A Metal-Free Entry to Phosphonylated Isoindoles by a Cascade of 5-*exo*-dig cyclization, [1,3]-Alkyl Shift and Aromatization Under Microwave Heating

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Supporting Information Table of Contents

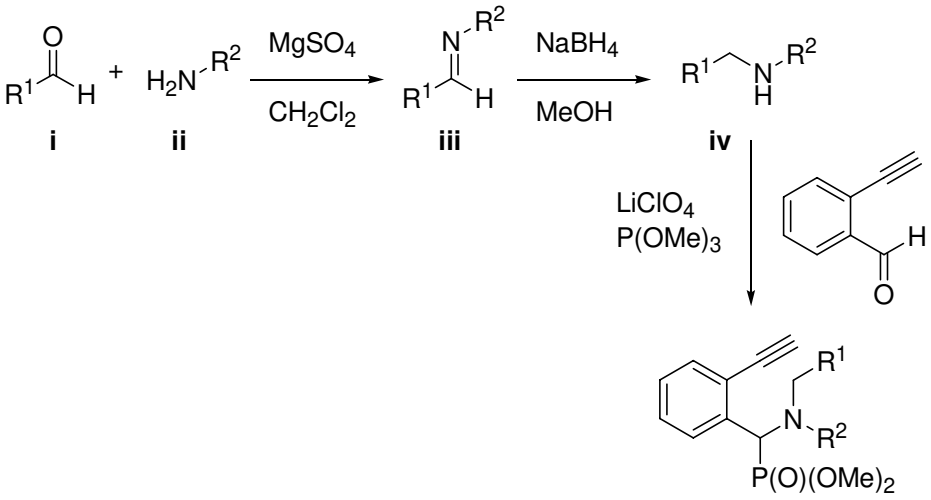
Microwave reactions: all microwave reactions were performed in the *CEM Focused Microwave™ Synthesis System, Model Discover*, with a selectable power output from 0-300 watts. The reactions were performed in 10-mL thick walled Pyrex reaction vessels closed with a Septa cap and equiped with a small stirring bar. The temperature control system uses a non-contact infrared sensor to measure temperature on the bottom of the vessel and is used in a feedback loop with the on-board computer to regulate the temperature from 25-250°C by adjusting the power output (1-watt increments). The pressure control, *IntelliVent™ Pressure Control System*, uses an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring is performed by a rotating magnetic plate located below the floor of the microwave cavity. Cooling of the vessel after the reaction is performed by a stream of clean air onto the vessel which decreases the temperature of a 2mL solution from ~150°C to ~40°C in less then 120 seconds. A ramp time of maximum 5 minutes is used during which the temperature increases from RT to the desired temperature. This temperature is maintained during the course of the reaction for the indicated time.

General remarks: High resolution ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were run on a Jeol JNM-EX 300 NMR. Peak assignments were obtained with the aid of DEPT, 2D-HSQC, 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Low resolution mass spectra were recorded on an Agilent 1100 Series VS (ES, 4000V) mass spectrometer. IR-spectra were obtained from a Perkin Elmer Spectrum One infrared spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Across, particle size 0.035-0.070 mm, Pore diameter ca. 6 nm).

Synthesis of aminophosphonates 2a-m: compounds **2a-m** were synthesized using a three component coupling between secondary amines **iv**, 2-ethynylbenzaldehyde and $P(OMe)_3$ mediated by $LiClO_4$ in diethylether as depicted in Scheme **i** and described by Azizi and coworkers (Azizi, N.; Saidi, M. R. *Tetrahedron* **2003**, *59*, 5329-5332).

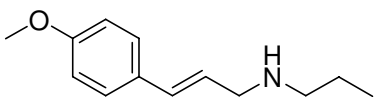
Synthesis of secondary amines iv: All secondary amines were synthesized using a reductive amination, except those used for the synthesis of **2l-m** who are commercially available. A suitable aldehyde **i** was dissolved in dry CH_2Cl_2 (freshly distilled from CaH_2) and 1 equivalent of amine **ii** and 2 equivalents of $MgSO_4$ were added. The mixture was allowed to stir at room temperature for 24 hours. After filtration of the solids and removal of the volatiles, the obtained aldimines **iii** were dissolved in dry MeOH. To this solution 1.1 equivalent of $NaBH_4$ was carefully added and stirring was continued for 4 hours. The reaction was quenched by the addition of $NaHCO_3$ (sat, aq) and the MeOH was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained amines **iv** were directly used for the synthesis of compounds **2.**

Scheme i



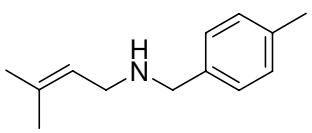
i **ii** **iii** **iv** **2a-m**

N-[(2E)-3-(4-methoxyphenyl)prop-2-enyl]-N-propylamine



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H, CH_3), 1.55 (sextet, *J* = 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 1.94 (s, 1H, NH), 2.63 (t, *J* = 7.3 Hz, 2H, $NC\underline{H}_2CH_2$), 3.40 (dd, *J* = 1.2 Hz, *J* = 6.5 Hz, 2H, $NC\underline{H}_2CH$), 3.80 (s, 3H, $PhOCH_3$), 6.18 (dt, *J* = 15.7 Hz, *J* = 6.5 Hz, 1H, $\underline{H}C$=CHPh), 6.47 (d, *J* = 15.7 Hz, 1H, $\underline{H}C$Ph), 6.84 (d, *J* = 8.8 Hz, 2H, 2 x CH_{arom}), 7.31 (d, *J* = 8.5 Hz, 2H, 2 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.86 ($CH_2\underline{C}H_3$), 23.28 ($\underline{C}H_2CH_3$), 51.40 ($N\underline{C}H_2CH_2$), 52.03 ($N\underline{C}H_2CH$), 55.04 (OCH_3), 113.91 (2 x CH_{arom}), 126.41 ($H\underline{C}$=CHPh), 127.36 (2 x CH_{arom}), 129.96 ($C_{q,arom}$), 130.54 (HC=$\underline{C}$HPh), 159.01 (C_q, Ph). **IR (cm^{-1}) ν_{max}:** 1608 (C=C), 3300 (br NH). **MS (ESI): m/z (%):** No $M+H^+$, 147.2 (M^+-NC_3H_8, 100).

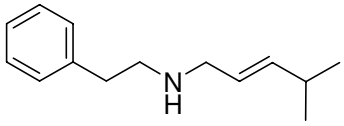
N-(4-methylbenzyl)-N-(3-methylbut-2-enyl)amine



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (br s, 3H, CH_3), 1.72 (br s, 3H, CH_3), 1.77 (s, 1H, NH), 2.33 (s, 3H, CH_3), 3.22 (d, *J* = 6.9 Hz,

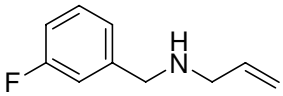
NC$\underline{H}_2$CH), 3.74 (s, 2H, NC$\underline{H}_2$C), 5.28 (t x septet, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H, NCH$_2$C$\underline{H}$), 7.11-7.26 (m, 4H, 4 x CH$_{arom}$). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 14.16 (CH$_2$$\underline{C}H_3$), 16.73 ($\underline{C}CH_3$), 20.65 ($\underline{C}H_2CH_3$), 32.44 (NCH$_2$$\underline{C}H_2$), 49.10 (N$\underline{C}H_2CH_2$), 58.35 (N$\underline{C}H_2$C), 125.51 ($\underline{C}$HPh), 126.20 (CH$_{arom}$), 128.14 (2 x CH$_{arom}$), 128.96 (2 x CH$_{arom}$), 137.33 ($\underline{C}CH_3$), 138.20 (C$_{q,arom}$). **IR (cm^{-1}) ν$_{max}$:** 1655 (C=C), 2950 (br NH). **MS (ESI): m/z (%):** 204.5 (M+H$^+$, 100).

N-[(2E)-4-methylpent-2-enyl]-N-(2-phenylethyl) amine



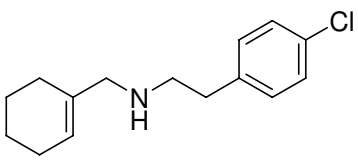
^{1}H-NMR (300 MHz, CDCl$_3$): δ 0.97 (d, *J* = 6.8 Hz, 6H, 2 x CH$_3$), 1.30 (br s, 1H, NH), 2.26 (octet, *J* = 6.8 Hz, 1H, CH), 2.78-2.90 (m, 4H, CH$_2$CH$_2$), 3.19 (d, *J* = 5.8 Hz, 2H, NC$\underline{H}_2$CH), 5.39-5.58 (m, 2H, $\underline{H}$C=C$\underline{H}$Ph), 7.17-7.32 (m, 5H, 5 x CH$_{arom}$). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 22.51 (2 x CH$_3$), 30.91 ($\underline{C}$H(CH$_3$)$_2$), 36.53 ($\underline{C}$H$_2$Ph), 50.65 (N$\underline{C}$H$_2$CH$_2$), 51.75 (N$\underline{C}$H$_2$CH), 125.24 (H$\underline{C}$=CHPh), 126.18 (CH$_{arom}$), 128.38 (2 x CH$_{arom}$), 128.80 (2 x CH$_{arom}$), 139.73 (HC=$\underline{C}$HPh), 140.22 (C$_q$, Ph). **IR (cm^{-1}) ν$_{max}$:** 1604 (C=C), 2958 (br NH). **MS (ESI): m/z (%):** 204.5 (M+H$^+$, 100).

Allyl-(3-fluorobenzyl)amine



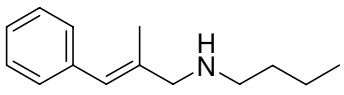
^{1}H-NMR (300 MHz, CDCl$_3$): δ 1.53 (br s, 1H, NH), 3.27 (dt, *J* = 1.2 Hz, *J* = 6.1 Hz, 2H, NC$\underline{H}_2$CH), 3.79 (s, 2H, NC$\underline{H}_2$Ph), 5.31 (dq, *J* = 1.2 Hz, *J* = 10.2 Hz, 1H, HC=C$\underline{H}_A$H$_B$), 5.20 (dq, *J* = 1.2 Hz, *J* = 17.1 Hz, 1H, HC=CH$_A$$\underline{H}_B$), 5.92 (ddt, *J* = 6.1 Hz, *J* = 10.2 Hz, *J* = 17.1 Hz, 1H, $\underline{H}$C=CH$_2$), 6.91-7.32 (m, 4H, 4 x CH$_{arom}$). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 51.74 (N$\underline{C}$H$_2$CH), 52.65 (N$\underline{C}$H$_2$Ph), 113.83 (d, *J* = 21.9 Hz, CH$_{arom}$), 114.96 (d, *J* = 20.8 Hz, CH$_{arom}$), 116.21 (HC=$\underline{C}$H$_2$), 123.70 (d, *J* = 3.5 Hz, CH$_{arom}$), 129.86 (d, *J* = 8.1 Hz, CH$_{arom}$), 136.67 (H$\underline{C}$=CH$_2$), 143.12 (d, *J* = 6.9 Hz, CH$_{q,arom}$), 163.08 (d, *J* = 245.8 Hz, FC$_{q,arom}$). **^{19}F-NMR (282 MHz, CDCl$_3$): δ** -113.41 (dd, *J* = 9.8 Hz, *J* = 16.8 Hz). **IR (cm^{-1}) ν$_{max}$:** 1590 (C=C), 1616 (C=C), 1644 (C=C), 2823 (br NH). **MS (ESI): m/z (%):** 166.3 (M+H$^+$, 100).

N-(4-methylbenzyl)-N-(3-methylbut-2-enyl)amine



^{1}H-NMR (300 MHz, CDCl$_3$): δ 1.48 (br s, 1H, NH), 1.52-1.67 (m, 4H, CH$_2$CH$_2$), 1.87-1.94 (m, 2H, CC$\underline{H}_2$), 1.96-2.05 (m, 2H, HCC$\underline{H}_2$), 2.74-2.84 (m, 4H, NCH$_2$CH$_2$), 3.11 (s, 2H, NCH$_2$), 5.54 (br s, HC), 7.14 (d, 2H, *J* = 8.4 Hz, 2H, 2 x CH$_{arom}$), 7.26 (d, 2H, *J* = 8.4 Hz, 2H, 2 x CH$_{arom}$). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 22.61 (CH$_2$), 22.82 (CH$_2$), 25.14 (HC$\underline{C}$H$_2$), 26.96 (C$\underline{C}$H$_2$), 35.81 ($\underline{C}$H$_2$Ph), 50.32 (N$\underline{C}$H$_2$CH$_2$), 56.13 (N$\underline{C}$H$_2$C), 122.86 (H$\underline{C}$=C), 128.61 (2 x CH$_{arom}$), 130.14 (2 x CH$_{arom}$), 131.93 (ClC$_{q,arom}$), 135.97 (C$_{q,arom}$), 138.77 ($\underline{C}$=CH). **IR (cm^{-1}) ν$_{max}$:** 1670 (C=C), 2925 (NH). **MS (ESI): m/z (%):** 250.2/252.2 (M+H$^+$, 100).

N-butyl-N-[(2E)-2-methyl-3-phenylprop-2-enyl]amine



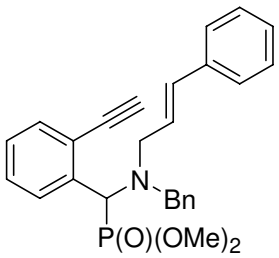
^{1}H-NMR (300 MHz, CDCl$_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.36 (s, 1H, NH), 1.37 (sextet, *J* = 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.47-1.57 (m, 2H, NCH$_2$C$\underline{H}_2$), 1.89 (d, *J* = 1.1 Hz, 3H, CH$_3$), 2.63 (t, *J* = 7.2 Hz, NC$\underline{H}_2$CH$_2$), 3.32 (s, 2H, NC$\underline{H}_2$C), 6.34 (br s, 1H, C$\underline{H}$Ph), 7.17-7.35 (m, 5H, 5 x CH$_{arom}$). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 14.16 (CH$_2$$\underline{C}H_3$), 16.73 ($\underline{C}CH_3$), 20.65 ($\underline{C}H_2CH_3$),

32.44 ($NCH_2\underline{C}H_2$), 49.10 ($N\underline{C}H_2CH_2$), 58.35 ($N\underline{C}H_2C$), 125.51 ($\underline{C}HPh$), 126.20 (CH_{arom}), 128.14 (2 x CH_{arom}), 128.96 (2 x CH_{arom}), 137.33 ($C\underline{C}H_3$), 138.20 ($C_{q,arom}$). **IR (cm^{-1}) ν_{max}:** 1655 (C=C), 2950 (br NH). **MS (ESI): m/z (%):** 204.5 ($M+H^+$, 100).

Typical procedure for the synthesis of compounds 2.

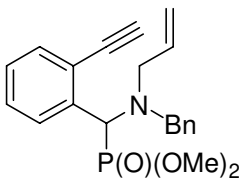
In a dry flask, 2-ethynylbenzaldehyde (3.84 mmol) is dissolved into diethylether (6mL, freshly distilled from Na-metal). To this solution is added $LiClO_4$ (7.5 equiv, 28.8 mmol, dried for 24h at 110°C). This mixture is stirred for 5 minutes. Subsequently secondary amine **iv** is added (2 equiv, 7.69 mmol, dissolved in 1mL dry diethylether). This mixture is stirred for 20 minutes after which $P(OMe)_3$ is added (1.5 equiv, 5.76 mmol). The reaction is stirred for 30 minutes after which water is very carefully added (20mL). The mixture is extracted with CH_2Cl_2 (3 x 20mL) and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained compounds were purified using either crystallization, column chromatography or acid/base extraction.

Dimethyl [benzyl-(3-phenylprop-2-enyl)amino](2-ethynylphenyl)methylphosphonate 2a



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 1H, CCH), 3.20 (dd, *J* = 7.4 Hz, *J* = 14.6 Hz, 1H, $NC\underline{H}_AH_BCH$), 3.45 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.63 (d, *J* = 14.0 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.75 (ddt, *J* = 2.5 Hz, *J* = 5.2 Hz, *J* = 14.6 Hz, 1H, $NCH_A\underline{H}_BCH$), 3.91 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.33 (d, *J* = 14.2 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.12 (d, *J* = 24.0 Hz, 1H, CHP), 6.18 (ddd, *J* = 15.7 Hz, *J* = 7.4 Hz, *J* = 5.2 Hz, 1H, $\underline{H}C$=CHPh), 6.48 (d, *J* = 15.7 Hz, 1H, $\underline{H}CPh$), 7.17-7.58 (m, 13H, 13 x CH_{arom}), 8.00 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 53.04 (d, *J* = 6.9 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 53.70 (d, *J* = 8.1 Hz, $N\underline{C}H_2CH$), 55.48 (d, *J* = 6.9 Hz, $N\underline{C}H_2Ph$), 58.85 (d, *J* = 160.1 Hz, CHP), 82.11 ($\underline{C}CH$), 82.17 ($C\underline{C}H$), 124.15 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 126.34 (2 x CH_{arom}), 126.86 (CH_{arom}), 127.35 (CH_{arom}), 127.70 ($H\underline{C}$=CHPh), 128.11 (CH_{arom}), 128.18 (2 x CH_{arom}), 128.57 (3 x CH_{arom}), 128.72 (3 x CH_{arom}), 130.73 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 132.58 ($\underline{C}HPh$), 133.45 (PCHCC$\underline{C}$H), 135.98 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 137.38 (C_q, Ph), 140.00 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.47. **IR (cm^{-1}) ν_{max}:** 1032 (P-O), 1056 (P-O), 1248 (P=O), 1641 (C=C), 2090 (alkyne). **MS (ESI): m/z (%):** 446.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.18. **Yield:** 68%.

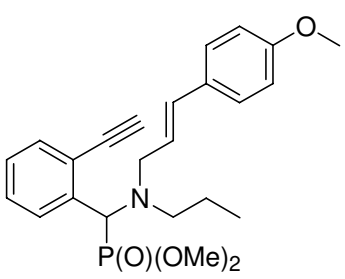
Dimethyl [allyl(benzyl)amino](2-ethynylphenyl)methylphosphonate 2b



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 1H, CCH), 3.06 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 1H, $NC\underline{H}_AH_BCH$), 3.44 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.52 (d, *J* = 14.2 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.66 (ddd, *J* = 1.5 Hz, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H, $NCH_A\underline{H}_BCH$), 3.96 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.23 (d, *J* = 14.2 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.03 (d, *J* = 24.5 Hz, 1H, CHP), 5.09 (d, *J* = 10.8 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.18 (dd, *J* = 1.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.83 (dddd, *J* = 4.5 Hz, *J* = 7.2 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz, 1H, $\underline{H}C=CH_2$), 7.19-7.44 (m, 7H, 7 x CH_{arom}), 7.56 (d, *J* = 7.7 Hz, 1H, PCHCC$\underline{H}$), 7.97 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 52.94 (d, *J* = 6.9 Hz, OCH_3), 53.72 (d, *J* = 6.9 Hz, OCH_3), 54.28 (d, *J* =

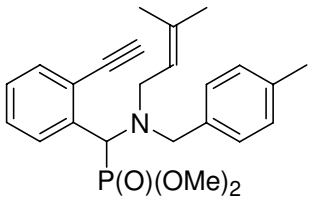
8.1 Hz, NCH$_2$CH), 55.18 (d, *J* = 8.1 Hz, NCH$_2$Ph), 58.64 (d, *J* = 161.5 Hz, CHP), 81.98 (CCH), 82.08 (CCH), 117.41 (HC=CH$_2$), 124.18 (d, *J* = 12.7 Hz, PCHCC), 126.80 (CH$_{para}$, Ph), 128.11 (3 x CH$_{arom}$), 128.64 (3 x CH$_{arom}$), 130.74 (d, *J* = 3.5 Hz, PCHCCH), 133.39 (PCHCCCH), 135.77 (d, *J* = 5.8 Hz, PCHC), 135.99 (HC=CH$_2$), 139.96 (C$_q$, Ph). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 26.25. **IR (cm^{-1}) ν$_{max}$:** 1035 (P-O),1058 (P-O), 1246 (P=O), 1642 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 370.2 (M+H$^+$, 100). **MP (°C):** 86-87. **Chromatography:** Hex/EtOAc 4/6 R$_f$ = 0.27. **Yield:** 59%.

Dimethyl (2-ethynylphenyl) [(propyl)[(2E)-3-(4-methoxyphenyl)prop-2-enyl]amino] methylphosphonate 2c



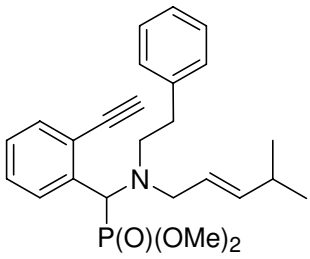
^{1}H-NMR (300 MHz, CDCl$_3$): δ 0.86 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.55 (sextet, *J* = 7.3 Hz, 2H, CH$_2$CH$_3$), 2.51 (ddd, *J* = 5.5 Hz, *J* = 7.3 Hz, *J* = 12.9 Hz, 1H, NCH$_A$H$_B$CH$_2$), 2.74-2.81 (m, 1H, NCH$_A$H$_B$CH$_2$), 3.07 (dd, *J* = 7.6 Hz, *J* = 14.3 Hz, 1H, NCH$_A$H$_B$CH), 3.22 (s, 1H, CCH), 3.47 (d, *J* = 9.6 Hz, 3H, OCH$_3$), 3.79 (s, 3H, PhOCH$_3$), 3.90-3.94 (m, 1H, NCH$_A$H$_B$CH), 3.92 (d, *J* = 10.5 Hz, 3H, OCH$_3$), 5.02 (d, *J* = 24.8 Hz, 1H, CHP), 6.04 (ddd, *J* = 14.7 Hz, *J* = 7.6 Hz, *J* = 5.5 Hz, 1H, HC=CHPh), 6.41 (d, *J* = 14.7 Hz, 1H, HCPh), 6.83 (d, *J* = 8.2 Hz, 2H, 2 x CH$_{arom}$), 7.25-7.41 (m, 2H, 2 x CH$_{arom}$), 7.26 (d, *J* = 8.3 Hz, 2H, 2 x CH$_{arom}$), 7.56 (d, *J* = 7.4 Hz, 1H, PCHCCH), 7.93 (d, *J* = 7.7 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 11.74 (CH$_2$CH$_3$), 21.31 (CH$_2$CH$_3$), 52.76 (d, *J* = 6.9 Hz, OCH$_3$), 53.07 (d, *J* = 10.4 Hz, NCH$_2$CH$_2$), 54.10 (d, *J* = 6.9 Hz, OCH$_3$), 54.20 (d, *J* = 5.8 Hz, NCH$_2$CH), 58.95 (d, *J* = 162.7 Hz, CHP), 81.54 (CCH), 82.38 (CCH), 114.00 (2 x CH$_{arom}$), 124.01 (d, *J* = 12.7 Hz, PCHCC), 126.32 (HC=CHPh), 127.42 (2 x CH$_{arom}$), 127.91 (CH$_{arom}$), 128.66 (CH$_{arom}$), 130.32 (C$_{q,arom}$), 130.73 (d, *J* = 3.5 Hz, PCHCCH), 131.30 (HC=CHPh), 133.39 (PCHCCCH), 136.12 (d, *J* = 6.9 Hz, PCHC), 159.01 (C$_q$, Ph). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 26.11. **IR (cm^{-1}) ν$_{max}$:** 1034 (P-O),1058 (P-O), 1248 (P=O), 1607 (C=C), 2098 (alkyne). **MS (ESI): m/z (%):** 428.3 (M+H$^+$, 100). **MP (°C):** 99-101. **Yield:** 81%.

Dimethyl [(4-methylbenzyl)-(3-methylbut-2-enyl)amino] (2-ethynylphenyl) methylphosphonate 2d



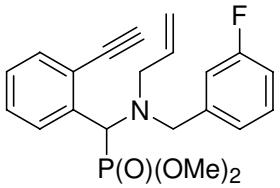
^{1}H-NMR (300 MHz, CDCl$_3$): δ 1.41 (s, 3H, CH$_3$), 1.65 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 3.03 (dd, *J* = 6.7 Hz, *J* = 13.5 Hz, 1H, NCH$_A$H$_B$CH), 3.06 (s, 1H, CCH), 3.40-3.51 (m, 1H, NCH$_A$H$_B$CH), 3.44 (d, *J* = 10.4 Hz, 3H, OCH$_3$), 3.53 (d, *J* = 13.8 Hz, 1H, NCH$_A$H$_B$Ph), 3.89 (d, *J* = 10.5 Hz, 3H, OCH$_3$), 4.15 (d, *J* = 13.8 Hz, 1H, NCH$_A$H$_B$Ph), 5.04 (d, *J* = 24.2 Hz, 1H, CHP), 5.26 (t*septet, *J* = 6.6 Hz, *J* = 1.2 Hz, 1H, HC=C), 7.06-7.43 (m, 6H, 6 x CH$_{arom}$), 7.55 (d, *J* = 7.7 Hz, 1H, PCHCCH), 7.96 (d, *J* = 8.0 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 18.19 (CH$_3$), 21.22 (CH$_3$), 26.06 (CH$_3$), 49.05 (d, *J* = 9.2 Hz, NCH$_2$CH), 52.87 (d, *J* = 6.9 Hz, OCH$_3$), 53.75 (d, *J* = 6.9 Hz, OCH$_3$), 55.15 (d, *J* = 8.1 Hz, NCH$_2$Ph), 58.86 (d, *J* = 160.4 Hz, CHP), 81.77 (CCH), 82.91 (CCH), 122.14 (HC=C), 124.08 (d, *J* = 11.5 Hz, PCHCC), 127.88 (CH$_{arom}$), 128.63 (CH$_{arom}$), 128.70 (4 x CH$_{arom}$), 130.79 (d, *J* = 3.5 Hz, PCHCCH), 133.33 (PCHCCCH), 134.95 (C$_{q,arom}$), 136.17 (d, *J* = 6.8 Hz, PCHC), 136.28 (C$_q$), 137.19 (C$_{q,arom}$). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 26.56. **IR (cm^{-1}) ν$_{max}$:** 1035 (P-O), 1057 (P-O), 1245 (P=O), 1637 (C=C), 2101 (alkyne). **MS (ESI): m/z (%):** 412.3 (M+H$^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R$_f$ = 0.32. **MP (°C):** 101.5. **Yield:** 48%.

Dimethyl (2-ethynylphenyl)[[(2E)-4-methylpent-2-enyl(2-phenylethyl)]amino] methylphosphonate 2e



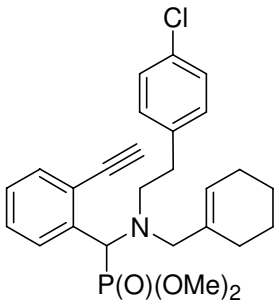
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.9 Hz, 3H, CH_3), 0.96 (d, *J* = 6.9 Hz, 3H, CH_3), 2.26 (octet, *J* = 6.9 Hz, 1H, CH), 2.69-2.85 (m, 3H, $C\underline{H}_2Ph$ + $NC\underline{H}_AH_BCH_2$), 2.99-3.11 (m, 2H, $NCH_A\underline{H}_BCH_2$ + $NC\underline{H}_AH_BCH$), 3.33 (s, 1H, CCH), 3.45 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.80 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.76-3.84 (m, 1H, $NCH_A\underline{H}_BCH$), 5.05 (d, *J* = 24.5 Hz, 1H, CHP), 5.33 (ddd, *J* = 15.4 Hz, *J* = 7.0 Hz, *J* = 5.6 Hz, 1H, $NCH_2C\underline{H}$), 5.52 (dd, *J* = 15.4 Hz, *J* = 6.9 Hz, 1H, $C\underline{H}CH(CH_3)_2$), 7.12-7.51 (m, 7H, 7 x CH_{arom}), 7.55 (d, *J* = 7.4 Hz, 1H, PCHCC$\underline{H}$), 7.89 (d, *J* = 7.7 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 22.51 (CH_3), 22.56 (CH_3), 30.99 (CH), 34.23 ($\underline{C}H_2Ph$), 52.49 (d, *J* = 10.4 Hz, $N\underline{C}H_2CH_2$), 52.80 (d, *J* = 8.1 Hz, OCH_3), 54.16 (d, *J* = 5.8 Hz, $N\underline{C}H_2CH$ + OCH_3), 59.51 (d, *J* = 163.8 Hz, CHP), 81.91 (C$\underline{C}$H), 82.55 ($\underline{C}$CH), 123.81 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 124.78 ($NCH_2\underline{C}H$), 125.89 (CH_{arom}), 127.96 (CH_{arom}), 128.26 (2 x CH_{arom}), 128.78 (CH_{arom}), 129.18 (2 x CH_{arom}), 130.60 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.44 (CH_{arom}), 136.25 (d, *J* = 4.6 Hz, PCH$\underline{C}$), 140.54 ($H\underline{C}CH(CH_3)_2$), 140.58 ($C_{q,arom}$). **^{31}P-NMR (MHz, $CDCl_3$): δ** 25.95. **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1060 (P-O), 1246 (P=O), 1604 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 426.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.56. **Yield:** 56%.

Dimethyl [allyl(3-fluorobenzyl)amino](2-ethynylphenyl)methylphosphonate 2f



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.05 (dd, *J* = 7.6 Hz, *J* = 14.3 Hz, 1H, $NC\underline{H}_AH_BCH$), 3.06 (s, 1H, CCH), 3.44 (d, *J* = 10.7 Hz, 3H, OCH_3), 3.53 (d, *J* = 14.4 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.71 (ddd, *J* = 2.0 Hz, *J* = 4.6 Hz, *J* = 14.3 Hz, 1H, $NCH_A\underline{H}_BCH$), 3.91 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.21 (d, *J* = 14.4 Hz, 1H, $NCH_A\underline{H}_BPh$), 4.99 (d, *J* = 24.8 Hz, 1H, CHP), 5.10 (dd, *J* = 10.6 Hz, *J* = 1.0 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.18 (dd, *J* = 1.0 Hz, *J* = 17.0 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.83 (dddd, *J* = 4.6 Hz, *J* = 7.6 Hz, *J* = 10.6 Hz, *J* = 17.0 Hz, 1H, $\underline{H}C=CH_2$), 6.87-7.44 (m, 6H, 6 x CH_{arom}), 7.56 (d, *J* = 7.7 Hz, 1H, PCHCC$\underline{H}$), 7.96 (d, *J* = 7.7 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 53.00 (d, *J* = 6.9 Hz, OCH_3), 53.62 (d, *J* = 6.9 Hz, OCH_3), 54.47 (d, *J* = 6.9 Hz, $N\underline{C}H_2CH$), 54.65 (d, *J* = 8.1 Hz, $N\underline{C}H_2Ph$), 58.53 (d, *J* = 161.5 Hz, CHP), 81.91 ($\underline{C}$CH), 82.11 (C$\underline{C}$H), 113.62 (d, *J* = 20.8 Hz, CH_{arom}), 115.26 (d, *J* = 21.9 Hz, CH_{arom}), 117.60 ($HC=\underline{C}H_2$), 124.08 (d, *J* = 2.3 Hz, CH_{arom}), 124.18 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 128.17 (CH_{arom}), 128.75 (CH_{arom}), 129.38 (d, *J* = 8.1 Hz, CH_{arom}), 130.64 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.45 (PCHCC$\underline{C}$H), 135.48 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 135.79 ($H\underline{C}=CH_2$), 142.90 (d, *J* = 6.9 Hz, C_q, Ph), 163.03 (d, *J* = 224.6 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.03. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -113.90 (dt, *J* = 6.6 Hz, *J* = 9.2 Hz). **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1058 (P-O), 1248 (P=O), 1615 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 388.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 6/4 R_f = 0.13. **Yield:** 72%.

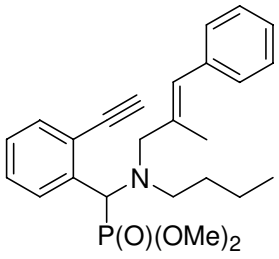
Dimethyl [[(cyclohex-1-en-1-ylmethyl)[2-(4-chlorophenyl)ethyl]]amino] (2-ethynylphenyl)methylphosphonate 2g



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.53-1.61 (m, 4H, CH_2CH_2), 1.86-1.97 (m, 4H, HCC$\underline{H}_2$ + CC$\underline{H}_2$), 2.57-2.68 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$), 2.74 (t, *J* = 6.6 Hz, 2H, NCH$_2$C$\underline{H}_2$), 2.84 (d, *J* = 12.9 Hz, NC$\underline{H}_A$H$_B$), 2.96-3.05 (m, 1H, NCH$_A\underline{H}_B$CH$_2$), 3.31 (s, 1H, CH_{alkyne}), 3.44 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.65 (d, *J* = 12.9 Hz, NCH$_A\underline{H}_B$), 3.82 (d, *J* = 10.7 Hz, 3H, OCH_3), 5.03 (d, *J* = 24.8 Hz, 1H, CHP), 5.52 (br s, 1H, CH), 7.09 (d, *J* = 8.4 Hz, 2H, 2 x CH_{arom}), 7.21 (d, *J* = 8.4 Hz, 2H, 2 x CH_{arom}), 7.29-7.39 (m, 2H, 2 x CH_{arom}), 7.57 (d, *J* = 7.4 Hz, 1H, PCHCC$\underline{H}$), 7.85 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 22.73 (CH_2), 22.91 (CH_2), 25.38 (CH_2), 26.77 (CH_2), 33.74 ($\underline{C}H_2$Ph), 52.58 (d, *J* = 10.4 Hz, N$\underline{C}H_2CH_2$), 52.91 (d, *J* = 6.9 Hz, OCH_3), 53.59 (d, *J* = 6.9 Hz, OCH_3), 59.00 (d, *J* = 162.7 Hz, CHP), 59.26 (d, *J* = 5.8 Hz, N$\underline{C}H_2$C), 81.71 (C$\underline{C}$H), 82.55 ($\underline{C}$CH), 123.87 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 124.72 (CH), 127.96 (CH_{arom}), 128.32 (2 x CH_{arom}), 128.73 (CH_{arom}), 130.37 (2 x CH_{arom}), 130.64 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 131.57 ($ClC_{q,arom}$), 133.44 (CH_{arom}), 135.96 ($C_{q,arom}$), 136.06 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 139.24 ($\underline{C}$=CH). **^{31}P-NMR (MHz, $CDCl_3$): δ** 26.21. **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1060 (P-O), 1244 (P=O), 2097 (alkyne). **MS (ESI): m/z (%):** 472.2/474.2 ($M+H^+$, 100). **MP (°C):** 103-104. **Yield:** 59%.

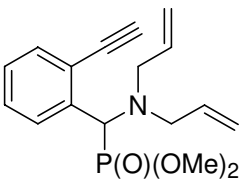
Dimethyl (2-ethynylphenyl){butyl[(2E)-2-methyl-3-phenylprop-2-enyl]amino} methylphosphonate 2h

For purification of **2h**: The mixture obtained after drying with $MgSO_4$ was dissolved in ether (100 mL) and washed twice with HCl (3N, 25 mL) to remove the excess of secondary amine. Afterwards the organic layer is made basic with NaOH (aq, 3N),extracted with ether three times (50 mL) and dried with $MgSO_4$.



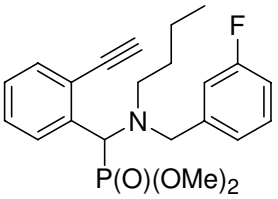
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.20-1.43 (m, 2H, $C\underline{H}_2CH_3$), 1.54 (m, 2H, NCH$_2$C$\underline{H}_2$), 1.92 (s, 3H, CCH_3), 2.44 (ddd, *J* = 6.1 Hz, *J* = 6.9 Hz, *J* = 12.9 Hz, 1H, NC$\underline{H}_A$H$_B$CH$_2$), 2.81-2.92 (m, 1H, NCH$_A\underline{H}_B$CH$_2$), 2.90 (d, *J* = 13.8 Hz, 1H, NC$\underline{H}_A$H$_B$C), 3.21 (s, 1H, CCH), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.84 (d, *J* = 13.8 Hz, 1H, NCH$_A\underline{H}_B$C), 3.91 (d, *J* = 10.7 Hz, 3H, OCH_3), 5.05 (d, *J* = 25.6 Hz, 1H, CHP), 6.43 (s, 1H, HC=C), 7.17-7.43 (m, 7H, 7 x CH_{arom}), 7.57 (d, *J* = 7.4 Hz, 1H, PCHCC$\underline{H}$), 7.93 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.27 ($CH_2\underline{C}H_3$), 16.65 ($C\underline{C}H_3$), 20.56 ($\underline{C}H_2CH_3$), 30.47 (NCH$_2\underline{C}H_2$), 51.00 (d, *J* = 11.5 Hz, N$\underline{C}H_2CH_2$), 52.84 (d, *J* = 6.9 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 58.30 (d, *J* = 163.8 Hz, CHP), 60.97 (d, *J* = 5.8 Hz, N$\underline{C}H_2$C), 81.45 (C$\underline{C}$H), 82.32 ($\underline{C}$CH), 124.19 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 126.11 (H$\underline{C}$=C), 126.81 (CH_{arom}), 127.94 (CH_{arom}), 128.12 (2 x CH_{arom}), 128.63 (CH_{arom}), 128.93 (2 x CH_{arom}), 130.80 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.42 (PCHCC$\underline{C}$H), 135.76 (d, *J* = 6.9 Hz, PCH$\underline{C}$), 137.35 ($\underline{C}$=CH), 138.45 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.38. **IR (cm^{-1}) ν_{max}:** 1036 (P-O),1059 (P-O), 1244 (P=O), 1598 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 426.2 ($M+H^+$, 100). **Yield:** 88%.

Dimethyl (diallylamino)(2-ethynylphenyl)methylphosphonate 2i



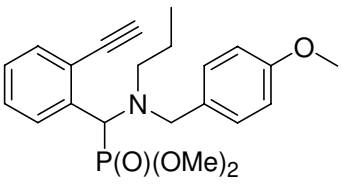
^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.06 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 2H, 2 x $NC\underline{H}_AH_BCH$), 3.26 (s, 1H, CCH), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.66 (ddt, *J* = 2.2 Hz, *J* = 2.5 Hz, *J* = 14.6 Hz, 2H, 2 x $NCH_A\underline{H}_BCH$), 3.90 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.97 (d, *J* = 24.2 Hz, 1H, CHP), 5.10 (d, *J* = 10.5 Hz, 2H, 2 x $HC{=}C\underline{H}_aH_b$), 5.19 (d, *J* = 17.2 Hz, 2H, 2 x $HC{=}CH_a\underline{H}_b$), 5.75-5.88 (m, 2H, 2 x $\underline{H}C{=}CH_2$), 7.27-7.41 (m, 2H, 2 x CH_{arom}), 7.72 (d, *J* = 7.5 Hz, 1H, PCHCC$\underline{H}$), 7.92 (d, *J* = 7.7 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 52.82 (d, *J* = 6.9 Hz, OCH_3), 54.05 (d, *J* = 8.1 Hz, 2 x $N\underline{C}H_2CH$), 54.15 (d, *J* = 6.9 Hz, OCH_3), 58.91 (d, *J* = 163.8 Hz, CHP), 81.97 (C$\underline{C}$H), 82.26 ($\underline{C}$CH), 117.04 (2 x HC=$\underline{C}H_2$), 123.95 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 127.99 (CH_{arom}), 128.70 (CH_{arom}), 130.66 (d, *J* = 4.6 Hz, PCHC$\underline{C}$H), 133.42 (CH_{arom}), 136.00 (d, *J* = 4.6 Hz, PCH$\underline{C}$), 136.15 (2 x H$\underline{C}{=}CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.16. **IR (cm^{-1}) ν_{max}:** 1047 (br P-O), 1239 (P=O), 1642 (C=C), 2095 (alkyne). **MS (ESI): m/z (%):** 320.2 ($M+H^+$, 100). **MP (°C):** 97. **Yield:** 79%.

Dimethyl (2-ethynylphenyl) [(butyl)(3-fluorobenzyl)amino]methylphosphonate 2j



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.4 Hz, 3H, CH_3), 1.09-1.36 (m, 2H, $C\underline{H}_2CH_3$), 1.48 (p, *J* = 7.2 Hz, 2H, $NCH_2C\underline{H}_2$), 2.45 (dt, *J* = 6.6 Hz, *J* = 13.0 Hz, 1H, $NC\underline{H}_AH_BCH_2$), 2.70-2.80 (m, 1H, $NCH_A\underline{H}_BCH_2$), 3.14 (s, 1H, CCH), 3.37 (d, *J* = 14.3 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.92 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.37 (d, *J* = 14.3 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.02 (d, *J* = 25.3 Hz, 1H, CHP), 6.87-7.43 (m, 6H, 6 x CH_{arom}), 7.57 (d, *J* = 7.5 Hz, 1H, PCHCC$\underline{H}$), 7.95 (d, *J* = 7.7 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.10 (CH_3), 20.32 ($\underline{C}H_2CH_3$), 30.32 ($NCH_2\underline{C}H_2$), 51.32 (d, *J* = 10.4 Hz, $N\underline{C}H_2CH_2$), 52.92 (d, *J* = 8.1 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 55.61 (d, *J* = 5.8 Hz, $N\underline{C}H_2Ph$), 58.30 (d, *J* = 163.8 Hz, CHP), 81.62 (C$\underline{C}$H), 82.11 ($\underline{C}$CH), 113.56 (d, *J* = 20.8 Hz, CH_{arom}), 115.37 (d, *J* = 21.9 Hz, CH_{arom}), 124.17 (d, *J* = 2.3 Hz, CH_{arom}), 124.23 (d, *J* = 11.5 Hz, PCHC$\underline{C}$), 128.09 (CH_{arom}), 128.70 (CH_{arom}), 129.38 (d, *J* = 8.1 Hz, CH_{arom}), 130.71 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.47 (PCHCC$\underline{C}$H), 135.47 (d, *J* = 6.9 Hz, PCH$\underline{C}$), 143.36 (d, *J* = 6.9 Hz, C_q, Ph), 163.00 (d, *J* = 224.6 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.37. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -114.00 (dt, *J* = 5.3 Hz, *J* = 9.5 Hz). **IR (cm^{-1}) ν_{max}:** 1036 (P-O),1058 (P-O), 1249 (P=O), 1614 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 404.2 ($M+H^+$, 100). **MP (°C):** 67. **Yield:** 65%.

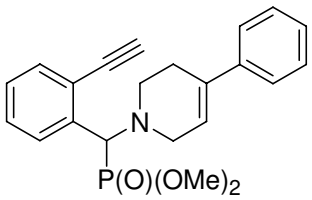
Dimethyl (2-ethynylphenyl)[(4-methoxybenzyl)(propyl)amino]methylphosphonate 2k



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.77 (t, *J* = 7.3 Hz, 3H, CH_3), 1.42-1.57 (m, 2H, $C\underline{H}_2CH_3$), 2.41 (ddd, *J* = 4.8 Hz, *J* = 8.3 Hz, *J* = 13.0 Hz, 1H, $NC\underline{H}_AH_BCH_2$), 2.61-2.72 (m, 1H, $NCH_A\underline{H}_BCH_2$), 3.16 (s, 1H, CCH), 3.27 (d, *J* = 13.5 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.47 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.79 (s, 3H, $PhOC\underline{H}_3$), 3.91 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.32 (d, *J* = 13.5 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.04 (d, *J* = 25.3 Hz, 1H, CHP), 6.83 (d, *J* = 8.7 Hz, 2H, 2 x CH_{arom}), 7.26-7.56 (m, 2H, 2 x CH_{arom}), 7.28 (d, *J* = 8.7 Hz, 2H, 2 x CH_{arom}), 7.57 (d, *J* = 6.0 Hz, 1H, PCHCC$\underline{H}$), 7.96 (d, *J* = 7.7 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.66 ($CH_2\underline{C}H_3$), 21.17 ($\underline{C}H_2CH_3$), 52.82 (d, *J* = 6.9 Hz, OCH_3), 52.98 (d, *J* = 10.4 Hz, $N\underline{C}H_2CH_2$), 53.80 (d, *J* = 6.9 Hz, OCH_3), 55.31 ($PhO\underline{C}H_3$), 55.39 (d, *J* = 5.8 Hz, NCH_2), 58.44 (d, *J* = 163.8 Hz, CHP), 81.50 (C$\underline{C}$H),

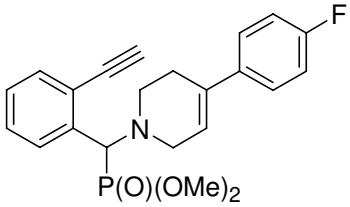
82.20 (CCH), 113.42 (2 x CH_{arom}), 124.19 (d, *J* = 12.7 Hz, PCHCC), 127.97 (CH_{arom}), 128.66 (CH_{arom}), 129.89 (2 x CH_{arom}), 130.82 (d, *J* = 3.5 Hz, PCHCCH), 132.37 ($C_{q,arom}$), 133.41 ($C_{q,arom}$), 135.77 (d, *J* = 6.9 Hz, PCHC), 158.51 ($C_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.31. **IR (cm^{-1}) ν_{max}:** 1034 (P-O), 1057 (P-O), 1246 (P=O), 1612 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 402.2 ($M+H^+$, 100). **MP (°C):** 82. **Yield:** 71%.

Dimethyl [(2-ethynylphenyl) -(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)methyl]-phosphonate 2l



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.44-2.66 (m, 2H, NCH_2CH_2), 2.75 (ddd, *J* = 4.4 Hz, *J* = 7.3 Hz, *J* = 11.4 Hz, 1H, $NCH_AH_BCH_2$), 3.31 (dt, *J* = 4.6 Hz, *J* = 11.4 Hz, 1H, $NCH_AH_BCH_2$), 3.34 (s, 1H, CCH), 3.43 (d, *J* = 2.9 Hz, 1H, NCH_AH_B), 3.44 (d, *J* = 2.9 Hz, 1H, NCH_AH_B), 3.50 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.92 (d, *J* = 22.0 Hz, 1H, CHP), 6.02 (br s, 1H, CH), 7.18-7.41 (m, 7H, 7 x CH_{arom}), 7.57 (dt, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H, PCHCCH), 7.94 (dt, *J* = 7.9 Hz, *J* = 2.5 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 28.29 (NCH_2CH_2), 47.97 (d, *J* = 6.9 Hz, NCH_2CH_2), 51.57 (d, *J* = 11.5 Hz, NCH_2CH), 53.06 (d, *J* = 8.1 Hz, OCH_3), 54.06 (d, *J* = 6.9 Hz, OCH_3), 63.07 (d, *J* = 161.5 Hz, CHP), 82.15 (CCH), 82.24 (CCH), 122.00 (HC=C), 123.85 (d, *J* = 11.5 Hz, PCHCC), 124.84 (2 x CH_{arom}), 127.02 (CH_{arom}), 128.06 (CH_{arom}), 128.37 (2 x CH_{arom}), 128.83 (CH_{arom}), 130.33 (d, *J* = 3.5 Hz, PCHCCH), 133.27 (PCHCCCH), 134.54 ($C_{q,arom}$), 135.12 (d, *J* = 2.0 Hz, PCHC), 140.80 (HC=C). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 24.96. **IR (cm^{-1}) ν_{max}:** 1036 (P-O), 1058 (P-O), 1245 (P=O), 1654 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 382.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.16. **Yield:** 75%.

Dimethyl [(2-ethynylphenyl) -(4-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl)methyl]-phosphonate 2m

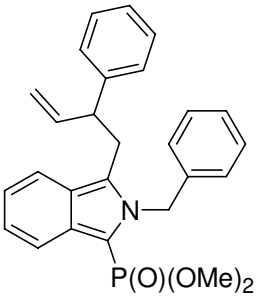


^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42-2.61 (m, 2H, NCH_2CH_2), 2.74 (ddd, *J* = 4.4 Hz, *J* = 7.4 Hz, *J* = 11.4 Hz, 1H, $NCH_AH_BCH_2$), 3.30 (dt, *J* = 3.3 Hz, *J* = 11.4 Hz, 1H, $NCH_AH_BCH_2$), 3.34 (s, 1H, CCH), 3.43 (br s, 2H, NCH_2), 3.50 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.91 (d, *J* = 22.0 Hz, 1H, CHP), 5.96 (br s, 1H, CH), 6.98 (t, *J* = 8.5 Hz, 2H, 2 x CH_{arom}), 7.26-7.44 (m, 4H, 4 x CH_{arom}), 7.57 (d, *J* = 7.6 Hz, 1H, PCHCCH), 7.93 (d, *J* = 8.0 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 28.53 (NCH_2CH_2), 47.91 (d, *J* = 8.1 Hz, NCH_2CH_2), 51.49 (d, *J* = 11.5 Hz, NCH_2CH), 53.09 (d, *J* = 8.1 Hz, OCH_3), 54.00 (d, *J* = 6.9 Hz, OCH_3), 63.04 (d, *J* = 161.5 Hz, CHP), 82.12 (CCH), 82.24 (CCH), 115.13 (d, *J* = 20.8 Hz, 2 x CH_{arom}), 121.86 (HC=C), 123.83 (d, *J* = 11.5 Hz, PCHCC), 126.36 (d, *J* = 20.8 Hz, 2 x CH_{arom}), 128.08 (CH_{arom}), 128.84 (CH_{arom}), 130.30 (d, *J* = 3.5 Hz, PCHCCH), 133.28 (PCHCCCH), 133.64 (HC=C), 135.11 ($C_{q,arom}$), 136.91 (d, *J* = 3.5 Hz, PCHC), 162.06 (d, *J* = 245.8 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 24.93. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -115.83 (tt, *J* = 9.8 Hz, *J* = 5.7 Hz). **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1057 (P-O), 1227 (P=O), 1602 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 400.2 ($M+H^+$, 100). **MP (°C):** 76-77. **Chromatography:** Hex/EtOAc 4/6 R_f = 0.21. **Yield:** 62%.

Typical procedure for the synthesis of isoindoles 4 and 14a-b.

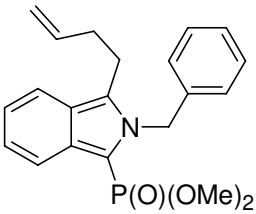
In a dry reaction tube, compounds **2** (0.5 mmol) are dissolved into a mixture of acetonitrile (3mL) and benzene (3mL). This solution is heated in a microwave to 165°C for 60 minutes. After this the progress of the reaction is checked by ^{31}P NMR from a sample take directly from the mixture. If this reveals the presence of remaining starting material, the reaction is placed back inside the microwave and is again heated to 165°C. After complete conversion the compound is coated on silica gel by removal of the volatiles in vacuo and purified by column chromatography.

Dimethyl 2-benzyl-3-(2-phenylbut-3-enyl)-2H-isoindol-1-ylphosphonate 4a



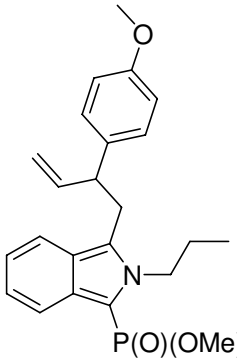
^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.17 (dd, *J* = 7.5 Hz, *J* = 15.1 Hz, 1H, C$\underline{H}_A$H$_B$CH), 3.43 (dd, *J* = 7.5 Hz, *J* = 15.1 Hz, 1H, CH$_A\underline{H}_B$CH), 3.48 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.49 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.62 (ps q, *J* = 7.5 Hz, C$\underline{H}$Ph), 4.98 (1H, d, *J* = 17.1 Hz, HC=C$\underline{H}_A$H$_B$), 5.07 (1H, d, *J* = 10.3 Hz, HC=CH$_A\underline{H}_B$), 5.19 (d, *J* = 16.8 Hz, 1H, NC$\underline{H}_A$H$_B$Ph), 5.53 (d, *J* = 16.8 Hz, 1H, NCH$_A\underline{H}_B$Ph), 6.10 (ddd, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 7.5 Hz, 1H, $\underline{H}C=CH_2$), 6.74-7.53 (m, 13H, 13 x CH_{arom}), 7.95 (d, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 32.18 ($\underline{C}H_2CH$), 49.63 (NCH_2), 50.20 ($\underline{C}HPh$), 52.33 (d, *J* = 3.5 Hz, 2 x OCH_3), 103.63 (d, *J* = 231.9 Hz, P$\underline{C}$), 115.71 (HC=$\underline{C}H_2$), 119.89 (CH_{arom}), 120.15 (CH_{arom}), 121.13 (CH_{arom}), 124.05 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.84 (CH_{arom}), 125.74 (2 x CH_{arom}), 127.02 (CH_{arom}), 127.39 (CH_{arom}), 127.65 (2 x CH_{arom}), 128.69 (4 x CH_{arom}), 131.07 (d, *J* = 9.2 Hz, N$\underline{C}$), 133.00 (d, *J* = 17.3 Hz, PC$\underline{C}$), 137.79 (C_q, Ph), 140.06 (H$\underline{C}$=CH_2), 142.80 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.66. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1049 (P-O), 1242 (P=O), 1702 (C=C). **MS (ESI): m/z (%):** 446.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.34. **Yield:** 82%.

Dimethyl 2-benzyl-3-but-3-enyl-2H-isoindol-1-ylphosphonate 4b



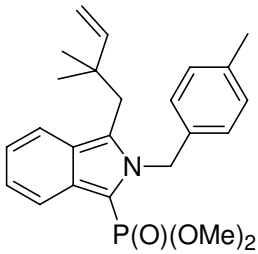
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.25 (ps q, *J* = 7.5 Hz, 2H, C$\underline{H}_2$CH), 3.02 (t, *J* = 7.3 Hz, 2H, C$\underline{H}_2$CH$_2$), 3.55 (d, *J* = 11.5 Hz, 6H, 2 x OCH_3), 4.97 (d, *J* = 10.7 Hz, 1H, HC=C$\underline{H}_A$H$_B$), 4.98 (d, *J* = 16.3 Hz, 1H, HC=CH$_A\underline{H}_B$), 5.77 (ddt, *J* = 7.3 Hz, *J* = 10.7 Hz, *J* = 16.3 Hz, 1H, $\underline{H}C=CH_2$), 5.84 (s, 2H, NCH_2), 6.87 (d, *J* = 6.6 Hz, 2 x CH_{arom}), 7.05 (t, *J* = 7.6 Hz, CH_{arom}), 7.17-7.29 (m, 4H, 4 x CH_{arom}), 7.62 (d, *J* = 8.5 Hz, PCCC$\underline{H}$), 7.93 (d, *J* = 8.8 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.93 (NC$\underline{C}H_2$), 33.97 ($\underline{C}H_2CH$), 50.12 (NCH_2), 52.48 (d, *J* = 5.8 Hz, 2 x OCH_3), 103.57 (d, *J* = 234.2 Hz, P$\underline{C}$), 116.05 (HC=$\underline{C}H_2$), 119.86 (CH_{arom}), 120.03 (CH_{arom}), 121.04 (CH_{arom}), 123.43 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.94 (CH_{arom}), 125.93 (2 x CH_{arom}), 127.48 (CH_{arom}), 128.72 (2 x CH_{arom}), 132.80 (d, *J* = 9.2 Hz, N$\underline{C}$), 132.82 (d, *J* = 17.3 Hz, PC$\underline{C}$), 137.01 (H$\underline{C}$=CH_2), 137.80 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.80. **IR (cm^{-1}) ν_{max}:** 1023 (P-O), 1049 (P-O), 1241 (P=O), 1698 (C=C). **MS (ESI): m/z (%):** 370.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 55/45 R_f = 0.25. **Yield:** 76%.

Dimethyl 3-[2-(4-methoxyphenyl)but-3-enyl]-2-propyl-2H-isoindol-1-ylphosphonate 4c



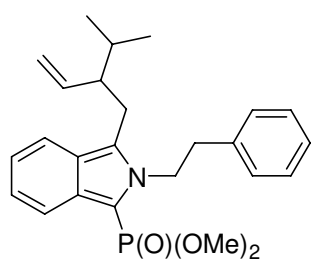
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.4 Hz, 3H, CH_3), 1.66-1.80 (m, 2H, $C\underline{H}_2CH_3$), 3.24 (dd, *J* = 8.0 Hz, *J* = 14.6 Hz, 1H, $C\underline{H}_AH_BCH$), 3.47 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 1H, $CH_A\underline{H}_BCH$), 3.67 (d, *J* = 11.8 Hz, 3H, OCH_3), 3.68 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.67-3.74 (m, 1H, C<u>H</u>Ph), 3.76 (s, 3H, $PhOC\underline{H}_3$), 4.00 (ddd, *J* = 6.3 Hz, *J* = 9.5 Hz, *J* = 14.0 Hz, 1H, $NC\underline{H}_AH_B$), 4.22 (ddd, *J* = 6.3 Hz, *J* = 9.5 Hz, *J* = 14.0 Hz, 1H, $NCH_A\underline{H}_B$), 5.01 (dt, *J* = 1.3 Hz, *J* = 17.1 Hz, 1H, $HC{=}C\underline{H}_AH_B$), 5.08 (dt, *J* = 1.3 Hz, *J* = 10.2 Hz, $HC{=}CH_A\underline{H}_B$), 6.11 (ddd, *J* = 17.1 Hz, *J* = 10.2 Hz, *J* = 7.0 Hz, 1H, <u>H</u>C=CH_2), 6.74-7.51 (m, 7H, 7 x CH_{arom}), 7.85 (d, *J* = 8.5 Hz, 1H, PCCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.38 ($CH_2\underline{C}H_3$), 25.58 ($\underline{C}H_2CH_3$), 32.22 ($\underline{C}H_2CH$), 48.25 (NCH_2), 49.39 (<u>C</u>HPh), 52.37 (d, *J* = 5.8 Hz, 2 x OCH_3), 55.34 ($PhOCH_3$), 102.33 (d, *J* = 234.2 Hz, P<u>C</u>), 114.05 (2 x CH_{arom}), 115.30 (HC=<u>C</u>H_2), 119.77 (2 x CH_{arom}), 120.69 (CH_{arom}), 123.77 (d, *J* = 13.8 Hz, PCC<u>C</u>), 124.52 (CH_{arom}), 128.54 (2 x CH_{arom}), 130.41 (d, *J* = 9.2 Hz, N<u>C</u>), 132.64 (d, *J* = 18.5 Hz, P<u>C</u>), 134.84 (C_q, Ph), 140.51 (H<u>C</u>=CH_2), 158.60 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.23. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1049 (P-O), 1246 (P=O), 1698 (C=C). **MS (ESI): m/z (%):** 428.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.15. **Yield:** 68%.

Dimethyl 3-(2,2-dimethylbut-3-enyl)-2-(4-methylbenzyl)-2H-isoindol-1-ylphosphonate 4d



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 6H, 2 x $C\underline{H}_3$), 2.27 (s, 3H, CH_3), 3.47 (d, *J* = 11.5 Hz, 6H, 2 x OCH_3), 4.93 (dd, *J* = 17.4 Hz, *J* = 1.1 Hz, 1H, $HC{=}C\underline{H}_AH_B$), 4.97 (dd, *J* = 10.7 Hz, *J* = 1.1 Hz, 1H, $HC{=}CH_A\underline{H}_B$), 5.82 (s, 2H, NCH_2), 5.84 (dd, *J* = 10.7 Hz, *J* = 17.4 Hz, 1H, <u>H</u>C=CH_2), 6.58 (d, *J* = 7.8 Hz, 2 x CH_{arom}), 7.02 (d, *J* = 7.8 Hz, 2 x CH_{arom}), 7.05-7.21 (m, 2H, 2 x CH_{arom}), 7.62-7.65 (m, 1H, PCCC<u>H</u>), 7.93 (d, *J* = 8.8 Hz, 1H, PCCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 21.09 (CH_3), 27.57 (2 x CH_3), 37.52 ($NC\underline{C}H_2$), 39.81 ($\underline{C}(CH_3)_2$), 50.21 (NCH_2), 52.30 (d, *J* = 4.6 Hz, 2 x OCH_3), 104.03 (d, *J* = 233.1 Hz, P<u>C</u>), 111.82 (HC=<u>C</u>H_2), 120.02 (CH_{arom}), 120.93 (CH_{arom}), 121.19 (CH_{arom}), 124.64 (CH_{arom}), 123.94 (d, *J* = 12.7 Hz, PCC<u>C</u>), 125.50 (2 x CH_{arom}), 129.28 (2 x CH_{arom}), 130.86 (d, *J* = 9.2 Hz, N<u>C</u>), 132.11 (d, *J* = 17.3 Hz, P<u>C</u>), 134.84 (C_q, Ph), 136.95 (C_q, Ph), 147.04 (H<u>C</u>=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.79. **IR (cm^{-1}) ν_{max}:** 1023 (P-O), 1051 (P-O), 1243 (P=O), 1638 (C=C). **MS (ESI): m/z (%):** 412.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.22. **Yield:** 47%.

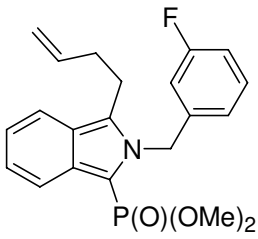
Dimethyl 3-[2-isopropylbut-3-enyl]-2-(2-fenylethyl)-2H-isoindol-1-ylphosphonate 4e



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 0.96 (d, *J* = 6.4 Hz, 3H, CH_3), 1.70 (octet, *J* = 6.4 Hz, 1H, $C\underline{H}(CH_3)_2$), 2.24 (tt, *J* = 6.4 Hz, *J* = 9.8 Hz, 1H, $CH_2C\underline{H}$), 2.76 (dd, *J* = 9.8 Hz, *J* = 14.9 Hz, 1H, $C\underline{H}_AH_BCH$), 2.98 (dd, *J* = 6.4 Hz, *J* = 14.9 Hz, 1H, $CH_A\underline{H}_BCH$), 3.05-3.20 (m, 2H, CH_2Ph), 3.74 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.75 (d, *J* = 11.5 Hz, 3H, OCH_3), 4.61 (dd, *J* = 1.7 Hz, *J* = 17.1 Hz, 1H, $HC{=}C\underline{H}_AH_B$), 4.61-4.79 (m, 2H, NCH_2), 4.82 (dt, *J* = 1.7 Hz, *J* = 9.8 Hz, $HC{=}CH_A\underline{H}_B$), 5.63 (dt, *J* = 17.1

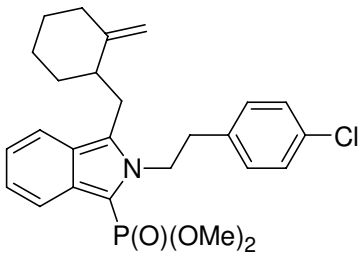
Hz, *J* = 9.8 Hz, 1H, HC=CH_2), 6.98-7.33 (m, 7H, 7 x CH_{arom}), 7.52 (d, *J* = 8.5 Hz, 1H, PCCCH), 7.86 (d, *J* = 8.8 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 18.85 (CH_3), 20.90 (CH_3), 27.90 (CH_2CH), 31.46 (CH(CH_3)$_2$), 38.88 (CH_2Ph), 48.90 (NCH_2), 51.51 (CHCH=CH_2), 52.53 (d, *J* = 4.6 Hz, 2 x OCH_3), 101.81 (d, *J* = 234.2 Hz, PC), 116.76 (HC=CH_2), 119.60 (CH_{arom}), 120.14 (CH_{arom}), 120.54 (CH_{arom}), 123.73 (d, *J* = 12.7 Hz, PCCC), 124.73 (CH_{arom}), 126.90 (CH_{arom}), 128.81 (2 x CH_{arom}), 129.01 (2 x CH_{arom}), 132.13 (d, *J* = 10.4 Hz, NC), 132.73 (d, *J* = 17.3 Hz, PCC), 138.23 (C_q, Ph), 138.58 (HC=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.44. **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1049 (P-O), 1247 (P=O), 1660 (C=C). **MS (ESI): m/z (%):** 426.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.32. **Yield:** 71%.

Dimethyl 3-but-2-enyl-2-(3-fluorobenzyl)-2H-isoindol-1-ylphosphonate 4f



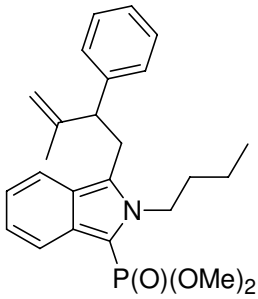
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (ps q, *J* = 7.4 Hz, 2H, CH_2CH), 3.01 (t, *J* = 7.4 Hz, 2H, NCCH_2), 3.59 (d, *J* = 11.6 Hz, 6H, 2 x OCH_3), 4.95-5.01 (m, 2H, HC=CH_2), 5.77 (ddt, *J* = 7.4 Hz, *J* = 9.9 Hz, *J* = 17.3 Hz, 1H, HC=CH_2), 5.85 (s, 2H, NCH_2Ph), 6.57 (d, *J* = 9.6 Hz, 1H, CH_{arom}), 6.69 (d, *J* = 7.7 Hz, 1H, CH_{arom}), 6.92 (dt, *J* = 8.4 Hz, *J* = 0.8 Hz, 1H, CH_{arom}), 7.04-7.26 (m, 3H, 3 x CH_{arom}), 7.62 (d, *J* = 8.5 Hz, 1H, PCCCH), 7.90 (d, *J* = 8.8 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.88 (NCCH_2), 33.97 (CH_2CH), 49.60 (NCH_2), 52.52 (d, *J* = 5.8 Hz, 2 x OCH_3), 103.69 (d, *J* = 234.2 Hz, PC), 113.04 (d, *J* = 23.1 Hz, CH_{arom}), 114.45 (d, *J* = 21.9 Hz, CH_{arom}), 116.18 (HC=CH_2), 119.89 (CH_{arom}), 119.96 (CH_{arom}), 121.21 (CH_{arom}), 121.58 (d, *J* 3.5 Hz, CH_{arom}), 123.48 (d, *J* = 13.9 Hz, PCCC), 125.13 (CH_{arom}), 130.30 (d, *J* = 8.1 Hz, CH_{arom}), 132.64 (d, *J* = 17.3 Hz, NC), 132.70 (d, *J* = 17.3 Hz, PCC), 136.86 (HC=CH_2), 140.49 (d, *J* = 6.9 Hz, $C_{q,arom}$), 163.23 (d, *J* = 245.8 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.56. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -112.48 (dt, *J* = 5.3 Hz, *J* = 7.2 Hz). **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1050 (P-O), 1243 (P=O), 1617 (C=C). **MS (ESI): m/z (%):** 388.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.36. **Yield:** 63%.

Dimethyl [2-[2-(4-chlorophenyl)-ethyl]-3-(2-methylene-cyclohexylmethyl)--2H-isoindol-1-yl]-phosphonate 4g



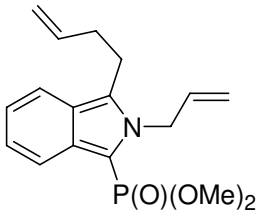
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12-1.70 (m, 6H, 3 x CH_2), 1.99-2.10 (m, 1H, CH_AH_B), 2.30-2.38 (m, 2H, CH_2CH + CH_AH_B), 2.88 (dd, *J* = 10.3 Hz, *J* = 14.7 Hz, 1H, NCCH_AH_B), 3.03 (dd, *J* = 4.3 Hz, *J* = 14.7 Hz, 1H, NCCH_AH_B), 3.09-3.17 (m, 2H, CH_2Ph), 3.77 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.78 (d, *J* = 11.5 Hz, 3H, OCH_3), 4.62 (1H, s, C=CH_AH_B), 4.64 (dt, *J* = 8.0 Hz, *J* = 13.8 Hz, 1H, NCH_AH_B), 4.74 (dt, *J* = 7.9 Hz, *J* = 13.8 Hz, 1H, NCH_AH_B), 4.76 (1H, s, C=CH_AH_B), 6.99-7.28 (m, 6H, 6 x CH_{arom}), 7.53 (d, *J* = 8.5 Hz, 1H, PCCCH), 7.82 (d, *J* = 8.5 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.97 (CH_2), 27.90 (NCCH_2), 28.47 (CH_2), 33.39 (CH_2), 35.75 (CH_2), 38.23 (NCH_2CH_2), 43.49 (CH), 48.53 (NCH_2), 52.68 (d, *J* = 3.5 Hz, 2 x OCH_3), 102.27 (d, *J* = 235.4 Hz, PC), 105.92 (C=CH_2), 119.45 (CH_{arom}), 120.22 (CH_{arom}), 120.78 (CH_{arom}), 123.93 (d, *J* = 12.7 Hz, PCCC), 124.93 (CH_{arom}), 128.89 (2 x CH_{arom}), 130.44 (2 x CH_{arom}), 132.02 (d, *J* = 9.2 Hz, NC), 132.45 (d, *J* = 17.3 Hz, PCC), 132.78 ($ClC_{q,arom}$), 136.57 ($C_{q,arom}$), 152.22 (C=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.25. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1049 (P-O), 1245 (P=O), 1644 (C=C). **MS (ESI): m/z (%):** 472.2/474.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.26. **Yield:** 40%.

Dimethyl 2-butyl-3-(3-methyl-2-phenylbut-3-enyl)-2H-isoindol-1-ylphosphonate 4h



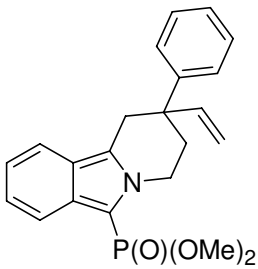
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.6 Hz, 3H, CH_3), 1.29 (sextet, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_3$), 1.59 (p, *J* = 7.6 Hz, 2H, $NCH_2C\underline{H}_2$), 1.66 (s, 3H, CH_3), 3.22 (dd, *J* = 9.5 Hz, *J* = 13.3 Hz, 1H, $C\underline{H}_AH_BCH$), 3.54-3.77 (m, 3H, $CH_A\underline{H}_BC\underline{H}$ + $NC\underline{H}_AH_B$), 3.64 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.65 (d, *J* = 11.6 Hz, 3H, OCH_3), 4.10 (dt, *J* = 7.6 Hz, *J* = 14.0 Hz, 1H, $NCH_A\underline{H}_B$), 5.08 (s, 1H, $HC=C\underline{H}_AH_B$), 5.11 (s, 1H, $HC=CH_A\underline{H}_B$), 6.85-7.20 (m, 7H, 7 x CH_{arom}), 7.42 (d, *J* = 8.3 Hz, 1H, PCCC$\underline{H}$), 7.86 (d, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 13.77 ($CH_2\underline{C}H_3$), 20.17 ($\underline{C}H_2CH_3$), 22.79 ($C\underline{C}H_3$), 30.83 ($\underline{C}H_2CH$), 34.12 ($NCH_2\underline{C}H_2$), 46.13 (NCH_2), 52.36 (d, *J* = 3.5 Hz, 2 x OCH_3), 52.87 ($\underline{C}HPh$), 101.90 (d, *J* = 234.2 Hz, P$\underline{C}$), 111.05 ($C=\underline{C}H_2$), 119.54 (CH_{arom}), 119.82 (CH_{arom}), 120.58 (CH_{arom}), 123.63 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.46 (CH_{arom}), 127.01 (CH_{arom}), 127.82 (2 x CH_{arom}), 128.44 (2 x CH_{arom}), 130.75 (d, *J* = 9.2 Hz, N$\underline{C}$), 132.77 (d, *J* = 17.3 Hz, P$\underline{C}$), 141.86 (C_q, Ph), 147.09 ($\underline{C}=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.24. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1048 (P-O), 1251 (P=O), 1701 (C=C). **MS (ESI): m/z (%):** 426.5 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.20. **Yield:** 40%.

Dimethyl 2-allyl-3-but-3-enyl-2H-isoindol-1-ylphosphonate 4i



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.43 (ps q, *J* = 7.4 Hz, 2H, $CH_2C\underline{H}_2CH$), 3.07 (t, *J* = 7.4 Hz, 2H, $C\underline{H}_2CH_2$), 3.71 (d, *J* = 11.6 Hz, 6H, 2 x OCH_3), 4.74 (br d, *J* = 17.1 Hz, *J* = 1.5 Hz, 1H, $NCH_2HC=C\underline{H}_AH_B$), 5.03 (br d, *J* = 10.3 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.09 (br d, *J* = 17.1 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.16 (dq, *J* = 10.5 Hz, *J* = 1.5 Hz, 1H, $NCH_2HC=CH_A\underline{H}_B$), 5.23 (dt, *J* = 1.5 Hz, *J* = 4.8 Hz, 2H, NCH_2), 5.86 (ddt, *J* = 7.4 Hz, *J* = 10.3 Hz, *J* = 17.1 Hz, 1H, $\underline{H}C=CH_2$), 6.03 (ddt, *J* = 4.8 Hz, *J* = 10.5 Hz, *J* = 17.1 Hz, 1H, $NCH_2\underline{H}C=CH_2$), 7.00-7.06 (m, 1H, CH_{arom}), 7.15-7.20 (m, 1H, CH_{arom}), 7.15-7.20 (m, 1H, CH_{arom}), 7.58-7.62 (m, 1H, CH_{arom}), 7.87 (d, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.68 ($NC\underline{C}H_2$), 34.06 ($CH_2\underline{C}H_2CH$), 48.96 (NCH_2), 52.62 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.77 (d, *J* = 234.2 Hz, P$\underline{C}$), 116.00 ($HC=\underline{C}H_2$), 116.14 ($NCH_2CH=\underline{C}H_2$), 119.79 (CH_{arom}), 119.83 (CH_{arom}), 120.84 (CH_{arom}), 123.25 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.80 (CH_{arom}), 132.44 (d, *J* = 9.2 Hz, N$\underline{C}$), 132.57 (d, *J* = 18.5 Hz, P$\underline{C}$), 134.31 ($NCH_2H\underline{C}=CH_2$), 137.12 ($H\underline{C}=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.97. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1050 (P-O), 1241 (P=O), 1641 (C=C). **MS (ESI): m/z (%):** 320.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 55/45 R_f = 0.25.

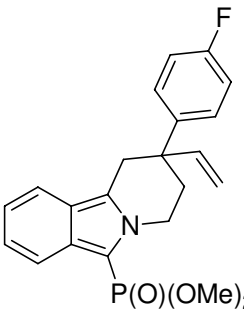
Dimethyl 2-phenyl-2-vinyl-1,2,3,4-tetrahydropyrido[2,1-a]isoindol-6-ylphosphonate 14a



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.41 (ddd, *J* = 5.6 Hz, *J* = 7.1 Hz, *J* = 13.3 Hz, 1H, $NCH_2C\underline{H}_AH_B$), 2.57 (ddd, *J* = 5.3 Hz, *J* = 7.7 Hz, *J* = 13.3 Hz, 1H, $NCH_2CH_A\underline{H}_B$), 3.49 (s, 2H, $NCC\underline{H}_2$), 3.64 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.66 (d, *J* = 11.6 Hz, 3H, OCH_3), 4.30 (ddd, *J* = 5.3 Hz, *J* = 7.1 Hz, *J* = 14.1 Hz, 1H, $NC\underline{H}_AH_B$), 4.50 (ddd, *J* = 5.6 Hz, *J* = 7.7 Hz, *J* = 14.1 Hz, 1H, $NCH_A\underline{H}_B$), 5.01 (d, *J* = 17.4 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.17 (d, *J* = 10.7 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.03 (dd, *J* = 10.7 Hz, *J* = 17.4 Hz, 1H, $\underline{H}C=CH_2$), 7.03-7.36 (m, 7H, 7 x CH_{arom}), 7.61-7.65 (m, 1H, CH_{arom}), 7.89 (d, *J* = 8.4 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 32.70 ($NC\underline{C}H_2$), 32.81 ($NCH_2\underline{C}H_2$), 42.24 (C_q), 43.66 (NCH_2), 52.39 (d, *J* = 3.5 Hz, OCH_3), 52.44 (d, *J* = 4.6 Hz,

OCH_3), 101.65 (d, *J* = 235.4 Hz, PC), 114.32 (HC=CH_2), 119.12 (CH_{arom}), 119.51 (CH_{arom}), 120.49 (CH_{arom}), 121.74 (d, *J* = 13.9 Hz, PCCC), 126.47 (2 x CH_{arom}), 129.96 (CH_{arom}), 128.44 (d, *J* = 9.2 Hz, NC), 128.73 (2 x CH_{arom}), 133.28 (d, *J* = 18.5 Hz, PCC), 143.47 (HC=CH_2), 144.08 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.29. **IR (cm^{-1}) ν_{max}:** 1021 (P-O), 1047 (P-O), 1243 (P=O), 1623 (C=C). **MS (ESI): m/z (%):** 382.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.14. **Yield:** 68%.

Dimethyl 2-(4-fluorophenyl)-2-vinyl-1,2,3,4-tetrahydropyrido[2,1-a]isoindol-6-ylphosphonate 14b

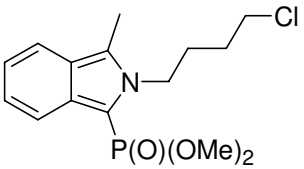


^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.38 (dt, *J* = 6.3 Hz, *J* = 13.8 Hz, 1H, $NCH_2CH_AH_B$), 2.52 (dt, *J* = 6.3 Hz, *J* = 13.8 Hz, 1H, $NCH_2CH_AH_B$), 3.45 (s, 2H, $NCCH_2$), 3.65 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.67 (d, *J* = 11.5 Hz, 3H, OCH_3), 4.27 (dt, *J* = 6.3 Hz, *J* = 14.7 Hz, 1H, NCH_AH_B), 4.51 (dt, *J* = 6.3 Hz, *J* = 14.7 Hz, 1H, NCH_AH_B), 4.99 (d, *J* = 17.6 Hz, 1H, $HC=CH_AH_B$), 5.17 (d, *J* = 10.7 Hz, 1H, $HC=CH_AH_B$), 5.99 (dd, *J* = 10.7 Hz, *J* = 17.6 Hz, 1H, $HC=CH_2$), 6.93-7.26 (m, 6H, 6 x CH_{arom}), 7.62 (dt, *J* = 0.9 Hz, *J* = 8.5 Hz, 1H, CH_{arom}), 7.89 (dt, *J* = 0.9 Hz, *J* = 8.5 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 32.85 ($NCCH_2$), 32.94 (NCH_2CH_2), 41.87 (C_q), 43.60 (NCH_2), 52.39 (d, *J* = 4.6 Hz, OCH_3), 52.42 (d, *J* = 4.6 Hz, OCH_3), 101.84 (d, *J* = 236.5 Hz, PC), 114.46 (HC=CH_2), 115.47 (d, *J* = 21.9 Hz, 2 x CH_{arom}), 119.05 (CH_{arom}), 119.51 (CH_{arom}), 120.58 (CH_{arom}), 121.73 (d, *J* = 12.7 Hz, PCCC), 125.13 (CH_{arom}), 128.09 (d, *J* = 11.5 Hz, NC), 128.22 (d, *J* = 8.1 Hz, 2 x CH_{arom}), 133.24 (d, *J* = 18.5 Hz, PCC), 139.77 (d, *J* = 3.5 Hz, $C_{q,arom}$), 143.38 (HC=CH_2), 161.64 (d, *J* = 246.9 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.17. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -115.68 - -155.78 (m). **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1048 (P-O), 1238 (P=O), 1602 (C=C), 1623 (C=C), 1636 (C=C), 1702 (C=C). **MS (ESI): m/z (%):** 400.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.17. **Yield:** 82%.

Synthesis of isoindole 13.

In a dry flask, 2-ethynylbenzaldehyde (3.84 mmol) is dissolved into diethylether (6mL, freshly distilled from Na-metal). To this solution is added $LiClO_4$ (7.5 equiv, 28.8 mmol, dried for 24h at 110°C). This mixture is stirred for 5 minutes. Subsequently pyrrolidine is added (2 equiv, 7.69 mmol, dissolved in 1mL dry diethylether). This mixture is stirred for 20 minutes after which $P(OMe)_3$ is added (1.5 equiv, 5.76 mmol). The reaction is stirred for 4 hours after which HCl (3N, 20mL) is very carefully added. The mixture is extracted with CH_2Cl_2 (3 x 20mL) and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained compound was purified using column chromatography.

Dimethyl 2-(4-chlorobutyl)-3-methyl-2H-isoindol-1-ylphosphonate 13



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.88-2.02 (m, 4H, $NCH_2CH_2CH_2$), 2.61 (s, 3H, CH_3), 3.59 (t, *J* = 6.2 Hz, 2H, CH_2Cl), 3.73 (d, *J* = 11.3 Hz, 6H, 2 x OCH_3), 4.55 (t, *J* = 7.6 Hz, 2H, NCH_2), 7.02 (t, *J* = 8.0 Hz, 1H, CH_{arom}), 7.17 (t, *J* = 8.0 Hz, 1H, CH_{arom}), 7.56 (d, *J* = 8.0 Hz, 1H, PCCCH), 7.80 (d, *J* = 8.0 Hz, 1H, PCCCCH). **^{13}C-NMR (75**

MHz, $CDCl_3$): δ 10.41 (CH_3), 28.96 (CH_2), 29.75 (CH_2), 44.53 ($ClCH_2$), 46.21 (NCH_2), 52.61 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.16 (d, *J* = 235.4 Hz, PC), 119.47 (CH_{arom}), 119.67 (CH_{arom}), 120.67 (CH_{arom}), 123.51 (d, *J* = 12.7 Hz, PCCC), 124.89 (CH_{arom}), 128.44 (d, *J* = 10.4 Hz, NC), 132.35 (d, *J* = 17.3 Hz, PCC). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.16. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1048 (P-O), 1245 (P=O), 1710 (C=C). **MS (ESI): m/z (%):** 330.2/332.3 ($M+H^+$, 100). **Chromatography:** EtOAc R_f = 0.59. **Yield:** 8%.

Synthesis of azepino isoindole 16: Compound **4i** (0.2 g, 0.63 mmol) was dissolved in benzene (20 mL) and the second generation Grubbs' catalyst (0.02 equiv, 0.011 g, 0.013 mmol) was added. The reaction was allowed to reflux for 16h under a N_2-atmosphere. The product was coated on silica gel by removal of the solvent in vacuo and purified by flash chromatography

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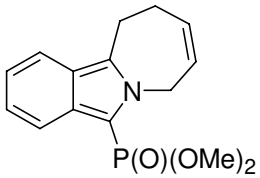
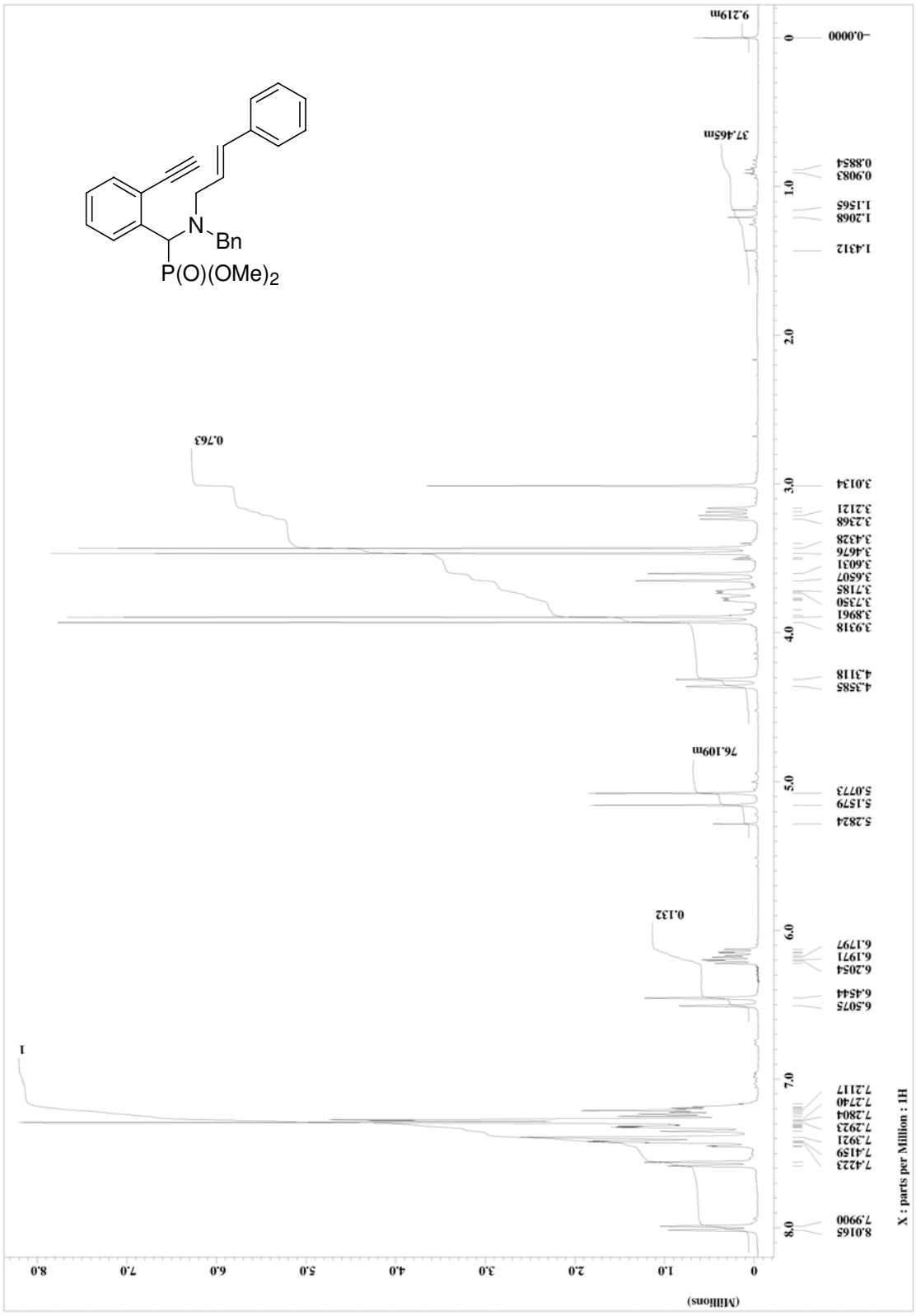
Dimethyl 10,11-dihydro-7H-azepino[2,1-a]isoindol-5-ylphosphonate 16



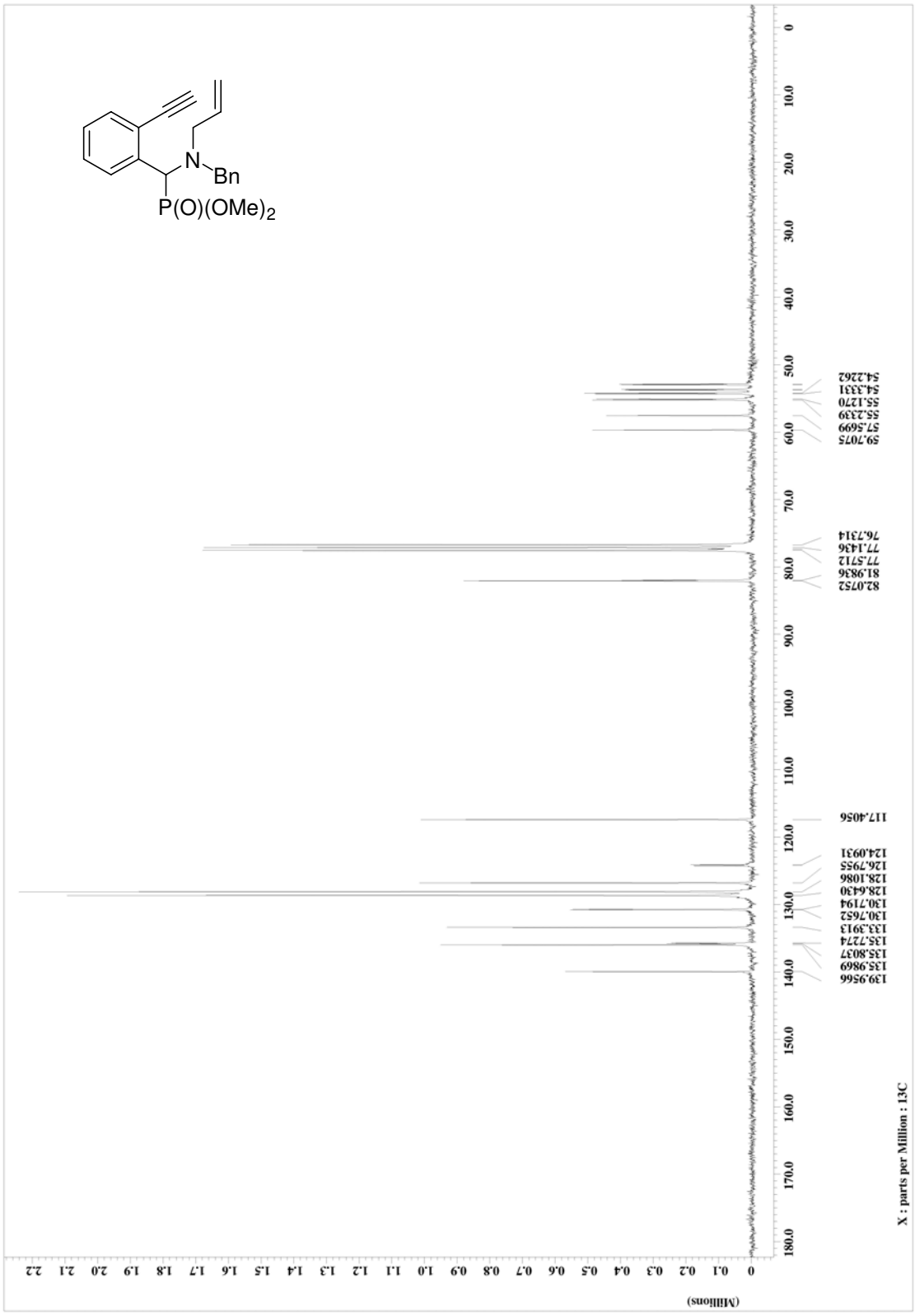
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42-2.48 (m, 2H, CH_2CH_2CH), 3.38 (t, *J* = 6.0 Hz, 2H, CH_2CH_2CH), 3.72 (d, *J* = 11.5 Hz, 6H, 2 x OCH_3), 5.24-5.28 (m, 2H, NCH_2), 5.75-5.94 (m, 2H, HC=CH), 7.03 (ddd, *J* = 1.0 Hz, *J* = 6.6 Hz, *J* = 8.4 Hz, 1H, CH_{arom}), 7.16 (ddd, *J* = 1.0 Hz, *J* = 6.6 Hz, *J* = 8.7 Hz, 1H, CH_{arom}), 7.58 (ddt, *J* = 1.0 Hz, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H, PCCCH), 7.90 (dt, *J* = 1.0 Hz, *J* = 8.7 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 21.86 ($NCCH_2$), 28.13 (CH_2CH_2CH), 43.98 (NCH_2), 52.59 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.46 (d, *J* = 234.2 Hz, PC), 119.08 (CH_{arom}), 119.75 (CH_{arom}), 120.72 (CH_{arom}), 122.26 (d, *J* = 12.7 Hz, PCCC), 122.62 (HC=CH), 124.44 (CH_{arom}), 132.09 (d, *J* = 17.3 Hz, PCC), 133.15 (NCH_2CH), 133.87 (d, *J* = 9.2 Hz, NC). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.26. **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1047 (P-O), 1224 (P=O), 1694 (C=C). **MS (ESI): m/z (%):** 292.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.20. **Yield:** 95%.

2a ^{13}C-Spectrum

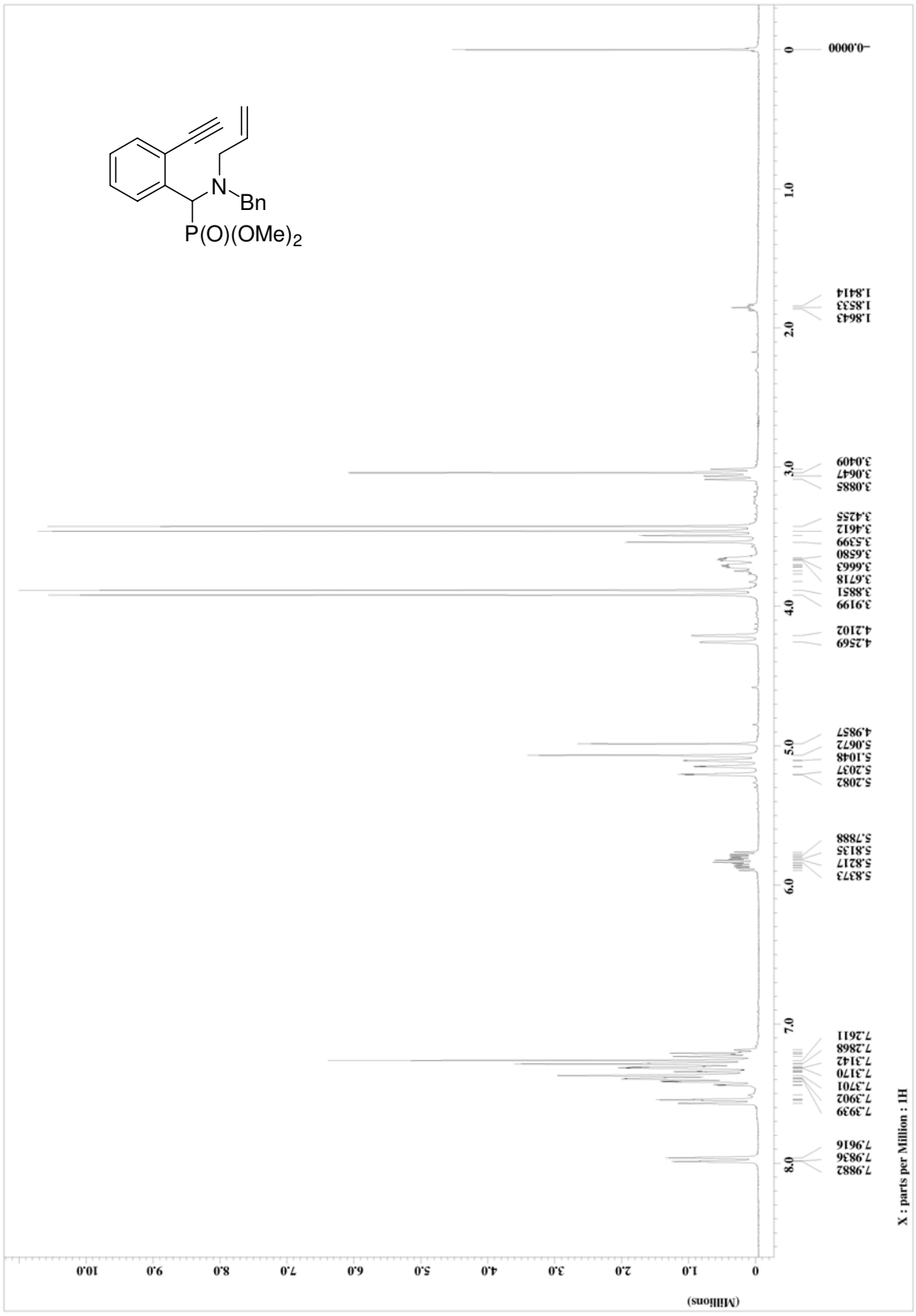
2a ^{1}H-Spectrum



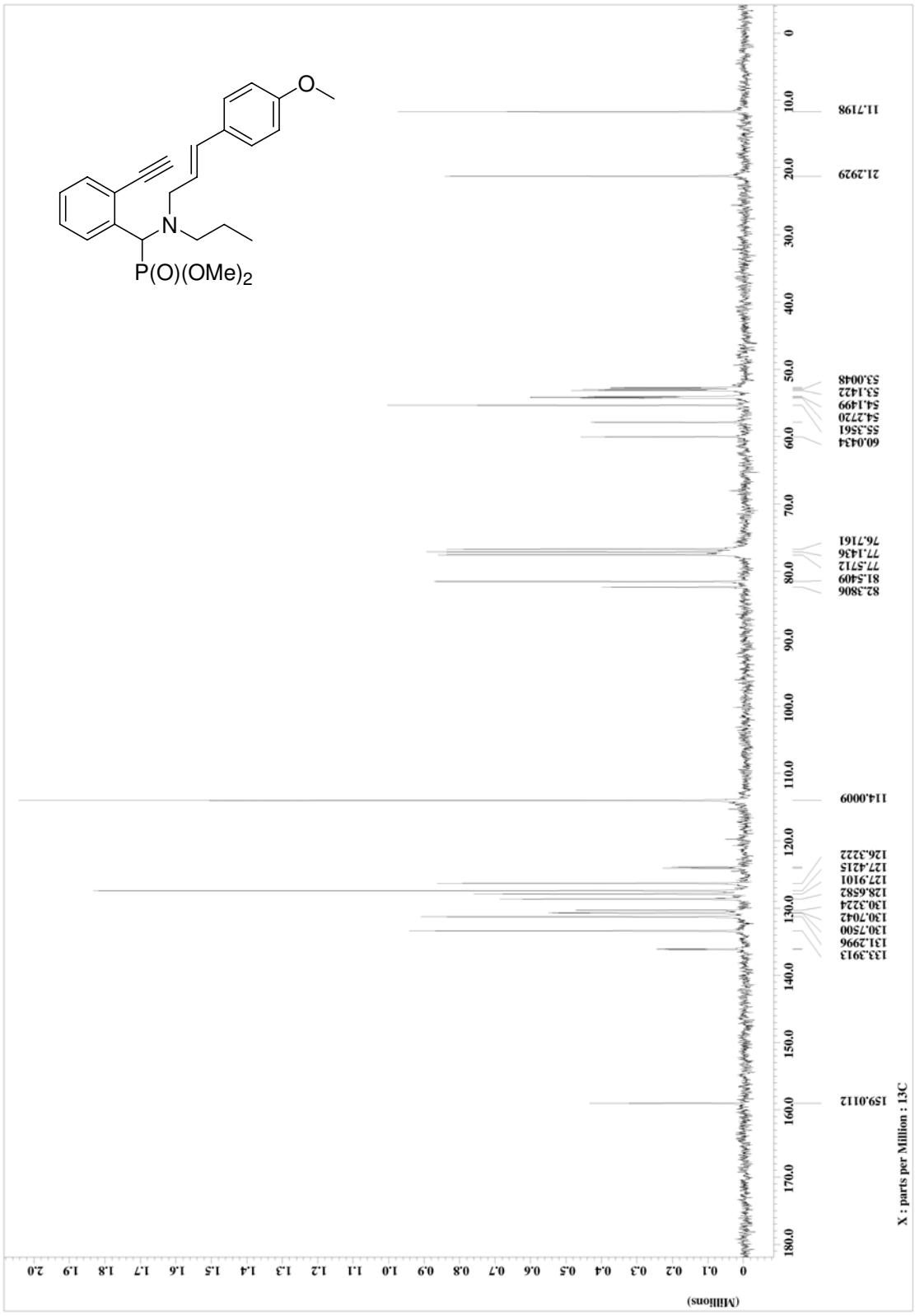
2b ^{13}C-Spectrum



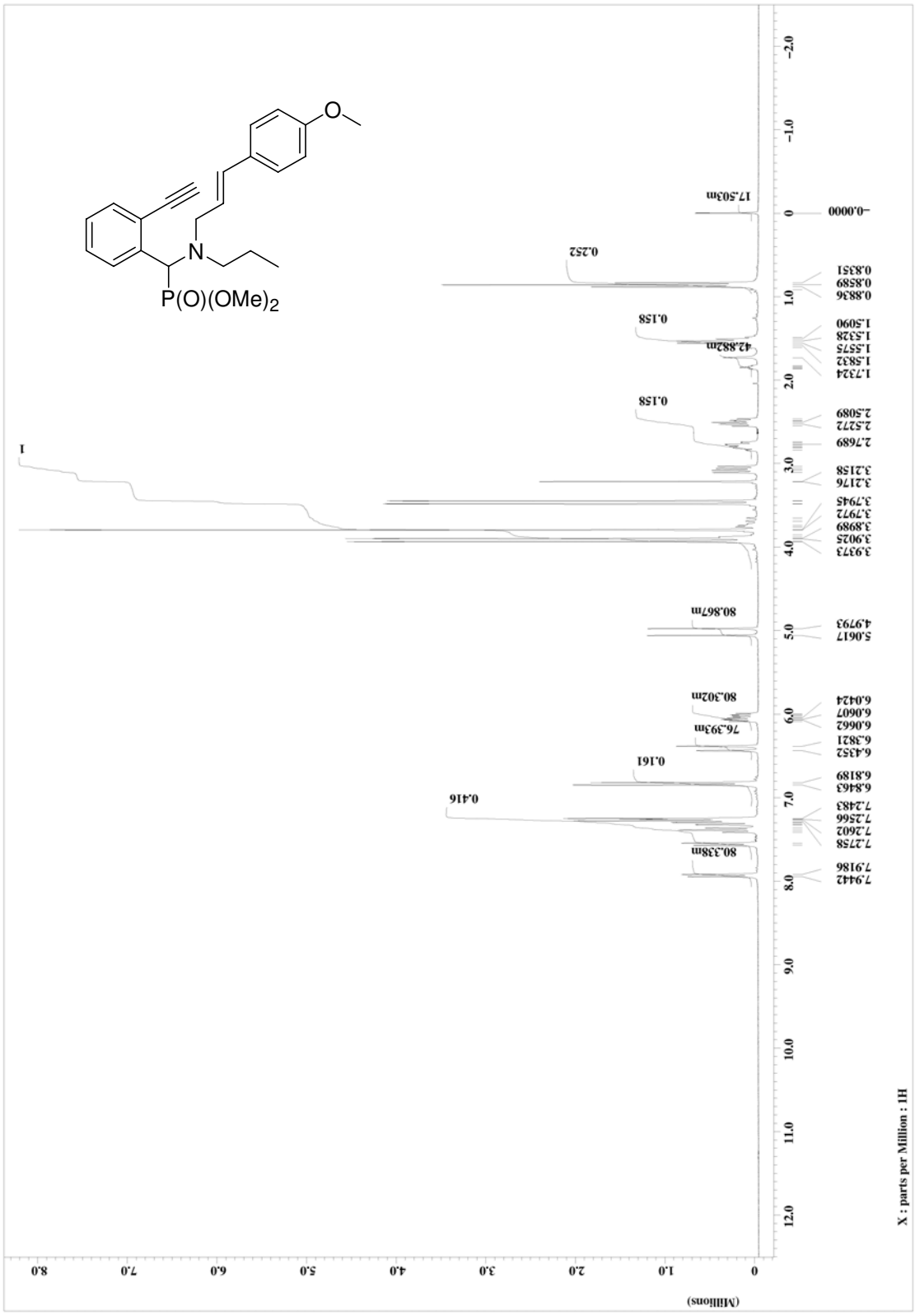
2b ^{1}H-Spectrum



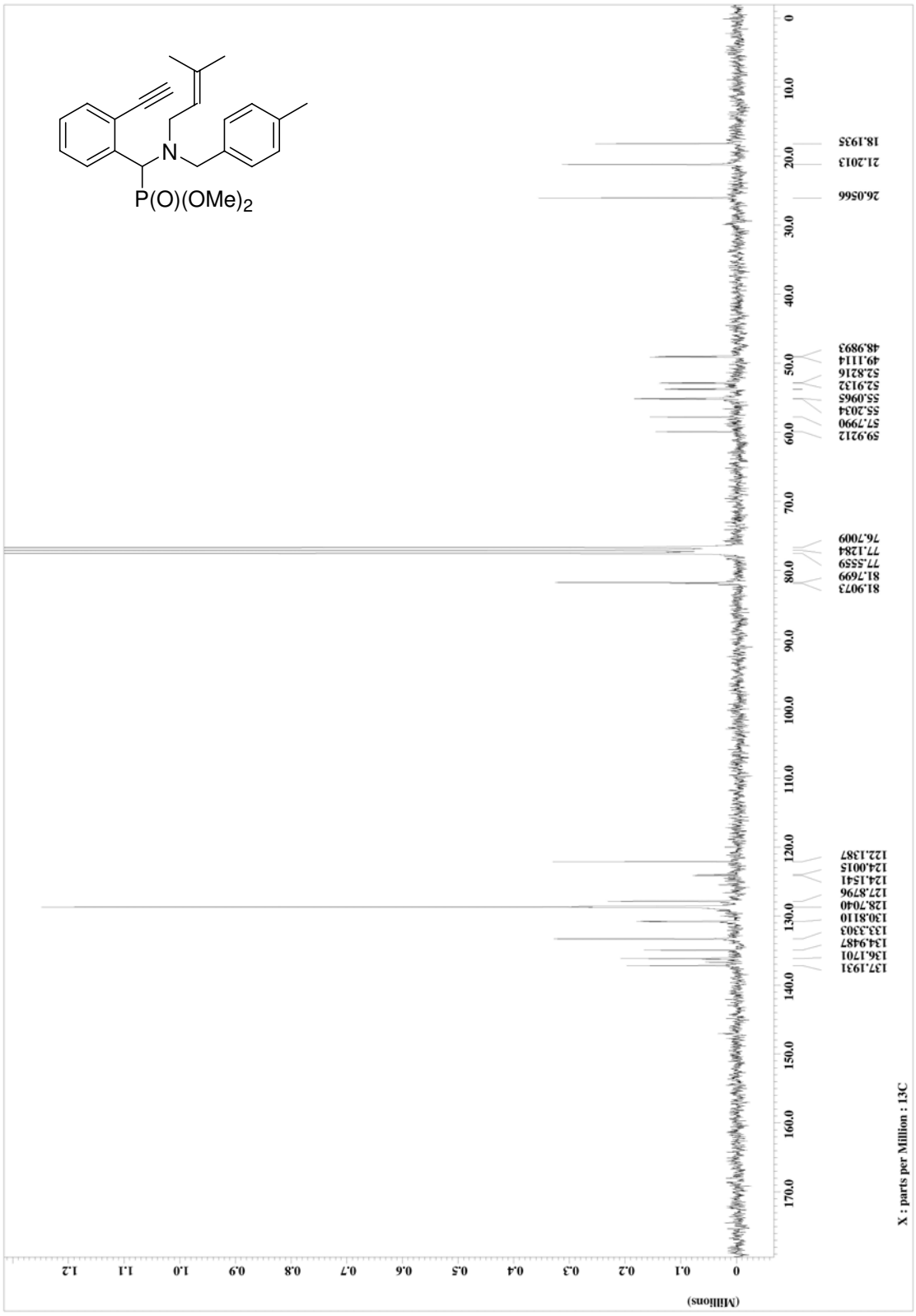
2c ^{13}C-Spectrum



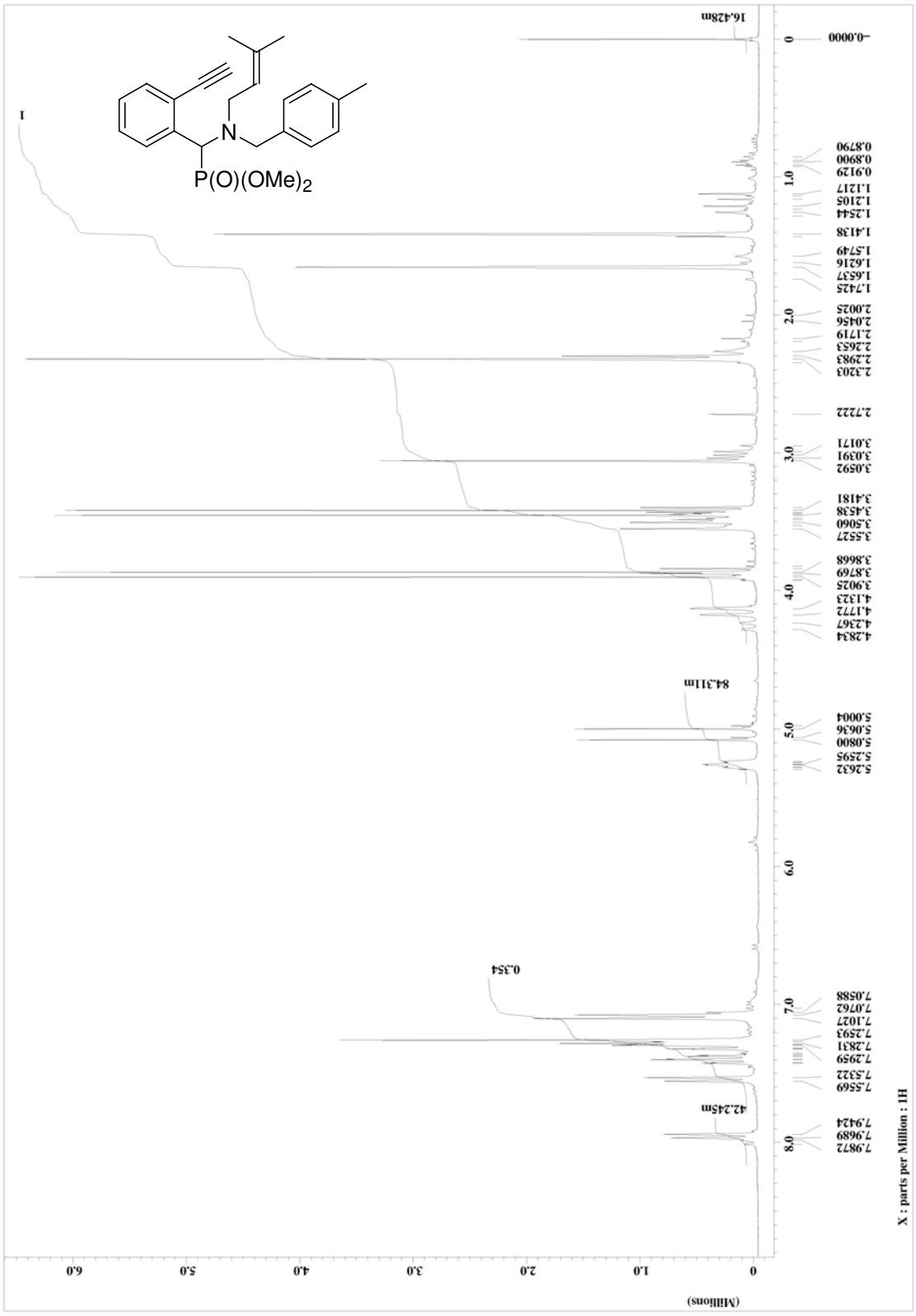
2c ^{1}H-Spectrum



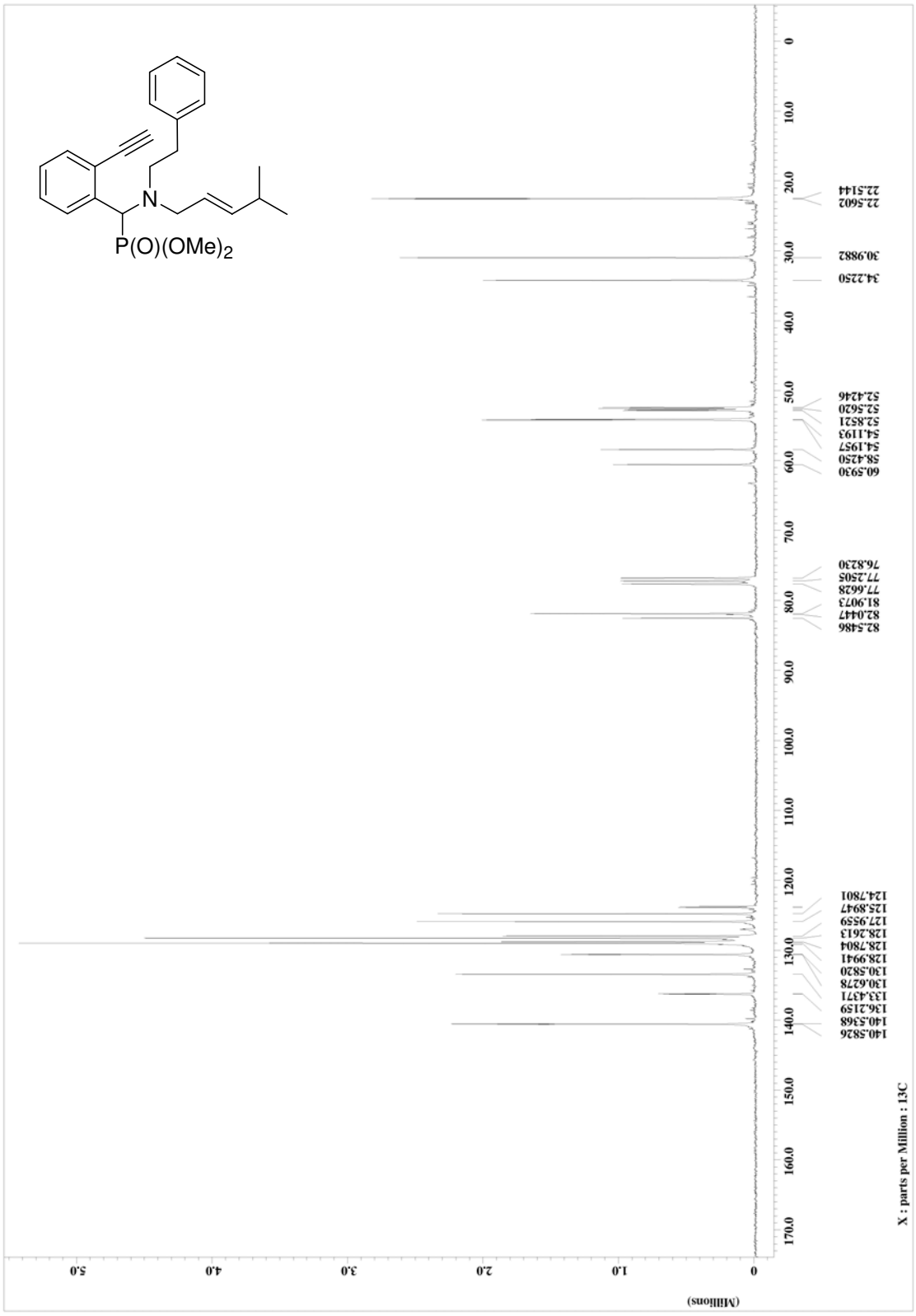
2d ^{13}C-Spectrum



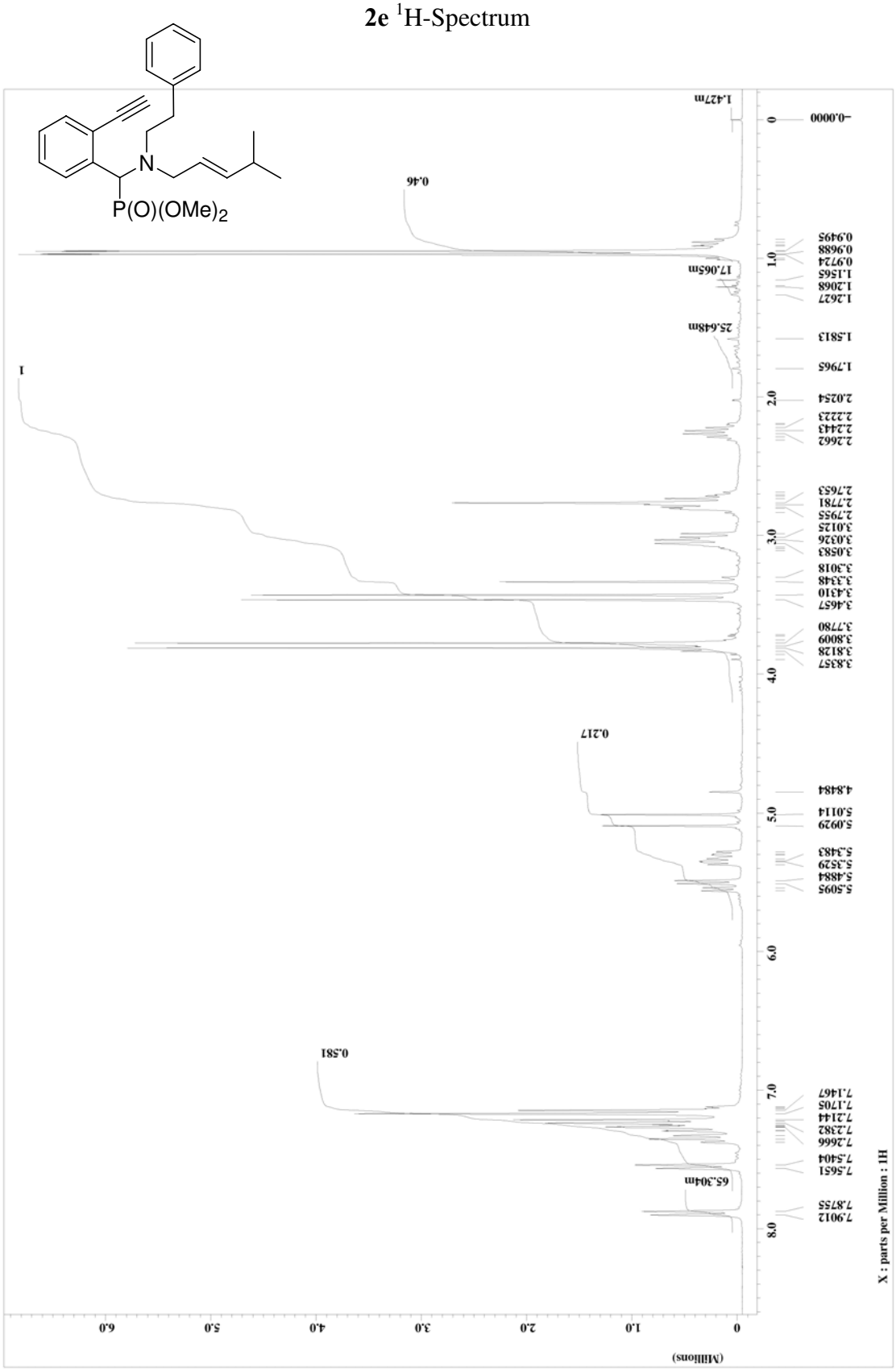
2d ^{1}H-Spectrum



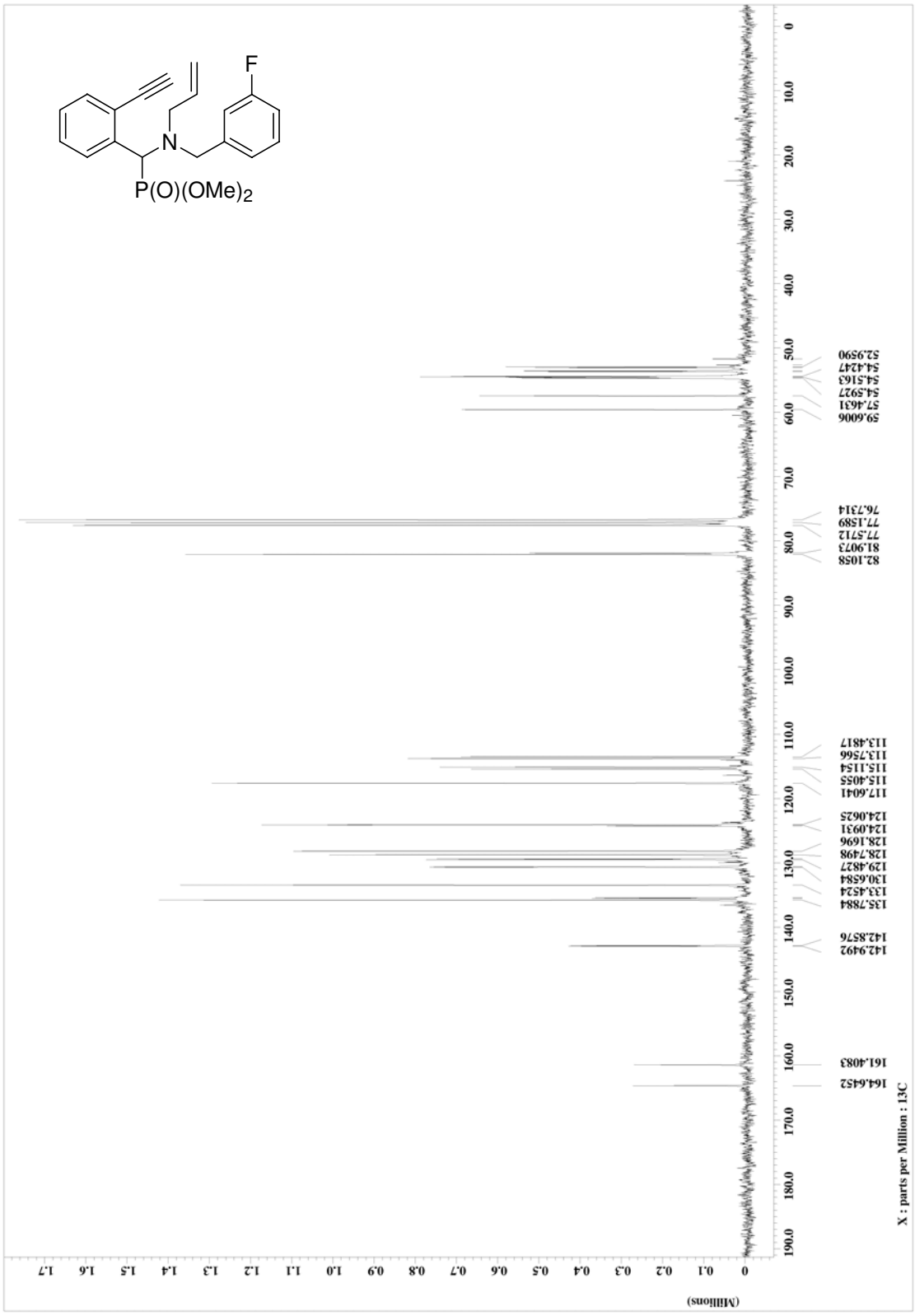
2e ^{13}C-Spectrum



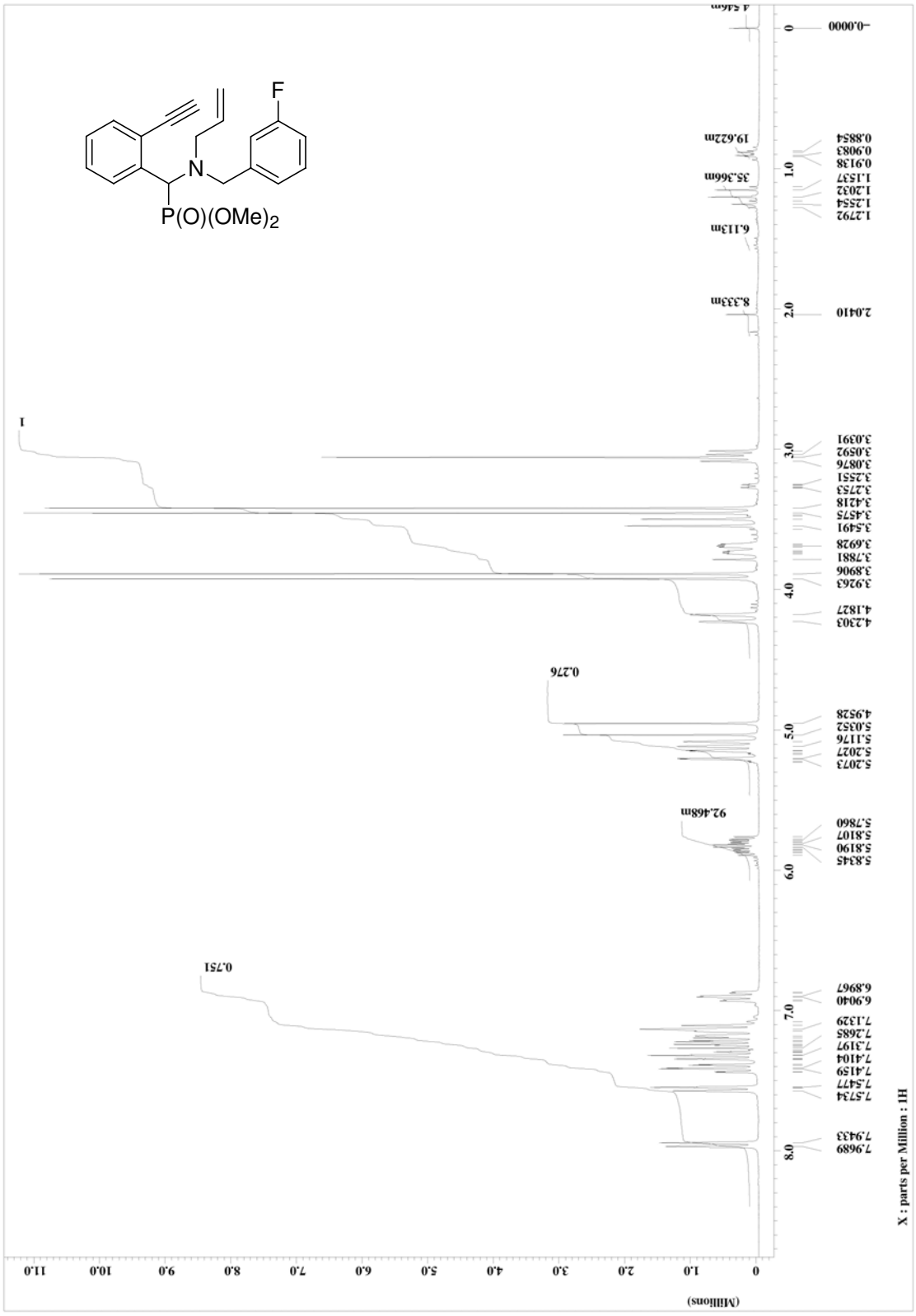
2e ^{1}H-Spectrum



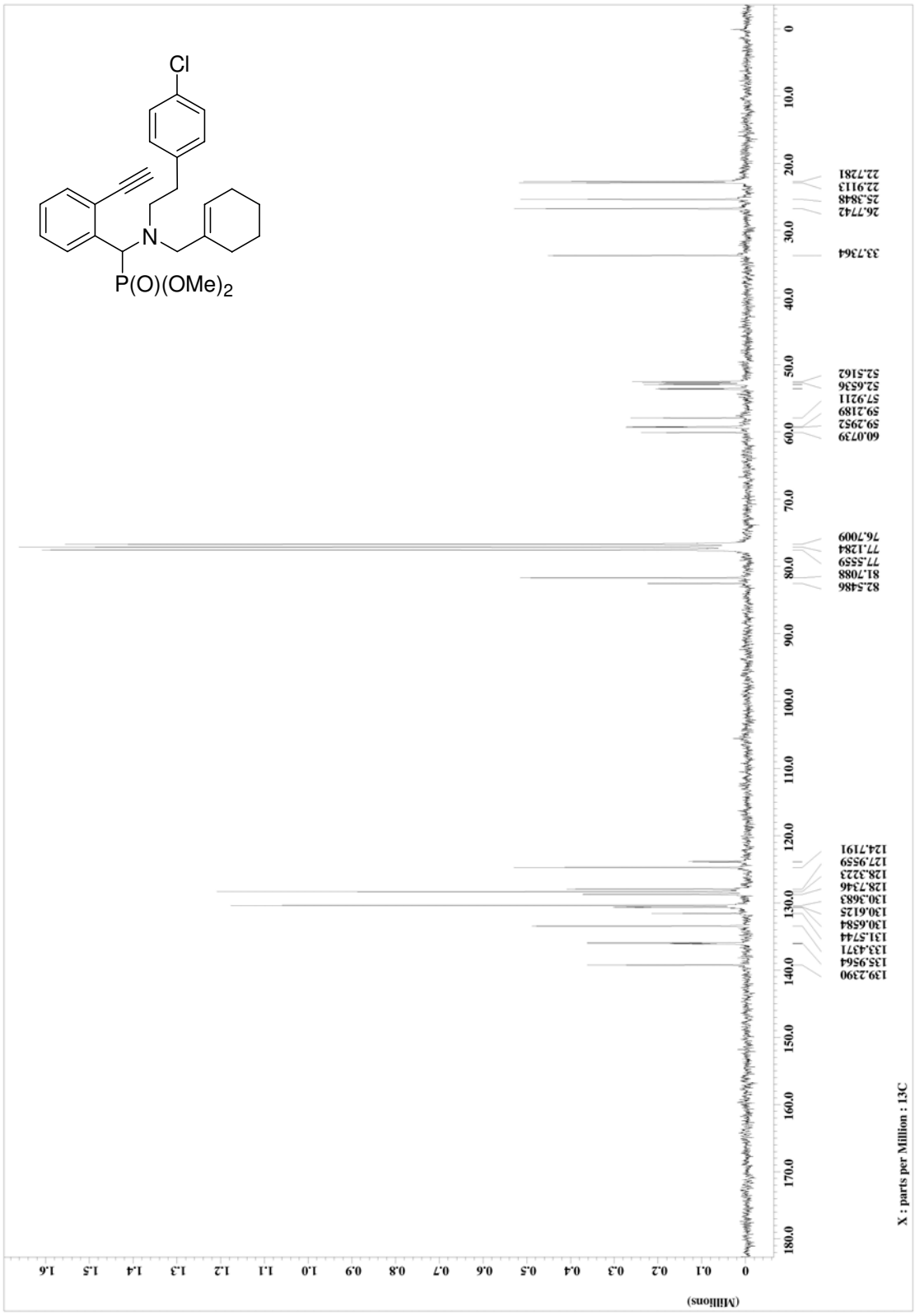
2f ^{13}C-Spectrum



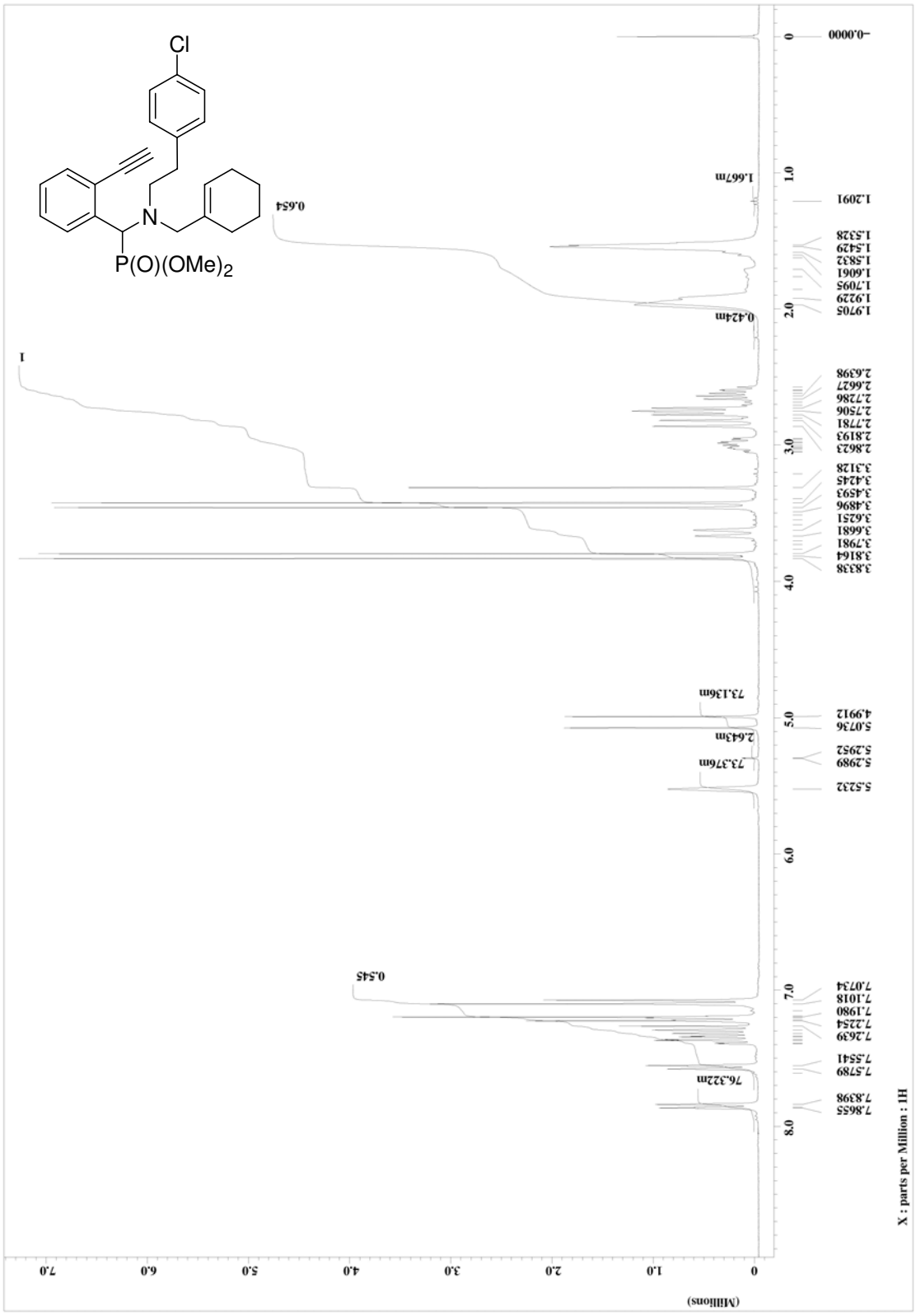
2f ^{1}H-Spectrum



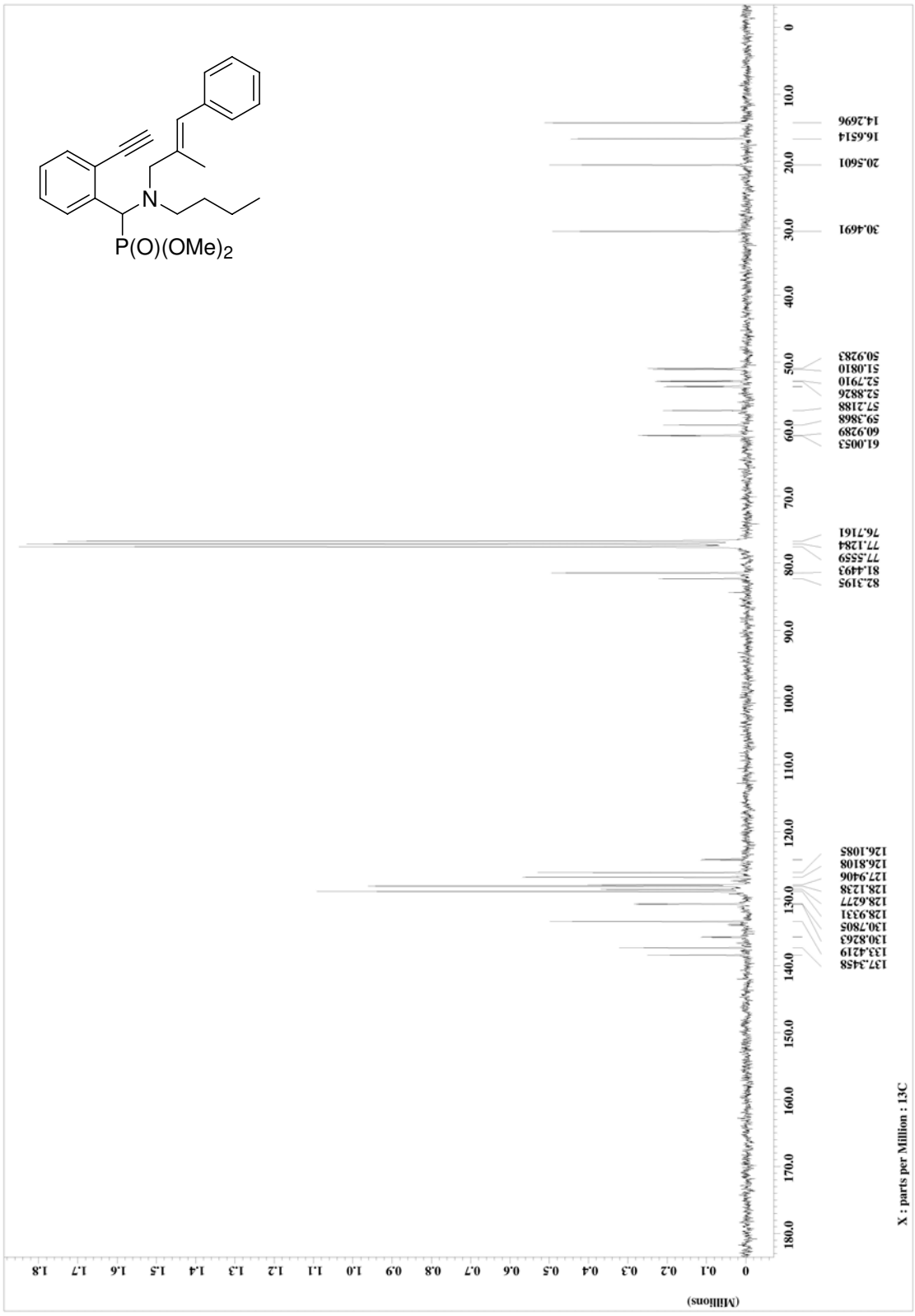
2g ^{13}C-Spectrum



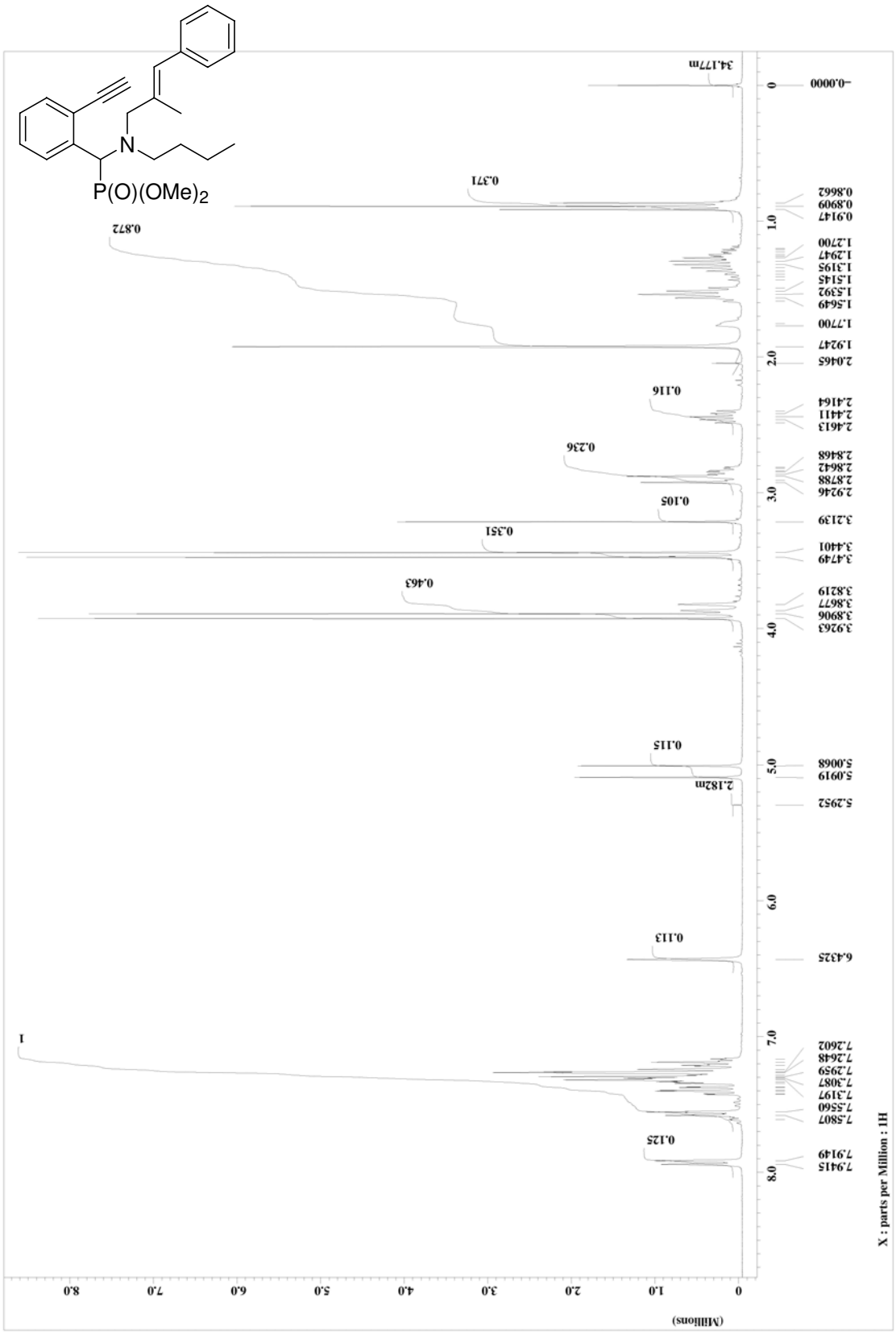
2g ^{1}H-Spectrum



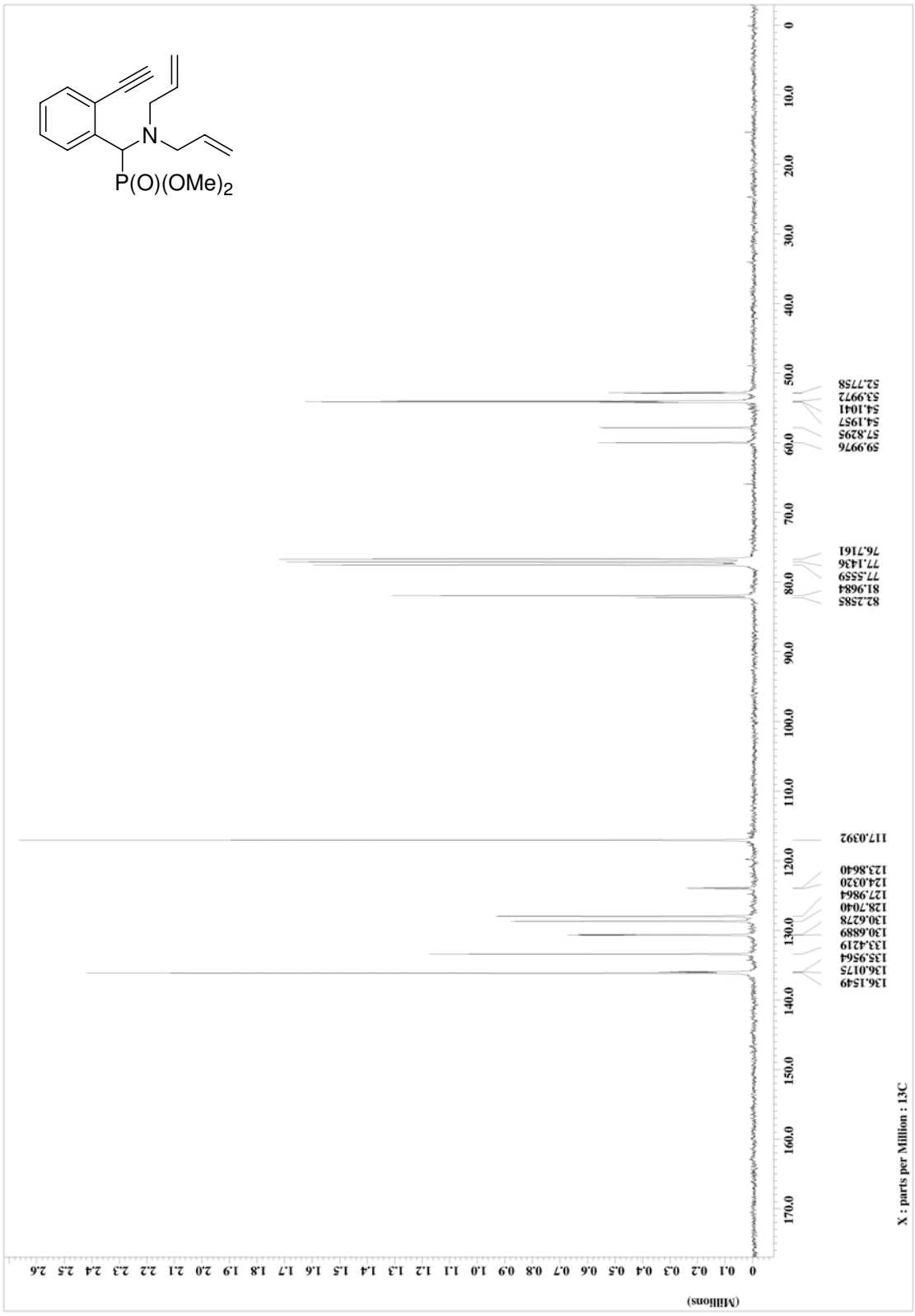
2h ^{13}C-Spectrum



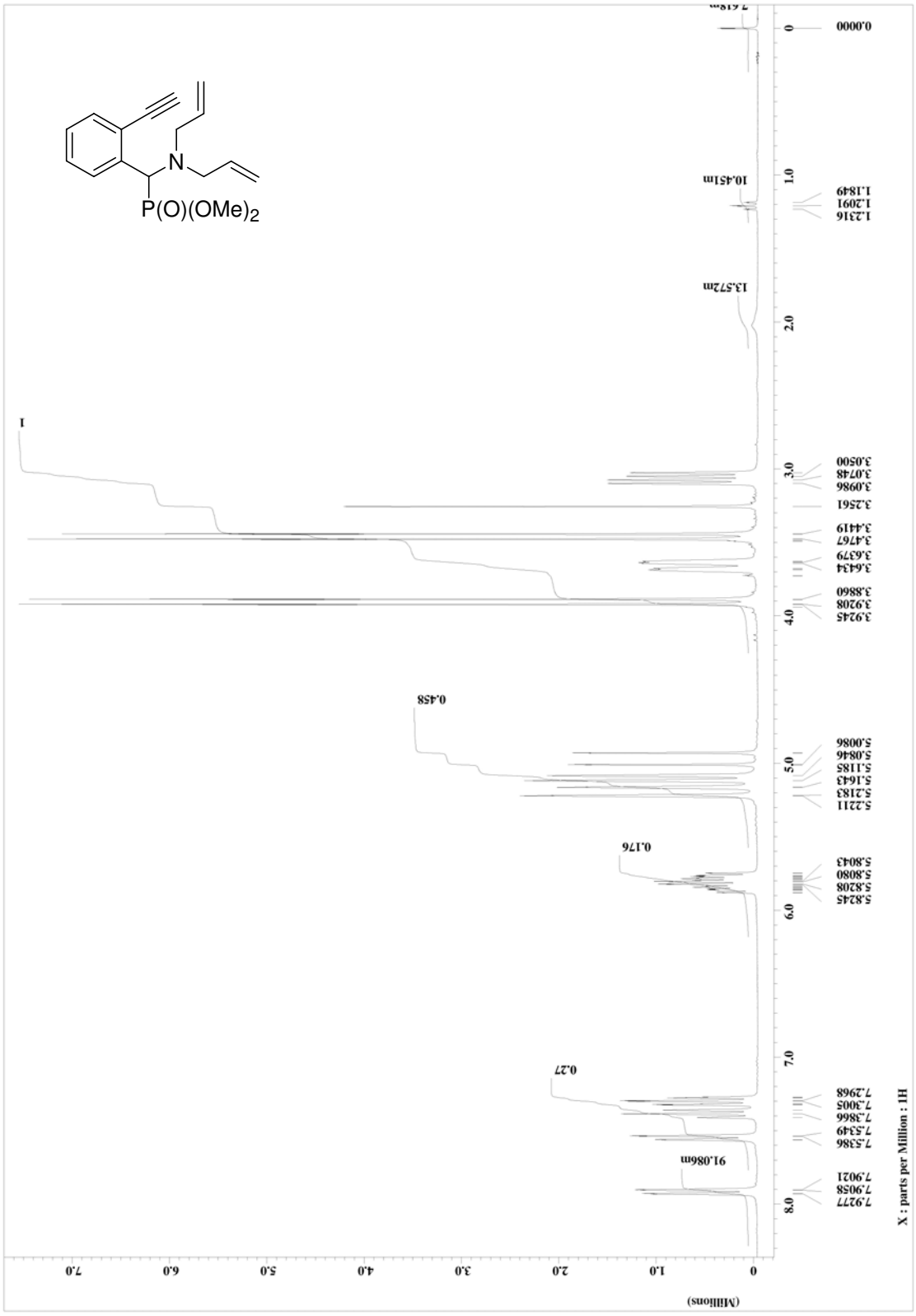
2h ^{1}H-Spectrum



2i ^{13}C-Spectrum



2i ^{1}H-Spectrum



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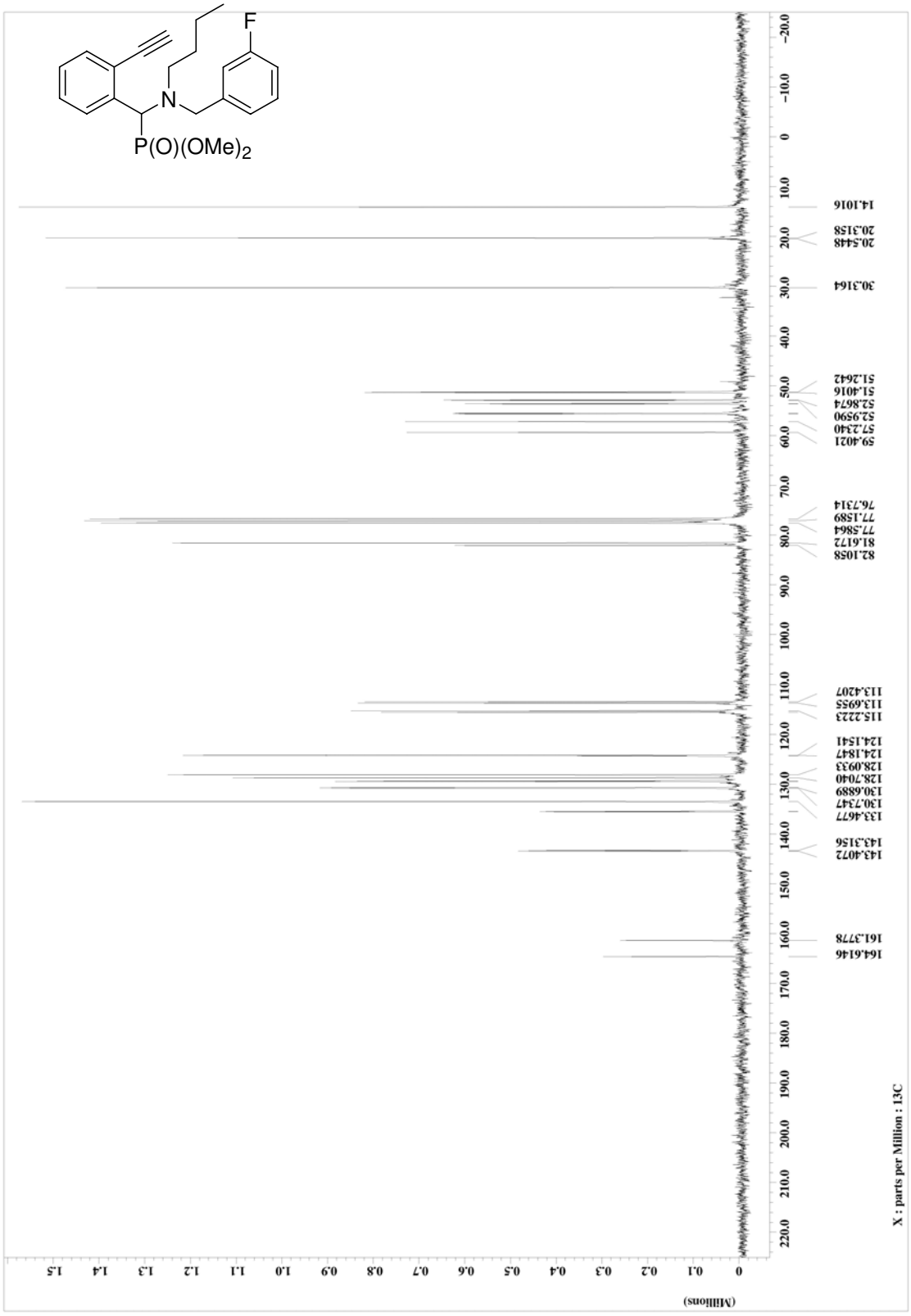

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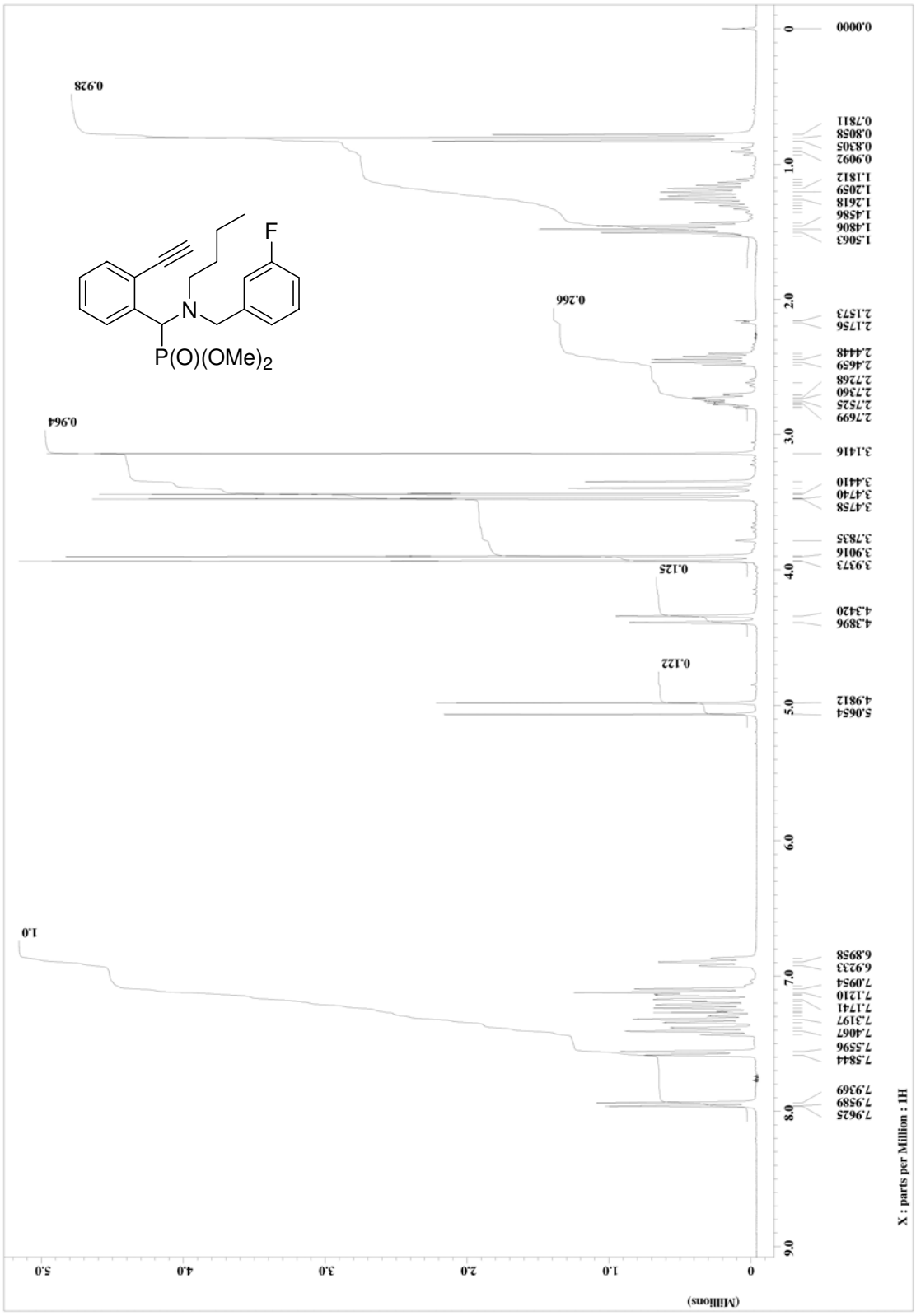
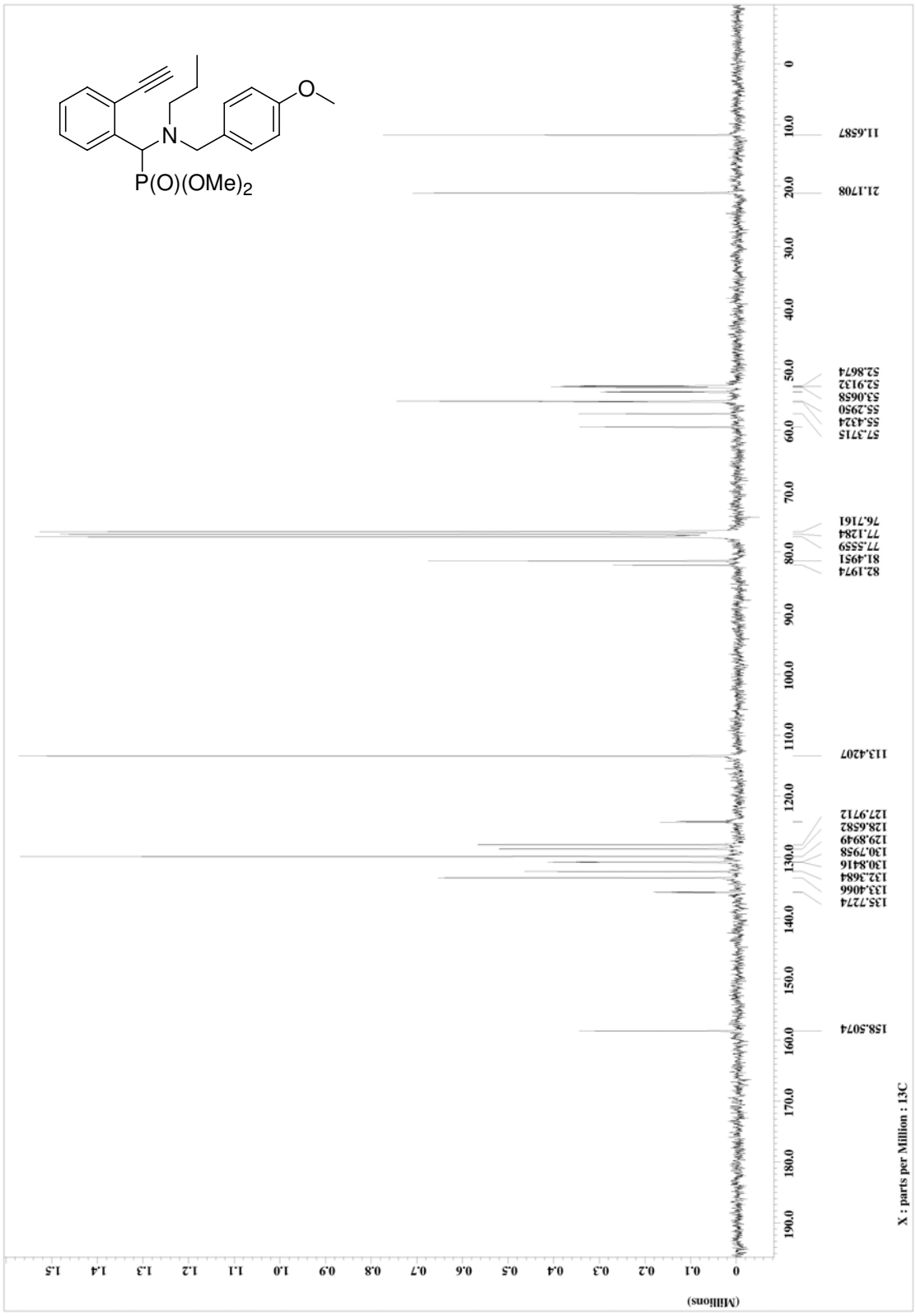
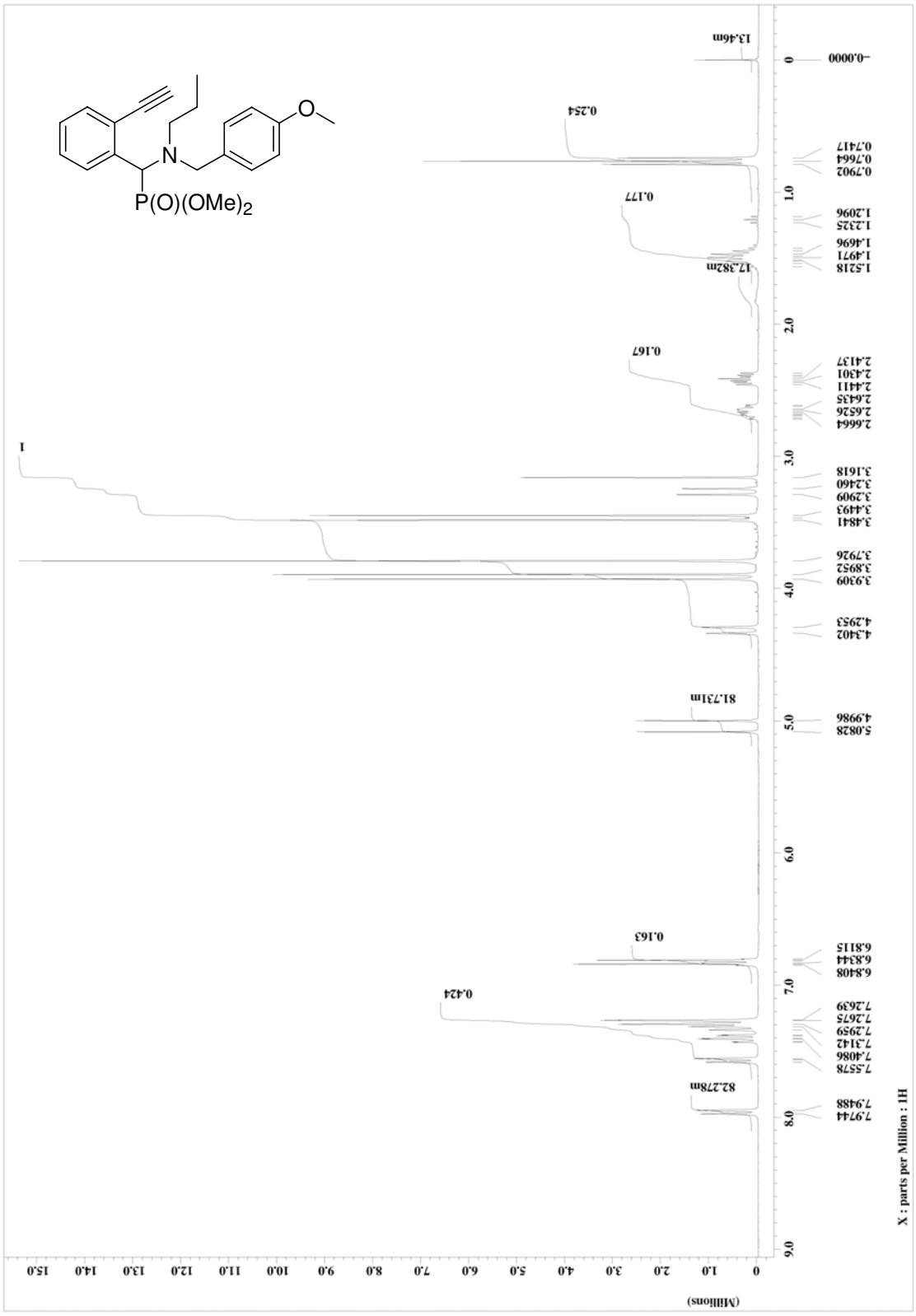


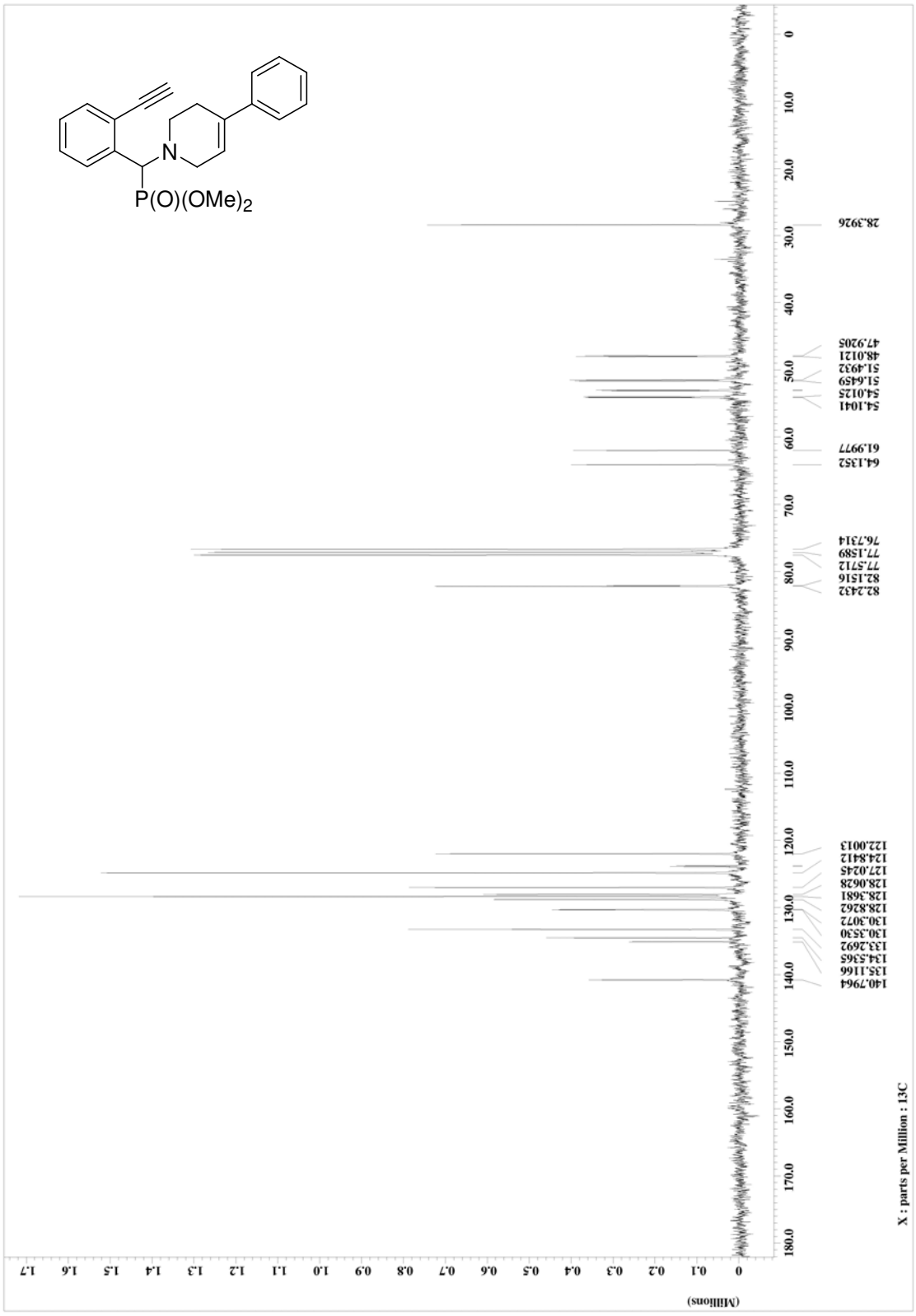
2k ^{13}C-Spectrum



2k ^{1}H-Spectrum



2l ^{13}C-Spectrum



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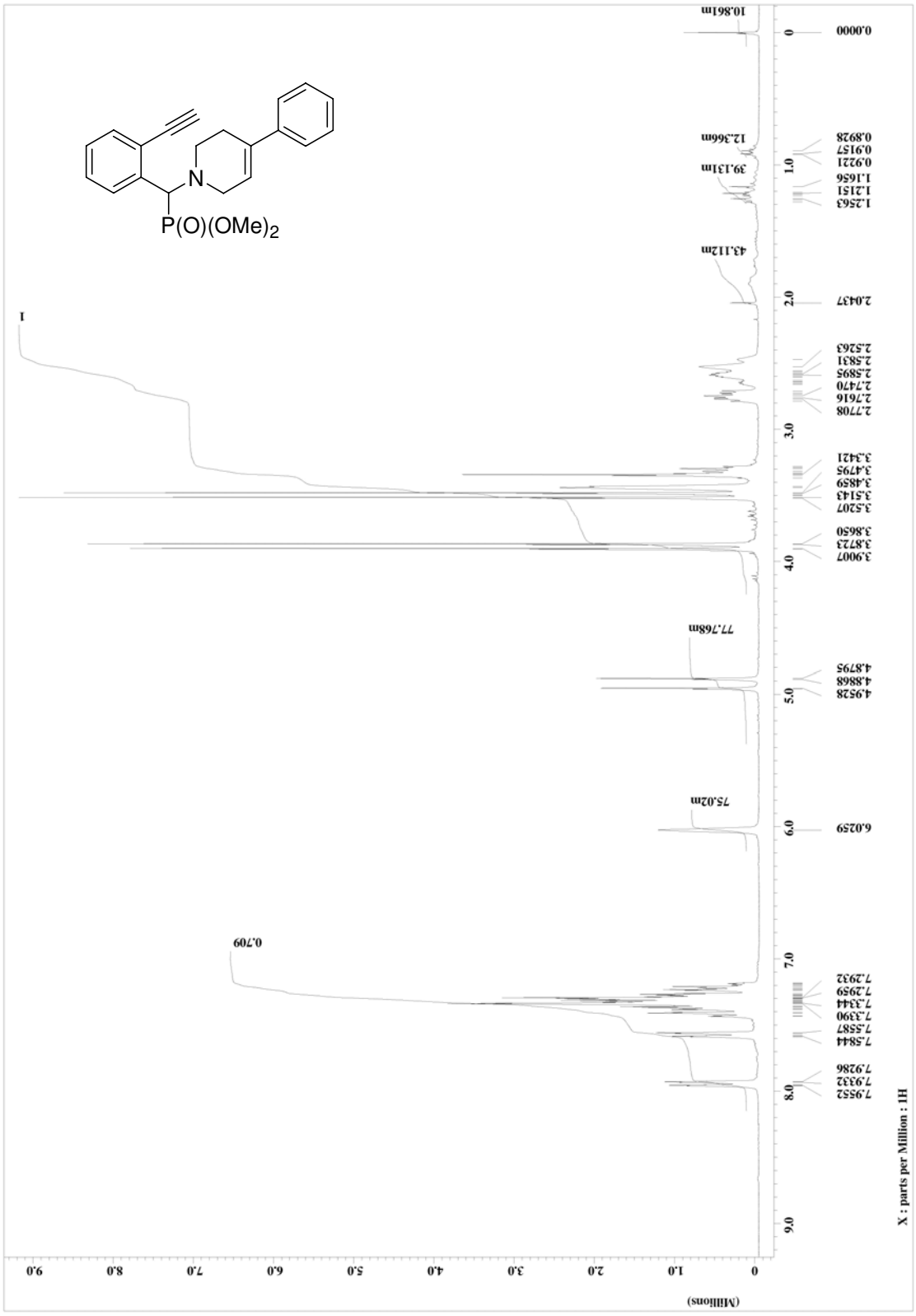
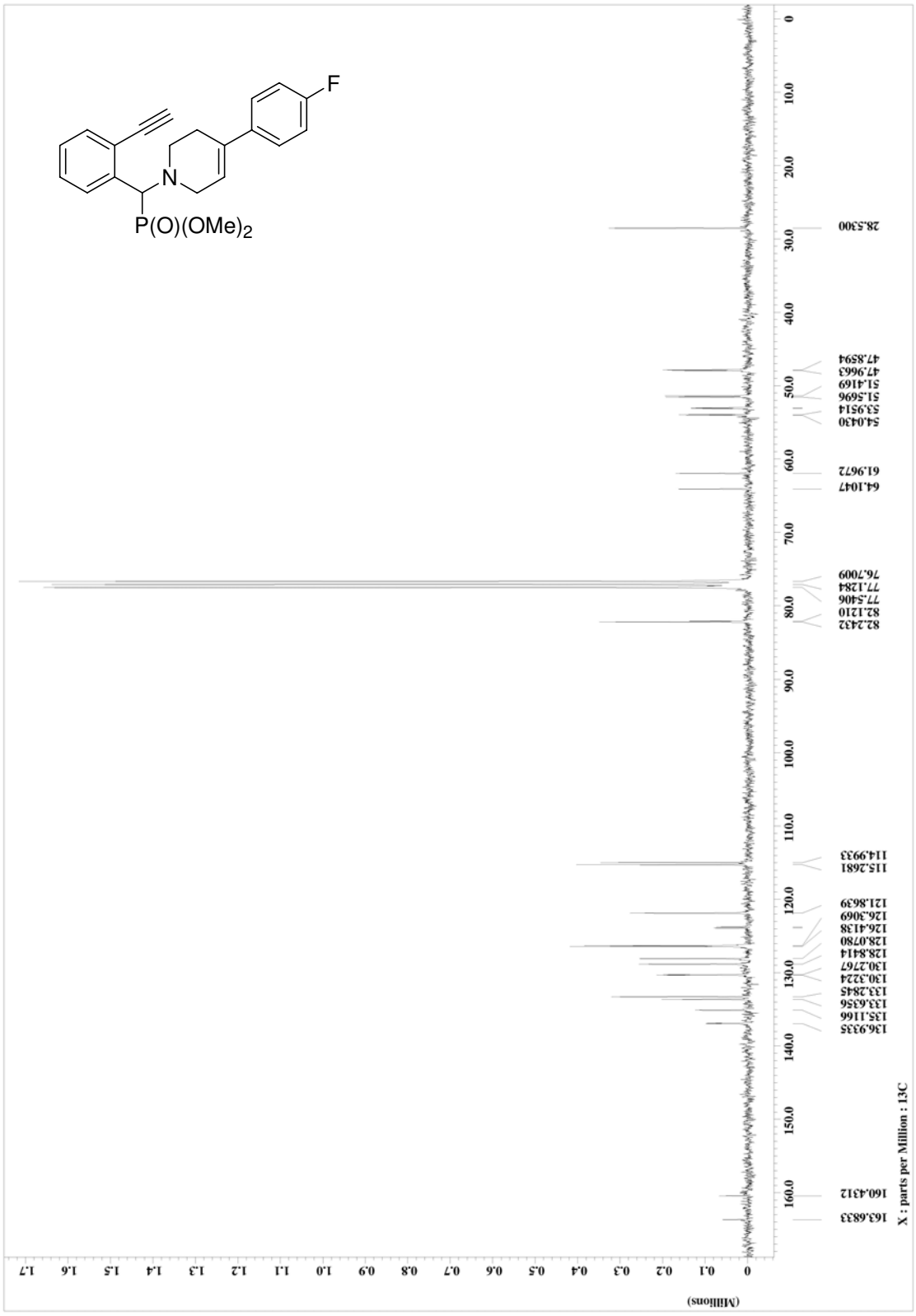
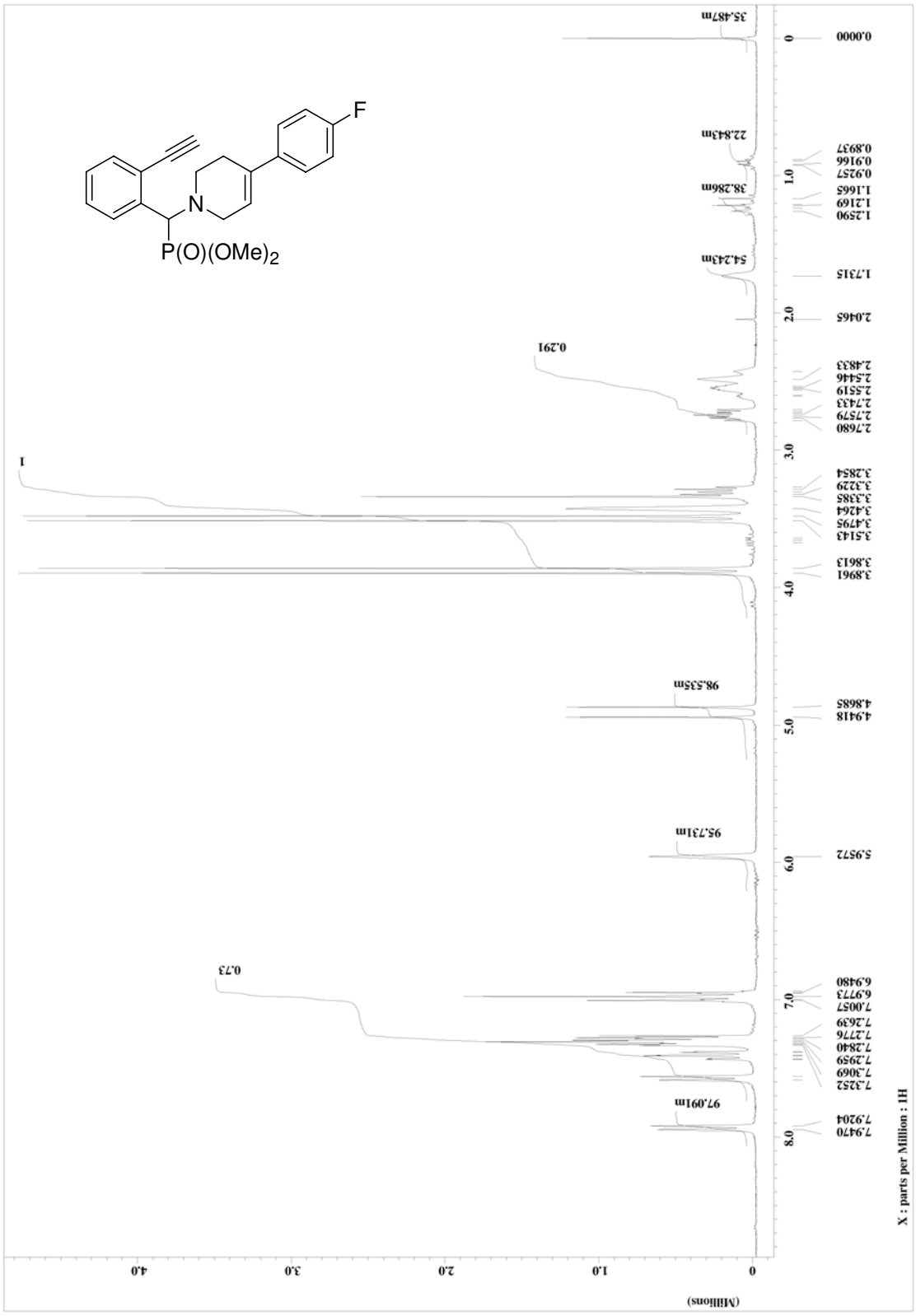


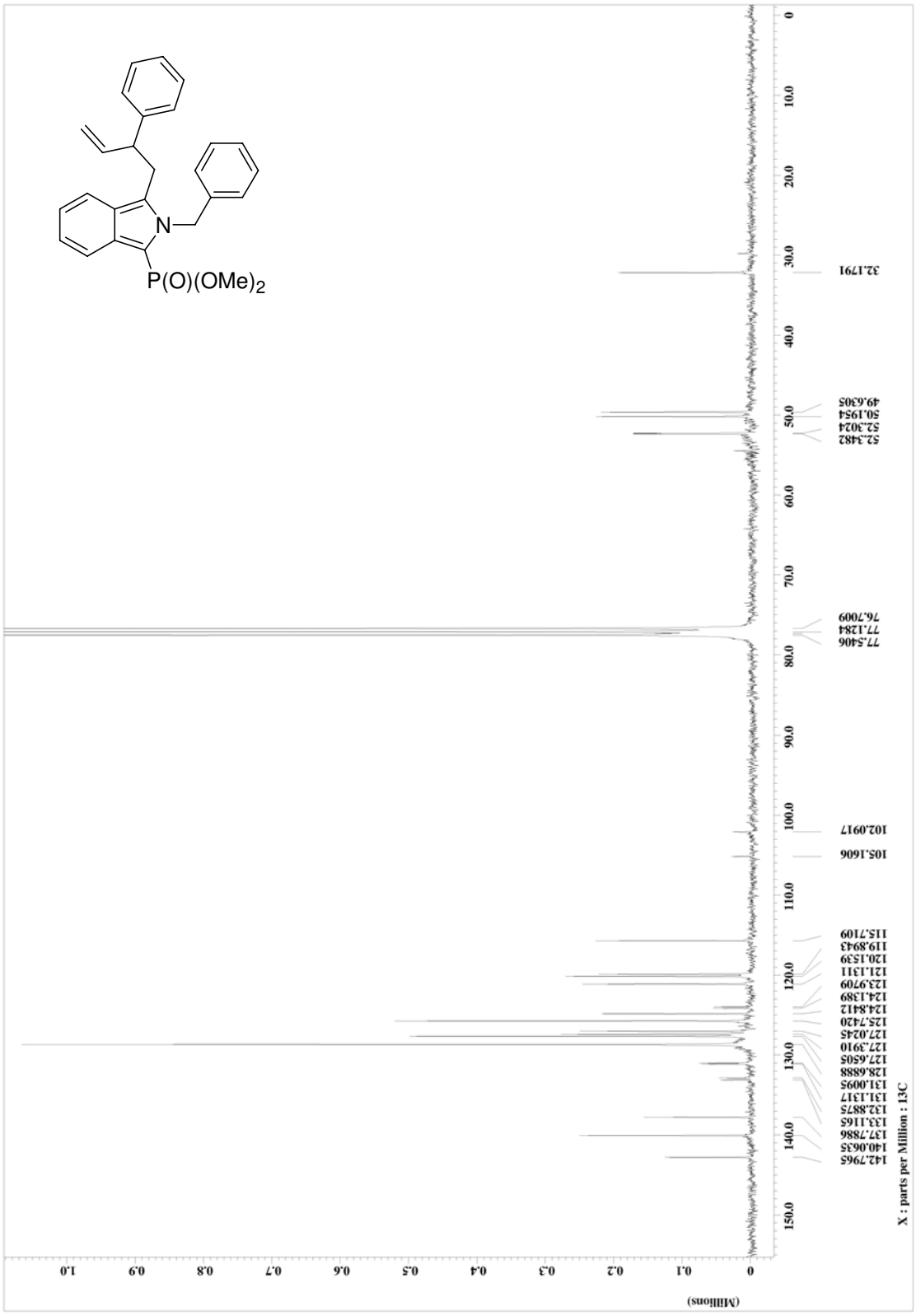
2m ^{13}C-Spectrum



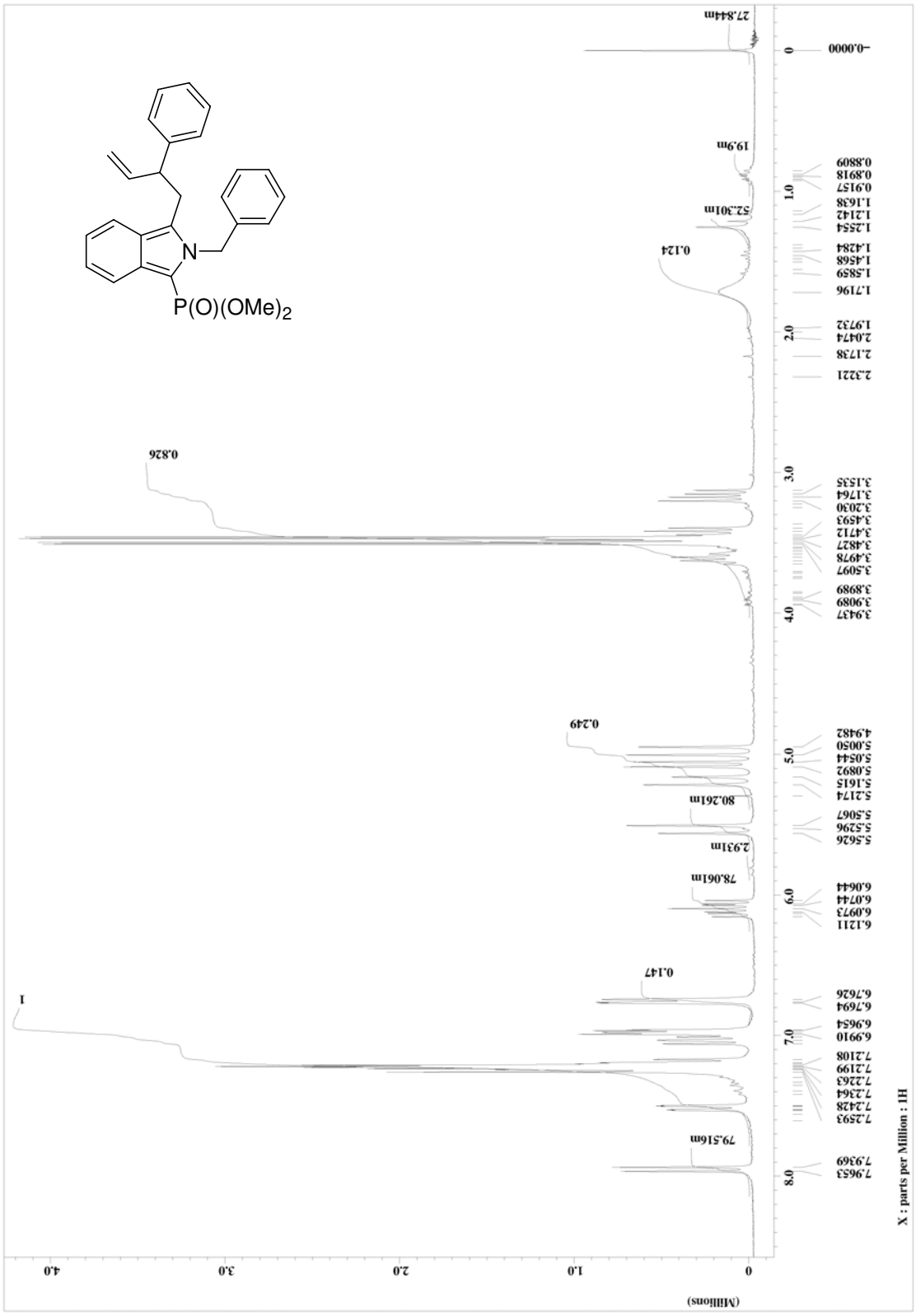
2m ^{1}H-Spectrum



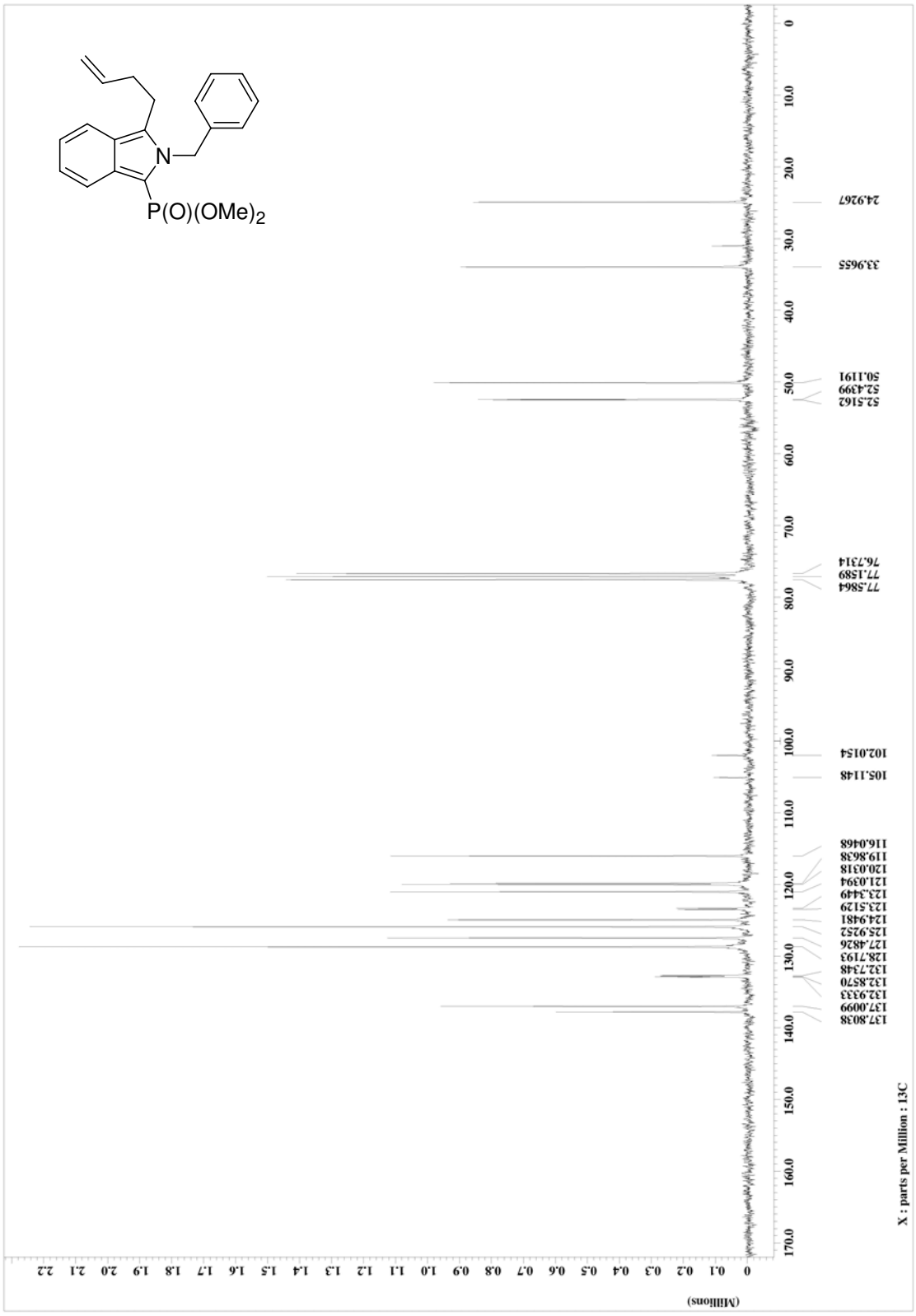
4a ^{13}C-Spectrum



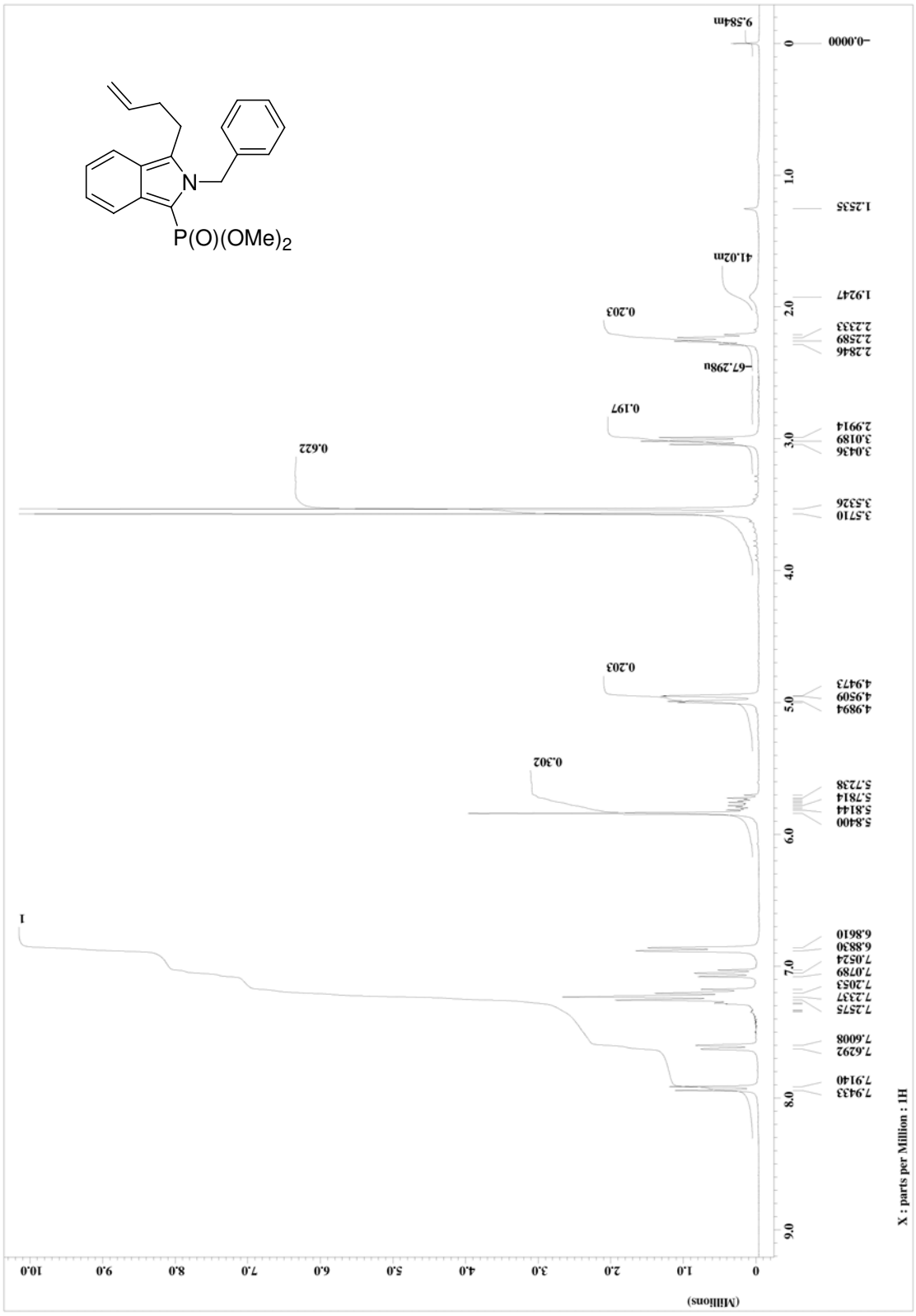
4a ^{1}H-Spectrum



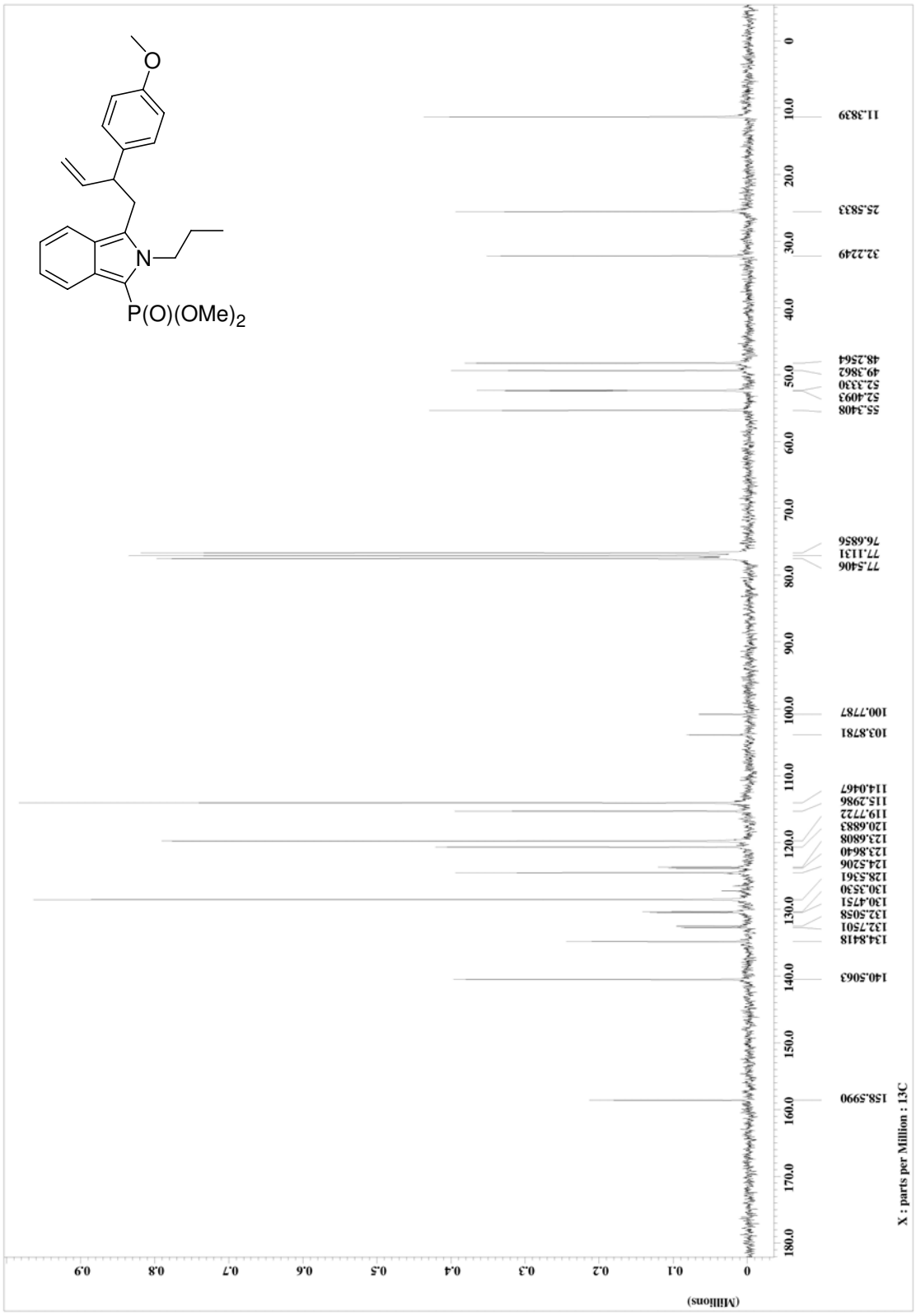
4b ^{13}C-Spectrum



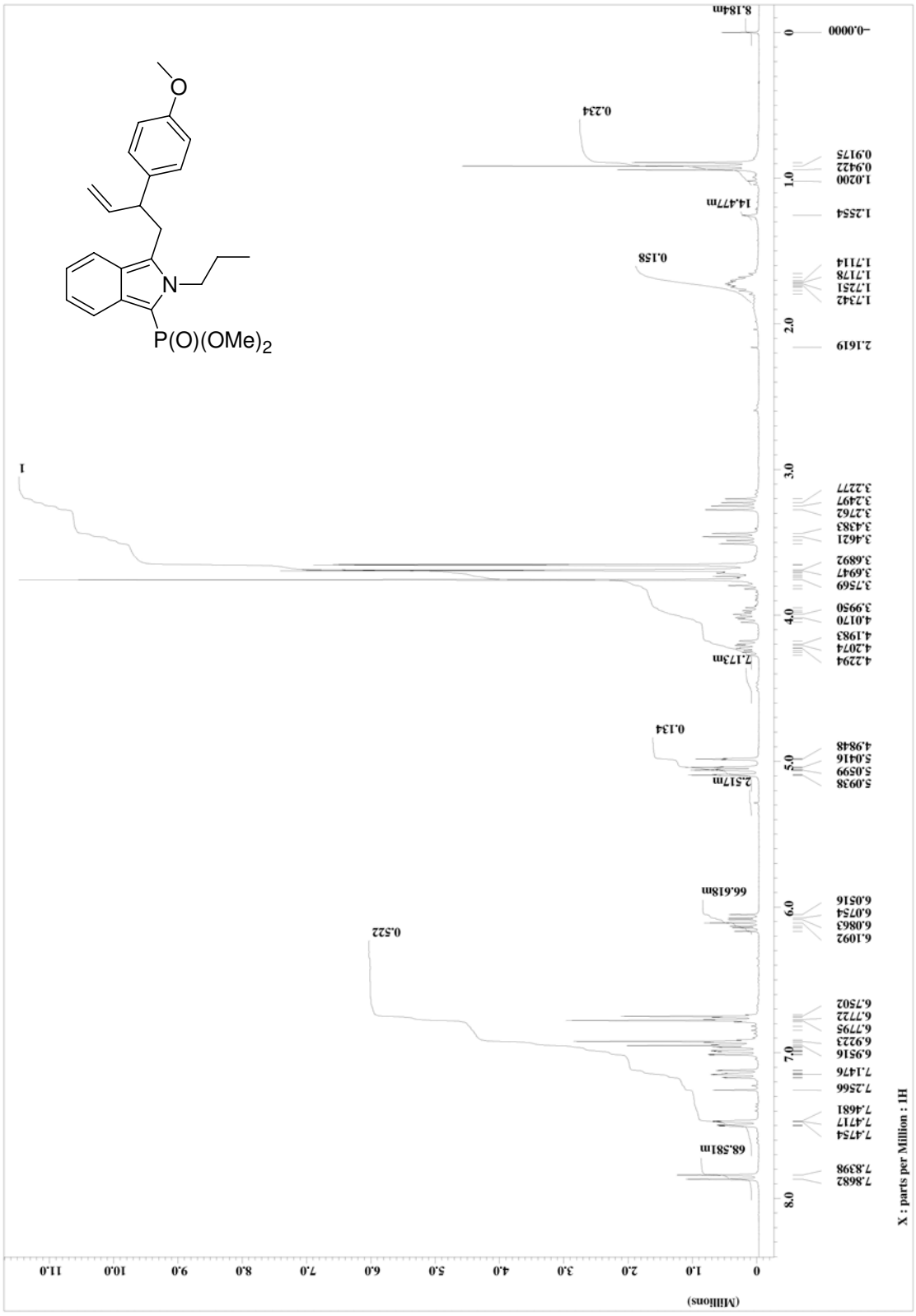
4b ^{1}H-Spectrum



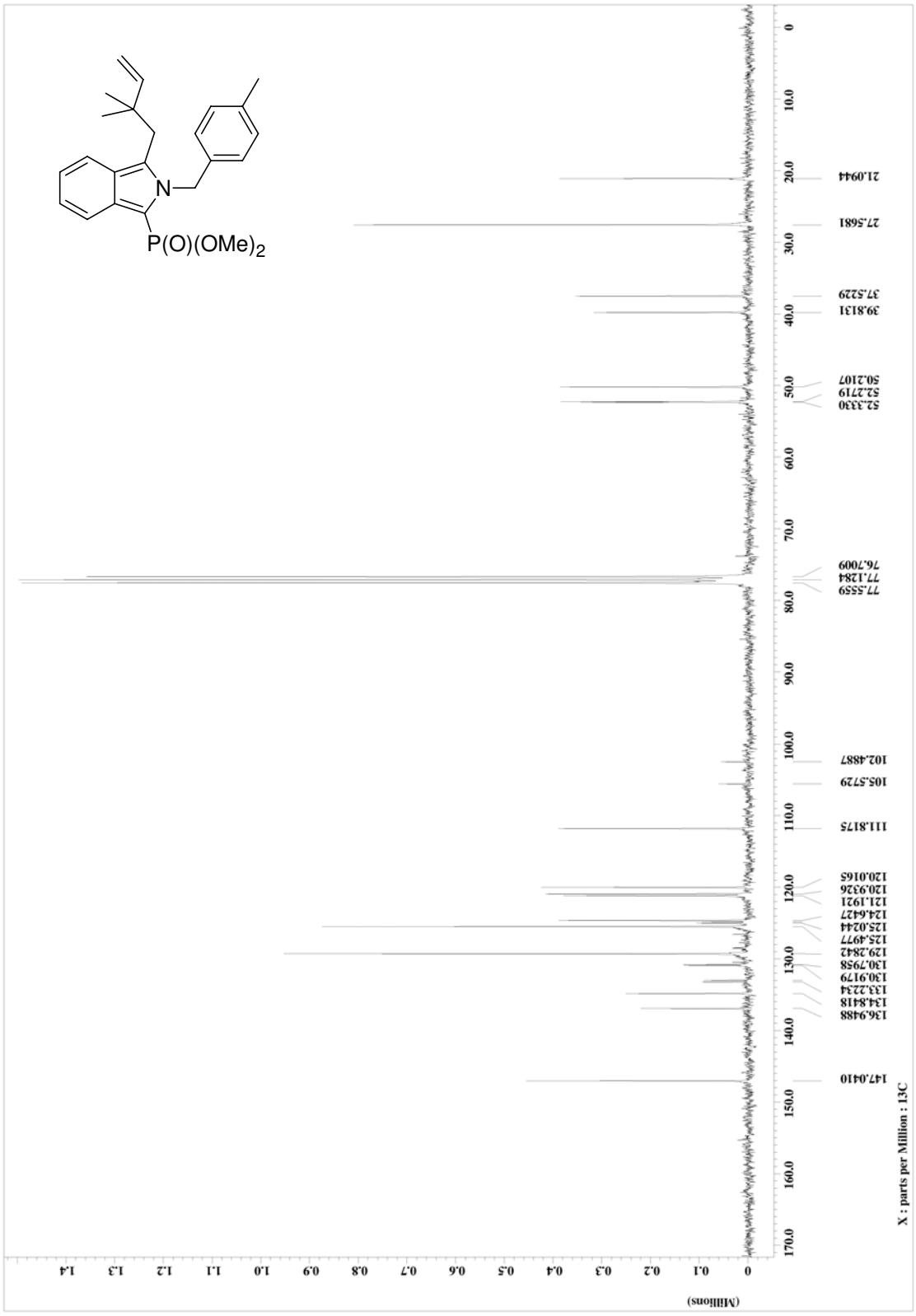
4c ^{13}C-Spectrum



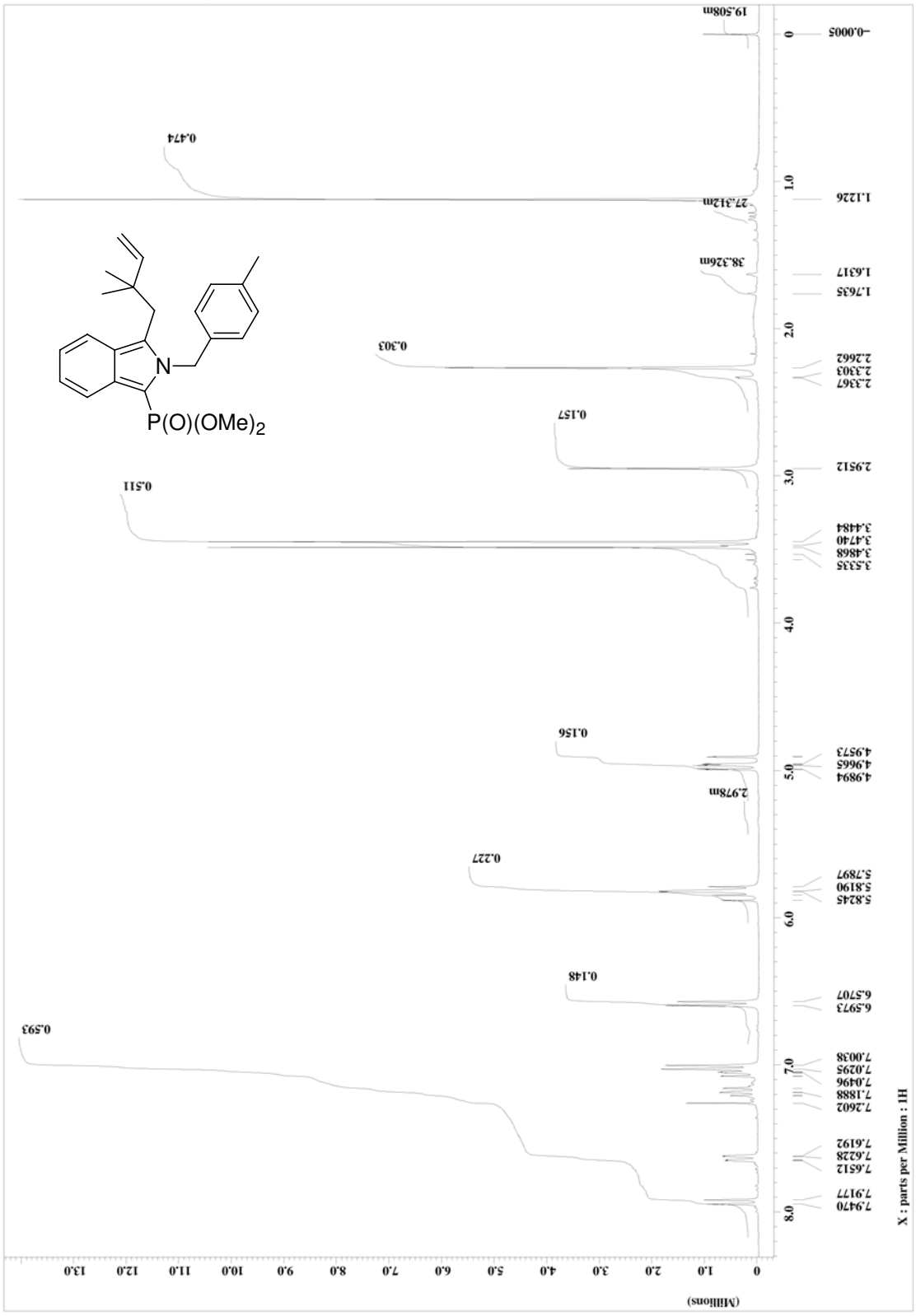
4c ^{1}H-Spectrum



4d ^{13}C-Spectrum



4d ^{1}H-Spectrum



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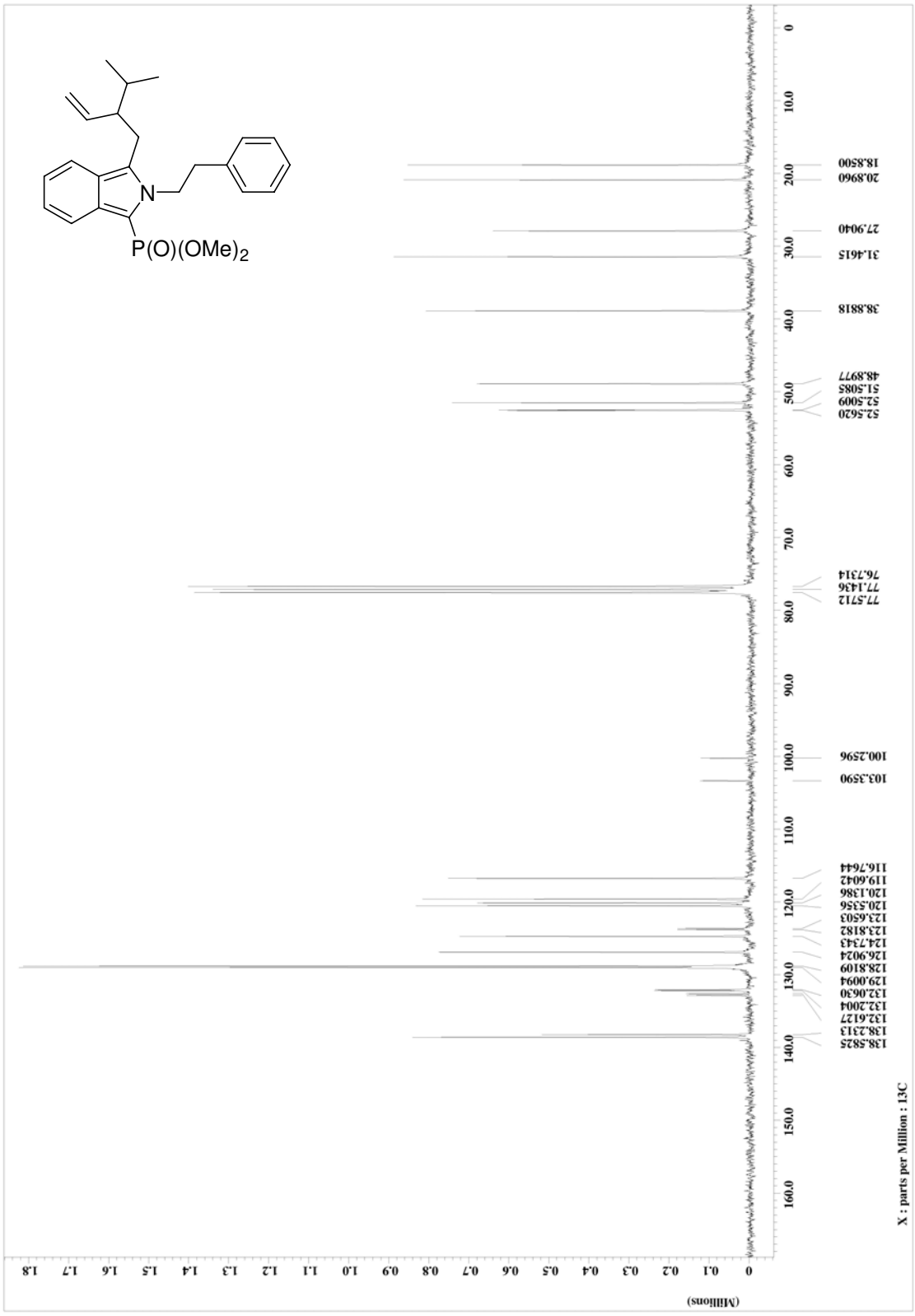
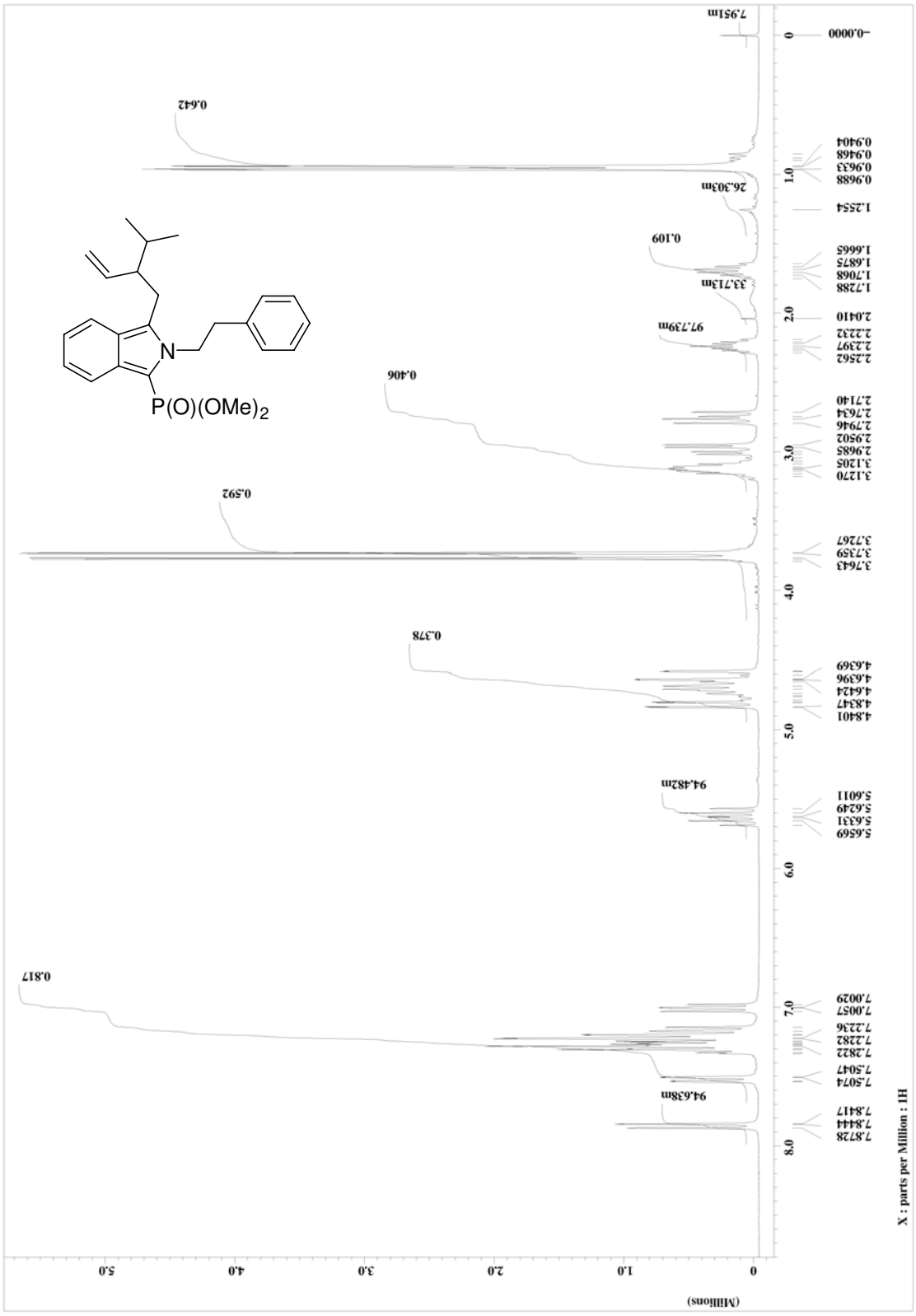
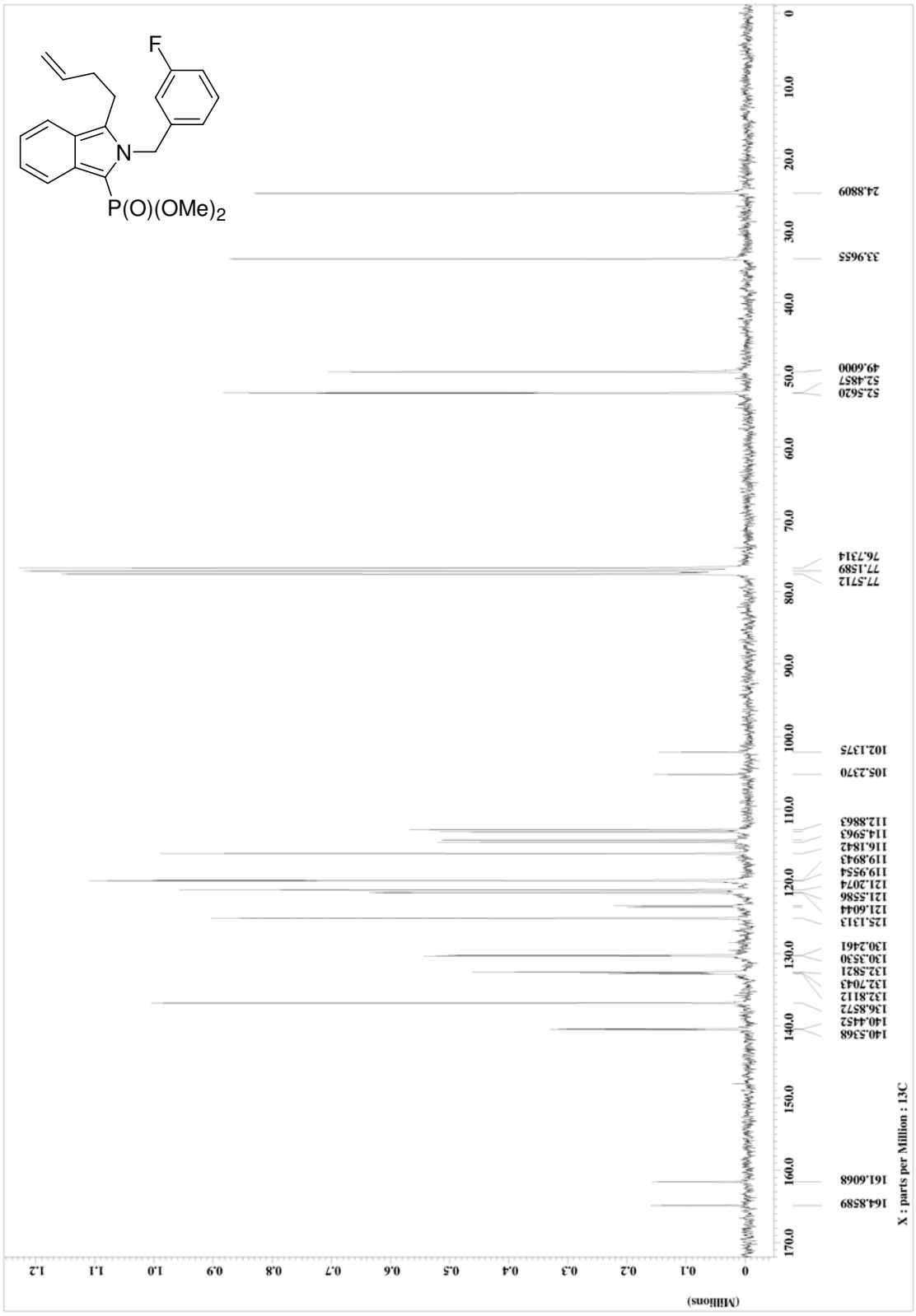


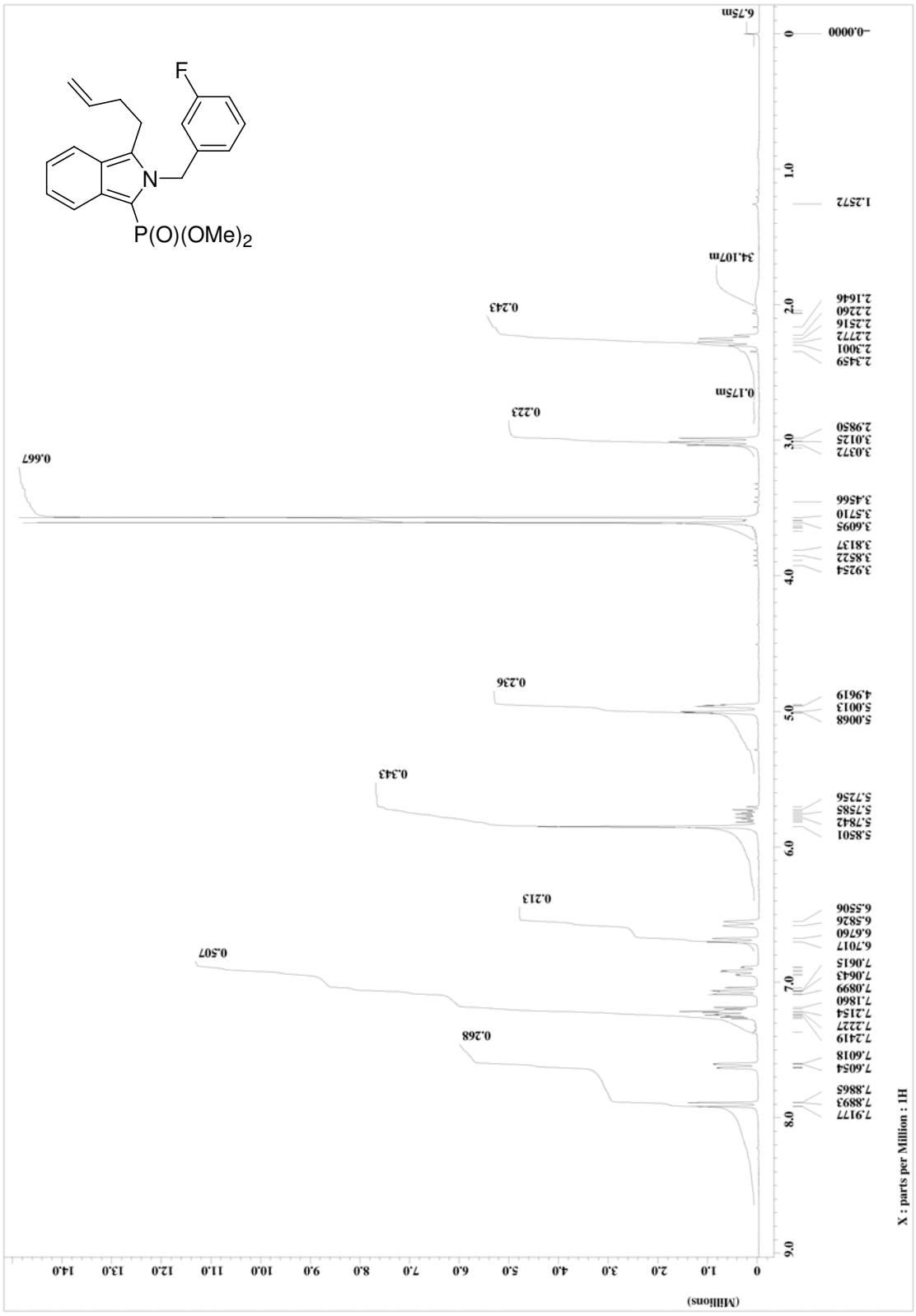
4e ^{1}H-Spectrum



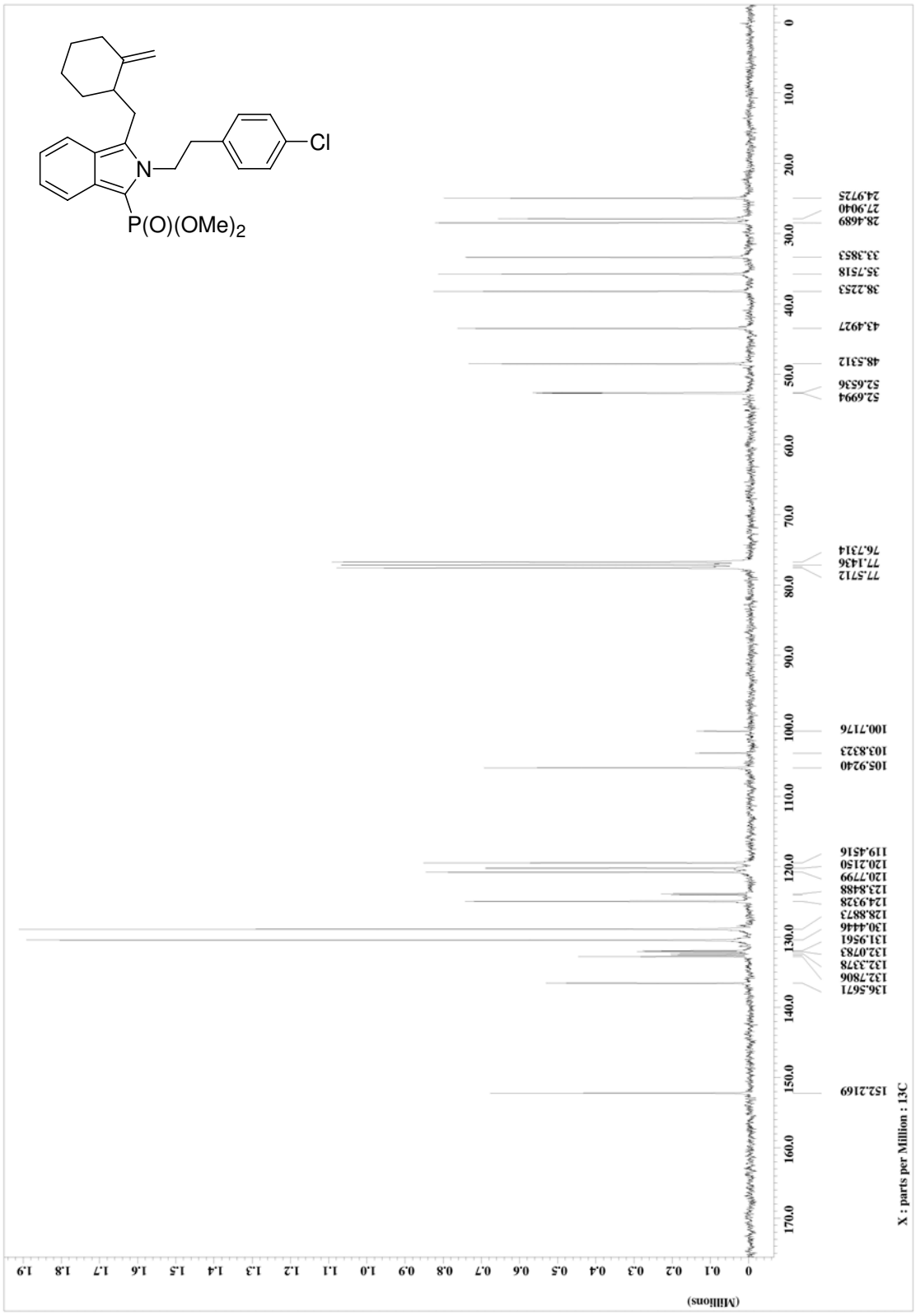
4f ^{13}C-Spectrum



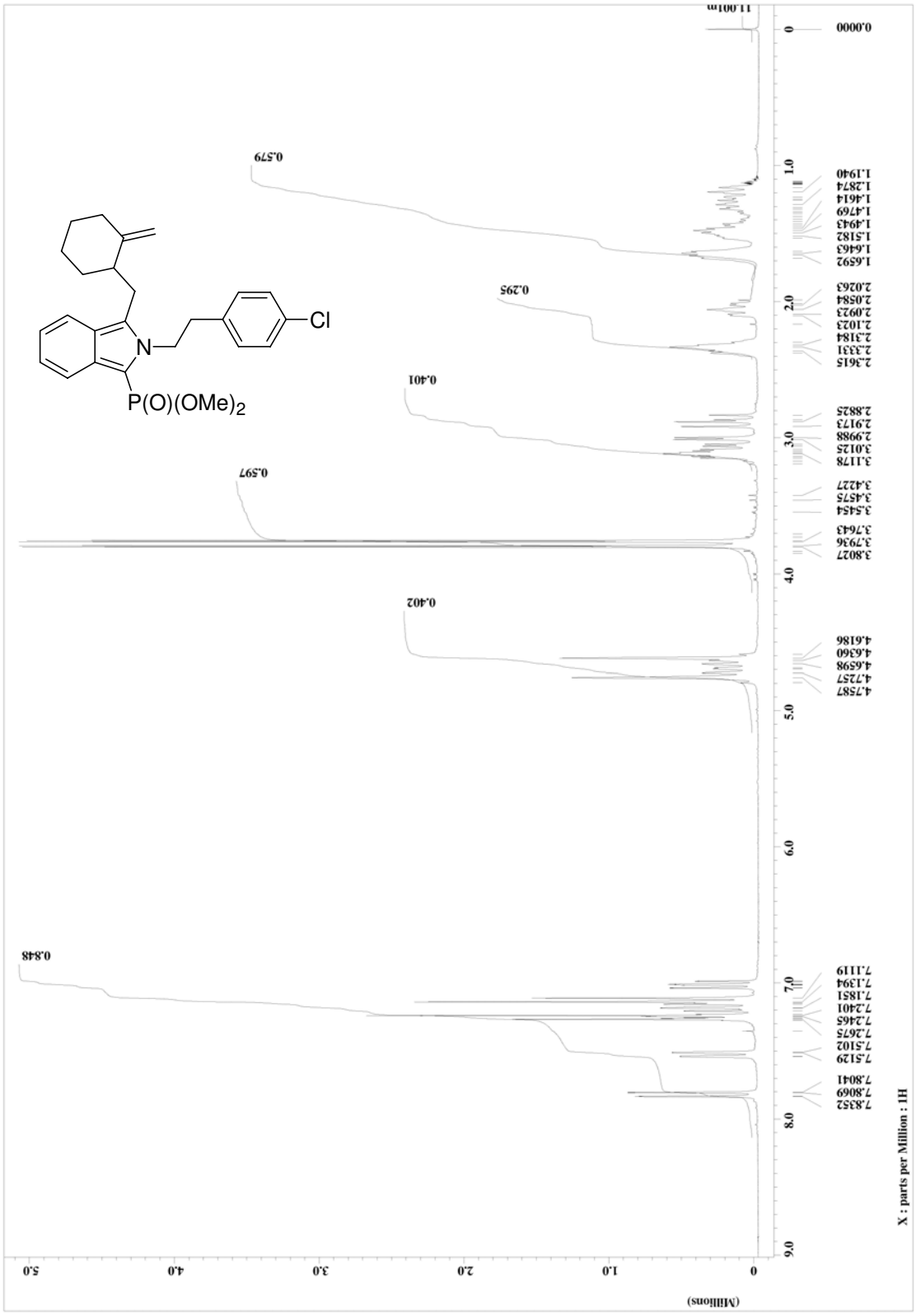
4f ^{1}H-Spectrum



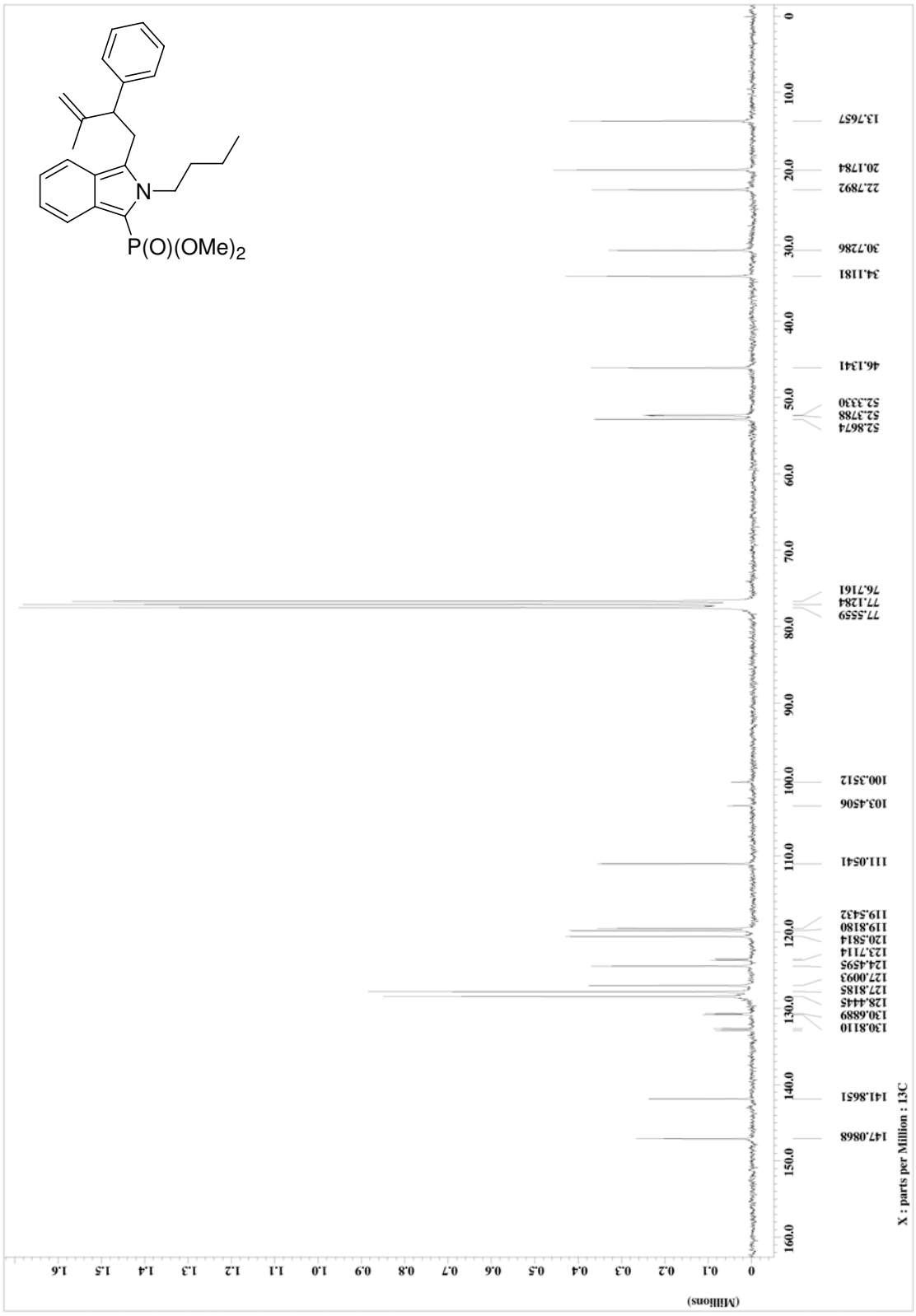
4g ^{13}C-Spectrum



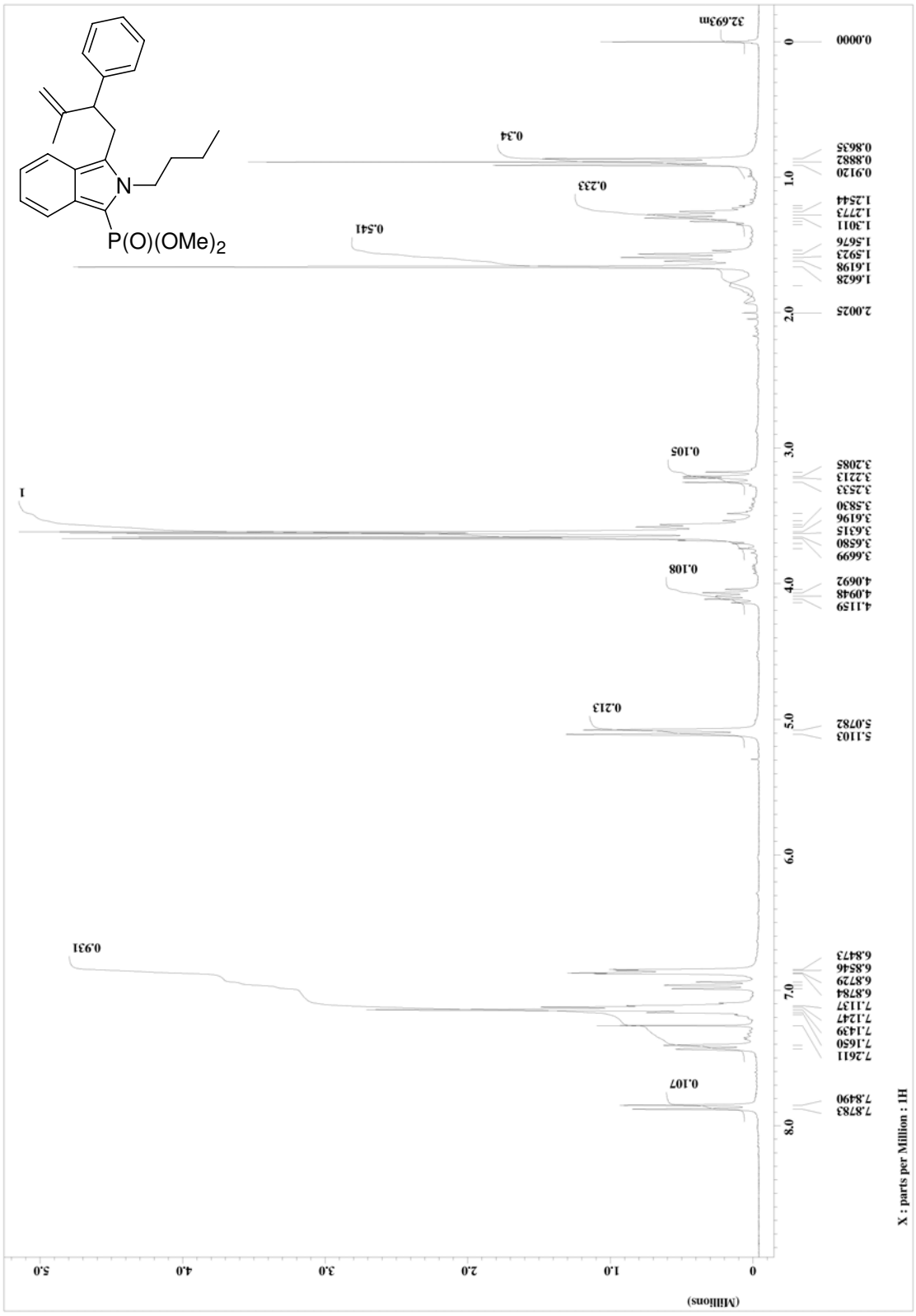
4g ^{1}H-Spectrum



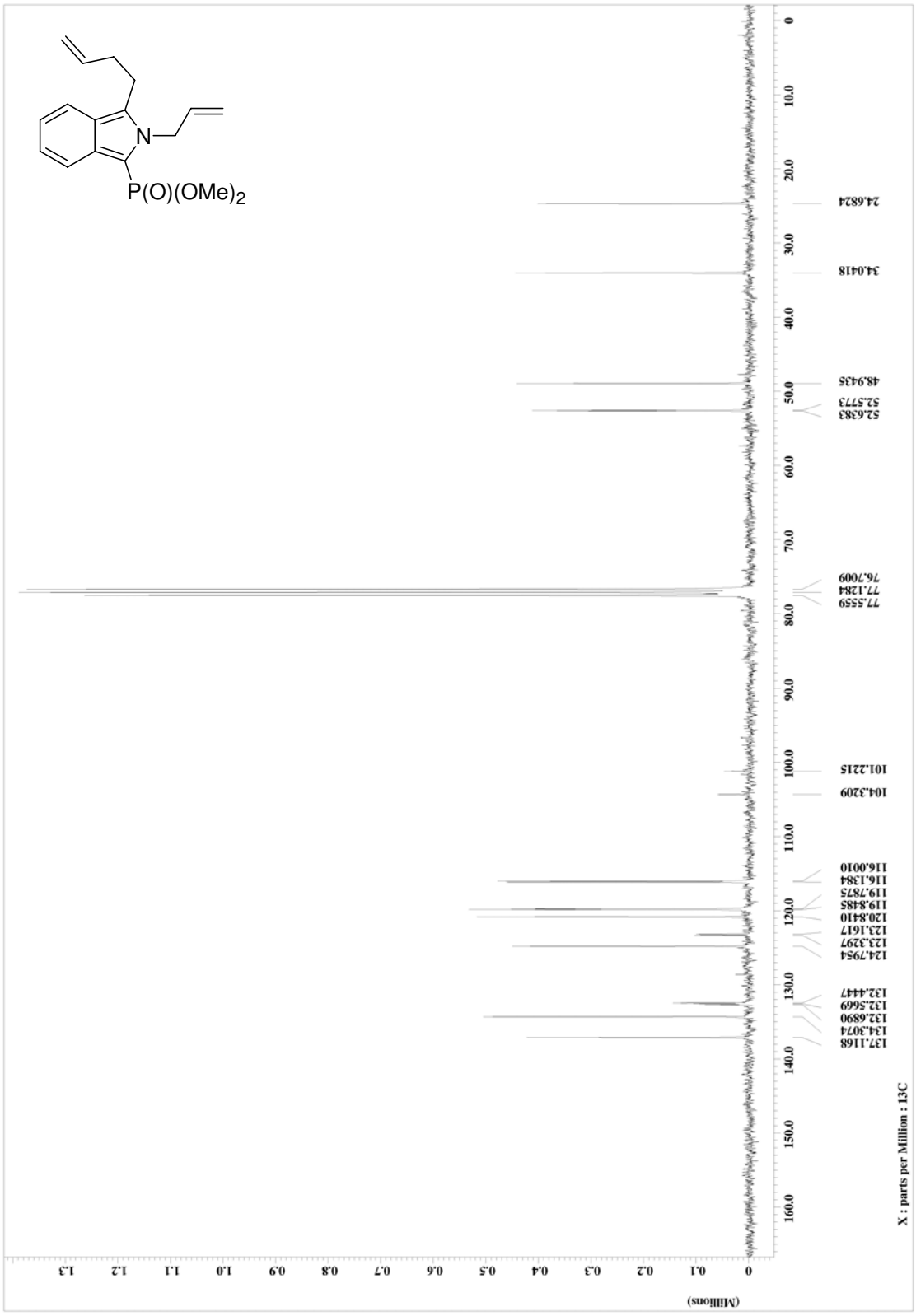
4h ^{13}C-Spectrum



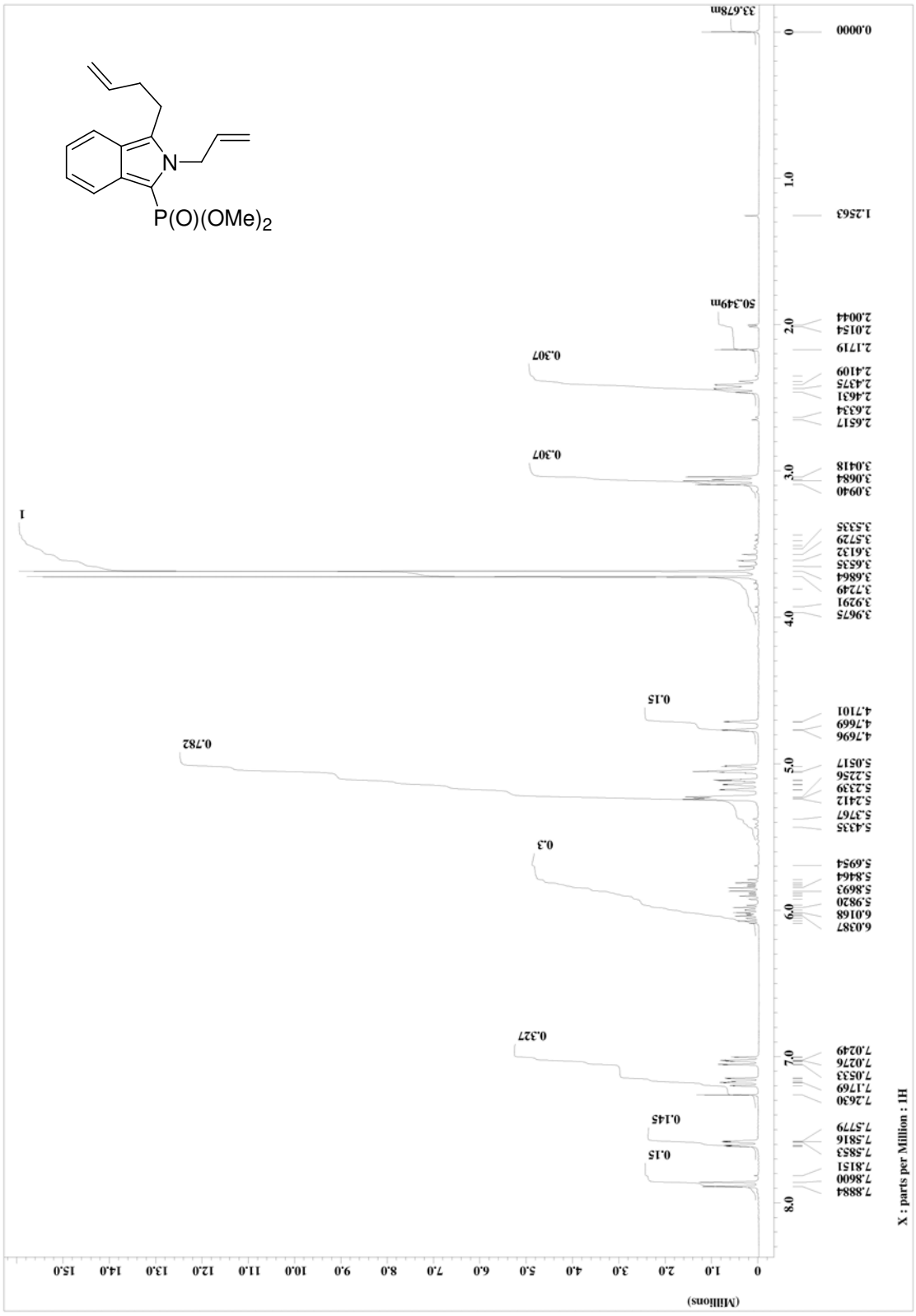
4h ^{1}H-Spectrum



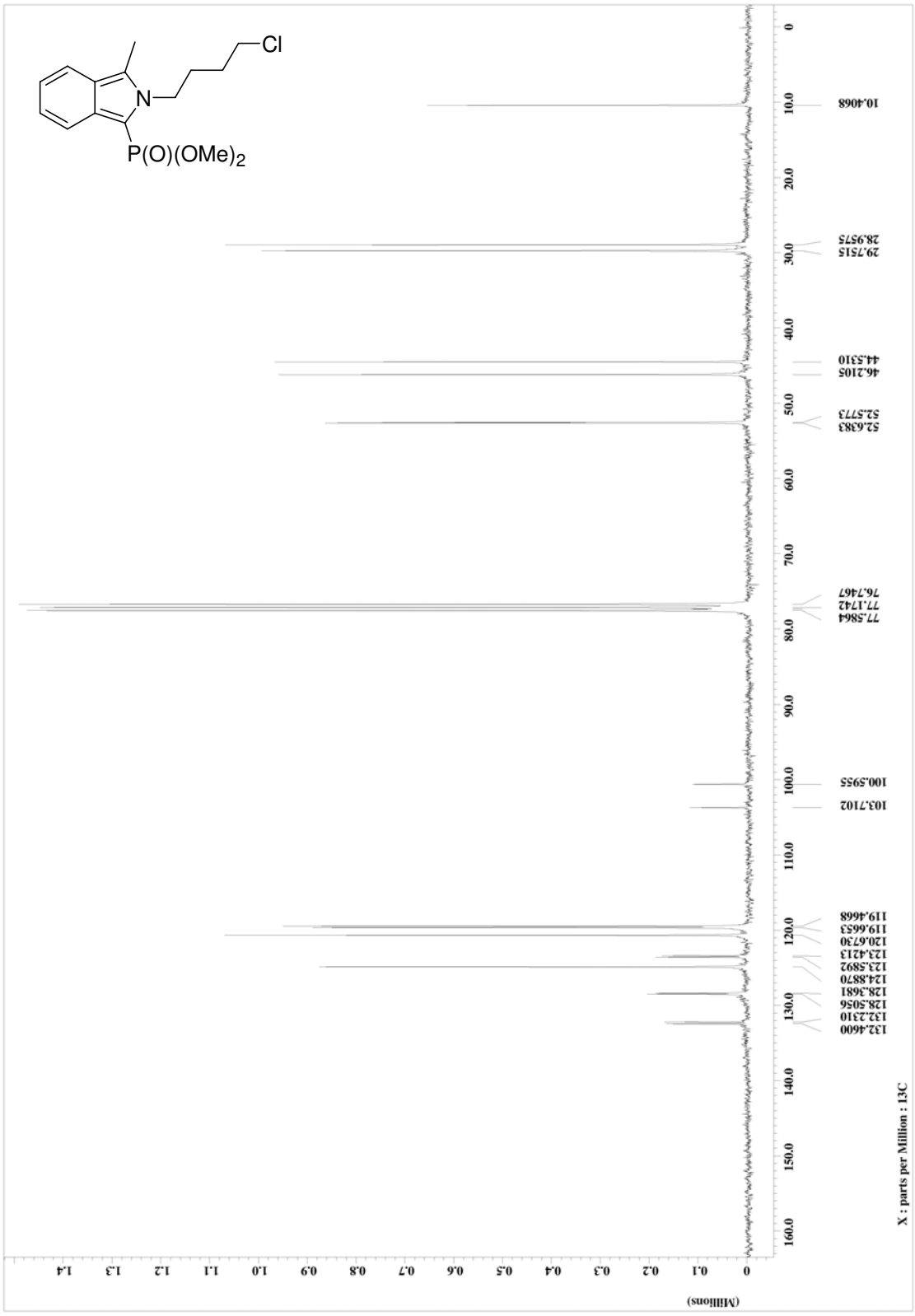
4i ^{13}C-Spectrum



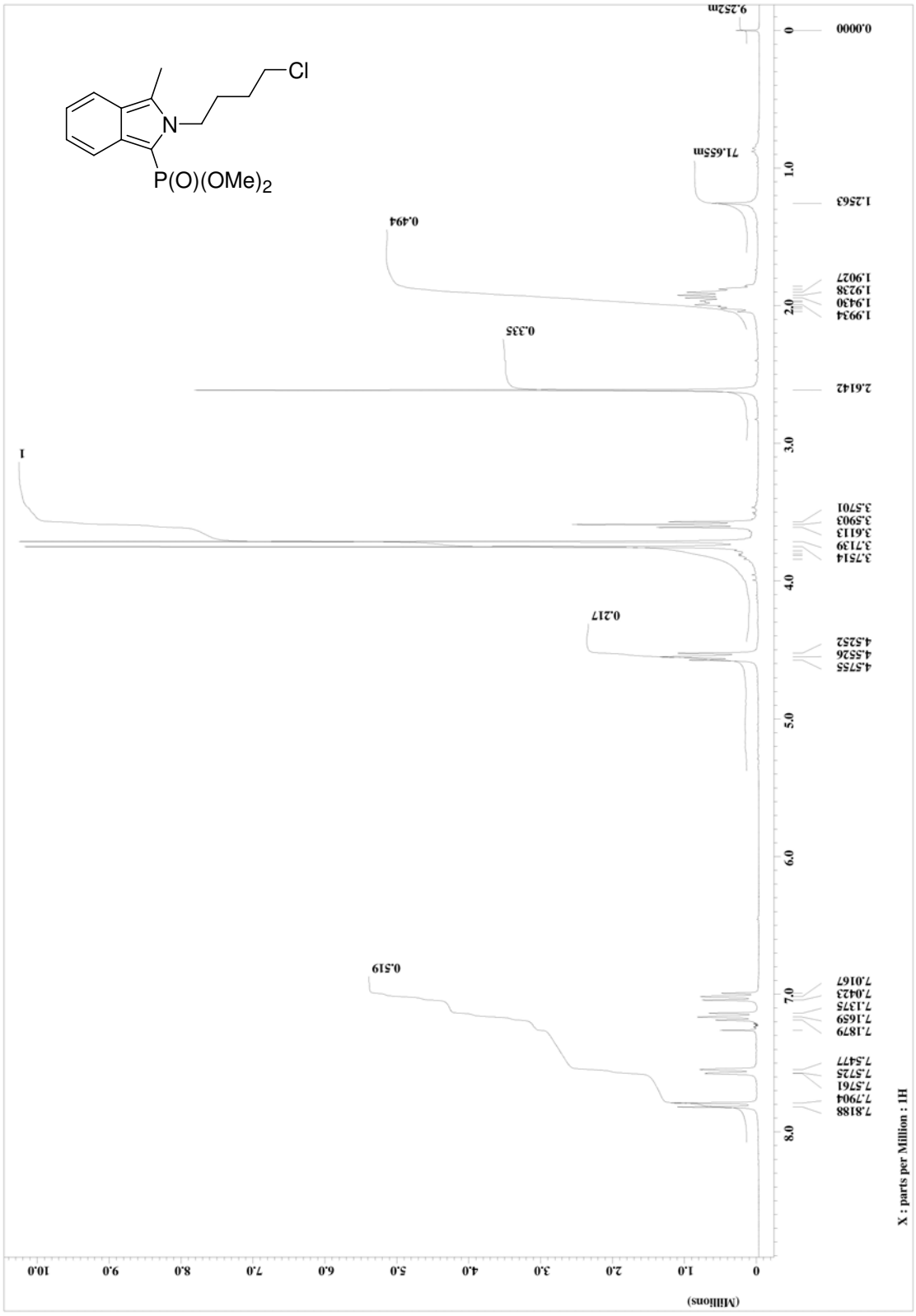
4i ^{1}H-Spectrum



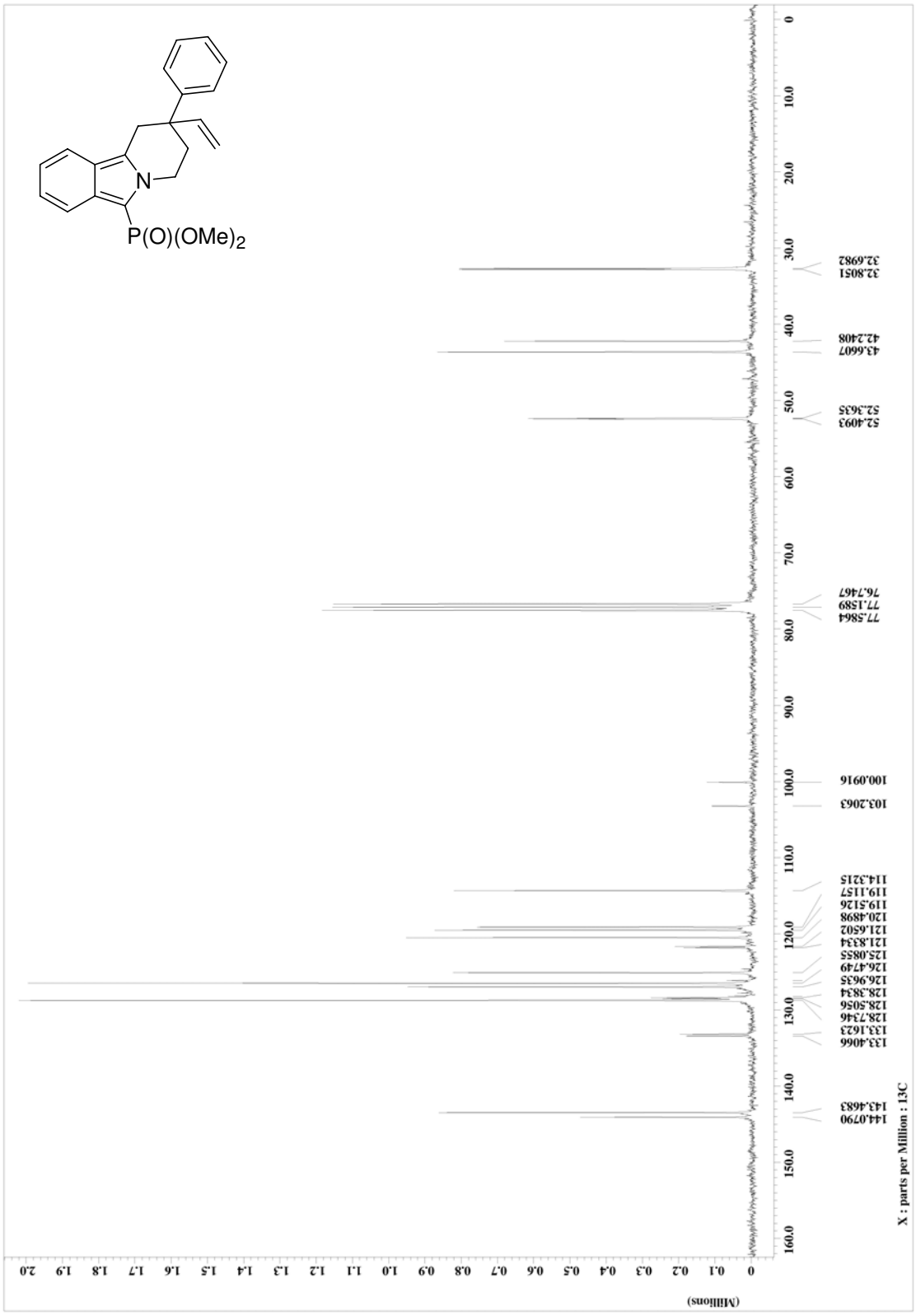
13 ^{13}C-Spectrum



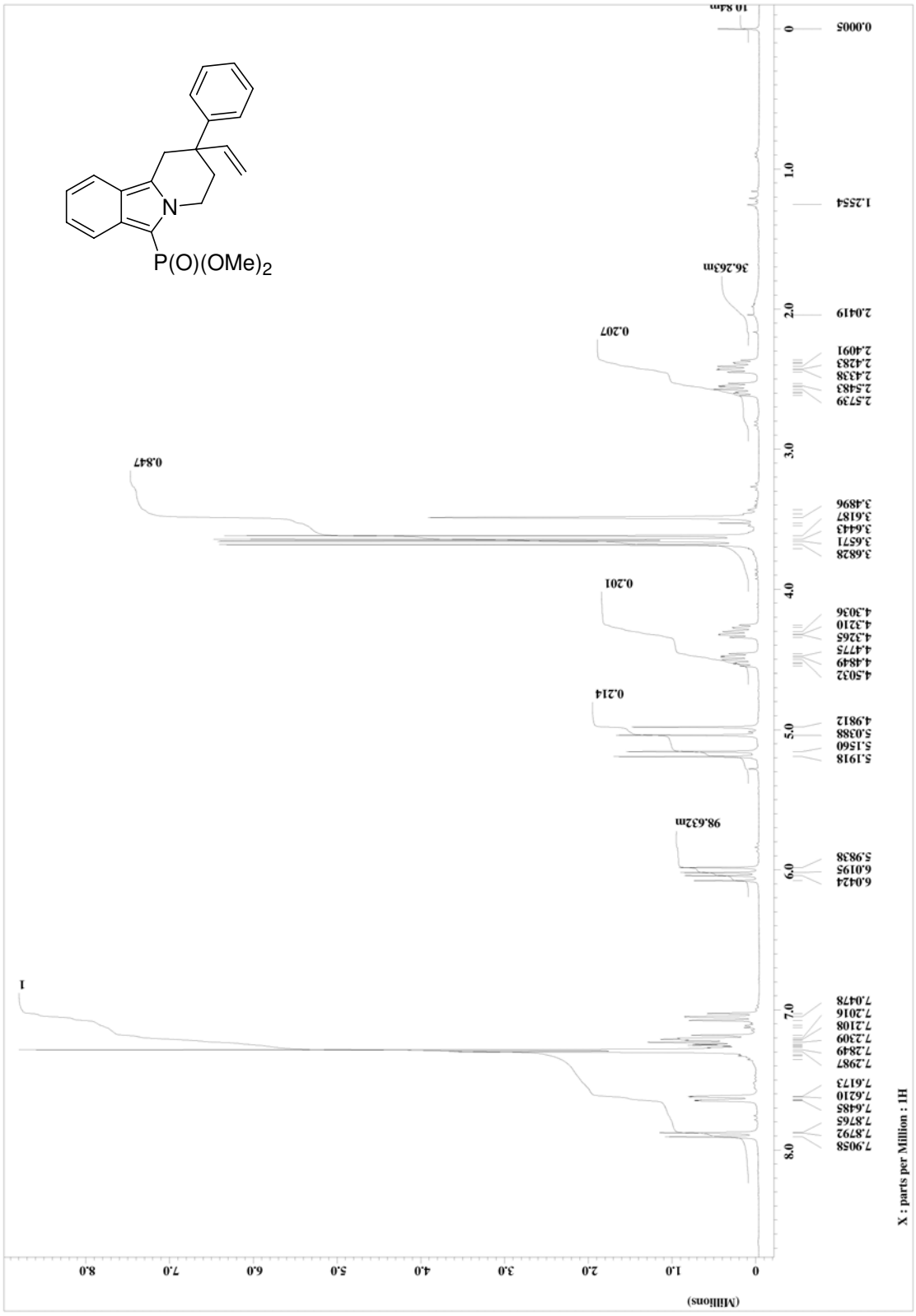
13 ^{1}H-Spectrum



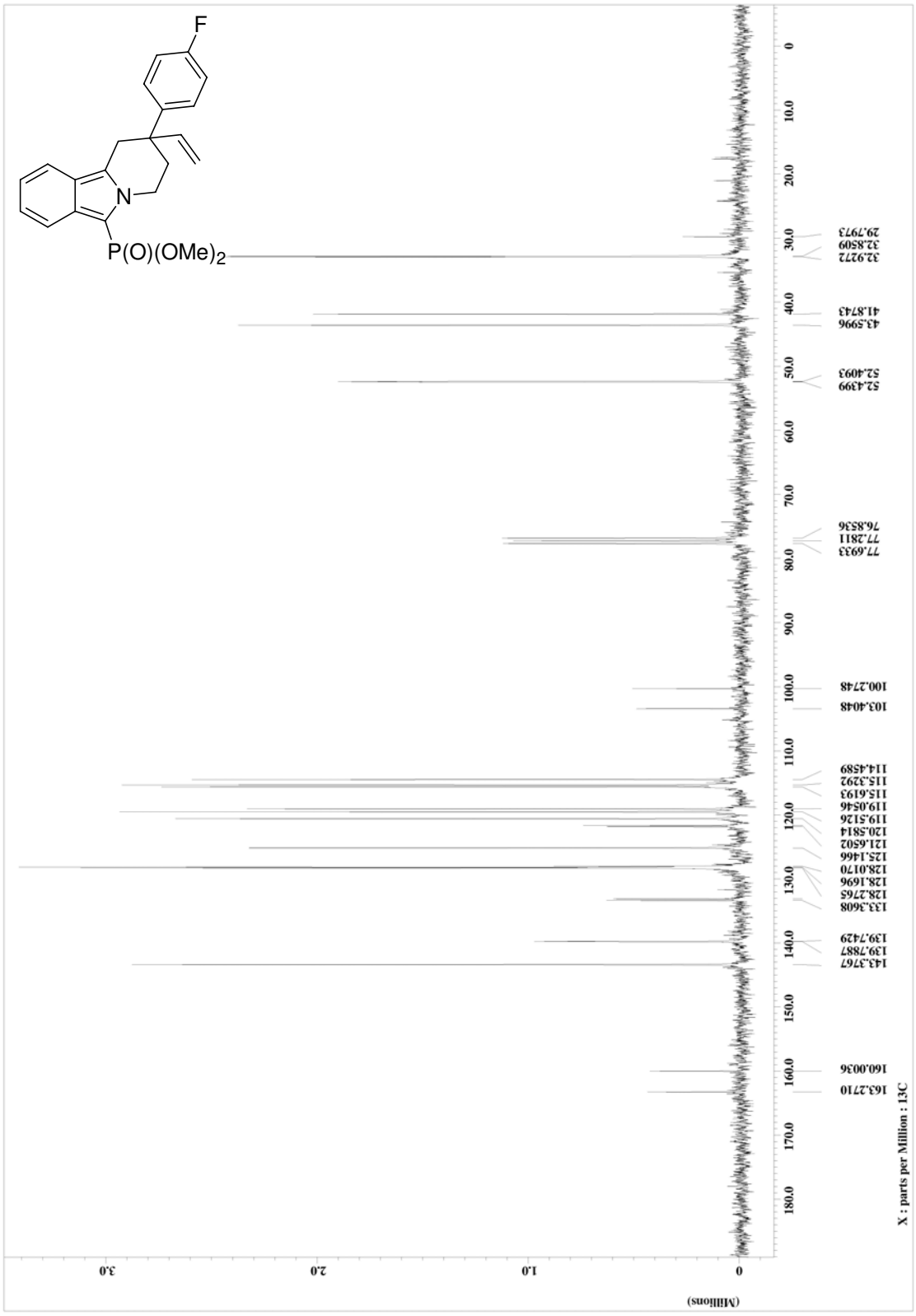
14a ^{13}C-Spectrum



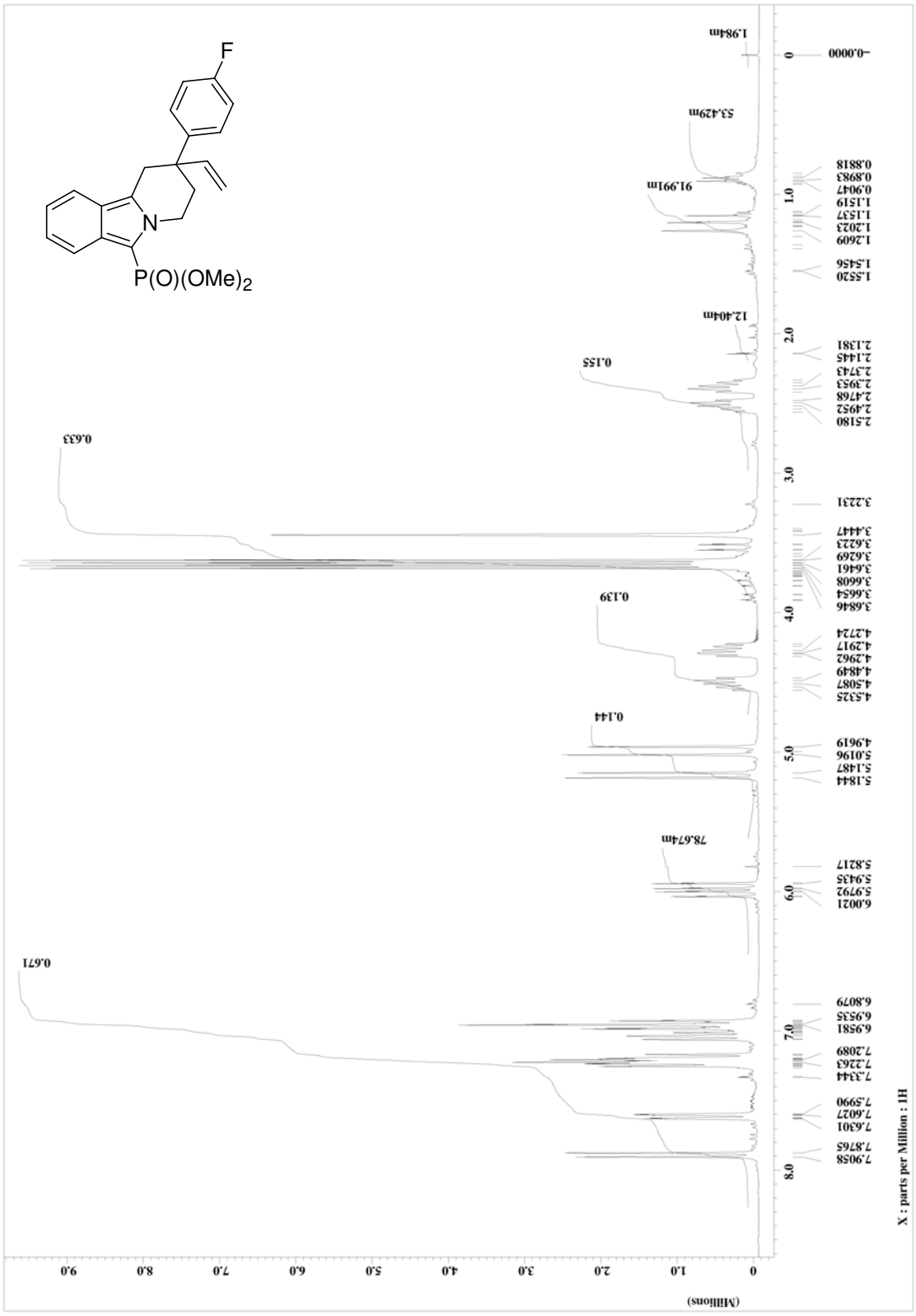
14a ^{1}H-Spectrum



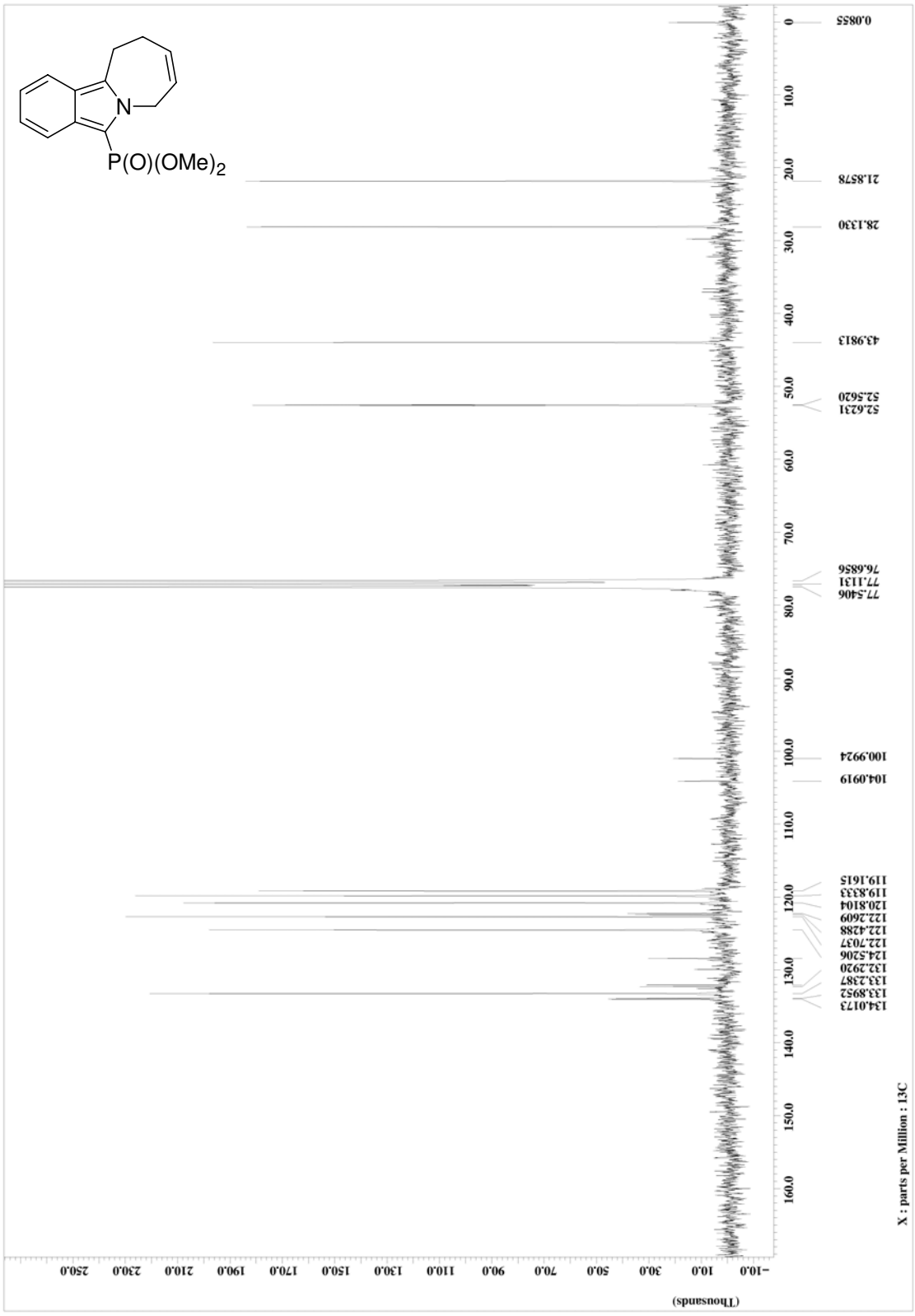
14b ^{13}C-Spectrum



14b ^{1}H-Spectrum



16 ^{13}C-Spectrum



16 ^{1}H-Spectrum