Supplementary Material (ESI) for Chemical Communications

One-Pot Tandem 1,4-1,2-Addition of Phosphites to Quinolines

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Experimental data

Microwave reactions: All microwave reactions were performed in the *CEM Focused Microwave™ Synthesis System*, *Model Discover*, with a selectable power output from 0 to 300 watts. The reactions were performed in 10-ml thick walled Pyrex reaction vessels closed with a 'snap-on' septa cap and equiped with a small stirring bar. The temperature control uses a non-contact infrared sensor to measure the 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 to 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 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 2 ml solution from ~150 °C to ~40 °C in less than 120 seconds. A ramp time of maximum 5 minutes is used during which the temperature increases from room temperature to the desired one. This temperature is maintained during the course of the reaction for the indicated time.

General remarks: All reactions were carried out using flame-dried glassware and dry solvents under a nitrogen atmosphere. All common reagents and solvents were obtained from commercial suppliers and used without any further purification unless otherwise noted. High-resolution ^{1}H NMR (300 MHz), ^{31}P NMR (121 MHz), ^{19}F NMR (282 MHz) and ^{13}C NMR (75 MHz) spectra were run with a JEOL EX 300 Eclipse NMR spectrometer. Peak assignments were obtained with the aid of DEPT, 2D-COSY, 2D-HSQC and 2D-HMBC spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Low resolution mass spectra were recorded with an Agilent 1100 Series VS (ES = 4000 V) mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. All compounds were analysed in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points of crystalline compounds were measured with a Büchi 540 apparatus. The elemental analysis was performed with a Perkin-Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by column chromatography in a glass column with silica gel (Acros, particle size, 0.035-0.070 mm, pore diameter ca. 6 nm). TLC was performed on aluminum backed plates coated with silica gel 60 with F254 indicator (Merck, 0.25 mm), using UV and $KMnO_4$ as a visualizing agent.
Data are reported as follows: chemical shift, integration, multiplicity (s: singlet, d: doublet, t: triplet, q: quadruplet, br: broad, m: multiplet), coupling constants (*J* in Hz), allocation of the peaks.

Typical procedure for the synthesis of silylated dimethyl phosphite (DMPTMS) 11

In a flame dried 250 ml flask, 1 equiv. of dimethyl phosphite (100 mmol, 11.00 g) is dissolved in 150 ml of dry dichloromethane. Triethylamine (1.2 equiv., 120 mmol, 12.15 g) is added to this solution, after which the mixture is stirred at 0° C under a nitrogen atmosphere. Subsequently, trimethylsilyl chloride (1.1 equiv., 110 mmol, 11.94 g) is dropped to the solution using a dry syringe. This mixture is stirred for 30 minutes at 0° C, followed by sampling to take a ^{31}P NMR spectrum. The formed $Et_3N.HCl$ salts are filtered of and the solvent is removed *in vacuo*. The residue is redissolved in dry diethyl ether to precipitate the remaining salts. After filtration and evaporation, the procedure is repeated until the salts are no longer formed. The silylated dimethyl phosphite is obtained as a colorless liquid with a typical smell. It can be stored at -30 °C for maximum one month in a well closed bulb. The yields vary from 70 to 75 %.

δ_P (121 MHz, $CDCl_3$) 128.51.

Supplementary Material (ESI) for Chemical Communications

Typical procedure for the synthesis of compounds 5 (under reflux conditions)

In a dry flask, quinoline or a derivative (2 mmol) is dissolved in dry dichloromethane together with DMPTMS (2.05 equiv., 4.1 mmol, 0.75 g or 3 equiv., 6 mmol, 1.09 g). The mixture is stirred at room temperature under a nitrogen atmosphere, after which the sulfuric acid (0.5 equiv. = 1 equiv. H^+, 1 mmol, 0.10 g) is added to the solution. The reaction is brought to reflux temperature and is follwed up by ^{31}P NMR (Figure S1). Whenever possible, conversions were calculated from the integrations in the ^{31}P NMR. An optimized acid-base extraction is used to isolate the end product. After removal of the solvent *in vacuo*, the residue is redissolved in 20 ml Et_2O and 40 ml 3 N HCl. After extraction with diethyl ether (3 x 15 ml), the aqueous phase is neutralized with 3 N NaOH, followed by another extraction using 60 ml dichloromethane (3 x 20 ml). This second organic phase is dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the pure end product could be obtained in moderate to good yields. In some cases chromatographic purification was required (petroleum ether / ethyl acetate (50 / 50), followed by acetonitrile / dichloromethane / methanol (80 / 17 / 3)). Since the end product exists as two pairs of diastereoisomers, the ratio of the minor and major compound was calculated from the ^{31}P NMR. In the following spectra, signals of the minor and major diastereoisomer are indicated with *m* and *M* respectively.

Typical procedure for the synthesis of compounds 5 (using microwave heating)

In a dry 10-ml thick walled Pyrex reaction vessel, quinoline or a derivative (2 mmol) is dissolved in 7 ml dry dichloromethane together with DMPTMS (1 equiv., 2 mmol, 0.36 g) and sulfuric acid (0.5 equiv. = 1 equiv. H^+, 1 mmol, 0.10 g). The head space is flushed with nitrogen before closing the tube with the 'snap-on' cap. The reaction is heated in a microwave to 45 °C for 30 minutes. After this, the progress of the reaction is checked by ^{31}P NMR with a sample take directly from the mixture. A second equivalent of DMPTMS (1.05 equiv., 2.1 mmol, 0.38 g) is added to the mixture, after which it is again heated to 45 °C for another 30 minutes. A new sample is taken from the solution to follow-up the reaction. If this reveals the presence of remaining starting material, the reaction is placed back inside the microwave and is again heated to 45 °C. After complete conversion, the end product is isolated using the same methodology as under reflux conditions. In the case of quinoline, 2.05 equiv. DMPTMS were added in two steps, this in contrast to the other substrates where 3 equiv. were added in three times.

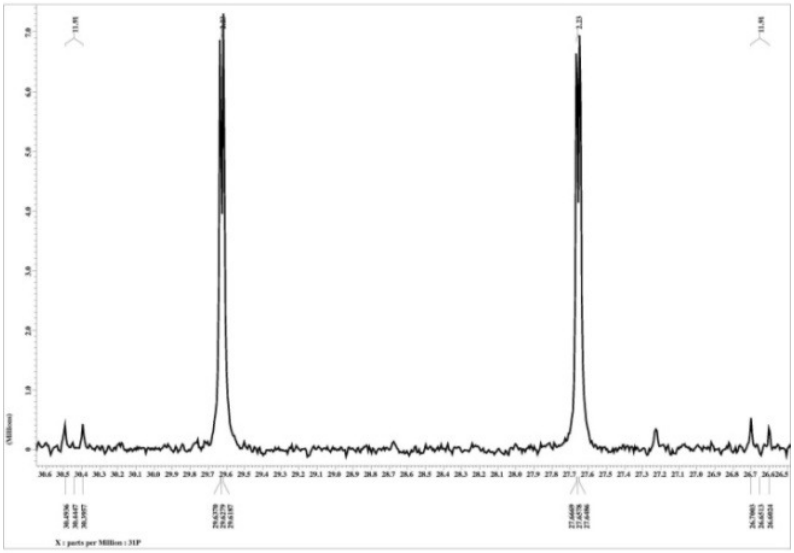
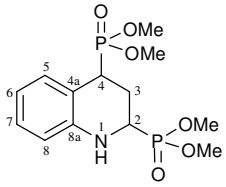


Fig. S1 Detail of a ^{31}P NMR spectrum showing the diastereomeric pair at δ = 26.65 ppm (J_{PP} = 11.9 Hz) and δ = 30.44 ppm (J_{PP} = 11.9 Hz) on one hand and at δ = 27.66 ppm (J_{PP} = 2.2 Hz) and δ = 29.63ppm (J_{PP} = 2.2 Hz) on the other hand

Product characterization

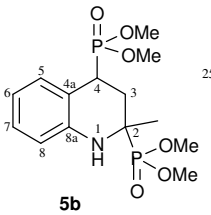
[4-(Dimethoxy-phosphoryl)-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.59g, 84%)



5a

Ratio: minor (*m*) / Major (*M*): 4 / 96. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.17 (*M*); **IR: ν_{max}/cm^{-1}** 3306 (NH), 1232 (P=O) and 1023 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 2.02-2.30 (1H, m, C$\underline{H}_A$CH_B, *M*), 2.49-2.62 (1H, m, CH_AC$\underline{H}_B$, *M*), 3.37 (1H, ~dt, $^2J_{HP}$ = 24.2 Hz, *J* = 5.0 Hz, C$\underline{H}$P, *M*), 3.66 (6H, d, $^3J_{HP}$ = 10.5 Hz, 2 x P(O)OC$\underline{H}_3$, *M*), 3.83 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.84 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 4.18 (1H, ddd, $^2J_{HP}$ = 12.4 Hz, *J* = 6.9 Hz, *J* = 3.3 Hz, NC$\underline{H}$P, *M*), 4.31 (1H, bs, N$\underline{H}$, *M*), 6.60 (1H, d, *J* = 8.3 Hz, $C_8\underline{H}$(Ph), *M*), 6.69 (1H, t, *J* = 7.7 Hz, $C_6\underline{H}$(Ph), *M*), 7.05 (1H, t, *J* = 7.7 H, $C_7\underline{H}$(Ph), *M*) and 7.17 (1H, d, *J* = 7.7 Hz, $C_5\underline{H}$(Ph), *M*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 22.38 (~t, $^2J_{CP}$ = 5.2 Hz, CH$\underline{C}H_2$CH, *M*), 34.13 (dd, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 15.0 Hz, $\underline{C}$HP, *M*), 45.39 (d, $^1J_{CP}$ = 161.5 Hz, N$\underline{C}$HP, *M*), 53.01 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.09 (d, $^2J_{CP}$ = 5.8, P(O)O$\underline{C}H_3$, *M*), 53.18 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.75 (d, $^2J_{CP}$ = 5.8 Hz, P(O)O$\underline{C}H_3$, *M*), 113.30 (d, *J* = 6.9 Hz, $\underline{C}_{4a}$(Ph), *M*), 115.41 (bs, $\underline{C}_8$H(Ph), *M*), 117.59 (d, *J* = 3.5 Hz, $\underline{C}_6$H(Ph), *M*), 128.28 (d, *J* = 3.5 Hz, $\underline{C}_7$H(Ph), *M*), 130.56 (d, *J* = 4.6 Hz, $\underline{C}_5$H(Ph), *M*) and 143.54 (dd, $^3J_{CP}$ = 11.5 Hz, *J* = 5.8 Hz, $\underline{C}_{8a}$(Ph), *M*); **δ_P (121 MHz, $CDCl_3$)** 26.63 (d, J_{PP} = 11.9 Hz, *m*), 27.62 (d, J_{PP} = 2.2 Hz, *M*), 29.62 (d, J_{PP} = 2.2 Hz, *M*) and 30.44 (d, J_{PP} = 11.9 Hz, *m*); **m/z (ESI)** 350.3 ($[M+H]^+$, 100 %).

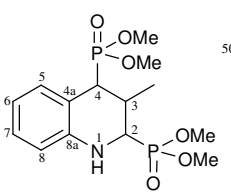
[4-(Dimethoxy-phosphoryl)-2-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.44g, 60%)



5b

Ratio: minor (*m*) / Major (*M*): 34 / 66. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.20 (*m* + *M*); **IR: ν_{max}/cm^{-1}** 3429 (NH), 1226 (P=O) and 1018 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 1.39 (3H, d, $^3J_{HP}$ = 15.4 Hz, C$\underline{H}_3$, *m*), 1.51 (3H, d, $^3J_{HP}$ = 14.3 Hz, C$\underline{H}_3$, *M*), 1.99 (1H, ddt, $^3J_{HP}$ = 34.1 Hz, *J* = 12.8 Hz, *J* = 12.1 Hz, CHC$\underline{H}_2$C, *M*), 2.21-2.35 (2H, m, CHC$\underline{H}_2$C, *m*), 2.49-2.63 (1H, m, CHC$\underline{H}_2$C, *M*), 3.41 (3H, d, $^3J_{HP}$ = 9.9 Hz, P(O)OC$\underline{H}_3$, *M*), 3.62-3.74 (2H, m, C$\underline{H}$P, *M* + *m*), 3.69 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.70 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.71 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.79 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *M*), 3.80 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.83 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.87 (3H, d, $^3J_{HP}$ = 9.9 Hz, P(O)OC$\underline{H}_3$, *m*), 4.18 (1H, bs, N$\underline{H}$, *m*), 4.32 (1H, bs, N$\underline{H}$, *M*), 6.58 (1H, d, *J* = 8.2 Hz, $C_8\underline{H}$(Ph), *M*), 6.61 (1H, d, *J* = 9.9 Hz, $C_8\underline{H}$(Ph), *m*), 6.69 (1H, t, *J* = 7.7 Hz, $C_6\underline{H}$(Ph), *M*), 6.74 (1H, t, *J* = 7.7 Hz, $C_6\underline{H}$(Ph), *m*), 7.02 (1H, t, *J* = 7.2 Hz, $C_7\underline{H}$(Ph), *M*), 7.06 (1H, t, *J* = 7.7 Hz, $C_7\underline{H}$(Ph), *m*), 7.73 (1H, d, *J* = 7.7 Hz, $C_5\underline{H}$(Ph), *M*) and 7.79 (1H, d, *J* = 7.7 Hz, $C_5\underline{H}$(Ph), *m*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 20.35 (d, $^2J_{CP}$ = 4.6 Hz, $\underline{C}H_3$, *m*), 25.64 (d, $^2J_{CP}$ = 5.8 Hz, $\underline{C}H_3$, *M*), 29.36 (CH$\underline{C}H_2$C, *m*), 30.23 (dd, $^1J_{CP}$ = 144.2 Hz, $^3J_{CP}$ = 12.7 Hz, $\underline{C}$HP, *m*), 31.99 (CH$\underline{C}H_2$C, *M*), 32.51 (d, $^1J_{CP}$ = 141.9 Hz, $\underline{C}$HP, *M*), 51.41 (dd, $^1J_{CP}$ = 155.8 Hz, $^3J_{CP}$ = 12.7 Hz, N$\underline{C}$P, *m*), 51.49 (dd, $^1J_{CP}$ = 161.0 Hz, $^3J_{CP}$ = 12.7 Hz, N$\underline{C}$P, *M*), 52.41 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *M*), 52.47 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *M* + *m*), 53.16 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *m*), 53.50 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.59 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *m*), 53.82 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 54.64 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *m*), 114.72 (s, $\underline{C}_8$H(Ph), *M*), 114.77 (d, *J* = 6.9 Hz, $\underline{C}_{4a}$(Ph), *M*), 114.90 (d, *J* = 5.8 Hz, $\underline{C}_{4a}$(Ph), *m*), 116.39 (s, $\underline{C}_8$H(Ph), *m*), 117.99 (s, $\underline{C}_6$H(Ph), *M*), 118.56 (s, $\underline{C}_6$H(Ph), *m*), 127.90 (s, $\underline{C}_7$H(Ph), *M*),128.16 (s, $\underline{C}_7$H(Ph), *m*), 128.99 (d, *J* = 5.8 Hz, $\underline{C}_5$H(Ph), *M*), 129.12 (d, *J* = 4.6 Hz, $\underline{C}_5$H(Ph), *m*), 142.25 (dd, $^2J_{CP}$ = 11.5 Hz, *J* = 9.2 Hz, $\underline{C}_{8a}$(Ph), *m*) and 142.73 (d, *J* = 9.2 Hz, $\underline{C}_{8a}$(Ph), *M*); **δ_P (121 MHz, $CDCl_3$)** 29.80 (d, J_{PP} = 7.4 Hz, *m*), 30.67 (d, J_{PP} = 2.2 Hz, *M*), 31.48 (d, J_{PP} = 7.4 Hz, *M*) and 31.50 (d, J_{PP} = 2.2 Hz, *m*); **m/z (ESI)** 364.2 ($[M+H]^+$,100 %), 254.2 ($[M-P(O)(OMe)_2+H]^+$, 47 %).

[4-(Dimethoxy-phosphoryl)-3-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.39g, 53%)

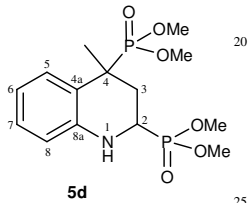


5c

Ratio: minor (*m*) / Major (*M*): 20 / 80. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.20 (*m* + *M*); **IR: ν_{max}/cm^{-1}** 3420 (NH), 1225 (P=O) and 1021 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 1.17 (3H, d, $^4J_{HP}$ = 6.6 Hz, C$\underline{H}_3$, *m*), 1.34 (3H, d, $^4J_{HP}$ = 6.6 Hz, C$\underline{H}_3$, *M*), 2.32-2.61 (1H, m, CHC$\underline{H}$CH, *M*), 2.70-2.88 (1H, m, CHC$\underline{H}$CH, *m*), 3.31-3.51 (1H, m, C$\underline{H}$P, *m*), 3.38 (1H, ~dt, $^2J_{HP}$ = 13.8 Hz, *J* = 4.4 Hz, C$\underline{H}$P, *M*), 3.42 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.63 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.64 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.70 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *m*), 3.71 (3H, d, $^3J_{HP}$ =

11.0 Hz, P(O)OCH$_3$, *M*), 3.76 (3H, d, $^3J_{HP}$ = 9.9 Hz, P(O)OCH$_3$, *M*), 3.78 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OCH$_3$, *m*), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OCH$_3$, *M*), 3.93-3.99 (1H, m, NCHP, *m*), 4.09 (1H, dd, $^2J_{HP}$ = 8.8 Hz, *J* = 5.5 Hz, NCHP, *M*), 4.73 (2H, bs, NH, *m* + *M*), 6.59 (1H, d, *J* = 8.3 Hz, C$_8$H(Ph), *M*), 6.60 (1H, ~t, *J* = 7.4 Hz, C$_6$H(Ph), *M*), 6.70 (1H, ~t, *J* = 7.2 Hz, C$_6$H(Ph), *m*), 7.00 (1H, ~t, *J* = 7.7 Hz, C$_7$H(Ph), *M*), 7.09 (1H, d, *J* = 7.7 Hz, C$_5$H(Ph), *M*), 7.15 (1H, ~t, *J* = 7.2 Hz, C$_7$H(Ph), *m*), 7.48 (1H, d, *J* =7.7 Hz, C$_5$H(Ph), *m*) and 7.51 (1H, s, C$_8$H(Ph), *m*); **δ_C (75 MHz, CDCl$_3$, Me$_4$Si)** 17.07 (s, CH$_3$, *M*), 17.25 (s, CH$_3$, *m*), 28.38 (s, CHCHCH, *m*), 29.27 (s, CHCHCH, *M*), 37.67 (d, $^1J_{CP}$ = 143.1 Hz, CHP, *m*), 41.13 (d, $^1J_{CP}$ = 137.9 Hz, $^3J_{CP}$ = 12.1 Hz, CHP, *M*), 51.96 (dd, $^1J_{CP}$ = 155.8 Hz, $^3J_{CP}$ = 5.8 Hz, NCHP, *M*), 51.96 (d, $^2J_{CP}$ = 6.9Hz, P(O)OCH$_3$, *M*), 52.29 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *m*), 52.60 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *m*), 52.64 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *m*), 52.89 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *m*), 53.01 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 53.22 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 53.27 (d, $^2J_{CP}$ = 5.8 Hz, P(O)OCH$_3$, *M*), 63.87 (dd, $^1J_{CP}$ = 153.5 Hz, $^3J_{CP}$ = 12.7 Hz, NCHP, *m*), 111.76 (s, C$_8$H(Ph), *m*), 114.34 (s, C$_8$H(Ph), *M*), 115.85 (d, *J* = 3.5 Hz, C$_{4a}$, *m* + *M*), 116.92 (s, C$_6$H(Ph), *M*), 117.15 (s, C$_6$H(Ph), *m*), 128.17 (d, *J* = 10.4 Hz, C$_7$H(Ph), *m*), 128.24 (s, C$_7$H(Ph), *M*), 128.98 (d, *J* = 5.8 Hz, C$_5$H(Ph), *m*), 130.24 (d, *J* = 4.6 Hz, C$_5$H(Ph), *M*), 142.67 (t, *J* = 6.3 Hz, C$_{8a}$(Ph), *M*) and 143.83 (d, *J* = 9.2 Hz, C$_{8a}$(Ph), *m*); **δ_P (121 MHz, CDCl$_3$)** 26.24 (*m*), 28.62 (d, J_{PP} = 1.5 Hz, *M*), 29.14 (d, J_{PP} = 1.5 Hz, *M*) and 31.27 (*m*); **m/z (ESI)** 364.2 ([M+H]$^+$, 100 %).

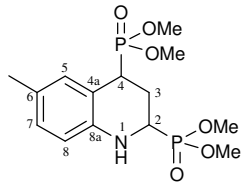
[4-(Dimethoxy-phosphoryl)-4-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.08g, 11%)



5d

Ratio: minor (*m*) / Major (*M*): 36 / 64. Yellow oil.
Chromatography: CH$_3$CN/CH$_2$Cl$_2$/MeOH 80/17/3 R_f = 0.16 (*M* + *m*); **IR: ν_{max}/cm^{-1}** 3418 (NH), 1234 (P=O) and 1016 (P-O); **δ_H (300 MHz, CDCl$_3$, Me$_4$Si)** 1.61 (d, $^3J_{HP}$ = 16.0 Hz, 6H, CH$_3$, *m* + *M*), 1.77 - 2.03 (m, 1H, CCH$_2$CH, *M*), 2.05 - 2.31 (m, 2H, CCH$_2$CH, *m*), 2.48 - 2.66 (m, 1H, CCH$_2$CH, *M*), 3.21 (s, 1H, NH, *M*), 3.36 (d, *J* = 2.2 Hz, 1H, NH, *m*), 3.50 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *m*), 3.52 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *M*), 3.60 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *m*), 3.64 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *M*), 3.77 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *m*), 3.77 (d, $^3J_{HP}$ = 9.9 Hz, 3H, P(O)OCH$_3$, *m*), 3.83 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *M*), 3.86 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OCH$_3$, *M*), 4.27 (ddd, $^2J_{HP}$ = 12.5 Hz, *J* = 6.5 Hz, *J* = 2.8 Hz, 2H, NCHP, *m* + *M*), 6.58 (d, *J* = 8.3 Hz, 1H, C$_8$H(Ph), *M*), 6.74 (dd, *J* = 15.4 Hz, *J* = 7.7 Hz, 1H, C$_6$H(Ph), *M*), 6.78 (dd, *J* = 13.5 Hz, *J* = 5.0 Hz, 1H, C$_6$H(Ph), *m*), 6.83 (d, *J* = 8.3 Hz, 1H, C$_8$H(Ph), *m*), 7.04 (~tt, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H, C$_7$H(Ph), *M*), 7.16 (~tt, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H, C$_7$H(Ph), *m*), 7.23 (~ddd, *J* = 7.7 Hz, *J* = 2.8 Hz, *J* = 1.7 Hz, 1H, C$_5$H(Ph), *m*) and 7.31 (~ddd, *J* = 7.7 Hz, *J* = 2.8 Hz, *J* = 1.7 Hz, 1H, C$_5$H(Ph), *M*); **δ_C (75 MHz, CDCl$_3$, Me$_4$Si)** 23.41 (s, CH$_3$, *m*), 23.97 (d, *J* = 2.3 Hz, CH$_3$, *M*), 31.96 (t, $^2J_{CP}$ = 5.2 Hz, CH$_2$, *M*), 34.83 (s, CH$_2$, *m*), 36.80 (dd, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 13.3 Hz, CP, *m*), 36.89 (dd, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 15.0 Hz, CP, *M*), 46.01 (d, $^1J_{CP}$ = 162.7 Hz, NCHP, *M*), 52.51 (d, $^2J_{CP}$ = 8.1 Hz, P(O)OCH$_3$, m), 53.05 (d, $^2J_{CP}$ = 8.1 Hz, P(O)OCH$_3$, *m*), 53.26 (d, $^2J_{CP}$ = 5.8 Hz, P(O)OCH$_3$, *m*), 53.35 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 53.45 (d, $^2J_{CP}$ = 9.2 Hz, P(O)OCH$_3$, *m*), 53.65 (d, $^2J_{CP}$ = 8.1 Hz, P(O)OCH$_3$, *M*), 53.70 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 53.93 (d, $^2J_{CP}$ = 5.7 Hz, P(O)OCH$_3$, *M*), 55.20 (d, $^1J_{CP}$ = 160.4 Hz, NCHP, *m*), 115.27 (d, *J* = 2.3 Hz, C$_8$H(Ph), *M*), 116.22 (d, *J* = 2.3 Hz, C$_8$H(Ph), *m*), 117.93 (d, *J* = 2.3 Hz, C$_6$H(Ph), *m*), 118.11 (d, *J* = 3.5 Hz, C$_6$H(Ph), *M*), 119.09 (d, *J* = 4.6 Hz, C$_{4a}$(Ph), *M*), 123.56 (d, *J* = 3.5 Hz, C$_{4a}$(Ph), *m*), 127.06 (d, *J* = 4.6 Hz, C$_5$H(Ph), *m*), 128.34 (d, *J* = 3.5 Hz, C$_7$H(Ph), *M*), 128.55 (d, *J* = 3.5 Hz, C$_7$H(Ph), *m*), 128.73 (d, *J* = 4.6 Hz, C$_5$H(Ph), *M*), 143.21 (d, *J* = 11.5 Hz, C$_{8a}$(Ph), *M*) and 143.29 (d, *J* = 11.5 Hz, C$_{8a}$(Ph), *m*); **δ_P (121 MHz, CDCl$_3$)** 26.98 (s), 27.55 (d, J_{PP} = 2.2 Hz), 31.97 (s) and 32.25 (d, J_{PP} = 2.2 Hz); **m/z (ESI)** 364.2 ([M+H]$^+$, 100 %).

[4-(Dimethoxy-phosphoryl)-6-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.52g, 72%)

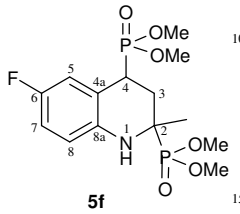


5e

Ratio: minor (*m*) / Major (*M*): 3 / 97. Yellow oil.
Chromatography: CH$_3$CN/CH$_2$Cl$_2$/MeOH 80/17/3 R_f = 0.16 (*M*); **IR: ν_{max}/cm^{-1}** 3448 (NH), 1224 (P=O) and 1020 (P-O); **δ_H (300 MHz, CDCl$_3$, Me$_4$Si)** 1.99-2.28 (1H, m, CHCH$_2$CH, *M*), 2.21 (3H, s, CH$_3$(Ph), *M*), 2.46-2.61 (1H, m, CHCH$_2$CH, *M*), 3.33 (1H, ~dt, $^2J_{HP}$ = 24.2 Hz, *J* = 4.4Hz, CHP, *M*), 3.65 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OCH$_3$, *M*), 3.66 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OCH$_3$, *M*), 3.81 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OCH$_3$, *M*), 3.82 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OCH$_3$, *M*), 4.15 (1H, ddd, $^2J_{HP}$ = 12.1 Hz, *J* = 6.9 Hz, *J* = 3.0 Hz, NCHP, *M*), 4.55 (1H, bs, NH, *M*), 6.54 (1H, d, *J* = 7.7 Hz, C$_8$H(Ph), *M*), 6.85 (1H, d, *J* = 8.3 Hz, C$_7$H(Ph), *M*) and 6.98 (1H, bs, C$_5$H(Ph), *M*); **δ_C (75 MHz, CDCl$_3$, Me$_4$Si)** 20.40 (s, CH$_3$(Ph), *M*), 22.60 (~t, $^2J_{CP}$ = 5.8 Hz, CHCH$_2$CH, *M*), 34.19 (dd, $^1J_{CP}$ = 140.8 Hz, *J* = 15.0 Hz, CHP, *M*), 45.53 (d, $^1J_{CP}$ = 161.5 Hz, NCHP, *M*), 53.00 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 53.17 (d, $^2J_{CP}$ = 8.1 Hz, 2 x P(O)OCH$_3$, *M*), 53.84 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$, *M*), 113.36 (d, *J* = 5.8 Hz, C$_{4a}$(Ph), *M*), 115.52 (d, *J* = 2.3 Hz,

$\underline{C}_8$H(Ph), *M*), 126.86 (d, *J* = 3.5 Hz, $\underline{C}_6$(Ph), *M*), 129.11 (d, *J* = 3.5 Hz, $\underline{C}_7$H(Ph), *M*), 130.89 (d, *J* = 4.6 Hz, $\underline{C}_5$H(Ph), *M*) and 141.05 (dd, *J* = 12.1 Hz, *J* = 6.3 Hz, $\underline{C}_{8a}$(Ph), *M*); **δ_P (121 MHz, $CDCl_3$)** 26.84 (d, J_{PP} = 11.9 Hz, *m*), 27.78 (d, J_{PP} = 2.2 Hz, *M*), 29.77 (d, J_{PP} = 2.2 Hz, *M*) and 30.53 (d, J_{PP} = 11.9 Hz, *m*); **m/z (ESI)** 364.2 ($[M+H]^+$, 100 %).

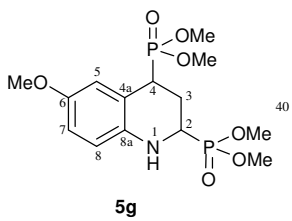
[4-(Dimethoxy-phosphoryl)-6-fluoro-2-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.14g, 19%)



5f

Ratio: minor (*m*) / Major (*M*): 34 / 66. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.33 (*m* + *M*); **IR: ν_{max}/cm^{-1}** 3297 (NH), 1226 (P=O) and 1016 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 1.37 (3H, d, $^3J_{HP}$ = 15.4 Hz, C$\underline{H}_3$, *m*), 1.49 (3H, d, $^3J_{HP}$ = 13.8 Hz, C$\underline{H}_3$, *M*), 1.96 (1H, ddt, $^3J_{HP}$ = 34.1 Hz, *J* = 14.3 Hz, *J* = 12.7 Hz, CHC$\underline{H}_2$C, *M*), 2.20-2.31 (2H, m, CHC$\underline{H}_2$C, *m*), 2.50-2.62 (1H, m, CHC$\underline{H}_2$C, *M*), 3.44 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.60-3.68 (2H, m, C$\underline{H}$P, *M* + *m*), 3.71 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.73 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *M*), 3.75 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *m*), 3.80 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *M*), 3.81 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *m*), 3.83 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.87 (3H, d, $^3J_{HP}$ = 9.9 Hz, P(O)OC$\underline{H}_3$, *m*),4.06 (1H, bs, N$\underline{H}$, *m*), 4.16 (1H, bs, N$\underline{H}$, *M*), 6.51 (1H, ddd, *J* = 8.8 Hz, *J* = 5.0 Hz, *J* = 1.4 Hz, $C_8\underline{H}$(Ph), *M*), 6.54 (1H, ddd, *J* = 8.8 Hz, *J* = 5.0 Hz, *J* = 1.7 Hz, $C_8\underline{H}$(Ph), *m*), 6.72-6.81 (1H, m, $C_7\underline{H}$(Ph), *M*), 6.78-6.84 (1H, m, $C_7\underline{H}$(Ph), *m*), 7.52 (1H, ddd, *J* = 11.6 Hz, *J* = 2.8 Hz, *J* = 1.7 Hz, $C_5\underline{H}$(Ph), *M*) and 7.57 (1H, ddd, *J* = 10.7 Hz, *J* = 2.8 Hz, *J* = 1.7 Hz, $C_5\underline{H}$(Ph), *m*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 20.10 (d, $^2J_{CP}$ = 3.5 Hz, $\underline{C}H_3$, *m*), 25.61 (d, $^2J_{CP}$ = 5.8 Hz, $\underline{C}H_3$, *M*), 29.07 (bs, CH$\underline{C}H_2$C, *m*), 30.38 (dd, $^1J_{CP}$ = 144.8 Hz, $^3J_{CP}$ = 11.5 Hz, $\underline{C}$HP, *m*), 31.70 (bs, CH$\underline{C}H_2$C, *M*), 32.64 (d, $^1J_{CP}$ = 143.1 Hz, $\underline{C}$HP, *M*), 51.47 (dd, $^1J_{CP}$ = 154.0 Hz, $^3J_{CP}$ = 12.7 Hz, N$\underline{C}$P, *M*), 52.47 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *M* + *m*), 52.61 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.19 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *m*), 53.54 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *M*), 53.63 (dd, $^1J_{CP}$ = 151.4 Hz, $^3J_{CP}$ = 6.9 Hz, N$\underline{C}$P, *m*), 53.77 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M* + *m*), 54.63 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *m*), 114.80 (d, J_{CF} = 23.1 Hz, $\underline{C}_7$H(Ph), *M*), 115.21 (d, J_{CF} = 19.6 Hz, $\underline{C}_7$H(Ph), *m*), 115.29 (d, *J* = 6.9 Hz, $\underline{C}_8$H(Ph), *M*), 115.60 (d, *J* = 5.8 Hz, $\underline{C}_5$H(Ph), *M*), 115.67 (d, *J* = 4.6 Hz, $\underline{C}_5$H(Ph), *m*), 116.08 (t, *J* = 6.9 Hz, $\underline{C}_{4a}$(Ph), *m* + *M*), 117.14 (d, *J* = 8.1 Hz, $\underline{C}_8$H(Ph), *m*), 138.47 (t, *J* = 10.4 Hz, $\underline{C}_{8a}$(Ph), *m*), 139.03 (d, *J* = 9.2 Hz, $\underline{C}_{8a}$(Ph), *M*), 155.55 (d, J_{CF} = 235.4 Hz, $\underline{C}_6$(Ph), *M*) and 155.89 (dd, J_{CF} = 237.7 Hz, *J* = 2.3 Hz, $\underline{C}_6$(Ph), *m*); **δ_P (121 MHz, $CDCl_3$)** 29.78 (d, J_{PP} = 8.2 Hz, *m*), 30.66 (d, J_{PP} = 1.5 Hz, *M*), 31.48 (d, J_{PP} = 8.9 Hz, *M*) and 31.53 (d, J_{PP} = 2.2 Hz, *m*); **δ_F (282 MHz, $CDCl_3$)** (-) 124.95 – (-) 125.06 (m, *m*) and (-) 125.75 – (-) 125.87 (m, *M*); **m/z (ESI)** 382.0 ($[M+H]^+$, 100 %).

[4-(Dimethoxy-phosphoryl)-6-methoxy-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.09g, 12%)

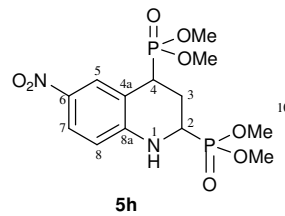


5g

Ratio: minor (*m*) / Major (*M*): 3 / 97. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.19 (*m* + *M*); **IR: ν_{max}/cm^{-1}** 3311 (NH), 1236 (P=O) and 1022 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 2.01-2.31 (1H, m, C$\underline{H}_A$CH_B, *M*), 2.35-2.63 (2H, m, C$\underline{H}_A$C$\underline{H}_B$, *m*), 2.48-2.62 (1H, m, CH_AC$\underline{H}_B$, *M*), 3.34 (1H, ~dt, $^2J_{HP}$ = 24.2 Hz, *J* = 5.0 Hz, C$\underline{H}$P, *M*), 3.48 (1H, dd, $^2J_{HP}$ = 15.1 Hz, *J* = 5.5 Hz, C$\underline{H}$P, *m*), 3.58 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *m*), 3.59 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.65 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC$\underline{H}_3$, *m*), 3.66 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *m*), 3.67 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.69 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.74 (3H, s, OC$\underline{H}_3$(Ph), *M*), 3.75 (3H, s, OC$\underline{H}_3$(Ph), *m*), 3.83 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 3.84 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC$\underline{H}_3$, *M*), 4.08-4.15 (2H, m, NC$\underline{H}$P, *m* + *M*), 4.15-4.18 (2H, bs, N$\underline{H}$, *m* + *M*), 6.57 (1H, d, *J* = 8.8 Hz, $C_8\underline{H}$(Ph), *M*), 6.70 (1H, dt, *J* = 8.8 Hz, *J* = 2.8 Hz, $C_7\underline{H}$(Ph), *M*), 6.75 (1H, ~t, *J* = 2.2 Hz, $C_7\underline{H}$(Ph), *m*), 6.79 (1H, ~t, *J* = 2.8 Hz, $C_5\underline{H}$(Ph), *M*), 7.09 (1H, ~t, *J* = 2.2 Hz, $C_5\underline{H}$(Ph), *m*) and 7.21 (1H, d, *J* = 8.8 Hz, $C_8\underline{H}$(Ph), *m*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 22.66 (~t, $^2J_{CP}$ = 5.8 Hz, CH$\underline{C}H_2$CH, *M*), 25.64 (d, $^2J_{CP}$ = 4.6 Hz, CH$\underline{C}H_2$CH, *m*), 33.80 (dd, $^1J_{CP}$ = 141.9 Hz, $^3J_{CP}$ = 8.1 Hz, $\underline{C}$HP, *m*), 34.48 (dd, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 15.0 Hz, $\underline{C}$HP, *M*), 45.71 (d, $^1J_{CP}$ = 161.5 Hz, N$\underline{C}$HP, *M*), 52.29 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *m*), 52.85 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *m*), 53.03 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.24 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.29 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 53.39 (d, $^2J_{CP}$ = 9.2 Hz, P(O)O$\underline{C}H_3$, *m*), 53.90 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O$\underline{C}H_3$, *M*), 54.67 (d, $^2J_{CP}$ = 8.1 Hz, P(O)O$\underline{C}H_3$, *m*), 55.65 (s, O$\underline{C}H_3$(Ph), *m*), 55.68 (dd, $^1J_{CP}$ = 153.5 Hz, $^3J_{CP}$ = 8.1 Hz, N$\underline{C}$HP, *m*), 55.76 (s, O$\underline{C}H_3$(Ph), *M*), 114.43 (d, *J* = 2.3 Hz, $\underline{C}_{4a}$(Ph), *m*), 114.56 (d, *J* = 5.8 Hz, $\underline{C}_{4a}$(Ph), *M*), 115.31 (dd, *J* = 6.4 Hz, *J* = 4.6 Hz, $\underline{C}_5$H(Ph) + $\underline{C}_7$H(Ph), *M*), 115.67 (s, $\underline{C}_5$H(Ph) + $\underline{C}_7$H(Ph), *m*), 116.72 (d, *J* = 2.3 Hz, $\underline{C}_8$H(Ph), *M*), 118.86 (d, *J* = 6.9 Hz, $\underline{C}_8$H(Ph), *m*), 137.42 (dd, *J* = 12.7 Hz, *J* = 6.9 Hz, $\underline{C}_{8a}$(Ph), *M*), 140.14 (dd, *J* = 8.1 Hz, *J* = 2.3 Hz, $\underline{C}_{8a}$(Ph), *m*), 151.78

(d, J = 2.3 Hz, $\underline{C}_6$(Ph), *m*) and 152.08 (d, J = 3.5 Hz, $\underline{C}_6$(Ph), *M*); **δ_P (121 MHz, $CDCl_3$)** 26.88 (d, J_{PP} = 11.2 Hz, *m*), 27.77 (d, J_{PP} = 2.2 Hz, *M*), 29.56 (d, J_{PP} = 2.2 Hz, *M*) and 30.37 (d, J_{PP} = 11.2 Hz, *m*); **m/z (ESI)** 380.2 ($[M+H]^+$, 100 %).

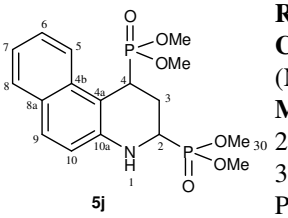
[4-(Dimethoxy-phosphoryl)-6-nitro-1,2,3,4-tetrahydro-quinolin-2-yl]-phosphonic acid dimethyl ester (0.41g, 51%)



5h

Ratio: minor (*m*) / Major (*M*): < 1 / 99. Yellow crystals.
Chromatography: CH_3CN/CH_2Cl_2/MeOH 80/17/3 R_f = 0.30 (*M*); **Melting point:** 181.0 °C – 182.0 °C (from MeOH); **Elemental analysis (%):** Found: C, 39.6; H, 4.6; N, 7.0 Calc. for $C_{13}H_{20}N_2O_8P_2$: C, 39.6; H, 5.1; N, 7.1; **IR: ν_{max}/cm^{-1}** 3281 (NH), 1234 (P=O) and 1038 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 2.00-2.31 (1H, m, $C\underline{H}_ACH_B$, *M*), 2.58 (1H, ~t, J = 12.1 Hz, $CH_AC\underline{H}_B$, *M*), 3.33 (1H, ~dt, $^2J_{HP}$ = 23.7 Hz, J = 3.9 Hz, C<u>H</u>P, *M*), 3.71 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC<u>H</u>$_3$, *M*), 3.80 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC<u>H</u>$_3$, *M*), 3.85 (3H, d, $^3J_{HP}$ = 10.5 Hz, P(O)OC<u>H</u>$_3$, *M*), 3.86 (3H, d, $^3J_{HP}$ = 11.0 Hz, P(O)OC<u>H</u>$_3$, *M*), 4.27 (1H, ddd, $^2J_{HP}$ = 12.1 Hz, J = 8.8 Hz, J = 3.3 Hz, NC<u>H</u>P, *M*), 6.19 (1H, d, J = 5.0 Hz, N<u>H</u>, *M*), 6.75 (1H, d, J = 8.8 Hz, $C_8\underline{H}$(Ph), *M*), 7.92 (1H, dt, J = 8.8 Hz, J = 2.2 Hz, $C_7\underline{H}$(Ph), *M*) and 8.07 (1H, t, J = 2.2 Hz, $C_5\underline{H}$(Ph), *M*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 21.29 (t, $^2J_{CP}$ = 4.6 Hz, CH<u>C</u>H$_2$CH, *M*), 33.81 (dd, $^1J_{CP}$ = 143.1 Hz, $^3J_{CP}$ = 13.9 Hz, <u>C</u>HP, *M*), 45.35 (d, $^1J_{CP}$ = 160.4 Hz, N<u>C</u>HP, *M*), 53.17 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 53.20 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 53.48 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 53.79 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 112.41 (d, J = 6.9 Hz, $\underline{C}_{4a}$(Ph), *M*), 114.06 (s, $\underline{C}_8$H(Ph), *M*), 124.63 (s, $\underline{C}_7$H(Ph), *M*), 126.90 (d, J = 4.6 Hz, $\underline{C}_5$H(Ph), *M*), 137.62 (d, J = 2.3 Hz, $\underline{C}_6$(Ph), *M*) and 149.41 (dd, J = 9.2 Hz, J = 4.6 Hz, $\underline{C}_{8a}$(Ph), *M*); **δ_P (121 MHz, $CDCl_3$)** 26.08 (d, J_{PP} = 2.2 Hz, *M*) and 28.16 (d, J_{PP} = 2.2 Hz, *M*); **m/z (ESI)** 395.0 ($[M+H]^+$, 100 %).

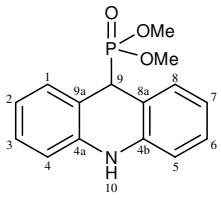
[4-(Dimethoxyfosforyl)-1,2,3,4-tetrahydrobenzo[f]chinolin-2-yl]fosfonzuur dimethylester (0.08g, 10%)



5j

Ratio: minor (*m*) / Major (*M*): 30 / 70. Yellow oil.
Chromatography: CH_3CN/CH_2Cl_2/MeOH (80/17/3) R_f = 0.12 (*M* + *m*). **IR: ν_{max}/cm^{-1}** 3312 (NH), 1623 (CH(Ph)), 1523 (CH(Ph)), 1478 (CH(Ph)), 1235 (P=O) and 1026 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 2.02 – 2.31 (m, 1H, CHC<u>H</u>$_2$CH, *M*), 2.32 – 2.48 (m, 1H, CHC<u>H</u>$_2$CH, *m*), 2.66 – 2.77 (m, 1H, CHC<u>H</u>$_2$CH, *M*), 2.82 – 2.93 (m, 1H, CHC<u>H</u>$_2$CH, *m*), 3.28 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *M*), 3.32 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *m*), 3.34 (d, $^3J_{HP}$ = 11.0 Hz, 3H, P(O)OC<u>H</u>$_3$, *m*), 3.65 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *M*), 3.76 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *m*), 3.77 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *m*), 3.83 (d, $^3J_{HP}$ = 10.5 Hz, 3H, P(O)OC<u>H</u>$_3$, *M*), 3.84 (d, $^3J_{HP}$ = 11.0 Hz, 3H, P(O)OC<u>H</u>$_3$, *M*), 4.06 (~dtd, J = 23.4 Hz, J = 5.1 Hz, J = 1.7 Hz, 2H,C<u>H</u>P, *M* + *m*), 4.49 (ddd, J = 12.7 Hz, J = 6.1 Hz, J = 3.9 Hz, 2H, NC<u>H</u>P, *M* + *m*), 4.62 (bs, 2H, N<u>H</u>, *M* + *m*), 6.84 (d, J = 8.8 Hz, 1H, $C_{10}\underline{H}$(Ph), *M*), 7.17 (d, J = 9.4 Hz, 1H, $C_{10}\underline{H}$(Ph), *m*), 7.22 (t, J = 7.7 Hz, 1H, $C_7\underline{H}$(Ph), *M*), 7.27 (t, J = 7.2 Hz, 1H, $C_7\underline{H}$(Ph), *m*), 7.44 (t, J = 7.7 Hz, 1H, $C_6\underline{H}$(Ph), *M*), 7.47 (t, J = 7.2 Hz, 1H, $C_6\underline{H}$(Ph), *m*), 7.56 (dd, J = 8.8 Hz, J = 2.8 Hz, 2H, $C_9\underline{H}$(Ph), *M* + *m*), 7.65 (dd, J = 8.3 Hz, J = 1.1 Hz, 1H, $C_8\underline{H}$(Ph), *M*), 7.69 (dd, J = 6.3 Hz, J = 2.8 Hz, 1H, $C_8\underline{H}$(Ph), *m*), 7.84 (d, J = 8.3 Hz, 1H, $C_5\underline{H}$(Ph), *m*) and 7.86 (d, J = 8.8 Hz, 1H, $C_5\underline{H}$(Ph), *M*); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 22.57 (t, $^2J_{CP}$ = 4.6 Hz, CH<u>C</u>H$_2$CH, *M*), 27.63 (d, $^2J_{CP}$ = 3.5 Hz, CH<u>C</u>H$_2$CH, *m*), 30.63 (dd, $^1J_{CP}$ = 144.8 Hz, $^3J_{CP}$ = 13.9 Hz, <u>C</u>HP, *m*), 30.79 (dd, $^1J_{CP}$ = 143.1 Hz, $^3J_{CP}$ = 15.0 Hz, <u>C</u>HP, *M*), 45.40 (d, $^1J_{CP}$ = 158.1 Hz, N<u>C</u>HP, *M*), 52.57 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *m*), 52.77 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 52.86 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *m*), 53.15 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, 2 x *M*), 53.71 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, 2 x *m*), 53.87 (d, $^2J_{CP}$ = 6.9 Hz, P(O)O<u>C</u>H$_3$, *M*), 55.93 (dd, J = 154.6 Hz, J = 2.3 Hz, N<u>C</u>HP, *m*), 103.55 (d, J = 6.9 Hz, $\underline{C}_{4a}$(Ph), *M*), 111.69 (d, J = 5.8 Hz, $\underline{C}_{4a}$(Ph), *m*), 118.23 (d, J = 3.5 Hz, $\underline{C}_{10}$H(Ph), *M*), 119.66 (d, J = 3.5 Hz, $\underline{C}_{10}$H(Ph), *m*), 121.63 (s, $\underline{C}_5$H(Ph), *m*), 121.81 (s, $\underline{C}_5$H(Ph), *M*), 121.96 (s, $\underline{C}_7$H(Ph), *M*), 122.71 (s, $\underline{C}_7$H(Ph), *m*), 126.59 (s, $\underline{C}_6$H(Ph), *M*), 126.73 (s, $\underline{C}_6$H(Ph), *m*), 127.98 (s, $\underline{C}_{8a}$(Ph), *M* + *m*), 128.33 (s, $\underline{C}_8$H(Ph), *m*), 128.39 (s, $\underline{C}_8$H(Ph), *M*), 129.05 (d, J = 3.5 Hz, $\underline{C}_9$H(Ph), *m*), 129.15 (d, J = 3.5 Hz, $\underline{C}_9$H(Ph), *M*), 131.67 (d, J = 4.6 Hz, $\underline{C}_{4b}$(Ph), *m*), 132.63 (d, J = 4.6 Hz, $\underline{C}_{4b}$(Ph), *M*), 141.02 (dd, J = 9.2 Hz, J = 6.9 Hz, $\underline{C}_{10a}$(Ph), *M*) and 145.08 (~t, J = 6.9 Hz, $\underline{C}_{10a}$(Ph), *m*); **δ_P (121 MHz, $CDCl_3$)** 27.13 (s, *m*), 28.02 (d, J_{PP} = 1.5 Hz, *M*), 28.46 (s, *m*) and 29.55 (d, J_{PP} = 1.5 Hz, *M*); **m/z (ESI)** 400.0 ($[M+H]^+$, 100 %).

(9,10-Dihydro-acridin-9-yl)-phosphonic acid dimethyl ester (0.52g, 90%)



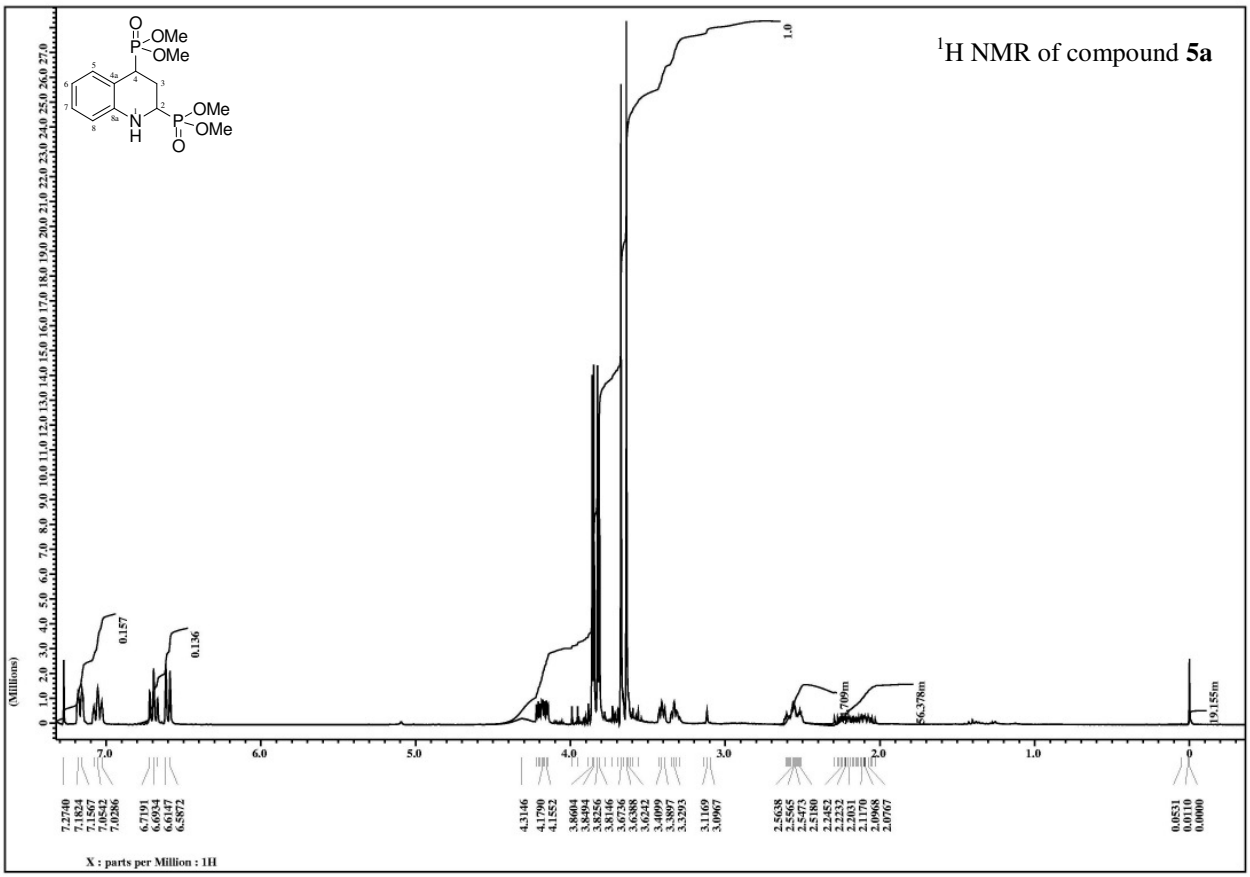
12

Green powder.

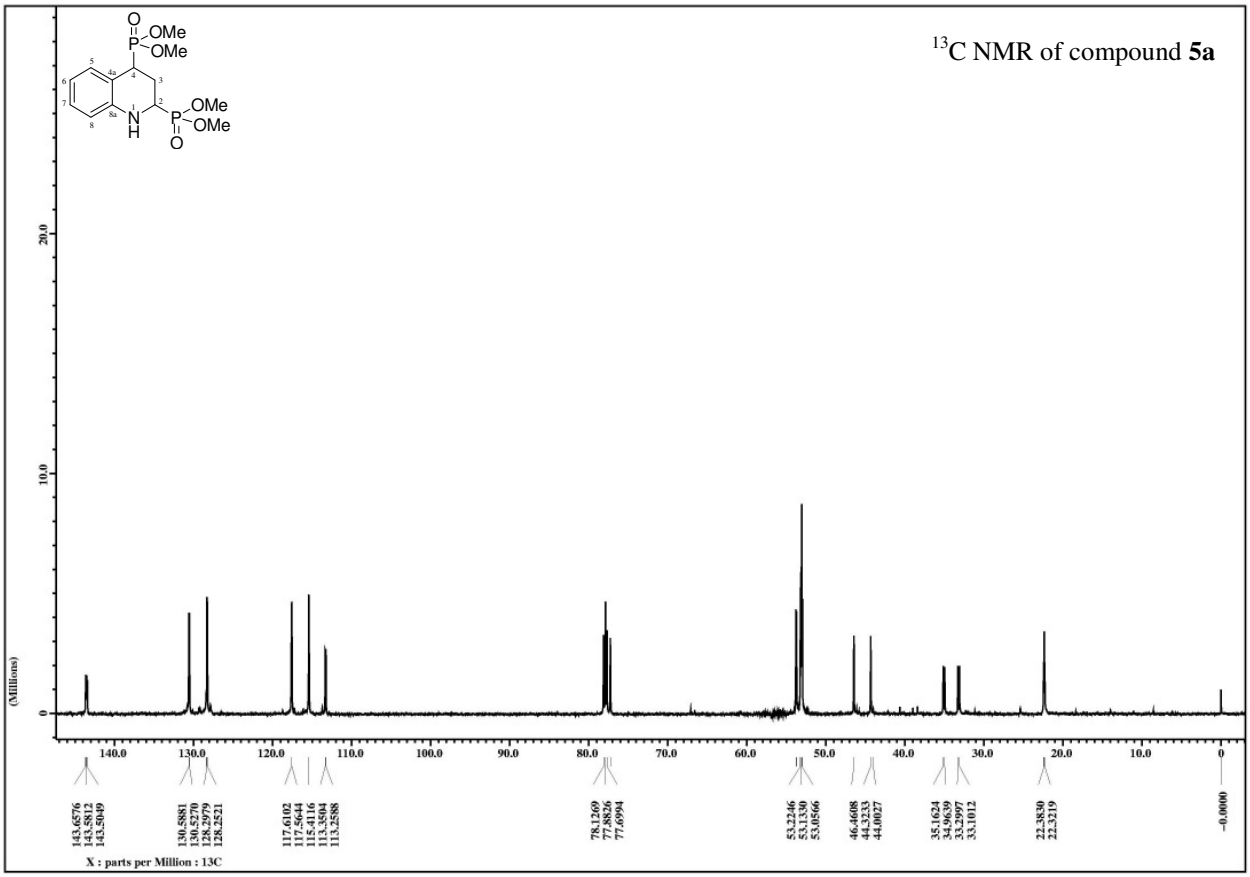
Melting point: 155.0 °C – 157.0 °C (from MeOH); **Elemental analysis (%):** Found: C, 62.2; H, 5.52; N, 4.8 Calc. for $C_{15}H_{16}NO_3P$: C, 62.3; H, 5.6; N, 4.8; **IR: ν_{max}/cm^{-1}** 3267 (NH), 1614 (CH(Ph)), 1585 (CH(Ph)), 1479 (CH(Ph)), 1219 (P=O) and 1023 (P-O); **δ_H (300 MHz, $CDCl_3$, Me_4Si)** 3.54 (d, $^3J_{HP}$ = 10.5 Hz, 6H, 2 x P(O)OC$\underline{H}_3$), 4.58 (d, $^2J_{HP}$ = 25.3 Hz, 1H, C$\underline{H}$P), 6.65 (d, J = 7.7 Hz, 2H, $C_{4+5}\underline{H}$(Ph)), 6.87 (t, J = 7.2 Hz, 2H, $C_{2+7}\underline{H}$(Ph)), 7.09 (~tt, J = 7.7 Hz, J = 1.7 Hz, 2H, $C_{3+6}\underline{H}$(Ph)) and 7.21 (~d, J = 7.7 Hz, 2H, $C_{1+8}\underline{H}$(Ph)); **δ_C (75 MHz, $CDCl_3$, Me_4Si)** 42.96 (d, $^1J_{CP}$ = 140.8 Hz, $\underline{C}$HP), 53.58 (d, $^2J_{CP}$ = 8.1 Hz, 2 x P(O)O$\underline{C}H_3$), 114.07 (d, J = 2.3 Hz, $\underline{C}_{4+5}$H(Ph)), 114.24 (d, J = 8.1 Hz, $\underline{C}_{8a+9a}$(Ph)), 120.61 (d, J = 3.5 Hz, $\underline{C}_{2+7}$H(Ph)), 128.23 (d, J = 3.5 Hz, $\underline{C}_{3+6}$H(Ph)), 129.99 (d, J = 4.6 Hz, $\underline{C}_{1+8}$H(Ph)) and 140.31 (d, J = 3.5 Hz, $\underline{C}_{4a+4b}$(Ph)); **δ_P (121 MHz, $CDCl_3$)** 24.99 (s); **m/z (ESI)** 290.3 ([M+H]$^+$, 10 %), 180.2 ([M-P(O)$(OMe)_2$+H]$^+$, 100 %).

Supplementary Material (ESI) for Chemical Communications

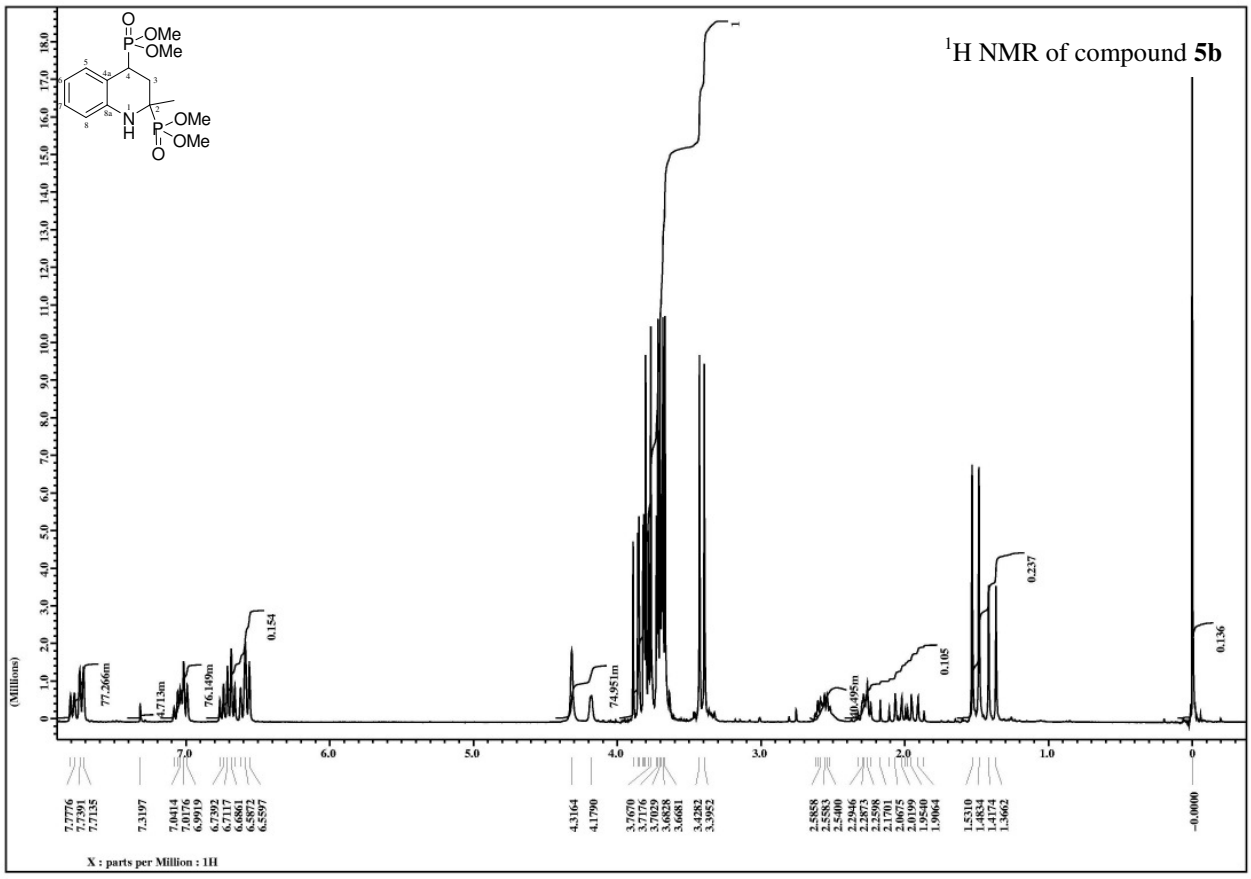
^{1}H NMR of compound **5a**



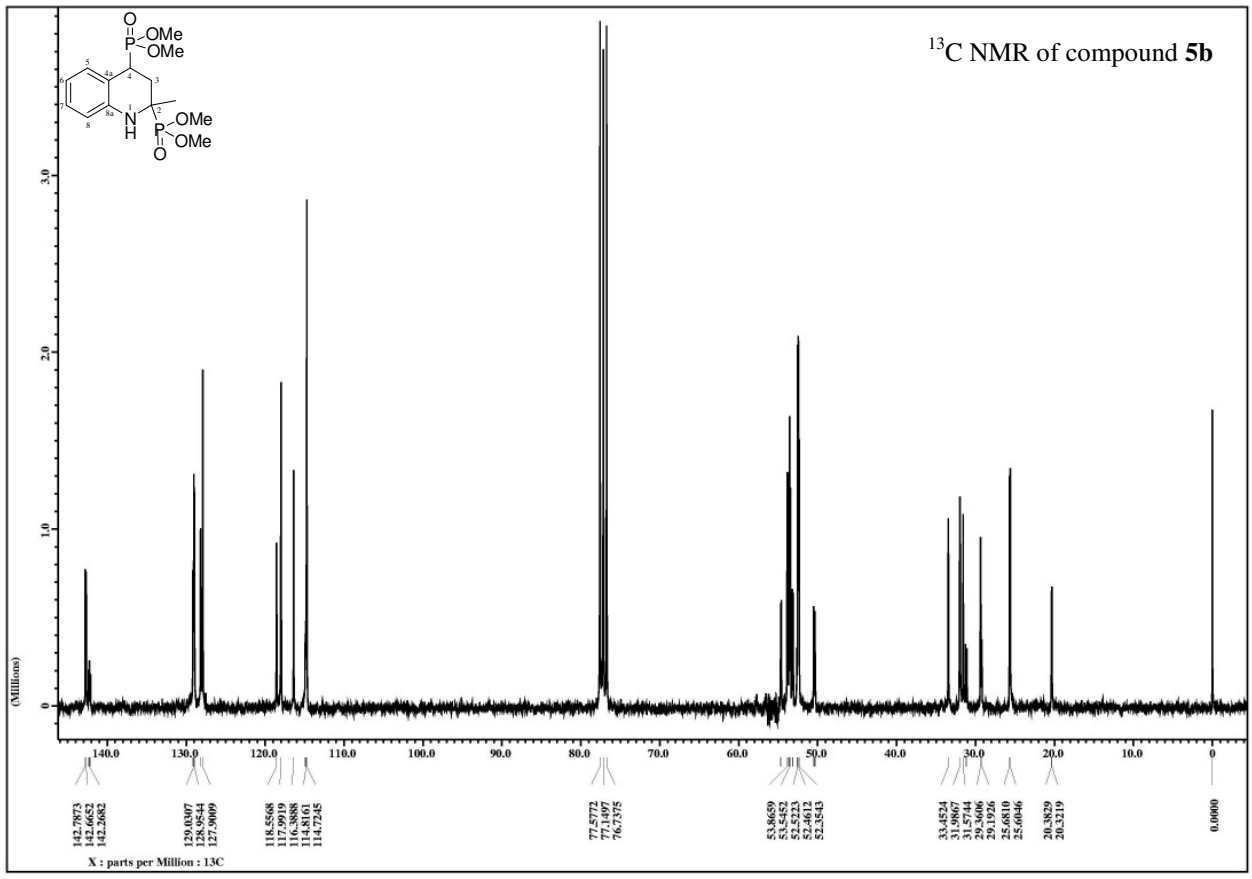
^{13}C NMR of compound **5a**



^{1}H NMR of compound **5b**

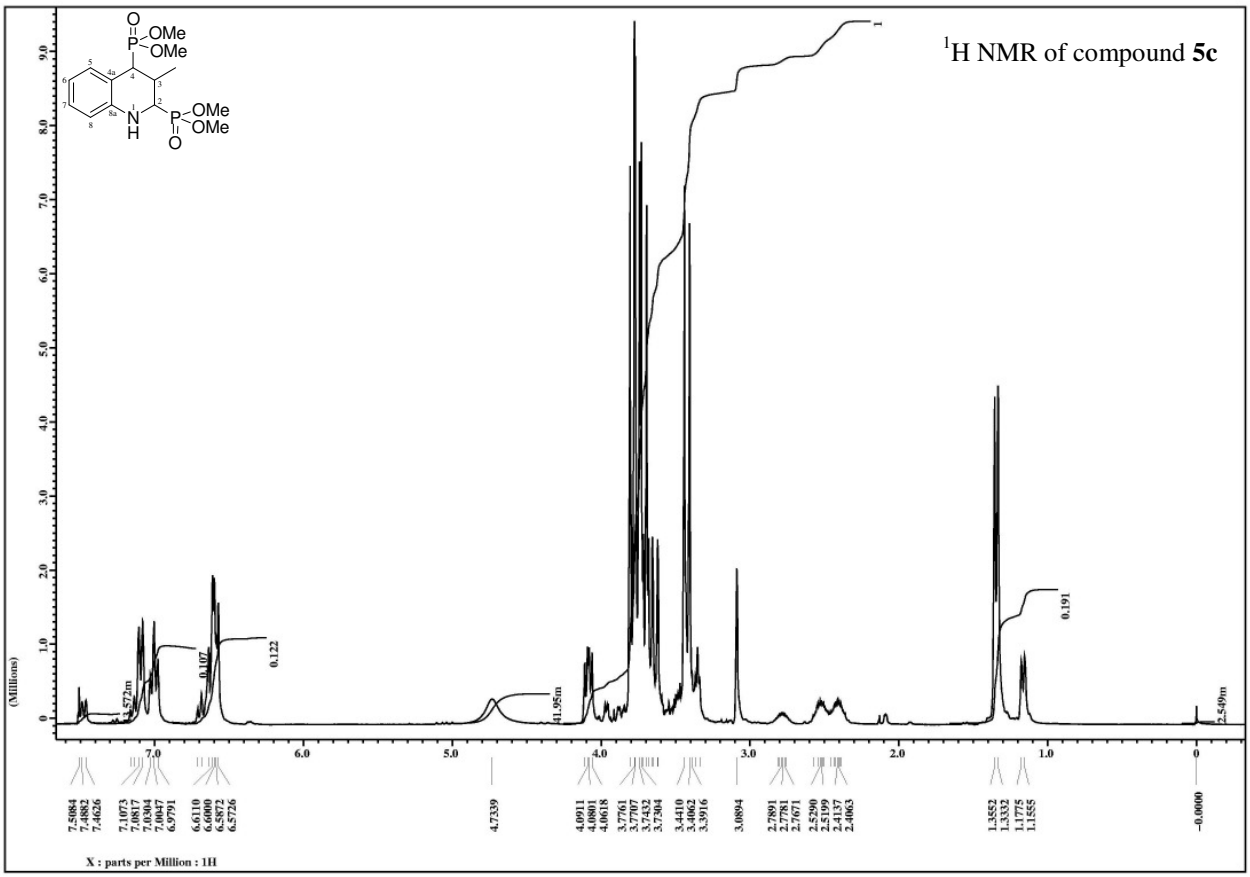


^{13}C NMR of compound **5b**

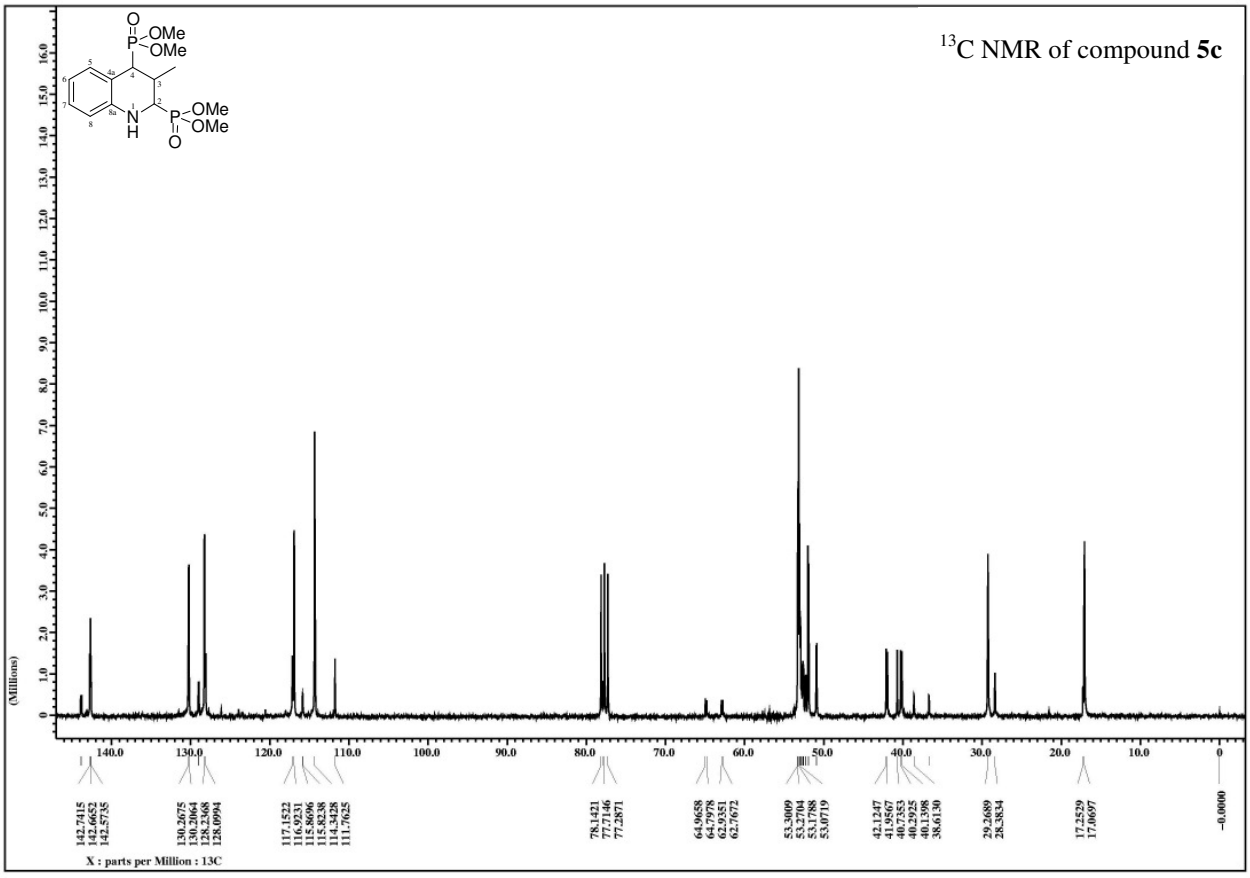


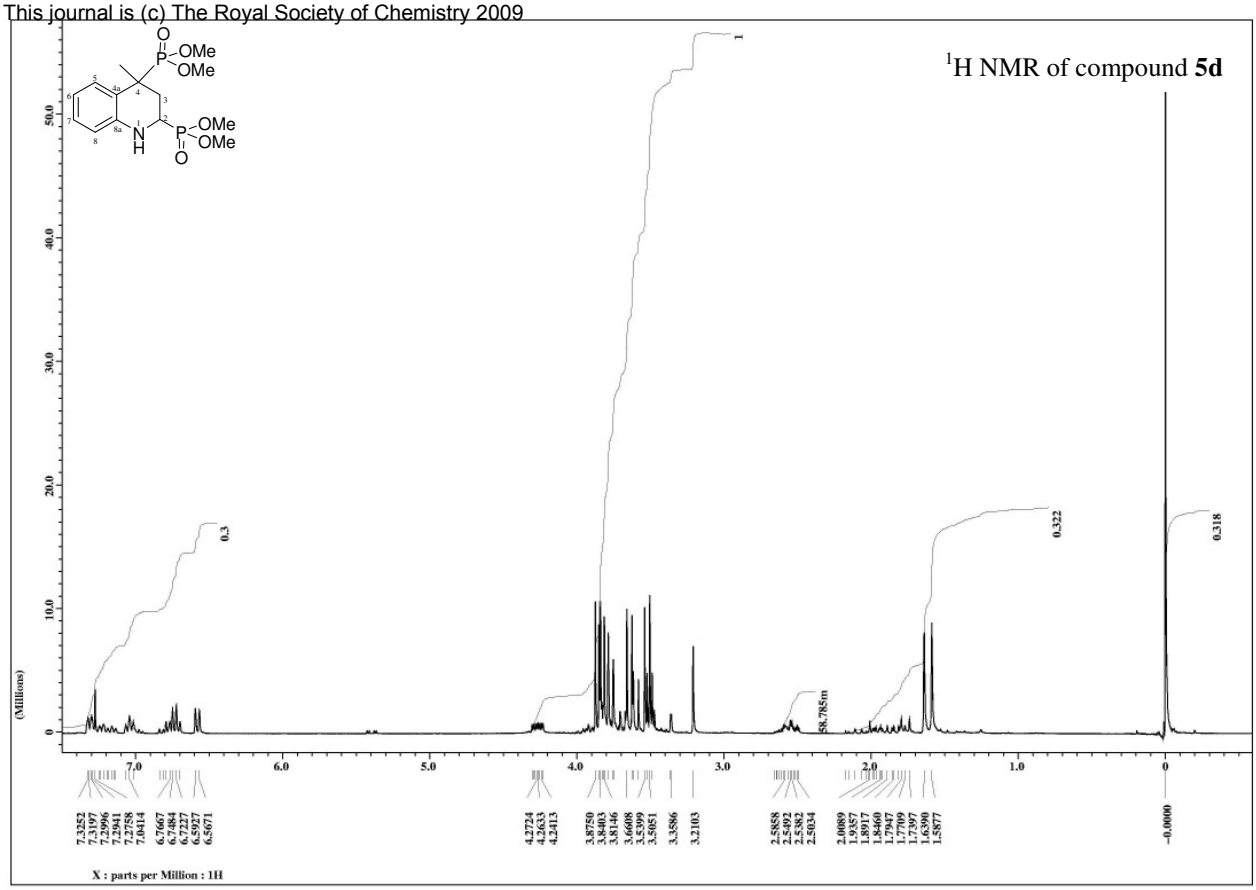
Supplementary Material (ESI) for Chemical Communications

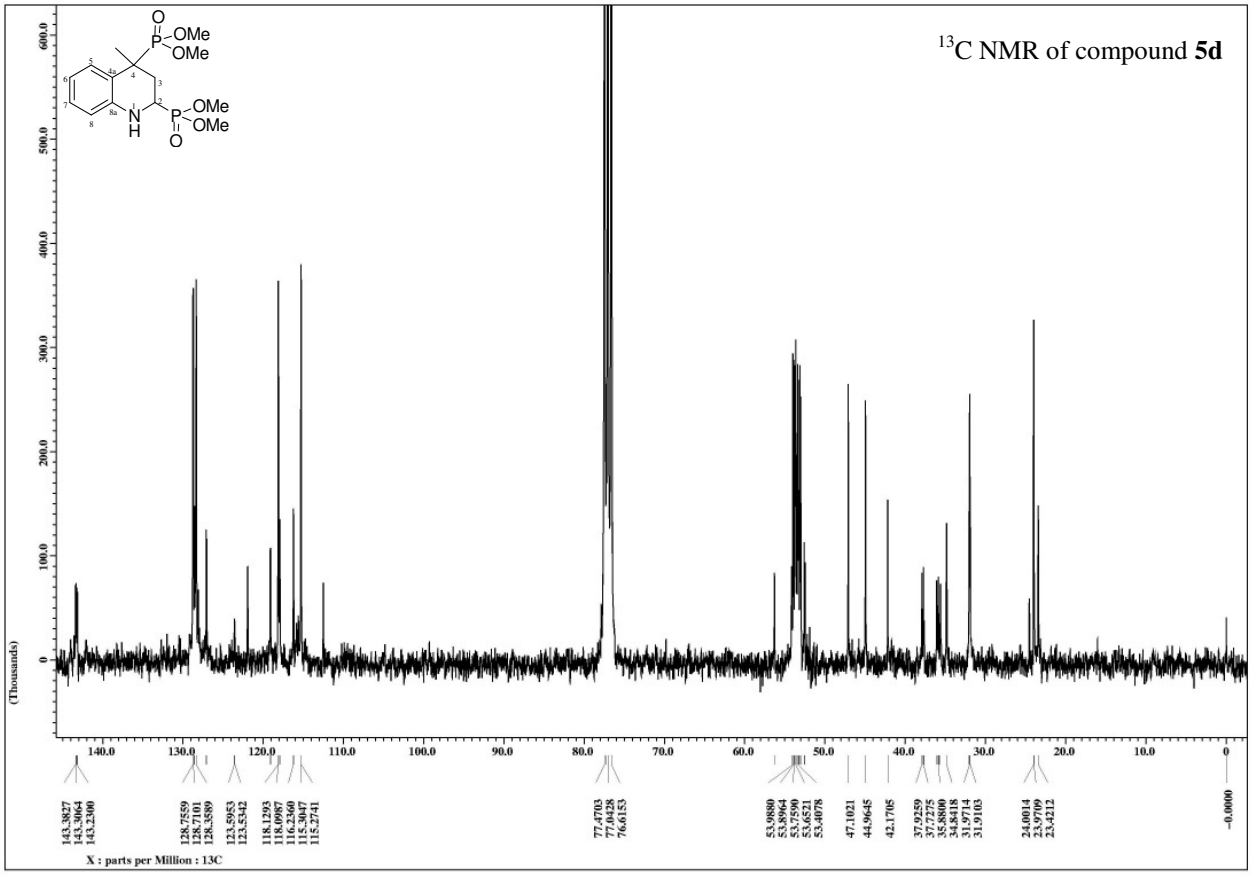
^{1}H NMR of compound **5c**



^{13}C NMR of compound **5c**

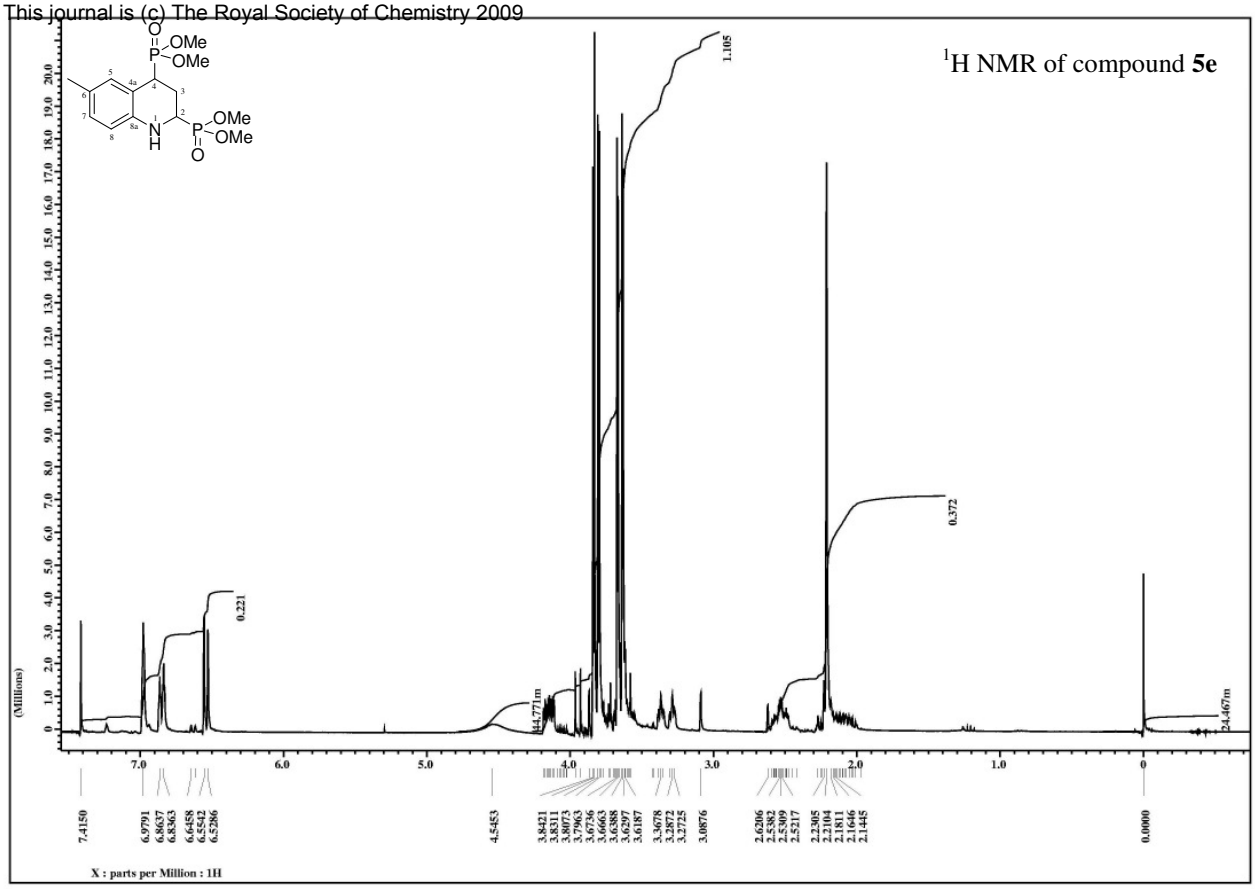



^{1}H NMR of compound **5d**
X : parts per Million : 1H

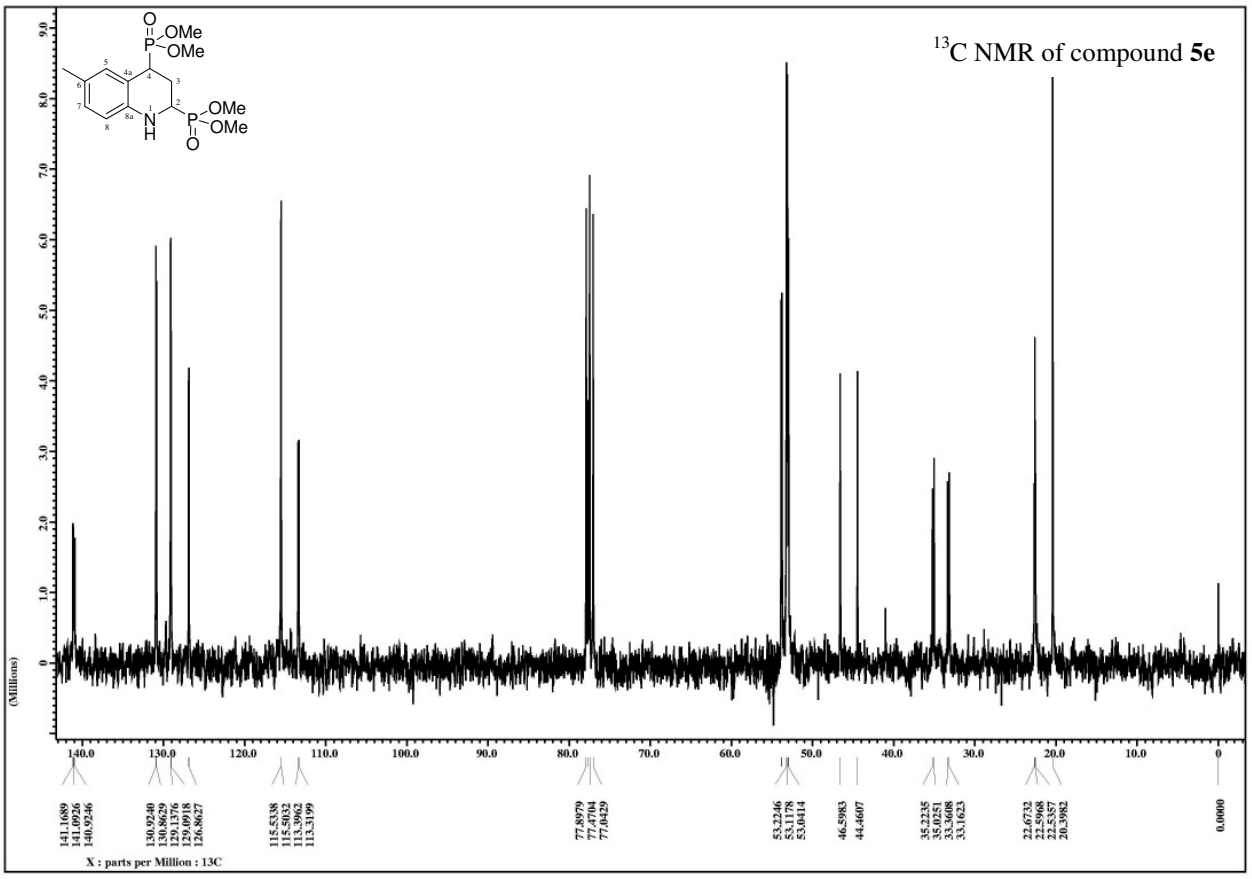

^{13}C NMR of compound **5d**
X : parts per Million : 13C

Supplementary Material (ESI) for Chemical Communications

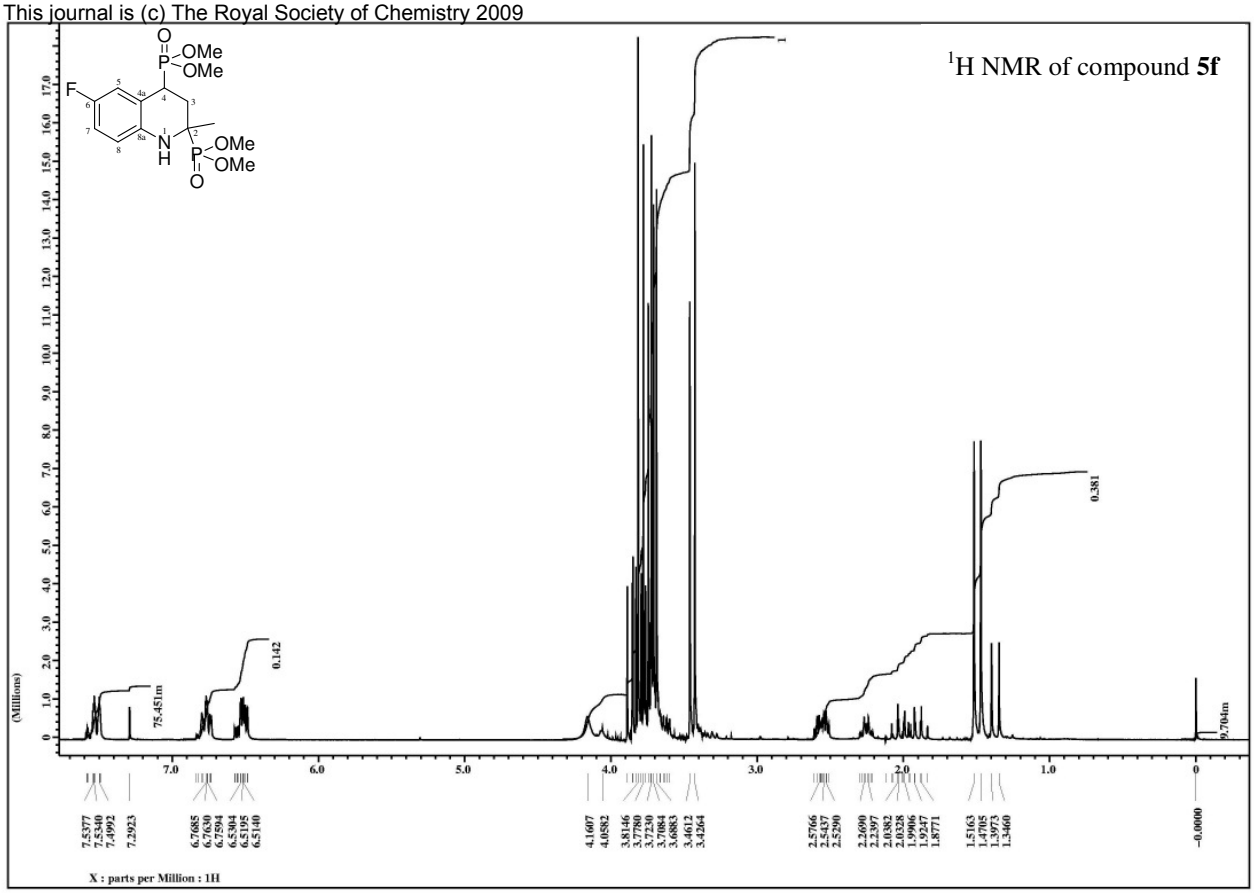
^{1}H NMR of compound **5e**



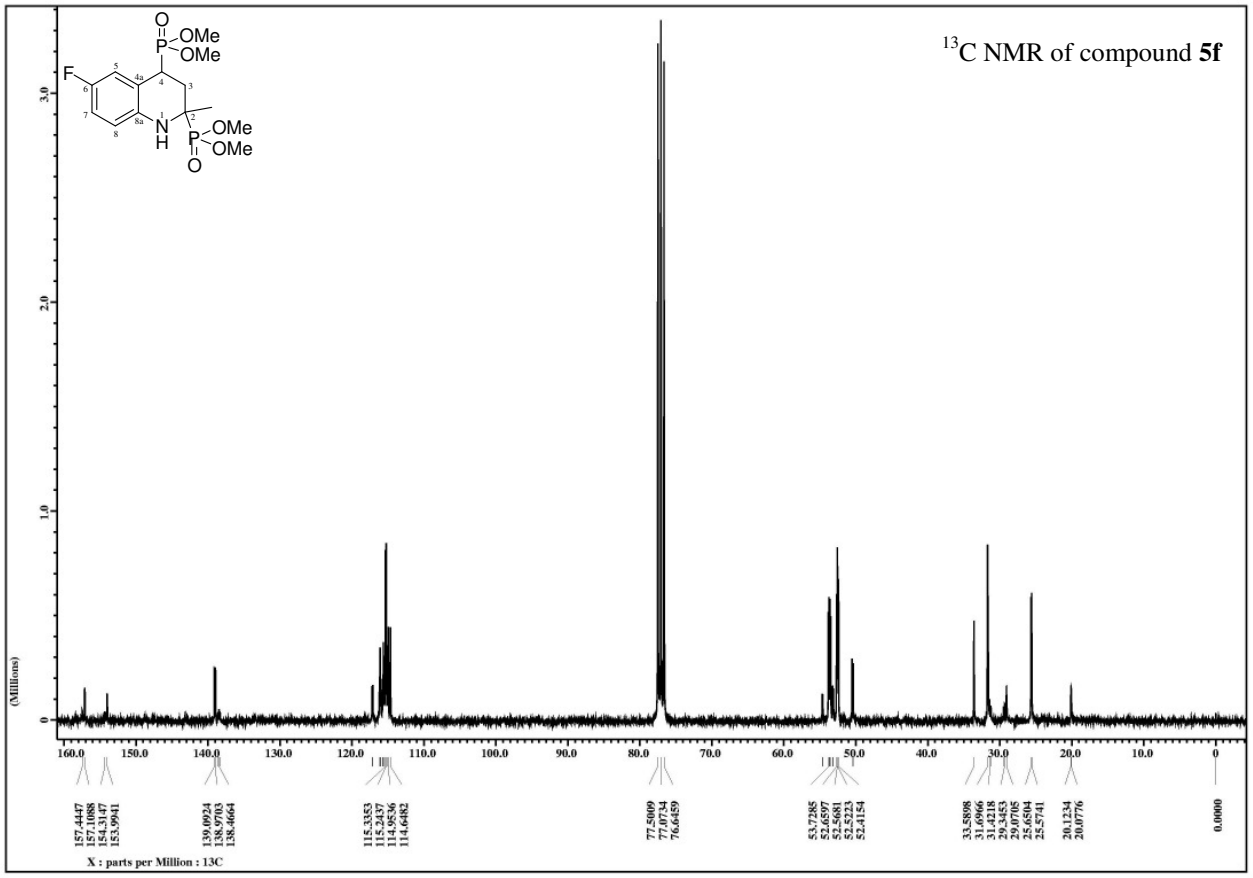
^{13}C NMR of compound **5e**



^{1}H NMR of compound **5f**

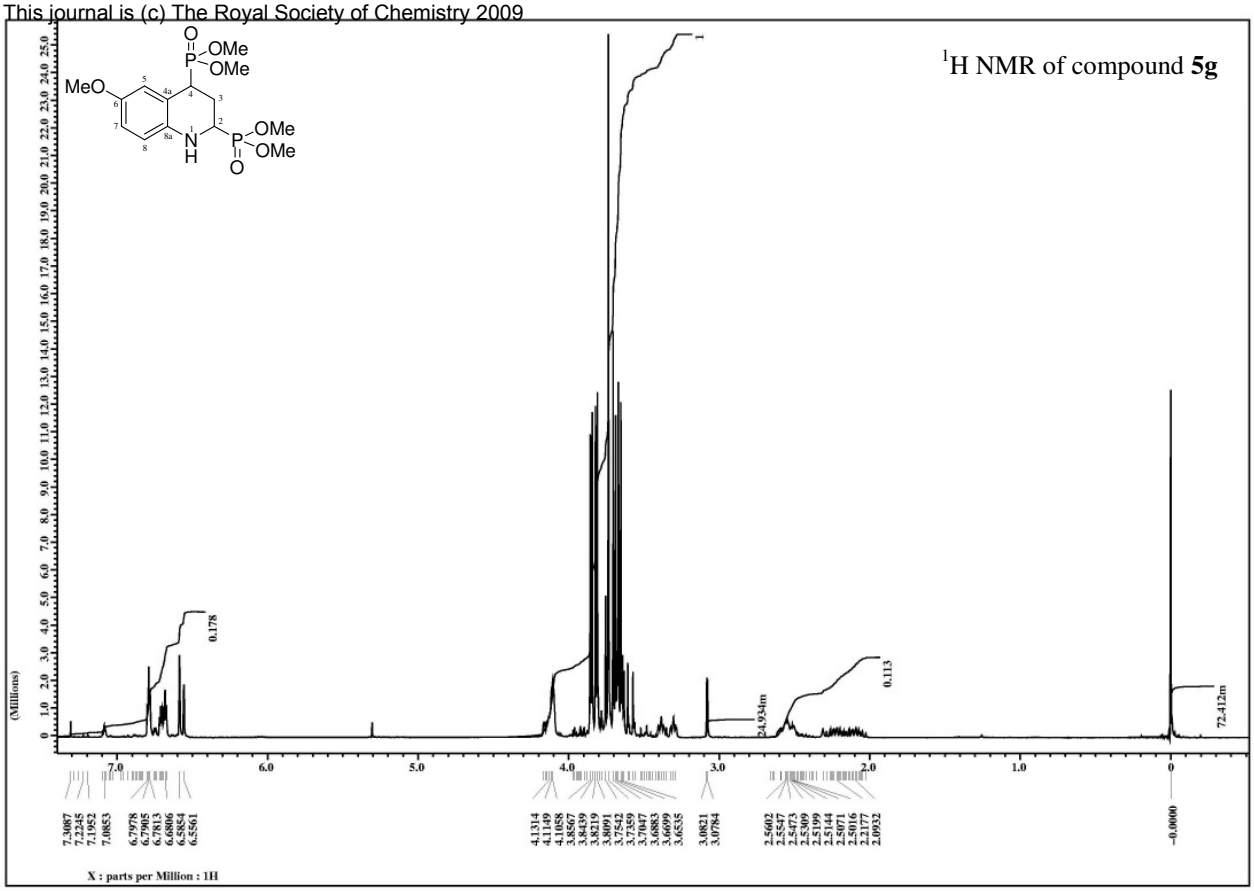


^{13}C NMR of compound **5f**

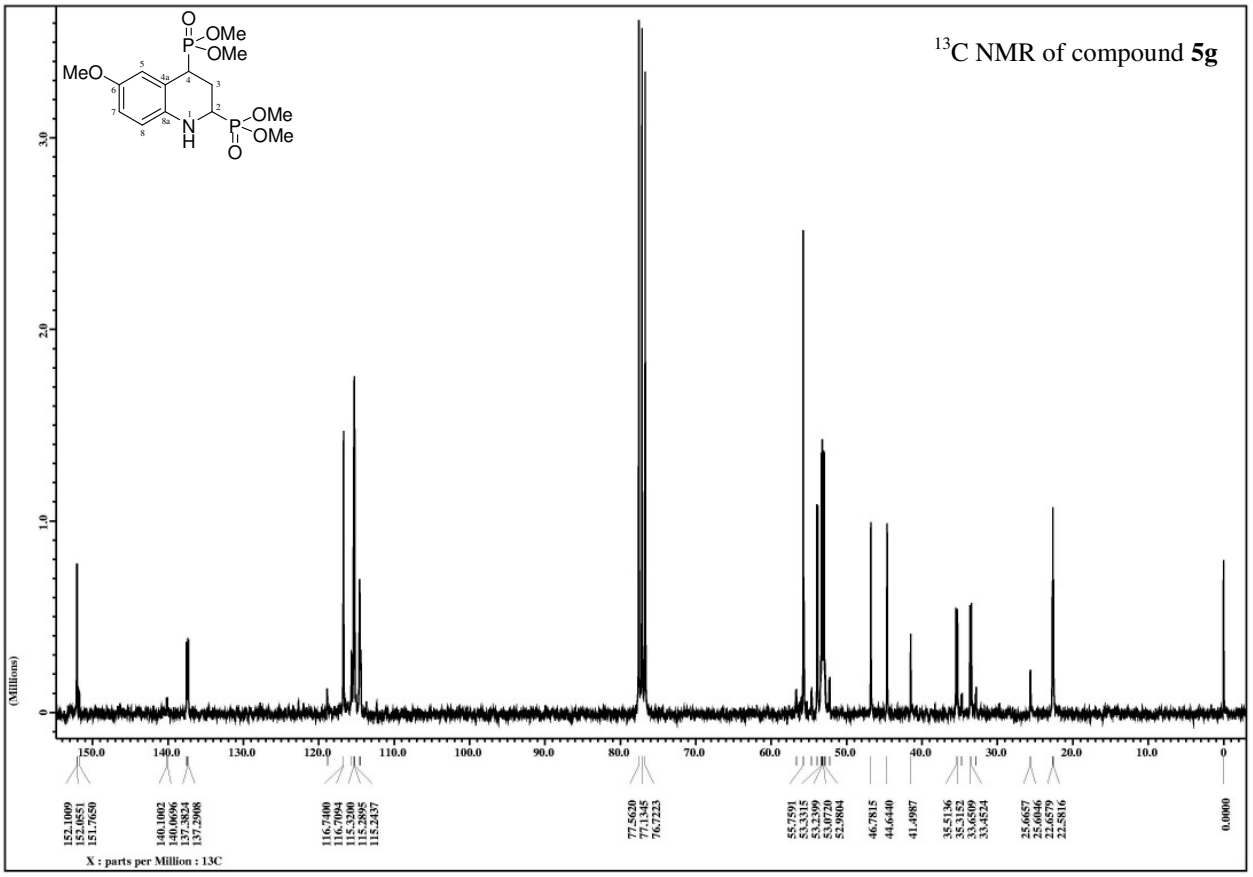


Supplementary Material (ESI) for Chemical Communications

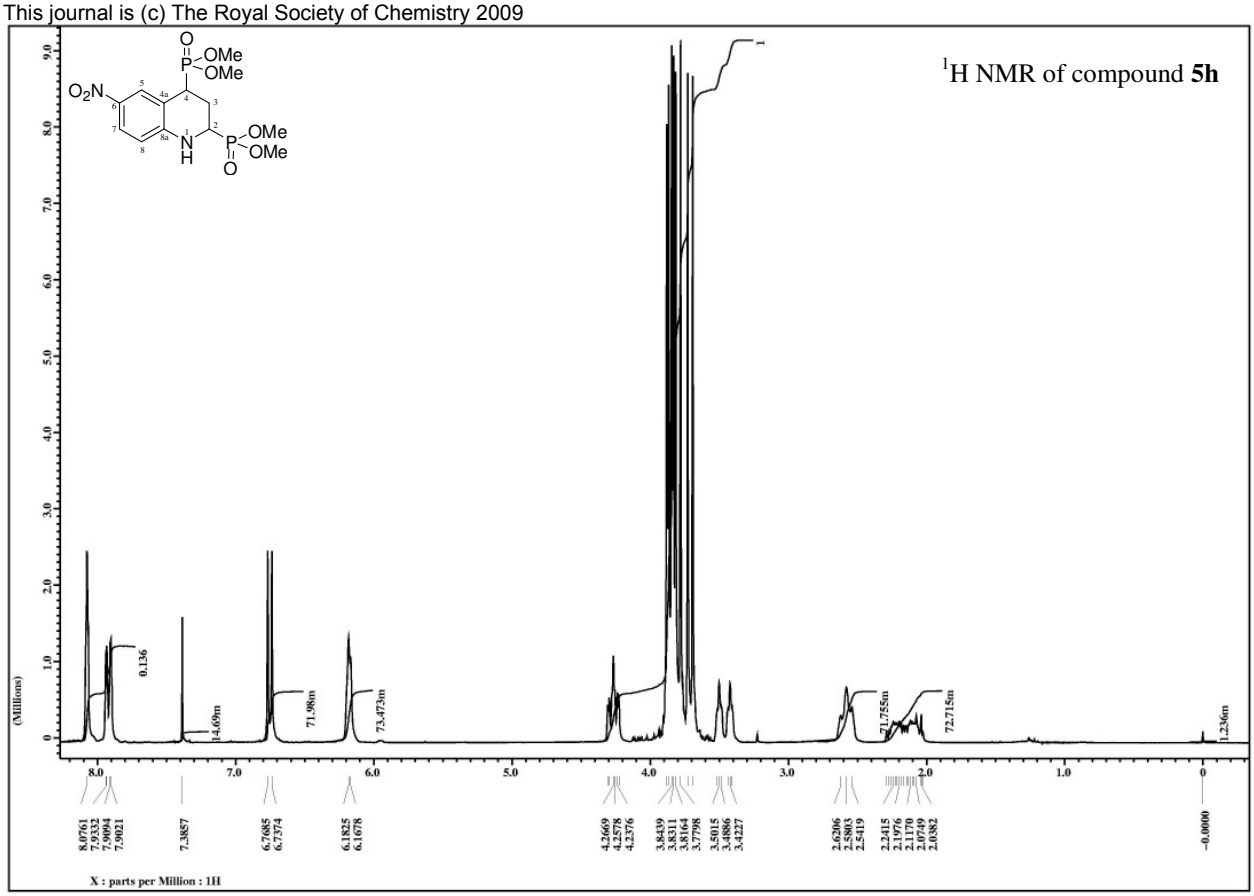
^{1}H NMR of compound **5g**



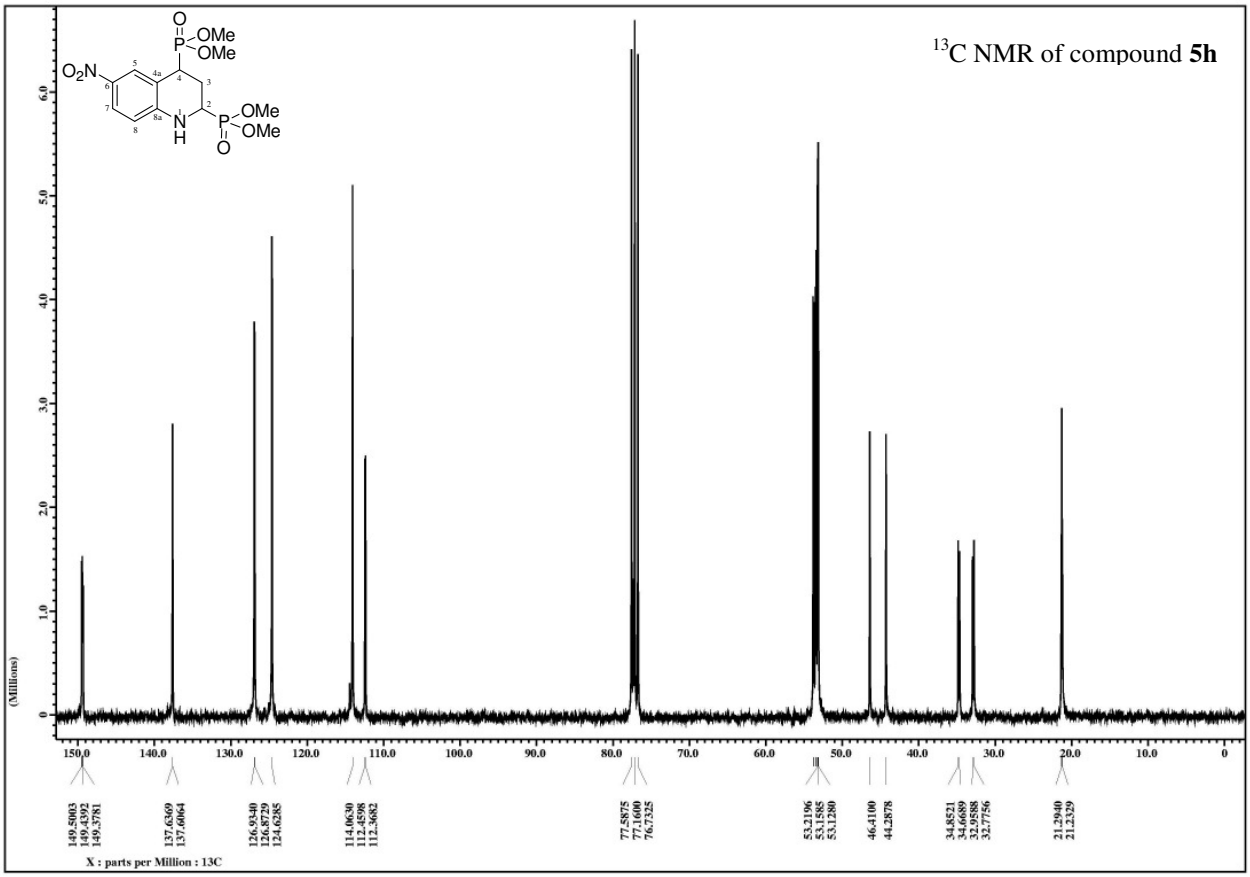
^{13}C NMR of compound **5g**



^{1}H NMR of compound **5h**

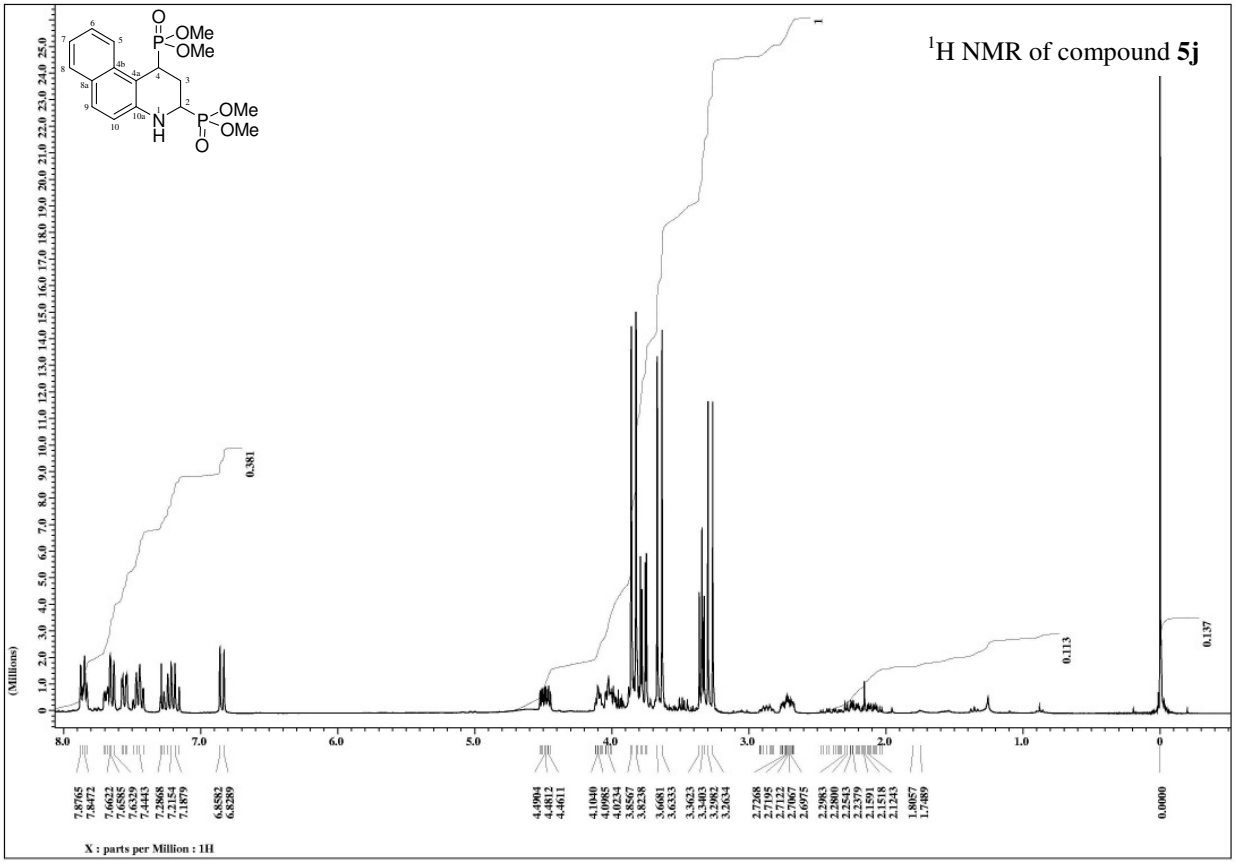


^{13}C NMR of compound **5h**

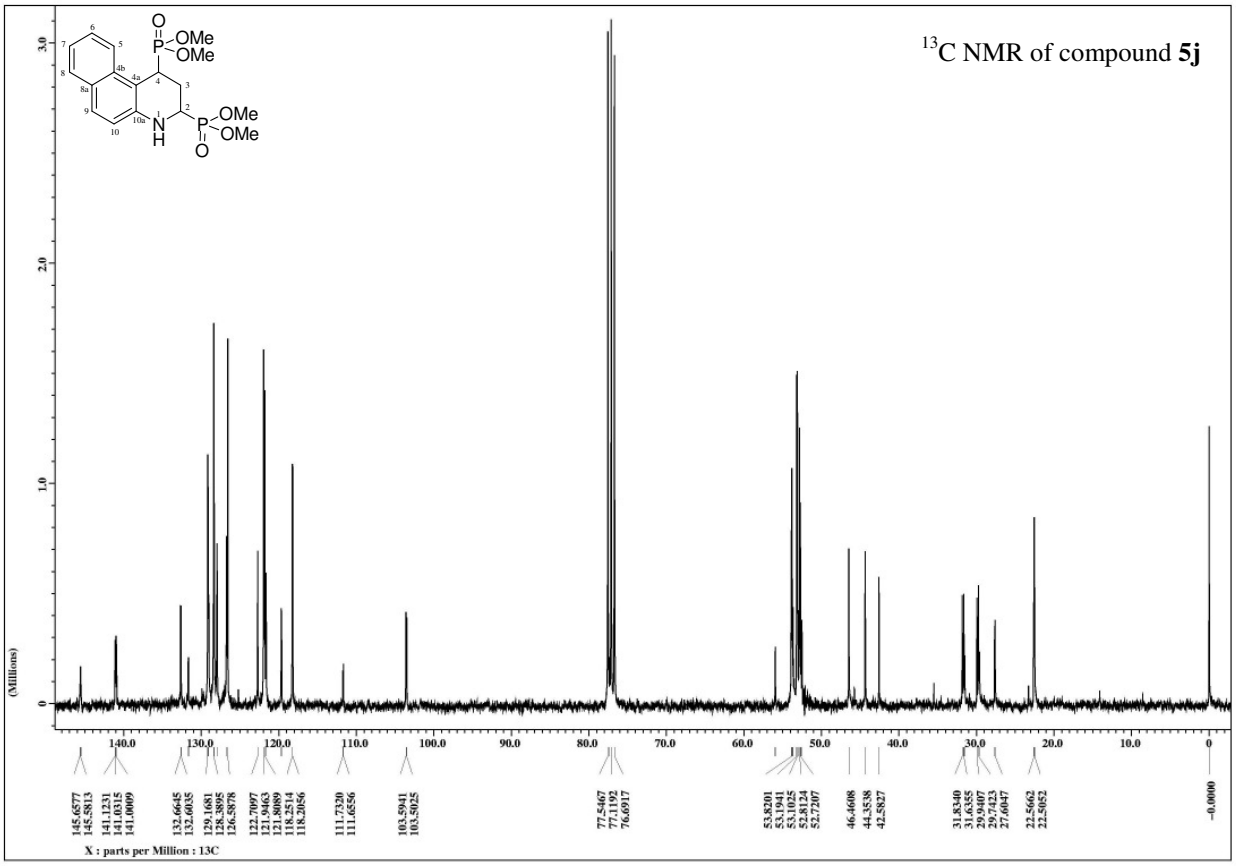


Supplementary Material (ESI) for Chemical Communications

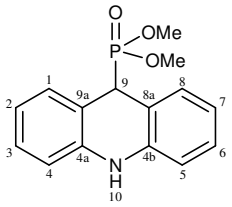
^{1}H NMR of compound **5j**



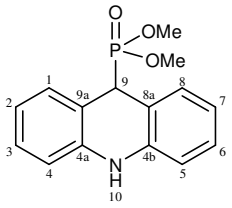
^{13}C NMR of compound **5j**



^{1}H NMR of compound **12**



^{13}C NMR of compound **12**



Supplementary Material (ESI) for Chemical Communications

Single crystal X-ray diffraction

*Crystal and molecular structure of (I) (compound **5h**)*

Compound (I) crystallizes in the triclinic $P\bar{1}$ space group with two molecules per unit cell. There is one independent molecule in the asymmetric unit of (I) (Figure S2). In the region of the dimethoxyphosphoryl group attached to atom C5, a disorder was identified and modeled as a superposition of two fragments, *i.e.* one defined by atoms O6, O7, O8, C13, H13A, H13B, H13C, H12A, H12B and H12C with an occupancy of 0.512(3), and the other by atoms O6`, O7`, O8`, C13`, H13A`, H13B`, H13C`, H12A`, H12B` and H12C` with an occupancy of 0.488(3). The disorder on atoms C and H, belonging to the dimethoxyphosphoryl group attached to atom C7, and on atom O1 of the nitro group, was also identified. The C10, H10A, H10B and H10C atoms and oxygen atom O1 are distributed over two positions, with occupancy factors of 0.837(8) and 0.163(8) and 0.79(7) and 0.21(7), respectively, while the C11, H11A, H11B, H11C atoms are distributed over three positions with occupancy factors of 0.464(8), 0.312(8) and 0.223(9). The geometric parameters and the intermolecular interactions are discussed below, but only for the major components of molecule (I).

Similarly, as it was observed for 7-nitro-1,2,3,4-tetrahydroquinoline[1], the tetrahydropyridine ring adopts an envelope conformation, with atom C6 lying 0.615(4) below the mean plane formed by the other five atoms of this ring. This plane and also the plane formed by the atoms of the nitro group are almost coplanar with the plane of the C1-C2-C3-C4-C8-C9 benzene ring, forming the dihedral angles of 1.3(1)° and 2.7(9)°, respectively. The phosphorus and oxygen atoms belonging to the dimethoxyphosphoryl group attached to the C7 atom of the tetrahydropyridine ring, *i.e.* the P1, O3, O4 and O5 atoms, lie 1.6525(9), 2.704(2), 1.377(3) and 1.938(3)Å, respectively, above the plane of the benzene ring, while the P2, O6, O7 and O8 atoms of the dimethoxyphosphoryl group attached to atom C5, lie 0.674(1), 0.522(7), 0.013(9) and 2.144(6) Å, respectively, below this plane.

The crystal packing of (I) is stabilized mainly by the conventional practically linear intermolecular N-H···O hydrogen bond (Table 1), which connects atom N1 of the tetrahydropyridine ring at (x, y, z), *via* H1, with atom O3 at (1-x, 1-y, -z), so generating a centrosymmetric $R_2^2(14)$ring[2] centered at (1/2, 1/2, 0) (Figure S3). As can be seen from Fig. 3, the rings of such type of crystal packing are further linked by the C-H···O, N-O···π and π···π intermolecular interactions, into an infinite chain running parallel to the *[001]* direction. The first C-H···O interaction between the C6 atom at (x, y, z), acting as a non-conventional hydrogen-bond donor, and the oxygen atom O2, belonging to the molecule at (1-x, 1-y, 1-z) (Table 1), generates a ring with the $R_2^2(16)$ graph-set descriptor.[2] The second N-O···π interaction exists between the O1 atom, belonging to the nitro group at (x, y, z), and the benzene ring C1-C2-C3-C4-C8-C9 (Cg1) of the molecule at (1-x, 1-y, 1-z) [O···Cg = 3.70(2)Å, N···Cg = 3.573(4) Å and N-O···Cg = 75(1)°], while the third π···π interaction involves the benzene C1-C2-C3-C4-C8-C9 ring (centroid Cg1). The perpendicular distance of the ring (centroid Cg1) from the plane containing the symmetry-related centroid Cg1 at (1-x, 1-y, 1-z) is 3.441Å, and the centroid-to-centroid separation is 4.088(2) Å; the planes of these rings make an angle of only 0.03°. Moreover, in the crystal structure of (I) there are also two other weak C-H···O hydrogen-bonds, *i.e.* C12-H12B···O4$^{(iii)}$ and C13-H13B···O7$^{(iv)}$ [symmetry codes: (iii) 1-x, -y, 1-z; (iv) 1-x, -y, -z] (Table 1), with the $R_2^2(18)$ and $R_2^2(6)$ graph-set descriptors,[2] respectively, which connect the molecules belonging to the adjacent above-mentioned chains, into an infinite two-dimensional sheet parallel to *(100)* (Figure S3).

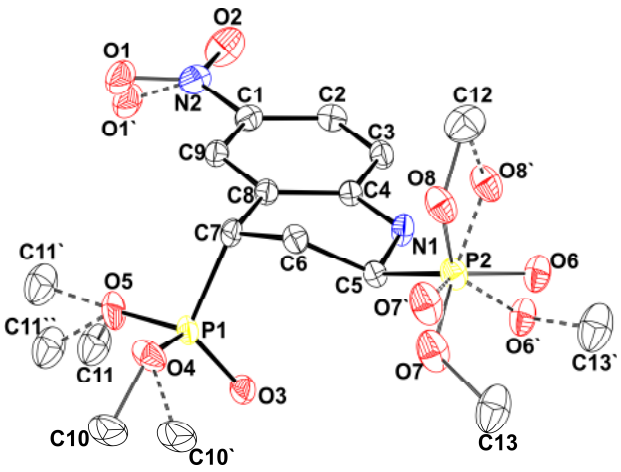


Fig. S2 A plot of the molecule (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 20% probability level and atoms are shown as small spheres of arbitrary radii. The disorder in atoms O1, O6, O7, O8, C10, C11 and C13 is represented by dashed bonds, with primed numbering for the minor components. H-atoms have been omitted for clarity.

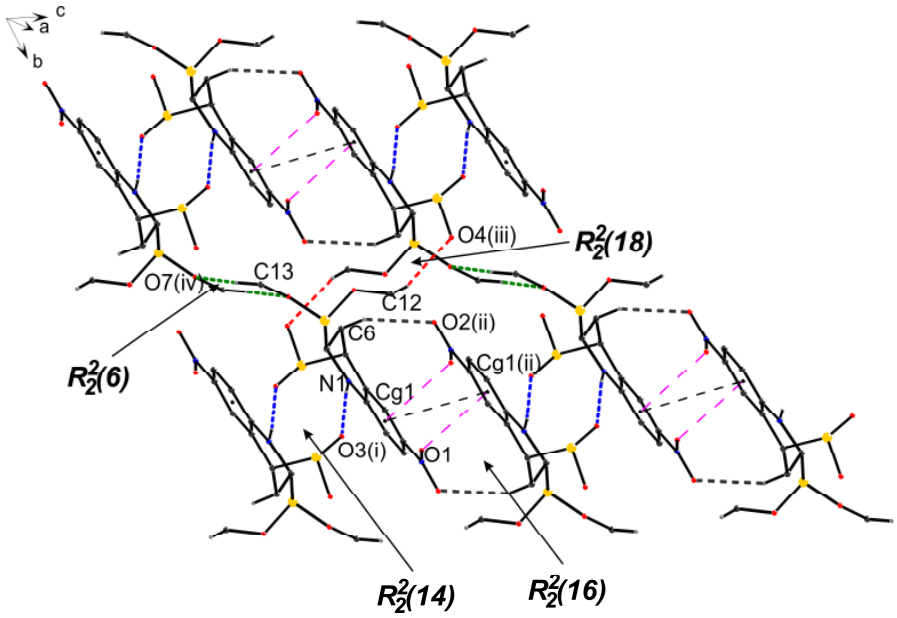


Fig. S3 Part of the crystal structure of (I), showing the chains which are built up from $R_2^2(14)$ and $R_2^2(16)$ rings, formed by the intermolecular N-H···O (blue dashed lines) and C-H···O (grey dashed lines) hydrogen-bonds, respectively, and additionally stabilized by the intermolecular N-O···π (thin purple dashed lines) and π···π interactions (thin grey dashed lines), as well as by the intermolecular hydrogen-bonds of type C-H···O, which connect the molecules belonging to the adjacent chains and can be described by the $R_2^2(18)$ and $R_2^2(6)$ graph-set descriptors (red and green dashed lines, respectively). All H-atoms and C- and O-atoms of the dimethoxyphosphoryl groups not involved in the intermolecular interactions and the minor disorder components of molecule (I), have been omitted for clarity. Symmetry codes: (i) 1-x, 1-y, -z; (ii) 1-x, 1-y, 1-z; (iii) 1-x, -y, 1-z; (iv) 1-x, -y, -z.

Supplementary Material (ESI) for Chemical Communications

Table 1 Hydrogen-bond geometry [Å, °] for (I)

D-H···A	D-H	H···A	D···A	D-H···A
N1-H1···O3$^{(i)}$	0.84(4)	2.20(4)	3.010(4)	164(4)
C6-H6A···O2$^{(ii)}$	0.92(4)	2.56(4)	3.390(5)	150(3)
C12-H12B···O4$^{(iii)}$	0.96	2.51	3.337(5)	145
C13-H13B···O7$^{(iv)}$	0.96	2.30	3.19(2)	154

Symmetry codes: (i) 1-x, 1-y, -z; (ii) 1-x, 1-y, 1-z; (iii) 1-x, -y, 1-z; (iv) 1-x, -y, -z.

Experimental

Crystallographic data of (I):

$C_{13}H_{20}N_2O_8P_2$, M = 394.25, triclinic, $P\bar{1}$, a = 10.0124(4) Å, b = 10.3614(5) Å, c = 10.4335(4) Å, α = 63.537(4) °, β = 80.792(3) ° and γ = 67.351(4) °, Z = 2 molecules per unit cell, D_c = 1.464 g/cm^3, $F(000)$ = 412, crystal size 0.35 x 0.13 x 0.09 mm. Diffraction data were collected at 293(2) K, using an Oxford Diffraction Xcalibur 3^{TM} diffractometer (graphite-monochromated MoK_α radiation, CCD detector). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 with SHELXL-97.[3] The disorder on O6, O7, O8 and C13, O1 and C10 atoms was resolved by finding alternative positions from the difference Fourier map, and was subsequently refined over two positions with the occupancies of 0.512(3), 0.79(7) and 0.837(8), respectively for the major components, while the resolved disorder on the C11 atom was refined over three positions with an occupancy of 0.464(8) for the major component. To assist in the refinement process, the anisotropic displacement parameters of the O and C atoms of the minor components were constrained to be the same as those of the major components. All aromatic H-atoms were positioned geometrically and constrained to ride on their parent atoms, with C-H distances of 0.93 Å and with $U_{iso}(H)$ values of 1.2$U_{eq}(C)$. H-atoms of the methyl group were positioned, using SHELXL97 HFIX instructions[3] with a C-H distance of 0.96 Å and with $U_{iso}(H)$ values of 1.5$U_{eq}(C)$. The hydrogen atoms, bonded to N1, C5, C6 and C7, were located in difference maps and refined with $U_{iso}(H)$ set at 1.2$U_{eq}(N)$ or 1.2$U_{eq}(C)$, giving an N-H distance of 0.83(3) Å and C-H distances in the range 0.89(3)-0.96(4) Å. $R[F^2 > 2\sigma(F^2)]$ = 0.057, $wR(F^2)$= 0.146, S = 1.06 for 3 389 independent reflections [2 307 reflections with $I > 2\sigma(I)$] and 278 parameters. Further details on the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Centre as the deposition number CCDC 747372.

References

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