Supporting Information

Experimental

General procedures

The product distribution for the reaction of PCl_3 for the synthesis of phosphorodiamidites/ phosphoramidite was examined in situ by ^{31}P NMR and ^{1}H-^{31}P coupled NMR. The phosphorodiamidites/ phosphoramidite were prepared in either 1-butyl-2,3-dimethylimidazolium bis{(trifluoromethyl)sulfonyl}imide ($[C_4dmim][NTf_2]$, 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide ($[C_4mim][NTf_2]$ or 1-methylpyrrolidinium bis{(trifluoromethyl)sulfonyl}imide ($[C_4mpyrr][NTf_2]$. The ionic liquids were prepared in house using standard literature methods from the appropriate bromide salt.[1] 1-Hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate ($[C_6mim][FAP]$) was supplied by Merck KGaA. All ionic liquids were dried under high vacuum for 2 h prior to use. The water content for each ionic liquid was measured using Karl Fischer titration. In each case, the water content for the dried ionic liquid was <0.04 wt%.

PCl_3, 3-hydroxypropionitrile, Hünig's base, diisopropylamine, ethylmethylamine, morpholine and pyrrolidine were obtained from Aldrich and used as supplied. DCM was distilled over calcium hydride prior to use. The activators, pyridinium trifluoroacetate (Py.TFA) and *N*-methylimidazolium triflate (NMI.Tf) were prepared according to procedures reported in the literature and were dried under high vacuum prior to use. Each nucleoside was azeotroped with acetonitrile three times and then dried under high vacuum prior to use.

Spectroscopic details

All the ^{31}P, ^{1}H-^{31}P, ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 or 400 MHz NMR spectrometer at 25 °C. For ionic liquid samples an aliquot was transferred directly into the NMR tube with no addition of deuterated solvents. The ^{31}P NMR chemical were recorded in parts per million (ppm) relative to an external probe using a sealed capillary containing triethylphosphate ($PO(OEt)_3$) in DMSO (solvent used for locking/shimming optimization) inside the NMR tube. The $PO(OEt)_3$ probe was referenced to 0.2 ppm. For the nucleotides the NMR was recorded in $CDCl_3$ referenced to 0.00 ppm using TMS for the ^{1}H NMR and 77.0 ppm using $CDCl_3$ for the ^{13}C NMR.

General experimental conditions

Phosphorodiamidtes

To a stirred solution of PCl_3 in dried $[NTf_2]^-$-based ionic liquid (2 eq) under an inert atmosphere of N_2, Hünig's Base (1 eq) was added. After vigorous stirring for 5 min, cyanoethanol (1 eq) was added and the reaction stirred for a further 30 min. The nucleophilic amine (4 eq) was then added and the reaction stirred for a further 120 min after which the reaction was complete. Isolation was achieved via extraction with anhydrous diethyl ether. $[C_6mim][FAP]$ was added to the extraction mixture after separation but prior to concentration to stabilize of the phosphorodiamidites.

Bis-(morpholino)-2-cyanoethoxyphosphite (1), synthesised in $[C_4mpyrr][NTf_2]$

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (t, 2H, *J*= 6.2 Hz, OCH_2CH_2CN), 3.01 (m, 4H, 2 NCH_2CH_2O), 3.57-3.65 (m, 4H, 2 NCH_2CH_2O), 3.88 (dt, 2H, *J*= 7.4, 6.2 Hz, OCH_2CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 20.7 (d, *J*= 7.5 Hz), 45.5 (d, *J*= 14.9 Hz), 60.0 (d, *J*=20.7 Hz), 68.3 (d, *J*=6.3 Hz), 117.62. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 130.6. **HRMS** (ES, M + H^+) calculated for $C_{11}H_{20}N_3O_3P$ 274.1321, found 274.1310.

2-Cyanoethyl-*N,N,N',N'*-ethylmethylphosphoramidite (2), synthesised in $[C_4mim][NTf_2]$

^{1}H NMR (300 MHz, $CDCl_3$) 1.06 (t, 6H, *J*=7.1 Hz, 2 NCH_2CH_3), 2.56 (d, 6H, *J*= 7.1 Hz, 2 NCH_3), 2.64 (t, 2H, *J*= 6.5 Hz, OCH_2CH_2CN), 3.12-2.86 (m, 4H, 2 NCH_2CH_3), 3.78 (dt, 2H, *J*=7.6, 6.4 Hz, OCH_2CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 14.7 (d, *J*= 4.4 Hz), 20.6 (d, *J*=7.5 Hz), 32.5 (d, *J*=8.8 Hz), 44.4 (d, *J*=28.3 Hz), 59.3 (d, *J*= 19.6 Hz), 118.2. **^{31}P NMR** (121 MHz, $CDCl_3$) 135.0. **HRMS** (ES, M + H^+) calculated for $C_{11}H_{20}N_3O_3P$ 218.1422, found 218.1428.

Bis-(pyrrolidino)-2-cyanoethoxyphosphite (3), synthesised in $[C_4mim][NTf_2]$

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75-1.79 (m, 8H, 2 NCH_2CH_2), 2.62 (t, 2H, *J*=6.2 Hz, OCH_2CH_2CN), 3.07-3.13 (m, 8H, 2 NCH_2CH_2), 3.81-3.88 (m, 2H, OCH_2CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 20.9 (d, *J*=6.6 Hz), 26.4 (d, *J*=4.8 Hz), 47.0 (d, *J*=15.8 Hz), 59.3 (d, *J*=19.6 Hz), 118.2. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 133.6. **HRMS** (ES, M + H^+) calculated for $C_{11}H_{20}N_3OP$ 242.1422, found 242.1412.

Bis-(2-cyanoethyl)-*N*, *N*-diisopropylphosphoramidite (4)

To a stirred solution of PCl_3 in dried $[C_4dmim][NTf_2]$ (2 eq) under an inert atmosphere of N_2, Hünig's base (2 eq) was added. After vigorous stirring for 5 min, cyanoethanol (2 eq) was added and the reaction stirred for a further 30 min. The nucleophilic amine (2 eq) was then added and the reaction stirred for a further 40 min after which the reaction was complete. Isolation was achieved via extraction with

anhydrous diethyl ether. [C_6mim][FAP] was added to the extraction mixture after separation but prior to concentration to stabilize of the phosphoramidite.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 12H, *J*=6.8 Hz, NCH(CH_3)$_2$), 2.66 (t, 4H, *J*= 6.2 Hz, 2 OCH_2CH_2CN), 3.56-3.69 (m, 2H, $NCH(CH_3)_2$), 3.77-3.96 (m, 4H, 2 OCH_2CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) 20.4 (d, *J*= 6.8), 24.6 (d, *J*=7.2), 43.3 (d, *J*=12.4), 58.5 (d, *J*=18.8), 117.6. **^{31}P NMR** (121 MHz, $CDCl_3$) 149.1. **HRMS** (ES, M+H) calculated for $C_{12}H_{22}N_3O_2P$ 272.1528, found 272.1530

The ^{31}P NMR spectra for the phosphorodiamidites, **1-4,** stabilized in [C_6mim][FAP] and ^{1}H, ^{13}C and ^{31}P NMR spectra for **4** in its pure form are shown in Figures **S1-S4**. In each case, the mole ratio of phosphorodiamidite to ionic liquid was typically 1:1. Each of the spectra shows the phosphorodiamidites/phosphoramidite at between 123-148 ppm, the $[FAP]^-$ anion at -150ppm and the internal standard ($PO(OEt)_3$) at 0.2ppm.

Figure S1 ^{31}P NMR of phosphorodiamidite, **1**, stabilized in [C_6mim][FAP]

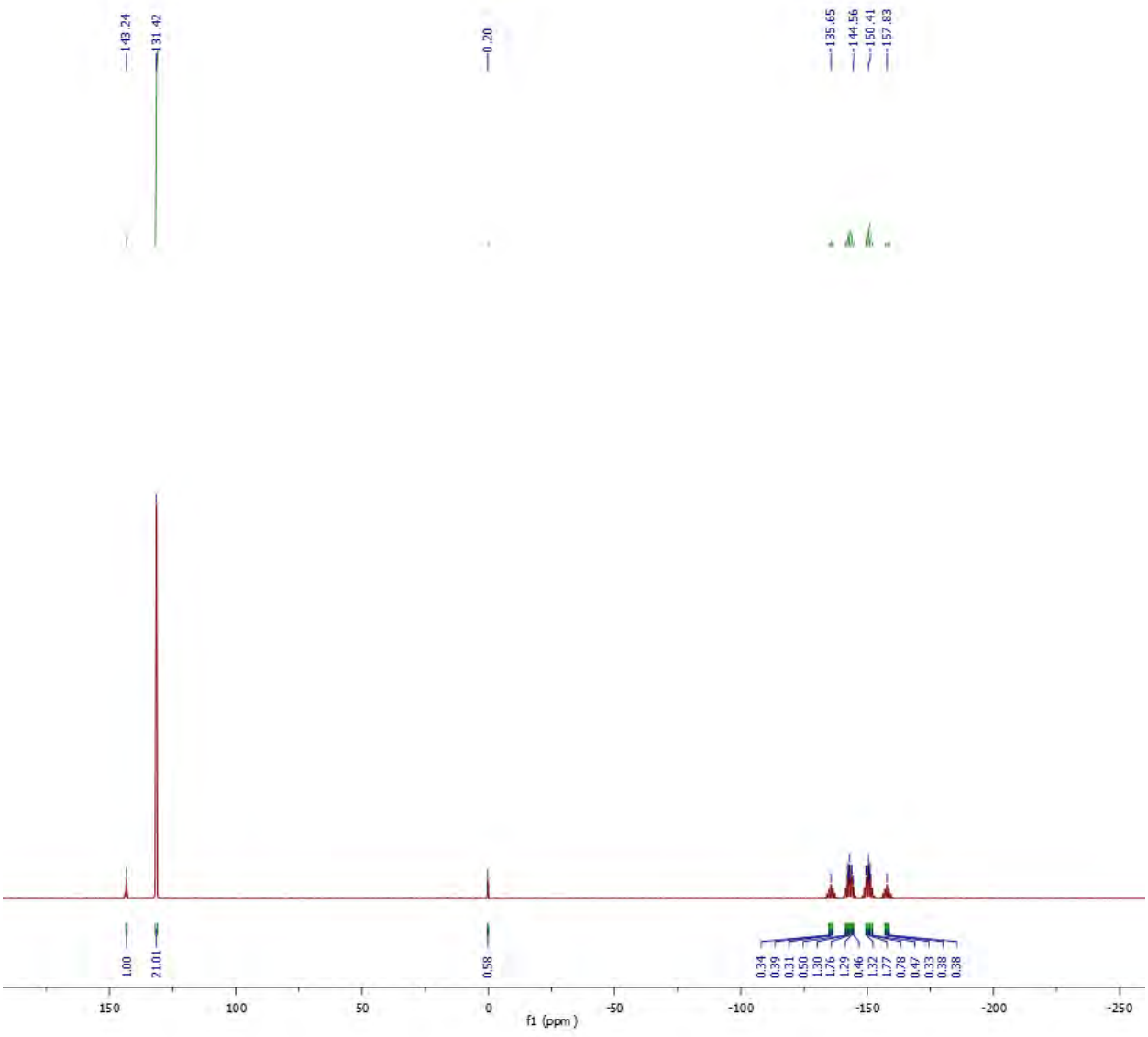


Figure S2 ^{31}P NMR of phosphorodiamidite, **2**, stabilized in [C_6mim][FAP]

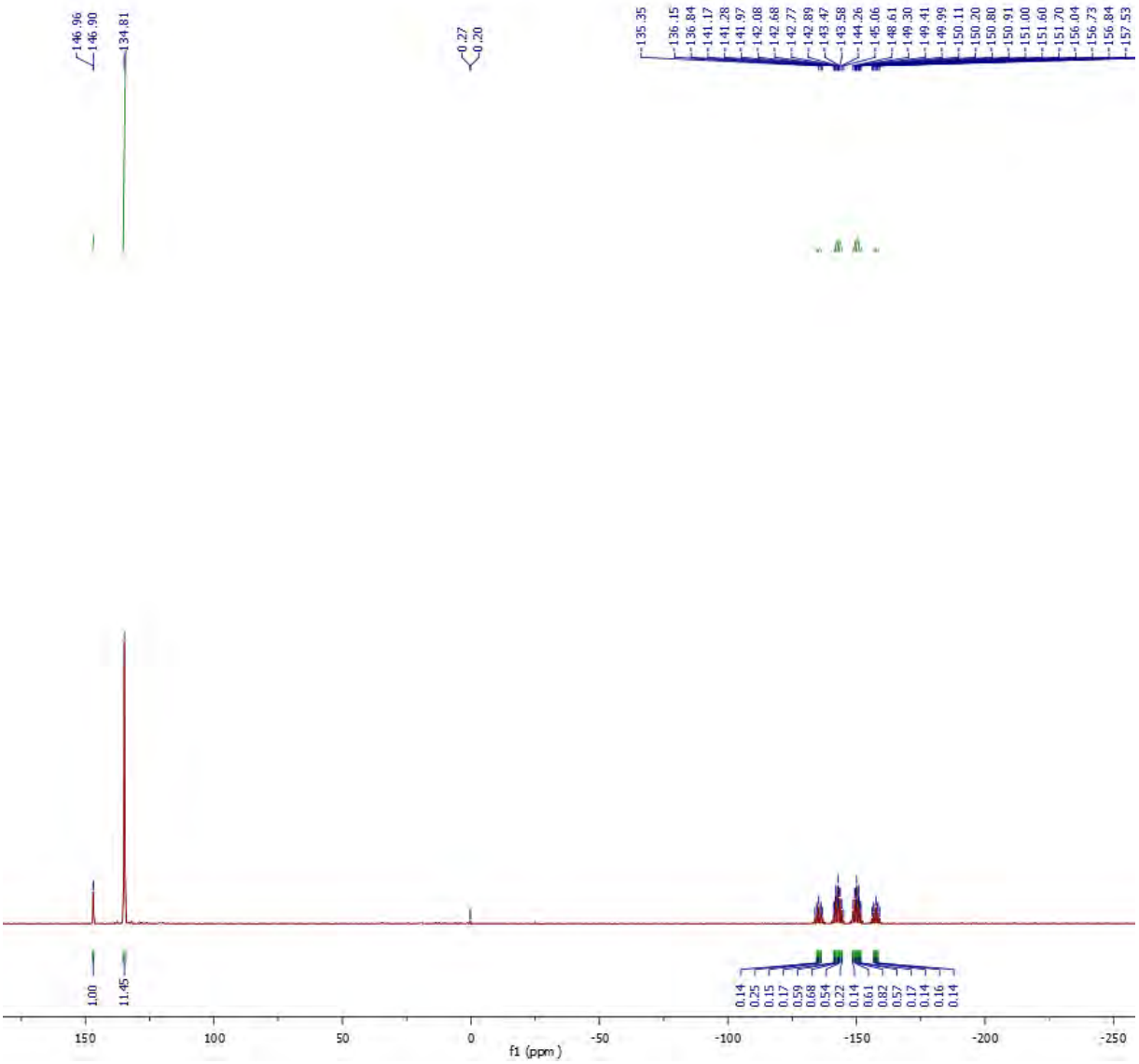


Figure S3 ^{31}P NMR of phosphorodiamidite, **3**, stabilized in [C_6mim][FAP]

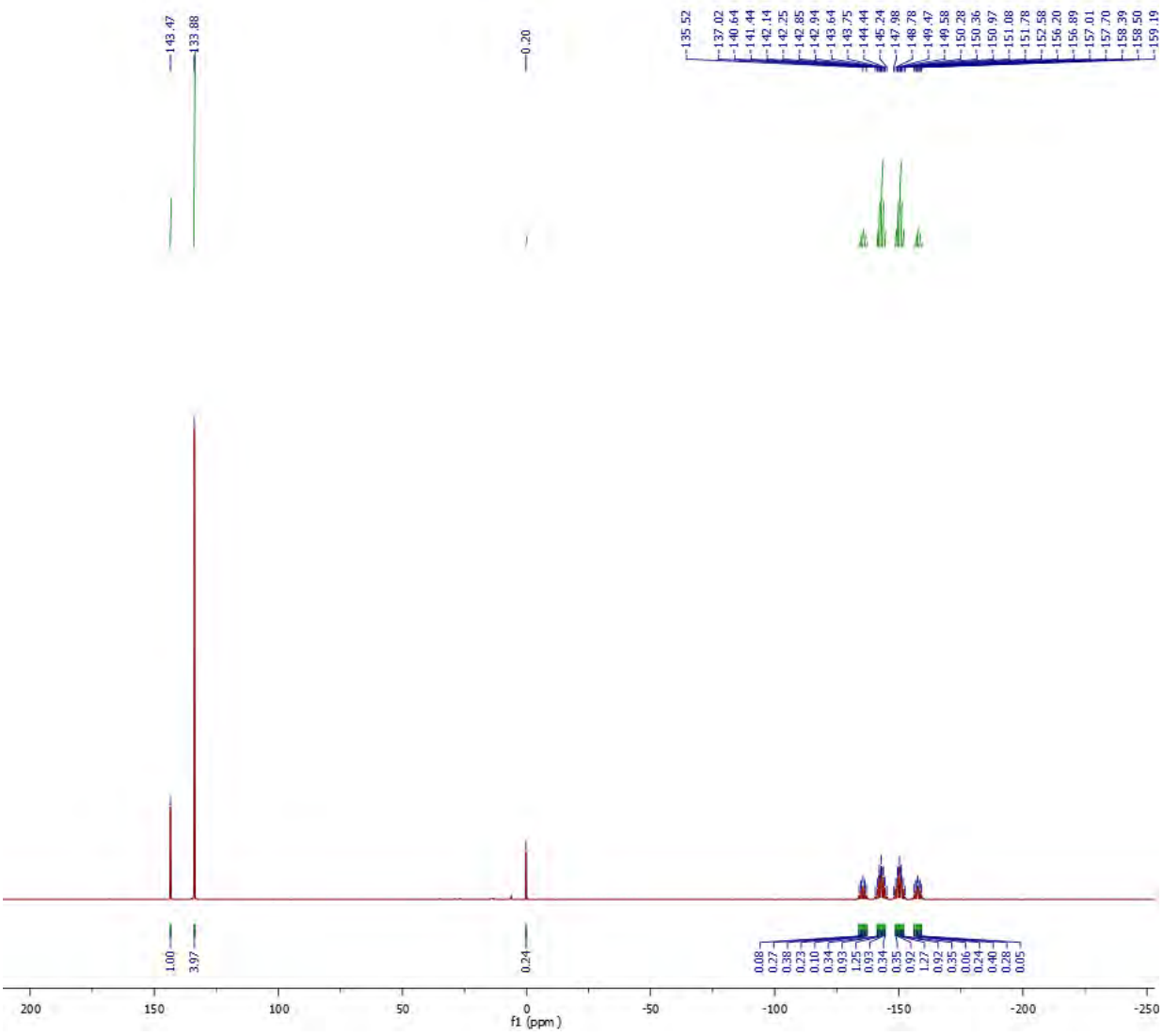
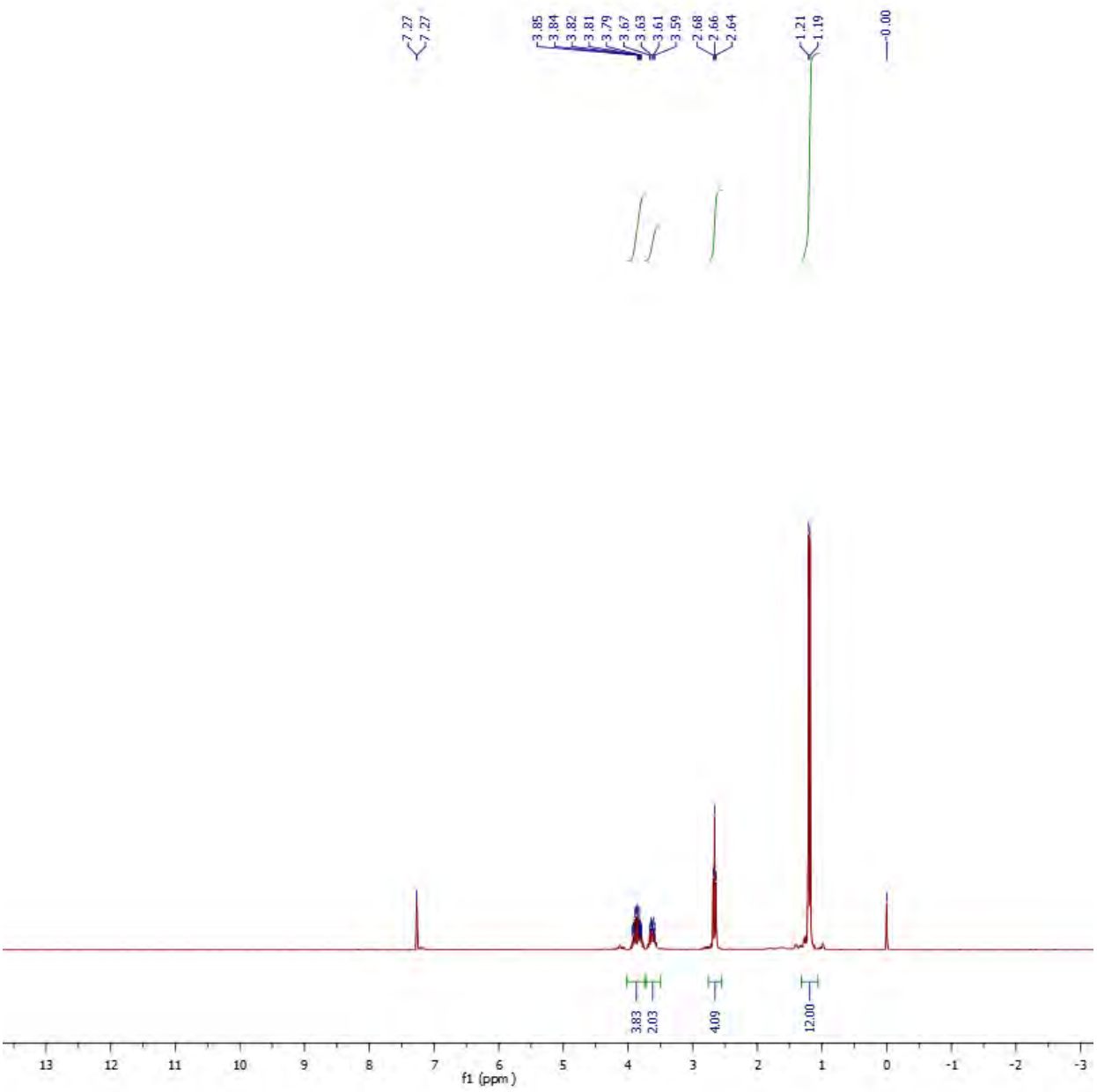
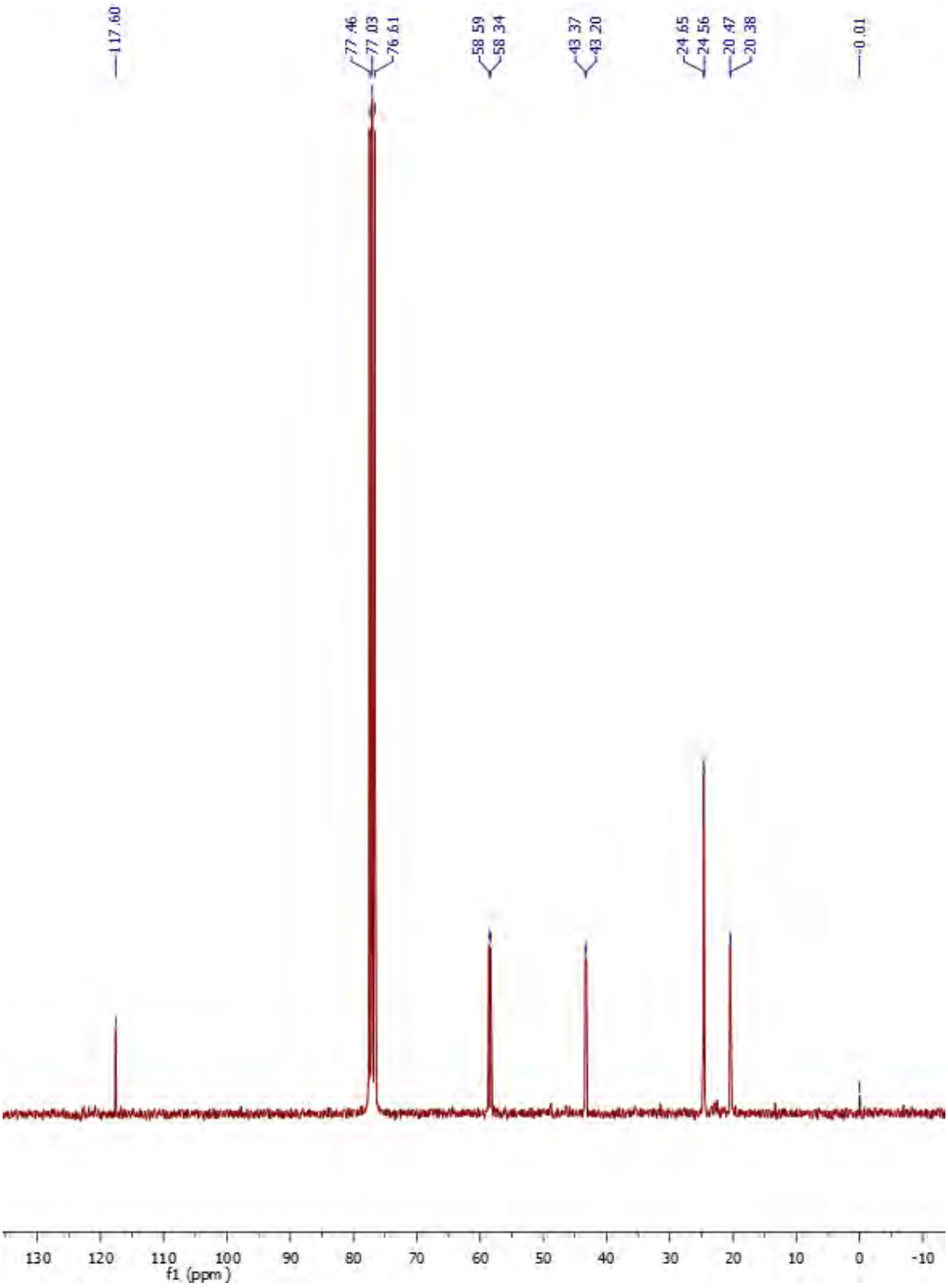


Figure S4 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR of phosphoramidite, **4**, as well as (d) ^{31}P NMR of phosphoramidite, **4**, stabilized in [C_6mim][FAP]

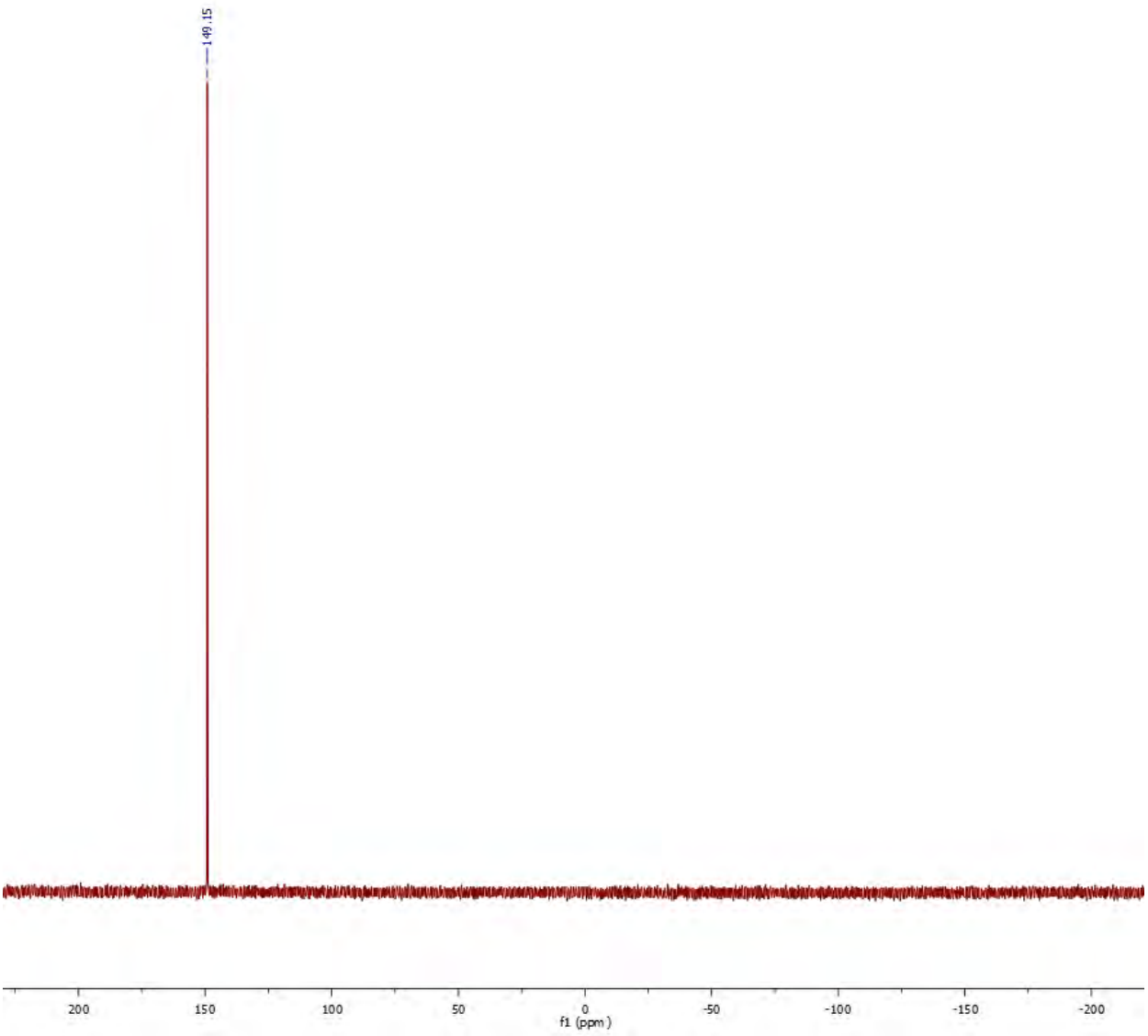
(a)



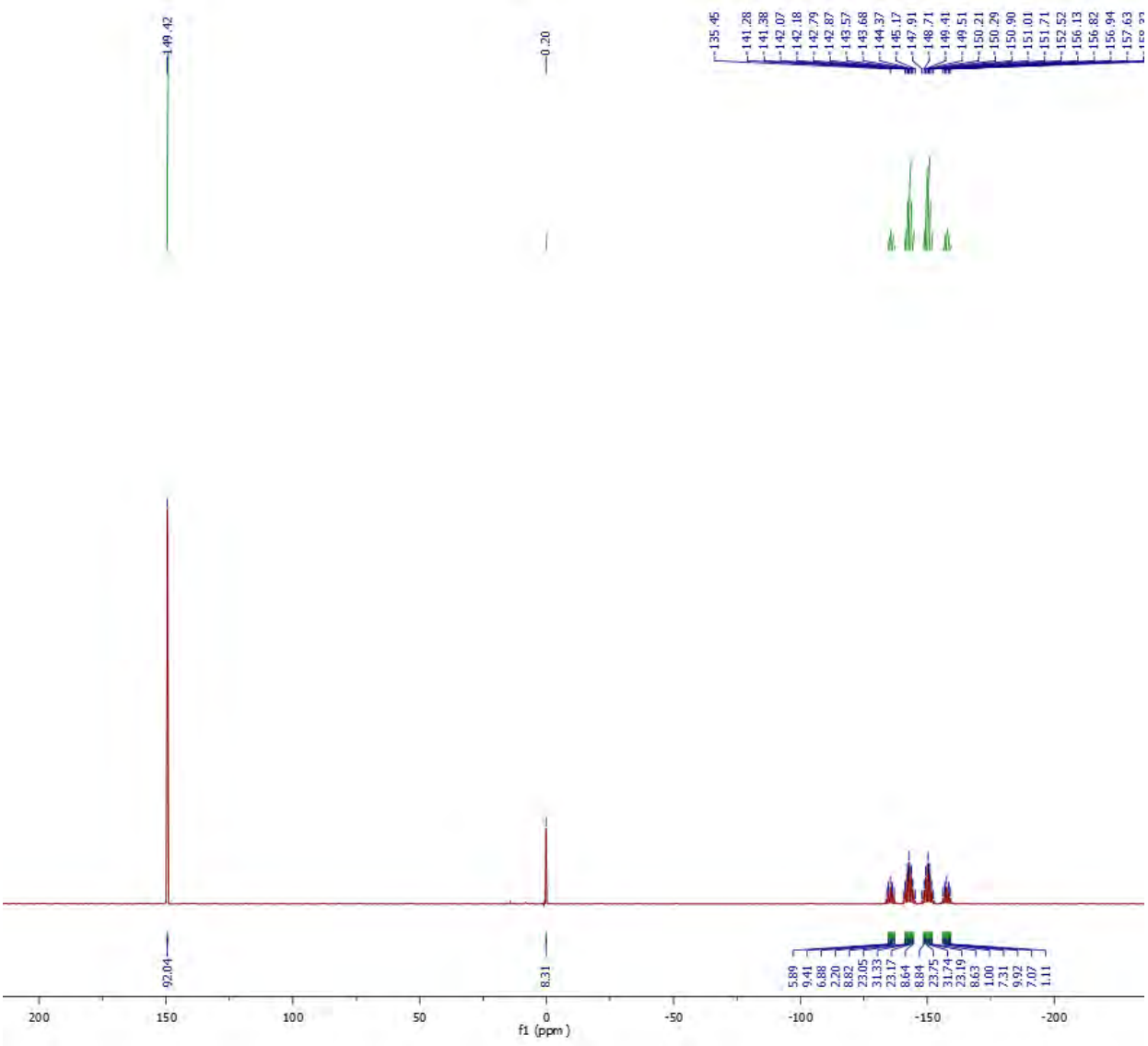
(b)



(c)



(d)



Phosphitylation Reactions

All ball mill reactions were carried out on a 40 mg scale based on the amount of protected nucleoside. This generally equated to 25-30 mg (2.5 eq) of activator and 100 μL of the [C_6mim][FAP] stabilized phosphorodiamidites (2 eq).

Activator Synthesis

***N*-Methylimidazole Triflate**

In a 2 neck round bottom flask, N-methylimidazole (1 eq) in DCM (10 ml) was added. The solution was stirred at room temperature for 30 min after which triflic acid was added (1.1 eq). Diethyl ether (10 ml) was then added to the solution to crystallise the salt and the mixture stirred for a further 30 min. The solution was the filtered, the solid washed with diethyl ether, collected and dried under high vacuum for 2 h to give 1.75g (75%) of *N*-methylimidazole triflate as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ ppm 3.99 (s, 3H, NC*H*$_3$), 7.59 (d, 2H, *J*= 7.2 Hz, NC*H*C*H*N), 8.99 (s, 1H, NC*H*N). **^{13}C NMR** (75 MHz, CD_3OD) δ ppm 35.4, 118.0, 122.9, 134.7 **^{19}F NMR** (CD_3OD) δ ppm -78.9 (s, C*F*$_3$). **CHNS Anal.** Calcd for $C_5H_8F_3N_2O_3S$: C, 25.9; H, 3.0; N, 12.1; S, 13.8 Found: C, 25.8; H, 2.77; N, 12.1; S, 13.5. **HRMS** (ES) +ve calc. 83.0609 found 83.0610; -ve calc. 148.9520 found 148.9520

Synthesis of Pyridinium Trifluoroacetate

Pyridine (1 eq) was placed in a 2 neck round bottom flask equipped with a magnetic stirrer and cooled in an ice-water bath to 0°C. 2 ml of water was added followed by slow addition of trifluoroacetic acid (1.1 eq) and the mixture was left to stir for a further 2 h. The mixture was then concentrated in vacuo at 70 °C. The resulting residue was then dried under high vacuum for 2 h to give 1.70 g (88%) of pyridinium trifluoroacetate as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.82-7.95 (m, 2H, 2 NCHC*H*CH), 8.35 (t, 1H, *J*= 7.8 Hz, NCHCHC*H*), 8.91 (d, 2H, *J*= 5.1 Hz, 2 NC*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 118.5, 126.9, 143.3, 144.3, 162.5 (q, *J*=37.6 Hz, C*F*$_3$). **^{19}F NMR** ($CDCl_3$) δ ppm -79.1 (s, C*F*$_3$). **CHNS Anal.** Calcd for $C_7H_6F_3NO_2$: C, 43.5; H, 3.1; N, 7.3 Found: C, 41.5; H, 2.66; N, 6.9. **HRMS** (ES) +ve calc. 80.0500 found 80.0504 ; -ve calc. 112.9850 found 112.9846.

Ball Milling

To the partially protected nucleoside (1 eq) was added the activator (2.5 eq) and [C_6mim][FAP]-stabilized phosphorodiamidite in [C_6mim][FAP] (2 eq). The mixture was shaken in a 1.5 ml steel vessel with a 5 mm diameter steel ball bearing in a Retsch MM400 mixer mill at 25Hz for 0.5 h. In bulk physical form, the ball-milled reactions were pastes.

All compounds are a diastereoisomeric mixture, hence the complex ^{1}H and ^{13}C spectra and 2 peaks in each of the ^{31}P NMR spectra. The diastereoisomeric ratio was determined from the ^{31}P NMR.

***N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite (1a).** Purification was achieved via filtration of the crude residue through

a short pad of silica gel (1:1 hexane: ethyl acetate, (1% NEt_3), to give **1a** as a white solid (1:1 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm -0.21 (s, 3H, $SiCH_3$), -0.17 (s, 3H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.60 (d, 3H, *J*= 6.9 Hz, CH_3), 0.75 (d, 3H, *J*=6.9 Hz, CH_3), 0.79 (s, 9H, $SiC(CH_3)_3$), 0.81 (s, 9H, $SiC(CH_3)_3$)), 0.84 (d, 3H, *J*= 6.8 Hz, CH_3), 0.92 (d, 3H, *J*= 6.8 Hz, CH_3), 1.65-1.68 (heptet, 1H, *J*= 6.8 Hz, *CH*), 1.84-1.89 (heptet, 1H, *J*= 6.8 Hz, C*H*), 2.74 (t, 2H, *J*= 6.1 Hz OCH_2CH_2CN), 2.97 (m, 6H, OCH_2CH_2CN, NCH_2CH_2O), 3.02-3.11 (m, 6H, NCH_2CH_2O, H-5), 3.41-3.49 (m, 4H, NCH_2CH_2O, H-5), 3.61-3.64 (m, 6H, NCH_2CH_2O, H-5), 3.88-4.00 (m, 2H, OCH_2CH_2CN), 4.06-4.12 (m, 2H, OCH_2CH_2CN), 3.77 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.16 (br. m, 1H, H-4), 4.29 (br. m, 1H, H-4), 4.36 (dd, 1H, *J*= 12.0 Hz, *J*= 4.9 Hz, H-3), 4.44 (m, 1H, H-3), 4.99 (dd, 1H, *J*= 7.8 Hz, *J*= 5.0 Hz, H-2), 5.15 (dd, 1H, *J*= 7.2 Hz, *J*= 5.5 Hz, H-2), 5.74 (d, 1H, *J*= 7.3 Hz, H-1), 5.85 (d, 1H, *J*= 7.8 Hz, H-1), 6.80-6.85 (m, 8H, trityl), 7.23 (s, 1H, N*H*), 7.24 (s, 1H, N*H*), 7.24-7.31 (m, 6H, trityl), 7.40-7.45 (m, 8H, trityl), 7.56 (d, 2H, *J*= 7.3 Hz, trityl), 7.59 (d, 2H, *J*= 7.2 Hz, trityl), 7.83 (s, 1H, N=C*H*-N), 7.88 (s, 1H, N=C*H*-N), 8.00 (s, 1H, N*H*), 8.52 (s, 1H, N*H*). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm -5.09, -5.08 ($SiCH_3$), -4.65, -4.77 ($SiCH_3$), 18.2-18.3 ($SiC(CH_3)_3$), 18.3-18.4 ($SiC(CH_3)_3$), 20.1-20.2 (OCH_2CH_2CN), 22.2 (Si-*C*-$(CH_3)_3$), 25.5-25.6 ($CHCH_3$), 35.9-36.0 ($CHCH_3$), 43.1-43.4 (NCH_2CH_2O), 55.1-55.2 (OCH_3), 57.6-57.7, 58.9-59.0 (OCH_2CH_2CN), 63.1 (C-5), 67.8-67.9 (NCH_2CH_2O), 72.2-72.3, 72.8-72.9 (C-3), 73.5-73.6 (C-2), 84.3-84.4 (C-4), 87.4 (C-1), 113.3-113.4 (trityl), 117.1, 117.7 (CN), 122.1-148.5 (trityl), 138.2 (N=*C*H-N), 155.6, 158.8, 178.4 (C=O), 178.7 (C=O) . **^{31}P NMR** (121 MHz, $CDCl_3$) δ ppm 145.0, 145.3. **HRMS** (ES, M- CH_3) calculated for $C_{47}H_{59}N_7O_{10}SiP$ 940.3830, found 940.3830.

***N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxycytidine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite (1b).** Purification was achieved via filtration of the crude residue through a short pad of silica gel (3:7 pentane: ethyl acetate, (1% NEt_3), to give **1b** as a white solid (1:0.7 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.23-2.35 (m, 2H, H-2), 2.50 (t, 2H, *J*= 6.2 Hz, OCH_2CH_2CN), 2.59-2.79 (m, 2H, H-2), 2.62 (t, 2H, *J*= 6.0 Hz, OCH_2CH_2CN), 3.02-3.03 (m, 4H, NCH_2CH_2O), 3.09-3.12 (m, 4H, NCH_2CH_2O), 3.38-3.46 (m, 2H, H-5), 3.50-3.53 (m, 4H, NCH_2CH_2O), 3.50-3.61 (m, 2H, H-5), 3.56-3.61 (m, 4H, NCH_2CH_2O), 3.69-3.83 (m, 4H, OCH_2CH_2CN,), 3.80 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.09-4.13 (m, 1H, H-4), 4.16-4.20 (m, 1H, H-4), 4.50-4.53 (m, 1H, H-3), 4.64-4.69 (m, 1H, H-3) 6.21-6.26 (m, 2H, H-1), 6.86-6.89 (m, 8H, trityl), 7.23-7.25 (m, 16H, trityl, N-CH=C*H*), 7.41-7.42 (m, 4H, trityl), 7.48-7.53 (m, 4H, benzoyl), 7.59-7.64 (m, 2H, benzoyl),

7.86-7.88 (m, 4H, benzoyl), 8.32-8.43 (m, 2H, N-C*H*=CH), 8.68 (br s, 2H, NH). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 20.2-20.3 (OCH_2CH_2CN), 41.7 (C-2), 43.3 (d, *J*=15.8 Hz, NCH_2CH_2O) 43.4 (d, *J*= 16.1 Hz, NCH_2CH_2O), 55.2-55.3 (OCH_3), 58.4-58.5 (OCH_2CH_2CN), 60.4 (C-5), 67.8-67.9 (NCH_2CH_2O), 70.7 (C-3), 85.4-85.5 (C-4), 87.1 (C-1), 96.9 (N-CH=*C*H) 113.1 (trityl), 117.5 (CN), 122.1, 123.5, 127.2 (benzoyl), 127.5, 128.1, 130.1, 135.1 (trityl), 129.0 (benzoyl), 133.3 (benzoyl), 135.2 (N-*C*H=CH), 143.9, 144.0(N-*C*H=CH), 158.7 (C=O), 162.2 (C=N). **^{31}P NMR** (121 MHz, $CDCl_3$) δ ppm 144.4, 144.6. HRMS (ES, $M+H^+$) calculated for $C_{44}H_{47}N_5O_9P$ 820.3111, found 820.3123

***N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyadenosine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite (1c).** Purification was achieved via filtration of the crude residue through a short pad of silica gel (3:7 pentane: ethyl acetate, (1% NEt_3), to give **1c** as a white solid (2:1 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.52 (t, *J*= 6.2 Hz, 2H, OCH_2CH_2CN), 2.55-2.65 (m, 2H, H-2), 2.63 (t, *J*= 6.2 Hz, 2H, OCH_2CH_2CN), 2.87-2.98 (m, 2H, H-2), 3.14-3.20 (m, 8H, NCH_2CH_2O), 3.34-3.46 (m, 4H, H-5), 3.54-3.56 (m, 4H, NCH_2CH_2O), 3.60-3.62 (m, 4H, NCH_2CH_2O), 3.77 (s, 12H, OCH_3), 3.76-3.80 (m, 2H, OCH_2CH_2CN), 3.87-3.91 (m, 2H, OCH_2CH_2CN), 4.11-4.16 (m, 1H, H-4), 4.28-4.31 (m, 1H, H-4), 4.72-4.75 (m, 1H, H-3), 4.84-4.86 (m, 1H, H-3), 6.48-6.52 (m, 2H, H-1), 6.79-6.81 (m, 8H, trityl), 7.19-7.29 (m, 14H, trityl), 7.38-7.39 (m, 4H, trityl), 7.53 (t, *J*= 7.5 Hz, 4H, benzoyl), 7.62 (t, *J*= 6.9 Hz, 2H, benzoyl), 8.01 (t, *J*= 7.4 Hz, 4H, benzoyl), 8.16 (s, 1H, N-C*H*=N), 8.21 (s, 1H, N-C*H*=N), 8.72 (br s, 2H, N=C*H*-N), 9.01 (br s, 2H, N*H*). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 20.2-20.4 (OCH_2CH_2CN), 39.3-39.3 (C-2), 43.3-43.5 (NCH_2CH_2O), 55.2 (OCH_3), 58.4-58.6 (OCH_2CH_2CN), 63.0-63.6 (C-5), 67.6-67.9 (NCH_2CH_2O), 73.5-74.0 (C-3), 84.6-84.8 (C-1), 85.6-86.0 (C-4), 113.1 (trityl), 117.4 (CN), 123.4, 126.9-130.0 (trityl, benzoyl), 132.9 (benzoyl) 141.6-141.7 (N-*C*H=N), 149.3, 152.5 (N=*C*H-H), 158.6, 164.7 (C=O). **^{31}P NMR** (121 MHz, $CDCl_3$) δ ppm 144.2, 144.4. **HRMS** (ES, $M+H^+$) calculated for $C_{45}H_{47}N_7O_8P$ 844.3324, found 844.3215

***N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N'*-ethylmethylphosphoramidite (2a).** Purification was achieved via filtration of the crude residue through a short pad of silica gel (1:1 hexane: ethyl acetate, (1% NEt_3), to give **2a** as a white solid (0.8:1 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm -0.21 (s, 3H, $SiCH_3$), -0.17 (s, 3H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.52 (d, 6H, *J*= 6.7 Hz, CH_3), 0.73 (d, 6H, *J*= 6.8 Hz, CH_3), 0.70 (s, 9H, $SiC(CH_3)_3$), 0.80 (s, 9H, $SiC(CH_3)_3$), 1.05-1.29 (m, 8H, NCH_2CH_3, $CHCH_3$), 2.42 (d, 3H, *J*= 6.8 Hz, NCH_3), 2.56 (d, 3H, *J*= 7.2 Hz, NCH_3), 2.60-2.77 (m, 4H, OCH_2CH_2CN) 2.84-2.90 (m, 2H, H-5), 3.00-3.04 (m, 4H,

NC*H*$_2$CH$_3$), 3.52-3.65 (m, 2H, H-5), 3.76-3.96 (m, 16H, OC*H*$_2$CH$_2$CN, OC*H*$_3$), 4.07-4.16 (m, 2H, H-4), 4.27-4.45 (m, 2H, H-3), 4.97-5.20 (m, 2H, H-2), 5.72 (d, 1H, *J*= 7.3 Hz, H-1), 5.86 (d, 1H, *J*= 7.8 Hz, H-1), 6.79-6.84 (m, 8H, trityl), 7.23-7.63 (trityl, 20H, N-H), 7.80 (s, 1H, NC*H*=N), 7.86 (s, 1H, NC*H*=N), 11.9 (br. s, 2H, N*H*). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm -5.13, -5.29 (Si*C*H$_3$), -4.77, -4.80 (Si*C*H$_3$), 14.6-14.7 (NCH$_2$*C*H$_3$), 14.7-14.8 (NCH$_2$*C*H$_3$), 18.2-18.3 (Si*C*(CH$_3$)$_3$), 18.3-18.4 (Si*C*(CH$_3$)$_3$), 19.9-20.0, 20.1-20.2 (OCH$_2$*C*H$_2$CN), 22.6 (Si-*C*-(CH$_3$)$_3$), 25.5-25.6 (*C*H$_3$), 29.6-29.7, 30.1-30.2 (N*C*H$_2$CH$_3$), 35.8 (*C*H), 44.2-44.4 (N*C*H$_3$), 55.3 (O*C*H$_3$), 57.1-57.2, 58.7-58.8 (O*C*H$_2$CH$_2$CN), 63.1-63.2 (C-5), 71.9-72.3 (C-3), 73.2, 75.0 (C-2), 84.5 (C-4), 87.3 (C-1), 113.1-113.3 (trityl), 117.2 (N*C*C=O), 117.8 (CN), 129.9, 130.1, 135.4, 135.7, 136.2 (trityl), 138.2 (N*C*H=N), 139.2, 144.8-148.4 (trityl), 155.6, 158.7, 178.2 (C=O), 178.7 (C=O). **^{31}P NMR** (121 MHz, $CDCl_3$) δ ppm 147.8, 147.9. **HRMS** (ES, M+H$^+$) calculated for $C_{47}H_{62}N_7O_9SiP$ 928.4194, found 928.4206

***N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxycytidine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N*'-ethylmethylphosphoramidite (2b).** Purification was achieved via filtration of the crude residue through a short pad of silica gel (1:1 hexane: ethyl acetate, (1% NEt_3), to give **2b** as a white solid (0.7:1 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.01-1.43 (m, 6H, NCH$_2$C*H*$_3$), 2.28-2.67 (m, 12H, H-2, NC*H*$_3$, OCH$_2$C*H*$_2$CN), 2.89-3.04 (m, 6H, H-2, NC*H*$_2$CH$_3$), 3.39-3.58 (m, 2H, H-5), 3.65-3.74 (m, 2H, H-5), 3.80 (br. s, 12H, OCH$_3$), 3.94-4.02 (m, 4H, OC*H*$_2$CH$_2$CN), 4.24-4.36 (m, 2H, H-4), 4.64-4.70 (m, 2H, H-3), 6.17-6.24 (m, 2H, H-1), 6.86-6.87 (m, 8H, trityl), 7.20-7.40 (m, 20H, trityl, N-CH=C*H*), 7.52-7.54 (m, 4H, benzoyl), 7.61-7.64 (m, 2H, benzoyl), 7.85-7.87 (m, 4H, benzoyl), 8.29 (br. m, 2H, N-C*H*=CH), 8.40 (br. s, 2H, N*H*). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 14.6 (N*C*H$_3$), 20.1-20.3 (OCH$_2$*C*H$_2$CN), 36.1 (N*C*H$_2$CH$_3$), 40.6-40.8 (C-2), 43.4 (N*C*H$_3$), 55.2, 55.5 (OCH$_3$), 57.4-57.9, 58.0-58.1 (O*C*H$_2$CH$_2$CN), 61.8 (C-5), 71.1-71.6 (C-3), 85.1-85.7 (C-4), 86.9-87.0 (C-1), 97.1 (N-CH=*C*H), 113.4 (trityl), 118.4 (CN), 122.1, 123.5, 127.4, 128.0, 128.1, 128.2, 129.1, 130.0, 130.1, 135.2 (trityl, benzoyl) 143.9-144.0 (N-*C*H=CH), 158.7 (C=O), 158.8 (C=O). **^{31}P NMR** (121 MHz, $CDCl_3$) δ ppm 147.2, 147.3. **HRMS** (ES, M+H$^+$) calculated for $C_{43}H_{47}N_5O_8P$ 792.3162, found 792.3126

***N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyadenosine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N*'-ethylmethylphosphoramidite (2c).** Purification was achieved via filtration of the crude residue through a short pad of silica gel (1:1 hexane: ethyl acetate, (1% NEt_3), to give **2c** as a white solid (0.7:1 diastereotopic mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04-1.37 (m, 6H, NCH$_2$C*H*$_3$), 2.47-2.77 (m, 10H, H-2, NC*H*$_3$, OCH$_2$C*H*$_2$CN), 2.90-3.22 (m, 6H, H-2, NC*H*$_2$CH$_3$), 3.31-3.47 (m, 4H, H-5), 3.68-3.78 (m, 4H,

OC*H*$_2$CH$_2$CN), 3.77 (s, 6H, OC*H*$_3$), 3.78 (s, 6H, OC*H*$_3$), 4.26-4.35 (m, 2H, H-4), 4.77-4.81 (m, 2H, H-3), 6.49-6.54 (m, 2H, H-1), 6.78-6.81 (m, 8H, trityl), 7.22-7.29 (m, 10H, trityl), 7.38-7.40 (m, 8H, trityl), 7.51-7.55 (m, 4H, benzoyl), 7.60-6.62 (m, 2H, benzoyl), 8.01-8.03 (m, 4H, benzoyl), 8.20-8.22, (m, 2H, N-C*H*=N), 8.73-8.74 (m, 2H, N=C*H*-N), 9.00 (br. s, 2H, N*H*). **^{13}C NMR** (125 MHz, CDCl$_3$) δ ppm 14.6-14.7 (NCH$_2$*C*H$_3$), 20.2-20.4 (OCH$_2$*C*H$_2$CN), 30.1-30.2 (N*C*H$_3$), 39.4 (C-2), 42.3-42.4, 42.6-42.7 (N*C*H$_3$), 55.2-55.3 (O*C*H$_3$), 58.0-58.2 (O*C*H$_2$CH$_2$CN), 63.2-63.3 (C-5), 73.2-73.5 (C-3), 84.8-84.9 (C-1), 85.7-85.8 (C-4), 113.1 (trityl), 117.5 (CN), 122.1, 123.4, 126.9, 127.8, 127.9, 128.1, 130.1, 132.8, 133.6, 135.6 (trityl, benzoyl), 141.6 (N-*C*H=N), 144.1, 152.3 (N=*C*H-N), 158.6 (C=O). **^{31}P NMR** (121 MHz, CDCl$_3$) δ ppm 146.9, 147.0. HRMS (ES, M+H$^+$) calculated for $C_{43}H_{47}N_7O_7P$ 816.3275, found 792.3265

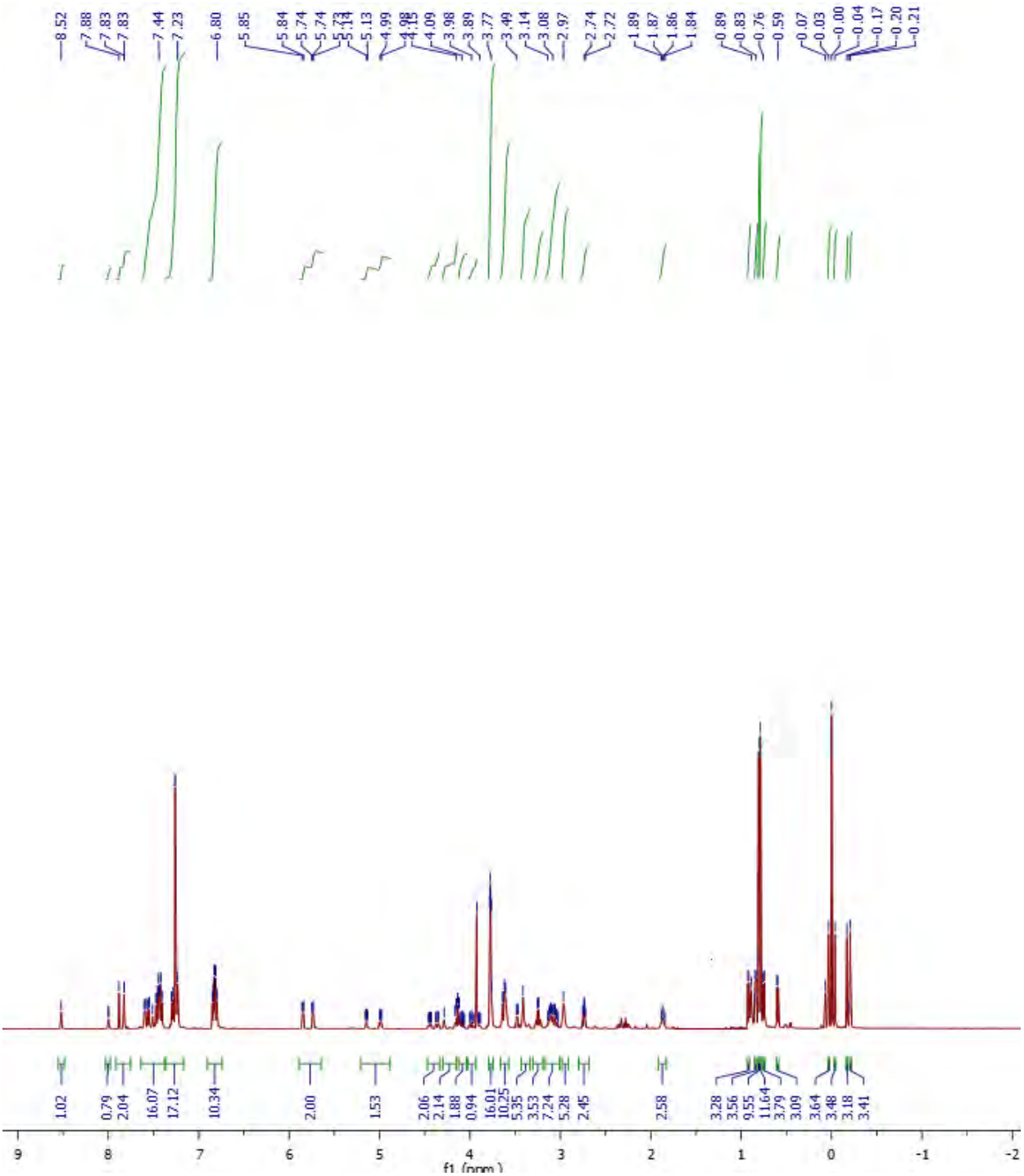
***N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O,O*-(2-cyanoethyl)-phosphoramidite (4a).** Purification was achieved via filtration of the crude residue through a short pad of silica gel 1:1 hexane: ethyl acetate, (1% NEt$_3$), to give **4a** as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm -0.21 (s, 3H, SiC*H*$_3$), -0.01 (s, 3H, SiC*H*$_3$), 0.80 (s, 9H, C*H*$_3$), 0.85 (d, J= 6.9 Hz, 3H, C*H*$_3$), 0.98 (d, J= 6.8 Hz, 3H, C*H*$_3$), 1.84-1.88 (m, 1H, C*H*), 2.54 (t, J= 6.0 Hz, 2H, OCH$_2$*C*H$_2$CN), 2.72 (t, J= 6.4 Hz, 2H, OCH$_2$*C*H$_2$CN), 3.22-3.25 (m, 1H, H-5), 3.59-3.62 (m, 1H, H-5), 3.78 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.91-3.96 (m, 2H, O*C*H$_2$CH$_2$CN), 4.10-4.16 (m, 2H, O*C*H$_2$CH$_2$CN), 4.30-4.31 (m, 1H, H-4), 4.65 (ddd, *J*= 9.2, 4.8, 1.8 Hz 1H, H-3), 4.97 (dd, *J*= 7.1, 4.8 Hz, 1H, H-2), 5.87 (d, *J*= 7.2 Hz, 1H, H-1), 6.80-6.87 (m, 4H, trityl), 7.20-7.53 (m, 10H, trityl, N*H*), 7.93 (s, 1H, N=C*H*-N), 12.2 (s, 1H, N*H*). **^{13}C NMR** (125 MHz, CDCl$_3$) δ ppm -5.34 (Si*C*H$_3$), -4.81 (Si*C*H$_3$), 18.5 (SiC(*C*H$_3$)$_3$), 19.3, (Si*C*(CH$_3$)$_3$), 20.0 (d, J= 4.3 Hz, OCH$_2$*C*H$_2$CN), 20.2 (d, J= 4.3 Hz, OCH$_2$*C*H$_2$CN), 25.5 (C*H*$_3$), 35.9 (C*H*), 55.4 (OC*H*$_3$), 56.9 (d, *J*= 7.2 Hz, O*C*H$_2$CH$_2$CN), 57.2 (d, *J*= 7.2 Hz, O*C*H$_2$CH$_2$CN), 63.1 (C-5), 74.0 (d, *J*= 14.2 Hz, C-3), 75.1 (C-2), 83.9 (C-4), 86.6 (C), 87.6 (C-1), 113.5 (trityl), 117.2 (N*C*C=O), 117.6 (CN), 121.1, 122.1, 123.5, 127.8, 128.0, 128.4, 130.0, 135.3, 135.7 (trityl), 138.7 (N=*C*H-N), 144.8, 147.6, 148.9, 158.8, 179.2 (C=O). **^{31}P NMR** (121 MHz, CDCl$_3$) δ ppm 137.9. **HRMS** (ES, M+H$^+$) calculated for $C_{47}H_{58}N_7O_{10}NaSiP$ 962.3650, found 962.3672

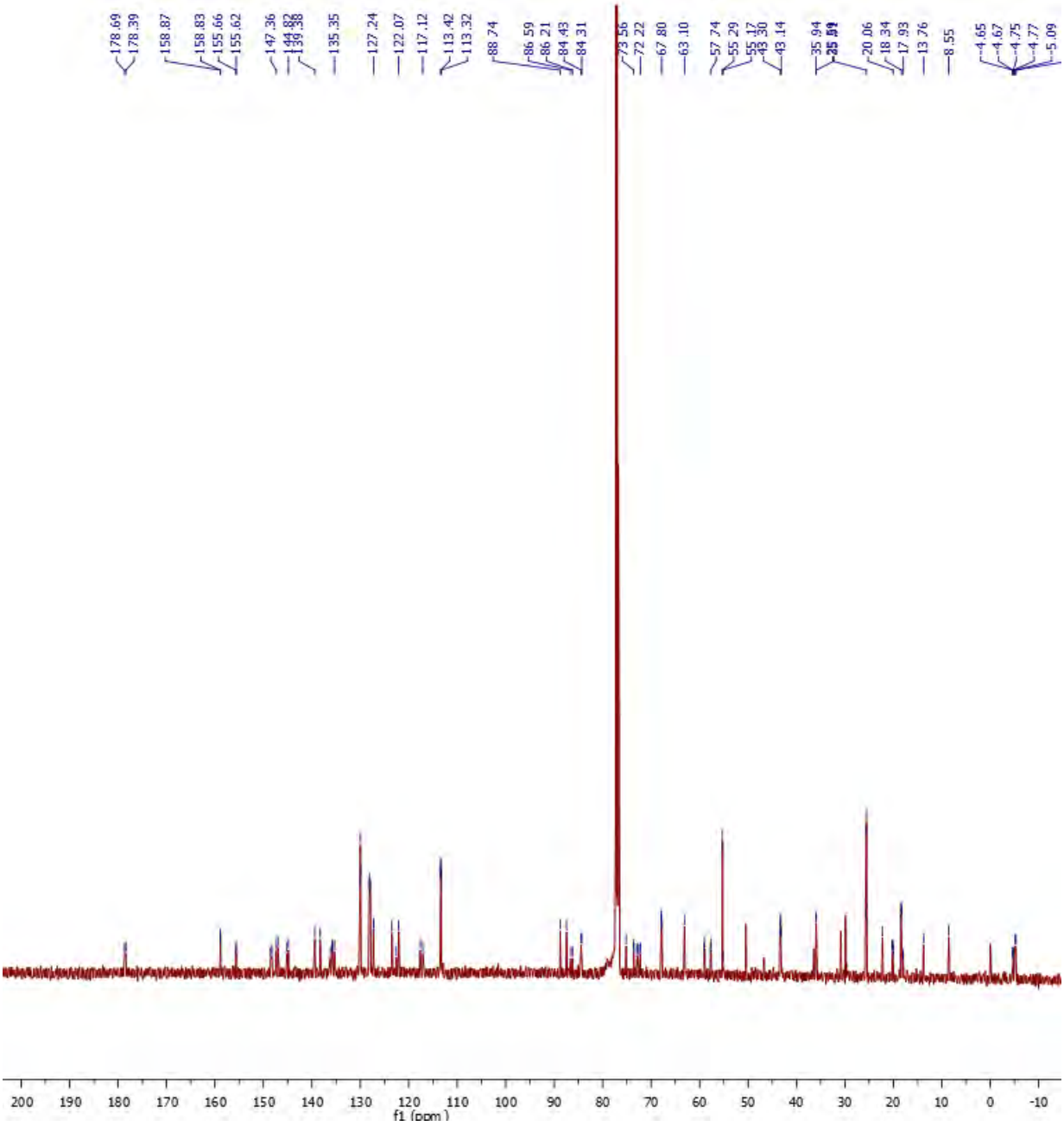
The corresponding ^{1}H, ^{13}C and ^{31}P NMR spectra for **1a-c**, **2a-c** and **4a** are shown in Figure **S5-S11**. The ^{31}P NMR and ^{1}H NMR spectra of **3a** stabilized in [C$_6$mim][FAP] is shown in Figure **S12**.

Figure S5 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite (**1a**).

(a)



(b)


178.69
178.39
158.87
158.83
155.66
155.62
147.36
135.35
127.24
122.07
117.12
113.42
113.32
88.74
86.59
86.21
84.43
84.31
73.56
72.22
67.80
63.10
57.74
55.29
43.14
35.94
20.06
18.34
17.93
13.76
8.55
-4.65
-4.67
-4.75
-4.77
-5.09
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(c)

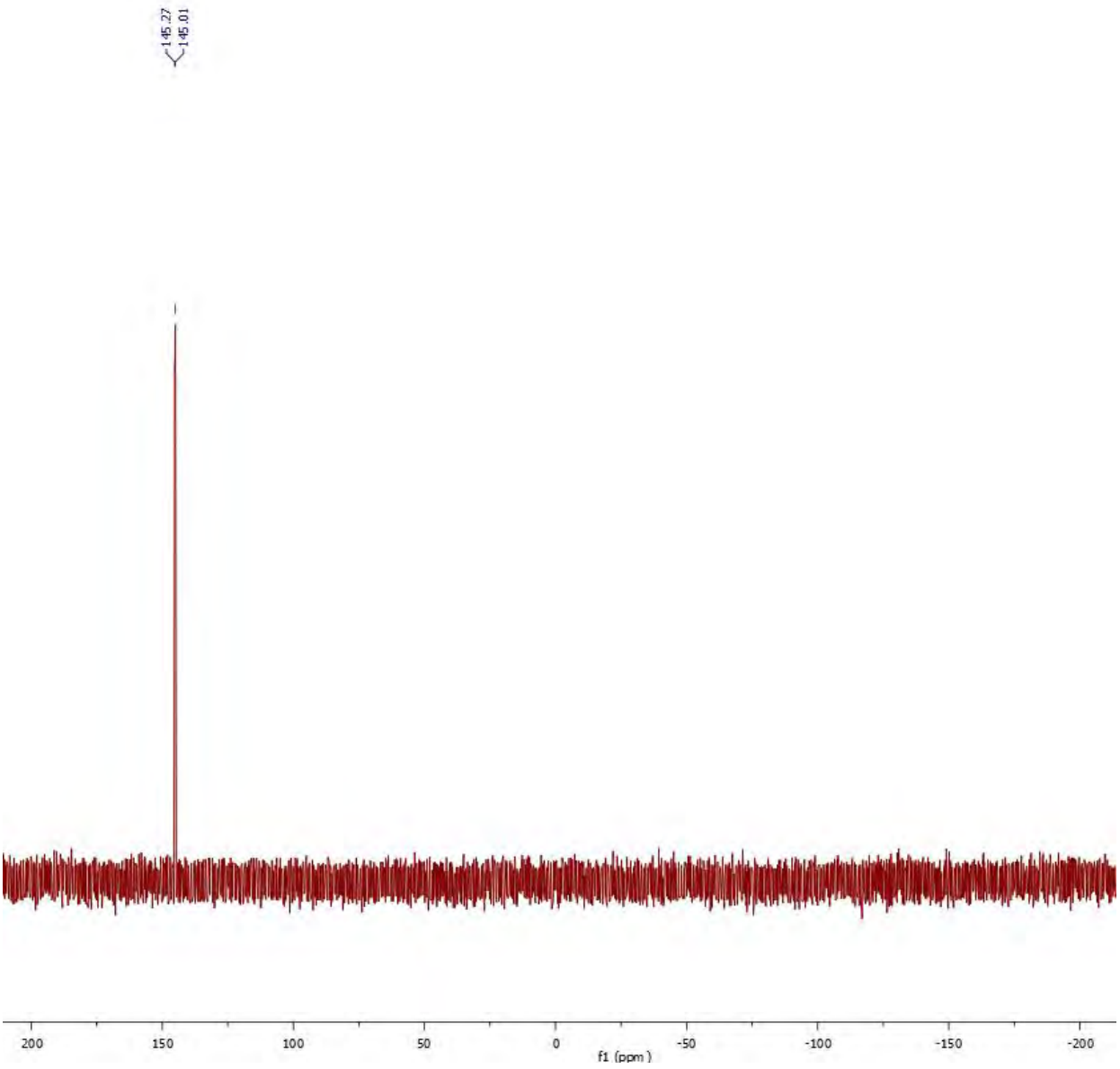
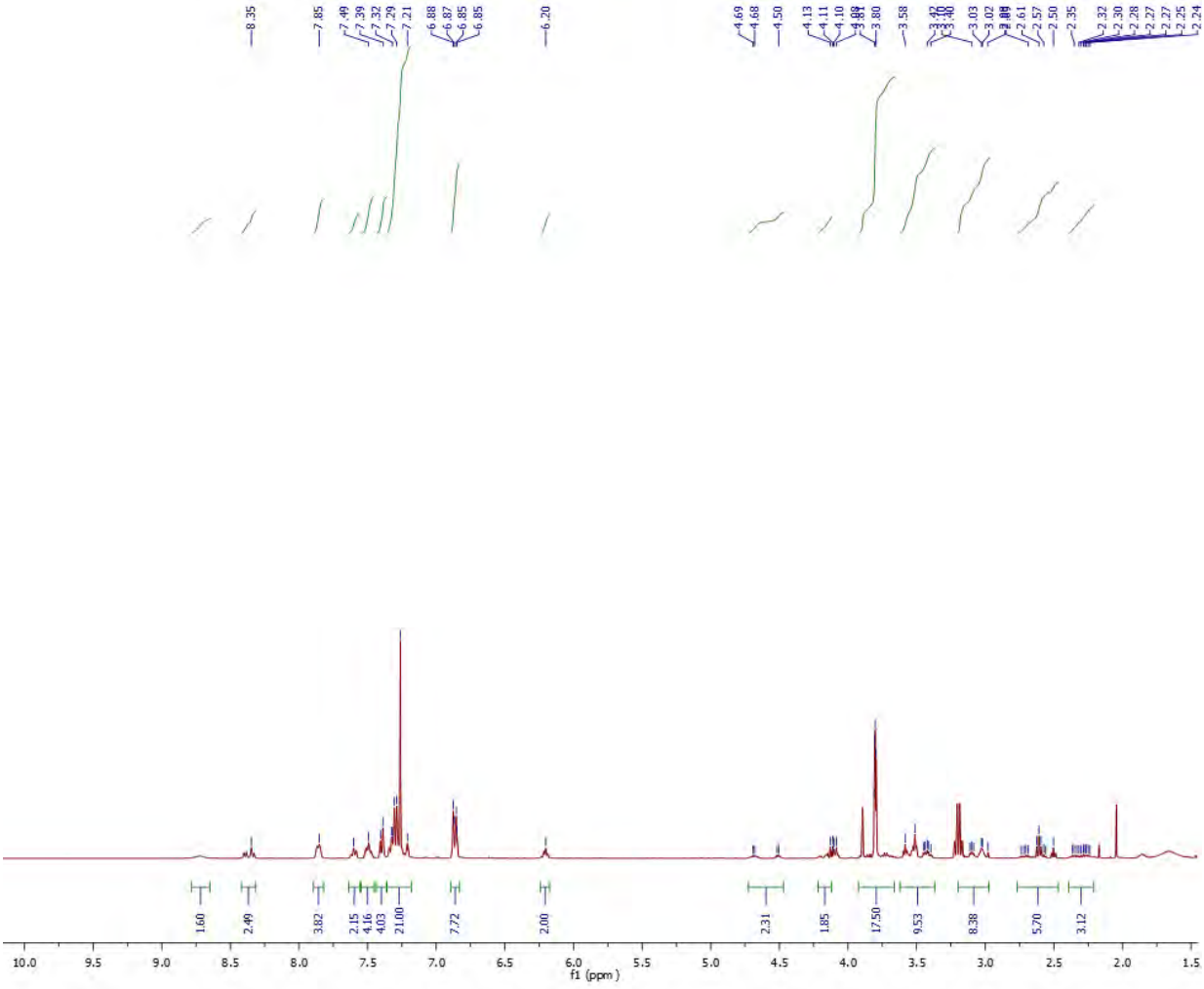
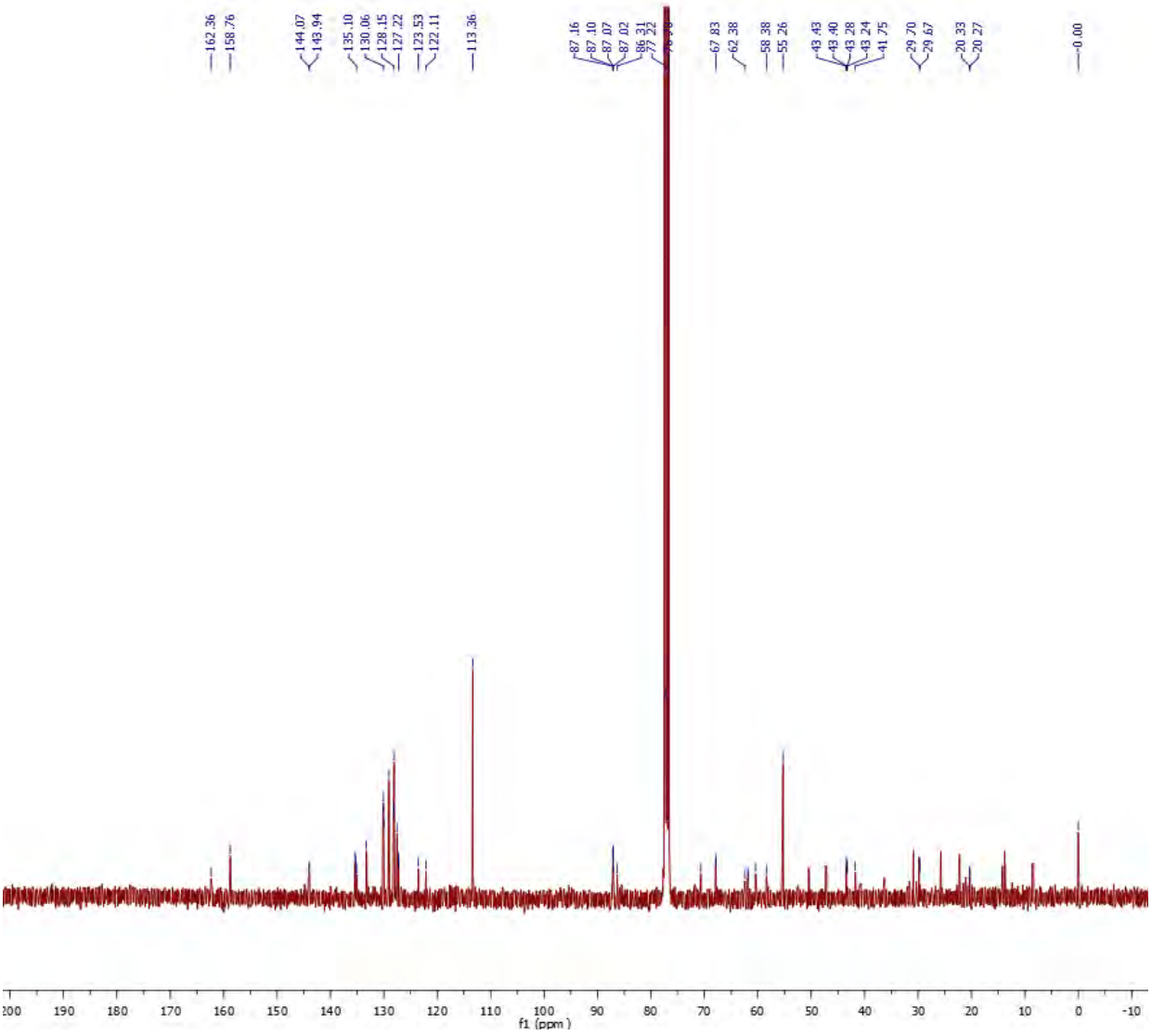


Figure S6 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxycytidine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite **(1b).**

(a)



(b)



(c)

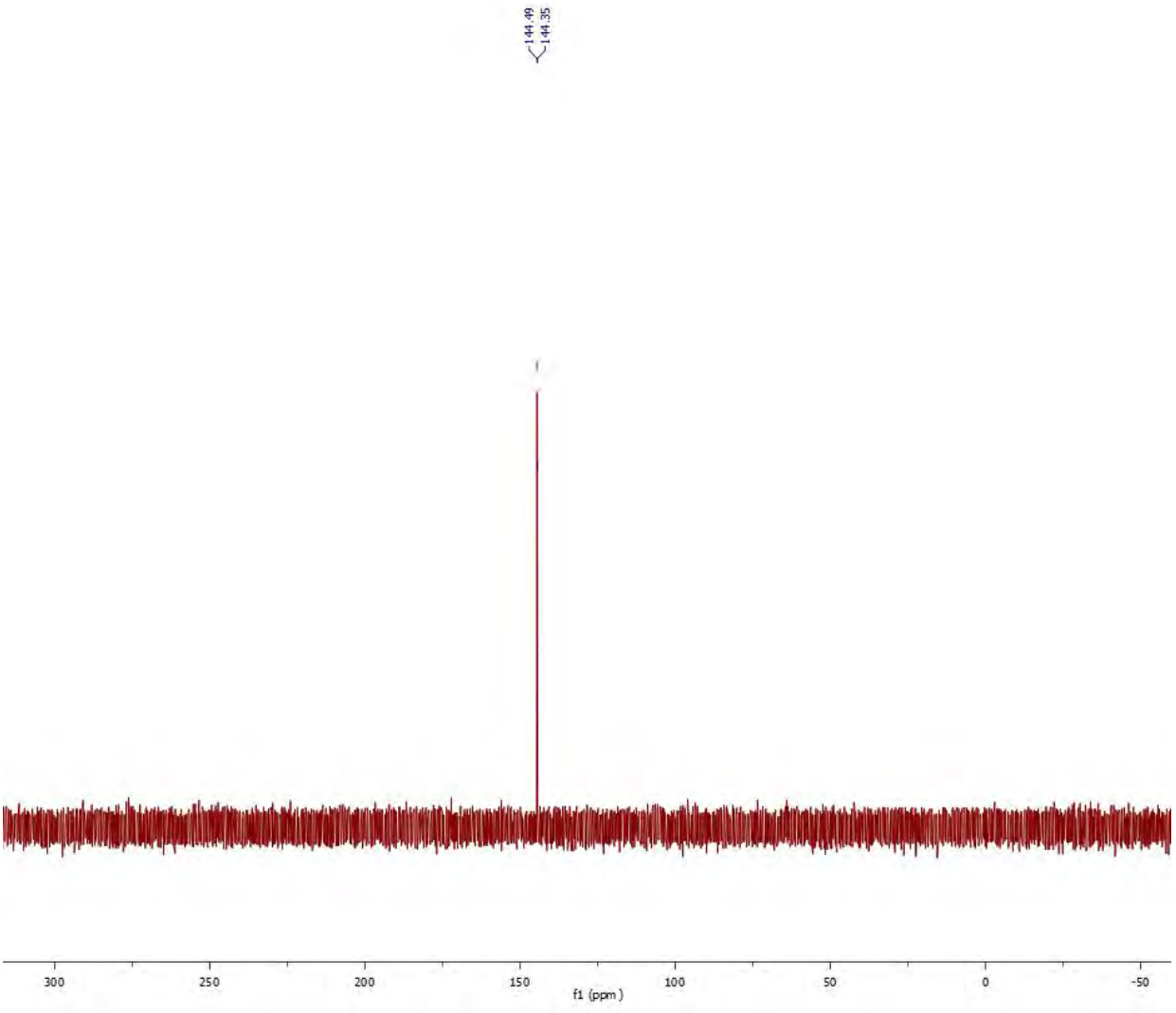
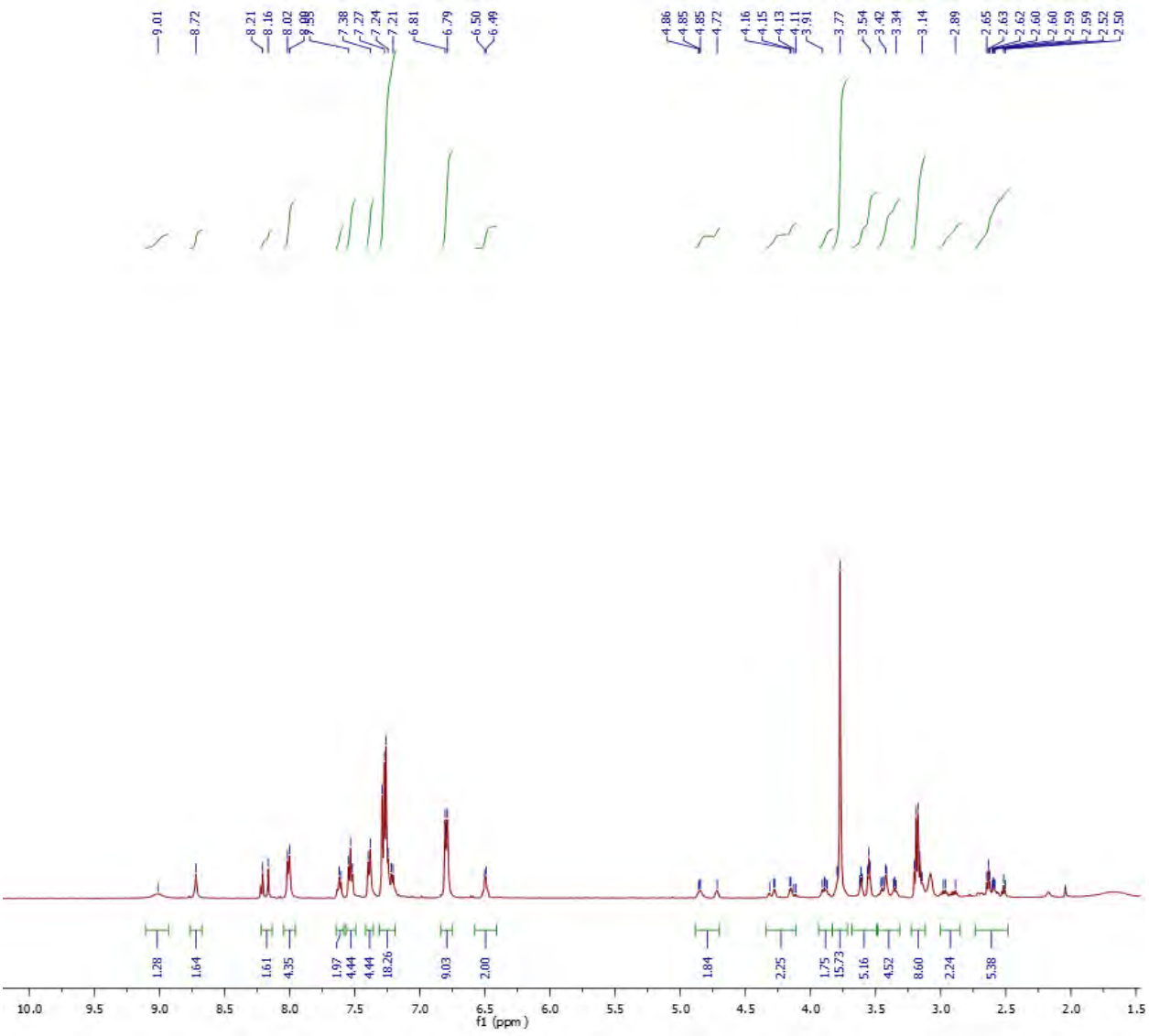
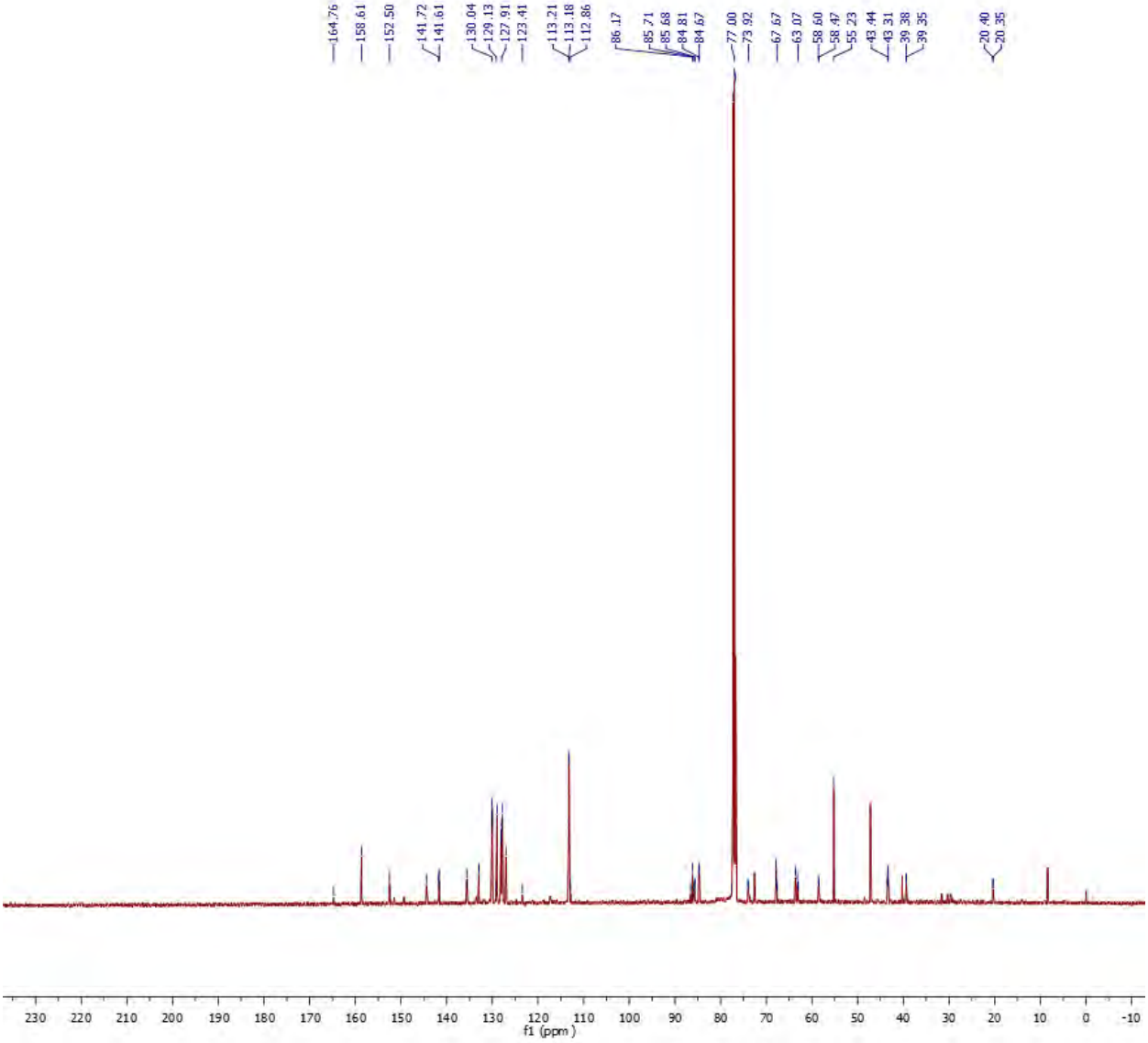


Figure S7 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyadenosine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-morpholinophosphoramidite (**1c**).

(a)



(b)


164.76
158.61
152.50
141.72
141.61
130.04
129.13
127.91
123.41
113.21
113.18
112.86
86.17
85.71
85.68
84.81
84.67
77.00
73.92
67.67
63.07
58.60
58.47
55.23
43.44
43.31
39.38
39.35
20.40
20.35
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(c)

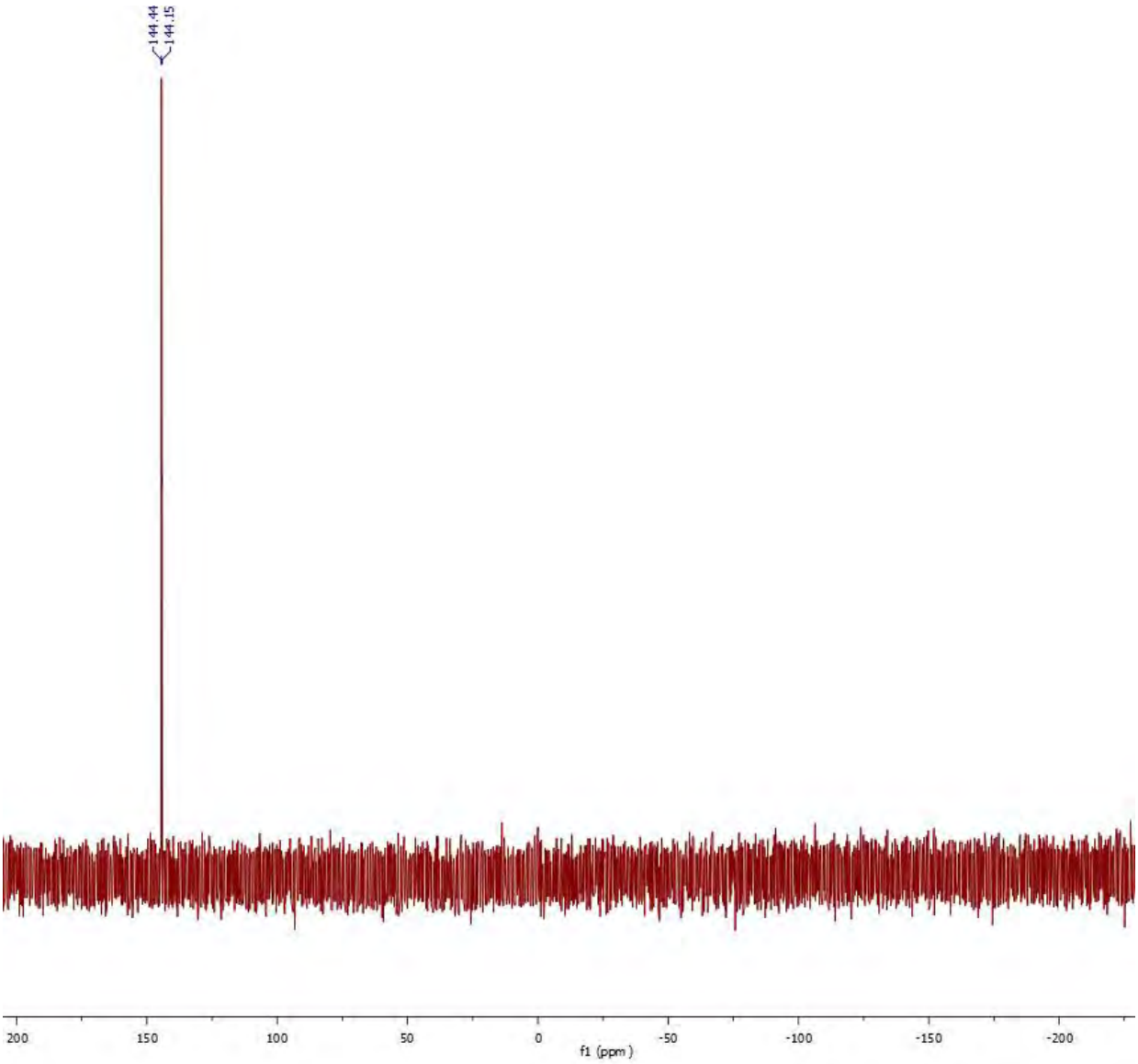
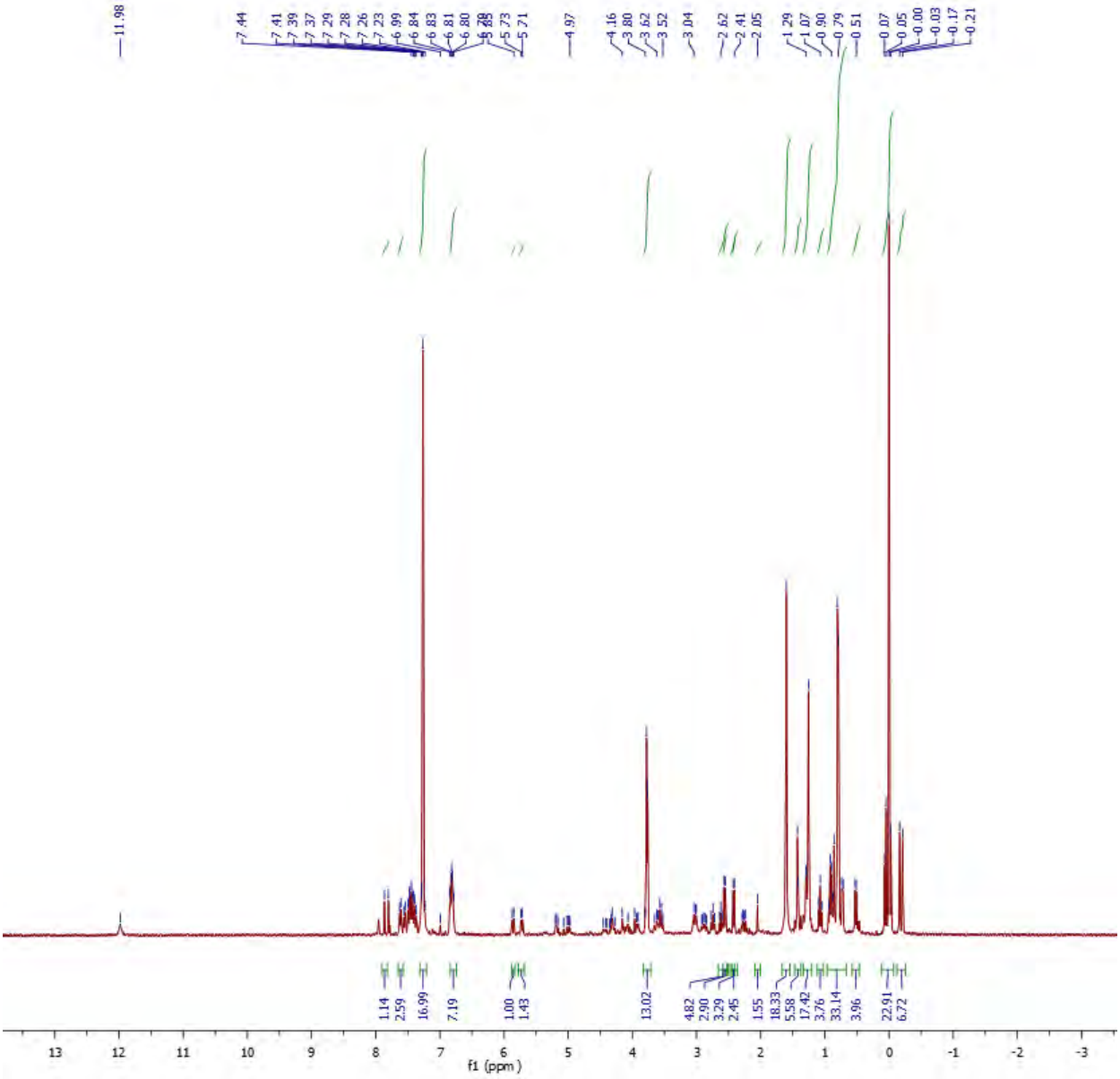
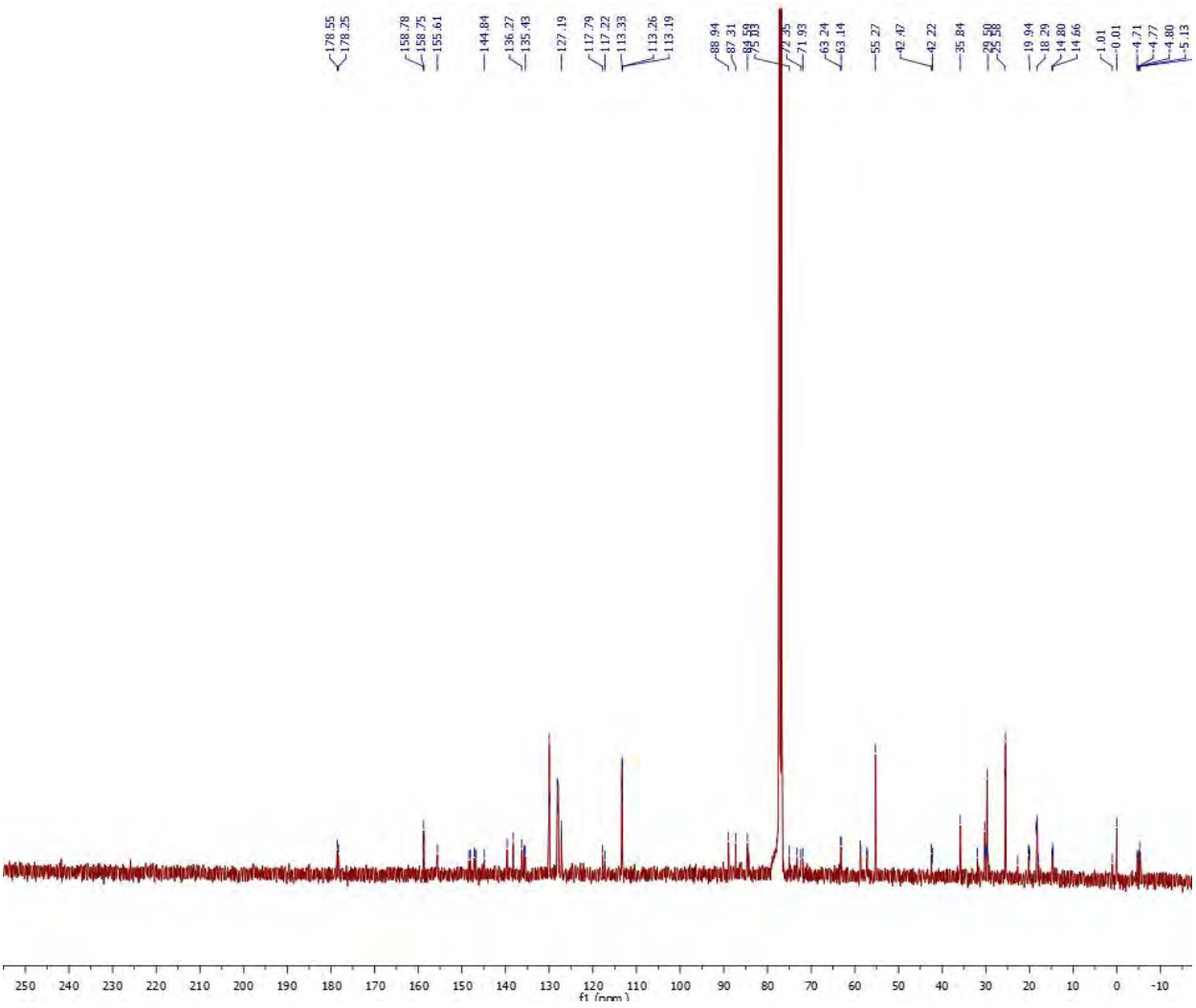


Figure S8 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N'*-ethylmethylphosphoramidite (**2a**).(a)



(b)


178.55
178.25
158.78
158.75
155.61
144.84
136.27
135.43
127.19
117.79
117.22
113.33
113.26
113.19
88.94
87.31
72.35
71.93
63.24
63.14
55.27
42.47
42.22
35.84
25.58
25.58
19.94
18.29
14.80
14.66
1.01
0.01
-4.71
-4.77
-4.80
-5.13
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(c)

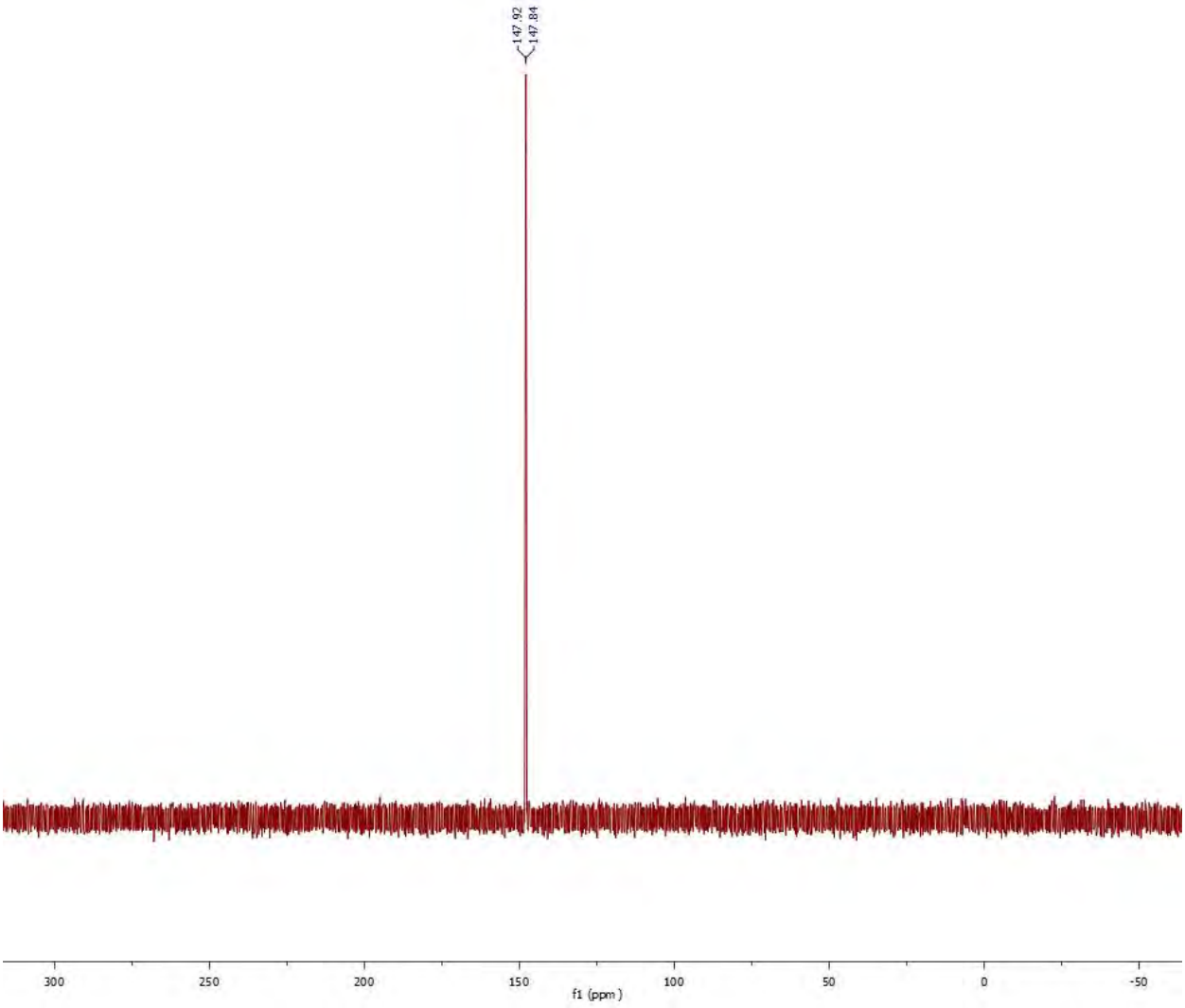
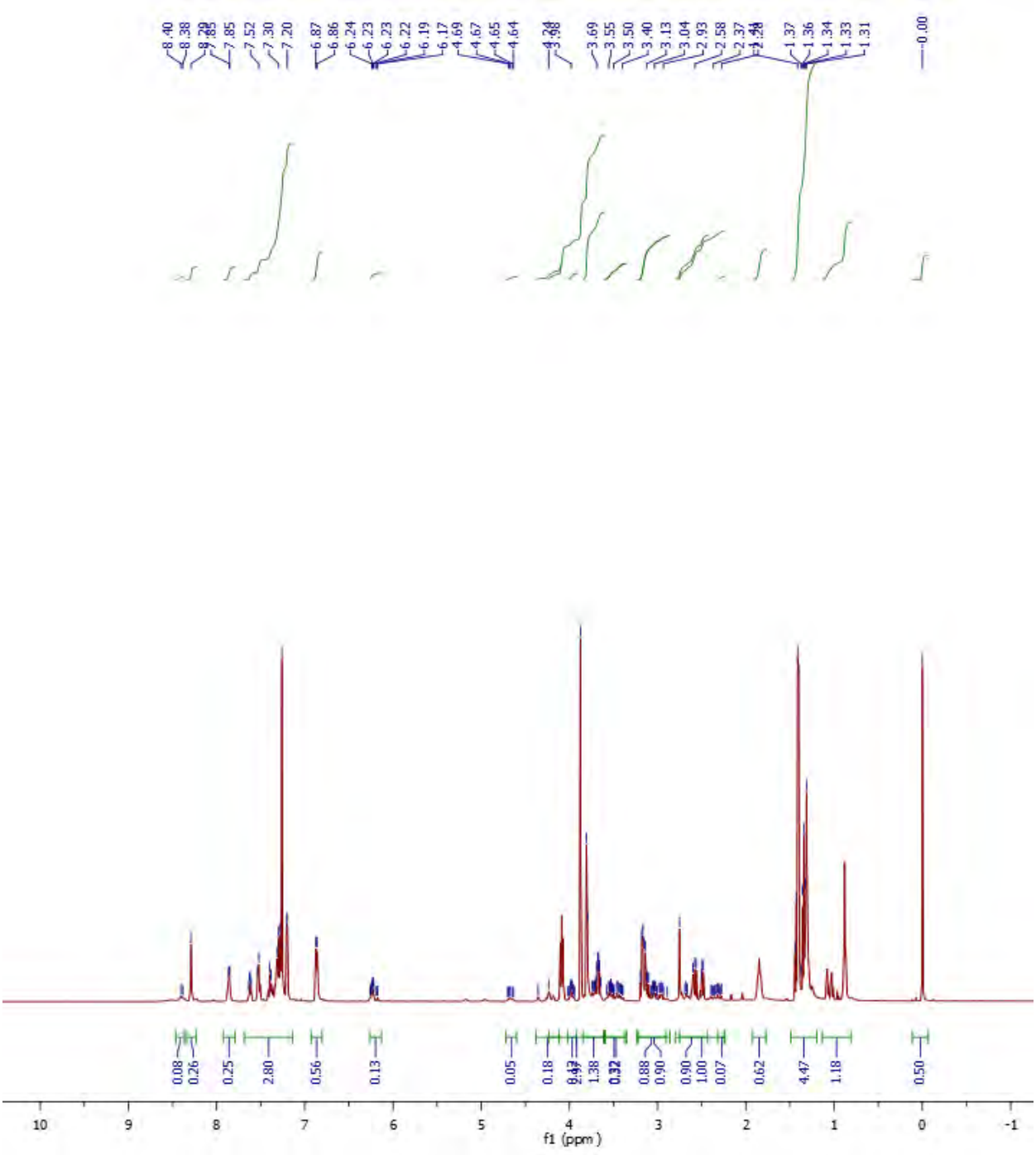
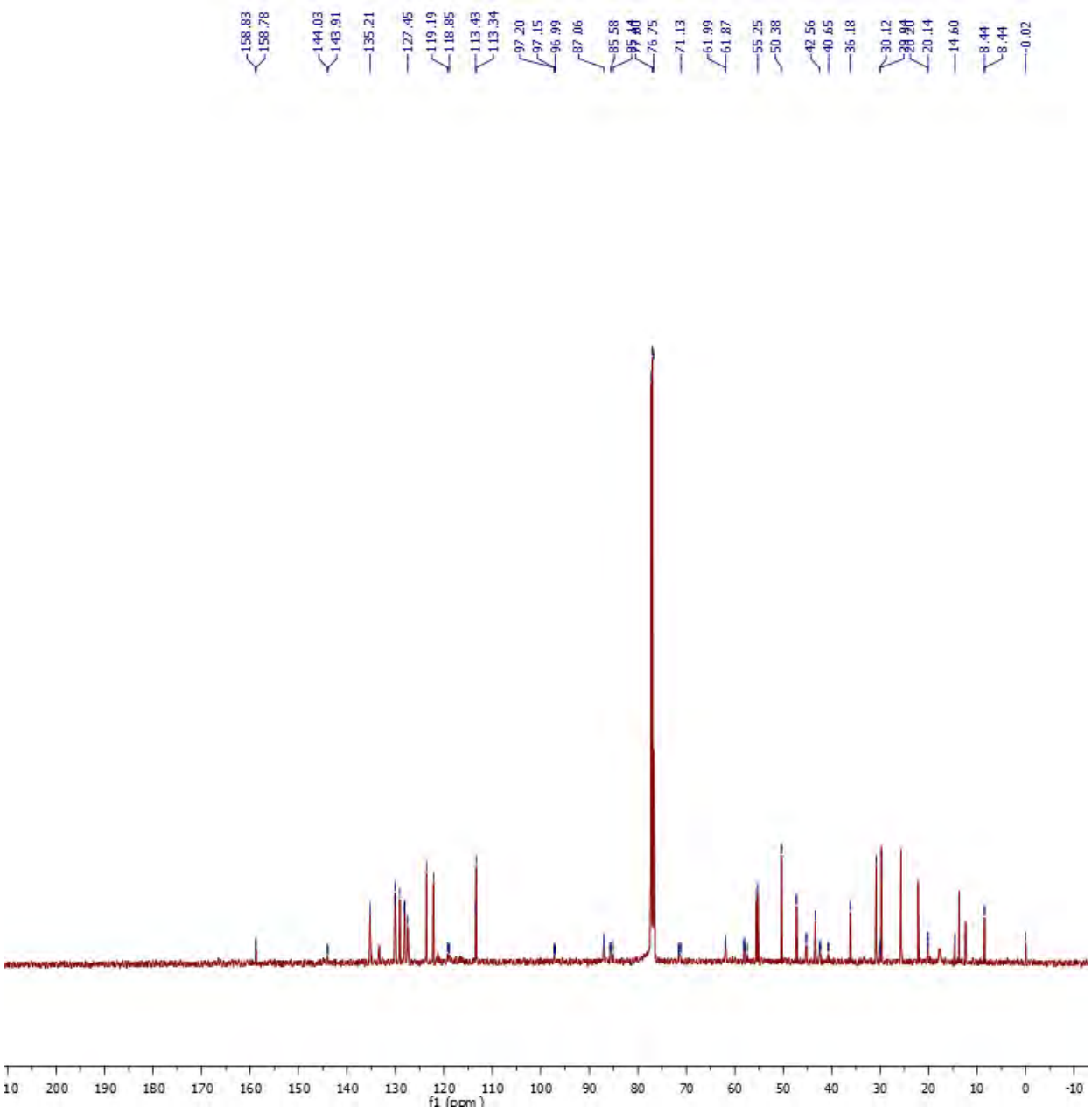


Figure S9 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxycytidine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N'*-ethylmethylphosphoramidite (**2b**).

(a)



(b)



(c)

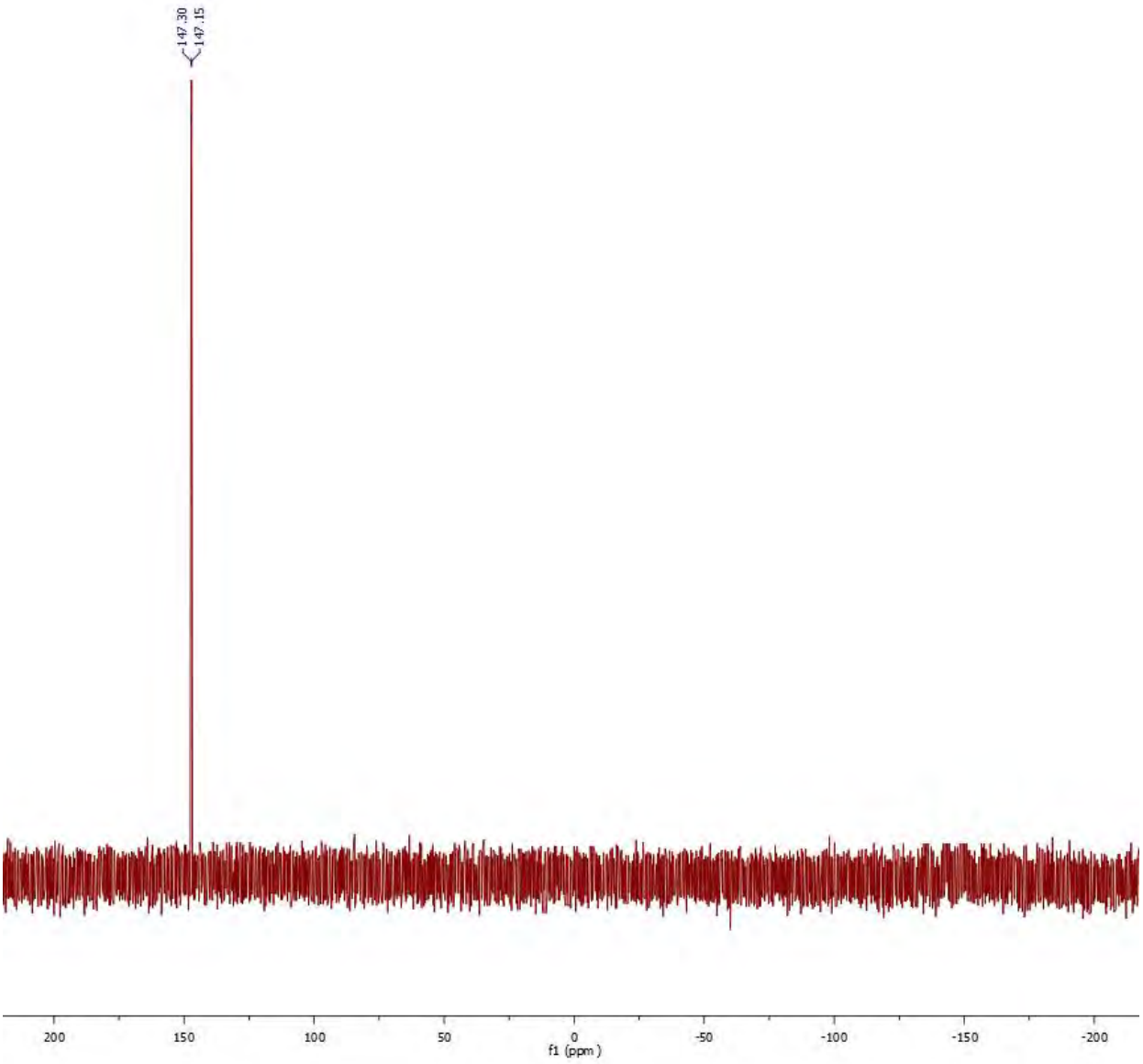
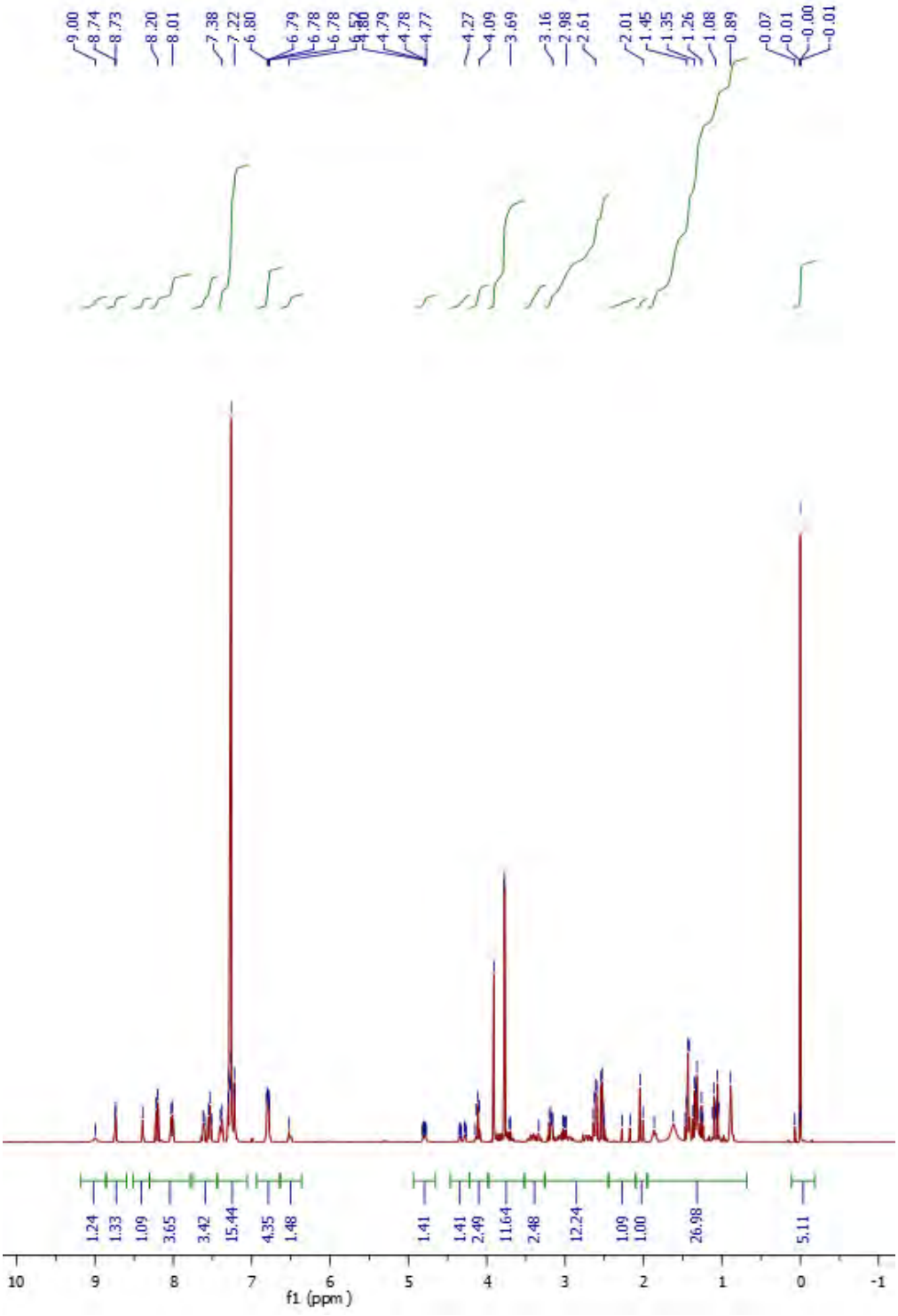
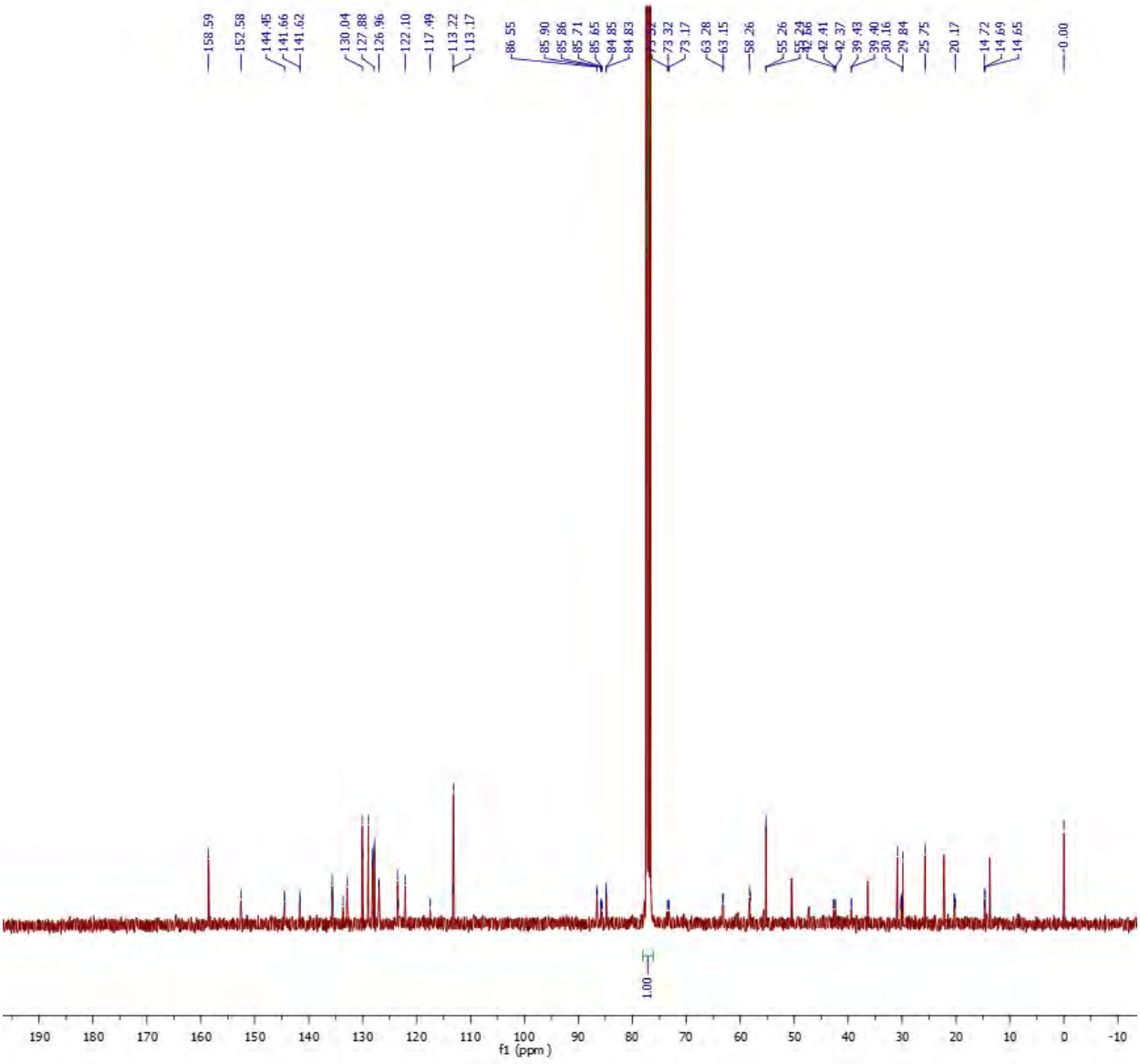


Figure S10 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Benzoyl-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyadenosine-3'-*O*-[*O*-(2-cyanoethyl)-*N,N'*-ethylmethylphosphoramidite (**2c**).(a)



(b)


158.59
152.58
144.45
141.66
141.62
130.04
127.88
126.96
122.10
117.49
113.22
113.17
86.55
85.90
85.86
85.71
85.65
84.85
84.83
73.32
73.17
63.28
63.15
58.26
55.26
42.41
42.37
39.43
39.40
30.16
29.84
25.75
20.17
14.72
14.69
14.65
-0.00
1.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(c)

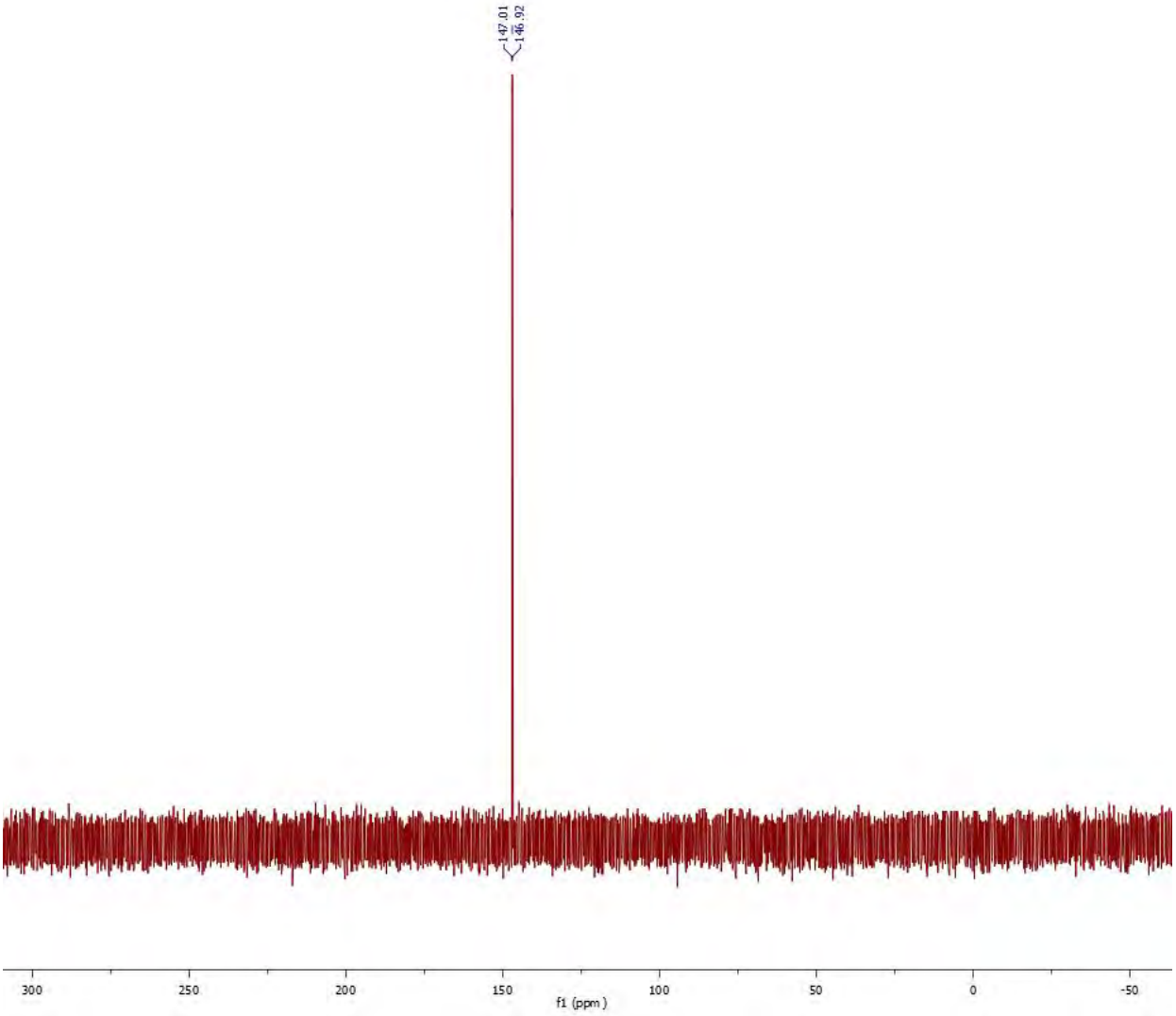
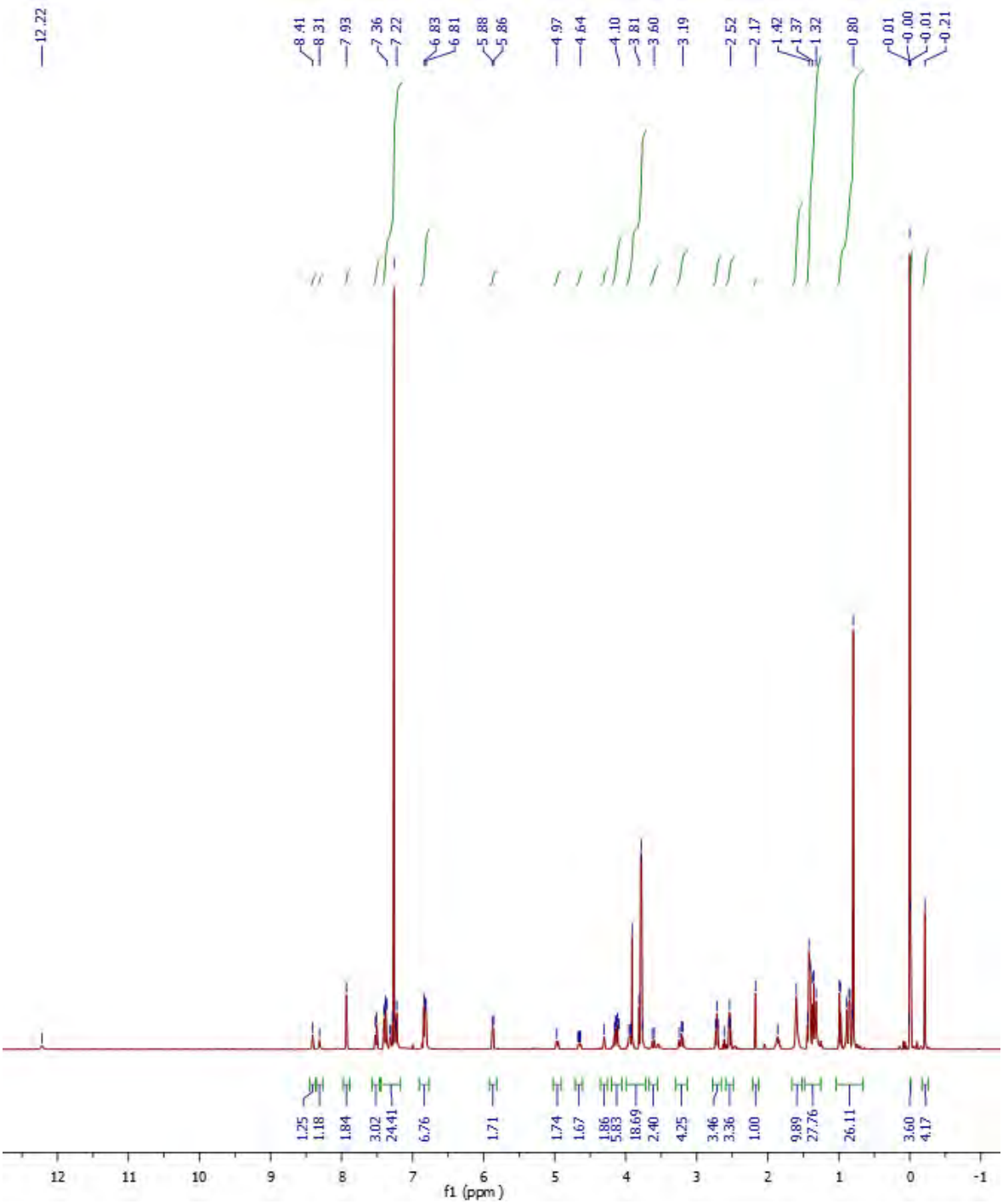
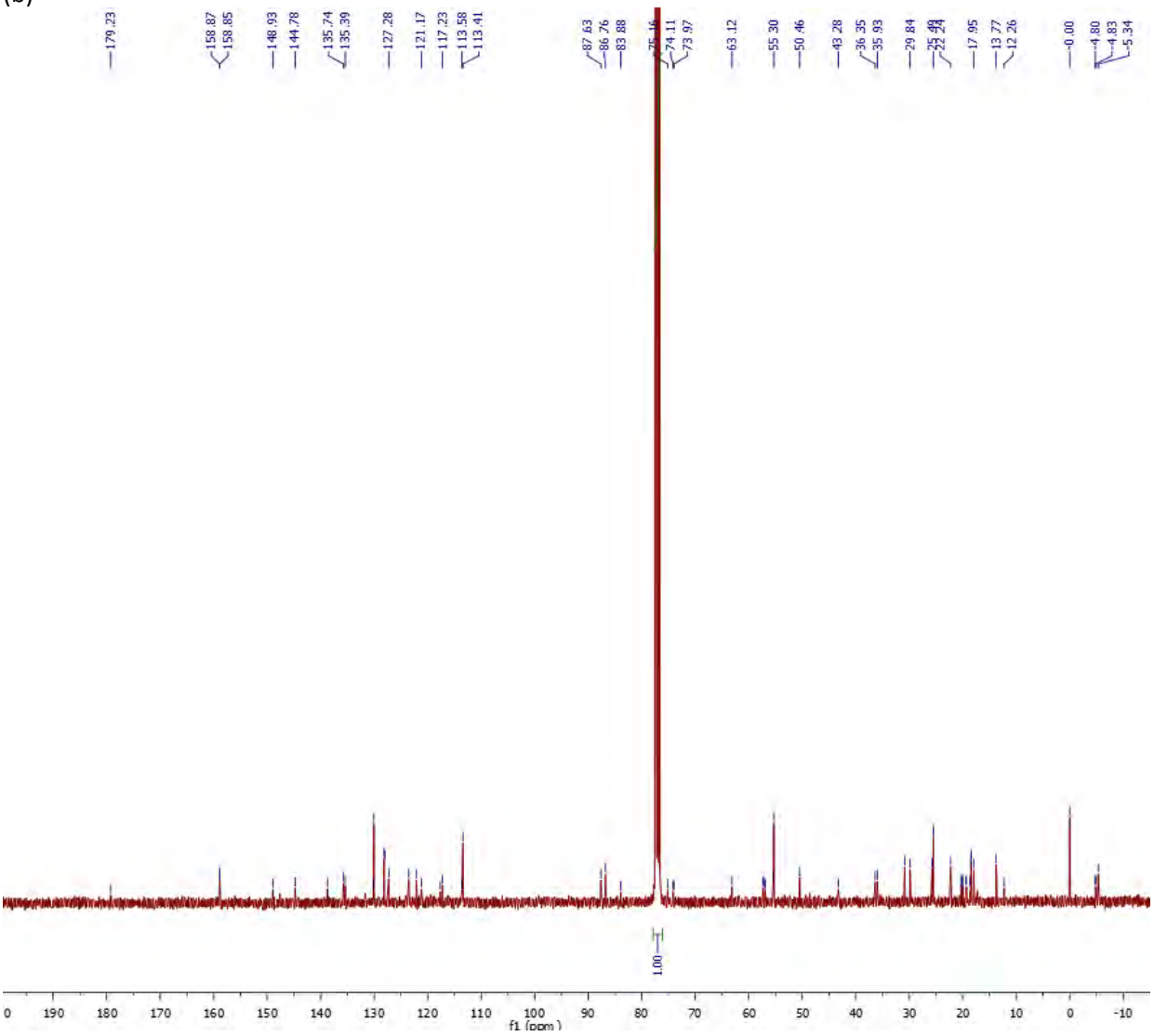


Figure S11 (a) ^{1}H, (b) ^{13}C and (c) ^{31}P NMR spectra of *N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O,O*-(2-cyanoethyl)-phosphoramidite (**4a**).(a)



(b)


179.23
158.87
158.85
148.93
144.78
135.74
135.39
127.28
121.17
117.23
113.58
113.41
87.63
86.76
83.88
75.16
74.11
73.97
63.12
55.30
50.46
43.28
36.35
35.93
29.84
25.49
25.24
17.95
13.77
12.26
0.00
-4.80
-4.83
-5.34
1.00
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(c)

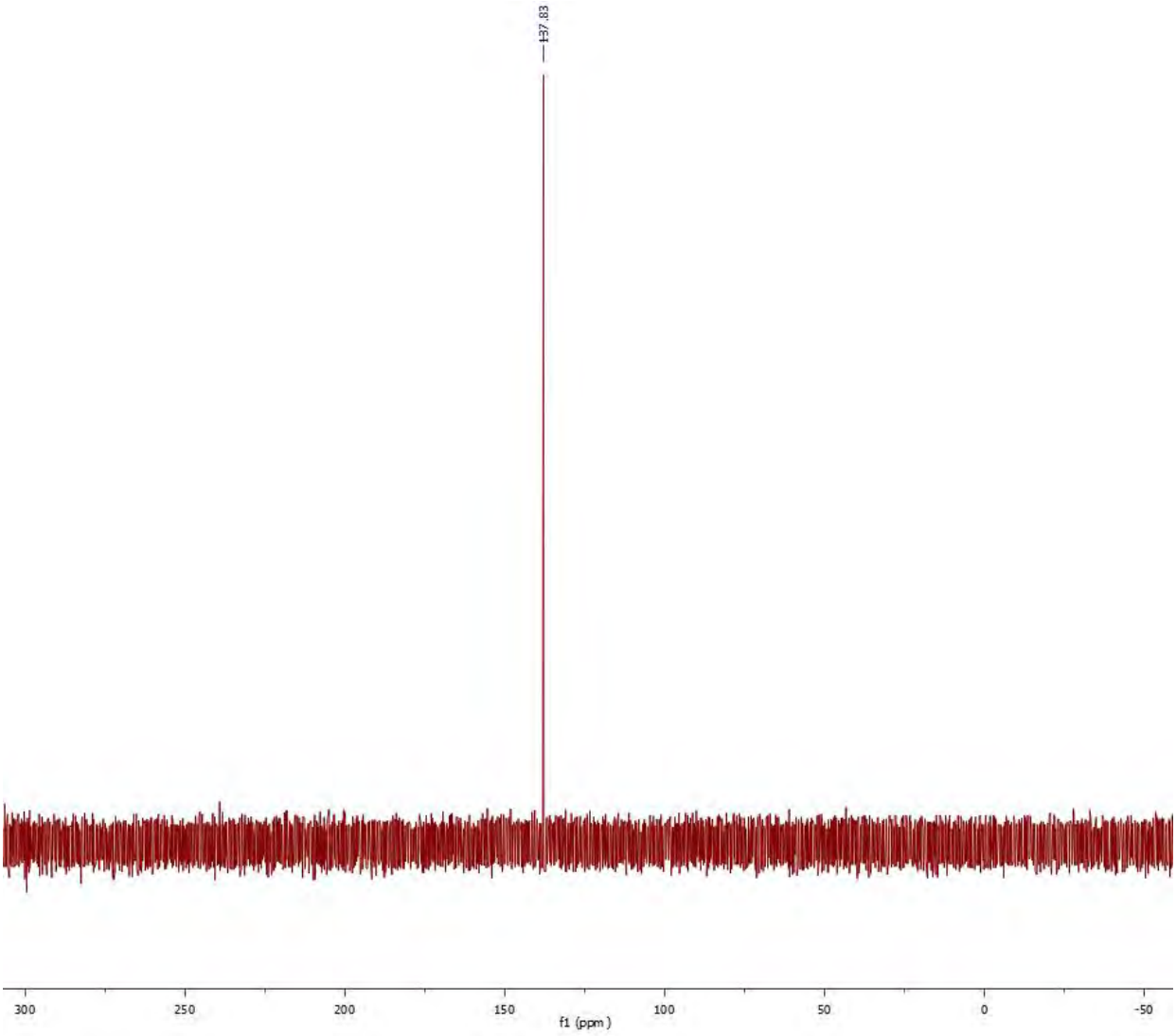
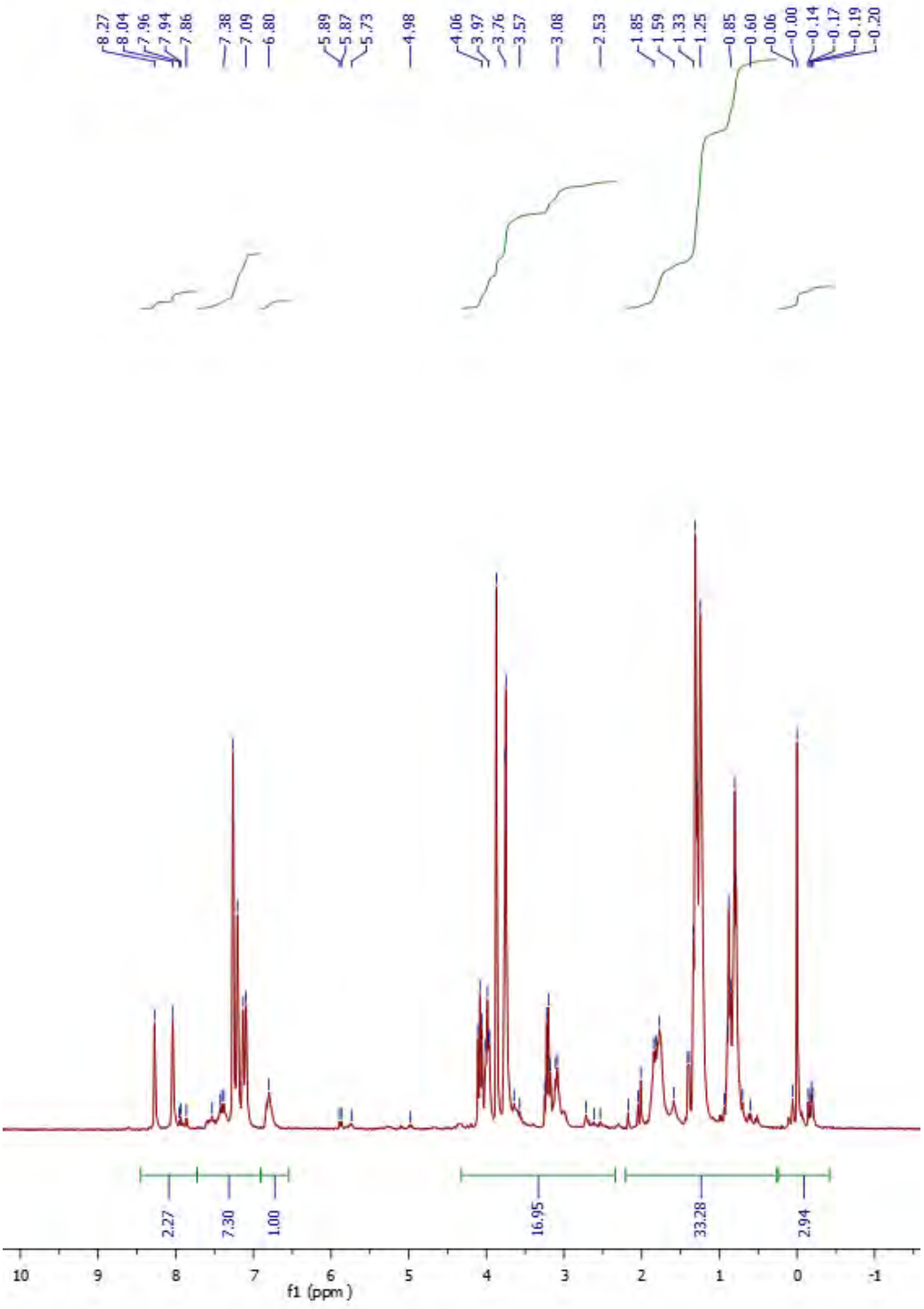
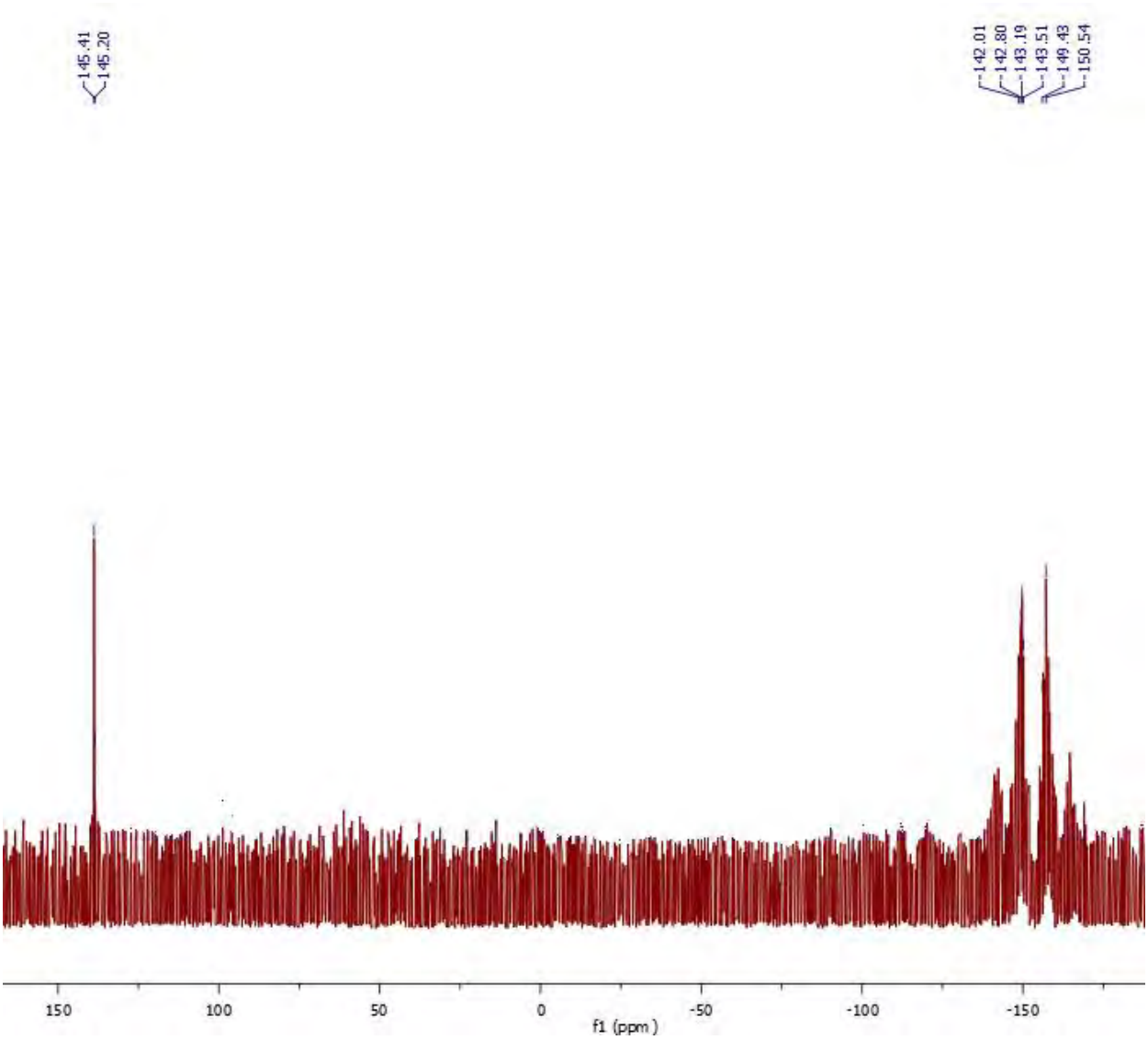


Figure S12 (a) ^{1}H and (b) ^{31}P NMR spectra of *N*-Isobutyryl-5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-TBDMS-guanosine-3'-*O*-[*O*-(2-cyanoethyl)-*N*-pyrrolidinophosphoramidite (**3a**) in stabilized in [C_6mim][FAP].(a)



(b)



References

1 P. Bonhôte, A. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168-1178