Accepted Manuscript

Synthesis of enantiopure free and *N*-benzyloxycarbonyl-protected 3-substituted homotaurines from naturally occurring amino acids

Yongpeng Zheng , Jiaxi Xu

PII: S0040-4020(14)00804-7

DOI: 10.1016/j.tet.2014.05.098

Reference: TET 25647

To appear in: *Tetrahedron*

Received Date: 9 February 2014

Revised Date: 8 May 2014

Accepted Date: 26 May 2014

Please cite this article as: Zheng Y, Xu J, Synthesis of enantiopure free and *N*-benzyloxycarbonyl-protected 3-substituted homotaurines from naturally occurring amino acids, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.05.098.

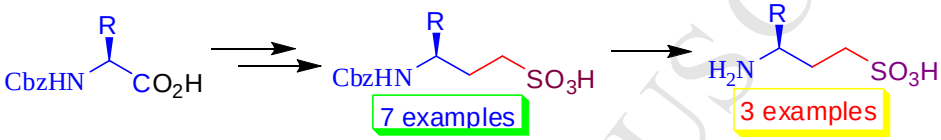
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of enantiopure free and *N*-benzyloxycarbonyl-protected 3-substituted homotaurines from naturally occurring amino acids.

Leave this area blank for abstract info.

Yongpeng Zheng, Jiaxi Xu*
State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China.



Tetrahedron
journal homepage: www.elsevier.com

Synthesis of enantiopure free and *N*-benzyloxycarbonyl-protected 3-substituted homotaurines from naturally occurring amino acids.

Yongpeng Zheng, Jiaxi Xu*
State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 Amino acid
Keyword_2 Aminoalkanesulfonic acid
Keyword_3 Homotaurine
Keyword_4 Homologation
Keyword_5 Synthesis

ABSTRACT

Enantiopure *N*-benzyloxycarbonyl-protected and free 3-substituted homotaurines were synthesized from naturally occurring amino acids via *N*-benzyloxycarbonyl protection, Arndt-Eistert homologation, reduction, esterification with thioacetic acid, and oxidation with performic acid. The current method is a convenient, practical, and salt-free method for the synthesis of enantiopure 3-substituted homotaurine with moderate to good yields.

1. Introduction

Homotaurine (3-amino-1-propanesulfonic acid [3APS], also called tramiprosate) is an important sulfur containing amino acid that has attracted much attention during the last two decades. Homotaurine was reported to inhibit Aβ fibril formation and to protect against Aβ toxicity in vitro assays[1] and was used as a candidate drug for treating Alzheimer's disease, but failed in the phase III trial.[2] Moreover calcium 3-(acetamido)propanesulfonate (acamprosate), a salt of *N*-acetylhomotaurine, is one of the few medications for the prevention of alcohol relapse in detoxified alcohol-dependent patients.[3] On the other hand, homotaurine has also been considered as structural analog and bioisosteres of γ-aminobutanoic acid (GABA), an important specific inhibitor of impulse transmission in the central nervous system.[4]

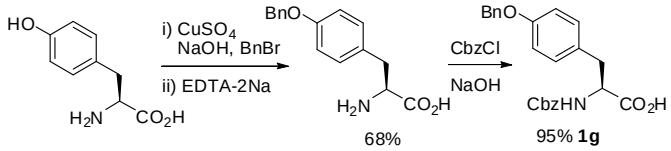
Besides homotaurine itself,[5] substituted homotaurines have been synthesized as well till now. 1-Carboxyhomotaurine was prepared from methyl 2,4-dibromobutanoate via multiple step synthesis.[6] Recently, various 1-substituted homotaurines were synthesized from 2-alkenonitriles by the Michael addition with thioacetic acid, reduction, and oxidation,[5] or from different olefins and *O*-ethyl *S*-2-phthalimidomethylxanthate via a radical addition and subsequent performic acid oxidation.[7] 2-Methylhomotaurine was prepared by addition of methacrolein with bisulfite and subsequent reductive amination.[8] 2-Phenylhomotaurine was synthesized from phenylstyrenesulfonate via addition of nitromethane and subsequent catalytic hydrogenation and hydrolysis.[9] Saclofen [2-(4-chlorophenyl)homotaurine], a competitive antagonist of GABA receptor, was prepared via addition of 1-(4-chlorophenyl)acrylonitrile with sodium bisulfate and subsequent reduction[10] or via the O_2-catalyzed radical addition of bisulfite to 2-(4-chlorophenyl)allylamine or its *N*-phthalyl derivative.[11] Alternatively, 2-substituted homotaurines were prepared through ring-opening reactions of 2-alkylpropane-1,3-sultones with ammonia or with NaN_3 followed by reduction.[12] Recently, both 1- and 2-substituted homotuarines were prepared via Michael addition of 2-alkenamides with thioacetic acid, and subsequent reduction and oxidation.[13] Synthesis of 3-substituted homotaurines were realized via the Horner-Wadsworth-Emmons reaction of *N*-protected α-aminoalkanals and ethyl(diethoxyphosphoryl)methanesulfonate and subsequent hydrogenation and deprotection,[14] or via the Wittig-Hornor condensation of benzyloxycarbonyl-α-phosphonoglycine trimethyl ester and subsequent Michael addition reaction, reduction, and deprotection.[15] The 3-carboxyhomotaurine was obtained through hydrolysis of 2-(2,5-dioxoimidazolidin-4-yl)ethanesulfonic acid[16] or via oxidation of homocysteine with peroxy acid.[17] Despite of these synthetic methods for substituted homotaurines, there is no general and versatile method reported for the synthesis of enantiopure substituted homotaurines.

Recently, we focus on the synthesis of various substituted homotaurines.[5,7,13] As a part of our ongoing interest in the synthesis and biological application of aminoalkanesulfonic acids,[18] we become interested in the synthesis of 3-substitued homotaurines. Herein, we present a general and effective synthesis of enantiopure 3-substitued homotaurines.

* Corresponding author. Tel.: +86-10-64435565; fax: +86-10-64435565; e-mail: jxxu@mail.buct.edu.cn

2. Results and Discussion

In our synthetic strategy, enantiopure free and *N*-protected 3-substituted homotuarines were prepared conveniently from a variety naturally occurring amino acids. The *N*-benzyloxycarbonyl (Cbz) α-amino acids (**1a-e**) were prepared from the corresponding amino acids and benzyl chloroformate using a reported method.[19] For the preparation of *N*,*N*'-DiCbz-lysine (**1f**), double amounts of benzyl chloroformate was used. For tyrosine with a phenolic hydroxyl group on its side-chain, *N*-Cbz-*O*-Bn-tyrosine (**1g**) was prepared via the sequence of formation of copper (II) complex with copper sulfate pentahydrate in the presence of sodium hydroxide solution, phenolic hydroxyl protection with benzyl bromide, and amino protection with benzyl chloroformate (Scheme 1).



Scheme 1 Synthesis of *N*-Cbz-*O*-Bn-tyrosine (**1g**).

The *N*-Cbz α-amino acids (**1a-g**) were further converted to the corresponding *N*-Cbz β-amino acids (**3a-g**) via the Arndt-Eistert homologation. The protected α-amino acids were activated by treatment with ethyl chloroformate in the presence of *N*-methylmorpholine (NMM) to form the corresponding mixed anhydrides, which were reacted with diazomethane (CH_2N_2) to give rise to the corresponding diazoketones **2a-g** in satisfactory to good yields of 38–86% (Scheme 2).[20] The diazoketones **2a-g** were then refluxed under the catalysis of silver benzoate in a mixture of 1,4-dioxane-water, affording the corresponding *β*-amino acids **3a-g** in good yields (73–93%) via the *Wolff* rearrangement.[21] The formation of the diazoketones and their *Wolff* rearrangement to the *β*-amino acids **3a-g** are well known to proceed without racemerization of the asymmetric centre.[22]

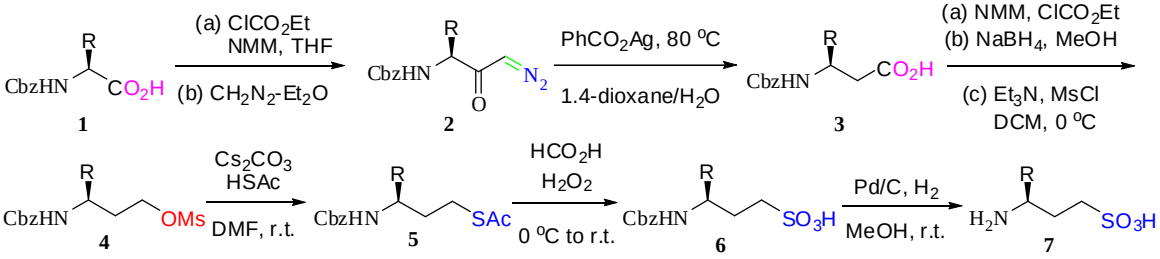
When conversion of *N*-Cbz lysine (**1f**) to its diazoketone **2f**, besides diazoketone **2f** was obtained in only 38% yield even the quantity of diazomethane was increased to more than six equivalents, in this reaction, a small amount (15% yield) of by-product, a diazoacetic mixed anhydride **2f'** was obtained. A reasonable mechanism for the formation of **2f'** is outlined in Scheme 3. It is assumed that diazomethane can first attack either of the two carbonyl groups in the mixed anhydride **A** to generate two different tetrahedral intermediates **B** and **C**. The intermediate **B** undergoes eliminations of carbon dioxide and ethoxide to form **D**, which is further deprotonated with ethoxide to generate the diazoketone **2f**. However, **C** undergoes eliminations to form either *N*-Cbz lysinate **1f** or diazoacetic mixed anhydride **E**, which is converted to byproduct **2f'** via deprotonation with ethoxide**.** The by-product **2f'** can be converted to the desired product **2f** in the reaction system through the reaction with diazomethane. This is possible reason why **2f'** was obtained in only small amount and these similar by-products were observed in trace, only on thin layer chromatographic analysis in other cases (Scheme 3).

For reduction of N-Cbz-protected amino acids to the corresponding alcohols, different convenient methods were evaluated. N-Cbz-β-amino acid **3a** was selected as a model to screen the selected methods. Meyers's sodium borohydride-iodine method afforded only the alcohol in 59%.[23] However, Abiko's procedure with sodium borohydride-sulfuric acid gave no desired alcohol possibly due to unstability of the Cbz group under strong acidic conditions.[24] Finally, using a method described by Kokotos[25] via sodium borohydride reduction of the mixed anhydride generated with ethyl chloroformate, the corresponding alcohol was obtained as pure liquid in high yield. Without further purification, it was directly reacted with methanesulfonyl chloride in dichloromethane (DCM) in the presence of triethylamine to afford the corresponding methanesulfonate **4a** in a good yield (72%). Similarly, the mesylates **4** were obtained in satisfactory to good overall yields (58–75%) and further treated with thioacetic acid (HSAc) and Cs_2CO_3 in DMF, during which the reaction flask was covered with aluminium foil to avoid sunlight, under stirring overnight to give rise to thioacetates **5** in yields of 54–89%.

Although in our previous studies, β-amino primary alcohols were converted into the corresponding thioacetates directly by the Mitsunobu reaction with HSAc, diethyl azodicarboxylate (DEAD), and triphenylphosphane,[26] purification was very tedious, and not reproducible on a large scale preparation in some cases due to formation of the Michael adduct of HSAc and DEAD. In the current study, the transformation was realized by displacement of the activated mesylates of the alcohols with cesium thioacetate because the γ-amino primary alcohol mesylates show less steric hindrance in the substitution. On the other hand, although direct displacement of mesylates **4** with sodium sulfite or bisulfite can produce the desired *N*-Cbz 3-substituted homotaurines **6**, purification (complete removal of excess inorganic salt) was very tedious. We selected two steps sequence of substitution with cesium thioacetate and oxidation with performic acid.

The prepared thioacetates **5** were oxidized to the corresponding sulfonic acids, enantiopure *N*-Cbz 3-substituted homotaurines **6**, in moderate to excellent yields using performic acid. Our synthetic strategy is a salt-free route and convenient for purification.

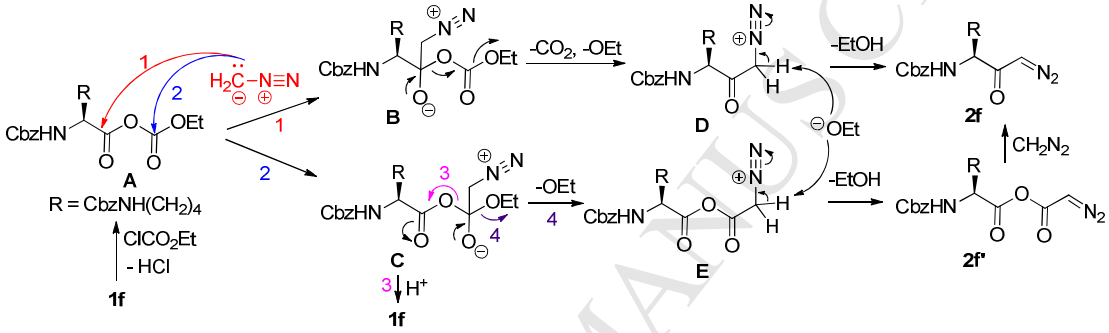
Generally, enantiopure *N*-Cbz 3-substituted homotaurines **6** are useful building blocks for synthesis of sulfonopeptides and other homotaurine-containing derivatives. However, in some cases, enantiopure 3-substitued homotuarines are also important biological molecules. *N*-Cbz 3-substituted homotaurines **6a-c** were selected to remove their Cbz protecting group. Enantiopure free 3-substituted homotaurines **7a-c** were obtained as colorless crystals in good yields by hydrogenolysis in methanol under an atmosphere of hydrogen in the presence of palladium on carbon powder.



Scheme 2 Reaction of unsymmetric diimines **1e-f** with acyl chlorides **2**.

Table 1 Facile synthesis of N-Cbz and free 3-substituted homotaurines.

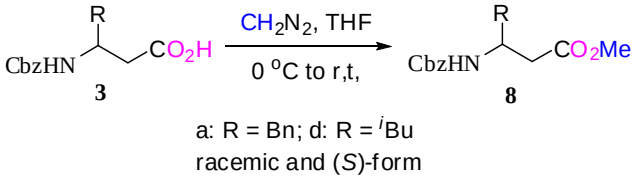
Entry	Cbz-AA **1**	R	Isolate yield (%)					
			2	**3**	**4**	**5**	**6**	**7**
1	**1a**	Bn	82	92	72	89	96	79
2	**1b**	Me	86	93	76	82	64	71
3	**1c**	^{i}Pr	75	82	71	54	52	89
4	**1d**	^{i}Bu	85	88	58	60	96	
5	**1e**	^{s}Bu	76	82	62	57	80	
6	**1f**	CbzNH$(CH_2)_4$	38	73	65	88	24	
7	**1g**	4-BnO$C_6H_4CH_2$	76	92	72	64	26	



Scheme 3 Proposed Mechanism of the formation of **2f** and **2f'**.

The specific rotation values of all prepared products were determined as well. It should be mentioned that the diazoketones **2b-f** with aliphatic side-chains show levorotation, while the diazoketones **2a** and **2g** with arylmethyl substituents show dextro-rotation. Inversely, *N*-Cbz homotaurines **6b-f** show dextro-rotation, while the *N*-Cbz homotaurines **6a** and **6g** exhibit levorotation. However, all corresponding β-amino acids **3** are levorotation and all mesylates **4** and thiacetates **5** are dextro-rotation in chloroform. To our doubts, our diazoketone **2a** is dextro-rotation, different from those reported in the references.[27-30] But our β-amino acid **3a** possesses the same rotation direction as the reported one.[31] To verify our results, we determined our starting materials and repeated the synthesis. The results indicate that our rotation direction for diazoketone **2a** is correct. It is not clear why the rotation direction of **2a** was reported in an opposite rotation direction, even from different groups.[27-30]

Because some of our products show small specific rotations, we doubt whether racemerization occurred during our synthesis. It is well-known that racemerization can only occur during conversion from *N*-Cbz-L-α-amino acids **1** to *N*-Cbz-L-β-amino acids **3**. The reactions from *N*-Cbz-L-β-amino acids **3** to 3-substituted homotaurines **6** and **7** do not involve nor affect the chiral center carbon atom. To answer the question and to provide a credible result, we only need to determine the optical purity of diazoketones **2** and *N*-Cbz-L-β-amino acids **3**. We selected two representative racemic amino acids, one with aromatic side-chain (phenylalanine) and the other with aliphatic side-chain (leucine), to prepare the corresponding racemic diazoketones *rac*-**2a** and *rac*-**2d**, which were further converted into racemic *N*-Cbz-β-amino acids *rac*-**3a** and *rac*-**3d**, followed the same procedures. However, unfortunately, it is very hard to realize good separation for racemic diazoketones *rac*-**2a** and *rac*-**2d**, racemic *N*-Cbz-β-amino acids *rac*-**3a** and *rac*-**3d** on HPLC chiral columns. Thus, both racemic and optically active *N*-Cbz-β-amino acids **3** were converted into their methyl esters **8** by treatment with diazomethane in THF under ice bath (Scheme 4). The racemic *N*-Cbz-β-amino acid methyl esters *rac*-**8a** and *rac*-**8d** were successfully separated on a HPLC AD-H chiral column and the enantiomeric excess values of **8a** and **8d** were determined under the same conditions. Only one of enantiomers was observed in each of cases. The results indicate that no racemerization occurred during our synthetic process as previously reported.[22]



Scheme 4 Synthesis of *N*-Cbz-L-β-amino acid methyl esters **8**.

3. Conclusion

In summary, a series of enantiopure *N*-protected 3-substituted homotaurines and 3-substitued homotaurines were conveniently synthesized from naturally occurring amino acids via *N*-benzyloxycarbonyl protection, the Arndt-Eistert homologation, reduction, esterification, and oxidation with performic acid. The current method is a general, convenient, and salt-free synthetic route to enantiopure 3-substituted homotaurines.

4. Experimental section

4.1 General

Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR NMR spectra were recorded at a Bruker AV 400 (400 MHz) in $CDCl_3$ or D_2O with TMS or DOH as the internal standards, respectively, and the chemical shifts (δ) are reported in ppm. IR spectra were taken directly on a Nicolet AVATAR 330 FT-IR spectrometer with KBr. HRMS spectra were obtained with an Agilent LC/MSD TOF mass spectrometer. Optical rotations were determined using a polarimeter using 3.5 i.d. × 100 mm cylindrical glass cell at sodium D line (589 nm), and were reported in concentration (c = 1 g/100 mL) at 20 °C. The enantiomeric excess (*ee*) was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH) at 1.00 mL/min, UV detection at 210 nm. TLC analysis was performed on silica gel GF_{254} plates. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel zcx II (200-300 mesh) with a mixture of petroleum ether and ethyl acetate as eluent.

Caution! Diazomethane is highly toxic and explosive. Hence, this reagent must carefully be handled in a ventilation hood.

4.2 General procedure for the synthesis of *N*-benzyloxycarbonyl protected amino acids 1

N-Benzyloxycarbonyl α-amino acids **1a-f** were prepared following the method described by Shi et al.[19b] After usually workup, all products were using direct in the next step without further purification.

*4.2.1 Synthesis of (S)-O-benzyl-N-benzyloxycarbonyltyrosine **(1g)***

4.2.1.1 Synthesis of (S)-O-Bn-Tyrosine

Tyrosine (7.25 g, 40 mmol) was dissolved in an aqueous solution of sodium hydroxide (2 mol/L, 20 mL). The resulting solution was stirred for 15 min at room temperature, and then warmed to 70 °C. A solution of $CuSO_4{\cdot}5H_2O$ (5 g, 20.4 mmol) in water (35 mL) was added dropwise, and the resulting solution was stirred for another 1 h. After addition of MeOH (100 mL) and NaOH (2 mol/L, 20 mL) in sequence, BnBr (5 mL, 8.55 g, 42 mmol) was added dropwise during 0.5 h. After the completion of the reaction, the solvent was removed by vacuum filtration, the solid product was washed with MeOH-H_2O (1/3, v/v) (60 mL) three times and then added to a solution of EDTA-2Na (8.74 g, 26 mmol) in 100 mL of water. The resulting solution was stirred further for 4.5 h at 70 °C. After filtration, washing with water and acetone, drying under infrared light, the final product was obtained as white solid, mp 222−223 °C, $[\alpha]_D^{20}$ = -9.4 (*c* 1.0, $CHCl_3$), Lit.[32] 219-221 °C, $[\alpha]_D^{20}$ = -9.3 (*c* 1.0, AcOH). 7.33 g, yield 68 %.

*4.2.1.2 Synthesis of (S)-O-Bn-N-Cbz-Tyrosine (**1g**)*

A solution of (*S*)-*O*-Bn-Tyrosine (8.14 g, 30 mmol) in THF (60 mL) was cooled to 0 °C followed by addition of a solution of NaOH (3 g, 75 mmol) in water (60 mL). Benzyl chloroformate (4.65 mL, 5.63 g, 33 mol) in THF (30 mL) was then added dropwise. The resulting mixture was stirred at 0 ºC for 2 h, then allowed to warm up to room temperature and stirred overnight. After addition of water (50 mL) followed by acidification with 10 % HCl to pH 1–2, the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic phase was washed with brine (2 x 100 ml) and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the pure (*S*)-*N*-Cbz-*O*-Bn-Tyrosine (**1g**) was obtained and further used without further purification.

Pale yellow solid, mp: 128–130 °C, 11.57 g, yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.85 (dd, J = 13.2, 8.4 Hz, 1H in CH_2), 3.10 (dd, J = 13.2, 12.0 Hz,1H in CH_2), 4.43 (dd, J = 12.0, 8.4 Hz, 1H, CH), 4.80 (d, J = 12.4 Hz, 1H in CH_2O), 4.82 (s, 2H, CH_2O), 5.00 (d, J = 12.4 Hz, 1H in CH_2O), 5.60 (d, J = 4.8 Hz, 1H, NH), 6.65–7.35 (m, 14H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.9, 56.2, 66.8, 69.8, 114.8, 127.5, 127.83, 127.89, 127.93, 128.4, 128.5, 128.9, 130.3, 136.2, 137.0, 156.6, 157.7, 177.5. HRMS (ESI) calcd for $C_{24}H_{24}NO_5$ $[M+H]^+$ *m/z*: 406.1649; found 406.1641.

4.3 General procedure for the preparation of the diazoketones 2

The Cbz-protected L-α-amino acid **1** (20 mmol) was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. To the solution was added *N*-methylmorpholine (NMM, 2.31 mL, 2.12 g, 21.0 mmol) and ethyl chloroformate (2.00 mL, 2.28 g, 21.0 mmol) successively. The mixture was stirred for 15 min. Then, a cooled solution of CH_2N_2 (4.20 g, 100 mmol) in Et_2O (200 mL) was added dropwise, and the yellow solution was allowed to warm to r.t. The reaction mixture was stirred until there was no acid remaining (TLC control). Excess CH_2N_2 was destroyed by addition of AcOH. The mixture was concentrated under reduced pressure, and the residue was taken up in EtOAc. The organic phase was washed successively with saturated aq. $NaHCO_3$ solution, 10% aq. citric acid, and brine, and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 5/1 v/v) to afford the product diazoketone **2**.

*4.3.1 Benzyl (S)-(4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate (**2a**)*

Pale yellow solid, mp: 85–87 °C, Lit.[29] 88 °C, 5.27 g, yield 82%, $[\alpha]_D^{20}$ = +11.8 (*c* 1.0, $CHCl_3$). Lit.[27] $[\alpha]_D^{25}$ = -42 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.03 (d, J = 6.0 Hz, 2H, CH_2), 4.40–4.60 (dt, J = 3.6, 6.0 Hz, 1H, CHN), 5.05 (d, J = 13.2 Hz, 1H in CH_2O), 5.09 (d, J = 13.2 Hz, 1H in CH_2O) , 5.20 (s, 1H, CHN_2), 5.44 (d, J = 3.6 Hz, 1H, NH), 7.13–7.36 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.7, 54.4, 58.9, 66.8, 127.3, 127.9, 128.1, 128.4, 128.5, 129.2, 136.1, 136.8, 155.6, 192.9.

*4.3.2 Benzyl (S)-(4-diazo-3-oxobutan-2-yl)carbamate (**2b**)*

Pale yellow solid, mp: 98-100 °C, Lit.[27] 91-92 °C, 4.27 g, yield 86%, $[\alpha]_D^{20}$ = -40.1 (*c* 1.0, $CHCl_3$), Lit.[27] $[\alpha]_D^{25}$ = 50.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CDC_3) δ: 1.33 (d, J = 6.8 Hz, 3H, CH_3), 4.16-4.46 (m, 1H, CH), 5.08 (d, J = 12.4 Hz, 1H in CH_2O), 5.12 (d, J = 12.4 Hz, 1H in CH_2O), 5.42 (s, 1H, CHN_2), 5.57 (br, 1H, NH), 7.29-7.50 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5, 53.5, 64.4, 66.9, 128.0, 128.1, 128.5, 136.1, 155.6, 193.8.

*4.3.3 Benzyl (S)-(1-diazo-4-methyl-2-oxopentan-2-yl)carbamate (**2c**)*

Pale yellow solid, mp: 72-75 °C, Lit.[30] 30-31 °C, 4.12 g, yield 75%, $[\alpha]_D^{20}$ = -24.5 (*c* 1.0, $CHCl_3$), Lit.[30] $[\alpha]_D^{20}$ = -31.5 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.89 (d, J = 7.2 Hz, 3H, CH_3), 0.99 (d, J = 7.2 Hz, 3H, CH_3), 2.02-2.16 (m, 1H, CH), 4.10-4.18 (m, 1H, CH), 5.11 (s, 2H, CH_2), 5.40 (s, 1H, CHN_2), 5.42 (br, 1H, NH), 7.33-7.36 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 19.4, 31.1, 54.7, 62.8, 67.0, 128.0, 128.2, 128.5, 136.2, 156.3, 193.2.

*4.3.4 Benzyl (S)-(1-diazo-5-methyl-2-oxohexan-2-yl)carbamate (**2d**)*

Yellow solid, mp: 66-68 °C, Lit.[30] 64-65 °C, 4.92 g, yield 85%, $[\alpha]_D^{20}$ = -40.8 (*c* 1.0, $CHCl_3$), Lit.[30] $[\alpha]_D^{20}$ = -53.6 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.8 Hz, 3H, CH_3), 0.94 (d, J = 6.8 Hz, 3H, CH_3), 1.46 (ddd, J = 13.6, 9.2, 5.6 Hz, 1H in CH_2), 1.57 (ddd, J = 13.6, 8.4, 4.8 Hz, 1H in CH_2), 1.65-1.75 (m, 1H, CH), 4.24-4.27 (m, 1H, CH), 5.10 (s, 2H, CH_2O), 5.34 (d, J = 6.4 Hz, 1H, NH), 5.44 (s, 1H, CHN_2), 7.30-7.39 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 23.0, 24.7, 41.5, 54.0, 56.3, 67.0, 128.0, 128.2, 128.5, 136.1, 156.0, 194.2.

4.3.5 Benzyl (S)-(1-diazo-4-methyl-2-oxohexan-2-yl)carbamate ***(2e)***

Pale yellow solid, m.p. 68-69 ^{o}C, Lit.[30] 63-64 ^{o}C, 4.40 g, yield 76%, $[\alpha]_D^{20}$ = -14.0 (*c* 1.0, $CHCl_3$), Lit.[30] $[\alpha]_D^{20}$ = -42.1 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.90 (t, J = 7.2, Hz, 3H, CH_3), 0.95 (d, J = 6.8 Hz, 3H, CH_3), 1.12 (ddq, J = 14.8, 9.2, 7.2 Hz, 1H in CH_2), 1.39-1.53 (ddq, J = 14.8, 4.0, 7.2 Hz, 1H in CH_2), 1.77-1.92 (m, 1H, CH), 4.08-4.25 (m, 1H, CH), 5.10 (s, 2H, CH_2O), 5.40 (br, 2H, NH & CHN_2), 7.28-7.44 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.5, 15.6, 24.5, 37.7, 54.9, 62.3, 67.1, 128.1, 128.2, 128.5, 136.2, 156.2, 193.2.

4.3.6 Benzyl (S)-(7-diazo-6-oxoheptane-1,5-diyl)dicarbamate ***(2f)***

Yellow solid, mp: 79.5-80.5 ^{o}C, 3.33 g, yield 38%, $[\alpha]_D^{20}$ = -12.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.40 (m, 2H, CH_2), 1.35-1.53 (m, 2H, CH_2), 1.55-1.64 (m, 1H in CH_2), 1.75-1.85 (m, 1H in CH_2), 3.12-3.22 (m, 2H, CH_2N), 4.13-4.28 (m, 1H, CHN), 4.93 (br, 1H, NH), 5.03 (d, J = 12.8 Hz, 1H in CH_2O), 5.07 (d, J = 12.8 Hz, 1H in CH_2O), 5.08 (d, J = 12.0 Hz, 1H in CH_2O), 5.09 (d, J = 12.0 Hz, 1H in CH_2O), 5.42 (s, 1H, CHN_2), 5.66 (d, J = 7.2 Hz, 1H, NH), 7.28-7.36 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 29.4, 31.7, 40.2, 53.9, 57.7, 66.6, 67.0, 128.0, 128.2, 128.44, 128.46, 136.1, 136.5, 156.1, 156.6, 193.8. IR (ν_{max}, cm^{-1}) 3329, 3033, 2928, 2865, 2107, 1701, 1638, 1529, 1454, 1365, 1249, 1142, 1027, 748, 697. HRMS (ESI) calcd for $C_{23}H_{26}N_4NaO_5$ $[M+Na]^+$ *m/z*: 461.1795; found 461.1785.

4.3.7 (S)-2,6-Bis(benzyloxycarbonylamino)hexanoic 2-diazoacetic anhydride ***(2f')***

Colouress liquid, 1.43 g, yield 15%, $[\alpha]_D^{20}$ = -2.70 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23-1.29 (m, 2H, CH_2), 1.31-1.52 (m, 2H, CH_2), 1.79-1.91 (m, 1H in CH_2), 1.99-2.11 (m, 1H in CH_2), 2.92-3.20 (m, 2H, CH_2N), 4.76 (br, 1H, CHN_2), 4.81 (dd, J = 9.6, 5.2 Hz, 1H, CHN), 5.07 (s, 2H, 2NH), 5.20 (d, J = 12.4 Hz, 2H in $2CH_2O$), 5.25 (d, J = 12.4 Hz, 2H in $2CH_2O$), 7.30-7.35 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.2, 28.2, 29.3, 40.6, 53.1, 63.4, 66.5, 69.2, 128.0, 128.38, 128.41, 128.5, 128.6, 134.6, 136.6, 153.2, 156.3, 190.9. IR (*V*max, cm^{-1}) 3360, 3083, 3064, 3033, 2930, 2866, 2019, 1790, 1713, 1644, 1520, 1498, 1455, 1360, 1286, 1110, 1027. HRMS (ESI) calcd for $C_{24}H_{26}N_4NaO_7$ $[M+Na]^+$ *m/z*: 505.1694; found 505.1691.

4.3.8 Benzyl (S)-(1-(4-(benzyloxy)phenyl)-4-diazo-3-oxobutan-2-yl)carbamate ***(2g)***

Pale yellowish solid, mp: 128-130 ^{o}C, 4.90 g, yield 76%, $[\alpha]_D^{20}$ = +17.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.91 (dd, J = 14.0, 6.8 Hz, 1H in CH_2), 2.97 (dd, J = 14.0, 7.2 Hz, 1H in CH_2), 4.20 (dd, J = 7.2, 6.8 Hz, 1H, CHN), 4.98 (s, 2H, CH_2O), 5.02 (d, J = 12.4 Hz, 1H in CH_2O), 5.07 (d, J = 12.4 Hz, 1H in CH_2O), 5.20 (s, 1H, CHN_2), 5.57 (d, J = 7.2 Hz, 1H, NH), 6.80-7.45 (m, 14H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.4, 54.4, 58.9, 66.8, 69.8, 114.9, 127.3, 127.8, 127.9, 128.0, 128.2, 128.36, 128.41, 130.2, 136.1, 136.8, 155.6, 157.7, 192.9. IR (*V*max, cm^{-1}) 3404, 3028, 2960, 2921, 2850, 2107, 1713, 1642, 1151, 1453, 1384, 1242, 1180, 1142, 1075, 1045, 739, 697. HRMS (ESI) calcd for $C_{25}H_{23}N_3NaO_4$ $[M+Na]^+$ *m/z*: 452.1581; found 452.1585.

*4.3.9 Benzyl (R/S)-(4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate (rac-****2a****)*

Scale: 598 mg, 2 mmol. Yellow liquid, 540 mg, yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.00 (dd, J = 16.0, 6.4 Hz, 1H in CH_2), 3.04 (dd, J = 16.0, 6.8 Hz, 1H in CH_2), 4.40–4.54 (m, 1H, CH), 5.05 (d, J = 13.6 Hz, 1H in CH_2), 5.08 (d, J = 13.6 Hz, 1H in CH_2), 5.21 (s, 1H, CHN_2), 5.45 (d, J = 6.0 Hz, 1H, NH), 7.10–7.37 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.4, 54.5, 58.8, 67.0, 127.0, 128.0, 128.2, 128.5, 128.6, 129.3, 136.0, 136.1, 155.7, 192.7.

*4.3.10 Benzyl (R/S)-(1-diazo-5-methyl-2-oxohexan-3-yl)carbamate (rac-****2d****)*

Scale: 520 mg, 1.96 mmol. Yellow solid, mp: 71–72 ^{o}C, 329 mg, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.4 Hz, 3H, CH_3), 0.94 (d, J = 6.4 Hz, 3H, CH_3), 1.46 (ddd, J = 13.6, 9.6, 5.6 Hz, 1H in CH_2), 1.57 (ddd, J = 13.6, 8.0, 4.8 Hz, 1H in CH_2), 1.63–1.72 (m, 1H, CH), 4.20-4.35 (m, 1H, CH), 5.07 (d, J = 12.0 Hz, 1H in CH_2), 5.11 (d, J = 12.0 Hz, 1H in CH_2), 5.34 (d, J = 7.6 Hz, 1H, NH), 5.43 (s, 1H, CHN_2), 7.27–7.38 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 23.0, 24.7, 41.4, 53.9, 56.3, 67.0, 128.0, 128.2, 128.5, 136.1, 156.0, 194.1.

4.4 General procedure for the synthesis of *N*-benzyloxycarbonyl protected β-amino acids 3

Diazoketone **2** (10 mmol) and silver benzoate (37 mg, 0.16 mmol) were dissolved in a mixture of 1,4-dixoane (30 mL) and water (20 mL). The resulting mixture was refluxed for 6 h and then filtered. The solvent was evaporated under reduced pressure. After the residue was dissolved in saturated aqueous Na_2CO_3 solution (50 mL), the resulting mixture was stirred for 1 h. The mixture was washed with diethyl ether (3 × 30 mL). The aqueous layer was acidified to pH 2 using 2 mol/L HCl–10 % aq. citric acid and extracted with EtOAc (3 × 40 mL). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to afford the amino acid in good yield.

4.4.1 (S)-3-(Benzyloxycarbonylamino)-4-phenylbutanoic acid ***(3a)***

White solid, mp: 124-125 ^{o}C, Lit.[33] 122.2-124.4 ^{o}C, 5.77 g, yield 92%, $[\alpha]_D^{20}$ = -18.4 (*c* 1.0, $CHCl_3$), Lit.[31] $[\alpha]_D^{27}$ = -16.4 (*c* 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (dd, J = 16.4, 5.2 Hz, 1H in CH_2), 2.60 (dd, J = 16.4, 4.8 Hz, 1H in CH_2), 2.87 (dd, J = 13.2, 7.6 Hz, 1H in CH_2), 2.96 (dd, J = 13.2, 5.6 Hz, 1H in CH_2), 4.24 (dddd, J = 7.6, 5.6, 5.2, 4.8 Hz, 1H, CH), 5.05 (d, J = 12.8 Hz, 1H in CH_2O), 5.09 (d, J = 12.8 Hz, 1H in CH_2O), 5.29 (d, J = 7.6 Hz, 1H, NH), 7.10–7.40 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.2, 40.1, 49.2, 66.8, 126.8, 128.0, 128.1, 128.5, 128.6, 129.3, 137.3, 155.7, 176.6.

*4.4.2 (S)-3-(Benzyloxycarbonylamino)butanoic acid (****3b****)*

White solid, mp: 110-113 ^{o}C, Lit.[34] 104-106 ^{o}C, 4.42 g, yield 93%, $[\alpha]_D^{20}$ = -16.8 (*c* 1.0, $CHCl_3$), Lit.[35] $[\alpha]_D^{20}$ = -15.7 (*c* 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (d, J = 6.8, 3H, CH_3), 2.53-2.66 (m, 2H, CH_2), 4.06-4.20 (m, 1H, CHN), 5.09 (d, J = 11.2 Hz, 1H in CH_2O), 5.11 (d, J = 11.2 Hz, 1H in CH_2O), 5.20 (d, J = 4.8 Hz, 1H, NH), 7.28–7.41 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 36.9, 54.4, 67.8, 128.2, 128.3, 128.5, 136.4, 156.2, 176.9.

4.4.3 (R)-3-(Benzyloxycarbonylamino)-4-methylpentanoic acid ***(3c)***

White solid, mp: 76-78 ^{o}C, Lit.[30] 30-31 ^{o}C, 4.25 g, yield 80%, $[\alpha]_D^{20}$ = -21.1 (*c* 1.0, $CHCl_3$), Lit.[36] $[\alpha]_D^{20}$ = -21.1 (*c* 1.38, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.4 Hz, 3H, CH_3), 0.94 (d, J = 6.4 Hz, 3H, CH_3), 1.79-1.93 (m, 1H, CH), 2.56 (dd, J = 14.0, 6.4 Hz, 1H in CH_2), 2.61 (dd, J = 14.0, 4.8 Hz, 1H in CH_2), 3.83 (ddd, J = 7.2, 6.4, 4.8 Hz, 1H, CHN), 5.07 (d, J = 12.4 Hz, 1H in CH_2O) , 5.12 (d, J = 12.4 Hz, 1H in CH_2O), 5.17 (d, J = 10.0 Hz, 1H, NH), 7.30-7.38 (m, 5H, ArH), 9.83 (br, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5, 19.3, 31.6, 36.8, 53.4, 66.8, 128.0, 128.1, 128.5, 136.4, 156.2, 176.9.

*4.4.4 (S)-3-(Benzyloxycarbonylamino)-5-methylhexanoic acid (**3d**)*

White solid, mp: 75-77 °C, Lit.[37] 76-78 °C, 4.92 g, yield 88%, $[\alpha]_D^{20}$ = -26.0 (*c* 1.0, $CHCl_3$), Lit.[38] $[\alpha]_D^{25}$ = -28.7 (*c* 2.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, J = 6.8 Hz, 3H, CH_3), 0.94 (d, J = 6.8 Hz, 3H, CH_3), 1.33 (ddd, J = 14.0, 7.6, 5.6 Hz, 1H in CH_2), 1.52 (ddd, J = 14.0, 9.6, 6.0 Hz, 1H in CH_2), 1.59-1.70 (m, 1H, CH), 2.54 (dd, J = 16.0, 4.4 Hz, 1H in CH_2), 2.62 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 3.96-4.14 (m, 1H, CHN), 5.09 (d, J = 11.2 Hz, 1H in CH_2O), 5.10 (d, J = 11.2 Hz, 1H in CH_2O), 5.16 (d, J = 8.8 Hz, 1H, NH), 7.30-7.36 (m, 5H, ArH), 9.23 (br, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 22.9, 24.9, 39.2, 43.4, 46.1, 66.8, 128.0, 128.1, 128.5, 136.4, 155.9, 176.9.

*4.4.5 (3R,4S)-3-(Benzyloxycarbonylamino)-4-methylhexanoic acid (**3e**)*

White solid, mp: 54-56 °C, 4.58 g, yield 82%, $[\alpha]_D^{20}$ = -25.1 (*c* 1.0, $CHCl_3$), Lit.[36] $[\alpha]_D^{20}$ = -30.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (d, J = 6.4 Hz, 3H, CH_3), 0.90 (t, J = 6.8 Hz, 3H, CH_3), 1.04-1.18 (m, 1H in CH_2), 1.39-1.53 (m, 1H in CH_2), 1.77-1.92 (m, 1H, CH), 2.53 (dd, J = 16.0, 6.0 Hz, 1H in CH_2), 2.60 (dd, J = 16.0, 4.4 Hz, 1H in CH_2), 3.90 (ddd, J = 7.2, 6.0, 4.4 Hz, 1H, CHN), 5.07 (d, J = 12.8 Hz, 1H in CH_2O), 5.11 (d, J = 12.8 Hz, 1H in CH_2O), 5.22 (d, J = 8.8 Hz, 1H, NH), 7.28-7.44 (m, 5H, ArH), 9.92 (br, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 11.3, 15.3, 25.4, 36.3, 38.0, 52.3, 66.8, 128.1, 128.5, 130.1, 136.4, 156.1, 177.1.

*4.4.6 (S)-3,7-Di(benzyloxycarbonylamino)heptanoic acid (**3f**)*

White solid, mp: 142-143 °C, 6.34 g, yield 74%, $[\alpha]_D^{20}$ = -16.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22-1.39 (m, 2H, CH_2), 1.43-1.68 (m, 4H, $2CH_2$), 2.54 (d, J = 5.6 Hz, 2H, CH_2), 3.05-3.23 (m, 2H, CH_2N), 3.85-4.08 (m, 1H, CHN), 4.95 (br, 1H, NH), 5.06 (s, 4H, $2CH_2O$), 5.38 (d, J = 7.6 Hz, 1H, NH), 7.26-7.42 (m, 10H, ArH), 9.16 (br, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 29.3, 33.7, 38.9, 40.5, 47.7, 66.66, 66.74, 128.1, 128.5, 130.1, 136.4, 136.5, 156.1, 156.6, 175.8. IR (*V*max, cm^{-1}) 3329, 3086, 3066, 3033, 2928, 2865, 2107, 1701, 1638, 1528, 1455, 1365, 1249, 1141, 1027. HRMS (ESI) calcd for $C_{23}H_{29}N_2O_6$ $[M+H]^+$ *m/z*: 429.2020; found 429.2012.

*4.4.7 (S)-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butanoic acid (**3g**)*

White solid, mp: 139-140 °C, 7.72 g, yield 92%, $[\alpha]_D^{20}$ = -14.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (dd, J = 16.0, 6.0 Hz, 1H in CH_2), 2.57 (dd, J = 16.0, 4.8 Hz, 1H in CH_2), 2.80 (dd, J = 13.6, 8.0 Hz, 1H in CH_2), 2.89 (dd, J = 13.6, 5.6 Hz, 1H in CH_2), 4.18(dddd, J = 8.0, 6.0, 5.6, 4.8 Hz, 1H, CH), 5.01 (s, 2H, CH_2O), 5.05 (d, J = 12.4 Hz, 1H in CH_2O), 5.08 (d, J = 12.4 Hz, 1H in CH_2O), 5.29 (d, J = 8.4 Hz, 1H, NH), 6.80-7.44 (m, 14H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.2, 39.2, 49.3, 66.7, 70.0, 115.0, 127.4, 127.9, 128.0, 128.1, 128.5, 128.6, 129.6, 130.3, 136.3, 137.0, 155.7, 157.7, 176.6. IR (ν_{max}, cm^{-1}) 3336, 3032, 2978, 2925, 2854, 1704, 1504, 1453, 1384, 1245, 1180, 1075, 1025, 736, 697. HRMS (ESI) calcd for $C_{25}H_{26}NO_5$ $[M+H]^+$ *m/z*: 420.1806; found 420.1817.

*4.4.8 (R/S)-3-(Benzyloxycarbonylamino)-4-phenylbutanoic acid (rac-**3a**)*

Scale: 480 mg, 1.48 mmol. Colorless liquid, 387 mg, yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (dd, J = 16.4, 5.2 Hz, 1H in CH_2), 2.60 (dd, J = 16.4, 4.8 Hz, 1H in CH_2), 2.88 (dd, J = 13.2, 7.6 Hz, 1H in CH_2), 2.97 (dd, J = 13.2, 5.6 Hz, 1H in CH_2), 4.16–4.28 (m, 1H, CH), 5.05 (d, J = 12.4 Hz, 1H in CH_2), 5.08 (dd, J = 12.4 Hz, 1H in CH_2), 5.26 (d, J = 8.0 Hz, 1H, NH), 7.08-7.38 (m, 10H, ArH).

*4.4.8 (R/S)-3-(Benzyloxycarbonylamino)-5-methylhexanoic acid (rac-**3d**)*

Scale: 578 mg, 2 mmol. Colorless liquid, 450 mg, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.4 Hz, 3H,CH_3), 0.92 (d, J = 6.4 Hz, 3H, CH_3), 1.29–1.38 (m, 1H in CH_2), 1.46–1.56 (m, 1H in CH_2), 1.60–1.70 (m, 1H, CH), 2.54 (dd, J = 16.0, 4.8 Hz, 1H in CH_2), 2.62 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 3.98–4.14 (m, 1H, CH), 5.09 (s, 2H, CH_2), 5.20 (d, J = 9.2 Hz, 1H, NH), 7.27–7.42 (m, 5H, ArH), 8.90 (br, 1H, CO_2H).

4.5 General procedure for the synthesis of 2-(*N*-benzyloxycarbonylamino)alkyl mesylates 4

Amino acid **3** (5 mmol) was dissoved in THF (10 mL) at 0 °C. *N*-Methylmorpholine (0.58 mL, 531 mg, 5.15 mmol) and ethyl chloroformate (0.50 mL, 570 mg, 5.25 mmol) were added successively under stirring. After 10 min, $NaBH_4$ (567 mg, 15 mmol) was added in one portion. MeOH (20 mL) was then added dropwise in the mixture over a period of 10 min at 0 °C. The solution was stirred for additional 20 min, and then neutralized with 1 mol/L HCl (4 mL). The organic solvents were evaporated under reduced pressure and the product was extracted with EtOAc (50 mL). The organic phase was washed consecutively with 1 mol/L HCl (10 mL), H_2O (20 mL), saturated aqueous Na_2CO_3 solution (20 mL), H_2O (20 mL), and brine (20 mL), dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was added to a solution of Et_3N (0.83 mL, 0.61 mg, 6 mmol) in CH_2Cl_2 (20 mL). After cooling to 0 °C, methanesulfonyl chloride (MsCl, 0.46 mL, 0.69 mg, 6 mmol) was added dropwise. The resulting solution was further stirred for 1- 4.5 h at r.t., followed by addition of CH_2Cl_2 (20 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (60 mL), and brine (30 mL). After drying (Na_2SO_4) and evaporating the solvent in vacuo, the mesylate was purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 6/1 v/v) or crystallized from a mixture of dichloromethane and hexanes.

*4.5.1 (S)-3-(Benzyloxycarbonylamino)-4-phenylbutyl methanesulfonate (**4a**)*

White solid, mp: 105-108 °C, 1.36 g, yield 72%, $[\alpha]_D^{20}$ = +9.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72-1.86 (m, 1H in CH_2), 1.96-2.08 (m, 1H in CH_2), 2.81-2.86 (m, 2H, CH_2), 2.92 (s, 3H, CH_3), 3.96-4.10 (m, 1H, CHN), 4.20-2.30 (m, 2H, in CH_2O), 4.69 (d, J = 8.8 Hz, 1H, NH), 5.03 (d, J = 12.4 Hz, 1H in CH_2O), 5.07 (d, J = 12.4 Hz, 1H in CH_2O), 7.14-7.37 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.7, 37.2, 41.2, 49.2, 66.7, 67.1, 126.8, 128.0, 128.2, 128.5, 128.6, 129.3, 136.4, 137.0, 155.9. IR (ν_{max}, cm^{-1}) 3375, 3031, 2952, 2921, 2850, 1718, 1530, 1350, 1176, 733, 697. HRMS (ESI) calcd for $C_{19}H_{24}NO_5S$ $[M+H]^+$ *m/z*: 378.1370; found 378.1371.

*4.5.2 (S)-3-(Benzyloxycarbonylamino)butyl methanesulfonate (**4b**)*

White solid, mp: 79.5-82.5 °C, 1.15 g, yield 76%, $[\alpha]_D^{20}$ = +11.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, J = 6.8

Hz, 3H, CH_3), 1.80-1.99 (m, 2H, CH_2), 2.97 (s, 3H, CH_3), 3.84-3.97 (m, 1H, CHN), 4.27 (t, *J* = 6.0 Hz, 2H, CH_2O), 4.68 (d, *J* = 5.2 Hz, 1H, NH), 5.09 (s, 2H, CH_2O), 7.28-7.55 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 21.2, 36.3, 37.2, 44.2, 66.7, 67.1, 128.1, 128.2, 128.5, 136.4, 155.8. IR (ν_{max}, cm^{-1}) 3378, 3036, 2968, 2929, 2853, 1701, 1520, 1349, 1174, 751, 706. HRMS (ESI) calcd for $C_{13}H_{20}NO_5S$ $[M+H]^+$ *m/z*: 302.1057; found 302.1052.

*4.5.3 (R)-3-(Benzyloxycarbonylamino)-4-methylpentyl methanesulfonate (**4c**)*

White solid, mp: 44-46 °C, 1.17 g, yield 71%, $[\alpha]_D^{20}$ = +22.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 1.65-1.82 (m, 2H, CH_2), 1.95-2.05 (m, 1H, CH), 2.95 (s, 3H, CH_3), 3.60-3.75 (m, 1H, CHN), 4.19-4.30 (m, 2H, CH_2O), 4.63 (d, *J* = 10.0 Hz, 1H, NH), 5.06 (d, *J* = 12.0 Hz, 1H in CH_2O), 5.11 (d, *J* = 12.0 Hz, 1H in CH_2O), 7.30-7.40 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 17.6, 19.0, 32.27, 32.33, 37.1, 53.0, 66.8, 67.5, 128.0, 128.2, 128.6, 136.4, 156.4. IR (ν_{max}, cm^{-1}) 3344, 3033, 2959, 2927, 2875, 1731, 1537, 1241, 738, 698. HRMS (ESI) calcd for $C_{15}H_{24}NO_5S$ $[M+H]^+$ *m/z*: 330.1370; found 330.1363.

*4.5.4 (S)-3-(Benzyloxycarbonylamino)-5-methylhexyl methanesulfonate (**4d**)*

Coloress liquid, 1.0 g, yield 58%, $[\alpha]_D^{20}$ = +1.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 0.92 (d, *J* = 6.8 Hz, 3H, CH_3), 1.28 (ddd, *J* = 14.0, 8.4, 6.0 Hz, 1H in CH_2), 1.40 (ddd, *J* = 14.0, 9.6, 5.2 Hz, 1H in CH_2), 1.60-1.80 (m, 2H, CH_2), 1.91-2.03 (m, 1H, CH), 2.95 (s, 3H, CH_3), 3.77-3.90 (m, 1H, CHN), 4.21-4.32 (m, 2H, CH_2O), 4.62 (d, *J* = 9.2 Hz, NH), 5.06 (d, *J* = 12.0 Hz, 1H in CH_2O), 5.11 (d, *J* = 12.0 Hz, 1H in CH_2O), 7.28-7.46 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 21.9, 23.0, 24.7, 35.4, 37.1, 44.7, 46.5, 66.7, 67.2, 128.0, 128.1, 128.5, 136.5, 156.1. IR (ν_{max}, cm^{-1}) 3373, 3026, 2957, 2928, 2870, 1713, 1531, 1352, 1175, 738, 698. HRMS (ESI) calcd for $C_{16}H_{25}NNaO_5S$ $[M+Na]^+$ *m/z*: 366.1346; found 366.1367.

*4.5.5 (3R,4S)-3-(Benzyloxycarbonylamino)-4-methylhexyl methanesulfonate (**4e**)*

Coloress liquid, 1.07 g, yield 62%, $[\alpha]_D^{20}$ = +12.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.89 (d, *J* = 6.4 Hz, 3H, CH_3), 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.02-1.17 (m, 1H, CH), 1.38-1.55 (m, 2H, CH_2), 1.60-1.72 (m, 1H in CH_2), 1.93-2.05 (m, 1H in CH_2), 2.89 (s, 3H, CH_3), 3.59-3.76 (m, 1H, CHN), 4.18 (ddd, *J* = 15.2, 10.4, 4.8 Hz, 1H in CH_2O), 4.26 (ddd, *J* = 15.2, 8.8, 6.0 Hz, 1H in CH_2O), 5.02 (br, 1H, NH), 5.04 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.10 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.28-7.43 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 11.4, 14.7, 24.9, 30.8, 36.7, 38.8, 51.8, 66.4, 67.6, 127.8, 127.9, 128.3, 136.4, 156.1. IR (ν_{max}, cm^{-1}) 3376, 3031, 2963, 2934, 2877, 1698, 1531, 1350, 1192, 772, 699. HRMS (ESI) calcd for $C_{16}H_{26}NO_5S$ $[M+H]^+$ *m/z*: 344.1526; found 344.1549.

*4.5.6 (S)-3,7-Di(benzyloxycarbonylamino)heptyl methanesulfonate (**4f**)*

Coloress liquid, 1.57 g, yield 64%, $[\alpha]_D^{20}$ = +0.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.30-1.40 (m, 2H, CH_2), 1.42-1.54 (m, 4H, $2CH_2$), 1.69-1.82 (m, 1H in CH_2), 1.87-1.99 (m, 1H in CH_2), 2.92 (s, 3H, CH_3), 3.10-3.23 (m, 2H, CH_2N), 3.67-3.80 (m, 1H, CHN), 4.20-4.28 (m, 2H, CH_2O), 4.88-4.98 (br, 2H, 2NH), 5.02 (d, *J* = 12.4 Hz, 2H in $2CH_2O$) 5.09 (d, *J* = 12.4 Hz, 2H in $2CH_2O$), 7.27-7.38 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 22.6, 29.4, 34.6, 34.8, 37.0, 40.4, 48.0, 66.5, 66.6, 67.1, 127.95, 127.97, 128.1, 128.40, 128.45, 128.77, 128.81, 129.3, 136.4, 136.5, 156.2, 156.5. IR (ν_{max}, cm^{-1}) 3311, 3061, 3026, 2924, 2851, 1691, 1528, 1453, 1191, 1142, 1101,1058. HRMS (ESI) calcd for $C_{24}H_{33}N_2O_7S$ $[M+H]^+$ *m/z*: 493.2003; found 493.2006.

*4.5.7 (S)-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butyl methanesulfonate (**4g**)*

White solid, mp: 122-123 °C, 1.74 g, yield 72%, $[\alpha]_D^{20}$ = +9.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.69-1.82 (m, 1H in CH_2), 1.92-2.07 (m, 1H in CH_2), 2.71-2.82 (m, 2H, CH_2), 2.91 (s, 3H, CH_3), 3.92-4.05 (m, 1H, CHN), 4.17-4.30 (m, 2H, CH_2O), 4.70 (d, *J* = 7.2 Hz, 1H, NH), 5.02 (s, 2H, CH_2O), 5.05 (s, 2H, CH_2O), 6.89-7.51 (m, 14H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 33.6, 37.1, 40.3, 49.3, 66.6, 67.1, 70.0, 114.9, 127.4, 127.9, 128.0, 128.1, 128.50, 128.54, 129.2, 130.3, 136.4, 136.9, 155.9, 157.6. IR (ν_{max}, cm^{-1}) 3334, 3033, 2926, 2853, 1693, 1531, 1512, 1352, 1171, 1026, 831, 737, 696. HRMS (ESI) calcd for $C_{26}H_{30}NO_6S$ $[M+H]^+$ *m/z*: 484.1788; found 484.1787.

4.6 General procedure for the synthesis of 2-(*N*-benzyloxycarbonylamino)alkyl thioacetates 5

Thioacetic acid (0.344 mL, 0.457 mg, 6.0 mmol) was added to a suspension of Cs_2CO_3 (1.06 g, 3.25 mmol) in DMF (20 mL). The mesylate **4** (5 mmol) was added in one portion to the above generated solution and the resulting solution was stirred at r.t. overnight, during which the reaction flask was covered with aluminium foil. The mixture was poured into distilled H_2O (300 mL), and extracted with EtOAc (100 mL). The organic layer was washed with H_2O (100 mL), $NaHCO_3$ (5% w/w, 100 mL), and brine (100 mL), and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica (petroleum ether/ethyl acetate: 10/1 v/v) to afford thioacetate **5**.

*4.6.1 (S)-S-3-(Benzyloxycarbonylamino)-4-phenylbutyl ethanethioate (**5a**)*

Pale yellow solid, mp: 65-67 °C, 1.20 g, yield 67%, $[\alpha]_D^{20}$ = +22.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.56-1.65 (m, 1H in CH_2), 1.73-1.82 (m, 1H in CH_2), 2.27 (s, 3H, CH_3), 2.73-2.79 (m, 2H, CH_2), 2.79- 2.84 (m, 1H in CH_2S), 2.97 (ddd, *J* = 13.6, 8.8, 5.2 Hz, 1H in CH_2S), 3.87-3.98 (m, 1H, CHN), 4.80 (d, *J* = 8.4 Hz, 1H, NH), 5.03 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.07 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.12-7.35 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 25.7, 30.5, 34.1, 41.0, 51.6, 66.4, 126.4, 127.86, 127.92, 128.35, 128.38, 129.3, 136.5, 137.3, 155.8, 195.7. IR (ν_{max}, cm^{-1}) 3365, 3028, 2952, 2926, 2866, 2850, 1723, 1533, 1447, 1258, 1143, 742, 701, 627. HRMS (ESI) calcd for $C_{20}H_{24}NO_3S$ $[M+H]^+$ *m/z*: 358.1471; found 358.1463.

*4.6.2 (S)-S-3-(Benzyloxycarbonylamino)butyl ethanethioate (**5b**)*

Pale yellow solid, mp: 71-72°C, 1.16 g, yield 82%, $[\alpha]_D^{20}$ = +6.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.17 (d, *J* = 6.8 Hz, 3H, CH_3), 1.66-1.75 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.82 (ddd, *J* = 13.6, 8.4, 7.2 Hz, 1H in CH_2S), 2.94 (ddd, *J* = 13.6, 8.0, 5.6 Hz, 1H in CH_2S), 3.72-3.87 (m, 1H, CHN), 4.66 (d, *J* = 6.4 Hz, 1H, NH), 5.07 (d, *J* = 12.0 Hz, 1H in CH_2O), 5.11 (d, *J* = 12.0 Hz, 1H in CH_2O), 7.26-7.48 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 21.1, 25.7, 30.5, 36.9, 46.5, 66.6, 128.0, 128.5, 136.5, 155.8, 195.8. IR (ν_{max}, cm^{-1}) 3336, 3033, 2959, 2923, 2850, 1691, 1524, 1450, 1245, 1139, 1056, 1101, 746, 697, 633. HRMS (ESI) calcd for $C_{14}H_{20}NO_3S$ $[M+H]^+$ *m/z*: 282.1158; found 282.1148.

*4.6.3 (R)-S-3-(Benzyloxycarbonylamino)-4-methylpentyl ethanethioate (**5c**)*

Pale yellow solid, mp: 58-60°C, 0.81 g, yield 52%, $[\alpha]_D^{20}$ = +8.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (d, *J* = 6.8 Hz, 3H, CH_3), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 1.56 (dheptet, *J* = 4.4, 6.8 Hz, 1H, CH), 1.70-1.82 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.78 (ddd, *J* = 13.6, 8.8, 7.2 Hz, 1H in CH_2S), 2.98 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H in CH_2S), 3.54-3.62 (m, 1H, CHN), 4.62 (d, *J* = 9.6 Hz, 1H, NH), 5.08 (d, *J* = 12.0 Hz, 1H in CH_2O), 5.11 (d, *J* = 12.0 Hz, 1H in CH_2O), 7.30-7.39 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.6, 18.9, 26.2, 30.6, 32.2, 32.7, 55.7, 66.7, 128.0, 128.1, 128.5, 136.6, 156.4, 195.8. IR (ν_{max}, cm^{-1}) 3341, 3036, 2959, 2927, 2869, 1693, 1530, 1239, 1134, 1110, 736, 696, 626. HRMS (ESI) calcd for $C_{16}H_{24}NO_3S$ $[M+H]^+$ *m/z*: 310.1471; found 310.1467.

*4.6.4 (S)-S-3-(Benzyloxycarbonylamino)-5-methylhexyl ethanethioate (**5d**)*

Pale yellow solid, mp: 60-61°C, 0.97 g, yield 60%, $[\alpha]_D^{20}$ = +1.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.0 Hz, 3H, CH_3), 0.91 (d, *J* = 6.0 Hz, 3H, CH_3), 1.24-1.36 (m, 2H, CH_2), 1.59-1.67 (m, 2H, CH_2), 1.71-1.82 (m, 1H, CH), 2.31 (s, 3H, CH_3), 2.82 (ddd, *J* = 14.0, 8.8, 7.2 Hz, 1H in CH_2S), 2.96 (ddd, *J* = 14.0, 9.2, 5.6 Hz, 1H in CH_2S), 3.71-3.85 (m, 1H, CHN), 4.54 (d, *J* = 9.2 Hz, NH), 5.09 (s, 2H, CH_2O), 7.30-7.41 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1, 23.0, 24.8, 25.7, 30.6, 35.9, 44.7, 49.0, 66.6, 128.01, 128.0, 128.5, 136.6, 156.0, 195.9. IR (ν_{max}, cm^{-1}) 3337, 3031, 2954, 2926, 2868, 1693, 1530, 1257, 1232, 1111, 1041, 730, 695, 630. HRMS (ESI) calcd for $C_{17}H_{26}NO_3S$ $[M+H]^+$ *m/z*: 324.1628; found 324.1624.

*4.6.5 (3R,4S)-S-3-(Benzyloxycarbonylamino)-4-methylhexyl ethanethioate (**5e**)*

Pale yellow solid, mp: 42-43°C, 0.92 g, yield 57%, $[\alpha]_D^{20}$ = +18.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.08 (ddq, *J* = 13.2, 7.6, 7.2 Hz, 1H in CH_2), 1.37-1.42 (m, 1H in CH_2), 1.48-1.60 (m, 2H, CH_2), 1.71-1.82 (m, 1H, CH), 2.31 (s, 3H, CH_3), 2.76 (ddd, *J* = 14.0, 8.8, 7.6 Hz, 1H in CH_2S), 3.00 (ddd, *J* = 14.0, 9.2, 4.8 Hz, 1H in CH_2S), 3.65 (ddd, *J* = 14.0, 9.6, 4.4 Hz, 1H, CHN), 4.68 (d, *J* = 9.2 Hz, 1H, NH), 5.10 (s, 2H, CH_2O), 7.28-7.42 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.7, 14.9, 25.2, 26.2, 30.6, 31.7, 38.9, 54.8, 66.6, 128.0, 128.5, 136.6, 156.3, 195.9. IR (ν_{max}, cm^{-1}) 3337, 3033, 2962, 2929, 2860, 1691, 1528, 1240, 1130, 1047, 733, 694, 624. HRMS (ESI) calcd for $C_{17}H_{26}NO_3S$ $[M+H]^+$ *m/z*: 324.1628; found 324.1634.

*4.6.6 (S)-S-3,7-Di(benzyloxycarbonylamino)heptyl ethanethioate (**5f**)*

Scale: 2 mmol, pale yellow solid, mp: 103-105°C, 0.83 g, yield 88%, $[\alpha]_D^{20}$ = +3.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29-1.37 (m, 2H, CH_2), 1.38-1.53 (m, 4H, $2CH_2$), 1.56-1.67 (m, 1H in CH_2), 1.67-1.78 (m, 1H in CH_2), 2.29 (s, 3H, CH_3), 2.73-2.83 (m, 1H in CH_2S), 2.93 (ddd, *J* = 13.6, 8.4, 5.6 Hz, 1H in CH_2S), 3.07-3.21 (m, 2H, CH_2N), 3.58-3.73 (m, 1H, CHN), 4.86 (d, *J* = 8.8 Hz, 1H, NH), 4.98 (br, 1H, NH), 5.05 (d, *J* = 11.2 Hz, 2H in $2CH_2O$), 5.08 (d, *J* = 11.2 Hz, 2H in CH_2O), 7.27-7.44 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 25.6, 29.4, 30.5, 34.6, 35.3, 40.5, 50.4, 66.4, 66.5, 127.91, 127.95, 128.36, 128.37, 136.4, 136.5, 156.2, 156.4, 195.8. IR (ν_{max}, cm^{-1}) 3322, 3086, 3067, 3030, 2916, 2850, 1689, 1520, 1454, 1383, 1246, 1180, 1141, 1075, 1026. HRMS (ESI) calcd for $C_{25}H_{33}N_2O_5S$ $[M+H]^+$ *m/z*: 473.2105; found 473.2106.

*4.6.7 (S)-S-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butyl ethanethioate (**5g**)*

Scale: 4 mmol; white solid, mp: 87-88 °C, 1.18 g, yield 64%, $[\alpha]_D^{20}$ = +20.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50-1.65 (m, 1H in CH_2), 1.72-1.85 (m, 1H in CH_2), 2.28 (s, 3H, CH_3), 2.67-2.81 (m, 3H, CH_2 & 1H in CH_2S), 2.93-3.00 (m, 1H in CH_2S), 3.80-3.95 (m, 1H, CHN), 4.75 (d, *J* = 8.4 Hz, 1H, NH), 5.01 (s, 2H, CH_2O), 5.04 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.08 (d, *J* = 12.4 Hz, 1H in CH_2O), 6.87 (d, *J* = 8.4 Hz, 2H, ArH), 7.04 (d, *J* = 8.4 Hz, 2H, ArH), 7.27-7.45 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 30.5, 34.1, 40.1, 51.7, 66.5, 69.9, 114.8, 127.4, 127.8, 127.9, 128.0, 128.4, 128.5, 129.6, 130.3, 136.5, 137.0, 155.9, 157.5, 195.8. IR (ν_{max}, cm^{-1}) 3347, 3032, 2975, 2925, 2871, 2849, 1693, 1511, 1384, 1243, 1180, 1141, 1076, 1044, 737, 698, 635. HRMS (ESI) calcd for $C_{27}H_{30}NO_4S$ $[M+H]^+$ *m/z*: 464.1890; found 464.1883.

4.7 General procedure for the synthesis of *N*-benzyloxycarbonyl 3-substituted homotaurines 6

30% H_2O_2 (1 mL) was dissolved in 98% formic acid (5 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h to afford peroxyformic acid. Thioacetate **5** (1 mmol) was dissolved in 98% formic acid (2 mL), and then the solution was added dropwise to the peroxyformic acid solution in an ice-water bath. The resulting solution was stirred overnight at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (PE/EA: 5/1, *v*/*v*) to afford pure *N*-benzyloxycarbonyl 3-substituted homotaurine **6**.

*4.7.1 (S)-3-Benzyloxycarbonylamino-4-phenylbutane-1-sulfonic acid (**6a**)*

White solid, mp: 69-71°C, 341 mg, yield 94%, $[\alpha]_D^{20}$ = -9.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, D_2O) δ: 2.13 (dddd, *J* = 14.4, 6.4, 4.4, 2.8 Hz, 1H in CH_2), 2.35 (ddt *J* = 14.4, 11.2, 7.6 Hz, 1H in CH_2), 2.79 (dd, *J* = 13.6, 9.6 Hz, 1H in CH_2), 3.15-3.25 (m, 2H, CH_2S), 3.28 (dd, *J* = 13.6, 4.0 Hz, 1H in CH_2), 4.32-4.41 (m, 1H, CHN), 5.32 (d, *J* = 12.8 Hz, 1H in CH_2O), 5.34 (d, *J* = 12.8 Hz, 1H in CH_2O), 7.15-7.48 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 38.9, 47.4, 57.9, 68.7, 127.2, 127.9, 128.4, 128.6, 128.8, 129.4, 135.0, 136.0, 150.9. IR (ν_{max}, cm^{-1}) 3368, 3029, 2953, 2869, 1725, 1497, 1455, 1307, 1151, 1065, 746, 699. HRMS (ESI) calcd for $C_{18}H_{22}NO_5S$ $[M+H]^+$ *m/z*: 364.1213; found 364.1207.

*4.7.2 (S)-3-Benzyloxycarbonylaminobutane-1-sulfonic acid (**6b**)*

Coloress liquid, 184 mg, yield 64%, $[\alpha]_D^{20}$ = +9.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (d, *J* = 6.4 Hz, 3H, CH_3), 2.01 (dddd, *J* = 13.6, 7.2, 6.8, 3.6 Hz, 1H in CH_2), 2.55 (dddd, *J* = 13.6, 10.4, 6.4, 4.8 Hz, 1H in CH_2), 3.28 (ddd, *J* = 13.2, 7.2, 4.8 Hz, 1H in CH_2S), 3.39 (ddd, *J* = 13.2, 10.4, 6.8 Hz, 1H in CH_2S), 4.28 (ddq, *J* = 6.4, 3.6, 6.4 Hz, 1H, CHN), 5.27 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.32 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.27-7.60 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.7, 25.6, 47.4, 53.3, 68.4, 127.7, 128.2, 128.5, 135.0, 150.7. IR (ν_{max}, cm^{-1}) 3332, 3034, 2977, 2927, 2850, 1727, 1529, 1455, 1301, 1252, 1061, 738, 697. HRMS (ESI) calcd for $C_{12}H_{18}NO_5S$ $[M+H]^+$ *m/z*: 288.0900; found 288.0889.

*4.7.3 (R)-3-Benzyloxycarbonylamino-4-methylpentane-1-sulfonic acid (**6c**)*

Coloress liquid, 170 mg, yield 54%, $[\alpha]_D^{20}$ = +15.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 2.13-2.22 (m, 1H in CH_2), 2.26-2.40 (m, 2H, CH & 1H in CH_2), 3.24 (ddd, *J* = 13.2, 7.2, 6.0 Hz, 1H in CH_2S), 3.30-3.37 (m, 1H in CH_2S), 4.07 (dt, *J* = 7.6, 4.8 Hz, 1H, CHN), 5.27 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.32 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.27-7.50 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 18.3, 19.3, 29.7, 48.3, 61.6, 68.5, 127.7, 128.2, 128.4, 135.0, 151.2. IR (ν_{max}, cm^{-1}) 3369, 3034, 2964, 2924, 2866, 1725, 1455,

1342, 1299, 1148, 1063, 736, 697. HRMS (ESI) calcd for $C_{14}H_{22}NO_5S$ $[M+H]^+$ *m/z*: 316.1213; found 316.1211.

*4.7.4 (S)-3-Benzyloxycarbonylamino-5-methylhexane-1-sulfonic acid (**6d**)*

Pale yellow solid, mp: 87-89 °C, 309 mg, yield 94%, $[\alpha]_D^{20}$ = +14.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, *J* = 6.4 Hz, 3H, CH_3), 0.94 (d, *J* = 6.4 Hz, 3H, CH_3), 1.51 (ddd, *J* = 13.2, 10.0, 4.4 Hz, 1H in CH_2), 1.56-1.66 (m, 1H, CH), 1.75 (ddd, *J* = 13.2, 9.2, 4.0 Hz, 1H in CH_2), 2.08-2.17 (m, 1H in CH_2), 2.53 (ddt, *J* = 13.6, 11.2, 7.2 Hz, 1H in CH_2), 3.30 (ddd, *J* = 13.2, 7.2, 4.4 Hz, 1H in CH_2S), 3.39 (ddd, *J* = 13.2, 11.2, 6.8 Hz, 1H in CH_2S), 4.21-4.28 (m, 1H, CHN), 5.26 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.33 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.29-7.47 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 23.4, 23.5, 24.9, 41.8, 47.5, 55.8, 68.6, 127.8, 128.3, 128.6, 135.0, 150.8. IR (ν_{max}, cm^{-1}) 3344, 3031, 2954, 2924, 2869, 2851, 1692, 1529, 1257, 1231, 1140, 1110, 1043, 736, 697. HRMS (ESI) calcd for $C_{15}H_{24}NO_5S$ $[M+H]^+$ *m/z*: 330.1370; found 330.1366.

*4.7.5 (3R,4S)-3-Benzyloxycarbonylamino-4-methylhexane-1-sulfonic acid (**6e**)*

Pale yellow solid, mp: 71-73 °C, 263 mg, yield 80%, $[\alpha]_D^{20}$ = +12.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 0.91 (t, *J* = 7.6 Hz, 3H, CH_3), 1.11-1.13 (m, 1H in CH_2), 1.28-1.40 (m, 1H in CH_2), 2.05-2.15 (m, 1H, CH), 2.14-2.23 (m, 1H in CH_2), 2.28-2.40 (m, 1H in CH_2), 3.24 (dt, *J* = 13.2, 7.2 Hz, 1H in CH_2S), 3.34 (dt, *J* = 13.2, 8.0 Hz, 1H in CH_2S), 4.17 (dt, *J* = 7.6, 5.2 Hz, 1H, CHN), 4.82-5.20 (br, 1H, NH), 5.27 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.34 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.28-7.47 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.8, 13.1, 18.8, 25.6, 36.1, 48.4, 60.7, 68.6, 127.8, 128.3, 128.5, 135.1, 151.2. IR (ν_{max}, cm^{-1}) 3380, 3033, 2963, 2930, 2872, 1727, 1455, 1384, 1304, 1150, 1040, 751, 696. HRMS (ESI) calcd for $C_{15}H_{24}NO_5S$ $[M+H]^+$ *m/z*: 330.1370; found 330.1364.

*4.7.6 (S)-3,7-Dibenzyloxycarbonylaminoheptane-1-sulfonic acid (**6f**)*

White solid, mp: 76-78 °C, 115 mg, yield 24%, $[\alpha]_D^{20}$ = +17.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28-1.37 (m, 2H, CH_2), 1.43-1.55 (m, 2H, CH_2), 1.57-1.70 (m, 2H, CH_2), 1.80-1.92 (m, 1H in CH_2), 2.04-2.12 (m, 1H in CH_2), 2.39-2.53 (m, 1H in CH_2S), 3.08-3.22 (m, 2H, CH_2), 3.26 (ddd, *J* = 12.8, 7.2, 4.8 Hz, 1H in CH_2S), 3.32-3.42 (m, 1H, CHN), 4.06-4.20 (m, 1H, NH), 4.77 (br, 1H, NH), 5.08 (s, 2H, CH_2O), 5.25 (d, *J* = 12.4 Hz, 1H in CH_2O), 5.32 (d, *J* = 12.4 Hz, 1H in CH_2O), 7.23-7.44 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 23.1, 29.6, 32.5, 40.5, 47.6, 58.9, 66.6, 68.6, 127.8, 128.0, 128.1, 128.3, 128.5, 128.6, 135.0, 136.6, 150.9, 156.4. IR (ν_{max}, cm^{-1}) 3397, 3061, 3032, 3006, 2949, 2923, 2846, 1720, 1523, 1454, 1384, 1303, 1267, 1143, 1074, 1020. HRMS (ESI) calcd for $C_{23}H_{31}N_2O_7S$ $[M+H]^+$ *m/z*: 479.1846; found 479.1856.

*4.7.7 (S)-3-Benzyloxycarbonylamino-4-(4-benzyloxyphenyl)butane-1-sulfonic acid (**6g**)*

Scale: 3 mmol, Yellow solid, mp: 116-117.5 °C, 374 mg, yield 26%, $[\alpha]_D^{20}$ = -1.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.08-2.15 (m, 1H in CH_2), 2.29-2.40 (m, 1H in CH_2), 2.74 (dd, *J* = 13.6, 9.6 Hz, 1H in CH_2), 3.12-3.25 (m, 3H, 1H in CH_2 & CH_2S), 4.28-4.36 (m, 1H, CHN), 5.03 (s, 2H, CH_2O), 5.30 (d, *J* = 13.6 Hz, 1H in CH_2), 5.33 (d, *J* = 13.6 Hz, 1H in CH_2), 6.91 (d, *J* = 8.6 Hz, 2H, ArH), 7.07 (d, *J* = 8.6 Hz, 2H, ArH), 7.30-7.51 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 38.1, 47.4, 58.0, 68.7, 70.0, 115.2, 127.4, 127.8, 128.0, 128.2, 128.4, 128.57, 128.59, 130.4, 135.0, 136.8, 150.9, 158.0. IR (ν_{max}, cm^{-1}) 3435, 3032, 2945, 2920, 2849, 1726, 1611, 1453, 1384, 1306, 1151, 1027, 740, 697. HRMS (ESI) calcd for $C_{25}H_{28}NO_6S$ $[M+H]^+$ *m/z*: 470.1632; found 470.1683.

4.8 General procedure for the synthesis of 3-substituted homotaurines 7

Pd/C (1.18 mg, 10 % mmol) and 10 mL of MeOH were added to a 50 mL dried three-necked, round-bottomed flask with a H_2 balloon. A solution of *N*-benzyloxycarbonyl 3-substituted homotaurine **6** (1 mmol) in MeOH (5 mL) was injected to the flask. The resulting mixture was stirred at room temperature overnight. After filtration and removal of the solvent under reduced pressure, the pure 3-substitued homotuarine **7** was obtained by crystallization from EtOH.

*4.8.1 (S)-3-Amino-4-phenylbutane-1-sulfonic acid (**7a**)*

White solid, mp: 291-293°C, 181 mg, yield 79%, $[\alpha]_D^{20}$ = +4.9 (*c* 1.0, D_2O). ^{1}H NMR (400 MHz, D_2O), δ: 2.16 (q, *J* = 6.8, 2H, CH_2), 2.92 (dd, *J* = 14.4, 8.2, Hz, 1H in CH_2), 3.03-3.10 (m, 2H, CH_2S), 3.14 (dd, *J* = 14.4, 6.0 Hz, 1H in CH_2), 3.75 (ddt, *J* = 8.2, 6.0, 6.8 Hz, 1H, CHN), 7.21-7.47 (m, 5H, ArH). ^{13}C NMR (100 MHz, D_2O) δ: 27.3, 37.7, 46.9, 51.9, 127.6, 129.1, 129.4, 153.2. IR (ν_{max}, cm^{-1}) 3422, 3060, 3026, 2945, 2929, 1690, 1629, 1528, 1497, 1454, 1209, 1173, 1040. HRMS (ESI) calcd for $C_{10}H_{16}NO_3S$ $[M+H]^+$ *m/z*: 230.0845; found 230.0838.

*4.8.2 (S)-3-Aminobutane-1-sulfonic acid (**7b**)*

White solid, mp: >300 °C, 108 mg, yield 71%, $[\alpha]_D^{20}$ = -4.6 (*c* 1.0, D_2O). ^{1}H NMR (400 MHz, D_2O), δ: 1.26 (d, *J* = 6.8 Hz, 3H, CH_3), 1.87-1.99 (m, 1H in CH_2), 2.00-2.13 (m, 1H in CH_2), 2.88-3.03 (m, 2H, CH_2S), 3.40-3.54 (m, 1H, CHN). ^{13}C NMR (100 MHz, D_2O) δ: 17.3, 29.2, 46.7, 47.0. IR (ν_{max}, cm^{-1}) 3421, 2975, 2923, 1617, 1528, 1446, 1267, 1230, 1200, 1161, 1093. HRMS (ESI) calcd for $C_4H_{12}NO_3S$ $[M+H]^+$ *m/z*: 154.0532; found 154.0526.

*4.8.3 (R)-3-Amino-4-methylpentane-1-sulfonic acid (**7c**)*

White solid, mp: 226-228 °C, 161 mg, yield 89%, $[\alpha]_D^{20}$ = +10.6 (*c* 1.0, D_2O). ^{1}H NMR (400 MHz, D_2O) δ: 0.93 (d, *J* = 7.2 Hz, 3H, CH_3), 0.95 (d, *J* = 7.2 Hz, 3H, CH_3), 1.88-2.02 (m, 2H, CH_2), 2.18 (dheptet,, *J* = 5.6, 7.2 Hz, 1H, CH), 2.89-3.03 (m, 2H, CH_2S), 3.21-3.28 (m, 1H, CHN). ^{13}C NMR (100 MHz, D_2O) δ: 16.4, 17.2, 24.7, 29.3, 47.0, 56.0. IR (ν_{max}, cm^{-1}) 3423, 2974, 2965, 2875, 1635, 1525, 1449, 1262, 1237, 1201, 1160, 1035. HRMS (ESI) calcd for $C_6H_{16}NO_3S$ $[M+H]^+$ *m/z*: 182.0845; found 182.0840.

4.9 General procedure for the synthesis of *N*-benzyloxycarbonylamino acid methyl esters 8

Cbz-protected β-amino acid **3** (50 mg) was dissolved in THF (2.5 mL) and the resulting solution was cooled to 0 °C. Diazomethane (approximate 41 mg, 1 mmol) in Et_2O (2 mL) was added dropwise, and the yellow solution was allowed to warm to r.t. The reaction mixture was stirred until the acid disappeared (TLC monitoring). Excess CH_2N_2 was destroyed by addition of AcOH. The mixture was concentrated under reduced pressure, and the residue was taken up in EtOAc. The organic phase was washed successively with saturated aq. Na_2CO_3 solution, water, and brine, and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 5/1 v/v) to afford the product methyl ester **8**.

*4.9.1 Methyl (R/S)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (rac-**8a**)*

Colorless liquid, 35 mg, yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (dd, J = 16.0, 5.6 Hz, 1H in CH_2), 2.54 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 2.84 (dd, J = 13.6, 8.0 Hz, 1H in CH_2), 2.95 (dd, J = 13.6, 6.4 Hz, 1H in CH_2), 3.66 (s, 3H, CH_3), 4.16–4.28 (m, 1H, CH), 5.07 (s, 2H, CH_2), 5.30 (d, J = 7.6 Hz, 1H, NH), 7.10–7.40 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.3, 40.2, 49.3, 51.7, 66.6, 126.7, 127.98, 128.04, 128.46, 128.55, 129.3, 136.5, 137.4, 155.6, 171.9. The enantiomers were determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH 90:10, 24 ^{o}C) at 1.00 mL/min, UV detection at 210 nm: t_R: 16.8 min, 20.7 min (see SI).

*4.9.2 Methyl (S)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (**8a**)*

Colorless liquid, 45 mg, yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (dd, J = 16.0, 5.6 Hz, 1H in CH_2), 2.54 (dd, J = 16.0, 5.6 Hz, 1H in CH_2), 2.83 (dd, J = 13.2, 7.6 Hz, 1H in CH_2), 2.95 (dd, J = 13.2, 6.4 Hz, 1H in CH_2), 3.67 (s, 3H, CH_3), 4.16–4.28 (m, 1H, CH), 5.07 (s, 2H, CH_2), 5.30 (d, J = 7.2 Hz, 1H, NH), 7.11–7.37 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.3, 40.2, 49.3, 51.7, 66.6, 126.7, 127.98, 120.05, 128.5, 128.6, 129.3, 136.5, 137.4, 155.6, 171.9. The ee was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH 90:10, 24 ^{o}C) at 1.00 mL/min, UV detection at 210 nm: t_R: 20.6 min, *ee* > 99 % (see SI).

*4.9.3 Methyl (R/S)-3-(benzyloxycarbonylamino)-5-methylhexanoate (rac-**8d**)*

Colorless liquid, 42 mg, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.8 Hz, 3H, CH_3), 0.92 (d, J = 6.8 Hz, 3H, CH_3), 1.29 (ddd, J = 14.0, 8.0, 5.6 Hz, 1H in CH_2), 1.49 (ddd, J = 14.0, 9.6, 6.0 Hz, 1H in CH_2), 1.60–1.70 (m, 1H, CH), 2.50 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 2.57 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 3.66 (s, 3H, CH3), 4.12 (ddd, J = 14.0, 9.6, 4.4 Hz, 1H, CH), 5.07 (d, J = 12.8 Hz, 1H in CH_2), 5.10 (d, J = 12.8 Hz, 1H in CH_2), 5.14 (d, J = 4.8 Hz, 1H, NH), 7.27–7.45 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 22.9, 24.9, 39.3, 43.5, 46.3, 51.6, 66.6, 128.00, 128.03, 128.5, 136.6, 155.7, 172.0. The enantiomers were determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH 95:5, 26 ^{o}C) at 1.00 mL/min, UV detection at 210 nm: t_R: 13.4 min, 14.8 min (see SI).

*4.9.4 Methyl (S)-3-(benzyloxycarbonylamino)-5-methylhexanoate (**8d**)*

Colorless liquid, 52 mg, yield 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 7.2 Hz, 3H, CH_3), 0.92 (d, J = 7.2 Hz, 3H, CH_3), 1.29 (ddd, J = 14.0, 8.0, 5.6 Hz, 1H in CH_2), 1.49 (ddd, J = 14.0, 9.2, 6.0 Hz, 1H in CH_2), 1.58–1.70 (m, 1H, CH), 2.50 (dd, J = 16.0, 5.6 Hz, 1H in CH_2), 2.57 (dd, J = 16.0, 5.2 Hz, 1H in CH_2), 3.65 (s, 3H, CH_3), 3.99–4.12 (m, 1H, CH), 5.07 (d, J = 12.8 Hz, 1H in CH_2), 5.10 (d, J = 12.8 Hz, 1H in CH_2), 5.16 (d, J = 8.8 Hz, 1H, NH), 7.27–7.44 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 22.9, 24.9, 39.3, 43.5, 46.3, 51.6, 66.5, 127.98, 128.01, 128.4, 136.6, 155.7, 172.0. The ee was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH 95:5, 26 ^{o}C) at 1.00 mL/min, UV detection at 210 nm: t_R: 13.4 min, *ee* > 99 % (see SI).

Acknowledgments

This work was supported by The National Basic Research Program of China (No. 2013CB328905) and National Natural Science Foundation of China (Nos. 21372025 and 21172017).

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of N-Cbz-O-Bn-Tyr **1g**, products **2**, **3**, **4**, **5**, **6**, **7**, and **8** and copies of HPLC profiles for the ee determination of **8a,d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

1. (a) Gervais, F.; Paquette, J.; Morissette, C.; Krzywkowski, P.; Yu, M.; Azzi, M.; Lacombe, D.; Kong, X. Q.; Aman, A.; Laurin, J.; Szarek, W. A.; Tremblay, P. *J. Neurobiol. Aging* **2007**, *28*, 537-547. (b) Kim, H.Y.; Kim, Y.; Han, G.; Kim, D. J. *J. Alzheimer's Dis.* **2010**, *22*, 73–85.
2. Saumier, D.; Duong, A.; Haine, D.; Garceau, D.; Sampalis, J. *J. Nutr. Health Aging* **2009**, *13*, 808–812.
3. Angelini, M.; Brahmbhatt, Y. *Formulary* **2007**, *42*, 14-31.
4. (a) Wellendorph, P.; Greenwood, J. R.; de Lichtenberg, A.; Nielsen, B.; Frund, B.; Brehm, L.; Clausen, R. P.; Brauner-Osborne, H. *J. Pharmacol. Exp. Ther.* **2005**, *315*, 346-351. (b) Pellicciari, R.; Marinozzi, M.; Macchiarulo, A.; Fulco, M. C.; Gafarova, J.; Serpi, M.; Giorgi, G.; Nielsen, S.; Thomsen, C. *J. Med. Chem.* **2007**, *50*, 4630-4641.
5. Ma, Y. H.; Xu, J. X. *Synthesis* **2012**, *44*, 2225-2230 and cited therein.
6. Zhao, R. Y.; Wilhelm, S. D.; Audette, C.; Jones, G.; Leece, B. A.; Lazar, A. C.; Goldmacher, V. S.; Sing, R.; Kovtun, Y.; Widdison, W. C.; Lambert, J. M.; Chari, R. V. *J. Med. Chem.* **2011**, *54*, 3606-3623.
7. Huang, Z. Y.; Xu, J. X. *Tetrahedron* **2013**, *69*, 1050-1056.
8. Smith, C. W.; Norton, D. G.; Ballard, S. A. *J. Am. Chem. Soc*. **1953**, *75*, 748-749.
9. Lipina, E. S.; Bodina, R. I.; Efimova, T. P.; Novikova, T. A.; Perekalin, V. V. *Pharm. Chem. J*. **1999**, *33*, 598-600.
10. Li, C. S.; Howson, W.; Dolle, R. E. *Synthesis* **1991**, 244-245.
11. (a) Abbenante, G.; Prager, R. H. *Aust. J. Chem*. **1990**, *43*, 213-214. (b) Abbenante, G.; Prager, R. H. *Aust. J. Chem*. **1992**, *45*, 1791-1800. (c) Abbenante, G.; Prager, R. H. *Aust. J. Chem*. **1992**, *45*, 1801-1810.
12. Bachand, B.; Atfani, M.; Samim, B.; Levesque, S.; Simard, D.; Kong, X. Q. *Tetrahedron Lett*. **2007**, *48*, 8587-85889.
13. Nai, Y. F.; Xu, J. X. *Helv. Chim. Acta*. **2013**, *96*, 1355-1365.
14. Kong, X. Q.; Wu, X.; Bouzide, A.; Valade, I.; Migneault, D.; Gervais, F.; Delorme, D.; Bachand, B.; Atfani, M.; Levesque, S.; Samim, B. WO2006085149 (*Chem. Abstr*. **2006**, *145*, 248852).
15. (a) Inguimbert. N.; Coric, P.; Dhotel, H.; Llorens-Cortes, C.; Fournie-Zaluski, M. C.; Roques, B. P. *J. Labelled. Compd. Radiopharm*. **2004**, *47*, 997-1005. (b) Inguimbert, N.; Coric, P.; Dhotel, H.; Bonnard, E.; Llorens-Cortes, C.; De, M. N.; Fournie-Zaluski, M. C.; Roques, B. P. *J. Pept. Res*. **2005**, *65*,175-188.
16. Helferich, B.; Ter Vehn, W. *J. Prakt. Chem*. **1964**, *26*, 90-94.
17. David, C.; Bischoff, L.; Meudal, H.; Mothe, A.; De Mota, N.; DaNascimento, S.; Llorens-Corles, C.; Fournie–Zaluski, M. C.; Roques, B. P. *J. Med. Chem*. **1999**, *42*, 5197-5211.
18. (a) Kakaei, S.; Xu, J. X. *Tetrahedron* **2013**, *69*, 9068-9075. (b) Kakaei, S.; Chen, N.; Xu, J. X. *Tetrahedron* **2013**, *69*, 302-309. (c) Chen, N.; Xu, J. X. *Tetrahedron* **2012**, *68*, 2513-2522. (d) Xu, C. X.; Xu, J. X. *Amino Acids* **2011**, *41*, 195-203. (e) Chen, N.; Jia, W. Y.; Xu, J. X. *Eur. J. Org. Chem.* **2009**, 5841-5846. (f) He, F. D.; Meng, F. H.; Song, X. Q.; Hu, W. X.; Xu, J. X., *Org. Lett*. **2009**, *11*, 3922-3925. (g) Chen, N.; Zhu, M.; Zhang, W.; Du, D.-M.; Xu, J. X. *Amino Acids* **2009**, *37*, 309-313. (h) Yu, H.; Cao, S. L.; Zhang, L. L.; Liu, G.; Xu, J. X. *Synthesis* **2009**, 2205-2209. (i) Zhang, W.; Wang, B. Y.; Chen, N.; Du, D.-M.; Xu, J. X. *Synthesis* **2008**, 197-200. (j) Wang, B. Y.; Zhang, W.; Zhang, L. L.; Du, D.-M.; Liu, G.; Xu, J. X. *Eur. J. Org. Chem*. **2008**, 350-355. (k) Hu, L. B.; Zhu, H.; Du, D.-M.; Xu, J. X. *J. Org. Chem*. **2007**, *72*, 4543-4546. (l) Huang, J. X.; Du, D.-M.; Xu, J. X. *Synthesis* **2006**, 315-319. (m) Huang, J. X.; Wang, F.; Du, D. M.; Xu, J. X. *Synthesis* **2005**, 2122-2128. (n) Xu, J. X.; Xu, S. *Synthesis* **2004**, 276-282. (o) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129-1134.
19. (a) Xu, J. X.; Yang, J. H. *Chemistry* (*Huaxue Tongbao)* **1998**, *(3)*, 22-29. (b) Shi, H.; Liu, K.; Leong, W. W. Y.; Yao, S. Q. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3945-3948.
20. Hughes, A. B.; Sleebs, B. E. *Helv. Chim. Acta* **2006**, *89*, 2611–2637.
21. For Reviews, see: (a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *14*, 2193-2256. (b) Ye, T.; Mc Kervey, M. A. *Chem. Rev.* **1994**, *94*, 1091-1160. (c)

Meier, H.; Zeller, K. P. *Angew, Chem. Int. Ed. Engl.* **1975**, *14*, 32-41.
22. (a) Vasanthakumar, G. R.; Patil, B. S.; Babu, V. V. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2087-2089. (b) Linder, M. R.; Steurer, S.; Podlech, J. *Org. Synth.* **2002**, *79*, 154-164. (c) Koch, K.; Podlech, J. *Syhth. Commun.* **2005**, *35*, 2789-2794.
23. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568–3571.
24. Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1992**, *33*, 5517-5518.
25. Kokotos, G.; Noula, C. *J. Org. Chem*. **1996**, *61*, 6994-6996.
26. (a) Wang, B. Y.; Zhang, W.; Zhang, L. L.; Du, D. M.; Liu, G.; Xu, J. X. *Eur. J. Org. Chem*. **2008**, 350–355. (b) Xu, J. X.; Xu, S. *Synthesis* **2004**, 276–282.
27. Patil, B. S.; Vasanthakumar, G. R.; Babu, V. V. S. *Synth. Commun.* **2003**, *33*, 3089-3096.
28. Kantharaju, B. S. P.; Buba, V. V. S. *Indian J. Chem.* **2004**, *43B*, 2152-2158.
29. Vasanthakumar, G. R.; Buba, V. V. S. *Indian. J. Chem*. **2003**, *42B*, 1691-1695.
30. Bures, F.; Kulhánek, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1347-1354.
31. Mukai, T.; Suganuma, N.; Soejima, K.; Sasaki, J.; Yamamoto, F.; Maeda, M. *Chem. Pharm. Bull*. **2008**, *56*, 260-265.
32. Koenig, K. H.; Kaul, L.; Kuge, M.; Schuster, M. *Liebigs Ann. Chem.* **1987**, 1115-1116.
33. Moutevelis-Minakakis, P.; Filippakou, M.; Sinanoglou, C.; Kokotos, G. *J. Pept. Sci*. **2006**, *12*, 377-382.
34. Veitia, M. S. L.; Brun, P. L.; Jorda, P.; Falguieres, A.; Ferroud, C. *Tetrahedron: Asymmetry* **2009**, *20*, 2077-2089.
35. Arvidsson, P. I.; Frackenpohl, J.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 1522-1553.
36. Koch, K.; Podlech, J. *Synth. Commun.* **2005**, *35*, 2789-2794.
37. Sutherland, A.; Willis, C. L. *J. Org. Chem*. **1998**, *63*, 7764-7769.
38. Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gomez-Bengoa, E.; Garcıa, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 9188-9189.

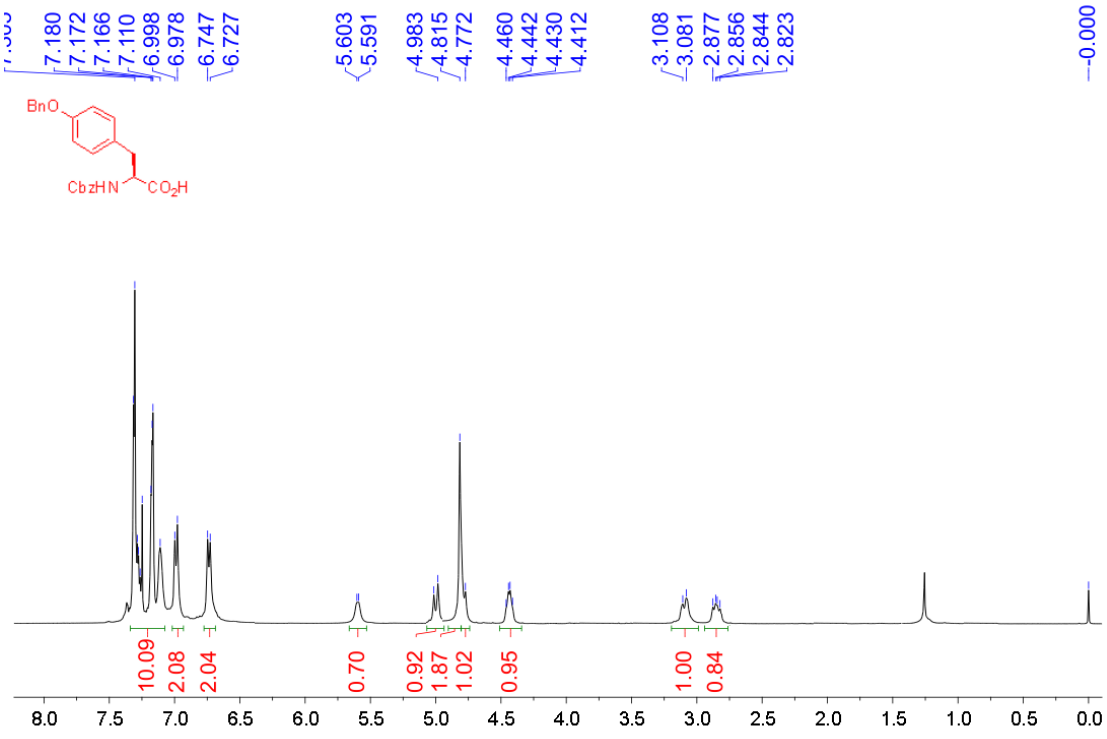
Synthesis of enantiopure free and *N*-benzyloxycarbonyl-protected 3-substituted homotaurines from naturally occurring amino acids

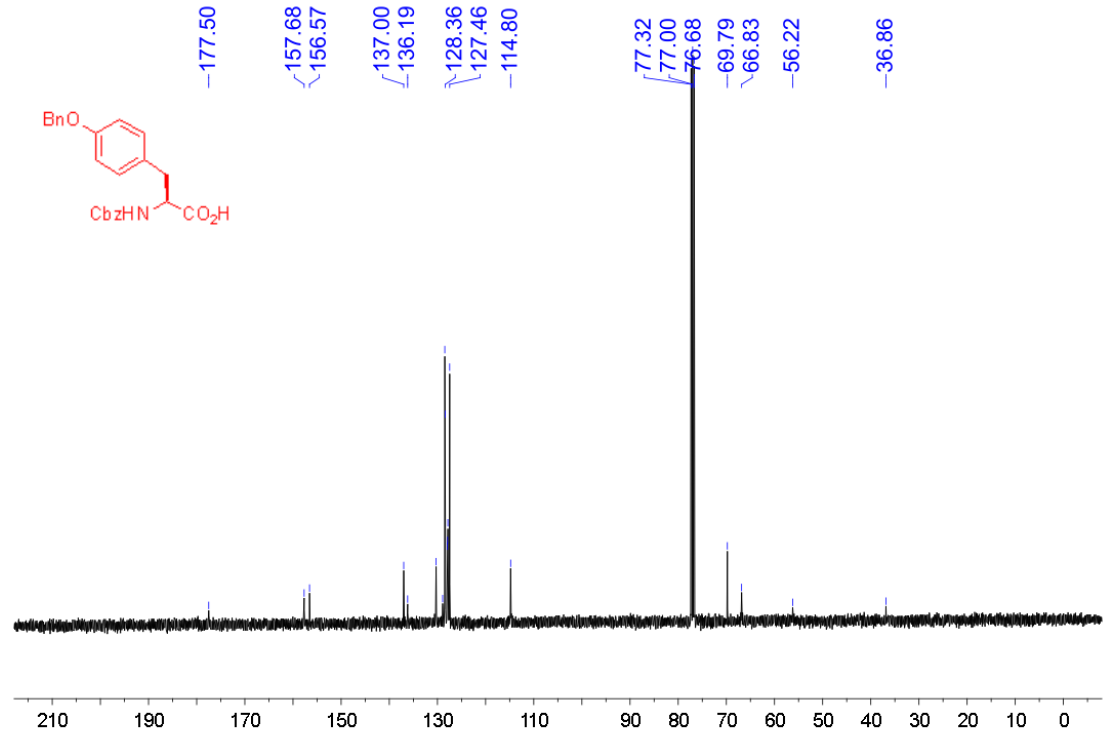
Yongpeng Zheng, Jiaxi Xu*

State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China.

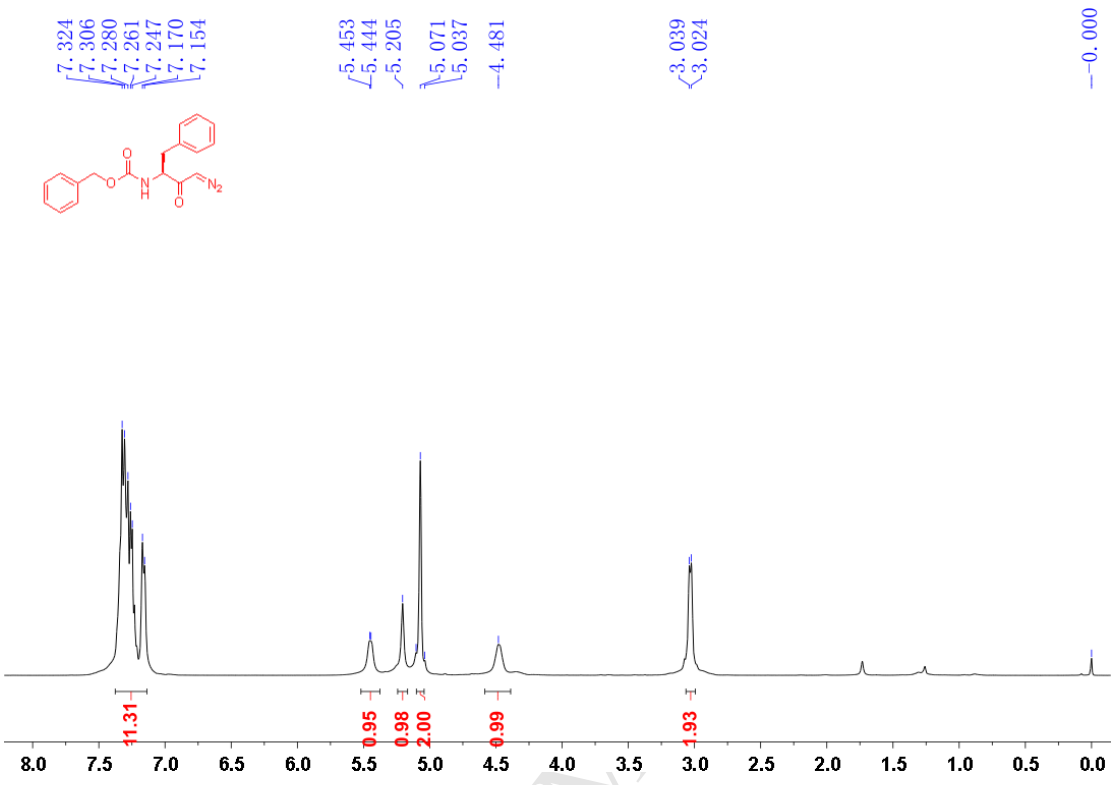
Supporting Information

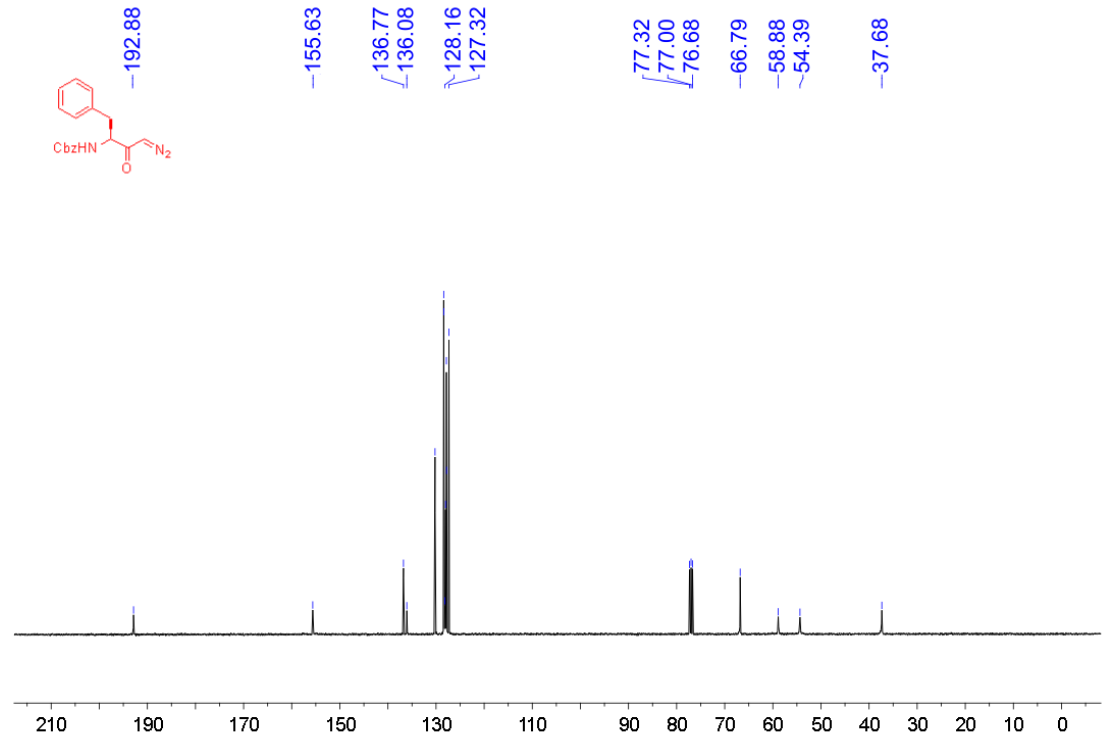
(*S*)-*O*-Benzyl-*N*-benzyloxycarbonyltyrosine **(1g)**



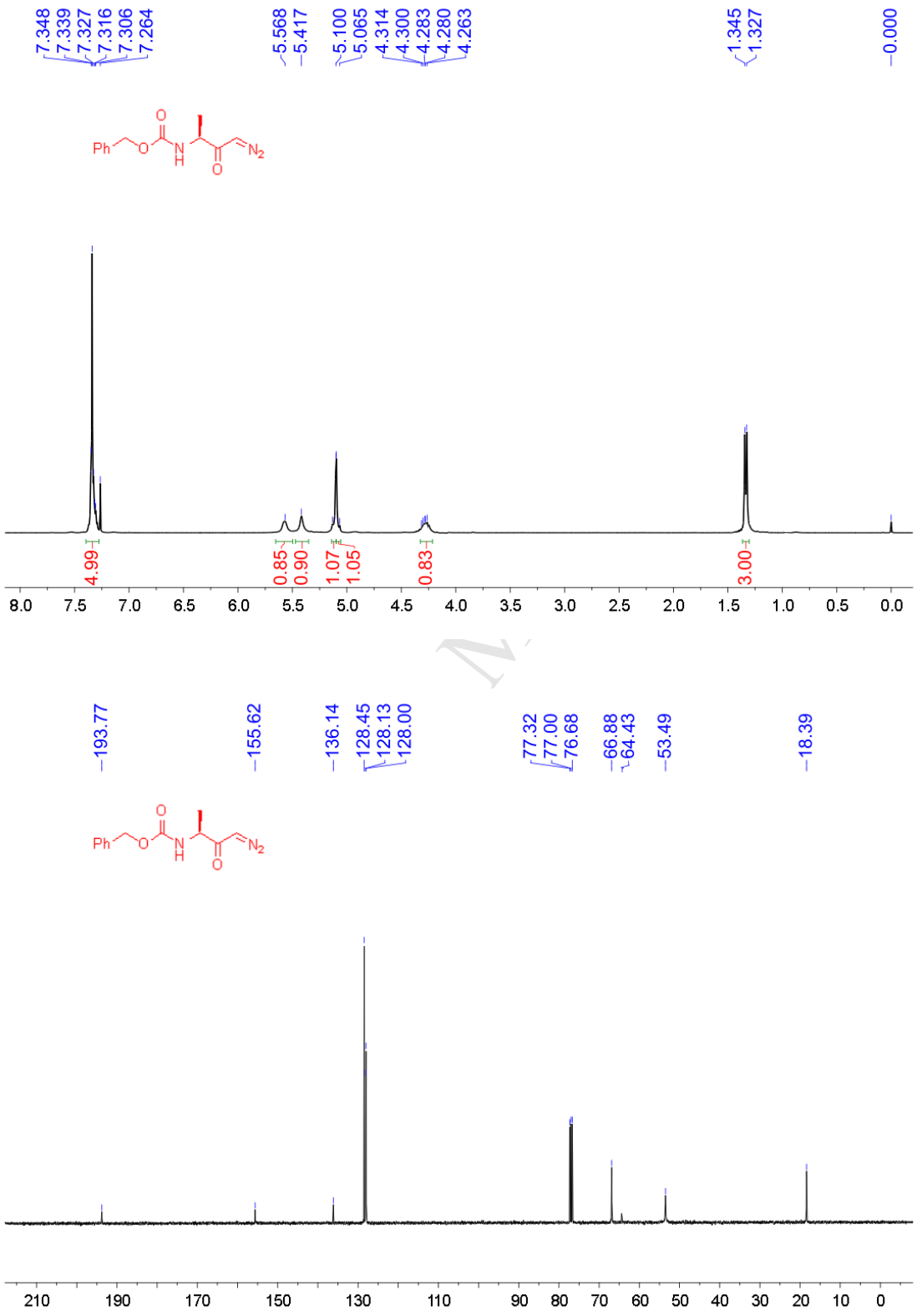


Benzyl (*S*)-4-diazo-3-oxo-1-phenylbutan-2-ylcarbamate (**2a**)

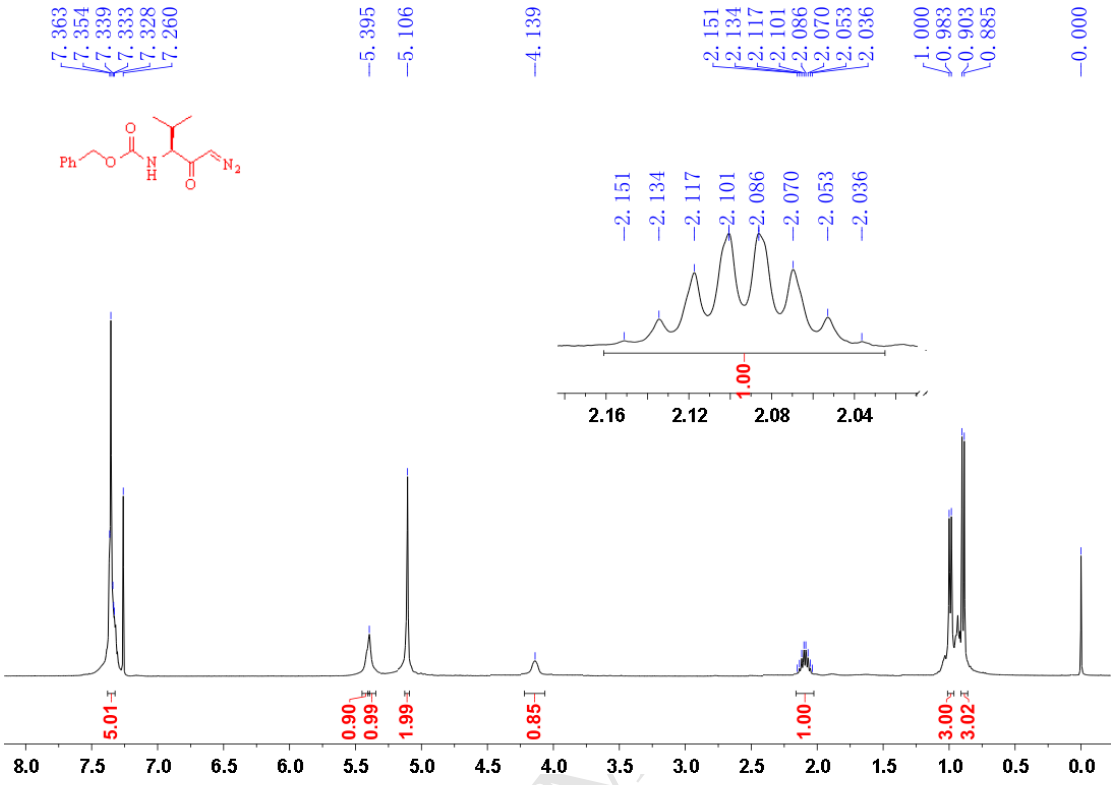


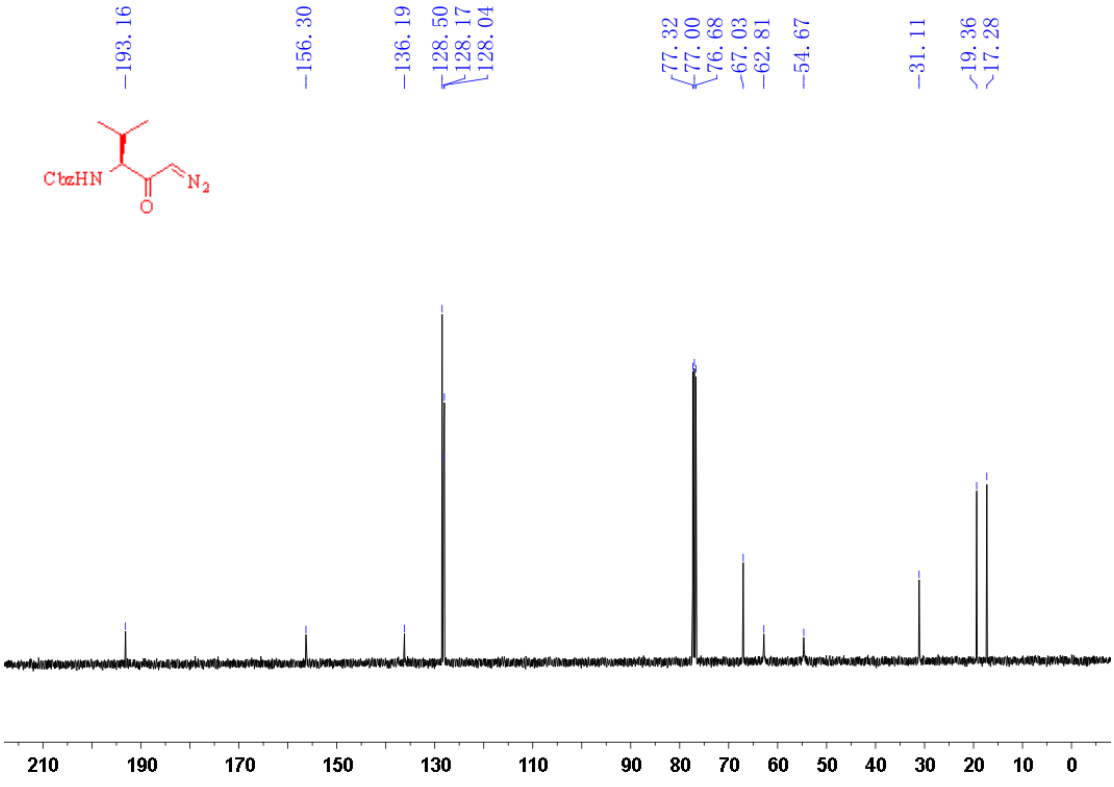


Benzyl (*S*)-4-diazo-3-oxobutan-2-ylcarbamate (**2b**)

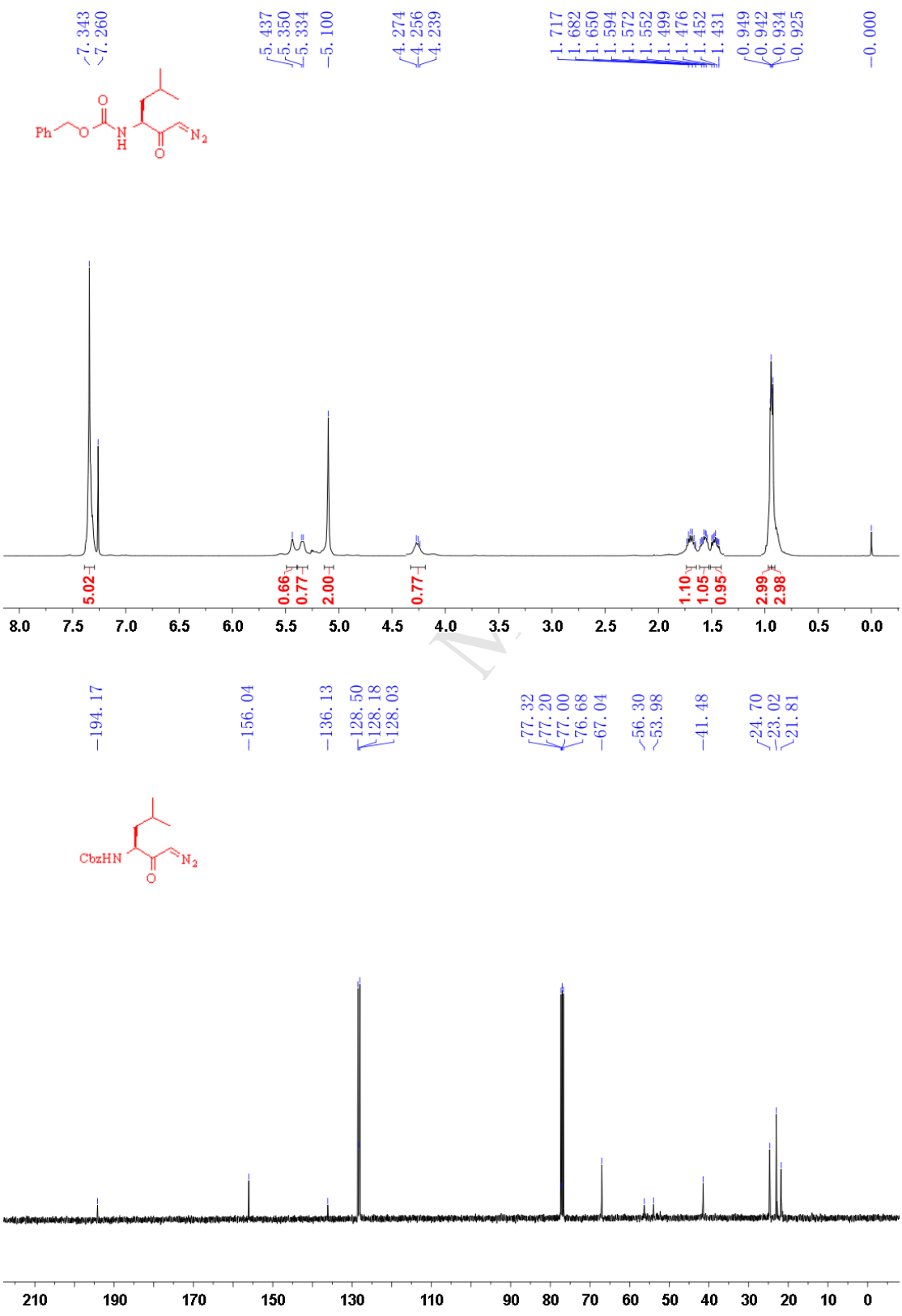


Benzyl (*S*)-1-diazo-4-methyl-2-oxopentan-2-ylcarbamate (**2c**)

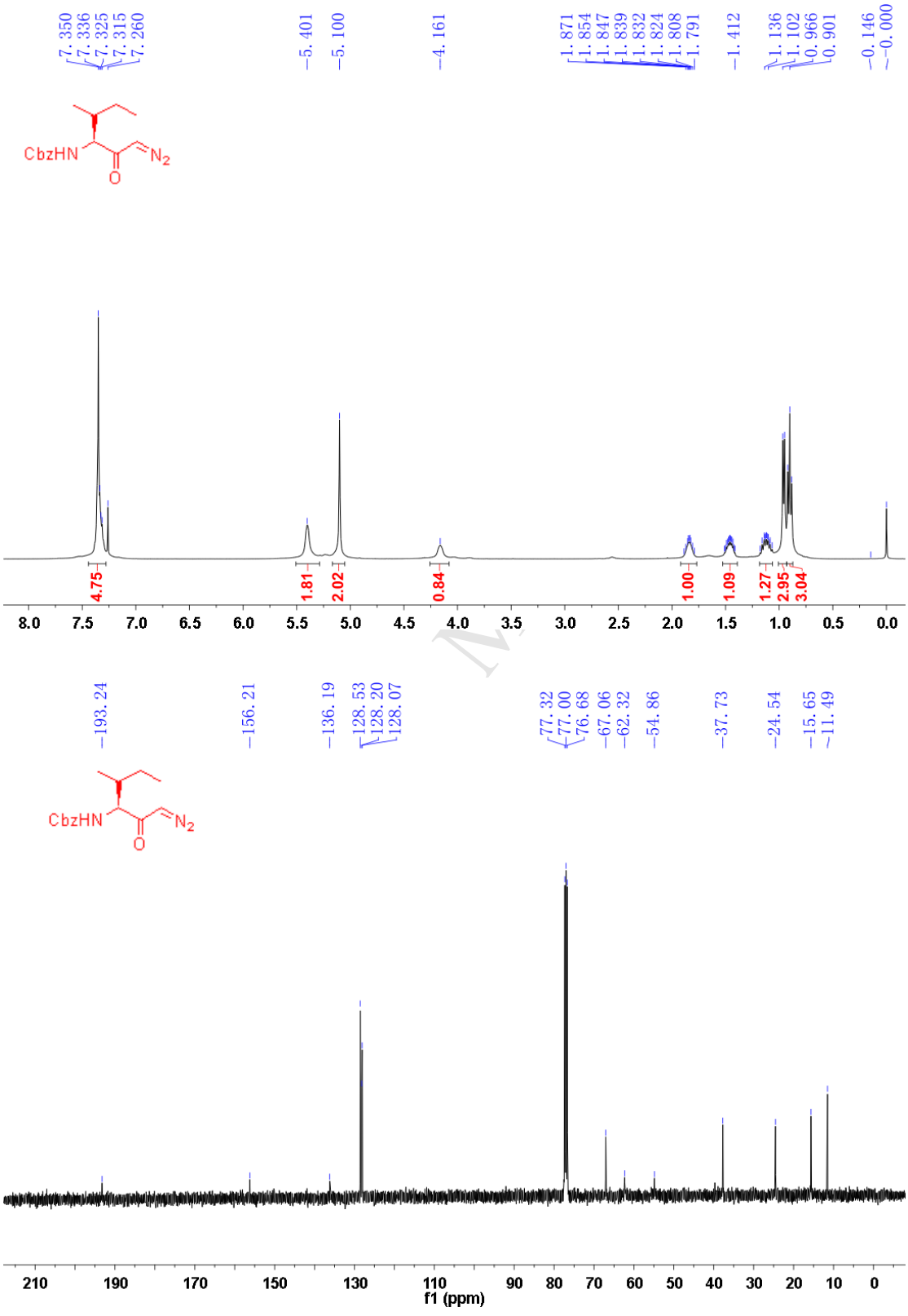




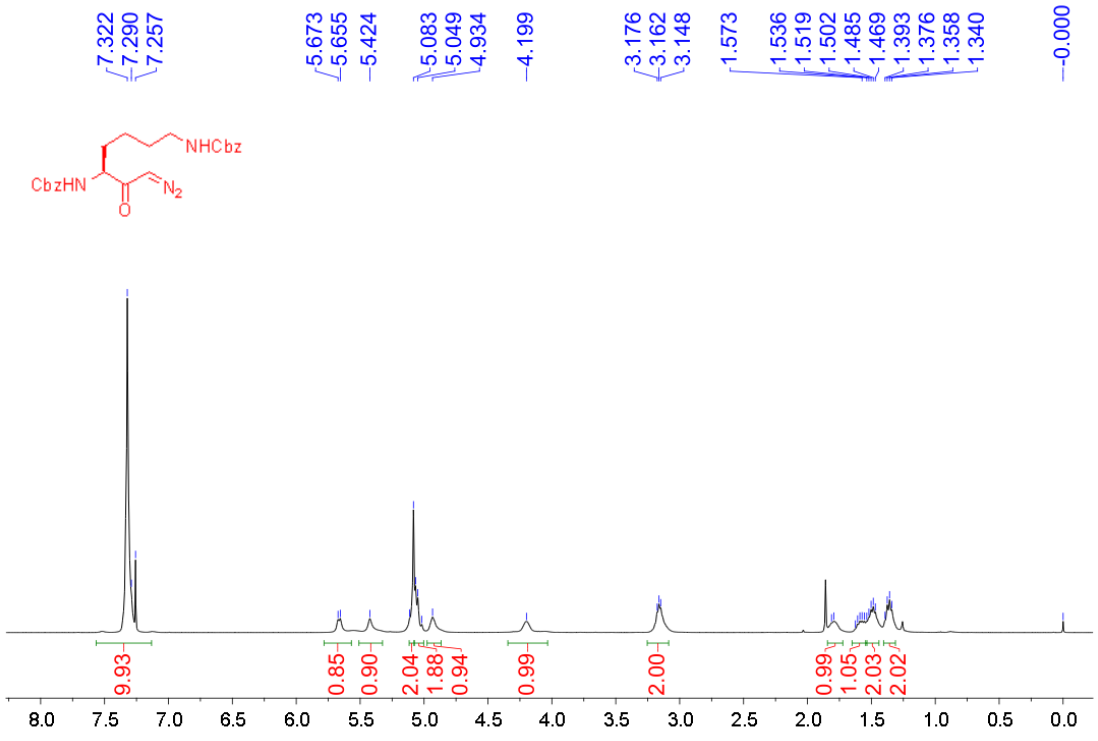
Benzyl (*S*)-1-diazo-5-methyl-2-oxohexan-2-ylcarbamate (**2d**)

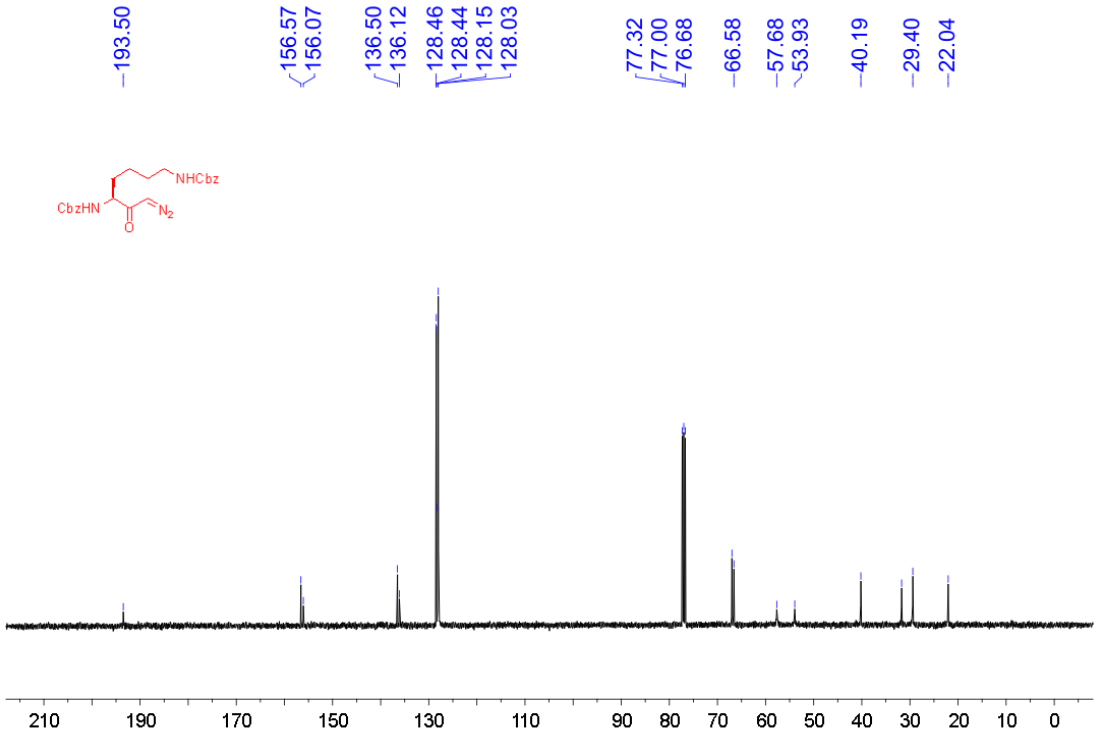


Benzyl (*S*)-1-diazo-4-methyl-2-oxohexan-2-ylcarbamate (**2e**)

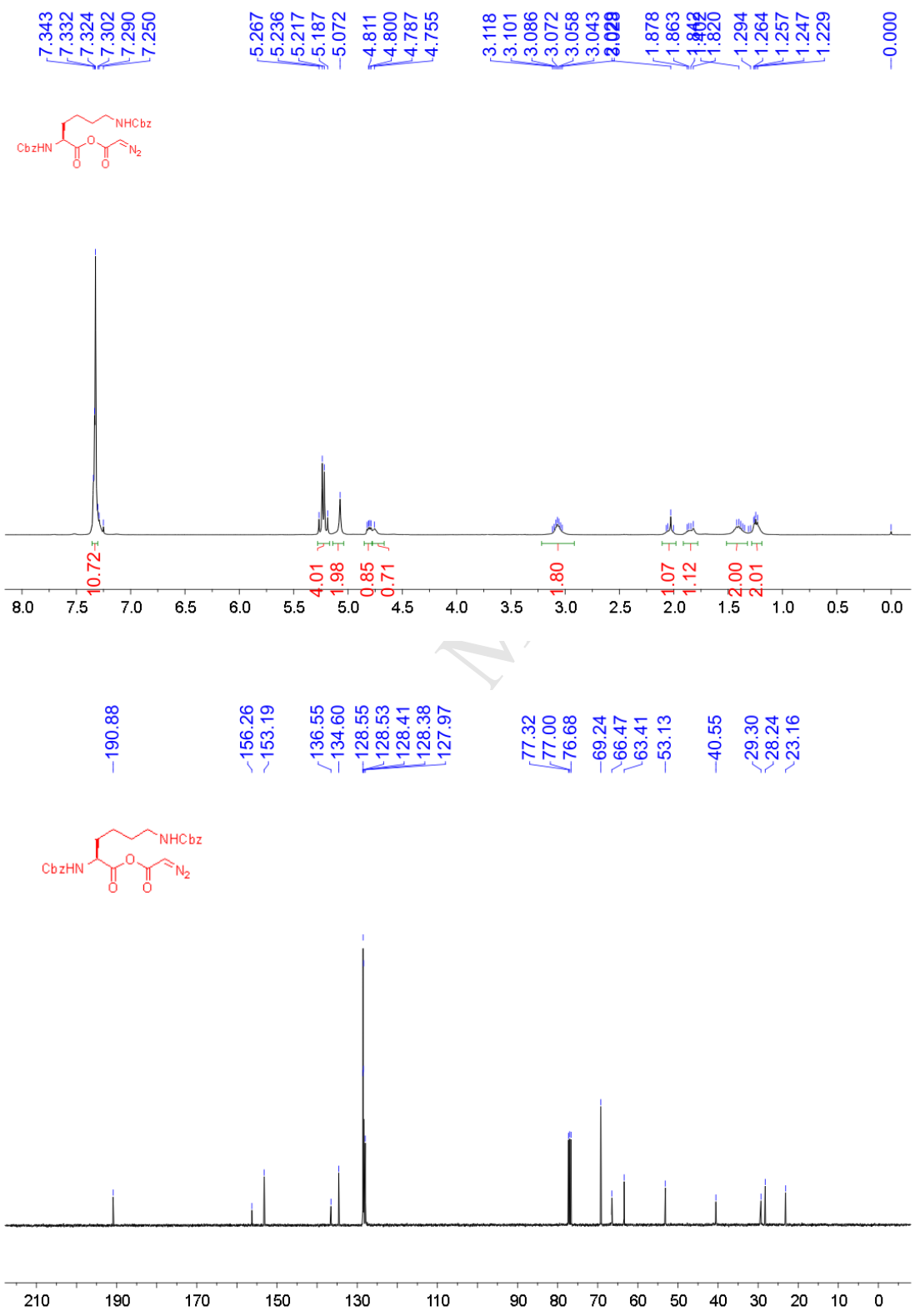


Benzyl (*S*)-7-diazo-6-oxoheptane-1,5-diyldicarbamate (**2f**)

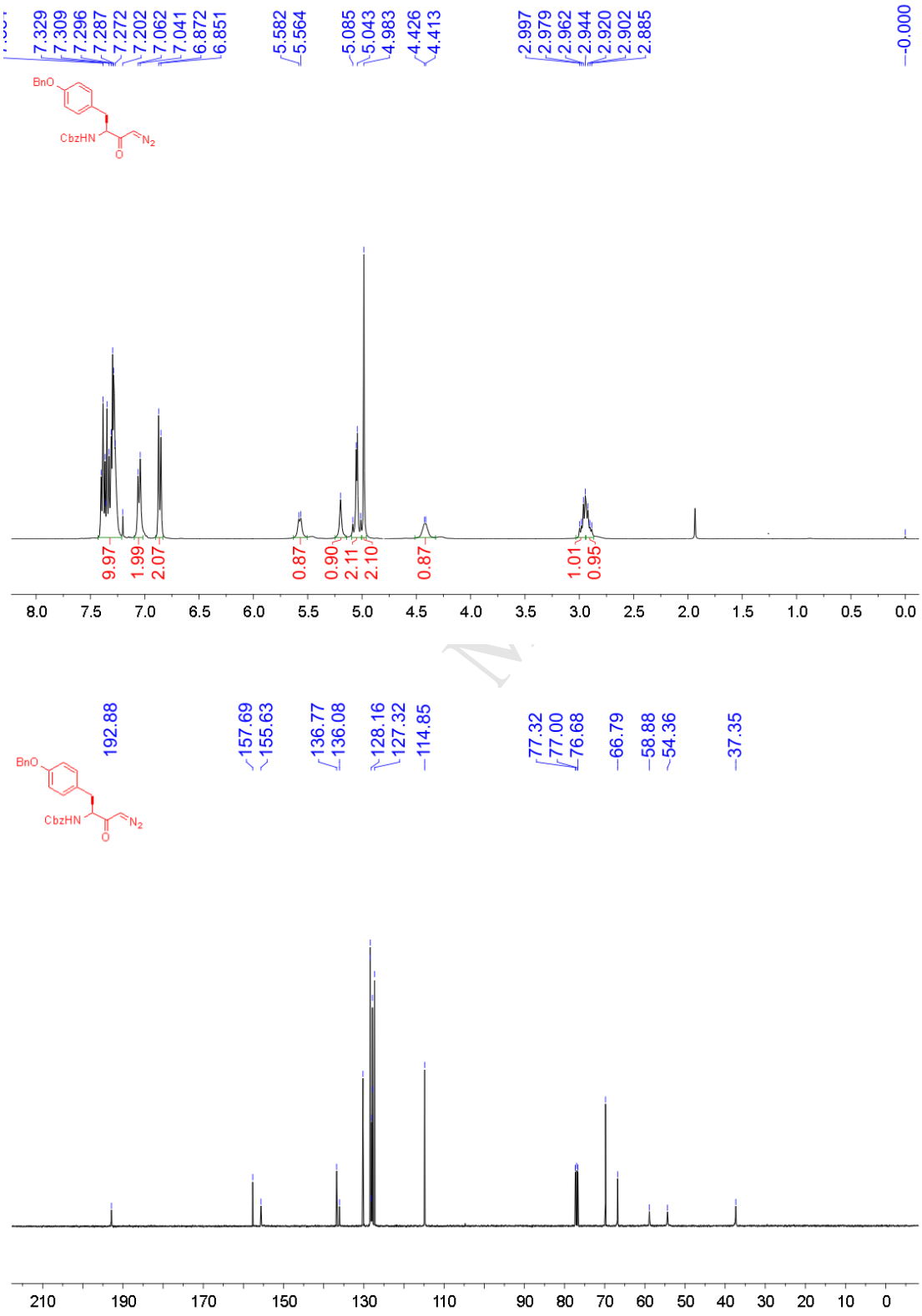




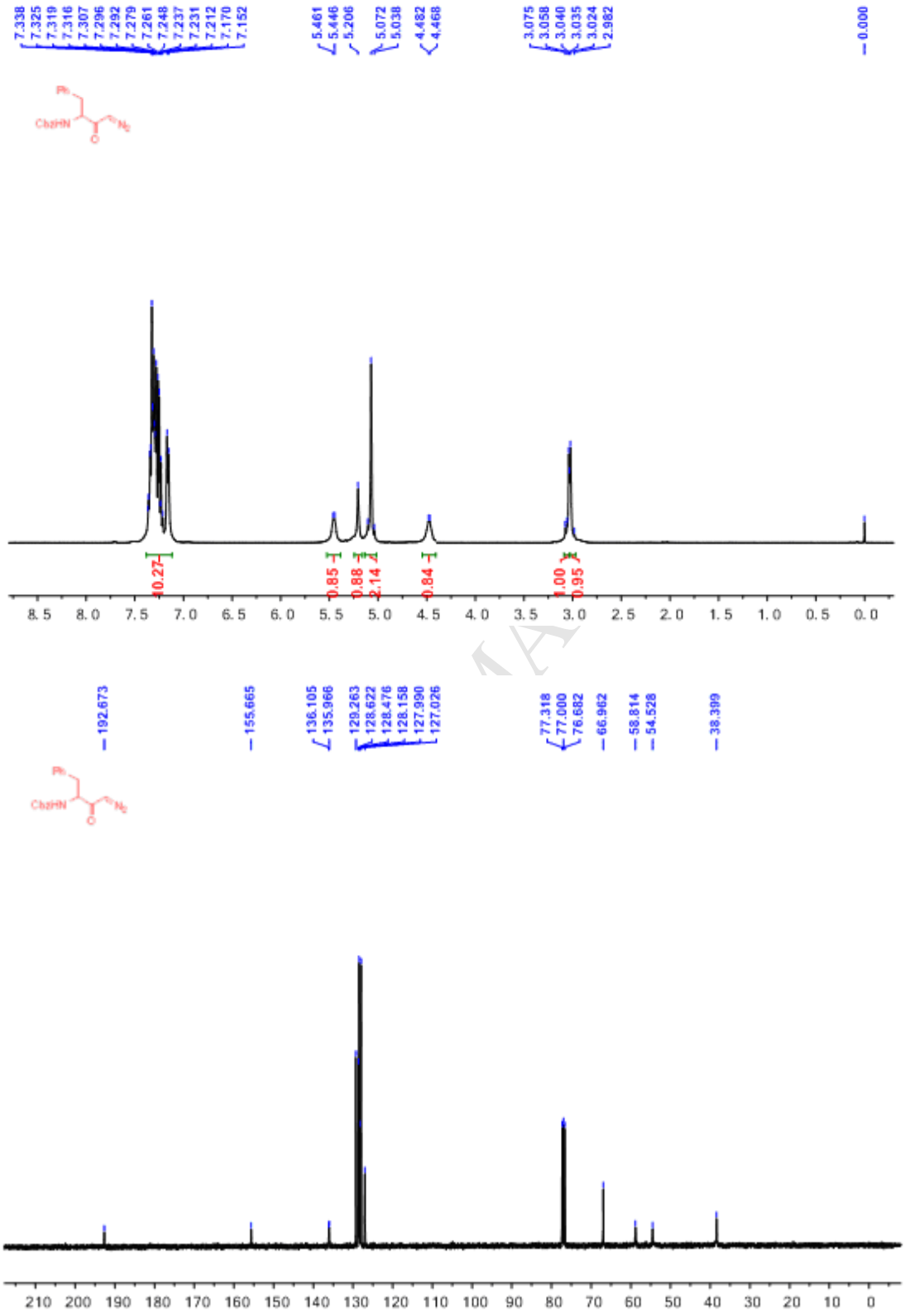
(*S*)-2,6-Bis(benzyloxycarbonylamino)hexanoic 2-diazoacetic anhydride (**2f'**)



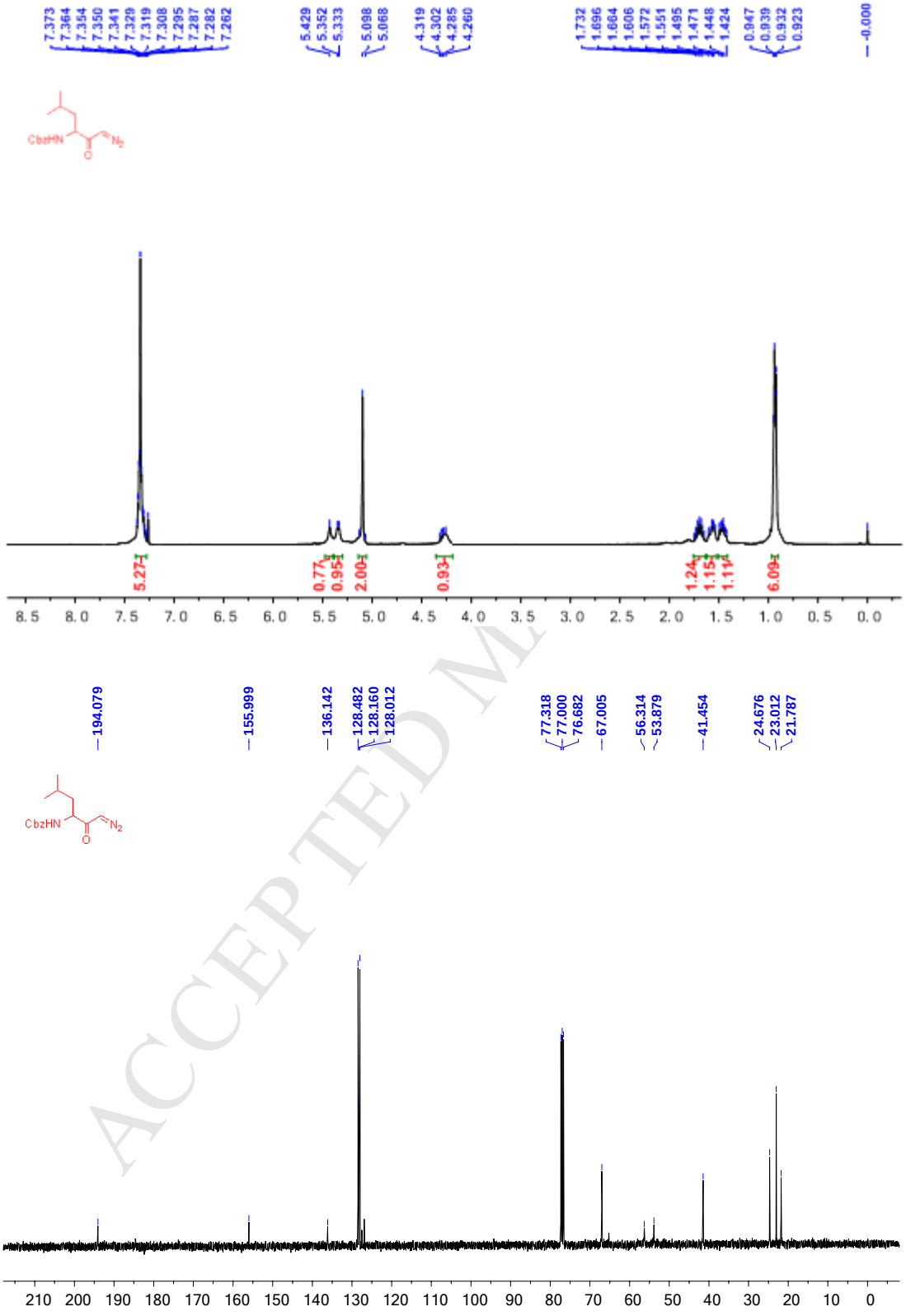
Benzyl (*S*)-1-(4-(benzyloxy)phenyl)-4-diazo-3-oxobutan-2-ylcarbamate (**2g**)



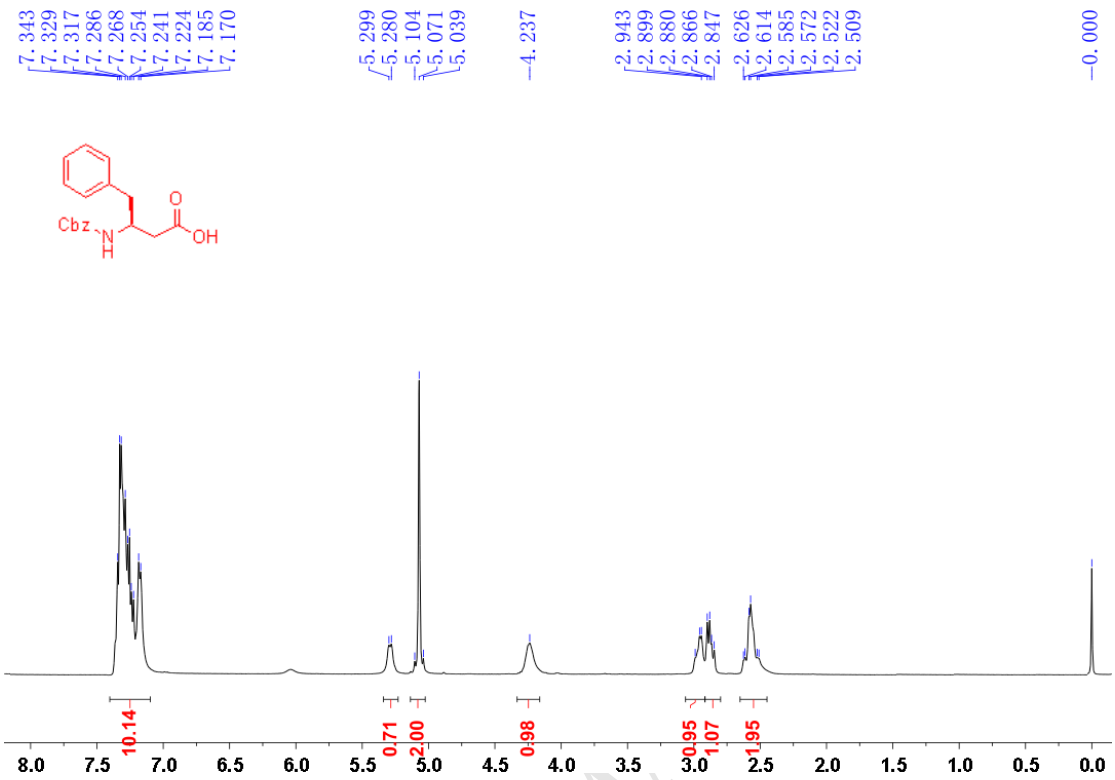
*Benzyl (4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate (rac-**2a**)*

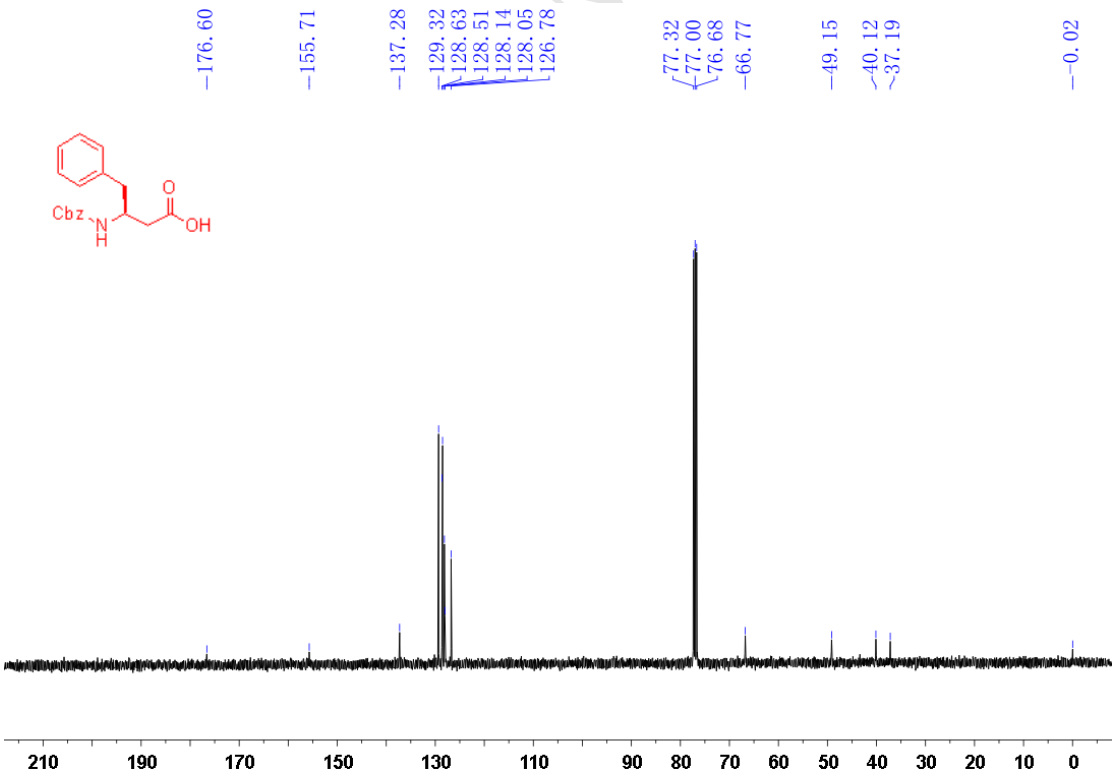


*Benzyl (1-diazo-5-methyl-2-oxohexan-3-yl)carbamate (rac-**2d**)*

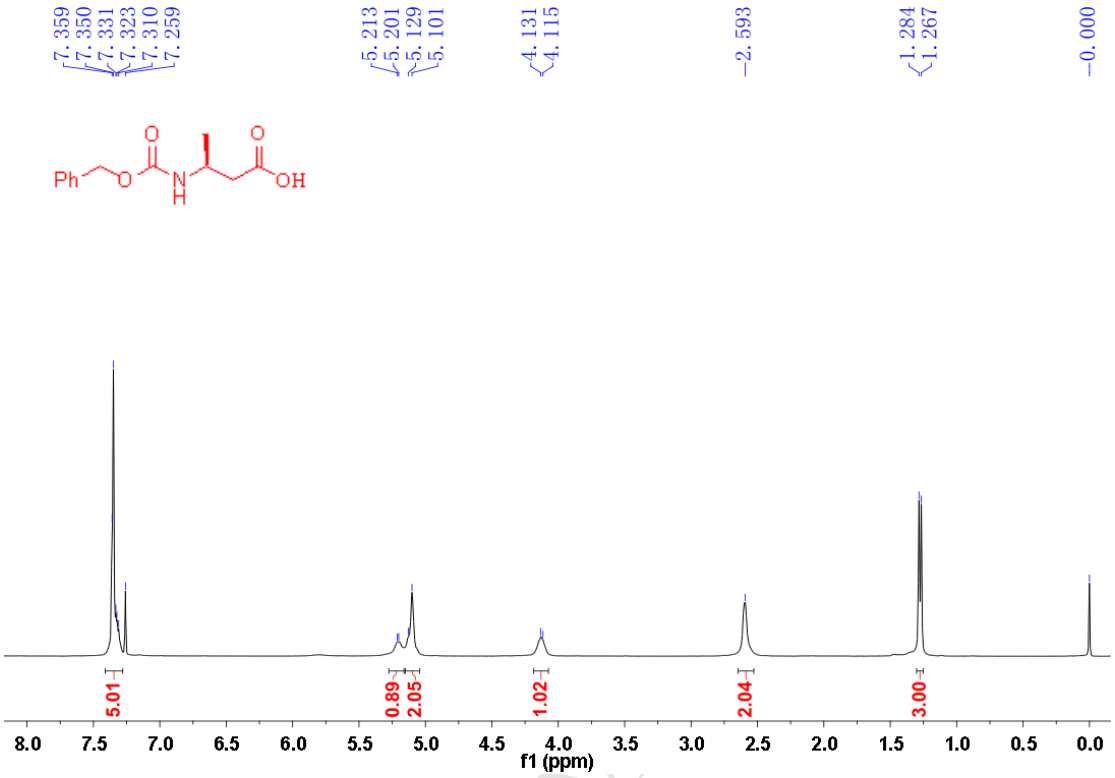


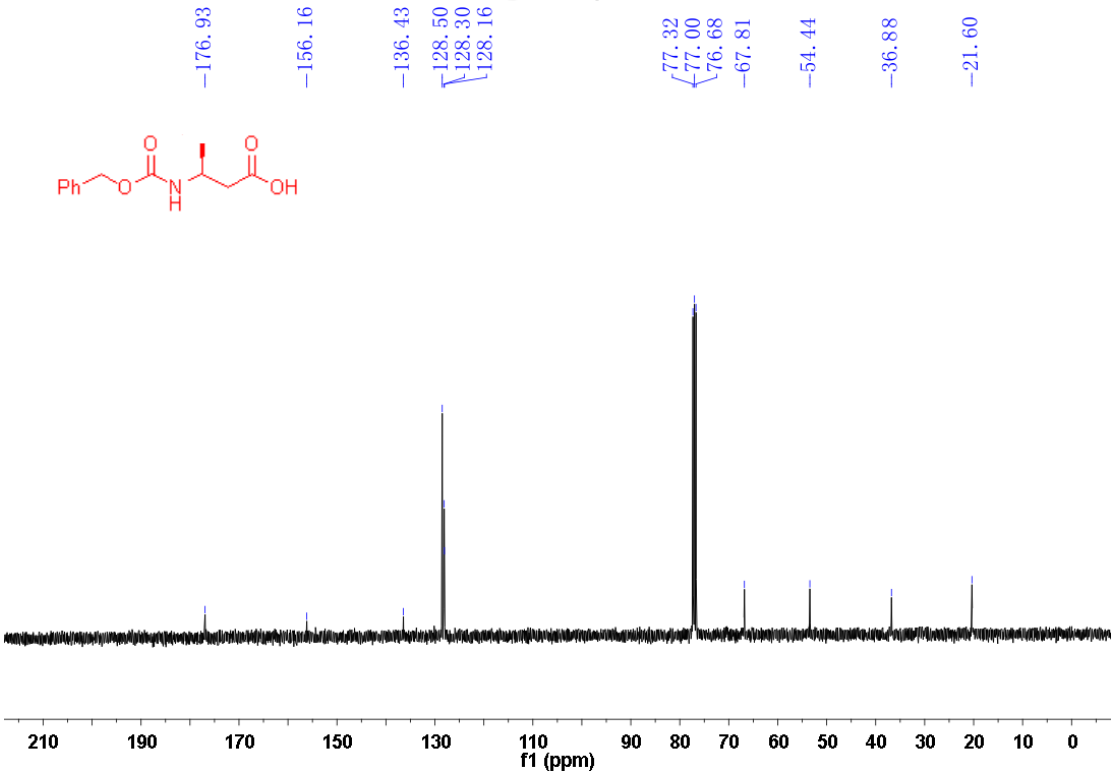
(*S*)-3-(Benzyloxycarbonylamino)-4-phenylbutanoic acid (**3a)**



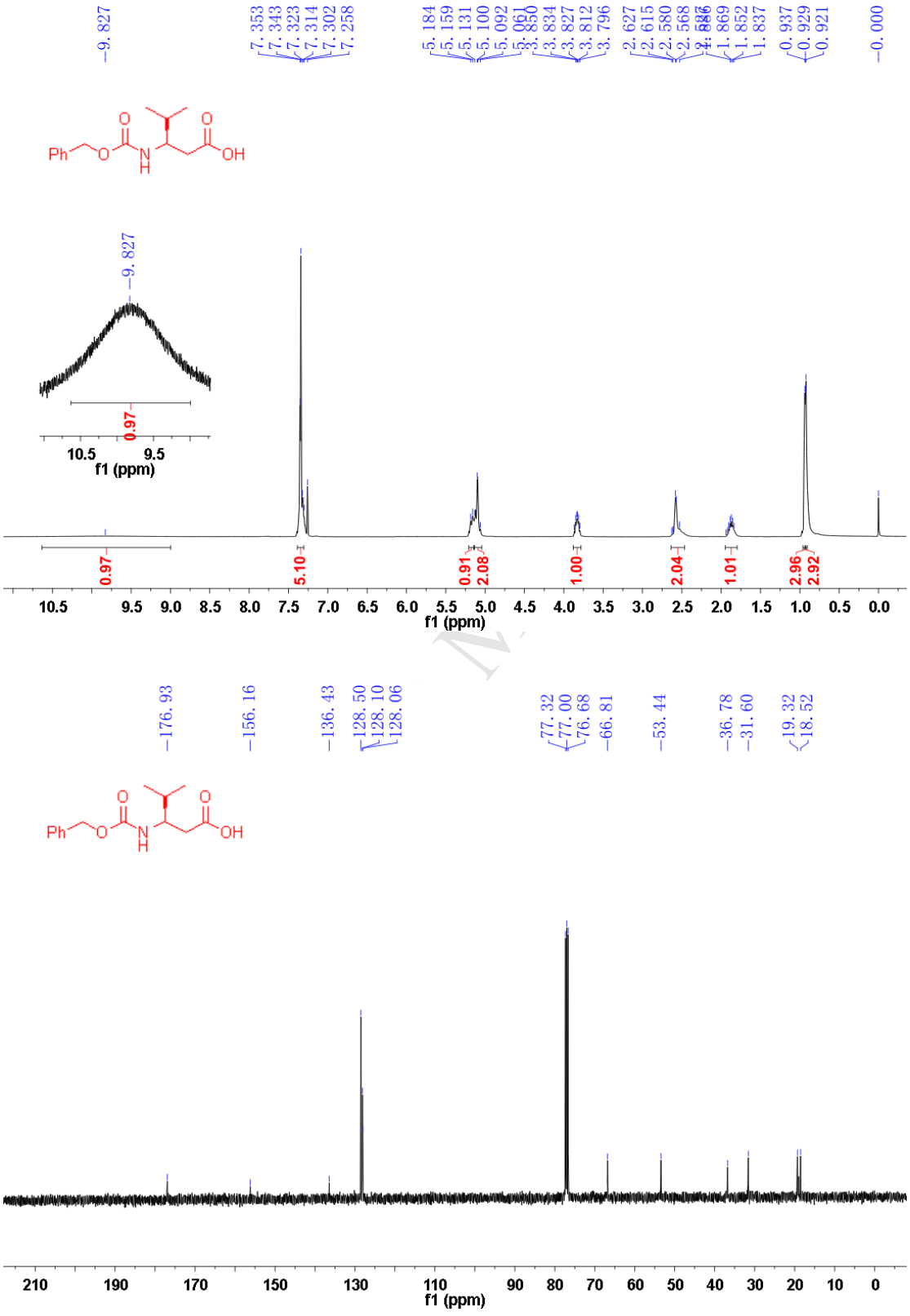


(*S*)-3-(Benzyloxycarbonylamino)butanoic acid (**3b**)

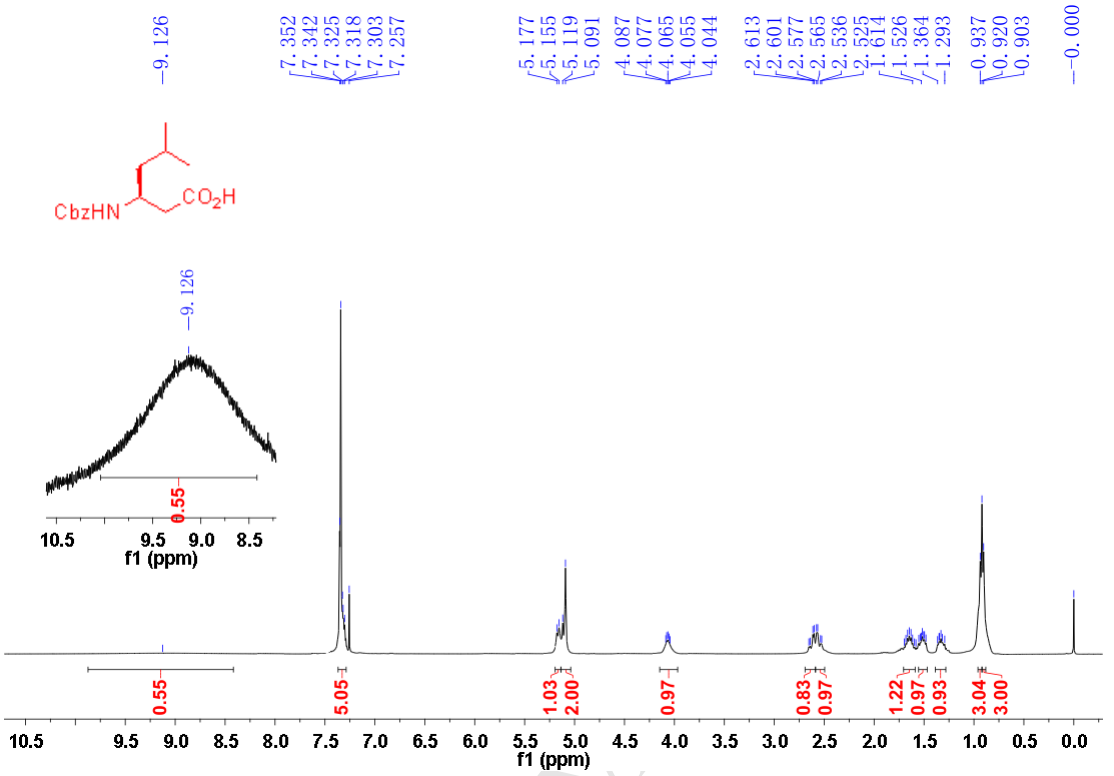


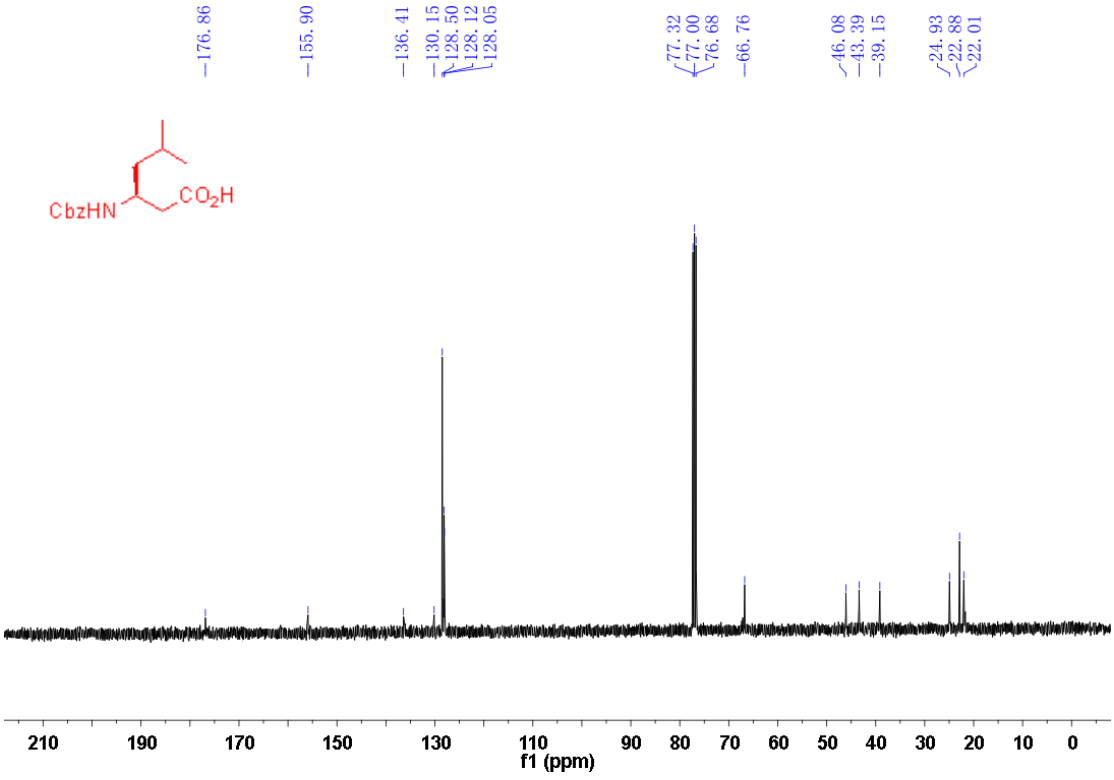


(*R*)-3-(Benzyloxycarbonylamino)-4-methylpentanoic acid (**3c**)

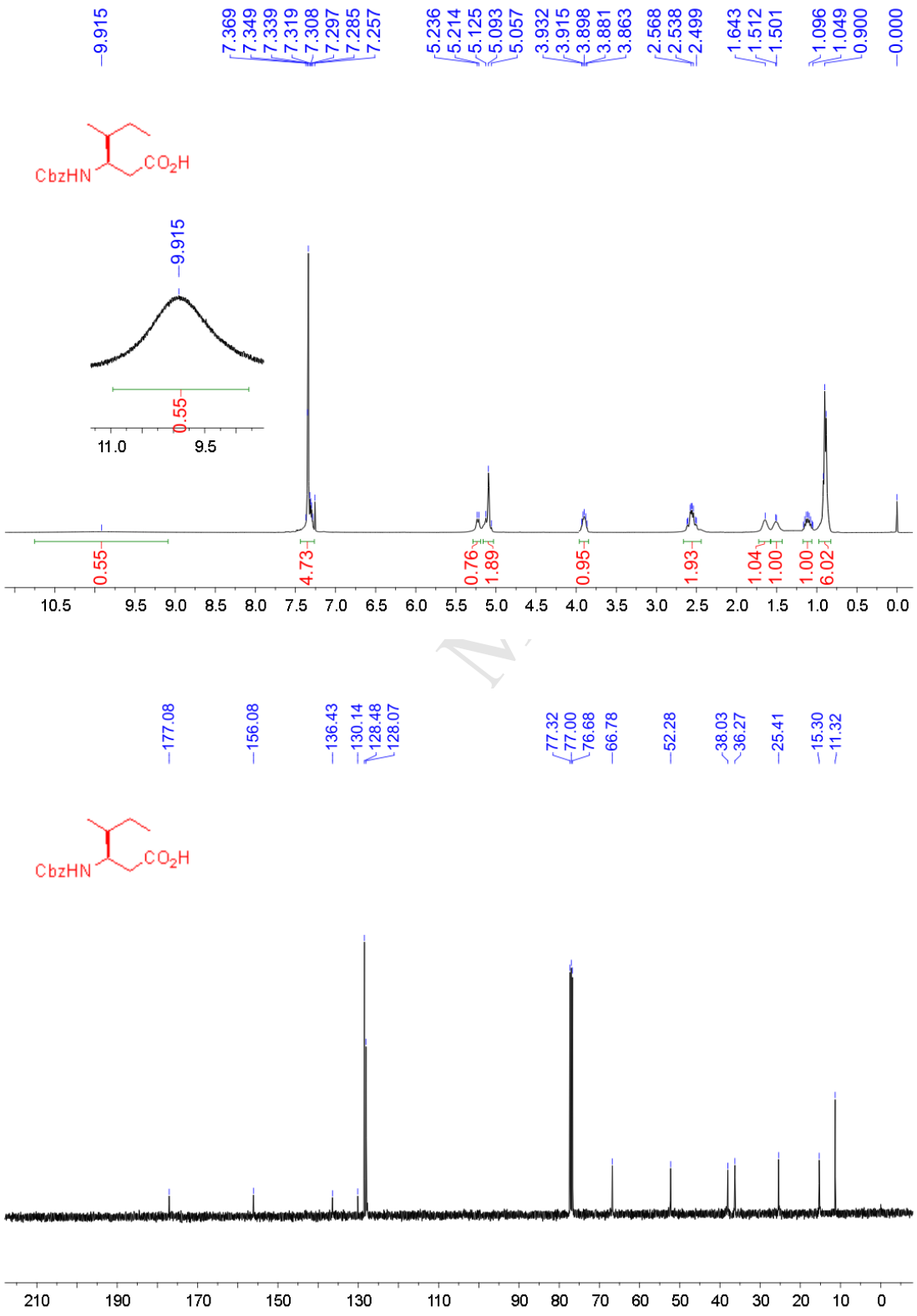


(*S*)-3-(Benzyloxycarbonylamino)-5-methylhexanoic acid (**3d**)

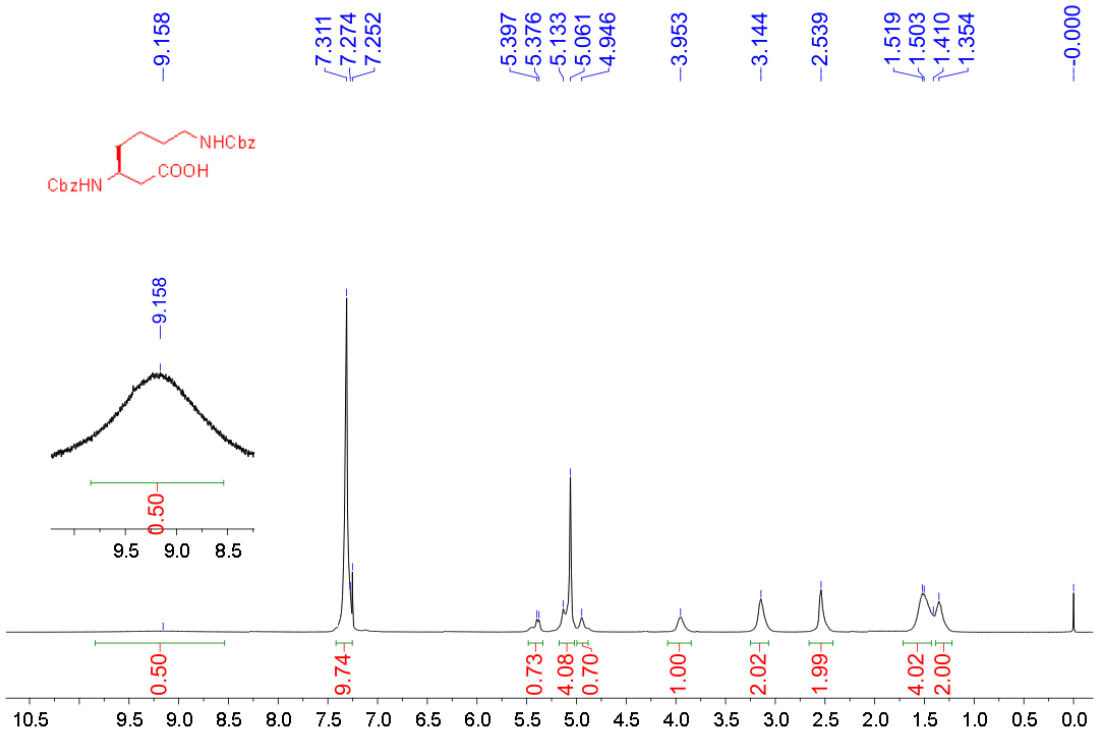


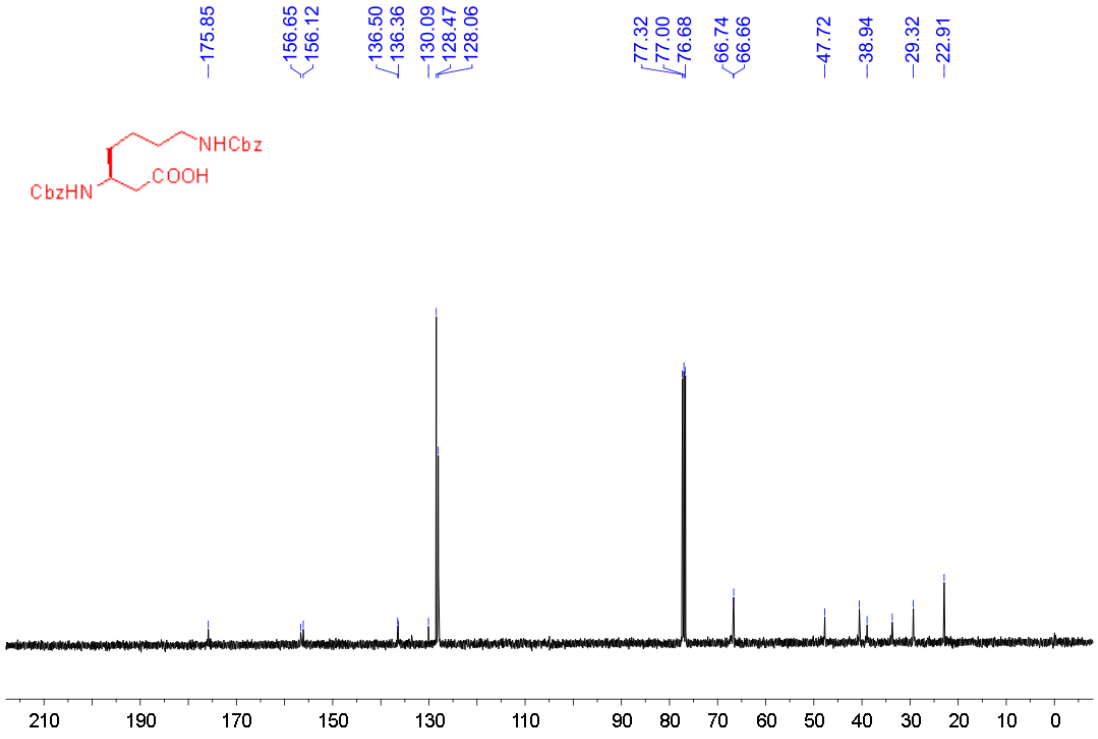


(3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-methylhexanoic acid (**3e**)

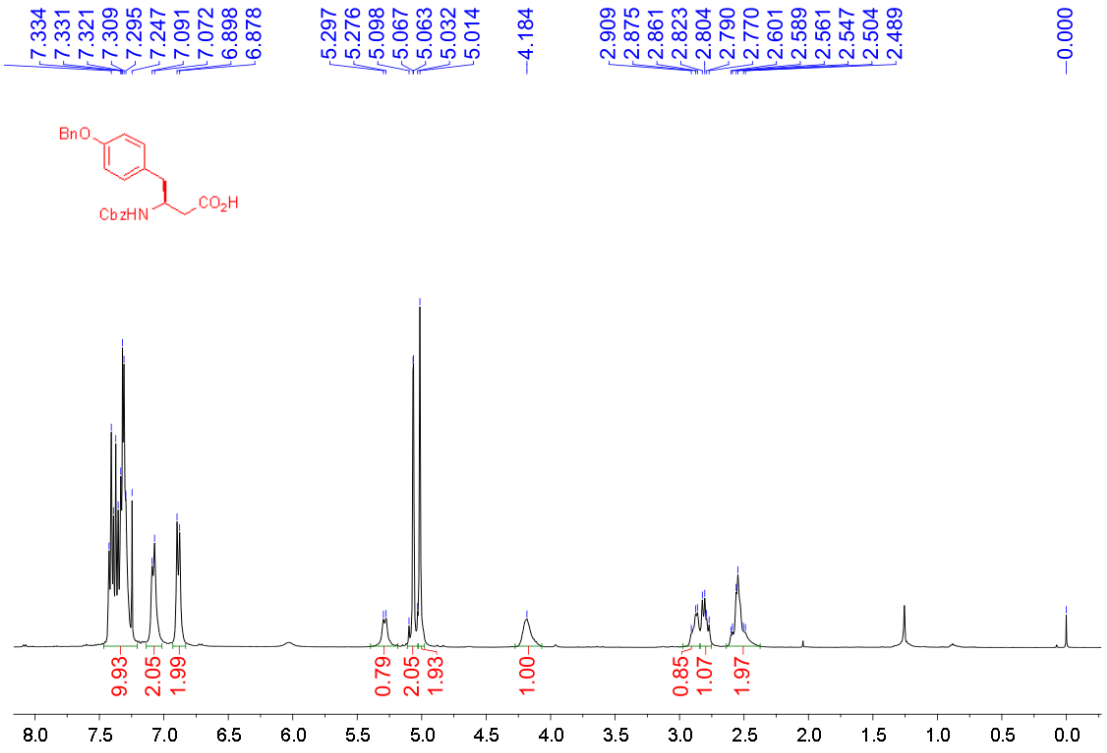


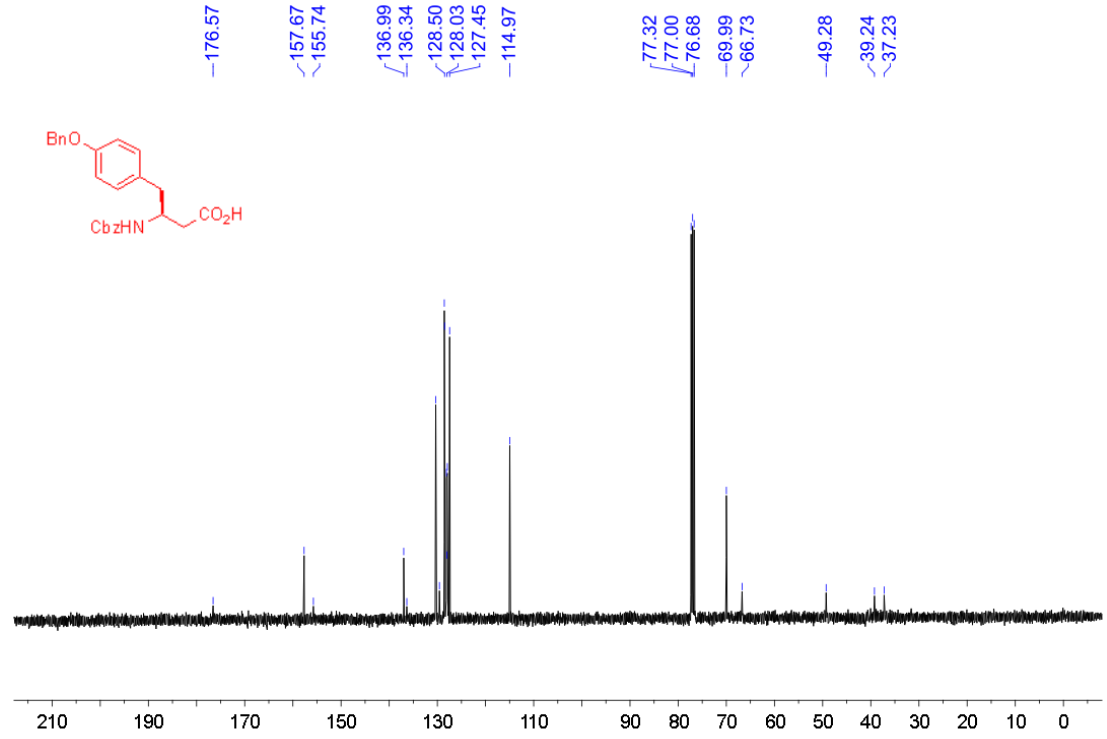
(*S*)-3,7-Di(benzyloxycarbonylamino)heptanoic acid (**3f**)



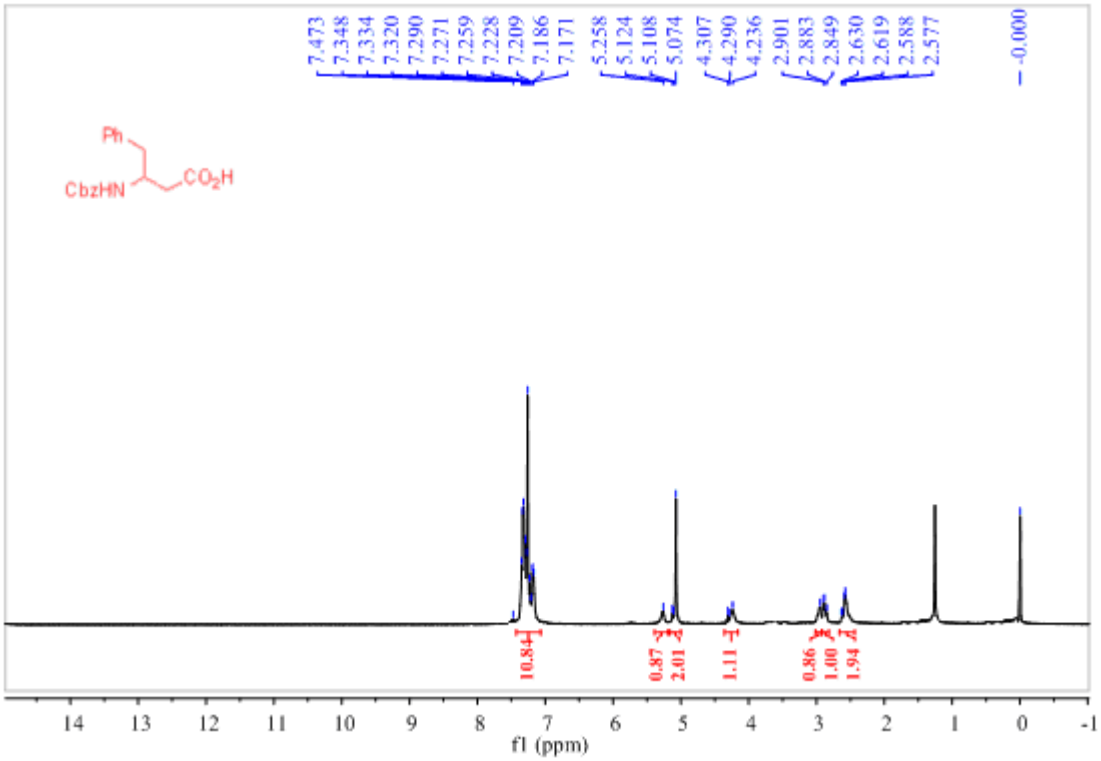


(*S*)-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butanoic acid (**3g**)

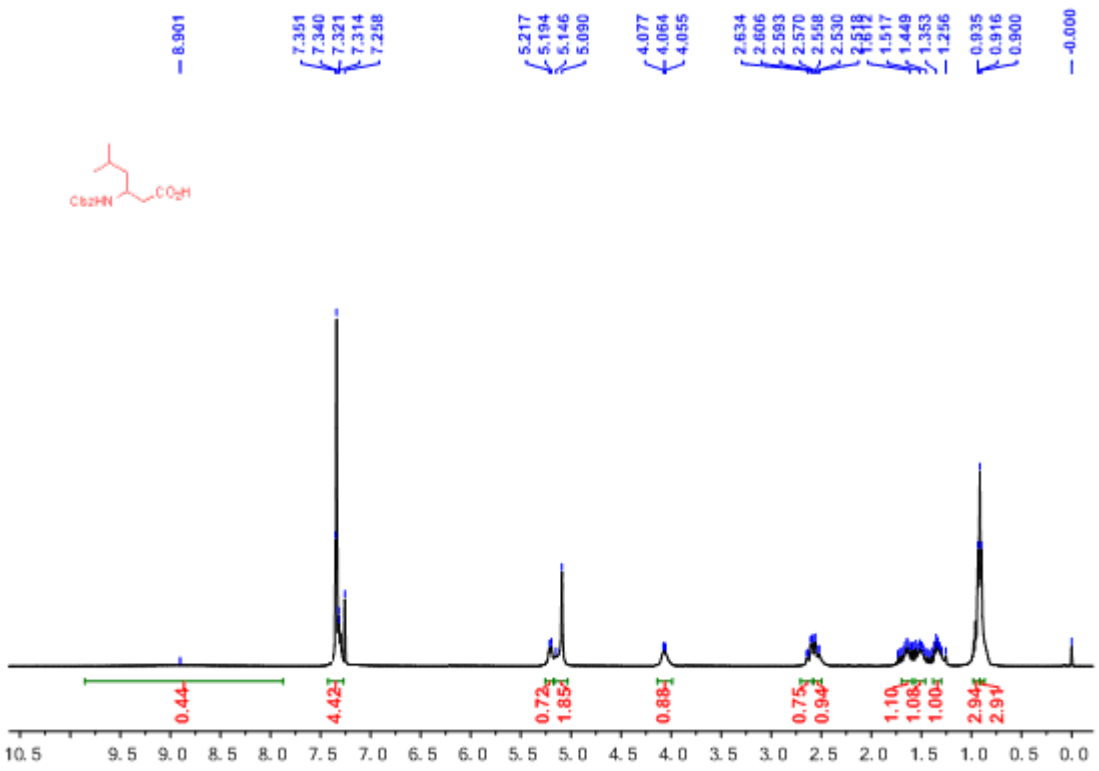




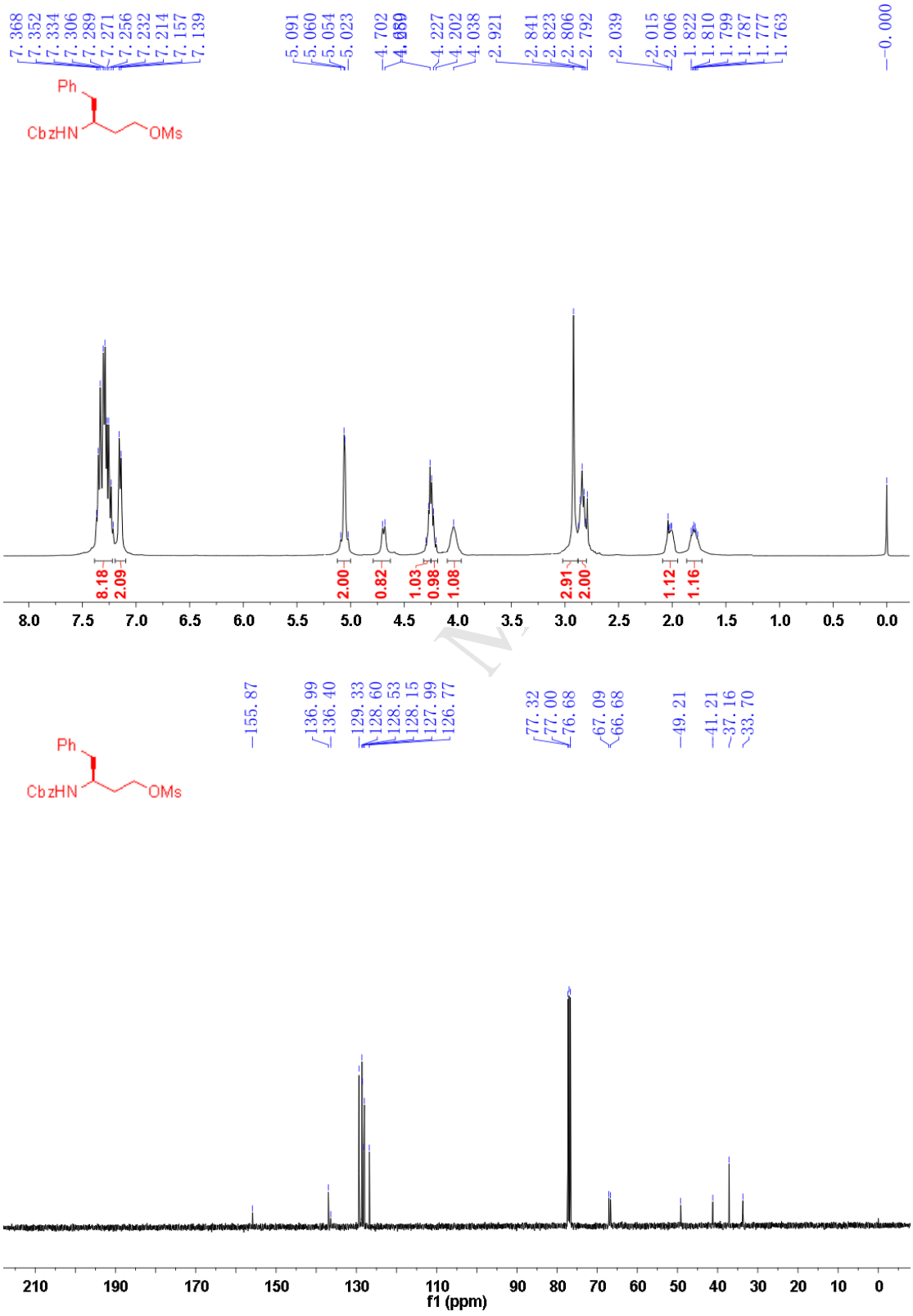
3-(Benzyloxycarbonylamino)-4-phenylbutanoic acid (*rac*-**3a**)



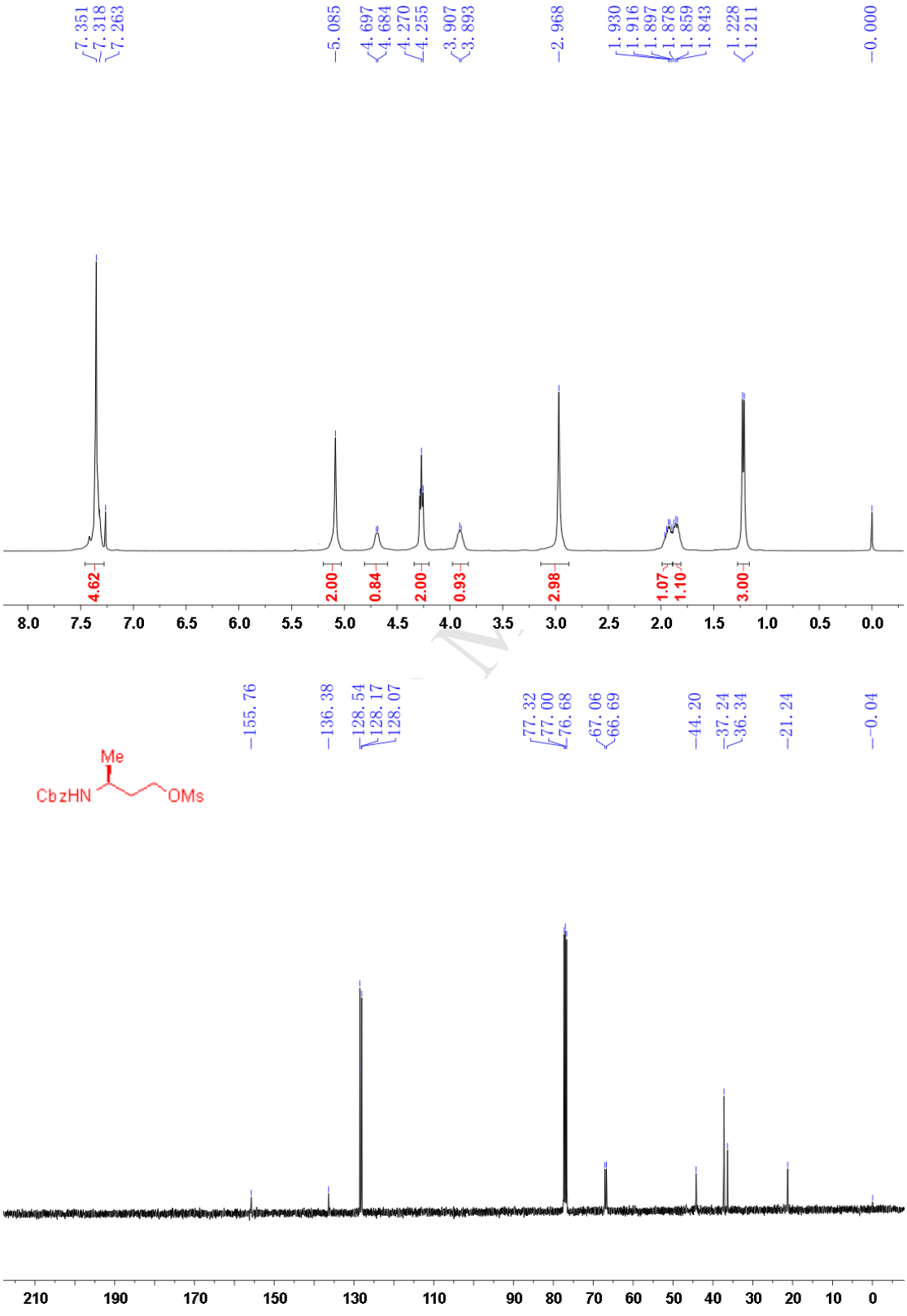
3-(Benzyloxycarbonylamino)-5-methylhexanoic acid (*rac*-**3d**)



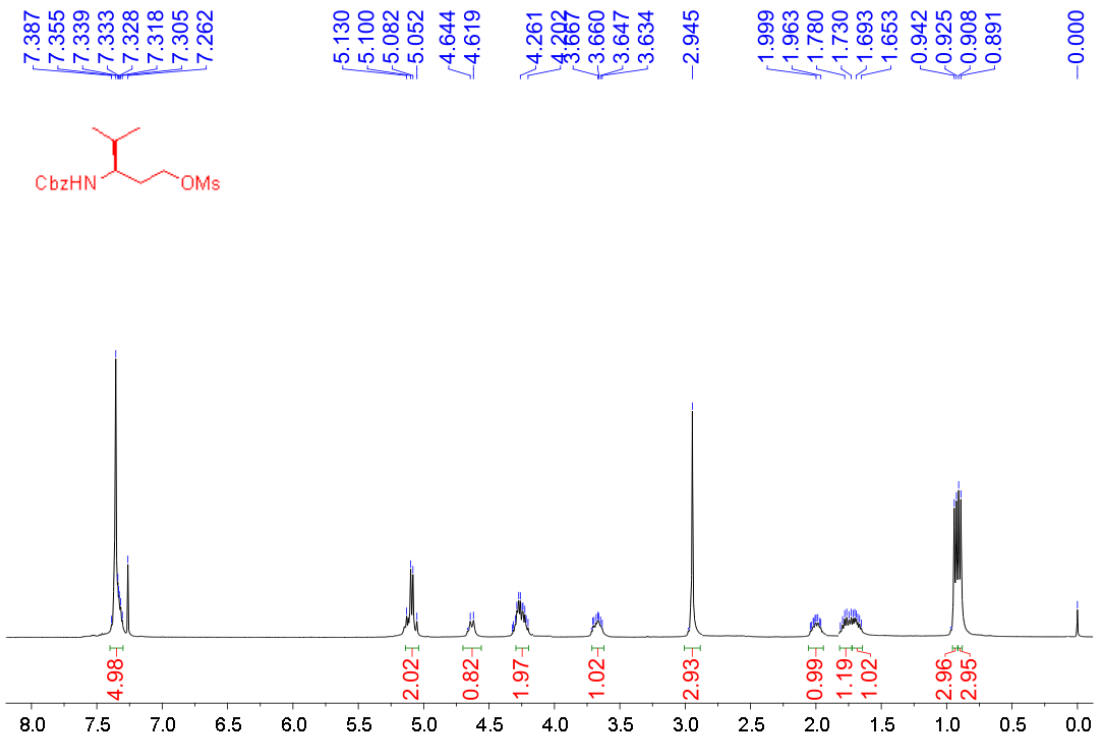
(*S*)-3-(Benzyloxycarbonylamino)-4-phenylbutyl methanesulfonate (**4a**)

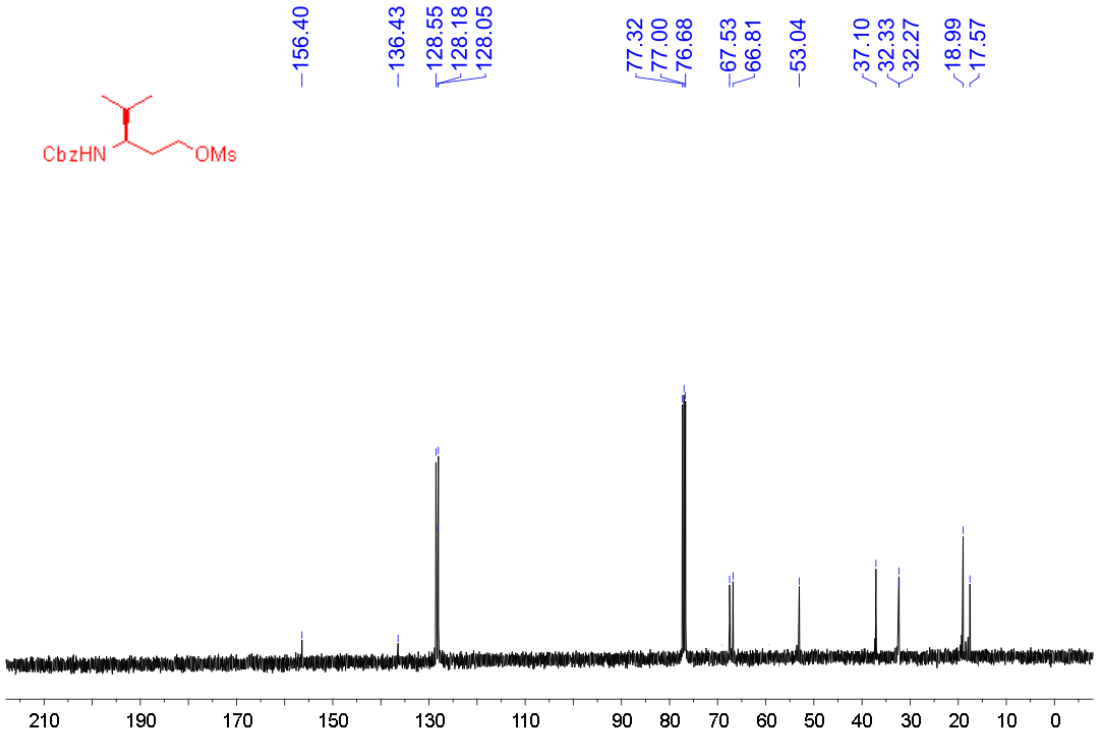


(*S*)-3-(Benzyloxycarbonylamino)butyl methanesulfonate (**4b**)

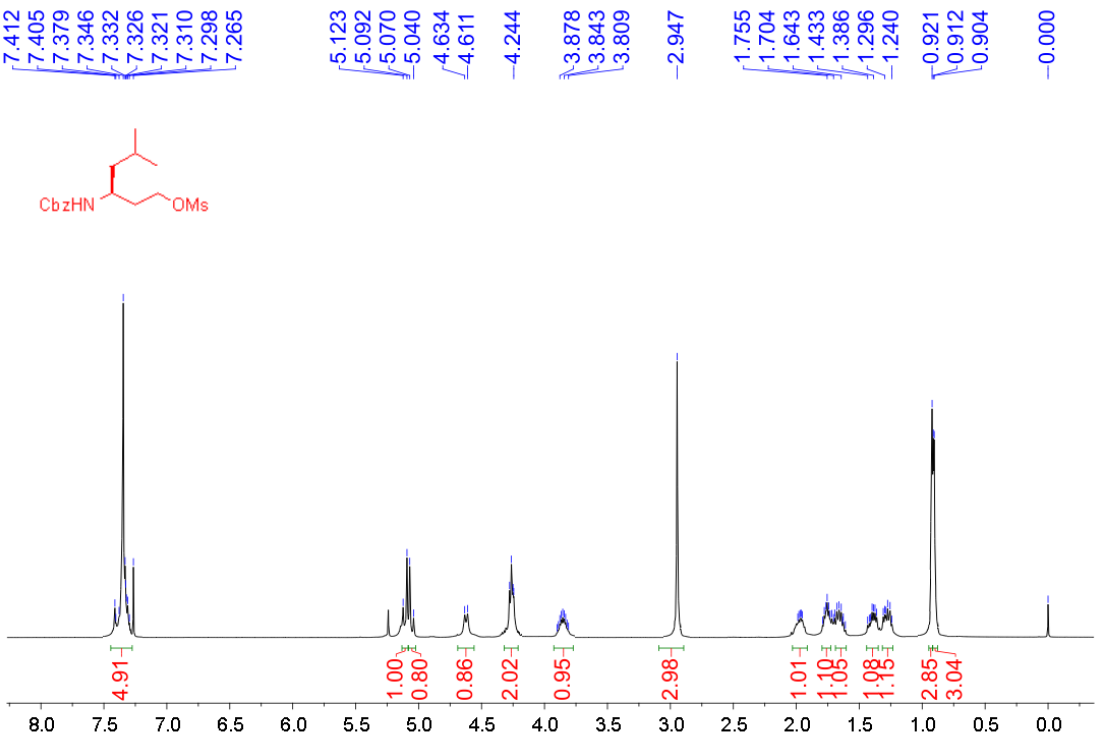


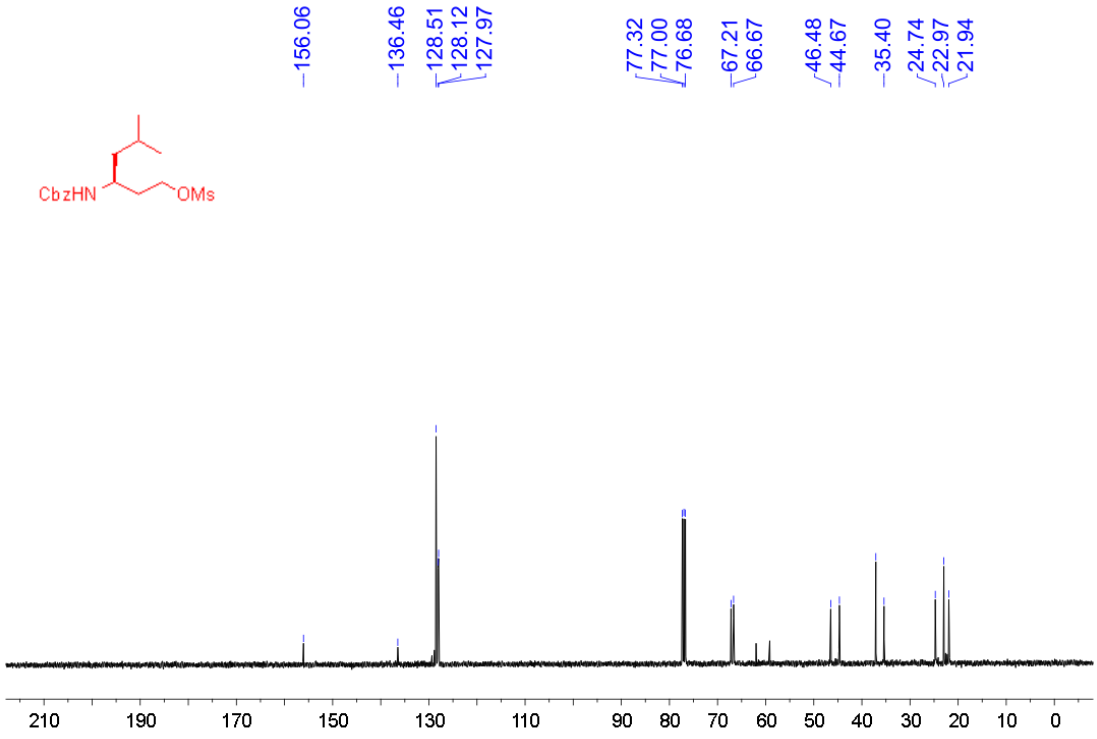
(*R*)-3-(Benzyloxycarbonylamino)-4-methylpentyl methanesulfonate (**4c**)



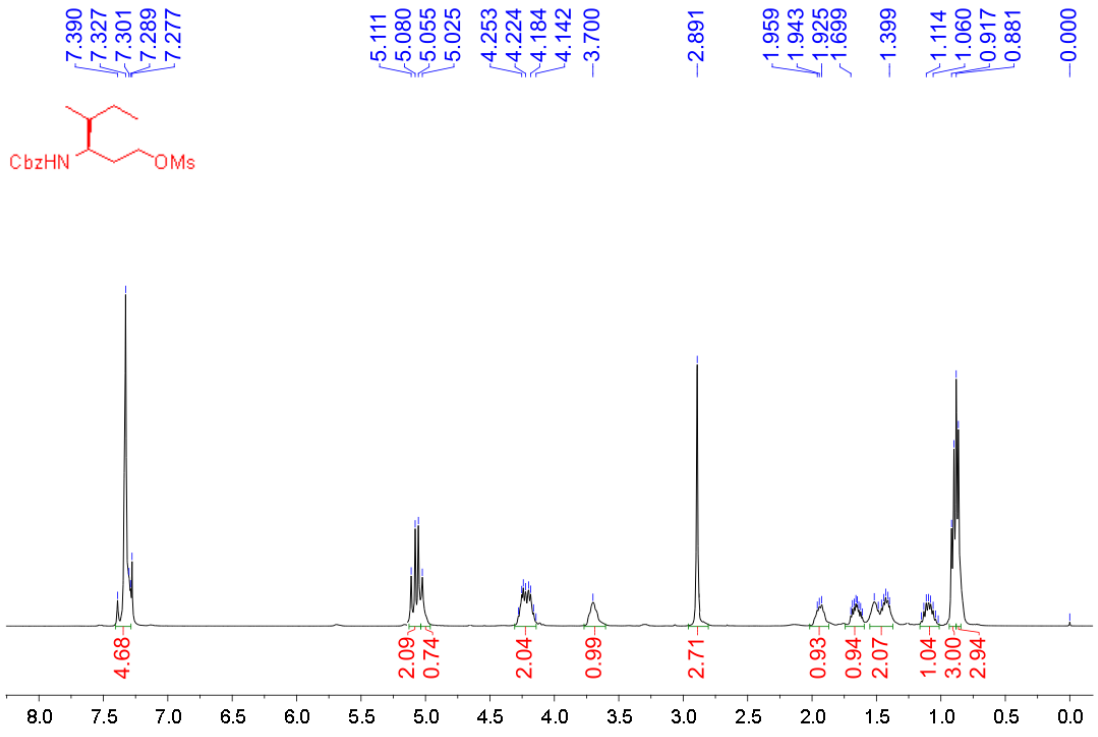


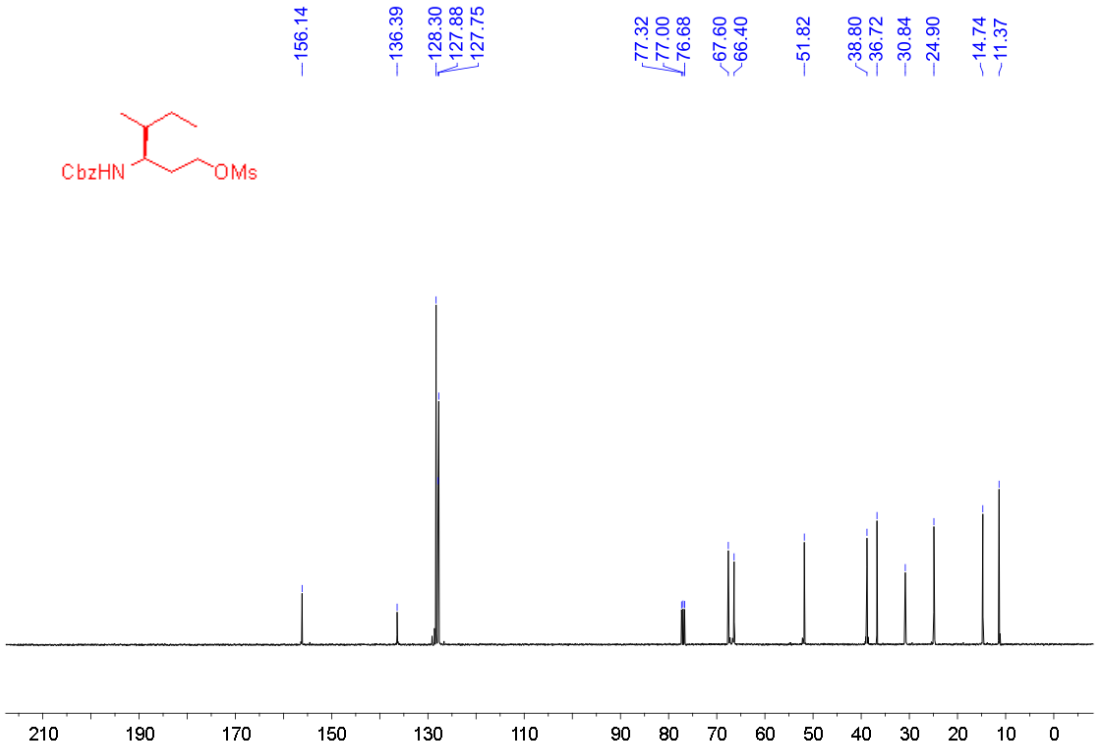
(*S*)-3-(Benzyloxycarbonylamino)-5-methylhexyl methanesulfonate (**4d**)



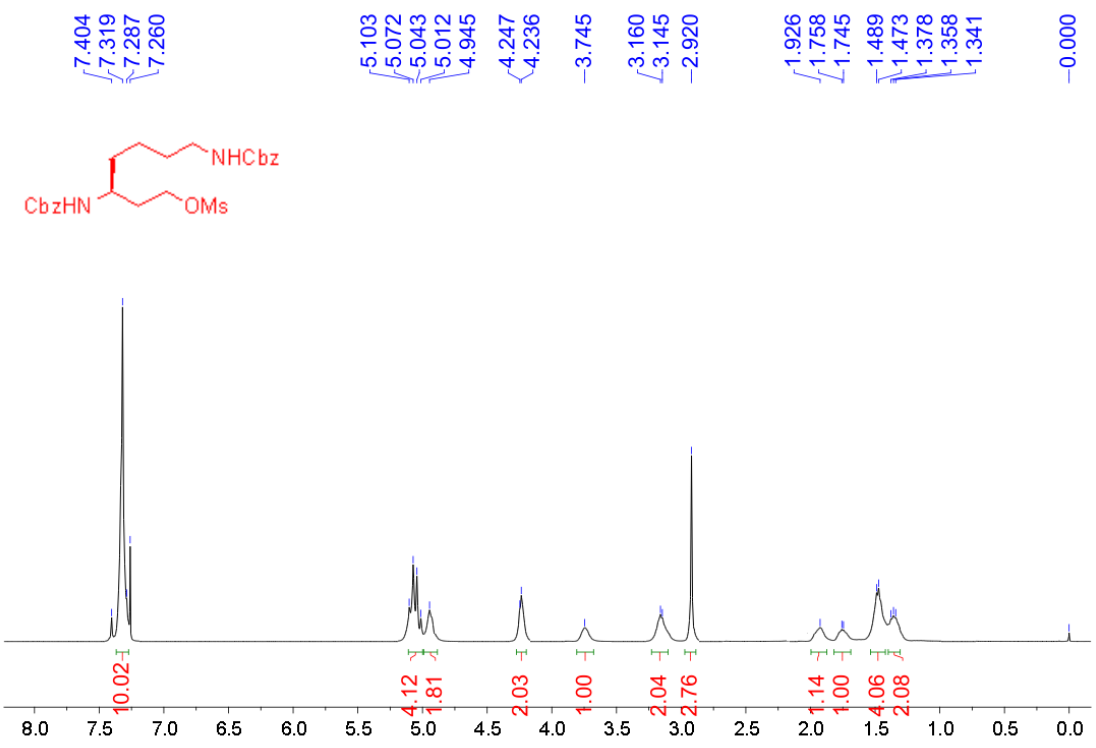


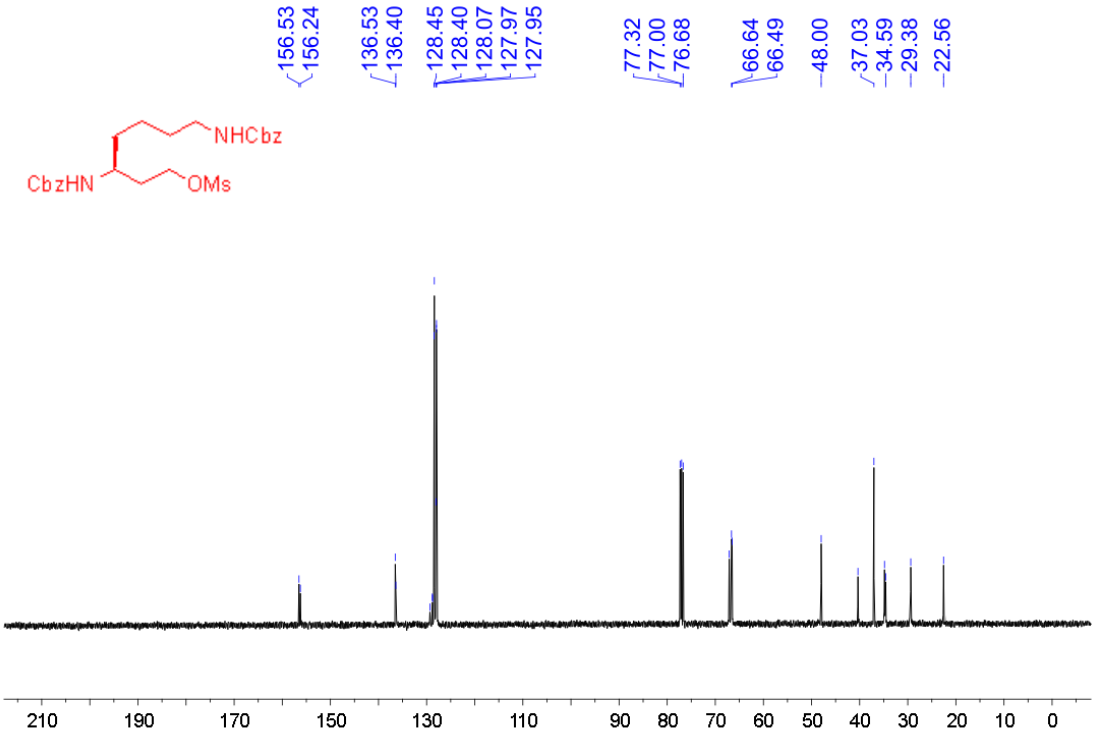
(3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-methylhexyl methanesulfonate (**4e**)



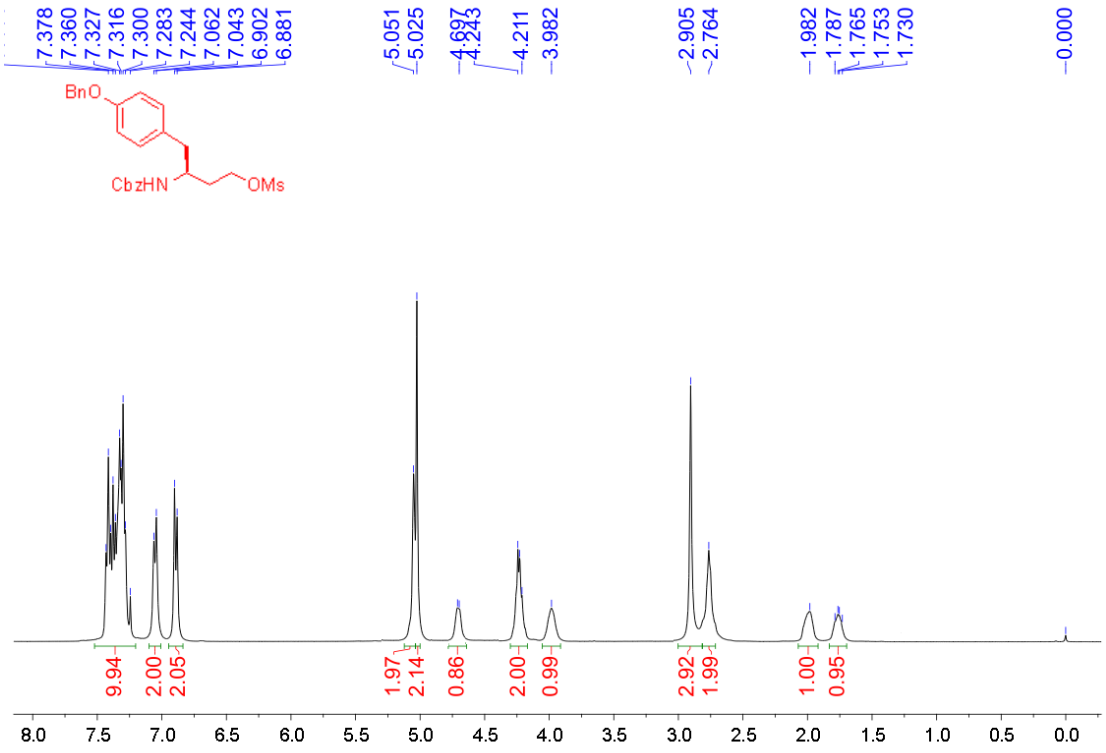


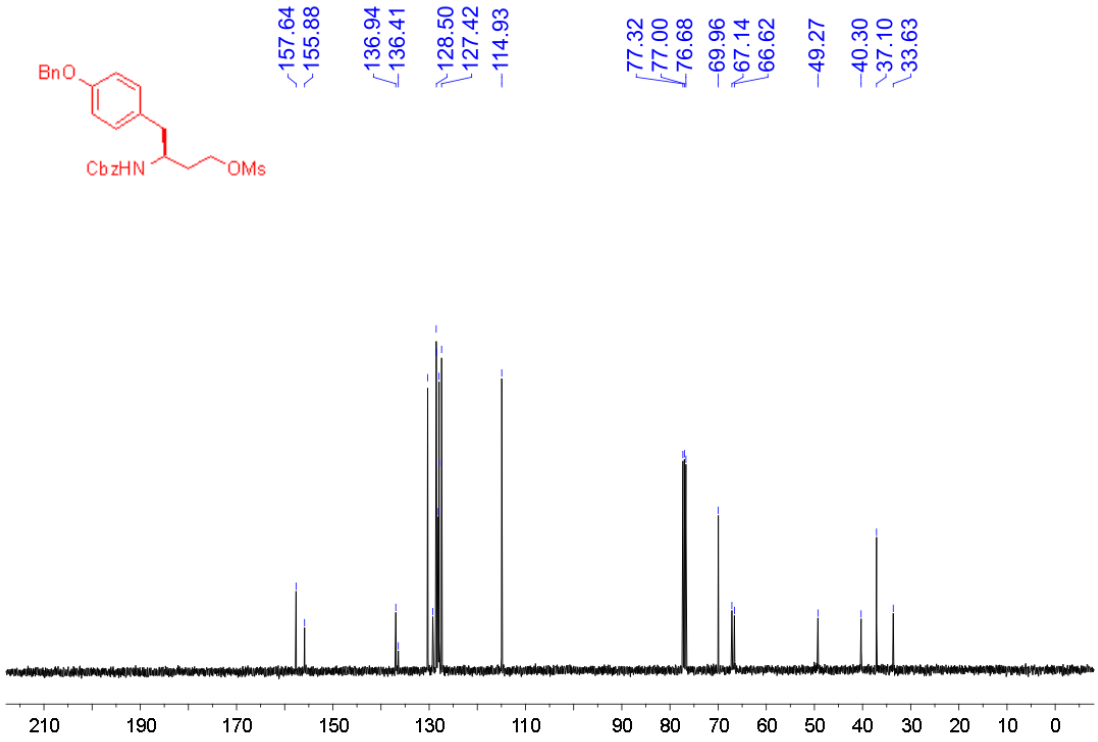
(*S*)-3,7-Di(benzyloxycarbonylamino)heptyl methanesulfonate (**4f**)



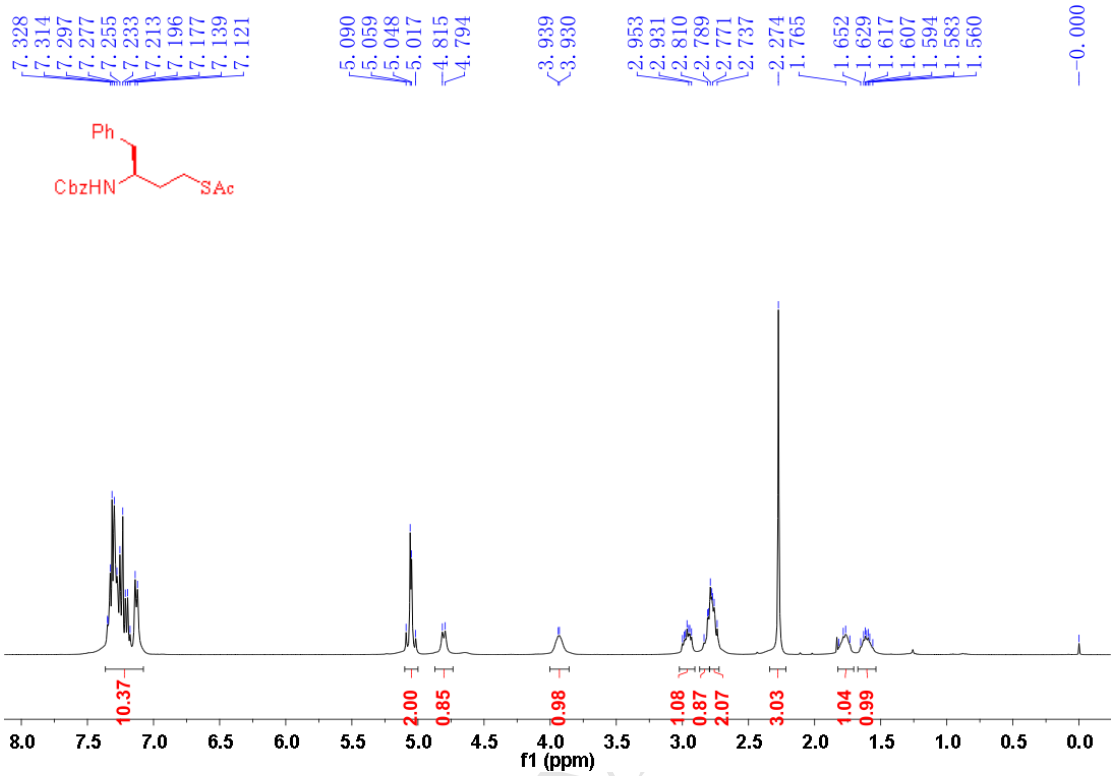


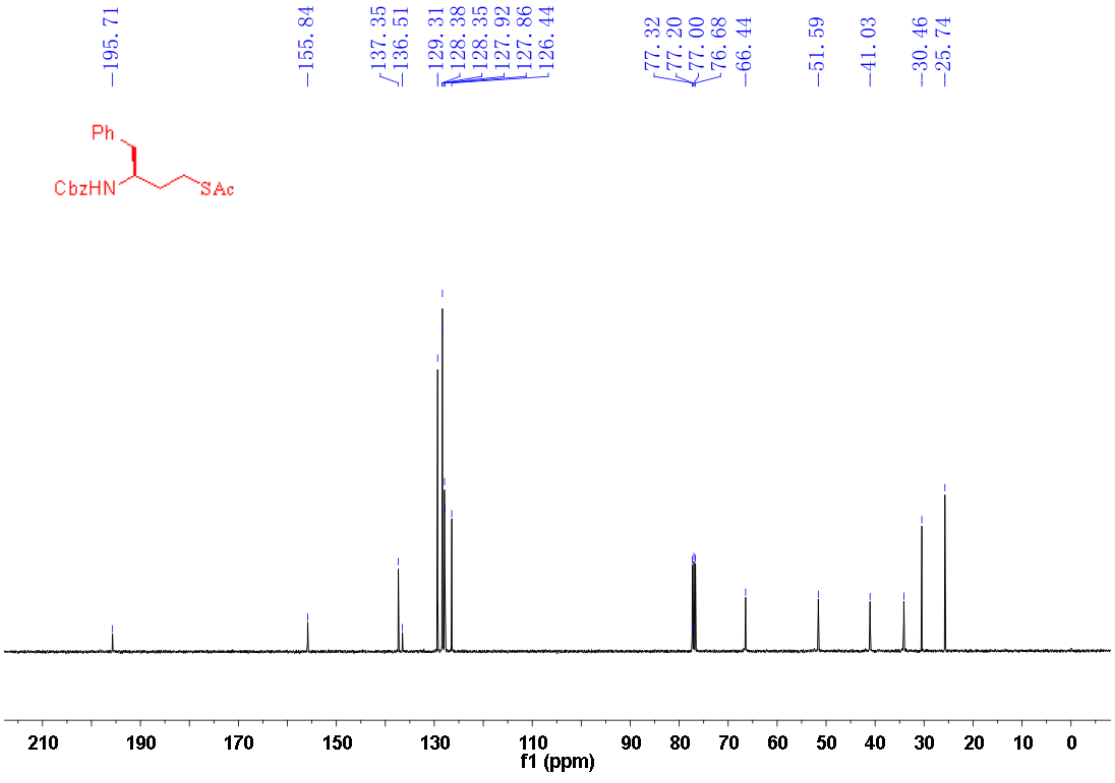
(*S*)-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butyl methanesulfonate (**4g**)



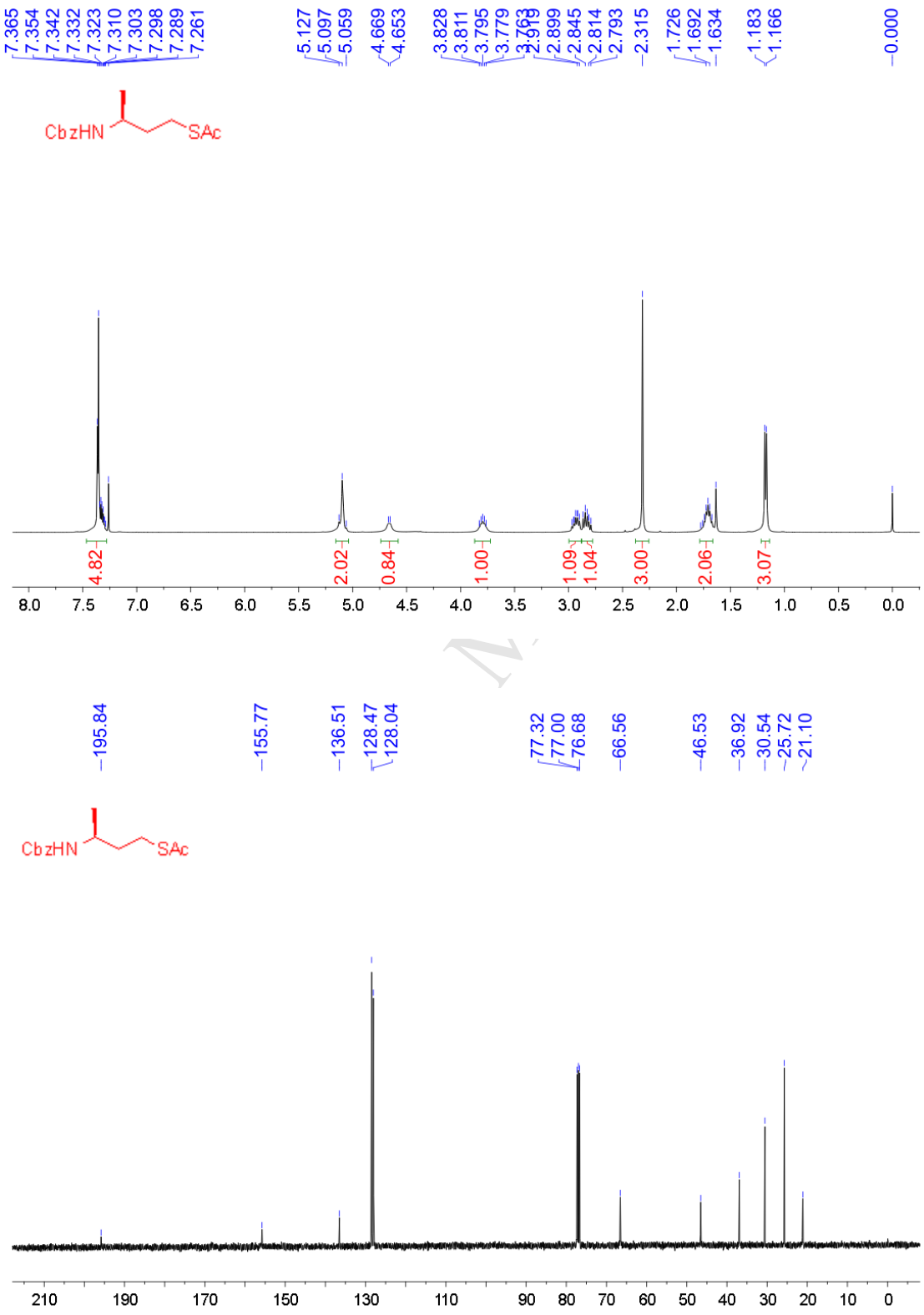


(*S*)-*S*-3-(Benzyloxycarbonylamino)-4-phenylbutyl ethanethioate (**5a**)

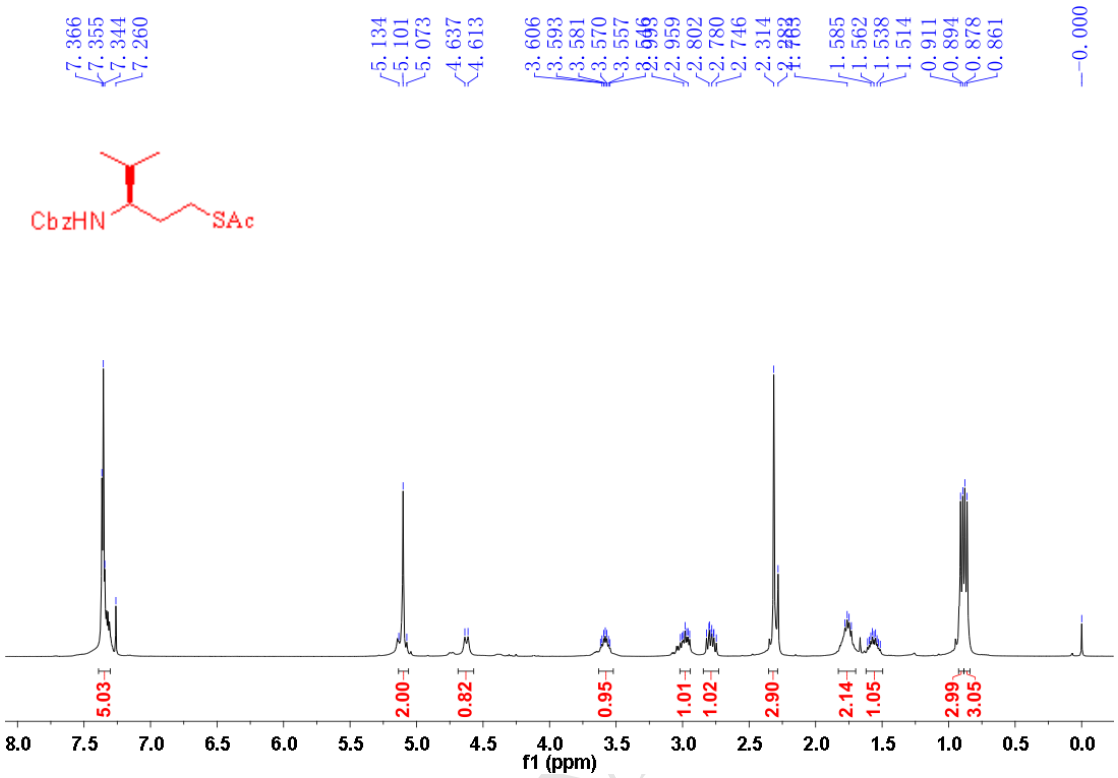


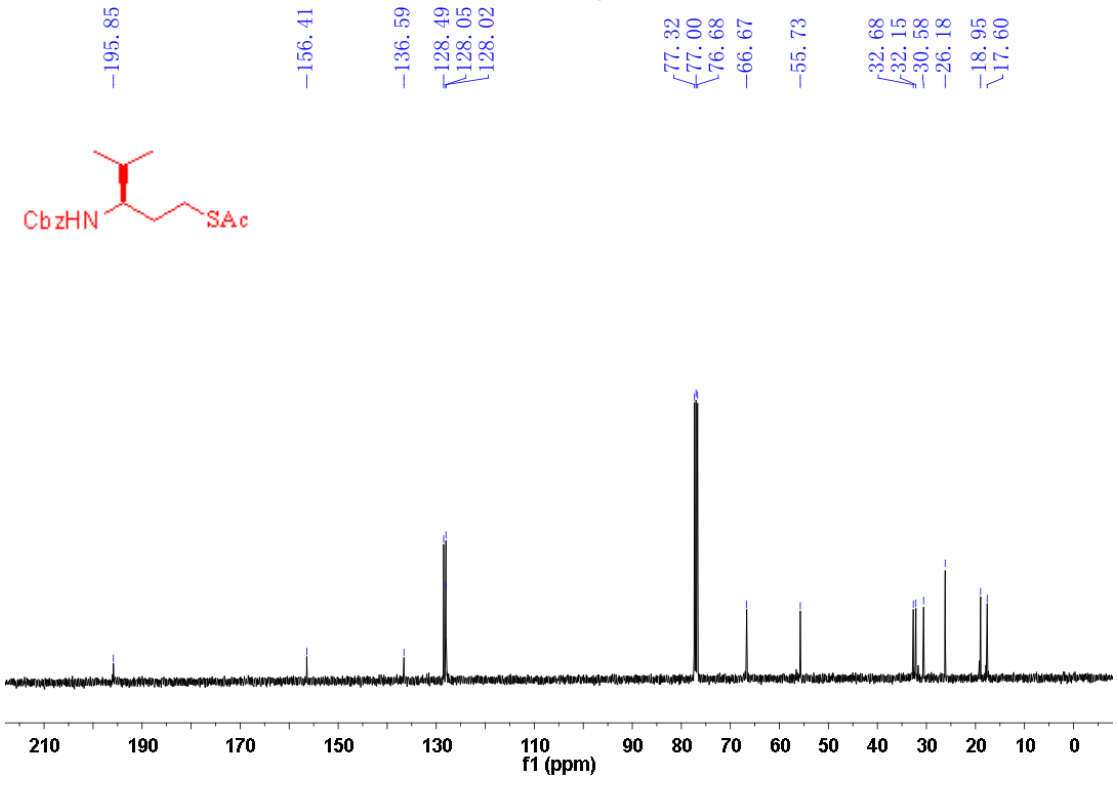


(*S*)-*S*-3-(Benzyloxycarbonylamino)butyl ethanethioate (**5b**)

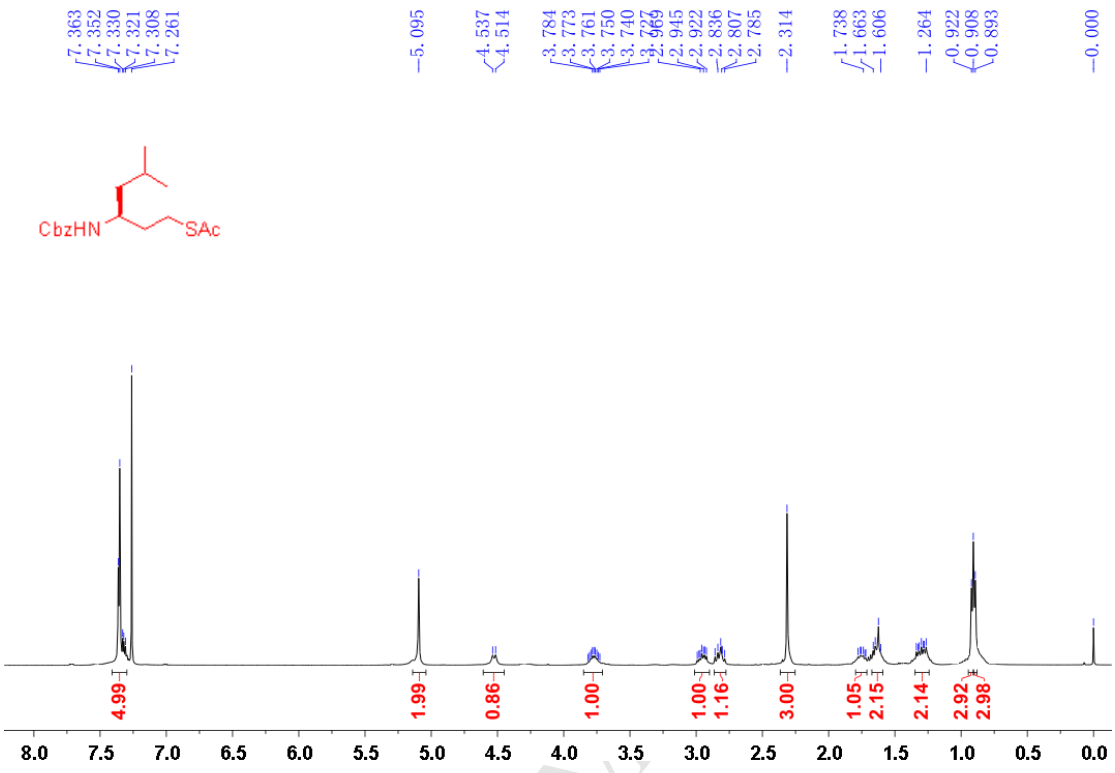


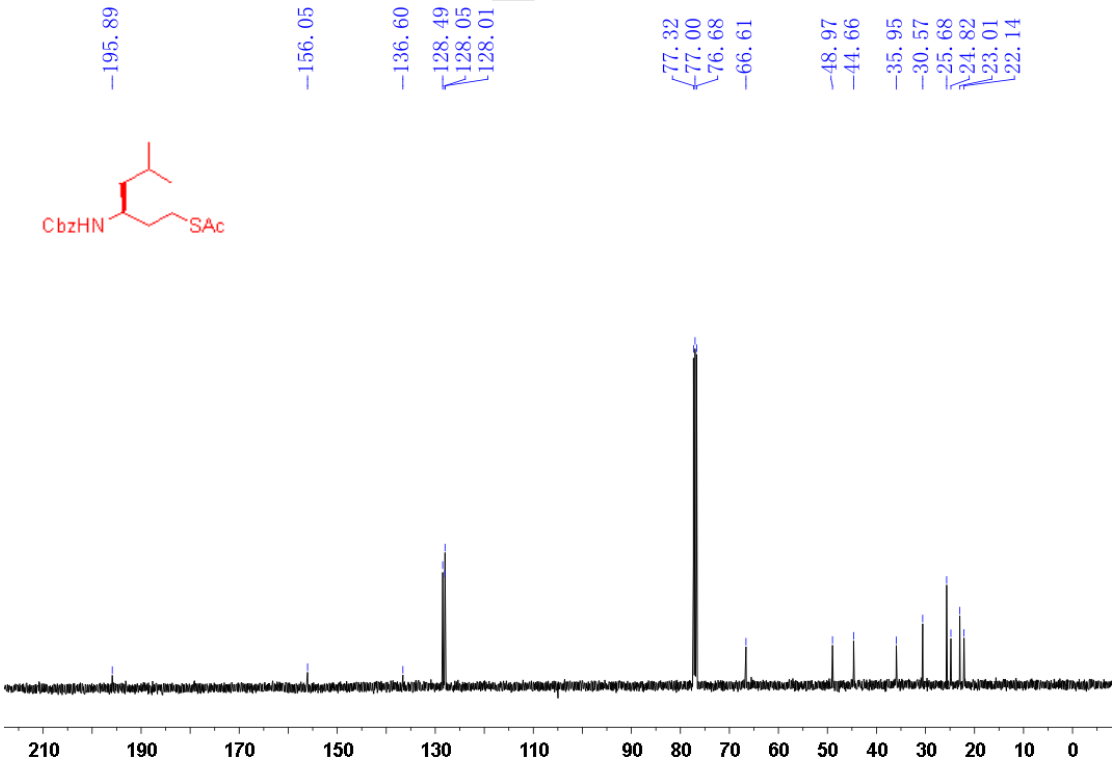
(*R*)-*S*-3-(Benzyloxycarbonylamino)-4-methylpentyl ethanethioate (**5c**)



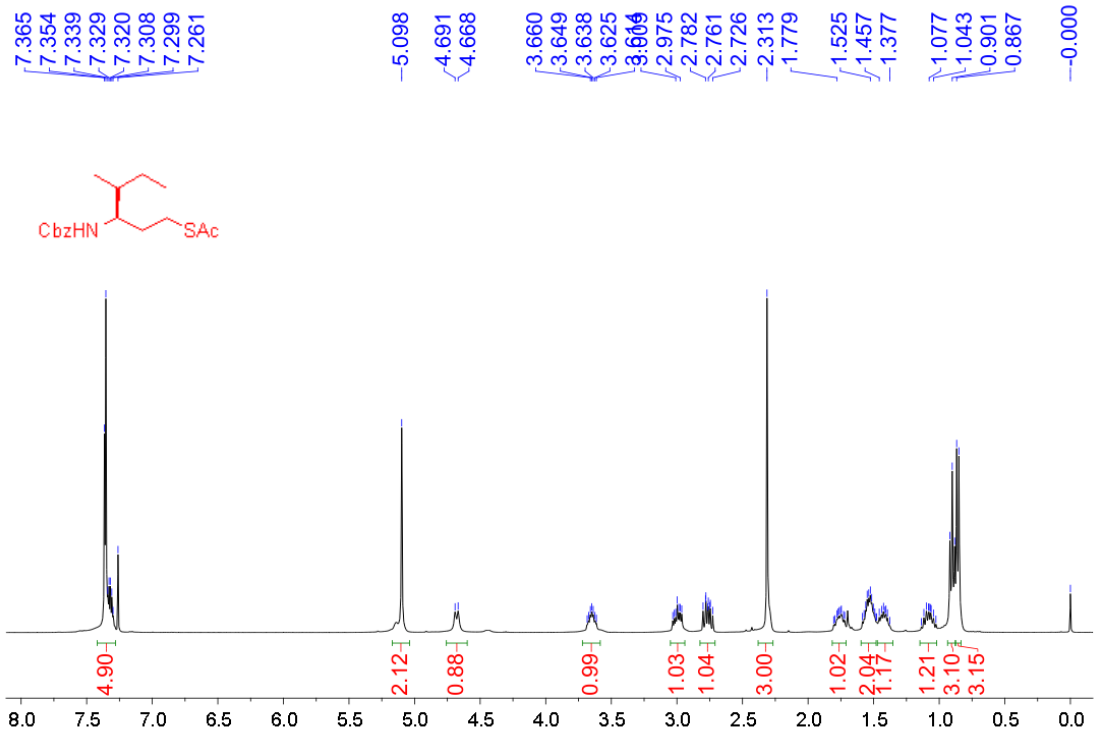


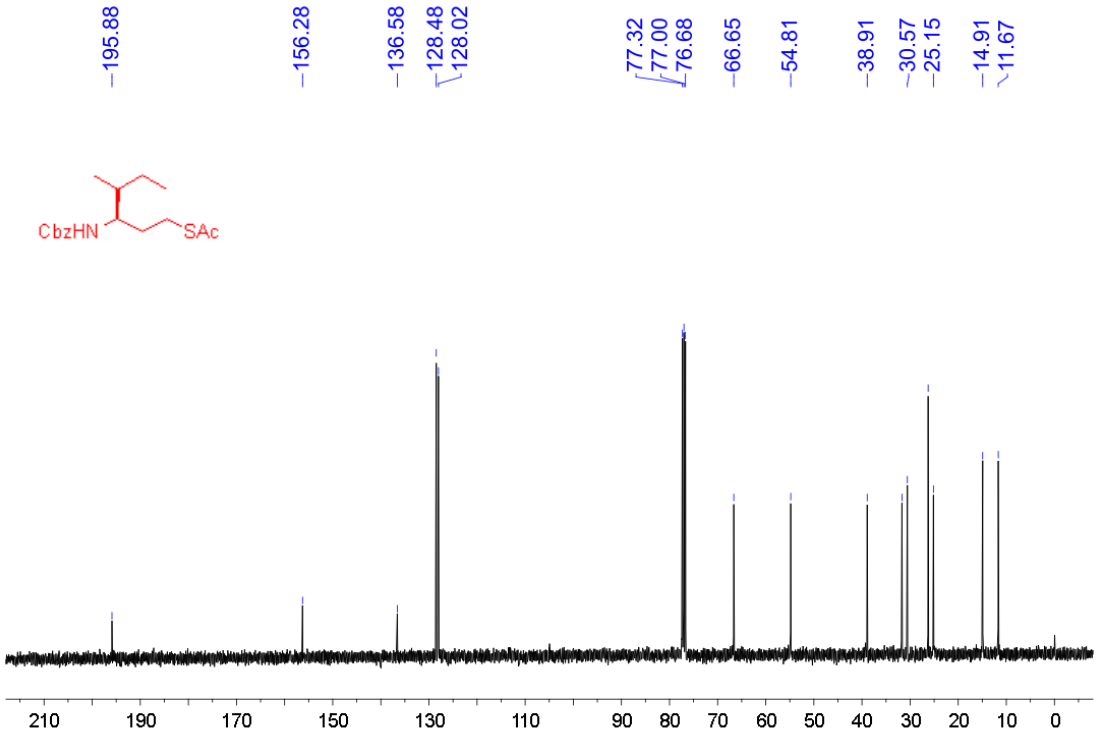
(*S*)-*S*-3-(Benzyloxycarbonylamino)-5-methylhexyl ethanethioate (**5d**)



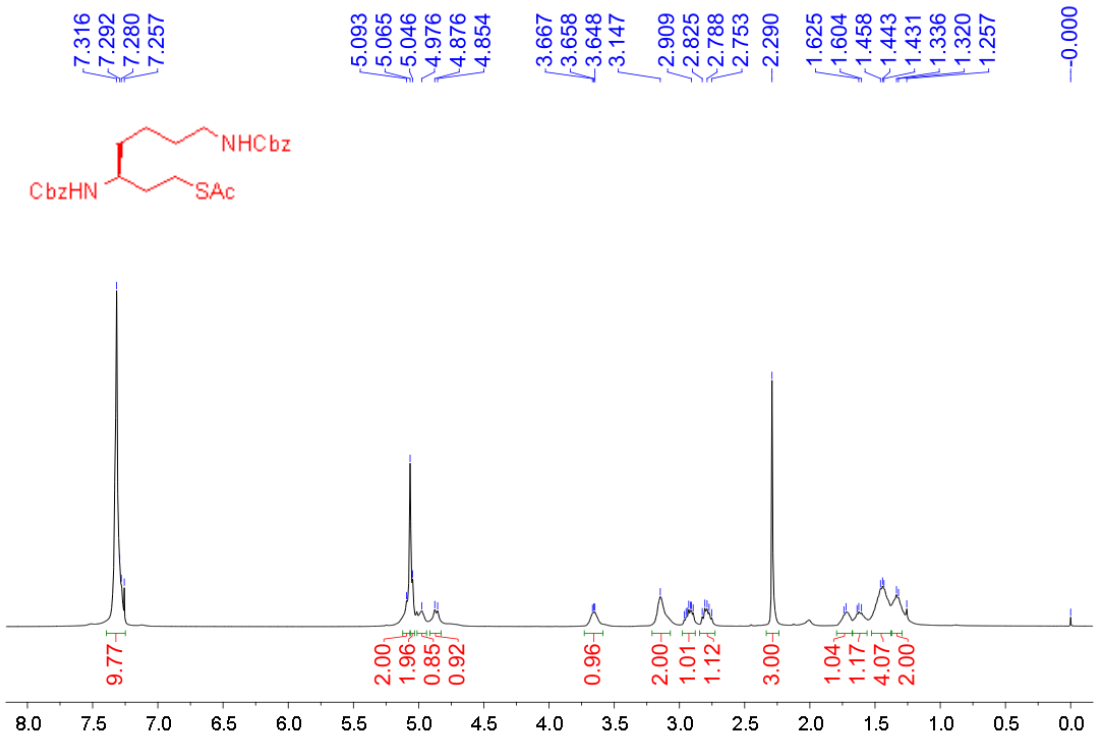


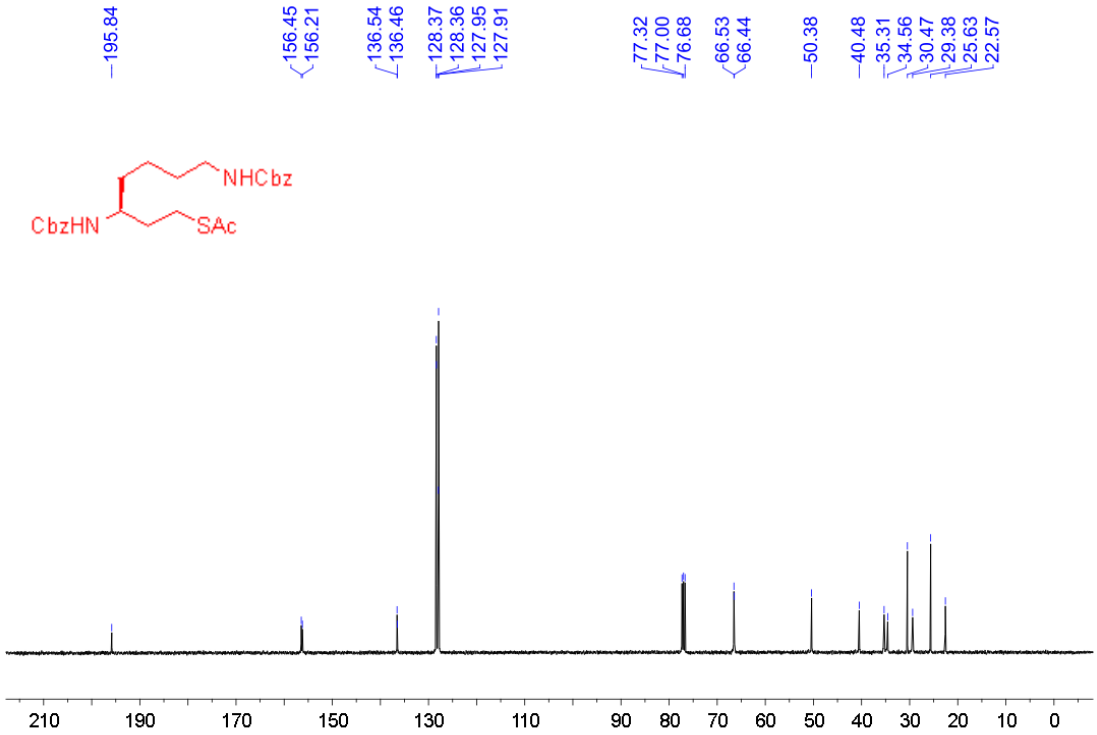
(3*R*,4*S*)-*S*-3-(Benzyloxycarbonylamino)-4-methylhexyl ethanethioate (**5e**)



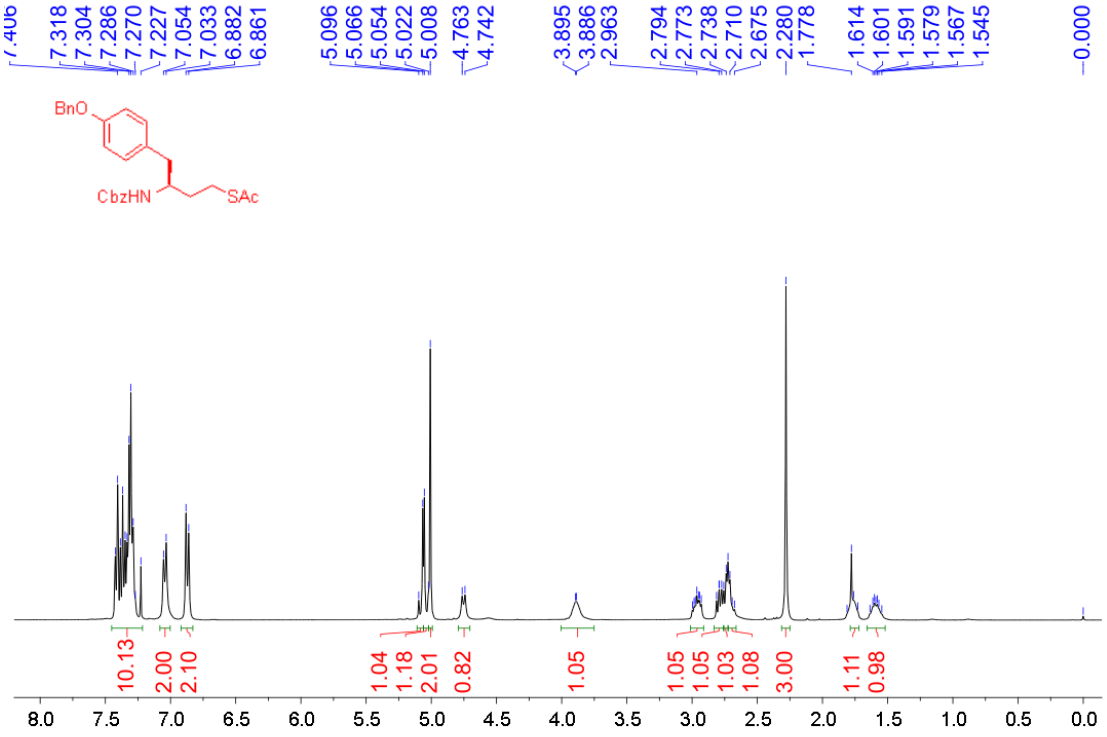


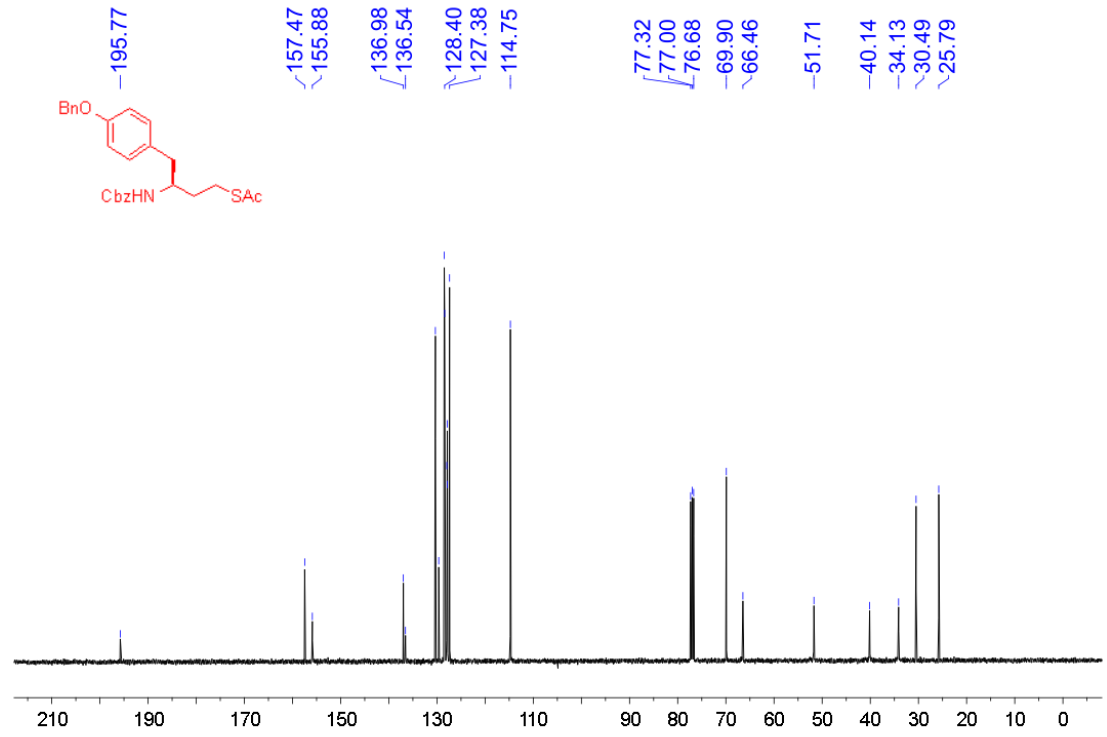
(*S*)-*S*-3,7-Di(benzyloxycarbonylamino)heptyl ethanethioate (**5f**)



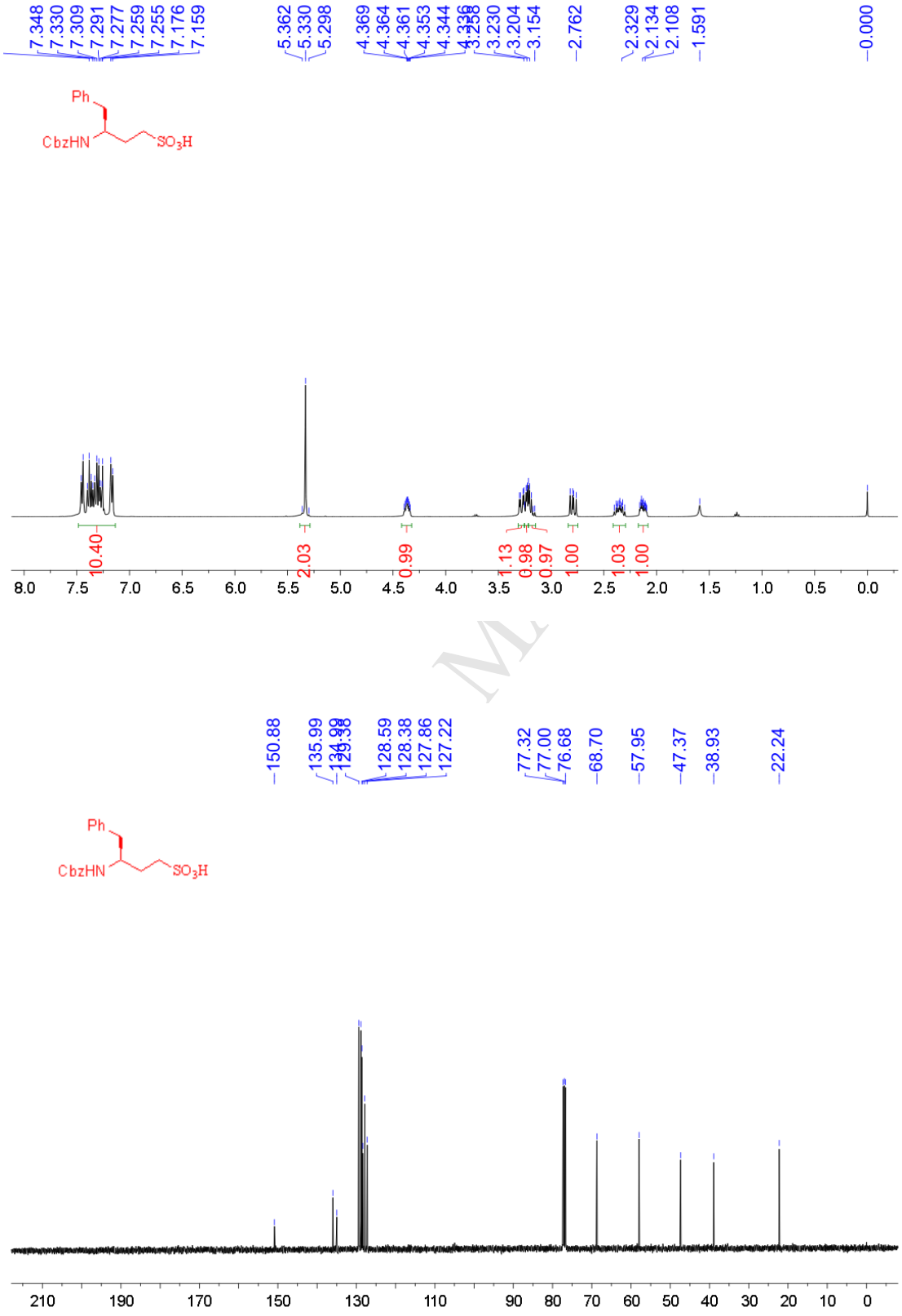


(*S*)-*S*-3-(Benzyloxycarbonylamino)-4-[4-(benzyloxy)phenyl]butyl ethanethioate (**5g**)

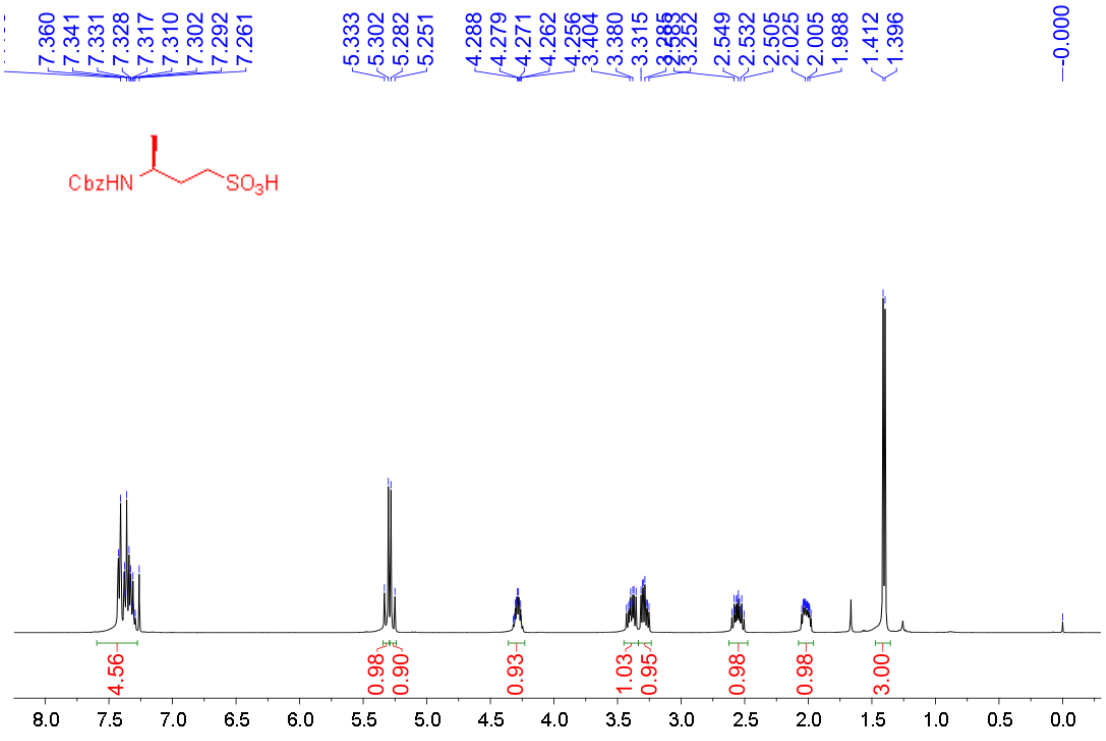


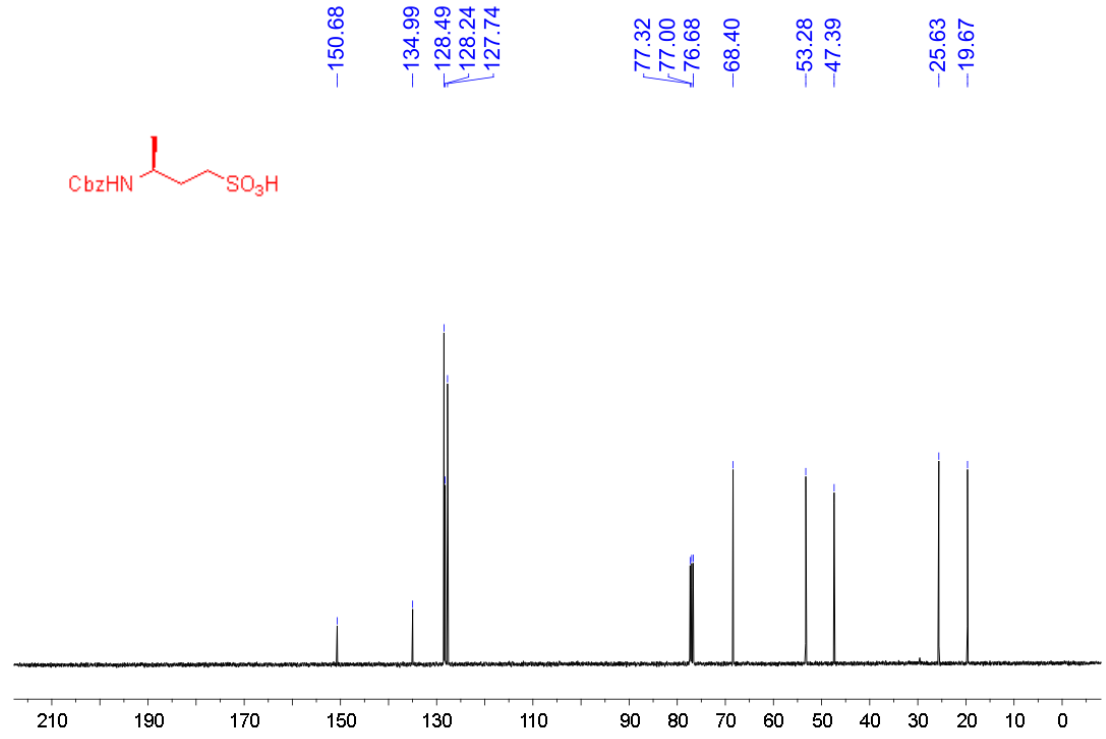


(*S*)-3-Benzyloxycarbonylamino-4-phenylbutane-1-sulfonic acid (**6a**)

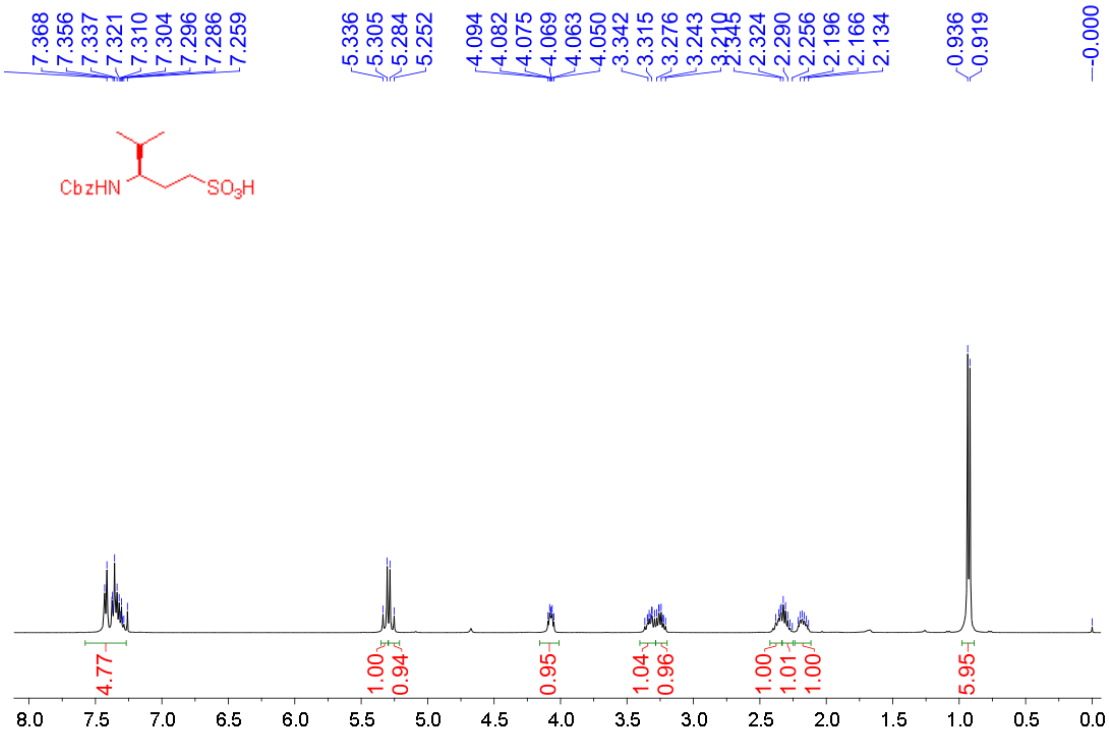


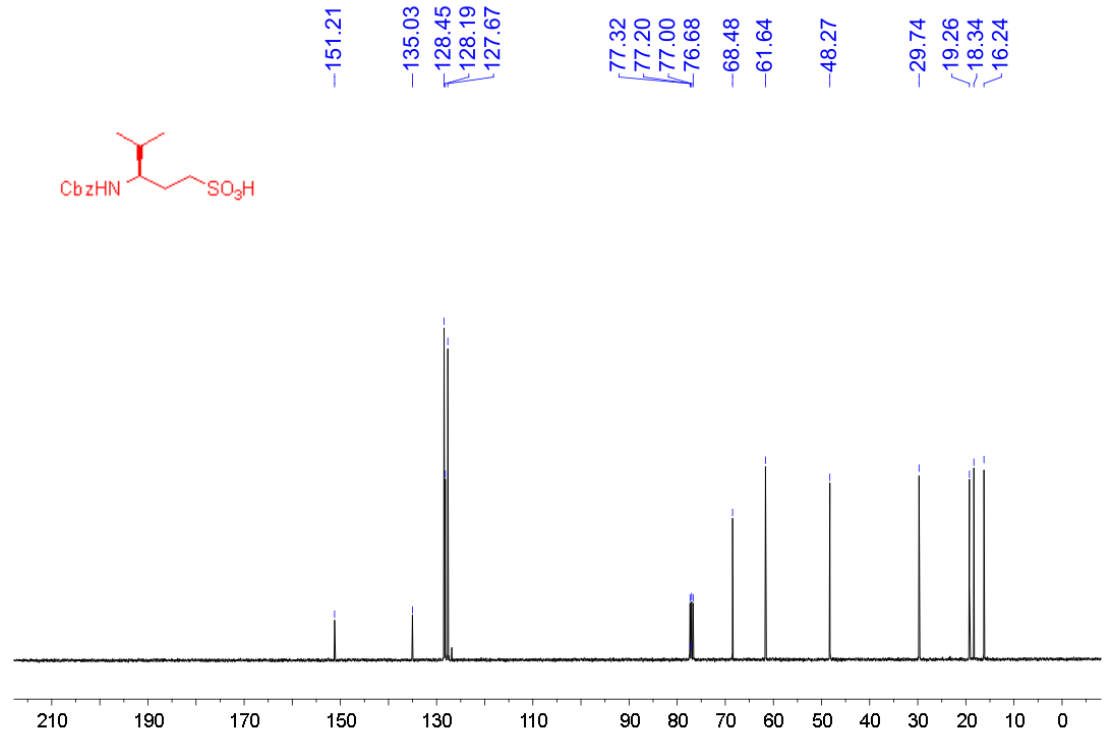
(*S*)-3-Benzyloxycarbonylaminobutane-1-sulfonic acid (**6b**)



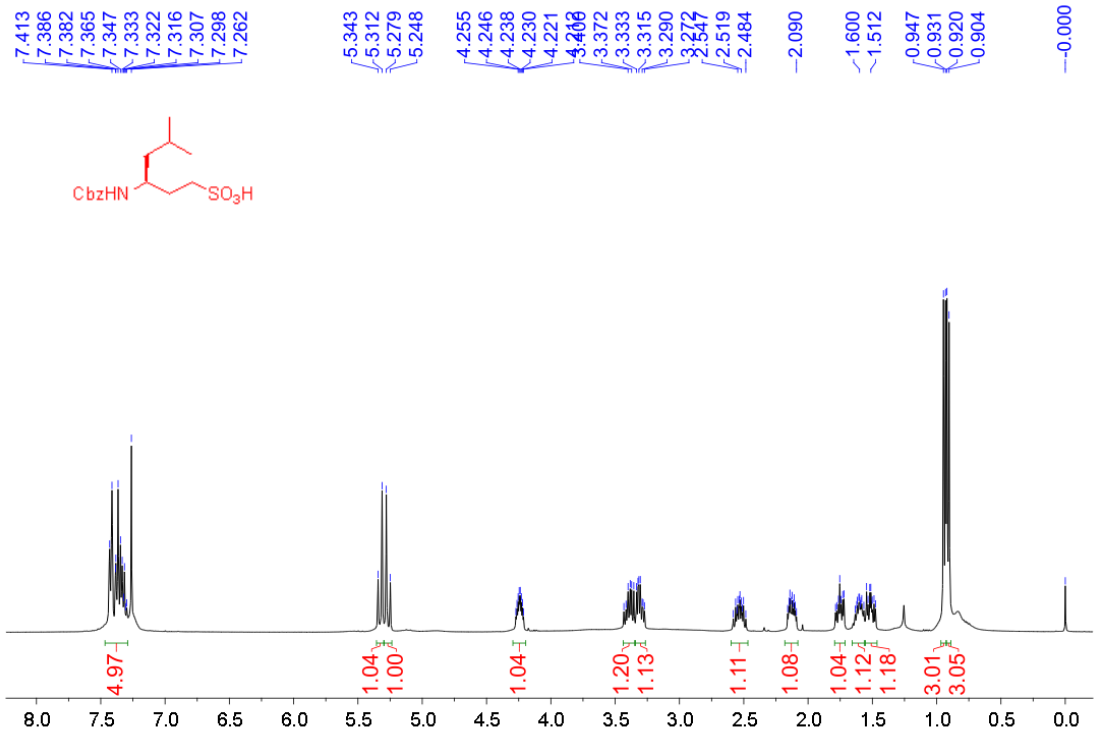


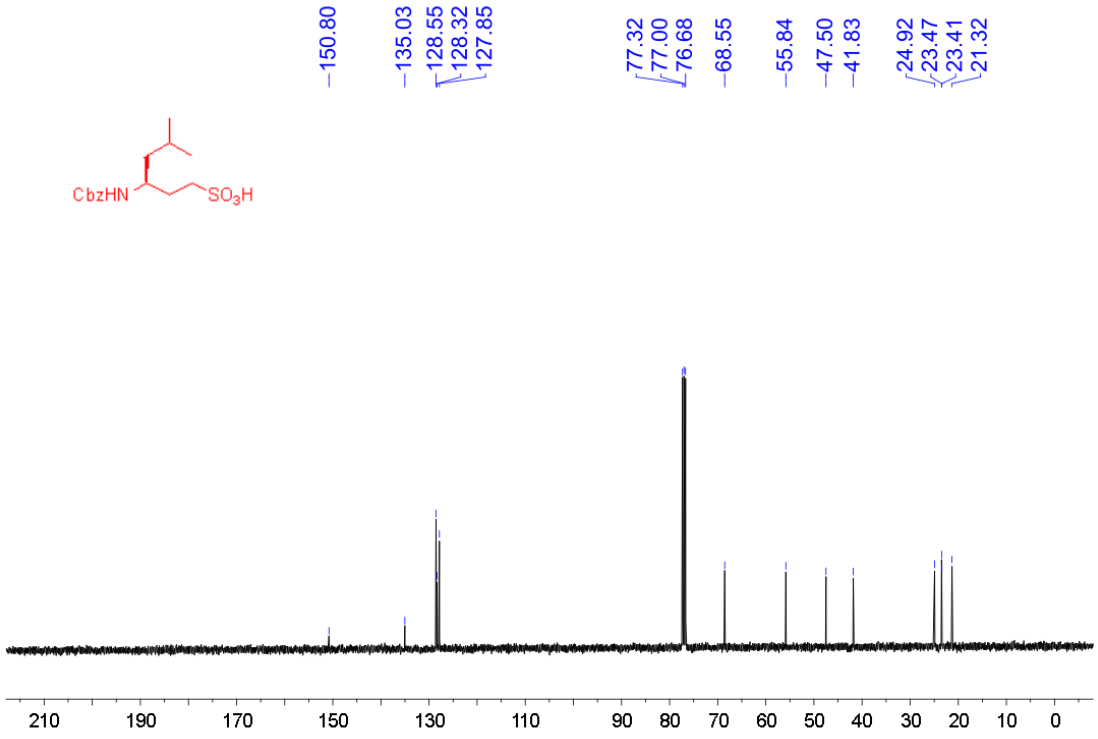
(*R*)-3-Benzyloxycarbonylamino-4-methylpentane-1-sulfonic acid (**6c**)



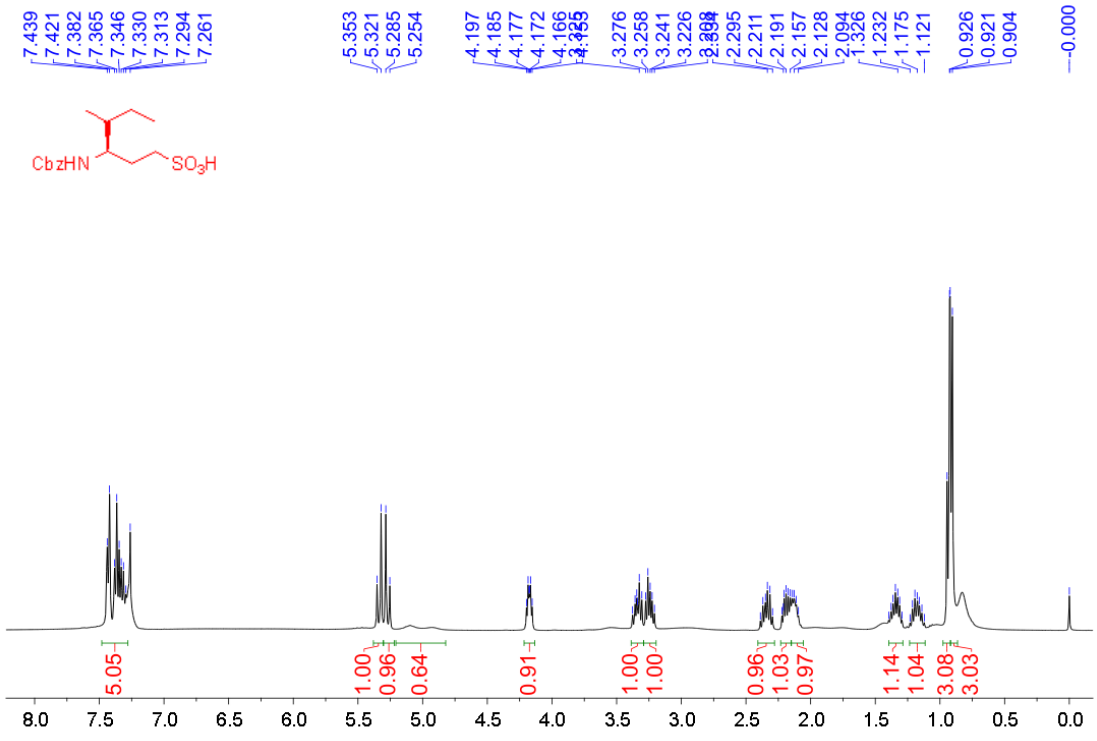


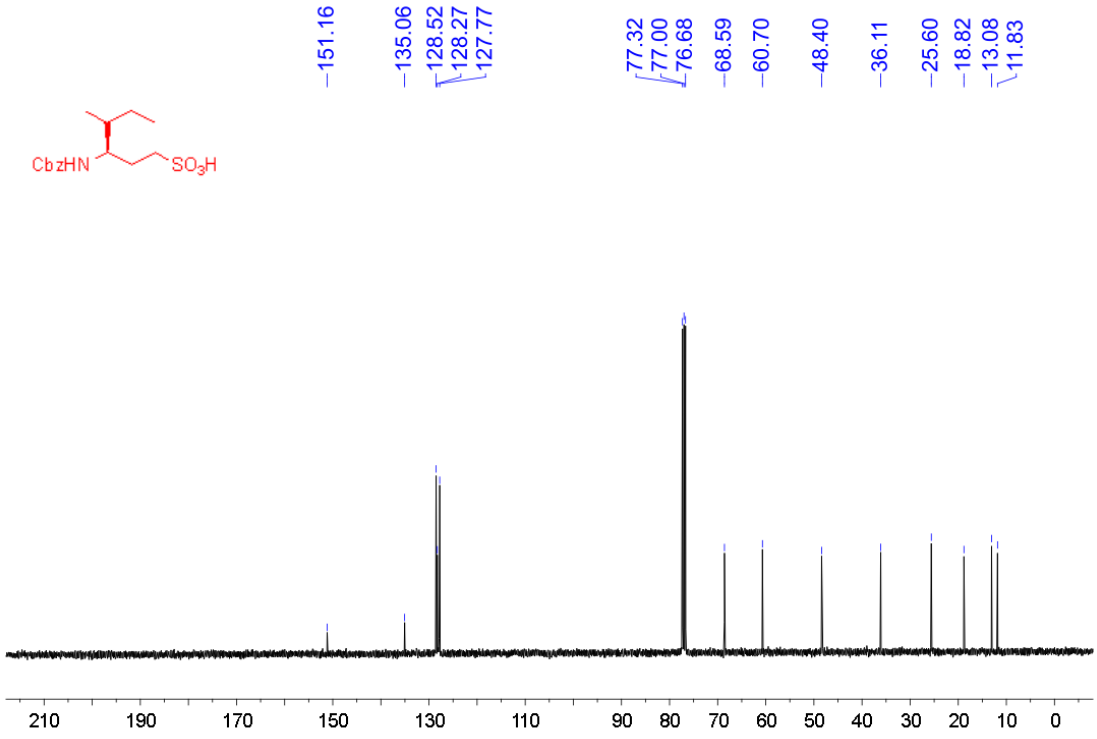
(*S*)-3-Benzyloxycarbonylamino-5-methylhexane-1-sulfonic acid (**6d**)



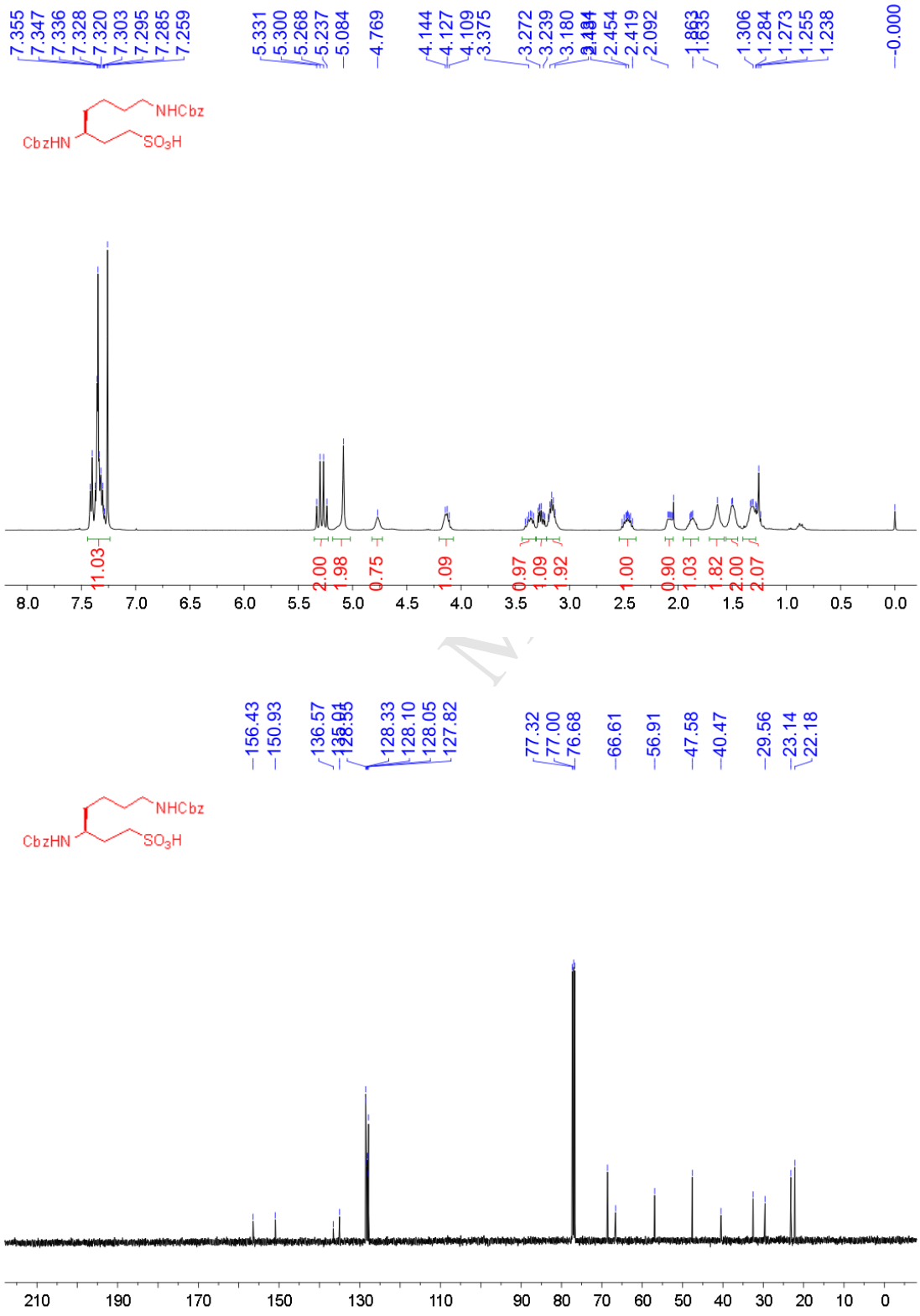


(*3R,4S*)-3-Benzyloxycarbonylamino-4-methylhexane-1-sulfonic acid (**6e**)

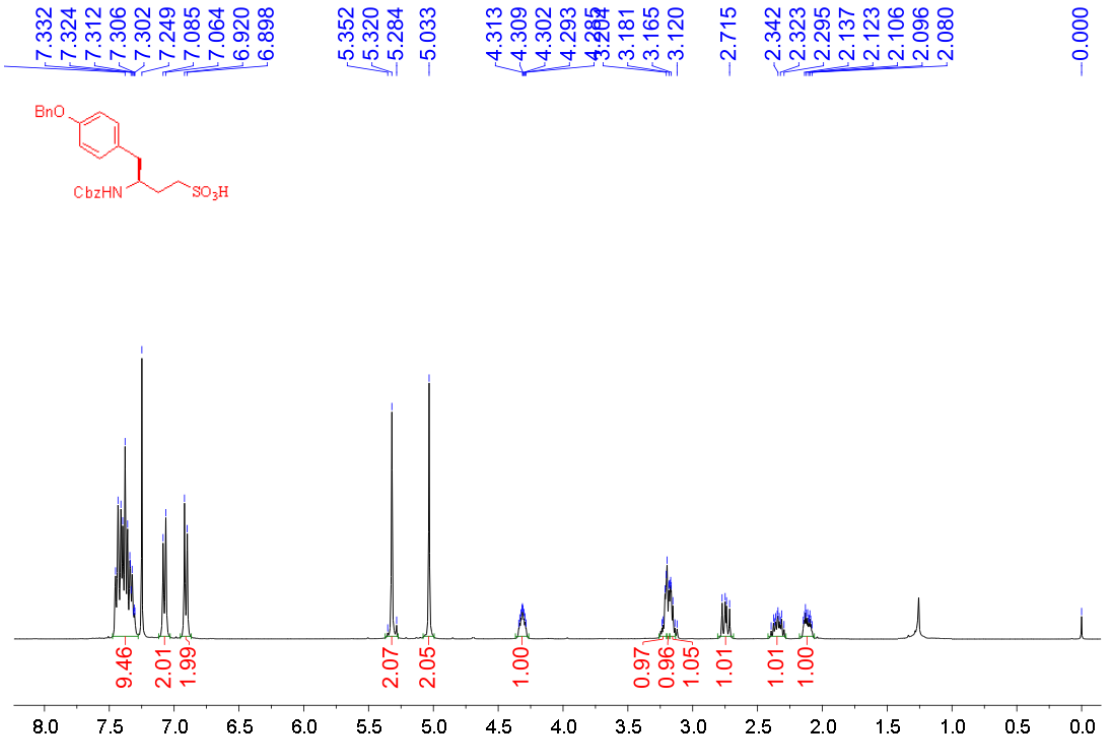


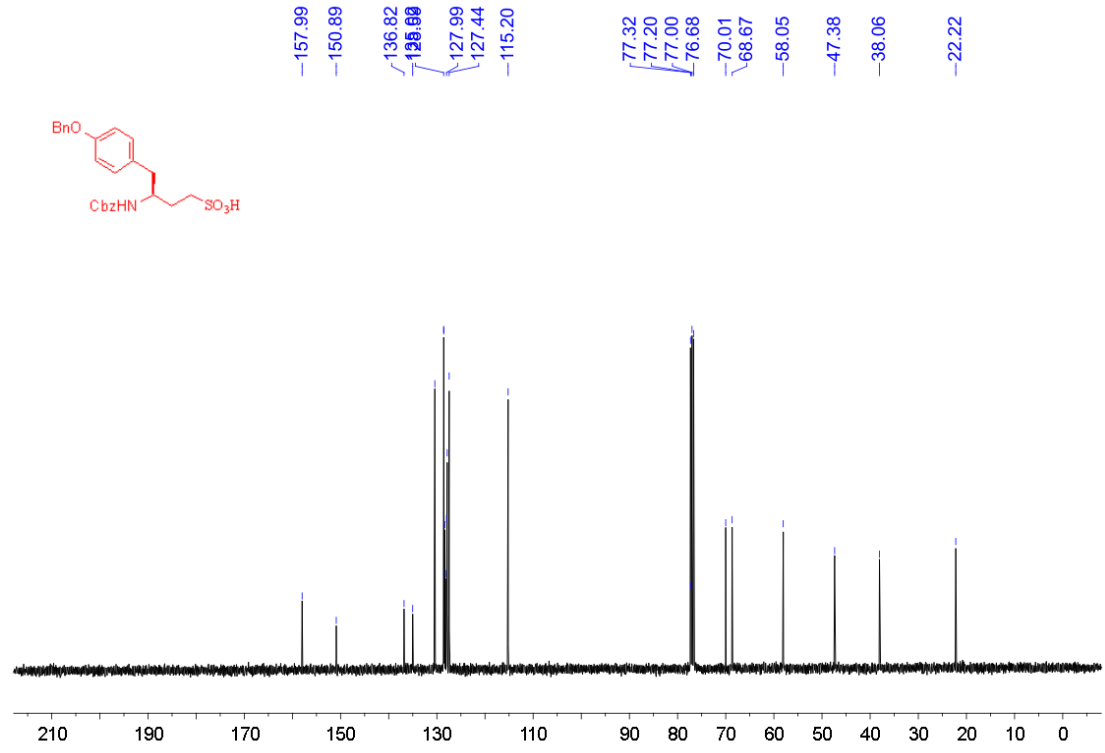


(*S*)-3,7-Dibenzyloxycarbonylaminoheptane-1-sulfonic acid (**6f**)

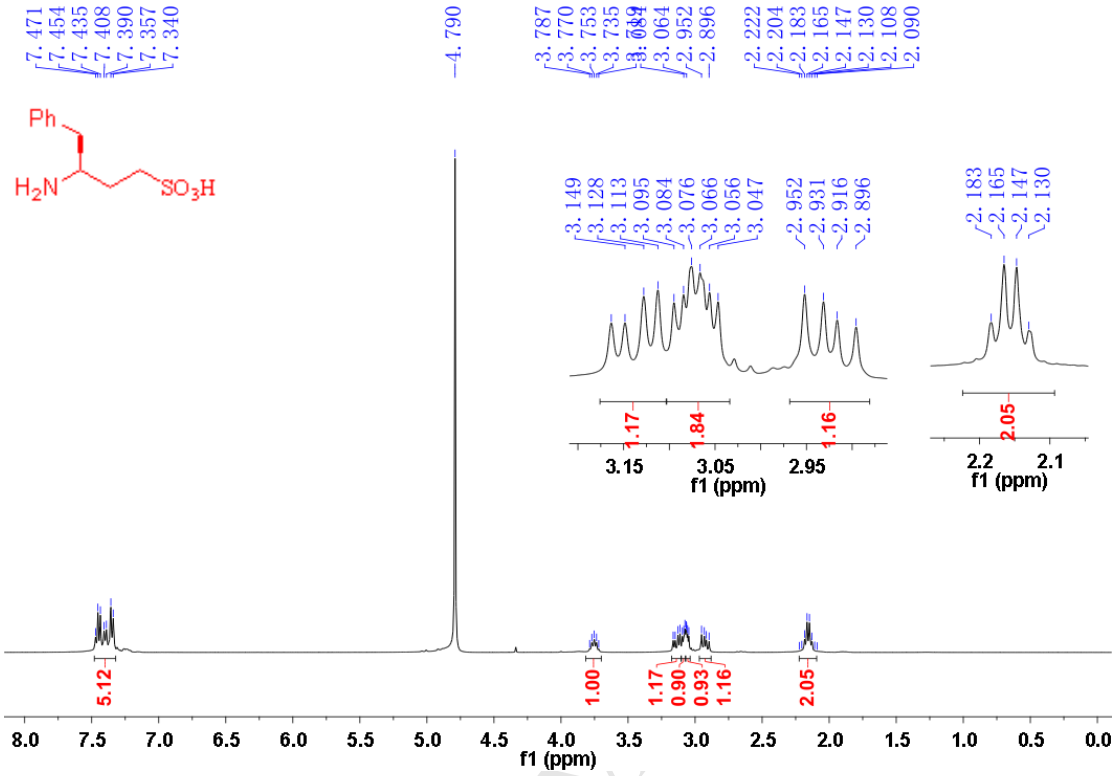


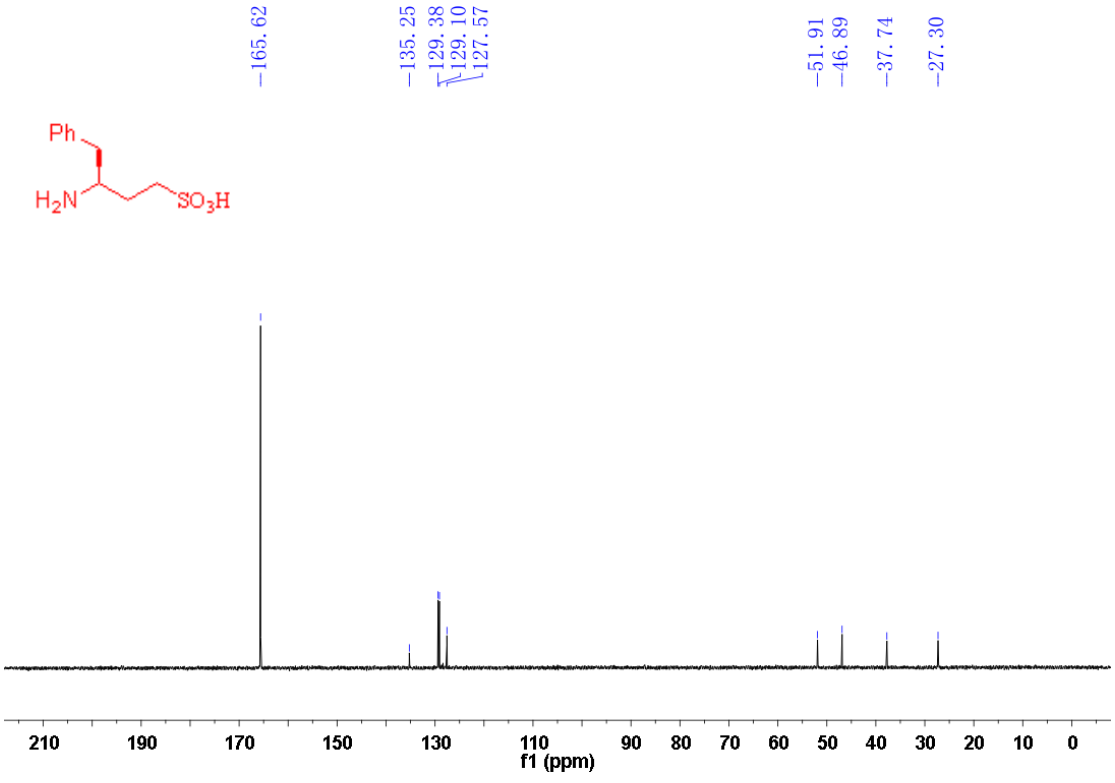
(*S*)-3-Benzyloxycarbonylamino-4-(4-benzyloxyphenyl)butane-1-sulfonic acid (**6g**)



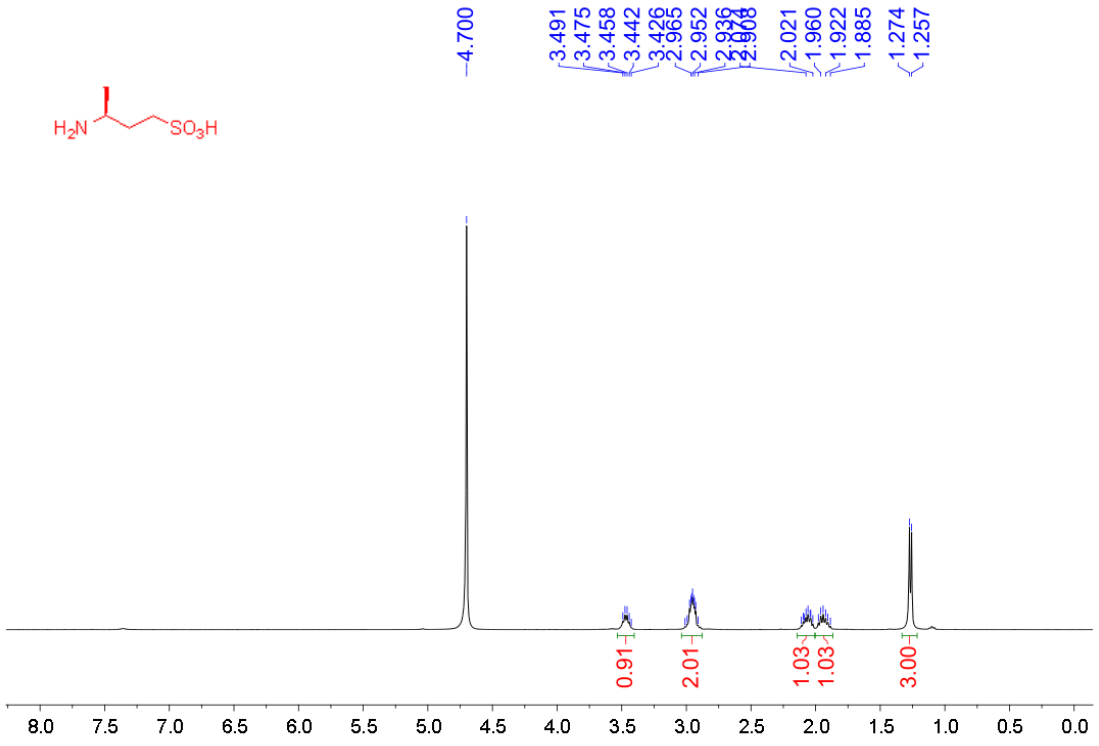


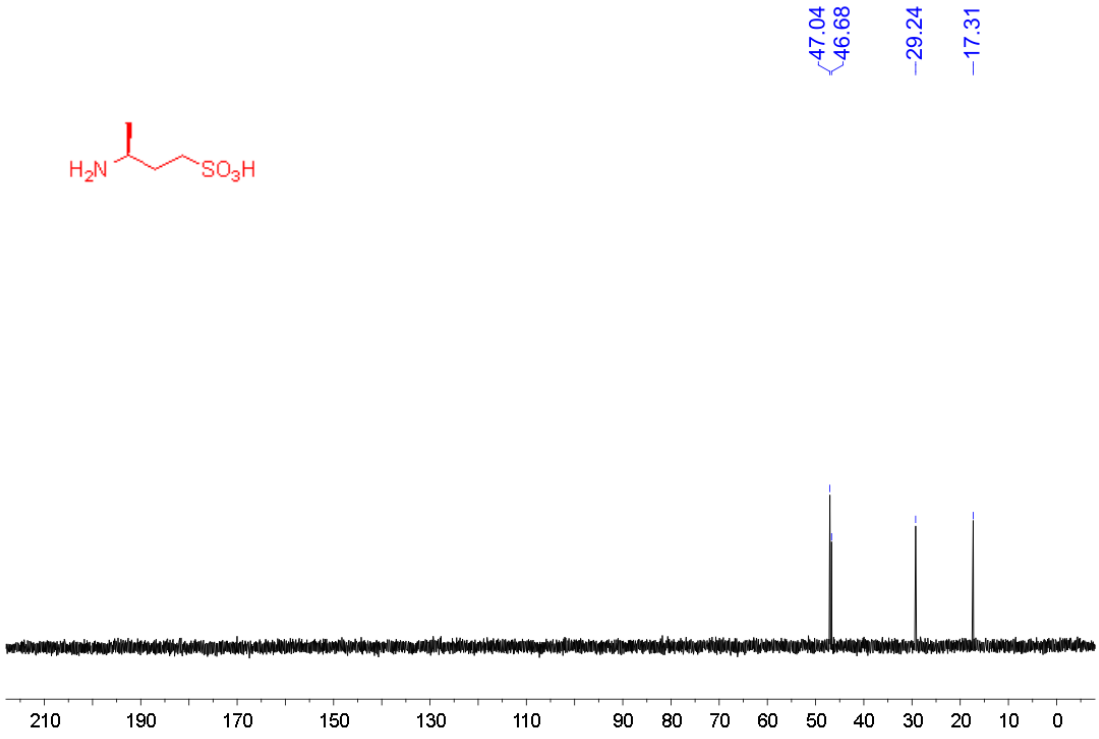
(*S*)-3-Amino-4-phenylbutane-1-sulfonic acid (**7a**)



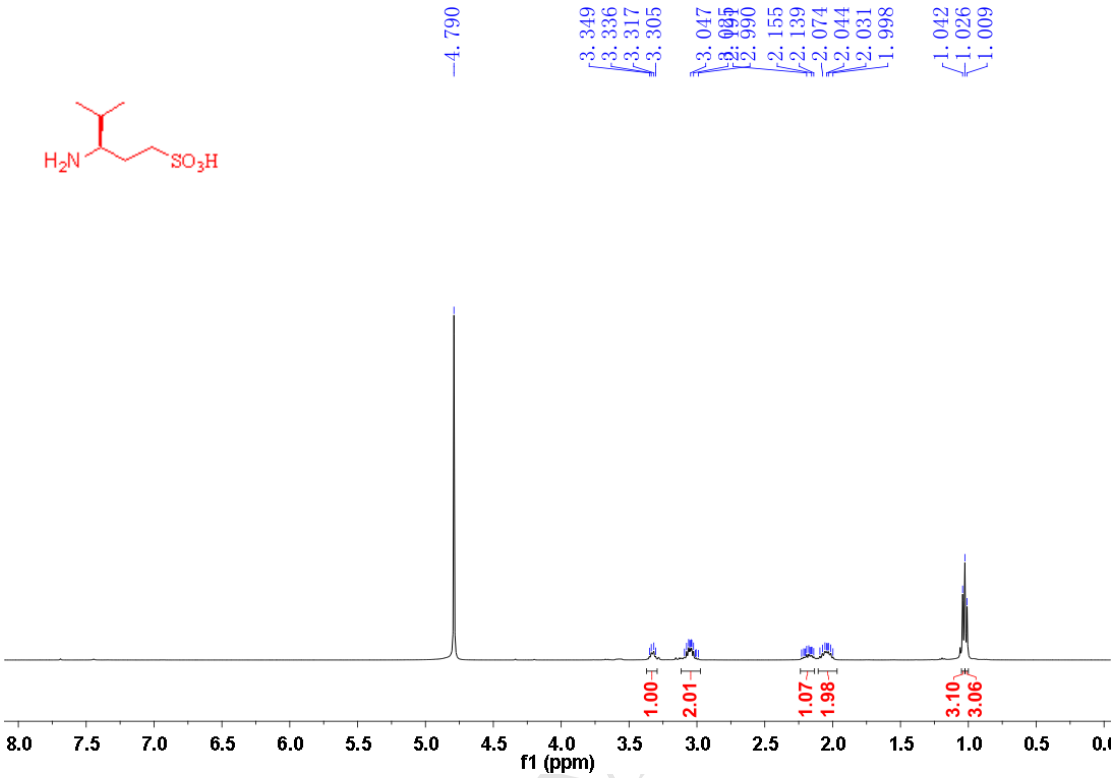


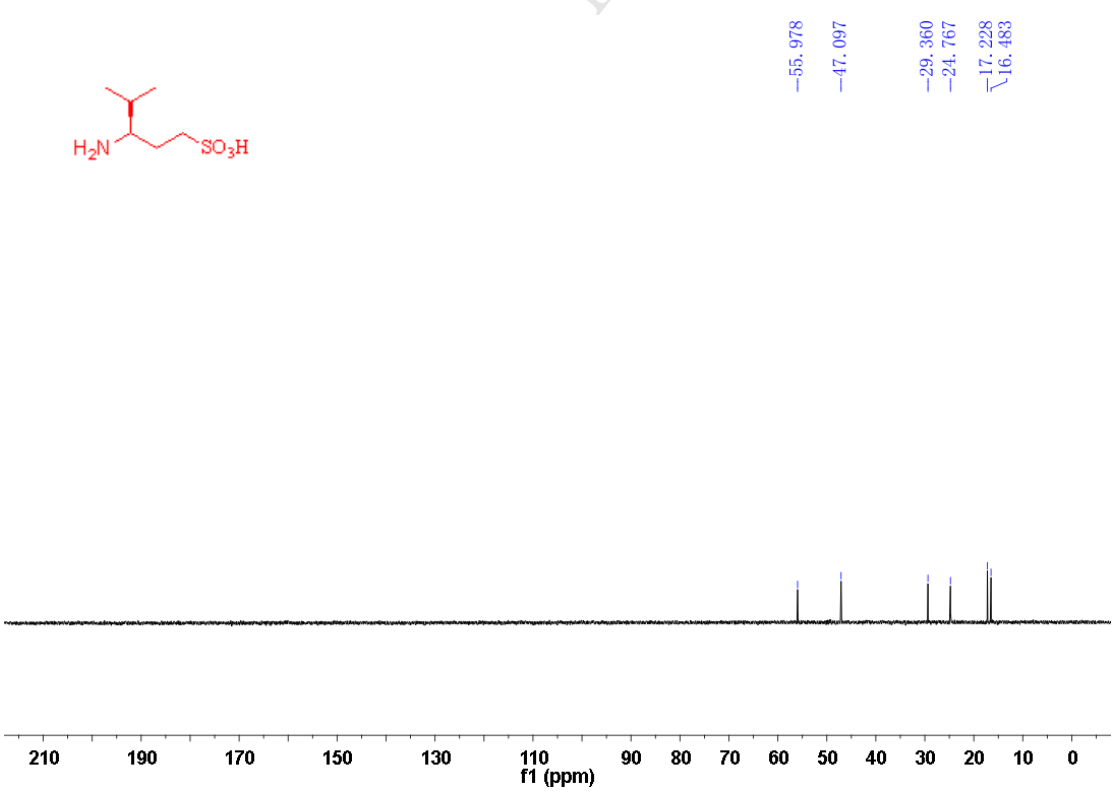
(*S*)-3-Aminobutane-1-sulfonic acid (**7b**)



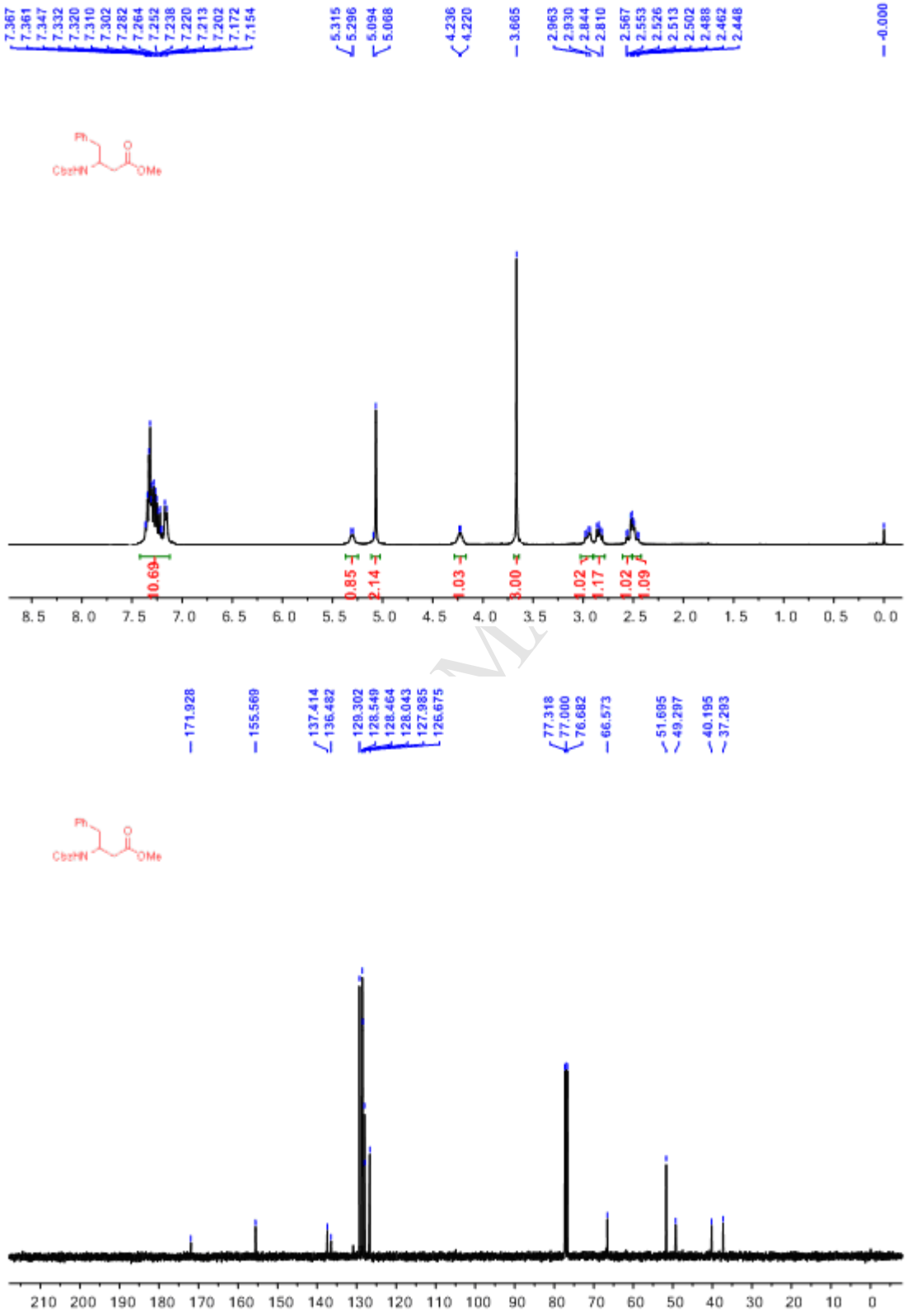


(*R*)-3-Amino-4-methylpentane-1-sulfonic acid (**7c**)

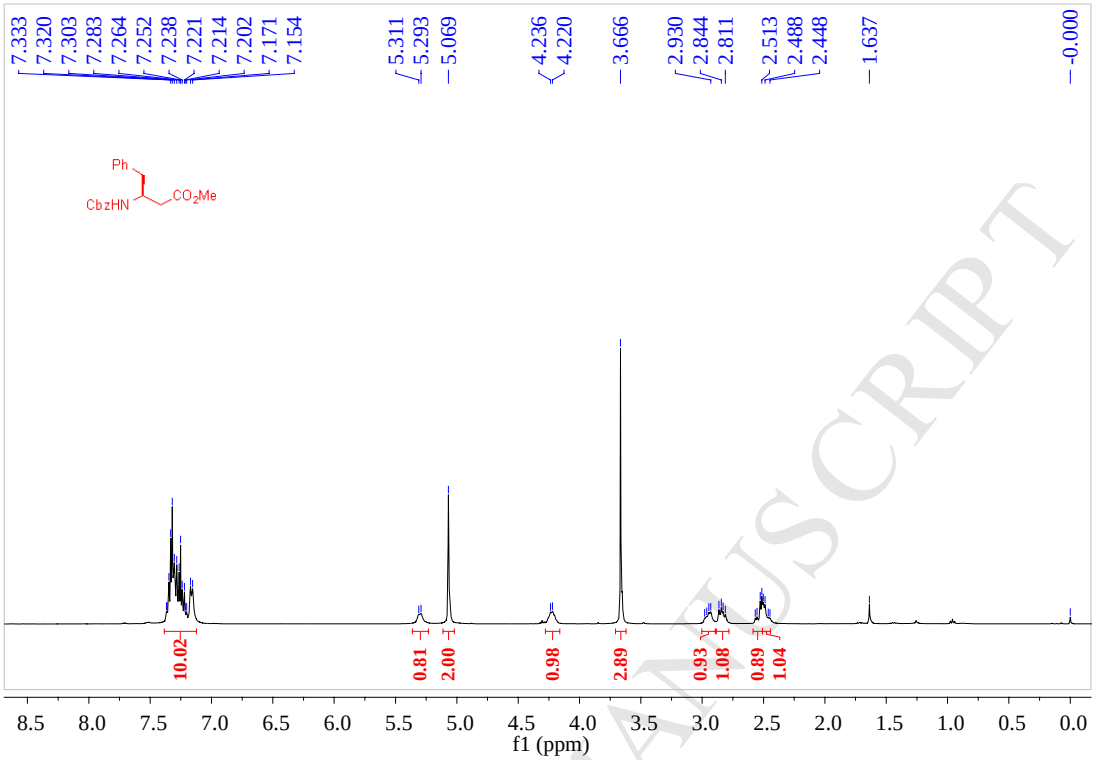


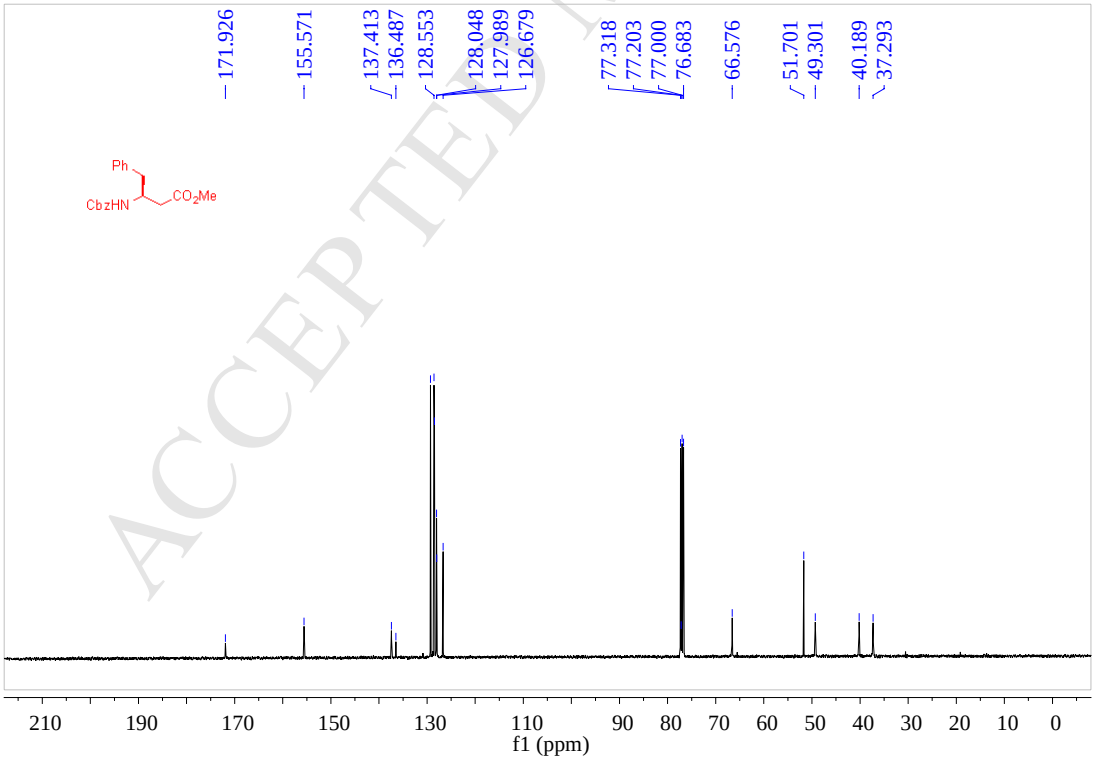


Methyl (*R/S*)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (*rac*-**8b**)

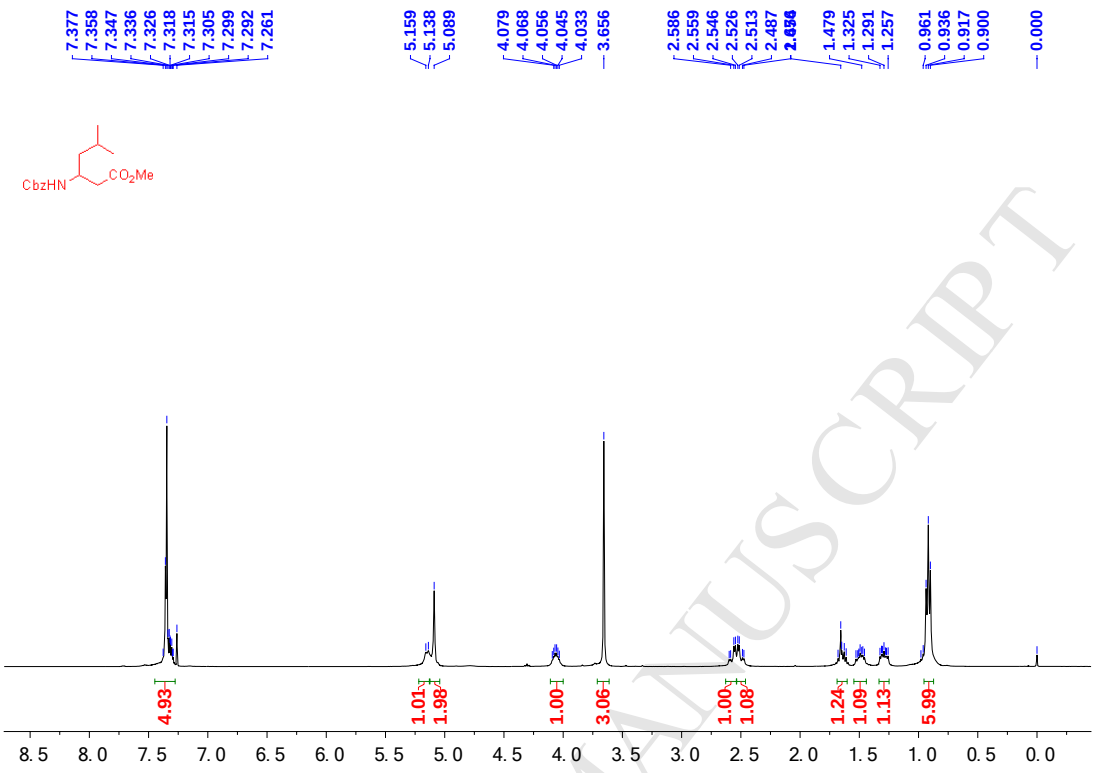


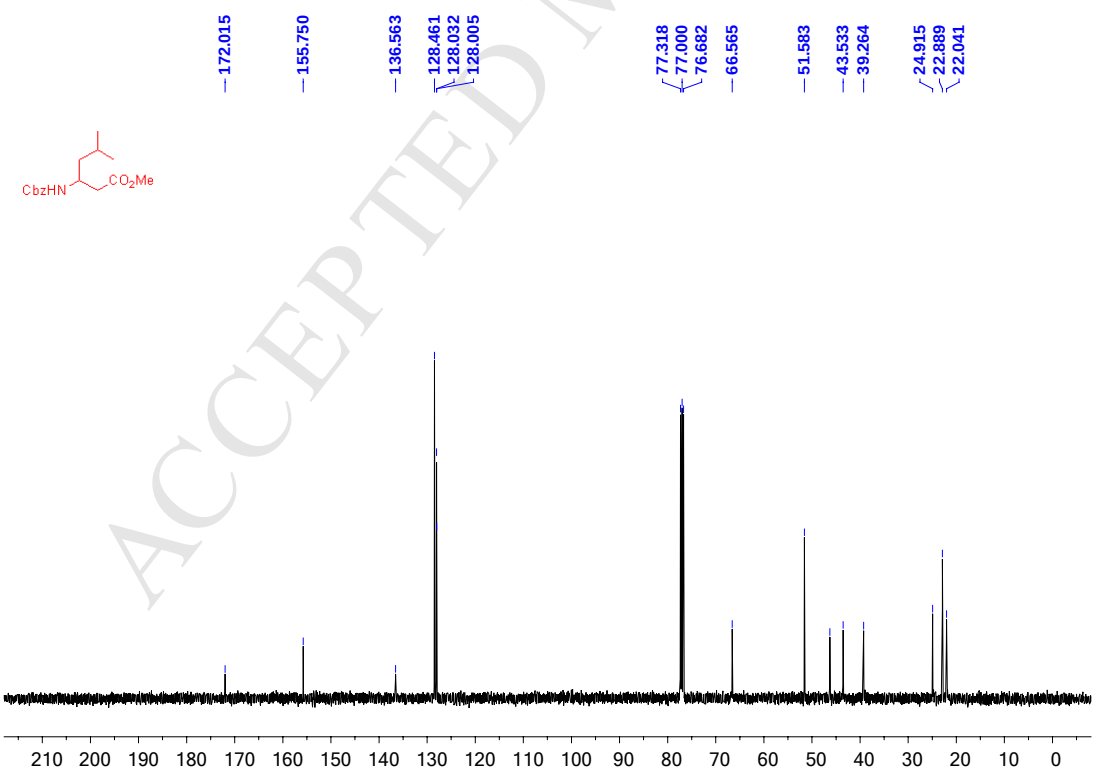
Methyl (*S*)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (**8b**)



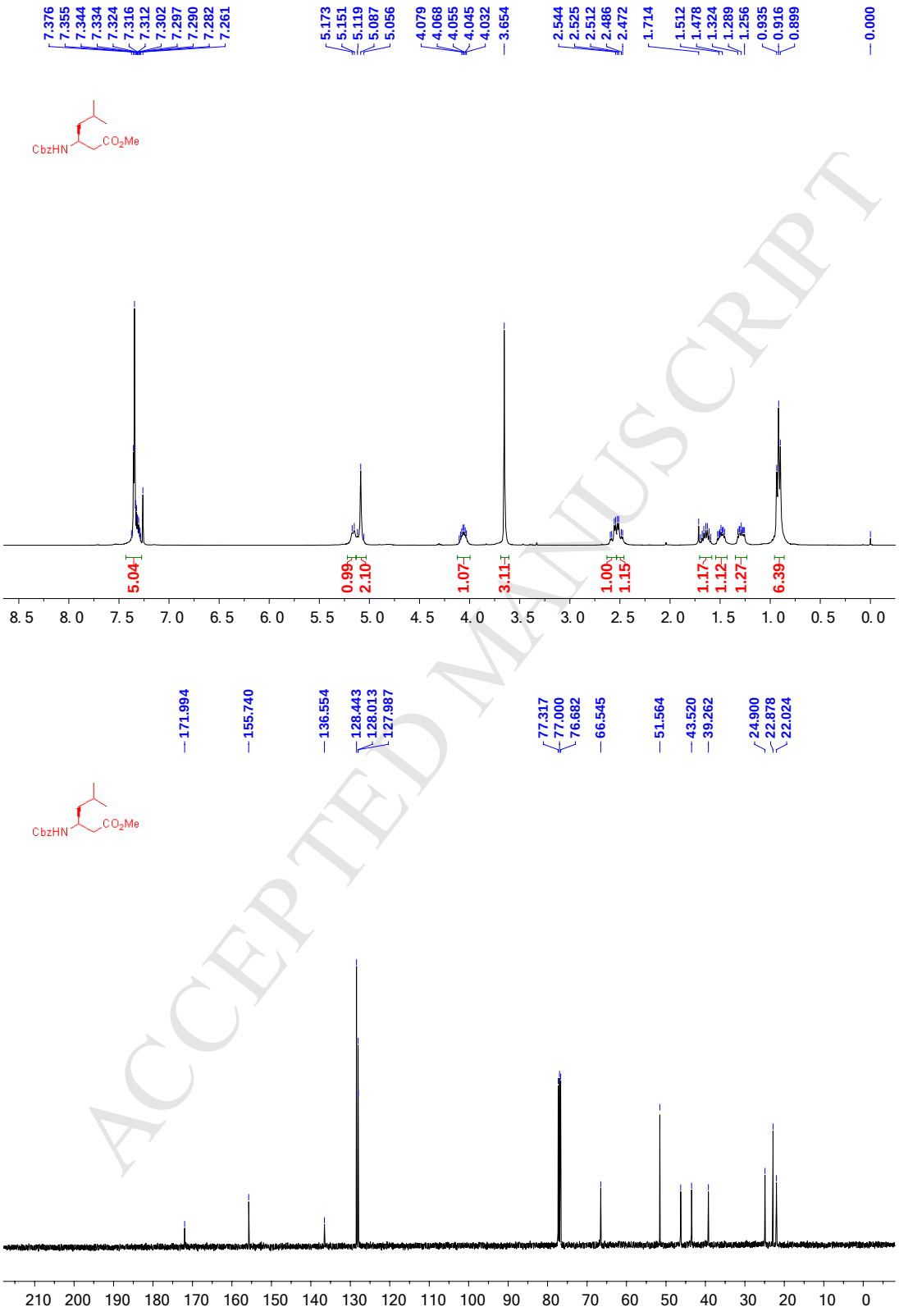


Methyl (*R/S*)-3-(benzyloxycarbonylamino)-5-methylhexanoate (*rac*-**8d**)



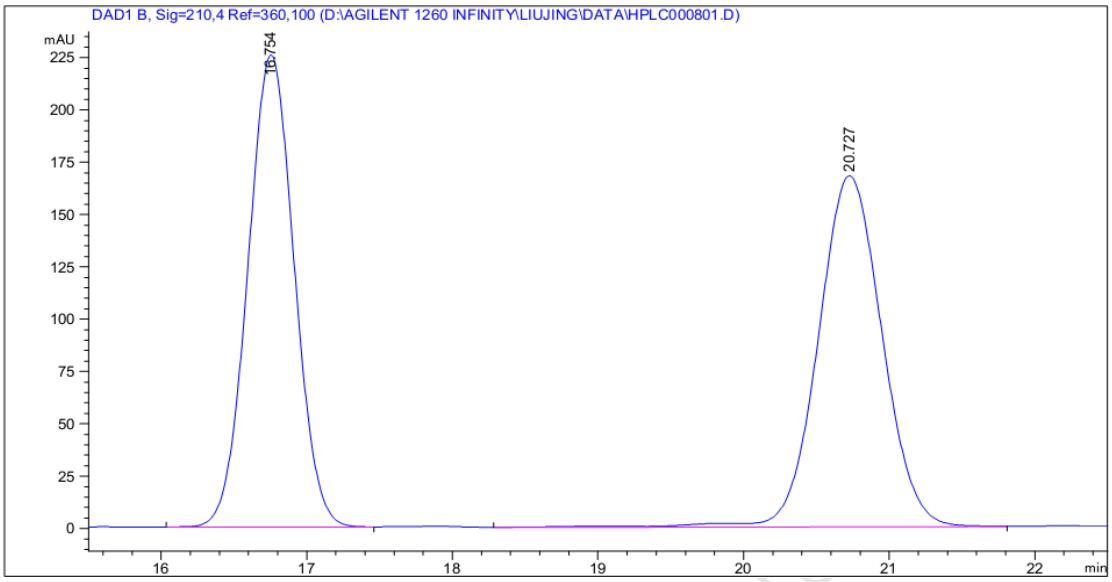


Methyl (*S*)-3-(benzyloxycarbonylamino)-5-methylhexanoate (**8d**)



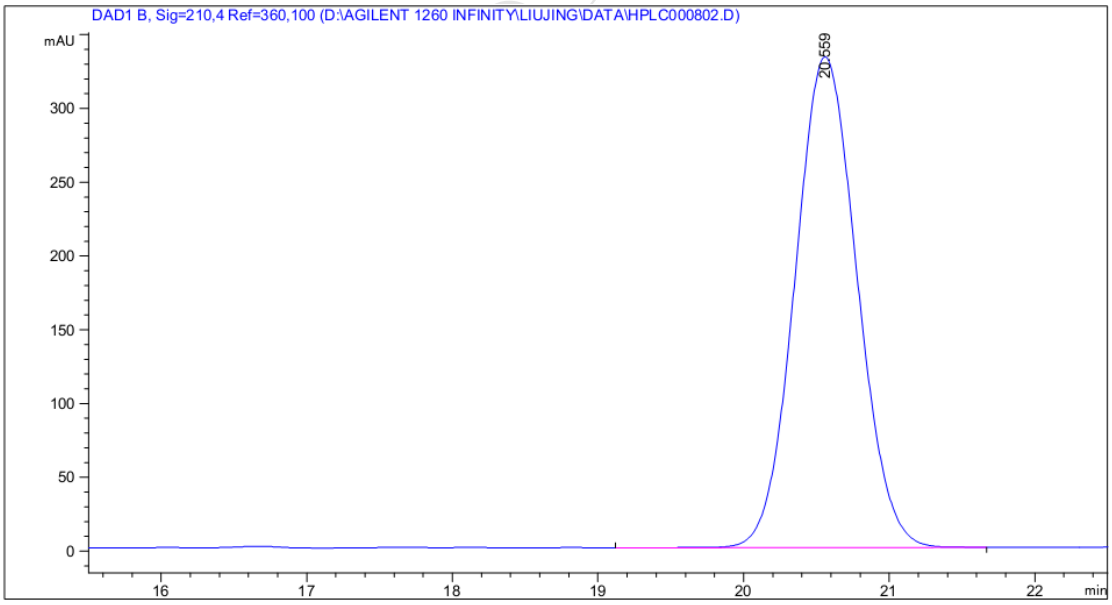
Copies of HPLC profiles of products 8

Methyl (*R/S*)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (*rac*-**8b**)



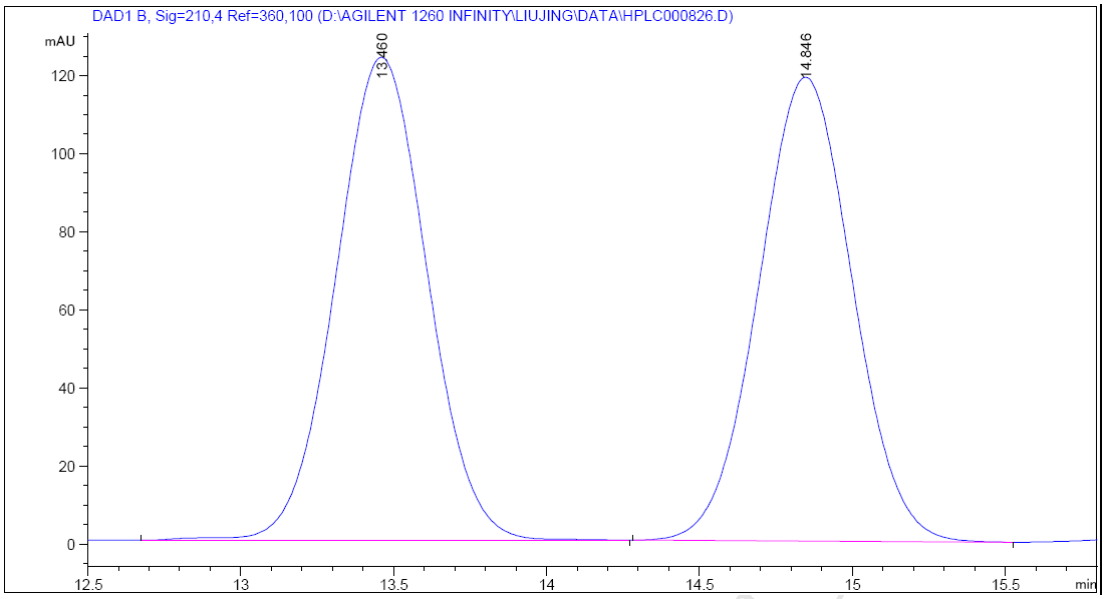
Peak #	Retention Time [min]		Peak Time [min]	Peak Area [mAU*s]	Peak Height [mAU]	Area Percent %
1	16.754	BV	0.3466	4999.21289	225.54561	49.3937
2	20.727	BV	0.4763	5121.94629	167.70621	50.6063

Methyl (*S*)-3-(benzyloxycarbonylamino)-4-phenylbutanoate (**8b**)



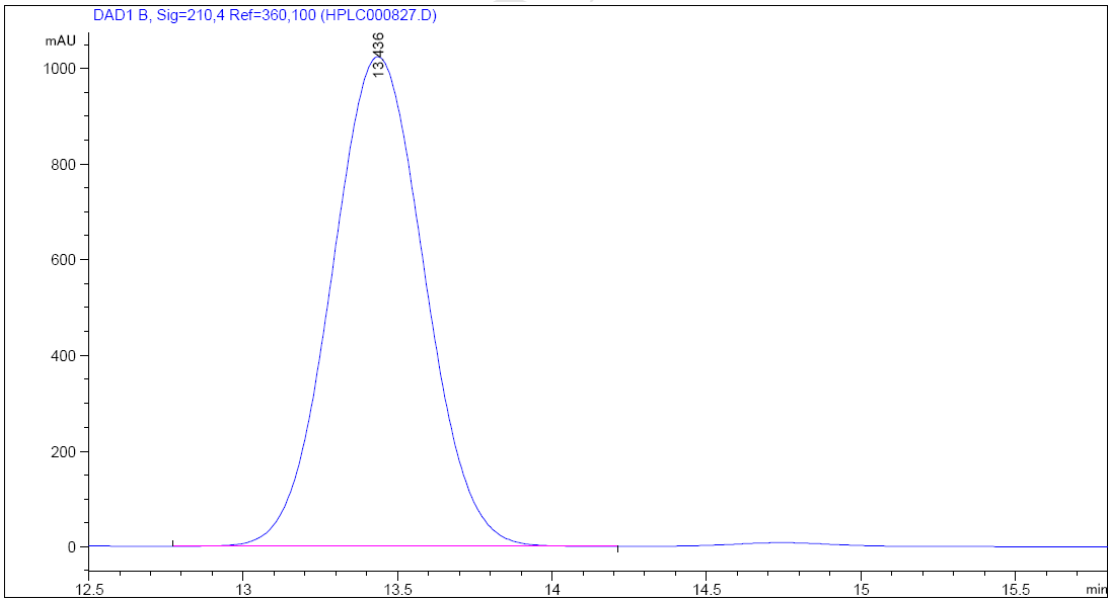
Peak #	Retention Time [min]		Peak Time [min]	Peak Area [mAU*s]	Peak Height [mAU]	Area Percent %
1	20.559	BB	0.4616	9846.49023	332.43939	100.0000

Methyl (*R/S*)-3-(benzyloxycarbonylamino)-5-methylhexanoate (*rac*-**8d**)



Peak #	Retention Time [min]		Peak Time [min]	Peak Area [mAU*s]	Peak Height [mAU]	Area Percent %
1	13.460	BB	0.3247	2573.87695	123.72169	50.3821
2	14.846	BB	0.3348	2534.83960	118.86618	49.6179

Methyl (*S*)-3-(benzyloxycarbonylamino)-5-methylhexanoate (**8d**)



Peak #	Retention Time [min]		Peak Time [min]	Peak Area [mAU*s]	Peak Height [mAU]	Area Percent %
1	13.436	BB	0.3276	2.13720e4	1023.35974	100.0000