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N + PC strategy for the synthesis of phosphinic pseudopeptides incorporating glycine isostere

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Table of Contents

General Experimental Procedures

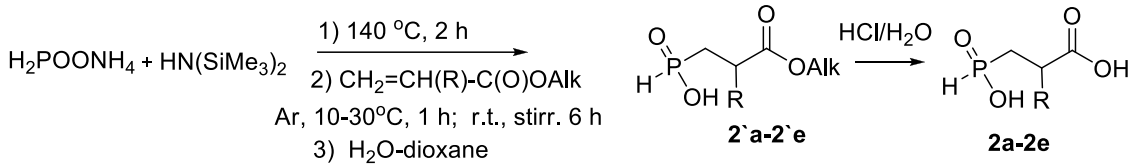
All reagents used in the reactions described in this manuscript are commercial, was purchased **from Acros Organics Ltd., Aldrich Chemical Co. Ltd., Alfa Aesar companies** and were used without additional purification. Reactions described in this paper were controlled using ^{31}P NMR spectroscopy and (or) TLC.

All of the compounds, for which spectral and analytical data are given, were homogenous by TLC. Analytical thin layer chromatography was carried out on silica-coated aluminium plates (silica gel Silufol-254, starch cohesive) using UV light as visualizing agent (254 nm), and using flame heat for control visualization. Also chromatograms were visualized in iodine vapor. Column chromatography was performed on silica gel 60 (Merck, 60-250 mesh) with the indicated eluent. All other reagents and solvents: acetic anhydride, acetyl chloride, trifluoroacetic acid, trifluoroacetic anhydride, dichloromethane, toluene and others were used dry. All reactions were performed under an atmosphere of argon with magnetic stirring. Melting points were determined on a Boetius PHMK apparatus or in open glass capillaries and are uncorrected.

The ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer ^{31}P and ^{13}C NMR spectra are fully proton decoupled, also, DEPT ^{13}C NMR experiment was carried out if necessary. ^{31}P NMR chemical shifts are reported on a δ scale (in ppm) downfield from 85% H_3PO_4.

Synthesis of Starting Materials

Phosphonous carboxylic acids (2a-e) were synthesized in according to the procedures reported earlier with minor modification. [S1-S4]



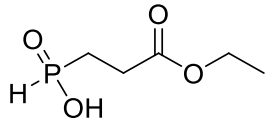
Esters **2`**: Alk=Me(d),Et(a-c,e); R=H(a), Me(b), i-Bu(c), CH_2COOMe(d), CH_2CH_2COOEt(e)
Acids **2**: R=H(a), Me(b), i-Bu(c), CH_2COOH(d), CH_2CH_2COOH(e)

General procedure 2-Carboxyethyl-2-substituted phosphonous acids (2a-e):

Ammonium hypophosphite (24.9 g, 0.3 mol) and hexamethydisilazane (96.8 g, 0.6 mol) were stirred for 2 hours at ~140°C. The corresponding α-substituted acrylate (0.1 mol) at 10-30°C during 1 hour was added slowly dropwise to the pre-cooled mixture under argon. The mixture was stirred at 10-30°C for 1 h, and then 6 hours at r.t. The mixture then was cooled to 5-10°C, and water – dioxane solution (25 ml, 1.4 mol of H_2O/10 ml of dioxane) was added slowly dropwise to the formed solution, and reaction mixture was evaporated *in vacuo*. The residue was partitioned between chloroform (120 ml) and 0.5N HCl solution (40 ml, pH~1). The water phase additionally was twice extracted with chloroform (100 ml). The organic extracts were combined and dried over sodium sulfate and evaporated *in vacuo*. The residue represented esters **2'(a-e)** and was isolated as colorless oil.

Hydrolysis of esters **2'a-e** (60 mmol) with 60 ml 3N HCl after 4 hours reflux gave free phosphonous carboxylic acid **2a-e** in 90-95% yields.

(2-Ethoxycarbonylethyl)phosphonous acid (2'a)



2`a

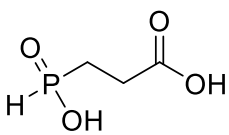
Yield = 47%, colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.02 (s, 1H, P(O)OH), 7.15 (d, $^1J_{PH}$ = 561.2 Hz, 1H, P(O)H), 4.11 (q, 2H, OCH_2), 2.45-2.70 (m, 2H, CH_2CO), 1.90-2.15 (m, 2H, $P(O)CH_2$), 1.22 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 35.9.

Anal. Calcd for $C_5H_{11}O_4P$; %: P 18.65. Found, %: P, 18.37.

(2-Carboxyethyl)phosphonous acid (2a)



2a

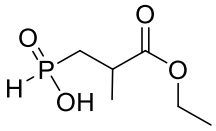
Yield = 91%, colorless very **viscous** oil.

^{1}H NMR (200 MHz, D_2O): δ = 6.95 (d, $^1J_{PH}$ = 558.6 Hz, 1H, P(O)H), 2.35-2.60 (m, 2H, CH_2CO), 1.75-2.00 (m, 2 H, $P(O)CH_2$).

^{31}P NMR (81 MHz, D_2O): δ = 36.80.

Calcd for $C_3H_7O_4P$; %: P, 22.43. Found, %: P, 22.17.

2-(Ethoxycarbonylpropyl)phosphonous acid (2`b)



2`b

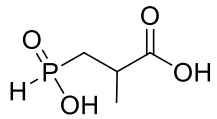
Yield = 76%, colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.71 (s, broad, 1H, P(O)OH), 7.05 (d, $^{1}J_{PH}$ = 561.8 Hz, 1H, P(O)H), 4.03 q (2H, OCH_2), 2.73 m {1H, CHC(O)}, 2.04 m (1H, one of CH_2P), 1.70 m (1H, another of CH_2P), 1.22 d (3H, $\underline{CH_3}CH$, $^{3}J_{HH}$.7.0 Hz), 1.18 t (3H, $\underline{CH_3}CH_2$, $^{3}J_{HH}$.7.1 Hz).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 35.84.

Calcd for $C_6H_{13}O_4P$; %: C, 40.01, H 7.27. Found, %: C, 40.83, 40.77; H 7.53, 7.63.

(2-Carboxypropyl)phosphonous acid (2b)



2b

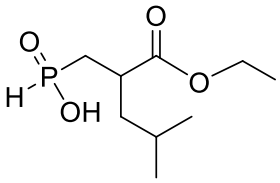
Yield = 93%, colorless oil.

^{1}H NMR (200 MHz, D_2O): δ = 6.96 (d, $^{1}J_{PH}$.= 560.0 Hz, 1H, PH,), 2.67 {m, CHC(O), 1H}, 1.98 m (1H, one of CH_2P), 1.72 m (1H, another of CH_2P), 1.10 (d, 3H, $^{3}J_{HH}$.7.1 Hz, CH_3).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 34.50.

Calcd for $C_4H_9O_4P$; %: P, 20.37. Found, %: P, 19.90, 19.84.

(2-Ethoxycarbonyl-4-methylpentyl)phosphonous acid (2`c)



2`c

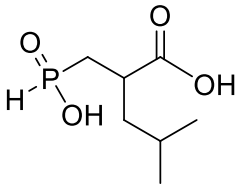
Yield = 68%, colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.36 (s, broad, 1H, P(O)OH), 7.16 (d, $^{1}J_{PH}$.= 558.3 Hz, 1H, PH,), 4.14 (q, 2H, OCH_2, $^{3}J_{HH}$.7.1 Hz), 2.82 m {1H, CHC(O)}, 1.95-2.25 (m, 1H, one of CH_2P), 1.73-1.92 (m, 1H, another of CH_2P), 1.47-1.70 {m, 2H, CH_2(i-Bu)}, 1.25-1.45 {m, 1H, CH(i-Bu)}, 1.25 (t, 3H, $^{3}J_{HH}$.7.1 Hz, CH_3), 0.91 (d, 3H, $^{3}J_{HH}$.6.2 Hz, $CH\underline{CH_3}$), 0.87 (d, 3H, $^{3}J_{HH}$.6.2 Hz, $CH\underline{CH_3}$).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 36.70.

Calcd for $C_9H_{19}O_4P$; %: P, 13.94. Found, %: P, 14.04, 14.14.

(2-Carboxy-4-methylpentyl)phosphonous acid (2c)



2c

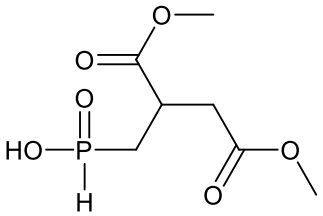
Yield = 97%, colorless oil.

^{1}H NMR (200 MHz, D_2O): δ = 7.00 (d, $^{1}J_{PH}$.= 547.5 Hz, 1H, PH), 2.73 {m, CHC(O), 1H}, 1.70-2.05 (m, 2H, CH_2P), 1.25-1.65 {m, 3H, CH_2+CH (i-Bu)}, 0.82 (d, 3H, $^{3}J_{HH}$.5.4 Hz, CH_3), 0.79 (d, 3H, $^{3}J_{HH}$.5.4 Hz, CH_3).

^{31}P NMR (81 MHz, D_2O): δ = 33.50 (pH own(~1), 27.4 (pH~9).

Calcd for $C_7H_{15}O_4P$; %: P, 15.95. Found, %: P, 16.07, 16.04.

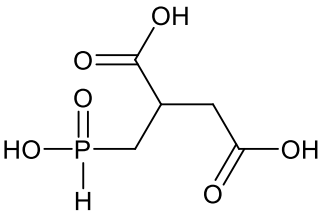
[2,3-Bis(methoxycarbonyl)propyl]phosphonous acid (2`d)



2`d

Yield = 73%, colorless oil.
^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.57 (s, broad, 1H, P(O)OH), 7.25 (d, $^{1}J_{PH}$.= 570.5 Hz, 1H, PH,), 3.72 (c, 3H, OCH_3), 3.68 (c, 3H, OCH_3), 3.22 {m, 1H, CHC(O)}, 2.78 {d, 2H, $^{3}J_{HH}$ 6.2 Hz, $\underline{CH_2}C(O)$}, 2.12-2.37 (m, 1H, one of CH_2P), 1.80-2.10 (m, 1H, another of CH_2P). **^{31}P NMR** (81 MHz, $CDCl_3$): δ = 35.90.
Calcd for $C_7H_{13}O_6P$; %: P, 13.82. Found, %: P, 14.05, 14.12.

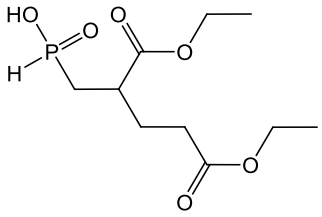
(2,3-Dicarboxypropyl)phosphonous acid (2d)



2d

Yield = 97%, m.p. 112-114°C.
^{1}H NMR (200 MHz, D_2O): δ = 7.04 (d, $^{1}J_{PH}$.= 558.2 Hz, 1H, PH,), 3.04 {m, 1H, CHC(O)}, 2.68 {d, 2H, $^{3}J_{HH}$ 6.2 Hz, $\underline{CH_2}C(O)$}, 1.97-2.40 (m, 1H, one of CH_2P), 1.70-1.95 (m, 1H, another of CH_2P).
^{31}P NMR (81 MHz, D_2O): δ = 33.10 (pH own(~1).
Calcd for $C_5H_9O_6P$; %: P, 15.80. Found, %: P, 16.02, 15.94.

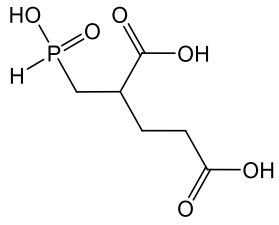
[2,4-Bis(ethoxycarbonyl)butyl]phosphonous acid (2`e)



2`e

Yield = 67%, colorless oil.
^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.65 (s, broad, 1H, P(O)OH), 6.97 (d, $^{1}J_{PH}$.= 560.3 Hz, 1H, PH,), 4.05 (q, 2H, OCH_2), 3.98 (q, 2H, OCH_2), 2.68 {m, 1H, CHC(O)}, 1.96 (m, 2H, CH_2P), 1.75-2.10 {m, 4H, $\underline{CH_2CH_2}C(O)$}, 1.21 (t, 3H, $^{3}J_{HH}$ 7.0 Hz, CH_3), 1.17 (t, 3H, $^{3}J_{HH}$ 7.0 Hz, CH_3).
^{31}P NMR (81 MHz, $CDCl_3$): δ = 33.90. Calcd for $C_{10}H_{19}O_6P$; %: P, 11.63. Found, %: P, 11.75, 11.82.

(2,4-Dicarboxybutyl)phosphonous acid (2e)

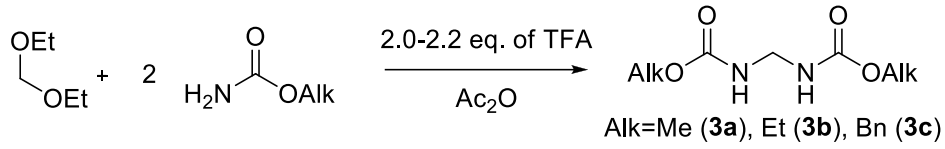


2e

Yield = 94%, colorless oil.
^{1}H NMR (200 MHz, D_2O): δ = 6.99 (d, $^{1}J_{PH}$.= 558.2 Hz, 1H, PH), 2.69 {m, 1H, CHC(O)}, 2.33 {t, broad, 2H, $^{3}J_{HH}$ 7.5 Hz, $CH_2C(O)$}, 1.65-2.30 (m, 2H, CH_2P+CH_2C).
^{31}P NMR (81 MHz, D_2O): δ = 34.60 {pH own (~1)}.
Calcd for $C_6H_{11}O_6P$; %: P, 14.74. Found, %: P, 14.92, 15.04.

Synthesis of dialkyl *N,N'*-methylenebiscarbamates 3a-c

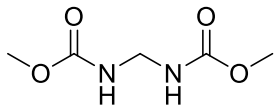
N,N'-Methylenebis(alkylcarbamates) **3a-c** were synthesized in accordance to scheme:



General procedure for the synthesis of dialkyl *N,N'*-methylenebiscarbamates **3a-c**.

Trifluoroacetic acid (TFA) (0.10-0.11 mmol) was slowly added dropwise to a stirred mixture of diethoxymethane (0.05 mol) and the corresponding alkyl carbamate (0.10 mol) in acetic anhydride (15-17 ml) at room temperature or slight cooling. The mixture was stirred for 3–5 h and diluted with toluene (15-20 ml). The resulting mass was evaporated *in vacuo*, and the residue was partitioned between chloroform (30 ml) and water (10 ml). The organic phase additionally was washed with water (10 ml), dried over sodium sulfate and evaporated *in vacuo*. The residue was crystallized from ether.

Dimethyl *N*,*N*'-methylenebiscarbamate (3a)



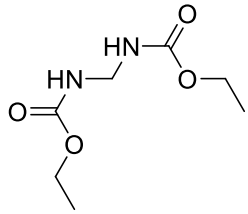
3a

Yield 3.48g, 43%, white solid, m.p. 113-115°C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.40-6.05 (m, 2H, 2NH), 4.48 (t, 2H, $^{3}J_{HH}$ 6.4 Hz, NCH_2), 3.66 (c, 6H, $2CH_3$).

^{13}C NMR (50 MHz, $CDCl_3$), δ_C, ppm: 157.3 (C=O), 52.2 (OCH_3), 48.0 (NCH_2). Calcd for $C_5H_{10}N_2O_4$; %: C, 37.04; H, 6.22; N, 17.28. Found: C, 36.90, 36.80; H, 6.44, 6.37; N, 17.26, 17.23.

Diethyl *N*,*N*'-methylenebiscarbamate (3b)



3b

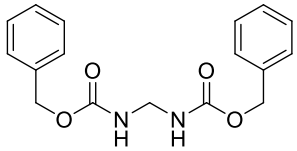
Yield 5.33g, 56%, white solid, m.p. 122-123°C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.40-5.95 (m, 2H, 2NH), 4.47 (t, 2H, $^{3}J_{HH}$ 6.6 Hz, NCH_2), 4.10 (q, 4H, $^{3}J_{HH}$ 7.1 Hz, $2CH_2O$), 1.22 (t, 6H, $^{3}J_{HH}$ 7.1 Hz, $2CH_3$).

^{13}C NMR (50 MHz, $CDCl_3$), δ_C, ppm: 156.9 (C=O), 61.0 (OCH_2), 47.9 (NCH_2), 14.4 (CH_3).

Calcd for $C_7H_{14}N_2O_4$; %: C, 44.20; H, 7.42; N, 14.73. Found: C, 43.92, 44.08; H, 7.56, 7.70; N, 14.66, 14.53.

Dibenzyl *N*,*N*'-methylenebiscarbamate (3c)



3c

Yield 9.58g, 61%, white solid, m.p. 139-140°C.

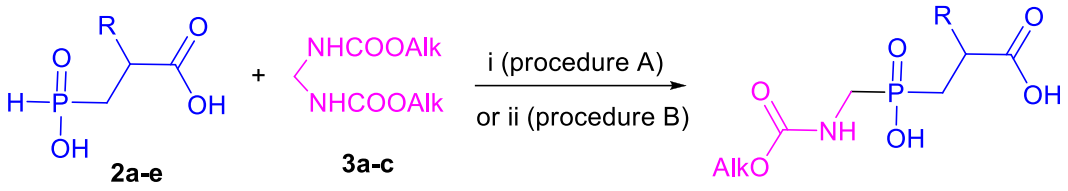
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 (m, broad, 10H, 2Ph), 5.72-5.92 (m, 2H, 2NH), 5.09 (s, broad, 4H, $2CH_2O$), 4.53 (t, 2H, $^{3}J_{HH}$ 6.4 Hz, NCH_2).

^{13}C NMR (50 MHz, $CDCl_3$), δ_C, ppm: 156.6 (C=O), 136.0, 128.5(2C), 128.2, 128.1(2C) (all arom.), 66.9 (CH_2O), 48.1 (NCH_2).

Calcd for $C_{17}H_{18}N_2O_4$; %: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.72, 64.68; H, 5.96, 5.90; N, 8.76, 8.63.

General approach for the synthesis of phosphinic *N*-protected pseudopeptides incorporating glycine isostere 1a-h

Amidoalkylation of phosphonous carboxylic acids 2a-e



2a R=H
2b R=Me
2c R = Bu^i
2d R = CH_2COOH
2e R = $(CH_2)_2COOH$

3a Alk = Me
3b Alk = Et
3c Alk = Bn

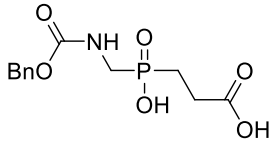
1a Alk = Bn, R = H (43/76)
1b Alk = Et, R = Me (n.d./63)
1c Alk = Bn, R = Me (29/67)
1d Alk = Me, R = Bu^i (46/71)
1e Alk = Et, R = Bu^i (58/68)
1f Alk = Me, R = CH_2COOH (n.d./51)
1g Alk = Bn, R = CH_2COOH (42/n.d.)
1h Alk = Et, R = $(CH_2)_2COOH$ (n.d./55)

Procedure A. Phosphonous acid **2a–e** (1.0 mmol) was stirred for 0.5 h in ethyl acetate (3–4 ml) at room temperature, and the corresponding dialkyl *N,N'*-methylenebiscarbamate **3** (1.0 mmol) was added by portions to the stirred solution. Then TFAA (2 mmol) (3-4 mmol TFAA for dicarboxylic acids **2d,e**) was slowly added dropwise to the resulting mixture, which then was stirred at room temperature for 15 to 20 hours. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, the mixture was evaporated *in vacuo*, and the residue was partitioned between chloroform and water (1:3). The resulting mass was filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography {eluent: chloroform-2-propanol (from 2 to 10%)}. The eluate was evaporated *in vacuo*, the residue crystallized spontaneously or after treatment with ether. The yields of phosphinic peptides were 29-58%.

Procedure B. The corresponding dialkyl *N,N'*-methylenebiscarbamate **3a-c** (1.0 mmol) in one portion was added to a stirred solution or suspension of the corresponding phosphonous carboxylic diacid **2a-e** (1.0 mmol) in a mixture of acetyl chloride/acetic anhydride (2:1, 3 ml) at ~ 5°C. The resulting mixture was stirred for 3 to 20 hours, the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, chloroform (5 ml) was added, and mixture was evaporated *in vacuo* and co-evaporated twice with chloroform (5 ml). The residue was partitioned between chloroform and water (1:3). Precipitated alkyl carbamate (usually, benzylcarbamate) was filtered off and discarded, and the aqueous part of the filtrate was washed with ether or benzene additionally and evaporated *in vacuo*. The residue was purified by silica gel column chromatography similar to procedure A. Some of phosphinic peptides were obtained as pale yellow viscous gums. The yields of phosphinic peptides were 51-76%.

N-Protected α-amino phosphinic acids **1a-h**, the products of reaction studied in the work, are mixture of conformers, perhaps more correct because it is associated with the presence of a chiral carbon atom and amide nitrogen in the molecule.

(*N*-Benzyloxycarbonylaminomethyl)(2-carboxyethyl)phosphinic acid (1a)



1a

Yield: 0.13 g, 43% **(procedure A**), 0.23 g, 76% **(procedure B);**

White solid. M.p. 137-138°C. TLC R_f ($CHCl_3$/i-PrOH: 4/1) = 0.30.

^{1}H NMR (200 MHz, d_6-DMSO) δ 7.61 (m, 1H, NH), 7.22-7.44 (m, 5H, Ph), 5.03 (s, 2H, CH_2O), 3.29 (dd, 2H, $^3J_{HH}$.7.0 Hz, $^2J_{PH}$.7.5 Hz, PCH_2N), 2.27-2.45 {m, 2H, $CH_2C(O)$}, 2.12-2.41 (dt, 2H, $^3J_{HH}$.7.5 Hz, $^2J_{PH}$.12.8 Hz, CH_2P).

^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 7.36 (m, broad, 5H, Ph), 6.62-6.83* (m, 1H, NH), 5.73-5.97 (m, 1H, NH), 5.10-5.27 (m, 2H, CH_2O), 3.83 (d, broad, 2H, $^3J_{HH}$.6.9 Hz, PCH_2N), 2.65-2.95 {m, 2H, $CH_2C(O)$}, 2.12-2.41 (m, 2H, CH_2P).

*Hereafter, signals marked with an asterisk refer to minor conformer forms.

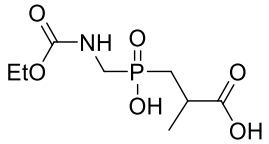
^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ_C, ppm: 177.5 (d, $^3J_{PC}$ 8.8 Hz, C=O), 158.0 (C=O), 134.9, 128.7(4C), 128.1 (all arom.), 69.2*, 68.6 (CH_2O), 40.1* (d, $^1J_{PC}$.99.2 Hz, NCH_2P), 39.6 (d, $^1J_{PC}$.102.8 Hz, NCH_2P), 26.0 {$\underline{C}H_2C(O)$}, 21.5 (d, $^1J_{PC}$.92.6 Hz, $P\underline{C}H_2C$).

Calcd for $C_{12}H_{16}NO_6P$; %: C, 47.85; H, 5.35; N, 4.65. Found: C, 47.52, 47.40; H, 5.62, 5.53; N, 4.46, 4.33. ^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO): δ 44.33.

^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 58.01.

HRMS (**NSI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{12}H_{15}NO_6P^-$ 300.0637, found 300.0642.

(*N*-Ethoxycarbonylaminomethyl)(2-carboxypropyl)phosphinic acid (1b)



1b

Yield 0.16g, 63% **(procedure B).** Colourless viscous gum. TLC R_f ($CHCl_3$/i-PrOH:4/1) ~ 0.25.

^{1}H NMR (200 MHz, D_2O) δ 4.01 (q, broad, 2H, $^3J_{HH}$.6.8 Hz CH_2O), 3.41 (d, broad, 2H, $^2J_{PH}$.7.3 Hz CH_2P), 2.63-2.87 (m, 1H, CHC(O)}, 1.98-2.80 (m, 1H, one of CH_2P), 1.65-1.93 (m, 1H, another of CH_2P), 1.19 (d, broad, 3H, $^3J_{HH}$ 6.8 Hz, CH_3), 1.13 (t, broad, 3H, $^3J_{HH}$.6.6 Hz, CH_3).

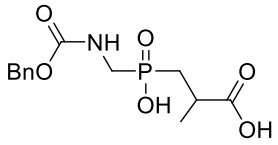
^{13}C {^{1}H} NMR (200 MHz, D_2O) δ 180.2 (d, $^3J_{PC}$ 8.4 Hz, NC=O), 158.8 ($C\underline{C}$=O), 63.7*, 63.5*, 62.7(CH_2O), 40.8*(d, $^1J_{PC}$.106.1 Hz, NCH_2P), 40.1 (d, $^1J_{PC}$.102.8 Hz, NCH_2P), 35.1* {d, $^2J_{PC}$ 2.9, $\underline{C}HC(O)$}, 34.1 {d, $^2J_{PC}$ 2.9, $\underline{C}HC(O)$}, 30.8* (d, $^1J_{PC}$ 88.6 Hz, $P\underline{C}H_2C$), 30.6 (d, $^1J_{PC}$.90.4 Hz, $P\underline{C}H_2C$), 18.8 (d, $^3J_{PC}$ 9.5, $\underline{C}H_3CH$), 18.5* (d, $^3J_{PC}$ 11.4, $\underline{C}H_3CH$), 14.2 ($\underline{C}H_3CH_2$), 13.7* ($\underline{C}H_3CH_2$).

^{31}P {^{1}H} NMR (81 MHz, D_2O) δ 47.34.

Calcd for $C_8H_{16}NO_6P$; %: C, 37.95; H, 6.37; P, 12.23. Found: C, 38.02, 37.83; H, 6.50, 6.63; P, 12.06, 11.87.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_8H_{15}NO_6P^-$ 252.0637, found 252.0644.

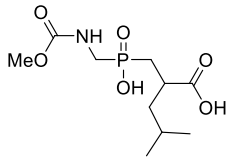
(*N*-Benzyloxycarbonylaminomethyl)(2-carboxypropyl)phosphinic acid (1c).



1c

Yield: 0.09 g, 29% (**procedure A**), 0.21g, 67% (**procedure B);**
White solid. M.p. 142-143°C. TLC R_f ($CHCl_3$/i-PrOH: 4/1) ~ 0.35.
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 7.36 (m, broad, 5H, Ph), 6.52-6.85* (m, 1H, NH), 5.62-6.00 (m, 1H, NH), 5.21* (c, 2H, CH_2O), 5.15 (c, 2H, CH_2O), 3.60-3.95 (m, PCH_2N), 2.80-3.20 (m, 1H, CHC(O)}, 2.25-2.60 (m, 1H, one of CH_2P), 1.83-2.23 (m, 1H, second of CH_2P), 1.41* (d, broad, 3H, $^3J_{HH}$.7.0 Hz, CH_3), 1.37 (d, broad, 3H, $^3J_{HH}$.7.0 Hz, CH_3).
^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 56.46.
Calcd for $C_{13}H_{18}NO_6P$; %: C, 49.53; H, 5.75; N, 4.44. Found: C, 49.27, 49.16; H, 6.05, 5.94; N, 4.75, 4.30.
HRMS (**NSI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{13}H_{17}NO_6P^-$ 314.0793, found 314.0796.

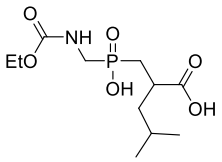
(*N*-Methoxycarbonylaminomethyl)(2-carboxy-4-methylpentyl)phosphinic acid (1d).



1d

Yield 0.13 g, 46% (**procedure A**), 0.20g, 71% (**procedure B**).
White solid. M.p. 95-97°C. TLC R_f ($CHCl_3$/EtOH:4/1) ~ 0.25-0.30.
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 6.50-6.80* (m, 1H*, NH), 5.65-6.05 (m, 1H, NH), 3.55 {m, 5H (3H, MeO + 2H, NCH_2P)}, 2.80-3.05 (m, 1H, CHCOO), 2.20-2.45 (m, 1H, one of CH_2P), 1.90-2.15 (m, 1H, second of CH_2P), 1.33-1.78 (m, 3H, CH_2+CH), 0.94 (d, 3H, $^3J_{HH}$.6.5 Hz, Me), 0.90 (d, 3H, $^3J_{HH}$.6.5 Hz, Me).
^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ 180.9 (d, $^3J_{PC}$ 2.6 Hz, NC=O), 158.8, 54.1* (MeO), 53.7 (MeO), 42.9 (d, $^3J_{PC}$ 12.9 Hz), 40.5* (d, $^1J_{PC}$ 105.4 Hz, NCH_2), 40.2 (d, $^1J_{PC}$ 102.5 Hz, NCH_2), 37.2, 28.9 (d, $^1J_{PC}$ 88.8 Hz, PCH_2), 25.6, 22.1, 21.8.
^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 56.04.
Calcd for $C_{10}H_{20}O_6P$; %: C, 42.71, H, 7.17, P, 11.01. Found, %: C, 42.47, 42.38; H, 7.33, 7.38; P, 10.92, 11.02.
HRMS (**NSI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{10}H_{19}NO_6P^-$ 280.0950, found 280.0953.

(*N*-Ethoxycarbonylaminomethyl)(2-carboxy-4-methylpentyl)phosphinic acid (1e).



1e

Yield 0.17g, 58% (**procedure A**), 0.20g, 68% (**procedure B**).
White solid. M.p. 122-123°C. TLC R_f ($CHCl_3$/EtOH:4/1) ~ 0.25-0.30.
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 6.45-6.70*(~40%) (m, 1H, NH), 5.35-5.95 (~60%) (m, 1H, NH), 4.15 (q, broad, 2H,

$^3J_{HH}$ 6.9 Hz, CH_2O), 3.70 (d, broad, 2H, $^2J_{PH}$ 6.4 Hz, CH_2P), 2.77-3.03 {m, 1H, CHC(O)}, 2.15-2.43 (m, 1H, one of CH_2P), 1.88-2.11 (m, 1H, another of CH_2P), 1.55-1.70 {m, 2H, CH_2(i-Bu)}, 1.33-1.47 {m, 1H, CH(i-Bu)}, 1.26 (t, broad, 3H, $^3J_{HH}$.6.9 Hz, CH_3), 0.92 (d, 3H, $^3J_{HH}$.6.4 Hz, CH_3), 0.89 (d, 3H, $^3J_{HH}$.6.4 Hz, CH_3).

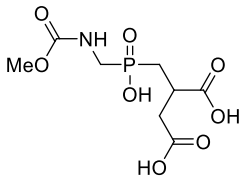
^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ 181.4 (NC=O), 158.6 (C<u>C</u>=O), 64.0* (CH_2O), 63.4 (CH_2O), 42.9 (d, $^3J_{PC}$ 12.8 Hz), 40.6* (d, $^1J_{PC}$ 100.3 Hz, NCH_2), 40.1 (d, $^1J_{PC}$ 100.3 Hz, NCH_2), 37.1, 28.7 (d, $^1J_{PC}$ 90.8 Hz, PCH_2), 25.6, 22.0, 21.8, 14.0 (<u>C</u>H_3CH_2), 13.6* (<u>C</u>H_3CH_2).

^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 54.51, 53.72*.

Calcd for $C_{11}H_{22}NO_6P$; %: C, 44.75, H, 7.51, P, 10.49. Found, %: C, 44.43, 44.53; H, 7.73, 7.67; P, 10.35, 10.22.

HRMS (**ESI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{11}H_{21}NO_6P^-$ 294.1107, found 294.1113.

(*N*-Methoxycarbonylaminomethyl)(2,3-dicarboxypropyl)phosphinic acid (1f)



1f

Yield 0.14g, 51% (**procedure B**). Colourless viscous gum. TLC R_f ($CHCl_3$/i-PrOH: 4/1) ~ 0.20.

^{1}H NMR (200 MHz, D_2O): δ 3.60 (c, broad, 3H, OCH_3), 3.21 (d, $^2J_{PH}$ 9.2 Hz, 2H, NCH_2P), 3.18* (d, $^2J_{PH}$ = 6.9 Hz, 2H, NCH_2P), 2.61-2.86 {m, 1H, CHC(O)}, 2.23-2.50 {m, 2H, $CH_2C(O)$}, 1.77-2.02 (m, 1H, one of CH_2P), 1.37-1.65 (m, second of CH_2P).

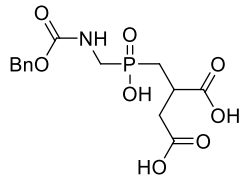
^{13}C {^{1}H} NMR (50 MHz, D_2O, δ_C, ppm): 177.8 (OC=O) (d, $^3J_{PC}$ = 7.7 Hz), 175.7 (OC=O), 159.2 (NC=O), 53.2 (CH_3O), 40.6* (d, $^1J_{PC}$.= 107.6 Hz, 2H, NCH_2P), 40.2 (d, $^1J_{PC}$.= 103.9 Hz, 2H, NCH_2P), 36.8 {d, $^3J_{PC}$.= 8.0 Hz, 2H, <u>C</u>$H_2C(O)$}, 36.4* {d, $^3J_{PC}$.= 9.5 Hz, 2H, <u>C</u>$H_2C(O)$}, 35.6 {d, $^2J_{PC}$.= 2.9 Hz, 1H, <u>C</u>HC(O)}, 28.5 (d, $^1J_{PC}$.90.8 Hz, 2H, P<u>C</u>H_2C).

^{31}P {^{1}H} NMR (81 MHz, D_2O, pH~1) : 54.60.

Calcd for $C_8H_{14}NO_8P$; %: C, 33.93, H, 4.98, P, 10.94. Found, %: C, 33.67, 33.73; H, 5.03, 5.11; P, 10.76, 10.61.

HRMS (**ESI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_8H_{13}NO_8P^-$ 282.0379, found 282.0385.

(*N*-Benzyloxycarbonylaminomethyl)(2,3-dicarboxypropyl)phosphinic acid (1g)



1g

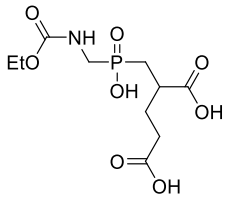
Yield 0.15g, 42% (**procedure A**). White solid. M.p. 167-169°C. TLC R_f ($CHCl_3$/i-PrOH: 4/1) = 0.30.

^{1}H NMR (200 MHz, d_6-DMSO) δ 7.61 (m, 1H, NH), 7.15-7.45 (m, 5H, Ph), 5.02 (s, broad, 2H, CH_2O), 3.29 (dd, 2H, $^3J_{HH}$.6.7 Hz, $^2J_{PH}$.7.1 Hz, PCH_2N), 2.82-3.04 {m, 1H, CHC(O)}, 2.53-2.78 (m, 2H, $CH_2C(O)$}, 1.92-2,13 (m, 1H, one of PCH_2), 1.63-1.85 (m, 1H, second of PCH_2). **^{13}C {^{1}H} NMR** (50 MHz, d_6-DMSO, δ_C, ppm): 175.1 (OC=O) (d, $^3J_{PC}$ = 13.2 Hz), 172.8 (C<u>C</u>=O), 156.2 (NC=O), 136.9, 128.3(2C), 127.7(3C) (all arom.), 65.6 (CH_2O), 41.6 (d, half of the doublet covered with solvent d_6-DMSO, NCH_2P), 35.7 (d, $^3J_{PC}$.= 3.0 Hz, 2H, <u>C</u>$H_2C(O)$},

34.8 {d, $^{2}J_{PC}$.= 2.9 Hz, 1H, CHC(O)}, 28.5 (d, $^{1}J_{PC}$.89.3 Hz, 2H, PCH$_2$C). ^{31}P {^{1}H} NMR (81 MHz, d$_6$-DMSO): δ 43.51. Calcd for $C_{14}H_{18}NO_8P \times H_2O$; %: C, 44.57, H, 5.34, P, 8.21. Found, %: C, 44.33, 44.20; H, 5.46, 5.51; P, 8.26, 8.21.

HRMS (ESI/Q-TOF) m/z: [M-H]$^-$calcd. for $C_{14}H_{17}NO_8P^-$ 358.0692, found 358.0699.

(*N*-Ethoxycarbonylaminomethyl)(2,4-dicarboxybutyl)phosphinic acid (1h)



1h

Yield 0.17g, 55% (**procedure B**). Colourless viscous gum. TLC R_f ($CHCl_3$/i-PrOH: 4/1) ~ 0.25.

^{1}H NMR (200 MHz, D_2O): δ 4.17-4.33* (q, broad, 2H, $^{3}J_{HH}$.7.0 Hz, OCH_2), 3.95-4.17 (q, broad, 2H, $^{3}J_{HH}$.7.0 Hz, OCH_2), 3.60-3.74* (m, 2H, one of NCH_2P), 3.32-3.50 (d, broad, 2H, $^{2}J_{HH}$.~6÷7 Hz, second of NCH_2P), 2.60-2.84 {m, 1H, CHC(O)}, 2.28-2.48 {m, 2H, $CH_2C(O)$}, 1.65-2.25 (m, 4H, CH_2P + CH_2CH), 1.25* (t, 3H*, $^{3}J_{HH}$~7.0 Hz, 3H) + 1.21* (t, 3H*, $^{3}J_{HH}$~7.0 Hz, 3H) + 1.16 (t, 3H, $^{3}J_{HH}$~7.0 Hz, 3H).

^{31}P {^{1}H} NMR (81 MHz, D_2O) : δ 45.86, 45.23*, 44.17*.

^{31}P {^{1}H} NMR (81 MHz, d$_6$-DMSO + one drop of TFA): δ 48.12*, 44.29, 41.59*.

Calcd for $C_{10}H_{18}NO_8P$; %: C, 38.59, H, 5.83, P, 9.95. Found, %: C, 38.33, 38.18; H, 6.23, 6.11; P, 9.55, 9.43.

HRMS (**NSI**/Q-TOF) m/z: [M-H]$^-$calcd. for $C_{10}H_{17}NO_8P^-$ 310.0692, found 310.0699.

References

S1 M. E. Dmitriev and V. V. Ragulin. *Tetrahedron Lett.*, 2010, **51**, 2613.

S2 M. E. Dmitriev, E.A. Rossinets and V. V. Ragulin. *Russ. J. Gen. Chem*. 2011, **81**, 1092 (*Zh. Obshch. Khim*., 2011, **81**, 898).

S3 M. E. Dmitriev and V. V. Ragulin. *Russ. J. Gen. Chem.* 2013, **83**, 1888. (*Zh. Obshch. Khim*., 2013, **83**, 1681).

S4 M. E. Dmitriev and V.V. Ragulin. *Tetrahedron Lett.*, 2012, **53**, 1634.

NMR spectra

N-Protected α-amino phosphinic acids, the reaction products studied in the work, are mixtures of conformers, because it is associated with the presence of a chiral α-carbon atom and amide nitrogen in the molecule. This manifests itself in the NMR spectra under various conditions.

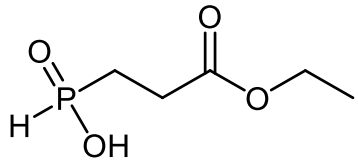
Nuclear magnetic resonance spectra were recorded on Bruker DPX-200 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). Tetramethylsilane (TMS) was used as internal standard (^{1}H NMR: TMS at 0.00 ppm; $CHCl_3$ at 7.25 ppm, D_2O at 4.75 ppm, DMSO-d_6 at 2.49 ppm; ^{31}P NMR chemical shifts are reported on δ scale (in ppm) downfield from 85% H_3PO_4; ^{13}C NMR: $CDCl_3$ at 77.00 ppm, DMSO-d6 at 39.5 ppm.

HRMS spectra

Negative mode high resolution mass spectra were acquired using AB Sciex TripleTOF 5600+ mass spectrometer. Duospray with electrospray ionization (**ESI**) (compounds **1b, 1e, 1f, 1g**) or nanospray ionization (**NSI**) (compounds **1a, 1c, 1d, 1h**) ion source was used. Samples were injected as dilute methanol solutions directly into the source at a rate of 20 μl min^{-1} in the case of duospray, or a chloroform-methanol mixture in the case of nanospray sourse with a flow rate of 0.5 μl min^{-1}. Mass spectra of all samples in the negative mode contained the $(M-H)^-$ ion peaks, the measured m/z and the isotopic patterns were compared with the theoretical ones. The experimental m/z values for $(M-H)^-$ peaks correspond to the theoretical calculated values, the discrepancies are < 0.001 Da.

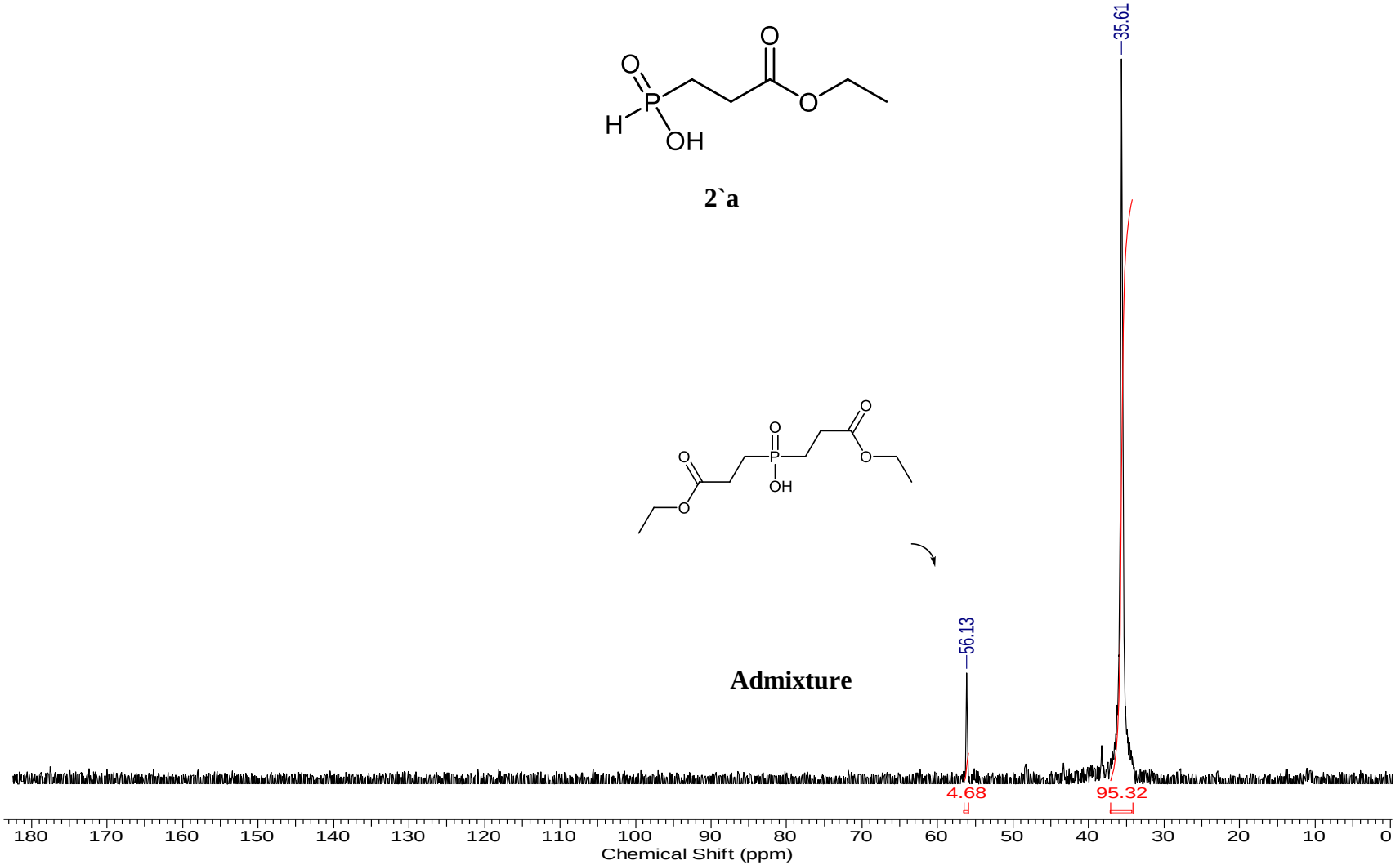
^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra of starting compounds {phosphonous carboxylic diacids 2a-e and dialkyl *N,N'*-methylenebiscarbamates 3a-c}

^{1}H NMR (200 MHz, $CDCl_3$)



2`a

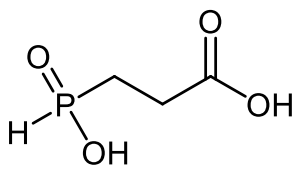
$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$):



2`a

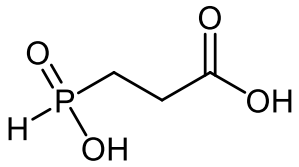
Admixture

^{1}H NMR (200 MHz, D_2O)



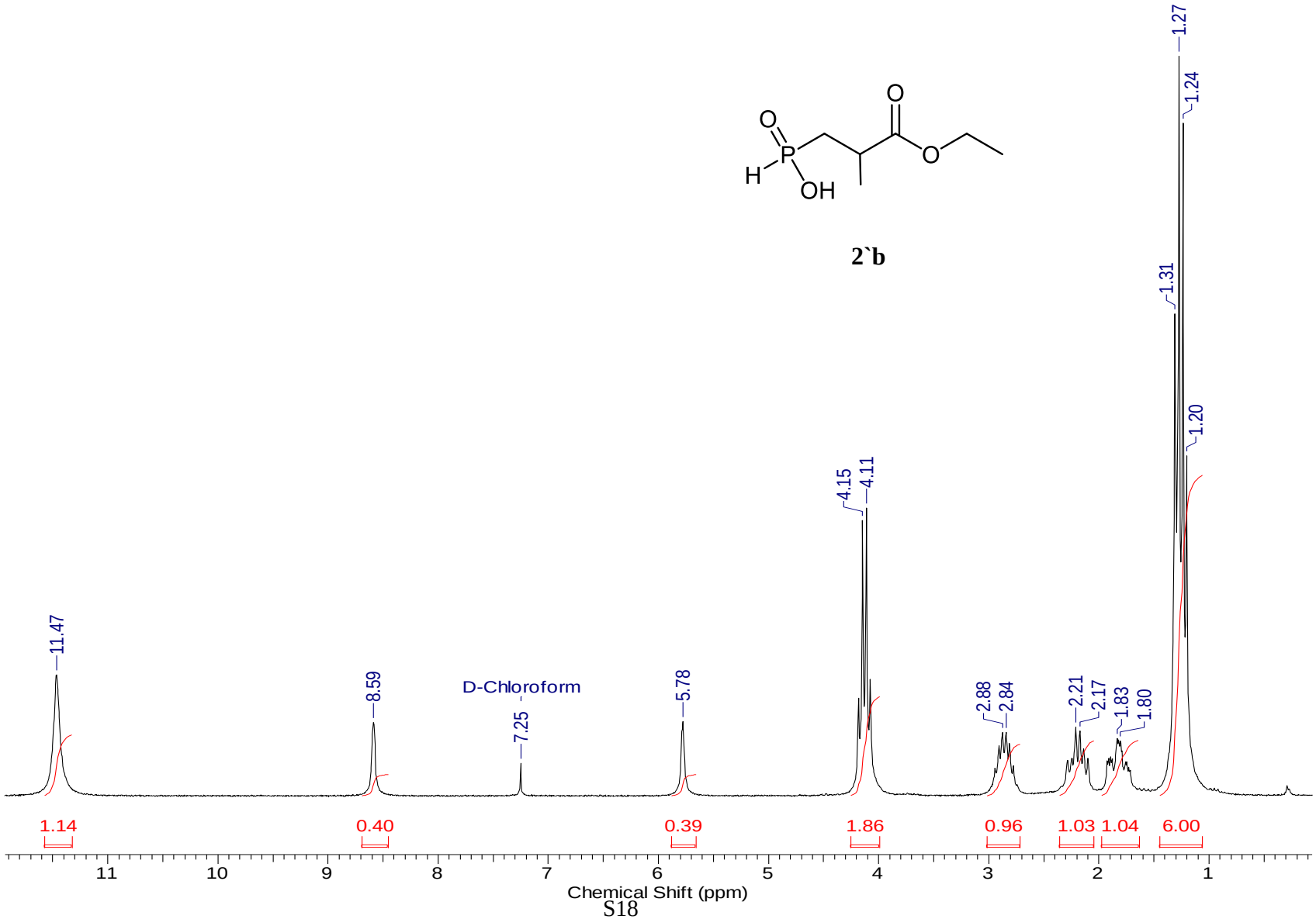
2a

$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O)

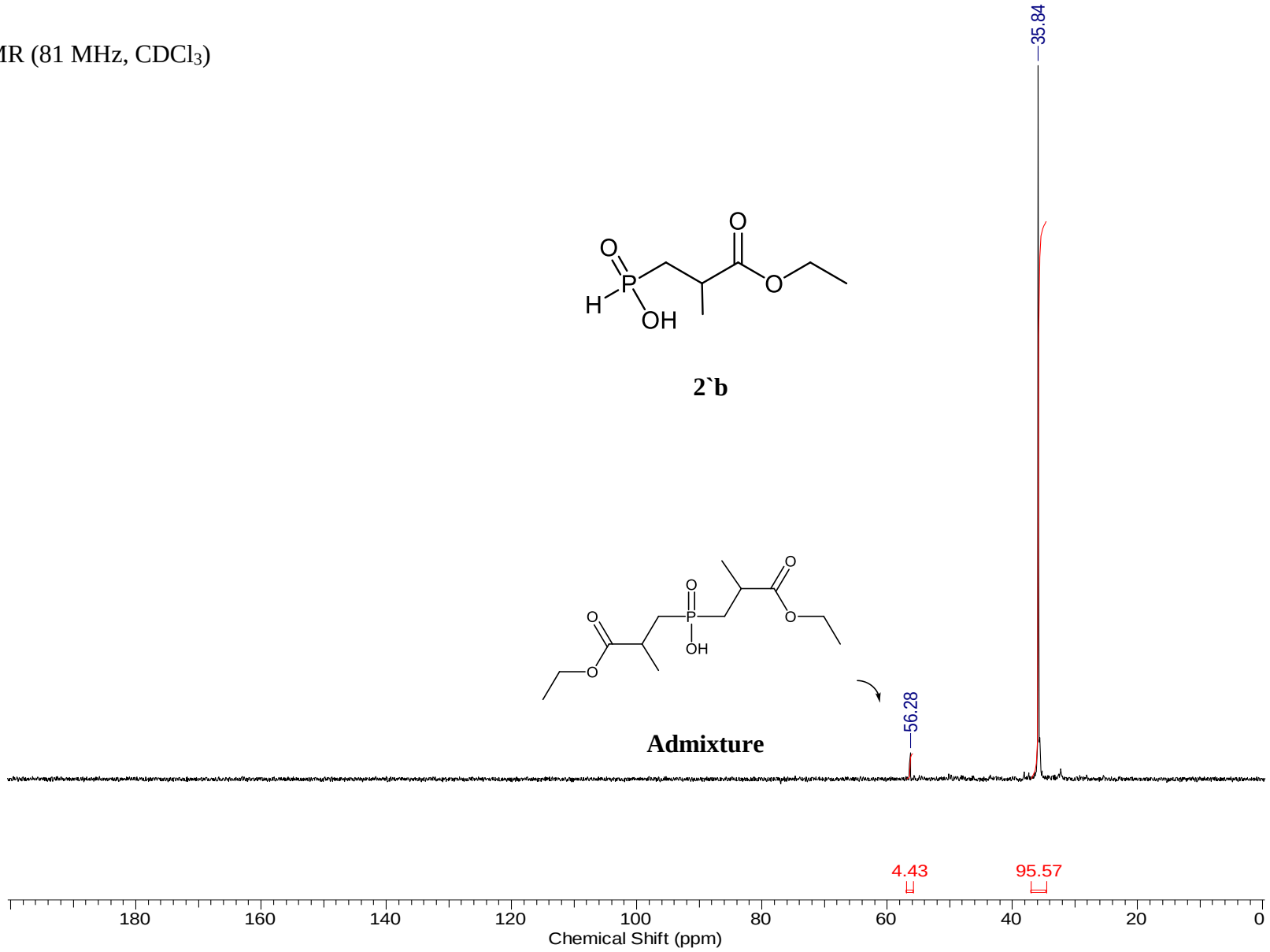


2a

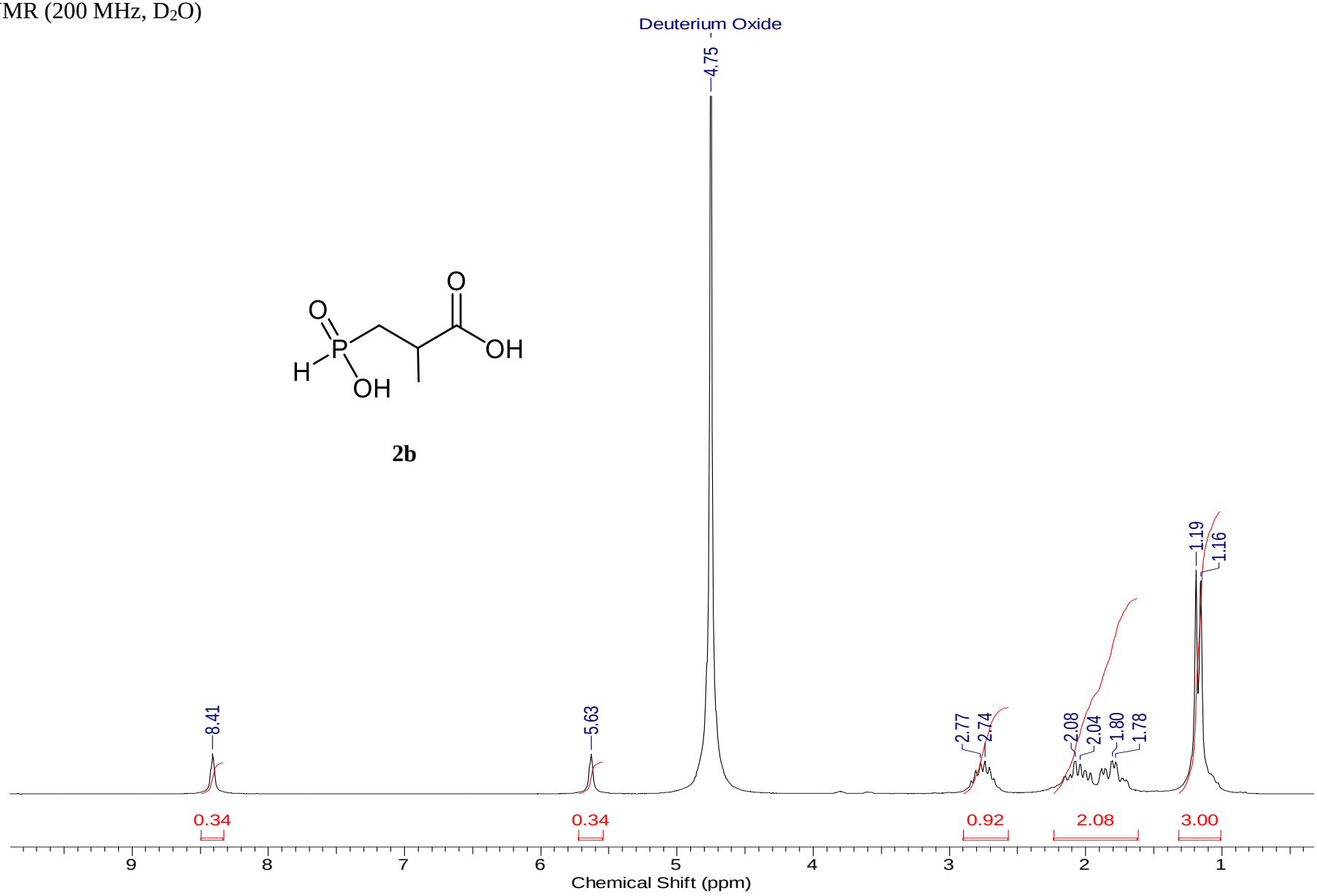
^{1}H NMR (200 MHz, $CDCl_3$)



$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$)

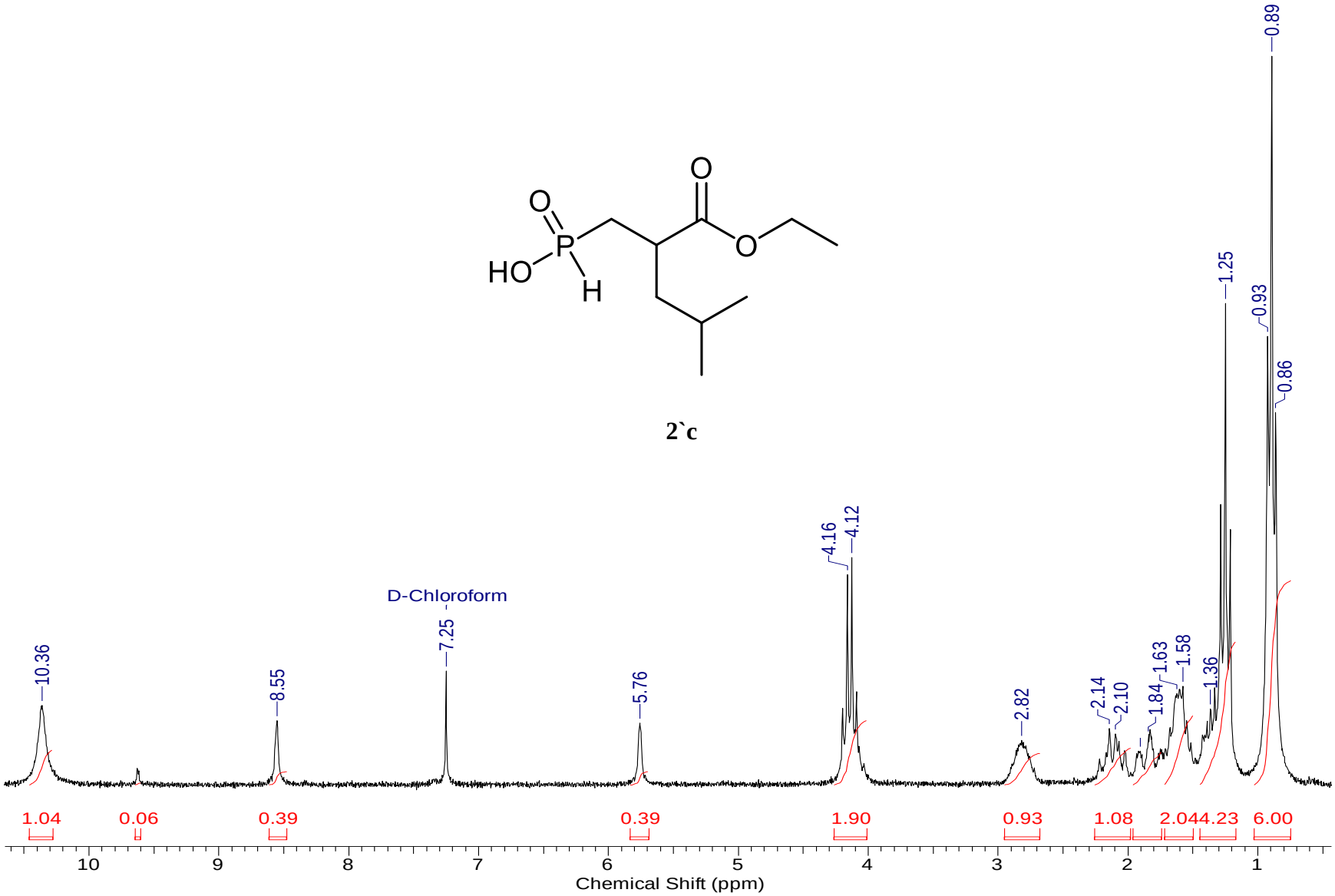


^{1}H NMR (200 MHz, D_2O)

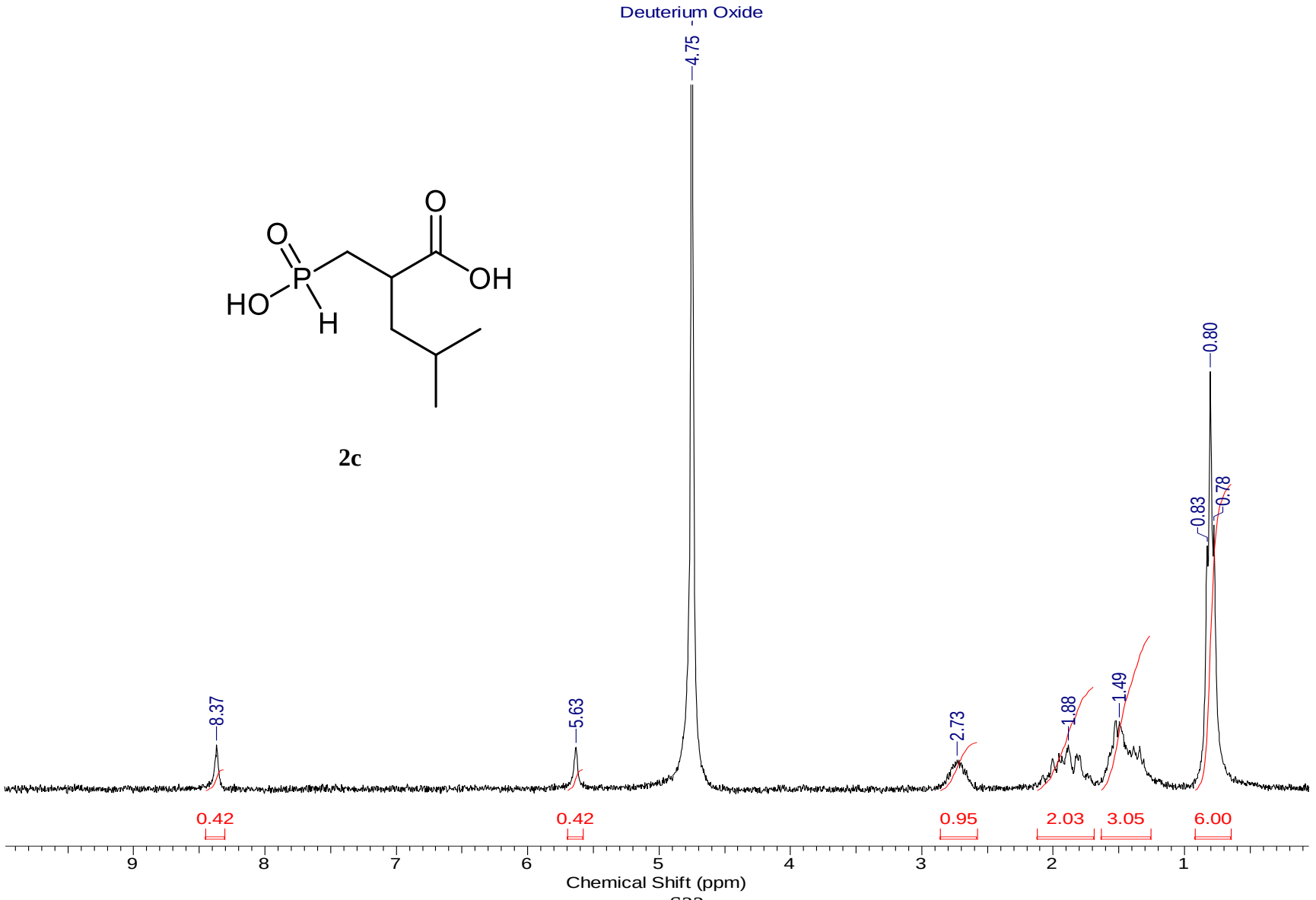


2b

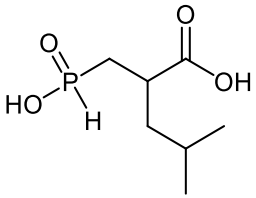
^{1}H NMR (200 MHz, $CDCl_3$)



^{1}H NMR (200 MHz, D_2O)

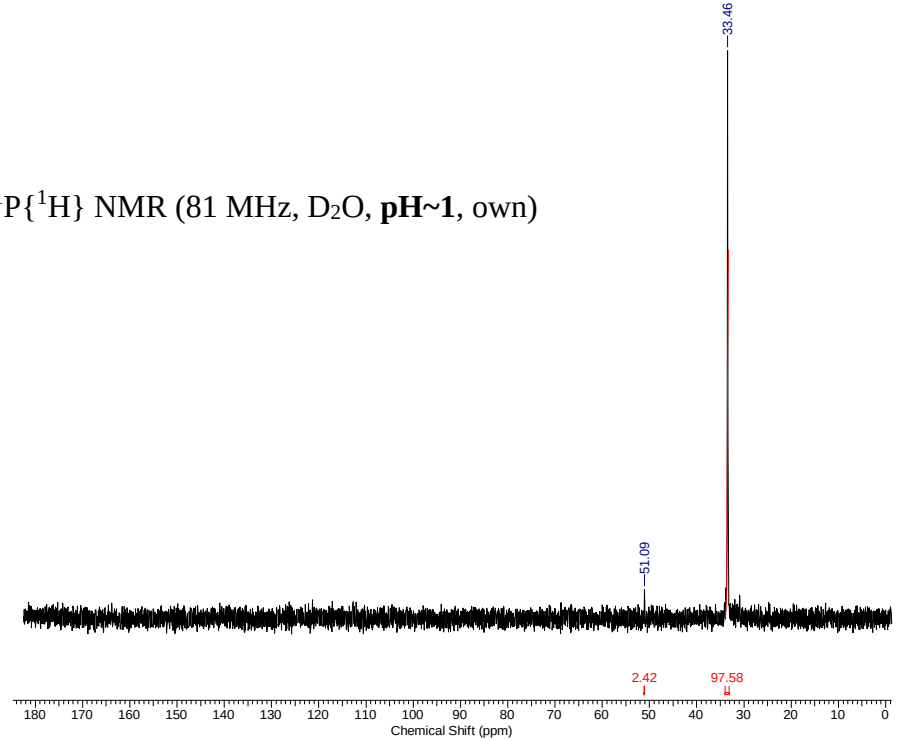


2c

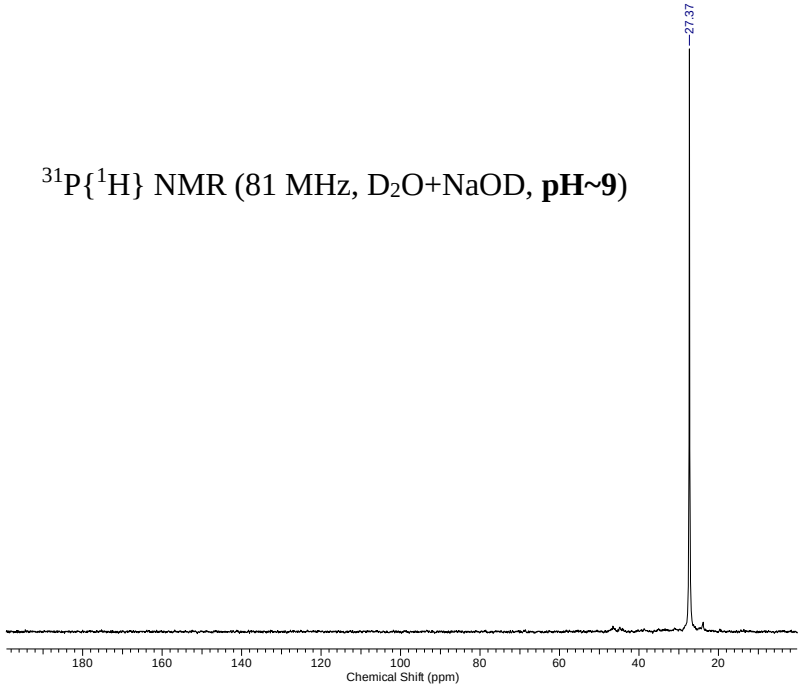


2c

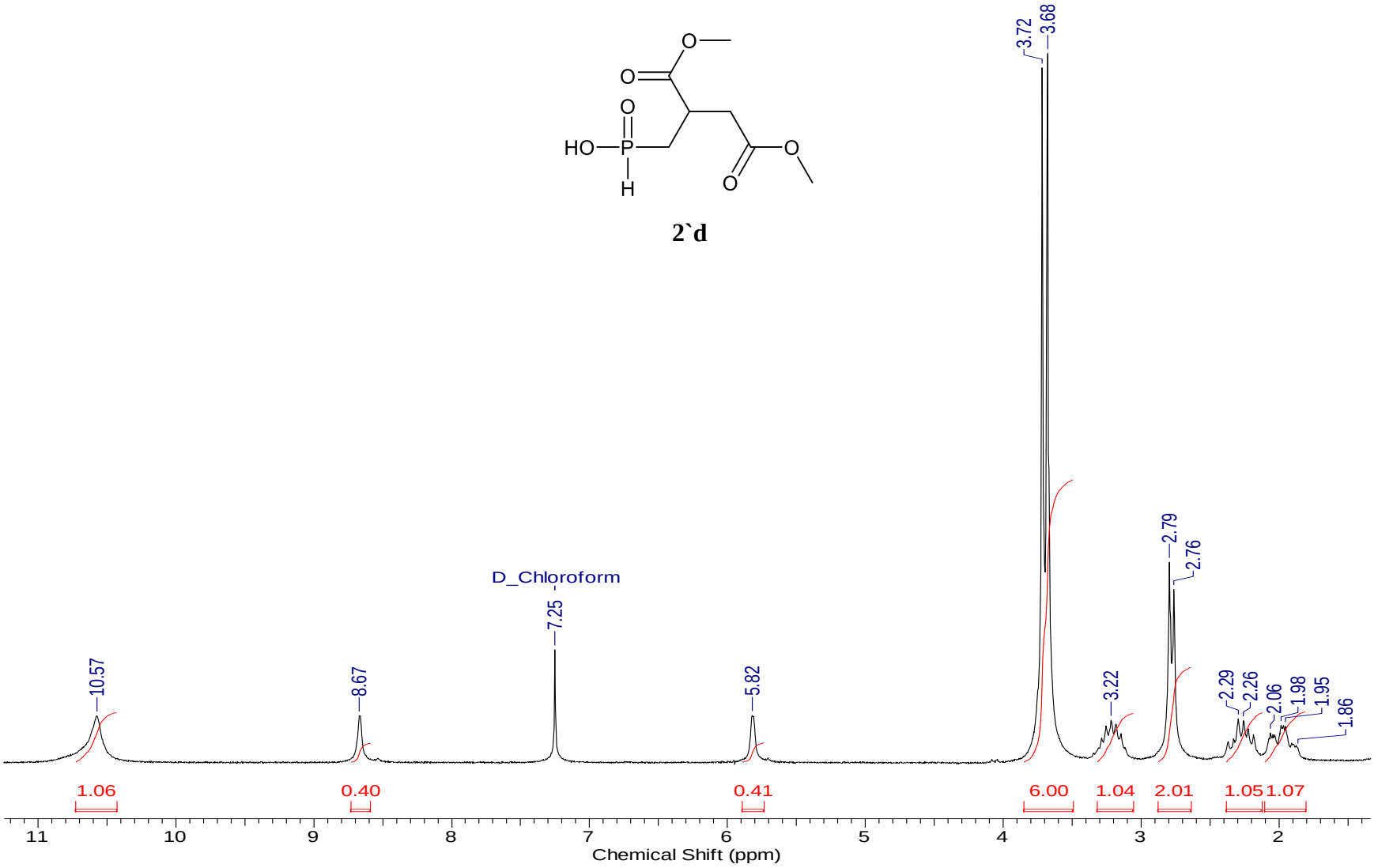
$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O, **pH~1**, own)



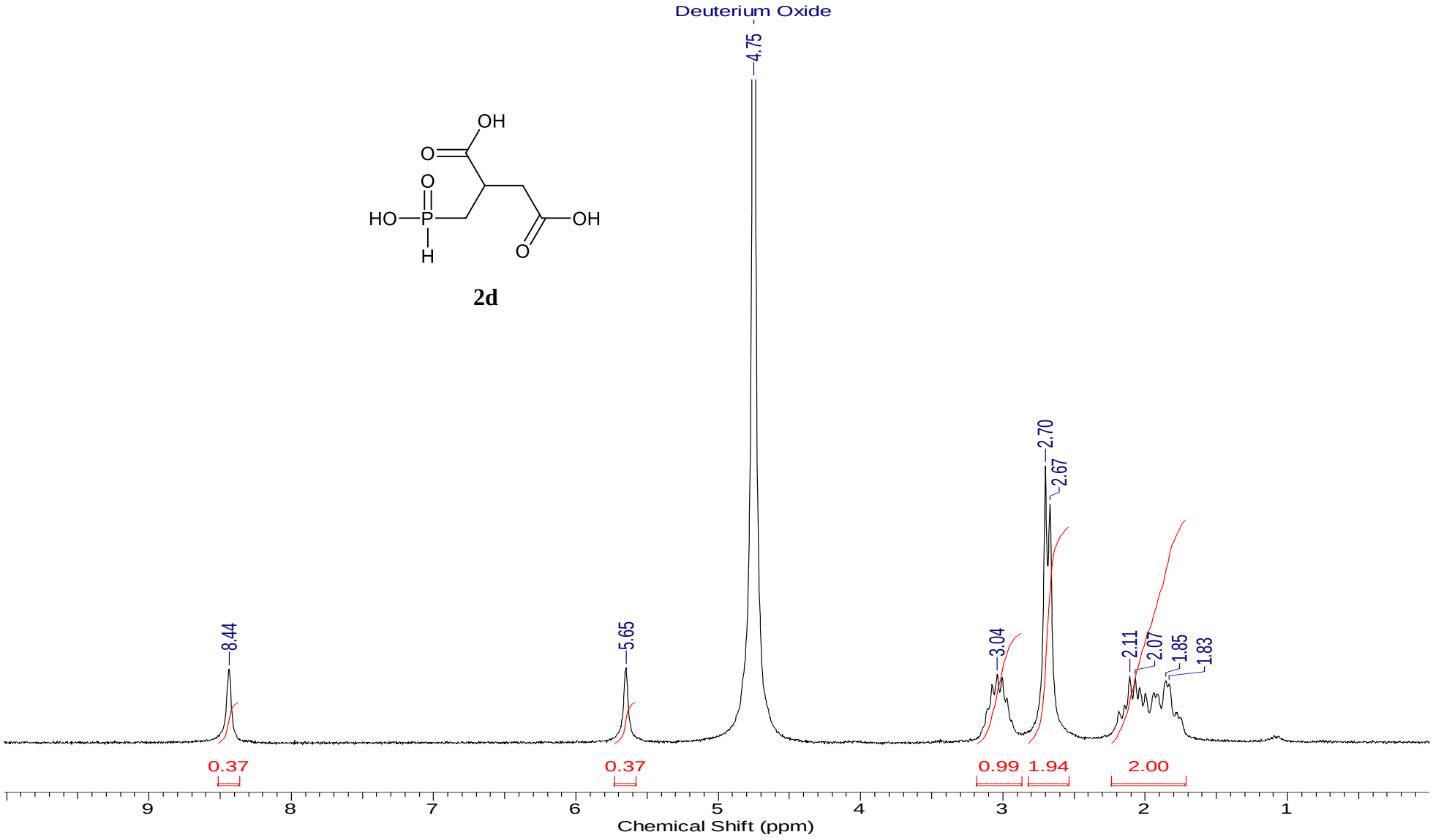
$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O+NaOD, **pH~9**)



^{1}H NMR (200 MHz, $CDCl_3$)

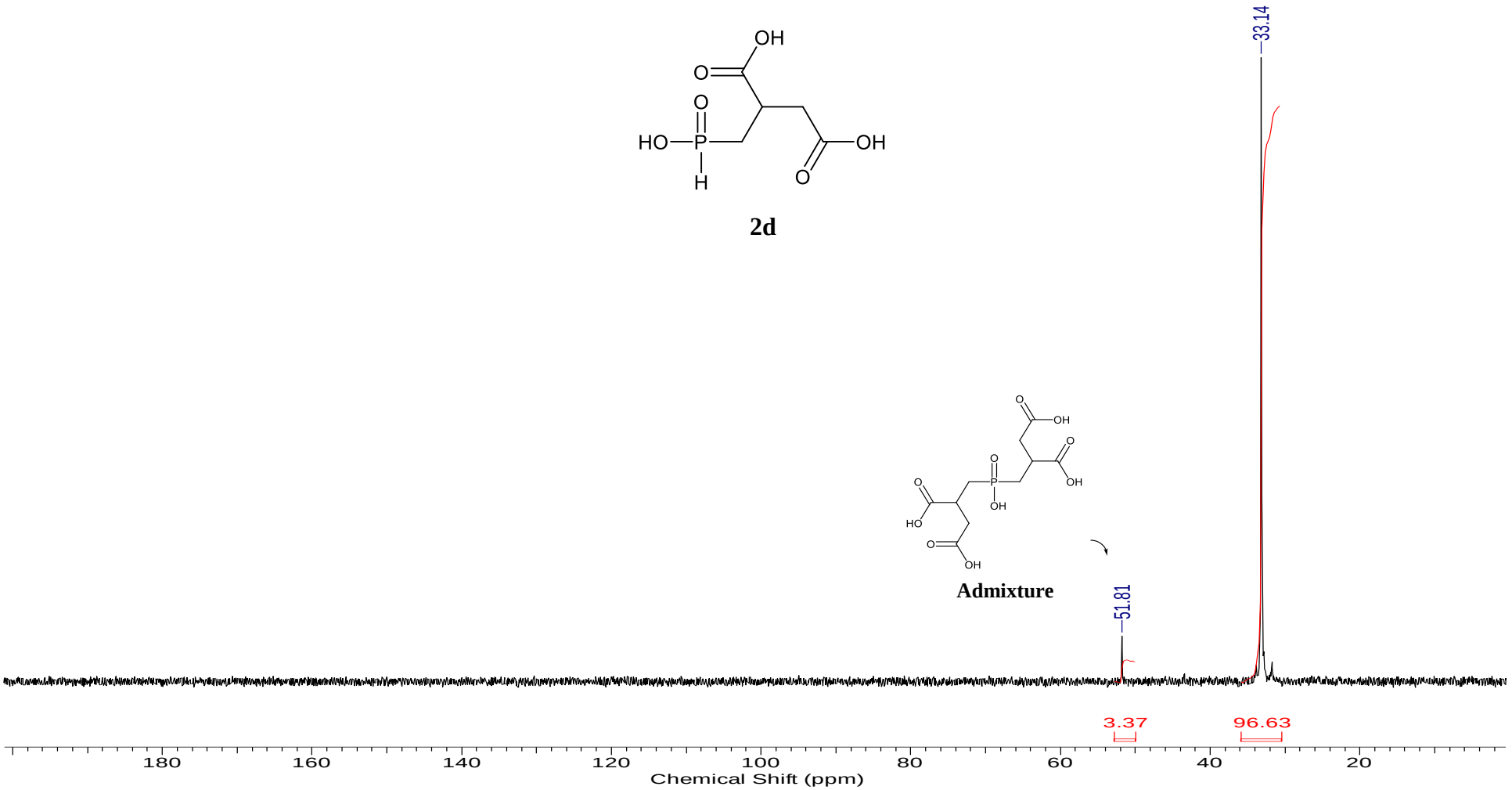


^{1}H NMR (200 MHz, D_2O)

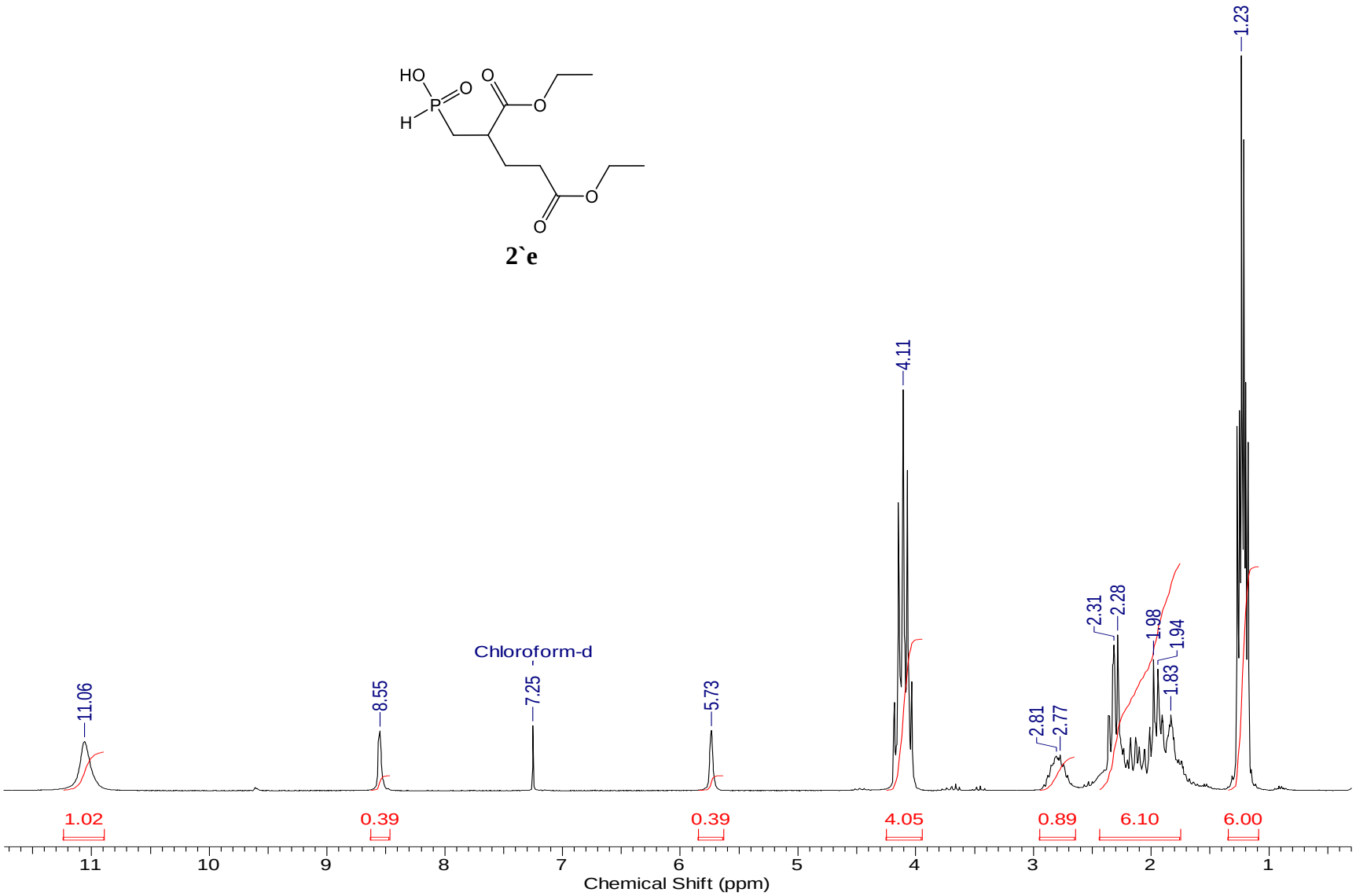


2d

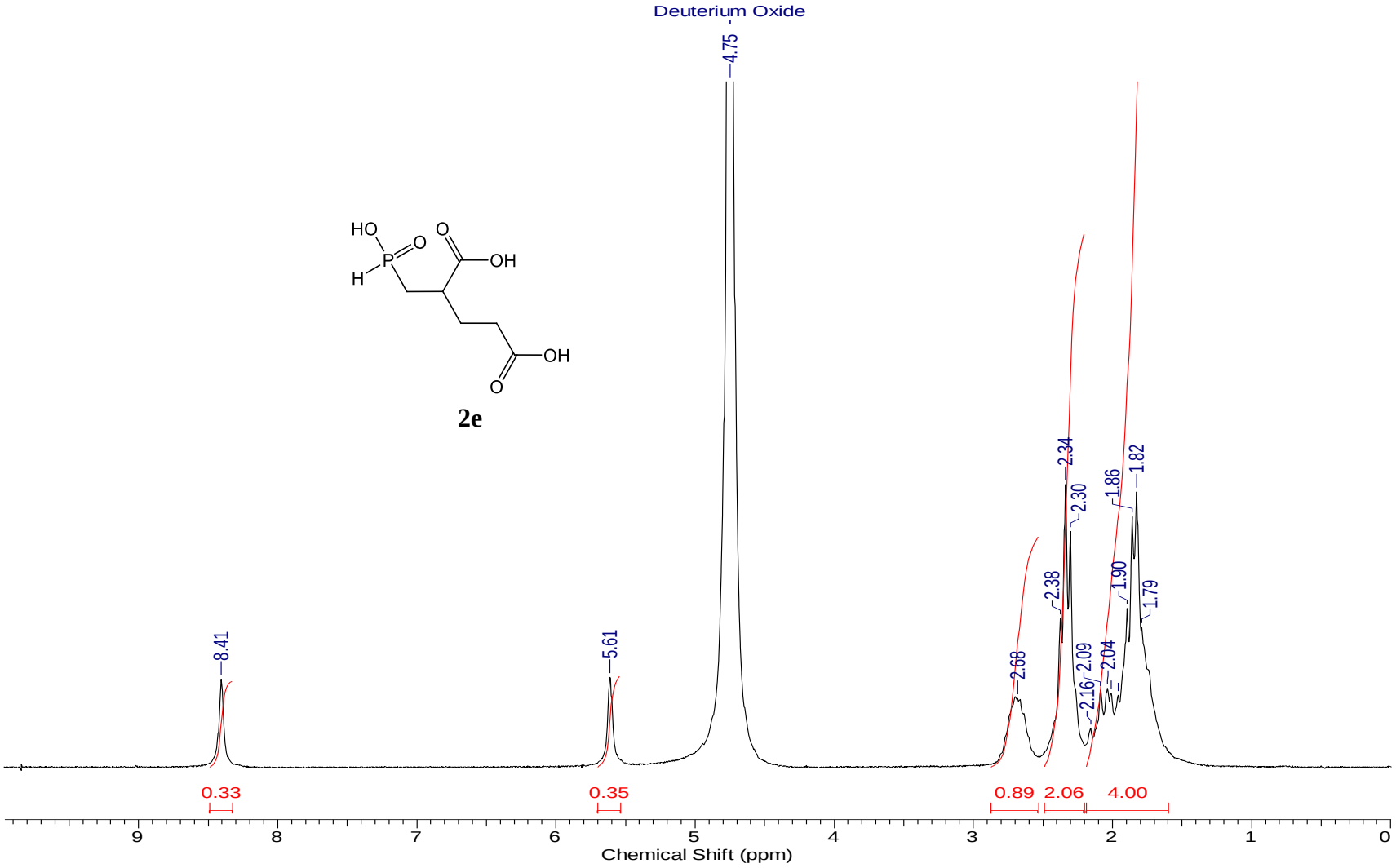
$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O)



^{1}H NMR (200 MHz, $CDCl_3$)

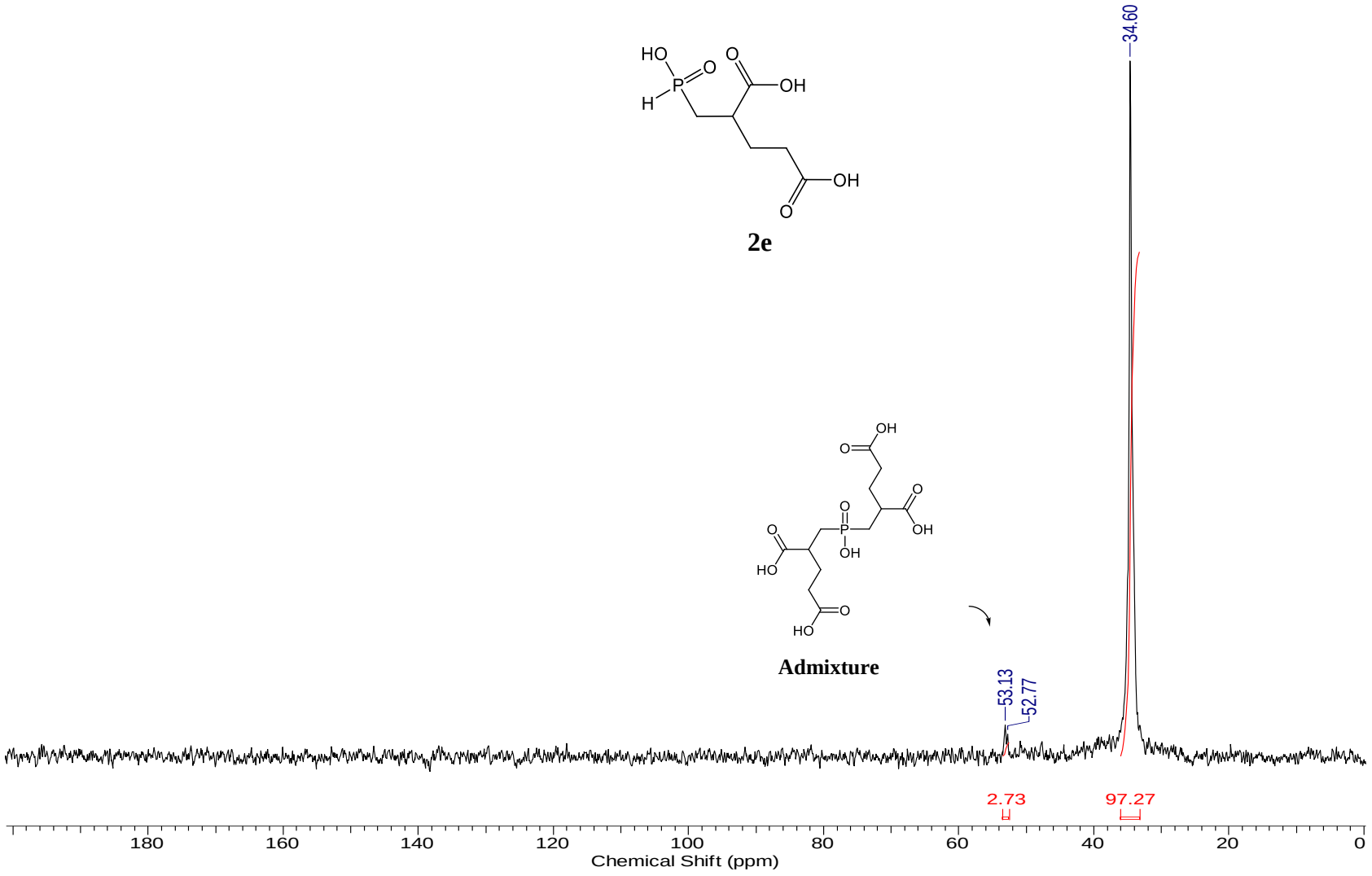


^{1}H NMR (200 MHz, D_2O)



2e

$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O)

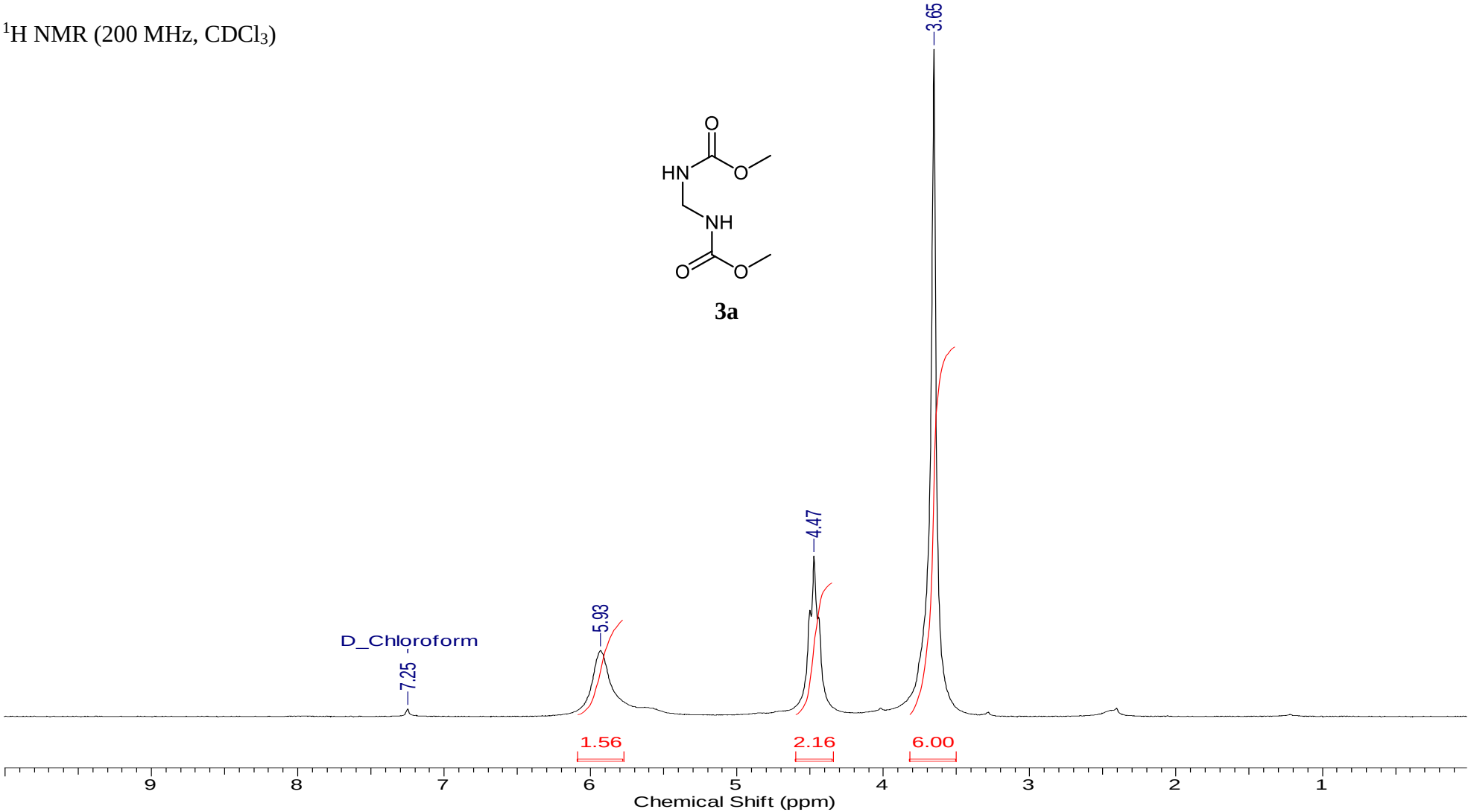


2e

Admixture

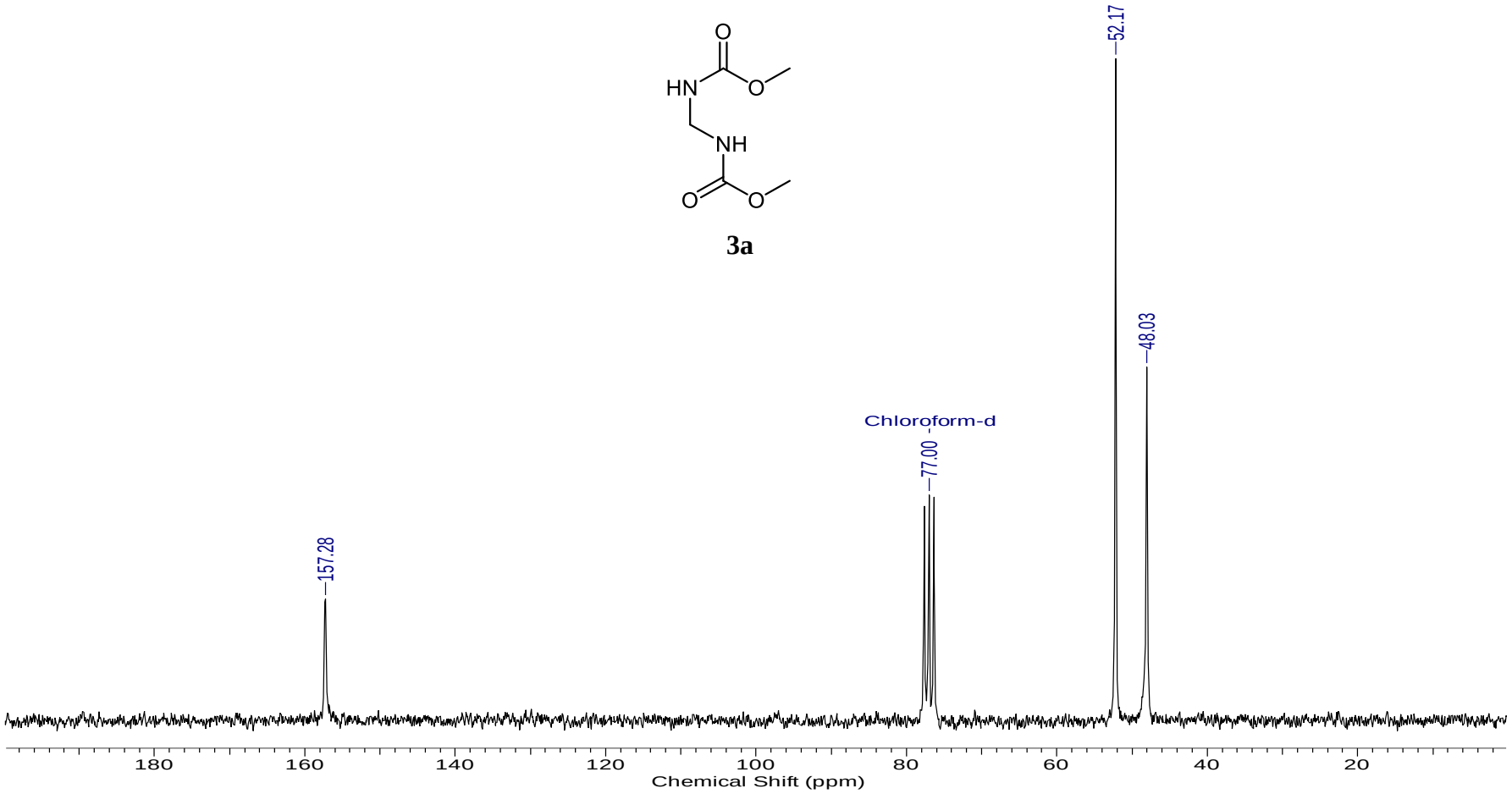
^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of starting compounds {dialkyl *N,N'*-methylenebiscarbamates 3a-c}

^{1}H NMR (200 MHz, $CDCl_3$)

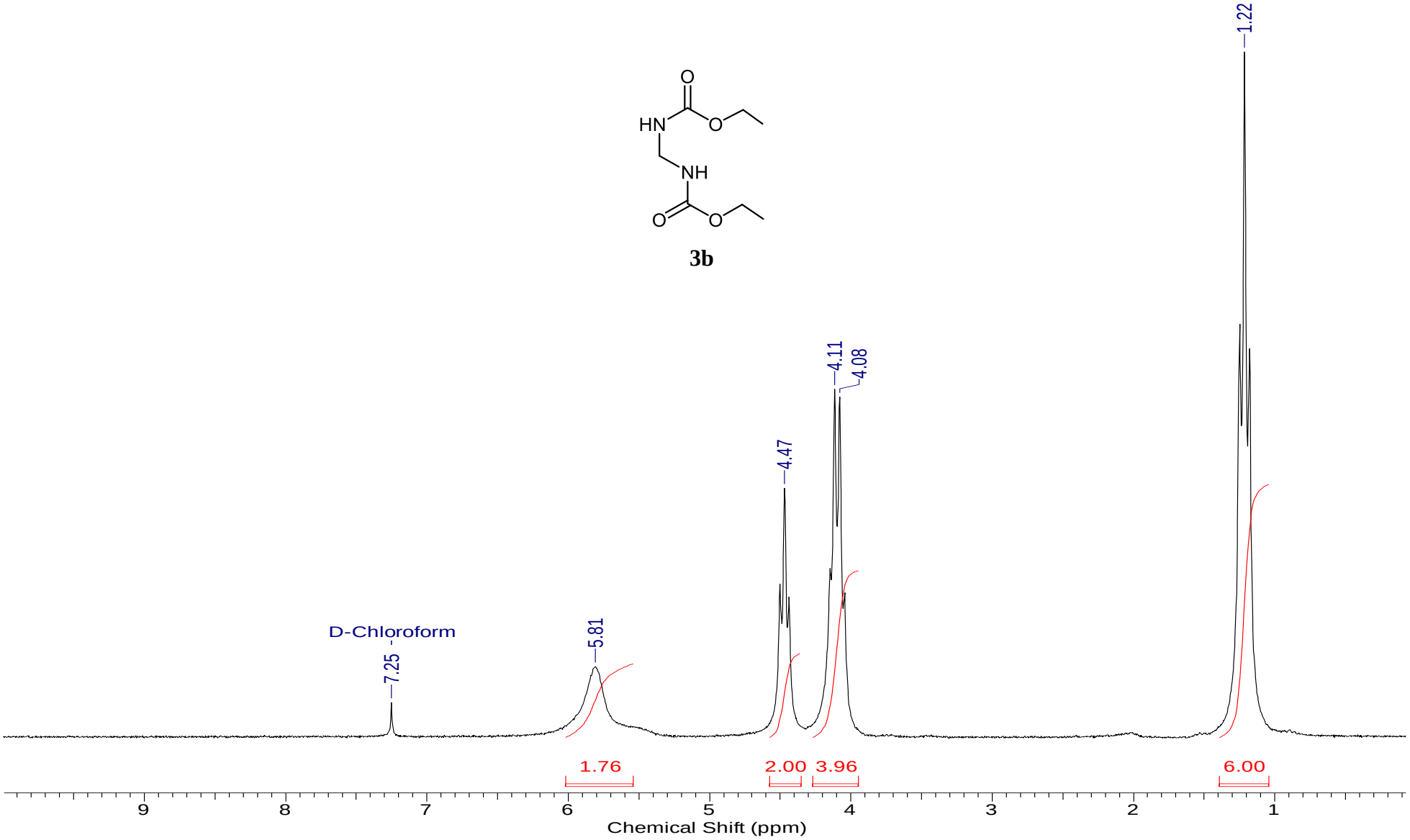


3a

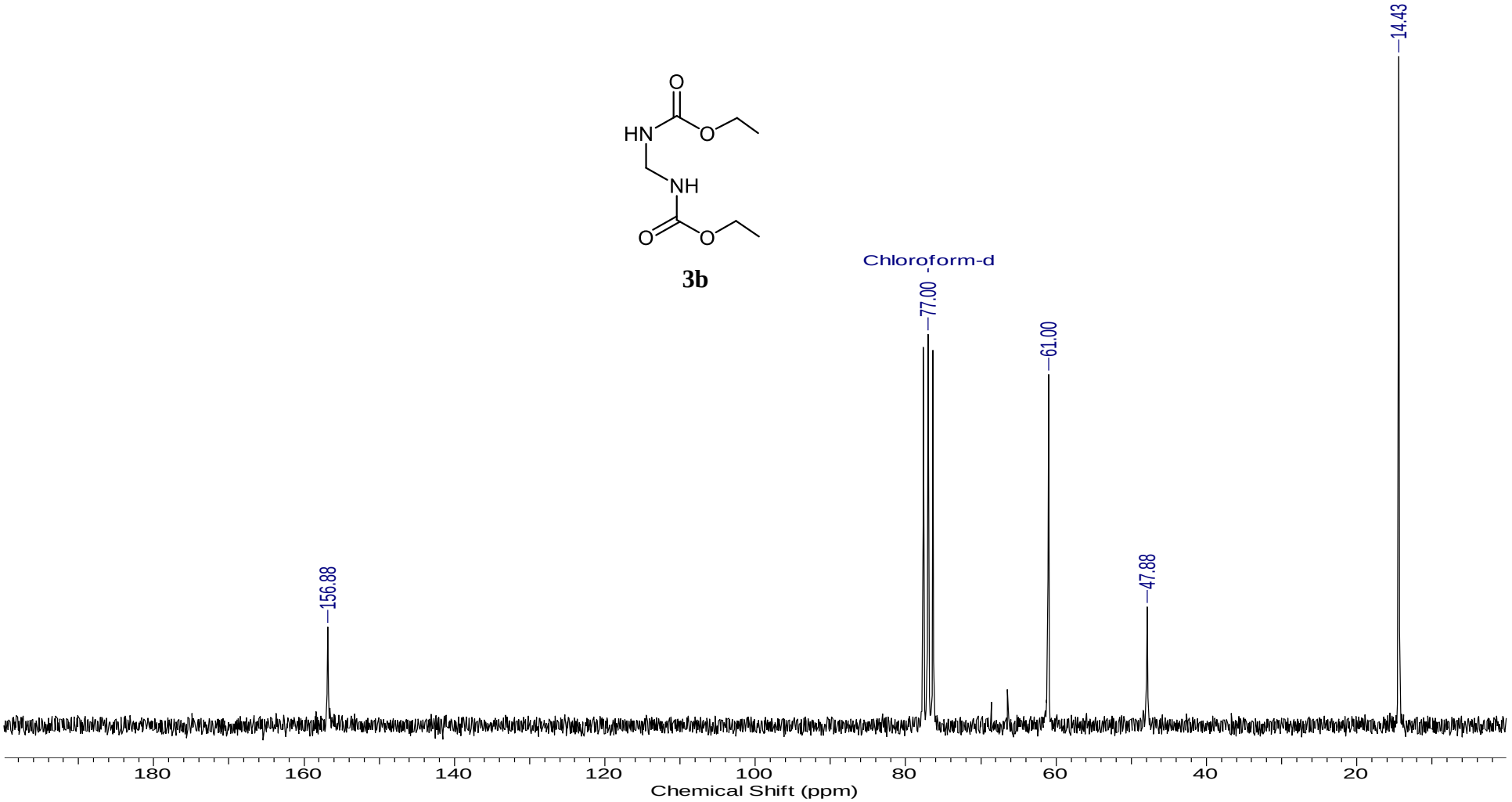
$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$)



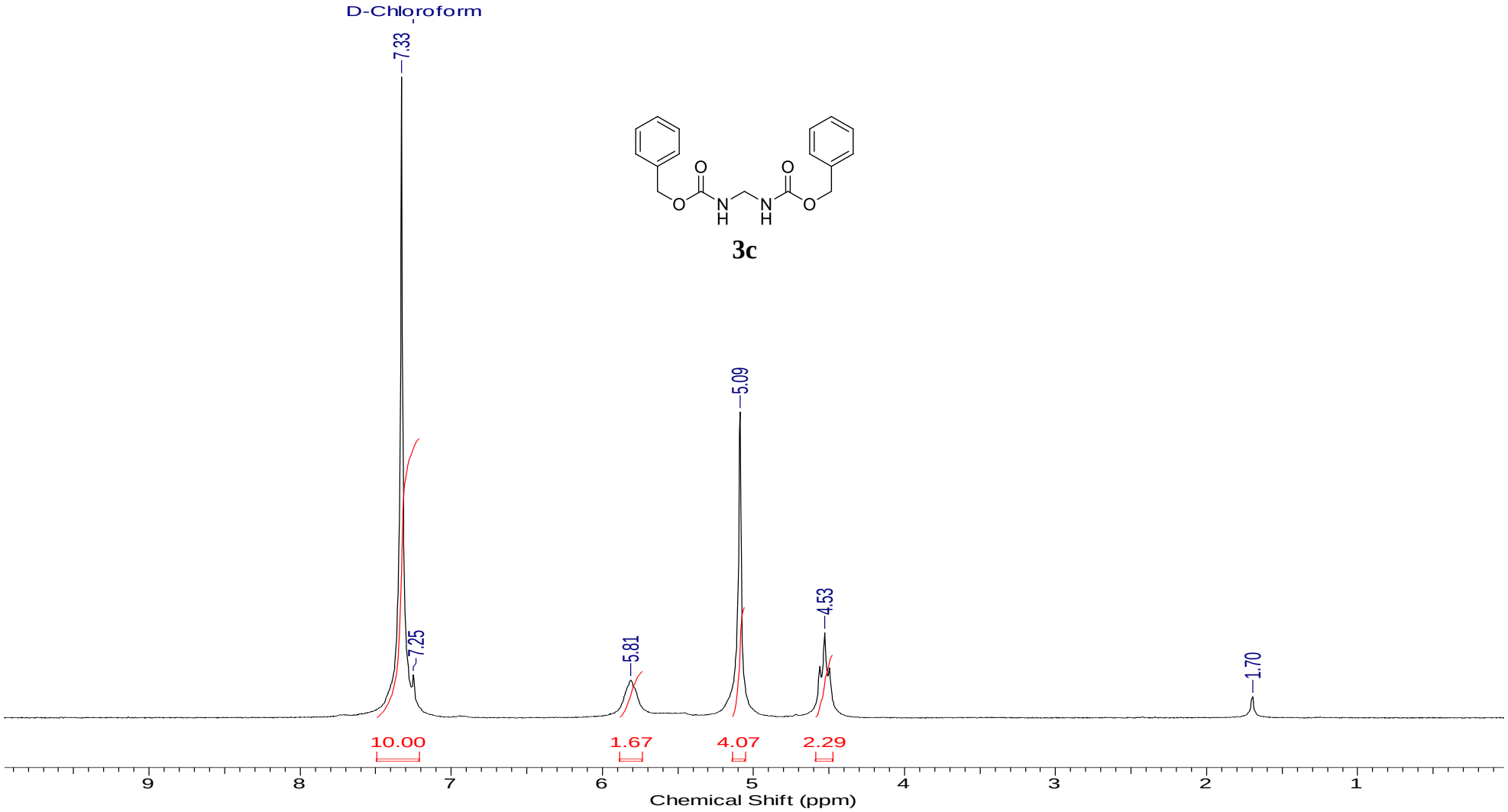
^{1}H NMR (200 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$)

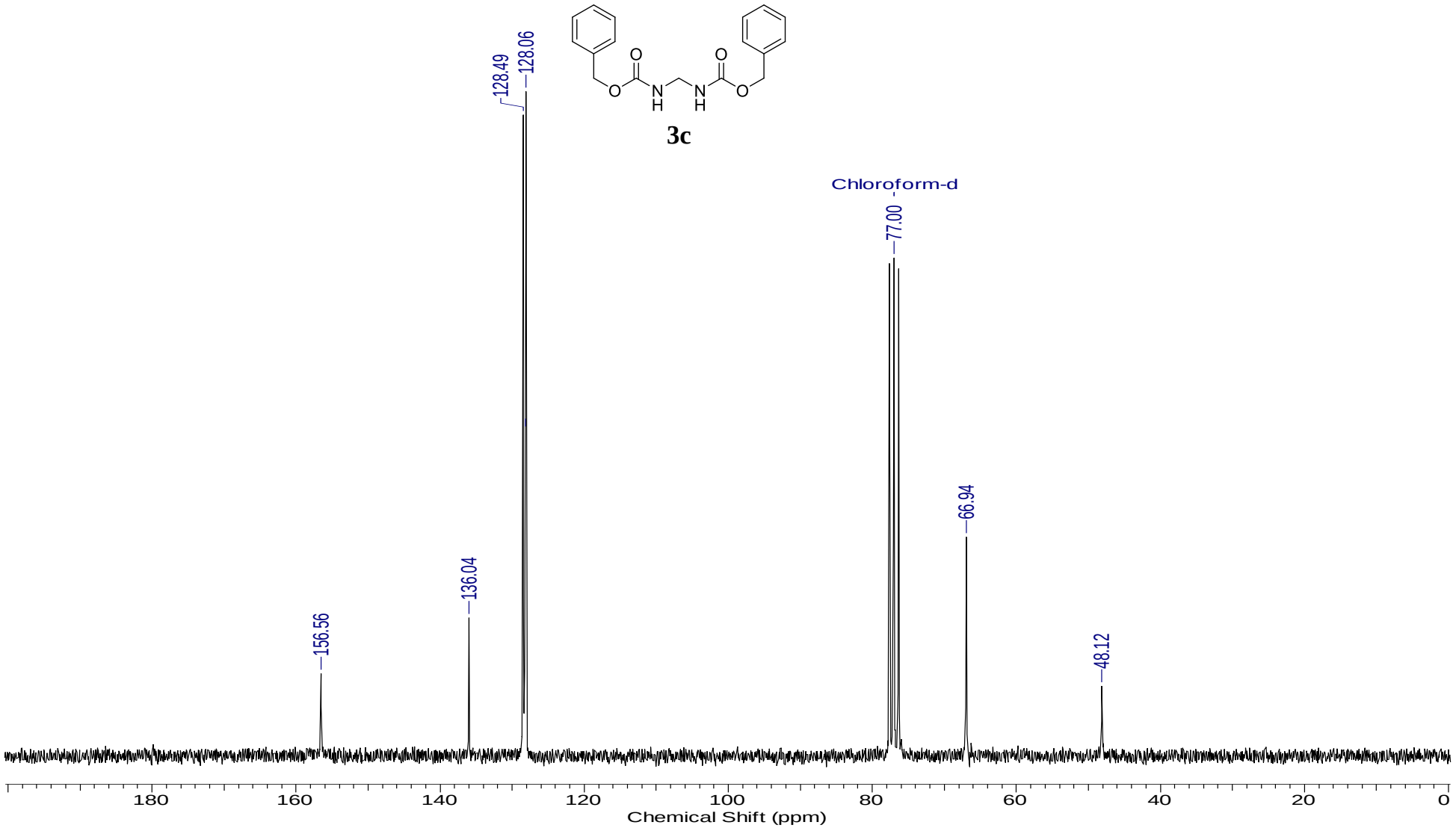


^{1}H NMR (200 MHz, $CDCl_3$)



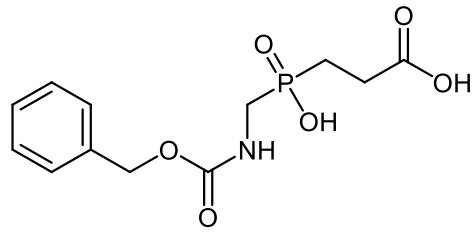
3c

$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$)



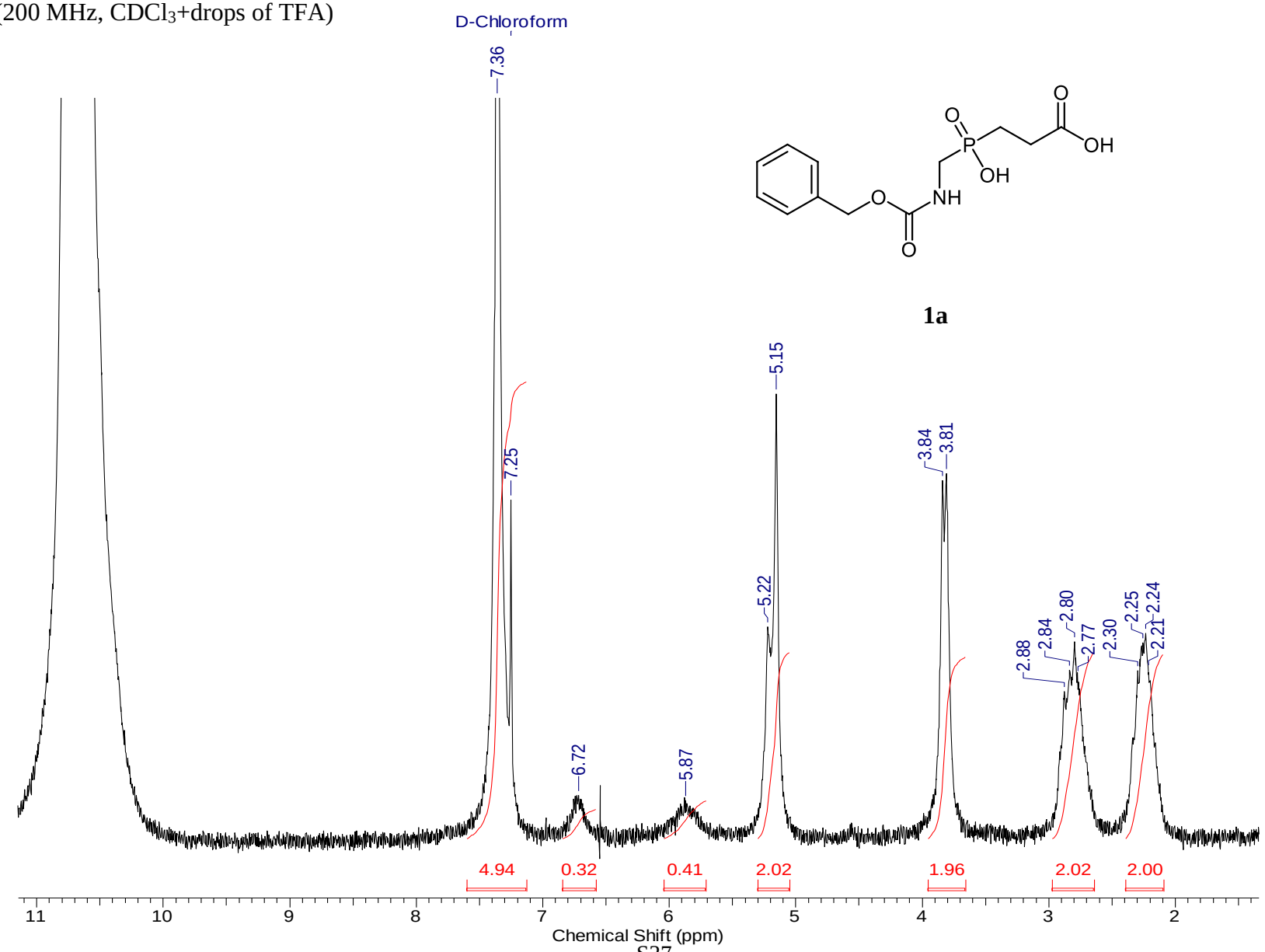
^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR and HRMS spectra of N-protected pseudopeptides 1a-h

^{1}H NMR (200 MHz, DMSO-d_6)



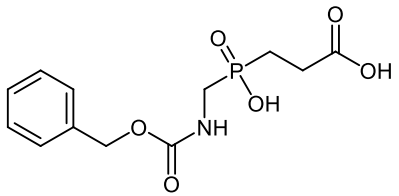
1a

^{1}H NMR (200 MHz, $CDCl_3$+drops of TFA)



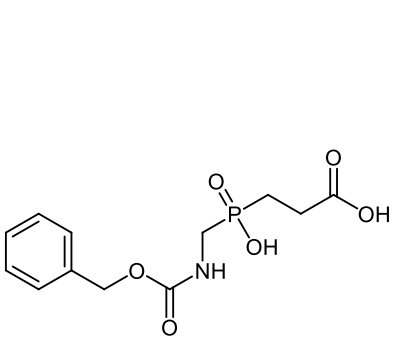
1a

$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$+drops of TFA)



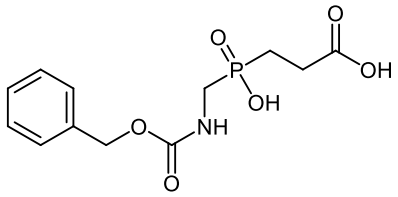
1a

$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$+DMSO-d6)



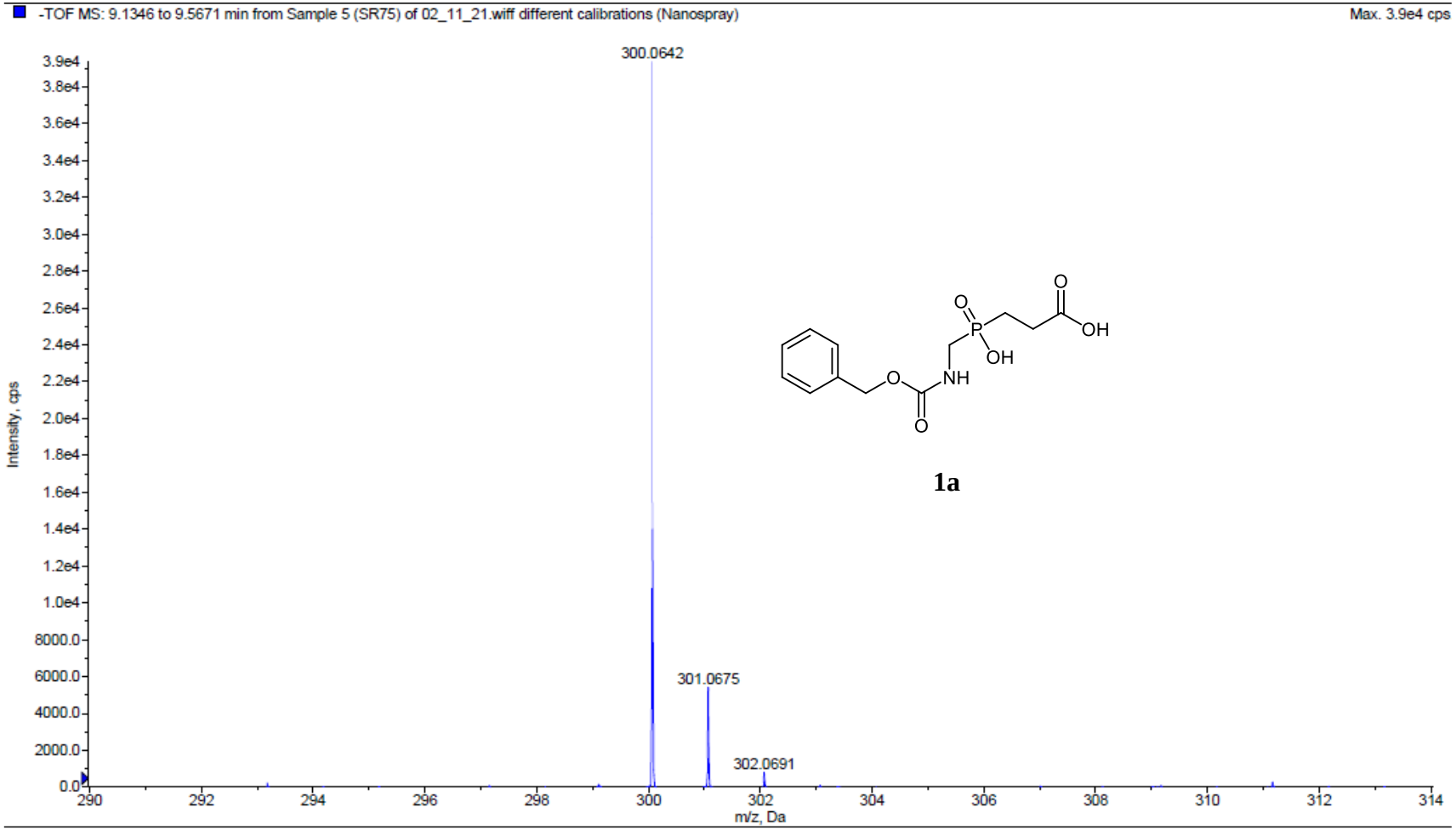
1a

$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$+drops of TFA)

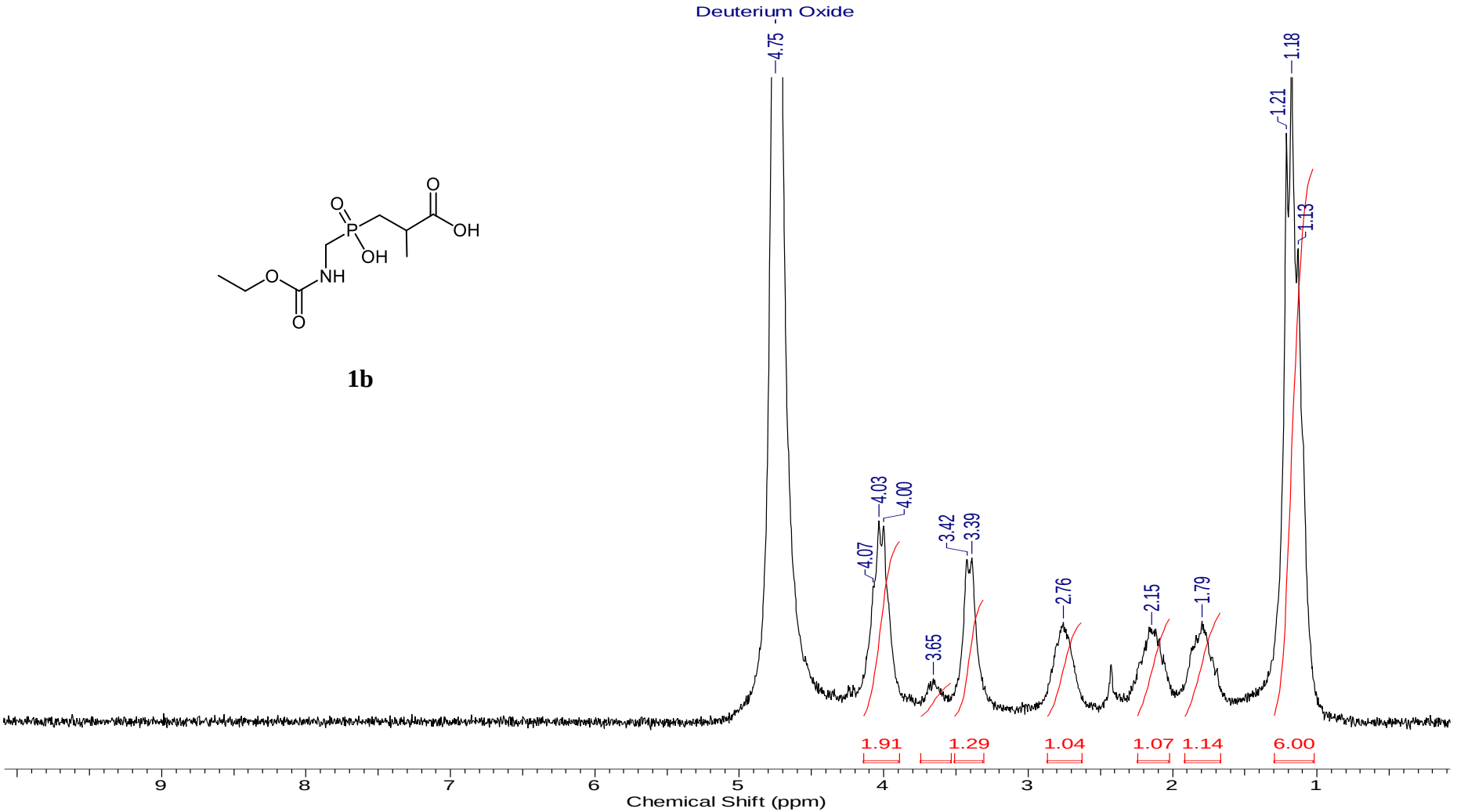


1a

1a. HRMS (NSI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{12}H_{15}NO_6P^-$ 300.0637, found 300.0642.

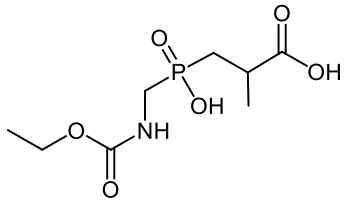


^{1}H NMR (200 MHz, D_2O)



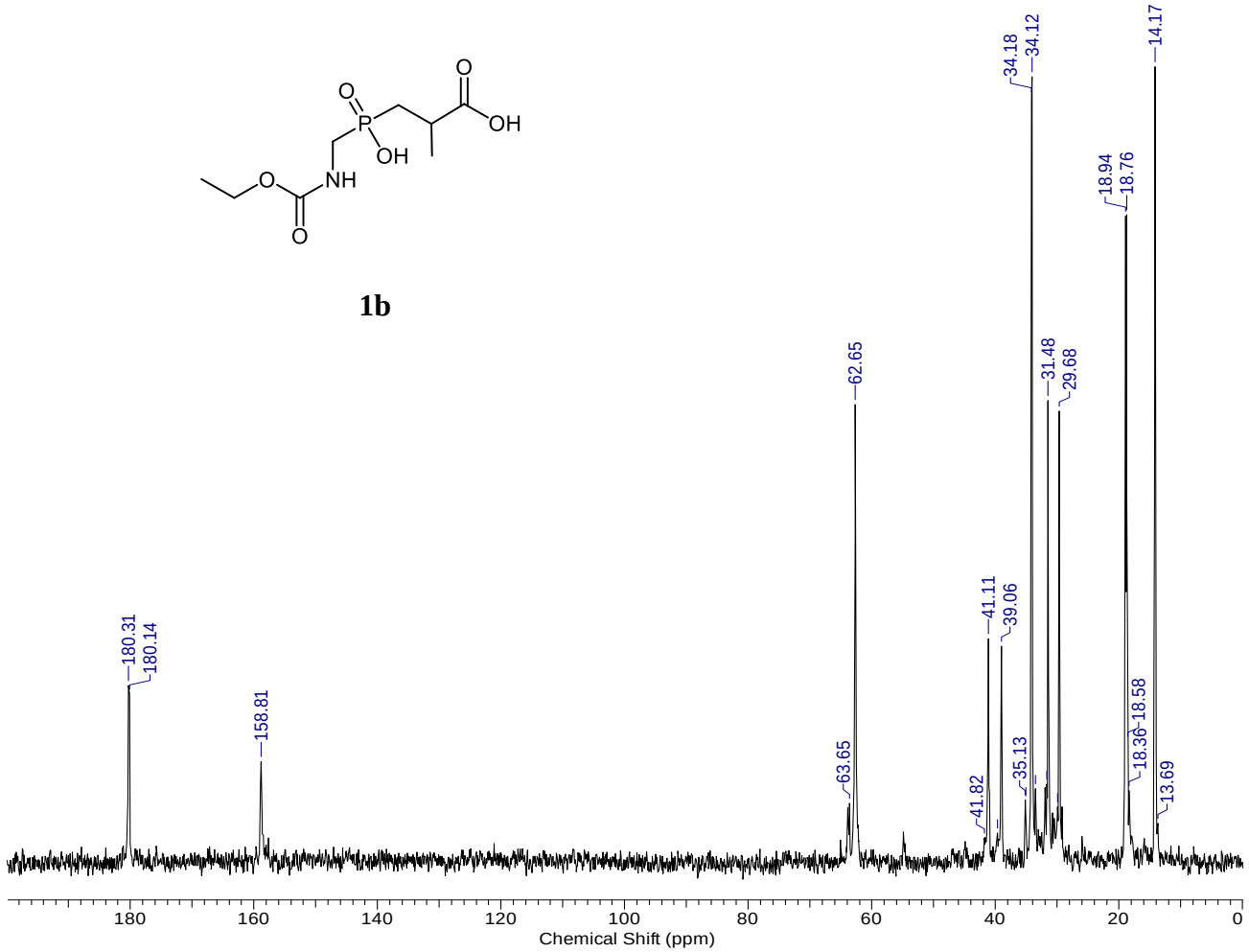
1b

$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O)



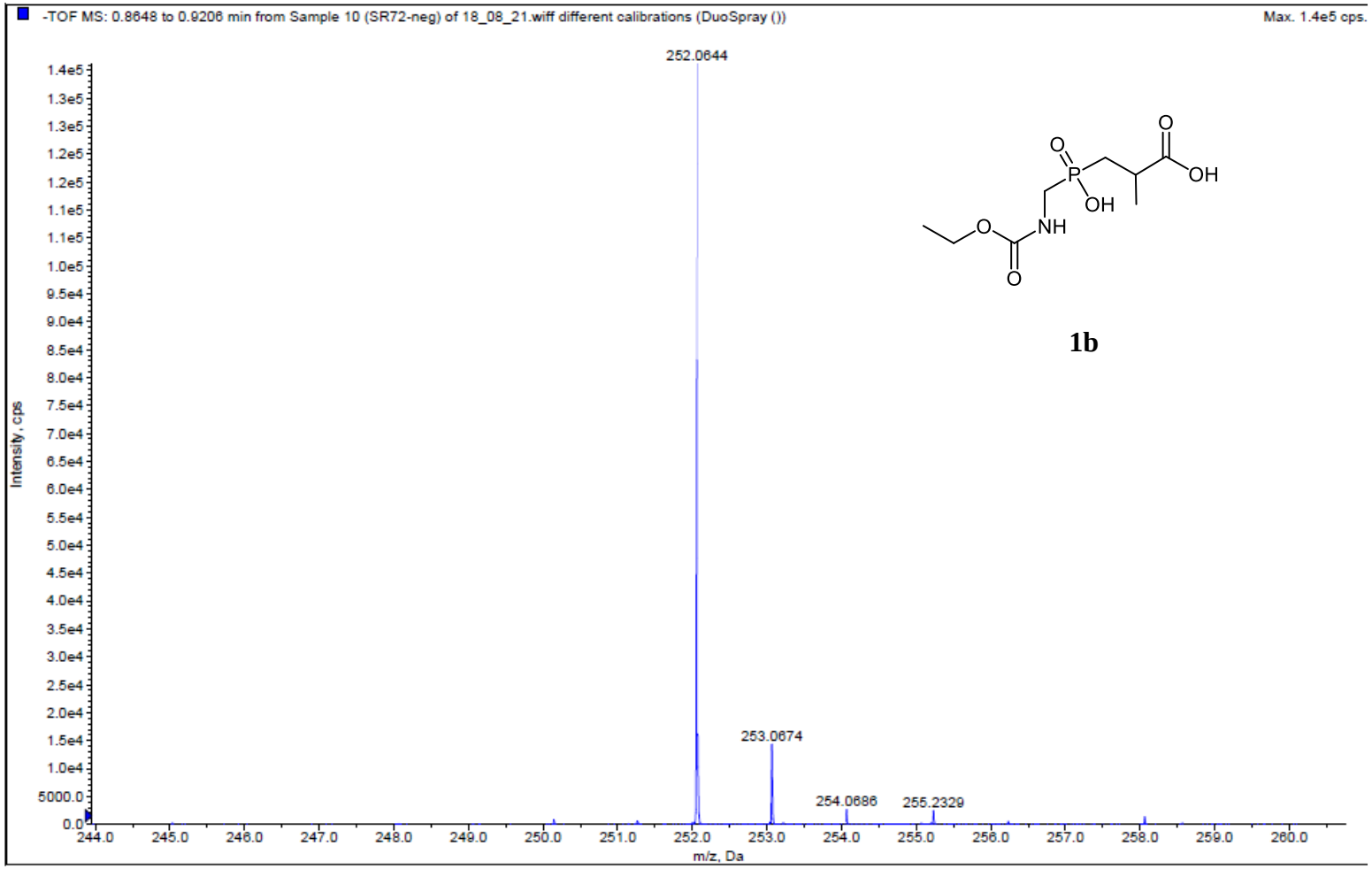
1b

$^{13}C\{^{1}H\}$ NMR (50 MHz, D_2O)

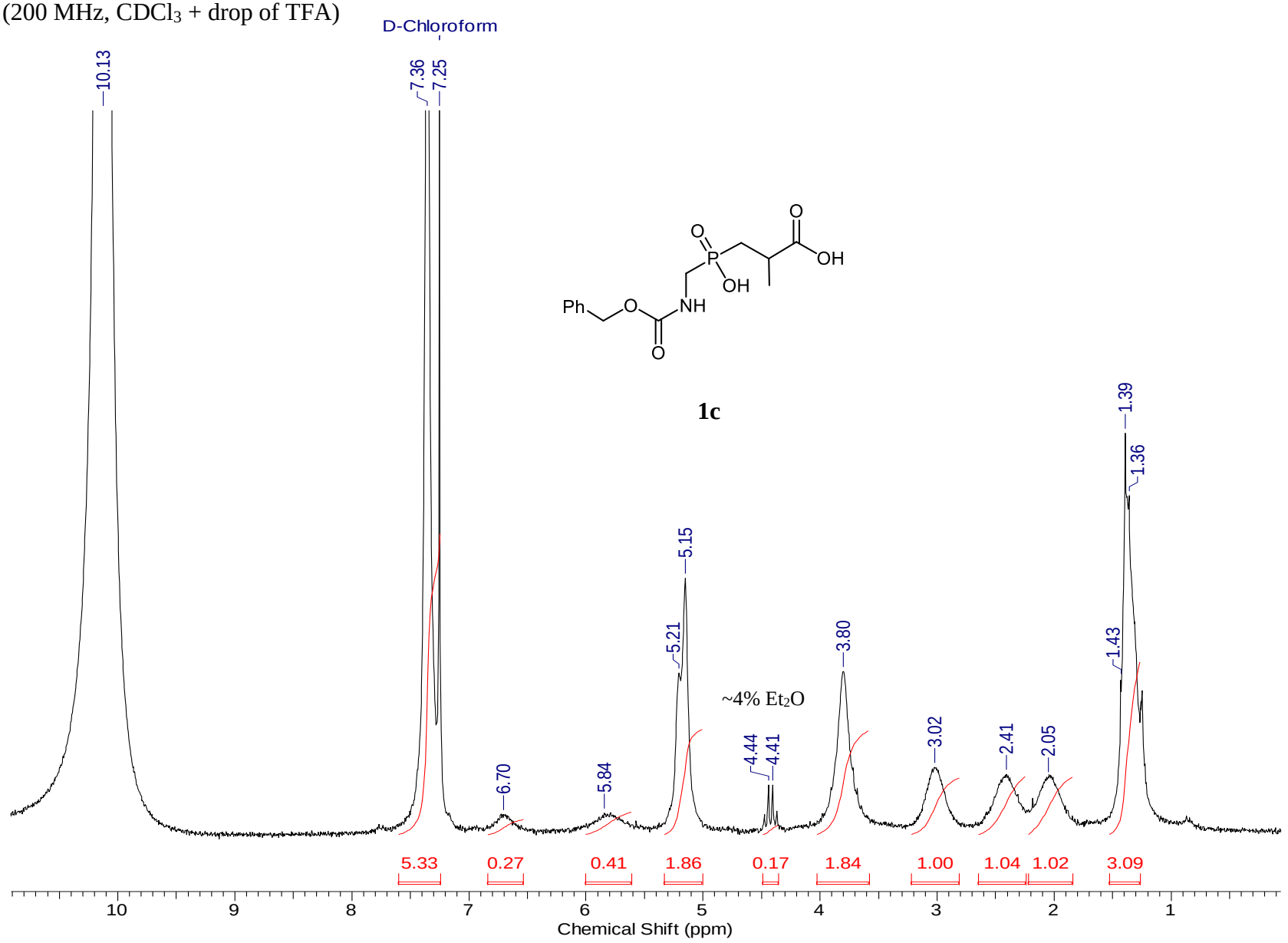


1b

1b. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_8H_{15}NO_6P^-$ 252.0637, found 252.0644.

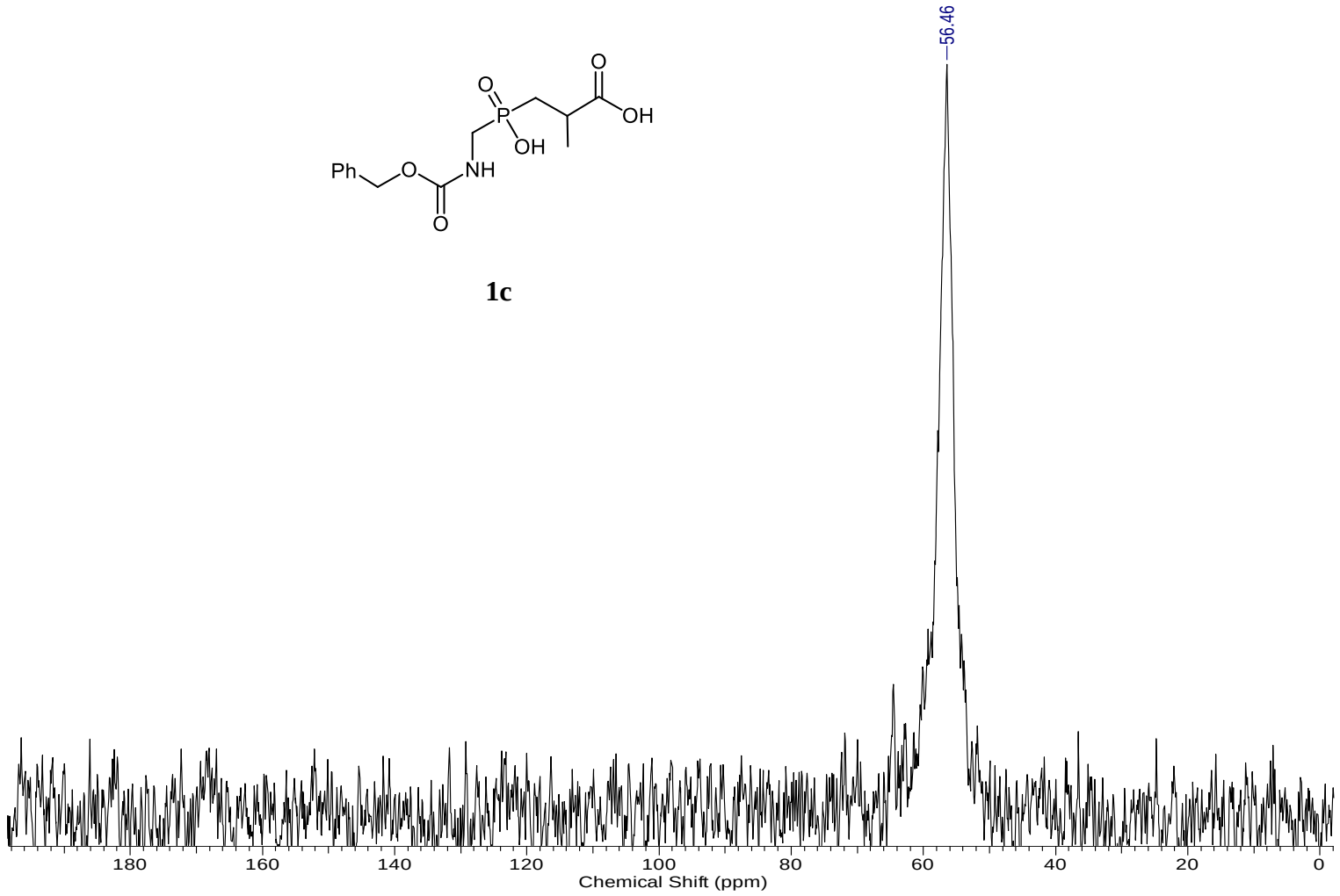


^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA)



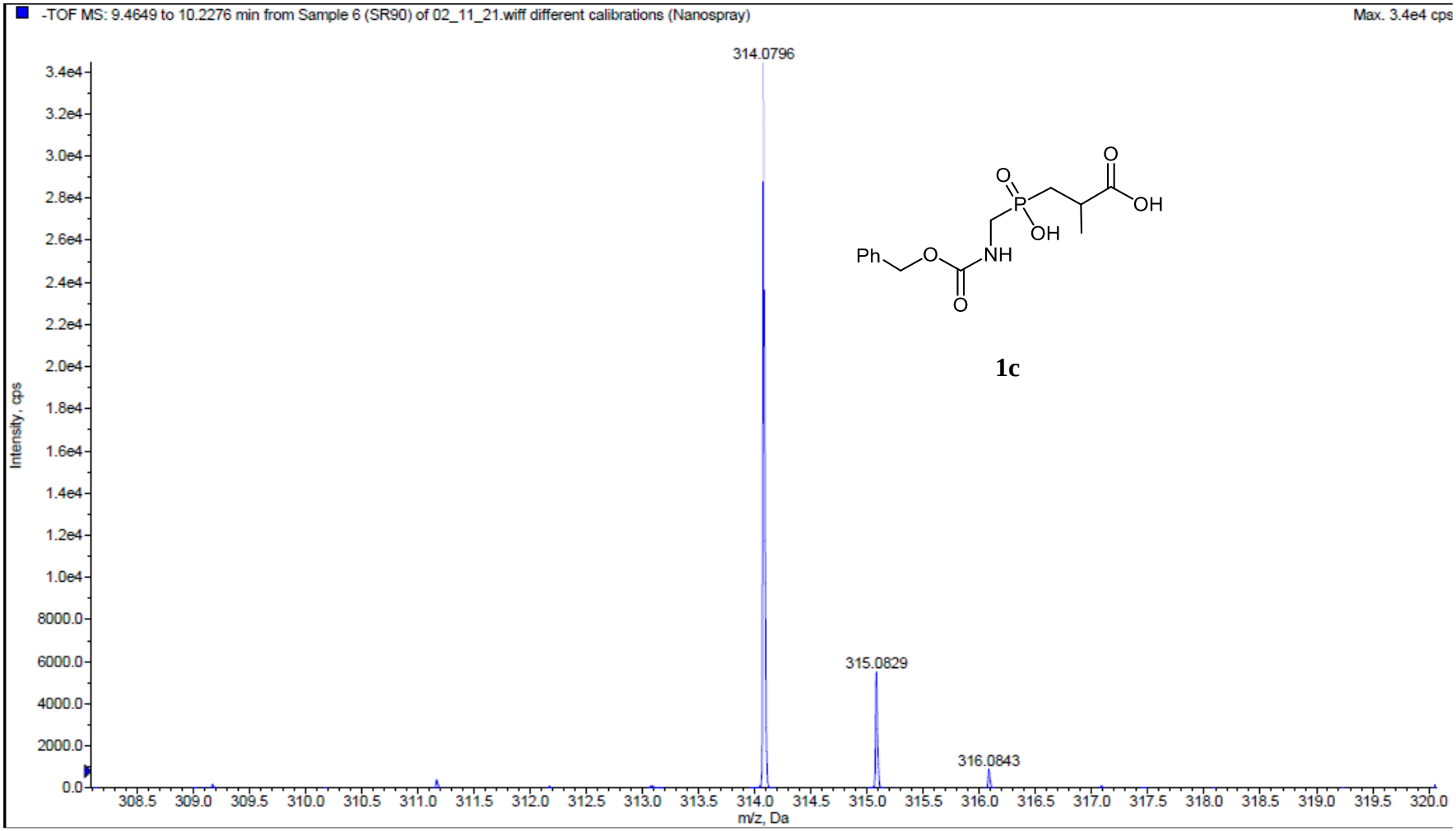
1c

$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$ + drop of TFA)

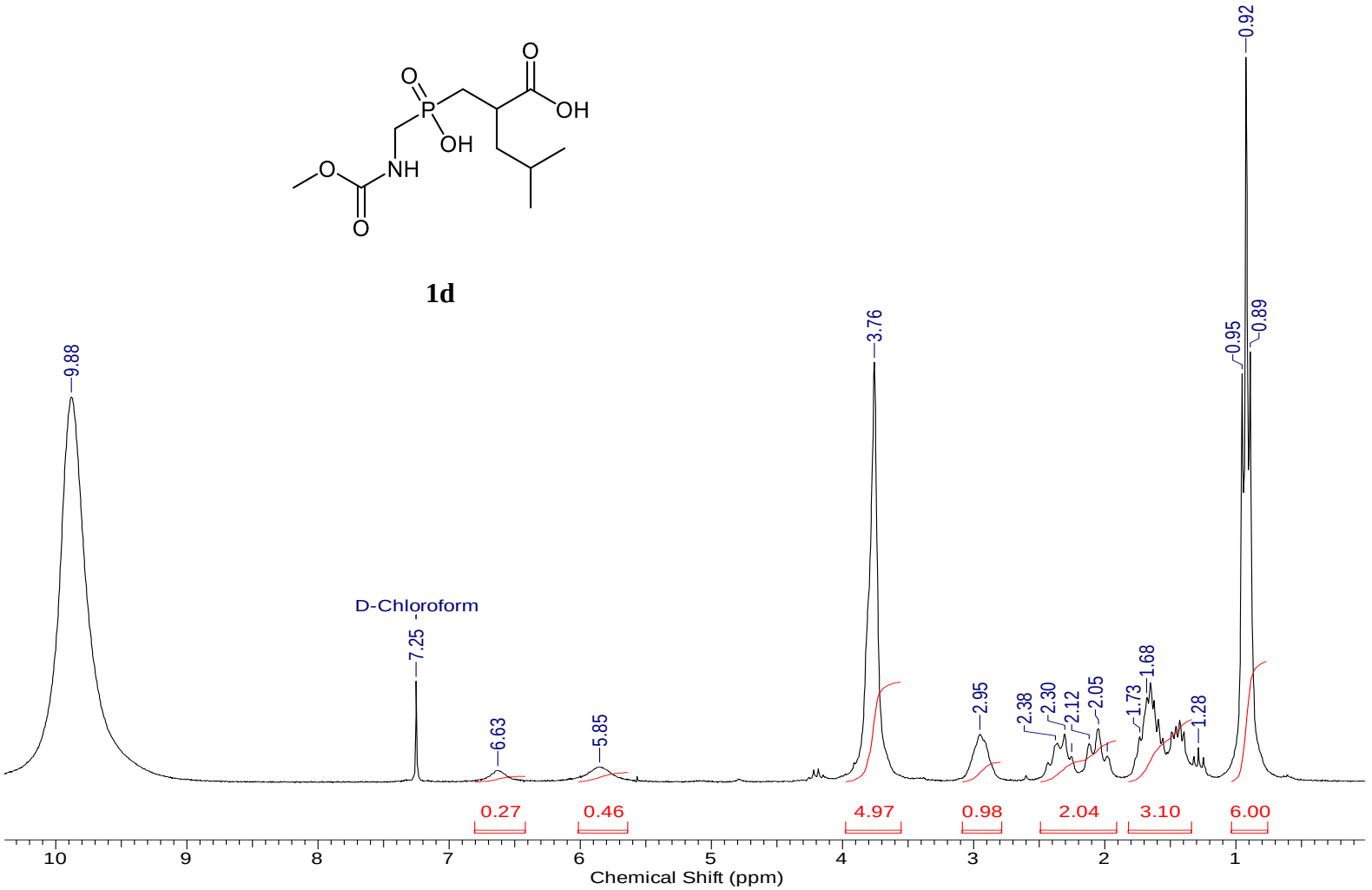


1c

1c. HRMS (NSI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{13}H_{17}NO_6P^-$ 314.0793, found 314.0796.

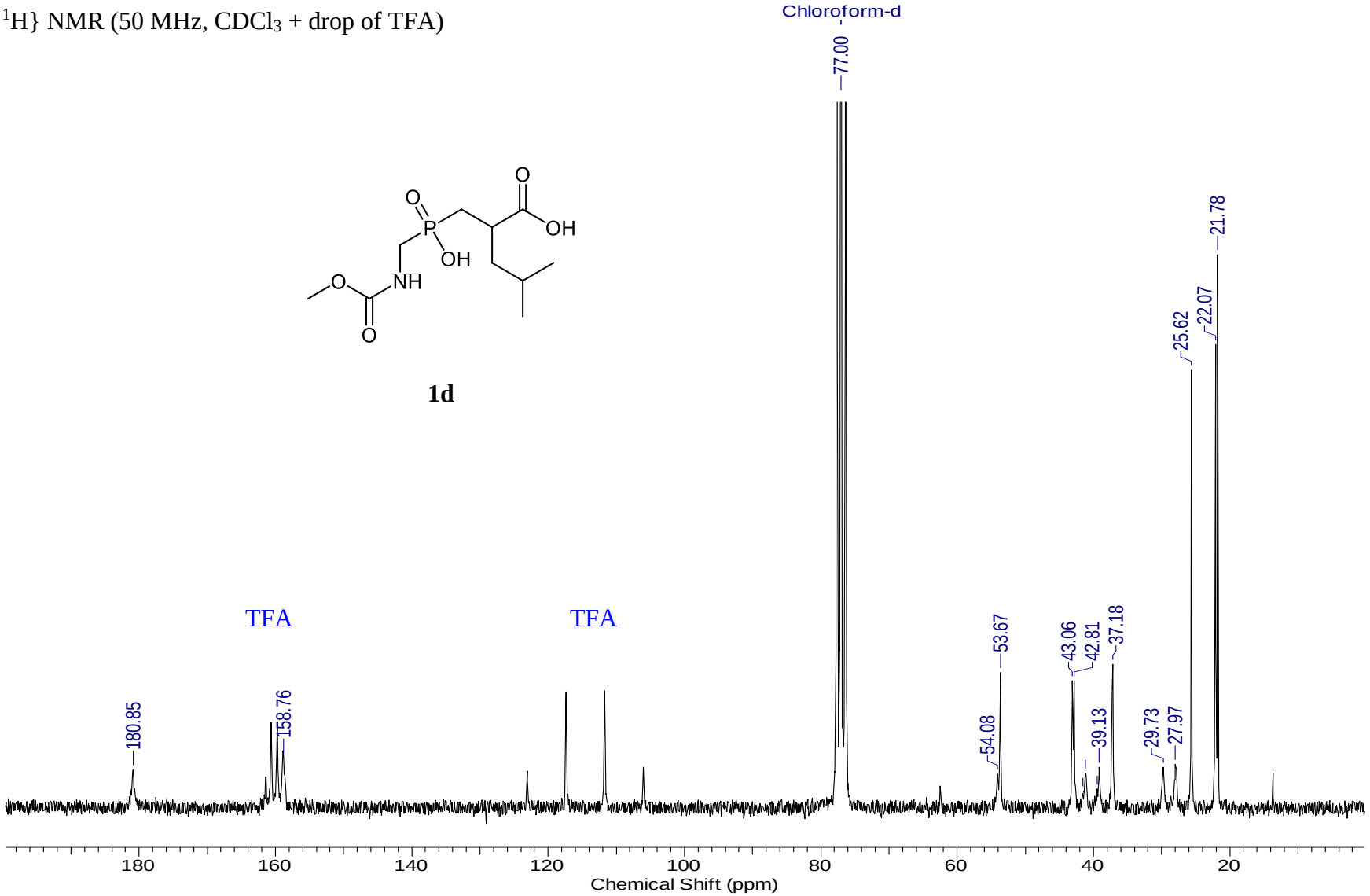


^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA)



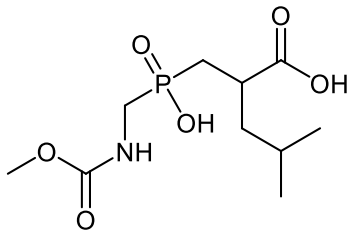
1d

$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$ + drop of TFA)



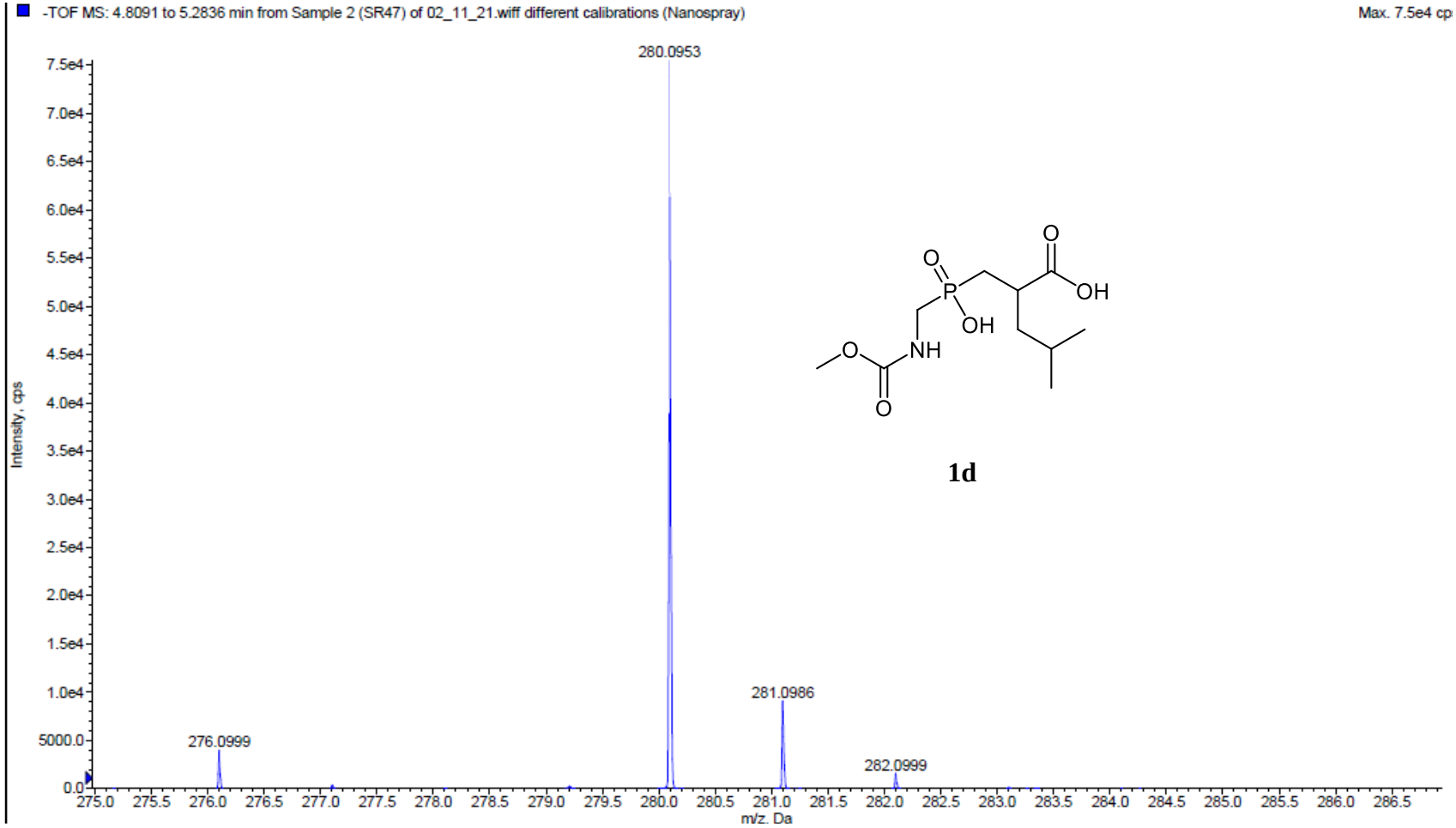
1d

$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$ + drop of TFA)

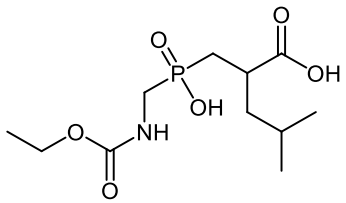


1d

1d. HRMS (NSI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{10}H_{19}NO_6P^-$ 280.0950, found 280.0953.

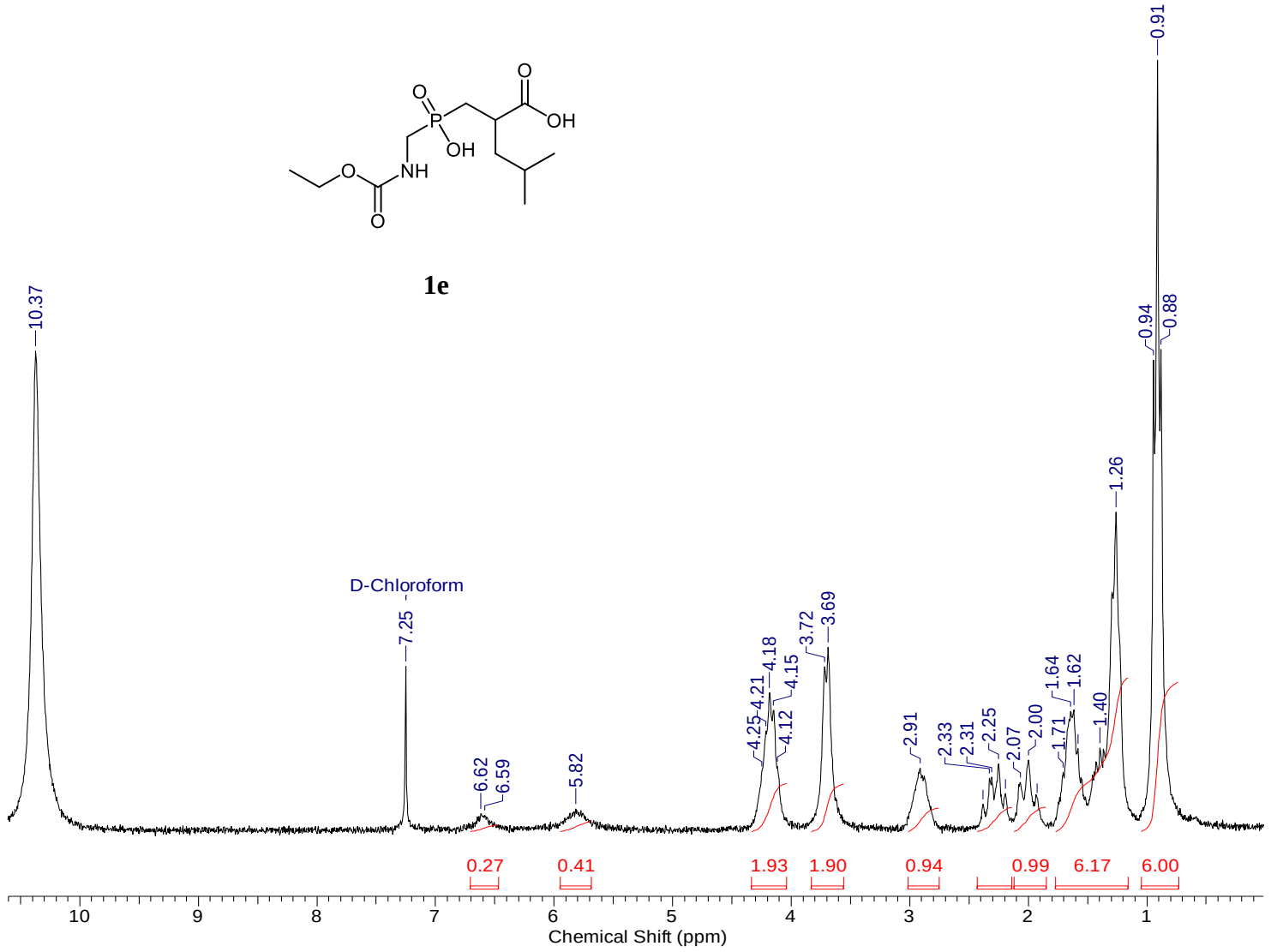


^{1}H NMR (200 MHz, DMSO-d6)



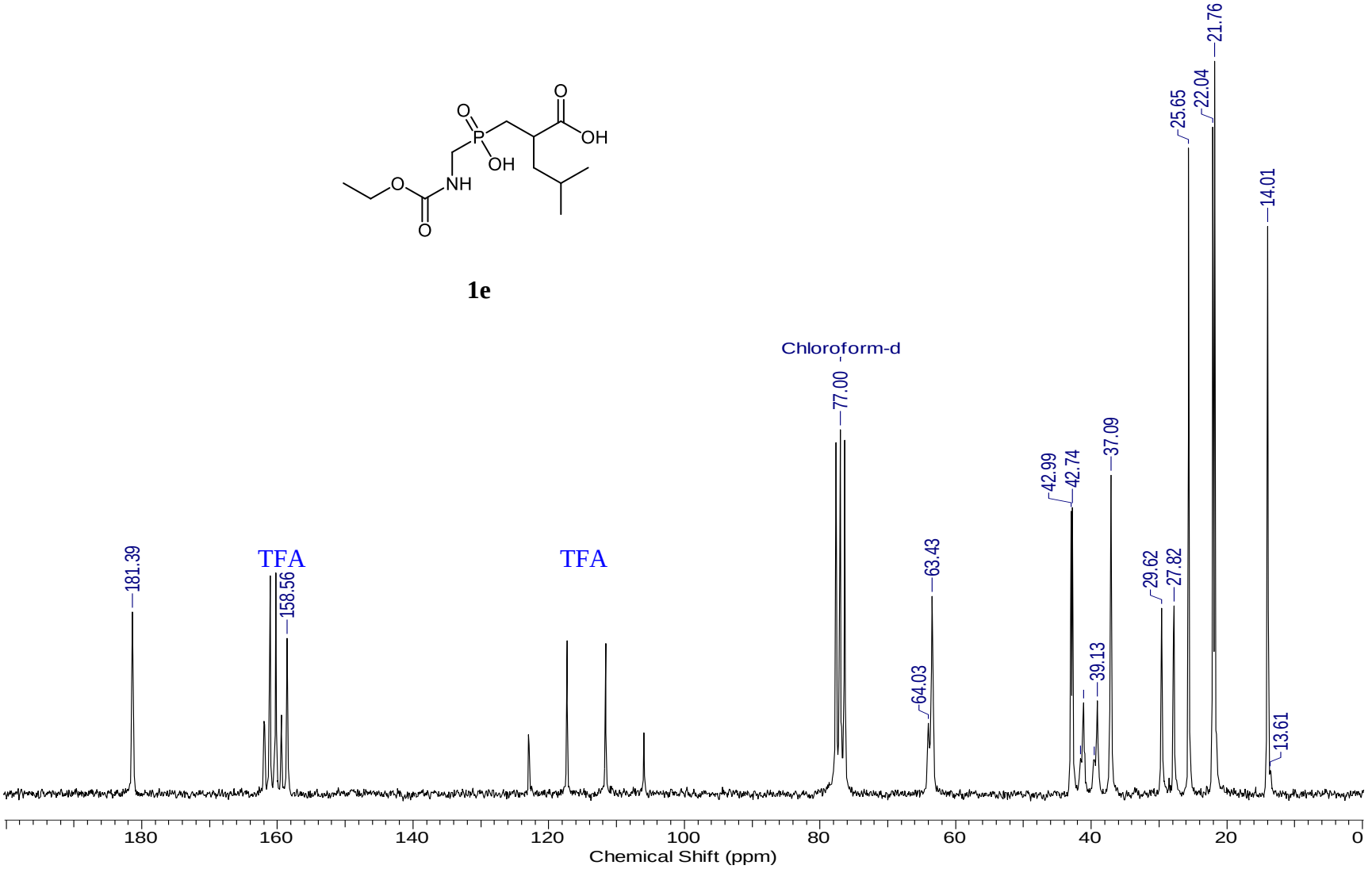
1e

^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA)

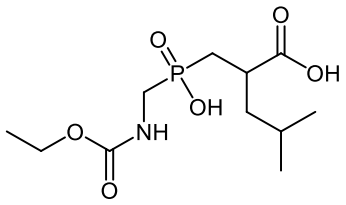


1e

$^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$ + drops of TFA)

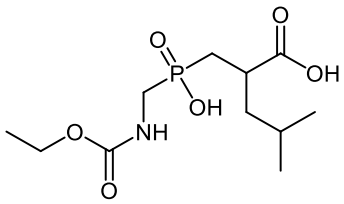


$^{31}P\{^{1}H\}$ NMR (81 MHz, DMSO-d6)

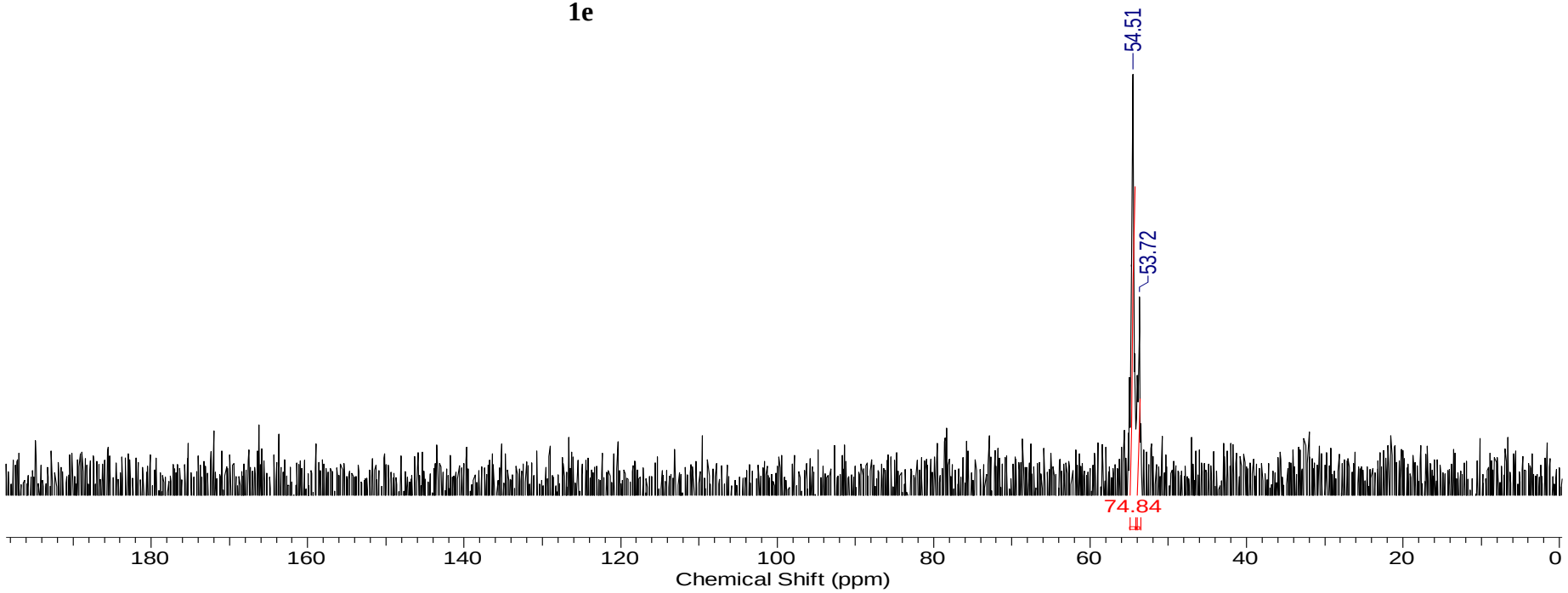


14

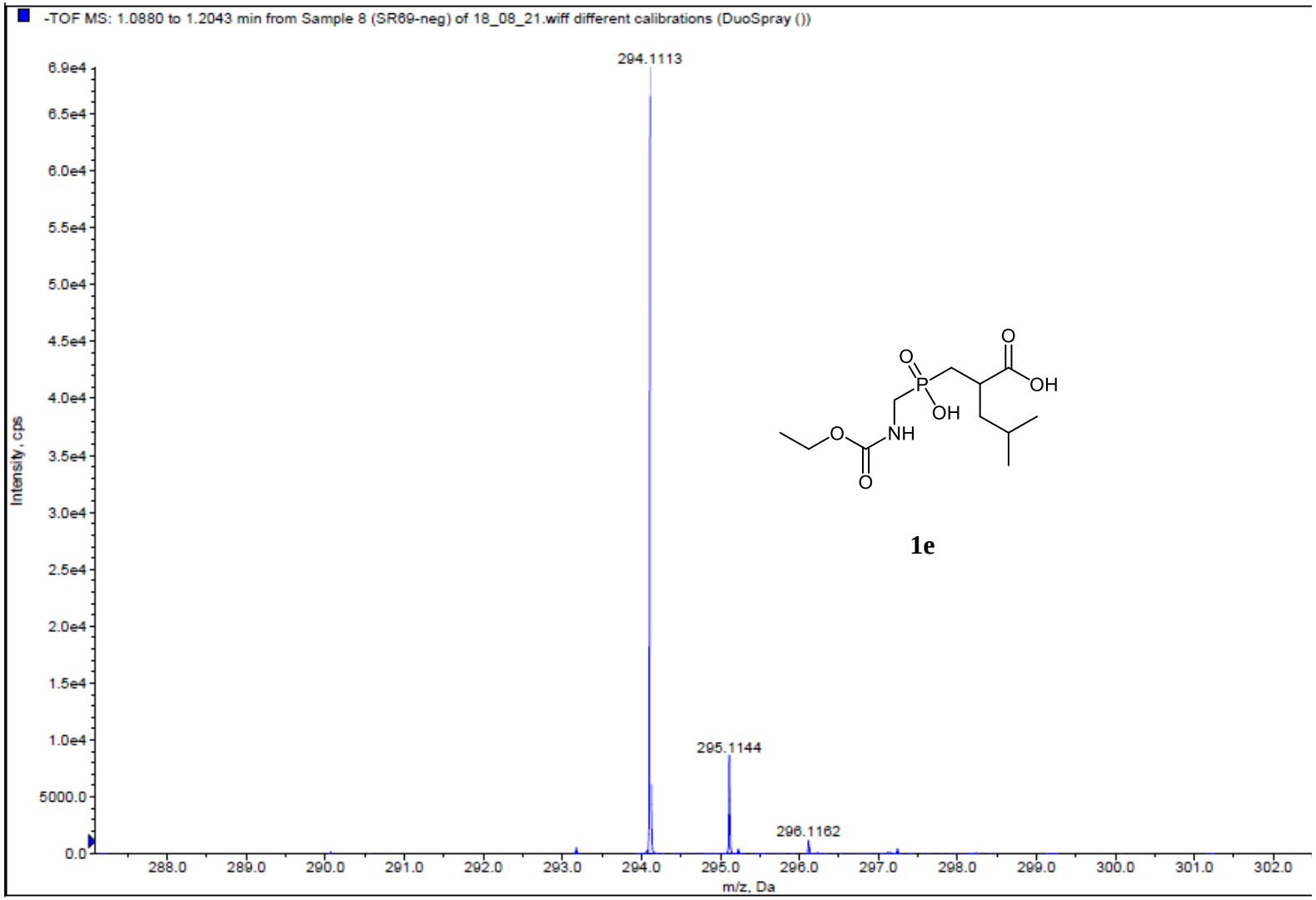
$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$ + drop of TFA)



1e

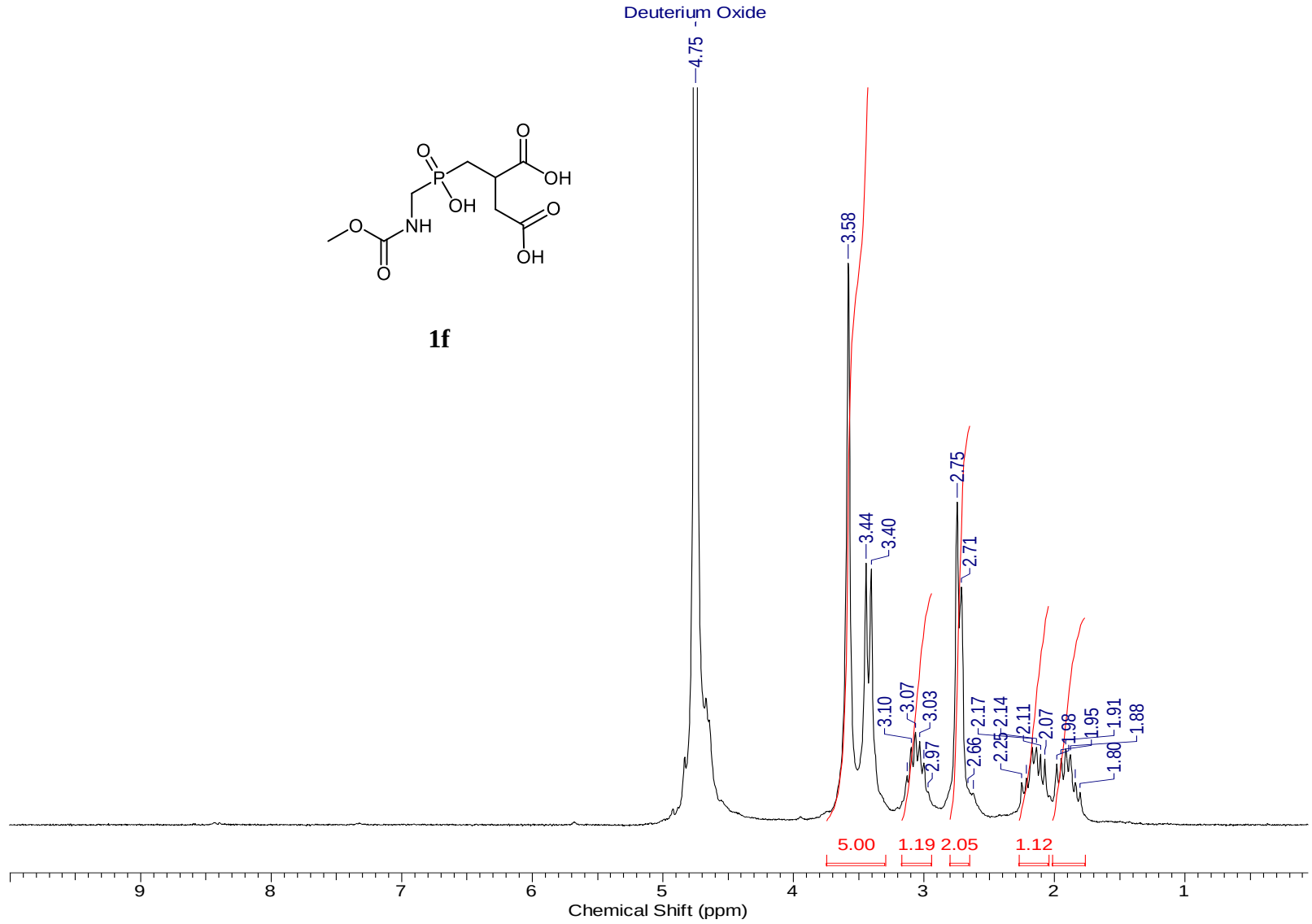


1e. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{11}H_{21}NO_6P^-$ 294.1107, found 294.1113.



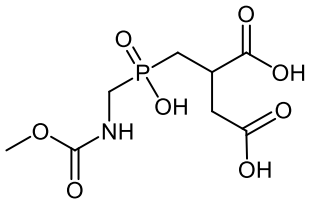
1e

^{1}H NMR (200 MHz, D_2O, pH~1, own)



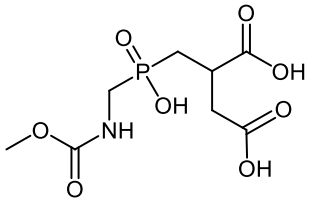
1f

$^{13}C\{^{1}H\}$ NMR (50 MHz, D_2O)



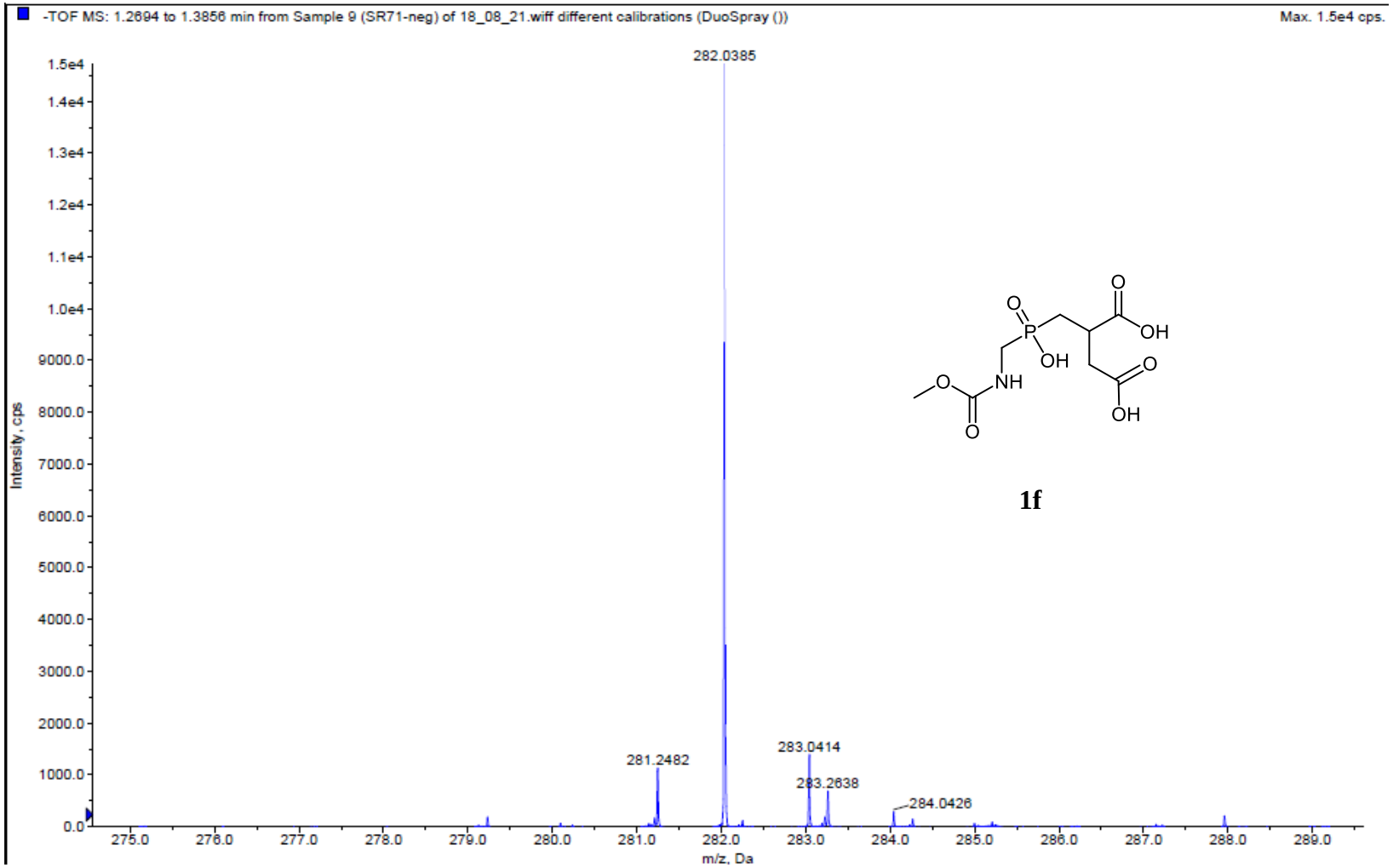
1f

$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O, pH~1, own)

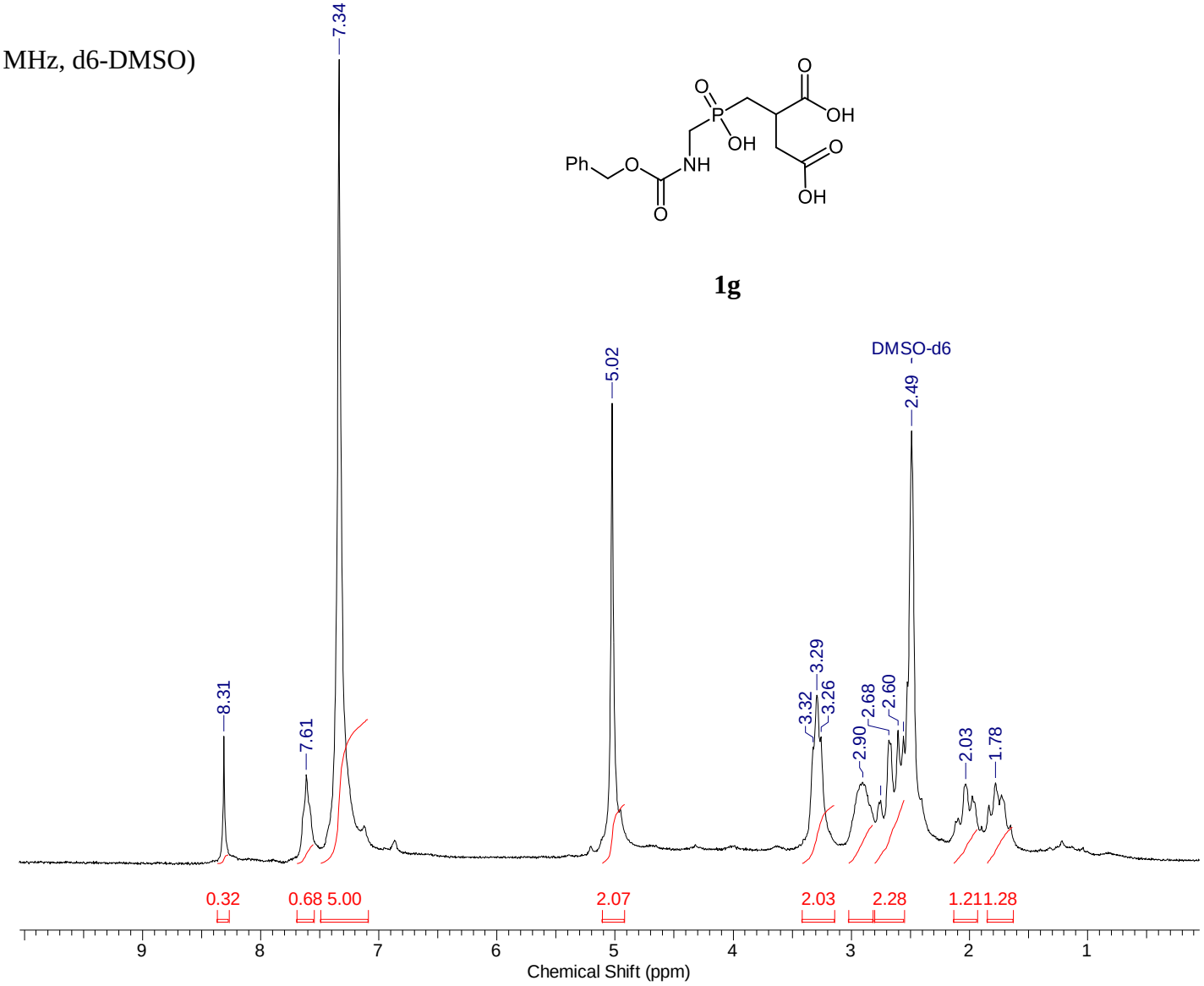


1f

1f. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_8H_{13}NO_8P^-$ 282.0379, found 282.0385.

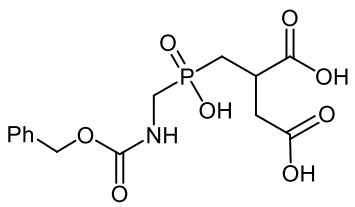


^{1}H NMR (200 MHz, d6-DMSO)



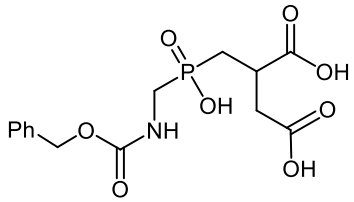
1g

$^{13}C\{^{1}H\}$ NMR (50 MHz, d6-DMSO + drops of $CDCl_3$)



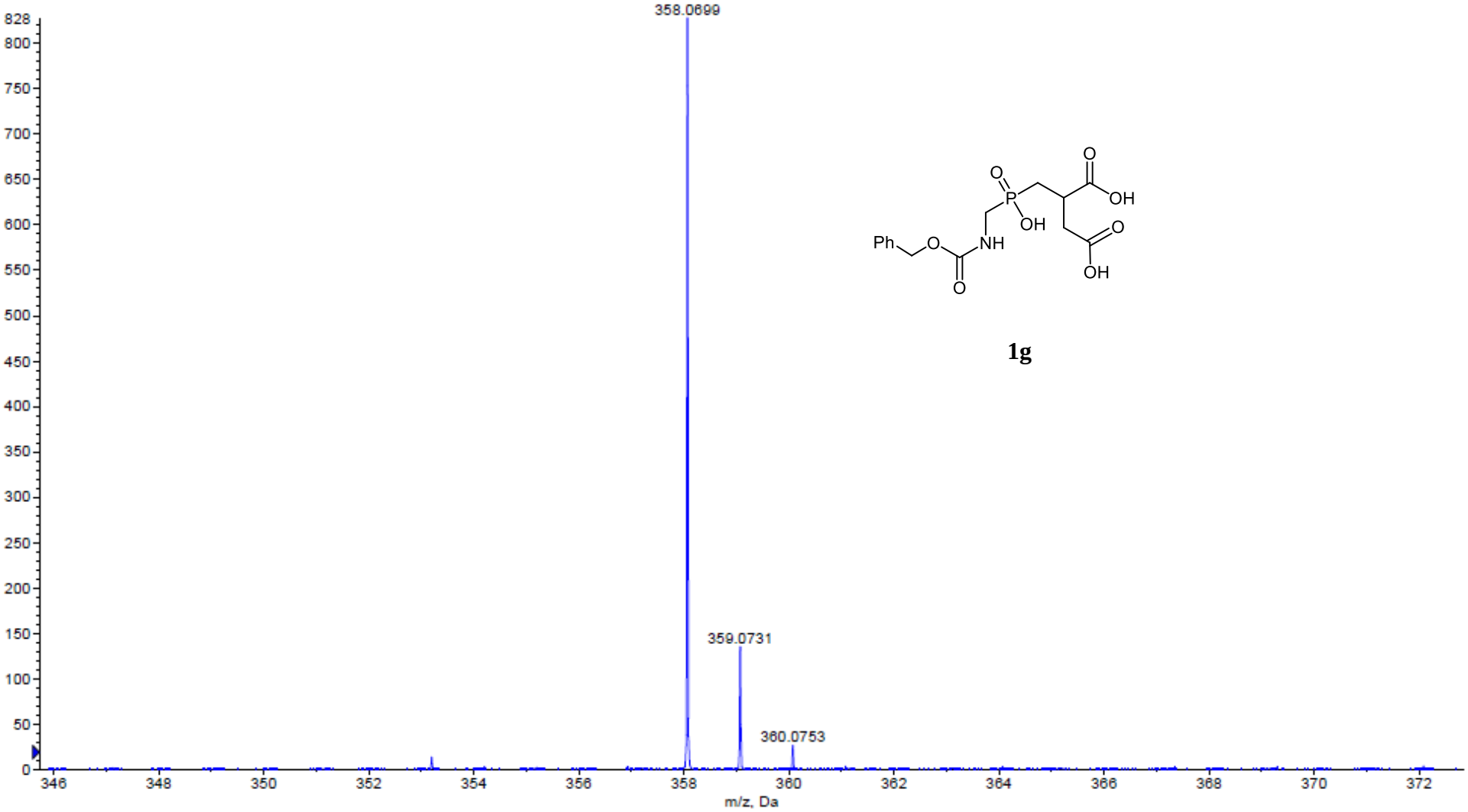
1g

$^{31}P\{^{1}H\}$ NMR (81 MHz, d6-DMSO)



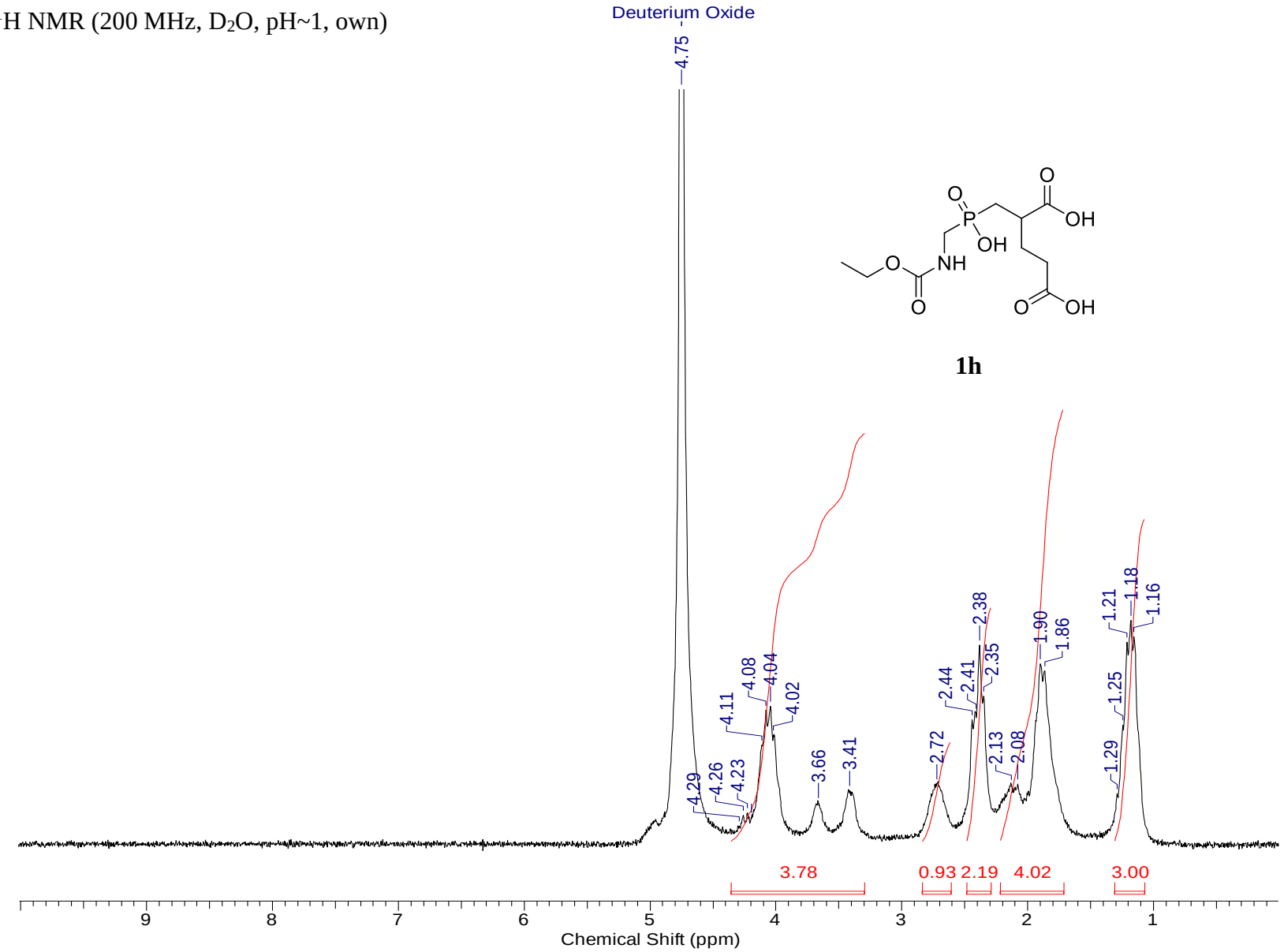
1g

1g. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{14}H_{17}NO_8P^-$ 358.0692, found 358.0699.



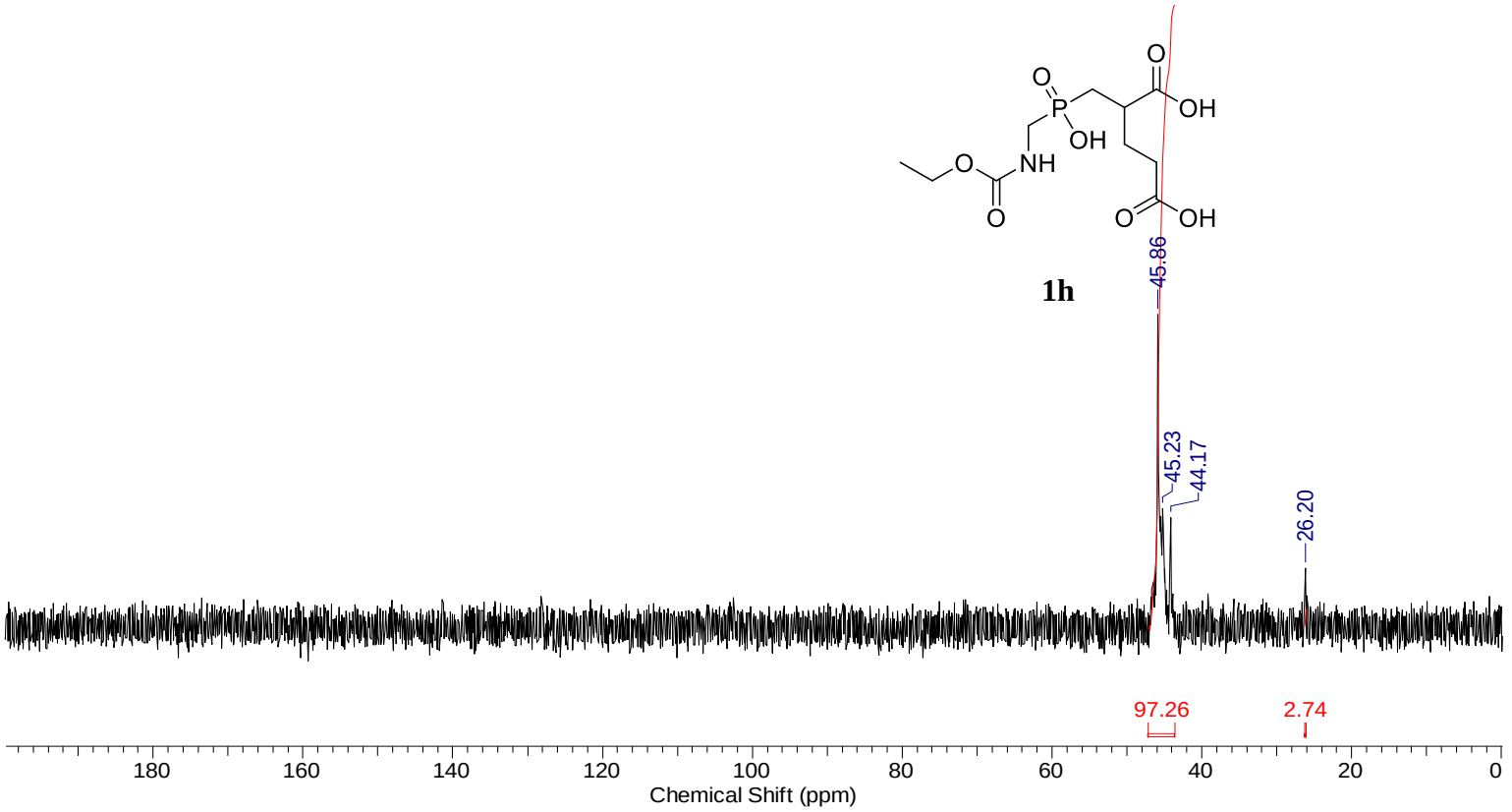
1g

^{1}H NMR (200 MHz, D_2O, pH~1, own)

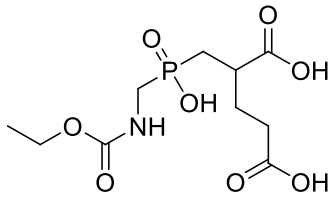


1h

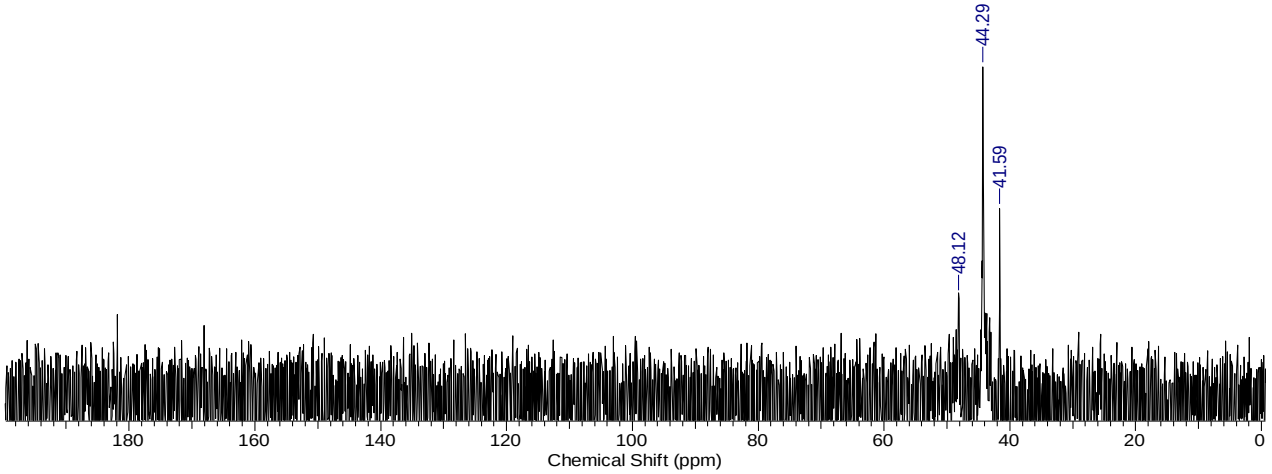
$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O, pH~1, own)



$^{31}P\{^{1}H\}$ NMR (81 MHz, D_6-DMSO + drops of TFA)



17



1h. HRMS (NSI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{10}H_{17}NO_8P^-$ 310.0692, found 310.0699.