Access to Substituted Cyclobutenes by Tandem [3,3]-Sigmatropic Rearrangement/[2+2] Cycloaddition of Dipropargylphosphonates under Ag/Co Relay Catalysis

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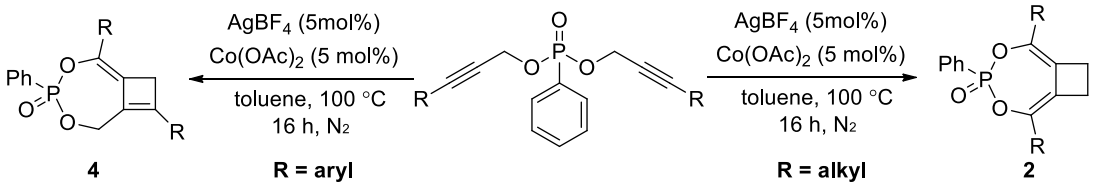
1. General information

The products were purified by column chromatography on Merck silica gel 60, particle size 0.040-0.063 mm (230-240 mesh, flash). For thin-layer chromatography (**TLC**) analysis, Merck precoated TLC plates (silica gel 60 GF254) were used. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or staining potassium permanganate solution followed by heating using a heat gun. Mass spectra were acquired on a Finnigan LCQ (ESI) spectrometer and high resolution mass spectra (**HRMS**) on a Finnigan/MAT 95XLT spectrometer. **Enantiomeric excesses** (ee) were determined by HPLC analysis on Agilent HPLC units. **^{1}H, ^{13}C and ^{31}P NMR** spectra were recorded on AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26 or DCM δ 5.32), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). All reactions were carried out under nitrogen atmosphere. All solvents were purified and dried according to standard methods prior to use. The dipropargylphosphonates were prepared via the reaction of phosphonic dichloride with propargylic alcohol according to the reported procedure.[1]

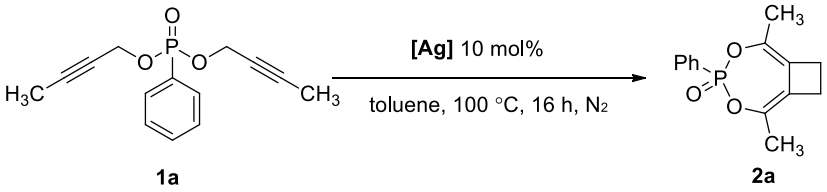
2. General procedure for the preparation of 2 or 4



To a solution of $AgBF_4$ (0.005 mmol) and $Co(OAc)_2$ (0.005 mmol) in toluene (1.0 mL) in a vial in the glovebox was added dipropargylphosphonate (0.1 mmol). The mixture was sealed and taken out of the glovebox. The reaction was heated to 100 °C and allowed to stir for 16 h. The crude mixture was cooled to ambient temperature and directly purified by flash column chromatography using hexanes/ethyl acetate (5:1) as eluent to afford the desired product **2** or **4** in pure form.

3. Screening of silver salts for optimization of 2a formation

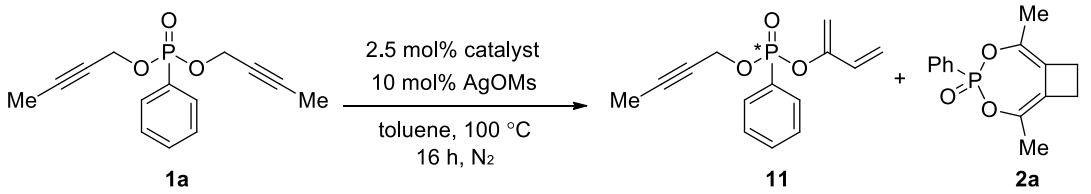
Table S1.

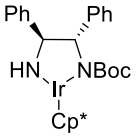
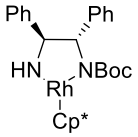
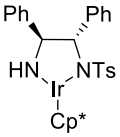
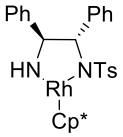
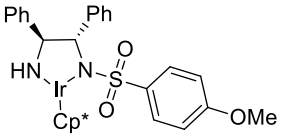
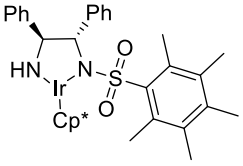
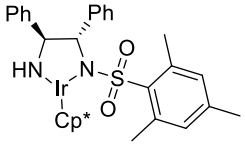
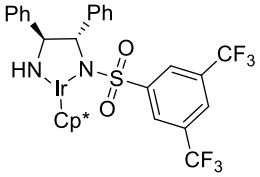
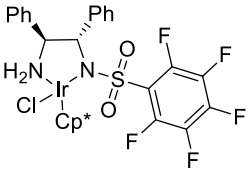


Entry	[Ag]	Conv. (%)	Yield (%)
1	$AgSbF_6$	100	trace
2	$AgPF_6$	100	60
3	AgOMs	N.R.	-
4	**$AgBF_4$**	**100**	**62**
5	AgOAc	N.R.	-
6	AgOTf	100	7
7	AgOTs	N.R.	-
8	$AgClO_4$	100	27
9	Silver(II) picolinate	N.R.	-

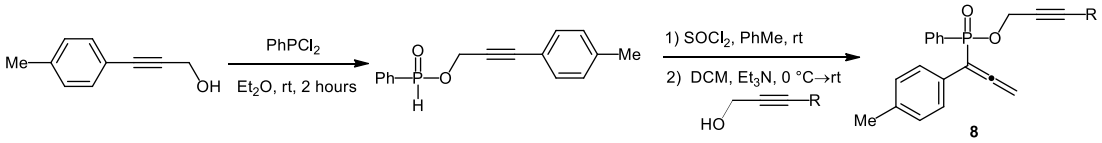
4. Attempted enantioselective desymmetrization of 1a

Table S2.



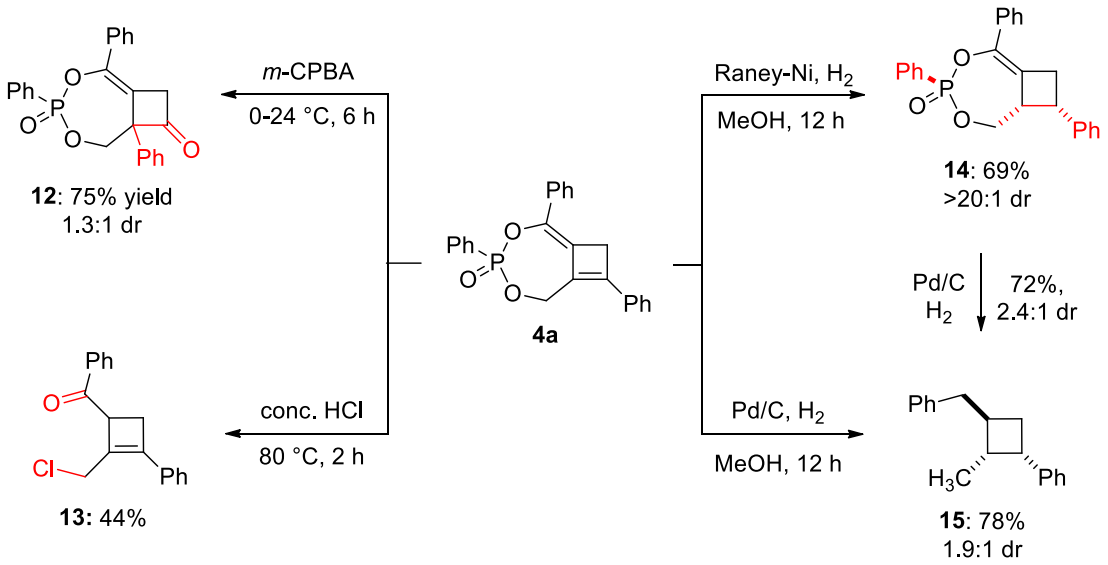
				
58% conv. 27% **11**, 3% ee 10% **2a**	25% **11**, <2% ee <2% **2a**	10% **11,** 44% ee <2% **2a**	68% conv. 13% **11**, 4% ee <2% **2a**	57% conv. 28% **11,** <2% ee <2% **2a**
				
60% conv. 30% **11,** <2% ee trace of **2a**	40% conv. 24%11, <2% ee <2% **2a**	55% conv. 19% **11,** 4% ee 3% **2a**	58% conv. 37% **11,** 33% ee 12% **2a**	

5. Procedure for the preparation of phosphinate 8.



A solution of dichlorophenylphosphine (10.0 mmol), 1-(4-Methylphenyl)-1-propyne-3-ol (15.0 mmol) in diethyl ether (25 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography to afford phosphinate. Phosphinate (5.0 mmol) and thionylchloride (7.5 mmol) was dissolved in toluene under Ar atmosphere at room temperature overnight. After removing thionylchloride and toluene by vacuum, the residue was dissolved in dry DCM. Then propargylic alcohol (5.0 mmol) was slowly added followed by trimethylamine at 0 °C. The reaction mixture was then warmed up to room temperature and was stirred at room temperature overnight. The solution was quenched with H_2O, extracted with CH_2Cl_2 and concentrated in vacuum, and the residue was purified by flash column chromatography to afford products **8**.

6. Further derivatization of 4a



a) Procedure for the synthesis of 12

To a solution of **4a** (0.1 mmol) in dry DCM (5 mL) was added *m*-CPBA (0.11 mmol) at 0 °C. The mixture was warmed up to room temperature and allowed to stir for 6 h. The reaction was quenched with sat. Na_2SO_3 and extracted with DCM (3×10 ml). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated by rotor vapor. The residue was purified by flash column chromatography on silica gel with hexanes/ethyl acetate (5:1 v/v) as the eluent.

b) Procedure for the synthesis of 13

To the conc. HCl was added **4a** (0.1 mmol). The mixture was allowed to stir at 80 °C for 2 h, and then diluted with H_2O. After extraction with DCM for three times, the combined organic phase was washed with sat. $NaHCO_3$ and brine. Concentration of the dried organic phase gave the crude product, which was subsequent purified by flash column chromatography on silica gel with hexanes/ethyl acetate (20:1 v/v) as the eluent.

c) Procedure for the synthesis of 14

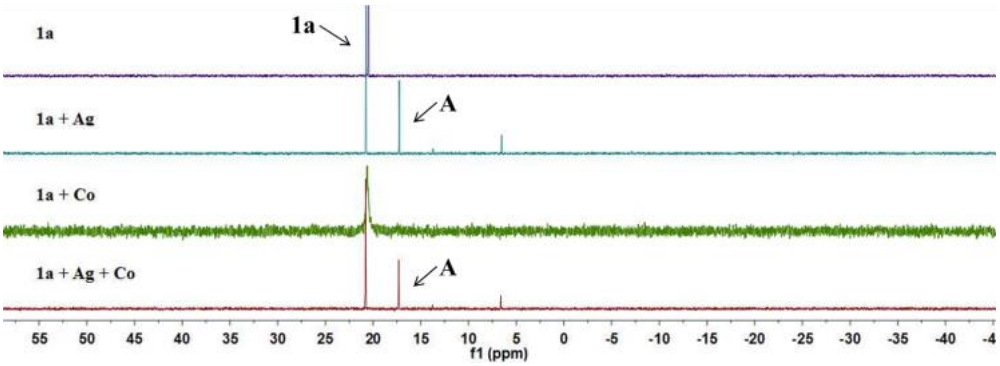
To a solution of **4a** (0.1 mmol) in MeOH (10 mL) was added Raney Ni (0.1 equiv.). After stirring under H_2 (balloon) at room temperature for 12 h, the reaction mixture was filtered through Celite® pad and concentrated by vacuo. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes and ethyl acetate (5:1 v/v) to give desired product.

d) Procedure for the synthesis of 15

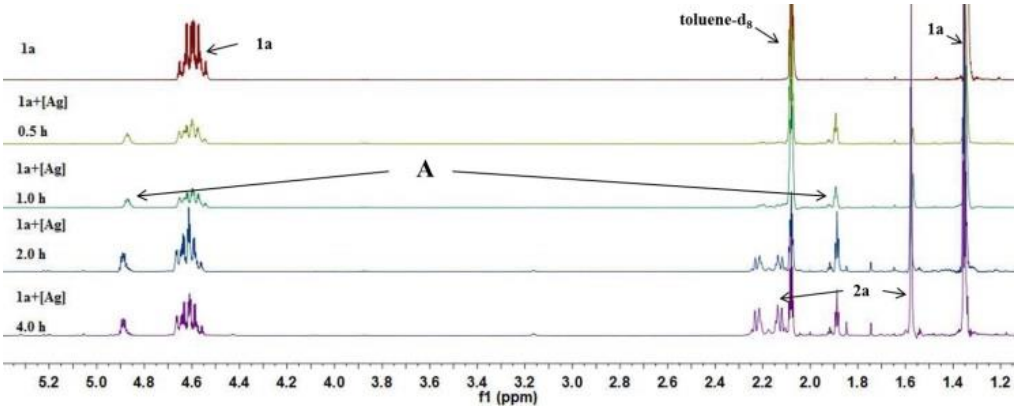
To a solution of **4a** (0.1 mmol) in MeOH (10 mL) was added 10% Pd/C (0.1 equiv.). After stirring under H_2 (balloon) at room temperature for 12 h, the reaction mixture was filtered through Celite® pad and concentrated by vacuo. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes and ethyl acetate (20:1 v/v) to give desired product.

7. Mechanism studies

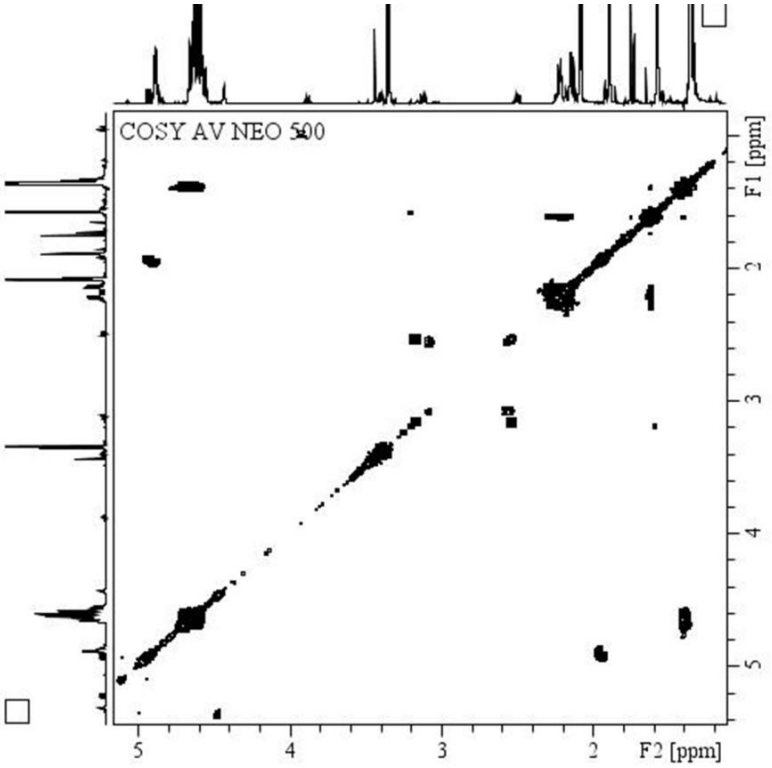
a) To the NMR tube was added **1a**, 10 mol% catalyst and toluene-d_8 in the glovebox. The mixture was taken outside and heated at 100 ℃ for 1 h before cooling to room temperature for ^{31}P NMR.



b) To a solution of **1a** in toluene-d_8 was added $AgBF_4$ (10 mol%) in a vial in the glovebox. After the designated time, an aliquot of 0.55 mL was taken via syringe and diluted for crude ^{1}H NMR.



c) 2D NMR for the crude mixture are as shown: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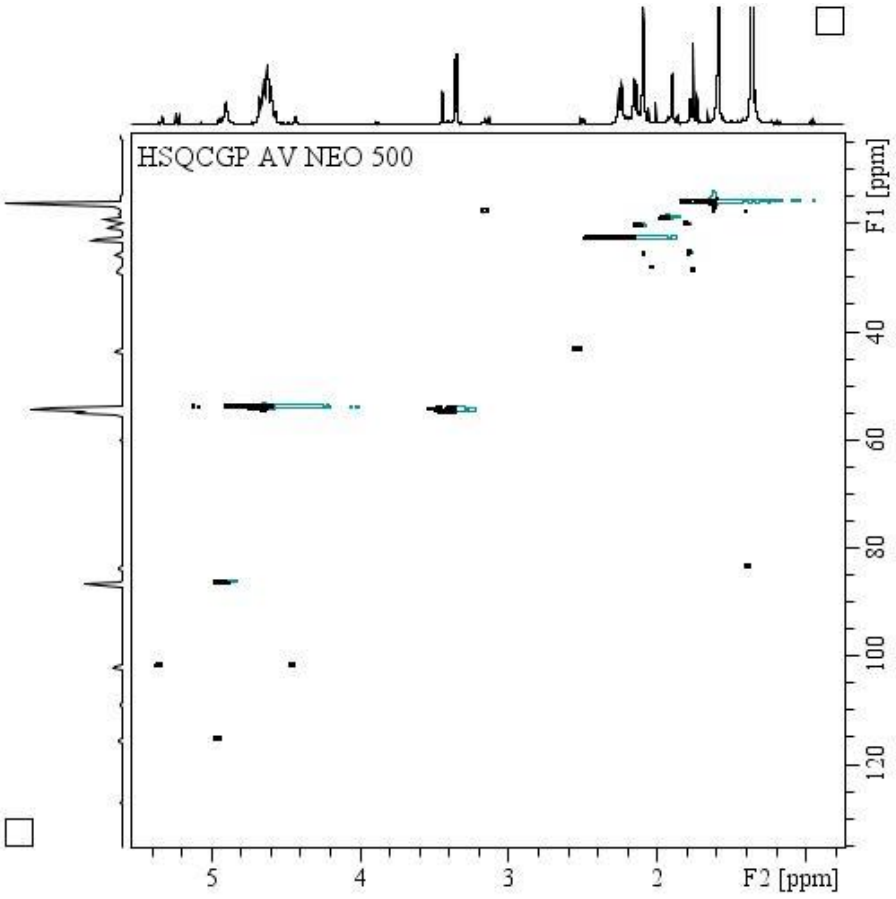
F1 [ppm]
F2 [ppm]
5
4
3
2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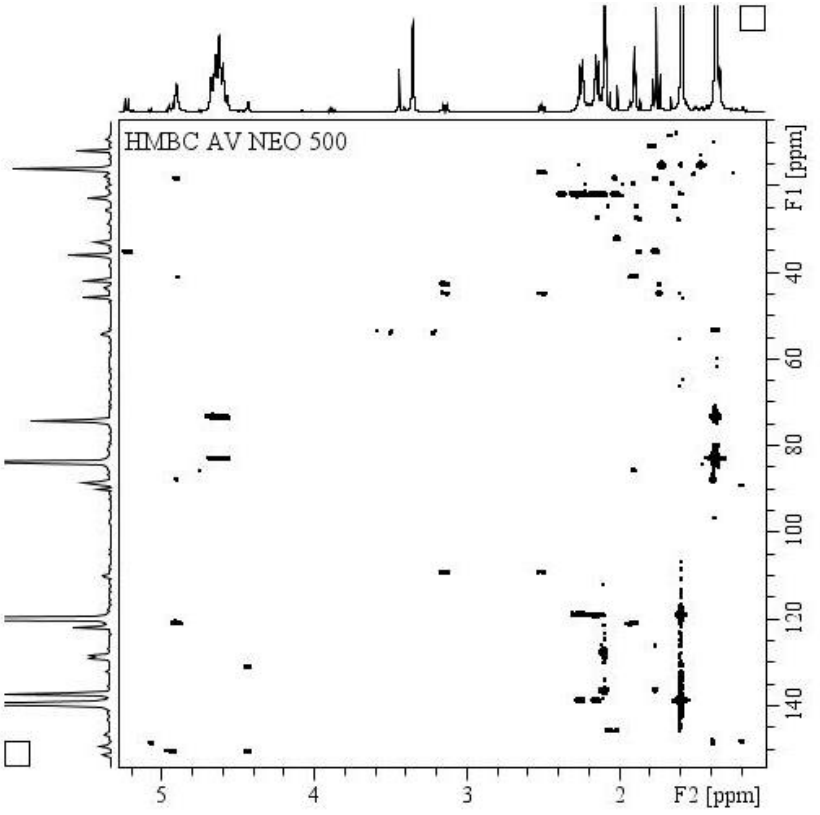
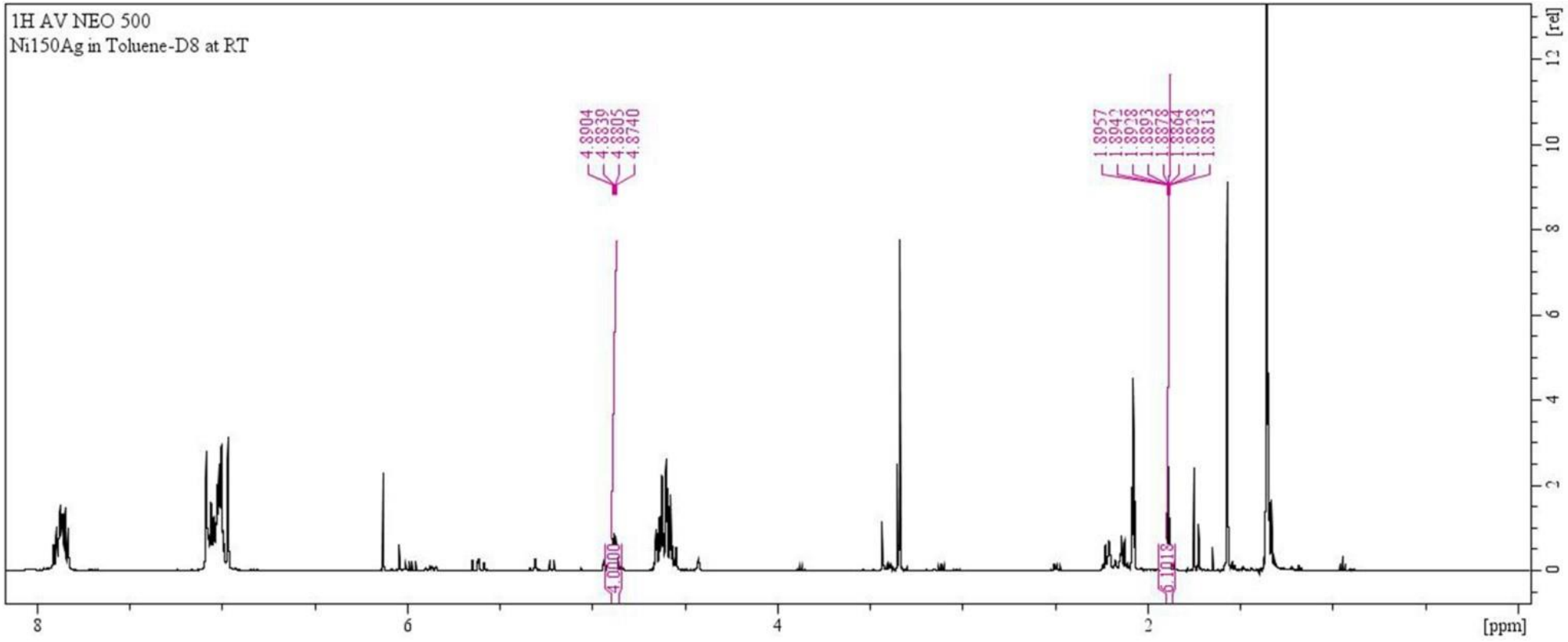
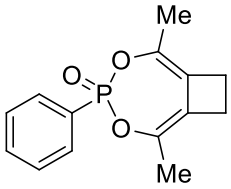
F1 [ppm]
F2 [ppm]
40
60
80
100
120
5
4
3
2


HMBC AV NEO 500
F1 [ppm]
40
60
80
100
120
140
5
4
3
2
F2 [ppm]


1H AV NEO 500
Ni150Ag in Toluene-D8 at RT
4.8904
4.8839
4.8805
4.8740
1.8957
1.8943
1.8928
1.8893
1.8878
1.8864
1.8828
1.8813
4.0000
6.1018
8
6
4
2
[ppm]
0
2
4
6
8
10
12 [rel]

8. Analytical data of the products

2,6-Dimethyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2a)



Colorless oil, 99% yield.

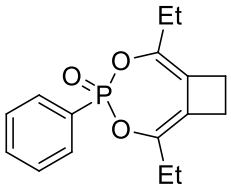
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.61 (dt, *J* = 7.2, 1.8 Hz, 1H), 7.55 – 7.44 (m, 2H), 2.73 – 2.48 (m, 4H), 1.85 (d, *J* = 4.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.42 (d, J_{CP} = 9.5 Hz), 133.00, 131.45 (d, J_{CP} = 10.4 Hz), 128.50 (d, J_{CP}= 16.1 Hz), 126.42 (d, J_{CP} = 198.4 Hz), 119.67 (d, J_{CP} = 2.9 Hz), 22.99, 16.54 (d, J_{CP} = 6.6 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ = 7.76.

HRMS (ESI) m/z Calcd for $C_{14}H_{15}O_3P$, $[M+Na]^+$: 285.0651; Found: 285.0659.

2,6-Diethyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2b)



Colorless oil, 97% yield.

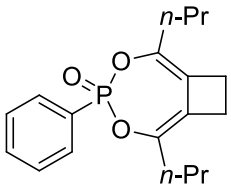
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 2H), 7.62 – 7.55 (m, 1H), 7.52 – 7.45 (m, 2H), 2.70 – 2.52 (m, 4H), 2.14 (q, *J* = 7.5 Hz, 4H), 1.07 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.08 (d, J_{CP} = 10.1 Hz), 132.89 (d, J_{CP} = 3.4 Hz), 131.48 (d, J_{CP} = 10.2 Hz), 128.45 (d, J_{CP} = 16.1 Hz), 126.67 (d, J_{CP} = 198.9 Hz), 118.89 (d, J_{CP} = 2.9 Hz), 24.09 (d, J_{CP} = 6.1 Hz), 23.20, 10.92.

^{31}P NMR (202 MHz, $CDCl_3$) δ 7.77.

HRMS (ESI) m/z Calcd for $C_{16}H_{19}O_3P$, $[M+Na]^+$: 313.0964; Found: 313.0960.

4-Phenyl-2,6-dipropyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2c)



Colorless oil, 88% yield.

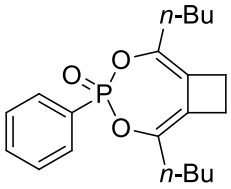
^{1}H NMR (500 MHz, $CDCl_3$) δ7.92 – 7.82 (m, 2H), 7.63 – 7.54 (m, 1H), 7.53 – 7.43 (m, 2H), 2.70 – 2.51 (m, 4H), 2.09 (t, *J* = 7.3 Hz, 4H), 1.60 – 1.45 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.90 (d, J_{CP} = 9.9 Hz), 132.84 (d, J_{CP} = 3.2 Hz), 131.47 (d, J_{CP} = 10.3 Hz), 128.42 (d, J_{CP} = 15.9 Hz), 126.76 (d, J_{CP} = 198.8 Hz), 119.61 (d, J_{CP} = 2.9 Hz), 32.60 (d, J_{CP} = 5.9 Hz), 23.19, 19.63, 13.55.

^{31}P NMR (202 MHz, $CDCl_3$) δ 7.66.

HRMS (ESI) m/z Calcd for $C_{18}H_{23}O_3P$, $[M+Na]^+$: 341.1277; Found: 341.1280.

2,6-Dibutyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2d)



Colorless oil, 92% yield.

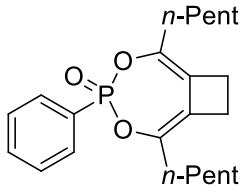
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.65 – 7.56 (m, 1H), 7.56 – 7.43 (m, 2H), 2.76 – 2.48 (m, 4H), 2.13 (t, *J* = 7.4 Hz, 4H), 1.60 – 1.44 (m, 4H), 1.42 – 1.30 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.06 (d, J_{CP} = 9.9 Hz), 132.85 (d, J_{CP} = 3.3 Hz), 131.46 (d, J_{CP} = 10.4 Hz), 128.44 (d, J_{CP} = 15.9 Hz), 126.78 (d, J_{CP} = 199.1 Hz), 119.41 (d, J_{CP} = 2.8 Hz), 30.34 (d, J_{CP} = 6.2 Hz), 28.34, 23.20, 22.13, 13.82.

^{31}P NMR (202 MHz, $CDCl_3$) δ 7.66.

HRMS (ESI) m/z Calcd for $C_{20}H_{27}O_3P$, $[M+Na]^+$: 369.1590; Found: 369.1588.

2,6-Dipentyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2e)



Colorless oil, 78% yield.

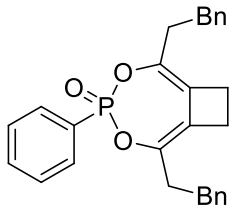
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 14.2, 7.6 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.48 (td, *J* = 7.6, 4.5 Hz, 2H), 2.69 – 2.49 (m, 4H), 2.10 (t, *J* = 7.4 Hz, 4H), 1.56 – 1.41 (m, 4H), 1.33 – 1.25 (m, 8H), 0.86 (dd, *J* = 8.8, 4.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.04 (d, J_{CP} = 10.1 Hz), 132.82, 131.42 (d, J_{CP} = 10.2 Hz), 128.40 (d, J_{CP} = 16.0 Hz), 119.35 (d, J_{CP} = 2.8 Hz), 31.18, 30.57 (d, J_{CP} = 6.2 Hz), 25.89, 23.17, 22.35, 13.94.

^{31}P NMR (202 MHz, $CDCl_3$) δ 7.55.

HRMS (ESI) m/z Calcd for $C_{22}H_{31}O_3P$, $[M+Na]^+$: 397.1903; Found: 397.1901.

2,6-Diphenethyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2f)



Colorless oil, 82% yield.

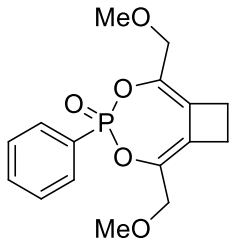
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H), 7.69 (td, *J* = 7.5, 1.3 Hz, 1H), 7.58 (td, *J* = 7.7, 4.7 Hz, 2H), 7.32 (dd, *J* = 10.3, 4.5 Hz, 4H), 7.28 – 7.21 (m, 6H), 2.90 – 2.79 (m, 4H), 2.51 – 2.40 (m, 4H), 2.40 – 2.30 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.10 (d, J_{CP} = 10.0 Hz), 141.16, 132.99 (d, J_{CP} = 3.1 Hz), 131.40 (d, J_{CP} = 10.3 Hz), 128.62, 128.48, 128.25, 125.96, 120.16 (d, J_{CP} = 2.8 Hz), 32.74 (d, J_{CP} = 6.1 Hz), 32.52, 22.88.

^{31}P NMR (202 MHz, $CDCl_3$) δ 7.53.

HRMS (ESI) m/z Calcd for $C_{28}H_{27}O_3P$, $[M+Na]^+$: 465.1590; Found: 465.1586.

2,6-Bis(methoxymethyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2g)



Yellowish oil, 71% yield.

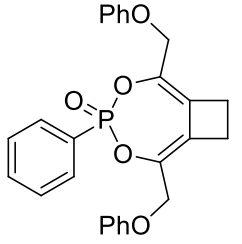
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.59 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.48 (td, *J* = 7.6, 4.7 Hz, 2H), 3.98 – 3.89 (m, 4H), 3.36 (d, *J* = 0.7 Hz, 6H), 2.83 – 2.69 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.70 (d, J_{CP} = 10.1 Hz), 133.31, 131.80 (d, J_{CP} = 10.7 Hz), 128.54 (d, J_{CP} = 16.2 Hz), 125.39 (d, J_{CP} = 198.5 Hz), 123.81 (d, J_{CP} = 3.0 Hz), 68.76 (d, J_{CP} = 6.5 Hz), 58.19, 23.69.

^{31}P NMR (202 MHz, $CDCl_3$) δ 8.30.

HRMS (ESI) m/z Calcd for $C_{16}H_{19}O_5P$, $[M+Na]^+$: 345.0862; Found: 345.0856.

2,6-Bis(phenoxymethyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2h)



Yellowish oil, 56% yield.

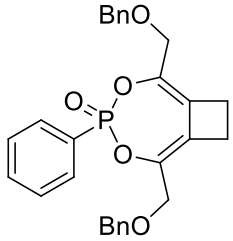
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1H), 7.49 (td, *J* = 7.8, 4.9 Hz, 2H), 7.31 – 7.26 (m, 4H), 6.98 (t, *J* = 7.4 Hz, 2H), 6.93 – 6.89 (m, 4H), 4.55 (s, 4H), 2.82 – 2.67 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.25, 138.48 (d, J_{CP} = 9.9 Hz), 133.44 (d, J_{CP} = 3.1 Hz), 131.76 (d, J_{CP} = 10.6 Hz), 129.55, 128.62 (d, J_{CP} = 16.4 Hz), 125.20 (d, J_{CP} = 197.5 Hz), 123.89 (d, J_{CP} = 3.2 Hz), 121.48, 114.82, 65.27 (d, J_{CP} = 7.5 Hz), 24.04.

^{31}P NMR (202 MHz, $CDCl_3$) δ 8.09.

HRMS (ESI) m/z Calcd for $C_{26}H_{23}O_5P$, $[M+Na]^+$: 469.1175; Found: 469.1171.

2,6-Bis((benzyloxy)methyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2i)



Yellowish oil, 99% yield.

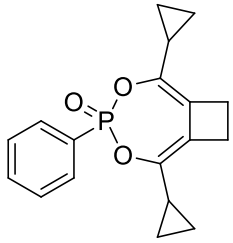
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.83 (m, 2H), 7.60 (td, *J* = 7.4, 1.3 Hz, 1H), 7.47 (td, *J* = 7.7, 4.8 Hz, 2H), 7.39 – 7.27 (m, 10H), 4.57 (dd, *J* = 34.4, 11.8 Hz, 4H), 4.05 (d, *J* = 1.6 Hz, 4H), 2.80 – 2.58 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.78 (d, J_{CP} = 10.1 Hz), 137.76, 133.29 (d, J_{CP} = 3.3 Hz), 131.78 (d, J_{CP} = 10.7 Hz), 128.55 (d, J_{CP} = 16.2 Hz), 128.39, 127.83, 127.75, 125.49 (d, J_{CP} = 198.6 Hz), 123.83 (d, J_{CP} = 3.1 Hz), 72.12, 66.29 (d, J_{CP} = 6.6 Hz), 23.74.

^{31}P NMR (202 MHz, $CDCl_3$) δ 8.25.

HRMS (ESI) m/z Calcd for $C_{28}H_{27}O_5P$, $[M+Na]^+$: 497.1488; Found: 497.1489.

2,6-Dicyclopropyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2j)



Colorless oil, 30% yield.

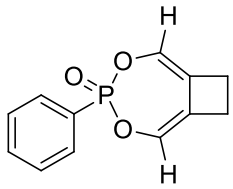
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (ddd, *J* = 14.2, 8.2, 1.4 Hz, 2H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.47 (td, *J* = 7.6, 4.6 Hz, 2H), 2.78 – 2.64 (m, 4H), 1.50 – 1.41 (m, 2H), 0.83 – 0.61 (m, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.84 (d, J_{CP} = 9.2 Hz), 132.91 (d, J_{CP} = 3.4 Hz), 131.29 (d, J_{CP} = 10.4 Hz), 128.49 (d, J_{CP} = 16.0 Hz), 126.44 (d, J_{CP} = 198.5 Hz), 118.72 (d, J_{CP} = 2.9 Hz), 23.33, 11.18 (d, J_{CP} = 7.1 Hz), 4.89, 4.24.

^{31}P NMR (202 MHz, $CDCl_3$) δ 8.04.

HRMS (ESI) m/z Calcd for $C_{18}H_{19}O_3P$, $[M+Na]^+$: 337.0964; Found: 337.0971.

4-Phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2k)



White solid, 63% yield.

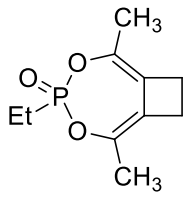
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.61 (td, *J* = 7.7, 1.3 Hz, 1H), 7.49 (td, *J* = 7.8, 4.8 Hz, 2H), 6.14 (d, *J* = 20.0 Hz, 2H), 2.82 – 2.63 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.27 (d, J_{CP} = 3.2 Hz), 131.71 (d, J_{CP} = 10.5 Hz), 131.45 (d, J_{CP} = 10.6 Hz), 128.59 (d, J_{CP} = 16.4 Hz), 125.77 (d, J_{CP} = 3.6 Hz), 125.71 (d, J_{CP} = 198.3 Hz), 22.98.

^{31}P NMR (202 MHz, $CDCl_3$) δ 8.97.

HRMS (ESI) m/z Calcd for $C_{12}H_{11}O_3P$, $[M+Na]^+$: 257.0338; Found: 257.0334.

4-Ethyl-2,6-dimethyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2l)



Colorless oil, 81% yield.

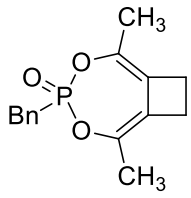
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 – 2.50 (m, 4H), 1.92 (dq, *J* = 18.6, 7.7 Hz, 2H), 1.81 (s, 6H), 1.31 – 1.21 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.71 (d, J_{CP} = 9.9 Hz), 119.19 (d, J_{CP} = 3.0 Hz), 22.96 (s), 17.52 (d, J_{CP} = 141.5 Hz), 16.44 (d, J_{CP} = 6.4 Hz), 6.18 (d, J_{CP} = 7.2 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ 22.88.

HRMS (ESI) m/z Calcd for $C_{10}H_{15}O_3P$, $[M+Na]^+$: 237.0651; Found: 237.0649.

4-Benzyl-2,6-dimethyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2m)



White solid, 83% yield.

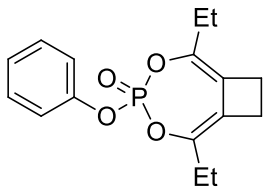
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 5H), 3.33 (d, *J* = 21.7 Hz, 2H), 2.57 (ddd, *J* = 17.0, 12.4, 9.2 Hz, 4H), 1.70 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.64 (d, J_{CP} = 9.9 Hz), 130.25 (d, J_{CP} = 9.2 Hz), 129.89 (d, J_{CP} = 7.1 Hz), 128.59 (d, J_{CP} = 3.0 Hz), 127.21 (d, J_{CP} = 3.7 Hz), 119.03, 31.72 (d, J_{CP} = 134.5 Hz), 23.08, 16.27 (d, J_{CP} = 7.1 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ 15.01.

HRMS (ESI) m/z Calcd for $C_{15}H_{17}O_3P$, $[M+Na]^+$: 299.0821; Found: 299.0824.

2,6-Diethyl-4-phenoxy-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2n)



Yellowish oil, 75% yield.

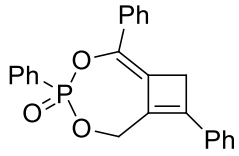
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 2.63 (s, 4H), 2.15 – 1.93 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.08 (d, J_{CP} = 7.1 Hz), 142.58 (d, J_{CP} = 9.8 Hz), 129.66 (s), 125.42, 120.08 (d, J_{CP} = 5.1 Hz), 118.15, 23.65 (d, J_{CP} = 8.6 Hz), 23.47 (s), 10.72.

^{31}P NMR (202 MHz, $CDCl_3$) δ -21.16.

HRMS (ESI) m/z Calcd for $C_{16}H_{19}O_4P$, $[M+Na]^+$: 329.0909; Found: 329.0913.

2,4,8-Triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4a)



White solid, 73% yield.

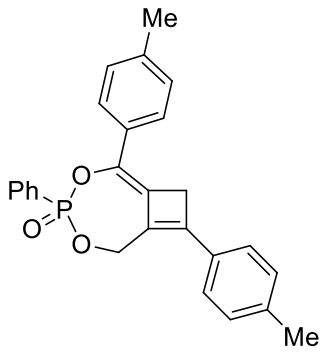
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.65 – 7.49 (m, 5H), 7.40 (dd, *J* = 10.4, 4.7 Hz, 2H), 7.34 – 7.22 (m, 6H), 5.45 (ddd, *J* = 15.3, 7.8, 4.3 Hz, 1H), 5.19 – 5.05 (m, 1H), 3.72 – 3.46 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.75, 137.54, 133.93 (d, J_{CP} = 7.9 Hz), 133.67 (d, J_{CP} = 10.2 Hz), 133.33, 133.11 (d, J_{CP} = 3.1 Hz), 131.59 (d, J_{CP} = 10.2 Hz), 128.87, 128.60, 128.49 (d, J_{CP} = 5.2 Hz), 128.34, 127.98, 126.68 (d, J_{CP} = 200.6 Hz), 126.48, 125.50, 121.70 (d, J_{CP} = 3.2 Hz), 63.13 (d, J_{CP} = 7.4 Hz), 34.60.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.61.

HRMS (ESI) m/z Calcd for $C_{24}H_{19}O_3P$, $[M+Na]^+$: 409.0964; Found: 409.0965.

4-Phenyl-2,8-di-p-tolyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4b)



Yellowish solid, 39% yield.

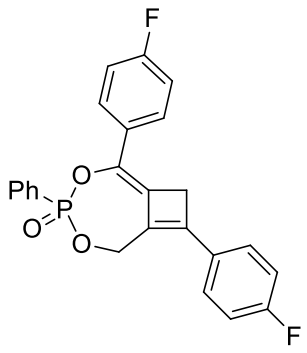
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 2H), 7.65 – 7.59 (m, 1H), 7.52 (td, *J* = 7.6, 4.7 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.13 (dd, *J* = 8.0, 3.5 Hz, 4H), 5.47 – 5.38 (m, 1H), 5.10 (dd, *J* = 25.0, 15.4 Hz, 1H), 3.63 – 3.48 (m, 2H), 2.36 (d, *J* = 18.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.42, 138.67, 137.85, 136.47, 133.52 (d, J_{CP} = 10.2 Hz), 133.04 (d, J_{CP} = 3.1 Hz), 131.62 (d, J_{CP} = 10.1 Hz), 131.24 (d, J_{CP} = 8.0 Hz), 130.78, 129.61, 129.07, 128.53 (d, J_{CP} = 15.8 Hz), 126.88 (d, J_{CP} = 200.4 Hz), 126.43, 125.40, 121.14 (d, J_{CP} = 3.2 Hz), 63.19 (d, J_{CP} = 7.4 Hz), 34.58, 21.48, 21.25.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.52.

HRMS (ESI) m/z Calcd for $C_{26}H_{23}O_3P$, $[M+Na]^+$: 437.1277; Found: 437.1288.

2,8-Bis(4-fluorophenyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4c)



Yellowish oil, 68% yield.

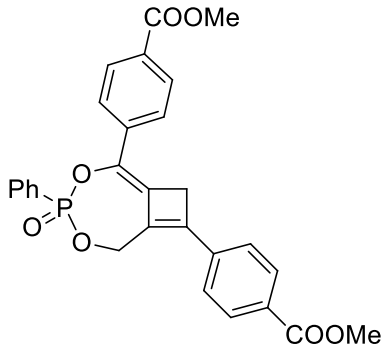
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 2H), 7.68 – 7.60 (m, 1H), 7.56 – 7.49 (m, 4H), 7.24 – 7.16 (m, 2H), 7.10 (dd, *J* = 12.0, 5.3 Hz, 2H), 7.05 – 6.97 (m, 2H), 5.42 (ddd, *J* = 15.3, 7.8, 4.0 Hz, 1H), 5.08 (dd, *J* = 25.2, 15.4 Hz, 1H), 3.57 (dt, *J* = 13.1, 3.1 Hz, 1H), 3.50 (ddd, *J* = 13.1, 4.1, 2.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.62 (d, J_{CF} = 250.7 Hz), 162.43 (d, J_{CF} = 248.8 Hz), 139.48, 136.89, 133.22 (d, J_{CP} = 3.1 Hz), 131.56 (d, J_{CP} = 10.2 Hz), 130.07 (d, J_{CF} = 8.1 Hz), 130.04 (d, J_{CF} = 8.0 Hz), 129.69 (d, J_{CP} = 3.4 Hz), 128.58 (d, J_{CP} = 15.9 Hz), 128.21 (d, J_{CF} = 8.2 Hz), 127.30 (d, J_{CF} = 8.0 Hz), 126.47 (d, J_{CP} = 199.2 Hz), 120.95, 116.14 (d, J_{CF} = 22.1 Hz), 115.42 (d, J_{CF} = 21.8 Hz), 63.02 (d, J_{CP} = 7.4 Hz), 34.54.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.73.

HRMS (ESI) m/z Calcd for $C_{24}H_{17}F_2O_3P$, $[M+Na]^+$: 445.0776; Found: 445.0778.

Dimethyl 4,4'-(4-oxido-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene-2,8-diyl) dibenzoate (4d)



White solid, 56% yield.

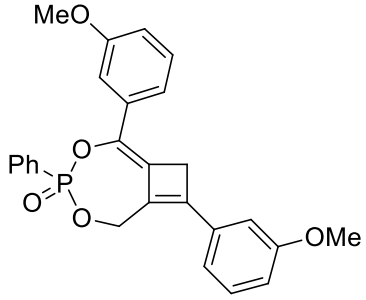
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 2H), 8.03 (ddd, *J* = 9.8, 8.5, 5.3 Hz, 4H), 7.74 – 7.64 (m, 3H), 7.58 (td, *J* = 7.7, 4.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.50 (ddd, *J* = 15.6, 7.3, 3.9 Hz, 1H), 5.18 (dd, *J* = 25.4, 15.7 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.71 (dt, *J* = 13.1, 3.0 Hz, 1H), 3.65 (ddd, *J* = 13.2, 4.1, 2.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.58, 166.40, 140.49, 140.34, 138.01 (d, J_{CP} = 7.9 Hz), 136.97, 133.93 (d, J_{CP} = 10.1 Hz), 133.42 (d, J_{CP} = 3.1 Hz), 131.61 (d, J_{CP} = 10.3 Hz), 130.20, 129.82, 129.70, 129.52, 128.68 (d, J_{CP} = 16.0 Hz), 126.40, 126.16 (d, J_{CP} = 200.8 Hz), 125.33, 63.06 (d, J_{CP} = 7.4 Hz), 123.55 (d, J_{CP} = 3.2 Hz), 52.28, 52.17, 34.85.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.93.

HRMS (ESI) m/z Calcd for $C_{28}H_{23}O_7P$, $[M+Na]^+$: 503.1254; Found: 503.1267.

2,8-Bis(3-methoxyphenyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4e)



Yellow oil, 92% yield.

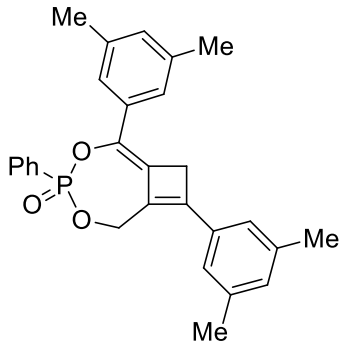
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 14.0, 8.2 Hz, 2H), 7.62 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.52 (dd, *J* = 12.2, 7.5 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 (s, 1H), 6.86 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.74 (s, 1H), 5.48 – 5.39 (m, 1H), 5.11 (dd, *J* = 25.1, 15.4 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 0.8 Hz, 3H), 3.64 – 3.51 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.86, 159.48, 140.70, 137.80, 135.24 (d, J_{CP} = 8.1 Hz), 134.55, 133.58 (d, J_{CP} = 10.3 Hz), 133.09 (d, J_{CP} = 3.1 Hz), 131.54 (d, J_{CP} = 10.1 Hz), 129.88, 129.33, 128.52 (d, J_{CP} = 16.0 Hz), 126.60 (d, J_{CP} = 200.4 Hz), 121.88 (d, J_{CP} = 3.2 Hz), 119.15, 118.15, 114.05, 113.29, 111.89, 111.42, 63.03 (d, J_{CP} = 7.3 Hz), 55.25, 55.21, 34.70.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.57.

HRMS (ESI) m/z Calcd for $C_{26}H_{23}O_5P$, $[M+Na]^+$: 469.1175; Found: 469.1184.

2,8-Bis(3,5-dimethylphenyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4f)



Yellowish oil, 60% yield.

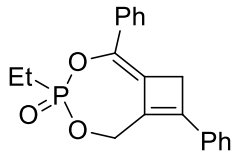
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.96 (m, 2H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1H), 7.52 (td, *J* = 7.7, 4.6 Hz, 2H), 7.19 (s, 2H), 6.93 (d, *J* = 24.9 Hz, 2H), 6.87 (s, 2H), 5.43 (dt, *J* = 15.1, 6.2 Hz, 1H), 5.10 (dd, *J* = 24.6, 15.3 Hz, 1H), 3.60 (dt, *J* = 13.3, 3.0 Hz, 1H), 3.51 (ddd, *J* = 13.2, 4.0, 2.0 Hz, 1H), 2.34 (s, 6H), 2.30 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.93, 138.38, 137.79, 137.11, 133.91 (d, J_{CP} = 7.9 Hz), 133.80 (d, J_{CP} = 10.3 Hz), 133.39, 132.99, 131.65 (d, J_{CP} = 10.1 Hz), 130.39, 129.77, 128.52 (d, J_{CP} = 15.8 Hz), 126.94 (d, J_{CP} = 199.8 Hz), 124.37, 123.44, 121.67, 63.17 (d, J_{CP} = 7.4 Hz), 34.79, 21.45, 21.33.

^{31}P NMR (202 MHz, $CDCl_3$) δ 20.44.

HRMS (ESI) m/z Calcd for $C_{28}H_{27}O_3P$, $[M+Na]^+$: 465.1590; Found: 465.1602.

4-Ethyl-2,8-diphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4g)



Yellowish oil, 80% yield.

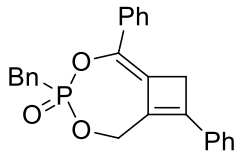
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 2H), 7.42 – 7.33 (m, 4H), 7.29 (q, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 5.34 (ddd, *J* = 15.3, 7.5, 3.9 Hz, 1H), 5.09 – 4.97 (m, 1H), 3.63 – 3.42 (m, 2H), 2.07 (dd, *J* = 18.9, 7.7 Hz, 2H), 1.35 (dt, *J* = 20.8, 7.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.42, 137.79, 134.14 (d, J_{CP} = 7.6 Hz), 133.42, 133.32, 128.86, 128.42, 128.37, 127.98, 126.44, 125.50, 121.47 (d, J_{CP} = 3.6 Hz), 62.84 (d, J_{CP} = 7.9 Hz), 34.49, 18.78 (d, J_{CP} = 145.1 Hz), 6.55 (d, J_{CP} = 7.0 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ 36.27.

HRMS (ESI) m/z Calcd for $C_{20}H_{19}O_3P$, $[M+Na]^+$: 361.0964; Found: 361.0965.

4-Benzyl-2,8-diphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4h)



White solid, 83% yield.

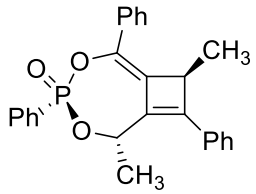
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.3, 3.4 Hz, 2H), 7.45 – 7.27 (m, 11H), 7.24 – 7.19 (m, 2H), 5.32 (ddd, *J* = 15.3, 7.9, 4.3 Hz, 1H), 5.02 (ddt, *J* = 24.6, 15.4, 2.6 Hz, 1H), 3.60 – 3.43 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.54, 137.57, 133.96 (d, J_{CP} = 7.4 Hz), 133.34, 130.54 (d, J_{CP} = 9.8 Hz), 129.98 (d, J_{CP} = 6.8 Hz), 128.86, 128.70 (d, J_{CP} = 3.1 Hz), 128.48, 128.32, 127.94, 127.25 (d, J_{CP} = 3.8 Hz), 126.45, 125.42, 121.66, 63.15 (d, J_{CP} = 8.0 Hz), 34.47, 33.25 (d, J_{CP} = 141.2 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ 28.60.

HRMS (ESI) m/z Calcd for $C_{25}H_{21}O_3P$, $[M+Na]^+$: 423.1121; Found: 423.1119.

2,8-Dimethyl-4,6,9-triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1(9),6-diene 4-oxide (4i)



Colorless oil, 50% yield

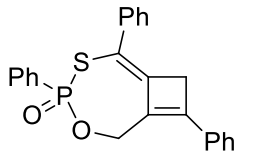
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.02 – 7.94 (m, 2H), 7.68 – 7.61 (m, 1H), 7.54 (ddd, *J* = 9.7, 6.0, 3.0 Hz, 4H), 7.46 – 7.30 (m, 8H), 5.84 – 5.77 (m, 1H), 4.09 (qd, *J* = 6.7, 2.2 Hz, 1H), 1.62 (dd, *J* = 6.6, 1.0 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 146.46, 141.22, 133.98 (d, J_{CP} = 7.9 Hz), 133.34 (d, J_{CP} = 9.6 Hz), 132.91, 132.89, 132.06, 131.46 (d, J_{CP} = 10.0 Hz), 128.74, 128.52,128.45, 128.40, 128.21, 128.13, 127.61, 127.60 (d, J_{CP} = 215.2 Hz), 126.87, 71.94 (d, J_{CP} = 7.6 Hz), 41.23, 19.35 (d, J_{CP} = 10.5 Hz), 14.74.

^{31}P NMR (202 MHz, CD_2Cl_2) δ 17.76.

HRMS (ESI) m/z Calcd for $C_{26}H_{23}O_3P$, $[M+Na]^+$: 437.1277; Found: 437.1284.

4,6,9-Triphenyl-3-oxa-5-thia-4-phosphabicyclo[5.2.0]nona-1(9),6-diene 4-oxide (6)



Yellowish oil, 38% yield.

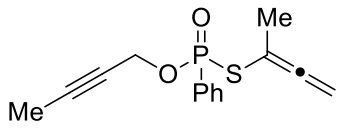
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.85 (ddd, *J* = 13.8, 8.0, 1.0 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.50 – 7.39 (m, 7H), 7.28 – 7.19 (m, 5H), 5.68 – 5.60 (m, 1H), 5.27 (dd, *J* = 23.2, 13.4 Hz, 1H), 3.52 (dd, *J* = 14.3, 2.6 Hz, 1H), 3.41 (d, *J* = 14.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 148.58, 142.18, 137.45, 136.62, 132.96, 132.88 (d, J_{CP} = 3.2 Hz), 132.82, 131.75, 131.20 (d, J_{CP} = 10.9 Hz), 129.70, 128.93, 128.49 (d, J_{CP} = 15.1 Hz), 128.27, 127.65, 127.52, 127.32, 61.54 (d, J_{CP} = 8.2 Hz), 37.52.

^{31}P NMR (202 MHz, CD_2Cl_2) δ 45.15.

HRMS (ESI) m/z Calcd for $C_{24}H_{19}O_2PS$, $[M+Na]^+$: 425.0736; Found: 425.0731.

O-but-2-yn-1-yl S-buta-2,3-dien-2-yl phenylphosphonothioate (7)



Colorless oil, 65% yield.

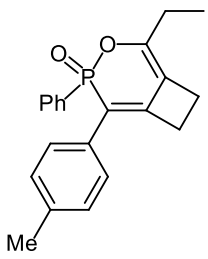
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 2H), 7.58 (dd, *J* = 8.0, 6.8 Hz, 1H), 7.54 – 7.47 (m, 2H), 4.87 – 4.80 (m, 2H), 4.51 (dddd, *J* = 7.3, 6.6, 3.3, 0.8 Hz, 2H), 1.90 (ddd, *J* = 4.2, 2.6, 0.9 Hz, 3H), 1.88 (td, *J* = 2.3, 0.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.02 (d, J_{CP} = 7.7 Hz), 132.67 (d, J_{CP} = 3.2 Hz), 131.71 (d, J_{CP} = 10.9 Hz), 131.31 (d, J_{CP} = 149.5 Hz), 128.35 (d, J_{CP} = 15.0 Hz), 88.21 (d, J_{CP} = 7.0 Hz), 84.73, 74.84 (d, J_{CP} = 4.2 Hz), 73.31 (d, J_{CP} = 10.0 Hz), 54.21 (d, J_{CP} = 5.4 Hz), 22.35, 3.72.

^{31}P NMR (202 MHz, $CDCl_3$) δ 44.68.

HRMS (ESI) m/z Calcd for $C_{14}H_{15}O_2PS$, $[M+Na]^+$: 301.0423; Found: 301.0428.

2-Ethyl-4-phenyl-5-(p-tolyl)-3-oxa-4-phosphabicyclo[4.2.0]octa-1,5-diene 4-oxide (9)



White solid, 57% yield.

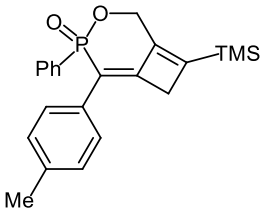
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 13.5, 8.3, 1.5 Hz, 2H), 7.46 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.5, 6.6, 3.7 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 3.51 – 3.24 (m, 1H), 3.17 – 2.91 (m, 3H), 2.36 (d, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 1.15 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.03 (d, J_{CP} = 4.4 Hz), 147.80 (d, J_{CP} = 14.0 Hz), 136.95, 132.56, 132.20 (d, J_{CP} = 2.9 Hz), 131.88 (d, J_{CP} = 11.4 Hz), 131.11, 130.65 (d, J_{CP} = 13.2 Hz), 129.31, 128.29 (d, J_{CP} = 13.9 Hz), 127.39 (d, J_{CP} = 8.5 Hz), 118.15 (d, J_{CP} = 22.3 Hz), 116.53, 115.33, 31.11 (d, J_{CP} = 13.7 Hz), 24. 63 (d, J_{CP} = 4.3 Hz), 21.15, 10.05.

^{31}P NMR (160 MHz, $CDCl_3$) δ 25.93 .

HRMS (ESI) m/z Calcd for $C_{21}H_{21}O_2P$, $[M+H]^+$: 337.1352; Found: 337.1347.

4-phenyl-5-(p-tolyl)-8-(trimethylsilyl)-3-oxa-4-phosphabicyclo[4.2.0]octa-1(8),5-diene 4-oxide (10)



White solid, 63% yield.

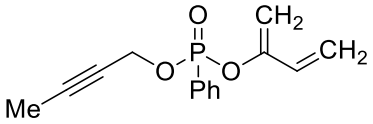
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 13.1, 7.6, 1.6 Hz, 2H), 7.45 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.37 (dd, *J* = 10.4, 5.8 Hz, 4H), 7.00 (d, *J* = 7.9 Hz, 2H), 5.27 – 5.14 (m, 1H), 4.81 (tdd, *J* = 15.8, 3.4, 1.9 Hz, 1H), 3.55 (dd, *J* = 14.1, 2.7 Hz, 1H), 3.36 – 3.14 (m, 1H), 2.23 (s, 3H), 0.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.45 (d, J_{CP} = 3.1 Hz), 152.00, 151.80, 149.35 (d, J_{CP} = 3.8 Hz), 137.31, 132.23 (d, J_{CP} = 3.0 Hz), 131.64 (d, J_{CP} = 10.8 Hz), 131.41, 130.46 (d, J_{CP}= 12.0 Hz), 130.00, 129.31, 128.43 (d, J_{CP}= 13.7 Hz), 127.53 (d, J_{CP}= 7.5 Hz), 116.73, 115.57, 63.46 (d, J_{CP}= 8.4 Hz), 39.43 (d, J_{CP} = 13.8 Hz), 21.16, -2.04.

^{31}P NMR (160 MHz, $CDCl_3$) δ 21.71.

HRMS (ESI) m/z Calcd for $C_{22}H_{25}O_2PSi$, $[M+H]^+$: 381.1434; Found: 381.1428.

But-2-yn-1-yl buta-2,3-dien-2-yl phenylphosphonate (11)



Colorless oil, 73% yield.

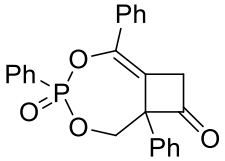
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.62 – 7.54 (m, 1H), 7.47 (tdd, *J* = 6.8, 4.5, 1.3 Hz, 2H), 6.15 (ddd, *J* = 17.0, 10.8, 2.2 Hz, 1H), 5.58 (dd, *J* = 16.9, 1.2 Hz, 1H), 5.18 (dq, *J* = 10.8, 1.1 Hz, 1H), 5.09 (q, *J* = 2.0 Hz, 1H), 4.76 (ddq, *J* = 10.0, 5.0, 2.5 Hz, 2H), 4.71 (t, *J* = 2.3 Hz, 1H), 1.79 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.01 (d, *J* = 8.2 Hz), 132.82 (d, *J* = 3.2 Hz), 131.98 (d, *J* = 10.3 Hz), 131.52 (d, *J* = 5.5 Hz), 128.41 (d, *J* = 15.6 Hz), 127.41 (d, *J* = 191.8 Hz), 116.25 , 102.12 (d, *J* = 4.2 Hz), 84.54 , 73.34 (d, *J* = 8.1 Hz), 54.88 (d, *J* = 4.8 Hz), 3.59 .

^{31}P NMR (202 MHz, $CDCl_3$) δ 16.65.

HRMS (ESI) m/z Calcd for $C_{24}H_{19}O_2PS$, $[M+H]^+$: 263.0832; Found: 263.0829.

2,4,7-Triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]non-1-en-8-one 4-oxide (12)



Colorless oil, 75% yield.

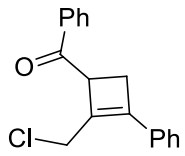
^{1}H NMR (500 MHz, Acetone-d_6) δ 8.05 – 7.97 (m, 3H), 7.69 – 7.65 (m, 1H), 7.57 – 7.48 (m, 9H), 7.37 – 7.30 (m, 2H), 5.59 – 5.39 (m, 2H), 3.59 (ddd, *J* = 13.2, 3.0, 1.9 Hz, 1H), 3.47 (ddd, *J* = 13.1, 3.1, 1.1 Hz, 1H).

^{13}C NMR (126 MHz, Acetone-d_6) δ 196.04 (d, *J* = 2.0 Hz), 144.13 , 135.27 , 134.24 (d, *J* = 3.1 Hz), 133.67 , 133.06 (d, *J* = 10.5 Hz), 131.79 , 131.34 , 130.90 , 130.35 , 130.18 , 129.87 , 129.75 , 129.413 (d, *J* = 151.3 Hz)128.87 , 82.32 (d, *J* = 6.4 Hz), 66.18 (d, *J* = 7.8 Hz), 43.53 (d, *J* = 2.5 Hz).

^{31}P NMR (202 MHz, Acetone-d_6) δ 14.49

HRMS (ESI) m/z Calcd for $C_{24}H_{19}O_4P$, $[M+Na]^+$: 425.0913; Found: 425.0916.

(2-(Chloromethyl)-3-phenylcyclobut-2-en-1-yl)(phenyl)methanone (13)



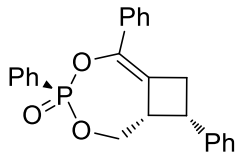
Yellowish oil, 44% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H), 7.63 – 7.59 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.33 (m, 5H), 4.69 (dd, *J* = 5.3, 2.0 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.40 (d, *J* = 12.2 Hz, 1H), 3.16 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.97 (dt, *J* = 12.8, 1.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.18, 143.58, 136.22, 134.77, 133.50, 133.37, 128.78, 128.66, 128.59, 128.20, 126.66, 44.90, 39.26, 32.05.

HRMS (APCI) m/z Calcd for $C_{18}H_{15}ClO$, $[M+H]^+$: 283.0884; Found: 283.0886.

(2,4,8-Triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]non-1-ene 4-oxide (14)



Colorless oil, 69% yield.

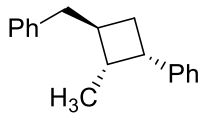
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.45 (m, 4H), 7.35 (qt, *J* = 14.5, 7.5 Hz, 7H), 7.25 – 7.21 (m, 1H), 4.29 (td, *J* = 11.0, 6.4 Hz, 1H), 4.21 – 4.11 (m, 1H), 3.95 (td, *J* = 9.7, 5.6 Hz, 1H), 3.76 – 3.57 (m, 2H), 3.38 (dt, *J* = 12.2, 5.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.85, 138.97, 133.74, 132.94, 131.64 (d, J_{CP} = 9.9 Hz), 128.63, 128.38 (d, J_{CP} = 2.0 Hz), 128.34 (d, J_{CP} = 154.0 Hz), 127.73, 127.09, 126.15, 124.19, 65.47 (d, J_{CP} = 6.6 Hz), 46.48, 37.14, 32.82.

^{31}P NMR (202 MHz, $CDCl_3$) δ 16.92.

HRMS (ESI) m/z Calcd for $C_{24}H_{21}O_3P$, $[M+Na]^+$: 411.1121; Found: 411.1122.

(3-Benzyl-2-methylcyclobutyl)benzene (15)



Colorless oil, 78% yield.

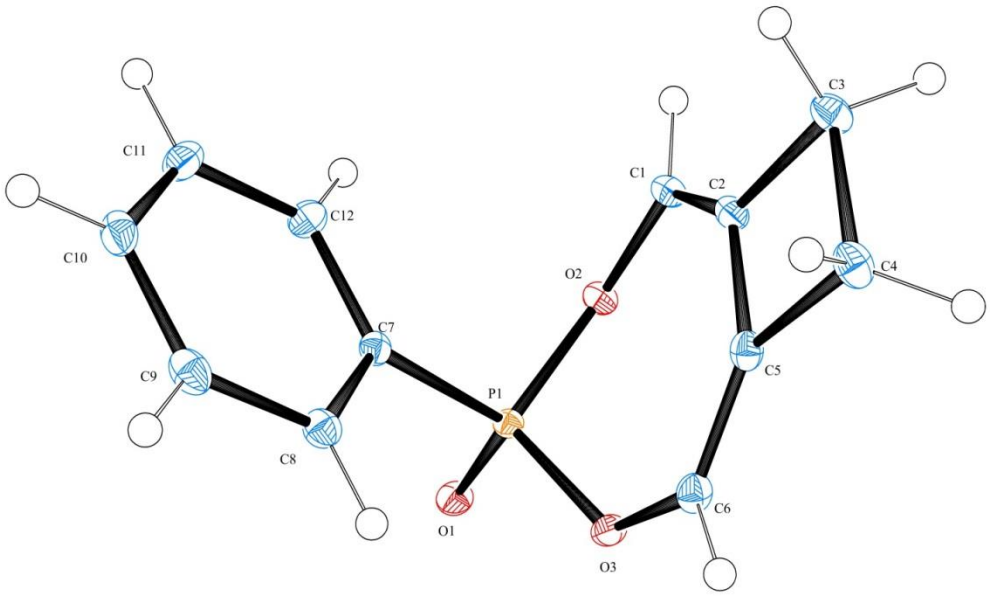
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.22-7.12 (m, 6H), 3.68 – 3.55 (m, 1H), 2.86 (qd, *J* = 13.7, 7.5 Hz, 2H), 2.79 – 2.59 (m, 1H), 2.53 – 2.39 (m, 1H), 2.33 – 2.02 (m, 2H), 0.76 (d, *J* = 7.3 Hz, 1H, *minor*), 0.59 (d, *J* = 7.1 Hz, 2H, *major*).

^{13}C NMR (126 MHz, $CDCl_3$, *major diastereomer*) δ 142.23 , 141.18 , 128.69 , 128.25 , 128.05 , 127.94 , 125.76 , 125.58 , 41.88 , 41.68 , 39.60 , 39.50 , 28.72 , 16.27 ; *minor diastereomer* δ 141.54 , 141.40 , 128.43 , 128.28 , 127.90 , 127.64 , 125.63 , 125.52 , 39.34 , 37.14 , 36.71 , 35.43 , 29.30 , 10.48.

HRMS (APCI) m/z Calcd for $C_{18}H_{20}$, $[M+H]^+$: 237.1638; Found: 237.1633.

9. X-ray crystallographic analysis

a) The structure of **2k** was assigned by X-ray crystallographic analysis:



Molecule's view of **2k:**

Table S3. Sample and crystal data for g546.

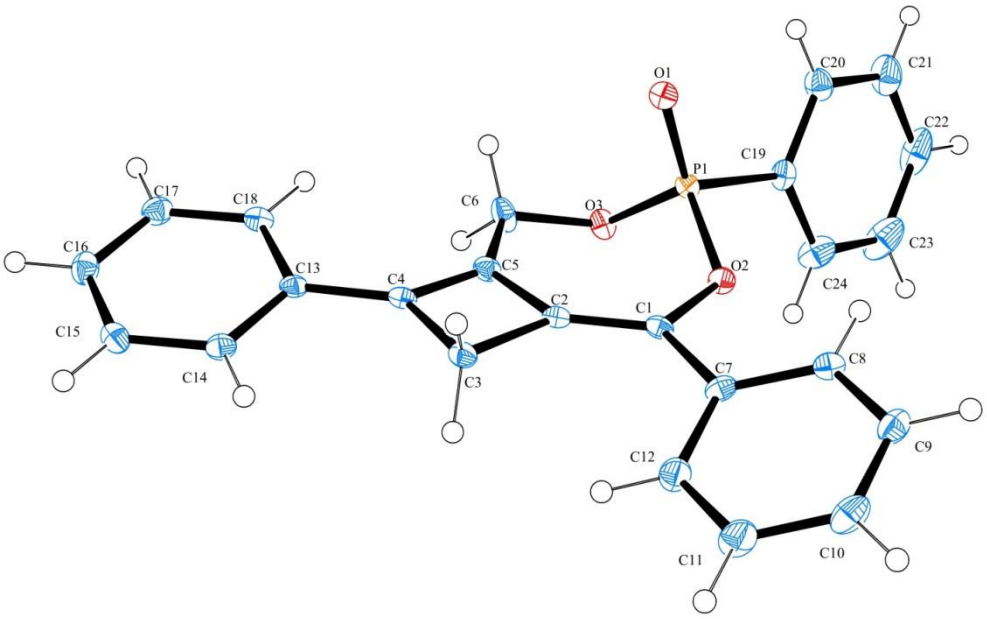
Identification code	g546	
Chemical formula	$C_{12}H_{11}O_3P$	
Formula weight	234.18 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	(0.080 x 0.160 x 0.350) mm^3	
Crystal system	monoclinic	
Space group	P 1 2(1)/c 1	
Unit cell dimensions	a = 8.145(3) Å	α = 90°
	b = 13.268(4) Å	β = 108.850(10)°
	c = 10.374(3) Å	γ = 90°
Volume	1061.0(6) $Å^3$	

Z	4
Density (calculated)	1.466 g/cm^3
Absorption coefficient	0.246 mm^{-1}
F(000)	488

Table S4. Data collection and structure refinement for g546.

Theta range for data collection	2.58 to 30.55°
Index ranges	-11<=h<=10, -16<=k<=18, -14<=l<=14
Reflections collected	11289
Independent reflections	3235 [R(int) = 0.0337]
Coverage of independent reflections	99.4%
Absorption correction	multi-scan
Max. and min. transmission	0.9810 and 0.9190
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3235 / 0 / 145
Goodness-of-fit on F^2	1.031
Final R indices	2751 data; I>2σ(I) R1 = 0.0344, wR2 = 0.0836
	all data R1 = 0.0442, wR2 = 0.0886
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0386P)^2+0.5991P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.422 and -0.366 eÅ^{-3}
R.M.S. deviation from mean	0.060 eÅ^{-3}

b) The structure of **4a** was assigned by X-ray crystallographic analysis



Molecule's view of **4a:**

Table S5. Sample and crystal data for g511.

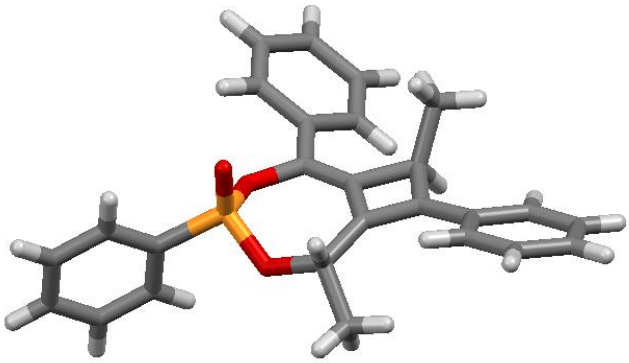
Identification code	g511	
Chemical formula	$C_{24}H_{19}O_3P$	
Formula weight	386.36 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	(0.174 x 0.271 x 0.567) mm^3	
Crystal system	monoclinic	
Space group	P 1 2(1)/c 1	
Unit cell dimensions	a = 14.464(6) Å	α = 90°
	b = 13.000(5) Å	β = 97.227(10)°
	c = 10.236(4) Å	γ = 90°
Volume	1909.4(13) $Å^3$	
Z	4	

Density (calculated)	1.344 g/cm^3
Absorption coefficient	0.167 mm^{-1}
F(000)	808

Table S6. Data collection and structure refinement for g511.

Theta range for data collection	2.54 to 29.36°
Index ranges	-19<=h<=19, -17<=k<=17, -14<=l<=14
Reflections collected	31186
Independent reflections	5211 [R(int) = 0.1016]
Coverage of independent reflections	99.3%
Absorption correction	multi-scan
Max. and min. transmission	0.9720 and 0.9110
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5211 / 0 / 253
Goodness-of-fit on F^2	1.037
Δ/σ_{max}	0.001
Final R indices	3840 data; I>2σ(I) R1 = 0.0548, wR2 = 0.1326
	all data R1 = 0.0818, wR2 = 0.1457
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0742P)^2+0.7139P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.499 and -0.574 eÅ^{-3}
R.M.S. deviation from mean	0.083 eÅ^{-3}

c) The structure of **4i** was assigned by X-ray crystallographic analysis:



Molecule's view of ***4i:***

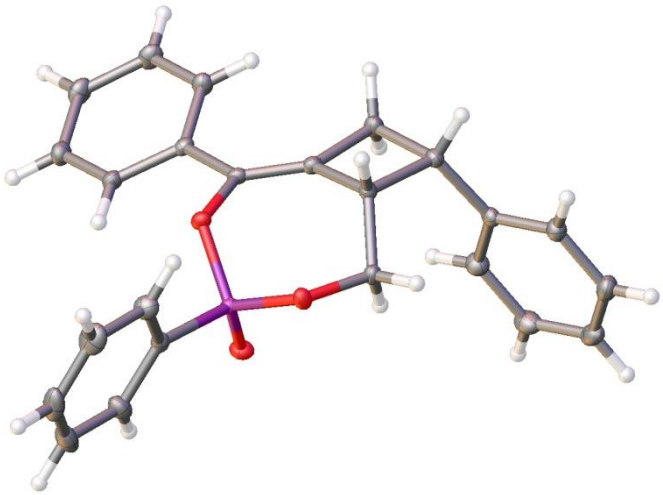
Table S7. Sample and crystal data for g766.

Identification code	g766	
Chemical formula	$C_{26}H_{23}O_3P$	
Formula weight	414.41 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	(0.112 x 0.233 x 0.344) mm^3	
Crystal system	monoclinic	
Space group	P 1 2(1)/c 1	
Unit cell dimensions	a = 14.668(5) Å	α = 90°
	b = 13.512(4) Å	β = 92.316(9)°
	c = 10.815(3) Å	γ = 90°
Volume	2141.7(11) $Å^3$	
Z	4	
Density (calculated)	1.285 g/cm^3	
Absorption coefficient	0.153 mm^{-1}	
F(000)	872	

Table S8. Data collection and structure refinement for g766.

Theta range for data collection	2.41 to 30.18°
Index ranges	-20<=h<=20, -19<=k<=18, -15<=l<=15
Reflections collected	31655
Independent reflections	6290 [R(int) = 0.0655]
Coverage of independent reflections	99.0%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9830 and 0.9490
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	6290 / 0 / 273
Goodness-of-fit on F^2	1.021
Δ/σ_{max}	0.001
Final R indices	4671 data; I>2σ(I) R1 = 0.0456, wR2 = 0.0968
	all data R1 = 0.0753, wR2 = 0.1073
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0446P)^2+0.9664P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.324 and -0.431 eÅ^{-3}
R.M.S. deviation from mean	0.065 eÅ^{-3}

d) The structure of **14** was assigned by X-ray crystallographic analysis:



Molecule's view of **14**

Table S9. Sample and crystal data for g807.

Identification code	g807	
Chemical formula	$C_{24}H_{21}O_3P$	
Formula weight	388.38 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	(0.134 x 0.237 x 0.304) mm^3	
Crystal system	monoclinic	
Space group	P 1 c 1	
Unit cell dimensions	a = 6.2565(10) Å	α = 90°
	b = 9.4325(10) Å	β = 96.178(4)°
	c = 16.395(2) Å	γ = 90°
Volume	961.9(2) $Å^3$	
Z	2	
Density (calculated)	1.341 g/cm^3	
Absorption coefficient	0.166 mm^{-1}	

F(000)	408

Table S10. Data collection and structure refinement for g807.

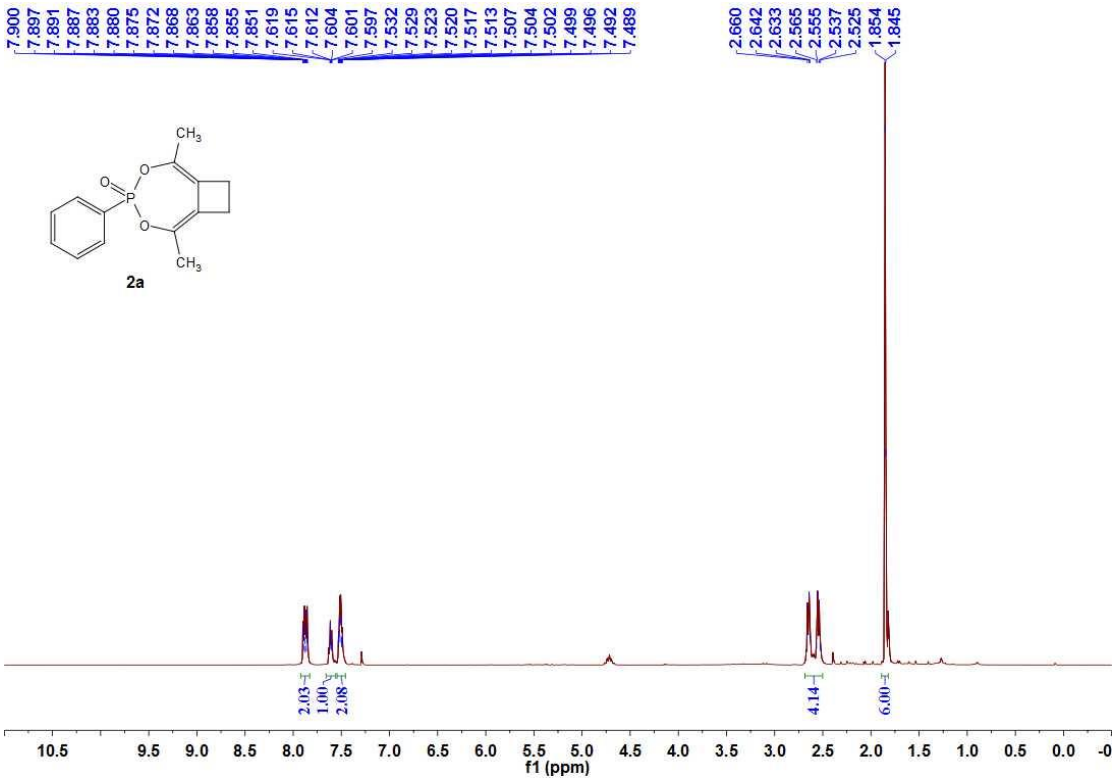
Theta range for data collection	2.50 to 30.59°	
Index ranges	-8<=h<=8, -13<=k<=13, -23<=l<=23	
Reflections collected	33800	
Independent reflections	5781 [R(int) = 0.0258]	
Coverage of independent reflections	99.7%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9780 and 0.9510	
Structure solution technique	direct methods	
Structure solution program	SHELXT, Acta Cryst., Sect. A 2015, A71, 3-8.	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	5781 / 2 / 254	
Goodness-of-fit on F^2	1.025	
Final R indices	5652 data; I>2σ(I)	R1 = 0.0252, wR2 = 0.0678
	all data	R1 = 0.0263, wR2 = 0.0685
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0475P)^2+0.1011P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.013(12)*	
Extinction coefficient	0.0180(40)	
Largest diff. peak and hole	0.272 and -0.219 eÅ^{-3}	
R.M.S. deviation from mean	0.044 eÅ^{-3}	

* Flack x determined using 2671 quotients [(I+)-(I-)]/[(I+)+(I-)]

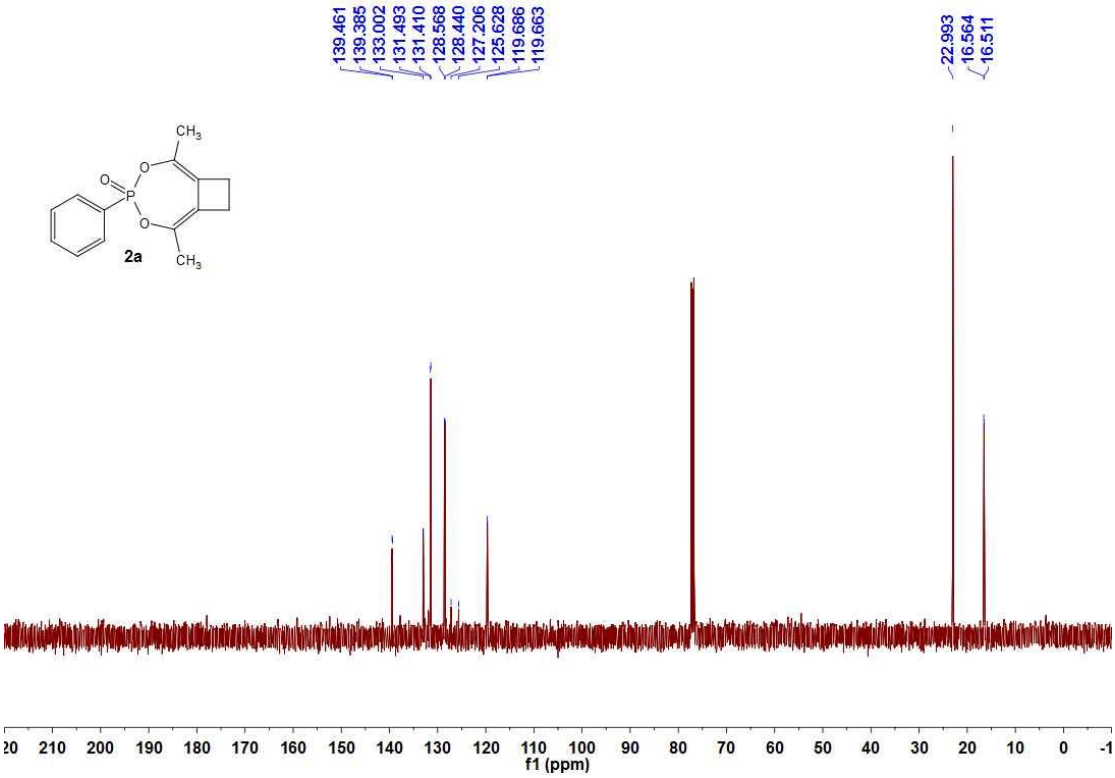
(Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).

10. NMR spectra

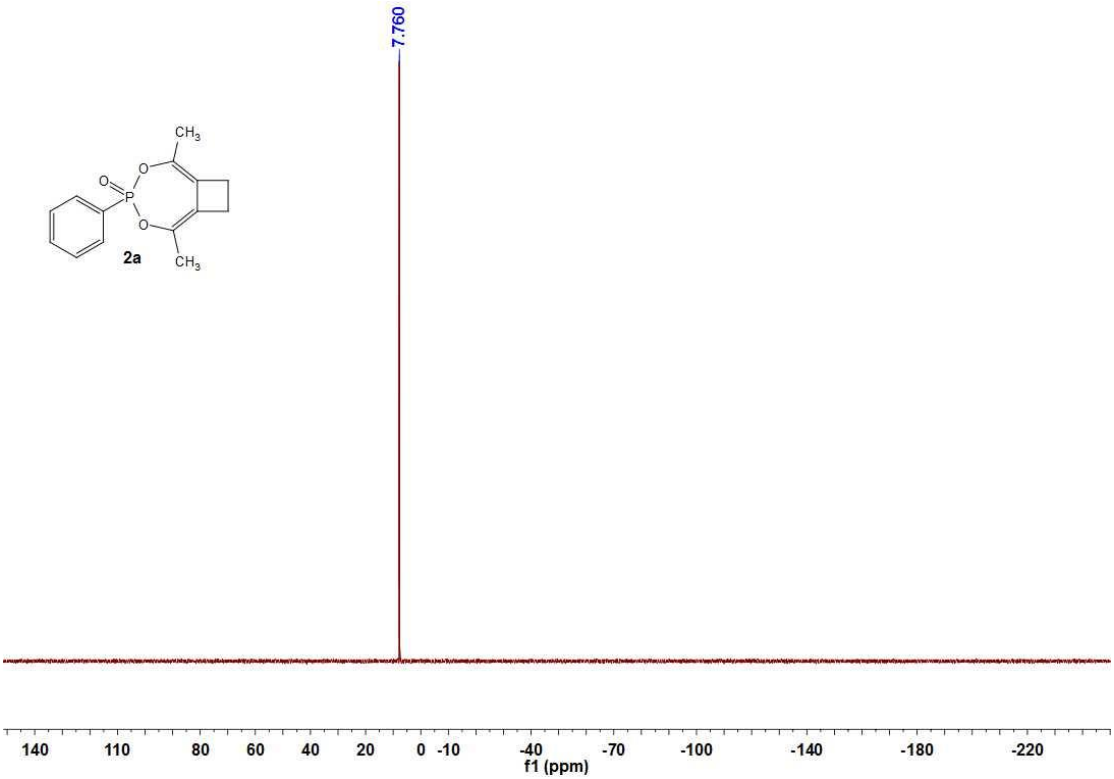
^{1}H NMR of **2a**



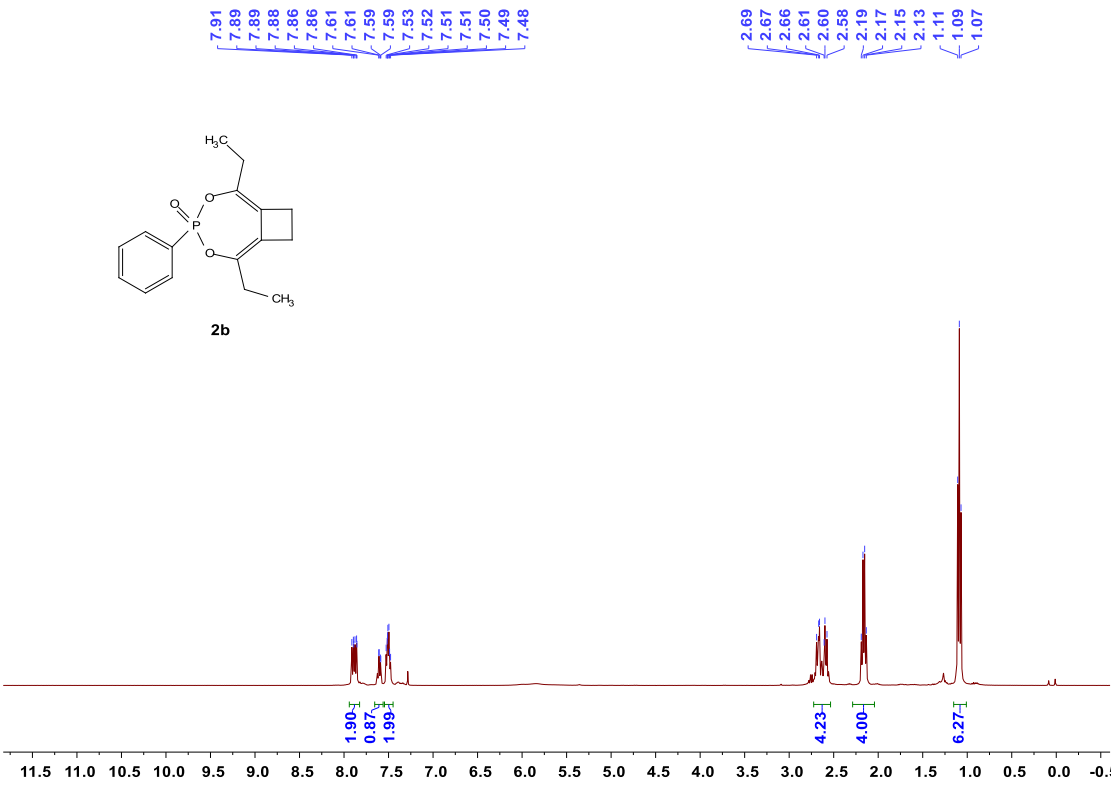
^{13}C NMR of **2a**



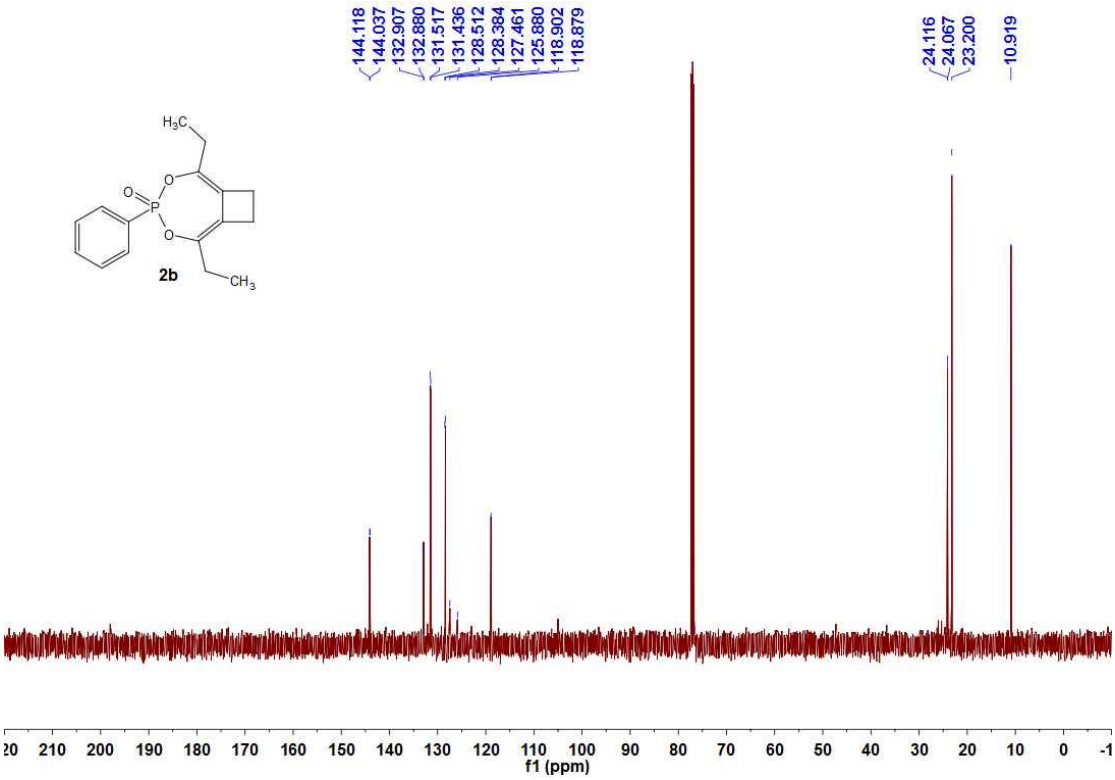
^{31}P NMR of **2a**



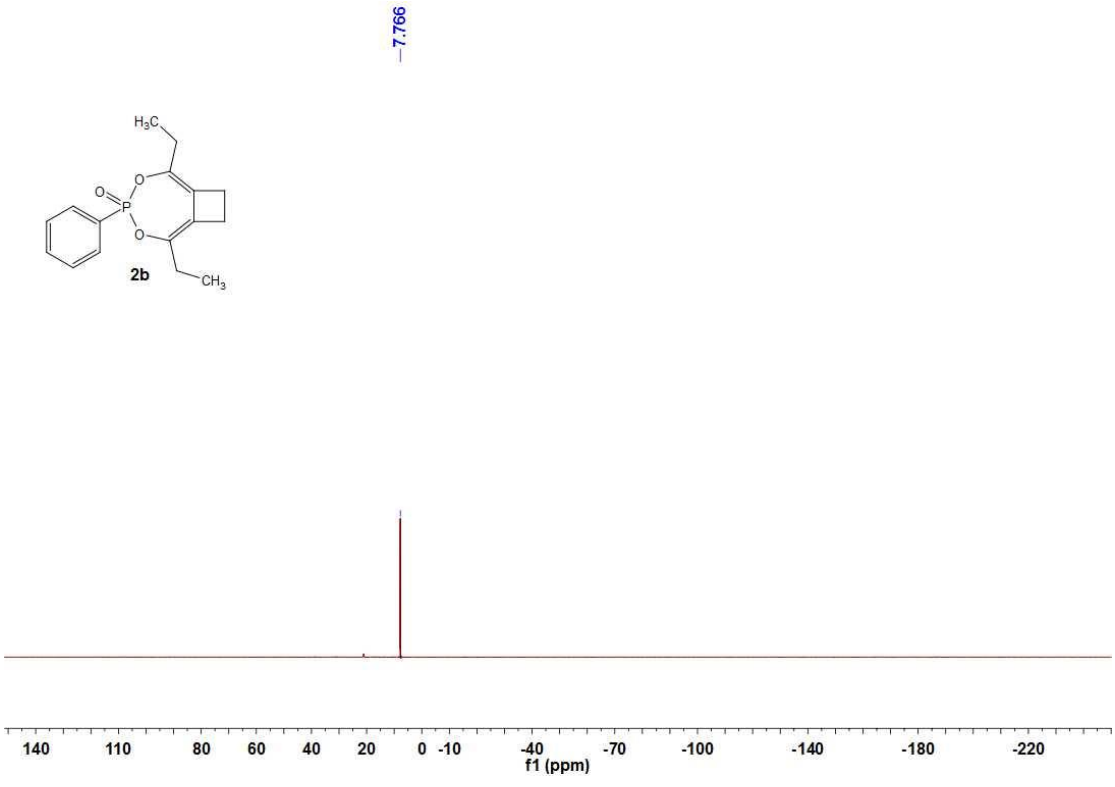
^{1}H NMR of **2b**



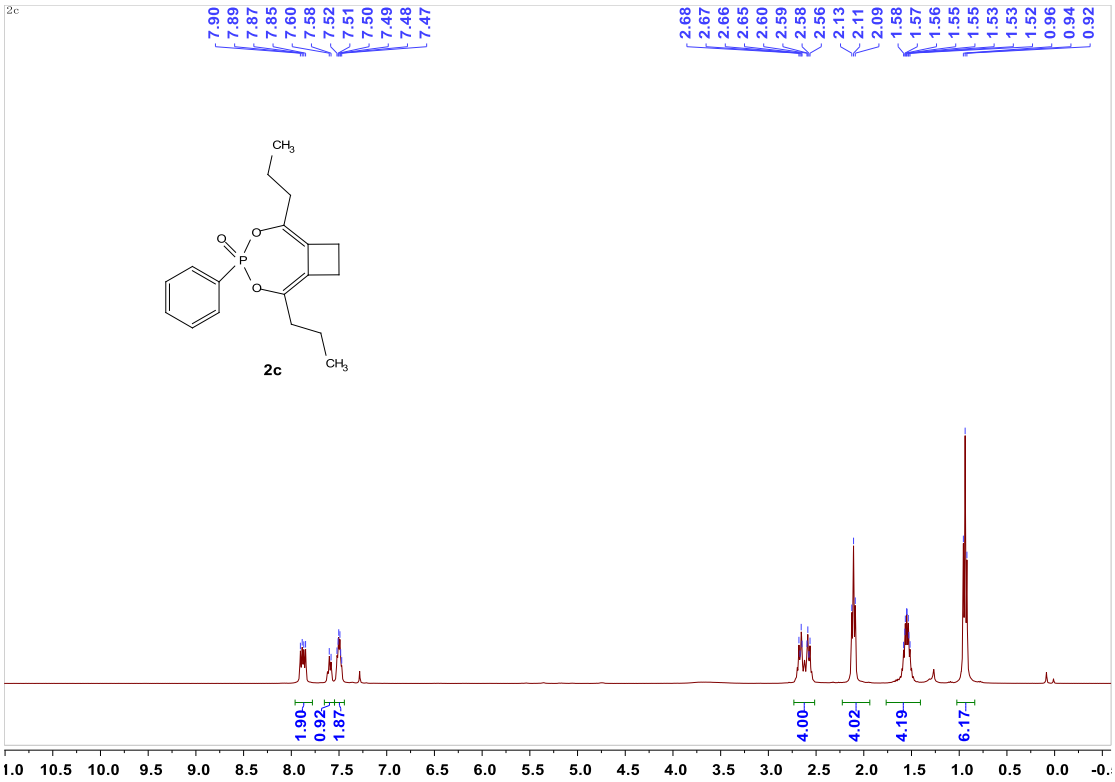
^{13}C NMR of **2b**



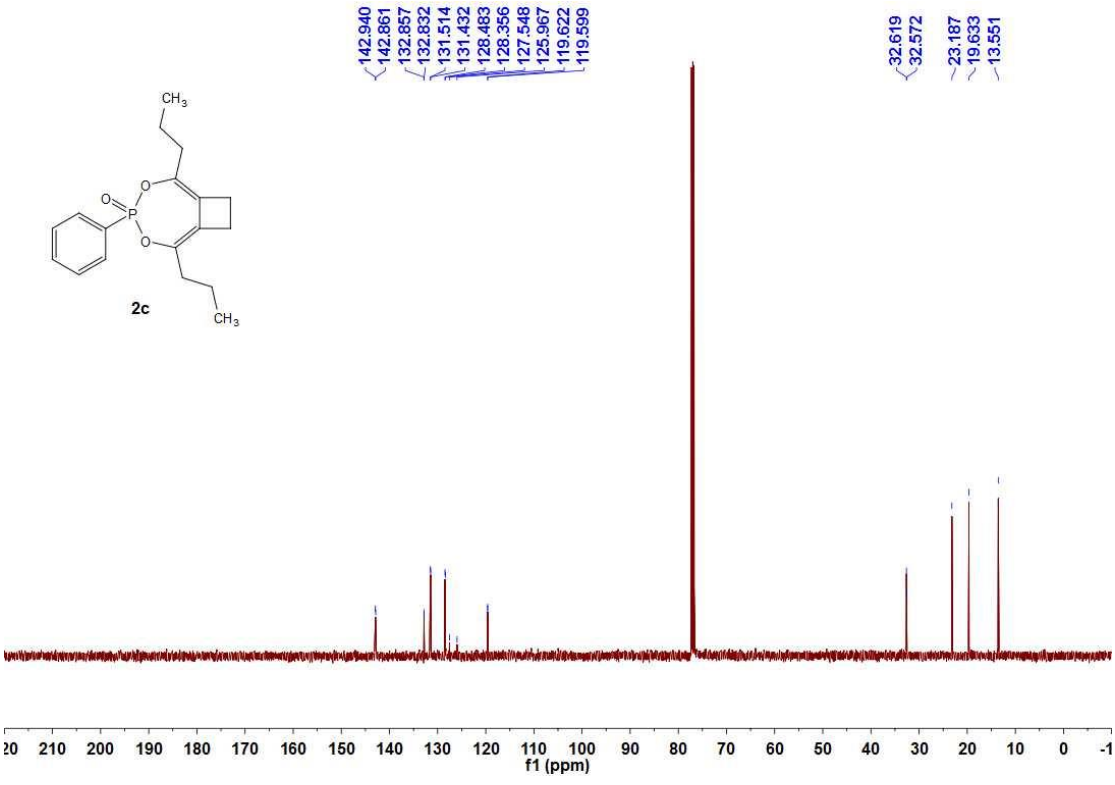
^{31}P NMR of **2b**



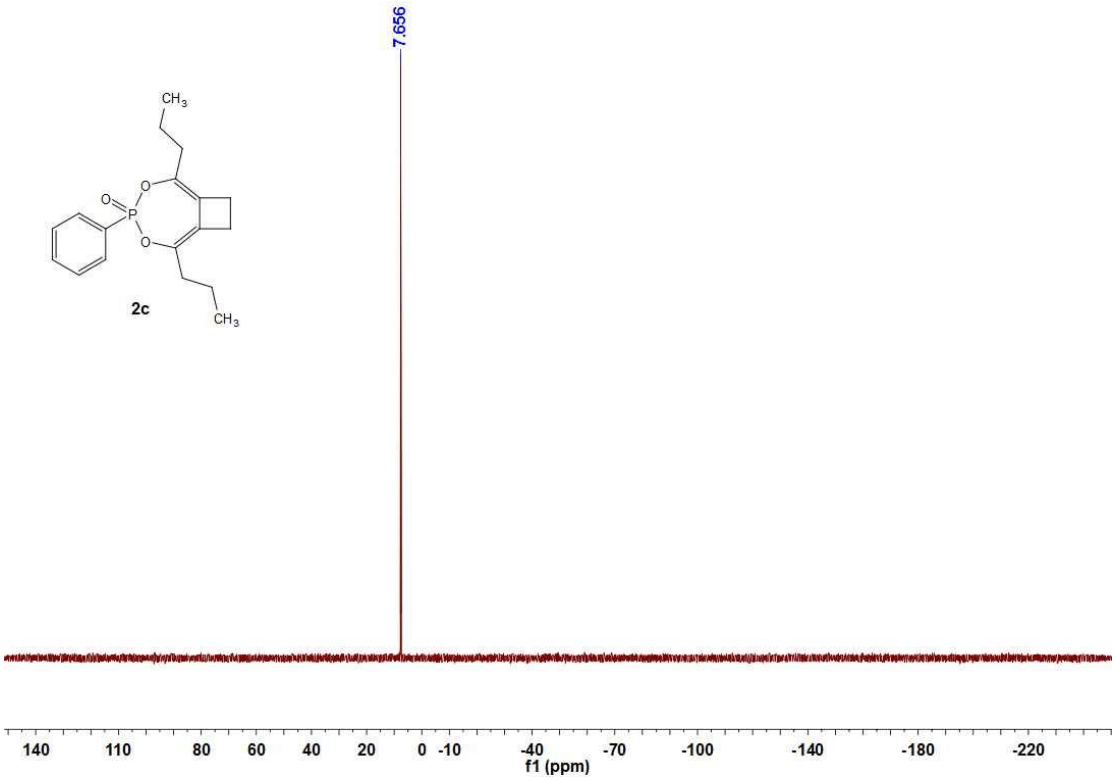
^{1}H NMR of **2c**



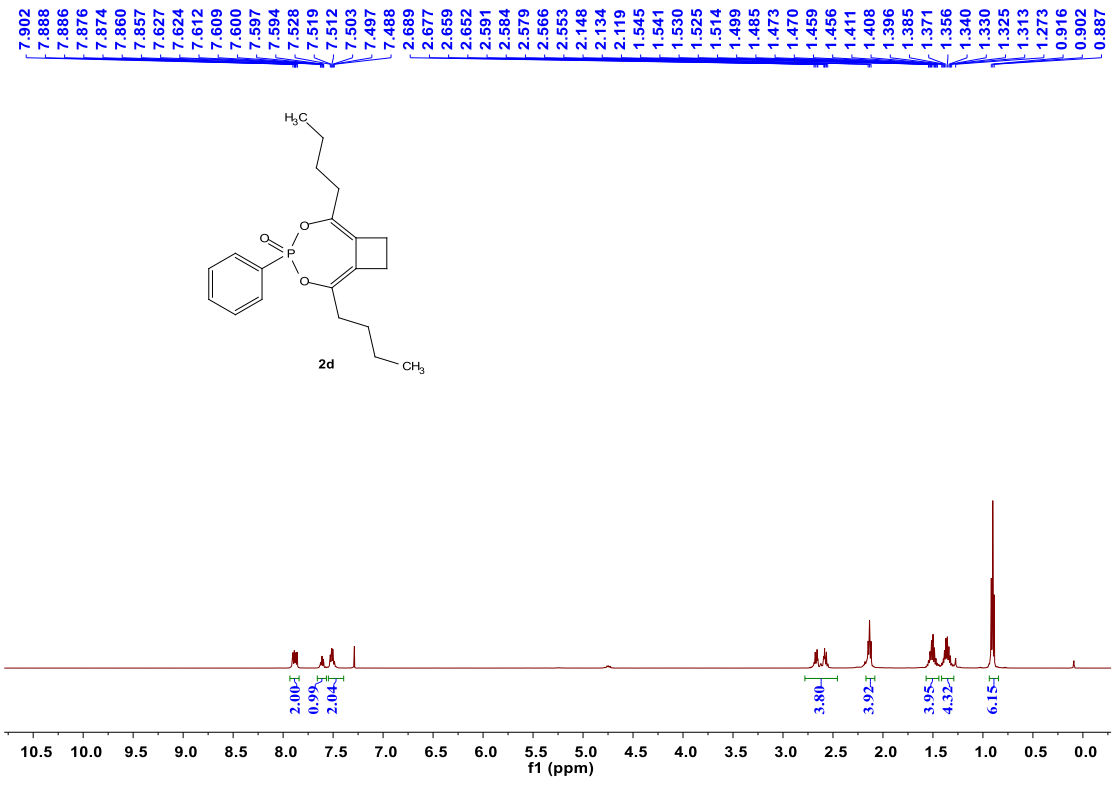
^{13}C NMR of **2c**



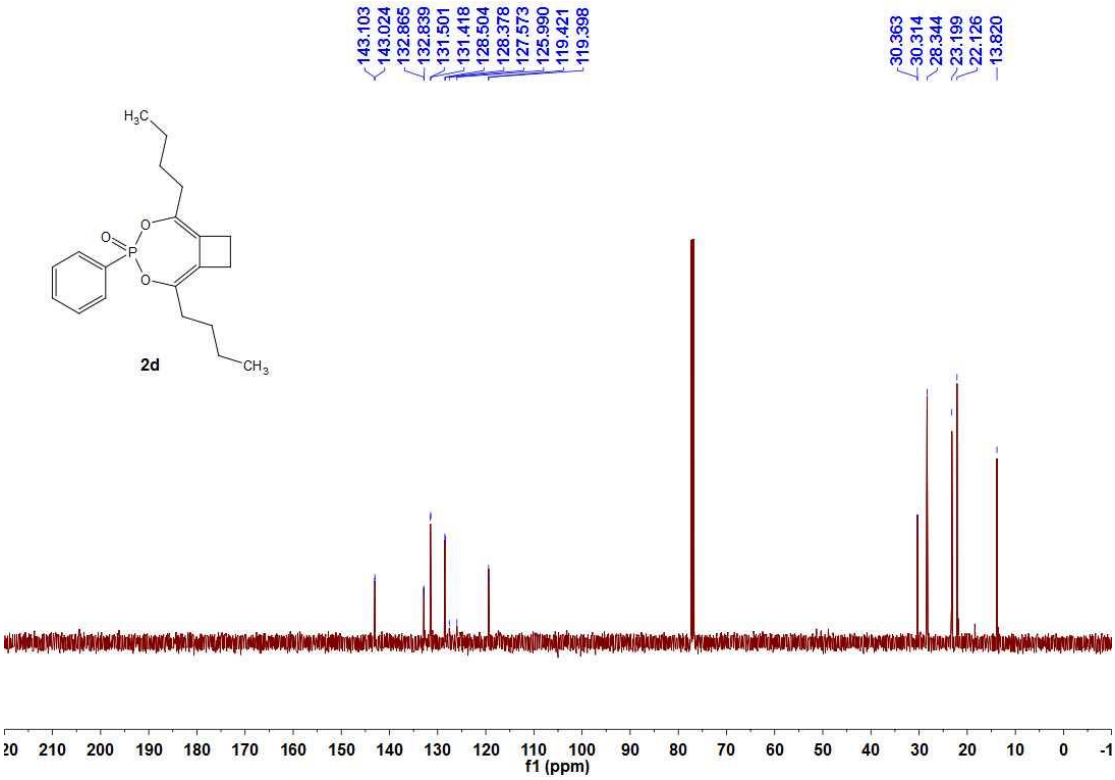
^{31}P NMR of **2c**



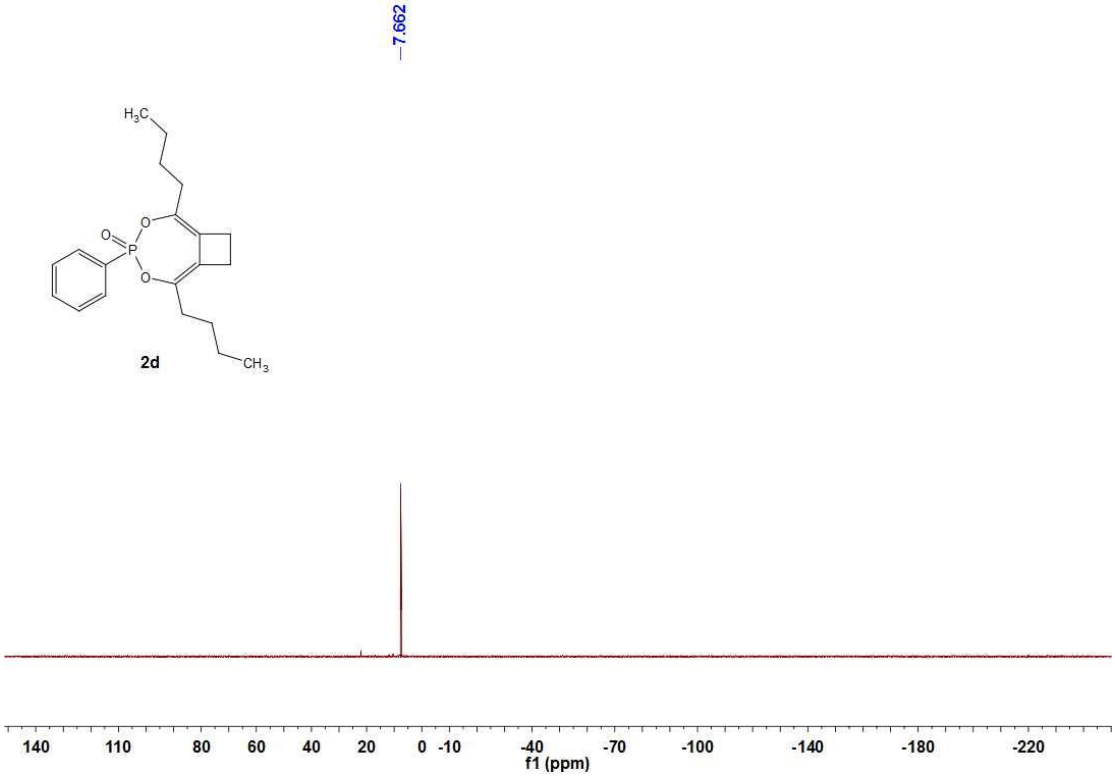
^{1}H NMR of **2d**



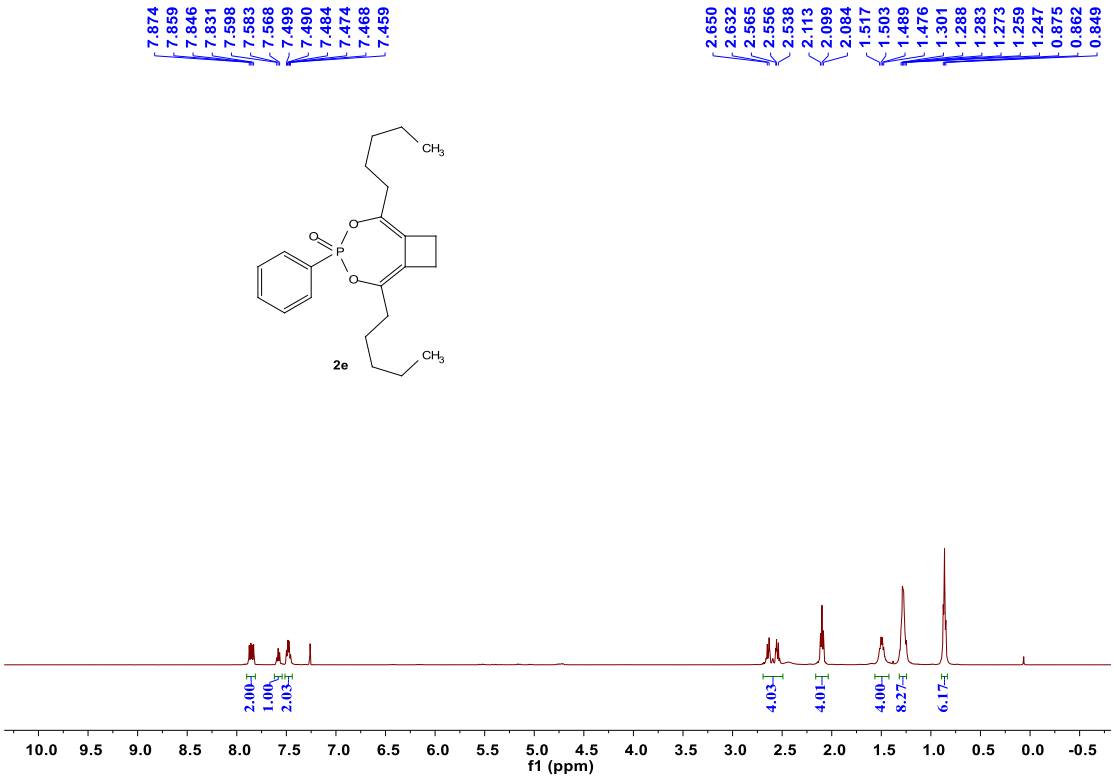
^{13}C NMR of **2d**



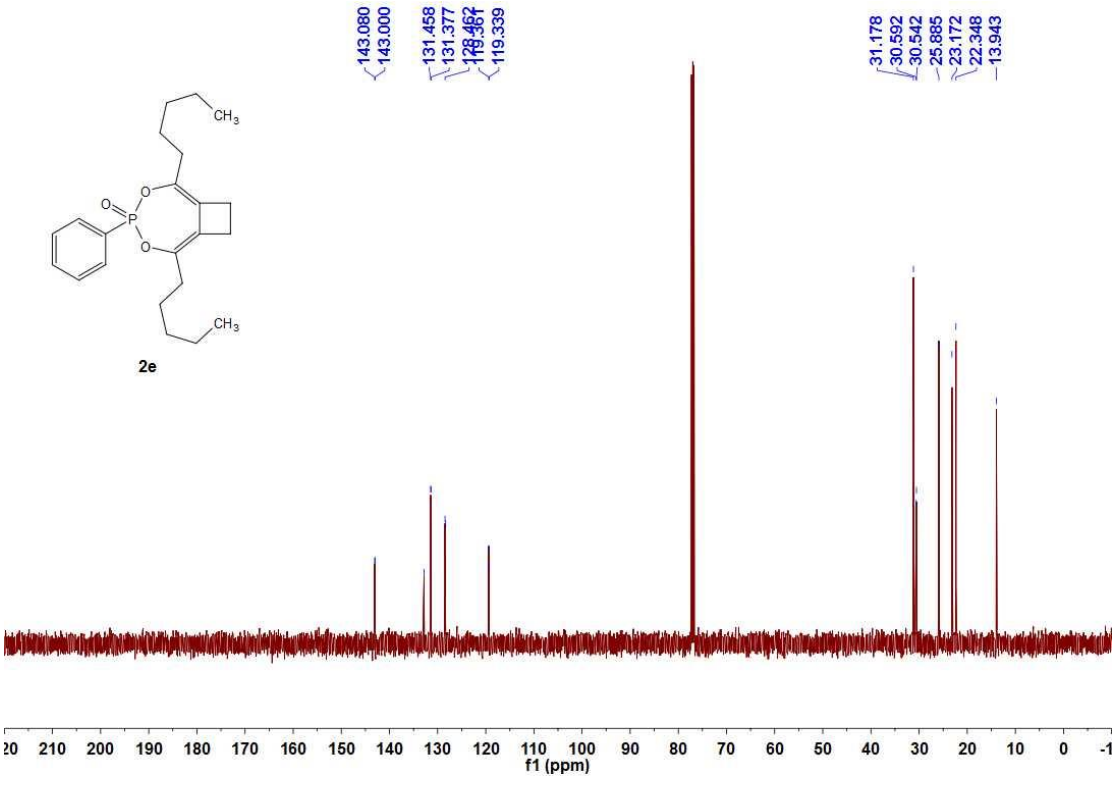
^{31}P NMR of **2d**



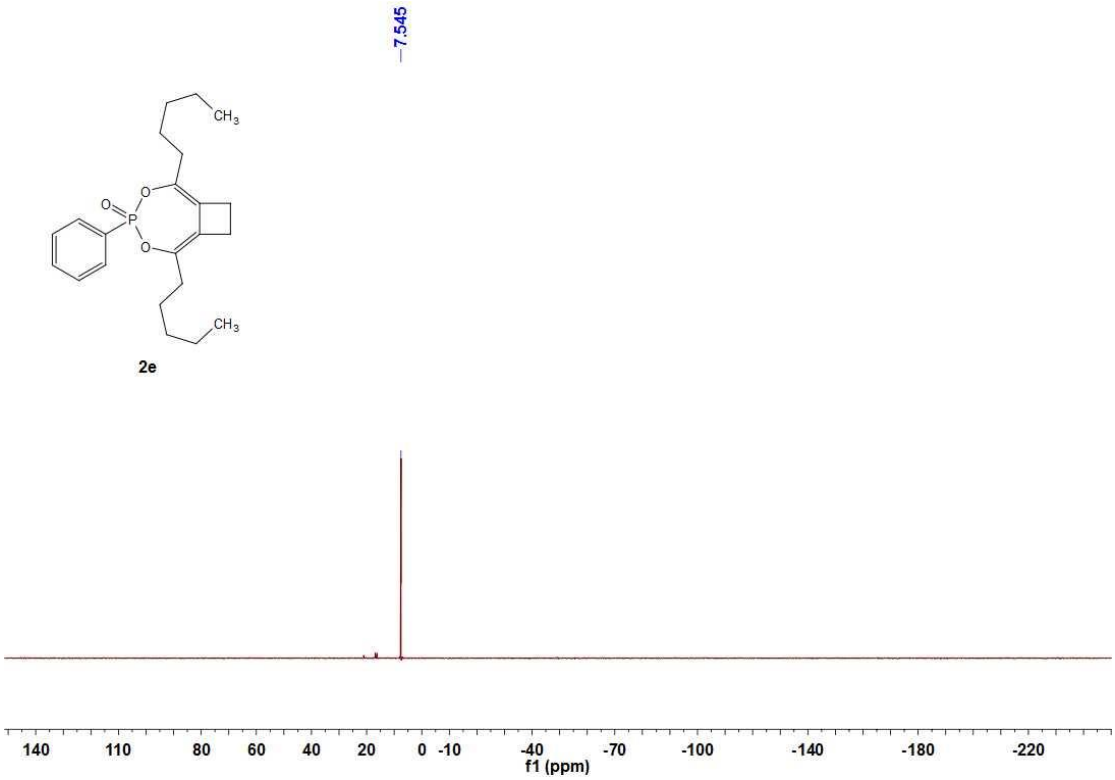
^{1}H NMR of **2e**



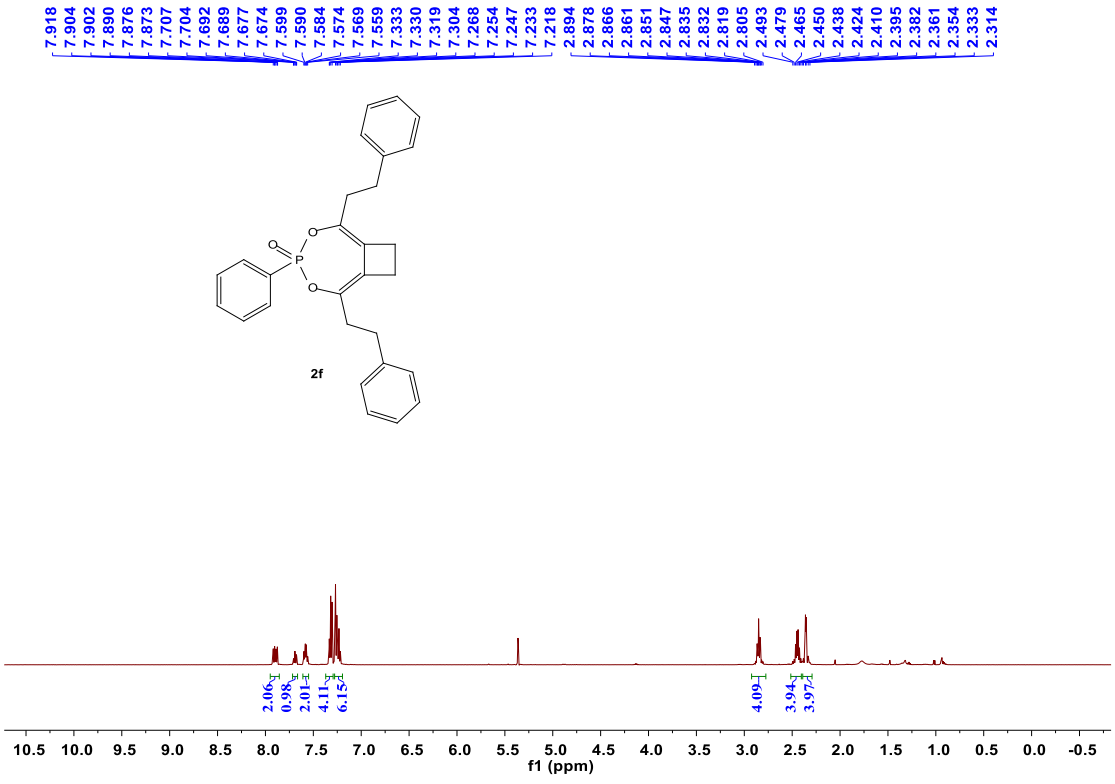
^{13}C NMR of **2e**



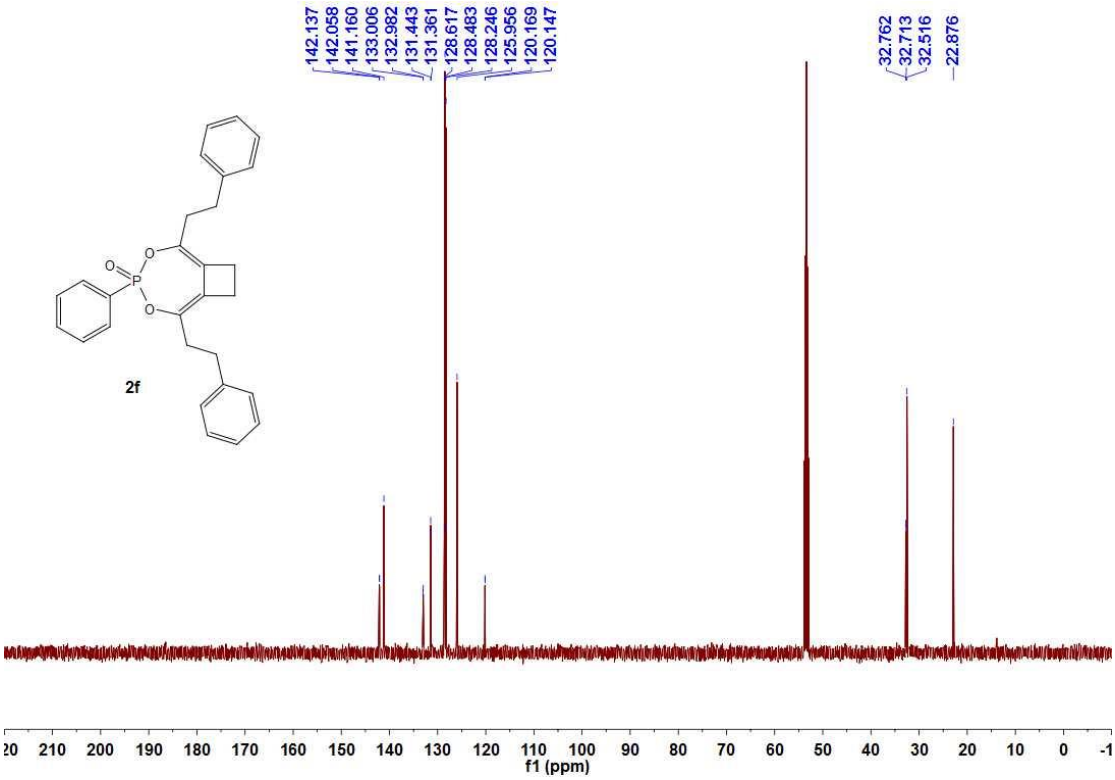
^{31}P NMR of **2e**



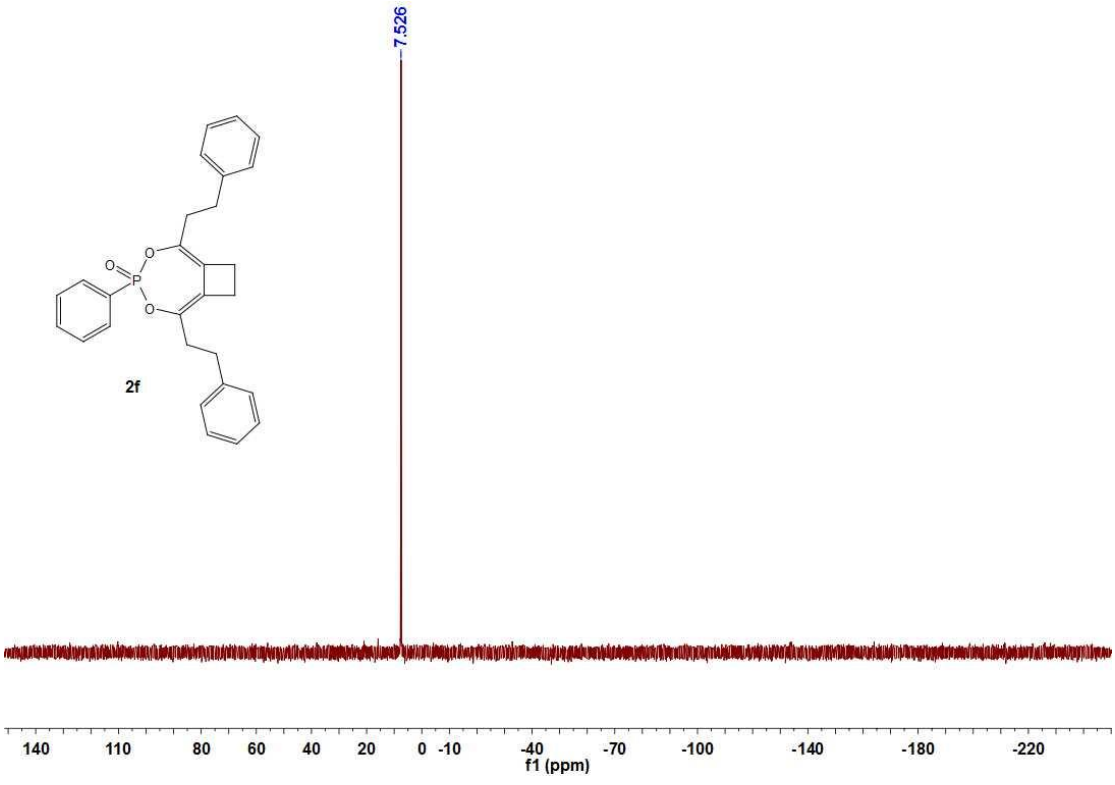
^{1}H NMR of **2f**



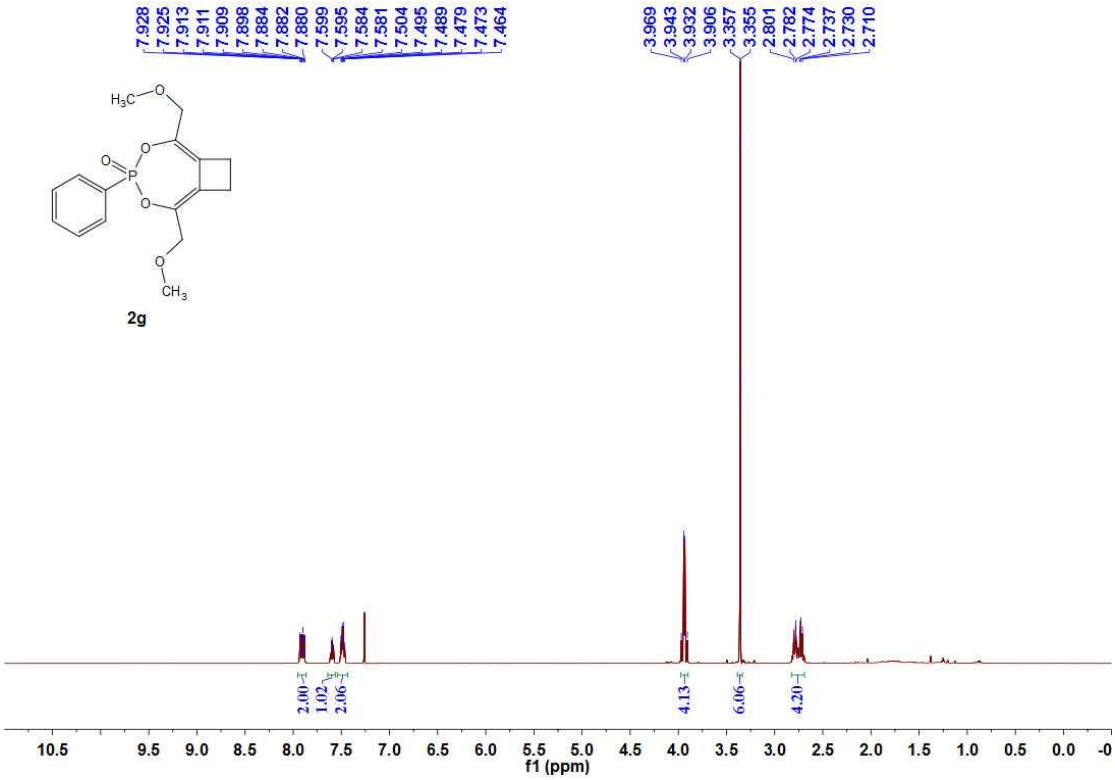
^{13}C NMR of **2f**



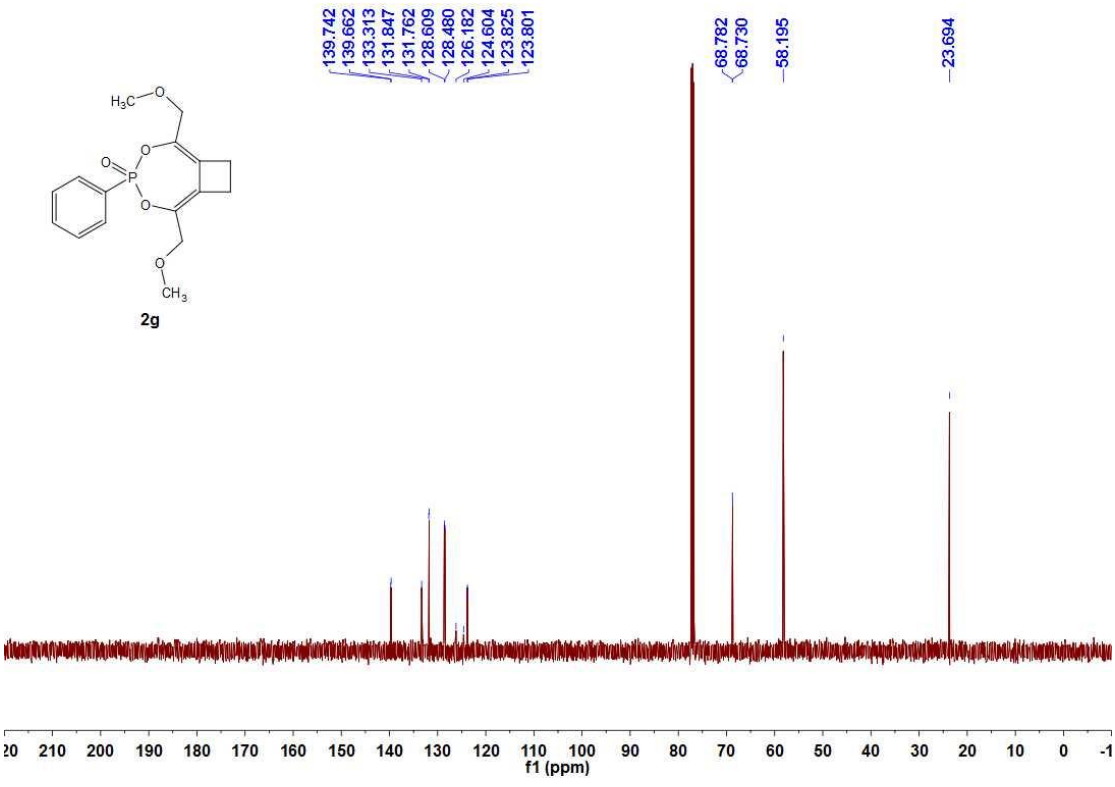
^{31}P NMR of **2f**



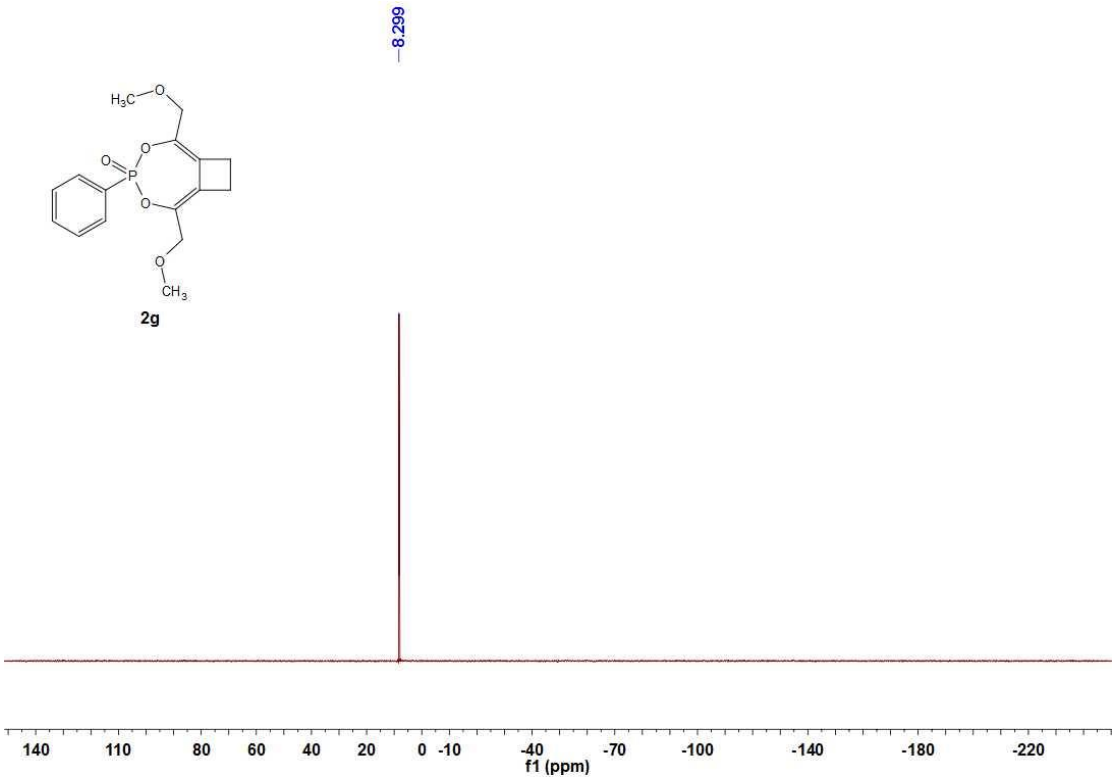
^{1}H NMR of **2g**



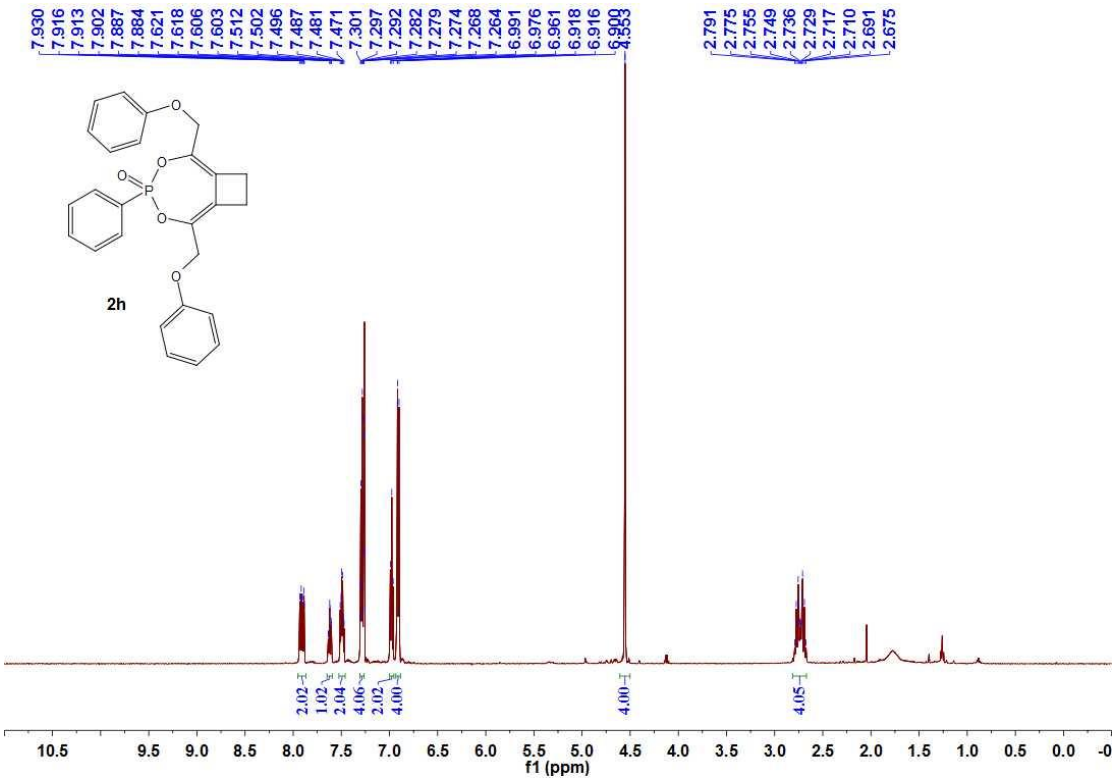
^{13}C NMR of **2g**



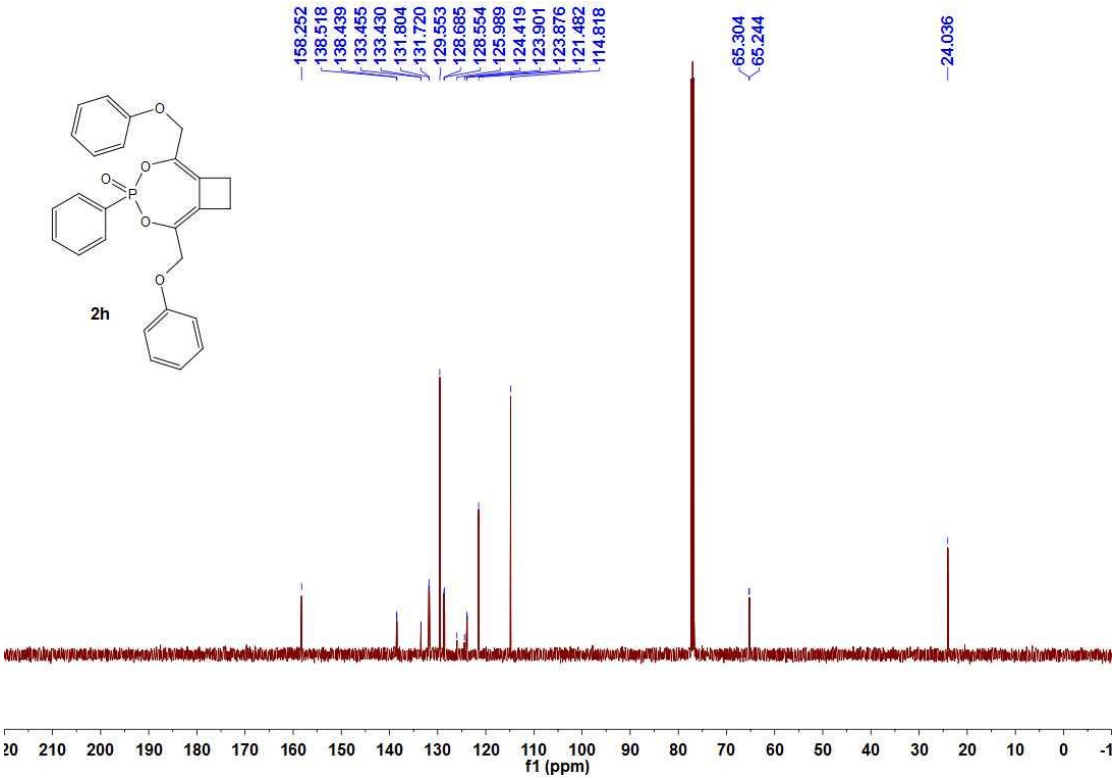
^{31}P NMR of **2g**



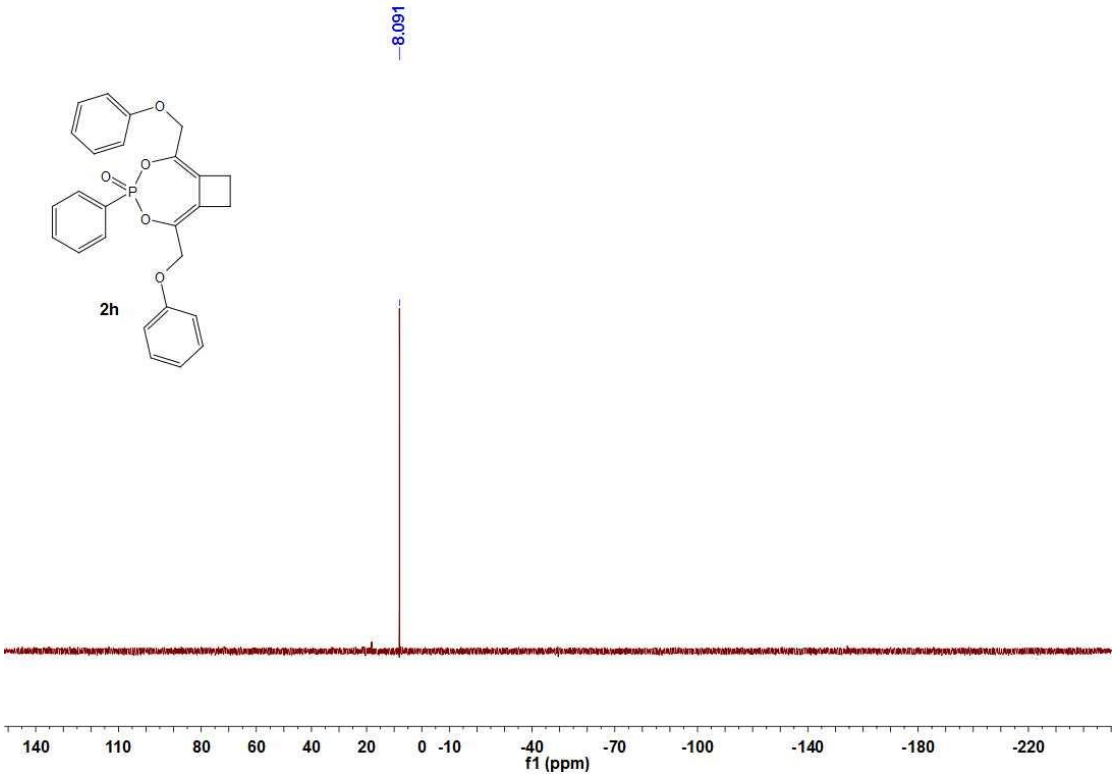
^{1}H NMR of **2h**



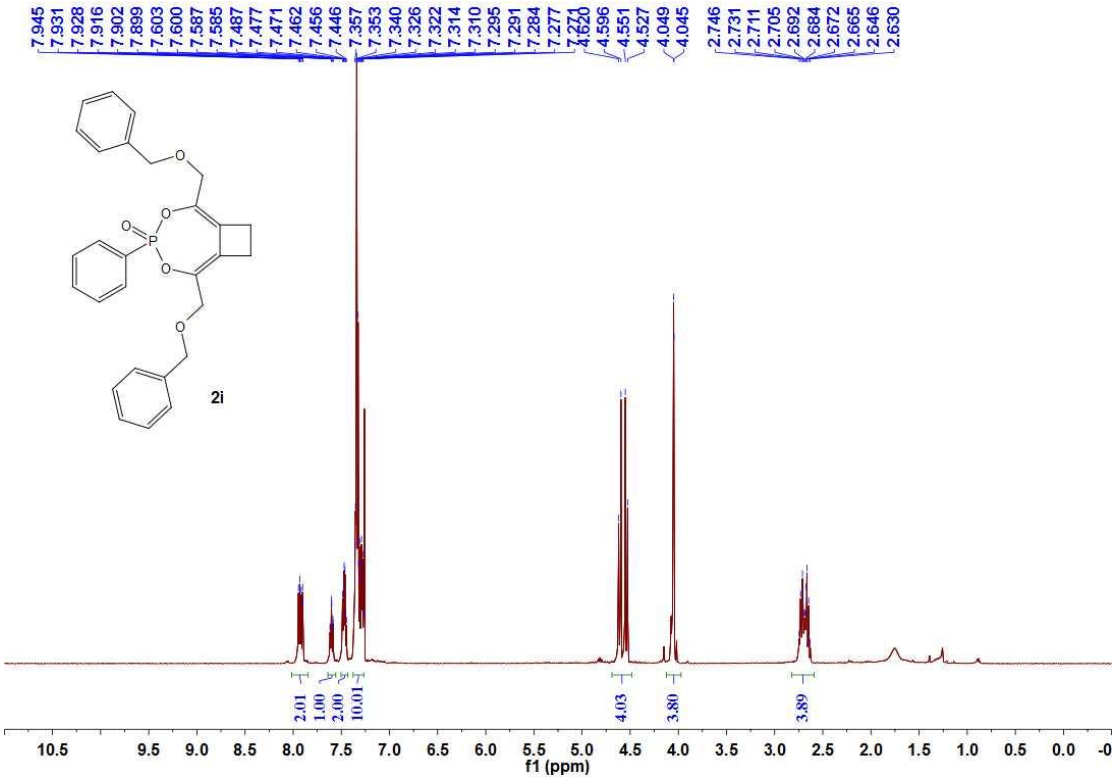
^{13}C NMR of **2h**



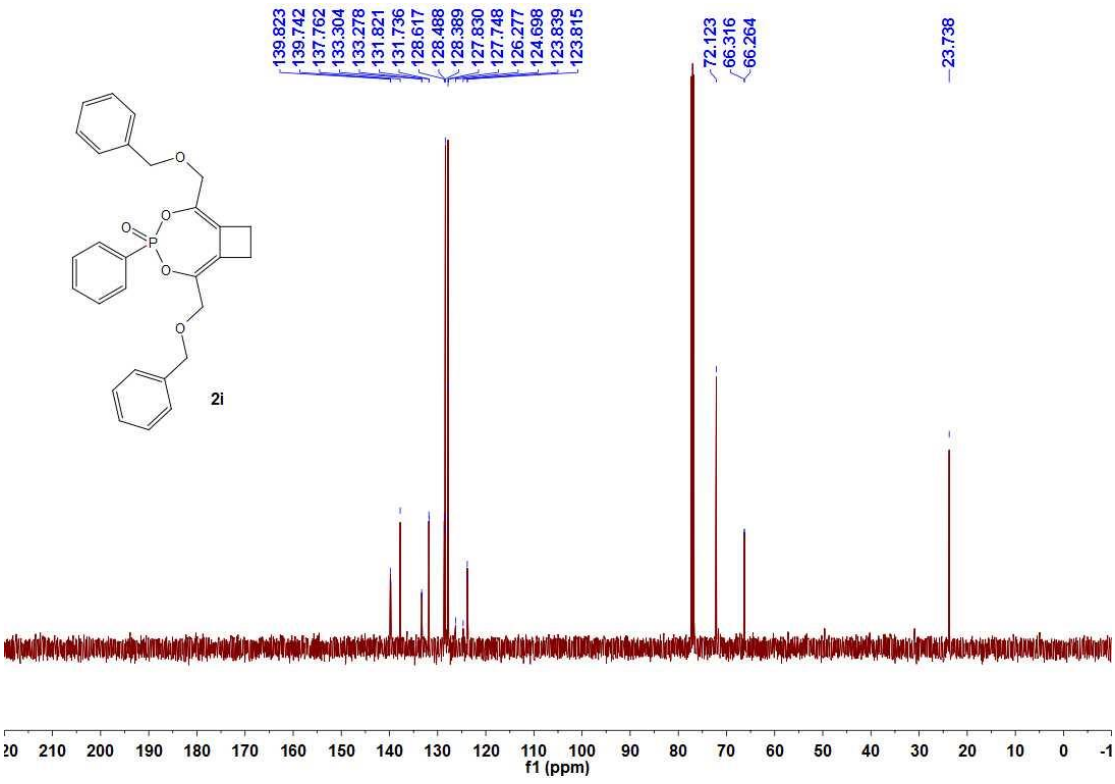
^{31}P NMR of **2h**



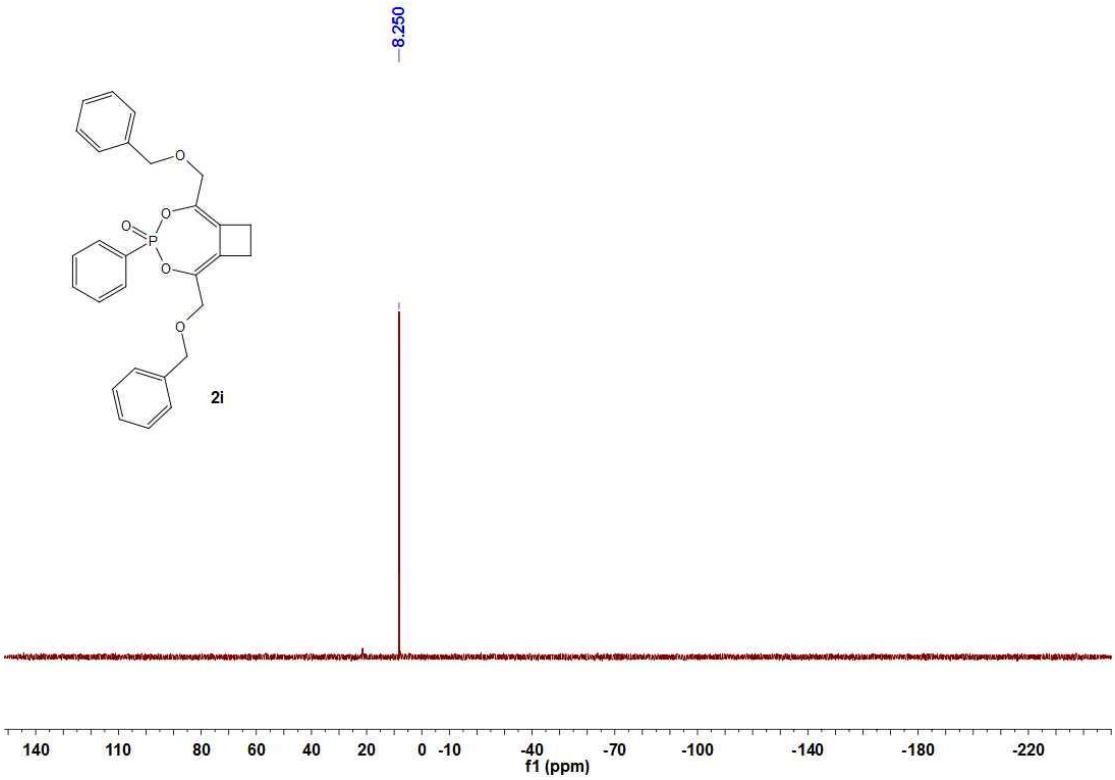
^{1}H NMR of **2i**



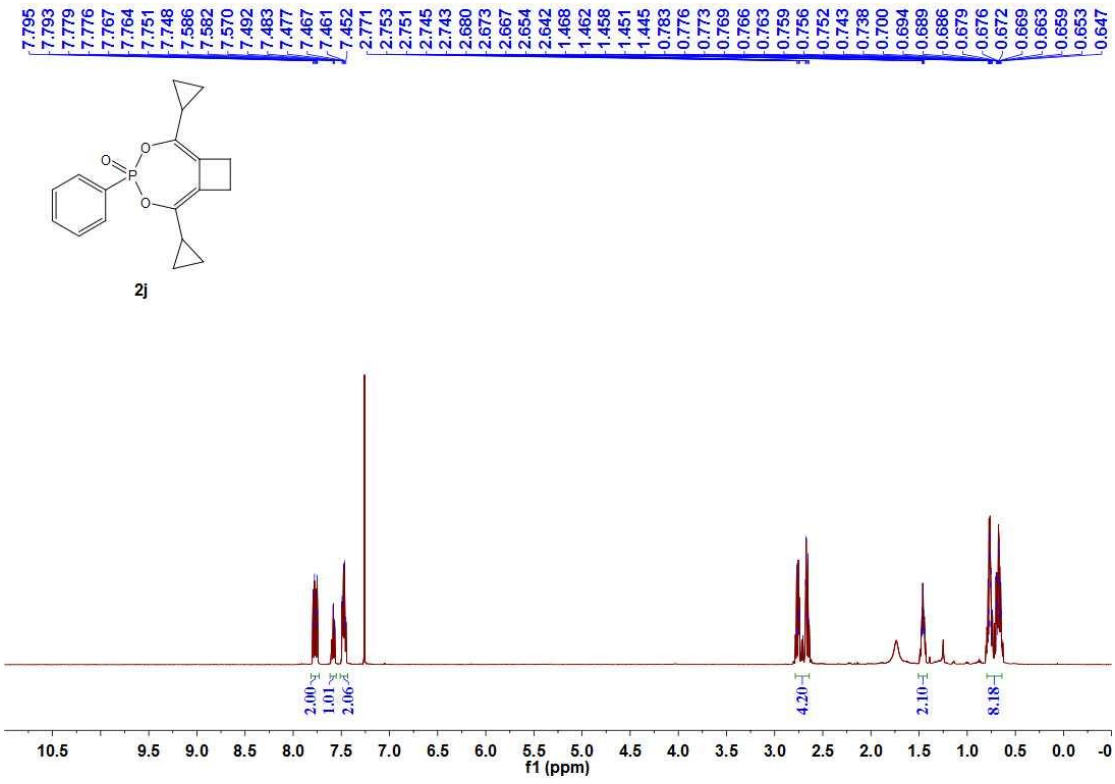
^{13}C NMR of **2i**



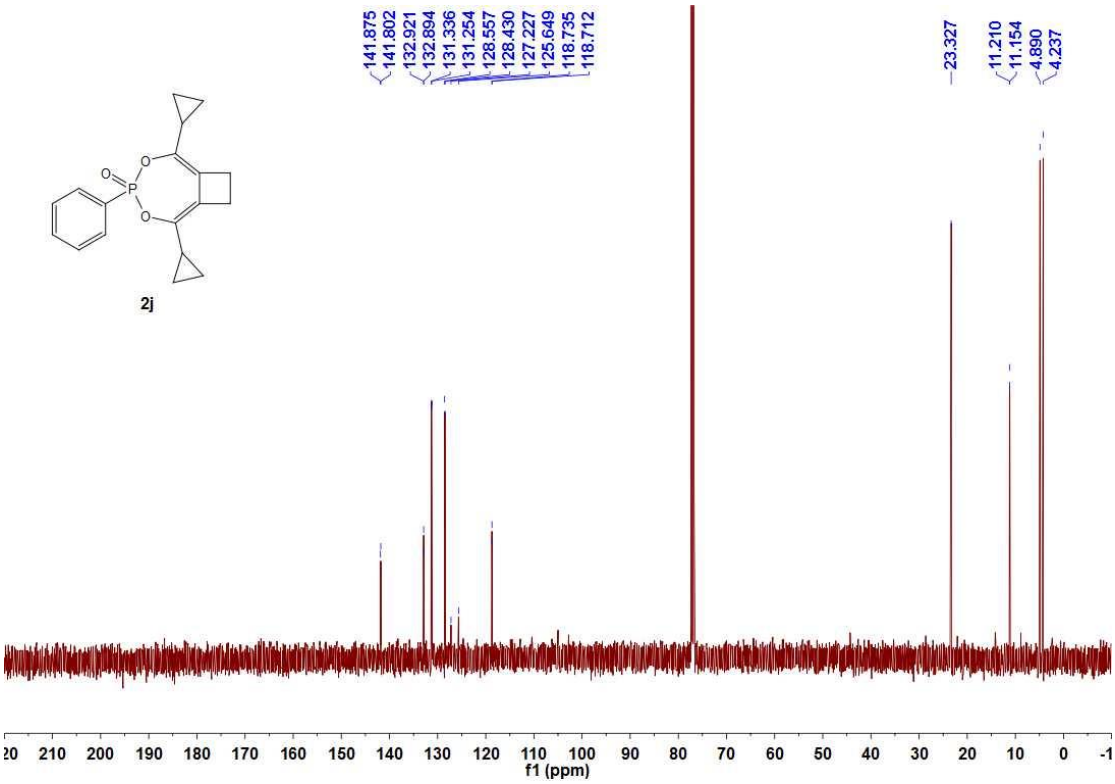
^{31}P NMR of **2i**



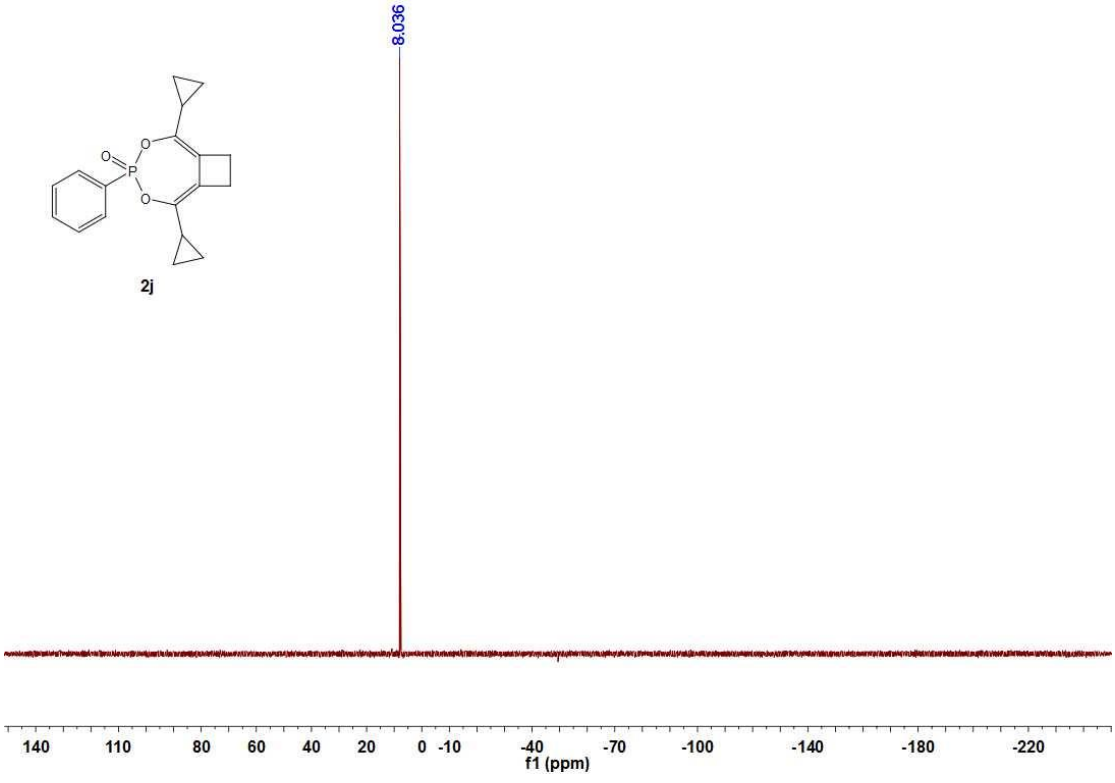
^{1}H NMR of **2j**



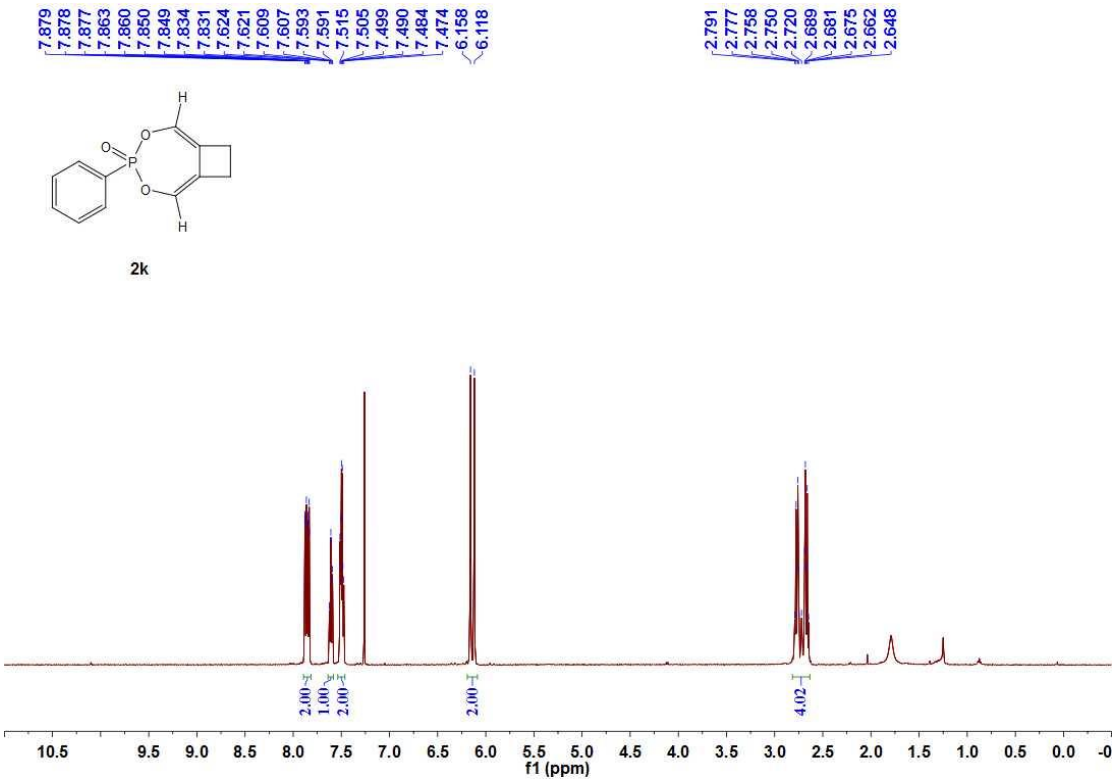
^{13}C NMR of **2j**



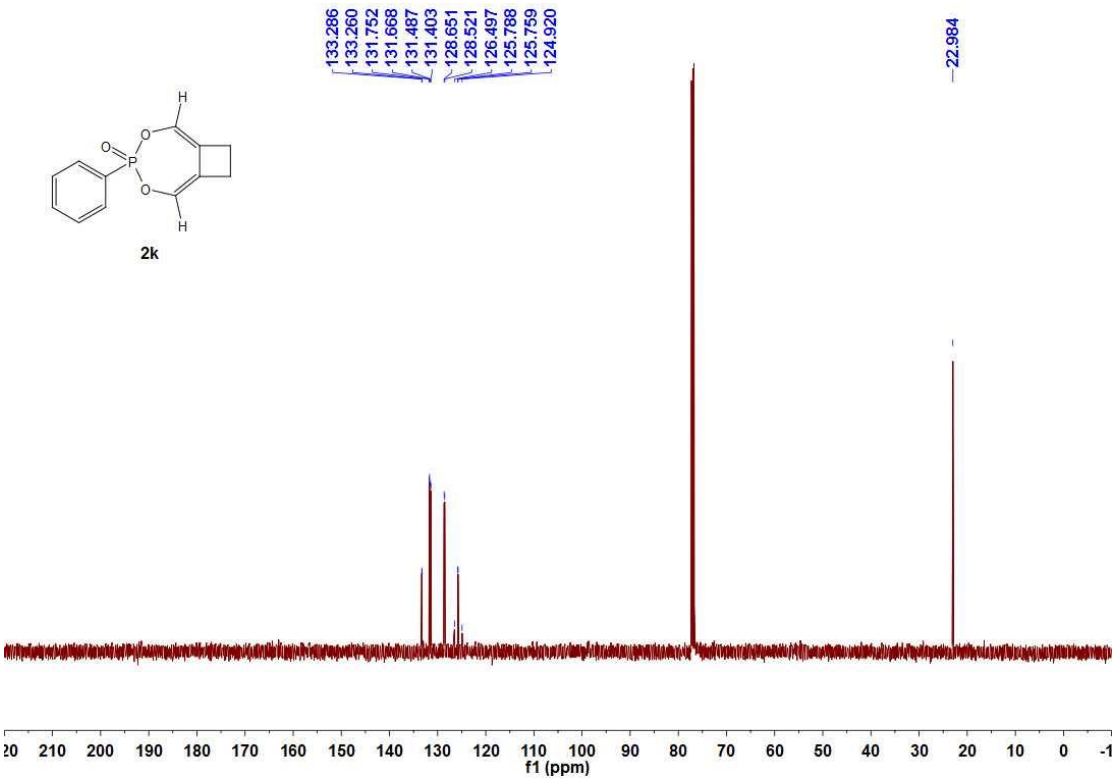
^{31}P NMR of **2j**



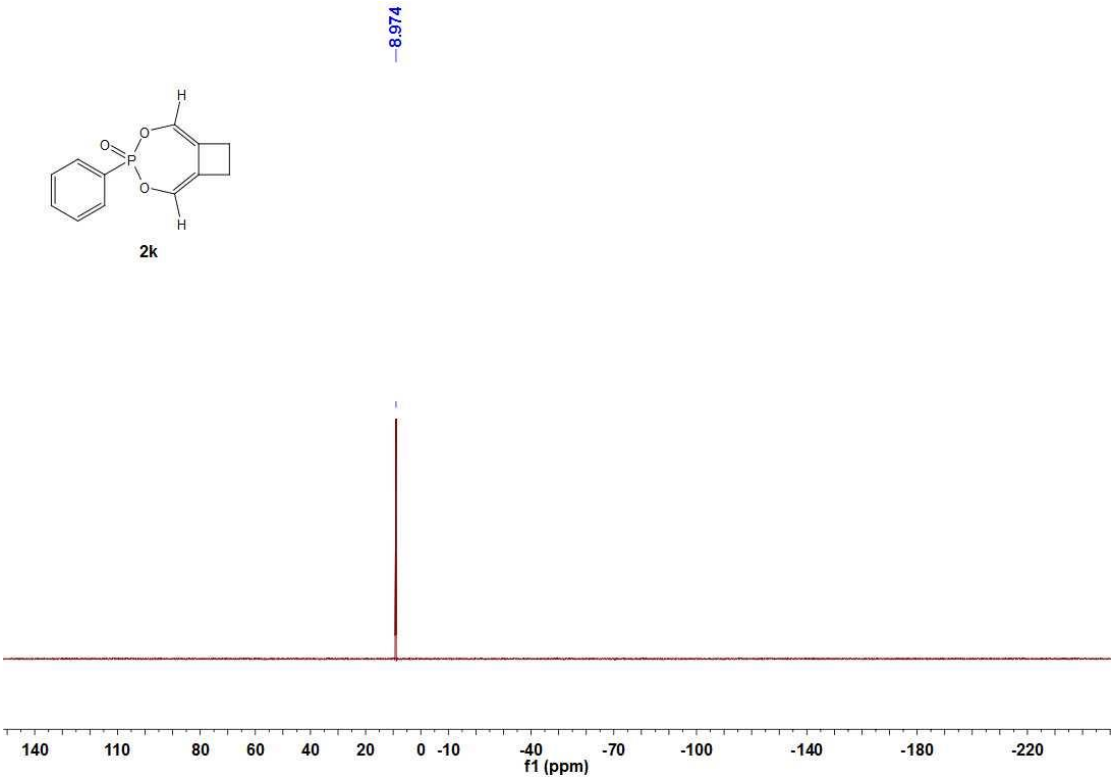
^{1}H NMR of **2k**



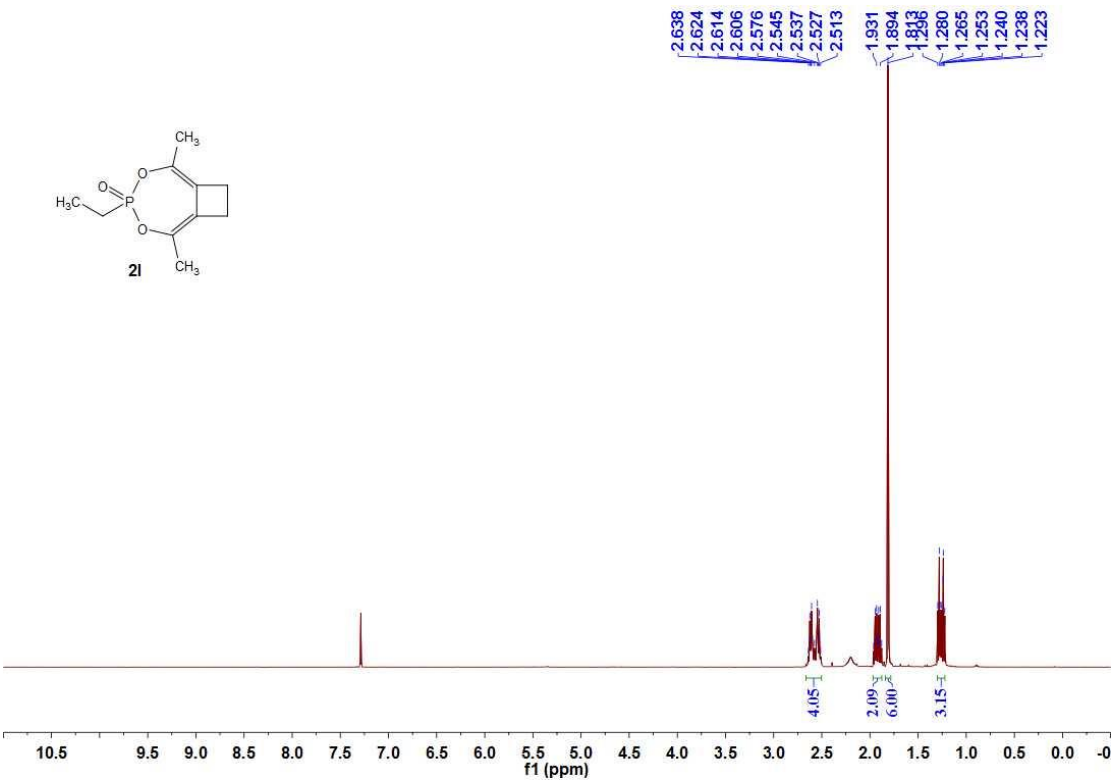
^{13}C NMR of **2k**



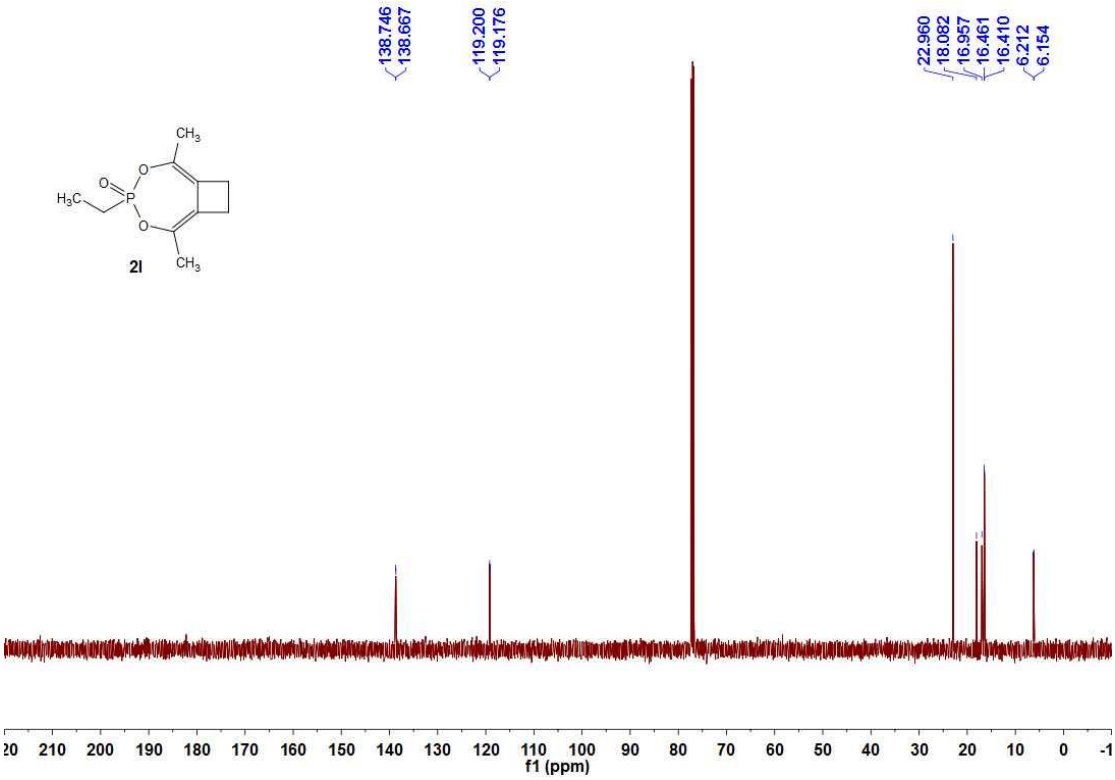
^{31}P NMR of **2k**



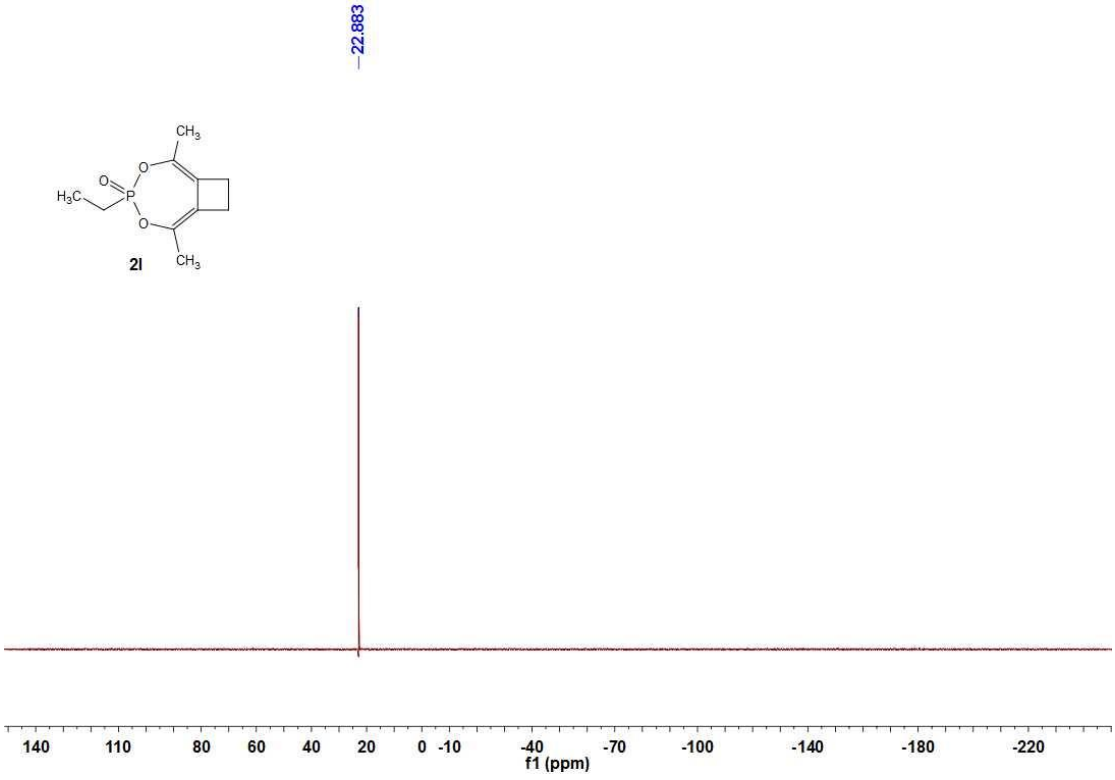
^{1}H NMR of **2l**



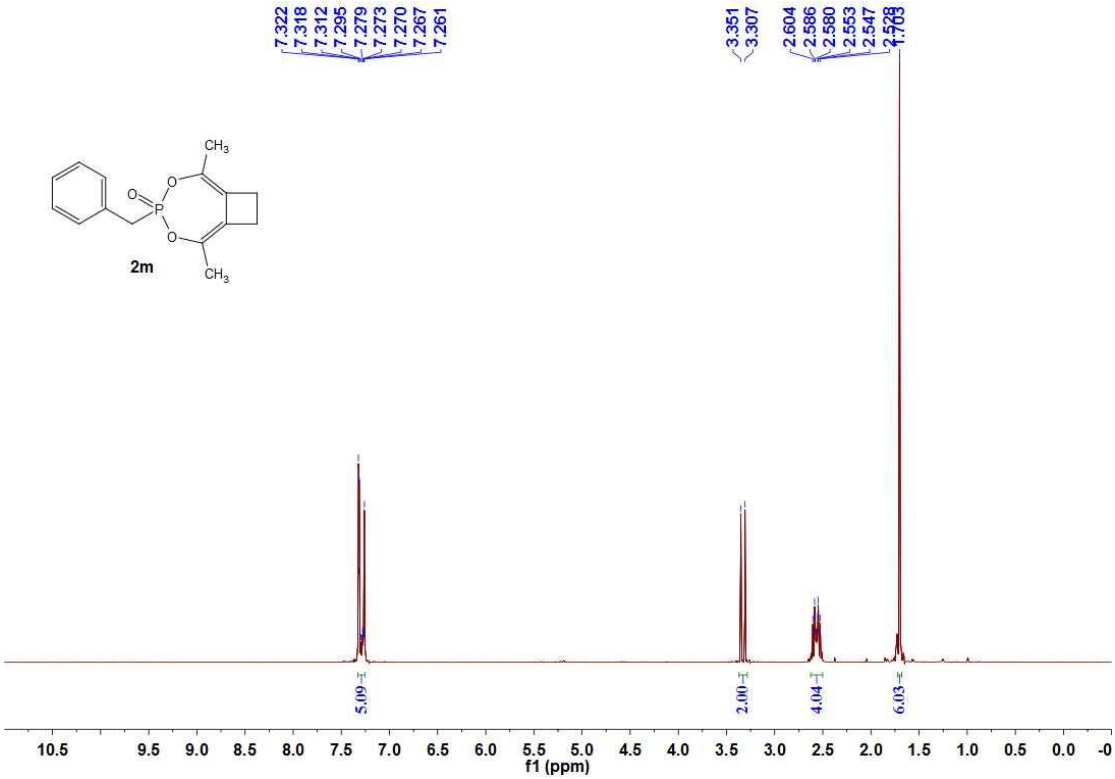
^{13}C NMR of **2l**



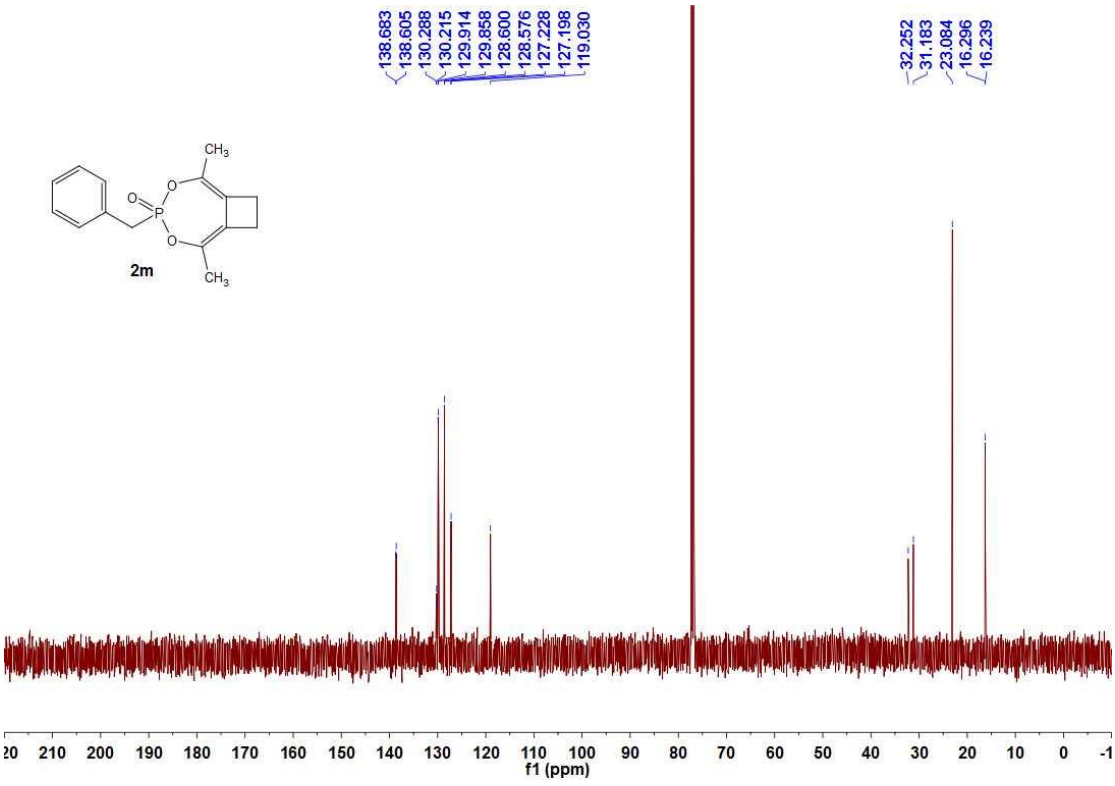
^{31}P NMR of **2l**



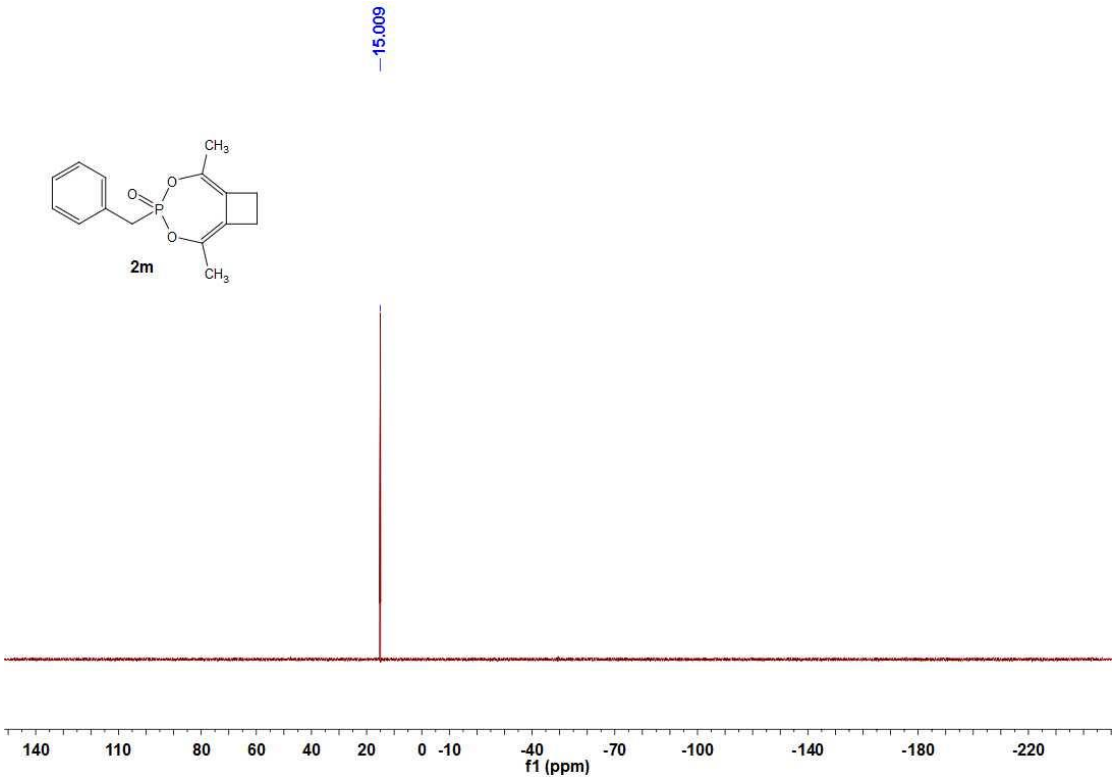
^{1}H NMR of **2m**



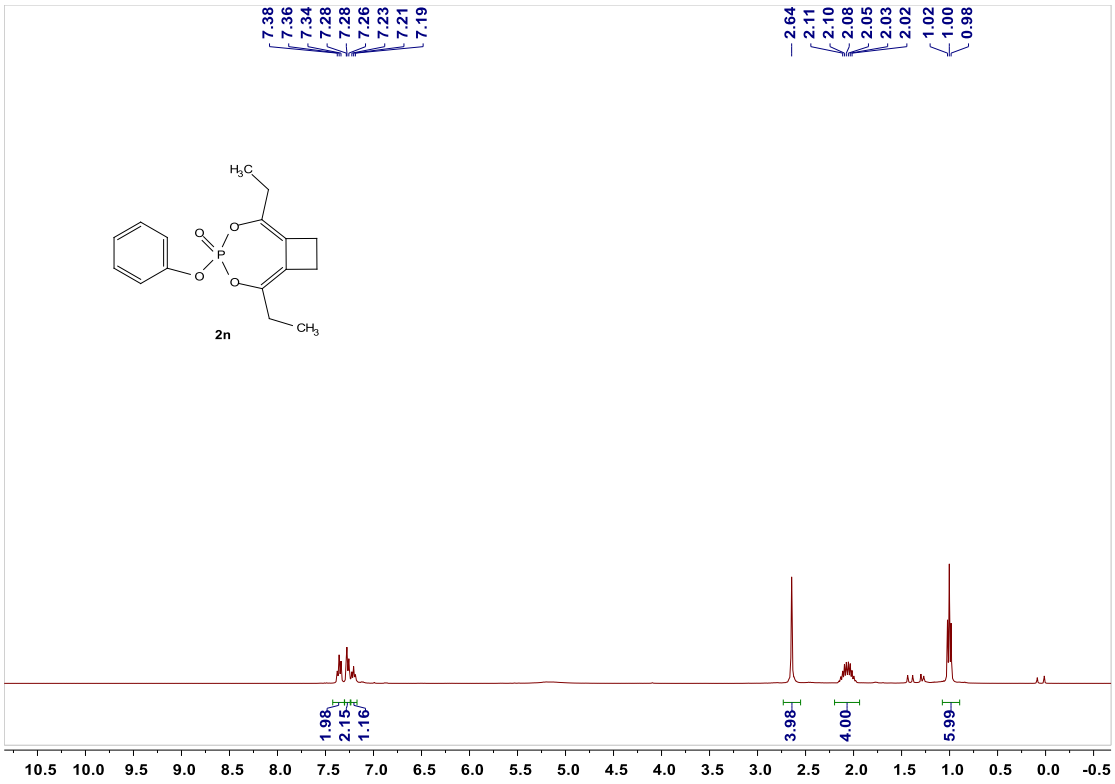
^{13}C NMR of **2m**



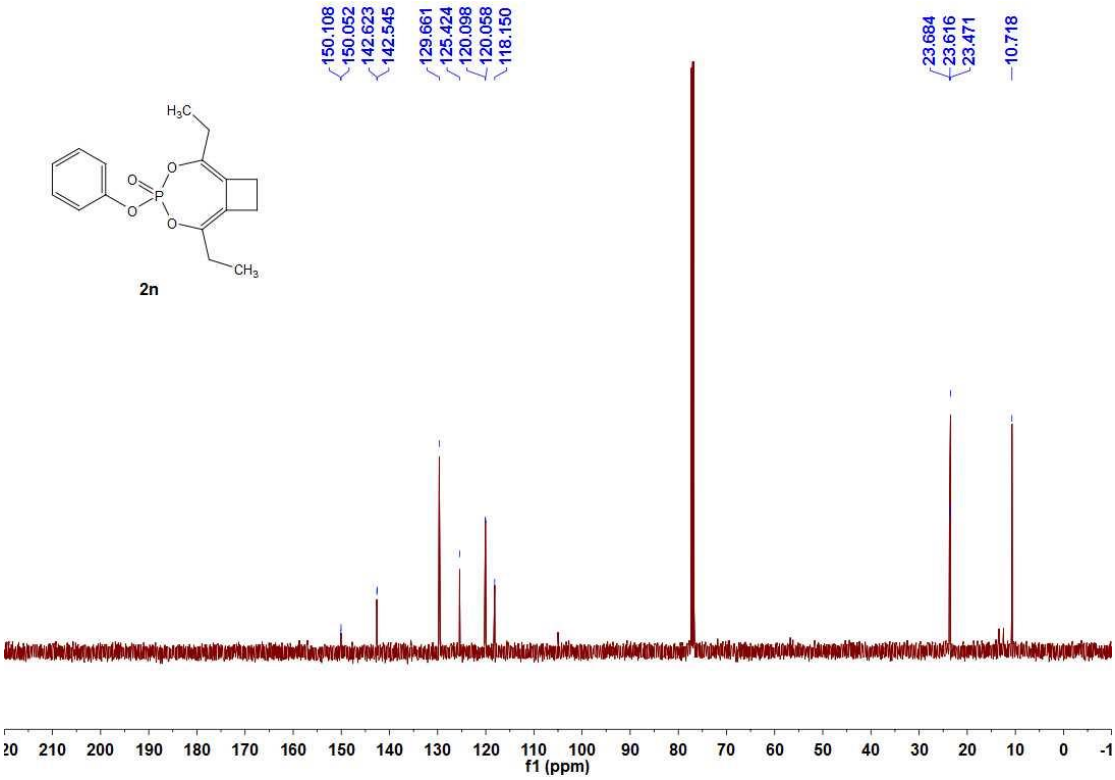
^{31}P NMR of **2m**



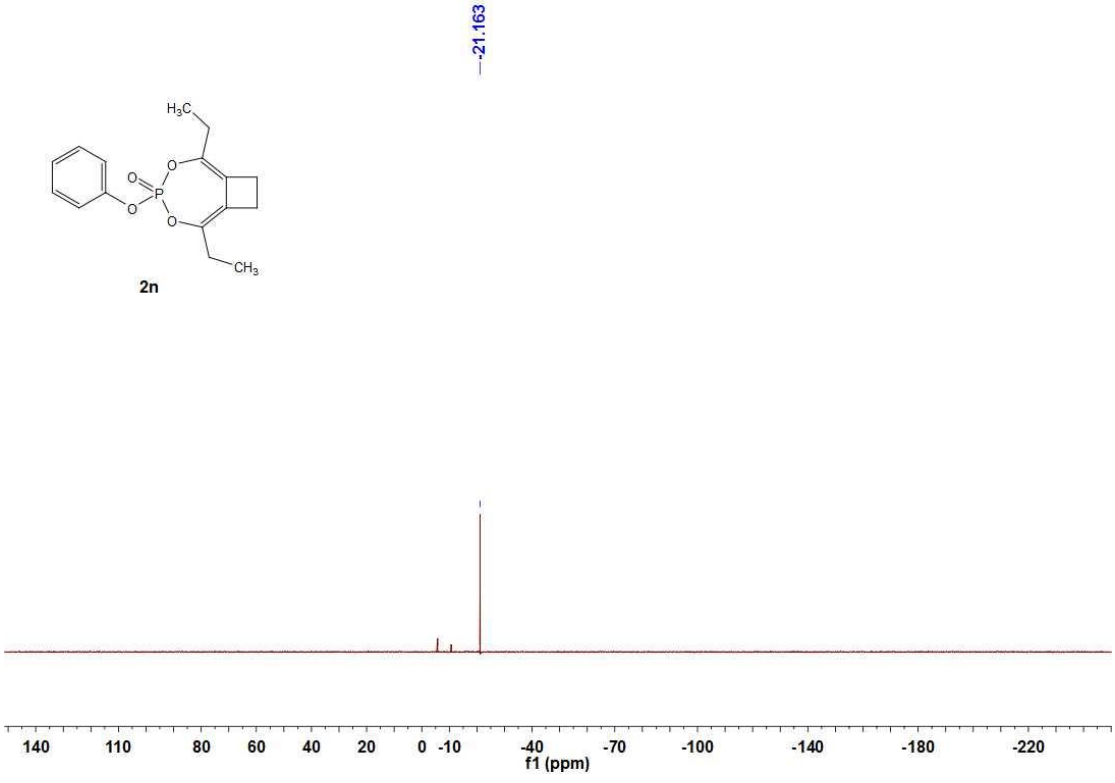
^{1}H NMR of **2n**



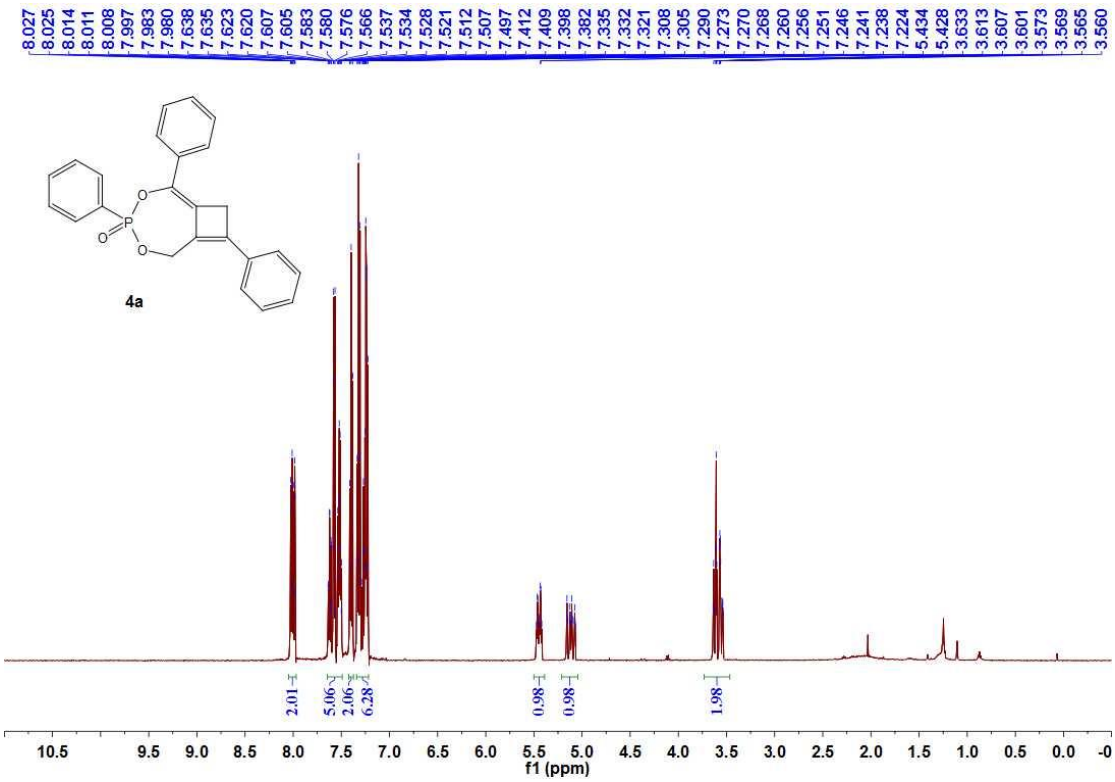
^{13}C NMR of **2n**



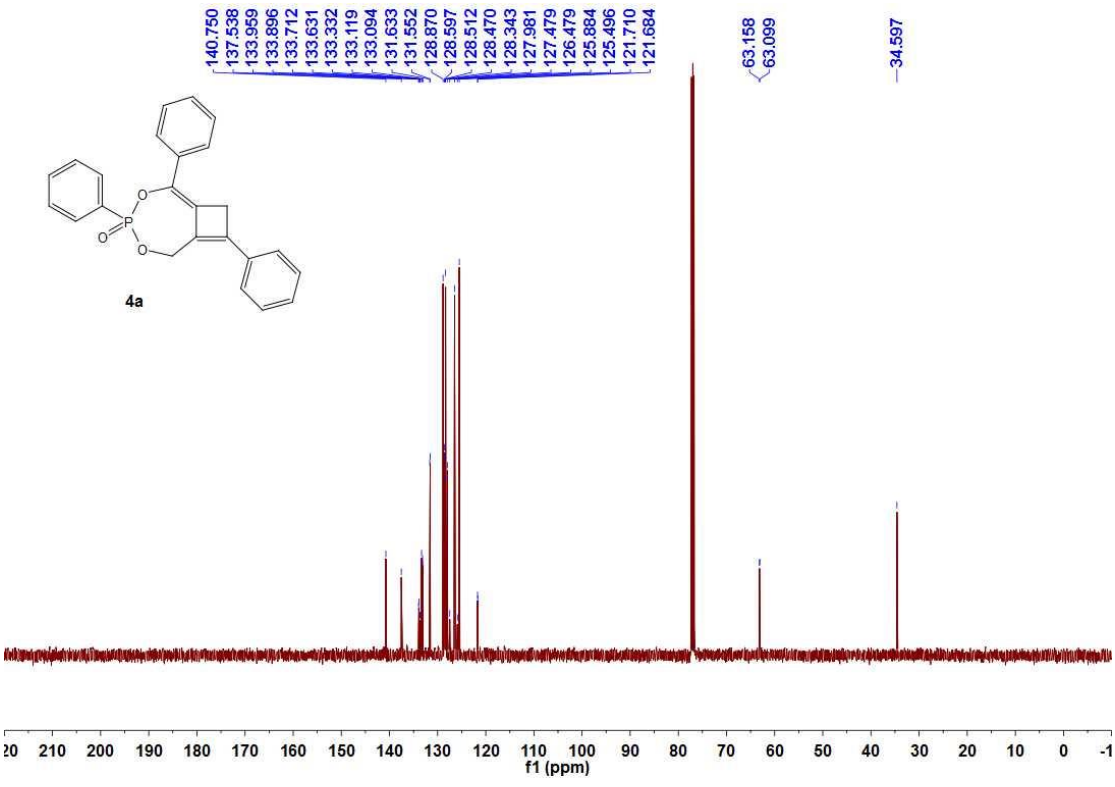
^{31}P NMR of **2n**



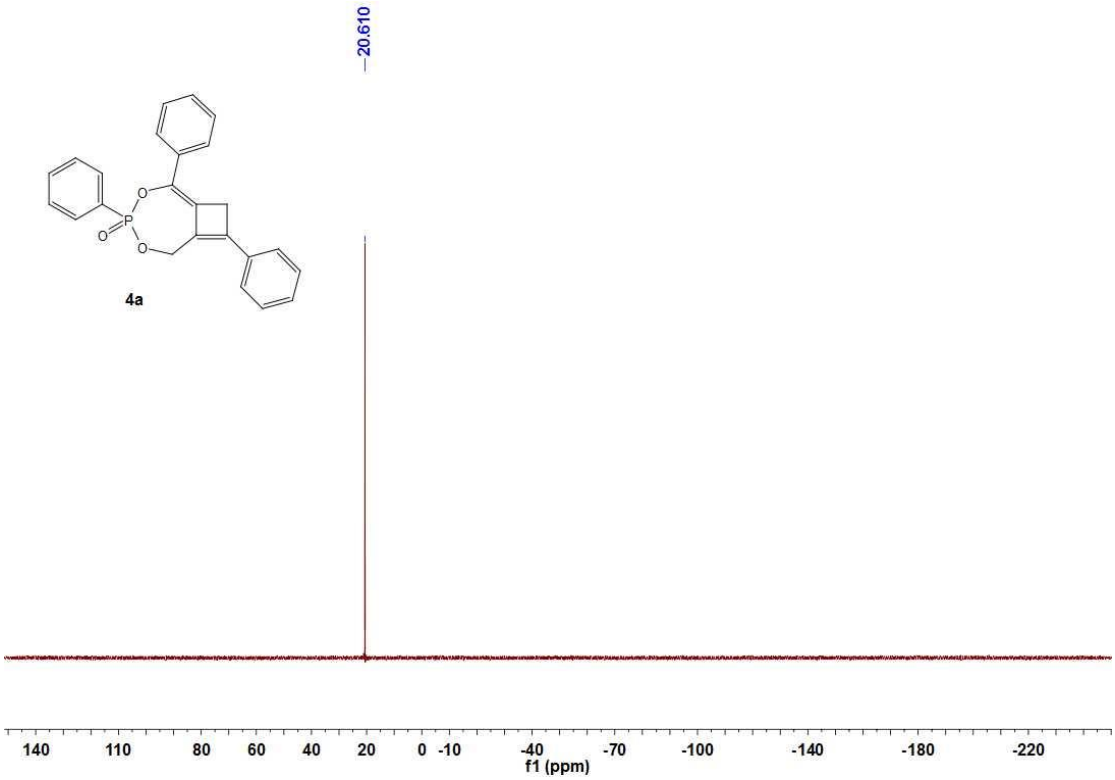
^{1}H NMR of **4a**



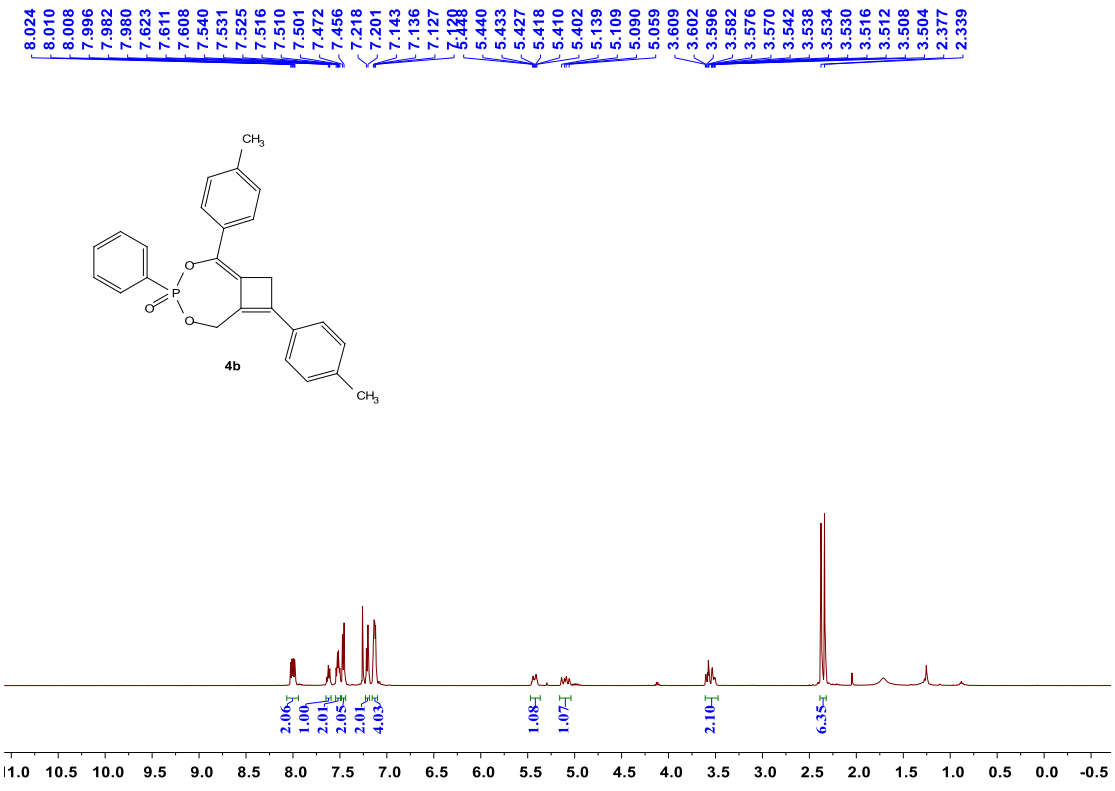
^{13}C NMR of **4a**



^{31}P NMR of **4a**



^{1}H NMR of **4b**



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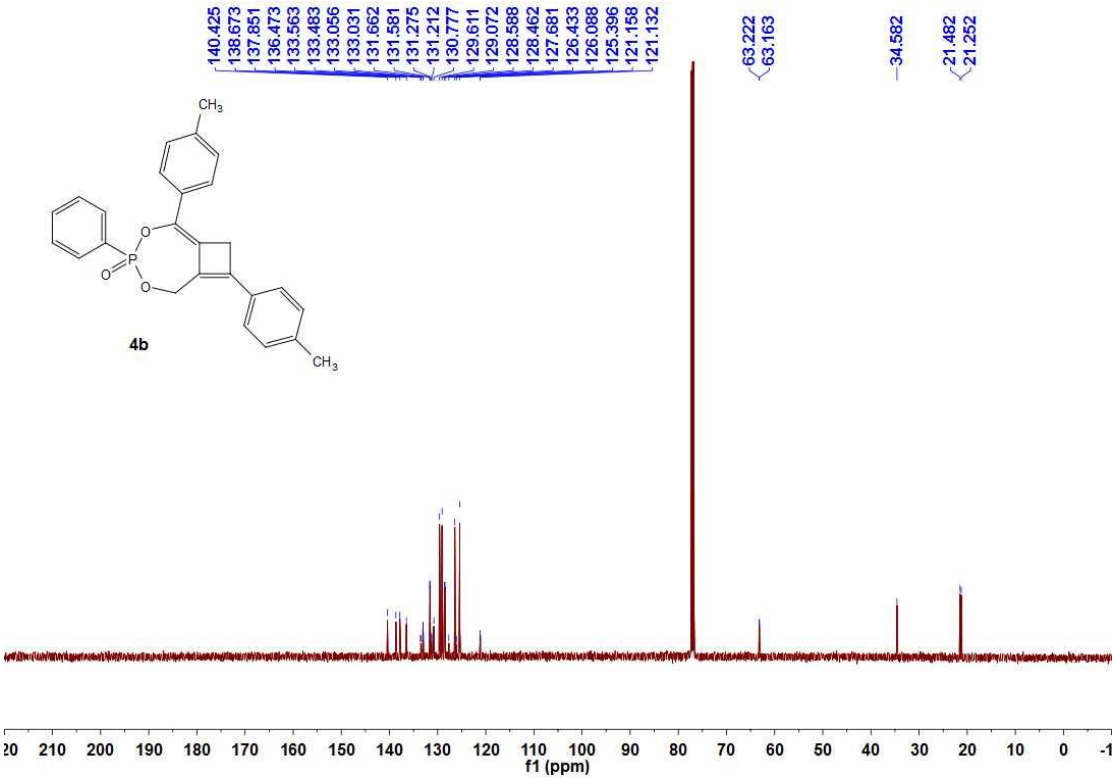

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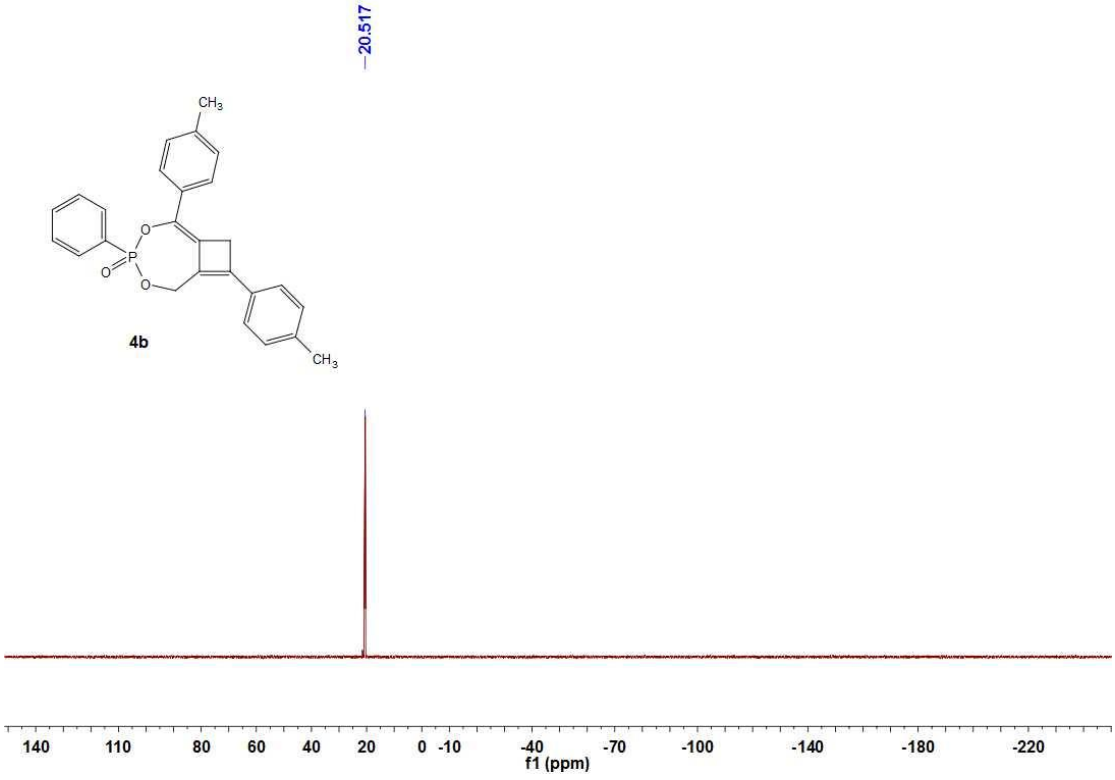

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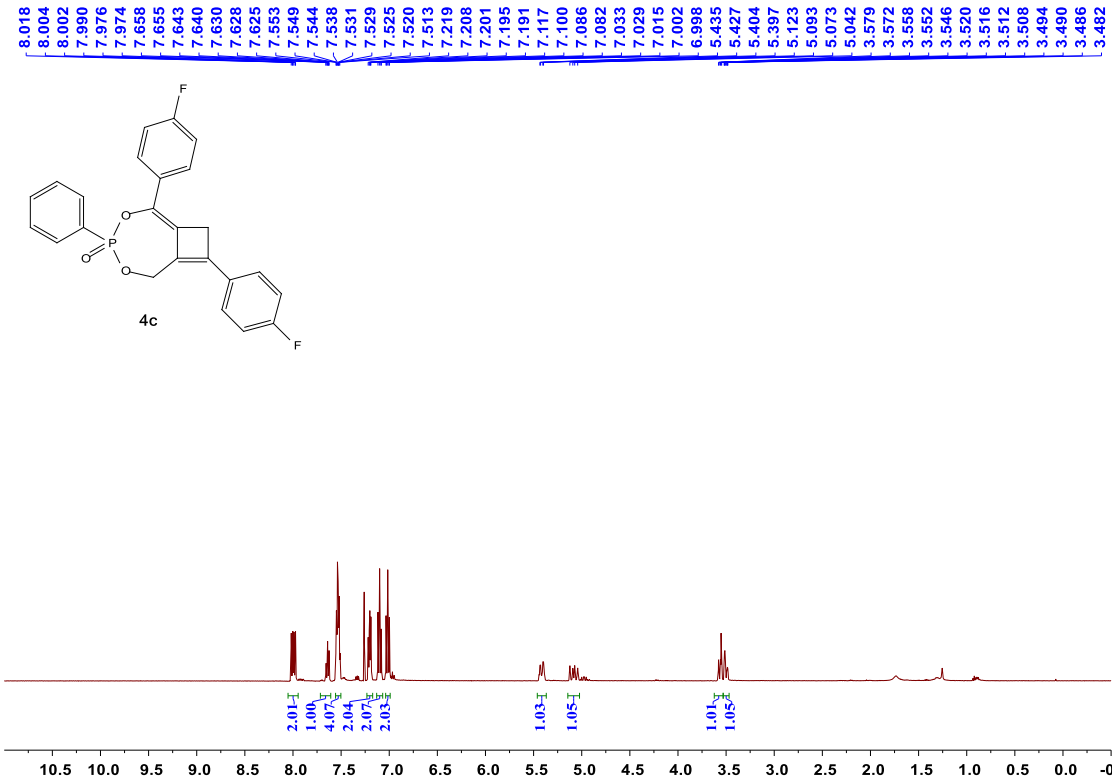
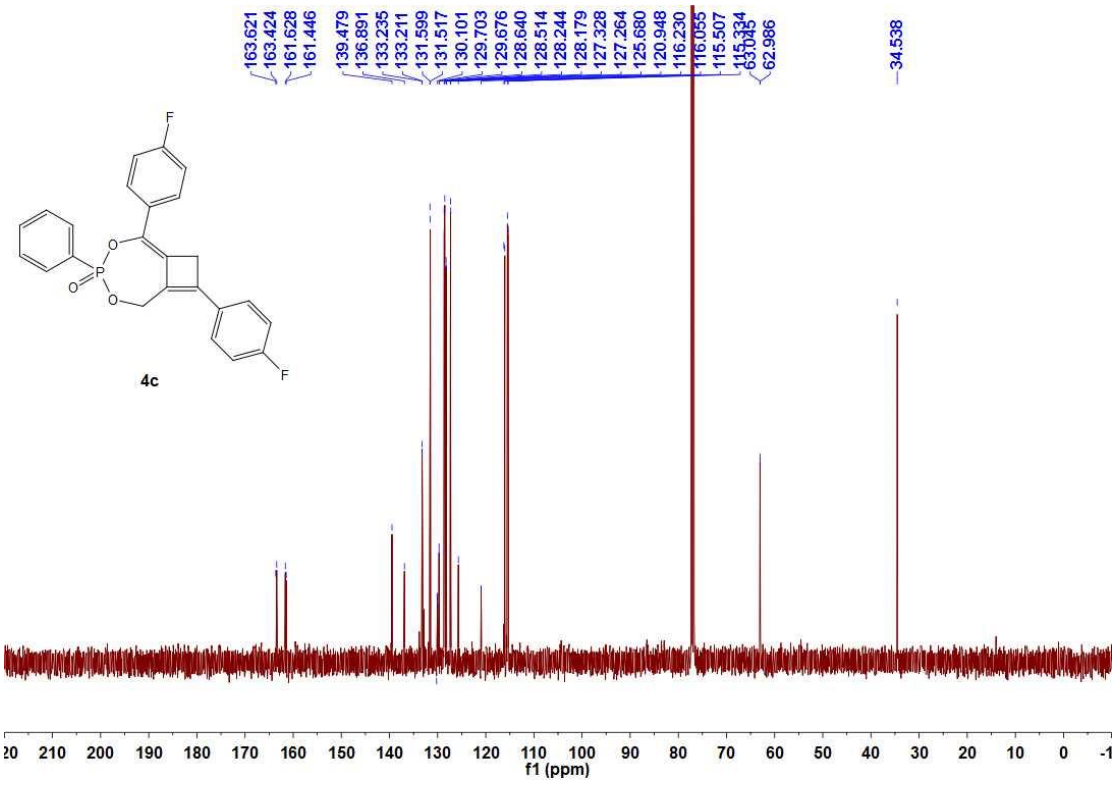


^{13}C NMR of **4c**



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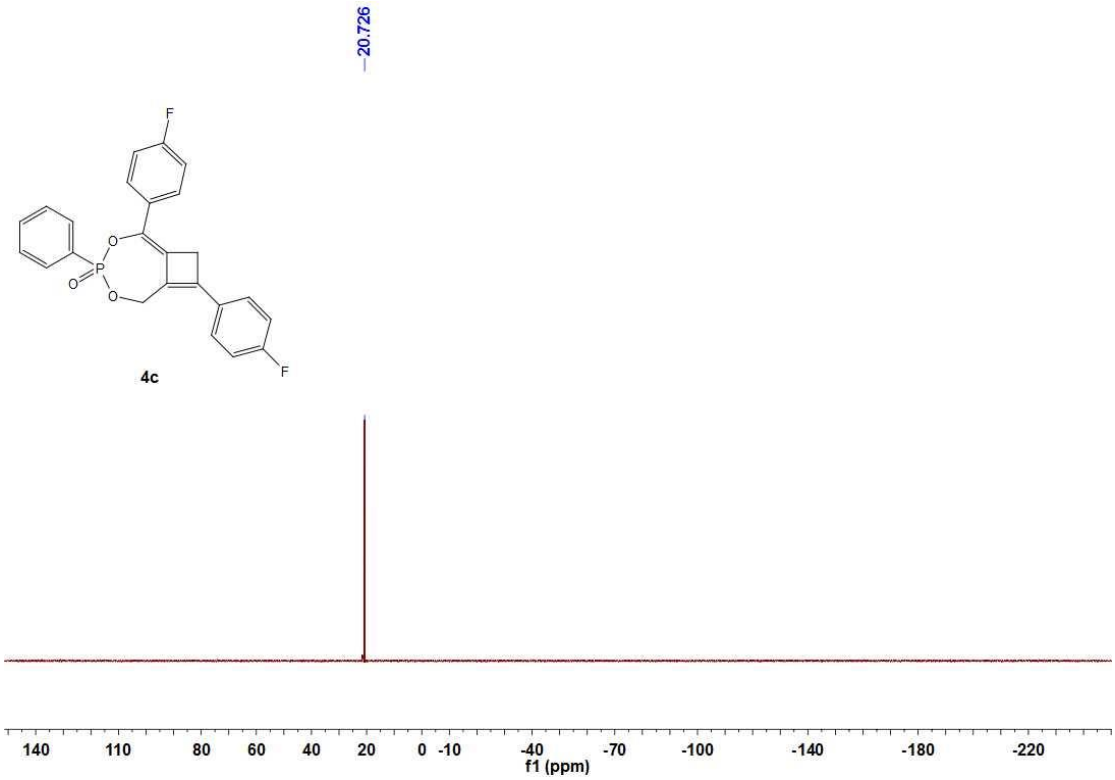

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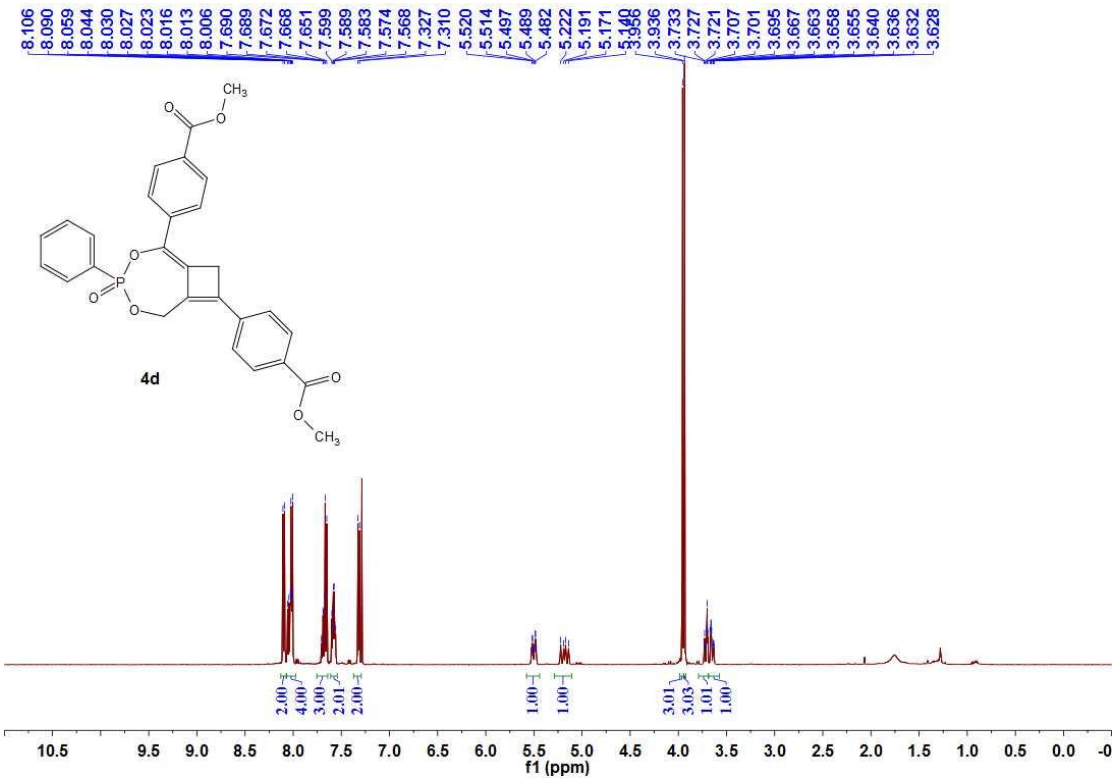

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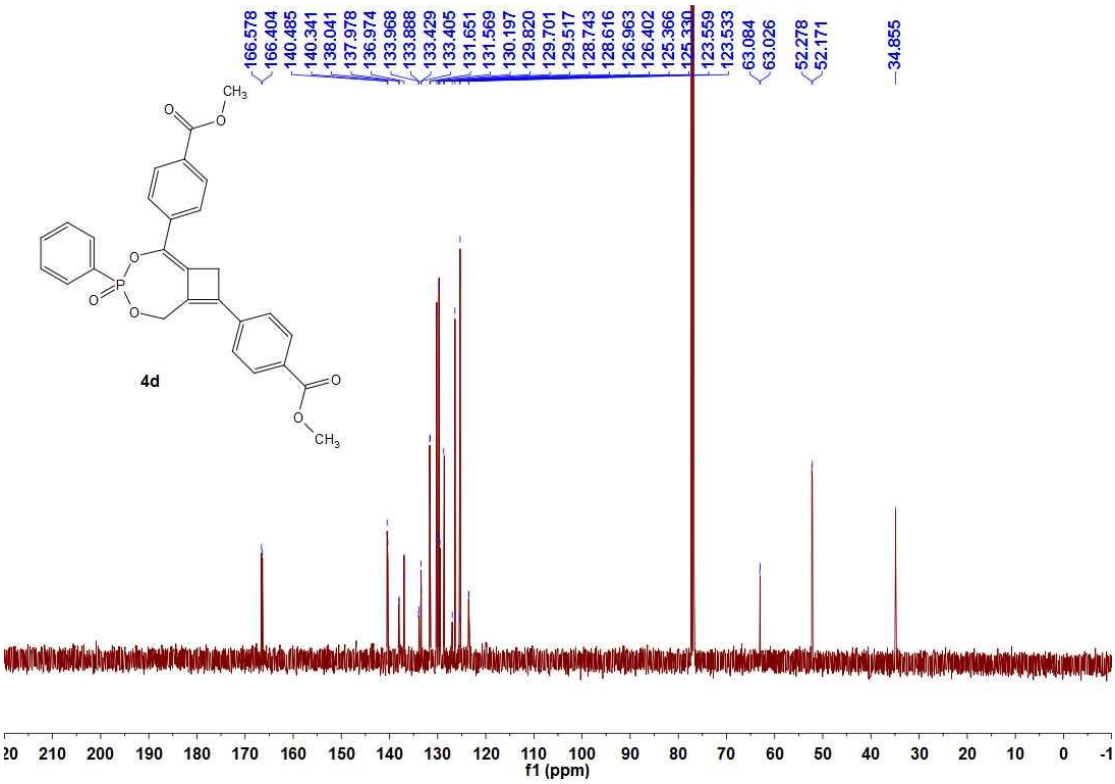

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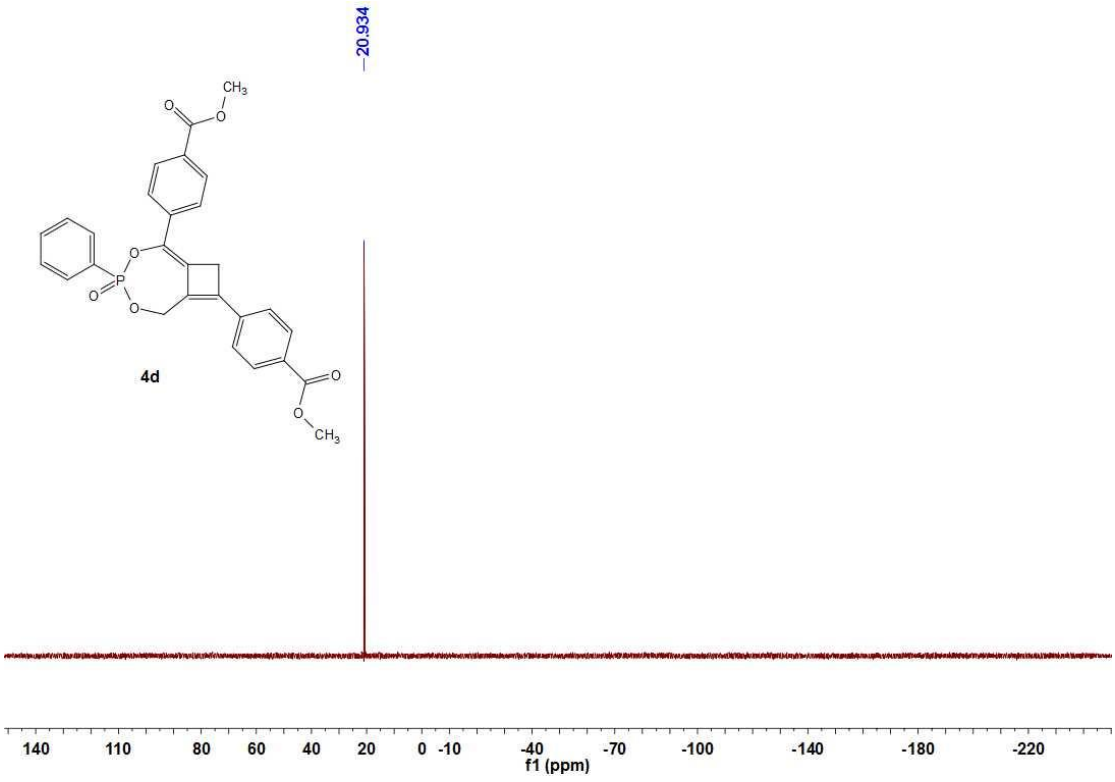

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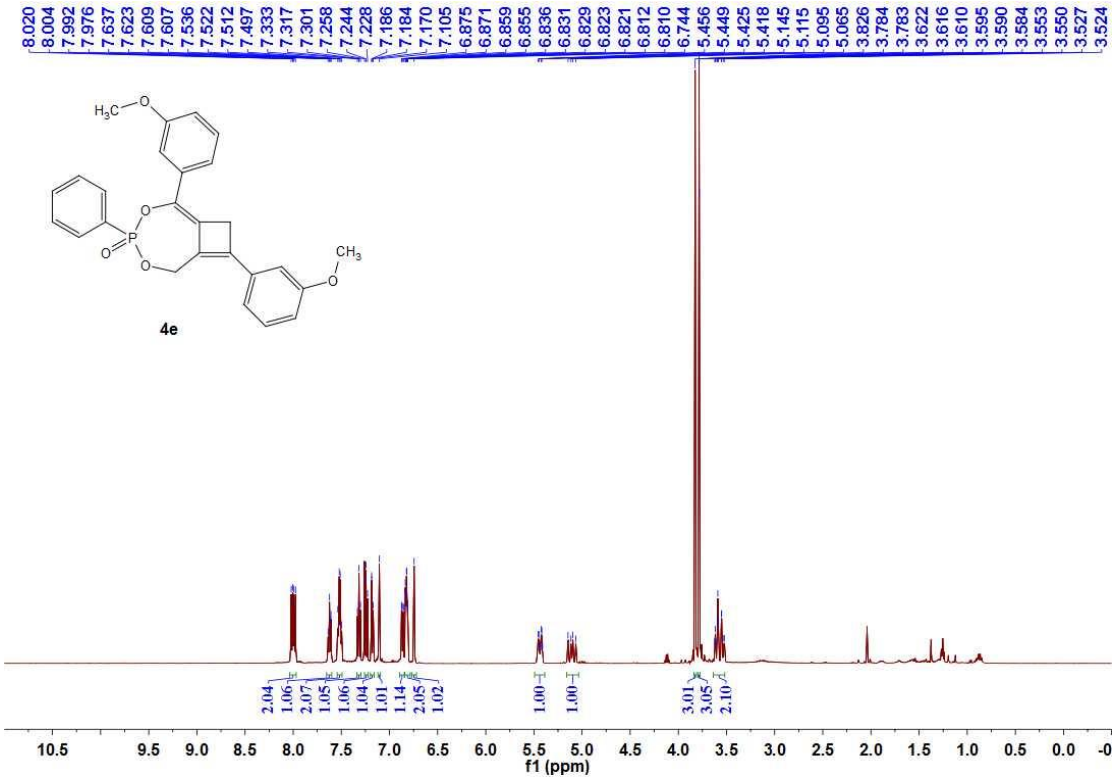
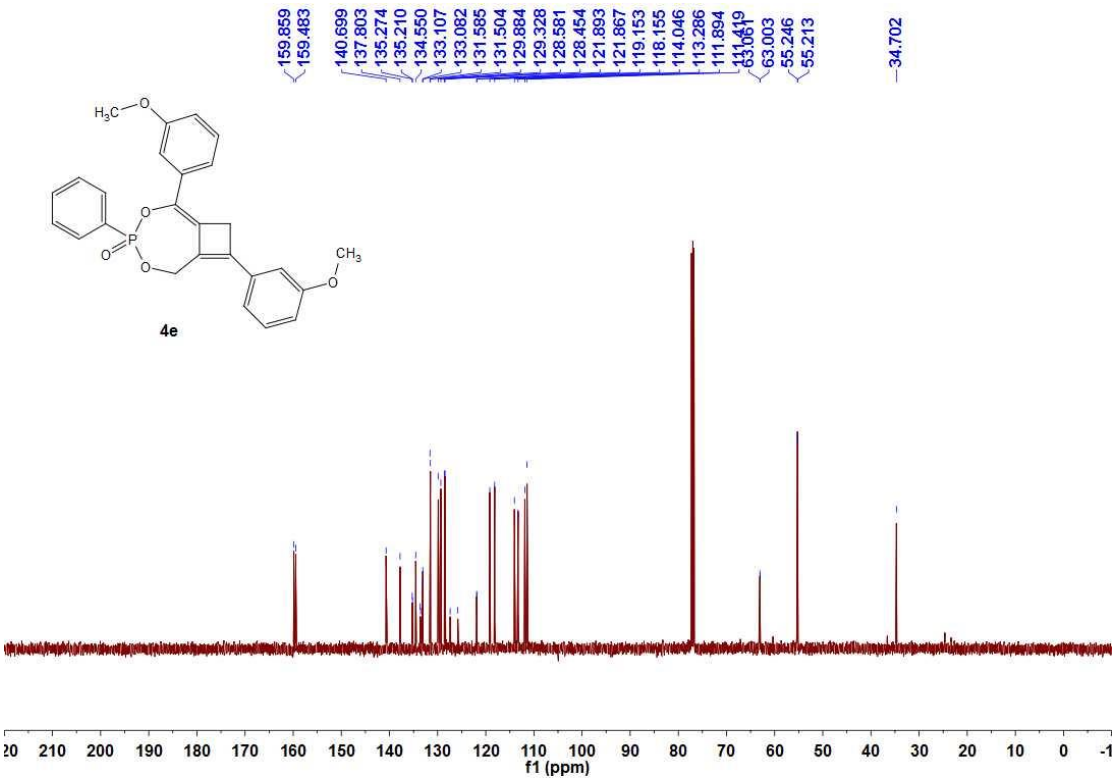
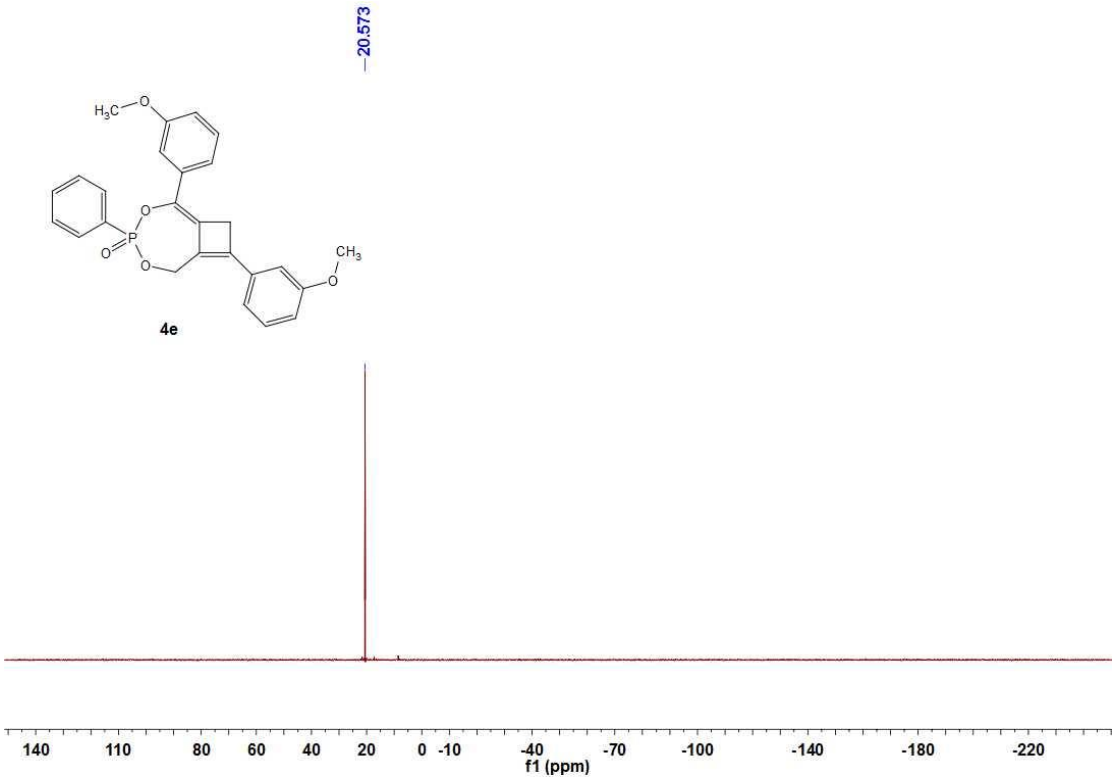


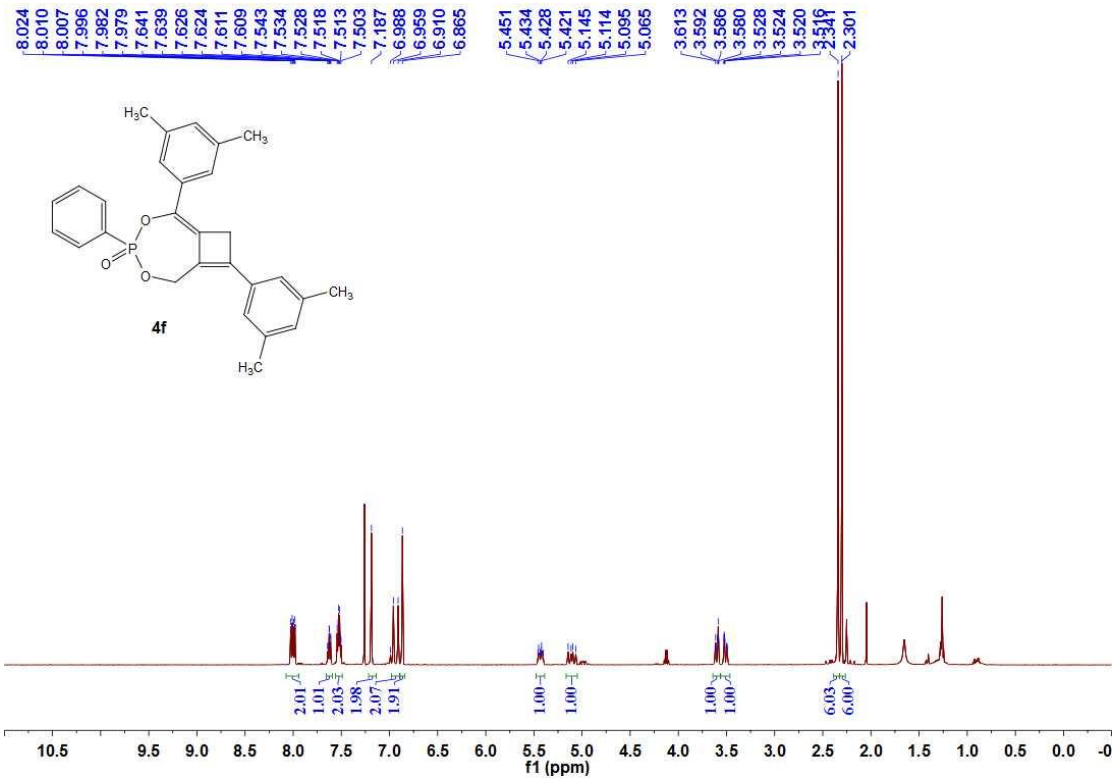
^{13}C NMR of **4e**



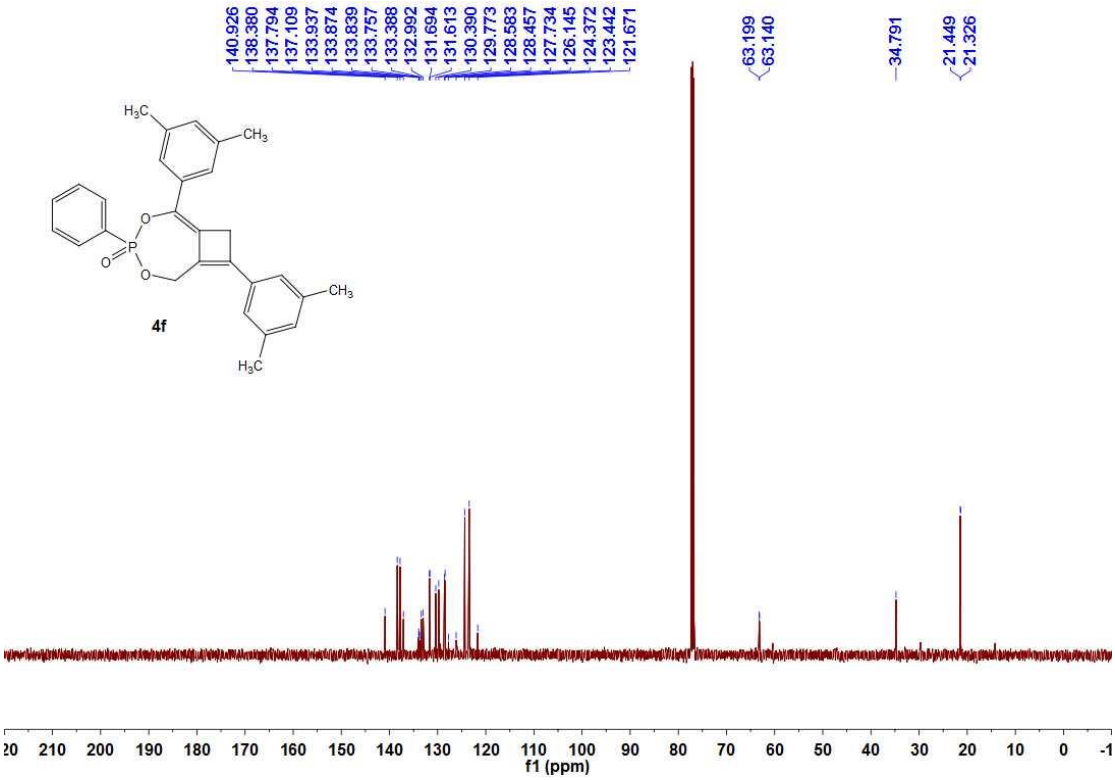
^{31}P NMR of **4e**



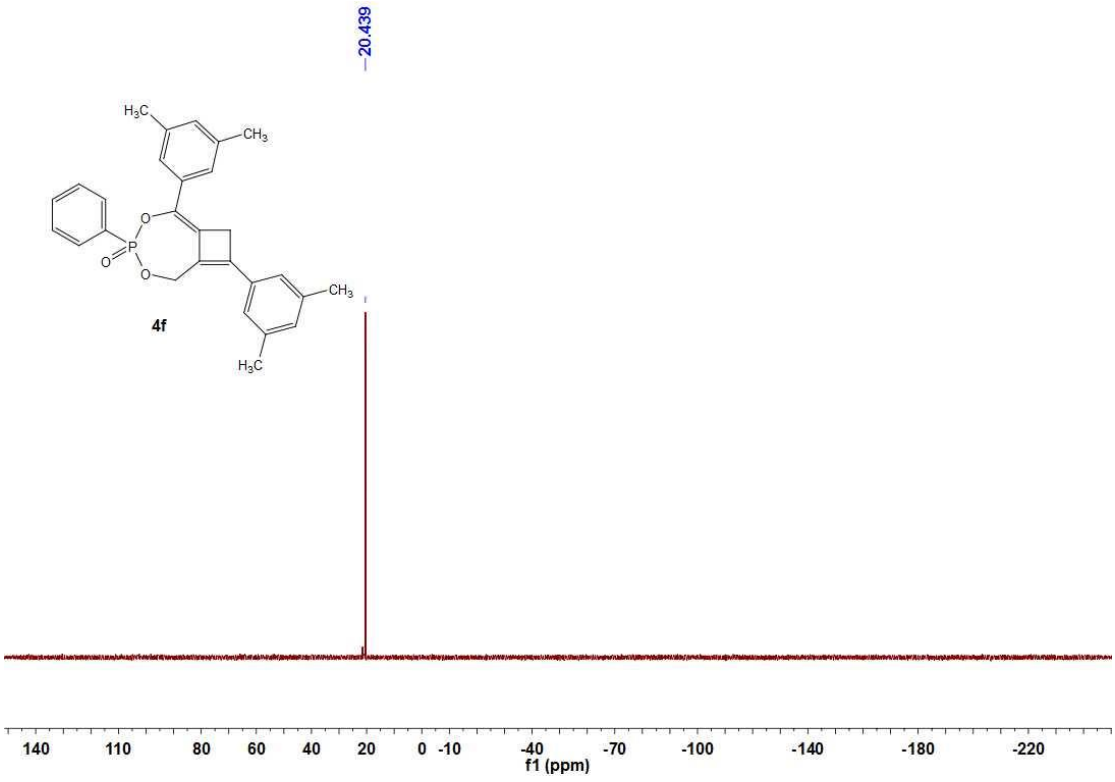
^{1}H NMR of **4f**



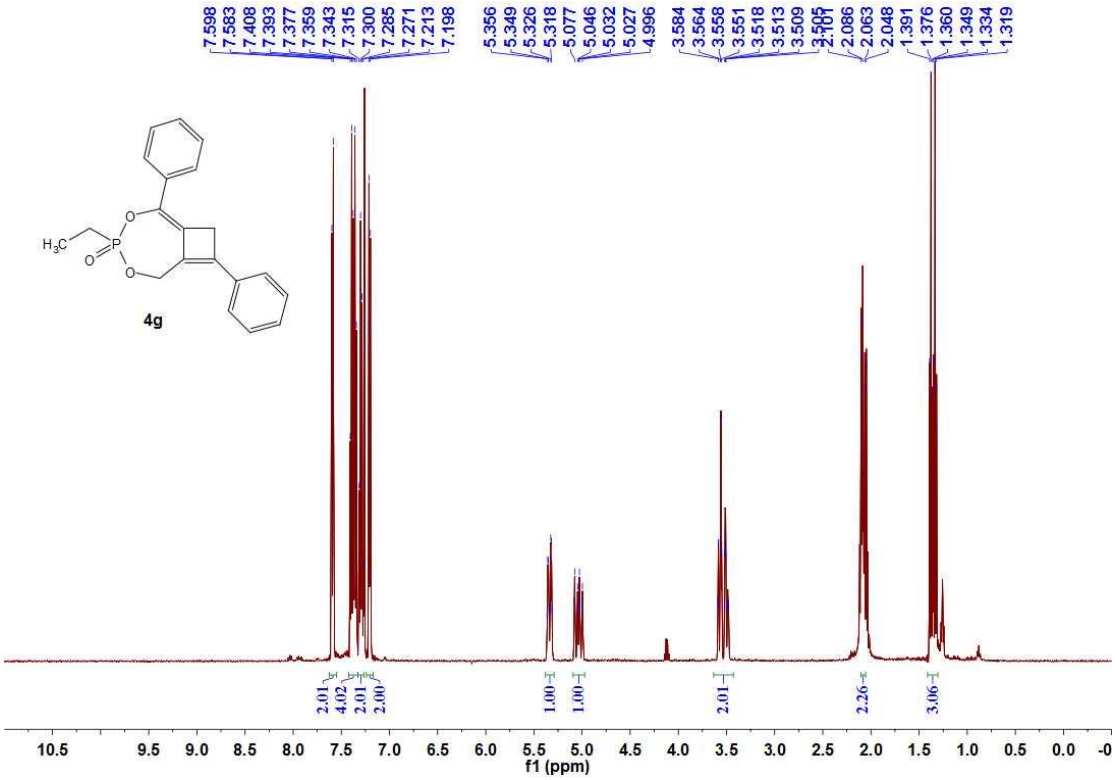
^{13}C NMR of **4f**



^{31}P NMR of **4f**



^{1}H NMR of **4g**



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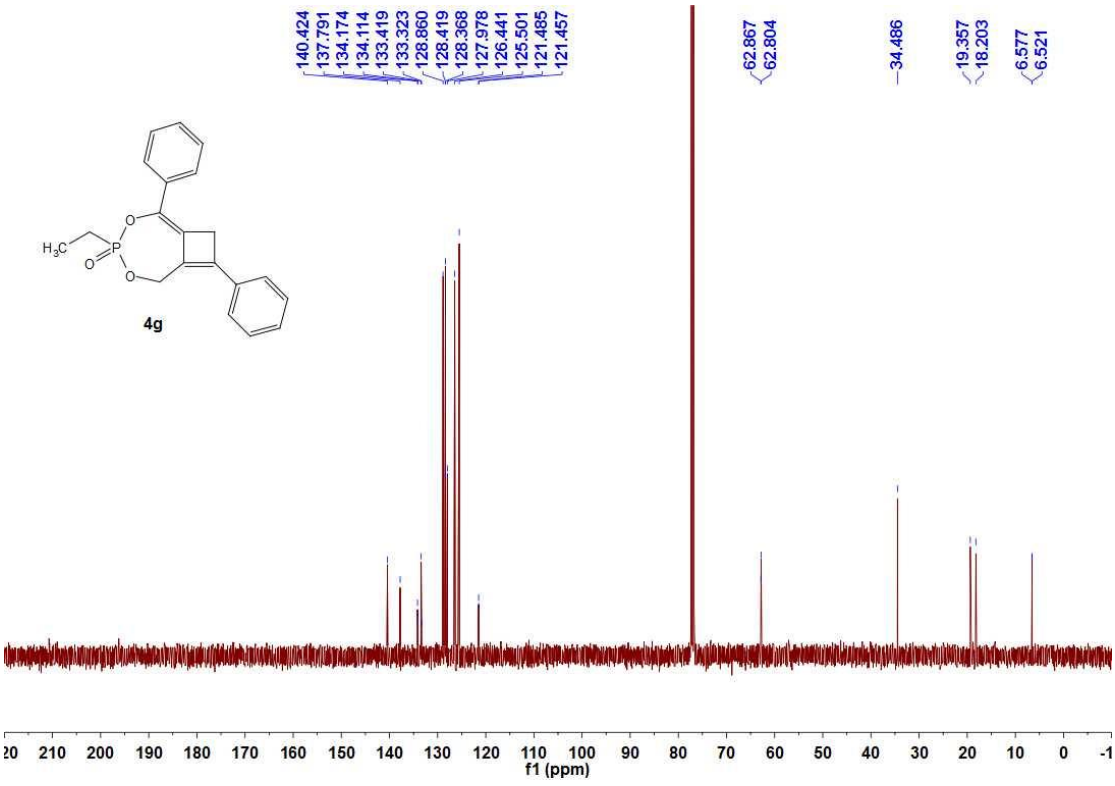

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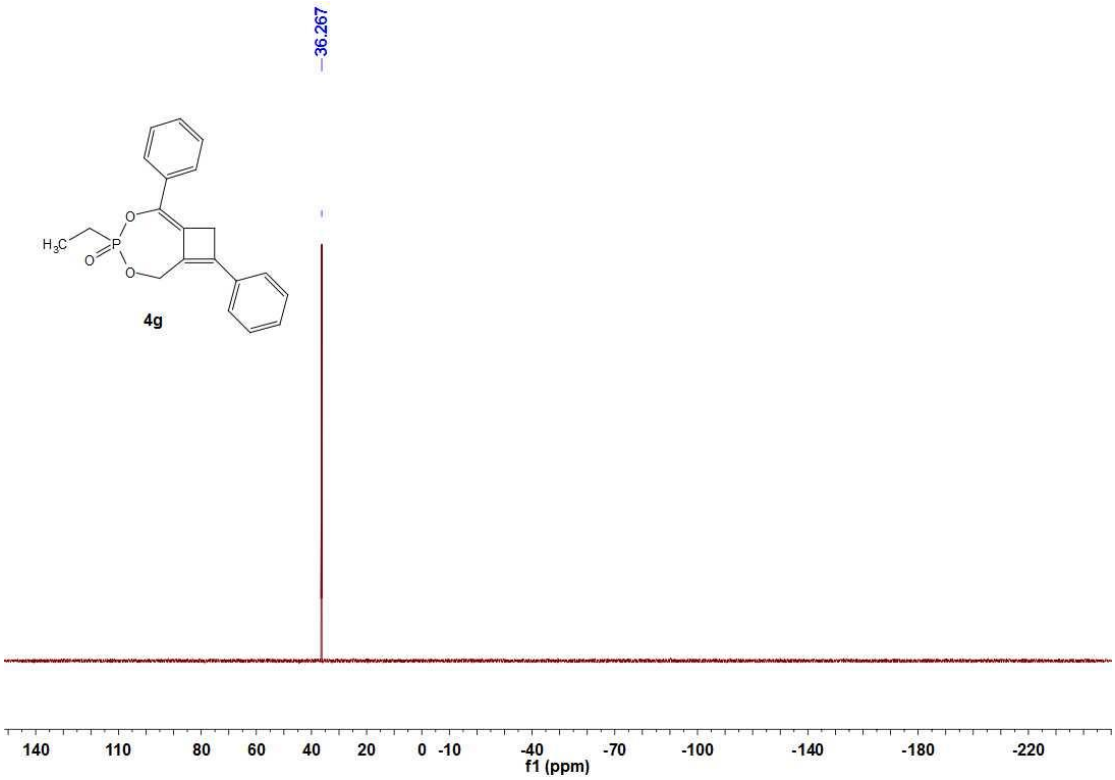
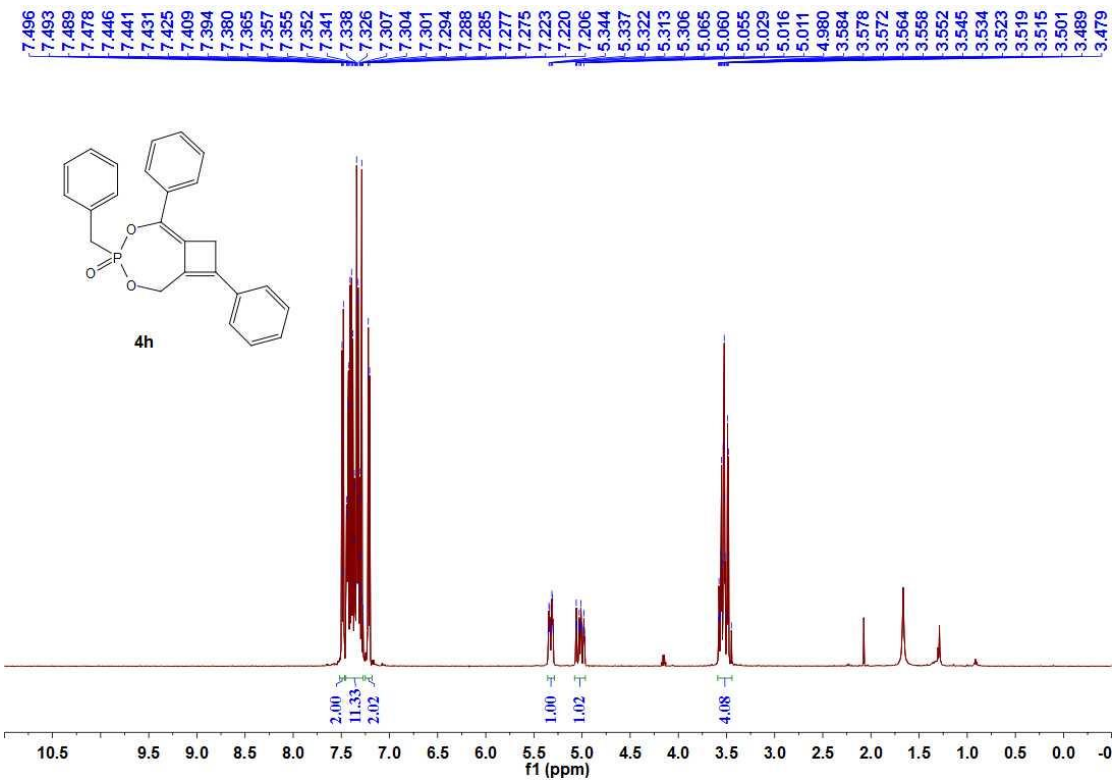


^{1}H NMR of **4h**



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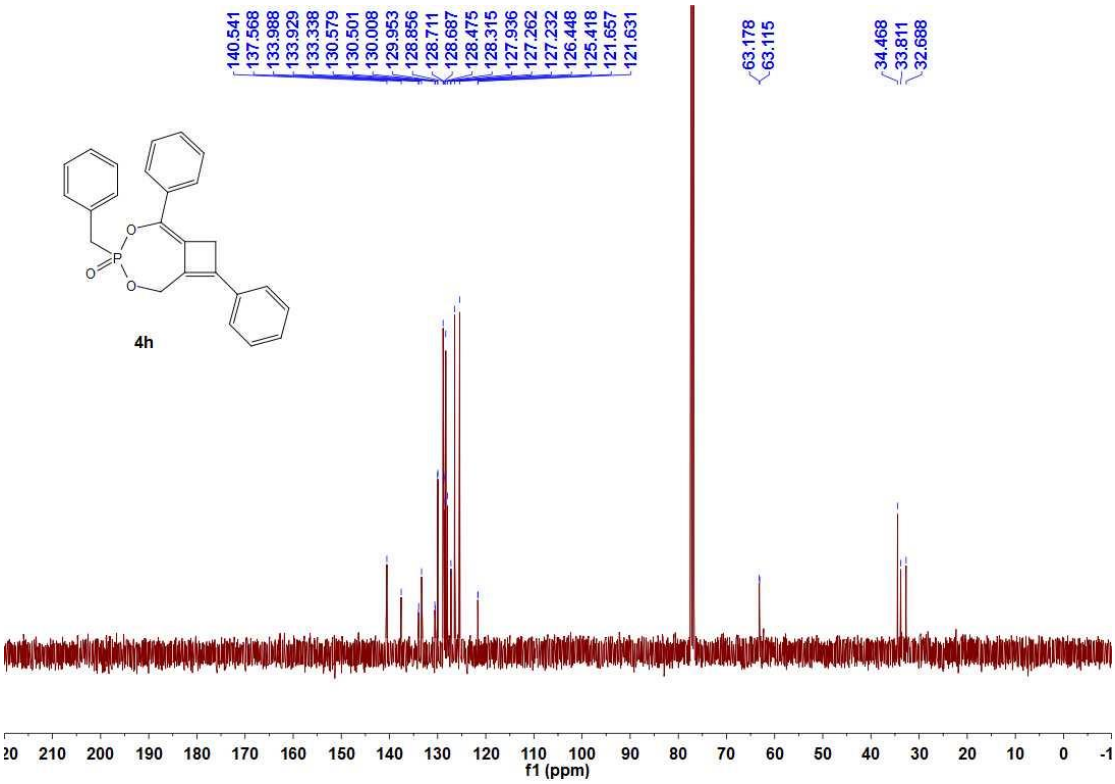

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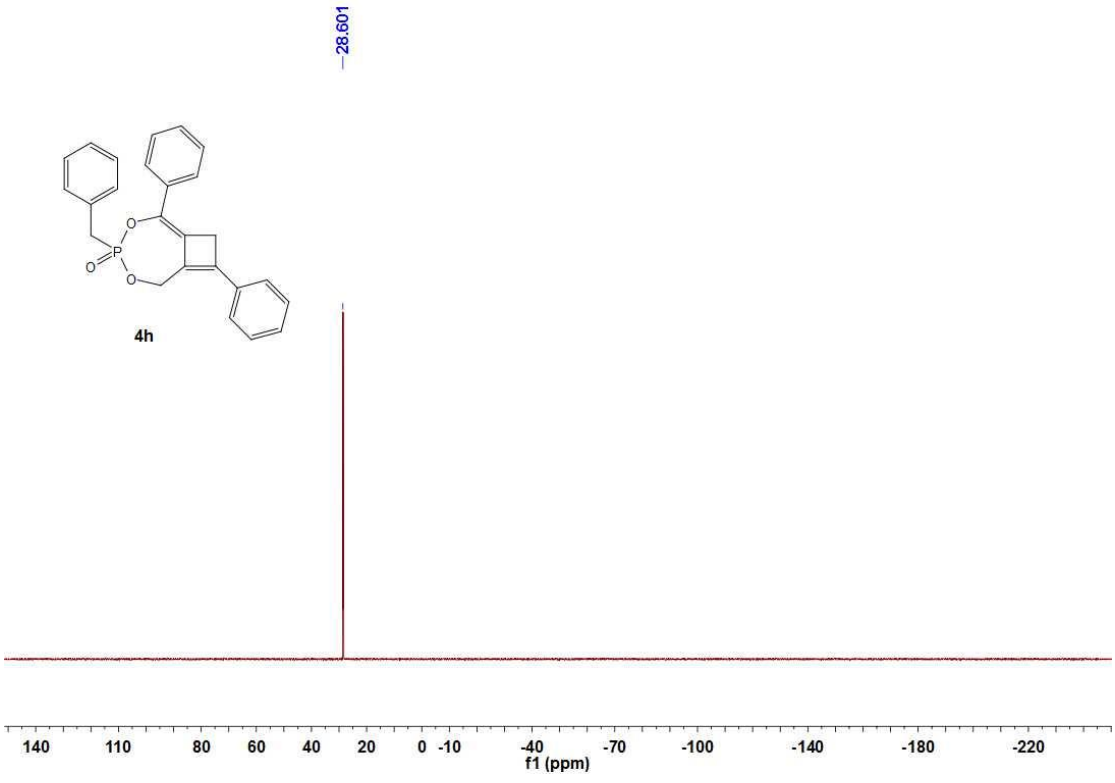
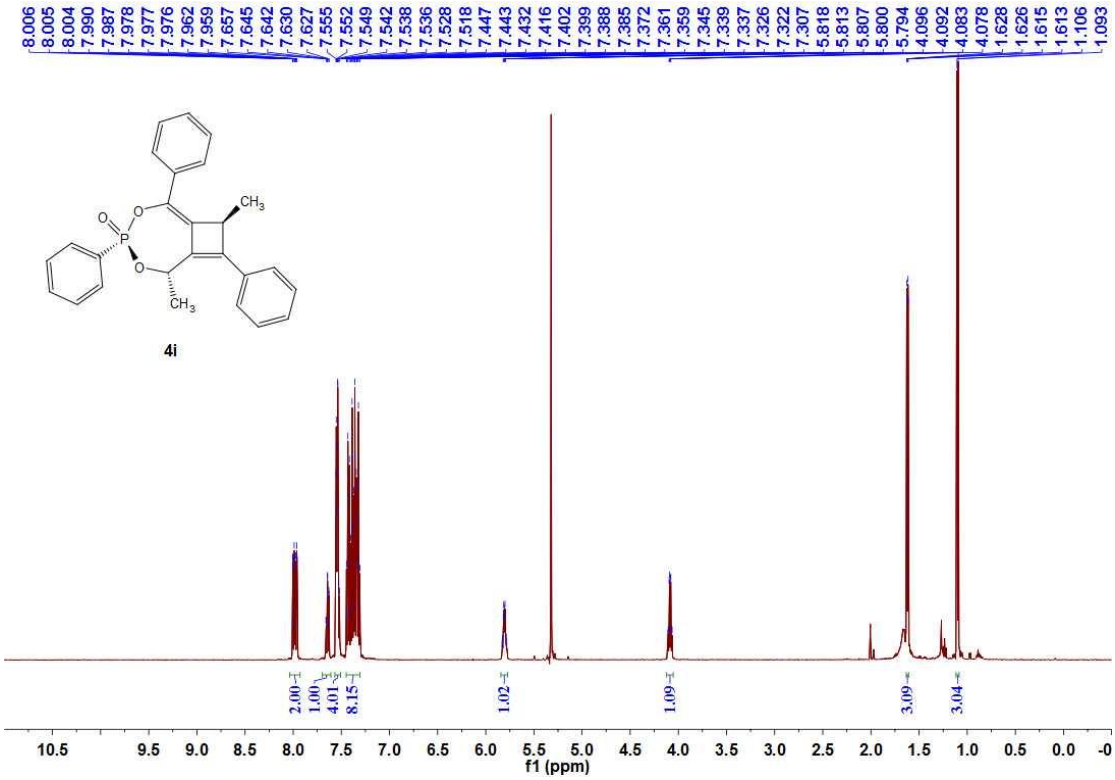
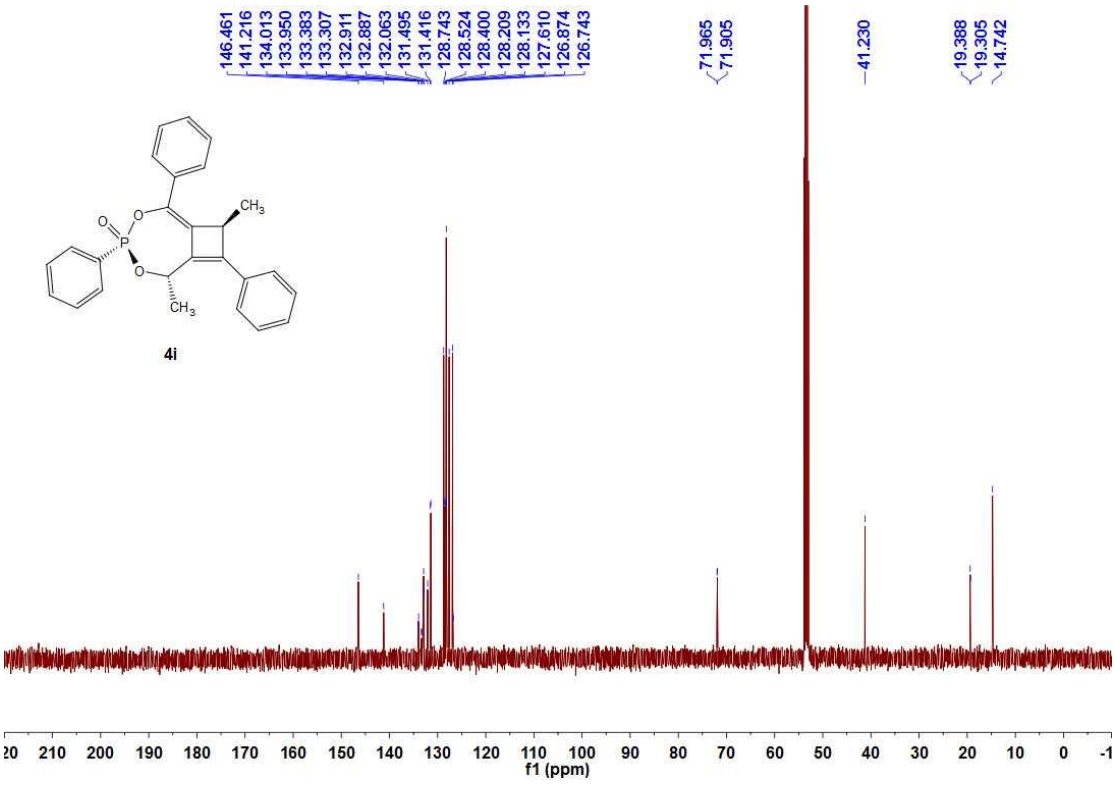


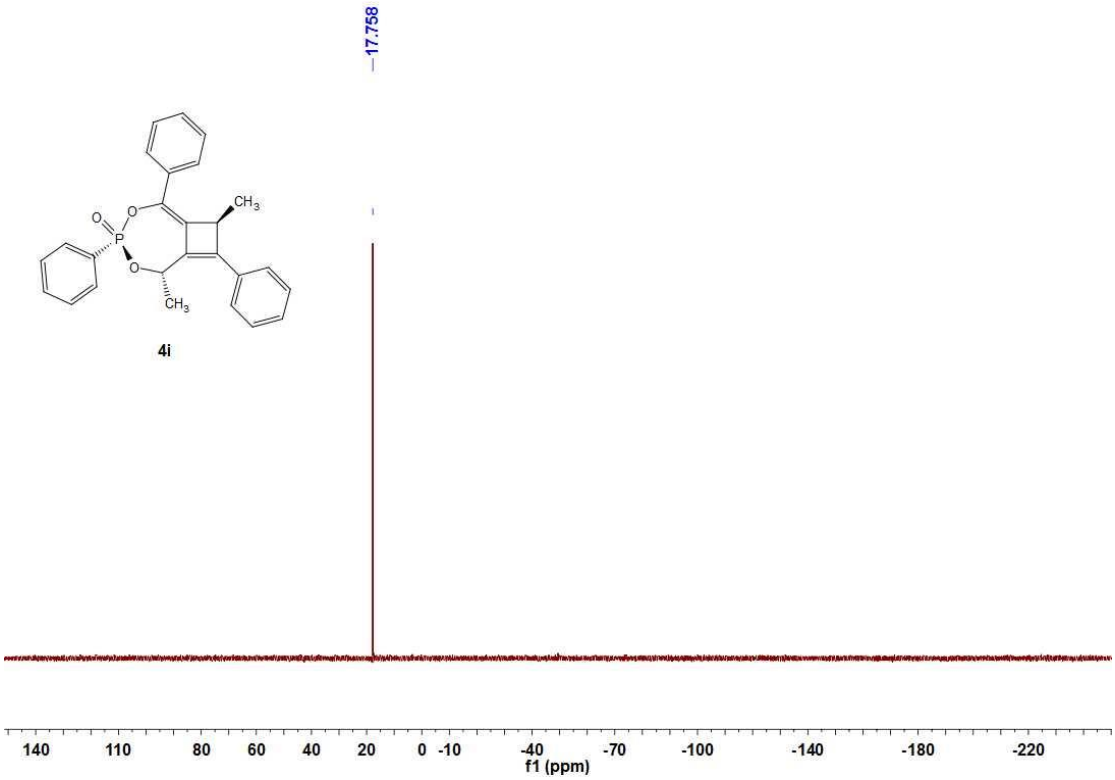
^{1}H NMR of **4i**



^{13}C NMR of **4i**



^{31}P NMR of **4i**



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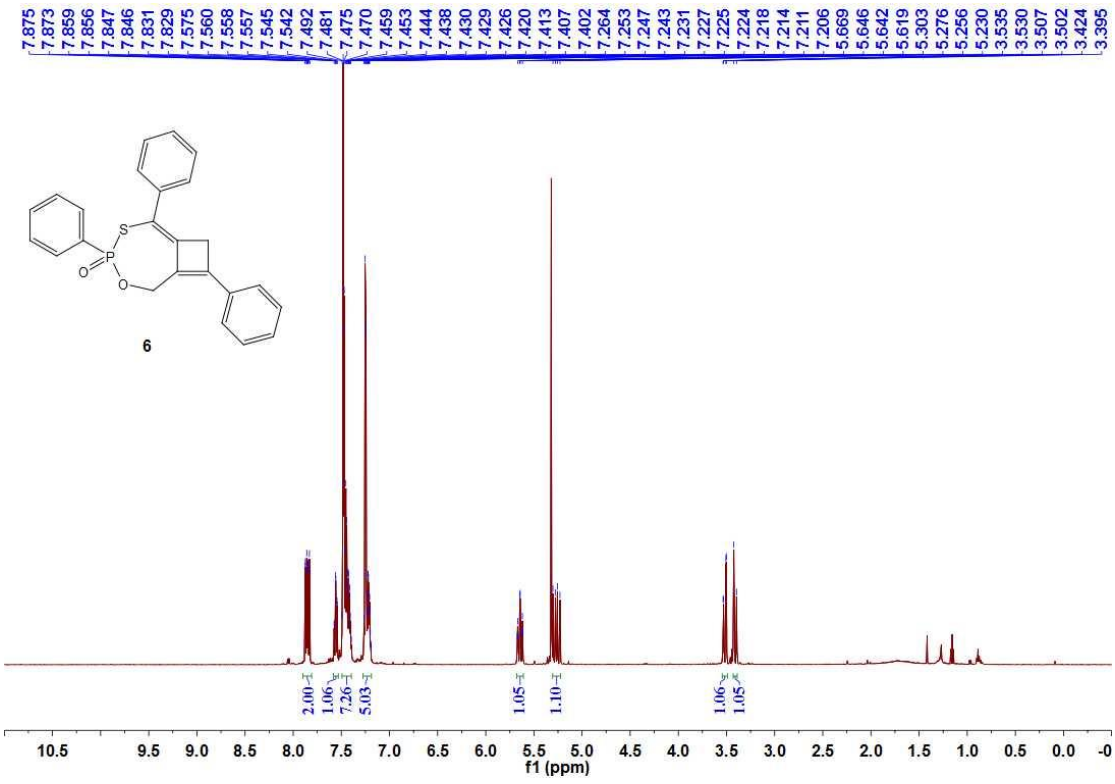

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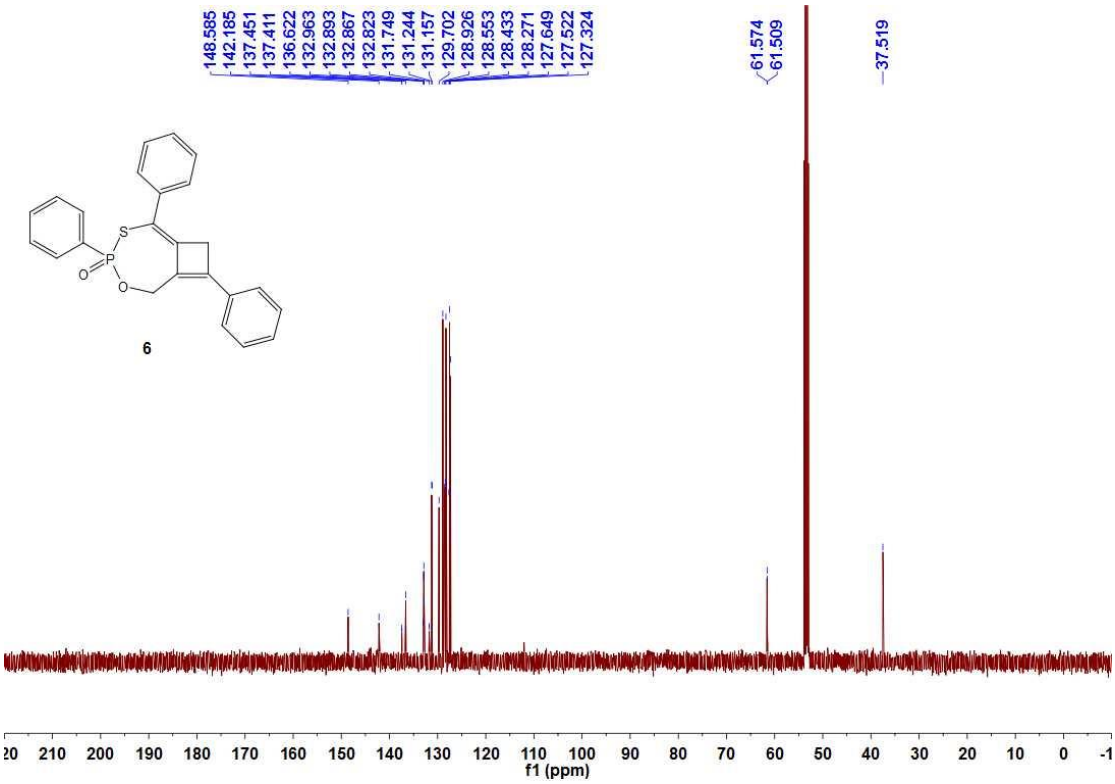
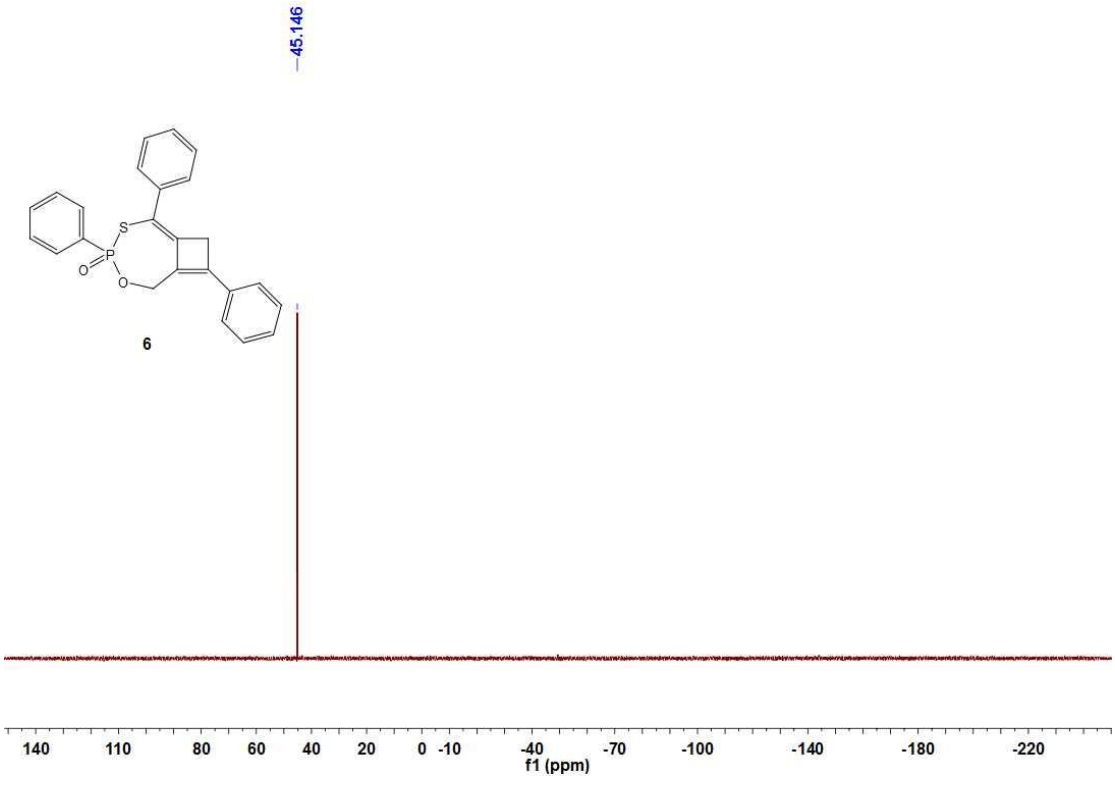
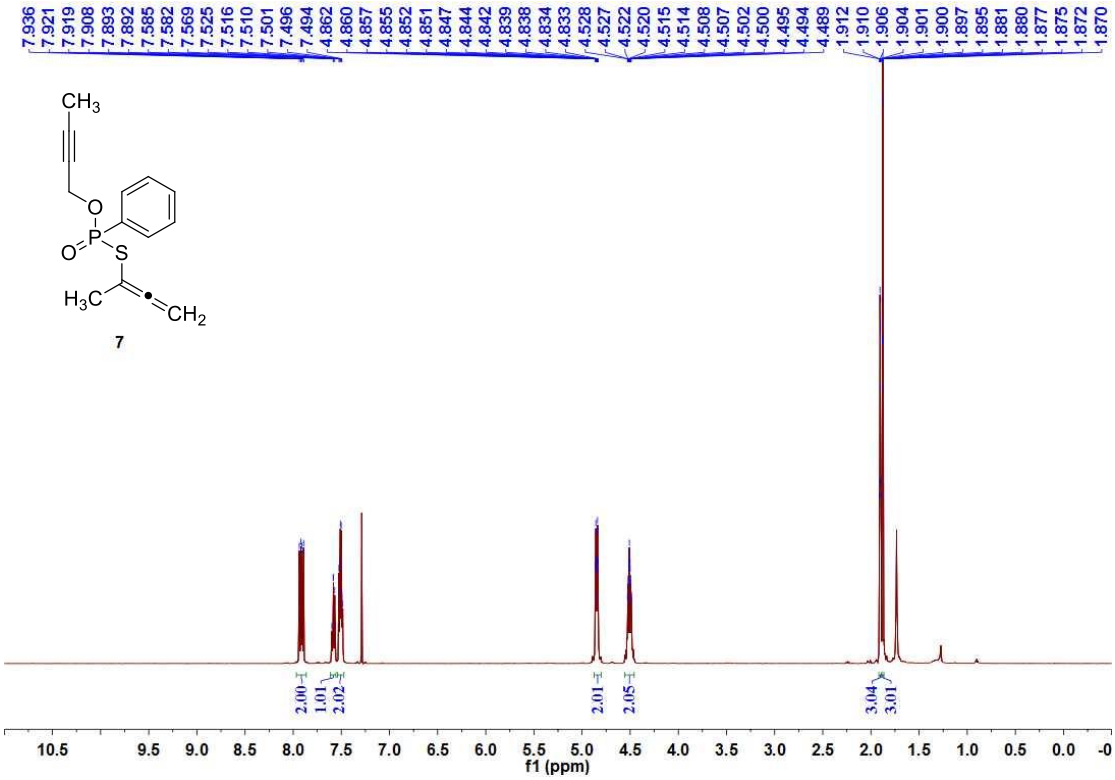


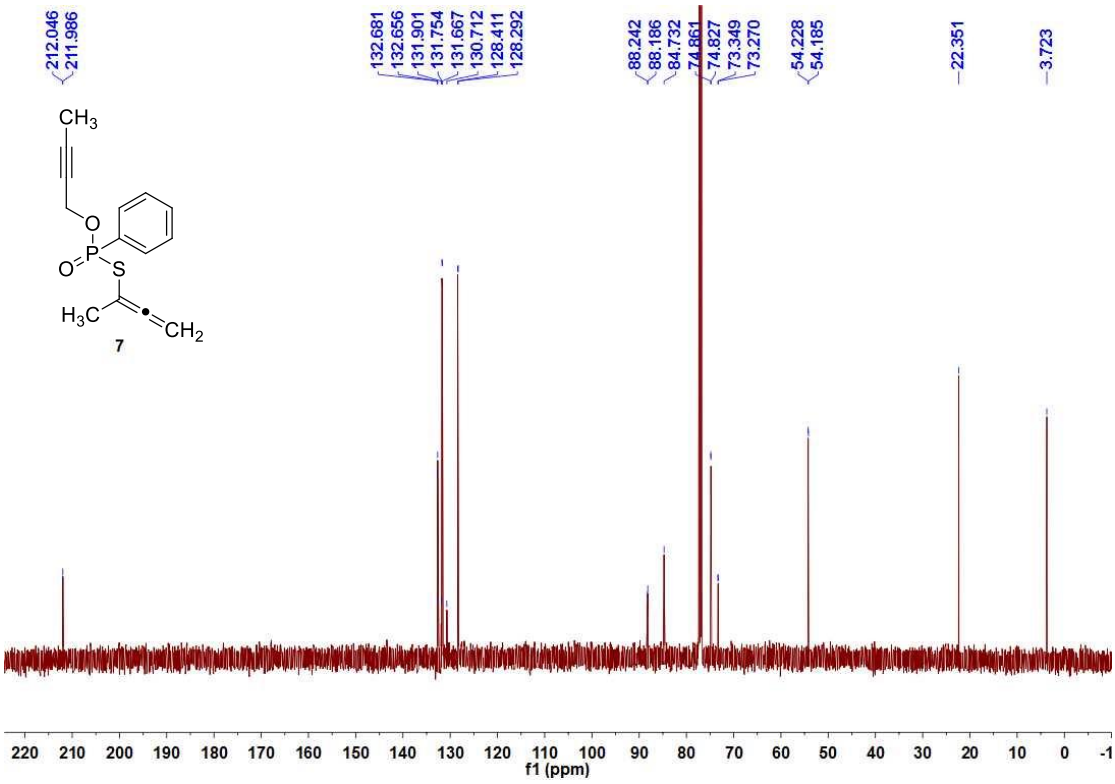
^{31}P NMR of **6**



^{1}H NMR of **7**



^{13}C NMR of **7**



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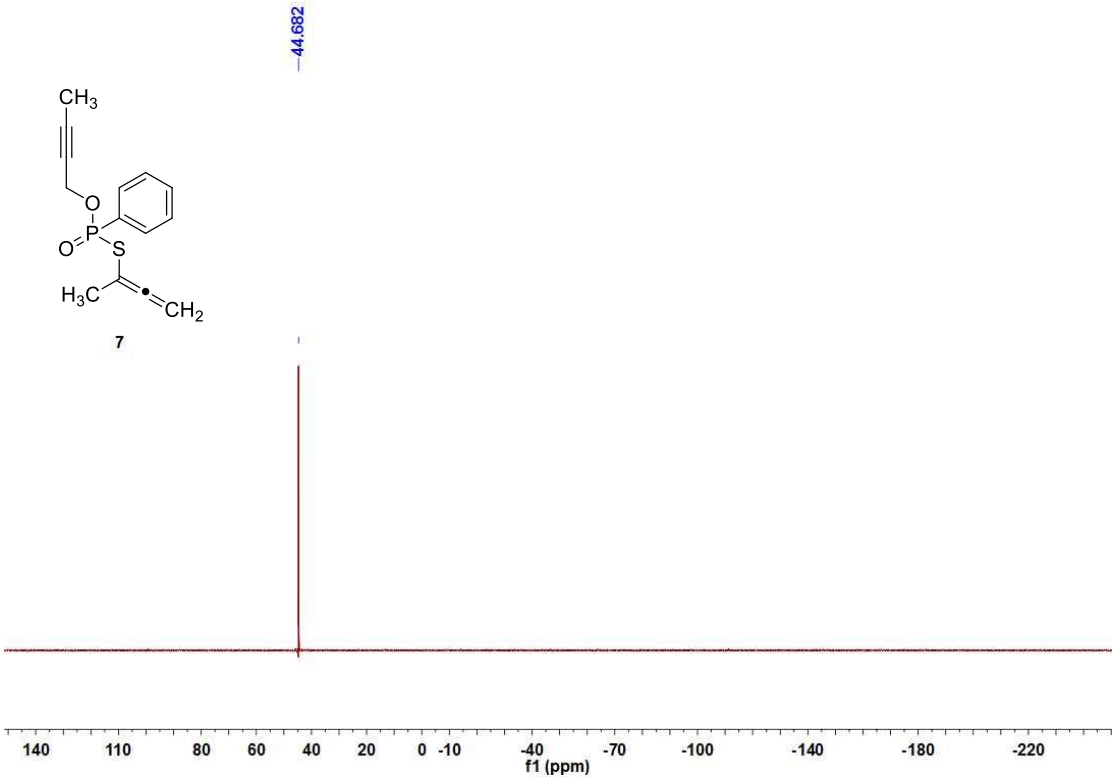
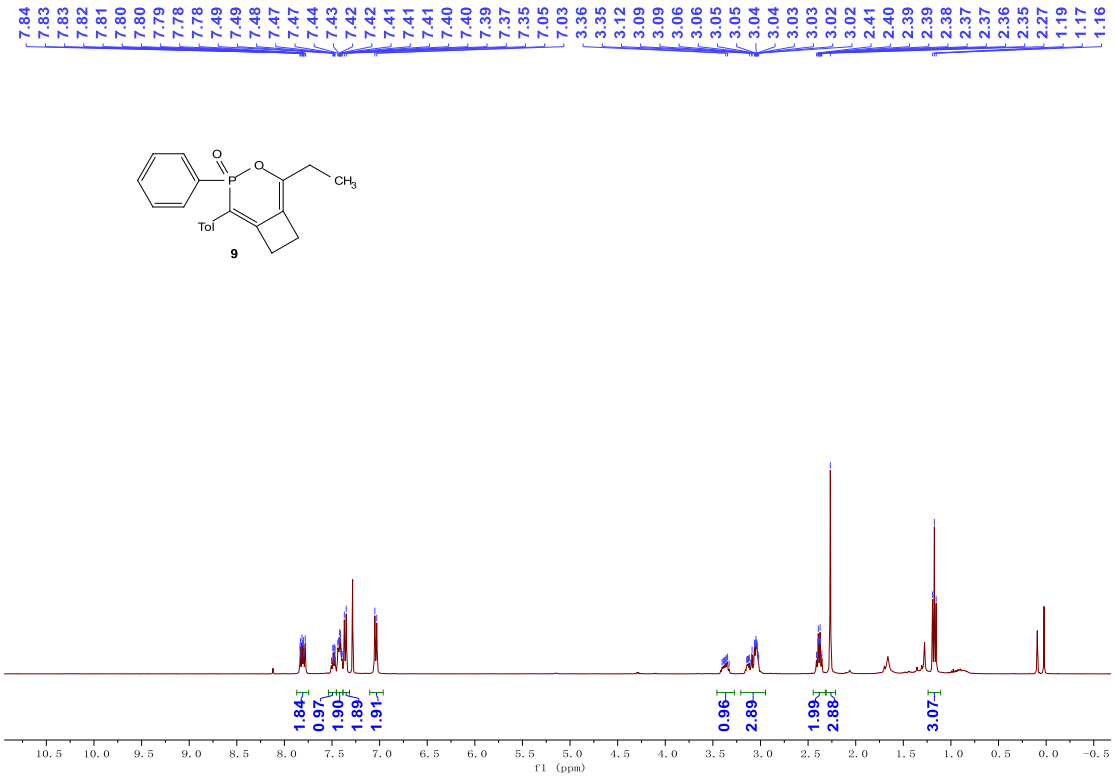


^{1}H NMR of **9**



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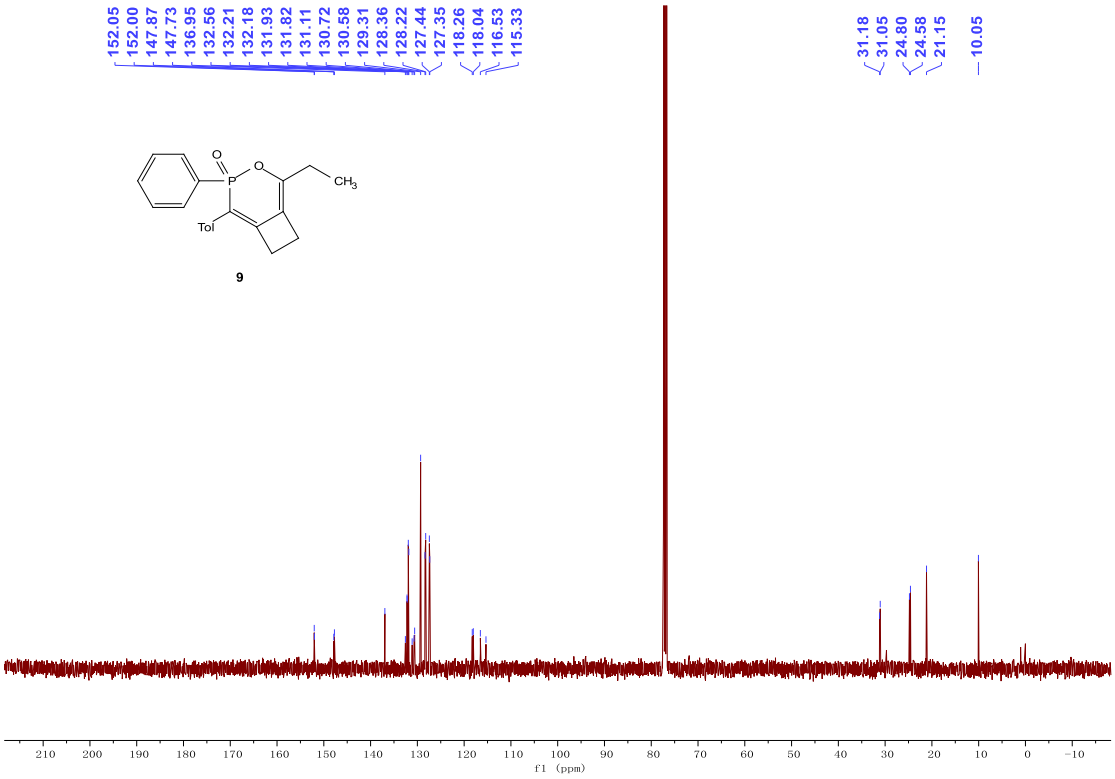
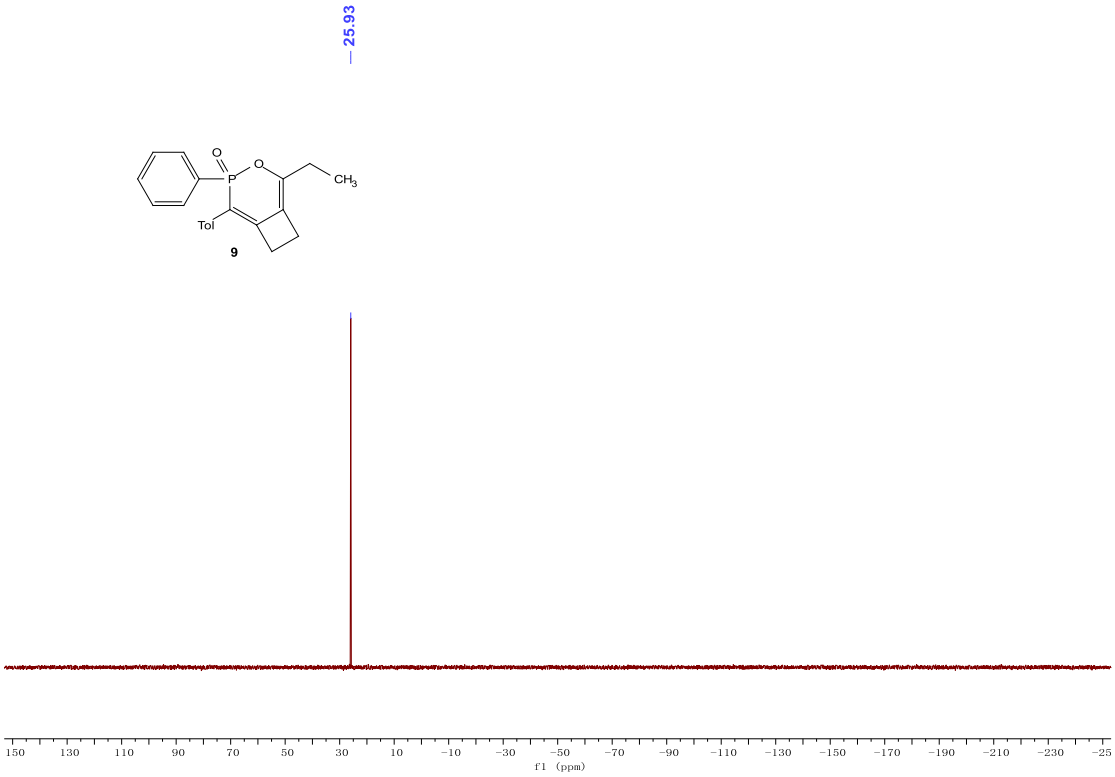
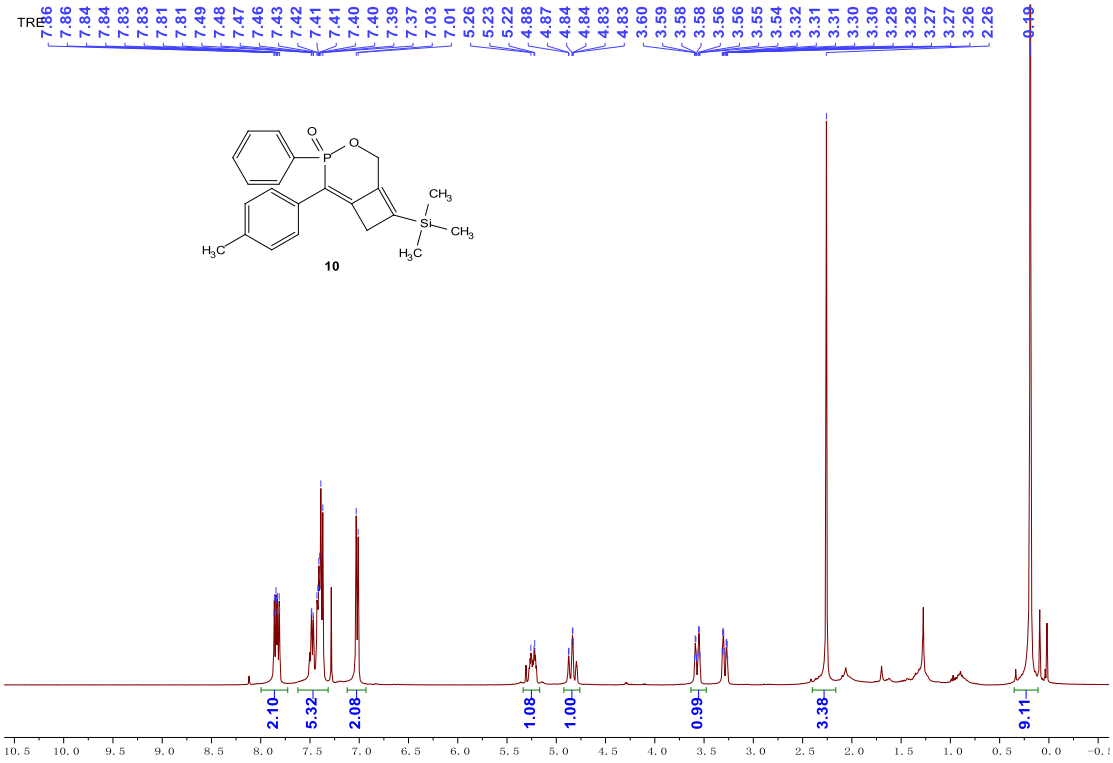


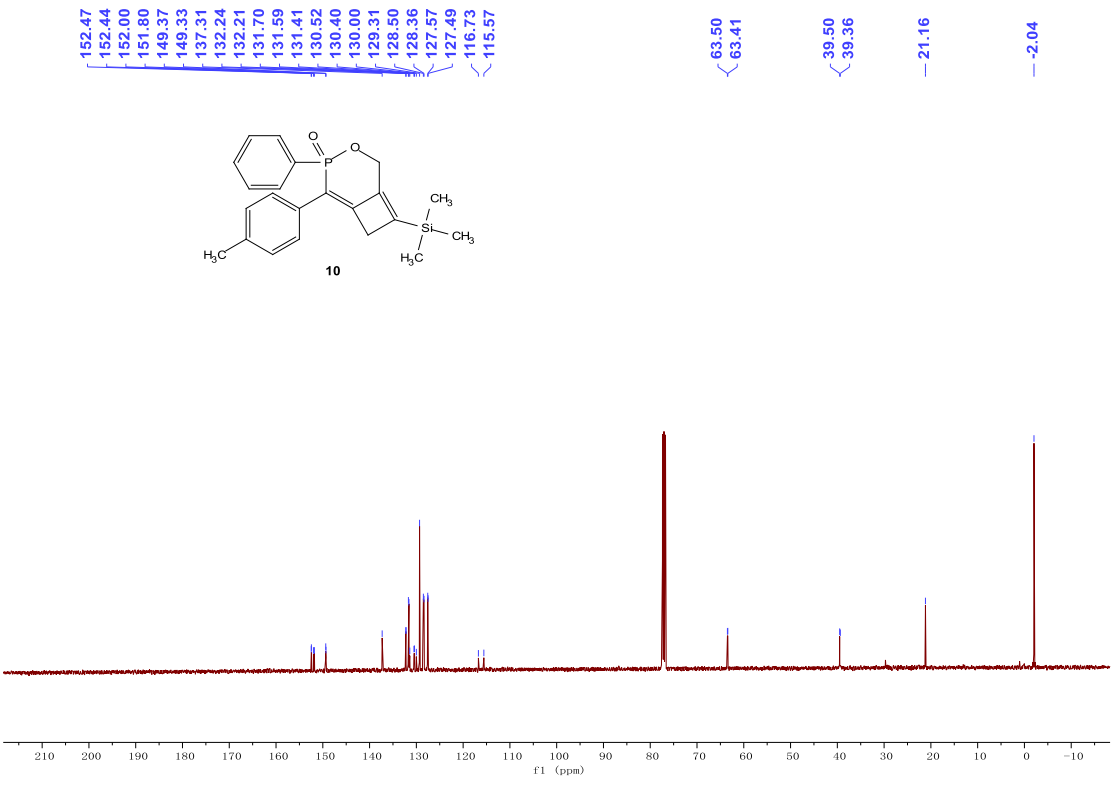
^{31}P NMR of **9**



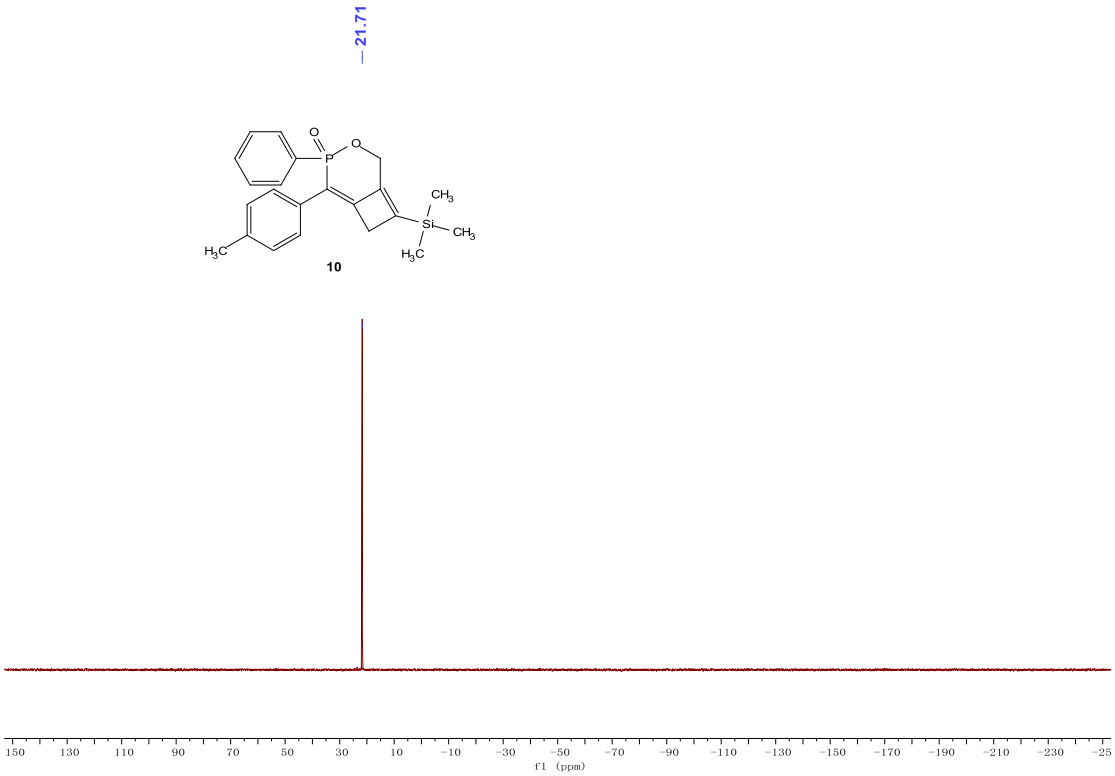
^{1}H NMR of **10**



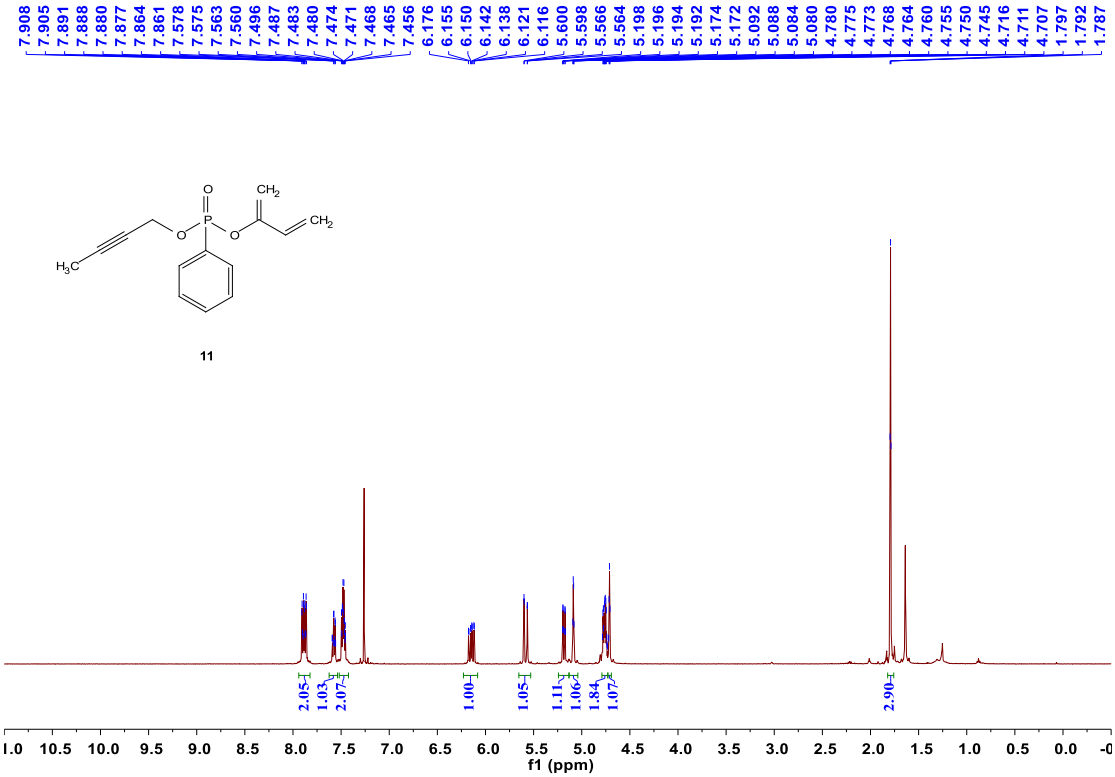
^{13}C NMR of **10**



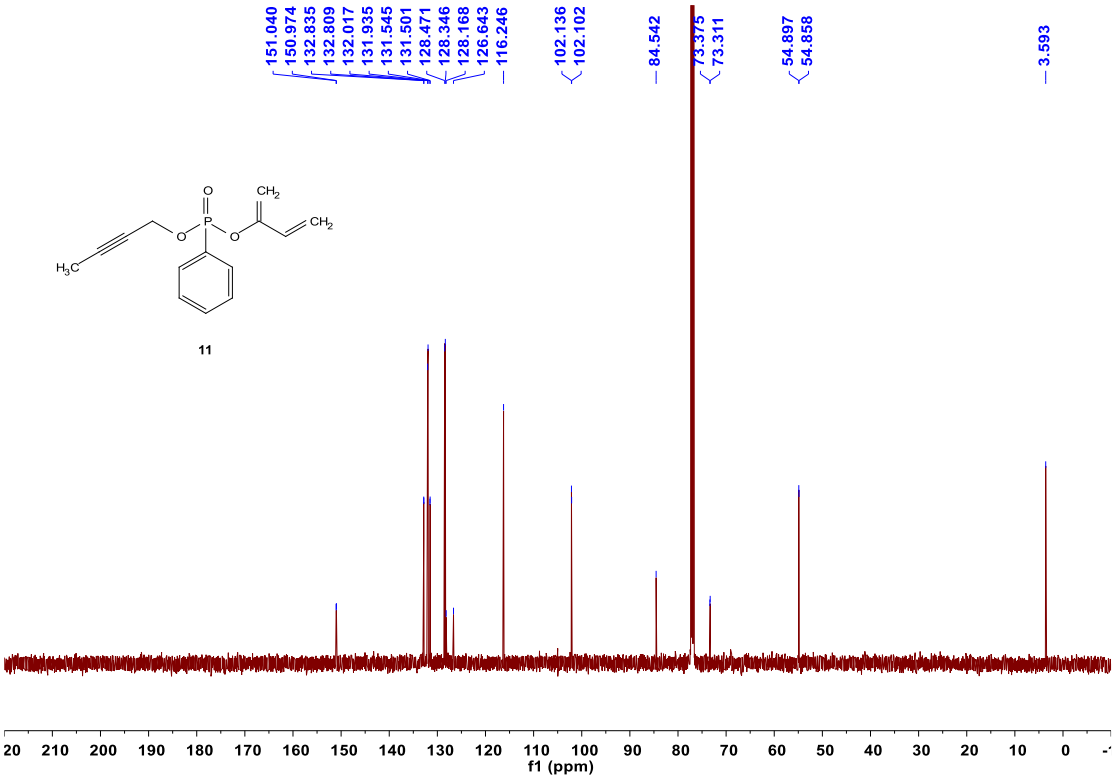
^{31}P NMR of **10**



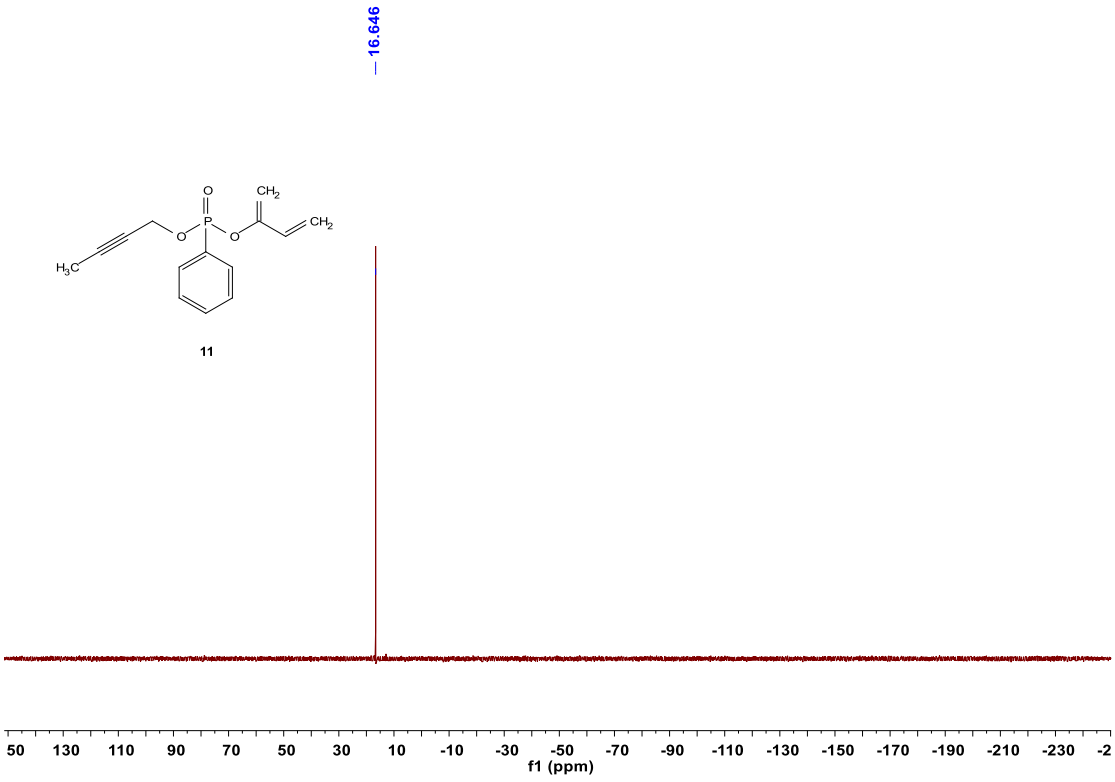
^{1}H NMR of **11**



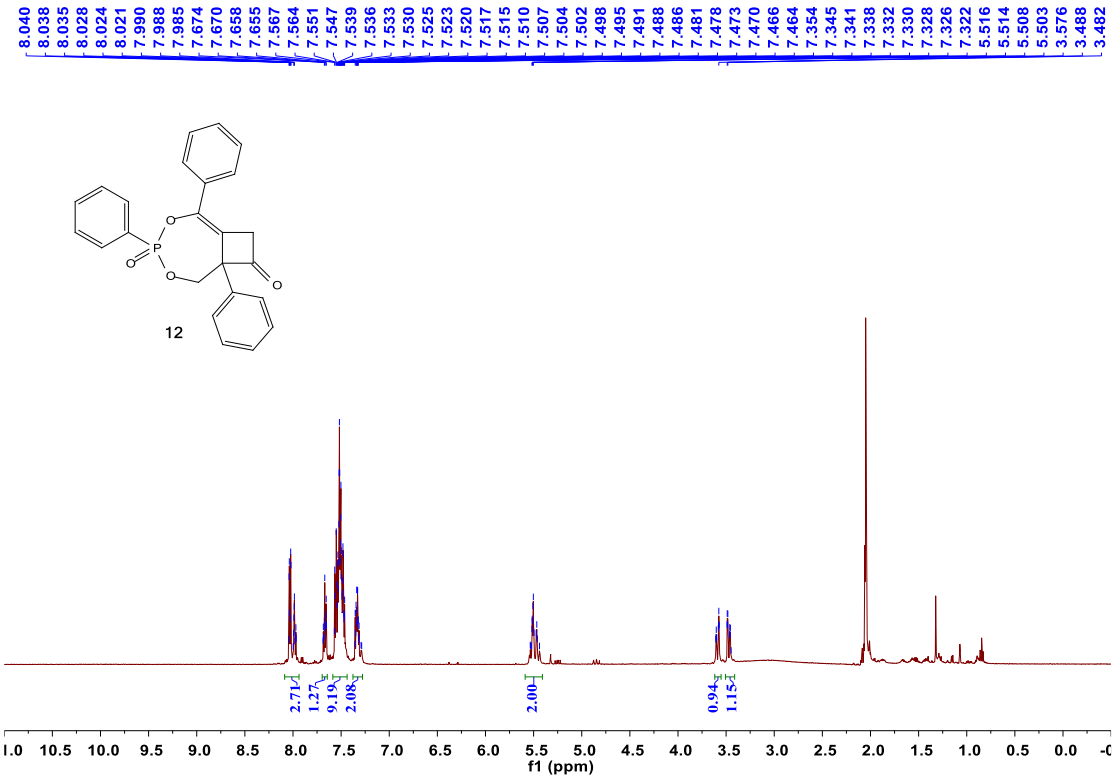
^{13}C NMR of **11**



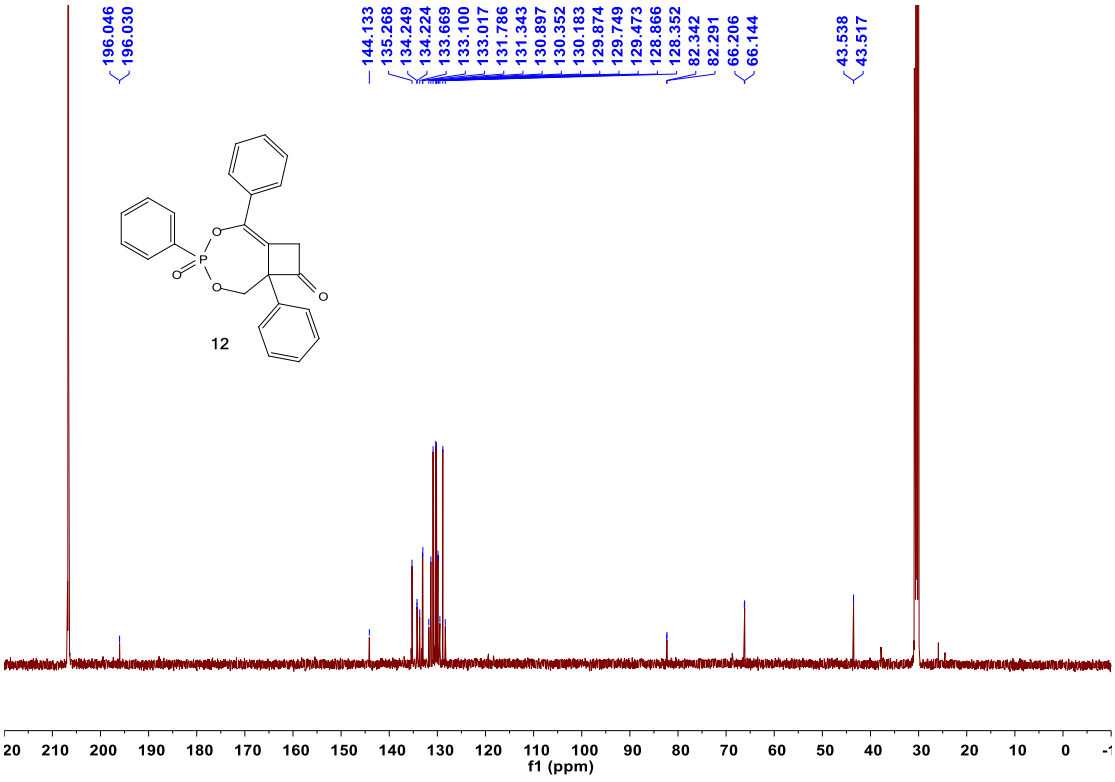
^{31}P NMR of **11**



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



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



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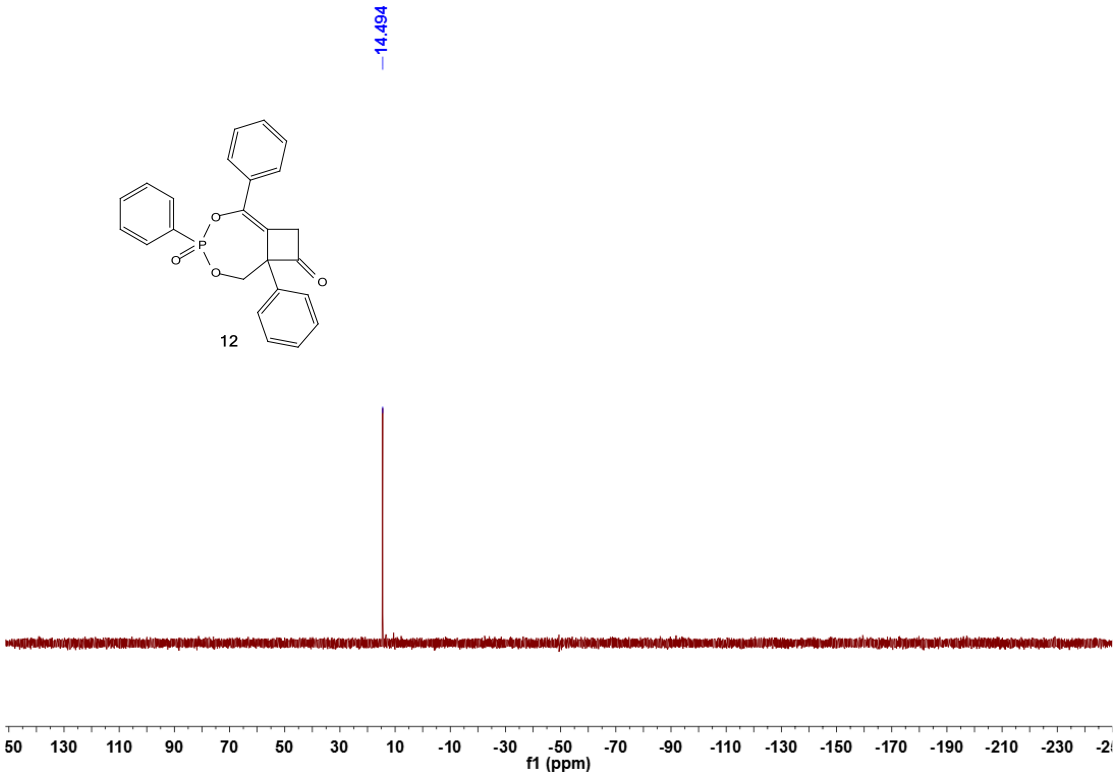
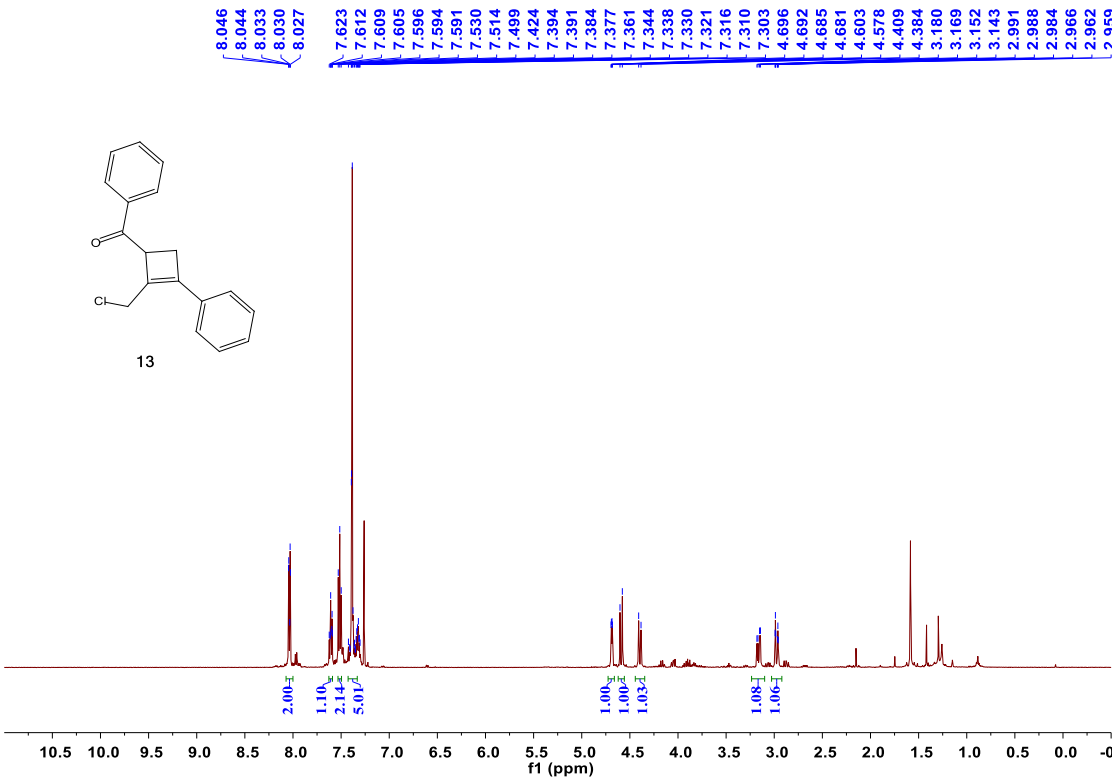


^{1}H NMR of **13**



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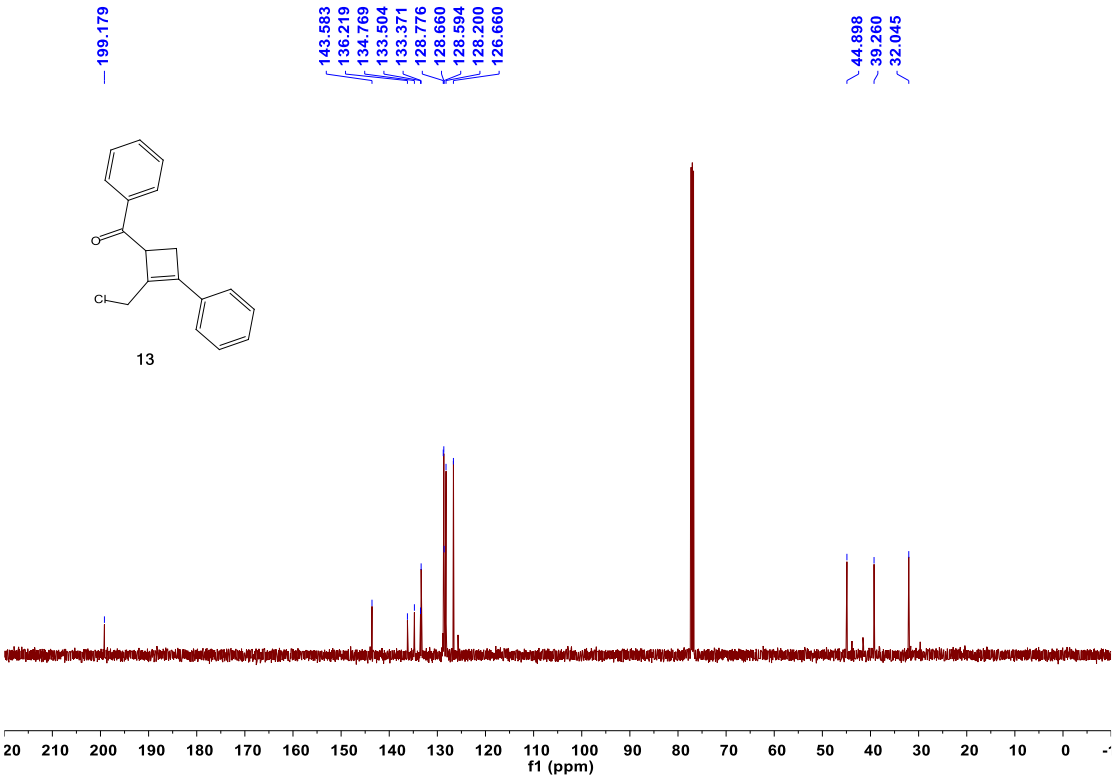
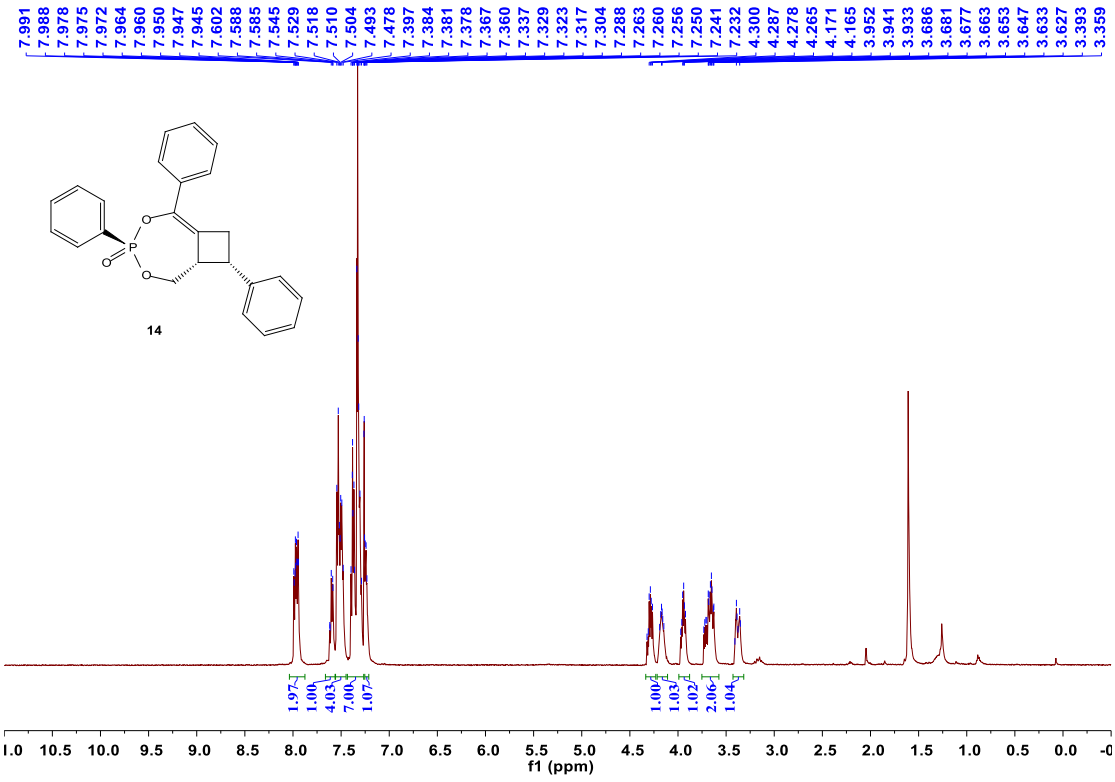
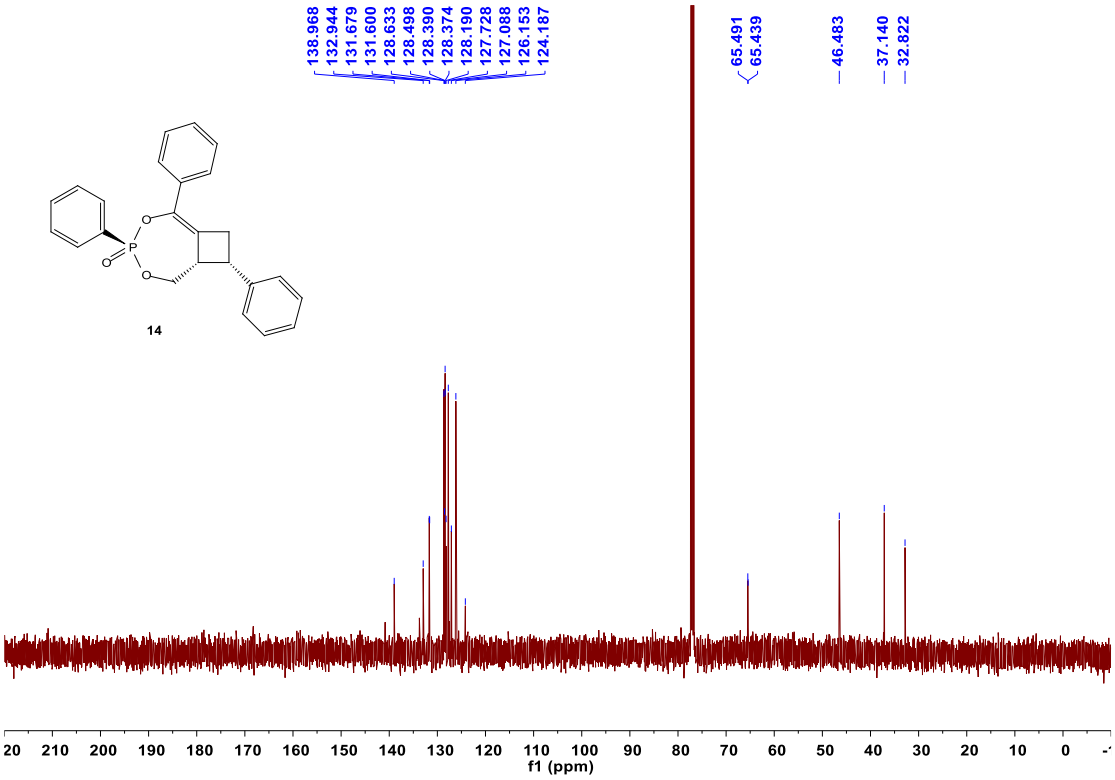


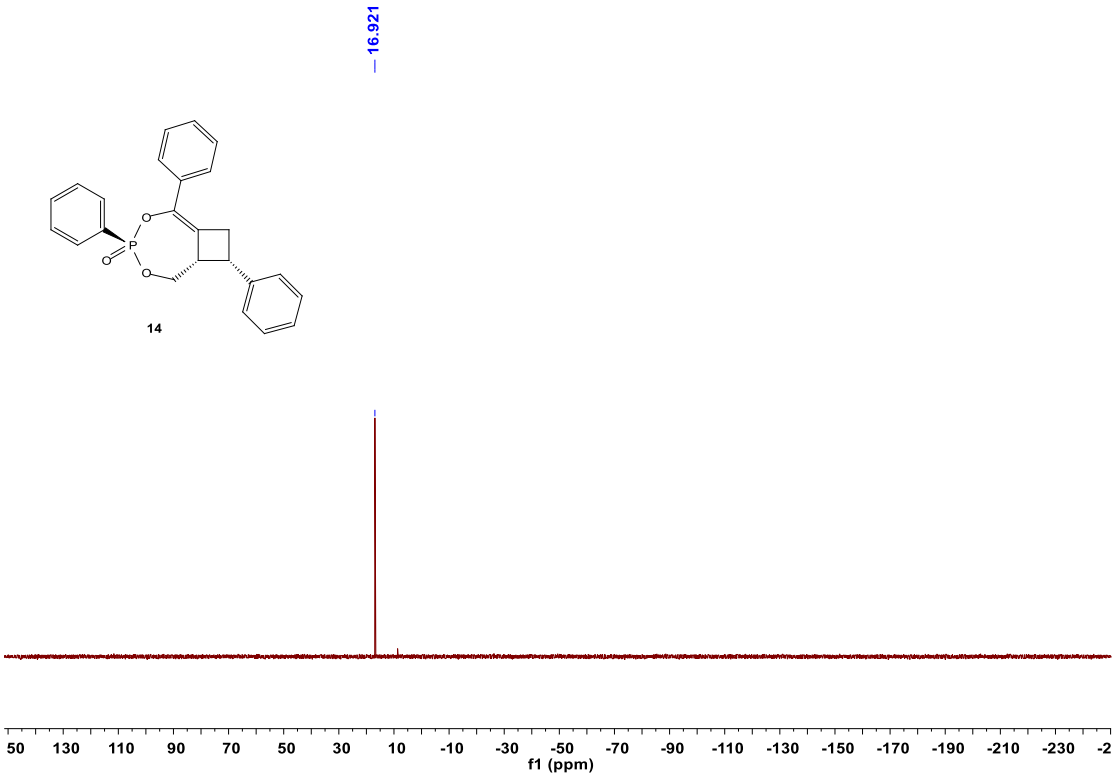
^{1}H NMR of **14**



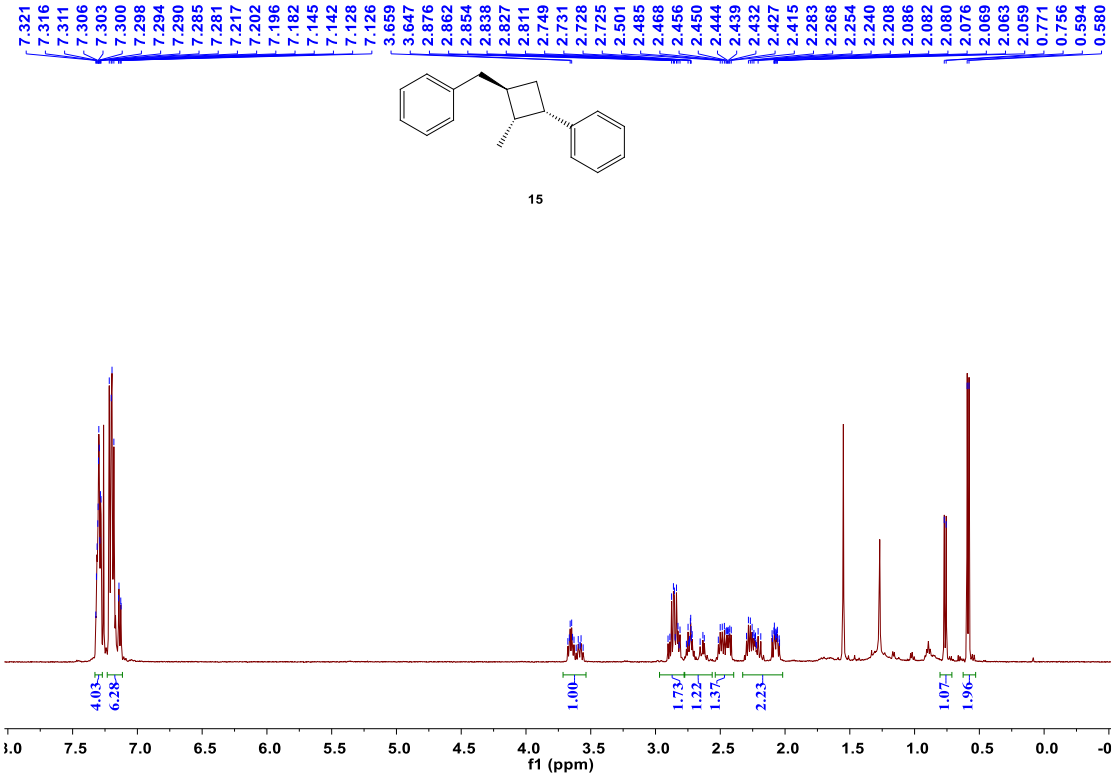
^{13}C NMR of **14**



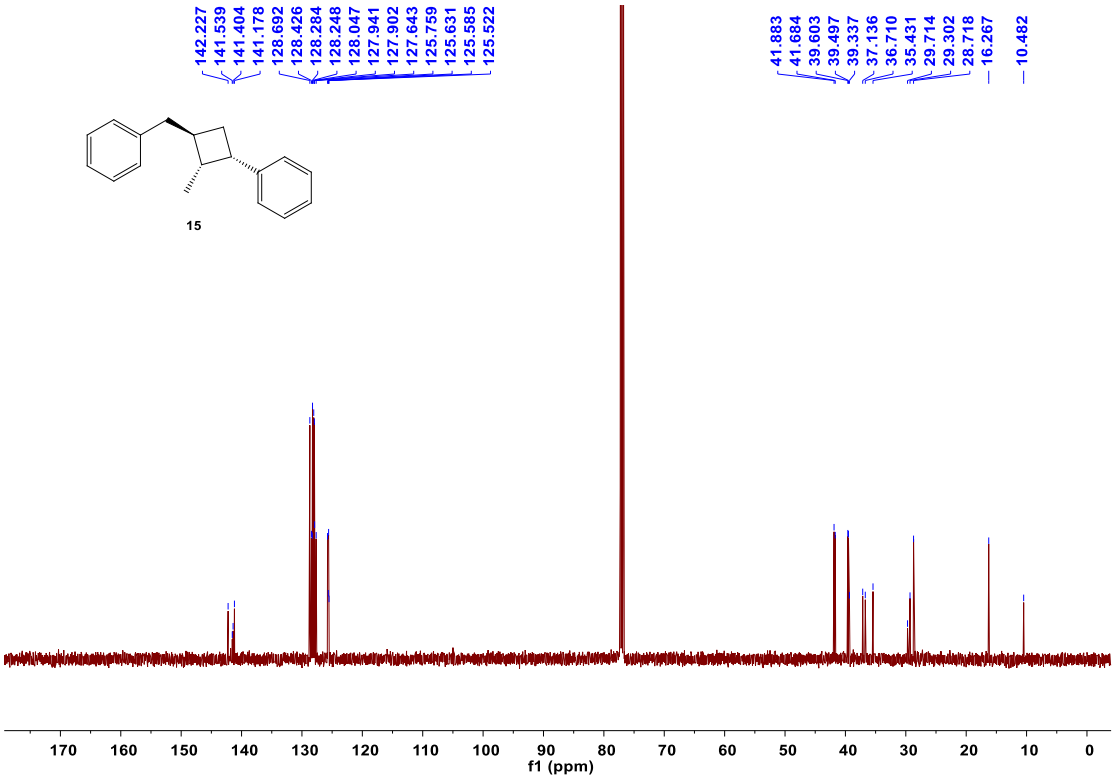
^{31}P NMR of **14**



^{1}H NMR of **15**



^{13}C NMR of **15**



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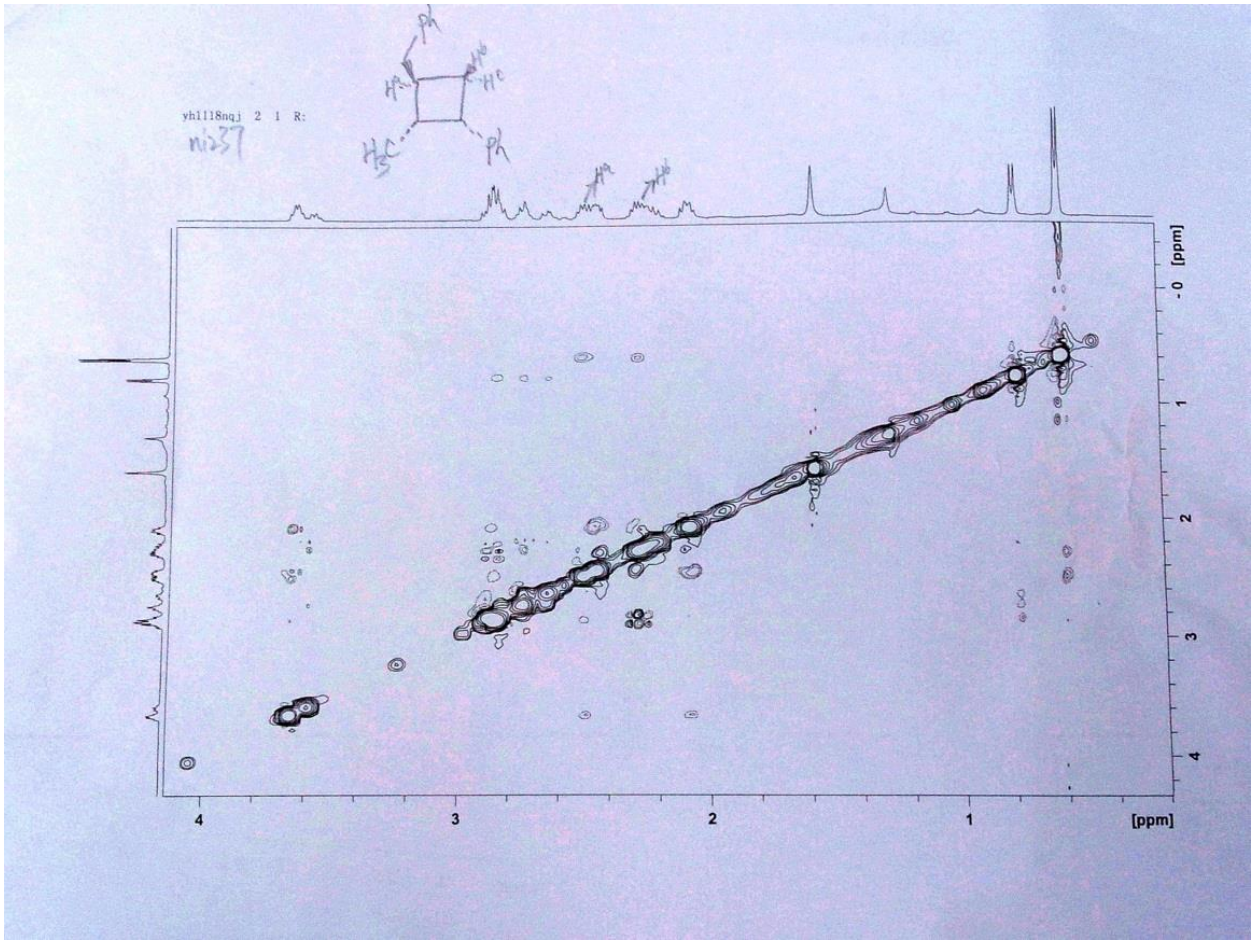

11. Bioscreening data

Material and methods

Cell cultures

Human derived colorectal cancer cell line, DLD1 was obtained from American Type Culture Collection (ATCC) and was maintained in DMEM medium supplemented with 10% fetal calf serum and 100U/ml penicillin-streptomycin (Sigma-Aldrich) in humidified 37oC incubator with 5% CO2. Cells were passaged and harvested with 0.25% trypsin for use in subsequent in vitro experiments. For all experiments, equal number of DLD1 cells were seeded for all conditions within the same experimental setup.

Cellular proliferation and IC50 determination

End point cellular proliferation was assessed using standard MTT assay.[2] Briefly, 0.5mg/ml of (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reagent was added to DLD1 cell culture that were treated with either the medium ring compounds at various concentrations or DMSO for 48 hours and incubated in a humidified 37oC incubator with 5% CO2 for two hours. The resultant purple formazan salt crystals were solubilised with DMSO before measurement at test wavelength of 570 nm (reference wavelength at 630 nm). Level of cellular proliferation was expressed as percentage relative to DMSO control. IC50 of the respective medium ring compound was subsequently determined using the variable slope model which incorporated the proliferation rate of DLD1 after treatment with the different medium ring compounds at dosage between 0.15mg/ml to 0.005 mg/ml for 48 hours.

On the other hand, real-time assessment of cellular proliferation and viability were assessed using xCELLigence real-time cell analysis (RTCA) assay (ACEA Bioscience, Inc. USA). DLD1 cells were seeded and rested overnight before addition of the respective compounds or DMSO as control. Impedance-based time-dependent cell response profiles (TCRPs) were recorded for 48 hours post treatment. The TCRPs showed changes in impedance which reflect the changes in cell density due to variation in cellular proliferation capacity, viability and apoptotic rate. Two or more independent experiments were carried out for all proliferation assays with 4-8 replicates per group.

Cellular apoptosis

Levels of cellular apoptosis in DLD1 cells treated with the respective compounds or DMSO for 48 hours were determined using FITC Annexin V apoptosis detection kit with 7-AAD (Biolegend, USA). Relative fluorescence were analysed using flow cytometer, BD Fortessa (BD Biosciences, USA) and data were tabulated using FlowJo™ v10.6 software (FlowJo, USA). Two independent experiments were carried out with at least two replicates for each condition tested.

Statistical analysis

All statistical analysis and graphing were done using GraphPad Prism (Graphpad Software, USA). Non-parametric, One-way ANOVA with Dunn's multiple comparison test were carried out for all multiple comparisons.

12. Reference

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