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Acetals in amidoalkylation of phosphonous carboxylic diacids

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General Experimental Procedures

All reagents used were commercial and purchased from Shanghai Macklin Biochemical Co., Ltd (Reakor) and were used without additional purification. All other reagents and solvents: acetic anhydride, acetyl chloride, dichloromethane, toluene and others were used dry. All reactions were performed under an atmosphere of argon with magnetic stirring.

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 homogeneous by TLC. Analytical thin layer chromatography was carried out on silica-coated aluminium plates (silica gel Silufol-254, starch cohesive) using under UV visualization (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.

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.

NMR spectra

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

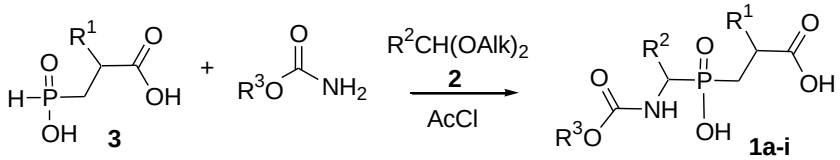
Nuclear magnetic resonance spectra were recorded on Bruker DPX-200 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). Tetramethylsilane (TMS) was used as internal standard (^{1}H NMR: TMS at 0.00 ppm; $CHCl_3$ at 7.25 ppm, D_2O at 4.75 ppm, DMSO-d_6 at 2.49 ppm; ^{31}P NMR 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-d_6 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). 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 source 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.

General approach for the synthesis of phosphinic *N*-protected dipeptides 1a-1i

Amidoalkylation of phosphonous carboxylic acids using acetals



R^1 = H, Me, Bu^i, Bn, CH_2COOH; R^2 = H, Me, Bn, CH_2CO_2Et;
R^3 = Me, Et, Bn; Alk= Me, Et

The corresponding acetal **2** (1.1÷1.2 mmol) was slowly added dropwise to freshly prepared solution of the corresponding phosphonous carboxylic diacid **3** (1.0 mmol) and alkyl carbamate (1.0 mmol) in 5÷6 ml of acetyl chloride at room temperature. The resulting mixture was stirred for 2 to 20 hours, the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, 5 ml of chloroform was added and mixture was evaporated *in vacuo* and then additionally coevaporated with 5 ml chloroform.

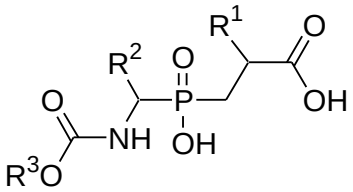
Procedure 1. Isolation of 1a-g. The residue was partitioned between ethyl acetate and water (3÷5 : 1). Precipitated unreacted alkylcarbamate was filtered off, and the organic part of filtrate was evaporated *in vacuo*. The wet residue was treated with ether and left for a while. Usually, the phosphinic peptides were isolated as white solids. The exceptions are **1a** and **1d**, which were isolated 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 diethyl ether.

Procedure 2. Isolation of 1h,i. The residue was partitioned between benzene and water (1 : 5). Precipitated carbamate was filtered off, and the aqueous part of the filtrate was washed with benzene additionally and was evaporated *in vacuo*. The wet residue was treated with petroleum ether (40/70) and left for a while. Then the petroleum ether was decanted over a semi-crystalline residue, which was re-treated with fresh diethyl ether, and phosphinic peptides **1h and 1i** were isolated as solids.

Procedure 3. Phosphinic peptides **1b,c,g** were additionally obtained by silica gel column chromatography of the residue formed after evaporation in vacuo of the organic phase from **procedure 1**. 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 peptides **1b, 1c** and **1g** were lower (43, 45 and 43%, respectively) than the yields of these compounds obtained by crystallization according to **procedure 1**. The spectral and physicochemical data were not significantly different in both cases.

N-Protected α-amino phosphinic acids **1a-i**, the products of reaction studied in the work, are mixture of diastereomers and conformers, because it is associated with the presence of a chiral carbon atoms and amide nitrogen in the molecule **1**. Some phosphinic peptides were successfully recrystallized from concentrated aqueous solution.

Characterization of phosphinic peptides 1a-i



Phosphinic peptides **1a-i**

***P*-[(*N*-Benzyloxycarbonylamino)methyl]-*P*-(3-hydroxy-3-oxopropyl)phosphinic acid (1a)**

($R^1 = R^2 = H$, $R^3 = Bn$).

Yield: 0.09 g, 29% **(**procedure 1**)**.
White solid. M.p. 134-135. Lit.[S1] m.p. 137-138°C. TLC R_f ($CHCl_3$/Pr^iOH: 4/1) = 0.30.
^{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 diastereomer and(or) conformer forms.
^{1}H NMR (200 MHz, DMSO-d_6) 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).
^{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.
^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$: DMSO-d_6 = 4 : 1) δ 44.33
HRMS (**NSI**/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{12}H_{15}NO_6P^-$ 300.0637, found 300.0642.

***P*-(3-Hydroxy-2-methyl-3-oxopropyl)-*P*-[1-(*N*-methoxycarbonylamino)-2-phenylethyl]-phosphinic acid (1b) (**$R^1 = Me$, $R^2 = Bn$, $R^3 = Me$).
Yield 0.19 g, 58% **(**procedure 1), 0.14 g, 43% **(**procedure 3).
White solid. M.p. 128-129°C. TLC R_f ($CHCl_3$/ i-PrOH~4/1) ~ 0.20.
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 7.20-7.70 (m, 5H, Ph), 6.40-6.60* and 5.65-5.90 (2m, 1H, NH), 4.20-4.55 (m, 1H, NCHP), 3.76*, 3.73*, 3.69*, 3.63, 3.51* (all s, 3H, CH_3O), 3.12-3.33 (m, 1H, $\underline{CH}$COOH), 2.70-3.12 (m, 2H, $\underline{CH_2}$Ph), 2.25-2.55 (m, 1H, one of CH_2P), 1.60-2.15 (m, 1H, another of CH_2P), 1.38, 1.28*, 1.24*, (3d, $^3J_{HH}$ 6.1 Hz, $^3J_{HH}$ 7.2 Hz and $^3J_{HH}$ 7.2 Hz, $CH\underline{CH_3}$).
^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ 181.7, 181.6* ($C\underline{C}$=O), 159.2*, 159.0*, 158.6 (3d, $^3J_{PC}$ 4.8, 4.4 and 4.1 Hz, NC=O), 135.2* (d, $^3J_{PC}$ 11.1 Hz, C arom.), 134.9 (d, $^3J_{PC}$ 11.4 Hz, C arom.), 130.1, 129.0, 128.9, 127.6, 127.3 (all arom. CH), 54.0* and 53.8 (CH_3O), 52.9* (d, $^1J_{PC}$ 102.1 Hz, NCHP), 51.9 (d, $^1J_{PC}$ 102.8 Hz, NCHP), 34.5*, 33.8 ($\underline{C}$HCOOH), 29.5 (d, $^1J_{PC}$ 88.1 Hz, CH_2P), 29.2 (d, $^1J_{PC}$ 87.8 Hz, CH_2P), 18.9 (d, $^3J_{PC}$ 11.4 Hz, $\underline{C}H_3C$), 18.7 (d, $^3J_{PC}$ 10.7 Hz, $\underline{C}H_3C$).
^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drops of TFA) δ 58.08, 57.85, 57.43*, 57.16*.

^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO) δ 46.32, 46.26, 45.80*, 45.54*.

Calcd for $C_{14}H_{20}NO_6P$; %: C, 51.07, H, 6.12, P, 9.41. Found, %: C, 50.80, 50.67; H, 6.07, 6.23; P, 9.35, 9.20.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{14}H_{19}NO_6P^-$ 328.0953, found 328.0959

***P*-[1-(*N*-Benzyloxycarbonylamino)-3-ethoxy-3-oxopropyl]-*P*-(3-hydroxy-2-methyl-3-oxopropyl)phosphinic acid (1c) (**R^1 = Me, R^2 =EtOC(O)CH_2, R^3 = Bn).

Yield 0.27 g, 67% **(**procedure 1), 0.18 g, 45% **(**procedure 3).

White solid. M.p. 127-130°C. TLC R_f ($CHCl_3$ / Pr^iOH~4/1) ~ 0.30.

^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 7.10-7.60 (m, 5H, Ph), 6.55-6.75* and 5.95-6.25 (m, 1H, NH), 5.24* and 5.13 {c (br.), 2H, PhC$\underline{H_2}$O}, 4.40-4.70 (m, 1H, PCHN), 4.15 {q (br.), $^3J_{HH}$ 6.6 Hz, CH_2O), 2.67-3.13 {m, 3H, C$\underline{H}$C(O)OH+CH_2C(O)}, 2.20-2.50 (m, 1H, one of PCH_2), 1.80-2.10 (m, 1H, another of PCH_2), 1.31 (d, 3H, $^3J_{HH}$ 5.7 Hz, CHC$\underline{H_3}$), 1.22 (t, 3H, $^3J_{HH}$ 6.6 Hz, $CH_2C\underline{H_3}$).

^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ 181.4 (d, $^3J_{PC}$ 5.2 Hz, CH$\underline{C}$=O), 172.8 (d, $^3J_{PC}$ 4.1 Hz, $CH_2\underline{C}$=O), 172.6*(d, $^3J_{PC}$ 4.1 Hz, $CH_2\underline{C}$=O), 157.6* (d, $^3J_{PC}$ 4.1 Hz, NC=O), 157.3 (d, $^3J_{PC}$ 3.3 Hz, NC=O), 134.8, 134.3*, 129.2, 129.1*, 128.7, 128.5*, 128.3*, 128.1 (all arom.), 69.5*, 68.8, 68.5*(all O$\underline{C}H_2$Ph), 63.0, 62.8*, 61.2*(all O$\underline{C}H_2CH_3$), 47.1 (d, $^1J_{PC}$ 103.2 Hz, PCHN), 46.9 (d, $^1J_{PC}$ 105.4 Hz, PCHN), 33.7 ($\underline{C}$HC=O), 29.4* (d, $^1J_{PC}$ 91.8 Hz, PCH_2), 29.2 (d, $^1J_{PC}$ 91.0 Hz, PCH_2), 29.1* (d, $^1J_{PC}$ 90.7 Hz, PCH_2), 18.9* (d, $^3J_{PC}$ 11.4 Hz, $\underline{C}H_3$CH), 18.7 (d, $^3J_{PC}$ 11.4 Hz, $\underline{C}H_3$CH), 13.9* and 13.5 ($\underline{C}H_3CH_2$).

^{31}P {^{1}H} NMR (81 MHz, CD_3CN+drop of TFA) δ 54.5*, 52.8, 51.7*.

^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 54.6, 53.6*.

Calcd for $C_{17}H_{24}NO_8P$; %: C, 50.87, H, 6.03, P, 7.72. Found, %: C, 50.55, 50.70; H, 6.24, 6.30; P, 7.54, 7.37.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{17}H_{23}NO_8P^-$ 400.1161, найдено 400.1168.

***P*-(2-Carboxy-4-methylpentyl)-*P*-[(*N*-ethoxycarbonylamino)methyl]phosphinic acid (1d) (**R^1 = Bu^i, R^2 = H, R^3 = Et).

Yield 0.10 g, 34% **(**procedure 1).

White solid. M.p. 125-126. Lit.[S1] m.p. 122-123°C. TLC R_f ($CHCl_3$/EtOH~4/1) ~ 0.25-0.30.

^{1}H NMR (200 MHz, $CDCl_3$+drops of TFA) δ 6.45-6.70* and 5.35-5.95 (2m, 1H, NH), 4.15 (q, broad, 2H, $^3J_{HH}$ 6.9 Hz, CH_2O), 3.70 (d, broad, 2H, $^2J_{PH}$ 6.4 Hz, NCH_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(of Bu^i)}, 1.33-1.47 {m, 1H, CH(of Bu^i)}, 1.26 (t, br., 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 (C$\underline{C}$=O), 158.6 (NC=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 ($\underline{C}H_3CH_2$), 13.6* ($\underline{C}H_3CH_2$).

^{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.

***P*-(2-Carboxy-4-methylpentyl)-*P*-[1-(*N*-methoxycarbonylamino)-2-phenylethyl]phosphinic acid (1e) (**R^1 = Bu^i, R^2 = Bn, R^3 = Me).

Yield 0.20 g, 54% **(**procedure 1). White solid. M.p. 200-202°C. TLC R_f ($CHCl_3$ / Pr^{i}OH~4/1) ~ 0.30.

^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA) δ 7.10-7.45 (m, 5H, Ph), 6.45-6.65* and 5.62-5.86 (m, 1H, NH), 4.15-4.53 (m, 1H, PCHN), 3.62 and 3.50* (c, 3H, CH_3O), 3.10-3.30 (m, 1H, C<u>H</u>COOH), 2.70-3.05 (m, 2H, C<u>H$_2$</u>Ph), 2.15-2.45 (m, 1H, one of PCH_2), 1.83-2.13 (m, 1H, another of PCH_2), 1.45-1.75 (m, 2H, C<u>H$_2$</u>CHMe$_2$), 1.27-1.47 (m, 1H, C<u>H</u>Me$_2$), 0.92 (d, 3H, $^3J_{HH}$ 6.1 Hz, CH<u>Me</u>), 0.89 (d, 3H, $^3J_{HH}$ 6.1 Hz, CH<u>Me</u>).

^{13}C {^{1}H} NMR (50 MHz, DMSO-d_6) δ 176.5 (d, $^3J_{PC}$ 7.3 Hz, CH<u>C</u>=O), 156.8 (NC=O), 138.6 (d, $^3J_{PC}$ 13.9 Hz, C arom.), 129.1, 128.3, 126.4 (all arom.), 52.5 (d, $^1J_{PC}$ 104.4 Hz, PCHN), 52.1* (d, $^1J_{PC}$ 103.6 Hz, PCHN), 51.7 (CH_3O), 43.2* (d, $^3J_{PC}$ 10.2 Hz, <u>C</u>H$_2$CHCOOH), 42.9 (d, $^3J_{PC}$ 8.8 Hz, <u>C</u>H$_2$CHCOOH), 37.1 (<u>C</u>HCOOH), 33.7*, 33.4*, 33.0 (<u>C</u>H$_2$Ph), 29.1 (d, $^1J_{PC}$ 88.6 Hz, PCH_2), 28.9* (d, $^1J_{PC}$ 88.2 Hz, PCH_2), 25.7 {<u>C</u>H(CH$_3$)$_2$}, 23.0* (CH<u>C</u>H$_3$), 21.9 (CH<u>C</u>H$_3$).

^{31}P {^{1}H} NMR (81 MHz, DMSO-d_6) δ 45.7.

^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$+drop of TFA) δ 58.5.

Calcd for $C_{17}H_{26}NO_6P$; %: C, 54.98, H, 7.06, P, 8.34. Found, %: C, 54.66, 54.72; H, 7.22, 7.30; P, 8.40, 8.23.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{17}H_{25}NO_6P^-$ 370.1425, found 370.1426.

***P*-(2-Benzyl-3-hydroxy-3-oxopropyl)-*P*-[1-(*N*-ethoxycarbonylamino)-2-phenylethyl]-phosphinic acid (1f) (**R^1 = Bn, R^2 = Bn, R^3 = Et).

Yield 0.2g, 48% **(**procedure 1). White solid. M.p. 97-100°C. TLC R_f ($CHCl_3$ / i-PrOH~4/1) ~ 0.25.

^{1}H NMR (200 MHz, d_6-acetone+drop of TFA) δ 6.90-7.55 (m, 11H, 2Ph+NH), 3.80-4.40 (m, 3H, CH_2O+PCHN), 2.75-3.40 (m, 4H, 2C<u>H$_2$</u>Ph), 2.20-2.55 (m, 1H, C<u>H</u>COOH), 0.80-1.75 (m, 5H: m, 1H, one of PCH_2, + m, 1H, another of PCH_2 + 1.04 t, 3H, $^3J_{HH}$ 6.9 Hz, CH_3+m, CH_3*).

^{31}P {^{1}H} NMR (81 MHz, d_6- acetone) δ 49.8*, 49.4, 48.4*.

^{31}P {^{1}H} NMR (81 MHz, d_6- acetone+drops of D_2O) δ 48.3, 47.3*.

Calcd for $C_{21}H_{26}NO_6P$; %: C, 60.14, H, 6.25, P, 7.38. Found, %: C, 59.76, 59.67; H, 6.42, 6.50; P, 7.40, 7.25.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $C_{21}H_{25}NO_6P^-$ 418.1425, found 418.1427.

***P*-(2-Benzyl-3-hydroxy-3-oxopropyl)-*P*-[1-(*N*-methyloxycarbonylamino)ethyl]phosphinic acid (1g) (**R^1 = Bn, R^2 = Me, R^3 = Me).

Yield 0.19 g, 58% **(**procedure 1), 0.14g, 43% **(**procedure 3). White solid. M.p. 146-148°C. TLC R_f ($CHCl_3$ / Pr^{i}OH~4/1) ~ 0.30.

^{1}H NMR (200 MHz, DMSO-d_6 +drop of TFA) δ 7.10-7.45 (m, 6H, Ph+NH), 3.60-3.75 (m, 1H, PCHN), 3.52 {c (br.), CH_3O}, 2.73-3.03 {m, 3H, C<u>H$_2$</u>Ph+C<u>H</u>C(O)OH}, 1.80-2.05 (m, 1H, one of PCH_2), 1.55-1.80 (m, 1H, another of PCH_2), 1.16 (dd, 3H, $^3J_{HH}$ 7.1 Hz, $^3J_{PH}$ 13.2 Hz, C<u>H$_3$</u>CH).

^{13}C {^{1}H} NMR (50 MHz, DMSO-d_6) δ 175.3 (d, $^3J_{PC}$ 5.9 Hz, CH<u>C</u>=O), 156.4 (NC=O), 139.0, 129.0, 128.2, 126.2 (all arom.), 51.6 (CH_3O), 46.1 (d, $^1J_{PC}$ 105.4 Hz, PCHN), 45.6* (d, $^1J_{PC}$ 106.5 Hz, PCHN), 40.7 (<u>C</u>HC=O), 38.5 (d, $^3J_{PC}$ 20.9 Hz, <u>C</u>H$_2$Ph), 27.8 (d, $^1J_{PC}$ 84.9 Hz, PCH_2), 27.4* (d, $^1J_{PC}$ 87.8 Hz, PCH_2), 14.0 (<u>C</u>H$_3$C).

^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO+drop of TFA) δ 44.7.

Calcd for $C_{14}H_{20}NO_6P$; %: C, 51.07, H, 6.12, P, 9.41. Found, %: C, 50.83, 50.67; H, 6.30, 6.27; P, 9.32, 9.20.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_{19}NO_6P^-$ 328.0955, found 328.0960.

***P*-[1-(*N*-Benzyloxycarbonylamino)ethyl]-*P*-[2,3-bis(carboxy)propyl]phosphinic acid (1h) (**R^1 = CH_2COOH, R^2 =Me, R^3 = Bn).

Yield 0.22 g, 59% (procedure 2). White solid. M.p. 154-156°C. TLC R_f ($CHCl_3$ / i-PrOH~4/1) ~ 0.30.

^{1}H NMR (200 MHz, DMSO-d_6 +drop of TFA) δ 7.10-7.65 (m, 6H, Ph+NH), 4.85-5.15 {c (br.), 2H, OC$\underline{H}_2$Ph}, 3.85-4.10* (m, 1H, PCHN), 3.60-3.85 (m, 1H, PCHN), 2.80-3.12 (m, 1H, C$\underline{H}$COOH), 2.55-2.80 (m, 2H, C$\underline{H}_2$COOH), 1.80-2.15 (m, 1H, one of PCH_2), 1.55-1.85 (m, 1H, another of PCH_2), 1.16 (dd, 3H, $^3J_{HH}$ 5.3 Hz, $^3J_{PH}$ 13.7 Hz, C$\underline{H}_3$CH), ~1.08* (partially closed, C$\underline{H}_3$CH).

^{1}H NMR (200 MHz, acetone-d_6 +drop of TFA) δ 7.20-7.40 (m, 5H, Ph), 6.85-7.00* and 6.65-6.80 (m, 1H, NH), 4.90-5.20 {c (br.), 2H, OC$\underline{H}_2$Ph}, 4.10-4.35 (m, 1H, PCHN), 3.14-3.34 (m, 1H, C$\underline{H}$COOH), 2.83 {d (br.), 2H, $^3J_{HH}$ 5.3 Hz, C$\underline{H}_2$COOH}, 2.40-2.60 (m, 1H, one of PCH_2), 2.10-2.32 (m, 1H, another of PCH_2), 1.53* (d, $^3J_{HH}$ 6.6 Hz, part of dd, partially closed, $\underline{CH}_3$CH), 1.42 (dd), $^3J_{HH}$ 7.1 Hz, $^3J_{PH}$ 15.4 Hz, C$\underline{H}_3$CH), 1.23* (dd, $^3J_{HH}$ 5.3 Hz, $^3J_{PH}$ 16.8 Hz, C$\underline{H}_3$CH).

^{13}C {^{1}H} NMR (50 MHz, DMSO-d_6) δ 175.3 (d, $^3J_{PC}$ 12.9 Hz, CH$\underline{C}$=O), 173.0 ($CH_2\underline{C}$=O), 155.9 (d, $^3J_{PC}$ 4.8 Hz, NC=O), 137.1, 128.5, 127.9, 127.8 (all arom.), 65.7 ($\underline{C}H_2$Ph), 46.2 (d, $^1J_{PC}$ 105.4 Hz, PCHN), 46.0* (d, $^1J_{PC}$ 105.8 Hz, PCHN), 35.9 and 35.7*($\underline{C}H_2$C=O), 34.9* and 34.8 ($\underline{C}$HC=O), 27.0 (d, $^1J_{PC}$ 88.1 Hz, PCH_2), 26.9* (d, $^1J_{PC}$ 89.2 Hz, PCH_2), 24.6* (d, $^1J_{PC}$ 82.9 Hz, PCH_2), 15.2* and 14.0 (CH_3).

^{31}P {^{1}H} NMR (81 MHz, DMSO-d_6 +drop of TFA) δ 53.8, 53.5, 52.6*, 52.1*

Calcd for $C_{15}H_{20}NO_8P$; %: C, 48.26, H, 5.40, P, 8.30. Found, %: C, 47.86, 47.96; H, 5.52, 5.60; P, 8.42, 8.52.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{15}H_{19}NO_8P^-$ 372.0848, found 372.0855.

***P*-[1-(*N*-Benzyloxycarbonyl)amino-3-ethoxy-3-oxopropyl]-*P*-[2,3-bis(carboxy)-propyl]phosphinic acid (1i) (**R^1 = CH_2COOH, R^2 = CH_2COOEt, R^3 = Bn).

Yield 0.30 g, 67% (procedure 2). White solid. M.p. 63-66°C. TLC R_f ($CHCl_3$ / Pr^iOH~4/1) ~ 0.20.

^{1}H NMR (200 MHz, DMSO-d_6 +drop of TFA) 8.23* and 7.65 {2c (br.), 1H, NH}, δ 7.10-7.50 (m, 5H, Ph), 5.01 {c (br.), 2H, PhC$\underline{H}_2$O}, 3.75-4.35 (m, 3H, PCHN+CH_2O), 2.85-3.10 (m, 1H, C$\underline{H}$COOH), 2.55-2.80 (m, 2H, C$\underline{H}_2$COOH), 1.90-2.20 (m, 1H, one of PCH_2), 1.65-1.85 (m, 1H, another of PCH_2), 1.11 {t (br.) and 0.79* t (br.) (3H, CH_3)}.

^{13}C {^{1}H} NMR (50 MHz, $CDCl_3$+drop of TFA) δ 175.5 (d, $^3J_{PC}$ 12.8 Hz, CH$\underline{C}$=O), 175.3* (d, $^3J_{PC}$ 12.4 Hz, CH$\underline{C}$=O), 173.3, 172.9* and 171.7* ($CH_2\underline{C}OOH$), 170.7 (d, $^3J_{PC}$ 16.5 Hz, $CH_2\underline{C}OOEt$), 156.3 (NC=O), 137.4, 128.7, 128.2, 128.0 (all arom.), 66.1, 65.3* (all O$\underline{C}H_2$Ph), 61.2, 60.7*, 60.4*(all O$\underline{C}H_2CH_3$), 48.3* (d, $^1J_{PC}$ 107.2 Hz, PCHN), 48.2 (d, $^1J_{PC}$ 106.5 Hz, PCHN), 36.1 (d, $^3J_{PC}$ 13.2 Hz, $\underline{C}H_2$COOH), 35.3 ($\underline{C}H_2$COOH), 33.4 ($\underline{C}H_2$COOEt), 27.5* (d, $^1J_{PC}$ 90.0 Hz, PCH_2), 27.3 (d, $^1J_{PC}$ 91.1 Hz, PCH_2), 16.6*, 14.2 ($\underline{C}H_3CH_2$).

^{31}P {^{1}H} NMR (81 MHz, DMSO-d_6 +drop of TFA) δ 51.9*, 46.5, 46.2*.

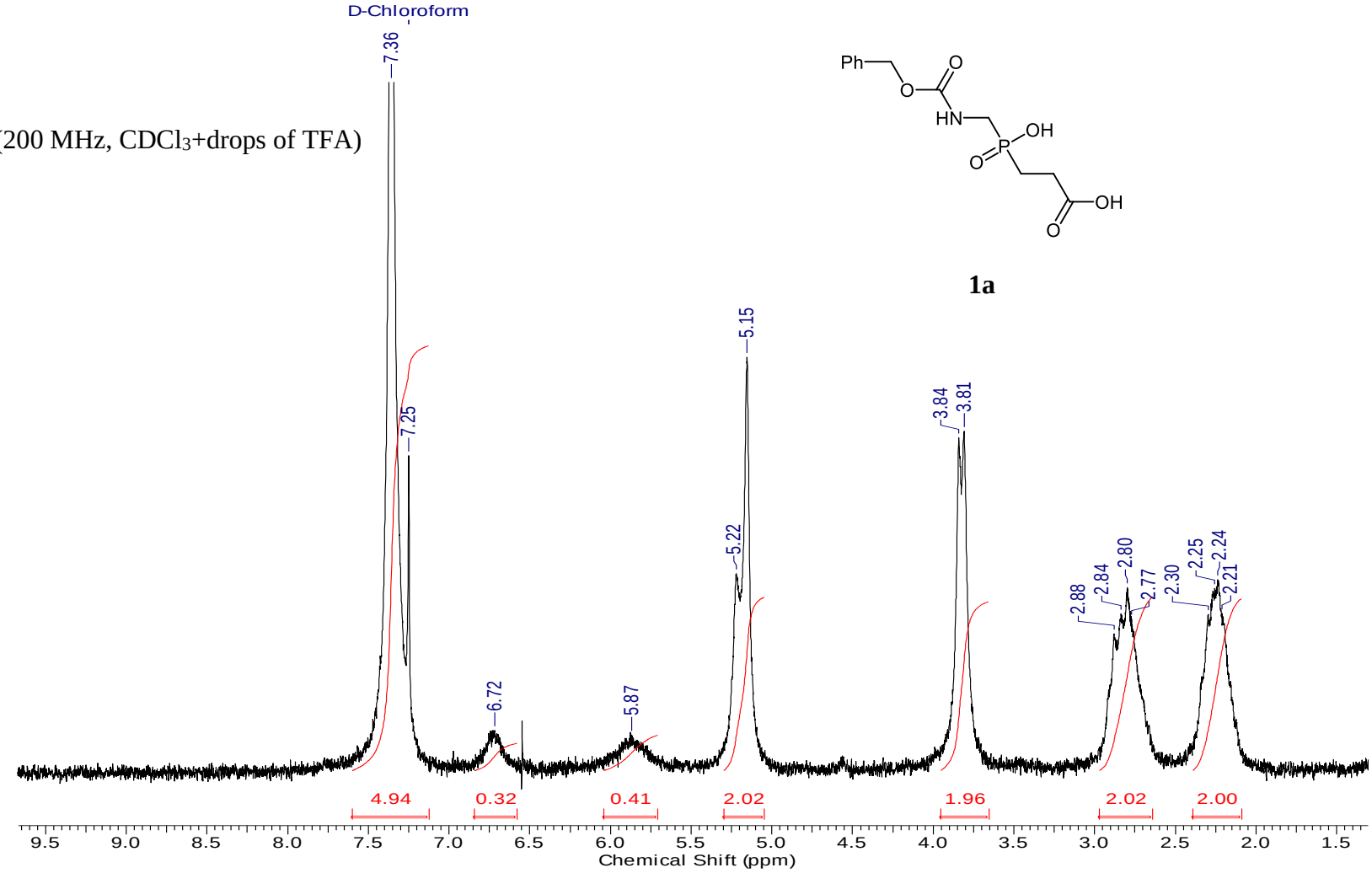
Calcd for $C_{18}H_{24}NO_{10}P$; %: C, 48.54, H, 5.43, P, 6.95. Found, %: C, 48.45, 48.37; H, 5.64, 5.73; P, 7.14, 7.37.

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{18}H_{23}NO_{10}P^-$ 444.1060, найдено 444.1067.

Copies of ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR and HRMS spectra of *N*-protected pseudo-peptides 1a-1i

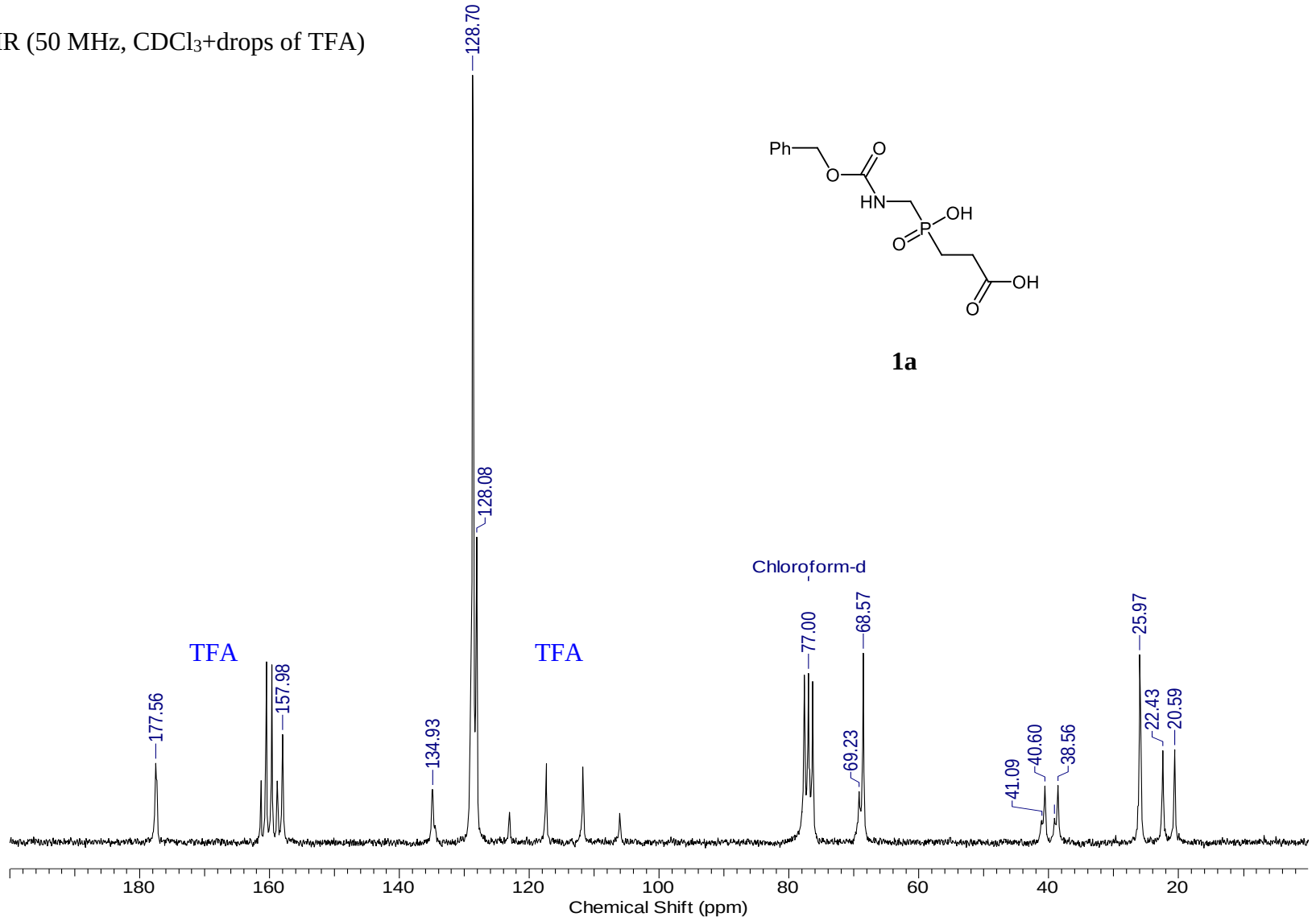
_P_-[(_N_-Benzyloxycarbonylamino)methyl]-_P_-(3-hydroxy-3-oxopropyl)phosphinic acid (1a)

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



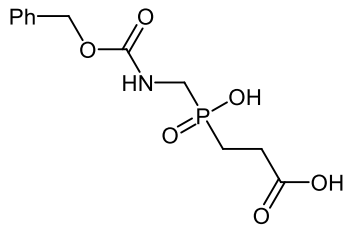
1a

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



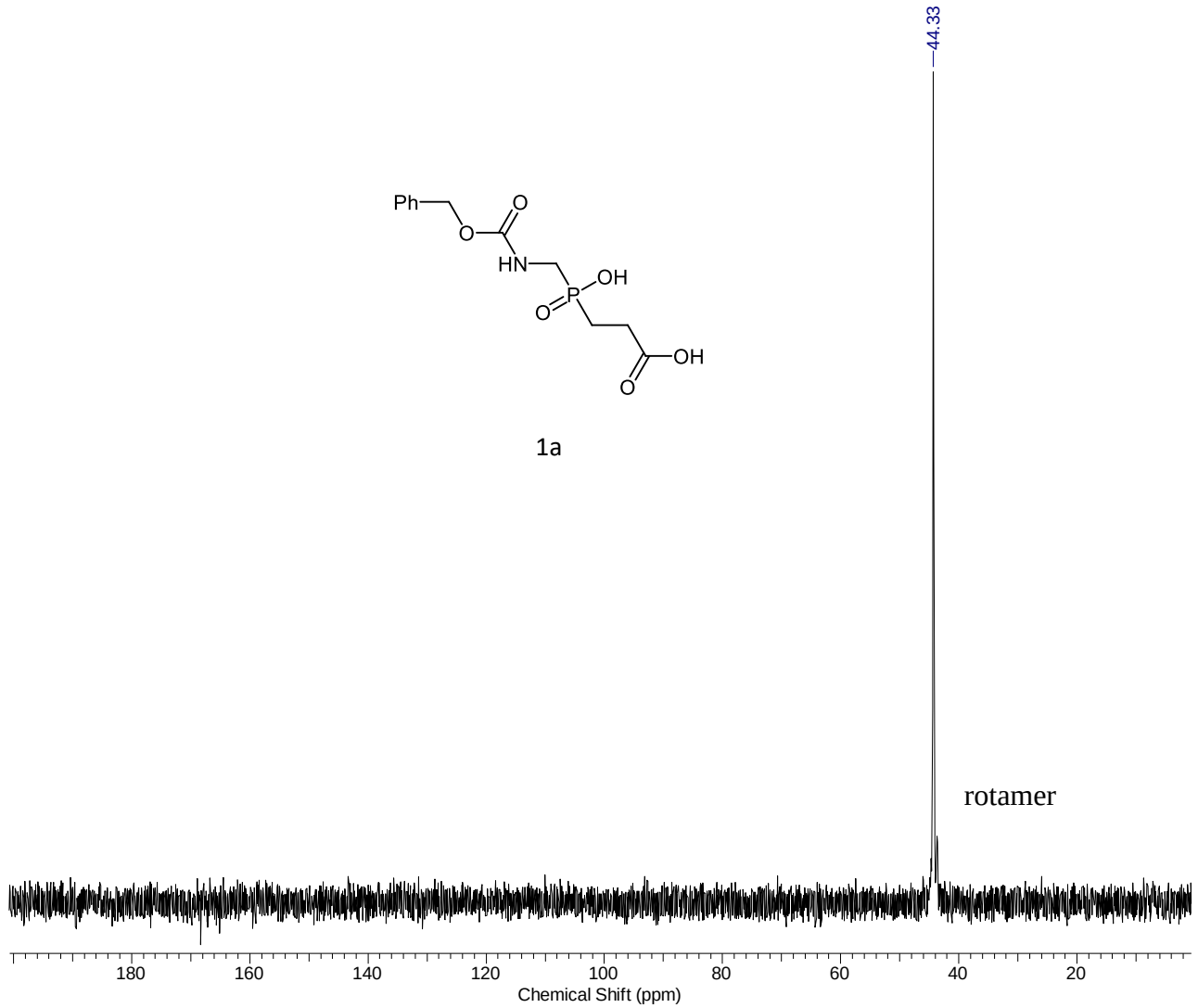
1a

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



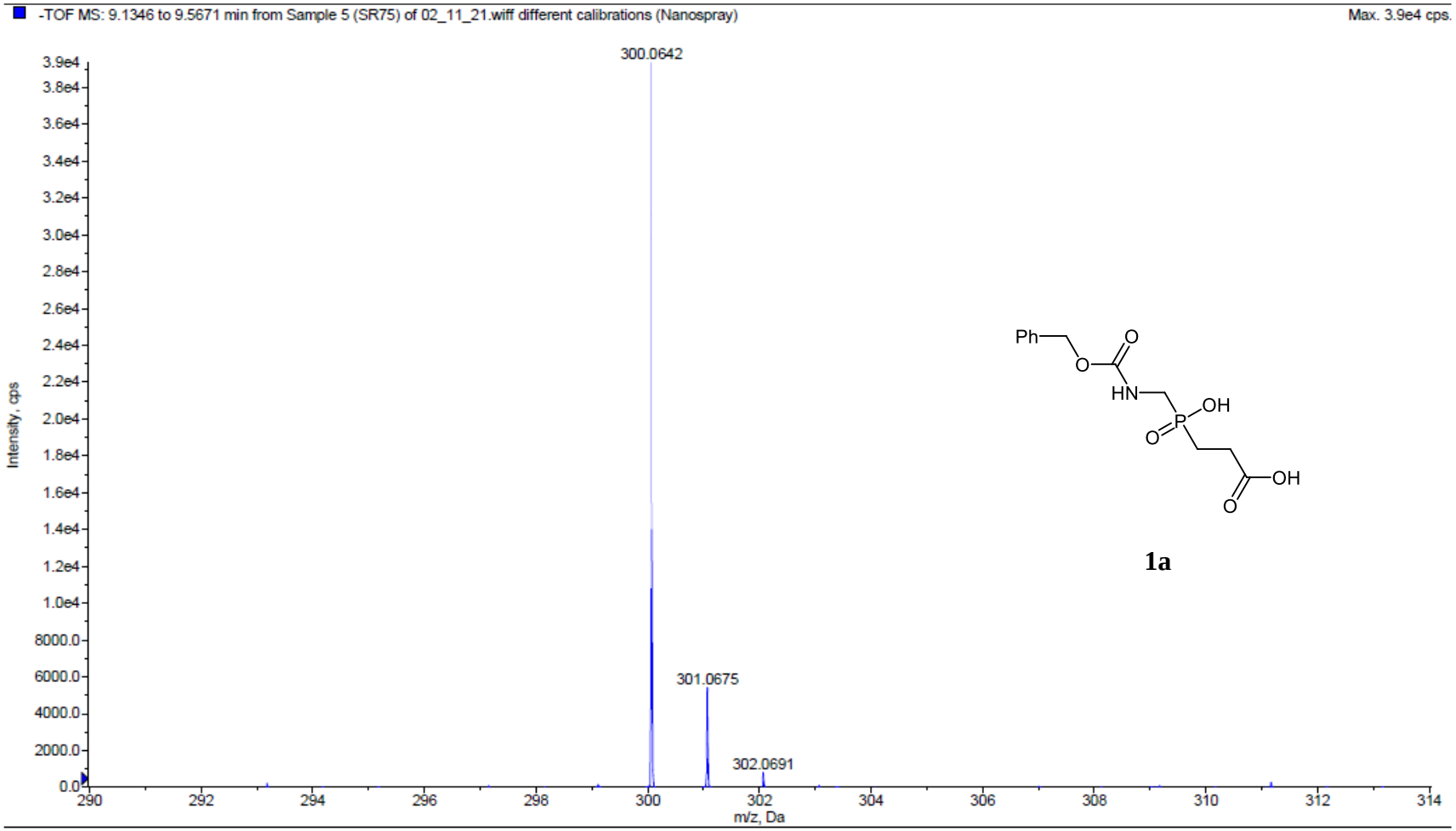
1a

$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$: DMSO-d_6 = 4 : 1)



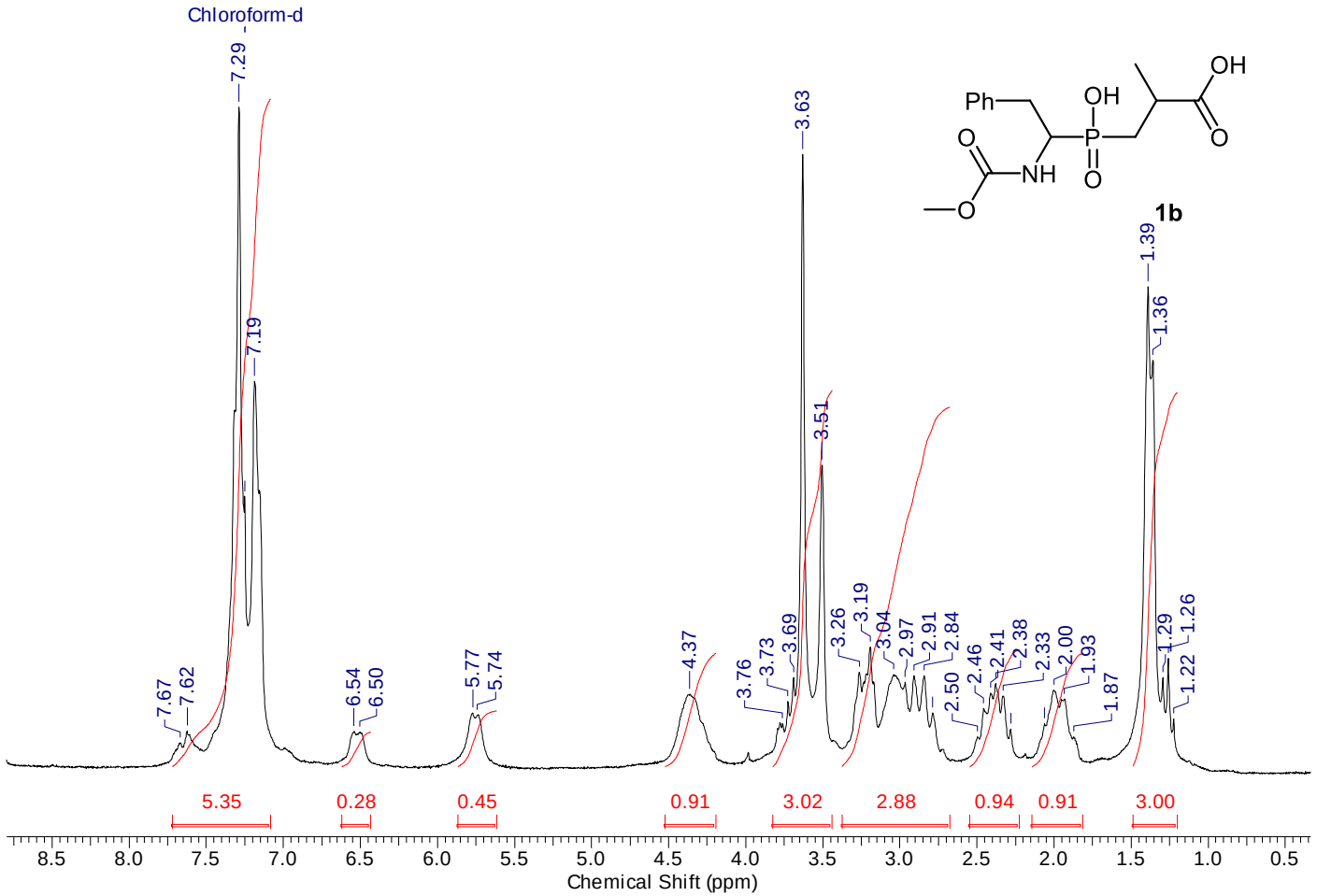
1a

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

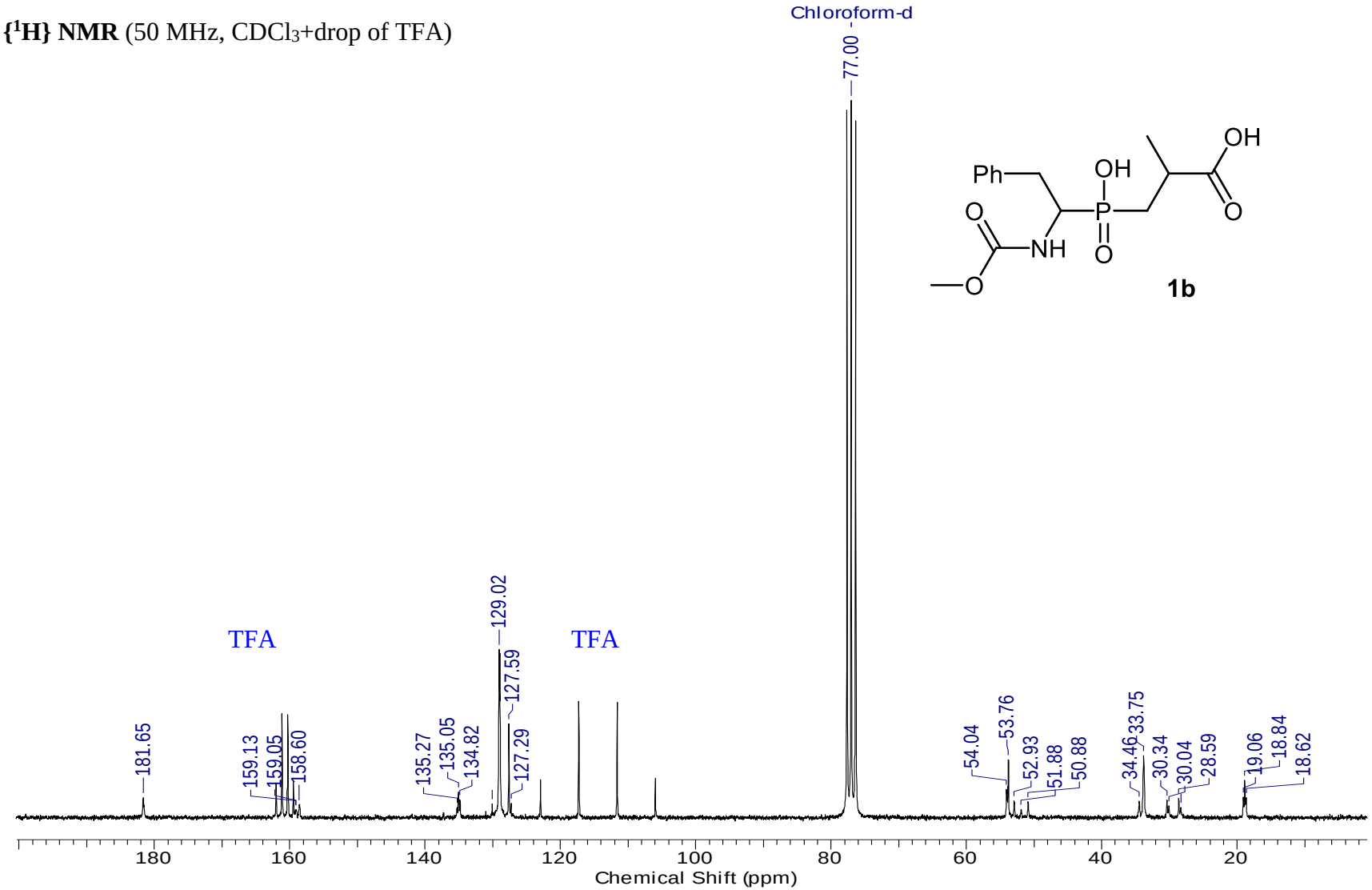


***P*-(3-Hydroxy-2-methyl-3-oxopropyl)-*P*-[1-(*N*-methoxycarbonylamino)-2-phenylethyl]-phosphinic acid (1b)**

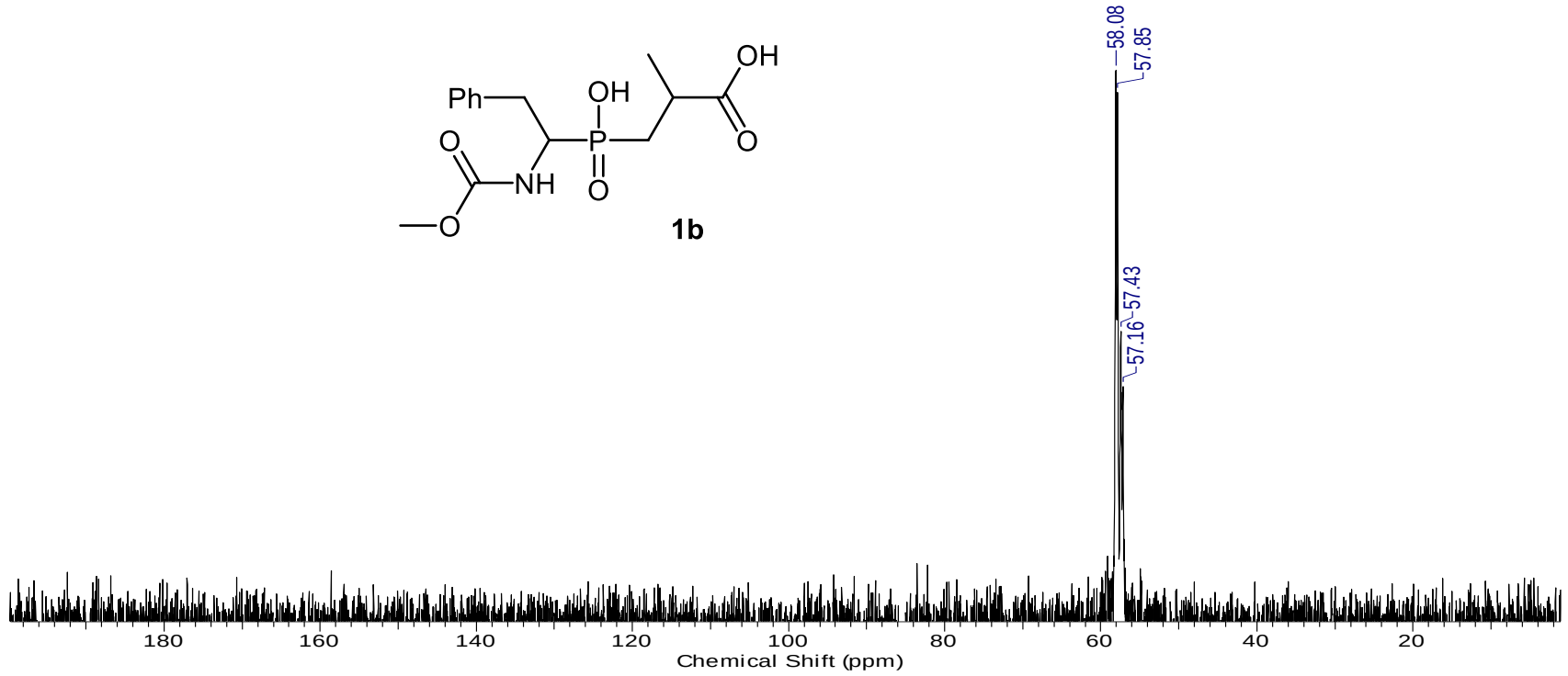
1b. **^{1}H NMR** (200 MHz, $CDCl_3$+drop of TFA)



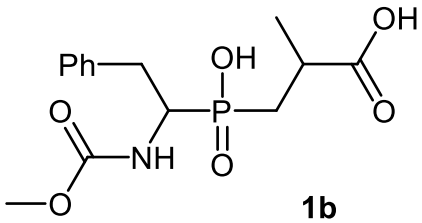
1b. **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$+drop of TFA)



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

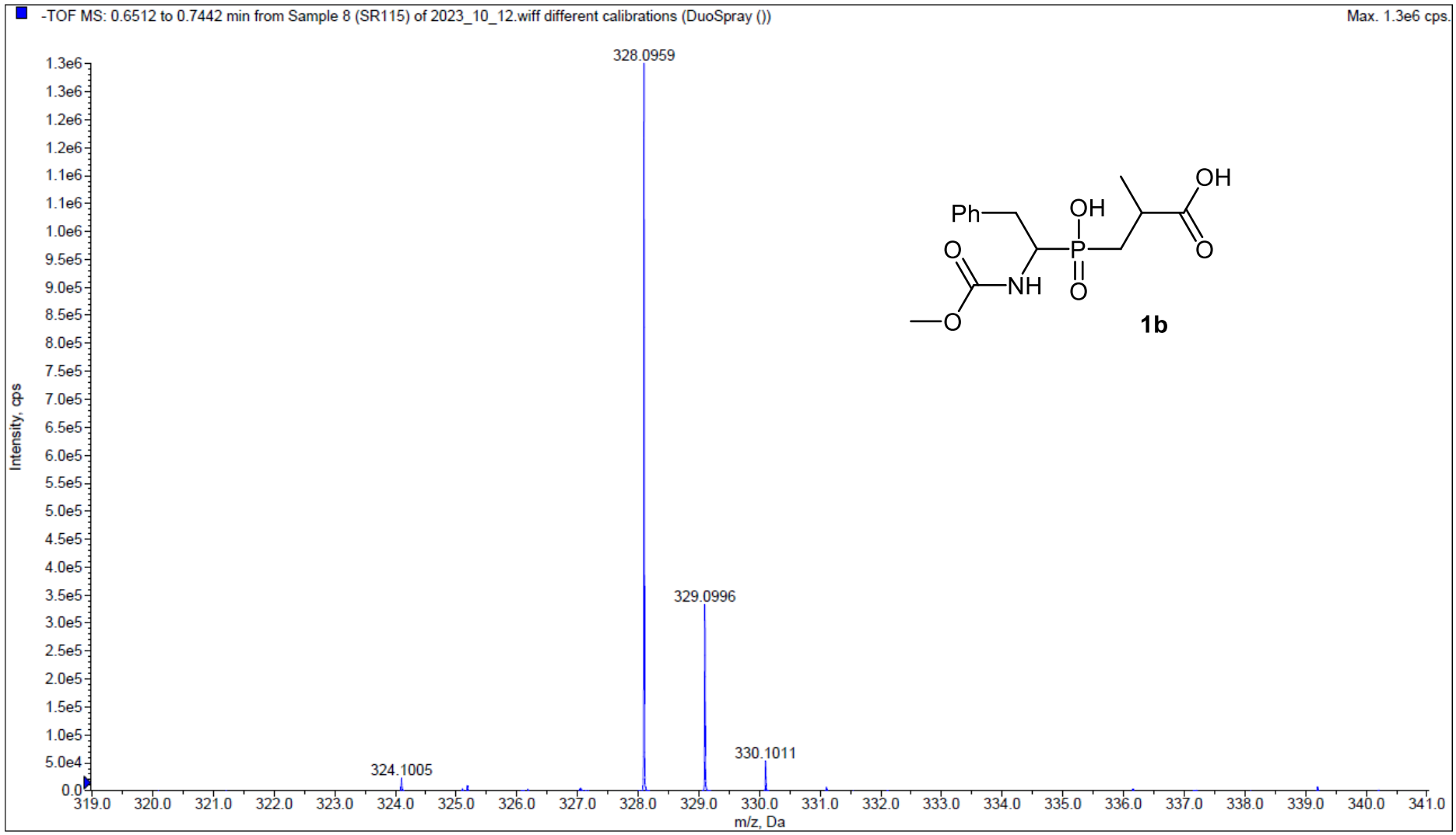


1b. **^{31}P {^{1}H} NMR** (81 MHz, d_6-DMSO)



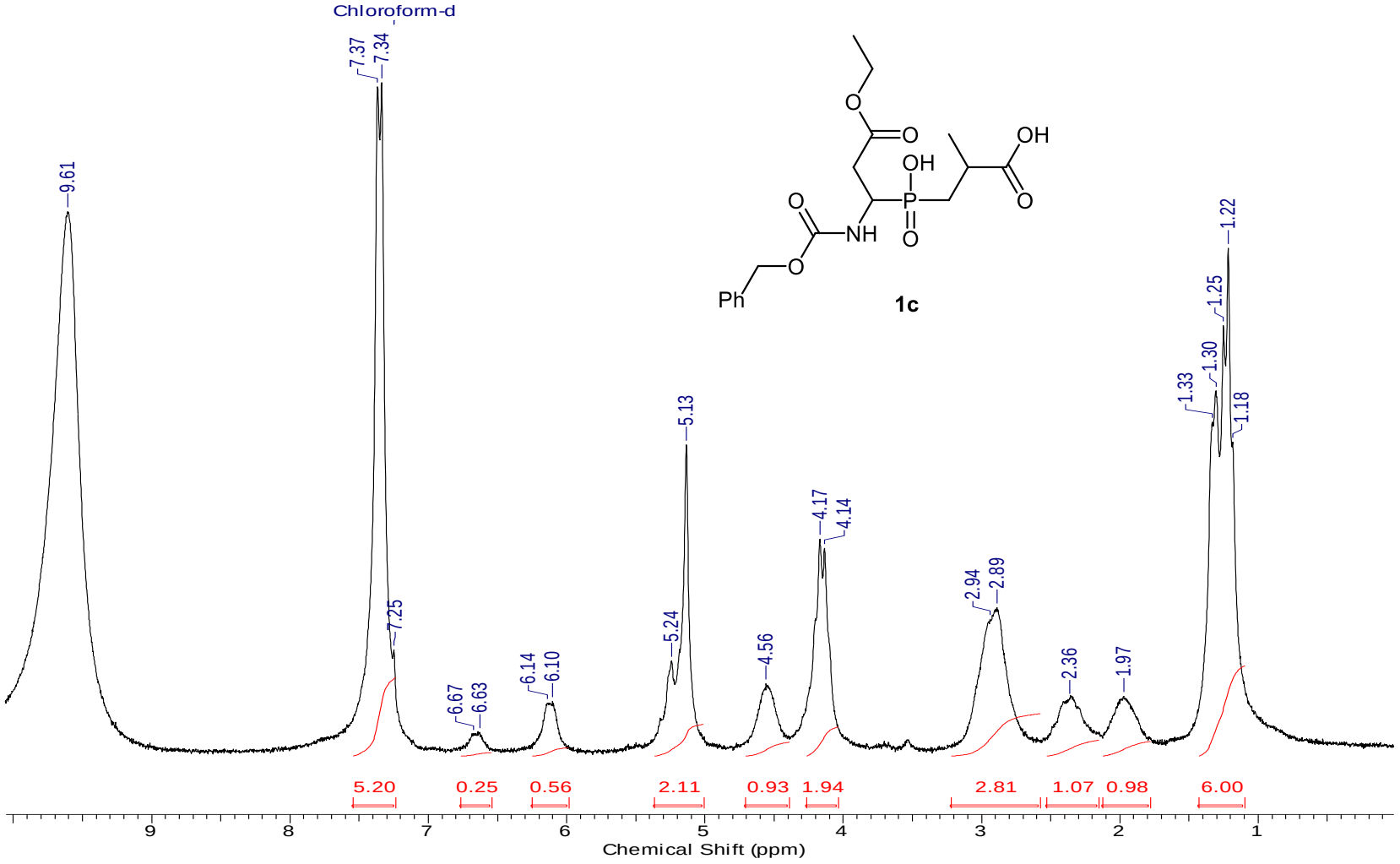
1b

1b. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{14}H_{19}NO_6P^-$ 328.0953, found 328.0959

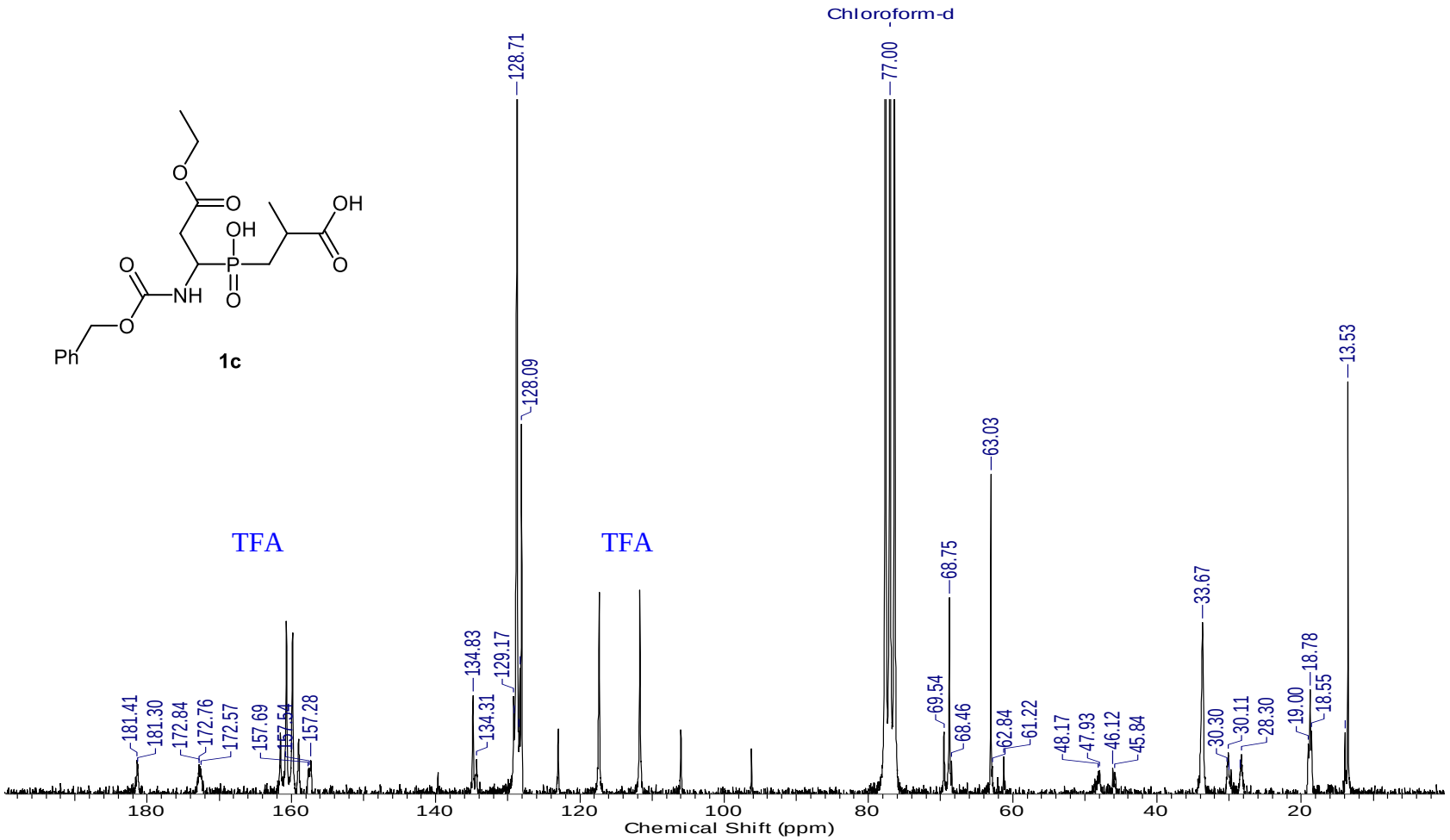


***P*-[1-(*N*-Benzyloxycarbonylamino)-3-ethoxy-3-oxopropyl]-*P*-(3-hydroxy-2-methyl-3-oxopropyl)phosphinic acid (1c)**

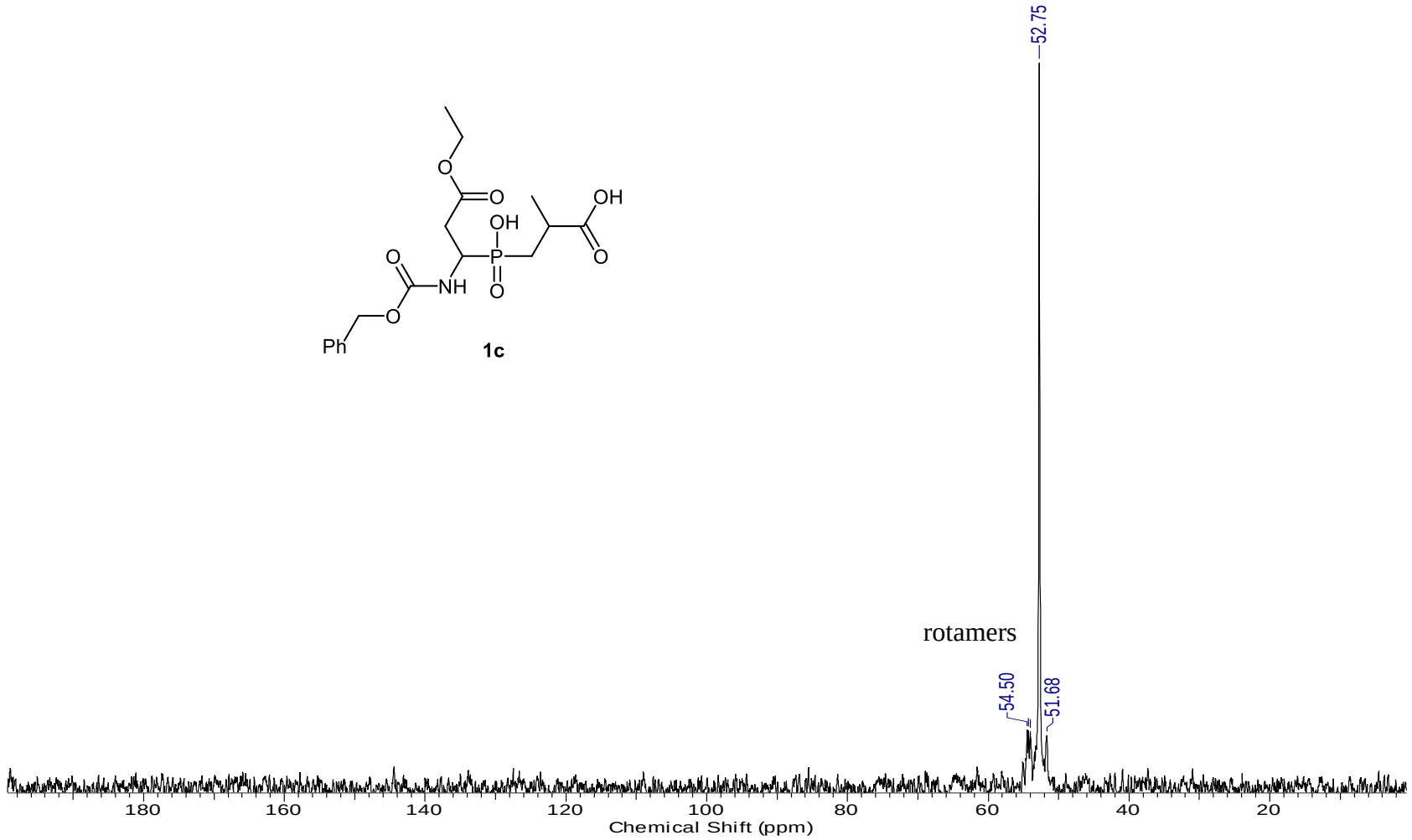
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA)



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

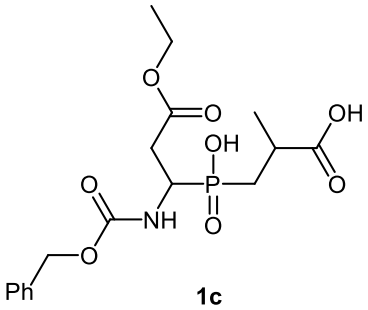


1c. **^{31}P {^{1}H} NMR** (81 MHz, CD_3CN+drop of TFA)



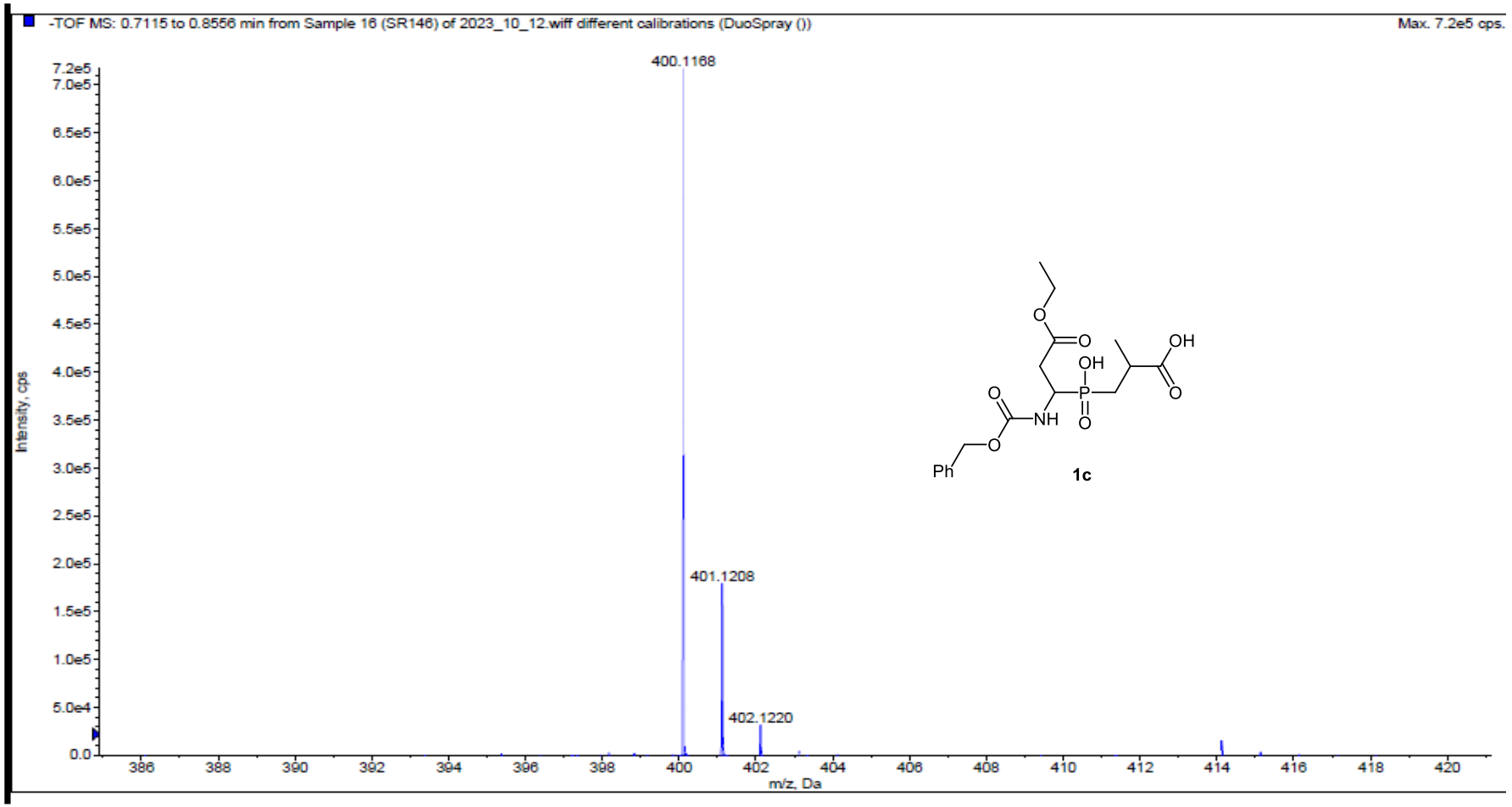
1c

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



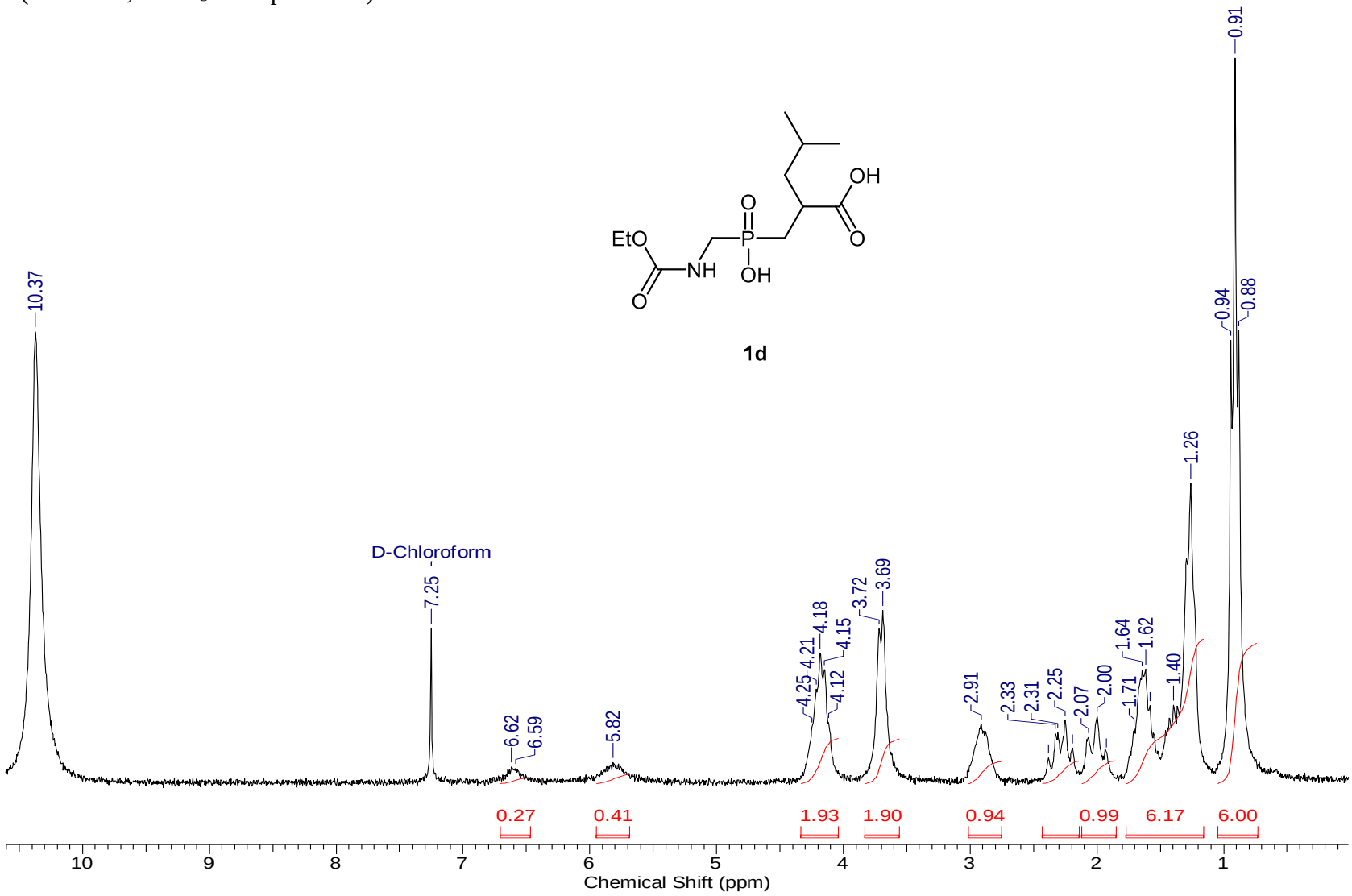
1c

1c. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{17}H_{23}NO_8P^-$ 400.1161, найдено 400.1168.

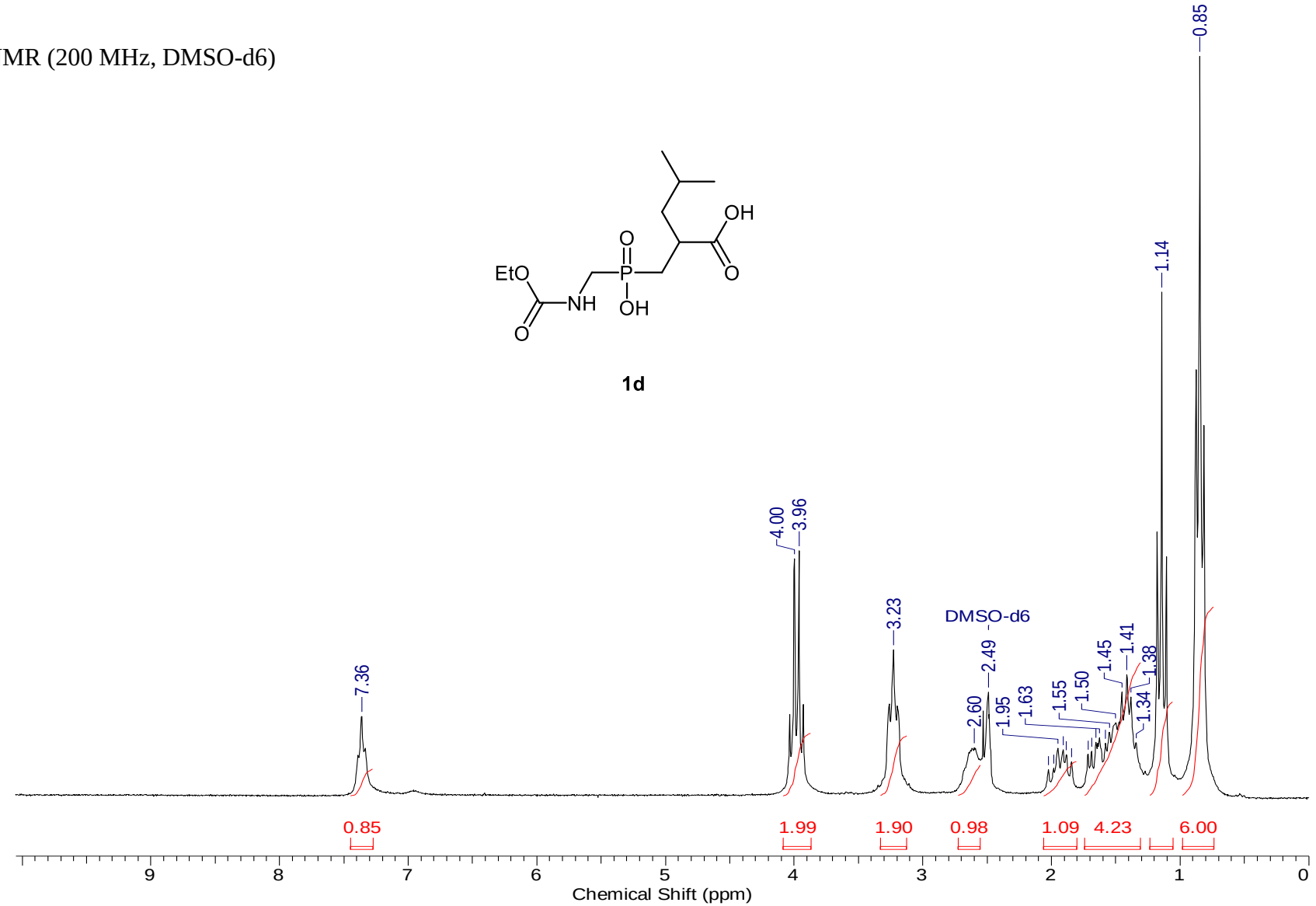


***P*-(2-Carboxy-4-methylpentyl)-*P*-[(*N*-ethoxycarbonylamino)methyl]phosphinic acid (1d)**

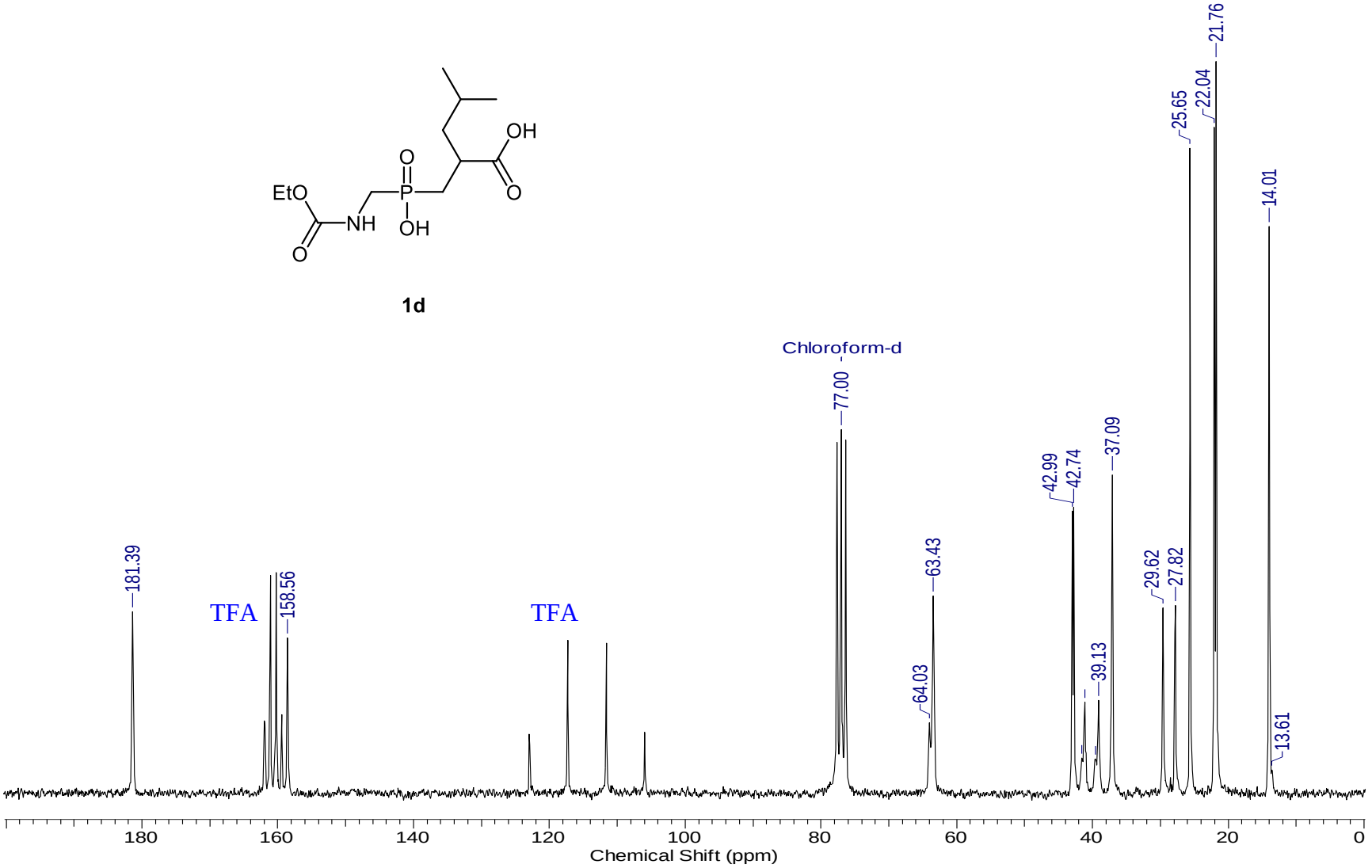
^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA)



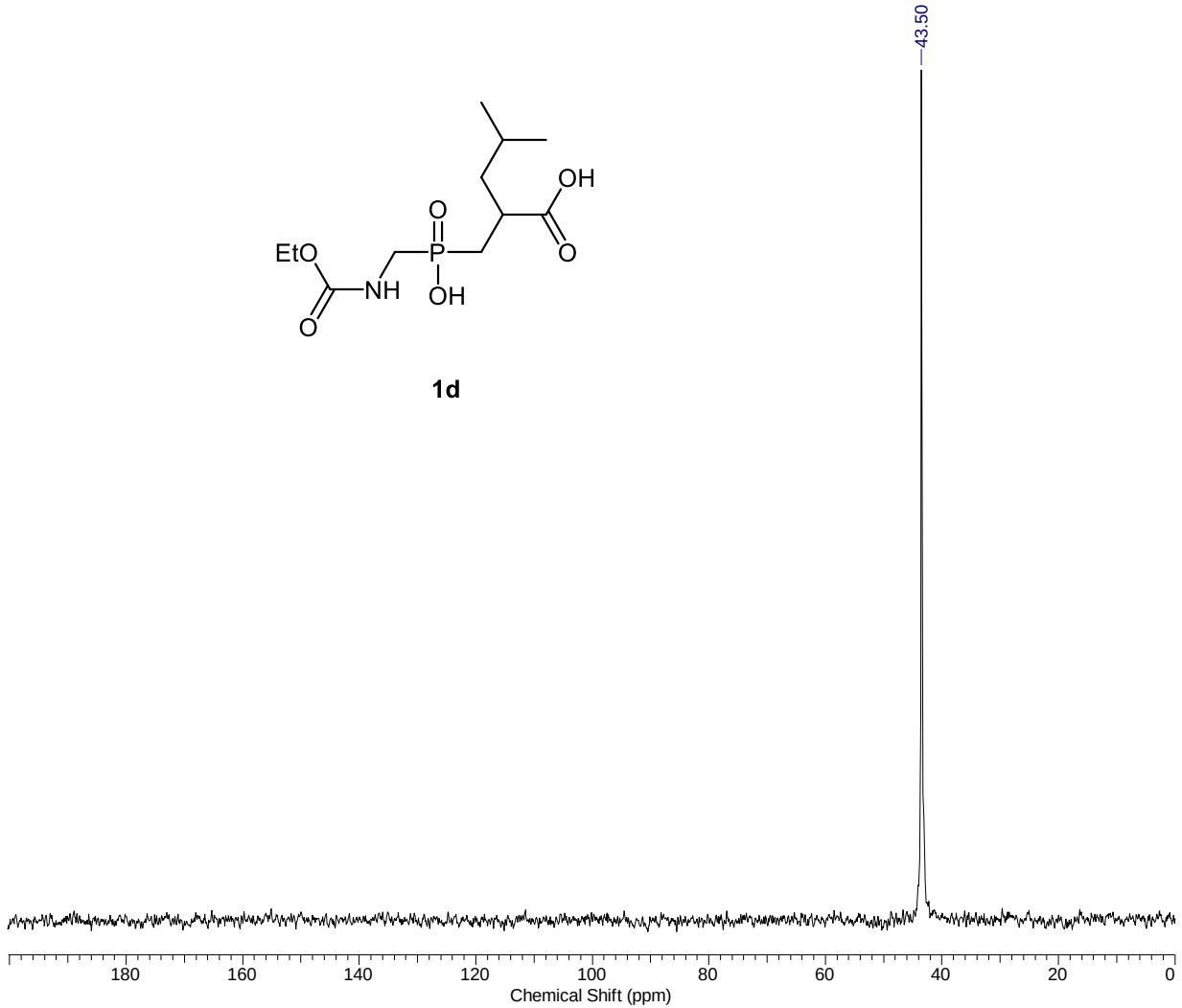
1d ^{1}H NMR (200 MHz, DMSO-d6)



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

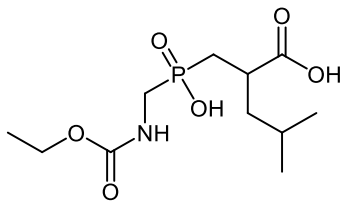


$^{31}P\{^{1}H\}$ NMR (81 MHz, DMSO-d6)

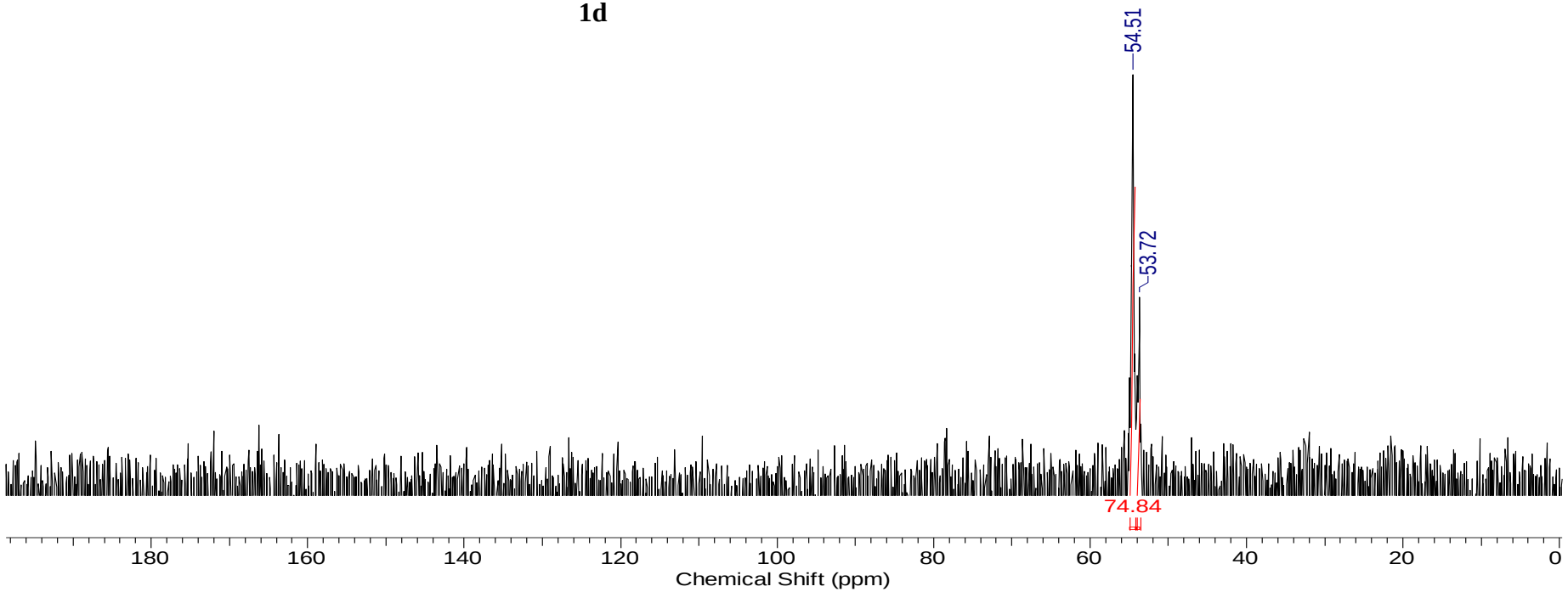


1d

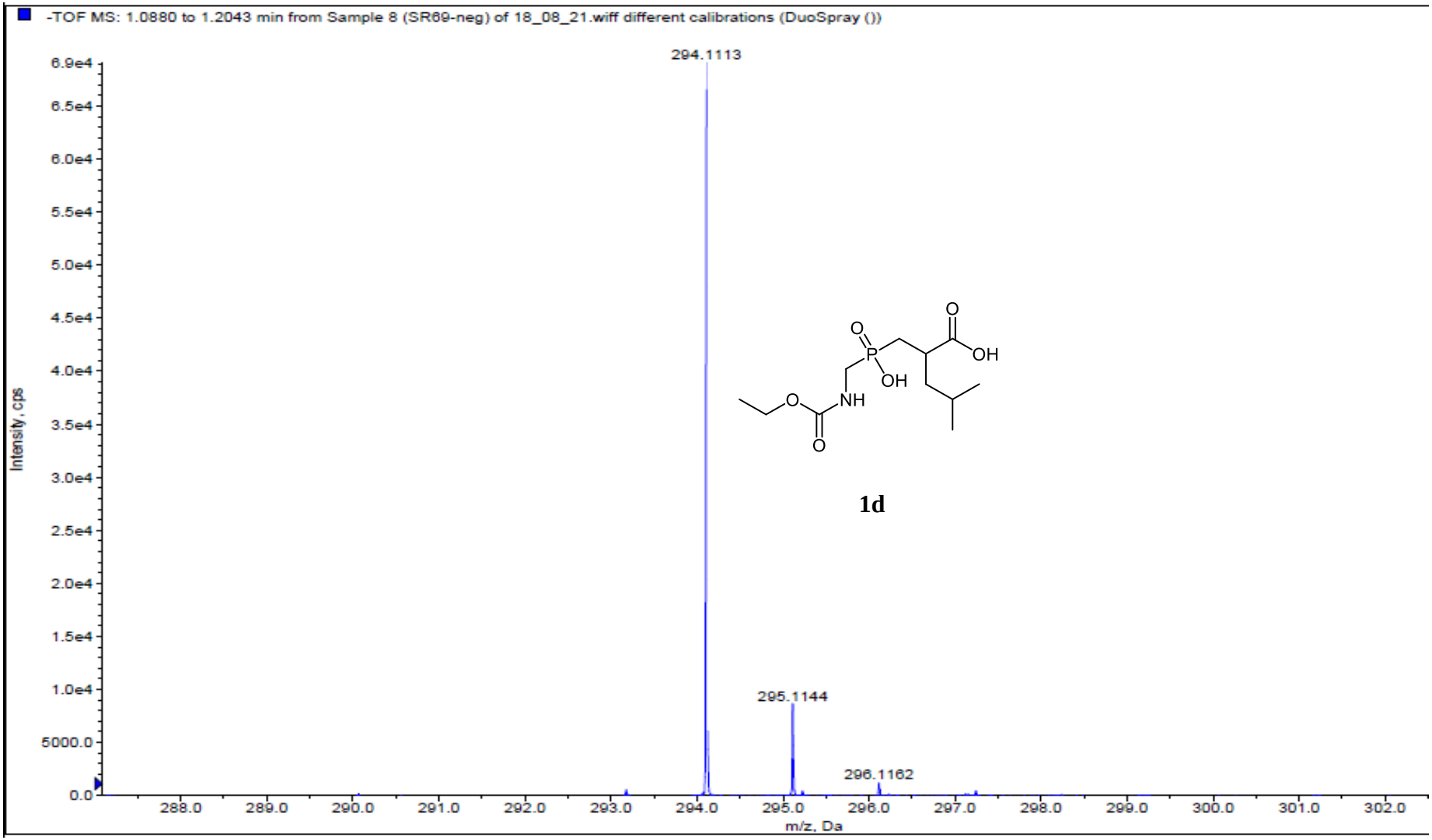
$^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$ + drop of TFA)



1d



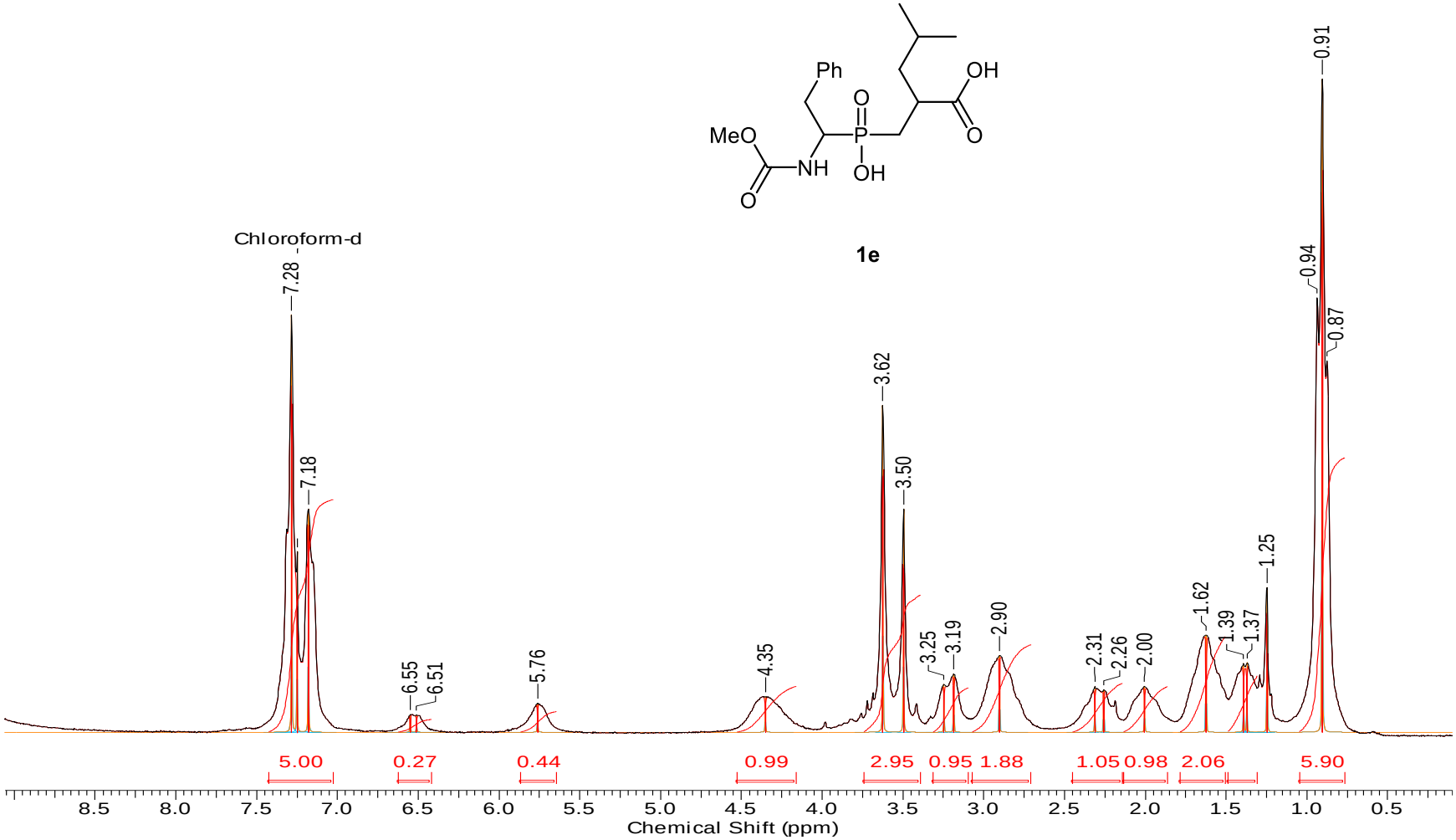
1d. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$calcd. for $C_{11}H_{21}NO_6P^-$ 294.1107, found 294.1113.



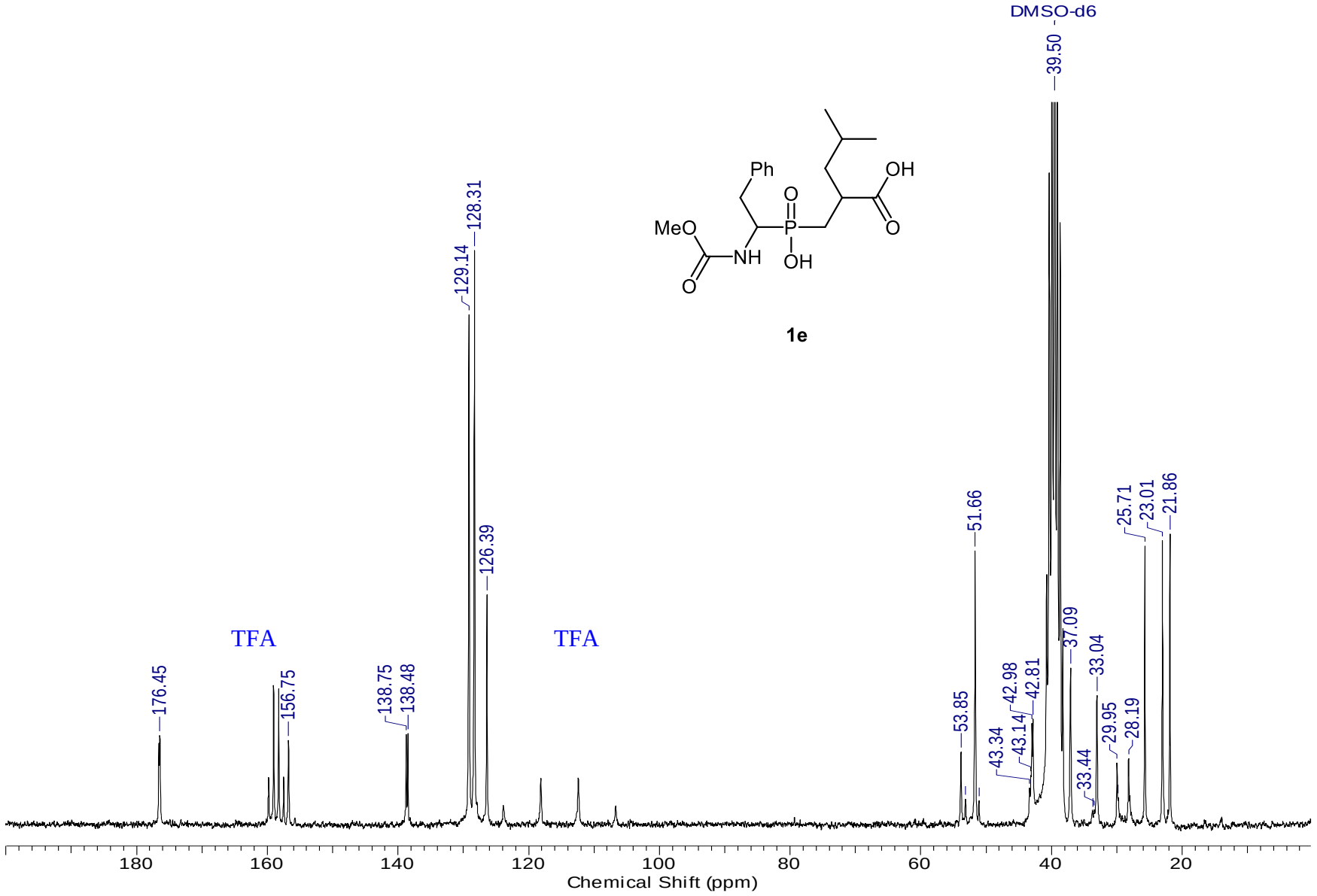
1d

***P*-(2-Carboxy-4-methylpentyl)-*P*-[1-(*N*-methoxycarbonylamino)-2-phenylethyl]phosphinic acid (1e).**

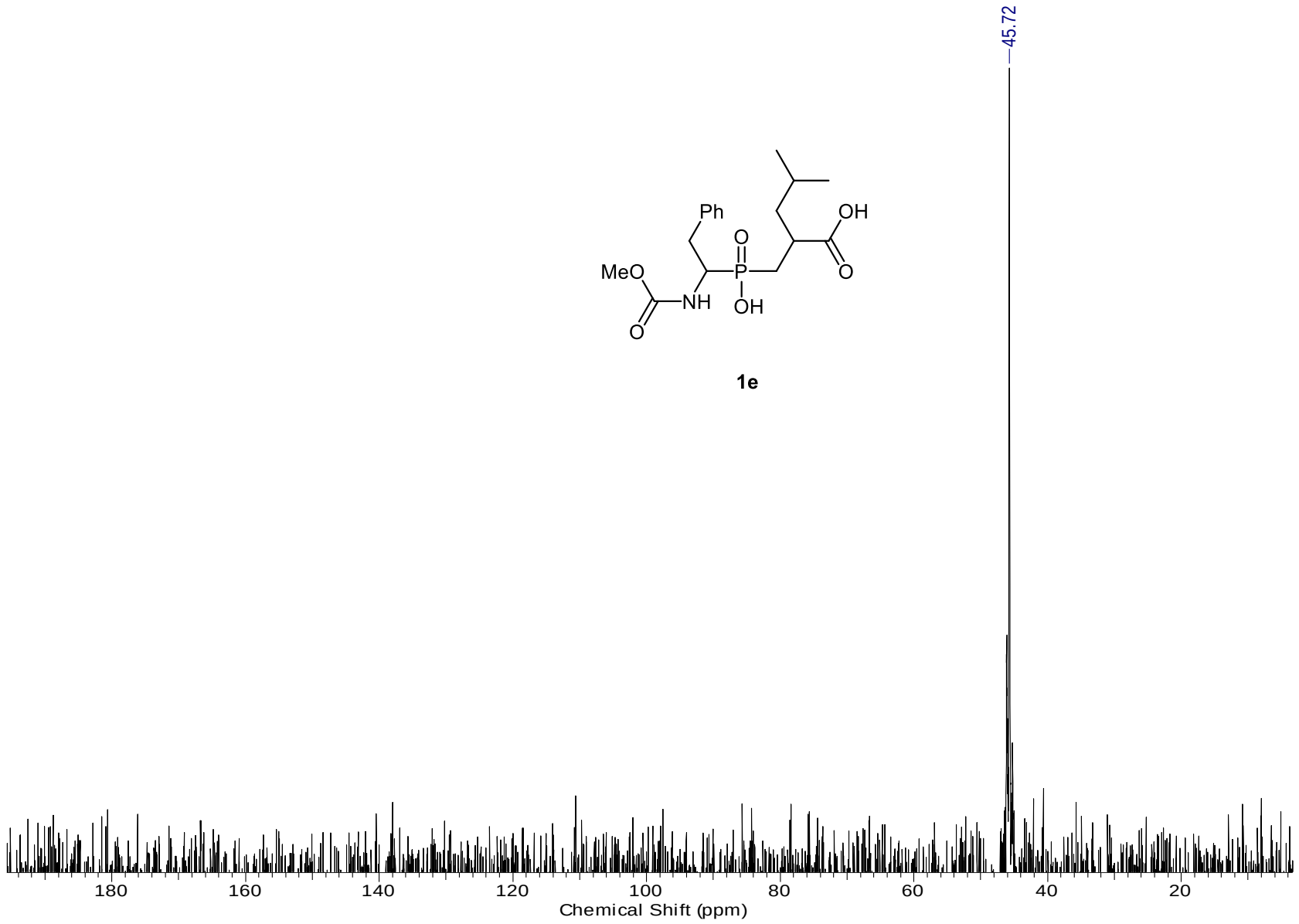
^{1}H NMR (200 MHz, $CDCl_3$+drop of TFA)



^{13}C {^{1}H} NMR (50 MHz, d_6-DMSO)

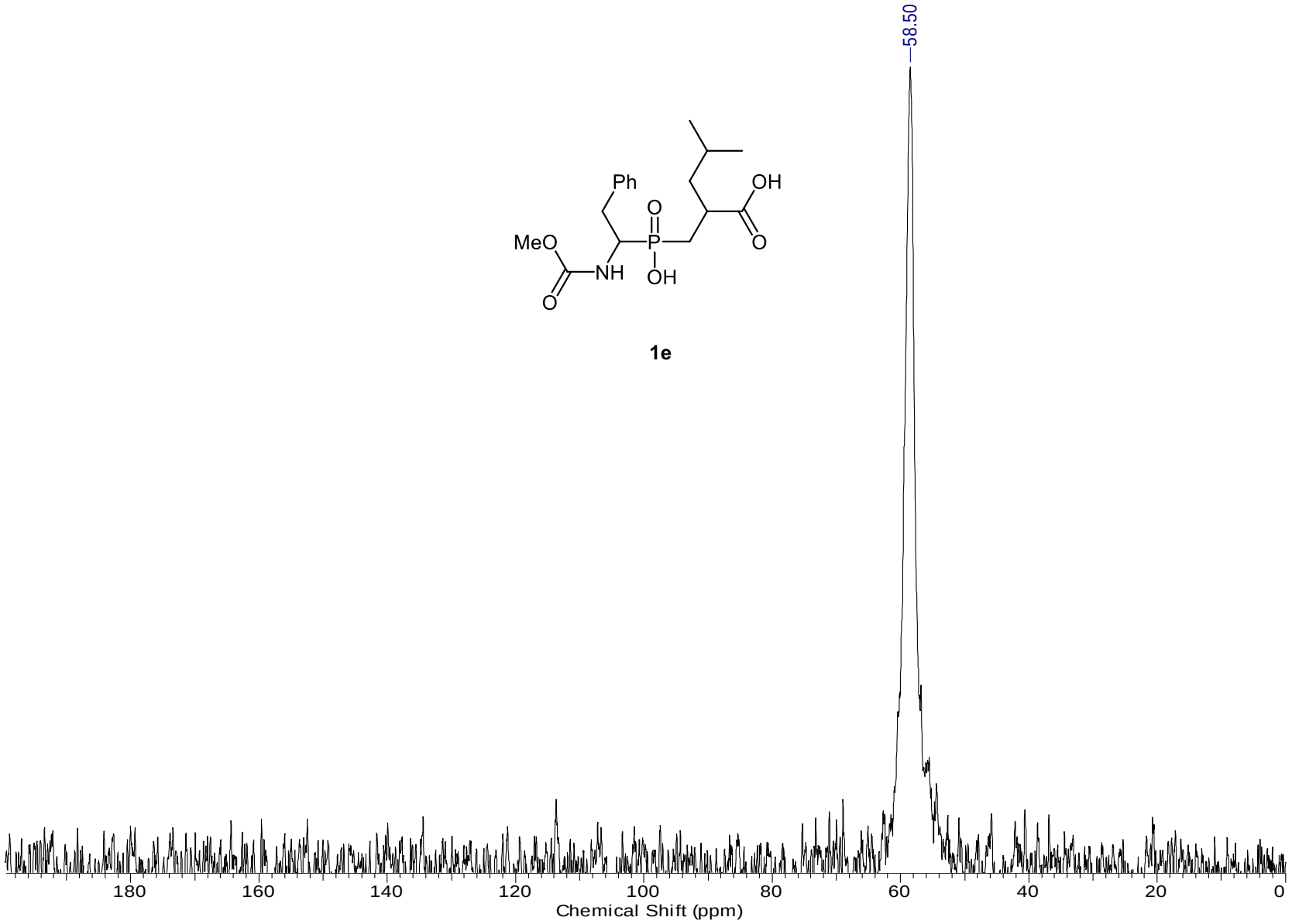


^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO)



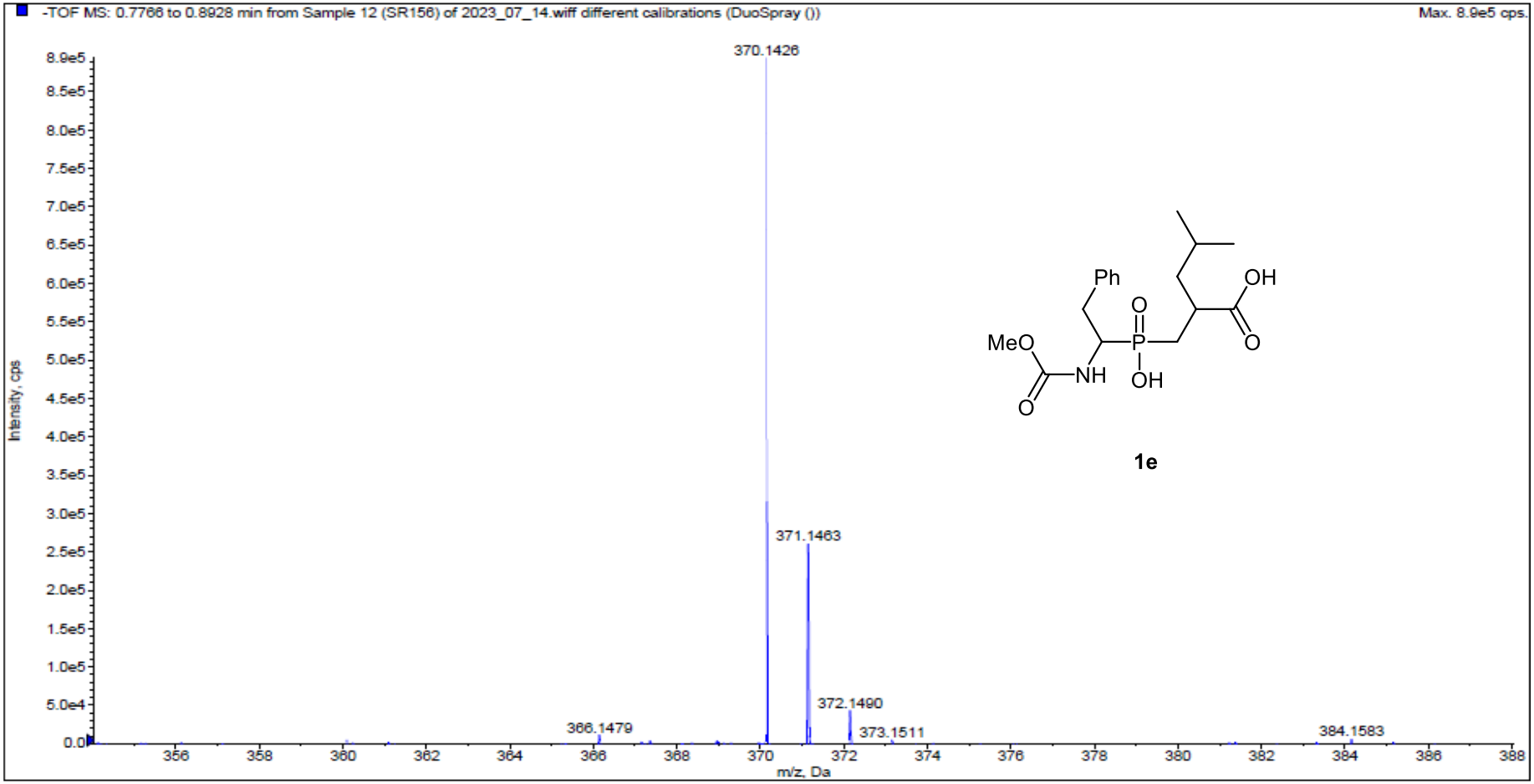
1e

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



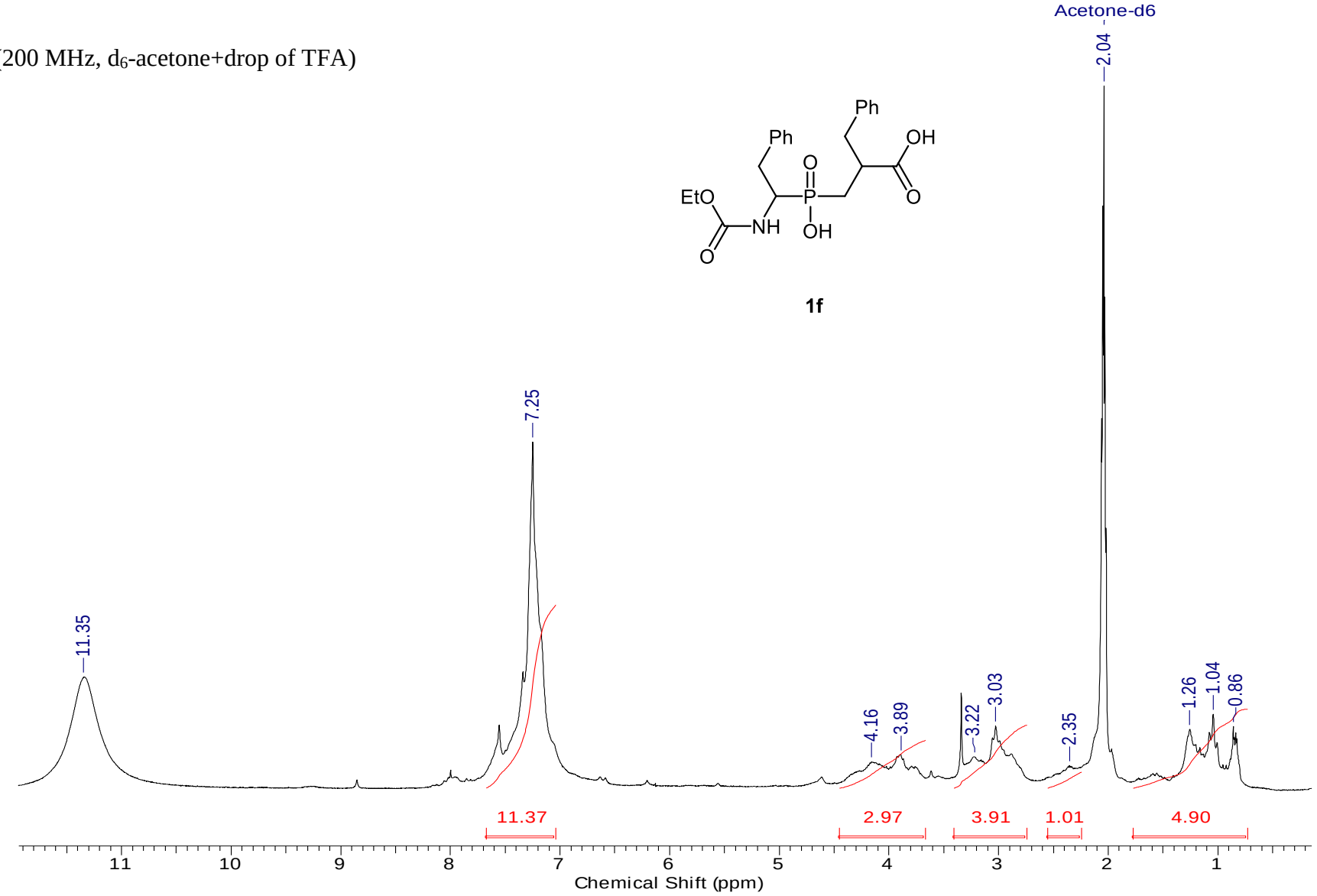
1e

1e HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{17}H_{25}NO_6P^-$ 370.1425, found 370.1426.

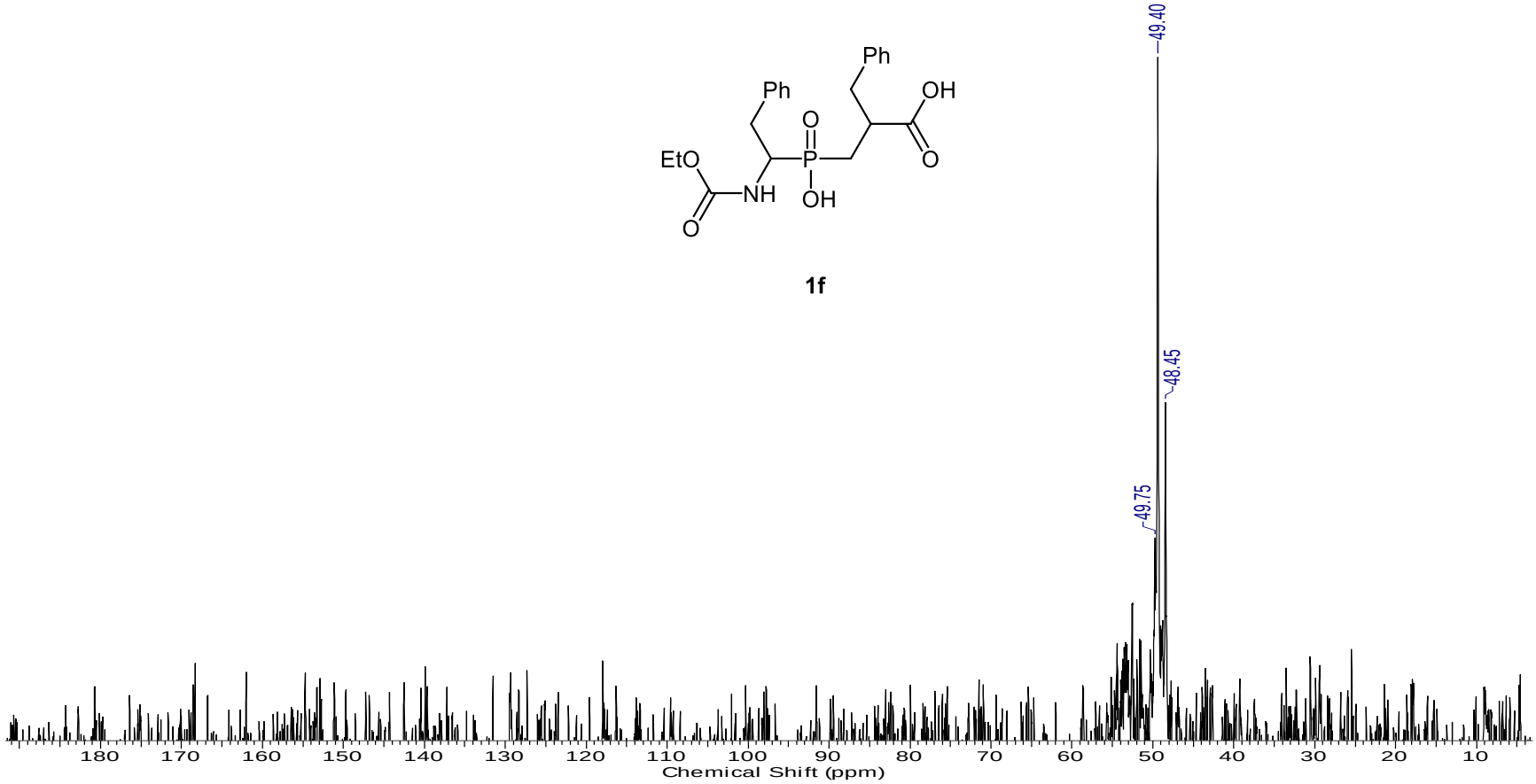


***P*-(2-Benzyl-3-hydroxy-3-oxopropyl)-*P*-[1-(*N*-ethoxycarbonylamino)-2-phenylethyl]phosphinic acid (1f).**

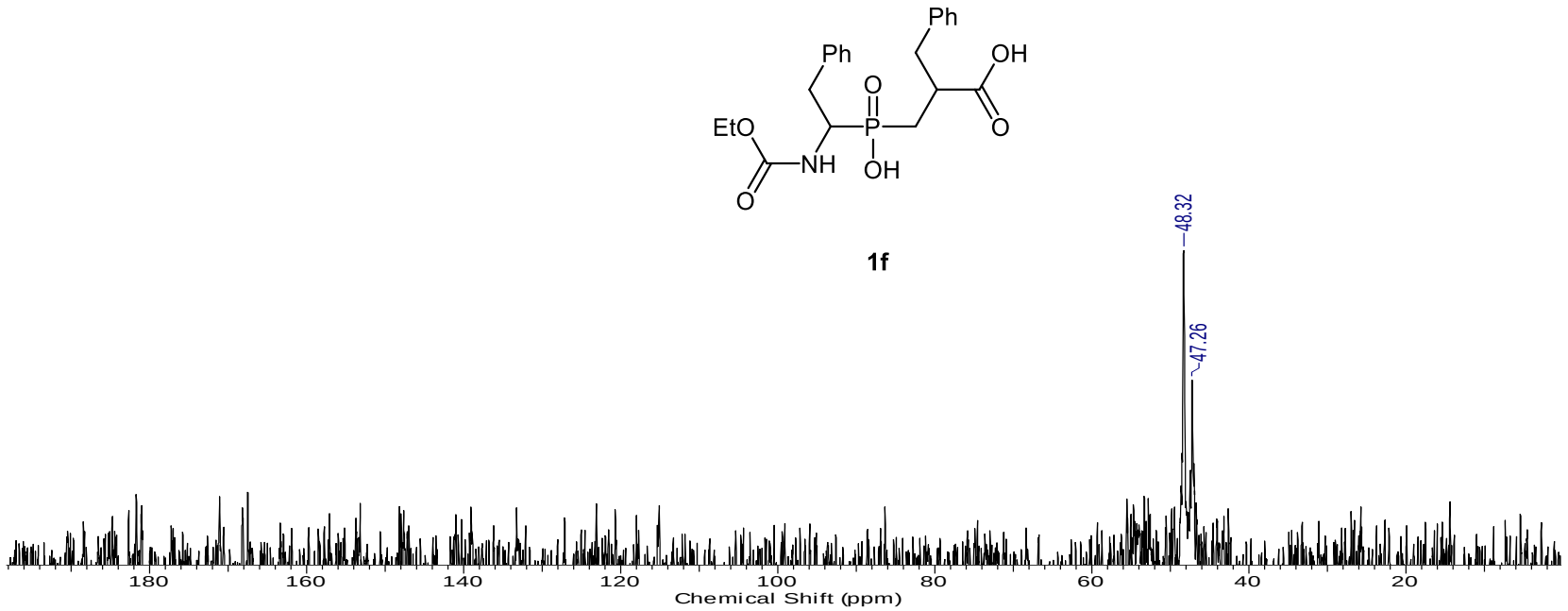
^{1}H NMR (200 MHz, d_6-acetone+drop of TFA)



^{31}P {^{1}H} NMR (81 MHz, d_6- acetone)

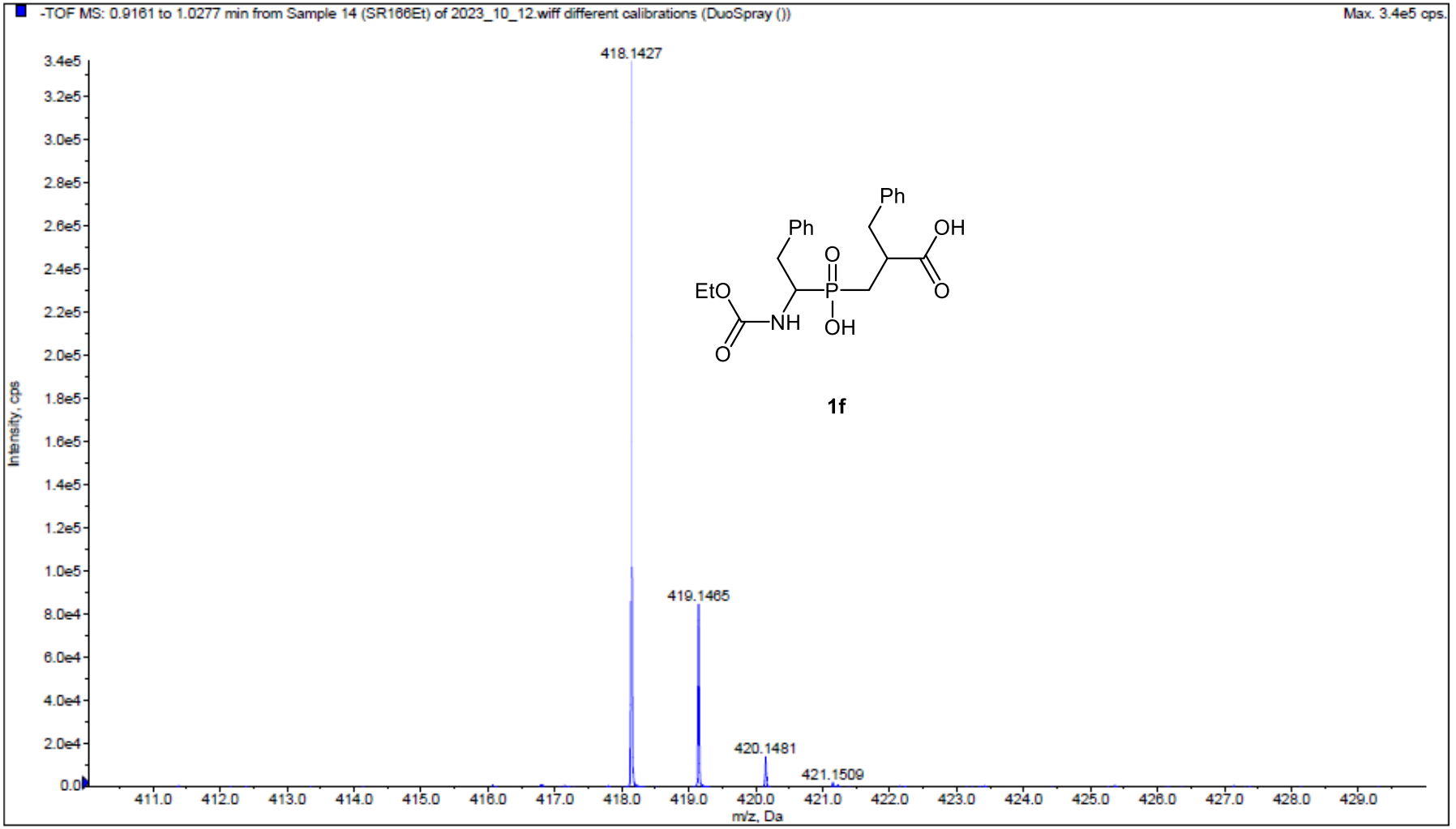


^{31}P {^{1}H} NMR (81 MHz, d_6- acetone+drops of D_2O)



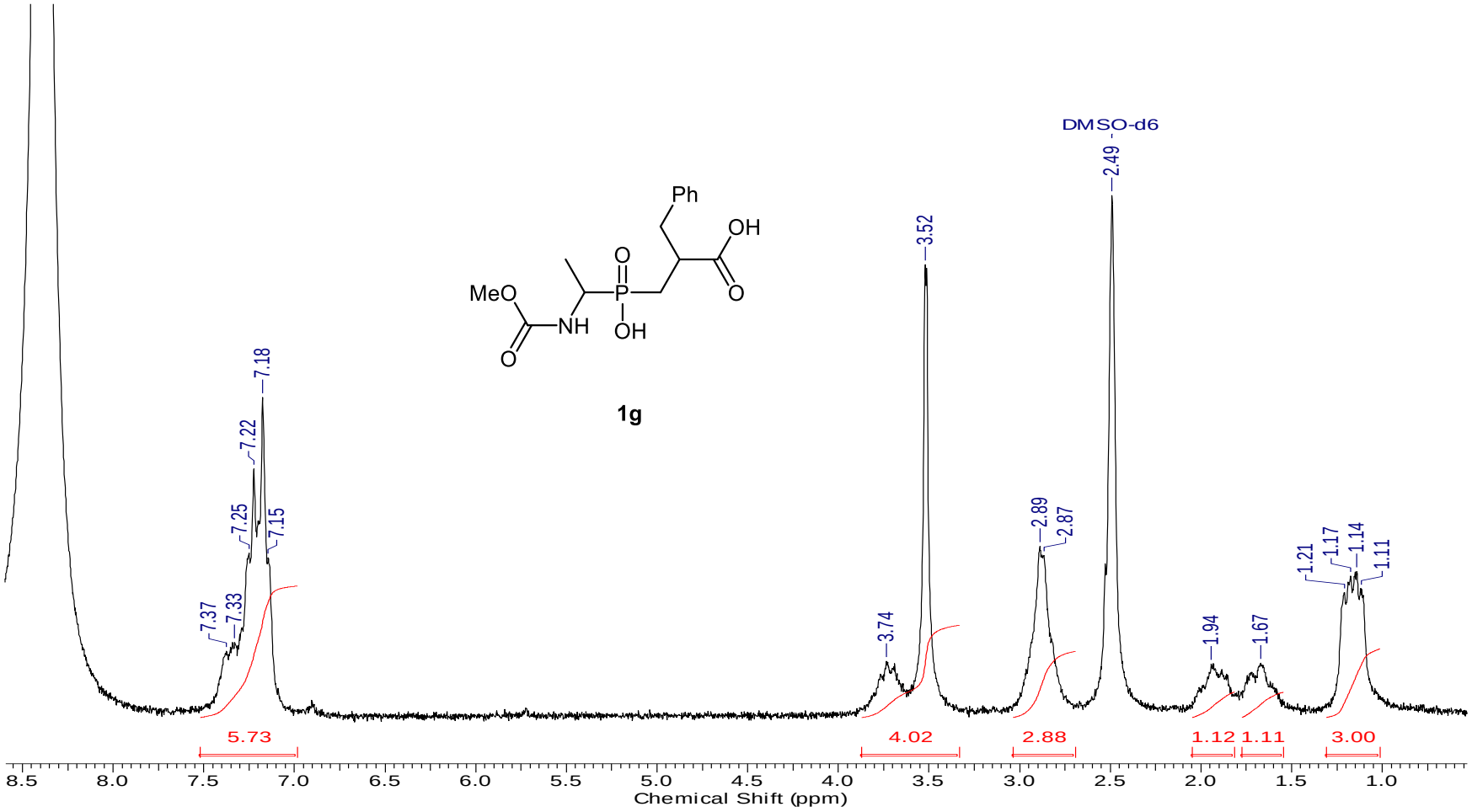
1f

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $C_{21}H_{25}NO_6P^-$ 418.1425, found 418.1427.

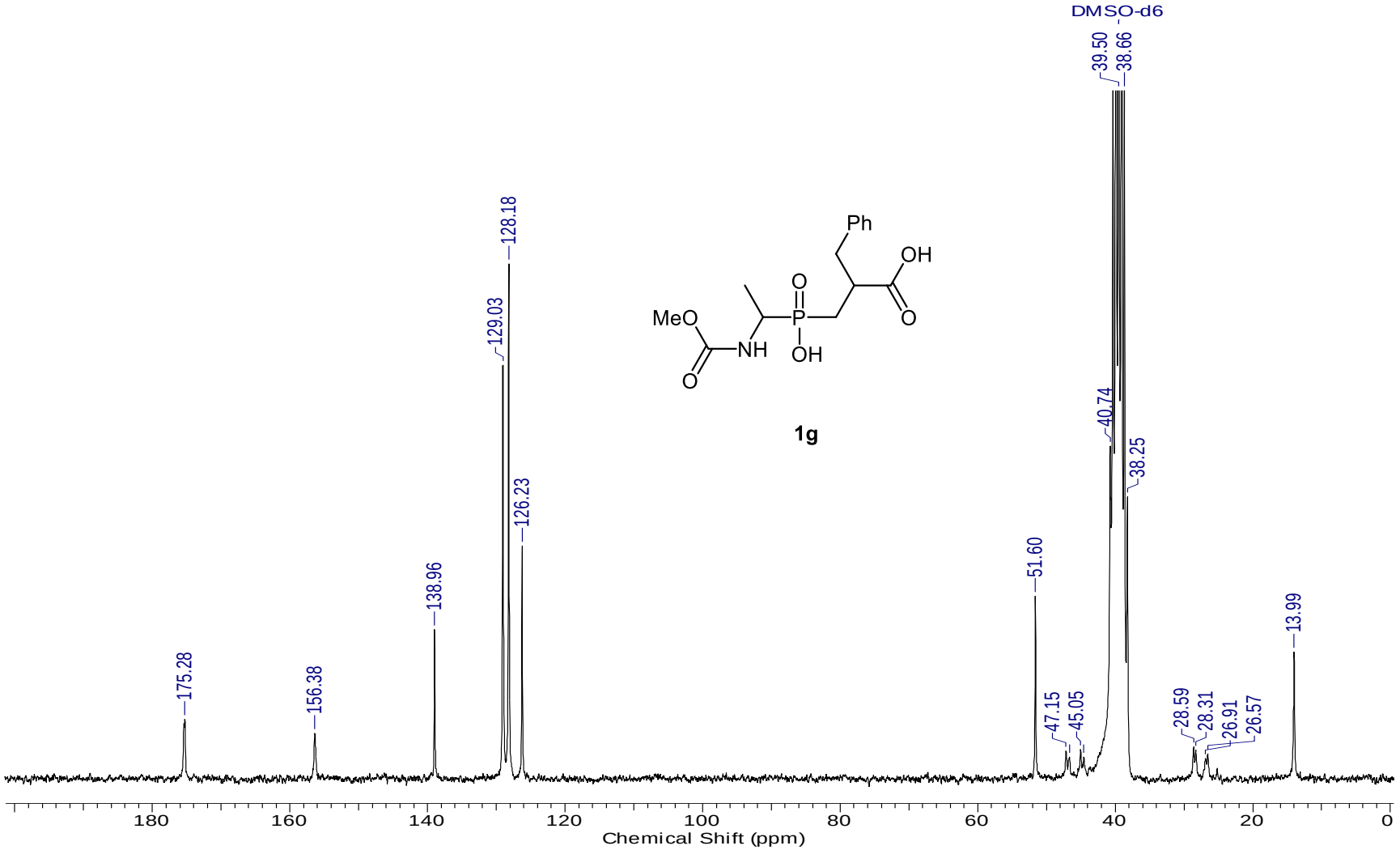


***P*-(2-Benzyl-3-hydroxy-3-oxopropyl)-*P*-[1-(*N*-methyloxycarbonylamino)ethyl]phosphinic acid (1g)**

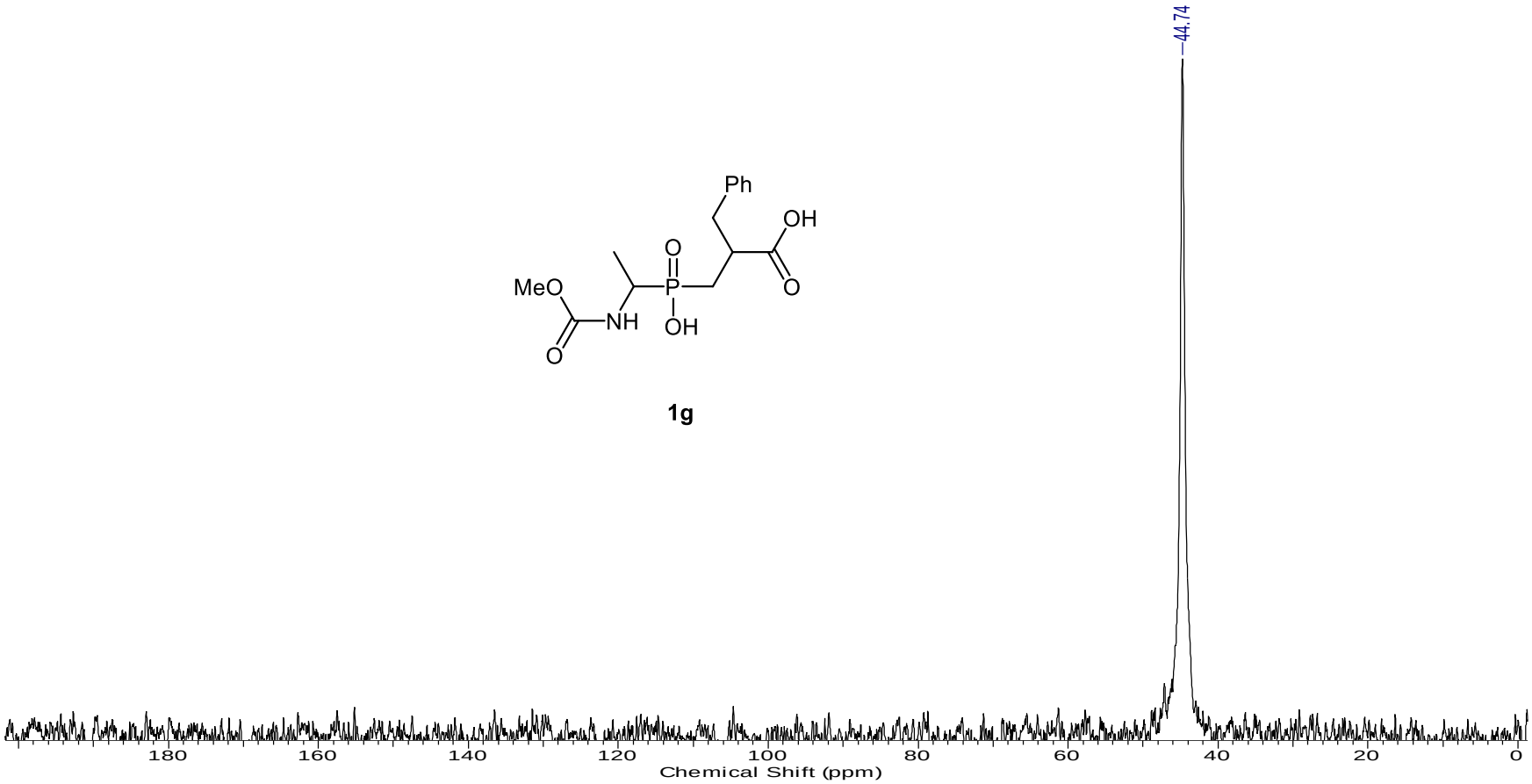
^{1}H NMR (200 MHz, d_6-DMSO+drop of TFA)



^{13}C {^{1}H} NMR (50 MHz, d_6-DMSO)

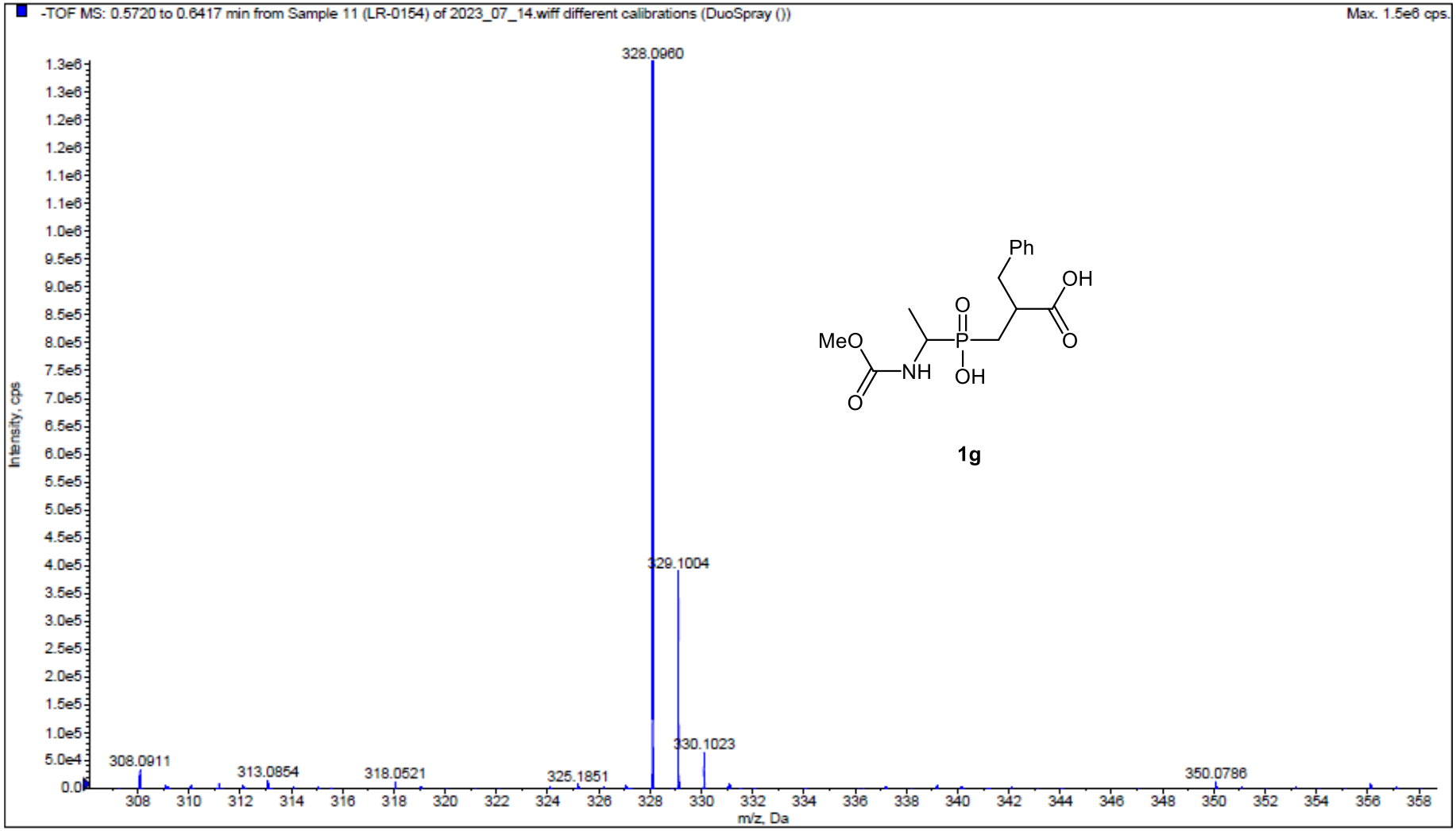


^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO)



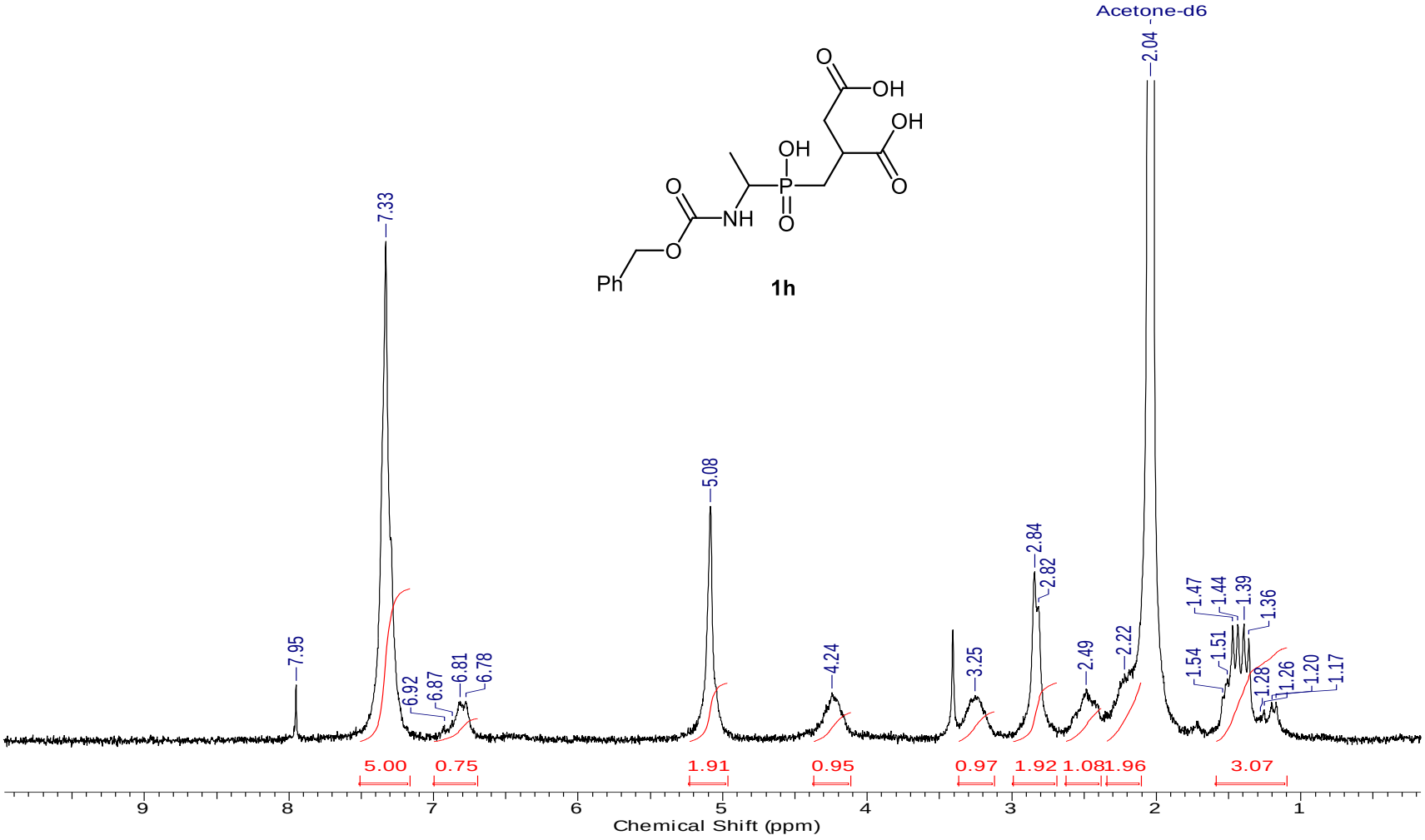
1g

1g. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_{19}NO_6P^-$ 328.0955, found 328.0960.

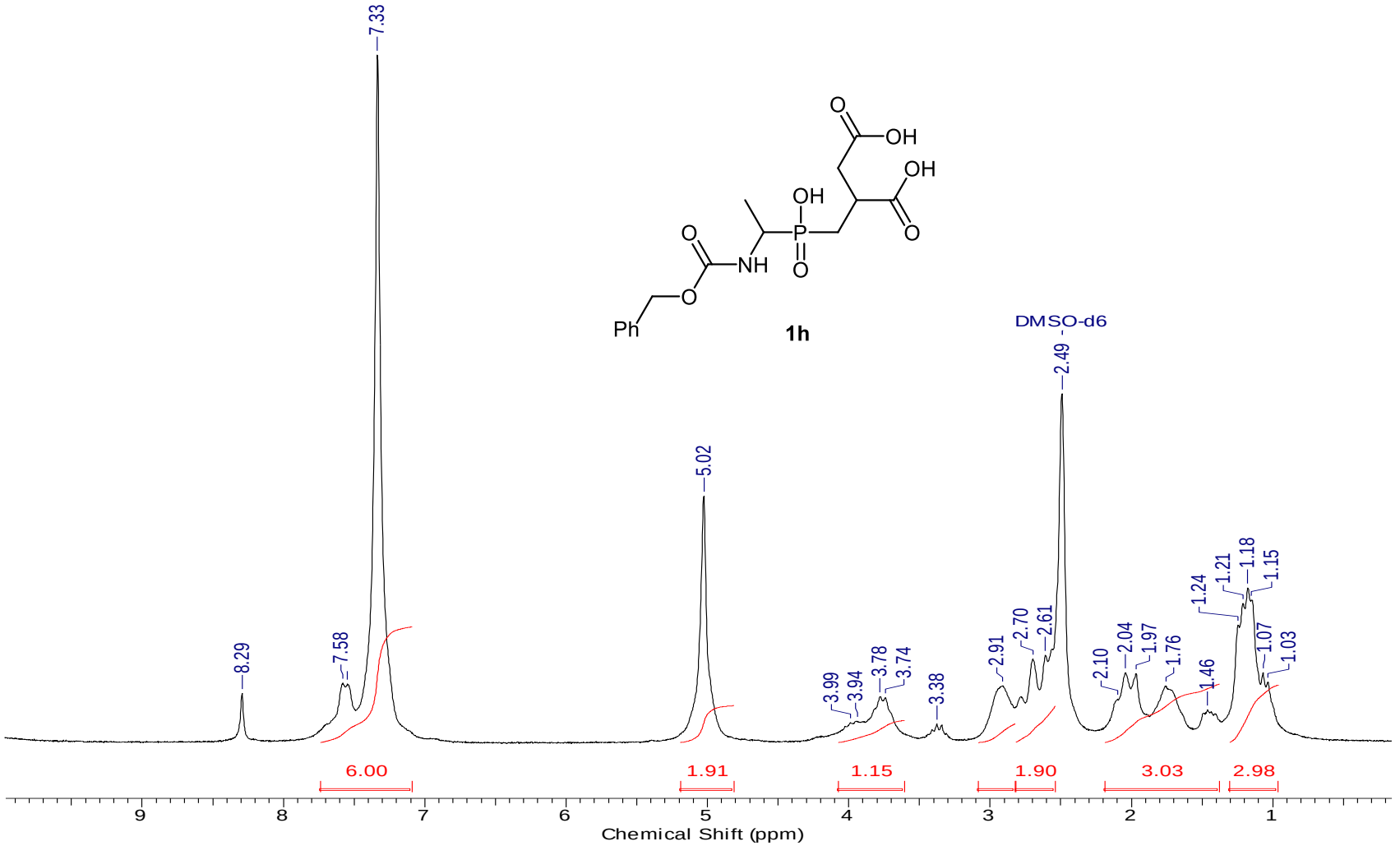


***P*-[1-(*N*-Benzyloxycarbonylamino)ethyl]-*P*-[2,3-bis(carboxy)propyl]phosphinic acid (1h)**

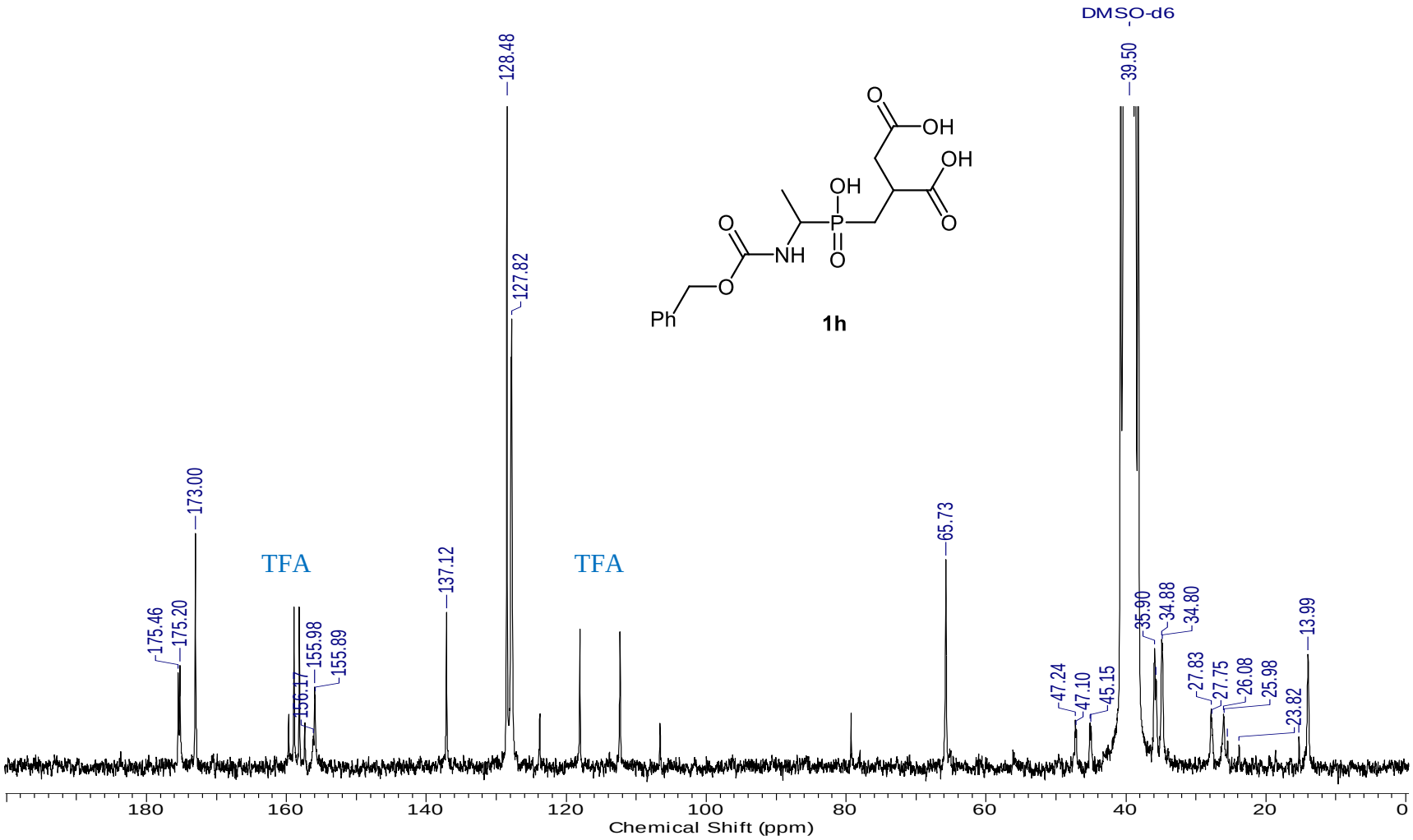
^{1}H NMR (200 MHz, d_6-acetone+drop of TFA)



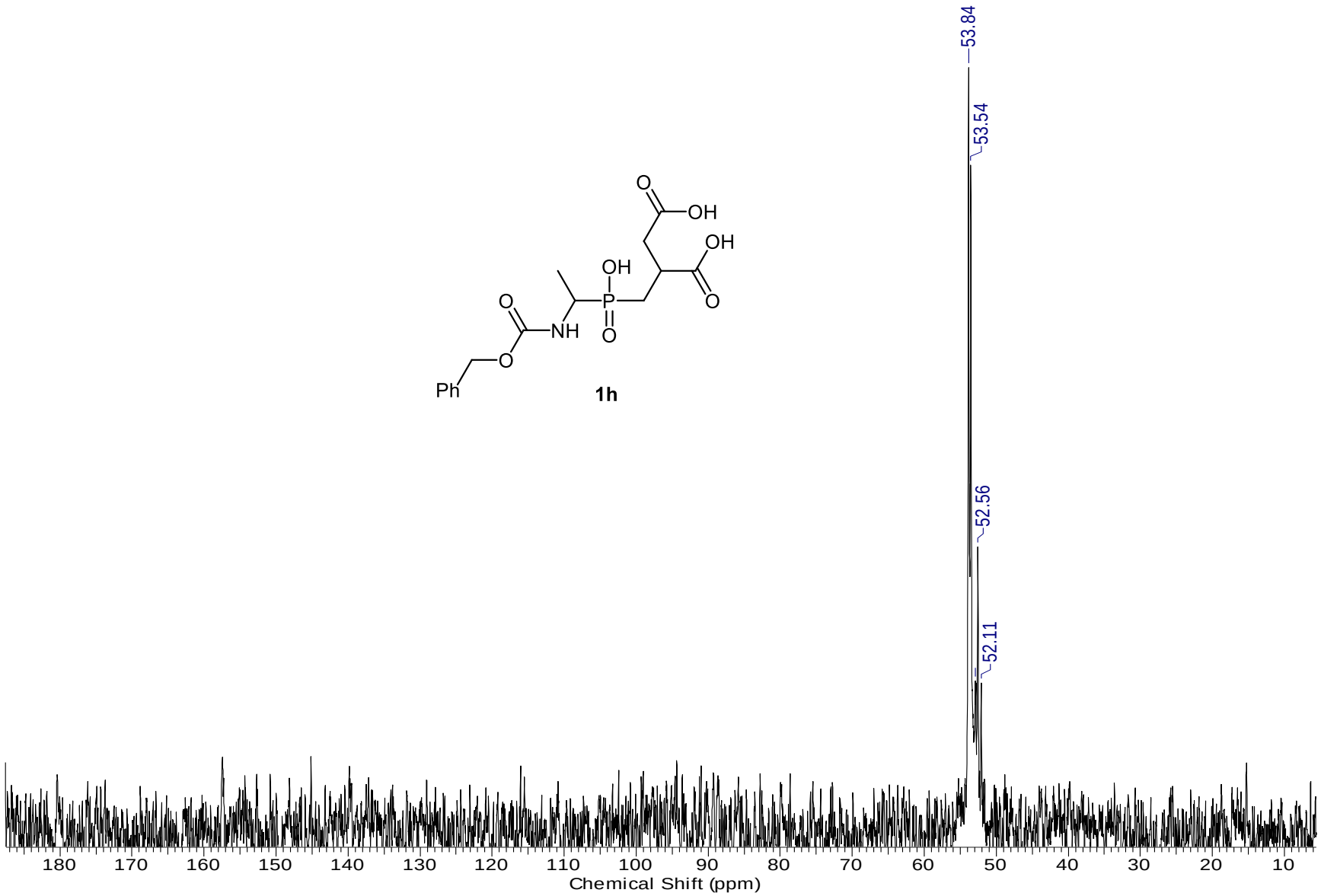
^{1}H NMR (200 MHz, d_6-DMSO+drop of TFA)



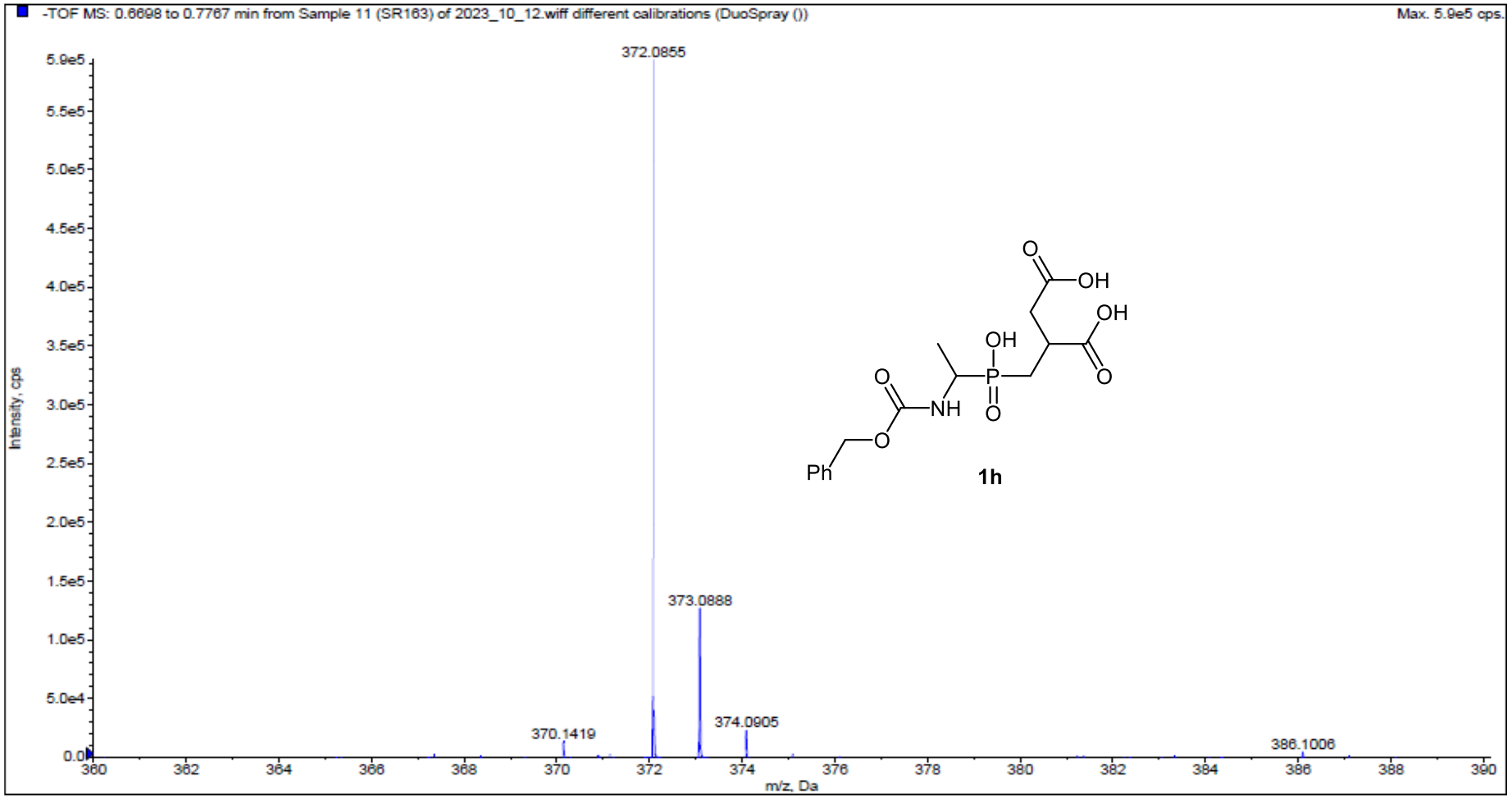
^{13}C {^{1}H} NMR (50 MHz, d_6-DMSO + drops of TFA)



^{31}P {^{1}H} NMR (81 MHz, d_6-DMSO+drop of TFA)

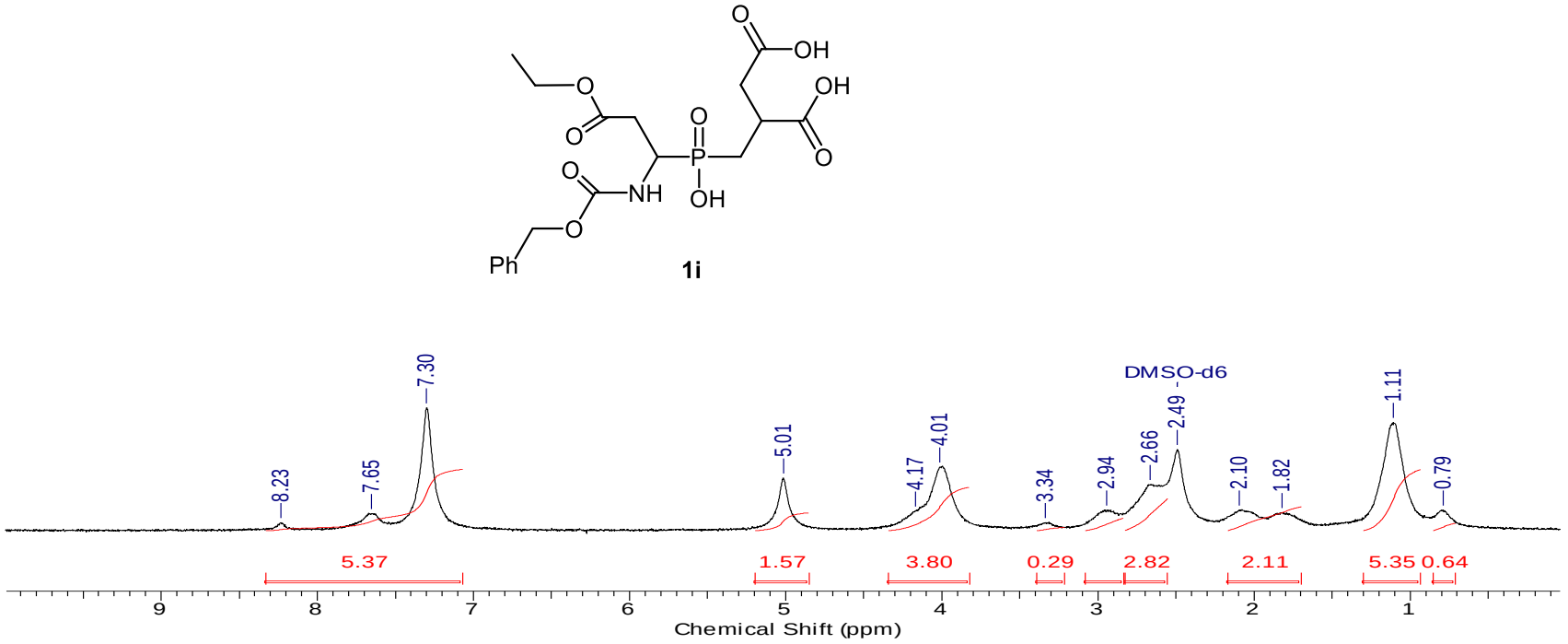


1h. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{15}H_{19}NO_8P^-$ 372.0848, found 372.0855.

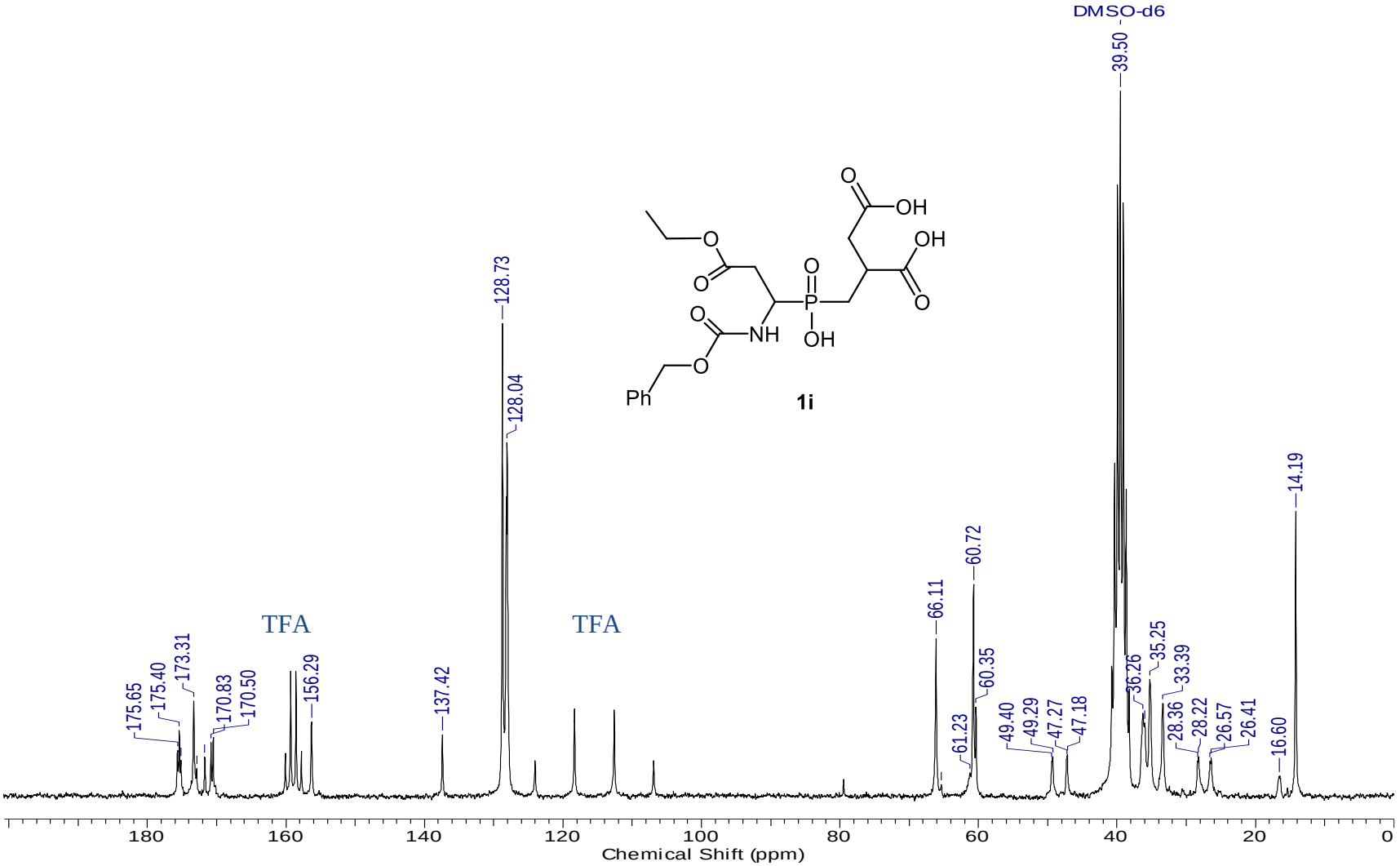


***P*-[1-(*N*-Benzyloxycarbonyl)amino-3-ethoxy-3-oxopropyl]-*P*-[2,3-bis(carboxy)-propyl]phosphinic acid (1i).**

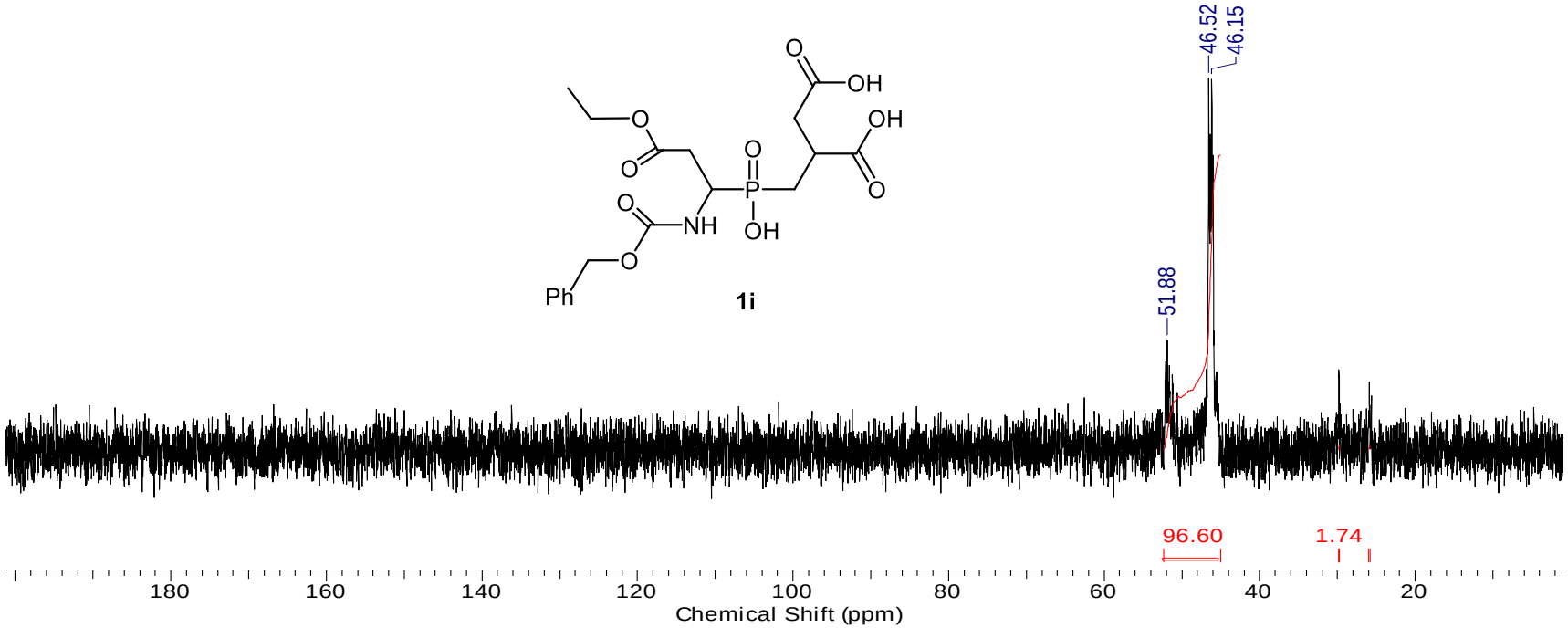
^{1}H NMR (200 MHz, d_6-DMSO+drop of TFA)



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

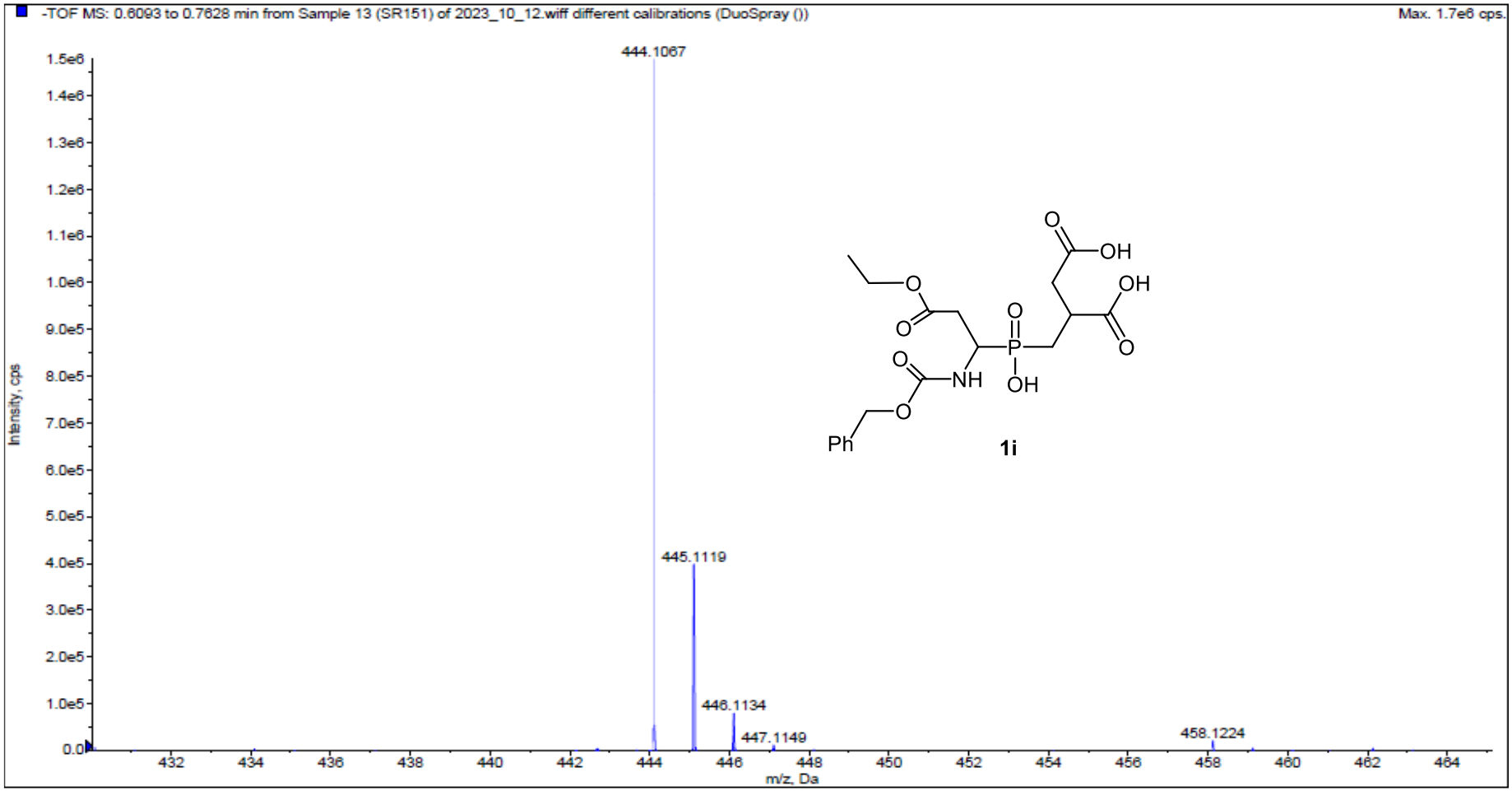


^{31}P {^{1}H} NMR (81 MHz, d6-DMSO+drop of TFA) δ 51.9*, 46.5, 46.2*.



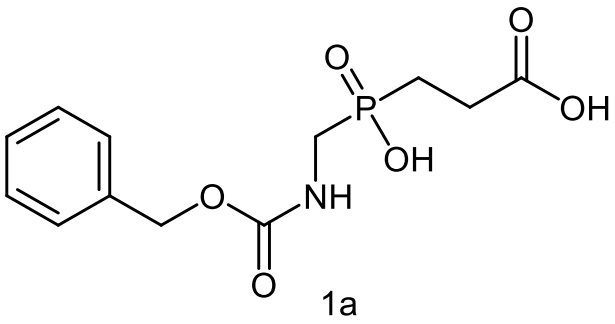
***P*-[1-(*N*-Benzyloxycarbonyl)amino-3-ethoxy-3-oxopropyl]-*P*-[2,3-bis(carboxy)-propyl]phosphinic acid (1i).**

HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ Calcd for $C_{18}H_{23}NO_{10}P^-$ 444.1060, Found 444.1067.

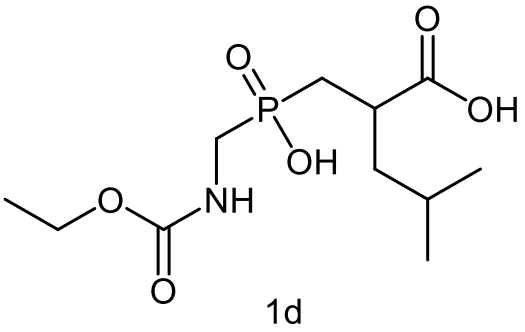


X-ray data

The X-ray single crystal diffraction data of structures **1a** and **1d** were collected at low temperature on STOE IPDS diffractometer equipped with Oxford Cryosystems Cryostream cooler [λ(Mo-Kα) = 0.71073 Å, graphite monochromator, φ-scans]. Data reduction with empirical absorption correction of experimental intensities (Scale3AbsPack program) was made with a CrysAlisPro software. The structures were solved by a charge flipping method using Superflip program.[S2] All non-hydrogen atoms were refined anisotropically by a full-matrix least squares method using SHELX-2018 program.[S3] The H-atoms were refined in a riding model with isotropic displacement parameters depending on U_{eq} of the connected atom. Main crystal and experimental data for the structures are listed in Table S1, S53.



1a



1d

Table S1. Crystal data and structural refinement parameters for **1d** and **1e**.

	1a	**1d**
Chemical formula	$C_{12}H_{16}NO_6P$	$C_{11}H_{22}NO_6P$
Mol. weight	301.23	295.27
Cell setting	Monoclinic	Monoclinic
Space group, *Z*	*P* $2_1/c$	*P* $2_1/n$
Temperature (K)	150	120
a (Å)	30.000(1)	14.6797(5)
b (Å)	4.8905(2)	5.7170(2)
c (Å)	9.4021(4)	19.4331(8)
β (°)	94.638(4)	105.737(4)
Cell volume (Å^3)	1374.9(1)	1569.8(1)
ρ (g·cm^{-3})	1.455	1.249
μ, cm^{-1}	0.225	0.195
Crystal size, mm^3	0.75*0.3*0.15	0.54*0.28*0.075
Refls collected / unique	10208/ 2673	14301/ 3732
R_{int}	0.0296	0.0256
θ_{max} (°)	26.029	27.873
Parameters refined	189	180
Final R_1, wR_2 [I>2σ(I)]	0.0471/ 0.1325	0.0549/ 0.1272
Goodness-of-fit	1.101	1.050
CCDC number	2334587	2334586

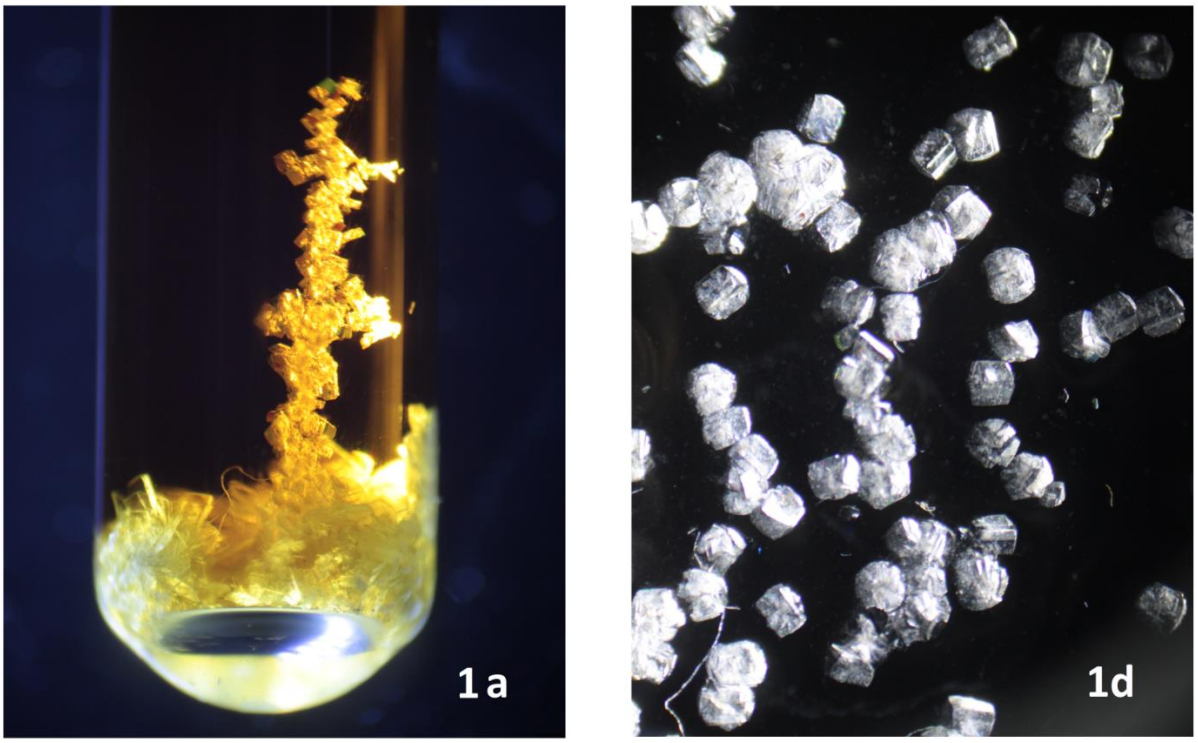


Figure S1. Photo for crystals of **1a** and **1d**.
Crystals of **1a** were obtained by precipitation with water from a solution in acetone-d_6+TFAA in an NMR tube.
Crystals of **1d** were grown by slow evaporation from a solution in acetonitrile

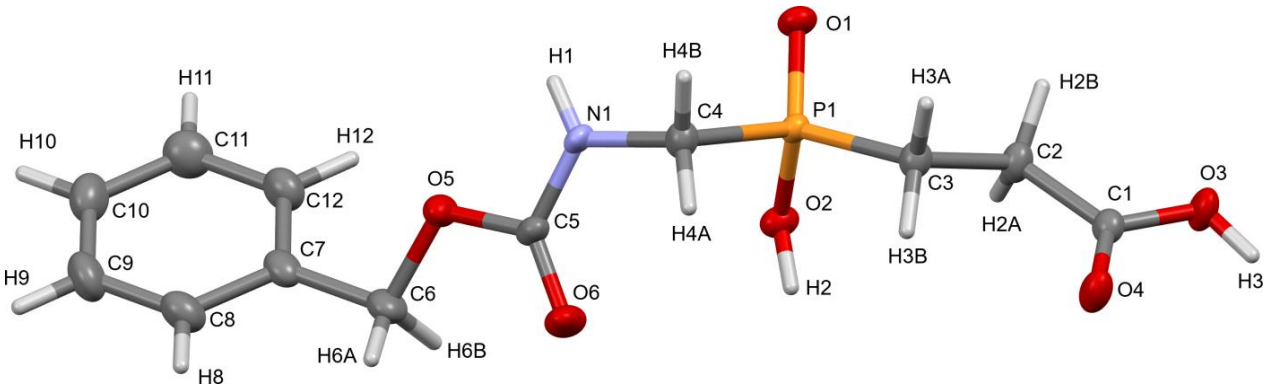


Figure S2. Molecular structure of **1a** with atom labeling.

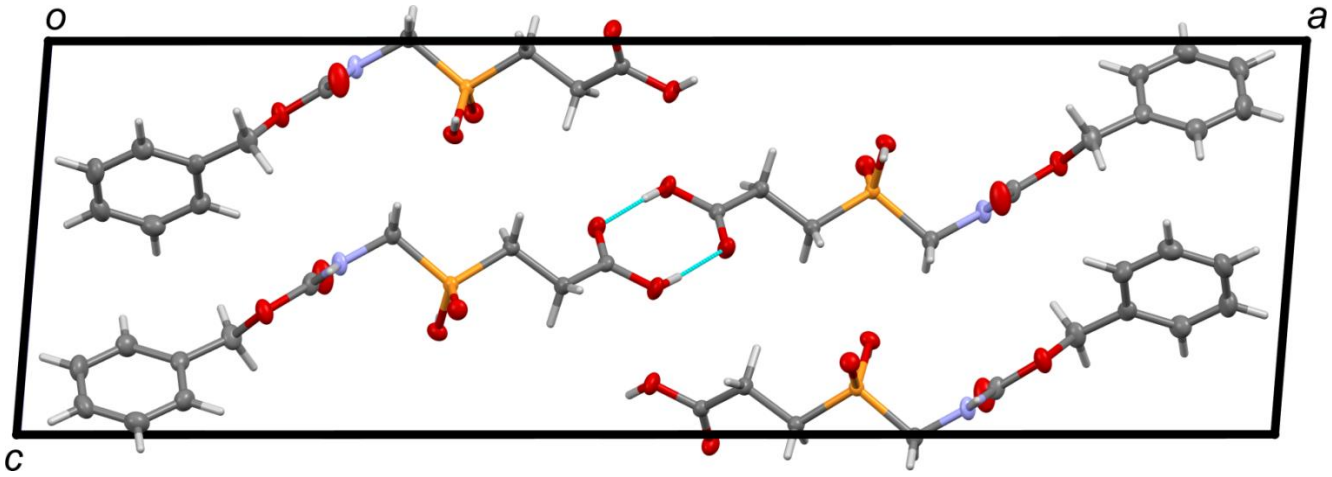


Figure S3. Projection of crystal structure of **1a** along b-axes**.** Molecules are connected by hydrogen bonds (labeled by cyan dashed lines) forming layers in (101) plane.

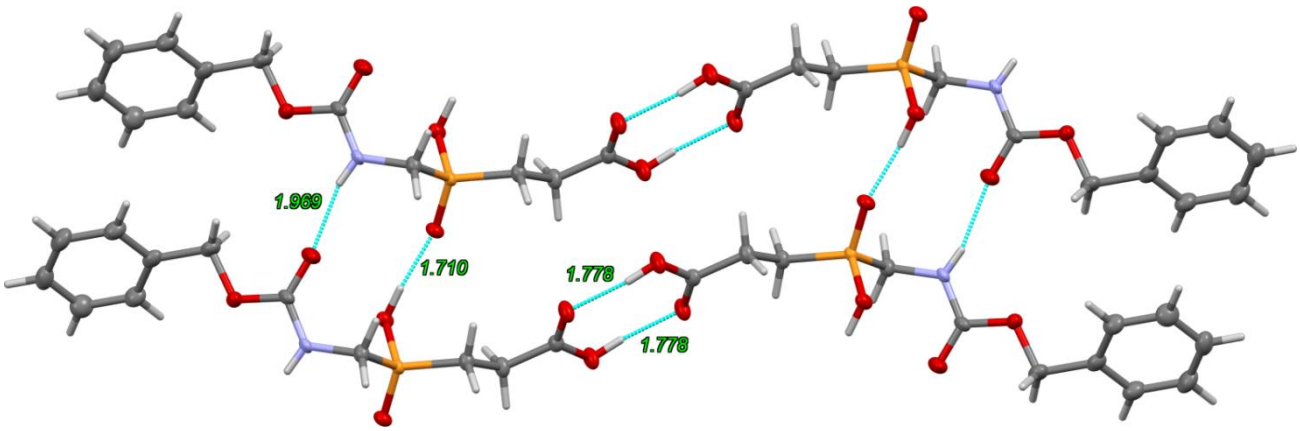


Figure S4. H-bond network in (101) plane of crystal **1a.** H-bond distances (in Å) shown in figure.
Distance X-H…Y**:** C-OH…O=C 2.653 Å, N-H…O=C 2.737 Å, P-OH…O=P 2.590 Å.
Distance X-H…Y**:** C-OH…O=C 1.778 Å, N-H…O=C 1.969 Å, P-OH…O=P 1.710 Å.

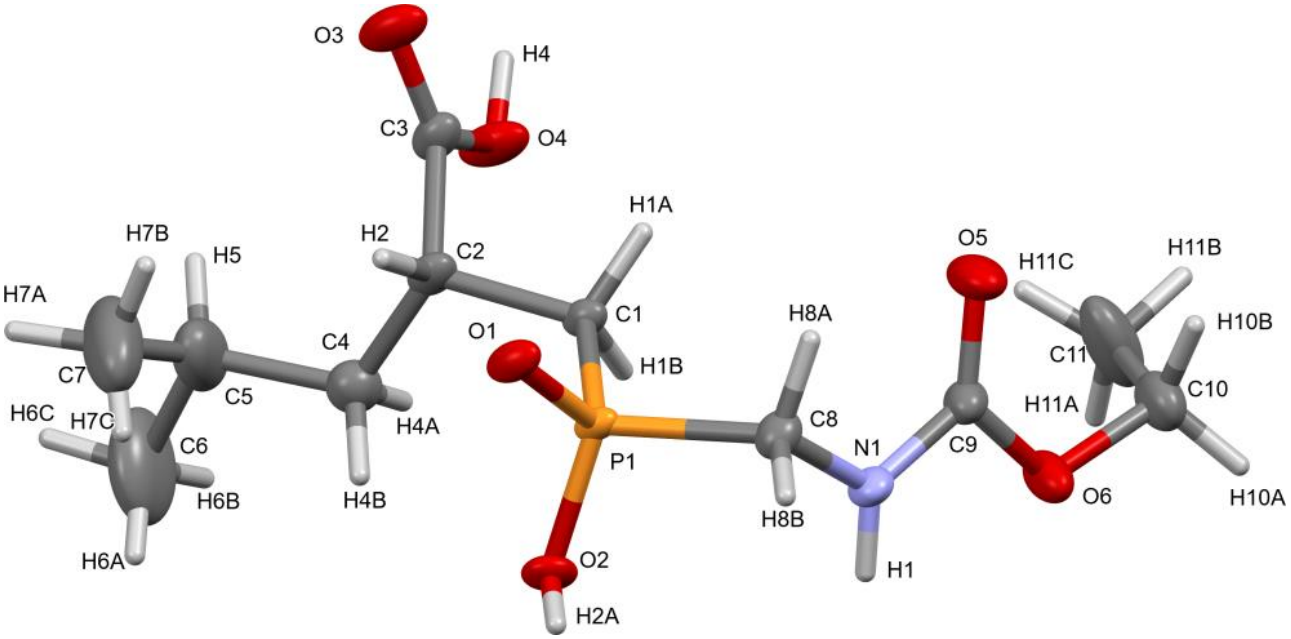


Figure S5. Molecular structure of **1d** with atom labeling**.**

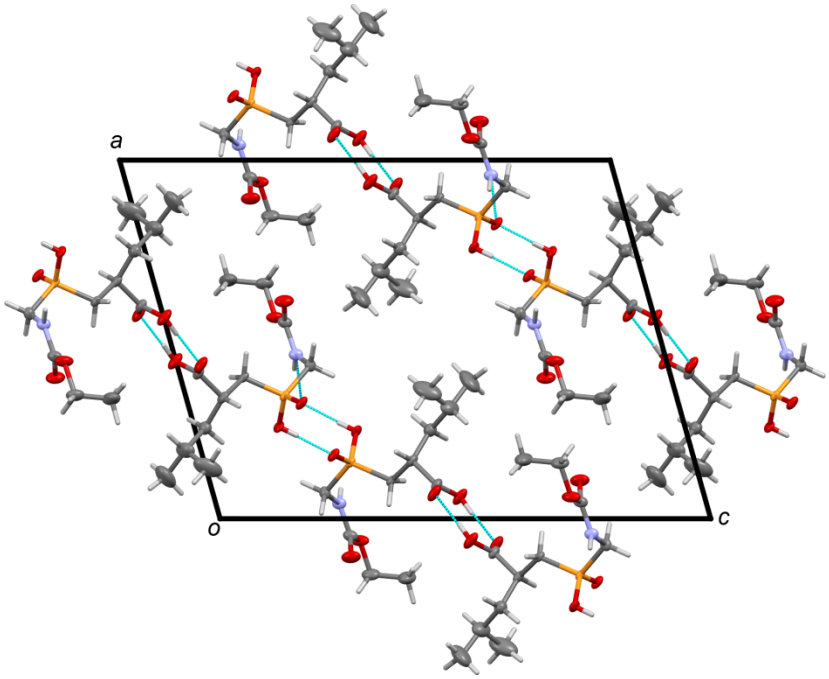


Figure S6. Projection of crystal structure of **1d** along b-axes**.** Molecules are connected by hydrogen bonds (labeled by cyan dashed lines) forming layers in (101) plane.

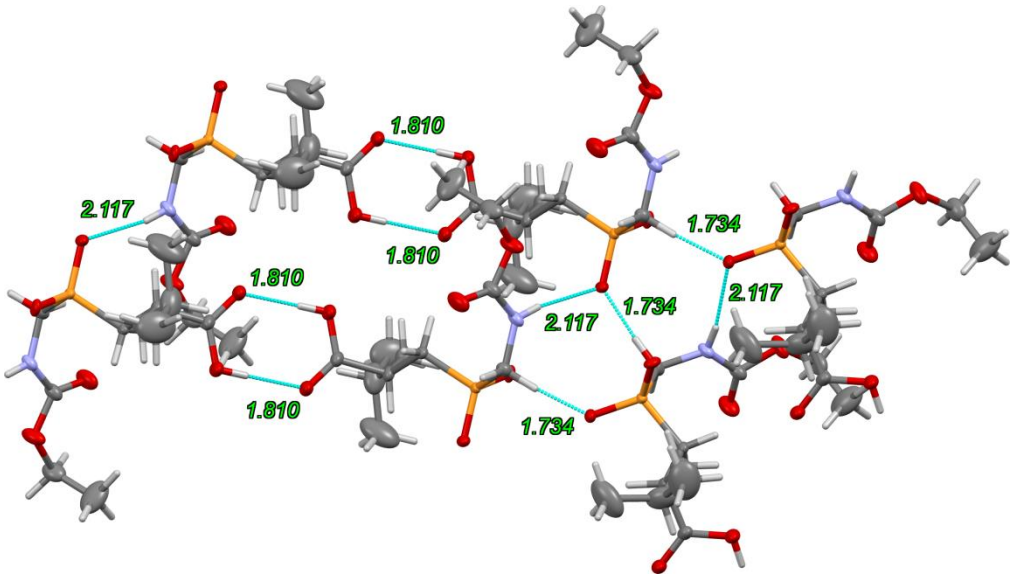


Figure S7. H-bond network in (101) plane of crystal **1d.** H-bond distances (in Å) shown in figure. Distance X-H…Y**:** C-OH…O=C 2.677 Å, N-H…O=P 2.954 Å, P-OH…O=P 2.517 Å. Distance X-H…Y**:** C-OH…O=C 1.810 Å, N-H…O=P 2.117 Å, P-OH…O=P 1.734 Å.

CCDC 2334586 and 2334587 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

References

S1. S. R. Golovash, A. V. Borodachev, M. E. Dmitriev and V. V. Ragulin, *Mendeleev Commun.*, 2023, **33**, 784; https://doi.org/10.1016/j.mencom.2023.10.015.

S2. L. Palatinus and G. Chapuis, *J. Appl. Crystallogr.*, 2007, **40**, 786; https://doi.org/10.1107/S0021889807029238.

S3. G. M. Sheldrick, *Acta Crystallogr.*, 2015, C**71**, 3; https://doi.org/10.1107/S2053229614024218.