Interrupted Polonovski strategy for the synthesis of functionalized amino acids and peptides

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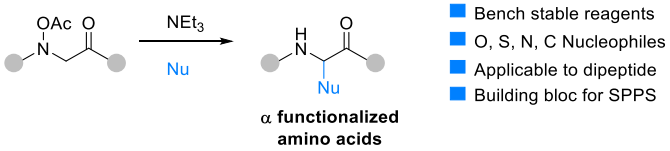
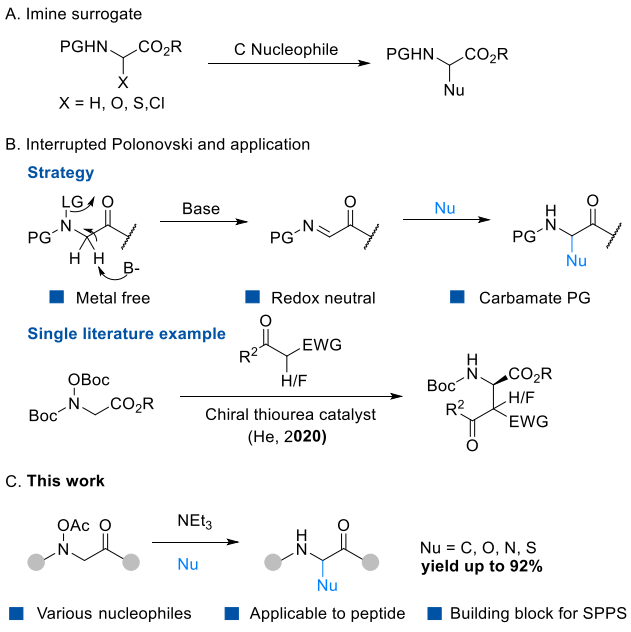


ABSTRACT: The α-functionalization of carbamate-protected hydroxylamine glycine derivatives, acting as imine surrogates via an interrupted Polonovski reaction, is described to access functionalized amino acid derivatives. The addition of C, N, O and S nucleophiles was achieved in a one-pot procedure in 37 to 92% yield. This method could be extended to dipeptide derivatives for the functionalization of both the C and N-terminus.

Non proteinogenic α amino-acids are an essential class of compounds in medicinal chemistry, agrochemistry and materials science. More than 60 peptide drugs have been approved worldwide, yet challenges remain with the use of endogenous peptide sequence, especially due to their limited stability.[1] To control the conformation and improve the stability or the activity, the peptide termini, side chains or backbone can be modified.[2] If the two prior approaches have been well studied on peptides,[3,4] site-selective backbone modification is more challenging as the C_α position is less reactive.[5] Therefore, most reported methods are limited to simple amino acid building blocks and there is an urgent need for efficient modification methods for more complex amino acid and peptide derivatives.

The α functionalization of glycine gives access to both natural and non-natural tertiary amino acid derivatives. The reactivity of synthetic precursors designed to access modified glycine can be divided in 3 categories: nucleophilic, electrophilic and radical. The electrophilic approach is especially attractive due to the availability of numerous nucleophiles enabling both C-C and C-X bond formation. Hence, α-imino esters have been used for a long time to synthesize unnatural amino acids because of their electrophilic character.[7] However, *N*-carbamoyl imines in particular suffer from instability due to water sensitivity or tautomerization when bearing enolizable α-hydrogens.[7] To avoid the issues associated with imino esters, several methods have been developed to access them *in situ*. Oxidation of *N*-aryl glycines gives access to imines *in situ* (Scheme 1A, X = H).[8,9] However, this approach requires *N*-aryl protecting groups, which are not easy to remove, and strong oxidative conditions. As second approach, *N*-carbamoyl α-imino ester surrogates not requiring a change in oxidation state have been developed.[10] *N*-carbamoyl *N,O*[11], *N,S*[12] and *N,Cl*[13] -acetals were employed successfully in Mannich, Friedel-Crafts, Strecker and allylation reactions. Moreover, these mixed acetals are also interesting as reactive units in prodrugs or potential covalent binders.[14] One example of bioactive compound is 15-Deoxyspergualin, an immunosuppressive agent bearing an isoserine.[15]

Scheme 1. Imine surrogates' strategies

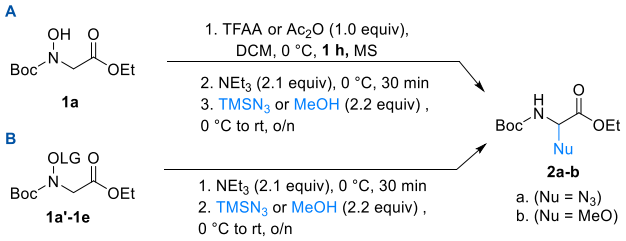


When considering the importance of such imine surrogates, efficient methods to access them are of high importance, but still remain limited. One approach established by Steglich and co-workers to form *N,S* -acetals is based on the conversion of serine,[16,17] threonine[18] or glutamic acid[19] residues. However, these methods still require the use of strong oxidants. *N,O* and *N,Cl* acetals can be accessed in one step from ethyl glyoxylate.[13,20] These surrogates are good imine precursors, but still suffer from limited stability. In particular, *N,Cl*-acetals are not bench stable and require low temperature for their functionalization. Therefore, there is an urgent need for more stable imine surrogates accessible in a simple manner on more functionalized substrates, such as peptides.

The Polonovski reaction is an interesting alternative approach to form imine surrogates *in situ* under mild conditions. It occurs when an amine *N*-oxide reacts with acetic anhydride.[21] Upon deprotonation by a base, the imine is formed *in situ* through elimination. This imine is then trapped by the leaving group to form an *N,O* acetal derivatives. Hence, an interrupted Polonovski strategy looks like an attractive method to access glycine derivatives under mild conditions (Scheme 1B). Surprisingly, there is only one single example of such a transformation: The He group used *N,O*-bis(*tert*-butoxycarbonyl) hydroxylamine methyl glycinates as imine surrogates for the asymmetric addition of diketones or diesters using a bifunctional organocatalyst.[22] We wondered if the interrupted Polonovski strategy could be extended to various nucleophilic heteroatoms and other carbon nucleophiles. Herein, we report a general α-functionalization of carbamate-protected hydroxylamine glycine derivatives under mild basic conditions through an interrupted Polonovski reaction (Scheme 1C). The addition of C, N, O and S nucleophiles was achieved in a one-pot procedure from bench stable reagents. Furthermore, the strategy was extended to dipeptide and the formed *N,S* acetals could be used in solid phase peptide synthesis.

We started our investigation using *N*-Boc hydroxyglycine **1a,** trifluoroacetic anhydride (TFAA) as activating reagent, triethylamine as the base and $TMSN_3$ or MeOH as the nucleophile. The choice of $TMSN_3$ was motivated by the fact that *N*-azide aminals are also good imine surrogates.[23] The starting materials are easily obtained in few steps starting from commercially available ethyl glyoxylate and hydroxylamine (See ESI for details). We were happy to observe azide aminal **2a** under the Polonovski Pottier conditions[24] in 53 % NMR yield (Table 1, entry 1). When moving to the traditional Polonovski leaving group (OAc), the yield increased to 66% (Table 1, entry 2). Replacing triethylamine by DIPEA resulted in a decrease in yield (Table 1, entry 3). Changing the solvent or the concentration did not improve the reaction (Table 1, entries 4-7). We investigated the effect of the leaving group on the nitrogen atom. When the leaving group was already installed on the starting material **1a'**, similar yields as in the one pot strategy were obtained: 71% for the azidated product **2a** and 70% for the methoxy product **2b** (Table 1, entry 8). The OBoc leaving group was also examined under the same conditions. The yield was higher for **2a**, but lower for **2b** (Table 1, entry 9). Further leaving groups were examined but gave lower yields (See SI, Table S2).

Table 1. Optimization of the azidation reaction[a]

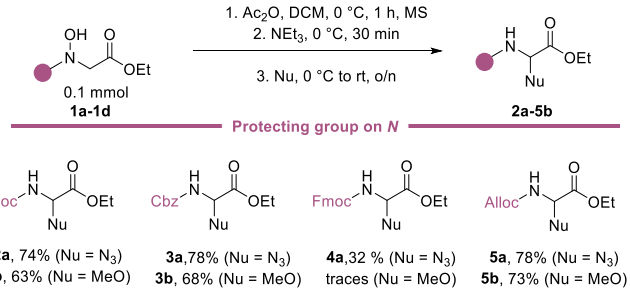


Entry	Conditions	LG	Deviation	Product	Yield (%)[b]
1	A	OTFA	DCM	**2a**	53
2	A	OAc	DCM	**2a**	66
3	A	OAc	DIPEA	**2a**	8
4	A	OAc	Toluene	**2a**	51
5	A	OAc	DME	**2a**	48
6	A	OAc	DCM (0.1 M)	**2a**	61
7	A	OAc	DCM (0.5 M)	**2a**	47
8	B	OAc	DCM	**2a**	71
				2b	70
9	B	OBoc	DCM	**2a**	80
				2b	64

[a] Reaction conditions: Glycine derivative **1a** (1.0 equiv.), $TMSN_3$ (2.2 equiv.) or MeOH (2.2 equiv.), NEt_3 (2.0 equiv.), solvent (0.2 M). The reactions were carried out under N_2 atmosphere on 0.1 mmol scale. [b]NMR yield determined using mesitylene as internal standard. [c]Isolated yield.

With the optimized conditions in hand, we explored the scope of protecting groups on nitrogen using triethylamine as the base and $TMSN_3$ and MeOH as the nucleophiles starting directly from the free hydroxylamines (Scheme 2). Starting from substrate **1a'**, **2a** and **2b** were isolated with similar yields compared to the NMR yields. *N*-Cbz hydroxyglycine **1b** afforded **3a** in 78% yield and **3b** in 68% yield. By contrast, *N*-Fmoc hydroxyglycine **1c** gave only 32% yield for **4a**, probably due to the base sensitivity of the Fmoc group. *N*-Alloc hydroxyglycine **1d** formed product **5a** and **5b** in good yield (78% and 73%, respectively).

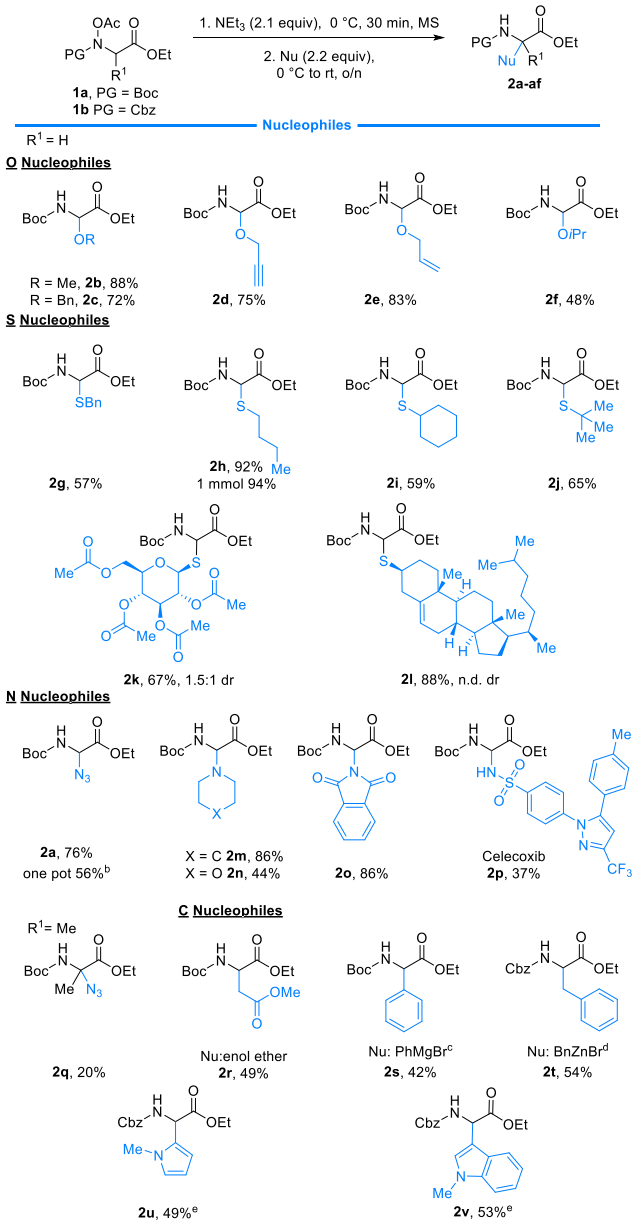
Scheme 2. Scope of amino groups[a]



[a] Reaction conditions: Glycine derivative **1** (1.0 equiv.), $TMSN_3$ or MeOH (2.2 equiv.), NEt_3 (2.0 equiv.), DCM (0.2 M), 21 °C, 2 h. Reactions were carried out under N_2 atmosphere on 0.10 mmol scale.

Various different nucleophiles were then examined (Scheme 3). On larger scale, more reproducible results and higher yields were obtained when starting from isolated acetylated substrates, so the two-step protocol was applied. Our method was efficient for the addition of methanol and benzylic alcohol on substrate **1a'** to give **2a** and **2b** in 88% and 72% yield. Propargylic and allyl alkoxy products **2d** and **2e** were formed in 75 and 83% yield. Isopropanol gave product **2f** in 48% yield.

Scheme 3. Scope of nucleophiles[a]

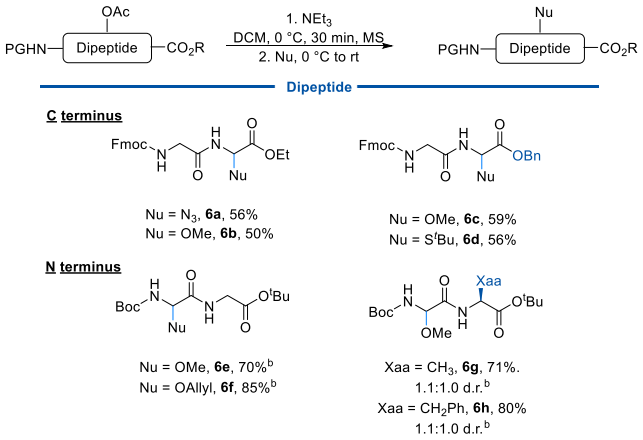


[a] Reaction conditions: Starting material **1a' or 1b'** (1.0 equiv.), base (2.0 equiv.), Nucleophile (2.2 equiv.), DCM (0.20 M), 0 °C to 23 °C, 16 h. Reactions were carried out under N_2 atmosphere on a 0.3 mmol scale. [b]From **1a**. [c]-20 °C, 1 h. [d]1 h. [e] TMSOTf (1.2 equiv.), 1 h.

Primary, benzylic, secondary and even tertiary thiols formed *N,S*-acetals **2g** to **2j** in 59–92% yield. More complex thioacetals **2k** and **2l** derived from thioglucose and thiocholesterol were formed in 67 and 88% yield as mixtures of diastereoisomers. *N,N*-acetals were synthesized in 86% (**2m**), 44% (**2n**) and 86% yield (**2o**). The yield of **2n** was lower due to the addition of water as side-reaction to give the N,O acetal in 39% yield. Celecoxib-functionalized product **2p** was obtained in 37% yield. A tertiary azide **2q** could be formed in 20% yield starting from the corresponding alanine derivative. C nucleophiles such as enol ethers, phenyl magnesium bromide and benzyl zinc bromide afforded the respective desired products **2r**, **2s** and **2t** in moderate yields without the need of Lewis acid addition. Finally, pyrrole and indole nucleophiles required in contrast the use of TMSOTf as Lewis acid to give compounds **2u**-**2v**. In this case, the protecting group was changed to Cbz (precursor **1b'**) because of its better tolerance to Lewis acids. All products were stable and were purified by column chromatography on silica gel.

After exploration of the scope of nucleophiles, we examined the reactivity on dipeptide (Scheme 4). The use of imine surrogates on dipeptides was reported only a few time for the CDC[5] strategy or using *N,S* -acetals.[16,17a] We were pleased to see that our methodology could be extended to dipeptides. We investigated modification both at the *N* and at the *C* termini. When the hydroxylamine was positioned on the *C* terminus, the reaction gave 56% for the azidated product **6a** and 50% yield for the methoxy product **6b**. Replacing the ethyl ester by a benzylic ester had very little impact on the yield of the alkoxy product **6c**. Thiol functionalized dipeptide **6d** was formed in 50%. The decrease of the yield compared to the glycine building block could be due to the instability of the Fmoc protecting group during the reaction. In fact, we were pleased to see that, for modification of the *N* terminus bearing a non-base sensitive Boc group, the *N,O*-acetal **6e** and **6f** were formed in 70 and 85 % yield. In addition to Gly, Ala and Phe were also tolerated in the dipeptides, providing **6g** and **6h** in 71 and 80% yield.

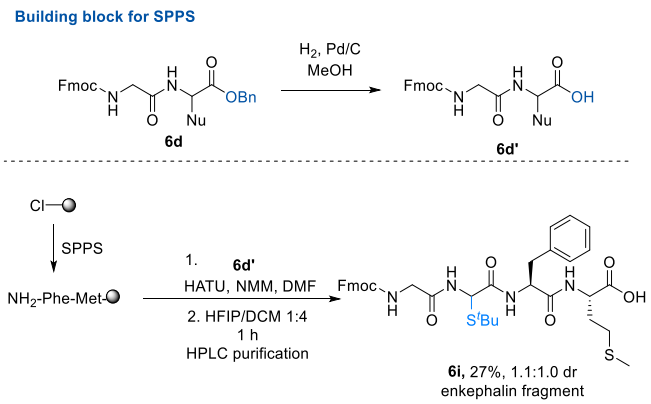
Scheme 4. Scope of dipeptides[a]



[a]Reaction conditions: Starting material (1.0 equiv.), base (2.0 equiv.), Nucleophile (2.2 equiv.), DCM (0.20 M), 0 °C to 23 °C, 16 h. Reactions were carried out under N_2 atmosphere on 0.2 mmol scale. [b]Base (3.0 equiv.), Nucleophile (4.0 equiv.)

Finally, we were wondering if it was possible to use the α functionalized dipeptides in solid phase synthesis to obtain longer peptides. After hydrogenation of **6d** to form **6d'**, coupling and resin cleavage, the tetrapetide **6i** could be obtained with high purity in 27% over 3 steps (Scheme 5). This tetrapeptide is a fragment of enkephalin, a pentapeptide involved in regulating nociception in the body.

Scheme 5. Use of N,S acetal 6d in solid phase synthesis[a]



To conclude, we have developed a new methodology to access α-functionalized amino acid derivatives under mild conditions. Various nucleophiles and C nucleophiles were added in moderate to excellent yields to imines generated in situ from hydroxylamine derivatives using a Polonovski-type reaction. Furthermore, the scope could be extended to dipeptides with modification both on N and C termini. Finally, a formed thioacetal building block could be incorporated into a tetrapeptide via solid phase synthesis.

ASSOCIATED CONTENT

Supporting Information

General methods, synthetic procedures, characterization data for reported and new compounds and copy of ^{1}H and ^{13}C NMR spectra for new compounds. (PDF)

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Author Contributions

E.M.D.A. discovered the reaction and performed preliminary experiments. C.M. optimized the reaction, investigated the scope of the reaction, application on solid phase and prepared the experimental parts and first draft of the manuscript. J.W. supervised the project, edited the manuscript and proof read the experimental part.

Notes

The authors declare no competing financial interest.

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Contents

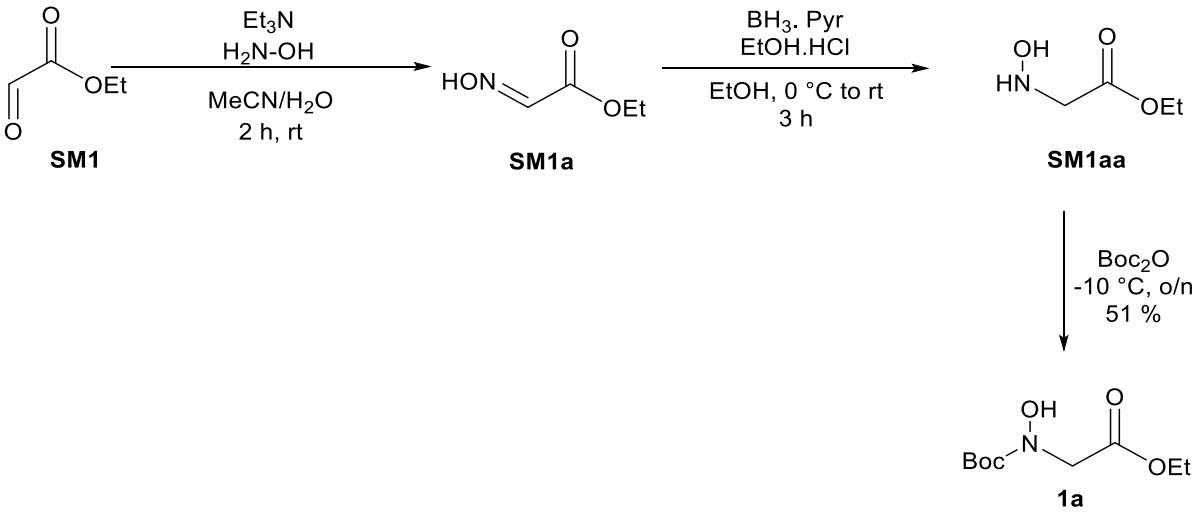
1. General methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography, technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem, or Merck and used as such unless otherwise stated. All the Fmoc-protected amino acids and Rink Amide MBHA resin were purchased from GL Biochem or Bachem. 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU, Bachem) and N,N-diisopropylethylamine (DIPEA, Iris Biotech GmbH) were used as received. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, with the solvents indicated as eluent under 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain, or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in $CDCl_3$, DMSO-d_6 CD_3OD, C_6D_6 and CD_2Cl_2, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm the internal methanol signal at 3.30 ppm, the internal dichloromethane signal at 5.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation).^{13}C-NMR spectra were recorded with 1H-decoupling on a Brucker DPX-400 100 MHz spectrometer in $CDCl_3$, DMSO-d_6, CD_3OD or CD_2Cl_2, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm, the internal methanol signal at 49.0 ppm and the internal dichloromethane signal at 54.0 ppm as standard. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm-1 (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API, LTQ Orbitrap ELITE ETD (Thermo fisher), Xevo G2-S QTOF (Waters), or LTQ Orbitrap ELITE ETD (Thermo fisher).

2. Chemical procedures

2.1 Preparation of glycine hydroxylamine

Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-hydroxyglycinate (1a)



Following a reported procedure,[1] hydroxylamine hydrochloride (3.40 g, 49.0 mmol, 2.00 equiv) was added to a mixture of solvent MeCN: H_2O (1 M) (9:1): acetonitrile (22.5 mL), water (2.50 mL). To this solution was added ethyl 2-oxoacetate 50% in toluene **SM1** (5.00 g, 4.57 mL, 24.5 mmol, 1.00 equiv), under nitrogen atmosphere. After brief stirring for 5 min at ambient temperature, triethylamine (2.48 g, 3.41 mL, 24.5 mmol, 1.00 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 h until TLC indicated complete consumption of ethyl glyoxylate. Then, the mixture was concentrated to dryness to obtain a gel. The crude was dissolved in ether (150 mL). The aqueous layer was extracted with ether (3 x 150 mL). The organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to obtain a yellowish oil, **SM1a** (2.87 g)**.** The crude **SM1a** was engaged in the next step without purification.

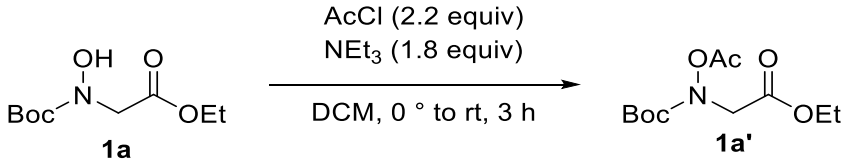
Following a reported procedure,[2] to a well-stirred solution of crude mixture of previous step, **SM1a** (2.87 g) in absolute ethanol (50.00 mL, 0.5 M) cooled to 0 °C, was added slowly borane pyridine complex (4.55 g, 6.12 mL, 49.0 mmol, 8.00 M, 2.00 equiv). Then, 7 N HCl in EtOH (20.2 g, 35.0 mL, 245 mmol, 7.00M, 10.0 equiv), prepared from absolute ethanol 22.5 mL and 37% HCl 12.5 mL, was added dropwise and the resulting mixture was stirred at ambient temperature for 3 h. Then, the solvent was evaporated under reduced pressure without exceeding 40 °C and the residue is dissolved in dichloromethane (200 mL). Solid sodium carbonate was added until gas evolution stopped and left to stir overnight. The salts were filtered off and the filtrate was evaporated to obtain **SM1aa** (1.97 g) as a brownish oil. The crude **SM1aa** was engaged in the next step without purification.

Following a reported procedure,[3] to a solution of crude mixture of previous step, **SM1aa** (1.95 g) in THF (30.00 mL, 0.8 M) was added Boc_2O (3.75 g, 17.2 mmol, 1.05 equiv) under nitrogen atmosphere. The mixture was stirred at -10 °C overnight with the cryostat. The reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc/pentane 0:100- 30:70) to give **1a** (1.84 g, 8.38 mmol, 51% yield) as a yellow oil.

R_f = 0.53 (Pentane/ethyl acetate 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 1H, O*H*), 4.29 – 4.18 (m, 2H, OC*H*$_2$CH$_3$) 4.18 (s, 2H, NC*H*$_2$CO), 1.49 (s, 9H, C*H*$_{3Boc}$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 157.4, 82.8, 61.7, 52.7, 28.3, 14.3.
IR (ν_{max}, cm^{-1}) 3349 (m), 2981 (m), 2936 (w), 1751 (s), 1707 (s), 1475 (m), 1396 (m), 1370 (s), 1248 (s), 1203 (s), 1163 (s).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_9H_{17}NNaO_5^+$ 242.0999; Found 242.1006.

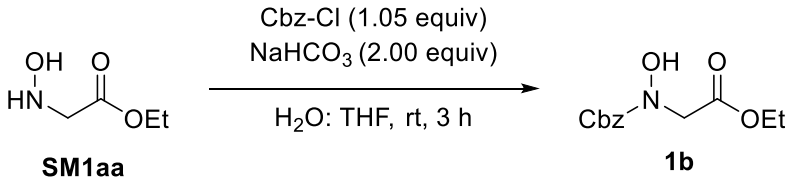
Ethyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycinate (1a')



Following a reported procedure,[3] **1a** (310 mg, 1.41 mmol, 1.00 equiv) was diluted in dry DCM (6.20 mL, 0.2 M). Then at 0 °C, acetyl chloride (244 mg, 222 µL, 3.11 mmol, 2.20 equiv) was added. The mixture was stirred for 5 min and, triethylamine (258 mg, 355 µL, 2.55 mmol, 1.80 equiv) was added. The reaction mixture was stirred at 0 °C for 3 h. Upon completion, the crude was diluted in water. The crude was extracted with EtOAc (3 x 100 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 20% EtOAc in pentane. The product came out around 12.5-15%, as a yellowish oil, **1a'** (320 mg, 1.22 mmol, 87% yield).

R$_f$ = 0.57 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 2H, NC*H*$_2$CO), 4.29 – 4.20 (m, 2H, OC*H*$_2$CH$_3$), 2.14 (s, 3H, C(O)C*H*$_3$), 1.48 (s, 9H, C*H*$_{3Boc}$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 168.1, 154.9, 83.5, 61.7, 52.5, 28.1, 18.6, 14.3.
IR (ν_{max}, cm^{-1}) 2984 (w), 2938 (w), 1796 (m), 1754 (s), 1725 (m), 1456 (w), 1411 (m), 1370 (s), 1252 (m), 1180 (s), 1159 (s), 1095 (m).
HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{11}H_{19}NNaO_6^+$ 284.1105; Found 284.1109.

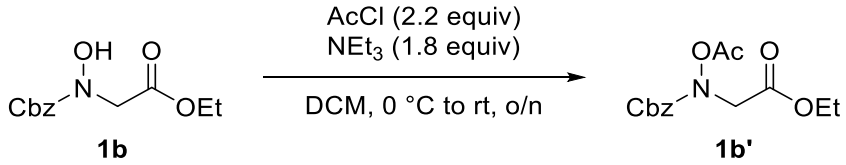
Ethyl *N*-((benzyloxy)carbonyl)-*N*-hydroxyglycinate (1b)



In a microwave vial, **SM1aa** (100 mg, 839 µmol, 1.00 equiv) and sodium bicarbonate (141 mg, 1.68 mmol, 2.00 equiv) were diluted in mixture (ratio 1:9, 0.8 M) water (200 µL) and THF (0.8 mL). Then, the mixture was stirred at room temperature and benzyl chloroformate (150 mg, 125 µL, 881 µmol, 1.05 equiv) in THF (0.5 mL) was added to the flask dropwise over 10 min with a syringe pump. The reaction mixture was stirred at rt during 3 h. Upon completion, the reaction mixture was quenched with H_2O.The reaction mixture was diluted in DCM (3 x 10 mL). The aqueous layer was extracted with DCM, the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography, silica gel, gradient from 0 to 40% EtOAc in pentane. The product came out around 40% EtOAc, as a transparent oil, **1b** (108 mg, 426 µmol, 51% yield).

R_f = 0.53 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H, Ar*H*), 6.41 (s, 1H, O*H*), 5.22 (s, 2H, ArCH_2), 4.33 (s, 2H, NCH_2CO), 4.22 (q, *J* = 7.2 Hz, 2H, OCH_2CH$_3$), 1.26 (td, *J* = 7.1, 4.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 157.6, 135.5, 128.6, 128.5, 128.3, 68.5, 61.8, 52.4, 14.1.
IR (ν_{max}, cm^{-1}) 3343 (m), 2991 (m), 2966 (m), 1746 (s), 1716 (s), 1501 (w), 1455 (m), 1349 (s), 1208 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{15}NNaO_5^+$ 276.0842; Found 276.0851.

Ethyl *N*-acetoxy-*N*-((benzyloxy)carbonyl)glycinate (1b')

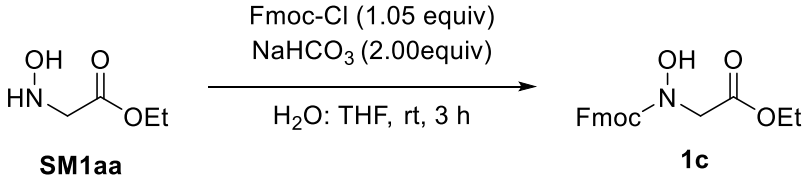


1b **1b'**

In a microwave vial, **1b** (565 mg, 2.23 mmol,1.00 equiv) was dissolved in dry DCM (7 mL, 0.3M). Then at 0 °C, acetyl chloride (385 mg, 350 µL, 4.91 mmol, 2.20 equiv) was added. The mixture was stirred for 5 min, triethylamine (406 mg, 560 µL, 4.02 mmol, 1.80 equiv) was added. The mixture was stirred at 0 °C for 2 h. The crude was diluted in water. The crude was extracted with DCM (3 x 10 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 20% EtOAc in pentane to give **1b'** (577 mg, 1.95 mmol, 88% yield) as a yellowish oil.

R_f = 0.2 (Pentane/ethyl acetate 90:10).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H, Ar*H*), 5.22 (s, 2H, ArCH_2), 4.34 (s, 2H, NCH_2CO), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 2.15 (s, 3H, COCH_3), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.7, 155.8, 135.4, 128.7, 128.5, 128.1, 68.8, 61.8, 52.4, 18.5, 14.2.
IR (ν_{max}, cm^{-1}) 3040 (w), 2986 (w), 2947 (w), 1754 (s), 1725 (s), 1718 (s), 1501 (m), 1457 (m), 1368 (m), 1344 (m), 1213 (m), 1170 (s), 1159 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{17}NNaO_6^+$ 318.0948; Found 318.0950.

Ethyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-hydroxyglycinate (1c)



SM1aa **1c**

In a microwave vial, **SM1aa** (100 mg, 839 µmol, 1.00 equiv) and sodium bicarbonate (141 mg, 1.68 mmol, 2.00 equiv) were diluted in a mixture (ratio 1:9, 0.8 M) water (200 µL) and THF (0.8mL). Then, the mixture was stirred at room temperature and Fmoc-Cl (228 mg, 881 µmol, 1.05 equiv) was diluted in 0.5 mL of THF added to the flask dropwise (over 1-2 min). The reaction mixture was stirred at room temperature during 3 h. Upon completion, the reaction mixture was quenched with H_2O.The mixture was diluted in DCM (3 x 10 mL). The aqueous layer was extracted with DCM, the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by flash chromatography, silica gel, with gradient from 0 to 40% EtOAc, product coming around 30% EtOAc in Pentane, **1c** (220 mg, 644 µmol, 77% yield) obtained as an off-white solid.

R_f = 0.26 (Pentane/ethyl acetate 80:20).
Mp: 83.2-84.5 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.61 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.41 (tt, *J* = 7.5, 0.9 Hz, 2H, Ar*H*), 7.31 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 6.47 (s, 1H, O*H*), 4.47 (d, *J* = 7.2 Hz, 2H, CH_2OCO),

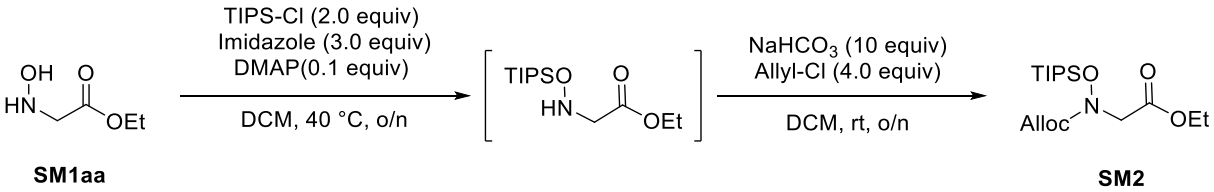
4.33 (s, 2H, NCH_2CO), 4.29 (t, *J* = 7.1 Hz, 1H, C*H*CH_2OCO), 4.23 (q, *J* = 7.2 Hz, 2H, OC$H_2$$CH_3$), 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 157.7, 143.6, 141.4, 128.0, 127.3, 125.3, 120.2, 68.9, 62.0, 52.5, 47.1, 14.3.

IR (ν_{max}, cm^{-1}) 3344 (m), 3060 (w), 2977 (w), 1748 (s), 1716 (s), 1450 (s), 1349 (m), 1208 (s).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NNaO_5^+$ 364.1155; Found 364.1158.

Ethyl *N*-((allyloxy)carbonyl)-*N*-((triisopropylsilyl)oxy)glycinate (SM2)



Imidazole (790 mg, 11.6 mmol, 3.00 equiv), chloro(triisopropyl)silane (1.07 g, 1.19 mL, 5.57 mmol, 2.00 equiv) and DMAP (47.3 mg, 387 µmol, 0.100 equiv) were added to **SM1aa** (332 mg, 2.79 mmol, 1.00 equiv) in dry DCM (23 mL, 0.1 M). The reaction was stirred overnight at 40 °C. The mixture was diluted with DCM (30 mL) and saturated aq. NH_4Cl solution (25 mL). The layers were separated and the aqueous layer was extracted twice with DCM (25 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtrated and the solvent was evaporated. The crude was engaged in the next step without purification.

The intermediate (250 mg, 908 µmol, 1.00 equiv) and $NaHCO_3$ (797 mg, 9.48 mmol, 10.4 equiv) in DCM (8.44 mL, 0.1 M) was treated with allyl chloride (457 mg, 403 µL, 3.79 mmol, 4.18 equiv) dropwise. The reaction mixture was stirred at rt overnight. Upon completion, the reaction was quenched with water. The organic layer was collected and the aq. layer extracted with additional DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography on silica: gradient from 0 to 5% EtOAc in pentane. The product was obtained **SM2** (220 mg, 612 µmol, 67% yield) as a transparent oil.

R_f = 0.4 (Pentane/ethyl acetate 95:5).

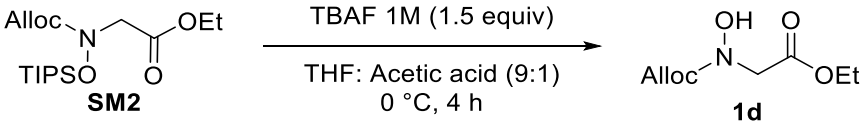
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, CH_2=C$_H$-CH_2), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2=C_H-CH_2), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H, CH_2=CH-CH_2), 4.67 (dt, *J* = 5.8, 1.4 Hz, 2H, CH_2=CH-CH_2), 4.27 – 4.17 (m, 2H, OC$H_2$$CH_3$), 4.21 (s, 2H, NC$H_2$CO), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.23 – 1.16 (m, 3H, SiC*H*), 1.13 – 1.03 (m, 18H, SiCH(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 159.7, 132.3, 118.6, 67.4, 61.4, 55.1, 18.0, 14.3, 12.3.

IR (ν_{max}, cm^{-1}) 2978 (m), 2952 (m), 2896 (m), 2876 (m), 1763 (s), 1716 (s), 1650 (m), 1409 (m), 1381 (m), 1329 (m), 1248 (m), 1189 (s).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{33}NNaO_5Si^+$ 382.2020; Found 382.2019.

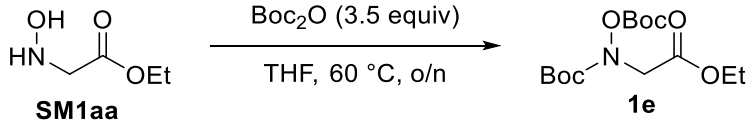
Ethyl *N*-((allyloxy)carbonyl)-*N*-hydroxyglycinate (1d)



To a solution of **SM2** (170 mg, 473 µmol, 1.00 equiv) in THF (3 mL, 0.5 M) was added acetic acid (340 µL). Then, at 0 °C**,** TBAF 1 M in THF (185 mg, 709 µL, 709 µmol, 1.00M, 1.50 equiv) was diluted in THF (0.5 mL) and added to the reaction mixture. The solution was stirred at 0 °C for 4 h, after which the starting material was no longer observed by TLC. Water was added to the flask and the reaction was extracted with Et_2O (2 mL). The organic layer was rinsed with brine, dried over Na_2SO_4, and concentrated in vacuo. The product was obtained by flash chromatography, gradient from 0 to 40% EtOAc in pentane to obtain **1d** (74.0 mg, 364 µmol, 77% yield) as a yellowish oil.

R_f = 0.25 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H, O*H*), 5.94 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1H, CH_2=C*H*-CH_2), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H, C*H*$_2$=CH-CH_2), 5.26 (dq, *J* = 10.5, 1.3 Hz, 1H, C*H*$_2$=CH-CH_2), 4.69 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2=CH-C*H*$_2$), 4.34 (s, 2H, NC*H*$_2$CO), 4.25 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$$CH_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 157.54, 132.0, 118.8, 67.5, 61.9, 52.4, 14.3.
IR (ν_{max}, cm^{-1}) 3348 (w), 2987 (w), 2934 (w), 2867 (w), 1752 (s), 1716 (s), 1650 (w), 1462 (m), 1451 (m), 1415 (m), 1379 (m), 1346 (m), 1210 (s), 1108 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{13}NNaO_5^+$ 226.0686; Found 226.0688.

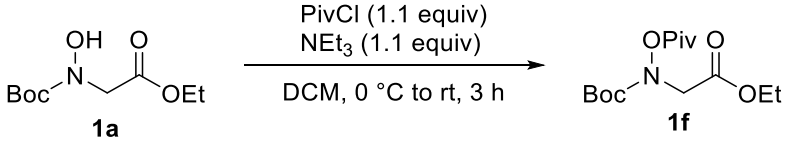
Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-((*tert*-butoxycarbonyl)oxy)glycinate (1e)



Following a reported procedure[3], to a solution of **SM1aa** (150 mg, 1.26 mmol, 1.00 equiv) in THF (2.30 mL, 0.5 M) was added Boc_2O (962 mg, 4.41 mmol, 3.50 equiv) under nitrogen atmosphere. The mixture was stirred at 60 °C overnight. The reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc /pentane 0:100- 20:80) to give **1e** (177 mg, 554 µmol, 44% yield) as a transparent oil.

R_f = 0.73 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 2H, NC*H*$_2$CO), 4.23 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$$CH_3$), 1.52 (s, 9H, C*H*$_{3Boc}$), 1.49 (s, 9H, C*H*$_{3Boc}$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 155.2, 152.1, 85.1, 83.4, 61.7, 52.3, 28.2, 27.8, 14.3.
IR (ν_{max}, cm^{-1}) 2985 (w), 2936 (w), 1788 (s), 1757 (m), 1728 (m), 1474 (w), 1461 (w), 1395 (m), 1372 (s), 1285 (m), 1233 (s), 1151 (s), 1099 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{25}NNaO_7^+$ 342.1523; Found 342.1538.

Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-(pivaloyloxy)glycinate (1f)

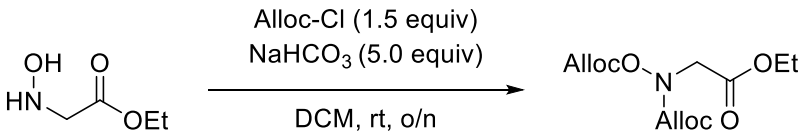


In a microwave vial, **1a** (72.8 mg, 332 µmol, 1.00 equiv) was diluted in dry DCM (1 mL, 0.3 M). Then at 0 °C, 2,2-dimethylpropanoyl chloride (44.0 mg, 45.0 µL, 365 µmol, 1.10 equiv) was added. The mixture was stirred for 5 min and triethylamine (37.0 mg, 50.9 µL, 365 µmol, 1.10 equiv) was added. The reaction mixture was stirred at 0 °C for 3 h. Upon completion, the crude was diluted in water. The crude was extracted with EtOAc (3 x 5 mL), the organic layers were washed with brine, dried over

$MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 10% EtOAc in pentane to give **1f** (78.0 mg, 257 µmol, 77% yield) as a transparent oil.

R_f = 0.24 (Pentane/ethyl acetate 90:10).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H, NHC*H_2*COO) 4.23 (q, *J* = 7.1 Hz, 2H, OC*H_2*CH_3), 1.48 (s, 9H, C*H_{3Boc}*), 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2C*H_3*), 1.26 (s, 9H, COO(C*H_3*)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 168.0, 155.0, 83.2, 61.6, 52.3, 38.3, 28.2, 27.1, 14.3.
IR (ν_{max}, cm^{-1}) 2981 (m), 2939 (w), 1779 (s), 1759 (s), 1724 (s), 1480 (m), 1462 (m), 1397 (m), 1372 (s), 1255 (m), 1208 (s), 1165 (s), 1087 (s), 1029 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{25}NNaO_6^+$ 326.1574; Found 326.1577.

Ethyl *N*-((allyloxy)carbonyl)-*N*-(((allyloxy)carbonyl)oxy)glycinate (1g)

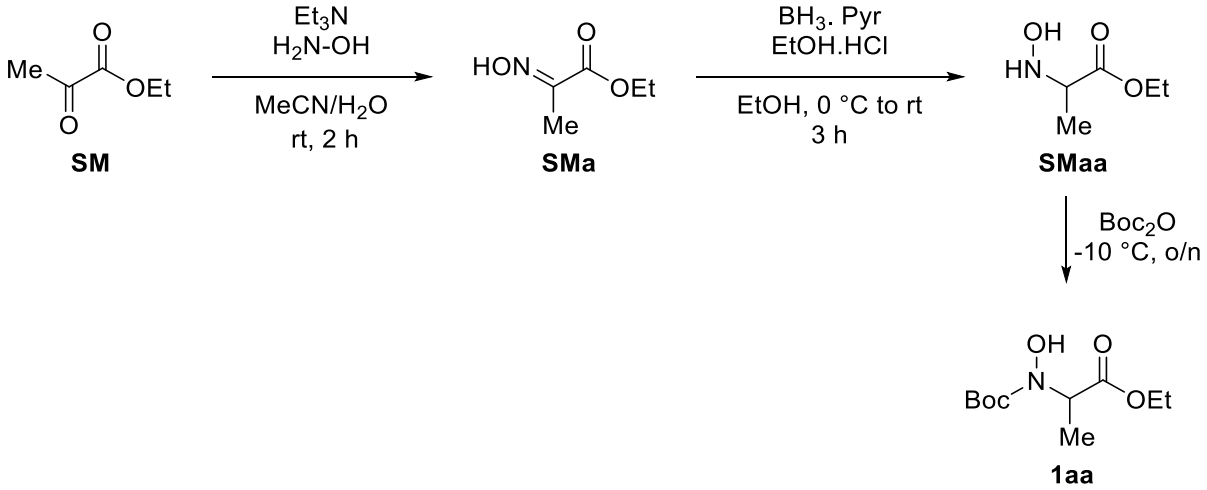


SM1aa **1g**

SM1aa (100 mg, 839 µmol, 1.00 equiv) and $NaHCO_3$ (353 mg, 4.20 mmol, 5.00 equiv) in DCM (1.50 mL, 0.8 M) was treated with allyl chloroformate (152 mg, 134 µL, 1.26 mmol, 1.50 equiv) dropwise. After 30 min, an addition 1 equiv of NaHCO3 was added to the reaction mixture. After 1h, the reaction was quenched with water. The organic layer was collected and the aqueous layer was extracted with additional DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by flash chromatography, silica gel, gradient 0 to 20% EtOAc in pentane to give **1g** (65.0 mg, 226 µmol, 27% yield) as transparent oil.

R_f = 0.44 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.84 (m, 2H, CH_2=C*H*-CH_2 x2), 5.44 – 5.32 (m, 2H, C*H_2*=CH-CH_2 x2), 5.33 – 5.23 (m, 2H, C*H_2*=CH-CH_2 x2), 4.73 (dt, *J* = 5.8, 1.3 Hz, 2H, CH_2=CH-C*H_2*), 4.71 (dt, *J* = 5.6, 1.5 Hz, 2H, CH_2=CH-C*H_2*), 4.37 (s, 2H, NC*H_2*CO), 4.23 (q, *J* = 7.1 Hz, 2H, OC*H_2*CH_3), 1.28 (t, *J* = 7.2 Hz, 3H, OCH_2C*H_3*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 156.0, 153.9, 131.5, 130.6, 120.1, 118.8, 70.3, 67.9, 61.9, 52.5, 14.3.
IR (ν_{max}, cm^{-1}) 3089 (w), 2996 (w), 2958 (w), 1793 (m), 1753 (m), 1734 (m), 1650 (w), 1412 (m), 1278 (m), 1201 (s), 1101 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{17}NNaO_7^+$310.0897 ; Found 310.0901.

Ethyl *N*-(tert-butoxycarbonyl)-*N*-hydroxyalaninate-(1aa)



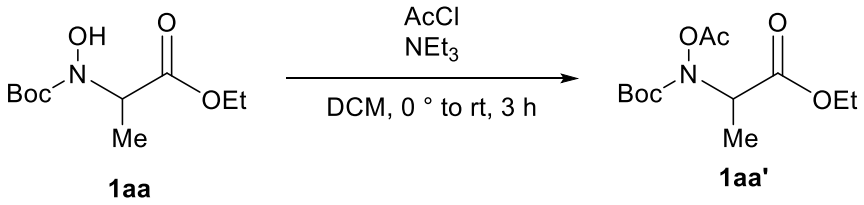
Following a reported procedure,[1] hydroxylamine hydrochloride (2.39 g, 34.4 mmol, 2.00 equiv) was added to a mixture of solvent MeCN: H_2O (8:1): acetonitrile (16 mL), water (2.0 mL). To this solution was added ethyl 2-oxopropanoate **SM** (2.00 g, 1.91 mL, 17.2 mmol, 1.00 equiv)**,** under nitrogen atmosphere. After brief stirring for 5 min at ambient temperature, triethylamine (1.74 g, 2.40 mL, 17.2 mmol, 1.00 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 h until TLC indicated complete consumption of ethyl glyoxylate. Then, the mixture was concentrated to dryness to obtain a gel. The crude was dissolved in ether (150 mL). The aqueous layer was extracted with ether (3 x 150 mL). The organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to obtain a white solid, **SMa** (2.15 g)**.** The crude **SMa** was engaged in the next step without purification.

Following a reported procedure,[2] to a well-stirred solution of **SMa** (1.25 g, 9.49 mmol, 1.00 equiv) in absolute ethanol (32.00 mL) cooled to 0 °C, was added slowly borane pyridine complex (3.04 g, 4.09 mL, 32.7 mmol, 8.00M, 2.00 equiv)**.** Then, 7 N HCl in EtOH (13.5 g, 23.4 mL, 164 mmol, 7.00M, 10.0 equiv), was added dropwise and the resulting mixture was stirred at ambient temperature for 3 h. Then, the solvent was evaporated under reduced pressure without exceeding 40 °C and the residue is dissolved in dichloromethane (100 mL). Solid sodium carbonate was added until gas evolution stopped and left to stir overnight. The salts were filtered off and the filtrate was evaporated to obtain **SMaa** (1.95 g) as a brownish oil. The crude **SMaa** was engaged in the next step without purification.

Following a reported procedure,[3] to a solution of **SMaa** (1.95 g, 14.6 mmol, 1.00 equiv) in THF (30.00 mL) was added Boc_2O (3.35 g, 15.3 mmol, 1.05 equiv) under nitrogen atmosphere. The mixture was stirred at -10 °C overnight with the cryostat. The reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc/pentane 0:100- 25:75) to give **1aa** (1.39 g, 5.95 mmol, 41% yield) as a yellow oil.

R_f=0.35 (Pentane:EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H, O*H*), 4.71 (q, *J* = 7.3 Hz, 1H, C*H*Me), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.52 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 1.50 (s, 9H, CH_{3Boc}), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 157.4, 82.6, 61.7, 57.9, 28.3, 14.5, 14.3.
IR (ν_{max}, cm^{-1}) 3342 (m), 2982 (m), 2941 (w), 1743 (s), 1712 (s), 1480 (m), 1452 (m), 1393 (s), 1372 (s), 1314 (s), 1255 (m), 1216 (s), 1171 (s), 1131 (s), 1070 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{19}NNaO_5^+$ 256.1155; Found 256.1164

Ethyl *N*-acetoxy-*N*-(tert-butoxycarbonyl)alaninate- (1aa')



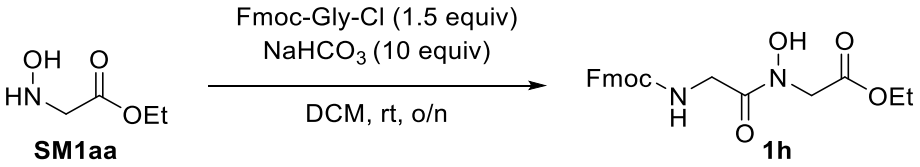
1aa **1aa'**

In a microwave vial, **1aa** (400 mg, 1.71 mmol, 1.00 equiv) was dissolved in dry DCM (6 mL, 0.3 M). Then at 0 °C, acetyl chloride (296 mg, 269 µL, 3.77 mmol, 2.20 equiv) was added. The mixture was stirred for 5 min, triethylamine (312 mg, 430 µL, 3.09 mmol, 1.80 equiv) was added. The mixture was stirred at 0 °C for 2 h. The crude was diluted in water. The crude was extracted with DCM (3 x 10 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 15% EtOAc in pentane to give **1aa'** (470 mg, 1.71 mmol, 98% yield) as a transparent oil.

R_f=0.3 (Pentane:EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (q, *J* = 7.3 Hz, 1H, C*H*Me), 4.21 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 2.15 (s, 3H, C(O)C*H*$_3$), 1.48 (s, 9H, C*H*$_{3Boc}$), 1.43 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.6, 155.1, 83.3, 61.7, 57.81, 28.2, 18.4, 14.3, 14.1.
IR (ν_{max}, cm^{-1}) 2984 (m), 2944 (w), 1800 (s), 1747 (s), 1722 (s), 1456 (w), 1372 (s), 1308 (m), 1257 (m), 1188 (s), 1169 (s), 1127 (s), 1064 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{21}NNaO_6^+$ 298.1261; Found 298.1251.

2.2 Preparation of peptide hydroxylamine

Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-hydroxyglycinate (1h)



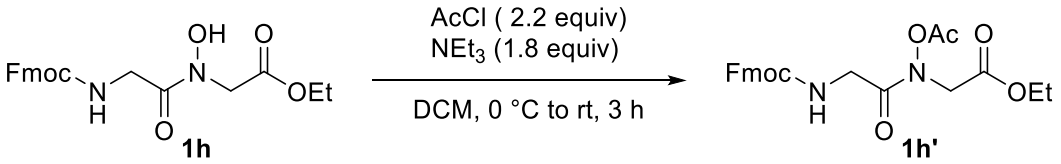
SM1aa **1h**

Following a reported procedure,[4] to a microwave vial, **SM1aa** (100 mg, 839 µmol, 1.00 equiv), Fmoc-Gly-Cl (398 mg, 1.26 mmol, 1.50 equiv) and sodium bicarbonate (705 mg, 8.39 mmol, 10.0 equiv) were diluted in dry dichloromethane (3.00 mL, 0.8 M) The reaction mixture was stirred at room temperature overnight. The residue was diluted with EtOAc (3 x 5 mL) and washed with 1M aq HCl (5 mL), sat. aq $NaHCO_3$ (5 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography, gradient from 20% to 100% EtOAc in pentane to give **1h** (176 mg, 442 µmol, 53% yield) as a white amorphous solid.

R_f = 0.10 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 7.5, 0.9 Hz, 2H, Ar*H*), 7.61 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.47 (s, 1H, OH), 7.40 (tt, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.31 (td, *J* = 7.4, 1.2 Hz, 2H, Ar*H*), 5.58 (s, 1H, N*H*), 4.49 (s, 2H, NOC*H*$_2$COO), 4.39 (d, *J* = 7.2 Hz, 2H, CHC*H*$_{2,Fmoc}$OCON), 4.29 (d, *J* = 5.1 Hz, 2H, NHC*H*$_2$CON), 4.28 – 4.20 (m, 3H, OC*H*$_2$CH$_3$ and C$_{Fmoc}$*H*CH$_2$OCON), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.6, 156.8, 143.9, 141.4, 127.9, 127.2, 125.3, 120.1, 67.5, 62.3, 49.6, 47.2, 42.4, 14.2.

IR (ν_{max}, cm^{-1}) 3396 (m), 3262 (m), 2985 (w), 2939 (w), 1731 (s), 1709 (s), 1676 (s), 1525 (m), 1465 (m), 1450 (s), 1400 (m), 1376 (m), 1273 (m), 1217 (s), 1161 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_6^+$ 421.1370; Found 421.1377.

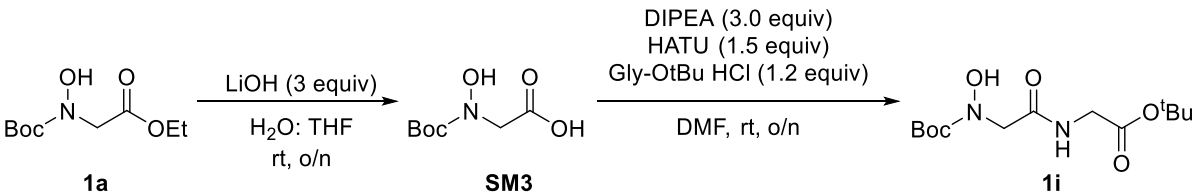
Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-acetoxyglycinate (1h')



In a microwave vial, **1h** (300 mg, 753 µmol, 1.00 equiv) was dissoled in dry DCM (2.5 mL, 0.3 M). Then at 0 °C, acetyl chloride (130 mg, 118 µL, 1.66 mmol, 2.20 equiv) was added. The reaction mixture was stirred for 5 min and triethylamine (137 mg, 189 µL, 1.36 mmol, 1.80 equiv) was added. The mixture was stirred at rt for 3 h. The crude was extracted with DCM (3 x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 20 to 60% AcOEt in pentane to give **1h'** (200 mg, 454 µmol, 60% yield) as a white amorphous solid.

$\mathbf{R_f}$ = 0.41 (Pentane/ethyl acetate 50:50).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.60 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.40 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 5.52 (s, 1H, N*H*), 4.46 (s, 2H, NCH_2COO), 4.39 (d, *J* = 7.2 Hz, 2H, CH_2OCO), 4.28 – 4.20 (m, 3H, NHCH_2COO and C*H*CH$_2$OCO), 4.12 (d, *J* = 4.7 Hz, 2H, NHCH_2CON), 2.24 (s, 3H, OCOCH_3), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.5, 1.0 Hz, 2H, Ar*H*), 7.60 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.40 (ddd, *J* = 7.8, 6.7, 1.0 Hz, 2H, Ar*H*), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 5.53 (s, 1H, N*H*), 4.46 (s, 2H, NOCH_2COO), 4.39 (d, *J* = 7.2 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.28 – 4.19 (m, 3H, OCH_2CH$_3$ and C$_{Fmoc}$*H*CH$_2$OCON), 4.12 (d, *J* = 4.7 Hz, 2H, NHCH_2CON), 2.24 (s, 3H, OC$H_{3,acetal}$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.75, 167.9, 166.9, 156.2, 144.0, 141.4, 127.9, 127.2, 125.3, 120.1, 67.4, 62.2, 50.5, 47.2, 42.3, 18.6, 14.3.
IR (ν_{max}, cm^{-1}) 3394 (m), 3359 (m), 3307 (s), 2950 (m), 2939 (m), 1737 (s), 1727 (s), 1713 (s), 1674 (s), 1528 (s), 1451 (s), 1269 (s), 1237 (s), 1212 (s), 1031 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{24}N_2NaO_7^+$ 463.1476; Found 463.1485.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-hydroxyglycylglycinate (1i)**

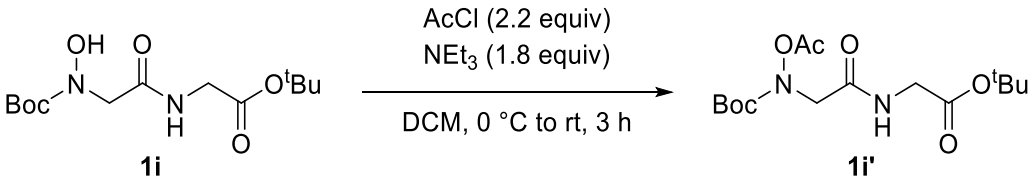


To a microwave vial, **1a** (100 mg, 456 µmol, 1.00 equiv) was diluted in a mixture ratio 2:1 (THF 4.7 mL /H_2O 2.3 mL). The vial was put under nitrogen atmosphere. Then**,** lithium hydroxide (32.8 mg, 1.37 mmol, 3.00 equiv) was added. The reaction turned yellow and was stirred at rt overnight. The mixture was evaporated in vacuo. Then, the reaction mixture was acidified to pH=1 with a solution of 10% $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to obtain a white off **SM3** (150 mg). The crude **SM3** was engaged in the next step without purification.

In a microwave flask, **SM3** (200 mg, 1.05 mmol, 1.00 equiv) and HATU (150 mg, 392 µmol, 1.50 equiv) were dissolved in dry N,N-dimethylformamide (2 mL, 0.5 M) at 0 °C. Then after 5 min of stirring, tert-butyl 2-aminoacetate hydrochloride (210 mg, 1.26 mmol, 1.20 equiv) and DIPEA (406 mg, 547 µL, 3.14 mmol, 3.00 equiv) were added at 0 °C. The mixture was allowed to warm to rt and was stirred for 18 h at rt. The reaction was diluted with EtOAc (20 mL) and washed with 1 M aq HCl (20 mL), sat. aq $NaHCO_3$ (20 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4. The crude was purified by column chromatography (SiO_2, gradient from 0 to 50% EtOAc in pentane) to give **1i** (131 mg, 430 µmol, 41% yield) as an amorphous white solid.

R_f = 0.36 (Pentane/ethyl acetate 50:50).
Mp: 58.8-60.9 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H, O*H*), 6.48 (s, 1H, N*H*), 4.21 (s, 2H, OHNCH_2), 3.98 (d, *J* = 5.1 Hz, 2H, NHCH_2COO*t*Bu), 1.51 (s, 9H, C(CH_3)$_3$), 1.48 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 169.0, 157.5, 83.3, 82.8, 54.5, 42.0, 28.3, 28.2.
IR (ν_{max}, cm^{-1}): 3334 (w), 2981 (m), 2935 (w), 1739 (m), 1687 (m), 1673 (m), 1545 (m), 1394 (m), 1368 (s), 1243 (s), 1158 (s), 1110 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{18}N_2NaO_6^+$ 285.1057; Found 285.1060.

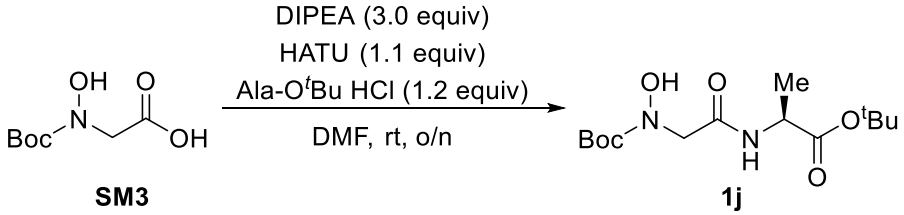
***tert*-Butyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycylglycinate (1i')**



In a microwave vial, **1i** (755 mg, 2.48 mmol, 1.00 equiv) was dissolved in dry DCM (8 mL, 0.3 M). Then at 0 °C, acetyl chloride (428 mg, 389 µL, 5.46 mmol, 2.20 equiv) was added. The reaction mixture was stirred for 5 min and triethylamine (452 mg, 622 µL, 4.47 mmol, 1.80 equiv) was added. The mixture was stirred at rt for 3 h. The crude was diluted in water, was extracted with DCM (3 x 10 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 50% EtOAc in pentane to give **1i'** (440 mg, 1.27 mmol, 51% yield) as a white solid.

R_f = 0.39 (DCM/ethyl acetate 85:15).
Mp: 89.6-90.8 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H, N*H*), 4.27 (s, 2H, OHNCH_2), 3.94 (d, *J* = 5.5 Hz, 2H, NHCH_2COOtBu), 2.17 (s, 3H, COCH_3), 1.49 (s, 9H, C(CH_3)$_3$), 1.47 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.4, 167.9, 154.3, 84.2, 82.2, 54.4, 42.0, 28.2, 28.1, 18.4.
IR (ν_{max}, cm^{-1}) 2981 (w), 2939 (w), 1793 (m), 1747 (s), 1736 (m), 1691 (m), 1543 (w), 1372 (m), 1244 (m), 1159 (s), 1092 (w).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{26}N_2NaO_7^+$ 369.1632; Found 369.1643.

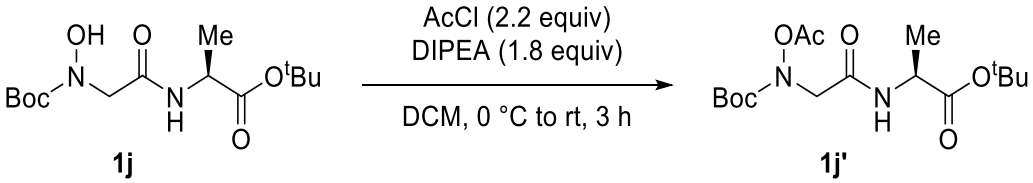
***tert*-Butyl *N*-(tert-butoxycarbonyl)-*N*-hydroxyglycyl-*L*-alaninate (1j)**



In a microwave flask, **SM3** (409 mg, 2.14 mmol, 1.00 equiv) and HATU (900 mg, 2.35 mmol, 1.10 equiv) were dissolved in dry DMF (4 mL, 0.5 M) at 0 °C. Then after 5 min of stirring, tert-butyl 2-aminopropanoate hydrochloride (466 mg, 2.57 mmol, 1.20 equiv) and DIPEA (829 mg, 1.12 mL, 6.42 mmol, 3.00 equiv) were added at 0 °C. The mixture was allowed to warm to rt and was stirred overnight. The reaction was diluted with EtOAc (40 mL) and washed with 1 M aq HCl (40 mL), sat. aq $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude was purified by column chromatography (SiO_2, gradient from 0 to 60% EtOAc in pentane) to give **1j** (297 mg, 934 µmol, 44% yield) as an amorphous white solid.

R_f = 0.42 (Pentane/ethyl acetate 50:50).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, *J* = 1.7 Hz, 1H, O*H*), 6.55 (d, *J* = 7.5 Hz, 1H, N*H*), 4.50 (td, *J* = 7.2, 2.0 Hz, 1H, C(=O)NHC*H*MeCO$_2$^{t}Bu), 4.29 – 4.05 (m, 2H, OHNCH_2), 1.50 (d, *J* = 2.1 Hz, 9H, C(CH_3)$_3$), 1.47 (d, *J* = 2.1 Hz, 9H, C(CH_3)$_3$), 1.40 (dd, *J* = 7.1, 2.1 Hz, 3H, C(=O)NHCHC$H_{3,Met}$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 168.0, 157.4, 83.3, 82.6, 54.2, 48.8, 28.3, 28.1, 18.8.
IR (ν_{max}, cm^{-1}) 3334 (w), 2981 (m), 2934 (w), 1735 (s), 1712 (s), 1533 (m), 1370 (s), 1247 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{26}N_2NaO_6^+$ 341.1683; Found 341.1693.

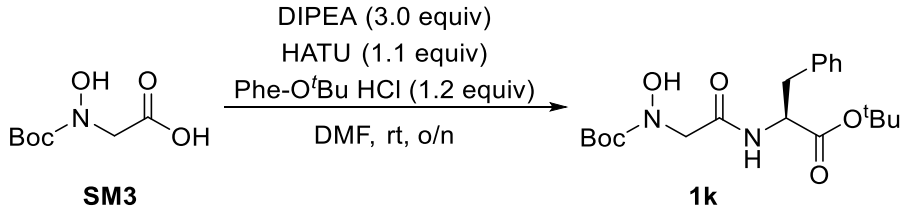
***tert*-Butyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycyl-*L*-alaninate (1j')**



1j (281 mg, 882 µmol, 1.00 equiv) was dissoled in dry DCM (3.8 mL, 0.2 M). Then at 0 °C, acetyl chloride (159 mg, 145 µL, 2.03 mmol, 2.30 equiv) was added. The mixture was stirred for 5 min and DIPEA (215 mg, 289 µL, 1.66 mmol, 1.88 equiv) was added. The rm was stirred at rt for 2 h. The crude was diluted in water, was extracted with DCM (3 x 10 mL), the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by chromatography on silica gel, gradient from 0 to 50% EtOAc in pentane to give **1j'** (440 mg, 1.27 mmol, 51% yield) as a yellowish oil.

R_f = 0.45 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 1H, N*H*), 4.45 (p, *J* = 7.3 Hz, 1H, C(=O)NHC*H*MeCO$_2$^{t}Bu), 4.31 – 4.15 (m, 2H, OAcNCH_2), 2.17 (s, 3H, COCH_3), 1.49 (s, 9H, C(CH_3)$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 1.37 (d, *J* = 7.2 Hz, 3H, C(=O)NHCHC$H_{3,Met}$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 169.4, 167.2, 154.3, 84.2, 81.9, 54.6, 48.8, 28.1, 28.1, 18.4, 18.3.
IR (ν_{max}, cm^{-1}) 3367 (w), 2981 (w), 2938 (w), 1793 (m), 1737 (s), 1688 (m), 1538 (m), 1370 (s), 1155 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{28}N_2NaO_7^+$ 383.1789; Found 383.1789.

***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-hydroxyglycyl-*L*-phenylalaninate (1k)**

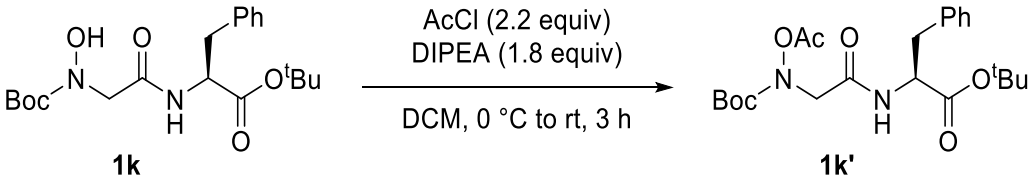


In a microwave flask, **SM3** (300 mg, 1.57 mmol, 1.00 equiv) and HATU (660 mg, 1.73 mmol, 1.10 equiv) were dissolved in dry DMF (3 mL, 0.5 M) at 0 °C. Then after 5 min of stirring, tert-butyl 2-amino-3-

phenylpropanoate hydrochloride (485 mg, 1.88 mmol, 1.20 equiv) and DIPEA (608 mg, 820 µL, 4.71 mmol, 3.00 equiv) were added at 0 °C. The mixture was allowed to warm to rt, and was stirred overnight. The mixture was allowed to warm to rt and was stirred overnight. The reaction was diluted with EtOAc (30 mL) and washed with 1 M aq HCl (30 mL), sat. aq NaHCO3 (30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude was purified by column chromatography (SiO_2, gradient from 0 to 40% EtOAc in pentane) to give **1k** (261 mg, 662 µmol, 42% yield) as an amorphous white solid.

R_f = 0.35 (Pentane/ethyl acetate 50:50).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 3H, Ar*H*), 7.20 – 7.10 (m, 2H, Ar*H*), 6.56 (s, 1H, O*H*), 6.45 (d, *J* = 8.0 Hz, 1H, N*H*), 4.78 (dt, *J* = 7.8, 5.9 Hz, 1H, C(=O)NHC*H*$CO_2{}^t$Bu), 4.16 (q, *J* = 17.1 Hz, 2H, OHNCH_2), 3.22 – 2.99 (m, 2H, CH_2Ph), 1.49 (s, 9H, C(CH_3)$_3$), 1.41 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.1, 157.3, 136.0, 129.7, 128.6, 127.2, 83.2, 82.9, 54.2, 53.6, 38.1, 28.3, 28.1.
IR (ν_{max}, cm^{-1}) 3320 (w), 2979 (m), 2934 (w), 1732 (s), 1708 (s), 1673 (m), 1530 (m), 1369 (s), 1249 (m), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{30}N_2NaO_6^+$ 417.1996; Found 417.1990.

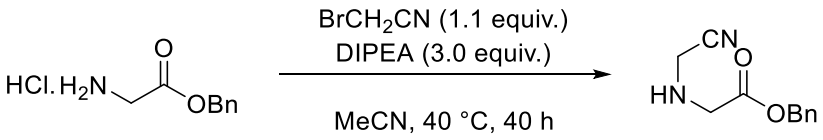
***tert*-Butyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycyl-*L*-phenylalaninate (1k')**



1k (200 mg, 507 µmol, 1.00 equiv) was dissolved in dry DCM (2.2 mL, 0.2 M). Then at 0 °C, acetyl chloride (87.6 mg, 79.6 µL, 1.12 mmol, 2.20 equiv) was added. The rm was stirred for 5 min and, DIPEA (118 mg, 159 µL, 913 µmol, 1.80 equiv) was added. The rm was stirred at rt for 2 h. The crude was diluted in water. The crude was extracted with DCM (3x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, gradient from 0 to 40% EtOAc in pentane) to give **1k'** (94.0 mg, 215 µmol, 42% yield) as a colourless oil.

R_f = 0.31 (Pentane/ethyl acetate 65:35).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 1H, N*H*), 7.30 – 7.15 (m, 5H, Ar*H*), 4.72 (q, *J* = 7.1 Hz, 2H, C(=O)NHC*H*$CO_2{}^t$Bu), 4.19 (s, 2H, OHNCH_2), 3.17 – 2.97 (m, 2H, CH_2Ph), 2.10 (s, 3H, COCH_3), 1.46 (s, 9H, C(CH_3)$_3$), 1.38 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.1, 167.3, 154.2, 136.5, 129.5, 128.5, 127.0, 84.1, 82.2, 54.5, 54.0, 38.1, 28.1, 28.0, 18.4.
IR (ν_{max}, cm^{-1}) 3374 (w), 2981 (w), 2934 (w), 1793 (m), 1735 (s), 1687 (m), 1530 (w), 1370 (s), 1253 (m), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{32}N_2NaO_7^+$ 459.2102; Found 459.2112.

Benzyl (cyanomethyl)glycinate (SM4a)

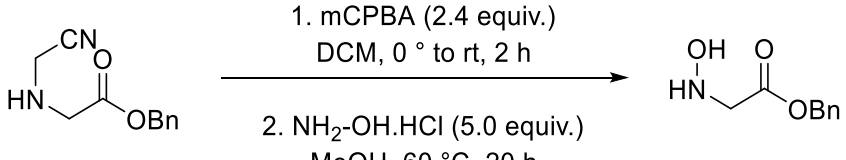


SM4 **SM4a**

SM4 (5.00 g, 24.8 mmol, 1.00 equiv) and DIPEA (9.61 g, 13.0 mL, 74.4 mmol, 3.00 equiv) were diluted in MeCN (50 mL, 0.5 M)**.** The flask was put under nitrogen atmosphere. Then, 2-bromoacetonitrile (3.27 g, 1.90 mL, 27.3 mmol, 1.10 equiv) was added over 10 min. The reaction was stirred at 40 °C for 40h. The reaction mixture was evaporated in vacuo. Then, the crude was dissolved in DCM, washed with $NaHCO_3$ sat. (30 mL), brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 60 %) to give **SM4a** (4.38 g, 21.4 mmol, 86% yield) as yellow oil.

R_f = 0.21 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.28 (m, 5H, Ar*H*), 5.19 (s, 2H, ArC*H*$_2$), 3.67 (s, 2H, NHC*H*$_2$CO$_2$Bn), 3.57 (s, 2H, NHC*H*$_2$CN).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 135.3, 128.8, 128.7, 128.6, 117.3, 67.2, 49.4, 36.9.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{12}N_2NaO_2^+$ 227.0791; Found 227.0791.
Consistent with reported data. [5]

Benzyl hydroxyglycinate (SM4aa)



SM4a **SM4aa**

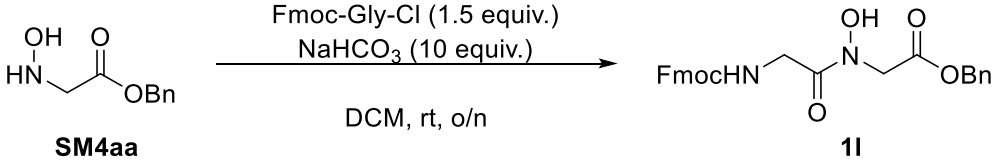
1st step: **SM4a** (2.54 g, 12.4 mmol, 1.00 equiv) was dissolved in dry dichloromethane (50 mL) and cooled to 0 °C. To the cooled mixture, mCPBA 70% (7.35 g, 29.8 mmol, 2.40 equiv) was added in 2 portions over 30 min. The solution was allowed to warm to rt and stirred for 1.5h. The reaction flask was then cooled to 0 °C prior to the addition of sat. aq. $NaHCO_3$ (50 mL) and sat. aq. $Na_2S_2O_3$ (50mL) and the resulting slurry stirred for an additional 30 min until two layers were observed. The organic layer was collected, and the aq phase was extracted with additional DCM (3x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Concentration on a rotary evaporator provided the crude nitrone intermediate as a white solid.

2nd step: The crude was dissoled in methanol (40 mL). Then, hydroxylamine hydrochloride (4.31 g, 62.1 mmol, 5.00 equiv) was added and stirred 18 h at 60 °C. The solution was concentrated to remove MeOH. The residue was dissolved in DCM and washed with sat. aq. $NaHCO_3$. The organic layer was collected, and the aq phase was extracted with additional DCM (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography (SiO_2, gradient from 0 to 70% EtOAc in pentane) to give a white solid, **SM4aa** (676 mg, 3.73 mmol, 30% yield).

R_f = 0.33 (Pentane/ethyl acetate 40:60).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H, Ar*H*), 5.22 (s, 2H, ArC*H*$_2$), 3.73 (s, 2H, NHC*H*$_2$CO$_2$Bn).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 135.5, 128.8, 128.7, 128.3, 67.1, 55.2.
IR (ν_{max}, cm^{-1}) 3429 (w), 3286 (m), 2924 (w), 1743 (s), 1456 (w), 1206 (s), 1199 (s).
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{12}NO_3^+$ 182.0812; Found 182.0808.

Consistent with reported data.[6]

Benzyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-hydroxyglycinate (1l)

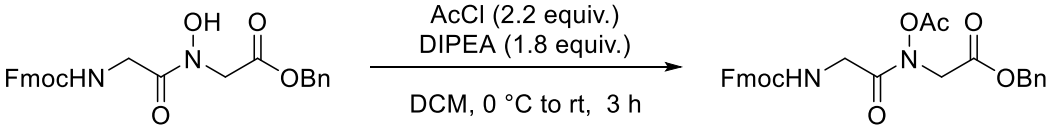


SM4aa **1l**

A rbf was charged with **SM4aa** (500 mg, 2.76 mmol, 1.00 equiv), Fmoc-Gly-Cl (1.31 g, 4.14 mmol, 1.50 equiv) and sodium bicarbonate (2.32 g, 27.6 mmol, 10.0 equiv) dissolved in dry dichloromethane (10.0 mL, 0.3 M) The reaction mixture was stirred at rt overnight under nitrogen atmosphere. The residue was diluted with EtOAc and washed with 1M aq HCl (15 mL), sat. aq $NaHCO_3$ (15 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 60 %) to give **1l** as a white amorphous solid (1.12 g, 2.44 mmol, 88% yield).

R_f = 0.19 (Pentane/ethyl acetate 50:50).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, H, O*H*), 7.76 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.60 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.46 – 7.27 (m, 9H, Ar*H*), 5.62 (t, *J* = 5.3 Hz, 1H, N*H*), 5.18 (s, 2H, CH_2Ph), 4.52 (s, 2H, NCH_2CO_2Bn), 4.38 (d, *J* = 7.2 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.28 (d, *J* = 5.2 Hz, 1H, $C_{Fmoc}H$CH$_2$OCON), 4.23 (t, *J* = 7.3 Hz, 1H, NHCH_2CON).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.7, 156.8, 143.8, 141.3, 134.7, 128.8, 128.5, 127.7, 127.1, 125.2, 120.0, 67.7, 67.4, 49.7, 47.1, 42.2. (1C unresolved)
IR (ν_{max}, cm^{-1}) 3372 (w), 3069 (w), 3040 (w), 2947 (w), 1753 (m), 1705 (s), 1673 (s), 1524 (m), 1450 (m), 1242 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}N_2NaO_6^+$ 483.1527; Found 483.1531.

Benzyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-acetoxyglycinate (1l')



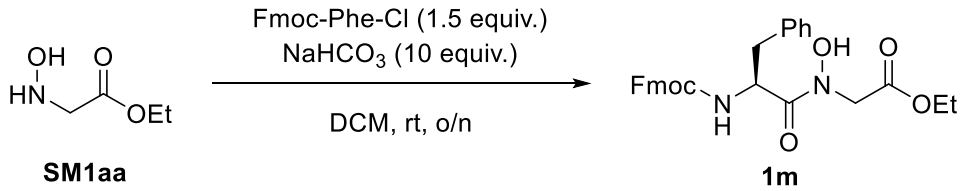
1l **1l'**

In a microwave vial, **1l** (350 mg, 760 µmol, 1.00 equiv) was dissoled in dry DCM (2.4 mL, 0.3 M). Then at 0 °C, acetyl chloride (131 mg, 119 µL, 1.67 mmol, 2.20 equiv) was added. The rm was stirred for 5 min and, DIPEA (177 mg, 238 µL, 1.37 mmol, 1.80 equiv) was added. The rm was stirred at rt for 3 h. The crude was diluted in water. The crude was extracted with AcOEt (3x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 40 %) to give **1l'** as a white amorphous solid (309 mg, 615 µmol, 81% yield).

R_f = 0.38 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.5, 1.0 Hz, 2H, Ar*H*), 7.61 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.44 – 7.28 (m, 9H, Ar*H*), 5.51 (s, 1H, N*H*), 5.20 (s, 2H, CH_2Ph), 4.51 (s, 2H, NCH_2CO_2Bn), 4.39 (d, *J* = 7.2 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.25 (d, *J* = 7.2 Hz, 1H, $C_{Fmoc}H$CH$_2$OCON), 4.11 (d, *J* = 4.6 Hz, 2H, NHCH_2CON), 2.21 (s, 3H, OC$H_{3,acetal}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 167.9, 166.7, 156.2, 144.0, 141.4, 135.0, 128.8, 128.6, 127.9, 127.2, 125.3, 120.1, 67.8, 67.4, 50.5, 47.2, 42.3, 18.5. (1C unresolved)
IR (ν_{max}, cm^{-1}) 3047 (w), 2951 (w), 2925 (m), 2853 (w), 1800 (m), 1751 (s), 1727 (s), 1704 (s), 1530 (m), 1520 (m), 1451 (m), 1243 (s), 1173 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{26}N_2NaO_7^+$ 525.1632; Found 525.1642.

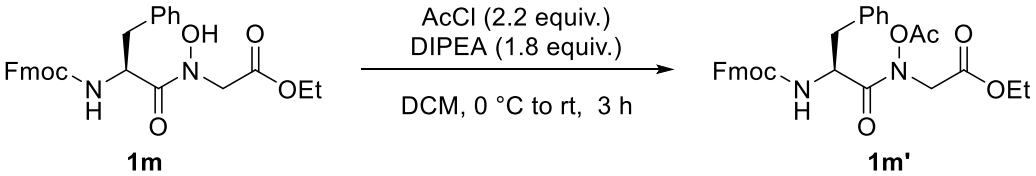
Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalanyl)-*N*-hydroxyglycinate (**1m**)



In a microwave vial, **SM1aa** (200 mg, 1.68 mmol, 1.00 equiv), Fmoc-Phe-Cl (1.02 g, 2.52 mmol, 1.50 equiv) and sodium bicarbonate (1.41 g, 16.8 mmol, 10.0 equiv) were diluted in dry dichloromethane (6.00 mL, 0.3 M) The reaction mixture was stirred at room temperature overnight. The residue was diluted with EtOAc (3 x 10 mL) and washed with 1 M aq HCl (10 mL), sat. aq $NaHCO_3$ (10 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 50 %) to give **1m** (591 mg, 1.21 mmol, 72% yield) as a white amorphous solid.

R_f = 0.41 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H, O*H*), 7.75 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.51 (dd, *J* = 7.5, 4.6 Hz, 2H, Ar*H*), 7.39 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.34 – 7.19 (m, 7H, Ar*H*), 5.55 (d, *J* = 8.5 Hz, 1H, N*H*), 5.24 (q, *J* = 7.3 Hz, 1H, NHC*H*), 4.42 (dd, *J* = 22.7, 17.7 Hz, 2H, N(OH)CH_2), 4.39 – 4.25 (m, 2H, CHC$H_{2,Fmoc}$OCON), 4.25 – 4.14 (m, 3H, OCH_2CH$_3$, $C_{Fmoc}H$CH$_2$OCON), 3.20 (dd, *J* = 13.8, 6.2 Hz, 1H, CH_2Ph), 3.01 (dd, *J* = 13.9, 7.4 Hz, 1H, CH_2Ph), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 168.6, 156. 6, 143.9 (rot 1), 143.8 (rot 2), 141.4, 136.3, 129.5, 128.7, 127.9, 127.2, 127.2, 125.3 (rot 1), 125.2 (rot 2), 120.1, 67.5, 62.0, 51.6, 49.6, 47.1, 37.9, 14.2.
IR (ν_{max}, cm^{-1}) 3340 (m), 2924 (m), 2857 (m), 1744 (m), 1722 (s), 1711 (s), 1655 (m), 1534 (m), 1498 (m), 1450 (m), 1394 (m), 1254 (m), 1207 (s), 1030 (m), 911 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{28}N_2NaO_6^+$ 511.1840; Found 511.1849.

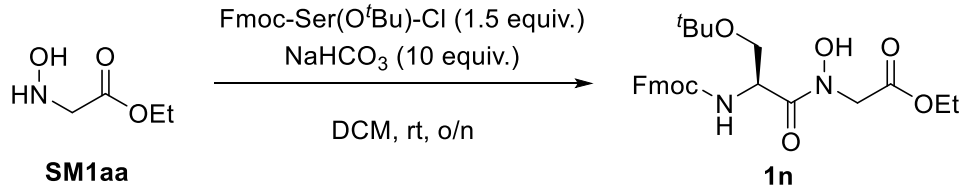
Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalanyl)-*N*-acetoxyglycinate **(1m')**



In a microwave vial, **1m** (300 mg, 614 µmol, 1.00 equiv) was dissolved in dry DCM (2.0 mL, 0.3 M). Then at 0 °C, acetyl chloride (106 mg, 96.4 µL, 1.35 mmol, 2.20 equiv) was added. The rm was stirred for 5 min and, DIPEA (143 mg, 193 µL, 1.11 mmol, 1.80 equiv) was added. The rm was stirred at rt for 3 h. The crude was diluted in water. The crude was extracted with AcOEt (3x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 40 %) to give **1m'** (241 mg, 407 µmol, 66% yield) as a white amorphous solid.

R_f = 0.17 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.50 (dd, *J* = 9.5, 7.5 Hz, 2H, Ar*H*), 7.39 – 7.33 (m, 2H, Ar*H*), 7.28 – 7.16 (m, 7H, Ar*H*), 5.45 (d, *J* = 9.0 Hz, 1H, N*H*), 4.91 – 4.80 (m, 1H, NHC*H*), 4.62 (d, *J* = 18.1 Hz, 1H, NOCH_2C), 4.32 (dd, *J* = 10.6, 7.4 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.27 – 4.15 (m, 3H, NOCH_2C, OCH_2CH$_3$), 4.12 (t, *J* = 7.2 Hz, 1H, C_{Fmoc}*H*CH$_2$OCON), 3.19 (dd, *J* = 14.1, 5.6 Hz, 1H, CH_2Ph), 2.89 (dd, *J* = 14.2, 7.0 Hz, 1H, CH_2Ph), 2.18 (s, 3H, OCH_3,*acetate*), 1.24 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 168.0, 166.9, 155.6, 143.9 (rot 1), 143.9 (rot 2), 141.3, 135.9, 129.7, 128.6, 127.8, 127.1, 127.1, 125.3 (rot1), 125.2 (rot2), 120.0, 67.2, 62.0, 52.2, 50.1, 47.2, 38.1, 18.6, 14.2.
IR (ν_{max}, cm^{-1}) 3059 (w), 2965 (w), 2929 (w), 1801 (m), 1745 (m), 1722 (m), 1685 (m), 1523 (m), 1448 (m), 1433 (m), 1395 (w), 1372 (m), 1244 (m), 1209 (s), 1168 (m), 1030 (m), 911 (m), 759 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{30}N_2NaO_7^+$ 553.1945; Found 553.1957.

Ethyl *N*-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-*L*-seryl)-*N*-hydroxyglycinate (**1n**)

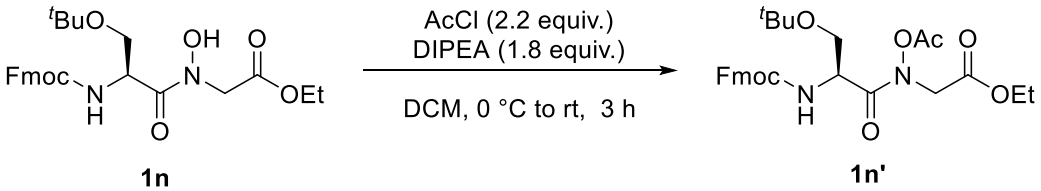


SM1aa **1n**

In a microwave vial, **SM1aa** (200 mg, 1.68 mmol, 1.00 equiv), Fmoc-Ser(O^{t}Bu)-Cl (1.01 g, 2.52 mmol, 1.50 equiv) and sodium bicarbonate (1.41 g, 16.8 mmol, 10.0 equiv) were diluted in dry dichloromethane (6.00 mL, 0.3 M) The reaction mixture was stirred at room temperature overnight. The residue was diluted with EtOAc (3 x 10 mL) and washed with 1 M aq HCl (10 mL), sat. aq $NaHCO_3$ (10 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 50 %) to give **1n** (470 mg, 939 µmol, 56% yield) as a white amorphous solid.

R_f = 0.40 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H, O*H*), 7.76 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.60 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.40 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.31 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 5.78 (d, *J* = 7.3 Hz, 1H, N*H*), 5.20 – 5.11 (m, 1H, NHC*H*), 4.67 (d, *J* = 17.5 Hz, 1H, NOCH_2C), 4.39 (t, *J* = 6.7 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.27 – 4.17 (m, 4H, OCH_2CH$_3$, NOCH_2C, C_{Fmoc}*H*CH$_2$OCON), 3.85 (t, *J* = 6.6 Hz, 1H, CH_2O^{t}Bu), 3.46 (dd, *J* = 10.3, 8.1 Hz, 1H, CH_2O^{t}Bu), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3) 1.27 (s, 9H, OC(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 167.6, 155.7, 144.0 (rot1), 143.9 (rot2), 141.6 (rot1), 141.4 (rot2), 127.9, 127.2, 125.3, 120.2 (rot1), 120.1 (rot2), 76.0, 67.3, 64.4, 61.7, 50.8, 49.4, 47.3, 27.1, 14.3.
IR (ν_{max}, cm^{-1}) 3269 (w), 2976 (m), 2938 (w), 1754 (m), 1721 (s), 1657 (s), 1516 (m), 1467 (m), 1449 (m), 1368 (m), 1231 (s), 1205 (s), 1086 (m), 1026 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{32}N_2NaO_7^+$ 507.2102; Found 507.2101.

Ethyl *N*-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-*L*-seryl)-*N*-acetoxyglycinate (**1n'**)

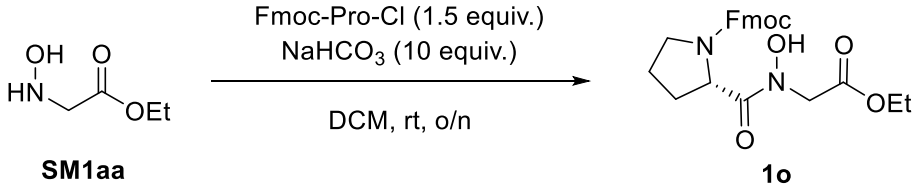


1n **1n'**

In a microwave vial, **1n'** (300 mg, 600 µmol, 1.00 equiv) was dissolved in dry DCM (2.0 mL, 0.3 M)**.** Then at 0 °C, acetyl chloride (104 mg, 94.2 µL, 1.32 mmol, 2.20 equiv) was added. The rm was stirred for 5 min and, DIPEA (140 mg, 188 µL, 1.08 mmol, 1.80 equiv) was added. The rm was stirred at rt for 3 h. The crude was diluted in water. The crude was extracted with AcOEt (3x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 50 %) to give **1n'** (265 mg, 503 µmol, 84% yield) as a white amorphous solid.

R_f = 0.46 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.5, 1.1 Hz, 2H, Ar*H*), 7.67 – 7.55 (m, 2H, Ar*H*), 7.40 (ddt, *J* = 8.5, 7.6, 0.9 Hz, 2H, Ar*H*), 7.31 (td, *J* = 7.4, 1.2 Hz, 2H, Ar*H*), 5.60 (d, *J* = 8.7 Hz, 1H, N*H*), 4.78 (q, *J* = 6.4 Hz, 1H, NHC*H*), 4.58 – 4.39 (m, 2H, NOCH_2C), 4.36 (d, *J* = 7.3 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.27 – 4.17 (m, 3H, OCH_2CH$_3$, C_{Fmoc}*H*CH$_2$OCON), 3.58 (m, 2H, CH_2O^{t}Bu), 2.22 (s, 3H, OCH_3,*acetate*), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.17 (s, 9H, OC(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.0, 155.9, 144.1 (rot1), 143.9 (rot2), 141.4 (rot1), 141.4 (rot2), 127.8, 127.2, 125.3, 120.1, 73.9, 67.4, 62.3, 61.9, 52.0, 50.6, 47.3, 27.4, 18.7, 14.2. (1C unresolved)
IR (ν_{max}, cm^{-1}) 2972 (m), 2929 (m), 1801 (m), 1749 (m), 1722 (s), 1690 (m), 1510 (m), 1450 (m), 1365 (m), 1233 (m), 1208 (s), 1196 (s), 1169 (s), 1095 (m), 1030 (m), 1024 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{34}N_2NaO_8^+$ 549.2207; Found 549.2211.

(9*H*-fluoren-9-yl)methyl (*S*)-2-((2-ethoxy-2-oxoethyl)(hydroxy)carbamoyl)pyrrolidine-1-carboxylate (**1o**)



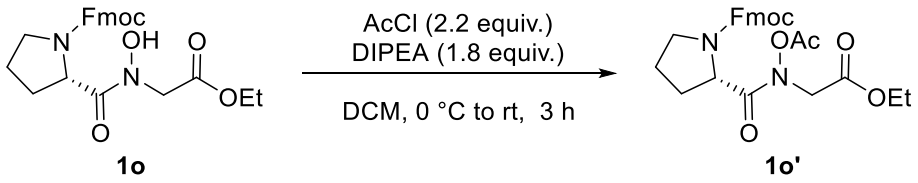
SM1aa **1o**

In a microwave vial, **SM1aa** (200 mg, 1.68 mmol, 1.00 equiv), Fmoc-Pro-Cl (896 mg, 2.52 mmol, 1.50 equiv) and sodium bicarbonate (1.41 g, 16.8 mmol, 10.0 equiv) were diluted in dry dichloromethane (6.00 mL, 0.3 M) The reaction mixture was stirred at room temperature overnight. The residue was diluted with EtOAc (3 x 10 mL) and washed with 1M aq HCl (10 mL), sat. aq $NaHCO_3$ (10 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 70 %) to give **1o** (512 mg, 1.13 mmol, 67% yield) as a white amorphous solid.

R_f = 0.26 (Pentane/ethyl acetate 40:60).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H, O*H*), 7.77 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.59 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.41 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.32 (td, *J* = 7.6, 1.1 Hz, 2H, Ar*H*), 5.09 – 4.95 (m, 1H, FmocNC*H*), 4.46 – 4.19 (m, 2H, CHC$H_{2,Fmoc}$OCON), 4.36 – 4.25 (m, 2H, N(OH)CH_2), 4.27 – 4.22 (m, 1H, C_{Fmoc}*H*CH$_2$OCON), 4.19 (td, *J* = 7.2, 3.8 Hz, 2H, OCH_2CH$_3$), 3.69 – 3.57 (m, 1H, NC$H_{2,Pro}$), 3.56 – 3.45 (m, 1H, NC$H_{2,Pro}$), 2.40 – 2.17 (m, 2H, C$H_{2,Pro}$), 2.15 – 2.04 (m, 1H, C$H_{2,Pro}$), 1.97 (ddd, *J* = 11.6, 7.4, 4.4 Hz, 1H, C$H_{2,Pro}$), 1.26 (td, *J* = 7.1, 1.2 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 168.3, 156.1, 144.0 (rot1), 143.8 (rot2), 141.5, 127.9, 127.2, 125.3 (rot1), 125.2 (rot2), 120.2, 68.3, 61.6, 55.4, 49.9, 47.3, 47.2, 29.1, 24.8, 14.2.
IR (ν_{max}, cm^{-1}) 3254 (w), 2982 (m), 2957 (w), 2893 (w), 1749 (m), 1698 (s), 1670 (s), 1473 (m), 1446 (s), 1423 (s), 1355 (m), 1239 (m), 1203 (s), 1127 (m), 1092 (m), 1027 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{26}N_2NaO_6^+$ 461.1683; Found 461.1686.

(9*H*-fluoren-9-yl)methyl (*S*)-2-(acetoxy(2-ethoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (1o')



In a microwave vial, **1o** (273 mg, 600 µmol, 1.00 equiv) was dissolved in dry DCM (2.0 mL, 0.3 M). Then at 0 °C, acetyl chloride (104 mg, 94.2 µL, 1.32 mmol, 2.20 equiv) was added. The rm was stirred for 5 min and, DIPEA (140 mg, 188 µL, 1.08 mmol, 1.80 equiv) was added. The rm was stirred at rt for 3 h. The crude was diluted in water. The crude was extracted with AcOEt (3x 5 mL), the organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, EtOAc/pentane gradient from 0 to 55 %) to give **1o'** (150 mg, 303 µmol, 51% yield) as a white amorphous solid.

R_f = 0.33 (Pentane/ethyl acetate 50:50).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.58 (s, 2H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.36 – 7.28 (m, 2H, Ar*H*), 6.38 (s, 1H, FmocNC*H*), 4.41 (s, 3H, CHC$H_{2,Fmoc}$OCON, C_{Fmoc}*H*CH_2OCON,), 4.20 (q, *J* = 7.1 Hz, 4H, NOCH_2C, OCH_2CH_3), 3.50 (d, *J* = 48.6 Hz, 2H, NC$H_{2,Pro}$), 2.30 (d, *J* = 66.7 Hz, 2H, C$H_{2,Pro}$), 2.08 (d, *J* = 15.7 Hz, 5H, C$H_{2,Pro}$, OC$H_{3,acetate}$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.8, 170.2, 166.6, 156.4, 144.0 (rot1), 143.9 (rot2), 141.5, 127.9 (rot1), 127.9 (rot2), 127.2, 125.2 (rot1), 125.1 (rot2), 120.2, 72.5 (rot1), 72.3 (rot2), 68.1, 62.7, 60.5, 47.3, 47.2, 28.1, 24.7, 20.7, 14.1.
IR (ν_{max}, cm^{-1}) 2983 (w), 2952 (w), 2926 (w), 2857 (w), 1801 (m), 1750 (m), 1700 (s), 1448 (m), 1418 (m), 1354 (m), 1246 (m), 1210 (m), 1170 (s), 1122 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2NaO_7^+$ 503.1789; Found 503.1789.

(The presence of rotamers is not allowing to resolve all peaks.)

2.3 General Method for the optimization of the reaction

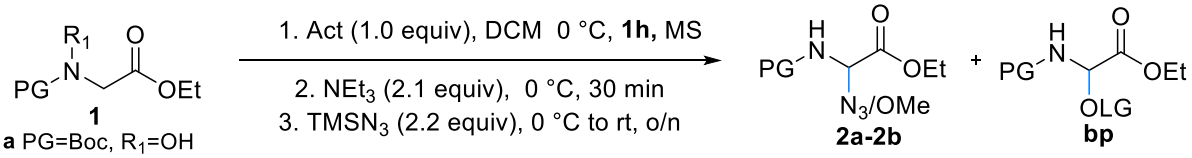
Condition A

A: hydroxylglycine **1a** (0.1 mmol, 1.00 equiv.) was dissolved in dry dichloromethane (0.2 M) at 0 °C with molecular sieves. Then, acetic anhydride (1.00 equiv.) or trifluoroacetic anhydride (1.00 equiv.) was added and the mixture was stirred at 0 °C under nitrogen for 1 hour, after which triethylamine (2.1 equiv.) was added. The reaction mixture was stirred for 30 min at 0 °C, then the chosen nucleophile (2.2 equiv.) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated in vacuo. Mesitylene (1 equiv.) was added and a ^{1}H NMR was taken (signal at 5.54 ppm for the azido product and 5.26 ppm for the OMe, both corresponding to the CH_α proton).

Condition B

B: The protected hydroxylglycine **1a'** (0.1 mmol, 1.00 equiv.) was dissolved in dry dichloromethane (0.2 M) at 0 °C with molecular sieves. Then, triethylamine (2.1 equiv.) was added stirred at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then the chosen nucleophile (2.2 equiv.) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated in vacuo. Mesitylene (1 equiv.) was added and a ^{1}H NMR was taken.

TABLE S1. SCREENING OF LEAVING GROUPS

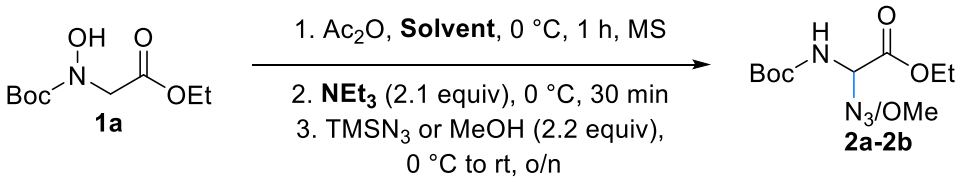


1a PG=Boc, R_1=OH
1e PG=Boc, R_1=OBoc
1g PG=Alloc, R_1=OAlloc
1a'PG=Boc, R_1=OAc
1f PG=Boc, R_1=OPiv

Entry	Substrate	Leaving groups	Nu	Yield%[b]
1	**1a**	OTFA	$TMSN_3$	69
			MeOH	66
2	**1e**	OBoc	$TMSN_3$	80
			MeOH	64
3	**1g**	OAlloc	$TMSN_3$	64
			MeOH	0
4	**1a**	OAc	$TMSN_3$	66
			MeOH	50
5	**1a'**	OAc	$TMSN_3$	75
			MeOH	79
6	**1f**	OPiv	$TMSN_3$	73
			MeOH	67

[a] Substrate **1** (0.10 mmol), **Leaving group** (0.10 mmol), NEt_3 (0.12 mmol), MeOH or $TMSN_3$ (0.22 mmol) and solvent (0.2 M) at 0 °C. With Molecular sieves [b] NMR yield given, calculated using 1 equiv. of mesitylene as internal standard.

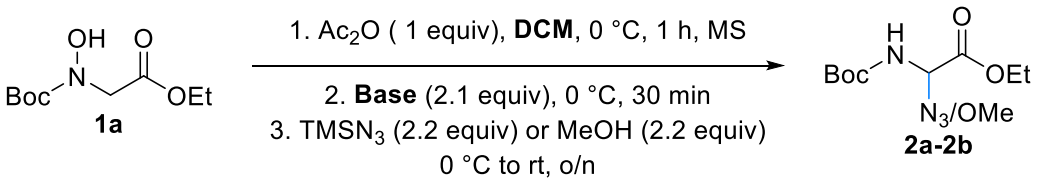
TABLE S2: SOLVENT SCREENING.



Entry	Nucleophile	Solvent	Yield%[b,c]
1a	**$TMSN_3$**	**DCM**	**66 (73)**
1b	**MeOH**		**50 (63)**
2a	$TMSN_3$	DME	48
2b	MeOH		58 (<47)
3a	$TMSN_3$	Chloroform	30
3b	MeOH		54 (56)
4a	$TMSN_3$	CPME	27
4b	MeOH		22
5a	$TMSN_3$	Toluene	51
5b	MeOH		31
6a	$TMSN_3$	THF	57
6b	MeOH		50 (<30)
7a	$TMSN_3$	DCE	50 (45)
7b	MeOH		61 (59)
8a	$TMSN_3$	Me-THF	30
8b	MeOH		35
9a	$TMSN_3$	HFIP	0
9b	MeOH		0
10a	$TMSN_3$	TFE	0
10b	MeOH		0
11a	$TMSN_3$ HFIP (1 eq.)	DCM	27

[a] Substrate **1a** (0.100 mmol), Ac_2O (0.10 mmol), base (0.21 mmol), nucleophile (0.22 mmol) and **solvent** (0.2 M) at 0 °C. [b] NMR yield given, calculated using 1 equiv. of mesitylene as internal standard. SM: starting material. [c] isolated yield in brackets

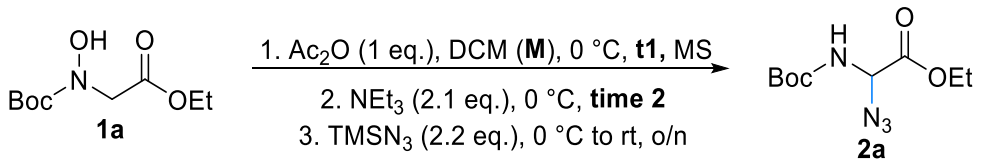
TABLE S3: BASE SCREENING.



Entry	Nucleophile	Base	Solvent	Yield%[b]
1a	**$TMSN_3$**	**Et_3N**	**DCM**	**66 (73)[c]**
1b	**MeOH**			**50 (63)[c]**
2a	$TMSN_3$	DBU	DCM	10
2b	MeOH			17
3a	$TMSN_3$	2,6 lutidine	DCM	0
3b	MeOH			0
4a	$TMSN_3$	DIPEA	DCM	8
4b	MeOH			19

[a] Substrate **1a** (0.100 mmol), Ac_2O (0.10 mmol), **base** (0.21 mmol), nucleophile (0.22 mmol) and DCM (0.2 M) at 0 °C. [b] NMR yield given, calculated using 1 equiv. of mesitylene as internal standard. SM: starting material.[c] isolated yield in brackets

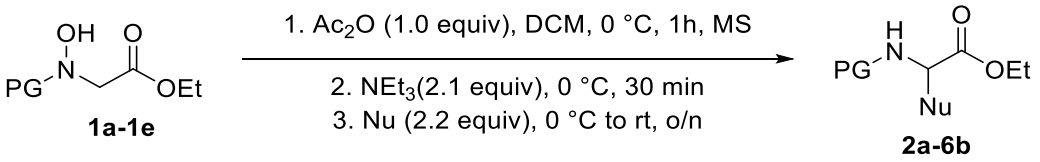
TABLE S4. TIME AND CONCENTRATION SCREENING.



Entry	Time 1	Time 2	Concentration	Yield%[b]
1	0 min	30 min	0.2 M	50
2	20 min	30 min	0.2 M	55
3	40 min	30 min	0.2 M	30
4	**60 min**	**30 min**	**0.2 M**	**65**
5	60 min	5 min	0.2 M	51
6	60 min	60 min	0.2 M	66
7	60 min	30 min	0.1 M	61
8	60 min	30 min	0.5 M	47

[a] Substrate **1a** (0.100 mmol), Ac_2O (0.10 mmol), base (0.21 mmol), $TMSN_3$ (0.22 mmol) and DCM (**M**) at 0 °C.
[b] NMR yield given, calculated using 1 equiv. of mesitylene as internal standard. SM: starting material.

TABLE S5. PROTECTING GROUP

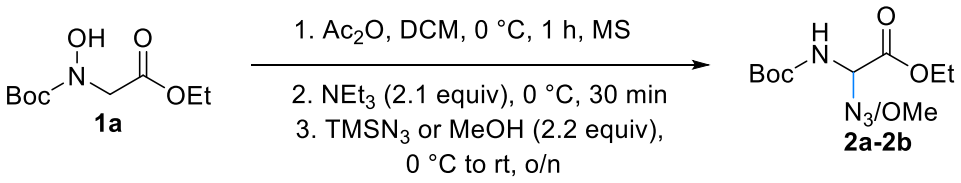


Entry	Protecting group	Nu	Yield%[b]
1	**Boc**	$TMSN_3$	73
		MeOH	63
2	**Fmoc**	$TMSN_3$	32
		MeOH	traces
3	**Cbz**	$TMSN_3$	78
		MeOH	68
4	**Alloc**	$TMSN_3$	78
		MeOH	78
5	**Fmoc-Gly**	$TMSN_3$	76
		MeOH	43

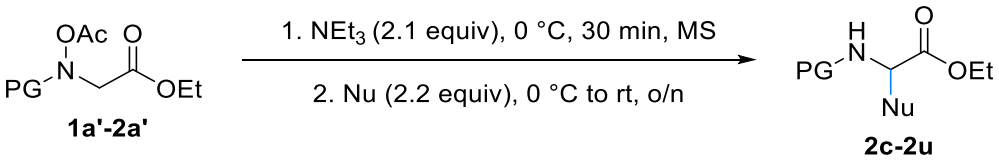
[a] Substrates **1** (0.10 mmol), Ac_2O (0.10 mmol), NEt_3 (0.21 mmol), MeOH or $TMSN_3$ (0.22 mmol) and solvent (0.2 M) at 0 °C. With Molecular sieves [b] NMR yield given, calculated using 1 equiv. of mesitylene as internal standard.

2.4. Scope of the Polonovski reaction

General procedure for Polonovski reaction



GP0: hydroxylglycine **1a** (0.1 mmol, 1.00 equiv.) was dissolved in dry dichloromethane (0.5 mL, 0.2 M) at 0 °C with molecular sieves. Then, acetic anhydride (1.00 equiv.) was added and the mixture was stirred at 0 °C under nitrogen for 1 hour, after which triethylamine (2.1 equiv.) was added. The reaction mixture was stirred for 30 min at 0 °C, then the chosen nucleophile (2.2 equiv.) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc) to afford the desired products **2a-5b**.



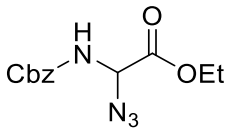
GP1: The protected hydroxylglycine **1a'** (1.00 equiv.) was dissolved in dry dichloromethane (0.2 M) at 0 °C with molecular sieves. Then, triethylamine (2.1 equiv.) was added stirred at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then nucleophiles (2.2 equiv.) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc) to afford the desired products **2c-2s**.

GP2: The protected hydroxylglycine **1b'** (1.00 equiv.) was dissolved in dry dichloromethane (0.2 M) at 0 °C with molecular sieves. Then, triethylamine (2.1 equiv.) was added stirred at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then nucleophiles (2.2 equiv.) with or without additive was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the crude was quenched with isopropanol, extracted with DCM, dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc) to afford the desired products **2t-2u**.

GP3: The protected hydroxylglycine **1a'** (1.00 equiv.) was dissolved in dry dichloromethane (0.2 M) at 0 °C with molecular sieves. Then, triethylamine (3.0 equiv.) was added stirred at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then nucleophiles (4.0 equiv.) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc) to afford the desired products **6h-6k**.

Glycine scope

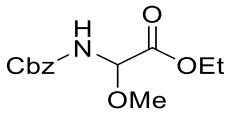
Ethyl 2-azido-2-(((benzyloxy)carbonyl)amino)acetate (3a)



Following GP1, using **1b** (25.7 mg, 101 µmol, 1.00 equiv) and trimethylsilyl azide (25.7 mg, 29.6 µL, 223 µmol, 2.20 equiv), ethyl 2-azido-2-(((benzyloxy)carbonyl)amino)acetate **3a** was obtained as a white solid (22.0 mg, 79.1 µmol, 78% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.63 (Pentane/ethyl acetate 80:20).
Mp: 60.5-62.3 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 3H, Ar*H*), 7.43 – 7.30 (m, 2H, Ar*H*), 5.95 (s, 1H, N*H*), 5.60 (d, *J* = 8.5 Hz, 1H, C*H*N_3), 5.17 (d, *J* = 3.4 Hz, 2H, ArC*H*$_2$), 4.31 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$$CH_3$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 155.3, 135.6, 128.8, 128.7, 128.5, 68.0, 67.0, 63.3, 14.2.
IR (ν_{max}, cm^{-1}) 3313 (w), 3042 (w), 2987 (w), 2114 (s), 1754 (s), 1733 (s), 1513 (m), 1465 (w), 1375 (m), 1331 (m), 1222 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}N_4NaO_4^+$ 301.0907; Found 301.0907.

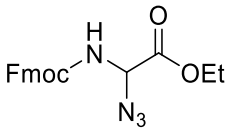
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-methoxyacetate (3b)



Following GP1, using **1b** (25.2 mg, 99.5 µmol, 1.00 equiv) and methanol (7.01 mg, 8.86 µL, 219 µmol, 2.20 equiv), ethyl 2-(((benzyloxy)carbonyl)amino)-2-methoxyacetate **3b** was obtained as a white amorphous solid (18.0 mg, 67.3 µmol, 68% yield) after purification by column chromatography on silica using gradient from 0 to 15% EtOAc in pentane.

R_f = 0.56 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.38 (m, 5H, Ar*H*), 5.85 (d, *J* = 9.5 Hz, 1H, N*H*), 5.33 (d, *J* = 9.5 Hz, 1H, C*H*OMe), 5.16 (s, 2H, ArC*H*$_2$), 4.26 (qd, *J* = 7.1, 1.8 Hz, 2H, OC*H*$_2$$CH_3$), 3.47 (s, 3H, OC*H*$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 155.8, 135.9, 128.8, 128.5, 128.4, 80.9, 67.6, 62.4, 56.4, 14.2.
IR (ν_{max}, cm^{-1}) 3437 (w), 3351 (w), 3034 (w), 2952 (w), 2834 (w), 1744 (s), 1731 (s), 1518 (s), 1457 (m), 1399 (w), 1377 (m), 1337 (m), 1239 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{17}NNaO_5^+$ 290.0999; Found 290.0995.

Ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-azidoacetate (4a)

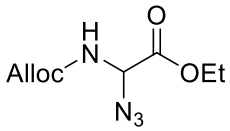


Following GP1, using **1c** (34.7 mg, 102 µmol, 1.00 equiv) and trimethylsilyl azide (24.6 mg, 28.3 µL, 213 µmol, 2.10 equiv), ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-azidoacetate **4a** was

obtained as a white solid (12.0 mg, 32.8 µmol, 32% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.39 (Pentane/ethyl acetate 80:20).
Mp: 104.0–105.0 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dt, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.59 (dt, *J* = 7.6, 1.1 Hz, 2H, Ar*H*), 7.42 (tt, *J* = 7.5, 0.9 Hz, 2H, Ar*H*), 7.33 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 5.98 (d, *J* = 8.6 Hz, 1H, N*H*), 5.60 (d, *J* = 8.5 Hz, 1H, C*H*N_3), 4.55 – 4.41 (m, 2H, ArCHC*H*$_2$), 4.33 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$$CH_3$), 4.25 (t, *J* = 6.9 Hz, 1H, ArC*H*CH_2), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 154.2, 142.4, 140.3, 126.9, 126.1, 123.9, 119.1, 66.8, 65.8, 62.2, 45.9, 13.0.
IR (ν_{max}, cm^{-1}) 3399 (w), 3305 (w), 3064 (w), 2930 (w), 2858 (w), 2114 (s), 1747 (s), 1733 (s), 1678 (w), 1513 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}N_4NaO_4^+$ 389.1220; Found 389.1227.

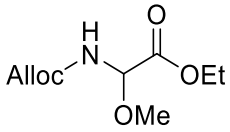
Ethyl 2-(((allyloxy)carbonyl)amino)-2-azidoacetate (5a)



Following GP1, using **1d** (20.6 mg, 101 µmol, 1.00 equiv) and trimethylsilyl azide (25.7 mg, 29.6 µL, 223 µmol, 2.20 equiv), ethyl 2-(((allyloxy)carbonyl)amino)-2-azidoacetate **5a** was obtained as a yellow oil (18.0 mg, 78.9 µmol, 78% yield), after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.7 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.86 (m, 2H, CH_2=C*H*-CH_2 and N*H*), 5.59 (d, *J* = 8.6 Hz, 1H, C*H*N_3), 5.35 (dq, *J* = 17.3, 1.6 Hz, 1H, C*H*$_2$=CH-CH_2), 5.27 (dq, *J* = 10.4, 1.3 Hz, 1H, C*H*$_2$=CH-CH_2), 4.64 (d, *J* = 5.8 Hz, 2H, CH_2=CH-C*H*$_2$), 4.32 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$$CH_3$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 155.0, 132.0, 118.8, 67.0, 66.8, 63.3, 14.2.
IR (ν_{max}, cm^{-1}) 3425 (w), 3349 (w), 2987 (w), 2937 (w), 2114 (s), 1747 (s), 1729 (s), 1649 (w), 1515 (m), 1461 (w), 1330 (m), 1229 (s), 988 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{12}N_4NaO_4^+$ 251.0751; Found 251.0743.

Ethyl 2-(((allyloxy)carbonyl)amino)-2-methoxyacetate (5b)

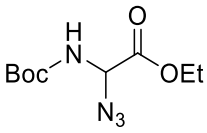


Following GP1, using **1d** (20.5 mg, 101 µmol, 1.00 equiv) and methanol (7.11 mg, 9.00 µL, 222 µmol, 2.20 equiv), 1-allyl 3-ethyl 2-methoxymalonate **5b** was obtained as a transparent oil (16.0 mg, 73.7 µmol, 73% yield), after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.19 (Pentane/ethyl acetate 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, CH_2=C*H*-CH_2), 5.82 (d, *J* = 8.7 Hz, 1H N*H*), 5.37 – 5.22 (m, 3H, C*H*OMe and C*H*$_2$=CH-CH_2), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H, C*H*$_2$=CH-CH_2), 4.62 (d, *J* = 5.7 Hz, 2H, CH_2=CH-C*H*$_2$), 4.27 (qd, *J* = 7.1, 1.7 Hz, 2H, OC*H*$_2$$CH_3$), 3.46 (s, 3H, OC*H*$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 155.7, 132.3, 118.4, 80.8, 66.4, 62.4, 56.4, 14.2.
IR (ν_{max}, cm^{-1}) 3415 (w), 3340 (m), 2989 (w), 2940 (m), 2836 (w), 1747 (s), 1728 (s), 1649 (w), 1521 (s), 1212 (s), 989 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_9H_{15}NNaO_5^+$ 240.0842; Found 240.0833.

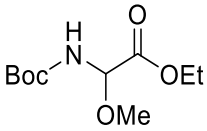
Ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)acetate (2a)



Following GP1, using **1a** (80.5 mg, 308 µmol, 1.00 equiv) and trimethylsilyl azide (78.1 mg, 90.0 µL, 678 µmol, 2.20 equiv), ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)acetate **2a** was obtained as a transparent oil (56.0 mg, 229 µmol, 74% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.32 (Pentane/ethyl acetate 95:5).
^{1}H NMR (400 MHz, CDCl3) δ 5.72 (s, 1H, N*H*), 5.54 (d, *J* = 8.8 Hz, 1H, C*H*N_3), 4.30 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$$CH_3$), 1.48 (s, 9H, C*H*$_{3Boc}$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 154.4, 81.6, 66.7, 63.1, 28.3, 14.2.
IR (ν_{max}, cm^{-1}) 3439 (w), 3348 (w), 2980 (m), 2936 (w), 2361 (w), 2336 (w), 2112 (s), 1752 (s), 1722 (s), 1506 (m), 1371 (m).
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_9H_{16}N_4NaO_4^+$ 267.1064; Found 267.1063.

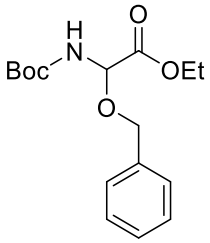
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetate (2b)



Following GP1, using **1a** (77.8 mg, 298 µmol, 1.00 equiv) and methanol (21.0 mg, 26.5 µL, 655 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetate **2b** was obtained as a transparent oil (43.7 mg, 188 µmol, 63% yield) after purification by column chromatography on silica using gradient from 0 to 15% EtOAc in pentane.

R_f = 0.22(Pentane/ethyl acetate 93:7).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (s, 1H, N*H*), 5.26 (d, *J* = 9.6 Hz, 1H, C*H*OMe), 4.26 (qd, *J* = 7.1, 2.5 Hz, 2H, OC*H*$_2$$CH_3$), 3.44 (s, 3H, OC*H*$_3$), 1.47 (s, 9H, C*H*$_{3Boc}$), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 155.0, 80.9, 80.5, 62.3, 56.1, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 3440 (w), 3340 (w), 2979 (m), 2935 (m), 2835 (w), 1750 (m), 1718 (s), 1506 (s), 1460 (m), 1370 (m), 1340 (m), 1252 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{19}NNaO_5^+$ 256.1155; Found 256.1155.

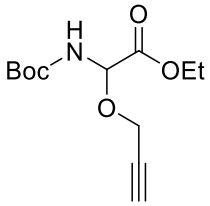
Ethyl 2-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate (2c)



Following GP1, using **1a'** (81.0 mg, 369 µmol, 1.00 equiv) and benzylalcohol (87.9 mg, 84.5 µL, 813 µmol, 2.20 equiv), ethyl 2-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate **2c** was obtained as a transparent oil (82.0 mg, 265 µmol, 72% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

$\mathbf{R_f}$ = 0.35 (Pentane/ethyl acetate 95:5).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 3H, Ar*H*), 7.29 – 7.18 (m, 2H, Ar*H*), 5.64 (s, 1H, N*H*), 5.38 (d, *J* = 9.6 Hz, 1H, C*H*OBz), 4.79 – 4.62 (m, 2H, ArCH_2), 4.23 (qq, *J* = 7.3, 3.7 Hz, 2H, OC$H_2$$CH_3$), 1.40 (s, 9H, C$H_{3Boc}$), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 155.0, 137.5, 128.5, 128.1, 128.0, 80.8, 79.2, 71.1, 62.2, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 3422 (w), 3352 (m), 2980 (m), 2931 (m), 2877 (w), 2365 (w), 1749 (s), 1722 (s), 1501 (s), 1457 (m), 1393 (m), 1371 (m), 1334 (m), 1248 (m), 1208 (s), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{23}NNaO_5^+$ 332.1468; Found 332.1468.

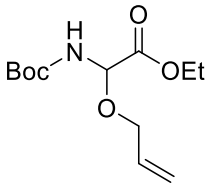
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(prop-2-yn-1-yloxy)acetate (2d)



Following GP1, using **1a'** (79.8 mg, 305 µmol, 1.00 equiv) and prop-2-yn-1-ol (37.7 mg, 38.8 µL, 672 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(prop-2-yn-1-yloxy)acetate **2d** was obtained as a transparent oil (59.0 mg, 229 µmol, 75% yield) after purification by column chromatography on silica using gradient from 0 to 15% EtOAc in pentane.

$\mathbf{R_f}$ = 0.34 (Pentane/ethyl acetate 92:8).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H, N*H*), 5.49 (d, *J* = 9.6 Hz, 1H, C*H*O_{prop}), 4.33 (d, *J* = 2.4 Hz, 2H, OCH_2C), 4.33-4.22 (m, 2H, OC$H_2$$CH_3$), 2.48 (t, *J* = 2.4 Hz, 1H, CH_2CCH), 1.47 (s, 9H, CH_{3Boc}), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 154.9, 81.1, 79.0, 78.6, 75.1, 62.4, 56.3, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 3351 (w), 3294 (w), 2981 (m), 2937 (w), 2123 (w), 1749 (s), 1721 (s), 1508 (s), 1454 (w), 1371 (s), 1346 (m), 1250 (m), 1212 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{19}NNaO_5^+$ 280.1155; Found 280.1153.

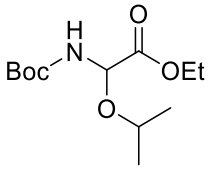
Ethyl 2-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate (2e)



Following GP1, using **1a'** (80.1 mg, 307 µmol, 1.00 equiv) and allyl alcohol (39.2 mg, 45.9 µL, 674 µmol, 2.20 equiv), ethyl 2-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate **2e** was obtained as a transparent oil (66.0 mg, 255 µmol, 83% yield) after purification by column chromatography on silica using gradient from 0 to 15% EtOAc in pentane.

$\mathbf{R_f}$ = 0.43 (Pentane/ethyl acetate 93:7).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H, CH_2=C*H*-CH_2), 5.64 (d, *J* = 9.6 Hz, 1H, N*H*), 5.38 (d, *J* = 9.2 Hz, 1H, C*H*OAllyl), 5.33 (dq, *J* = 17.3, 1.6 Hz, 1H, CH_2=CH-CH_2), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H, CH_2=CH-CH_2), 4.25 (qd, *J* = 7.2, 2.5 Hz, 2H, OC$H_2$$CH_3$), 4.21 – 4.11 (m, 2H, CH_2=CH-CH_2), 1.47 (s, 9H, CH_{3Boc}), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 155.0, 133.8, 118.1, 80.8, 78.8, 69.9, 62.2, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 3447 (w), 3364 (w), 2981 (m), 2934 (w), 2871 (w), 1750 (s), 1721 (s), 1649 (w), 1503 (s), 1459 (m), 1371 (s), 1342 (m), 1248 (m), 1208 (s), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{21}NNaO_5^+$ 282.1312; Found 282.1313.

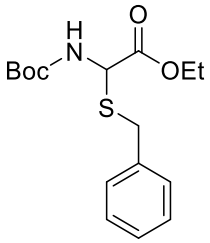
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-isopropoxyacetate (2f)



Following GP1, using **1a'** (81.9 mg, 313 µmol, 1.00 equiv) and 2-propanol (41.4 mg, 52.7 µL, 690 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-isopropoxyacetate **2f** was obtained as a transparent oil (39.0 mg, 149 µmol, 48% yield) after purification by column chromatography on silica using gradient from 0 to 15% EtOAc in pentane.

$\mathbf{R_f}$ = 0.26 (Pentane/ethyl acetate 95:5).
^{1}H NMR (400 MHz, CDCl3) δ 5.60 (d, *J* = 9.9 Hz, 1H, N*H*), 5.38 (d, *J* = 9.8 Hz, 1H, C*H*O^{i}Pr), 4.24 (qd, *J* = 7.1, 1.2 Hz, 2H, OC$H_2$$CH_3$), 3.98 (hept, *J* = 6.2 Hz, 1H, C*H*$(CH_3)_2$), 1.46 (s, 9H, CH_{3Boc}), 1.31 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.21 (t, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$).
^{13}C NMR (101 MHz, CDCl3) δ 168.6, 155.0, 80.6, 71.3, 62.0, 28.4, 23.1, 22.0, 14.2.
IR (ν_{max}, cm^{-1}) 2976 (m), 2933 (w), 1743 (m), 1718 (s), 1495 (s), 1455 (w), 1393 (w), 1368 (m), 1329 (s), 1253 (m), 1231 (m), 1161 (s), 1051 (m), 1026 (m).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{12}H_{23}NNaO_5^+$ 284.1468; Found 284.1459.

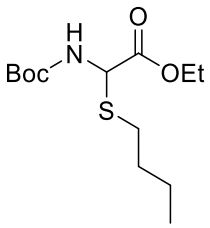
Ethyl 2-(benzylthio)-2-((*tert*-butoxycarbonyl)amino)acetate (2g)



Following GP1, using **1a'** (78.7 mg, 301 µmol, 1.00 equiv) and phenylmethanethiol (82.3 mg, 77.6 µL, 663 µmol, 2.20 equiv), ethyl 2-(benzylthio)-2-((*tert*-butoxycarbonyl)amino)acetate **2g** was obtained as a transparent oil (56.0 mg, 172 µmol, 57% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

$\mathbf{R_f}$ = 0.30 (Pentane/ethyl acetate 95:5).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, Ar*H*), 5.37 (s, 1H, N*H*), 5.35 – 5.24 (d, *J* = 8.4 Hz, 1H, C*H*S), 4.24 – 4.08 (m, 2H, OCH_2CH$_3$), 3.94 (d, *J* = 13.4 Hz, 1H, ArCH_2), 3.87 (d, *J* = 13.0 Hz, 1H, ArCH_2), 1.44 (s, 9H, CH_{3Boc}), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 154.1, 137.4, 129.2, 128.7, 127.4, 80.8, 62.3, 55.8, 35.3, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 3426 (m), 3379 (m), 3342 (m), 2980 (m), 2933 (w), 1739 (m), 1718 (s), 1717 (s), 1495 (s), 1455 (w), 1368 (m), 1328 (s), 1256 (m), 1235 (m), 1161 (s), 1052 (m), 1028 (m).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{16}H_{23}NNaO_4S^+$ 348.1240; Found 348.1243.

Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(butylthio)acetate (2h)



Following GP1, using **1a'** (80.0 mg, 306 µmol, 1.00 equiv) and butane-1-thiol (60.8 mg, 72.6 µL, 674 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(butylthio)acetate **2h** was obtained as a yellowish oil (82.0 mg, 281 µmol, 92% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

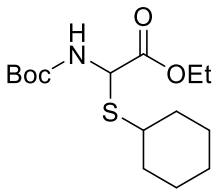
On 1mmol scale:

To a solution of **1a'** (266 mg, 1.02 mmol, 1.00 equiv) in 5 mL of dry CH_2Cl_2 cooled down to 0 °C with activated molecular sieves was added triethylamine (206 mg, 284 µL, 2.04 mmol, 2.00 equiv), the reaction mixture was stirred at 0 °C for 30 minutes. Then, 1-butanethiol (202 mg, 241 µL, 2.24 mmol, 2.20 equiv) was added slowly and the cooling bath was removed and the reaction mixture was stirred overnight at rt. The crude was concentrated in vacuo. The crude was purified by column chromatography (SiO2, gradient from 0 to 10% EtOAc in pentane) to give **2h** (279 mg, 957 µmol, 94% yield) as a transparent oil.

$\mathbf{R_f}$ = 0.22 (Pentane/ethyl acetate 97:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (d, *J* = 9.2 Hz, 1H, N*H*), 5.29 (d, *J* = 9.2 Hz, 1H, C*H*SCH_2), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.68 (qt, *J* = 12.5, 7.4 Hz, 2H, SCH_2), 1.63 – 1.58 (m, 2H, SCH_2CH_2), 1.46 (s, 9H, CH_{3Boc}), 1.40 (q, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 0.91 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 154.2, 80.8, 62.2, 55.5, 31.6, 30.6, 28.4, 22.1, 14.2, 13.7.
IR (ν_{max}, cm^{-1}) 2977 (m), 2961 (m), 2929 (w), 2872 (w), 1743 (s), 1721 (s), 1494 (m), 1469 (m), 1368 (m), 1327 (s), 1256 (m), 1237 (m), 1164 (s), 1051 (m), 1028 (m).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{13}H_{25}NNaO_4S^+$ 314.1397; Found 314.1396.

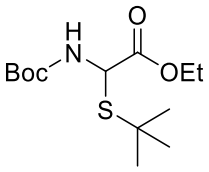
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(cyclohexylthio)acetate (2i)



Following GP1, using **1a'** (78.3 mg, 300 µmol, 1.00 equiv) and cyclohexanethiol (76.6 mg, 80.7 µL, 659 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(cyclohexylthio)acetate **2i** was obtained as a transparent oil (56.0 mg, 176 µmol, 59% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.26 (Pentane/ethyl acetate 97:3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 2H, N*H* and C*H*SCH), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.94 (tt, *J* = 10.5, 3.5 Hz, 1H, $SCH(CH_2)_2$), 2.11 – 2.02 (m, 1H, CH_2 cyclohexyl), 1.97 (d, *J* = 12.2 Hz, 1H, CH_2 cyclohexyl), 1.76 (qd, *J* = 6.2, 2.7 Hz, 2H, CH_2 cyclohexyl), 1.64 – 1.57 (m, 1H, CH_2 cyclohexyl), 1.46 (s, 9H, CH_{3Boc}), 1.44 – 1.12 (m, 5H, CH_2 cyclohexyl), 1.30 (d, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 154.3, 80.7, 62.2, 54.8, 44.3, 34.3, 33.8, 28.4, 26.3, 26.1, 25.7, 14.2.
IR (ν_{max}, cm^{-1}) 2982 (w), 2932 (m), 2854 (w), 1744 (s), 1718 (s), 1509 (m), 1496 (m), 1451 (m), 1392 (w), 1368 (m), 1327 (s), 1258 (m), 1170 (s), 1163 (s), 1051 (m), 1028 (m).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{15}H_{27}NNaO_4S^+$ 340.1553; Found 340.1555.

Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(*tert*-butylthio)acetate (2j)

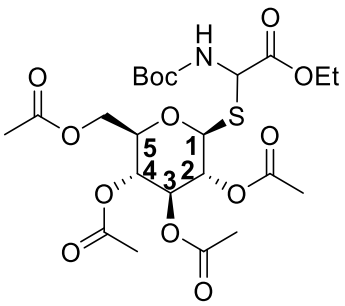


Following GP1, using **1a'** (80.2 mg, 307 µmol, 1.00 equiv) and 2-methylpropane-2-thiol (60.9 mg, 76.1 µL, 675 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(*tert*-butylthio)acetate **2j** was obtained as a transparent oil (58.0 mg, 199 µmol, 65% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.27 (Pentane/ethyl acetate 97:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 2H, N*H* and C*H*SCH), 4.21 (q, *J* = 7.1 Hz, 2H, OC$H_2$$CH_3$), 1.44 (s, 9H, C$H_{3Boc}$), 1.42 (s, 9H, SC(C$H_3$)$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 154.1, 80.6, 62.0, 54.2, 45.7, 31.3, 28.4, 14.1.
IR (ν_{max}, cm^{-1}) 2978 (m), 2939 (w), 1744 (s), 1716 (s), 1501 (m), 1462 (m), 1393 (w), 1368 (m), 1325 (s), 1256 (m), 1218 (m), 1163 (s), 1050 (m), 1029 (m).
HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{13}H_{25}NNaO_4S^+$ 314.1397; Found 314.1395.

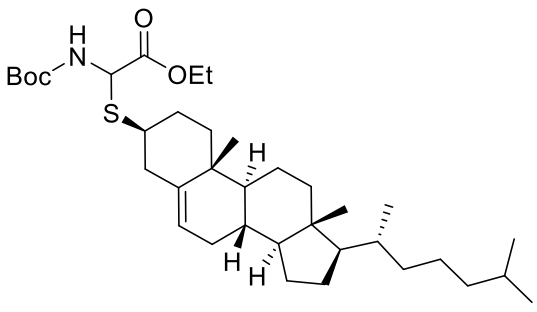
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((1-((*tert*-butoxycarbonyl)amino)-2-ethoxy-2-oxoethyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2k)



Following GP1, using **1a'** (79.6 mg, 305 µmol, 1.00 equiv) and 2,3,4,6-tetra-O-acetyl-1-thio-*β*-D-glucopyranose (249 mg, 684 µmol, 2.20 equiv), (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((1-((*tert*-butoxycarbonyl)amino)-2-ethoxy-2-oxoethyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate **2k** was obtained as an off white solid (118 mg, 209 µmol, 67% yield) (mixture of diastereoisomers, 1.5:1.0 dr determined by NMR, signal of the C*H*S at 5.59 and 5.39 ppm) after purification by column chromatography on silica using gradient from 0 to 60% EtOAc in pentane.

R_f = 0.25 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 9.9 Hz, 0.36H, N*H*$_{diamin}$), 5.70 (d, *J* = 8.2 Hz, 0.38H, N*H*$_{diamaj}$), 5.59 (d, *J* = 9.9 Hz, 0.42H, C*H*$_{diamin}$S), 5.39 (d, *J* = 8.2 Hz, 0.44H, C*H*$_{diamaj}$S), 5.23 (td, *J* = 9.3, 5.8 Hz, 1H, C_3*H*OAc), 5.12 – 4.94 (m, 2H, C_2*H*OAc and C_4*H*OAc), 4.81 (d, *J* = 3.4 Hz, 0.58H, C_1*H*$_{diamaj}$S), 4.78 (d, *J* = 3.5 Hz, 0.42H, C_1*H*$_{diamin}$S), 4.32 – 4.05 (m, 4H, OC*H*$_2$CH$_3$ and C_5HC*H*$_2$OAc), 3.68 (dddd, *J* = 24.6, 10.2, 5.3, 2.3 Hz, 1H, C_5*H*CH$_2$OAc), 2.12 (s, 1.19H, C*H*$_3$acyl1$_{diamin}$), 2.09 (s, 1.65H, C*H*$_3$acyl1$_{,diamaj}$), 2.03 (s, 1.54H, C*H*$_3$ acyl2$_{,diamin}$), 2.02 (s, 1.31H, C*H*$_3$ acyl3$_{,diamin}$), 2.02 (s, 1.68H, C*H*$_3$ acyl2$_{,diamaj}$), 2.01 (s, 1.45H, C*H*$_3$ acyl3$_{,diamin}$), 2.00 (s, 1.09H, C*H*$_3$ acyl4$_{,diamin}$), 1.99 (s, 1.59H, C*H*$_3$ acyl4$_{,diamin}$), 1.46 (s, 5H, C*H*$_{3Boc,diamaj}$), 1.45 (s, 4H, C*H*$_{3Boc,diamin}$), 1.30 (td, *J* = 7.2, 1.8 Hz, 3H, OCH$_2$C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 , 170.3, 169.6 ($C_{q,min}$), 169.5 ($C_{q,maj}$), 169.4, 168.8 ($C_{q,min}$), 168.0 ($C_{q,maj}$), 154.4 (*C*H$_{3Boc,min}$), 153.6 (*C*H$_{3Boc,maj}$), 82.4 (CH_{maj}), 81.6 (CH_{min}), 81.2 ($C_{q,Boc,min}$), 81.0 ($C_{q,Boc,maj}$), 76.1 (CH_{maj}), 76.1 (CH_{min}), 74.0 (CH_{maj}), 73.8 (CH_{min}), 70.2 (CH_{min}), 69.8 (CH_{maj}), 68.5 (CH_{min}), 68.1 (CH_{maj}), 62.6 (CH_{2maj}), 62.5 (CH_{2min}), 62.4 (CH_{2min}), 61.8 (CH_{2maj}), 55.5 (CHS_{diamin}), 54.8 (CHS_{diamaj}), 28.4 (C*H*$_{3Boc,diamin}$), 28.4 (C*H*$_{3Boc,diamaj}$), 20.9(C_{acetal}), 20.9 (C_{acetal}), 20.8 (C_{acetal}), 20.7 (C_{acetal}), 14.2 (OCH$_2$*C*H$_{3,\ diamin}$), 14.1 (OCH$_2$*C*H$_{3,diamaj}$).
IR (ν_{max}, cm^{-1}) 3384 (s), 2985 (m), 2947 (m), 1757 (s), 1750 (s), 1746 (s), 1721 (s), 1714 (s), 1520 (m), 1503 (m), 1498 (m), 1372 (s), 1331 (m), 1246 (s), 1240 (s), 1232 (s), 1173 (s), 1163 (s), 1102 (m), 1051 (s), 1048 (s), 1033 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{35}NNaO_{13}S^+$ 588.1721; Found 588.1731.

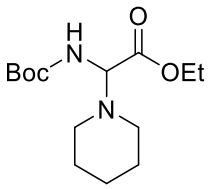
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)thio)acetate (2l)



Following GP1, using **1a'** (79.5 mg, 304 µmol, 1.00 equiv) and thiocholesterol (270 mg, 669 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)thio)acetate **2l** was obtained as a white sticky oil (162 mg, 268 µmol, 88% yield) (mixture of diastereoisomers, could not be determined) after purification by column chromatography on silica using gradient from 0 to 5% EtOAc in pentane.

R_f = 0.39 (Pentane/ethyl acetate 97:3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, *J* = 8.7 Hz, 3H, N*H*, C*H*SCH and C=C*H*), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 2.83 (tt, *J* = 12.0, 4.3 Hz, 1H, OC*H*S), 2.42 – 2.26 (m, 2H, SCHCH_2C=C), 2.05 – 1.76 (m, 6H, C$H_{aliphatic}$), 1.65 – 1.50 (m, 6H, C$H_{aliphatic}$), 1.45 (s, 9H, CH_{3Boc}), 1.43 – 1.39 (m, 4H, C$H_{aliphatic}$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.21 – 1.02 (m, 10H, C$H_{aliphatic}$), 0.99 (s, 3H, $CH_{3,methyl}$), 0.91 (d, *J* = 6.5 Hz, 3H, $CH_{3,methyl}$), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H, CH(CH_3)$_2$), 0.67 (s, 3H, $CH_{3,methyl}$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 154.2 ($C_{q,diamin}$), 154.1 ($C_{q,diamaj}$), 141.6 ($C_{q,diamin}$), 141.5 ($C_{q,diamaj}$), 121.6 (C_{diamaj}), 121.5 (C_{diamin}), 80.7, 62.2, 56.9, 56.3, 54.7 (C_{diamaj}), 54.6 (C_{diamin}), 50.4 (C_{diamaj}), 50.4 (C_{diamin}), 45.1, 42.5, 40.5, 39. 9, 39.8, 39.7, 39.7, 36.9, 36.8, 36.3, 35.9, 32.0, 31.9, 30.4, 29.9, 28.4, 28.4, 28.2, 24.4, 24.0, 22.9, 22.7, 21.0, 19.5, 18.9, 14.2, 12.0. (Mixture of diastereoisomers).
IR (ν_{max}, cm^{-1}) 3437 (m), 3371 (m), 3297 (w), 2976 (m), 2939 (m), 2868 (w), 2855 (w), 1739 (m), 1721 (s), 1491 (m), 1468 (m), 1393 (w), 1368 (m), 1328 (m), 1256 (m), 1224 (m), 1173 (s), 1163 (s), 1109 (w), 1049 (m), 1028 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{61}NNaO_4S^+$ 626.4214; Found 626.4228.

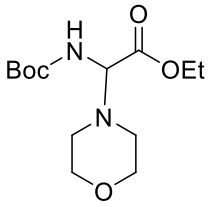
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(piperidin-1-yl)acetate (2m)



Following GP1, using **1a'** (79.6 mg, 305 µmol, 1.00 equiv) and piperidine (57.1 mg, 66.2 µL, 670 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(piperidin-1-yl)acetate **2m** was obtained as a white solid (75.0 mg, 262 µmol, 86% yield). after purification by column chromatography on silica using gradient from 0 to 20% EtOAc in pentane.

R_f = 0.21 (Pentane/ethyl acetate 92:8).
Mp: 43.4 - 44.1 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (s, 1H, N*H*), 5.00 (d, *J* = 8.8 Hz, 1H, C*H*N), 4.26 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 2.56 (ddd, *J* = 11.1, 6.9, 4.0 Hz, 2H, NCH_2CH$_2$), 2.43 (ddd, *J* = 11.1, 6.9, 3.9 Hz, 2H, NCH_2CH$_2$), 1.63 – 1.56 (m, 4H, NCH$_2$CH_2), 1.46 (s, 9H, CH_{3Boc}), 1.43 – 1.38 (m, 2H, NCH$_2$CH$_2$CH_2), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 155.7, 80.0, 72.1, 61.9, 49.4, 28.4, 26.0, 24.2, 14.4.
IR (ν_{max}, cm^{-1}) 3436 (w), 3379 (w), 2979 (m), 2936 (m), 2855 (w), 2816 (w), 1743 (m), 1719 (s), 1491 (m), 1472 (m), 1368 (m), 1329 (m), 1248 (m), 1224 (m), 1177 (s), 1162 (s), 1102 (m), 1049 (m), 1028 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{26}N_2NaO_4^+$ 309.1785; Found 309.1782.

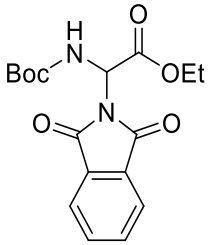
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-morpholinoacetate (2n)



Following GP1, using **1a'** (80.4 mg, 308 µmol, 1.00 equiv) and morpholine (59.0 mg, 58.4 µL, 677 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-morpholinoacetate **2n** was obtained as a yellowish oil (39.0 mg, 135 µmol, 44% yield) after purification by column chromatography on silica using gradient from 0 to 30% EtOAc in pentane.

R_f = 0.26 (Pentane/ethyl acetate 65:35).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H, N*H*), 4.99 (d, *J* = 8.7 Hz, 1H, C*H*N), 4.26 (qd, *J* = 7.1, 2.2 Hz, 2H, OC$H_2$$CH_3$), 3.77 – 3.64 (m, 4H, O(CH_2)$_2$), 2.65 (ddd, *J* = 11.7, 5.4, 3.5 Hz, 2H NC$H_2$$CH_2$), 2.52 (ddd, *J* = 11.1, 5.9, 3.6 Hz, 2H NC$H_2$$CH_2$), 1.45 (s, 9H, C$H_{3Boc}$), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 155.5, 80.4, 71.3, 66.9, 62.1, 48.4, 28.4, 14.4.
IR (ν_{max}, cm^{-1}) 3462 (m), 3007 (m), 2867 (m), 1745 (s), 1720 (s), 1612 (m), 1510 (m), 1456 (m), 1394 (m), 1371 (s), 1310 (m), 1206 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{24}N_2NaO_5^+$ 311.1577; Found 311.1579.

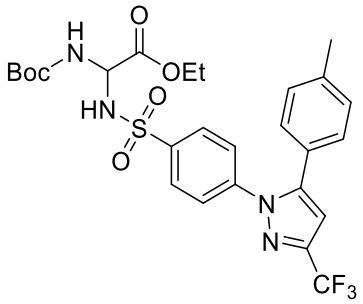
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisoindolin-2-yl)acetate (2o)



Following GP1, using **1a'** (80.2 mg, 307 µmol, 1.00 equiv) and phtalimide potassium salt (126 mg, 675 µmol, 2.20 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisoindolin-2-yl)acetate **2o** was obtained as a white amorphous solid (92.0 mg, 264 µmol, 86% yield) after purification by column chromatography on silica using gradient from 0 to 30% EtOAc in pentane.

R_f = 0.39 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 2H, Ar*H*), 7.80 – 7.69 (m, 2H, Ar*H*), 6.42 (d, *J* = 8.8 Hz, 1H, N*H*), 6.13 – 5.92 (m, 1H, C*H*N), 4.25 (q, *J* = 7.1 Hz, 2H, OC$H_2$$CH_3$), 1.43 (s, 9H, C$H_{3Boc}$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 166.8, 154.4, 134.6, 131.8, 124.0, 81.1, 63.2, 56.5, 28.1, 14.1.
IR (ν_{max}, cm^{-1}) 3367 (w), 2979 (w), 2936 (w), 2359 (w), 2345 (w), 1782 (w), 1750 (m), 1725 (s), 1504 (w), 1386 (m), 1368 (m), 1321 (m), 1253 (m), 1159 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_6^+$ 371.1214; Found 371.1218.

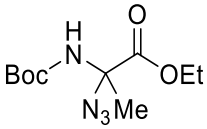
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonamido)acetate (2p)



Following GP1, using **1a'** (79.1 mg, 303 µmol, 1.00 equiv) and celecoxib (203 mg, 666 µmol, 2.20 equiv) pre-mixed for 30 min with K_3PO_4 (129 mg, 606 µmol, 2.00 equiv), ethyl 2-((*tert*-butoxycarbonyl)amino)-2-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonamido)acetate **2p** was obtained as a white amorphous solid (66.0 mg, 113 µmol, 37% yield) after purification by column chromatography on silica using gradient from 0 to 30% EtOAc in pentane.

R_f = 0.22 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H, Ar*H*), 7.49 – 7.40 (m, 2H, Ar*H*), 7.22 – 7.14 (m, 2H, Ar*H*), 7.13 – 7.08 (m, 2H, Ar*H*), 6.73 (s, 1H, C$H_{Pyrazole}$), 6.11 (s, 1H, N$H_{sulfonamide}$), 5.53 (s, 1H, N*H*), 5.15 (d, *J* = 7.1 Hz, 1H, C*H*N), 4.31 – 4.12 (m, 2H, OCH_2CH_3), 2.38 (s, 3H, CH_3), 1.36 (s, 9H, C(CH_3)$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.53.
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 154.6, 145.3, 144.2 (q, *J* = 38.7 Hz), 142.8, 140.3, 139.9, 129.9, 128.8, 128.2, 125.8, 125.5, 121.2 (q, *J* = 270.0 Hz), 106.5, 81.6, 63.2, 61.7, 28.2, 21.5, 14.1.
IR (ν_{max}, cm^{-1}) 3361 (w), 3293 (w), 2983 (w), 2929 (w), 1749 (m), 1685 (m), 1521 (m), 1509 (m), 1473 (m), 1450 (m), 1372 (m), 1345 (m), 1305 (m), 1282 (m), 1237 (s), 1163 (s), 1133 (s), 1094 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{29}F_3N_4NaO_6S^+$ 605.1652; Found 605.1670.

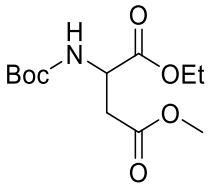
Ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)propanoate (2q)



Following GP1, using **1aa'** (78.7 mg, 286 µmol, 1.00 equiv) and trimethylsilyl azide (72.5 mg, 82.7 µL, 629 µmol, 2.20 equiv), ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)propanoate **2q** was obtained as a yellow oil (14.7mg, 57.0 µmol, 20% yield) after purification by column chromatography on silica using gradient from 0 to 20% EtOAc in pentane.

R_f = 0.39 (Pentane/ethyl acetate 90:10).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H, N*H*), 4.36 – 4.24 (m, 2H, OCH_2CH$_3$), 1.67 (s, 3H, CH_3), 1.45 (s, 9H, CH_{3Boc}), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 153.8, 73.8, 63.0, 28.3 (Boc+ CH_3), 14.2. (1C unresolved)
IR (ν_{max}, cm^{-1}) 3404 (m), 3343 (m), 2123 (s), 1714 (s), 1704 (s), 1685 (m), 1535 (m), 1518 (s), 1286 (m), 1267 (s), 1250 (s), 1156 (s), 1109 (s), 1020 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{18}N_4NaO_4^+$ 281.1220; Found 281.1230.

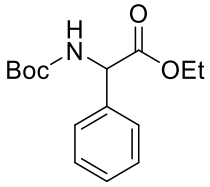
1-Ethyl 4-methyl (*tert*-butoxycarbonyl)aspartate (2r)



Following GP1, using **1a'** (77.2 mg, 295 µmol, 1.00 equiv) and tert-butyl-(1-methoxyethenoxy)-dimethylsilane (122 mg, 142 µL, 650 µmol, 2.20 equiv), 1-ethyl 4-methyl (*tert*-butoxycarbonyl)aspartate **2r** was obtained as a transparent oil (42.7.0 mg, 149 µmol, 49% yield) after purification by column chromatography on silica using gradient from 0 to 25% EtOAc in pentane.

R_f = 0.5 (Pentane/ethyl acetate 80:20).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, *J* = 8.6 Hz, 1H, N*H*), 4.55 (dt, *J* = 9.2, 4.7 Hz, 1H, NC*H*), 4.21 (qd, *J* = 7.1, 1.6 Hz, 2H, OCH_2CH$_3$), 3.69 (s, 3H, OCH_3), 3.00 (dd, *J* = 16.9, 4.7 Hz, 1H, CH_2COOMe), 2.82 (dd, *J* = 16.9, 4.7 Hz, 1H, CH_2COOMe), 1.45 (s, 9H, CH_{3Boc}), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 171.2, 155.6, 80.2, 61.9, 52.1, 50.2, 36.9, 28.4, 14.2.
IR (ν_{max}, cm^{-1}) 2983 (w), 2957 (w), 1757 (s), 1742 (s), 1722 (s), 1507 (m), 1444 (m), 1368 (m), 1291 (m), 1217 (m), 1170 (s), 1026 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{21}NNaO_6^+$ 298.1261; Found 298.1271.

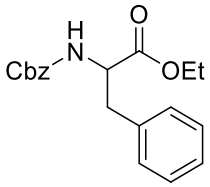
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate (2s)



Following GP1, using **1a'** (80.3 mg, 307 µmol, 1.00 equiv)) and phenylmagnesium bromide 3 M in diethyl ether (61.3 mg, 113 µL, 338 µmol, 3.00 M, 1.10 equiv) at – 20 °C, ethyl 2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate **2s** was obtained as a white solid (36.0 mg, 129 µmol, 42% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane.

R_f = 0.23 (Pentane/ethyl acetate 95:5).
Mp: 61 – 61.8 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H, Ar*H*), 5.55 (d, *J* = 7.1 Hz, 1H, N*H*), 5.30 (d, *J* = 7.6 Hz, 1H, C*H*Ph), 4.28 – 4.08 (m, 2H, OCH_2CH$_3$), 1.43 (s, 9H, CH_{3Boc}), 1.21 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.0, 137.2, 129.0, 128.5, 127.2, 80.3, 61.9, 57.8, 28.5, 14.2.
IR (ν_{max}, cm^{-1}) 3448 (w), 3353 (w), 2982 (w), 2367 (w), 1742 (s), 1714 (s), 1519 (m), 1495 (s), 1454 (m), 1392 (m), 1367 (m), 1322 (m), 1251 (m), 1172 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{21}NNaO_4^+$ 302.1363; Found 302.1363.

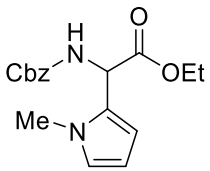
Ethyl ((benzyloxy)carbonyl)phenylalaninate (2t)



Following GP2, using **1b'** (90.3 mg, 306 µmol, 1.00 equiv), benzylzinc bromide in THF 0.5 M (51.4 mg, 435 µL, 218 µmol, 0.50 M, 2.20 equiv), ethyl ((benzyloxy)carbonyl)phenylalaninate **2t** was obtained as a white yellow oil (54.0 mg, 165 µmol, 54% yield) after purification by column chromatography on silica using gradient from 0 to 10% EtOAc in pentane and then from 0 to 1% EtOAc in DCM.

$\mathbf{R_f}$ = 0.26 (Pentane/ethyl acetate 90:10).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 6H, Ar*H*), 7.28 – 7.22 (m, 2H, Ar*H*), 7.14 – 7.08 (m, 2H, Ar*H*), 5.23 (d, *J* = 8.3 Hz, 1H, N*H*), 5.10 (d, *J* = 2.5 Hz, 2H, ArCH_2), 4.64 (dt, *J* = 8.3, 5.9 Hz, 1H, NHCHC$_{Bz}$), 4.21 – 4.09 (m, 2H, OCH_2CH$_3$), 3.20 – 3.04 (m, 2H, ArCH_2), 1.23 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 155.7, 136.4, 135.9, 129.5, 128.7, 128.7, 128.3, 128.2, 127.2, 67.1, 61.6, 55.0, 38.4, 14.2.
IR (ν_{max}, cm^{-1}) 3432 (w), 3375 (w), 3342 (w), 3062 (w), 3033 (w), 2982 (w), 2943 (w), 1743 (s), 1724 (s), 1522 (m), 1502 (m), 1455 (m), 1347 (m), 1256 (m), 1213 (s), 1083 (m), 1056 (m), 1029 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}NNaO_4^+$ 350.1363; Found 350.1369.

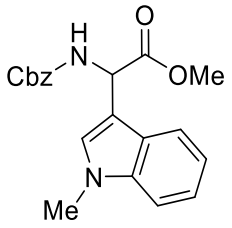
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1*H*-pyrrol-2-yl)acetate (2u)



Following GP2, using **1b'** (90.0 mg, 305 µmol, 1.00 equiv), 1-methylpyrrole (54.4 mg, 59.8 µL, 671 µmol, 2.20 equiv) and TMSOTf (81.3 mg, 66.2 µL, 366 µmol, 1.20 equiv), ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrrol-2-yl)acetate **2u** was obtained as a white amorphous solid (47.0 mg, 149 µmol, 49% yield) after purification by column chromatography on silica using gradient from 0 to 25% EtOAc in pentane.

$\mathbf{R_f}$ = 0.22 (Pentane/ethyl acetate 90:10).
Mp: 112.9 – 113.6 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H, Ar*H*), 6.60 (t, *J* = 2.3 Hz, 1H, Ar*H*N), 6.04 (qd, *J* = 3.8, 2.2 Hz, 2H, Ar*H*), 5.47 (q, *J* = 8.3 Hz, 2H, N*H* and NC*H*Ar), 5.12 (s, 2H, ArCH_2), 4.38 – 4.14 (m, 2H, OCH_2CH$_3$), 3.67 (s, 3H, $CH_{3pyrrole}$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 155.7, 136.3, 128.7, 128.4, 128.2, 127.33, 123.74, 107.8, 107.5, 67.3, 62.1, 50.7, 34.2, 14.2.
IR (ν_{max}, cm^{-1}) 3433 (m), 3392 (m), 3360 (m), 2981 (w), 2938 (m), 2851 (w), 2810 (w), 1743 (s), 1719 (s), 1498 (m), 1465 (w), 1368 (m), 1329 (m), 1250 (m), 1223 (m), 1200 (m), 1163 (m), 1098 (w), 1051 (m), 1029 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_4^+$ 339.1315; Found 339.1326.

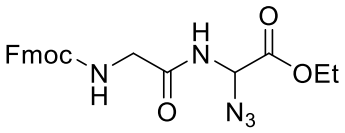
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1*H*-indol-2-yl)acetate (2v)



Following GP2, using **1b'** (89.0 mg, 301 µmol, 1.00 equiv), 1-methylindole (87.0 mg, 82.8 µL, 663 µmol, 2.20 equiv) + TMSOTf (80.4 mg, 65.5 µL, 362 µmol, 1.20 equiv), ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-indol-2-yl)acetate **2v** was obtained as a yellowish oil (58.0 mg, 158 µmol, 53% yield) after purification by column chromatography on silica using gradient from 0 to 30% EtOAc in pentane.

$\mathbf{R_f}$ = 0.14 (Pentane/ethyl acetate 85:15).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.37 – 7.29 (m, 6H, Ar*H*), 7.29 – 7.24 (m, 1H, Ar*H*), 7.19 – 7.09 (m, 2H, Ar*H*), 5.71 (d, *J* = 7.5 Hz, 1H, N*H*), 5.64 (d, *J* = 7.4 Hz, 1H, C*H*C_{indole}), 5.12 (d, *J* = 5.4 Hz, 2H, ArCH_2), 4.27 (dq, *J* = 10.9, 7.2 Hz, 1H, OCH_2CH_3), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H, OCH_2CH_3), 3.76 (s, 3H, $CH_{3indole}$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 155.7, 137.3, 136.4, 128.6, 128.2, 128.0, 126.0, 122.4, 120.0, 119.4, 109.9, 109.7, 67.1, 61.9, 51.4, 33.0, 14.2.
IR (ν_{max}, cm^{-1}) 3396 (m), 3363 (m), 3339 (m), 3065 (w), 2983 (w), 2940 (w), 1743 (s), 1717 (s), 1503 (m), 1484 (m), 1372 (m), 1336 (m), 1332 (m), 1281 (m), 1218 (m), 1199 (m), 1050 (m), 1027 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_4^+$ 389.1472; Found 389.1467.

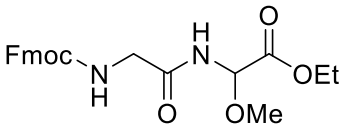
Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-azidoacetate (6a)



Following GP1, using **1h'** (87.9 mg, 200 µmol, 1.00 equiv) and trimethylsilyl azide (50.6 mg, 58.3 µL, 439 µmol, 2.20 equiv), ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-azidoacetate **6a** was obtained as a white amorphous solid (47.0 mg, 111 µmol, 56% yield) after purification by column chromatography on silica using gradient from 20 to 50% EtOAc in pentane.

R_f = 0.44 (Pentane/ethyl acetate 65:35).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.59 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.41 (tt, *J* = 7.5, 0.9 Hz, 2H, Ar*H*), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 7.08 (s, 1H, N*H*), 5.77 (d, *J* = 8.0 Hz, 1H, C*H*N_3), 5.35 (s, 1H, N*H*), 4.46 (d, *J* = 6.9 Hz, 2H, ArCHC*H*$_2$), 4.31 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$$CH_3$), 4.24 (t, *J* = 6.9 Hz, 1H, ArC*H*CH_2), 3.98 (s, 2H, NHC*H*$_2$CO), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 166.5, 156.8, 143.8, 141.5, 127.9, 127.3, 125.2, 120.2, 67.6, 64.7, 63.5, 47.2, 44.6, 14.2.
IR (ν_{max}, cm^{-1}) 3414 (m), 3298 (m), 3066 (m), 2937 (m), 2853 (m), 2114 (s), 1740 (s), 1707 (s), 1685 (s), 1520 (s), 1450 (m), 1240 (s), 1213 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}N_5NaO_5^+$ 446.1435; Found 446.1437.

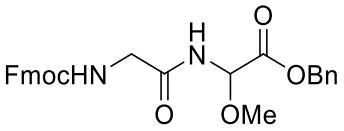
Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6b)



Following GP1, using **1h'** (86.2 mg, 196 µmol, 1.00 equiv) and methanol (13.8 mg, 17.4 µL, 431 µmol, 2.20 equiv), ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate **6b** was obtained as a white amorphous solid (40.0 mg, 97.0 µmol, 50% yield) after purification by column chromatography on silica using gradient from 20 to 50% EtOAc in pentane.

R_f = 0.42 (Pentane/ethyl acetate 50:50).
^{1}H NMR (400 MHz, DMSO) δ 8.89 (d, *J* = 9.0 Hz, 1H, N*H*), 7.90 (dt, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.72 (dd, *J* = 7.4, 1.1 Hz, 2H, Ar*H*), 7.57 (t, *J* = 6.2 Hz, 1H, N*H*), 7.42 (td, *J* = 7.5, 1.2 Hz, 2H, Ar*H*), 7.33 (td, *J* = 7.4, 1.2 Hz, 2H, Ar*H*), 5.34 (d, *J* = 9.0 Hz, 1H, C*H*OMe), 4.30 (d, *J* = 7.7 Hz, 2H, ArCHC*H*$_2$), 4.27 – 4.21 (m, 1H, ArC*H*CH_2), 4.15 (qd, *J* = 7.1, 1.0 Hz, 2H, OC*H*$_2$$CH_3$), 3.82 – 3.62 (m, 2H, NHC*H*$_2$CO), 3.25 (s, 3H, OC*H*$_3$), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$).
^{13}C NMR (101 MHz, DMSO) δ 170.1, 167.6, 156.5, 143.8, 140.7, 127.6, 127.1, 125.2, 120.1, 78.0, 65.7, 61.1, 55,0, 46.6, 43.1, 13.9.
IR (ν_{max}, cm^{-1}) 3338 (w), 3060 (w), 2951 (m), 2926 (s), 2854 (m), 1739 (s), 1724 (s), 1688 (s), 1519 (s), 1451 (m), 1371 (m), 1248 (s), 1208 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{24}N_2NaO_6^+$ 435.1527; Found 435.1526.

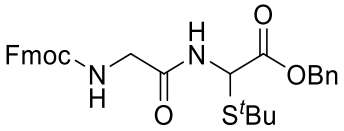
Benzyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6c)



Following GP1, using **1l'** (102 mg, 203 µmol, 1.00 equiv) and methanol (13.0 mg, 16.4 µL, 406 µmol, 2.00 equiv), **6c** was obtained as a white amorphous solid (57.0 mg, 120 µmol, 59% yield) after purification by column chromatography on silica using gradient from 0 to 60% EtOAc in pentane.

R_f = 0.31 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.59 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.43 – 7.28 (m, 9H, Ar*H*), 6.95 (d, *J* = 9.1 Hz, 1H, N*H*), 5.57 (d, *J* = 9.1 Hz, 1H, C*H*OMe), 5.39 (s, 1H, N*H*), 5.22 (d, *J* = 3.1 Hz, 2H, CH_2Ph), 4.43 (d, *J* = 6.9 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.22 (t, *J* = 6.9 Hz, 1H, $C_{Fmoc}H$CH$_2$OCON), 3.95 (q, *J* = 4.2 Hz, 2H, NHCH_2CON), 3.45 (s, 3H, OCH_3).
^{13}C NMR (101 MHz, $CDCl_3$) 169.7, 167.7, 156.7, 143.8, 141.5, 134.8, 128.9, 128.8, 128.6, 127.9, 127.3, 125.2, 120.2, 78.5, 68.1, 67.5, 57.1, 47.2, 44.7.
IR (ν_{max}, cm^{-1}) 3397 (w), 3308 (m), 3062 (w), 2951 (w), 1748 (m), 1726 (s), 1689 (s), 1519 (s), 1451 (m), 1255 (m), 1212 (m), 1108 (s), 1086 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{26}N_2NaO_6^+$ 497.1683; Found 497.1690.

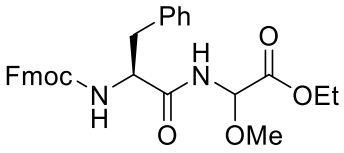
Benzyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-(*tert*-butylthio)acetate (6d)



Following GP1, using **1l'** (101 mg, 200 µmol, 1.00 equiv), 2-methylpropane-2-thiol (39.7 mg, 49.6 µL, 440 µmol, 2.20 equiv), **6d** was obtained as a white amorphous solid (60.0 mg, 113 µmol, 56% yield) after purification by column chromatography on silica using gradient from 0 to 40% EtOAc in pentane.

R_f = 0.29 (Pentane/ethyl acetate 65:35).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.59 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.42 – 7.26 (m, 9H, Ar*H*), 6.70 (d, *J* = 8.6 Hz, 1H, N*H*), 5.56 (d, *J* = 8.6 Hz, 1H, C*H*S), 5.39 (s, 1H, N*H*), 5.19 (s, 2H, CH_2Ph), 4.42 (d, *J* = 6.8 Hz, 2H, CHC$H_{2,Fmoc}$OCON) , 4.22 (t, *J* = 7.0 Hz, 1H, $C_{Fmoc}H$CH$_2$OCON), 3.99 – 3.75 (m, 2H, NHCH_2CON), 1.38 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 167.8, 156.6, 143.9, 141.5, 135.1, 128.7, 128.6, 128.3, 127.9, 127.3, 125.2, 120.2, 67.9, 67.5, 52.4, 47.2, 46.2, 44.7, 31.3.
IR (ν_{max}, cm^{-1}) 3363 (w), 3303 (w), 3062 (w), 2961 (w), 2370 (w), 2341 (w), 1739 (s), 1674 (s), 1522 (s), 1452 (m), 1322 (m), 1251 (m), 1213 (m), 1157 (m), 1105 (w).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{32}N_2NaO_5S^+$ 555.1924; Found 555.1929.

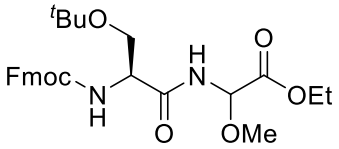
Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6e)



Following GP1, using **1m'** (118 mg, 222 µmol, 1.00 equiv) and methanol (12.8 mg, 16.2 µL, 400 µmol, 1.80 equiv), ethyl 2-((S)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)-2-methoxyacetate **6e** was obtained as a white amorphous solid (59.0 mg, 117 µmol, 53% yield) (mixture of diastereoisomers, 2.2:1.0 dr determined by NMR with the crude NMR, signal of the OCH_3 at 3.42 and 3.31 ppm) after purification by column chromatography on silica using gradient from 20 to 55% EtOAc in pentane.

R_f = 0.41 (Pentane/ethyl acetate 55:45).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (ddt, *J* = 7.5, 2.0, 0.9 Hz, 2H, Ar*H*), 7.57 – 7.49 (m, 2H, Ar*H*), 7.40 (tp, *J* = 7.6, 1.0 Hz, 2H, Ar*H*), 7.35 – 7.14 (m, 7H, Ar*H*), 6.78 (s, 1H, N*H*), 5.45 (dd, *J* = 13.2, 9.1 Hz, 1H, C*H*OMe), 5.33 – 5.22 (m, 1H, N*H*), 4.55 – 4.40 (m, 2H, CHC$H_{2,Fmoc}$OCON), 4.34 (d, *J* = 8.3 Hz, 1H, NHC*H*), 4.26 – 4.13 (m, 3H, OCH_2CH$_3$, $C_{Fmoc}H$CH$_2$OCON), 3.39 (s, 2H, OCH_3, dia maj), 3.33 (s, 1H, OCH_3, dia min), 3.12 (s, 2H, CH_2Ph), 1.32 – 1.24 (m, 3H, OCH$_2$CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 167.6 (dia min), 167.4 (dia maj), 156.0, 143.9 (rot 1), 143.8 (rot 2), 141.5, 136.0, 129.4, 129.0 (dia min), 129.0 (dia maj), 127.9, 127.4 (dia min), 127.4 (dia 1), 127.3, 125.2 (rot 1), 125.1 (rot2), 120.2, 78.5 (dia min), 78.5 (dia maj), 67.4 (dia min), 67.3 (dia maj), 62.5 (dia min), 62.4 (dia maj), 56.8 (dia min), 56.7 (dia maj), 56.4, 47.3 (dia min), 47.2 (dia maj), 38.4, 14.2.
IR (ν_{max}, cm^{-1}) 3062 (w), 3040 (w), 2982 (w), 2934 (w), 1748 (m), 1700 (m), 1670 (s), 1531 (m), 1509 (m), 1449 (m), 1254 (m), 1206 (m), 1105 (m), 1080 (m), 1031 (m).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{30}N_2NaO_6^+$ 525.1996; Found 525.2004.

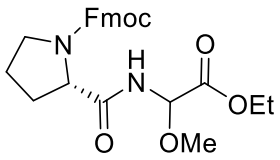
Ethyl 2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(*tert*-butoxy)propanamido)-2-methoxyacetate (**6f**)



Following GP1, using **1n'** (108 mg, 205 µmol, 1.00 equiv) and methanol (14.5 mg, 18.3 µL, 451 µmol, 2.20 equiv), ethyl 2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(*tert*-butoxy)propanamido)-2-methoxyacetate **6f** was obtained as a white amorphous solid (32.0 mg, 64.2 µmol, 31% yield) (mixture of diastereoisomers, 1: 1.42 ratio based on the peak at 1.23 and 1.22 ppm for the O^{t}Bu after purification) after purification by column chromatography on silica using gradient from 0 to 50% EtOAc in pentane.

R_f = 0.46 (Pentane/ethyl acetate 60:40).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.60 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.40 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.32 (t, *J* = 7.4 Hz, 2H, Ar*H*), 5.73 (s, 1H, N*H*), 5.54 (t, *J* = 8.9 Hz, 1H, C*H*OMe), 4.42 (d, *J* = 7.1 Hz, 2H, CHC$H_{2,Fmoc}$OCON), 4.37 – 4.29 (m, 1H, NHC*H*) 4.25 (dt, *J* = 11.4, 7.0 Hz, 3H, $C_{Fmoc}H$CH$_2$OCON, OCH_2CH$_3$), 3.86 (dd, *J* = 8.8, 3.9 Hz, 1H, CH_2O^{t}Bu), 3.49 – 3.37 (m, 4H, OCH_3, CH_2O^{t}Bu), 1.32 (td, *J* = 7.0, 4.2 Hz, 3H, OCH$_2$CH_3), 1.23 (s, 3.43H, OC(CH_3)$_{3\ dia\ min}$), 1.22 (s, 4.72H, OC(CH_3)$_{3\ dia\ maj}$). One NH is not resolved.
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (dia maj), 171.3 (dia min), 167.6 (dia maj), 167.6 (dia min), 156.2, 143.9, 143.8, 141.4, 127.9, 127.2, 125.2, 120.1, 78.6 (dia maj), 78.4 (dia min), 74.7 (dia min), 74.6 (dia maj), 67.4, 62.3, 61.8, 56.6 (dia min), 56.5 (dia maj), 54.7, 47.3, 27.4, 14.2 (dia maj), 14.2 (dia min).
IR (ν_{max}, cm^{-1}) 3047 (w), 2975 (w), 2944 (w), 2888 (w), 2835 (w), 1743 (m), 1721 (m), 1683 (m), 1505 (m), 1451 (w), 1333 (w), 1213 (m), 1195 (m), 1102 (m), 1084 (m), 1029 (w).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{34}N_2NaO_7^+$ 521.2258; Found 521.2269.

(9*H*-fluoren-9-yl)methyl (2*S*)-2-((2-ethoxy-1-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate-6 (6g)

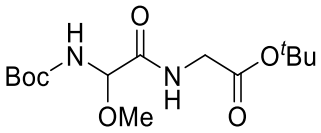


Following GP1, using **1o'** (88.9 mg, 180 µmol, 1.00 equiv) and methanol (10.1 mg, 12.8 µL, 316 µmol, 1.76 equiv), (9*H*-fluoren-9-yl)methyl (2*S*)-2-((2-ethoxy-1-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate-6 **6g** was obtained as a white amorphous solid (50.0 mg, 110 µmol, 61% yield) (mixture of diastereoisomers, 1.1:1.0 dr determined by NMR with the crude NMR, signal of the OCH_3 at 3.42 and 3.33 ppm) after purification by column chromatography on silica using gradient from 0 to 60% EtOAc in pentane.

R_f = 0.26 (Pentane/ethyl acetate 50:50).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.62 (s, 2H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.34 (t, *J* = 7.6 Hz, 2H, Ar*H*), 5.53 (d, *J* = 9.6 Hz, 1H, C*H*OMe), 4.53 – 4.38 (m, 3H, CHC$H_{2,Fmoc}$OCON, FmocNC*H*), 4.32 – 4.20 (m, 3H, C_{Fmoc}*H*CH_2OCON, OCH_2CH_3), 3.59 – 3.33 (m, 2H, NC$H_{2,Pro}$), 3.46 (s, 1.53H, OC$H_{3,}$ dia maj), 3.43 (s, 1.26H, OC$H_{3,}$ dia min), 2.43 – 2.14 (m, 2H, C$H_{2,Pro}$), 2.01 (d, *J* = 42.2 Hz, 2H, C$H_{2,Pro}$), 1.32 – 1.28 (m, 3H, OCH_2CH_3).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 167.7, 156.1, 143.8, 141.3, 127.8 (dia maj), 127.8 (dia min), 127.1 (dia maj), 127.1 (dia min), 125.1 (dia maj), 125.0 (dia min), 120.0, 78.5, 67.9, 62.2, 60.7, 56.5, 47.2 (dia maj), 47.1 (dia min), 29.7 (dia maj), 29.7 (dia min), 24.6, 22.7, 14.0.
IR (ν_{max}, cm^{-1}) 2961 (m), 2924 (m), 1747 (m), 1699 (s), 1685 (s), 1517 (m), 1448 (m), 1417 (s), 1352 (m), 1260 (m), 1195 (m), 1107 (s), 1091 (s), 1023 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}N_2NaO_6^+$ 475.1840; Found 475.1841.

(The presence of rotamers is not allowing to resolve all peaks.)

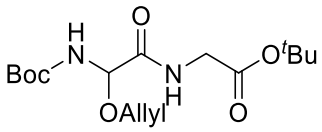
***tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)glycinate (6h)**



Following GP3, using **1i'** (68.5 mg, 198 µmol, 1.00 equiv) and methanol (25.3 mg, 32.0 µL, 791 µmol, 4.00 equiv)**,** *tert*-butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)glycinate **6h** was obtained as a transparent oil (44.0 mg, 138 µmol, 70% yield) after purification by column chromatography on silica using gradient from 20 to 50% EtOAc in pentane.

R_f = 0.37 (Pentane/ethyl acetate 65:35).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 5.2 Hz, 1H, N*H*), 5.50 (s, 1H, N*H*), 5.27 (d, *J* = 8.9 Hz, 1H, C*H*OMe), 3.95 (d, *J* = 5.3 Hz, 2H, NHCH_2COO^{t}Bu), 3.44 (s, 3H, OCH_3), 1.47 (s, 9H, CH_{3Boc}), 1.46 (s, 9H, CH_{3Boc}).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 168.0, 155.8, 82.7, 81.2, 80.7, 55.6, 42.1, 28.4, 28.2.
IR (ν_{max}, cm^{-1}) 2979 (w), 2938 (w), 2835 (w), 1743 (m), 1725 (m), 1687 (s), 1516 (m), 1368 (m), 1249 (m), 1235 (m), 1159 (s), 1087 (m).
HRMS (Nanochip-based ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{14}H_{27}N_2O_6^+$ 319.1864; Found 319.1864.

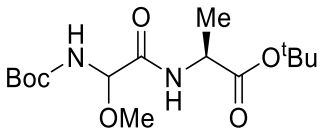
***tert*-Butyl (2-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)acetyl)glycinate (6i)**



Following GP3, using **1i'** (69.9 mg, 202 µmol, 1.00 equiv) and allyl alcohol (46.9 mg, 54.9 µL, 807 µmol, 4.00 equiv), *tert*-Butyl (2-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)acetyl)glycinate **6i** was obtained as a transparent oil (59.0 mg, 171 µmol, 85% yield) after purification by column chromatography on silica using gradient from 20 to 50% EtOAc in pentane.

R_f = 0.40 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H, N*H*), 5.99 – 5.88 (m, 1H, CH_2=C*H*-CH_2), 5.49 (s, 1H, N*H*), 5.40 (d, *J* = 8.9 Hz, 1H, C*H*OAllyl), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1H, C*H*$_2$=CH-CH_2), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H, C*H*$_2$=CH-CH_2), 4.26 – 4.08 (m, 2H, CH_2=CH-C*H*$_2$), 3.89 (dd, *J* = 5.2, 0.9 Hz, 2H, NHC*H*$_2$COO^{t}Bu), 1.48 (s, 9H, C*H*$_{3Boc}$), 1.46 (s, 9H, C*H*$_{3Boc}$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 168.1, 155.8, 133.7, 118.2, 82.7, 80.7, 79.6, 69.4, 42.2, 28.4, 28.2.
IR (ν_{max}, cm^{-1}) 3415 (m), 3333 (m), 3009 (w), 2982 (w), 2935 (w), 1725 (s), 1692 (s), 1685 (s), 1509 (m), 1368 (m), 1249 (m), 1231 (m), 1159 (s), 1062 (m), 1025 (m).
HRMS (Nanochip-based ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{28}N_2NaO_6^+$ 367.1840; Found 367.1840.

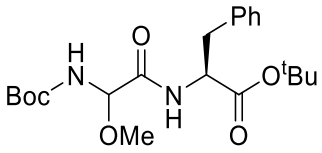
***tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)-*L*-alaninate (6j)**



Following GP3, using **1j'** (75.0 mg, 208 µmol, 1.00 equiv)and methanol (26.7 mg, 33.7 µL, 832 µmol, 4.00 equiv)**,** *tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)-*L*-alaninate **6j** was obtained as a transparent oil (49.0 mg, 147 µmol, 71% yield) (mixture of diastereoisomers, 1.1:1.0 dr determined by NMR with the crude NMR, signal of the CH_3 Ala at 1.40 and 1.38 ppm) after purification by column chromatography on silica using gradient from 0 to 40% EtOAc in pentane. (After purification dr is 1.02:1.00 based on the signal of the CH_3 Ala at 1.40 and 1.38 ppm)

R_f = 0.44 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 13.0, 7.6 Hz, 1H, N*H*), 5.50 (d, *J* = 11.1 Hz, 1H, N*H*), 5.24 (dd, *J* = 16.5, 9.0 Hz, 1H,C*H*(OMe)), 4.43 (p, *J* = 7.1 Hz, 1H, C(=O)NHC*H*MeCO$_2$^{t}Bu), 3.43 (s, 1.55 H, OC*H*$_3$, Dia min), 3.43 (s, 1.58H, OC*H*$_3$,Dia maj), 1.47 (d, *J* = 1.2 Hz, 9H, C(C*H*$_3$)$_3$, Mixture of dia), 1.46 (s, 9H, C(C*H*$_3$)$_3$), 1.40 (d, *J* = 2.1 Hz, 1.66H, C*H*$_3$, Dia min), 1.38 (d, *J* = 2.1 Hz, 1.74H, C*H*$_3$,Dia maj).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 167.4 (Dia 1), 167.2 (Dia 2), 155.8, 82.4, 81.1, 80.7, 55.7 (Dia 1), 55.4 (Dia 2), 48.9 (Dia 1), 48.8 (Dia 2), 28.4, 28.1, 18.6 (Dia 1), 18.6 (Dia 2).
IR (ν_{max}, cm^{-1}) 3363 (w), 2981 (w), 2938 (w), 1730 (s), 1686 (s), 1677 (m), 1511 (m), 1369 (m), 1249 (m), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{28}N_2NaO_6^+$ 355.1840; Found 355.1839.

***tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)-*L*-phenylalaninate (6k)**



Following GP3, using **1k'** (75.0 mg, 208 µmol, 1.00 equiv)and methanol (26.7 mg, 33.7 µL, 832 µmol, 4.00 equiv)**,** *tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)-*L*-alaninate **6k** was obtained as a transparent oil (56.0 mg, 137 µmol, 80% yield) (mixture of diastereoisomers, 1.14:1 dr determined by NMR, signal of the CH_3 OMe at 3.38 and 3.36 ppm after purification) after purification by column chromatography on silica using gradient from 0 to 40% EtOAc in pentane.

R_f = 0.44 (Pentane/ethyl acetate 70:30).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 3H, Ar*H*), 7.16 (td, *J* = 8.0, 1.6 Hz, 2H, Ar*H*), 6.97 (t, *J* = 9.7 Hz, 1H, N*H*), 5.48 (s, 1H, N*H*), 5.21 (t, *J* = 10.4 Hz, 1H, C*H*OMe), 4.72 (ddt, *J* = 10.0, 7.9, 6.2 Hz, 1H, C(=N)C*H*C(O)O^{t}Bu), 3.38 (s, 1.74H, dia maj, OCH_3), 3.38 (s, 1.19H, dia min, OCH_3), 3.17 – 2.99 (m, 2H, CH_2Ph), 1.45 (s, 5.02H, dia maj, C(CH_3)$_3$), 1.45 (s, 4.00H, dia min, C(CH_3)$_3$), 1.41 (s, 5.40H, dia maj, C(CH_3)$_3$), 1.41 (s, 3.38H, dia min, C(CH_3)$_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (Dia 1), 170.2 (Dia 2), 167.5 (Dia 2), 167.3 (Dia 1), 155.9, 136.1, 129.7 (Dia 1), 129.6 (Dia 2), 128.6 (Dia 2), 128.6 (Dia 1), 127.2, 82.8 (dia 1), 82.7 (dia 2), 81.1, 80.7, 55.6 (Dia 1), 55.4 (Dia 2), 53.8 (Dia 2), 53.7 (Dia 1), 38.4 (Dia 1), 38.1 (Dia 2), 28.4, 28.1.
IR (ν_{max}, cm^{-1}) 3363 (w), 2981 (w), 2938 (w), 1730 (s), 1686 (s), 1677 (m), 1511 (m), 1369 (m), 1249 (m), 1158 (s).
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{28}N_2NaO_6^+$ 355.1840; Found 355.1839.

2.5 Application on SPPS

HPLC-MS analysis

HPLC-MS measurements were performed on an Agilent 1290 Infinity HPLC system with a G4226a 1290 Autosampler, a G4220A 1290 Bin Pump and a G4212A 1290 DAD detector, connected to a 6130 Quadrupole LC/MS, coupled with a Waters XBridge C18 column (250 x 4.6 mm, 5 µm). Water:acetonitrile 95:5 (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase, at a flow rate of 0.6 mL.min-1 . The gradient was programmed as follows:

Method 1. 100% A to 100% B in 20 minutes then isocratic for 5 minutes.

The column temperature was set up to 25 °C. Low-resolution mass spectrometric measurements were acquired using the following parameters: positive electrospray ionization (ESI), temperature of drying gas = 350 °C, flow rate of drying gas = 12 L. min^{-1}, pressure of nebulizer gas = 60 psi, capillary voltage = 2500 V and fragmentor voltage = 70 V.

Preparative HPLC

Preparative RP-HPLC were performed on an Agilent 1260 HPLC system with a G2260A 1260 Prep ALS Autosampler, a G1361a 1260 Prep Pump, a G1365C 1260 MWD detector and a G1364B 1260 FC-PS collector, coupled with a Waters XBridge semi-preparative C18 column (19 x 150 mm, 5 µm). Water (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase at a flow rate of 20 $mL.min^{-1}$.

Method 2: 100% A to 100% B in 20 minutes then isocratic for 5 minutes.

Solid-Phase Peptide Synthesis (SPPS):

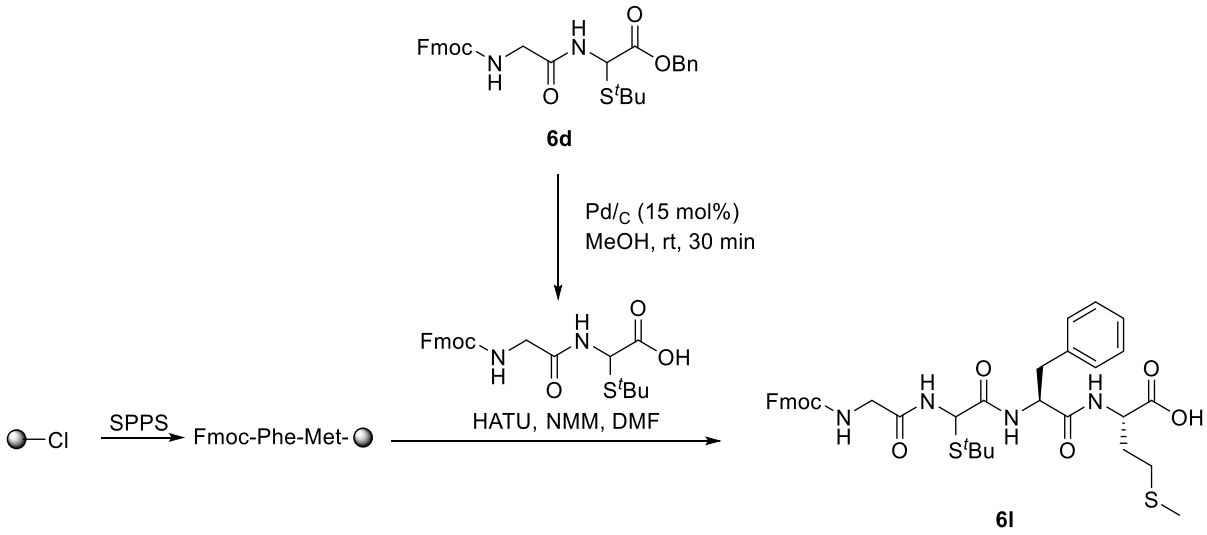
Peptides were synthesized by hand using standard Fmoc SPPS-chemistry and 2-chlorotrityl chloride resin (1.38 mmol/g, 100-200 mesh). The first amino acid was loaded on the resin by incubation of the Fmoc-protected monomer (3 equiv of the number of active sites on the resin), DIPEA (4 equiv) in dichloromethane for 2 h. Each coupling cycle was initiated by Fmoc deprotection achieved by shaking the resin with 800 µL of 20% v/v 4 piperidine in dimethylformamide (DMF), over 10 minutes twice. Then the resin was washed with DMF (1500 µL x4). The coupling was carried out by shaking 2-chlorotrityl chloride resin with a Fmoc-protected monomer (5.0 equiv.), HATU (5.0 equiv.), N-Methylmorpholine (10.0 equiv.), in DMF (1.3 mL), over 60 minutes. The synthesis was finished by deprotection of Fmoc using 20% v/v piperidine in dimethylformamide at 400 rpm, over 10 minutes two times. The N-terminus was either left unprotected. Next, washing steps were performed with dimethylformamide (5 x 1 mL). Finally, resin was dried with dichloromethane (5 x 3 mL).

Peptide cleavage and deprotection:

Peptides without protecting groups

Peptides were deprotected and cleaved from the resin by treatment with a 20% solution of HFIP in DCM. The resulting mixture was shaken for 1 hour at room temperature. The resin was removed by filtration and peptides were precipitated in cold diethyl ether (50 mL), followed by a 2 hours incubation at -20 °C. Peptides were pelleted by centrifugation at 4000 rpm, for 5 minutes. Finally, the mother liquors were carefully removed.

Peptide Fmoc-Gly-Gly(S^{t}Bu)-Phe-Met (6l)



In a microwave vial, **6d** (46.0 mg, 86.4 µmol, 1.00 equiv) and palladium on charcoal 10% (14.4 mg, 136 µmol, 1.57 equiv) were added. The vial was submitted to vacuum/nitrogen cycle (3x). Then, dry MeOH (1.9 mL) was added to the vial. The mixture was stirred under H_2 atmosphere for 30 min. The reaction mixture was filtered through celite and concentrated. Then, the intermediate was submitted the next step without purification.

The intermediate 0.5M in DMF (37.0 mg, 167 µL, 83.6 µmol, 0.500M, 1.67 equiv) was dissolved in 167uL of DMF. Then, HATU 0.5M in DMF (31.7 mg, 167 µL, 83.5 µmol, 0.500M, 1.67 equiv) and NMP (25.3 mg, 62.5 µL, 250 µmol, 4.00M, 5.00 equiv) were added to the solution. The activated carboxylic acid was added to the Fmoc-Phe-Met on Trt resin (0.05 mmol) and the mixture was stirred for 1 h without protection of atmosphere or light. The peptide was cleaved from the resin by treatment with 20% v/v HFIP in DCM (2 mL). For the isolation, the crude was subjected to Prep-HPLC (mixture of diastereoisomers, 1.12:1 dr based on UV spectra), followed by lyophilization. The desired product **6l** (9.70 mg, 13.5 µmol, 27% yield) was isolated by Method 2.

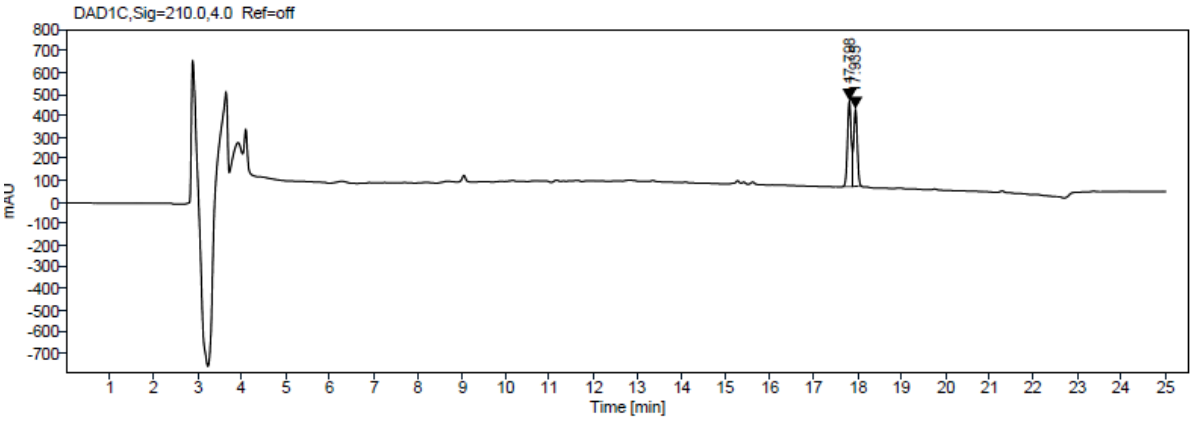


FIGURE 1. HPLC-UV chromatogram (210 nm) of **6i** crude by Method 1

^{1}H NMR (400 MHz, DMSO) δ 12.70 (s, 1H, COO*H*), 8.50 (d, *J* = 8.1 Hz, 0.44 H, N*H*, Dia min), 8.44 (d, *J* = 9.1 Hz, 0.49H, N*H,* Dia min), 8.40 (d, *J* = 9.0 Hz, 0.49H, N*H,* Dia maj),8.32 (d, *J* = 8.0 Hz, 1H, N*H*), 8.15 (d, *J* = 7.8 Hz, 0.62H, N*H*, Dia maj), 7.89 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.71 (dd, *J* = 7.5, 2.3 Hz, 2H, Ar*H*), 7.52 (dt, *J* = 9.2, 6.2 Hz, 1H, N*H*), 7.42 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.33 (ddt, *J* = 7.4, 6.1, 1.4 Hz, 2H, Ar*H*), 7.29 – 7.12 (m, 5H, Ar*H*), 5.54 (d, *J* = 9.0 Hz, 0.52H, C*H*S^{t}Bu, Dia maj), 5.50 (d, *J* = 9.1 Hz, 0.47H, C*H*S^{t}Bu, Dia min),

4.56 – 4.39 (m, 1H, NHCH_{Phe}), 4.36 – 4.30 (m, 1H, CH_{Fmoc}), 4.30 – 4.25 (m, 2H, (CH_2)$_{Fmoc}$), 4.25 – 4.19 (m, 1H, NCH_{Met}), 3.63 (d, *J* = 6.4 Hz, 2H, FmocNHCH_2), 3.02 (td, *J* = 13.9, 4.4 Hz, 1H, CH_2Ph), 2.85 – 2.72 (m, 1H, CH_2Ph), 2.48 – 2.41 (m, 2H, CH_2CH$_2$S), 2.03 (s, 1.74H, CH$_2$SCH_3, Dia maj), 2.03 (s, 1.57H, CH$_2$SCH_3, Dia min), 2.01 – 1.92 (m, 1H, CH_2SCH$_3$), 1.92 – 1.79 (m, 1H, CH_2SCH$_3$), 1.27 (s, 5H, C(CH_3)$_3$, Dia maj), 1.21 (s, 4H, C(CH_3)$_3$, Dia min).

^{13}C NMR (101 MHz, DMSO) δ 173.1 (Dia maj), 173.0 (Dia min), 171.1 (Dia maj), 170.4 (Dia min), 168.2 (Dia min), 168.0 (Dia maj), 167.9 (Dia min), 167.8 (Dia maj), 156.4, 143.8, 140.7, 137.5 (Dia min), 137.38 (Dia maj), 129.4 (Dia min), 129.3(Dia maj), 128.0 (Dia min), 127.9 (Dia maj), 127.6, 127.1, 126.2, 125.25, 120.1, 65.7, 54.0 (Dia min), 53.6 (Dia maj), 53.5 (Dia maj), 53.4 (Dia min), 51.0 (Dia min), 51.0 (Dia maj), 46.6, 44.3, 44.2 (Dia maj), 43.4, 43.4 (Dia maj), 40.2, 40.2, 40.0, 39.9, 39.8, 39.7, 39.5, 39.3, 39.1, 38.9, 37.2, 31.0 (Dia maj), 30.9 (Dia min), 30.8 (dia maj), 30.7 (dia min), 29.6 (dia min), 29.5 (dia maj), 14.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{37}H_{45}N_4O_7S_2^+$ 721.2724; Found 721.2718.

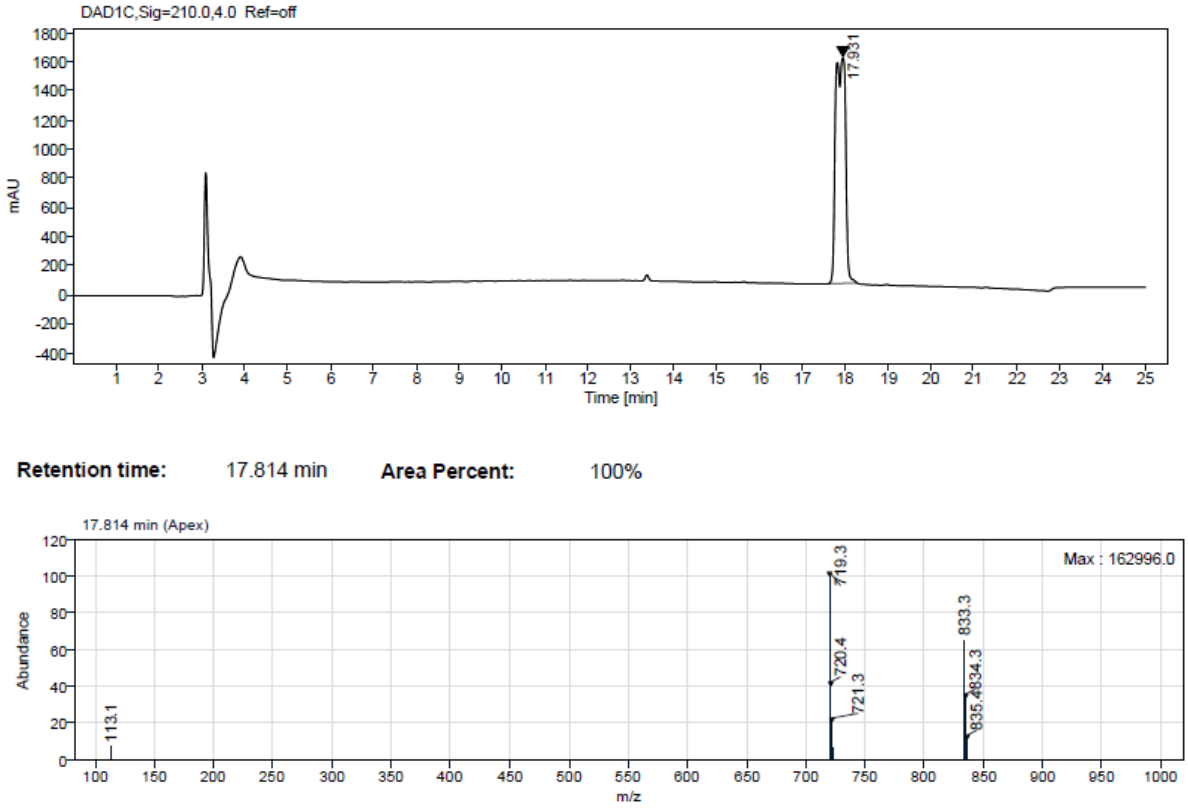
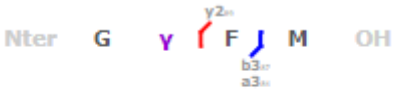


FIGURE 2. HPLC-UV chromatogram (210 nm) and MS(ESI) of **6i** by Method 1 after purification

TABLE 1. MS/MS fragmentation of **6i**



γ = Gly(C4H8S)
Nter = C15H11O2

Sequence	Type	MF	MF mass	m/z	Intensity	Similarity
FM	y2	C14H21N2O3S(+1)	297.1273	297.1267	4.308197	88.81%
GGF	b3	C32H34N3O5S(+1)	572.2219	572.2214	100.0231	87.25%
GGF	a3	C31H34N3O4S(+1)	544.227	544.2265	1.174592	83.63%

3. References

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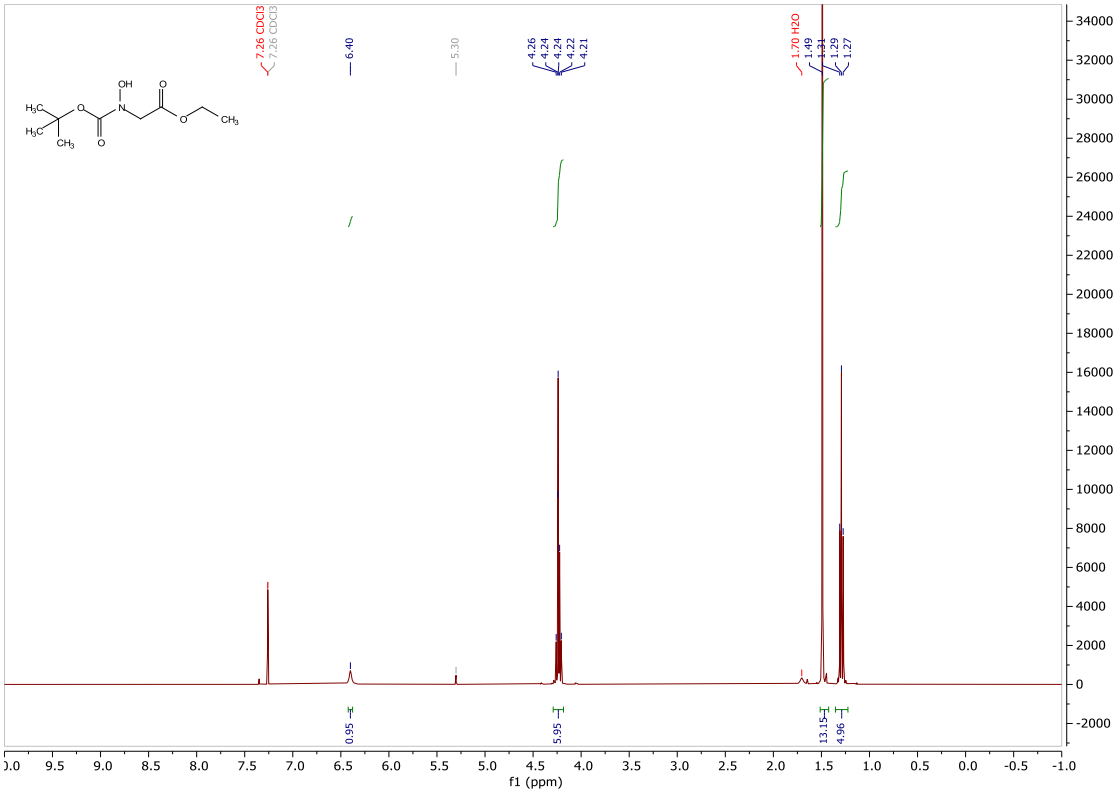
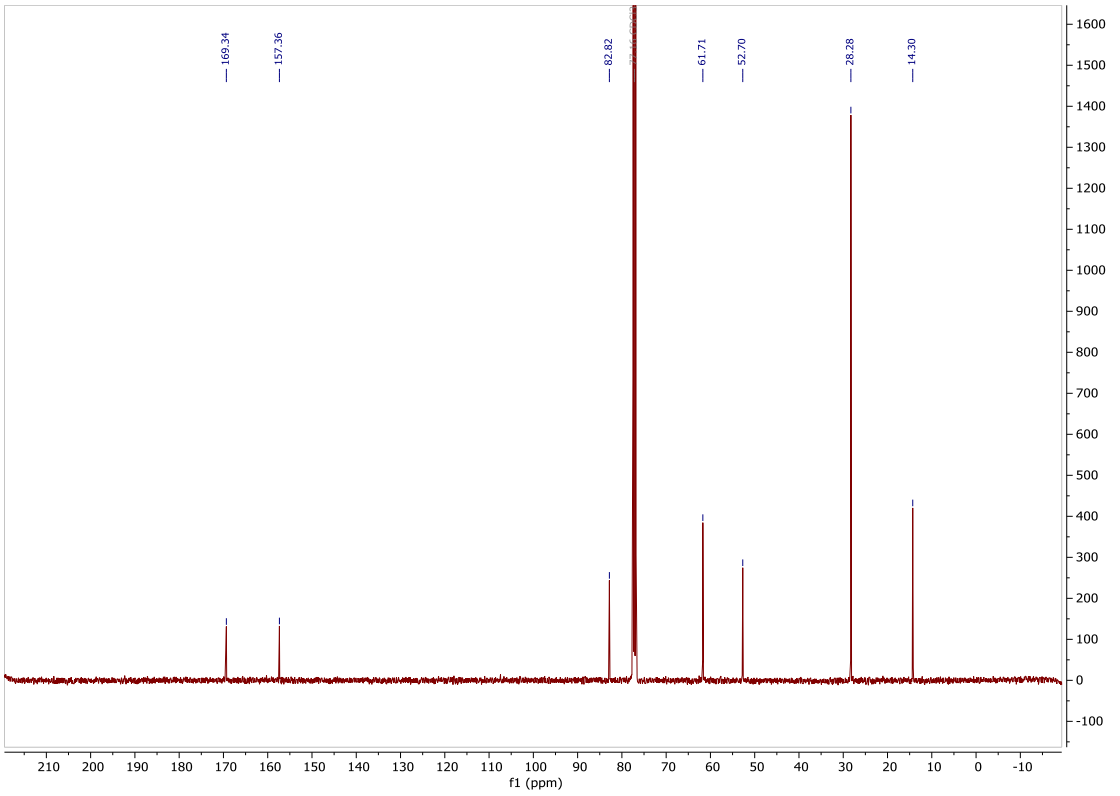
4. NMR Spectra

Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-hydroxyglycinate (1a)

^{1}H NMR (400 MHz, Chloroform-*d*)

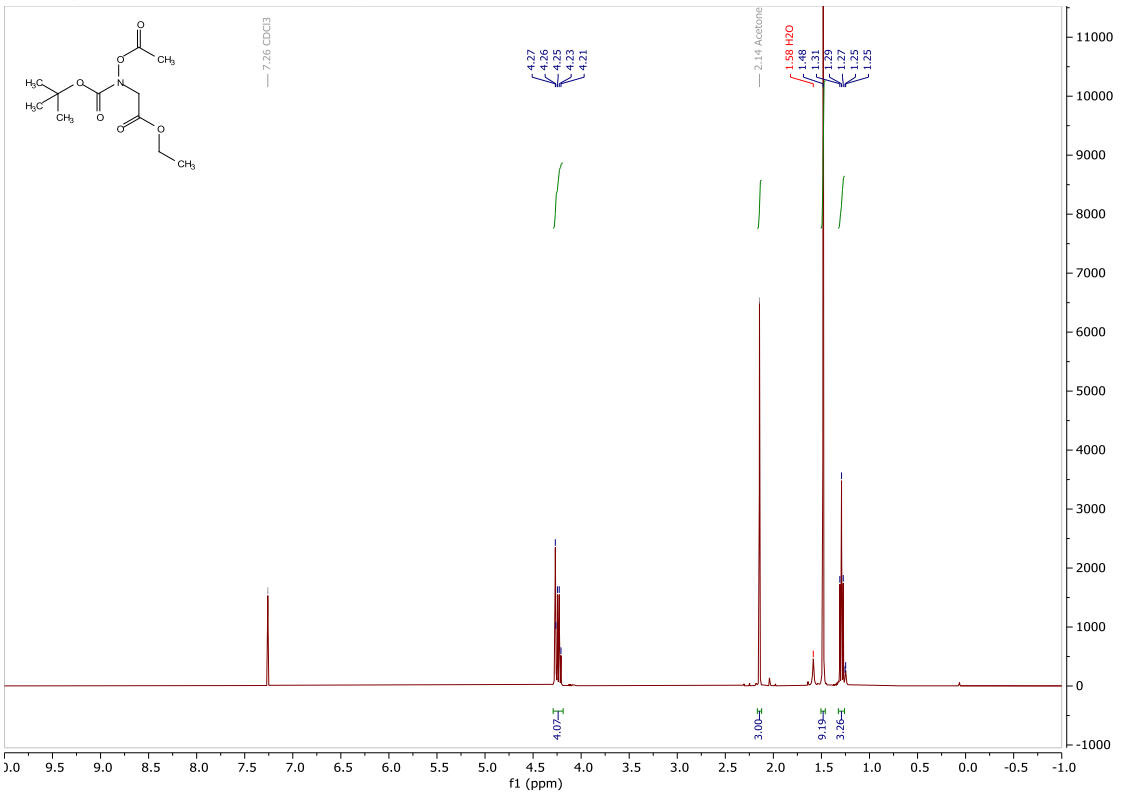


^{13}C NMR (101 MHz, Chloroform-*d*)

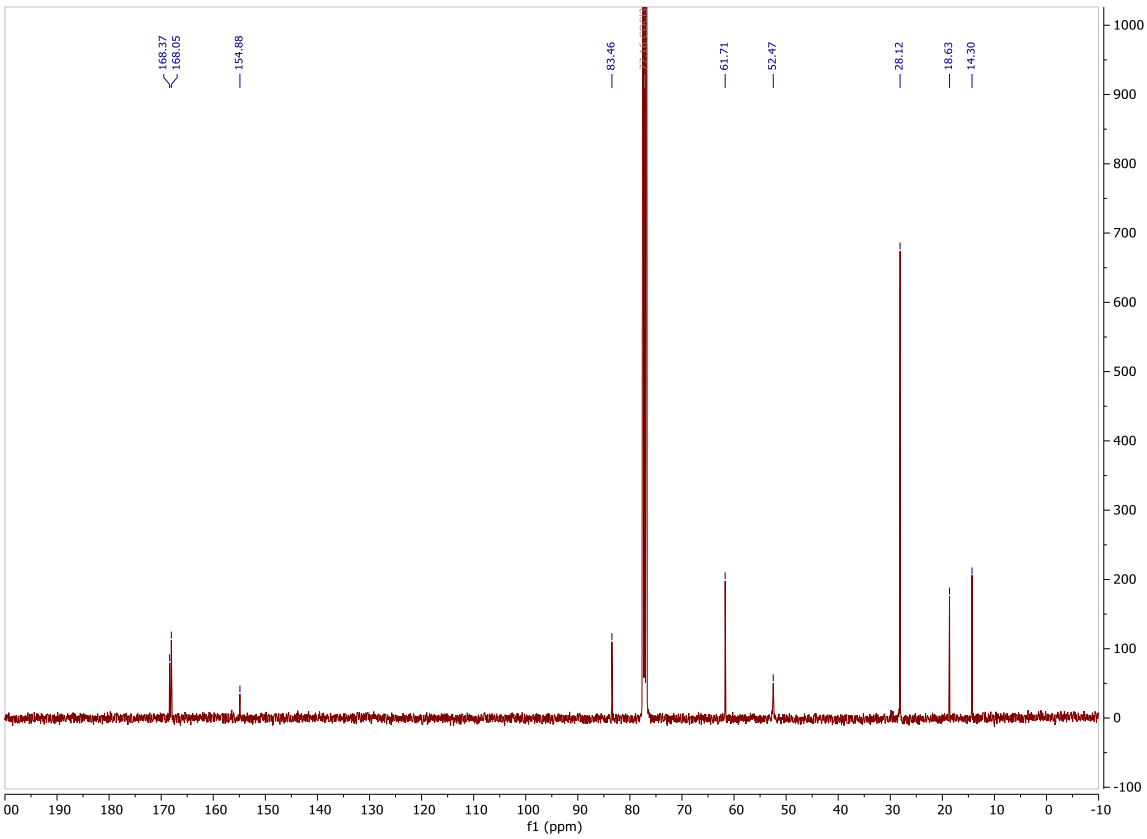


Ethyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycinate (1a')

^{1}H NMR (400 MHz, Chloroform-*d*)

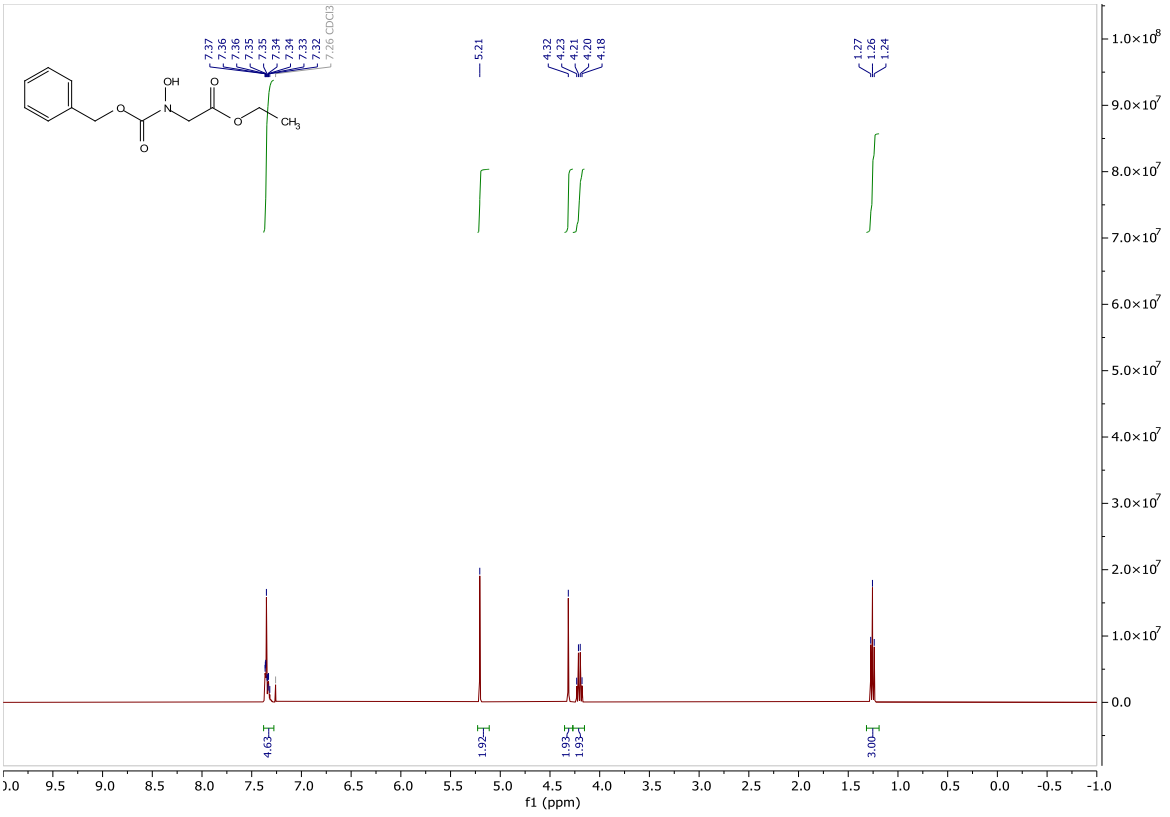


^{13}C NMR (101 MHz, Chloroform-*d*)

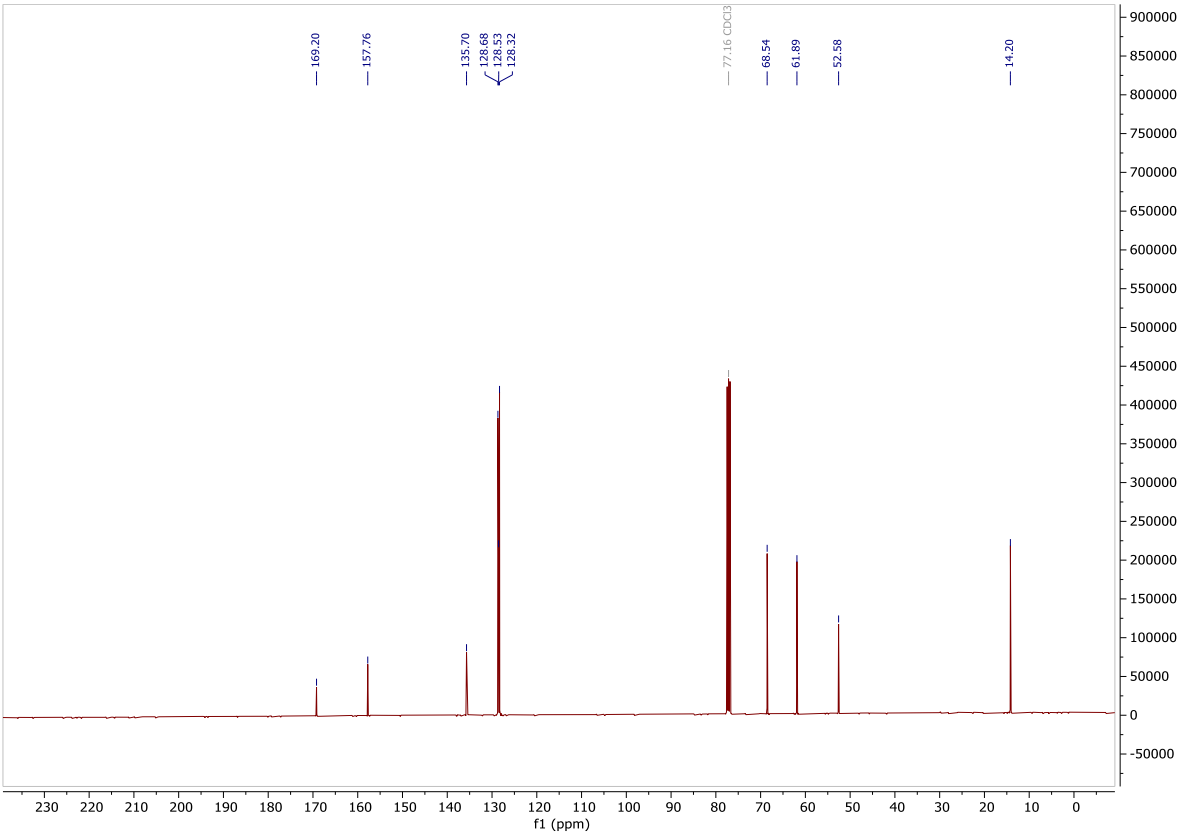


Ethyl *N*-((benzyloxy)carbonyl)-*N*-hydroxyglycinate (1b)

^{1}H NMR (400 MHz, Chloroform-*d*)

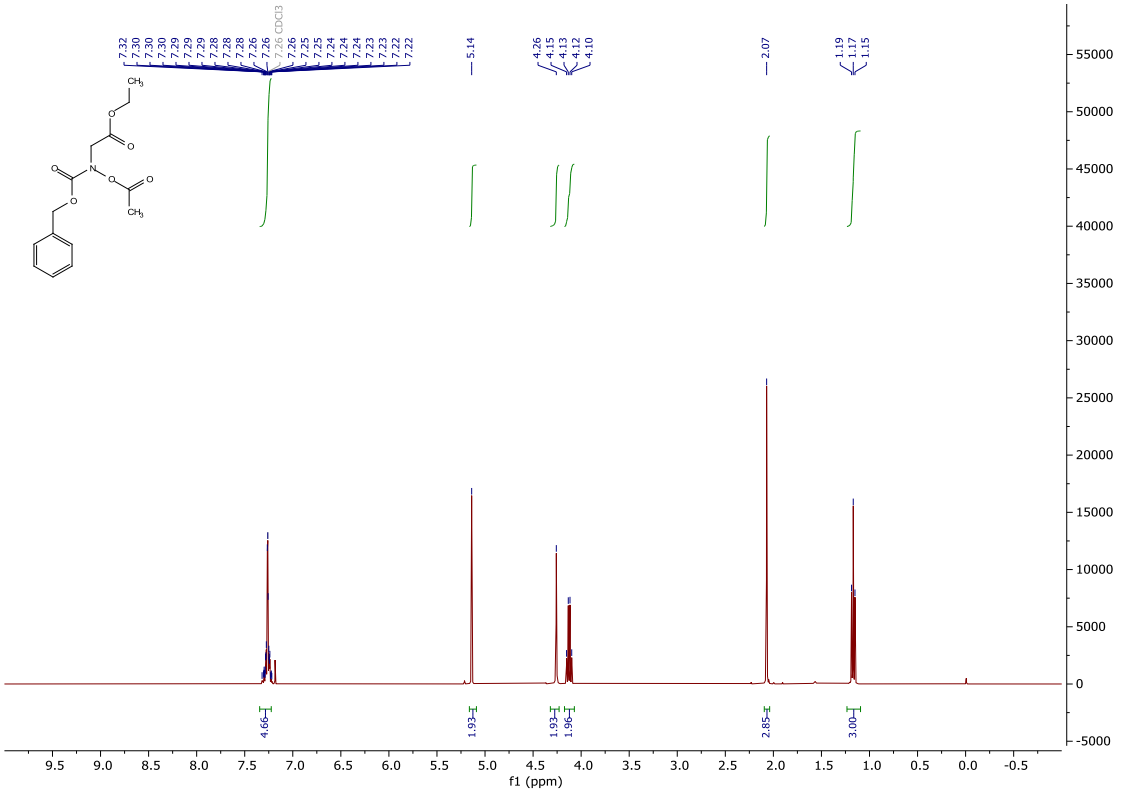


^{13}C NMR (101 MHz, Chloroform-*d*)

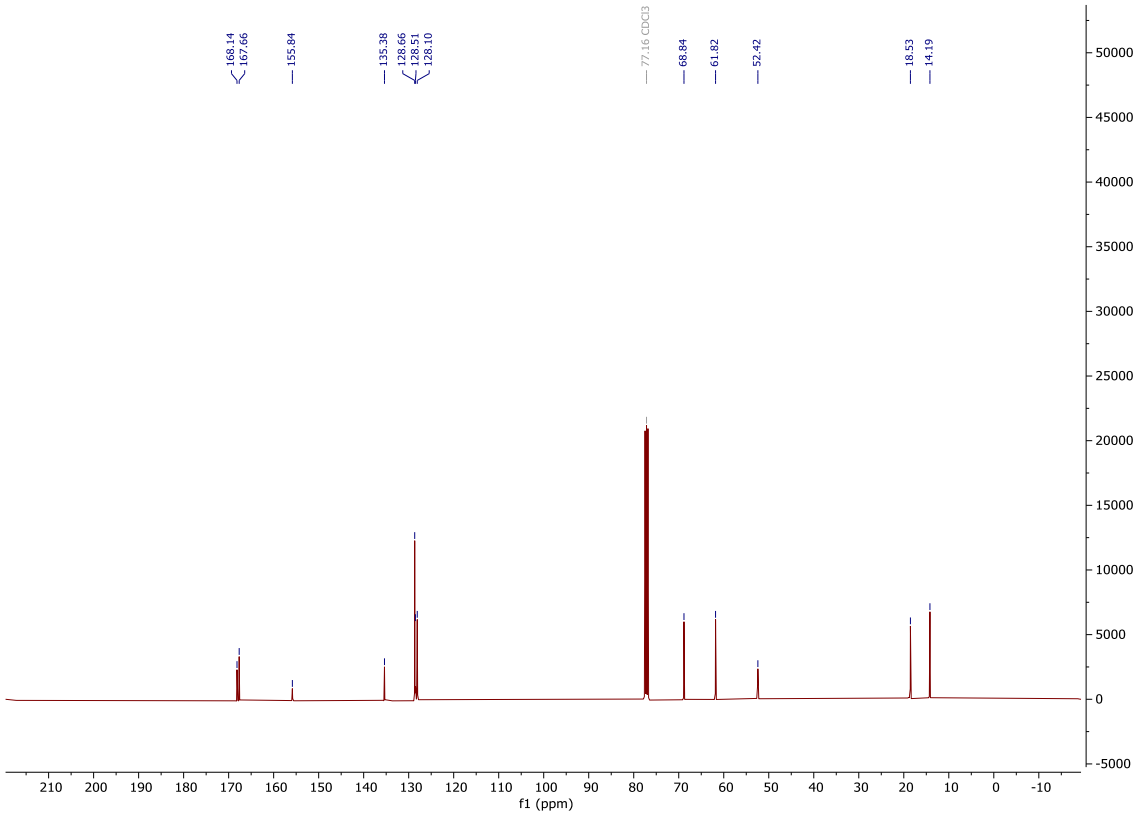


Ethyl *N*-acetoxy-*N*-((benzyloxy)carbonyl)glycinate (1b')

^{1}H NMR (400 MHz, Chloroform-*d*)

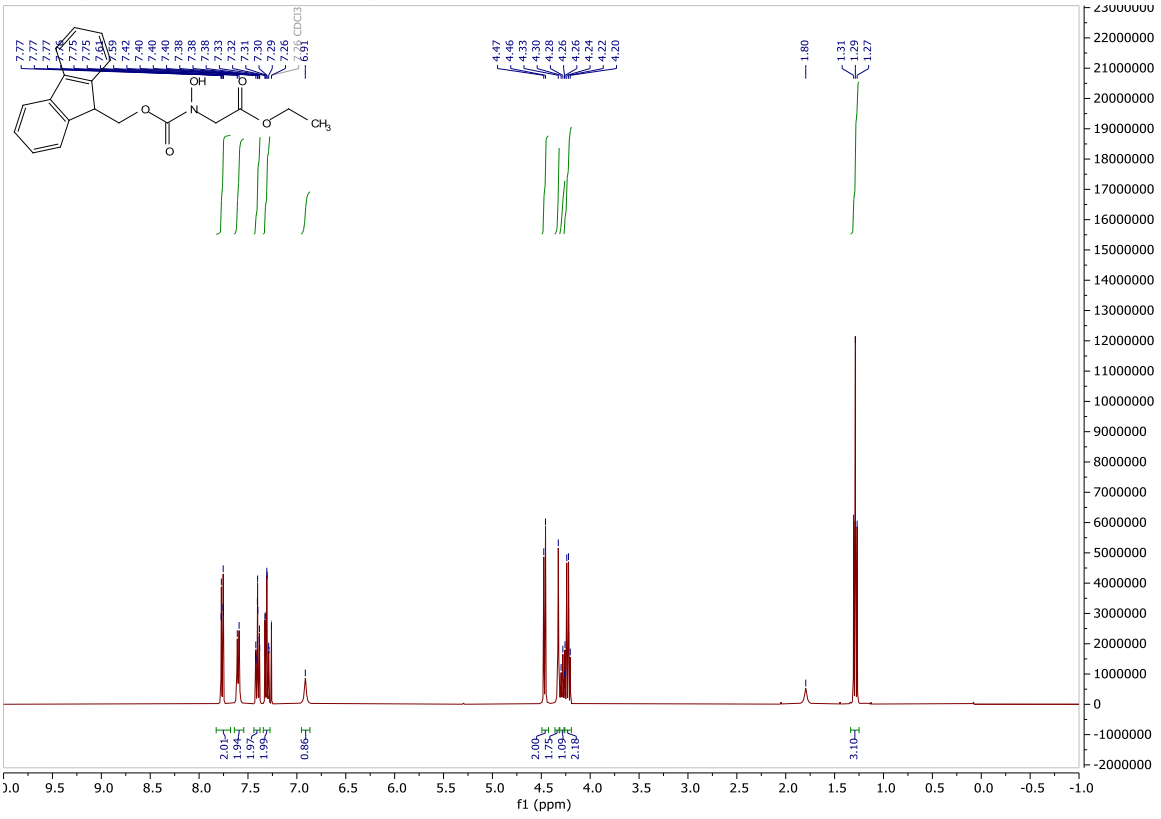


^{13}C NMR (101 MHz, Chloroform-*d*)

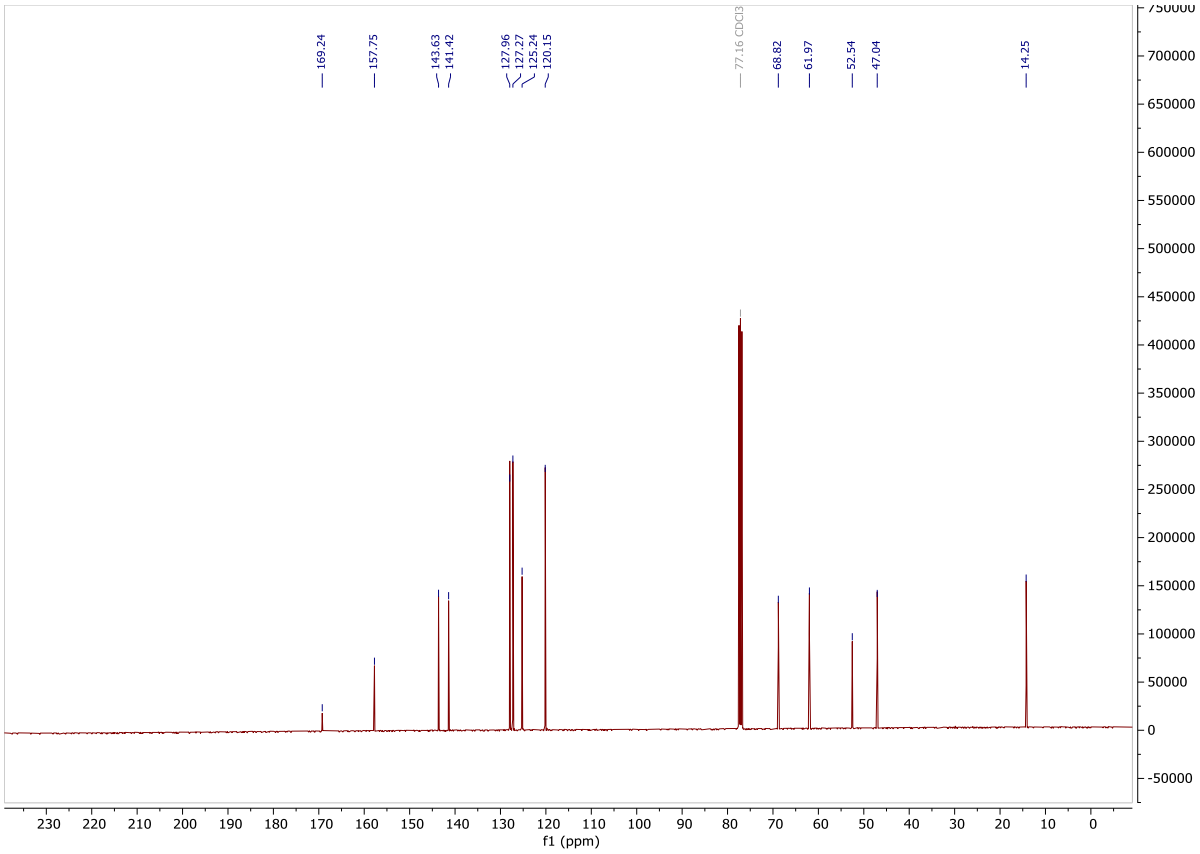


Ethyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-hydroxyglycinate (1c)

^{1}H NMR (400 MHz, Chloroform-*d*)

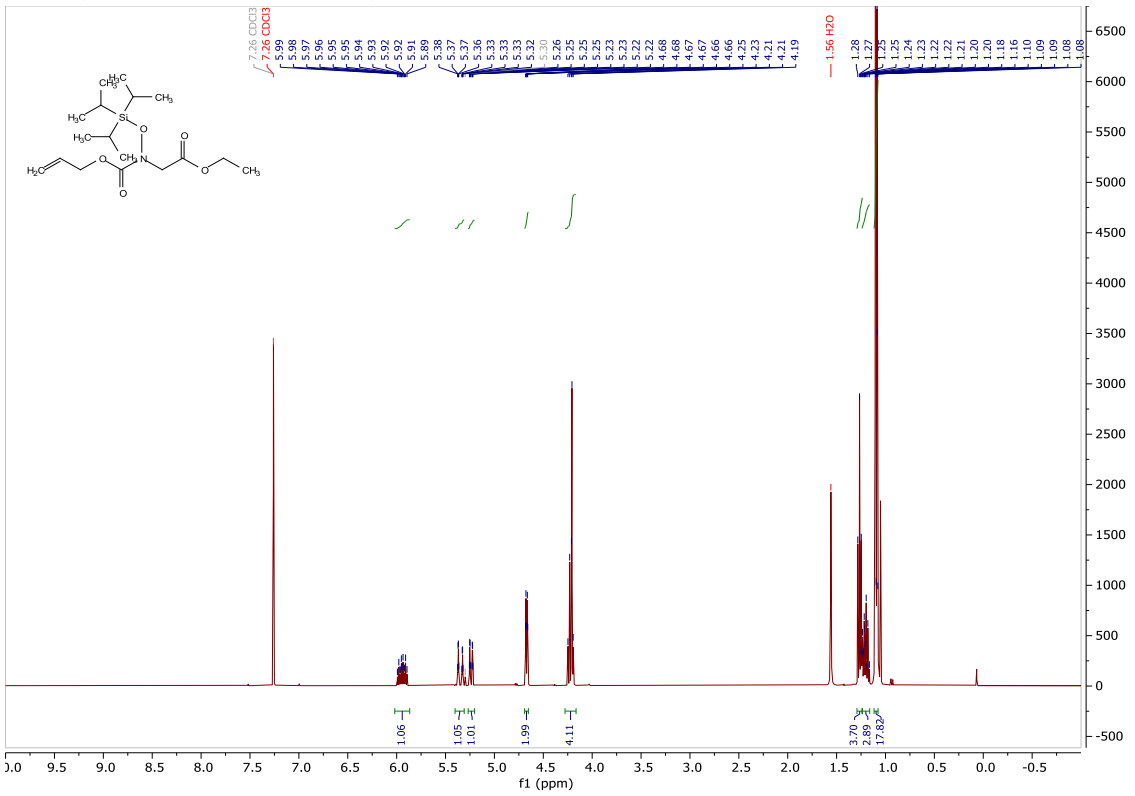


^{13}C NMR (101 MHz, Chloroform-*d*)

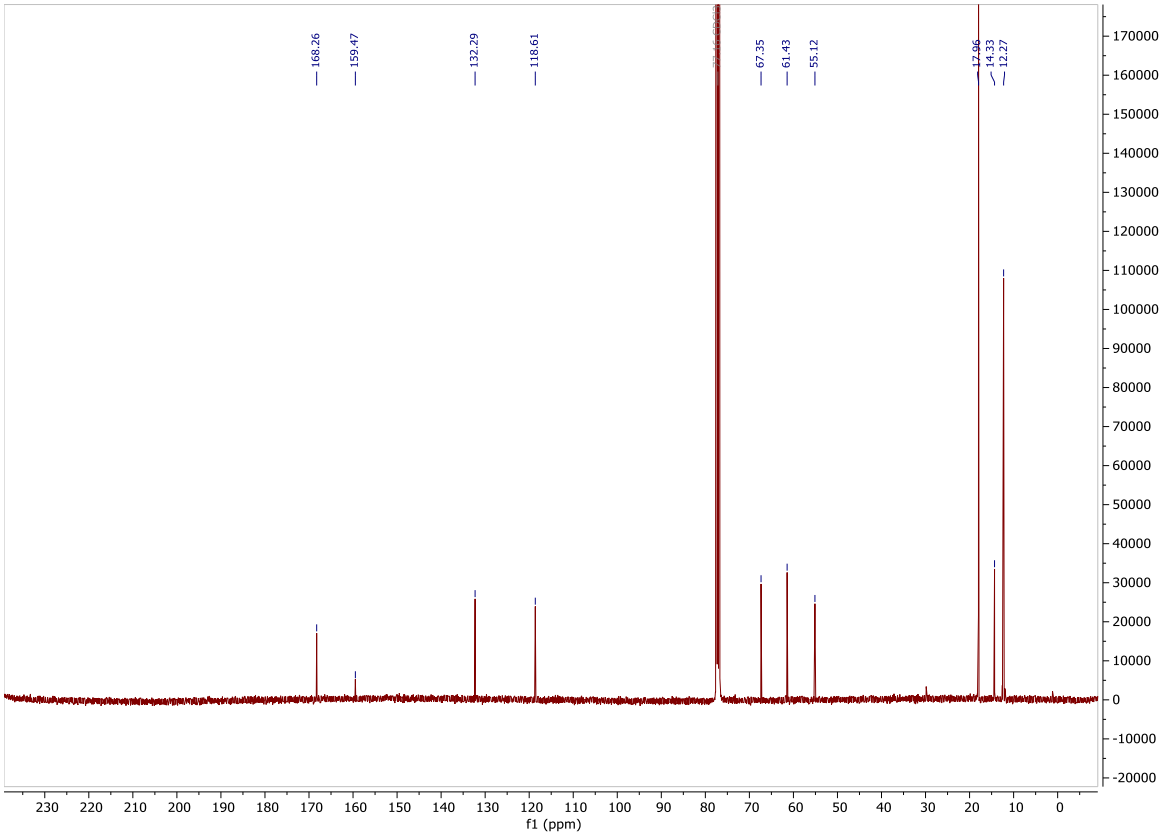


Ethyl *N*-((allyloxy)carbonyl)-*N*-((triisopropylsilyl)oxy)glycinate (SM2)

^{1}H NMR (400 MHz, Chloroform-*d*)

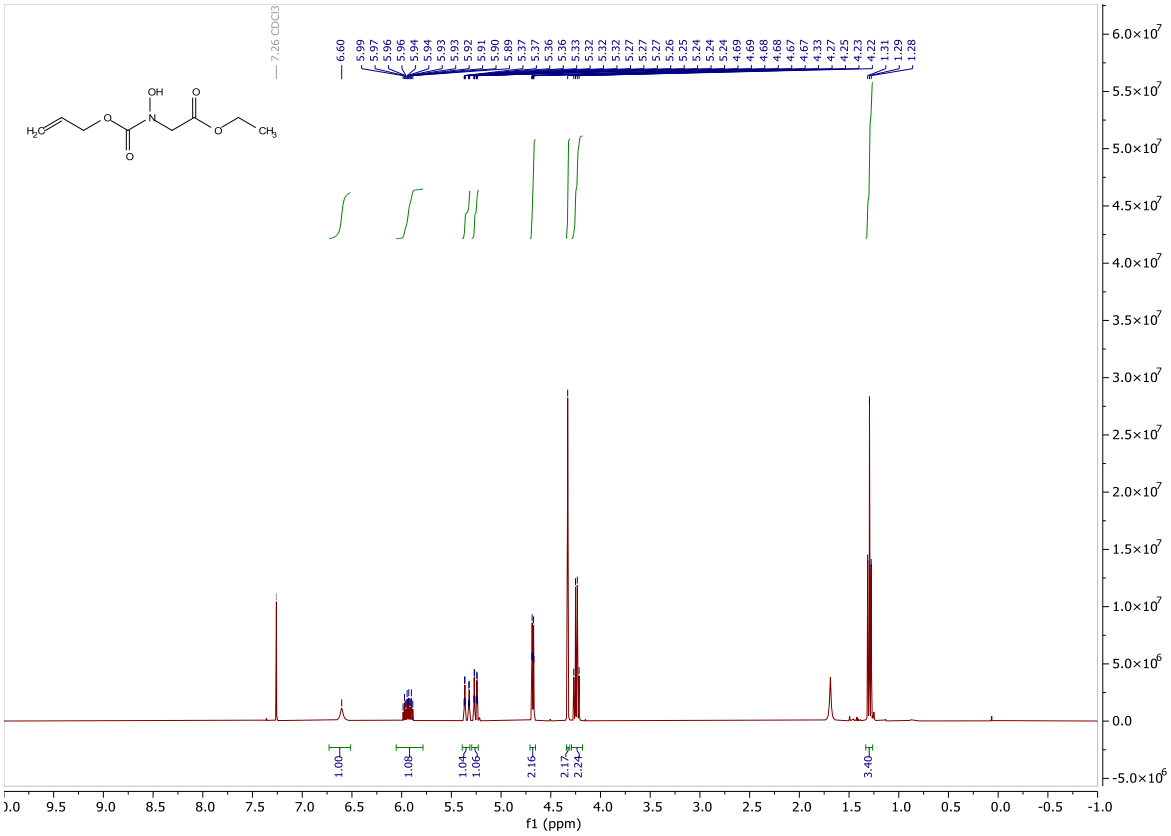


^{13}C NMR (101 MHz, Chloroform-*d*)

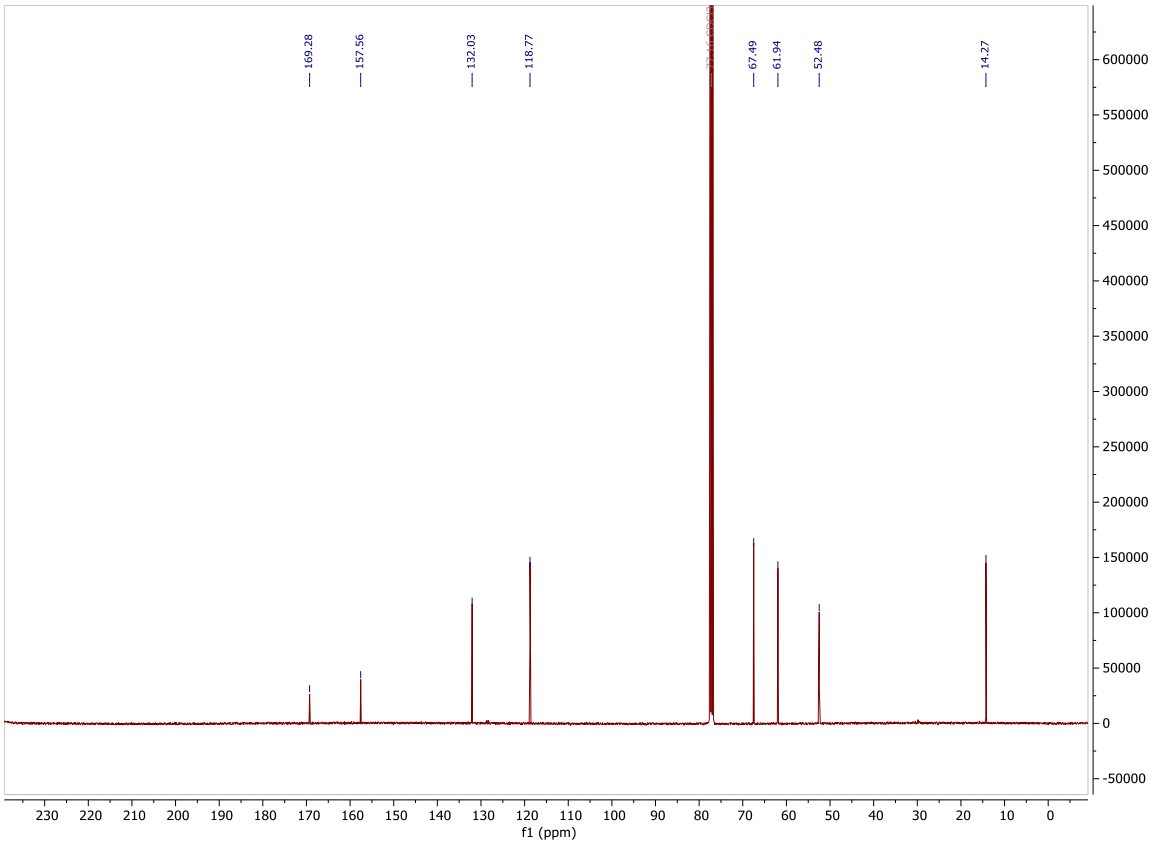


Ethyl *N*-((allyloxy)carbonyl)-*N*-hydroxyglycinate (1d)

^{1}H NMR (400 MHz, Chloroform-*d*)

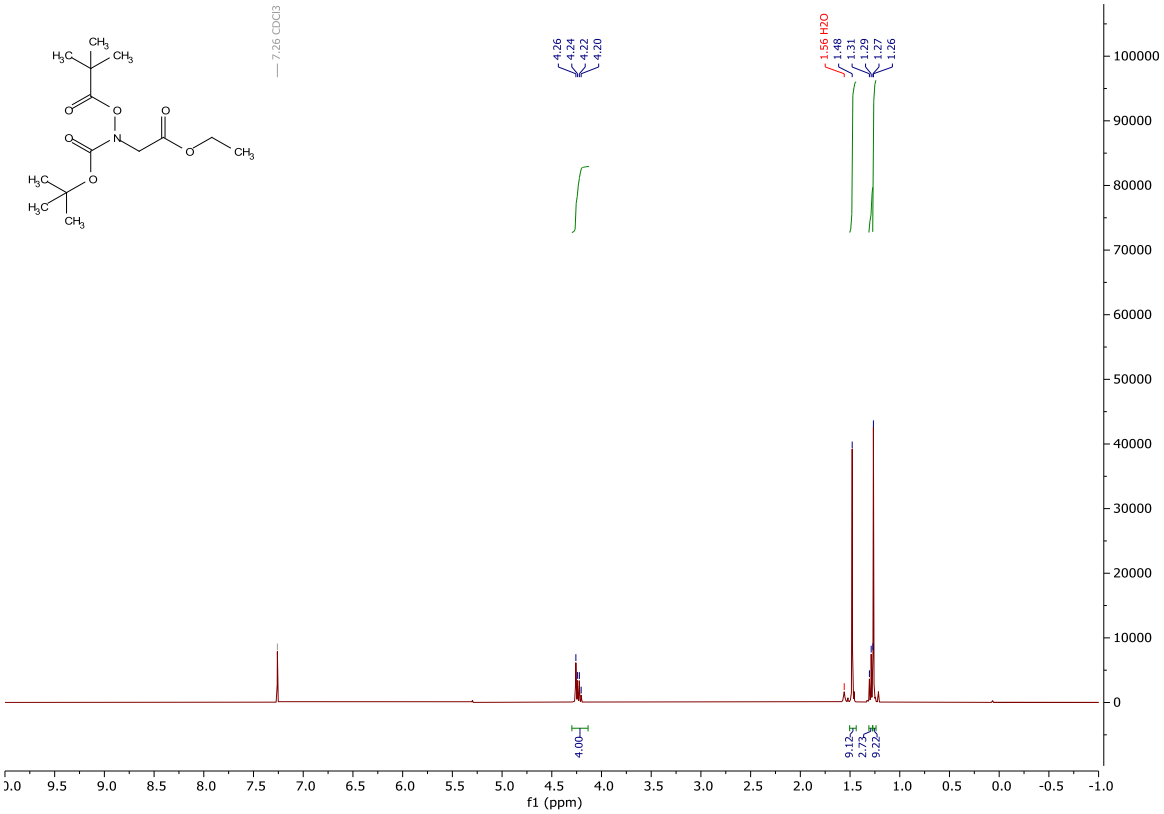


^{13}C NMR (101 MHz, Chloroform-*d*)

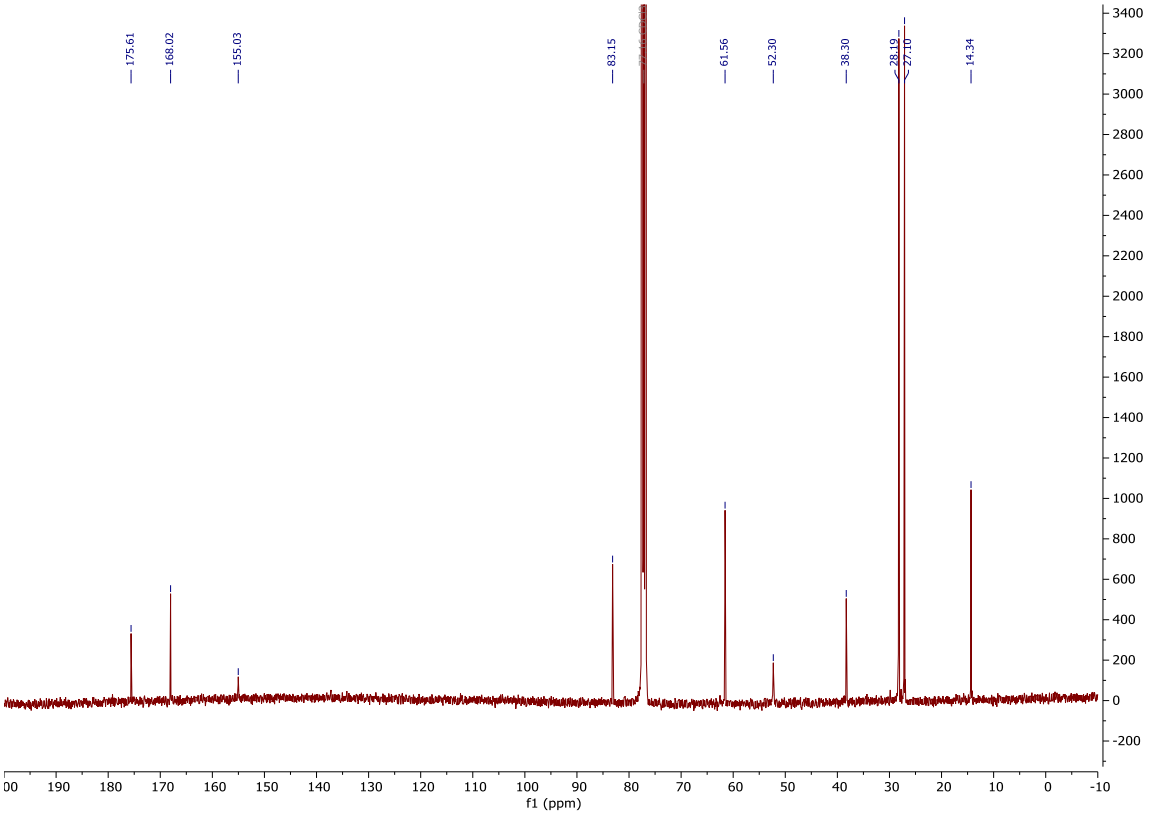


Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-(pivaloyloxy)glycinate (1e)

^{1}H NMR (400 MHz, Chloroform-*d*)

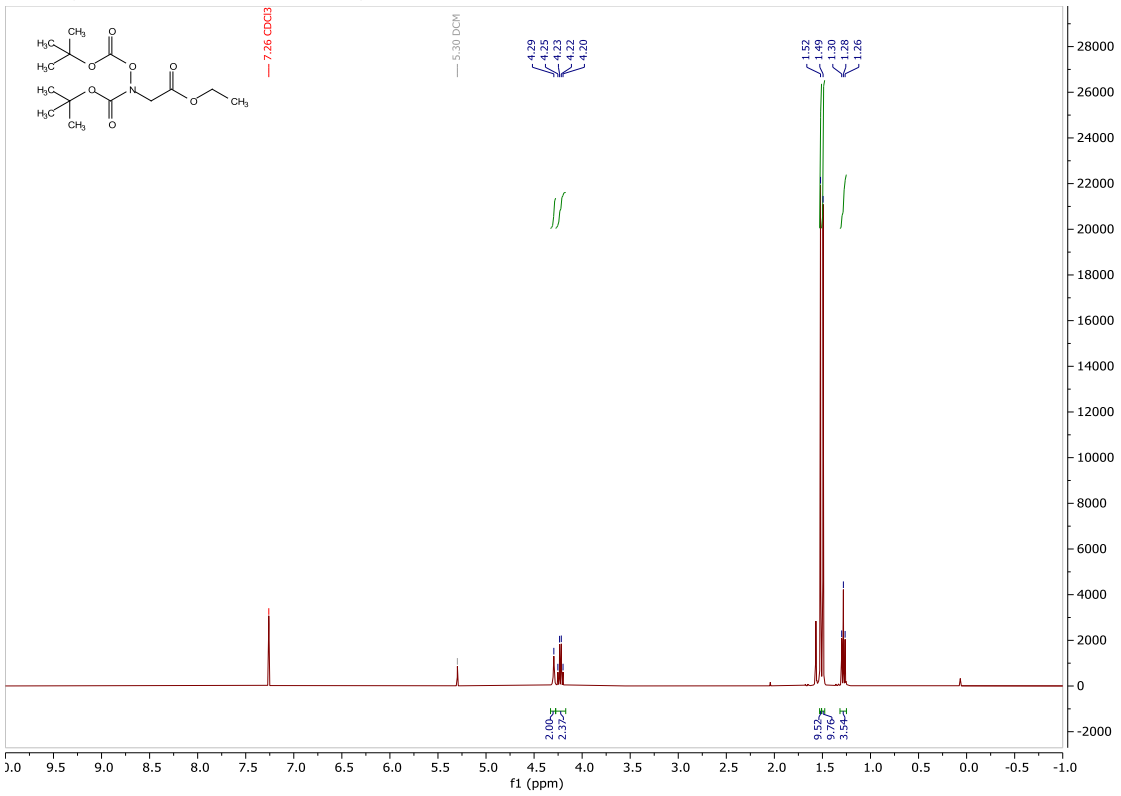


^{13}C NMR (101 MHz, Chloroform-*d*)

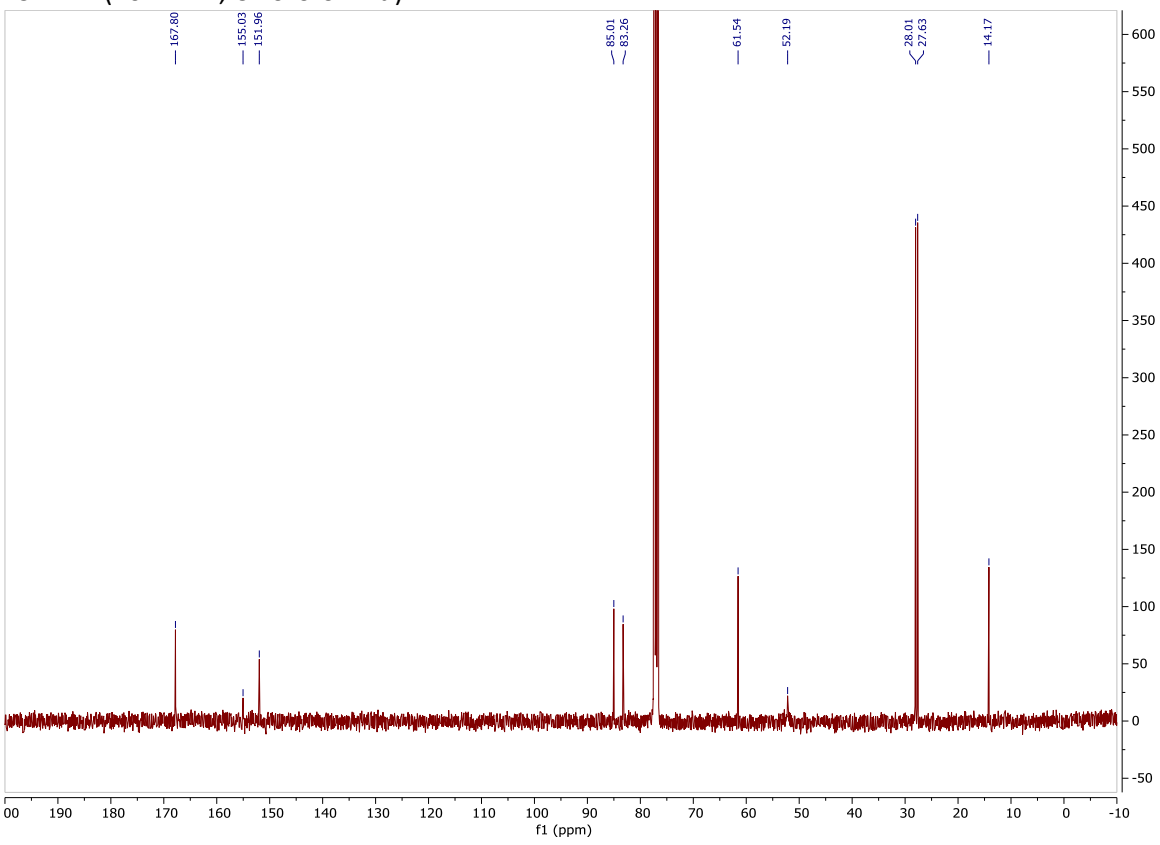


Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-((*tert*-butoxycarbonyl)oxy)glycinate (1f)

^{1}H NMR (400 MHz, Chloroform-*d*)

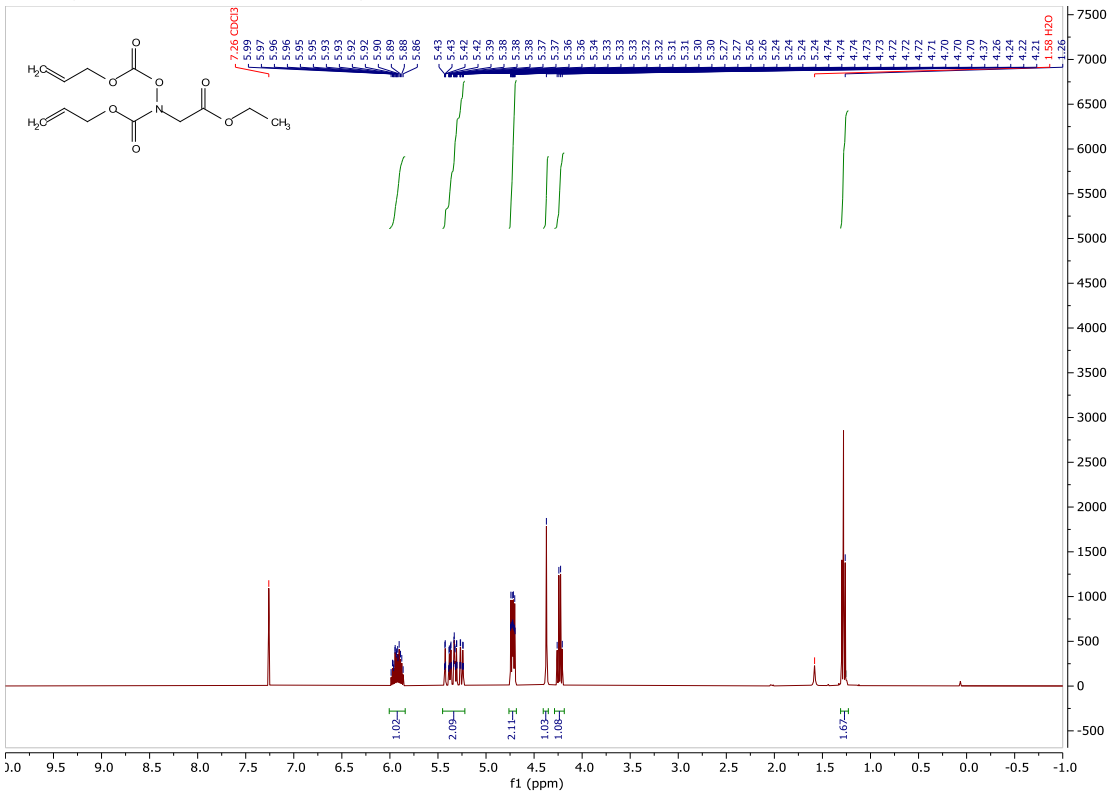


^{13}C NMR (101 MHz, Chloroform-*d*)

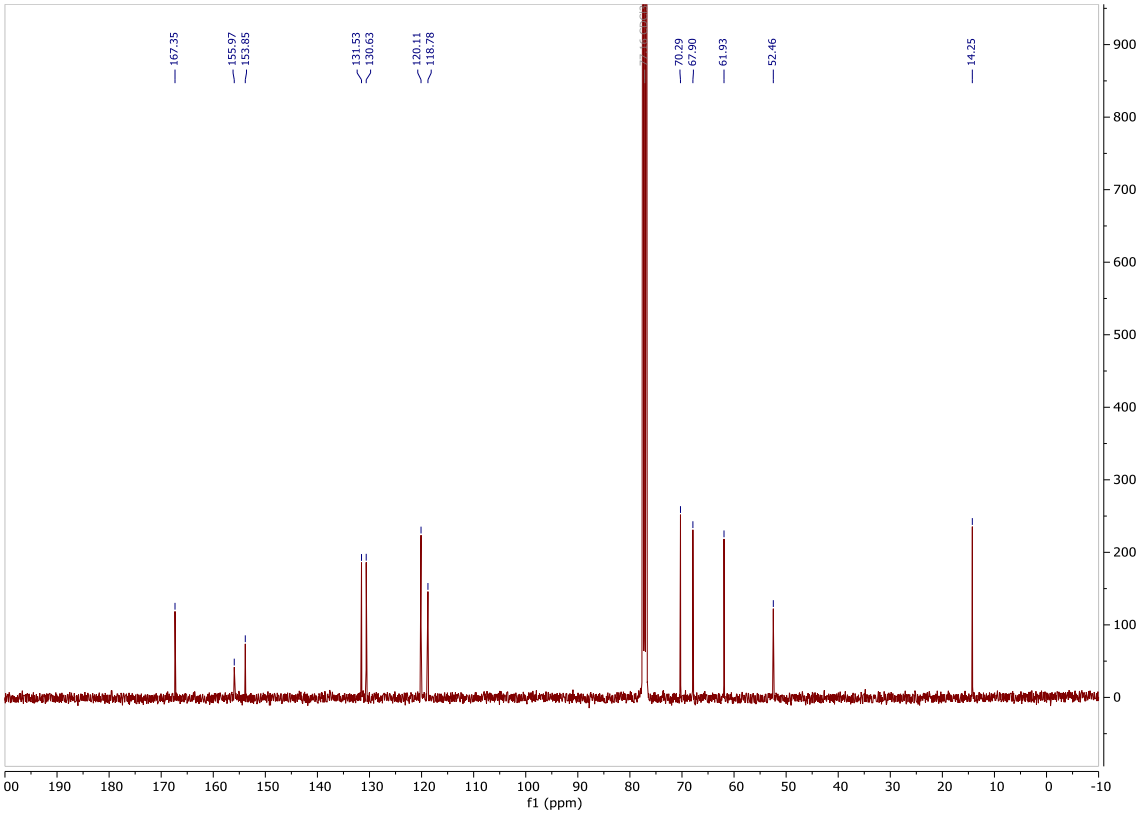


Ethyl *N*-((allyloxy)carbonyl)-*N*-(((allyloxy)carbonyl)oxy)glycinate (1g)

^{1}H NMR (400 MHz, Chloroform-*d*)

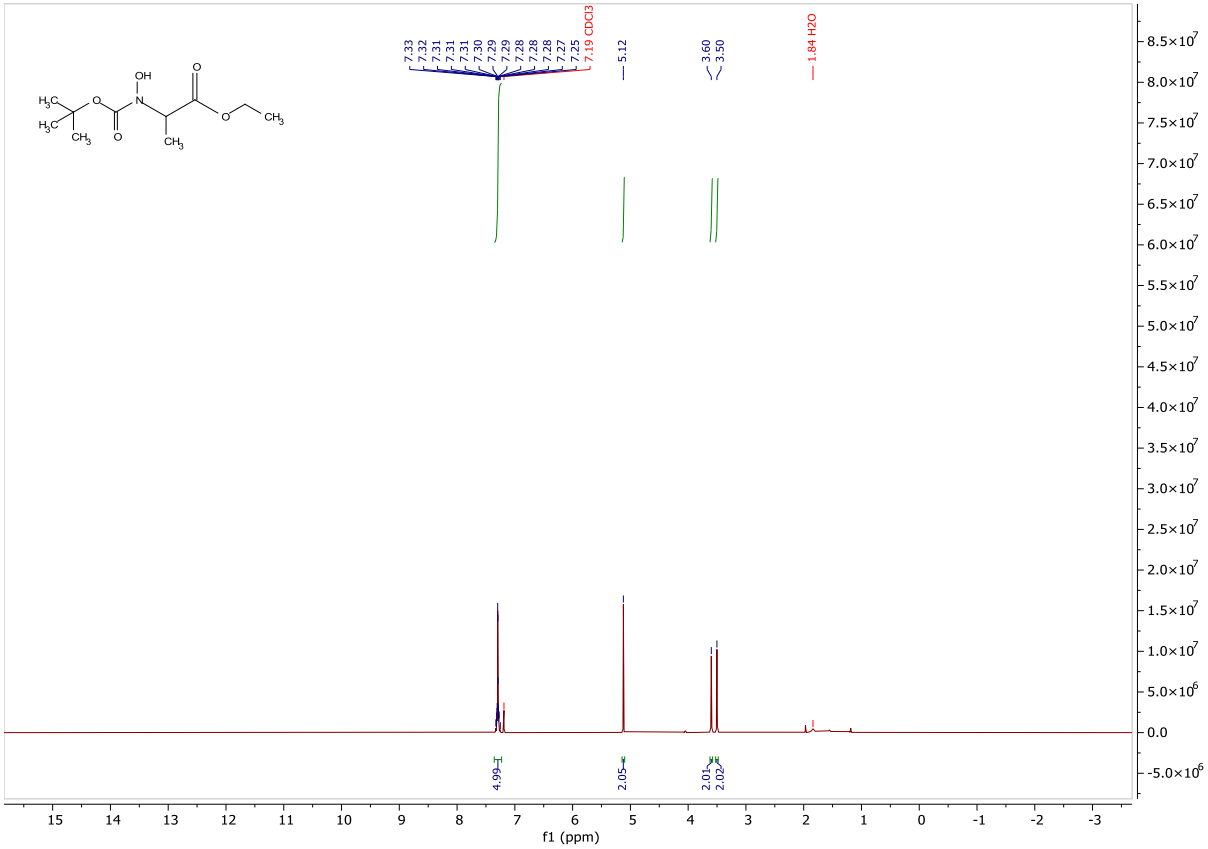


^{13}C NMR (101 MHz, Chloroform-*d*)

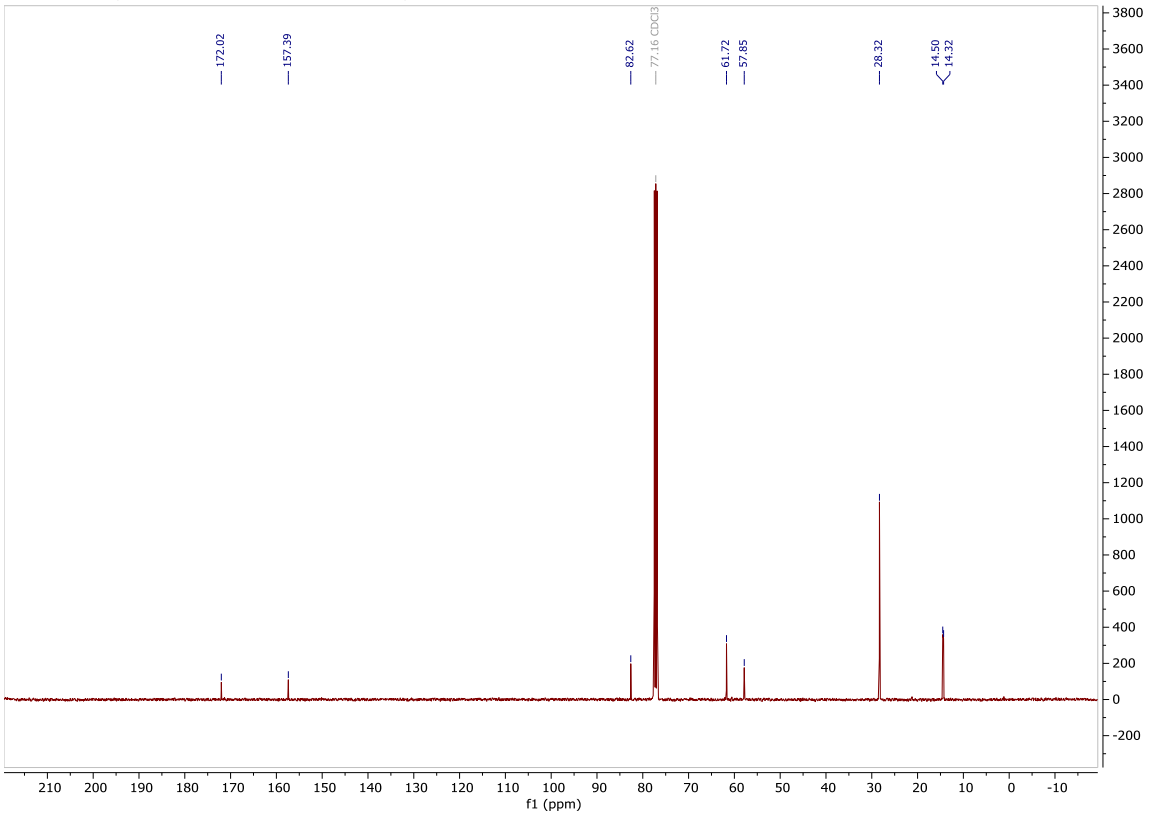


Ethyl *N*-(tert-butoxycarbonyl)-*N*-hydroxyalaninate (1aa)

^{1}H NMR (400 MHz, Chloroform-*d*)

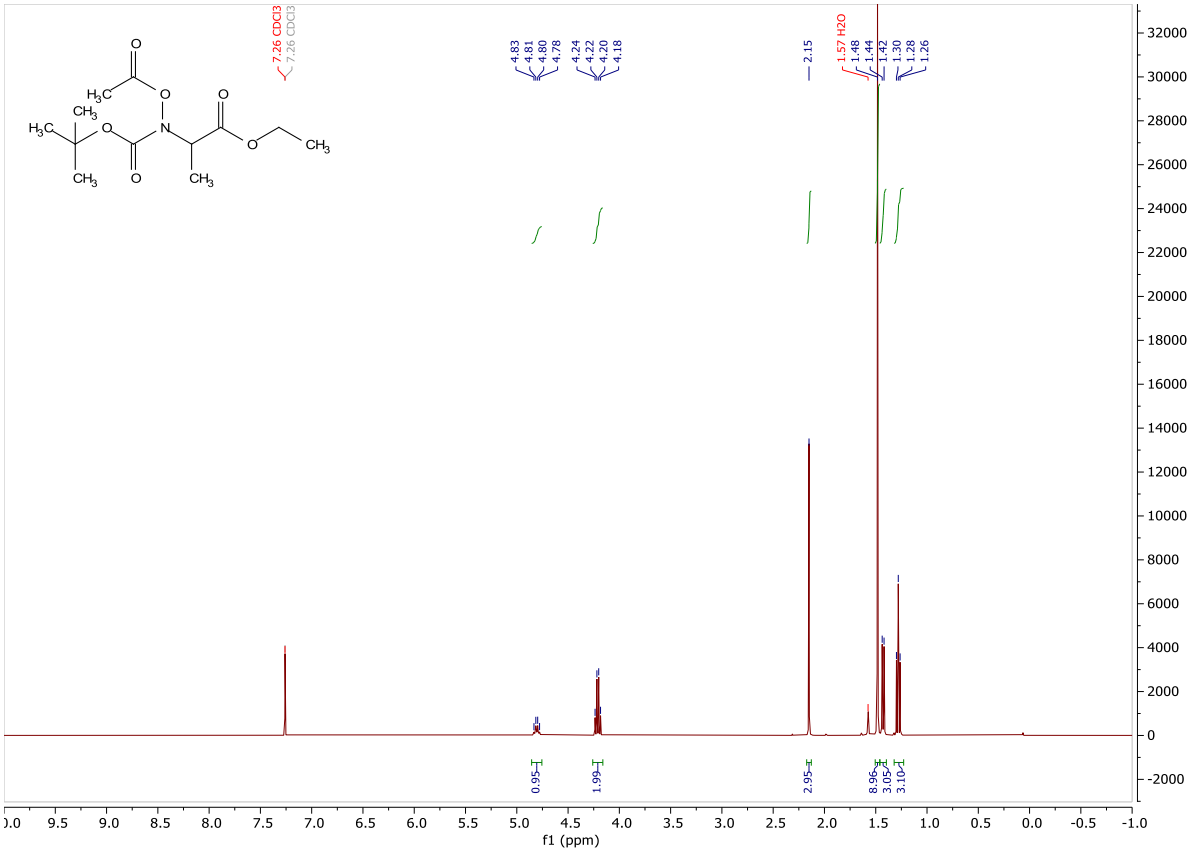


^{13}C NMR (101 MHz, Chloroform-*d*)

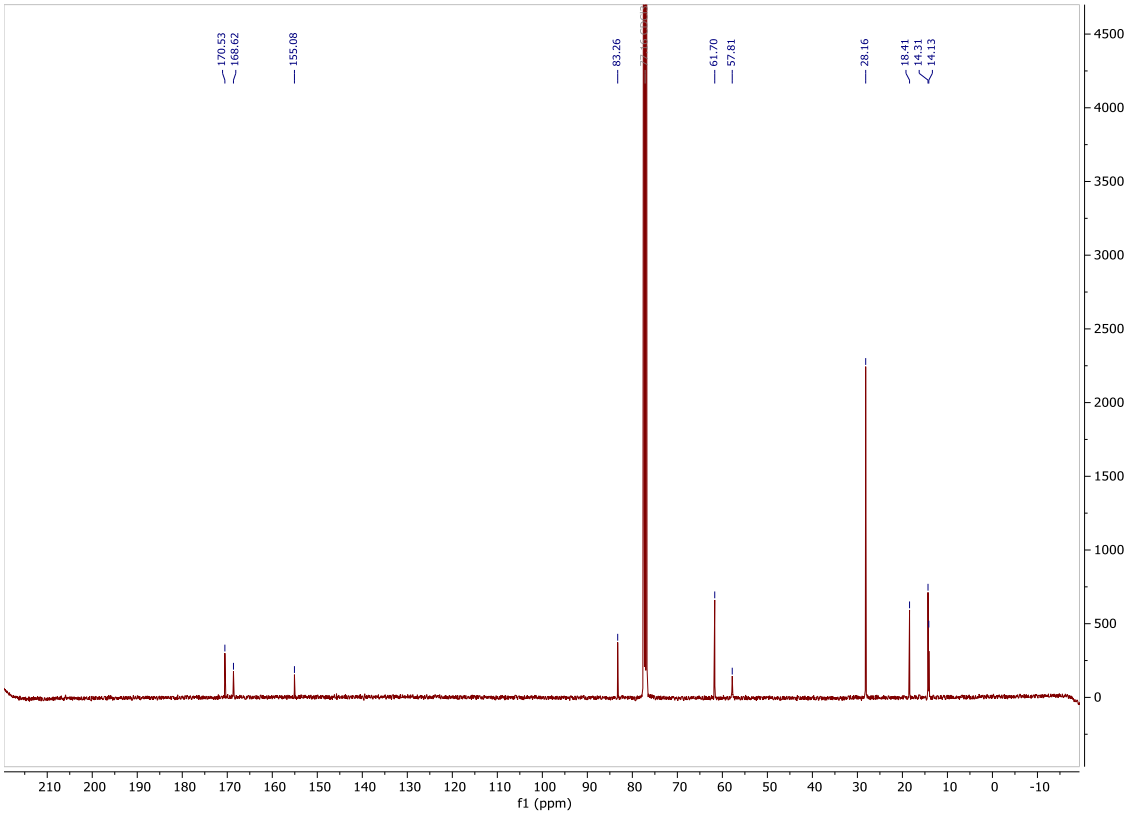


Ethyl *N*-acetoxy-*N*-(tert-butoxycarbonyl)alaninate- (1aa')

^{1}H NMR (400 MHz, Chloroform-*d*)

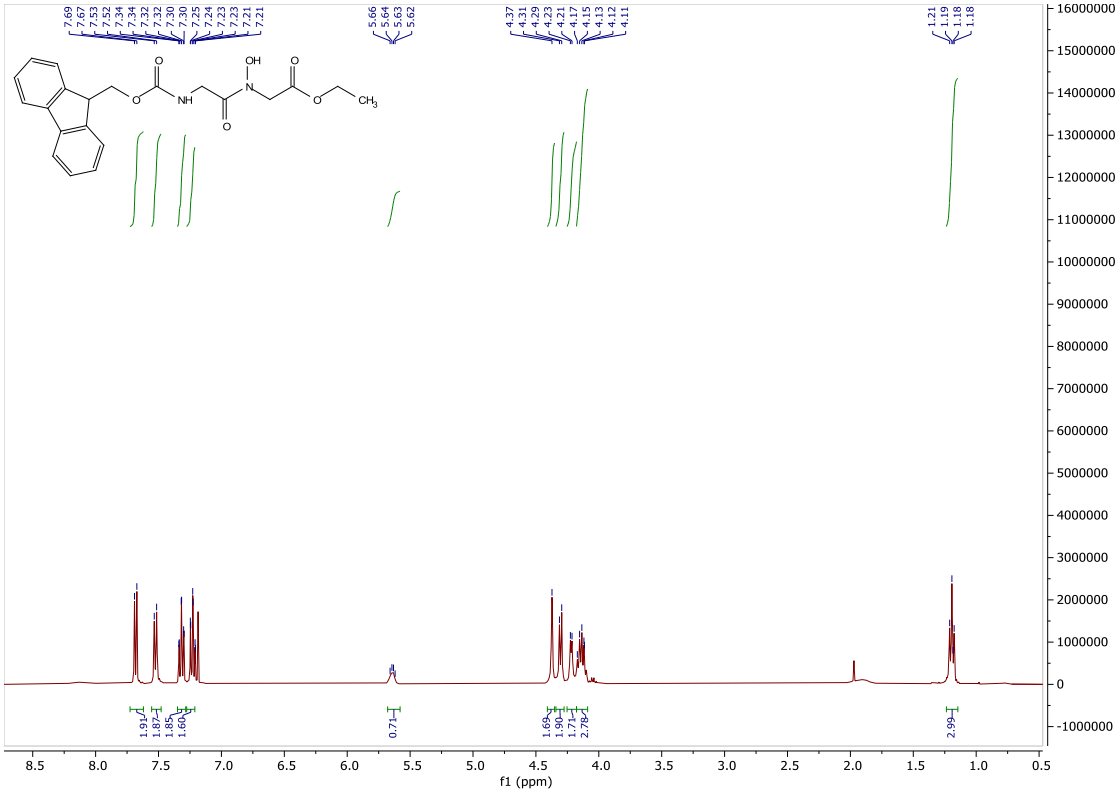


^{13}C NMR (101 MHz, Chloroform-*d*)

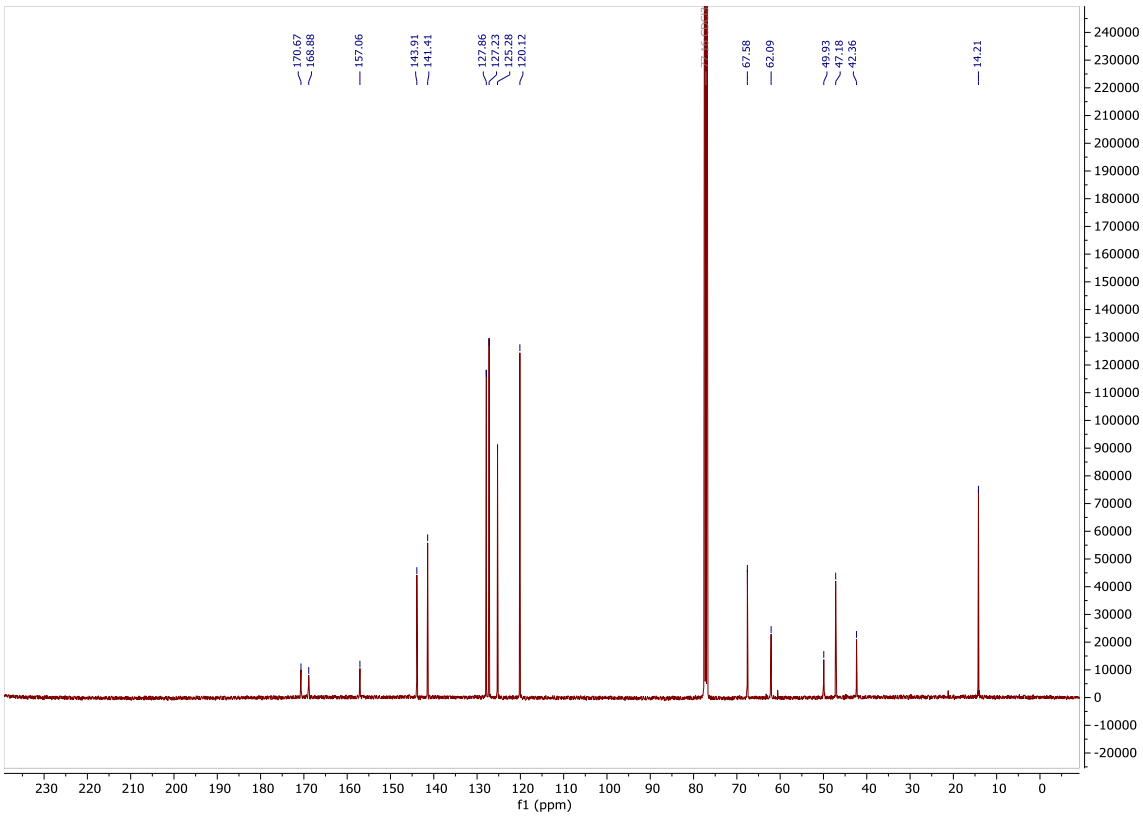


Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-hydroxyglycinate (1h)

^{1}H NMR (400 MHz, Chloroform-*d*)

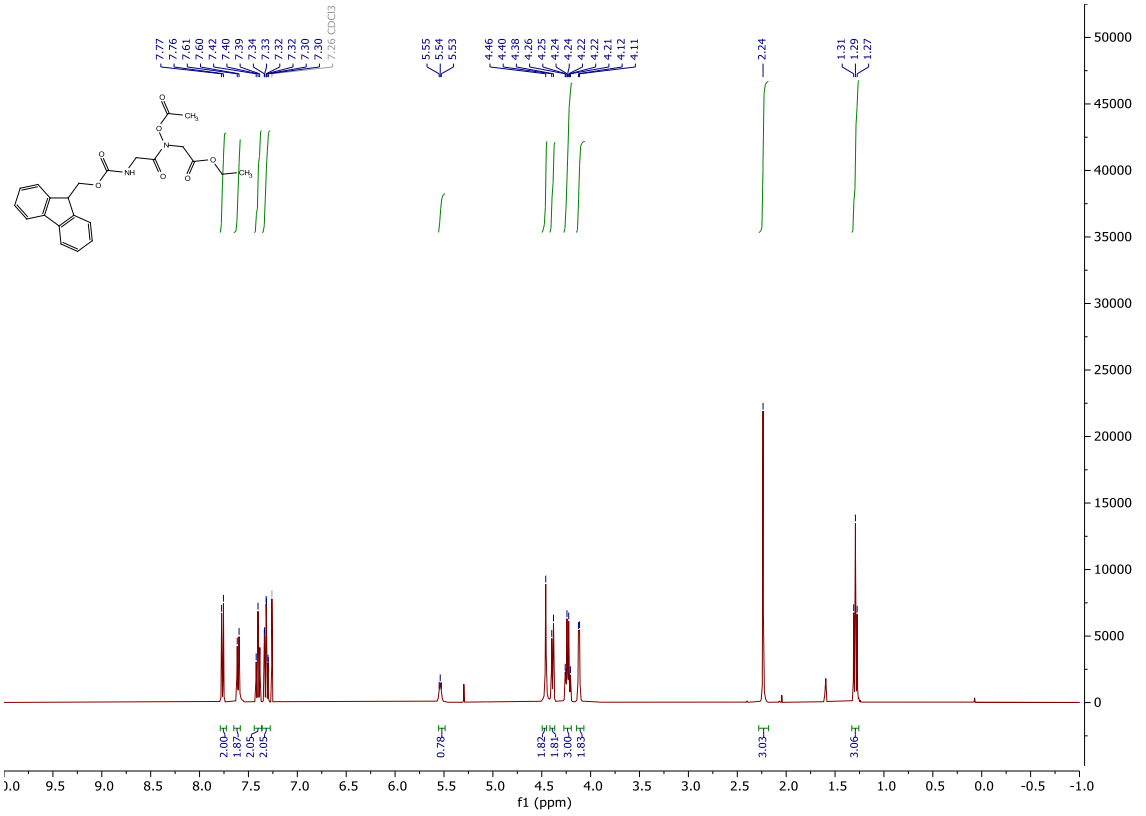


^{13}C NMR (101 MHz, Chloroform-*d*)

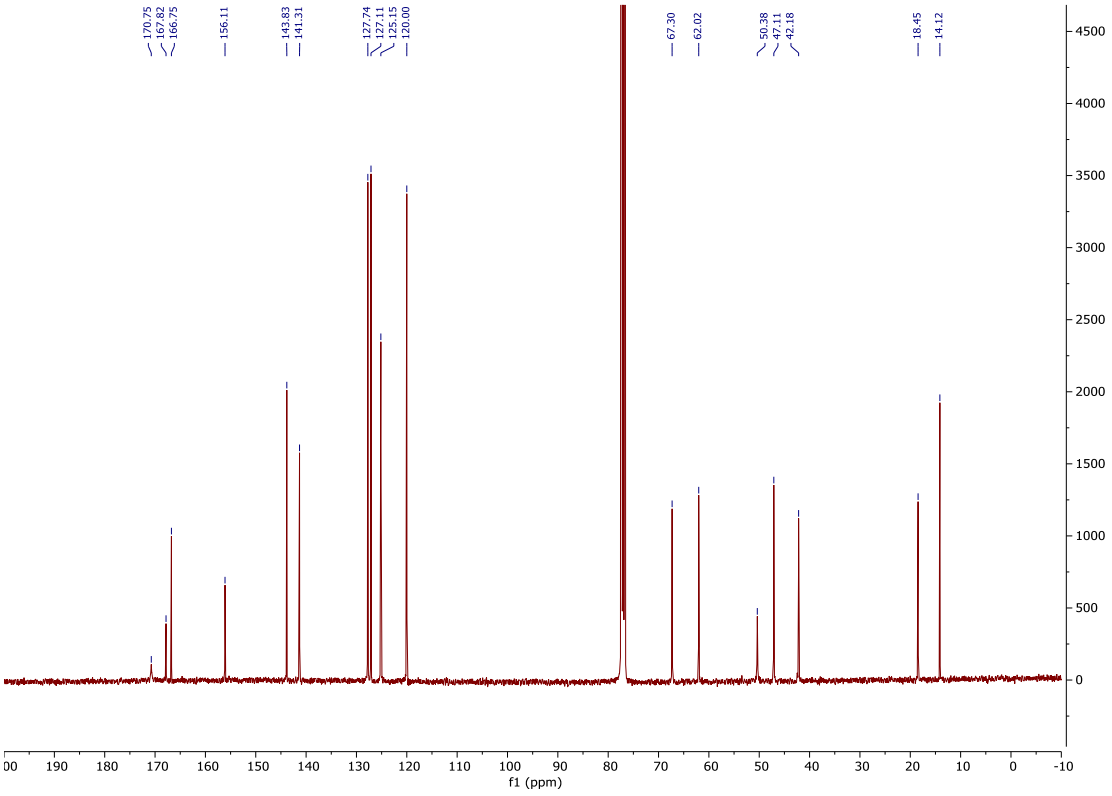


Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-acetoxyglycinate (1h')

^{1}H NMR (400 MHz, Chloroform-*d*)

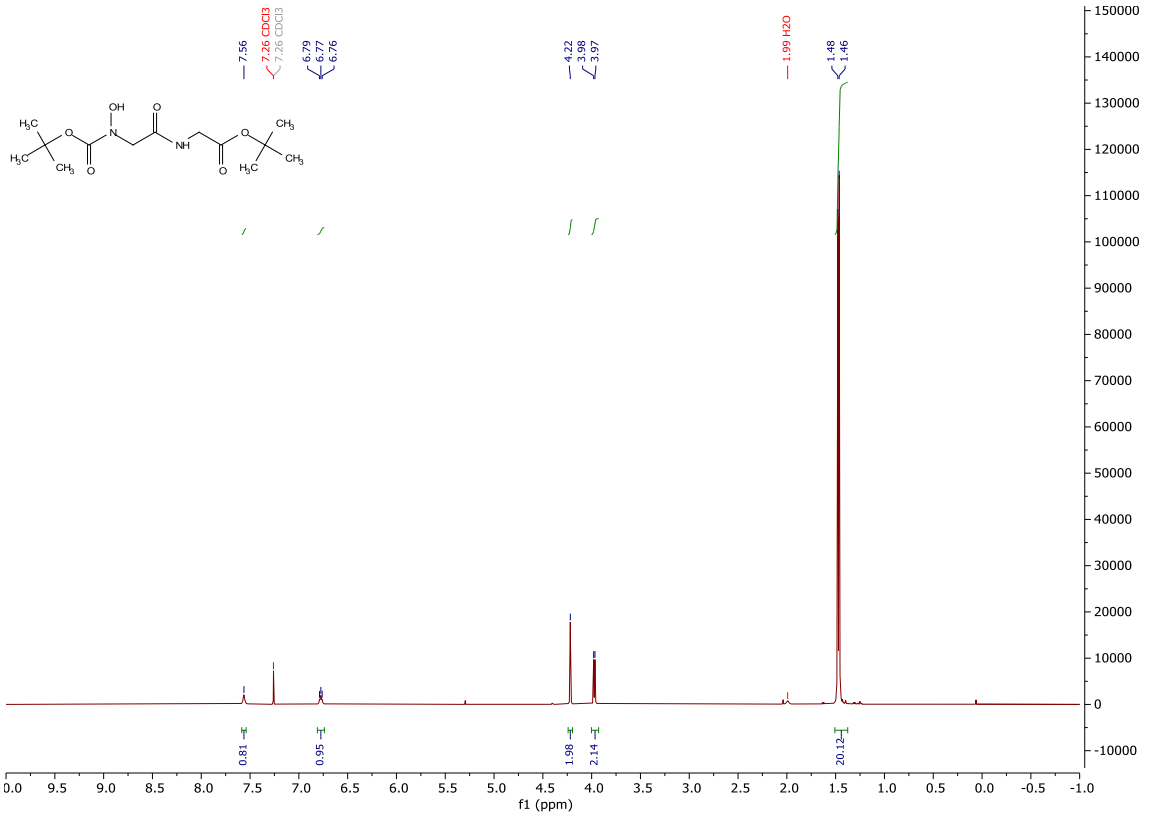


^{13}C NMR (101 MHz, Chloroform-*d*)

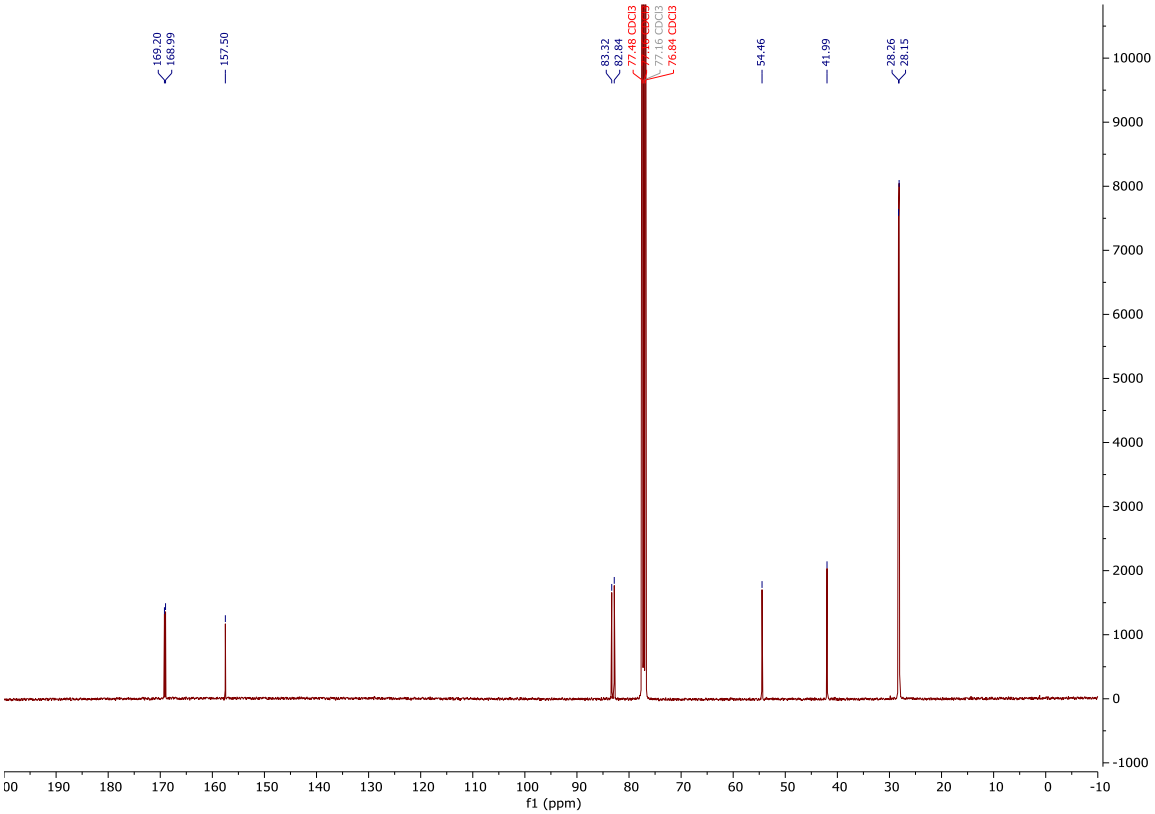


***tert*-Butyl *N*-(*tert*-butoxycarbonyl)-*N*-hydroxyglycylglycinate (1i)**

^{1}H NMR (400 MHz, Chloroform-*d*)

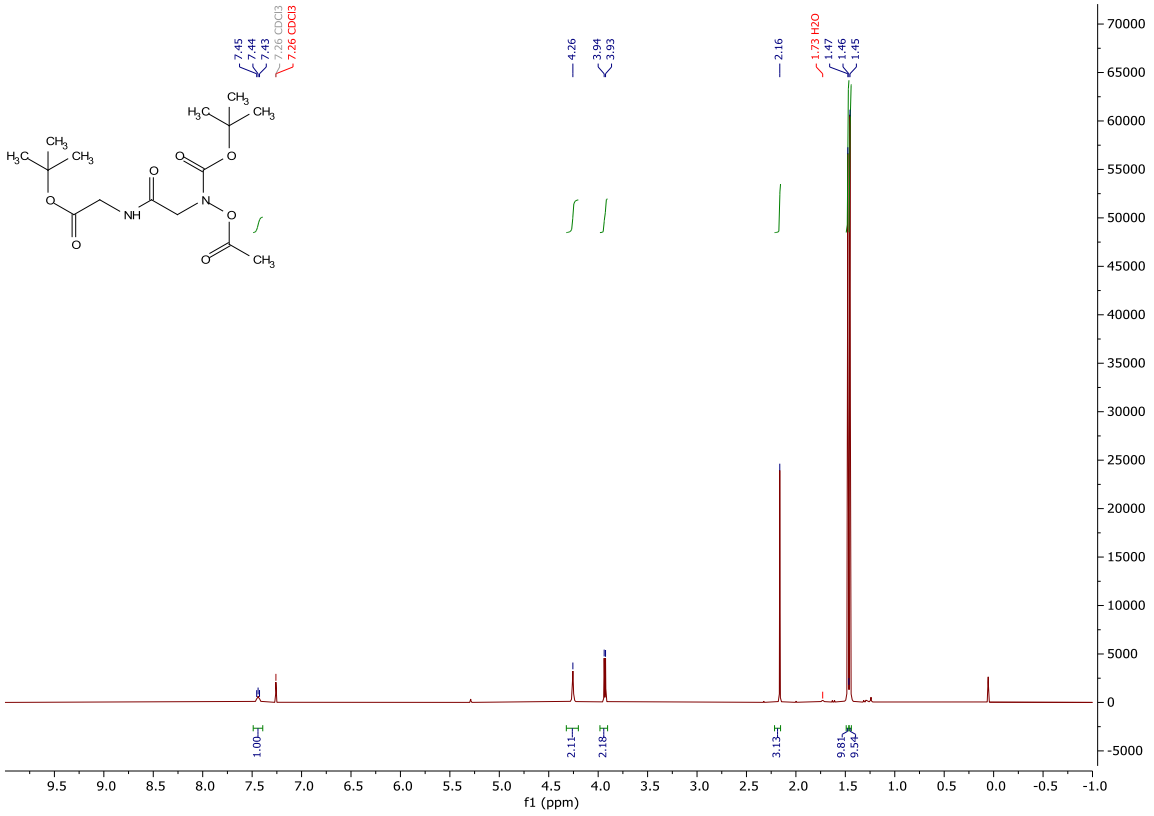


^{13}C NMR (101 MHz, Chloroform-*d*)

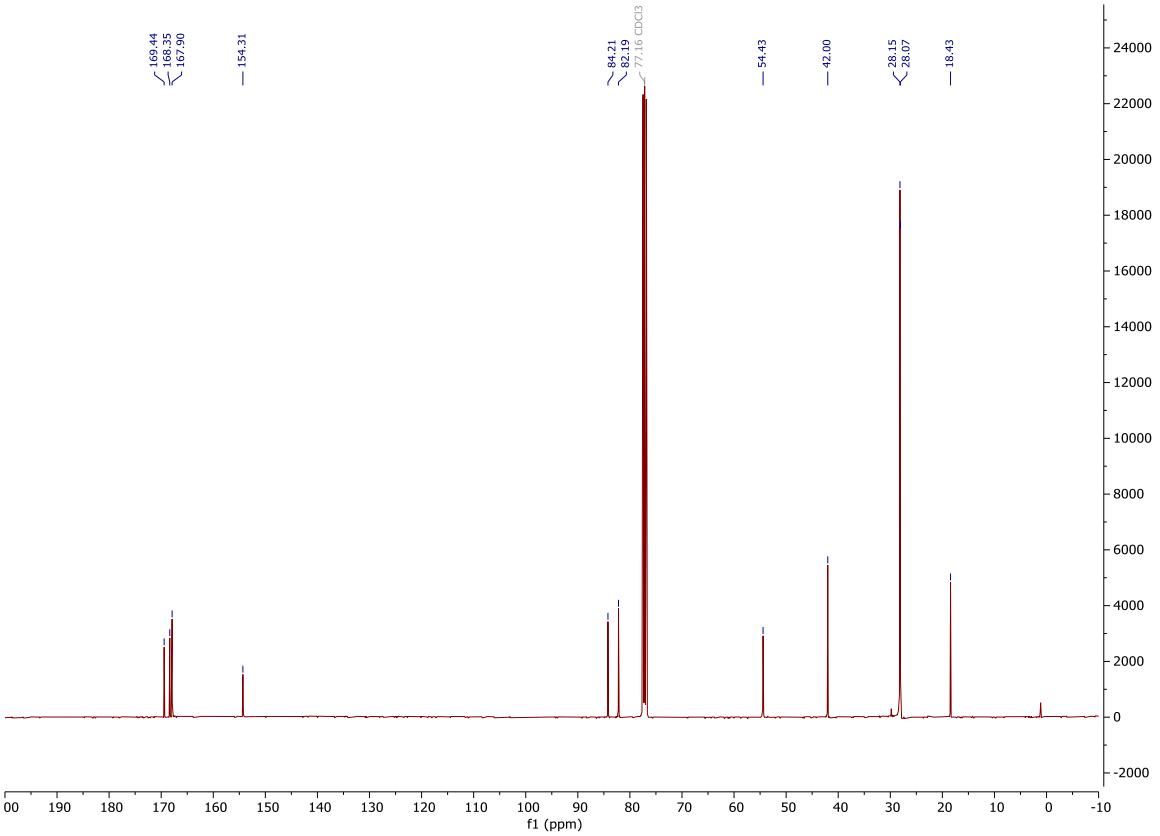


tert-Butyl _N_-acetoxy-N-(_tert_-butoxycarbonyl)glycylglycinate (1i')

^{1}H NMR (400 MHz, Chloroform-_d_)

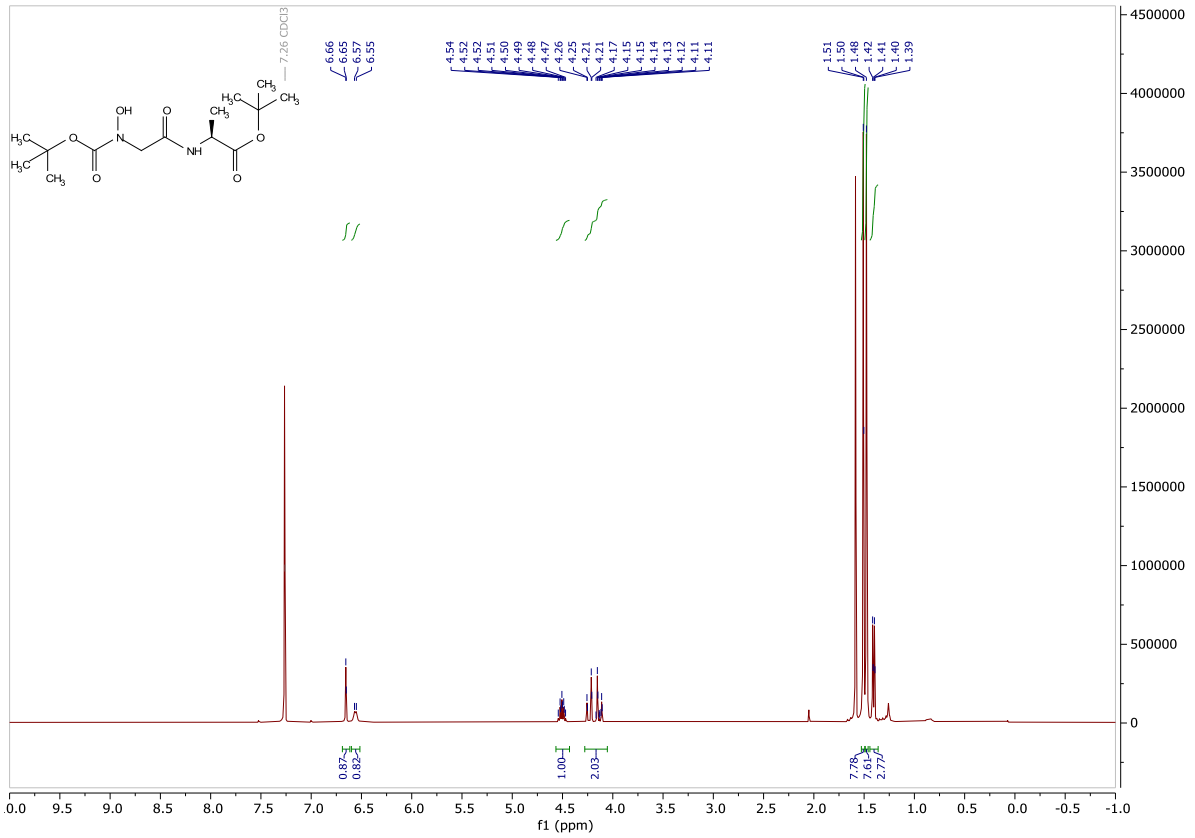


^{13}C NMR (101 MHz, Chloroform-_d_)

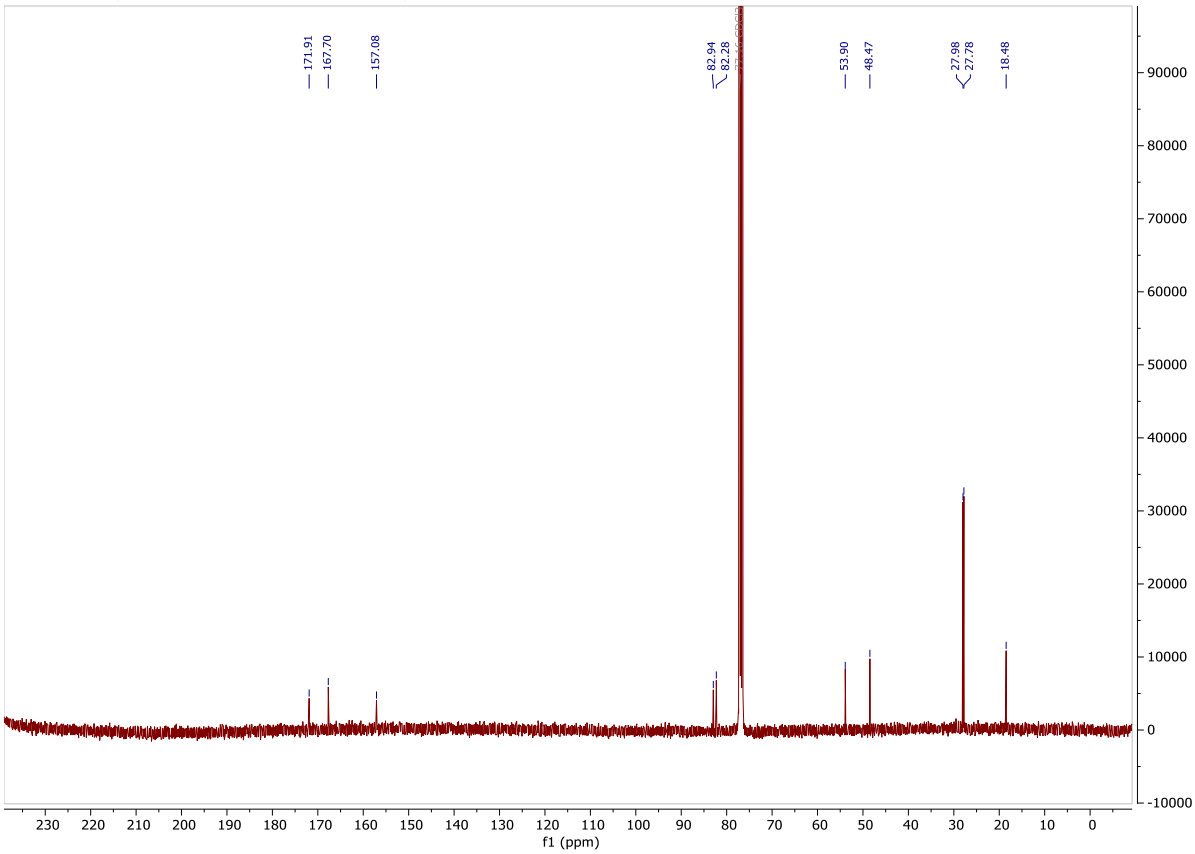


tert-Butyl *N*-(tert-butoxycarbonyl)-*N*-hydroxyglycyl-*L*-alaninate (1j)

^{1}H NMR (400 MHz, Chloroform-*d*)

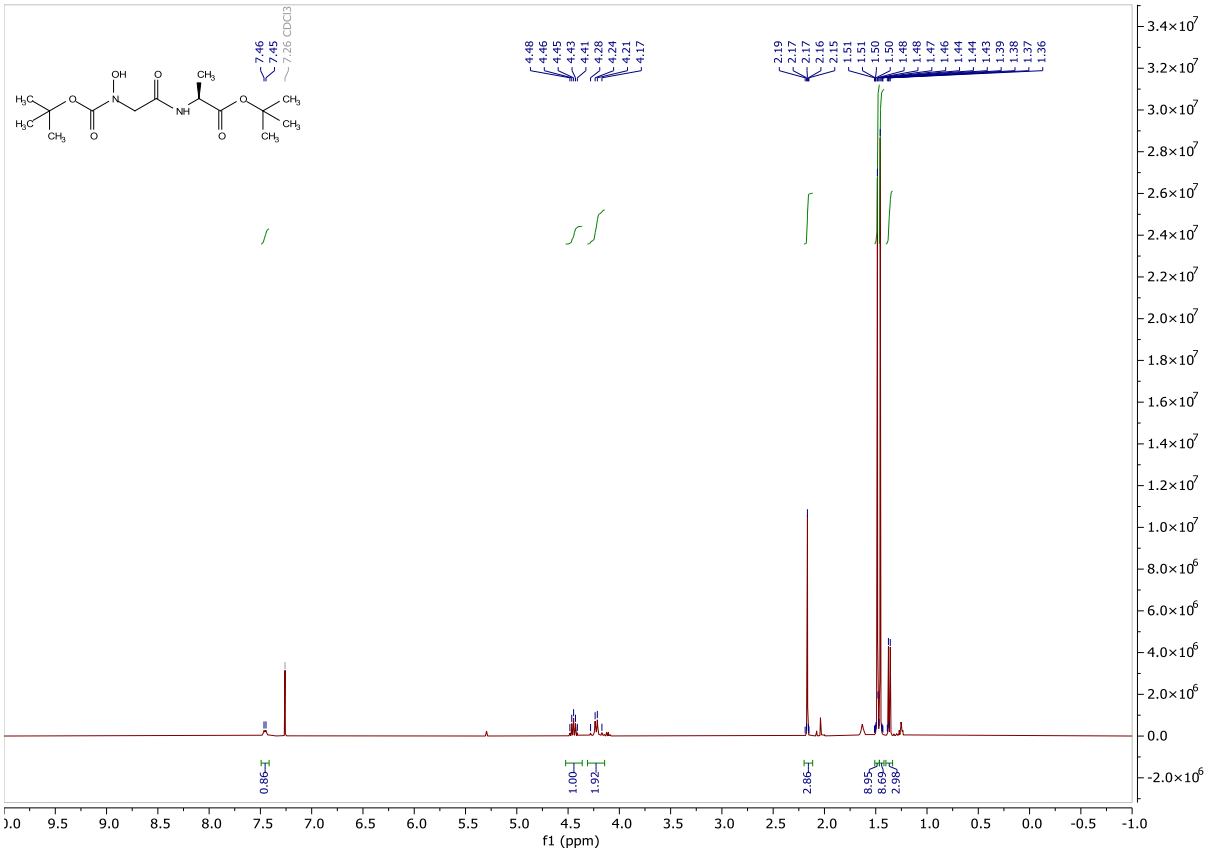


^{13}C NMR (101 MHz, Chloroform-*d*)

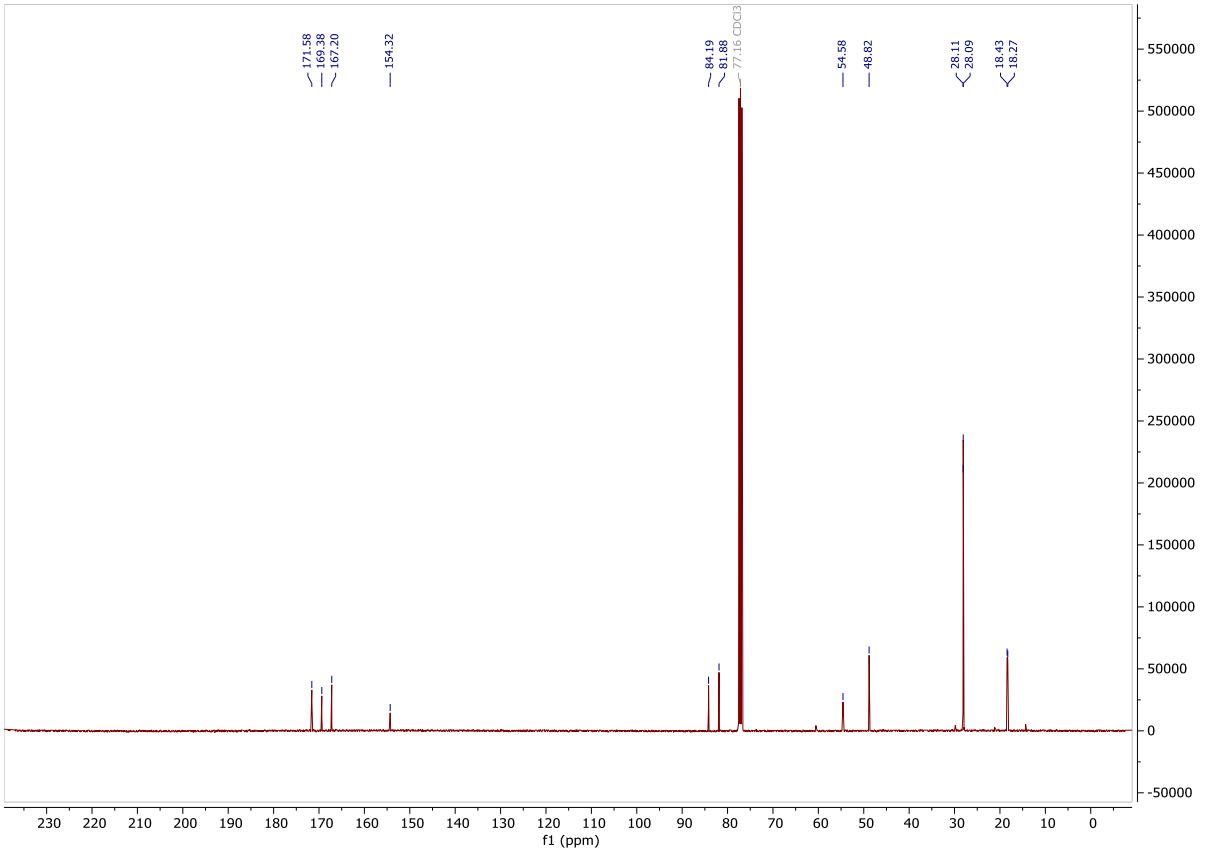


tert-Butyl _N_-acetoxy-_N_-(_tert_-butoxycarbonyl)glycyl-_L_-alaninate (1j')

^{1}H NMR (400 MHz, Chloroform-_d_)

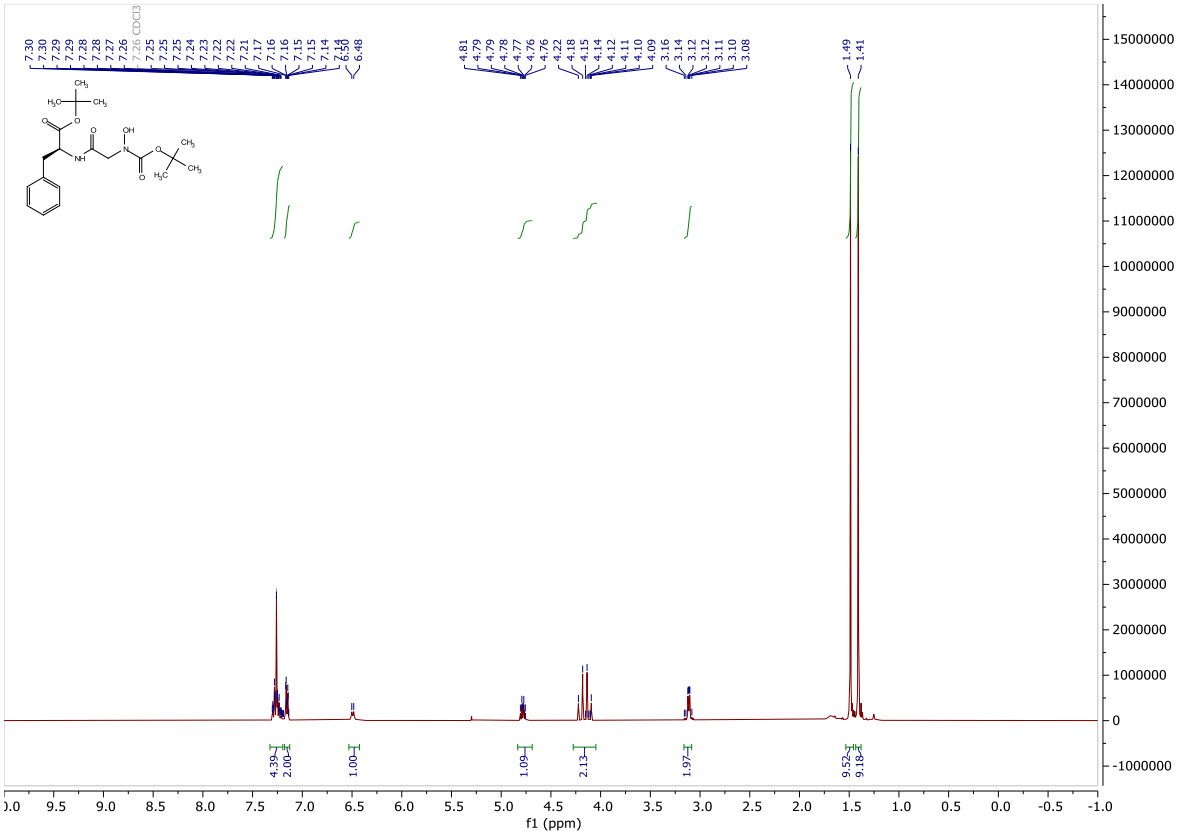


^{13}C NMR (101 MHz, Chloroform-_d_)

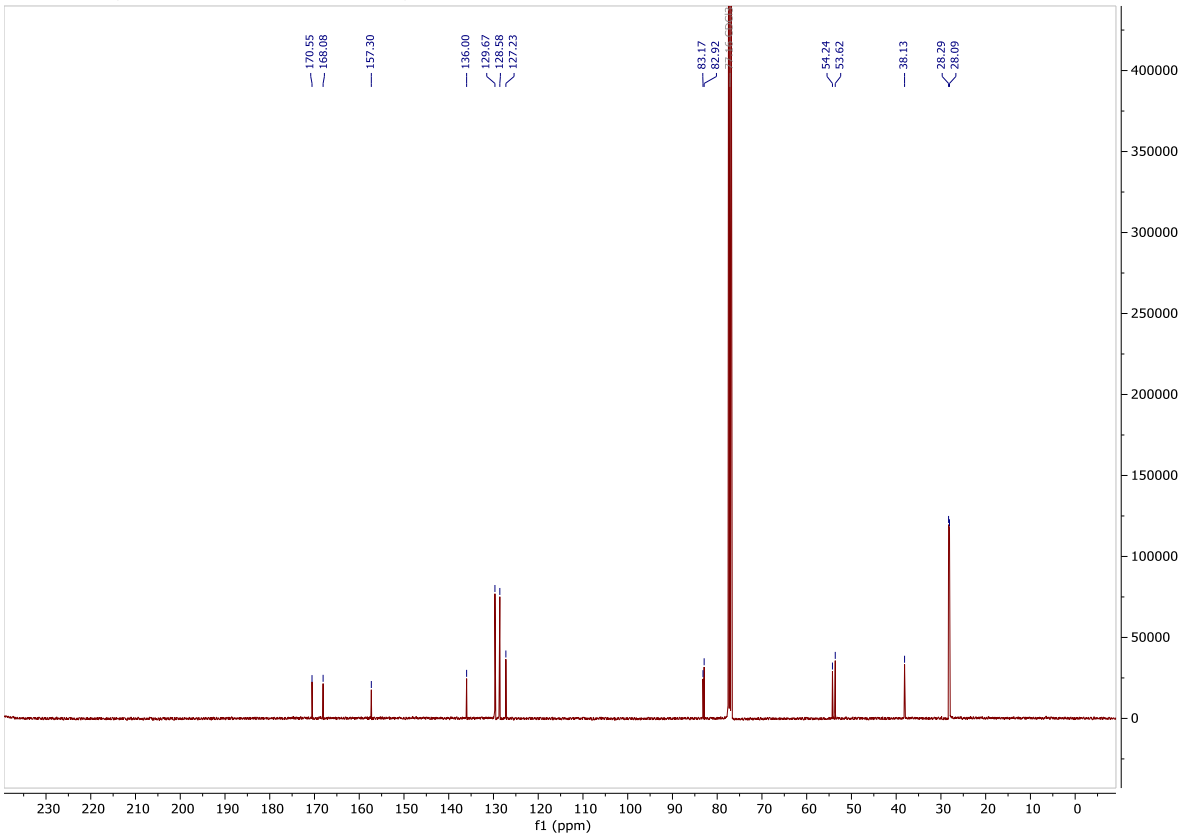


tert-Butyl _N_-(_tert_-butoxycarbonyl)-_N_-hydroxyglycyl-_L_-phenylalaninate (1k)

^{1}H NMR (400 MHz, Chloroform-_d_)

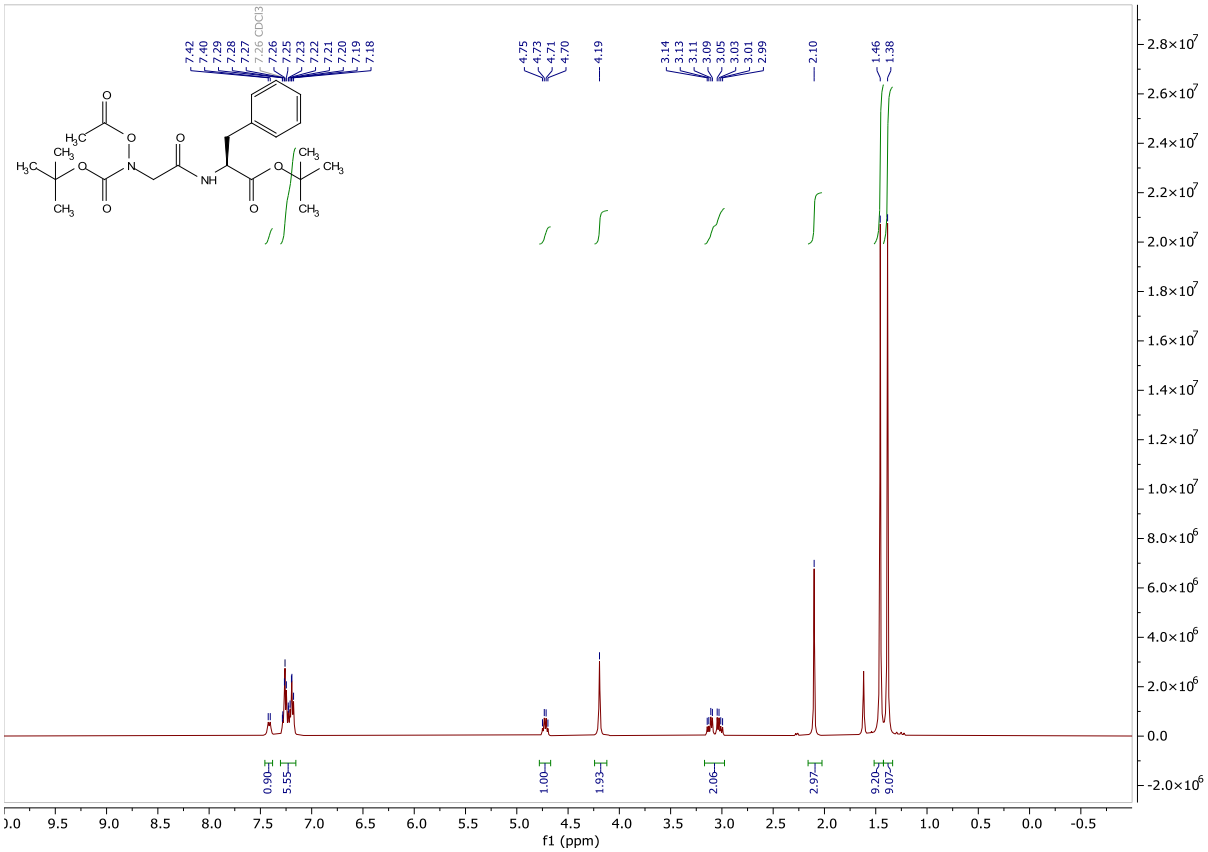


^{13}C NMR (101 MHz, Chloroform-_d_)

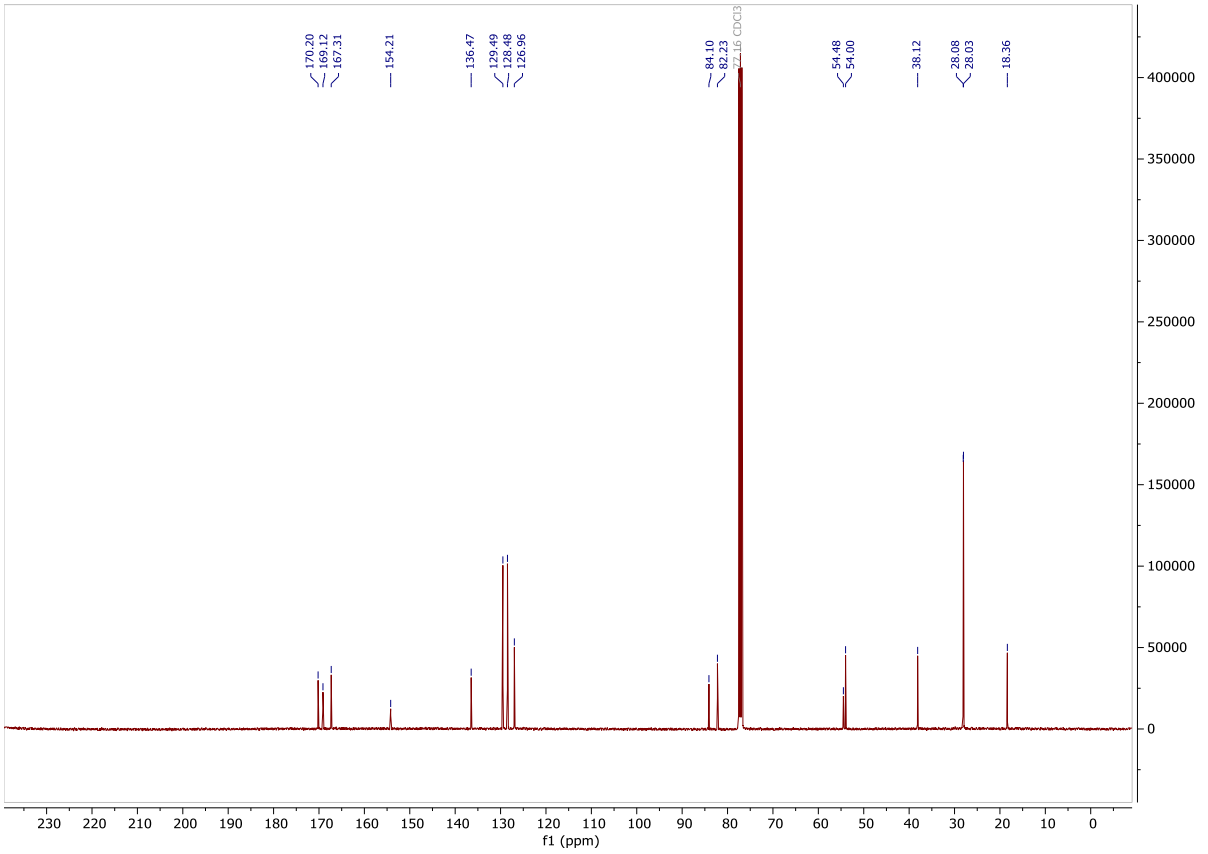


***tert*-Butyl *N*-acetoxy-*N*-(*tert*-butoxycarbonyl)glycyl-*L*-phenylalaninate (1k')**

^{1}H NMR (400 MHz, Chloroform-*d*)

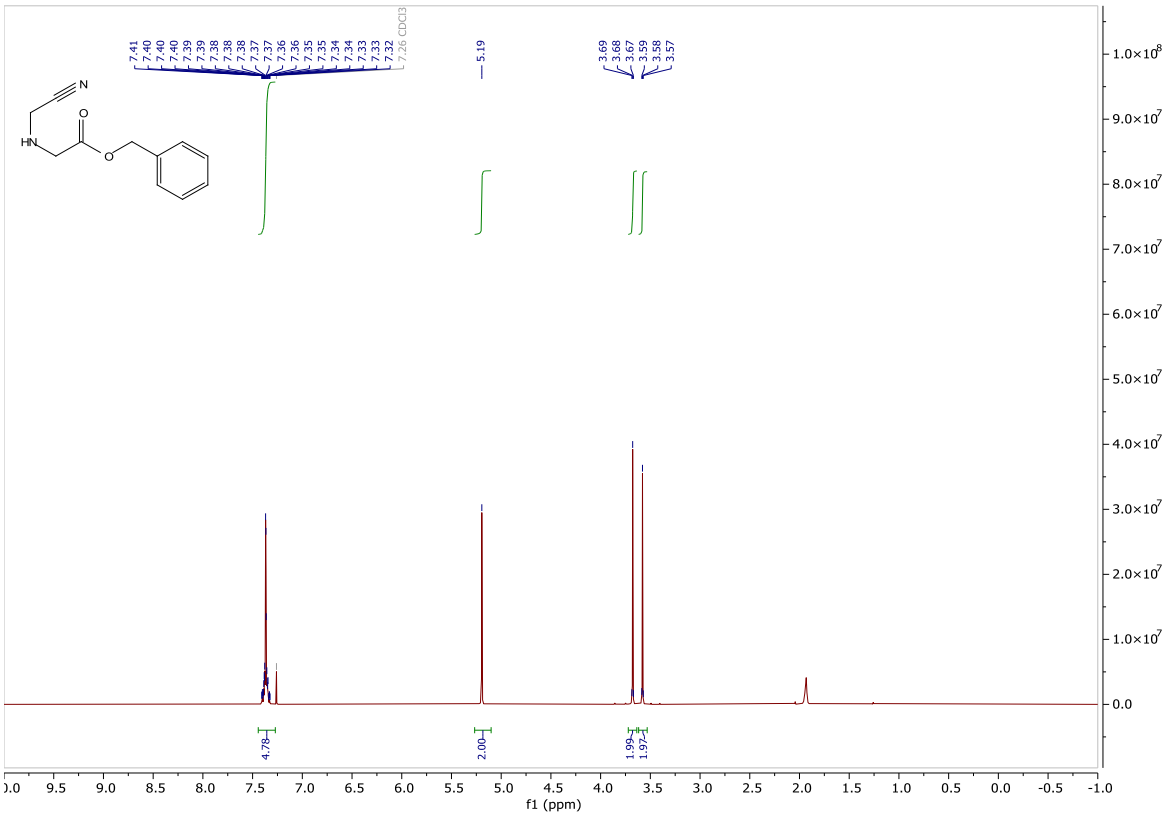


^{13}C NMR (101 MHz, Chloroform-*d*)

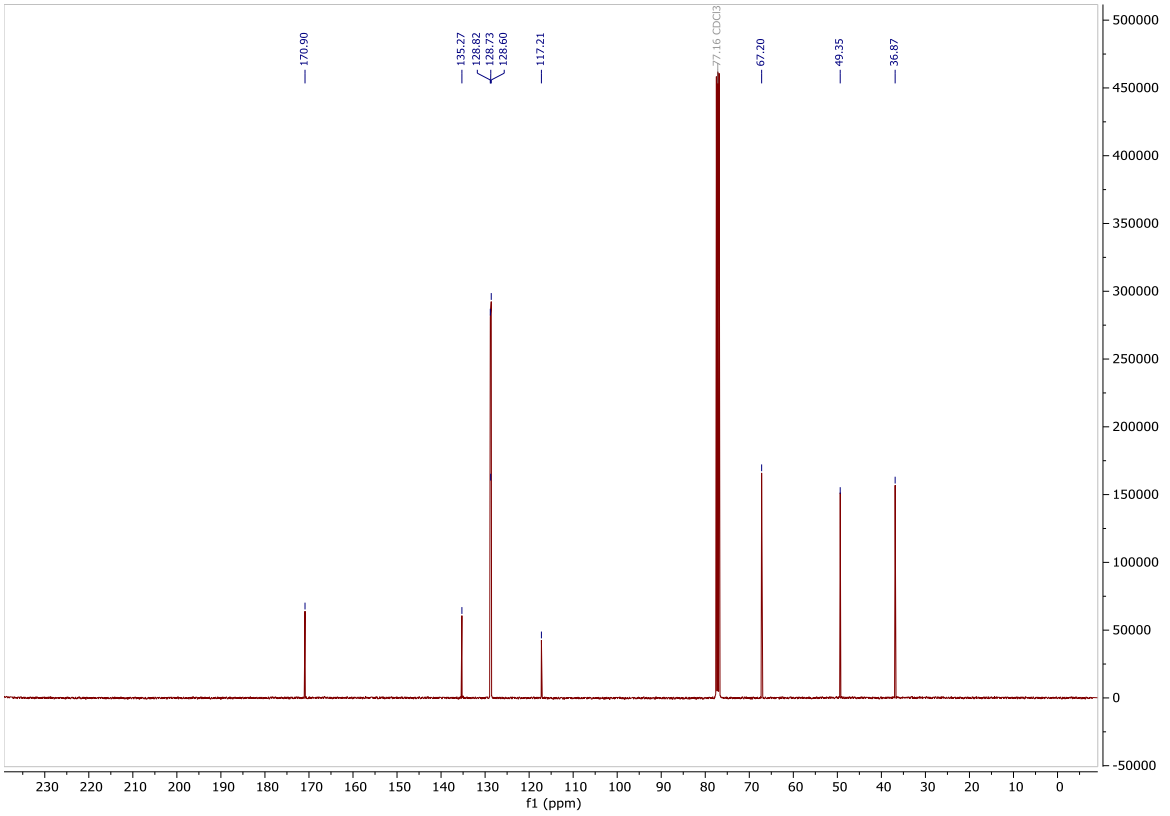


Benzyl (cyanomethyl)glycinate (SM4a)

^{1}H NMR (400 MHz, Chloroform-*d*)

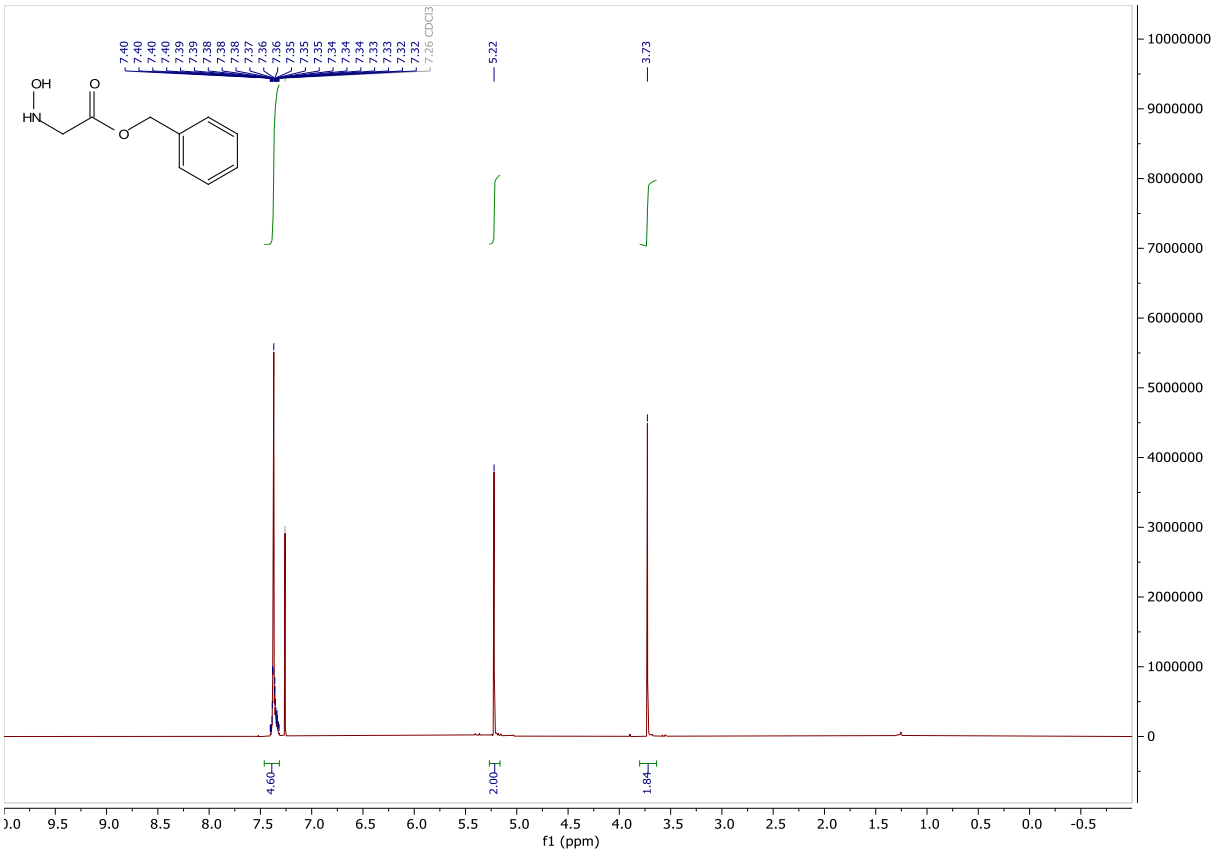


^{13}C NMR (101 MHz, Chloroform-*d*)

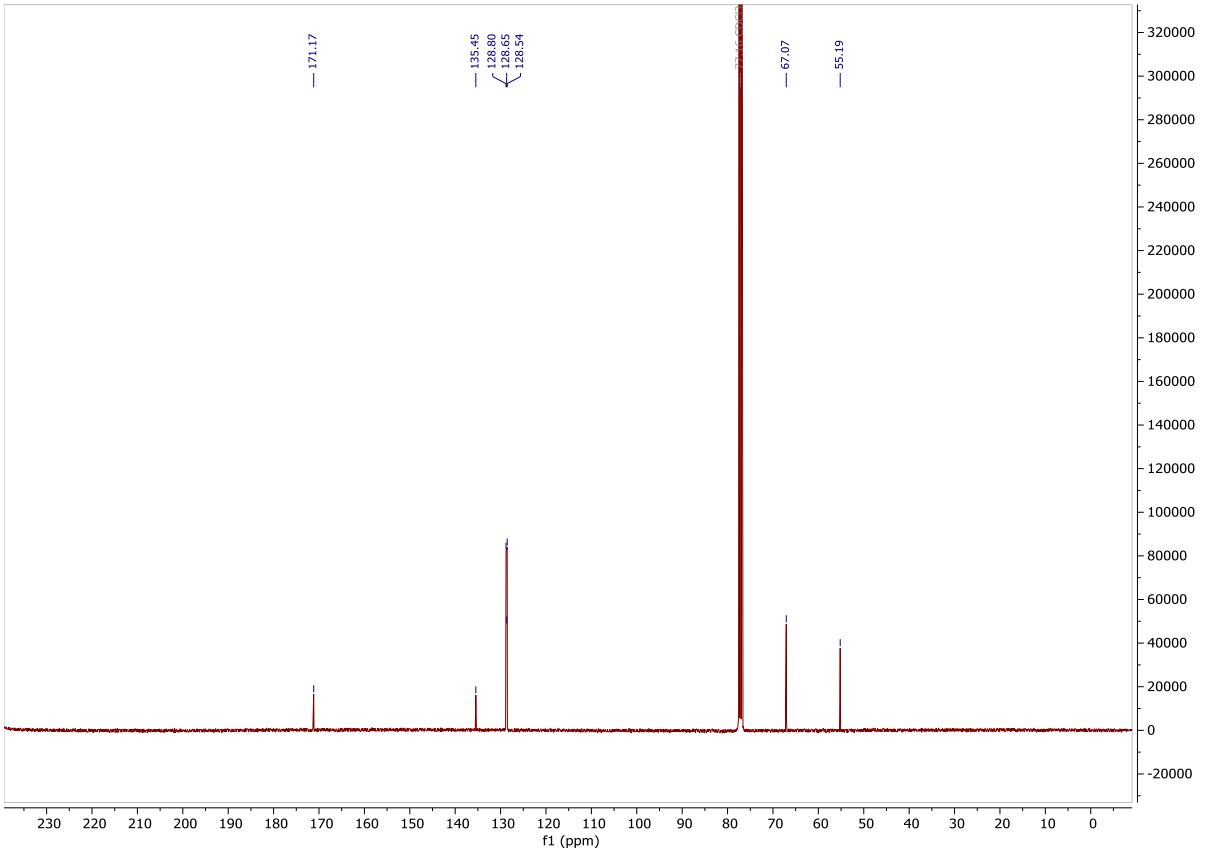


Benzyl hydroxyglycinate (SM4aa)

^{1}H NMR (400 MHz, Chloroform-*d*)

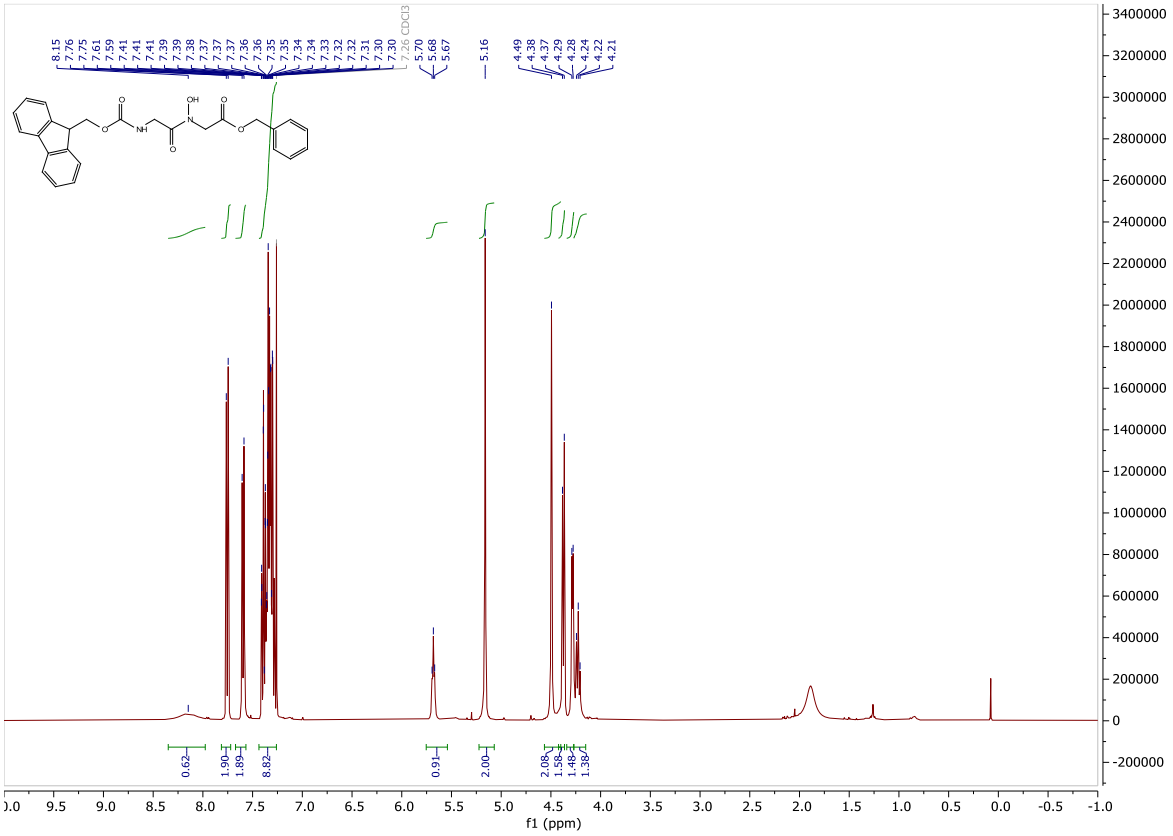


^{13}C NMR (101 MHz, Chloroform-*d*)

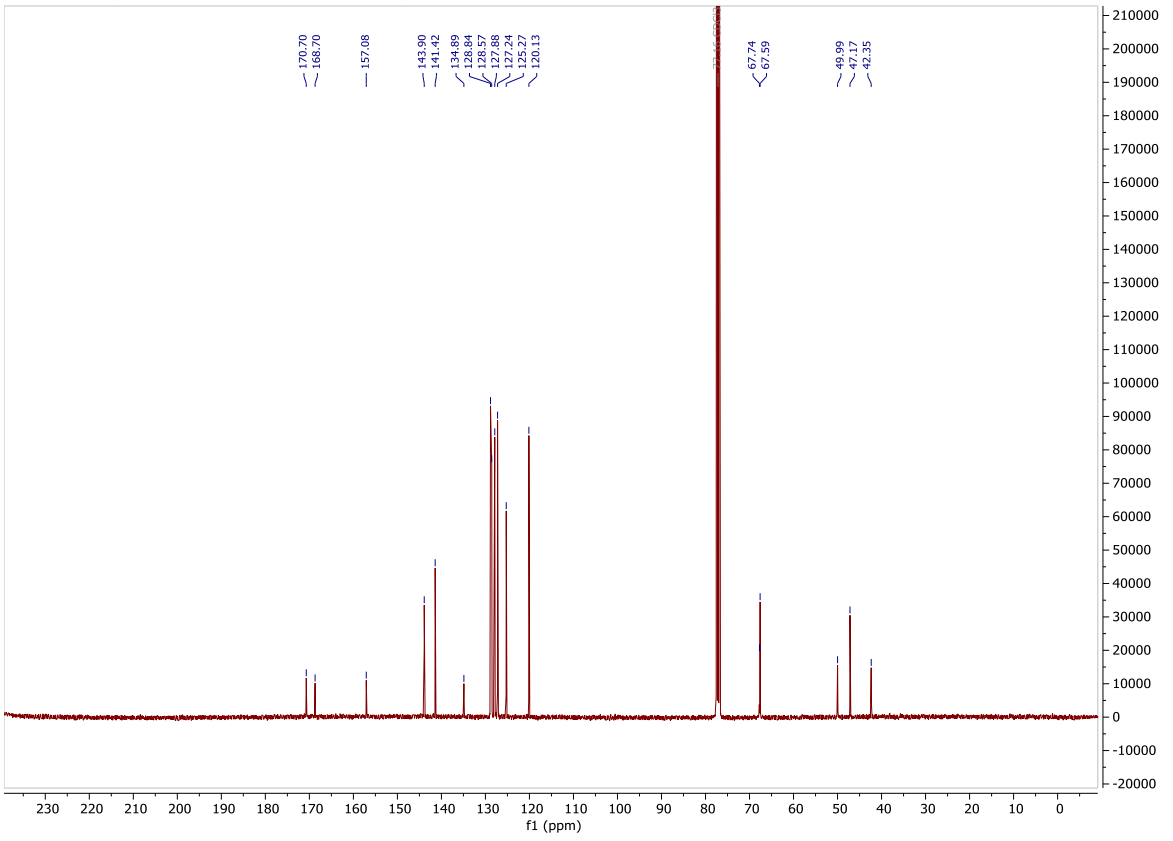


Benzyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-hydroxyglycinate (1l)

^{1}H NMR (400 MHz, Chloroform-*d*)

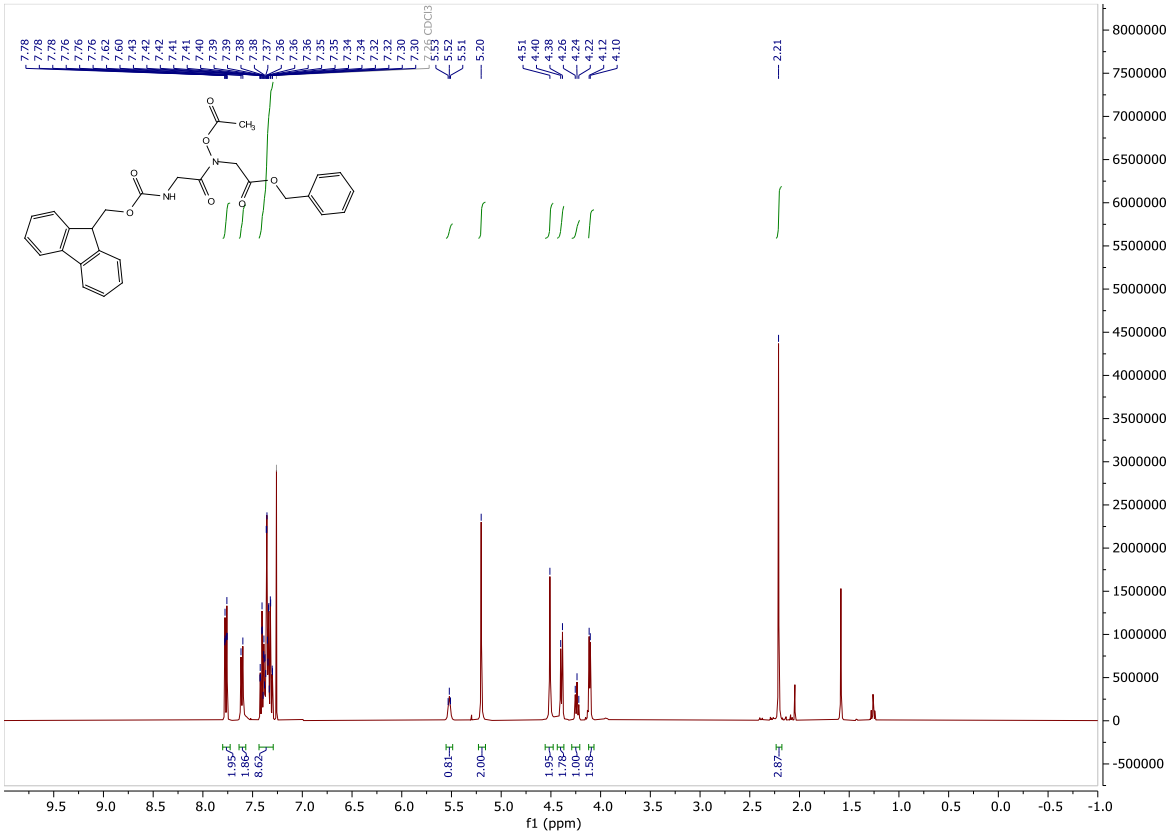


^{13}C NMR (101 MHz, Chloroform-*d*)

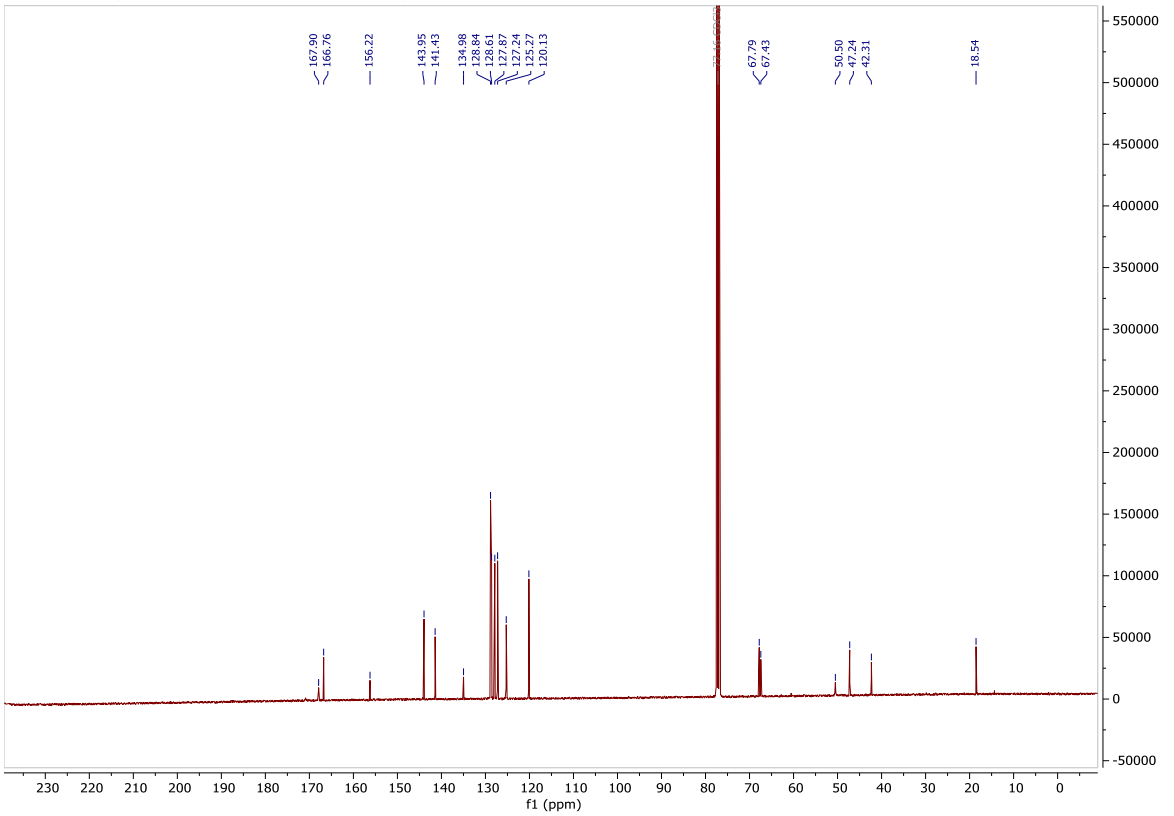


Benzyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-acetoxyglycinate (1l')

^{1}H NMR (400 MHz, Chloroform-*d*)

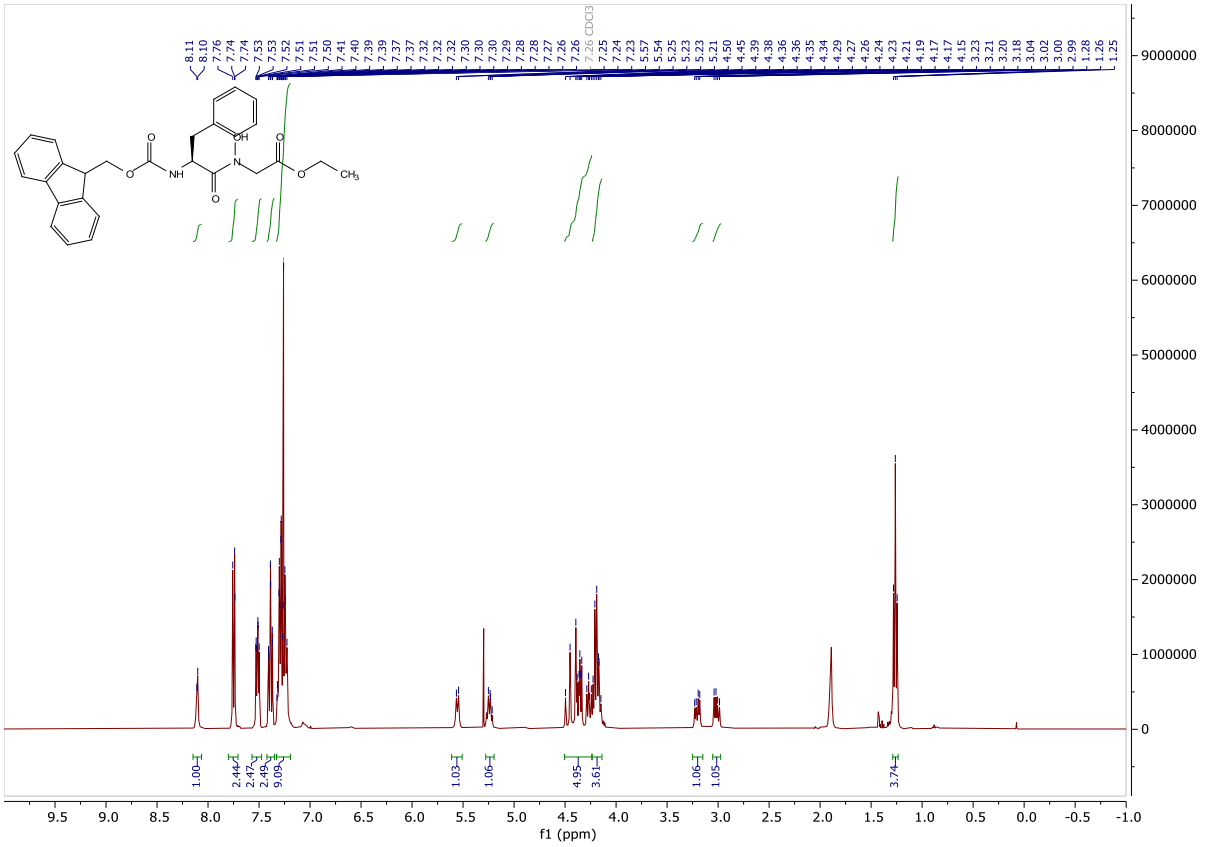


^{13}C NMR (101 MHz, Chloroform-*d*)

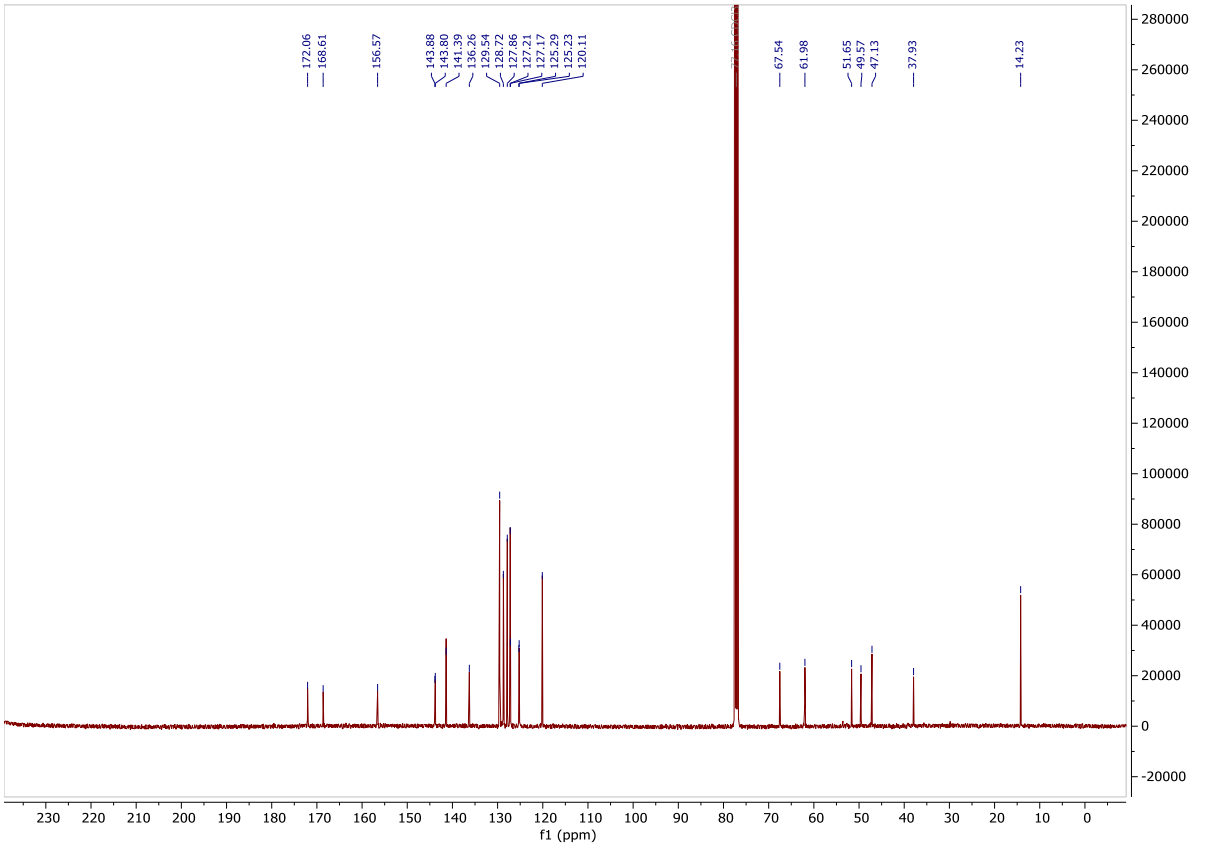


Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalanyl)-*N*-hydroxyglycinate (**1m**)

^{1}H NMR (400 MHz, Chloroform-*d*)

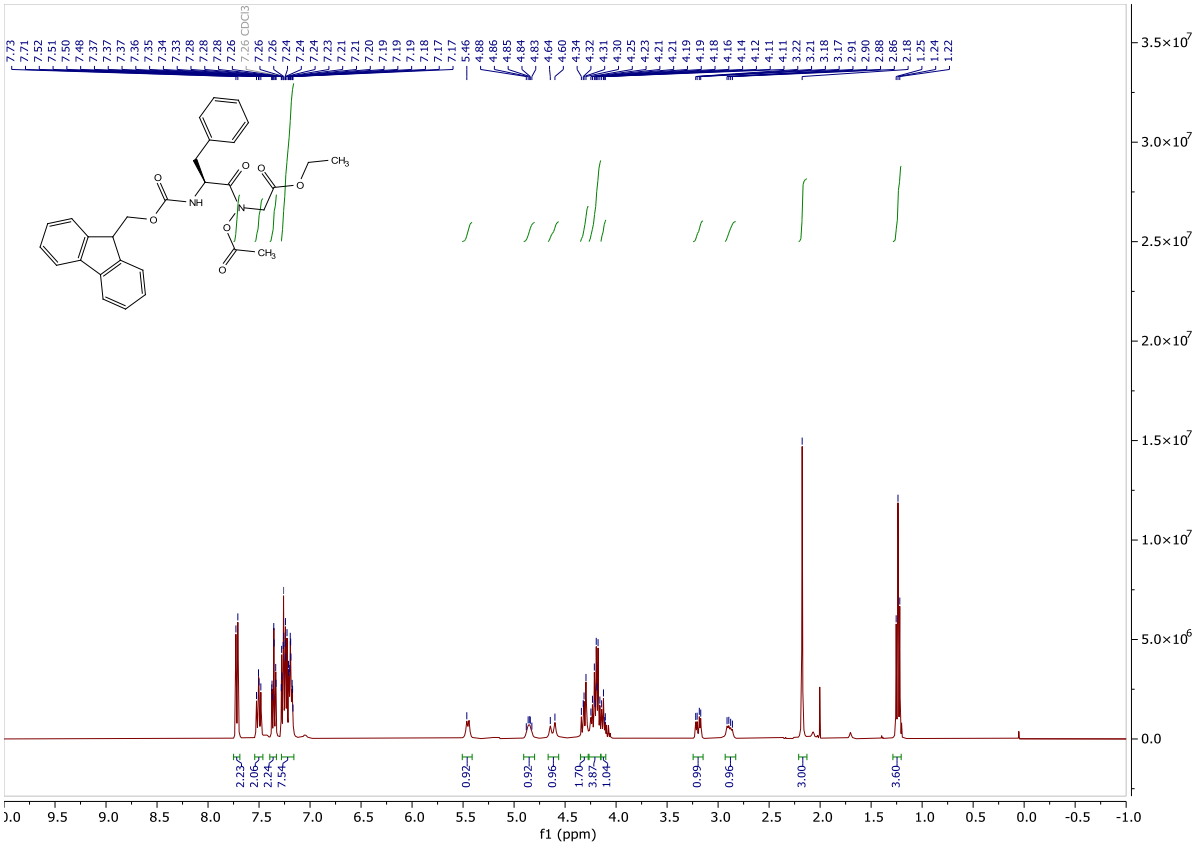


^{13}C NMR (101 MHz, Chloroform-*d*)

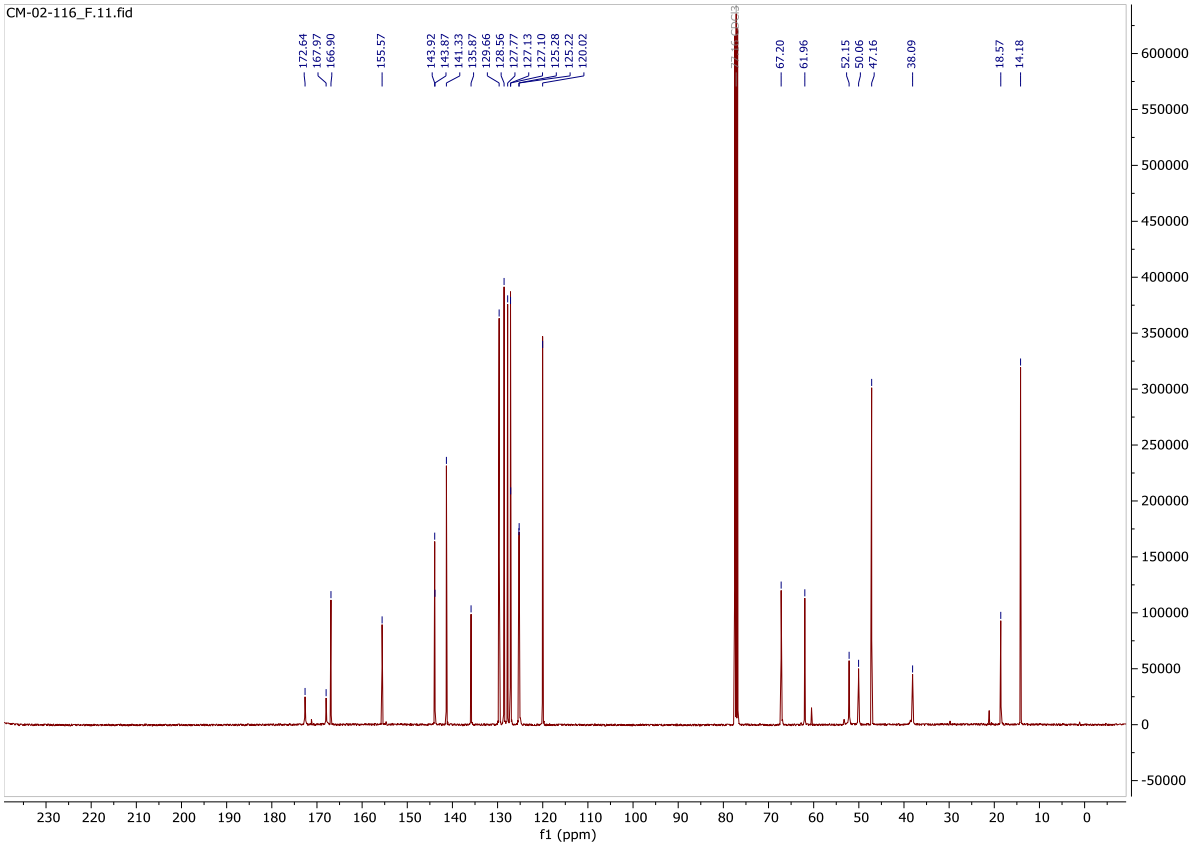


Ethyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalanyl)-*N*-acetoxyglycinate **(1m')**

^{1}H NMR (400 MHz, Chloroform-*d*)

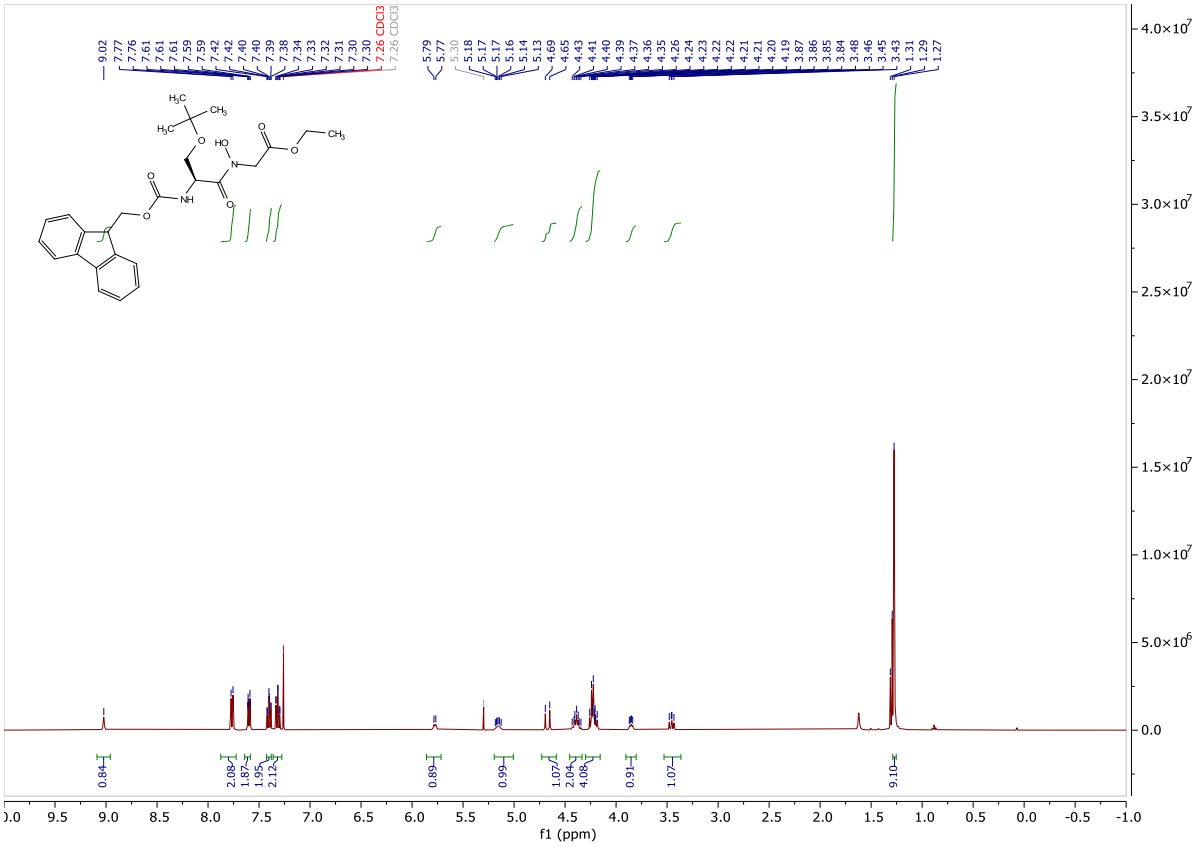


^{13}C NMR (101 MHz, Chloroform-*d*)

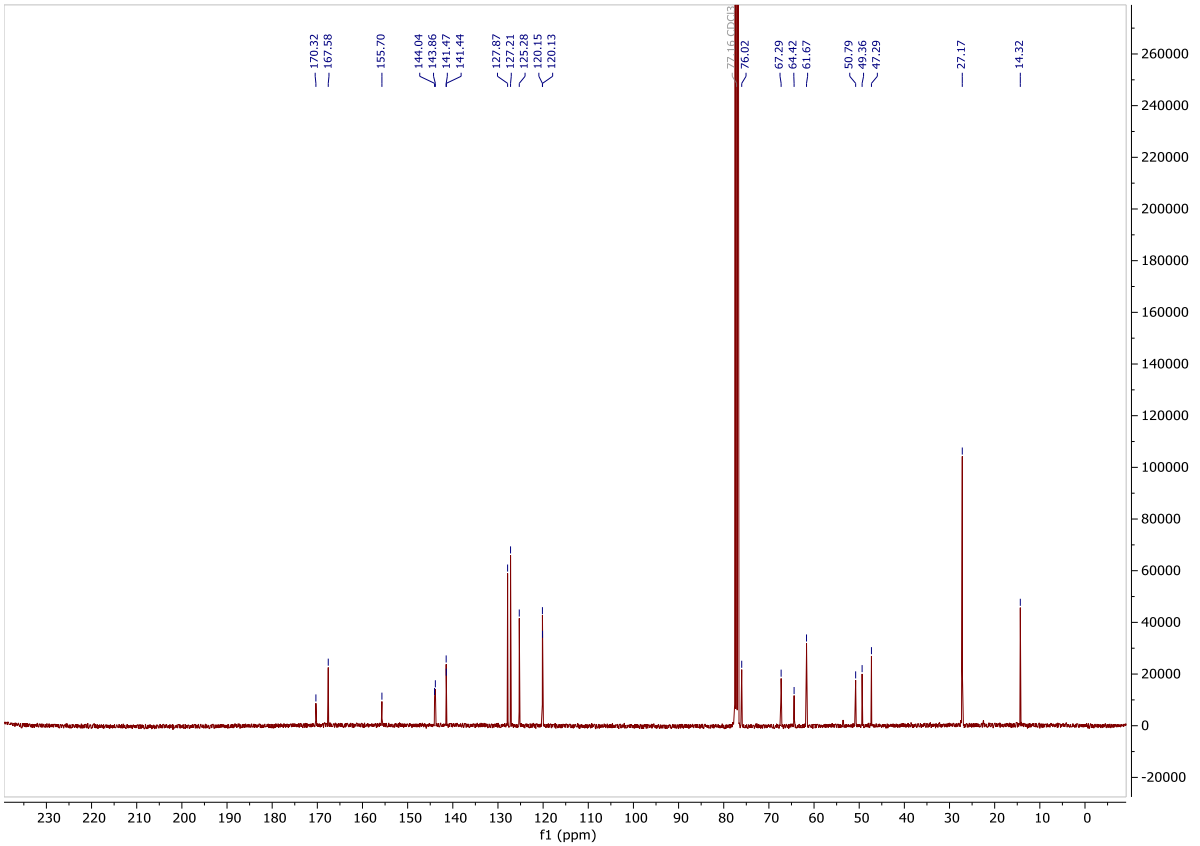


Ethyl *N*-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-*L*-seryl)-*N*-hydroxyglycinate (**1n**)

^{1}H NMR (400 MHz, Chloroform-*d*)

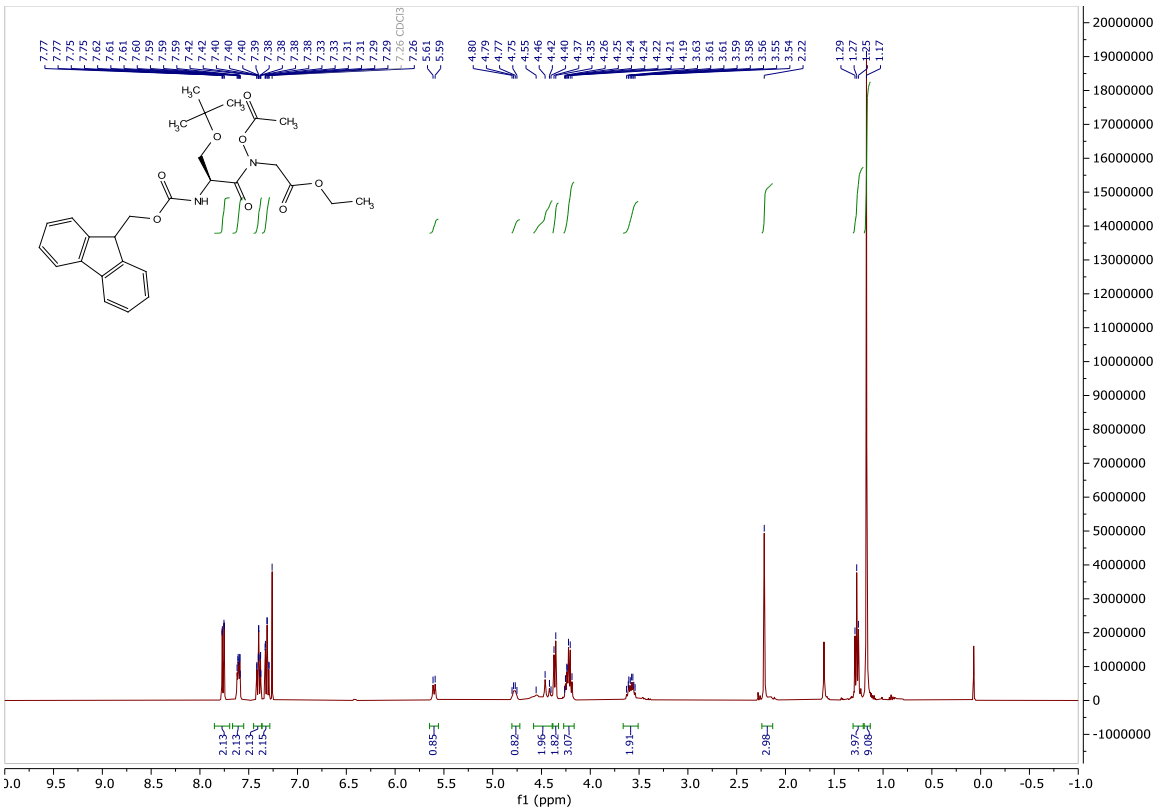


^{13}C NMR (101 MHz, Chloroform-*d*)

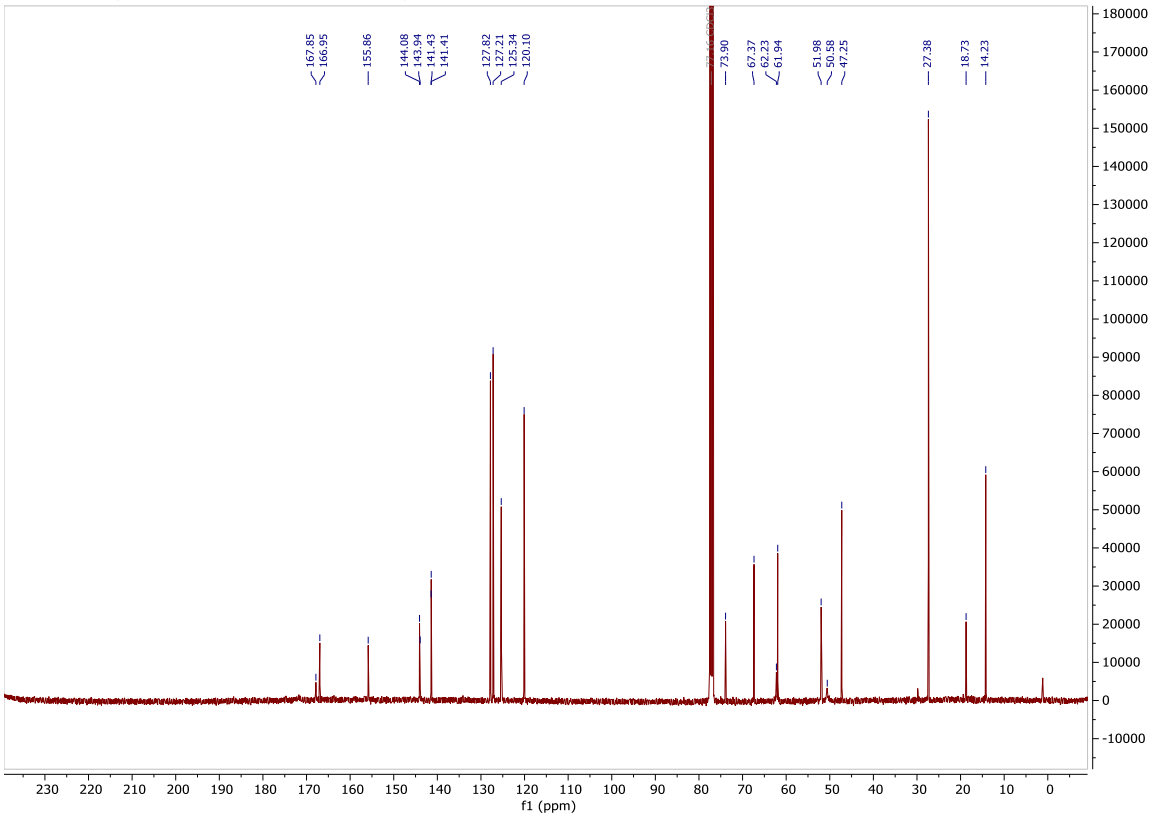


Ethyl *N*-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-*L*-seryl)-*N*-acetoxyglycinate (**1n'**)

^{1}H NMR (400 MHz, Chloroform-*d*)

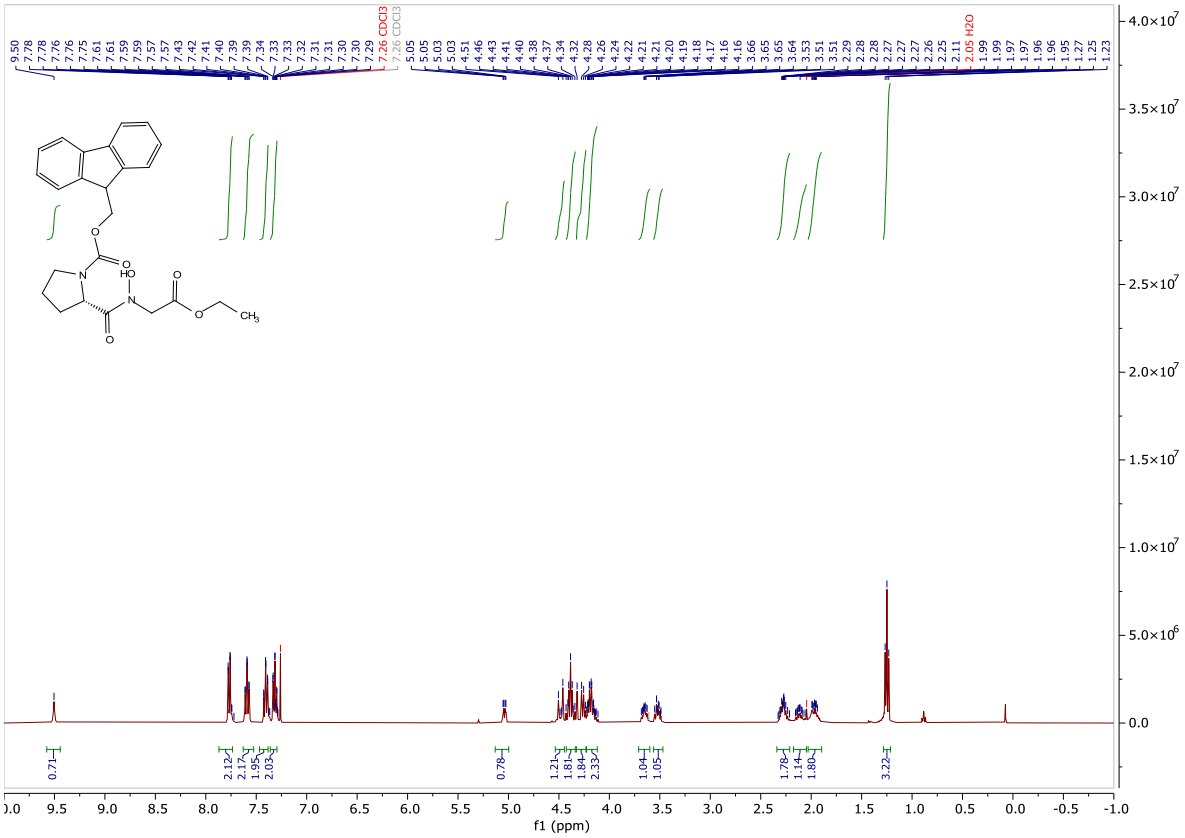


^{13}C NMR (101 MHz, Chloroform-*d*)

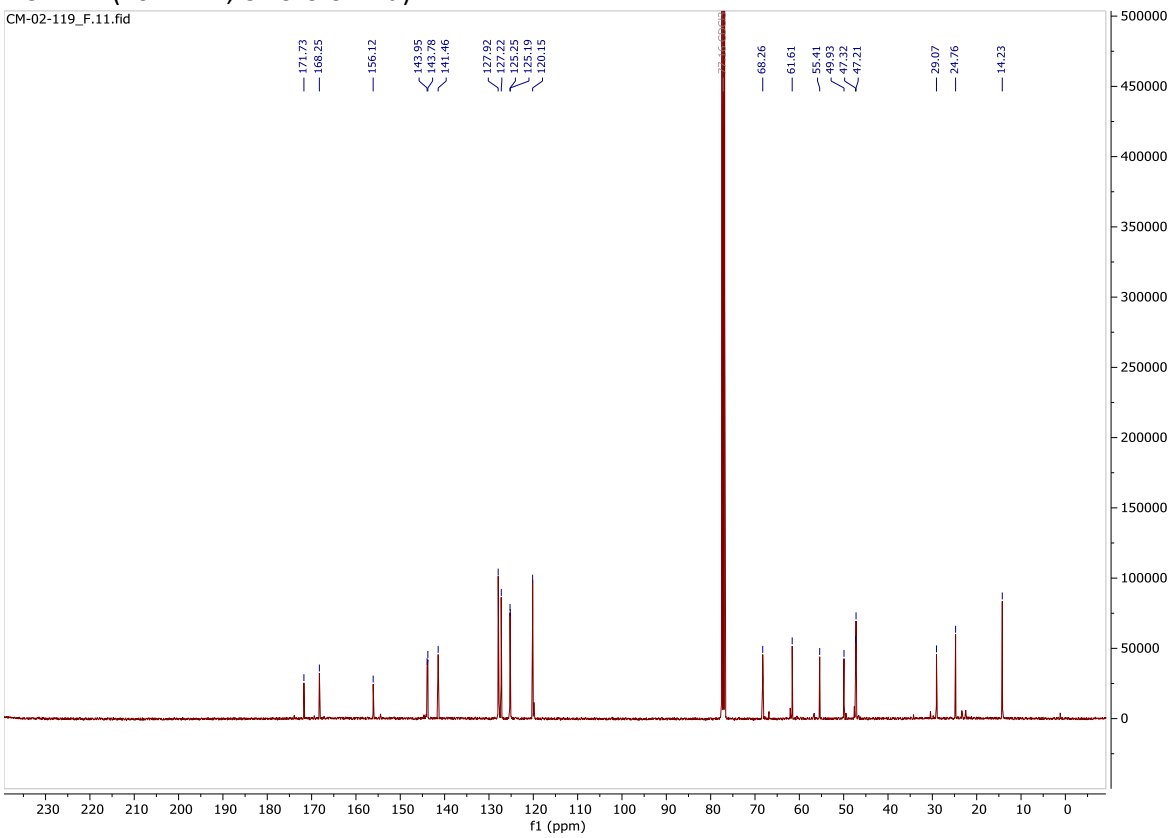


(9*H*-fluoren-9-yl)methyl (*S*)-2-((2-ethoxy-2-oxoethyl)(hydroxy)carbamoyl)pyrrolidine-1-carboxylate (**1o**)

^{1}H NMR (400 MHz, Chloroform-*d*)

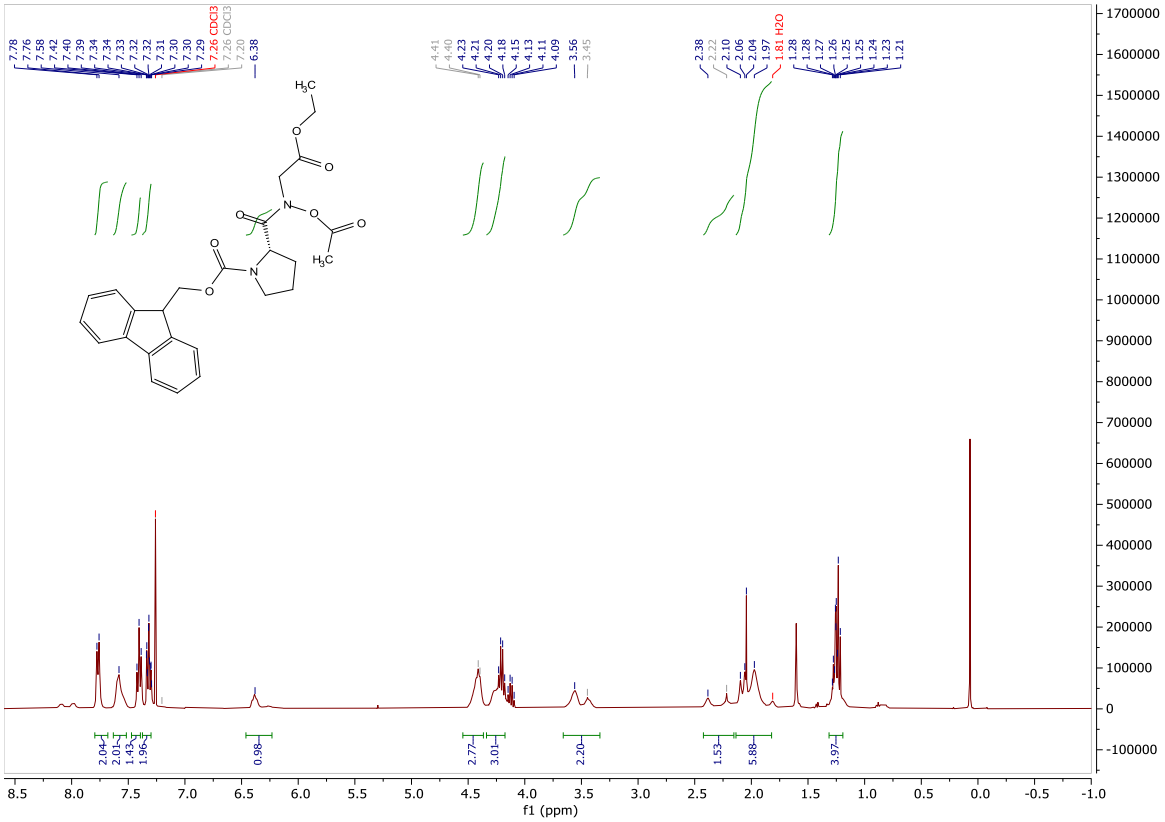


^{13}C NMR (101 MHz, Chloroform-*d*)

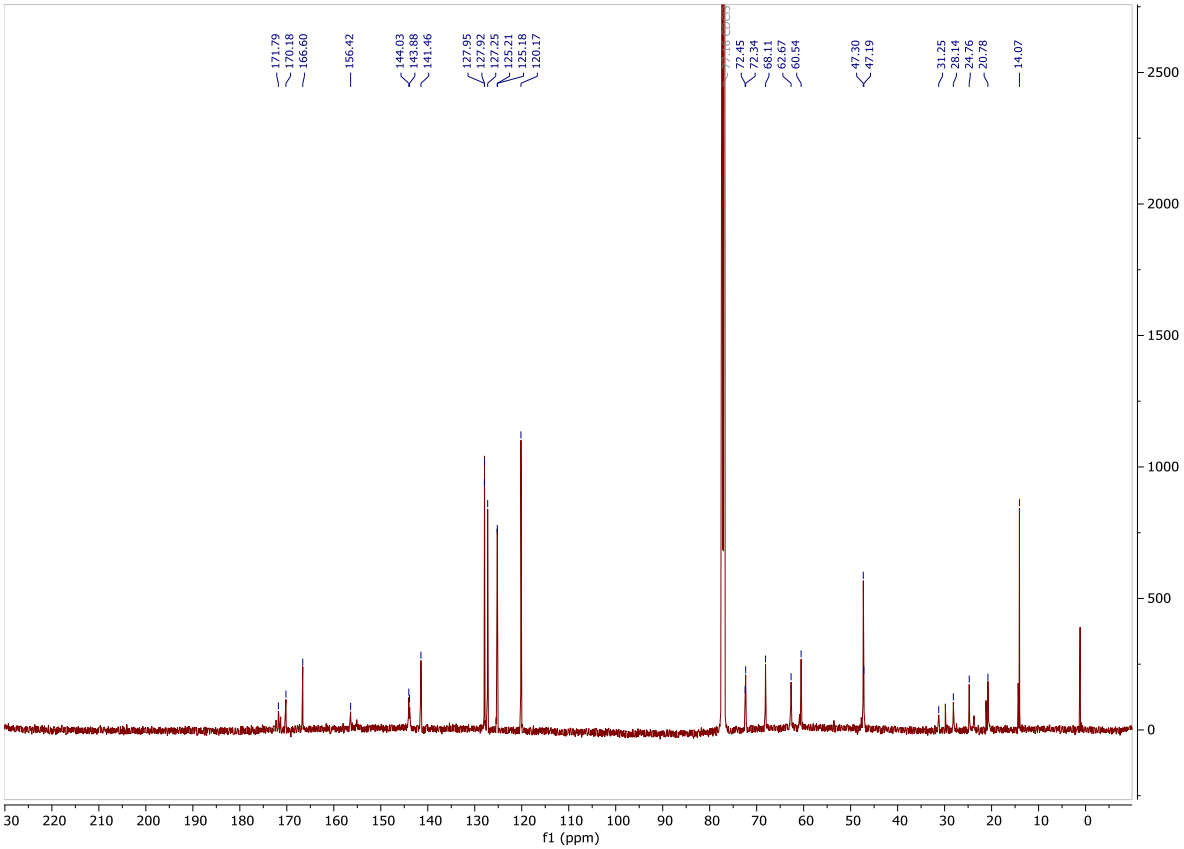


(9*H*-fluoren-9-yl)methyl (*S*)-2-(acetoxy(2-ethoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (**1o'**)

^{1}H NMR (400 MHz, Chloroform-*d*)

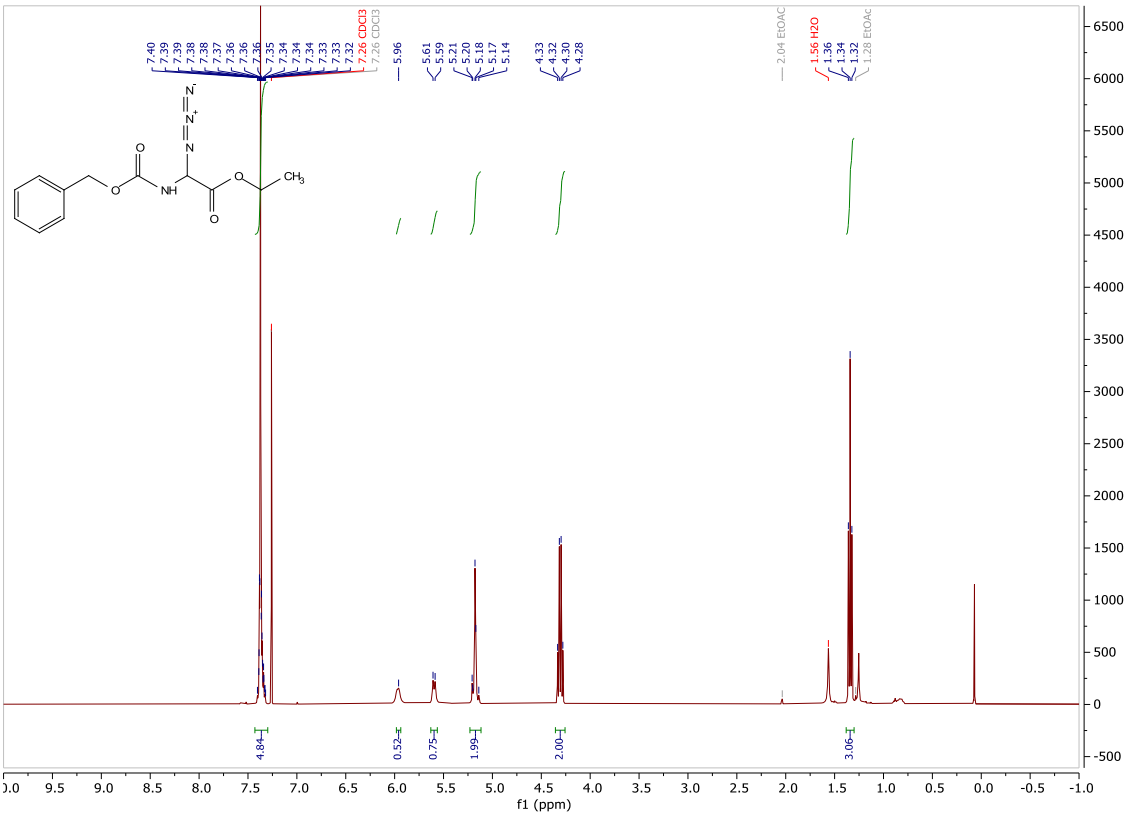


^{13}C NMR (151 MHz, Chloroform-*d*)

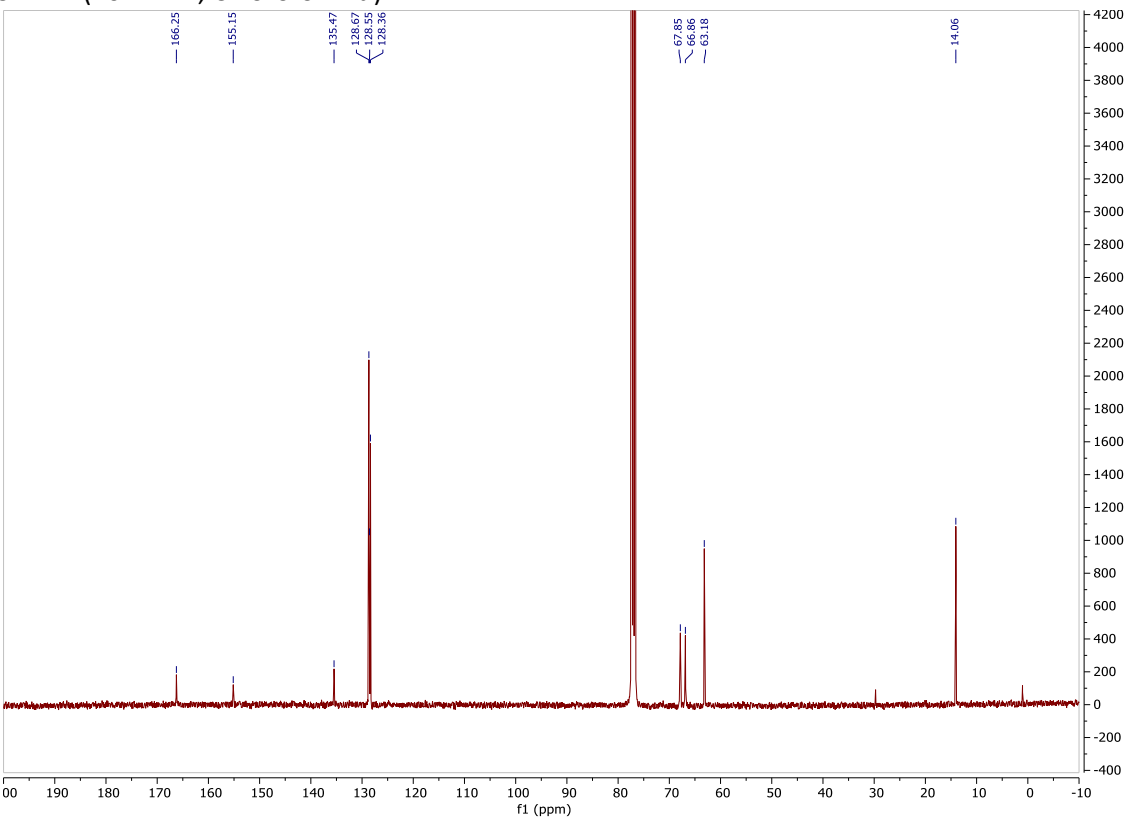


Ethyl 2-azido-2-(((benzyloxy)carbonyl)amino)acetate (3a)

^{1}H NMR (400 MHz, Chloroform-*d*)

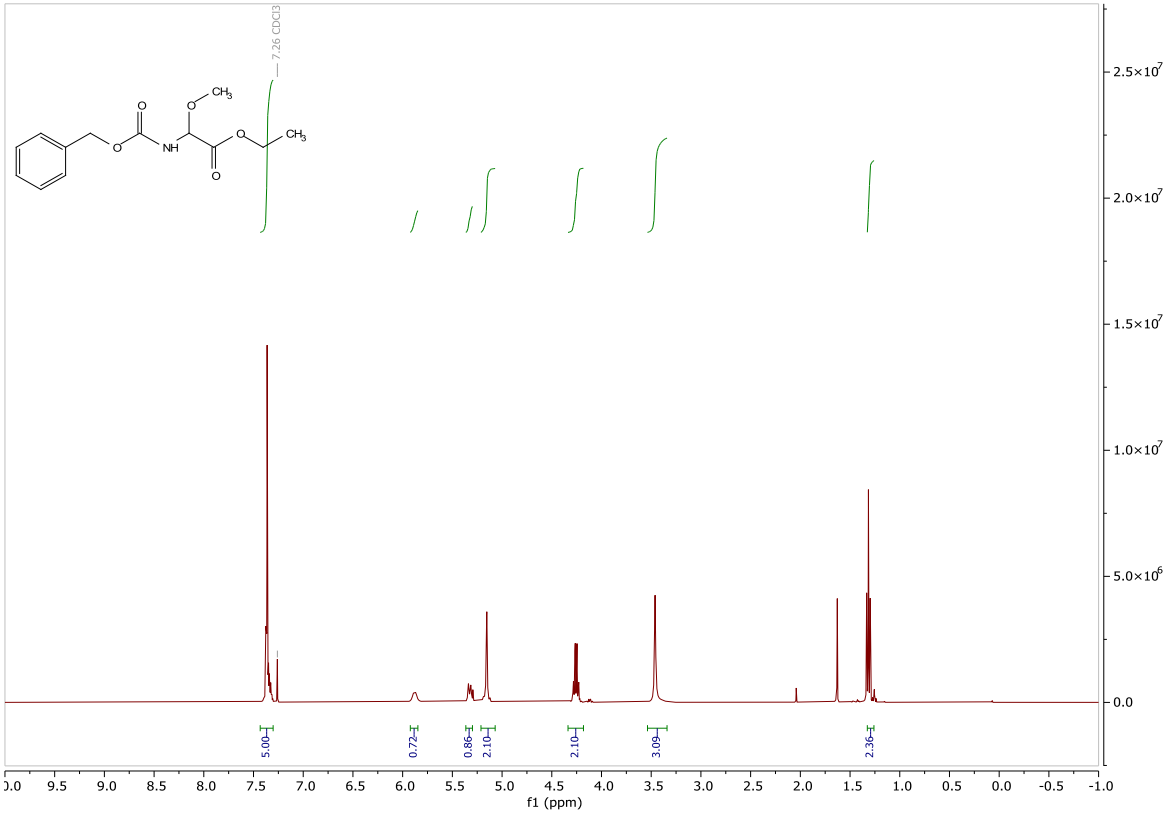


^{13}C NMR (101 MHz, Chloroform-*d*)

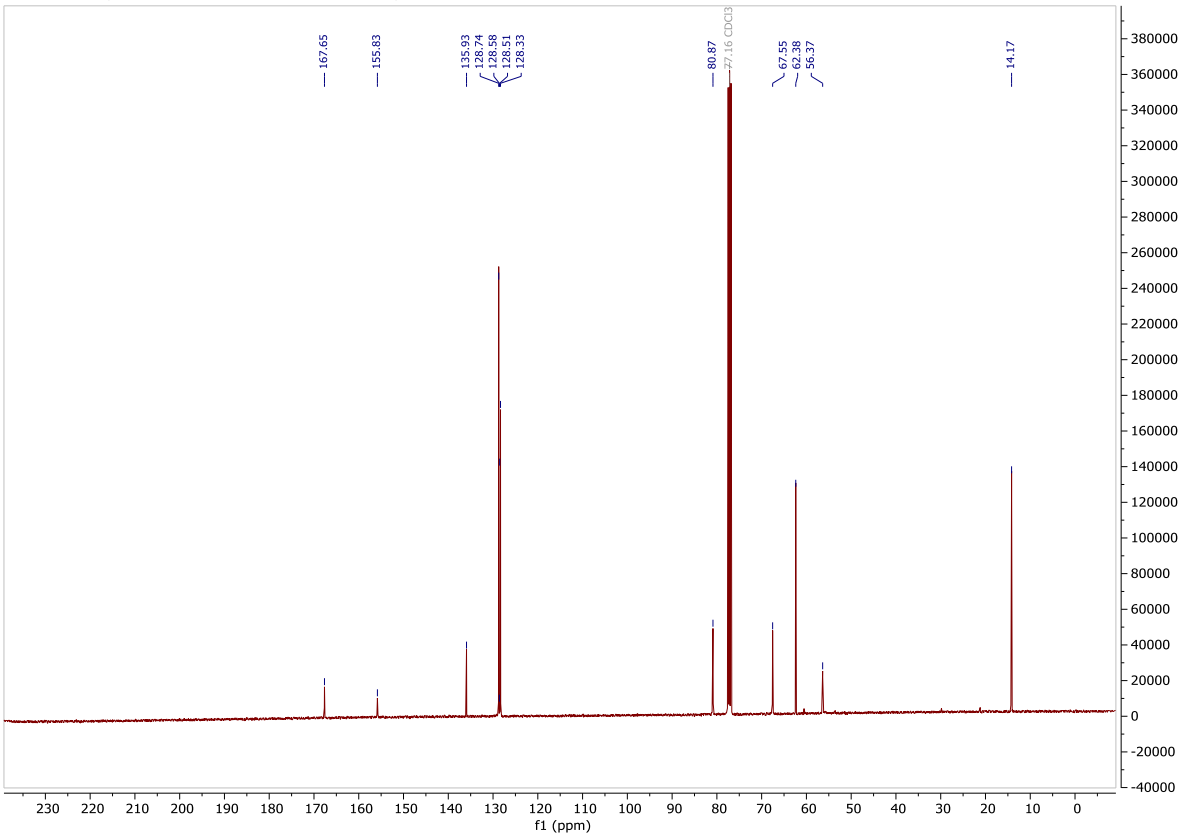


Ethyl 2-(((benzyloxy)carbonyl)amino)-2-methoxyacetate (3b)

^{1}H NMR (400 MHz, Chloroform-*d*)

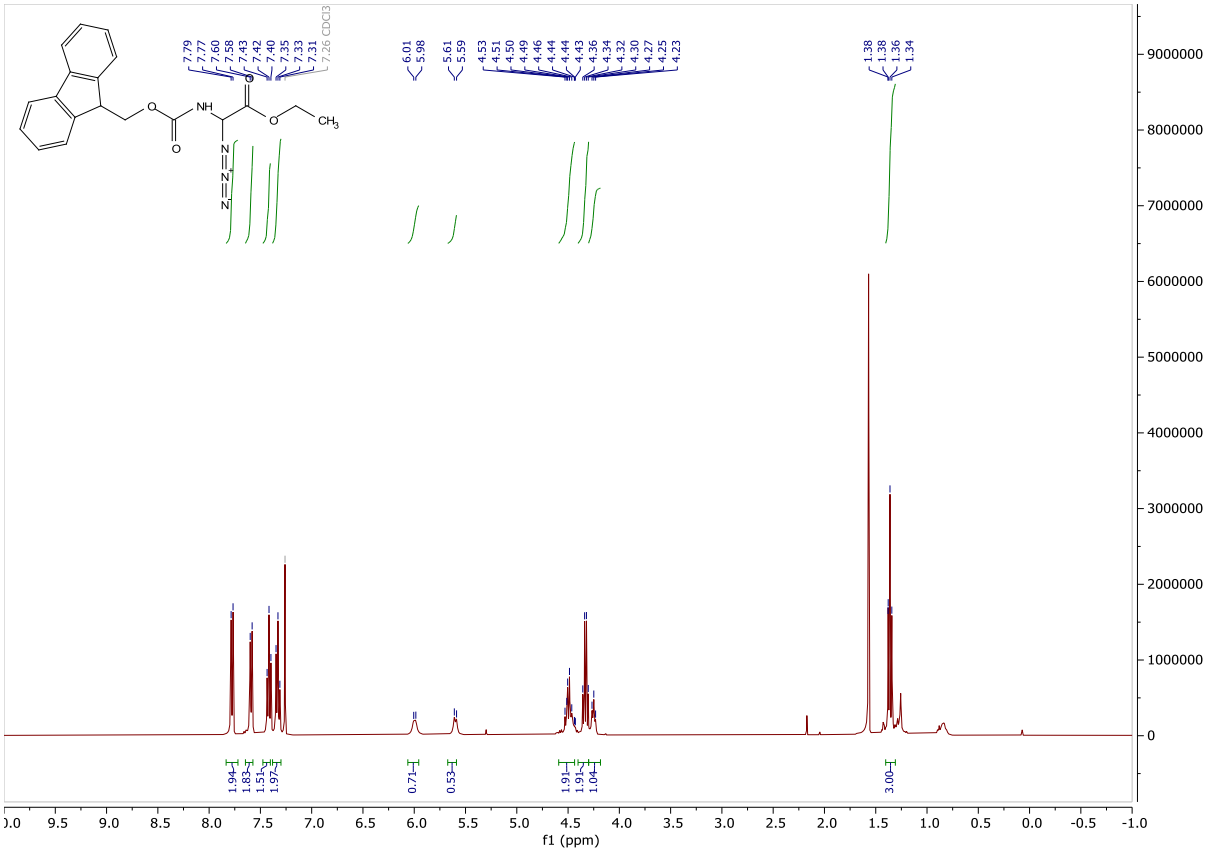


^{13}C NMR (101 MHz, Chloroform-*d*)

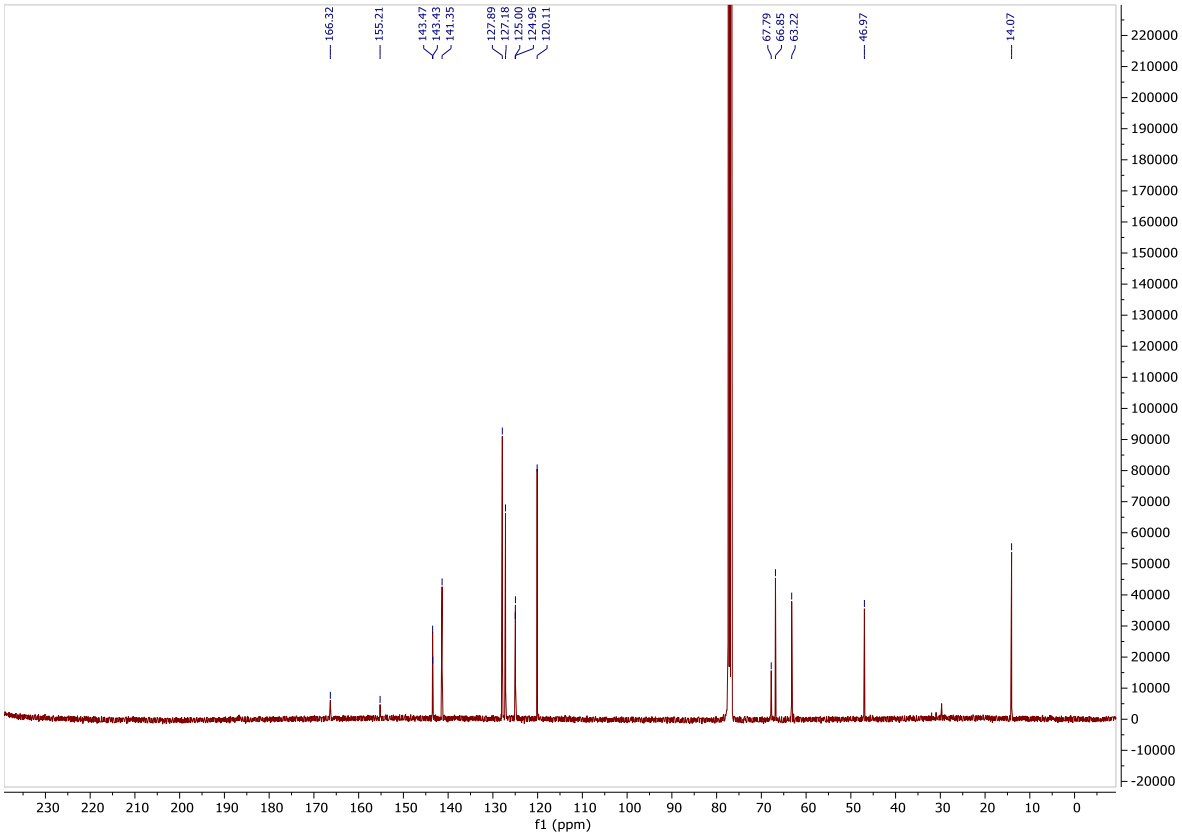


Ethyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-azidoacetate (4a)

^{1}H NMR (400 MHz, Chloroform-*d*)

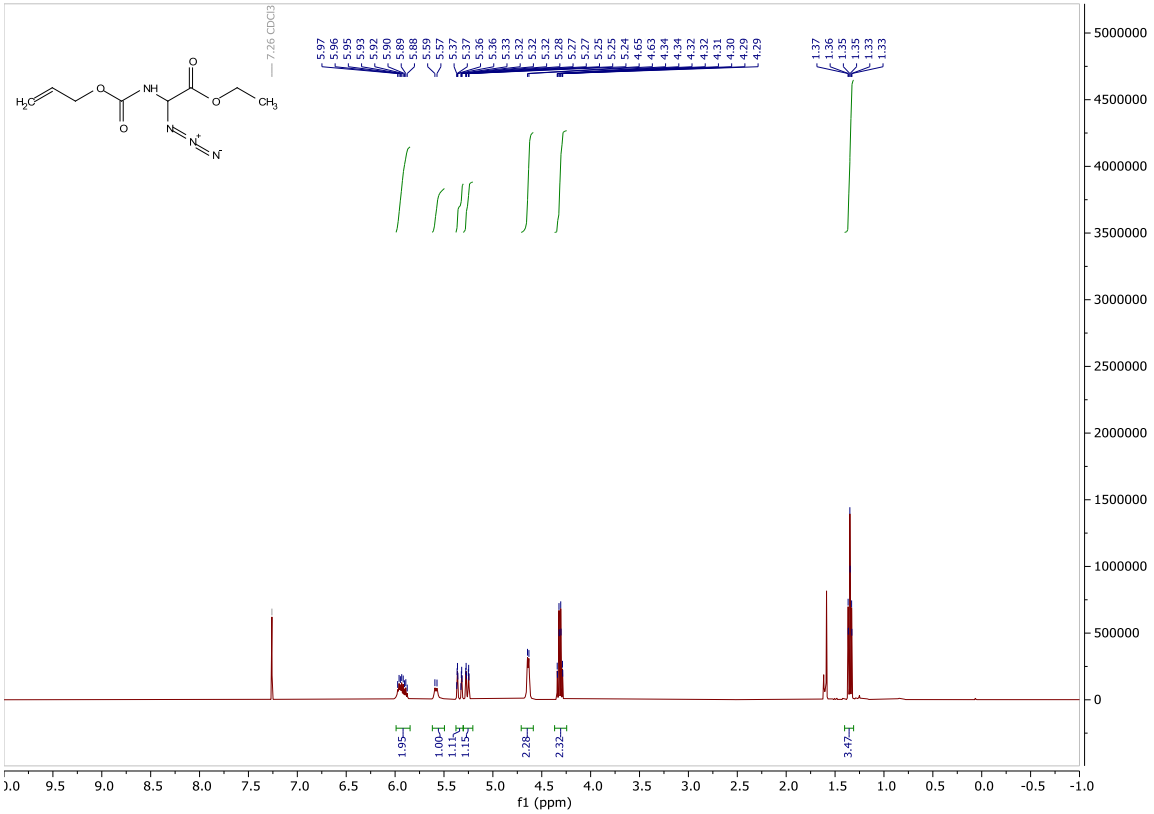


^{13}C NMR (101 MHz, Chloroform-*d*)

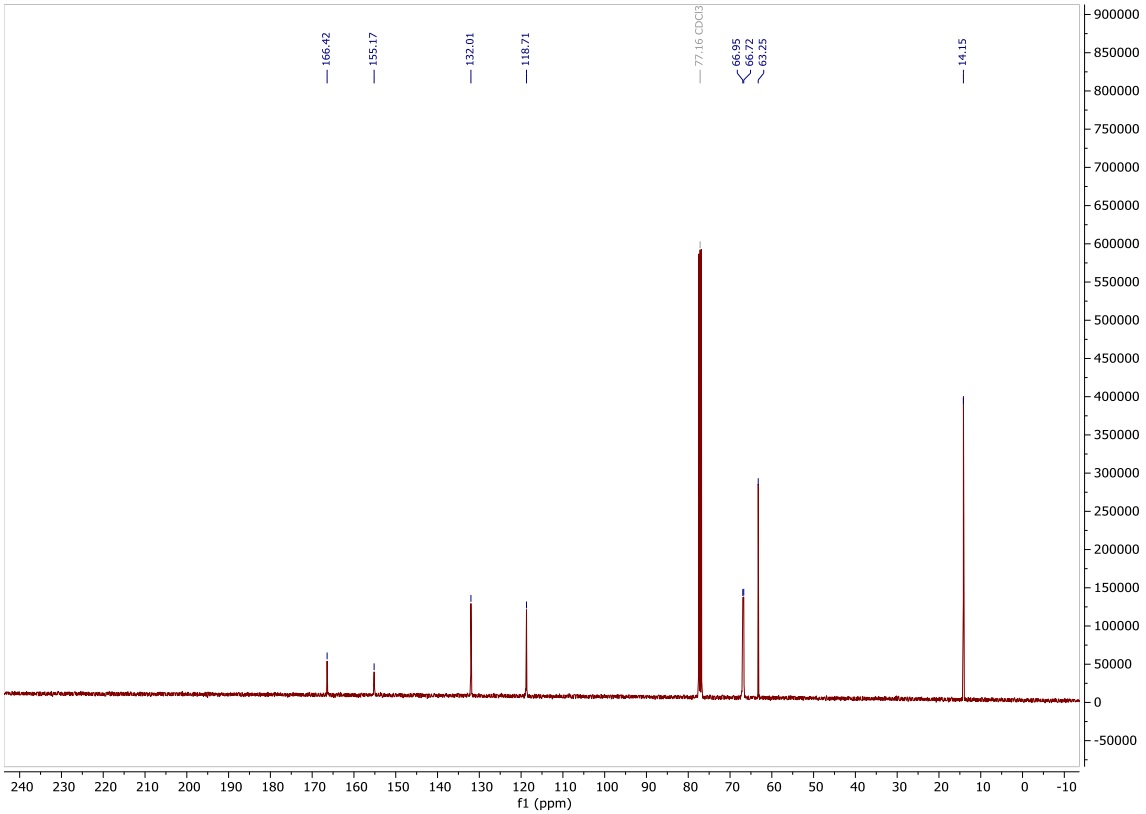


Ethyl 2-(((allyloxy)carbonyl)amino)-2-azidoacetate (5a)

^{1}H NMR (400 MHz, Chloroform-*d*)

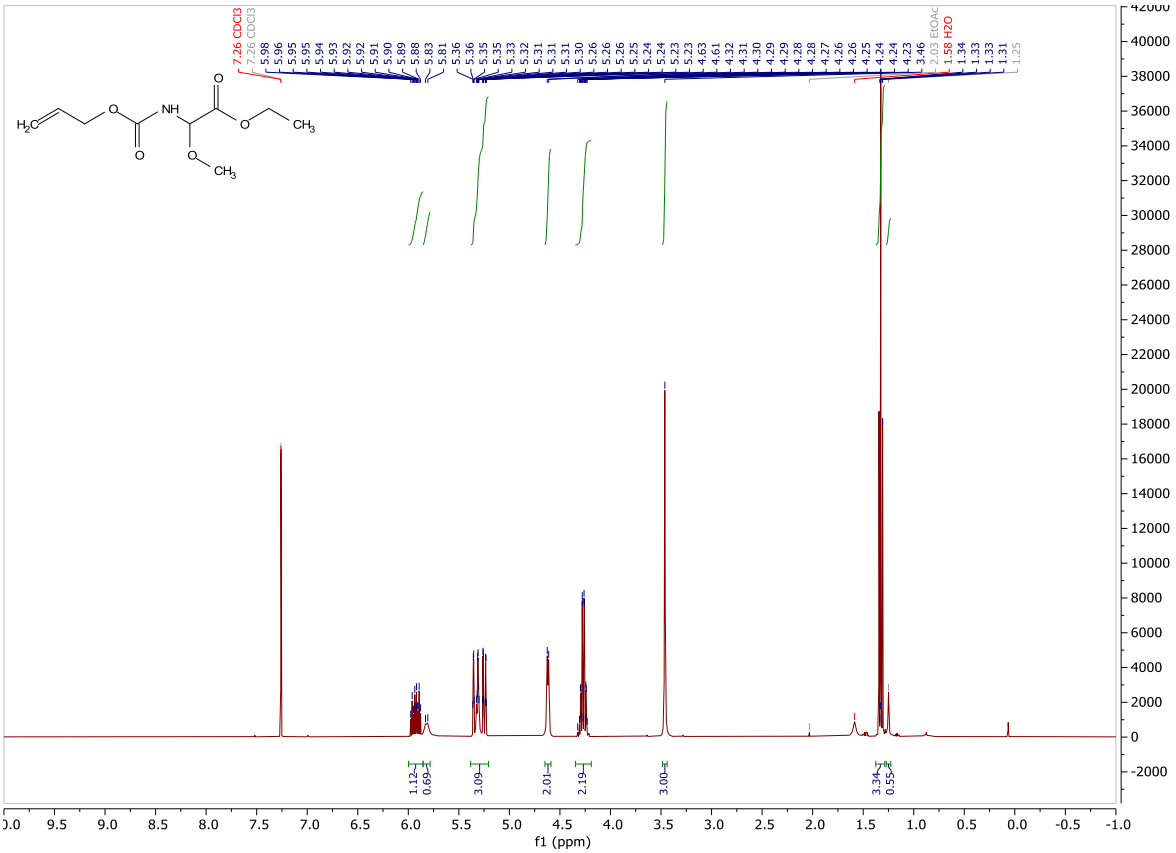


^{13}C NMR (101 MHz, Chloroform-*d*)

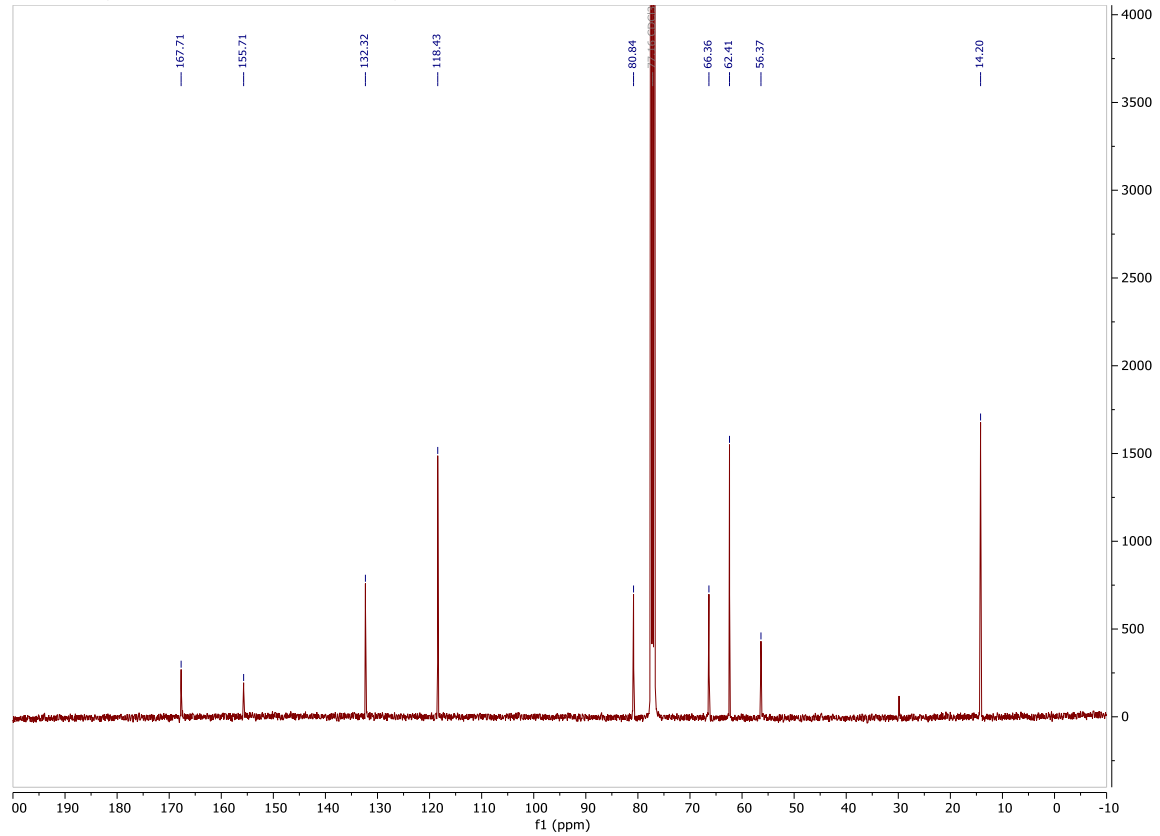


Ethyl 2-(((allyloxy)carbonyl)amino)-2-methoxyacetate (5b)

^{1}H NMR (400 MHz, Chloroform-*d*)

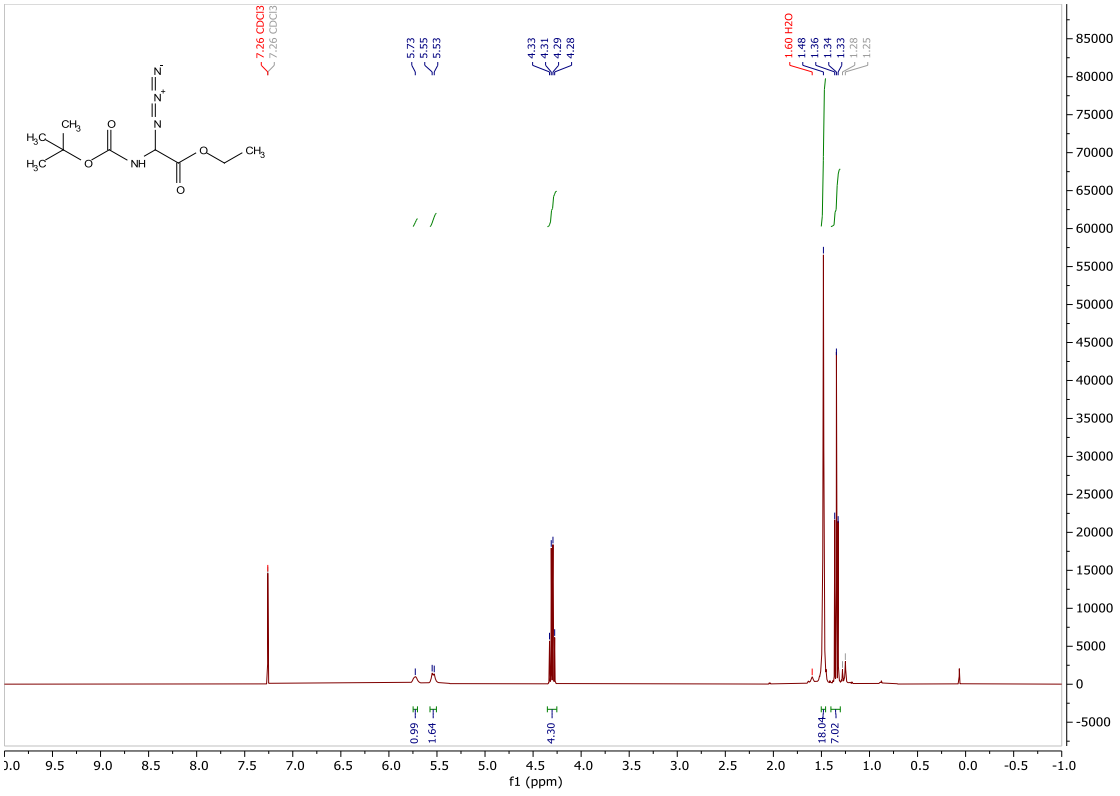


^{13}C NMR (101 MHz, Chloroform-*d*)

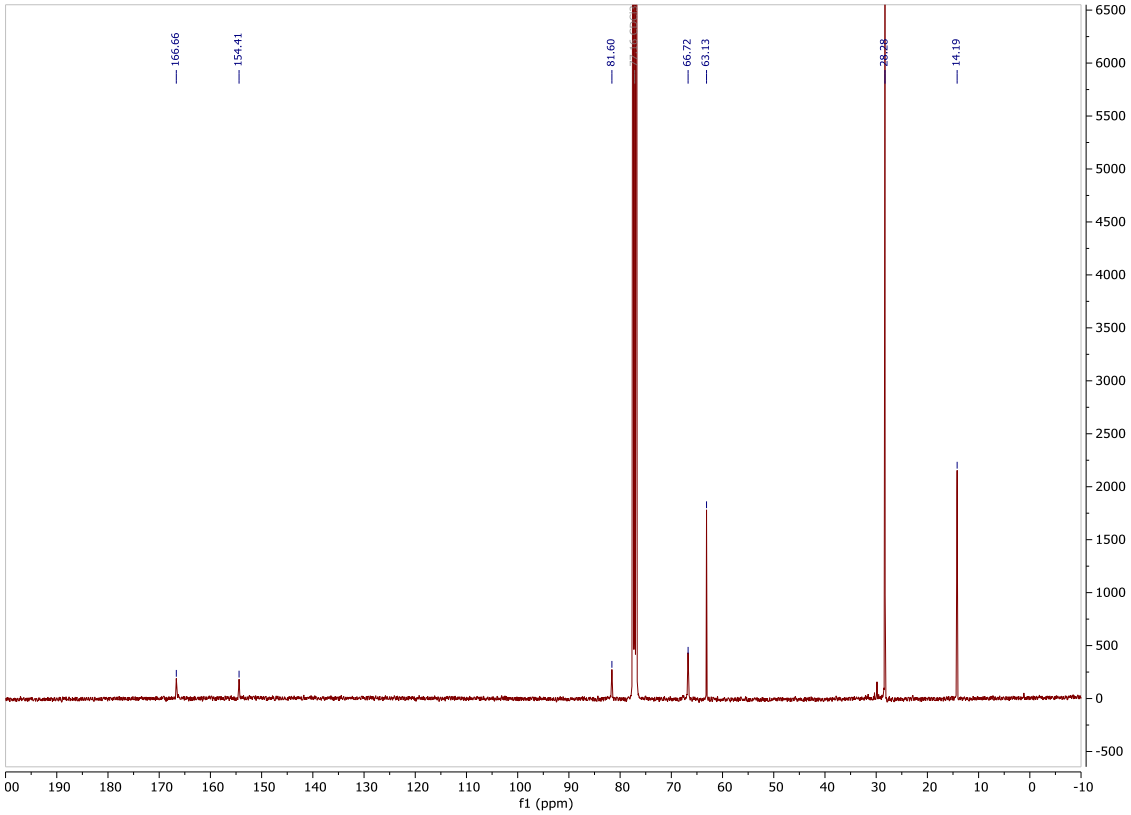


Ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)acetate (2a)

^{1}H NMR (400 MHz, Chloroform-*d*)

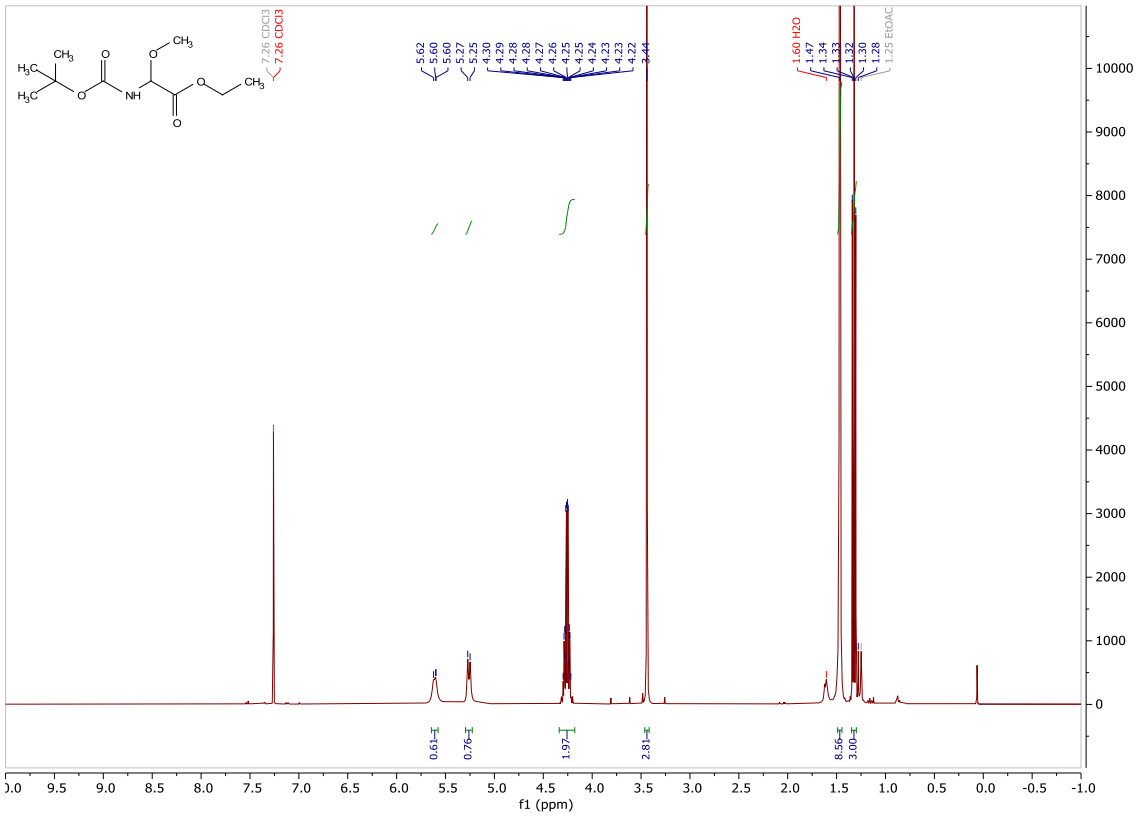


^{13}C NMR (101 MHz, Chloroform-*d*)

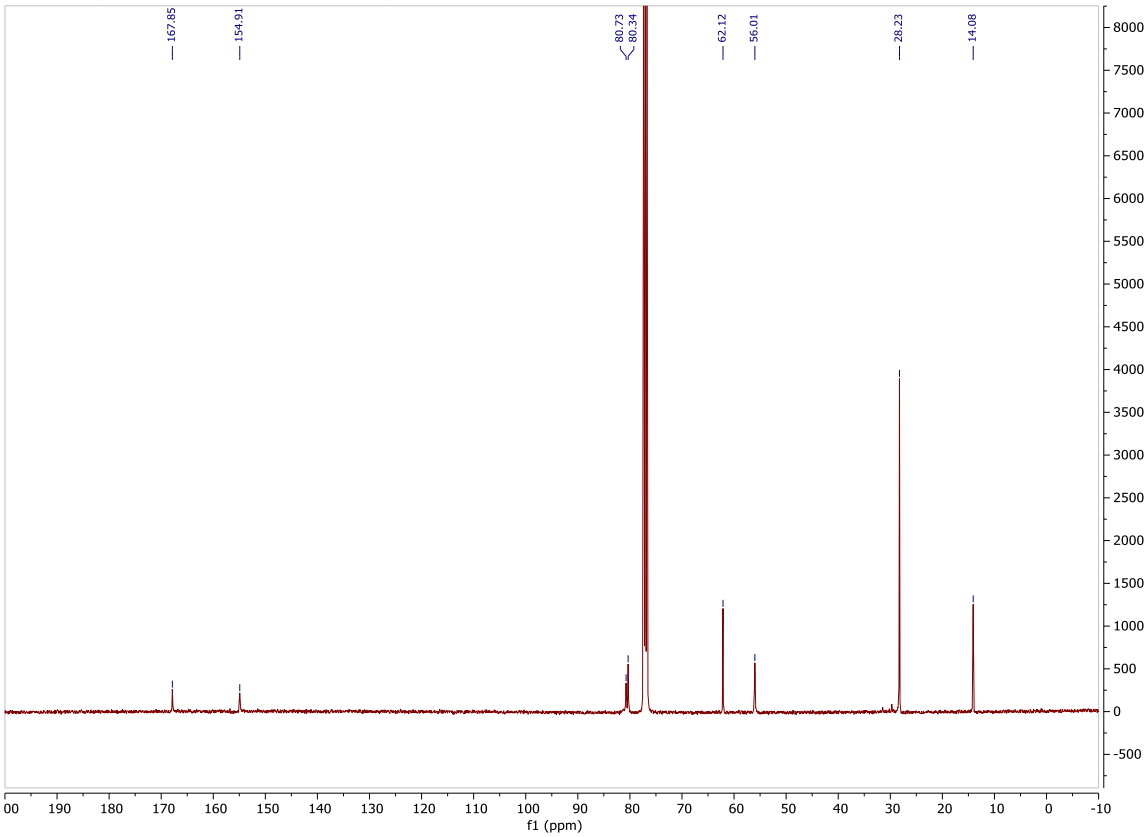


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetate (2b)

^{1}H NMR (400 MHz, Chloroform-*d*)

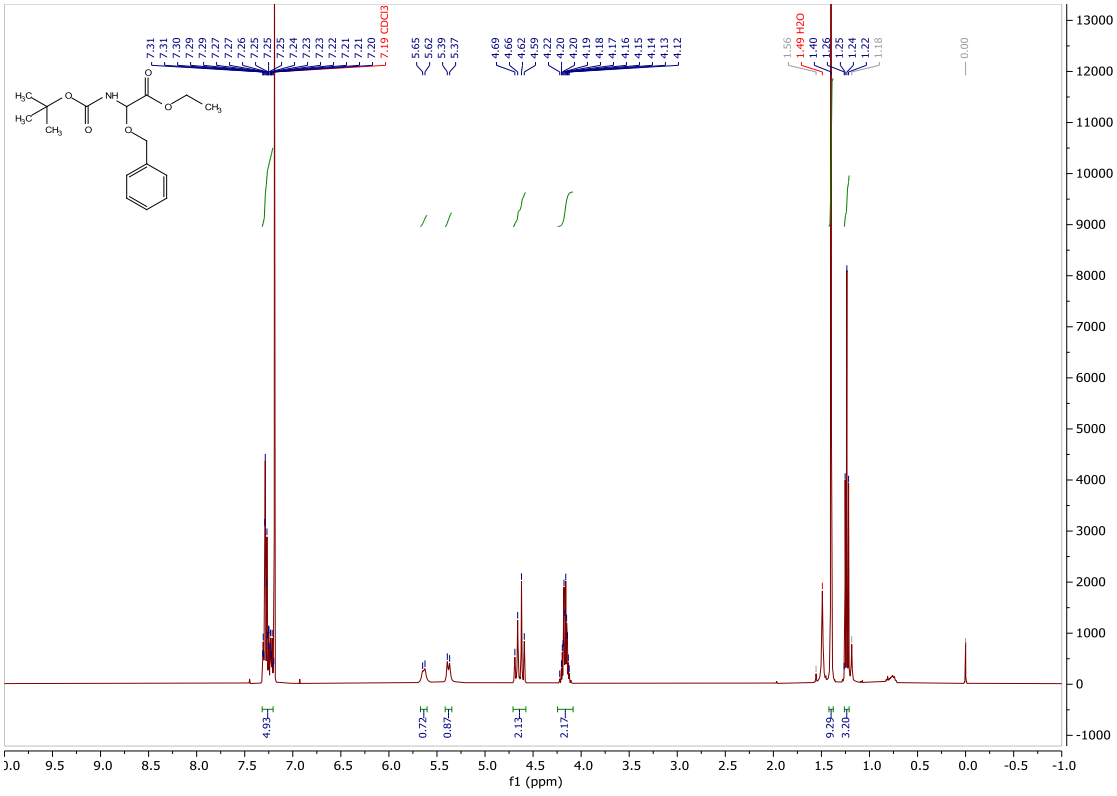


^{13}C NMR (101 MHz, Chloroform-*d*)

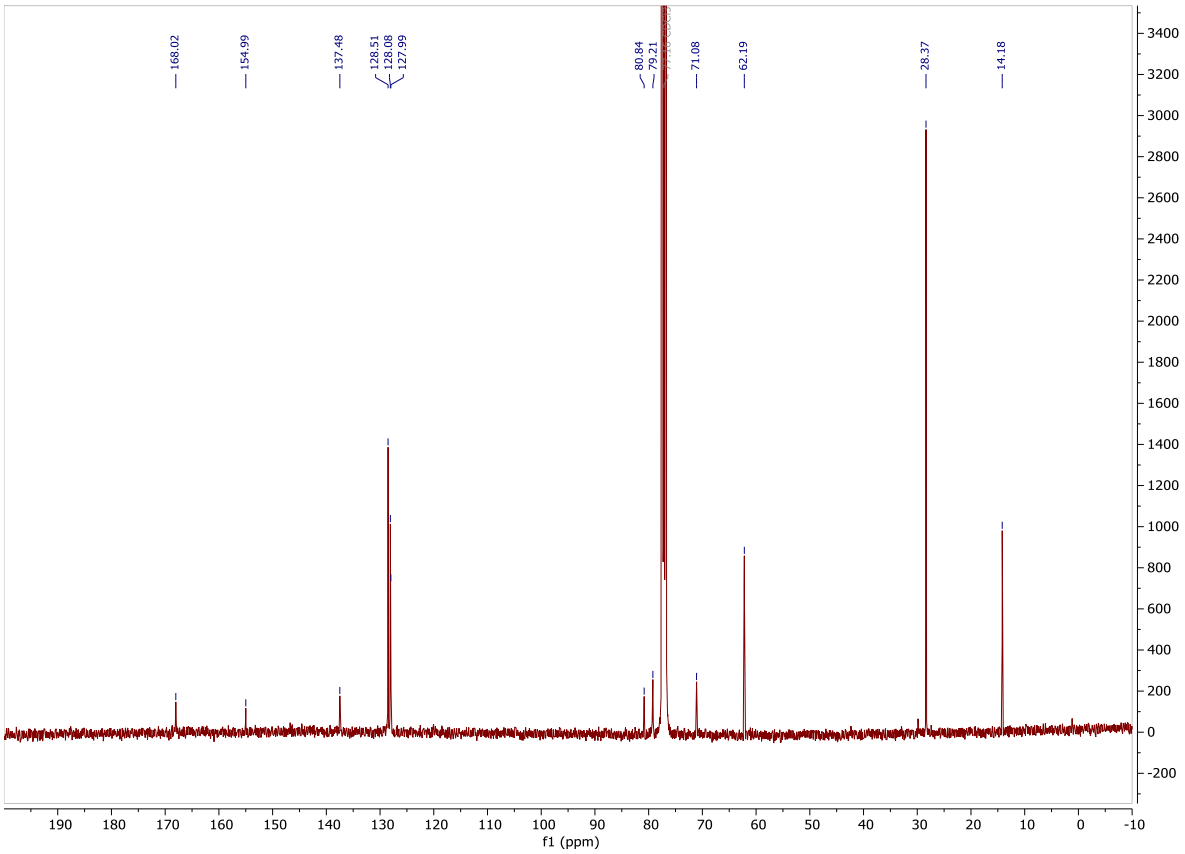


Ethyl 2-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate (2c)

^{1}H NMR (400 MHz, Chloroform-*d*)

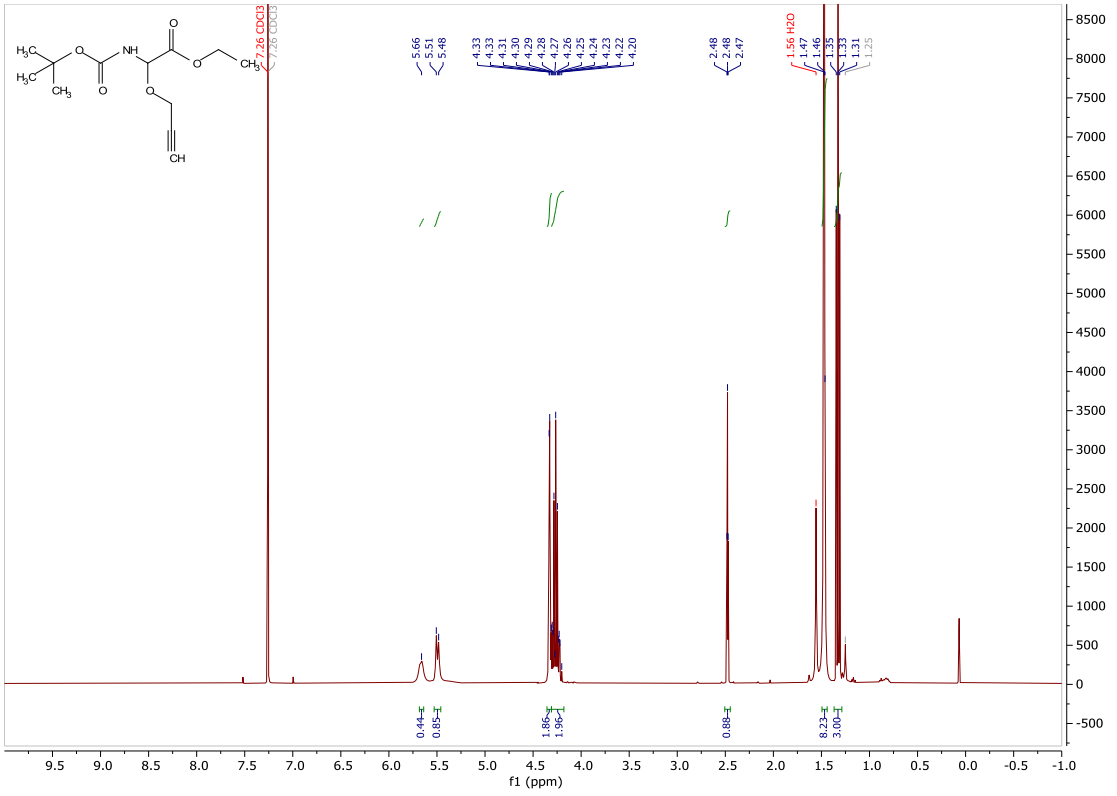


^{13}C NMR (101 MHz, Chloroform-*d*)

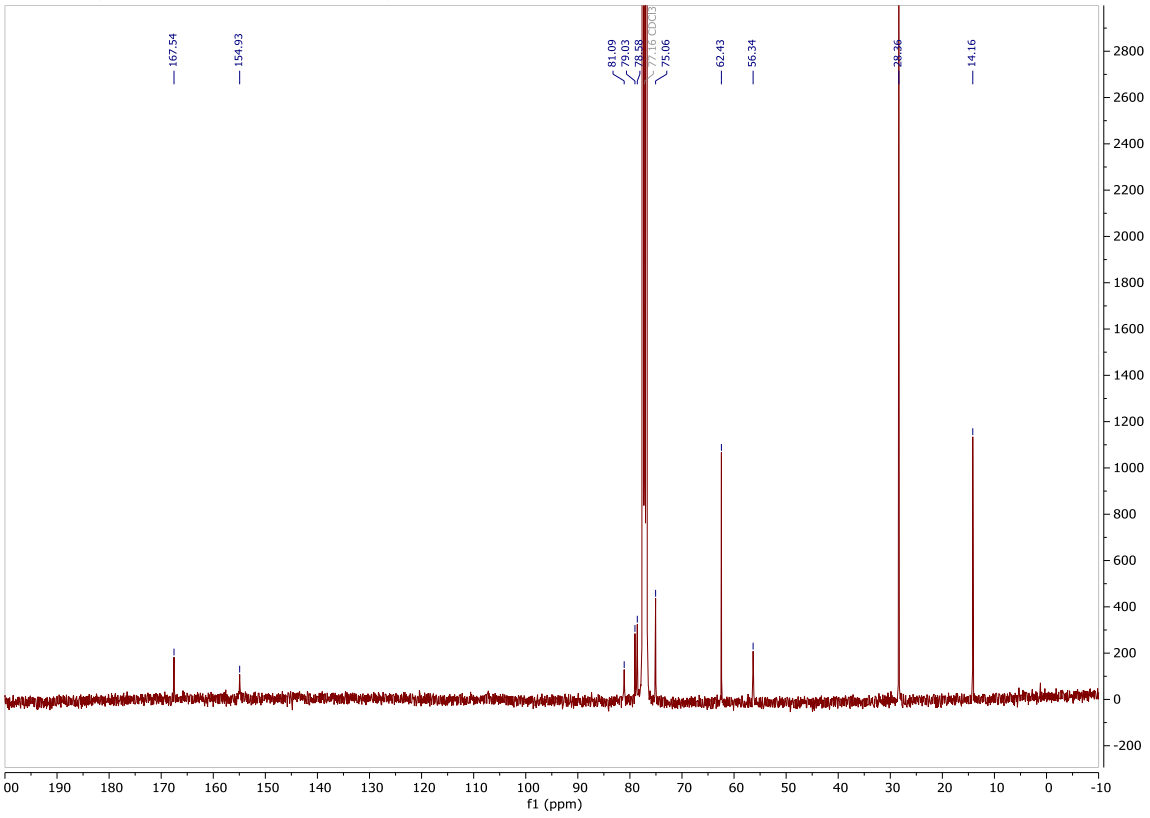


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(prop-2-yn-1-yloxy)acetate (2d)

^{1}H NMR (400 MHz, Chloroform-*d*)

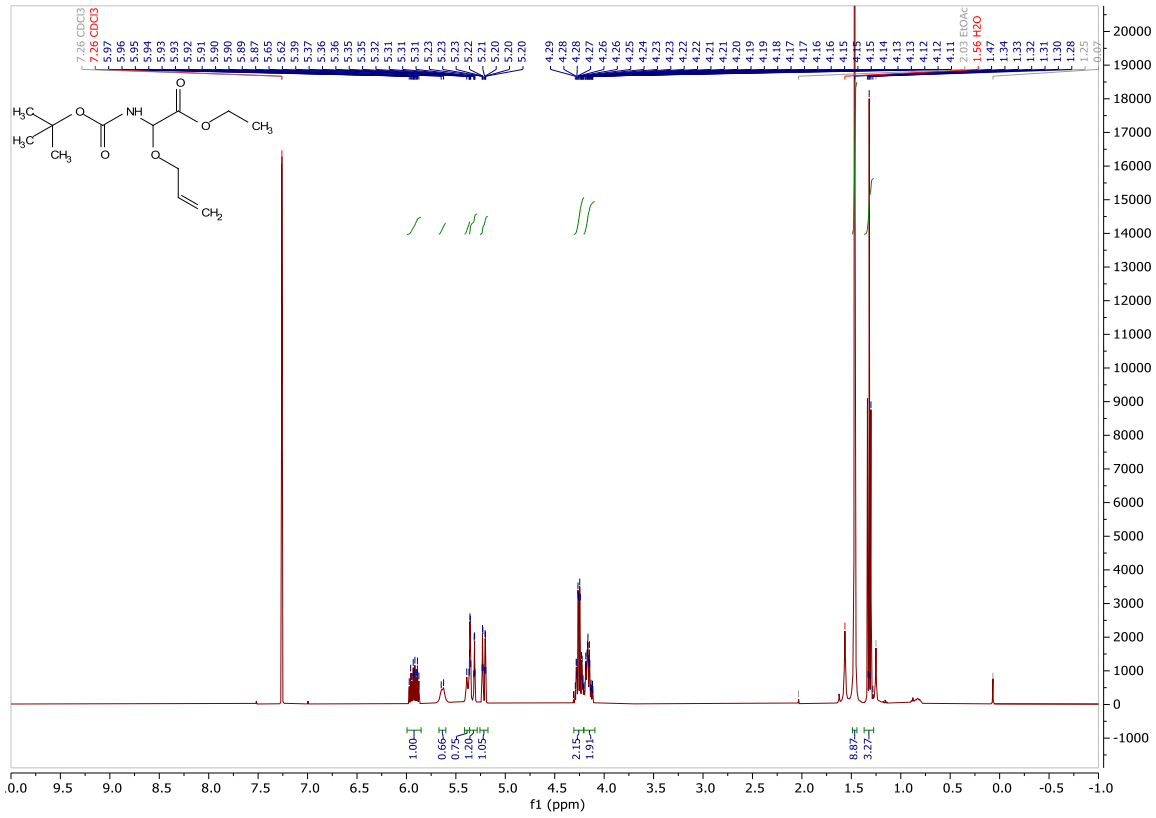


^{13}C NMR (101 MHz, Chloroform-*d*)

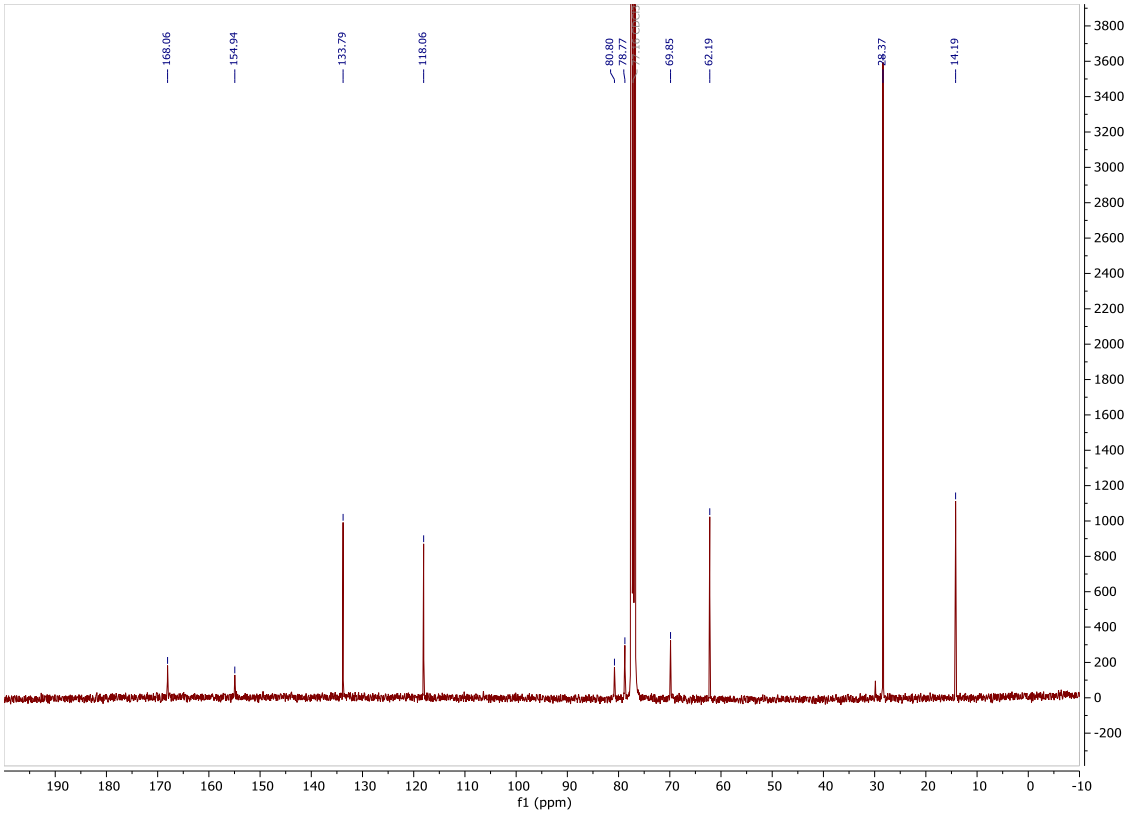


Ethyl 2-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)acetate (2e)

^{1}H NMR (400 MHz, Chloroform-*d*)

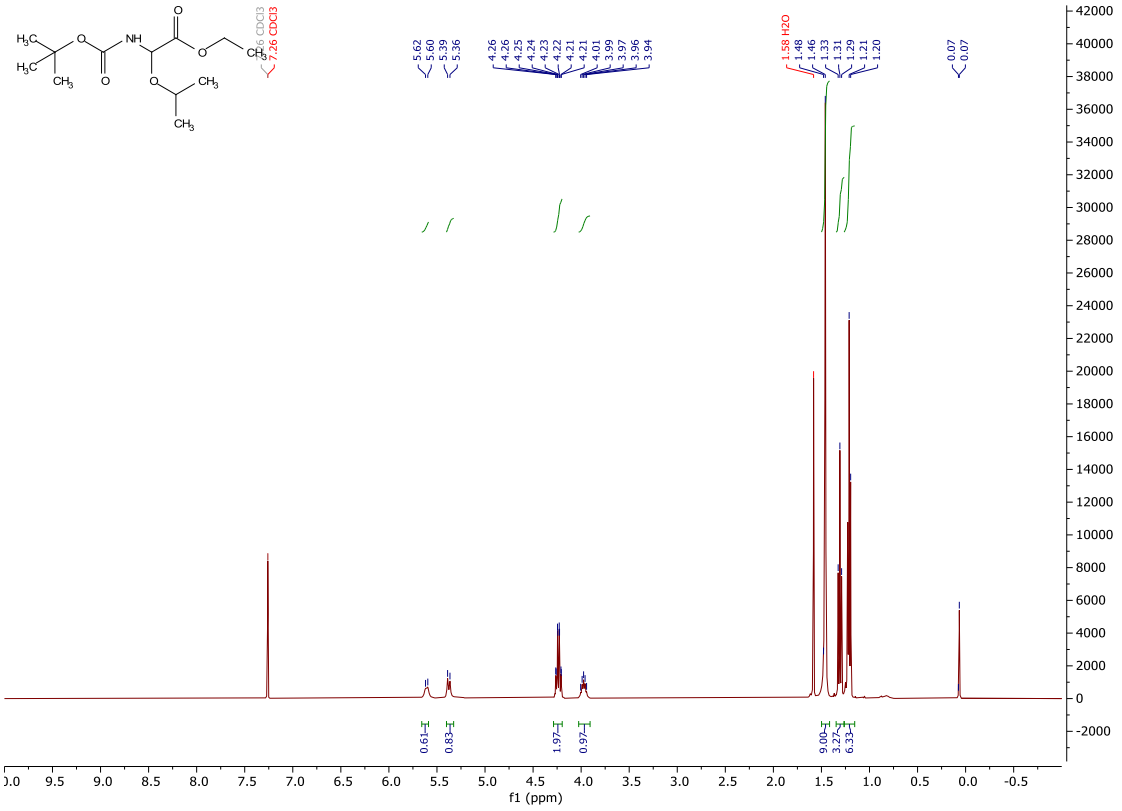


^{13}C NMR (101 MHz, Chloroform-*d*)

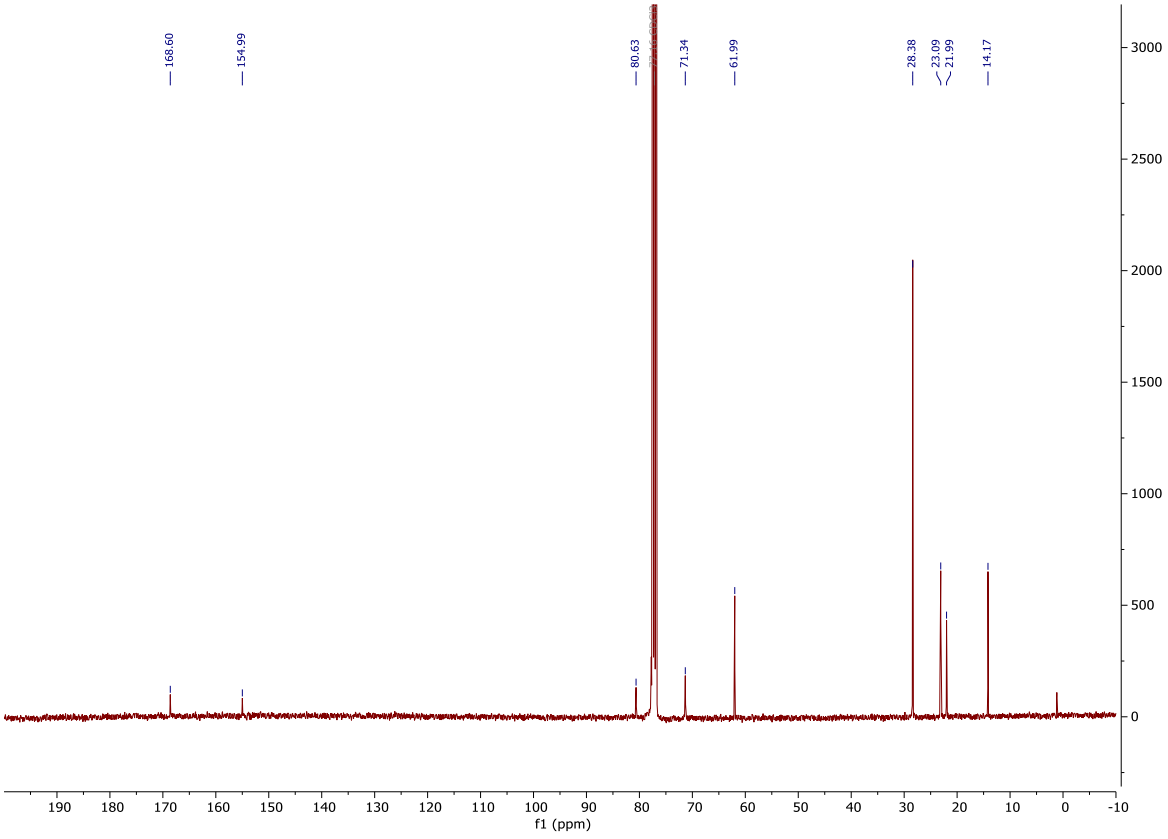


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-isopropoxyacetate (2f)

^{1}H NMR (400 MHz, Chloroform-*d*)

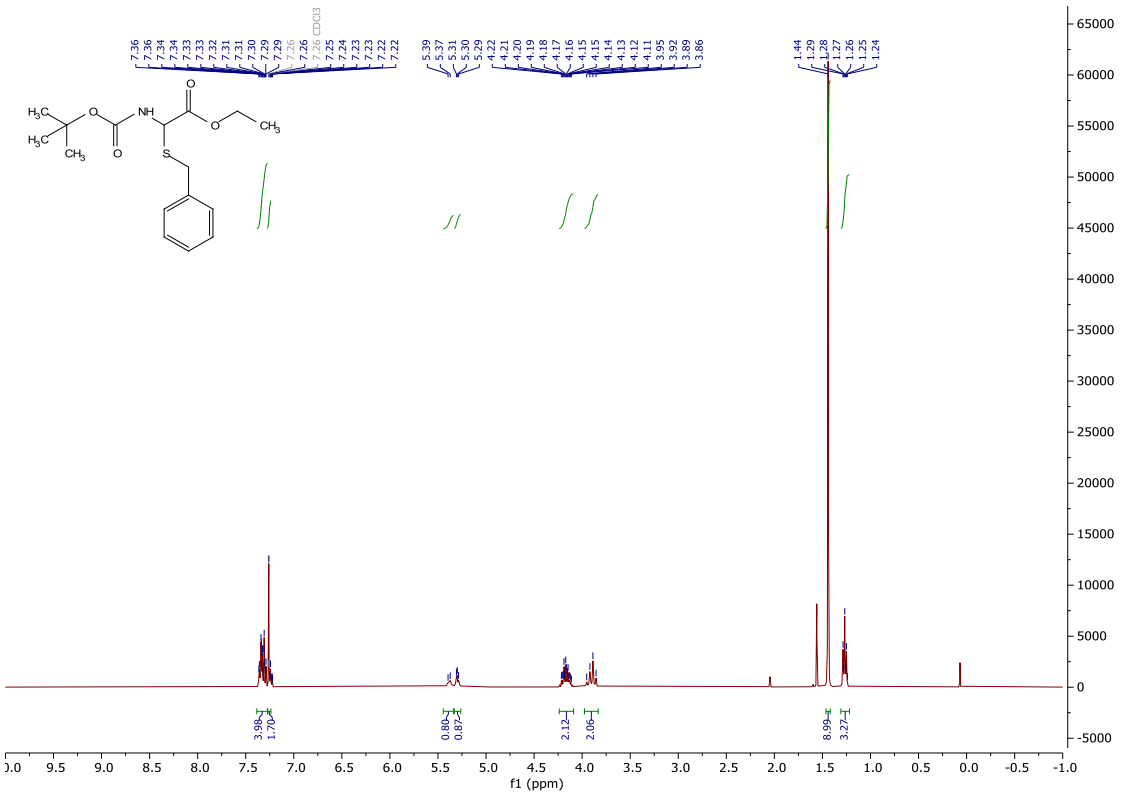


^{13}C NMR (101 MHz, Chloroform-*d*)

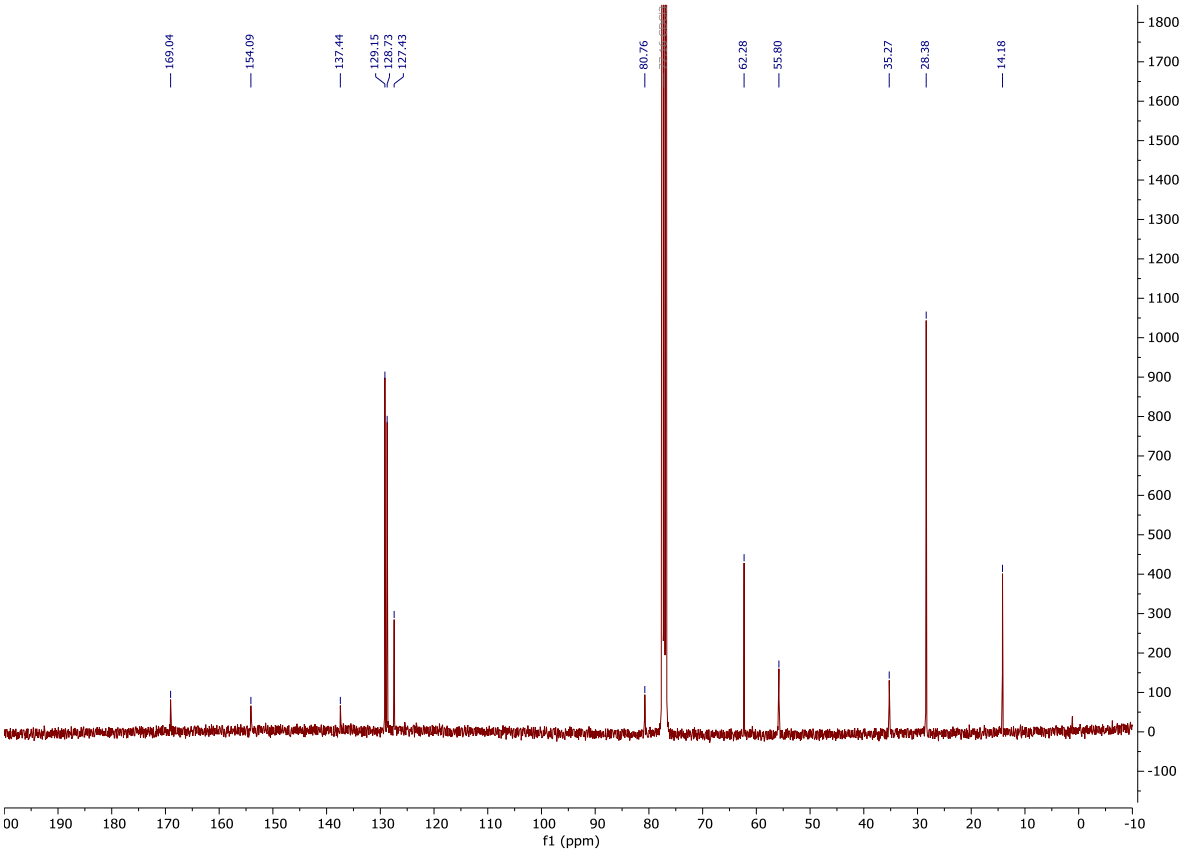


Ethyl 2-(benzylthio)-2-((*tert*-butoxycarbonyl)amino)acetate (2g)

^{1}H NMR (400 MHz, Chloroform-*d*)

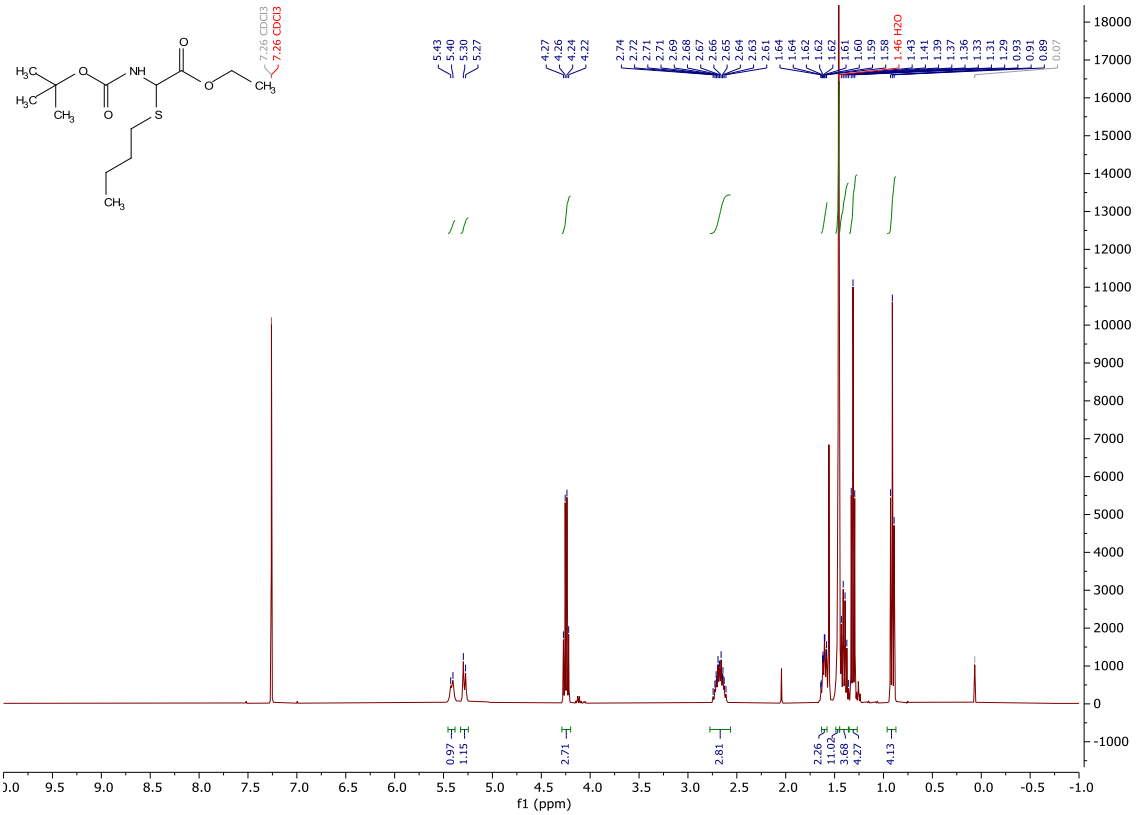


^{13}C NMR (101 MHz, Chloroform-*d*)

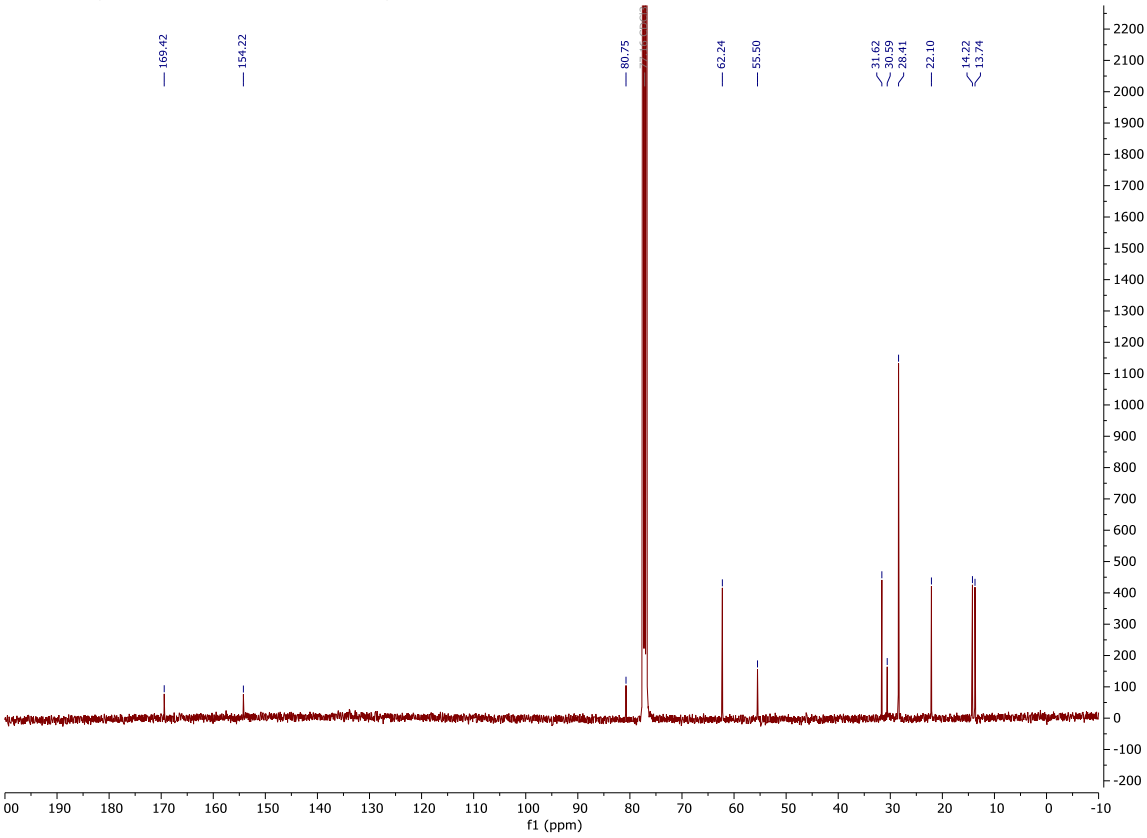


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(butylthio)acetate (2h)

^{1}H NMR (400 MHz, Chloroform-*d*)

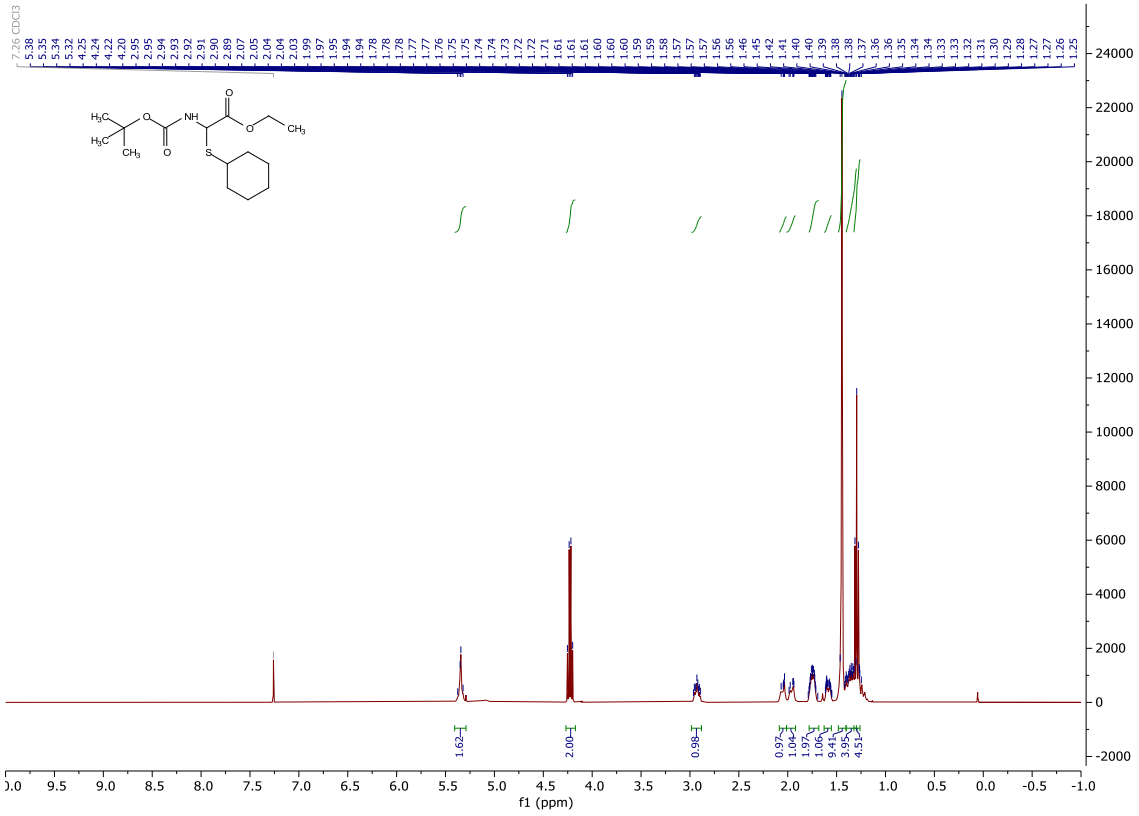


^{13}C NMR (101 MHz, Chloroform-*d*)

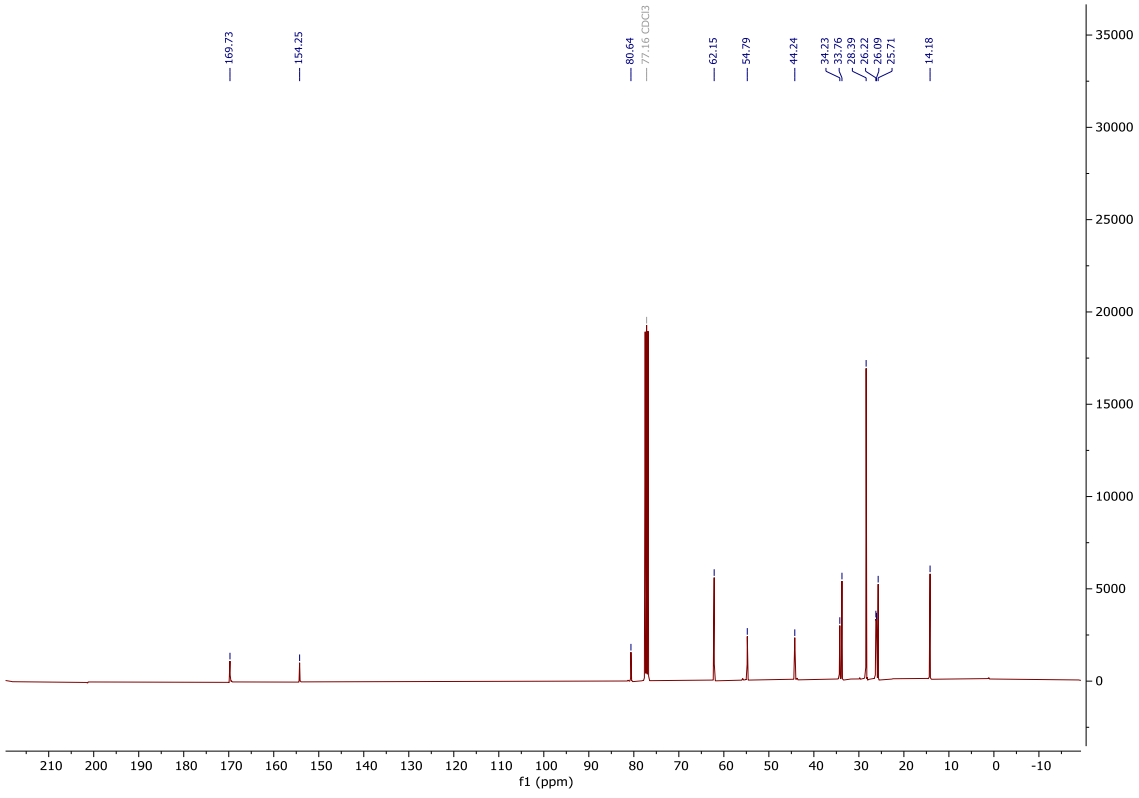


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(cyclohexylthio)acetate (2i)

^{1}H NMR (400 MHz, Chloroform-*d*)

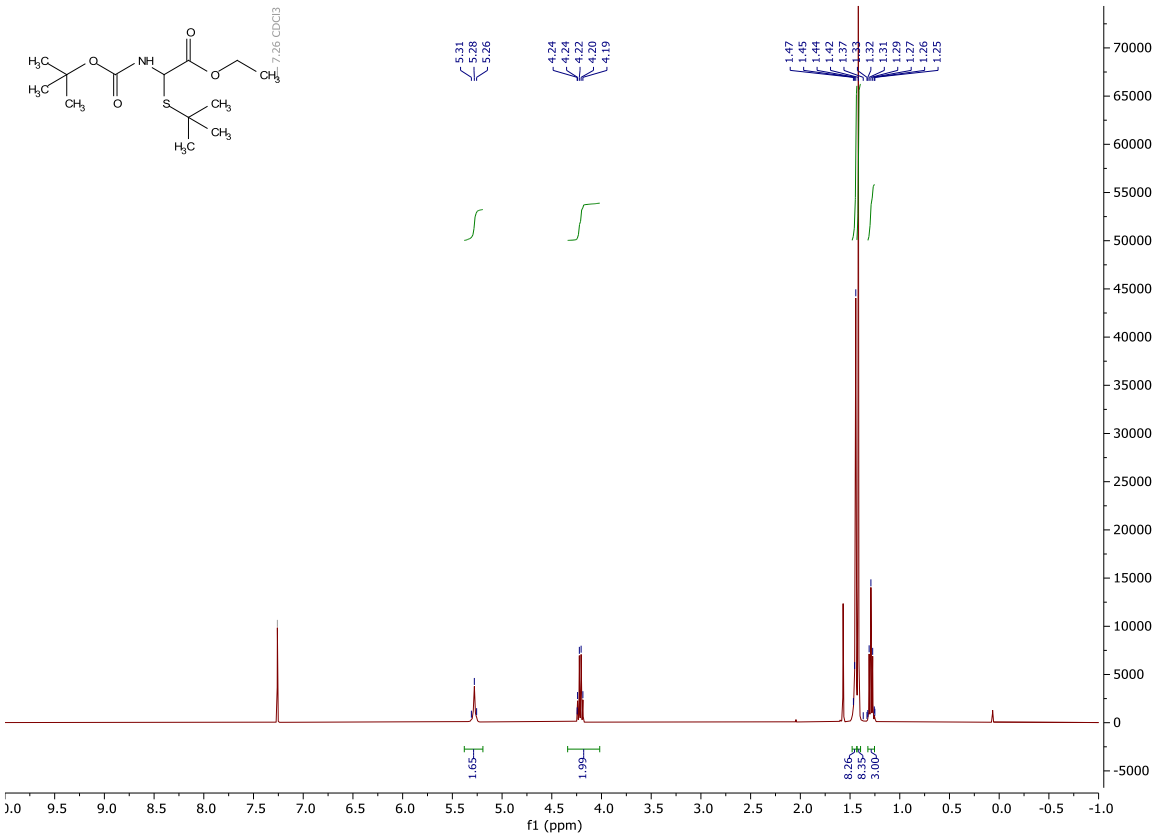


^{13}C NMR (101 MHz, Chloroform-*d*)

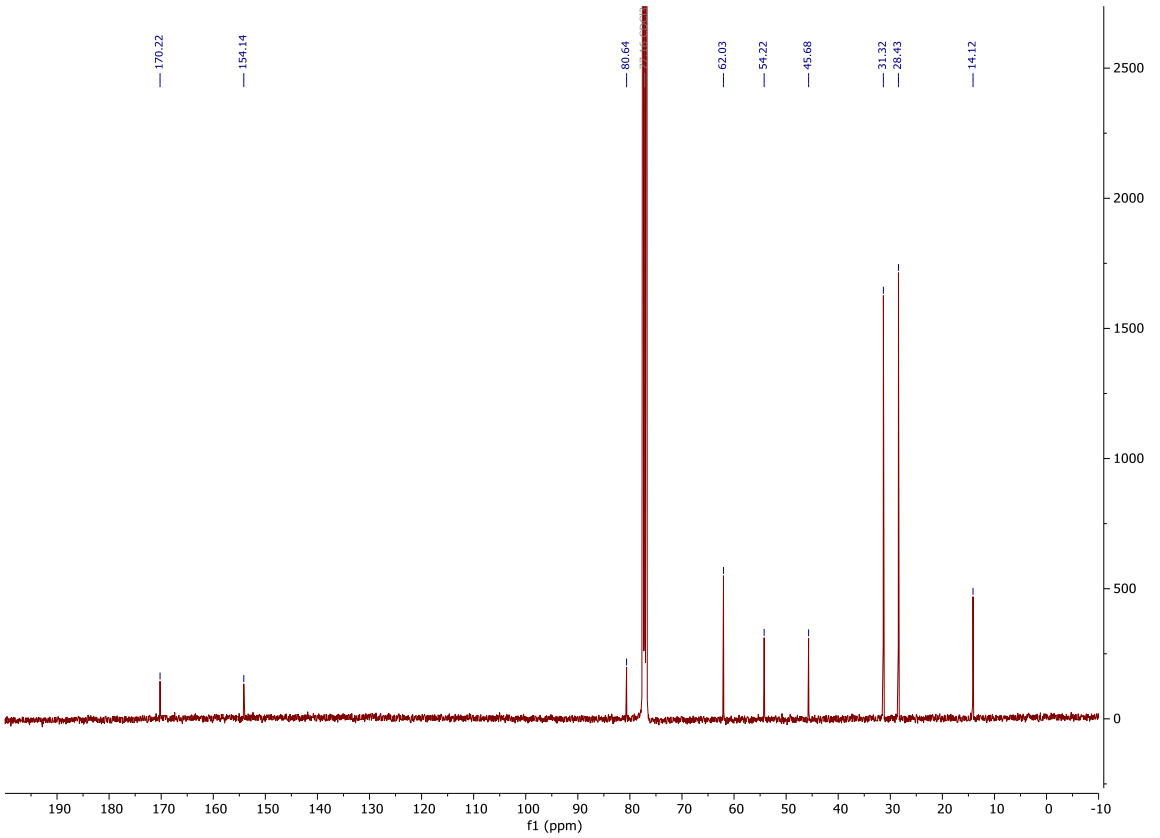


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(*tert*-butylthio)acetate (2j)

^{1}H NMR (400 MHz, Chloroform-*d*)



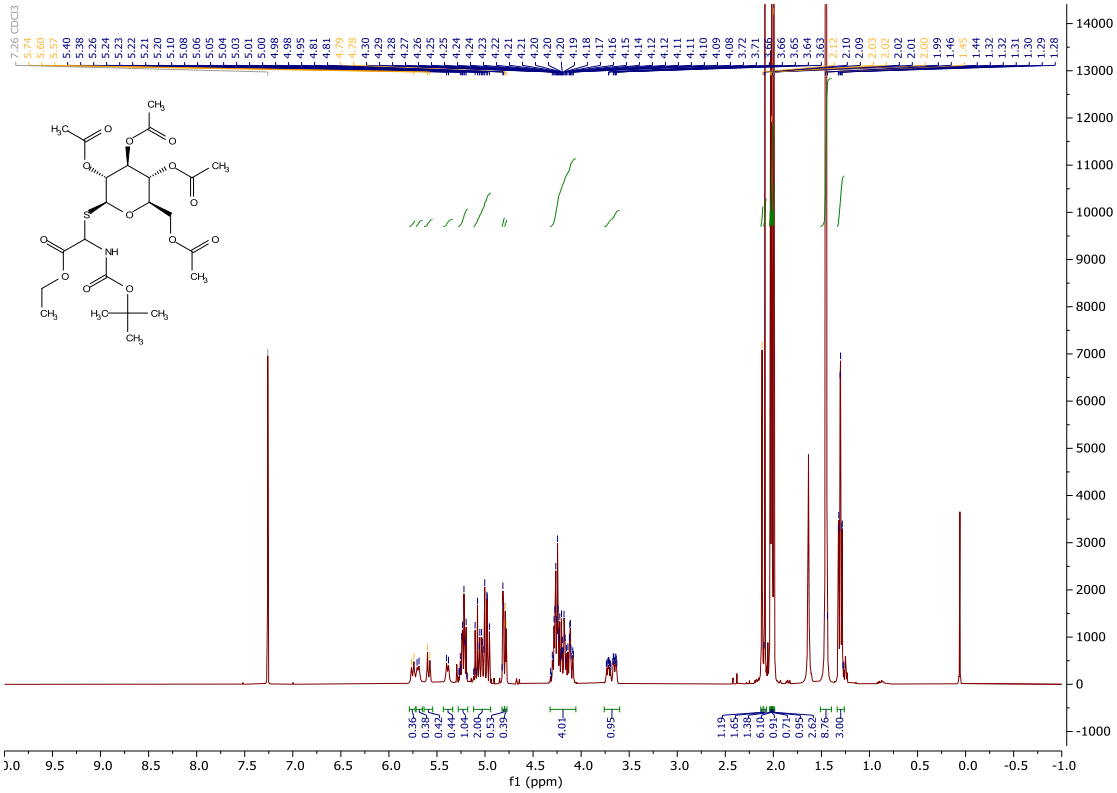
^{13}C NMR (101 MHz, Chloroform-*d*)



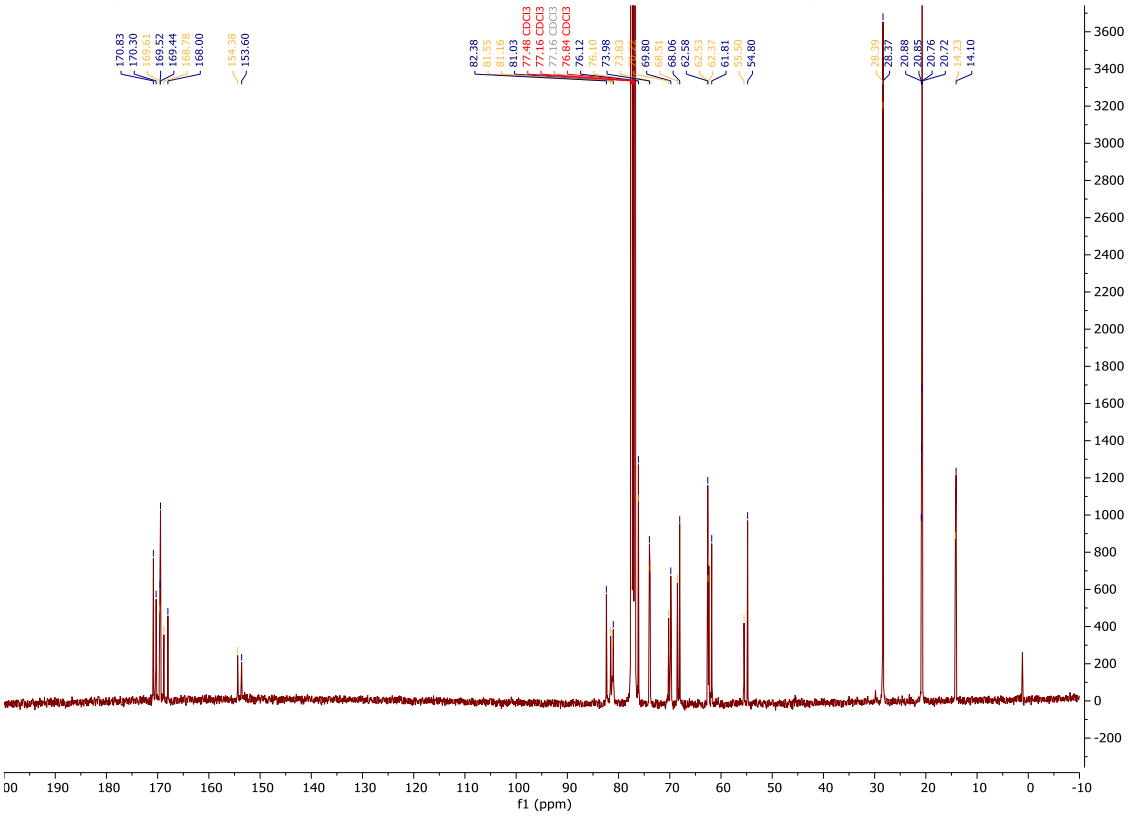
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((1-((*tert*-butoxycarbonyl)amino)-2-ethoxy-2-oxoethyl)thio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2k)

Yellow is the minor diastereoisomers, blue the major one.

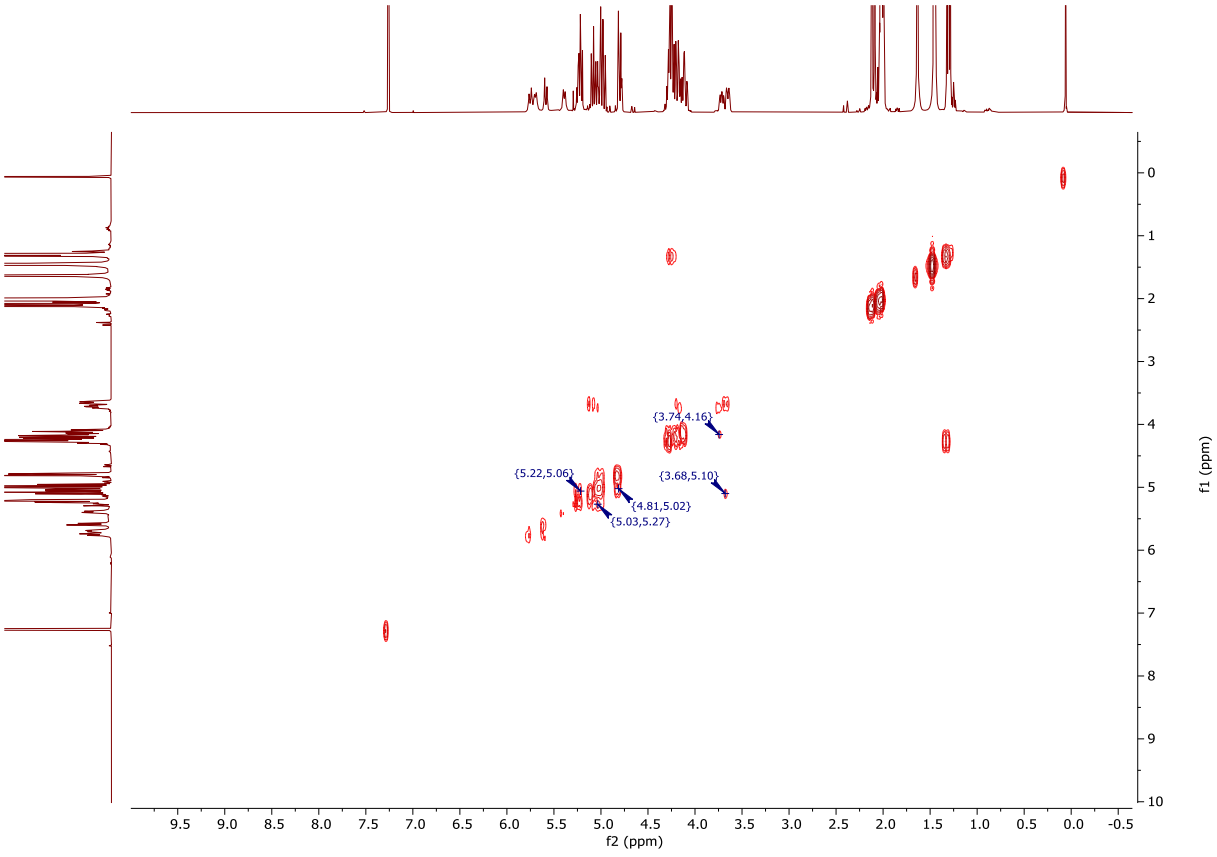
^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)



^{13}C NMR (101 MHz, Chloroform-*d,* mixture of two diastereoisomers)

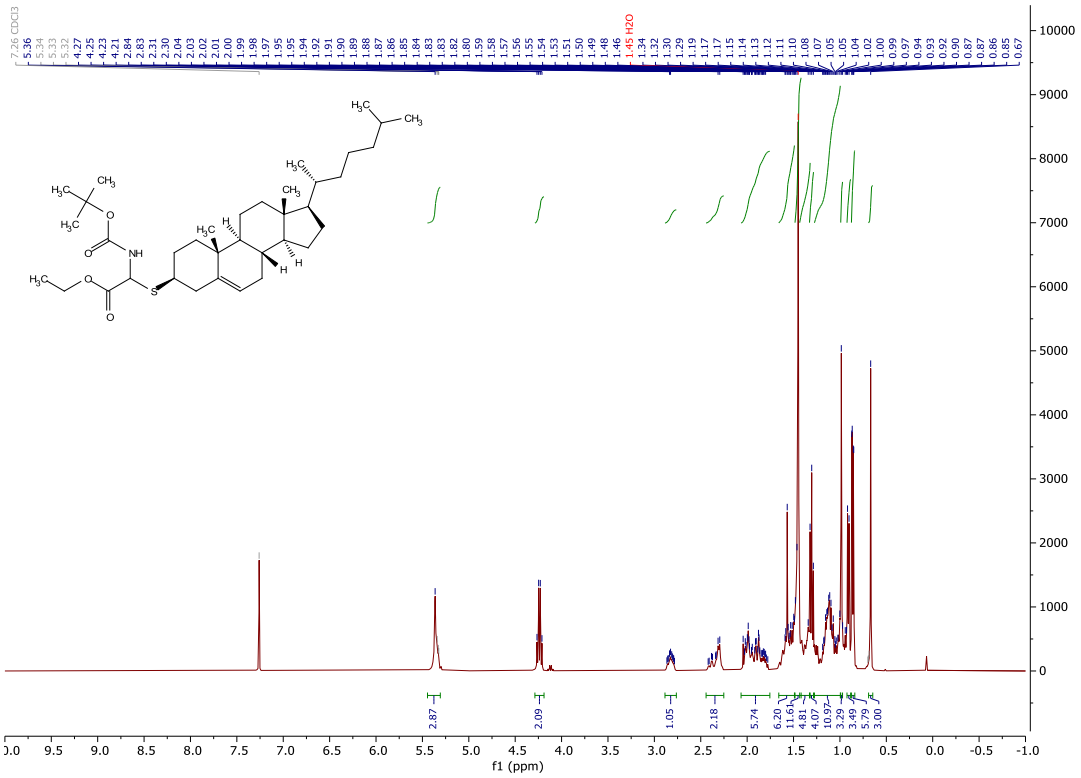


COSY (Chloroform-*d*, 298 K, mixture of two diastereoisomers)

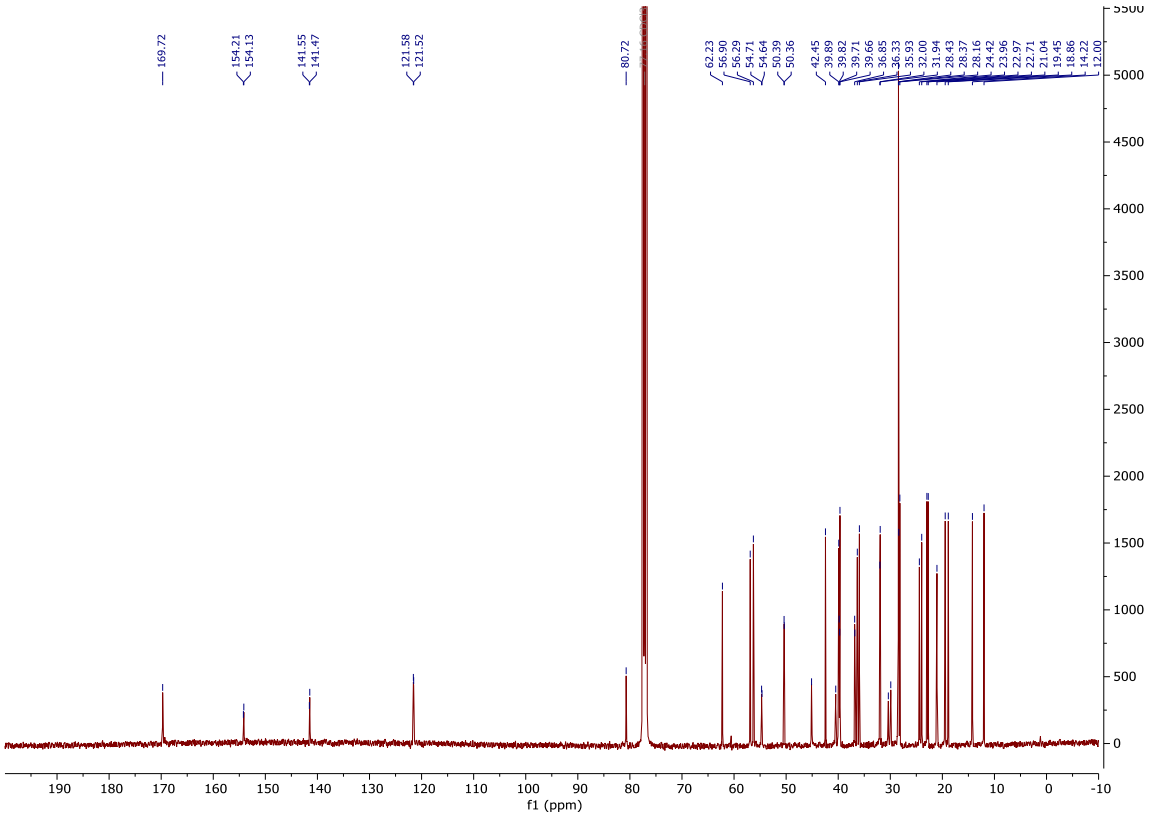


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)thio)acetate (2l)

^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)

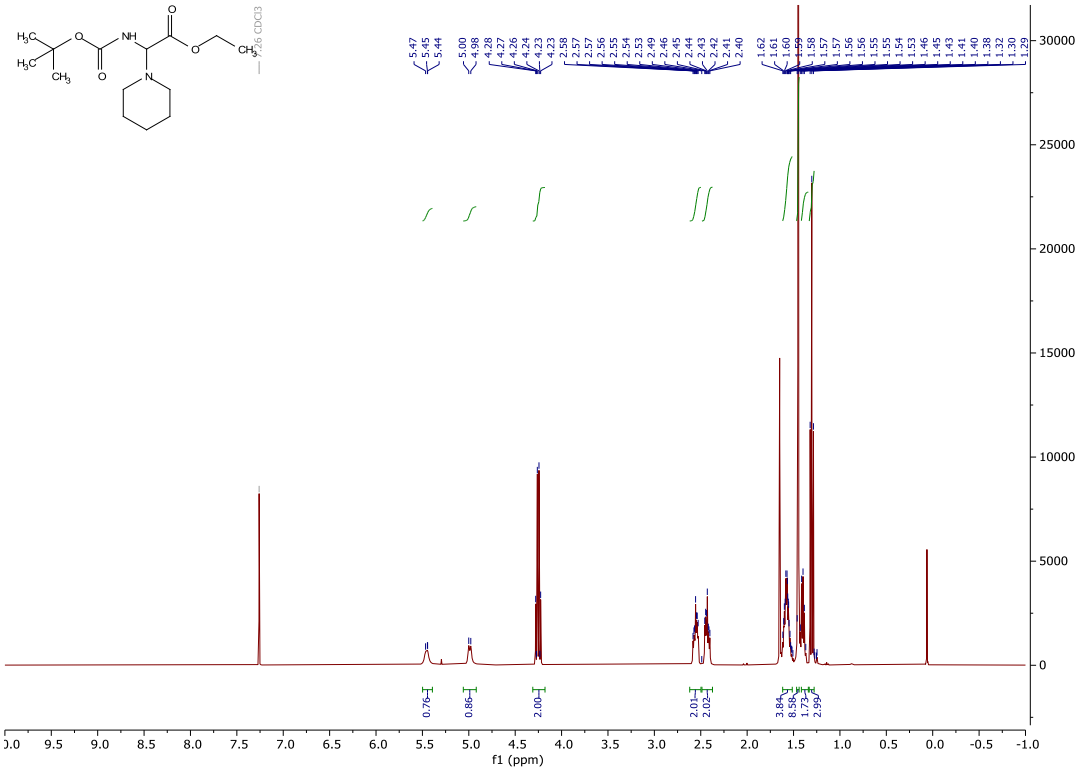


^{13}C NMR (101 MHz, Chloroform-*d,* mixture of two diastereoisomers)

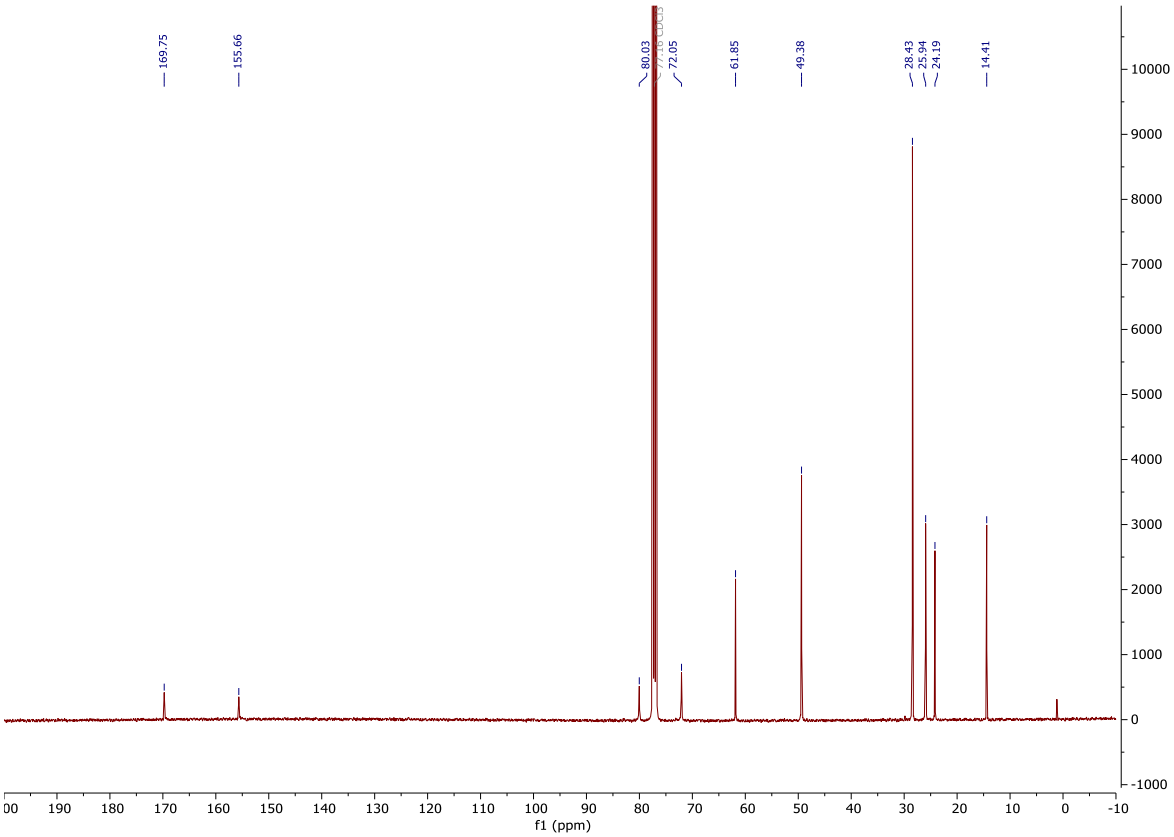


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(piperidin-1-yl)acetate (2m)

^{1}H NMR (400 MHz, Chloroform-*d*)

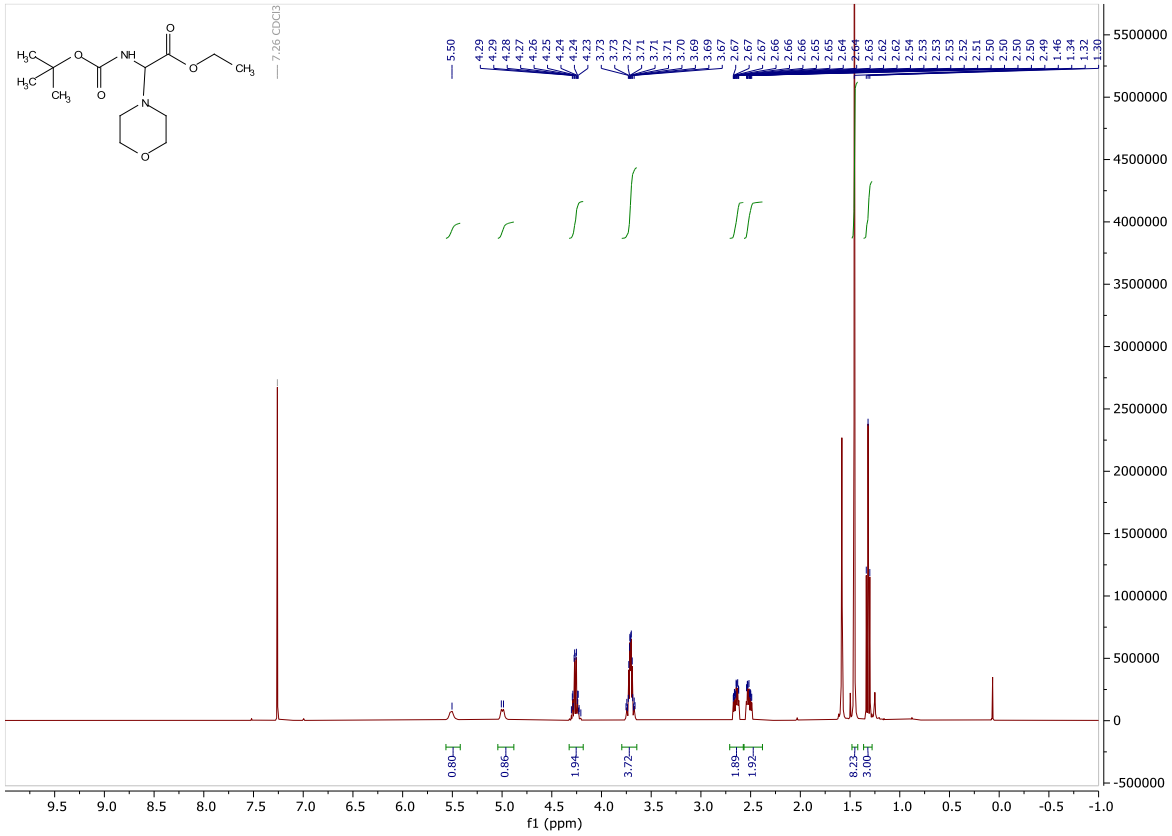


^{13}C NMR (101 MHz, Chloroform-*d*)

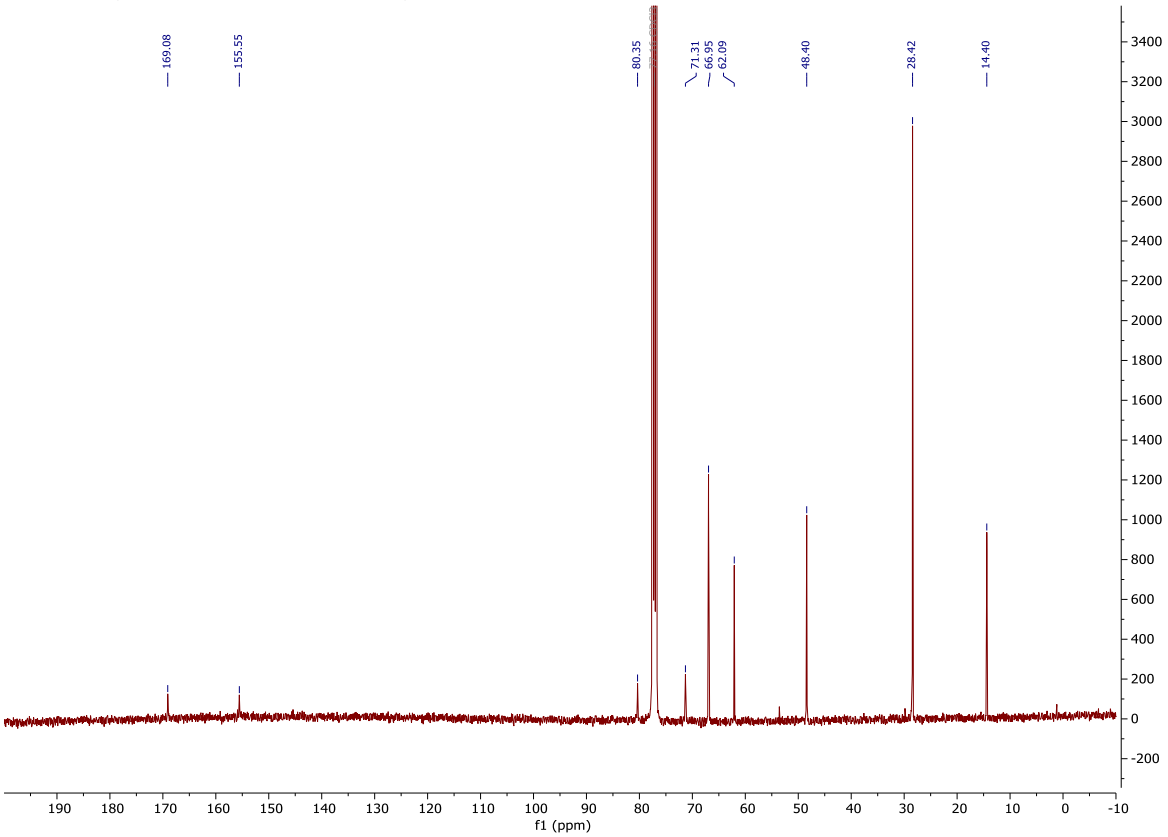


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-morpholinoacetate (2n)

^{1}H NMR (400 MHz, Chloroform-*d*)

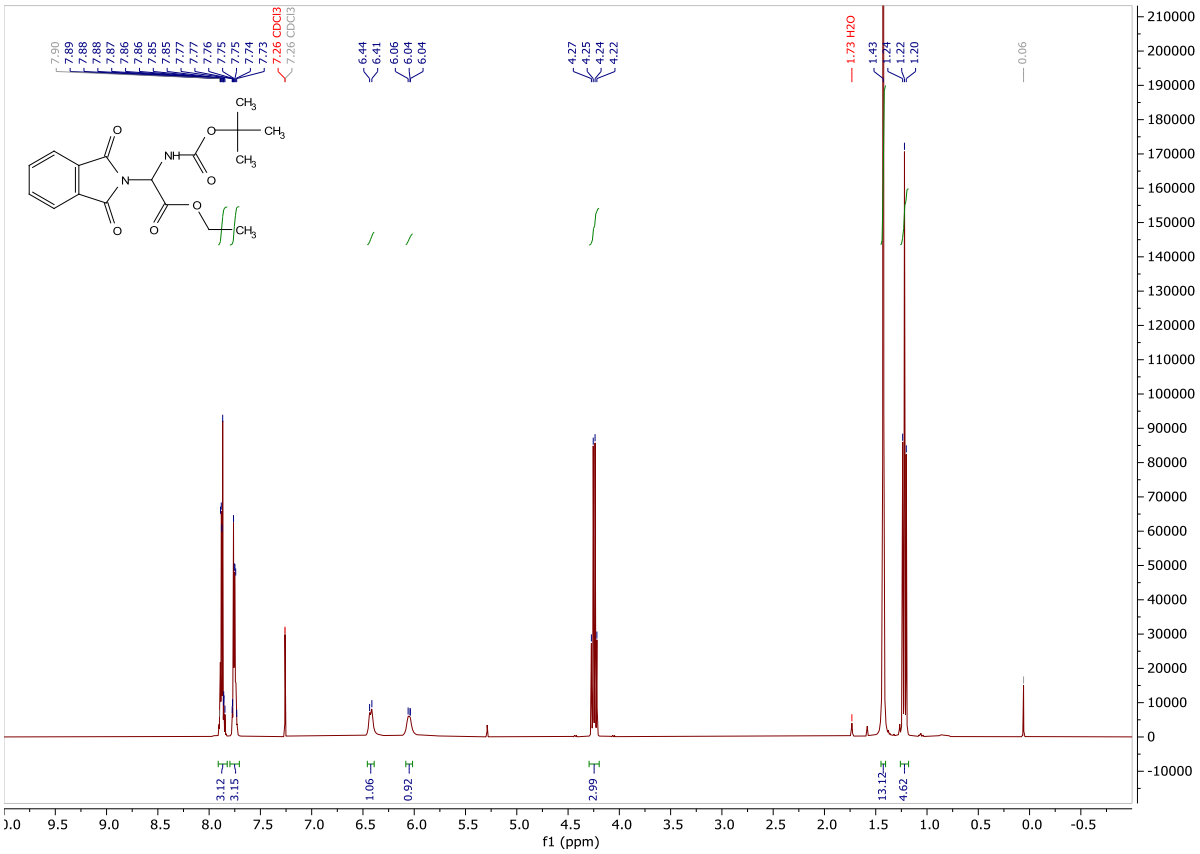


^{13}C NMR (101 MHz, Chloroform-*d*)

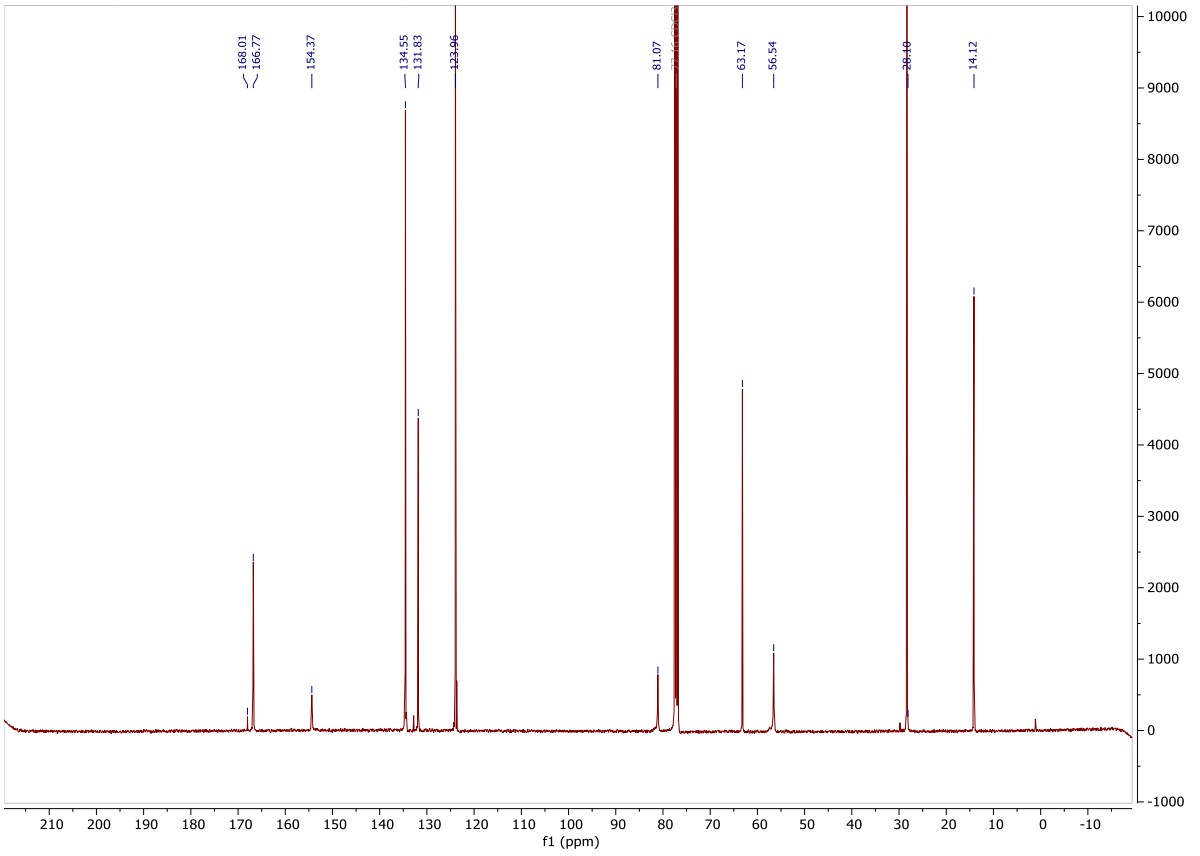


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisoindolin-2-yl)acetate (2o)

^{1}H NMR (400 MHz, Chloroform-*d*)

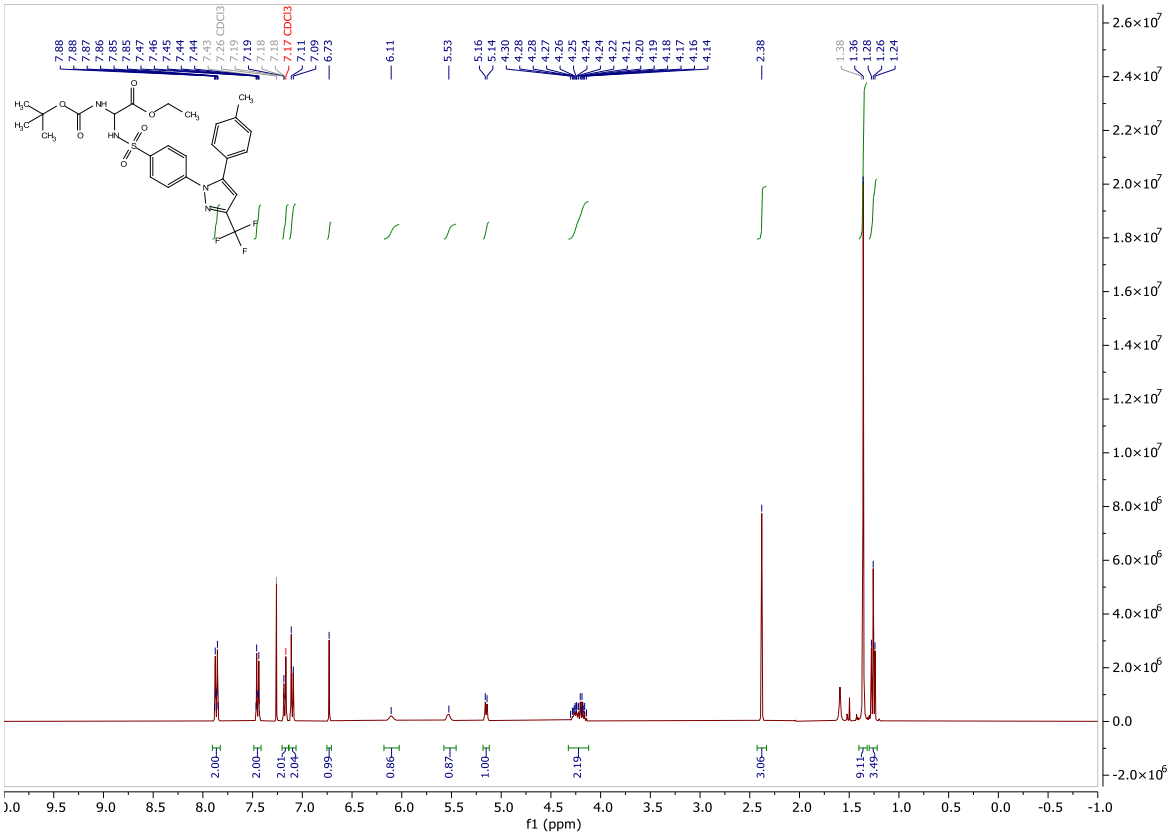


^{13}C NMR (101 MHz, Chloroform-*d*)

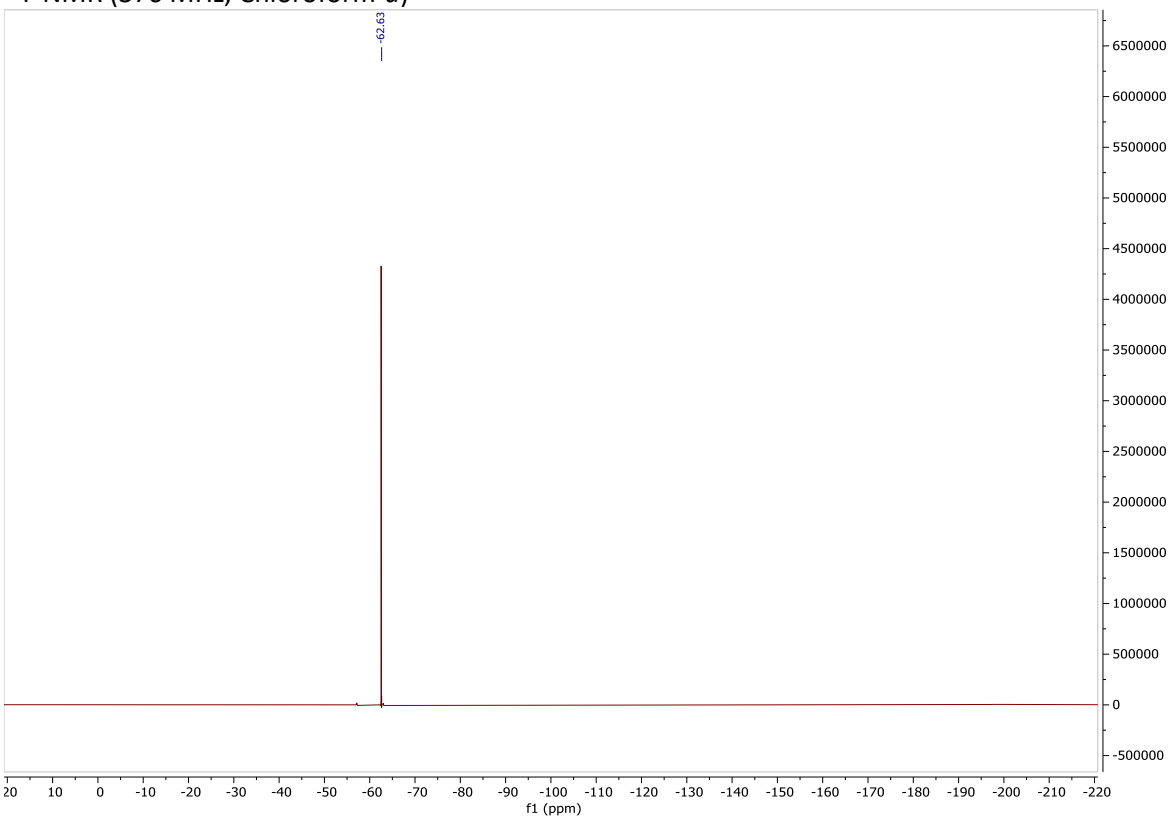


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonamido)acetate (2p)

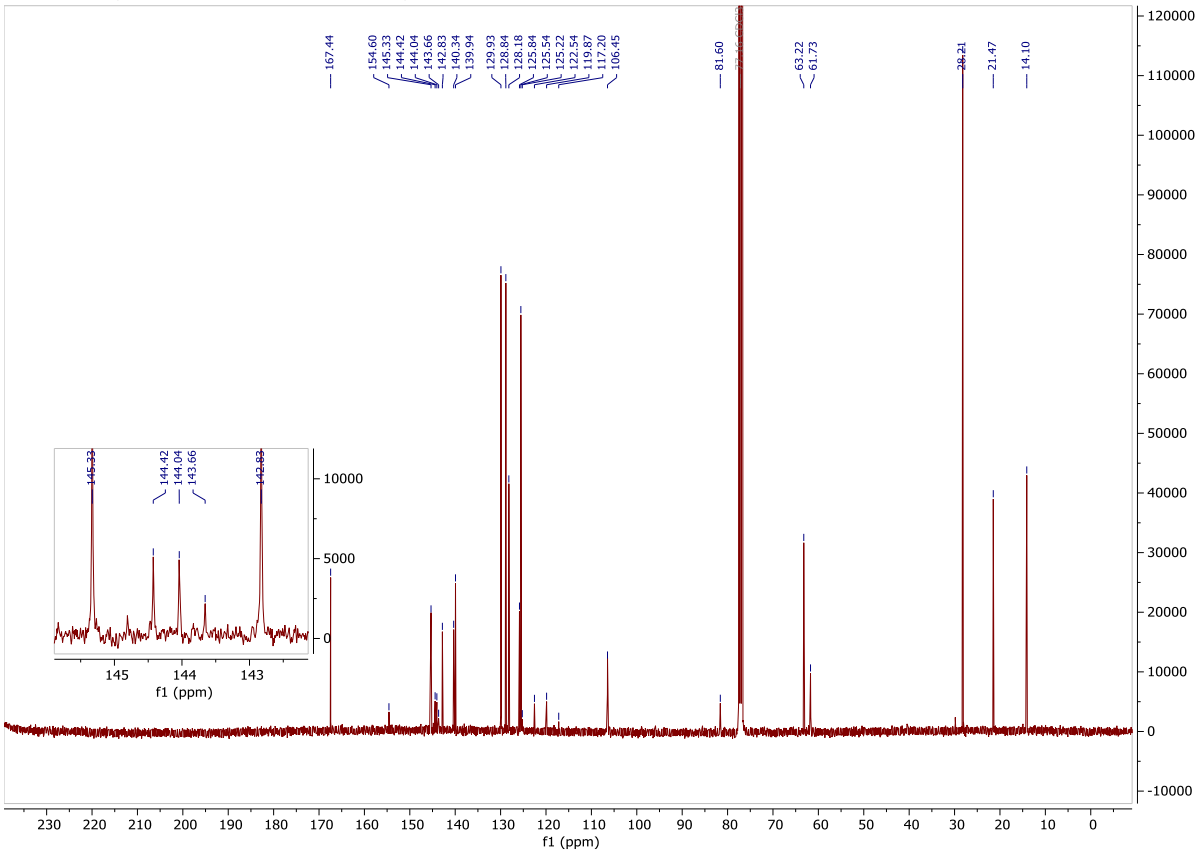
^{1}H NMR (400 MHz, Chloroform-*d*



^{19}F NMR (376 MHz, Chloroform-*d*)

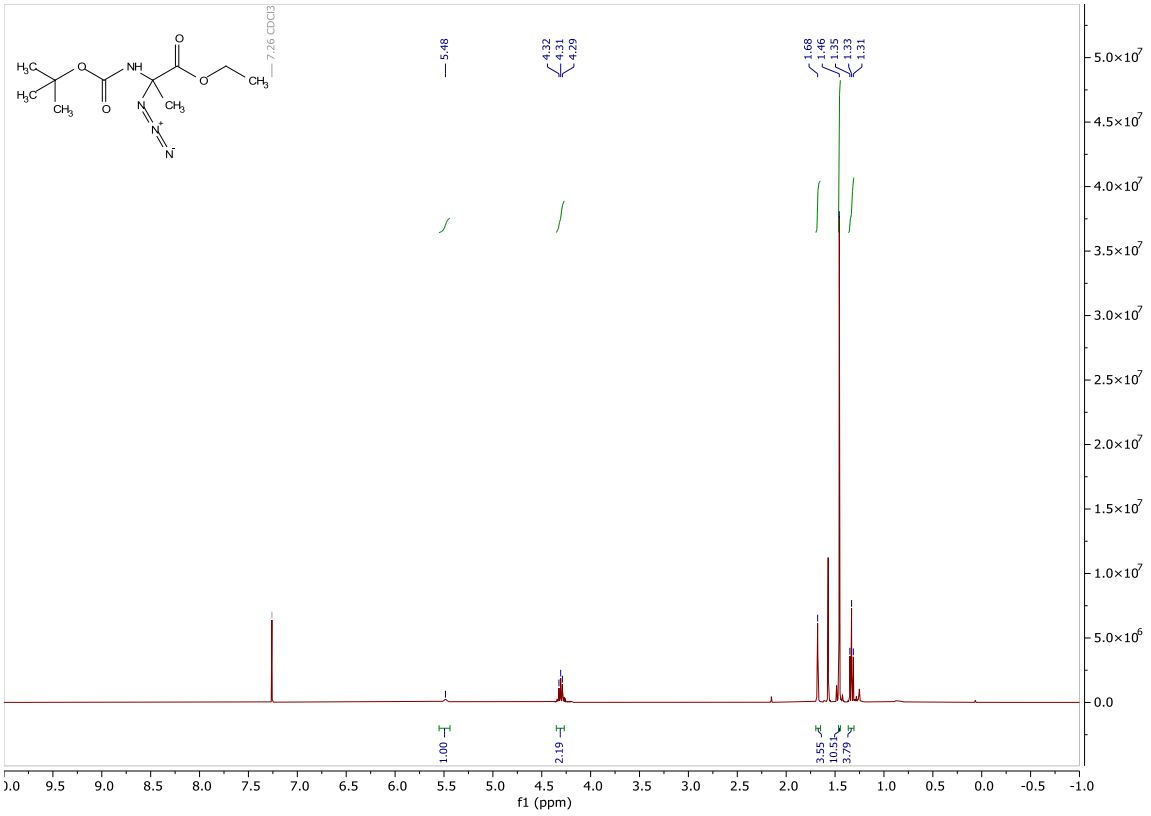


^{13}C NMR (101 MHz, Chloroform-*d*)

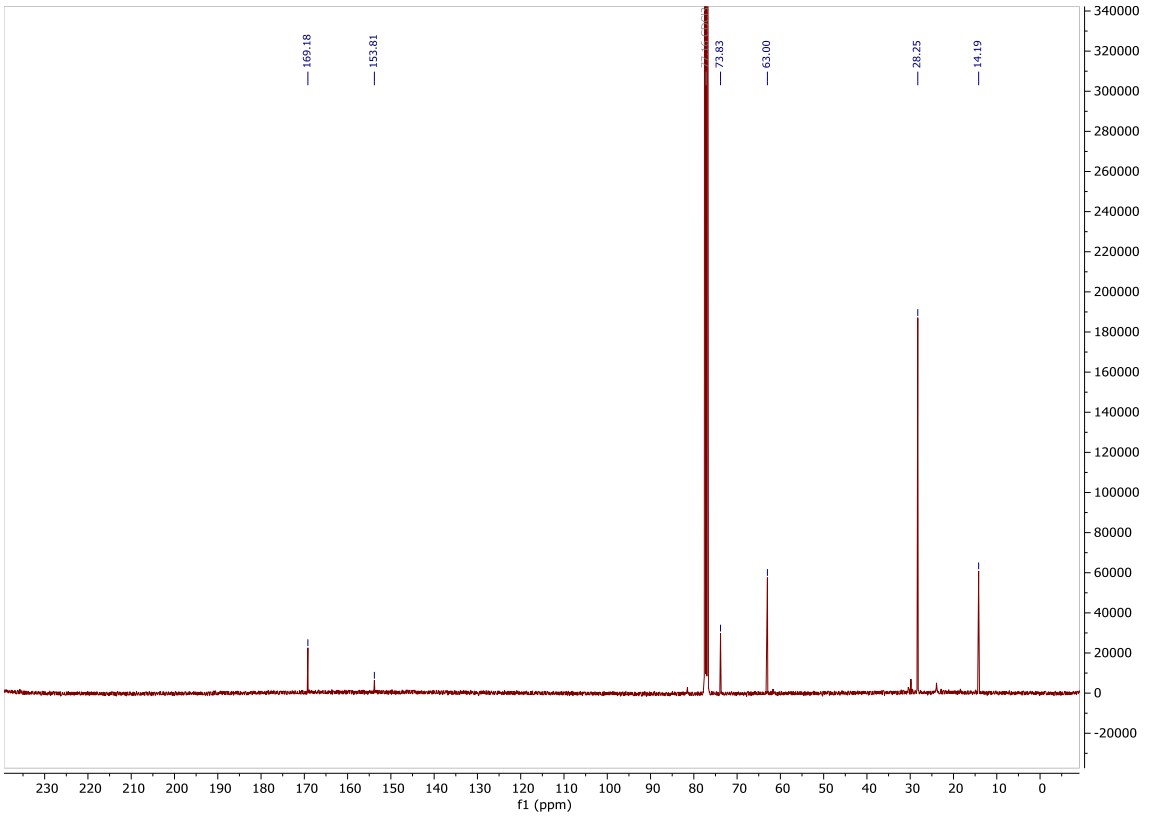


Ethyl 2-azido-2-((*tert*-butoxycarbonyl)amino)propanoate (2q)

^{1}H NMR (400 MHz, Chloroform-*d*)

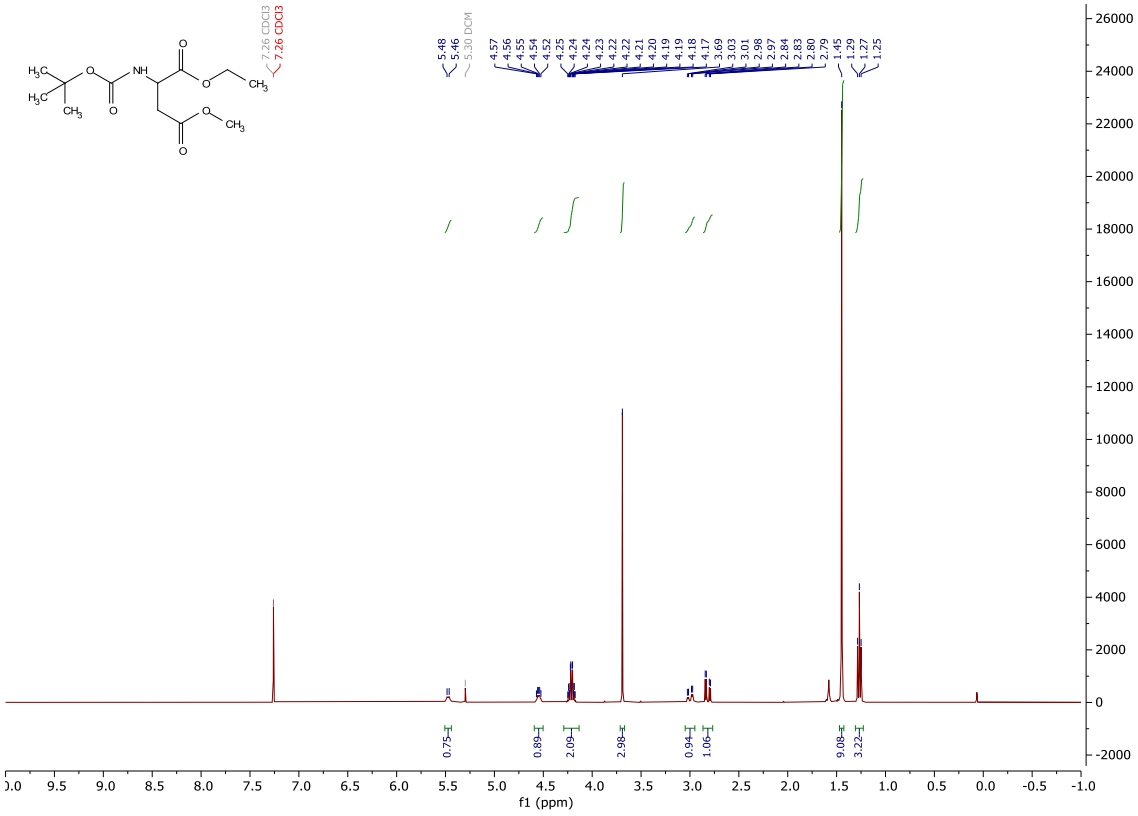


^{13}C NMR (101 MHz, Chloroform-*d*)

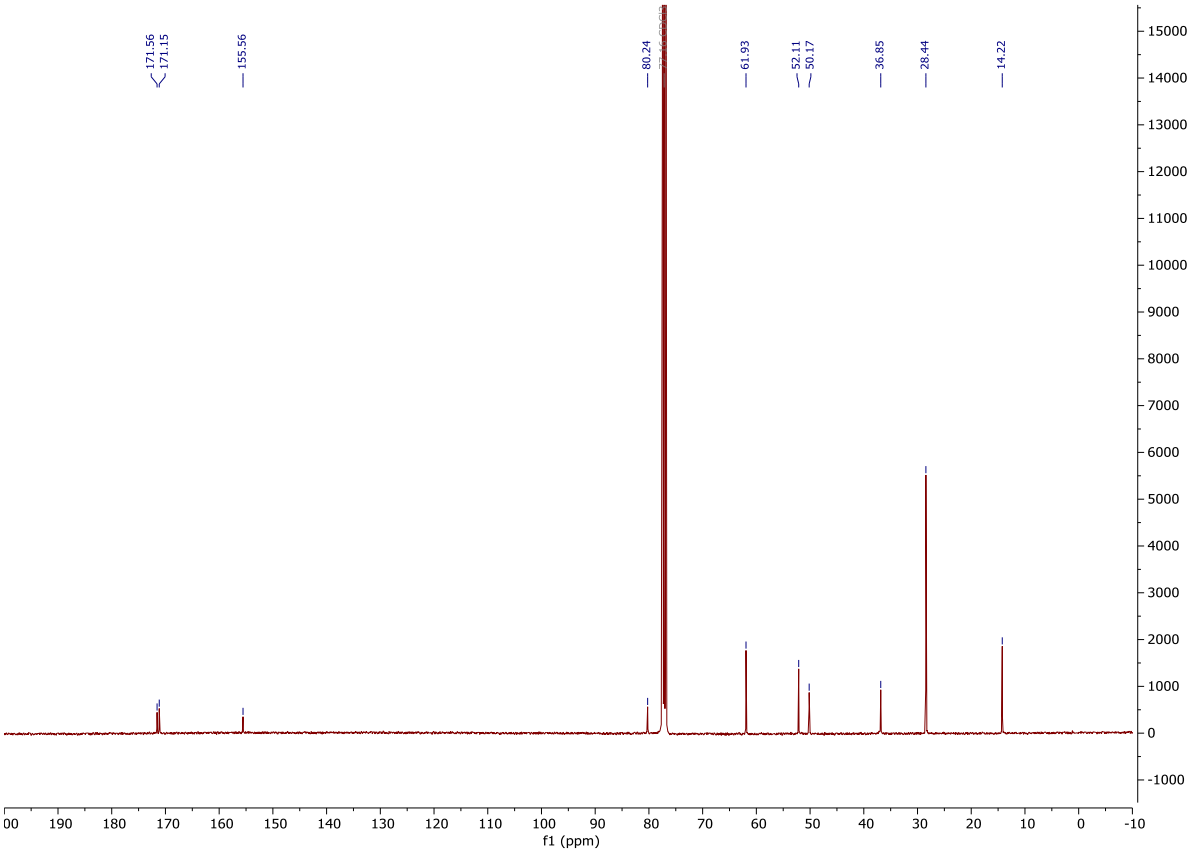


1-ethyl 4-methyl (*tert*-butoxycarbonyl)aspartate (2r)

^{1}H NMR (400 MHz, Chloroform-*d*)

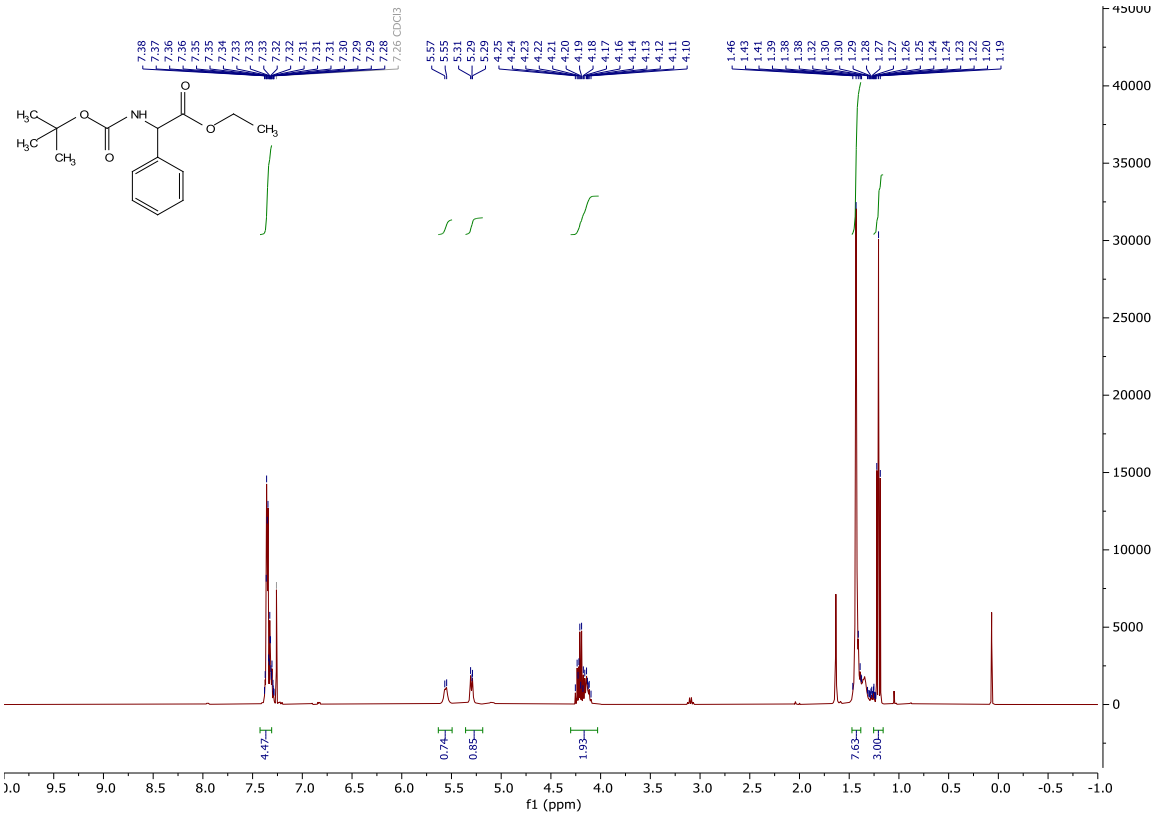


^{13}C NMR (101 MHz, Chloroform-*d*)

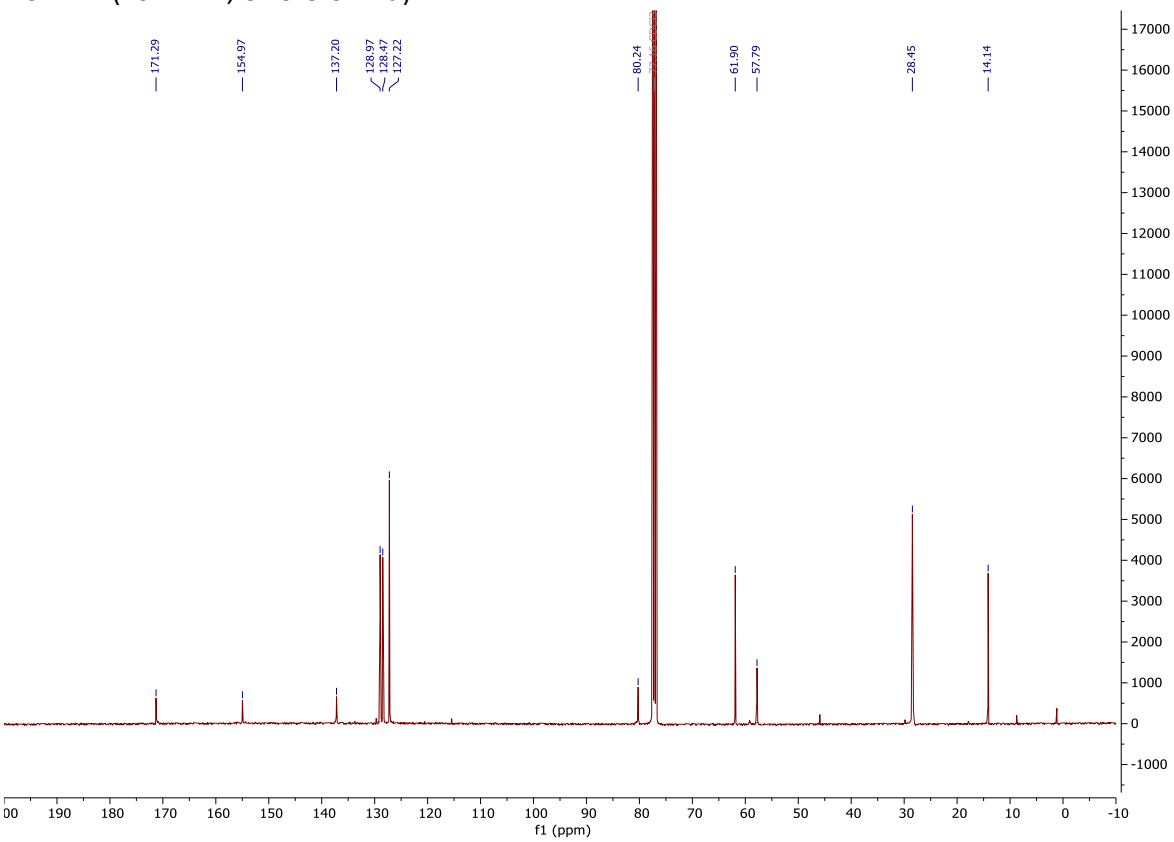


Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate (2s)

^{1}H NMR (400 MHz, Chloroform-*d*)

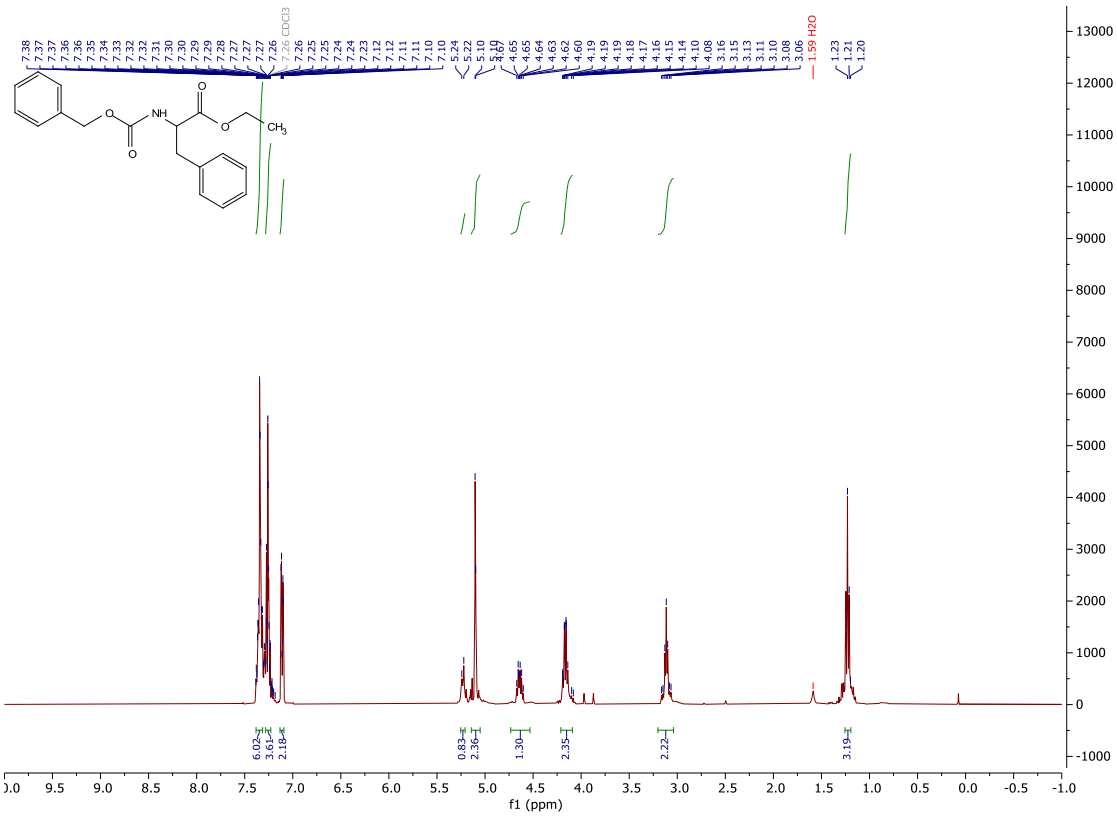


^{13}C NMR (101 MHz, Chloroform-*d*)

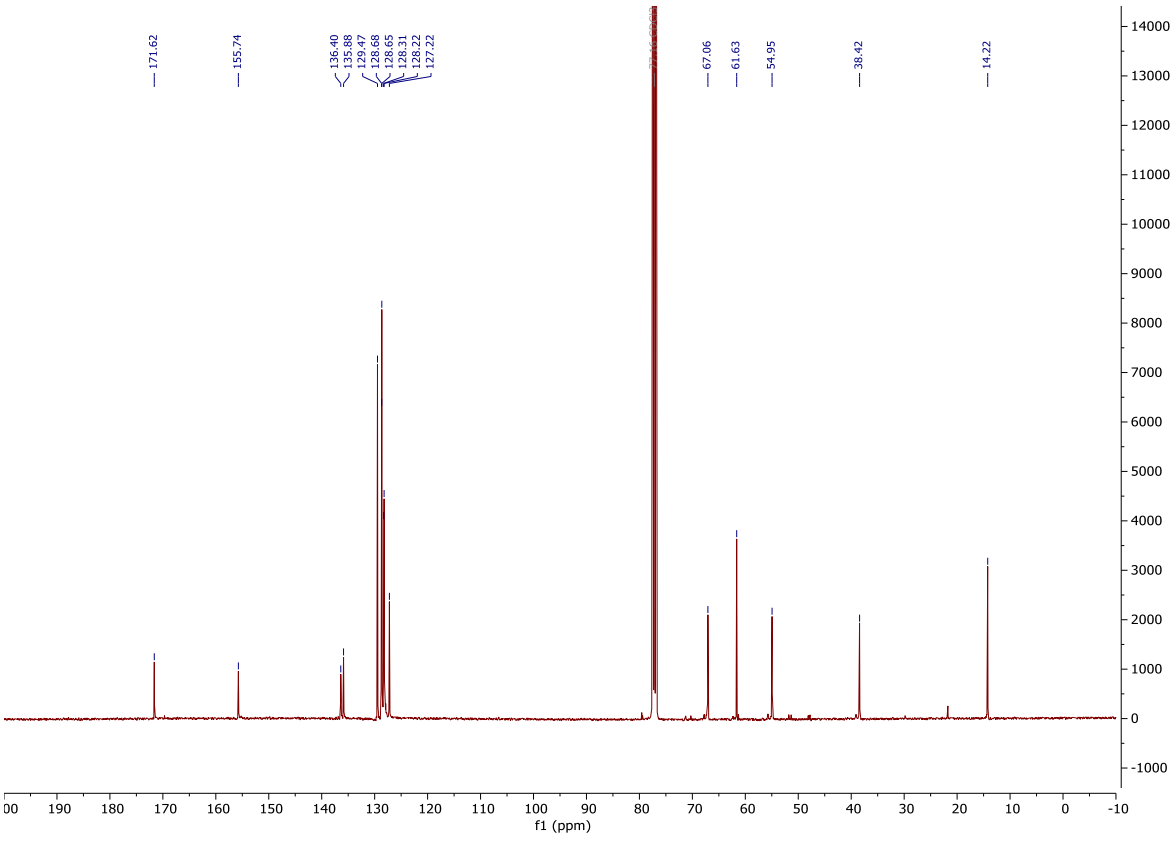


Ethyl ((benzyloxy)carbonyl)phenylalaninate (2t)

^{1}H NMR (400 MHz, Chloroform-*d*)

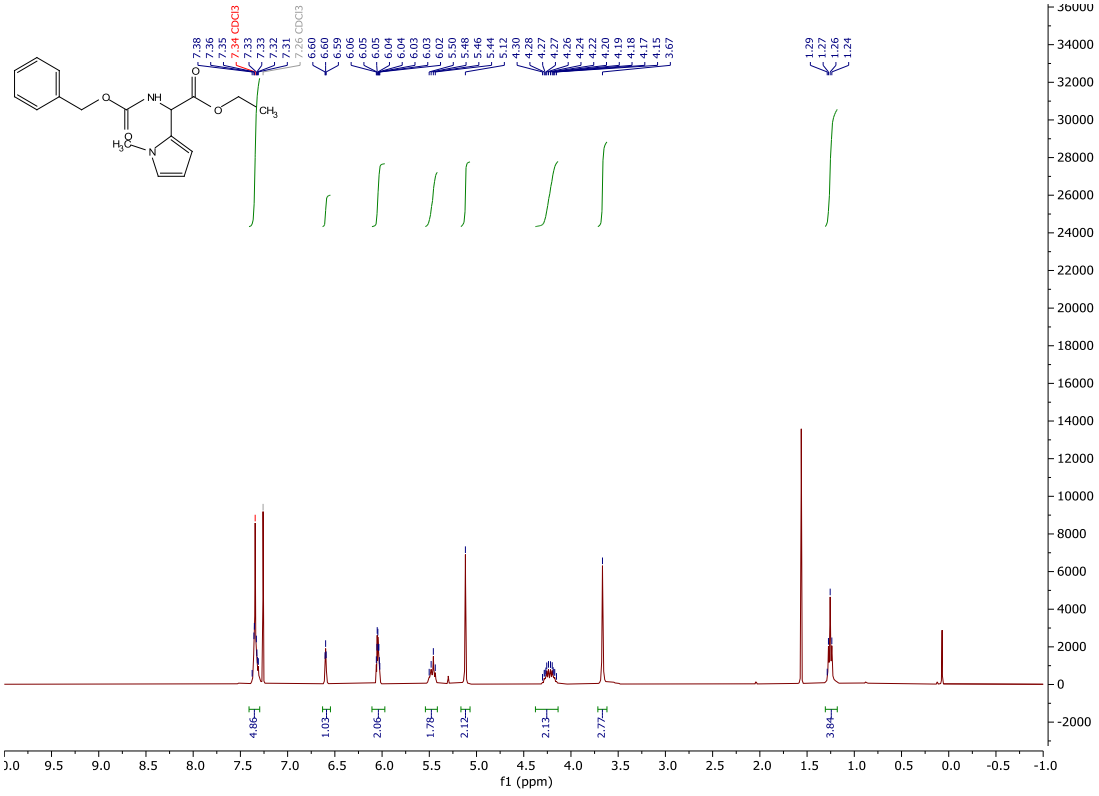


^{13}C NMR (101 MHz, Chloroform-*d*)

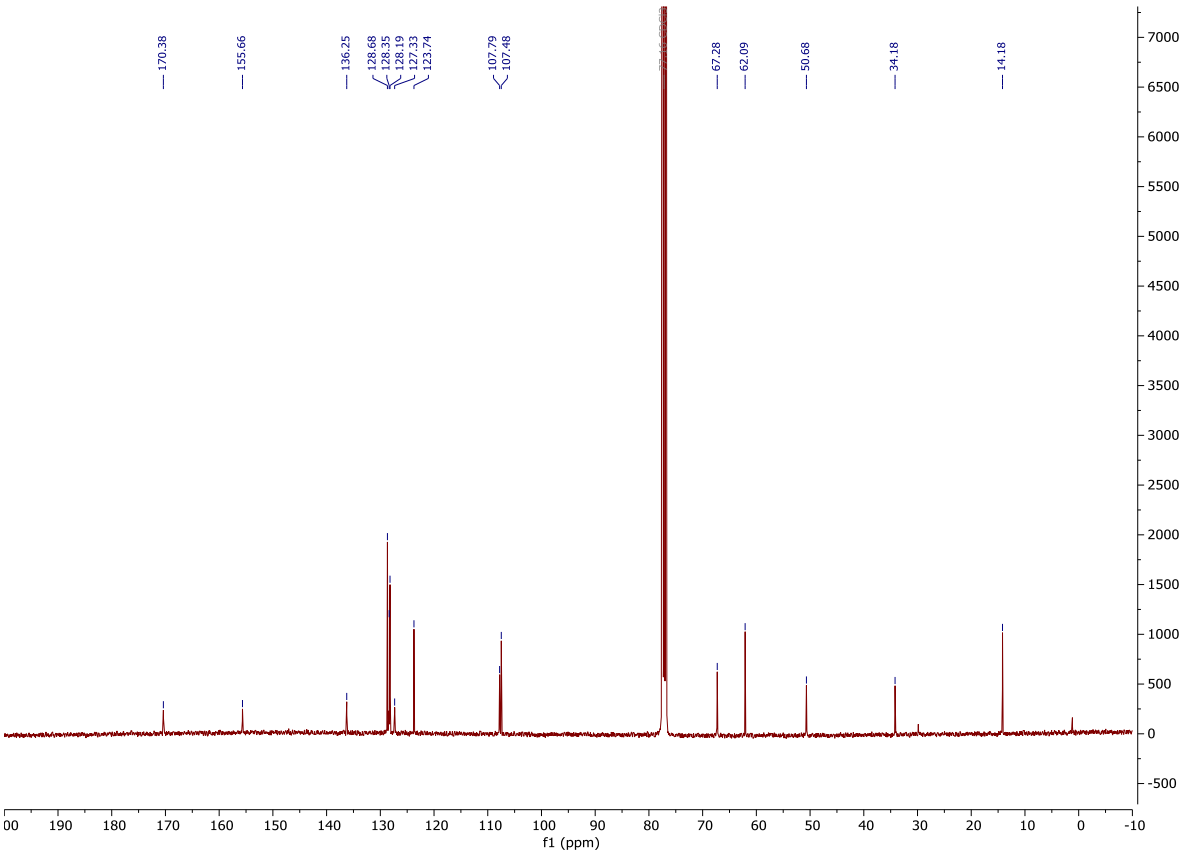


Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1*H*-pyrrol-2-yl)acetate (2u)

^{1}H NMR (400 MHz, Chloroform-*d*)

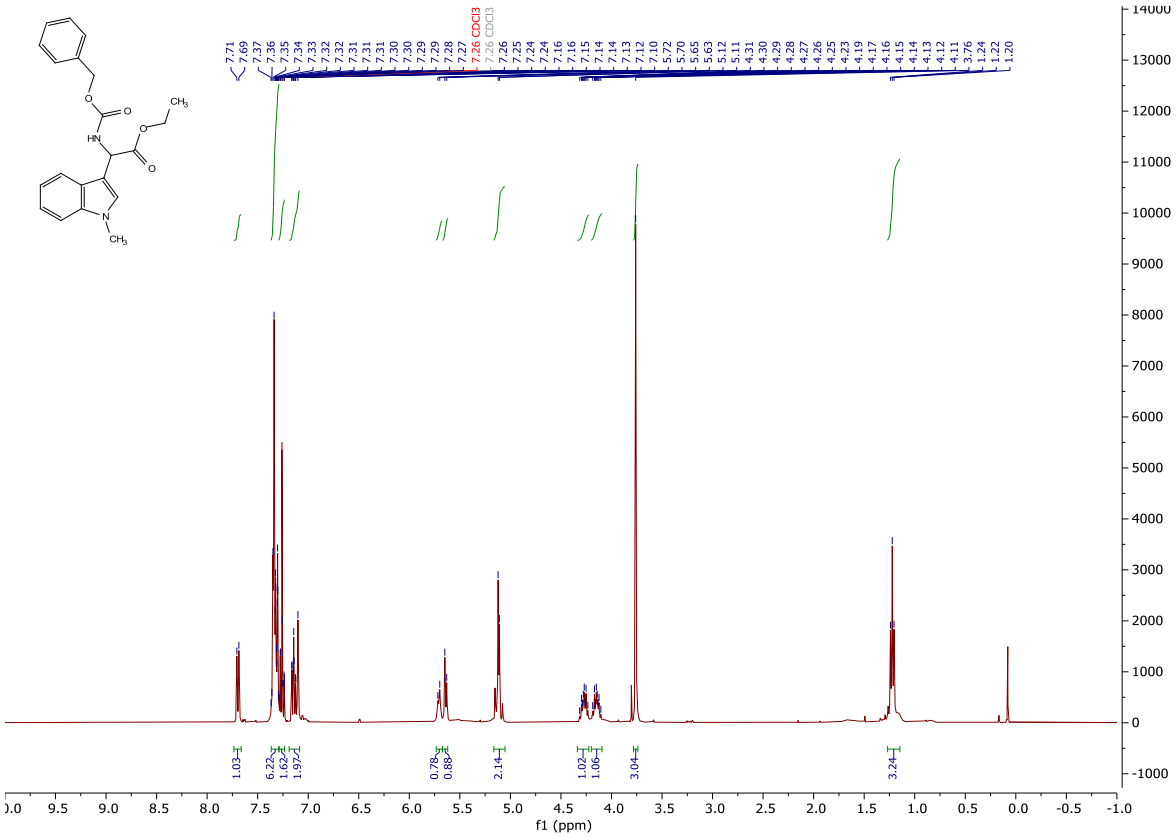


^{13}C NMR (101 MHz, Chloroform-*d*)

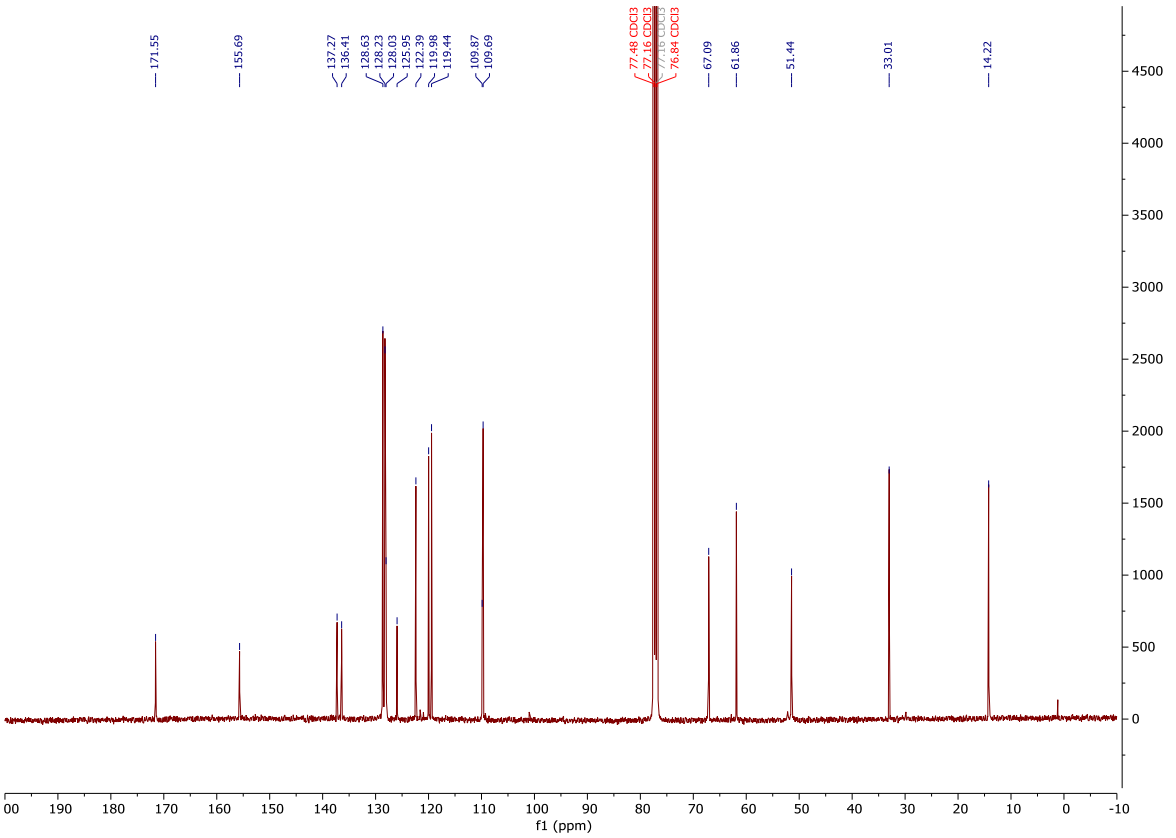


Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1*H*-indol-2-yl)acetate (2v)

^{1}H NMR (400 MHz, Chloroform-*d*)

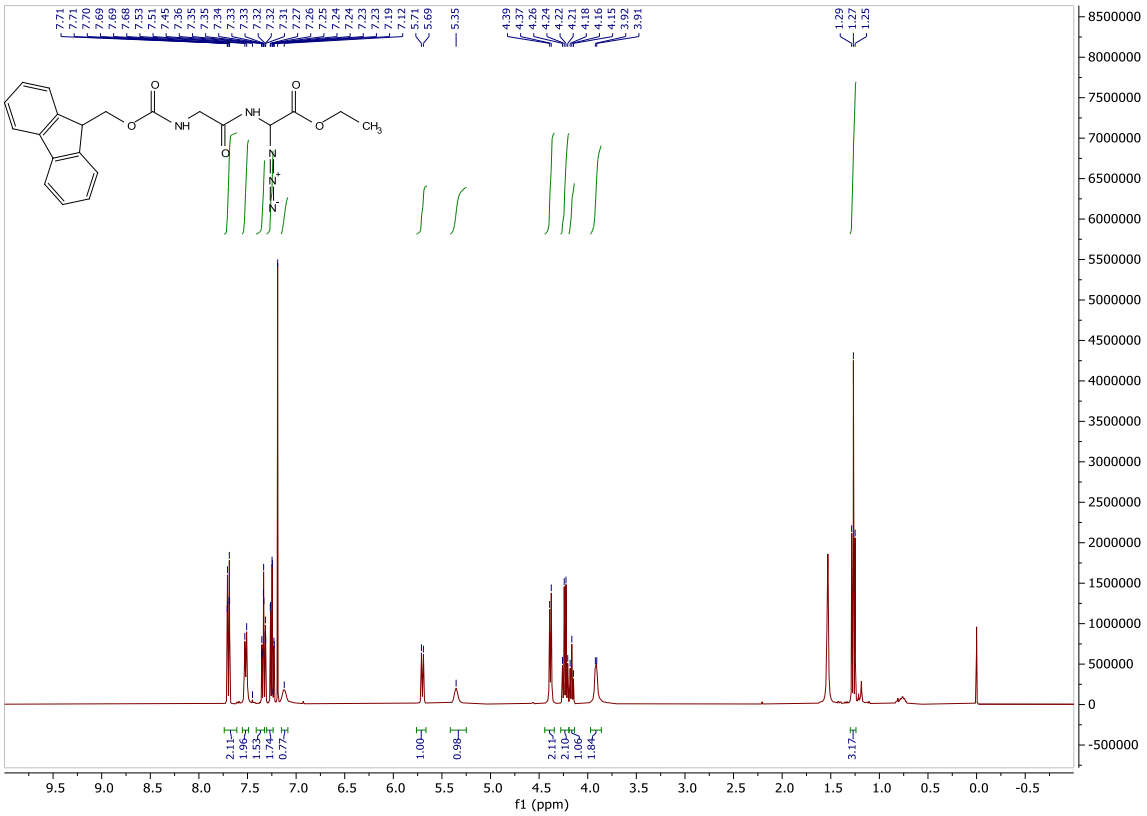


^{13}C NMR (101 MHz, Chloroform-*d*)

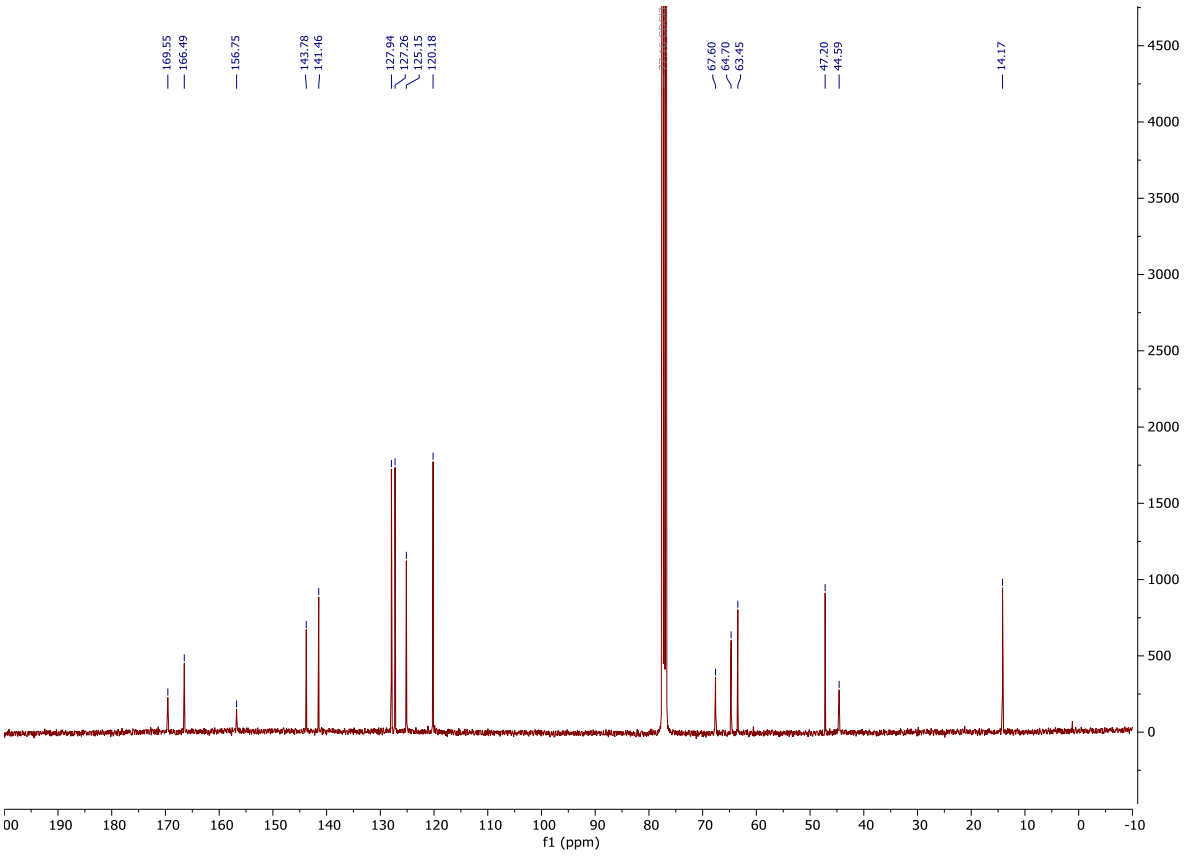


Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-azidoacetate (6a)

^{1}H NMR (400 MHz, Chloroform-*d*)

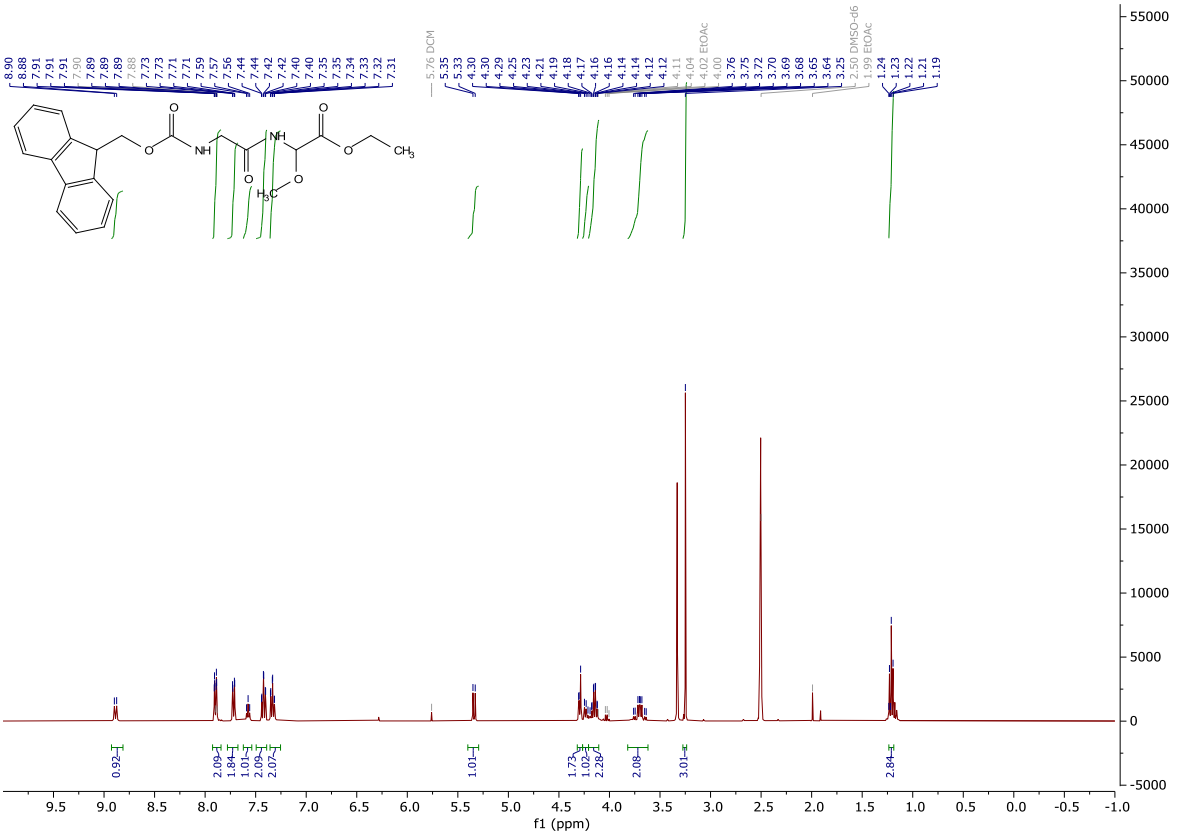


^{13}C NMR (101 MHz, Chloroform-*d*)

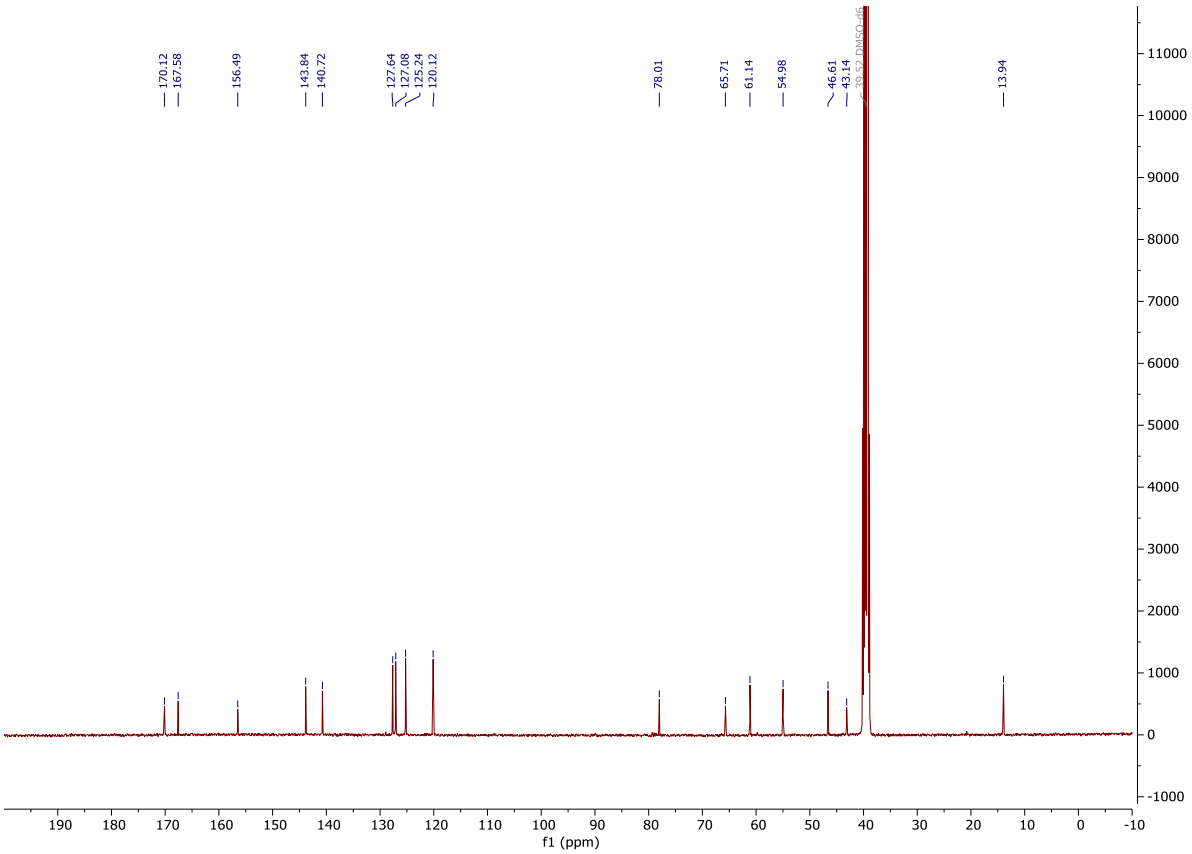


Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6b)

^{1}H NMR (400 MHz, DMSO-*d6*)

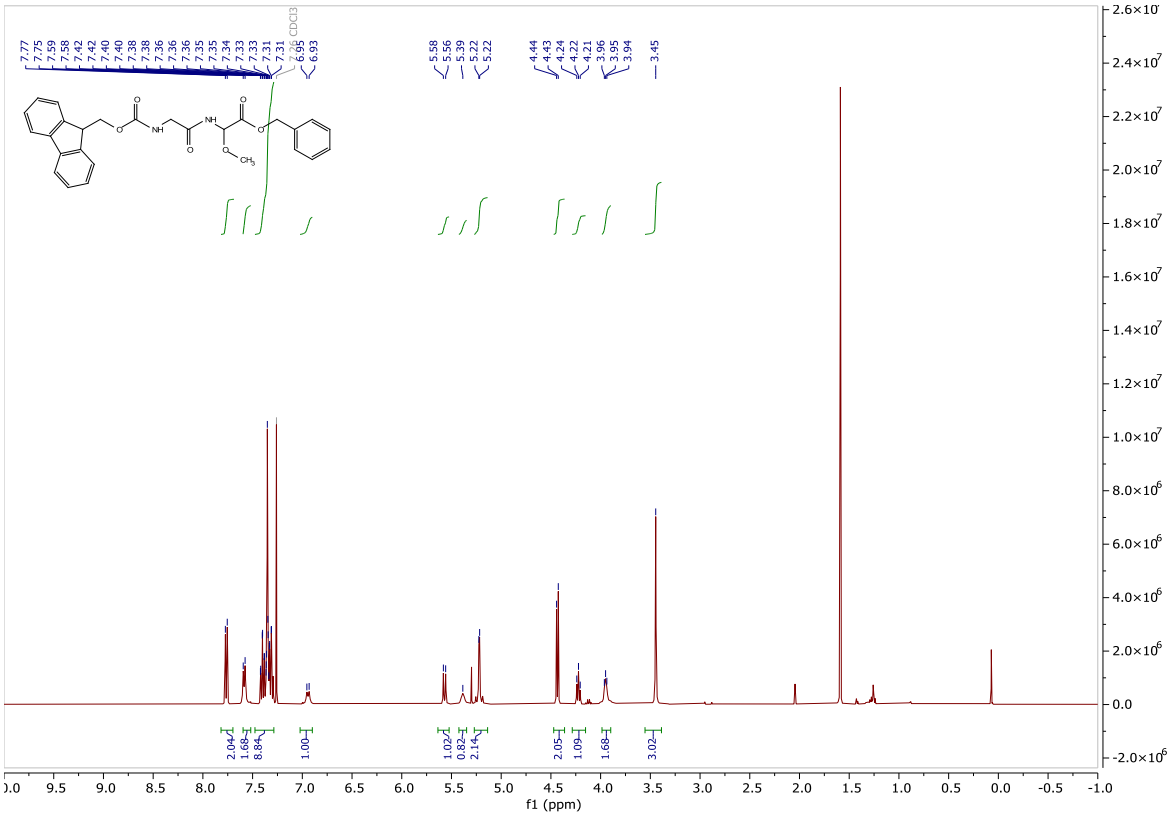


^{13}C NMR (101 MHz, Chloroform-*d*)

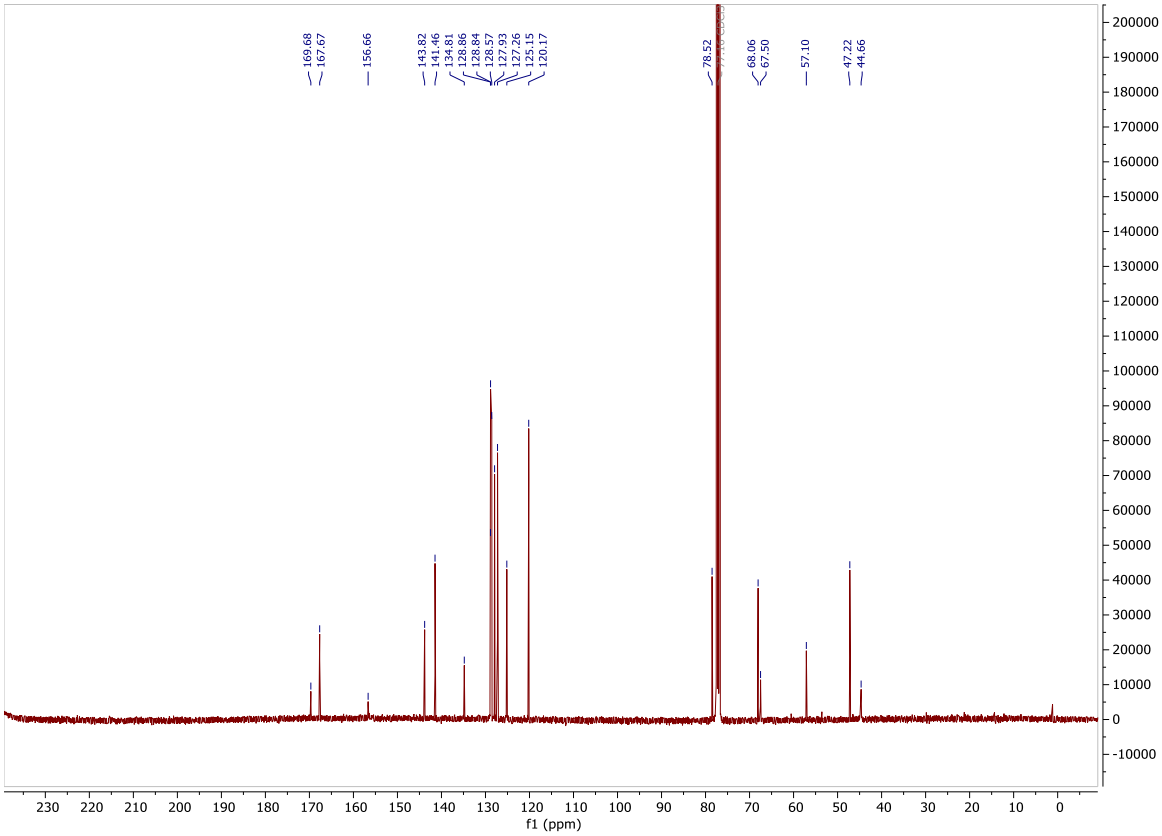


Benzyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6c)

^{1}H NMR (400 MHz, Chloroform-*d*)

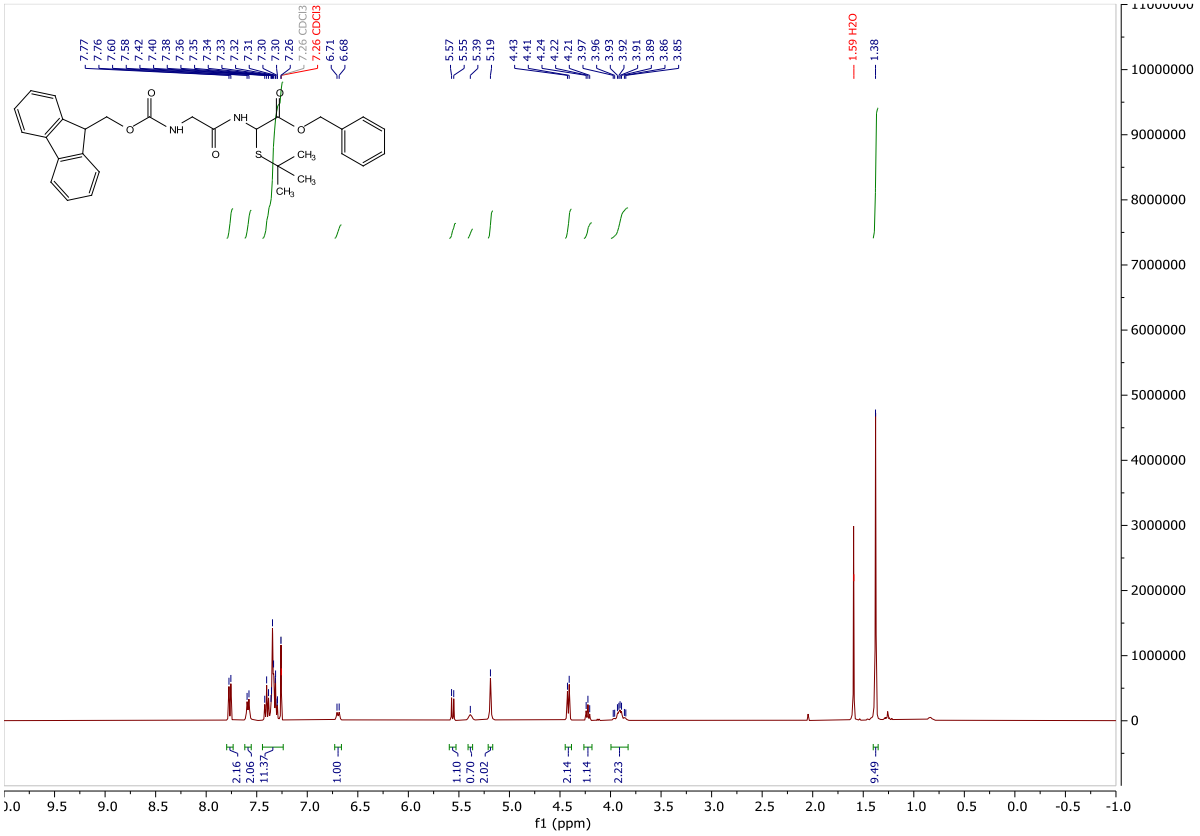


^{13}C NMR (101 MHz, Chloroform-*d*)

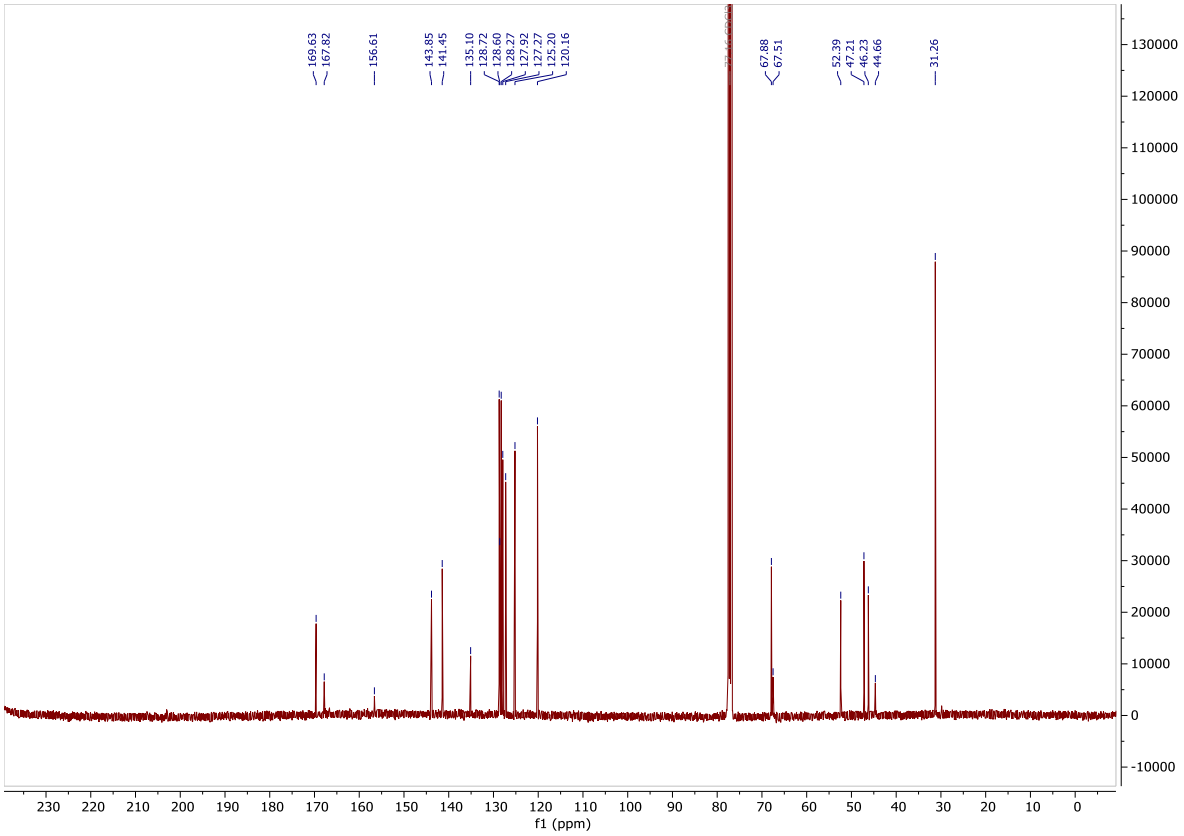


Benzyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-(*tert*-butylthio)acetate (6d)

^{1}H NMR (400 MHz, Chloroform-*d*)

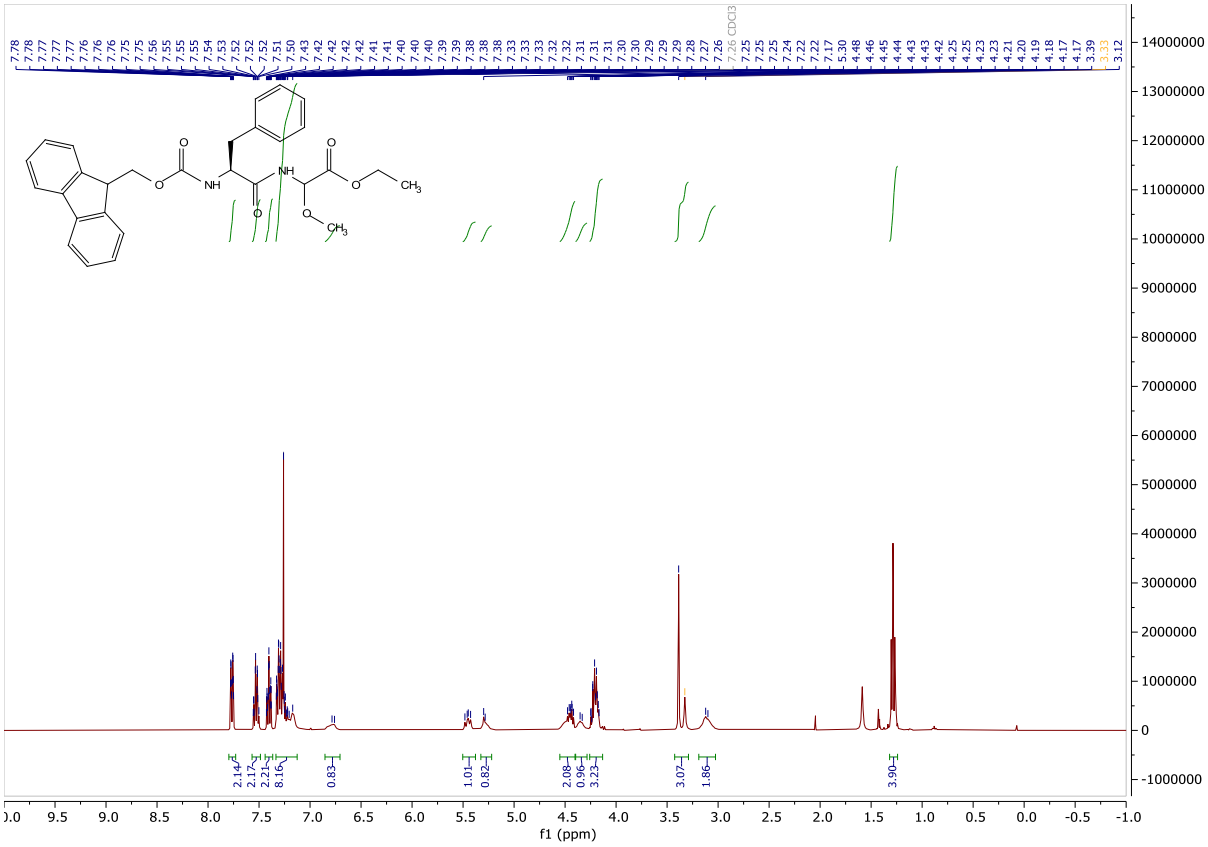


^{13}C NMR (101 MHz, Chloroform-*d*)

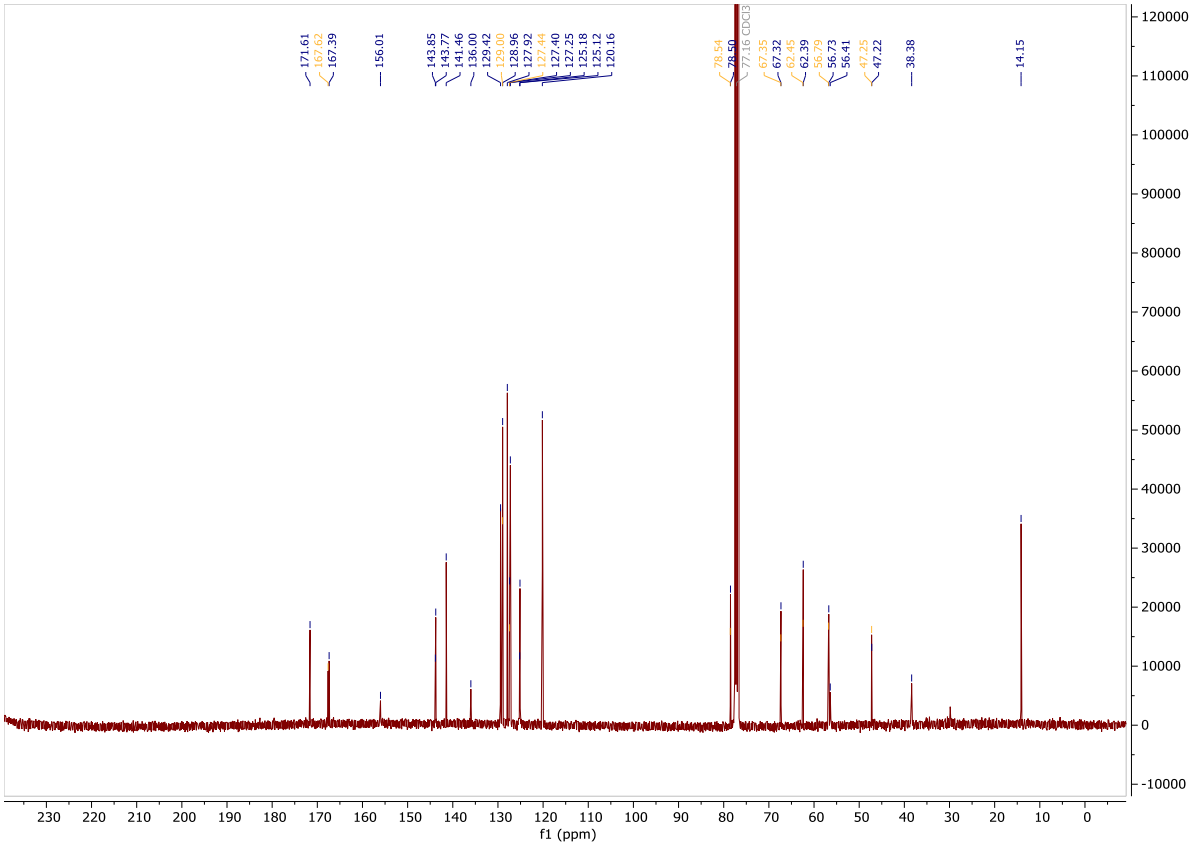


Ethyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-2-methoxyacetate (6e)

^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)

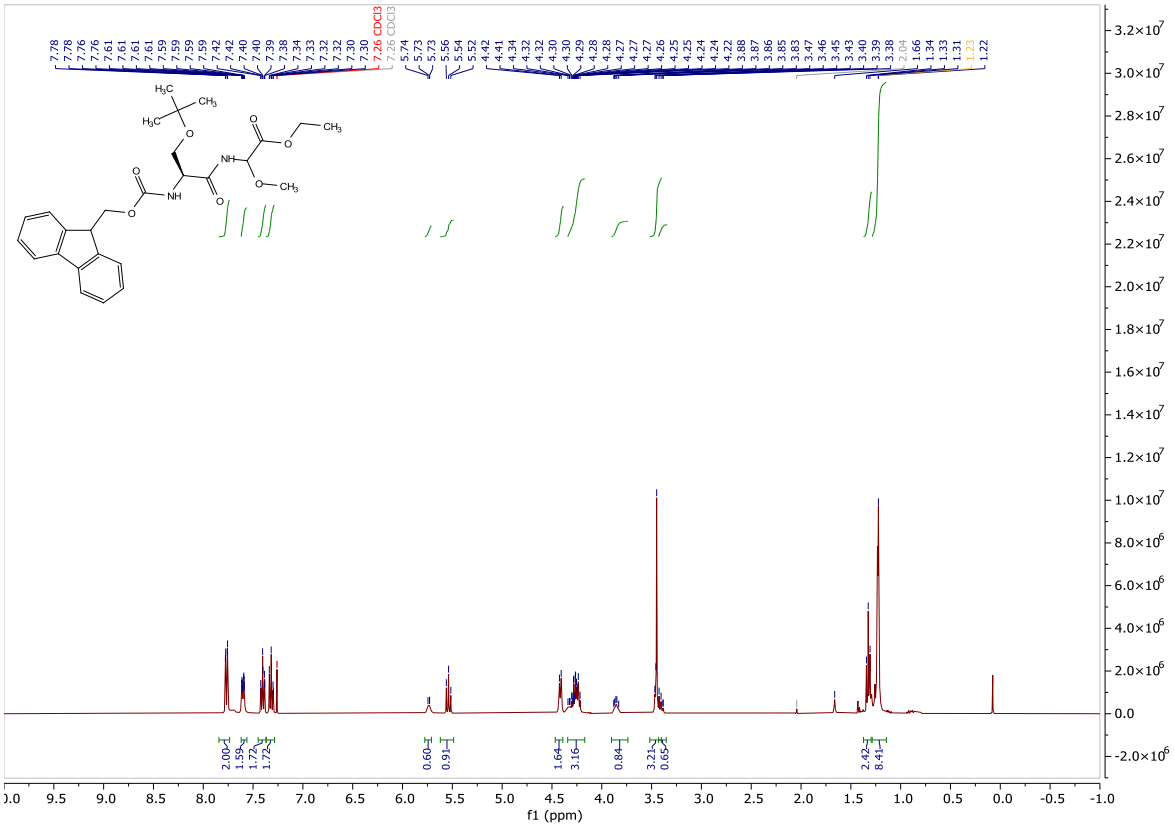


^{13}C NMR (101 MHz, Chloroform-*d*)

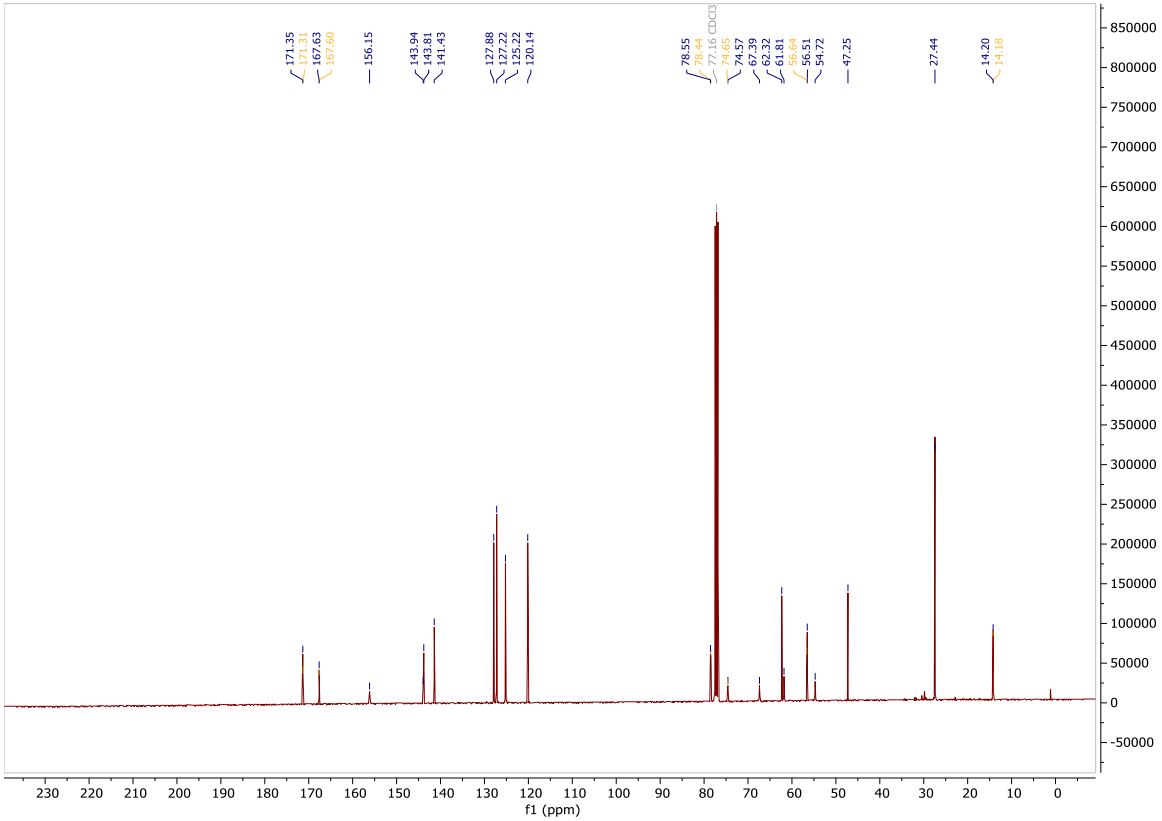


Ethyl 2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(*tert*-butoxy)propanamido)-2-methoxyacetate (**6f**)

^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)

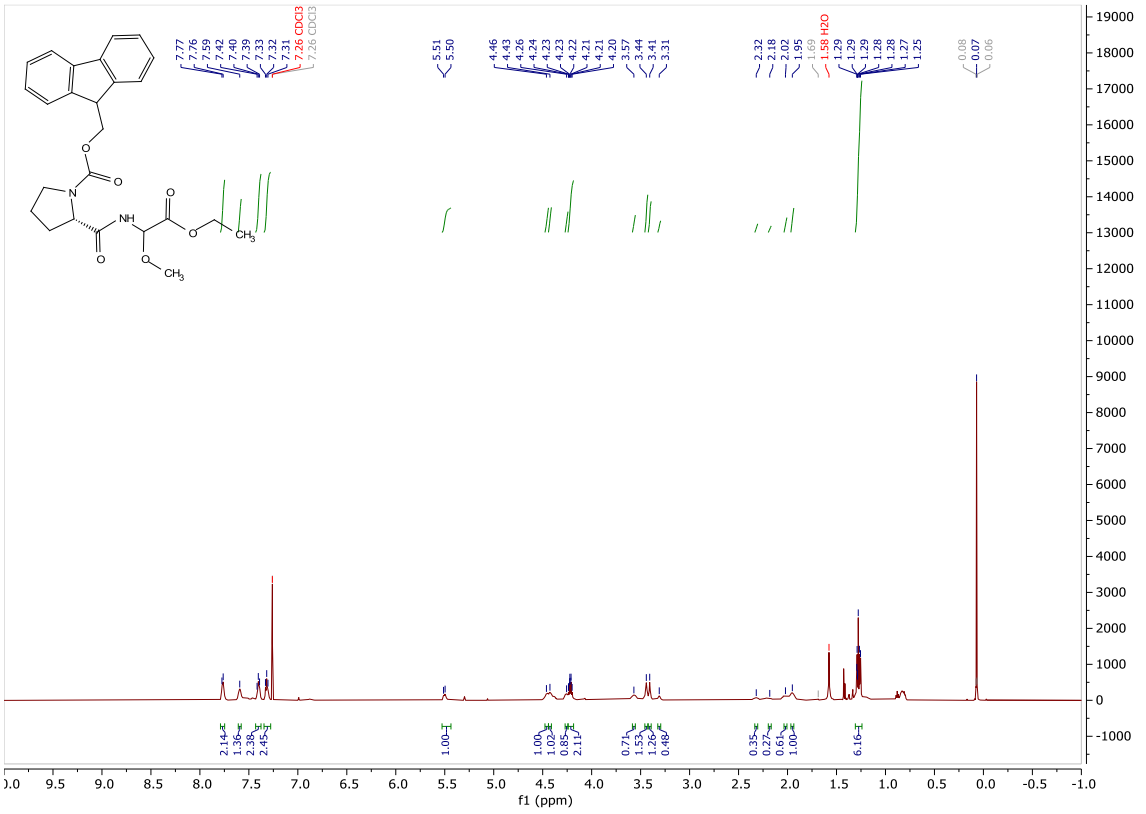


^{13}C NMR (101 MHz, Chloroform-*d*)

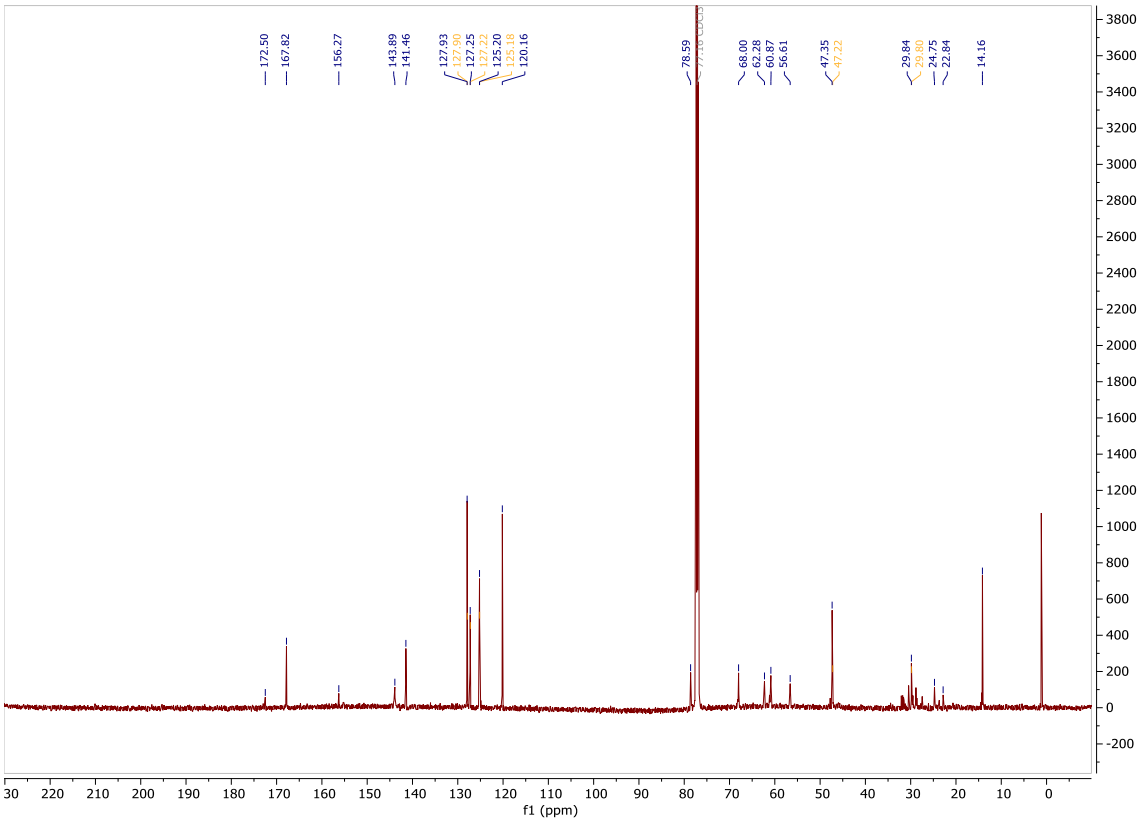


(9*H*-fluoren-9-yl)methyl (2*S*)-2-((2-ethoxy-1-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate-6 (**6g**)

^{1}H NMR (600 MHz, Chloroform-*d,* mixture of two diastereoisomers)

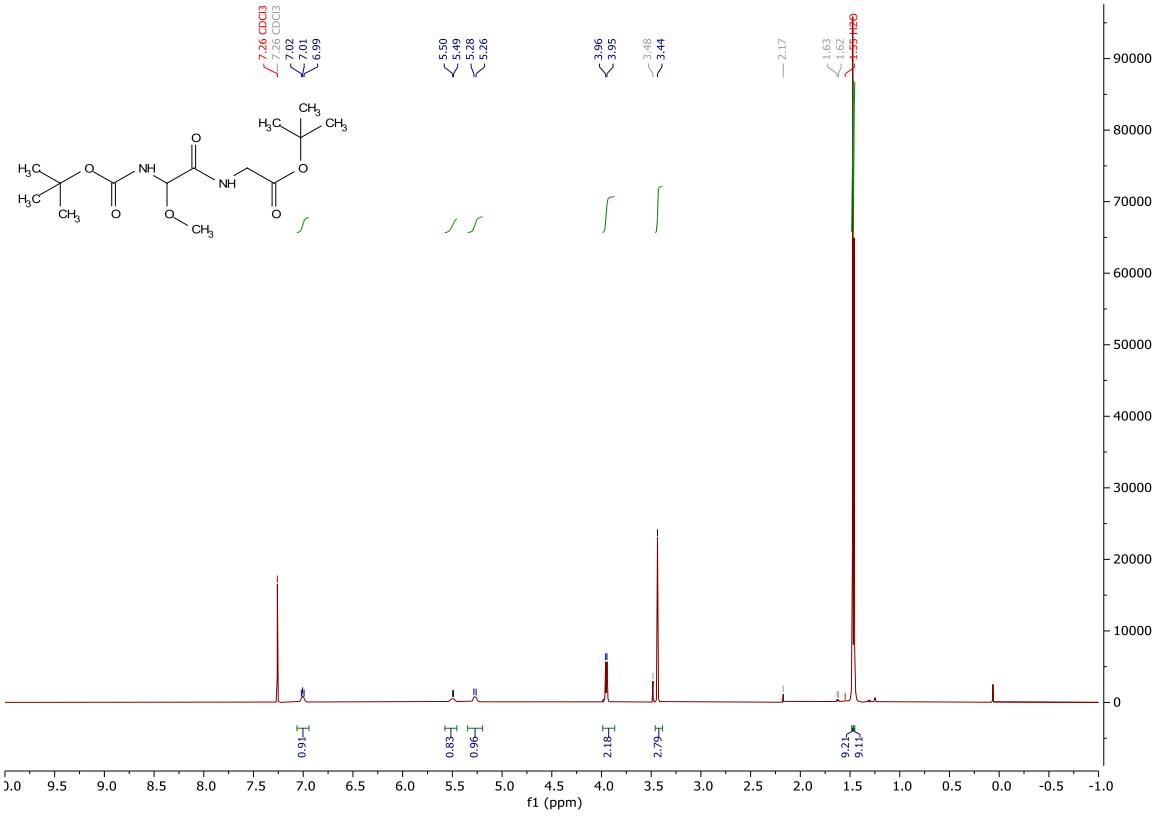


^{13}C NMR (151 MHz, Chloroform-*d*)

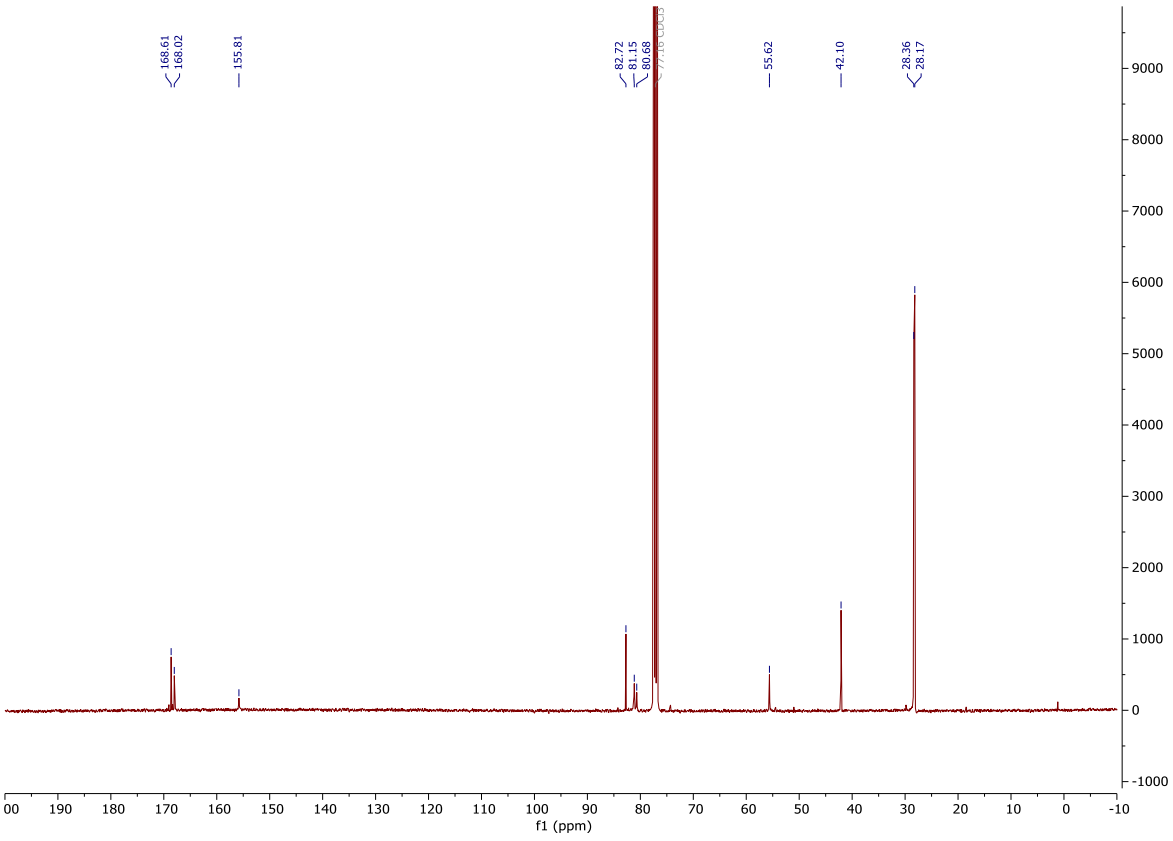


***tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)-2-methoxyacetyl)glycinate (6h)**

^{1}H NMR (400 MHz, Chloroform-*d*)

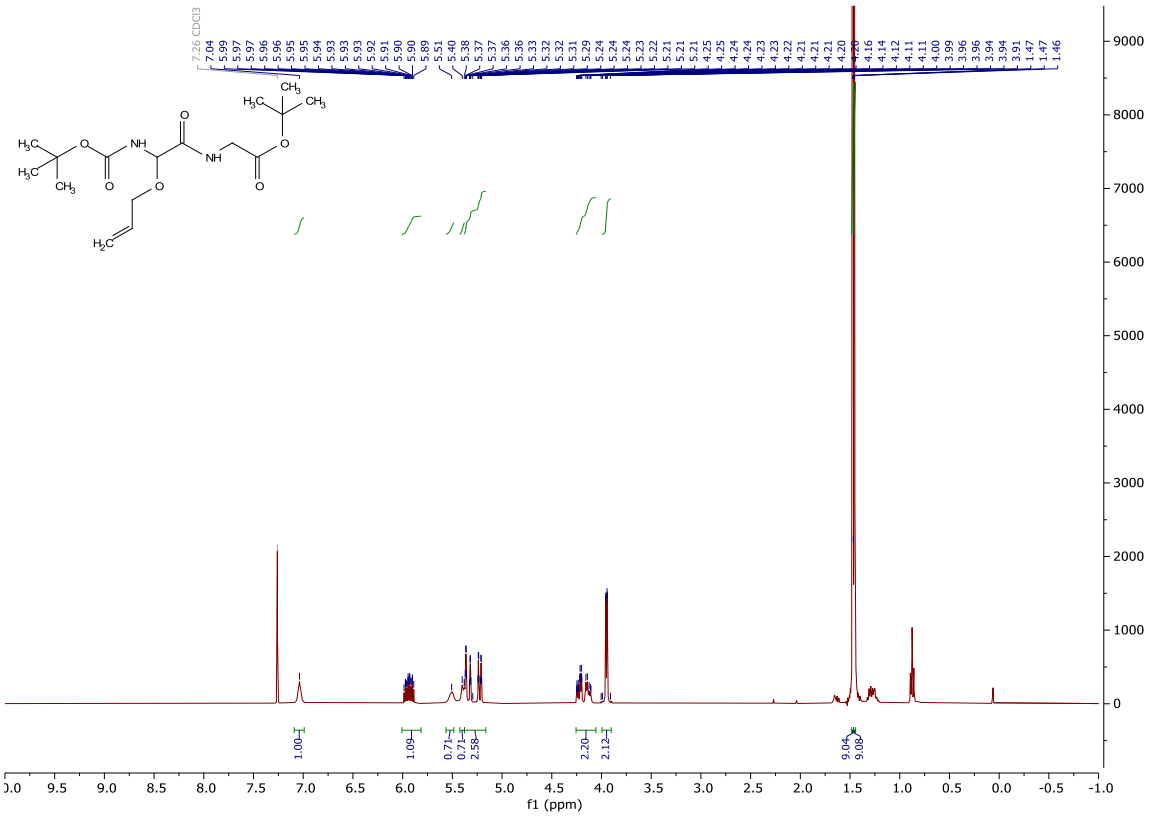


^{13}C NMR (101 MHz, Chloroform-*d*)

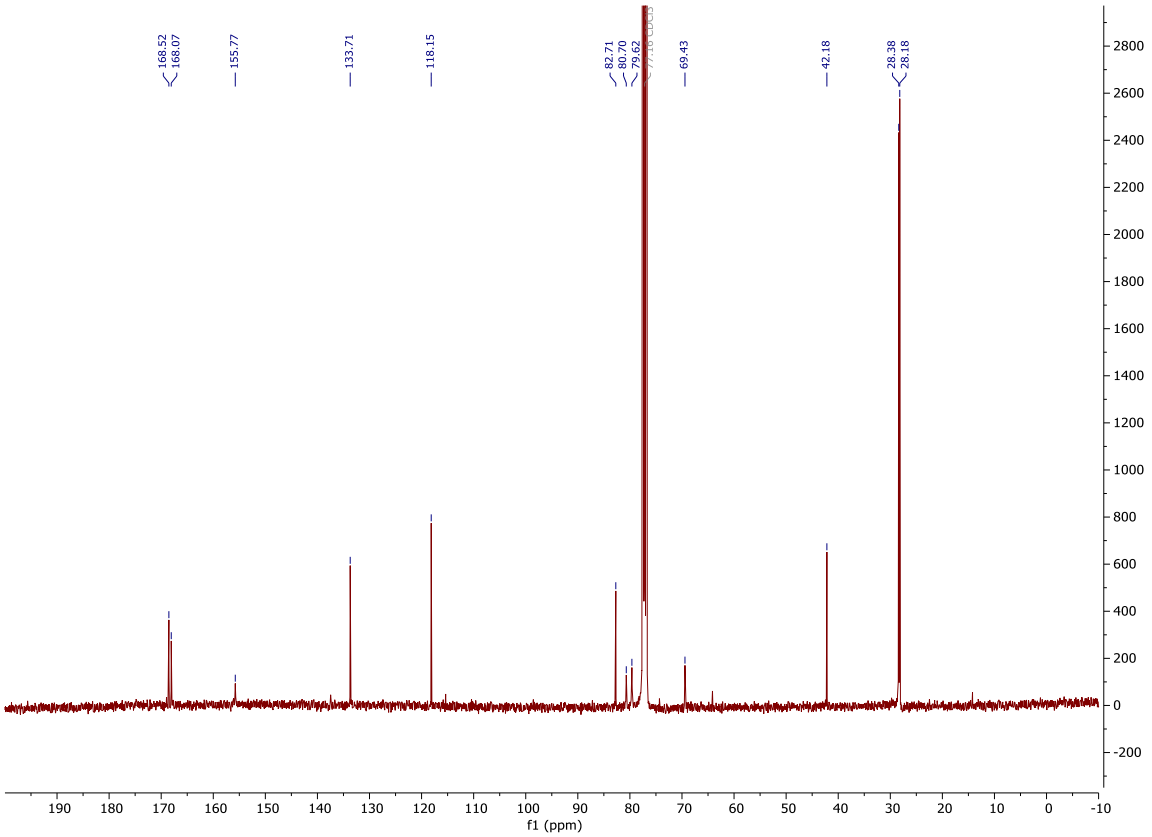


tert-Butyl (2-(allyloxy)-2-((_tert_-butoxycarbonyl)amino)acetyl)glycinate (6i)

^{1}H NMR (400 MHz, Chloroform-*d*)

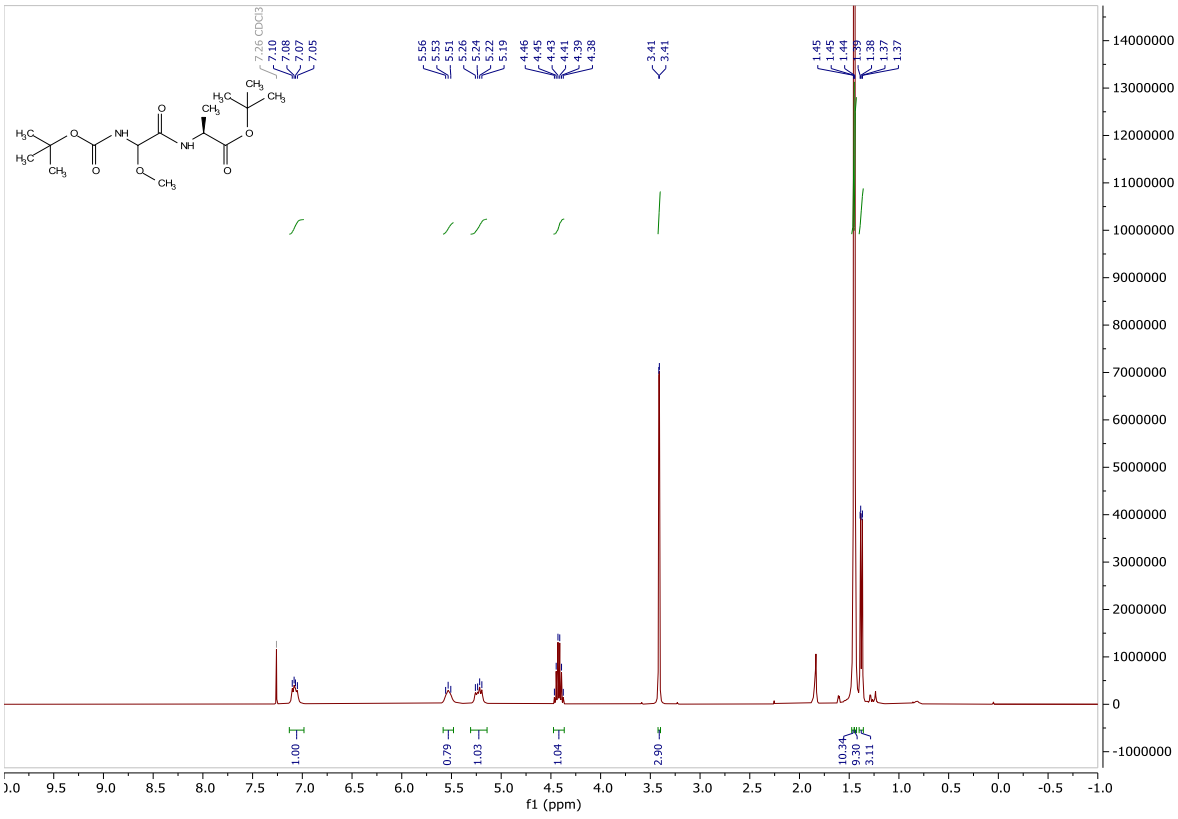


^{13}C NMR (101 MHz, Chloroform-*d*)

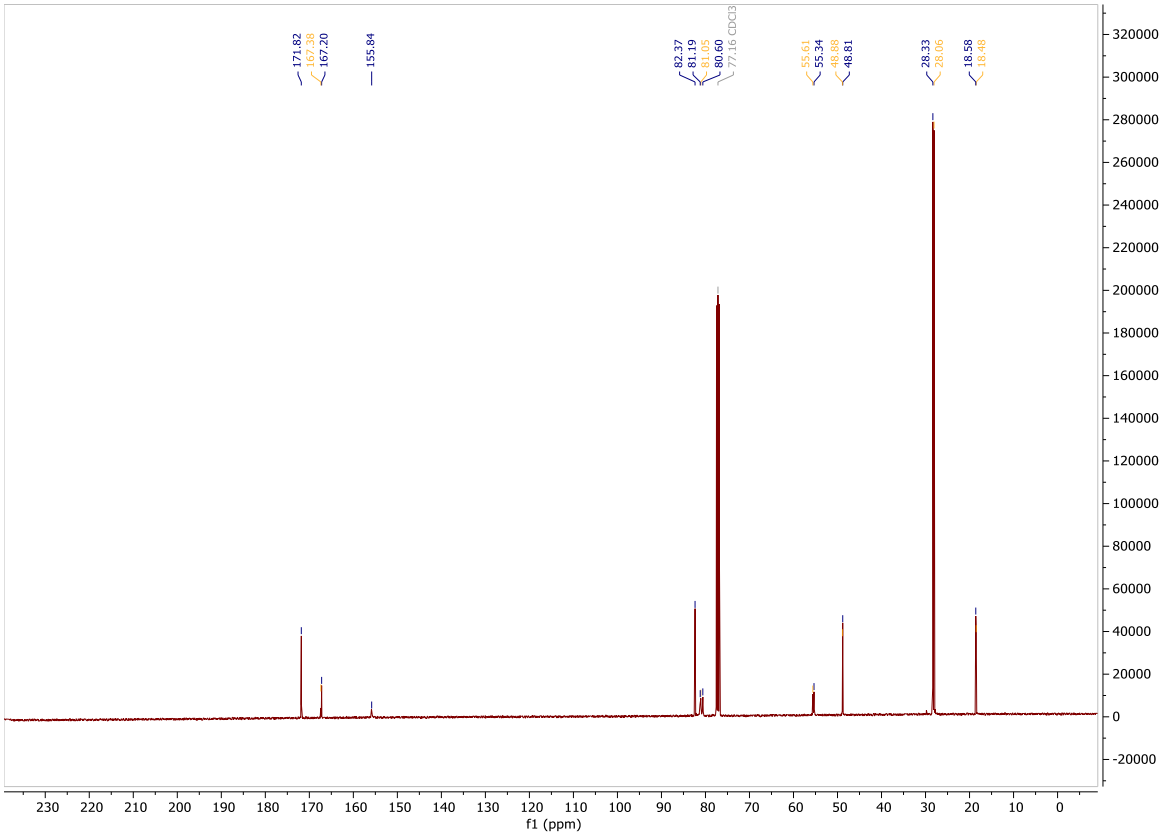


tert-Butyl (2-((_tert_-butoxycarbonyl)amino)-2-methoxyacetyl)-_L_-alaninate (6j)

^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)

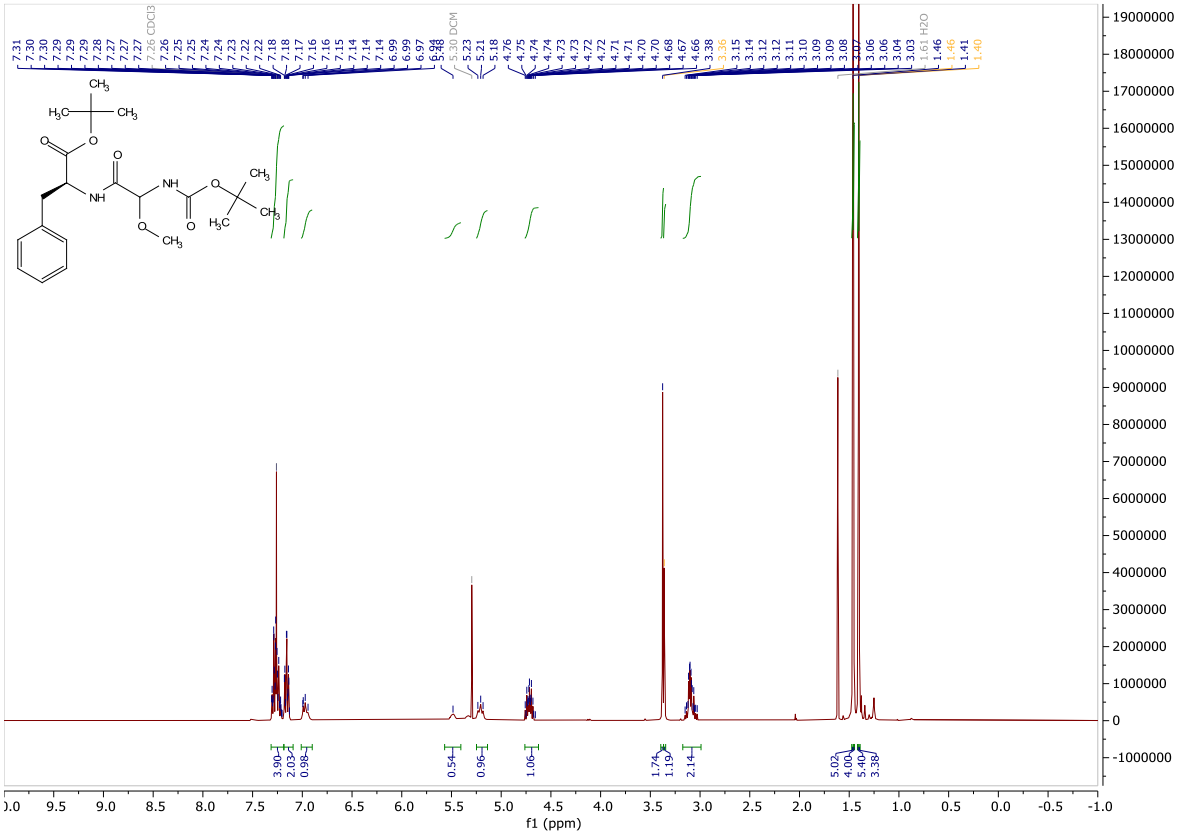


^{13}C NMR (101 MHz, Chloroform-*d*)

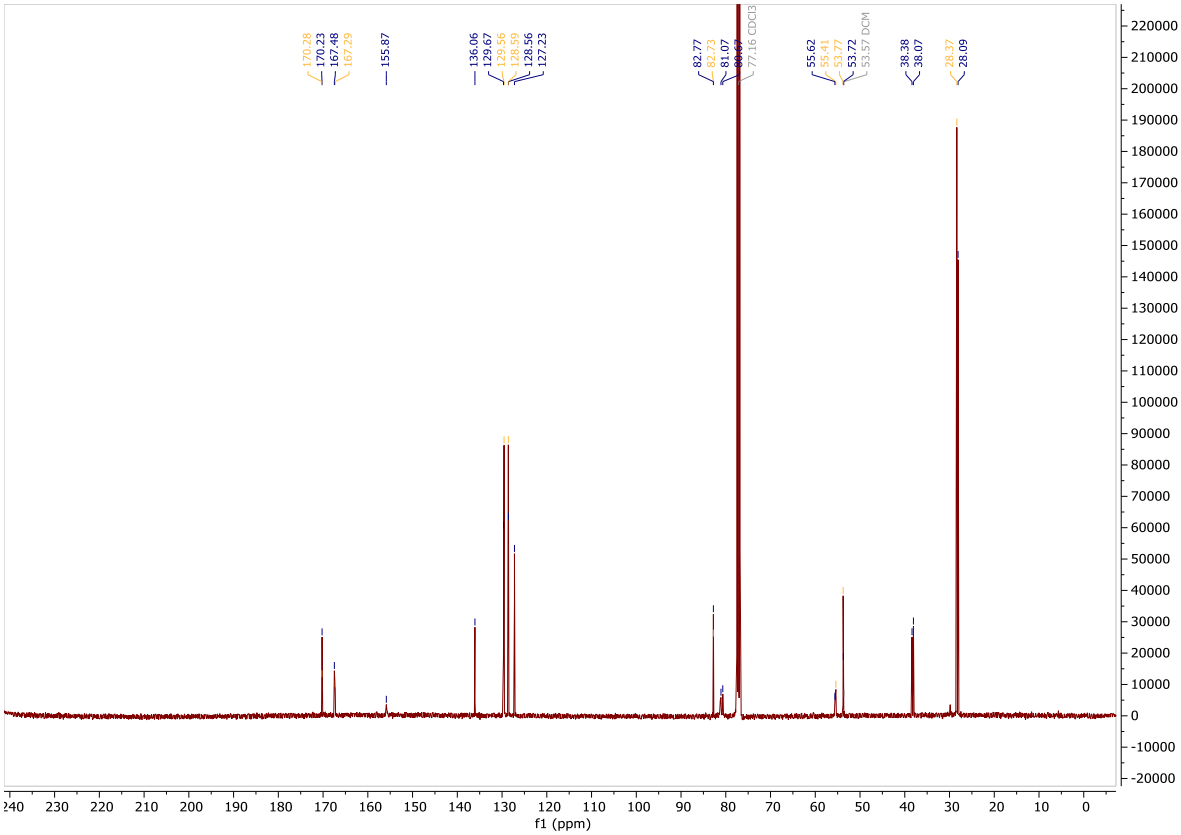


tert-Butyl (2-((_tert_-butoxycarbonyl)amino)-2-methoxyacetyl)-_L_-phenylalaninate (6k)

^{1}H NMR (400 MHz, Chloroform-*d,* mixture of two diastereoisomers)

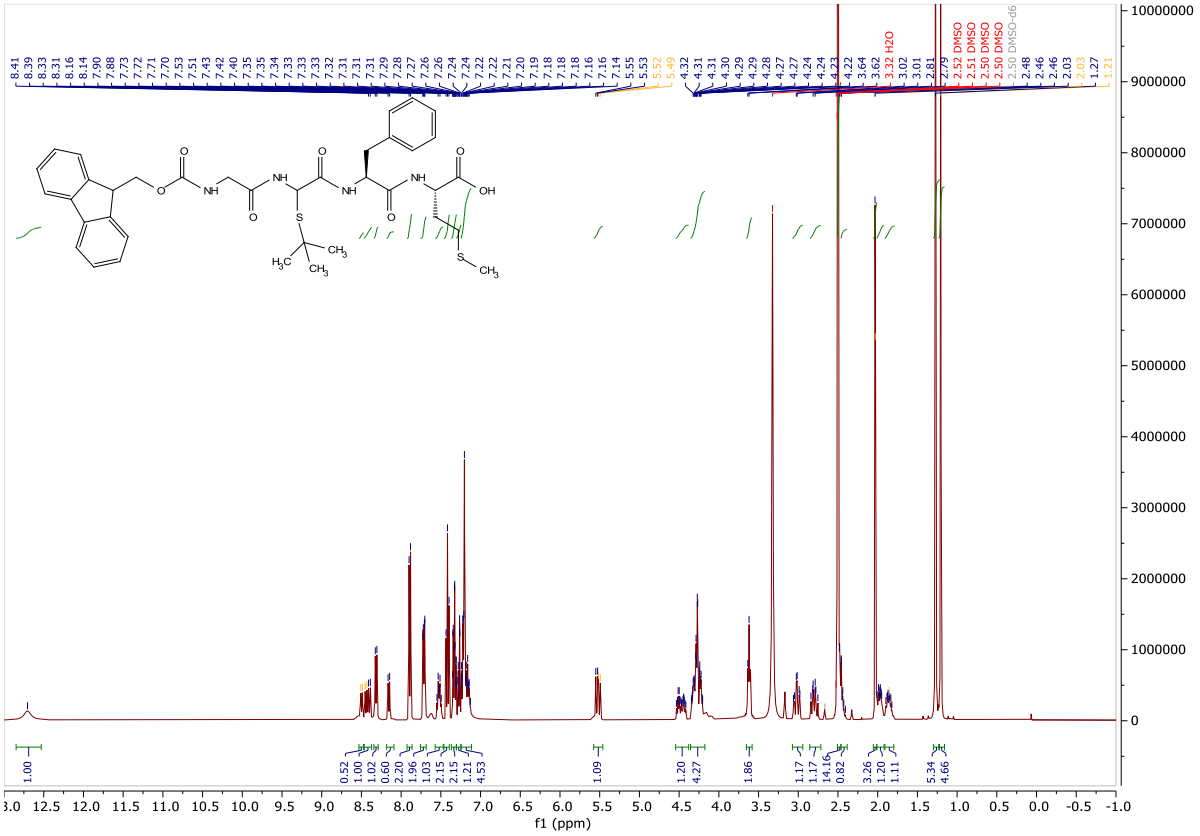


^{13}C NMR (101 MHz, Chloroform-*d*)



Fmoc-G-G(S^{t}Bu)-F-M (6l)

^{1}H NMR (400 MHz, DMSO-*d6,* mixture of two diastereoisomers)



^{13}C NMR (101 MHz, Chloroform-*d*)