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Simple and effective synthesis of functionalized (hydroxymethylene)bis(phosphonic) acids

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Table of Contents

Additional Experimental Details

General Methods and Remarks

All operations with $(Me_3SiO)_3P$ (**1**) were conducted in a dry argon atmosphere using standard Schlenk techniques.

^1H NMR (400.130 MHz), ^{13}C NMR (100.613 MHz) and ^{31}P NMR (161.976 MHz) spectra were recorded on Bruker 400 or Agilent 400 spectrometers (at 295 K). Chemical shifts in the spectra are given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR spectra) or 85% aqueous H_3PO_4 (for ^{31}P NMR spectra). Elemental analyses were carried out using a HeraeusVarioElementar instrument.

Solvents were used as received.

All reagent used, $(Me_3Si)_2NH$, H_3PO_3, PhC(O)Cl, are commercially available compounds (Aldrich, Acros). Commercial $(Me_3SiO)_3P$ (**1**) (>95%) was purchased from Aldrich (https://www.sigmaaldrich.com/RO/en/product/aldrich/93412; 100 mL for 1100 euro). Phosphorous acid, H_3PO_3, was dried in desiccator overnight over P_4O_{10} in vacuum. Acid chlorides, 3,4,5-$(MeO)_3C_6H_2C(O)Cl$,[S1] 3-$MeOC_6H_4CH_2C(O)Cl$,[S2] were prepared from the corresponding carboxylic acids under reflux in CH_2Cl_2 with $SOCl_2$ /DMF (cat) and used without purification.

Synthesis

Technical tris(trimethylsilyl) phosphite, $(Me_3SiO)_3P$ 1 (a mixture of tris(trimethylsilyl) phosphite, $(Me_3SiO)_3P$ (1)/ bis(trimethylsilyl) phosphite, $HP(O)(OSiMe_3)_2$ (2)/ tris(trimethylsilyl) phosphate, $P(O)(OSiMe_3)_3$ (3))

Into a 250 mL round bottom flask, phosphorous acid (15.35 g, 187.20 mmol, 1.0 equiv.), hexamethyldisilazane (117.7 mL, 90.42 g, 561.60 mmol, 3.0 equiv.) and trimethylsilyl chloride (1.0 mL, 0.85 g, 7.90 mmol, 4 mol. %) were loaded. The mixture was refluxed for 10 h. Technical tris(trimethylsilyl) phosphite, $(Me_3SiO)_3P$ (**1**) (30.52 g, 40%), representing an inseparable mixture of $(Me_3SiO)_3P$ (**1**)/ $HP(O)(OSiMe_3)_2$ (**2**)/ $P(O)(OSiMe_3)_3$ (**3**) (ratio 71:20:9 according to ^{31}P NMR spectroscopy), was obtained after distillation, b.p. 104 ºC (29 Torr), as a transparent colorless liquid. The system was purged with argon. As reported for $(Me_3SiO)_3P$ (**1**), b.p. 129-130 (28 Torr),[S3] b.p. 90-92 (20 Torr).[S4]

Tris(trimethylsilyl) phosphite, $(Me_3SiO)_3P$ (1): ^1H NMR (δ, ppm, 400.130 MHz, $CDCl_3$): 0.16 (s, 27H, $3OSiMe_3$).
$^{13}C\{^1H\}$ NMR (δ, ppm, 100.613 MHz, $CDCl_3$): 1.61 (d, $^3J_{31P\text{-}13C}$ 3.1 Hz, $OSiMe_3$).
$^{31}P\{^1H\}$ NMR (δ, ppm, 161.976 MHz, $CDCl_3$): 113.59.

Bis(trimethylsilyl) phosphite, $HP(O)(OSiMe_3)_2$ (2): ^1H NMR (δ, ppm, 400.130 MHz, $CDCl_3$): 6.68 (d, $^1J_{31P\text{-}1H}$ 698.4 Hz, 1H, PH), 0.28 (s, 18H, $OSiMe_3$). ^1H NMR spectrum corresponds to the literature data.[S4]
$^{13}C\{^1H\}$ NMR (δ, ppm, 100.613 MHz, $CDCl_3$): 0.28 (d, $^3J_{31P\text{-}13C}$ 1.5 Hz, $OSiMe_3$).
$^{31}P\{^1H\}$ NMR (δ, ppm, 161.976 MHz, $CDCl_3$): -13.58.

Tris(trimethylsilyl) phosphate, $P(O)(OSiMe_3)_3$ (3): ^1H NMR (δ, ppm, 400.130 MHz, $CDCl_3$): 0.25 (s, 27H, $SiMe_3$).
$^{13}C\{^1H\}$ NMR (δ, ppm, 100.613 MHz, $CDCl_3$): 0.59 (d, $^3J_{31P\text{-}13C}$ 1.5 Hz, $OSiMe_3$).
$^{31}P\{^1H\}$ NMR (δ, ppm, 161.976 MHz, $CDCl_3$): -25.60. ^{31}P NMR spectrum corresponds to the literature data.[S5]

Synthesis of [aryl(hydroxy)methanediyl]bis(phosphonic) acids, RC(OH)[P(O)(OH)$_2$]$_2$. <u>General procedure.</u> Technical $(Me_3SiO)_3P$ **1** (20.02 g of **1-3** mixture containing 14.84 g, 49.70 mmol of **1**) was added dropwise to an acid chloride RC(O)Cl **4a-c** (24.85 mmol). The reaction mixture was stirred at room temperature for 3 h and then refluxed for 1 h. After that, methanol (25.0 mL, 19.80 g, 618.80 mmol) was added, and this was stirred for 1 h. The mixture was concentrated approximately in three times on a rotary evaporator, and CCl_4 (15 mL) was added. The precipitate formed was filtered off and washed with CCl_4 (3×5 mL) and then was dried by benzene vacuum evaporation.

[Hydroxy(phenyl)methanediyl]bis(phosphonic) acid, PhC(OH)[P(O)(OH)$_2$]$_2$ 5a

<u>Method 1.</u> Obtained using *General Procedure* from benzoyl chloride **4a** (3.49 g, 24.85 mmol) and technical $(Me_3SiO)_3P$ **1** (20.02 g containing 14.84 g, 49.70 mmol of **1**). Yield: 73% (4.86 g, 18.14 mmol). White powder, m.p. 183 °C; m.p.[S6] 186 °C.

<u>Method 2.</u> Commercially available $(Me_3SiO)_3P$ **1** (>95%) (4.74 g, 12.45 mmol) was added dropwise to PhC(O)Cl **4a** (0.87 g, 6.22 mmol). The reaction mixture was stirred at room temperature for 3 h and then refluxed for 1 h. After that methanol (6.0 mL, 4.95 g, 154.70 mmol) was added, and this was stirred for 1 h. The mixture was concentrated approximately in three times on a rotary evaporator and CCl_4 (5 mL) was added. The precipitate formed was filtered off and washed with CCl_4 (3×5 mL) and then was dried by benzene vacuum evaporation. Yield: 76% (1.27 g). White powder.

^{1}H NMR (δ, ppm, 400.130 MHz, DMSO-d$_6$): 7.80-7.76 (m, 2H, Ph$_H$), 7.54 (br s, 5H, 5OH), 7.29-7.23 (m, 2H, Ph$_H$), 7.20-7.14 (m, 1H, Ph$_H$).

^{13}C{^{1}H} NMR (δ, ppm, 100.613 MHz, DMSO-d$_6$): 138.39 (t, $^2J_{31P\text{-}13C}$ 3.5 Hz, *ipso*-Ph$_C$), 126.82 (t, $^4J_{31P\text{-}13C}$ 2.3 Hz, *m*-Ph$_C$), 126.60 (t, $^3J_{31P\text{-}13C}$ 4.3 Hz, *o*-Ph$_C$), 125.91 (t, $^5J_{31P\text{-}13C}$ 2.9 Hz, *p*-Ph$_C$), 75.62 (t, $^1J_{31P\text{-}13C}$ 142.3 Hz, C[P(O)(OH)$_2$]$_2$).

^{31}P{^{1}H} NMR (δ, ppm, 161.976 MHz, DMSO-d$_6$): 14.93.

[Hydroxy(3,4,5-trimethoxyphenyl)methanediyl]diphosphonic acid,

3,4,5-$(MeO)_3C_6H_2C(OH)[P(O)(OH)_2]_2$ (5b)

Obtained using *General Procedure* from 3,4,5-$(MeO)_3C_6H_2C(O)Cl$ **4b** (2.87 g, 12.43 mmol) and technical $(Me_3SiO)_3P$ **1** (10.00 g containing 7.44 g, 24.87 mmol **1**). Yield: 54% (2.40 g). White powder.

Elemental analysis: Calc. for $C_{10}H_{16}O_{10}P_2$ (358.1756): C 33.53, H 4.50. Found: C 33.27, H 4.62.

^{1}H NMR (δ, ppm, 400.130 MHz, DMSO-d_6): 7.12 (t, $^3J_{13C-31P}$ 2.3 Hz, 2H, Ar_H), 6.95 (br s, 5H, 5OH), 3.73 (s, 6H, 2OMe), 3.65 (s, 3H, OMe).

^{13}C{^{1}H} NMR (δ, ppm, 100.613 MHz, DMSO-d_6): 151.73 (t, $^4J_{13C-31P}$ 3.7 Hz, *m*-Ar_C), 136.31 (t, $^5J_{13C-31P}$ 3.1 Hz, *p*-Ar_C), 132.83 (t, $^2J_{31P-13C}$ 3.3 Hz, *ipso*-Ar_C), 104.77 (t, $^3J_{13C-31P}$ 4.6 Hz, Ar_{CH}), 75.28 (t, $^1J_{13C-31P}$ 145.0 Hz, $C[P(O)(OH)_2]_2$).

^{31}P{^{1}H} NMR (δ, ppm, 161.976 MHz, DMSO-d_6): 15.88.

[1-Hydroxy-2-(3-methoxyphenyl)ethane-1,1-diyl]diphosphonic acid,

3-$MeOC_6H_4CH_2C(OH)[P(O)(OH)_2]_2$ (5c)

Obtained using *General Procedure* from 3-$MeOC_6H_4CH_2C(O)Cl$ **4c** (3.44 g, 18.65 mmol) and technical $(Me_3SiO)_3P$ **1** (15.05 g containing 11.16 g, 37.31 mmol of **1**). Yield: 30% (1.75 g). White powder.

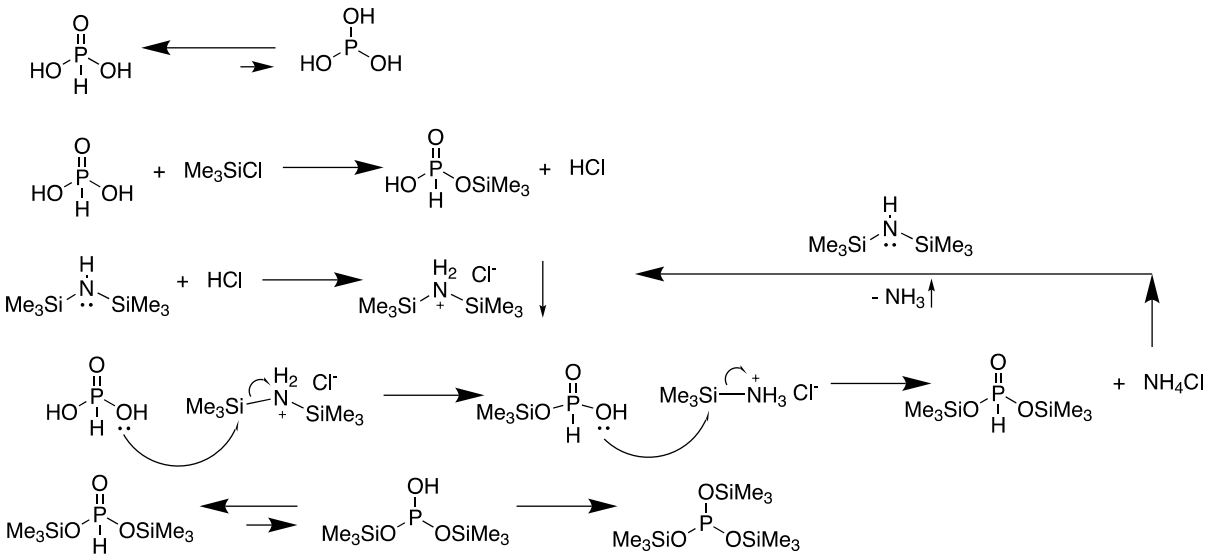
Elemental analysis: Calc. for $C_9H_{14}O_8P_2$ (312.1502): C 34.63, H 4.52. Found: C 34.41, H 4.38.

^{1}H NMR (δ, ppm, 400.130 MHz, DMSO-d_6): 8.65 (br s, 5H, 5OH), 7.09-7.03 (m, 1H, Ar_H), 6.97 (br s, 1H, Ar_H), 6.92 (d, *J* 7.6 Hz, 1H, Ar_H), 6.68 (dd, *J* 8.2 Hz, *J* 2.6 Hz, 1H, Ar_H), 3.02 (s, 3H, OMe), 3.14 (t, $^1J_{13C-31P}$ 134.0 Hz, CP_2).

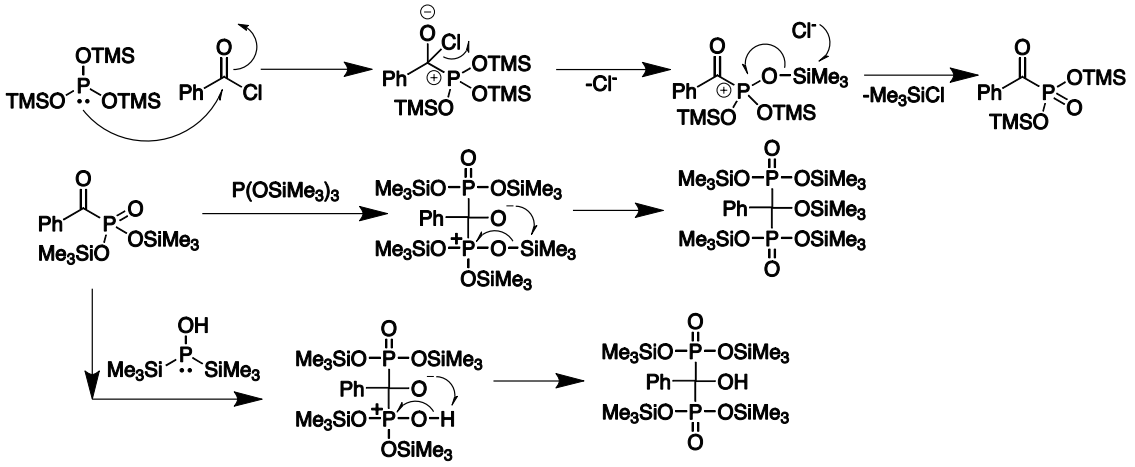
^{13}C{^{1}H} NMR (δ, ppm, 100.613 MHz, DMSO-d_6): 158.16 (Ar_C), 127.75, 123.87 (Ar_C), 120.57, 117.08 (Ar_C), 111.19 (br s, Ar_{CH}), 73.29 (t, $^1J_{13C-31P}$ 140.6 Hz, $C[P(O)(OH)_2]_2$), 54.71 (OMe), 38.50 (br s, CH_2).

^{31}P{^{1}H} NMR (δ, ppm, 161.976 MHz, DMSO-d_6): 19.42.

Mechanism of the formation of $(Me_3SiO)_3P$ (1)



Mechanism of the formation of (hydroxymethyl)phosphonates (using benzoyl chloride)



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NMR Spectra of the Compounds Obtained

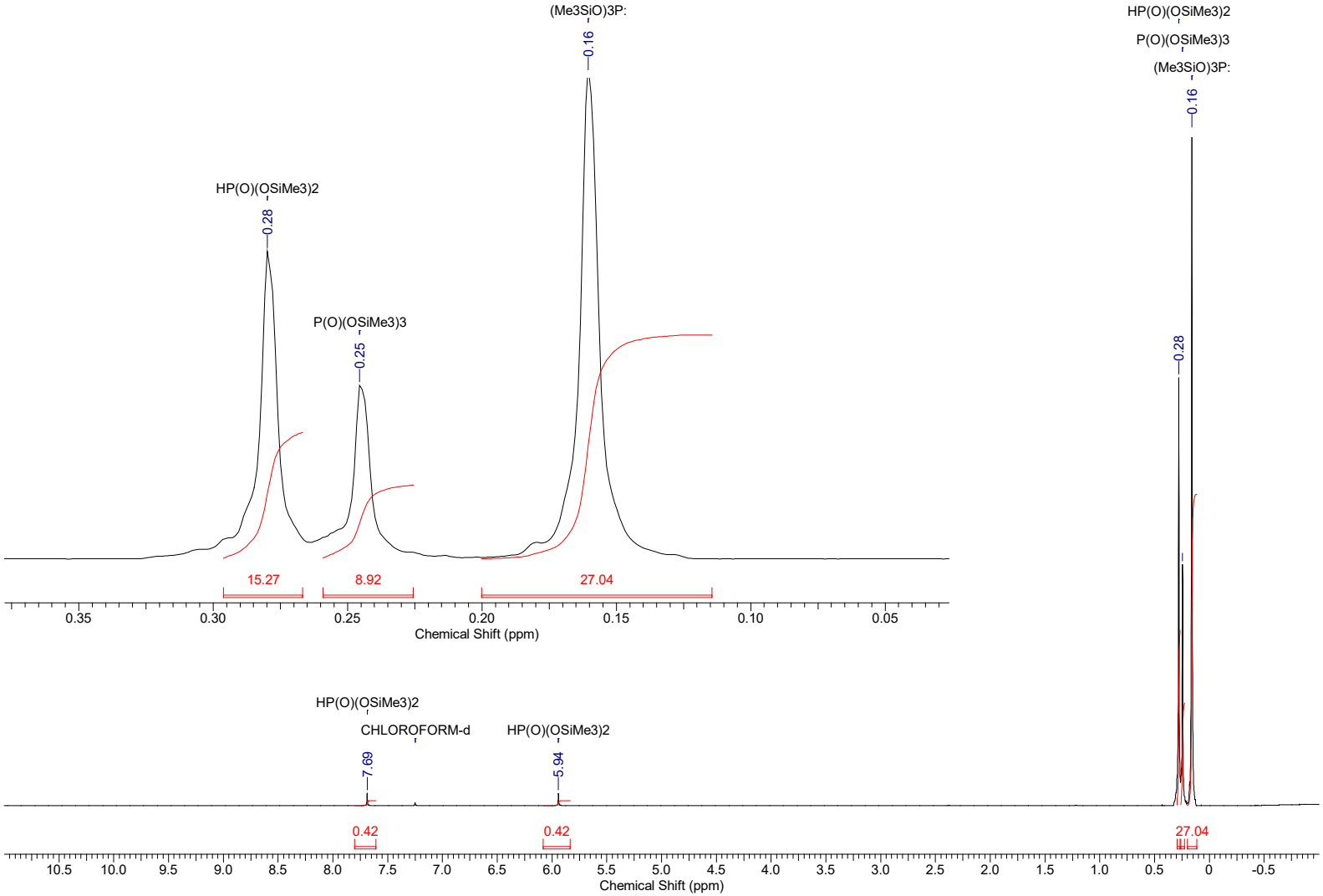

Fig. S1. ^{1}H NMR spectrum of technical $(Me_3SiO)_3P$ (**1**) (mixture of $(Me_3SiO)_3P$ (**1**), $HP(O)(OSiMe_3)_2$ (**2**), $P(O)(OSiMe_3)_3$ (**3**)) ($CDCl_3$, RT).

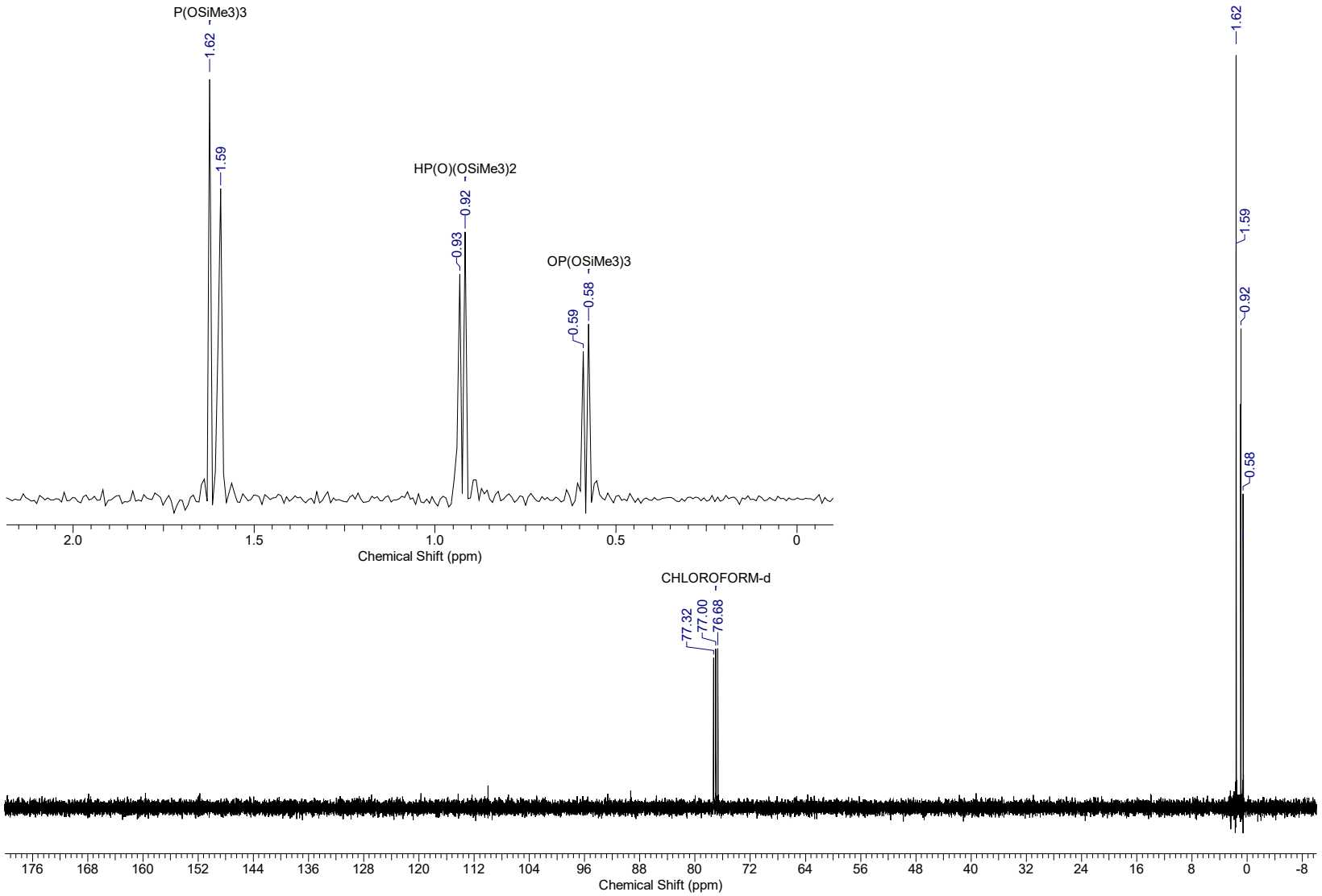

Fig. S2. $^{13}C\{^{1}H\}$ NMR spectrum of technical $(Me_3SiO)_3P$ (**1**) (mixture of $(Me_3SiO)_3P$ (**1**), $HP(O)(OSiMe_3)_2$ (**2**), $P(O)(OSiMe_3)_3$ (**3**)) ($CDCl_3$, RT).

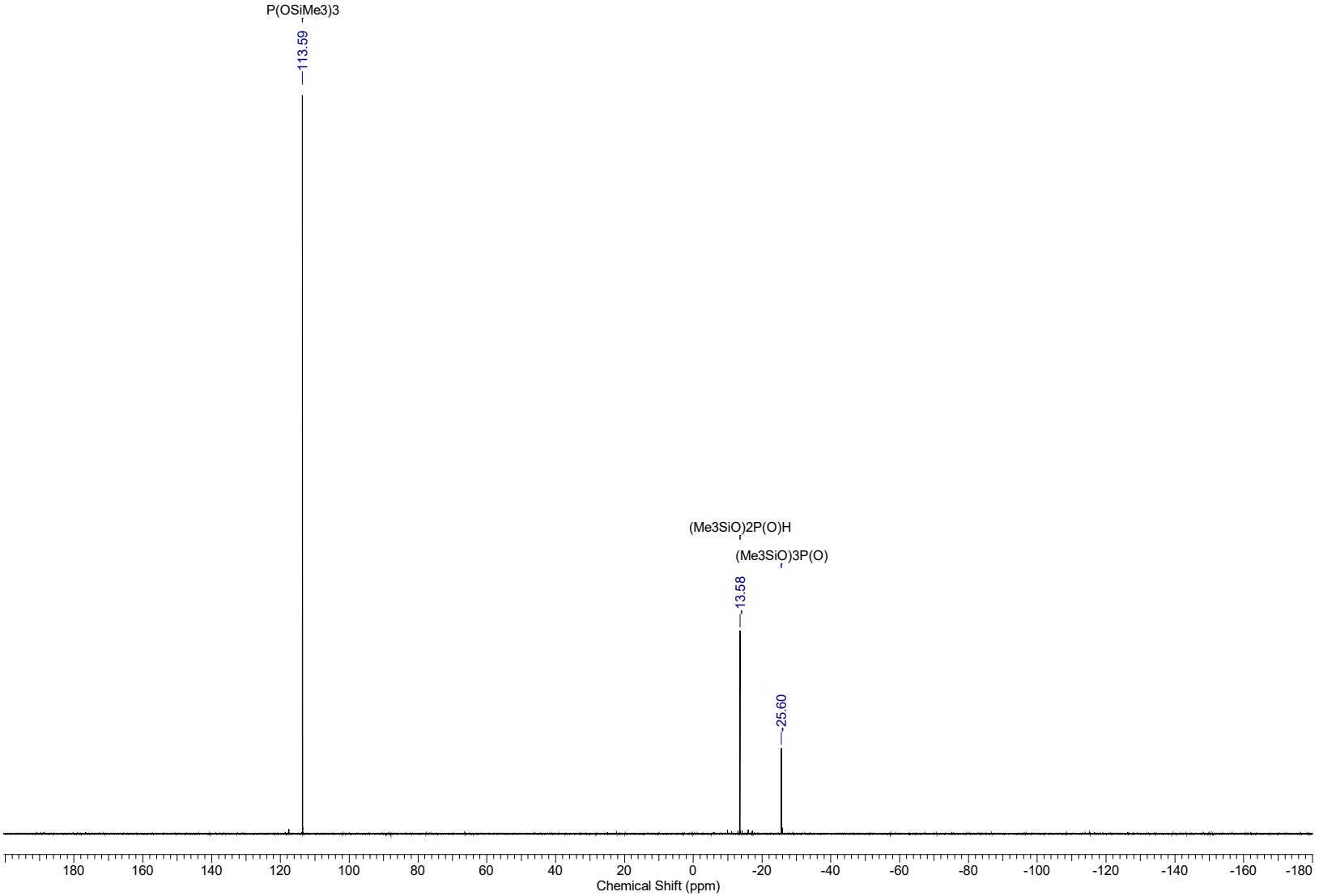

Fig. S3. $^{31}P\{^{1}H\}$ NMR spectrum of technical $(Me_3SiO)_3P$ (**1**) (mixture of $(Me_3SiO)_3P$ (**1**), $HP(O)(OSiMe_3)_2$ (**2**), $P(O)(OSiMe_3)_3$ (**3**)) ($CDCl_3$, RT).

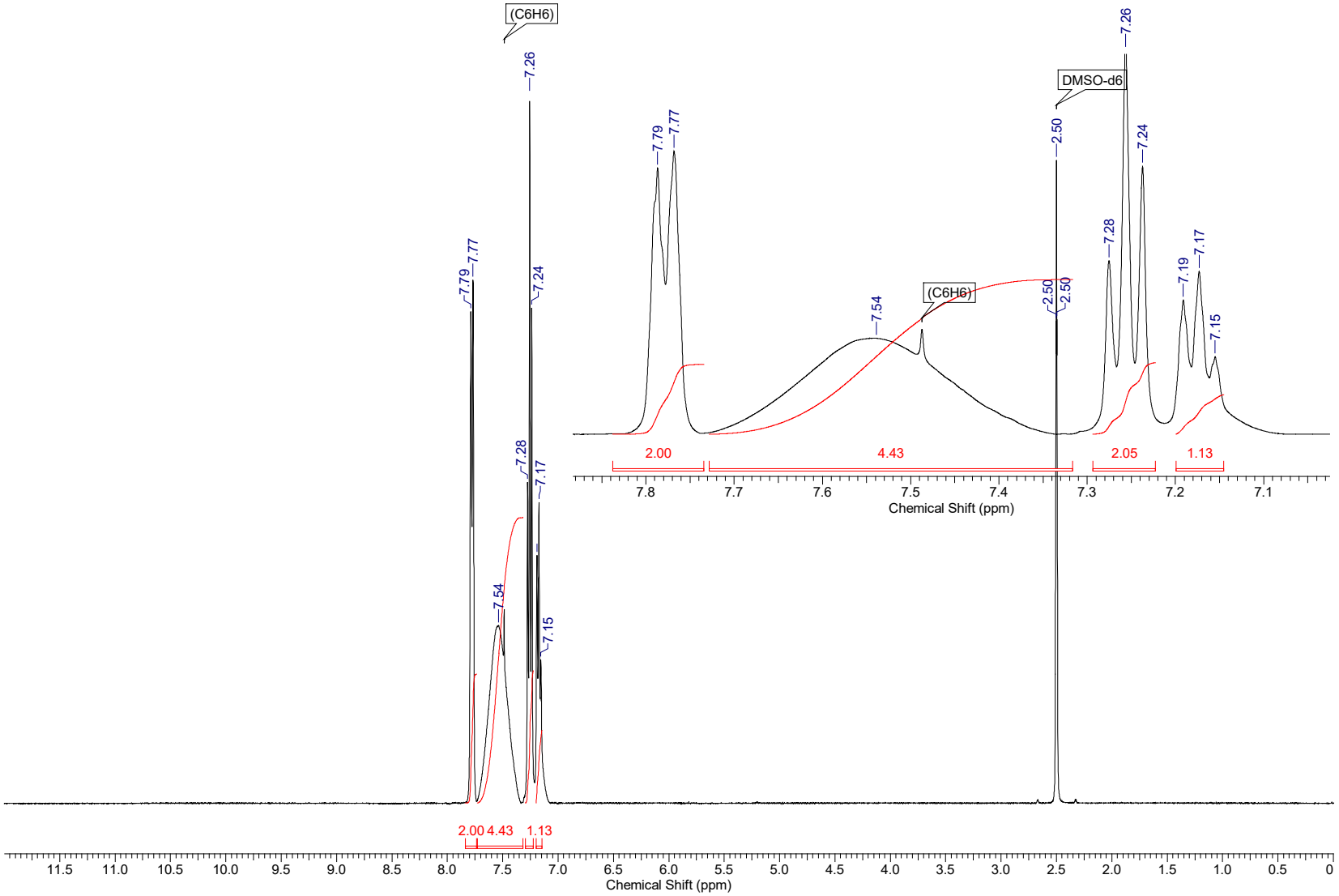

Fig. S4. ^{1}H NMR spectrum of PhC(OH)[P(O)(OH)$_2$]$_2$ (**5a**) (DMSO-d$_6$, RT).

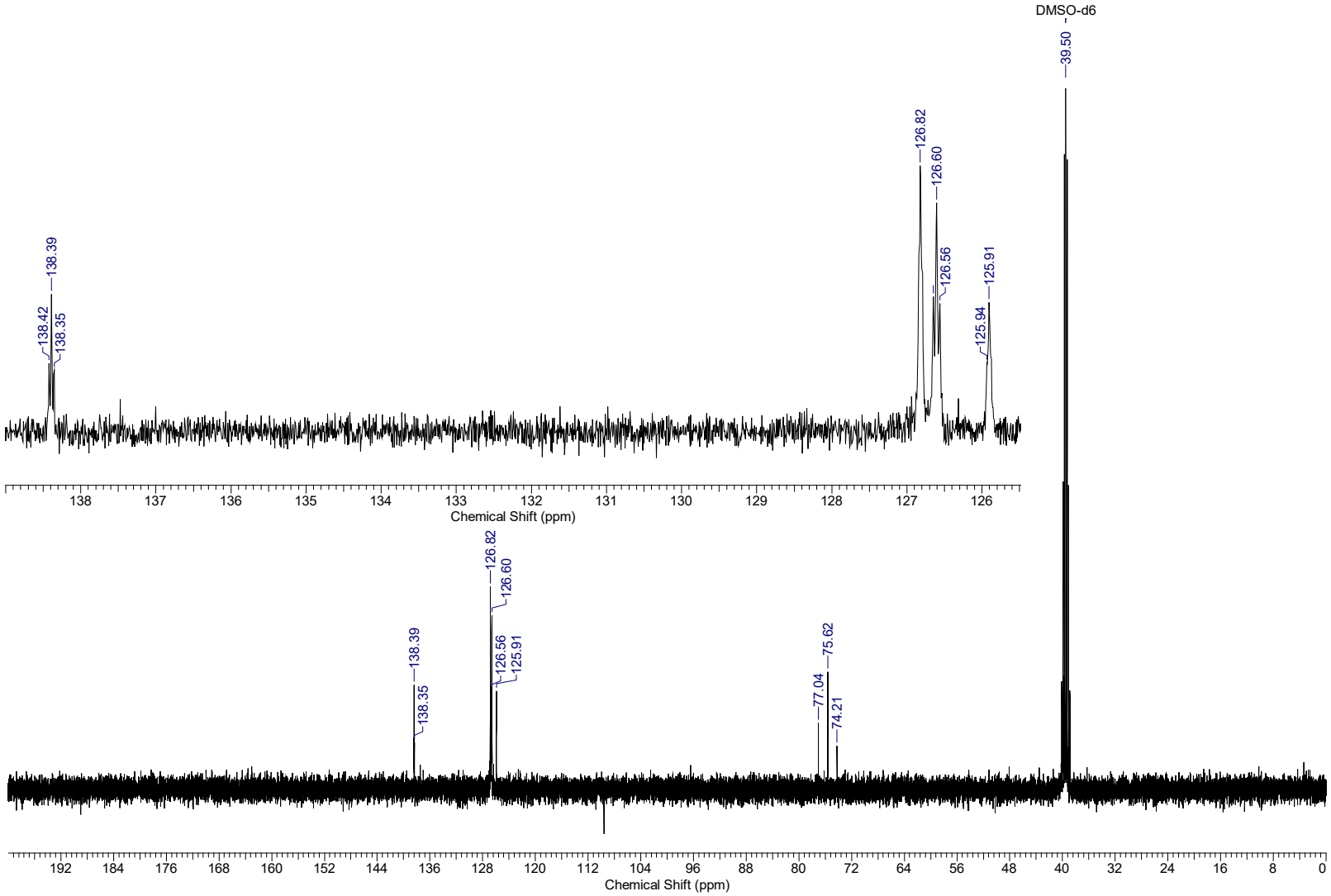

Fig. S5. $^{13}C\{^{1}H\}$ NMR spectrum of $PhC(OH)[P(O)(OH)_2]_2$ (**5a**) (DMSO-d_6, RT).

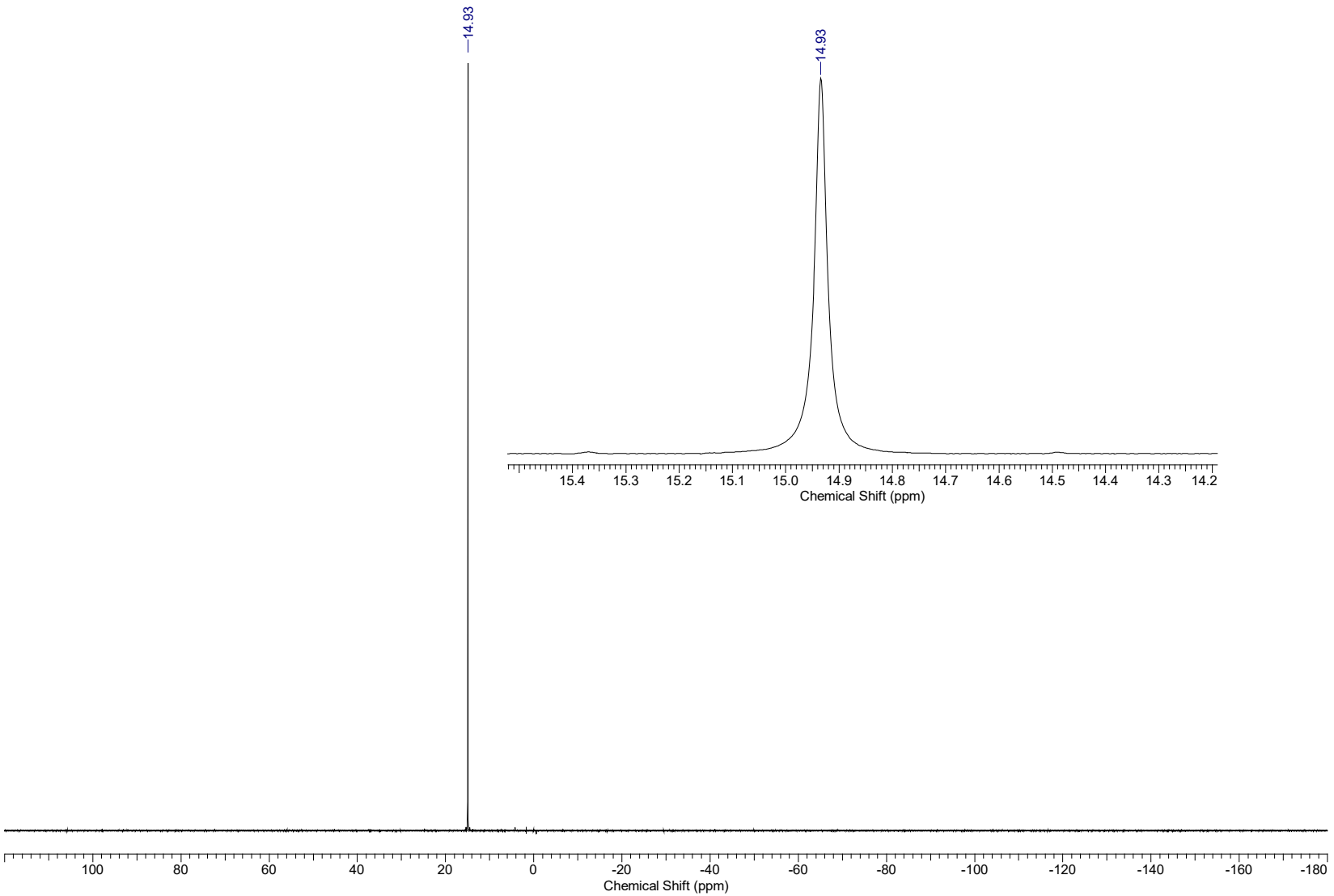

Fig. S6. $^{31}P\{^{1}H\}$ NMR spectrum of $PhC(OH)[P(O)(OH)_2]_2$ (**5a**) (DMSO-d_6, RT).

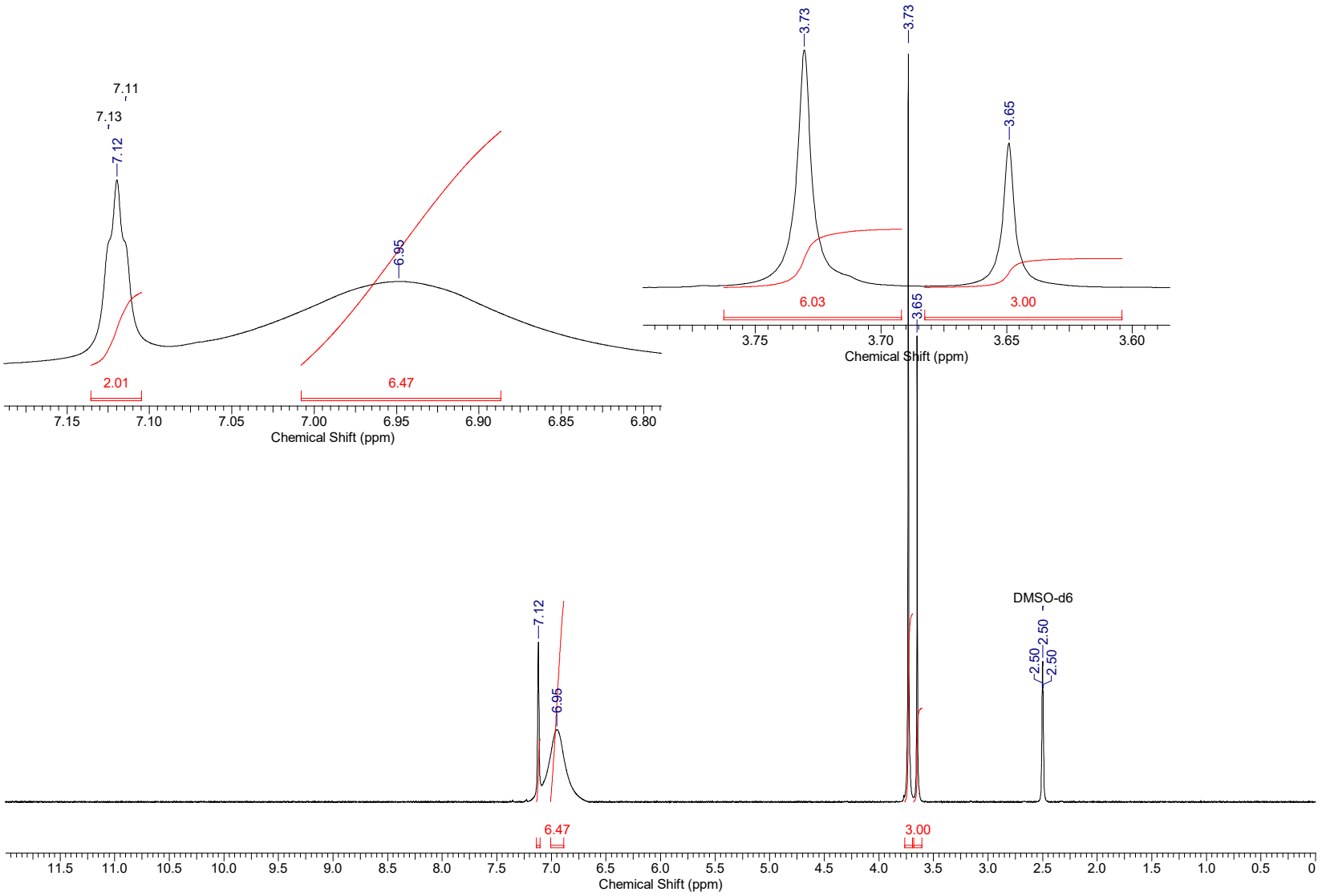

Fig. S7. ^{1}H NMR spectrum of 3,4,5-$(MeO)_3C_6H_2C(OH)[P(O)(OH)_2]_2$ (**5b**) (DMSO-d_6, RT).

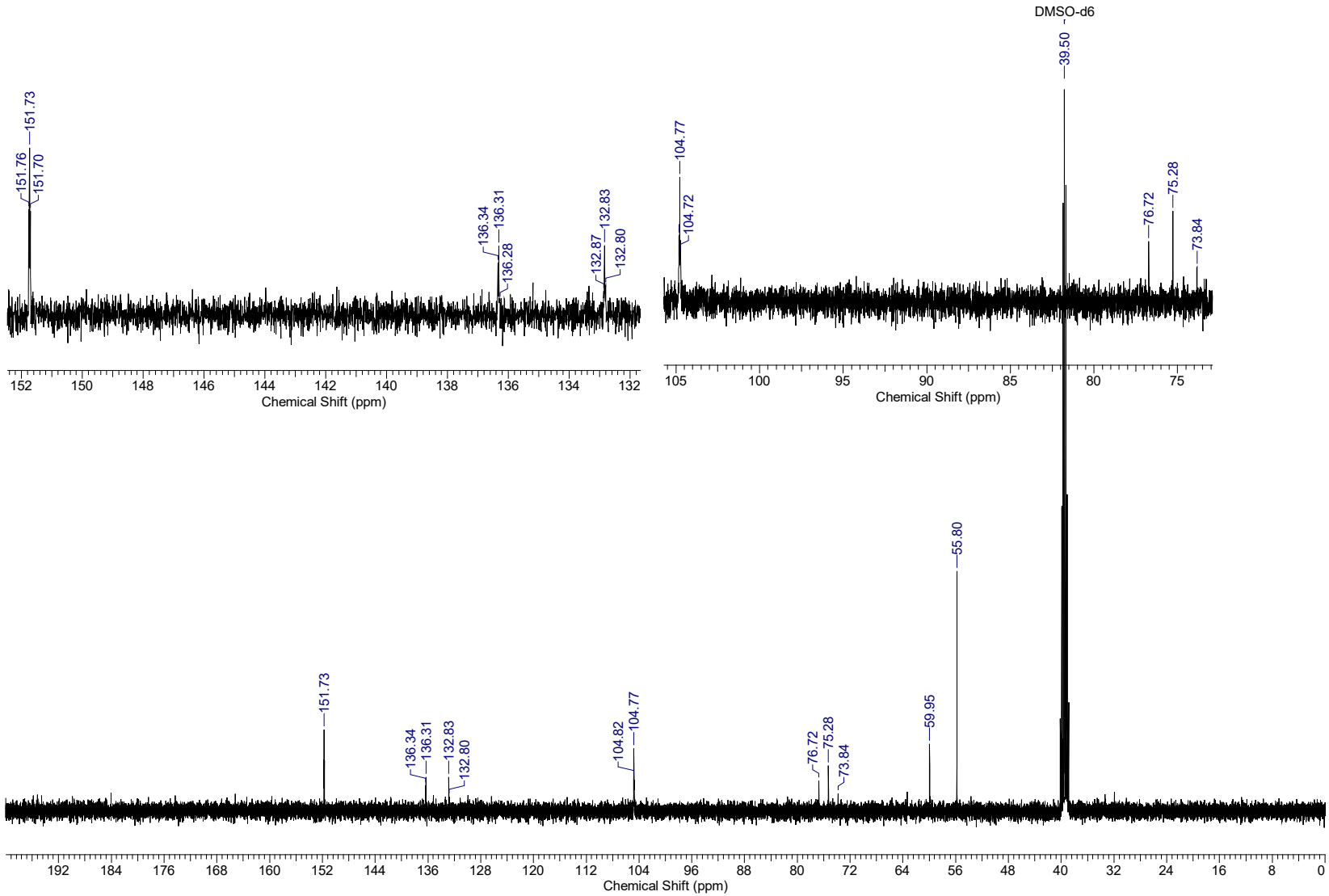

Fig. S8. $^{13}C\{^{1}H\}$ NMR spectrum of 3,4,5-$(MeO)_3C_6H_2C(OH)[P(O)(OH)_2]_2$ (**5b**) (DMSO-d_6, RT).

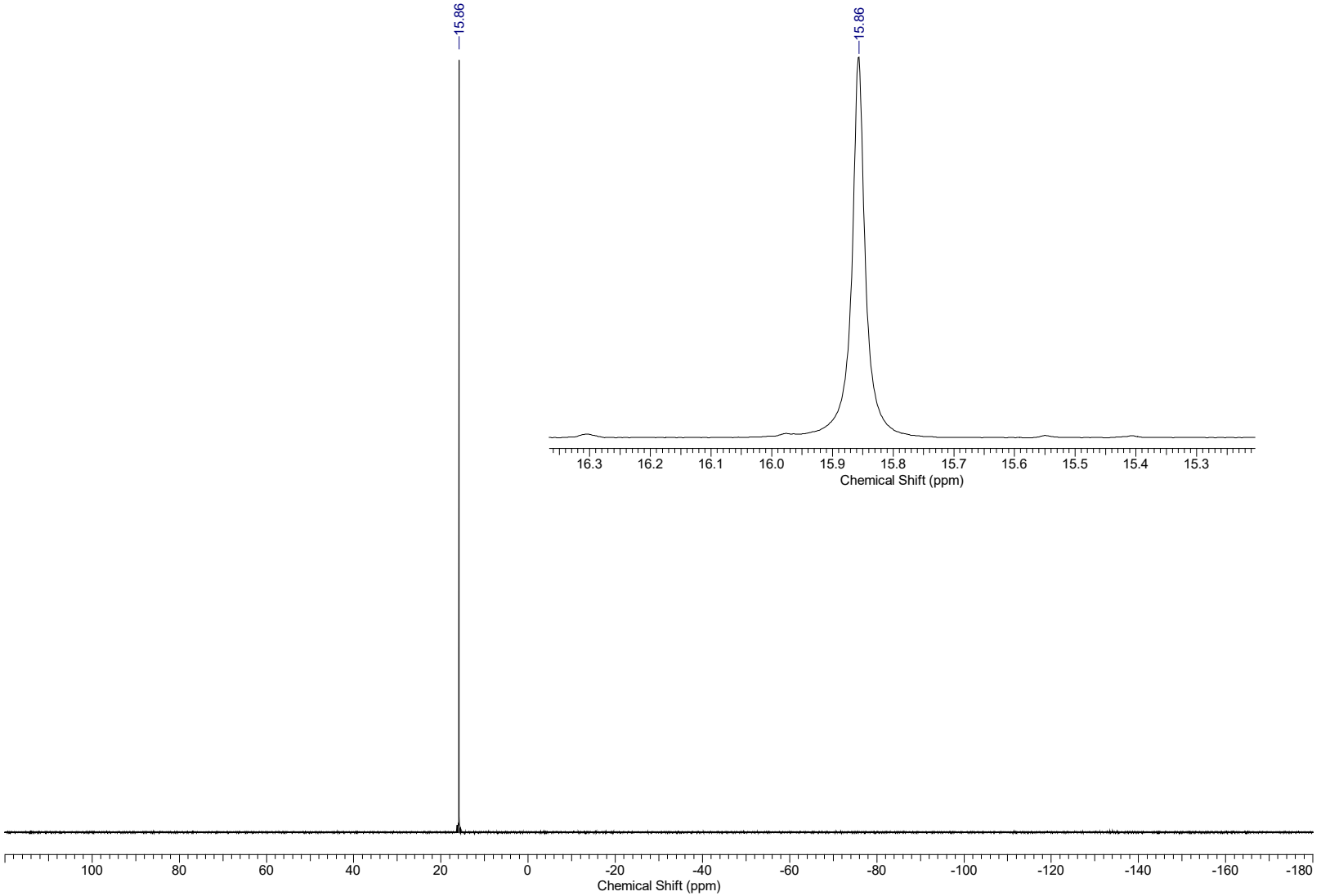

Fig. S9. $^{31}P\{^{1}H\}$ NMR spectrum of 3,4,5-$(MeO)_3C_6H_2C(OH)[P(O)(OH)_2]_2$ (**5b**) (DMSO-d_6, RT).

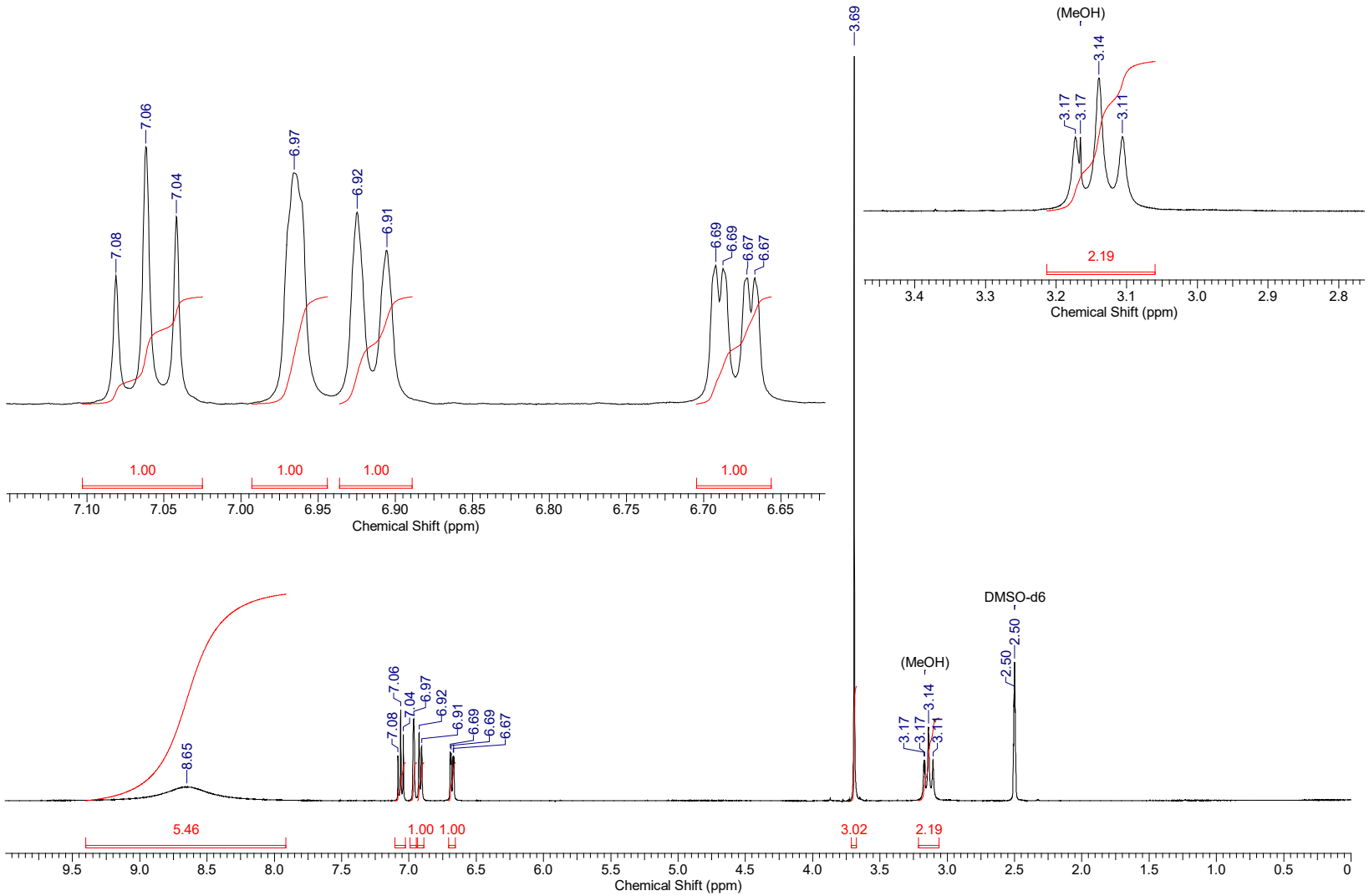

Fig. S10. ^{1}H NMR spectrum of 3-$MeOC_6H_4CH_2C(OH)[P(O)(OH)_2]_2$ (**5c**) (DMSO-d_6, RT).

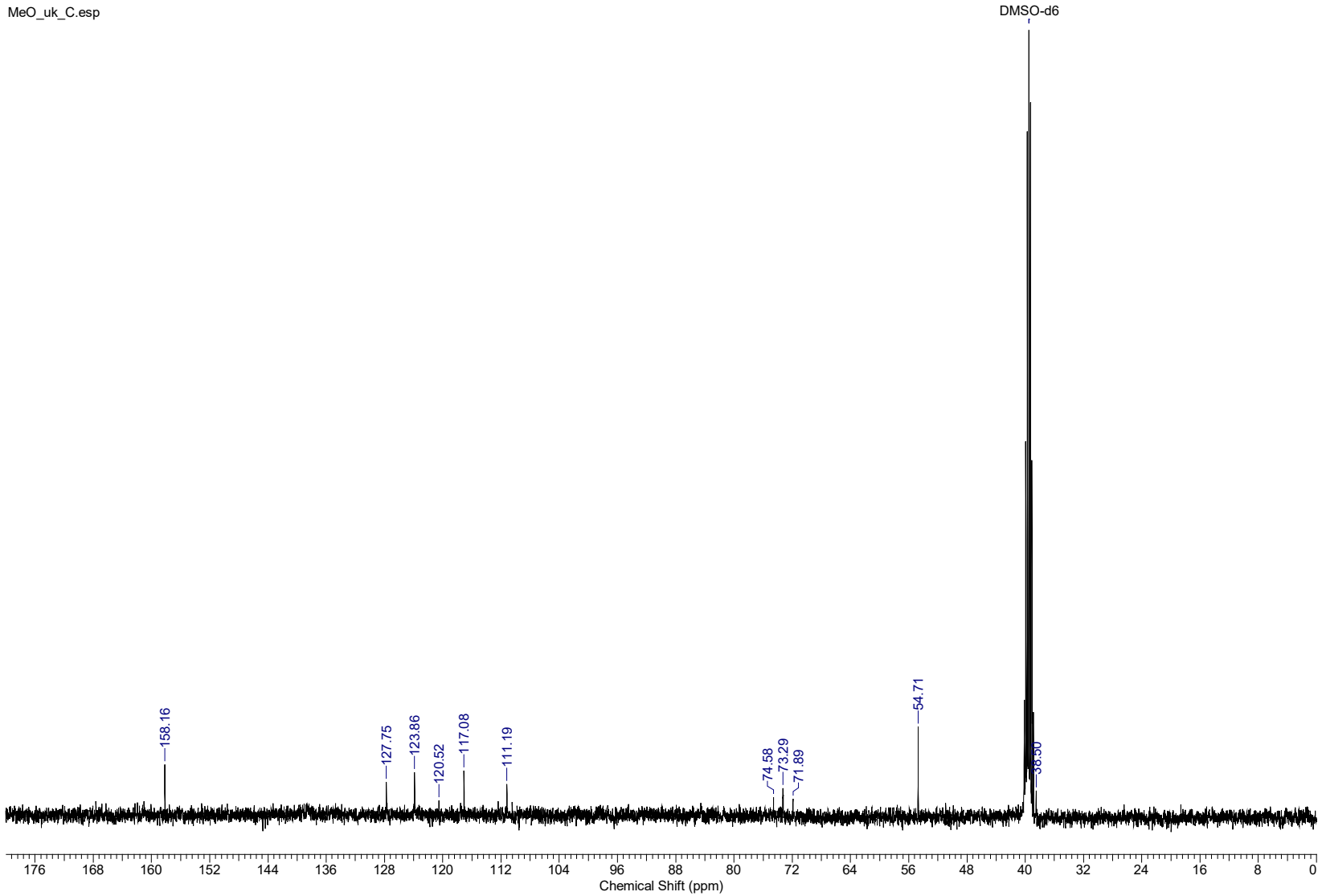

Fig. S11. $^{13}C\{^{1}H\}$ NMR spectrum of 3-$MeOC_6H_4CH_2C(OH)[P(O)(OH)_2]_2$ (**5c**) (DMSO-d_6, RT).

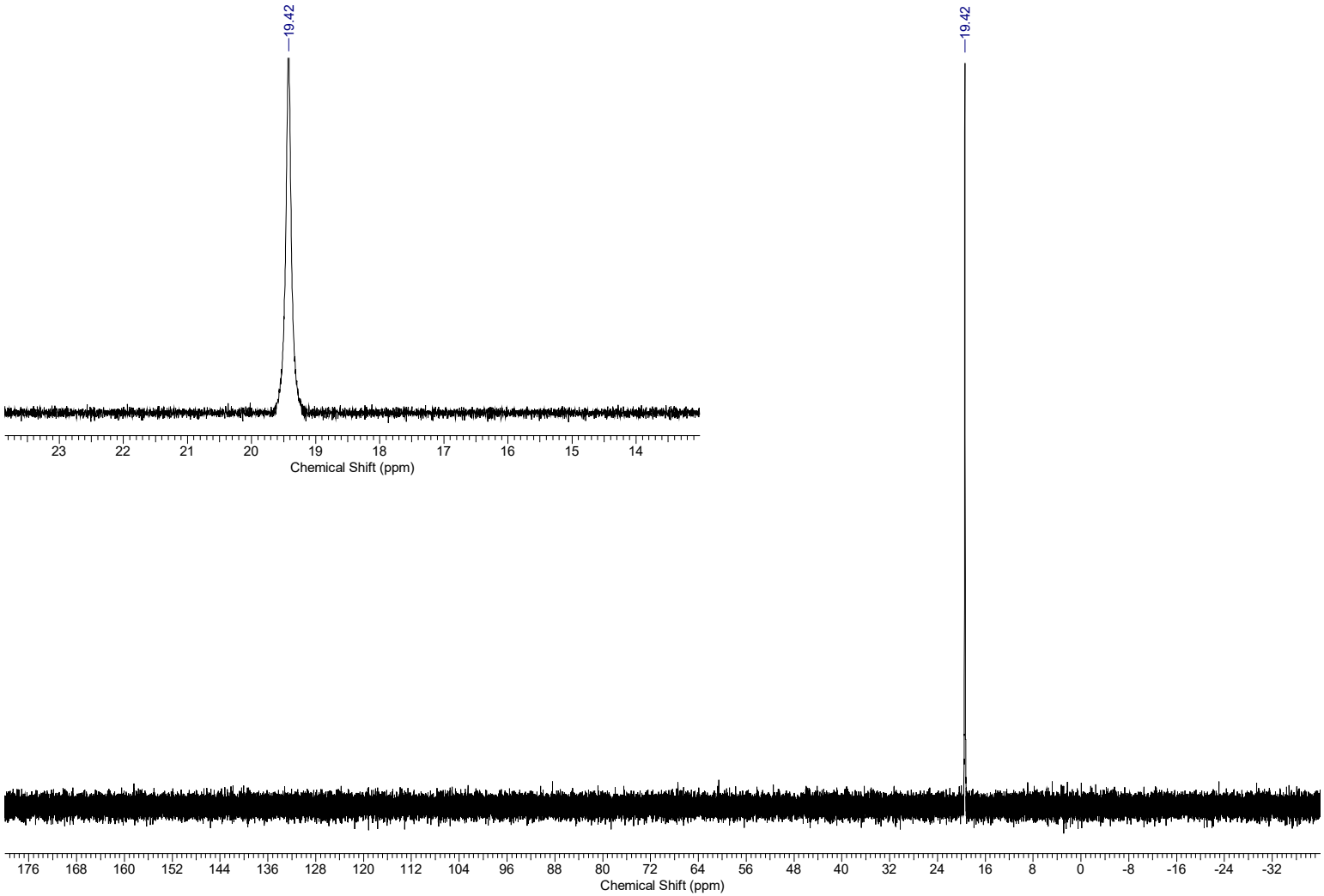

Fig. S12. $^{31}P\{^{1}H\}$ NMR spectrum of 3-$MeOC_6H_4CH_2C(OH)[P(O)(OH)_2]_2$ (**5c**) (DMSO-d_6, RT).