**Electronic supplementary materials** *Mendeleev Commun.*, 2019, **29**, 498–499

# Efficient and stereoselective synthesis of (*S*)-α-propargylglycine derivatives from allenylboronic acid

**Veronika A. Morozova, Irina P. Beletskaya and Igor D. Titanyuk**

## Experimental

### 1. General

Nuclear magnetic resonance ($^1$H NMR, $^{13}$C NMR) spectra were measured at 25 °C in an indicated solvent with Bruker AV-400 spectrometer or Agilent 400-MR spectrometer. $^1$H and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz respectively. The proton chemical shifts are reported in ppm from the residual proton signal of solvent. High resolution mass spectra (HRMS) were measured on a Bruker maXis instrument using electrospray ionization (ESI). IR spectra were recorded with the Specord UR-20 infrared spectrometer. Optical rotation values recorded using VNIEKI Prodmash polarimeter. Analytical thin layer chromatography (TLC) was performed on Silica gel 60 $F_{254}$ Plates (Merck, 0.25 mm thickness). Silica gel column chromatography was performed using Silica 60 (Macherey-Nagel, 0.040 – 0.063 mm) using indicated solvent systems. Reagents were purchased from commercial supplier (Sigma-Aldrich) and were used without further purification. Benzyl azide (0.5 M sln in $CH_2Cl_2$) was purchased from Sigma-Aldrich. Starting azides explored for preparation of conjugates **8** and **10** were synthesized according to published procedures[S1,S2]. 5-(4-azidophenyl)-10,20-bis(4-*tert*-butylphenyl)-15-mesitylporphyrin zinc was a gift of Dr. V. S. Tyurin (Frumkin Institute of physical chemistry and electrochemistry).
Anhydrous dichloromethane was prepared by distillation from calcium hydrate. Anhydrous diethyl ether was prepared by distillation from sodium.

### 2. Preparation of allenylboronic acid (1)

#### 2.1. Allenylmagnesium bromide

In a three-necked flask equipped with a reflux condenser, propargyl bromide (0.36 g, 2.4 mmol, 80% solution in toluene) was added to a mixture of Mg (1.1 g, 45 mmol) and $HgCl_2$ (32 mg, 0.117 mmol) in 60 ml of dry ether under argon atmosphere. The mixture was heated to 40 °C until bubbles began to release. Then the rest propargyl bromide (2.826 g, 19 mmol, 80% solution in toluene) was added to the reaction mixture in small portions. After the addition was complete, the mixture was stirred at room temperature for 1.5 hours until it became cloudy white. The resulting solution was decanted into another flask to get rid of excess Mg. **Important!** The solution of allenylmagnesium bromide is not stable during storage, it is necessary to use it immediately after preparation.

**2.2. Allenylboronic acid**

Freshly prepared allenylmagnesium bromide solution (60 ml in ether, ~ 20 mmol) and a solution of trimethyl borate (2.78 g, 26.7 mmol) in ether (30 ml) were added simultaneously, but separately, over 1 h period to 25 ml of ether maintained at -78 °C. The mixture was stirred at -78 °C for more 2 h (heavy precipitate was formed) and then was warmed to 0 °C, when cold HCl (2 *M* aq., 40 ml) was added. The two-phase mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with $Et_2O$-$CH_2Cl_2$solvent mixture (5:1, 3 x 20 ml). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuum to a volume about 20 ml (anhydrous, concentrated allenylboronic acid is unstable). The yield of boronic acid was not determined, therefore, for further reactions, it was conventionally assumed that all propargyl bromide was transformed into boronic acid.

**3. 2-{*N*-[(*S*)-1-Phenylethyl]amino}pent-4-ynoic acid** (**4**)

To a stirred solution of glyoxalic acid monohydrate (920 mg, 10 mmol) in $CH_2Cl_2$ (10 ml) (*S*)-1-phenylethylamine (1.212 g, 10 mmol) was added in one portion, and the solution stirred for 5 min. Then allenylboronic acid **7** (15 ml, 15 mmol, 1.5 equiv based on propargyl bromide used in the previous step) was added, and the reaction mixture was stirred vigorously at room temperature for 24 h. The precipitate was isolated by filtration and washed with ether (10 ml). The crude material gave good spectroscopic data, while $^1$H-NMR indicated 81:19 *dr*. No additional purification required. White powder. Yield: 1.996 g (91%). Major diastereomer (*R*,*S*) (signals taken from mixture): $^1$H NMR (methanol-$d_4$/$D_2O$, 400 MHz) δ: 7.55-7.35 (m, 5H), 4.51 (m, 1H), 3.53 (dd, $J_1$ = 4.7 Hz, $J_2$ = 7.0 Hz, 1H), 2.93-2.85 and 2.78-2.68 (m, 2H), 2.56 (m, 1H), 1.68 (d, $J$ = 5.9 Hz, 3H); $^{13}$C NMR (methanol-$d_4$/$D_2O$, 100 MHz) δ: 184.1, 135.4, 129.5, 129.0, 128.0, 75.3, 74.0, 58.9, 56.1, 19.7, 18.3. Minor diastereomer (*S*,*S*) (signals taken from mixture): $^1$H NMR (methanol-$d_4$, 400 MHz) δ: 7.55-7.35 (m, 5H), 4.43 (q, 1H, $J$ = 6.0 Hz,), 3.53 (dd, 1H, $J_1$ = 4.7 Hz, $J_2$ = 7.0 Hz), 2.93-2.85 and 2.78-2.68 (m, 2H), 2.50 (m, 1H), 1.61 (d, 3H, $J$ = 5.9 Hz);

Analysis (mixture): Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45; found: C, 71.68; H, 6.90; N, 6.53.

**4. *N*-[(*S*)-(1-Phenylethyl)amino]pent-4-ynoic acid methyl ester (5)**

To a stirred suspension of amino acid **4** (434 mg, 2 mmol) in methanol (5 ml), $SOCl_2$ (714 mg, 6 mmol) was added. The mixture was refluxed for 3 h and then stirred at room temperature for 12 h. pH was adjusted to ~9 with aqueous $K_2CO_3$. Excess of methanol was removed in vacuum and then the aqueous phase was extracted with ether (3 x10-ml). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuum. Purification of the residue by column chromatography (EtOAc/petrol ether, 1:15 v/v) gave separated diastereomers **(*R*,*S*)-5** and **(*S*,*S*)-5** in a total yield 423 mg (89%). Major diastereomer: (*R*)-*N*-[(*S*)-(1-phenylethyl)amino]-pent-4-ynoic acid methyl ester (**(*R*,*S*)-5**). Yellow oil. Yield 301 mg (63%).

$[\alpha]_D^{20}$ = -44.9° (*c* 2.58, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.23 (m, 5H), 3.86 (q, $J$ = 6.5 Hz, 1H), 3.64 (s, 3H), 3.44 (t, $J$ = 5.5 Hz, 1H), 2.58 (m, 2H), 2.14 (bs, NH), 2.04 (s, 1H), 1.37 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 173.5, 144.6, 128.5, 127.2, 126.8, 79.5, 71.1, 57.1, 55.8, 52.0, 23.8, 22.7; Analysis: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; found: C, 72.46; H, 7.16; N, 6.31.

Minor diastereomer: (*S*)-*N*-[(*S*)-(1-phenylethyl)amino]pent-4-enoic acid methyl ester (**(*S,S*)-5**). Yellow oil. Yield 120 mg (25 %) contaminated with 30% (R,S) isomer. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.25 (m, 5H), 3.79 (q, *J* = 6.6 Hz, 1H), 3.74 (s, 3H), 3.21 (t, *J* = 5.8 Hz, 1H), 2.51 (m, 2H), 2.11 (bs, NH), 2.04 (s, 1H), 1.35 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 174.3, 144.7, 128.5, 127.2, 126.9, 79.5, 71.1, 57.1, 56.6, 51.9, 23.9, 22.8.

**5. Cu$^{I}$-Catalyzed 1,3-dipolar cycloaddition of amino ester (*R,S*)-5. General Procedure**

To a stirred solution of CuI (19 mg, 0.1 mmol, 0.1 eq.) and DIPEA (65 mg, 0.5 mmol, 0.5 eq.) in DMF (2 ml) amino ester (*R,S*)-**5** (231 mg, 1 mmol, 1 eq.) and corresponding azide (1 mmol, 1 eq) were added. The mixture was stirred at room temperature for 24 hours under argon atmosphere. Then 50 ml of water and 50 ml of ethyl acetate were added. The organic layer was separated; the aqueous layer was washed with 3 × 50 ml of ethyl acetate. The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuum. Purification of the product was carried out by column chromatography on silica.

**5.1. Methyl 3-(1-benzyl-*1H*-1,2,3-triazol-4-yl)-*N*-[(*S*)-1-phenylethyl]-D-alaninate (7)**

Obtained from **(*R,S*)-5** and benzyl azide. Chromatography: ethyl acetate/petrol ether 2:1 v/v. Yellow oil. Yield 324 mg (87%). $[\alpha]_D^{20}$ = -19,7° (*c* 1,522, $CHCl_3$); IR (KBr): 702, 731, 1204, 1559, 1630, 1736, 3325; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.10 (m, 11H), 5.44 (s, 2H), 3.76 (dd, $J_1$ = 6.7 Hz, $J_2$ = 13.1 Hz, 1H), 3.61 (s, 3H), 3.38 (m, 1H), 2.95 (dd, $J_1$ = 4.6 Hz, $J_2$ = 9.9 Hz, 2H), 2.12 (bs, NH), 1.27 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 174.6, 144.9, 144.2, 135.0, 129.1, 128.7, 128.5, 127.9, 127.2, 126.8, 122.1, 58.6, 56.1, 54.0, 51.8, 29.2, 23.3. Analysis: Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37; found: C, 69.07; H, 6.72; N, 15.14.

**5.2. Methyl (2*R*)-3-(1-((3a*R*,5*S*,6*R*,6a*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)-1*H*-1,2,3-triazol-4-yl)-2-((*S*)-1-phenylethylamino)propanoate (8)**

Obtained from **(*R,S*)-5** and 3-azido-3-deoxy-1,2:5,6-bis(O,O-propylidene)-D-glucofuranose. Chromatography: ethyl acetate/petrol ether 2:1 v/v. Yellow oil. Yield 258 mg (50%). $[\alpha]_D^{20}$ = +54.0° (*c* 0.28, $CHCl_3$); IR (KBr): 702, 764, 1217, 1552, 1603, 1736, 3300-3700; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (s, 1H), 7.23 (m, 5H), 5.95 (m, 1H), 5.12 (m, 1H), 4.81 (m, 1H), 4.41 (m, 1H), 4.25 (m, 1H), 3.96 (m, 1H), 3.79 (m, 1H), 3.60 (m, 1H), 3.55 (s, 3H), 3.48 (m, 1H), 3.06 (m, 2H), 2.03 (bs, NH), 1.62 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.26 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 174.6, 144.9, 143.7, 128.5, 127.2, 126.8, 122.6, 113.6, 110.1, 104.2, 79.2, 78.0, 75.3, 65.6, 62.5, 58.6, 56.2, 51.8, 29.4, 26.7, 26.4, 26.2, 25.1, 23.3; Analysis: Calcd for $C_{26}H_{36}N_4O_7$: C, 60.45; H, 7.02; N, 10.85; found: C, 60.54; H, 7.18; N, 10.92.

**5.3. Compound 9**

To a stirred solution of CuI (3.8 mg, 0.02 mmol) and DIPEA (3 mg, 0.023 mmol) in THF/$CH_3CN$ (5:1, 1 ml) amino ester **(*R,S*)-5** (10 mg, 0.043 mmol, 1.26 eq) and 5-(4-azidophenyl)-15-(4-*tert*-butylphenyl)-10,20-dimesitylporphyrin zinc (30 mg, 0.034 mmol, 1 eq) were added. The mixture was stirred at 60 °C for 3 h and at room temperature for 24 hours under argon atmosphere. The solvents were evaporated in vacuum. Purification of the product was carried out by column chromatography on silica using $CH_2Cl_2$, then ethyl acetate/petrol

ether 2:1 v/v. Red solid. Yield 26 mg (69%). $[\alpha]_D^{20}$ = -114.3° (*c* 0.04, $CH_3OH$); $^1H$ NMR ($CDCl_3$, 400 MHz) δ: 8.80 (d, *J* = 1.5 Hz, 4H), 8.73 (s, 4H), 8.30 (m, 2H), 7.79 (m, 3H), 7.31-7.22 (m, 14H), 3.83-3.58 (m, 3H), 3.55 (s, 3H), 3.35 (m, 1H), 2.64 (s, 6H), 2.63 (s, 3H), 2.35 (bs, NH), 1.88 (s, 6H), 1.86 (s, 12H), 1.32 (d, *J* = 6.6 Hz, 3H); IR (KBr): 734, 805, 1005, 1540, 1615, 1746; MS (MALDI-TOF) m/z: 1074 ($[M-CH_3]^+$).

### 5.4. Methyl 2-(*tert*-butoxycarbonylamino)-3-(4-((*R*)-3-methoxy-3-oxo-2-((*S*)-1-phenylethylamino)propyl)-*1H*-1,2,3-triazol-1-yl)propanoate (10)

Obtained from **(*R,S*)-5** and racemic methyl 3-azido-2-(*N*-Boc-amino)propionate.
Chromatography: ethyl acetate/petrol ether 1:2 v/v, then pure ethyl acetate. Colorless oil . Yield 351 mg (74%). IR (KBr, 1:1 diastereomeric mixture): 704, 764, 1167, 1504, 1600, 1716, 1734; $^1H$ NMR ($CDCl_3$, 400 MHz, 1:1 diastereomeric mixture) δ: 7.35 (d, *J* = 6.0 Hz, 1H), 7.29-7.20 (m, 4H), 7.12-7.19 (m, 1H), 5.40 (bs, NH), 4.72 (m, 3H), 3.78 (m, 1H), 3.73 (s, 3H), 3.58 (m, 1H), 3.53 (s, 3H), 3.07 (dd, $J_1$ = 5.9 Hz, $J_2$ = 14.9 Hz, 1H), 2.97 (dd, $J_1$ = 6.2 Hz, $J_2$ = 14.9 Hz, 1H), 2.13 (bs, NH), 1.41 (s, 9H), 1,29 (d, *J* = 2.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz, 1:1 diastereomeric mixture) δ: 174.4, 169.5, 144.9, 143.7, 128.5, 127.2, 126.7, 123.3, 80.6, 58.4, 56.1, 56.0, 53.7, 53.0, 51.8, 50.9, 50.8, 29.0, 28.9, 28.2, 23.4; Analysis: Calcd for $C_{23}H_{33}N_5O_6$: C, 58.09; H, 6.99; N, 14.73; found: C, 85.21; H, 7.08; N, 14.40.

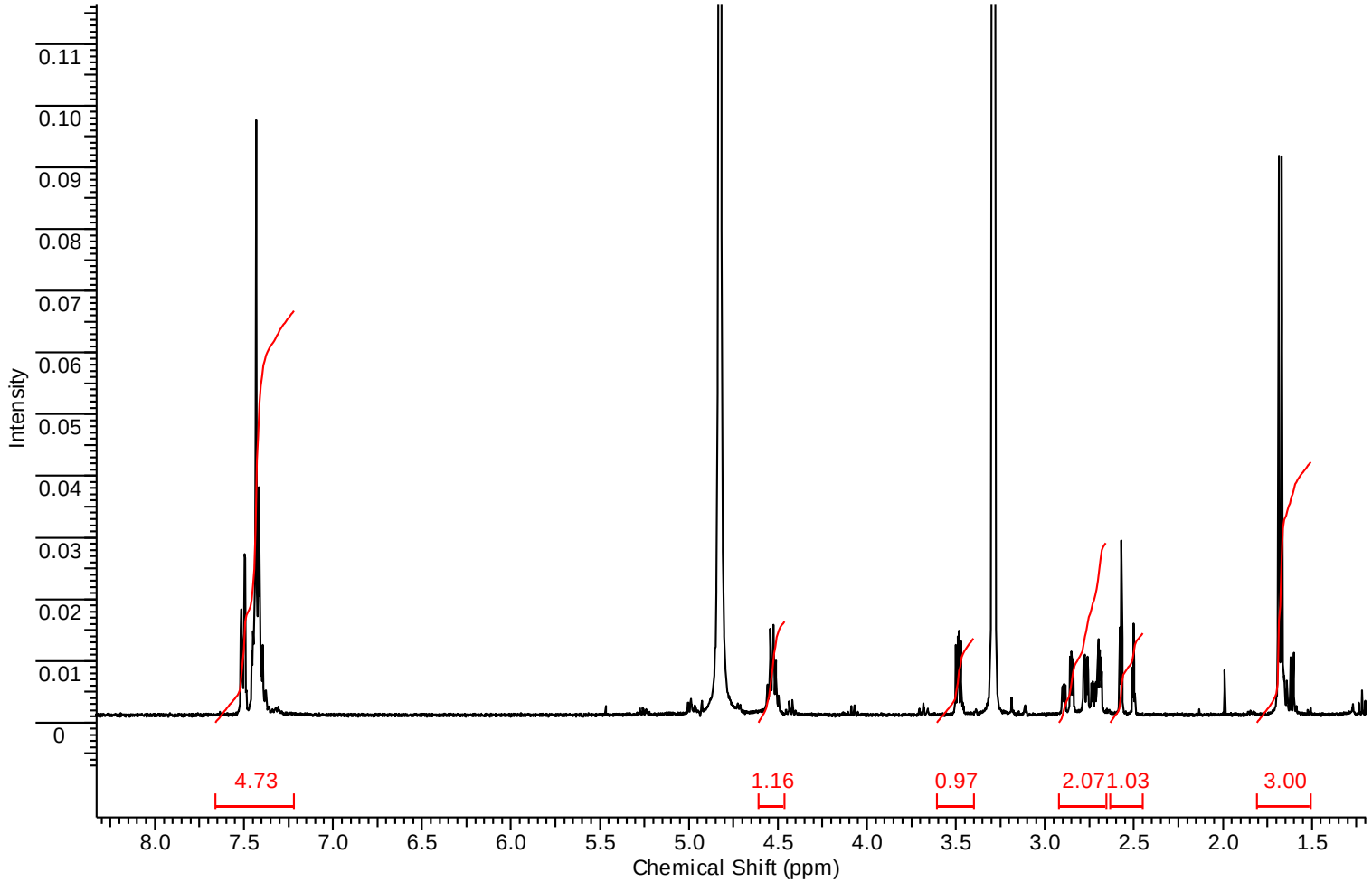
## References

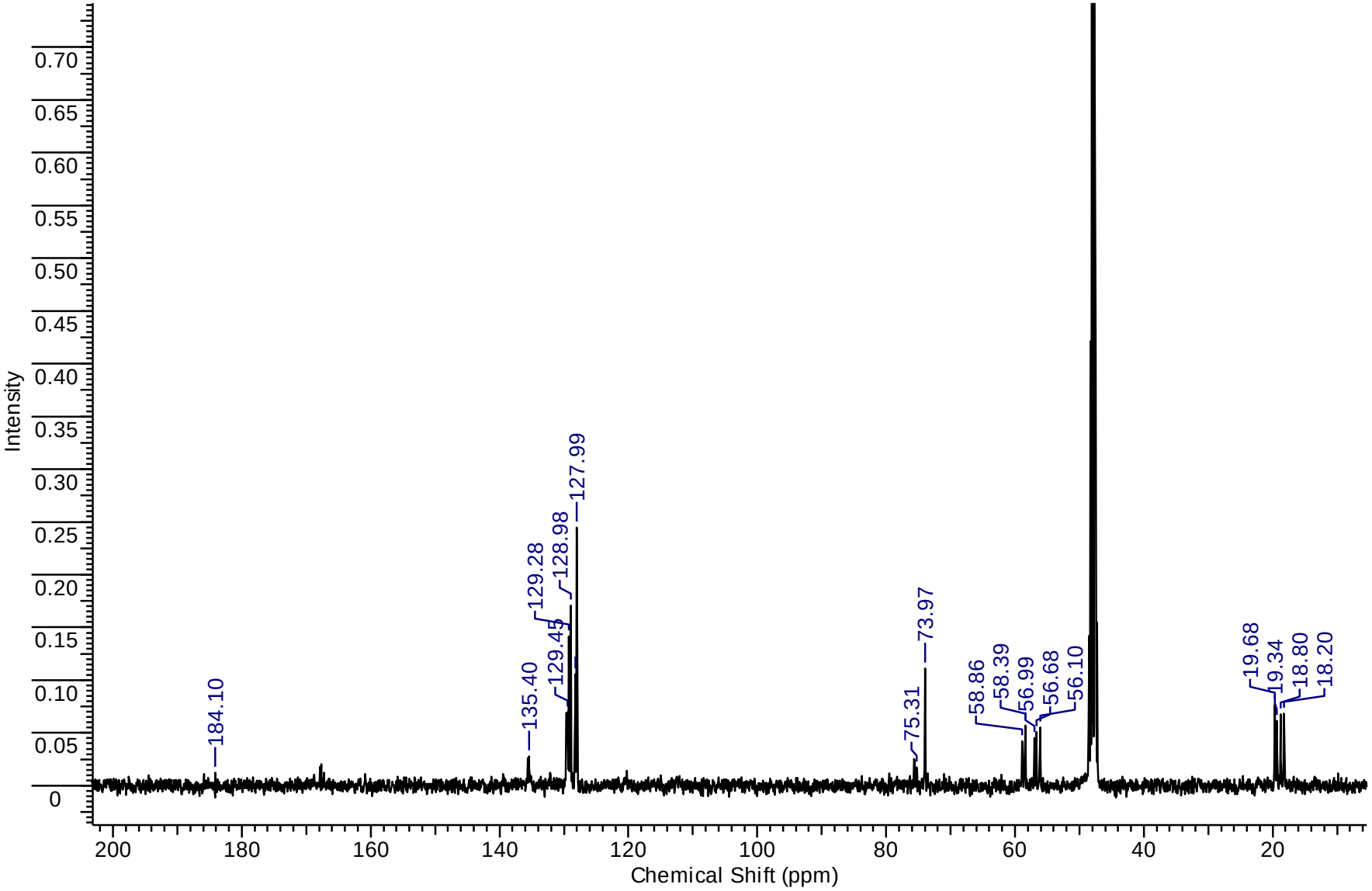

S1. D. Shetty, J. M. Jeong, C. H. Ju, Y. J. Kim, J.-Y. Lee, Y.-S. Lee, D. S. Lee, J.-K. Chung and M. C. Lee, *Bioorg. Med. Chem*., 2010, **18**, 7338.

S2. A-P. Wang, C. Liu, S. Yang, Z. Zhao and P. Lei, *Tetrahedron*, 2016, **72**, 285.

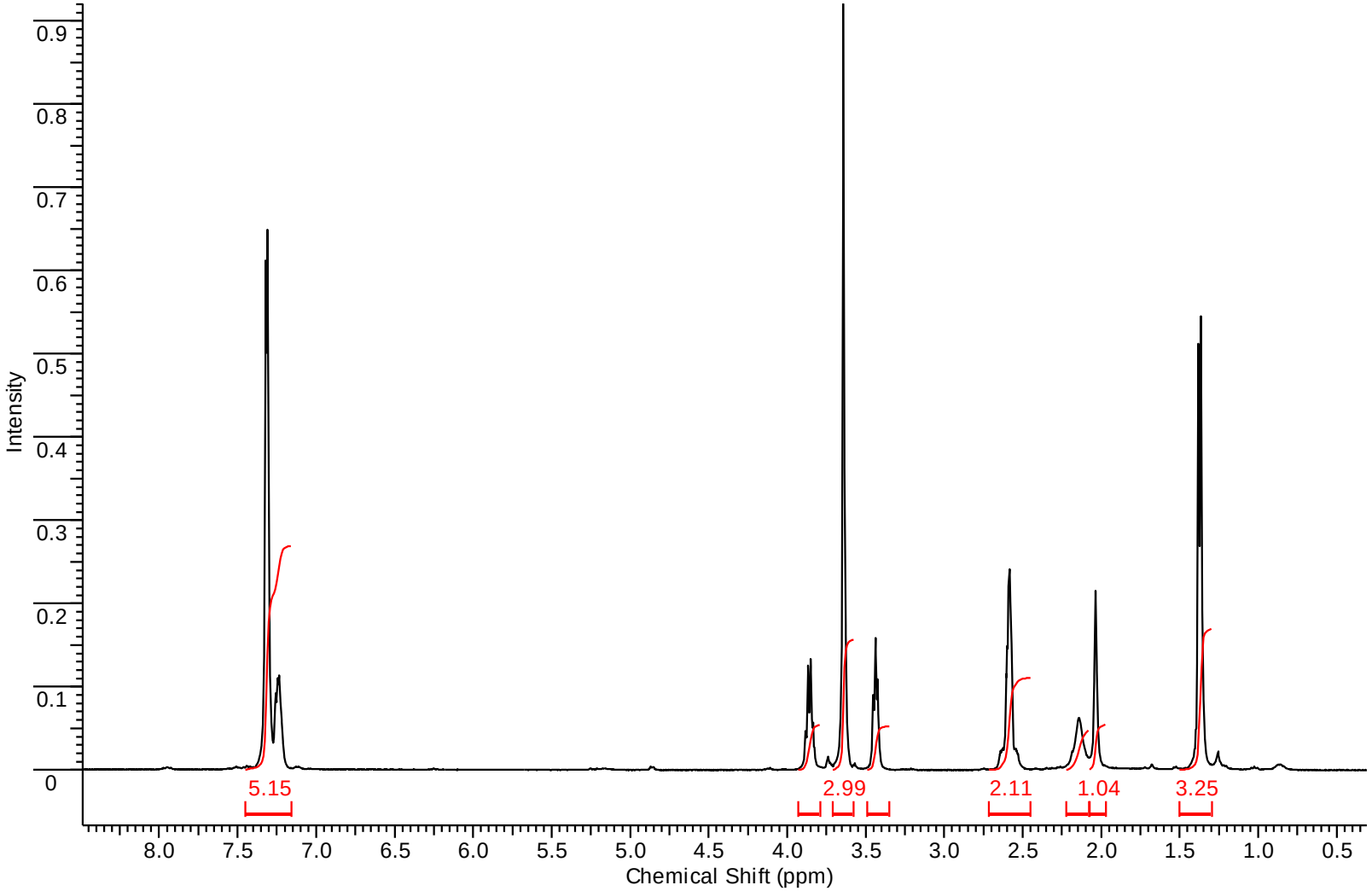
## $^{1}H$ and $^{13}C$ NMR spectra of compounds

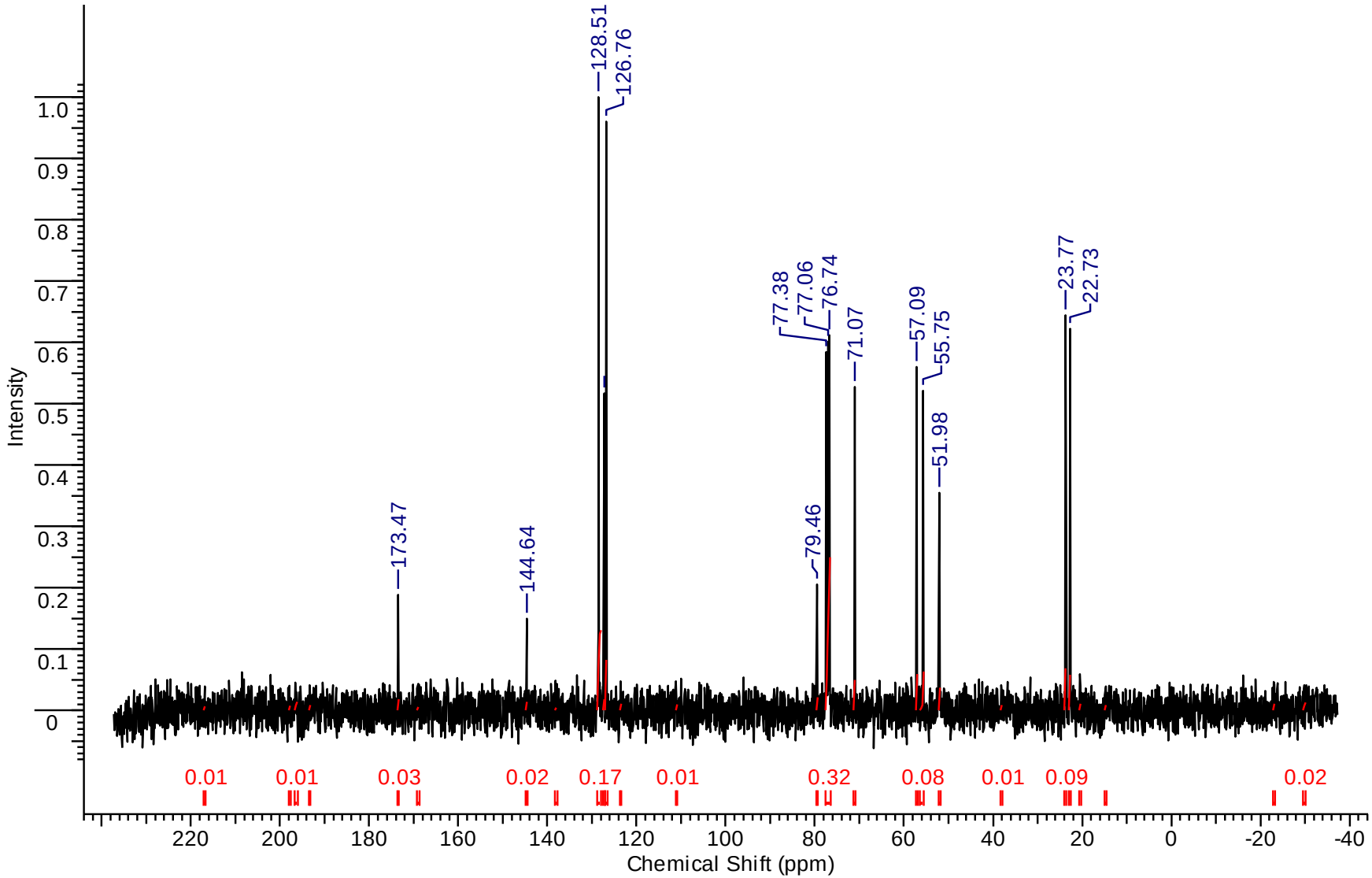
*N-[(S)-1-phenylethyl]pentynoic acid* (**4**)*[dr 81:19]*($CD_3OD/D_2O$)



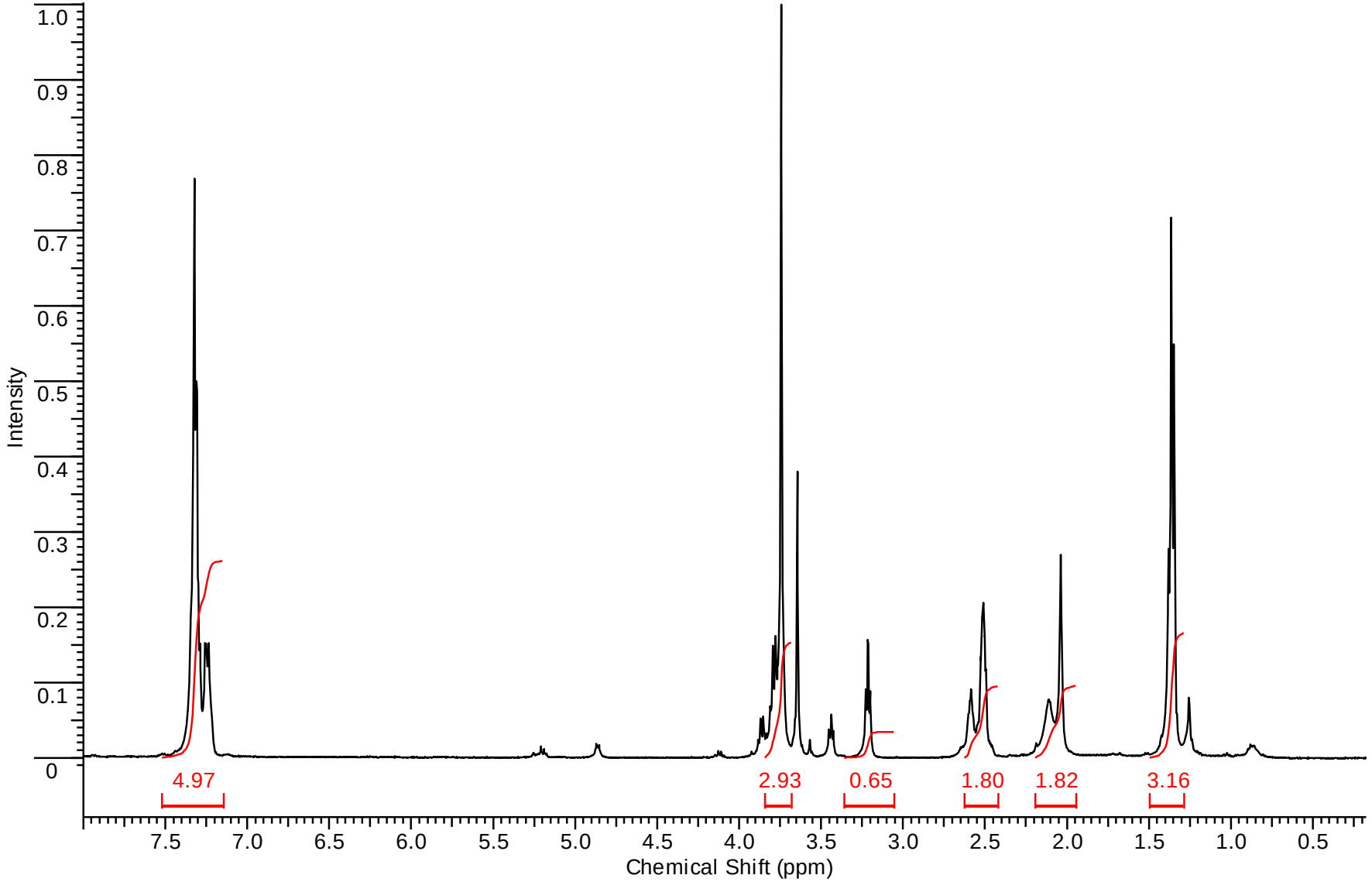

Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)
184.10
135.40
129.45
129.28
128.98
127.99
75.31
73.97
58.86
58.39
56.99
56.68
56.10
19.68
19.34
18.80
18.20

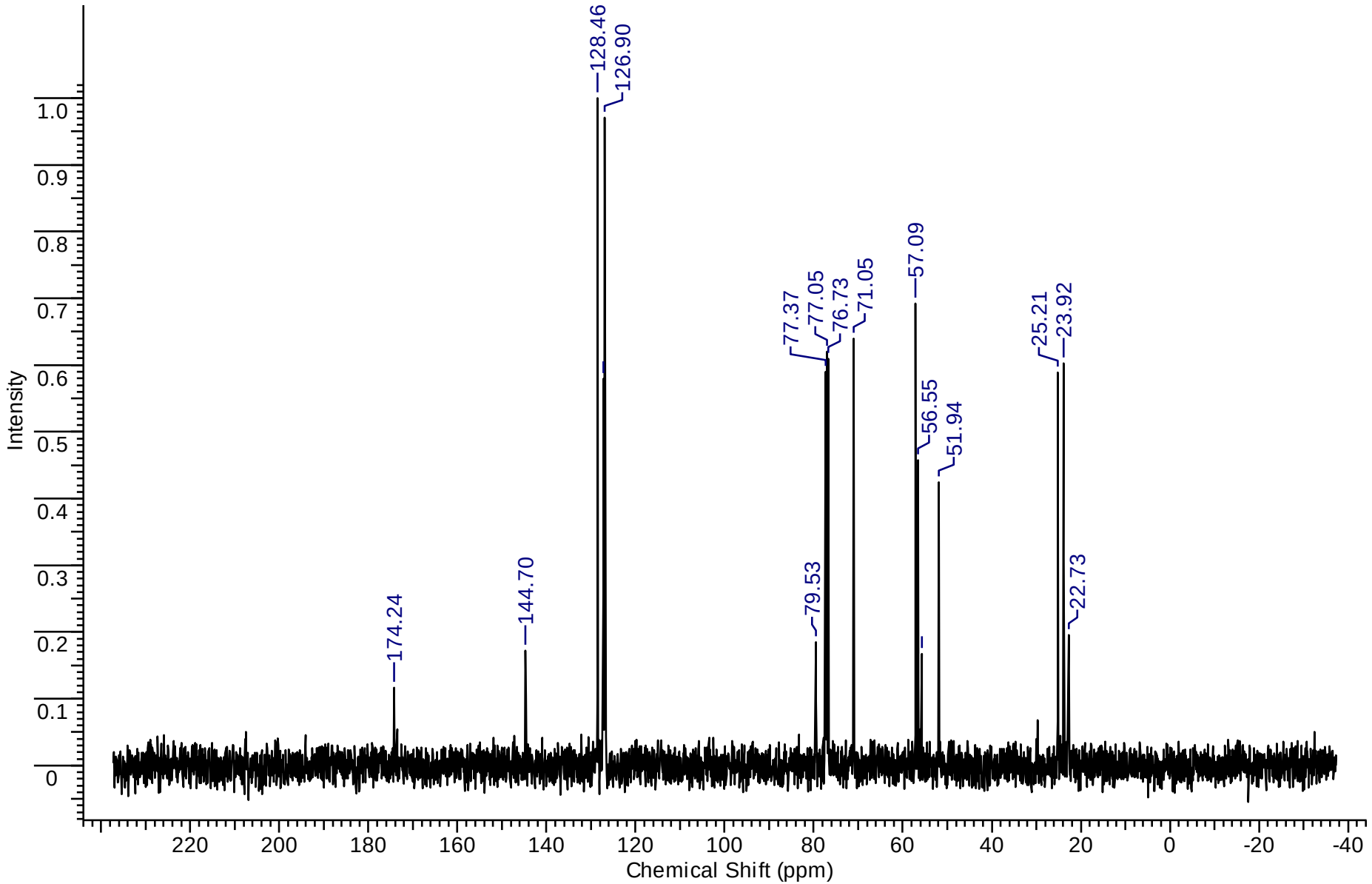
*(R)-N-[(S)-(1-phenylethyl)amino]pent-4-ynoic acid methyl ester* (**(*R*,*S*)-5**) ($CDCl_3$)



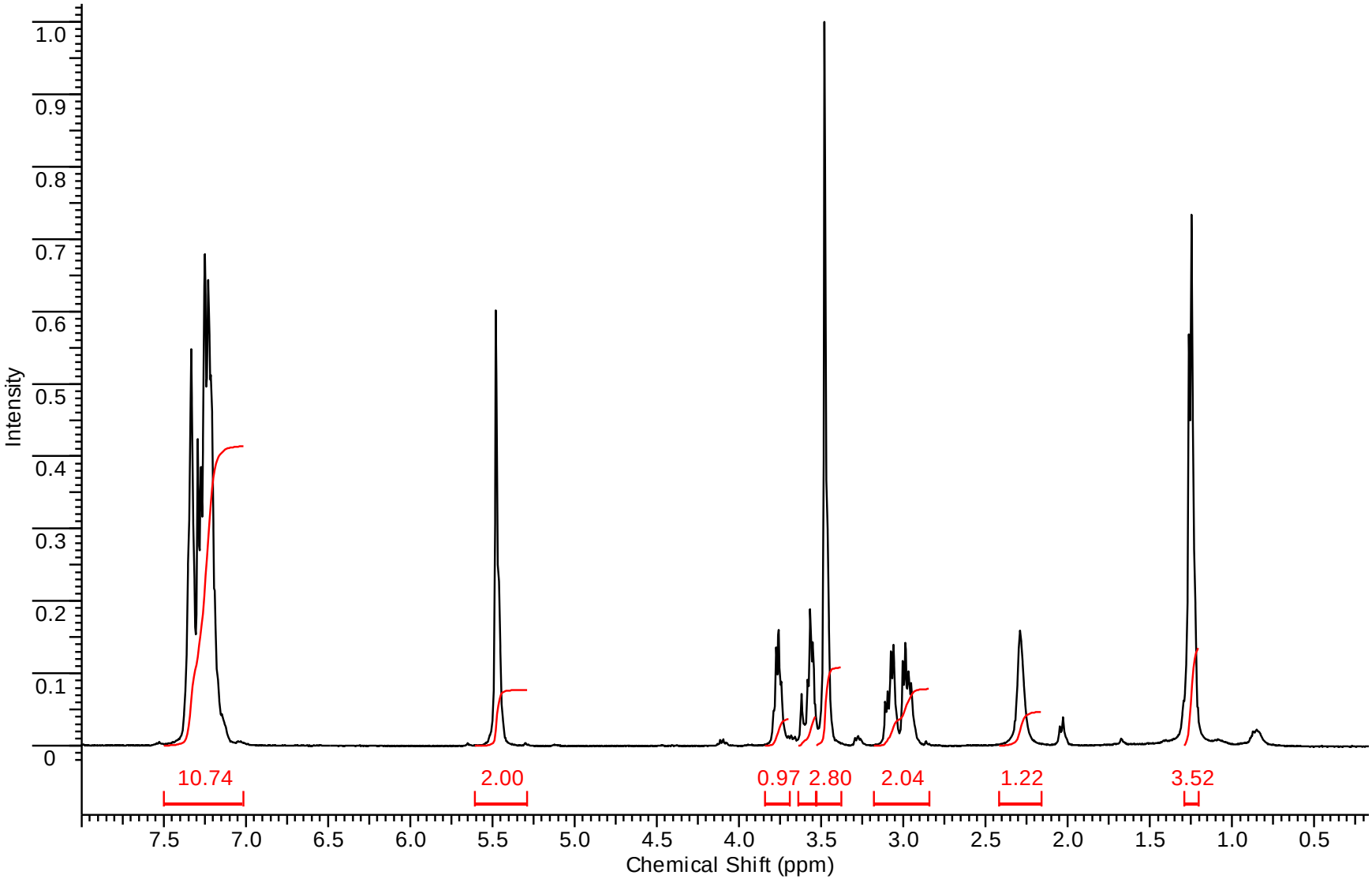

Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
128.51
126.76
77.38
77.06
76.74
71.07
57.09
55.75
51.98
23.77
22.73
173.47
144.64
79.46
0.01
0.01
0.03
0.02
0.17
0.01
0.32
0.08
0.01
0.09
0.02
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)

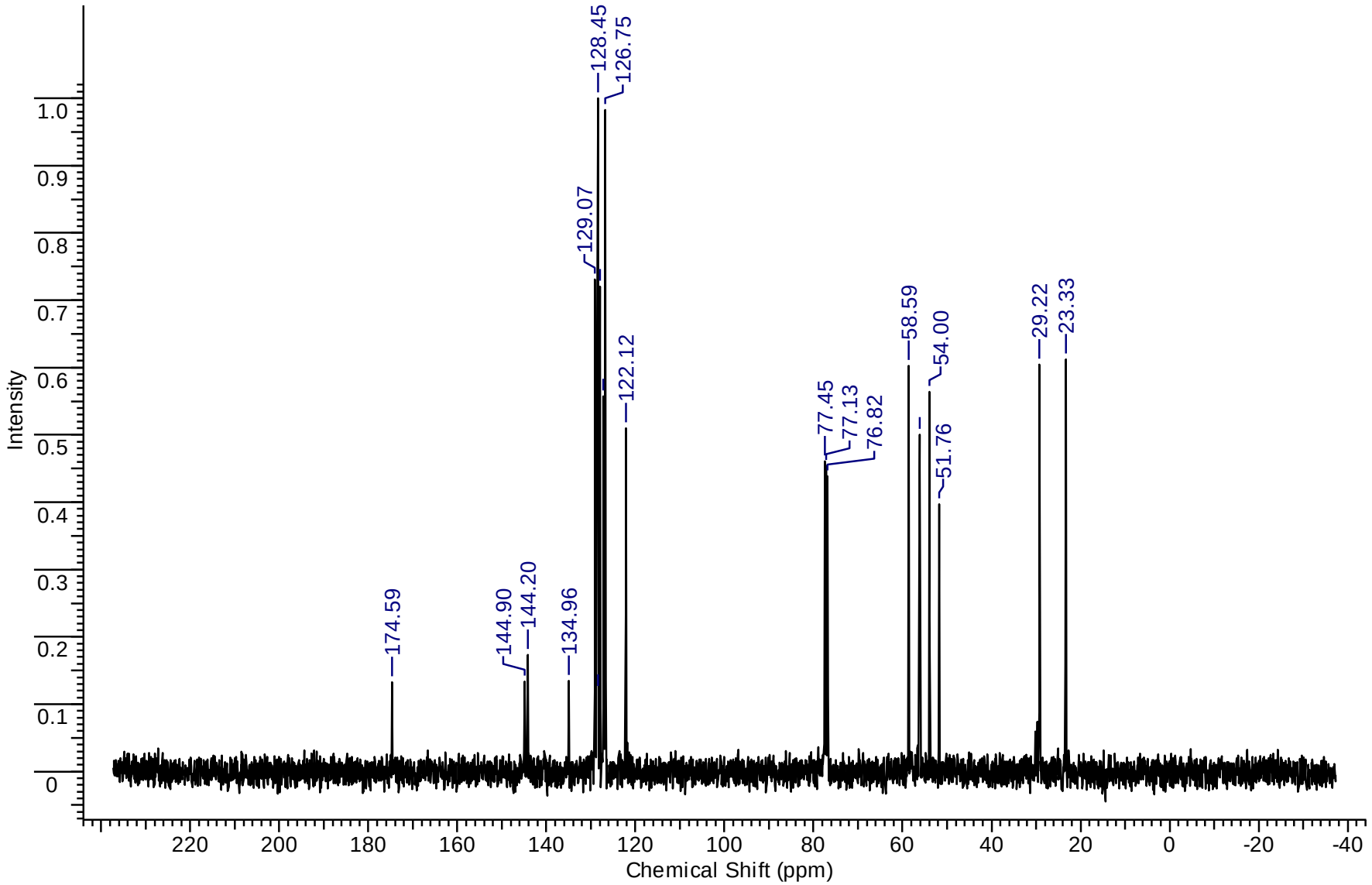
*(S)-N-[(S)-(1-phenylethyl)amino]pent-4-ynoic acid methyl ester* (**(*S,S*)-5**) (contaminated with **(*R,S*)-5**)



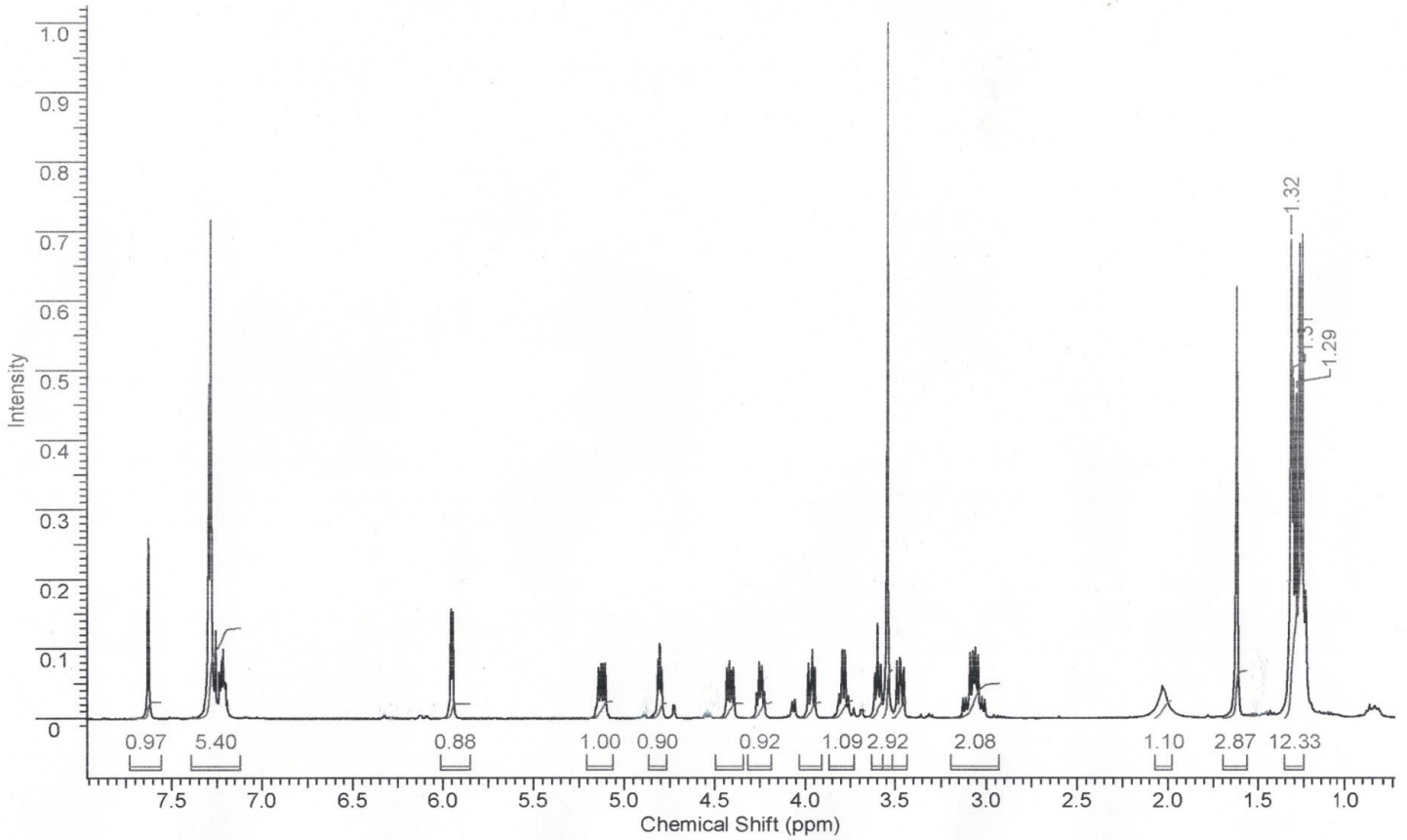

128.46
126.90
77.37
77.05
76.73
71.05
57.09
56.55
51.94
25.21
23.92
174.24
144.70
79.53
22.73
Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)

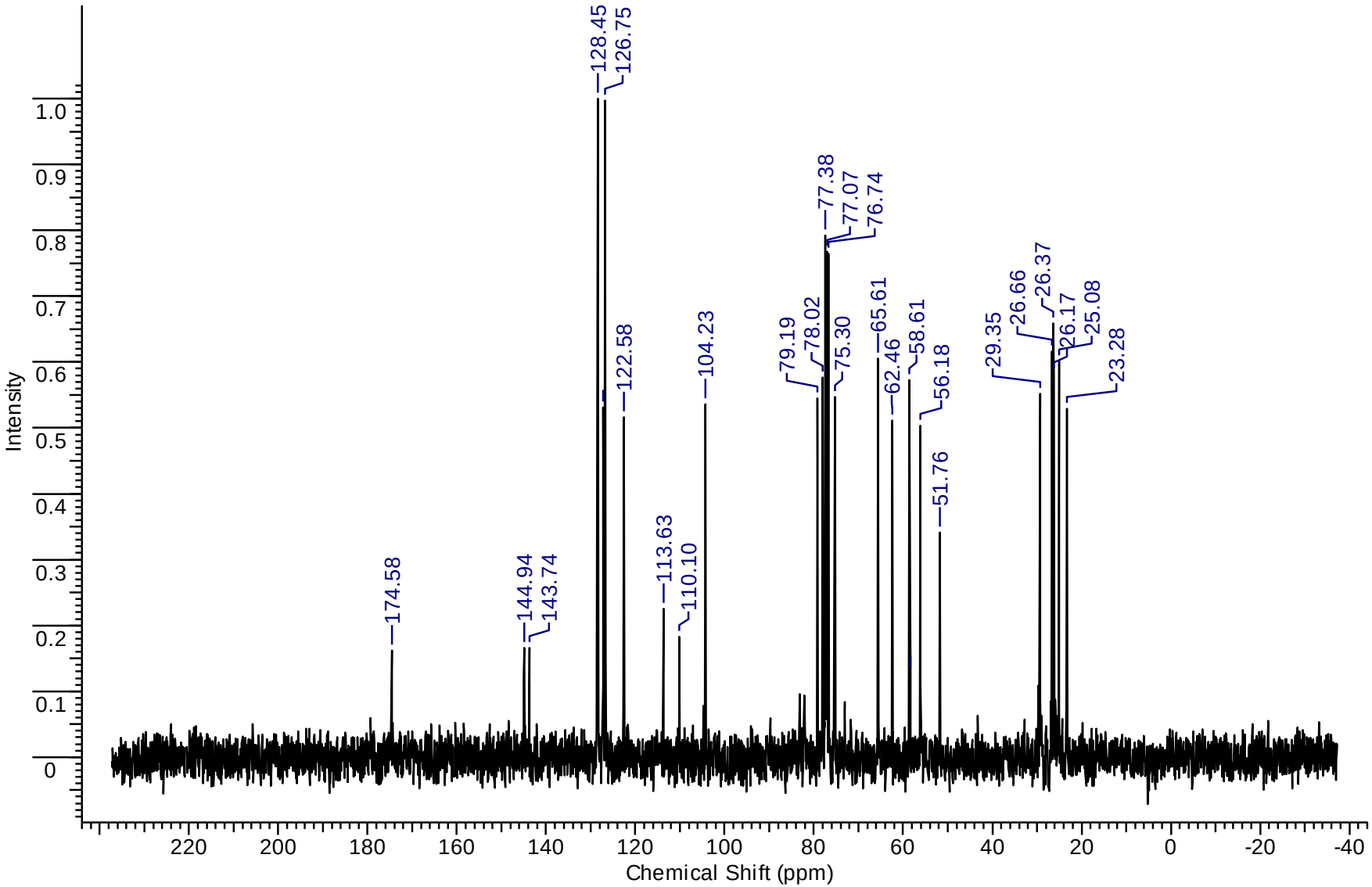
*Methyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-N-[(1S)-1-phenylethyl]-D-alaninate* **(7)**



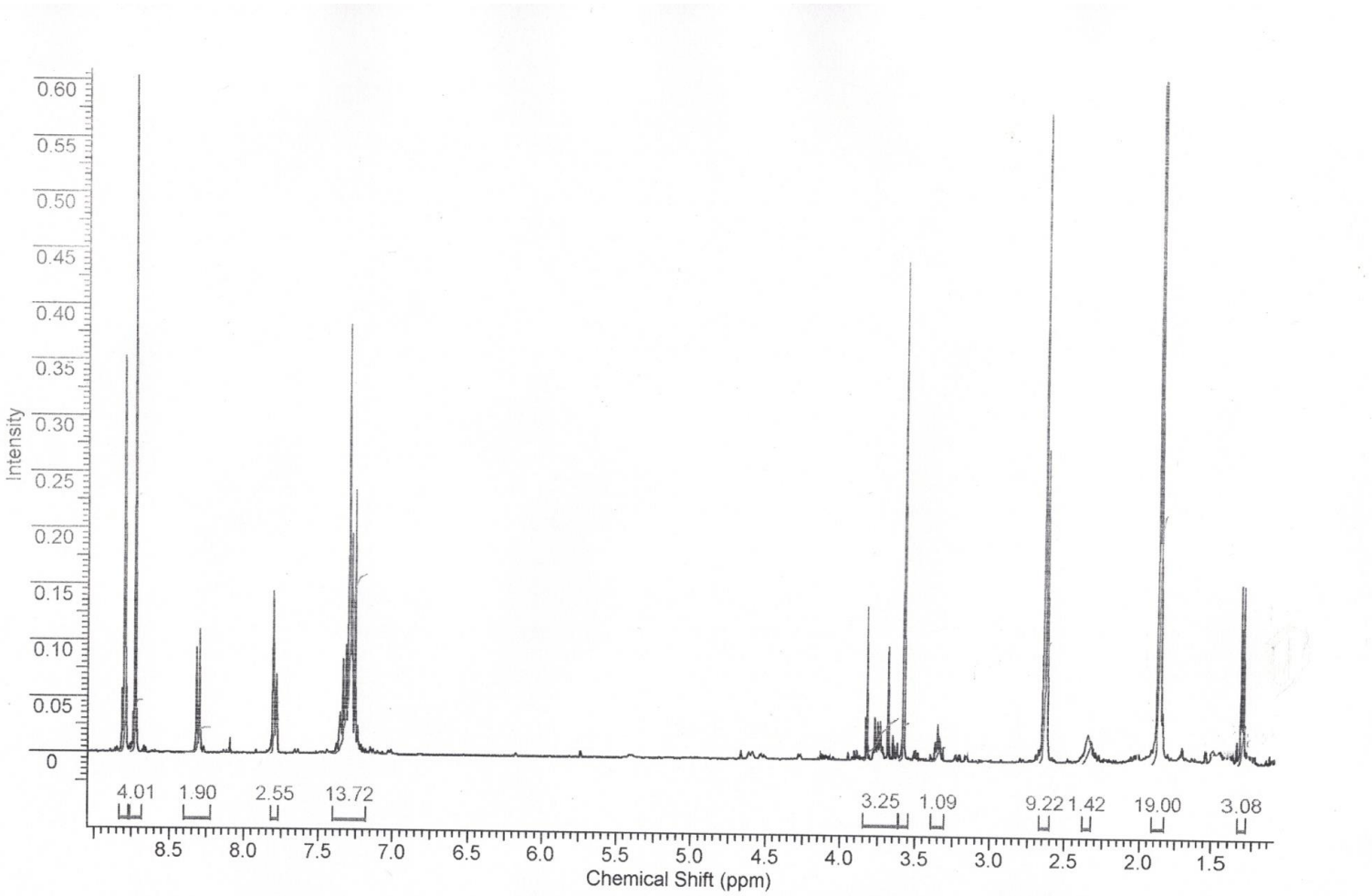

Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)
174.59
144.90
144.20
134.96
129.07
128.45
126.75
122.12
77.45
77.13
76.82
58.59
54.00
51.76
29.22
23.33

*Methyl (2R)-3-(1-((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)-2-((S)-1-phenylethylamino)propanoate* **(8)**

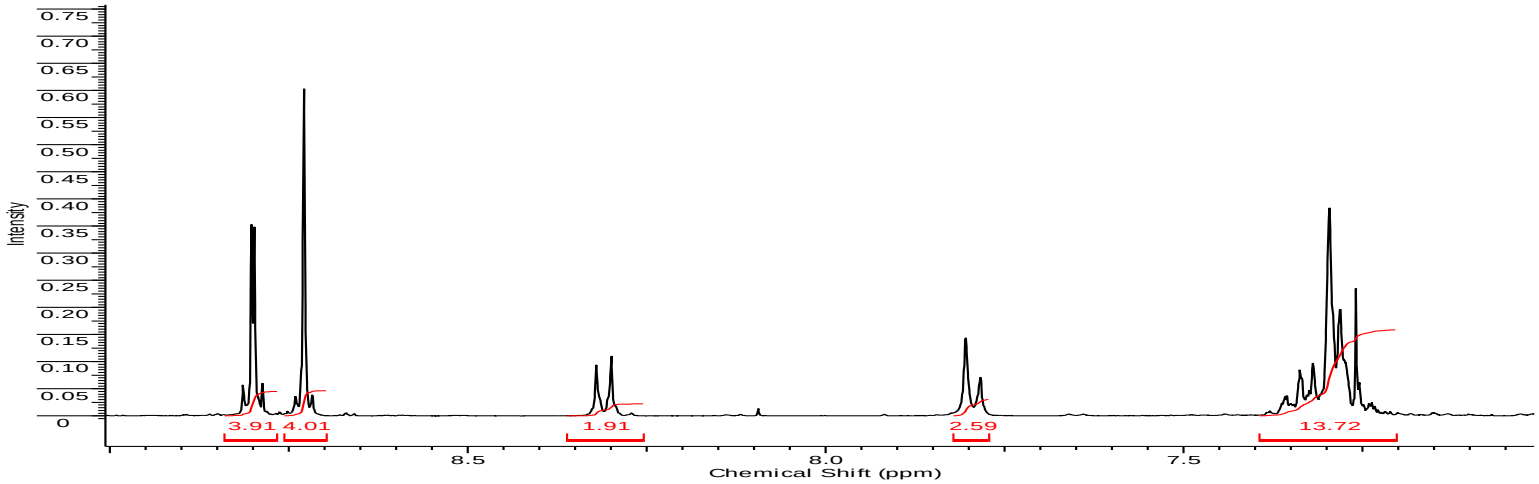


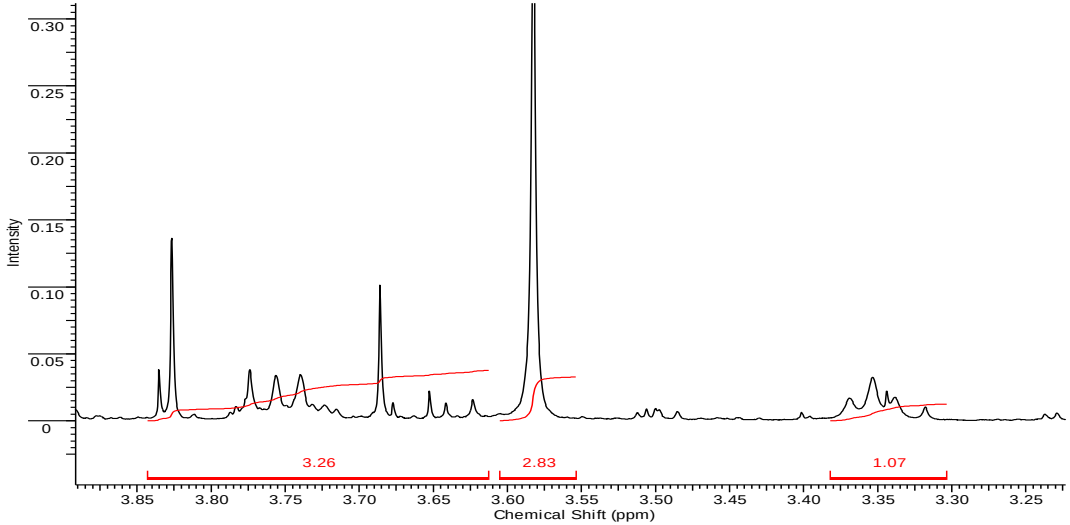

128.45
126.75
77.38
77.07
76.74
122.58
104.23
79.19
78.02
75.30
65.61
62.46
58.61
56.18
51.76
29.35
26.66
26.37
26.17
25.08
23.28
174.58
144.94
143.74
113.63
110.10
Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)

*Compound* **9**

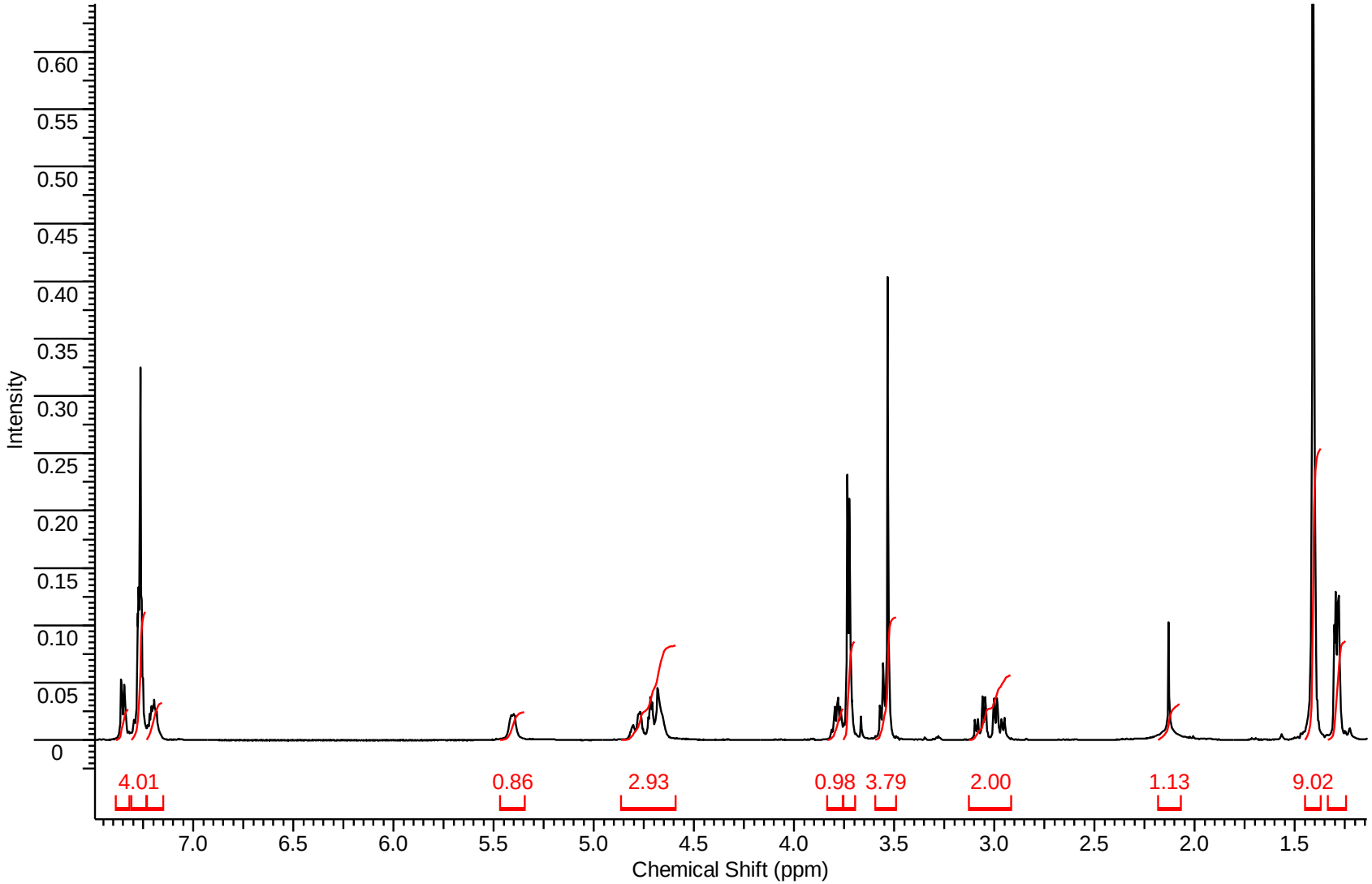

Intensity
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
4.01
1.90
2.55
13.72
3.25
1.09
9.22
1.42
19.00
3.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

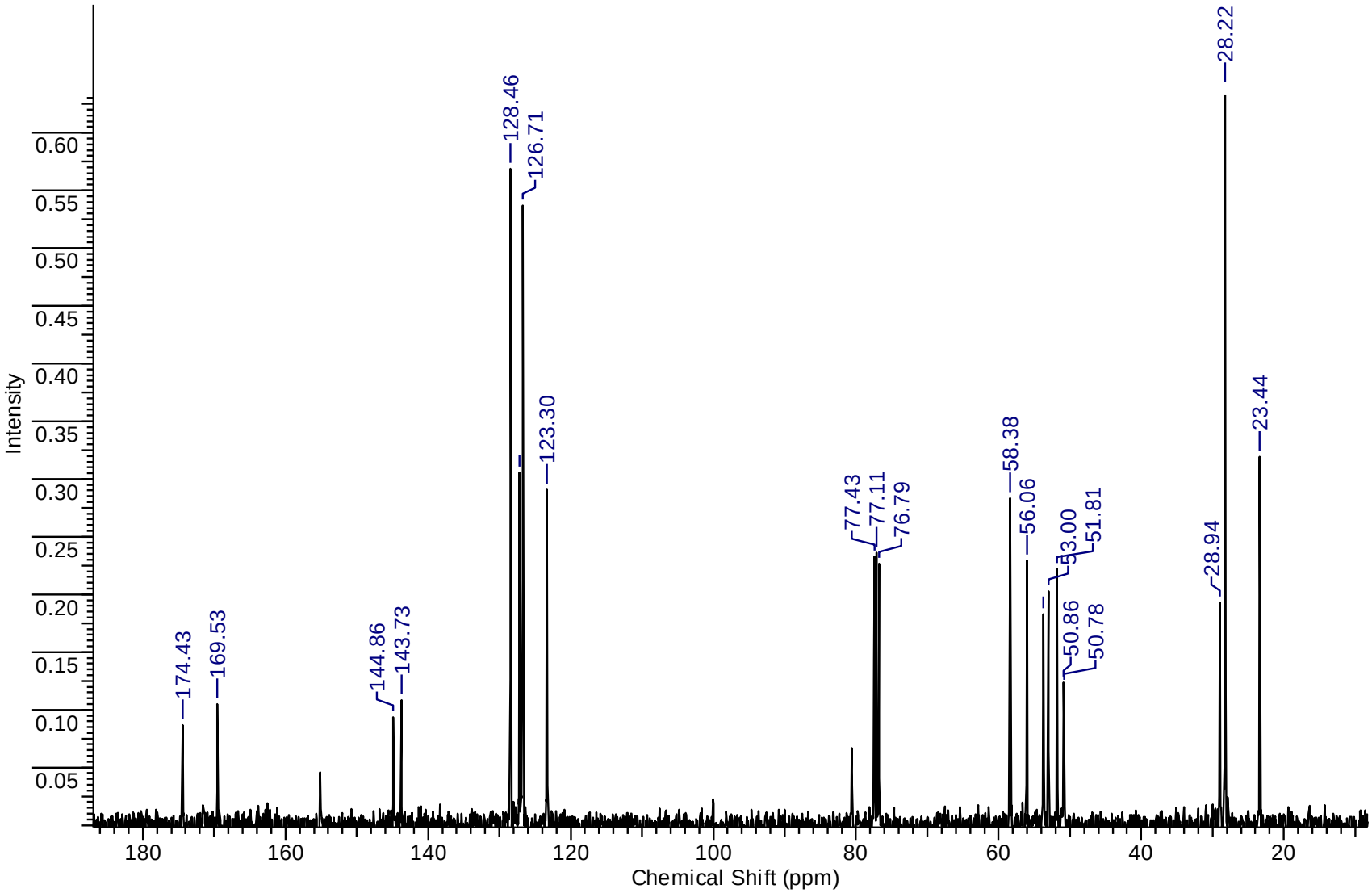
*Compound* **9** (selected regions)



*Methyl 2-(tert-butoxycarbonylamino)-3-(4-((R)-3-methoxy-3-oxo-2-((S)-1-phenylethylamino)propyl)-1H-1,2,3-triazol-1-yl)propanoate* **(10)**




Intensity
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)
174.43
169.53
144.86
143.73
128.46
126.71
123.30
77.43
77.11
76.79
58.38
56.06
53.00
51.81
50.86
50.78
28.94
28.22
23.44