Supplementary material

Synthesis and stability of 1-aminoalkylphosphonic acid quaternary ammonium salts

Anna Brol and Tomasz K. Olszewski

Faculty of Chemistry, Wrocław University of Science and Technology, ul. Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland.

Correspondence to: tomasz.olszewski@pwr.edu.pl

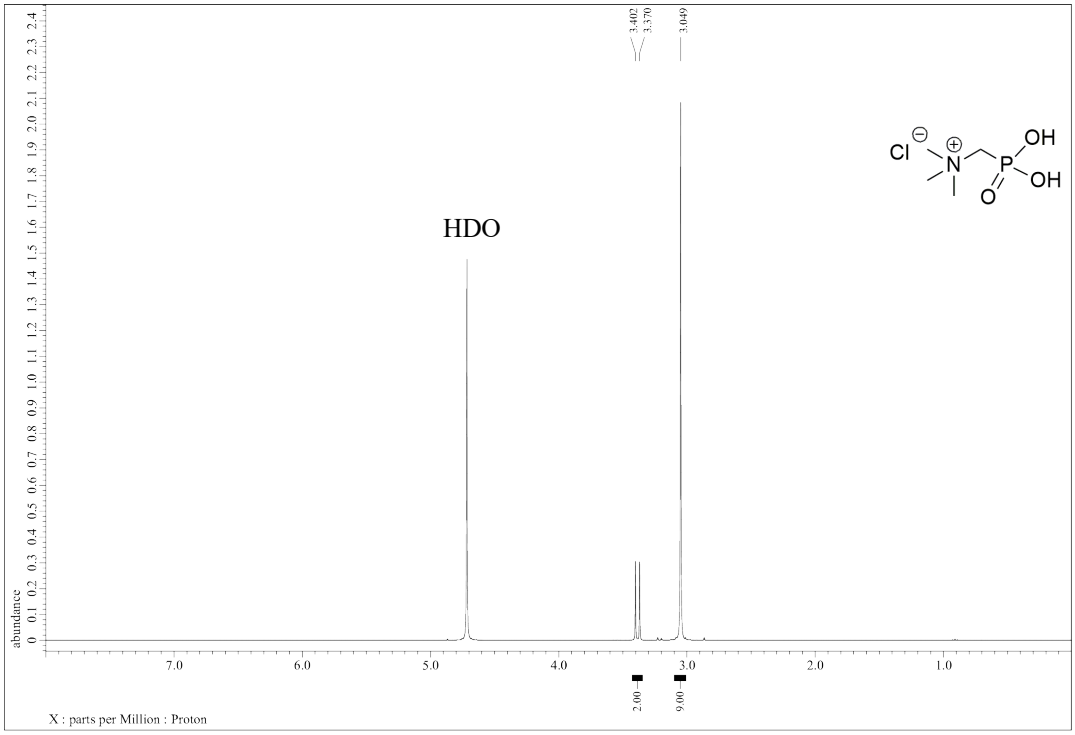
Table of contents

^{1}H, ^{13}C{^{1}H}, ^{31}P NMR Spectra and HRMS Data ... 2
N,N,N-trimethyl-*N*-(phosphonomethyl)ammonium chloride **2'a** ... 2
N,N,N-trimethyl-*N*-(1-phosphonoethyl)ammonium chloride **2'b** ... 4
N,N,N-trimethyl-*N*-(2-methyl-1-phosphonopropyl)ammonium chloride **2'c** ... 6
N,N,N-trimethyl-*N*-[phenyl(phosphono)methyl]amonium chloride **2'd** ... 8
N,N,N-trimethyl-*N*-(1-methyl-1-phosphonoethyl)ammonium chloride **2'e** ... 10
N,N,N-trimethyl-*N*-(1-phenyl-1-phosphononoethyl)ammonium chloride **2'f** ... 12
N,N,N-trimethyl-*N*-(1-methyl-2-phenyl-1-phosphonoethyl)ammonium chloride **2'g** ... 14
N,N,N-trimethyl-*N*-(1-phosphonocyclopentyl)ammonium chloride **2'i** ... 18
N,N,N-trimethyl-*N*-[(4-methoxyphenyl)(phosphono)methyl]amonium chloride **2'j** ... 20
Identification of degradation products ... 22
Spectra of reference materials ... 23
1-Hydroxy-1-phenylethylphosphonic acid **6** (prepared and used as reference material) ... 23
1-Hydroxycyclohexylphosphonic acid **10** (prepared and used as reference material) ... 25
Spectra of reaction mixtures after heating with NaOH ... 27
Experimental Section ... 32

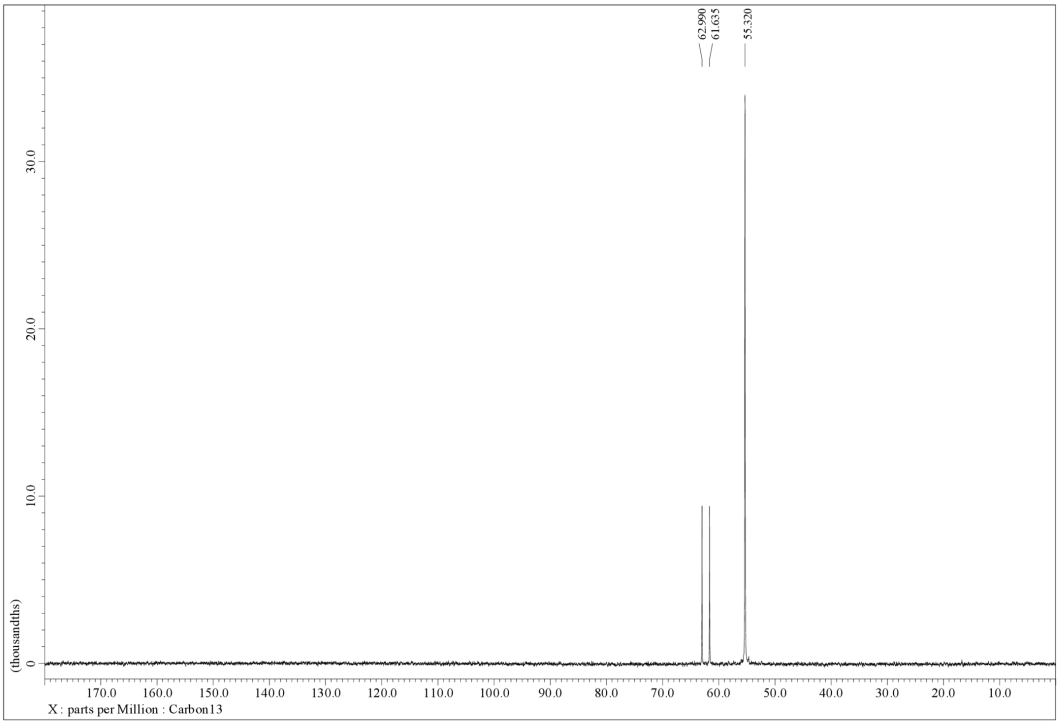
^{1}H, $^{13}C\{^{1}H\}$, ^{31}P NMR Spectra and HRMS Data

N,N,N-trimethyl-*N*-(phosphonomethyl)ammonium chloride **2'a**

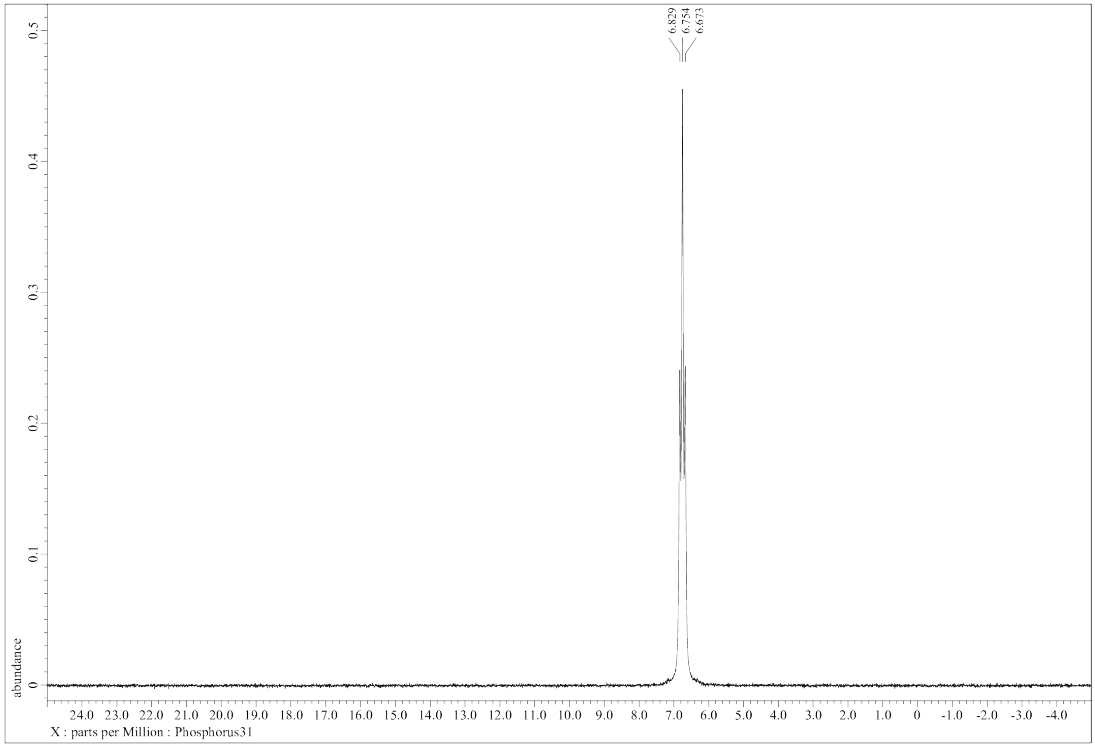
^{1}H NMR (50mg, 600uL D_2O, 400MHz) spectrum of **2'a**



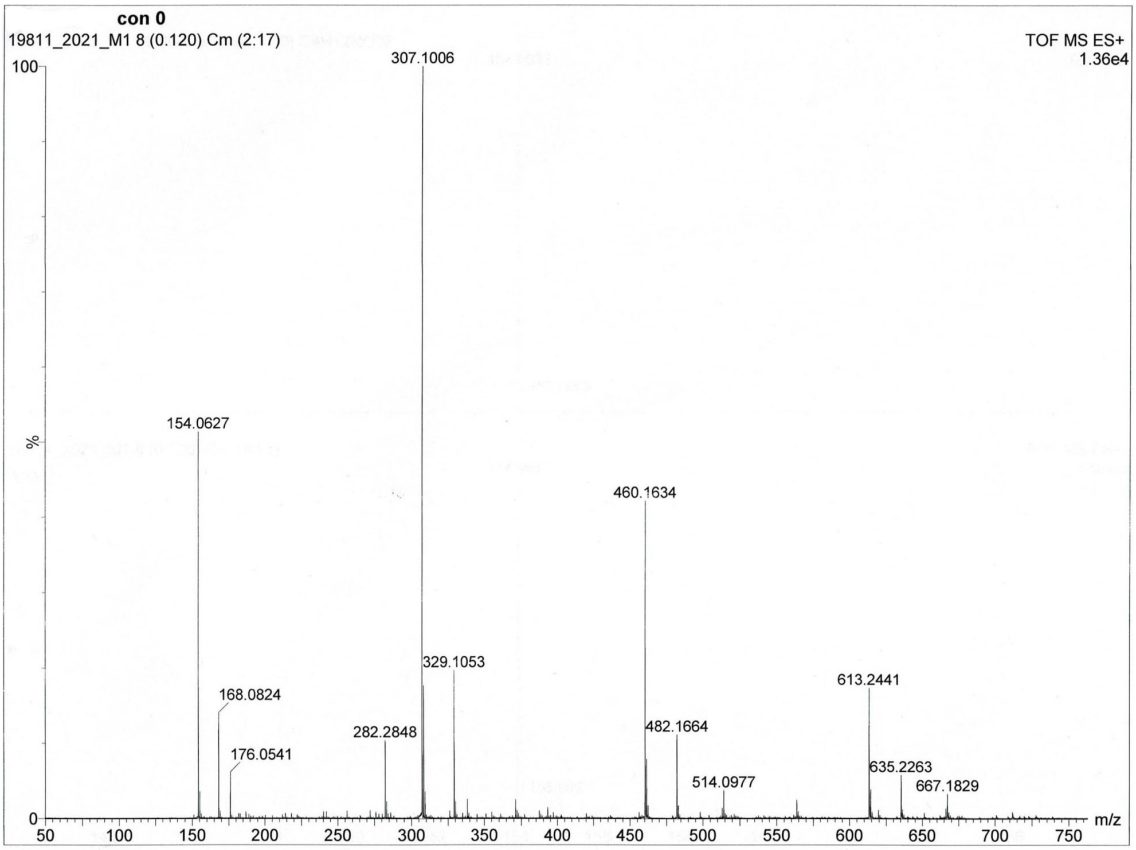
$^{13}C\{^{1}H\}$ NMR (50mg, 600uL D_2O, 100MHz) spectrum of **2'a**



^{31}P NMR (50mg, 600uL D_2O, 162MHz) spectrum of **2'a**

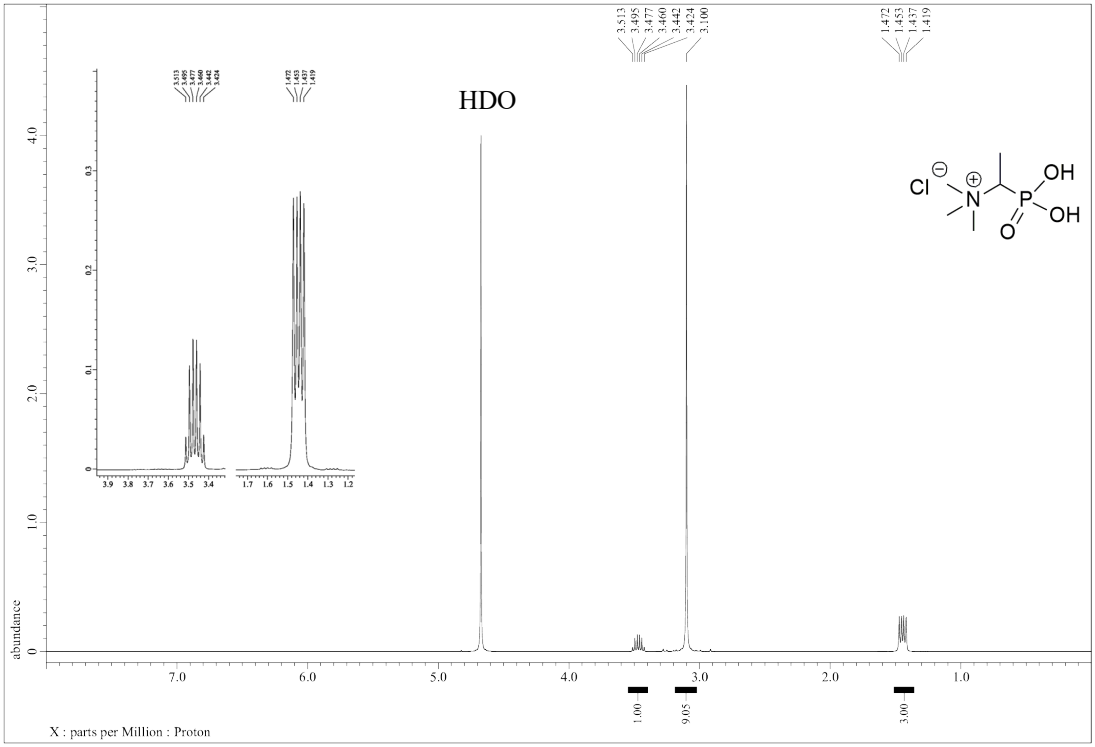


HRMS (TOF-ES+) calcd for $C_4H_{12}NO_3P$ [M+H]+ m/z: 154.0633, found: 154.0627

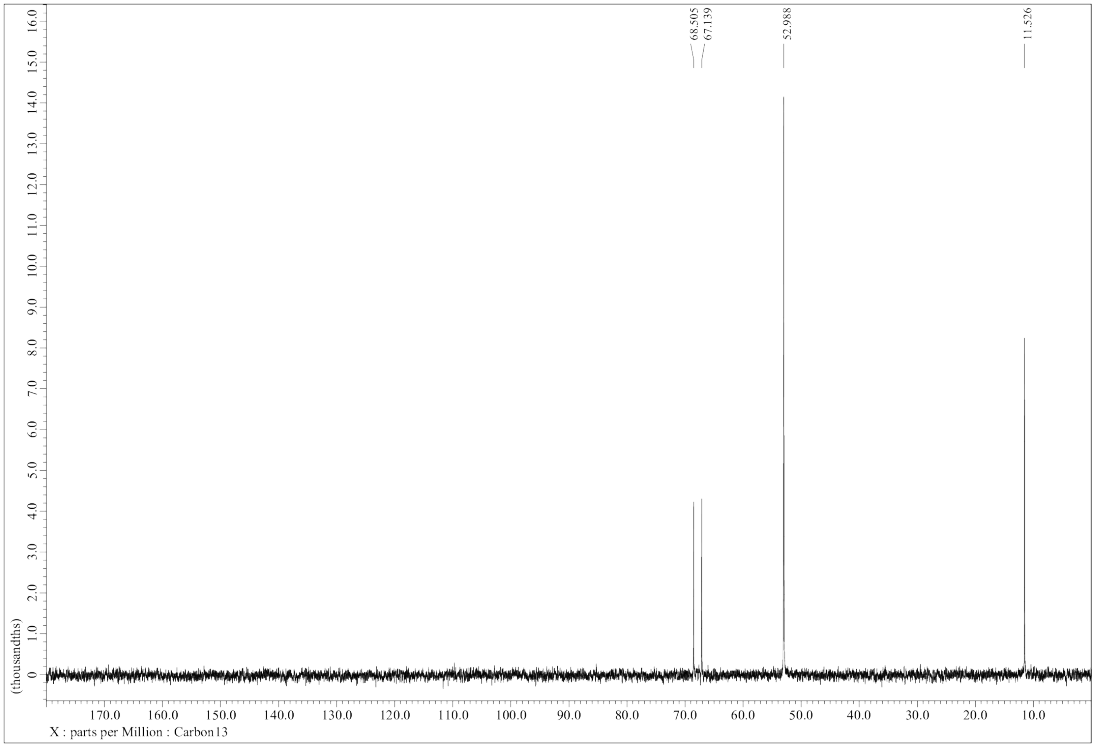


N,N,N-trimethyl-*N*-(1-phosphonoethyl)ammonium chloride **2'b**

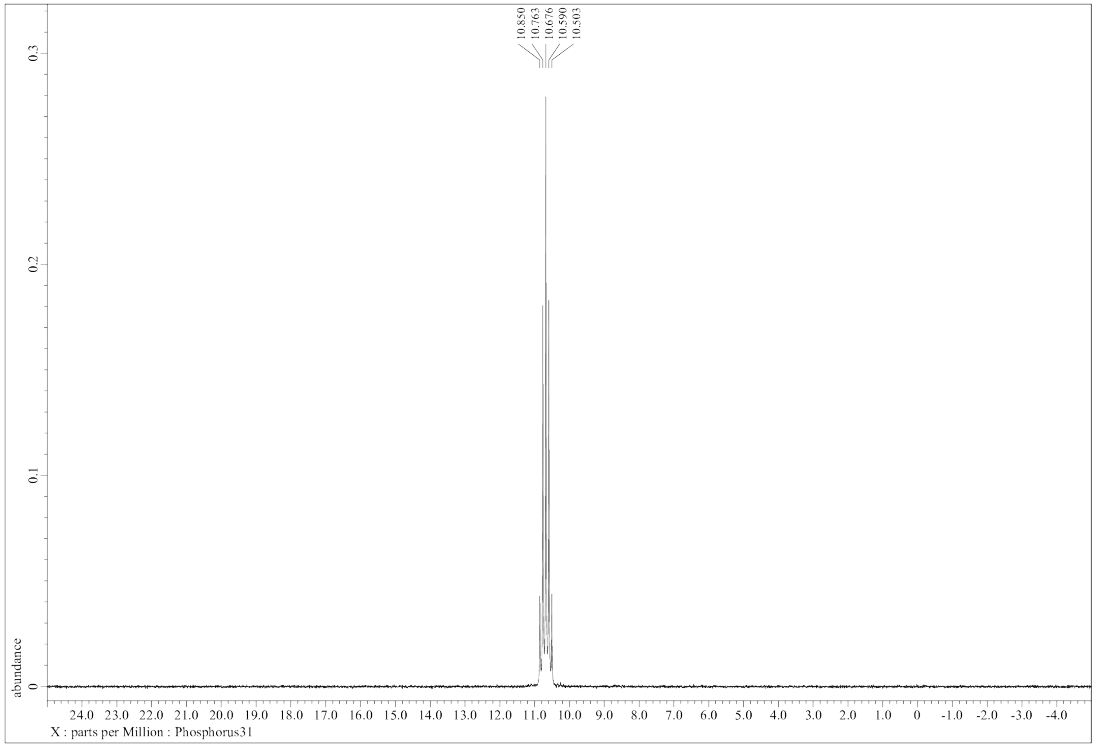
^{1}H NMR (22mg, 600uL D_2O, 400MHz) spectrum of **2'b**



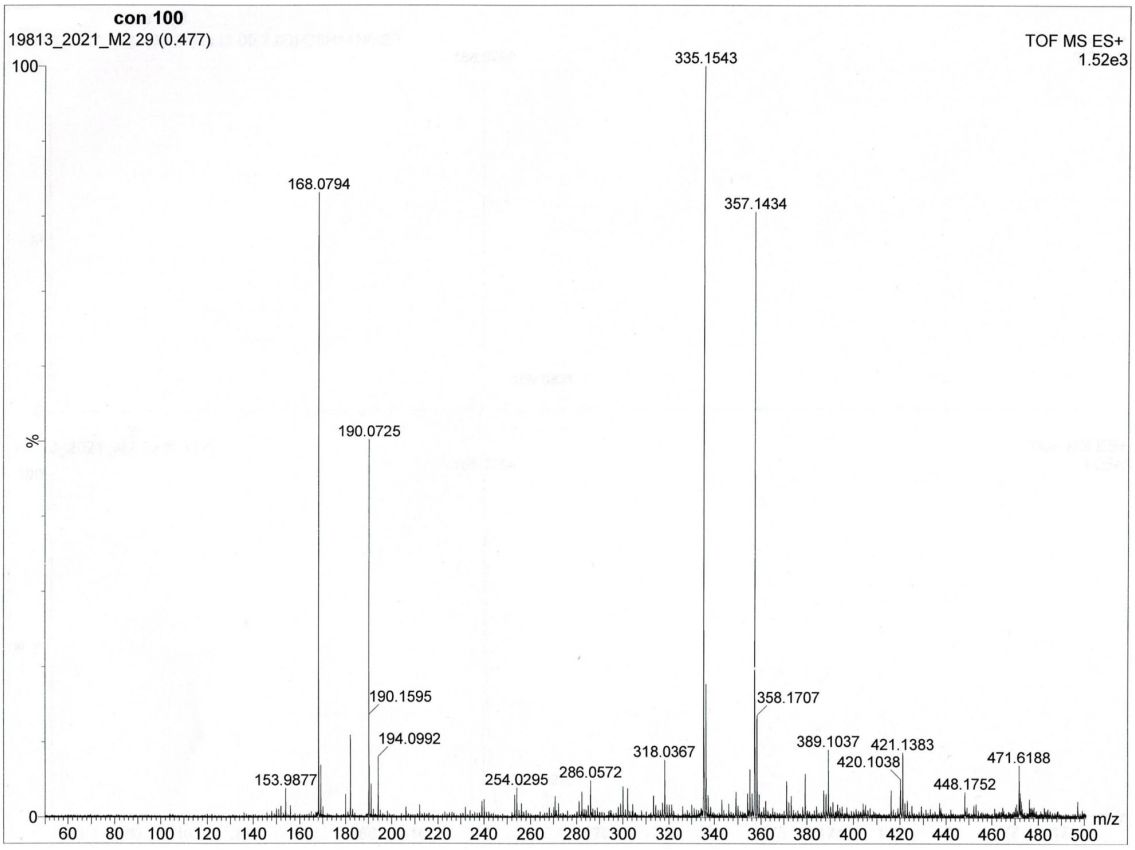
^{13}C{^{1}H} NMR (22mg, 600uL D_2O, 100MHz) spectrum of **2'b**



^{31}P NMR (22mg, 600uL D_2O, 162MHz) spectrum of **2'b**

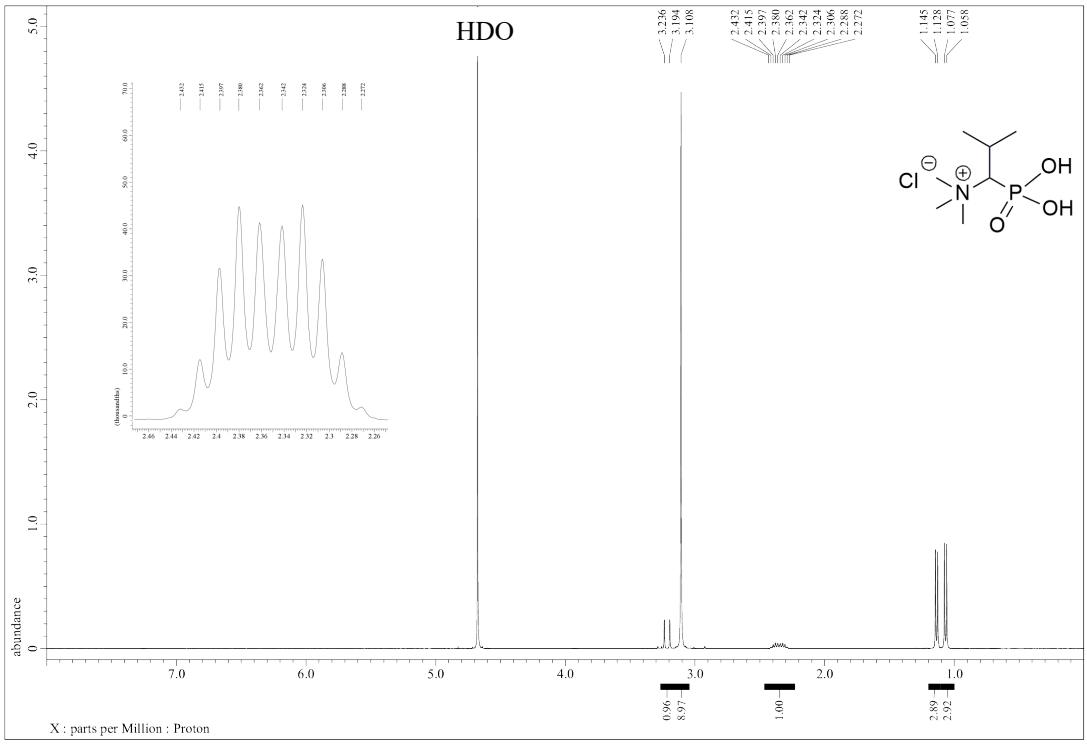


HRMS (TOF-ES+) calcd for $C_5H_{14}NO_3P$ [M+H]+ m/z: 168.0790, found: 169.0794

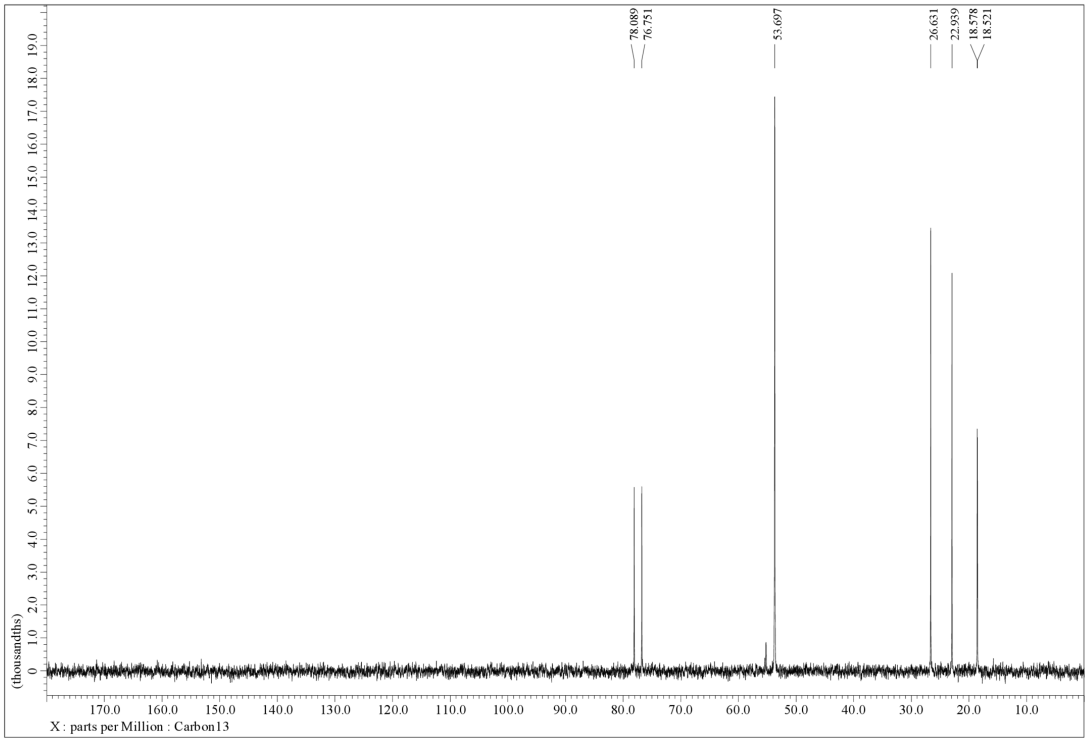


N,N,N-trimethyl-*N*-(2-methyl-1-phosphonopropyl)ammonium chloride **2'c**

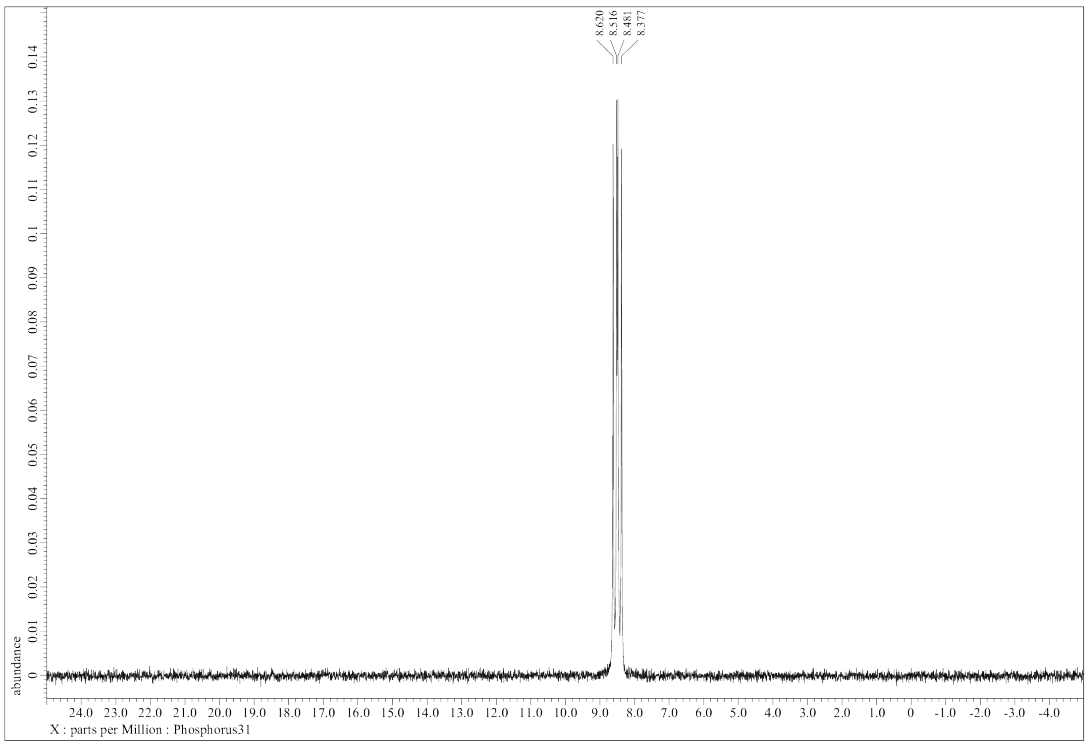
^{1}H NMR (17mg, 600uL D_2O, 400MHz) spectrum of **2'c**



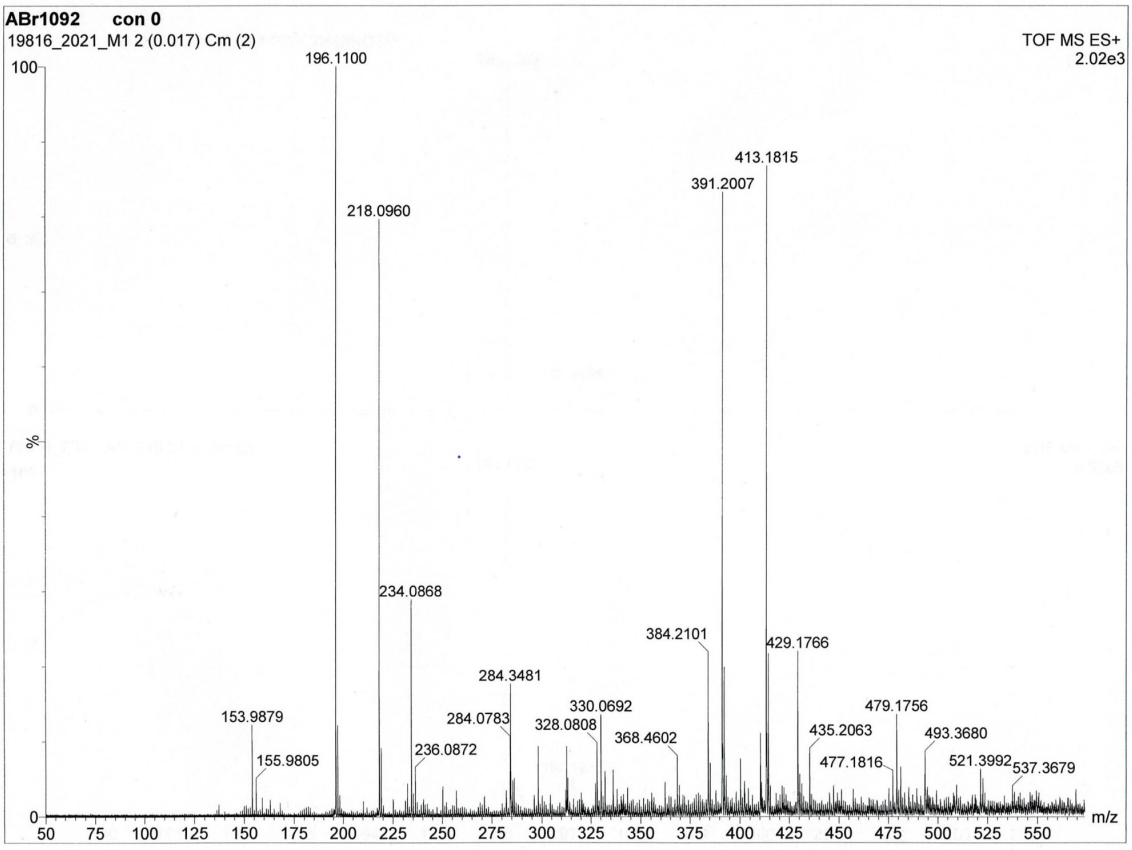
^{13}C{^{1}H} NMR (21mg, 600uL D_2O, 100MHz) spectrum of **2'c**



^{31}P NMR (17mg, 600uL D_2O, 162MHz) spectrum of **2'c**

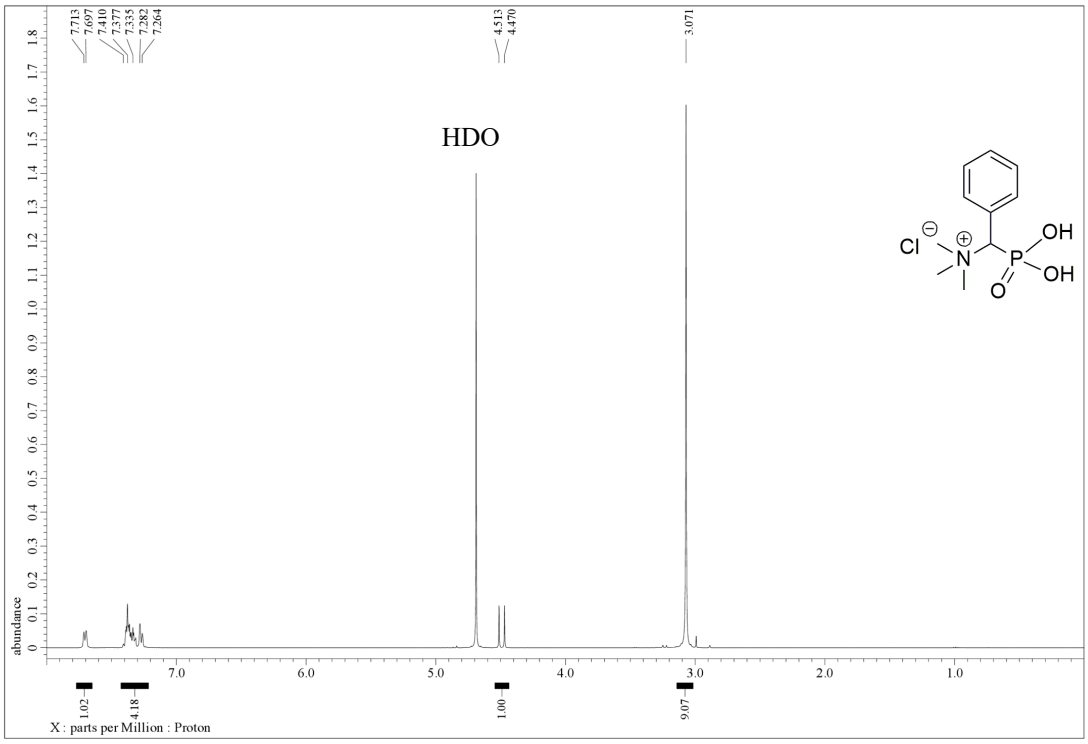


HRMS (TOF-ES+) calcd for $C_7H_{18}NO_3P$ [M+H]+ m/z: 196.1103, found: 196.1100

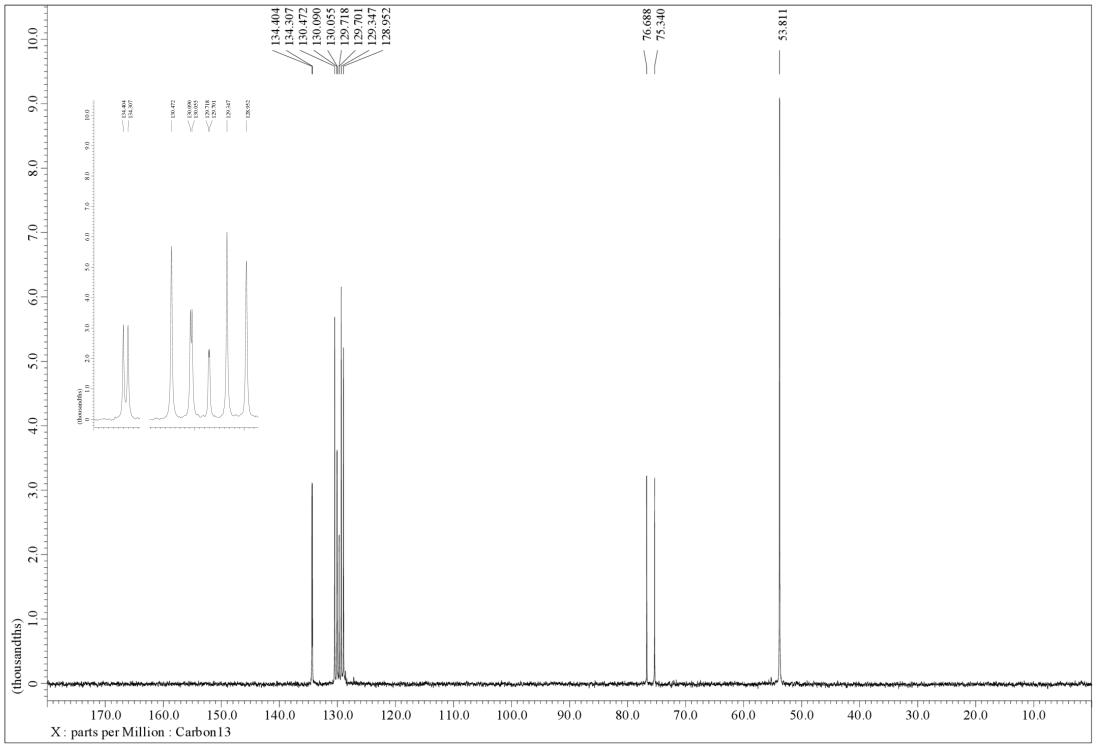


N,N,N-trimethyl-*N*-[phenyl(phosphono)methyl]ammonium chloride **2'd**

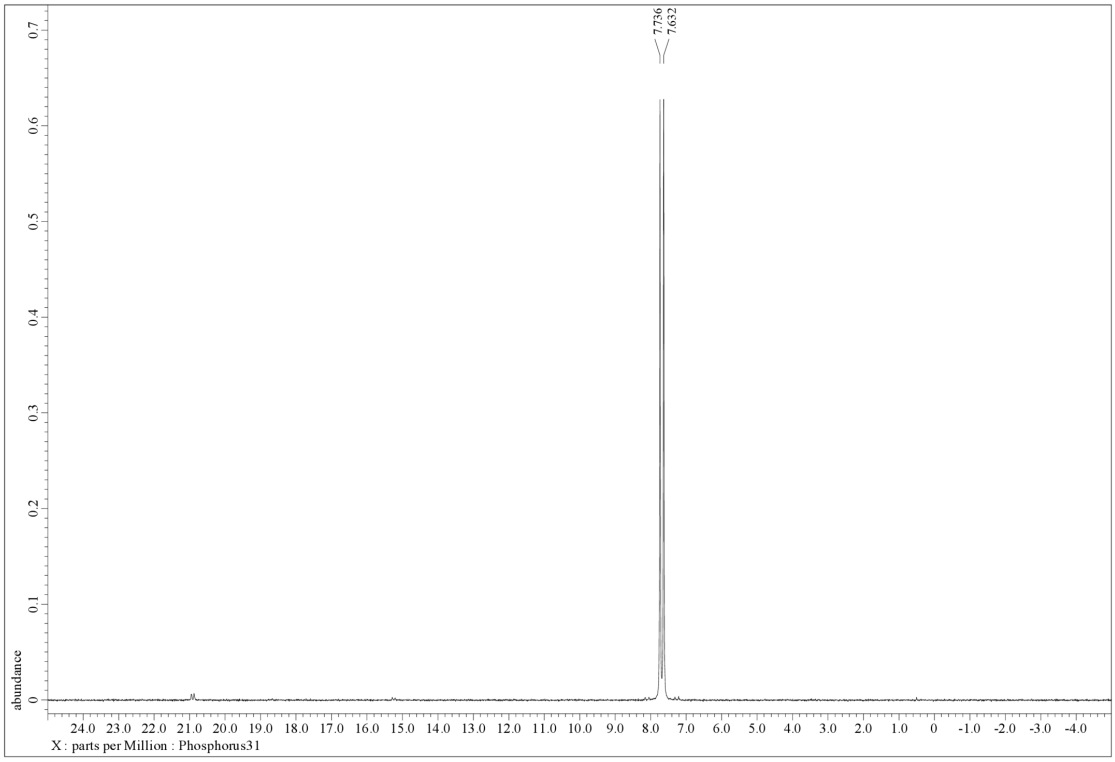
^{1}H NMR (31mg, 550uL D_2O, 400MHz) spectrum of **2'd**



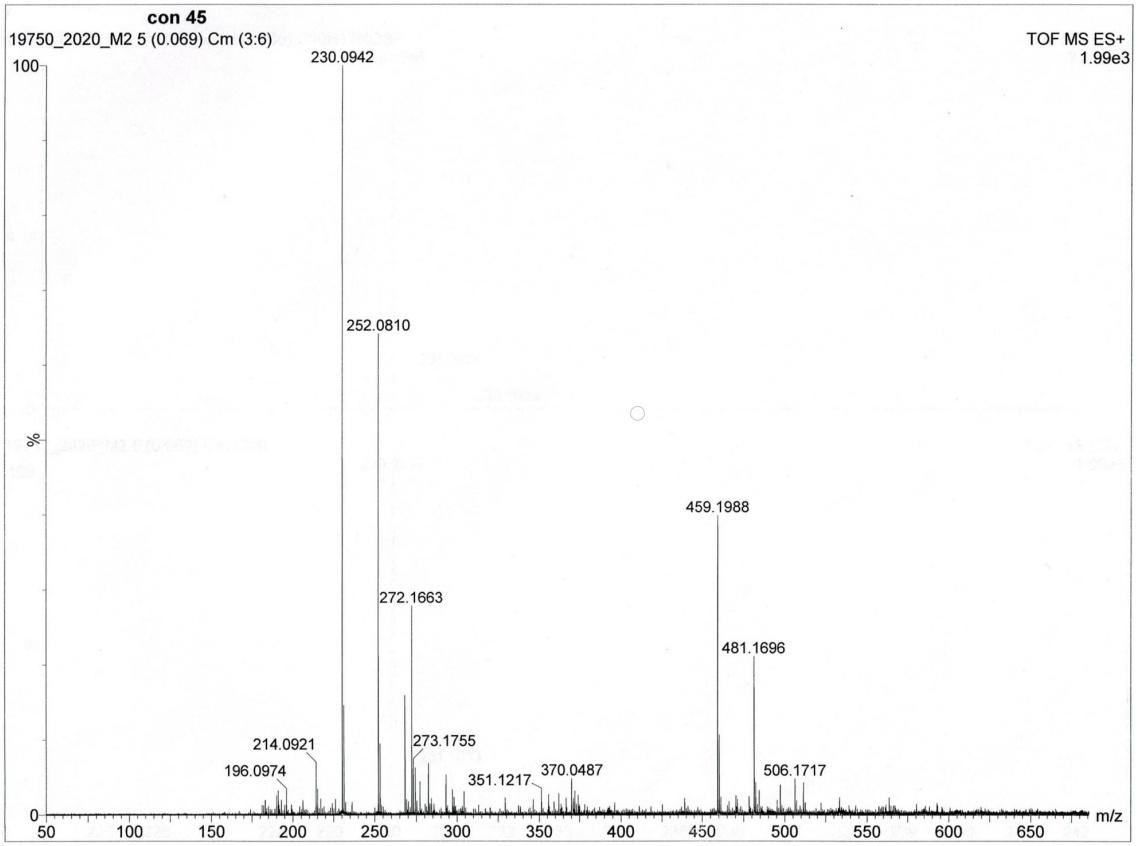
^{13}C{^{1}H} NMR (31mg, 550uL D_2O, 100MHz) spectrum of **2'd**



^{31}P NMR (31mg, 550uL D_2O, 162MHz) spectrum of **2'd**

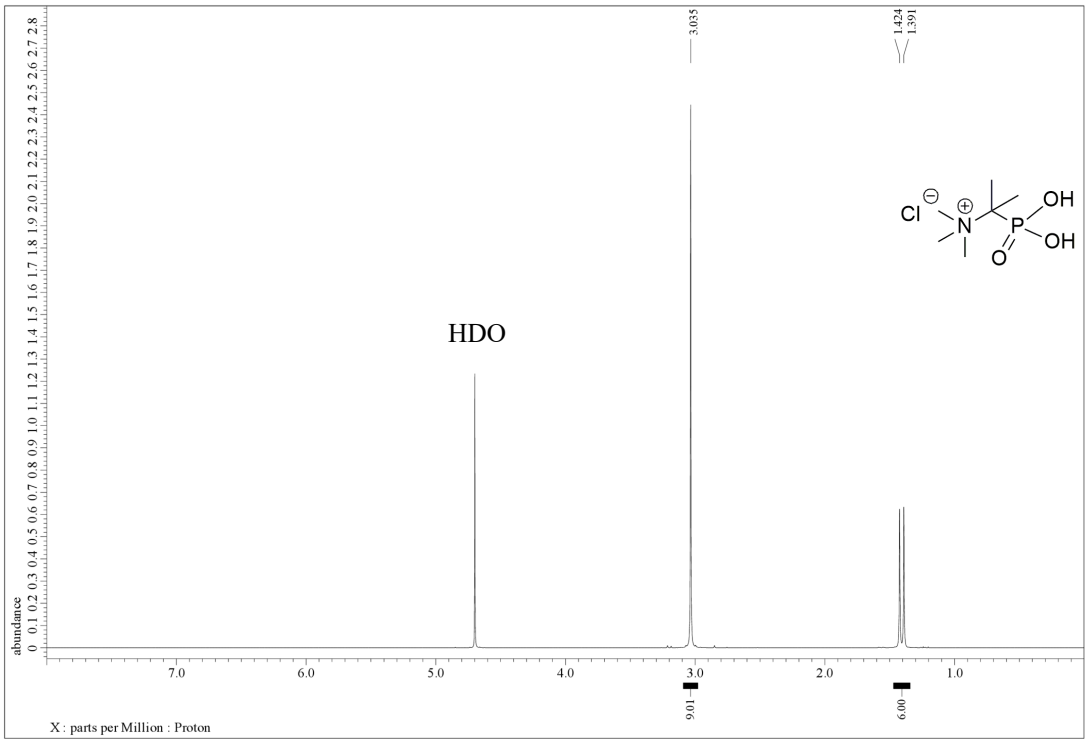


HRMS (TOF-ES+) calcd for $C_{10}H_{17}NO_3P$ [M+H]+ m/z: 230.0946, found: 230.0942

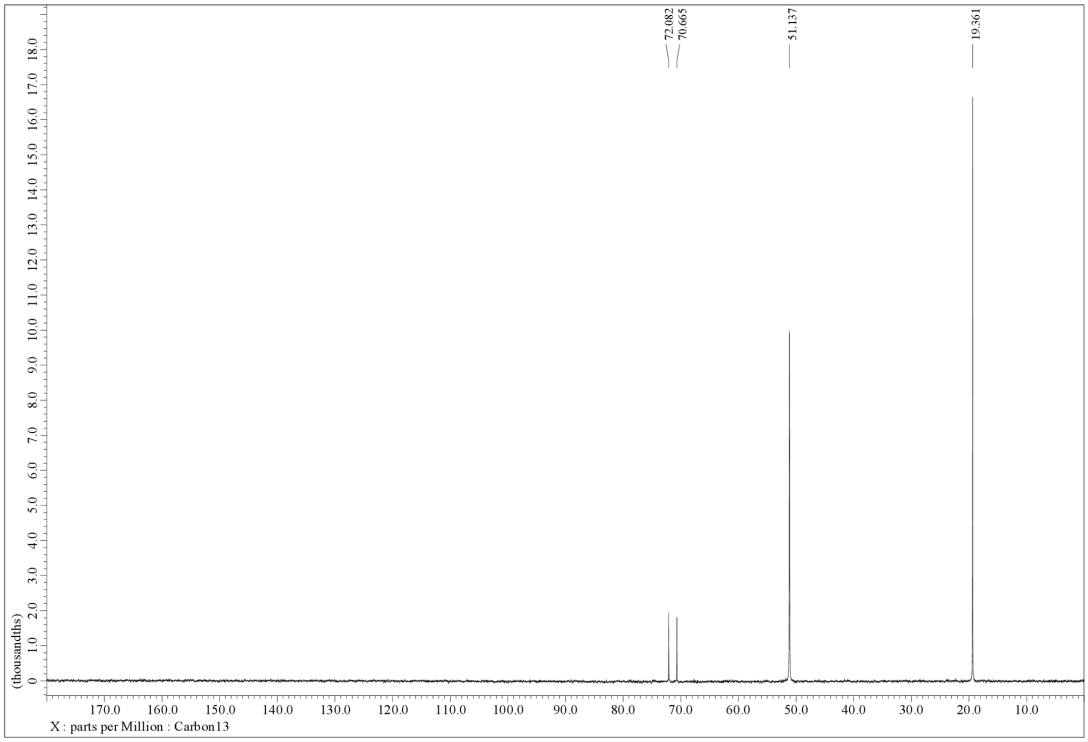


N,N,N-trimethyl-*N*-(1-methyl-1-phosphonoethyl)ammonium chloride **2'e**

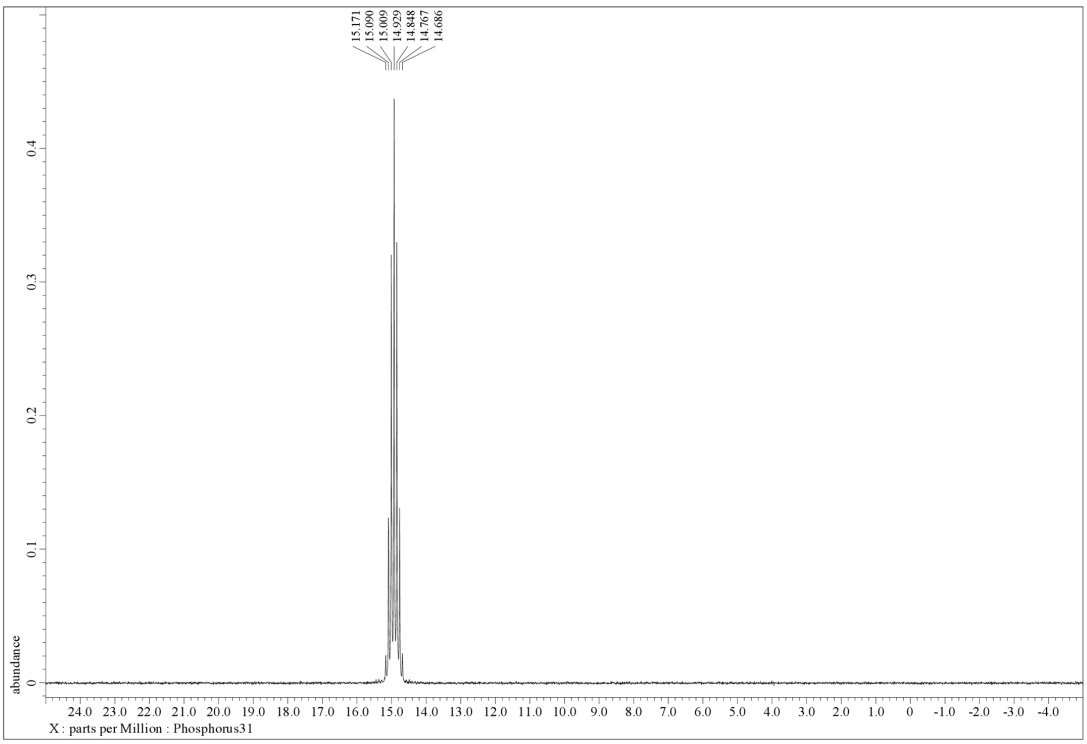
^{1}H NMR (33mg, 550uL D_2O, 400MHz) spectrum of **2'e**



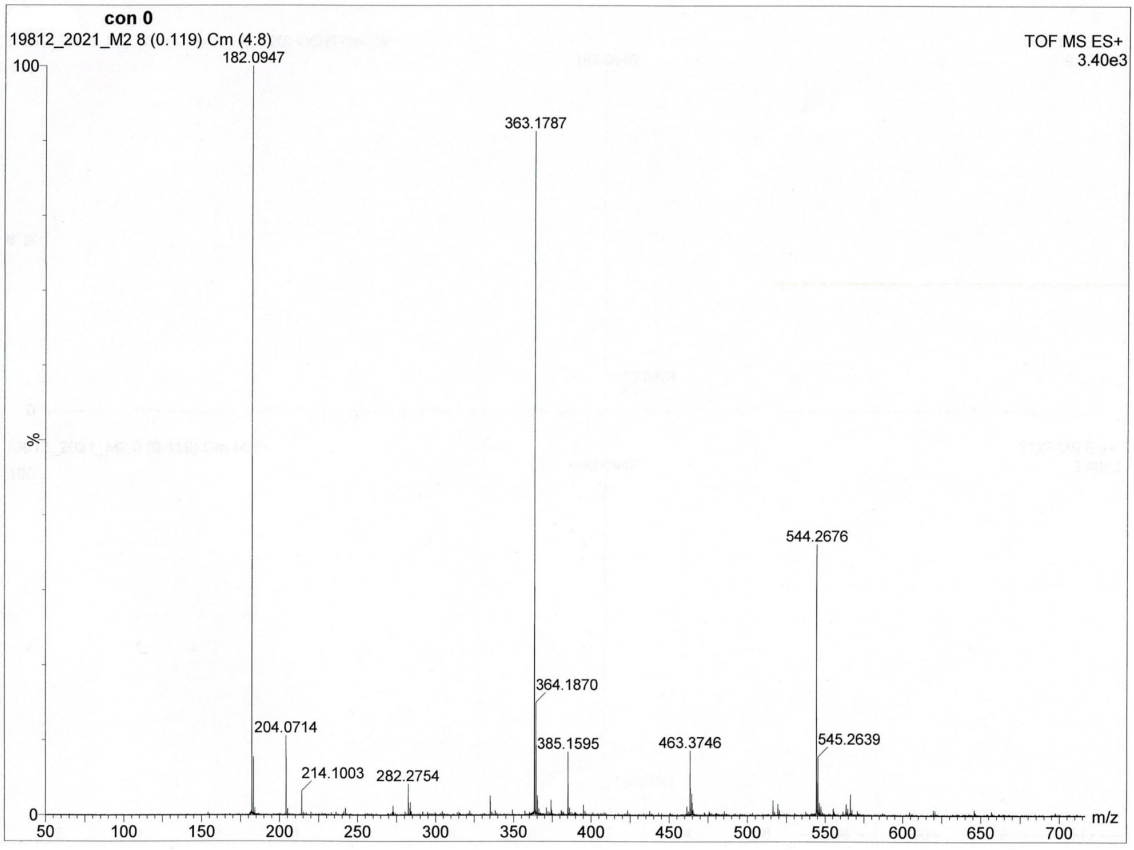
^{13}C{^{1}H} NMR (33mg, 550uL D_2O, 100MHz) spectrum of **2'e**



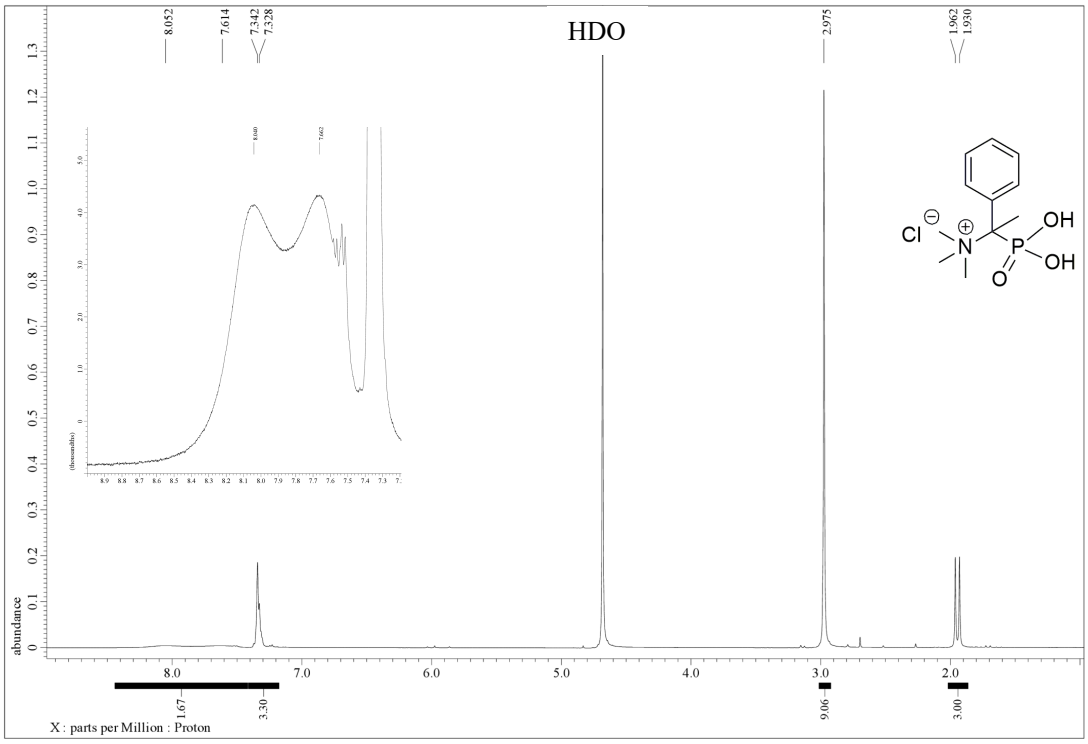
^{31}P NMR (33mg, 550uL D_2O, 162 MHz) spectrum of **2'e**



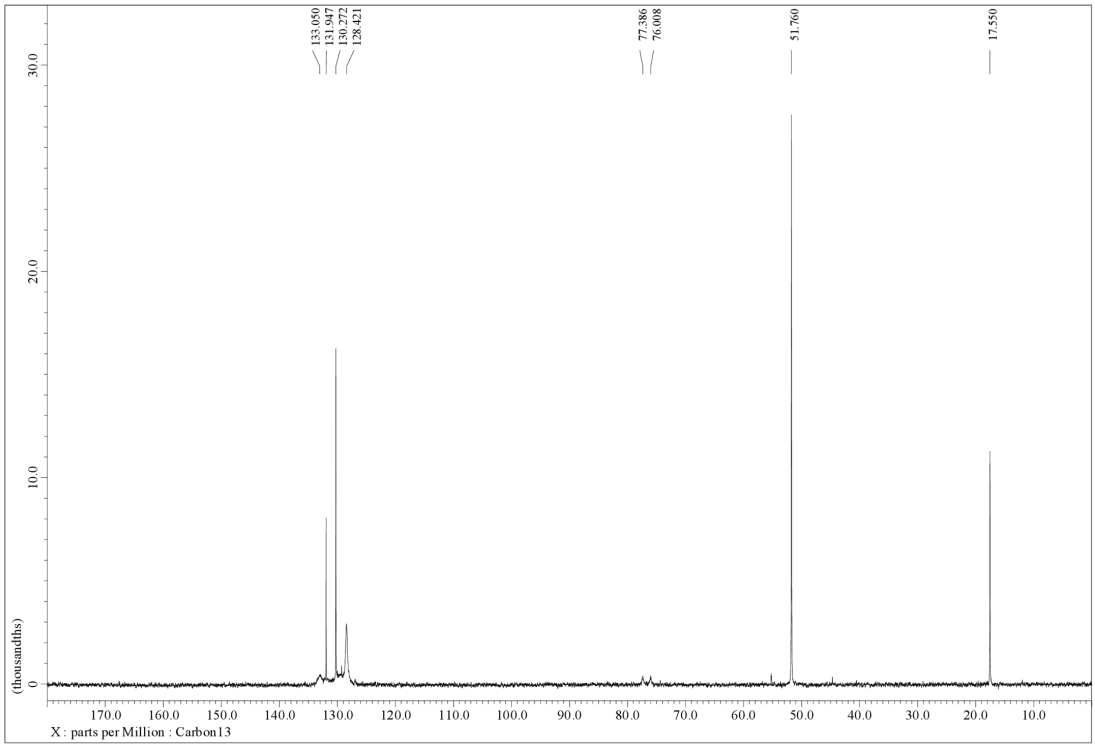
HRMS (TOF-ES+) calcd for $C_6H_{17}NO_3P$ [M+H]+ m/z: 182.0946, found: 182.0947



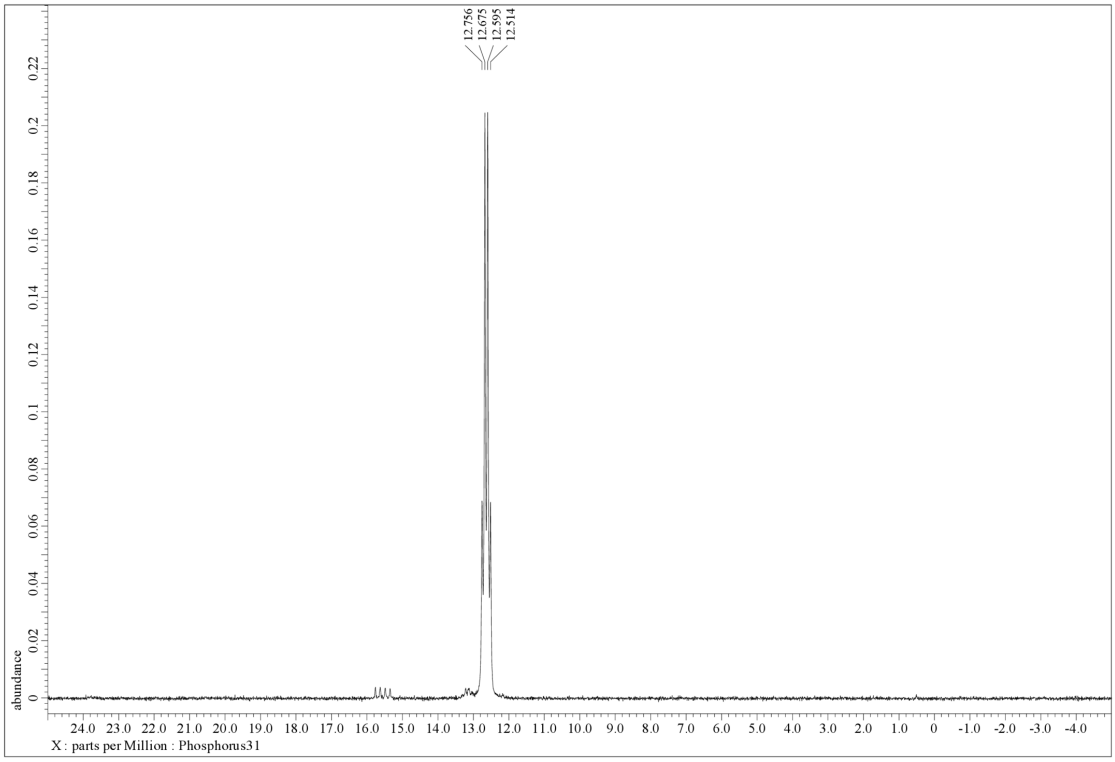
N,N,N-trimethyl-*N*-(1-phenyl-1-phosphononoethyl)ammonium chloride **2'f**
^{1}H NMR (40mg, 600uL D_2O, 400MHz) spectrum of **2'f**



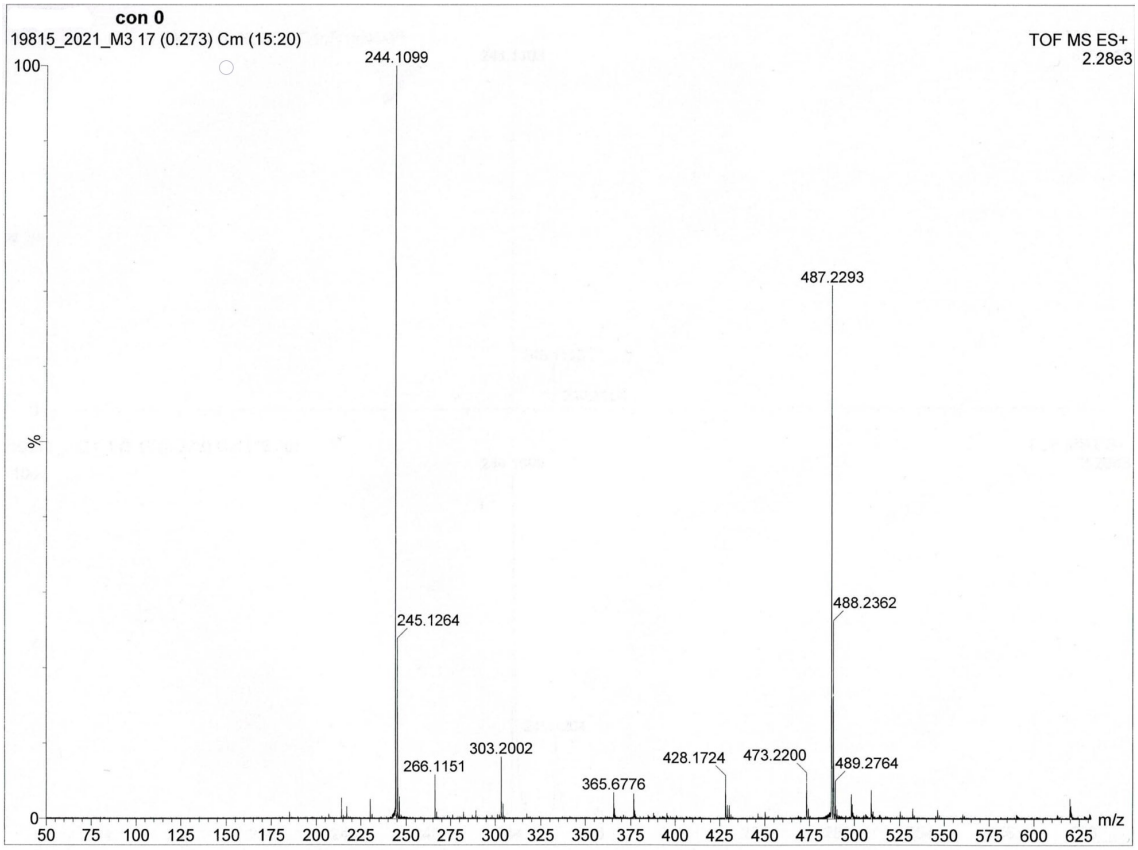
^{13}C{^{1}H} NMR (40mg, 600uL D_2O, 100MHz) spectrum of **2'f**



^{31}P NMR (40mg, 600uL D_2O, 162MHz) spectrum of **2'f**

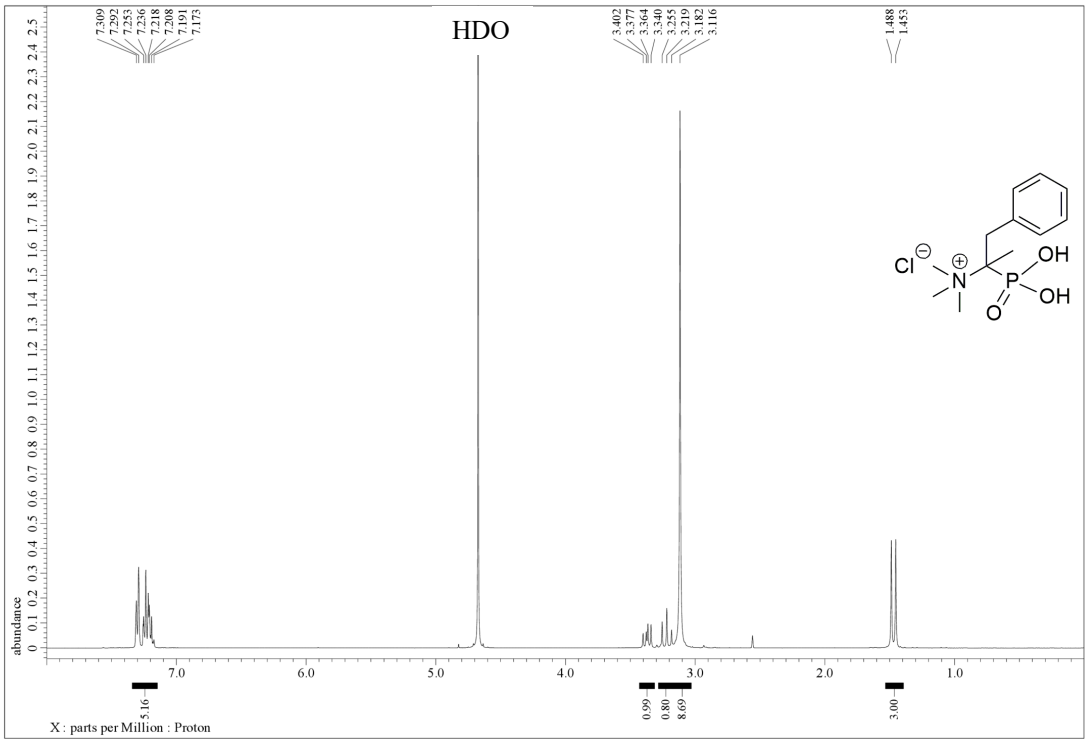


HRMS (TOF-ES+) calcd for $C_{11}H_{18}NO_3P$ [M+H]+ m/z: 244.1103, found: 244.1099

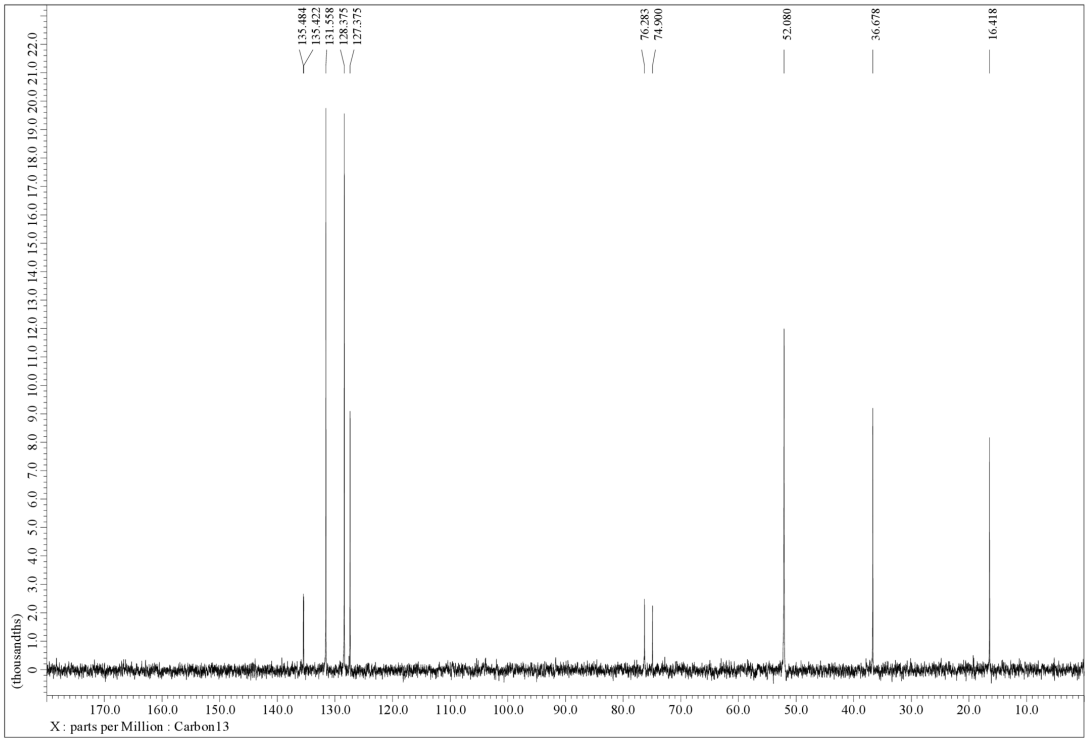


N,N,N-trimethyl-*N*-(1-methyl-2-phenyl-1-phosphonoethyl)ammonium chloride **2'g**

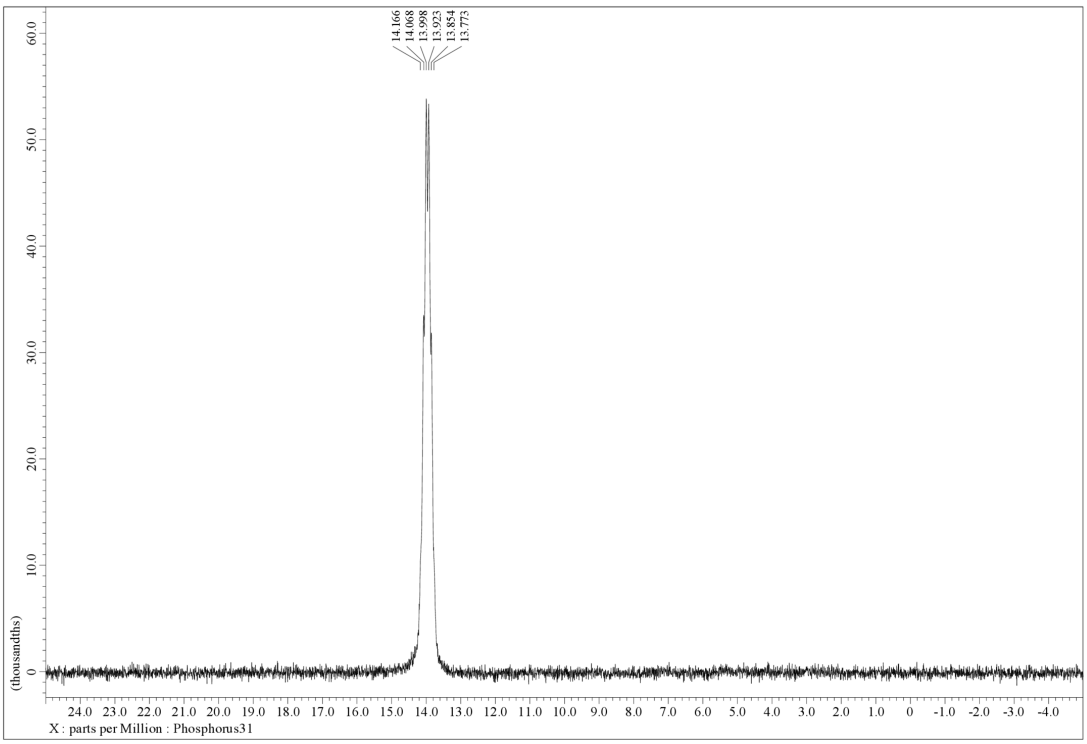
^{1}H NMR (21mg, 600uL D_2O, 400MHz) spectrum of **2'g**



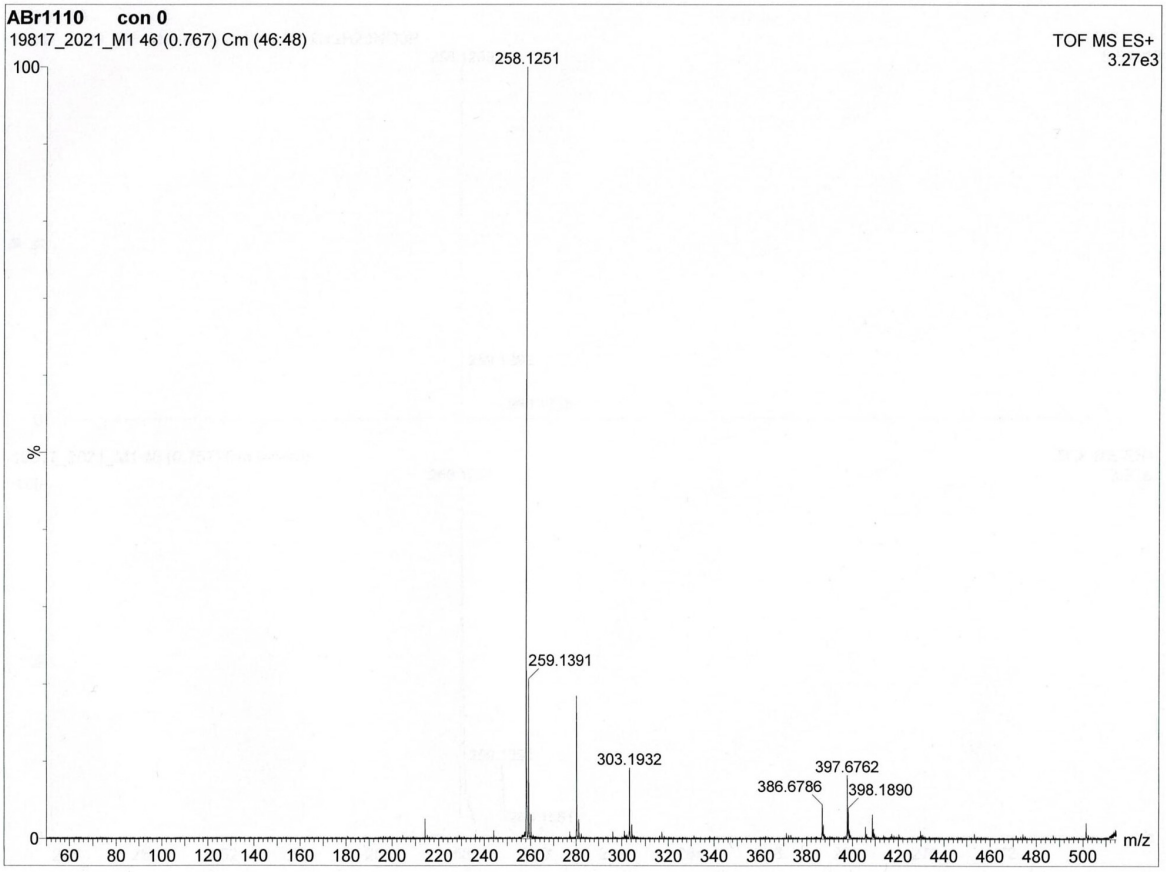
^{13}C{^{1}H} NMR (21mg, 600uL D_2O, 100MHz) spectrum of **2'g**



^{31}P NMR (21mg, 600uL D_2O, 162MHz) spectrum of **2'g**

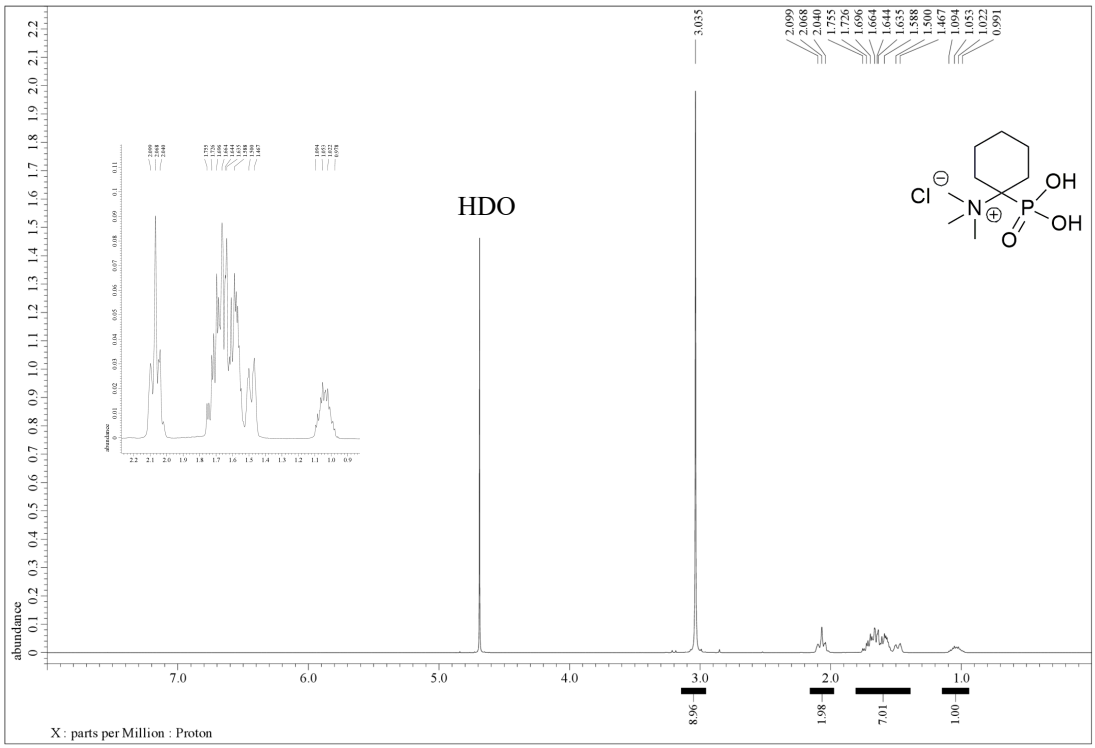


HRMS (TOF-ES+) calcd for $C_{12}H_{20}NO_3P$ [M+H]+ m/z: 258.1259, found: 258.1251

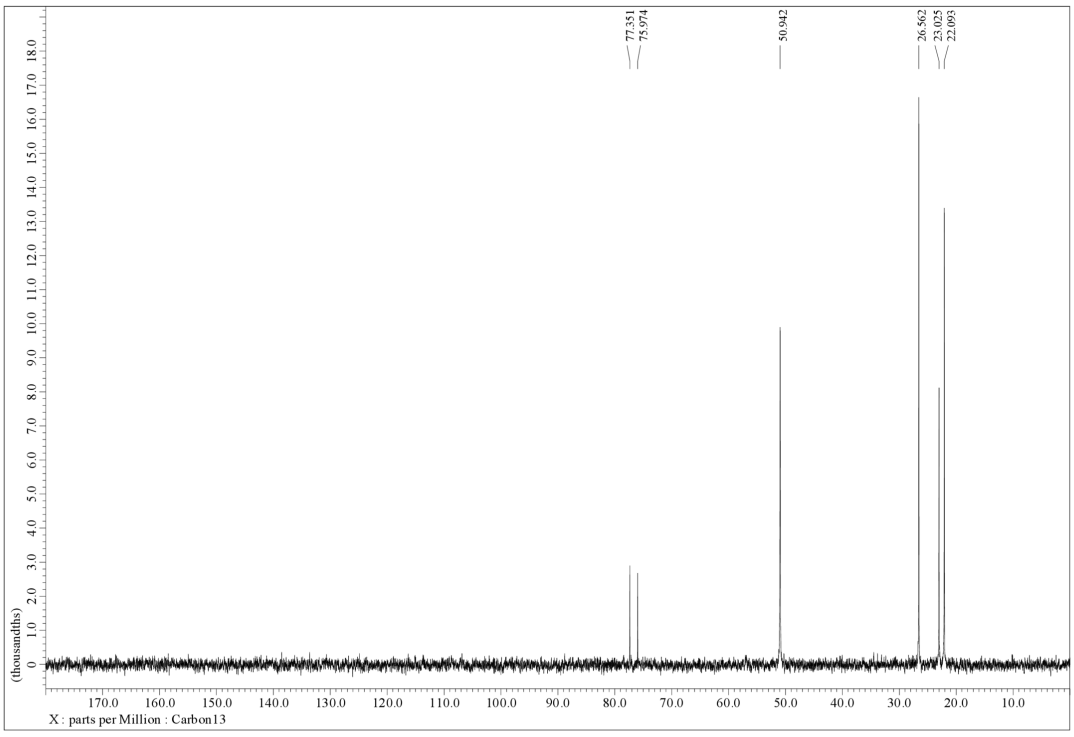


N,N,N-trimethyl-*N*-(1-phosphonocyclohexyl)ammonium chloride **2'h**

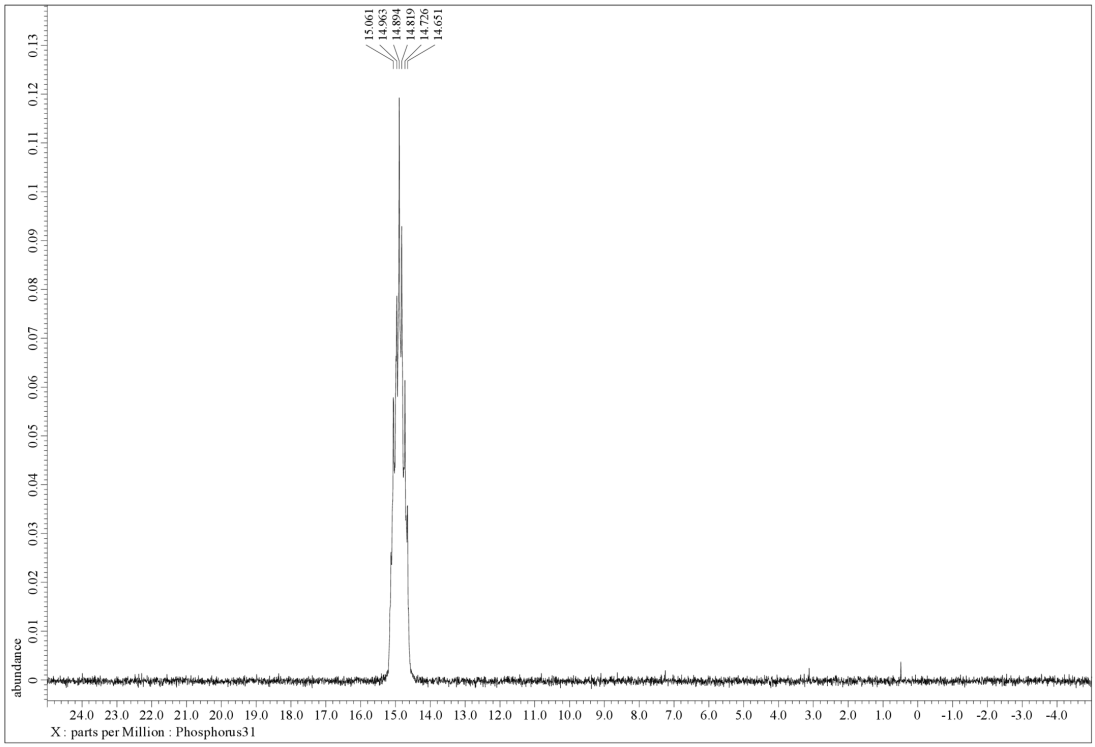
^{1}H NMR (23mg, 550uL D_2O, 400MHz) spectrum of **2'h**



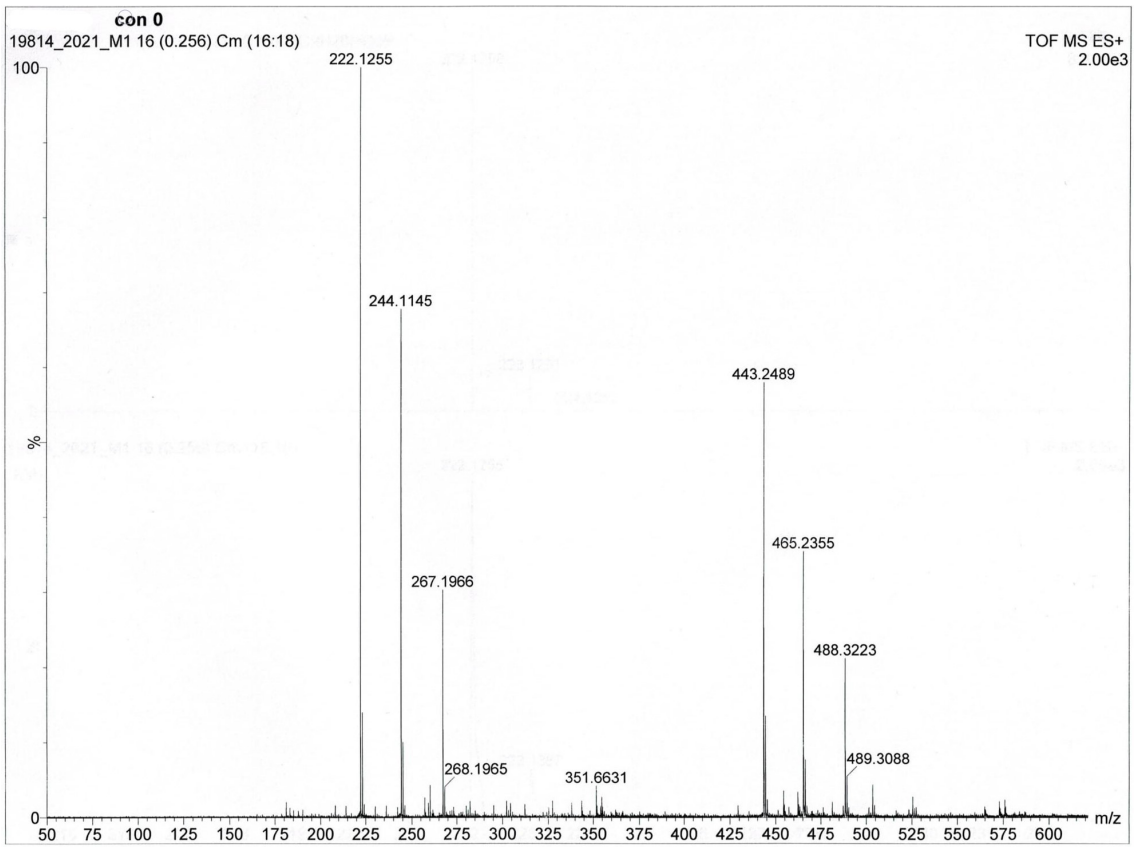
^{13}C{^{1}H} NMR (21mg, 550uL D_2O, 100MHz) spectrum of **2'h**



^{31}P NMR (23mg, 550uL D_2O, 162MHz) spectrum of **2'h**

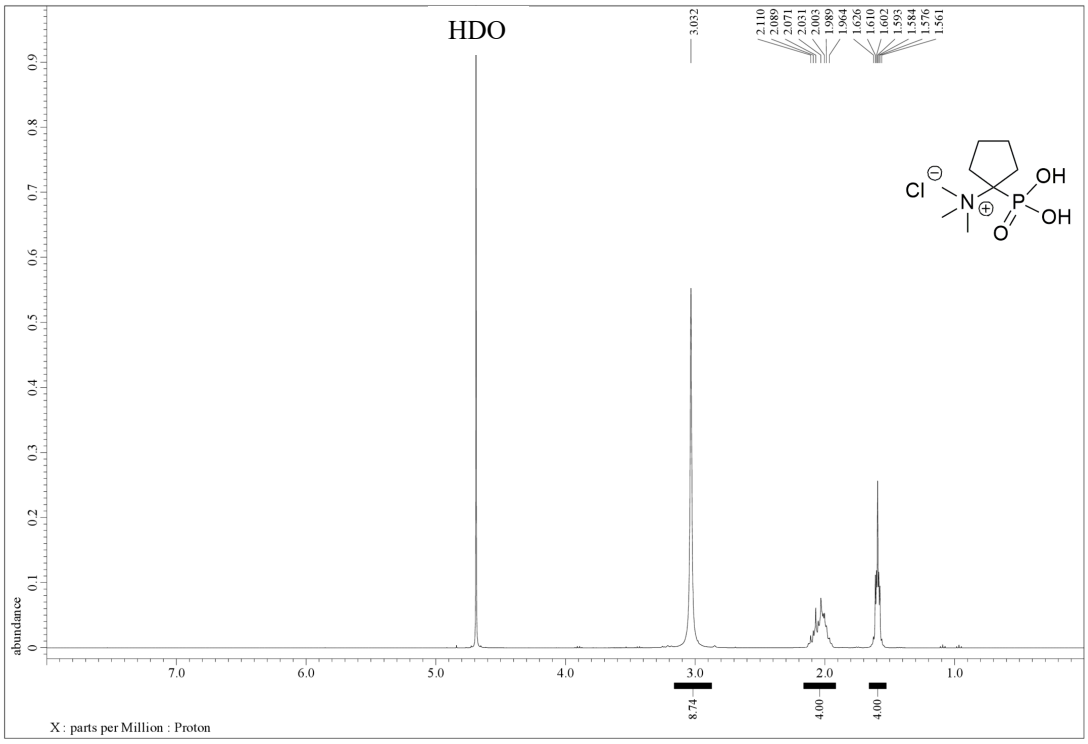


HRMS (TOF-ES+) calcd for $C_9H_{20}NO_3P$ [M+H]+ m/z: 222.1259, found: 222.1255

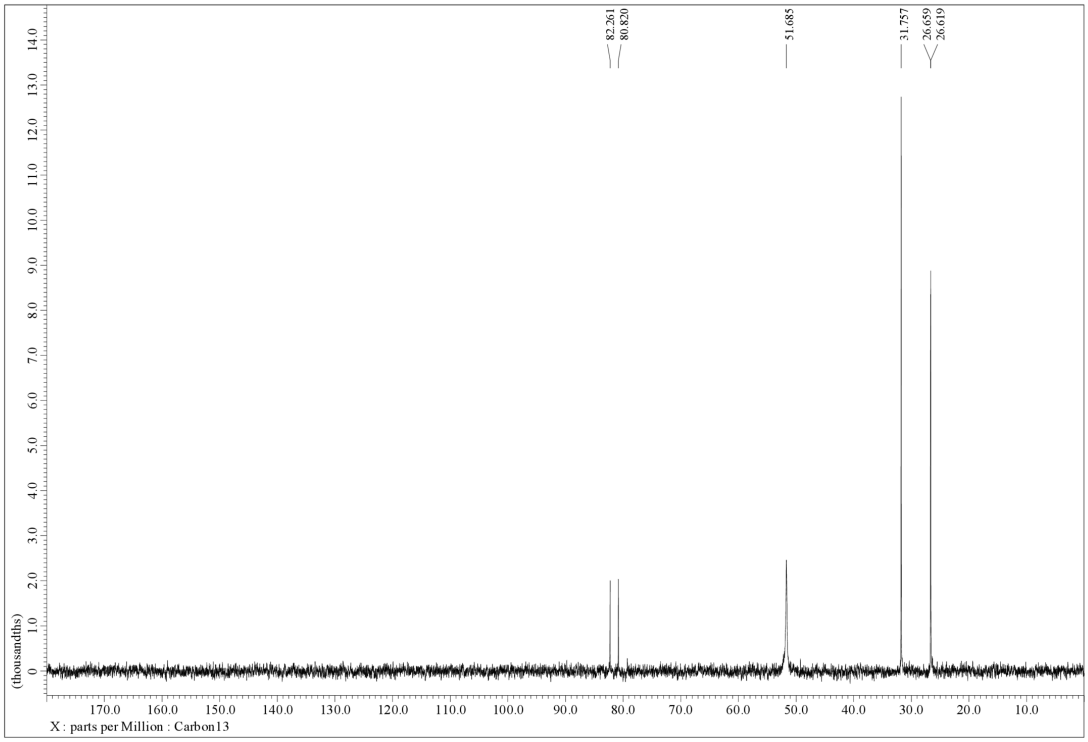


N,N,N-trimethyl-*N*-(1-phosphonocyclopentyl)ammonium chloride **2'i**

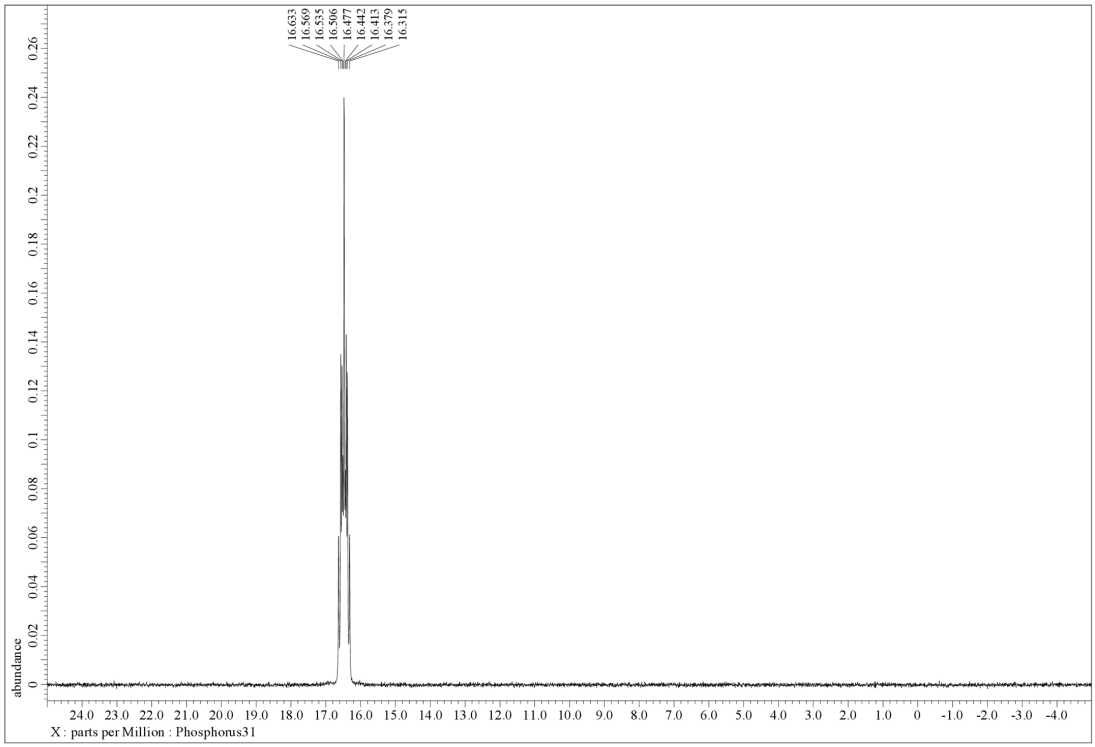
^{1}H NMR (29mg, 550uL D_2O, 400MHz) spectrum of **2'i**



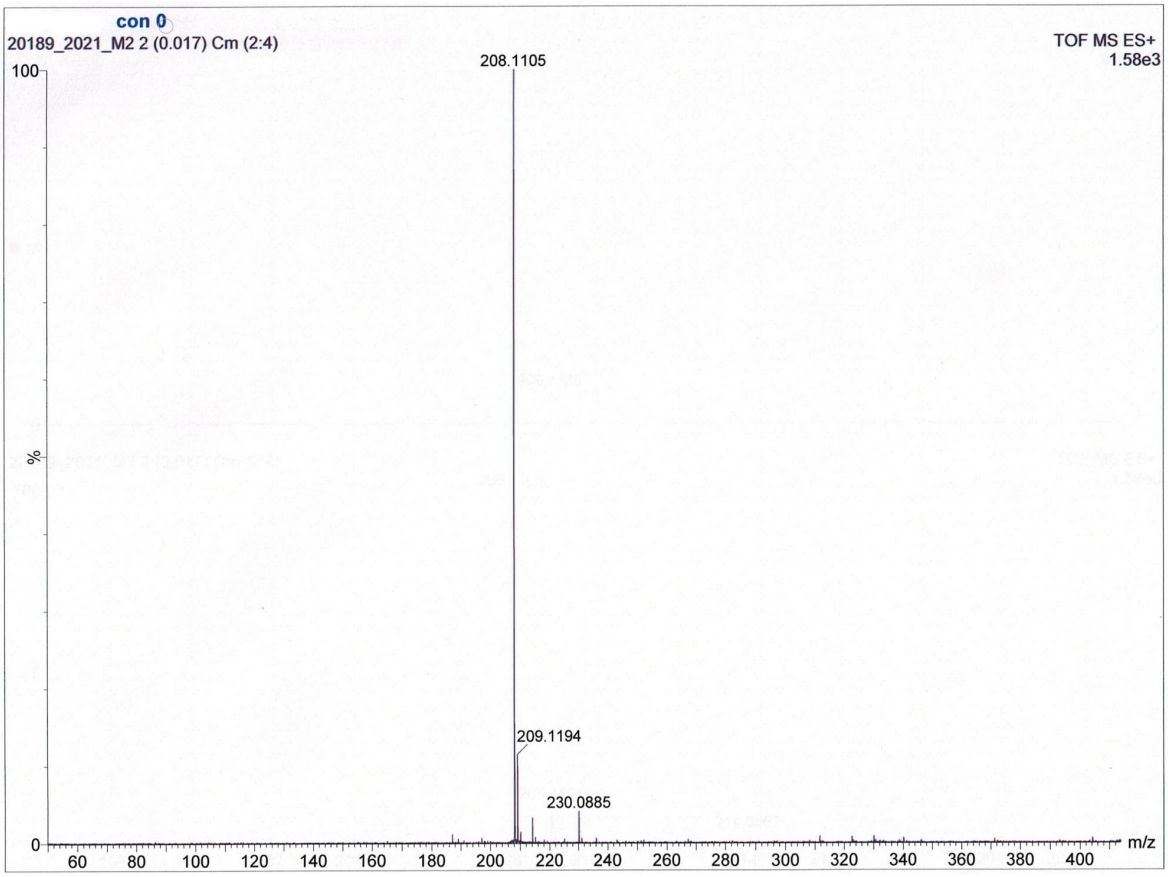
^{13}C{^{1}H} NMR (40mg, 550uL D_2O, 100MHz) spectrum of **2'i**



^{31}P NMR (29mg, 550uL D_2O, 162MHz) spectrum of **2'i**

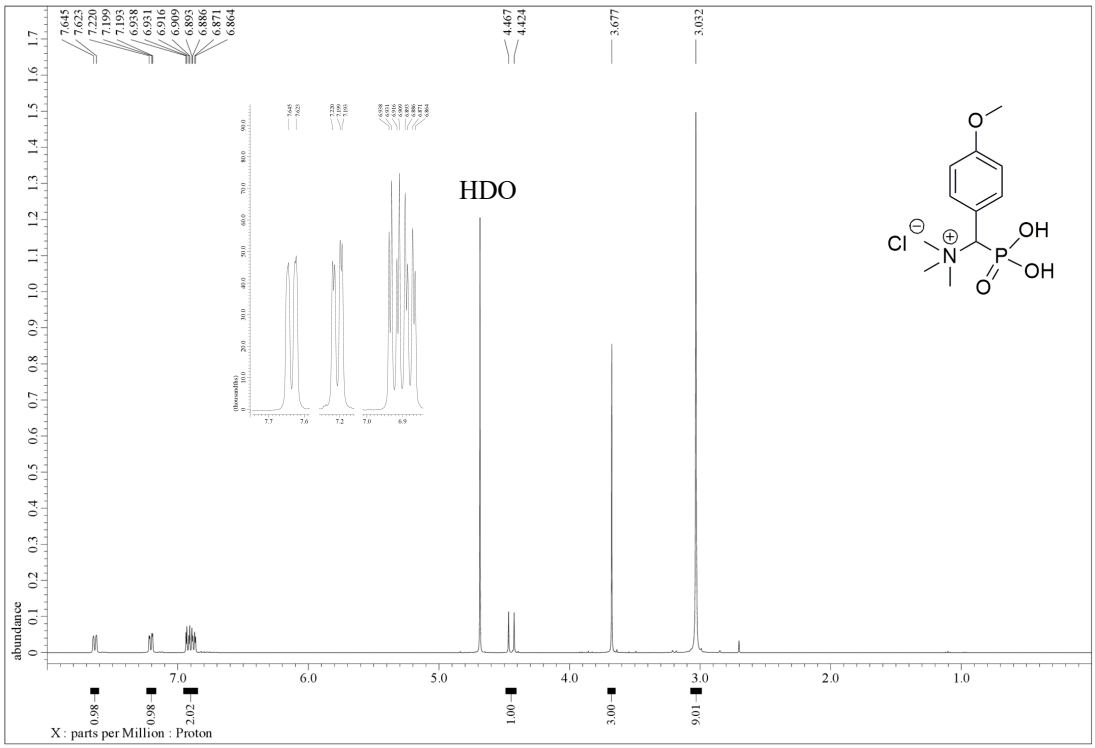


HRMS (TOF-ES+) calcd for $C_8H_{18}NO_3P$ [M+H]+ m/z: 208.1103, found: 208.1105

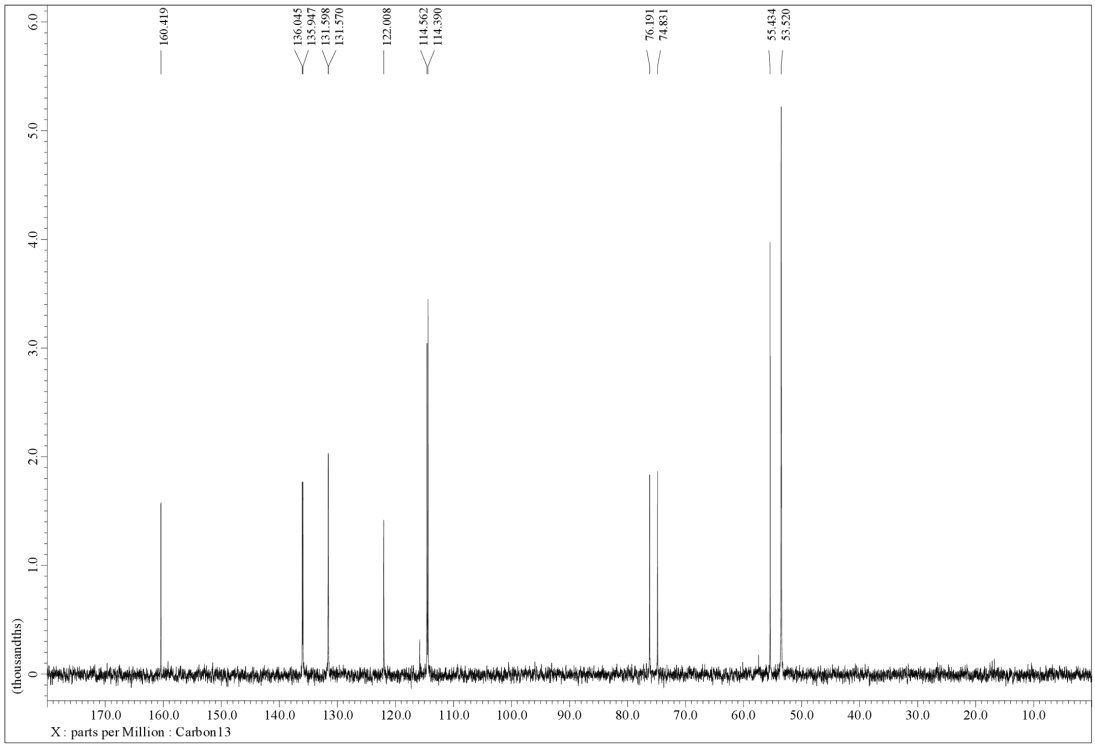


N,N,N-trimethyl-*N*-[(4-methoxyphenyl)(phosphono)methyl]ammonium chloride **2'j**

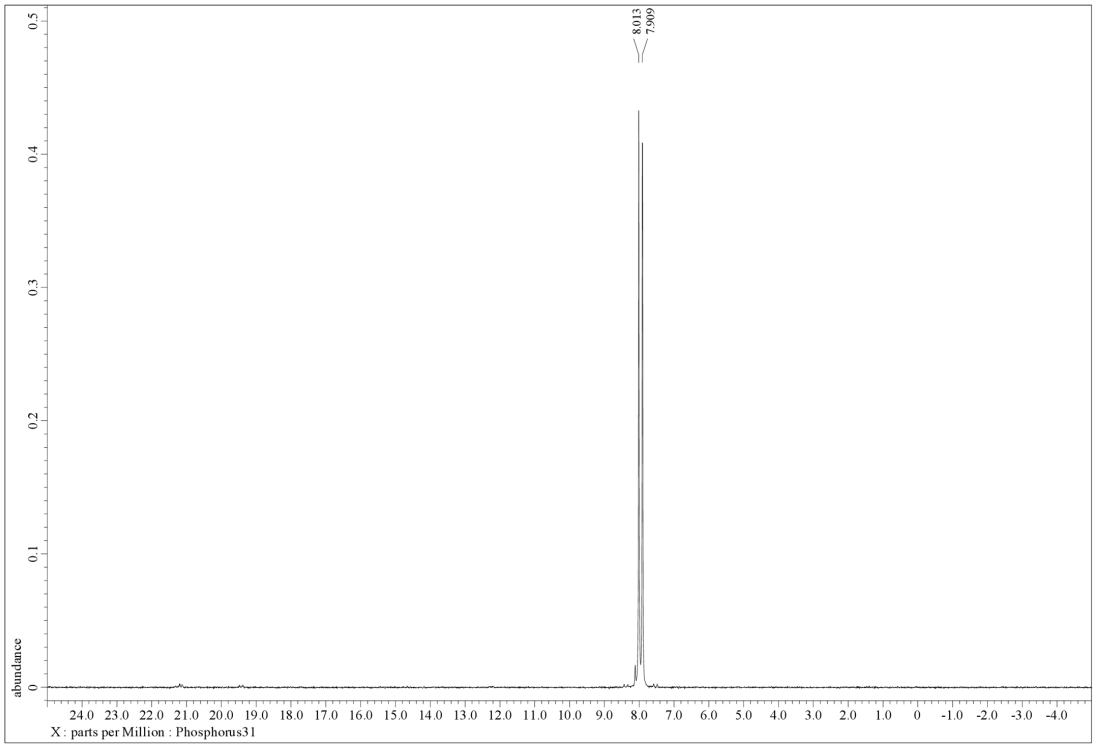
^{1}H NMR (33mg, 550uL D_2O, 100MHz) spectrum of **2'j**



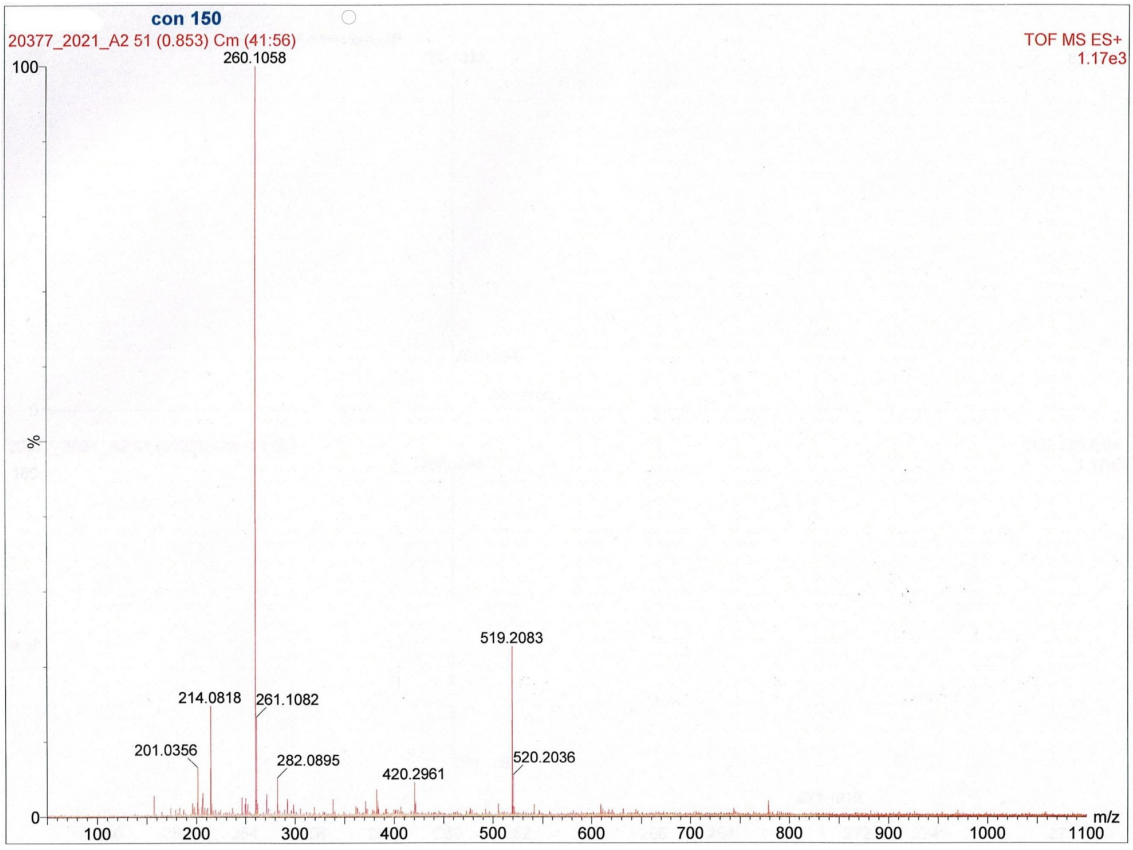
^{13}C{^{1}H} NMR (24mg, 550uL D_2O, 100MHz) spectrum of **2'j**



^{31}P NMR (33mg, 550uL D_2O, 162MHz) spectrum of **2'j**



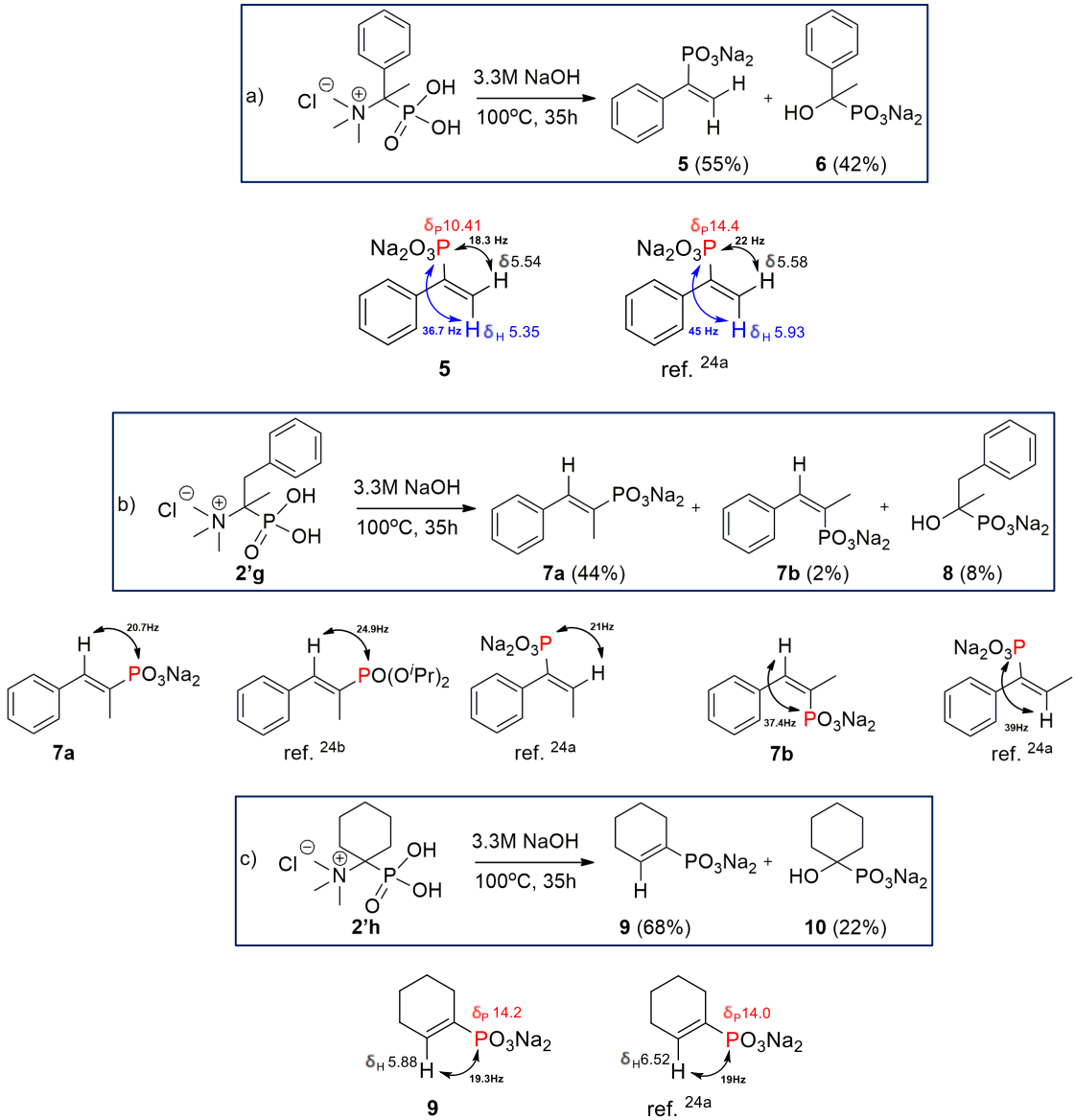
HRMS (TOF-ES+) calcd for $C_{11}H_{18}NO_4P$ [M+H]+ m/z: 260.1052, found: 260.1058



Identification of degradation products

The degradation products (olefins) were identified by comparison of the chemical shifts of signals on ^{1}H and ^{31}P NMR spectra with values reported in literature for exact or similar structures (Scheme S1) while the formation of 1-hydroxyalkylphosphonic acids **7** and **10** was confirmed by the addition of standards (synthesised appropriate 1-hydroxyalkylphosphonic acids). Given references correspond to those cited in the main article.

Chemical shifts on ^{31}P NMR spectra of phosphonic compounds are strongly dependent on pH of the measured solutions.[1] Thus, the differences in measured chemical shifts of compounds **5** and **9** compared to the literature values (ref. [24a]) are caused by different pH of the solutions. For compound **5** chemical shift measured in 3.3M NaOH is δ_P = 10.41, whereas in the literature spectrum was measured for disodium salt in H_2O (slightly basic conditions) and δ_P = 14.4. Similarly, for compound **9** chemical shift measured in 3.3M NaOH is δ_P = 14.2, whereas in the literature spectrum was measured for disodium salt in H_2O (slightly basic conditions) and δ_P = 14.0.

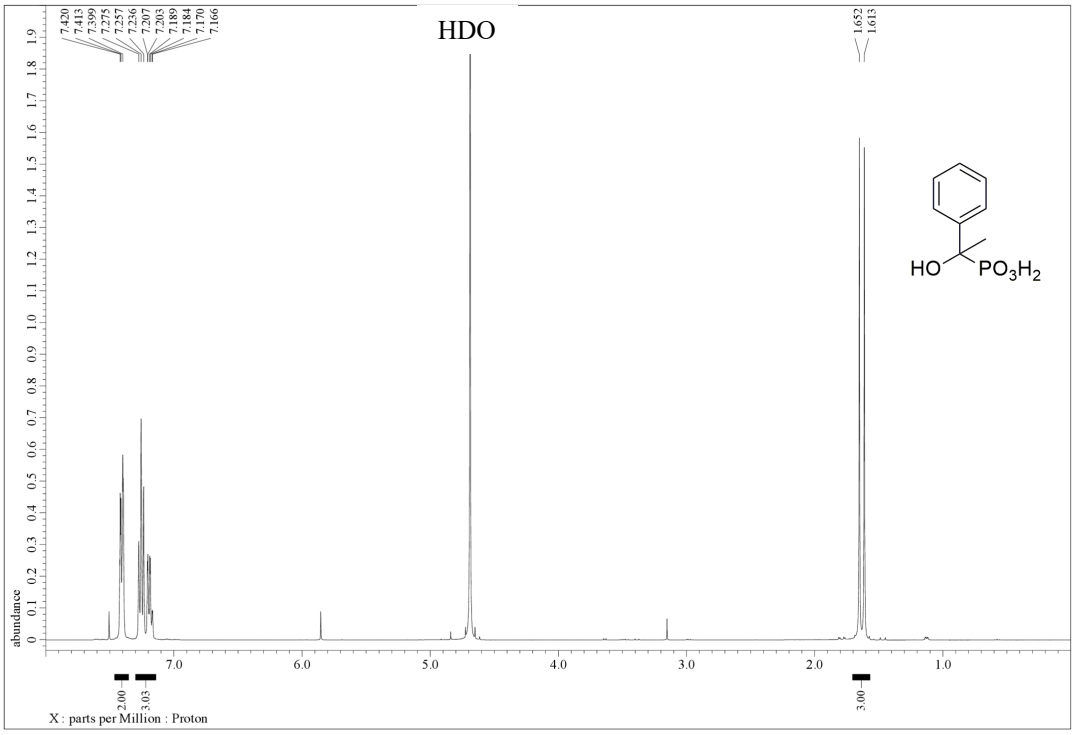


Scheme S1. Identification of degradation products by comparison of chemical shifts and coupling constants.

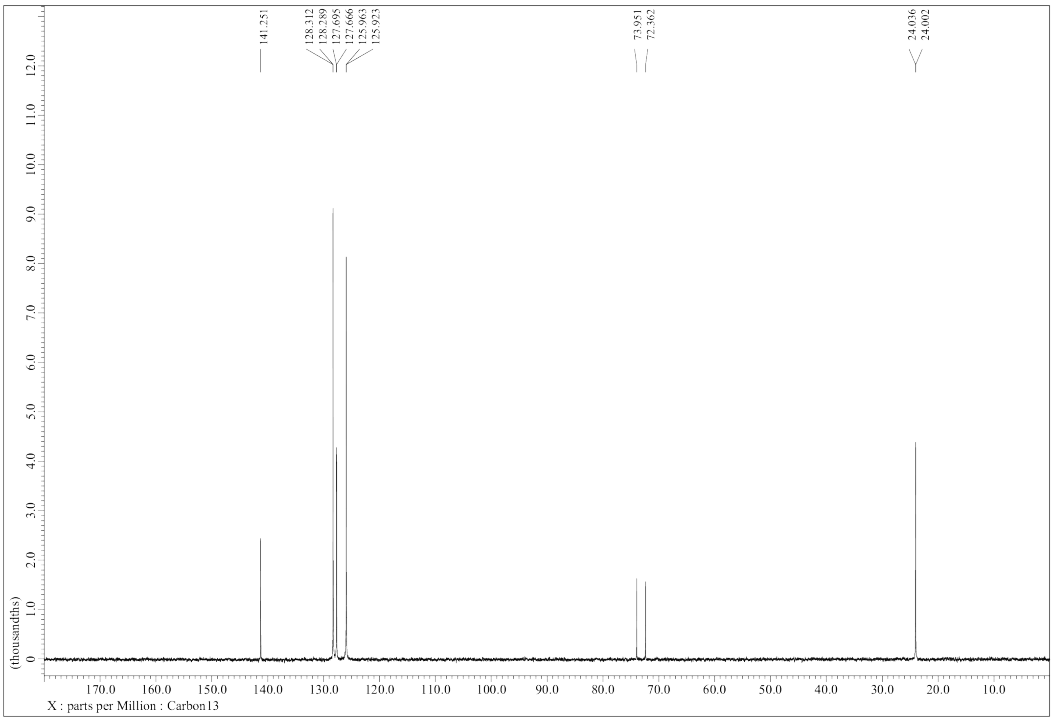
Spectra of reference materials

1-Hydroxy-1-phenylethylphosphonic acid **6** (prepared and used as reference material)

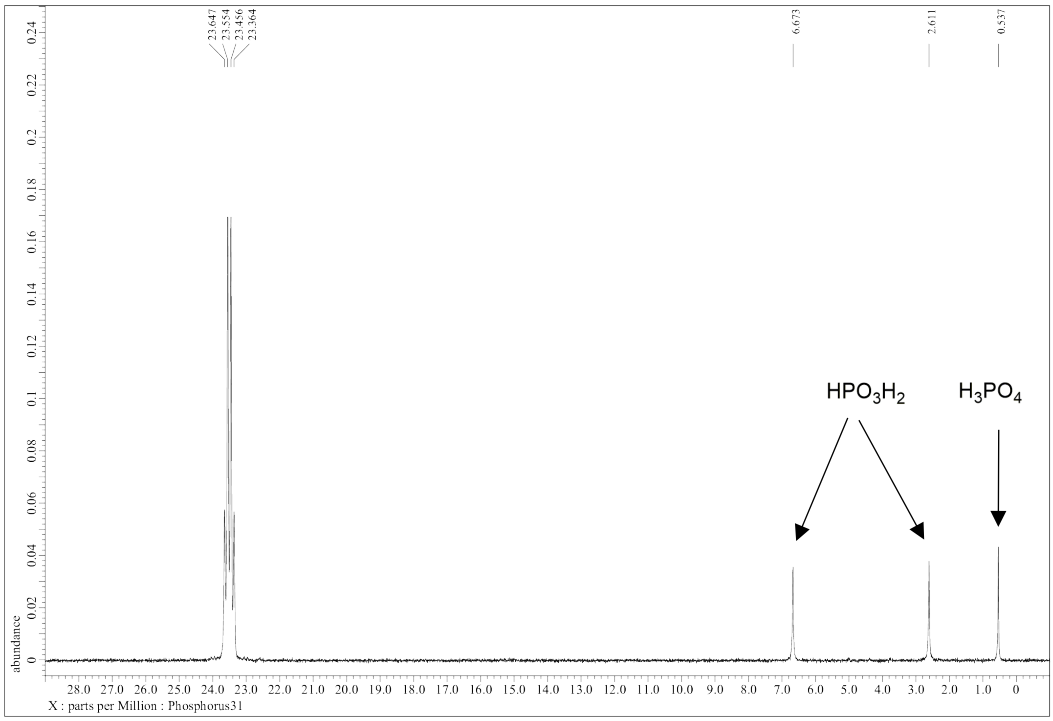
^{1}H NMR (17mg, 550uL D_2O, 400MHz) spectrum of crude **6**



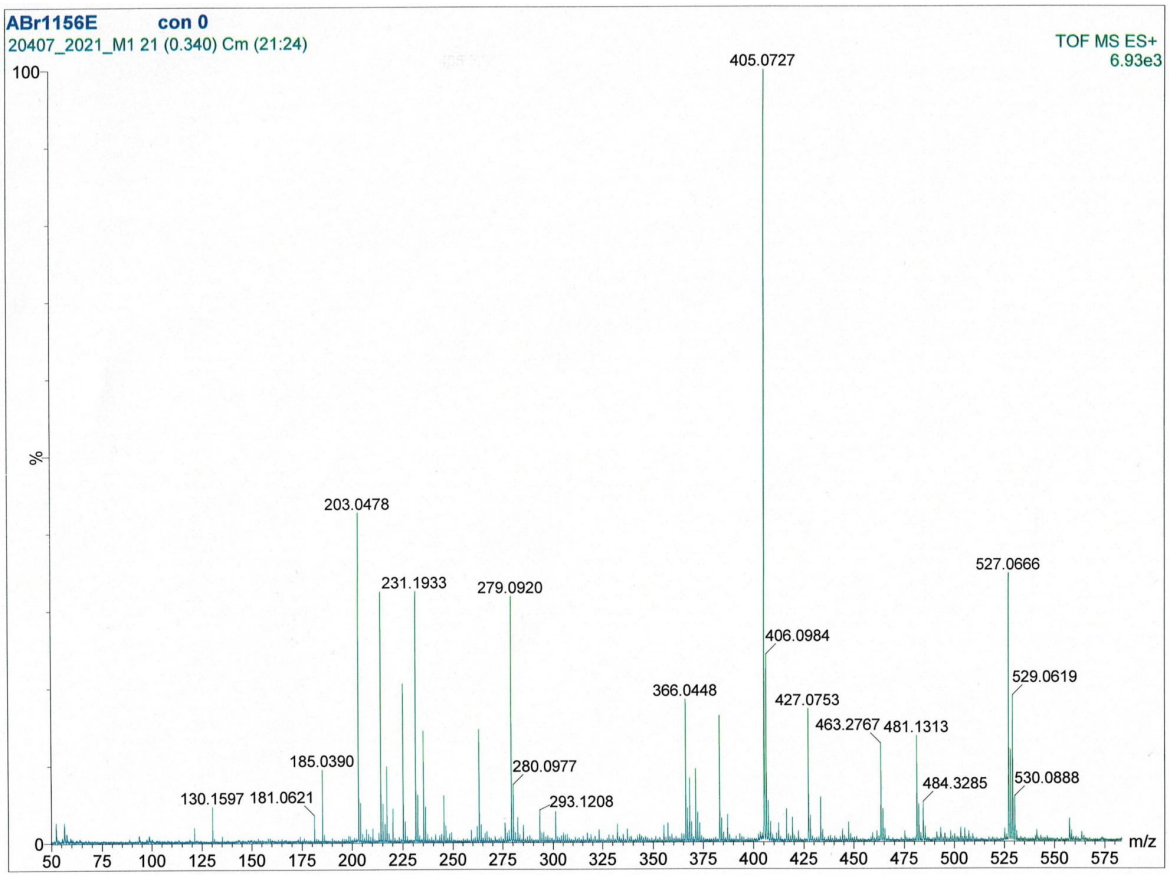
^{13}C{^{1}H} NMR (17mg, 550uL D_2O, 100MHz) spectrum of crude **6**



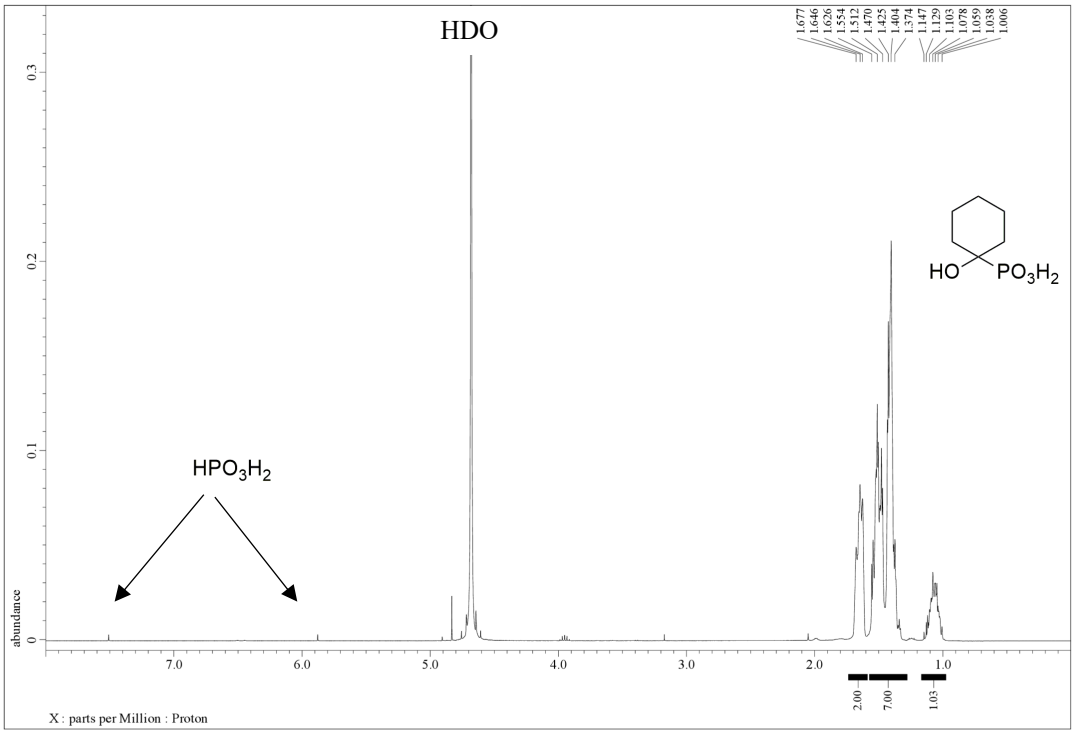
^{31}P NMR (17mg, 550uL D_2O, 162MHz) spectrum of crude **6**



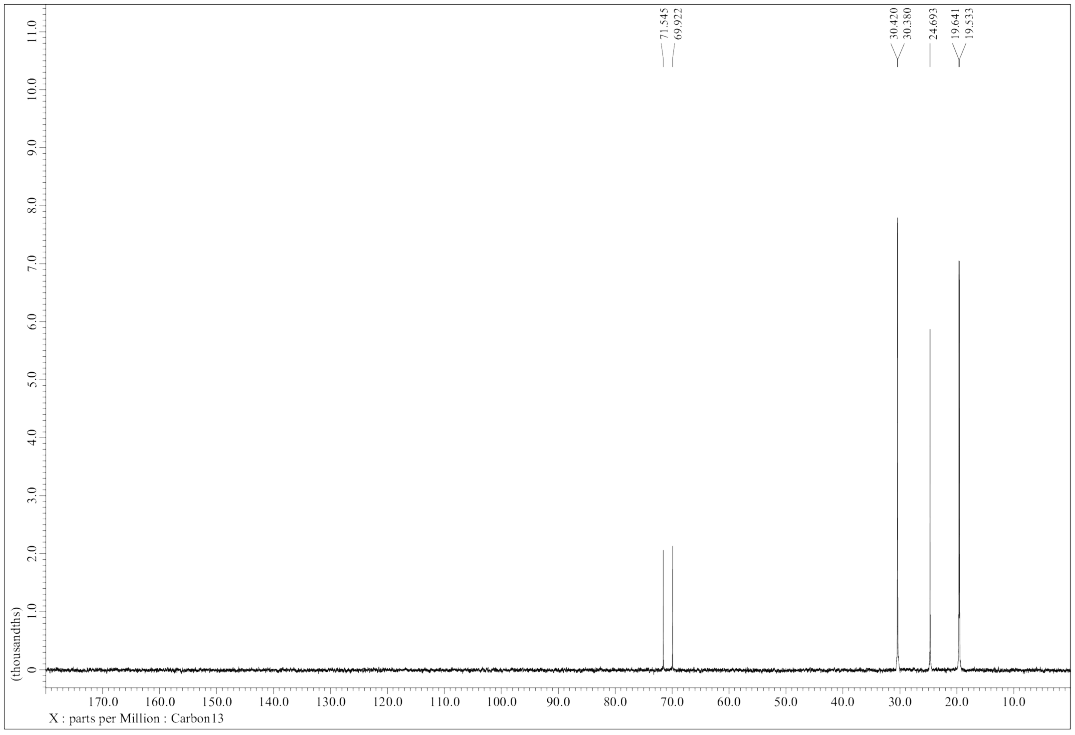
HRMS (TOF-ES+) calcd for $C_8H_{11}O_4P$ [M]+ m/z: 203.0473, found: 203.0478



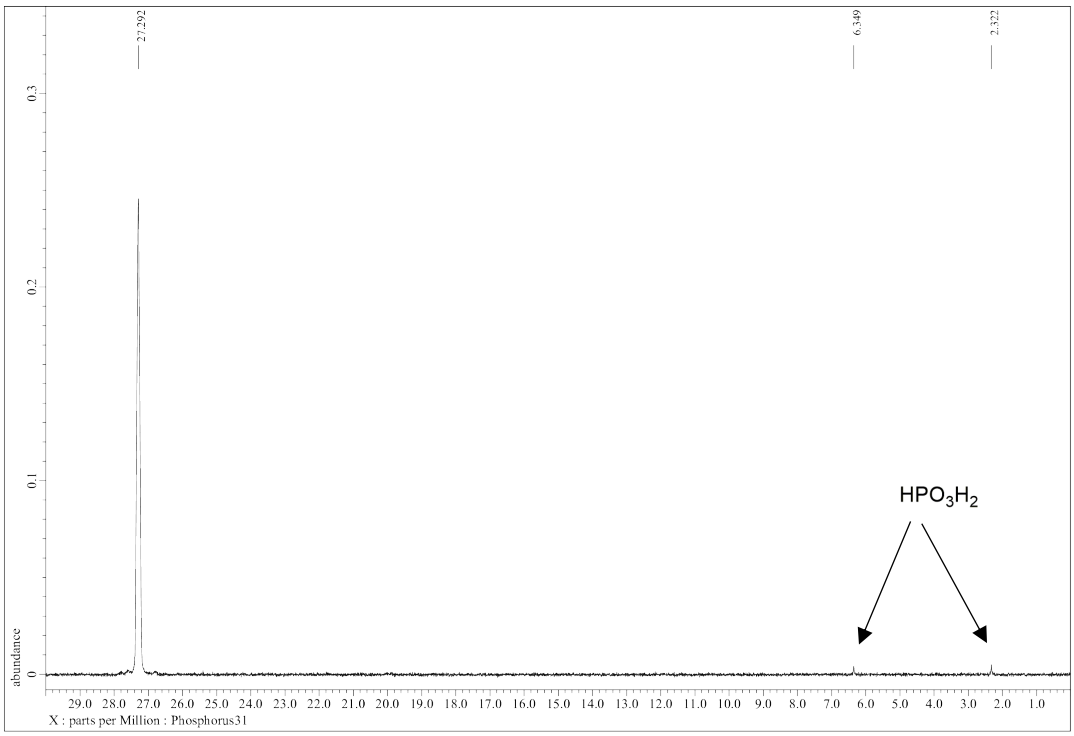
1-Hydroxycyclohexylphosphonic acid **10** (prepared and used as reference material)
^{1}H NMR (17mg, 550uL D_2O, 400MHz) spectrum of **10**



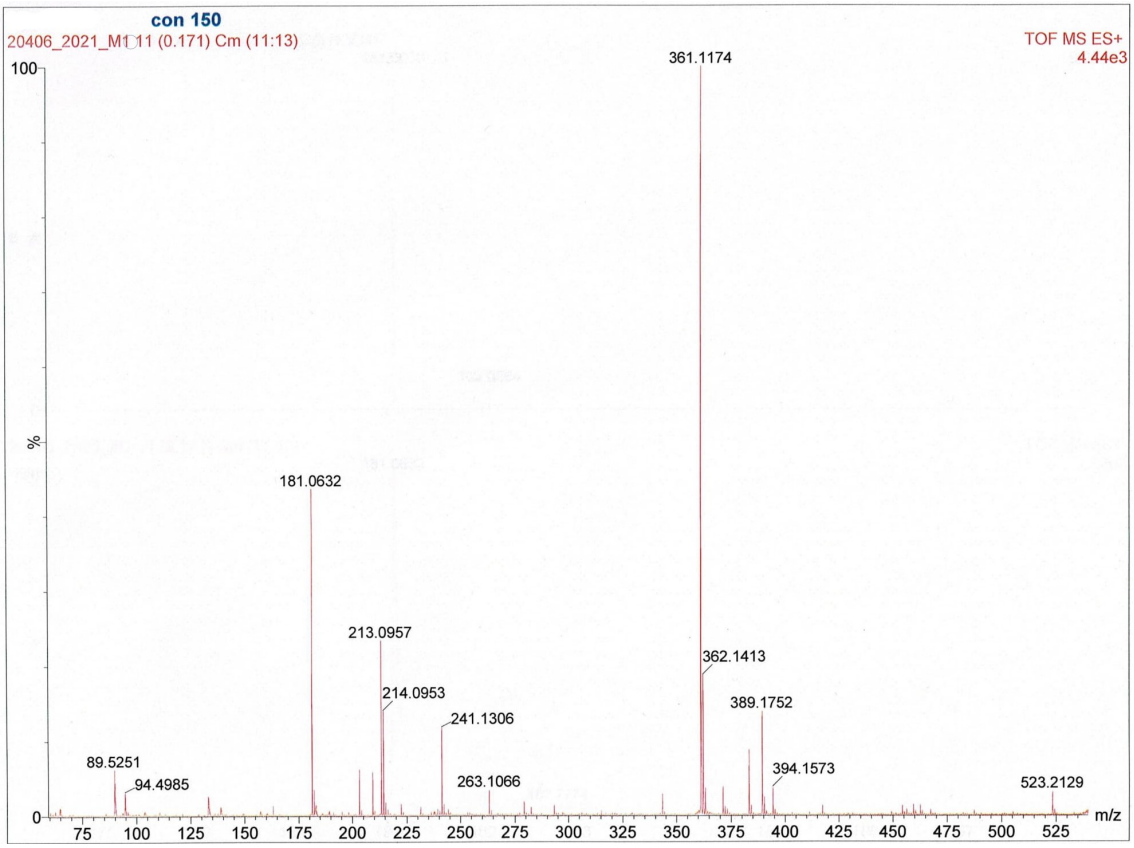
^{13}C{^{1}H} NMR (22mg, 550uL D_2O, 100MHz) spectrum of **10**



^{31}P NMR (17mg, 550uL D_2O, 162 MHz) spectrum of **10**

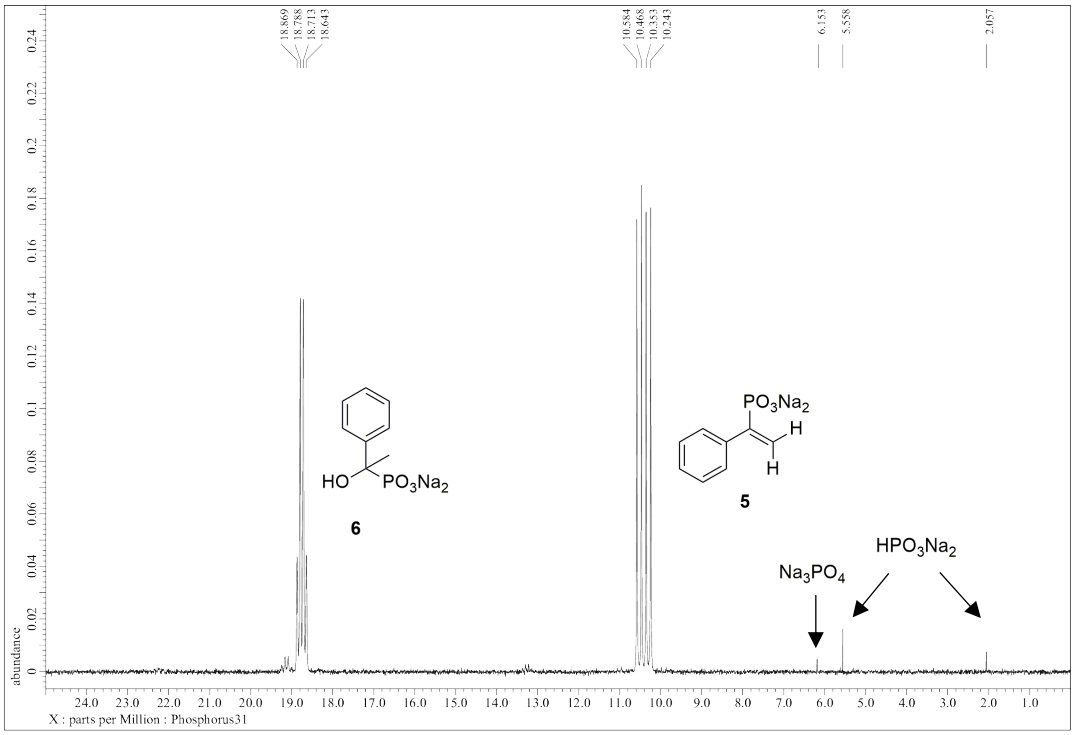


HRMS (TOF-ES+) calcd for $C_6H_{13}NO_4P$ [M]+ m/z: 181.0630, found: 181.0632

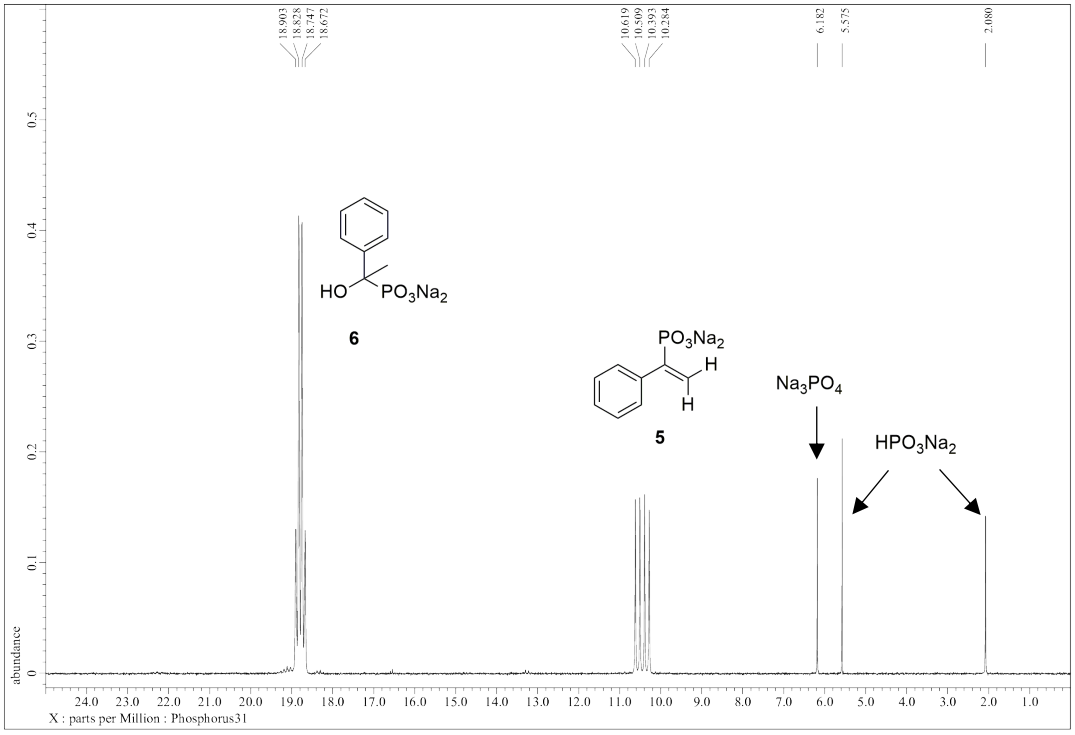


Spectra of reaction mixtures after heating with NaOH

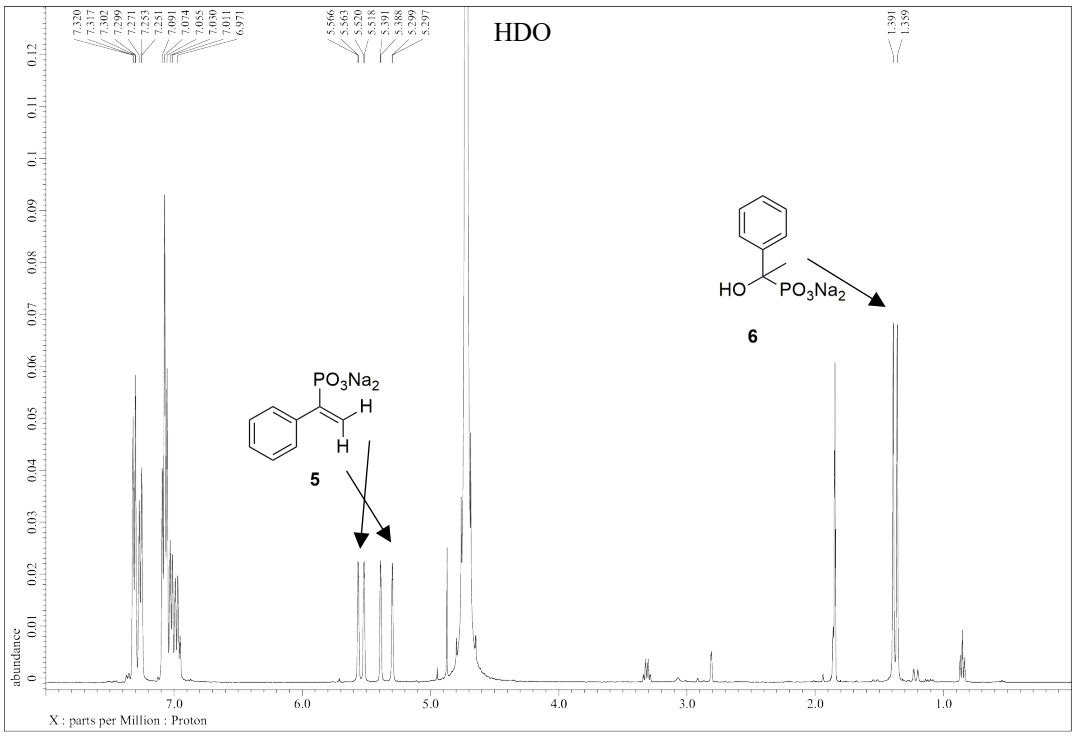
^{31}P NMR spectrum of reaction mixture after heating **2'f** with 3.3M NaOH



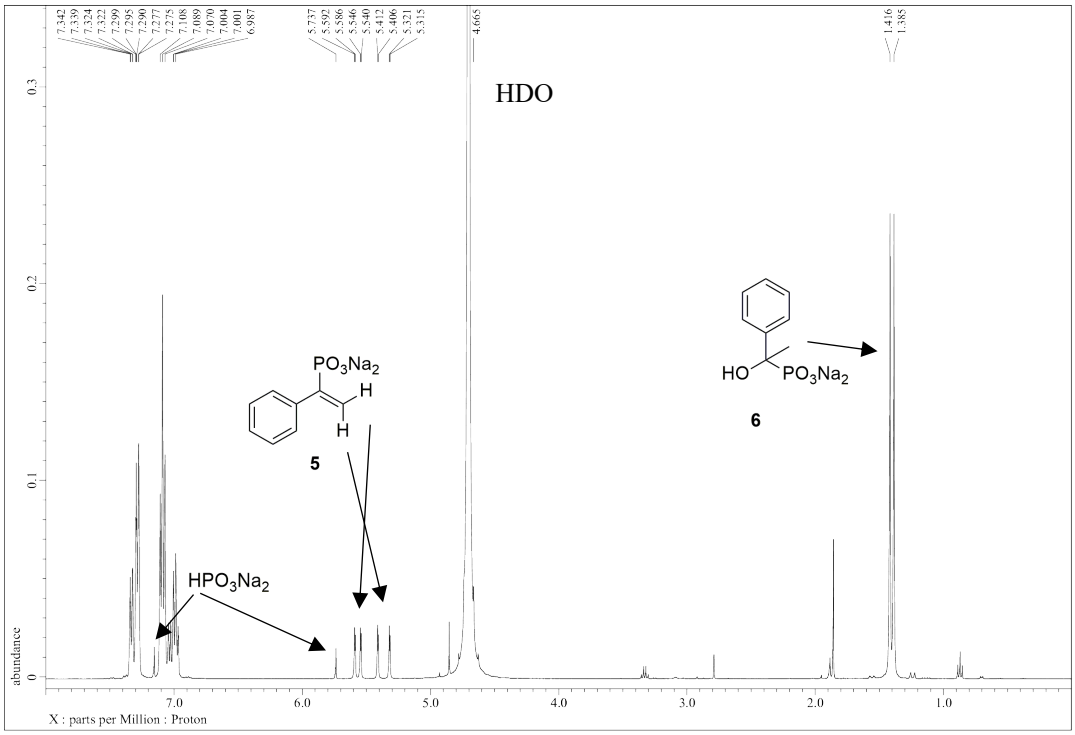
^{31}P NMR spectrum of reaction mixture after heating **2'f** with 3.3M NaOH after addition of 1-hydroxy-1-phenylethylphosphonic acid **6** (as standard)



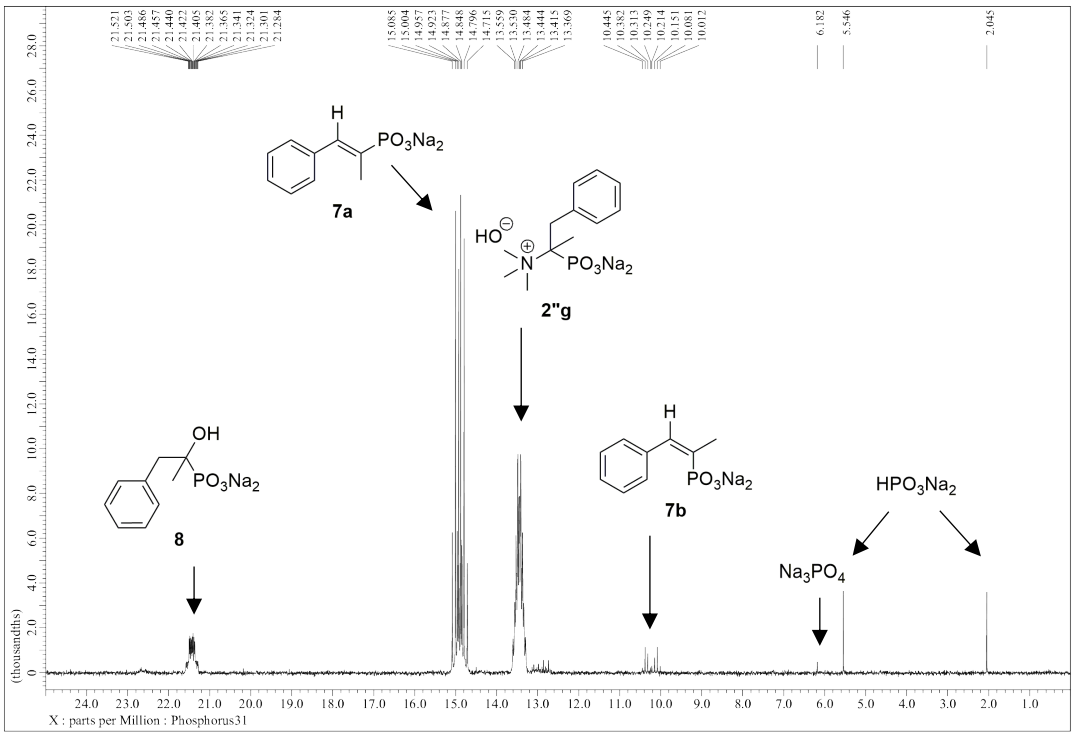
^{1}H NMR spectrum of reaction mixture after heating **2'f** with 3.3M NaOH



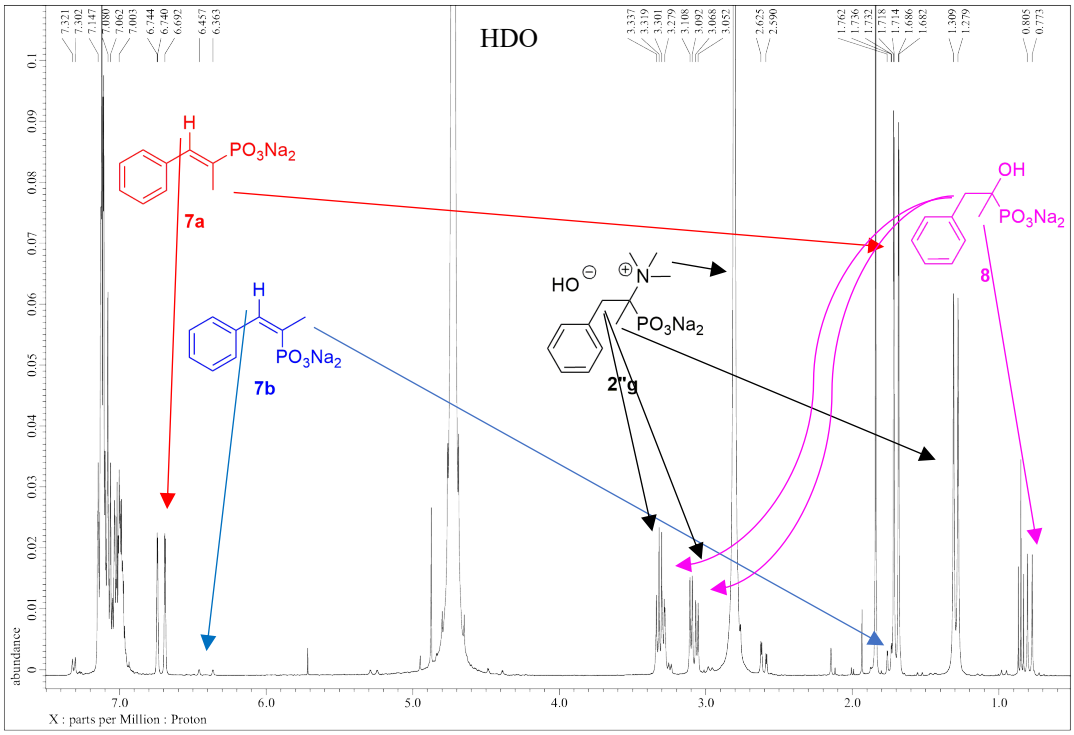
^{1}H NMR spectrum of reaction mixture after heating **2'f** with 3.3M NaOH after addition of 1-hydroxy-1-phenylethylphosphonic acid **6** (as standard)



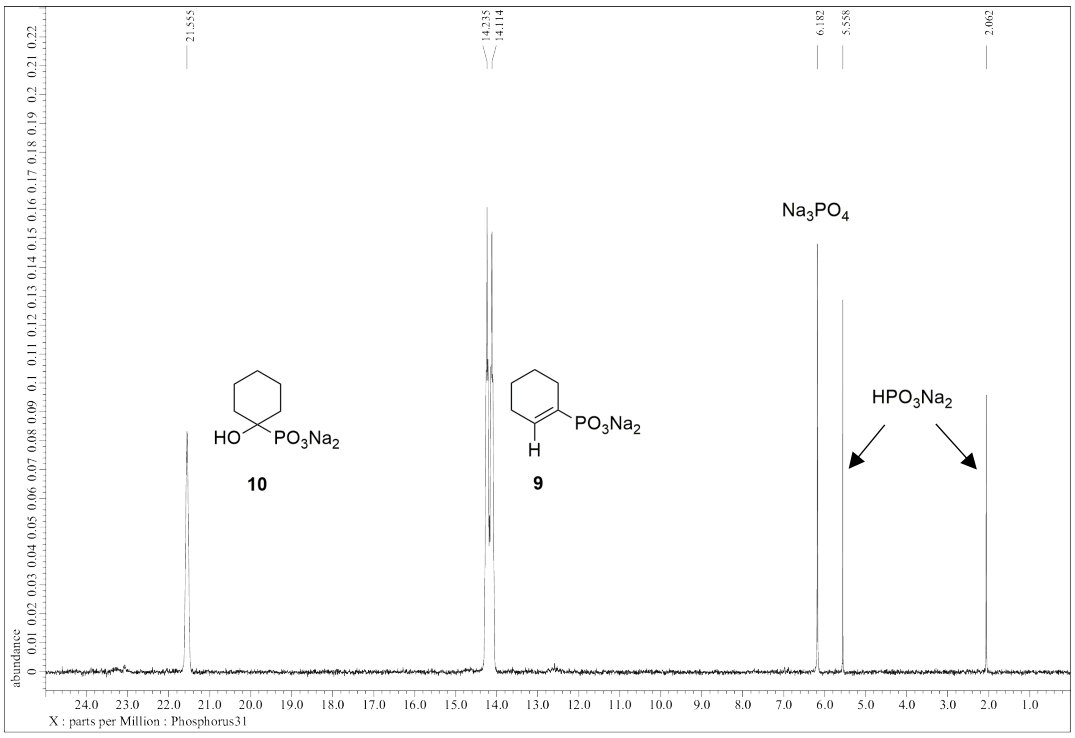
^{31}P NMR spectrum of reaction mixture after heating **2'g** with 3.3M NaOH



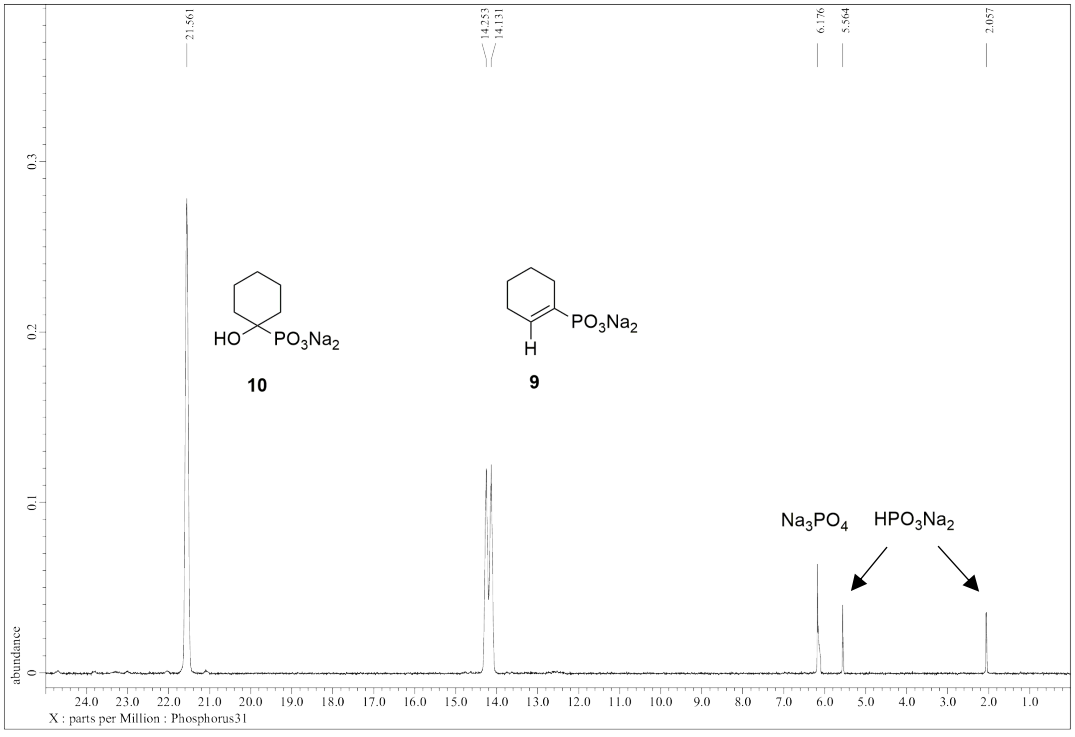
^{1}H NMR spectrum of reaction mixture after heating **2'g** with 3.3M NaOH



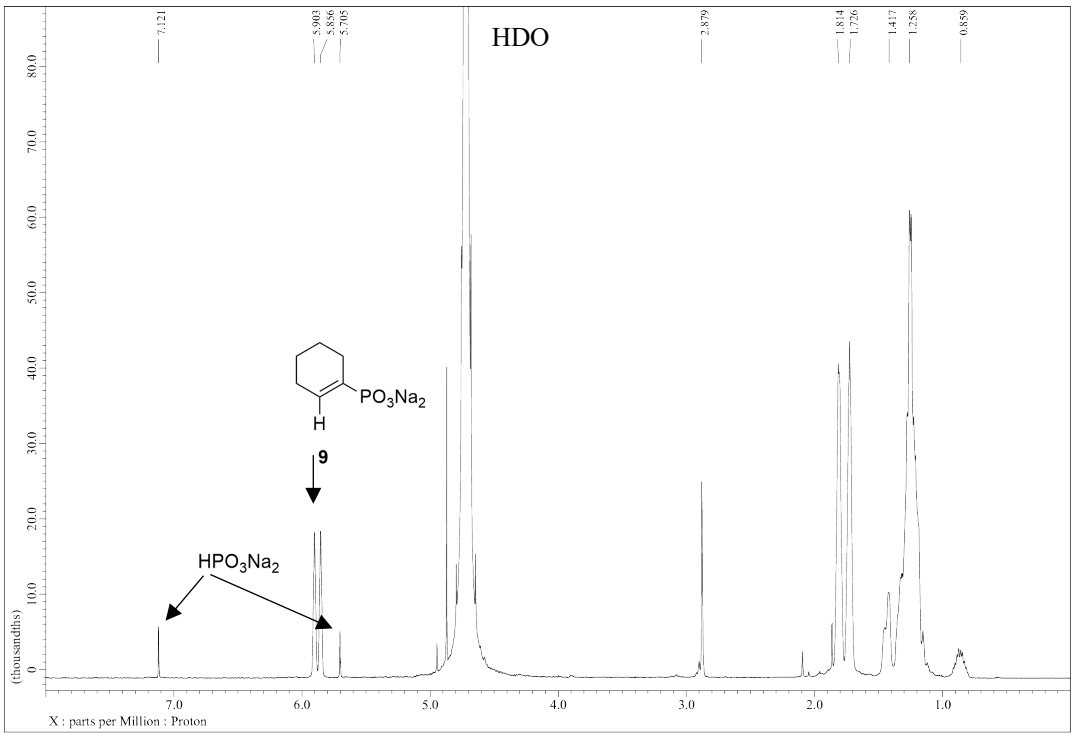
^{31}P NMR spectrum of reaction mixture after heating **2'h** (contaminated with 6% of HPO_3H_2) with 3.3M NaOH



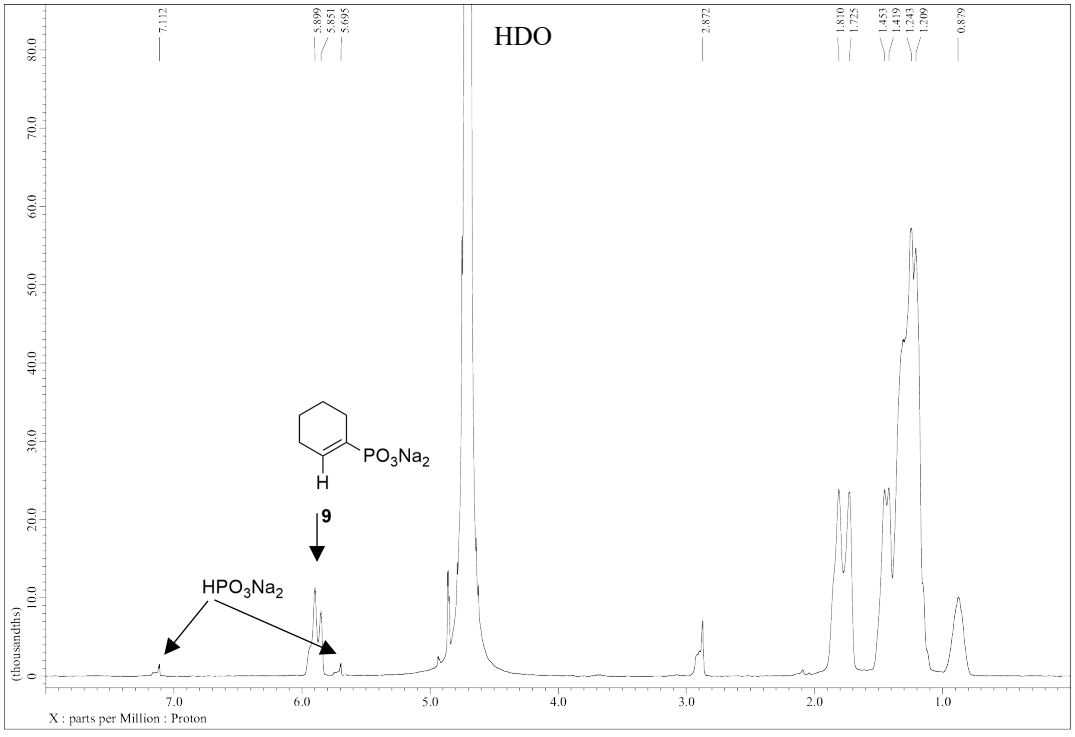
^{31}P NMR spectrum of reaction mixture after heating **2'h** (contaminated with 6% of HPO_3H_2) with 3.3M NaOH after addition of 1-cyclohexylphosphonic acid **10** (as reference material).



^{1}H NMR spectrum of reaction mixture after heating **2'h** (contaminated with 6% of HPO_3H_2) with 3.3M NaOH



^{1}H NMR spectrum of reaction mixture after heating **2'h** (contaminated with 6% of HPO_3H_2) with 3.3M NaOH after addition of 1-cyclohexylphosphonic acid **10** (as reference material).



Experimental Section

General

Solvents and NaOH were purchased from Chempur and Stanlab and used without purification. Dimethyl sulfate and deuterium oxide was purchased from Sigma-Aldrich. Reactions that required heating were performed in heating mantle or in heating block apparatus with external temperature control. ^{1}H, $^{13}C\{^{1}H\}$ and ^{31}P NMR spectra were collected on Jeol 400yh instrument (400MHz for ^{1}H NMR, 162MHz for ^{31}P NMR and 100MHz for ^{13}C NMR) and were processed with dedicated software (Delta 5.0.5). NMR experiments recorded in D_2O were referenced to the respective residual ^{1}H or ^{13}C signals of the solvent. Multiplicities are reported using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. High resolution mass spectra were collected using electrospray ionization on Waters LCT Premier XE TOF instrument. Since all compounds **2'** melted with vigorous decomposition therefore the melting/decomposition points were determined at constant 5°C/min at Digimelt Apparatus.

Synthesis of starting materials

1-Aminoalkylphosphonic acid **1a-1j** were obtained by Sorokas' protocol[2] in reaction of appropriate carbonyl compound with acetamide, acetyl chloride and PCl_3 in acetic acid.

Experimental procedures

Caution note: Dimethyl sulfate is extremely toxic. Contact with the liquid or inhaling the vapor should be avoided. This reagent should be handled with great caution and all actions should be performed under the hood.

Synthesis of quaternary ammonium methylsulfates 2 and 4

Method A

The appropriate 1-aminoalkylphosphonic acid **1** (5.0 mmol) was dissolved in NaOH solution (25 mmol, 1.00 g in 8 ml of water) and stirred for 10 minutes. Subsequently, Me_2SO_4 (20 mmol, 2.52 g, 1.89 ml) was added dropwise over 3 minutes. The initially two-phase mixture

homogenized after 60 minutes. Stirring was continued for 48 hours at 20 °C. The progress of the reaction was controlled by means of ^{31}P NMR.

Method B

The appropriate 1-aminoalkylphosphonic acid **1** (5.0 mmol) was dissolved in NaOH solution (30 mmol, 1.20 g in 10 ml of water) and stirred for 10 minutes. Subsequently, Me_2SO_4 (30 mmol, 3.78 g, 2.84 ml) was added dropwise over 3 minutes. The initially two-phase mixture homogenized after 60 minutes. Stirring was continued for 48 hours at 20 °C. The progress of the reaction was controlled by means of ^{31}P NMR. If conversion was not satisfactory, another portion of NaOH solution (10 mmol, 0.40 g, in 2 ml of water) was added to a stirred solution and after 10 minutes Me_2SO_4 (10 mmol, 1.26 g, 0.95 ml) was added dropwise. The progress of the was controlled by means of ^{31}P NMR. This step was repeated until result was satisfactory (full conversion of the substrate).

Hydrolysis of quaternary ammonium methylsulfates 2 and 4 and isolation of 2'a - 2'j

Reaction mixture was added to aq. 12M HCl (1 ml of acid per 1 ml of mixture) and subsequently refluxed for 4 hours. After that time reaction was cooled down and aqueous solution of $BaCl_2$ (1.0 mmol per 1.0 mmol of Me_2SO_4) was added dropwise. After 1 hour, precipitated $BaSO_4$ was removed by centrifugation (5000 rpm, 5 minutes), washed with water and centrifuged again. Combined aqueous layers were evaporated under reduced pressure to dryness. To resulting semisolid residue 10 ml of EtOH (99.8%) was added and the mixture was refluxed for 3 minutes. After cooling, precipitated NaCl was removed by suction and washed with EtOH (99.8%) (4 x 3 ml). Collected filtrates were evaporated under reduced pressure, yielding crude phosphonic acid quaternary ammonium derivatives **2'**. Crude products **2'** were purified by crystallization from EtOH (99.8%) (1.5 ml of EtOH per 1.0 g of crude product) and precipitated by addition of Et_2O (4.5 to 6.0 ml) and cooling in -20 °C. Precipitated products were filtered off, washed with cold Et_2O (4 x 2 ml) and dried in vacuo.

N,N,N-trimethyl-N-(phosphonomethyl)ammonium chloride (2'a). Compound **2'a** was prepared by following the method A procedure, starting from **1a** (1.11 g, 10.0 mmol). **2'a** was obtained (0.88 g, 48% isolated yield) as a white solid which decomposes at 146 °C. ^{1}H NMR

(50 mg, 0.60 ml D_2O): δ 3.39 (d, 2H, J = 12.8 Hz), 3.05 (s, 9H). ^{31}P NMR (50 mg, 0.60 ml D_2O): δ 6.75 (t, J = 13.1 Hz). $^{13}C\{^1H\}$ NMR (50 mg, 0.60 ml D_2O): δ 62.3 (d, J = 136.1 Hz), 55.3 (3C). HRMS (TOF-ES+) calcd for $C_4H_{12}NO_3P$ $[M+H]^+$ m/z: 154.0633, found: 154.0627.

N,N,N-trimethyl-N-(1-phosphonoethyl)ammonium chloride (2'b). Compound **2'b** was prepared by following the method A procedure, starting from **1b** (0.63 g, 5.0 mmol). **2'b** was obtained (0.60 g, 59% isolated yield) as a white solid which decomposes at 200 °C. ^1H NMR (22 mg, 0.60 ml D_2O): δ 3.47 (doublet of quartets, J = 7.3 Hz, J = 14.1 Hz, 1H), 3.10 (s, 9H), 1.45 (dd, 3H, J = 7.3 Hz, J = 13.8 Hz). ^{31}P NMR (22 mg, 0.60 ml D_2O): δ 10.92 (quintet, J = 14.0 Hz). $^{13}C\{^1H\}$ NMR (22 mg, 0.60 ml D_2O): δ 67.8 (d, J = 137.3 Hz), 53.0 (3C), 11.5. HRMS (TOF-ES+) calcd for $C_5H_{14}NO_3P$ $[M+H]^+$ m/z: 168.0790, found: 169.0794.

N,N,N-trimethyl-N-(2-methyl-1-phosphonopropyl)ammonium chloride (2'c). Compound **2'c** was prepared by following the method B procedure (8.0 moles of NaOH and Me_2SO_4 per 1 mole of 1-APA in total), starting from **1c** (0.77 g, 5.0 mmol). **2'c** was obtained (0.91g, 67% isolated yield) as a white solid which decomposes at 120 °C. ^1H NMR (17 mg, 0.60ml D_2O): δ 3.22 (d, J = 16.8 Hz, 1H), 3.11 (s, 9H), 2.26-2.33 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.3 Hz, 3H). ^{31}P NMR (17 mg, 0.60 ml D_2O): δ 8.50 (dd, J = 16.8 Hz, J = 22.4 Hz). $^{13}C\{^1H\}$ NMR (21 mg, 0.60 ml D_2O): δ 77.4 (d, J = 134.4 Hz), 53.7 (3C), 26.6, 22.9, 18.6 (d, J = 5.8 Hz). HRMS (TOF-ES+) calcd for $C_7H_{18}NO_3P$ $[M+H]^+$ m/z: 196.1103, found: 196.1100.

N,N,N-trimethyl-N-[phenyl(phosphono)methyl]ammonium chloride (2'd). Compound **2'd** was prepared by following the method A procedure, starting from **1d** (0.94 g, 5.0 mmol). **2'd** was obtained (1.01 g, 76% isolated yield) as a white solid which decomposes at 188°C. ^1H NMR (31 mg, 0.55ml D_2O): δ 7.70 (d, 1H, J = 7.0 Hz), 7.25-7.42 (m, 4H), 4.49 (d, 1H, J = 17.1 Hz), 3.07 (s, 9H). ^{31}P NMR (31 mg, 0.55ml D_2O): δ 7.68 (d, J = 16.8 Hz). $^{13}C\{^1H\}$ NMR (31 mg, 0.55 ml D_2O): δ 134.4 (d, J = 9.8 Hz), 130.5, 130.1 (d, J = 3.5 Hz), 129.7 (d, J = 1.7Hz), 129.3, 129.0, 76.0 (d, J = 135.6 Hz), 53.8 (3C). HRMS (TOF-ES+) calcd for $C_{10}H_{17}NO_3P$ $[M+H]^+$ m/z: 230.0946, found: 230.0942.

N,N,N-trimethyl-N-(1-methyl-1-phosphonoethyl)ammonium chloride (2'e). Compound **2'e** was prepared by following the method A procedure, starting from **1e** (0.70 g, 5.0 mmol). **2'e** was obtained (0.85 g, 78% isolated yield) as a white solid which decomposes at 213 °C. ^1H NMR

(33 mg, 0.55 ml D_2O): δ 3.04 (s, 9H), 1.41 (d, 6H, J = 13.1 Hz). ^{31}P NMR (33 mg, 0.55 ml D_2O): δ 14.93 (septet, J = 13.1 Hz). $^{13}C\{^1H\}$ NMR (33 mg, 0.55 ml D_2O): δ 71.4 (d, J = 142.5 Hz), 51.1 (3C), 19.4 (2C). HRMS (TOF-ES+) calcd for $C_6H_{17}NO_3P$ $[M+H]^+$ m/z: 182.0946, found: 182.0947.

N,N,N-trimethyl-N-(1-phenyl-1-phosphononoethyl)ammonium chloride (2'f). Compound **2'f** was prepared by following the method B procedure (8.0 moles of NaOH and Me_2SO_4 per 1.0 mole of 1-APA in total), starting from **1f** (0.50 g, 2.5 mmol). **2'f** was obtained (0.47 g, 67% isolated yield) as a white solid which turn into yellow gum during storing. ^1H NMR (40 mg, 0.60 ml D_2O): δ 7.40-8.40 (m, 2H), 7.10-7.20 (m, 3H), 2.98 (s, 9H), 1.95 (d, J = 13.1 Hz, 3H). ^{31}P NMR (40mg, 0.60 ml D_2O): δ 12.67 (quartet, J = 13.1 Hz). $^{13}C\{^1H\}$ NMR (40 mg, 0.60 ml D_2O): δ 133.1 (broad, 1C), 131.9, 130.3 (2C), 128.4 (broad, 2C), 76.7 (broad d, J = 138.5 Hz), 51.8 (3C), 17.6. HRMS (TOF-ES+) calcd for $C_{11}H_{18}NO_3P$ $[M+H]^+$ m/z: 244.1103, found: 244.1099.

N,N,N-trimethyl-N-(1-methyl-2-phenyl-1-phosphonoethyl)ammonium chloride (2'g). Compound **2'g** was prepared by following the method A procedure, starting from **1g** (0.51 g, 2.5 mmol). **2'g** was obtained (0.59 g, 80% isolated yield) as a white solid which decomposes at 140 °C. ^1H NMR (21 mg, 0.60 ml D_2O): δ 7.16-7.33 (m, 5H), 3.37 (dd, J = 9.6 Hz, J = 14.8 Hz, 1H), 3.22 (dd, J = 14.4 Hz, J = 14.4 Hz, 1H), 3.12 (s, 9H), 1.47 (d, J = 13.8 Hz, 3H). ^{31}P NMR (21 mg, 0.60 ml D_2O): δ 14.05 (doublet of doublets of quartets, J unmarked). $^{13}C\{^1H\}$ NMR (21 mg, 0.60 ml D_2O): δ 135.5 (d, J = 6.3 Hz), 131.6 (2C), 128.4 (2C), 127.4, 75.6 (d, J = 139.0 Hz), 52.1 (3C), 36.7, 16.4. HRMS (TOF-ES+) calcd for $C_{12}H_{20}NO_3P$ $[M+H]^+$ m/z: 258.1259, found: 258.1251.

N,N,N-trimethyl-N-(1-phosphonocyclohexyl)ammonium chloride (2'h). Compound **2'h** was prepared by following the method B procedure (10.0 moles of NaOH and Me_2SO_4 per 1.0 mole of 1-APA in total), starting from **1h** (0.90 g, 5.0 mmol). **2'h** was obtained (0.51 g, 40% isolated yield) as a white solid which decomposes at 183°C. ^1H NMR (23 mg, 0.55 ml D_2O): δ 3.06 (s, 9H), 2.01-2.17 (m, 2H), 1.41-1.80 (m, 7H), 0.97-1.15 (1H). ^{31}P NMR (23 mg, 0.55 ml D_2O): δ 14.88m. $^{13}C\{^1H\}$ NMR (21 mg, 0.60 ml D_2O): δ 76.7 (d, J = 138.5 Hz), 50.9 (3C), 26.6 (2C), 23.0, 22.1 (2C). HRMS (TOF-ES+) calcd for $C_9H_{20}NO_3P$ $[M+H]^+$ m/z: 222.1259, found: 222.1255.

N,N,N-trimethyl-N-(1-phosphonocyclopentyl)ammonium chloride (2'i). Compound **2'i** was prepared by following the method B procedure (6.0 moles of NaOH and Me_2SO_4 per 1.0 mole of 1-APA in total), starting from **1i** (0.83 g, 5.0 mmol). **2'i** was obtained (1.04 g, 86% isolated yield) as a yellowish solid which decomposes at 201 °C. ^{1}H NMR (29 mg, 0.55 ml D_2O): δ 3.03 (s, 9H), 1.93-2.15 (m, 4H), 1.52-1.66 (m, 4H). ^{31}P NMR (29 mg, 0.55 ml D_2O): δ 16.48 (tt, *J* = 10.3Hz, *J* = 15.0 Hz). ^{13}C{^{1}H} NMR (40 mg, 0.55 ml D_2O): δ 81.5 (d, *J* = 144.8 Hz), 51.5 (3C), 21.7, 21.6. HRMS (TOF-ES+) calcd for $C_8H_{18}NO_3P$ $[M+H]^+$ m/z: 208.1103, found: 208.1105.

N,N,N-trimethyl-N-[(4-methoxyphenyl)(phosphono)methyl]ammonium chloride (2'j). Compound **2'j** was prepared by following the method A procedure, starting from **1j** (0.94 g, 5.0 mmol). **2'j** was obtained (1.29 g, 87% isolated yield) as a white solid which decomposes at 182 °C. ^{1}H NMR (33 mg, 0.55 ml D_2O): δ 7.63 (dd, 1H, *J* = 8.9 Hz, *J* unmarked), 7.21 (dd, 1H, *J* = 8.6 Hz, *J* = 2.1 Hz), 6.92 (dd, 1H, *J* = 8.9 Hz, J = 2.8 Hz), 6.88 (dd, *J* = 8.6 Hz, *J* = 2.8 Hz), 4.45 (d, 1H, *J* = 17.1 Hz), 3.68 (s, 3H), 3.03 (s, 9H). ^{31}P NMR (33 mg, 0.55 ml D_2O): δ 7.96 (d, *J* = 16.8 Hz). ^{13}C{^{1}H} NMR (24 mg, 0.55 ml D_2O): δ 160.4, 136.0 (d, *J* = 9.8 Hz), 131.6 (d, *J* = 2.9 Hz), 122.0 (d, 1.7 Hz), 114.6, 114.4, 75.5 (d, *J* = 136.7 Hz), 55.4, 53.5 (3C). HRMS (TOF-ES+) calcd for $C_{11}H_{18}NO_4P$ $[M+H]^+$ m/z: 260.1052, found: 260.1058.

Test of stability of compounds 2' in alkaline medium

Solution of *N,N,N*-trialkyl-*N*-(1-phosphonoalkyl)ammonium salt **2'** (0.15mmol) in 3.3M NaOH in D_2O (2.0mmol, 0.60ml) was heated at 100°C for 35hours. Inorganic solid precipitated in the test tube. Subsequently ^{1}H and ^{31}P NMR spectra were recorded. Afterwards, reference materials (corresponding hydroxy- phosphonates) were added, and spectra were recorded again. In the case of salt **2'h** crude product, containing 6%mol of phosphonic acid, was used.

Identification of degradation products

The degradation products (olefins) were identified by comparison of the chemical shifts on ^{1}H and ^{31}P NMR spectra with values reported in literature for exact or similar structures while the formation of 1-hydroxyalkylphosphonic acids **6** and **10** was confirmed by the addition of prepared standards.

1-Phenylvinylphosphonic acid (5). ^{1}H NMR (in 3.3M NaOH, D_2O): δ 5.54 dd, J= 1.2 Hz, J_{HP} = 18.3 Hz), 5.34(dd, J = 1.2 Hz, J_{HP} = 36.7 Hz). ^{31}P NMR (in 3.3M NaOH, D_2O): δ 10.41 (dd, J_{HP} = 18.3 Hz, J_{HP} = 36.0 Hz).

(*E*)-1-Methyl-2-phenylvinylphosphonic acid (7a). ^{1}H NMR (in 3.3M NaOH, D_2O): δ 6.72 (doublet of quartets, J = 1.5 Hz, J_{HP} = 20.8Hz, 1H), 1.65 (dd, J = 1.5 Hz, J_{HP} = 12.8 Hz, 3H). ^{31}P NMR (in 3.3M NaOH, D_2O): δ 14.90 (doublet of quartets, J_{HP} = 20.6 Hz, J = 13.1 Hz).

(*Z*)-1-Methyl-2-phenylvinylphosphonic acid (7b). ^{1}H NMR (in 3.3M NaOH, D_2O): δ 6.41 (d, J_{HP} = 37.0 Hz, 1H), 1.75 (dd, J = 1.5Hz, J_{HP} = 10.7 Hz, 3H). ^{31}P NMR (in 3.3M NaOH, D_2O): δ 10.23 (doublet of quartets, $J_{HP(trans)}$ = 37.4 Hz, J_{HP} = 10.7 Hz).

2-Hydroxy-3-phenylpropan-2-ylophosphonic acid (8). ^{1}H NMR (in 3.3M NaOH, D_2O): δ 2.60 (dd, J = 13.8 Hz, J = 3.1 Hz, 1H), 0.79 (d, J = 12.8 Hz, 3H). ^{31}P NMR (in 3.3M NaOH, D_2O): δ 21.43 (doublet of doublets of quartets, J = 12.6 Hz, J = 6.5 Hz, J = 2.8 Hz).

Cyclohex-1-enylphosphonic acid (9). ^{1}H NMR (in 3.3M NaOH, D_2O): δ 5.88 (broad doublet, J_{HP} = 19.0Hz, 1H), ^{31}P NMR (in 3.3M NaOH, D_2O): δ 14.18 (doublet of quintets, J = 19.6 Hz, J = 3.7 Hz).

Synthesis of 1-hydroxyalkylphosphonic acids used as reference materials (standards)

1-Hydroxy-1-(phenyl)ethylphosphonic acid (6) was obtained by Sekines' et al.[3] method, starting from tris(trimethylsilyl)phospite and acetophenone (1.20 g, 10.0 mmol). Crude **6** (contaminated with 12%mol of phosphonic acid and 5%mol of phosphoric acid) was obtained (1.59 g, 72% yield) as white solid. Crystallization attempts failed, therefore crude **6** was used as a reference material. ^{1}H NMR (17 mg, 0.55 ml D_2O): δ 7.36-7.44 (m, 2H), 7.14-7.29 (m, 3H), 1.62 (d, J = 15.3 Hz, 3H). ^{31}P NMR (17 mg, 0.55 ml D_2O): δ 23.51 (quartet, J = 15.3 Hz). ^{13}C{^{1}H} NMR (27 mg, 0.55 ml D_2O): δ 141.3, 128.3, 128.3,127.7 (d, J = 2.9 Hz), 126.0, 125.9, 73.2 (d, J = 159.7 Hz), 24.0 (d, J = 3.5 Hz). HRMS (TOF-ES+) calcd for $C_8H_{11}O_4P$ [M]+ m/z: 203.0473, found: 203.0478.

1-Hydroxycyclohexylphosphonic acid (10) was synthesized according to Goldeman and Sorokas' protocol.[4] Compound **10** was obtained (1.20 g, 70% isolated yield) as white solid. ^{1}H NMR (17 mg, 0.55 ml D_2O): δ 1.58-1.69 (m, 2H), 1.30-1.55 (m, 7H), 0.97-1.14 (m, 1H). ^{31}P

NMR (17 mg, 0.55 ml D_2O): δ 27.3 (broad s). $^{13}C\{^1H\}$ NMR (22mg, 550uL D_2O): δ 70.7 (d, *J* = 163.2 Hz), 30.4, 30.4, 24.7, 19.6, 19.5. HRMS (TOF-ES+) calcd for $C_6H_{13}NO_4P$ [M]+ m/z: 181.0630, found: 181.0632.

References

1. S. Pietri, M. Miollan, S. Martel, F. Le Moigne, B. Blaive, M. Culcasi. *J. Biol. Chem.,* **2000***, 275*, 19505-19512.

2. M. Soroka. Liebigs Ann. Chem. **1990**. *4*, 331-334.

3. M. Sekine, I. Yamamoto, A. Hashizume, T. Hata. *Chemistry Letters*, **1977**, *6*, 485-488.

4. W. Goldeman, M. Soroka. *Synthesis*, **2006**, 18, 3019-3024.