Supporting Information

A CHIRAL PHOSPHORAMIDITE REAGENT FOR THE SYNTHESIS OF INOSITOL PHOSPHATES

Estelle Durantie,[†] Samuel Huwiler,[‡] Jean-Christophe Leroux, and Bastien Castagner*[,§]

Institute of Pharmaceutical Sciences
Department of Chemistry and Applied Biosciences ETH Zurich
Vladimir Prelog Weg 3, CH 8093 Zurich (Switzerland)
E-mail: bastien.castagner@mcgill.ca

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1. General Information

Reactions requiring dry conditions were performed under an atmosphere of argon in dried glassware.

All chemicals were reagent grade and used as supplied unless stated otherwise.

Solvents for reactions (diethylether, *N*,*N*-dimethylformamide, methylene chloride, methanol, acetonitrile, acetone) were purchased of analytical grade from commercial suppliers and used without further purification unless stated otherwise. Solvents for extractions and chromatography were technical grade and distilled prior to use.

Ultrapure water was prepared by a Barnstead Nanopure system (Thermo Fischer Scientific, Reinach, Switzerland).

Analytical thin layer chromatography (TLC) was performed on pre-coated *Merck* silica gel 60 F_{254} plates and visualized with UV light or cerium molybdate stain.

Flash column chromatography was carried out on *Fluka* silica gel 60 (230-400 mesh). Ion exchange column chromatography was performed with Dowex® 50WX8-400 resin (Sigma-Aldrich, St. Louis, USA).

Concentration *in vacuo* was performed at ~ 10 mbar and 40 °C unless stated otherwise, drying at ~10^{-2} mbar at room temperature (rt).

Lyophilizations were performed on a Christ Freeze Dryer Alpha 2-4 LSC (Birsfelden, Switzerland).

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a *Bruker AV 400 MHz* spectrometer or a *Bruker AV 500 MHz* spectrometer. NMR data are reported as follows: chemical shifts (δ, ppm, relative to residual solvent peaks), integration, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*, Hz).

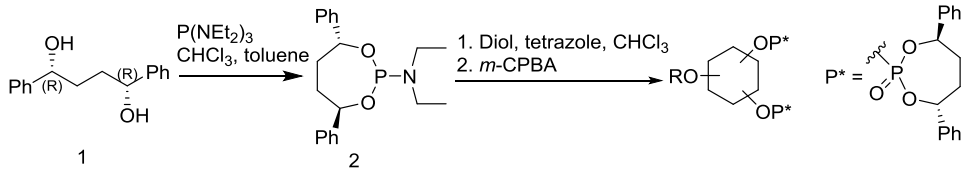
High-resolution mass spectra (HR ESI) were performed by the MS service at the Laboratory for Organic Chemistry, ETH Zurich.

Optical rotations were obtained using a JASCO P-2000 polarimeter. Optical rotations are reported as follows: $[\alpha]^{T}$ (c = 1.00 corresponds to 10.0 mg·mL^{-1} , solvent) with T = temperature of the measurement in °C.

2. Procedure

2.1. General procedures

Phosphorylation reaction



Procedure A: All the solvents used were dried and degassed and the glassware was flame-dried under vacuum followed by argon flush – purge.

In situ preparation of (1*R*,4*R*)-1,4-diphenylbutane-*N,N*-diethylphosphoramidite **2**: A solution of (1*R*,4*R*)-1,4-diphenylbutandiol **1**[1,2] in $CHCl_3$ (5.5 equiv, 1 M) was added to boiling toluene. The hexaethyl phosphorous triamide solution in toluene (5.5 equiv, 1 M) was then added dropwise over a period of 30 min and then stirred for a further 10 min. An aliquot was taken to verify the purity by ^{1}H and ^{31}P NMR.

The solution of tetrazole in acetonitrile (ACN) (0.45M, 23 equiv) was added to the *in situ* prepared phosphoramidite **2**, followed by addition of the solution of inositol in $CHCl_3$ (1 equiv, 0.02M). The reaction mixture was stirred at rt for 20 h. A solution of *m*-CPBA (75% w/w, 10 equiv) in CH_2Cl_2 was dried over Na_2SO_4, added at -10 °C to the reaction mixture and stirred at rt for an additional 45 min. The mixture was then diluted in EtOAc, treated with solution of aqueous Na_2SO_3 and washed with a saturated solution of aqueous $NaHCO_3$ and with brine. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The obtained residue was purified by flash chromatography as indicated.

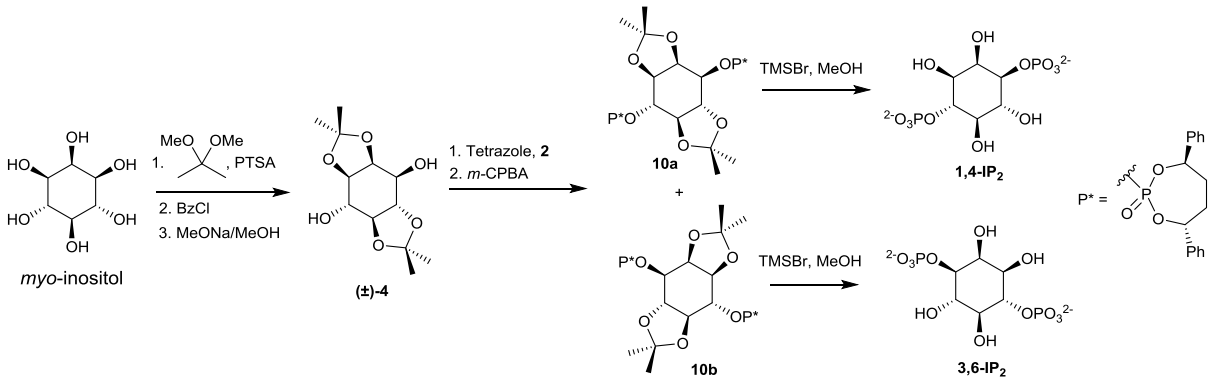
Full deprotection using TMSBr

Procedure B: Protected inositol phosphate (1 equiv) in MeOH/DCM 30% (0.05 M) was treated with TMSBr (56 equiv) and stirred for 2 h. The reaction mixture was then degassed with N_2 and the evacuated HBr was neutralized in a gas trap with 1 M NaOH solution. After 1 to 2 h, the reaction mixture was concentrated to dryness. The crude was triturated with acetone and then with ACN to afford clean bisphosphate.

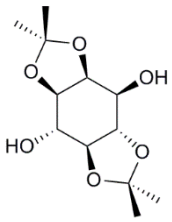
Ion exchange to afford the Li^+ salt

Procedure C: Dowex H^+ was equilibrated to Li^+ by passing an aqueous solution of LiOH 2 M and washed with nanopure H_2O until obtaining a neutral pH. The solution of inositol phosphate was then loaded on the column to afford the Li^+ salt which was further dried by lyophilization.

2.2. Synthesis of 1,4- and 3,6-diphosphate *myo*-inositol 1,4-IP_2 and 3,6-IP_2

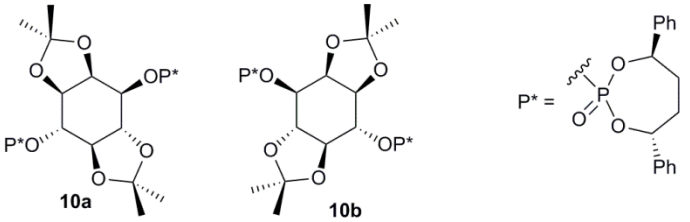


Synthesis of (±)-1,2;5,6-di-*O*-isopropylidene-myo-inositol (±)-4



(±)-4 was prepared following the procedure described by Kheronsky *et. al.*[3]; ^{1}H NMR spectrum was in accordance with literature.

Synthesis of the 2,3:5,6-di-isoproylidene-1,4-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol 10a and the 1,2:4,5-di-isoproylidene-3,6-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol 10b



Synthesized from (±)-2,3:5,6-di-isoproylidene-*myo*-inositol **(±)-4** following procedure A. The obtained residue was purified by flash chromatography (SiO_2, EtOAc/hexane 30 -> 40%) to afford the

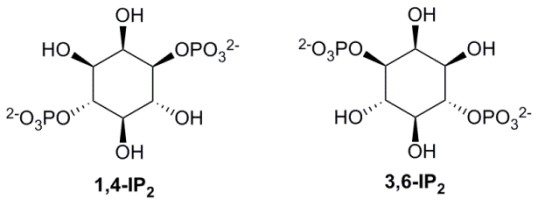
diastereomeric mixture **10a** and **10b** as white solid (64 mg, 87%). Crystallization of the mixture by slow evaporation method in *i*PrOH afforded diastereomer **10a** (dr >99:1, 16%[a]). Diastereomer **10b** was obtained by recrystallization of the resulting mother liquor in *i*PrOH (dr >99:1, 13%[a]).

[a] Yield based on the diastereomer itself, which represent 50% of the racemic starting material.

10a: $[\alpha]_D^{25}$ +29.2 (*c* 0.26, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.28-7.42 (20H, m, Ph), 5.53-5.61 (2H, m, CH-Ph), 5.42 (1H, dd, *J* 10.0, 7.2 Hz, CH-Ph), 5.34 (1H, dd, *J* 9.1, 7.6 Hz, CH-Ph), 4.66 (1H, ddd, *J* 9.9, $^3J_{HP}$ 8.8, *J* 4.1 Hz, H-C3), 4.53-4.61 (2H, m, H-C6, H-C2), 4.17 (1H, dd, *J* 6.2, 4.6 Hz, H-C1), 3.92 (1H, t, *J* 9.9 Hz, H-C4), 3.25 (1H, t, *J* 10.1 Hz, H-C5), 2.20-2.39 (4H, m, CH_2), 2.04-2.17 (4H, m, CH_2), 1.51 (3H, s, *i*Pr), 1.30 (3H, s, *i*Pr), 0.88 (3H, s, *i*Pr), 0.70 (3H, s, *i*Pr); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 141.5 (d, $^3J_{CP}$ 10.9 Hz, *i*Ph), 141.1 (d, $^3J_{CP}$ 10.6 Hz, *i*Ph), 140.4 (d, $^3J_{CP}$ 9.9 Hz, *i*Ph),140.2 (d, $^3J_{CP}$ 10.0 Hz, *i*Ph), 128.6 (2xPh), 128.54 (Ph), 128.47 (2xPh), 128.40 (2xPh), 128.37 (2xPh), 128.3 (Ph), 128.0 (Ph), 127.9 (Ph), 126.0 (2xPh), 125.9 (2xPh), 125.8 (2xPh), 125.6 (2xPh), 113.0 (**C**$(CH_3)_2$), 111.1 (**C**$(CH_3)_2$), 80.5 (d, $^2J_{CP}$ 6.0 Hz, CH-Ph), 80.2 (d, $^2J_{CP}$ 6.0 Hz, CH-Ph), 80.1 (d, $^3J_{CP}$ 4.2 Hz, C1), 79.8 (d, $^2J_{CP}$ 2.6 Hz, CH-Ph), 79.6 (d, $^2J_{CP}$ 4.4 Hz, C6), 79.2 (d, $^2J_{CP}$ 2.5 Hz, CH-Ph), 76.8 (C2), 76.5 (d, $^3J_{CP}$ 3.3 Hz, C5), 74.9 (d, $^3J_{CP}$ 6.3 Hz, C4), 73.9 (d, $^2J_{CP}$ 3.6 Hz, C3), 38.5 (CH_2), 38.1 (CH_2), 37.5 (CH_2), 37.1 (CH_2), 28.0 (CH_3), 26.2 (CH_3), 26.1 (CH_3), 25.9 (CH_3); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, $CDCl_3$) δ (ppm) -0.72 (1P), -1.51 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_{44}H_{51}O_{12}P_2$ requires 833.2850, found 833.2842].

10b: $[\alpha]_D^{25}$ +9.8 (*c* 0.17, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.27-7.45 (20H, m, Ph), 5.53-5.61 (2H, m, CH-Ph), 5.36 (1H, t, *J* 8.6 Hz, CH-Ph), 5.29 (1H, t, *J* 8.4 Hz, CH-Ph), 4.80 (1H, ddd, *J* 11.0, $^3J_{HP}$ 6.8, *J* 4.3 Hz, H-C3), 4.54 (1H, ddd, *J* 10.5, 9.0, $^3J_{HP}$ 6.8 Hz, H-C6), 4.35 (1H, t, *J* 4.5 Hz, H-C2), 4.03 (1H, t, *J* 9.9 Hz, H-C4), 3.99-4.03 (1H, m, H-C1), 3.46 (1H, dd, *J* 10.3, 9.9 Hz, H-C5), 2.20-2.36 (4H, m, CH_2), 2.02-2.19 (4H, m, CH_2), 1.43 (3H, s, *i*Pr), 1.39 (3H, s, *i*Pr), 1.14 (3H, s, *i*Pr), 0.52 (3H, s, *i*Pr); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 141.2 (d, $^3J_{CP}$ 7.4 Hz, *i*Ph), 141.1 (d, $^3J_{CP}$ 7.6 Hz, *i*Ph), 140.4 (d, $^3J_{CP}$ 9.9 Hz, *i*Ph), 140.2 (d, $^3J_{CP}$ 10.0 Hz, *i*Ph), 128.6 (4xPh), 128.5 (2xPh), 128.42 (Ph), 128.40 (2xPh), 128.3 (Ph), 128.2 (Ph), 128.0 (Ph), 126.0 (2xPh), 125.9 (2xPh), 125.8 (2xPh), 125.7 (2xPh), 113.2 (**C**$(CH_3)_2$), 110.8 (**C**$(CH_3)_2$), 80.53 (d, $^2J_{CP}$ 3.8 Hz, CH-Ph), 80.48 (d, $^2J_{CP}$ 3.5 Hz, CH-Ph), 80.2 (d, $^2J_{CP}$ 4.4 Hz, C6), 79.8 (d, $^3J_{CP}$ 3.9 Hz, C1), 79.6 (d, $^2J_{CP}$ 2.8 Hz, CH-Ph), , 79.2 (d, $^2J_{CP}$ 2.6 Hz, CH-Ph), 76.7 (d, $^3J_{CP}$ 3.6 Hz, C5), 76.4 (C2), 75.3 (d, $^3J_{CP}$ 7.9 Hz, C4), 74.6 (d, $^2J_{CP}$ 4.0 Hz, C3), 38.3 (CH_2), 38.2 (CH_2), 37.3 (CH_2), 37.1 (CH_2), 28.4 (CH_3), 27.1 (CH_3), 27.0 (CH_3), 24.7 (CH_3); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, $CDCl_3$) δ (ppm) -1.53 (1P), -1.76 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_{44}H_{51}O_{12}P_2$ requires 833.2850, found 833.2849].

Synthesis of 1,4-diphosphate *myo*-inositol 1,4-IP$_2$ and 3,6-diphosphate *myo*-inositol 3,6-IP$_2$



Synthesized from **10a** and **10b** according to procedure B, except amount of TMSBr (21 equiv), reaction time 2h.

1,4-IP$_2$ was obtained as a white solid (1.9 mg, 5.7 µmol, 89%); **3,6-IP$_2$** was obtained as a white solid (0.5 mg, 1.49 µmol, 41%).

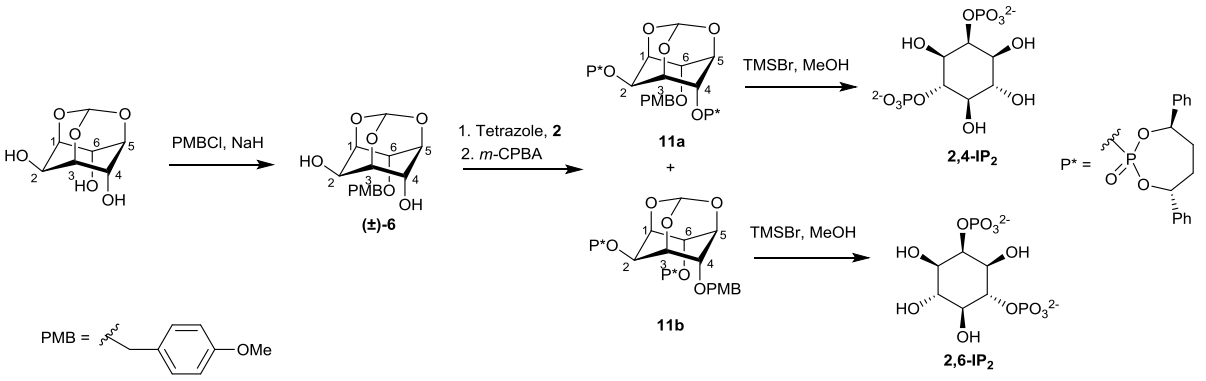
^{1}H NMR (400 MHz, MeOD) δ (ppm) 4.35 (1H, q, *J* 9.2 Hz, H-C6), 4.19 (1H, t, *J* 2.6 Hz, H-C2), 4.04 (1H, ddd, *J* 9.8, $^3J_{HP}$ 8.5, *J* 2.6 Hz, H-C3/1), 3.86 (1H, t, *J* 9.5 Hz, H-C6/4), 3.60 (1H, dd, *J* 9.6, 2.6 Hz, H-C1/3), 3.42 (1H, t, *J* 9.2 Hz, H-C5); **^{13}C NMR** (101 MHz, MeOD) δ (ppm) 81.3 (d, $^2J_{CP}$ 6.1 Hz, C6/4), 78.8 (d, $^2J_{CP}$ 5.7 Hz, C3/1), 75.0 (d, $^3J_{CP}$ 2.2 Hz, C5), 72.6-72.7 (2C, m, C2, C4/6), 72.0 (d, $^3J_{CP}$ 3.2 Hz, H-C1/3); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, MeOD) δ (ppm) 1.25 (1P), -0.07 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_6H_{15}O_{12}P_2$ requires 341.0033, found 341.0037].

1,4-IP$_2$: $[\alpha]_D^{23}$ -4.55 (*c* 0.124, H_2O, pH 7); {lit. $[\alpha]_D^{22}$ +1.6 (*c* 1.3, H_2O, free acid)}[4] [b]

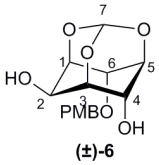
3,6-IP$_2$: $[\alpha]_D^{23}$ +7.95 (*c* 0.029, H_2O, pH 7); {lit. $[\alpha]_D^{22}$ -1.4 (*c* 1.8, H_2O, free acid)}[4] [b]

[b] The optical rotations measured are opposite to the known optical rotation reported in the literature, but measurements have been repeated several times giving similar values. As mentioned by Miller *et al.*,[5] that have encountered the same phenomenon, optical rotations of inositol phosphates have low magnitude and are dependent on sample preparation (i.e. counter ion, pH). In the present case, optical rotation of each compound was measured on the sample without any further preparation, thus it is assumed to be the free acid form, however due to the low concentration, the pH was neutral. Nonetheless, the absolute configuration is certain as it has been determined by X-Ray analysis in the previous step (compound **10a**).

2.3. Synthesis of 2,4- and 2,6-diphosphate *myo*-inositol inositol 2,4-IP_2 and 2,6-IP_2



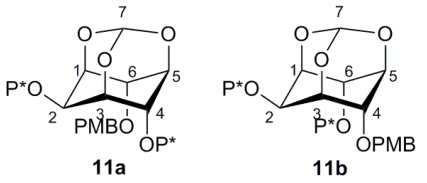
Synthesis of (±)-6-*O*-(*p*-methoxybenzyl)-*myo*-inositol orthoformate (±)-6



To a solution of *myo*-inositol orthoformate (200 mg, 1.05 mmol, 1 equiv) in DMF dry (7.5 mL, 0.14 M) at 0 °C was added portionwise NaH (60% in oil w/w; 42 mg, 1.06 mmol, 1.01 equiv). The reaction mixture was then treated with PMBCl (153 µL, 1.16 mmol, 1.1 equiv) and stirred at rt for 4 h. The mixture was neutralized with MeOH and concentrated *in vacuo* at 60 °C. The crude was diluted with EtOAc and washed with H_2O and then with brine. The organic phase was dried over Na_2SO_4 filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, EtOAc/hexane 50%) afforded **(±)-6** as a colorless oil (244 mg, 0.78 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23 (2H, d, *J* 8.7 Hz, Ph), 6.90 (2H, d, *J* 8.7 Hz, Ph), 5.43 (1H, d, *J* 1.3 Hz, H-C7), 4.61 (1H, d, *J* 11.3 Hz, CH_2-Ph), 4.57 (1H, d, *J* 11.3 Hz, CH_2-Ph), 4.44 (1H, dtd, *J* 10.3, 3.9, 2.1 Hz, H-C6), 4.40 (1H, td, *J* 3.9, 2.0 Hz, H-C4), 4.23-4.25 (1H, m, H-C5), 4.18-4.22 (2H, m, H-C3, H-C1), 4.06 (1H, d, *J* 11.8 Hz, H-C2), 3.81 (3H, s, O-CH_3), 3.77 (1H, d, *J* 10.3 Hz, OH-C6), 3.23 (1H, d, *J* 11.8 Hz, OH-C2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.1 (*i*Ph), 129.9 (2xPh), 127.9 (*i*Ph), 114.3 (2xPh), 102.7 (C7), 74.8 (C1), 73.8 (C4), 72.8 (CH_2-Ph), 72.3 (C3), 67.9 (C6), 67.3 (C5), 60.7 (C2), 55.3 (O-CH_3); [***m/z*** (ESI) $(M+Na)^+$ $C_{15}H_{18}NaO_7$ requires 333.0945, found 333.0943].

Synthesis of the 6-*O*-(*p*-methoxybenzyl)-2,4-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol orthoformate 11a and 6-*O*-(*p*-methoxybenzyl)-2,4-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol orthoformate 11b



Synthesized from **(±)-6** following procedure A. The obtained residue was purified by flash chromatography (SiO_2, EtOAc/hexane 30 -> 50%); **11a** was obtained in ratio 10:1 and was repurified by FC (SiO_2, EtOAc/toluene 10 -> 20%) to obtain pure **11a**[c] as a white solid (dr > 99:1, 24%[a]). **11b** [a] was obtained in a ratio 14:1, and was repurified by FC (SiO_2, EtOAc/toluene 10 -> 20%) to obtain pure **11b** [c] as a white solid (dr > 99:1, 16%[a]).

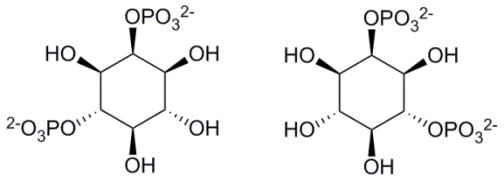
[a] Yield based on the diastereomer itself, which represent 50% of the racemic starting material.
[c] Absolute configuration was determined with the deprotected inositol bisphosphates **2,6-IP$_2$** and **2,4-IP$_2$**.

11a[c]: $[\alpha]_D^{23}$ +29.0 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.47 (4H, m, Ph), 7.15-7.39 (16H, m, Ph), 6.97 (2H, d, *J* 8.6 Hz, Ph), 6.67 (2H, d, *J* 8.6 Hz, Ph), 5.66 (1H, dd, *J* 9.4, 7.4 Hz, CH-Ph), 5.45-5.54 (2H, m, CH-Ph), 5.43 (1H, d, $^5J_{HH}$ 1.1 Hz, H-C7), 5.28 (1H, dd, *J* 9.4, 7.4 Hz, CH-Ph), 5.20 (1H, dt, $^3J_{HP}$ 7.4, $^3J_{HH}$ 3.5 Hz, H-C6), 5.14 (1H, dd, $^3J_{HP}$ 7.2, $^5J_{HH}$ 1.1 Hz, H-C2), 4.58 (1H, br, H-C1), 4.28 (1H, br, H-C5), 4.23 (1H, br, H-C3), 4.19 (1H, d, $^2J_{HH}$ 11.5, CH_2-Ph), 4.11 (1H, d, $^2J_{HH}$ 11.5, CH_2-Ph), 4.08 (1H, br, H-C4), 3.72 (3H, s, O-CH_3), 2.35-2.42 (2H, m, CH_2), 2.13-2.27 (4H, m, CH_2), 1.95-2.01 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) 159.5 (*i*Ph), 140.6 (d, $^3J_{CP}$ 10.4 Hz, 2x*i*Ph), 140.3 (d, $^3J_{CP}$ 9.9 Hz, *i*Ph), 140.1 (d, $^3J_{CP}$ 9.9 Hz, *i*Ph), 129.7 (2xPh), 129.1 (*i*Ph), 128.77 (2xPh), 128.76 (2xPh), 128.72 (2xPh), 128.68 (2xPh), 128.53 (Ph), 128.50 (Ph), 128.45 (Ph), 128.34 (Ph), 125.93 (4xPh), 125.85 (2xPh), 125.8 (2xPh), 113.9 (2xPh), 102.9 (C7), 81.2 (d, $^2J_{CP}$ 6.1 Hz, CH-Ph), 80.8 (d, $^2J_{CP}$ 6.2 Hz, CH-Ph), 80.2 (d, $^2J_{CP}$ 3.6 Hz, CH-Ph), 79.9 (d, $^2J_{CP}$ 2.6 Hz, CH-Ph), 72.1 (C4), 71.2 (t, $^3J_{CP}$ 5.4 Hz, C1), 70.9 (d, $^2J_{CP}$ 4.8 Hz, C6), 70.8 (CH_2-Ph), 70.5 (d, $^3J_{CP}$ 3.0 Hz, C3), 68.0 (d, $^3J_{CP}$ 5.0 Hz, C5), 67.1 (d, $^2J_{CP}$ 3.3 Hz, C2), 55.4 (O-CH_3), 37.6 (CH_2), 37.5 (CH_2), 37.3 (CH_2), 36.9 (CH_2); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, $CDCl_3$) δ (ppm) -0.82(1P), -1.84 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_{47}H_{49}O_{13}P_2$ requires 883.2643, found 883.2620].

11b[c]: $[\alpha]_D^{25}$ +43.0 (*c* 0.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.43 (2H, d, *J* 6.9 Hz, Ph), 7.24-7.39 (18H, m, Ph), 7.16 (2H, d, *J* 8.6 Hz, Ph), 6.69 (2H, d, *J* 8.6 Hz, Ph), 5.64 (1H, dd, *J* 9.8, 7.4 Hz, CH-Ph), 5.52 (1H, dd, *J* 9.9, 7.4 Hz, CH-Ph), 5.48 (1H, dd, *J* 10.0, 7.4 Hz, CH-Ph), 5.44 (1H, d, $^5J_{HH}$ 0.5 Hz,

H-C7), 5.07-5.15 (3H, m, CH-Ph, H-C2, H-C4), 4.58 (1H, br, H-C5), 4.54 (1H, d, $^2J_{HH}$ 11.3, CH_2-Ph), 4.50-4.52 (1H, m, H-C1), 4.46 (1H, d, $^2J_{HH}$ 11.3, CH_2-Ph), 4.33 (1H, br, H-C6), 4.15 (1H, br, H-C3), 3.71 (3H, s, O-CH_3), 1.92-2.44 (8H, m, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 159.4 (*i*Ph), 140.4 (d, $^3J_{CP}$ 4.6 Hz, *i*Ph), 140.3 (d, $^3J_{CP}$ 4.2 Hz, *i*Ph), 140.1 (d, $^3J_{CP}$ 10.2 Hz, *i*Ph), 140.0 (d, $^3J_{CP}$ 10.3 Hz, *i*Ph), 129.6 (2xPh), 129.3 (*i*Ph), 128.8 (2xPh), 128.69 (4xPh), 128.68 (2xPh), 128.6 (Ph), 128.5 (Ph), 128.40 (Ph), 128.39 (Ph), 126.1 (2xPh), 125.84 (2xPh), 125.76 (2xPh), 125.7 (2xPh), 113.9 (2xPh), 102.9 (C7), 81.0 (d, $^2J_{CP}$ 6.3 Hz, CH-Ph), 80.9 (d, $^2J_{CP}$ 6.1 Hz, CH-Ph), 79.8 (d, $^2J_{CP}$ 2.9 Hz, CH-Ph), 79.6 (d, $^2J_{CP}$ 3.1 Hz, CH-Ph), 72.8 (C6), 71.3 (CH_2-Ph), 70.94 (dd, $^3J_{CP}$ 8.3, 5.4 Hz, C3), 70.89 (d, $^3J_{CP}$ 3.8 Hz, C1), 70.7 (d, $^2J_{CP}$ 4.1 Hz, C4), 67.7 (d, $^3J_{CP}$ 1.2 Hz, C5), 67.3 (d, $^2J_{CP}$ 4.1 Hz, C2), 55.3 (O-CH_3), 37.5 (CH_2), 37.3 (CH_2), 36.82 (CH_2), 36.76 (CH_2); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, $CDCl_3$) δ (ppm) -0.90(1P), -1.32 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_{47}H_{49}O_{13}P_2$ requires 883.2643, found 883.2631].

Synthesis of 2,4-di-*O*-phosphate *myo*-inositol 2,4-IP$_2$ and 2,6-di-*O*-phosphate *myo*-inositol 2,6-IP$_2$



Synthesized from **11a** and **11b** according to procedure B with a reaction time of 1.5 h. **2,4-IP$_2$** was obtained as a white solid (3.9 mg, 95%); **2,6-IP$_2$** was obtained as a white solid (3.7 mg, 87%); respectively.

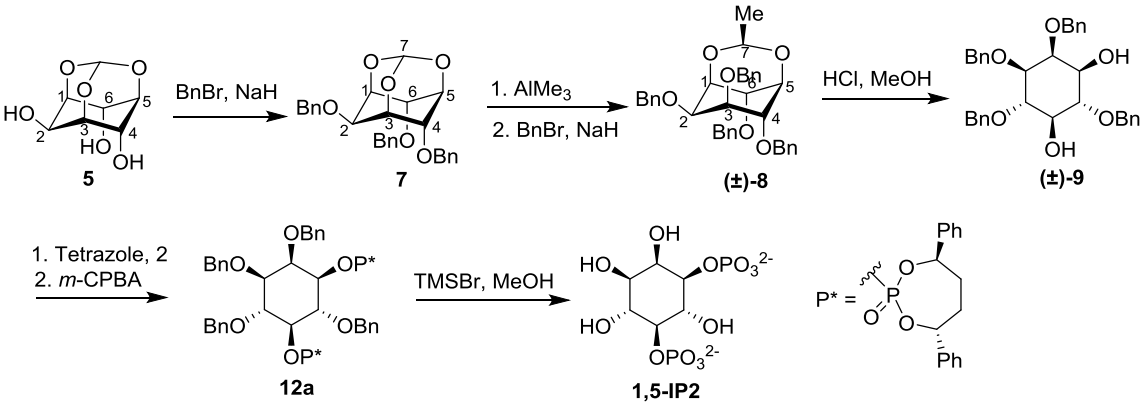
^{1}H NMR (400 MHz, MeOD) δ (ppm) 4.70 (1H, dt, $^3J_{HP}$ 8.2, *J* 2.0 Hz, H-C2), 4.32 (1H, q, $^3J_{HP}$ 9.2, *J* 9.2 Hz, H-C6), 3.74 (1H, d, *J* 9.4 Hz, H-C1), 3.67 (1H, t, *J* 9.5 Hz, H-C4), 3.55 (1H, dt, *J* 9.9, 2.0 Hz, H-C3), 3.43 (1H, t, *J* 9.1 Hz, H-C5); **^{13}C NMR** (101 MHz, MeOD) δ (ppm) 81.3 (d, $^2J_{CP}$ 6.3 Hz, C2), 81.1 (d, $^2J_{CP}$ 6.2 Hz, C6), 75.3 (d, $^3J_{CP}$ 3.6 Hz, C5), 73.9 (C4), 71.9 (d, $^3J_{CP}$ 3.3 Hz, C3), 71.2 (t, $^3J_{CP}$ 3.3 Hz, C1); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, MeOD) δ (ppm) 1.10 (1P), 0.74 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_6H_{15}O_{12}P_2$ requires 341.0033, measured 341.0034].

Absolute configuration was determined by optical rotation measurement that was compared with literature.[6] In order to ensure the comparison with the literature, the samples were prepared in similar condition. Hence, compounds **2,4-IP$_2$** and **2,6-IP$_2$** were prepared according to procedure C to obtain the lithium salt.

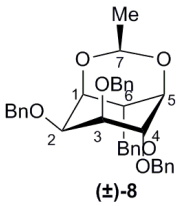
2,4-IP$_2$: $[\alpha]_D^{23}$ +10.78 (*c* 0.117, H_2O, lithium salt, pH =7);

2,6-IP$_2$: $[\alpha]_D^{23}$ -7.43 (*c* 0.183, H_2O, lithium salt,pH =7) {lit. $[\alpha]_D^{22}$ -4.3 (*c* 0.7, H_2O, pH = 10)}[6]

2.4. Synthesis of 1,5-diphosphate *myo*-inositol 1,5-IP_2



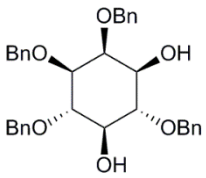
Synthesis of (±)-2,3,4,6-*tetra*-*O*-benzyl-1,5-*O*-ethyldiene *myo*-inositol (±)-8



To a solution of (±)-2,4,6-*tri*-*O*-benzyl-1,5-*O*-ethyldiene *myo*-inositol (483 mg, 1.01 mmol, 1 equiv) in DMF dry (10.1 mL, 0.1 M) at 0 °C was added portionwise NaH (60% in oil w/w; 57 mg, 1.42 mmol, 1.4 equiv). The reaction mixture was then treated with benzyl chloride (217 µL, 1.72 mmol, 1.7 equiv) and stirred for 20 h. The mixture was neutralized with MeOH and concentrated *in vacuo* at 60 °C. The crude was diluted with EtOAc and washed with H_2O and then with brine. The organic phase was dried over Na_2SO_4 filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, EtOAc/hexane 10%) afforded **(±)-8** as a white solid (528 mg, 0.93 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20-7.38 (20H, m, Ph), 5.38 (1H, q, *J* 4.8 Hz, H-C7), 4.78 (1H, d, *J* 11.7 Hz, CH_2-Ph), 4.77 (1H, d, *J* 11.9 Hz, CH_2-Ph), 4.73 (1H, d, *J* 11.9 Hz, CH_2-Ph), 4.68 (1H, d, *J* 11.4 Hz, CH_2-Ph), 4.65 (1H, d, *J* 11.6 Hz, CH_2-Ph), 4.54 (1H, d, *J* 11.7 Hz, CH_2-Ph), 4.48 (1H, d, *J* 11.7 Hz, CH_2-Ph), 4.42-4.45 (1H, m), 4.41 (1H, d, *J* 11.5 Hz, CH_2-Ph), 4.35 (1H, dd, *J* 3.6, 1.9 Hz), 4.30 (1H, t, *J* 7.9 Hz), 4.12 (1H, t, *J* 7.5 Hz), 4.06 (1H, d, *J* 8.0 Hz), 3.97 (1H, td, *J* 4.0, 0.9 Hz), 1.25 (3H, d, *J* 4.9 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 138.5 (*i*Ph), 138.4 (*i*Ph), 137.9 (*i*Ph), 137.6 (*i*Ph), 128.50 (2xPh), 128.47 (2xPh), 128.4 (2xPh), 128.3 (2xPh), 128.2 (2xPh), 128.1 (2xPh), 127.92 (Ph), 127.90 (2xPh), 127.58 (Ph), 127.6 (2C, Ph), 127.52 (Ph), 127.47 (Ph), 90.9 (C7), 80.9, 76.3, 73.4, 73.3, 72.4 (CH_2-Ph), 72.32 (CH_2-Ph), 72.26 (CH_2-Ph), 71.3 (CH_2-Ph), 69.8, 68.6, 20.8 (CH_3); [***m/z*** (ESI) $(M+Na)^+$ $C_{36}H_{38}NaO_6$ requires 589.2561, found 589.2556].

Synthesis of (±)-2,3,4,6-*tetra*-*O*-benzyl *myo*-inositol (±)-9

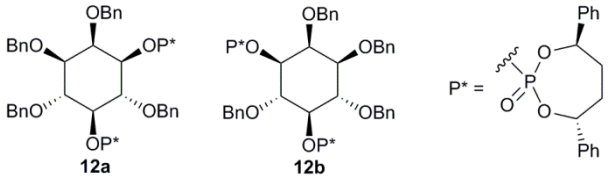


(±)-9

A solution of **(±)-8** (60.9 mg, 107 µmol, 1 equiv) in MeOH (6.5 mL, 0.02 M) at 0 °C was treated with HCl_{cc} (75 µL, 900 µmol, 8.4 equiv) and stirred at rt for 2.5 h. The mixture was concentrated *in vacuo* at 40 °C and co-evaporated with toluene. Purification by flash column chromatography (SiO_2, EtOAc/hexane 30%) afforded **(±)-9** as a white solid (52.6 mg, 97 µmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28-7.41 (20H, m, Ph), 5.01 (1H, d, *J* 11.6 Hz, CH_2-Ph), 5.01 (1H, d, *J* 11.2 Hz, CH_2-Ph), 4.92 (1H, d, *J* 11.3 Hz, CH_2-Ph), 4.81 (1H, d, *J* 11.3 Hz, CH_2-Ph), 4.79 (1H, d, *J* 11.2 Hz, CH_2-Ph), 4.76 (1H, d, *J* 11.6 Hz, CH_2-Ph), 4.70 (2H, s, CH_2-Ph), 4.08 (1H, t, *J* 2.5 Hz, H-C2), 3.93 (1H, t, *J* 9.4 Hz, H-C4), 3.72 (1H, t, *J* 9.3 Hz, H-C6), 3.55 (1H, td, *J* 9.2, 2.0 Hz, H-C5), 3.48-3.55 (1H, m, H-C1), 3.47 (1H, dd, *J* 9.8, 2.4 Hz, H-C3), 2.54 (1H, d, *J* 2.1 Hz, OH-C6), 2.34 (1H, d, *J* 6.3 Hz, OH-C1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 138.83 (*i*Ph), 138.82 (*i*Ph), 138.81 (*i*Ph), 138.23 (*i*Ph), 128.64 (3xPh), 128.59 (2xPh), 128.5 (2xPh), 128.2 (2xPh), 128.1 (2xPh), 127.91 (3xPh), 127.90 (2xPh), 127.88 (Ph), 127.8 (Ph), 127.7 (2xPh), 81.8 (C6), 81.4 (C4), 81.0 (C3), 77.2 (C2),75.6 (CH_2-Ph), 75.2 (C5), 75.1 (CH_2-Ph), 74.9 (CH_2-Ph), 72.9 (CH_2-Ph), 72.3 (C1); [***m/z*** (ESI) $(M+Na)^+$ $C_{34}H_{36}NaO_6$ requires 563.2404, found 563.2405].

Synthesis of the 2,3,4,6-tetra-*O*-benzyl-1,5-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol 12a and the 1,2,4,6-tetra-*O*-benzyl-3,5-(di-*O*-(1*R*,4*R*)-1,4-diphenylbutanephospho) *myo*-inositol 12b



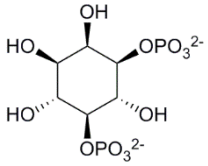
12a **12b**

Synthesized from **(±)-9**; the obtained residue was purified by flash chromatography (SiO_2, EtOAc/ hexane 30->40%) affording the diastereomeric mixture **12a** and **12b** as white solid (229 mg, 98%). Crystallization of the mixture by vapor diffusion method (EtOAc/Et_2O) afforded diastereomer **12a** (dr >99:1, 52%[a]). Mother liquor was crystallized in *i*PrOH, and diastereomer **12b** was recovered (dr 85:15, 11[a]).

[a] Yield based on the diastereomer itself, which represent 50% of the racemic starting material.

12a: $[\alpha]_D^{23}$ +43.1 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.43 (2H, dd, *J* 7.8, 1.6 Hz, Ph), 7.29-7.38 (8H, m, Ph), 7.05-7.26 (28H, m, Ph), 7.01 (2H, t, *J* 7.3 Hz, Ph), 5.59 (1H, dd, *J* 10.1, 6.9 Hz, CH-Ph), 5.53 (1H, td, *J* 7.2, 4.9 Hz, CH-Ph), 5.37 (1H, dd, *J* 10.2, 7.5 Hz, CH-Ph), 5.14 (1H, dd, *J* 10.4, 6.9 Hz, CH-Ph), 4.97 (1H, d, *J* 10.3, CH_2-Ph), 4.89 (1H, d, *J* 11.5, CH_2-Ph), 4.81 (1H, d, *J* 11.5, CH_2-Ph), 4.63 (1H, d, *J* 10.3, CH_2-Ph), 4.51 (1H, d, *J* 10.8, CH_2-Ph), 4.44-4.51 (1H, m, H-C5), 4.44-4.46 (1H, m, H-C2), 4.43 (1H, d, *J* 11.3, CH_2-Ph), 4.36 (1H, d, *J* 11.3, CH_2-Ph), 4.25 (1H, d, *J* 10.8, CH_2-Ph), 4.08-4.17 (2H, m, H-C1, H-C6), 3.87 (1H, t, *J* 9.5 Hz, H-C4), 3.30 (1H, dd, *J* 9.8, 2.3 Hz, H-C3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) 140.8 (d, $^3J_{CP}$ 10.2 Hz, *i*Ph), 140.4 (d, $^3J_{CP}$ 10.0 Hz, *i*Ph), 140.3 (d, $^3J_{CP}$ 9.0 Hz, *i*Ph), 140.2 (d, $^3J_{CP}$ 10.2 Hz, *i*Ph), 138.2 (*i*Ph), 138.7 (*i*Ph) 138.1 (*i*Ph), 137.9 (*i*Ph), 128.69 (2xPh), 128.68 (2xPh), 128.49 (2xPh), 128.45 (3xPh), 128.34 (3xPh), 128.30 (2xPh), 128.28 (2xPh), 128.14 (Ph), 128.11 (Ph), 128.4 (2xPh), 128.0 (2xPh), 128.91 (2xPh), 127.89 (2xPh), 127.7 (2xPh), 127.64 (Ph), 127.55 (Ph), 127.54 (2xPh), 127.31 (Ph), 127.0 (Ph), 125.9 (4xPh), 125.74 (2xPh), 125.67 74 (2xPh), 81.32 (dd, $^2J_{CP}$ 6.5, $^4J_{CP}$ 2.6 Hz, C5), 80.71 (d, $^2J_{CP}$ 6.2 Hz, CH-Ph), 80.69 (d, $^2J_{CP}$ 6.2 Hz, CH-Ph), 80.1 (C3), 79.6 (d, $^2J_{CP}$ 3.0 Hz, CH-Ph), 79.3 (d, $^3J_{CP}$ 2.4 Hz, C4), 79.1 (d, $^2J_{CP}$ 2.8 Hz, CH-Ph), 78.6 (dd, $^3J_{CP}$ 9.0, 4.2 Hz, C6), 78.1 (dd, $^2J_{CP}$ 4.8, $^4J_{CP}$ 1.6, Hz, C1), 76.3 (C2), 75.5 (CH_2-Ph), 75.3 (CH_2-Ph), 74.8 (CH_2-Ph), 72.8 (CH_2-Ph), 38.1 (CH_2), 37.6 (CH_2), 37.1 (CH_2), 37.0 (CH_2); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, $CDCl_3$) δ (ppm) -1.49(1P), -2.24 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_{50}H_{51}O_{12}P_2$ requires 1113.4102, found 1113.4087].

Synthesis of 1,5-diphosphate *myo*-inositol 1,5-IP$_2$



1,5-IP$_2$

To a solution of **12a** (15.0 mg, 16.6 µmol, 1 equiv) dissolved in a minimum amount of CH_2Cl_2 was added methanol (9 mL, 1.8 mM) and Pd on activated carbon 10 % (w/w) (point of spatula). The reaction mixture was evacuated and flushed with hydrogen gas (operation repeated several times during the reaction time) and was vigorously stirred at rt for 1.5 h. The reaction mixture was flushed with nitrogen, filtered through a pad of celite and concentrated to dryness. Suspension in acetone, then acetonitrile and chloroform afforded clean product **1,5-IP$_2$** as a white solid (3.2 mg, 89%).

1,5-IP$_2$: $[\alpha]_D^{23}$ -4.85 (*c* 0.094, H_2O, lithium salt, pH =7)[d]; **^{1}H NMR** (400 MHz, MeOD) δ (ppm) 4.20 (1H, br, H-C2), 4.03-4.10 (1H, m, H-C1), 3.91-4.02 (2H, m, H-C6, H-C5), 3.81 (1H, t, *J* 9.0 Hz, H-C4), 3.44 (1H, dd, *J* 9.7, 2.5 Hz, H-C3); **^{13}C NMR** (101 MHz, MeOD) δ (ppm) 81.1 (d, $^2J_{CP}$ 6.4 Hz), 77.2 (d, $^2J_{CP}$ 5.0 Hz), 71.7 (br), 71.0 (C2), 70.9 (C3), 70.6 (br); **^{31}P NMR** (162 MHz, ^{1}H-decoupled, MeOD) δ (ppm) 0.94 (1P), 0.04 (1P); [***m/z*** (ESI) $(M+H)^+$ $C_6H_{15}O_{12}P_2$ requires 341.0033, measured 341.0034].

[d] **1,5-IP$_2$** lithium salts were prepared following the procedure C for optical rotation measurement.

3. X-Ray Crystallographic Structure

Compound 10a, CCDC 1457084

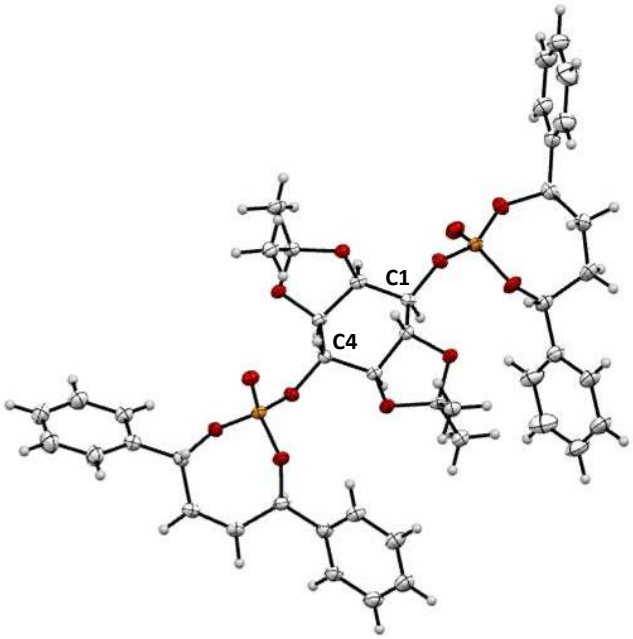


Figure S1 X-Ray structure of compound **10a**

Compound 12a, CCDC 1457083

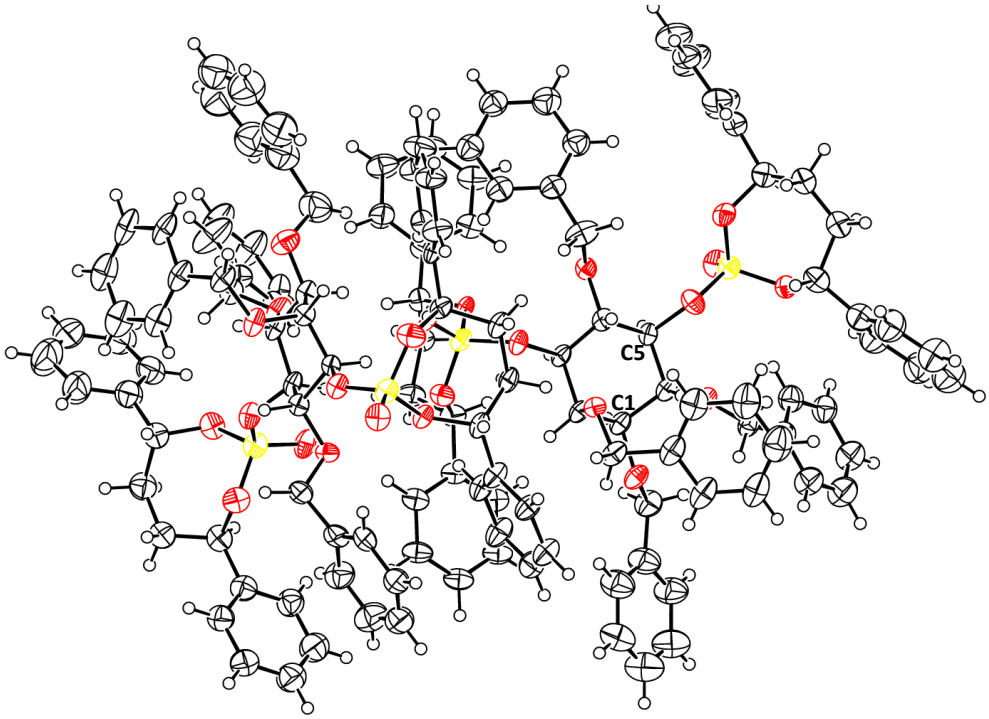


Figure S2 X-Ray structure of compound **12a**

The quality of the crystal was poor however it was sufficient for assigning the absolute configuration.

4. References

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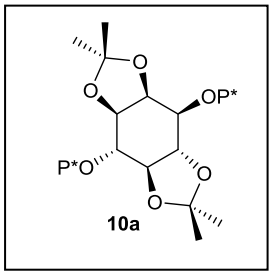
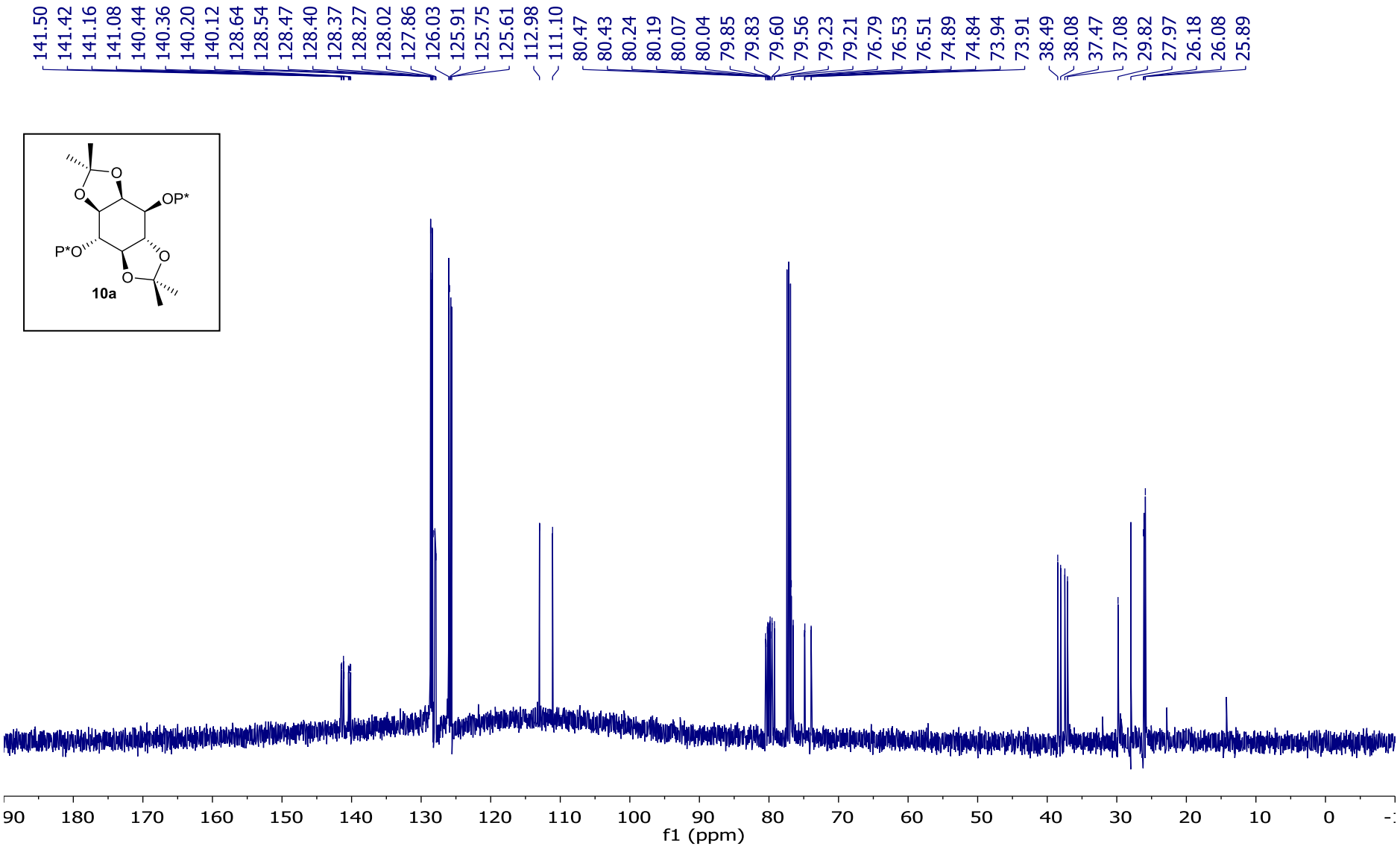
5. NMR spectroscopy spectra

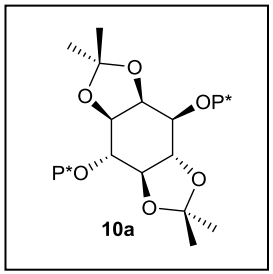
^{1}H NMR, 400 MHz, $CDCl_3$



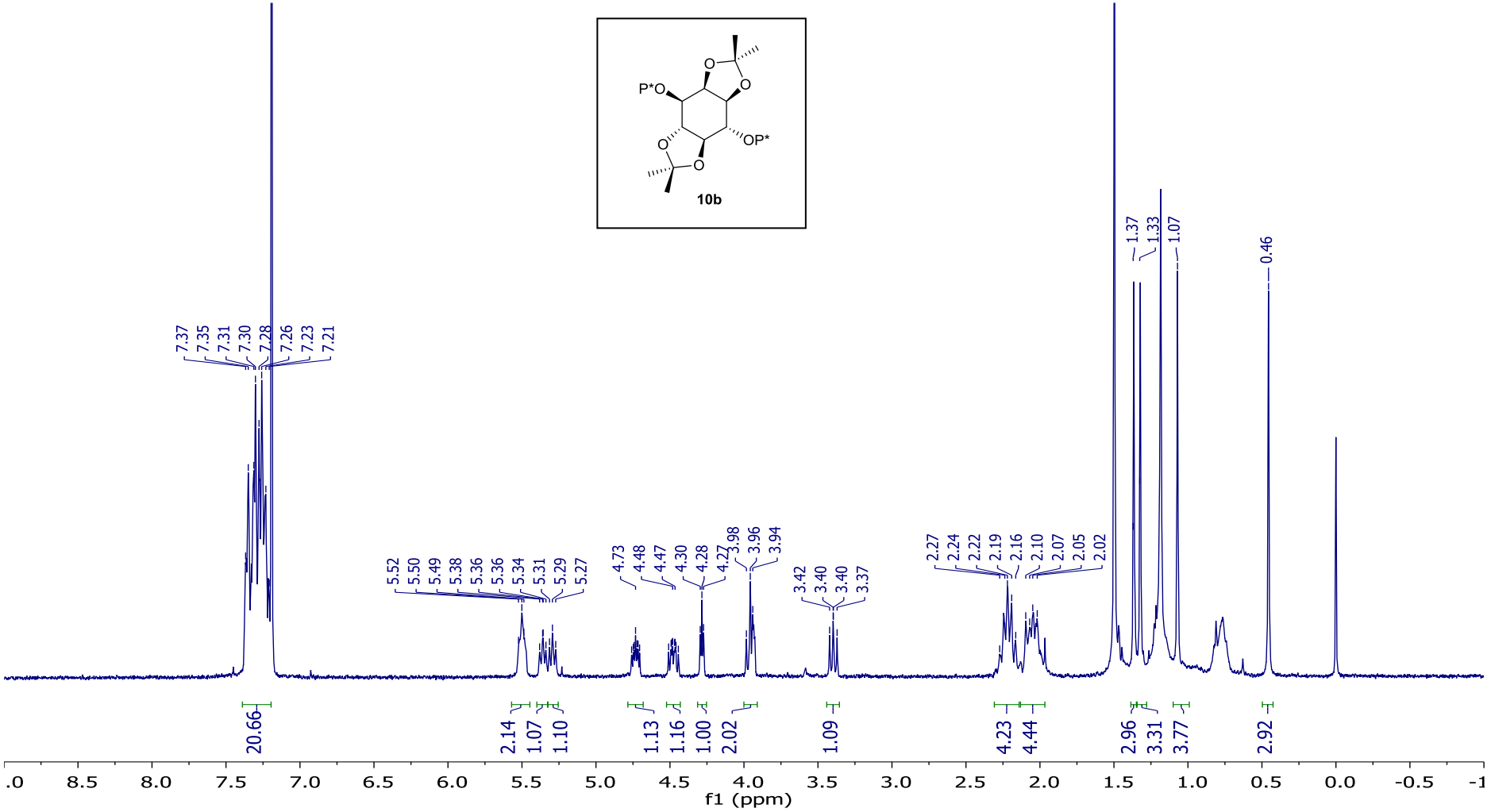
^{13}C NMR, 126 MHz, $CDCl_3$



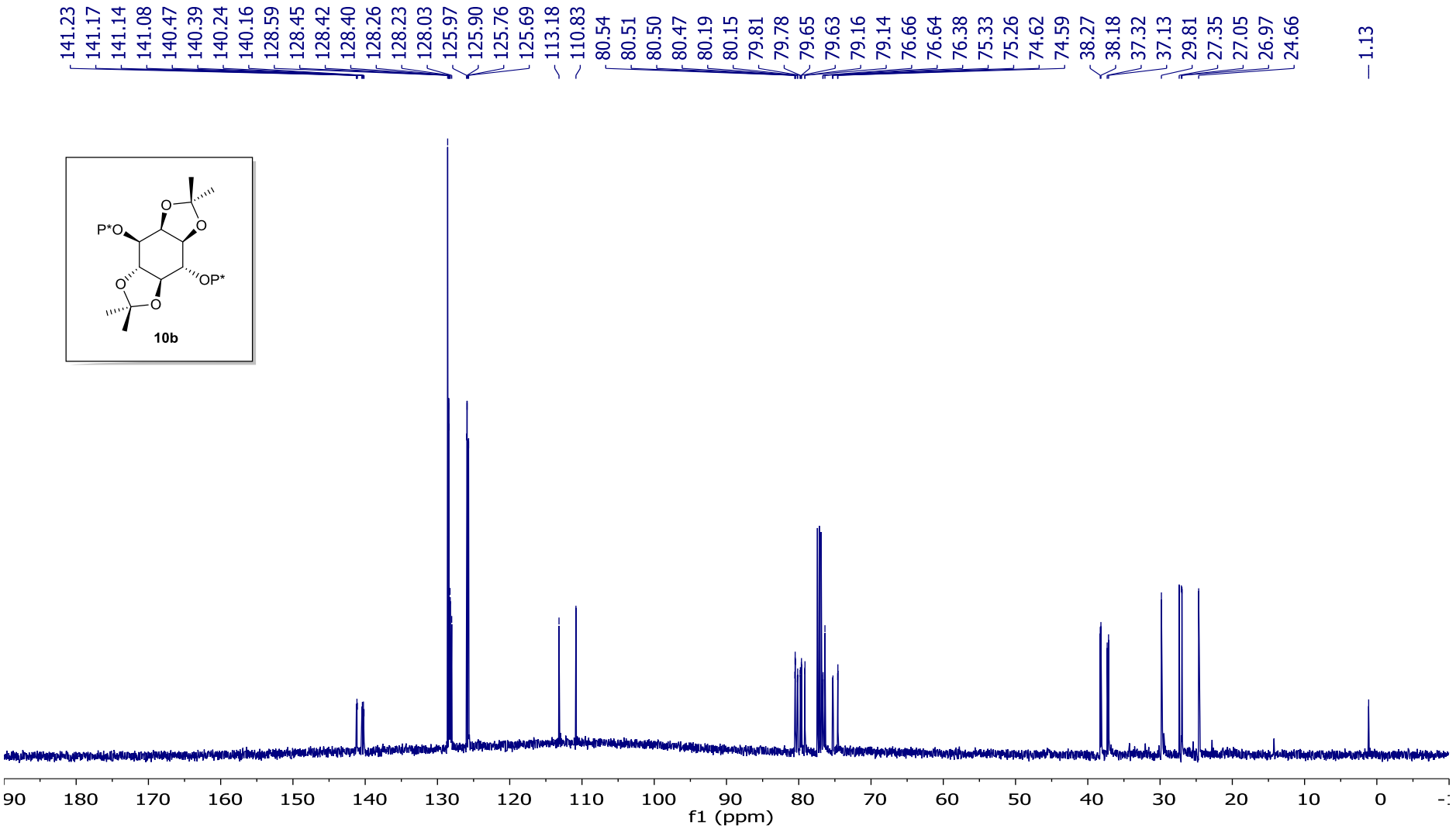
^{31}P NMR, 162 MHz, $CDCl_3$



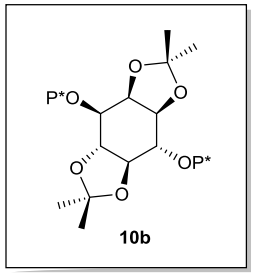
^{1}H NMR, 400 MHz, $CDCl_3$



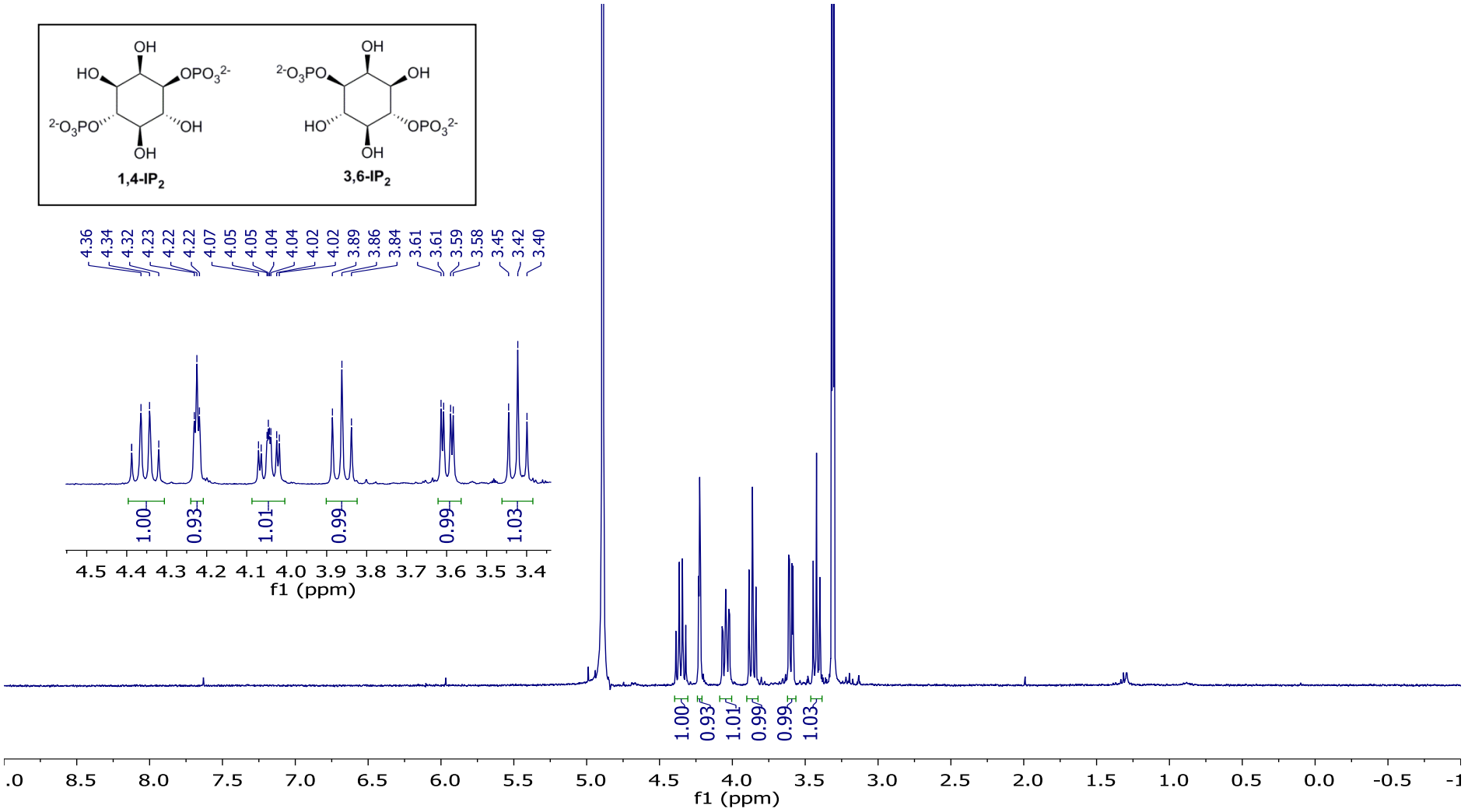
^{13}C NMR, 126 MHz, $CDCl_3$



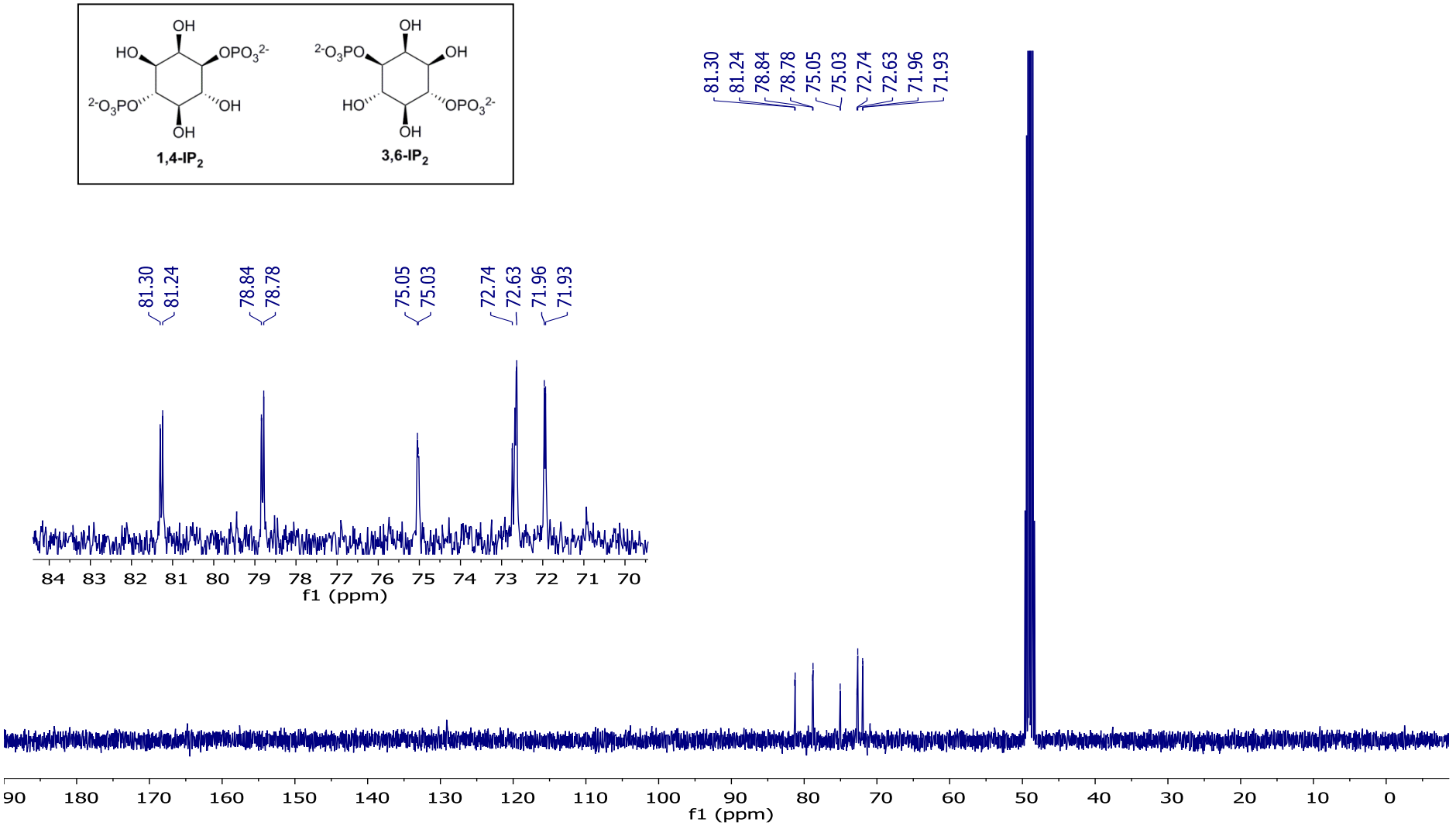
^{31}P NMR, 162 MHz, $CDCl_3$



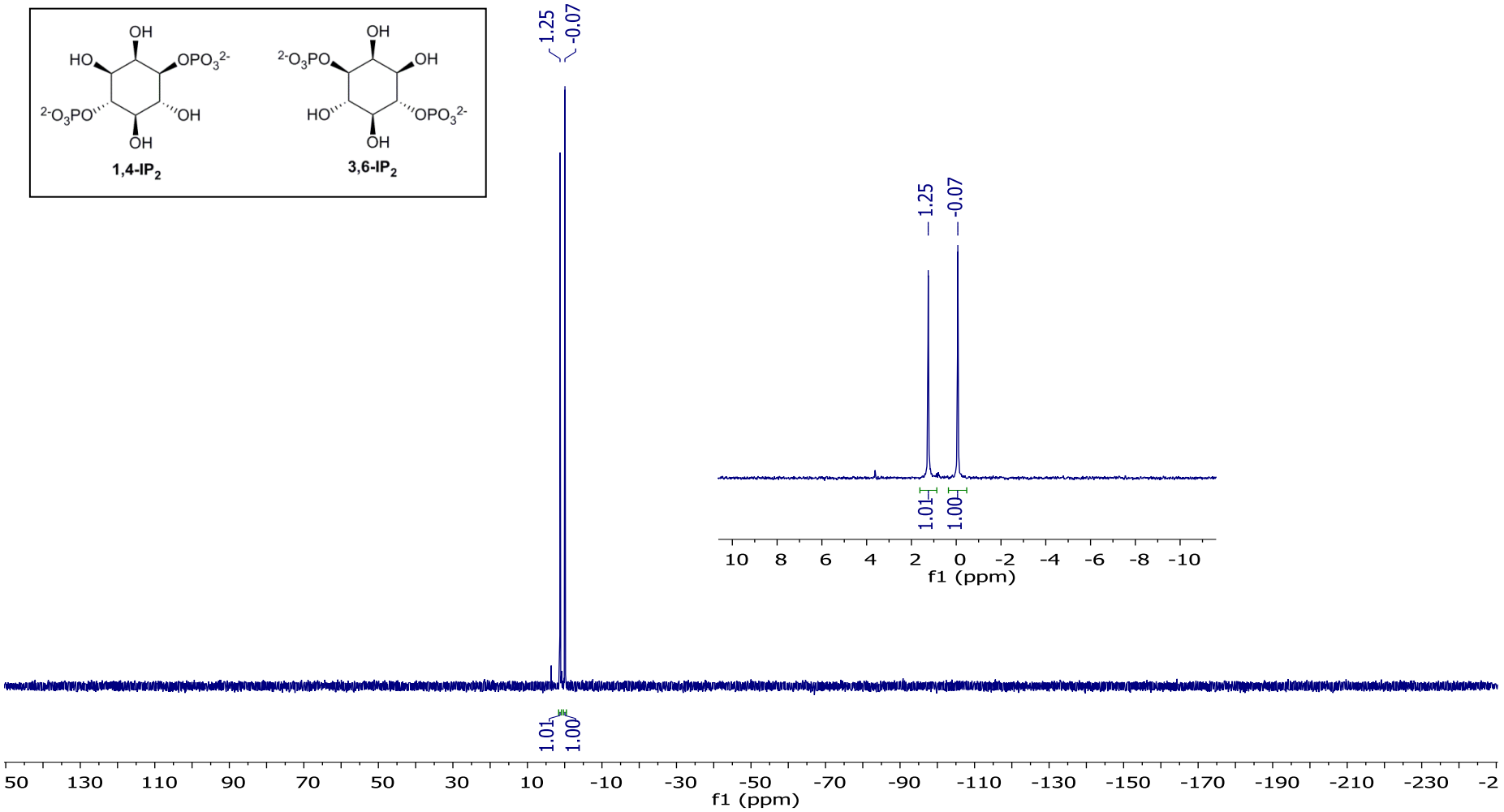
^{1}H NMR, 400 MHz, MeOD



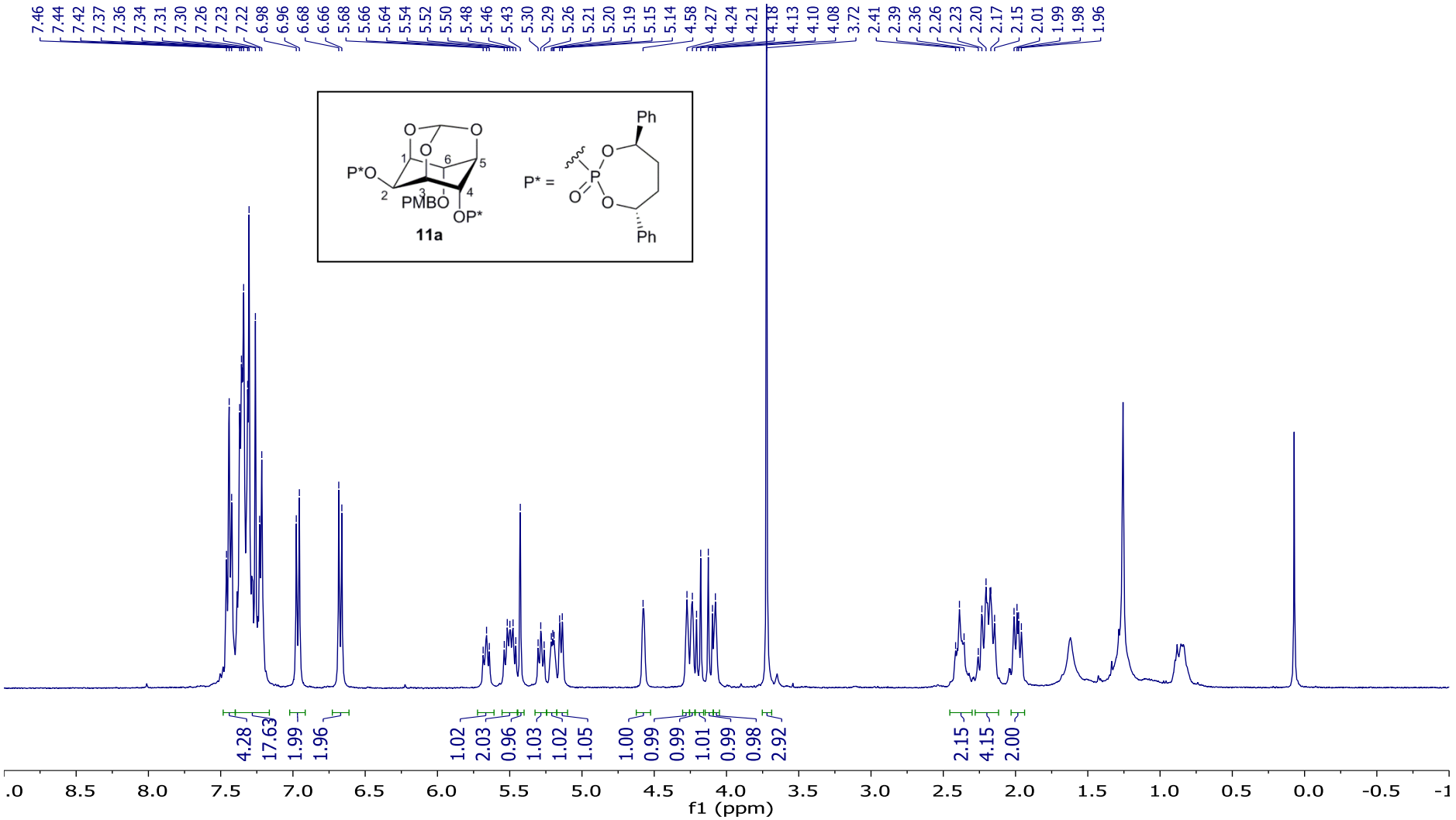
^{13}C NMR, 101 MHz, MeOD



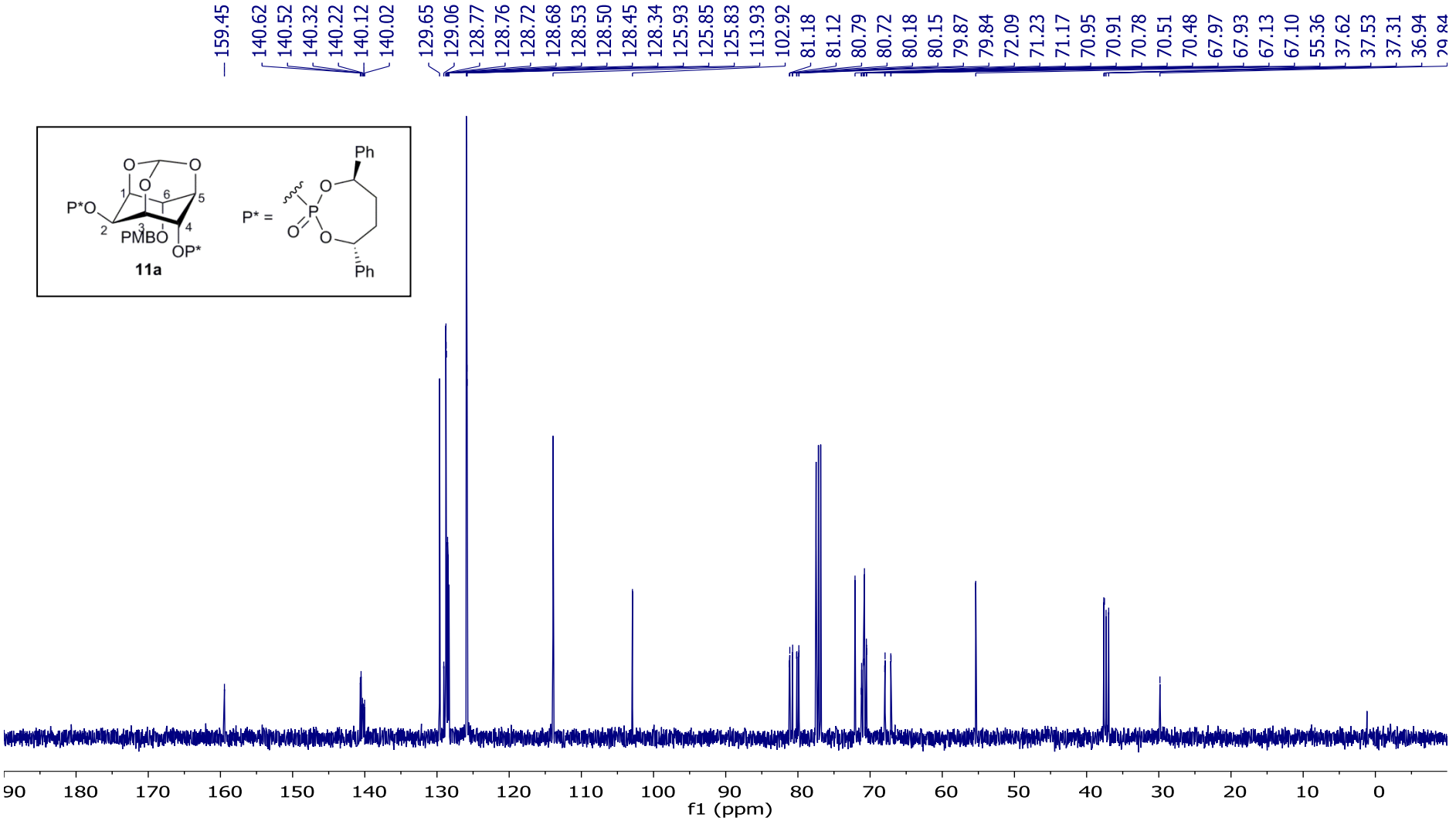
^{31}P NMR, 162 MHz, MeOD



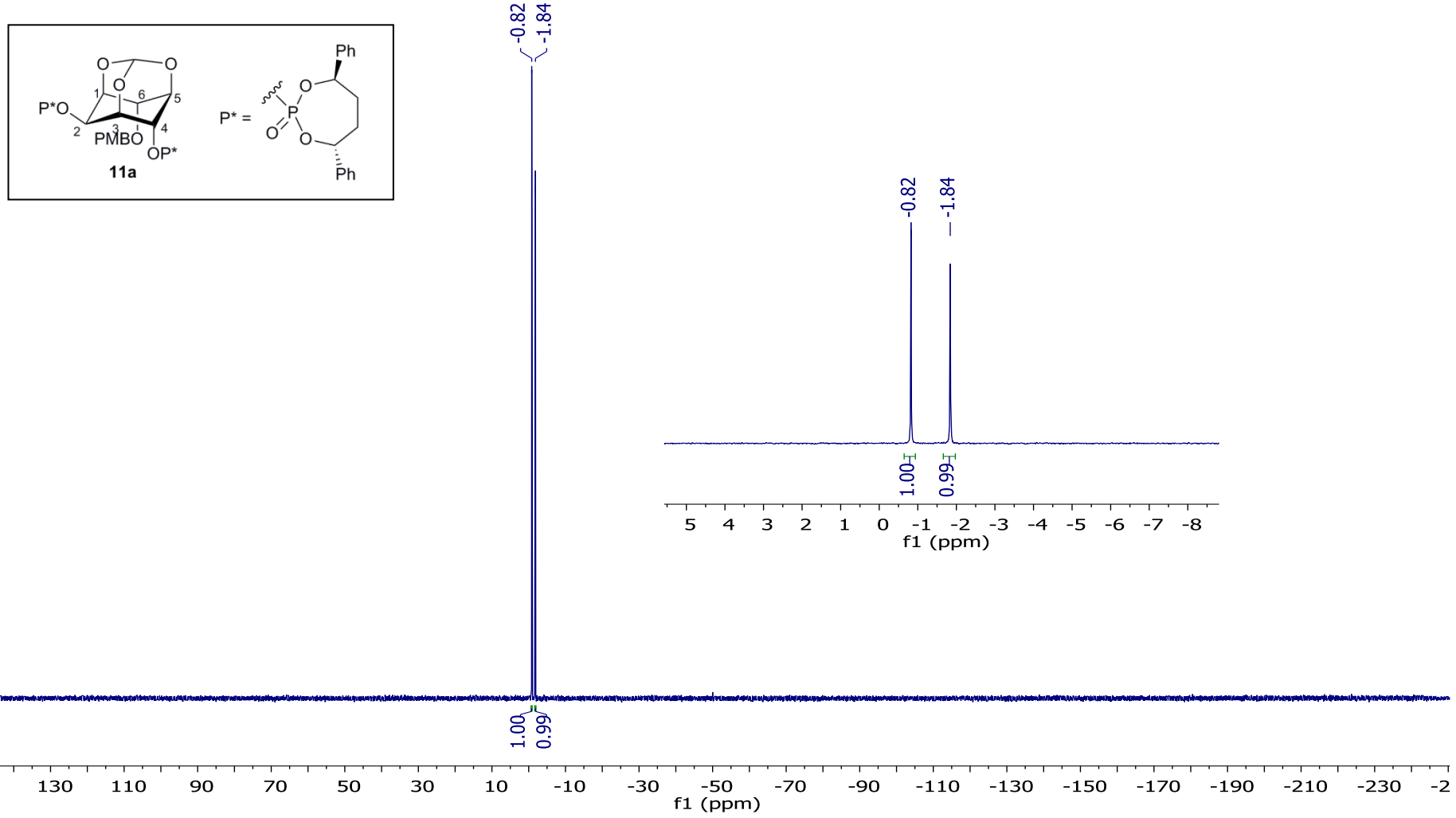
^{1}H NMR, 400 MHz, $CDCl_3$



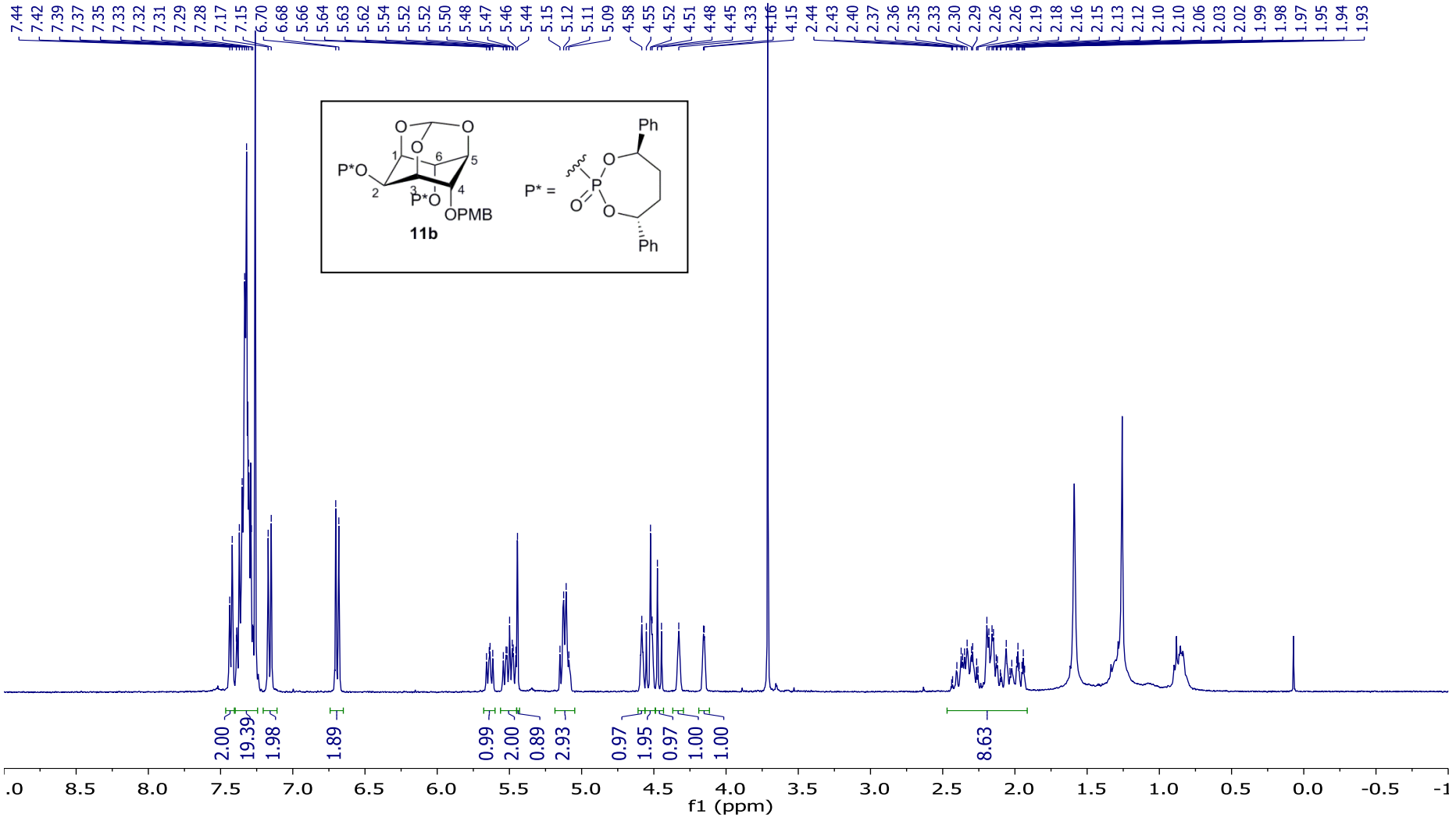
^{13}C NMR, 101 MHz, $CDCl_3$



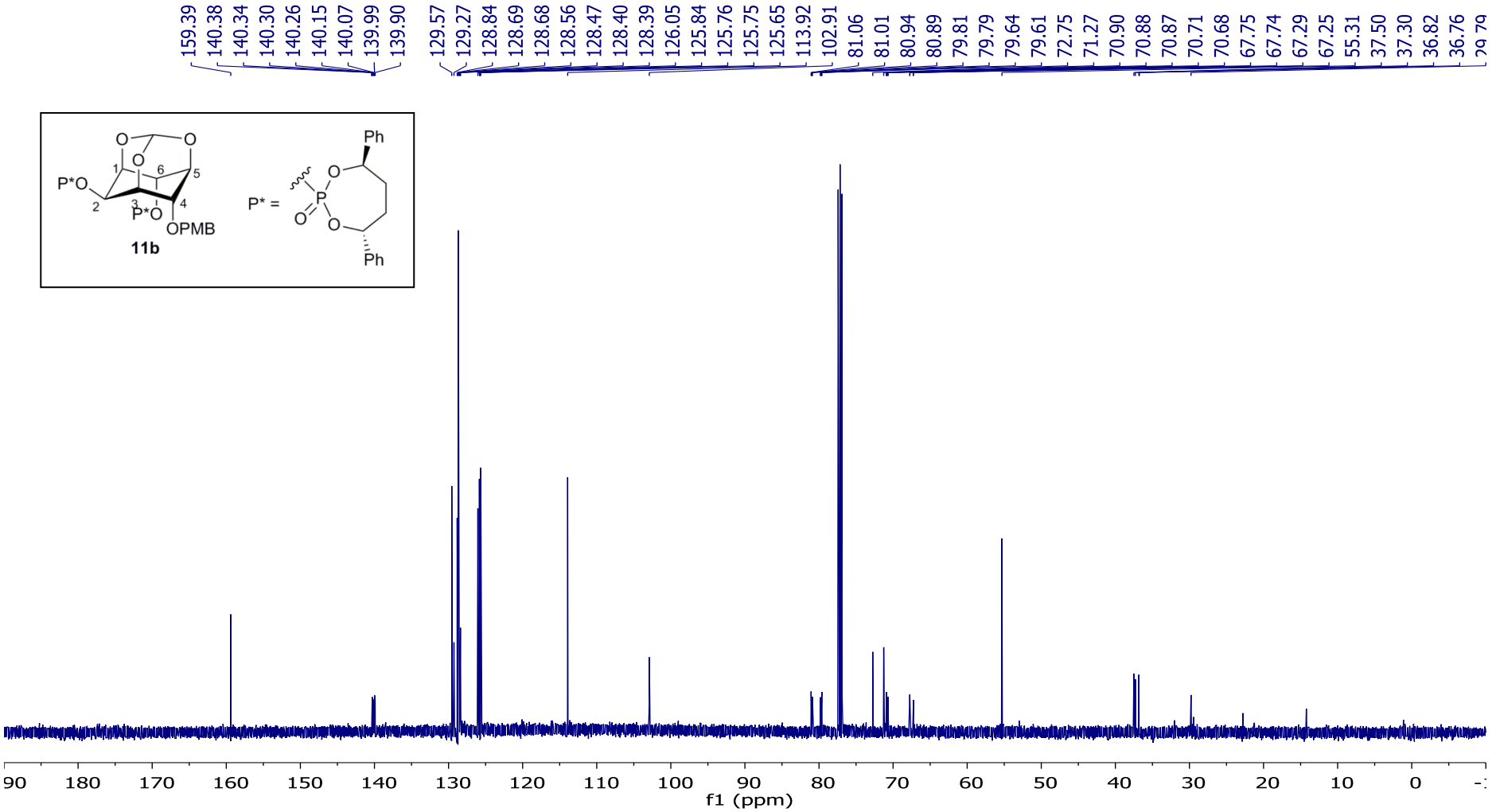
^{31}P NMR, 162 MHz, $CDCl_3$



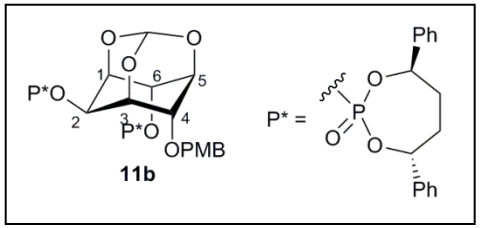
^{1}H NMR, 400 MHz, $CDCl_3$

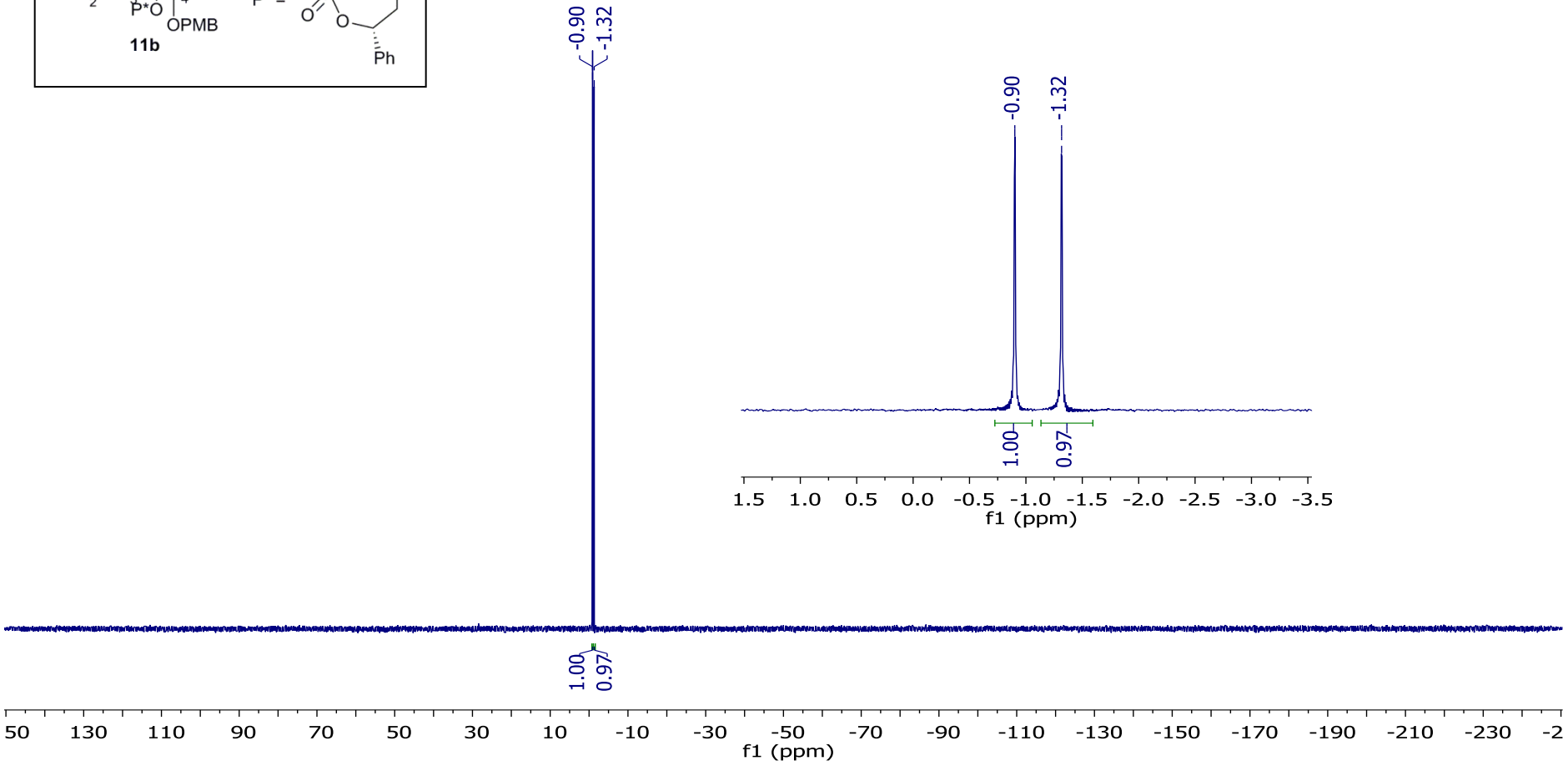


^{13}C NMR, 126 MHz, $CDCl_3$

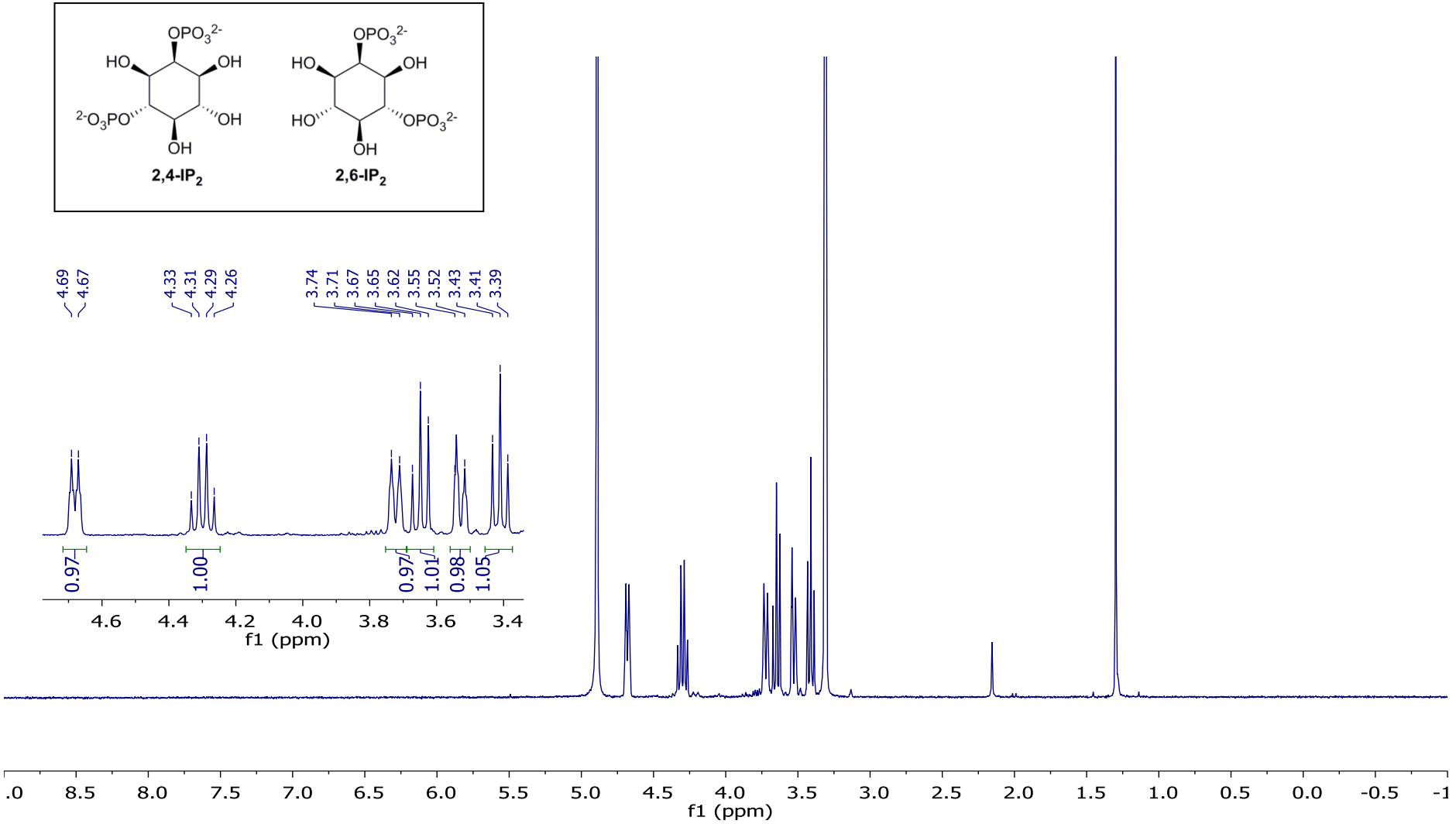


^{31}P NMR, 162 MHz, $CDCl_3$

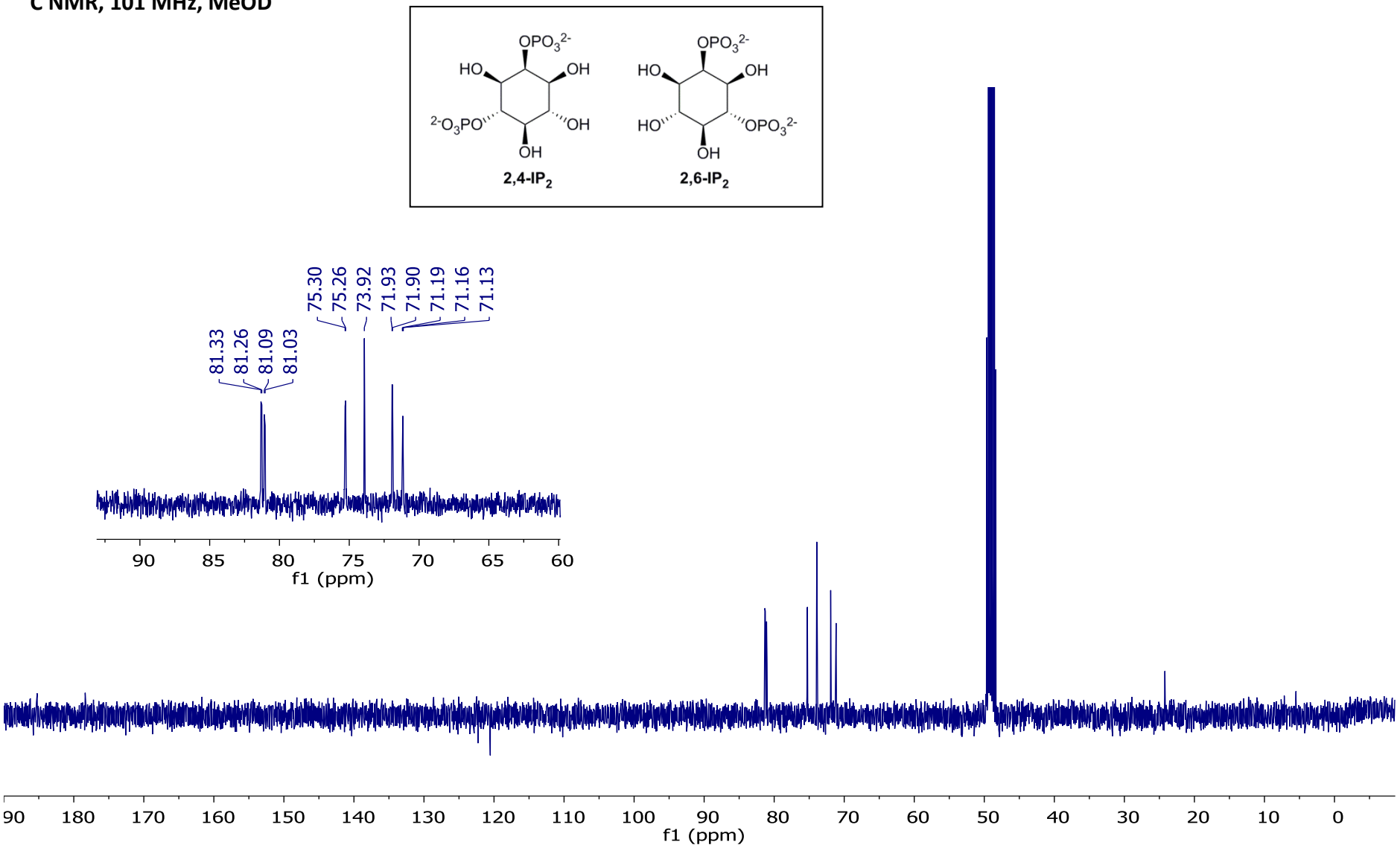




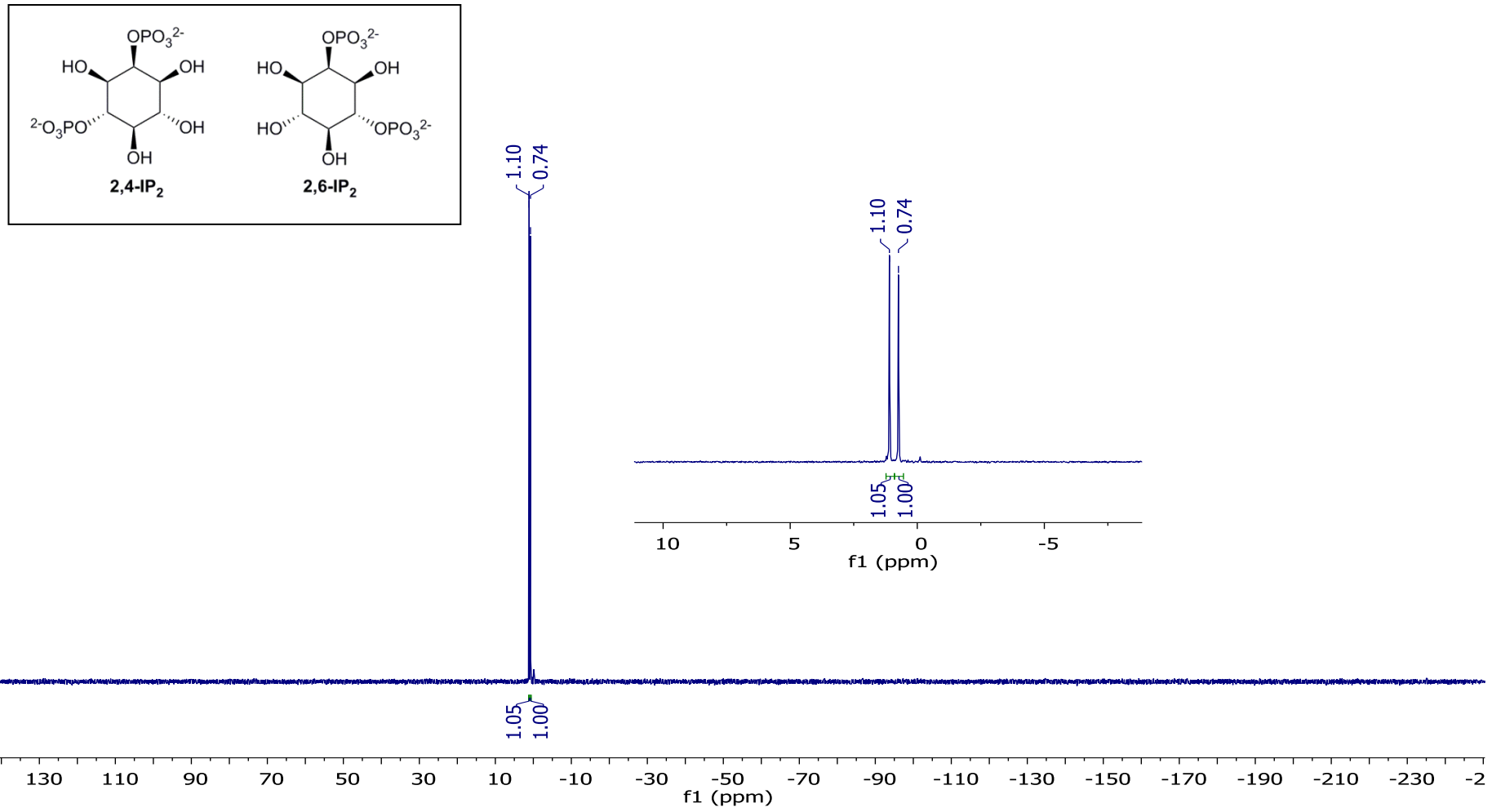
^{1}H NMR, 400 MHz, MeOD



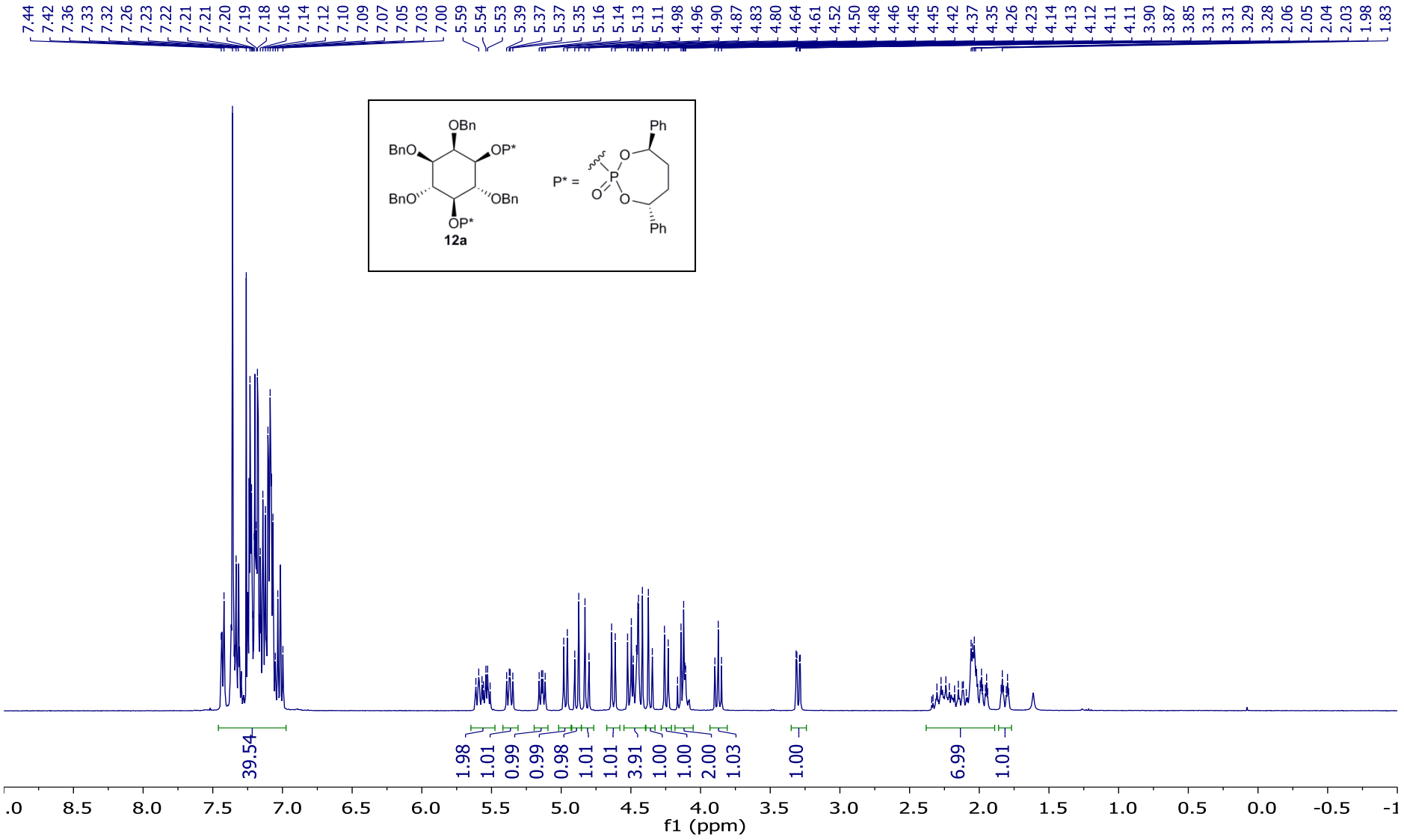
^{13}C NMR, 101 MHz, MeOD



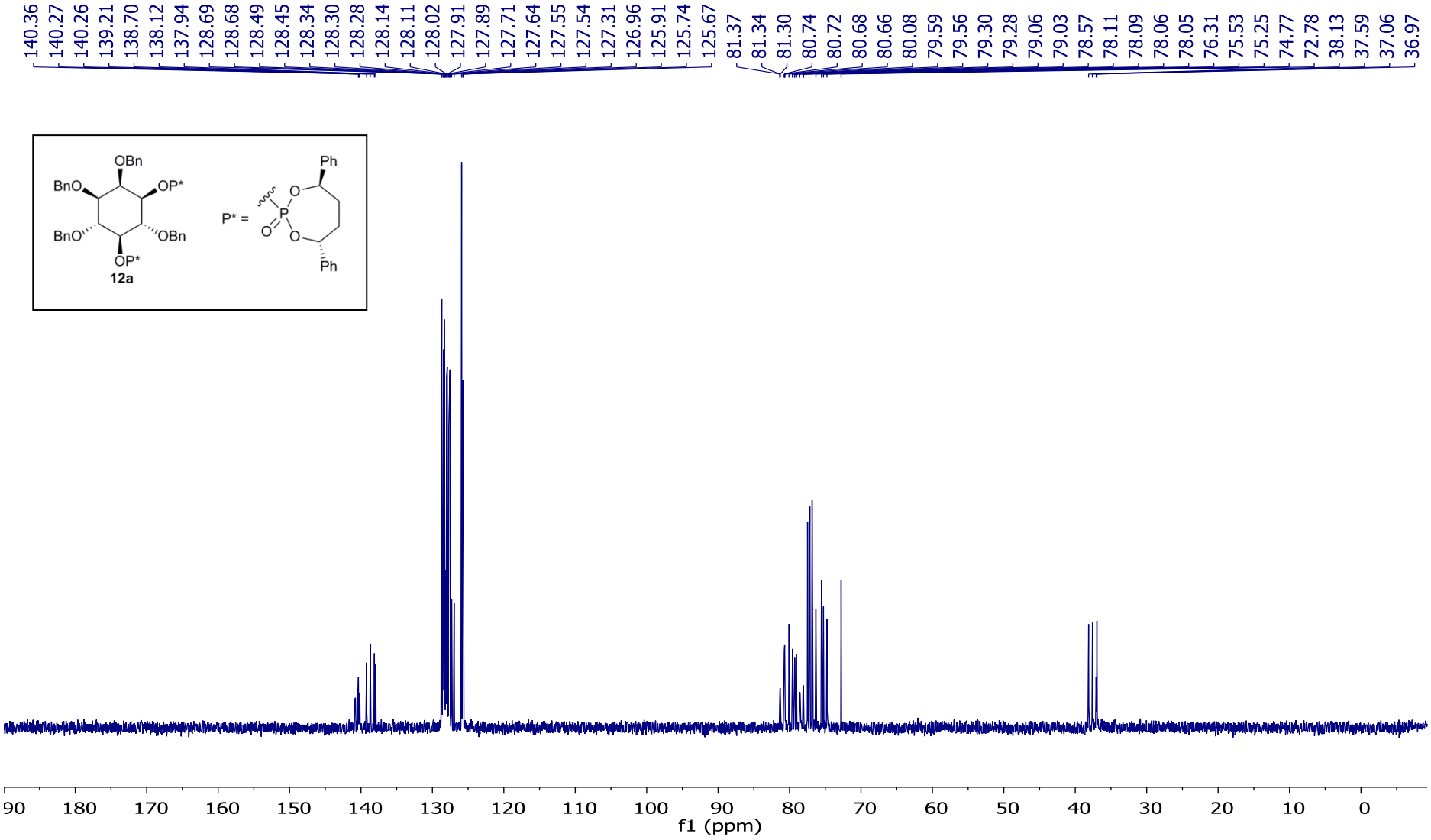
^{31}P NMR, 162 MHz, MeOD



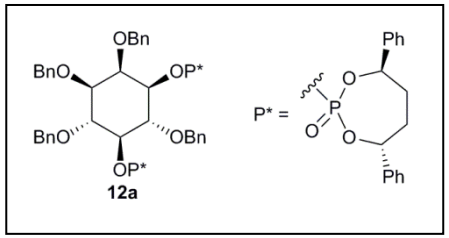
^{1}H NMR, 400 MHz, $CDCl_3$



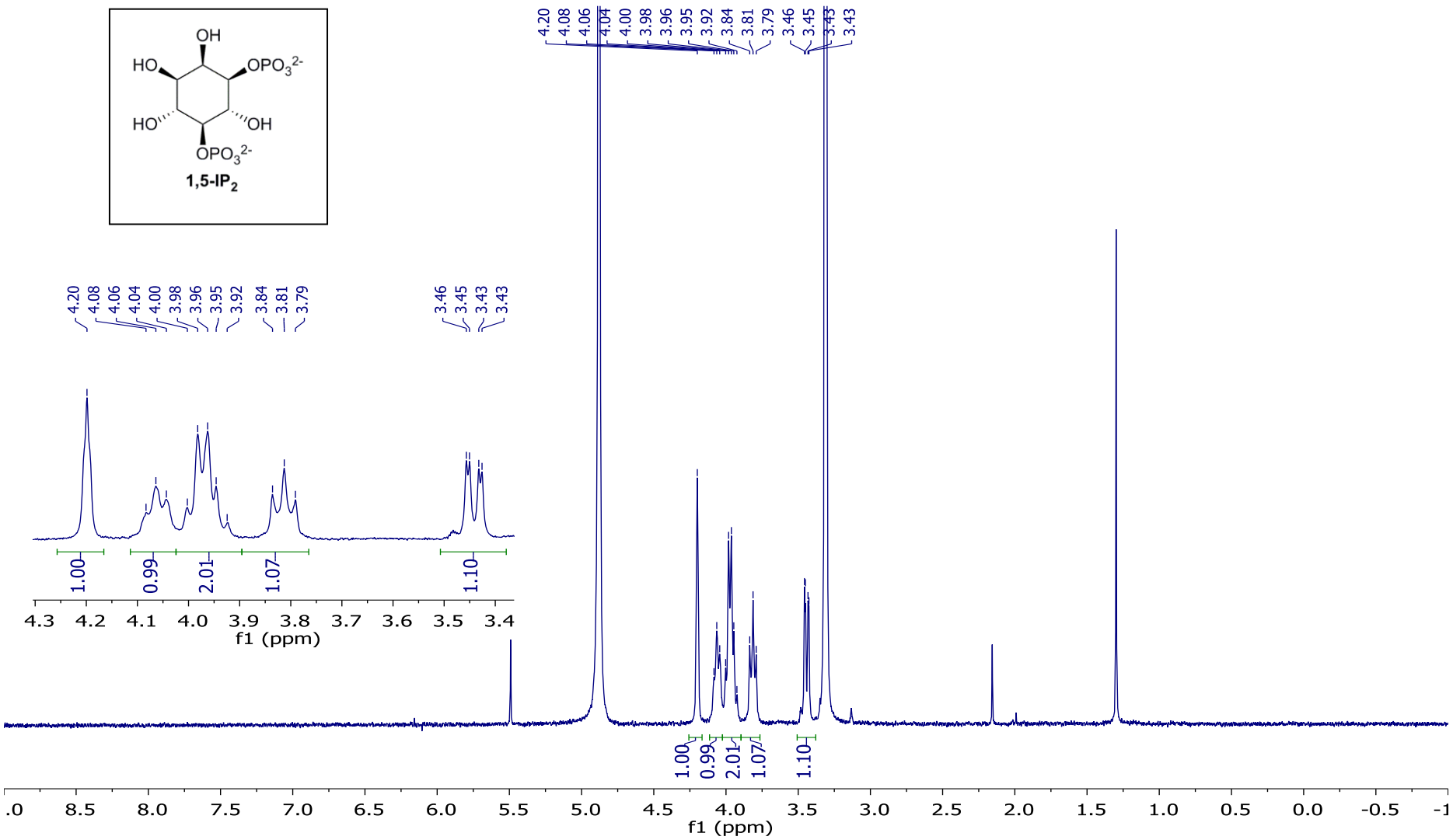
^{13}C NMR, 101 MHz, $CDCl_3$



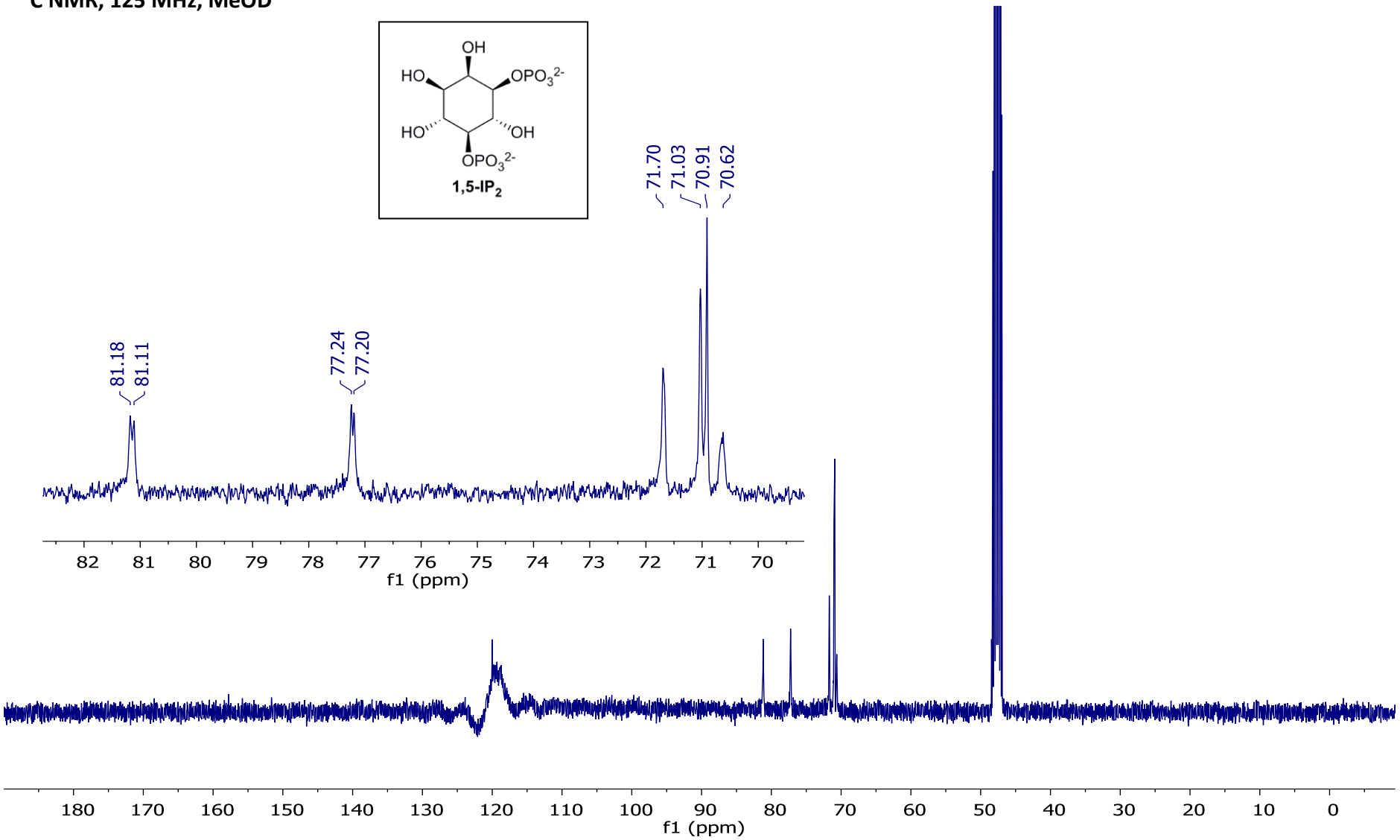
^{31}P NMR, 162 MHz, $CDCl_3$



^{1}H NMR, 400 MHz, MeOD



^{13}C NMR, 125 MHz, MeOD



^{31}P NMR, 162 MHz, MeOD