Supporting Information: Irreversible Inhibition of DNA Polymerase β by Small Molecule Mimics of a DNA Lesion.

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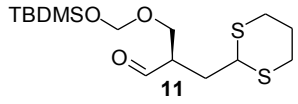
Contents:

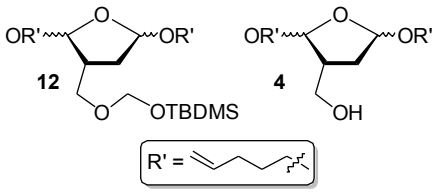
General Methods. Oligonucleotides were synthesized on an Applied Biosystems Incorporated 394 oligonucleotide synthesizer. Oligonucleotide synthesis reagents were purchased from Glen Research (Sterling, VA). All chemicals were purchased from either Sigma-Aldrich or Fisher and were used without further purification. dNTPs and terminal deoxynucleotide transferase were obtained from New England Biolabs. DNA polymerase β was obtained from Trevigen. α-^{32}P-cordycepin was purchased from Perkin Elmer. C18-Sep-Pak cartridges were obtained from Waters. Quantification of radiolabeled oligonucleotides was carried out using a Molecular Dynamics Phosphorimager 840 equipped with ImageQuant Version 5.1 software. Fluorescence data were collected on a Varian Cary Eclipse fluorescence spectrophotometer.



11

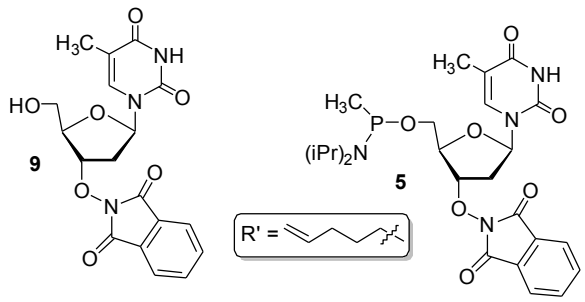
Preparation of 11. To a solution of α,α-diphenylprolinol trimethylsilyl ether catalyst (65.1 mg, 0.2 mmol) at 25 °C in toluene (4 mL) was added solid phosphate buffer pH 7 (50 mg) followed by aqueous formaldehyde solution (250 μL, 3 mmol, 37 wt %). Aldehyde **10** (Kodama, T.; Greenberg, M. M. *J. Org. Chem.* **2005**, *70*, 9916.) (177 mg, 1 mmol) was added in one portion to the vigorously stirred suspension and the resulting mixture was stirred for 24 h. The 2 layers were then separated and the toluene was evaporated under reduced pressure (bath temperature < 40 °C). The residue was then redissolved in DCM (3 mL) and added to a premixed solution of imidazole (87.5 mg, 1.3 mmol) and TBDMSCl (150 mg, 1.3 mmol) in 2 mL of DCM that had been stirring for 20 min at 0 °C. The resulting mixture was stirred for 7 h at 0 °C before concentrating under vacuum. Purification on silica gel using 10 % EtOAc in hexanes afforded 105 mg (30 %) of **11**. ^{1}H NMR ($CDCl_3$) δ 9.76 – 9.75 (m, 1H), 4.87 – 4.78 (m, 2H), 4.06 (t, *J* = 7.5 Hz, 1H), 3.92 – 3.73 (m, 2H), 2.96 – 2.87 (m, 1H), 2.87 – 2.77 (m, 4H), 2.31 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.97 – 1.85

(m, 2H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.3, 90.1, 49.0, 44.6, 31.5, 29.68, 29.67, 25.8, 25.70, 25.69, 18.1, -5.00, -5.01; IR (film) 2928, 2896, 2856, 1726, 1471, 1252, 1115, 1039, 833, 778 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{15}H_{31}O_3SiS_2$ 351.1478, found 351.1484.

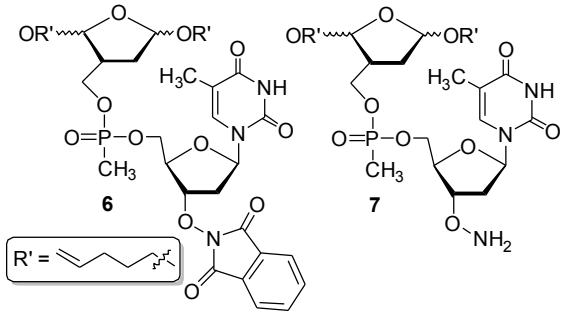


Preparation of 4 via 12. To a solution of **11** (49.4 mg, 0.14 mmol) and 4-penten-1-ol (120.4 mg, 1.4 mmol) in dry acetonitrile (2 mL) was added Selectfluor™ (147.8 mg, 0.42 mmol) at 25 °C. The resulting solution was left to stir overnight. The acetonitrile was evaporated under vacuum and a mixture of Et_2O and hexanes (1:10) was added to the residue. The solid was filtered and the filtrate was concentrated under vacuum. The resulting oil was eluted on silica gel with Et_2O-hexanes mixture (1:10), affording **12** as an inseparable mixture of isomers. The desilylation was carried out as follows. A solution of TBAF•3H_2O (63 mg, 0.2 mmol) in THF (1 mL) was cooled to 0 °C and **12** in THF (1 mL) was added. The resulting mixture was stirred for 2 h at RT. THF was evaporated under vacuum and the column chromatography purification of the residue using as eluent 30% EtOAc in hexanes, resulted in separation of two fractions. (**4_fraction1**): yield 48 % (13.7 mg); ^{1}H NMR ($CDCl_3$) δ 5.90 – 5.72 (m, 2H), 5.23 – 5.11 (m, 2H), 5.07 – 4.91 (m, 4H), 3.93 – 3.62 (m, 4H), 3.48 – 3.35 (m, 2H), 2.69 – 2.17 (m, 3H), 2.10 (q, *J* = 8.2 Hz, 4H), 1.72 – 1.60 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.19, 138.17, 138.0, 137.9, 115.0, 114.9, 114.77, 114.75, 106.9, 105.3, 104.2, 103.8, 67.6, 67.5, 67.3, 67.1, 63.7, 60.3, 45.7, 42.6, 34.3, 31.9, 30.34, 30.29, 30.27, 30.24, 28.88, 28.86, 28.82, 28.7; IR (film) 2938, 1640, 1443, 1356, 1227, 1095, 1023, 968, 909, 774 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{15}H_{26}O_4Na$ 293.1723, found 293.1722. (**4_fraction2**): yield 52 % (14.9 mg); ^{1}H NMR ($CDCl_3$) δ 5.89 – 5.75 (m, 2H), 5.24 – 5.13 (m, 1H), 5.12 – 4.89 (m, 5H), 3.84 – 3.68 (m, 2H), 3.69 – 3.54 (m, 2H), 3.49 – 3.34 (m, 2H), 2.67 – 2.47 (m, 1H), 2.22 – 2.00 (m, 5H), 1.89 – 1.78

(m, 1H), 1.75 – 1.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 138.31, 138.29, 138.24, 138.0, 114.9, 114.69, 114.66, 114.63, 107.3, 105.3, 104.9, 104.7, 67.9, 67.6, 67.27, 67.17, 63.6, 60.7, 46.7, 44.5, 34.4, 32.2, 30.42, 30.35, 28.9, 28.8, 28.7; IR (film) 2937, 1640, 1445, 1362, 1230, 1091, 1044, 965, 909, 876 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{15}H_{26}O_4Na$ 293.1723, found 293.1731.



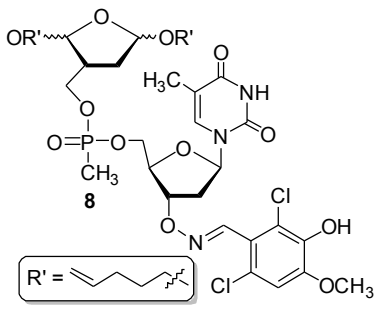
Preparation of 5. To a solution of **9** (0.50 g, 1.3 mmol) in DCM (30 mL, the solubility in DCM is very poor) was added DIPEA (450 μL, 2.6 mmol). The mixture was cooled to 0°C and N,N-diisopropylamino methyl phosphonamidic chloride (0.36 mg, 2.0 mmol) was added dropwise. The mixture was allowed to warm to 25 °C and stirred for 4 h. The solution becomes clear when the reaction is complete. The DCM layer was washed with $NaHCO_3$ solution and then with brine. The organic phase was dried over $NaSO_4$. The solvent was evaporated under vacuum and the residue was purified by column chromatography using a mixture of DCM and EtOAc (1:1) with 1% Et_3N, yielding 0.41 g (60%) of **5** as white crystals. ^{1}H NMR (acetone-d_6) δ 10.02 (br s, 1 H), 7.89 (m, 4 H), 7.68, 7.56 (each s, 1 H), 6.52 (m, 1 H), 5.08 (m, 1 H), 4.51 (m, 1 H), 3.85 (m, 2 H), 3.62 (m, 1 H), 3.53 (m, 2 H), 2.71 (dd, 1 H, J = 14.7, 5.6 Hz), 2.37 (m, 1 H), 1.86 (dd, 3 H, J = 3.9, 1.1 Hz), 1.17 (m, 9 H), 1.08 (t, 6 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 205.2, 205.0, 163.6, 163.3, 150.3, 135.4, 135.3, 134.79, 134.77, 129.17, 129.15, 123.3, 110.1, 88.62, 88.55, 84.8, 84.5, 82.83, 82.76, 82.72, 82.66, 67.2, 66.5, 44.2, 44.0, 43.9, 36.5, 36.4, 25.3, 24.1, 23.5, 17.1, 17.0, 16.9, 11.73, 11.68; ^{31}P NMR ($CDCl_3$) δ 125.25, 123.41. IR (film) 2966, 1753, 1681, 1466, 1363, 1277, 1184, 1123, 1062, 970, 876, 701 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{25}H_{34}N_4O_7P$ 533.2165, found 533.2155.



Preparation of 7. To a solution of **5** (112 mg, 0.21 mmol) and **4** (54 mg, 0.2 mmol) in MeCN (500 μL) was added 5-ethylthio-1H-tetrazole (1.0 mL, 0.25 mmol, 0.25 M solution in MeCN) via syringe under argon and the resulting mixture was stirred for 2 h, at which time t-BuOOH in decane (0.2 mL, 5 M solution) was added and the solution was stirred for an additional 30 min. The solvent was evaporated under vacuum and the residue was loaded on silica gel column. Elution with DCM containing 3 % MeOH gave 68 mg (63 %) of the phthalimide nucleotide (**6**) as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H), 7.85 – 7.79 (m, 4H), 7.43, 7.40, 7.38, 7.35 (each s, 1H), 6.44 (t, J = 7.0 Hz, 1H), 5.89 – 5.72 (m, 2H), 5.22 – 5.11 (m, 1H), 5.08 – 4.89 (m, 6H), 4.56 (m, 1H), 4.42 – 4.19 (m, 2H), 4.12 – 3.86 (m, 2H), 3.81 – 3.63 (m, 2H), 3.46 – 3.30 (m, 2H), 2.86 – 2.73 (m, 1H), 2.72 – 2.61 (m, 1H), 2.33 – 2.19 (m, 1H), 2.17 – 2.03 (m, 5H), 1.93, 1.92 (each d, J = 1.2 Hz, 3H), 1.89 – 1.74 (m, 1H), 1.73 – 1.61 (m, 4H), 1.58 – 1.44 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.74, 163.72, 163.4, 150.0, 149.9, 138.24, 138.19, 135.6, 135.5, 134.92, 134.91, 128.7, 123.9, 114.73, 114.68, 111.43, 111.37, 106.4, 106.3, 104.50, 104.48, 87.49, 87.48, 85.8, 85.7, 81.4, 81.3, 81.2, 68.1, 67.68, 67.67, 67.65, 67.34, 67.33, 66.0, 65.9, 64.9, 45.3, 45.22, 45.20, 36.6, 36.5, 34.28, 34.25, 30.32, 30.30, 30.27, 28.9, 28.79, 28.77, 12.5, 12.4, 11.8, 11.6, 10.3, 10.2; ^{31}P NMR ($CDCl_3$) δ 31.98, 31.62, 31.28; IR (film) 2929, 1735, 1688, 1467, 1370, 1312, 1277, 1249, 1187, 1106, 977, 913, 877, 702 cm^{-1}; FAB-HRMS (M + Na^+) calcd for $C_{34}H_{44}N_3O_{12}NaP$ 740.2555, found 740.2569.

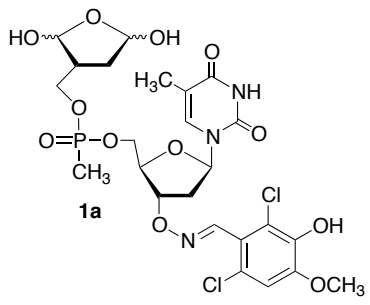
To a solution of **6** (68 mg, 0.095 mmol) in THF (1 mL) was added a solution of hydrazine in water (0.2 mL, 6 wt %). After stirring the solution at 25 °C for 5 min, the solvents were evaporated under vacuum and the residue was purified by column chromatography using DCM

with 5 % methanol. This afforded 44 mg (81 %) of **7** as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 7.48, 7.45, 7.44, 7.43 (each d, *J* = 1.2 Hz, 1H), 6.33 – 6.24 (m, 1H), 5.80 (m, 2H), 5.49 (s, 2H), 5.21 – 5.11 (m, 1H), 5.05 – 4.91 (m, 5H), 4.37 – 4.25 (m, 3H), 4.25 – 4.14 (m, 1H), 4.13 – 3.91 (m, 2H), 3.77 – 3.66 (m, 2H), 3.45 – 3.33 (m, 2H), 2.72 – 2.62 (m, 1H), 2.54 – 2.45 (m, 1H), 2.16 – 2.05 (m, 5H), 1.96 (m, 1H), 1.94, 1.93 (each d, *J* = 1.2 Hz, 3H), 1.86 – 1.76 (m, 1H), 1.71 – 1.60 (m, 4H), 1.57 – 1.47 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.5, 150.3, 150.2, 138.23, 138.18, 138.17, 135.2, 135.1, 134.3, 123.5, 114.75, 114.69, 111.39, 111.38, 106.5, 106.3, 105.1, 104.49, 104.48, 102.3, 100.0, 85.1, 83.4, 83.3, 81.83, 81.77, 68.1, 67.71, 67.68, 67.4, 67.3, 65.91, 65.85, 65.8, 45.30, 45.26, 45.2, 36.80, 36.75, 34.4, 34.3, 30.32, 30.30, 28.79, 28.77, 12.53, 12.47, 11.9, 11.8, 10.4, 10.3; ^{31}P NMR ($CDCl_3$) δ 31.99, 31.56, 31.19; IR (film) 2925, 1696, 1466, 1416, 1365, 1233, 1097, 988, 910, 820, 713 cm^{-1}; FAB-HRMS (M + Na^+) calcd for $C_{26}H_{42}N_3O_{10}NaP$ 610.2500, found 610.2491.



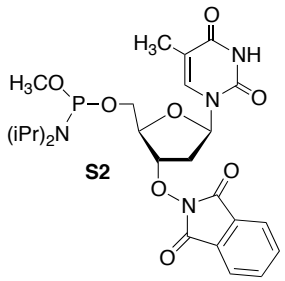
Preparation of 8. Alkoxyamine **7** (22 mg, 0.037 mmol) was added to a solution of 2,6-dichloro-3-hydroxy-4-methoxy benzaldehyde (10 mg, 0.043 mmol) and acetic acid (10 mg, 10 μL, 0.16 mmol) in DMSO (300 μL). The resulting mixture was incubated at 37°C for 5 h. DMSO was evaporated under high vacuum and the residue was purified by column chromatography using 3 % methanol solution in DCM, affording 20.8 mg of **8** (79 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.99, 8.97, 8.95 (each s, 1H), 8.32 (s, 1H), 7.52, 7.50, 7.48, 7.46 (each d, *J* = 1.2 Hz, 1H), 6.87 (s, 1H), 6.46 (m, 1H), 6.32 (m, 1H), 5.85 – 5.74 (m, 2H), 5.13 (m, 1H), 5.02 – 4.92 (m, 6H), 4.43 – 4.01 (m, 5H), 3.93 (s, 3H), 3.70 (m, 2H), 3.39 (m, 2H), 2.68 (m, 2H), 2.25 – 2.04 (m, 6H), 1.95, 1.94 (each d, *J* = 1.2 Hz, 3H), 1.86 – 1.74 (m, 2H), 1.71 – 1.60 (m, 4H), 1.59 – 1.49 (m, 3H); ^{13}C NMR ($CDCl_3$)

δ 163.5, 150.4, 148.1, 146.7, 141.8, 138.3, 138.19, 138.18, 135.2, 135.1, 125.4, 120.7, 120.2, 114.72, 114.71, 114.67, 114.66, 111.5, 111.3, 106.5, 106.4, 105.1, 104.50, 104.49, 85.3, 85.2, 82.5, 68.1, 67.70, 67.68, 67.4, 67.3, 56.6, 56.4, 45.3, 37.4, 37.3, 34.3, 30.32, 30.30, 28.80, 28.77, 12.54, 12.48, 10.44; ^{31}P NMR ($CDCl_3$) δ 31.98, 31.52, 31.19; IR (film) 2940, 1690, 1599, 1491, 1275, 1245, 1061, 1008, 968, 915, 833, 767 cm^{-1}; HRMS (M + Na^+) calcd for $C_{34}H_{46}N_3O_{12}NaPCl_2$ 812.2088, found 812.2111; ε_{268} = 24,240 $cm^{-1}M^{-1}$ in MeCN.

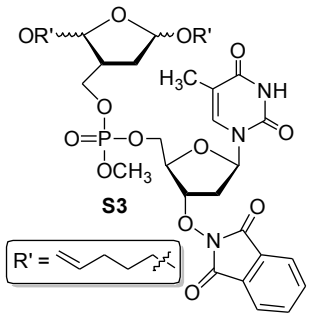


1a

Preparation of 1a. To a solution of **8** (23 mg, 0.029 mmol) in MeCN (with 1 % water) (0.5 mL) was added solution of NBS (12.9 mg, 0.073 mmol) in MeCN (0.1 mL) at -5 °C. The reaction mixture was stirred for 3 min, at which time it was quenched with 0.1 mL of a saturated solution of $Na_2S_2O_3$ and $NaHCO_3$. The organic layer was separated and the solvent was evaporated under reduced pressure at RT. The residue was redissolved in 100 μL MeCN / water mixture (1:4) and loaded on C18 silica gel column, made from a Pasteur pipette (1.5 g silica). The product was eluted using a mixture of MeCN and water: 3×1 mL of 20 % MeCN; 3×1 mL of 30 % MeCN; 3×1 mL of 50 % (Total: 9 fractions 1 mL each). Two main components were isolated as a mixture (fraction 8), representing the cyclic and the dialdehyde forms – 10.5 mg (56 %). ^{1}H NMR (CD_3CN) δ 8.28 (s, 1H), 7.45 (s, 1H), 7.00 (s, 1H), 6.31 – 6.21 (m, 1H), 5.50 – 4.84 (m, 3H), 4.40 – 4.31 (m, 1H), 4.27 – 4.18 (m, 2H), 4.10 – 3.90 (m, 2H), 3.82 (s, 3H), 3.75 – 3.52 (m, 2H), 3.48 – 3.25 (m, 2H), 2.62 – 2.44 (m, 1H), 2.37 – 2.16 (m, 2H), 1.81 (m, 4H), 1.63 – 1.37 (m, 6H); ^{31}P NMR (CD_3CN) δ 32.08, 32.05, 32.00, 31.93, 31.90, 31.87, 31.83, 31.81, 31.74, 31.62, 31.59, 31.55, 31.52, 31.48, 31.45, 31.44, 31.42, 31.35, 31.31, 22.81; HRMS (M + H^+) calcd for $C_{24}H_{29}Cl_2N_3O_{11}P$ 636.0917, found 636.0931; ε_{270} = 20,000 $cm^{-1}M^{-1}$ in 50 % MeCN in water.

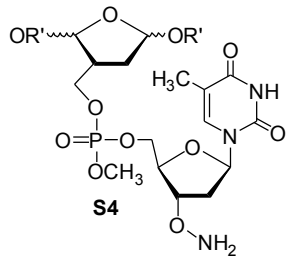


Preparation of the methoxy phosphoramidite of 9 (S2). To a solution of alcohol **9** (200 mg, 0.50 mmol) and DIPEA (260 mg, 2.00 mmol) in DCM (5 mL) was added N,N-diisopropylamino methoxy phosphonamidic chloride (157 mg, 0.80 mmol) at 0°C. The resulting solution was stirred at 25 °C for 1 h. The solvent was evaporated and the residue was purified by column chromatography using a gradient 10 % - 20 % EtOAc in DCM with 1 % of Et_3N, yielding 160 mg (60 %) of **S2**. ^{1}H NMR (CD_3CN) δ 9.20 (s, 1H), 7.84 (m, 4H), 7.63, 7.55 (each m, 1H), 6.42 (td, *J* = 8.5, 5.6 Hz, 1H), 4.99 (m, 1H), 4.45 (m, 1H), 3.77 (m, 2H), 3.49 (m, 2H), 3.37, 3.33 (each d, *J* = 13.4 Hz, 3H), 2.62, 2.59 (each d, *J* = 6.2, 1H), 2.27 (m, 1H), 1.85, 1.84 (each d, *J* = 0.5 Hz, 3H), 1.13 (m, 12H); ^{13}C NMR (CD_3CN) δ 164.0, 163.6, 150.52, 150.46, 135.7, 135.5, 134.8, 129.1, 123.3, 117.3, 110.5, 88.4, 88.3, 84.6, 84.4, 82.29, 82.26, 82.20, 82.16, 63.8, 63.7, 62.9, 62.7, 50.2, 50.1, 49.9, 49.1, 44.95, 44.89, 42.66, 42.54, 36.3, 36.0, 24.04, 24.02, 24.01, 23.97, 23.95, 23.94, 23.90, 22.28, 22.26, 22.05, 22.04, 20.1, 11.6; ^{31}P NMR (CD_3CN) δ 149.46, 149.23; IR (film) 2967, 1735, 1682, 1465, 1364, 1184, 970, 876, 700 cm^{-1}; MALDI-TOF MS (M + Na^+) calcd for $C_{25}H_{33}N_4NaO_8P$ 571.2, found 571.2.



Coupling of methoxy phosphoramidite with 4 (S3). The above methoxy phosphoramidite (**S2**, 52 mg, 0.10 mmol) and **4** (27 mg, 0.10 mmol) were dissolved in anhydrous MeCN (0.5 mL). 5-Ethylthio-1H-tetrazole (0.50 mL, 0.13 mmol, 0.25 M solution in MeCN) was added to the reaction mixture via syringe under argon and the resulting solution was stirred for an hour at RT. *t*-BuOOH in decane (0.10 mL, 5 M solution) was added to the reaction mixture and stirred for additional 20 min. The solvents were evaporated under vacuum and the residue was purified by column chromatography using DCM

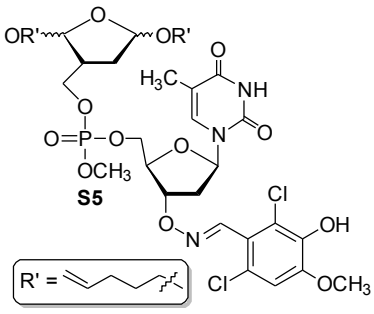
with 3 % MeOH, yielding 60 mg (82 %) of **S3**. ^{1}H NMR ($CDCl_3$) δ 9.13 (d, *J* = 4.7 Hz, 1H), 7.83, 7.77 (each m, 4H), 7.37 (m, 1H), 6.47 (m, 1H), 5.78 (m, 2H), 5.12 (m, 1H), 4.96 (m, 6H), 4.54 (s, 1H), 4.31 (m, 2H), 4.02 (m, 2H), 3.76 (m, 3H), 3.68 (m, 2H), 3.37 (m, 2H), 2.76 (ddd, *J* = 14.4, 5.8, 1.8 Hz, 1H), 2.66 (m, 1H), 2.24 (m, 1H), 2.07 (m, 6H), 1.90 (s, 3H), 1.81 (m, 1H), 1.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.74, 163.73, 163.68, 150.2, 138.22, 138.21, 138.17, 138.15, 135.4, 134.9, 128.7, 123.9, 114.71, 114.69, 114.67, 114.60, 111.49, 111.44, 107.2, 106.2, 106.1, 105.1, 104.8, 104.5, 87.6, 87.5, 85.37, 85.31, 81.1, 81.0, 68.0, 67.68, 67.67, 67.65, 67.34, 67.25, 63.4, 54.70, 54.69, 49.9, 46.7, 45.20, 45.18, 45.14, 45.11, 36.6, 34.16, 34.10, 30.34, 30.30, 30.27, 28.84, 28.81, 28.76, 22.93, 22.91, 12.42, 12.40; ^{31}P NMR ($CDCl_3$) δ 0.07, 0.02, -0.00, -0.03, -0.09; IR (film) 2937, 1735, 1690, 1467, 1369, 1276, 1017, 877, 703 cm^{-1}; HRMS (M + Na^+) calcd for $C_{34}H_{44}N_3NaO_{13}P$ 756.2509, found 756.2496.



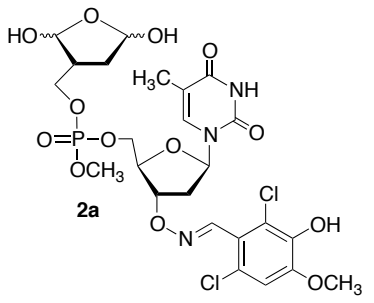
S4

Preparation of the alkoxyamine S4. To a solution of **S3** (60 mg, 0.08 mmol) in THF (0.5 mL) was added hydrazine (0.05 mL, 6 % solution in water) and the mixture was stirred for 5 min at 25 °C. The volatile components were evaporated under vacuum and the residue was purified by column chromatography using DCM with 4.5 % MeOH, yielding 38 mg (77 %) of **S4**. ^{1}H NMR ($CDCl_3$) δ 9.14 (s, 1H), 7.43 (m, 1H), 6.31 (m, 1H), 5.80 (m, 2H), 5.48 (s, 2H), 5.13 (m, 1H), 4.98 (m, 5H), 4.36 (m, 1H), 4.28 (m, 3H), 4.05 (m, 2H), 3.80, 3.79 (each d, *J* = 11.2 Hz, 3H), 3.69 (m, 2H), 3.37 (m, 2H), 2.68 (m, 1H), 2.47 (ddd, *J* = 14.0, 5.7, 1.6 Hz, 1H), 2.08 (m, 5H), 1.98 (m, 1H), 1.92 (t, *J* = 1.4 Hz, 3H), 1.81 (m, 1H), 1.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.7, 150.45, 150.43, 138.21, 138.16, 138.15, 135.2, 134.2, 123.5, 114.74, 114.73, 114.72, 114.69, 111.5, 111.4, 106.27, 106.24, 106.20, 105.1, 104.5, 84.9, 83.42, 83.40, 83.38, 81.62, 81.54, 68.10, 68.04, 68.0, 67.71, 67.69, 67.4, 54.62, 54.60, 54.56, 54.55, 45.21, 45.14, 36.72,

36.68, 34.21, 34.20, 34.18, 30.31, 30.30, 30.28, 28.77, 28.75, 12.44, 12.43; ^{31}P NMR ($CDCl_3$) δ 0.37, 0.35, 0.31, 0.28, 0.19, 0.17, 0.15, 0.13; IR (film) 2937, 1691, 1467, 1274, 1032, 857 cm^{-1}; HRMS (M + Na^+) calcd for $C_{26}H_{42}N_3NaO_{11}P$ 626.2455, found 626.2460.

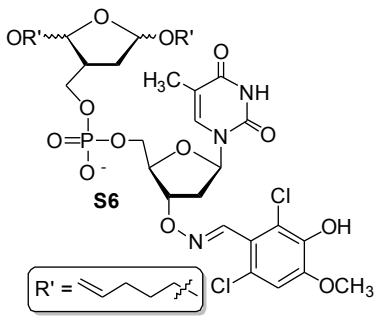


Preparation of the oxime of the methyl phosphate triester (S5). A solution of **S4** (32 mg, 0.05 mmol), 2,6-dichloro-3-hydroxy-4-methoxybenzaldehyde (15.5 mg, 0.07 mmol) and AcOH (9 mg, 0.15 mmol) in DMSO (0.5 mL) was incubated at 37 °C overnight. The DMSO was evaporated under vacuum and the residue was purified by column chromatography using DCM with 3 % MeOH, yielding 36 mg (84 %) of the oxime as a foam. ^{1}H NMR ($CDCl_3$) δ 9.17 (s, 1H), 8.31 (s, 1H), 7.48 (m, 1H), 6.86 (s, 1H), 6.50 (m, 1H), 6.40 (s, 1H), 5.80 (m, 2H), 5.13 (dt, *J* = 5.3, 2.5 Hz, 1H), 4.98 (m, 6H), 4.42 (m, 1H), 4.32 (m, 2H), 4.06 (m, 2H), 3.92 (s, 3H), 3.81 (m, 3H), 3.71 (m, 2H), 3.38 (m, 2H), 2.62 (m, 2H), 2.18 (m, 1H), 2.09 (q, *J* = 6.9 Hz, 5H), 1.95 (s, 3H), 1.80 (m, 1H), 1.65 (p, *J* = 7.6 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 163.6, 150.5, 148.2, 146.8, 141.8, 138.24, 138.17, 135.2, 125.4, 120.6, 120.2, 114.72, 114.67, 111.71, 111.66, 111.3, 106.24, 106.21, 104.5, 102.3, 85.0, 82.5, 82.2, 82.1, 67.7, 67.4, 66.9, 56.6, 54.65, 54.60, 45.22, 45.15, 37.3, 34.18, 34.15, 30.31, 30.30, 30.29, 28.85, 28.77, 28.76, 12.5; ^{31}P NMR ($CDCl_3$) δ 0.28, 0.26, 0.09, 0.04; IR (film) 2941, 1690, 1439, 1275, 1017, 953 cm^{-1}; HRMS (M+ Na^+) calcd for $C_{34}H_{46}Cl_2N_3NaO_{13}P$ 828.2043, found 828.2044.



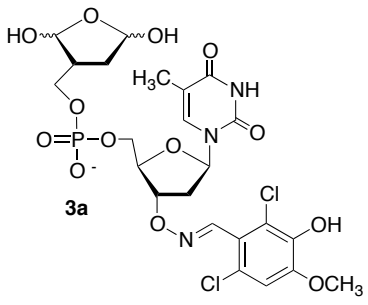
Preparation of 2a. To a solution of **S5** (10 mg, 0.012 mmol) in MeCN (0.5 mL) with 1 % water was added NBS (6 mg, 0.035 mmol) in MeCN (0.06 mL) at 0°C. The solution was stirred for 5 min before it was quenched with 1:1 mixture of saturated

solutions of $Na_2S_2O_3$ and $NaHCO_3$ (0.03 mL). The organic layer was separated and the solvent was evaporated under vacuum. The residue was redissolved in a mixture of water and MeCN (1:1) (0.04 mL) and then diluted with water (0.06 mL) before it was loaded on the column (the solution becomes cloudy after the dilution because of poor solubility of the product). The product was purified on a column made of a Pasteur pipette (with 1 g of C18 silica) using a gradient 20 % - 50 % MeCN in water (collected about 12 fractions 1 mL each). The fractions containing the desired product were combined and lyophilized, yielding 5.5 mg (66 %) of **2a** as a white powder. ^{1}H NMR (CD_3CN) δ 8.31 (s, 1H), 7.45 (s, 1H), 7.03 (s, 1H), 6.29 (m, 1H), 5.46 - 5.16 (m, 2H), 4.94 (m, 1H), 4.36 (m, 1H), 4.29 (m, 2H), 4.03 (m, 2H), 3.87 (s, 3H), 3.75 (m, 3H), 2.52 (m, 2H), 2.31 (m, 2H), 1.84 (m, 4H); ^{31}P NMR (CD_3CN) δ -0.16, -0.25; MALDI-TOF MS (dialdehyde form M + Na^+) calcd for $C_{24}H_{28}Cl_2N_3NaO_{12}P$ 674.068, found 673.759.



Preparation of S6. To a solution of **S5** (95 mg, 0.12 mmol) in DMF (0.5 mL) was added disodium 2-carbamoyl-2-cyanoethylene-1,1-dithiolate (See: Söderbück, E. *Acta. Chem. Scand*. **1970**, *24*, 228-234 for preparation of the reagent.) (61.9 mg, 0.24 mmol) in DMF (0.5 mL) and the mixture was incubated at 25 °C for 1 h. DMF was evaporated under vacuum and the residue was purified by C18 silica using a gradient 20 % - 50 % MeCN in water. The fractions containing the desired product were lyophilized yielding 94 mg (99 %) of **S6** as white powder. The sodium salt was converted to TBA (tetrabutylammonium) salt using Dowex 50WX8-400 cation exchange resin. A Pasteur pipette was loaded with 1 mL of slurry (1.7 meq / mL) and washed with a solution of TBA-OH until protons are fully exchanged by TBA (pH of the collected solution becomes basic). The column is washed with distilled water several times (to wash out the excess TBA-OH). The

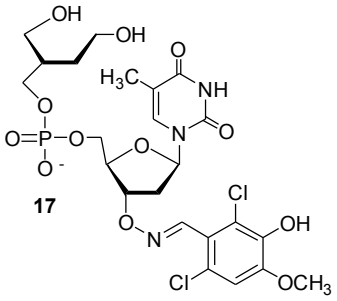
solution of compound in water (0.5 mL) was passed through the column very slowly (1 drop per second). The column is washed with 30 % MeCN in water until (the TBA salt is very hydrophobic and is not fully soluble in water) all the material comes out. The solutions were combined and lyophilized yielding 113 mg (93 %) of **S6** as a white powder. ^{1}H NMR (MeOH-d_4) δ 8.32 (s, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.02 (s, 1H), 6.46 (m, 1H), 5.81 (m, 2H), 5.12 (m, 1H), 5.06 (d, *J* = 6.3 Hz, 1H), 5.02 (m, 2H), 4.98 (m, 1H), 4.92 (m, 2H), 4.41 (m, 1H), 4.14 (m, 2H), 3.91 (s, 3H), 3.84 (m, 2H), 3.67 (m, 2H), 3.35 (m, 2H), 3.23 (m, 8H), 2.56 (m, 2H), 2.43 (m, 1H), 2.08 (m, 5H), 1.96 (s, 3H), 1.90 (m, 1H), 1.65 (m, 12H), 1.41 (h, *J* = 7.4 Hz, 8H), 1.02 (t, *J* = 7.4 Hz, 12H); ^{13}C NMR (MeOH-d_4) δ 165.0, 149.2, 146.31, 146.29, 142.8, 138.15, 138.13, 136.6, 123.9, 120.7, 120.5, 113.7, 111.2, 110.8, 106.69, 106.65, 104.81, 104.78, 84.9, 83.8, 83.4, 83.3, 67.21, 67.19, 66.97, 66.95, 65.61, 65.56, 65.27, 65.21, 65.17, 58.12, 58.09, 58.06, 55.7, 45.45, 45.37, 36.8, 33.75, 33.67, 30.1, 28.74, 28.71, 23.4, 19.34, 19.33, 19.31, 12.58, 12.57, 11.4; ^{31}P NMR (MeOH-d_4) δ 0.08, 0.03, -0.03, -0.04; IR (film) 2936, 1688, 1466, 1238, 1056, 957, 831, 732; HRMS (M^-) calcd for $C_{33}H_{43}Cl_2N_3O_{13}P$ 790.1916, found 790.1904.



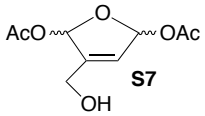
3a

Preparation of 3a. To a solution of **S6** (6 mg, 0.006 mmol) in MeCN (0.6 mL) with 3 % water and phosphate solid buffer pH 7 (20 mg) was added NBS (3.2 mg, 0.018 mmol) in MeCN (0.05 mL) under vigorous stirring at 0°C. The stirring was continued for 5 min and a 1:1 mixture of saturated solutions of $Na_2S_2O_3$ and $NaHCO_3$ (0.1 mL) was added. The reaction flask was connected to vacuum and MeCN was evaporated. The residue (water and salts) was diluted with water and purified by C18 silica (1 g) on a column made of a Pasteur pipette using a gradient 5 % - 20 % MeCN in water (collected about 12 fractions 1 mL each). The fractions were combined and lyophilized yielding

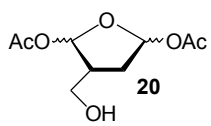
1.4 mg (33 %) of **3a** as white powder. ^{1}H NMR (D_2O) δ 8.30 (s, 1H), 7.89 (s, 1H), 6.99 (s, 1H), 6.45 (m, 1H), 5.62 - 5.33 (m, 2H), 5.06 (m, 2H), 4.49 (m, 2H), 4.15 (m, 1H), 4.07 (m, 2H), 3.87 (s, 3H), 2.62 (m, 2H), 2.46 (m, 2H), 1.91 (m, 4H); ^{31}P NMR (162 MHz, D_2O) δ 2.16, -0.07, -0.12; MALDI-TOF MS (dialdehyde form M + Na^+) calcd for $C_{23}H_{26}Cl_2N_3NaO_{12}P$ 660.053, found 660.010.



Preparation of 17. A solution of **3a** (20 μL, 5 mM) in water was reduced with $NaBH_4$ (2 μL, 100 mM). The excess reducing agent was quenched with AcOH after 5 min. TLC analysis of the product (eluted with 40 % MeCN in water on C18 silica plates) shows a similar R_f with the starting material. MALDI-TOF MS (diol form M + Na^+) calcd for $C_{23}H_{30}Cl_2N_3NaO_{12}P$ 664.084, found 660.043.

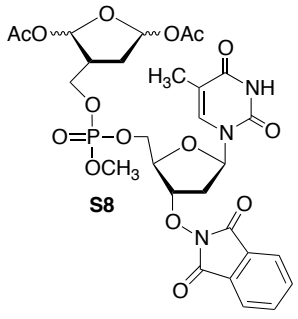


Preparation of S7. To a suspension of $Pb(OAc)_4$ (2 g, 4.5 mmol) in glacial AcOH (10 mL) was added 3-hydroxymethylfuran (400 mg, 4.1 mmol) and the mixture was stirred at 25 °C for 20 h (the solution becomes clear). AcOH was evaporated and Et_2O was added to the residue. The precipitate was filtered, the filtrate was collected, evaporated and the residue was purified by column chromatography using DCM with 30 % EtOAc, yielding 600 mg (68 %) of **S7** as a mixture of 2 major isomers (ratio 2:1, according to ^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ 6.94 (m, 1H), 6.74 (m, 1H), 6.09 (m, 1H), 4.33 (m, 2H), 2.13, 2.10 (each d, J = 12.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.35, 170.34, 170.0, 169.9, 145.5, 145.3, 125.0, 124.7, 101.3, 100.6, 99.99, 99.91, 99.4, 57.6, 57.5, 21.16, 21.14, 21.05; IR (film) 1737, 1374, 1222, 1178, 967 cm^{-1}; HRMS (M + NH_4^+) calcd for $C_9H_{16}NO_6$ 234.0972, found 234.0980.



Preparation of 20. A solution of **S7** (600 mg, 2.7 mmol) in EtOAc (60 mL) was placed in a hydrogenation apparatus. 5 % Rhodium on alumina

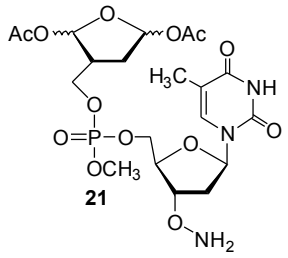
(300 mg) was added and the hydrogenation was carried out at 70 psi for 14 h. The solution was filtered off through alumina and the EtOAc was evaporated in vacuo. The residue was purified by silica gel chromatography using DCM with 50 % EtOAc to elute the first diastereomer **20a** (90 mg), followed by 60 % EtOAc to elute the second component **20b**, which represent a mixture of several diastereomers, but the major one represent about 90 % (170 mg) of the mixture. Total amount of isolated material represented 260 mg (44 %). **20a:** ^{1}H NMR ($CDCl_3$) δ 6.41 (dd, *J* = 5.9, 1.2 Hz, 1H), 6.33 (s, 1H), 3.81 (m, 1H), 3.67 (m, 1H), 2.49 (m, 2H), 2.04 (d, *J* = 1.9 Hz, 6H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.7, 100.6, 98.5, 62.6, 45.9, 31.9, 21.18, 21.17; IR (film) 1737, 1365, 1225, 1093, 964 cm^{-1}; HRMS (M + NH_4^+) calcd for $C_9H_{18}NO_6$ 236.1129, found 236.1134. **20b:** ^{1}H NMR ($CDCl_3$) δ 6.31 (m, 2H), 3.68 (m, 2H), 2.63 (m, 1H), 2.41 (m, 1H), 2.10 (m, 6H), 1.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.1, 99.08, 99.06, 99.03, 98.7, 98.2, 71.5, 71.0, 68.5, 64.5, 64.2, 60.8, 60.4, 48.1, 46.8, 45.4, 39.8, 39.1, 35.1, 34.8, 31.8, 25.2, 21.4, 21.21, 21.17; IR (film) 1737, 1371, 1227, 1102, 958 cm^{-1}; HRMS (M + NH_4^+) calcd for $C_9H_{18}NO_6$ 236.1129, found 236.1128.



S8

Preparation of S8. To a solution of **20b** (170 mg, 0.33 mmol) and **S2** (60 mg, 0.27 mmol) in anhydrous MeCN (2 mL) was added a solution of 5-ethylthio-1H-tetrazole in MeCN (1.32 mL, 0.33 mmol, 0.25 M solution). The resulting mixture was stirred for 1 h at 25 °C at which time *t*-BuOOH in decane (0.20 mL, 5 M solution) was added and the mixture was stirred for an additional 20 min. The solvents were evaporated under vacuum and the residue was purified by column chromatography using DCM with 3 % MeOH, yielding 160 mg (87 %) of **S8** as a mixture of 4 diastereomers, according to the ^{31}P NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H), 7.79 (m, 4H), 7.36 (s, 1H), 6.44 (m, 1H), 6.38 (m,

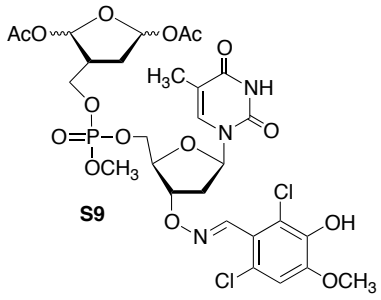
1H), 6.33 (m, 1H), 5.00 (m, 1H), 4.54 (s, 1H), 4.33 (m, 2H), 4.14 (m, 2H), 3.77 (ddd, *J* = 11.5, 6.2, 5.5 Hz, 3H), 2.75 (m, 1H), 2.64 (m, 1H), 2.49 (m, 1H), 2.31 (m, 1H), 2.03 (m, 3H), 1.98 (m, 3H), 1.88 (m, 3H), 1.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.53, 169.51, 169.50, 169.47, 169.43, 163.86, 163.84, 163.76, 163.74, 150.23, 150.20, 135.8, 134.9, 128.7, 123.9, 111.43, 111.39, 111.37, 111.28, 99.30, 99.25, 99.22, 98.12, 98.10, 98.05, 87.4, 85.6, 81.1, 81.0, 67.3, 66.9, 54.90, 54.87, 54.84, 54.81, 54.79, 54.76, 44.15, 44.13, 44.11, 44.08, 44.06, 44.04, 36.56, 36.48, 36.43, 36.39, 31.60, 31.58, 31.56, 31.54, 27.0, 21.16, 21.14, 21.04, 21.02, 21.01, 14.9, 12.4; ^{31}P NMR ($CDCl_3$) δ -0.15, -0.31, -0.43, -0.53; IR (film) 2345, 1731, 1687, 1467, 1367, 1227, 1016, 970, 877, 731, 701 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{28}H_{32}N_3NaO_{15}P$ 704.1469, found 704.1463.



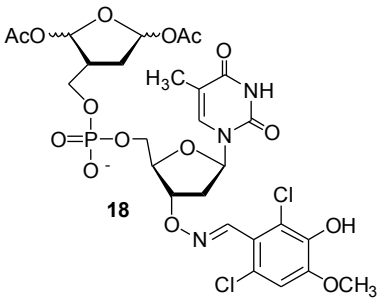
21

Preparation of 21. The above phthalimide, **S8** (160 mg, 0.23 mmol) in THF (3 mL) was treated with hydrazine (0.2 mL, 6 % solution in water) for 10 min. TLC analysis shows complete reaction. The volatile components were evaporated under vacuum and the residue was purified by column chromatography using DCM with 4.5 % MeOH, yielding 60 mg (48 %) of free **21** as a mixture of 4 diastereomers according to the ^{31}P NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1H), 7.42 (s, 1H), 6.41 (m, 1H), 6.36 (m, 1H), 6.29 (m, 1H), 5.60 (s, 2H), 4.35 (m, 1H), 4.28 (m, 3H), 4.14 (m, 2H), 3.80 (ddd, *J* = 11.2, 4.6, 2.8 Hz, 3H), 2.65 (m, 1H), 2.51 (m, 2H), 2.04 (m, 6H), 1.98 (m, 1H), 1.92 (m, 3H), 1.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.50, 169.48, 169.47, 169.45, 169.44, 169.43, 169.42, 163.81, 163.80, 150.47, 150.45, 135.36, 135.34, 135.33, 134.3, 123.4, 111.44, 111.42, 111.40, 111.32, 99.23, 99.21, 99.19, 99.17, 98.09, 98.08, 98.06, 98.05, 85.03, 84.98, 84.96, 83.36, 83.34, 83.28, 81.62, 81.60, 81.58, 81.52, 68.23, 68.22, 68.18, 68.17, 68.16, 66.88, 66.87, 66.84, 66.83, 66.81, 66.79, 54.78, 54.75, 54.72, 54.70, 54.69, 54.65, 44.15, 44.13, 44.11, 44.08, 44.06, 44.05, 44.01, 36.63, 36.58, 31.62, 31.59, 31.57, 21.16, 21.14,

21.08, 21.07, 12.40, 12.39; ^{31}P NMR ($CDCl_3$) δ 0.14, -0.05, -0.12, -0.18; IR (film) 2345, 1745, 1688, 1470, 1367, 1227, 1099, 1004, 968, 906 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{20}H_{30}N_3NaO_{13}P$ 574.1414, found 574.1424.

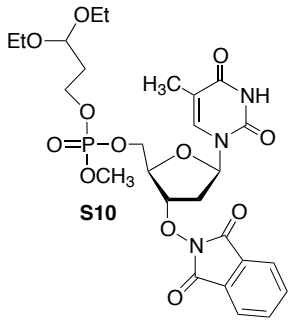


Preparation of S9. A solution of **21** (30 mg, 0.05 mmol), 2,6-dichloro-3-hydroxy-4-methoxybenzaldehyde (15 mg, 0.07 mmol) and AcOH (9 mg, 0.15 mmol) in DMSO (0.5 mL) was incubated at 37 °C overnight. The DMSO was evaporated under vacuum and the residue was purified by column chromatography using DCM with 3 % MeOH, yielding 45 mg (100 %) of the oxime as a foam. ^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H), 8.28 (s, 1H), 7.44 (s, 1H), 6.83 (s, 1H), 6.44 (m, 1H), 6.39 (m, 1H), 6.33 (m, 1H), 4.94 (m, 1H), 4.40 (m, 1H), 4.33 (m, 2H), 4.15 (m, 2H), 3.89 (s, 3H), 3.79 (ddd, *J* = 11.2, 3.9, 1.7 Hz, 3H), 2.64 (m, 1H), 2.49 (m, 1H), 2.17 (m, 1H), 2.00 (m, 6H), 1.91 (s, 3H), 1.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.42, 169.39, 163.81, 163.80, 150.55, 150.54, 148.4, 146.8, 142.1, 135.3, 125.1, 120.5, 120.4, 111.54, 111.53, 111.51, 111.45, 111.3, 99.22, 99.19, 99.16, 98.04, 98.00, 85.0, 82.3, 82.1, 67.9, 66.8, 56.6, 54.79, 54.76, 54.73, 54.70, 54.67, 44.13, 44.06, 40.8, 37.19, 37.14, 31.60, 31.58, 31.56, 21.15, 21.14, 21.13, 21.05, 21.04, 12.4; ^{31}P NMR ($CDCl_3$) δ 0.01, -0.10, -0.20, -0.28; IR (film) 2957, 1749, 1690, 1275, 1228, 1017, 970, 862 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{28}H_{34}Cl_2N_3NaO_{15}P$ 776.1002, found 776.0981.



Preparation of 18. To a solution of the above oxime (45 mg, 0.06 mmol) in DMF (0.2 mL) was added disodium 2-carbamoyl-2-cyanoethylene-1,1-dithiolate (31.2 mg, 0.12 mmol) in DMF (0.2 mL) and the mixture was incubated at 25 °C for 1h. DMF was evaporated under vacuum and the residue was purified

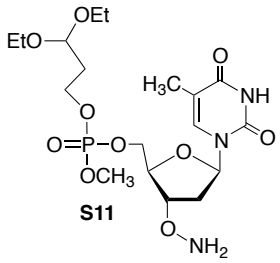
by C18 silica using a gradient 10 % - 40 % MeCN in water. The fractions containing the desired product were lyophilized yielding 32 mg (78 %) of sodium salt **18** as white powder. ^{1}H NMR (D_2O) δ 8.11 (s, 1H), 7.72 (s, 1H), 6.76 (s, 1H), 6.35 (m, 1H), 6.25 (d, *J* = 5.3 Hz, 1H), 6.21 (d, *J* = 8.5 Hz, 1H), 5.00 (m, 1H), 4.41 (s, 1H), 4.13 (m, 2H), 3.97 (m, 2H), 3.81 (s, 3H), 2.65 (q, *J* = 8.5 Hz, 1H), 2.56 (m, 1H), 2.49 (p, *J* = 8.2, 7.2 Hz, 1H), 2.35 (dt, *J* = 14.9, 7.5 Hz, 1H), 2.03 (m, 6H), 1.90 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (D_2O) δ 172.60, 172.56, 172.49, 166.10, 166.08, 151.1, 149.2, 142.5, 137.1, 123.9, 120.0, 119.2, 111.21, 111.20, 100.1, 98.9, 83.1, 56.2, 30.8, 20.55, 20.45, 11.7; ^{31}P NMR (D_2O) δ -0.28, -0.29; HRMS (M^-) calcd for $C_{27}H_{31}Cl_2N_3O_{15}P$ 738.0875, found 738.0874; $\varepsilon_{270\ nm}$ = 18800 $cm^{-1}M^{-1}$ in water.



S10

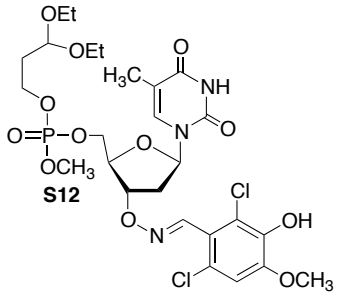
Preparation of S10. To a solution of **S2** (52 mg, 0.1 mmol) and 3,3-diethoxy-1-propanol (19 mg, 0.13 mmol) in anhydrous MeCN (0.5 mL) was added a solution of 5-ethylthio-1H-tetrazole in MeCN (0.5 mL, 0.13 mmol, 0.25 M solution) and the resulting mixture was stirred for 1 h at 25 °C. *t*-BuOOH in decane (0.10 mL, 5 M solution) was added to the reaction mixture and stirring was continued for an additional 20 min. The solvents were evaporated under vacuum and the residue was purified by column chromatography using DCM with 3.5 % MeOH, yielding 40 mg (65 %) of **S10** as a mixture of 2 diastereomers, according to the ^{31}P NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 9.04 (s, 1H), 7.83, 7.78 (each m, 4H), 7.41 (s, 1H), 6.50 (m, 1H), 4.98 (d, *J* = 6.3 Hz, 1H), 4.61 (q, *J* = 5.7 Hz, 1H), 4.55 (m, 1H), 4.31 (m, 2H), 4.14 (q, *J* = 6.6 Hz, 2H), 3.78, 3.77 (each d, *J* = 11.2 Hz, 3H), 3.60 (m, 2H), 3.46 (m, 2H), 2.76 (ddd, *J* = 14.6, 5.8, 1.9 Hz, 1H), 2.24 (m, 1H), 1.97 (dt, *J* = 11.3, 5.8 Hz, 2H), 1.91 (s, 3H), 1.45 (d, *J* = 6.3 Hz, 2H), 1.17 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 163.74, 163.68, 150.16, 150.14, 135.46, 135.43, 134.9, 128.7, 123.9, 111.50, 111.47, 102.6, 99.52, 99.47, 87.63, 87.61, 85.2,

81.19, 81.10, 67.1, 64.98, 64.93, 64.87, 61.86, 61.72, 61.68, 61.59, 59.2, 54.62, 54.58, 54.57, 54.52, 47.4, 36.71, 36.68, 35.8, 34.68, 34.64, 34.61, 34.58, 22.9, 19.3, 15.32, 15.28, 15.27, 12.4; ^{31}P NMR ($CDCl_3$) δ 0.04, -0.01; IR (film) 2973, 1736, 1690, 1467, 1373, 1277, 1187, 1126, 1033, 877, 703 cm^{-1}; HRMS (M + Na^+) calcd for $C_{26}H_{34}N_3NaO_{12}P$ 634.1778, found 634.1752.



S11

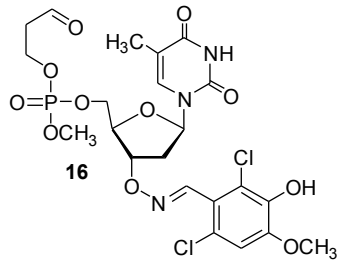
Preparation of S11. Phthalimide **S10** (35 mg, 0.06 mmol) in THF (0.5 mL) reacted with hydrazine (0.1 mL, 6 % solution in water) for 5 min at 25 °C. The volatile components were evaporated and the residue was purified by column chromatography using DCM with 5 % MeOH, yielding 24 mg (89 %) of **S11** as an oil. ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 7.46 (m, 1H), 6.32 (ddd, *J* = 8.9, 5.6, 3.4 Hz, 1H), 5.50 (s, 2H), 4.63 (q, *J* = 5.6 Hz, 1H), 4.37 (d, *J* = 6.3 Hz, 1H), 4.30 (m, 3H), 4.16 (m, 2H), 3.81, 3.80 (each d, *J* = 11.2 Hz, 3H), 3.64 (m, 2H), 3.49 (m, 2H), 2.48 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.00 (m, 3H), 1.93 (t, *J* = 1.2 Hz, 3H), 1.90 (s, 1H), 1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 163.7, 150.42, 150.40, 135.3, 111.49, 111.44, 99.53, 99.50, 84.94, 84.91, 83.53, 83.49, 81.68, 81.60, 67.9, 64.84, 64.79, 64.73, 61.72, 61.67, 61.58, 54.52, 54.49, 54.47, 54.43, 36.80, 36.74, 34.71, 34.64, 15.30, 15.28, 12.40; ^{31}P NMR ($CDCl_3$) δ 0.39, 0.28; IR (film) 2972, 1691, 1467, 1274, 1033, 857 cm^{-1}; HRMS (M + Na^+) calcd for $C_{18}H_{32}N_3NaO_{10}P$ 504.1723, found 504.1724.



S12

Preparation of S12. A solution of **S11** (28 mg, 0.06 mmol), 2,6-dichloro-3-hydroxy-4-methoxybenzaldehyde (17 mg, 0.08 mmol) and AcOH (9 mg, 0.15 mmol) in DMSO (0.5 mL) was incubated at 37°C overnight. The DMSO was evaporated under vacuum and the residue was purified by column chromatography using DCM with 4 % MeOH, yielding 40 mg (97 %) of **S12** as a foam. ^{1}H NMR ($CDCl_3$) δ 9.26

(s, 1H), 8.31 (s, 1H), 7.51 (m, 1H), 6.85 (s, 1H), 6.51 (m, 1H), 6.48 (m, 1H), 4.97 (d, J = 7.0 Hz, 1H), 4.62 (td, J = 5.7, 3.6 Hz, 1H), 4.42 (m, 1H), 4.33 (m, 2H), 4.17 (q, J = 6.7 Hz, 2H), 3.91 (s, 3H), 3.80 (d, J = 11.2 Hz, 3H), 3.63 (m, 2H), 3.48 (m, 2H), 2.63 (dd, J = 14.1, 5.9 Hz, 1H), 2.16 (m, 1H), 1.99 (q, J = 6.4 Hz, 2H), 1.95 (s, 3H), 1.17 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 163.7, 150.61, 150.60, 148.2, 146.8, 141.9, 135.3, 125.4, 120.6, 120.2, 111.69, 111.64, 111.3, 99.55, 99.52, 85.00, 84.99, 82.6, 82.27, 82.21, 64.89, 64.84, 64.78, 61.75, 61.73, 61.61, 56.6, 54.57, 54.53, 54.51, 54.47, 37.46, 37.40, 34.71, 34.69, 34.65, 34.63, 15.3, 12.4; ^{31}P NMR ($CDCl_3$) δ 0.30, 0.17; IR (film) 2973, 1690, 1492, 1440, 1274, 1032, 860 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{26}H_{36}Cl_2N_3NaO_{12}P$ 706.1311, found 706.1289.



Preparation of 16. A solution of **S12** (40 mg, 0.06 mmol) was refluxed in acetone (1 mL) in presence of pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) and water (0.05 mL) for 5 h. TLC analysis shows insignificant amount of starting material. The solvents were evaporated and the residue was purified by column chromatography on silica using DCM with 5 % MeOH, yielding 26 mg (76 %) of **16** as a white solid. ^{1}H NMR (CD_3CN) δ 9.68 (m, 1H), 9.28 (s, 1H), 8.29 (s, 1H), 7.46 (s, 1H), 7.03 (s, 1H), 6.32 (m, 1H), 5.45 (s, 1H), 4.97 (m, 1H), 4.34 (m, 3H), 4.27 (m, 2H), 3.89 (s, 3H), 3.73 (d, J = 11.2 Hz, 3H), 2.79 (td, J = 5.9, 1.3 Hz, 2H), 2.53 (dd, J = 14.0, 5.7 Hz, 1H), 2.28 (dt, J = 15.6, 8.4 Hz, 1H), 1.85 (d, J = 1.1 Hz, 3H); ^{13}C NMR (CD_3CN) δ 200.10, 200.08, 163.7, 150.5, 148.9, 146.7, 142.4, 135.55, 135.53, 124.4, 120.5, 119.9, 111.8, 110.7, 84.91, 84.87, 82.46, 82.44, 82.1, 82.0, 67.4, 61.67, 61.66, 61.62, 61.61, 56.4, 54.34, 54.33, 54.31, 54.27, 54.25, 43.55, 43.48, 36.45, 36.44, 11.5; ^{31}P NMR (CD_3CN) δ -0.17, -0.28; IR (film) 2956, 1680, 1487, 1439, 1263, 1032, 841, 731 cm^{-1}; HRMS (M + Na$^+$) calcd for $C_{22}H_{27}Cl_2N_3O_{11}P$ 610.0760, found 610.0765.

Synthesis of oxime library. The library was prepared and stored in 96 well PCR plates. A solution of alkoxyamine **7** in DMSO (1.16 mL, 17.4 mM) was aliquoted into 232 wells (5 μL in each, 87 nmol). Solutions of each aldehyde (232) in DMSO (150 mM) were added to each well (0.7 μL, 105 nmol), followed by the addition of a solution of acetic acid in DMSO (1 μL, 300 nmol). The plates were sealed and incubated at 37 °C for 12 h. DMSO and acetic acid were evaporated in a desiccator under high vacuum for 5 h. The contents of each well were redissolved in 22 μL of DMSO to provide a 4 mM solution of oxime and stored at -20 °C.

Screening of inhibitor library

a. Deprotection. To screen the library, 5 μL of DMSO solutions of **8** were transferred to another set of plates and placed under vacuum to remove DMSO. The contents of each well were redissolved in 5 μL of acetonitrile containing 12 mM of N-bromosuccinimide. After 20 min incubation at 0 °C, 1 μL of $Na_2S_2O_3$ solution in water (100 mM) and additional 4 μL of acetonitrile were added.

b. Pol β inhibition. A solution of Pol β (10 nM) in 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20, was added to a 96 well format microtiter plate (360 μL in each well). It is worth noting that the well should be full in order to get accurate fluorescence data (~380 μL). The solutions of inhibitors in acetonitrile produced above (10 μL) were transferred to the plates containing Pol β and incubated for 20 min (final concentration of the inhibitor was ~50 μM). To determine the polymerase activity in the presence of each inhibitor, a solution of **13** (3.8 μL, 5 μM) and dTTP (3.8 μL, 10 mM) were also added (to make final [**13**] = 50 nM and 100 μM of dTTP). The plates were immediately placed in the microtiter plate reader and the measurements were recorded.

Inhibition of Pol β studied by fluorescence as a function of concentration of specific inhibitors. Solution of Pol β (360 μL, 10 nM) in 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20, was added to the wells of a 96 well format microtiter plate. It is worth noting that the well should be full in order to get accurate fluorescence data (~ 380 μL). The solutions of inhibitors (40x) in acetonitrile obtained after pentenyl deprotection (10 μL) were transferred to the wells containing Pol β and incubated for 20 min. To determine the polymerase activity of enzyme in the presence of each inhibitor, solutions of ternary complex **13** (3.8 μL, 5 μM) and dTTP (3.8 μL, 10 mM) were also added (to make final 50 nM of **13** and 100 μM of dTTP). The plates were placed immediately in the microtiter plate reader Cary Eclipse Varian and the measurements started.

Time dependent inhibition of Pol β via fluorescence spectroscopy. Pol β (360 μL, 10 nM) in 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20, was added to 5 wells of a 96 well format microtiter plate. The inhibitor solution (40 x, 10 μL) was added to the first well and preincubated for 20 min. At this time, the same portion of inhibitor was added to the second well. Equal amounts of inhibitor were added subsequent wells after an additional 20, 35, and 40 min. Once the inhibitor was added to the fifth well, solutions of ternary complex **13** (3.8 μL, 5 μM) and dTTP (3.8 μL, 10 mM) were also added and the fluorescence measurement was started immediately. This procedure yielded the activity of Pol β (10 nM) after different preincubation times (0, 5, 20, 40, 60 min) with the inhibitor.

Time dependent inactivation of Pol β by 1a (3a) via gel electrophoresis. A solution (CH_3CN) of **1a** or **3a** (10 μL) was added to Pol β (400 μL, 5 nM) in 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20. The final inhibitor concentration varied between 5 and 30 μM. At specific times (0-40 min), which represent the

preincubation periods, aliquots (25 μL) were mixed with 3'-^{32}P-**15** (1 μL, 5 μM). Aliquots (4 μL) of the reactions were removed (5, 10, 15, 20, 30 min) and unreacted dRP was stabilized by reacting with $NaBH_4$ (1 μL, 0.5 M). The aliquots containing reducing agent were kept on ice for 1 h before mixing with loading buffer (5 μL) and analyzing by 20 % denaturing PAGE. The preincubation times for each inhibitor concentration varied: 5 μM – 0, 10, 20, 30, 40 min; 10, 15 μM – 0, 5, 10, 15, 20 min; 20 μM – 0, 1, 3, 5, 10 min; 30 μM – 0, 1, 2, 3, 5 min.

Dialysis of Pol β – inhibitor 1a (3a) reaction. Pol β (500 nM) was preincubated with the inhibitor **1a** or **3a** (50 μM) for 30 min in a solution containing 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl, 0.01 % Tween 20 and 10 % glycerol. An aliquot (5 μL) was diluted to 500 μL and placed in a dialysis cassette. A similar dialysis was set up using Pol β that was not reacted with **3a**. The experiment was carried out in triplicate. Dialysis was carried out in the reaction buffer. The remaining lyase activity of the enzyme was measured on aliquots (25 μL, 0, 1, 2, 3 days) using 3'-^{32}P-**15** (200 nM). Aliquots (4 μL, 5, 10, 15, 20, 30 min) from the reactions were stabilized with $NaBH_4$ solution (1 μL, 0.5 M). The aliquots were kept on ice for 1 h before mixing with loading buffer (5 μL) and analyzing by 20 % denaturing PAGE.

IC50 value for inhibitor 1a and 3a. Pol β (500 nM) was preincubated with inhibitor **3a** (0, 2.5, 5, 7.5, 10, 20, 30, 40, 50, 70, 100 μM) for 30 min in a solution containing 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20. Aliquots (1 μL) were diluted to 100 μL. The remaining lyase activity of the enzyme was determined using 3'-^{32}P-**15** (200 nM). Aliquots (4 μL) were removed at indicated time points (5, 10, 15, 20, 30 min) and stabilized with $NaBH_4$ solution (1 μL, 0.5 M). The aliquots were kept on ice for 1 h before mixing with loading buffer (5 μL) and separating by 20 % denaturing PAGE. The IC_{50} for **1a** was determined in the same manner except the inhibitor concentration range was between 0

and 200 μM. The relative activities were fit to the following sigmoidal equation: Relative Activity = A2 + [(A1-A2) / (1 + (x/x0)^p)], where x = concentration of inhibitor, A2 = minimum enzyme activity, A1 = maximum enzyme activity, x0 = IC_{50}, and p – Hill slope, which characterizes the slope of the curve at its midpoint. The data were fit iteratively using Origin 6.1.

Specificity of the inhibitor 3a for Pol β against Klenow (exo$^-$). A 96 well format microtiter plate was used to probe the polymerase activity of Pol β and Klenow (exo-) in the presence of inhibitor **3a**. The plate was charged with the solution containing **13** (50 nM), dTTP (5, 25, 50, 75 μM) and **3a** (0, 25, 50 μM) in 50 mM HEPES buffer pH = 7.5, 5 mM $MgCl_2$, 0.2 mM EDTA, 50 mM KCl and 0.01 % Tween 20. The volume of the solution in each well is ~400 μL. Pol β (final concentration, 10 nM) or Klenow exo- (final concentration 5 nM) is added and the measurement of the fluorescence is started immediately.

Cell Culture and Clonogenic Survival. DU 145 cells were obtained from the American Type Culture Collection (ATCC, HTB-81, Manassas, VA) and maintained in RPMI 1640 culture medium (Sigma-Aldrich R8758, St. Louis, MO), supplemented with 10% fetal bovine serum (Sigma-Aldrich F6178, St. Louis, MO). SV40-transformed mouse embryonic fibroblasts (MEFs) were obtained from Sam Wilson, NIEHS. MEFs were maintained in high glucose DMEM culture medium supplemented with 10% FBS and glutamax. Cultures were grown at 37°C in a humidified atmosphere of 5% carbon dioxide (DU145 cells) or 10% carbon dioxide (MEFs) without any antibiotics and subcultured when they reached confluence. For clonogenic survival analysis the appropriate number of cells were grown in standard 6-well tissue culture dishes in the growth media (2 mL per well). After 2 days the cells were treated with Pol β inhibitors (**3a** or **18**) by addition of sterile stock solution in water directly to the growth media to the desired final concentrations. Cells were treated similarly with methyl methanesulfonate

(MMS, Sigma-Aldrich, St. Louis, MO). For combined treatments **18** was added to the cells first followed by MMS. The compounds remained present throughout the entire assay. Two weeks after the treatment the cells were fixed and stained with 0.2% solution of crystal violet in 50% methanol. Colonies with ≥ 50 cells were counted. All treatments were carried out in triplicate.

Preparation of cell lysates. Cells were harvested by mild trypsinzation. The cells were then washed three times with phosphate buffered saline. Cell pellets were suspended in 1 X Passive Lysis Buffer (PBL, Promega Corporation, E1941, Madison, WI) at concentration of 1 x 10^7 cells per mL and frozen in aliquots at - 80° C. Protein concentrations were determined by Bio-Rad protein assay dye (Bio-Rad, 500-0006, Hercules, CA) according to the manufacturer's protocol and using bovine serum albumin as a standard.

Assessing the lyase activity of DU145 cell extracts (lysates) in the presence of an inhibitor. DU145 cell extract (2.94 mg / mL of protein, 10 x 10^6 cells / mL) was diluted 1:6 with HM buffer (3.5 μL diluted with 20.5 μL of buffer). Solutions of **3a** or **18** (all 25 X in water, 1 μL, 0, 10, 20, 50, 100 μM) were preincubated with the diluted cell extract for 1 h. The dRP substrate, 3'-^{32}P-**15** (1 μL, 25 X) was added to obtain 200 nM desired concentration and aliquots (4 μL) were collected at specific time points and stabilized with $NaBH_4$ (1 μL, 1 M). The aliquots were kept on ice for 1 h before mixing with loading buffer (5 μL). The samples were analyzed by 20 % denaturing PAGE and quantified using a phosphorimager.

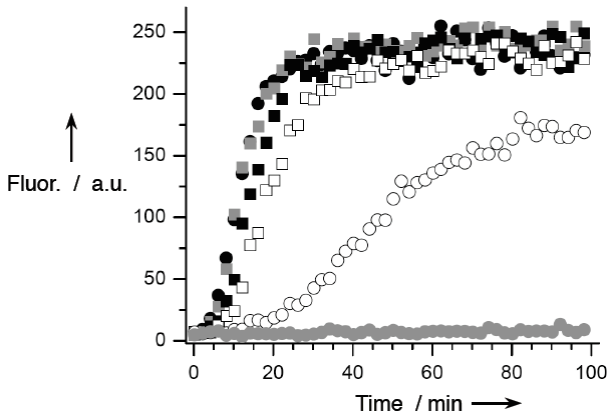
Assessing the effect of 18 on lyase activity of mouse embryonic fibroblast lysates. Cell lysate (32 μg protein) from the corresponding cell line (obtained from Dr. Sam Wilson, NIEHS) was incubated in HM buffer with or without **18** (50 μM) for 40 min at 25 °C (10 μL total volume), at which time 3'-^{32}P-**15** (2 μL, final concentration: 100 nM) was added. Aliquots (4 μL) were removed at 5, 15, and 25 min and frozen in dry-ice, except for Pol λ wild type

lysates, from which aliquots were removed at 2, 5, and 10 min. When the reactions were complete, $NaBH_4$ (1 μL, 0.5 M) was added to each aliquot. The aliquots were kept on ice for 1 h before mixing with loading buffer (5 μL). The samples were analyzed by 20 % denaturing PAGE and quantified using a phosphorimager.

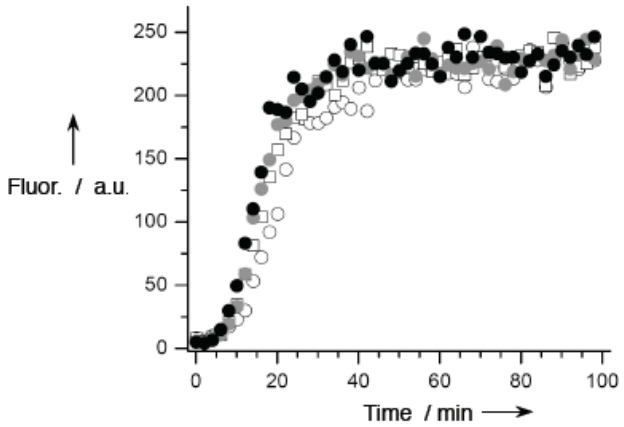
Supporting Information Table 1. Rate dependence of product formation on presence of inhibitor as a function of cell type.

Cell Type	Inhibitor	Rate ($\times 10^{-1}$ %•min^{-1})[a]	n[b]
Pol β wt	-	17.2 ± 5.2	6
Pol β wt	+	9.2 ± 2.4	4
Pol β -	-	7.0 ± 2.1	6
Pol β -	+	5.5 ± 1.5	6
Pol λ -	-	15.9 ± 4.4	10
Pol λ -	+	9.1 ± 2.3	12
Pol β/λ -	-	15.0 ± 4.0	12
Pol β/λ -	+	11.0 ± 4.0	10
Pol λ wt[c]	-	23.7 ± 3.7	3
Pol λ wt[c]	+	12.4 ± 3.2	4

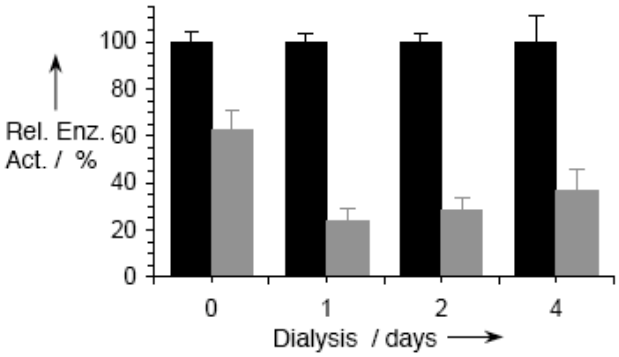
[a]Reactions carried out in the presence of 32 μg protein. Aliquots taken at 5, 15, and 25 min. Rates are reported as the average ± std. dev. of n reactions. [b]Number of reactions used to determine average and standard deviation. [c]Aliquots taken at 2, 5, and 10 min.



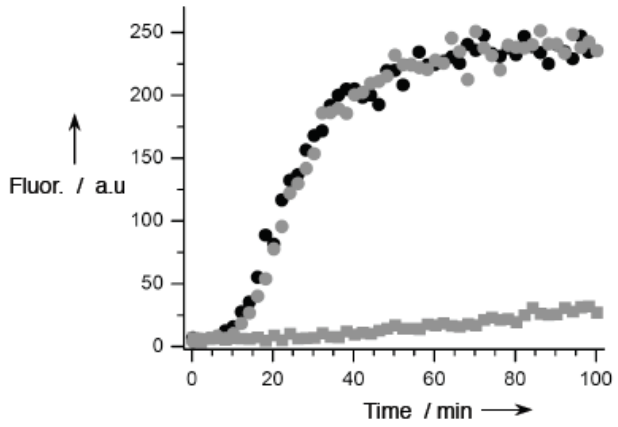
Supporting Information Figure 1. Concentration dependence of Pol β strand displacement synthesis inhibition by **2a**. [**2a**] (μM): 0, ●; 1, ■; 5, ■; 10, □; 25, ○; 50, ●



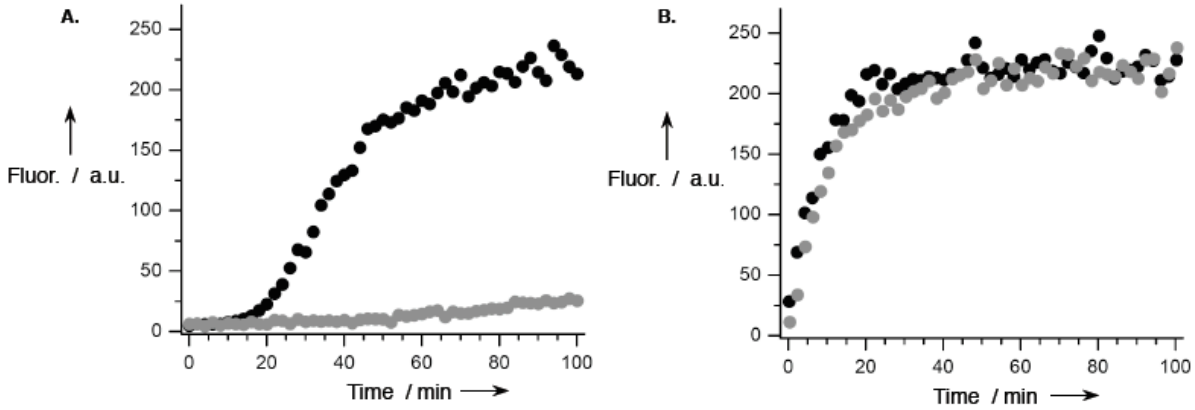
Supporting Information Figure 2. Concentration dependence of Pol β strand displacement synthesis inhibition by **16**. [**16**] (μM): 0, ●; 25, ●; 50, □; 150, ○



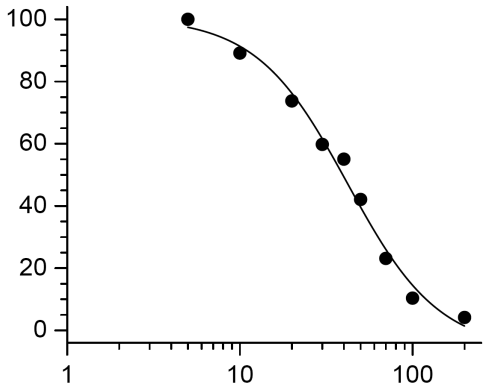
Supporting Information Figure 3. Relative Pol β activity with and without **3a** following dialysis. [**3a**] (μM): 0, ■; 20, ■



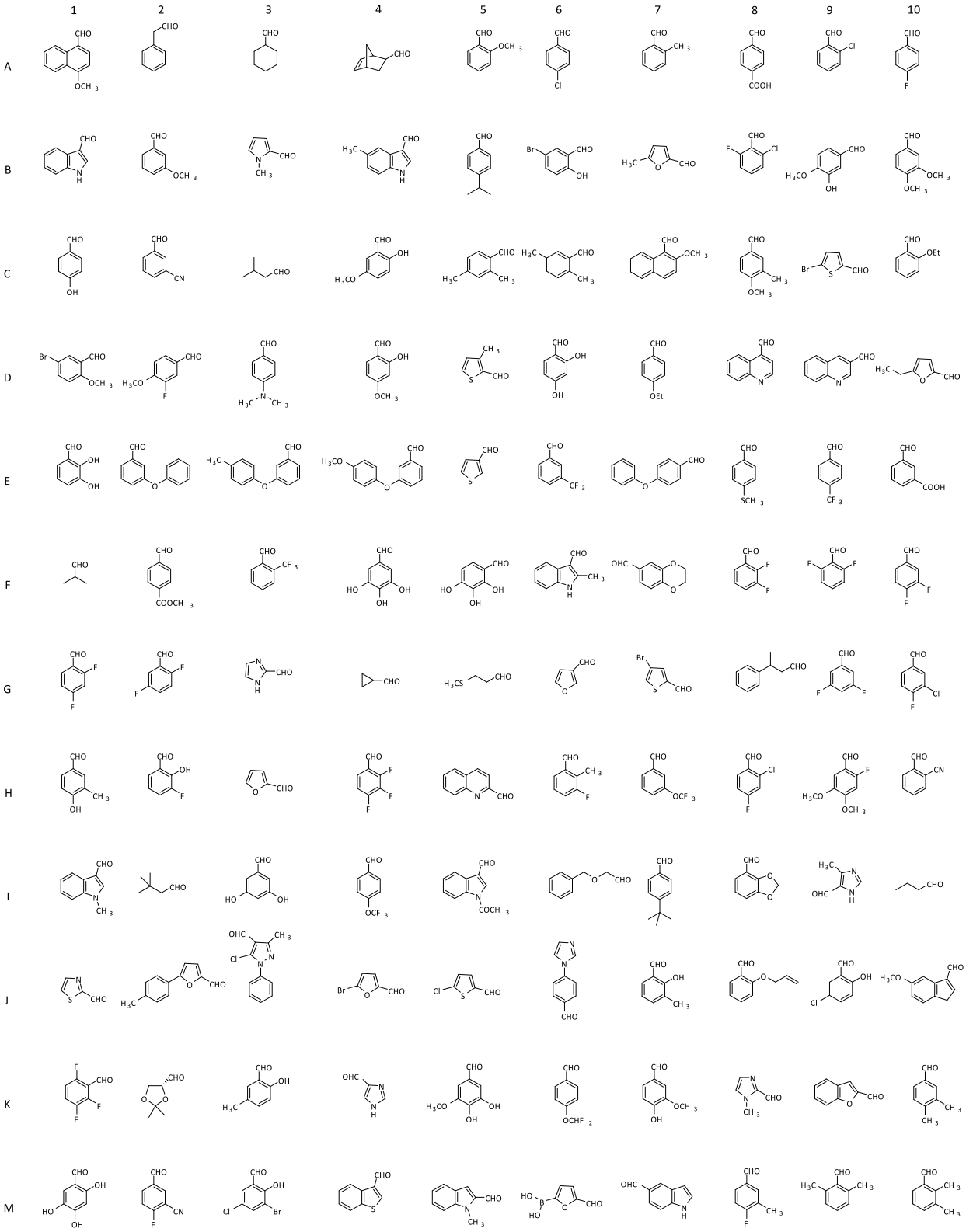
Supporting Information Figure 4. Pol β polymerase activity in the absence of inhibitor and the presence of **3a** or its reduced form, **17**. No inhibitor, ●; **17**, 20 μM, ●; **3a**, 20 μM, ■



Supporting Information Figure 5. Selectivity for Pol β inhibition by **3a**. A) Effect on Pol β. B) Effect on Klenow exo⁻. [**3a**] (μM), 0, ●; 10, ●



Supporting Information Figure 6. IC_{50} of Pol β inactivation by **1a** (30 min preincubation).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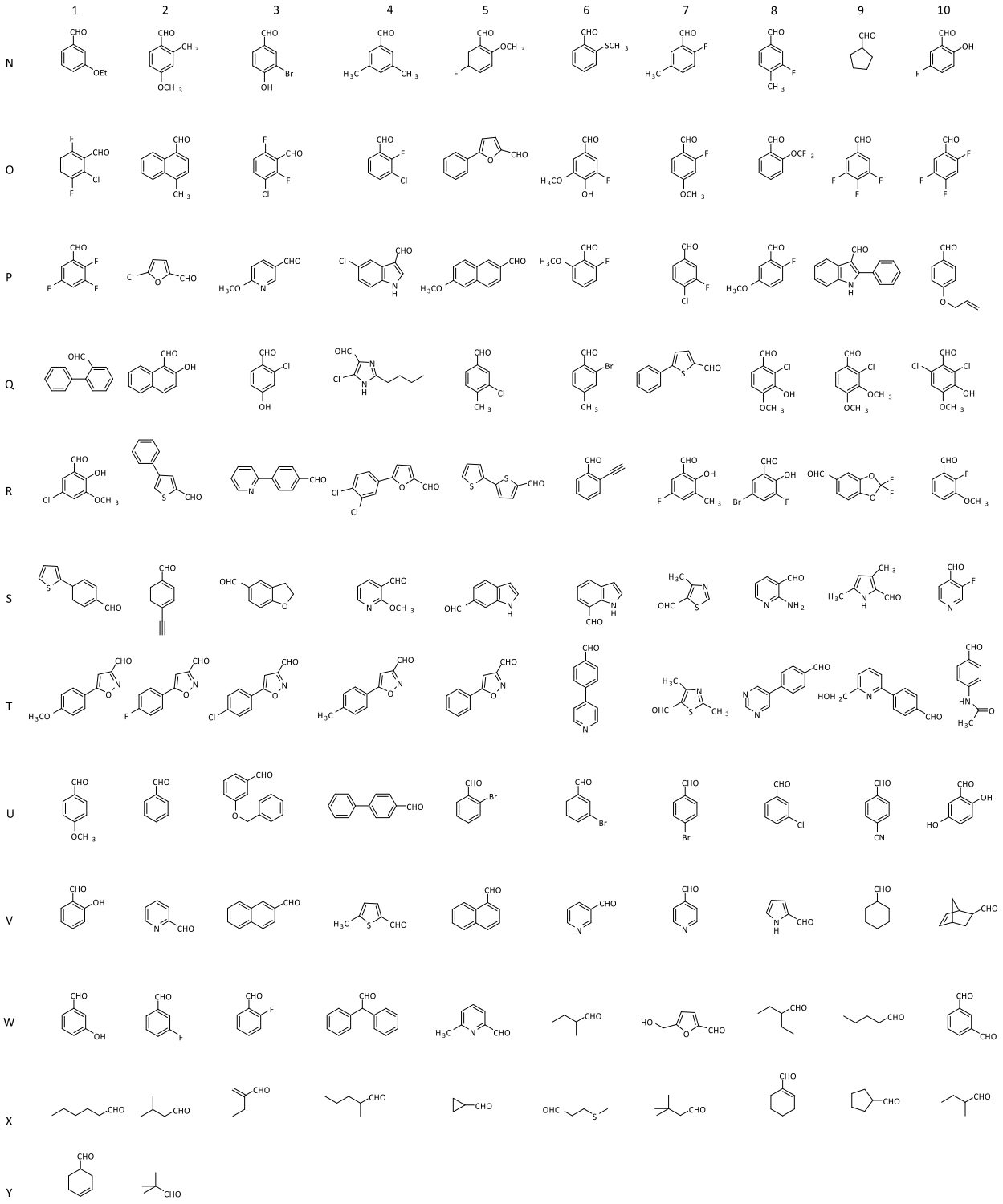
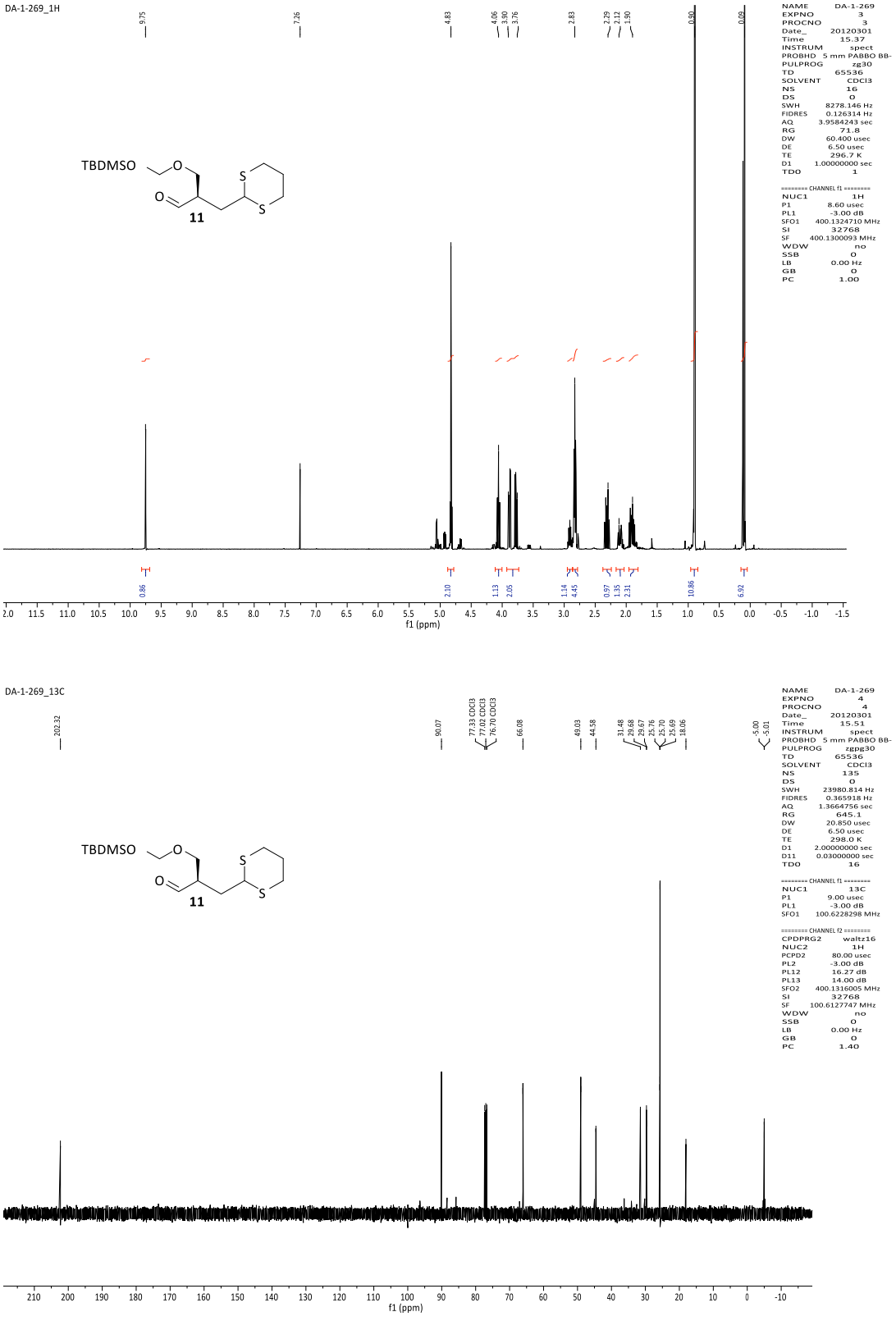
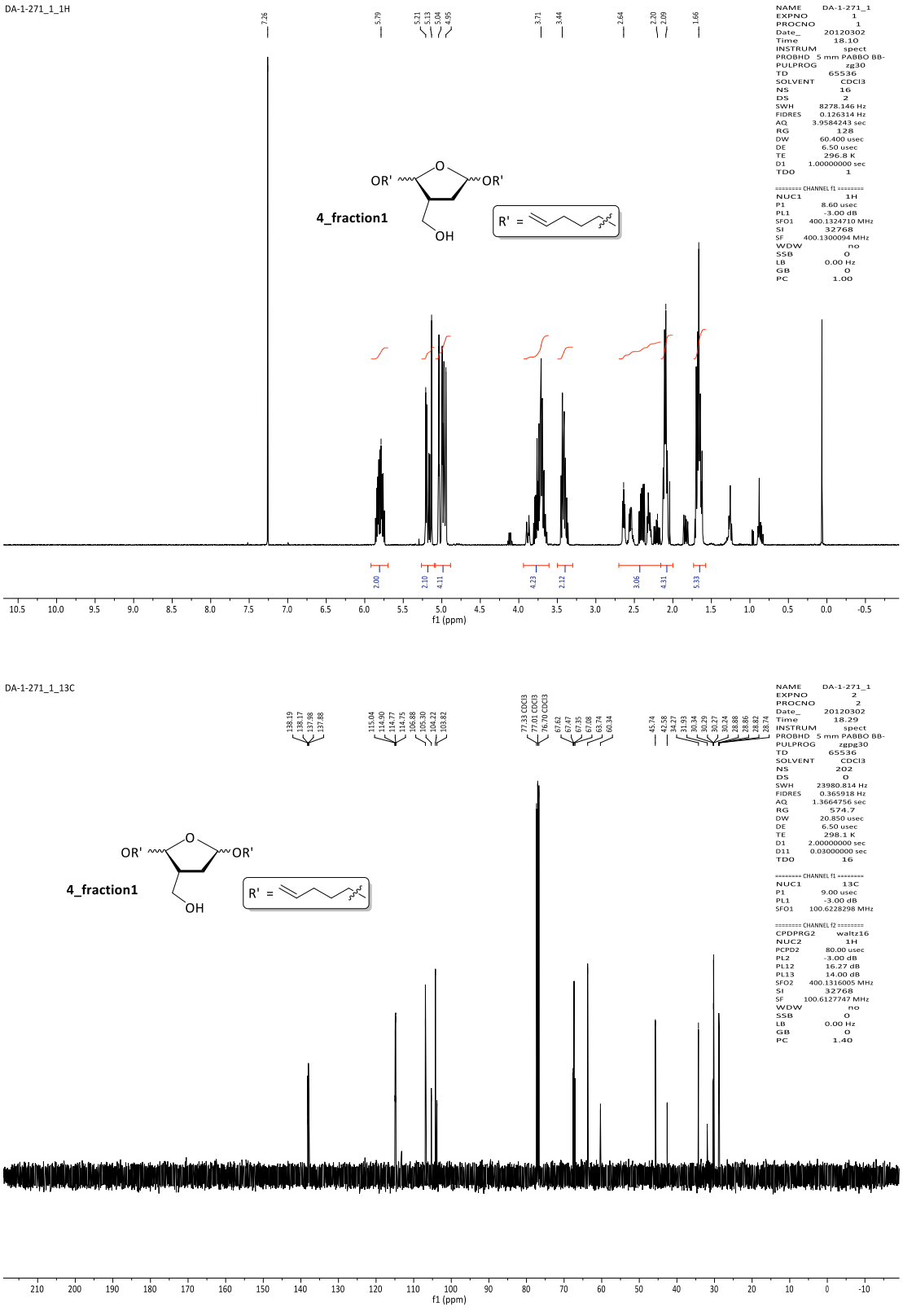


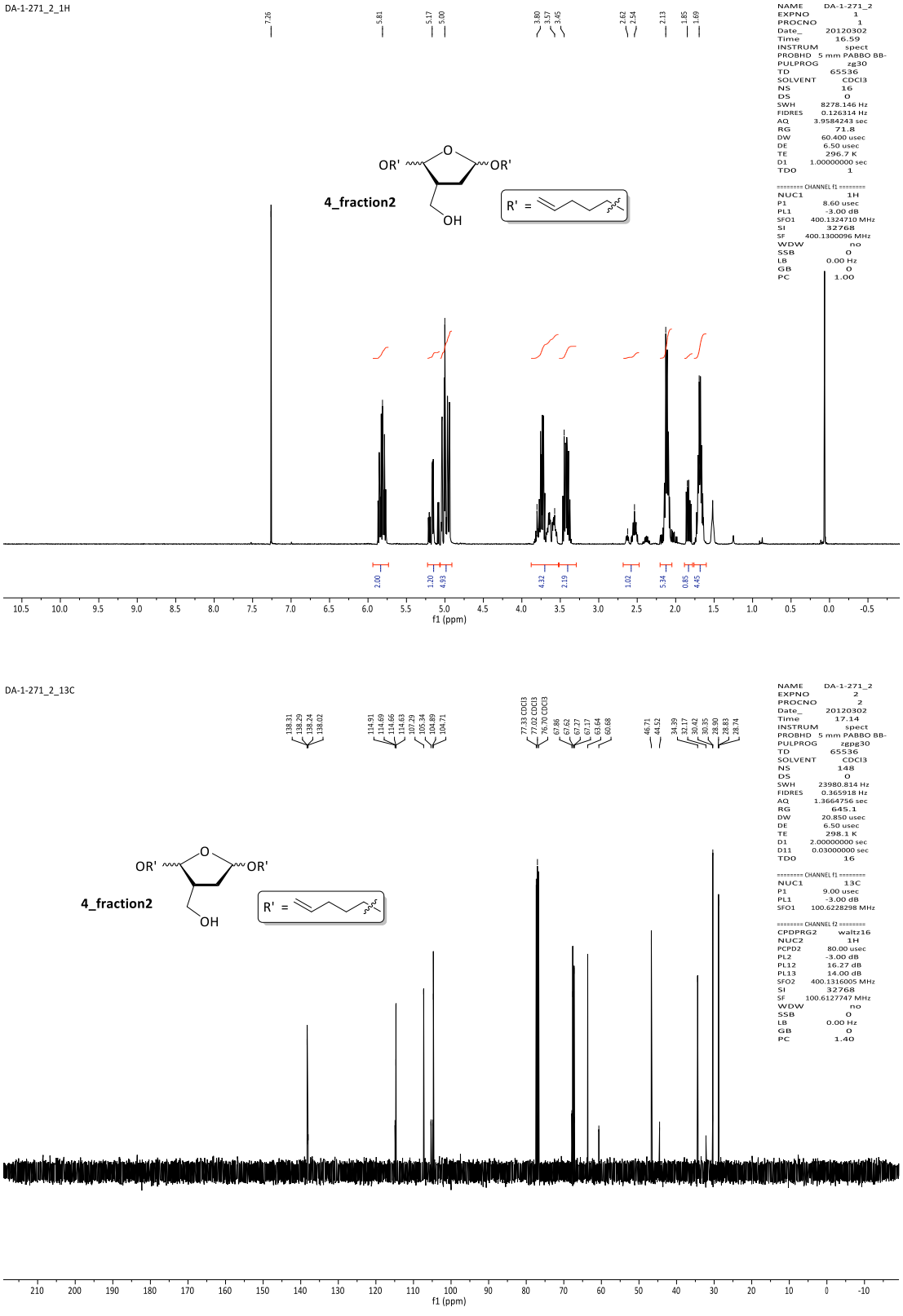
Supporting Information Figure 7. Chart of aldehydes used to prepare oxime library.



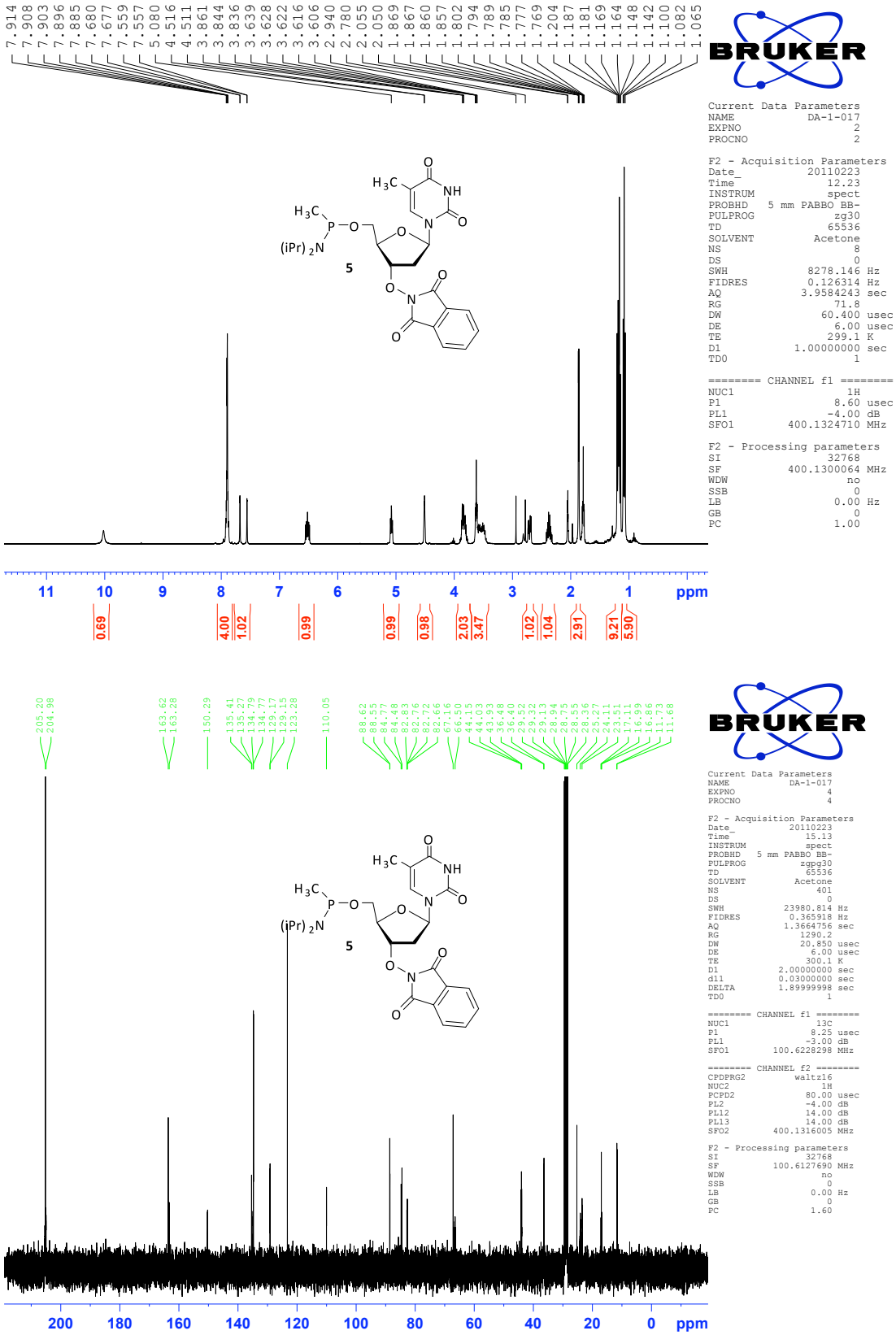
Supporting Information Figure 8. ^{1}H and ^{13}C NMR spectra of **11** in $CDCl_3$.



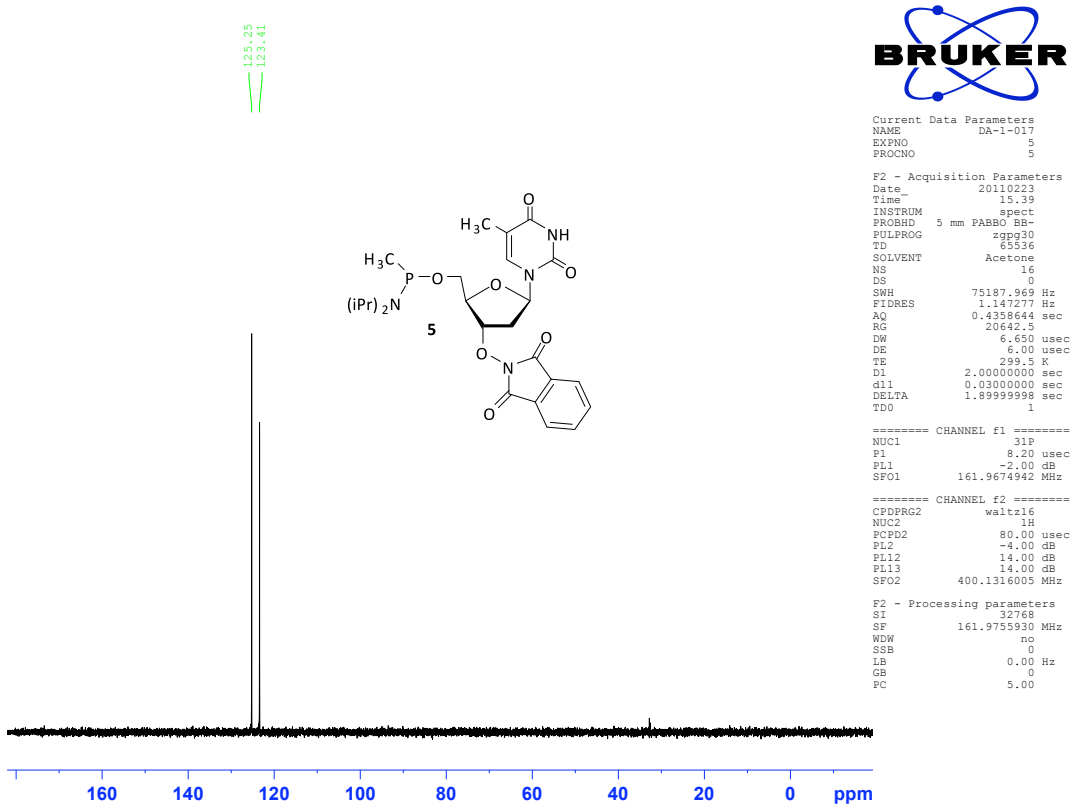
Supporting Information Figure 9. ^{1}H and ^{13}C NMR spectra of **4_fraction1** in $CDCl_3$.



Supporting Information Figure 10. ^{1}H and ^{13}C NMR spectra of **4_fraction2** in $CDCl_3$.



Supporting Information Figure 11. ^{1}H and ^{13}C NMR spectra of **5** in acetone-d_6.

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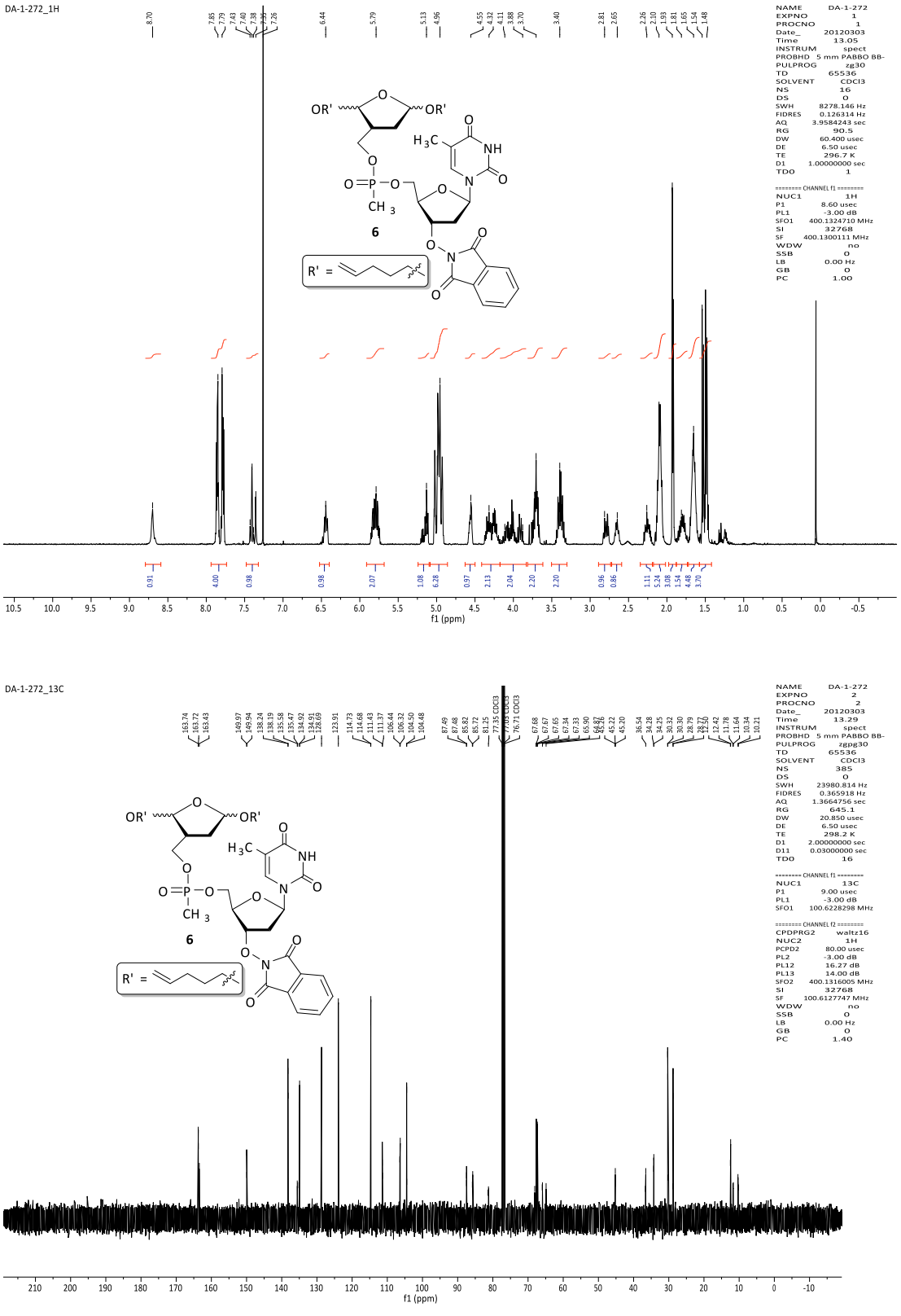
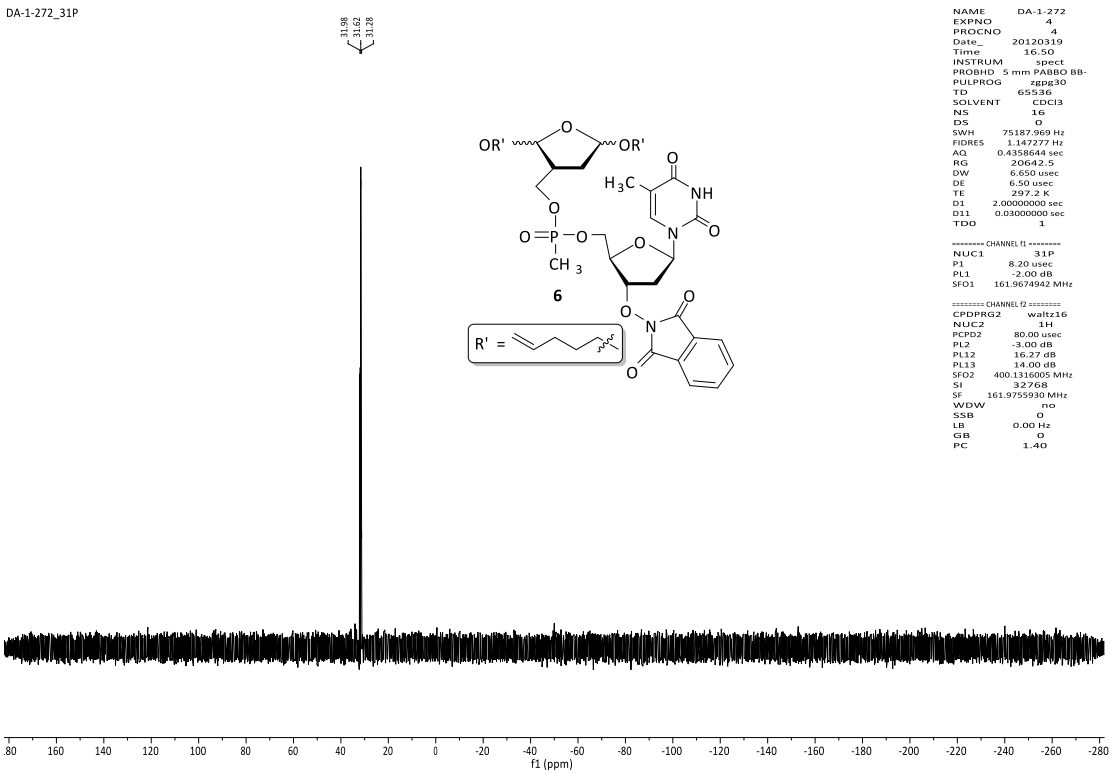
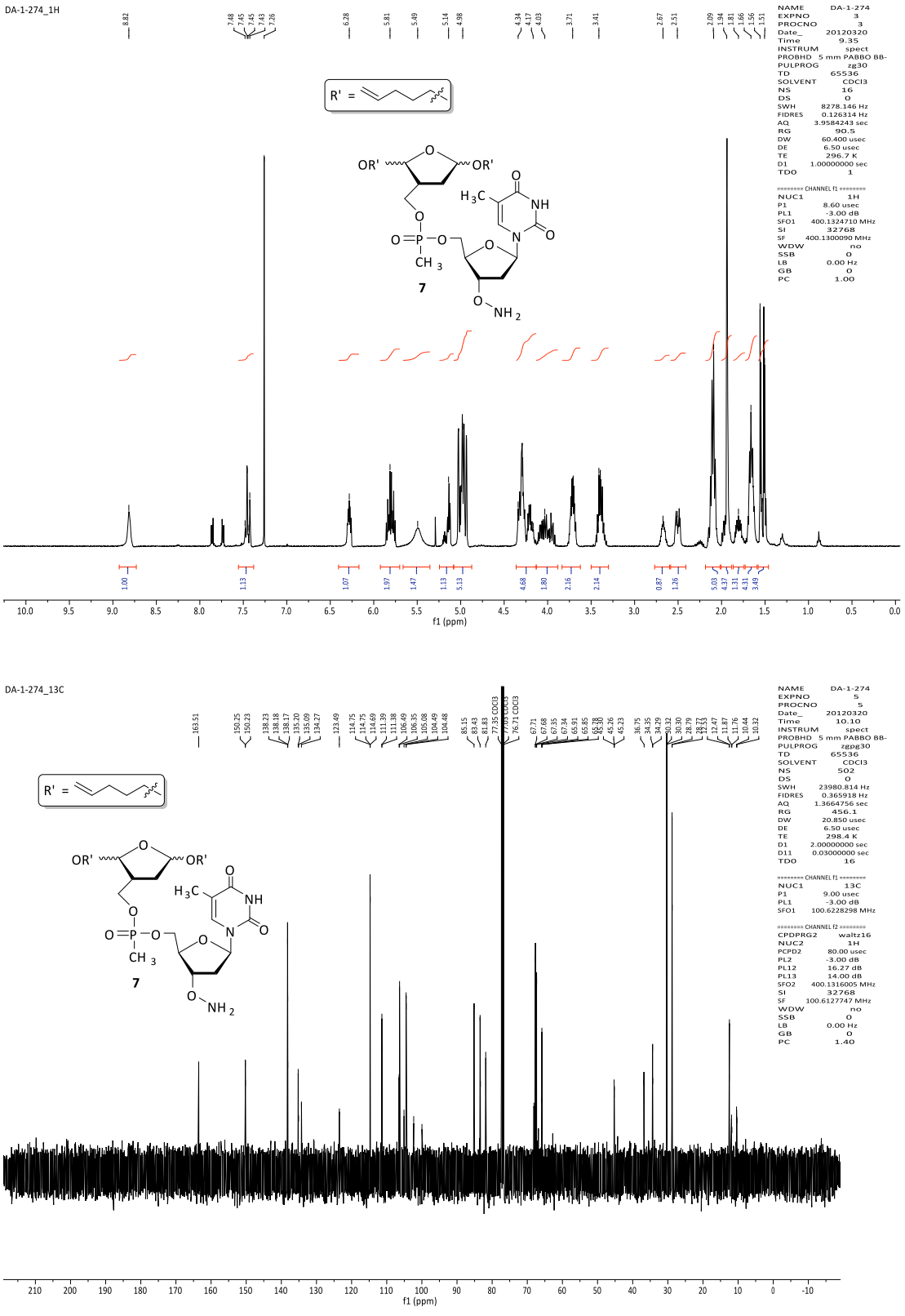
Supporting Information Figure 12. ^{31}P NMR spectra of **5** in acetone-d_6.



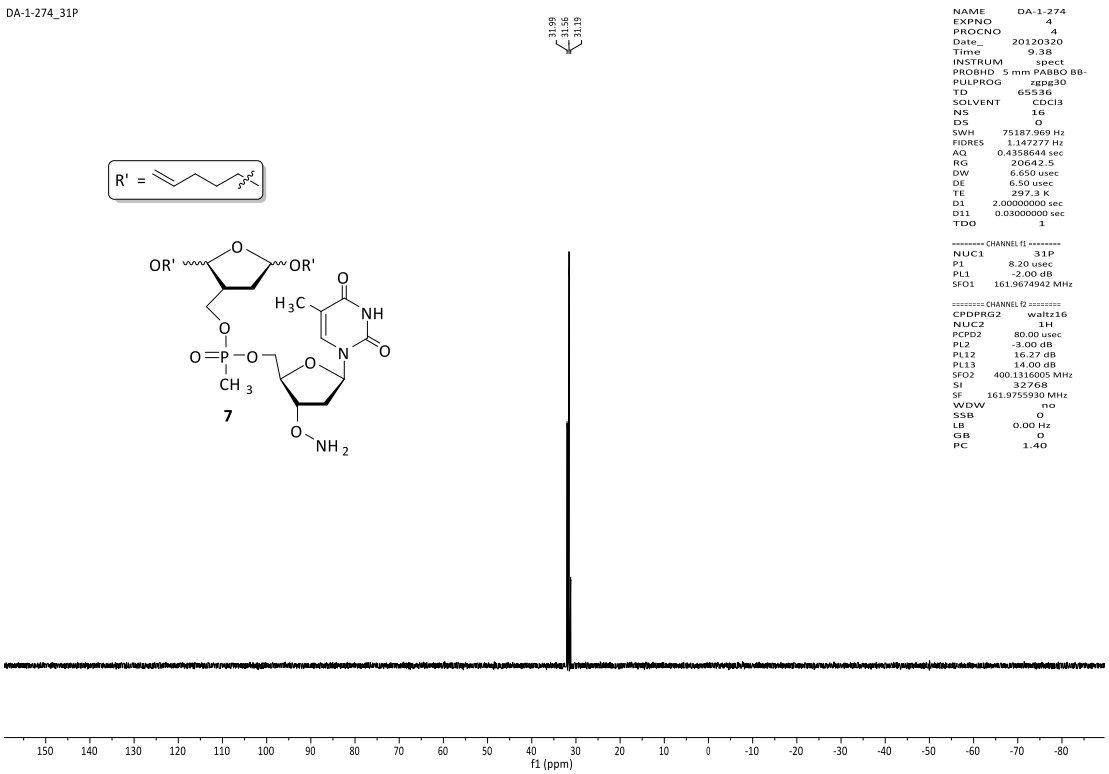
Supporting Information Figure 13. ^{1}H and ^{13}C NMR spectra of **6** in $CDCl_3$.



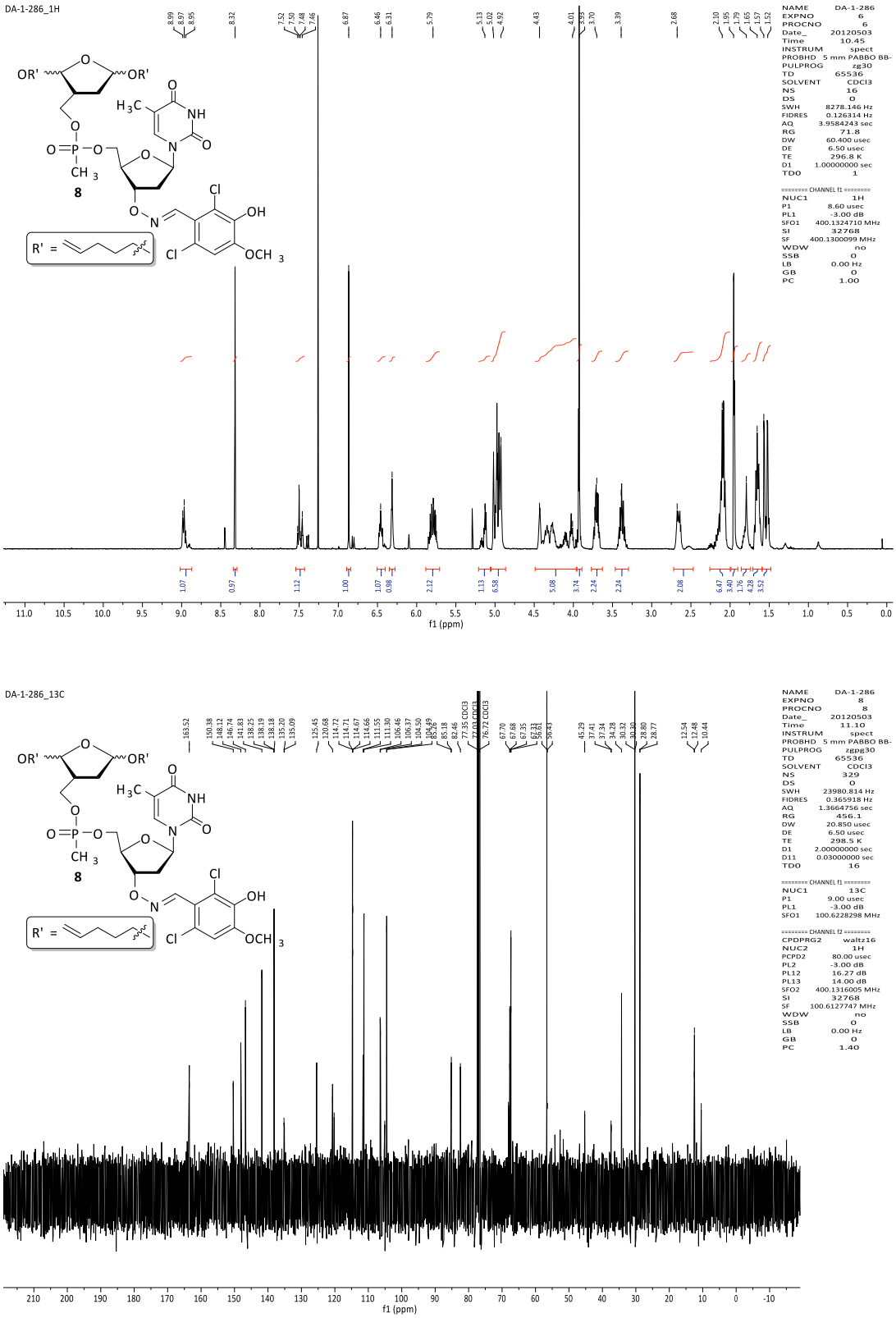
Supporting Information Figure 14. ^{31}P NMR spectra of **6** in $CDCl_3$.



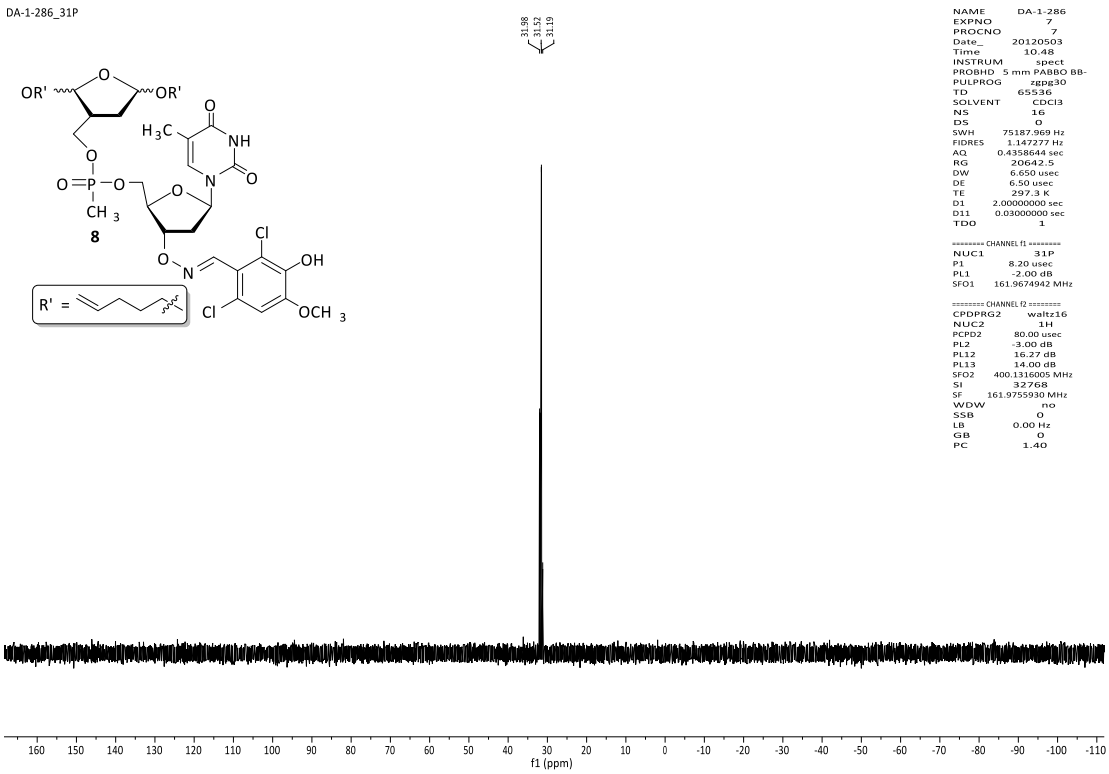
Supporting Information Figure 15. ^{1}H and ^{13}C NMR spectra of **7** in $CDCl_3$.



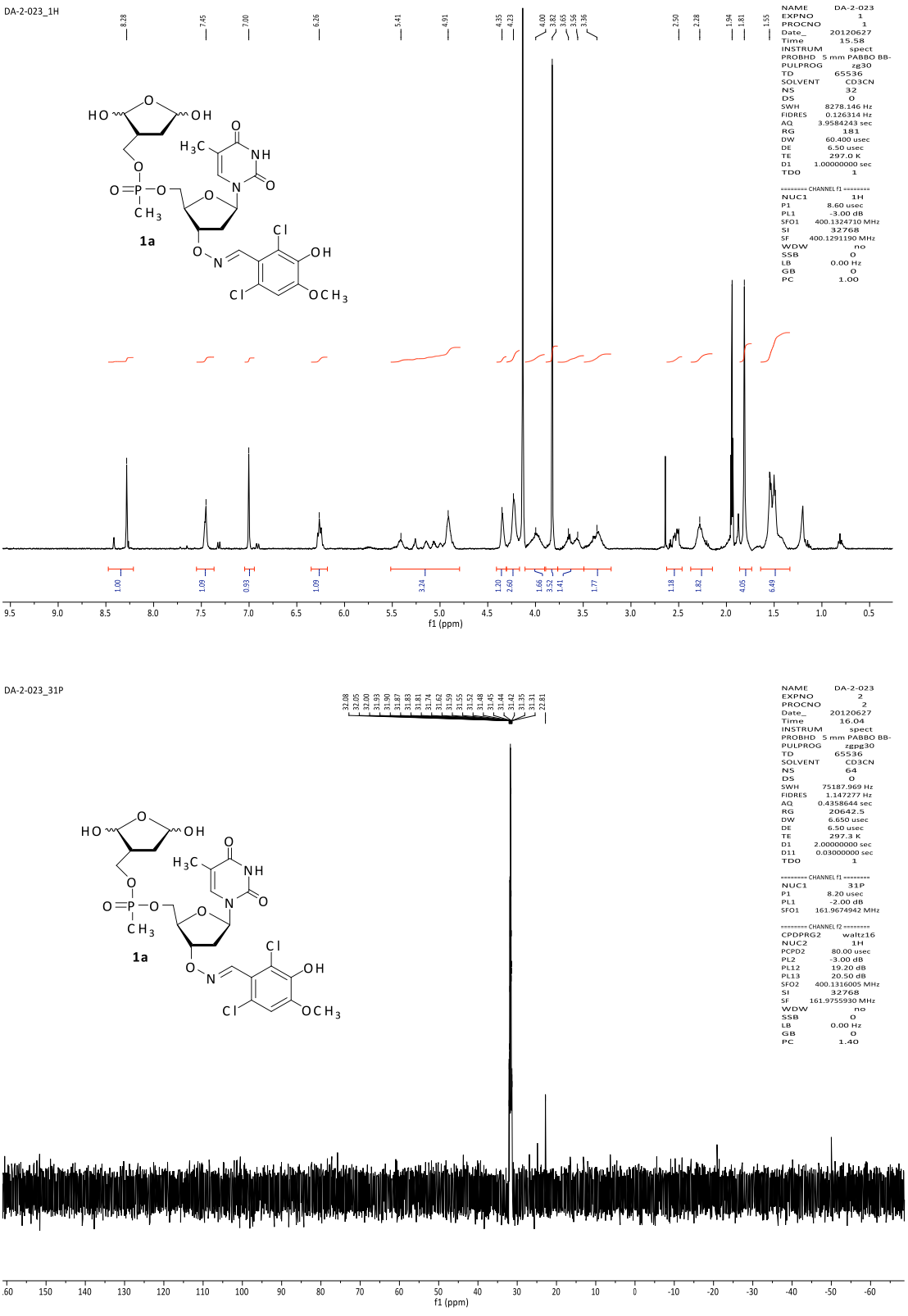
Supporting Information Figure 16. ^{31}P NMR spectrum of **7** in $CDCl_3$.



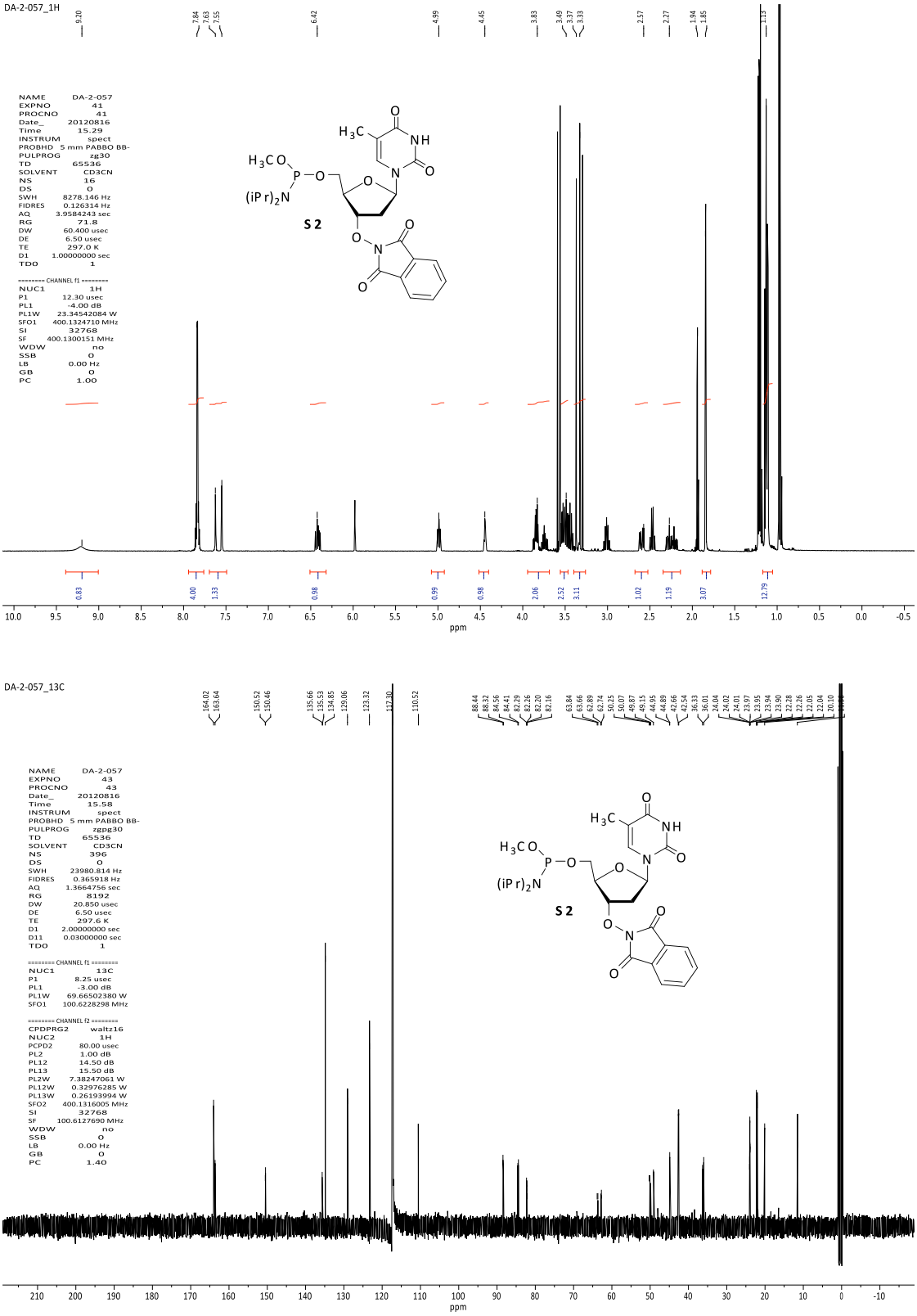
Supporting Information Figure 17. ^{1}H and ^{13}C NMR spectra of **8** in $CDCl_3$.



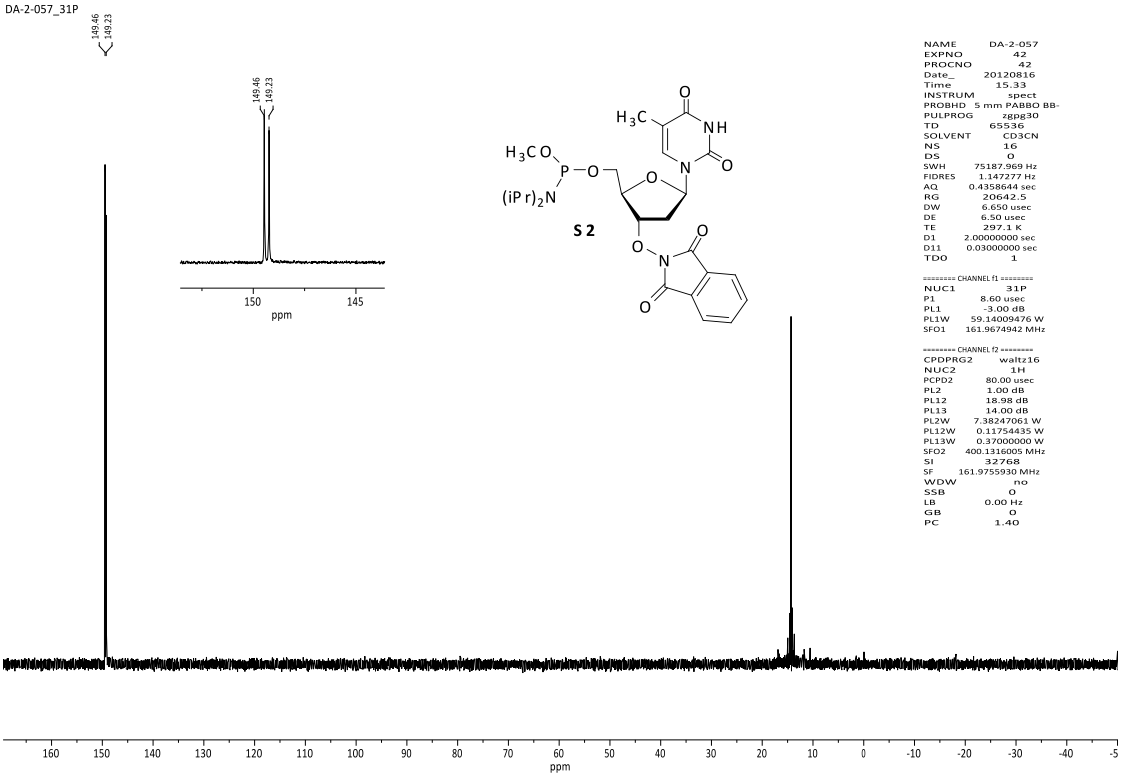
Supporting Information Figure 18. ^{31}P NMR spectrum of **8** in $CDCl_3$.



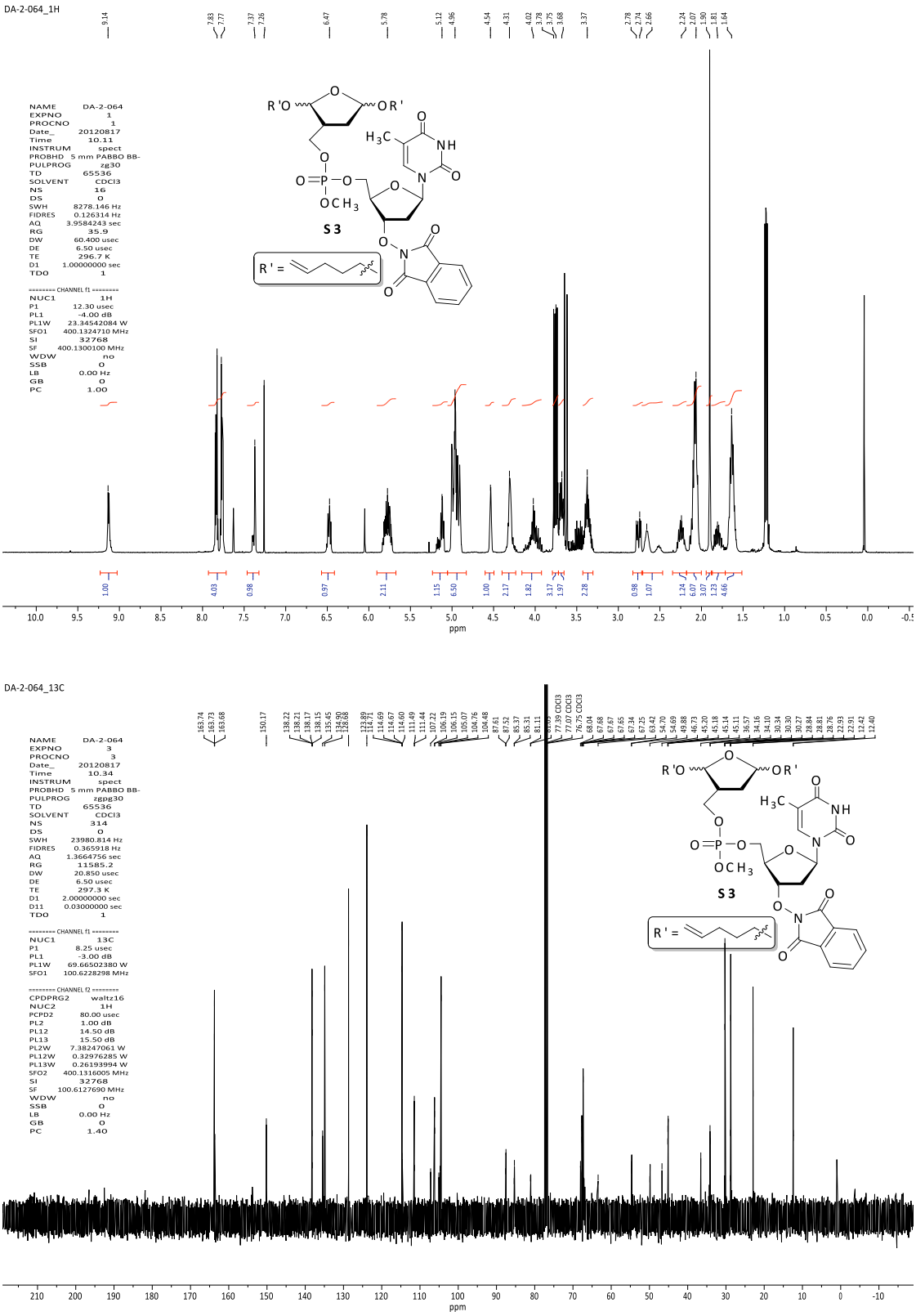
Supporting Information Figure 19. ^{1}H and ^{31}P NMR spectra of **1a** in acetonitrile-d_3.



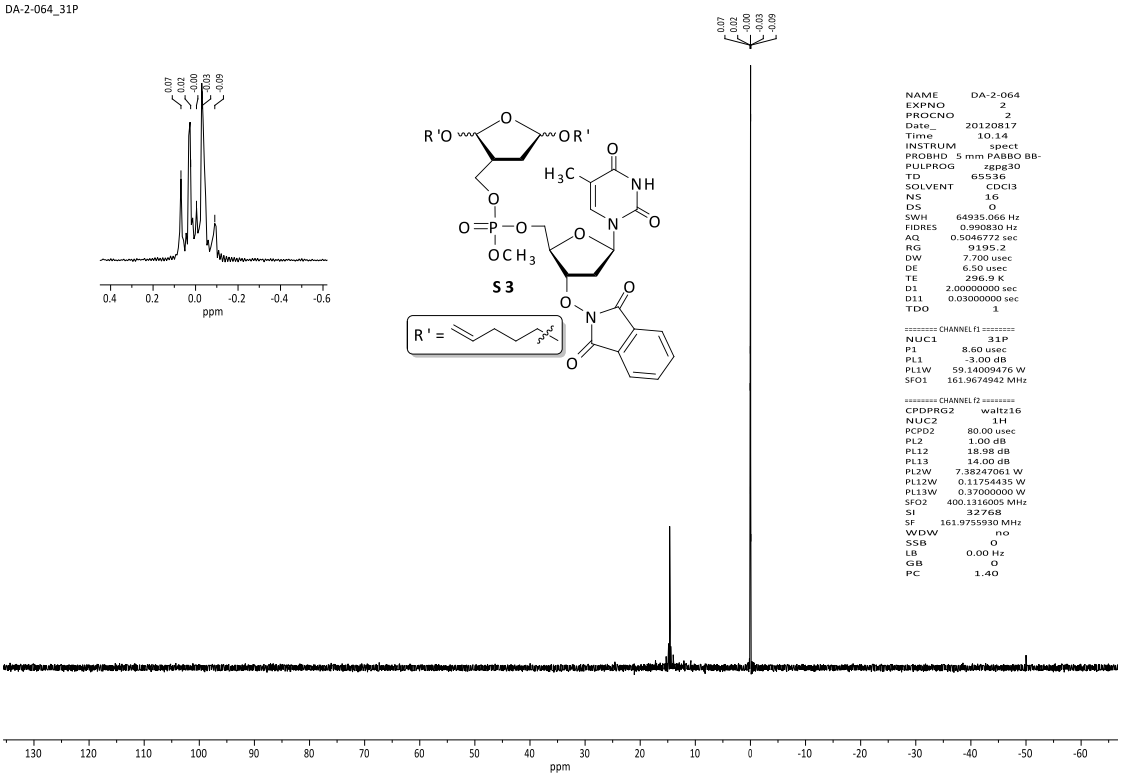
Supporting Information Figure 20. ^{1}H and ^{13}C NMR spectra of **S2** in acetonitrile-d_3.



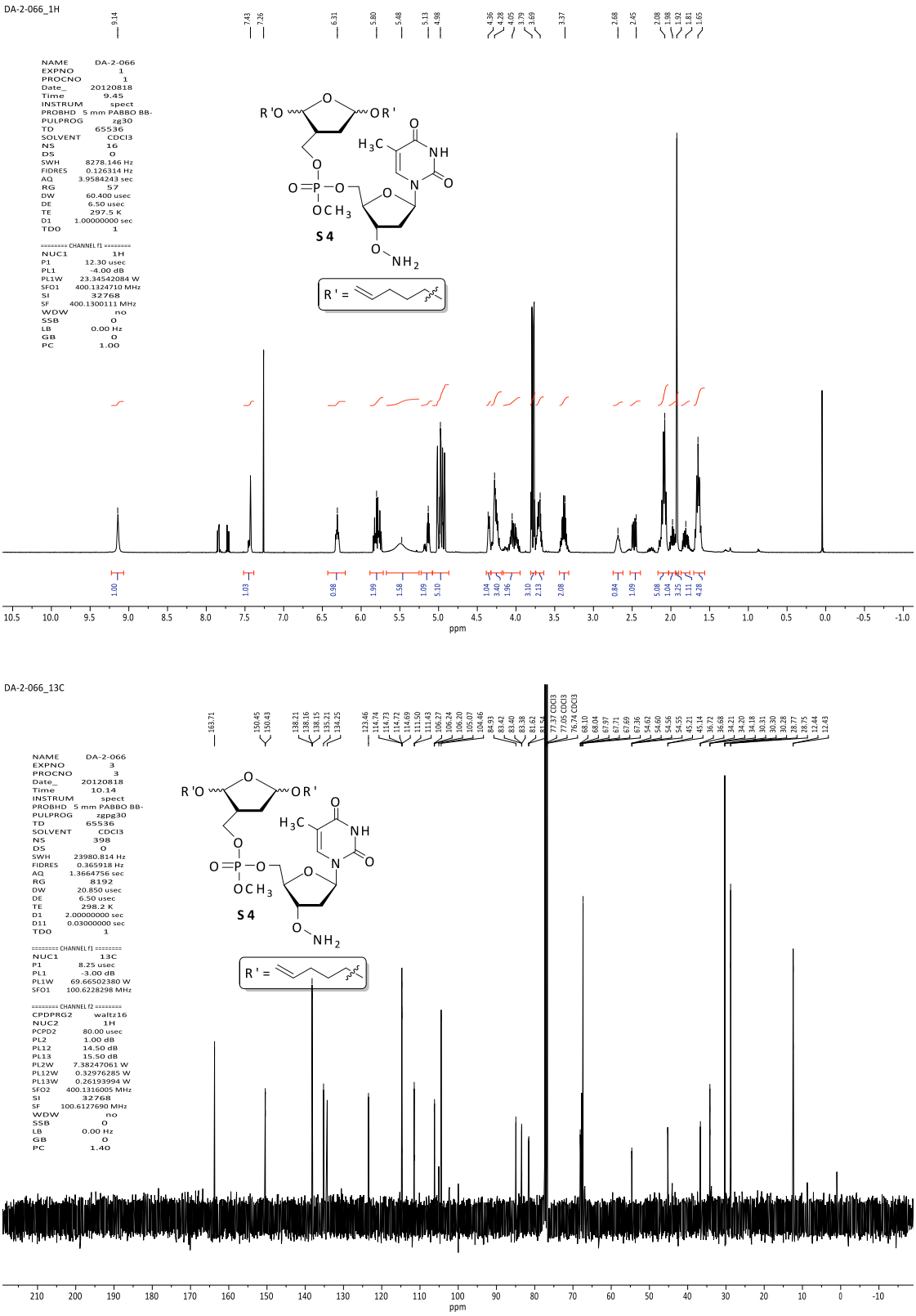
Supporting Information Figure 21. ^{31}P NMR spectrum of **S2** in acetonitrile-d_3.



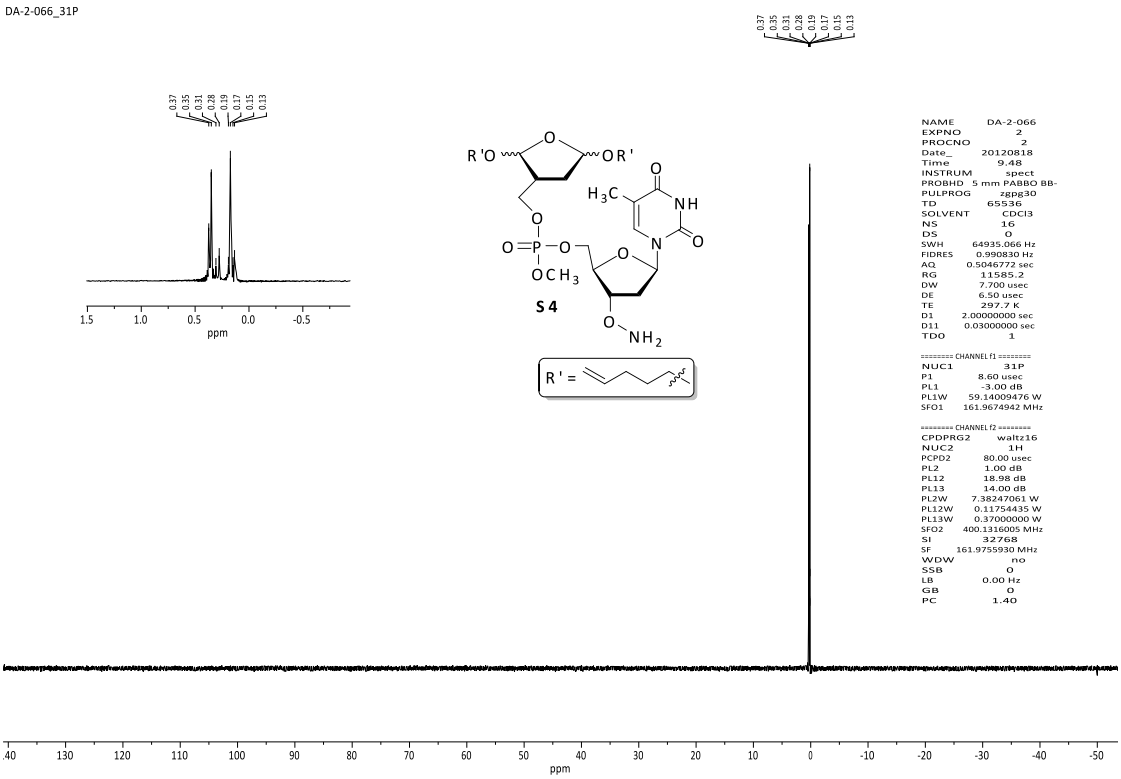
Supporting Information Figure 22. ^{1}H and ^{13}C NMR spectra of **S3** in $CDCl_3$.



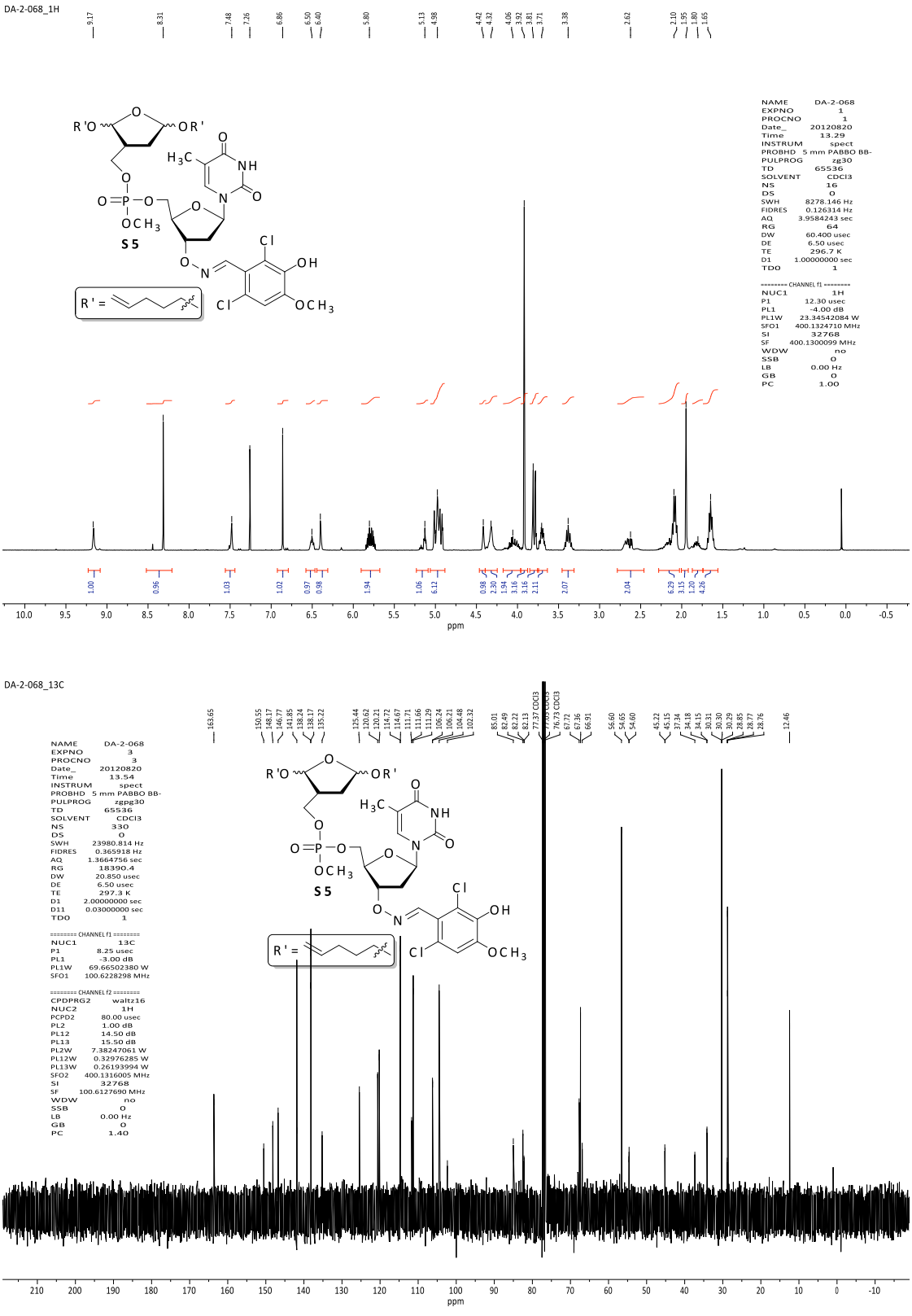
Supporting Information Figure 23. ^{31}P NMR spectrum of **S3** in $CDCl_3$.



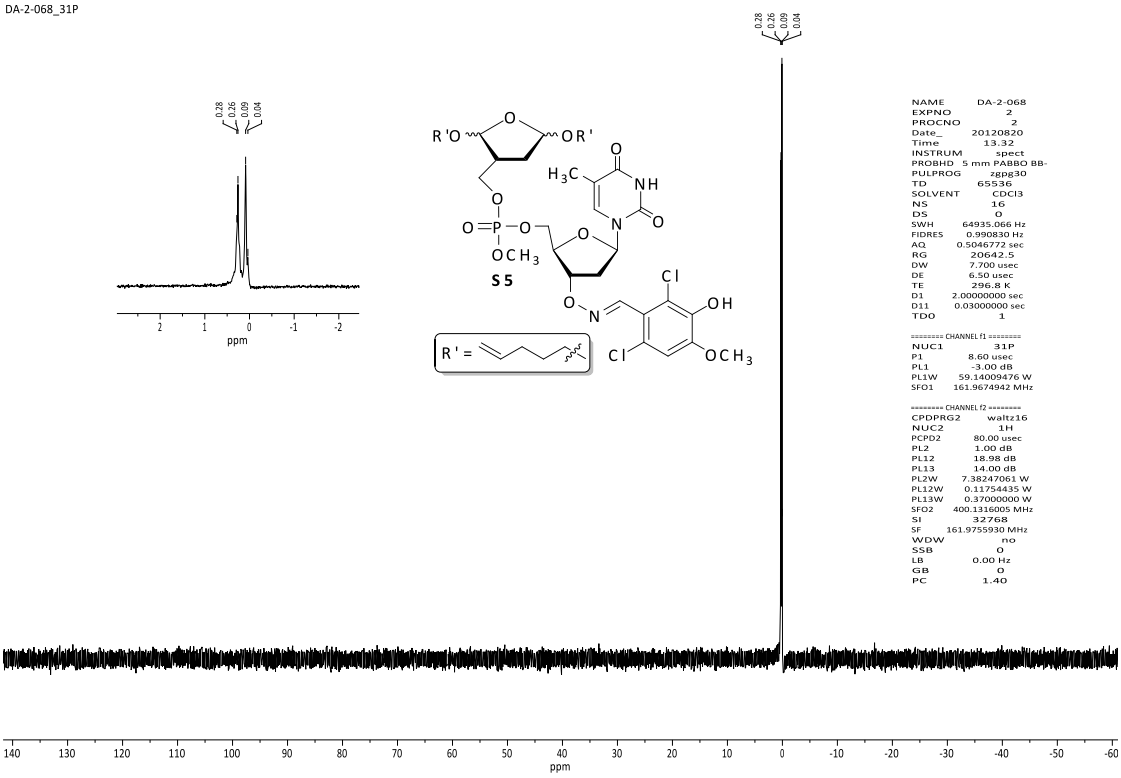
Supporting Information Figure 24. ^{1}H and ^{13}C NMR spectra of **S4** in $CDCl_3$.



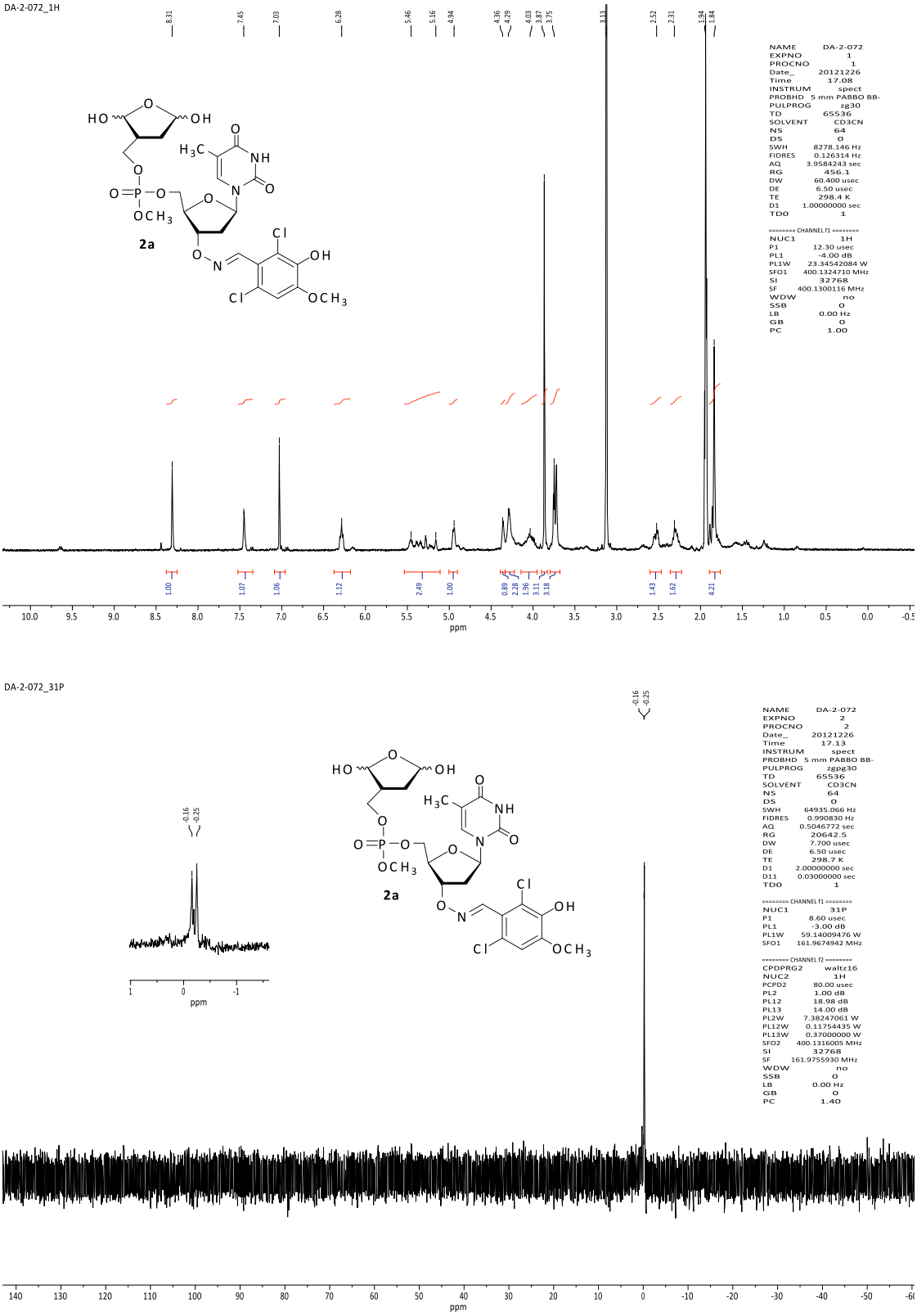
Supporting Information Figure 25. ^{31}P NMR spectrum of **S4** in $CDCl_3$.



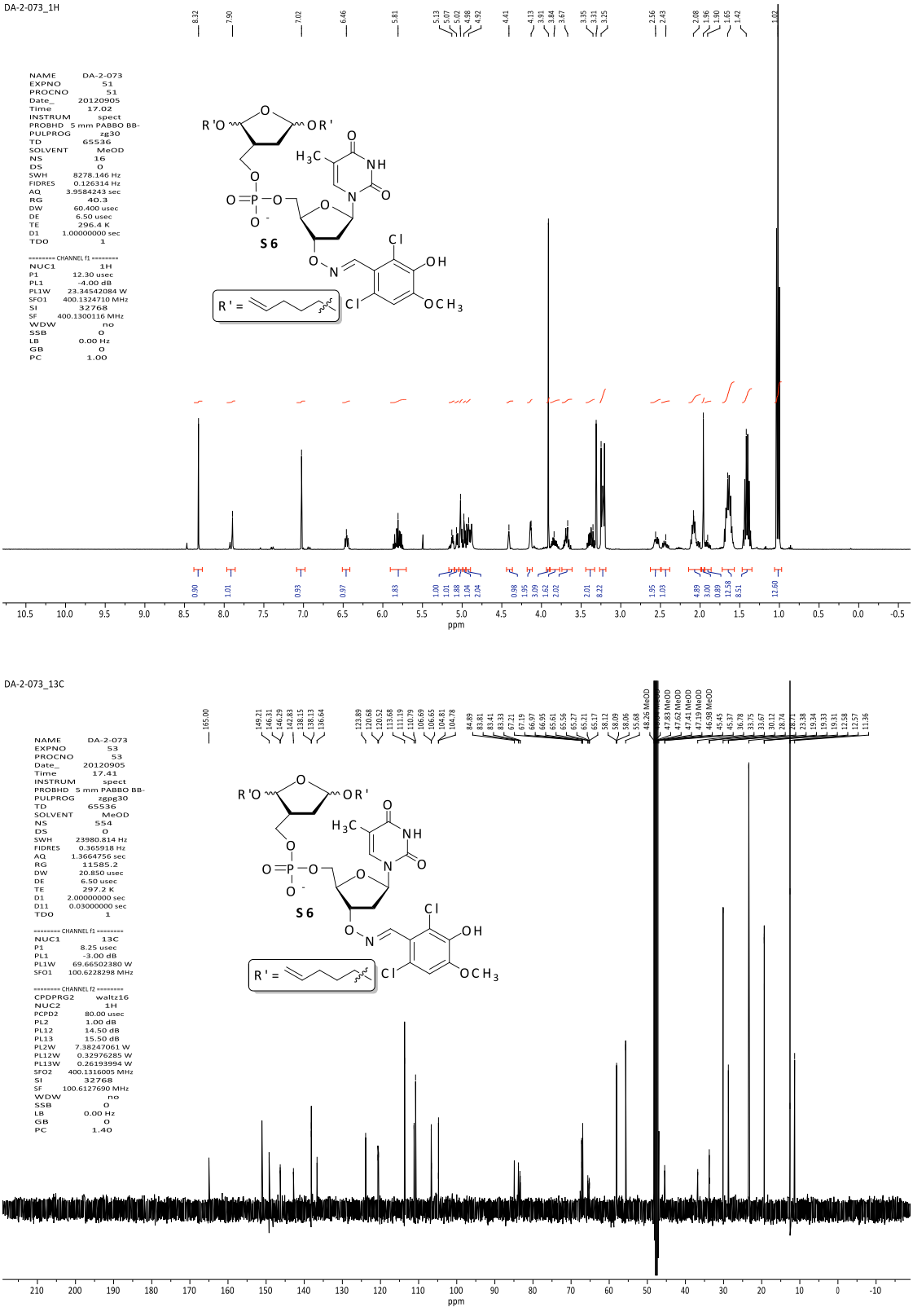
Supporting Information Figure 26. ^{1}H and ^{13}C NMR spectra of **S5** in $CDCl_3$.



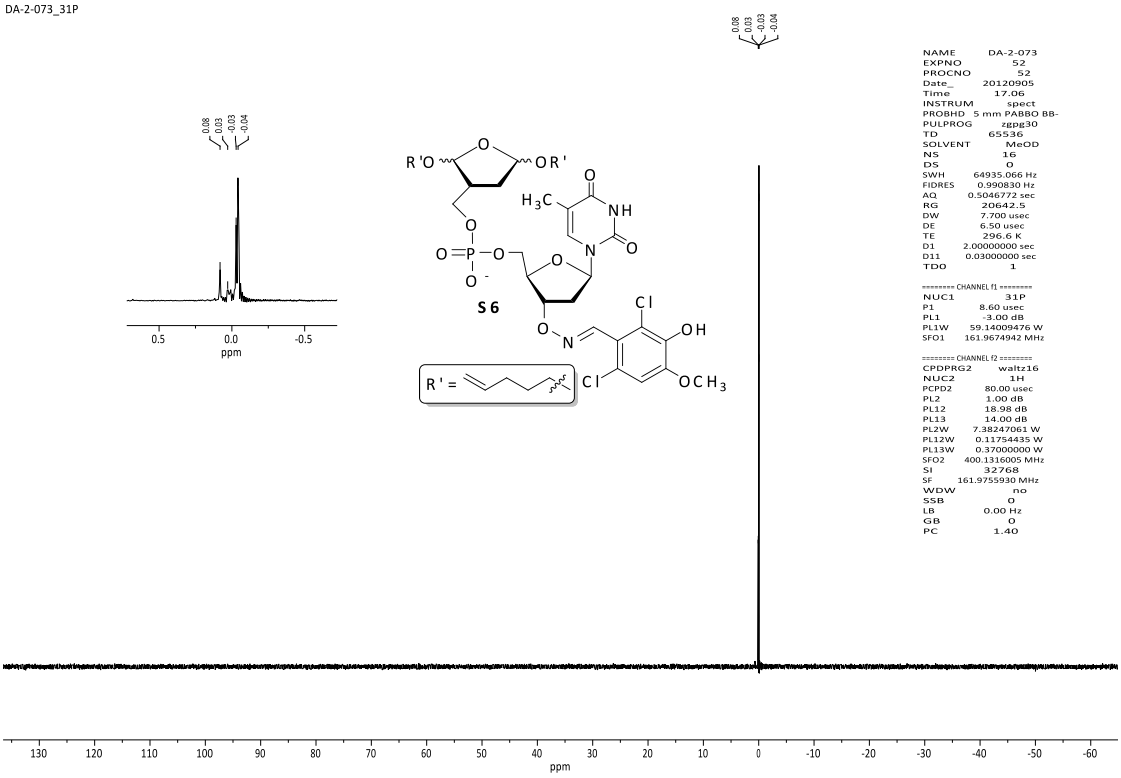
Supporting Information Figure 27. ^{31}P NMR spectrum of **S5** in $CDCl_3$.



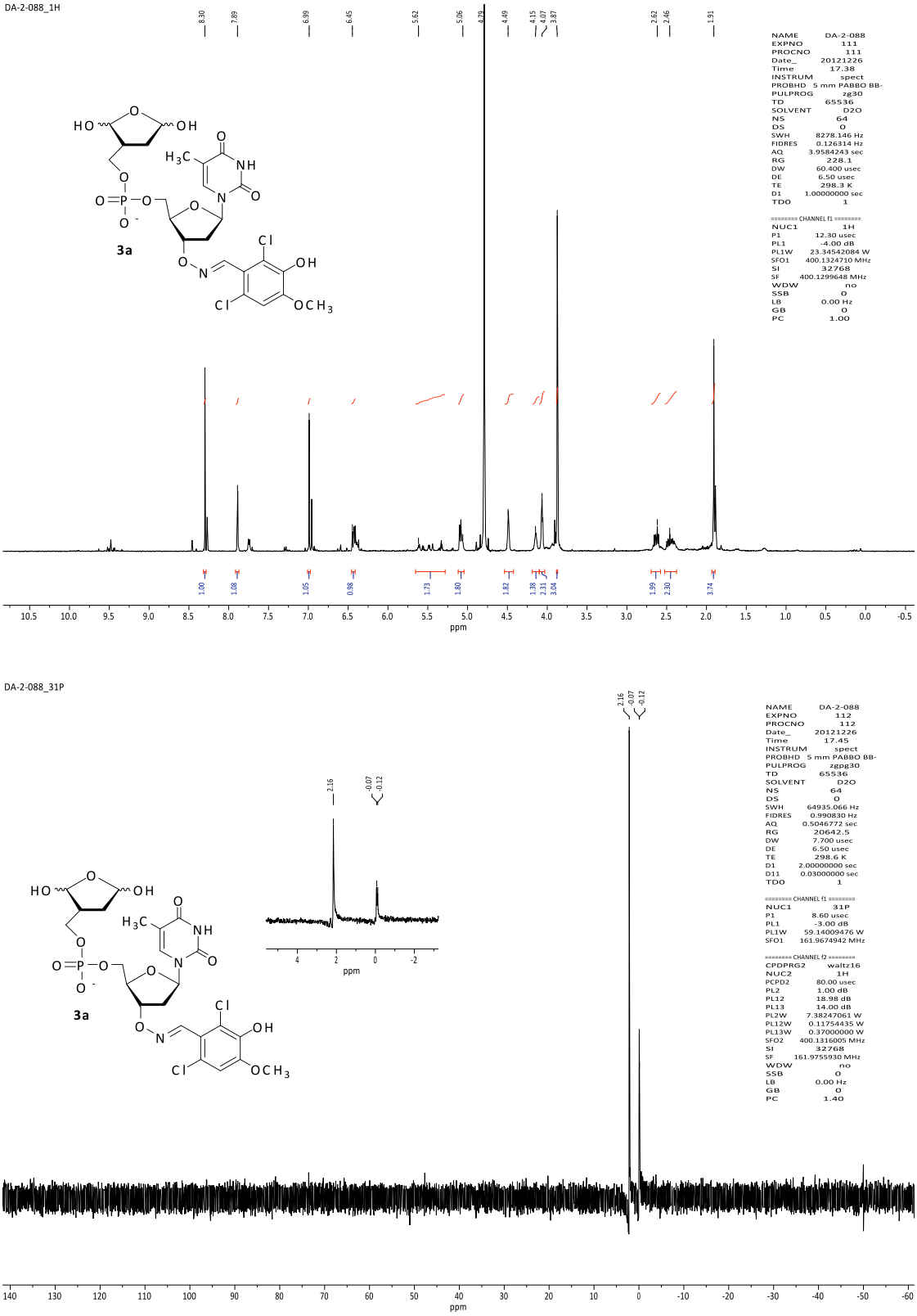
Supporting Information Figure 28. ^{1}H and ^{31}P NMR spectra of **2a** in acetonitrile-d_3.



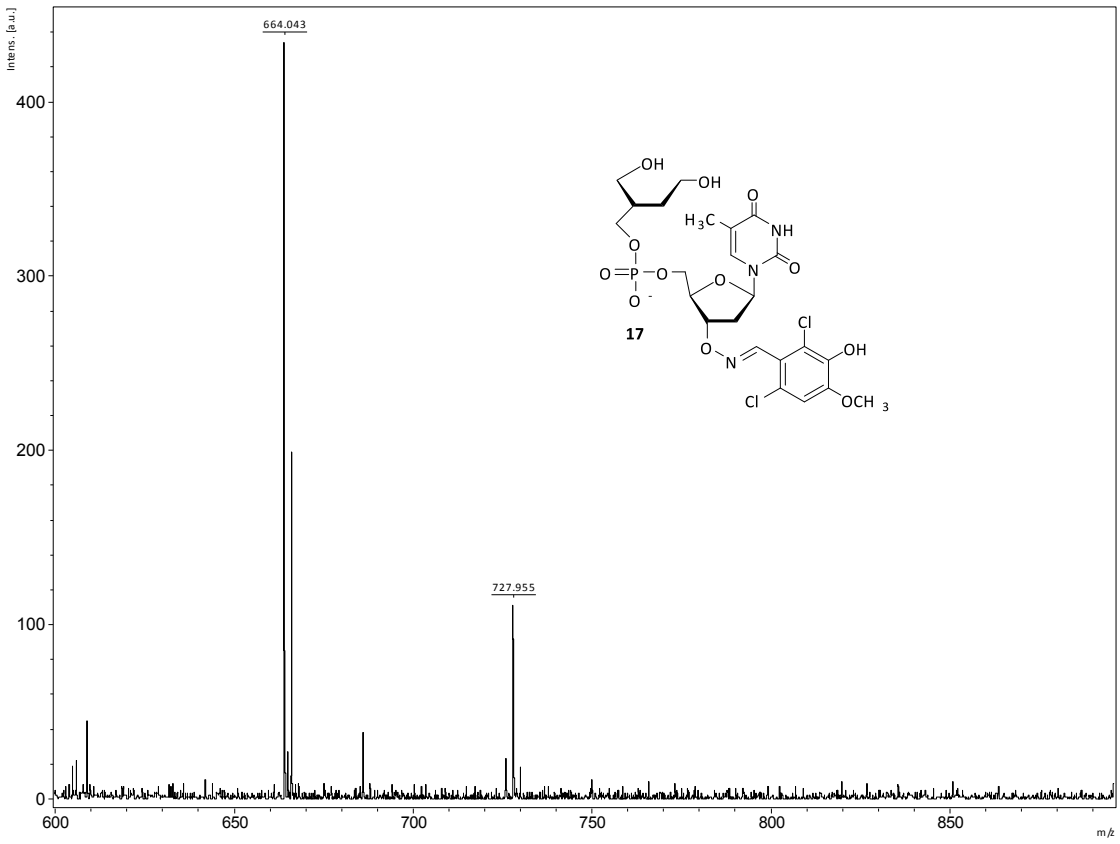
Supporting Information Figure 29. ^{1}H and ^{13}C NMR spectra of **S6** in methanol-d_4.



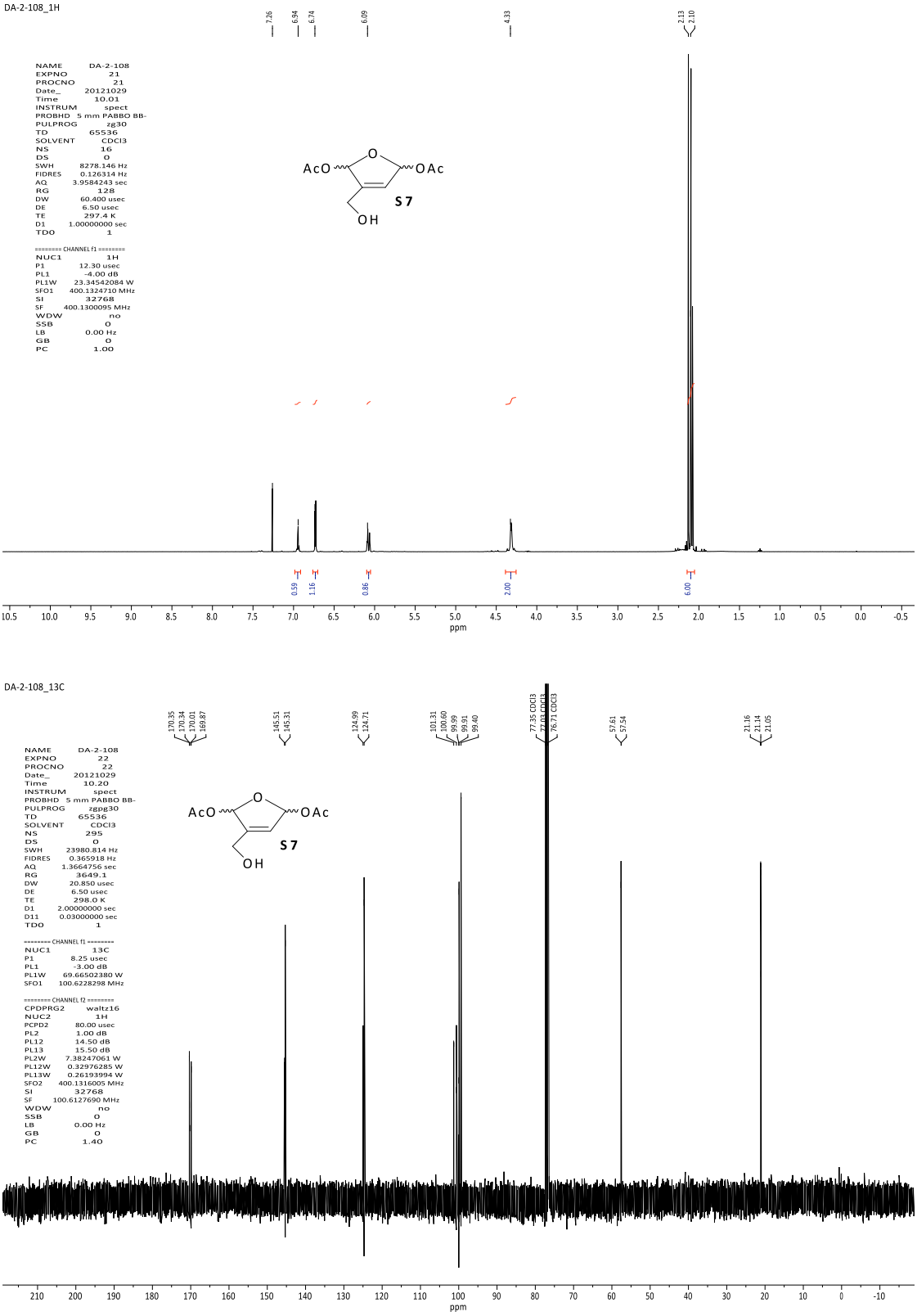
Supporting Information Figure 30. ^{31}P NMR spectrum of **S6** in methanol-d_4.



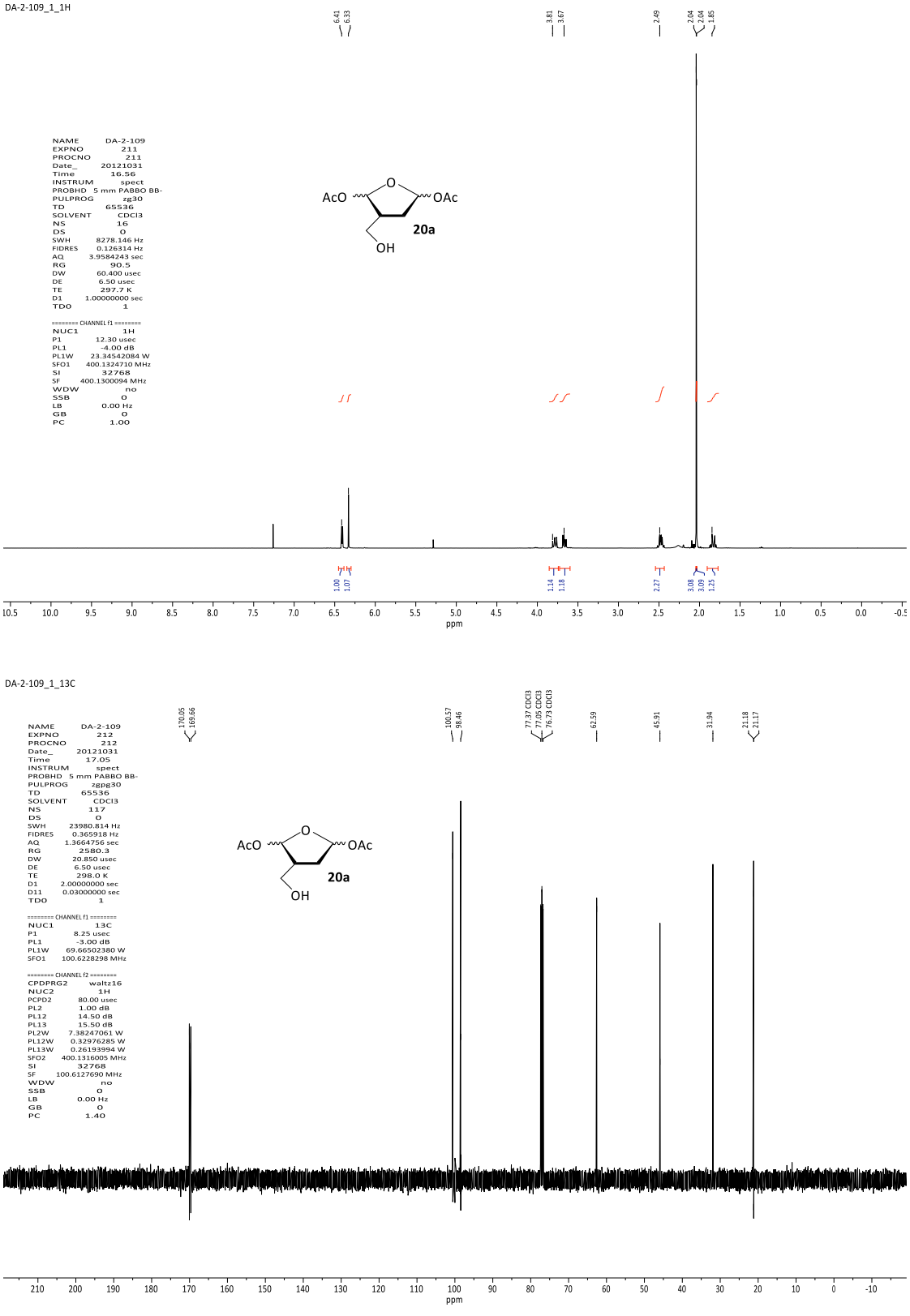
Supporting Information Figure 31. ^{1}H and ^{31}P NMR spectra of **3a** in D_2O.



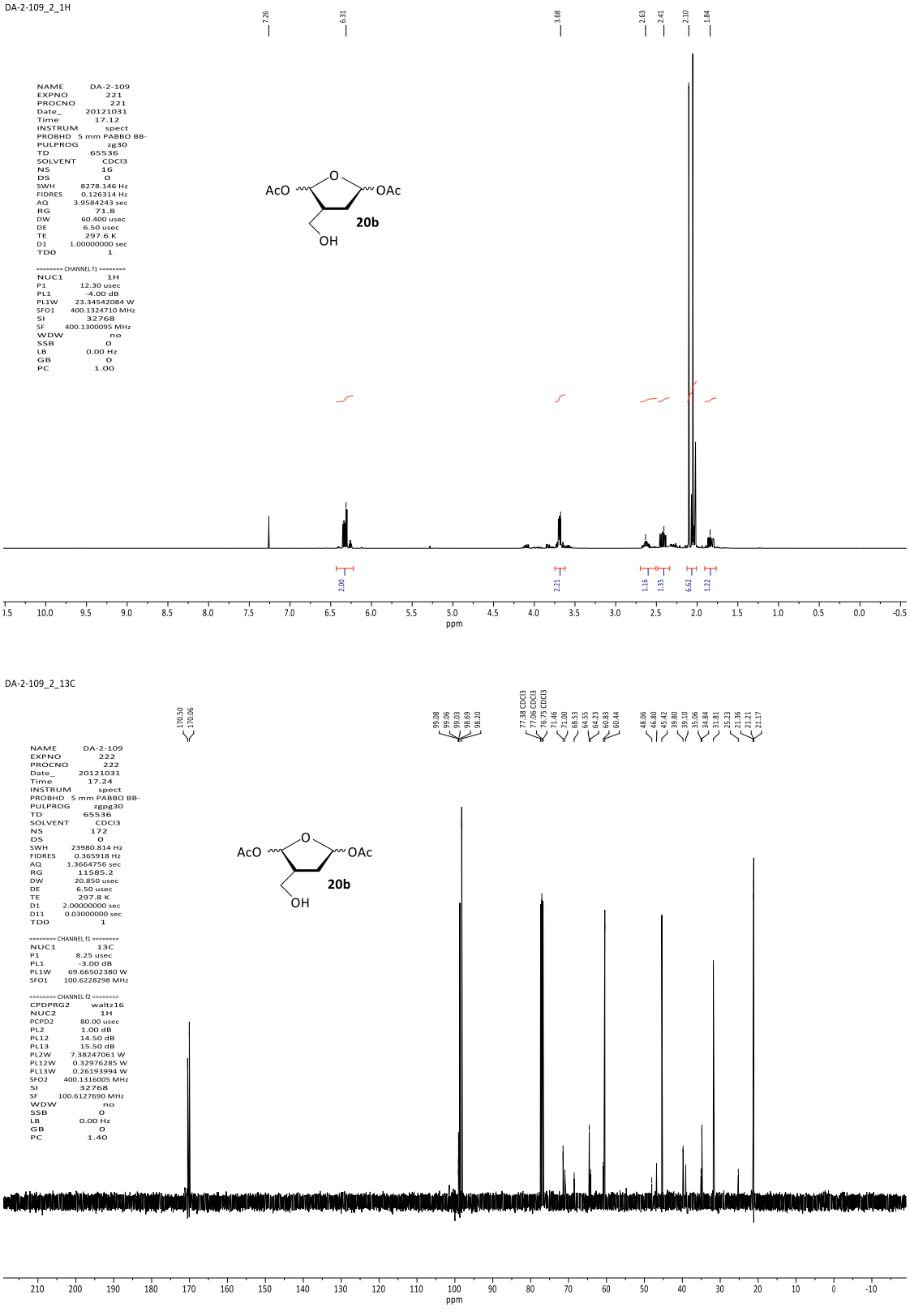
Supporting Information Figure 32. MALDI-TOF MS spectra of **17**.



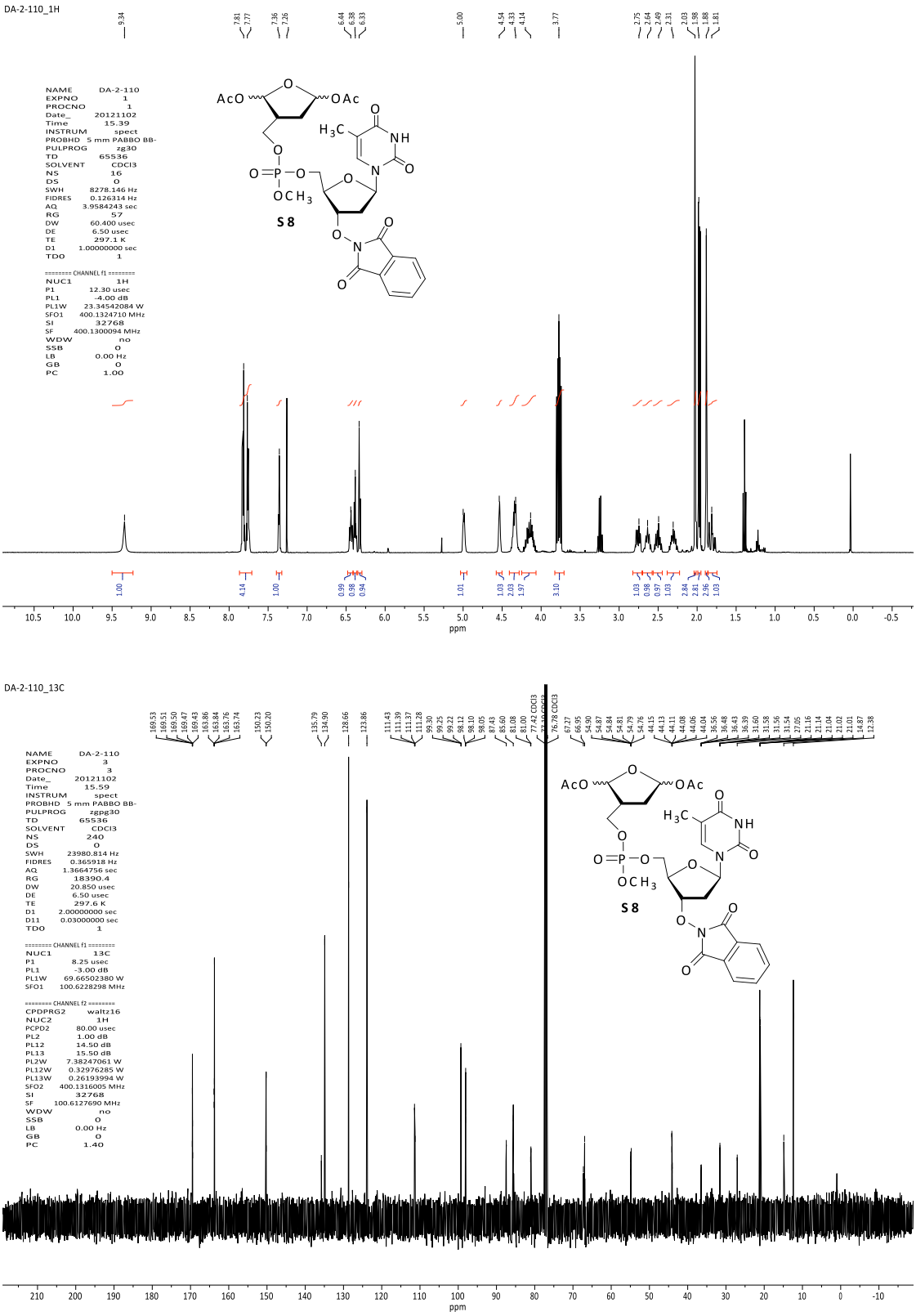
Supporting Information Figure 33. ^{1}H and ^{13}C NMR spectra of **S7** in $CDCl_3$.



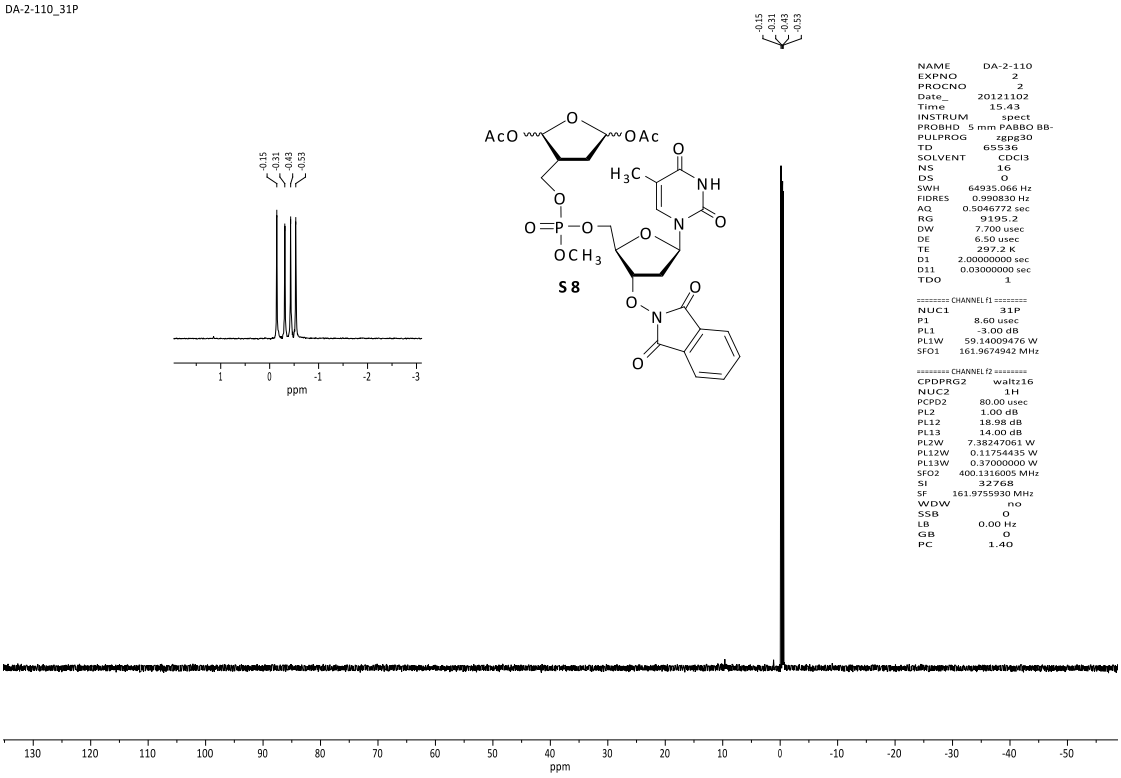
Supporting Information Figure 34. ^{1}H and ^{13}C NMR spectra of **20a** in $CDCl_3$.



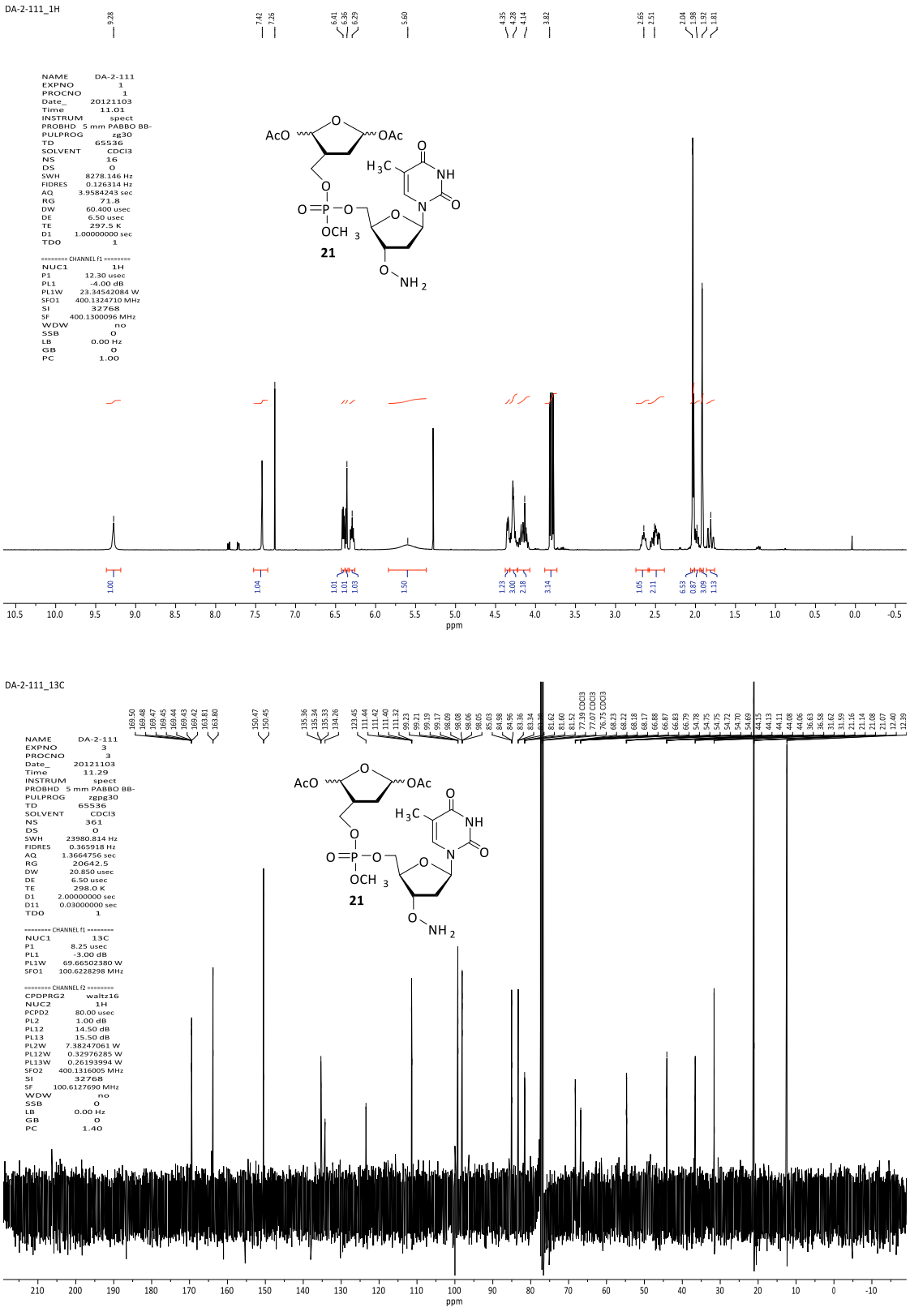
Supporting Information Figure 35. ^{1}H and ^{13}C NMR spectra of **20b** in $CDCl_3$.



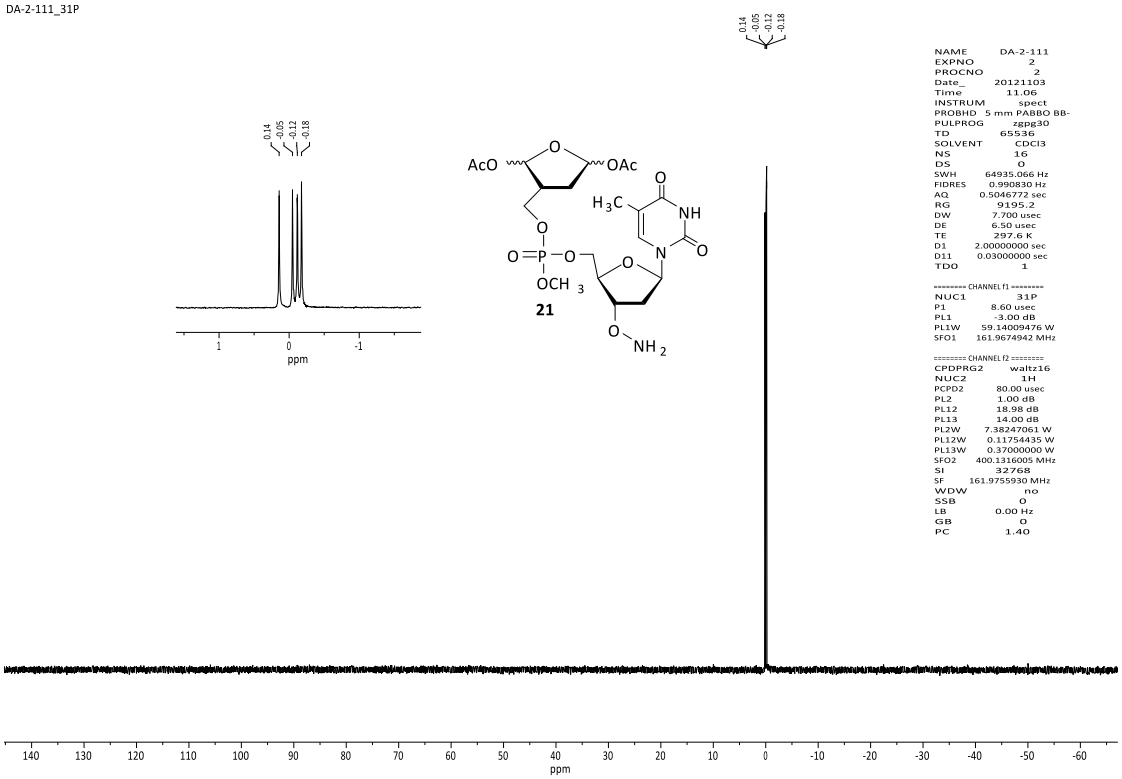
Supporting Information Figure 36. ^{1}H and ^{13}C NMR spectra of **S8** in $CDCl_3$.



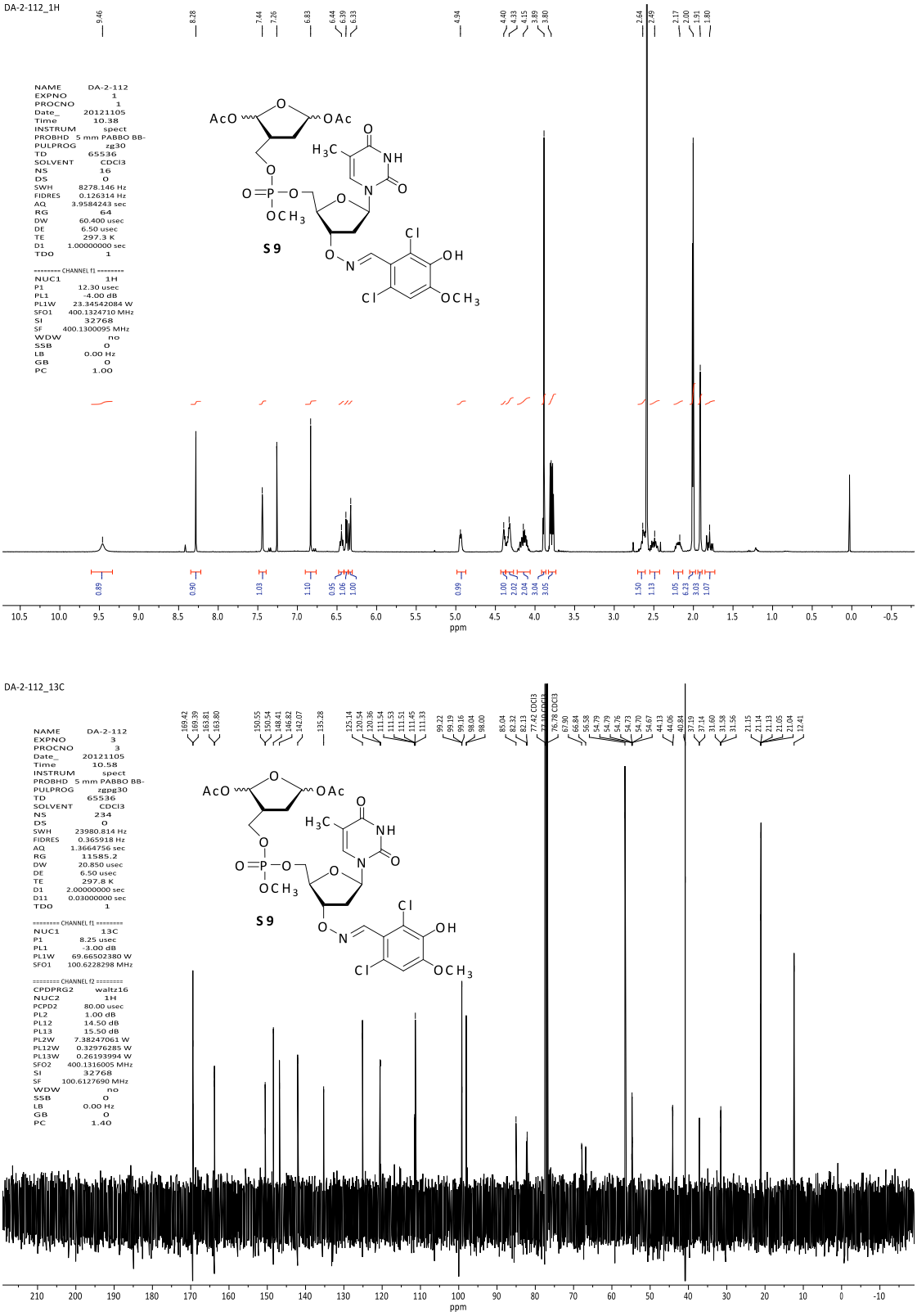
Supporting Information Figure 37. ^{31}P NMR spectrum of **S8** in $CDCl_3$.



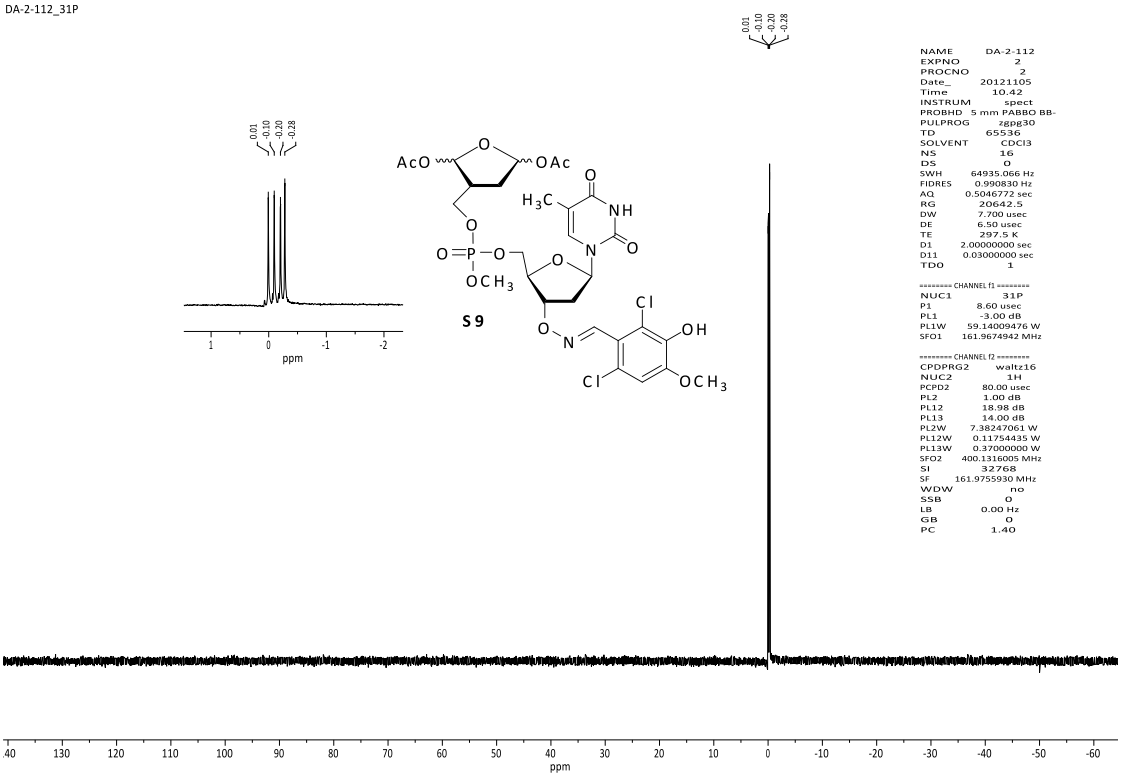
Supporting Information Figure 38. ^{1}H and ^{13}C NMR spectra of **21** in $CDCl_3$.



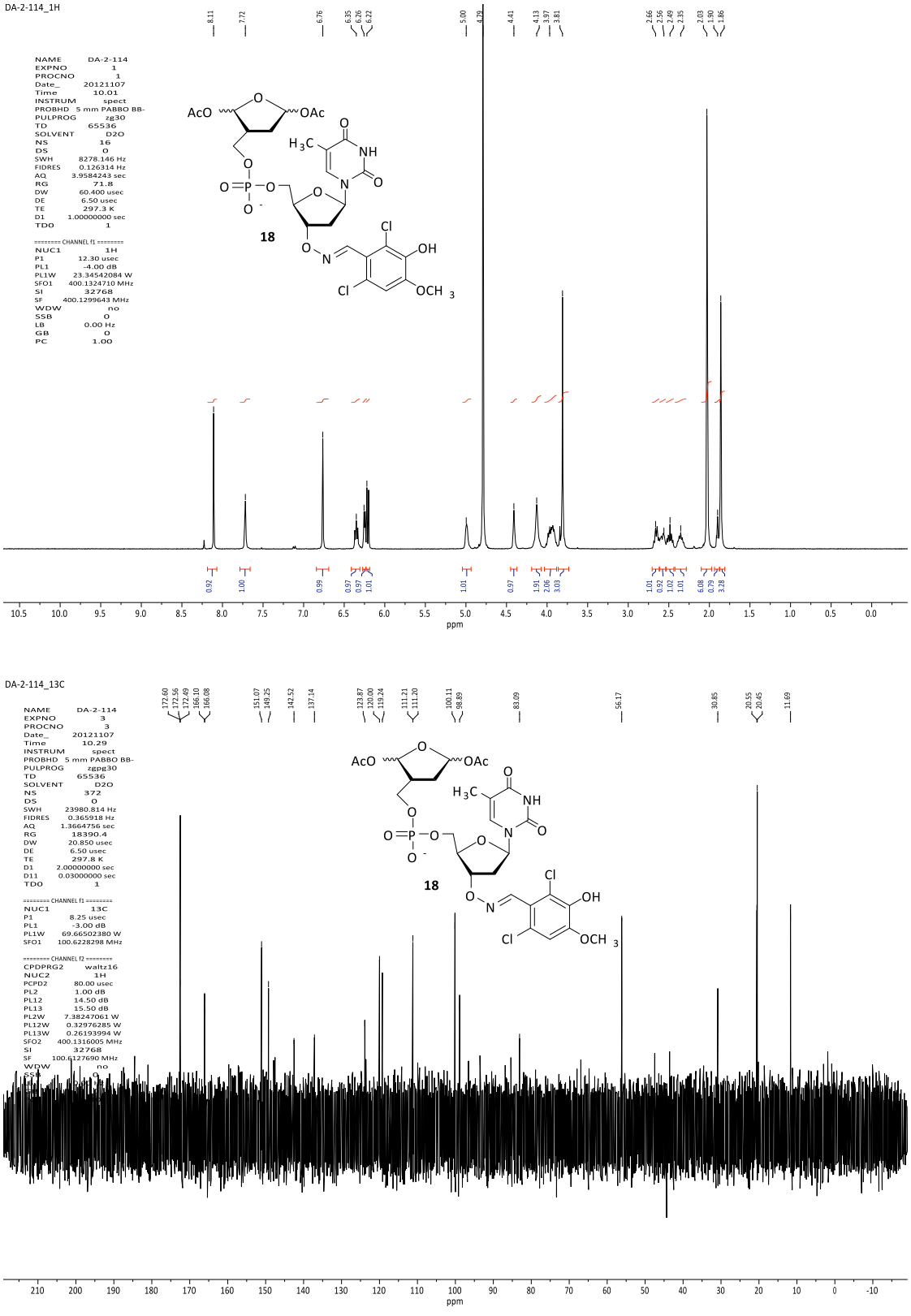
Supporting Information Figure 39. ^{31}P NMR spectrum of **21** in $CDCl_3$.



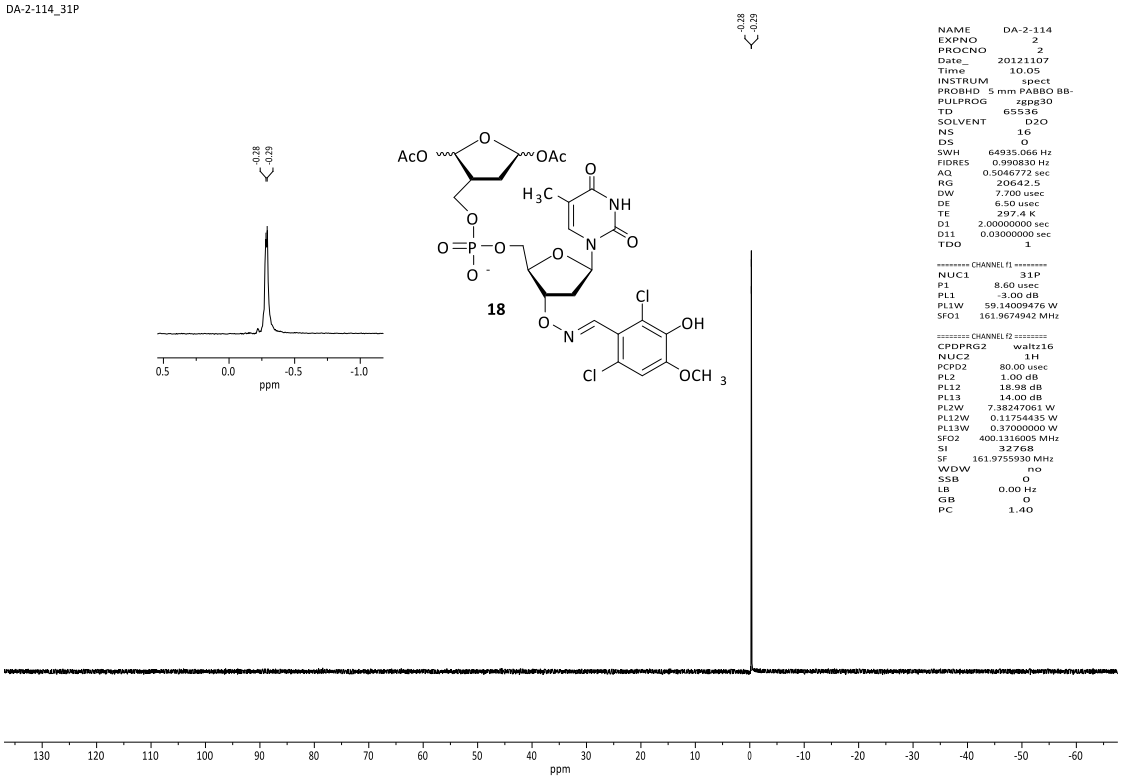
Supporting Information Figure 40. ^{1}H and ^{13}C NMR spectra of **S9** in $CDCl_3$.



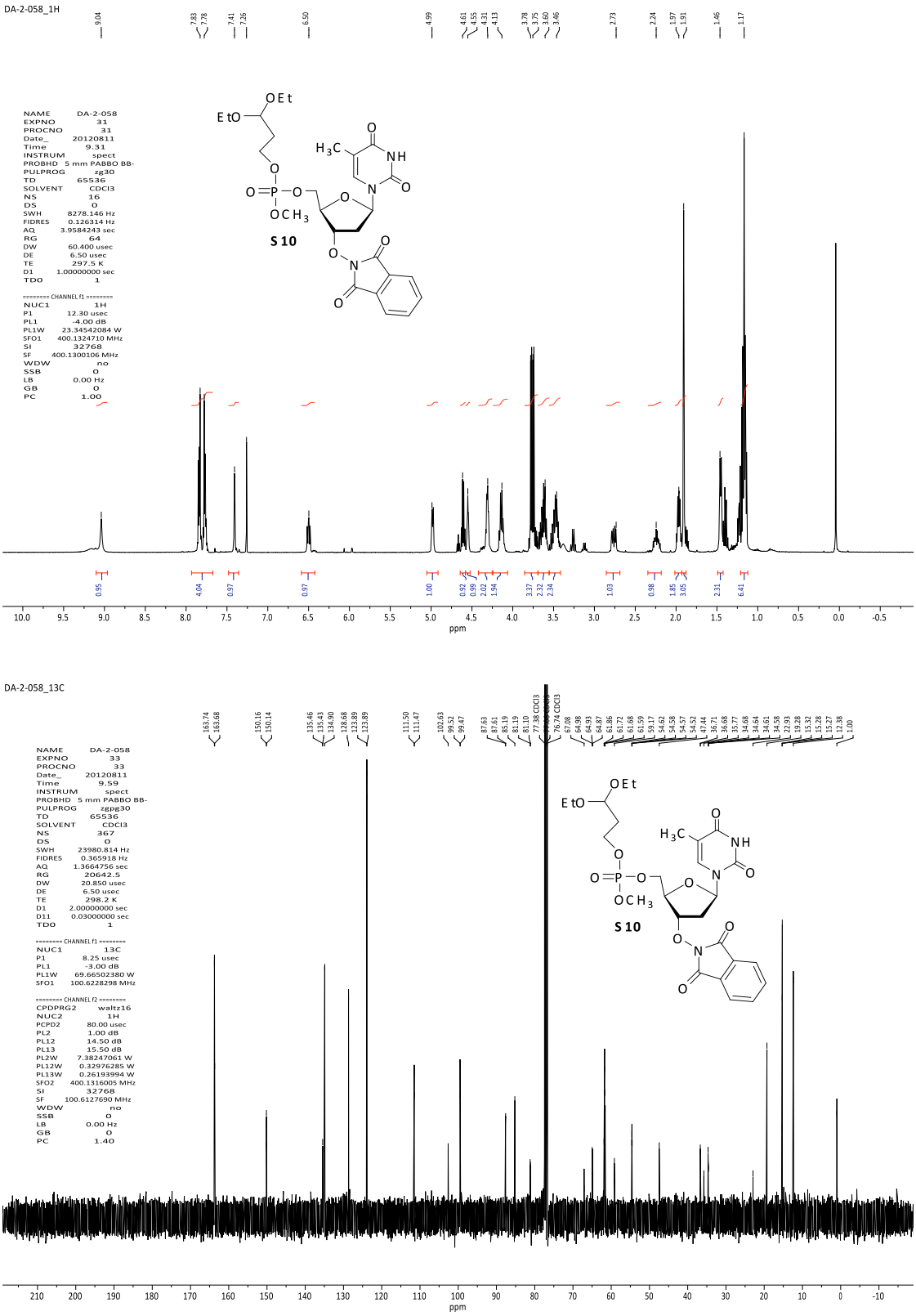
Supporting Information Figure 41. ^{31}P NMR spectrum of **S9** in $CDCl_3$.



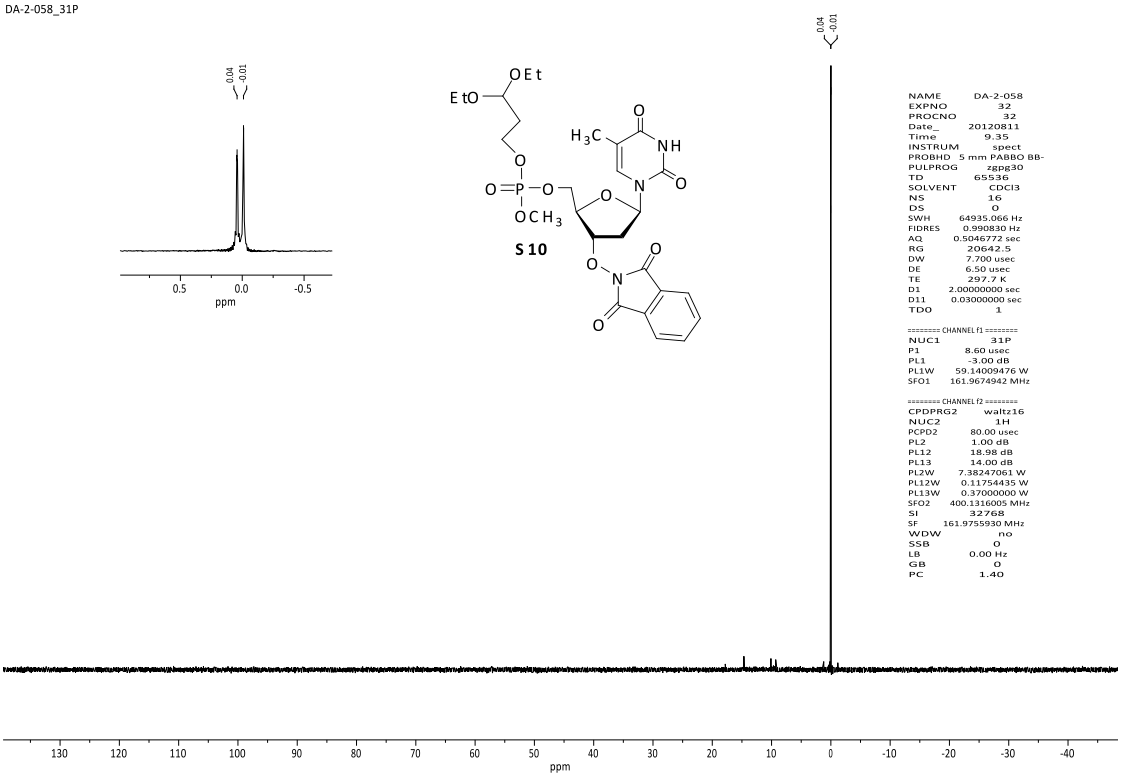
Supporting Information Figure 42. ^{1}H and ^{13}C NMR spectra of **18** in D_2O.



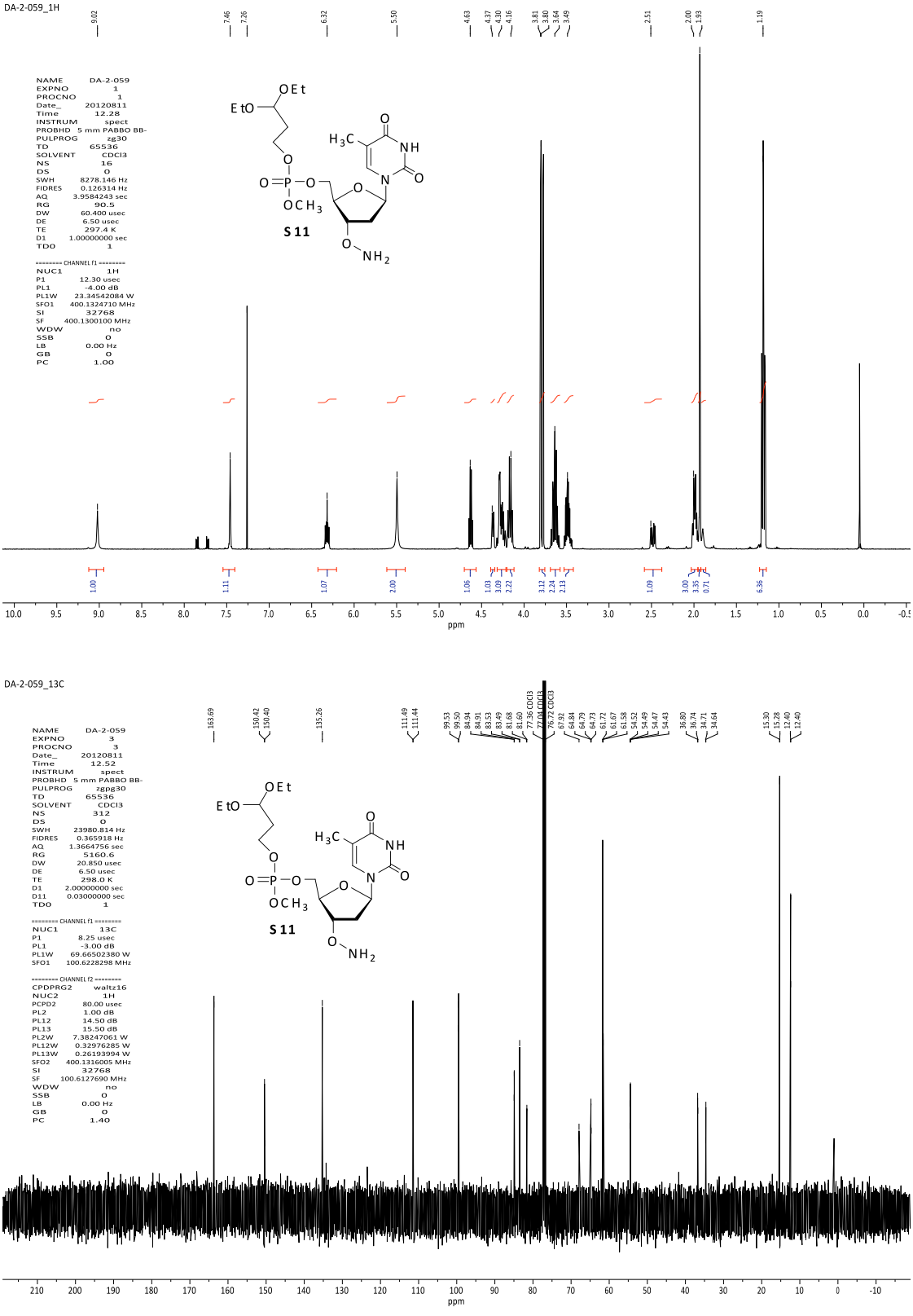
Supporting Information Figure 43. ^{31}P NMR spectrum of **18** in D_2O.



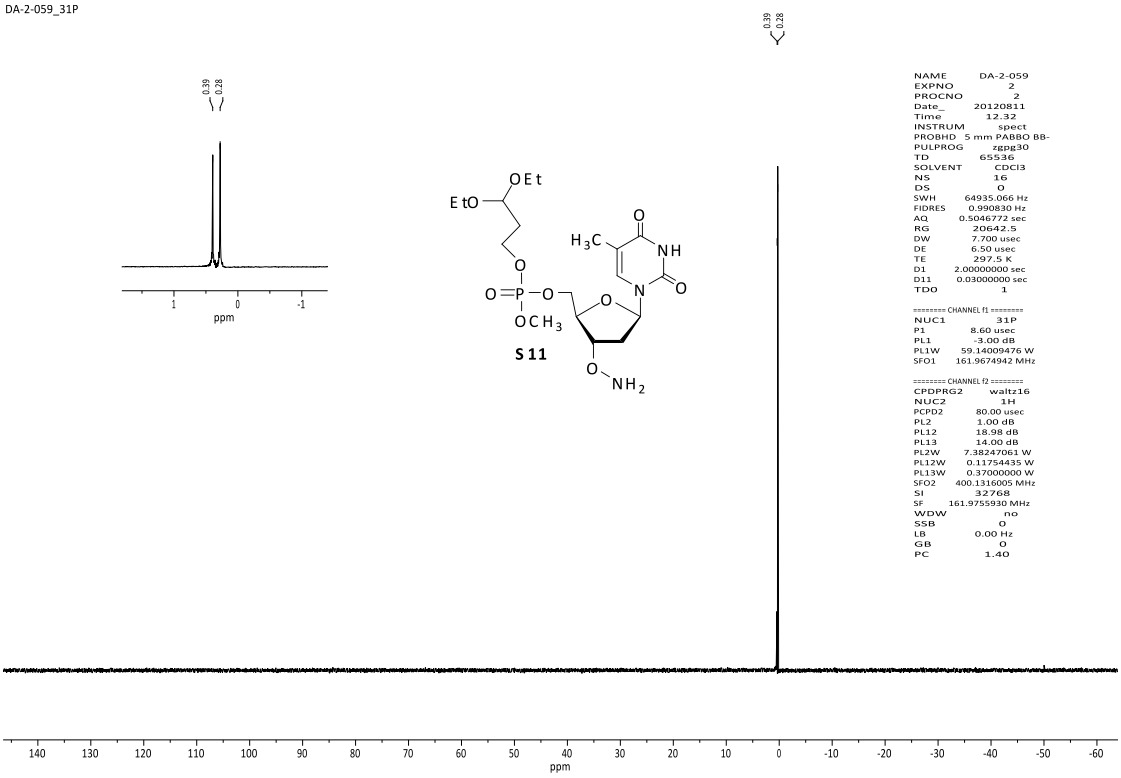
Supporting Information Figure 44. ^{1}H and ^{13}C NMR spectra of **S10** in $CDCl_3$.



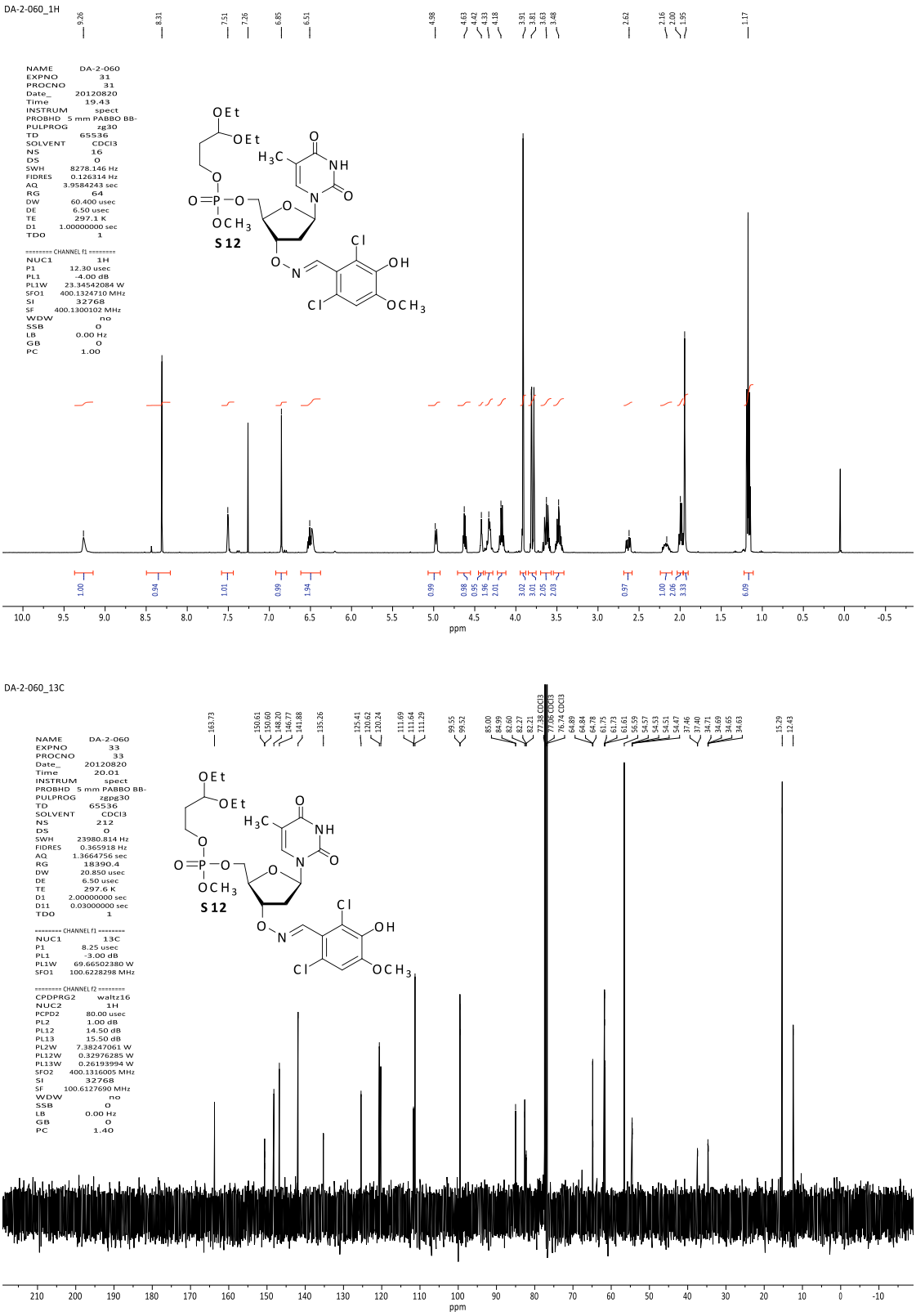
Supporting Information Figure 45. ^{31}P NMR spectrum of **S10** in $CDCl_3$.



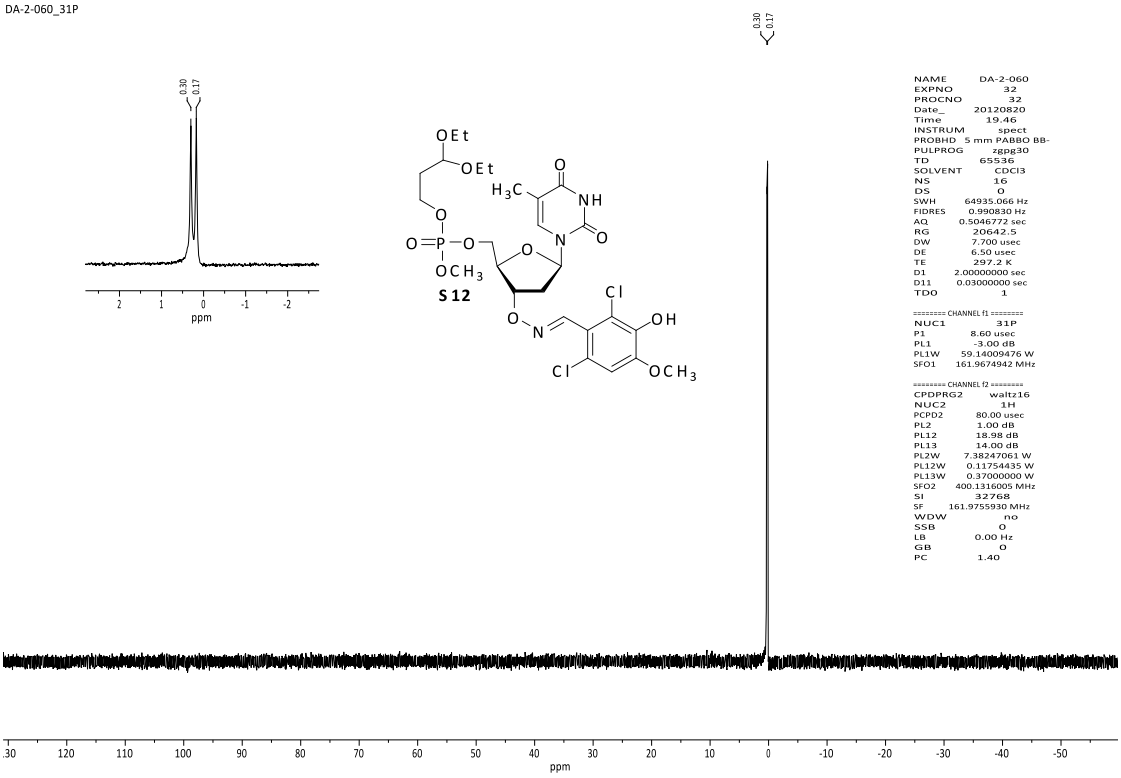
Supporting Information Figure 46. ^{1}H and ^{13}C NMR spectra of **S11** in $CDCl_3$.



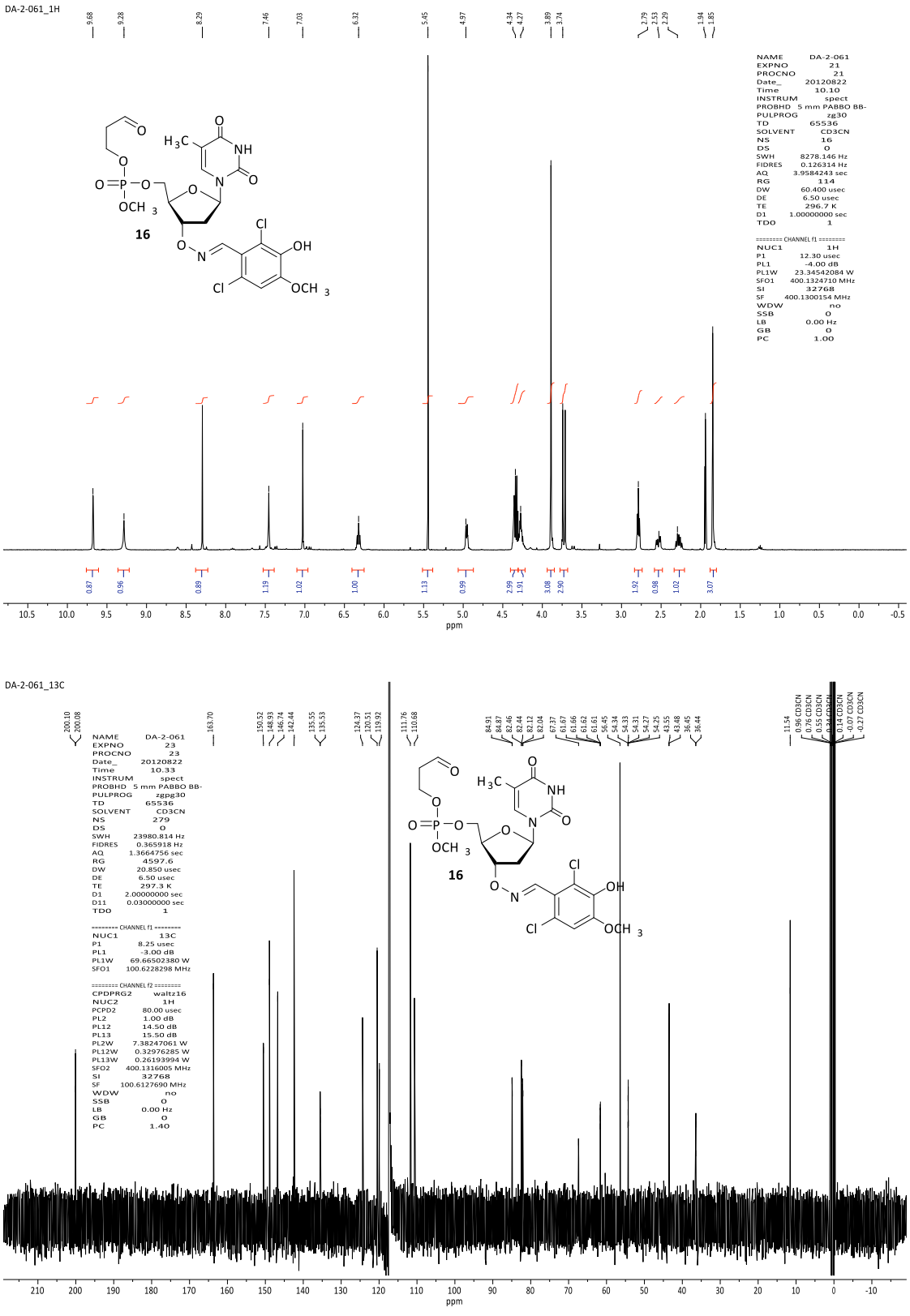
Supporting Information Figure 47. ^{31}P NMR spectrum of **S11** in $CDCl_3$.



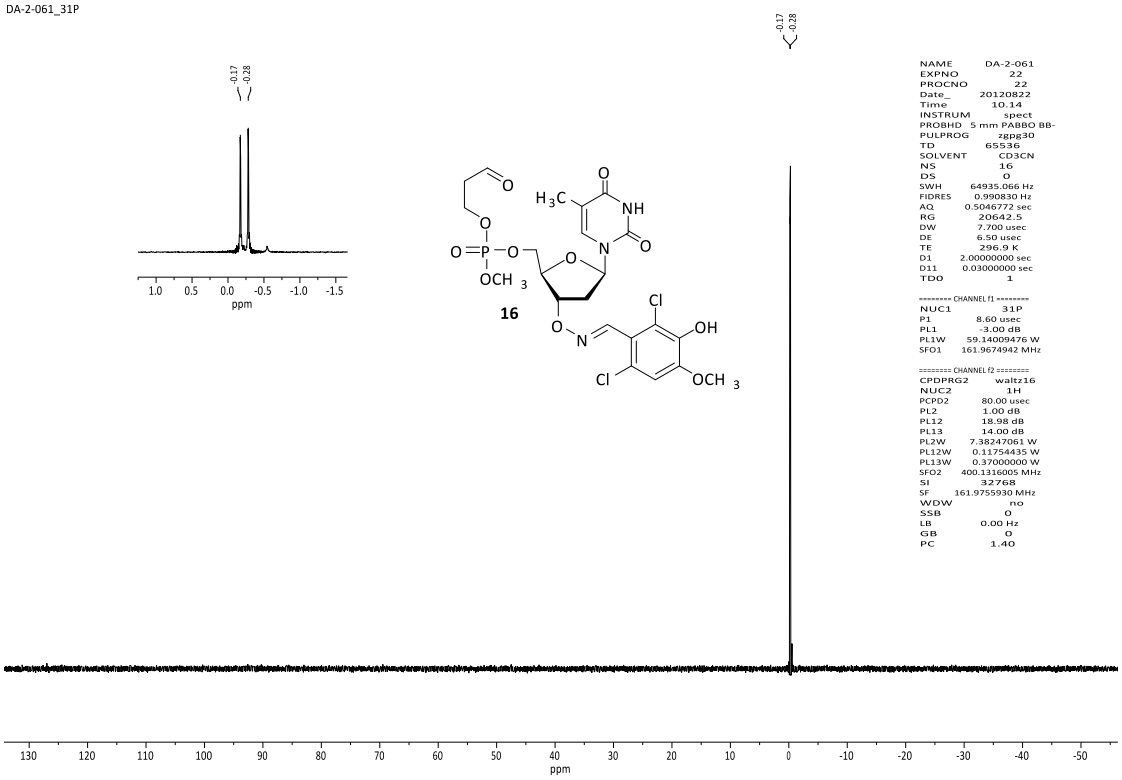
Supporting Information Figure 48. ^{1}H and ^{13}C NMR spectra of **S12** in $CDCl_3$.



Supporting Information Figure 49. ^{31}P NMR spectrum of **S12** in $CDCl_3$.



Supporting Information Figure 50. ^{1}H and ^{13}C NMR spectra of **16** in acetonitrile-d_3.



Supporting Information Figure 51. ^{31}P NMR spectrum of **16** in acetonitrile-d_3.