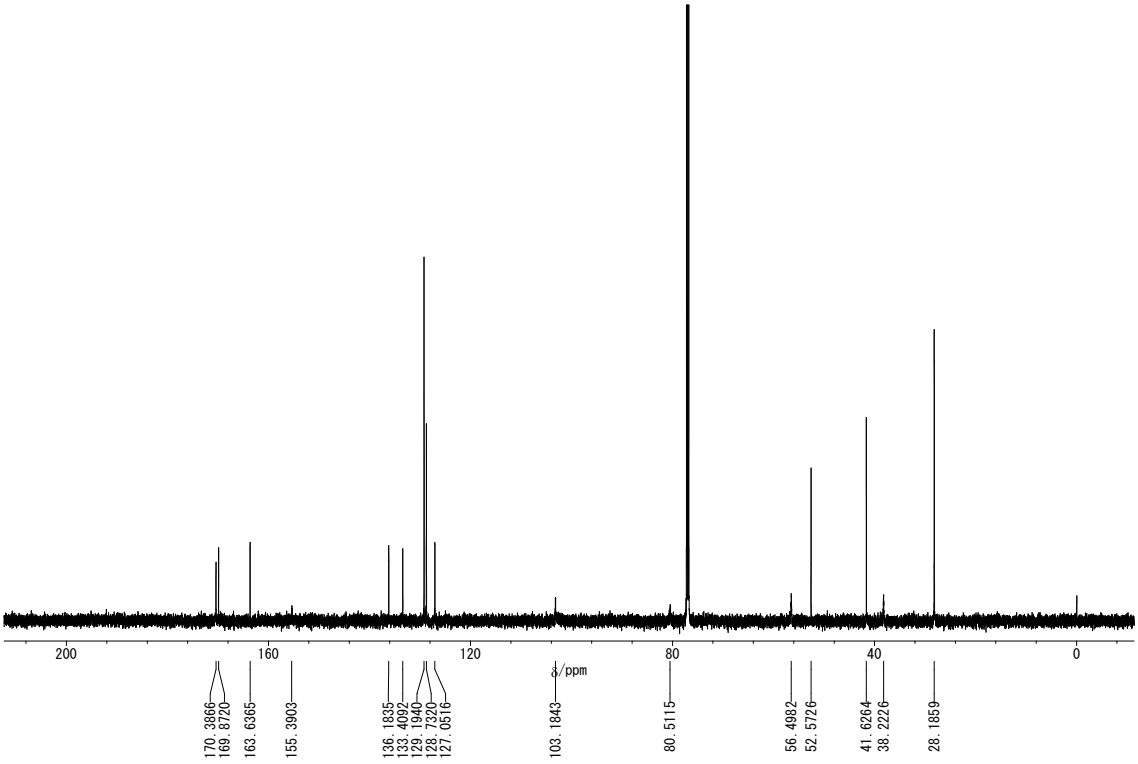
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (*tert*-butoxycarbonyl)-*L*-phenylalanyl-*L*-serylglycinate ($CDCl_3$)



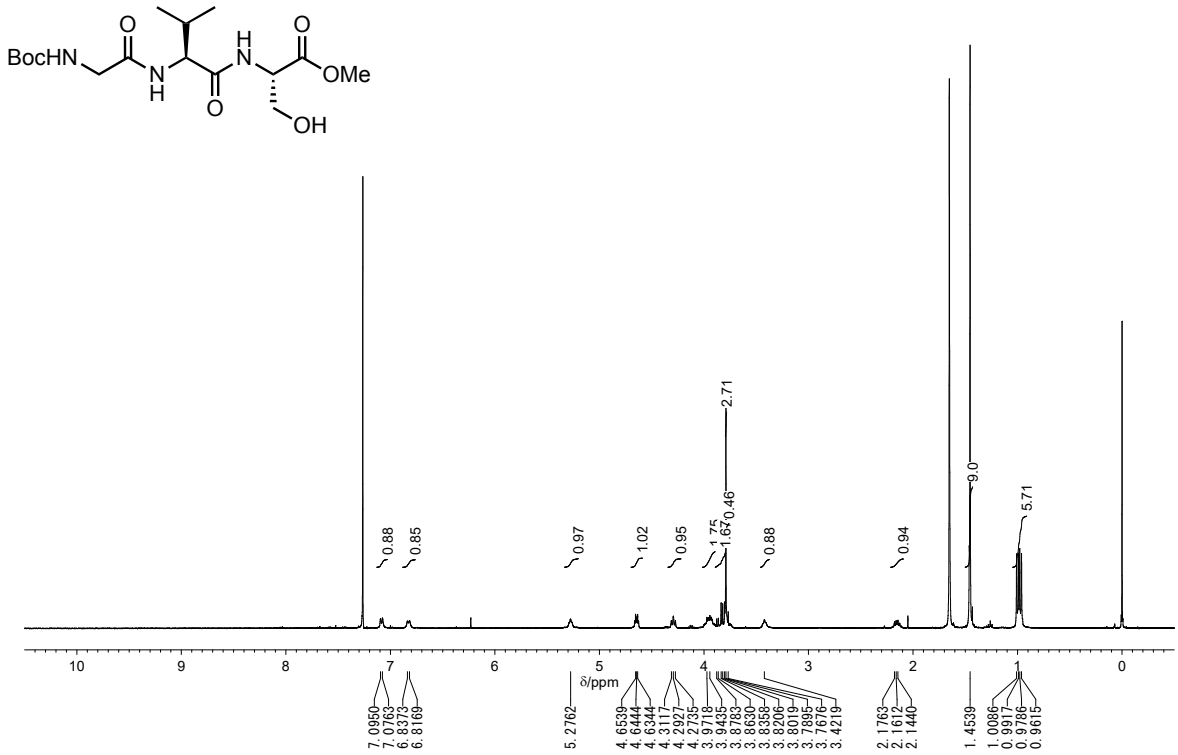



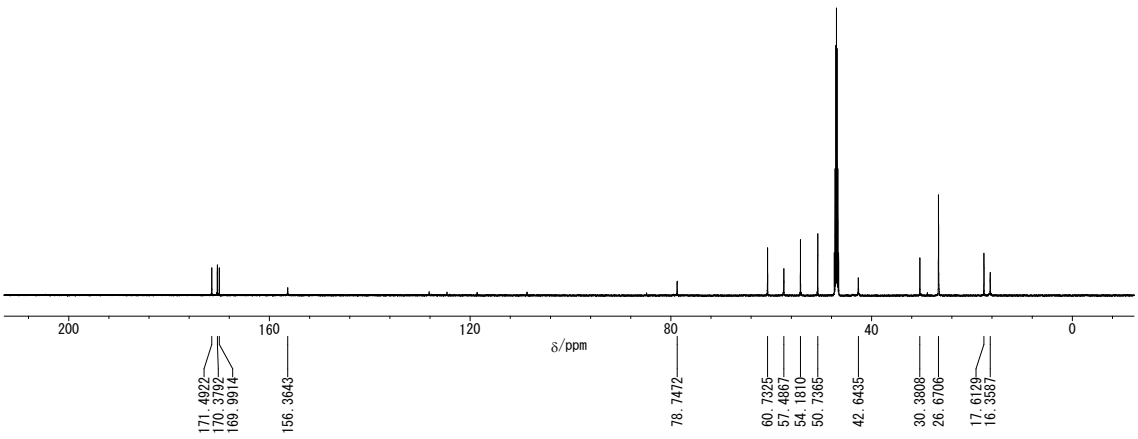
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (*S*)-(2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)acryloyl)glycinate (**2g**) ($CDCl_3$)



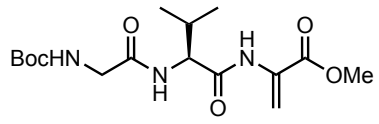



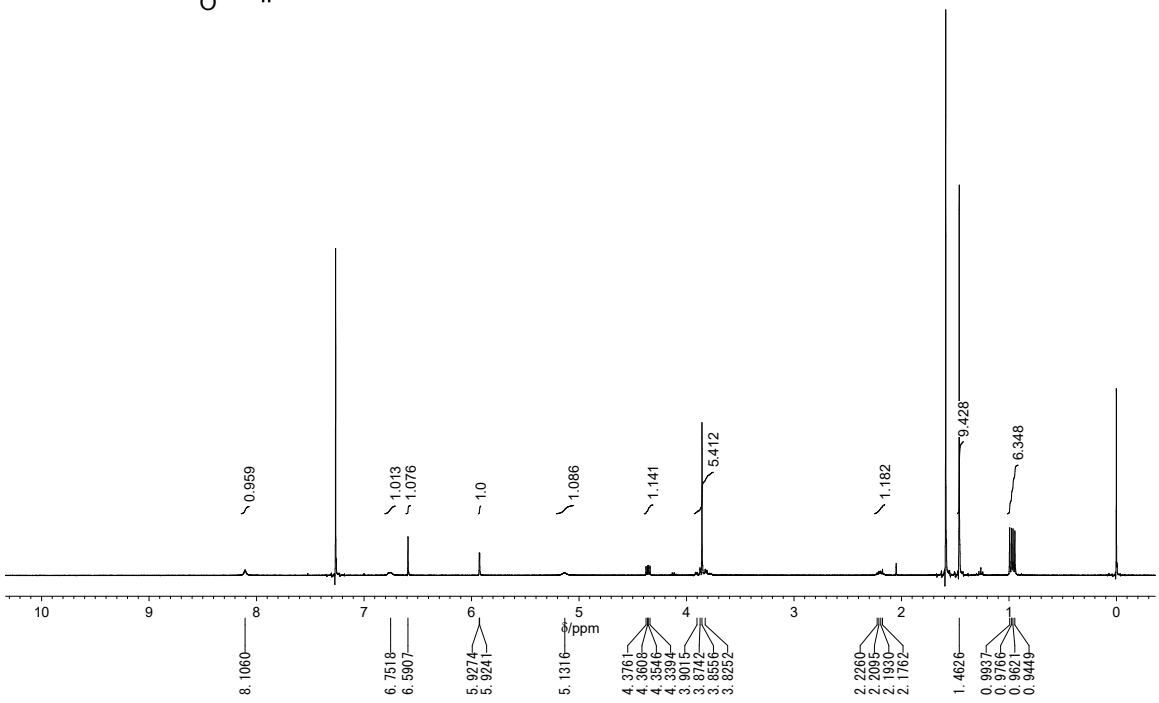
$^{1}$H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (150 MHz, $CD_3OD$) spectra of methyl (*tert*-butoxycarbonyl)glycyl-*L*-valyl-*L*-serinate (**6b**)

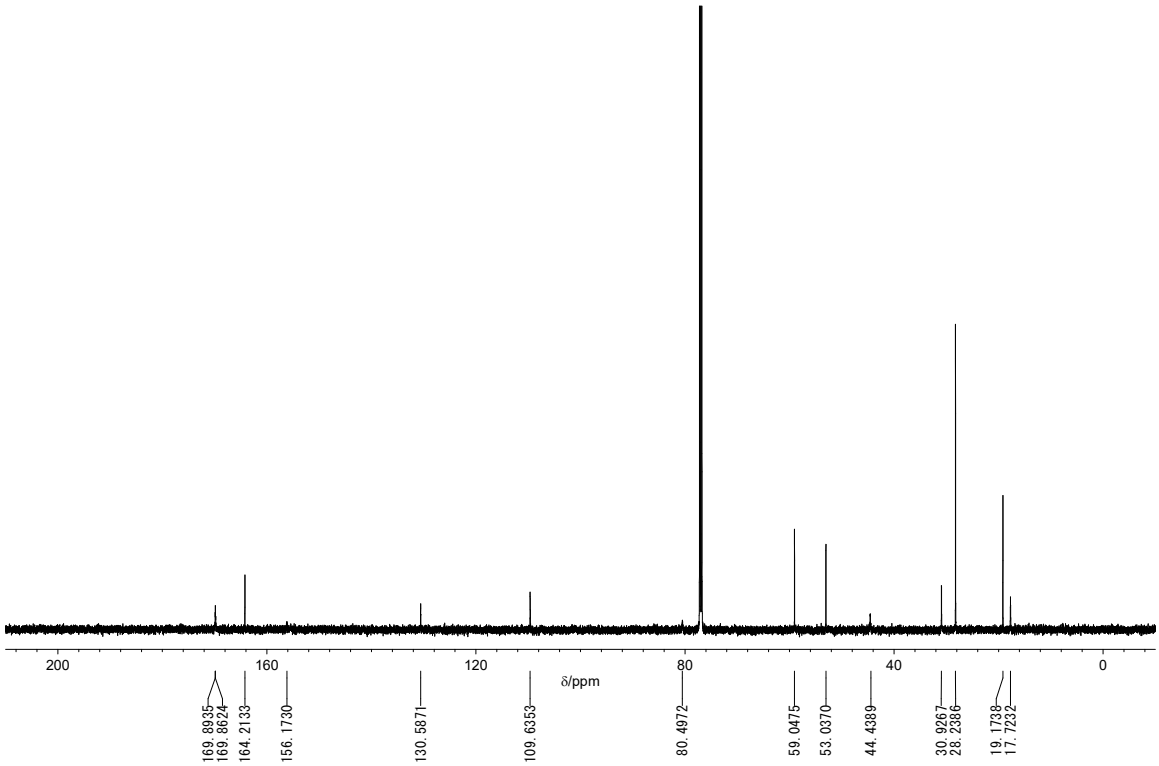


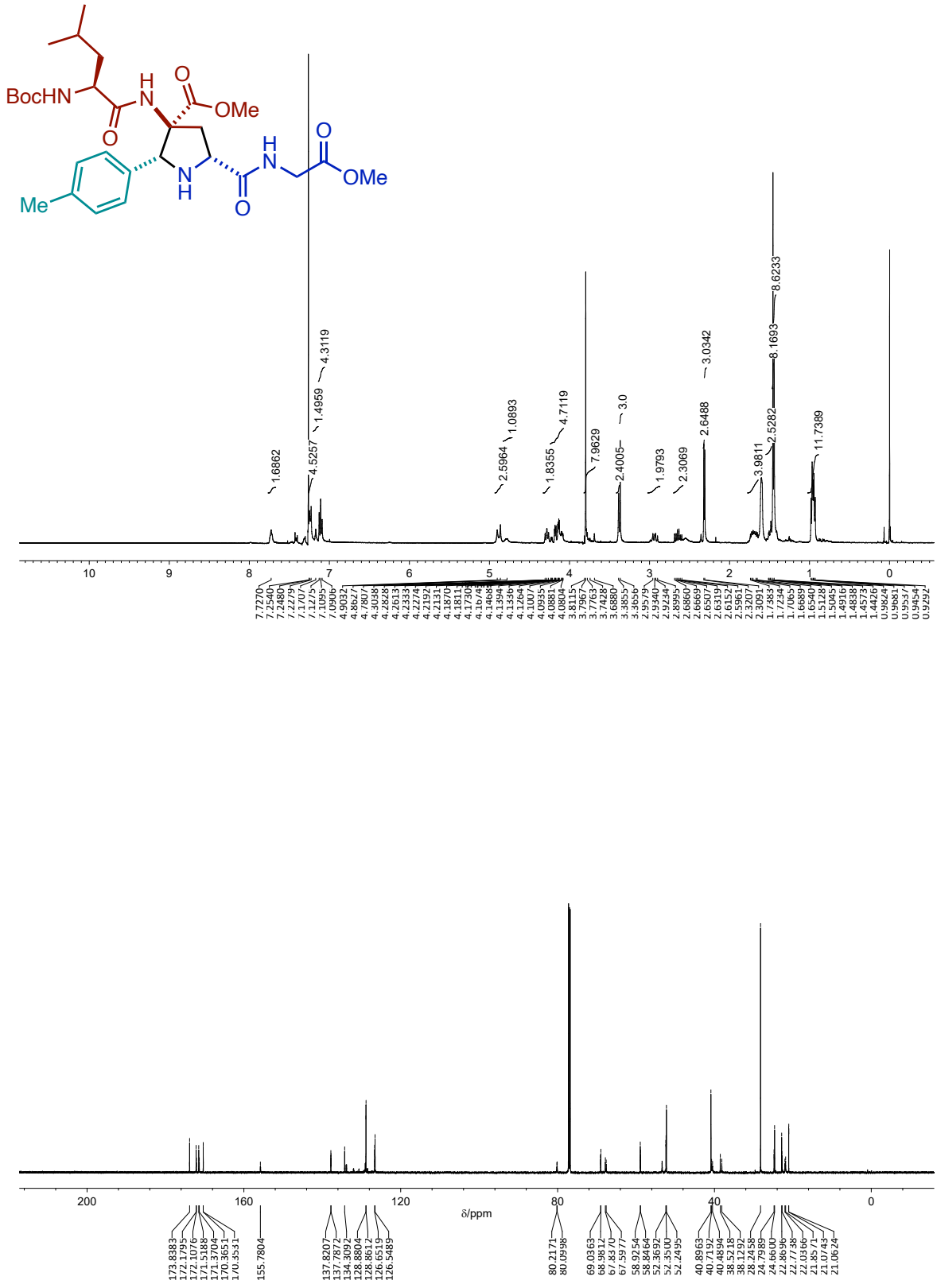
$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (*S*)-9-isopropyl-2,2-dimethyl-12-methylene-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (**7b**) ($CDCl_3$)



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8a**) ($CDCl_3$)



$^{1}$H NMR (400 MHz) and $^{13}$C{$^{1}$H} NMR (150 MHz) spectra of methyl (2*R**,3*S**,5*R**)-3-((*S*)-2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-methylbutanamido)-5-((2-methoxy-2-oxoethyl)carbamoyl)-2-(*p*-tolyl)pyrrolidine-3-carboxylate (**8b**) ($CDCl_3$)