**Supporting Information**

# Switching between P-Acylation and O-Acylation of H-Phosphonates with Chloroformates by Changing Acyl Pyridinium and Acyl Ammonium Ions in a Microflow Reactor

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**General techniques**

NMR spectra were recorded on a JEOL-ECS400 (400 MHz for $^{1}H$, 100 MHz for $^{13}C$, 162 MHz for $^{31}P$) or JEOL-ECZ400 (400 MHz for $^{1}H$, 100 MHz for $^{13}C$, 162 MHz for $^{31}P$) instrument in the indicated solvent. Chemical shifts are reported in units of parts per million (ppm) relative to tetramethylsilane (0.00 ppm) for $^{1}H$ NMR and $CDCl_3$ (77.0 ppm) and phosphoric acid (0.00 ppm) for $^{31}P$ NMR. Multiplicities were reported by using the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, brs; broad singlet, dd; double doublet, ddd; double double doublet, dddd; double double double doublet, dt; double triplet, dq; double quartet, m; multiplet, *J*; coupling constants in Hertz (Hz). IR spectra were recorded on a JASCO Corporation FT/IR-4100 FT-IR Spectrometer. Only the strongest and/or structurally important peaks were reported as the IR data given in $cm^{-1}$. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics Compact in electrospray ionization (ESI) method. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 10% ethanolic phosphomolybdic acid and/or ethanolic *p*-anisaldehyde contains acetic acid and $H_2SO_4$. Flash column chromatography was performed on Silica Gel PSQ 60B purchased from Fuji Silysia Chemical LTD. Gel permeation chromatography (GPC) for purification was performed on Japan Analytical Industry Model LaboACE LC-5060 (recycling preparative HPLC) on a Japan Analytical Industry Model UV-254 LA ultraviolet detector and RI-700 LA refractive index detector with a polystyrene gel column (JAIGEL-2HR, 20 mm × 600 mm), using chloroform as solvent (10 mL/min). Analytical HPLC was carried out using a JASCO PU-4580 HPLC pump system with a JASCO MD-2018 PDA Detector, a Shimadzu CTO 20A Column Oven, a JASCO LG-4580 Quaternary Gradient Unit, a JASCO DG4580 Degassing Unit, a JASCO AS-4550 Autosampler, and a JASCO LC-NetII/ADC Interface Box. MeOH, EtOH, $CH_2Cl_2$, and $CH_3CN$ were dried by flame-dried molecular sieves 3Å.

**Micro-flow reactor setup**

A stainless steel T-shape mixer was purchased from Sanko Seiki Co. Ltd. (inner diameter: 0.25 mm). Teflon® (PTFE: polytetrafluoroethylene) tubes (inner diameter: 0.80 mm) were purchased from Senshu Scientific Co., Ltd. PEEK fittings, PEEK unions, SUS Tubes (inner diameter: 0.80 mm), SUS fittings and SUS unions (inner diameter: 0.80 mm) were purchased from GL Science Inc. Solutions were introduced to a micro-flow system with syringe pumps (Harvard PHD ULTRA) equipped gastight syringes (SGE 10 mL). The gastight syringes and the Teflon tubes were connected with joints purchased from Flon Industry Co., Ltd.

The employed micro-flow systems for the synthesis of phosphonoformate ester, phosphite, or phosphate using chloroformate are shown in **Figure S-1**. The gastight syringes and the T-shape mixers 1 and 2 were connected with the Teflon tubes and SUS tubes (for controlling the temperature of solutions). The T-shape mixers 1 and 2 were connected with the reaction tube 1 (Teflon tube). The T-shape mixer 2 was connected with the reaction tube 2 (Teflon tube). The T-shape mixers and reaction tubes were immersed in water bath.

The employed micro-flow systems for the synthesis of phosphate using triphosgene are shown in **Figure S-2**. The gastight syringes and the T-shape mixers 1, 2, and 3 were connected with the Teflon tubes and SUS tubes (for controlling the temperature of solutions). The T-shape mixers 1 and 2 were connected with the reaction tube 1 (Teflon tube). The T-shape mixers 2 and 3 were connected with the reaction tube 2 (Teflon tube). The T-shape mixer 3 was connected with the reaction tube 3 (Teflon tube). The T-shape mixers and reaction tubes were immersed in water bath.

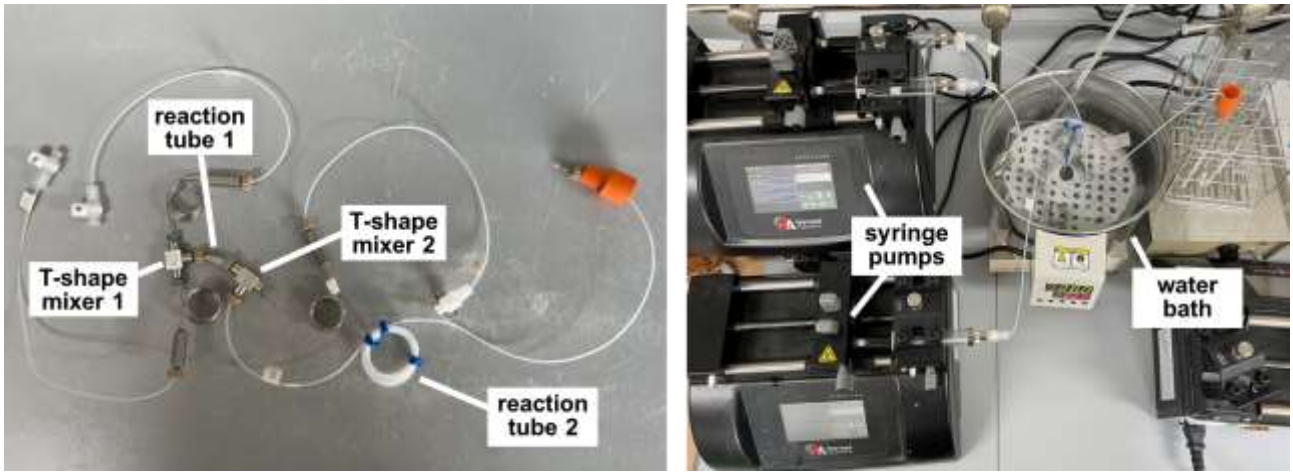



**Figure S1.** Micro-flow reactor set-up for the synthesis of phosphonoformate esters **3** or phosphotriesters **9**

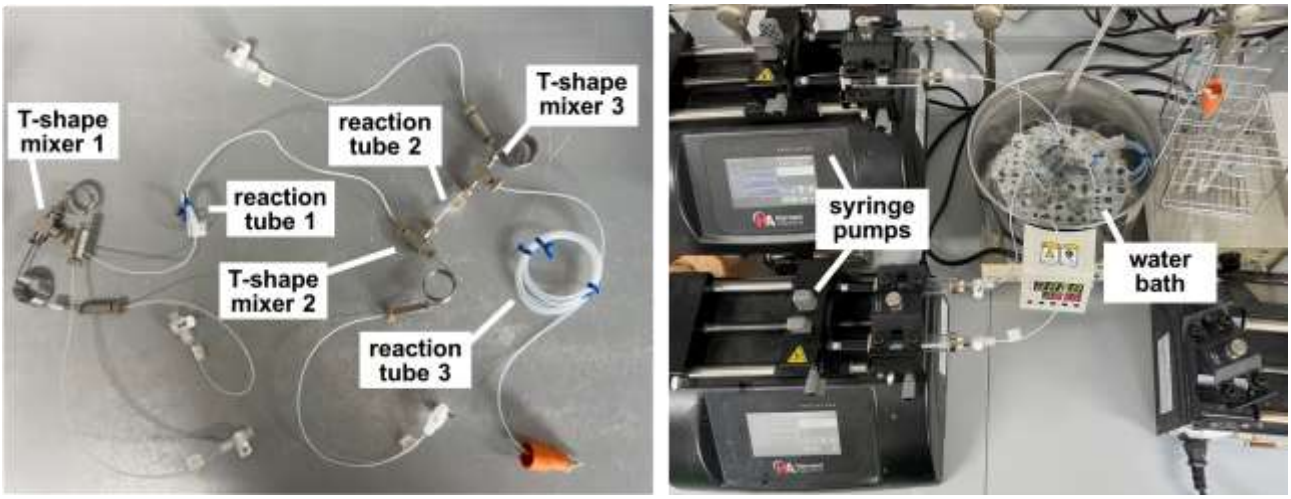
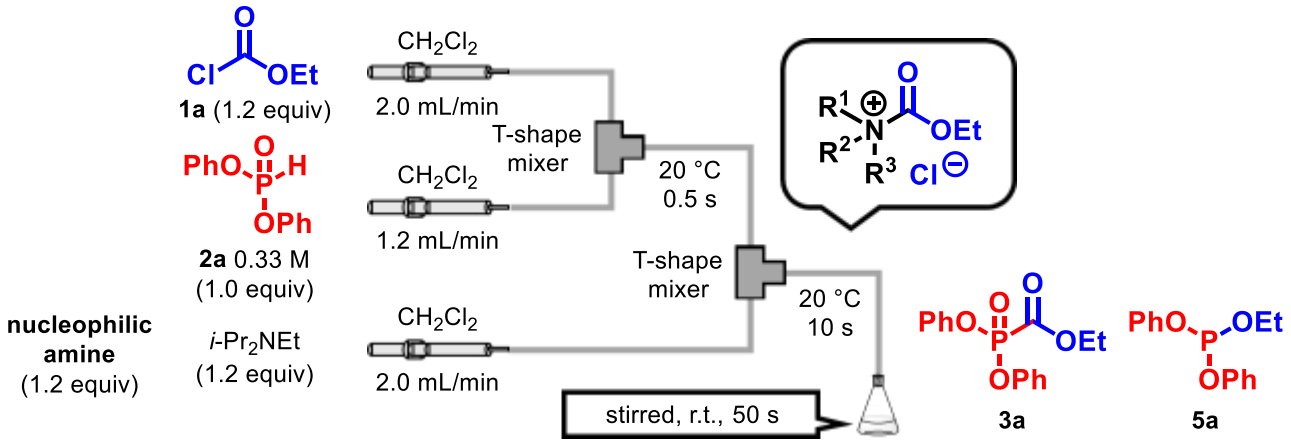



**Figure S2.** Micro-flow reactor set-up for the synthesis of phosphotriesters **9** from alcohol and triphosgene

## Examination of nucleophilic amines

**Table S-1. Examination of nucleophilic amines for the synthesis of 3a and 5a**



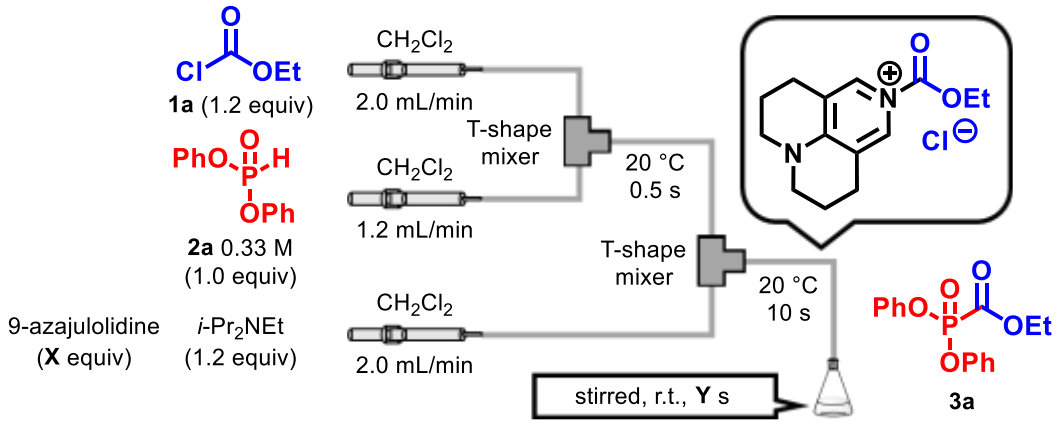

| entry | nucleophilic amine | NMR yield [%] | | |
|---|---|---|---|---|
| | | **1a** | **3a** | **5a** |
| 1 | - | 90 | trace | n.d. |

| | | | | |
|---|---|---|---|---|
| 2 | pyridine | n.d. | trace | n.d. |
| 3 | NMI | 36 | 57 | n.d. |
| 4 | DMAP | 19 | 57 | n.d. |
| 5 | 4-morpholinopyridine | 11 | 42 | n.d. |
| 6 | 4-pyrrolidinopyridine | 12 | 55 | n.d. |
| 7 | 9-azajulolidine | 16 | 74 | n.d. |
| 8 | NMM | 38 | 4 | 45 |
| 9 | $Me_2NBn$ | 27 | 4 | 38 |
| 10 | *N*-methylpiperidine | 7 | 6 | 83 |
| 11 | *N*-methylpyrrolidine | 2 | 5 | 90 |
| 12 | $Me_2NEt$ | 3 | 5 | 90 |
| 13 | $NMe_3$ | 1 | 5 | 90 |

A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of **nucleophilic amine** (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) was added, the reaction mixture was washed with 1 M HCl aq. and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1H$ NMR analysis using 1,1,2-trichloroethane as an internal standard.

**Examination of reaction conditions for the synthesis of phosphonoformate ester (3a)**

**Table S2. Examination of amounts of 9-azajulolidine and reaction times for the synthesis of 3a**

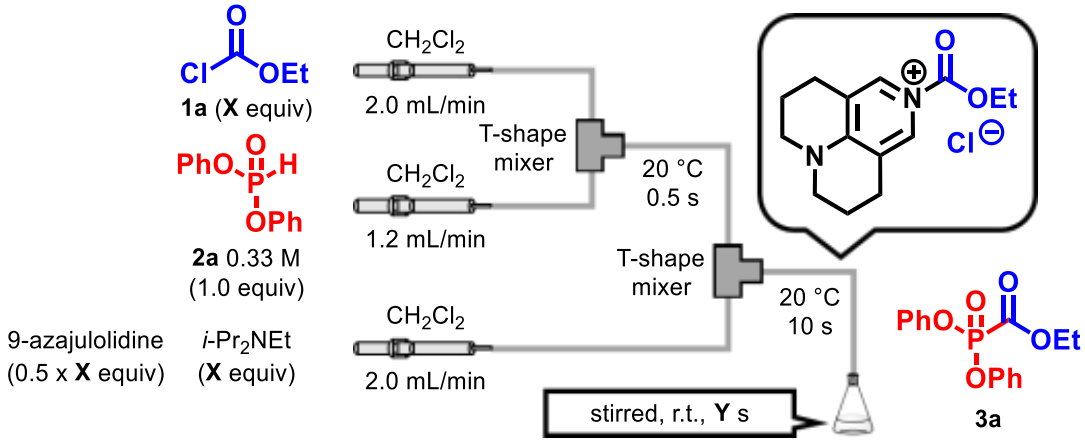



| entry | **X** [equiv] | **Y** [s] | NMR yield [%] |
|---|---|---|---|
| 1 | 0.1 | 60 | 32 |
| 2 | 0.6 | 60 | 76 |

| | | | |
|---|---|---|---|
| 3 | 1.2 | 60 | 74 |
| 4 | 0.6 | 30 | 66 |
| 5 | 0.6 | 120 | 74 |
| 6 | 0.6 | 180 | 71 |

A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of 9-azajulolidine (**X** equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **Y** s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1H$ NMR analysis using 1,1,2-trichloroethane as an internal standard.

**Table S3. Examination of amounts of 1a and reaction times for the synthesis of 3a**

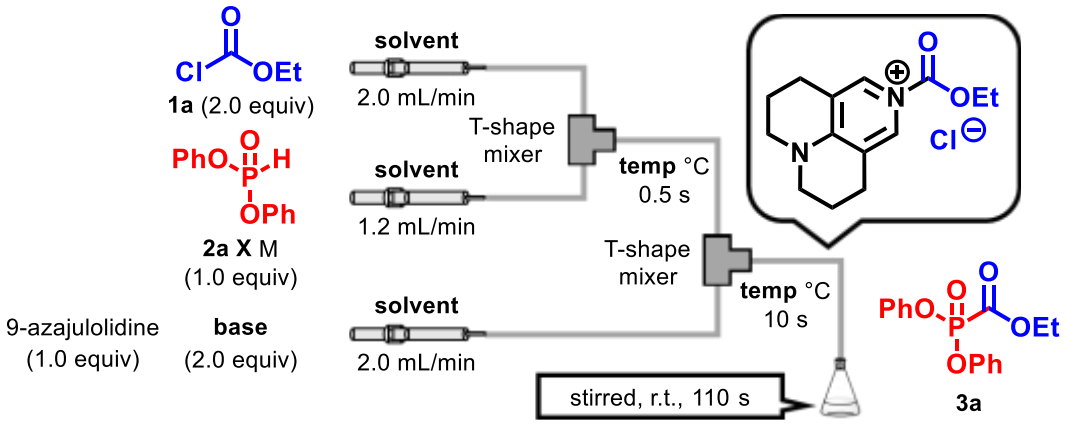



| entry | **X** [equiv] | **Y** [s] | NMR yield [%] |
|---|---|---|---|
| 1 | 1.2 | 60 | 76 |
| 2 | 1.2 | 120 | 74 |
| 3 | 2.0 | 60 | 84 |
| 4 | 2.0 | 120 | 89 |
| 5 | 3.0 | 60 | 80 |
| 6 | 3.0 | 120 | 79 |

A solution of ethyl chloroformate (**1a**) (**X** equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner

diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 μL, reaction time: 0.5 s) at the same temperature. A solution of 9-azajulolidine (0.5 × **X** equiv) and *i*-Pr$_2$NEt (**X** equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 μL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **Y** s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1$H NMR analysis using 1,1,2-trichloroethane as an internal standard.

**Table S4. Examination of bases, solvents, temperatures, and concentrations for the synthesis of 3a**



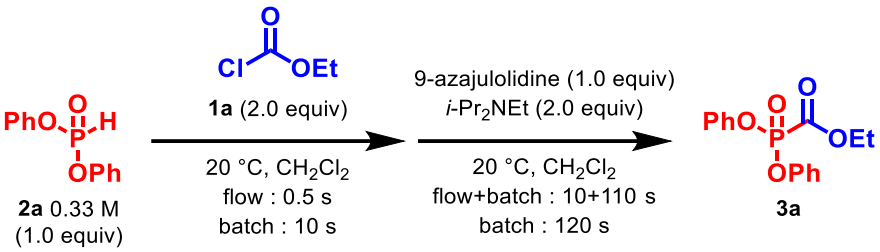

| entry | **base** (p*K*aH[a]) | **solvent** | **temp** [°C] | **X** [M] | NMR yield [%] |
|---|---|---|---|---|---|
| 1 | $Et_2NBn$ (9.5[1]) | $CH_2Cl_2$ | 20 | 0.33 | 40 |
| 2 | *i*-Pr$_2$NEt (11.4[2]) | $CH_2Cl_2$ | 20 | 0.33 | 89 (76)[b] |
| 3 | DBU (12.0[3]) | $CH_2Cl_2$ | 20 | 0.33 | 85 |
| 4 | *i*-Pr$_2$NEt | $CH_3CN$ | 20 | 0.33 | 72 |
| 5 | *i*-Pr$_2$NEt | THF | 20 | 0.33 | 69 |
| 6 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 0 | 0.33 | 68 |
| 7 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 40[c] | 0.33 | 89 |
| 8 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 0.17 | 87 |
| 9 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 0.67 | 87 |

a) p*K*a of conjugated acid. b) isolated yield. c) A back pressure regulator was used.

A solution of ethyl chloroformate (**1a**) (2.0 equiv) in **solvent** (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (**X** M, 1.0 equiv) in **solvent** (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at **temp** °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 μL, reaction time: 0.5 s) at the same temperature. A solution of 9-azajulolidine (1.0 equiv) and **base** (2.0 equiv) in **solvent** (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm,

volume: 867 μL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s (for **X** = 0.33 M and 0.67 M) or 30 s (for **X** = 0.17 M) at room temperature under argon. After being stirred for 110 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1H$ NMR analysis using 1,1,2-trichloroethane as an internal standard. The residue was purified by GPC.

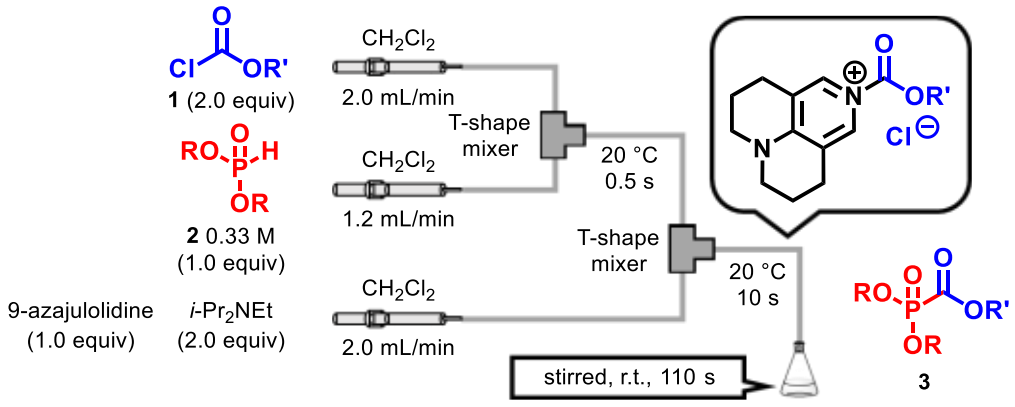
**Table S5. Comparison between micro-flow and batch conditions**




| entry | **method** | isolated yield [%] |
|---|---|---|
| 1 | micro-flow | 76 |
| 2 | batch | 71 |

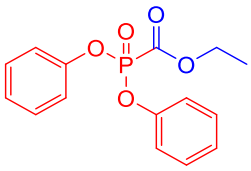
Micro-flow and batch conditions for synthesis of **3a** were compared. Quantities of compounds, solvents, and temperatures were identical to those of flow conditions. To a vigorously stirred (magnetic stirrer, 1,000 rpm) solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (0.50 mL), a solution of ethyl chloroformate (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (0.30 mL) was added in one portion at 20 °C under argon atmosphere. After being stirred for 10 s at the same temperature, a solution of 9-azajulolidine (0.20 M, 1.0 equiv) and *i*-$Pr_2NEt$ (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (0.50 mL) was added in one portion at 20 °C under argon atmosphere. After being stirred for 120 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by GPC.

**General procedure for the synthesis of phosphonoformate ester 3**



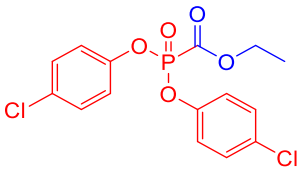
A solution of chloroformate **1** (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of *H*-phosphonate **2** (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of 9-azajulolidine (0.20 M, 1.0 equiv) and *i*-$Pr_2NEt$ (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 110 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by GPC.

**Ethyl (diphenoxyphosphoryl)formate (3a)**



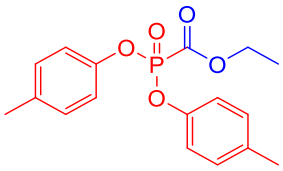
Purification method: **3a** was obtained by GPC.
23.2 mg, 0.0758 mmol, 76%
Colorless oil; IR (neat): 2984, 1725, 1489, 1296, 1197, 959 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 4H), 7.29-7.20 (m, 6H), 4.35 (dq, *J* = 1.2, 7.2 Hz, 2H), 1.31 (dt, *J* = 2.0, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.8 (d, *J* = 278.4 Hz), 149.7 (d, *J* = 8.6 Hz), 129.9, 125.9, 120.5 (d, *J* = 4.8 Hz), 63.0 (d, *J* = 4.7 Hz), 13.9 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -12.72 ppm; HRMS (ESI): calcd for $[C_{15}H_{15}O_5P+Na]^+$ 329.0549, found 329.0549.

**Ethyl (bis(4-chlorophenoxy)phosphoryl)formate (3b)**



Purification method: **3b** was obtained by GPC.
22.0 mg, 0.0586 mmol, 59%
Colorless oil; IR (neat): 2983, 1726, 1485, 1301, 1188, 962 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 4H), 7.25-7.21 (m, 4H), 4.37 (dq, *J* = 1.2, 7.2 Hz, 2H), 1.33 (dt, *J* = 1.6, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.3 (d, *J* = 279.4 Hz), 148.0 (d, *J* = 8.6 Hz), 131.6, 129.9, 121.9 (d, *J* = 3.8 Hz), 63.3 (d, *J* = 4.8 Hz), 13.9 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -12.75 ppm; HRMS (ESI): calcd for $[C_{15}H_{13}Cl_2O_5P+Na]^+$ 396.9770, found 396.9771.

**Ethyl (bis(*p*-tolyloxy)phosphoryl)formate (3c)**

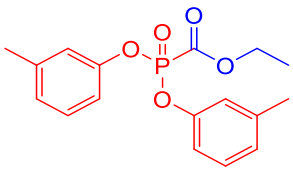


Purification method: **3c** was obtained by GPC.

23.6 mg, 0.0706 mmol, 71%

Colorless oil; IR (neat): 2983, 1724, 1504, 1295, 1187, 965 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.14 (brs, 8H), 4.34 (dq, *J* = 1.6, 7.2 Hz, 2H), 2.32 (s, 6H), 1.31 (dt, *J* = 1.6, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.9 (d, *J* = 277.4 Hz), 147.5 (d, *J* = 7.6 Hz), 135.5, 130.3, 120.2 (d, *J* = 4.7 Hz), 62.8 (d, *J* = 4.8 Hz), 20.7, 13.9 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -12.30 ppm; HRMS (ESI): calcd for $[C_{17}H_{19}O_5P+Na]^+$ 357.0862, found 357.0862.

**Ethyl (bis(*m*-tolyloxy)phosphoryl)formate (3d)**

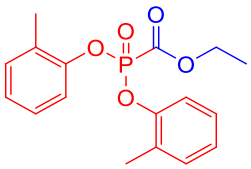


Purification method: **3d** was obtained by GPC.

25.9 mg, 0.0775 mmol, 78%

Colorless oil; IR (neat): 2983, 1722, 1487, 1296, 1136, 967 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.09-7.02 (m, 6H), 4.36 (dq, *J* = 1.2, 7.2 Hz, 2H), 2.35 (s, 6H), 1.31 (dt, *J* = 1.6, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.9 (d, *J* = 278.4 Hz), 149.6 (d, *J* = 8.6 Hz), 140.2, 129.5, 126.6, 121.1 (d, *J* = 3.8 Hz), 117.4 (d, *J* = 4.8 Hz), 62.9 (d, *J* = 4.7 Hz), 21.3, 13.9 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -12.67 ppm; HRMS (ESI): calcd for $[C_{17}H_{19}O_5P+Na]^+$ 357.0862, found 357.0859.

**Ethyl (bis(*o*-tolyloxy)phosphoryl)formate (3e)**



Purification method: **3e** was obtained by GPC.

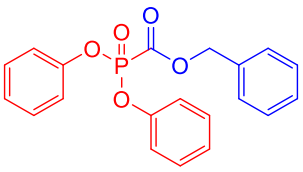
24.8 mg, 0.0742 mmol, 74%

1.33 g, 3.98 mmol, 66% (scaled-up synthesis: the resultant mixture was collected for 900 s)

Colorless oil; IR (neat): 2983, 1725, 1492, 1299, 1164, 966 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.22-7.09 (m, 6H), 4.40-4.34 (m, 2H), 2.28 (s, 6H), 1.31 (dt, *J* = 1.2, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.2 (d, *J* = 280.4 Hz), 148.6 (d, *J* = 8.6 Hz), 131.5, 129.5 (d, *J* = 5.7 Hz), 127.1, 125.7,

120.3 (d, $J$ = 1.9 Hz), 62.9 (d, $J$ = 4.8 Hz), 16.3, 13.9 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -12.88 ppm; HRMS (ESI): calcd for $[C_{17}H_{19}O_5P+Na]^+$ 357.0862, found 357.0862.

**Benzyl (diphenoxyphosphoryl)formate (3f)**

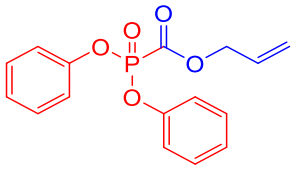


Purification method: **3f** was obtained by GPC.

24.6 mg, 0.0668 mmol, 67%

Colorless oil; IR (neat): 1725, 1489, 1295, 1186, 960 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36-7.18 (m, 15H), 5.30 (d, $J$ = 1.2 Hz, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.7 (d, $J$ = 277.5 Hz), 149.6 (d, $J$ = 8.6 Hz), 133.9, 129.9, 128.8, 128.72, 128.66, 125.9, 120.5 (d, $J$ = 4.8 Hz), 68.3 (d, $J$ = 4.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -13.07 ppm; HRMS (ESI): calcd for $[C_{20}H_{17}O_5P+Na]^+$ 391.0706, found 391.0706.

**Allyl (diphenoxyphosphoryl)formate (3g)**

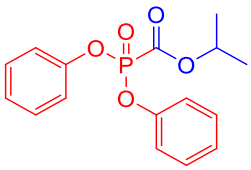


Purification method: **3g** was obtained by GPC.

23.2 mg, 0.0729 mmol, 73%

Colorless oil; IR (neat): 1726, 1488, 1295, 1187, 959 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 4H), 7.29-7.21 (m, 6H), 5.93-5.83 (m, 1H), 5.36-5.28 (m, 2H), 4.79-4.77 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $J$ = 279.3 Hz), 149.6 (d, $J$ = 8.6 Hz), 130.2, 129.9, 125.9, 120.5 (d, $J$ = 3.8 Hz), 120.3, 67.1 (d, $J$ = 5.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -12.96 ppm; HRMS (ESI): calcd for $[C_{16}H_{15}O_5P+Na]^+$ 341.0549, found 341.0549.

**Isopropyl (diphenoxyphosphoryl)formate (3h)**

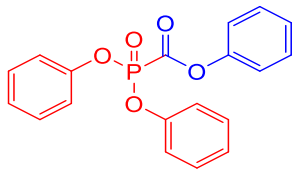


Purification method: **3h** was obtained by GPC.

20.1 mg, 0.0628 mmol, 63%

Colorless oil; IR (neat): 2984, 1720, 1488, 1295, 1183, 957 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38-7.20 (m, 10H), 5.25-5.18 (m, 1H), 1.28-1.26 (m, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.3 (d, $J$ = 277.5 Hz), 149.7 (d, $J$ = 8.6Hz), 129.8, 125.8, 120.6 (d, $J$ = 4.8 Hz), 71.7 (d, $J$ = 4.7 Hz), 21.5 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -12.62 ppm; HRMS (ESI): calcd for $[C_{16}H_{17}O_5P+Na]^+$ 343.0706, found 343.0705.

**Phenyl (diphenoxyphosphoryl)formate (3i)**

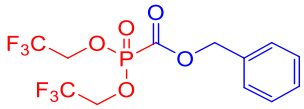


Purification method: **3i** was obtained by GPC.

20.5 mg, 0.0579 mmol, 58%

Colorless oil; IR (neat): 1743, 1487, 1296, 1180, 962 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.42-7.34 (m, 10H), 7.29-7.23 (m, 3H), 7.08-7.06 (m, 2H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 163.4 (d, $J$ = 283.1 Hz), 149.7 (d, $J$ = 9.6 Hz), 149.6 (d, $J$ = 7.6 Hz), 130.0, 129.7, 126.9, 126.1, 121.0, 120.6 (d, $J$ = 4.8 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -13.23 ppm; HRMS (ESI): calcd for $[C_{19}H_{15}O_5P+Na]^+$ 377.0549, found 377.0547.

**Benzyl (bis(2,2,2-trifluoroethoxy)phosphoryl)formate (3k)**



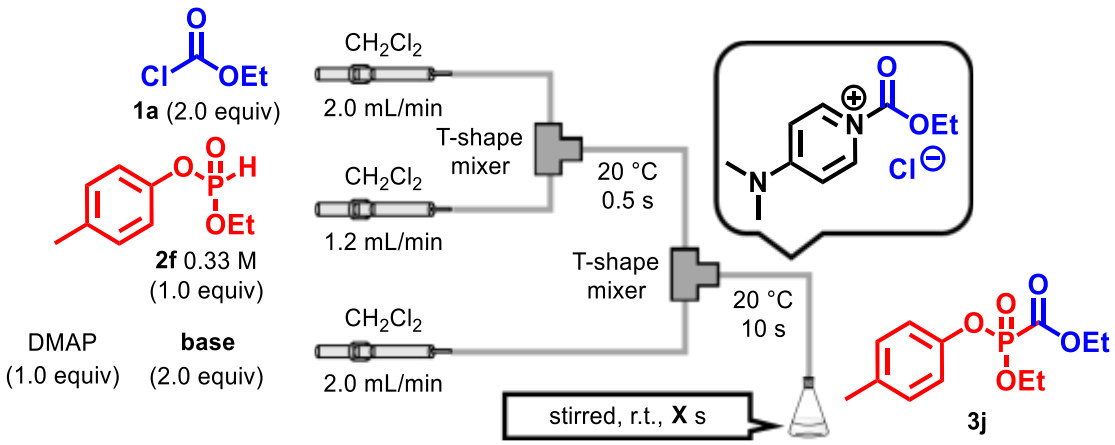
Purification method: **3k** was obtained by GPC.

17.2 mg, 0.0452 mmol, 45%

Colorless oil; IR (neat): 2976, 1729, 1275, 1176, 1068 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H), 5.33 (d, $J$ = 0.8 Hz, 2H), 4.61-4.46 (m, 4H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.0 (d, $J$ = 283.2 Hz), 133.5, 129.1, 128.8, 128.7, 121.9 (dq, $J$ = 8.6, 276.5 Hz), 68.8 (d, $J$ = 4.8 Hz), 63.6 (dq, $J$ = 5.7, 39.1 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -4.58 ppm; HRMS (ESI): calcd for $[C_{12}H_{11}F_6O_5P+Na]^+$ 403.0141, found 403.0143.

**Examination of reaction conditions for the synthesis of 3j**

**Table S6. Preliminary examination of bases and reaction times for the synthesis of 3j**



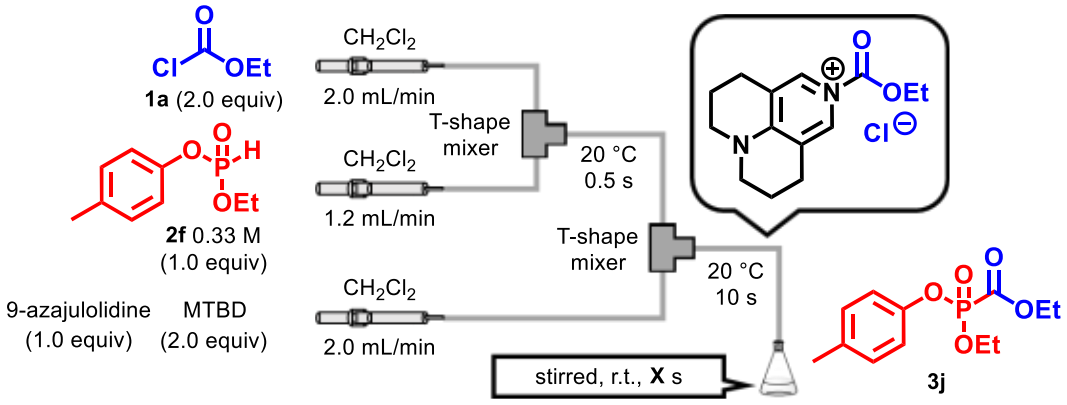

| entry | **base** (p*K*aH[a]) | **X** [s] | NMR yield [%] |
|---|---|---|---|
| 1 | *i*-$Pr_2$NEt (11.4) | 30 | 8 |
| 2 | *i*-$Pr_2$NEt | 60 | 9 |

| | | | |
|---|---|---|---|
| 3 | *i*-Pr$_2$NEt | 120 | 13 |
| 4 | MTBD (13.0[3)]) | 30 | 48 |
| 5 | MTBD | 60 | 48 |
| 6 | MTBD | 120 | 49 |

a) p*K*a of conjugated acid

A solution of ethyl chloroformate (**1a**) (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of ethyl *p*-tolyl *H*-phosphonate (**2f**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of DMAP (0.20 M, 1.0 equiv) and **base** (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **X** s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) was added, the reaction mixture was washed with 1 M HCl aq. and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1$H NMR analysis using 1,1,2-trichloroethane as an internal standard.

**Table S7. Examination of reaction times for the synthesis of 3j**



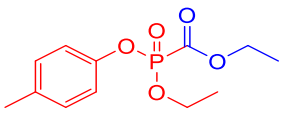

| entry | **X** [s] | NMR yield [%] |
|---|---|---|
| 1 | 120 | 75 |
| 2 | 180 | 78 (62)[a)] |

a) isolated yield.

A solution of ethyl chloroformate (**1a**) (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of ethyl *p*-tolyl *H*-phosphonate (**2f**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of 9-azajulolidine (0.20 M, 1.0 equiv) and MTBD (0.40 M, 2.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same

temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **X** s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) and Hexane (1 mL) were added, the reaction mixture was washed with 1 M HCl aq. three times and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1$H NMR analysis using 1,1,2-trichloroethane as an internal standard. The residue was purified by GPC.

**Ethyl (ethoxy(*p*-tolyloxy)phosphoryl)formate (3j)**



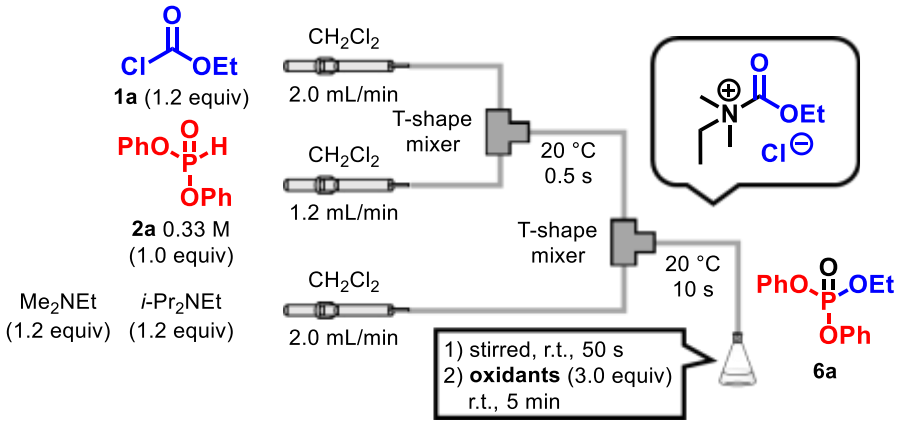
Purification method: **3j** was obtained by GPC.

17.0 mg, 0.0624 mmol, 62%

Colorless oil; IR (neat): 2986, 1720, 1506, 1285, 1196, 1033, 947 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.13 (brs, 4H), 4.43-4.30 (m, 4H), 2.32 (s, 3H), 1.42 (t, *J* = 6.8 Hz, 3H), 1.34-1.30 (m, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 165.9 (d, *J* = 273.7 Hz), 147.5 (d, *J* = 8.6 Hz), 135.2, 130.2, 120.2 (d, *J* = 4.8 Hz), 65.3 (d, *J* = 6.7 Hz), 62.4 (d, *J* = 4.7 Hz), 20.7, 16.2 (d, *J* = 5.7 Hz), 14.0 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -8.01 ppm; HRMS (ESI): calcd for $[C_{12}H_{17}O_5P+Na]^+$ 295.0706, found 295.0708.

**Examination of reaction conditions for the synthesis of phosphotriester (6a)**

**Table S8. Examination of oxidants for the synthesis of 6a**

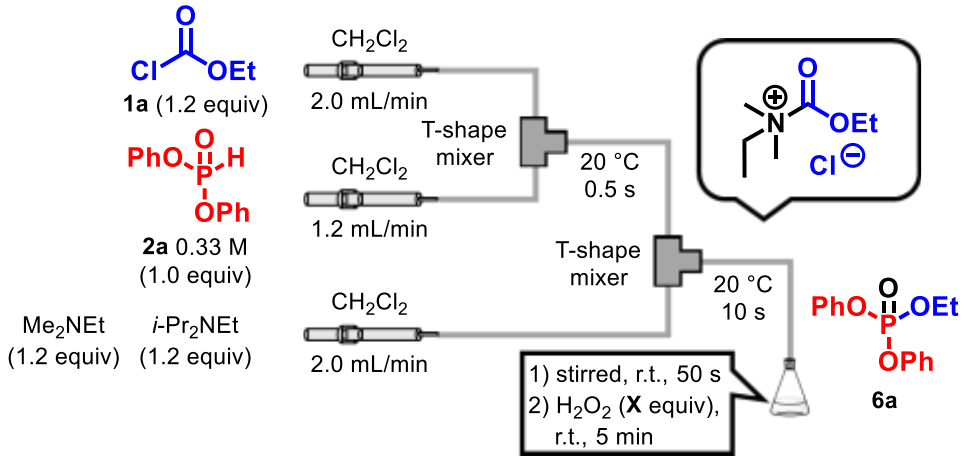



| entry | **oxidant** | isolated yield [%] |
|---|---|---|
| 1 | *m*CPBA | 76 |
| 2 | *t*-BuOOH | 75 |
| 3 | $H_2O_2$ | 77 |

A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A

solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, **oxidant** (3.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography.

**Table S9. Examination of amounts of the oxidant for the synthesis of 6a**




| entry | **X** [equiv] | HPLC yield [%] |
|---|---|---|
| 1 | 1.0 | 71 |
| 2 | 2.0 | 83 |
| 3 | 3.0 | 80 |
| 4 | 4.0 | 79 |
| 5 | 5.0 | 80 |

A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (**X** equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined by HPLC-UV analysis (conditions: COSMOSIL 5C18-AR-II 4.6 mm I.D. × 150 mm; $CH_3CN$+0.1% formic acid/$H_2O$+0.1% formic acid, 0-3 min: 30 to 60%, 3-19

min: 60 to 100%, 19-21 min: 100%, 21-23 min: 100 to 30 %, 23-25 min: 30%; flow rate: 1.0 mL/min; detection wavelength: 254 nm; temperature: 40 °C; retention time: 7.7 min) using a calibration curve shown in **Figure S3**.

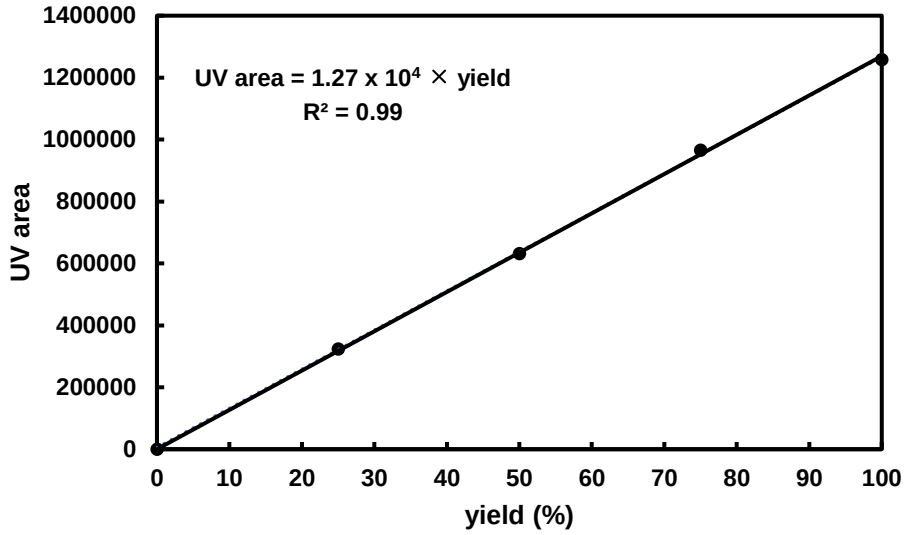
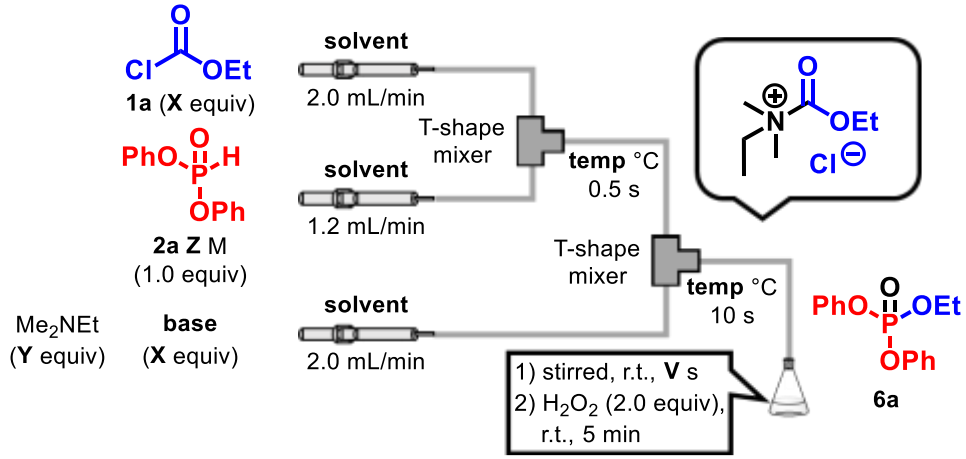



**Figure S3. Calibration curve of 6a**

**Table S10. Examination of reaction conditions for the synthesis of 6a**



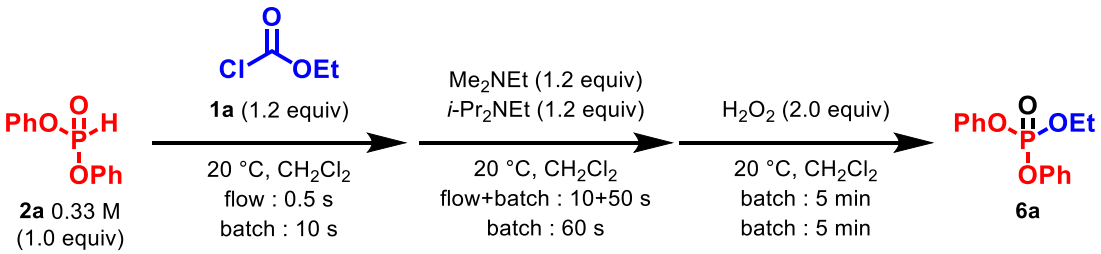

| entry | base (p*K*aH[a]) | solvent | temp [°C] | X [equiv] | Y [equiv] | Z [M] | V [s] | HPLC yield [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | $Et_2NBn$ (9.5) | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 60 | 45 |
| 2 | *i*-$Pr_2NEt$ (11.4) | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 60 | 83 (79[b]) |
| 3 | DBU (11.9) | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 60 | 49 |
| 4 | *i*-$Pr_2NEt$ | THF | 20 | 1.2 | 1.2 | 0.33 | 60 | 25 |
| 5 | *i*-$Pr_2NEt$ | $CH_3CN$ | 20 | 1.2 | 1.2 | 0.33 | 60 | 18 |
| 6 | *i*-$Pr_2NEt$ | DCE[c] | 20 | 1.2 | 1.2 | 0.33 | 60 | 76 |
| 7 | *i*-$Pr_2NEt$ | DCE[c] | 0 | 1.2 | 1.2 | 0.33 | 60 | 60 |
| 8 | *i*-$Pr_2NEt$ | DCE[c] | 40 | 1.2 | 1.2 | 0.33 | 60 | 71 |
| 9 | *i*-$Pr_2NEt$ | $CH_2Cl_2$ | 20 | 1.0 | 1.0 | 0.33 | 60 | 55 |
| 10 | *i*-$Pr_2NEt$ | $CH_2Cl_2$ | 20 | 1.1 | 1.1 | 0.33 | 60 | 66 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 11 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.3 | 1.3 | 0.33 | 60 | 80 |
| 12 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 0.6 | 0.33 | 60 | 67 |
| 13 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.17 | 60 | 68 |
| 14 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.67 | 60 | 77 |
| 15 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 10 | 31 |
| 16 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 30 | 74 |
| 17 | *i*-Pr$_2$NEt | $CH_2Cl_2$ | 20 | 1.2 | 1.2 | 0.33 | 120 | 79 |

a) p*K*a of conjugated acid. b) isolated yield. c) DCE = 1,2-dichloroethane.

A solution of ethyl chloroformate (**1a**) (**X** equiv) in **solvent** (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (**Z** M, 1.0 equiv) in **solvent** (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at **temp** °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 μL, reaction time: 0.5 s) at the same temperature. A solution of Me$_2$NEt (**Y** equiv) and **base** (**X** equiv) in **solvent** (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 μL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **V** s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined by HPLC-UV analysis (conditions: COSMOSIL 5C18-AR-II 4.6 mm I.D. × 150 mm; $CH_3CN$+0.1% formic acid/$H_2O$+0.1% formic acid, 0-3 min: 30 to 60%, 3-19 min: 60 to 100%, 19-21 min: 100%, 21-23 min: 100 to 30 %, 23-25 min: 30%; flow rate: 1.0 mL/min; detection wavelength: 254 nm; temperature: 40 °C; retention time: 7.7 min) using a calibration curve shown above (**Figure S3**). The residue was purified by column chromatography.

**Table S11. Comparison between micro-flow and batch conditions**

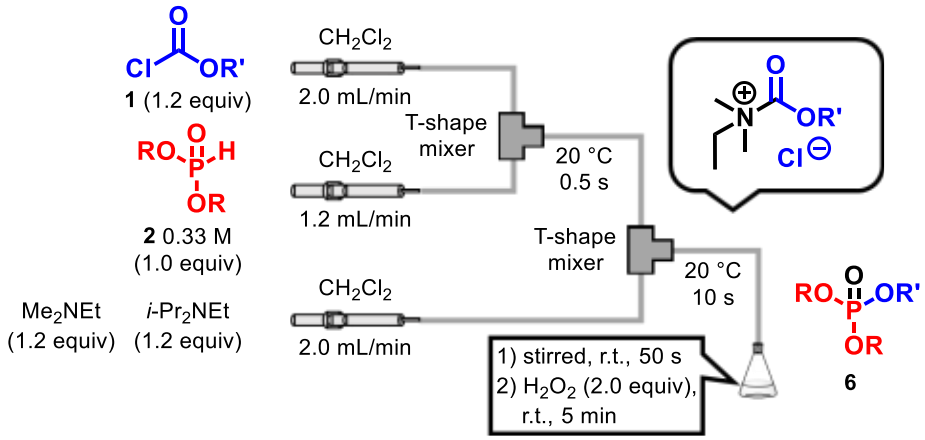



| entry | **method** | isolated yield [%] |
|---|---|---|
| 1 | micro-flow | 79 |
| 2 | batch | 75 |

Micro-flow and batch conditions for synthesis of **6a** were compared. Quantities of compounds, solvents, and temperatures were identical to those of flow conditions. To a vigorously stirred (magnetic stirrer, 1,000 rpm) solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (0.50 mL), a solution of ethyl

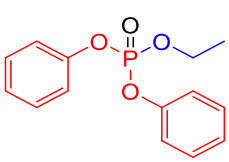
chloroformate (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (0.30 mL) was added in one portion at 20 °C under argon atmosphere. After being stirred for 10 s at the same temperature, a solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (0.50 mL) was added in one portion at 20 °C under argon atmosphere. After being stirred for 60 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC.

**General procedure for the synthesis of phosphotriesters 6**




A solution of chloroformate **1** (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of *H*-phosphonate **2** (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography or preparative TLC.

**Ethyl diphenyl phosphate (6a)**

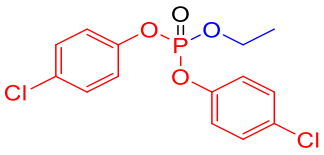


Purification method: **6a** was obtained by column chromatography (Hexane : EtOAc = 4 : 1).
22.0 mg, 0.0791 mmol, 79%

1.26 g, 4.53 mmol, 75% (scaled-up synthesis: the resultant mixture was collected for 900 s)
Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 8.0, 8.0 Hz, 4H), 7.26-7.17 (m, 6H), 4.33 (dq, *J* = 6.8, 8.8 Hz, 2H), 1.37 (dt, *J* = 0.8, 6.8 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.6 (d, *J* = 7.6 Hz), 129.7, 125.2, 120.0 (d, *J* = 5.8 Hz), 65.5 (d, *J* = 6.7 Hz), 16.0 (d, *J* = 6.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -11.26 ppm.

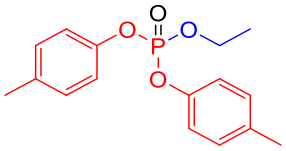
The observed $^{1}$H and $^{13}$C NMR spectra were well consistent with those reported in the previous report.[4)]

**Bis(4-chlorophenyl) ethyl phosphate (6b)**



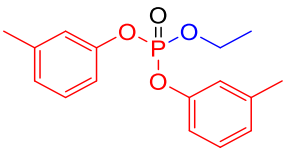

Purification method: **6b** was obtained by column chromatography (Hexane : EtOAc = 17 : 3) and GPC.
16.7 mg, 0.0481 mmol, 48%
Colorless oil; IR (neat): 2985, 1301, 1198, 1039, 955 $cm^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 4H), 7.18-7.14 (m, 4H), 4.32 (dq, *J* = 7.2, 8.8 Hz, 2H), 1.38 (dt, *J* = 1.2, 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.9 (d, *J* = 6.6 Hz), 130.8, 129.8, 121.4 (d, *J* = 4.8 Hz), 65.9 (d, *J* = 6.6 Hz), 16.1 (d, *J* = 6.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -11.38 ppm; HRMS (ESI): calcd for $[C_{14}H_{13}Cl_2O_4P+Na]^+$ 368.9821, found 368.9819.

**Ethyl di-*p*-tolyl phosphate (6c)**




Purification method: **6c** was obtained by preparative TLC (Hexane : EtOAc = 17 : 3).
23.2 mg, 0.0757 mmol, 76%
Colorless oil; IR (neat): 2985, 1290, 1194, 1041, 957 $cm^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.14-7.08 (m, 8H), 4.30 (dq, *J* = 7.2, 8.4 Hz, 2H), 2.32 (s, 6H), 1.35 (dt, *J* = 1.2, 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.4 (d, *J* = 7.7 Hz), 134.8, 130.1, 119.7 (d, *J* = 3.9 Hz), 65.3 (d, *J* = 6.7 Hz), 20.7, 16.0 (d, *J* = 5.8 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -10.80 ppm; HRMS (ESI): calcd for $[C_{16}H_{19}O_4P+Na]^+$ 329.0913, found 329.0912.

**Ethyl di-*m*-tolyl phosphate (6d)**

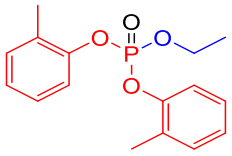



Purification method: **6d** was obtained by column chromatography (Hexane : EtOAc = 17 : 3).

22.8 mg, 0.0744 mmol, 74%

Colorless oil; IR (neat): 2985, 1242, 1141, 1042, 965 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, $J$ = 7.6, 8.0 Hz, 2H), 7.04-6.98 (m, 6H), 4.35-4.28 (m, 2H), 2.34 (s, 6H), 1.39-1.35 (m, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 150.5 (d, $J$ = 7.7 Hz), 140.0, 129.4, 126.0, 120.6 (d, $J$ = 4.7 Hz), 116.9 (d, $J$ = 4.7 Hz), 65.3 (d, $J$ = 5.7 Hz), 21.3, 16.0 (d, $J$ = 6.7 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -11.22 ppm; HRMS (ESI): calcd for $[C_{16}H_{19}O_4P+Na]^+$ 329.0913, found 329.0911.

**Ethyl di-*o*-tolyl phosphate (6e)**

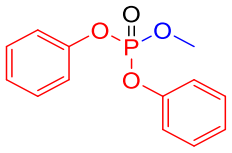


Purification method: **6e** was obtained by column chromatography (Hexane : EtOAc = 17 : 3).

18.2 mg, 0.0594 mmol, 59%

Colorless oil; IR (neat): 2985, 1289, 1171, 1039, 958 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.30 (d, $J$ = 7.6 Hz, 2H), 7.20-7.06 (m, 6H), 4.33 (dq, $J$ = 7.2, 8.4 Hz, 2H), 2.25 (s, 6H), 1.37 (dt, $J$ = 0.8, 7.2 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 149.2 (d, $J$ = 6.6 Hz), 131.4, 129.4 (d, $J$ = 6.7 Hz), 127.0, 125.2, 119.9 (d, $J$ = 2.0 Hz), 65.4 (d, $J$ = 5.8 Hz), 16.2, 16.1 (d, $J$ = 6.7 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -10.71 ppm; HRMS (ESI): calcd for $[C_{16}H_{19}O_4P+Na]^+$ 329.0913, found 329.0912.

**Methyl diphenyl phosphate (6f)**



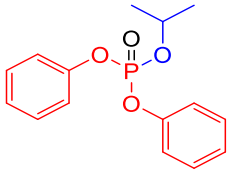
Purification method: **6f** was obtained by preparative TLC (Hexane : EtOAc = 4 : 1).

22.9 mg, 0.0789 mmol, 79%

Colorless oil; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 4H), 7.24-7.17 (m, 6H), 3.95 (d, $J$ = 11.6 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 150.5 (d, $J$ = 7.7 Hz), 129.8, 125.4, 120.0 (d, $J$ = 4.7 Hz), 55.4 (d, $J$ = 6.6 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -10.18 ppm.

The observed $^{1}H$ and $^{13}C$ NMR spectra were well consistent with those reported in the previous report.[5)]

**Isopropyl diphenyl phosphate (6g)**



Purification method: **6g** was obtained by preparative TLC (Hexane : EtOAc = 17 : 3).

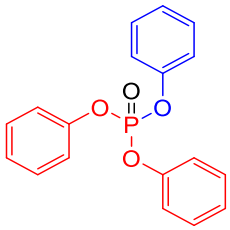
7.5 mg, 0.0257 mmol, 26%

Colorless oil; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 4H), 7.26-7.16 (m, 6H), 4.93-4.85 (m, 1H), 1.36

(d, $J$ = 6.0 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.6 (d, $J$ = 7.6 Hz), 129.7, 125.2, 120.1 (d, $J$ = 4.7 Hz), 74.9 (d, $J$ = 6.7 Hz), 23.5 (d, $J$ = 4.8 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -12.12 ppm.

The observed $^{1}$H and $^{13}$C NMR spectra were well consistent with those reported in the previous report.[4)]

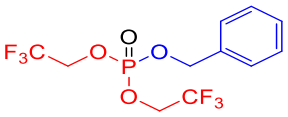
**Triphenyl phosphate (6h)**



Purification method: **6h** was obtained by preparative TLC (Hexane : EtOAc = 4 : 1) and GPC.
25.9 mg, 0.0794 mmol, 79%
Amorphous solid; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 6H), 7.25-7.18 (m, 9H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.4 (d, $J$ = 7.6 Hz), 129.8, 125.6, 120.1 (d, $J$ = 5.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -17.06 ppm

The observed $^{1}$H and $^{13}$C NMR spectra were well consistent with those reported in the previous report.[4),6)]

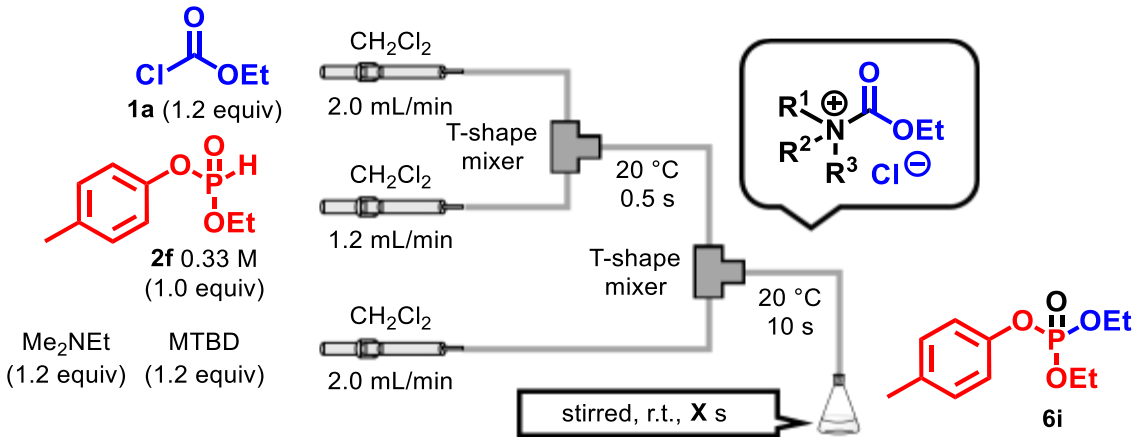
**Ethyl di-*p*-tolyl phosphate (6j)**



Purification method: **6j** was obtained by preparative TLC (Hexane : EtOAc = 17 : 3).
23.2 mg, 0.0757 mmol, 76%
Colorless oil; IR (neat): 2970, 1273, 1174, 1081 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 5H), 5.15 (d, $J$ = 8.4 Hz, 2H), 4.36-4.24 (m, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 134.5 (d, $J$ = 5.7 Hz), 129.2, 128.8, 128.3 122.2 (dq, $J$ = 9.5, 276.5 Hz), 70.8 (d, $J$ = 5.7 Hz), 63.8 (dq, $J$ = 4.8, 38.1 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -1.75 ppm; HRMS (ESI): calcd for $[C_{11}H_{11}F_6O_4P+Na]^+$ 375.0191, found 375.0193.

**Examination of reaction times for the synthesis of phosphotriester (6i)**

**Table S12. Examination of reaction times for the synthesis of 6i**




| entry | **X** [s] | HPLC yield [%] |
|---|---|---|
| 1 | 30 | 12 |
| 2 | 60 | 25 |
| 3 | 120 | 35 |
| 4 | 180 | 43 |
| 5 | 240 | 51(55)[a)] |
| 6 | 300 | 51 |

a) isolated yield.

A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of ethyl *p*-tolyl *H*-phosphonate (**2f**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and MTBD (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for **X** s at the same temperature under argon, $H_2O_2$ (3.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined by HPLC-UV analysis (conditions: COSMOSIL 5C18-AR-II 4.6 mm I.D. × 150 mm; $CH_3CN$+0.1% formic acid/$H_2O$+0.1% formic acid, 0-3 min: 30 to 60%, 3-19 min: 60 to 100%, 19-21 min: 100%, 21-23 min: 100 to 30 %, 23-25 min: 30%; flow rate: 1.0 mL/min; detection wavelength: 254 nm; temperature: 40 °C; retention time: 7.7 min) using a calibration curve shown in **Figure S4**.

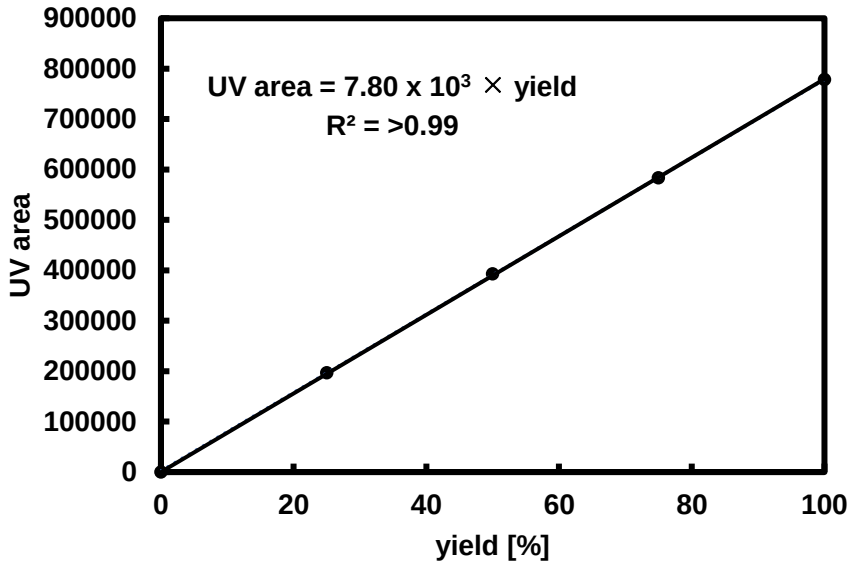
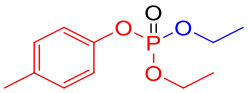



**Figure S4. Calibration curve of 6i**

As shown in the table, the condition of entry 3 afforded **6i** in highest yield. Therefore, the residue was purified by preparative TLC (Hexane : EtOAc = 3 : 2), and **6i** was obtained in 55% yield.

**Diethyl *p*-tolyl phosphate (6i)**

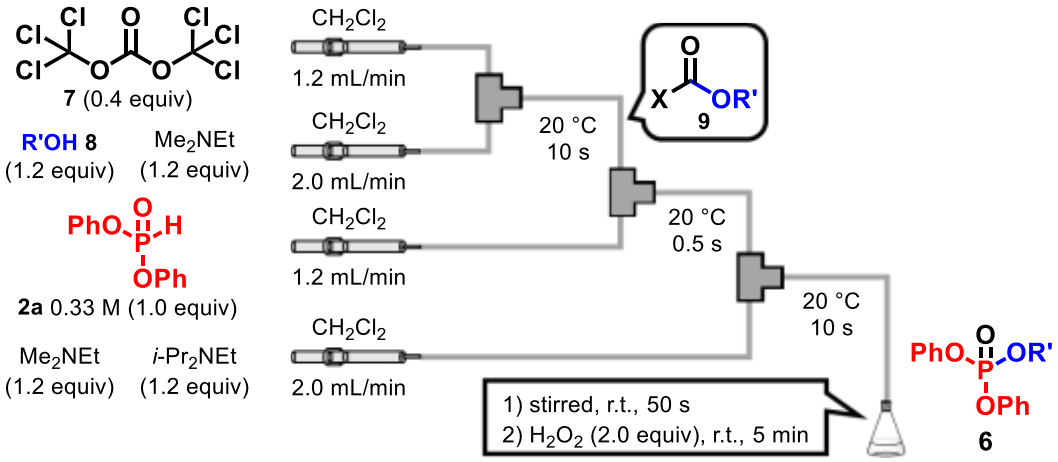


Purification method: **6i** was obtained by preparative TLC (Hexane : EtOAc = 3 : 2).

13.5 mg, 0.0553 mmol, 55%

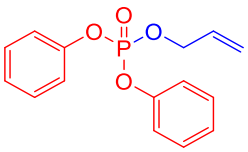
Colorless oil; IR (neat): 2985, 1280, 1218, 1031, 963 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.13-7.08 (m, 4H), 4.25-4.16 (m, 4H), 2.31 (s, 3H), 1.34 (dt, $J$ = 0.8, 7.2 Hz, 6H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 148.5 (d, $J$ = 6.7 Hz), 134.5, 130.1, 119.6 (d, $J$ = 4.8 Hz), 64.4 (d, $J$ = 5.7 Hz), 20.7, 16.0 (d, $J$ = 6.7 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -5.44 ppm; HRMS (ESI): calcd for $[C_{11}H_{17}O_4P+Na]^+$ 267.0757, found 267.0760.

**General procedure for the one-flow synthesis of phosphotriesters 6 from alcohols 8**




A solution of triphosgene (**7**) (0.13 M, 0.4 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) and a solution of alcohol **8** (0.24 M, 1.2 equiv) and $Me_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 1,061 mm, volume: 533 µL, residence time: 10 s) at the same temperature. A solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 72.9 mm, volume: 36.7 µL, residence time: 0.5 s). A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 2 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 3 (inner diameter: 0.80 mm, length: 2,122 mm, volume: 1,067 µL, residence time: 10 s). After being eluted for *ca.* 90 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography or preparative TLC.

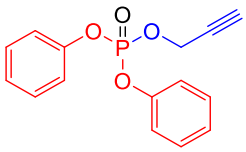
**Allyl diphenyl phosphate (6k)**



Purification method: **6k** was obtained by column chromatography (Hexane : EtOAc = 3 : 1).
22.9 mg, 0.0789 mmol, 79%
Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 4H), 7.24-7.17 (m, 6H), 5.99-5.89 (m, 1H), 5.37 (ddd, *J* = 1.2, 1.2, 16.8 Hz, 1H), 5.28-5.25 (m, 1H), 4.73 (dddd, *J* = 1.2, 1.2, 5.6, 8.8 Hz, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.5 (d, *J* = 7.7 Hz), 131.8 (d, *J* = 6.7 Hz), 129.7, 125.3, 120.0 (d, *J* = 4.8 Hz), 118.9, 69.4 (d, *J* = 5.7 Hz) ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ -11.22 ppm.

The observed $^{1}H$ and $^{13}C$ NMR spectra were well consistent with those reported in the previous report.[4)]

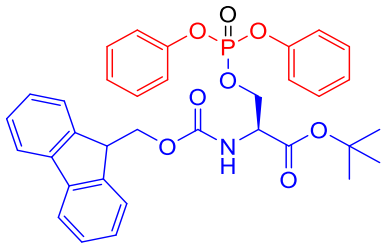
**Diphenyl propargyl phosphate (6l)**



Purification method:**6l** was obtained by column chromatography (Hexane : EtOAc = 3 : 1).
23.6 mg, 0.0819 mmol, 82%
Colorless oil; IR (neat): 3066, 2360, 1289, 1188, 1041, 956 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 4H), 7.26-7.18 (m, 6H), 4.84 (dd, *J* = 2.4, 10.4 Hz, 2H), 2.58 (t, *J* = 2.4 Hz, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 150.3 (d, *J* = 6.7 Hz), 129.8, 125.5, 120.1 (d, *J* = 4.7 Hz), 76.8, 56.3 (d, *J* = 4.8 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -11.25 ppm.

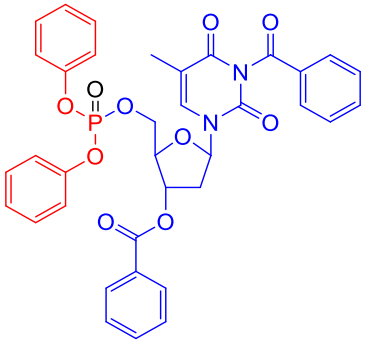
The observed $^{1}H$ and $^{13}C$ NMR spectra were well consistent with those reported in the previous report.[7)]

**Diphenyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-(*tert*-butoxycarbonyl)-ethan-1-yl phosphate (6m)**



Purification method: **6m** was obtained by column chromatography (Hexane : EtOAc = 3 : 2).
49.6 mg, 0.0806 mmol, 81%
Colorless oil; IR (neat): 3315, 3066, 2979, 1726, 1295, 1189, 957 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.58 (dd, *J* = 2.4, 7.2 Hz, 2H), 7.39 (dd, *J* = 7.2, 8.0 Hz, 2H), 7.35-7.27 (m, 6H), 7.22-7.15 (m, 6H), 5.66 (d, *J* = 7.2 Hz, 1H), 4.66-4.55 (m, 2H), 4.53-4.50 (m, 1H), 4.38 (dd, *J* = 7.6, 10.4 Hz, 1H), 4.31 (dd, *J* = 7.2, 10.4 Hz, 1H), 4.19 (dd, *J* = 7.2, 7.6 Hz, 1H), 1.44 (s, 9H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 167.4, 155.7, 150.3 (d, *J* = 6.7 Hz), 143.7, 141.2, 129.8 (d, *J* = 2.8 Hz), 127.7, 127.0, 125.5 (d, *J* = 3.9 Hz), 125.1, 120.0, 119.9, 83.4, 68.8 (d, *J* = 5.7 Hz), 67.3, 54.7 (d, *J* = 8.6 Hz), 47.0, 27.8 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -11.58 ppm; HRMS (ESI): calcd for $[C_{34}H_{34}NO_8P+Na]^+$ 638.1914, found 638.1914.

***N*3-Bz-3'-*O*-Bz-thymidine-5'-yl diphenyl phosphate (6n)**



Purification method: **6n** was obtained by preparative TLC (Hexane : EtOAc = 1 : 1).

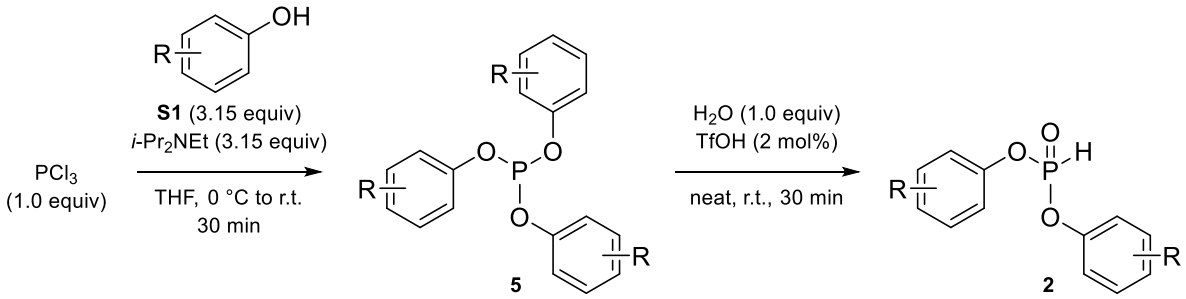
57.1 mg, 0.0836 mmol, 84%

Colorless oil; IR (neat): 3070, 2953, 1749, 1704, 1663, 1270, 1189, 957 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 8.02-8.00 (m, 2H), 7.94-7.92 (m, 2H), 7.66-7.58 (m, 3H), 7.51-7.43 (m, 4H), 7.40-7.34 (m, 4H), 7.28-7.21 (m, 6H), 6.48 (dd, *J* = 5.6, 9.2 Hz, 1H), 5.53-5.52 (m, 1H), 4.71 (ddd, *J* = 2.8, 6.8, 10.8 Hz, 1H), 4.65 (ddd, *J* = 2.4, 6.4, 10.8 Hz, 1H), 4.39-4.38 (m, 1H), 2.59 (dd, *J* = 5.6, 14.4 Hz, 1H), 2.21 (dd, *J* = 6.4, 9.2, 14.4 Hz, 1H), 1.83 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 168.7, 166.0, 162.5, 150.1 (d, *J* = 6.7 Hz), 149.4, 135.0, 134.6, 133.7, 131.5, 130.4, 130.0, 129.9, 129.7, 129.1, 128.8, 128.6, 125.9, 120.0 (d, *J* = 4.8 Hz), 111.9, 84.7, 83.0 (d, *J* = 7.6 Hz), 74.8, 68.3 (d, *J* = 5.7 Hz), 37.3, 12.4 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ -11.31 ppm; HRMS (ESI): calcd for $[C_{36}H_{31}N_2O_{10}P+Na]^+$ 705.1609, found 705.1609.

**Preparation of *H*-phosphonates 2**

**Preparation of di-aryl *H*-phosphonates 2**

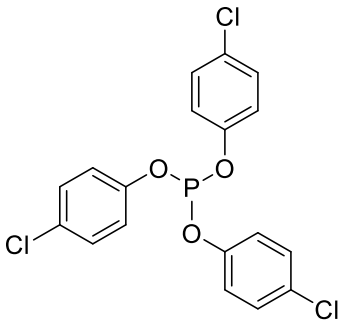
Di-aryl *H*-phosphonates **2** were prepared by modified procedures of previous reports.[8)]




To a THF solution (10 mL) of $PCl_3$ (0.35 mL, 4.01 mmol, 1.0 equiv) was added a THF solution (10 mL) of phenol **S1** (12.6 mmol, 3.15 equiv) and *i*-$Pr_2NEt$ (2.16 mL, 12.6 mmol, 3.15 equiv) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After the precipitated amine hydrochloride was removed by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give phosphite **5**.

To a mixture of phosphite **5** (1.5 mmol, 1.0 equiv) and $H_2O$ (27.0 μL, 1.5 mmol, 1.0 equiv) was added TfOH (2.6 μL, 0.030 mmol, 2.0 mol%) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The residue was purified by GPC.

**Tris(4-chlorophenyl) phosphite (5b)**



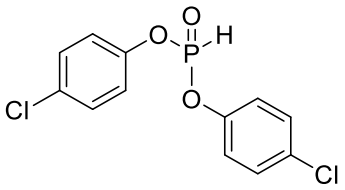
Purification method: **5b** was obtained by column chromatography (Hexane : EtOAc = 20 : 1).

1.269 g, 3.07 mmol, 77%

Colorless oil; IR (neat): 1200, 867, 750 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 6H), 7.05-7.02 (m, 6H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 149.7 (d, $J$ = 2.9 Hz), 129.8, 121.9 (d, $J$ = 6.6 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 127.48 ppm.

The observed $^{1}H$ and $^{13}C$ NMR spectra were well consistent with those reported in the previous report.[8a)]

**Di-*p*-tolyl phosphonate (2b)**

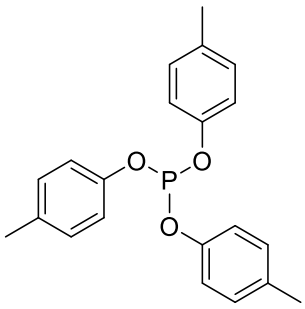


Purification method: **2b** was obtained by GPC.

422.1 mg, 1.393 mmol, 93%

Colorless oil; IR (neat): 3097, 2452, 1278, 1199, 949, 831 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 4H), 7.29 (d, $J$ = 738.0 Hz, 1H), 7.16-7.12 (m, 4H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 147. 6 (d, $J$ = 7.6 Hz), 131.4, 130.1, 121.8 (d, $J$ = 4.8 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 0.54 ppm; HRMS (ESI): calcd for $[C_{12}H_9Cl_2O_3P+Na]^+$ 324.9559, found 324.9559.

**Tri-*p*-tolyl phosphite (5c)**



Purification method: **5c** was obtained by column chromatography (Hexane : EtOAc = 20 : 1).

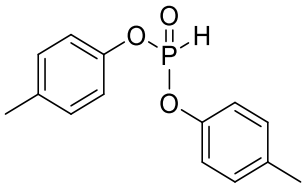
1.1391 g, 3.23 mmol, 81%

Colorless oil; IR (neat): 2922, 1198, 865 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.10 (d, $J$ = 8.0 Hz, 6H), 7.02

(d, $J$ = 8.0 Hz, 6H), 2.31 (s, 9H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.3 (d, $J$ = 2.8 Hz), 133.6, 130.1, 120.5 (d, $J$ = 6.7 Hz), 20.7 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ 129.14 ppm.

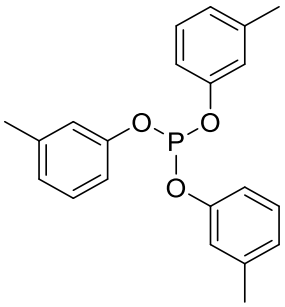
The observed $^{1}$H and $^{13}$C NMR spectra were well consistent with those reported in the previous report.[8a)]

**Di-*p*-tolyl phosphonate** (**2c**)



Purification method: **2c** was obtained by GPC.
372.0 mg, 1.419 mmol, 94%
Colorless oil; IR (neat): 2924, 2443, 1280, 1195, 953 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, $J$ = 725.2 Hz, 1H), 7.14 (d, $J$ = 8.8 Hz, 4H), 7.07 (dd, $J$ = 1.6, 8.8 Hz, 4H), 2.32 (s, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 147.0 (d, $J$ = 7.7 Hz), 135.4, 130.4, 120.1 (d, $J$ = 4.7 Hz), 20.7 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ 1.55 ppm; HRMS (ESI): calcd for $[C_{14}H_{15}O_3P+Na]^+$ 286.0685, found 286.0685.

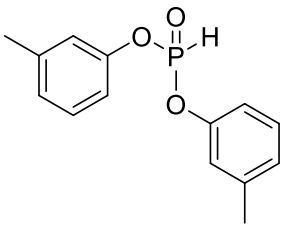
**Tri-*m*-tolyl phosphite** (**5d**)



Purification method: **5d** was obtained by column chromatography (Hexane : EtOAc = 20 : 1).
1.1419 g, 3.24 mmol, 81%
Colorless oil; IR (neat): 2919, 1137, 932 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.21-7.17 (m, 3H), 6.96-6.94 (m, 9H), 2.33 (s, 9H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 151.6 (d, $J$ = 3.8 Hz), 139.8, 129.3, 124.9, 121.4 (d, $J$ = 6.7 Hz), 117.7 (d, $J$ = 7.6 Hz), 21.3 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): δ 128.89 ppm.

The observed $^{1}$H and $^{13}$C NMR spectra were well consistent with those reported in the previous report.[8a)]

**Di-*m*-tolyl phosphonate** (**2d**)

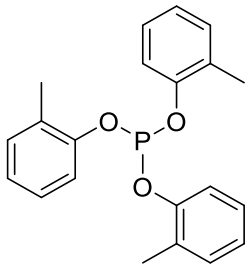


Purification method: **2d** was obtained by GPC.

396.7 mg, 1.410 mmol, 93%

Colorless oil; IR (neat): 2922, 2432, 1243, 1151, 959 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 726.8 Hz, 1H), 7.26-7.21 (m, 2H), 7.03-6.98 (m, 6H), 2.34 (s, 6H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 149.2 (d, *J* = 8.6 Hz), 140.3, 129.6, 126.5, 121.1 (d, *J* = 4.7 Hz), 117.4 (d, *J* = 4.8 Hz), 21.2 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 1.05 ppm; HRMS (ESI): calcd for $[C_{14}H_{15}O_3P+Na]^+$ 286.0685, found 286.0685.

**Tri-*o*-tolyl phosphite** (**5e**)



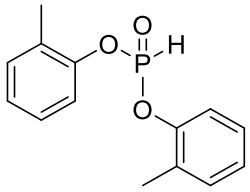
Purification method: **5e** was obtained by column chromatography (Hexane : EtOAc = 20 : 1).

1.2048 g, 3.42 mmol, 85%

Colorless oil; IR (neat): 2926, 1173, 876 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.20-7.16 (m, 6H), 7.14-7.10 (m, 3H), 7.04-7.01 (m, 3H), 2.20 (s, 9H, e) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 150.2 (d, *J* = 1.9 Hz), 131.3, 129.9 (d, *J* = 2.9 Hz), 126.8, 124.0, 120.3 (d, *J* = 10.5 Hz), 16.6 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 131.49 ppm.

The observed $^{1}H$ and $^{13}C$ NMR spectra were well consistent with those reported in the previous report.[8a)]

**Di-*o*-tolyl phosphonate** (**2e**)



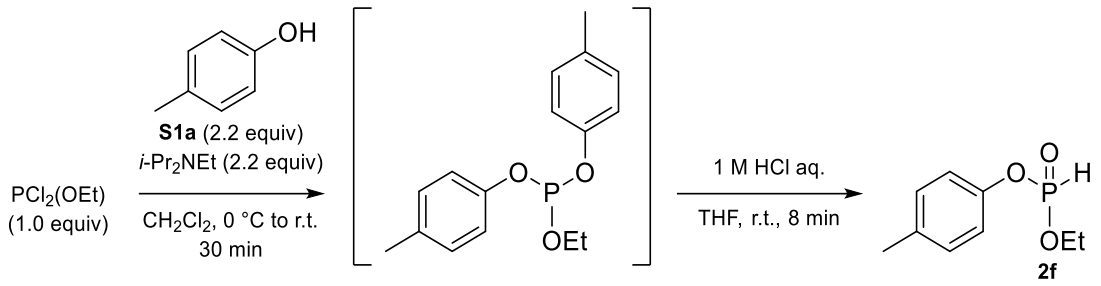
Purification method: **2e** was obtained by GPC.

396.7 mg, 1.410 mmol, 93%

Colorless oil; IR (neat): 2928, 2444, 1276, 1172, 954 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 722.4 Hz, 1H), 7.23-7.21 (m, 4H), 7.19-7.15 (m, 2H), 7.14-7.10 (m, 2H), 2.27 (s, 6H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 148.0 (d, *J* = 7.6 Hz), 131.6, 129.5 (d, *J* = 5.7 Hz), 127.2, 125.7, 120.4 (d, *J* = 2.9 Hz), 16.3 ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 0.27 ppm; HRMS (ESI): calcd for $[C_{14}H_{15}O_3P+Na]^+$ 286.0685, found 286.0684.

**Preparation of aryl alkyl *H*-phosphonate (2f)**

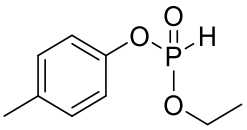
Aryl alkyl *H*-phosphonates (**2f**) was prepared by modified procedures of previous reports.[8b)]




To a $CH_2Cl_2$ solution (20 mL) of ethyl dichlorophosphite (2.00 mL, 17.5 mmol, 1.0 equiv) was added a $CH_2Cl_2$ solution (20 mL) of *p*-cresol (**S1a**) (4.16 g, 38.5 mmol, 2.2 equiv) and *i*-$Pr_2NEt$ (6.58 mL, 38.5 mmol, 2.2 equiv) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After the reaction mixture was diluted with $CH_2Cl_2$, 1 M HCl aq. was added. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was used for the next reaction without further purification.

To a THF solution (30 mL) of above mixture was added 1 M HCl aq. (4.0 mL) at room temperature. The reaction was monitored by TLC every 2 min. After the phosphite was disappeared (6~8 min), the reaction mixture was diluted with $CH_2Cl_2$ to separate the aqueous layer and the organic layer. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography.

**Ethyl *p*-tolyl phosphonate** (**2f**)

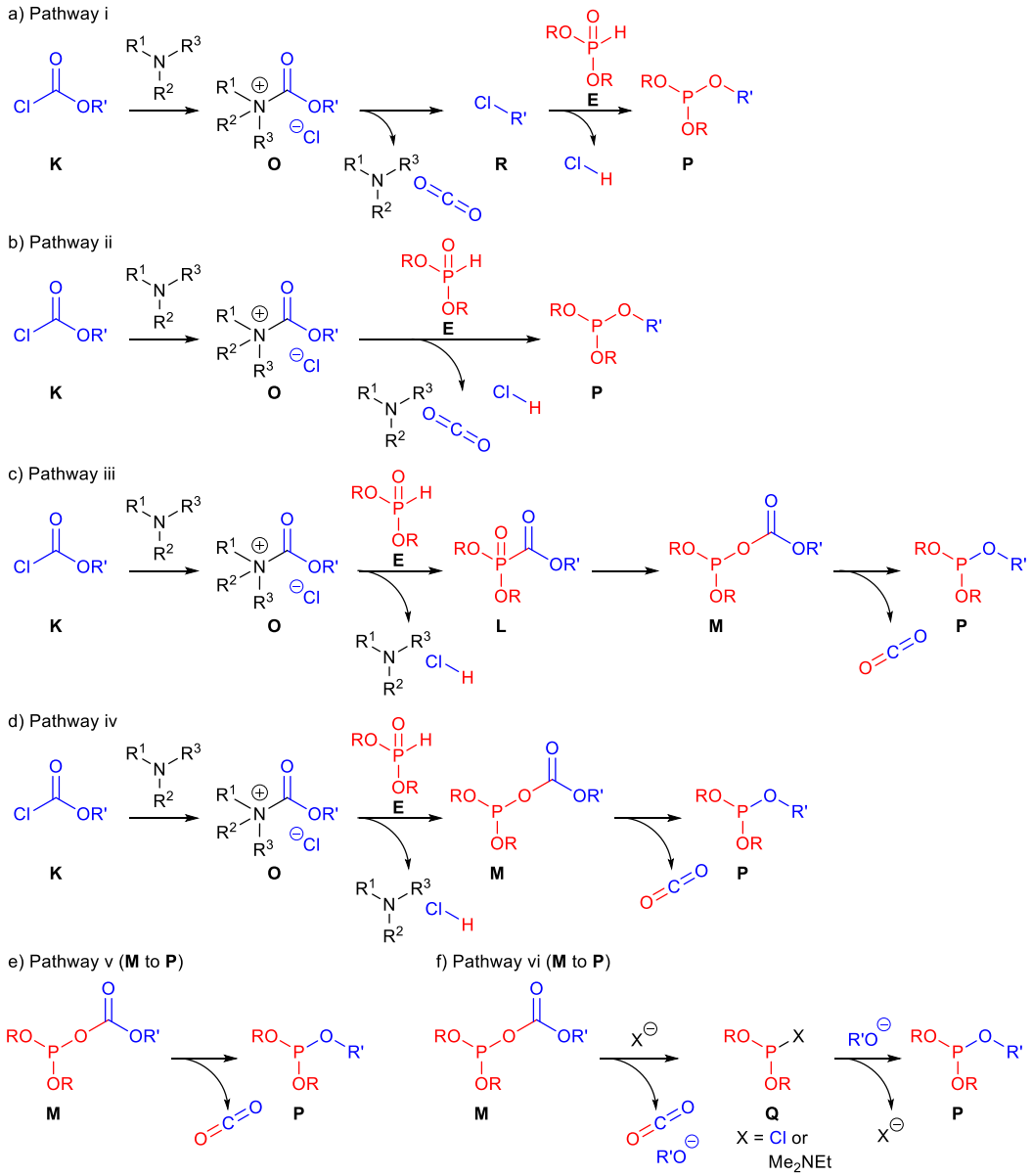



Purification method: **2f** was obtained by column chromatography (Hexane : EtOAc = 4 : 1 ~ 3 : 2 ~ 2 : 3).
2.60 g, 13.0 mmol, 74%

Colorless oil; IR (neat): 2925, 2436, 1270, 1206, 1168, 1047, 977 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.08-7.05 (m, 2H), 7.02 (d, *J* = 710.0 Hz, 1H), 4.31-4.21 (m, 2H), 2.32 (s, 6H), 1.37 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 147.1 (d, *J* = 6.7 Hz), 135.0, 130.3, 120.1 (d, *J* = 4.7 Hz), 62.6 (d, *J* = 5.7 Hz), 20.6, 16.2 (d, *J* = 6.7 Hz) ppm; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 4.98 ppm; HRMS (ESI): calcd for $[C_9H_{13}O_3P+Na]^+$ 223.0495, found 223.0492.

**Mechanistic Investigation**

The reaction mechanism for the unexpected formation of phosphite **P** from *H*-phosphonate **E** and chloroformate **K** was investigated. Four pathways were assumed for phosphite formation (Scheme S1). Pathway i includes the attack of the chloride ion on the R' group in acyl ammonium ion **O** generating alkyl chloride **R** concomitant with decarboxylation.[9] The subsequent O-alkylation of **E** with **R** affords phosphite **P** (Scheme S1a). Pathway ii includes the direct attack of the oxygen atom in **E** on the R' group in **O** affording **P** concomitant with decarboxylation (Scheme S1b). Pathway iii includes the P-acylation of **E** with **O** and subsequent P-to-O acyl migration of **L** affording **M**. The decarboxylation of **M** affords **P** (Scheme S1c). Pathway iv includes the O-acylation of **E** with **O** and the subsequent decarboxylation of **M** affording **P** (Scheme S1d). In pathways iii and iv, two decarboxylation pathways are possible, v and vi. Pathway v includes intramolecular nucleophilic substitutions (Scheme S1e), whereas pathway vi includes intermolecular nucleophilic substitutions (Scheme S1f). The latter pathway may include the nucleophilic attack of $X^-$ on **M** generating **Q** in situ and the subsequent nucleophilic attack of $R'O^-$ on **Q** affording **P**.

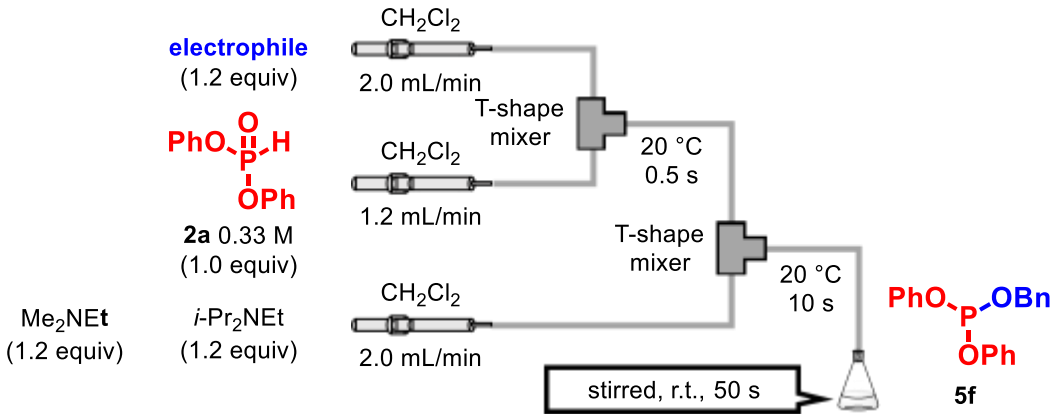



**Scheme S1. Consideration of reaction mechanism**

**Examination of electrophiles**

Pathway i was examined by using electrophiles. A solution of **electrophile** (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) was added, the reaction mixture was washed with 1 M HCl aq. and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1H$ NMR analysis using 1,1,2-trichloroethane as an internal standard.

**Table S13. Examination of reaction of 2a with benzyl chloroformate (1b) and benzyl chloride (S2)**




| entry | electrophile | NMR yield [%] | |
|---|---|---|---|
| | | **2a** | **5f** |
| 1 | benzyl chloroformate (**1b**) | 11 | 78 |
| 2 | benzyl chloride (**S2**) | >99 | n.d. |

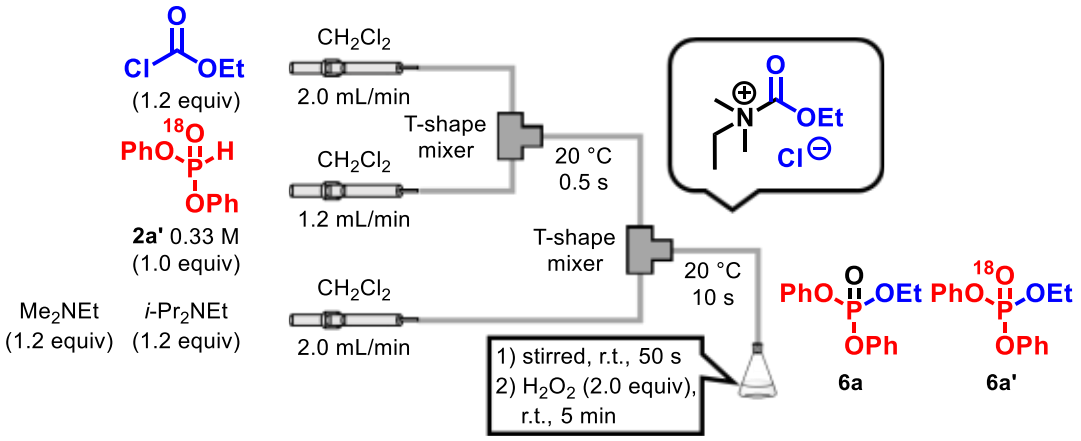
Although the use of benzyl chloroformate (**1b**) as an electrophile afforded **5f**, the use of benzyl chloride (**S2**) as an electrophile did not afford **5f** (Table S13). These results indicate that pathway i is not plausible.

**Exploration of reaction mechanism using isotope-labeled *H*-phosphonate**

Pathway ii was examined by using isotope-labeled substrate. $^{18}O$-Diphenyl *H*-phosphonate (**2a'**) was prepared by modified procedures of preparation of di-aryl *H*-phosphonates ($H_2{}^{18}O$ was used instead of $H_2O$). The isotope ratio was determined by LC-MS analysis[10] (The isotope ratio was $^{18}O$ : $^{16}O$ = 96 : 4). A solution of ethyl chloroformate (**1a**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of $^{18}O$-diphenyl *H*-phosphonate (**2a'**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner

diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of $Me_2NEt$ (0.24 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The isotope ratio was determined by LC-MS analysis.

**Table S14. Examination of the synthesis of phosphotriester using $^{18}$O-diphenyl *H*-phosphonate (2a')**



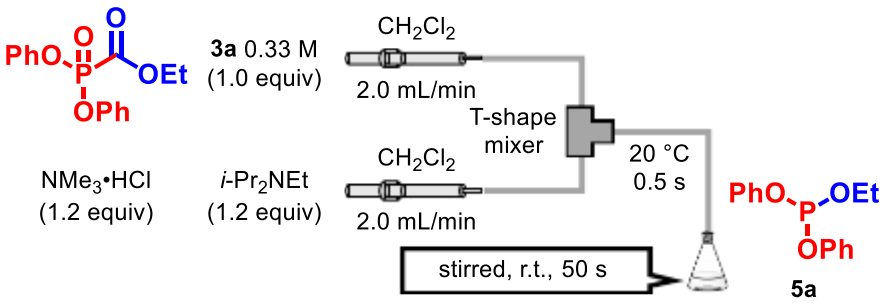

| entry | isotope ratio [%] | |
|---|---|---|
| | **6a** | **6a'** |
| 1 | 3 | 97 |

The isotope ratio (**6a**:**6a'** = 97:3) analyzed using LC-MS, indicated that most isotopically labeled oxygen atoms in **2a'** were eliminated during the reaction process (Table S14). If the reaction proceeds via pathway ii, most isotopically labeled oxygen atoms should remain; therefore, pathway ii is not plausible.

**Examination of reaction from phosphonoformate ester 3**

Pathway iii was examined by using *P*-acyl product. A solution of phosphonoformate ester (**3a**) (0.20 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of $NMe_3$•HCl (0.40 M, 1.2 equiv) and *i*-$Pr_2NEt$ (0.40 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through the reaction tube (inner diameter: 0.80 mm, length: 1,061 mm, volume: 533 µL, residence time: 10 s) at the same temperature. After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, the reaction was quenched with 1 M HCl aq. (1 mL) and $CH_2Cl_2$ (5 mL). After additional $CH_2Cl_2$ (5 mL) was added, the reaction mixture was washed with 1 M HCl aq. and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1$H NMR using 1,1,2-trichloroethane as an internal standard.

**Table S15. Examination of reaction from phosphonoformate ester (3a)**



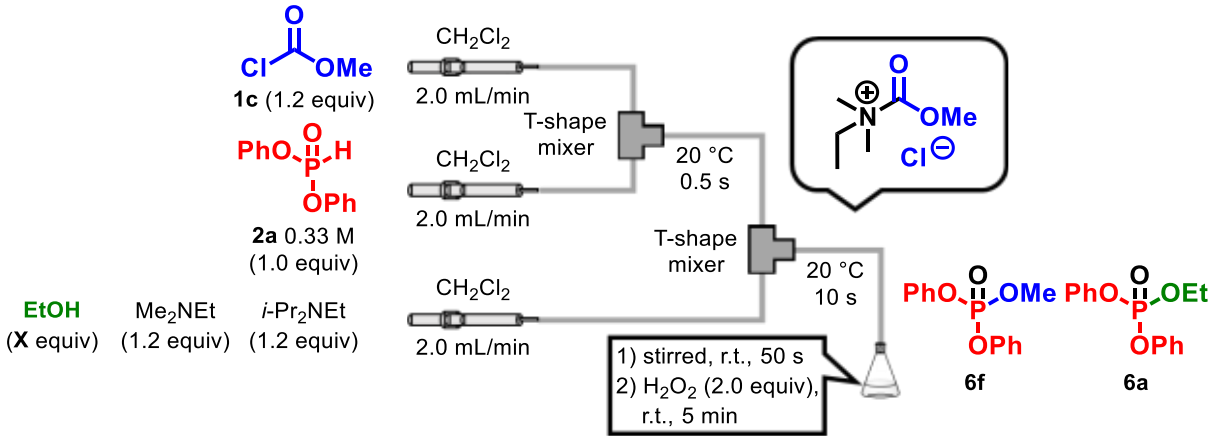

| entry | NMR yield [%] | |
|---|---|---|
| | **3a** | **5a** |
| 1 | >99 | n.d. |

Although *P*-acyl product **3a** was treated under the reaction conditions to produce phosphite **5a**, **5a** was not generated (Table S15). These results indicated that P-acylation and subsequent P-to-O acyl migration (pathway iii) did not occur.

**Examination of intramolecular/intermolecular nucleophilic substitution**

Pathway v and vi was examined by introducing alcohol. A solution of methyl chloroformate (**1c**) (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (0.33 M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 μL, reaction time: 0.5 s) at the same temperature. A solution of EtOH (**X** equiv), $Me_2NEt$ (0.24 M, 1.2 equiv), and *i*-$Pr_2NEt$ (0.24 M, 1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 μL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1$H NMR using triphenylmethane as an internal standard.

**Table S16. Examination of O-acylation with/without different alcohol**

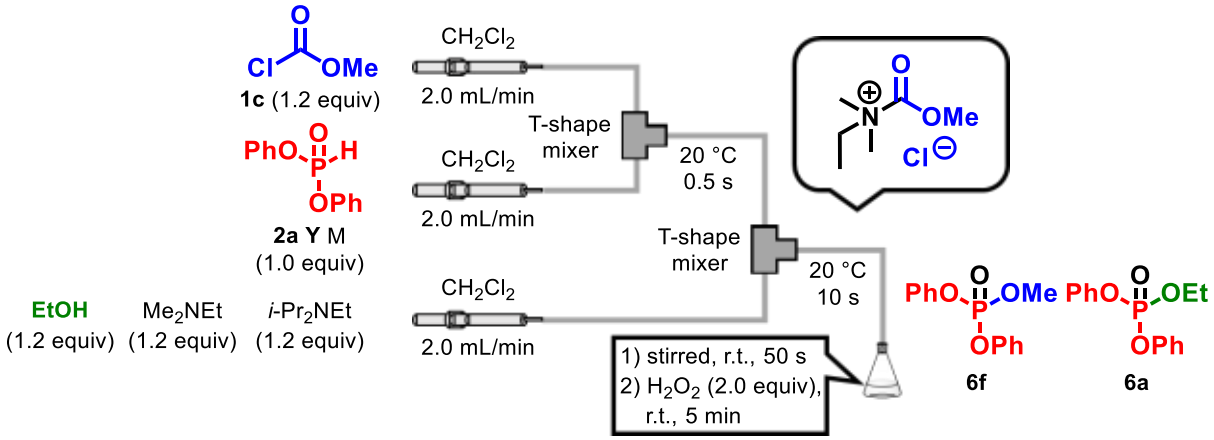



| entry | **X** [equiv] | NMR yield [%] | |
|---|---|---|---|
| | | **6f** | **6a** |
| 1 | 0 | 83 | n.d. |
| 2 | 1.2 | 45 | 38 |

According to the results, **6a** and **6b** were obtained in comparable yields (Table S16). From these results, pathway vi is plausible. For further investigation of pathway v, we examined concentrations of the reaction as follows.

A solution of methyl chloroformate (**1c**) (1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and a solution of diphenyl *H*-phosphonate (**2a**) (**Y** M, 1.0 equiv) in $CH_2Cl_2$ (flow rate: 1.2 mL/min) was introduced to the T-shape mixer at 20 °C with the syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.80 mm, length: 53.1 mm, volume: 26.7 µL, reaction time: 0.5 s) at the same temperature. A solution of EtOH (1.2 equiv), $Me_2NEt$ (1.2 equiv), and *i*-$Pr_2NEt$ (1.2 equiv) in $CH_2Cl_2$ (flow rate: 2.0 mL/min) and resultant mixture from reaction tube 1 were introduced to the T-shape mixer at the same temperature with the syringe pumps, and the mixture was passed through reaction tube 2 (inner diameter: 0.80 mm, length: 1,724 mm, volume: 867 µL, residence time: 10 s). After being eluted for *ca.* 45 s to reach a steady state, the resultant mixture was collected for 15 s at room temperature under argon. After being stirred for 50 s at the same temperature under argon, $H_2O_2$ (2.0 equiv) was added to the reaction mixture. After being stirred for *ca.* 5 min, the reaction mixture was washed with 1 M HCl aq., sat. $NaHCO_3$ aq., and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Yields were determined via $^1H$ NMR using triphenylmethane as an internal standard.

**Table S17. Examination of concentrations of O-acylation with different alcohol**




| entry | **Y** [M] | NMR yield [%] | | NMR ratio **6f** / **6a** |
|---|---|---|---|---|
| | | **6f** | **6a** | |
| 1 | 0.083 | 53 | 33 | 1.61 |
| 2 | 0.17 | 45 | 37 | 1.22 |
| 3 | 0.33 | 45 | 38 | 1.18 |
| 4 | 0.67 | 40 | 43 | 0.93 |

The NMR yield ratio of **6f** to **6a** increases as the concentration of the reaction mixture decreases. These results indicate that both intramolecular nucleophilic substitution (pathway v) and sequential intermolecular nucleophilic substitution (pathway vi) are possible, depending on the concentration of the nucleophile.

**DFT calculation**

We speculated that the difference in the chemical hardness between acyl pyridinium ions and acyl ammonium ions derived from chloroformate was the key to the switching of the acylation. Therefore, we used DFT calculation for estimating Peason's chemical hardness[11] and other parameters.

All calculations were carried out using the Gaussian 16 program.[12] The DFT calculations were carried out using the long-range and dispersion-corrected ωB97X-D functional.[13] The 6-31G+(d,p) basis set was used for all atoms.[14] The optimized molecule structures were verified by vibrational analysis; equilibrium structures did not have imaginary frequencies. Methyl group was used as the alkyl group of chloroformate to reduce the calculation cost. Atom charge was evaluated by NBO 3.1 program.[15]

acyl pyridinium ion

| | | | |
|---|---|---|---|
| C | -5.06974400 | 0.65046900 | -0.06971500 |
| H | -5.40218000 | 1.68133000 | -0.15960600 |
| H | -5.41191600 | 0.20665500 | 0.86533600 |
| H | -5.40589200 | 0.05311900 | -0.91738400 |
| O | -3.62359300 | 0.72380400 | -0.07117100 |
| C | -2.99520600 | -0.42651700 | 0.02934300 |

| | | | |
|---|---|---|---|
| O | -3.47304900 | -1.52259000 | 0.12205000 |
| C | -0.77578700 | -1.33929400 | 0.11941800 |
| C | -0.99299400 | 1.00988600 | -0.09519400 |
| C | 0.58105800 | -1.26270800 | 0.12997000 |
| H | -1.31373700 | -2.27594700 | 0.20242900 |
| C | 0.35604500 | 1.17773300 | -0.12098000 |
| H | -1.67852900 | 1.84266600 | -0.17245300 |
| C | 1.20421900 | 0.02455800 | 0.00089700 |
| N | -1.56619500 | -0.22794200 | 0.01624000 |
| N | 2.53142500 | 0.14635900 | -0.00562400 |
| C | 3.20663400 | 1.45182000 | -0.03038800 |
| H | 4.09750400 | 1.36225900 | 0.59765100 |
| H | 3.54309500 | 1.64786000 | -1.05617400 |
| C | 3.43213300 | -1.01553800 | 0.01204400 |
| H | 4.28670900 | -0.76608900 | -0.62323800 |
| C | 1.44027700 | -2.49119900 | 0.27193900 |
| H | 0.90801900 | -3.37030300 | -0.09914400 |
| C | 0.97825200 | 2.54083300 | -0.27268400 |
| H | 1.14665300 | 2.74874900 | -1.33665400 |
| H | 0.29983000 | 3.31138700 | 0.10167100 |
| C | 2.31059200 | 2.57161200 | 0.47230900 |
| H | 2.81863100 | 3.52621900 | 0.31957000 |
| H | 2.14174800 | 2.45793000 | 1.54860500 |
| H | 1.65219900 | -2.66735800 | 1.33381800 |
| H | 3.80687700 | -1.14668900 | 1.03488400 |
| C | 2.74953200 | -2.27935400 | -0.48431100 |
| H | 3.42382100 | -3.12580000 | -0.33751900 |
| H | 2.55363500 | -2.19843100 | -1.55901100 |

Energy = -765.207303 [hartree]

acyl ammonium ion

| | | | |
|---|---|---|---|
| C | -2.74366100 | -0.25551400 | 0.00001400 |
| H | -3.24865200 | -1.21726400 | -0.00095300 |
| H | -2.97855400 | 0.31837700 | -0.89607200 |
| H | -2.97887000 | 0.31670700 | 0.89708700 |
| O | -1.32287600 | -0.58338200 | -0.00000600 |
| C | -0.49937200 | 0.42706800 | -0.00000100 |
| O | -0.71515000 | 1.59811100 | -0.00001400 |

| | | | |
|---|---|---|---|
| N | 0.92606600 | -0.10596800 | -0.00001200 |
| C | 1.88161700 | 1.05308000 | -0.00006000 |
| H | 1.71127100 | 1.65724600 | 0.88901400 |
| H | 2.89207500 | 0.64559900 | -0.00000200 |
| H | 1.71132800 | 1.65709100 | -0.88925000 |
| C | 1.14156200 | -0.94216900 | 1.23510100 |
| H | 0.46604700 | -1.79476200 | 1.21067900 |
| H | 2.17889300 | -1.27691700 | 1.23702500 |
| H | 0.94679400 | -0.32553100 | 2.11320300 |
| C | 1.14150400 | -0.94228100 | -1.23502200 |
| H | 2.17874900 | -1.27730500 | -1.23683500 |
| H | 0.46578600 | -1.79472000 | -1.21064200 |
| H | 0.94697800 | -0.32567400 | -2.11320000 |

Energy = -402.613610 [hartree]

*H*-phosphonate

| | | | |
|---|---|---|---|
| P | -0.01929100 | 1.49365700 | -0.50286900 |
| O | -0.56287400 | 2.79750200 | 0.01632700 |
| O | 1.46941400 | 1.28949000 | 0.41039900 |
| O | -0.77947500 | 0.19341300 | 0.48435000 |
| C | -2.04178200 | -0.19247600 | 0.26927100 |
| C | -4.67393700 | -1.13348800 | -0.11308600 |
| C | -3.06266400 | 0.68516300 | -0.14073000 |
| C | -2.36587300 | -1.54329600 | 0.49091500 |
| C | -3.66472800 | -2.00277300 | 0.30617600 |
| C | -4.35639000 | 0.20681300 | -0.33276500 |
| H | -2.82593900 | 1.73479700 | -0.27916900 |
| H | -1.57297100 | -2.21147100 | 0.81370200 |
| H | -3.89062600 | -3.05119700 | 0.48697900 |
| H | -5.13139200 | 0.90048300 | -0.65038200 |
| H | -5.68817400 | -1.49360400 | -0.26056100 |
| C | 2.35986300 | 0.31992900 | 0.15994900 |
| C | 4.35150700 | -1.62891500 | -0.27887700 |
| C | 2.02385000 | -0.93947100 | -0.36680800 |
| C | 3.70662000 | 0.58188900 | 0.46648800 |
| C | 4.68487200 | -0.38197600 | 0.25453000 |
| C | 3.01712300 | -1.89160600 | -0.58490100 |
| H | 0.98497100 | -1.16614400 | -0.57407500 |

| | | | |
|---|---|---|---|
| H | 3.95429300 | 1.55693400 | 0.87421100 |
| H | 5.71899300 | -0.15598800 | 0.50385400 |
| H | 2.73629100 | -2.85938800 | -0.99353300 |
| H | 5.11664500 | -2.38127700 | -0.44757900 |

Energy = -1030.222930 [hartree]

**Consideration of results from DFT calculation**

We estimated the Pearson's chemical hardness η of the electrophiles using calculated results based on the previous report.[11] The electrophiles with higher η should have higher hardness. The calculation results indicated that acyl pyridinium ions have a lower chemical hardness (higher chemical softness) than acyl ammonium ions (Fig. S5a and S5b). This is reasonable because the HOMO of the acyl pyridinium ion is more delocalized than that of the acyl ammonium ion. Reportedly, phosphorus atoms as nucleophiles prefer soft electrophiles.[16] Therefore, it is conceivable that the soft P-nucleophile preferentially reacts with the relatively soft acyl pyridinium electrophile. By contrast, the oxygen atom of *H*-phosphonate is more negatively charged than the phosphorus atom (Fig. S5c). Therefore, we speculate that O-nucleophiles preferentially react with localized acylammonium ions rather than with P-nucleophiles.

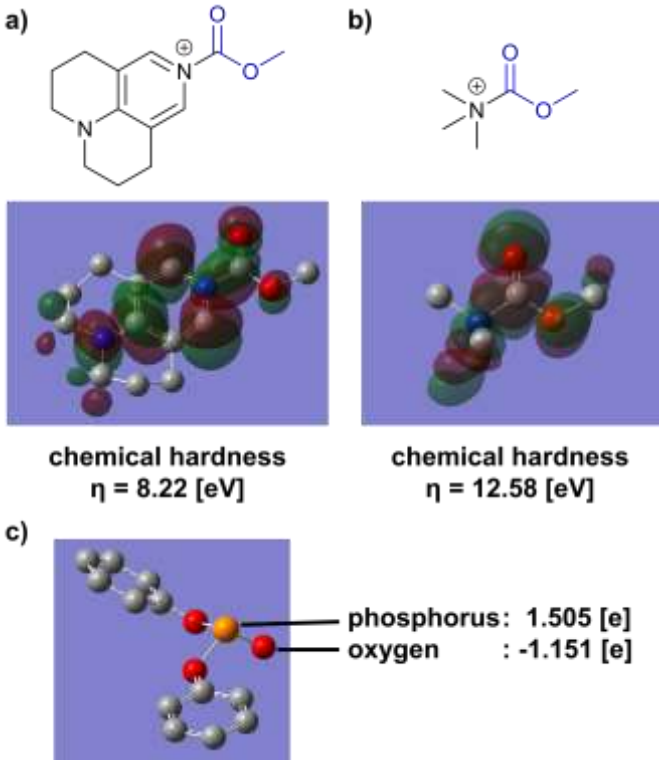



**Figure S5. HOMO and chemical hardness of acyl pyridinium ion (a) and acyl ammonium ion (b). NBO charge of phosphorus and oxygen atom of diphenyl *H*-phosphonate (2a) (c).**

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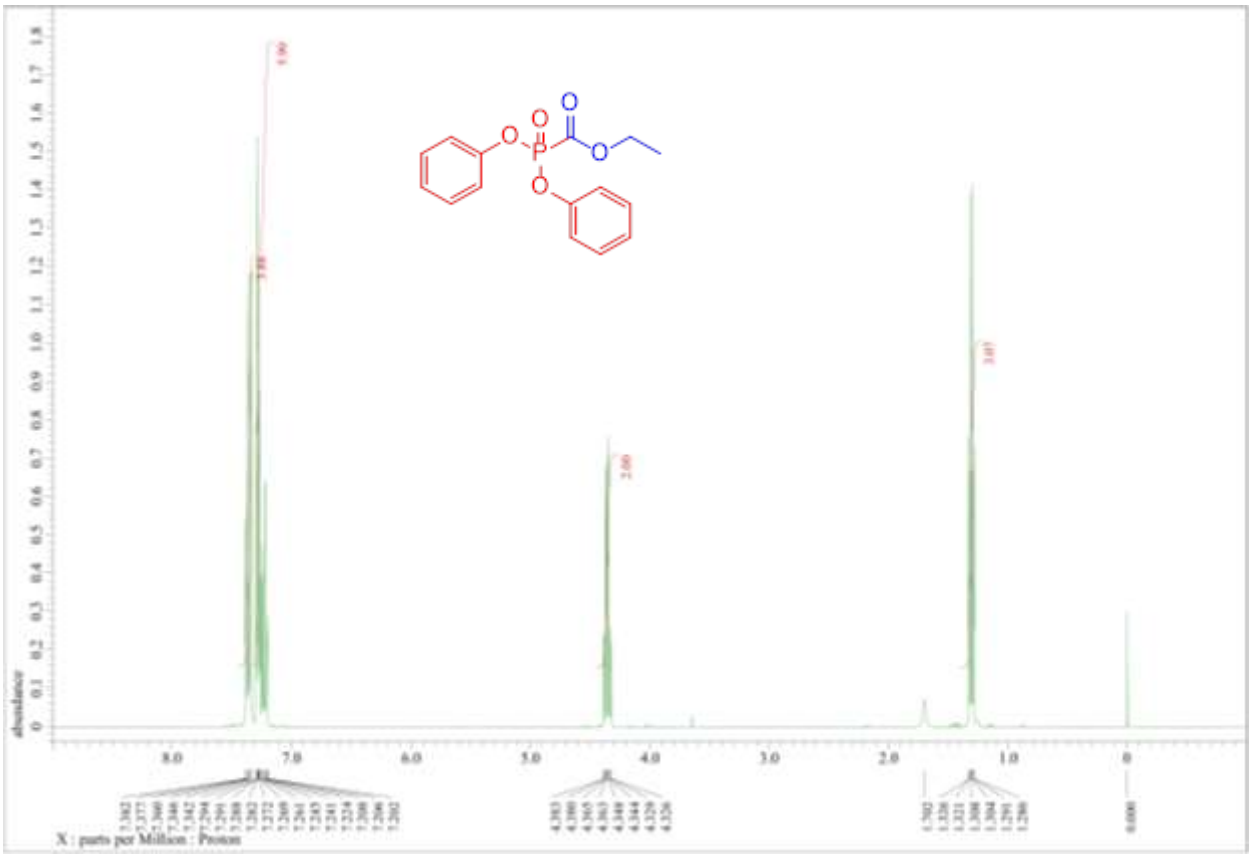
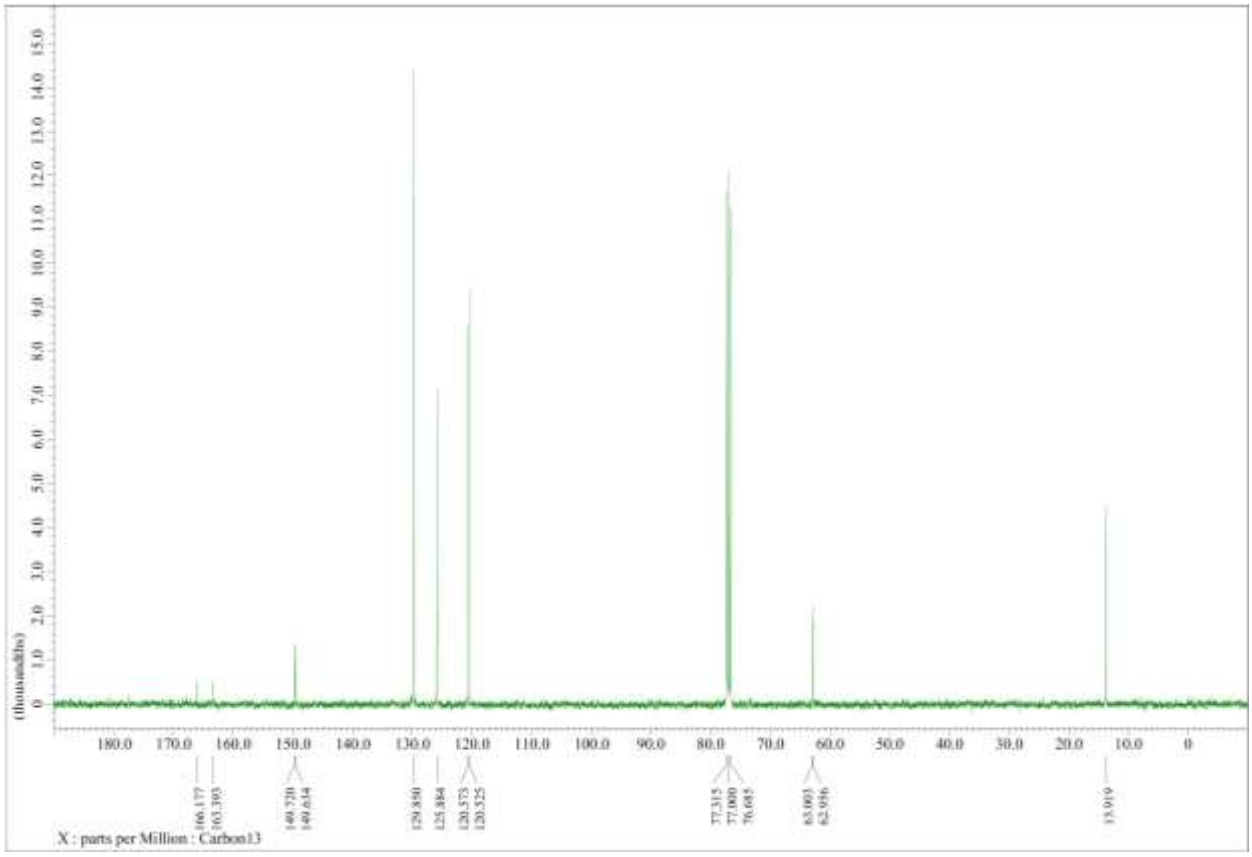
**NMR spectra**

**Ethyl (diphenoxyphosphoryl)formate (3a)**

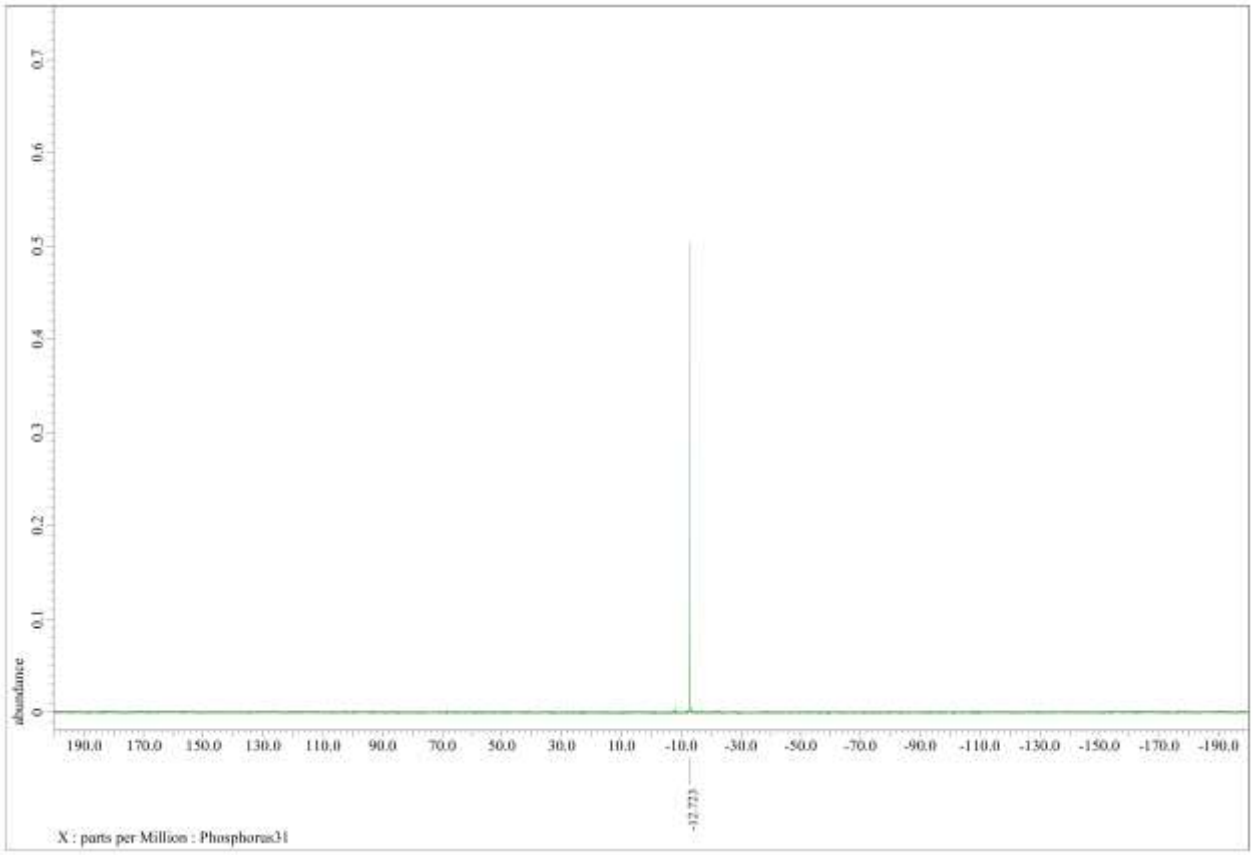
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

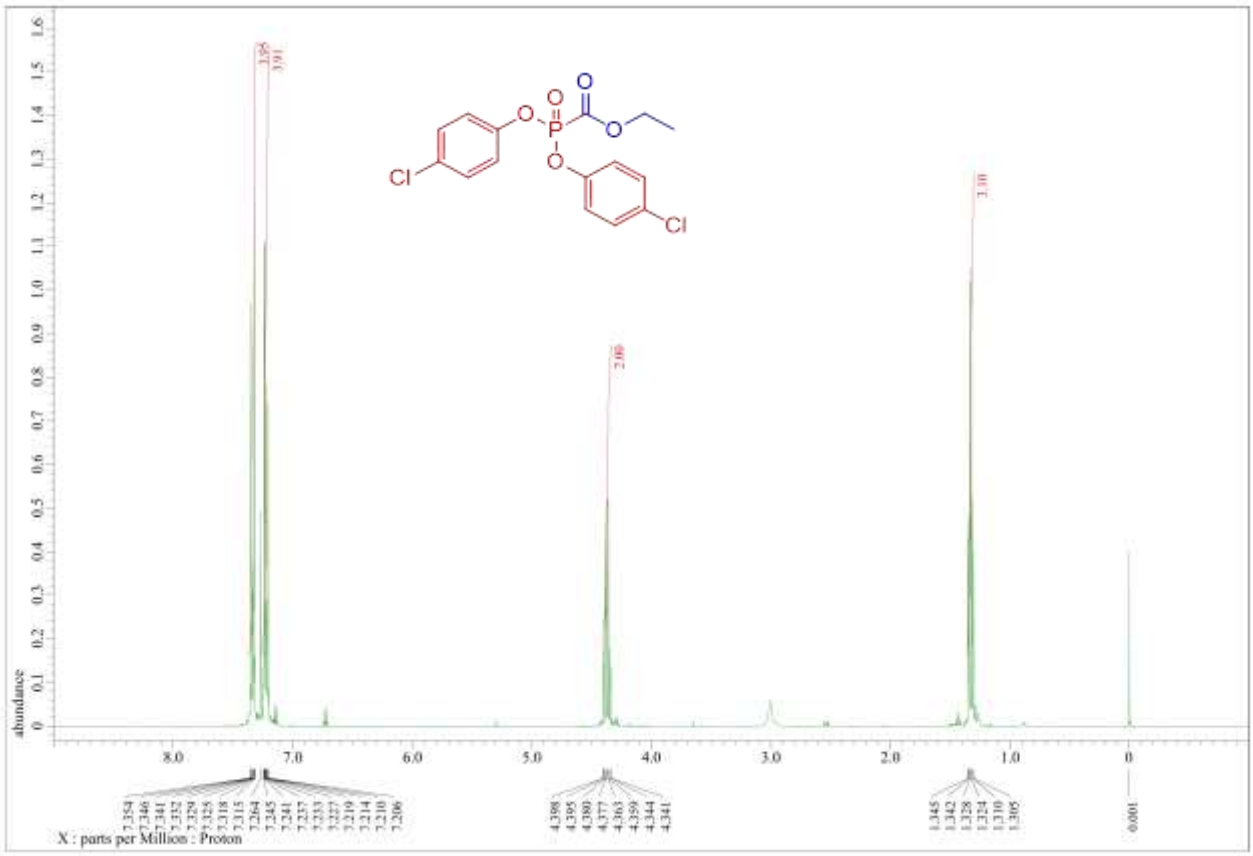


($^{31}$P NMR, 162 MHz, $CDCl_3$)

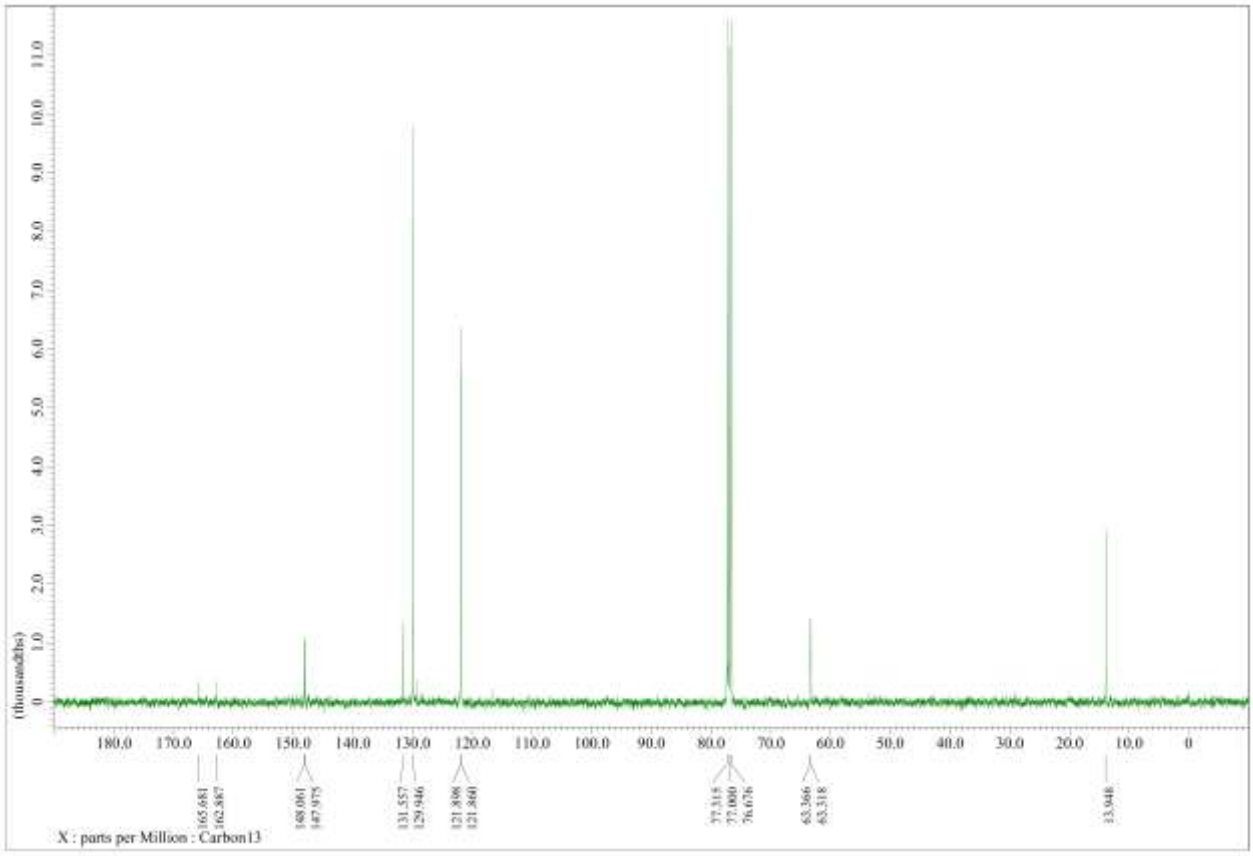



**Ethyl (bis(4-chlorophenoxy)phosphoryl)formate (3b)**

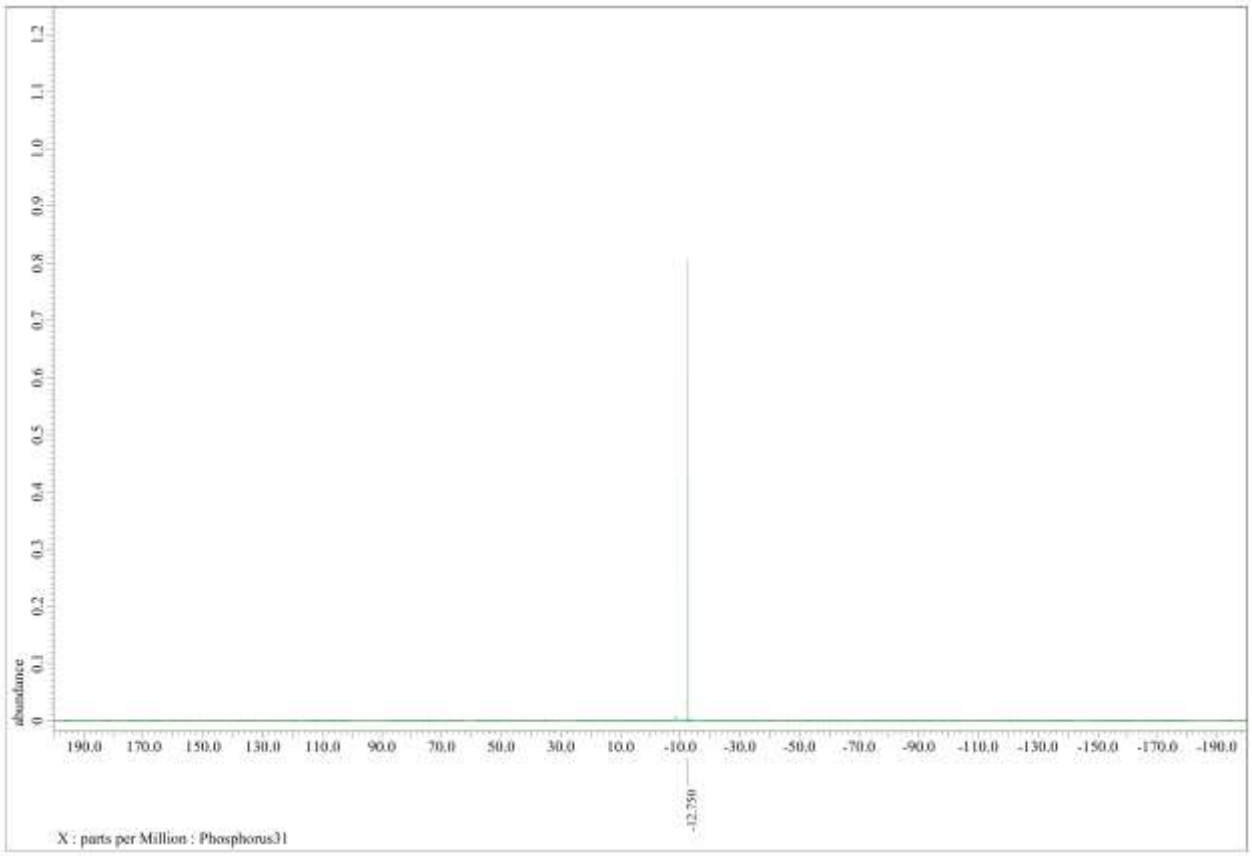
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

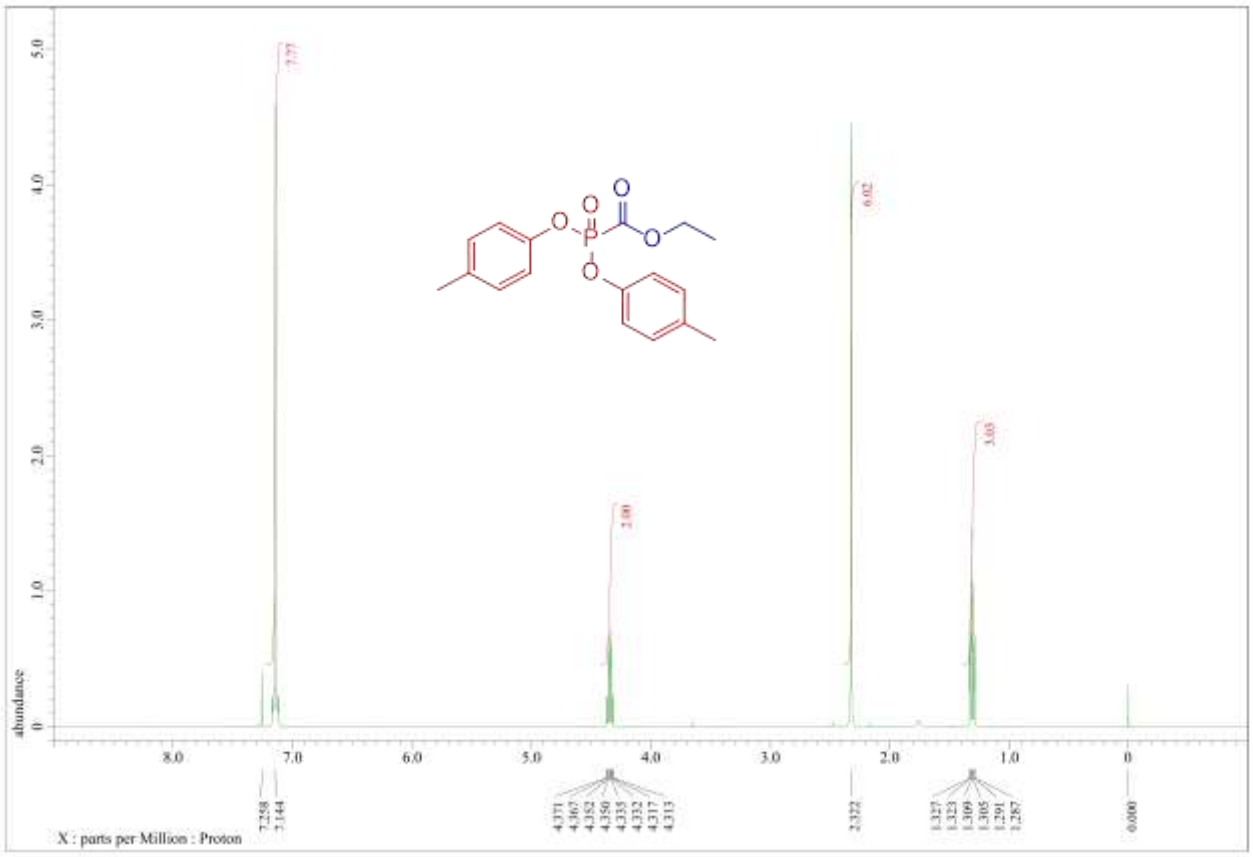



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

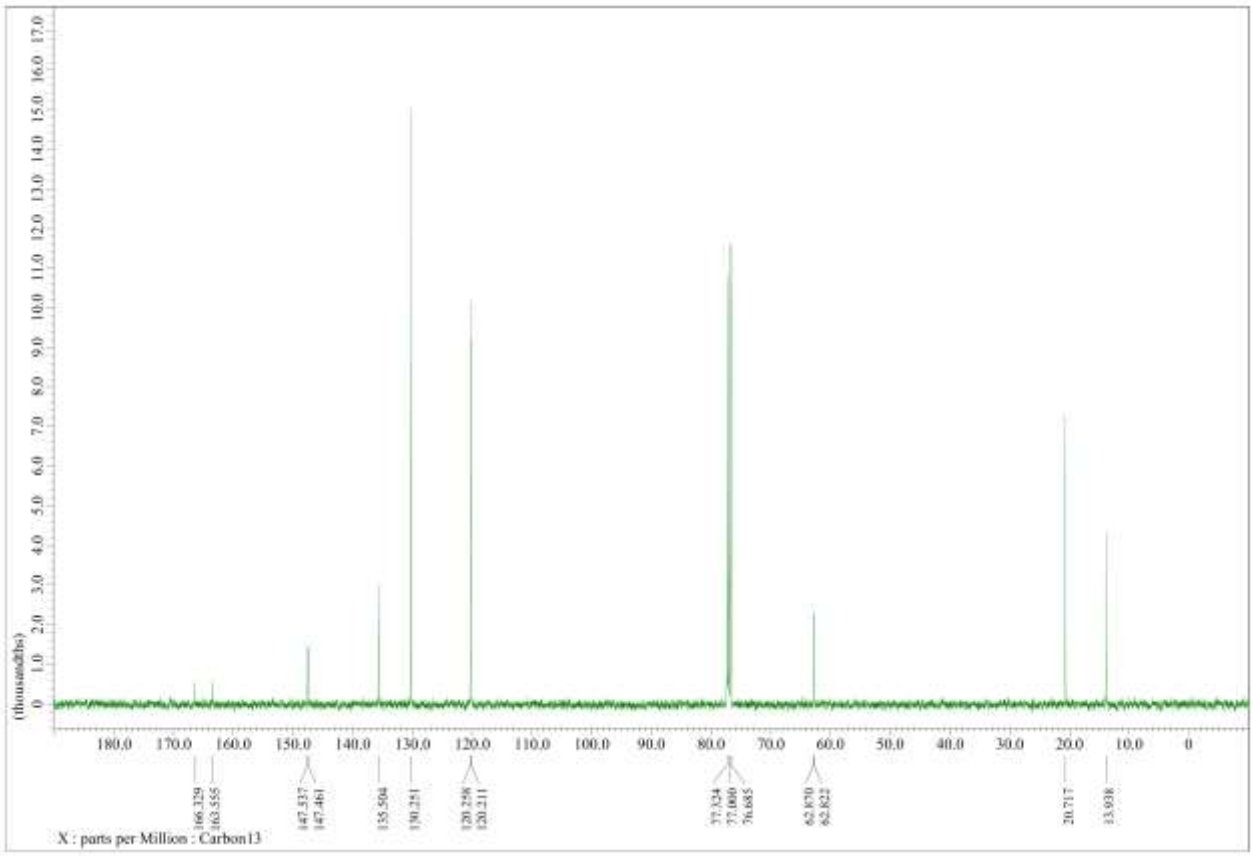


**Ethyl (bis(*p*-tolyloxy)phosphoryl)formate (3c)**

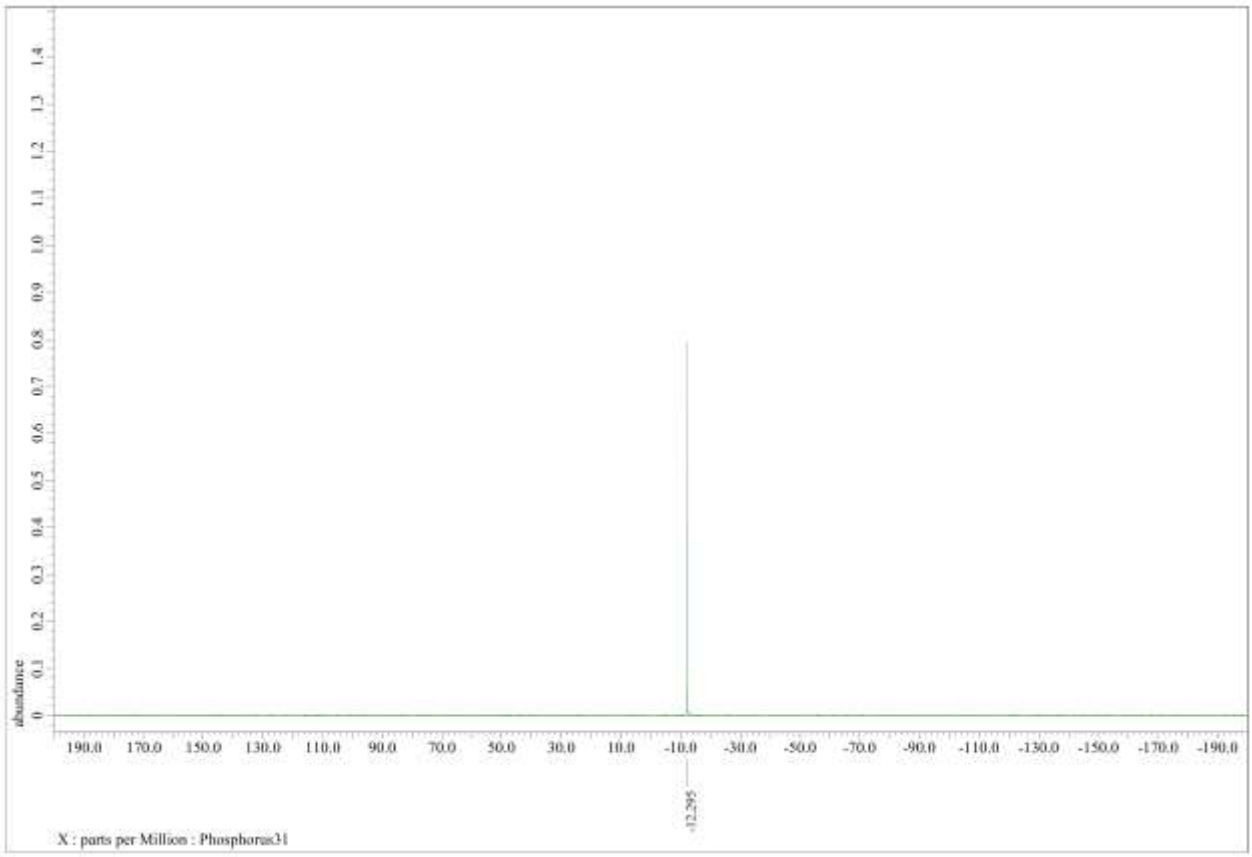
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

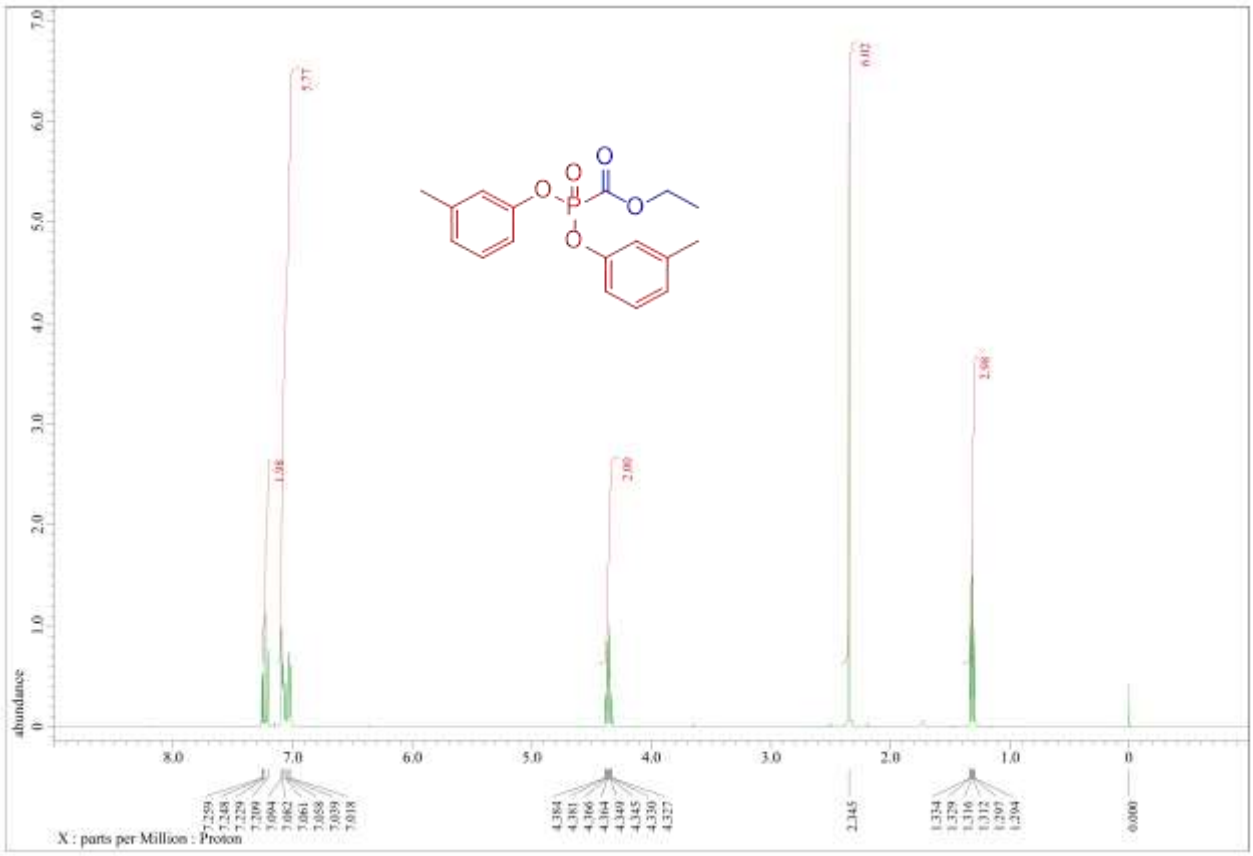


($^{31}$P NMR, 162 MHz, $CDCl_3$)

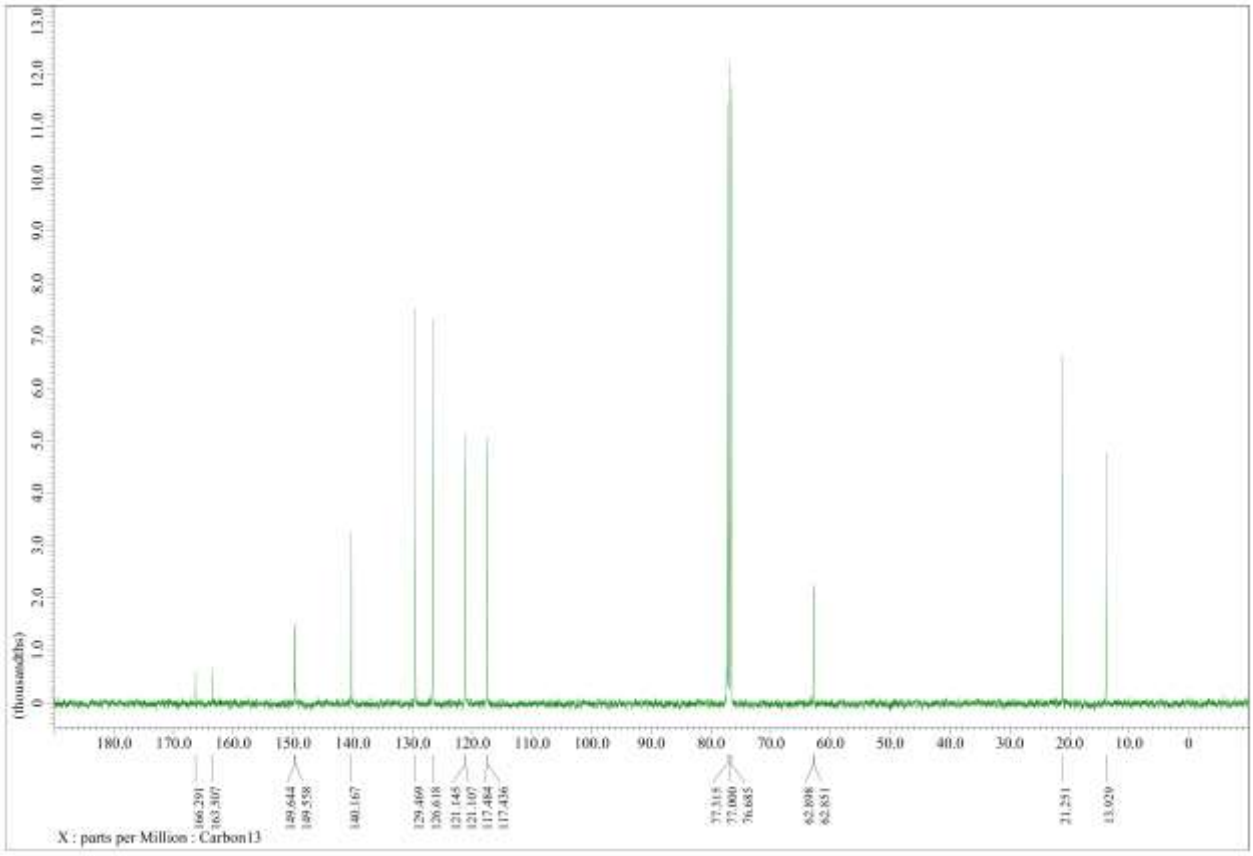



**Ethyl (bis(*m*-tolyloxy)phosphoryl)formate (3d)**

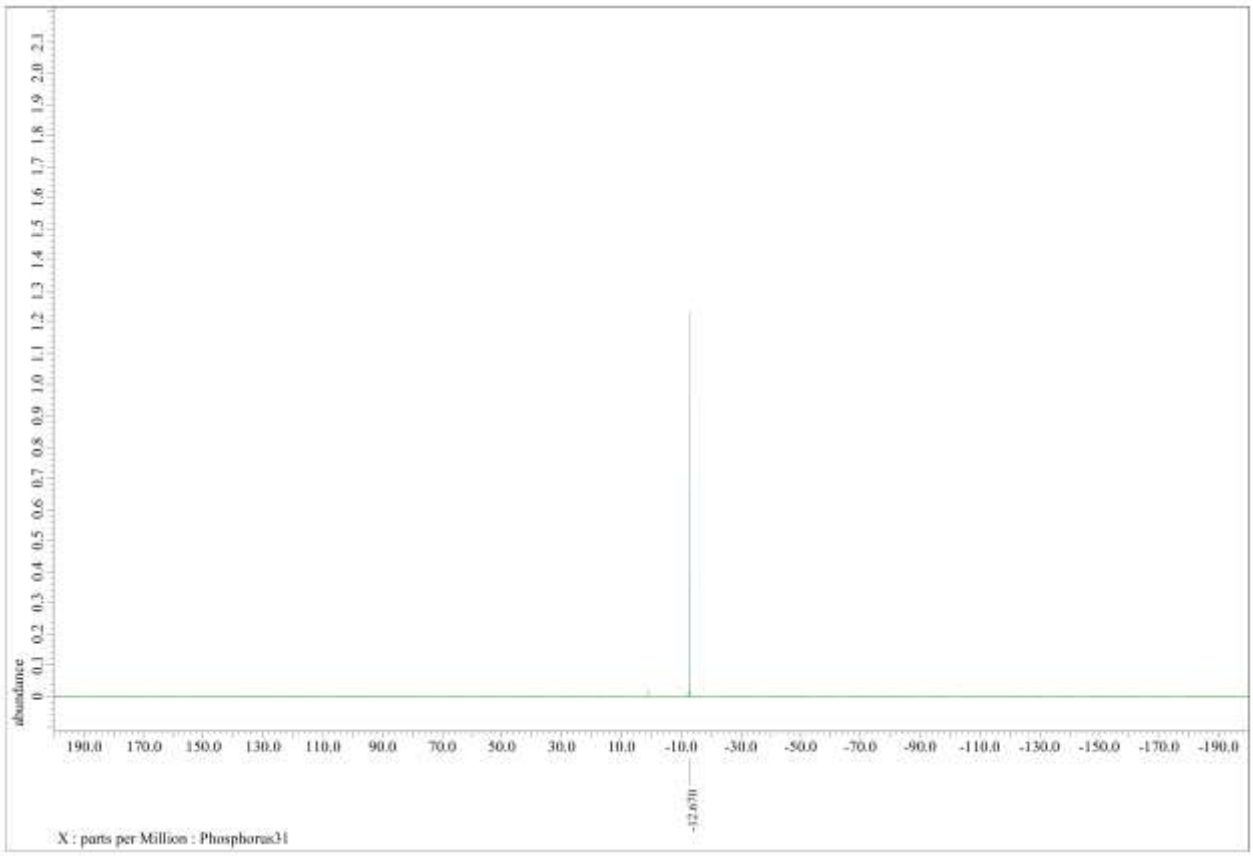
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

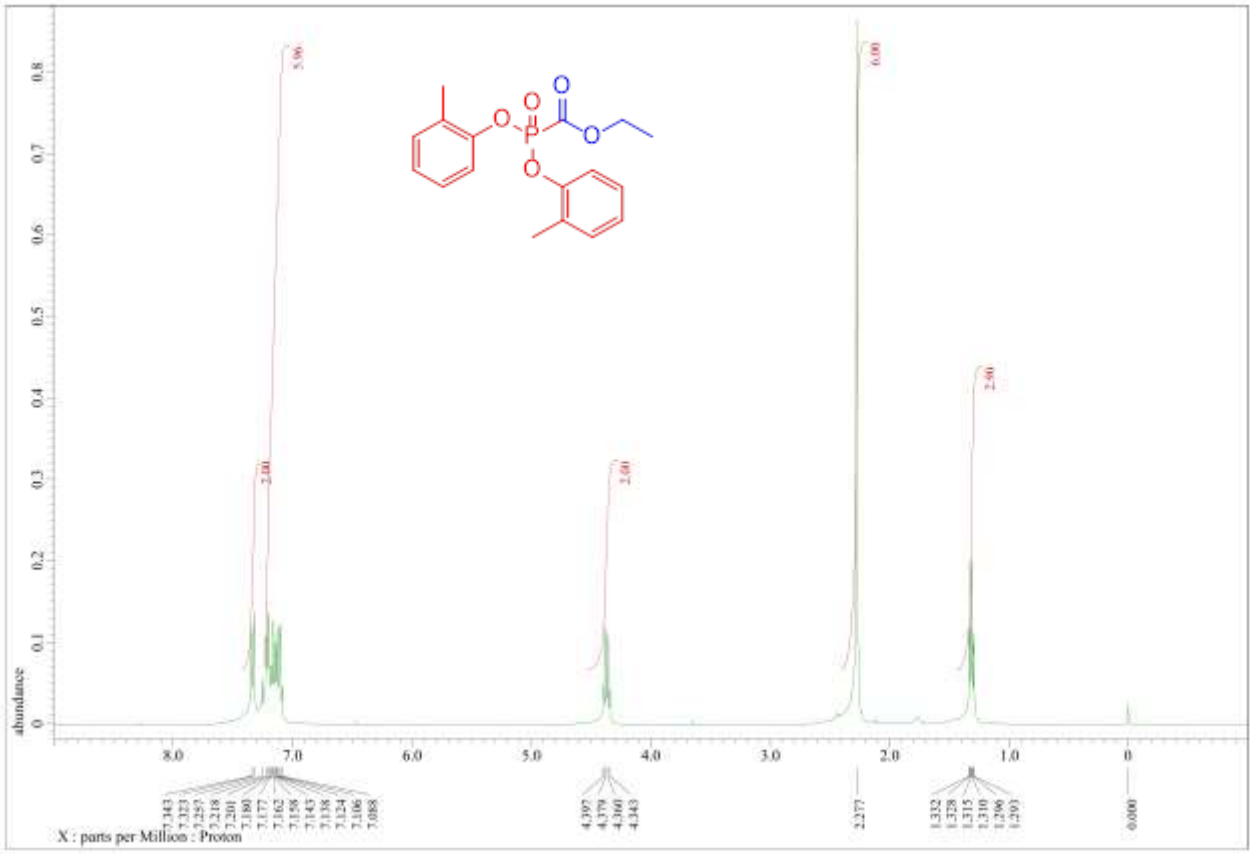



($^{31}$P NMR, 162 MHz, $CDCl_3$)

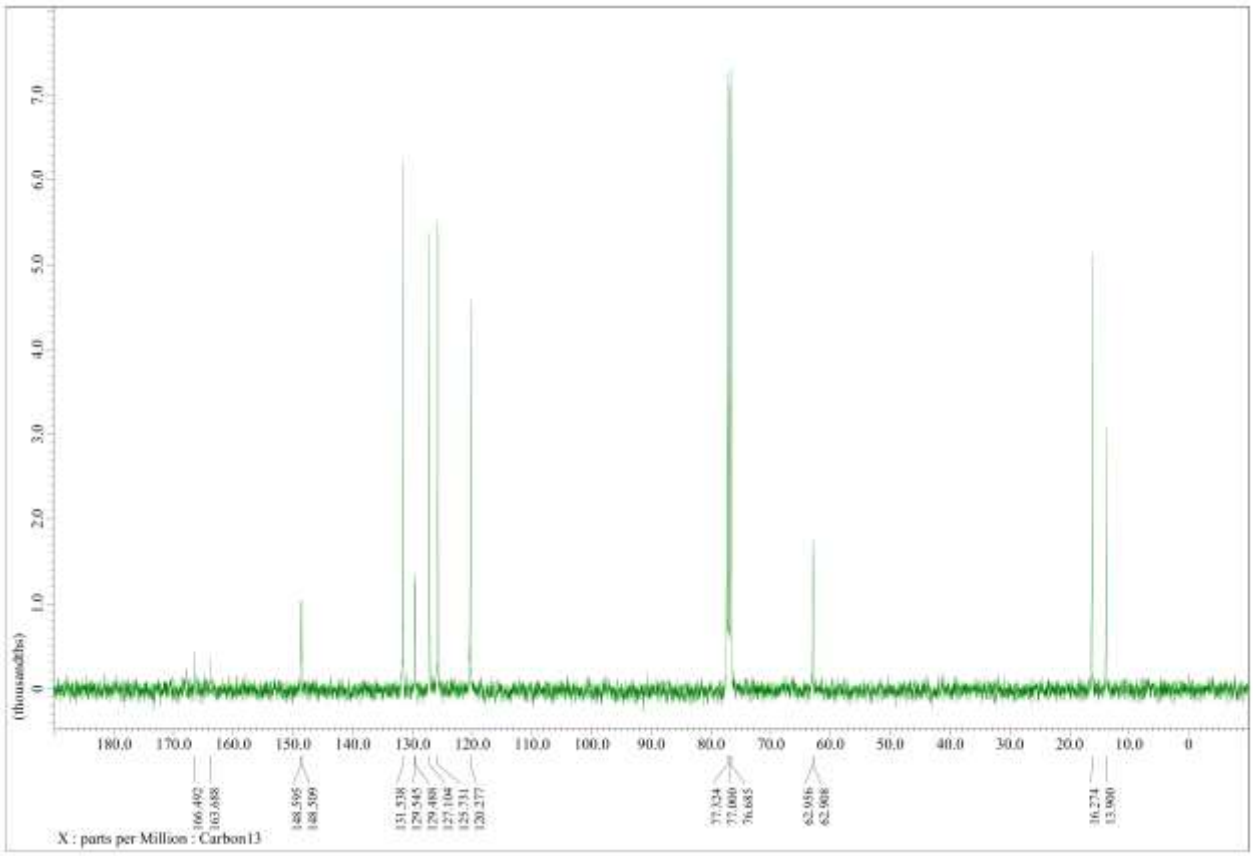


**Ethyl (bis(*o*-tolyloxy)phosphoryl)formate (3e)**

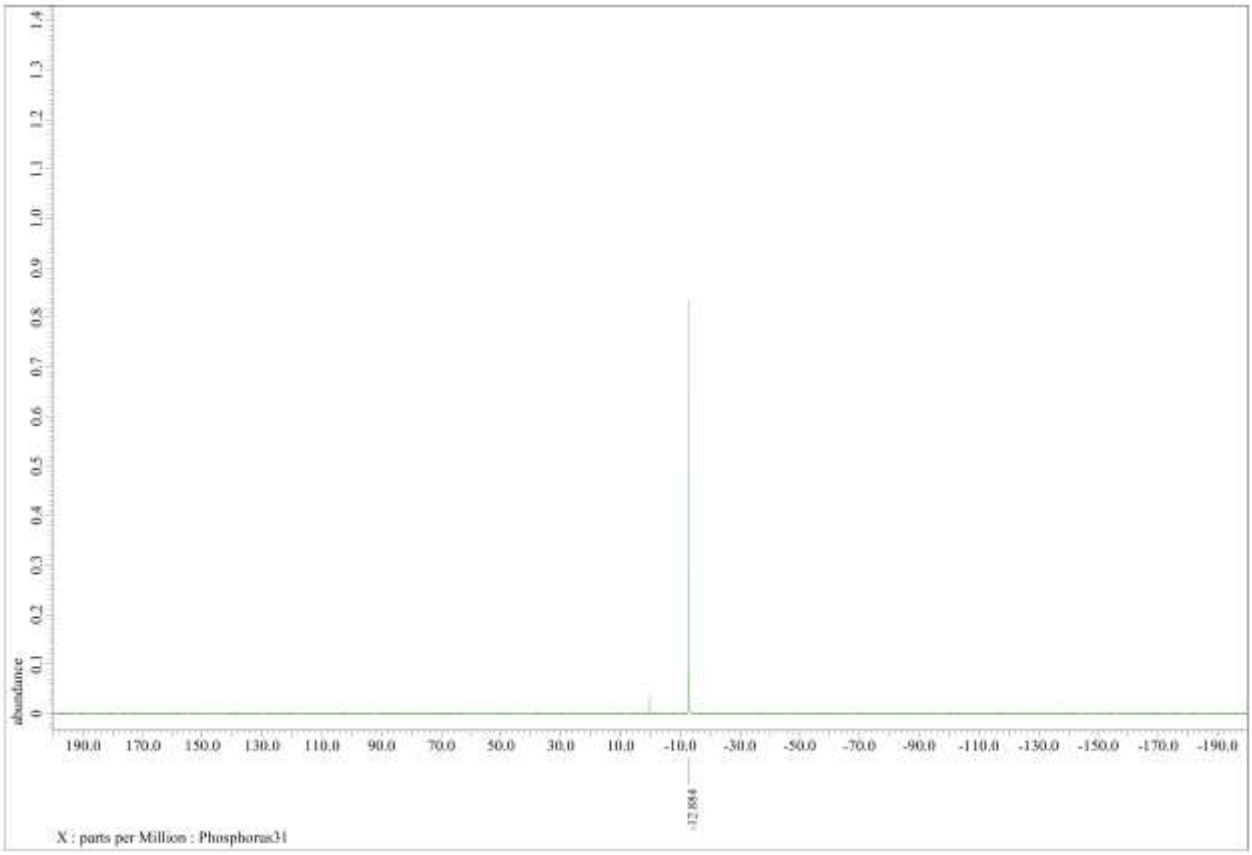
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

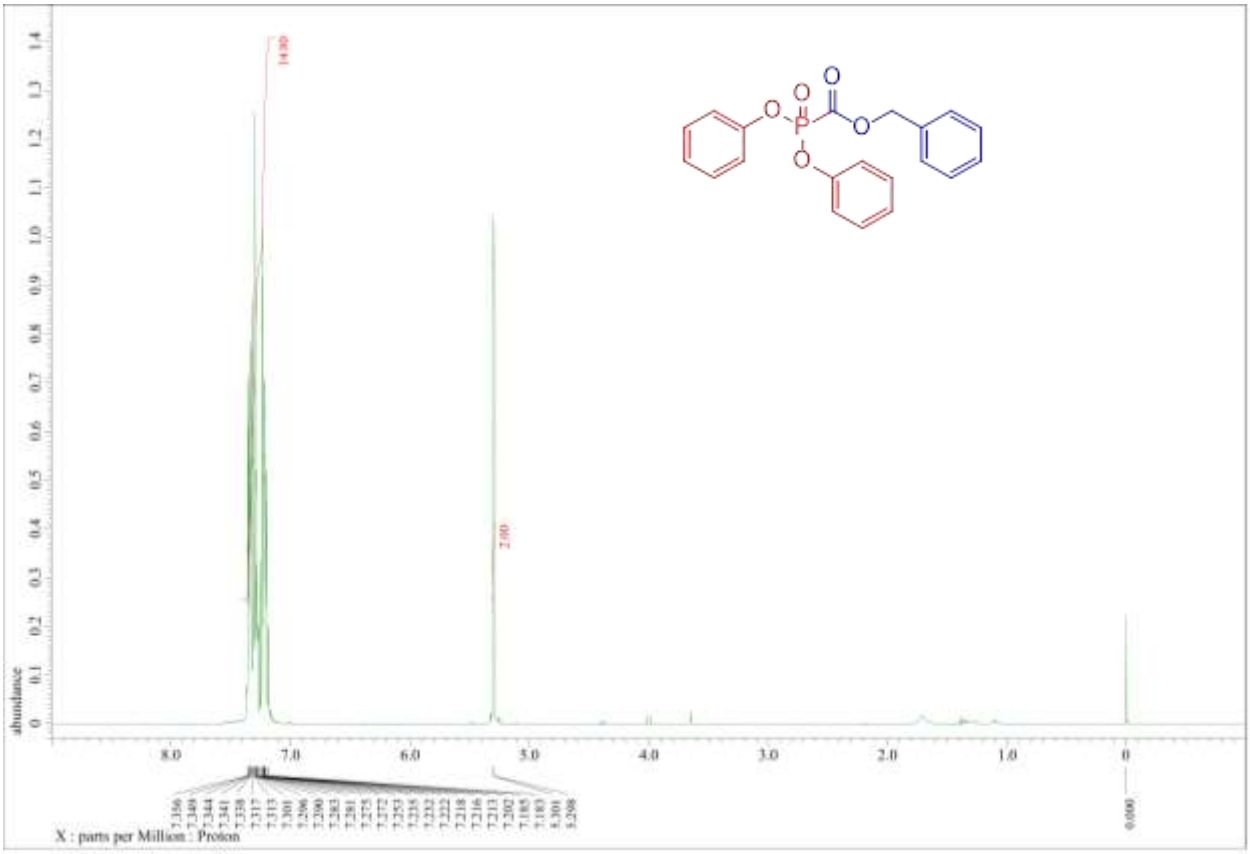


($^{31}$P NMR, 162 MHz, $CDCl_3$)

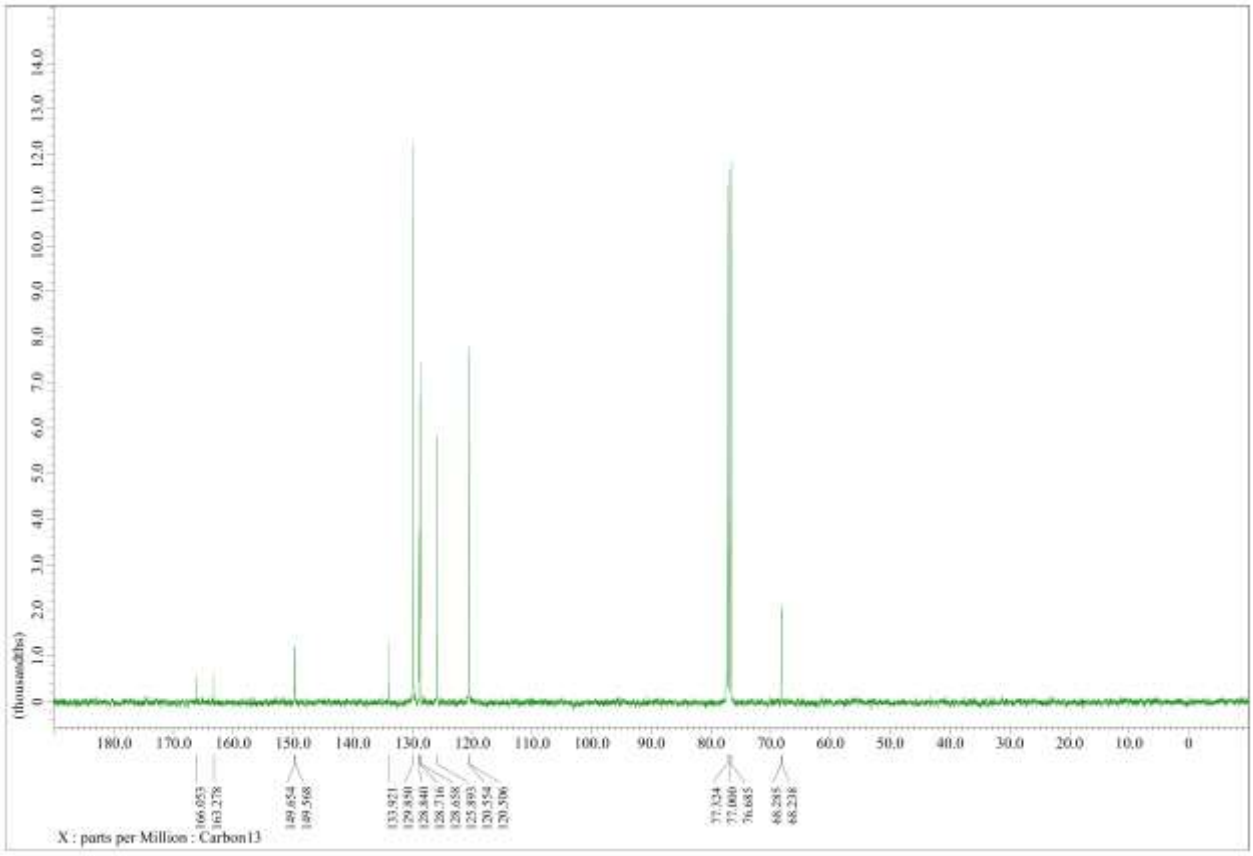



**Benzyl (diphenoxyphosphoryl)formate (3f)**

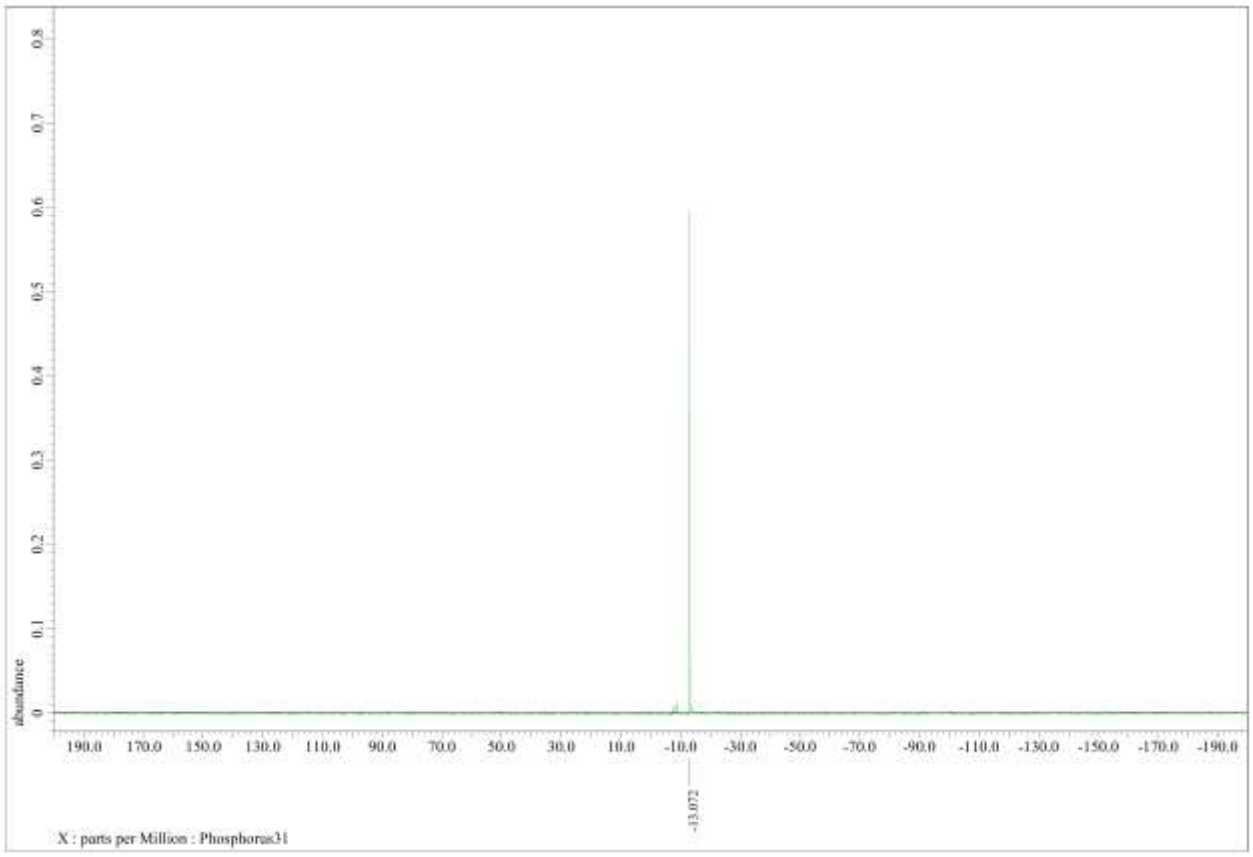
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

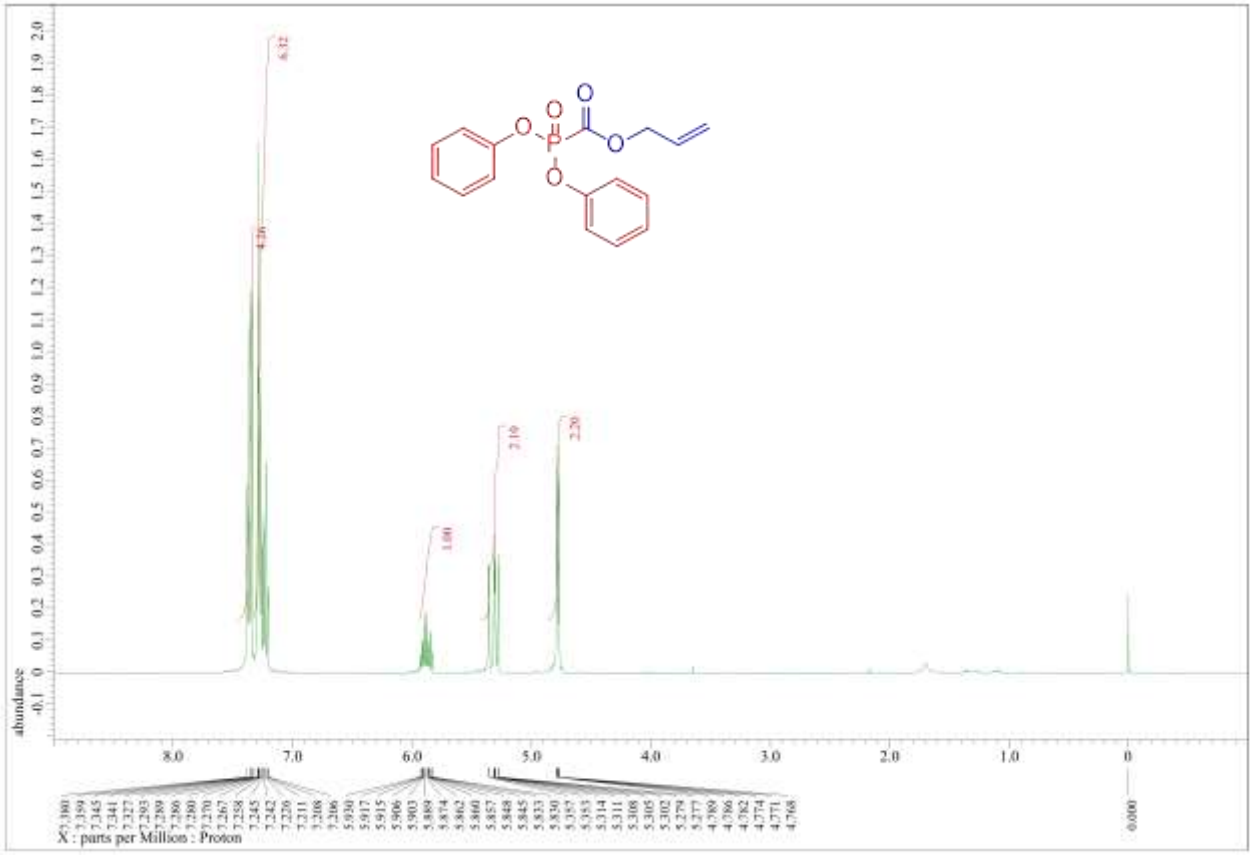



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

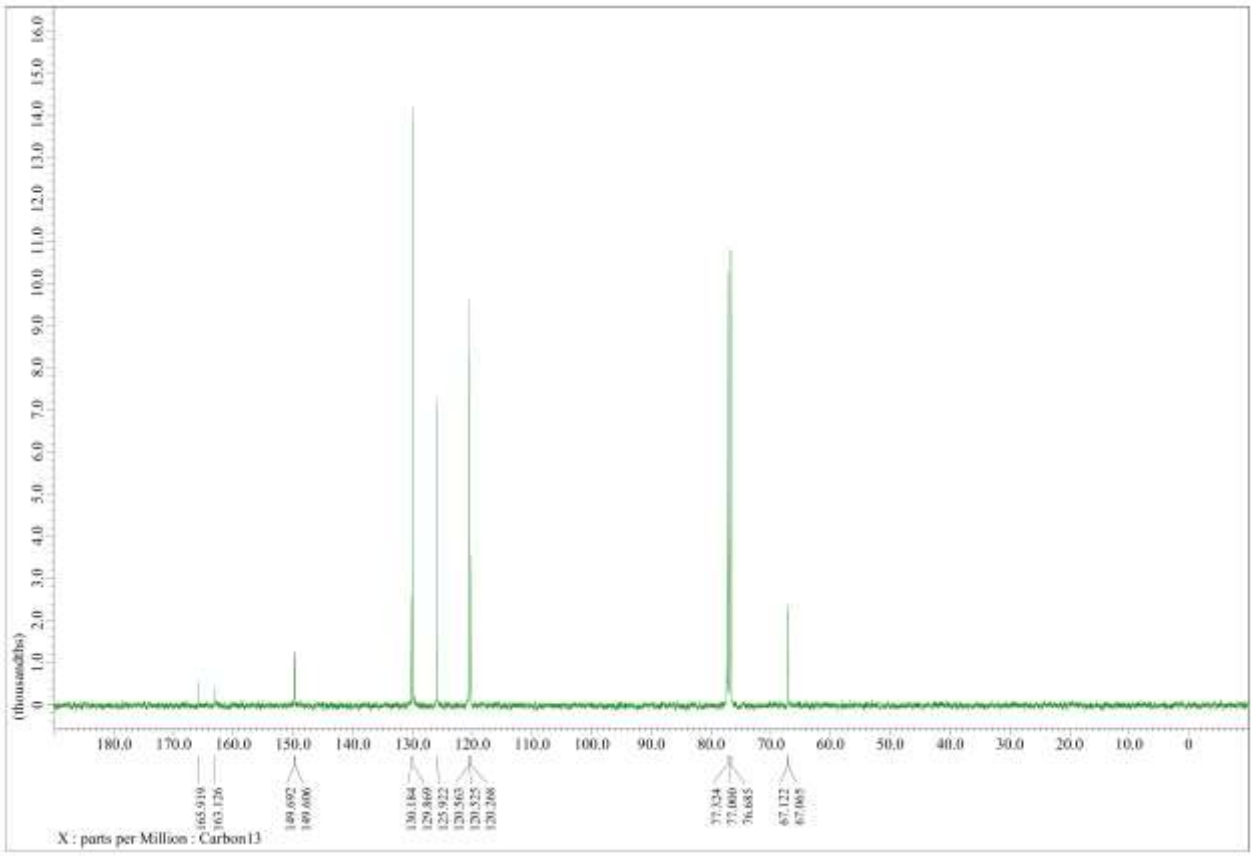


**Allyl (diphenoxyphosphoryl)formate (3g)**

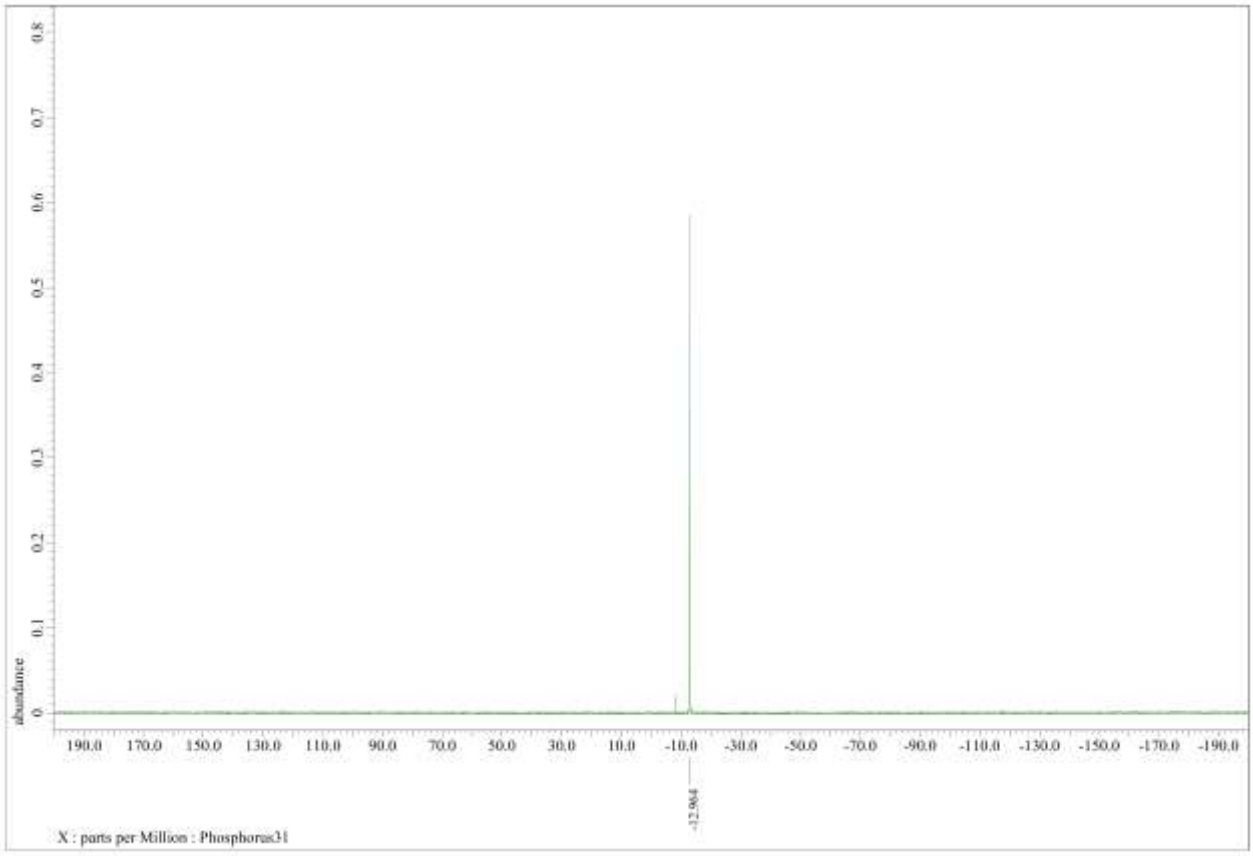
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

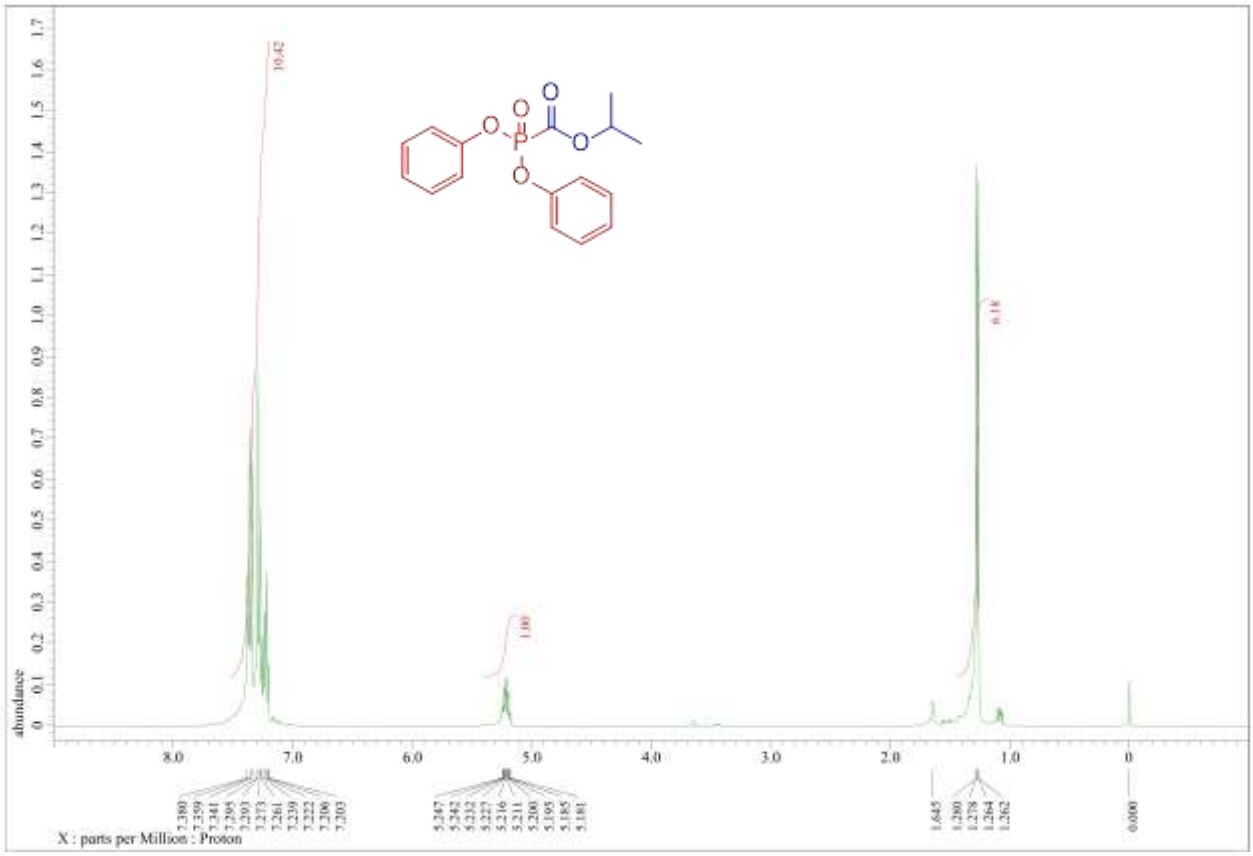


($^{31}$P NMR, 162 MHz, $CDCl_3$)

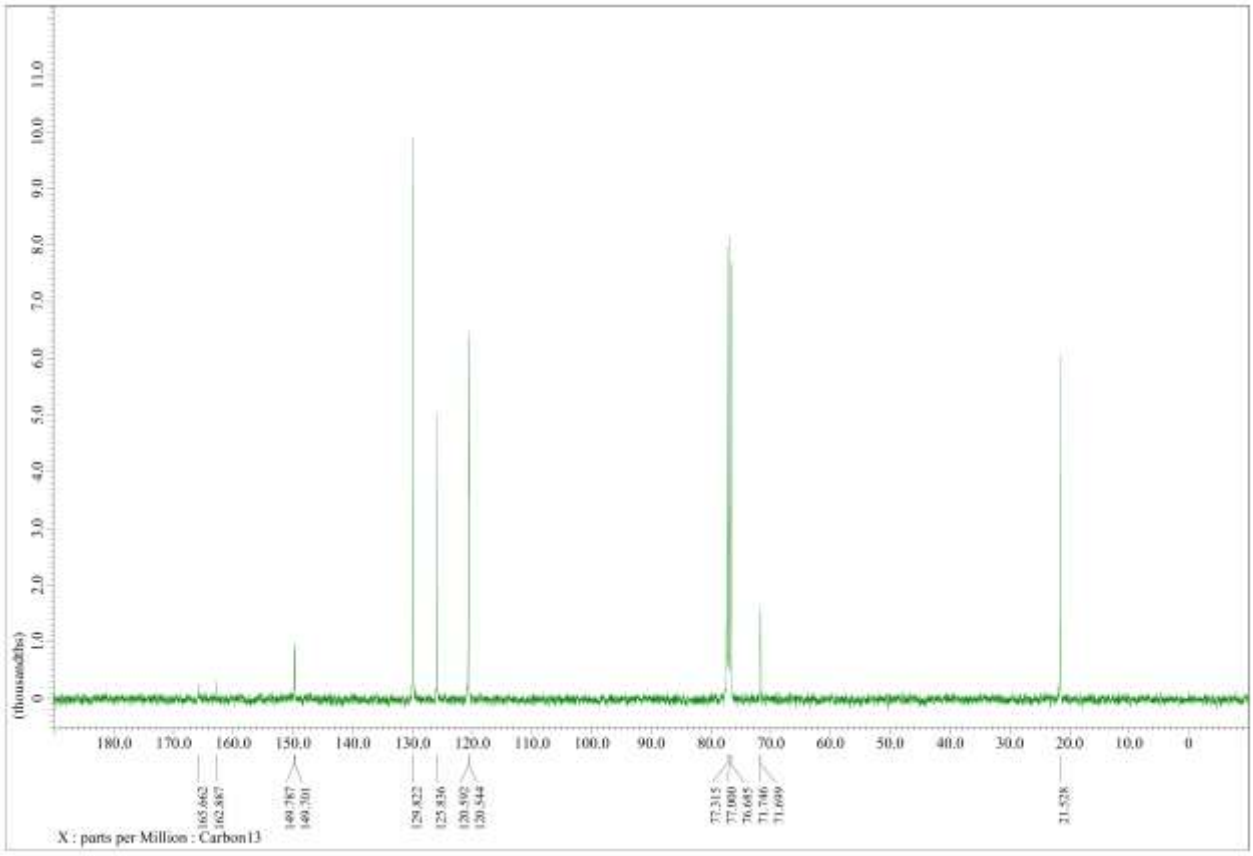



**Isopropyl (diphenoxyphosphoryl)formate (3h)**

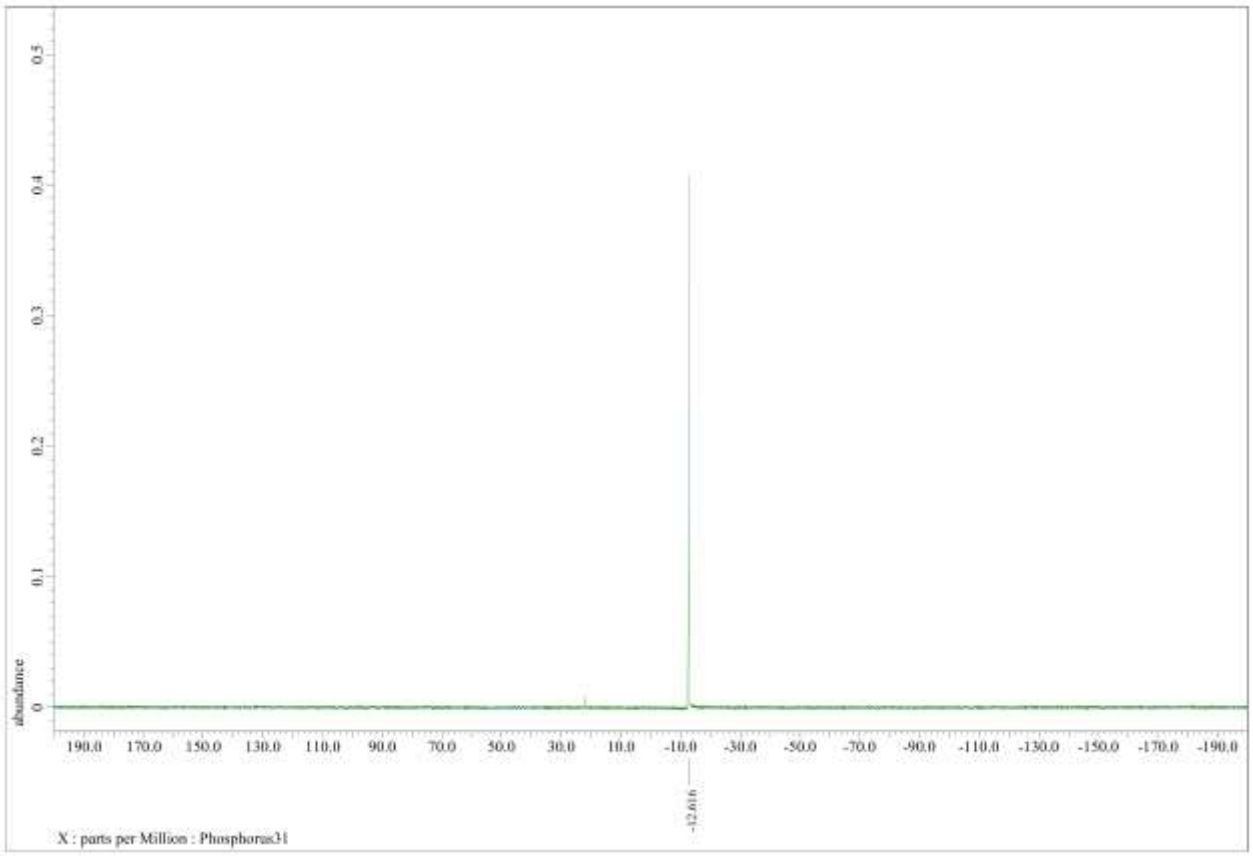
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

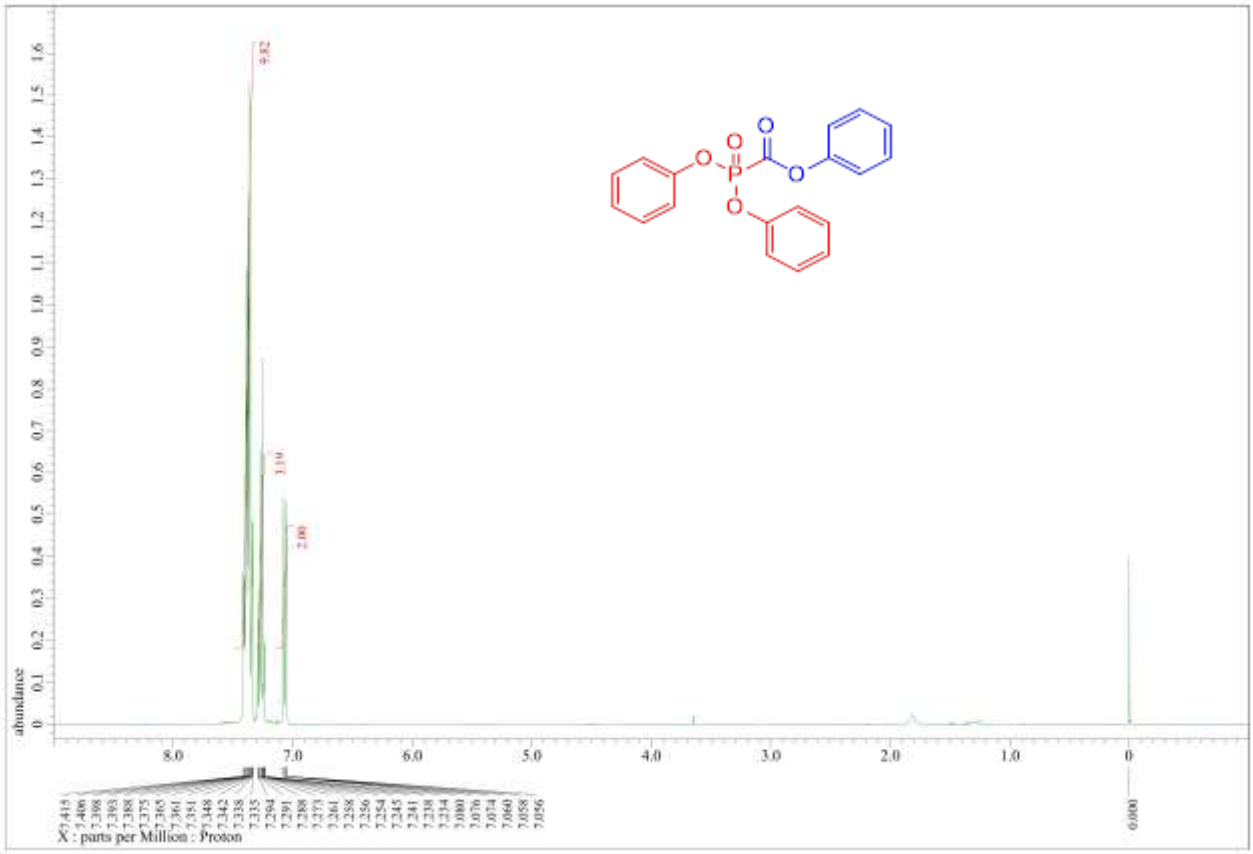



($^{31}$P NMR, 162 MHz, $CDCl_3$)

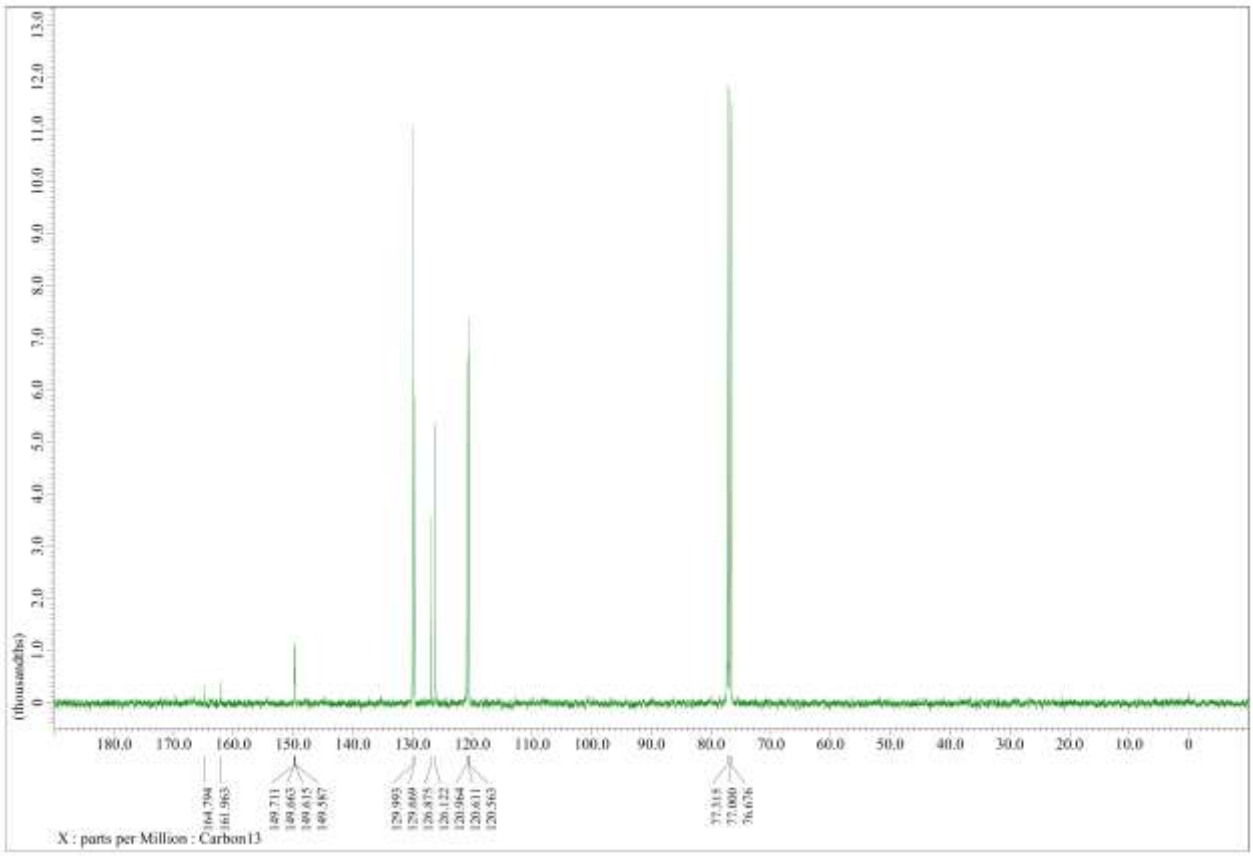


**Phenyl (diphenoxyphosphoryl)formate (3i)**

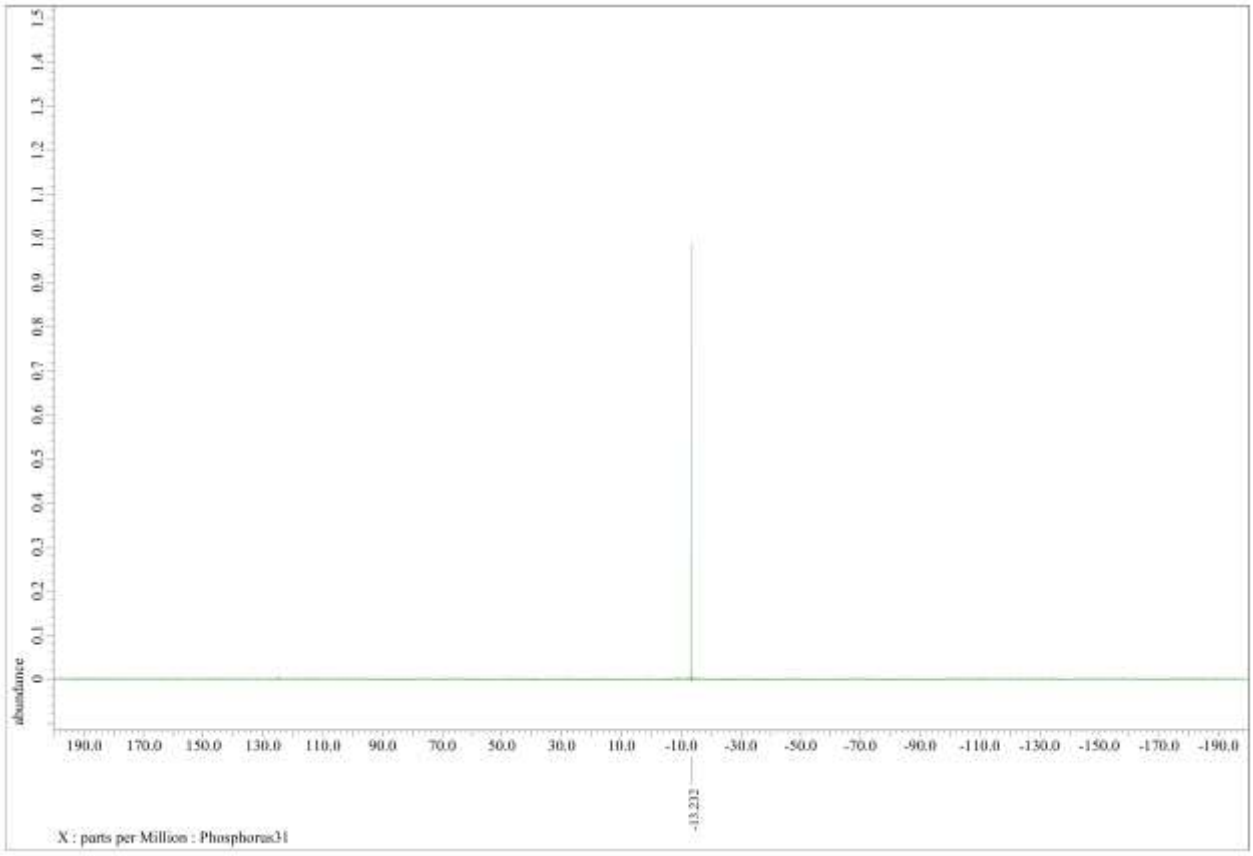
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

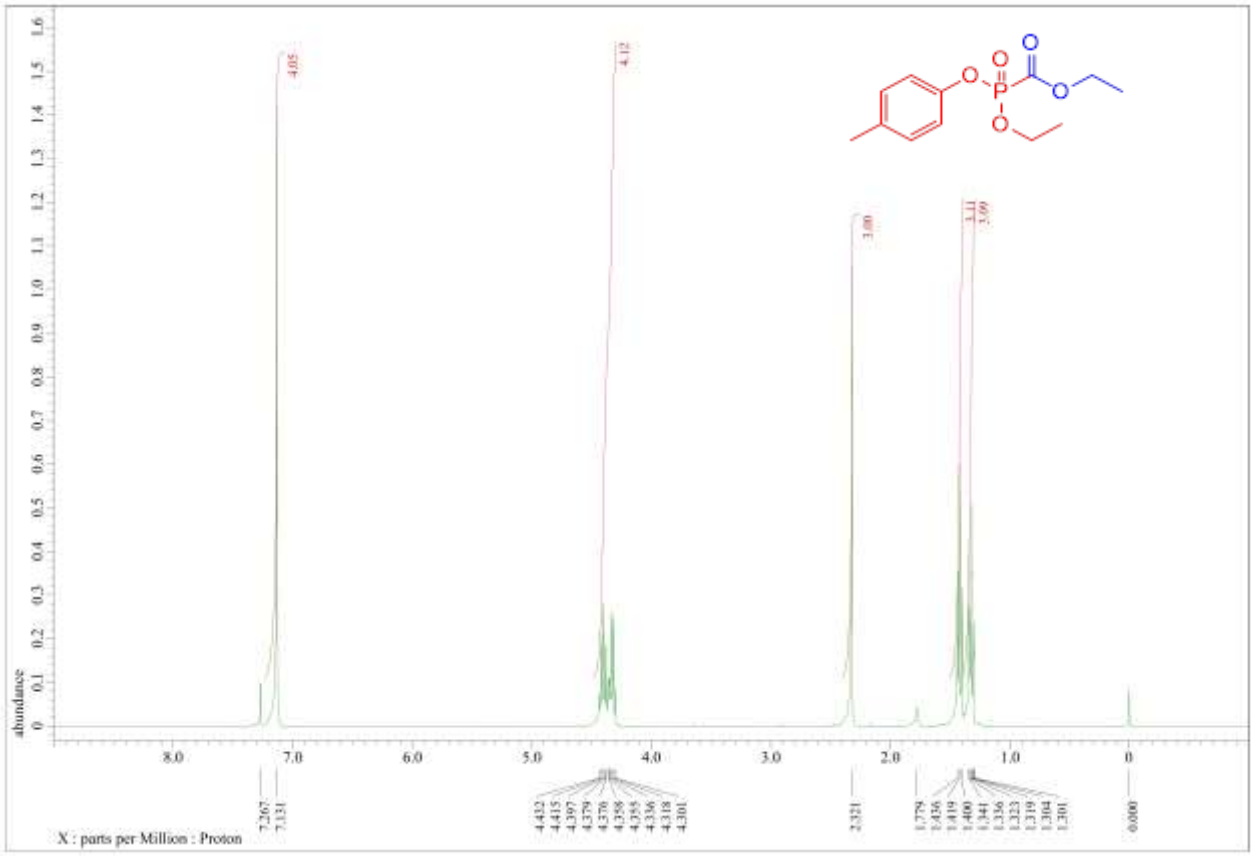


($^{31}$P NMR, 162 MHz, $CDCl_3$)

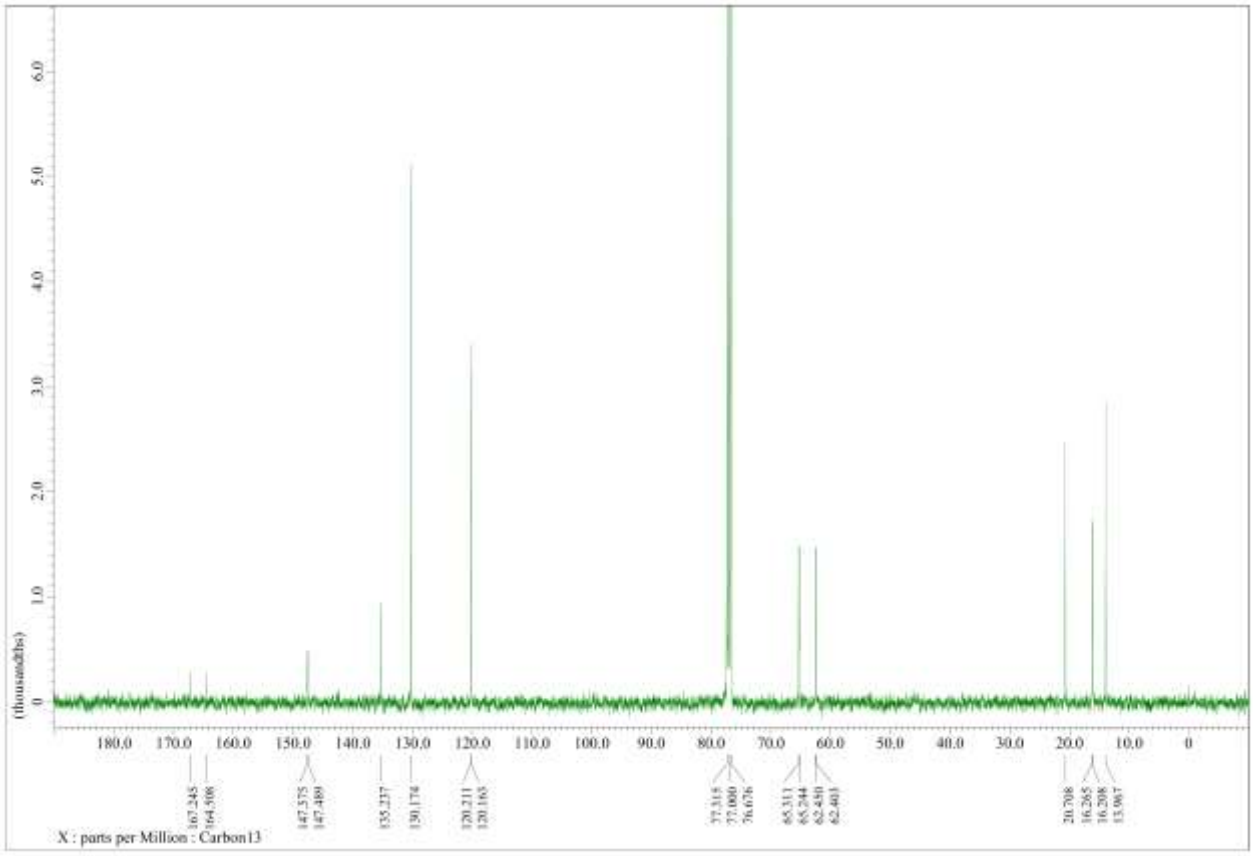



**Ethyl (ethoxy(*p*-tolyloxy)phosphoryl)formate (3j)**

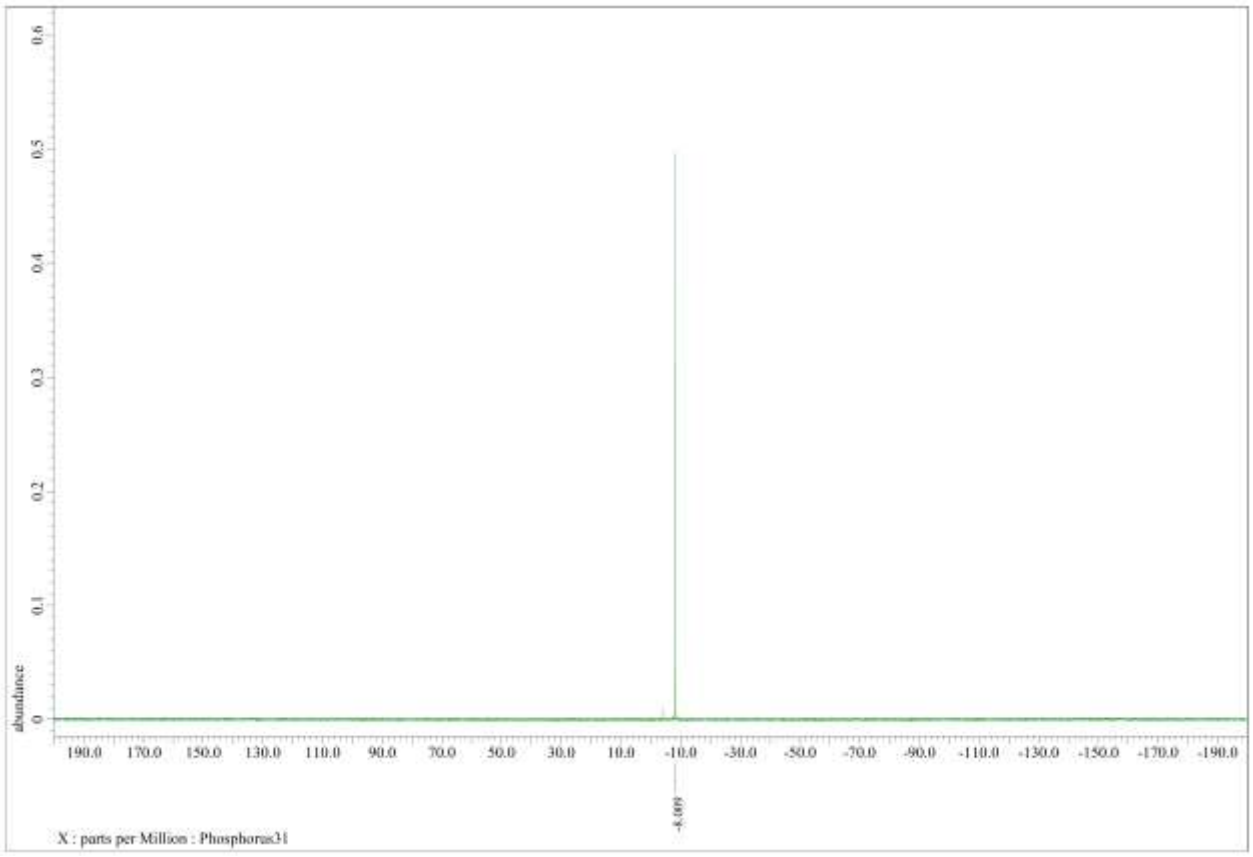
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

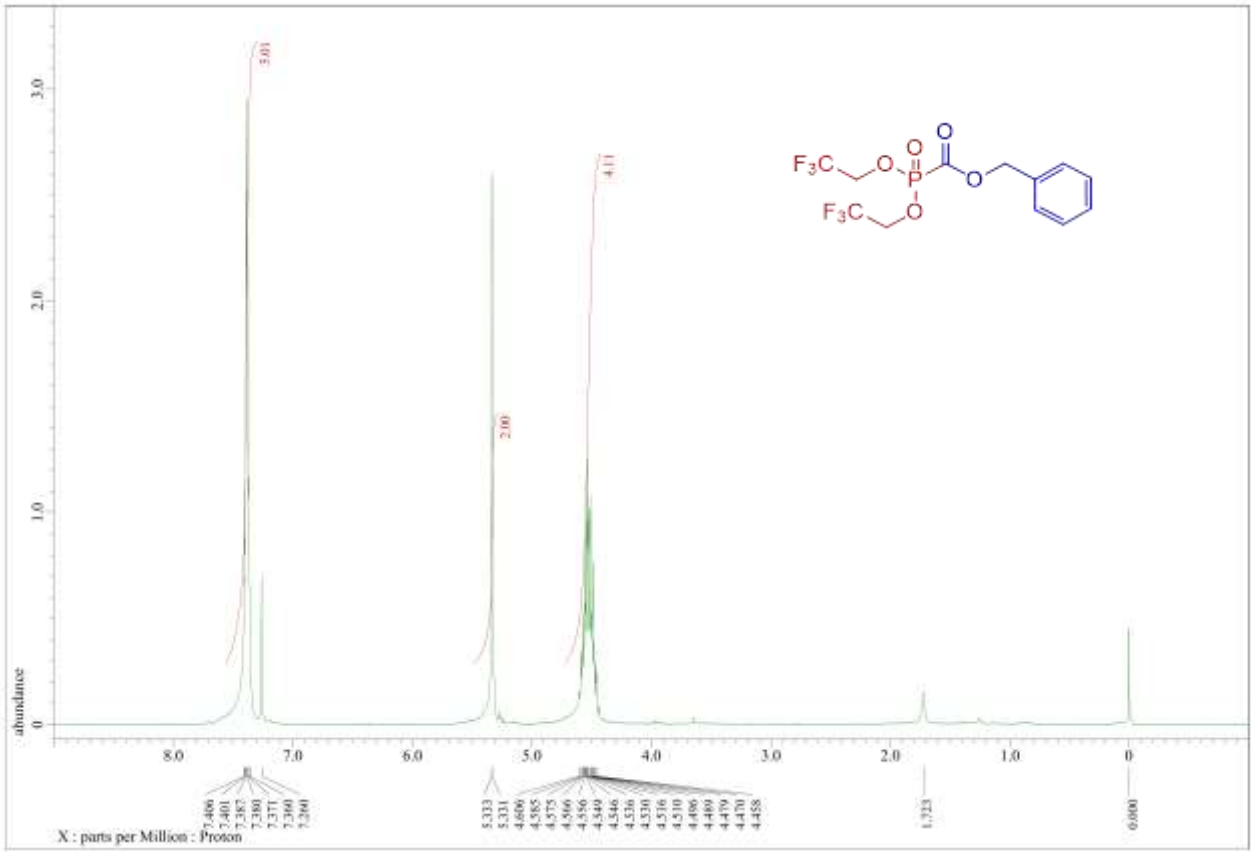



($^{31}$P NMR, 162 MHz, $CDCl_3$)

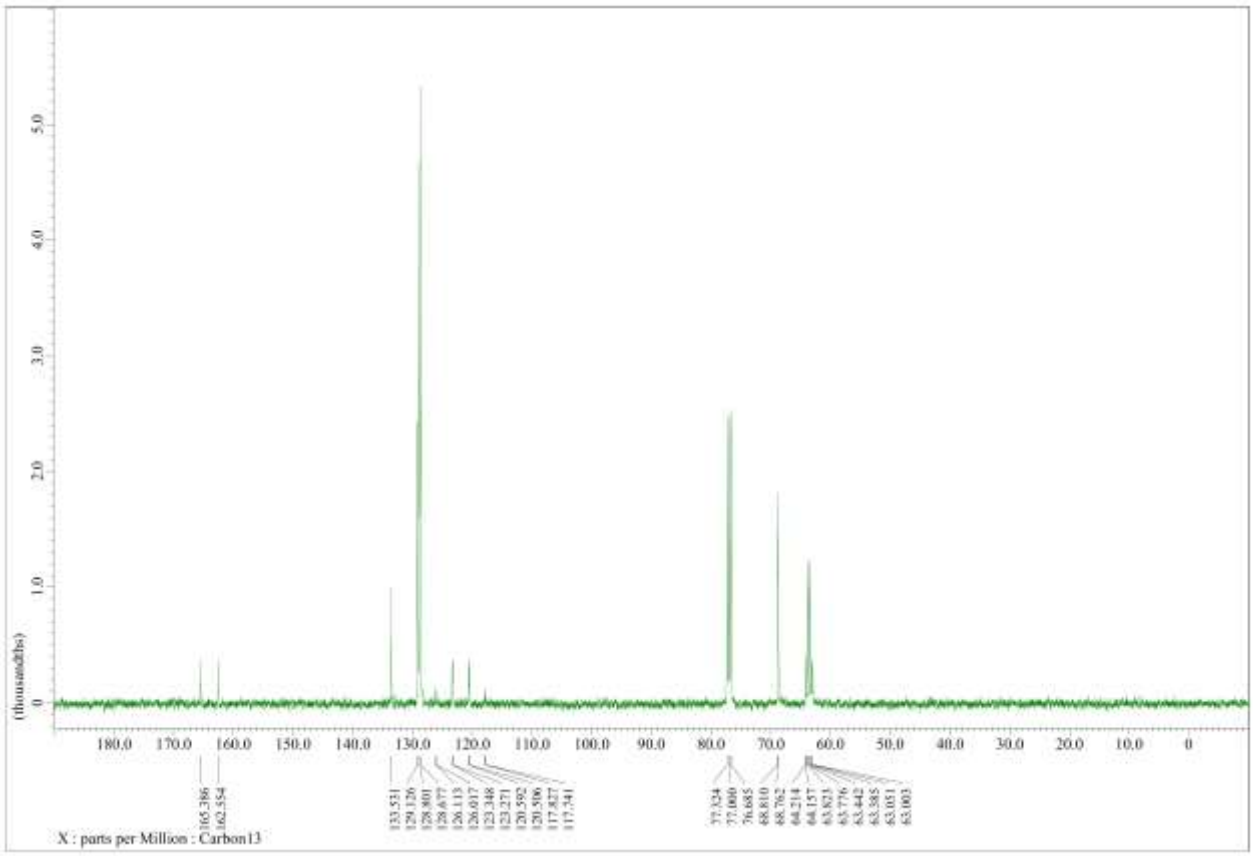


**Benzyl (bis(2,2,2-trifluoroethoxy)phosphoryl)formate (3k)**

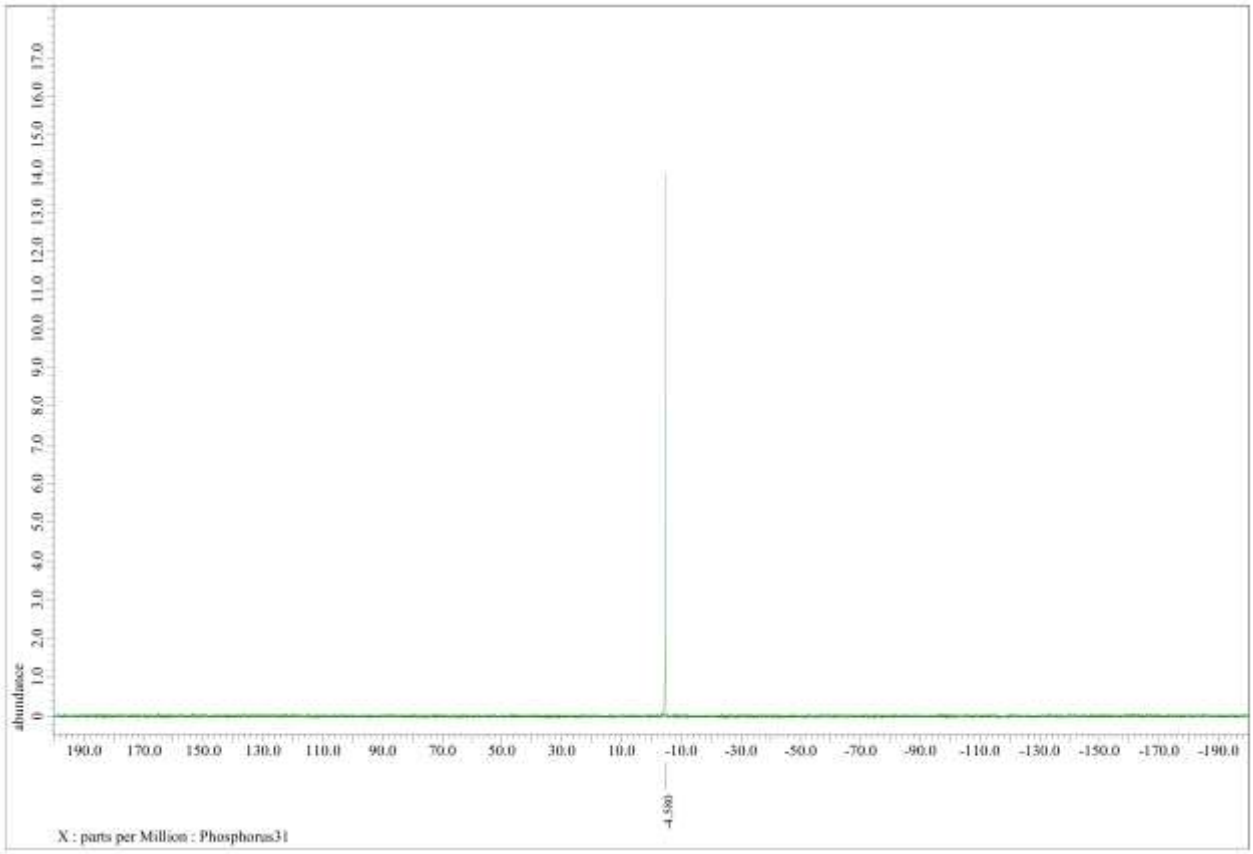
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

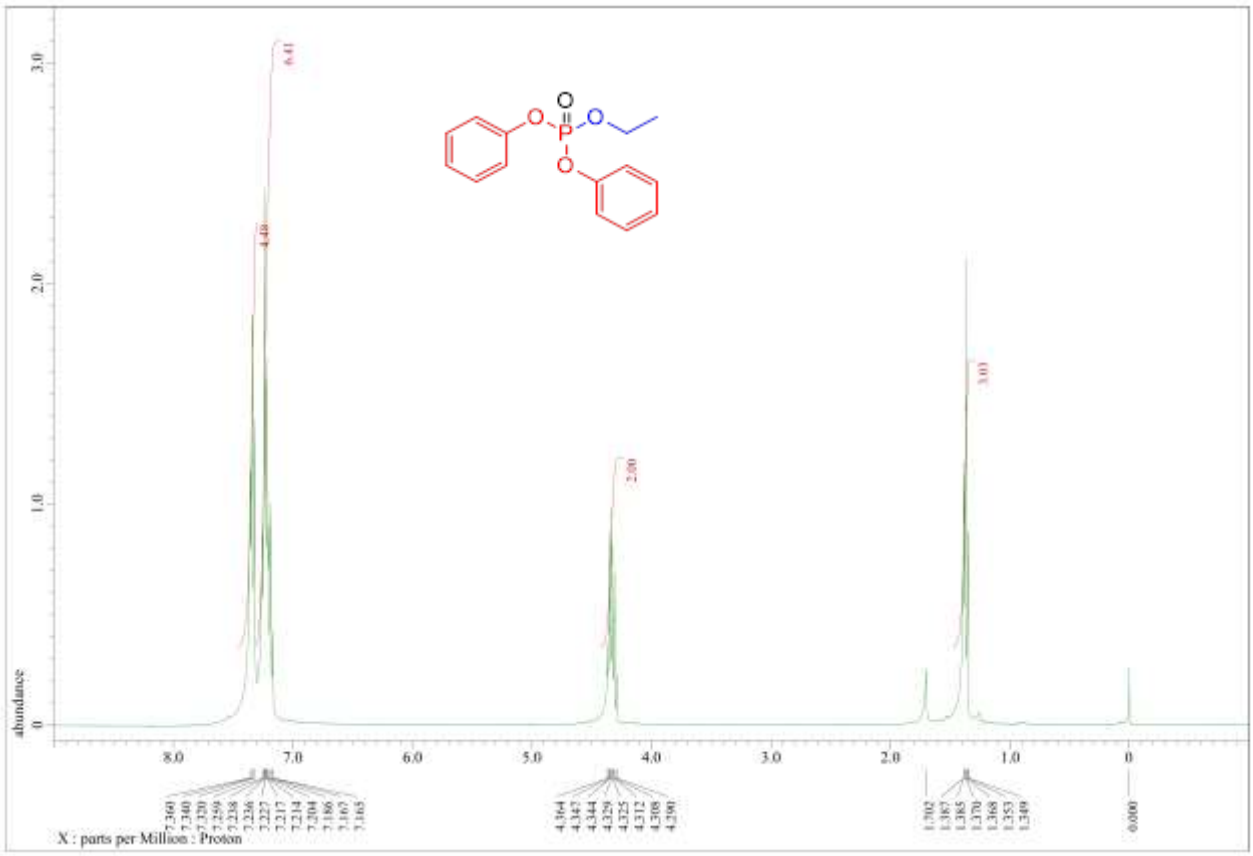


($^{31}$P NMR, 162 MHz, $CDCl_3$)

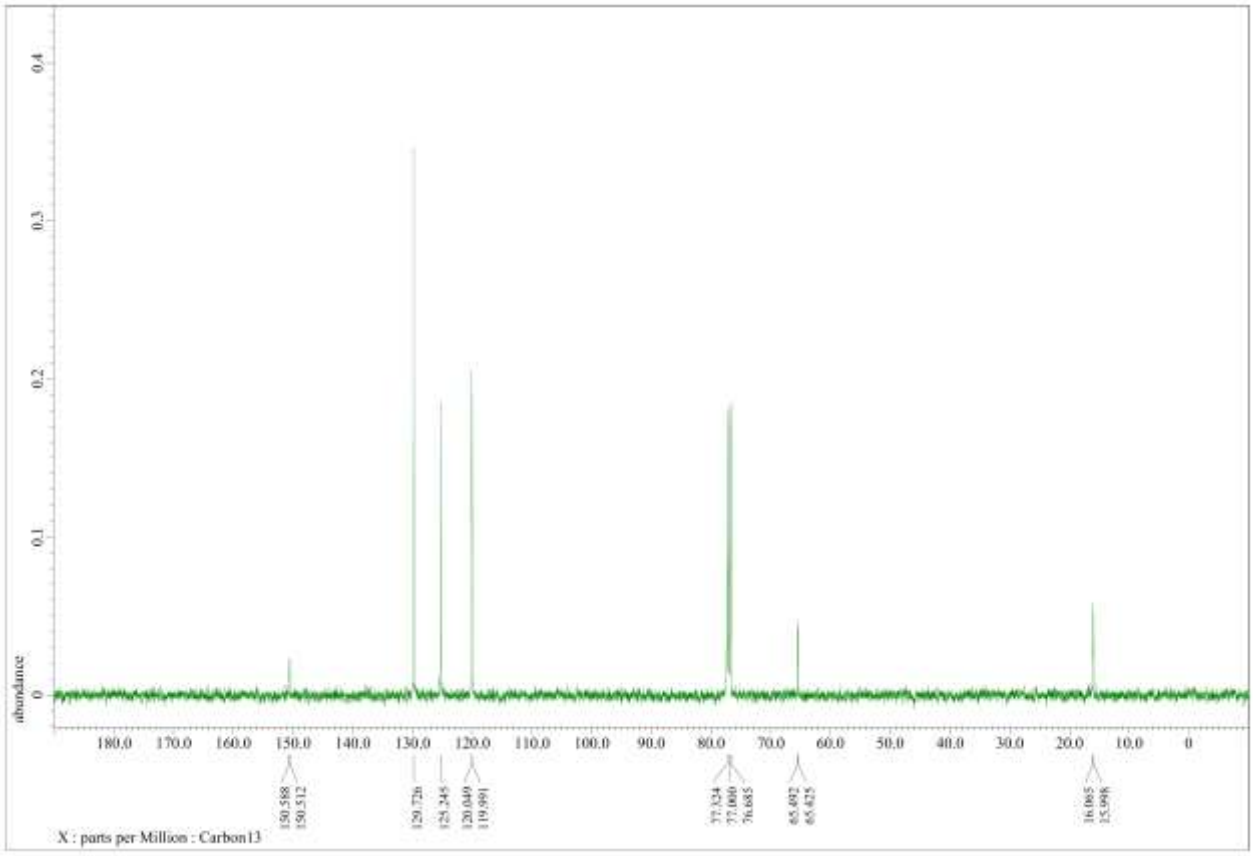



**Ethyl diphenyl phosphate (6a)**

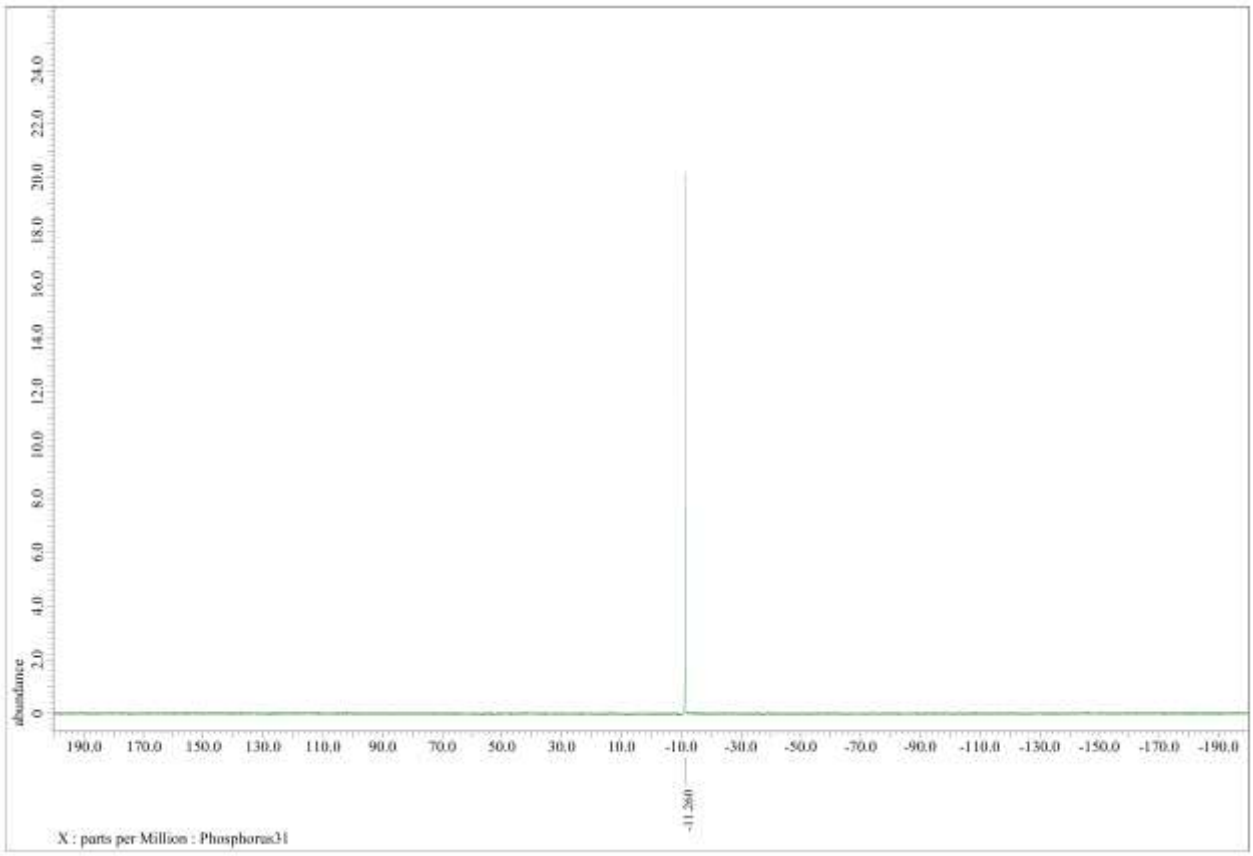
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

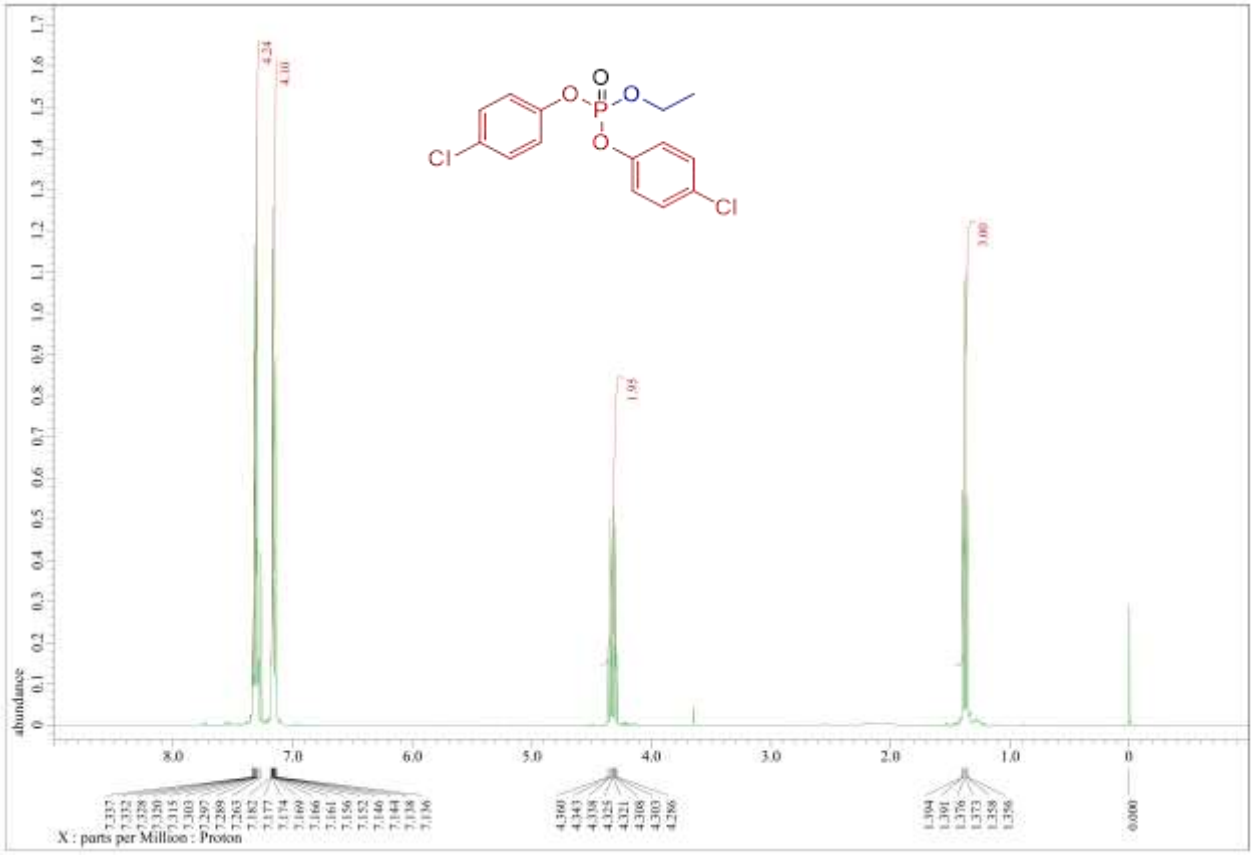



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

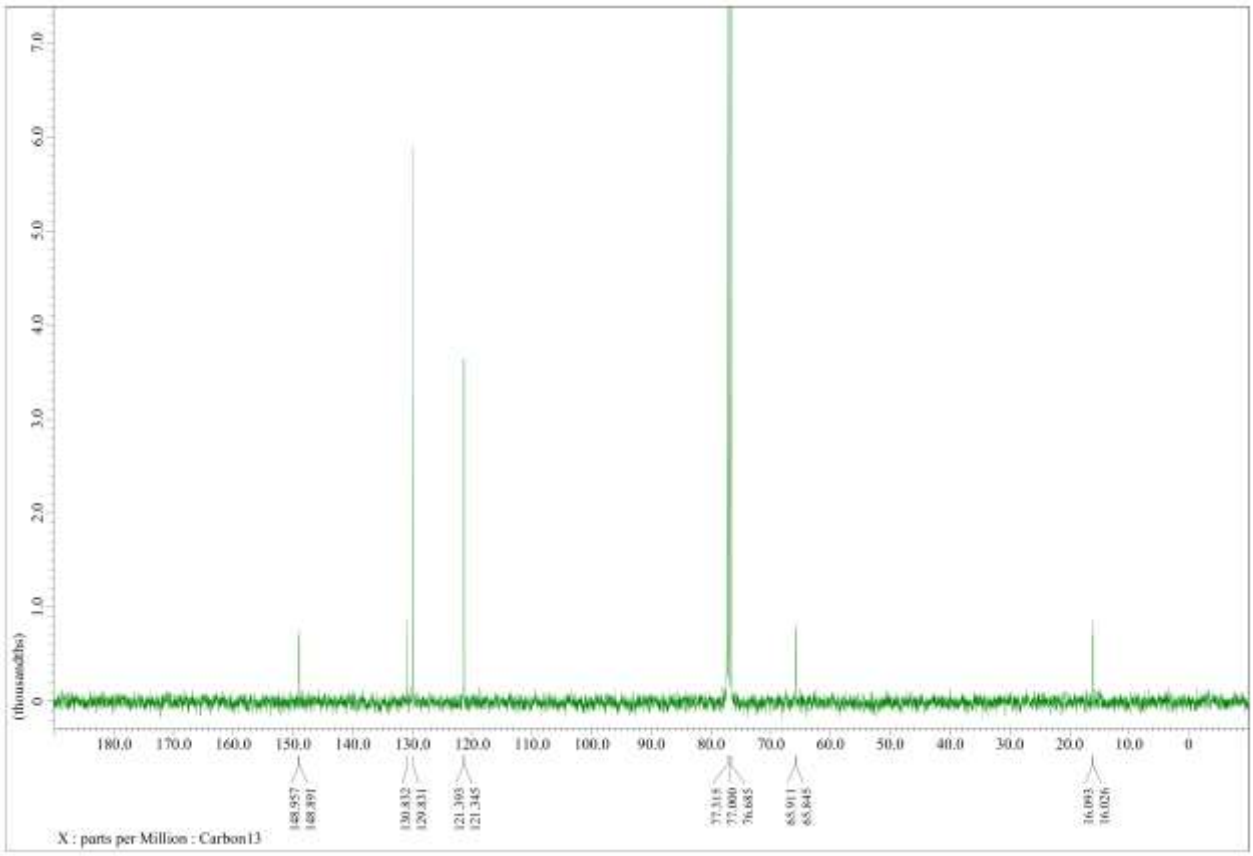


**Bis(4-chlorophenyl) ethyl phosphate (6b)**

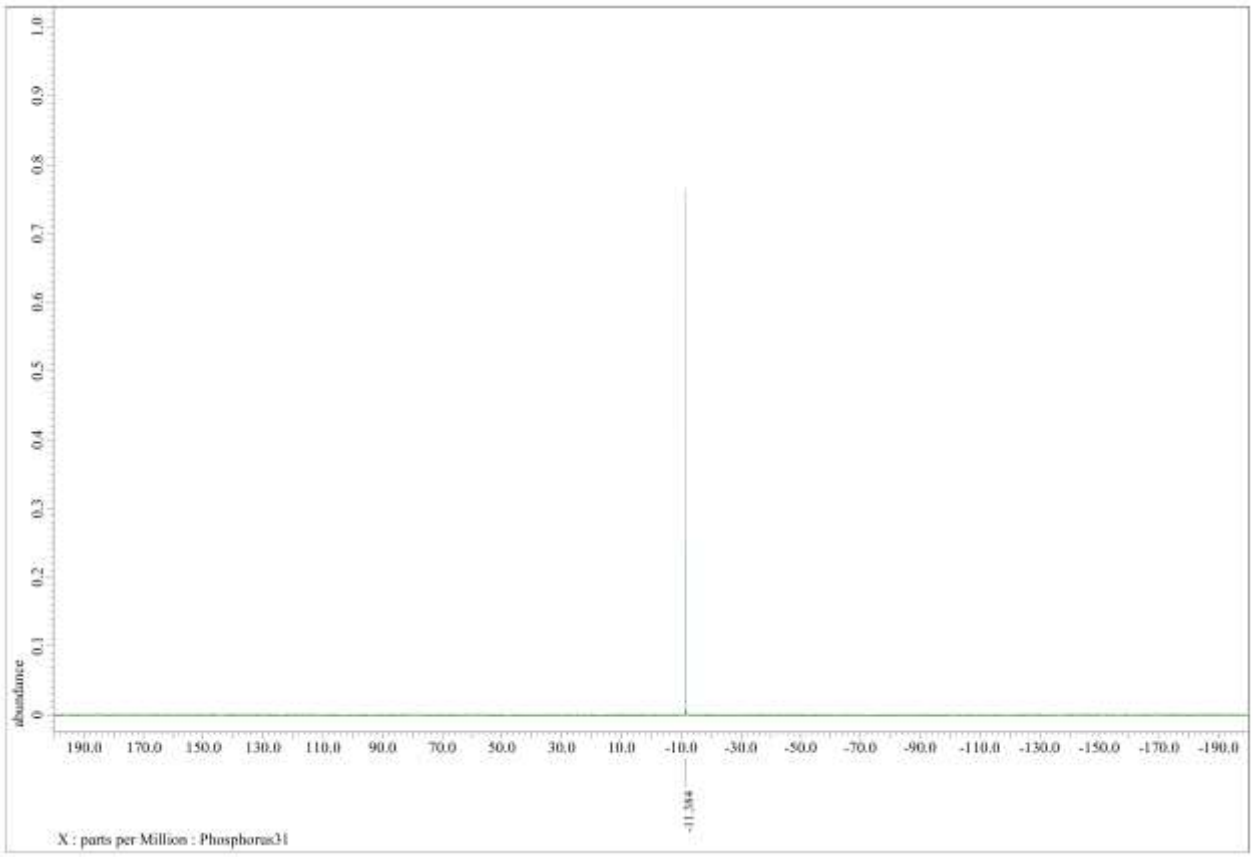
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

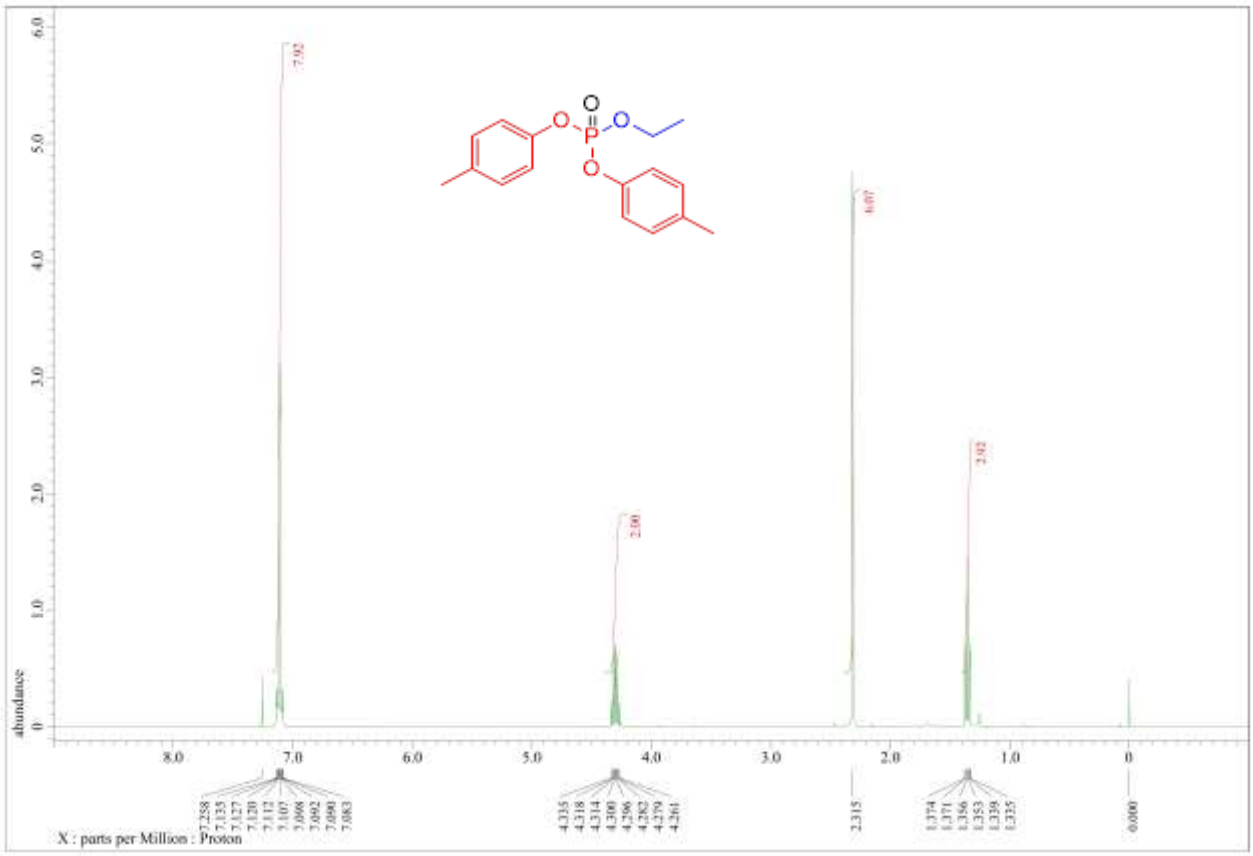


($^{31}$P NMR, 162 MHz, $CDCl_3$)

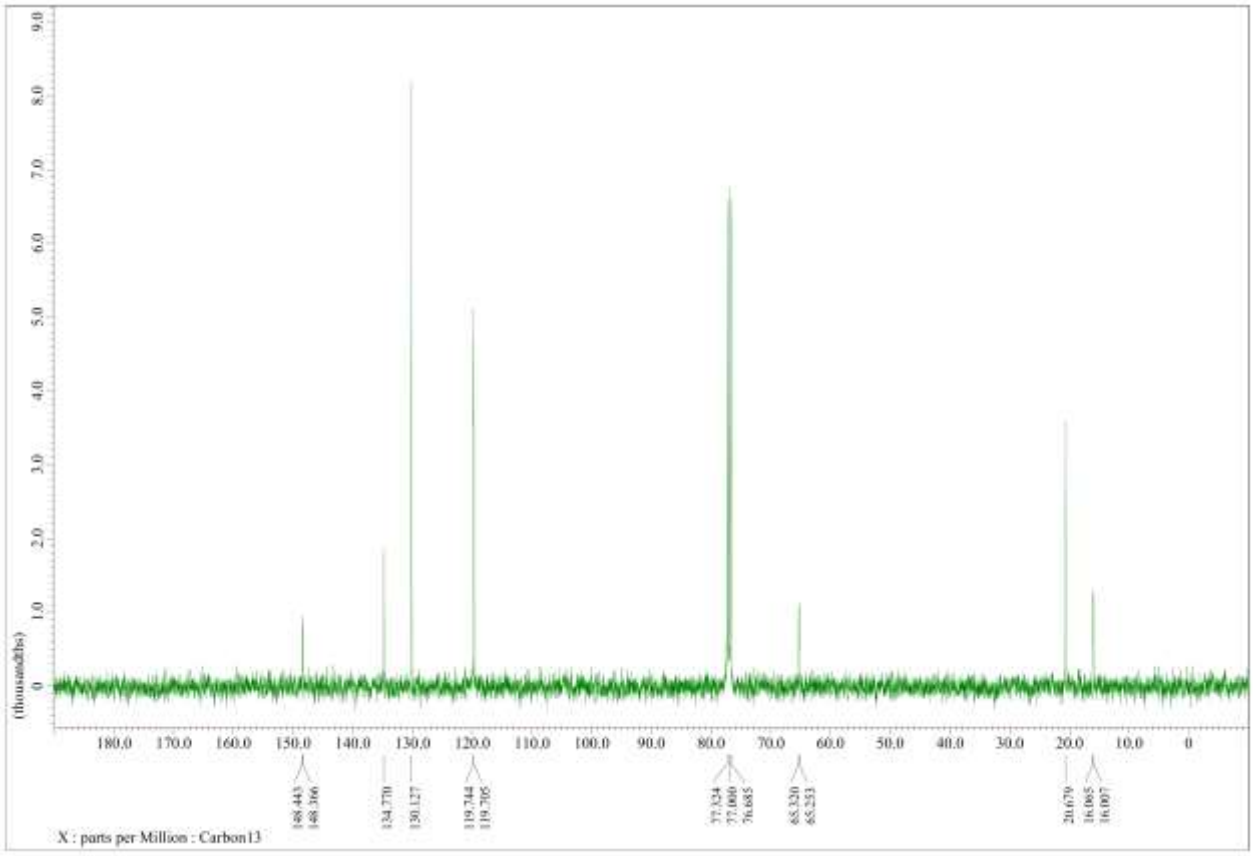



**Ethyl di-*p*-tolyl phosphate (6c)**

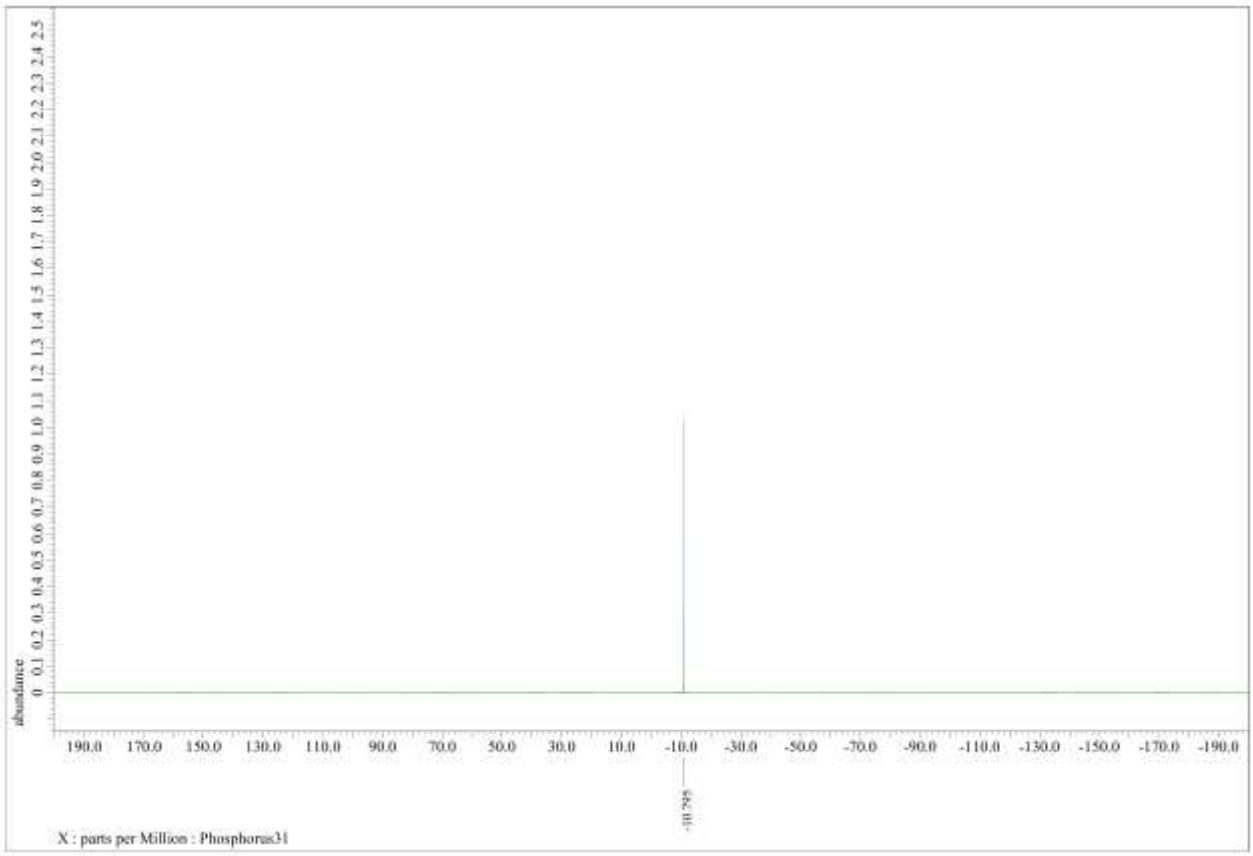
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

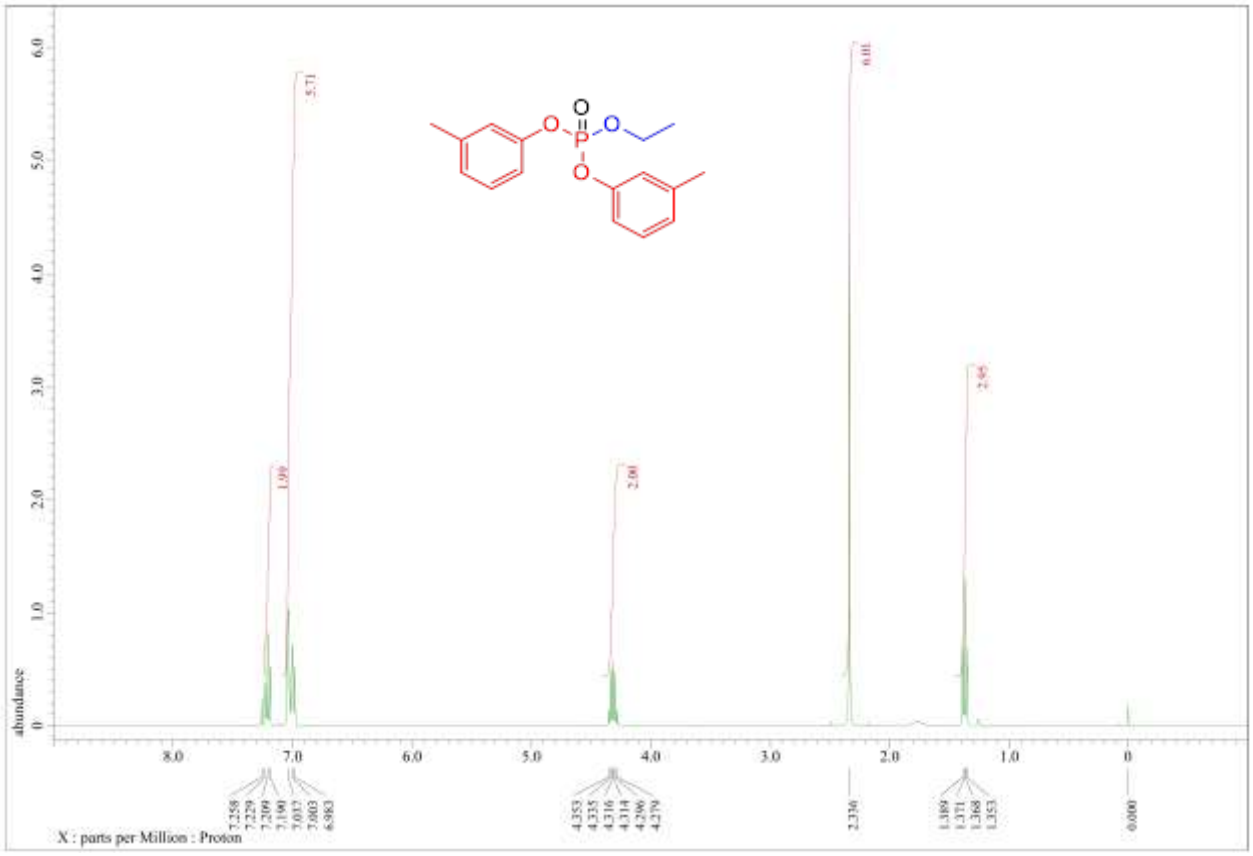



($^{31}$P NMR, 162 MHz, $CDCl_3$)

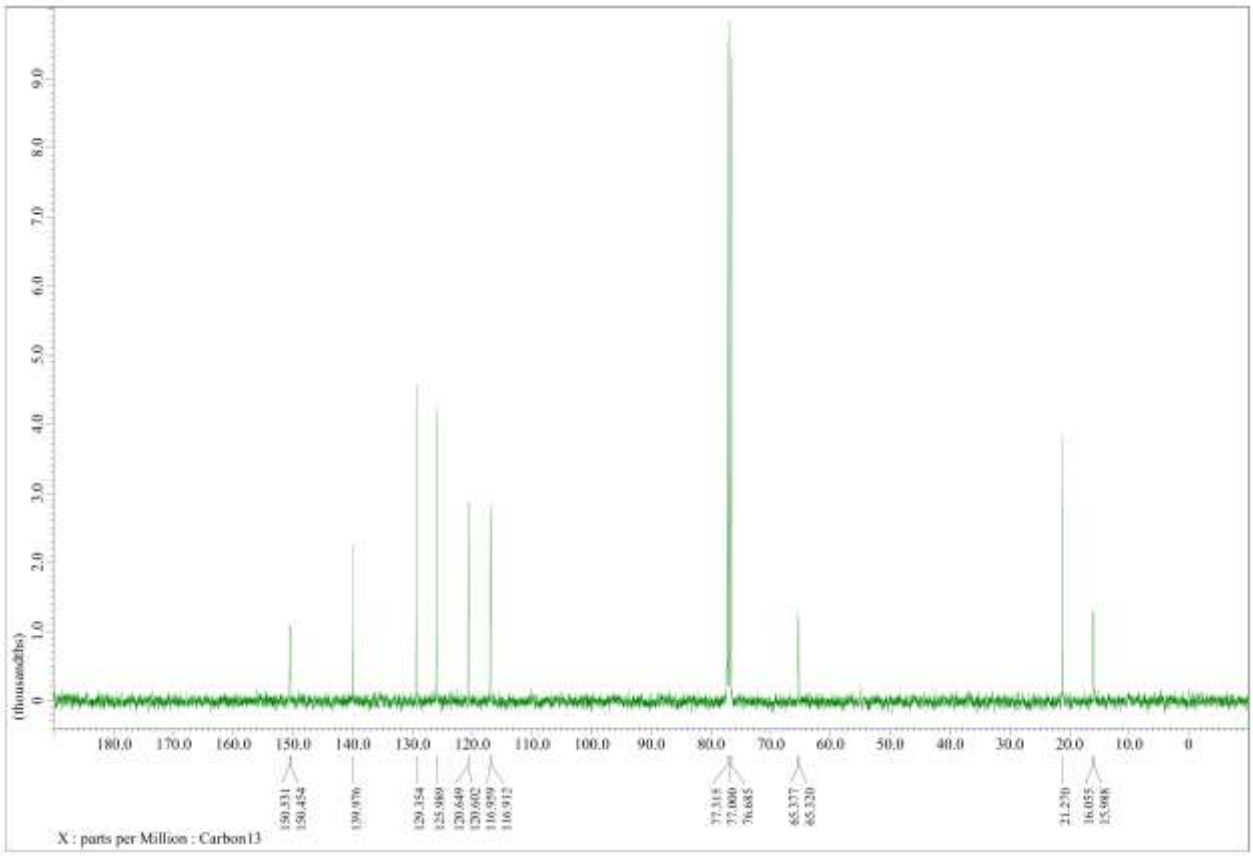


**Ethyl di-*m*-tolyl phosphate (6d)**

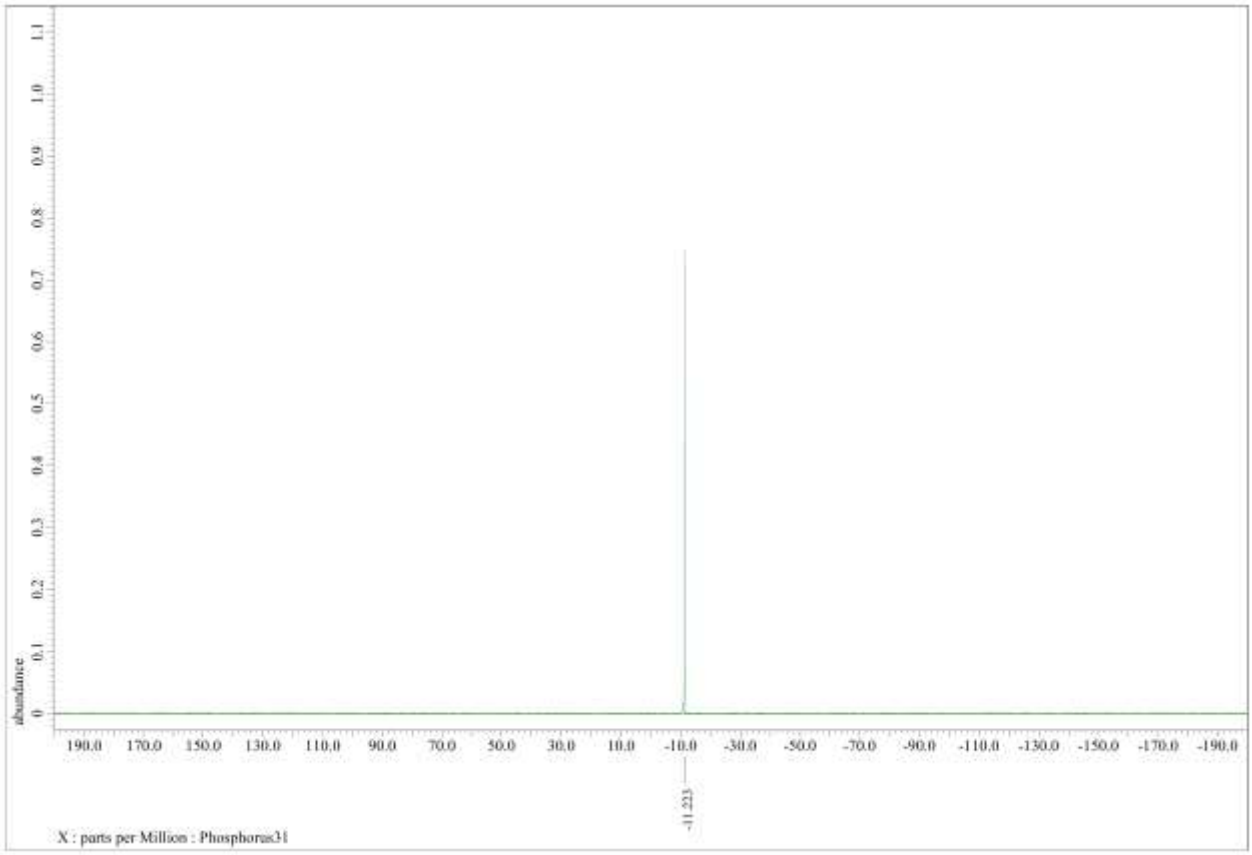
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

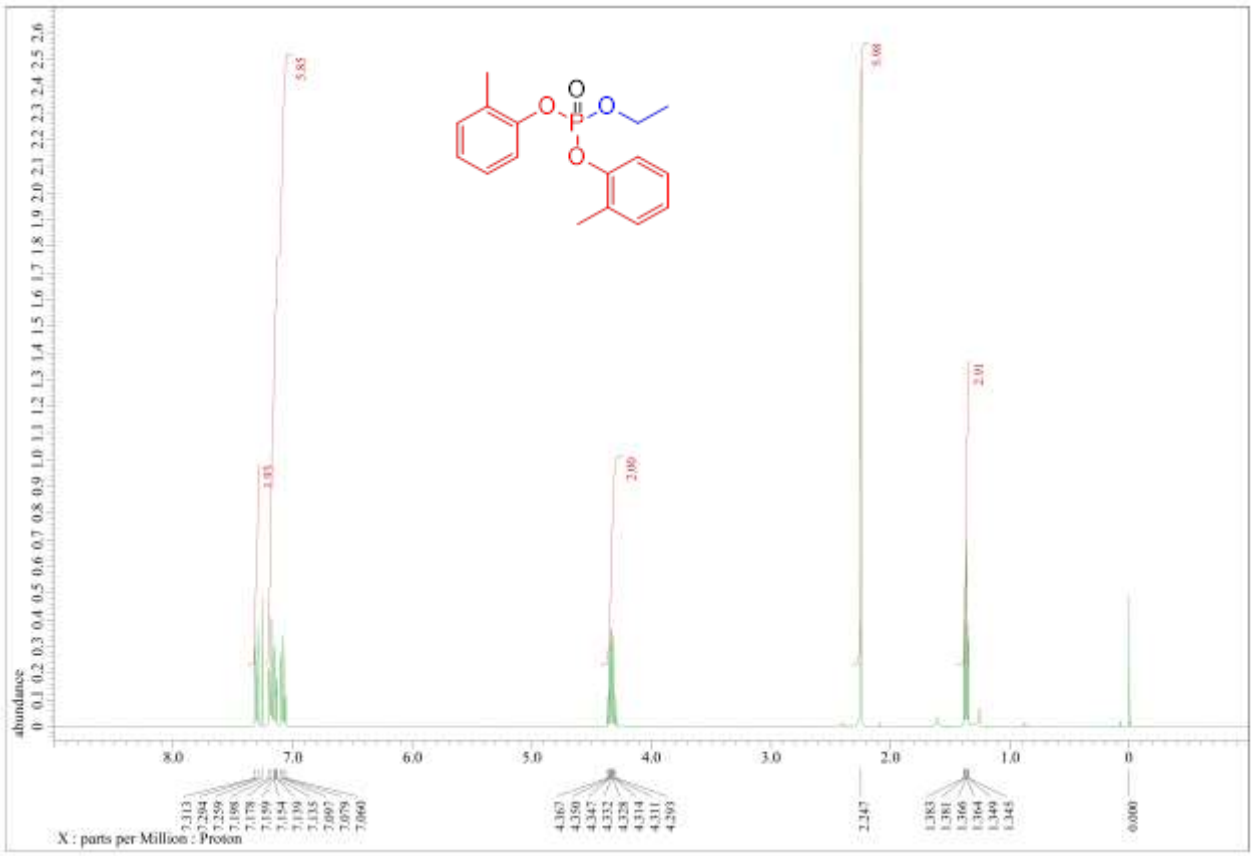


($^{31}$P NMR, 162 MHz, $CDCl_3$)

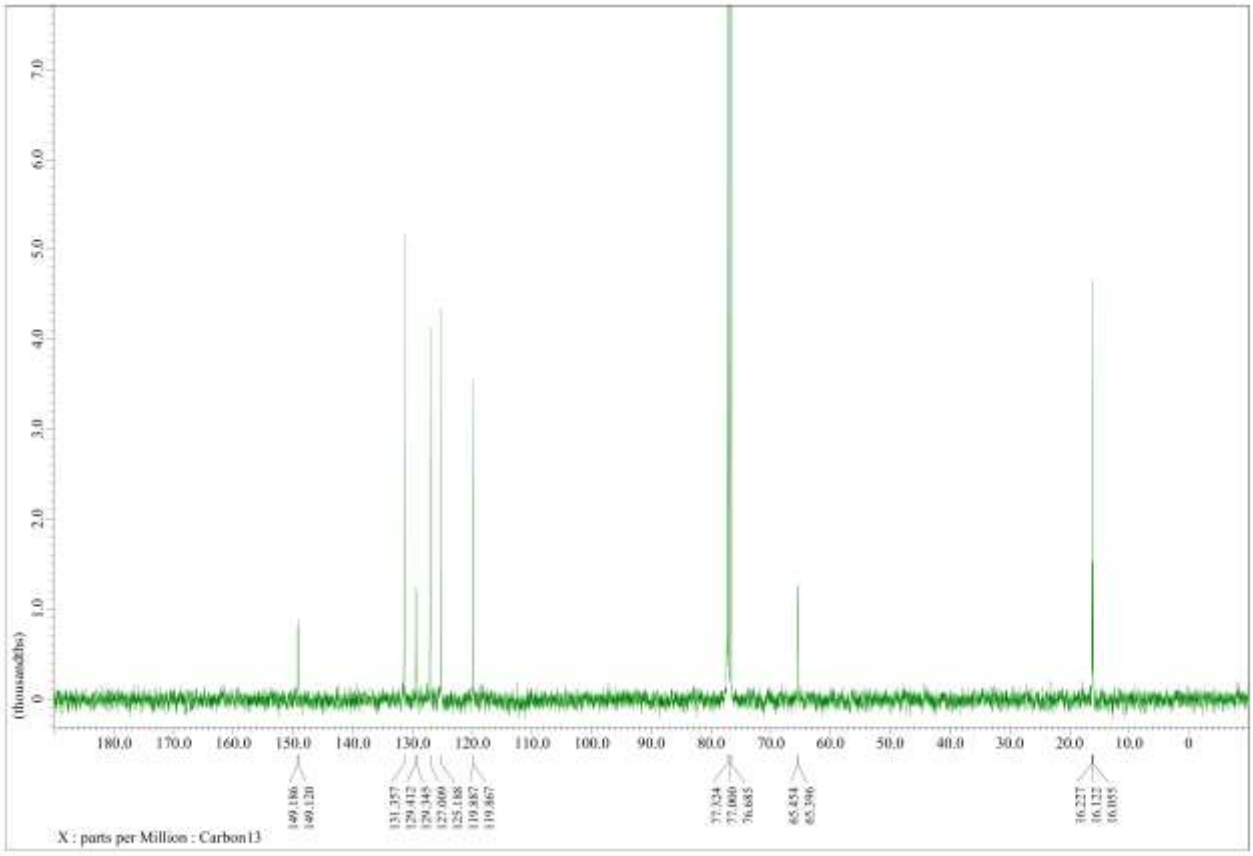



**Ethyl di-*o*-tolyl phosphate (6e)**

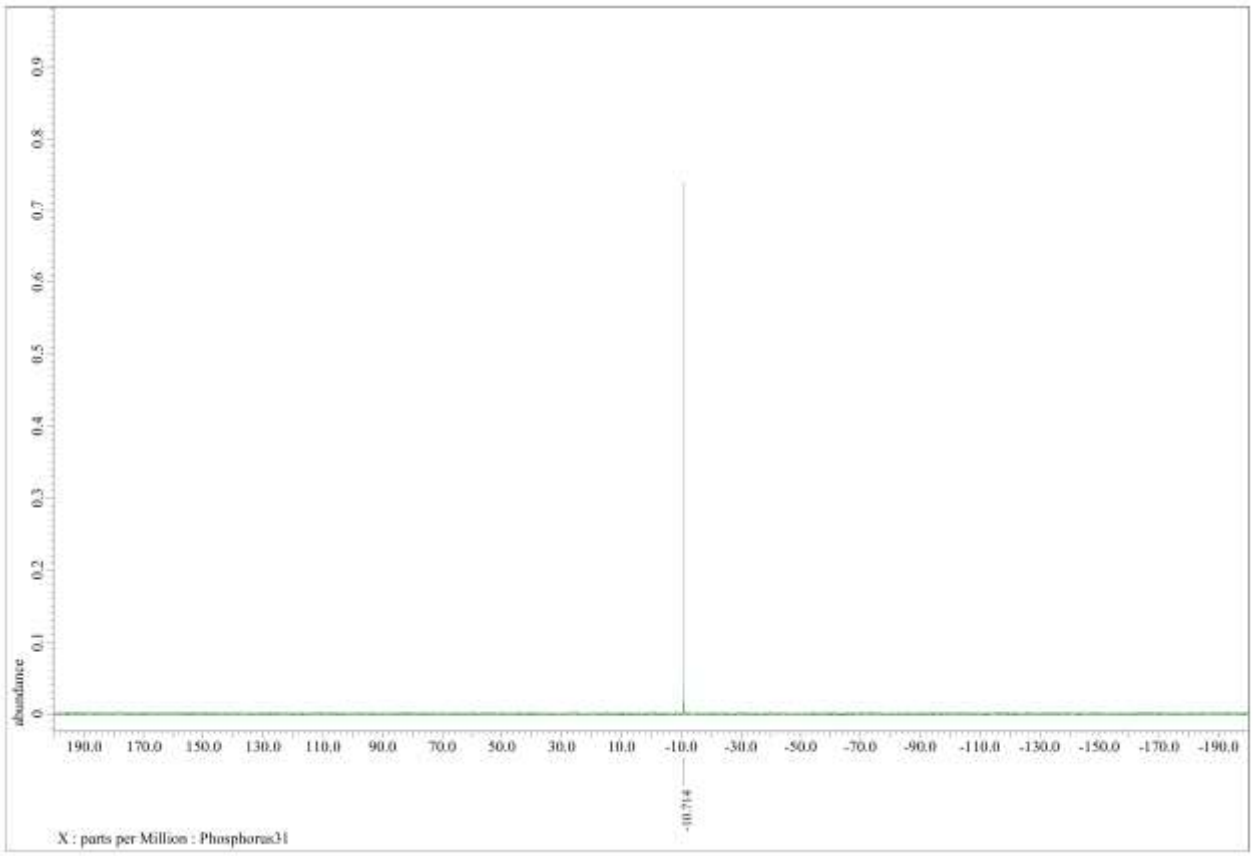
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

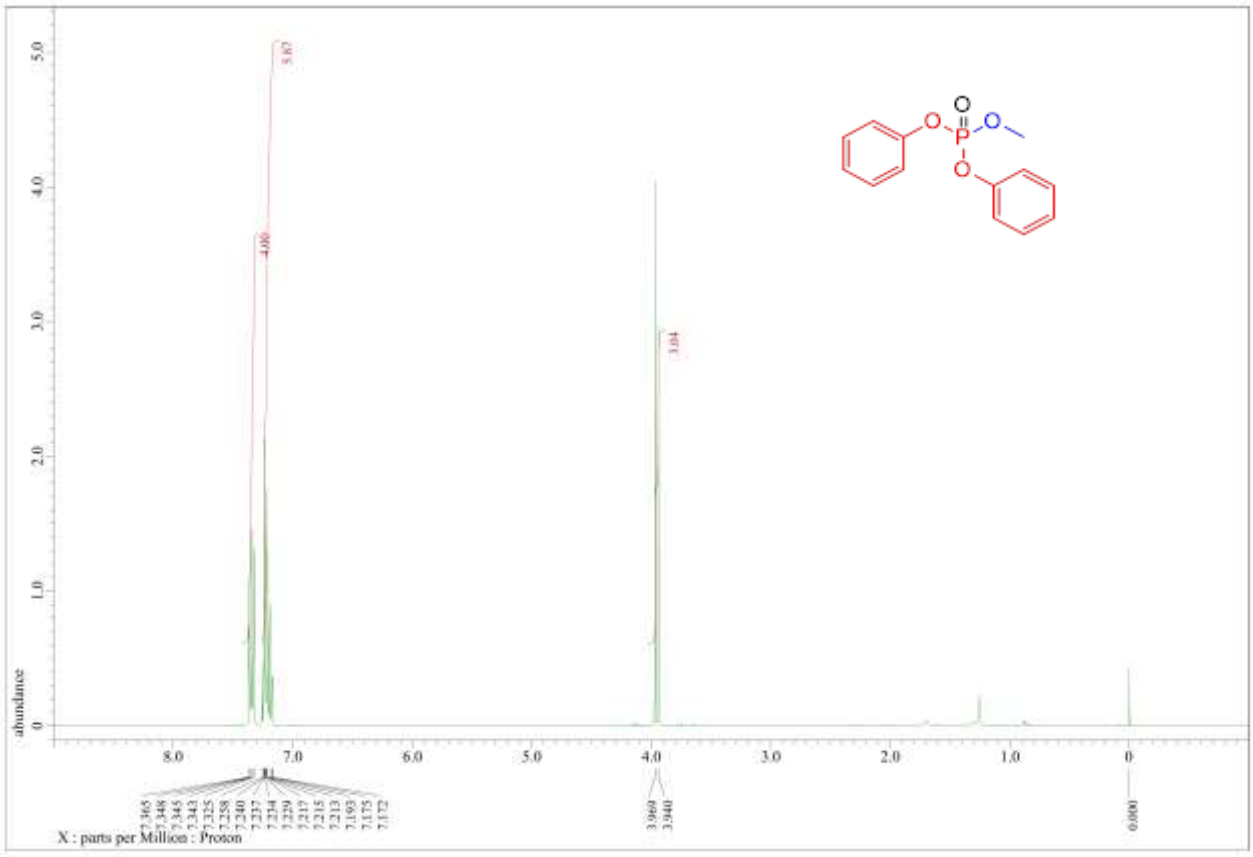



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

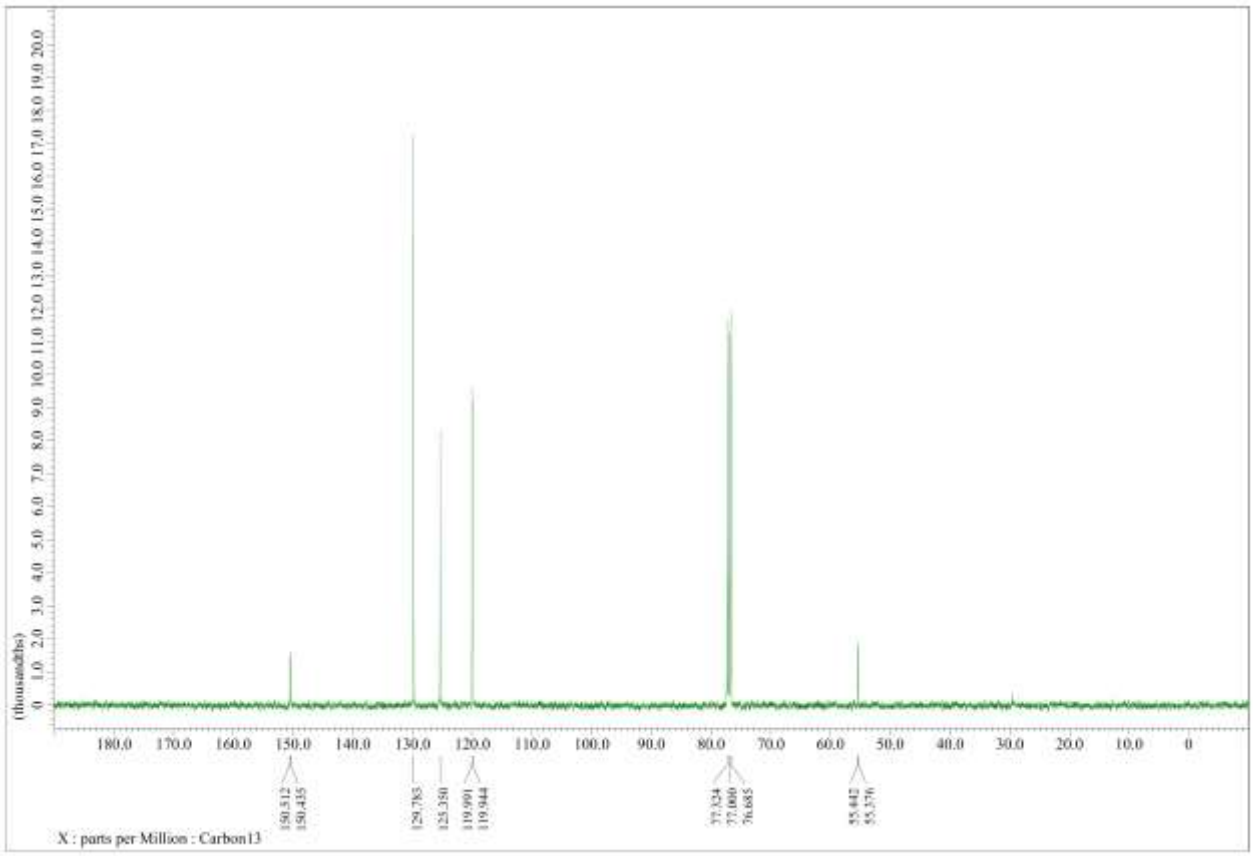


**Methyl diphenyl phosphate (6f)**

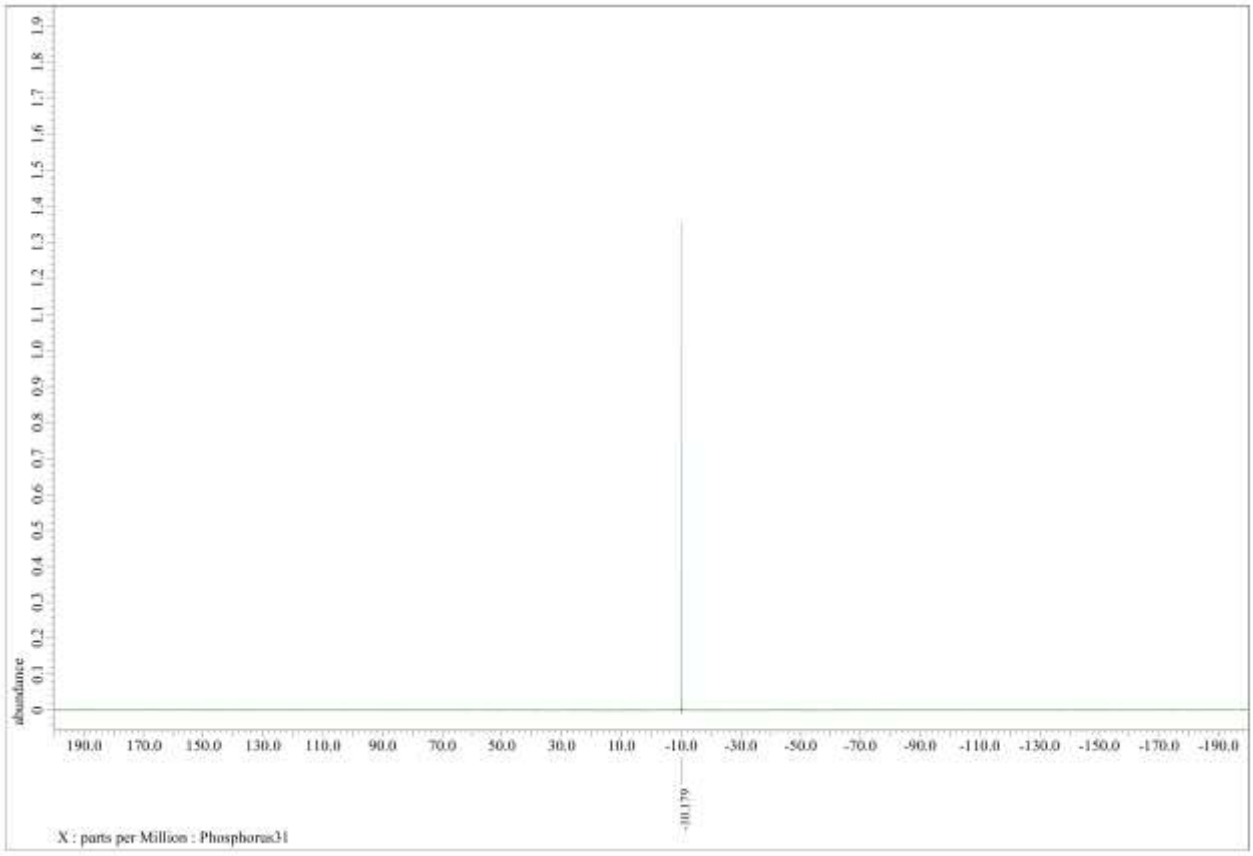
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

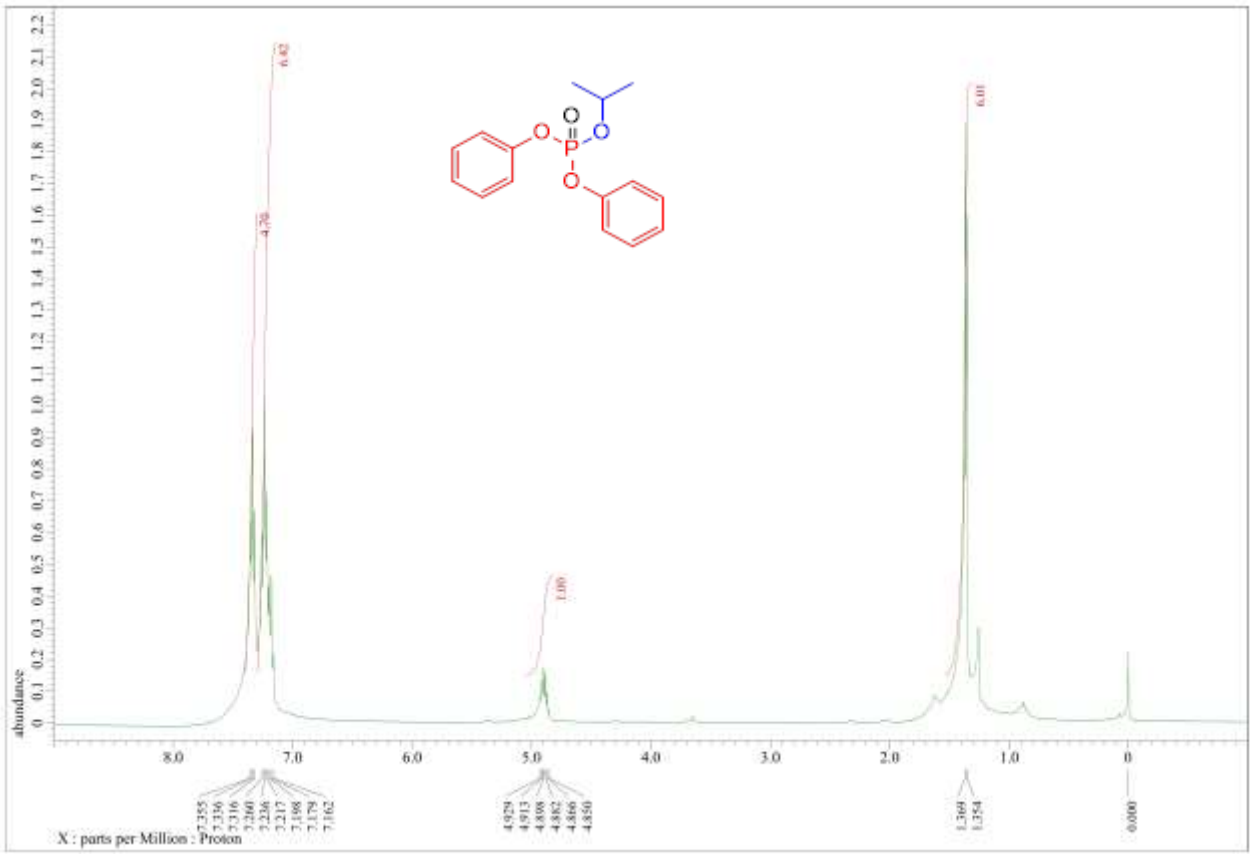


($^{31}$P NMR, 162 MHz, $CDCl_3$)

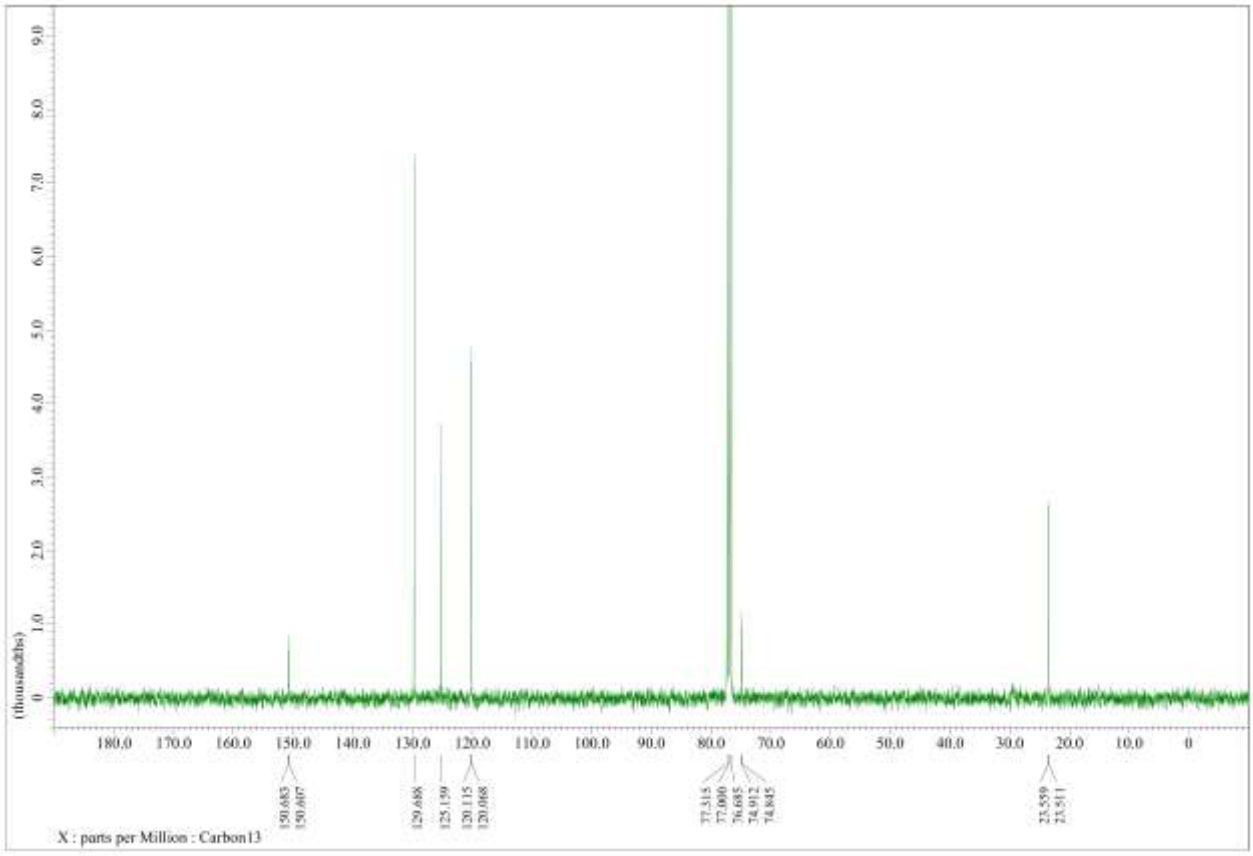



**Isopropyl diphenyl phosphate (6g)**

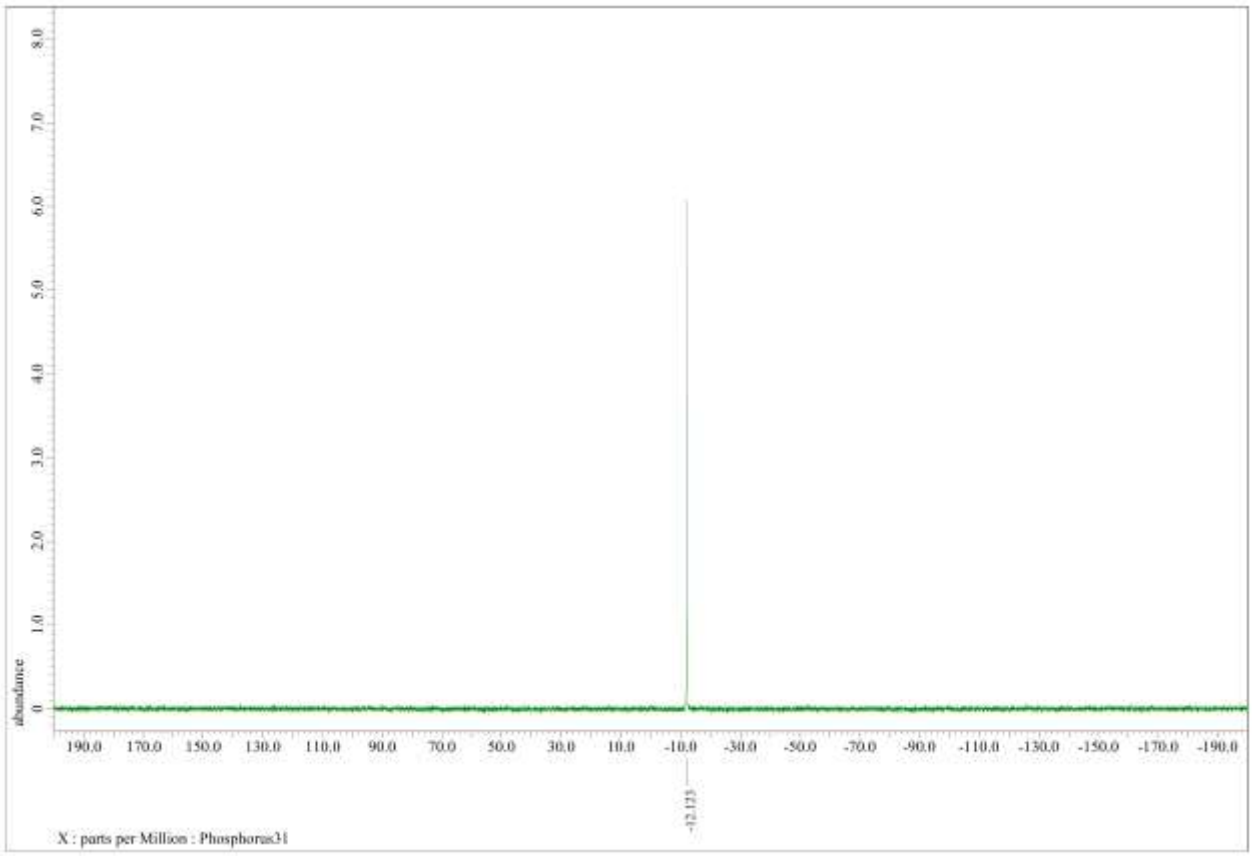
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

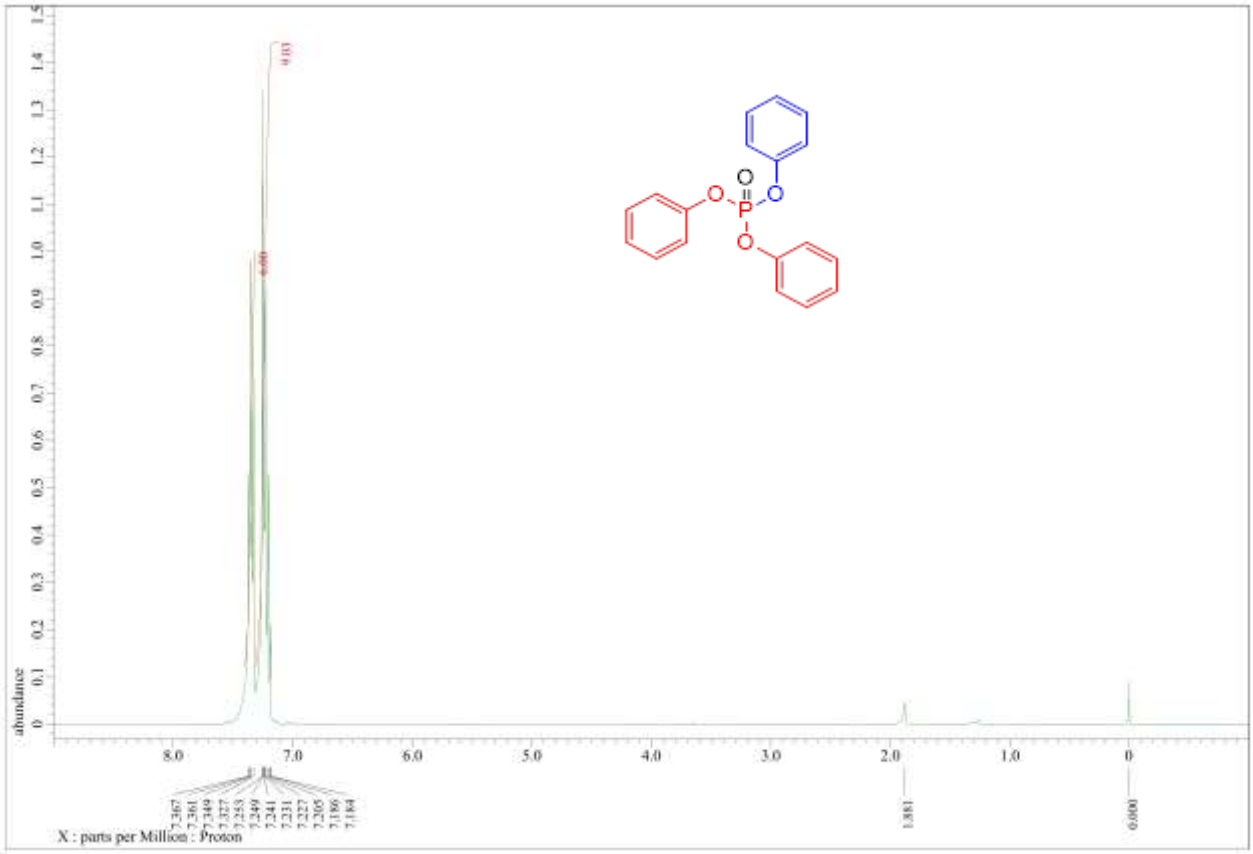



($^{31}$P NMR, 162 MHz, $CDCl_3$)

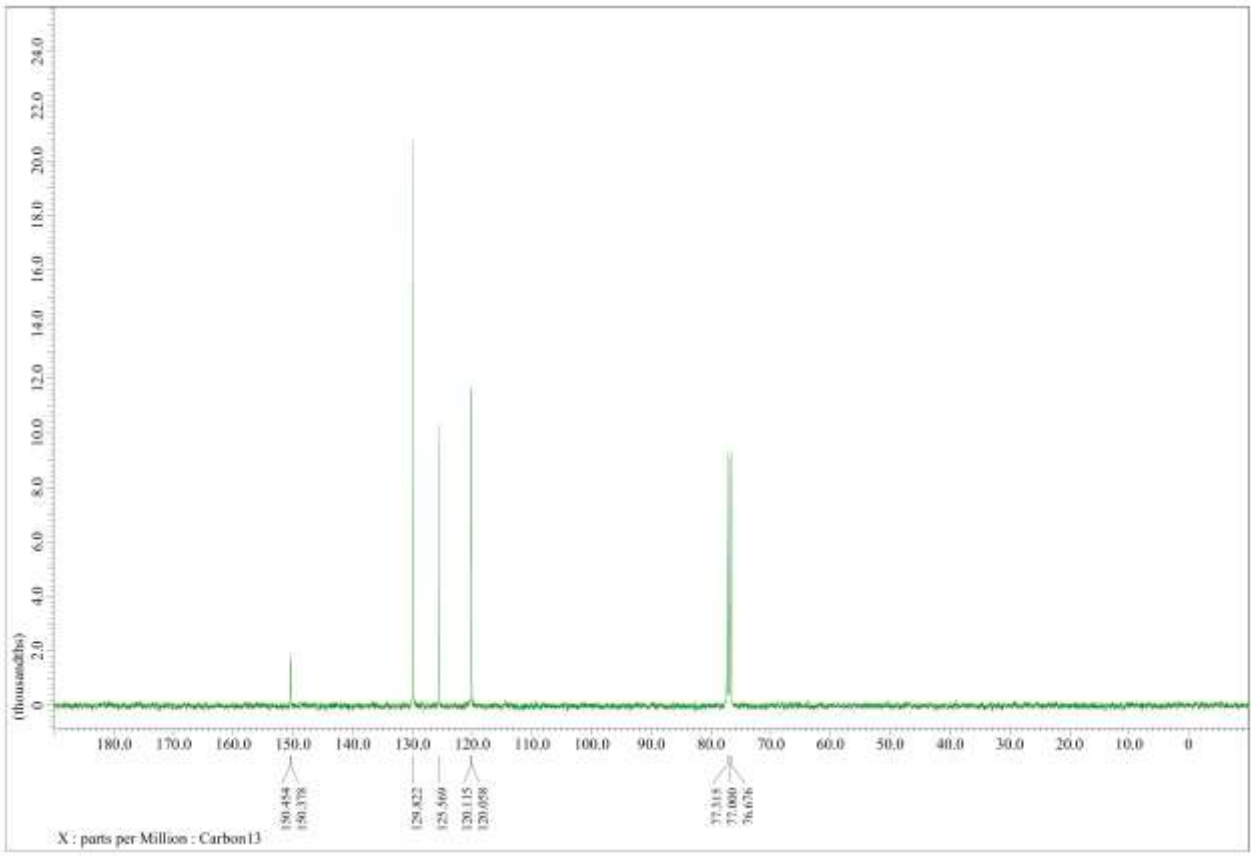


**Triphenyl phosphate (6h)**

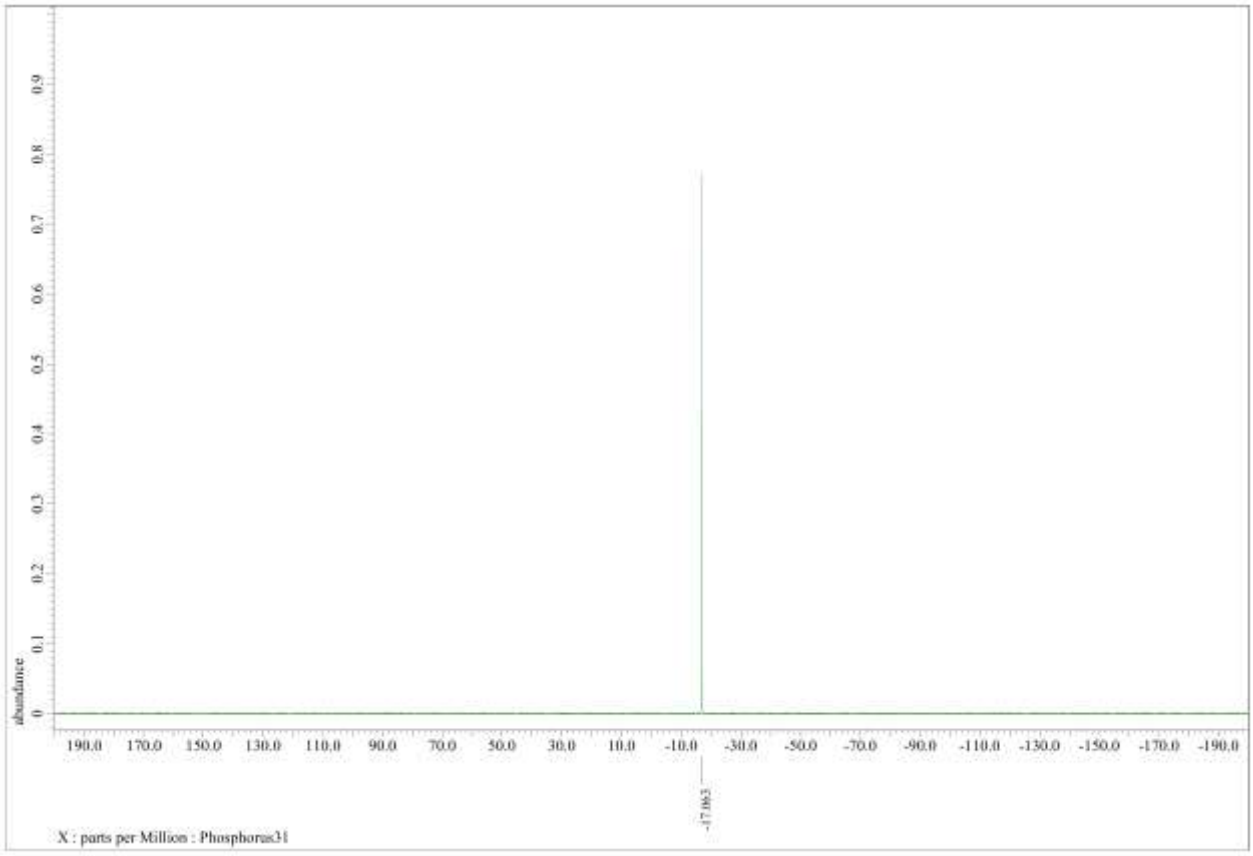
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

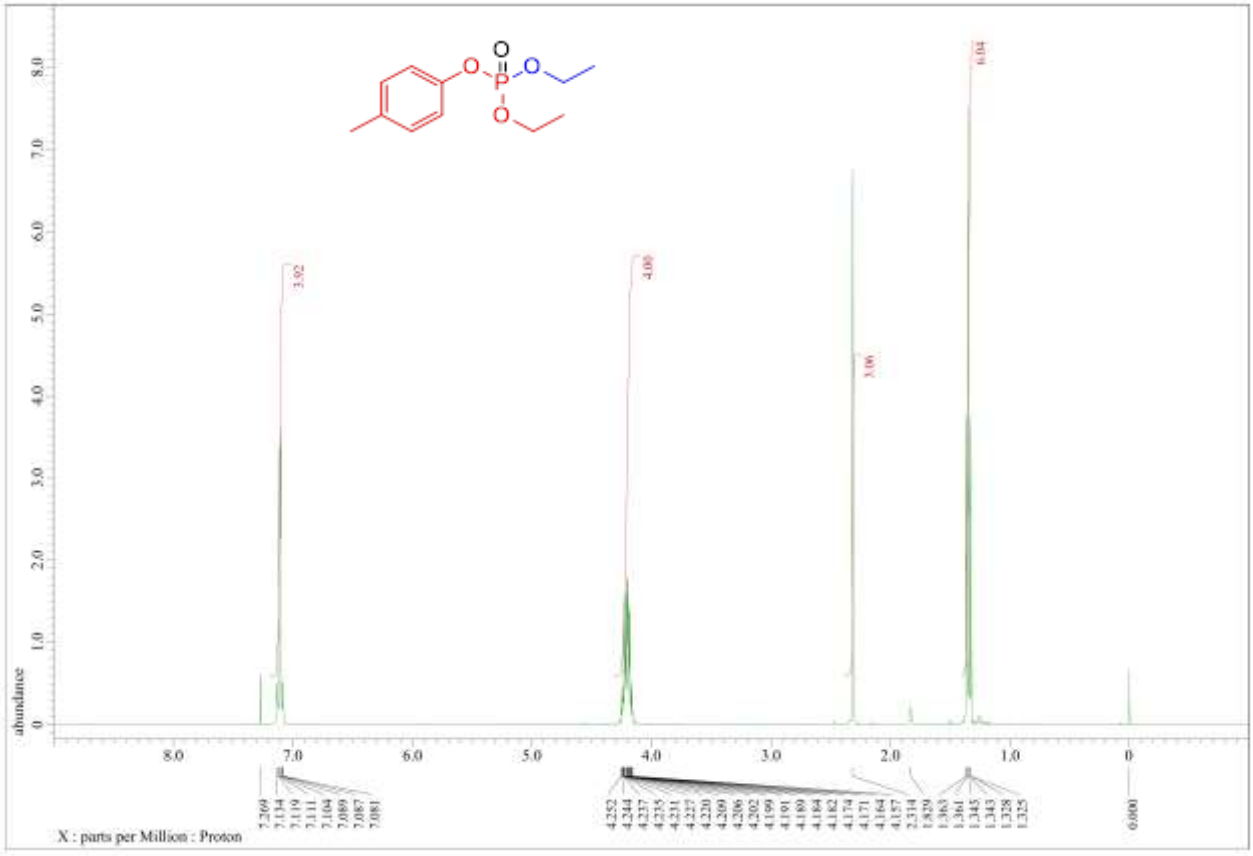


($^{31}$P NMR, 162 MHz, $CDCl_3$)

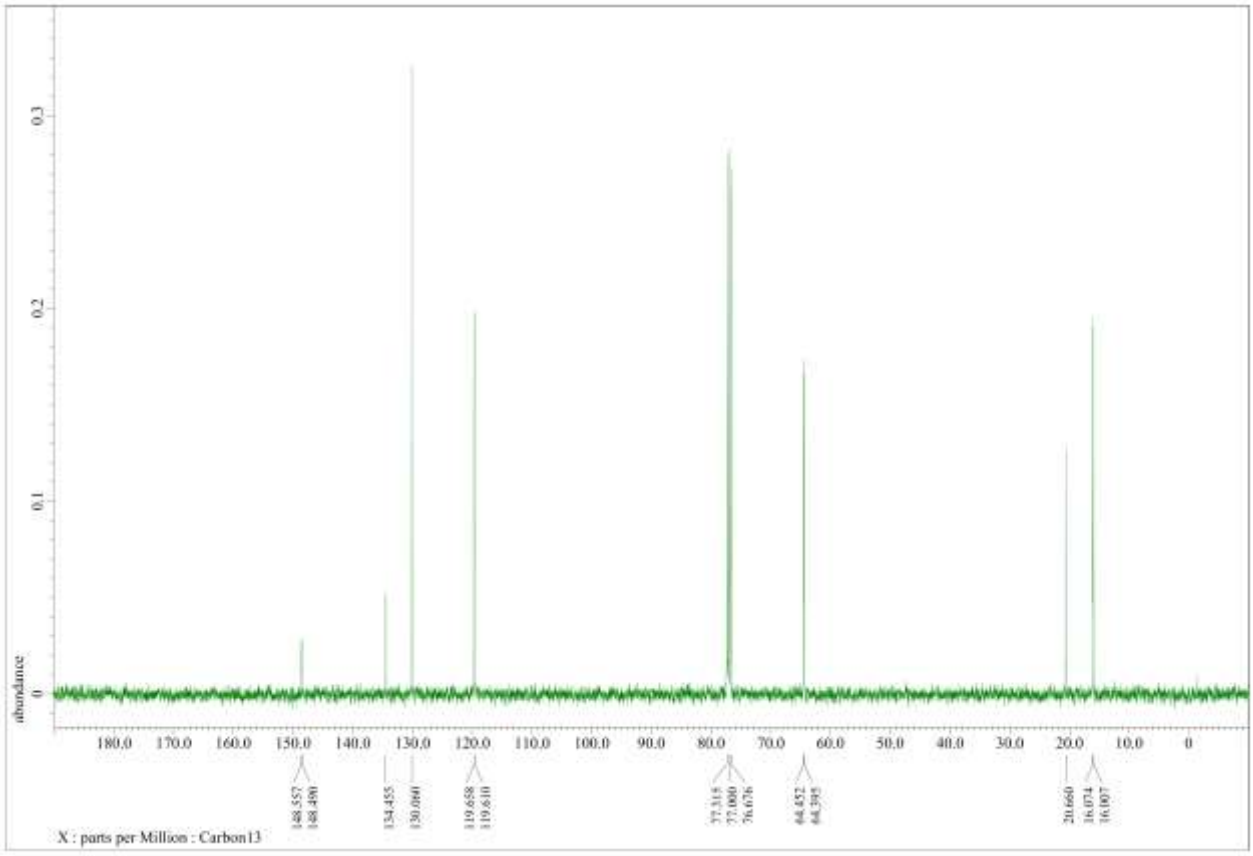



**Diethyl *p*-tolyl phosphate (6i)**

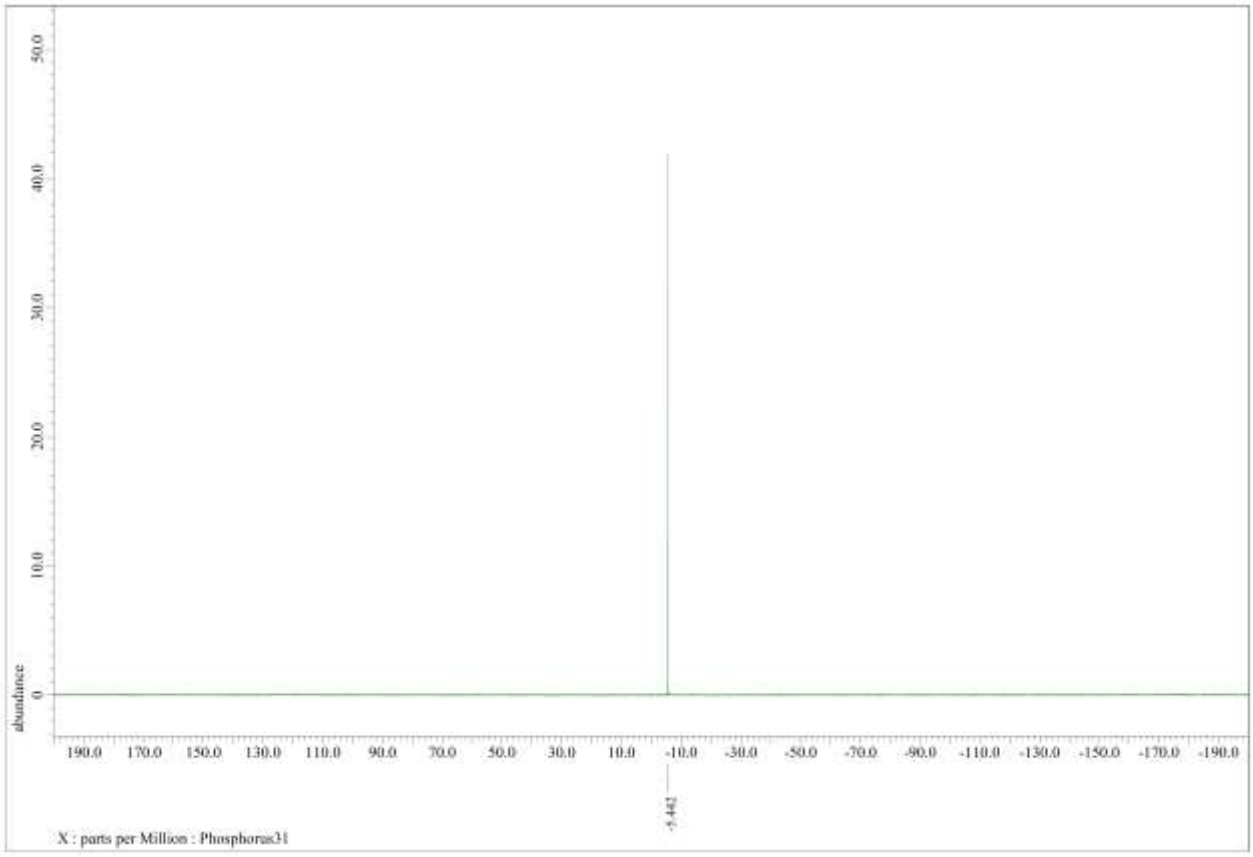
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

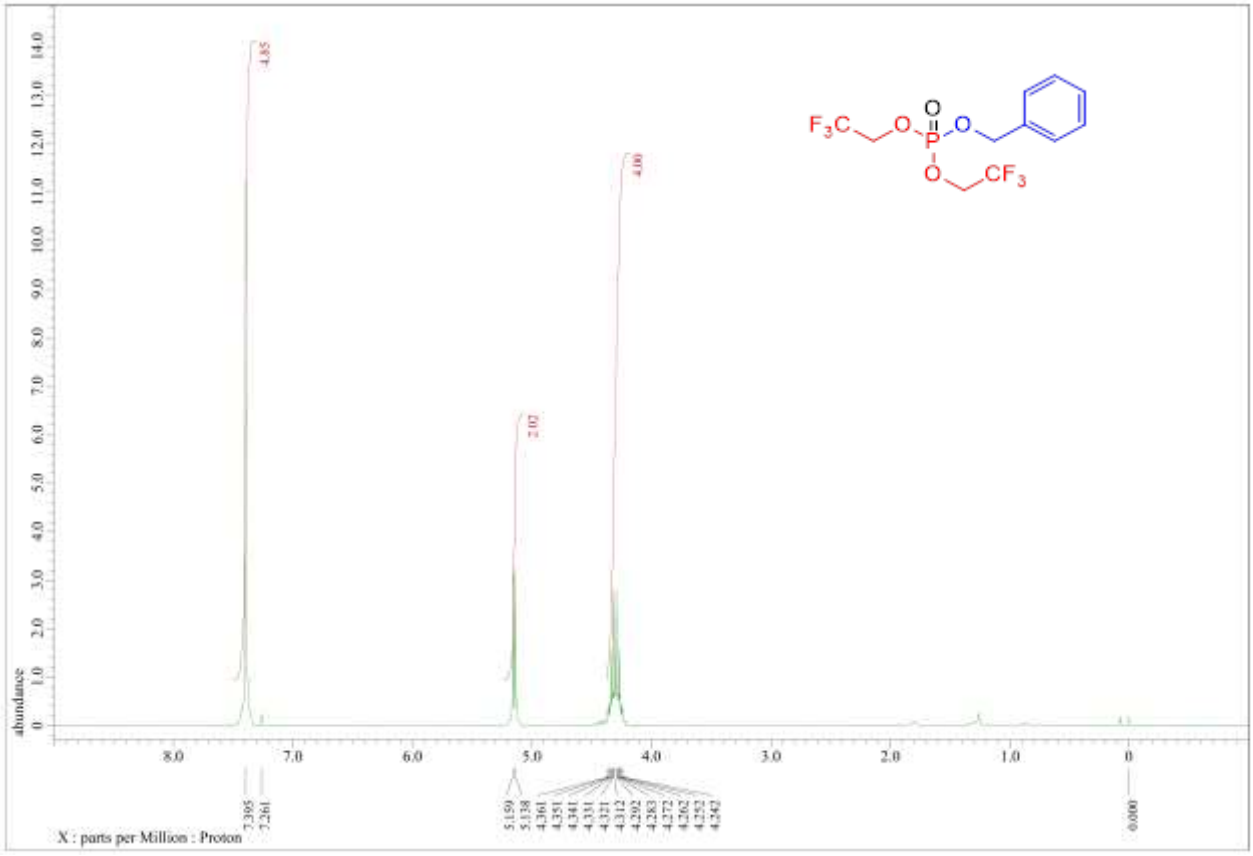



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

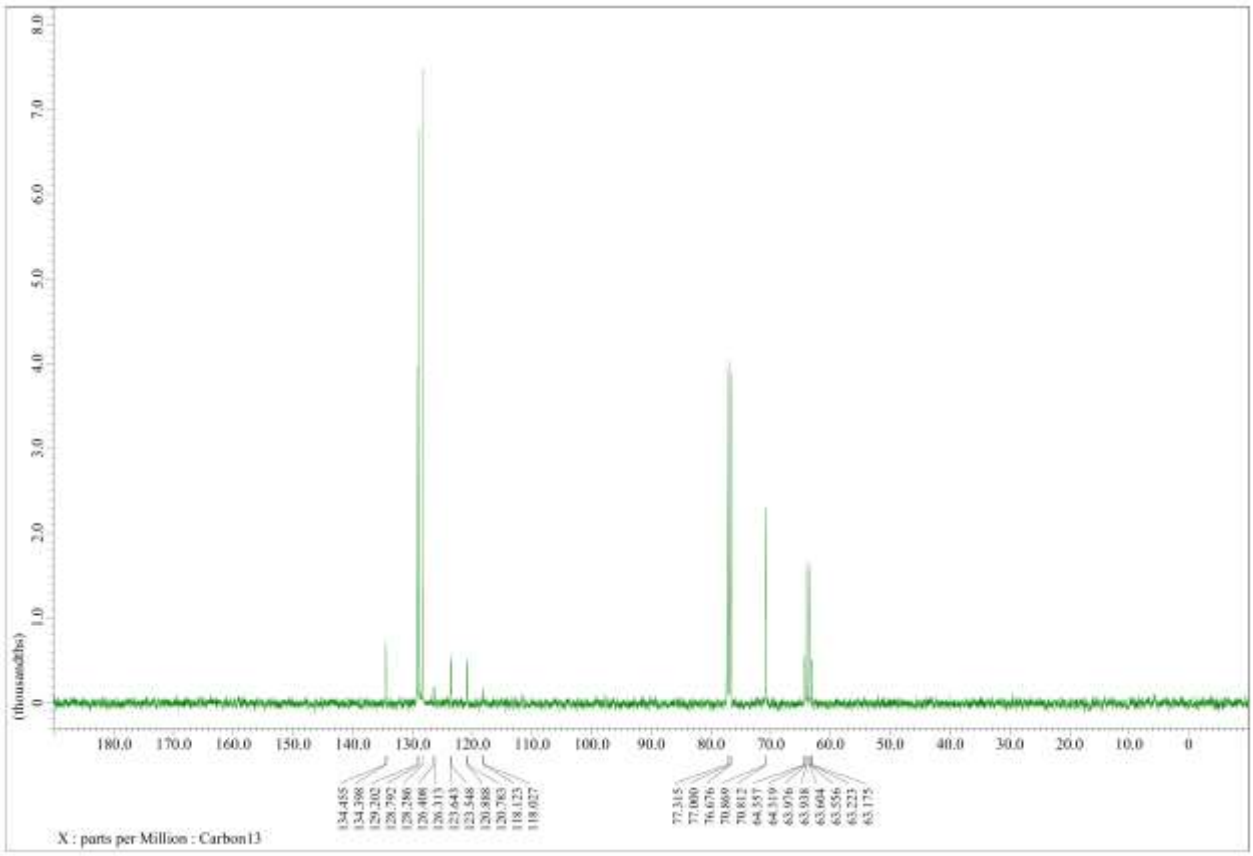


**Benzyl bis(2,2,2-trifluoroethyl) phosphate (6j)**

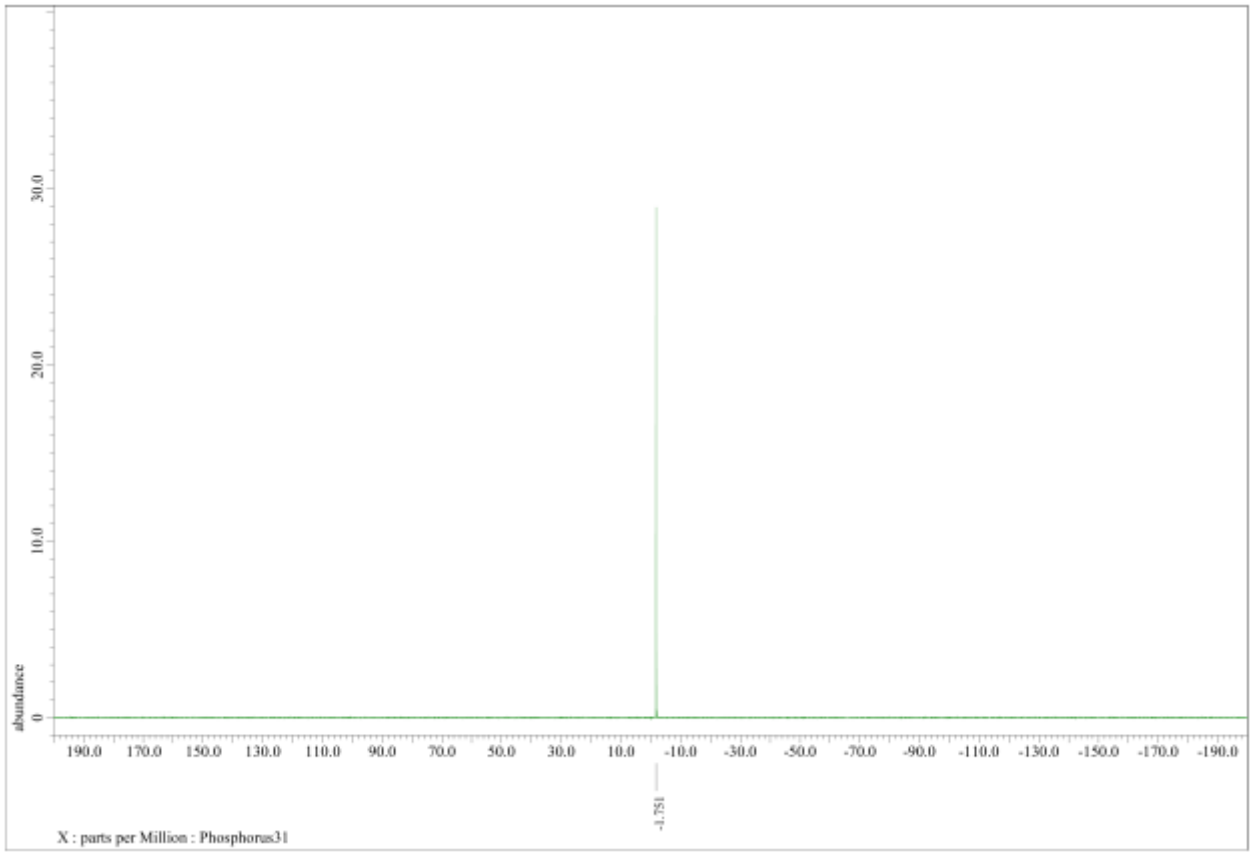
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

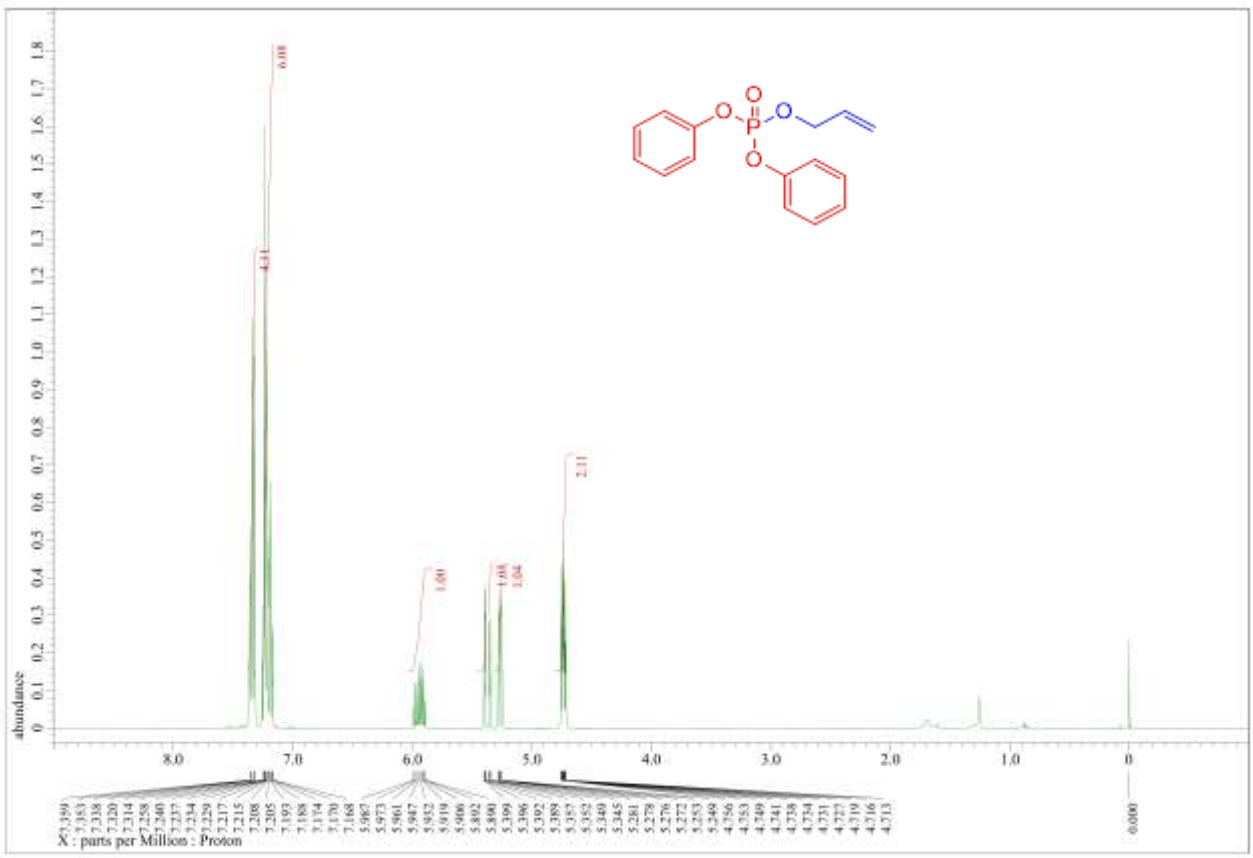


($^{31}$P NMR, 162 MHz, $CDCl_3$)

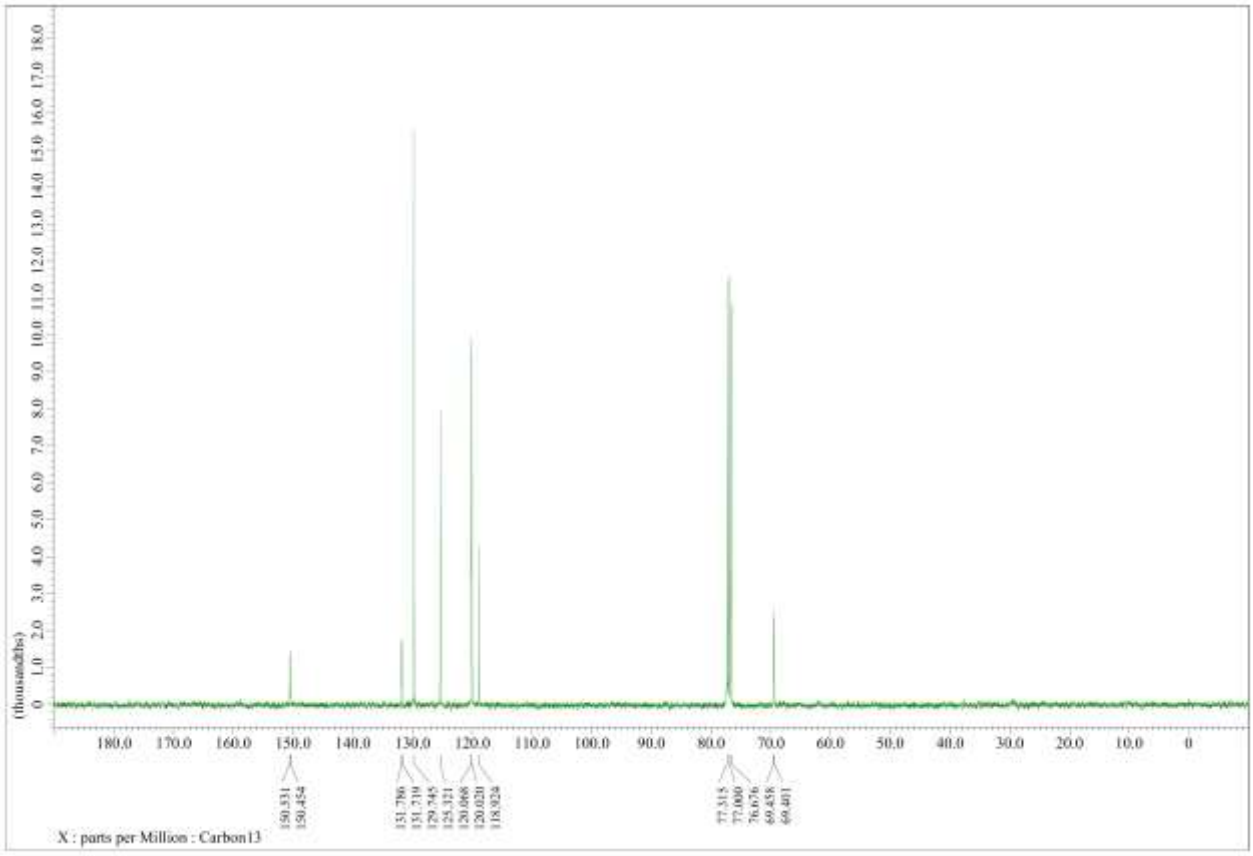



**Allyl diphenyl phosphate (6k)**

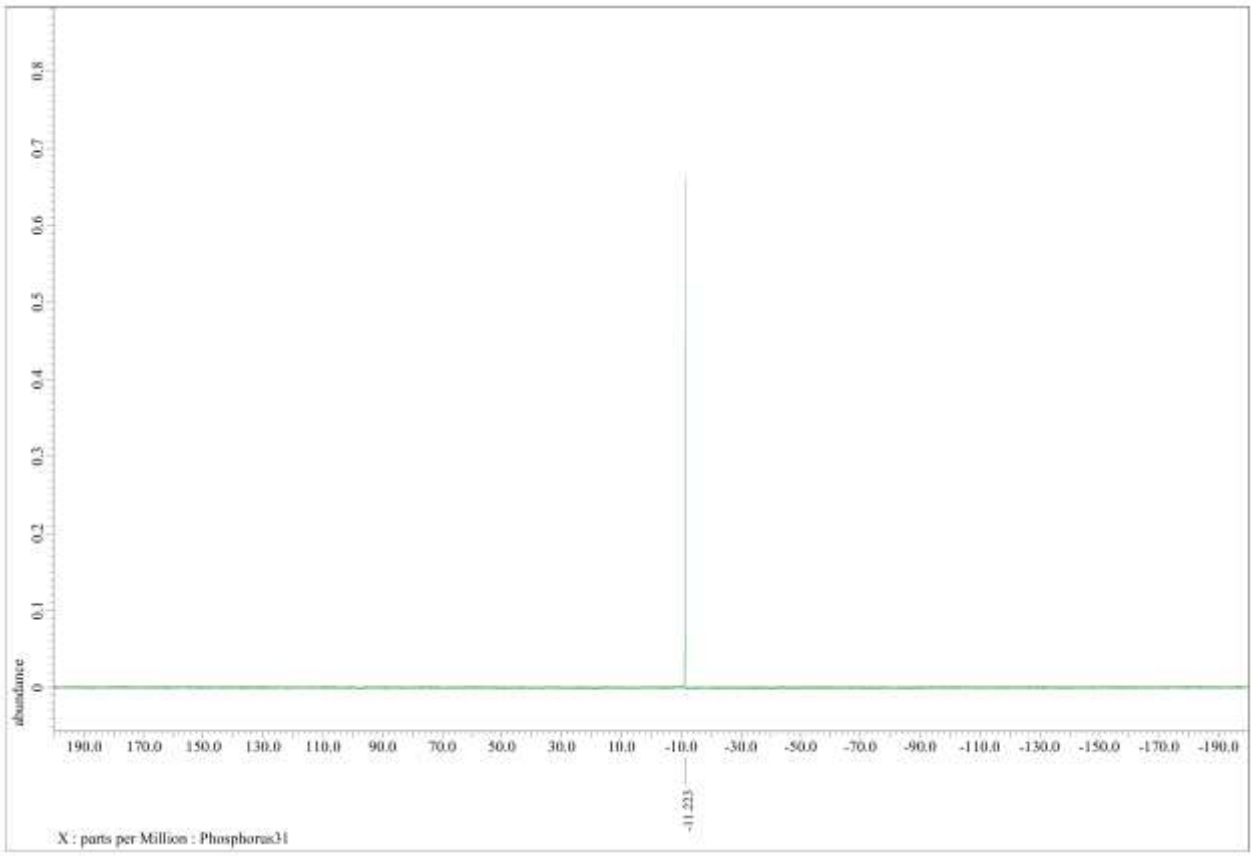
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

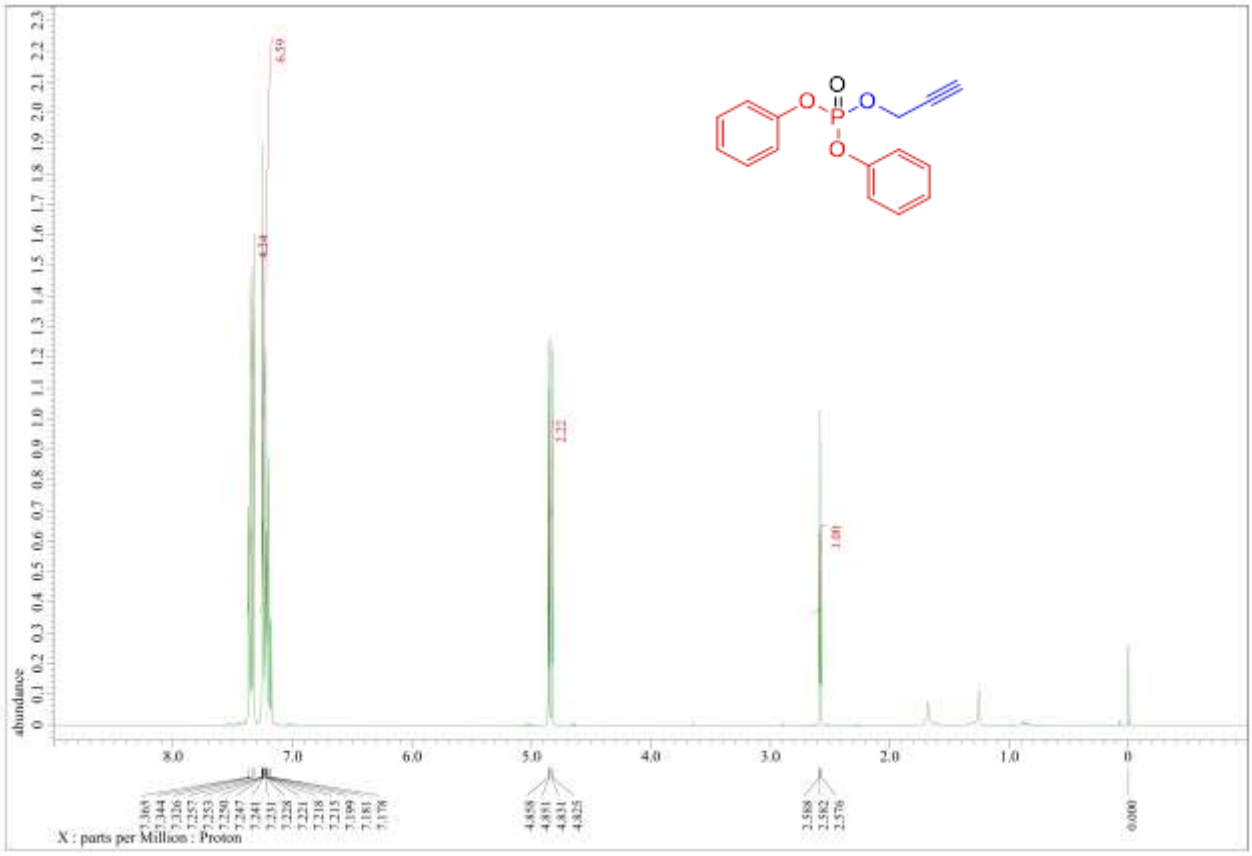



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

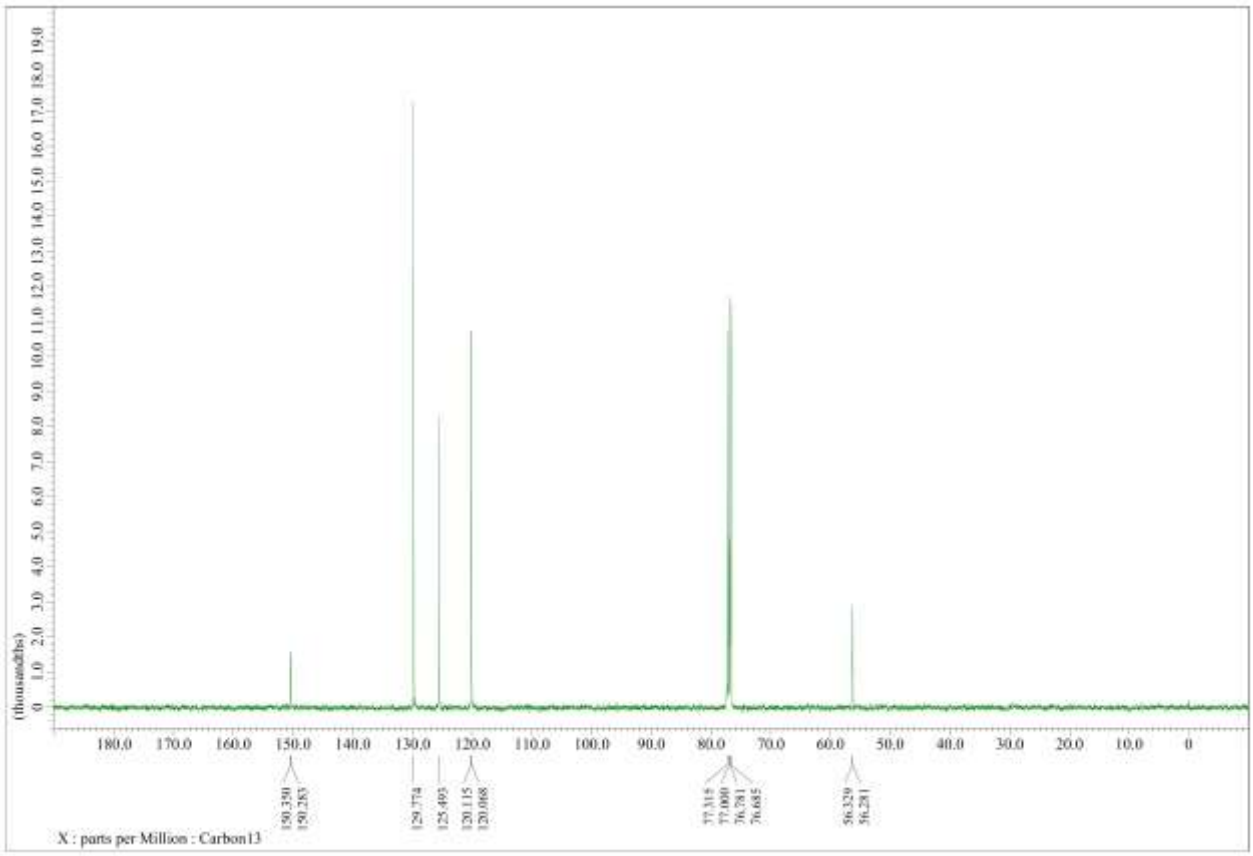


**Diphenyl propargyl phosphate (6l)**

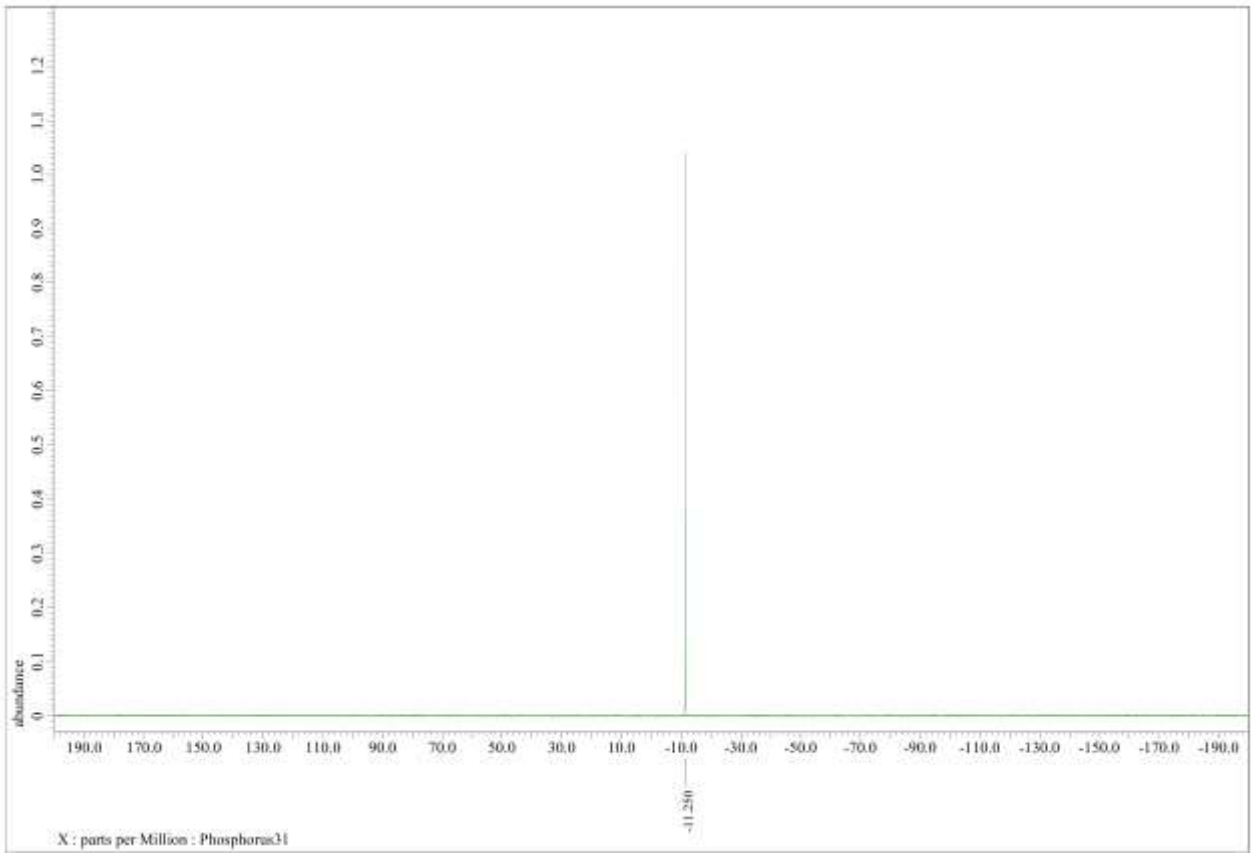
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

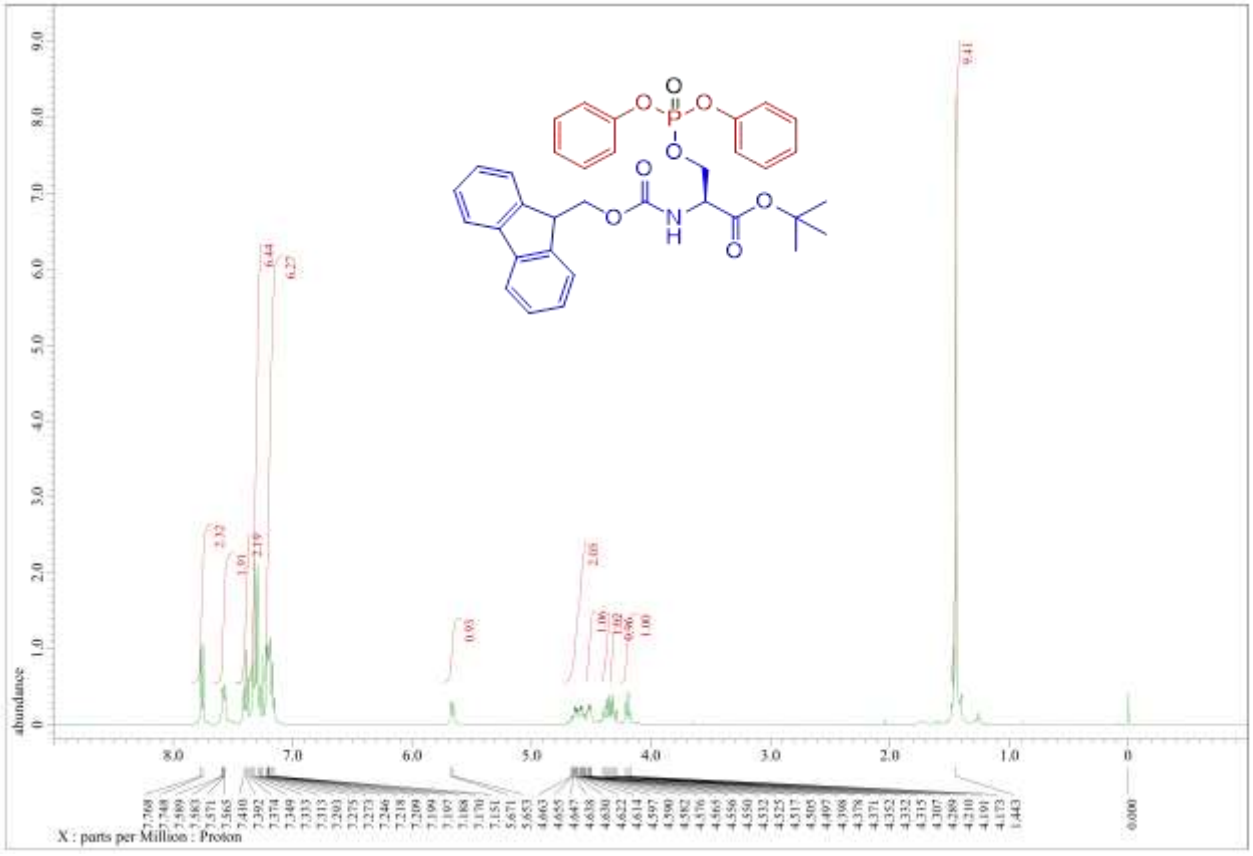


($^{31}$P NMR, 162 MHz, $CDCl_3$)

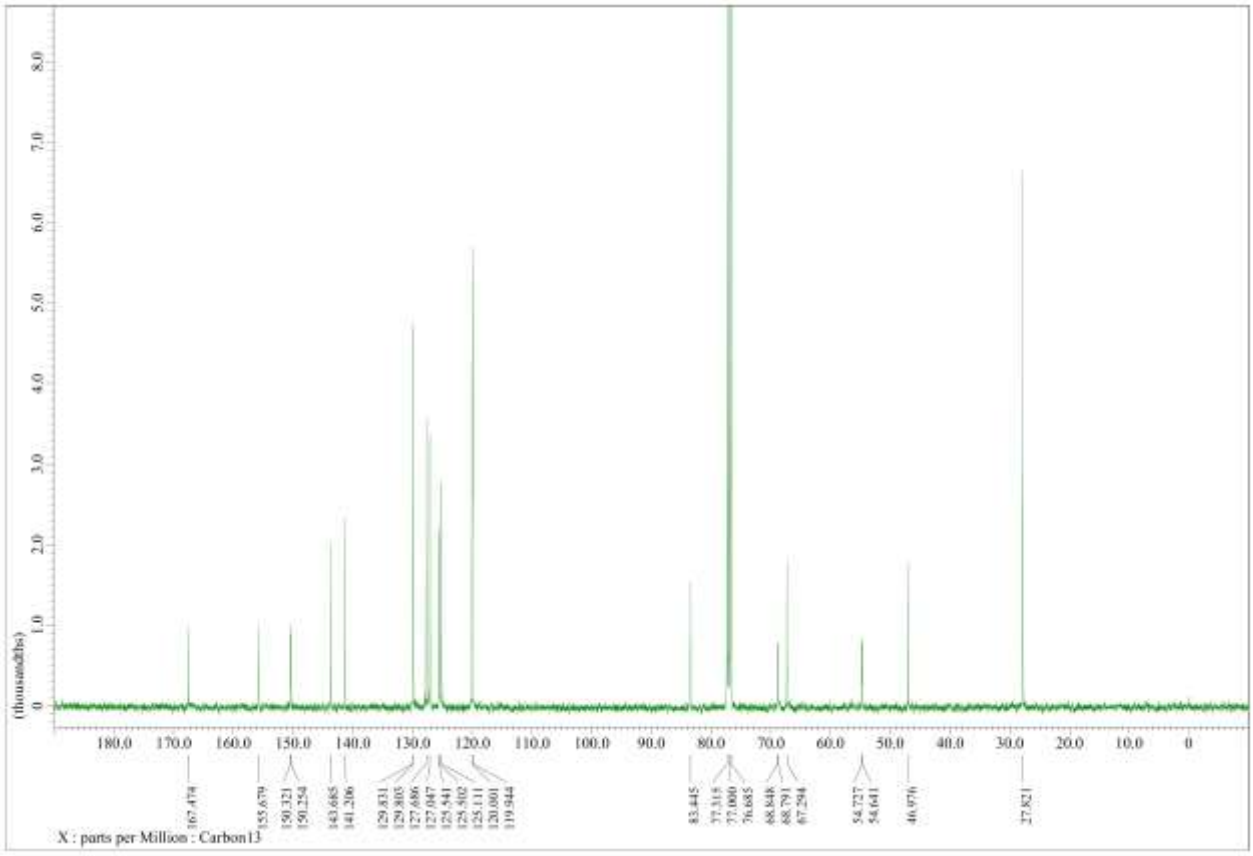



**Diphenyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-(*tert*-butoxycarbonyl)-ethan-1-yl phosphate (6m)**

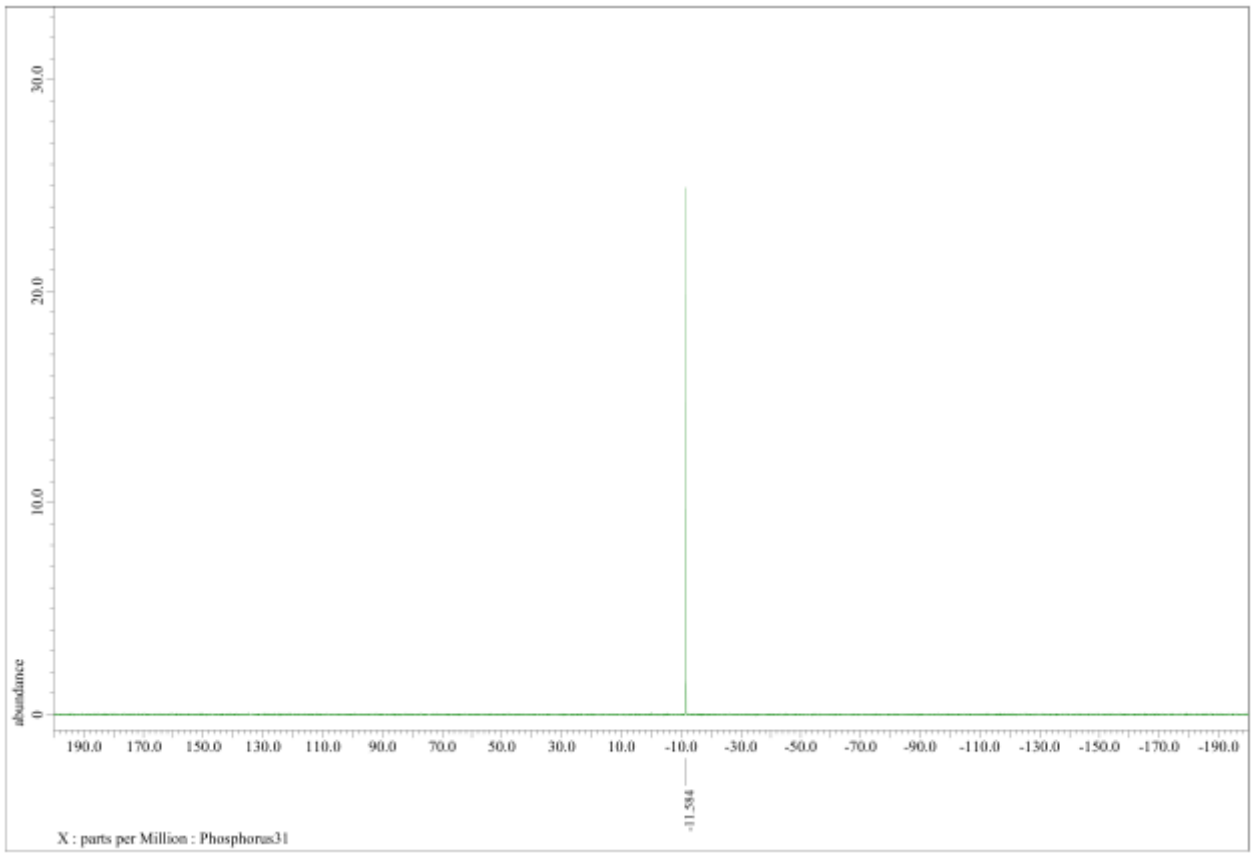
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

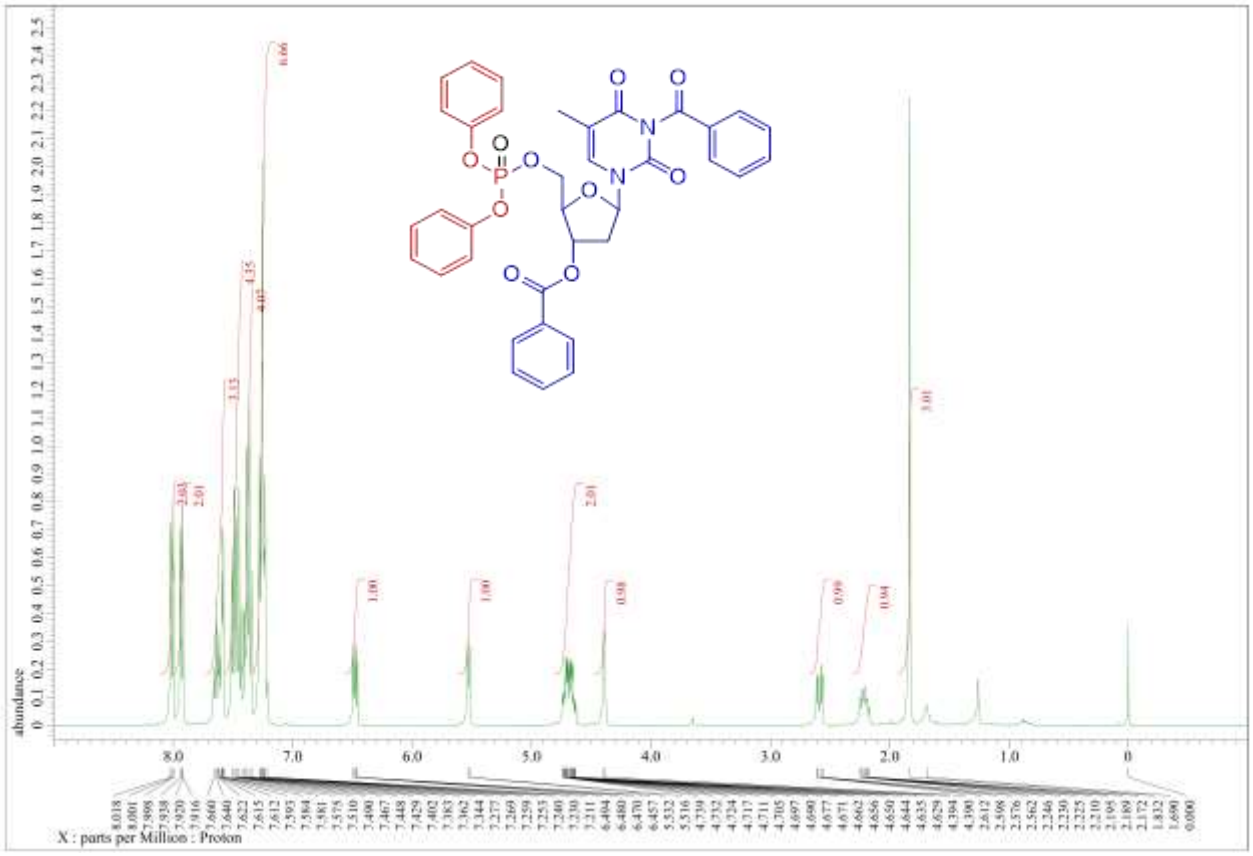



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

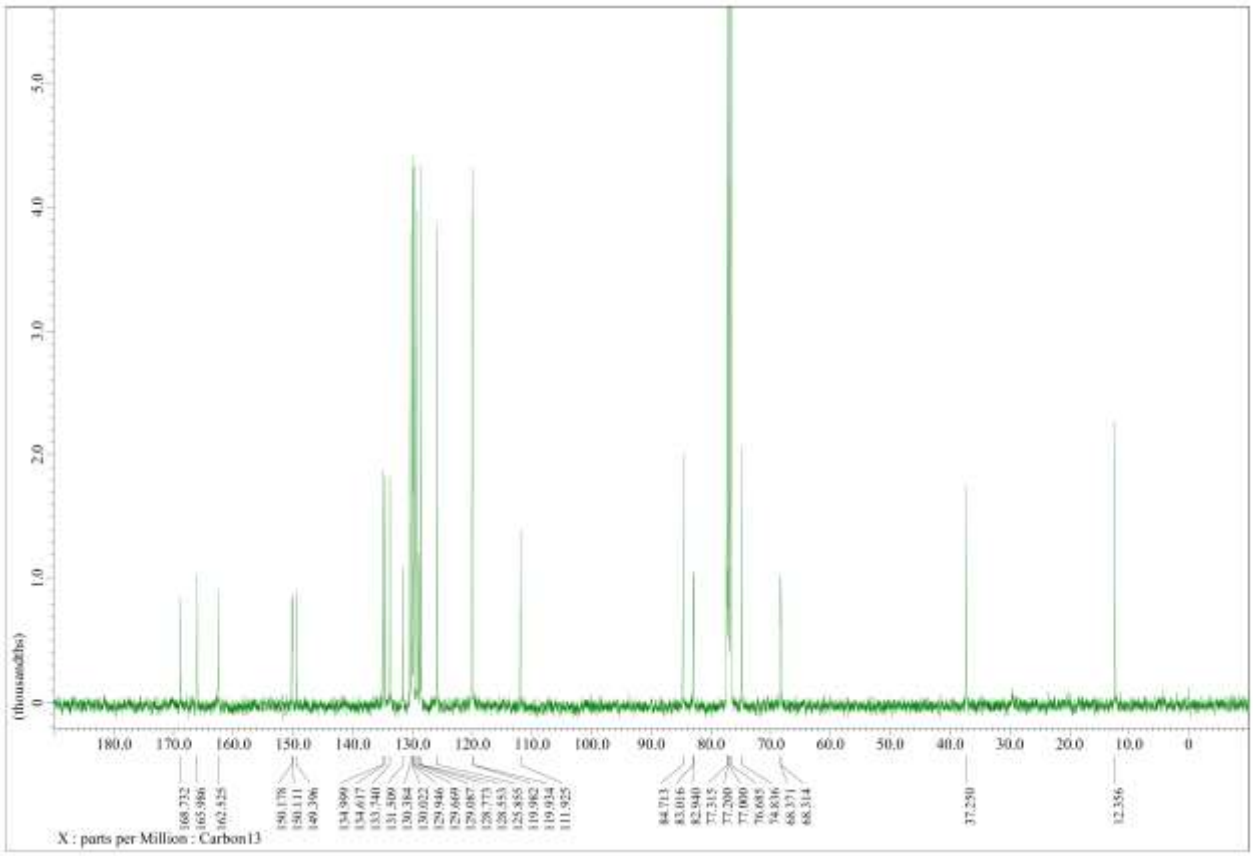


***N*3-Bz-3'-*O*-Bz-thymidine-5'-yl diphenyl phosphate (6n)**

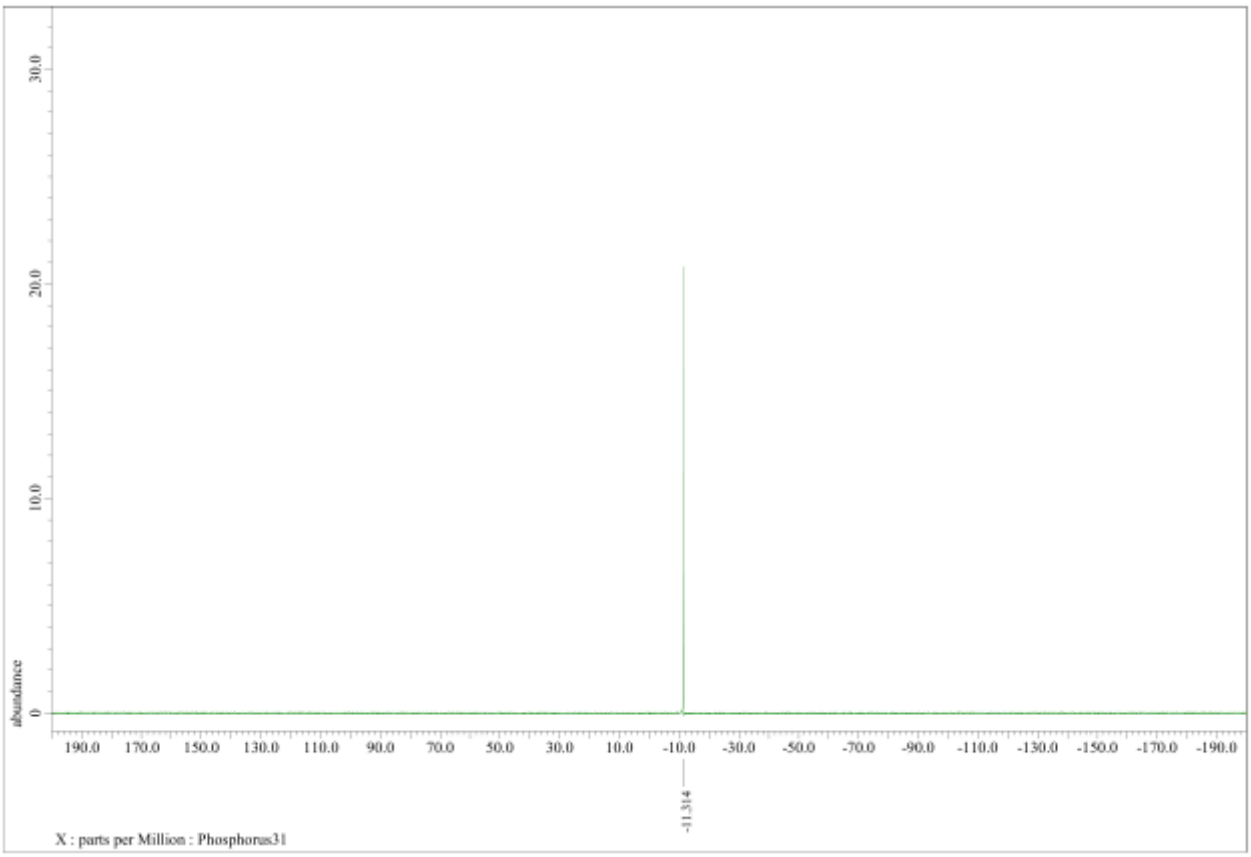
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}$C NMR, 100 MHz, $CDCl_3$)

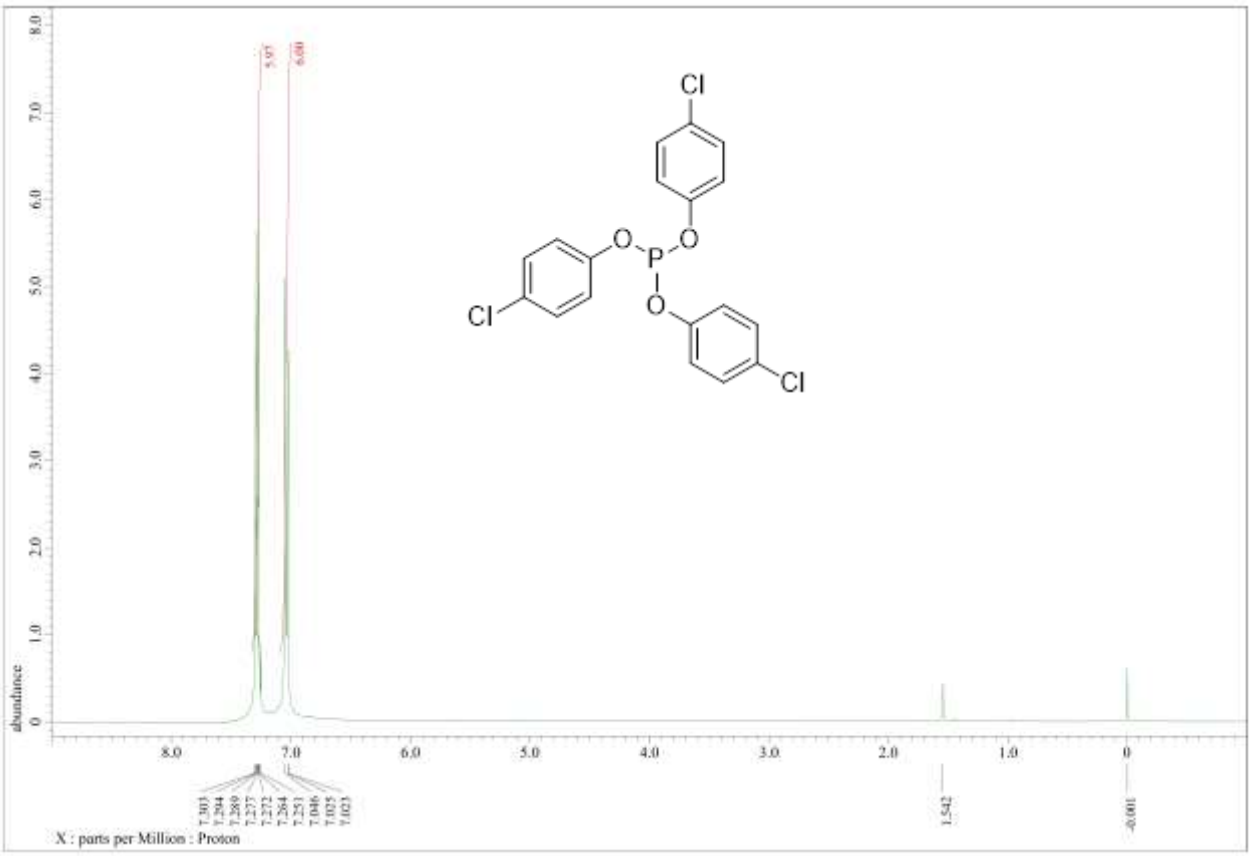


($^{31}$P NMR, 162 MHz, $CDCl_3$)

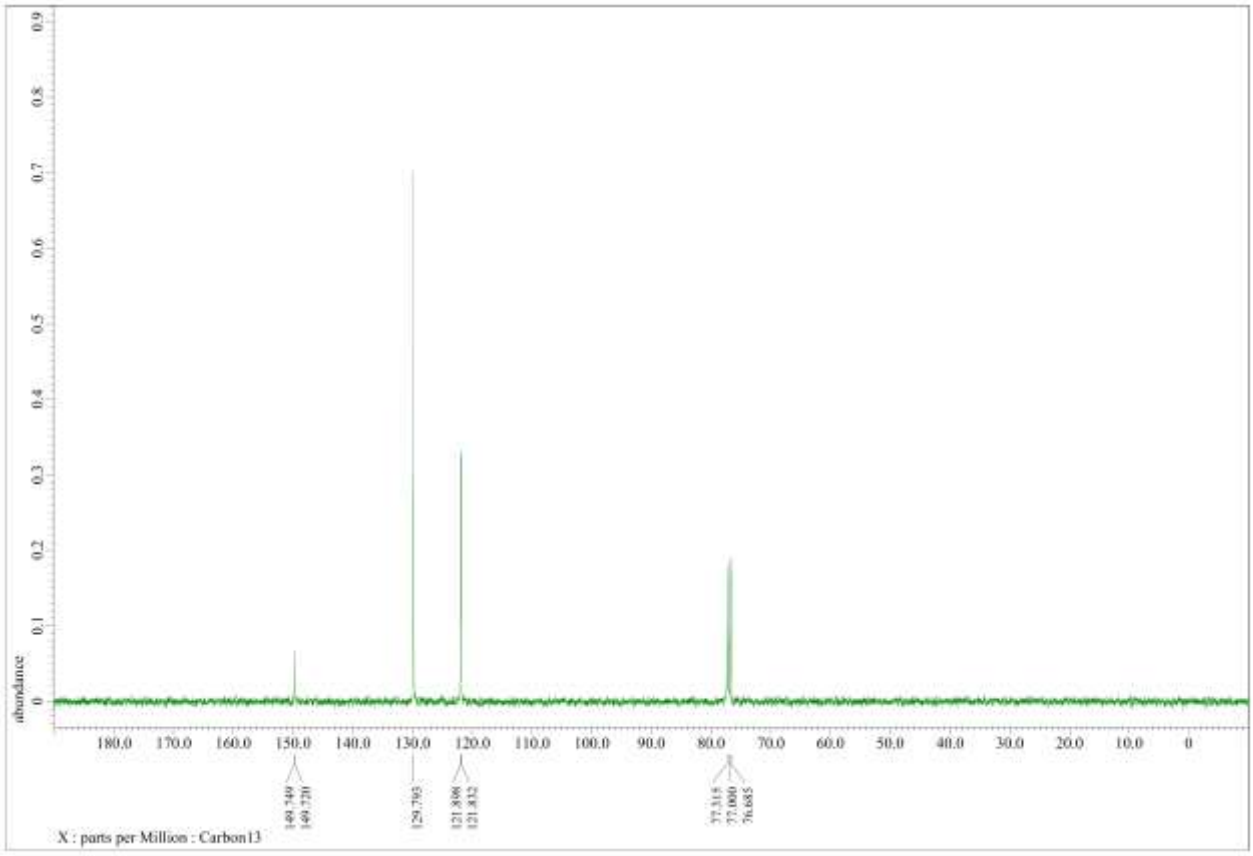



**Tris(4-chlorophenyl) phosphite (5b)**

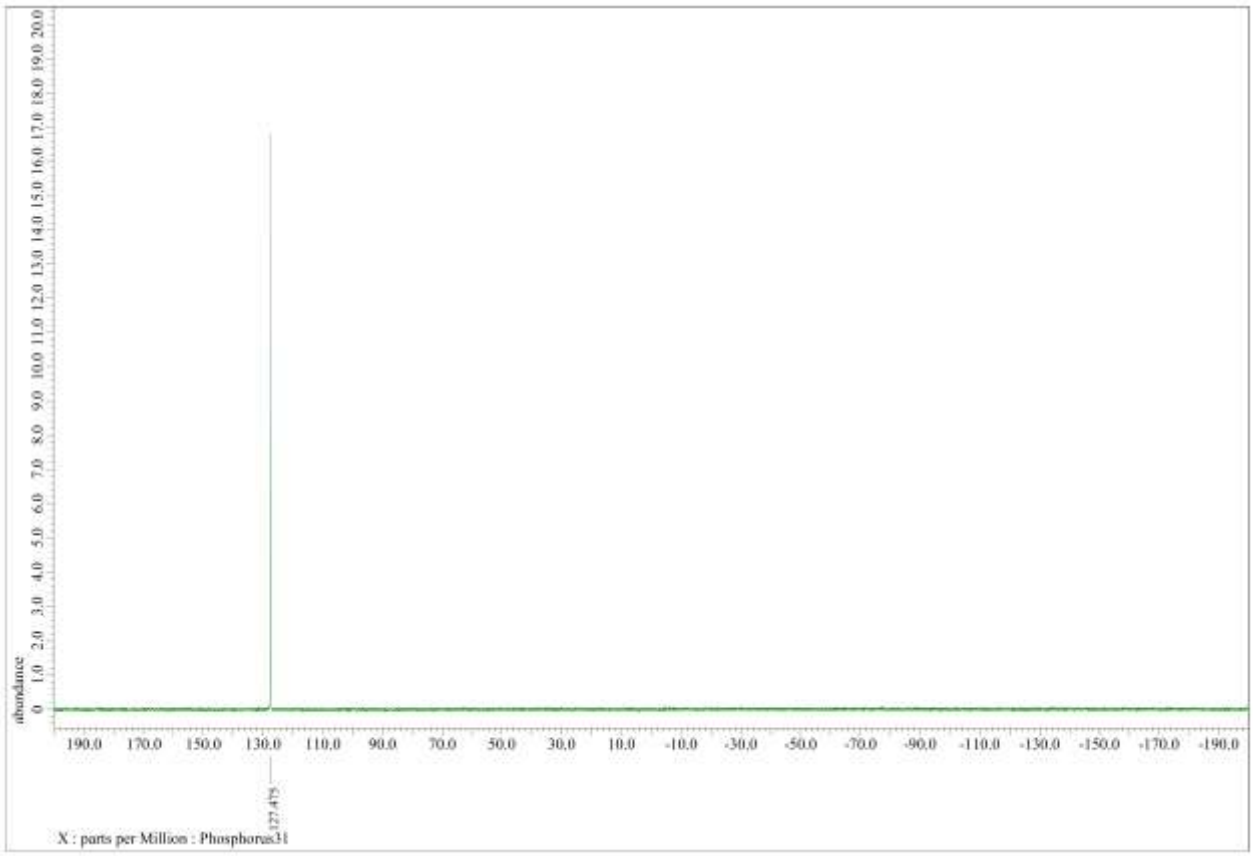
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

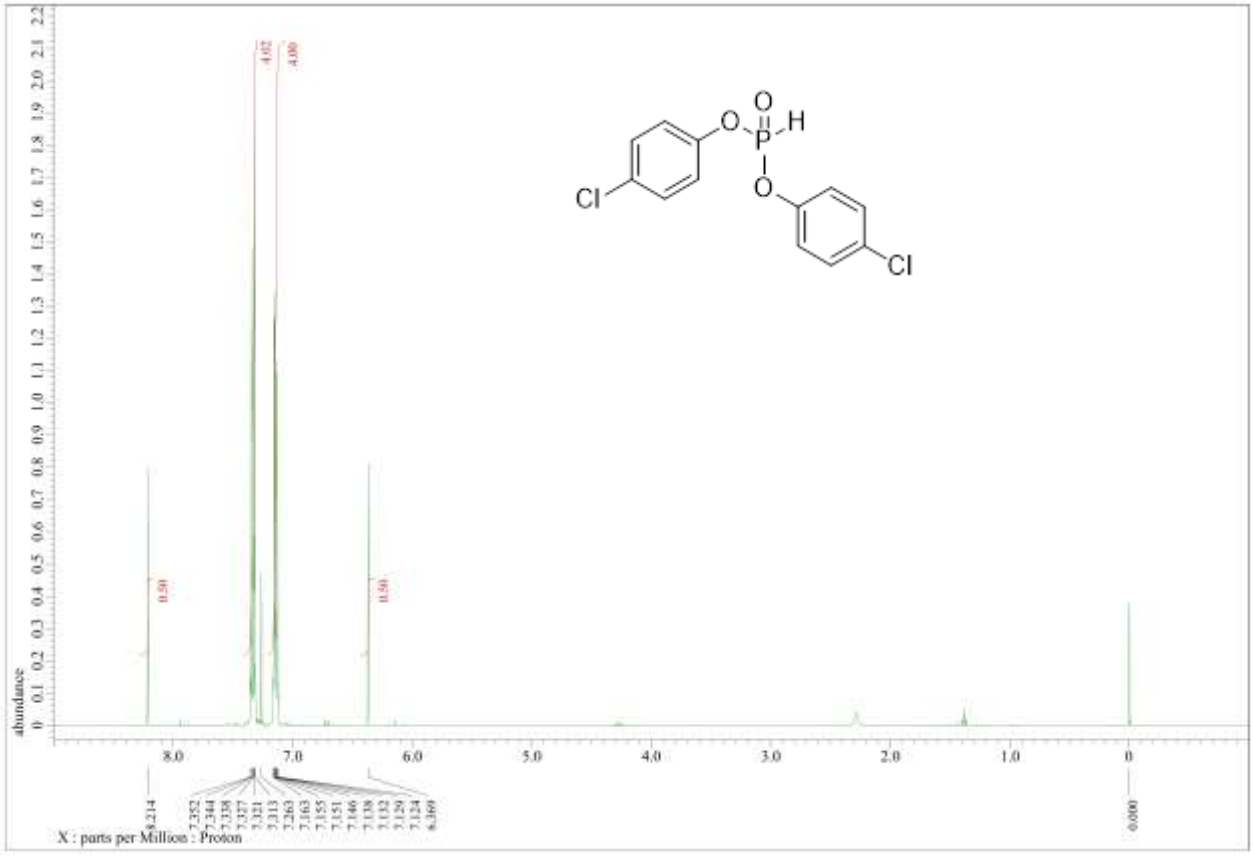



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

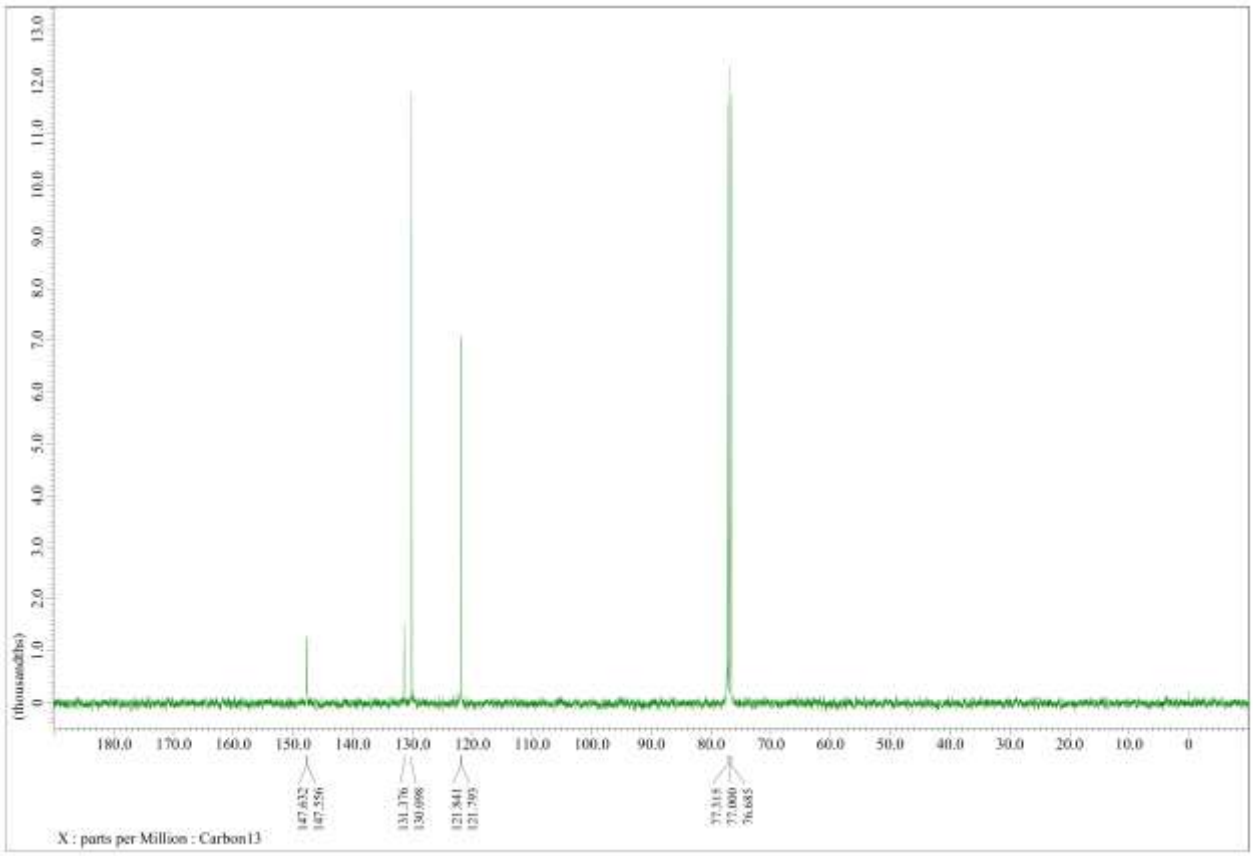


**Di-*p*-tolyl phosphonate (2b)**

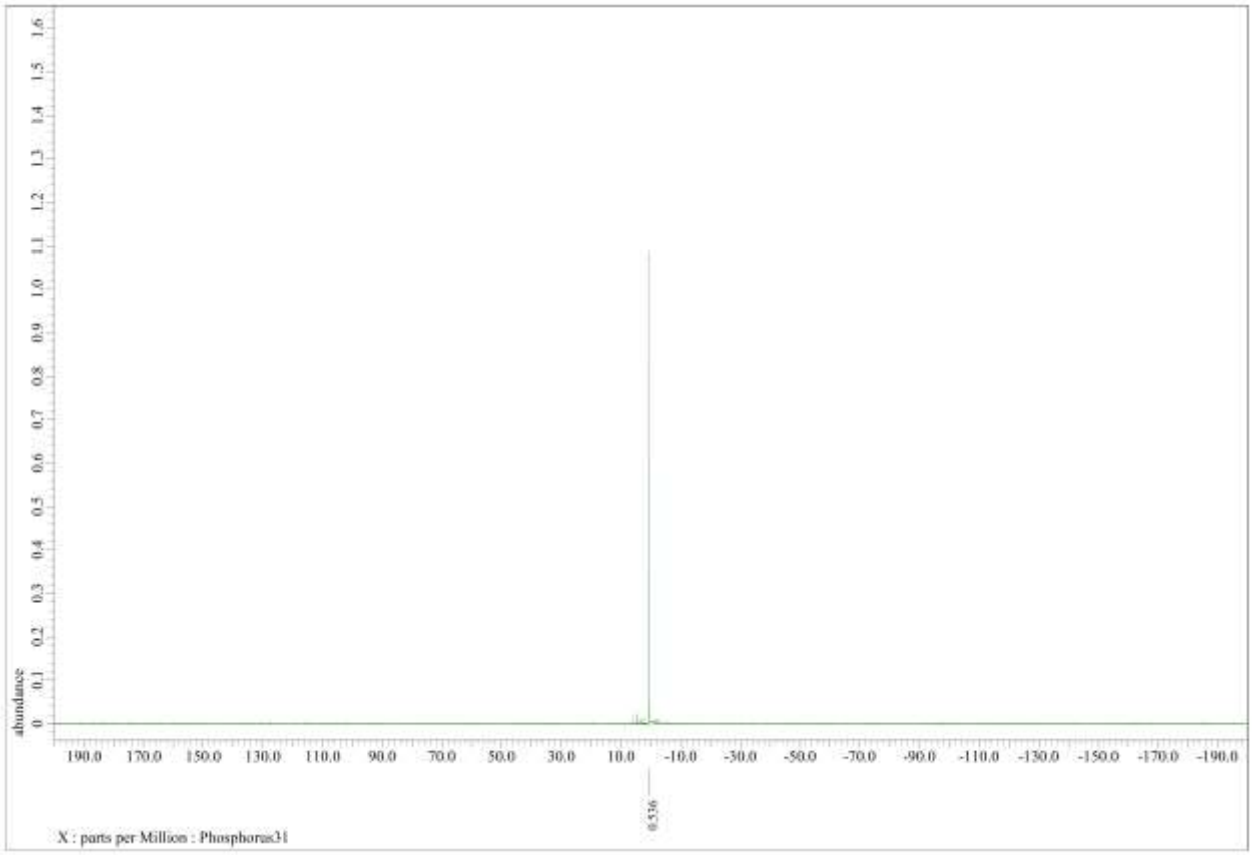
($^1$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)



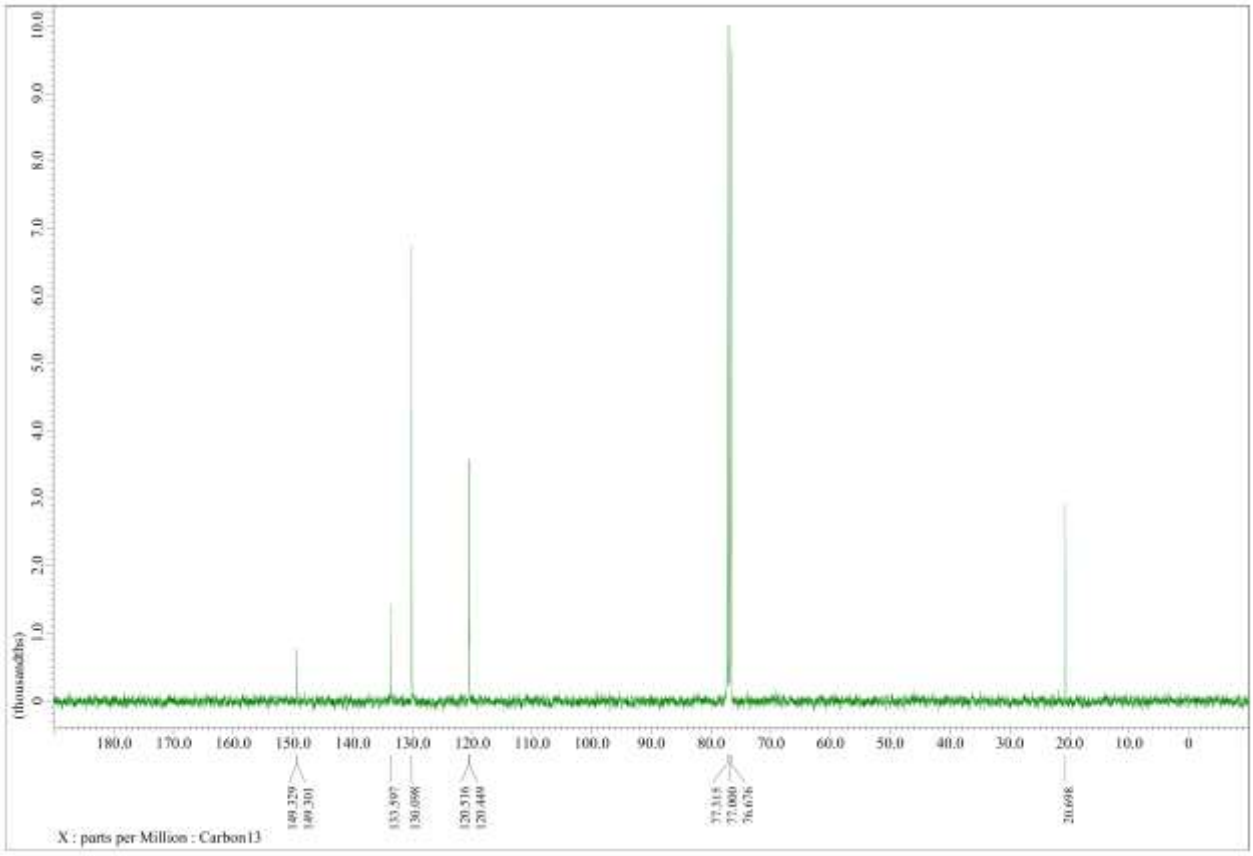
($^{31}$P NMR, 162 MHz, $CDCl_3$)



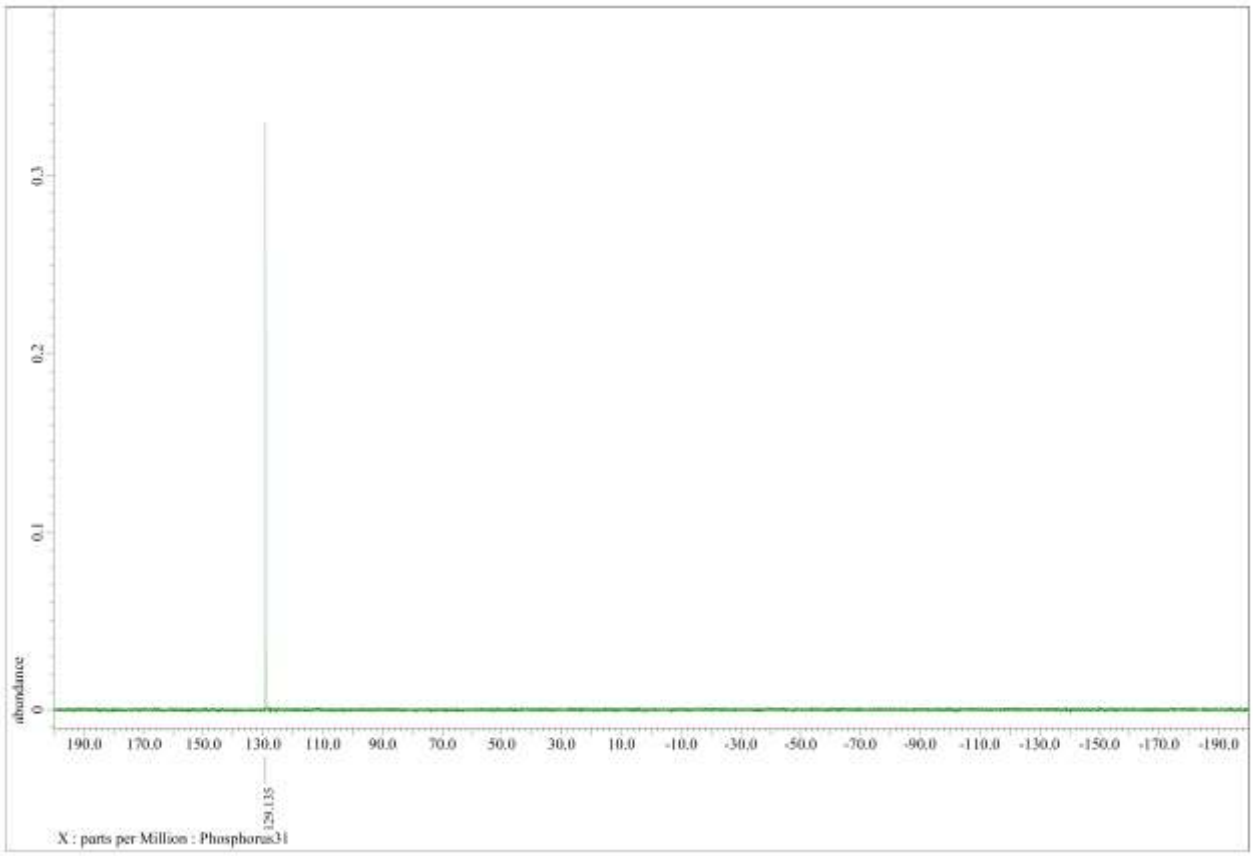

**Tri-*p*-tolyl phosphite (5c)**

($^{1}$H NMR, 400 MHz, $CDCl_3$)

($^{13}$C NMR, 100 MHz, $CDCl_3$)

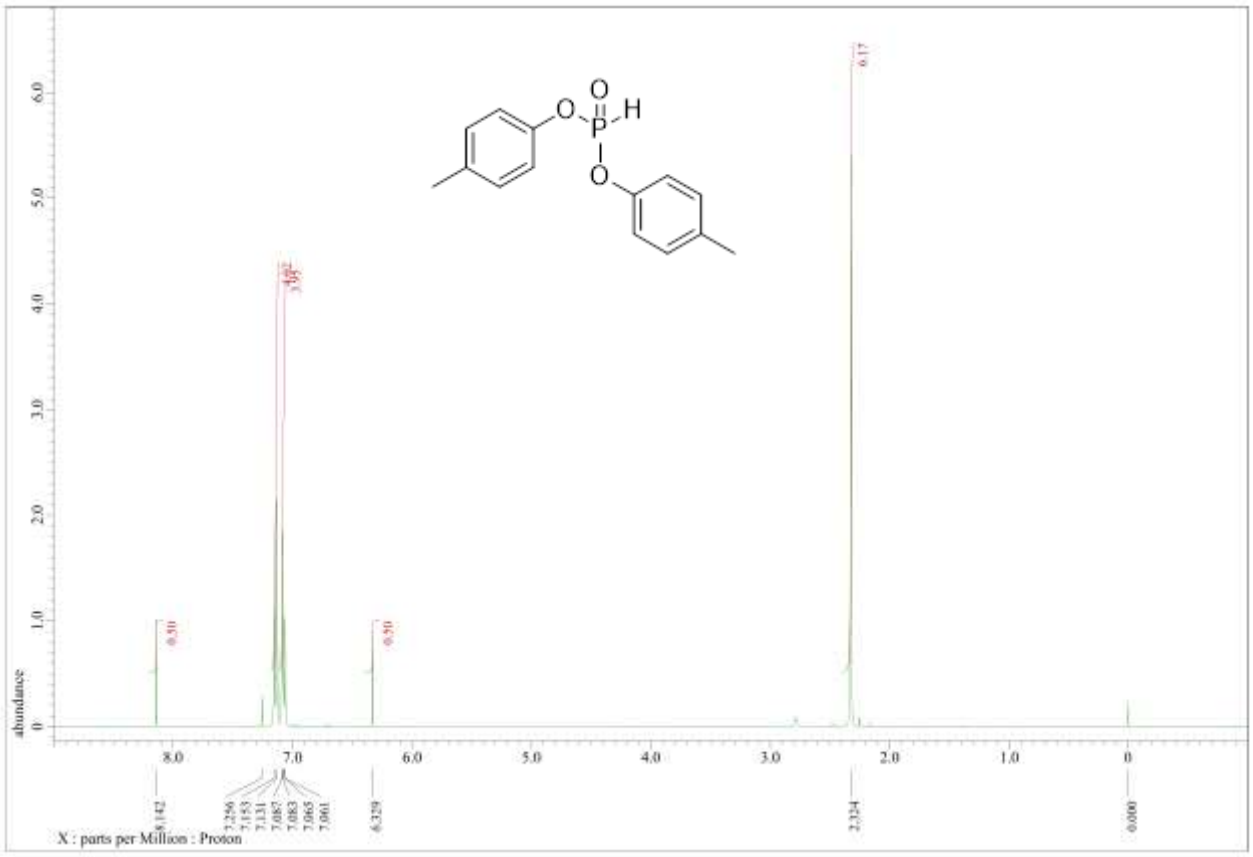



($^{31}$P NMR, 162 MHz, $CDCl_3$)

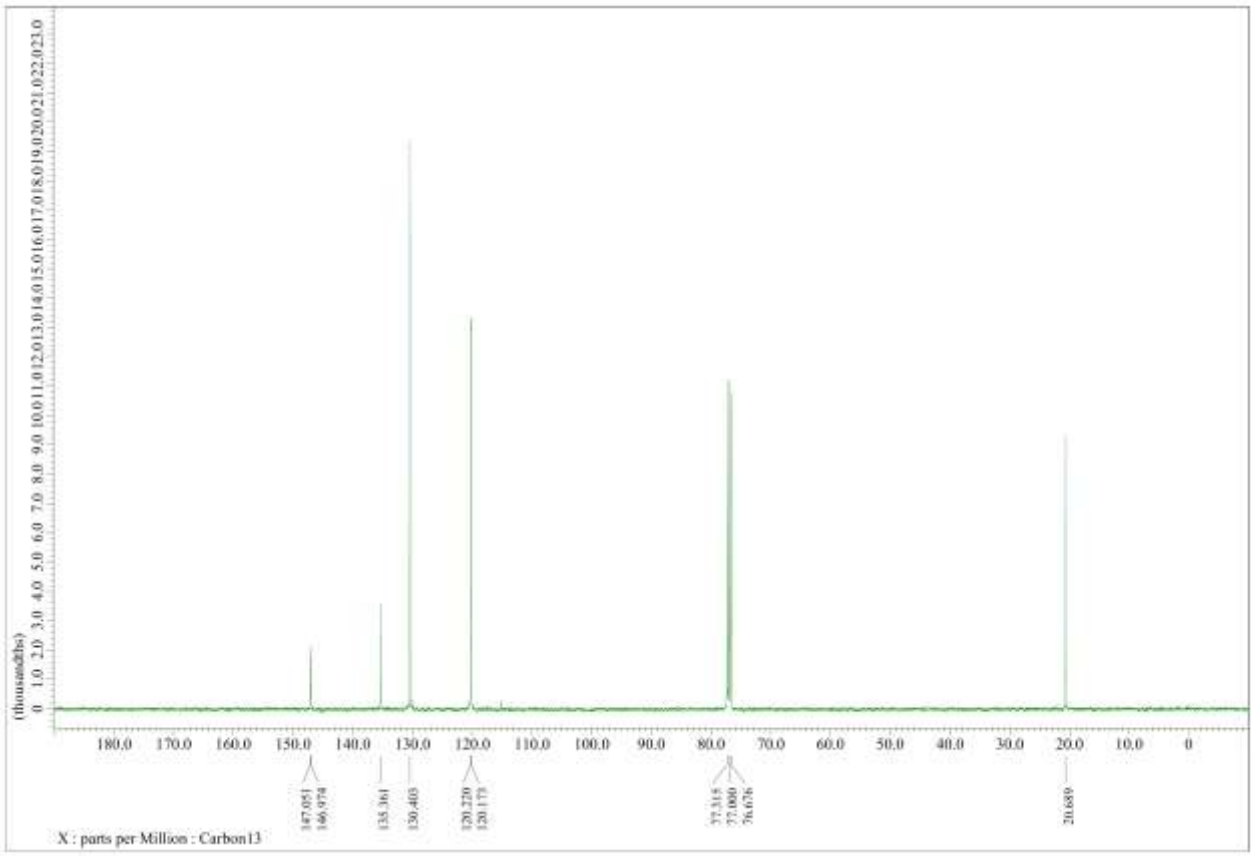


**Di-*p*-tolyl phosphonate (2c)**

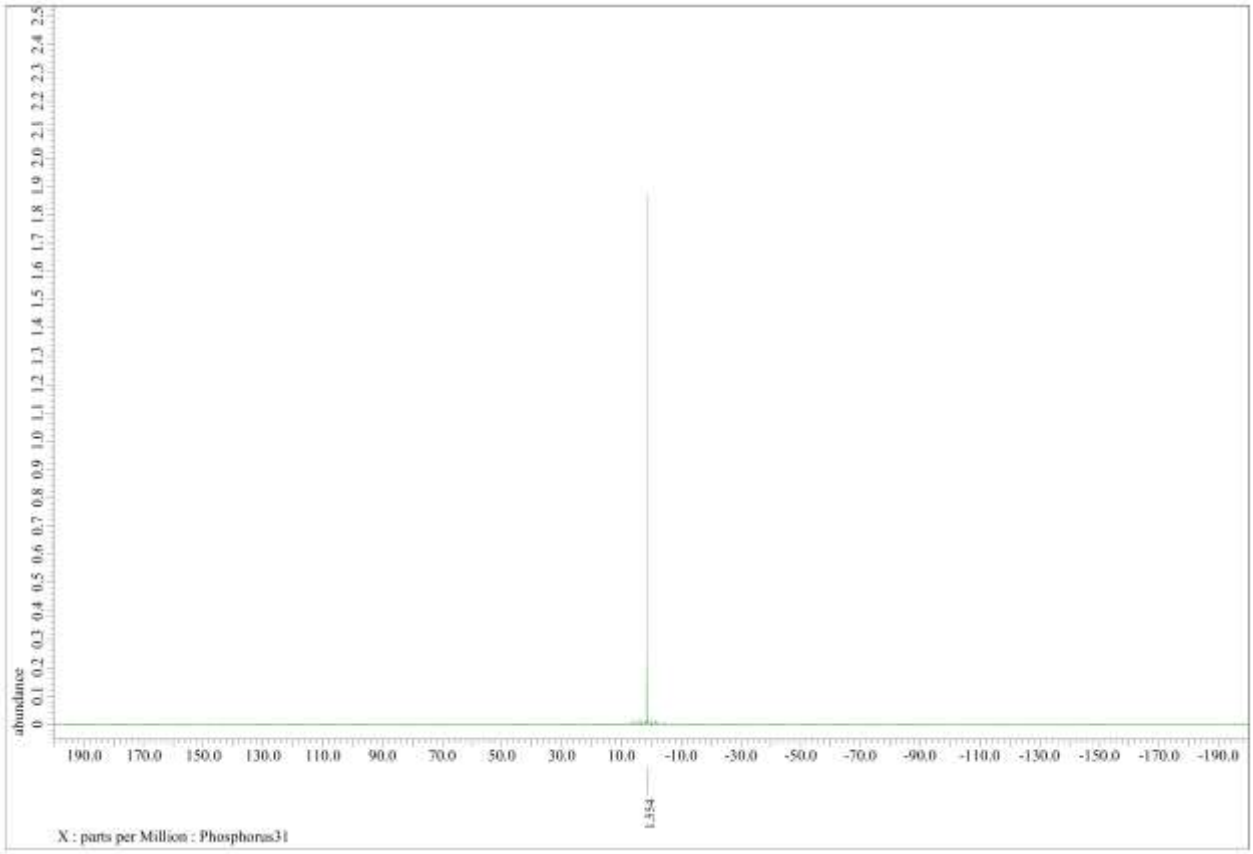
($^{1}$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

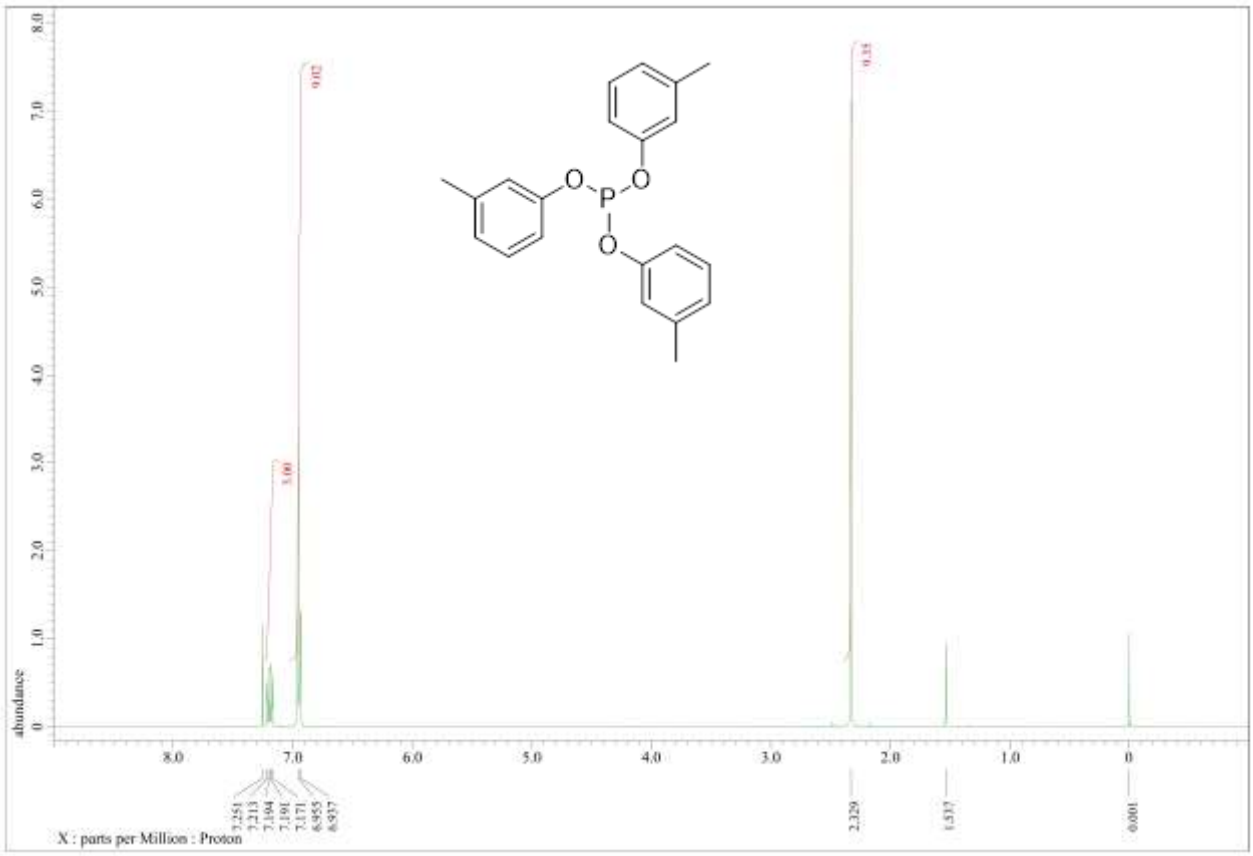


($^{31}$P NMR, 162 MHz, $CDCl_3$)

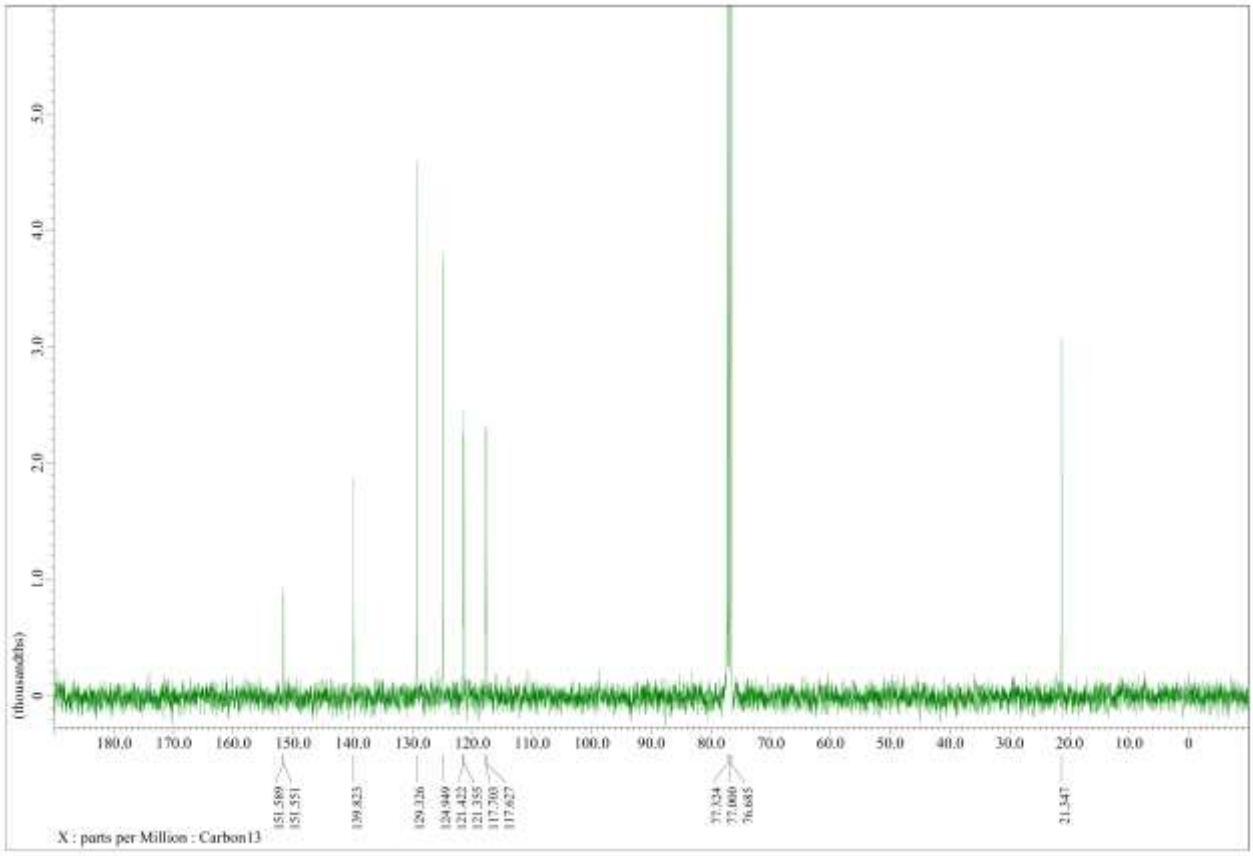



**Tri-*m*-tolyl phosphite (5d)**

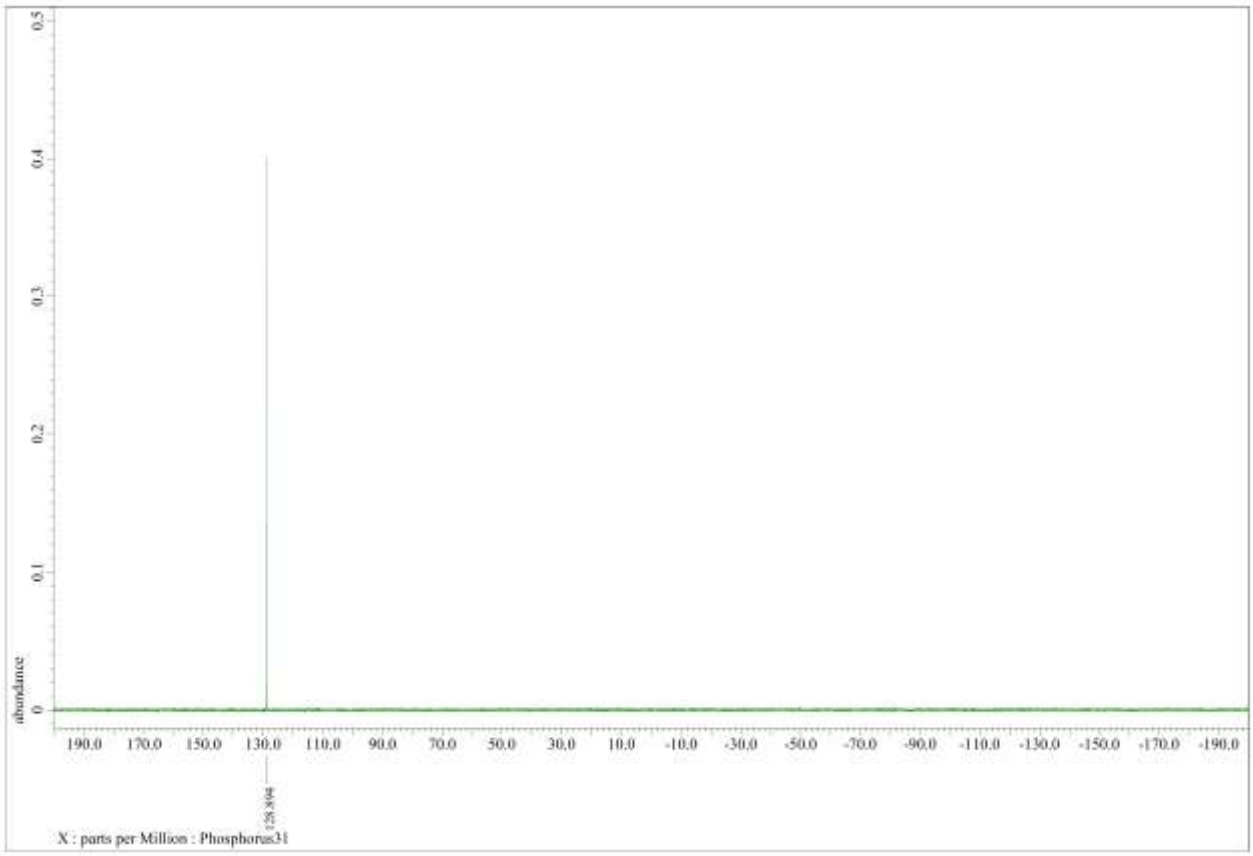
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)

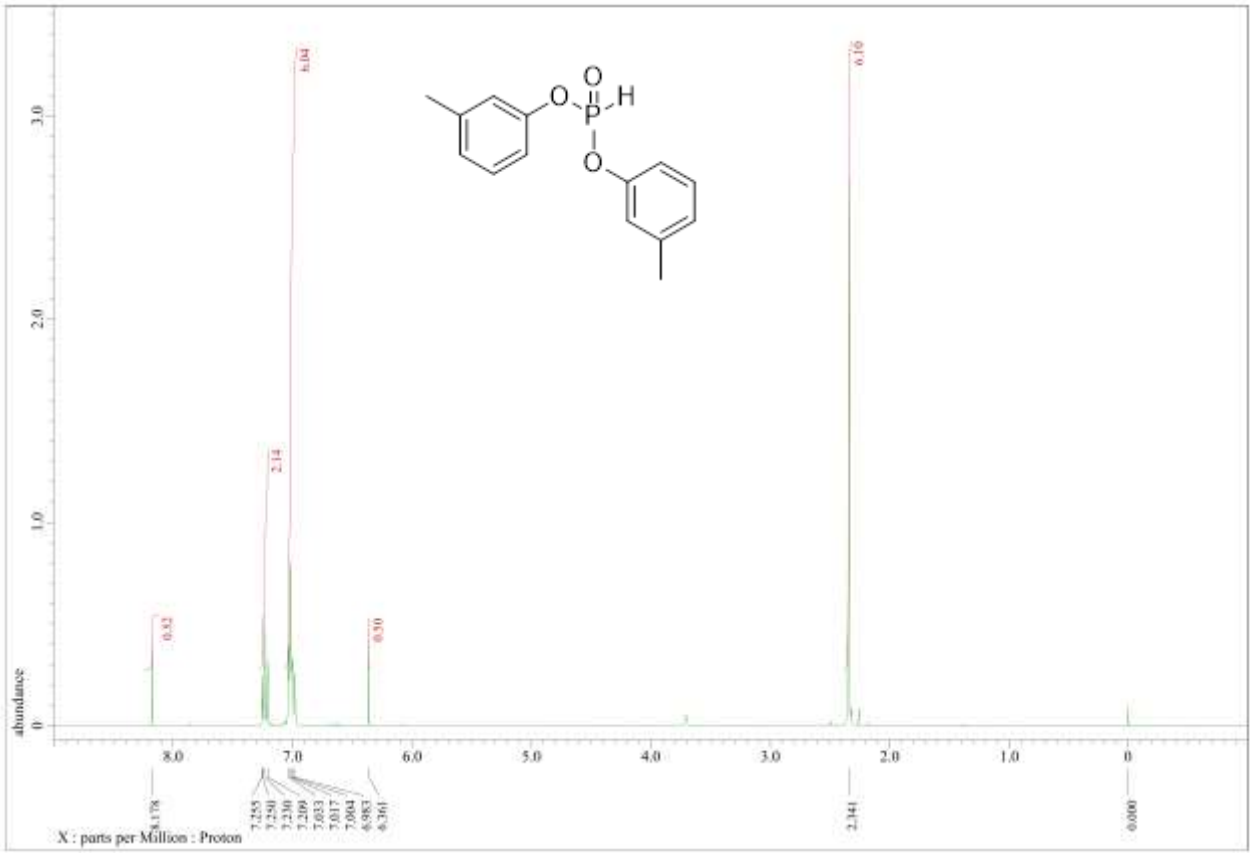



($^{31}P$ NMR, 162 MHz, $CDCl_3$)

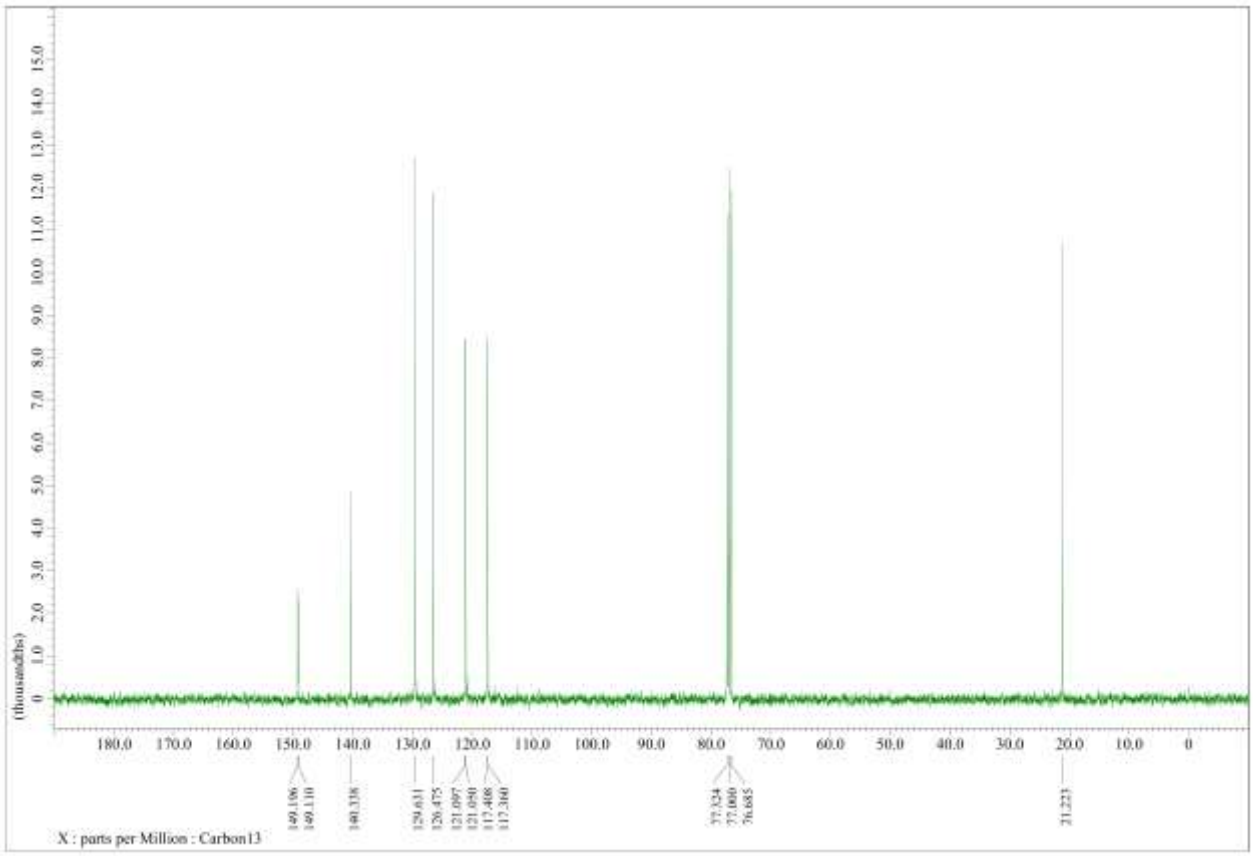


**Di-*m*-tolyl phosphonate (2d)**

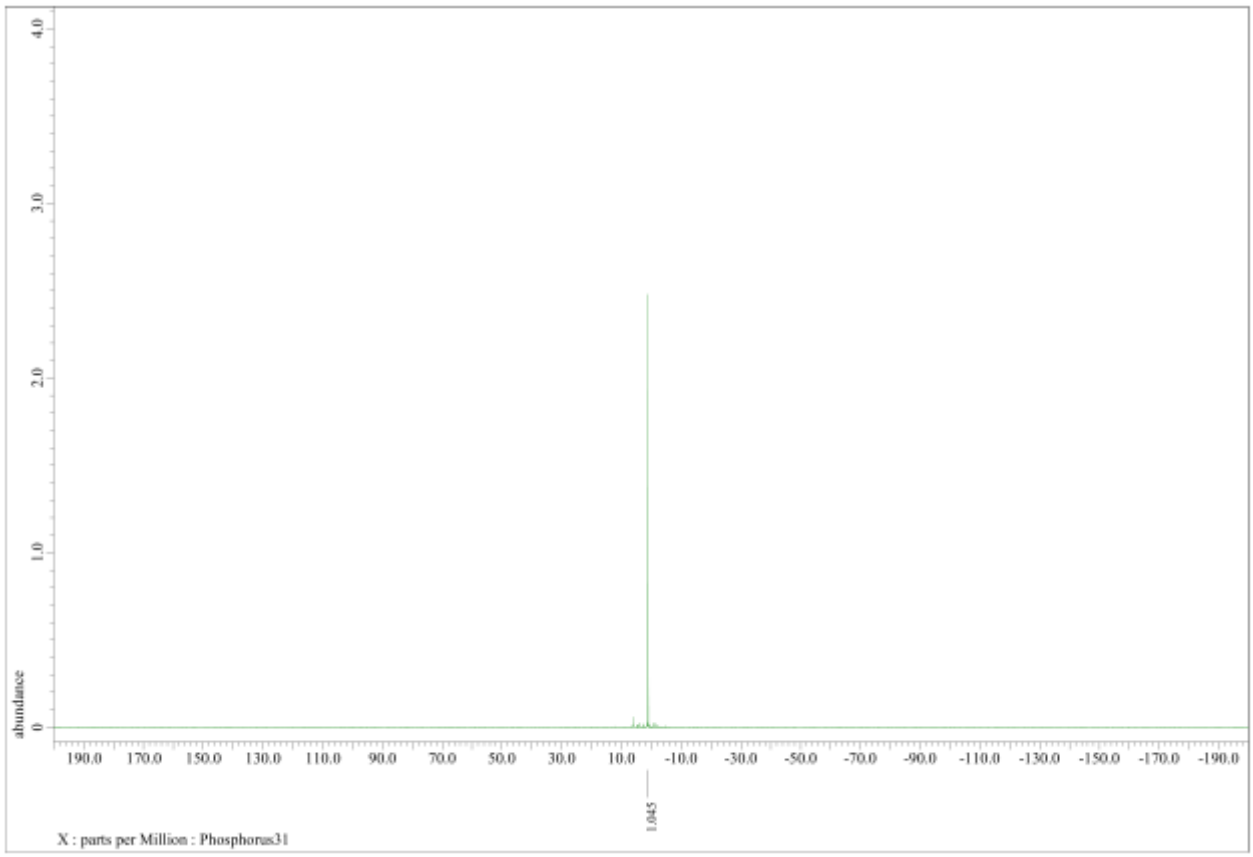
($^1$H NMR, 400 MHz, $CDCl_3$)




($^{13}$C NMR, 100 MHz, $CDCl_3$)

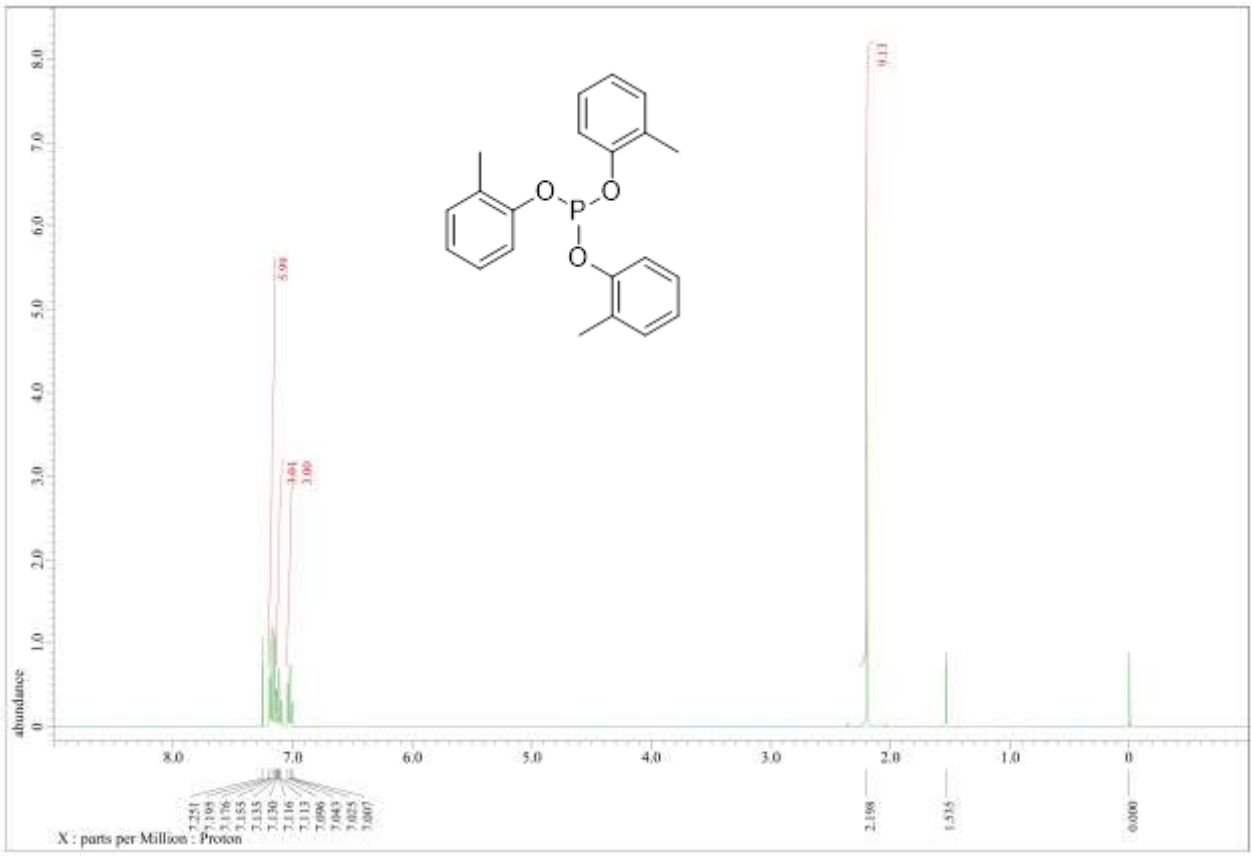


($^{31}$P NMR, 162 MHz, $CDCl_3$)

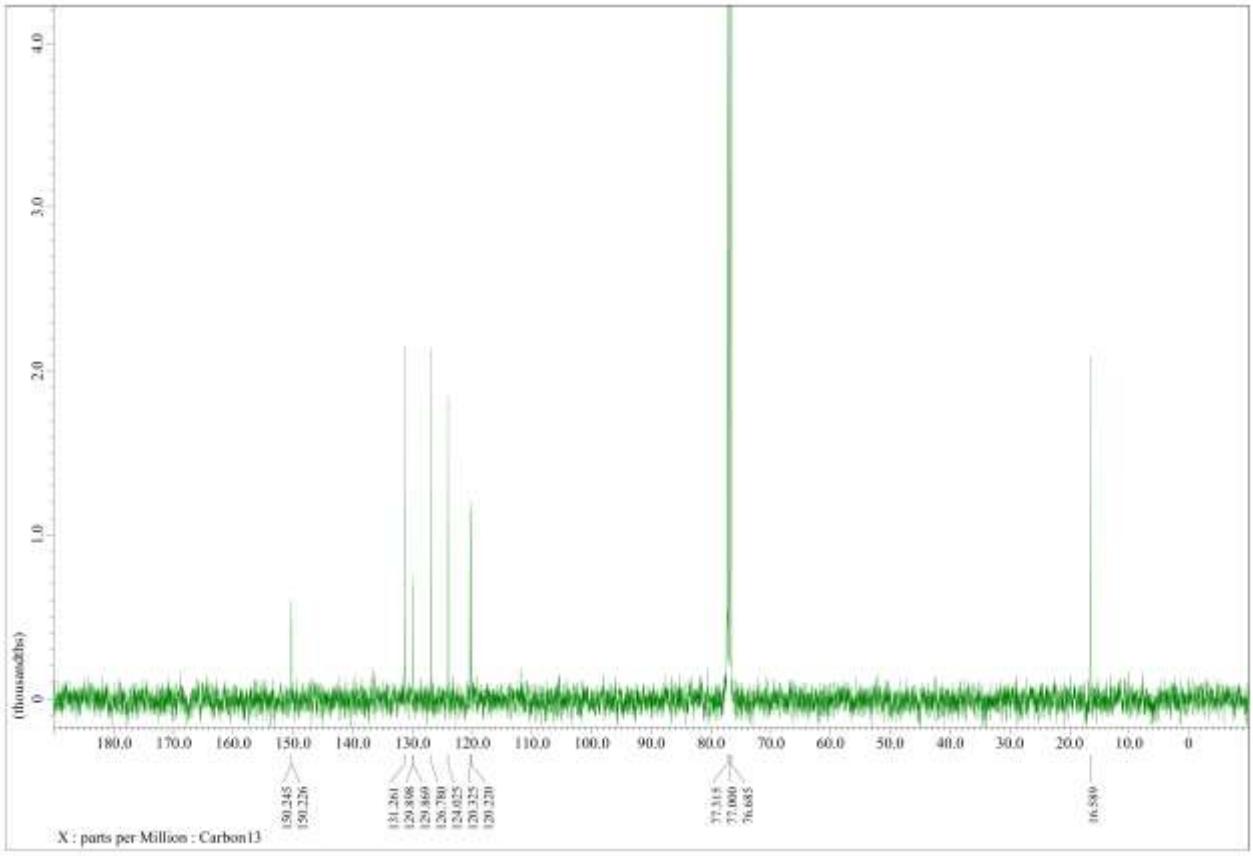



**Tri-*o*-tolyl phosphite (5e)**

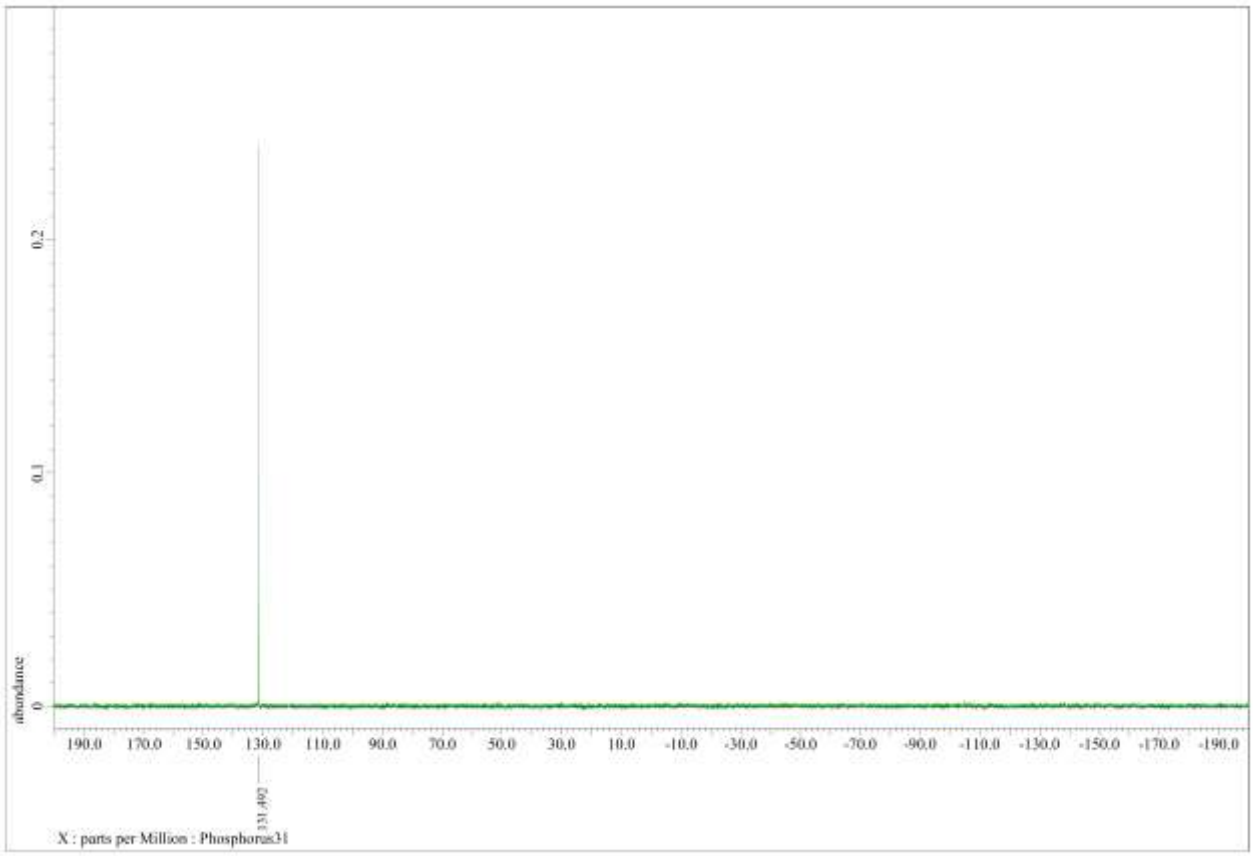
($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)



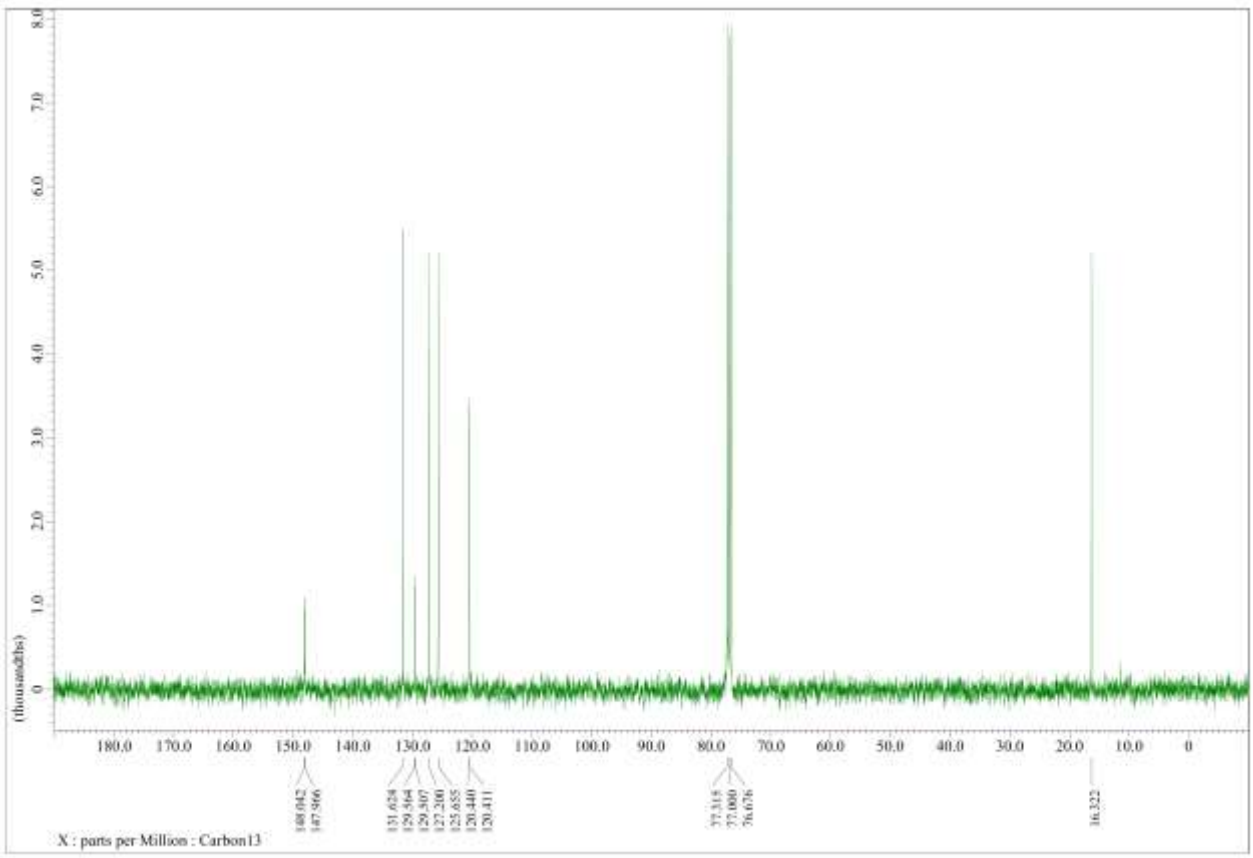

($^{31}P$ NMR, 162 MHz, $CDCl_3$)



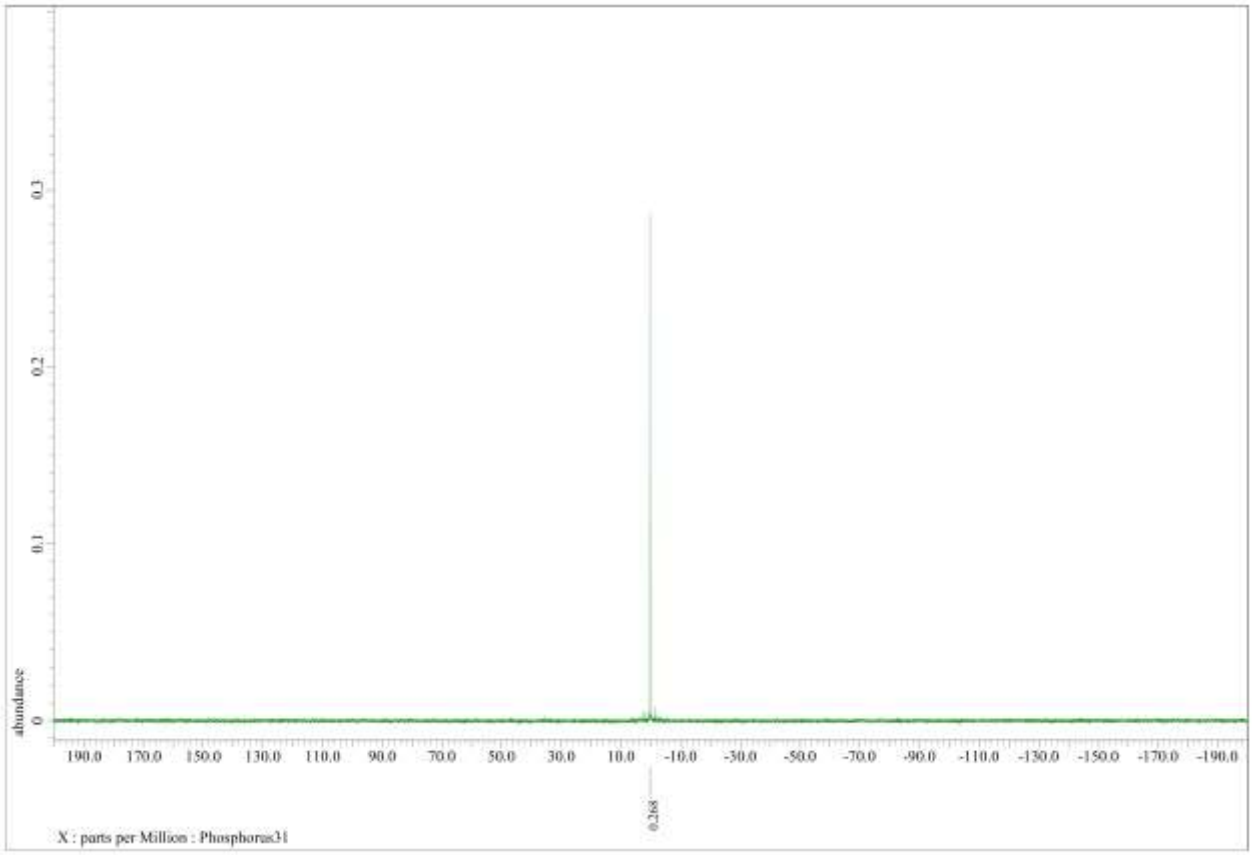
**Di-*o*-tolyl phosphonate (2e)**

($^{1}$H NMR, 400 MHz, $CDCl_3$)


($^{13}$C NMR, 100 MHz, $CDCl_3$)

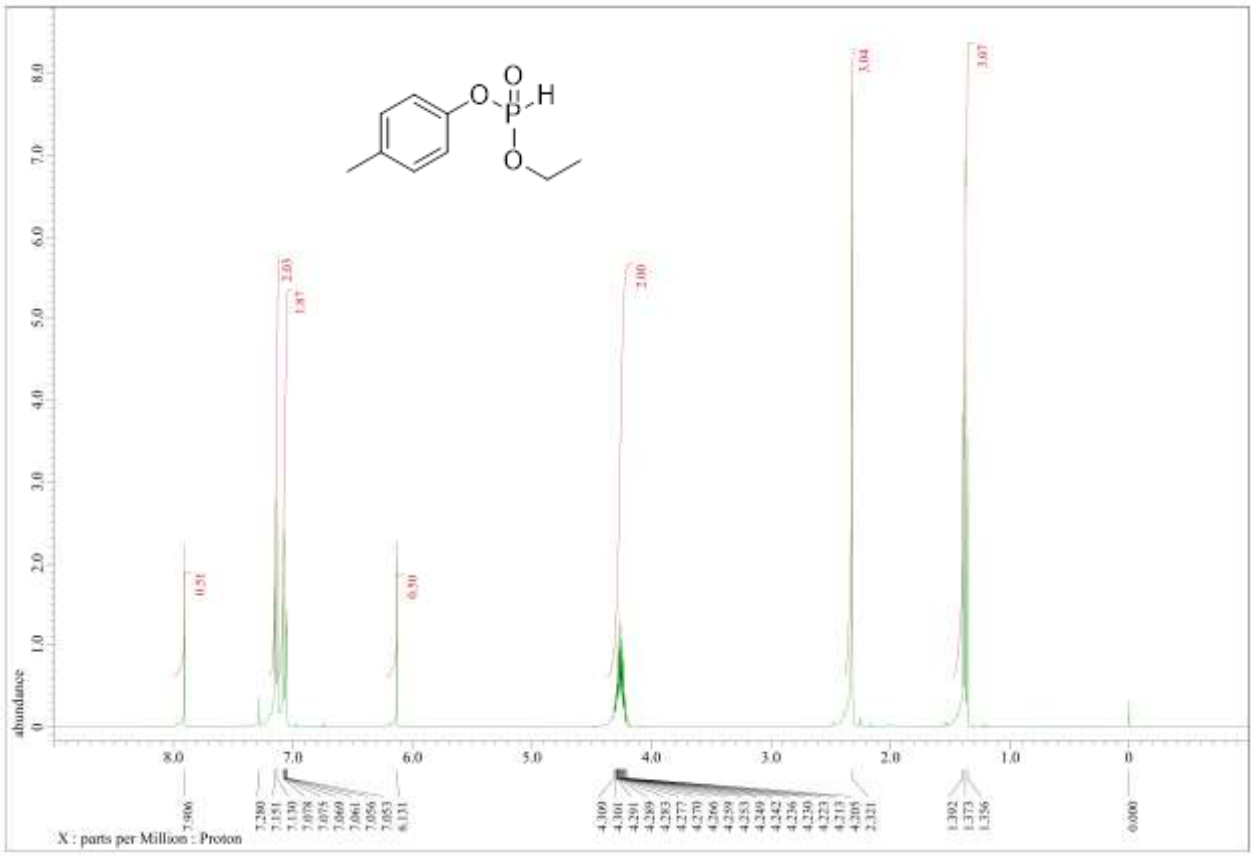


($^{31}$P NMR, 162 MHz, $CDCl_3$)

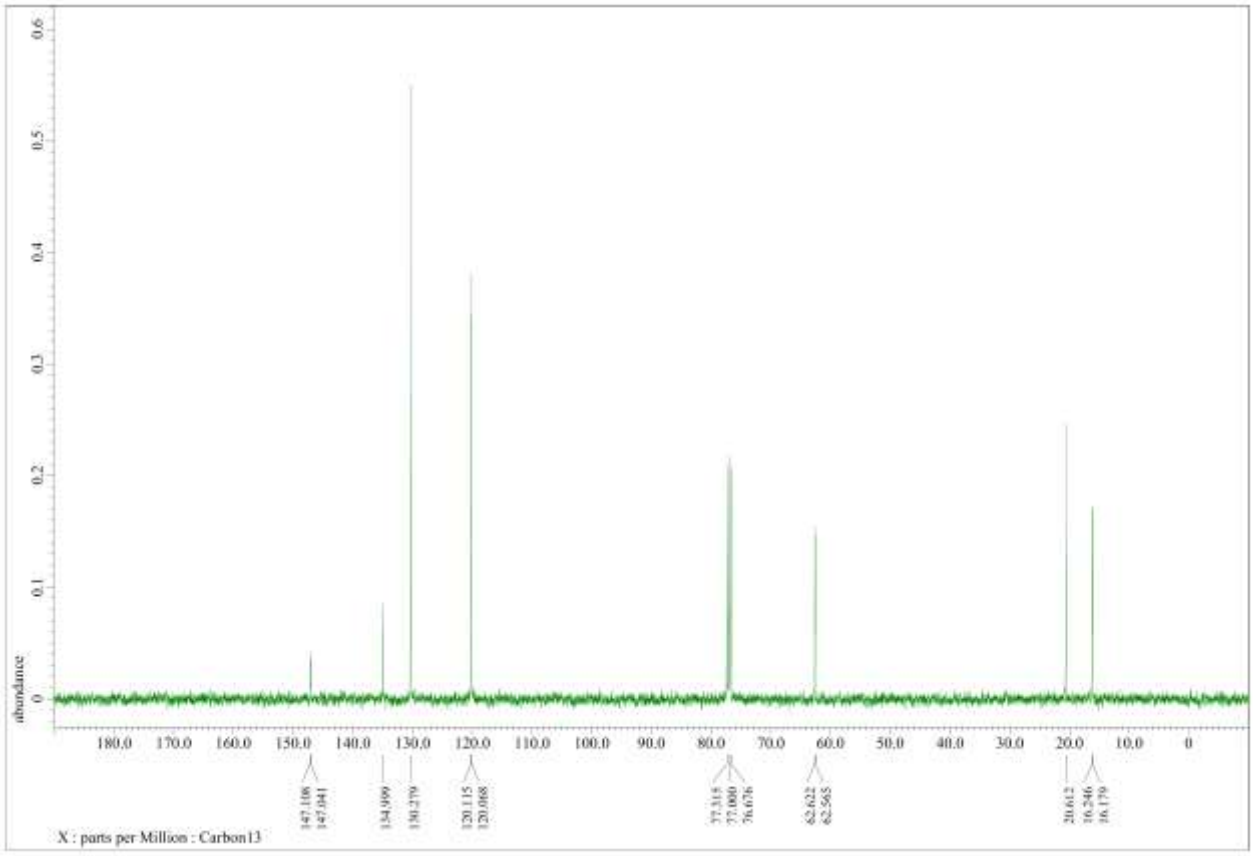



**Ethyl *p*-tolyl phosphonate (2f)**

($^{1}$H NMR, 400 MHz, $CDCl_3$)



($^{13}C$ NMR, 100 MHz, $CDCl_3$)




($^{31}P$ NMR, 162 MHz, $CDCl_3$)